TECHNISCHE UNIVERSITÄT WIEN
Vienna University of Technology

Diploma Thesis

Towards the Total Synthesis of Providencin

Submitted at the

Institute of Applied Synthetic Chemistry

of the Vienna University of Technology

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and

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Date

Michael Steinacher

In the beginning God created the heaven and the earth. And the carbonyl group.

P. J. Kocieński, *Protecting Groups* 3rd Ed.

Thanks & Acknowledgements

I would like to thank:

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All the people from the second floor for provision of entertainment and nourishment.

(shoutout: LEKG)

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My parents for creating me and supporting me on my way through life since anno 1993.

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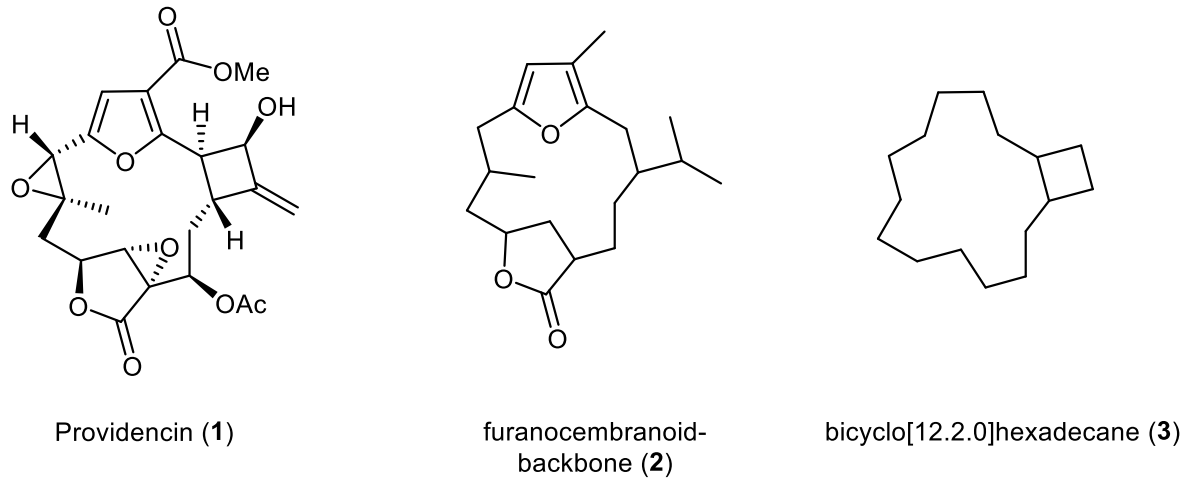
1 Introduction

1.1 Providencin

In the year 2003, Rodriguez *et. al* reported[1] the isolation of 20 mg (0.012 % dry weight) of a new natural product from the sea plume *Antillogorgia Kallos*, which is prevalent in shallow coral reefs throughout the southern Caribbean Sea. Providencin (**1**) (Scheme 1) is a highly oxygenated furanocembranoid (**2**) derivative, possessing a unique bicyclo[12.2.0]hexadecane (**3**) ring system. The structure and relative configuration of providencin were established based on extensive 2D-NMR experimentation and X-ray crystallographic studies. Biological testing revealed cytotoxic activity against breast (MCF7) lung (NCI-H460) and CNS (SF268) cancer cell lines.



Providencin (**1**) furanocembranoid-backbone (**2**) bicyclo[12.2.0]hexadecane (**3**)

Scheme 1: The Structure of Providencin in different Levels of Abstraction

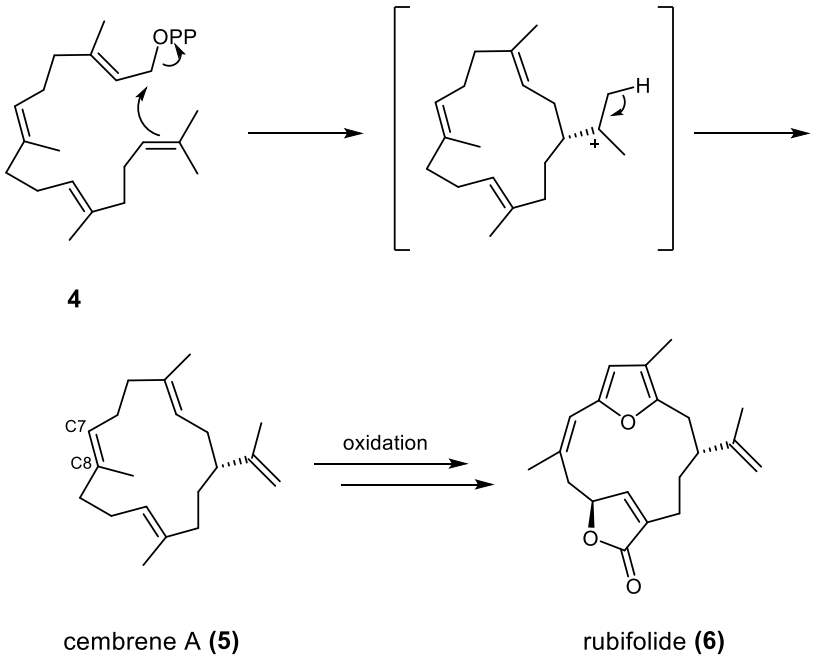
Providencin features a trisubstituted furan attached to an unusual methylenecyclobutanol fragment, a butenolide moiety and two epoxides, all fused to the central 13-membered macrocycle. This cycle is highly strained due to the rigid furan ring and the *trans*-fused epoxides, leading to a challenging macrocyclization in the late stages of the synthesis. Furthermore, the molecule contains nine stereogenic centres and the presence of nine oxygen atoms leads to a high level of reactivity.

The sum of its structural intricacies renders providencin a daunting, yet also highly rewarding target for total synthesis. If a robust synthesis were to be found, providencin and possible derivates could be submitted for more extensive medicinal testing. Moreover, the absolute configuration of providencin is still unknown and could be established by total synthesis.

2 Biosynthesis

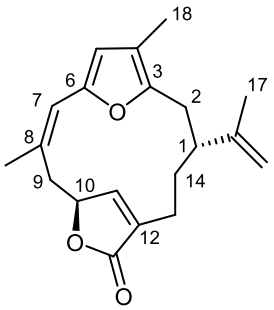
2.1 Furanocembranoids

The biosynthesis of furanocembranoids (Scheme 2) generally starts with "type A" cyclization of geranylgeranylpyrophosphate (**4**) (GGPP)[2]. The intermediate carbocation is trapped by elimination to give the natural product cembrene A (**5**), also known as neocembrene. Oxidative closing of the furan- and butenolide rings combined with $\Delta^{7,8}$ – isomerization then leads to simple furanocembranoids such as rubifolide (**6**)**.** It is presumed these oxidations are performed by cytochrome P450 monooxygenases, however, little is known about the specific enzymes involved.

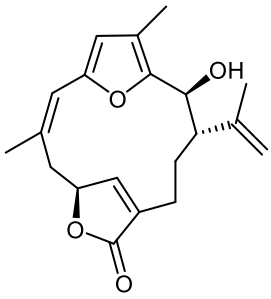


Scheme 2: Biosynthesis of the Furanocembranoid Backbone

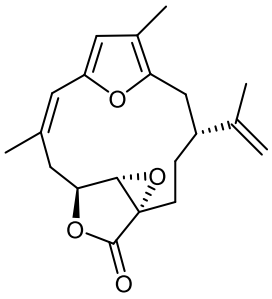
Starting from molecules like **6,** primary metabolism leads to a wide variety of more complex structures with higher levels of oxidation. Some general observations can be made about the most common metabolic transformations (Scheme 3). The "benzylic" position at C2 is often hydroxylated (**7**) or acetylated (**14**). The similar C18 occurs in hydroxylated form (**15**)**,** as an aldehyde (**10**) and frequently as methyl ester (**9**). The activated C13 is hydroxylated or acetylated (**10**) in many compounds. Epoxidation is very common at the conjugated double bonds C7-C8 (**10**) and C11-C12 (**8**). A less common pattern is the oxidation of C17 to an aldehyde or methyl ester.



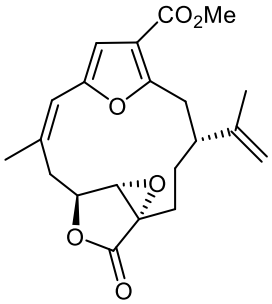
6



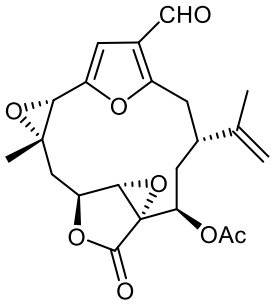
bipinnatin **(7)**



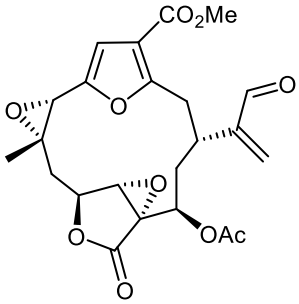
coralloidolide **(8)**



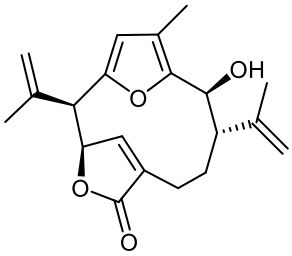
pukalide **(9)**



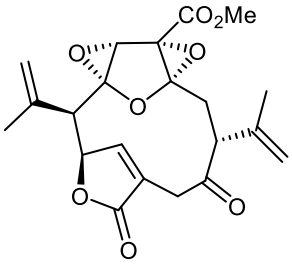
lophotoxin **(10)**



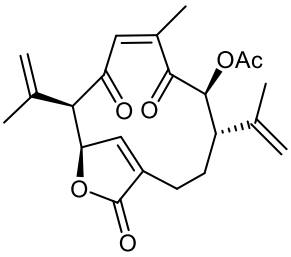
bipinnatin E **(11)**



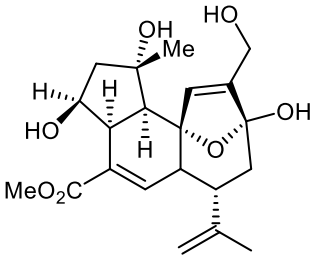
kallolide A **(12)**



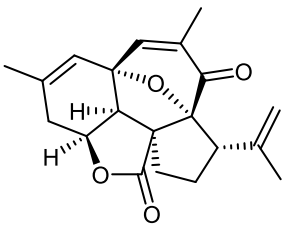
diepoxygorgiacerone **(13)**



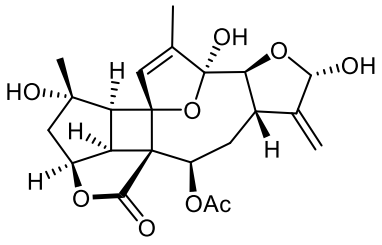
kallolide A **(14)**



mandapamate **(15)**



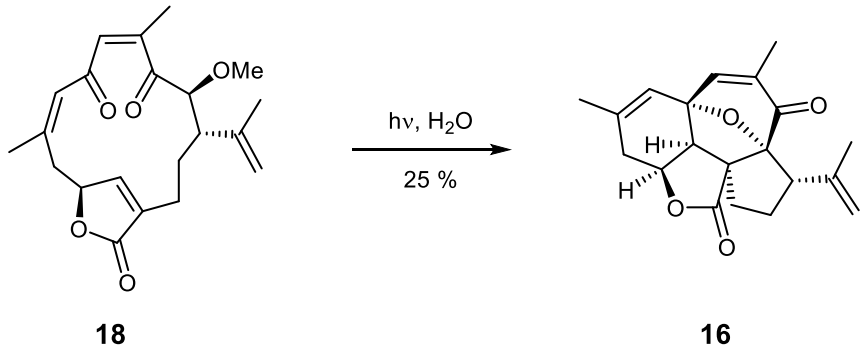
intricarene **(16)**



bielschowskysin **(17)**

Scheme 3: Selected Furanocembranoids and rearranged Furanocembranoids

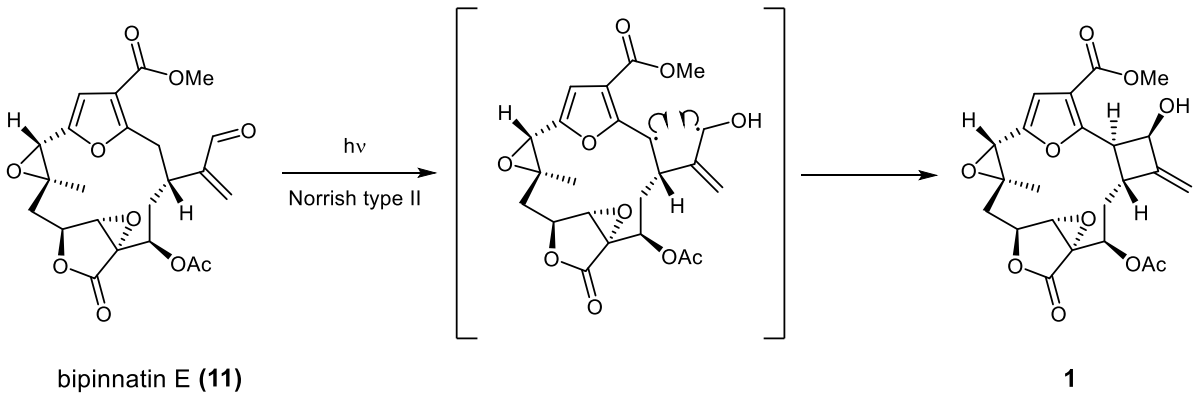
The furan moiety provides ample opportunity for further oxidation and the resulting structures (**13**, **14**) can undergo extensive isomerization to form complicated natural products (**15, 16, 17**)**.** It is unclear whether these rearrangements proceed thermally, photochemically or with the aid of enzymes. Trauner *et al.* achieved a serendipitous total synthesis of intricarene (**16**) by irradiating **18** with a reptile lamp (mimicking UV intensity in coral reefs) as a model study towards the synthesis of bielschowskysin (**17**)[3] (Scheme 4).



Scheme 4: Trauner´s serendipitous Synthesis of Intricarene

2.2 Providencin Biosynthesis

Pattenden *et al.* have proposed[4] bipinnatin E (**11**) as the direct precursor in the biosynthesis of providencin. A Norrish type II reaction would form the cyclobutane moiety (Scheme 5). The feasibility of this mechanism is supported by experiments on a test substrate: Pattenden successfully created a cyclobutane ring by irradiating a simplified analog of **11** with UV-light. His product was a single diastereomer of incorrect configuration. (see chapter 3.2.1).



Scheme 5: Biosynthesis of Providencin as proposed by Pattenden

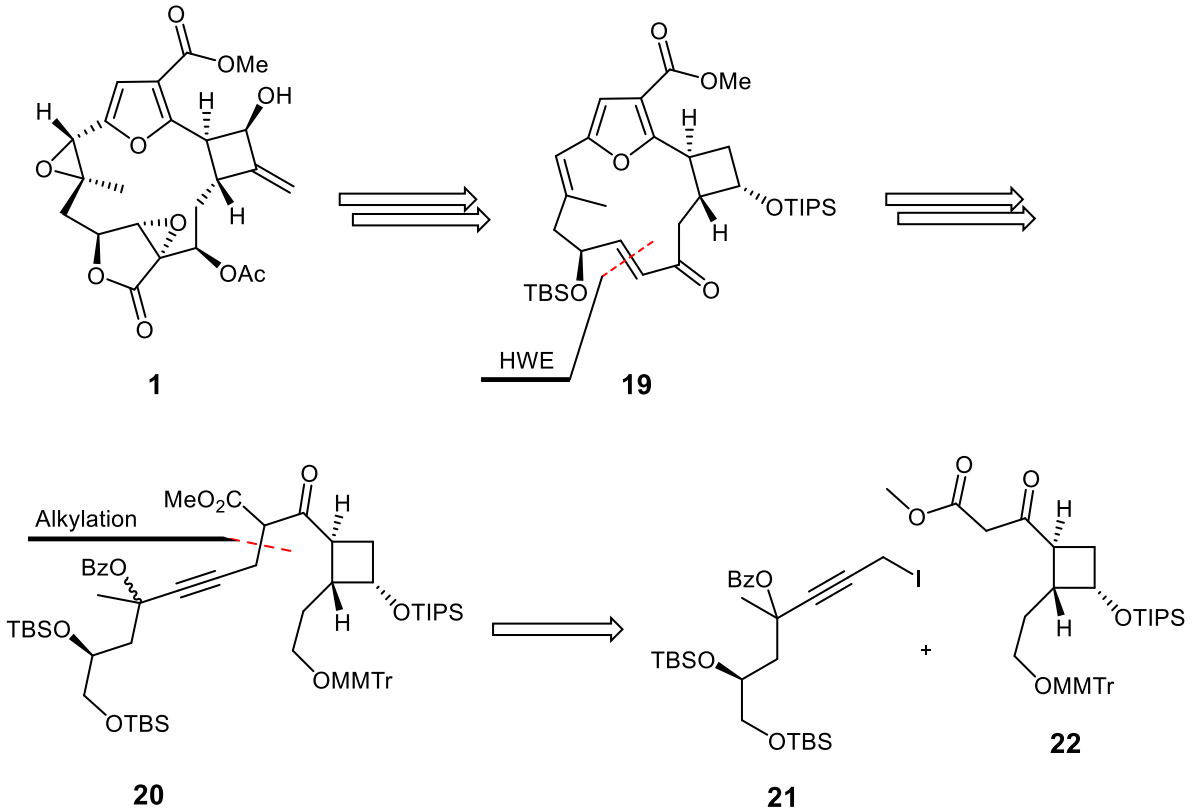
3 State of the Art

In the years since its discovery, multiple research groups reported progress towards the total synthesis of providencin. These reports range from the preparation of small model systems to the synthesis of 17-deoxyprovidencin by Mulzer *et al*. However, as of 2019, no complete total synthesis of providencin has been reported.

3.1 Mulzer *et. al.*

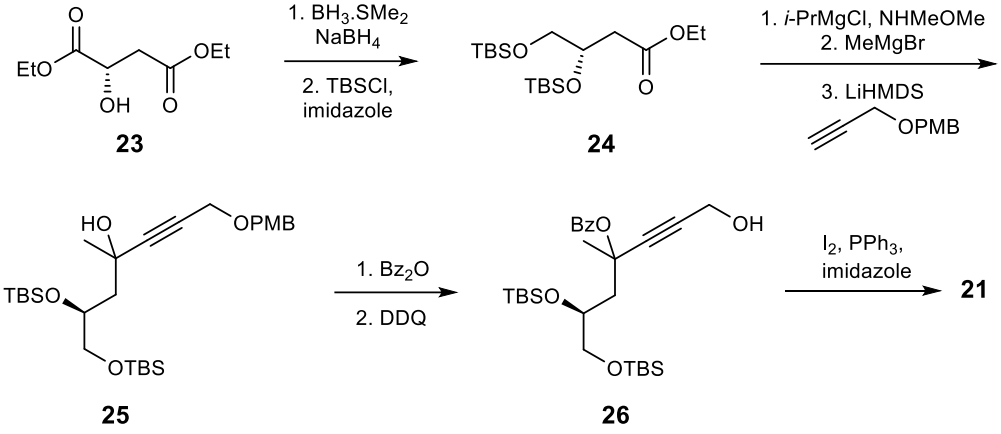
3.1.1 First-Generation Approach (Horner Wadsworth Emmons)[10]

Mulzer's first approach (Scheme 6) was based around the idea of connecting fragments **21** and **22** *via* alkylation to form **20** and ring closing by Horner-Wadsworth-Emmons reaction to give **19.** Ten more steps, including allylic oxidation at the cyclobutane ring could have led to providencin.



Scheme 6: Retrosynthesis for Mulzer´s First-Generation Approach

For the synthesis (Scheme 7) of western fragment **21,** (*S*)-malic ester **23** was used as starting material. Chemoselective reduction and protection lead to **24**, which was converted into the Weinreb-amide[18] and alkylated with MeMgBr. Alkyne addition gave **25** and **26** was generated by benzylation and PMB deprotection with DDQ. Iodination yielded finished building block **21**.

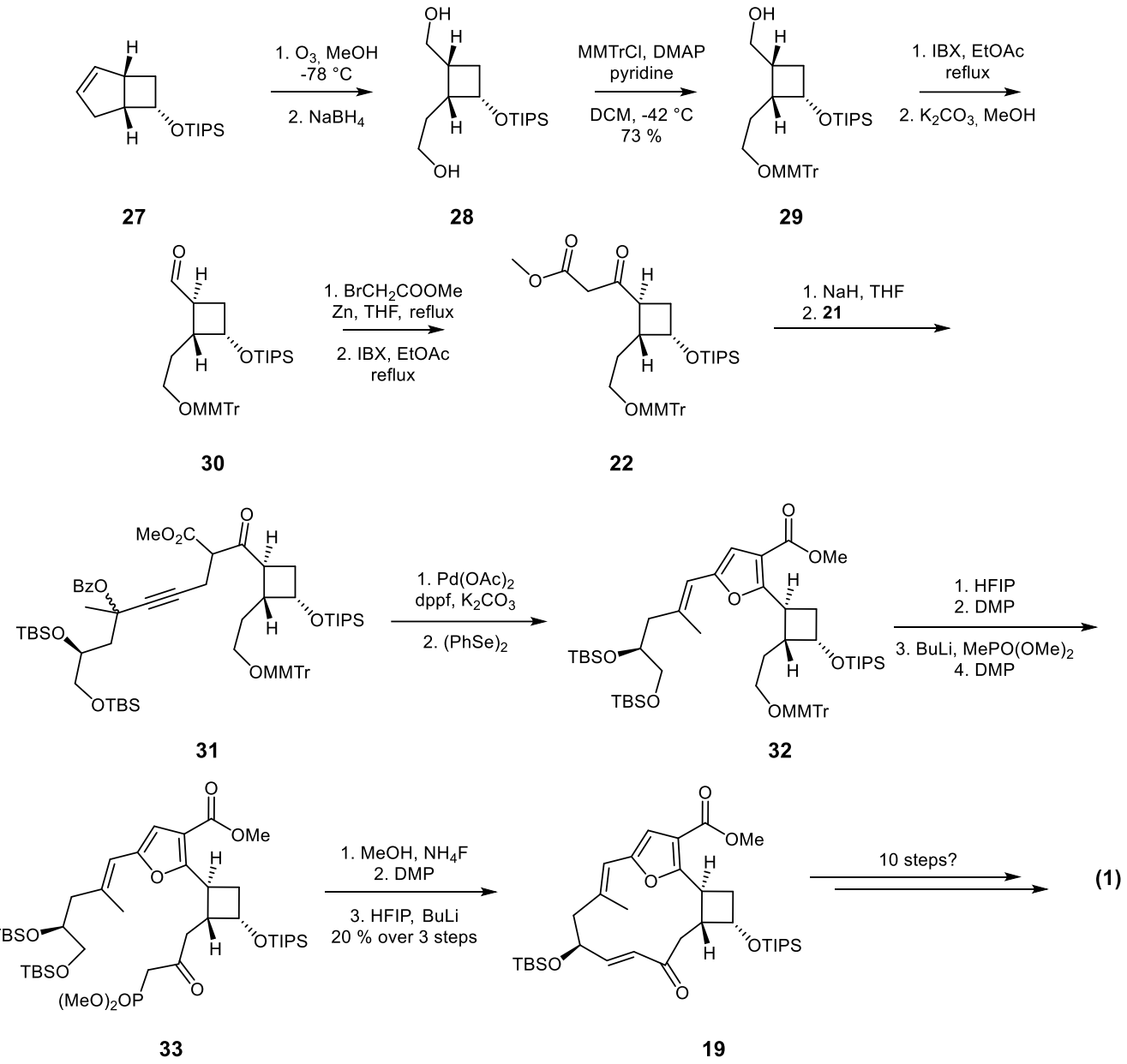


*Scheme 7: Synthesis of Building Block **21***

The main sequence (Scheme 8) commenced from ketone **27**, which was obtained by chiral resolution of racemic starting material. Ozonolysis and reductive workup gave **28** which was selectively protected with MMTr to differentiate the primary alcohols (**29**). Oxidation and equilibration led to *trans*-diastereomer **30**. Reformatsky reaction with bromoacetate and IBX oxidation completed building block **22** and set the stage for alkylation with **21** after the β-keto-ester was deprotonated by NaH (**31**).

