TECHNISCHE UNIVERSITÄT WIEN
Vienna University of Technology

DIPLOMA THESIS

Towards the Total Synthesis of Euphosalicin

Submitted at the

Institute of Applied Synthetic Chemistry
of the Vienna University of Technology

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dedicated to Mela

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1 Introduction

Within the plant family *Euphorbiaceae* the genus *Euphorbia* is the largest. It consists of over 2000 known species, spread globally, however mainly distributed in America and tropical Africa.[1] The genus faced increasing interest because of its promising biological activities like antitumor, antiviral and cytotoxic properties, as well as different vascular effects and the reversal of multidrug resistance (MDR).[1,2] Additionally, the Euphorbia species has shown antibacterial activity in several studies.[3,4]

Multidrug resistance reversal ability is considered the most interesting characteristic of the genus, because of its potential use in cancer treatment. All of the mentioned activities were attributed to specific types of diterpenes, including jatrophone, jatrophane and their derivatives.[5,6]

Jatrophone's most noteworthy structural features are a cyclopentene fragment and an annulated 12-membered macrocycle bridged by an oxygen atom. Jatrophane, however, does not have an oxygen bridge in its structure, but its highly oxidized five membered ring has to be pointed out. Both, jatrophone as well as jatrophane share the carbon skeleton illustrated in *Figure 1.1*.

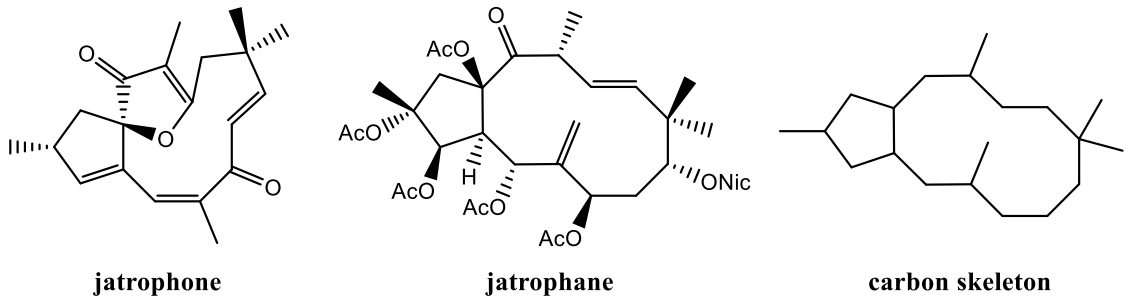

Figure 1.1 Jatrophone, jatrophane and their carbon skeleton (Ac: acetyl, Nic: nicotinoyl) [7]

A significant number of various types of cancer is hardly treatable. This is often due to the fact that these cancers are resistant to a wide range of anticancer drugs or their combinations. A possible solution might be the treatment of cancer cells with substances that provide MDR-reversal activity.[8]

Their potential origins in the ability to bind and therefore inhibit the P-glycoprotein P-gp, which is a member of membrane transport proteins. P-gp is capable of pumping drugs out of tumor cells, what results in reduced intracellular drug concentrations. This reduces the cytotoxicity of anticancer drugs significantly.
Since its isolation in 1970[7], evidence for MDR-reversal abilities of jatrophone and its derivatives has been collected and studies on their P-gp binding process have been made. They also confirmed that jatrophane diterpenes can meet the expectations.[8,9]

In 2001, *Hohmann et al.*[10] found jatrophane diterpenoid euphosalicin on investigations of Euphorbia salicifolia, an *Euphorbiaceae* species, distributed mainly in central and south-eastern Europe. They carried out numerous experiments to determine the