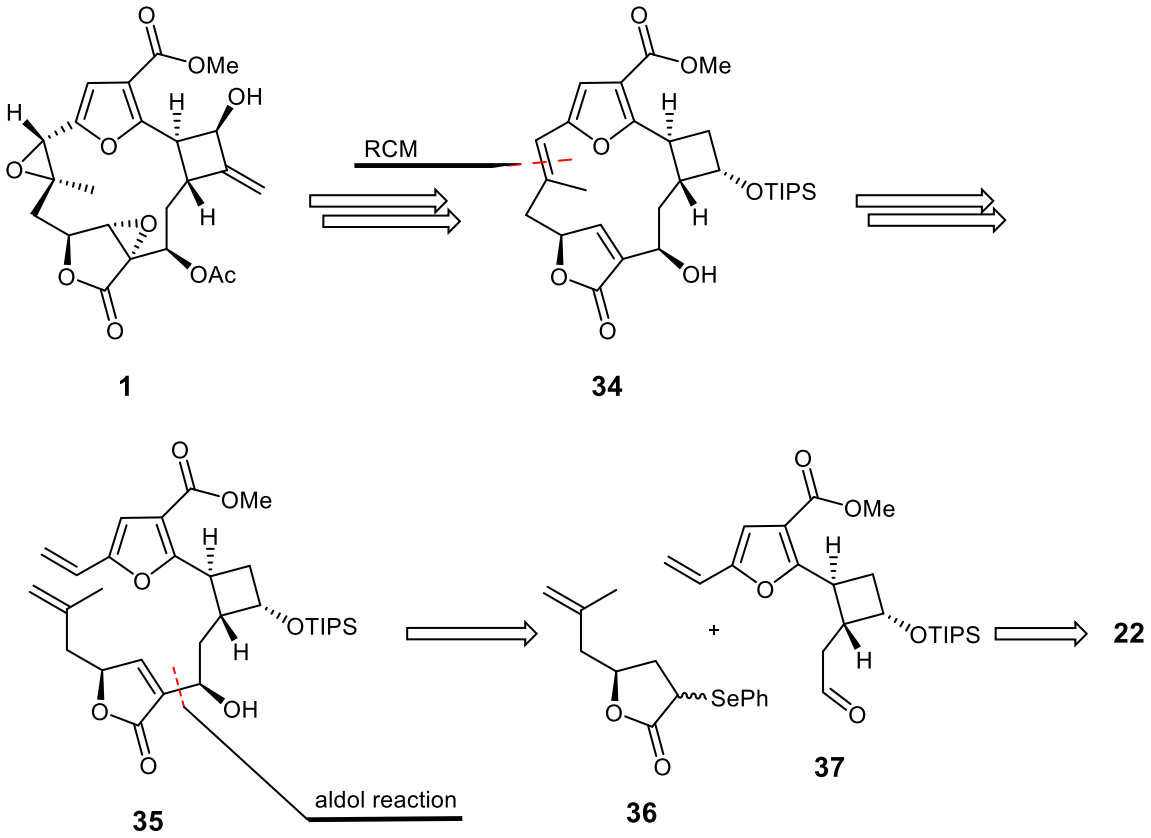
The campaign was continued by Wipf-cyclization to create the furan moiety and equilibration by reversible addition of phenylselenyl radical fixed the adjacent double bond in *trans*-configuration (**32**). The labile MMTr protecting group was cleaved with HFIP and after oxidation with DMP, keto phosphonate **33** was formed. Selective deprotection of primary alcohol and oxidation allowed for HWE macrocyclization, performed with BuLi in HFIP.

Mulzer *et al.* planned to elaborate product **19** into providencin in ten additional steps, but no further progress was published on this route.



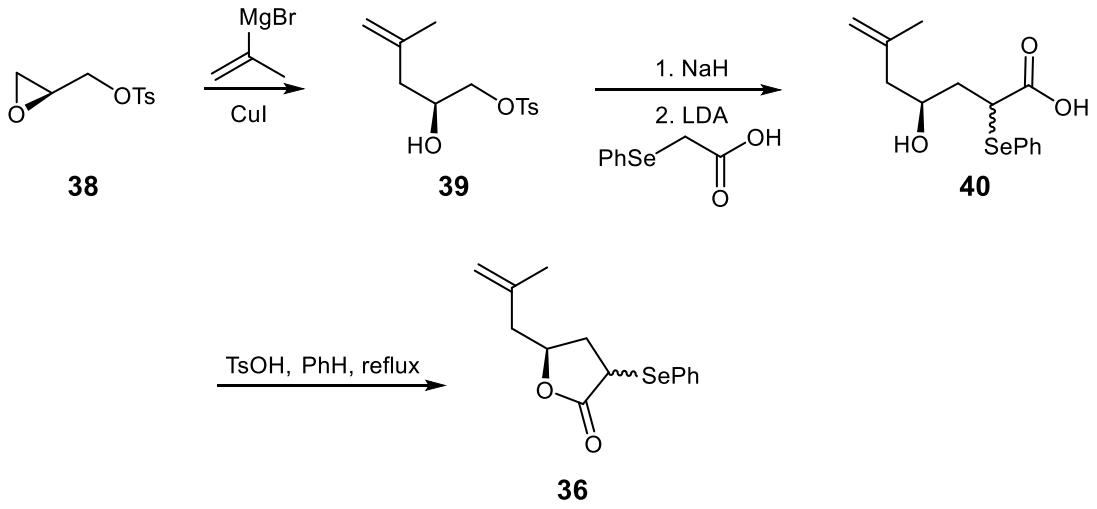
Scheme 8: Mulzer´s First Generation Approach

3.1.2 Second Generation Approach (Ring Closing Metathesis)[10]



Scheme 9: Retrosynthetic Planning for the Second-Generation Approach

Mulzer's second-generation strategy (Scheme 9) was centered around ring-closing metathesis of compound **35**, which was formed by aldol reaction of **36** and **37**. The furan in **37** is created from **22** by the same Wipf-cyclization strategy that led to **32** in the first-generation approach.

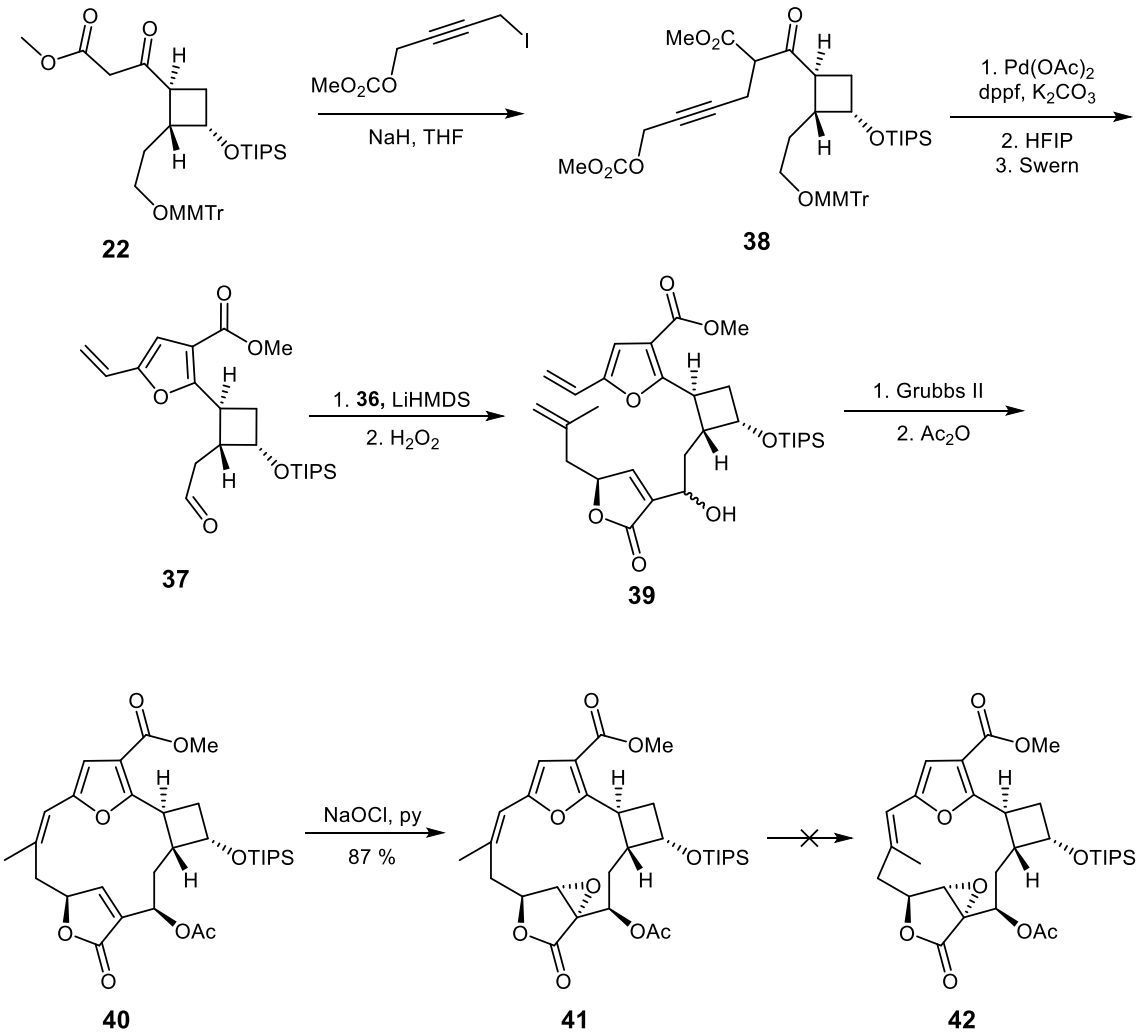


*Scheme 10: Synthesis of Selenolactone **36***

Synthesis of fragment **36** (Scheme 10) started from tosylated (*R*)-glycidol **38**. Cuprate addition gave alcohol **39** and reconversion to the epoxide followed by treatment with (phenylseleno)acetate dianion furnished hydroxyacid **40.** Cylization under acidic conditions yielded phenylseleno substituted lactol **36**.

The main pathway (Scheme 11) diverged from the first-generation approach after compound **22**. A different sidechain was added by alkylation to give **38** and subsequent Wipf-cyclization led to vinylfuran **37**. Selenolactone **36** was enolized with LiHMDS and added to **37** to give a mixture of four isomers. Oxidative elimination of phenylselenide produced **39** as a mixture of two epimers. Ring closing metathesis was successfully performed by Grubbs II - catalyst and the resulting two diastereomers were separable by chromatography. Acetylation of the correct diastereomer led to **40** and after some experimentation, epoxidation with sodium hypochlorite in pyridine provided epoxide **41** in 87 % yield.

All attempts to convert the C7 – C8 double bond from the (*Z*)- into the (*E*)-isomer failed for the time being and more progress was only reported five years later.

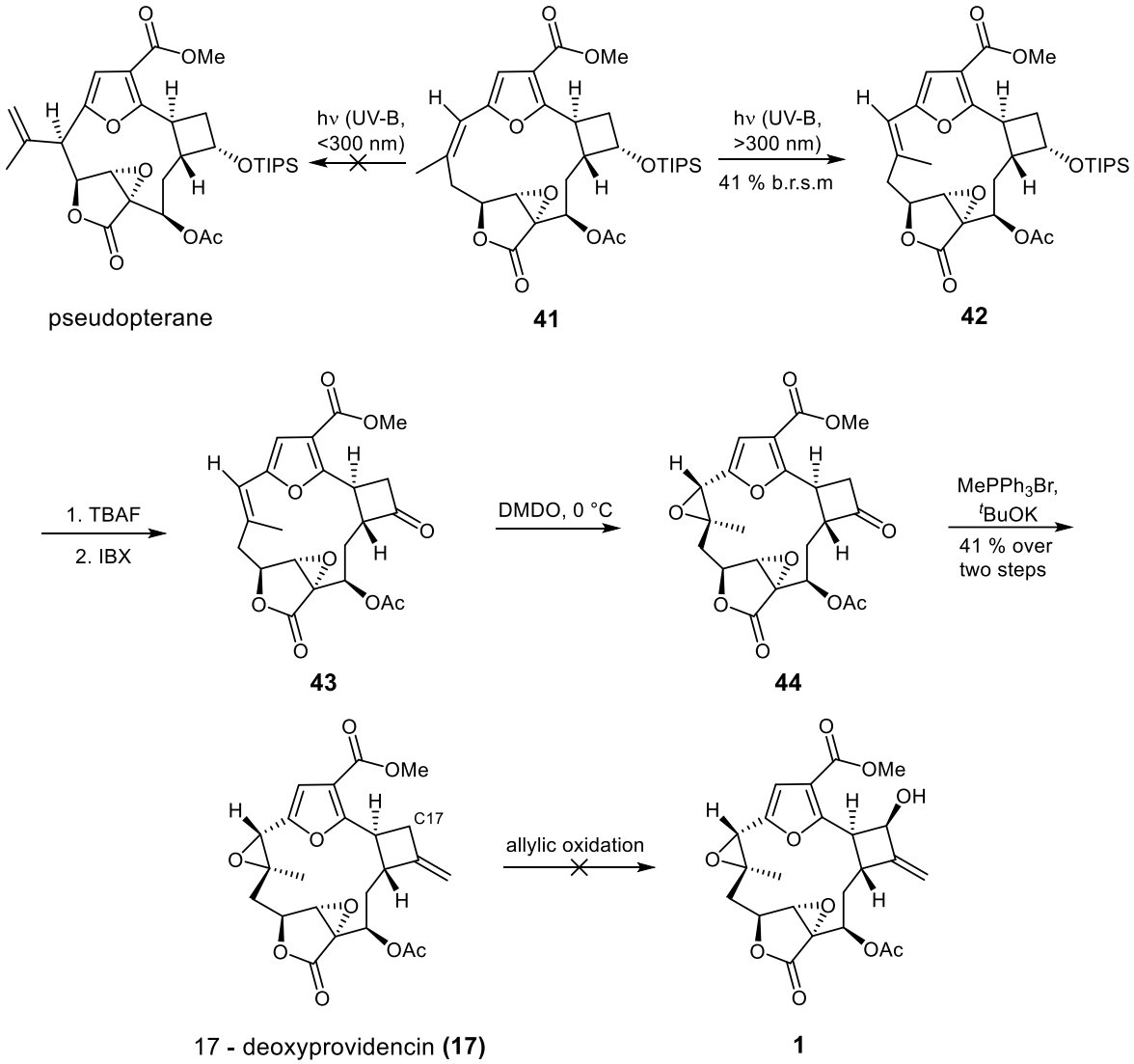


Scheme 11: Mulzer´s Second-Generation Approach

3.1.3 17-Deoxyprovidencin (2014)[9]

Mulzer *et al.* published their synthesis of deoxyprovidencin (**17**) (Scheme 12) in 2014. At the end of their second-generation synthesis, they had been unable to isomerize the (*Z*)-double bond in **41** to the (*E*)-isomer. They found that the transformation could be achieved by irradiating **43** with UV-B light in a Pyrex© vessel. Pyrex© glass blocks wavelengths below 300 nm, therefore inhibiting furanocembranoid – pseudopterane rearrangement[2]. From **42**, TIPS deprotection with TBAF and IBX oxidation led to **43** and the second epoxide was introduced with DMDO in acetone to give **44**. Wittig olefination finally completed deoxyprovidencin (**17**) in 1.7 % overall yield over 17 steps.

The planned endgame for the approaches by Mulzer was allylic oxidation at C17. Even though model compounds had been created to investigate the reaction, no successful method could be found and the total synthesis of providencin failed in the last step.

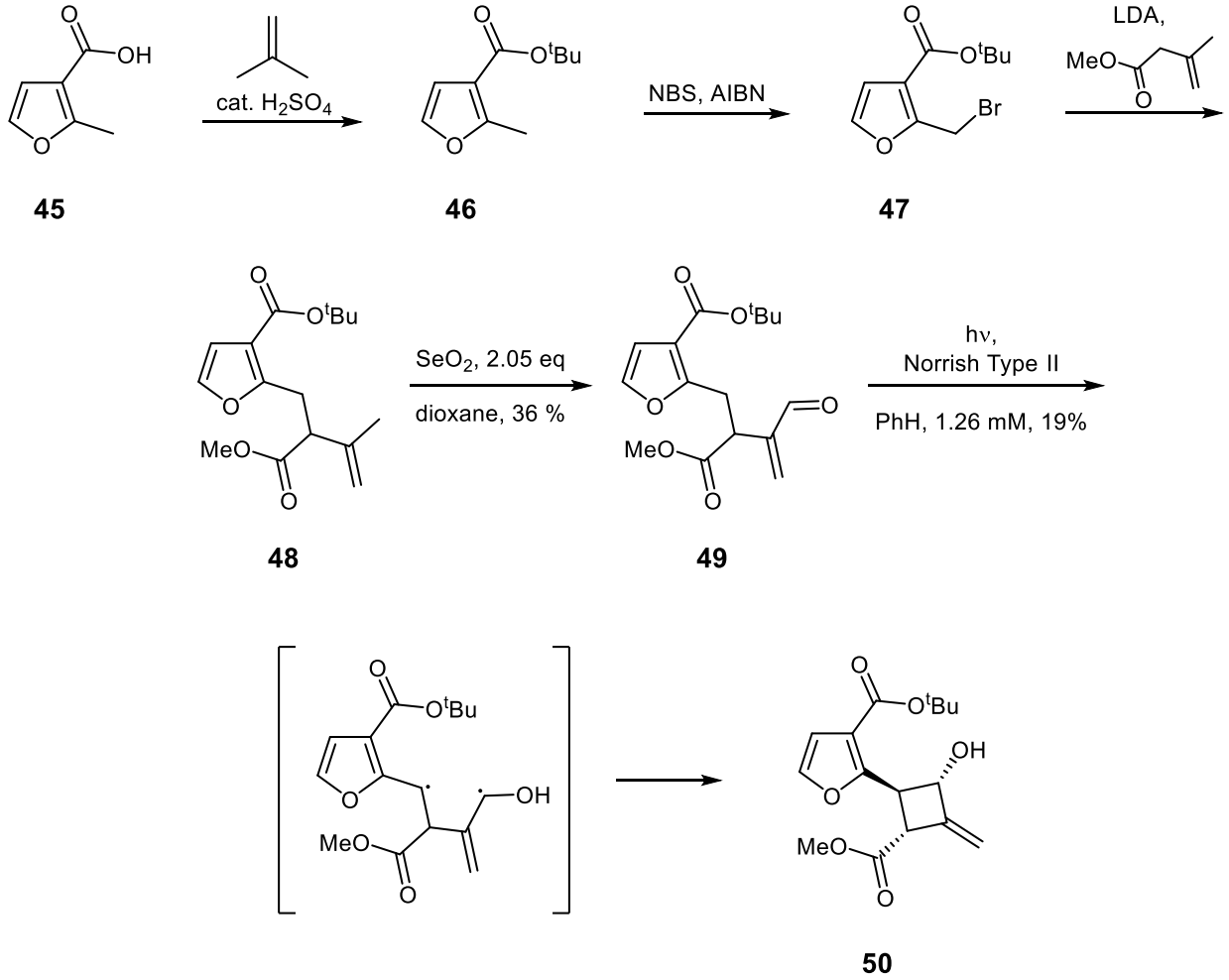


*Scheme 12: Mulzer´s Synthesis of Deoxyprovidencin (**17**)*

3.2 Pattenden *et al.*

3.2.1 Synthesis of a Furan Methylenecyclobutanol Moiety (2006)[4]

Pattenden *et al.* reported a successful model reaction which supported their theory for the biosynthetic origin of providencin (see chapter 2.2). Their synthetic route (Scheme 13) started with 2 – methyl - 3-furoic acid (**45**), which was converted into the *t*-butyl ester **46** with isobutene and catalytic sulfuric acid. The next step was "benzylic" bromination with NBS/AIBN to give **47**. Methyl 3-methylbut-2-enoate was deprotonated with LDA at -78 °C and **47** was added slowly, giving exclusively **48**. Two equivalents of selenium dioxide were employed to convert the allylic methyl group into the corresponding carbonyl compound **49** in 36 % yield.

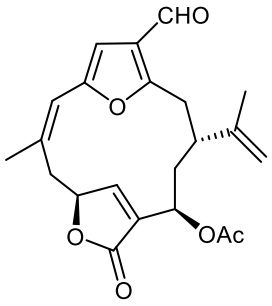


Scheme 13: Pattenden´s Model Compound

With **49** in hand, the proposed Norrish type II reaction could be attempted. Irradiation of dilute **49** in benzene with a 400 W medium pressure Hg lamp lead to **50** as a single diastereomer in 19 % yield. It should be noted that **50** does not exhibit the same relative stereochemistry as the natural product. Pattenden *et al.* propose that the conformational bias in the strained macrocyclic natural product precursor would lead to the observed stereochemistry *in vivo*.

3.2.2 Synthesis of a Fragment *en route* to bis-Deoxylophotoxin (2001)[7]

For his synthesis of bis-deoxylophotoxin (**51**) (Scheme 14), Pattenden created fragment **56** that was later used by White.

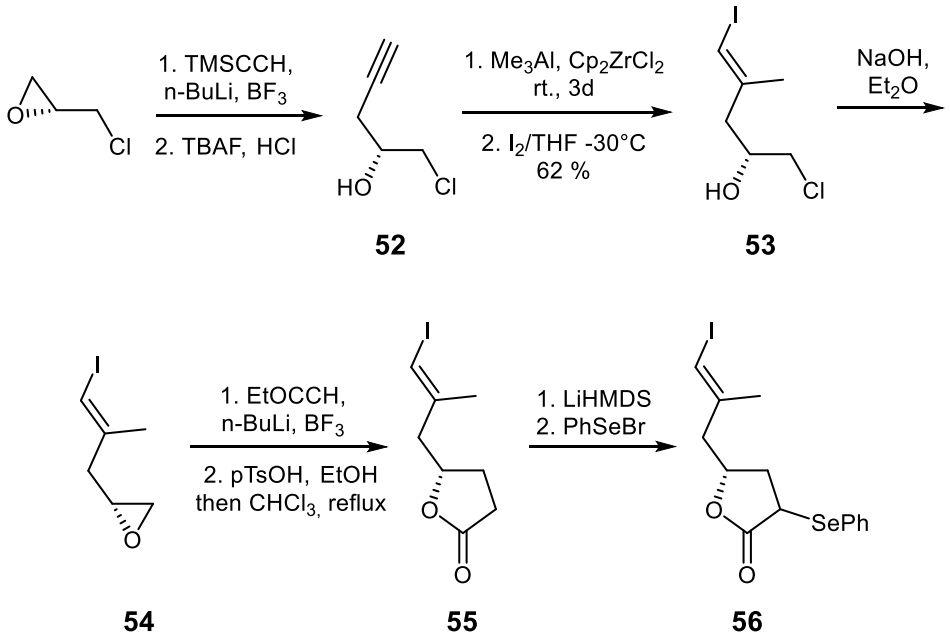


bis-deoxylophotoxin (**51**)

Scheme 14: Bis-Deoxylophotoxin

The synthesis (Scheme 15) started with commercial (-)-epichlorohydrin . Treatment with the lithium salt of TMS-acetylene and sequential TMS deprotection furnished **52**. The alkyne underwent carbomethylation – iodation according to Negishis[8] protocol to give **53** and intramolecular ring closing initiated by NaOH formed epoxide **54**. The less hindered epoxide position was attacked by the lithium salt of ethoxyacetylene and lactone **55** was then formed with catalytic TsOH. Compound **55** was converted into the lithium enolate with LiHMDS and nucleophilic attack on (phenylseleno)bromide gave **56**.

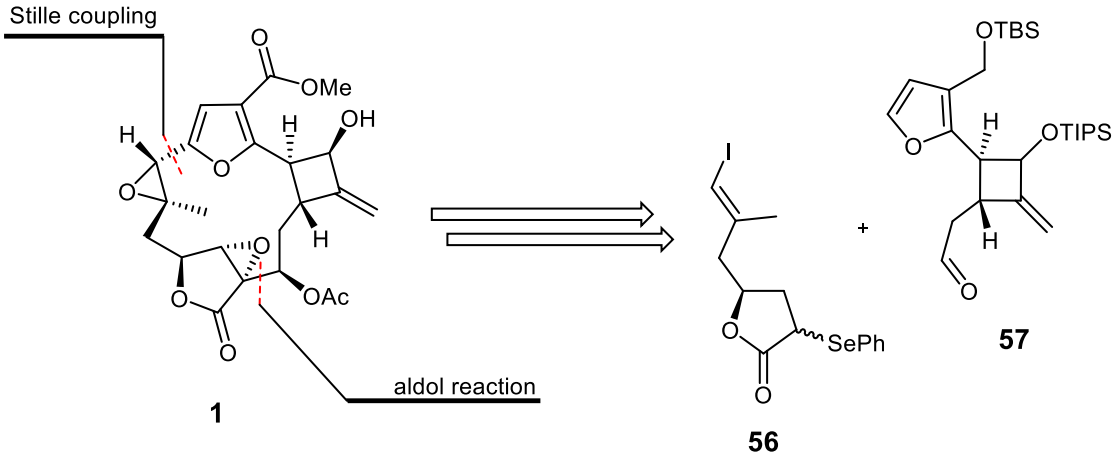
Building block **56** is useful for the construction of many furanocembranoids.



Scheme 15: Pattenden´s Phenylselenide Building Block

3.3 White *et al.*

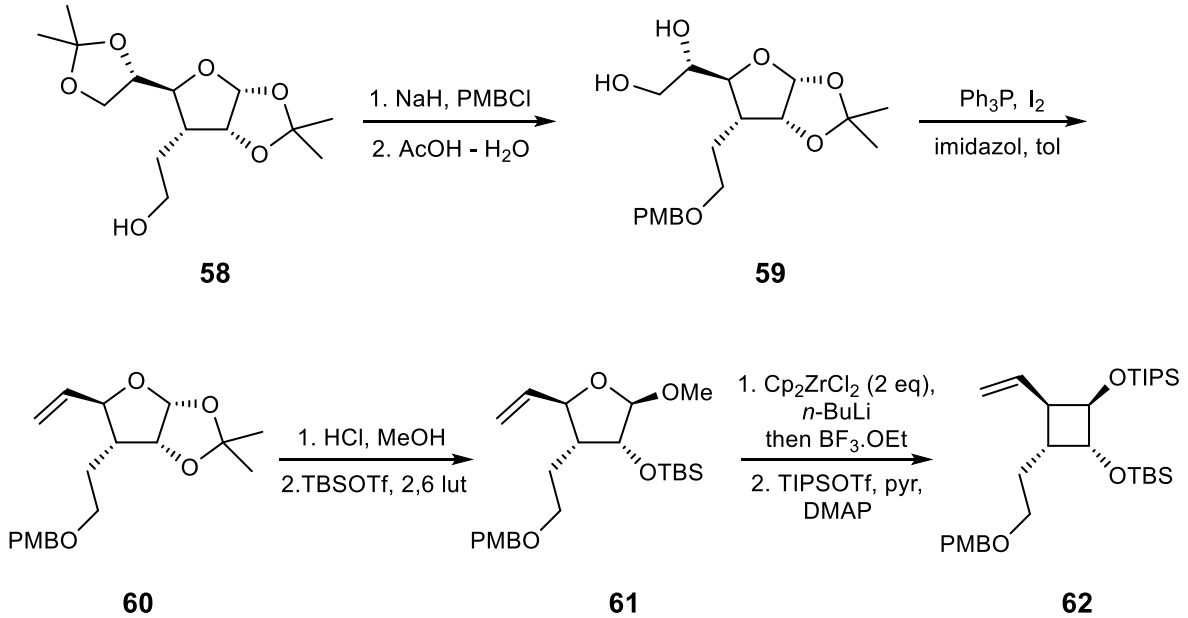
The synthetic approach (Scheme 16) by White *et al.* was based around disconnection of C5 - C6, which can be performed by Stille coupling and disconnection of C11 - C12, which could be performed by aldol reaction. These two disconnections lead to fragments **56** (see chapter 3.2.2) and **57**.



Scheme 16: White´s Retrosynthesis

3.3.1 Construction and Assembly of two Major Subunits (2014)[2]

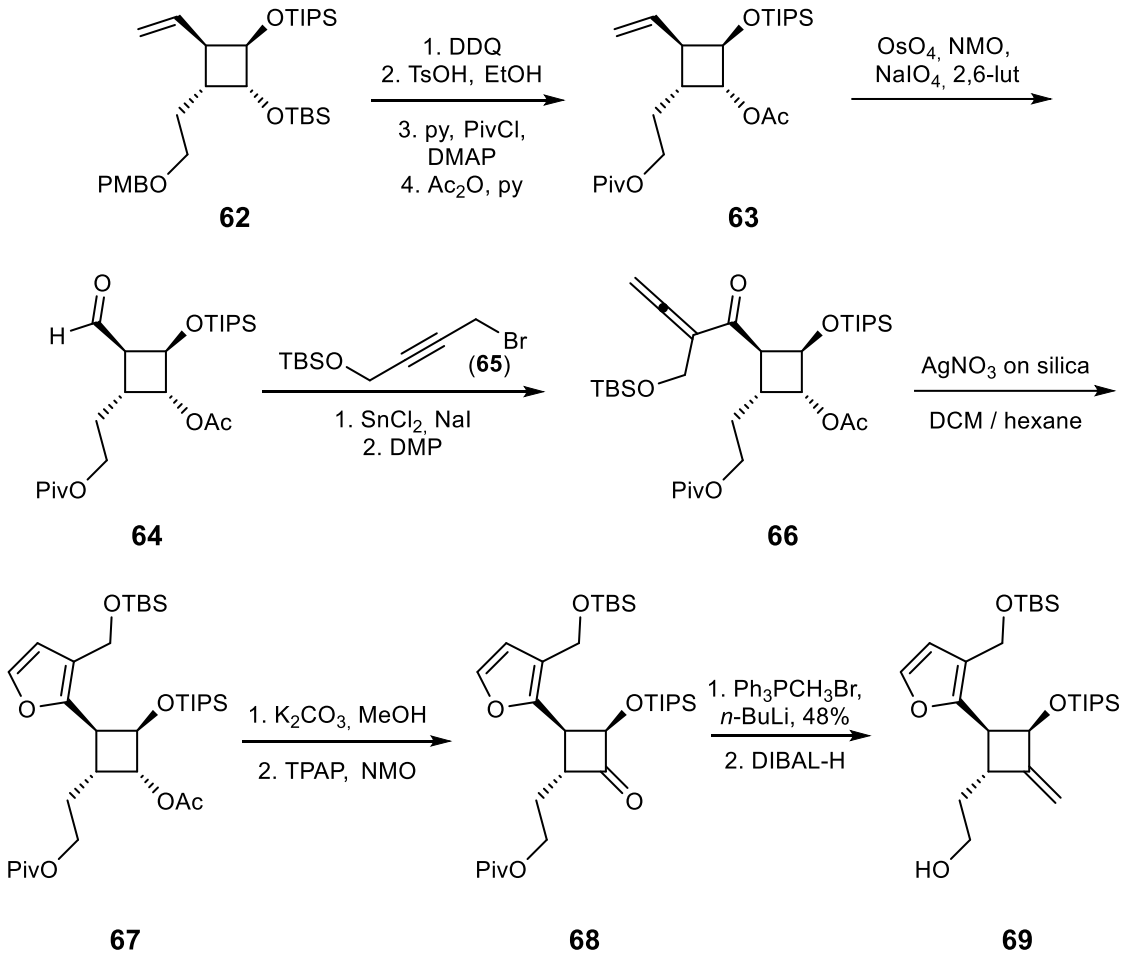
White's synthesis (Scheme 17) started from known alcohol **58**, obtained from D-glucose in four steps[11]. Protection of the primary alcohol with PMBCl and selective acetal cleavage led to **59**, which was dehydrated with triphenyl phosphine and iodine to give **60**. Acetal cleavage in methanol and TBS-protection gave furanoside **61.** The compound was deoxygenated with 2 eq. of dicyclopentadienylzirconium(0), generated from dicyclopentadienylzirconium(II)dichloride *in situ* with *n*-BuLi. Subsequent TIPS-protection gave cyclobutane fragment **62**.



*Scheme 17: Synthesis of Cyclobutane **62***

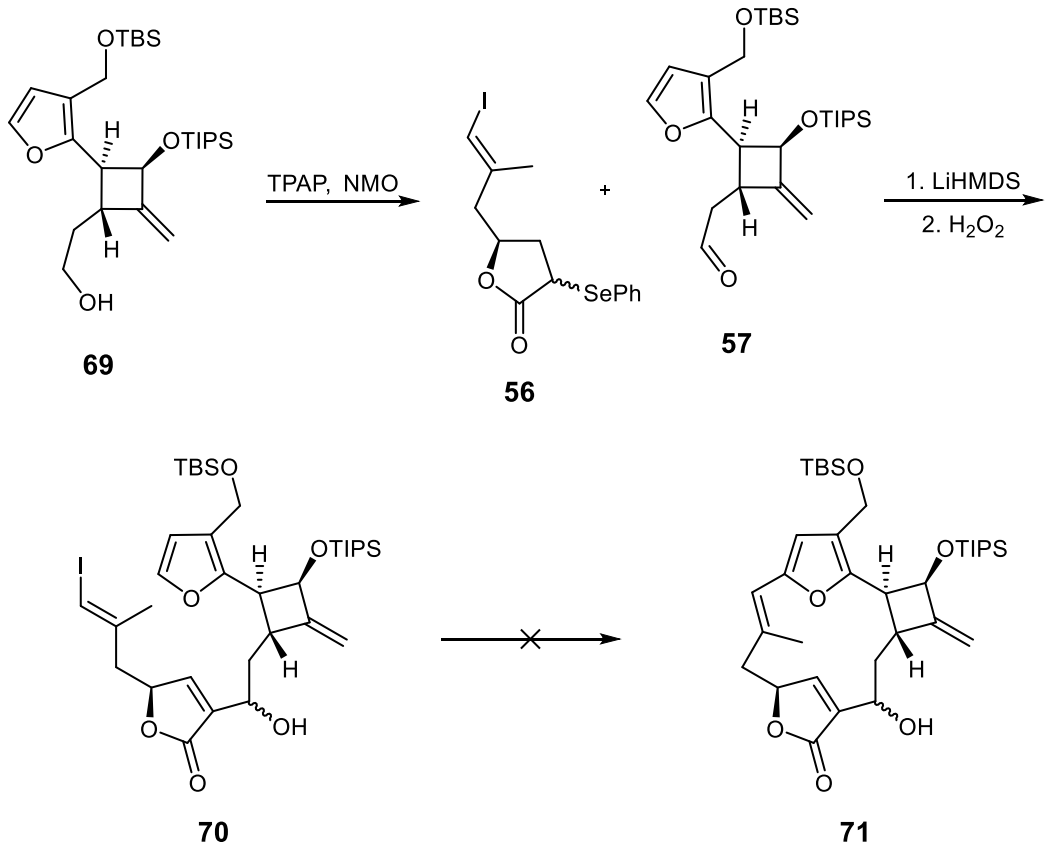
From **62** the campaign continued with oxidative PMB deprotection (Scheme 18), selective deprotection of TBS but not TIPS with TsOH in ethanol, pivalate protection of the primary alcohol and acetate protection of the secondary alcohol (**63**). Oxidative cleavage of vinyl with catalytic OsO_4 in presence of an excess of IO_4 yielded **64**. Allenic ketone **66** was achieved by adding alkynyl bromide **65** to **64** in the presence of catalytic $SnCl_2$ and sodium iodide and subsequent oxidation with DMP.

The furan ring was attained by exposing **66** to the conditions described by Marshall (**67**) and cleavage of acetate with potassium carbonate in methanol followed by oxidation with Ley's reagent[12] gave cyclobutanone **68**. Wittig olefination of **68** worked only in moderate yields and led to partial cleavage of pivalate. Treatment with DIBAL-H afforded finished building block **57**.



*Scheme 18: Synthesis of "northern" building block **69***

Starting from **57**, two distinct pathways were possible: attaching fragment **56** *via* cross-aldol reaction and macrocyclization by Stille coupling or arranging the reactions the opposite way, starting with Stille coupling and subsequent macrocyclization by aldol reaction.

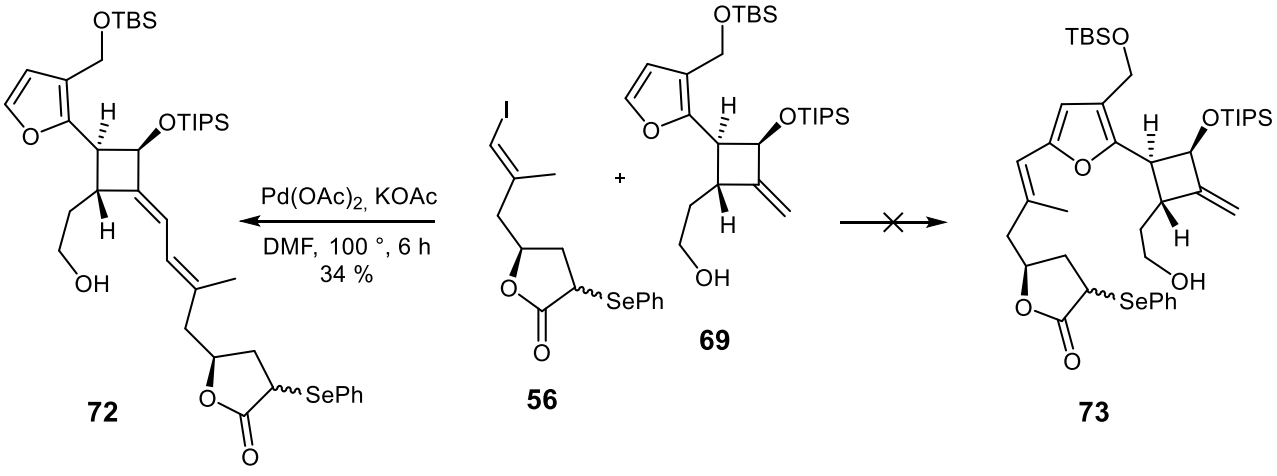


Scheme 19: "Aldol First" - Pathway

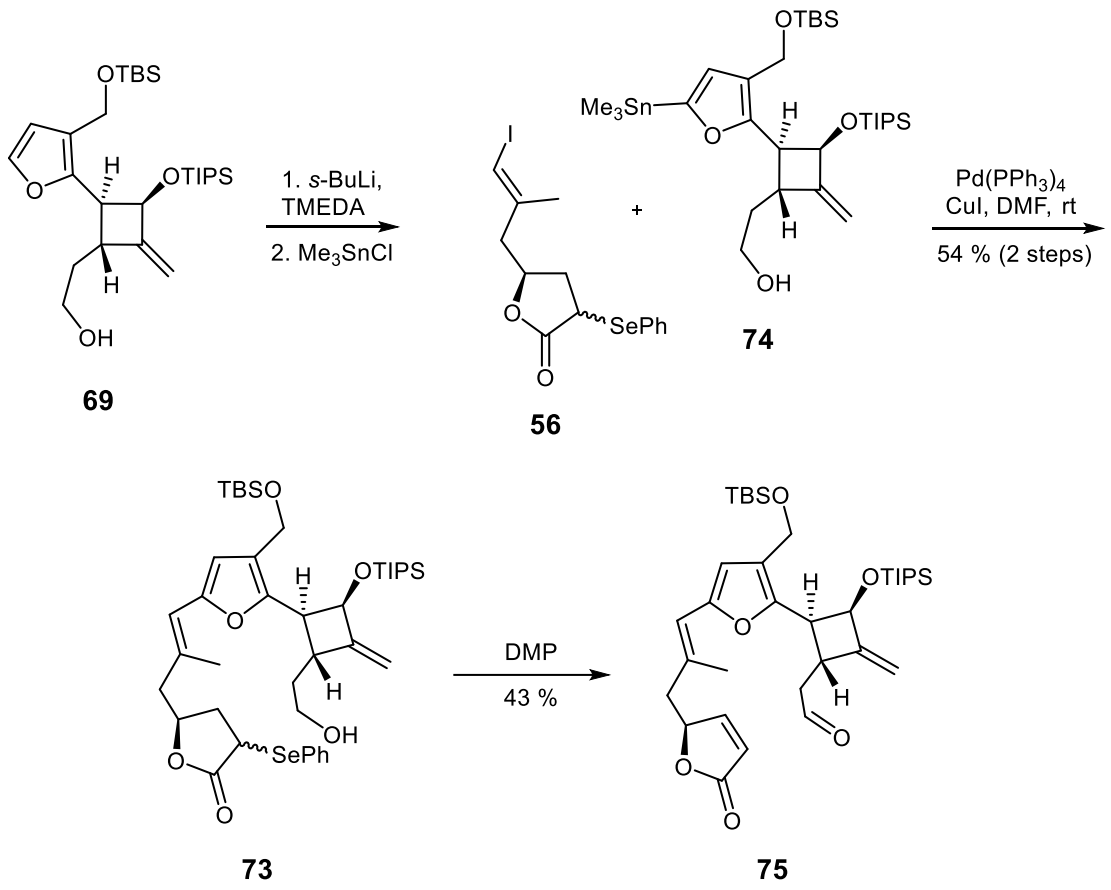
White *et al.* initially attempted the "Aldol First" pathway (Scheme 19). Compound **69** was oxidized with Ley's reagent[12] to give aldehyde **57** and the lithium enolate of **56** (see chapter 3.2.2) was then added, which gave compound **70** in 4:3 diastereomeric ratio.

All attempts to close the macrocycle *via* furan C-H activation failed and this approach had to be abandoned.

Attempts to attach **56** to **69** by furan C-H activation failed and gave the Heck product.



*Scheme 20: Unwanted Heck-reaction of **56** and **69***



Scheme 21: "Stille First" - Approach

The last investigated route was the “Stille first” - approach: Compound **69** was successfully stannylated with *sec*-BuLi in the presence of TMEDA to give **74**. Stille reaction with **56** was performed by copper(I) mediated palladium catalysis at room temperature (**73**). The next reaction step was DMP-oxidation of the primary alcohol in order to prepare the substrate for intramolecular aldol reaction. This led to oxidative elimination of selenide in all cases, forming butenolide **75** as the sole product.

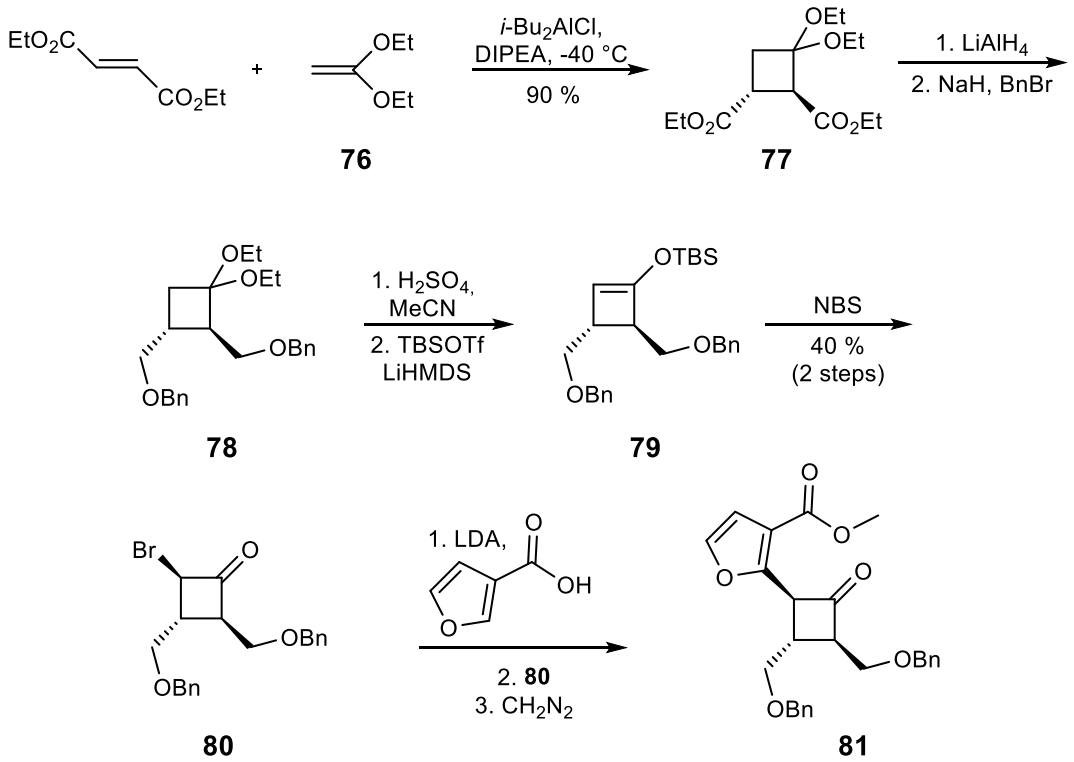
Since there is no obvious pathway from **75** to the target molecule, White *et al.* abandoned their synthetic route and no further progress was published.

3.4 Wood

3.4.1 Construction of a Furanyl-Cyclobutanone Fragment (2011)[3]

Wood *et al.* published their synthesis of cyclobutanone **81** in 2011:

The synthesis commenced from diethyl fumarate, and a cycloaddition with diethyl ketene acetal **76** gave ketal **77** in good yield. The ester functions were reduced with lithium aluminium hydride and the two resulting primary alcohols benzylated with sodium hydride and benzyl bromide **78**. The ketal was cleaved with sulfuric acid in acetonitrile and reaction with TBS-friflate and LiHMDS gave the silyl-enolate **79**. Bromination of **79** yielded **80** in moderate yield. Furan-3-carboxylic acid was selectively lithiated at C2 with LDA and **80** was added at -78 °C. The crude mixture was treated with diazomethane to give **81** in 60 % yield over three steps.

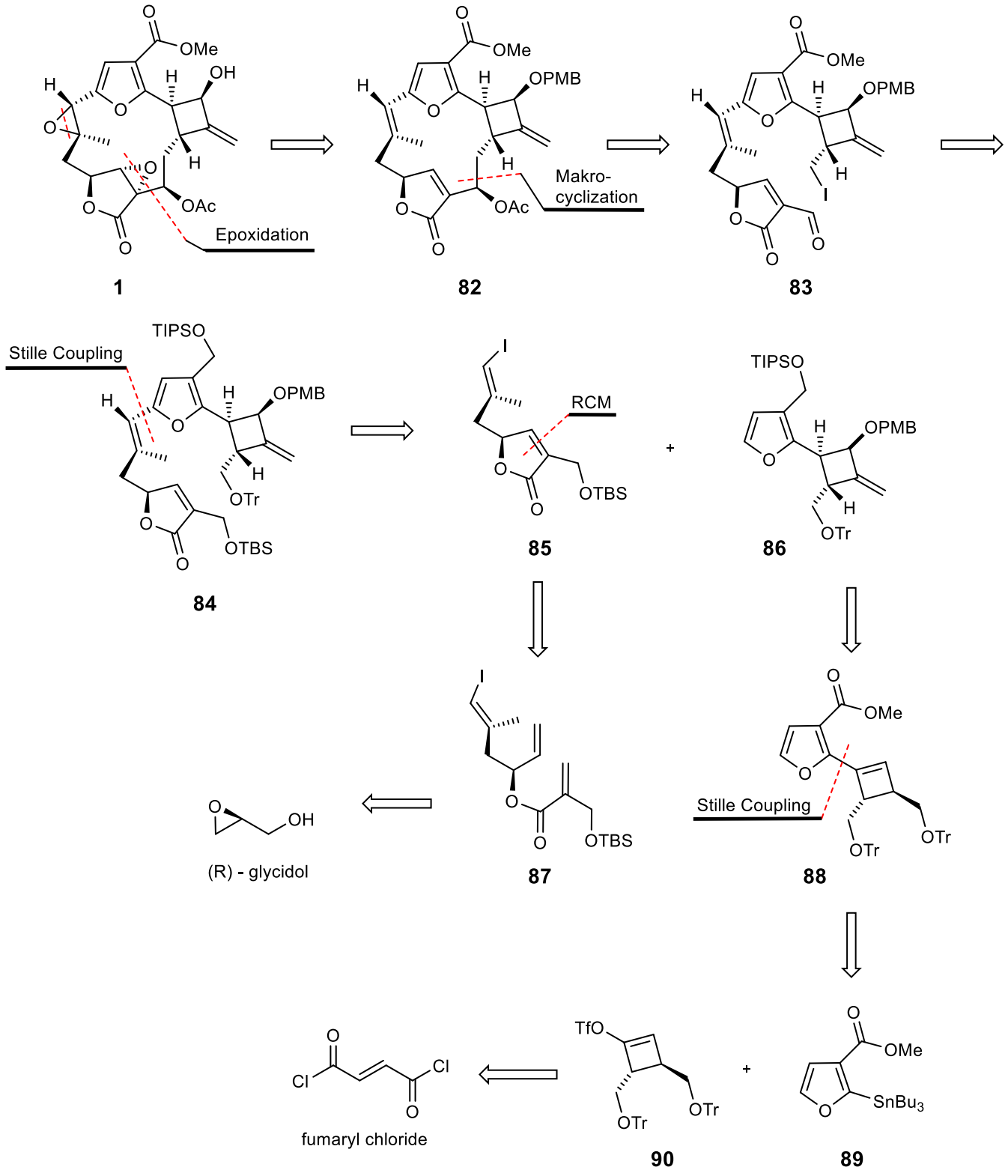


Scheme 22: Synthesis of Wood´s cyclobutanone

No further progress has been published since.

4 Synthetic Work

4.1 Retrosynthetic Analysis



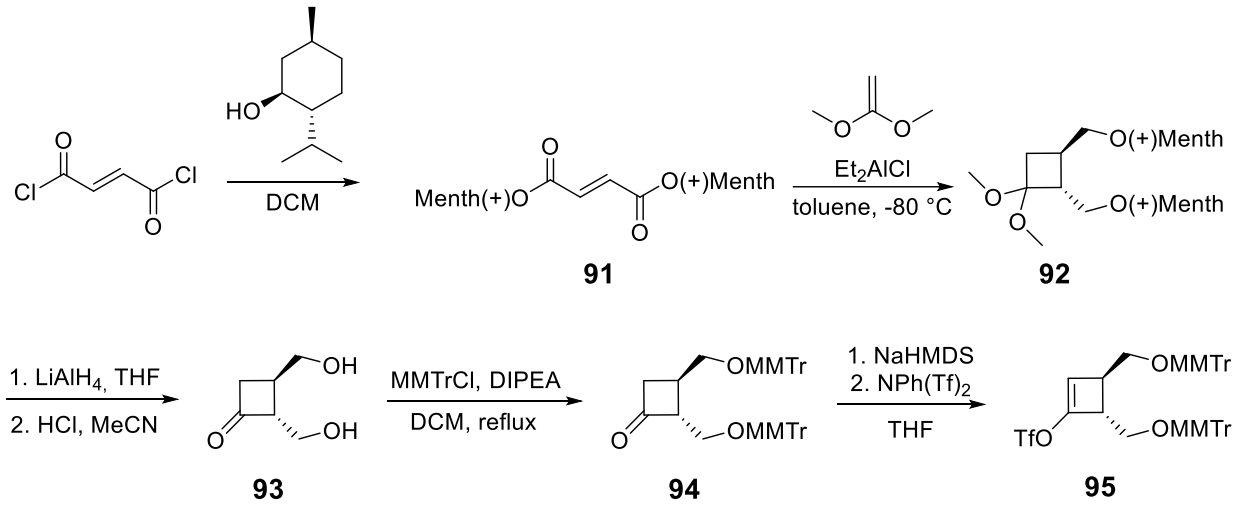
Scheme 23: Our Retrosynthetic Analysis – Construction of Providencin by Stille Reaction and Takai - Utimoto Macrocyclization

We propose (Scheme 22) the construction of providencin (**1**) from **82** by using the epoxidation procedures developed by Mulzer *et al.* for their synthesis of deoxyprovidencin (see chapter 3.1). Intermediate **82** could be obtained from **83** by Takai – Utimoto macrocyclization[13] and acetylation. Iodide **83** is the product of several functional group manipulations starting from compound **84**. Stille reaction could be employed to give **84**, leading to iodide **85** and stannane **86** as synthetic building blocks.

Iodide **85** can be obtained by ring closing metathesis from **87**, which can be prepared from commercial (*R*) - glycidol in a short synthetic sequence.

Building block **86** can be obtained from **88** by a sequence of eight reaction steps, followed by stannylation. Disconnection of **88** by another Stille reaction leads to simple stannane **89** and triflate **90**, which can be elaborated from fumaryl chloride in six steps.

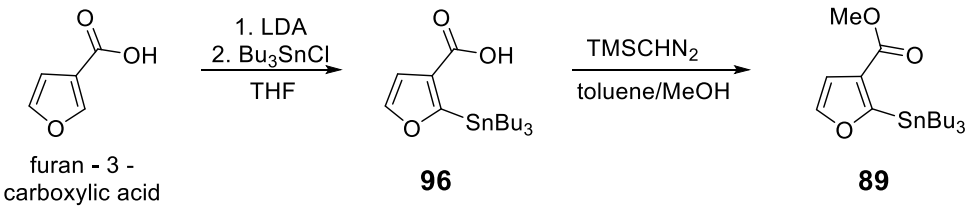
4.2 Monomethoxy Trityl - Approach



*Scheme 24: Synthesis of building block **95***

The synthesis started from fumaryl dichloride. The diester **91** of fumaric acid with unnatural (+)-menthol was obtained by stirring fumaryl chloride with (+) – menthol overnight. Menthol was employed as a chiral auxiliary for the next reaction, enantioselective cycloaddition of dimethyl ketene acetal catalyzed by diethyl aluminium chloride[16]. This reaction gave ketal **92** in 80 % yield.