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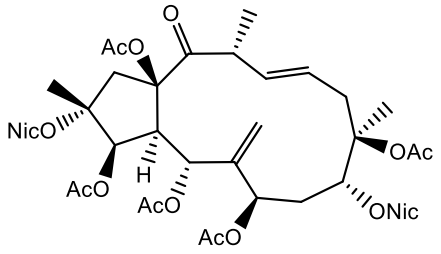
structure, including X-ray crystallography and NMR spectroscopy, to secure knowledge about the absolute configuration. The investigations resulted in the structure shown in *Figure* 1.2 for euphosalicin.[10]



euphosalicin

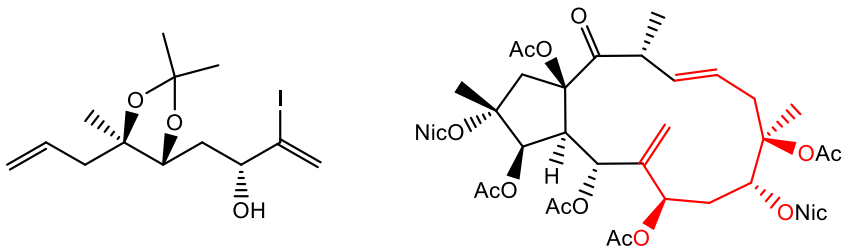
Figure 1.2 Structure of euphosalicin [10]

The similarity to the jatrophane skeleton can easily be recognized, most notably the cyclopentane fragment, as well as the macrocycle. However, the macrocycle is a 13-membered ring, which differs from the jatrophane skeleton. Obviously one of the geminal methyl groups is incorporated in the carbocycle, leading to the ring extension. This rearrangement could be a possible explanation for the observed higher flexibility of euphosalicin, in comparison to other jatrophane diterpenoids. The cyclopentane fragment is highly oxidized, just like in jatrophane itself.

Euphosalicin has been examined in terms of MDR-reversal ability. It showed considerable potency in inhibiting the pump activity of P-gp in mouse lymphoma cells. The compound was found to be up to three times more active in concerns of its MDR-reversal ability than varapamil, a positive control substance.[10,11]

However, out of 2600 g fresh plant material only 15 mg of euphosalicin could be isolated.[10] Considering its use in human cancer therapy, further testings on this compound have to be made and therefore greater amounts of the compound are needed. Its high potential in multidrug resistance ability, as well as the challenging structural properties, make euphosalicin a very interesting synthetic target. A total synthesis of the title compound would not only allow further investigations concerning its properties, it may also pioneer the development of new drugs with similar structural features.

In the course of this diploma thesis the emphasis has been set on the synthetic route towards a key intermediate (*Figure 1.3*) on the way to euphosalicin. The structural element, which is built by the mentioned intermediate, is highlighted in red.



key intermediate **euphosalicin**

Figure 1.3 Structure of the key intermediate and euphosalicin

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2 State of the Art

2.1 Total Syntheses of Jatrophane Derivatives

2.1.1 *Smith et al.* 1981

Smith et al.[12] reported the synthesis of normethyljatrophone **1** and jatrophone **2** back in 1981. Despite **1** and **2** being racemic mixtures, Smith's syntheses were the first of jatrophane diterpenes.