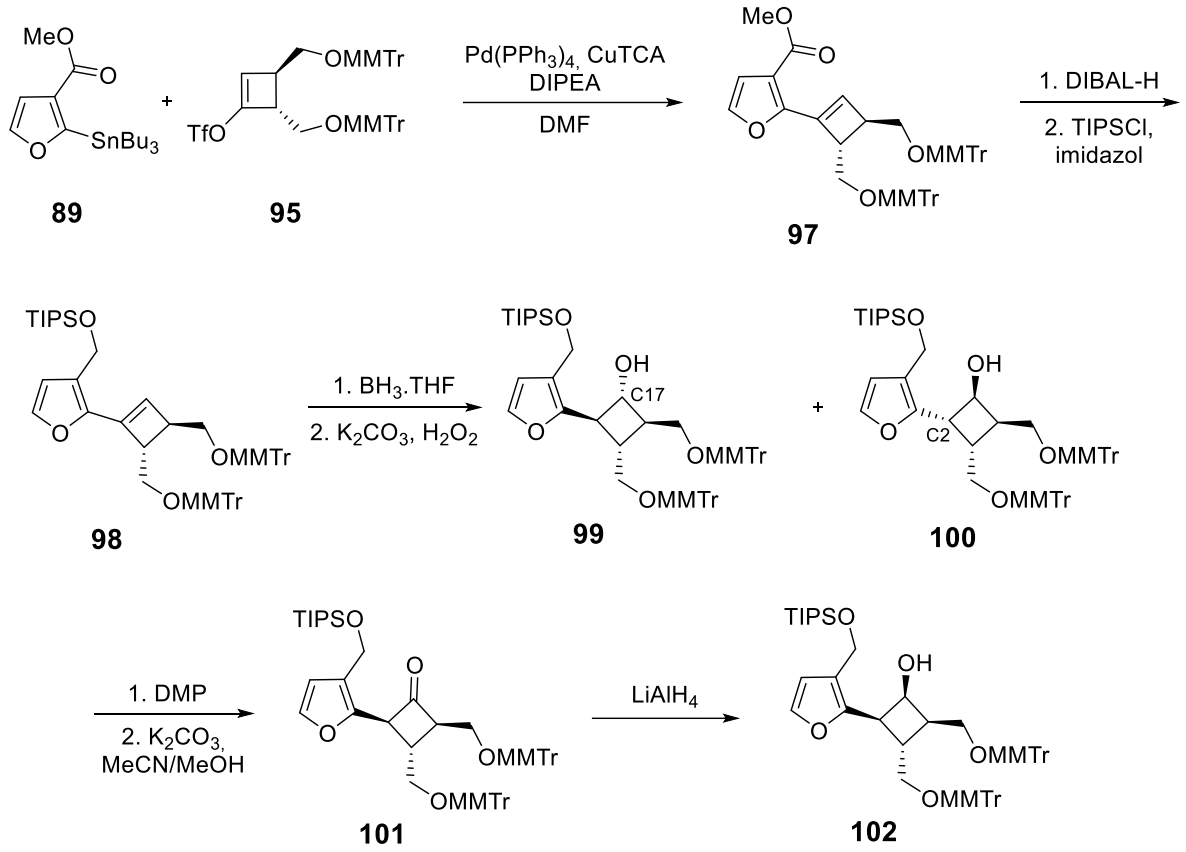
Menthol was cleaved by reduction with lithium aluminium hydride and could be separated by partitioning the crude product between hexane and water and reused after purification by sublimation. The ketal was hydrolyzed with hydrochloric acid in acetonitrile and the product **93** was protected with monomethoxy trityl chloride to give ketone **94**. Triflate **95** was formed with NaHMDS and $NPhTf_2$.



*Scheme 25: Synthesis of Stannane **89***

For the first Stille coupling, stannane **89** was needed (Scheme 24). Furan-3-carboxylic acid was regioselectively lithiated[6] and then converted to the tributylsstannyl derivate **96** by addition of $SnBu_3Cl$. This reaction was low-yielding initially, but results were improved by keeping reagents in exact stoichiometric ratios and improving the procedure for large-scale preparation of LDA. Acid **96** was methylated by TMS-Diazomethane, giving stannane **89** in an optimized yield of 75 % over two steps after chromatography.

Copper-mediated Stille coupling of **89** with **95** proceeded rapidly even at room temperature (Scheme 25). Methyl ester **97** was reduced by DIBAL-H and the resulting primary alcohol protected with TIPSCl to give **98** in 50 % yield over three steps. Both of these reactions did not proceed to completion in the first attempt. It was found that residual **89** (1.5 equivalents had been used) from the coupling reaction was responsible for the higher than expected use of reagents. The problem was solved adding a surplus of reagents based on the amount of **89** used in the Stille coupling.

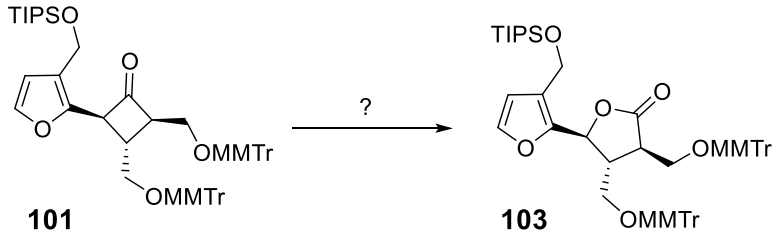


*Scheme 26: Synthesis of Cyclobutanol **102***

The next step was hydroboration - oxidation. This reaction was initially very low yielding. Every aspect of the reaction was optimized and it was found that the yield peaks at a certain reaction time and declines significantly thereafter. The initial method of performing the reaction overnight was partly responsible for the low yields and the time for quenching the reaction was found to be 6 h of reaction time. Optimized yields still never surpassed 55 %, giving an inseparable mixture of diastereomers **99** and **100** in a diastereomeric ratio of 3:1.

To arrive at correct stereochemistry, **100** had to be epimerized at C2 and **99** had to be inverted at C17 (providencin nomenclature). This was achieved by DMP oxidation[14] and subsequent reversible deprotonation with K_2CO_3 in MeOH/THF to give cyclobutanone **101**. Complete equilibration was observed after 30 min but formation of a Bayer-Villiger-like sideproduct (**103**) was observed (Scheme 26). An earlier experiment in $^{18}O_2$-saturated THF/MeOH had shown no incorporation of ^{18}O into the molecule, so air was ruled out as the source of oxidant. The next idea for the oxygen source was

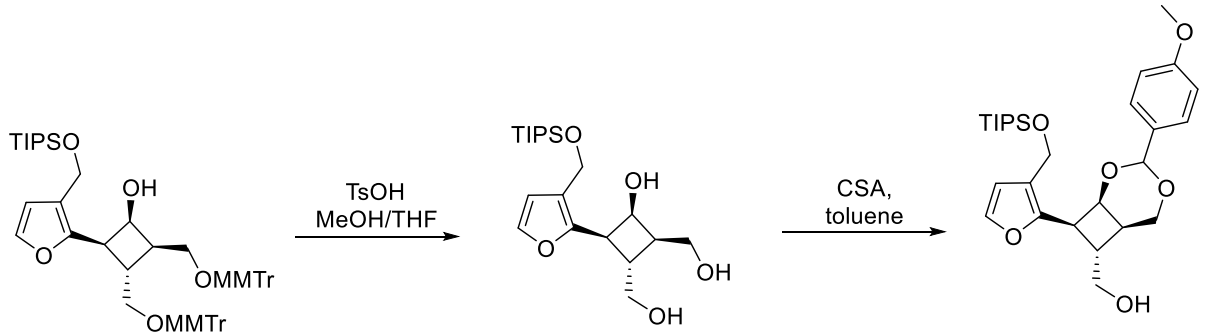
the presence of peroxides in THF and an alternative solvent system was devised for the reaction. In MeCN/MeOH (**101** is insoluble in pure methanol), side-product formation was significantly diminished to 14 % and overall recovery of organic material was increased from 60 to 95 %.



101 **103**

Scheme 27: Side-Product Formation during Equilibration

Screening of several reducing agents revealed lithium aluminium hydride as the most useful, giving cyclobutanol **102** in 80 % yield and 4:1 diastereomeric ratio in favour of the desired diastereomer.



102 **104** **105**

*Scheme 28: Route to PMB-Acetal **105***

The next step was MMTr deprotection. After unsuccessful attempts with TsOH in MeCN (cleavage of TIPS) and boronic acid in THF/H_2O (no reaction), TsOH in MeOH/THF led to successful isolation of triol **104**.

In order to assess the stereochemistry of the cyclobutane unit, PMB acetal **105** was generated from **104**. Dry zinc chloride in THF with anisaldehyde dimethyl acetal furnished a single product but with just 50 % conversion of starting material. An attempt to provide **105** with catalytic CSA in toluene gave full conversion of starting material but a mixture of different products. It was possible to separate **105** from this mixture by chromatography.

4.3 Trityl – Approach

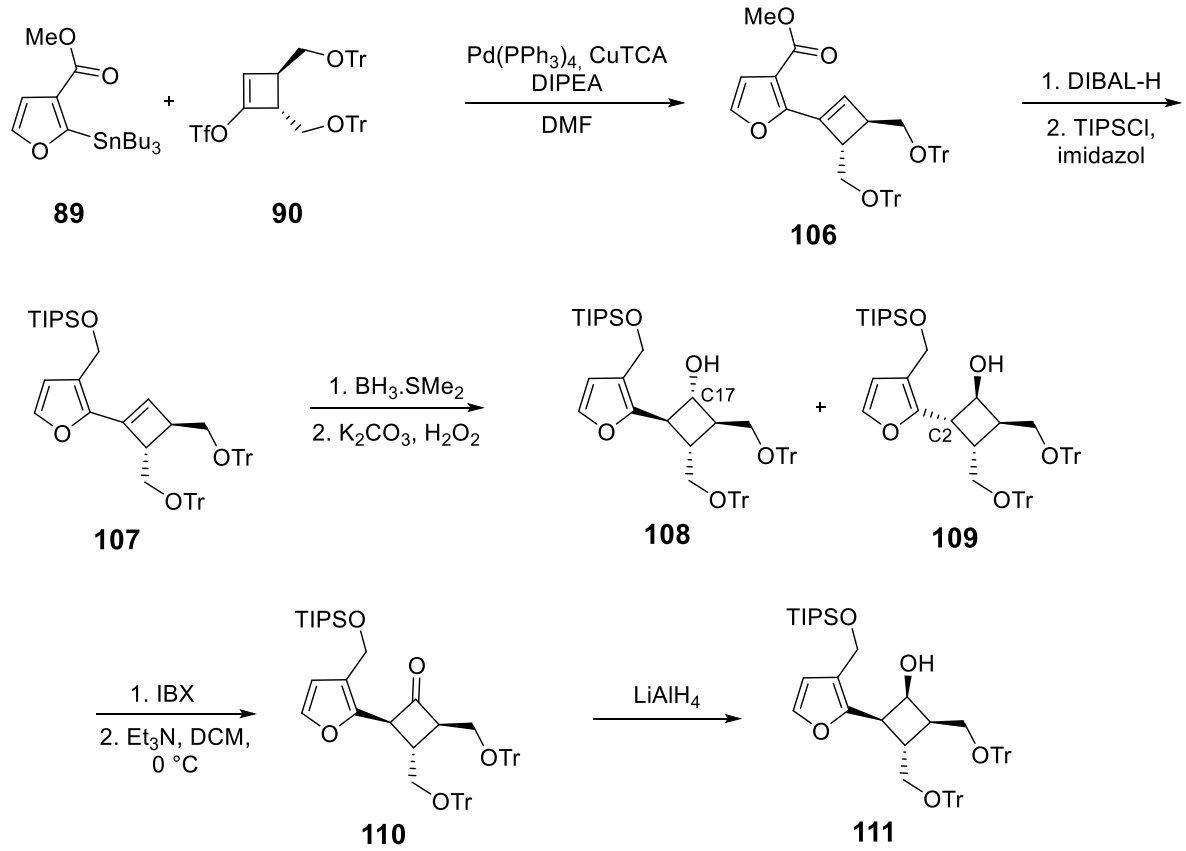
After all the material from the MMTr campaign had been used, the protecting group was switched to more stable trityl protecting group in the hope of increasing overall yield.

Triflate **90** was made by the same synthetic route as **95** before, the only difference being exchange of TrCl for MMTrCl in the protection step. The change of protecting group did not greatly affect yields until **107**.

Hydroboration proved to be tedious again. The optimized reaction conditions for the hydroboration of MMTr-protected substrate **98** did not lead to good results for **107** and renewed optimization was necessary. Ten hours of reaction time with 2.5 equivalents of borane – dimethyl sulfide complex were found to be appropriate and gave **108** and **109** as a 1:1 mixture.

Oxidation with IBX was found to give slightly better yields than DMP oxidation and provided easier scale-up.

Equilibration was harder compared to the MMTr-approach because the higher share of material with incorrect configuration at C2 necessitated an increase of reaction time from 30 min to 2 h. This led to significant decomposition of unstable ketone **110**. After some experimentation, equilibration in triethylamine/DCM at 0 °C afforded good yields and led to further suppression of the Bayer-Villiger side-product to 4 %.

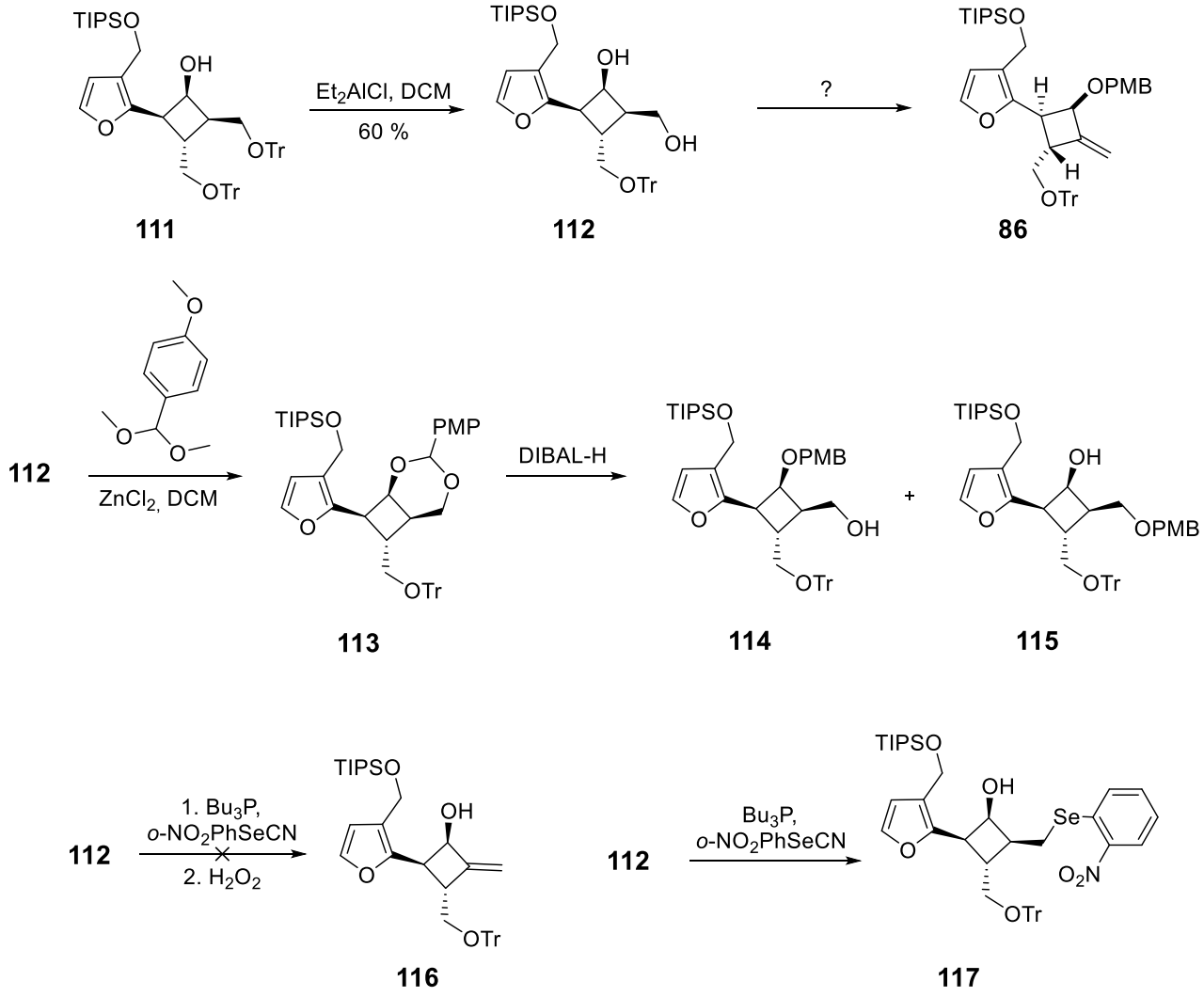


*Scheme 29: Synthesis of Tritylated Cyclobutanol **111***

Reduction of **110** with lithium aluminium hydride was uneventful and yielded **111**. Treatment of **111** with diethyl aluminium chloride regioselectively cleaved the trityl group nearest to the free hydroxy group and gave diol **112** in 60 % yield.

Starting from **112**, different ways towards fragment **86** were investigated. PMB-Acetal **113** was formed by the zinc chloride -based procedure already employed in the synthesis of **105.** The reaction proceeded to completion this time, as fresh reagents were used. Regioselective reduction with DIBAL-H proved to be problematic. Even after addition of six equivalents of DIBAL-H at room temperature, conversion of starting material stopped at 40 %. The product was a 3:2 mixture of wanted regioisomer **114** with unwanted **115.**

Another approach was the chemoselective Grieco-elimination[17] of the primary alcohol in **112** in the presence of the free secondary alcohol to give **116**. Following the Grieco – protocol resulted in decomposition in the oxidation step. When no oxidant was added, selenide **117** could be isolated from the reaction mixture and purified by chromatography.



*Scheme 30: Towards Fragment **86***

5 Conclusion and Outlook

In the course of this work, we were able to synthesize an advanced building block applicable for the total synthesis of providencin. Beginning from fumaryl dichloride, diol **112** was synthesized in a sequence of 14 steps in 4 % overall yield.

The key synthetic transformations are an enantioselective Lewis acid-catalyzed cycloaddition reaction to form the cyclobutane ring, a copper-assisted Stille-coupling under very mild conditions and the regioselective deprotection of just one of two trityl protecting groups.

Further progress included the regioselective functionalization of **112** to give monoprotected **114** and **115** and primary selenide **117.**

A suitable oxidizing agent must be found to effect elimination in selenide **117** in order to prepare building block **86** as substrate for the second Stille reaction. After successful coupling, conditions for the macrocyclization will have to be developed and providencin could then be achieved in a small number of further steps.

6 Experimental Section

6.1 General Procedures

Most of the reagents and solvents were purchased from Merck & Co., TCI or ACROS Organics and were used without further purification unless otherwise noted. All air- and moisture-sensitive reactions were carried out in flame-dried, argon-flushed Schlenk flasks sealed with rubber septa, and dry solvents and reagents were introduced using disposable PP syringes and hypodermic needles. Dry DCM, Et_2O, MeOH, toluene and THF were provided by a PURESOLV® facility. Solvents were deoxygenated using four pump – freeze - thaw cycles. Flash column chromatography and DCVC were performed using silica gel 60 (Merck, 40-63 µm). Thin-layer chromatography was performed on Merck aluminium sheets precoated with silica gel (TLC Silica gel 60 F_{254}) and visualization was done by staining in either ceric ammonium molybdate in EtOH / H_2SO_4 or anisaldehyde in EtOH / H_2SO_4.

Mass spectra were obtained on a Thermo Vanquish Q Exactive Hybrid Quadrupole-Orbitrap. IR spectra were recorded on a Perkin Elmer Spectrum 65 FT IR spectrometer equipped with a specac MK II Golden Gate Single Reflection ATR unit.

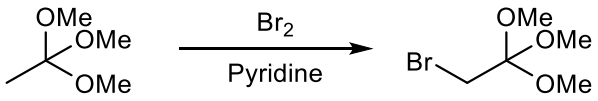
Specific Rotations were measured on an Antor Paar MCP 500 polarimeter at 20 °C and 589 nm.

^{1}H and ^{13}C NMR spectra were recorded on either Bruker Avance 400 (400 and 100 MHz) or Bruker Avance III 600 (600 and 150 MHz) instruments. Chemical shifts were reported in parts per million (ppm, δ) relative to Me_4Si (0 ppm) as the internal reference. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and b = broad), coupling constant in Hz, integration.

For substances known to literature, spectral data can be found in the respective original papers.

6.2 Initial Reactions

6.2.1 2-Bromo-1,1,1-trimethoxyethane



Procedure according to [5]

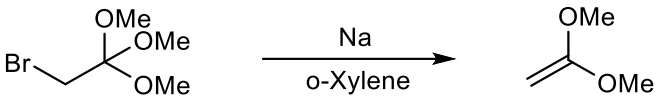
A vigorously stirred solution of trimethyl orthoacetate (68 mL, 532 mmol, 1 eq) in dry pyridine (43 mL, 532 mmol, 1 eq) was cooled to -5 °C and bromine (85 g, 532 mmol, 1 eq) was added dropwise over 4 h, keeping the temperature below 0 °C. The orange suspension was then stirred overnight.

For workup, the reaction mixture was extracted with 4 x 100mL PE/EE 2:1 and the combined organic phases washed with sat. aq. $NaHCO_3$, $Na_2S_2O_3$, water and brine. The mixture was dried over Na_2SO_4 and then concentrated under reduced pressure.

The crude product was purified with distillation at 8 mbar (b.p. 55 – 60 °C) giving 49.7 g of a colorless liquid (47%).

Spectroscopical data identical as reported in literature.

6.2.2 1,1-Dimethoxyethene

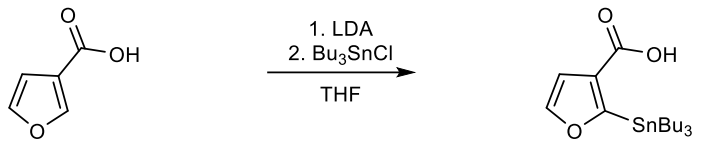


Procedure according to [5]

In a three necked flask, sodium (9.9 g, 400 mmol, 2 eq) in o-xylene (130 mL) was heated to reflux. The Substrate (35 g, 200 mmol, 1 eq) was added dropwise over 1 h and the solution was stirred for another 30 min. The reflux condenser was exchanged for a Vigreux column (80 cm) and the product was separated per azeotropic distillation at 105°C and ambient pressure, yielding 11.1 g of 70 vol. % solution of product in o-xylene (50 % yield).

Spectroscopical data identical as reported in literature.

6.2.3 2-(Tributylstannyl)furan-3-carboxylic acid (**96**)



Molecular Weight: 112,08 Molecular Weight: 401,13

Procedure according to [6].

In a Schlenk flask, dry diisopropylamine (7.5 mL, 53.5 mmol, 2.0 eq) was cooled to -10 °C and *n*-BuLi (2.5 N in hexane, 21.5 mL, 2.0 eq) was added dropwise. The resulting milky slurry was warmed up to room temperature and after 10 min formed a transparent gel, which was dissolved in THF (20 mL) and cooled to -80 °C. A solution of furan-3-carboxylic acid in THF (3.0 g, 26.8 mmol, 1 eq, 40 mL THF) was added dropwise over 15 min and stirring was continued for 1 h. A small sample was quenched with 10 x the amount of D_2O and brought to pH 2 with 0.1 N HCl. The mixture was diluted with DCM, the organic phase was freed of solvent *in vacuo* and ^{1}H-NMR was recorded. When NMR showed complete (> 85 %) deuteration of C2, Bu_3SnCl (7.5 mL, 28.1 mmol, 1.05 eq) was added dropwise to the reaction mixture and stirring was continued for 30 min.

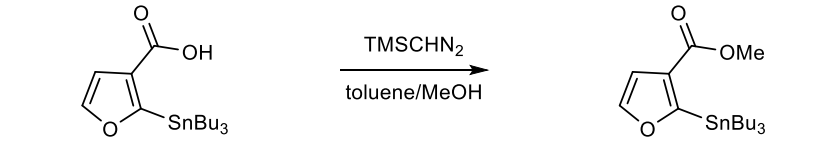
When TLC showed complete conversion, the reaction was warmed up to ambient temperature, H_2O (20 mL) was added and the mixture was acidified with 2 N HCl until pH 5. The phases were separated and the aqueous phase extracted with diethyl ether (3 x 150 mL). The combined organic phases were reduced *in vacuo* to yield 12 g of crude **96** which was used for the next step without further purification.

Rf: 0.50 (hexanes/ethyl acetate: 20/1)

HRMS for $C_{17}H_{30}O_3Sn$: $[M+Na]^+$ calcd. 425.1115, found: 425.1102

Spectroscopical data identical as reported in literature.

6.2.4 Methyl 2-(tributylstannyl)furan-3-carboxylate (**89**)



Molecular Weight: 401,13 Molecular Weight: 415,16

In a round bottom flask, crude stannane **96** (12 g, 30 mmol, 1 eq) was dissolved in toluene (190 mL) / MeOH (60 mL). $TMSCHN_2$ (2N in diethyl ether, 17 mL, 1.15 eq) was added dropwise and the solution was stirred for 1 h. When TLC indicated complete conversion, the solvents were evaporated *in vacuo*, giving 12 g of crude brown liquid.

Purification was performed by DCVC (12 x silica, 100 % hexanes), giving 8.5 g of colorless liquid (75 % over two steps).

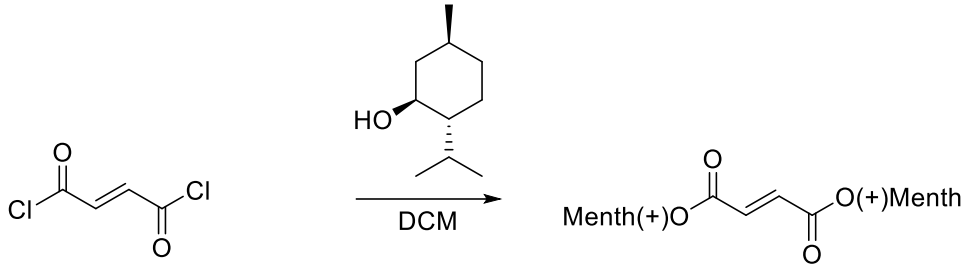
Rf: 0.81 (toluene/diethyl ether: 20/1)

HRMS for $C_{17}H_{30}O_3Sn$: $[M+Na]^+$ calcd. 425.1115, found: 425.1102

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.58 (s, 1H), 6.66 (s, 1H), 3.75 (s, 3H) 1.47 (m, 6H), 1.24 (m, 6H), 1.08 (t, J = 8.8 Hz, 6H), 0.81 (t, J = 7.2 Hz, 9H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8, 165.1, 147.9, 129.1, 109.6, 51.2, 28.9, 27.2, 13.7, 10.6

6.2.5 Dimenthyl Fumarate (**91**)



To a solution of (+) - menthol (30 g, 3 eq) in dry DCM (80 mL) was added fumaryl chloride (7 mL, 10 g, 1 eq) in one batch. The solution was stirred for 20h (HCl formation!), until TLC indicated completeness and no further gas formation was observed.

The mixture was diluted with 500 mL Et_2O and washed with aq. HCl (5 %, 3 x 150 mL), sat. aq. Na_2CO_3 (2 x 150 mL), sat. aq. $NaHCO_3$ (2 x 150 mL) and brine (3 x 150 mL). The solvents were removed at 200 mbar to give 36 g of a crude colorless crystalline material.

Purification was performed by DCVC (800 g Silica, PE/DCM) with a gradient according to Table 1, giving 22.5 g of colorless crystalline material (95 %).

Table 1

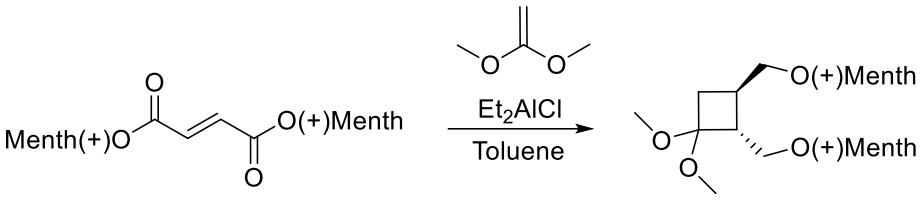
V (mL)	500	500	500	500	3000	1000	500	500
% DCM	10	12	16	20	25	33	50	100 % EE

Rf: 0.48 (hexanes/ethyl acetate: 5/1)

$[\alpha]^{20}_D$ = -100.0 (c = 1.0, CH_2Cl_2)

Spectroscopical data identical as reported in literature[15].

6.2.6 Cycloaddition (**92**)



In a 1 L Schlenk flask, dimenthyl fumarate (**91**) (23.3 g, 60 mmol, 1 eq) was dissolved in dry toluene (120 mL) and cooled to -90 °C. A solution of Et_2AlCl (1 N in heptane, 118.8 mL, 2.0 eq) was added dropwise over 1 h and the dark red solution was stirred for 15 min. Dimethyl keteneacetal (6.81 mL, 65 mmol, 1.1 eq) was added dropwise over 30 min (directly into solution to prevent freezing on vessel wall), the solution was warmed to -78 °C and stirred for 2 h.

After TLC showed complete consumption of starting material, MeOH (10 mL) was added and stirred for 30 min, the mixture was diluted with hexanes (300 mL) and aq. NaOH (20 %, 12 mL) was added and the mixture warmed to 5 °C. The aqueous phase was absorbed with $MgSO_4$ (20 g) and the remaining solution filtered over Celite©, rinsing with hexanes (700 mL). Solvents were removed *in vacuo* to give 31 g of crude yellow oil, which was used directly for the next step without further purification.

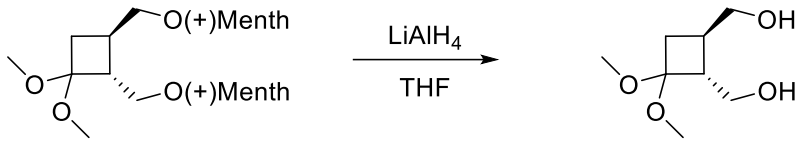
R_f: 0.47 (PE/EE: 4/1)

HRMS for $C_{28}H_{48}O_6$: $[M+Na]^+$ calcd. 503.3349, found: 503.3341

$[\alpha]^{20}_D$ = +28.7 (c = 1.0, CH_2Cl_2)

Spectroscopical data identical as reported in literature[15].

6.2.7 Menthol Ester Reduction



A solution of ester **92** (31 g, 60 mmol, 1 eq) in THF (70 mL) was added to a suspension of $LiAlH_4$ (3.4 g, 90 mmol) in anhydrous THF (90 mL). The mixture was heated to 55 °C for 1 h and cooled down to 5 °C when TLC indicated complete conversion. The reaction was quenched by adding H_2O (3.4 mL), 15 % aq. NaOH (3.4 mL) and again H_2O (10 mL). The mixture was stirred for 15 min, then 50 g of dry $MgSO_4$ were added and stirring was continued for 30 min.

The mixture was filtered over Celite© with EtOAc (1000 mL), giving a light-yellow solution that was reduced under 50 mbar of vacuum. The resulting oil was dissolved in hexanes (200 mL) and washed with water (4 x 100 mL). The combined aqueous phases were washed with hexanes (50 mL), saturated with $(NH_4)_2SO_4$ and extracted with EtOAc (12 x 250 mL) until no further product could be detected in the extracts by TLC. The combined EtOAc - extracts were evaporated at 50 mbar to yield a colorless oil (9.9 g, 86 %) which was used for the next step without further purification.

The combined hexane extracts were evaporated at 50 mbar to yield a white crystalline solid, which was purified by sublimation to yield pure (+) - menthol (18 g, 80% overall recovery).

R_f: 0.34 (100 % EtOAc)

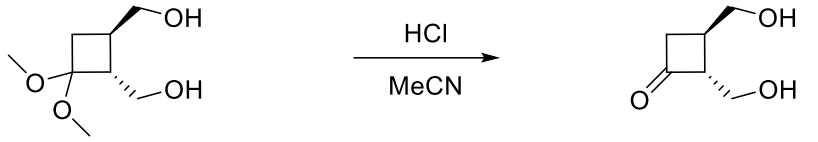
HRMS for $C_8H_{16}O_4$: $[M+Na]^+$ calcd. 199.0947, found: 199.0943

$[\alpha]^{20}_D$ = +10.4 (c = 1.0, CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.69 (m, 3H), 3.50 (t, J = 4.6 Hz, 1H), 3.12 (s, 6H), 2.34 – 2.21 (m, 2H), 2.02 (m, 1H), 1.68 (bs, 2H), 1.63 (dd, J1 = 12 Hz, J2 = 8 Hz, 1H),

^{13}C NMR (100 MHz, $CDCl_3$): δ = 101.8, 66.0, 61.9, 50.2, 48.8, 48.5, 31.7, 31.4

6.2.8 Ketal Hydrolysis (**93**)



Molecular Weight: 176,21 Molecular Weight: 130,14

Ketal (3.6 g, 20.4 mmol, 1 eq) was dissolved in MeCN (100 mL) and aq. HCl (0.2 N, 0.8 mL, 0.008 eq) was added, immediately turning the solution orange. After 2.5 h TLC indicated complete conversion and solid $NaHCO_3$ (60 mg, 70 mmol, 0.035 eq) was added.

The solution was filtrated and the solvent removed at 50 mbar, giving 2.7 g of crude mixture, which was used for the next step without further purification.

R_f: 0.20 (100 % EtOAc)

HRMS for $C_6H_{10}O_3$: $[M+Na]^+$ calcd. 153.0528, found: 153.0523

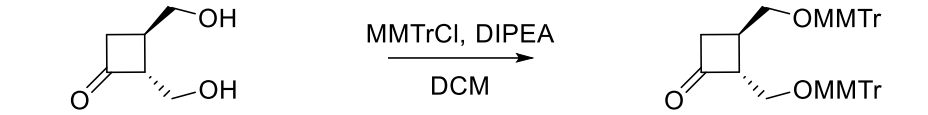
$[\alpha]^{20}_D$ = +10.6 (c = 1.0, CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.88 (q, J = 5 Hz, 1H), 3.78 – 3.68 (m, 2H), 3.67 – 3.58 (m, 1H), 3.25 (m, 1H), 3.13 (bs, 2H), 2.90 (qd, J1 = 5.8 Hz, J2 = 2.8 Hz, 1H), 2.76 (qd, J1 = 5.7 Hz. J2 = 2.8 Hz, 1H), 2.50 (m, 1H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.0, 66.1, 65.3, 59.5, 47.2, 30.9

6.3 Monomethoxytrityl Pathway

6.3.1 Monomethoxytrityl protection (**94**)



Molecular Weight: 130,14 Molecular Weight: 674,84

To a solution of crude diol **93** (1.4 g, 11 mmol, 1 eq) in dry DCM (10 mL) was added pyridine (20 mL), MMTrCl (7.1 g, 21 mmol, 1.9 eq) and imidazole (0.08 g, 1 mmol) and the mixture was stirred overnight. The reaction was quenched with sat. aq. NH_4Cl and diluted with toluene (150 mL). The organic phase was separated, washed with sat. aq. Na_2CO_3 and water, dried with $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (100 x silica, toluene/diethyl ether: 100/1) to give **3** (5.9 g, 77% over two steps) as a colorless oil.

R_f: 0.29 (hexanes/ethyl acetate: 15/1)

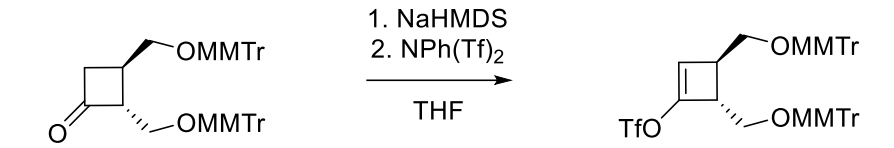
$[\alpha]^{20}_D$ = + 14.8 (c = 1.0, CH_2Cl_2)

HRMS for $C_{46}H_{42}O_5$: $[M+Na]^+$ calcd. 697.2930, found: 697.2921

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 – 7.29 (m, 8H), 7.24 – 7.10 (m, 16H), 6.76 – 6.70 (m, 4H), 3.69 (s, 3H), 3.68 (s, 3H), 3.37 (q, J = 4.7 Hz, 1H), 3.28 (q, J = 4.9 Hz, 1H), 3.20 – 3.11 (m, 3H), 3.01 (qd, J1 = 8.7 Hz, J2 = 2.4 Hz, 1H), 2.79 – 2.65 (m, 2H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.8, 158.5, 144.5, 144.4, 144.3, 130.4, 130.3, 128.4, 127.8, 126.9, 113.1, 86.3, 86.2, 65.8, 63.2, 60.7, 55.2, 48.1, 28.4

6.3.2 Triflate Formation (**95**)



Molecular Weight: 674,84

Molecular Weight: 806,89

In a Schlenk flask, 0.6 N solution of NaHMDS in toluene (21.2 mmol, 1.6 eq) was diluted with anhydrous THF (70 mL) and cooled to -90 °C. Starting material (8.5 g, 13.1 mmol, 1 eq) dissolved in dry THF (30 mL) was added dropwise over 10 min. After 2.5 h, a solution of $NPh(Tf)_2$ (8.0 g, 22.4 mmol, 1.7 eq) in THF (20 mL) was added fast and the reaction was warmed up to -78 °C. After TLC indicated complete conversion the reaction was warmed up to 0 °C, diluted with toluene (100 mL) and quenched with sat. aq. $NaHCO_3$.

After stirring for 30 min, the organic phase was separated, washed with 3 x sat. aq. $NaHCO_3$, water, and brine and dried with Na_2SO_4.The solvent was evaporated *in vacuo*, giving 11 g of a crude orange oil.

The product was purified by flash column chromatography (50 x silica, toluene/ethyl acetate: 70/1), giving 8.55 g of colorless oil (81 %).

R_f: 0.66 (hexanes/ethyl acetate: 15/1)

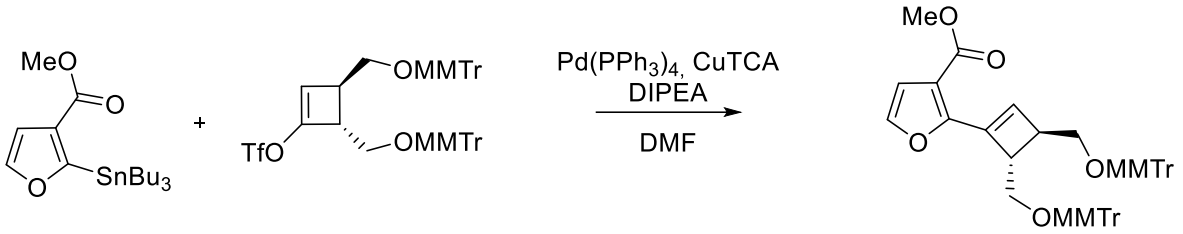
HRMS for $C_{47}H_{41}F_3O_7S$: $[M+Na]^+$ calcd. 829.2423, found: 829.2415

$[\alpha]^{20}_D$ = +24.5 (c = 1.0, CH_2Cl_2)

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.37 – 7.27 (m, 4H), 7.26 – 7.11 (m, 20H), 6.77 – 6.70 (m, 4H), 5.49 (s, 1H), 3.68 (d, J = 1.6 Hz), 3.26 – 3.00 (m, 4H), 2.96 (t, J = 5.2 Hz, 1H), 2.59 (t, J = 5.4 Hz, 1H)

^{13}C NMR (100 MHz, CD_2Cl_2): δ = 158.6, 144.4, 128.9, 128.1, 127.8, 119.1, 118.5, 86.6, 64.6, 40.9

6.3.3 Stille Reaction (**97**)



Molecular Weight: 806,89

Molecular Weight: 782,93

In a Schlenk flask, triflate **95** (3.0 g, 3.72 mmol, 1 eq) and stannane **89** (2.0 g, 4.82 mmol, 1.3 eq) were dissolved in degassed DMF (15 mL). Against a counterflow of argon, $Pd(PPh_3)_4$ (82 mg, 0.19 mmol, 0.05 eq), CuTCA (1.5 g, 7.44 mmol, 2 eq) and DIPEA (11.4 mL, 65 mmol, 17 eq) were added in one batch and the reaction was stirred vigorously for 1 h. When TLC indicated complete conversion of **1**, the reaction was quenched with a mix of sat. aq. Na_2CO_3 (20 mL) and TMEDA (20 mL) and stirred for 15 min.

The mixture was diluted with toluene (150 mL) and washed with sat. aq. NH_4Cl (6x 15 mL) until no significant discoloration was observed in the aqueous phase and then washed with sat aq. $NaHCO_3$ and brine. The combined aqueous phases were reextracted with toluene (2x 200 mL) and the resulting organic phases washed again with NH_4Cl, $NaHCO_3$ and brine. The combined organic phases were dried over Na_2SO_4 and the solvents removed in high vacuum, yielding 3 g of a brown oil which was used for the next step without further purification.

R_f: 0.50 (Tol/Et_2O : 20/1)

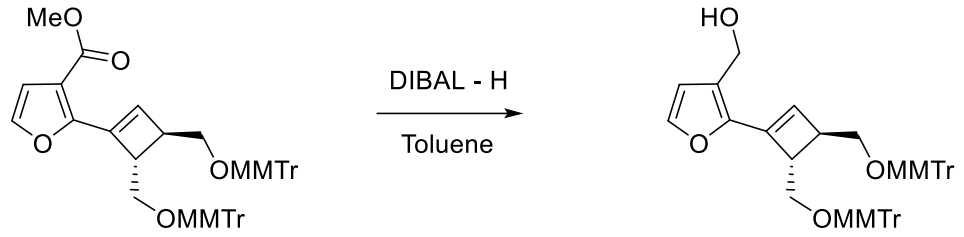
HRMS for $C_{52}H_{46}O_7$: $[M+Na]^+$ calcd. 805.3142, found: 805.3138

$[\alpha]^{20}_D$ = +27.2 (c = 1.0, CH_2Cl_2)

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.38 – 7.07 (m, 24H), 6.77 – 6.70 (m, 4H), 6.68 – 6.63 (m, 2H), 5.47 (s, 1H), 3.72 – 3.64 (m, 9H), 3.27 – 3.02 (m, 4H), 2.96 (t, J = 5 Hz, 1H), 2.69 – 2.58 (m, 1H)

^{13}C NMR (100 MHz, CD_2Cl_2): δ = 158.6, 144.4, 141.1, 136.0, 135.0, 133.5, 131.0, 130.3, 129.2, 128.3, 127.9, 127.3, 126.9, 117.3, 113.1, 86.3, 64.6, 61.7, 58.7, 55.2, 50.7, 38.8, 35.7

6.3.4 DIBAL-H Reduction (**98**)



Molecular Weight: 782,93 Molecular Weight: 754,92

In a Schlenk flask, ester **97** (2.2 g, 2.84 mmol, 1 eq) was dissolved in anhydrous toluene (50 mL) and cooled to -80 °C. DIBAL – H (1 N in hexanes, 8.5 mL, 8.5 mmol, 3 eq) was added dropwise to the dark red solution and stirring was continued for 2 h. After TLC showed complete consumption of the starting material, MeOH (2 mL) and sat. aq. NaK tartrate (10 mL) were added and the mixture was warmed to ambient temperature.

More toluene was added (50 mL), the phases were separated and the organic phase was washed with sat. aq. $NaHCO_3$, H_2O and brine. The aqueous phase was reextracted with toluene (2 x 50 mL), the combined organic phases were dried over Na_2SO_4 and the solvent was evaporated *in vacuo*, giving 2.4 g of a biphasic dark brown mixture.

The crude mixture was washed with n-Hexane (2x 30 mL) to remove residual furanyl stannane, yielding 1.9 g of a dark brown oil, which was used for the next step without further purification.

R_f: 0.53 (hexanes/ethyl acetate: 1/1)

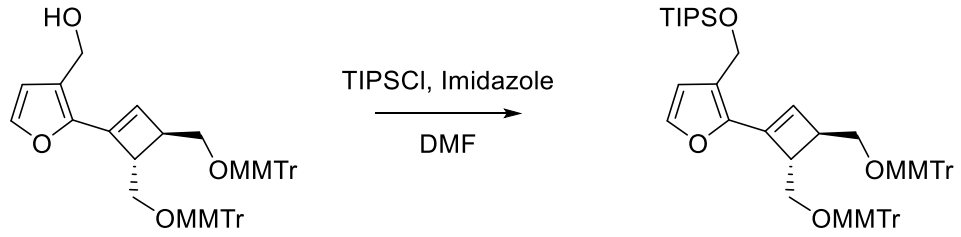
HRMS not found

$[\alpha]^{20}_D$ = +33.6 (c = 1.0, CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (d, J = 7.6 Hz, 4H), 7.31 (t, J = 6.6 Hz, 4H) 7.25 – 7.10 (m, 17H), 6.70 (dd, J1 = 12.8 Hz, J2 = 8.8 Hz, 4H), 6.35 (d, J = 1.6 Hz, 1H), 6.13 (s, 1H), 4.40 (q, J = 9.6 Hz, 2H), 3.69 (s, 3H), 3.68 (s, 3H), 3.37 (q, J = 4.4 Hz, 1H), 3.26 – 3.20 (m, 1H), 3.16 (d, J = 6.3 Hz, 1H), 3.03 – 2.94 (m, 2H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.5, 146.3, 144.8, 144.7, 136.8, 136.1, 130.4, 129.2, 138.5, 127.7, 126.8, 122.3, 113.0, 111.9, 86.0, 66.1, 63.9, 56.4, 55.2, 46.8, 45.6,

6.3.5 TIPS Protection (**99**)



Molecular Weight: 754,92 Molecular Weight: 911,27

In a Schlenk flask, alcohol **98** (2.5 g, 3.3 mmol, 1 eq) was dissolved in anhydrous DMF (6 mL). Imidazole (676 mg, 9.9 mmol, 3 eq) and TIPSCl (0.84 mL, 4.0 mmol, 1.2 eq) were added at once and the reaction mixture was stirred for 3 h. After TLC indicated complete conversion, the reaction was diluted with toluene (50 mL) and stirred with sat. aq. $NaHCO_3$ (10 mL) overnight.

The phases were separated and the organic phase was washed with H_2O (6x) and brine. The aqueous phase was reextracted with toluene and the reextracted organic phase washed with H_2O (3x) and brine. The combined organic phases were dried over Na_2SO_4 and the solvents were evaporated *in vacuo*, yielding 4.5 g of crude product.

The product was purified by DCVC (50 x silica, hexanes/ethyl acetate: 20/1), to give 1.7 g of a colorless oil (56 % over three steps).

R_f: 0.64 (hexanes/ethyl acetate: 3/1)

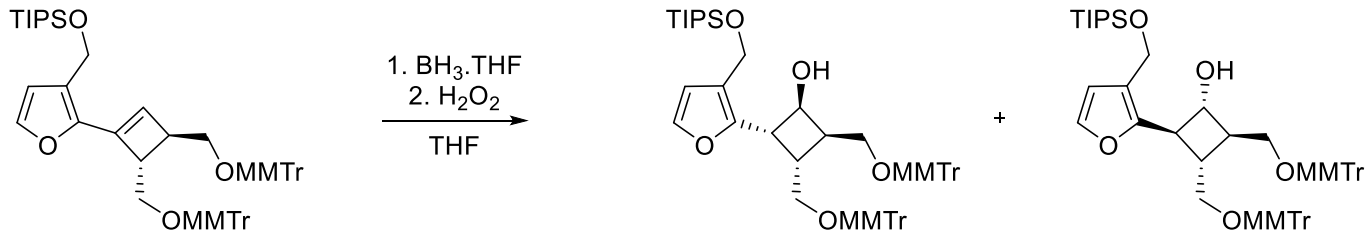
HRMS for $C_{60}H_{66}O_6Si$: $[M+Na]^+$ calcd. 933.4527, found: 933.4520

$[\alpha]^{20}_D$ = +31.3 (c = 1.0, CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 – 7.29 (m, 8H) 7.25 – 7.10 (m, 17H), 6.70 (dd, J1 = 12.8 Hz, J2 = 8.8 Hz, 4H), 6.40 (s, 1H), 5.98 (s, 1H), 4.56 (q, J = 13.2 Hz, 2H), 3.68 (s, 3H), 3.67 (s, 3H), 3.34 (q, J = 4.2 Hz, 1H), 3.21 (dd, J1 = 9.2 Hz, J2 = 6.4 Hz, 1H), 3.14 (d, J = 6.8 Hz, 2H), 3.02 – 2.94 (m, 2H), 0.98 – 0.93 (m, 21H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.4, 144.9, 140.1, 137.2, 136.1, 130.4, 128.5, 128.0, 127.7, 126.7, 126.6, 124.1, 113.0, 112.9, 111.7, 85.9, 85.7, 66.6, 66.3, 64.0, 57.5, 56.8, 55.2, 47.0, 45.4, 18.1, 17.9, 17.8, 12.0

6.3.6 Hydroboration - Oxidation (**99** / **100**)



Molecular Weight: 911,27

Molecular Weight: 929,28

In a Schlenk flask, cyclobutene **98** (1260 mg, 1.41 mmol, 1 eq) was dissolved in anhydrous THF (16 mL). Borane tetrahydrofuran complex (1 N in THF, 2 mL, 2 mmol, 1.4 eq) was added dropwise and the mixture stirred until TLC indicated 90 % consumption of the starting material (5.5 h).

The boranes were oxidized by adding sat. aq. K_2CO_3 (2 mL) and 35 % aq. H_2O_2 (2 mL) and stirring for 30 min. The mixture was quenched by cooling to 0° C, adding sat. aq. $Na_2S_2O_3$ (6 mL, exothermic!) and stirring for 15 min. Toluene (100 mL) and solid NaCl were added and the phases were separated. The organic phase was washed with sat. aq. $NaHCO_3$, H_2O and brine and dried over Na_2SO_4. Solvents were evaporated under reduced pressure to give 1.65 g of crude Product.

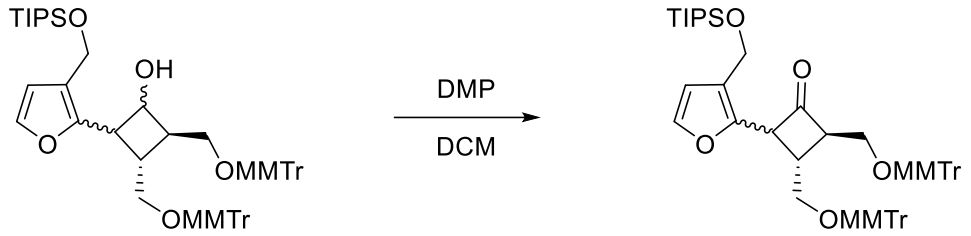
Purification was performed by flash chromatography over the 100-fold amount of silica and a gradient of hexanes/ethyl acetate (product at 20-30 % EE), to give 740 mg of a colorless oil (57 %, isomers not separated).