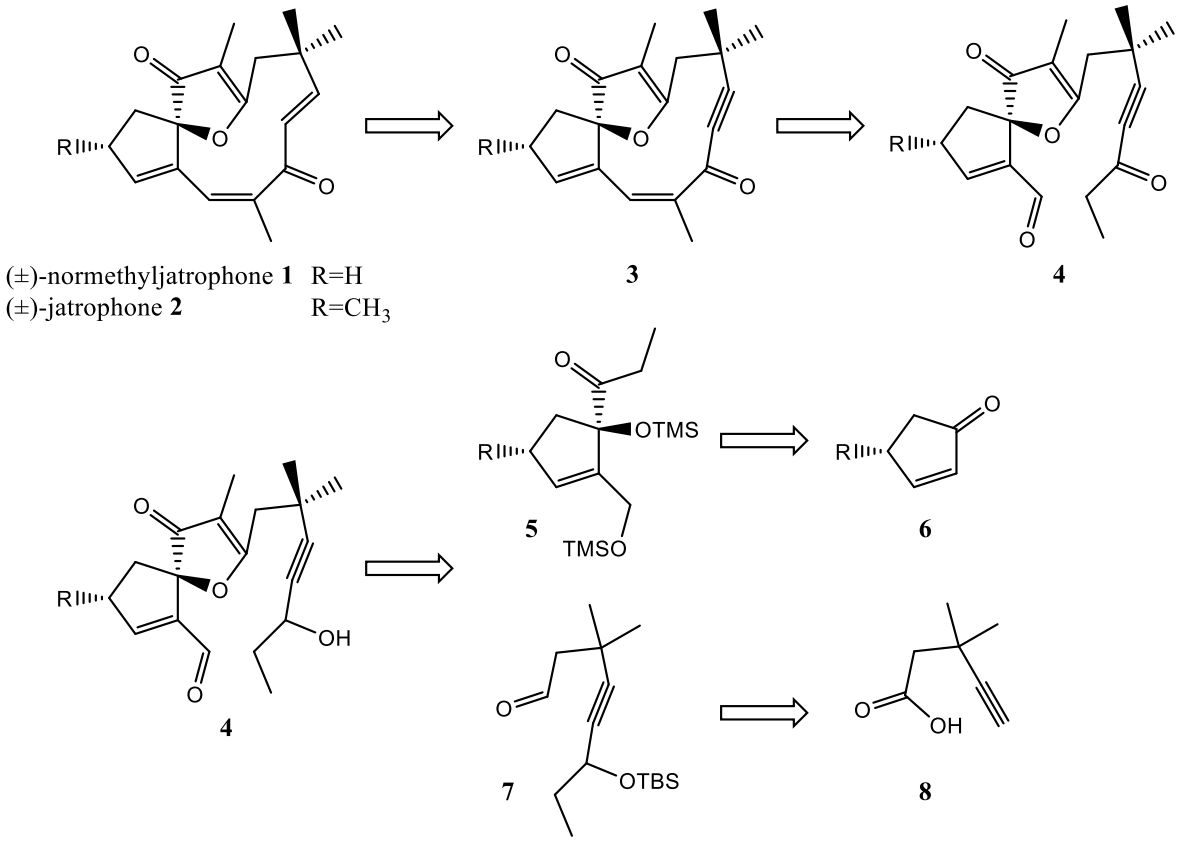

Figure 2.1

The key reaction in Smith's approach was planned to be an intramolecular Mukaiyama aldol reaction of intermediate **4**, followed by reduction of the triple bond using Lindlar's catalyst. Crucial synthon **4** was intended to be constructed by another aldol reaction between ketone **5** and aldehyde **7**, which could be available from enone **6** and acid **8**, respectively.

Concerning the synthesis of **7**, acid **8** was treated with excess base, the formed dianion was reacted with propanal to give alkyne **9**. After protection, intermediate **10** was reduced with $LiAlH_4$ and immediately reoxidized to furnish aldehyde **7**.

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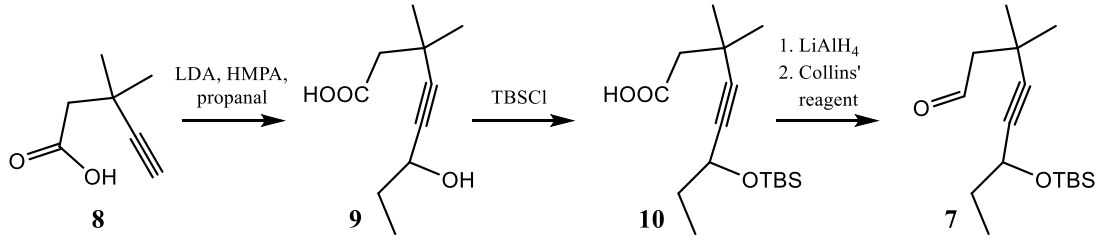

Figure 2.2

Enone **6** was the starting point for preparation of ketone **5**. It was converted in five steps into hydroxyl enone **11**, which in turn was protected and underwent a Corey-Seebach reaction resulting in intermediate **12**. Treatment with acid and subsequent addition of trimethylsilyl chloride afforded desired ketone **5**.