R_f: 0.54 (hexanes/ethyl acetate: 3/1)

HRMS for $C_{60}H_{68}O_7Si$: $[M+Na]^+$ calcd. 951.4632, found: 951.4627

Diastereomers not separated, for NMR see 6.3.9

6.3.7 Dess-Martin Oxidation



Molecular Weight: 929,28 Molecular Weight: 927,27

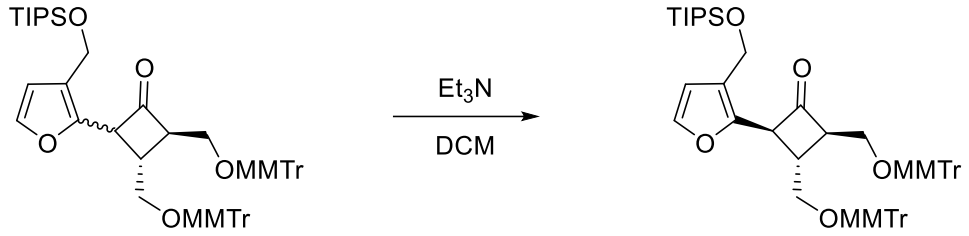
In a round bottom flask, DMP (285 mg, 6.7 mmol, 1.25 eq) and $NaHCO_3$ (550 mg) were suspended in DCM (10 mL) and a drop of water was added. After stirring vigorously for 15 min, a solution of cyclobutanol (500 mg, 5.4 mmol, 1 eq) in 5 mL of DCM was added. Stirring was continued until TLC indicated complete conversion (30 min) and the whole mixture was filtered over silica (7.5 g, 100 % DCM). After solvent evaporation, ketones were isolated as a colorless oil (450 mg, 90 %).

R_f: 0.60 (PE/EE : 3/1)

HRMS for $C_{60}H_{66}O_7Si$: $[M+Na]^+$ calcd. 949.4476, found: 949.4469

Isotopes not separated, NMR see 6.3.8

6.3.8 Equilibration (**101**)



Molecular Weight: 927,27 Molecular Weight: 927,27

In a round bottom flask, ketones (400 mg, 0.43 mmol, 1 eq) were dissolved in a degassed mixture of MeOH (20 mL) and MeCN (4 mL). To the slightly yellow solution, K_2CO_3 (50 mg) was added, immediately giving a strong yellow color. After 60 min, the reaction was quenched with sat. aq. NH_4Cl until a precipitate formed. The mixture was diluted with EtOAc (150 mL), washed with brine (2x) and dried over Na_2SO_4. After evaporation, 380 mg of a yellow resin were isolated, which was used for the next step without further purification.

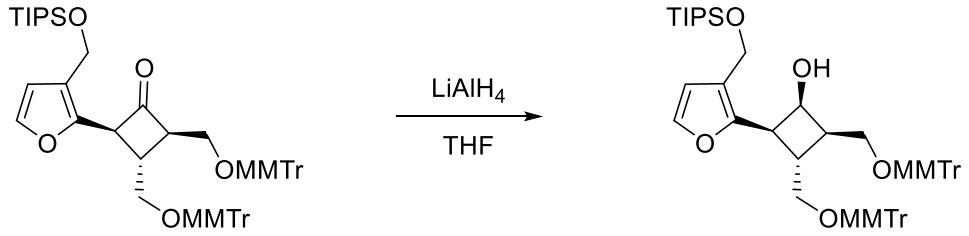
R_f: 0.60 (PE/EE : 3/1)

HRMS for $C_{60}H_{66}O_7Si$: $[M+Na]^+$ calcd. 949.4476, found: 949.4469

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.37 (d, J = 7.6 Hz, 4H), 7.29 – 7.08 (m, 21H), 6.70 (dd, J1 = 11.8 Hz, J2 = 8.8 Hz, 4H), 6.33 (d, J = 1.6 Hz, 1H), 4.49 (d, J = 2.8 Hz, 2H), 4.33 (d, J = 8.8 Hz, 1H) 3.68 (d, J = 2.8 Hz, 1H), 3.41 – 3.10 (m, 6H), 0.95 (s, 21H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.4, 158.5, 144.4, 144.0, 135.6, 135.5, 130.4, 130.2, 128.5, 128.3, 127.8, 126.9, 126.8, 122.3, 113.1, 110.9, 86.4, 86.3, 64.7, 60.3, 60.0, 57.4, 56.9, 34.7, 28.9, 27.2, 18.0, 12.0,

6.3.9 Stereoselective Reduction (**102**)



Molecular Weight: 927,27 Molecular Weight: 929,28

In a Schlenk flask, $LiAlH_4$ (12 mg, 0.32 mmol, 2 eq) was suspended in anhydrous THF (0.6 mL). The grey suspension was cooled to -80 °C and ketone **101** (150 mg, 0.16 mmol, 1eq) in THF (2 mL) was added dropwise. TLC showed complete conversion after 2 h and the reaction was quenched with MeOH (0.3 mL). Saturated aqueous solutions of NaK tartrate (1 mL) and $NaHCO_3$ (0.3 mL) were added, the mixture was diluted with toluene (10 mL), warmed to ambient temperature, and stirred overnight.

The phases were separated and the organic fraction washed with sat. aq. $NaHCO_3$ and brine. The volatiles were removed *in vacuo*, to give 140 mg of crude product.

Purification was performed by flash column chromatography (hexanes/ethyl acetate: 10 / 1) and yielded 112 mg (75 %) of a slightly yellow resin.

R_f: 0.54 (hexanes/ethyl acetate: 3/1)

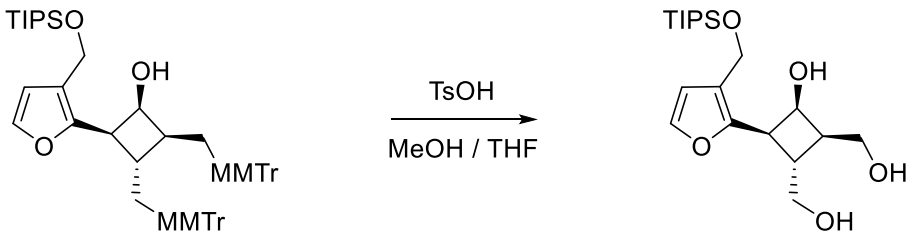
HRMS for $C_{60}H_{68}O_7Si$: $[M+Na]^+$ calcd. 951.4632, found: 951.4627

$[\alpha]^{20}_D$ = -8.1 (c = 1.0, CH_2Cl_2)

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.37 (d, J = 6.1 Hz, 4H), 7.30 – 7.05 (m, 21H), 6.69 (t, J = 8.6 Hz, 4H), 6.30, (s, 1H), 4.48 (s, 2H), 3.68 (s, 6H), 3.40 (m, 2H), 3.24 – 3.05 (m, 4H), 2.88 (d, J = 2 Hz, 1H), 2.49 (m, 1H), 0.97 (s, 21H)

^{13}C NMR (100 MHz, CD_2Cl_2): δ = 158.4, 149.2, 144.7, 141.3, 136.3, 130.3, 129.3, 128.5, 127.7, 127.2, 126.7, 113.2, 113.0, 111.4, 70.4, 65.5, 61.8, 57.3, 55.2, 41.3, 39.8, 39.3, 18.0, 12.0

6.3.10 MMTr Deprotection (**104**)



Molecular Weight: 897,28 Molecular Weight: 384,59

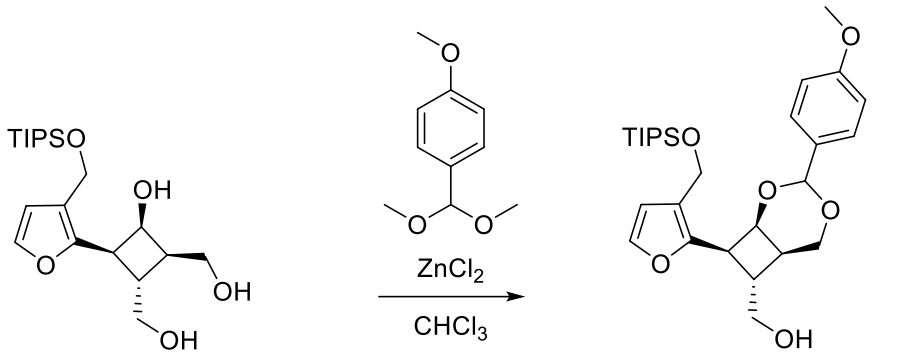
In a round bottom flask, alcohol **102** (50 mg, 0.054 mmol, 1eq) was suspended in MeOH (2 mL) and THF (30 drops) was added dropwise until a homogenous solution was achieved. Solid *para*-toluenesulfonic acid (1 mg) and a drop of water were added and the reaction was stirred for 20 min, quenched with $NaHCO_3$ and filtered over silica (chloroform/ethyl acetate/methanol: 47/47/6).

Rf: 0.30 (chloroform/ethyl acetate/methanol: 47/47/6)

HRMS for $C_{20}H_{36}O_5Si$: $[M+Na]^+$ calcd. 407.2230, found: 407.2222

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.04 (s, 1H), 6.24 (s, 1H), 4.40 (m, 2H), 3.84 (m, 2H), 3.68 (dd, J1 = 5.4 Hz, J2 = 4.1 Hz, 1H), 3.46 – 3.15 (m, 4H), 2.23 (m, 1H), 1.05 (s, 21H)

6.3.11 PMB Acetal (**105**)



Molecular Weight: 384,59 Molecular Weight: 502,72

In a Schlenk flask, triol **104** (5 mg, 0.013 mmol, 1 eq) was dissolved in dry chloroform (0.5 mL). Anisaldehyde dimethyl acetal (2 drops) and $ZnCl_2$ (0.5 N in dry THF, 40 µL, 1.5 eq) were added and the mixture was stirred for 1 h.

The reaction mixture was diluted with DCM (10 mL) and washed with sat. aq. $NaHCO_3$ and brine. The volatiles were removed under high vacuum, to give 3.4 mg of crude product.

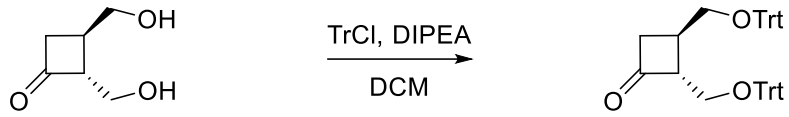
Rf: 0.74 (EE)

HRMS for $C_{28}H_{42}O_6Si$: $[M+Na]^+$ calcd. 525.2649, found: 525.2643

^{1}H NMR (400 MHz, C_6D_6): δ = 7.55 (d, J = 6.0 Hz, 2H), 7.14 (s, 1H) 6.80 (d, J = 6.0 Hz, 2H), 6.46 (s, 1H), 5.14 (s, 1H), 4.86 (d, J = 8.4 Hz, 1H), 4.69 (d, J = 8.5 Hz, 1H), 4.44 (t, J = 3.2 Hz, 1H), 3.80 (d, J = 8.1 Hz, 1H), 3.67 (sept, J = 3.2 Hz, 1H), 3.56 (dd, J1 = 8.4 Hz, J2 = 2.8 Hz), 3.47 (q, J = 3.5 Hz), 3.37 (t, J = 3.0 Hz, 1H), 3.26 (s, 3H), 1.11 ppm (s, 21H)

6.4 Trityl Pathway

6.4.1 Trityl Protection



Molecular Weight: 130,14 Molecular Weight: 614,79

In a Schlenk flask, diol **93** (2.7 g, 20.8 mmol, 1 eq) was dissolved in anhydrous DCM (100 mL). Trityl chloride (12.2 g, 43.6 mmol, 2.1 eq) and dry DIPEA (10.2 mL, 60 mmol, 3 eq) were added at once and the yellow mixture heated to reflux for 24 h.

After TLC indicated complete conversion, the reaction was cooled to ambient temperature and diluted with DCM (200 mL). The organic phase was washed with sat. aq. $NaHCO_3$, H_2O, and brine and the solvent was removed under reduced pressure, giving 15 g of a dark red oil.

The product was purified by MPLC (100x silica, Tol/MTBE: 50/1), giving 7.1 g of yellowish oil (56 % over two steps).

R_f: 0.76 (Tol/Et_2O: 20/1)

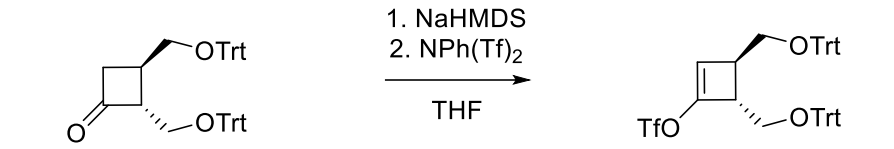
HRMS for $C_{44}H_{38}O_3$: $[M+Na]^+$ calcd. 637.2719, found: 637.2712

$[\alpha]^{20}_D$ = -16.9 (c = 1.0, CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 – 7.27 (m, 12H), 7.25 – 7.05 (m, 18H), 3.34 (q, J = 4.5 Hz, 1H), 3.28 (q, J = 4.6 Hz, 1H), 3.15 (m, 3H), 3.01 (m, 1 H), 2.80 – 2.66 (m, 2H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.7, 144.3, 144.0, 143.9, 129.1, 128.8, 127.9, 127.1, 125.3, 86.7, 86.5, 65.9, 63.2, 60.8, 48.1, 28.4,

6.4.2 Triflate Formation (**90**)



Molecular Weight: 614,79 Molecular Weight: 746,84

In a Schlenk flask, 0.6 N solution of NaHMDS in toluene (11.72 mmol, 1.5 eq) was diluted with anhydrous THF (40 mL) and cooled to -90 °C. Starting material (4.8 g, 7.81 mmol, 1 eq) dissolved in dry THF (30 mL) was added dropwise over 10 min. After 2.5 h, a small sample was quenched with D_2O and complete deprotonation was confirmed by NMR. A Solution of $NPH(Tf)_2$ (4330 mg, 12.11 mmol, 1.55 eq) in THF (20 mL) was added fast and the reaction was warmed up to -78 °C. After TLC indicated complete conversion

The phases were separated and the organic phase was washed with H_2O (6x) and brine. The aqueous phase was reextracted with toluene and the resulting organic phase washed with H_2O (3x) and brine. The combined organic phases were dried over Na_2SO_4 and the solvents were evaporated *in vacuo*, yielding 4.5 g of crude product.

The product was purified by DCVC (50x silica, hexanes/diethyl ether: 20/1), giving 2.4 g of colorless oil (52 % over three steps).

R_f: 0.75 (hexanes/ethyl acetate: 3/1)

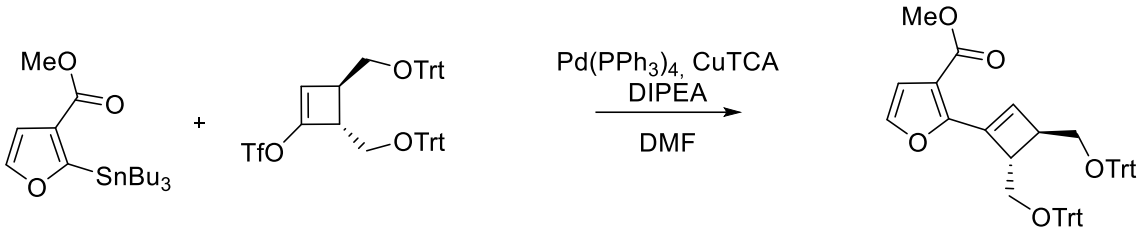
HRMS for $C_{45}H_{37}F_3O_5S$: $[M+Na]^+$ calcd. 769.2212, found: 769.2204

$[\alpha]^{20}_D$ = -27.6 (c = 1.0, CH_2Cl_2)

^{1}H NMR (400 MHz, C_6D_6): δ = 7.37 – 7.26 (m, 12H), 7.25 – 7.11 (m, 18H), 5.49 (s, 1H), 3.21 (m, 2H), 3.13 (m, 1H), 3.04 (m, 1H), 2.95 (t, J = 4.1 Hz, 1H), 2.60 (t, J = 4.2 Hz, 1H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.5, 141.1, 130.2, 128.2, 127.8, 126.9, 117.5, 113.0, 86.1, 64.6, 55.1, 50.6, 38.7

6.4.3 Stille Reaction (**106**)



Molecular Weight: 746,84

Molecular Weight: 722,88

In a Schlenk flask, triflate **90** (3.8 g, 5.1 mmol, 1 eq) and stannane **89** (3.1 g, 7.63 mmol, 1.5 eq) were dissolved in degassed DMF (20 mL). Against a counterflow of argon, $Pd(PPh_3)_4$ (110 mg, 0.25 mmol, 0.05 eq), CuTCA (1.94 g, 10 mmol, 2 eq) and DIPEA (4 mL, 23 mmol, 4.5 eq) were added in one batch and the reaction was stirred vigorously for 1 h. When TLC indicated complete conversion of **1**, the reaction was quenched with a mix of sat. aq. Na_2CO_3 (20 mL) and TMEDA (20 mL) and stirred for 15 min.

The mixture was diluted with toluene (150 mL) and washed with sat. aq. NH_4Cl (6x 15 mL) until no significant discoloration was observed in the aqueous phase and then washed with sat aq. $NaHCO_3$ and brine. The combined aqueous phases were reextracted with toluene (2x 200 mL) and the resulting organic phases washed again with NH_4Cl, $NaHCO_3$ and brine. The combined organic phases were dried over Na_2SO_4 and the solvents removed in high vacuum, to give 3 g of a brown oil which was used for the next step without further purification.

R_f: 0.50 (Tol/Et_2O: 20/1)

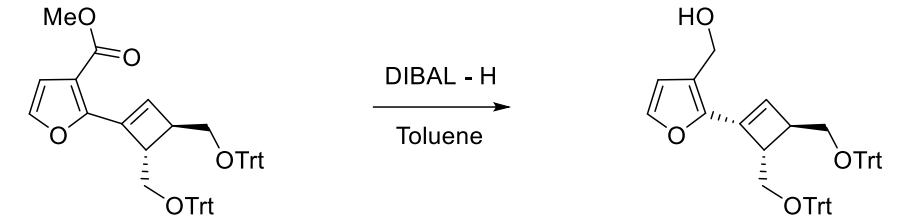
HRMS for $C_{50}H_{42}O_5$: $[M+Na]^+$ calcd. 745.2930, found: 745.2921

$[\alpha]^{20}_D$ = -29.2 (c = 1.0, CH_2Cl_2)

^{1}H NMR (400 MHz, C_6D_6): δ = 7.43 – 7.04 (m, 31H), 6.69 (s, 1H), 6.62 (s, 1H), 3.70 (s, 3H), 3.40 (bs, 1H), 3.24 (t, J = 8.4 Hz, 1H), 3.19 (d, J = 8 Hz, 2H), 3.07 (bs, 2H)

^{13}C NMR (100 MHz, C_6D_6): δ = 163.6, 153.1, 144.3, 140.9, 135.5, 128.8, 127.7, 126.8, 114.3, 112.0, 66.0, 63.6, 51.4, 47.0, 45.2

6.4.4 DIBAL-H Reduction



Molecular Weight: 722,88 Molecular Weight: 694,87

In a Schlenk flask, crude ester **106** (5 mmol, 1 eq) was dissolved in anhydrous toluene (50 mL) and cooled to -80 °C. DIBAL – H (1 N in hexane, 20 mL, 20 mmol, 4 eq) was added dropwise to the dark-red solution and stirring was continued for 2 h. After TLC showed complete consumption of starting material, MeOH (5 mL) and sat. aq. NaK tartrate (30 mL) were added and the mixture was warmed to ambient temperature.

More toluene was added (150 mL), the phases were separated and the organic phase was washed with sat. aq. $NaHCO_3$, H_2O and brine. The aqueous phase was reextracted with toluene (2x 150 mL), the combined organic phases were dried over Na_2SO_4 and the solvents were evaporated *in vacuo*, giving 4.5 g of a biphasic dark brown mixture.

The crude product was washed with n-Hexane (2x 50 mL) yielding 4 g of a dark brown oil, which was used for the next step without further purification.

R_f: 0.21 (hexanes/diethyl ether: 3/1)

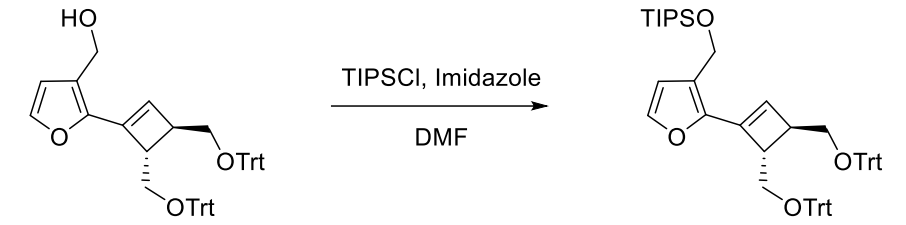
HRMS for $C_{49}H_{42}O_4$: $[M+Na]^+$ calcd. 717.2981, found: 717.2972

$[\alpha]^{20}_D$ = -35.0 (c = 1.0, CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (d, J = 7.6 Hz, 4H), 7.31 (t, J = 6.6 Hz, 4H) 7.25 – 7.10 (m, 17H), 6.70 (dd, J1 = 12.8 Hz, J2 = 8.8 Hz, 4H), 6.35 (d, J = 1.6 Hz, 1H), 6.13 (s, 1H), 4.40 (q, J = 9.6 Hz, 2H), 3.69 (s, 3H), 3.68 (s, 3H), 3.37 (q, J = 4.4 Hz, 1H), 3.26 – 3.20 (m, 1H), 3.16 (d, J = 6.3 Hz, 1H), 3.03 – 2.94 (m, 2H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.5, 146.3, 144.8, 144.7, 136.8, 136.1, 130.4, 129.2, 138.5, 127.7, 126.8, 122.3, 113.0, 111.9, 86.0, 66.1, 63.9, 56.4, 55.2, 46.8, 45.6,

6.4.5 TIPS Protection (**107**)



Molecular Weight: 694,87 Molecular Weight: 851,22

In a Schlenk flask, crude alcohol (5.0 mmol, 1 eq) was dissolved in anhydrous DMF (20 mL). Imidazole (1020 mg, 15 mmol, 3 eq) and TIPSCl (1.28 mL, 6 mmol, 1.2 eq) were added at once and the reaction mixture was stirred for 3 h. After TLC indicated complete conversion, the reaction was diluted with toluene and stirred with sat. aq. $NaHCO_3$ (20 mL) overnight.

The phases were separated and the organic phase was washed with H_2O (6x) and brine. The aqueous phase was reextracted with toluene and the resulting organic phase washed with H_2O (3x) and brine. The combined organic phases were dried over Na_2SO_4 and the solvents were evaporated *in vacuo*, yielding 4.5 g of crude product.

The product was purified by DCVC (50x silica, hexanes/diethyl ether: 20/1), giving 2.4 g of a colorless oil (52 % over three steps).

R_f: 0.75 (hexanes/ethyl acetate: 3/1)

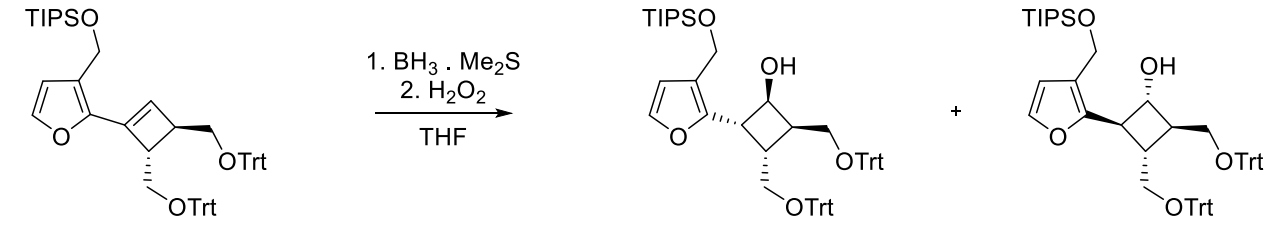
HRMS for $C_{58}H_{62}O_4Si$: $[M+Na]^+$ calcd. 873.4315, found: 873.4309

$[\alpha]^{20}_D$ = - 41.0 (c = 1.0, CH_2Cl_2)

^{1}H NMR (400 MHz, C_6D_6): δ = 7.40 – 7.25 (m, 12H), 7.25 – 7.05 (m, 18H), 6.42 (s, 1H), 6.00 (s, 1H), 4.55 (q, J = 13.1 Hz, 2H), 3.33 (m, 1H), 3.23 – 3.09 (m, 4H), 2.96 (m, 1H), 0.96 (s, 21H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.8, 144.4, 141.0, 137.1, 128.7, 128.6, 127.9, 127.6, 126.8, 124.1, 111.7, 86.2, 86.0, 66.3, 64.0, 57.5, 46.9, 45.3, 18.0, 12.0

6.4.6 Hydroboration – Oxidation (**108** + **109**)



Molecular Weight: 851,22

107

Molecular Weight: 869,23

108 **109**

In a round bottom flask, **107** (2.4 g, 3 mmol, 1 eq) was dissolved in anhydrous THF (60 mL). Borane dimethyl sulfide complex (2N in THF, 3.3 mL, 6.6 mmol, 2.2 eq) was added dropwise and the mixture stirred until TLC indicated 90 % consumption of the starting material (9 h).

The boranes were oxidized by adding sat. aq. K_2CO_3 and 35 % aq. H_2O_2 (12 mL) and stirring for 30 min. The mixture was quenched by cooling to 0° C, adding sat. aq. $Na_2S_2O_3$ (50 mL, exothermic!) and stirring for 15 min. Toluene (300 mL) and solid NaCl were added and the phases were separated. The organic phase was washed with sat. aq. $NaHCO_3$, H_2O and brine and dried over Na_2SO_4. Solvents were evaporated under reduced pressure to give 2.6 g of crude product.

Purification was performed by flash chromatography over the 100-fold amount of silica and a gradient of hexanes/diethyl ether (product at 20-30 % Et_2O), giving 1.2 g of a colorless oil (49 %).

Minor Isomer (**108**)

R_f: 0.67 (toluene/diethyl ether: 20/1)

$[\alpha]^{20}_D$ = -5.7 (c = 1.0, CH_2Cl_2)

^{1}H NMR (400 MHz, C_6D_6): δ = 7.50 – 7.31 (m, 6H), 7.31 – 7.05 (m, 24H), 7.03 (s, 1H), 6.23 (s, 1H), 4.57 (q, J = 6.8 Hz, 1H), 4.44 (s, 2H), 3.53 (t, J = 7.6 Hz, 1H), 3.38 (m, 2H), 3.03 (t, J = 8.9 Hz), 2.89 (t, J = 2 Hz, 1H), 2.68 – 2.44 (m, 3H), 0.95 (s, 21H)

^{13}C NMR (100 MHz, C_6D_6): δ = 144.3, 144.0, 140.6, 128.6, 128.5, 128.4, 127.6, 127.1, 126.8, 120.8, 111.0, 87.2, 86.3, 69.8, 64.0, 62.9, 57.3, 42.6, 41.2, 36.7, 17.9, 12.0

Major Isomer (**109**)

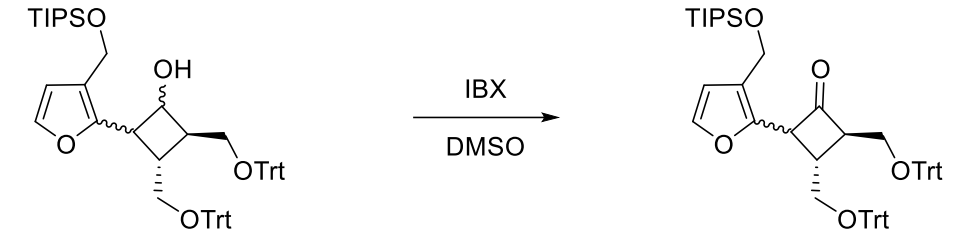
R_f: 0.63 (toluene/diethyl ether: 20/1)

$[\alpha]^{20}_D$ = +13.7 (c = 1.0, CH_2Cl_2)

^{1}H NMR (400 MHz, C_6D_6): δ = 7.43 – 7.05 (m, 31H), 6.33 (s, 1H), 4.64 (q, J = 8.5 Hz, 2H), 4.06 (s, 1H), 3.17 – 3.06 (m, 4H), 2.97 (t, J = 7.2 Hz, 1H), 2.34 (bs, 1H), 2.24 (bs, 1H), 2.11 (bs, 1H), 0.96 (s, 21H)

^{13}C NMR (100 MHz, C_6D_6): δ = 150.7, 144.3, 140.5, 120.0, 111.3, 86.2, 71.2, 65.4, 64.0, 57.1, 45.7, 43.7, 34.6, 17.8, 12.0

6.4.7 IBX Oxidation



Molecular Weight: 869,23 Molecular Weight: 867,21

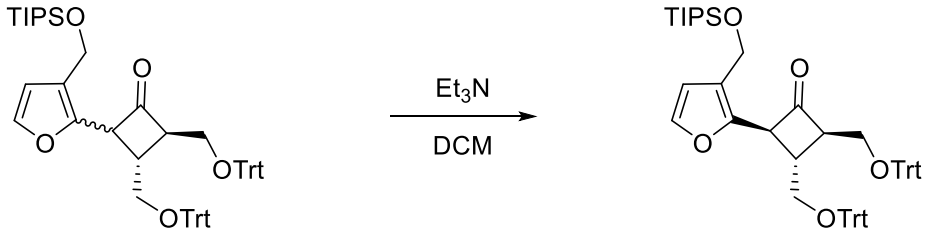
In a round bottom flask, the crude mixture of **108** and **109** (740 mg, 0.8 mmol, 1 eq) were dissolved in DMSO (not dry, 10 mL). IBX (740 mg, 2.64 mmol, 3.3 eq) was added in one batch and the mixture was stirred until TLC indicated complete conversion (90 min). The solution was diluted with Et_2O (50 mL), leading to precipitation of IBX as a white solid, and washed with water (3 x 1.5 mL). Then, n-hexane (5 mL) was added, leading to precipitation of more IBX and the solution was washed again with water (3 x 1,5 mL). This process was repeated three times (until no further precipitation of IBX was observed), followed by washing with brine (2 x 2 mL). The organic phase was dried over Na_2SO_4 and the solvents were removed under reduced pressure, yielding 750 mg of a colorless viscous oil.

The product was purified by flash chromatography (50 x silica, hexanes/diethyl ether: 10/1), giving 650 mg of a colorless oil (88 %). The product decays rapidly at room temperature to form a yellow oil.

The mixture of isomers was not separated, for analytics see chapter 6.4.8.

R_f: 0.60 (hexanes/ethyl acetate: 3/1)

6.4.8 Equilibration (**110**)



Molecular Weight: 867,21 Molecular Weight: 867,21

In a round bottom flask, cyclobutanone (880 mg, 0.95 mmol, 1 eq) was dissolved in DCM (200 mL). The slightly yellow solution was cooled to 0 °C and Et_3N (5 mL) was added dropwise. After 75 min, the reaction was quenched with sat. aq. NH_4Cl. The phases were separated and the organic fraction washed with sat. aq. $NaHCO_3$ and brine. Volatiles were removed *in vacuo*, yielding 870 mg of crude Product, which was used for the next step without further purification.

The product decays rapidly at room temperature to form a yellow oil.

For analytical purposes, the compound was purified by flash column chromatography (100 x silica, n-hexane/diethyl ether: 5:1)

R_f: 0.60 (hexanes/ethyl acetate: 3/1)

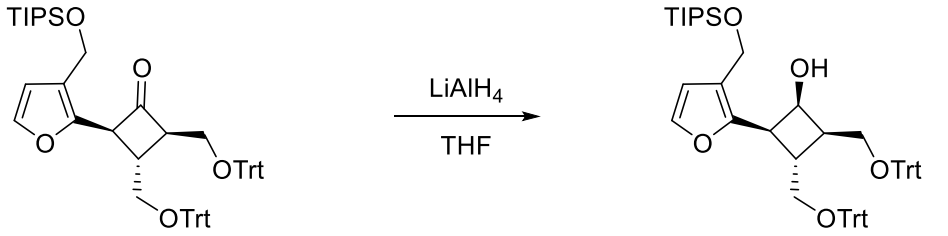
HRMS for $C_{58}H_{62}O_5Si$: $[M+Na]^+$ calcd. 889.4265, found: 889.4258

$[\alpha]^{20}_D$ = -3.2 (c = 1.0, CH_2Cl_2)

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.40 – 7.35 (m, 6H), 7.30 – 7.25 (m, 6H), 7.22 – 7.10 (m, 19H), 6.33 (s, 1H), 4.50 (d, J = 4.0 Hz, 2H), 4.33 (d, J = 8.0 Hz, 1H), 3.42 – 3.10 (m, 6H), 0.96 (s, 21H)

^{13}C NMR (100 MHz, CD_2Cl_2): δ = 149.5, 144.3, 140.8, 128.6, 127.7, 126.9, 120.4, 111.5, 70.1, 65.6, 61.9, 57.2, 41.1, 39.7, 39.3, 29.7, 17.8, 12.0

6.4.9 Diastereoselective Reduction (**111**)



Molecular Weight: 867,21 Molecular Weight: 869,23

In a Schlenk flask, $LiAlH_4$ (60 mg, 1.6 mmol, 1.75 eq) was suspended in anhydrous THF (10 mL). The grey suspension was cooled to -80 °C and cyclobutanone **110** (830 mg, 0.9 mmol, 1 eq) in THF (10 mL) was added dropwise. TLC showed complete conversion after 2 h and the reaction was quenched with MeOH (1 mL). Saturated aqueous solutions of NaK tartrate (6 mL) and $NaHCO_3$ (1.5 mL) were added, the mixture was diluted with toluene (30 mL), warmed to ambient temperature, and stirred overnight.

The phases were separated and the organic fraction washed with sat. aq. $NaHCO_3$ and brine. The volatiles were removed *in vacuo*, yielding 800 mg of crude product.

Purification was performed by DCVC (hexanes/diethyl ether: 10 / 1) and yielded 650 mg (69 %) of a slightly yellow viscous resin.

R_f: 0.50 (PE/EE : 3/1)

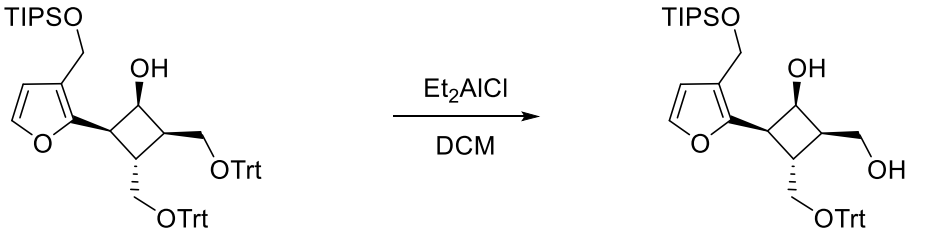
HRMS for $C_{58}H_{62}O_5Si$: $[M+Na]^+$ calcd. 891.4421, found: 891.4416

$[\alpha]^{20}_D$ = +1.9 (c = 1.0, CH_2Cl_2)

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.38 – 7.32 (m, 6H), 7.28 – 7.22 (m, 6H), 7.21 – 7.08 (m, 19H), 6.31 (s, 1H), 4.48 (s, 2H), 3.42 (t, J = 8.0 Hz, 1H), 3.32 (t, J = 8.1 Hz, 1H), 3.18 – 3.01 (m, 4H), 2.77 (d, J = 5.2 Hz, 1H), 2.47 (m, 1H), 0.96 (s, 21H)

^{13}C NMR (100 MHz, CD_2Cl_2): δ = 149.5, 144.2, 140.8, 128.6, 127.7, 126.8, 120.4, 111.5, 86.6, 86.2, 70.1, 65.6, 61.9, 57.2, 41.1, 39.7, 39.3, 29.7, 17.8, 12.0

6.4.10 Regioselective Trityl Cleavage (**112**)



Molecular Weight: 869,23 Molecular Weight: 626,91

In a Schlenk flask, cyclobutanol **111** (650 mg, 0.75 mmol, 1 eq) was dissolved in anhydrous DCM (13 mL) and cooled to -40 °C. Et_2AlCl (1 N in heptane, 0.7 mL, 0.9 eq) was added dropwise, giving a yellow color immediately. After 20 min, the reaction mixture was warmed to -20 °C and then stirred for another 60 min. When TLC indicated 70 % conversion, the reaction was quenched with Et_3N (5 mL) and then warmed up to ambient temperature. The mixture was diluted with 40 mL of EtOAc, 6 mL of sat. aq. NaK tartrate were added and stirring was continued overnight.

The phases were separated and the organic phase washed with sat. aq. $NaHCO_3$ and brine. The aqueous phase was reextracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over Na_2SO_4 and all volatiles were removed *in vacuo*, giving 630 mg crude mixture of product and starting material.

Purification was done by flash chromatography using 40 g of Silica. After the starting material had been isolated (hexanes/ethyl acetate: 10/1), the polarity of the eluent was increased to isolate the product (hexanes/ethyl acetate: 2/1). After evaporation, 200 mg of impure starting material and 230 mg of pure product (49 %) were isolated.

R_f: 0.35 (hexanes/ethyl acetate: 1/1)

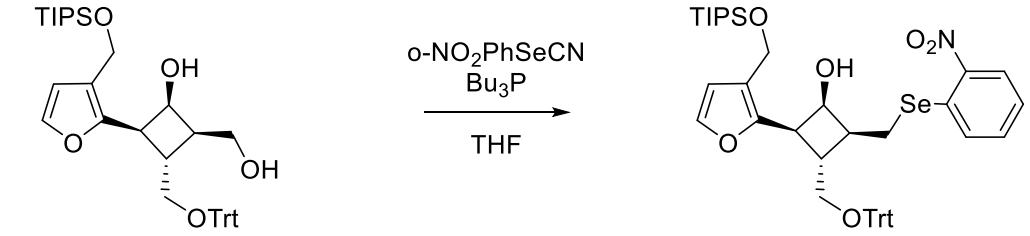
HRMS for $C_{39}H_{50}O_5Si$: $[M+Na]^+$ calcd. 649.3326, found: 649.3317

$[\alpha]^{20}_D$ = +11.3 (c = 1.0, CH_2Cl_2)

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.36 – 7.30 (m, 6H), 7.26 – 7.11 (m, 10H), 6.31 (s, 1H), 4.52 (t, J = 8.0 Hz, 1H), 4.46 (s, 2H), 3.73 – 3.01 (m, 6H), 2.77 (m, 1H), 0.96 (s, 21H)

^{13}C NMR (100 MHz, CD_2Cl_2): δ = 149.8, 144.2, 140.9, 128.6, 127.7, 126.9, 119.9, 111.8, 86.5, 70.4, 65.4, 61.4, 57.1, 42.5, 38.7, 38.2, 29.7, 17.7, 11.9

6.4.11 Selenide Formation (**117**)



Molecular Weight: 626,91 Molecular Weight: 810,98

In a Schlenk flask, diol **112** (15 mg, 0.024 mmol, 1 eq) was dissolved in dry degassed THF (1 mL) and tributylphosphine (1 N in THF, 0.072 ml, 0.072 mmol, 3 eq) and *o*-nitrophenyl cyanoselenide (16 mg, 0.072 mmol, 3 eq) were added to the mixture, giving a dark red color.

After 1 h, the solvent was evaporated *in vacuo* and the product was purified by column chromatography (100 x silica, hexanes/diethyl ether 5/1).

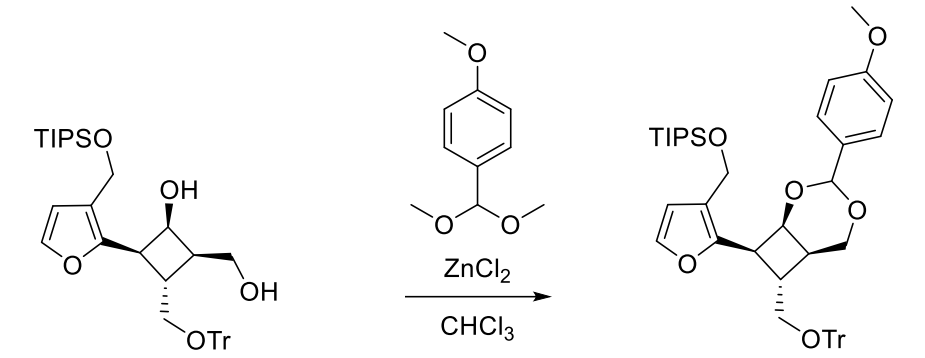
Rf: 0.73 (hexanes/ethyl acetate: 1/1)

HRMS for $C_{45}H_{53}NO_6SeSi$: $[M+Na]^+$ calcd. 834.2705, found: 834.2703

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 8.16 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 7.33–7.01 (m, 16H), 6.32 (d, J = 2 Hz, 1H), 4.48 (s, 2H), 3.43 (m, 1H), 3.21 (m, 2H), 3.13-2.95 (m, 3H), 2.94 (d, J = 3.6 Hz, 1H), 0.96 (s, 21H)

^{13}C NMR (100 MHz, CD_2Cl_2): δ = 148.4, 144.1, 144.0, 141.0, 133.7, 133.5, 129.4, 128.7, 127.8, 127.0, 126.3, 125.2, 120.4, 111.9, 86.5, 69.6, 65.1, 57.2, 43.6, 39.8, 38.5, 24.5, 17.8, 11.9

6.4.12 Cyclic PMB Acetal (**113**)



Molecular Weight: 367,58 Molecular Weight: 485,72

In a Schlenk flask, diol **112** (15 mg, 0.024 mmol, 1 eq) was dissolved in dry DCM (0.3 mL). Anisaldehyde dimethyl acetal (23 µL, 0.12 mmol, 5 eq) and $ZnCl_2$ (0.7 N in THF, 72 µL, 2.1 eq) were added and the mixture was stirred for 1 h.

The reaction mixture was diluted with Et_2O (3 mL) washed 2x with sat. aq. $NaHCO_3$ and brine and dried over Na_2SO_4. The solvent was removed *in vacuo*, yielding 32 mg of crude product.

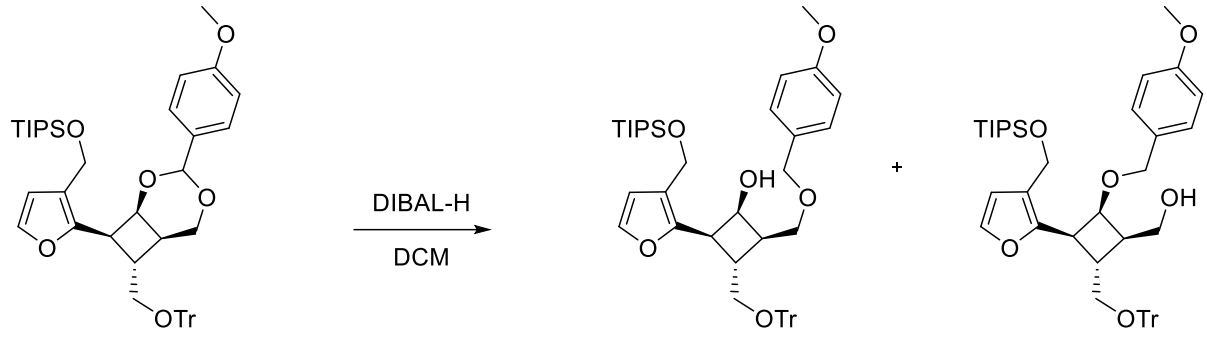
Purification was performed by flash column chromatography (100 x silica, n-hexane/benzene: 2/1) and after evaporating all volatiles on high vacuum overnight, 14 mg (78 %) of pure product were isolated.

Rf: 0.78 (hexanes/ethyl acetate: 1/1)

HRMS for $C_{47}H_{56}O_6Si$: $[M+Na]^+$ calcd. 767.3744, found: 767.3737

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.56 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 6.0 Hz, 6H), 7.29 (t, J = 7.5 Hz), 7.14-7.00 (m, 13H), 6.79 (d, J = 8.4 Hz), 6.50 (s, 1H), 5.16 (s, 1H), 4.90 (d, J = 12.6 Hz, 1H), 4.76 (d, J = 12.4 Hz, 1H), 4.47 (t, J = 4.8 Hz, 1H), 3.97 (m, 1H), 3.84 (d, J = 12.0 Hz, 1H), 3.32 (m, 3H), 3.26 (s, 3H), 2.72 (m, 1H), 0.96 (s, 21H)

6.4.13 Cyclic PMB Acetal Opening (**114**) + (**115**)



Molecular Weight: 485,72 — **113**

Molecular Weight: 487,73 — **115** — **114**

In a Schlenk flask, acetal **113** (7 mg, 0.0094 mmol, 1 eq) was dissolved in dry DCM (0.5 mL). DIBAL-H (0.1 N in DCM, 0.56 mL, 0.056 mmol, 6 eq) was added and after 3 h (TLC: partial conversion), MeOH (3 tr.) and sat. aq. NaK tartrate (0.3 mL) were added and the mixture was stirred overnight.

The reaction mixture was diluted with Et_2O (3 mL) washed with sat. aq. $NaHCO_3$ and brine and dried over Na_2SO_4. The solvent was removed *in vacuo*, yielding 10 mg of crude product mixture.

Purification was performed by flash column chromatography (100 x silica, n-hexane/ethyl acetate: 30/1, 20/1, 13/1), giving **113** (3 mg, 42 %), product **115** (1.5 mg, 21 %) and byproduct **114** (1.1 mg, 16 %).

Product Rf: 0.22 (hexanes/ethyl acetate: 4/1)

Byproduct Rf: 0.34 (hexanes/ethyl acetate: 4/1)

HRMS for $C_{47}H_{58}O_6Si$: $[M+Na]^+$ calcd. 769.3901, found: 769.3893

7 Bibliography

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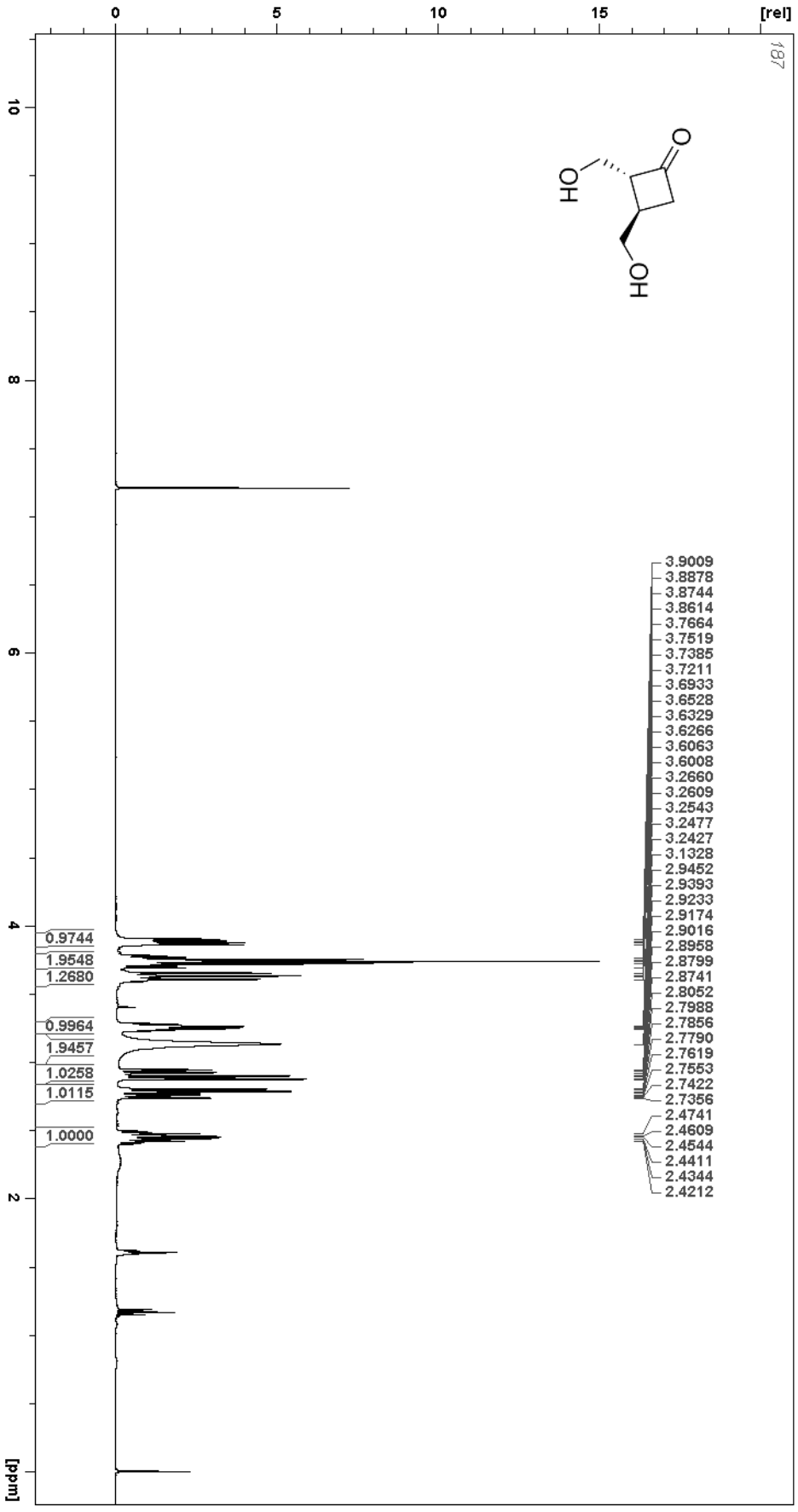
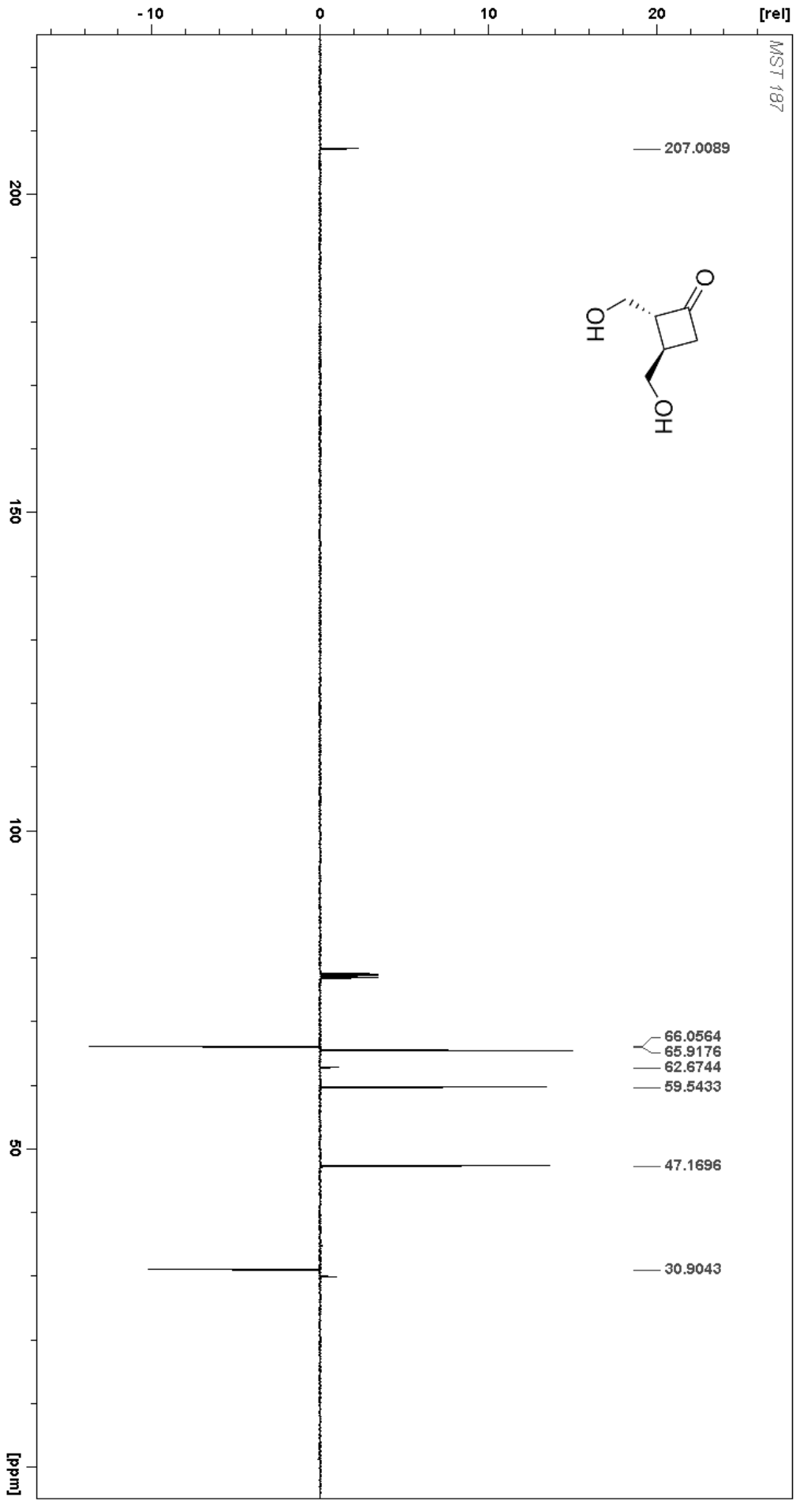
8 Abbreviations