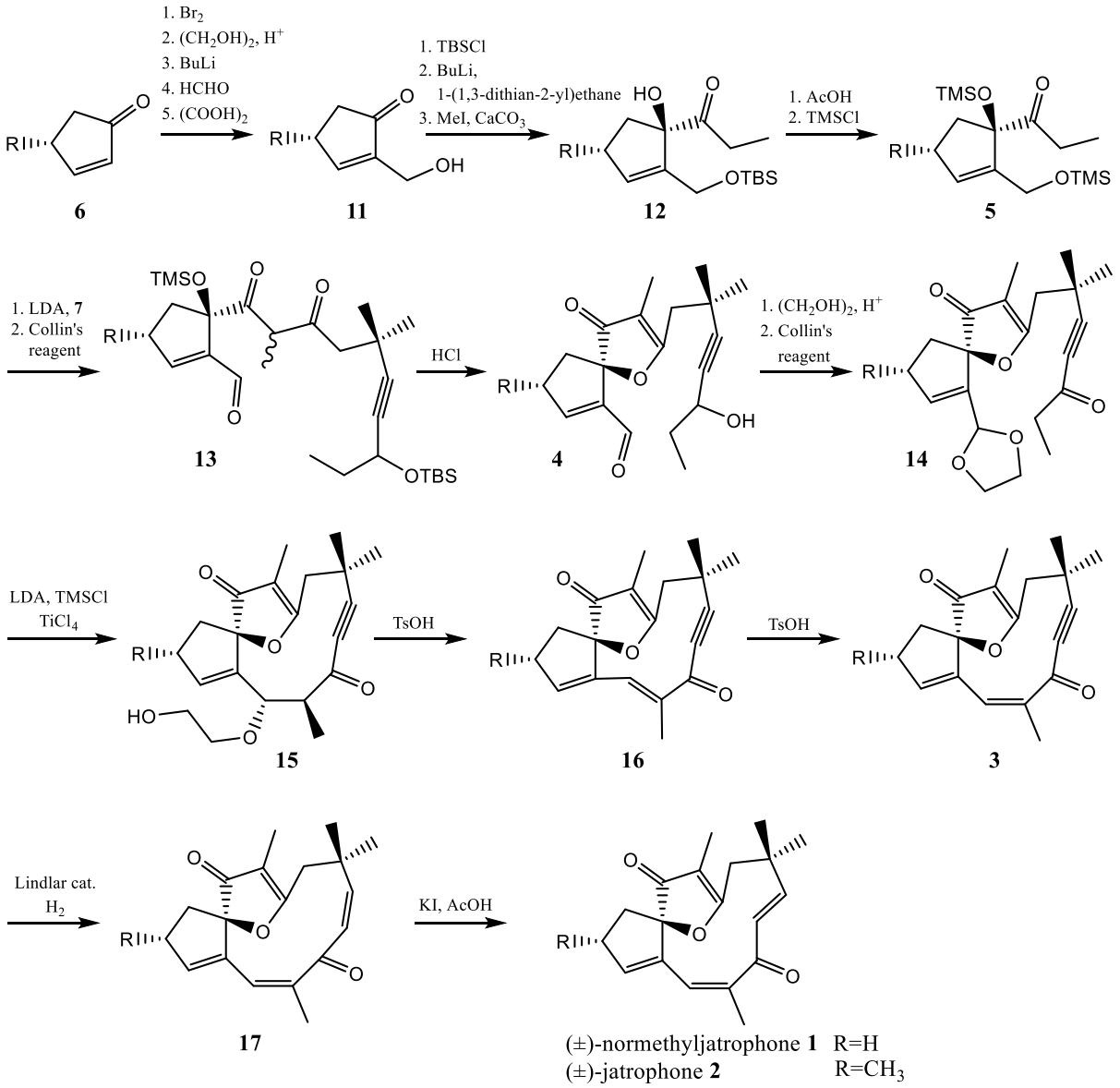

Figure 2.3

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With intermediates **5** and **7** in hand, the synthesis was continued with their coupling by means of an aldol reaction. The product was treated with Collin's reagent to furnish compound **13**. Cleavage of both silyl protection groups under acidic conditions led to cyclization product **4**. Protection of the aldehyde, followed by oxidation of the hydroxyl group gave intermediate **14**, setting the stage for the crucial Mukaiyama aldol reaction. Its implementation resulted in compound **15**. Treatment with *p*-toluenesulfonic acid led to (*E*)-isomer **16**, further exposure with TsOH gave desired (*Z*)-product **3**. Reduction of the triple bond with Lindlar's catalyst resulted in **17**, which was converted into normethyljatrophone **1** and jatrophone **2** likewise, by iodine mediated isomerization.

Additionally, *Smith et al.* succeeded in the total synthesis of two other jatrophone derivatives in 1989, namely (+)-hydroxyjatrophone A and (+)-hydroxyjatrophone B.[13]

2.1.2 *Hegedus et al.* 1990