Ac	Acyl
Aq.	Aqueous
Bn	Benzyl
n-BuLi	*n*-Butyl lithium
s-BuLi	*sec* – Butyl lithium
Bz	Benzoyl
CNS	Central Nervous System
CSA	Camphor sulfonic acid
CuTCA	Copper(I) thiophene-2-carboxylate
DCM	Dichloromethane
DCVC	Dry Column Vacuum Chromatography
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	Diisobutyl Aluminium Hydride
DIPEA	Diisopropylethylamine “Hünig’s Base”
DMAP	N,N – Dimethyl 4-Aminopyridine
DMDO	Dimethyldioxirane
DMF	Dimethylformamide
DMP	Dess Martin Periodinane[14]
dr	Diastereomeric Ratio
Et	Ethyl
EE	Ethyl Acetate
GGPP	Geranylgeranylpyrophosphate
HFIP	Hexafluoroisopropanol
HRMS	High Resolution Mass Spectroscopy
HWE	Horner – Wadsworth - Emmons
IBX	2-Iodoxybenzoic acid
LDA	Lithium diisopropyl amine
LiHMDS	Lithium Hexamethyldisilazane
2,6 lut	2,6-Lutidine
Me	Methyl
(+)Menth	(+)Menthyl-
MMTr	Monomethoxytrityl-
MPLC	Medium Pressure Liquid Chromatography

NBS	*N*-Bromo Succinimide
NaHMDS	Sodium Hexamethyldisilazane
NMO	N-Methylmorpholin-N-Oxide
NMR	Nuclear Magnetic Resonance
OPP	O-Pyrophosphate
PE	Petroleum Ether
Ph	Phenyl-
Piv	Pivaloyl-
PMB	*para*-Methoxybenzyl-
PMP	*para*-Methoxyphenyl-
PP	Pyrophosphate
PP	Polypropylene
Py	Pyridine
RCM	Ring Closing Methatesis
TBAF	Tetrabutylammonium Fluoride
TBS	*tert*-Butyldimethylsilyl-
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl-
TLC	Thin Layer Chromatography
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl-
Tol	Toluene
TPAP	Tetrapropylammonium perruthenate
Tr	Trityl-
Ts	*para*-Toluenesulfone-
UV	Ultraviolet

9 Selected Spectra

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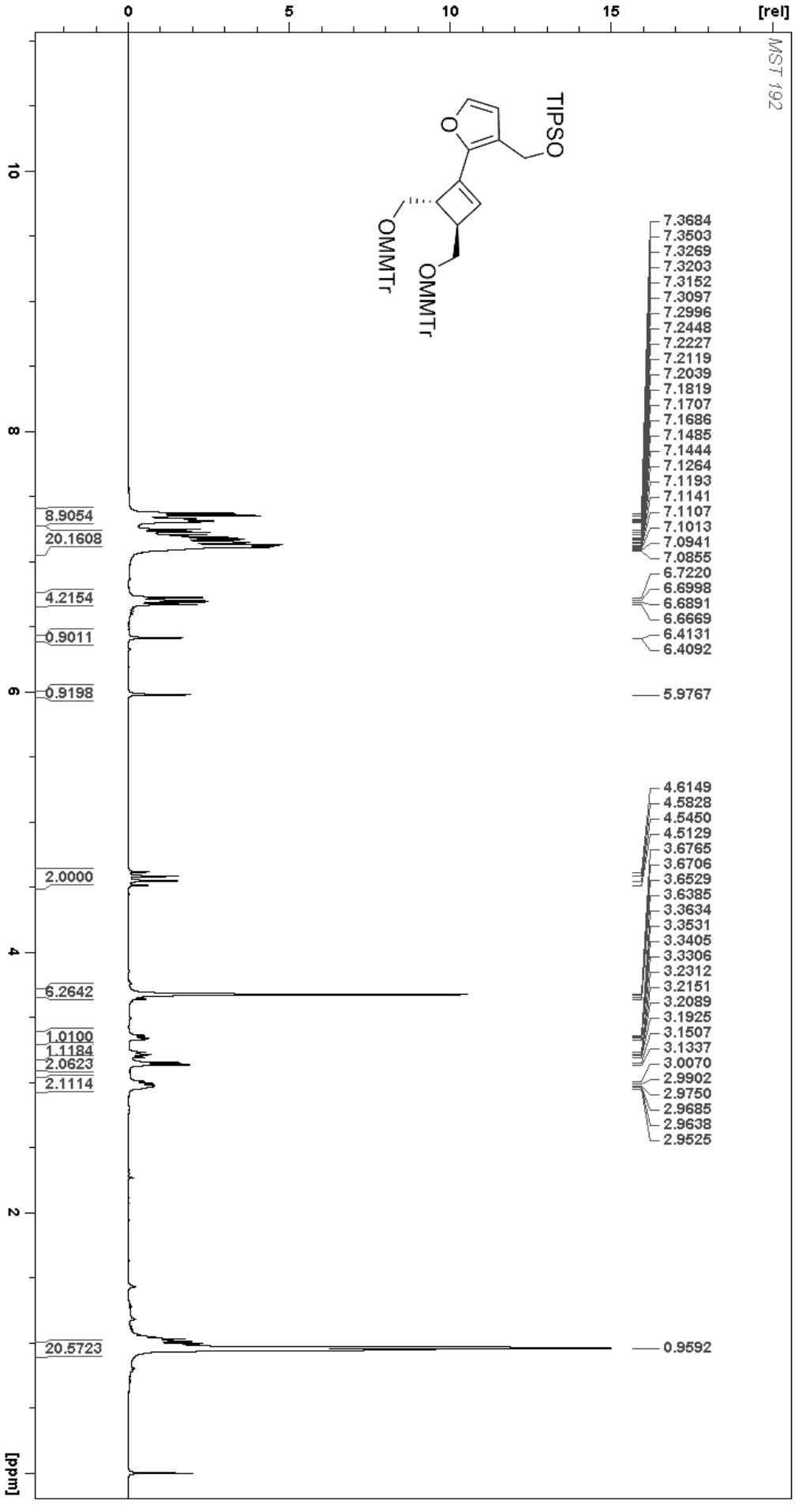
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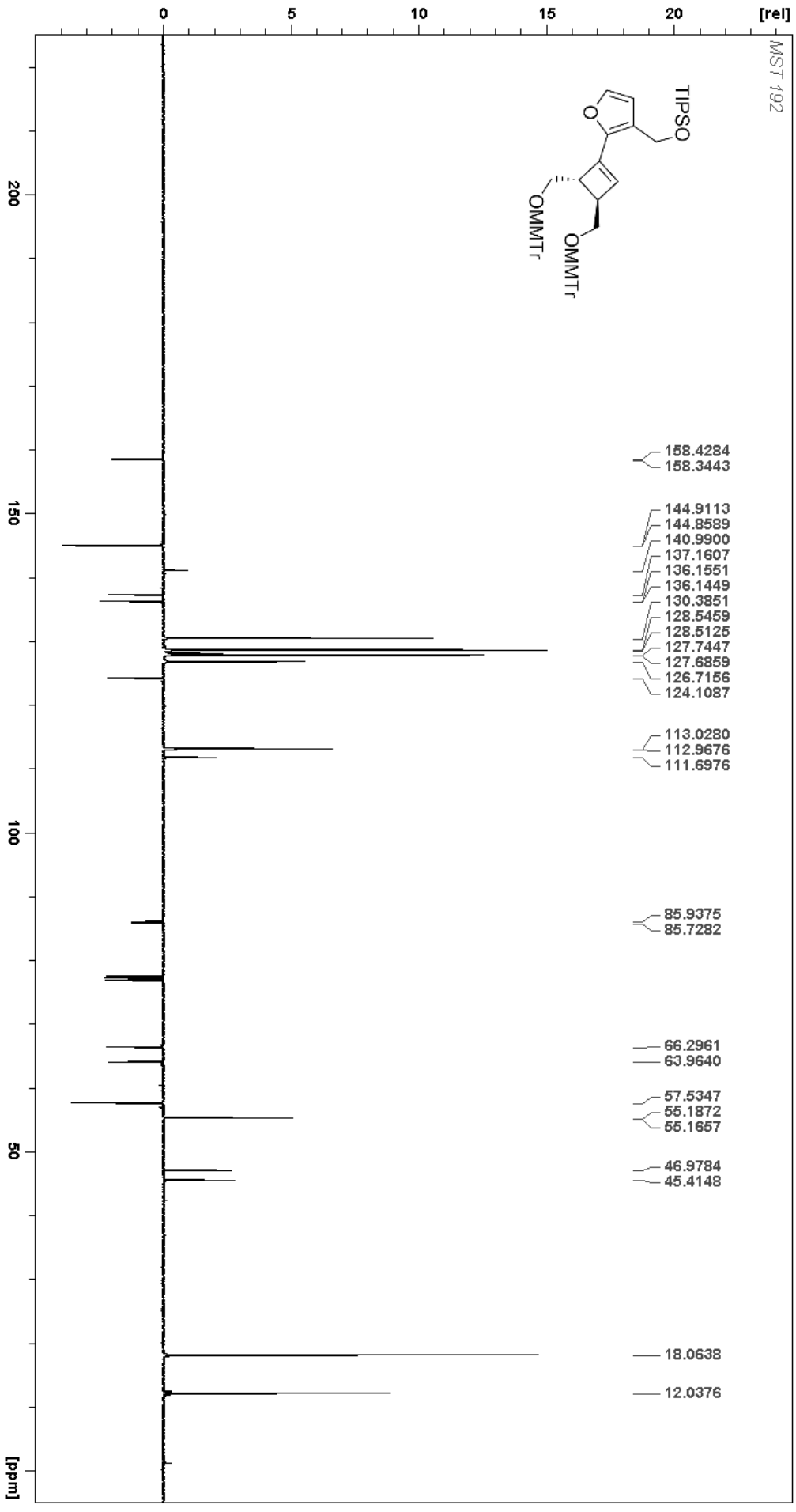
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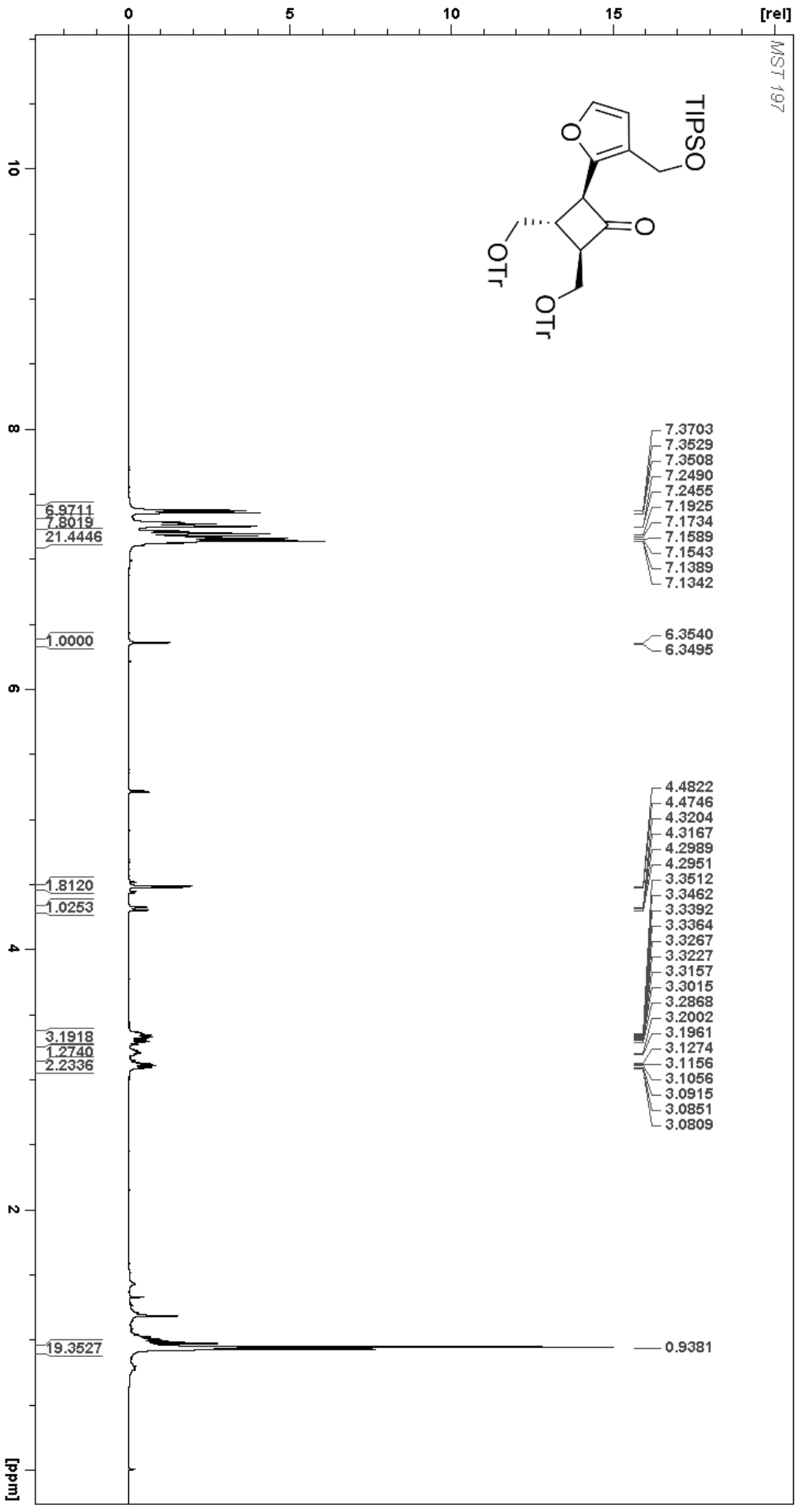
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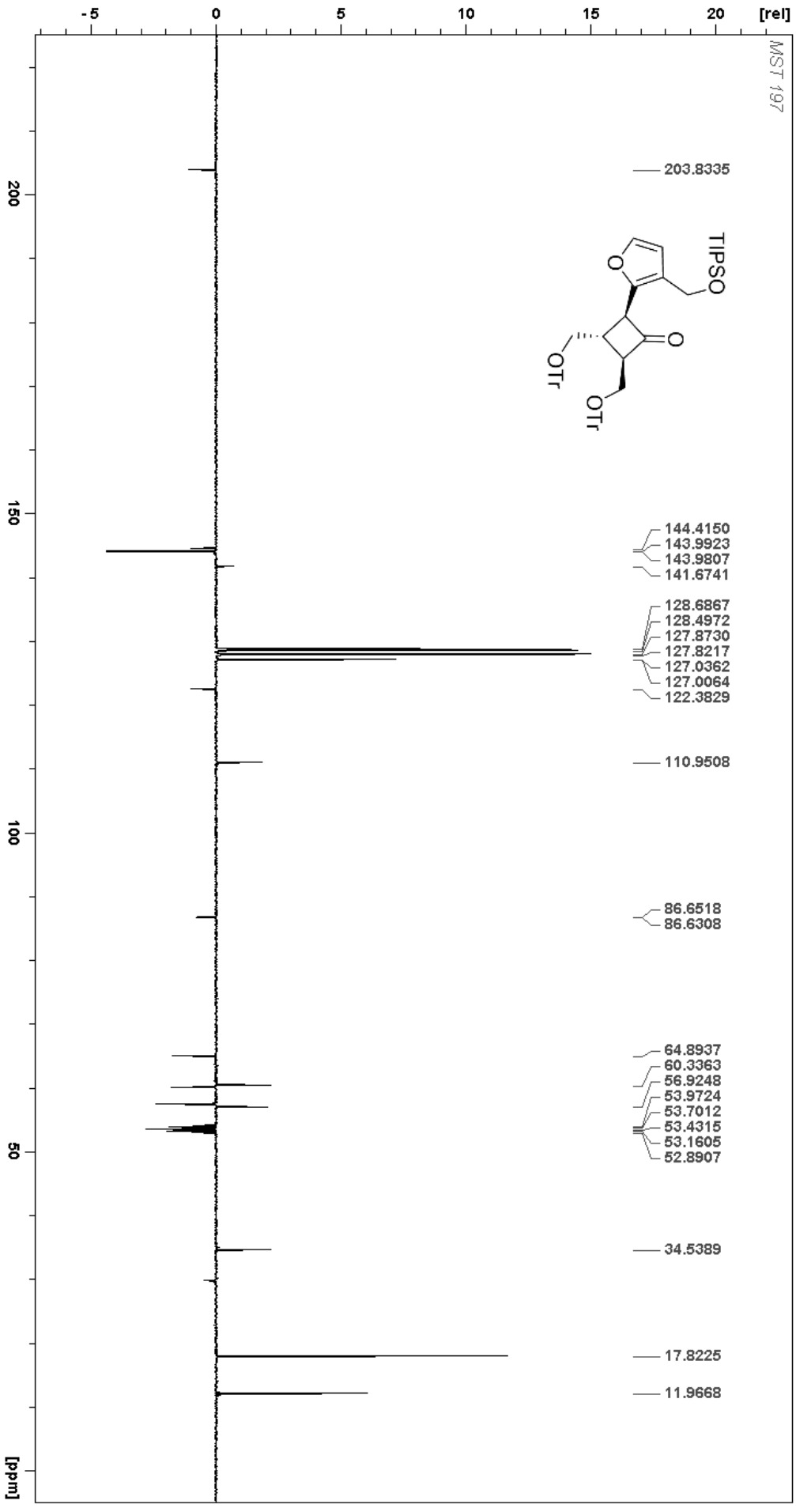
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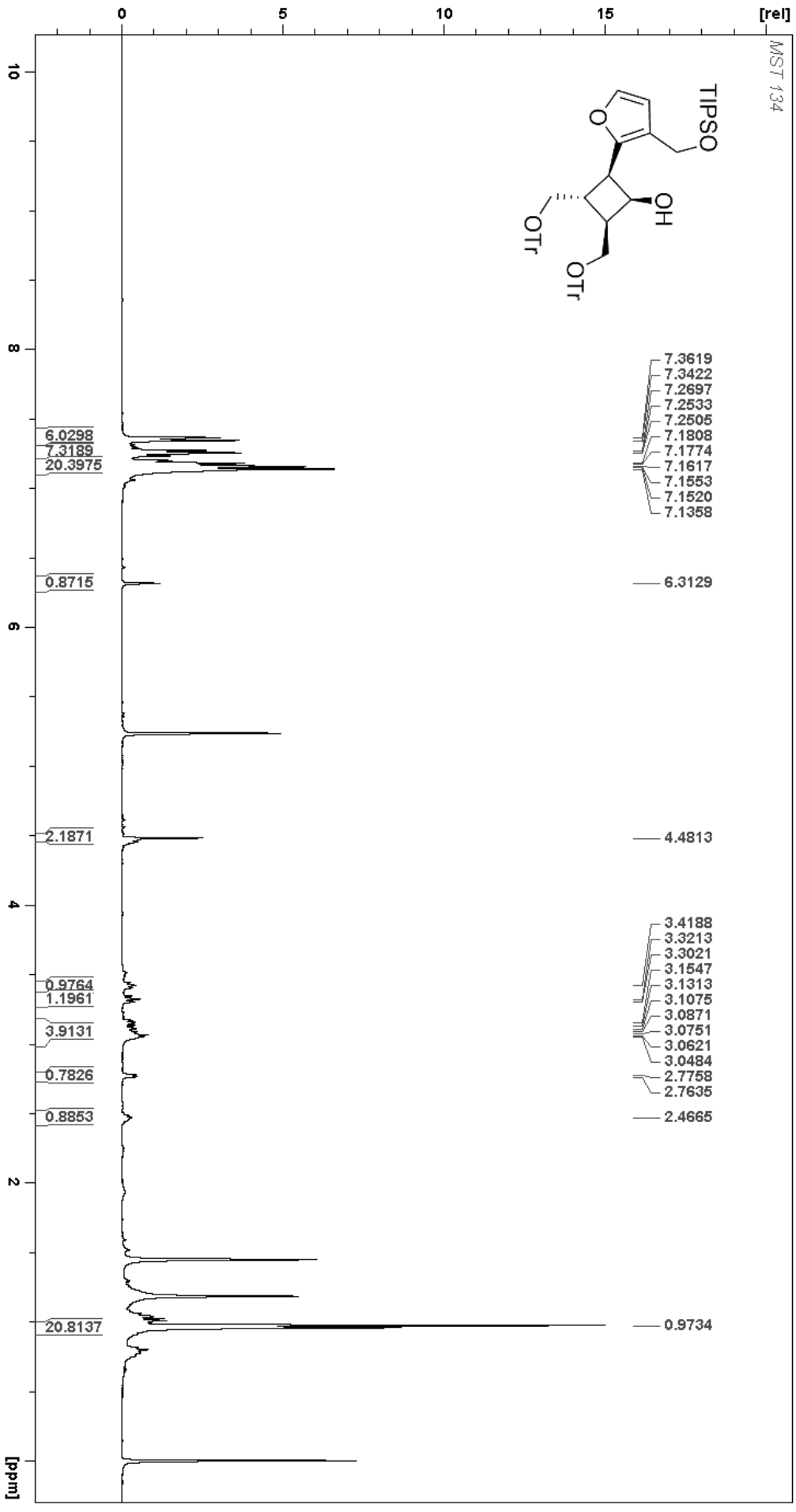
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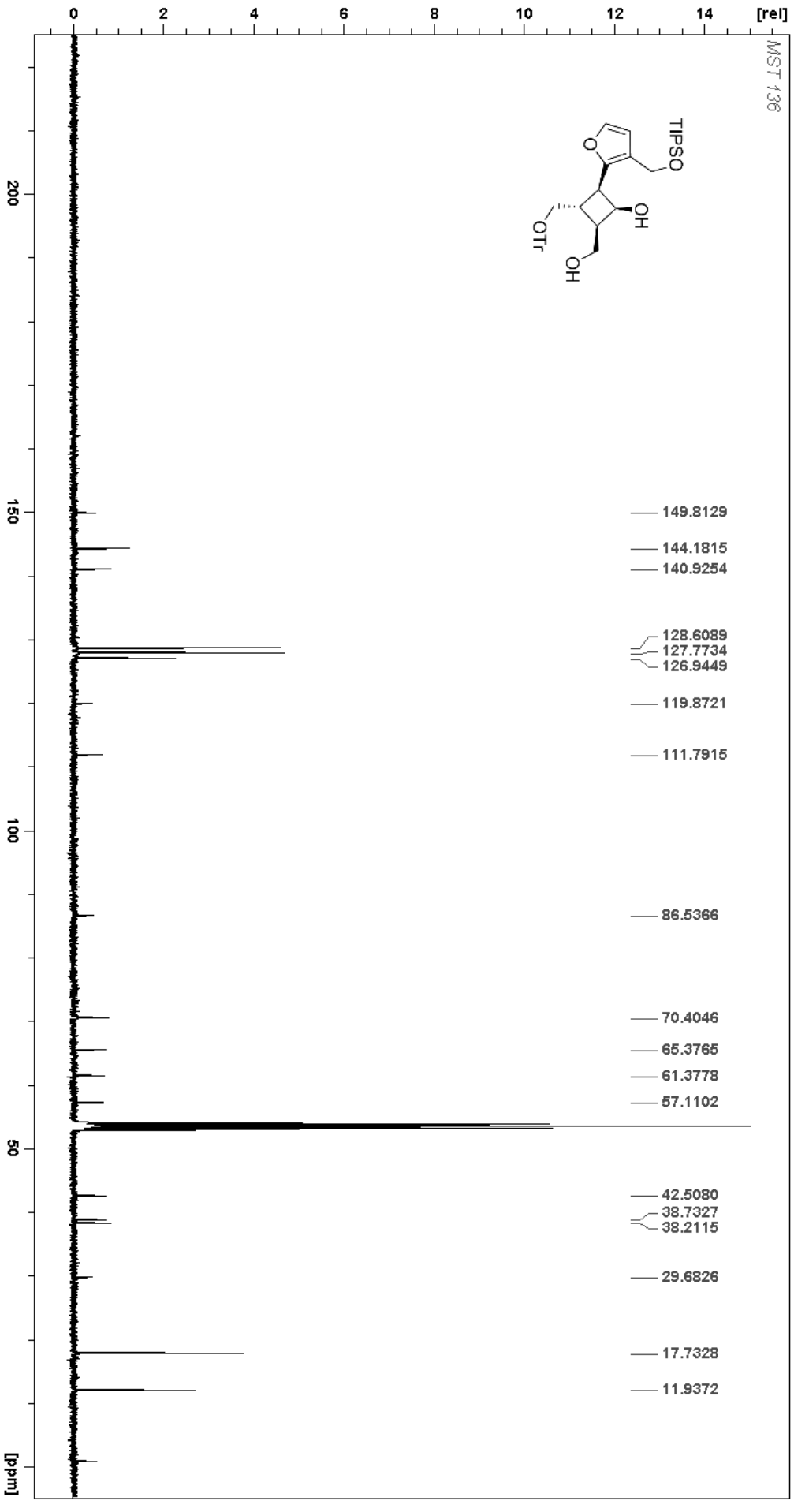
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