Nine years later, *Hegedus et al.*[14] described another synthesis of (±)-jatrophone **2**, where a palladium catalyzed intramolecular carbonylative coupling reaction was the macrocycle-building step. Therefore, required compound **18** was planned to be synthesized by an aldol reaction of ketone **19** and aldehyde **20**.

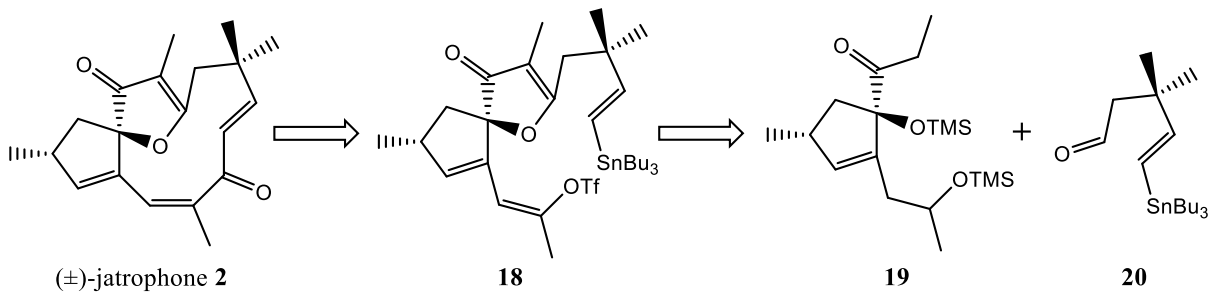

Figure 2.4

Intermediate **20** was accessible *via* an 1,4-addition of cuprate **22** to dimethylacrylate **21**, followed by reduction of the resulting ester.

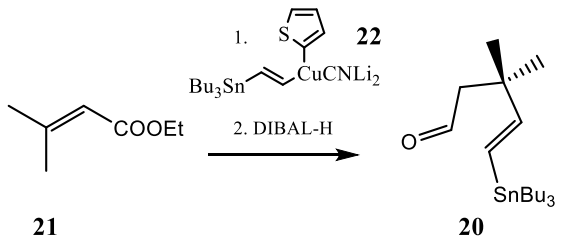

Figure 2.5

Hegedus' approach was closely related to the synthesis done by *Smtih et al.*[12] Bromination and protection of the carbonyle group of racemic ketone **23** were done likewise, after lithium-halogen exchange, the resulting lithium organyle was treated with propylene oxide. After protection, ketale **24** was formed, which in continuation was deprotected and consequently underwent a Corey-Seebach reaction. Mercury mediated dithiane cleavage provided diastereomers **25a** and **25b**. Routine

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protecting group manipulations on **25b** afforded intermediate **19**, which was then joined with aldehyde **20** in an aldol reaction. Corey-Kim oxidation gave diketone **26**.

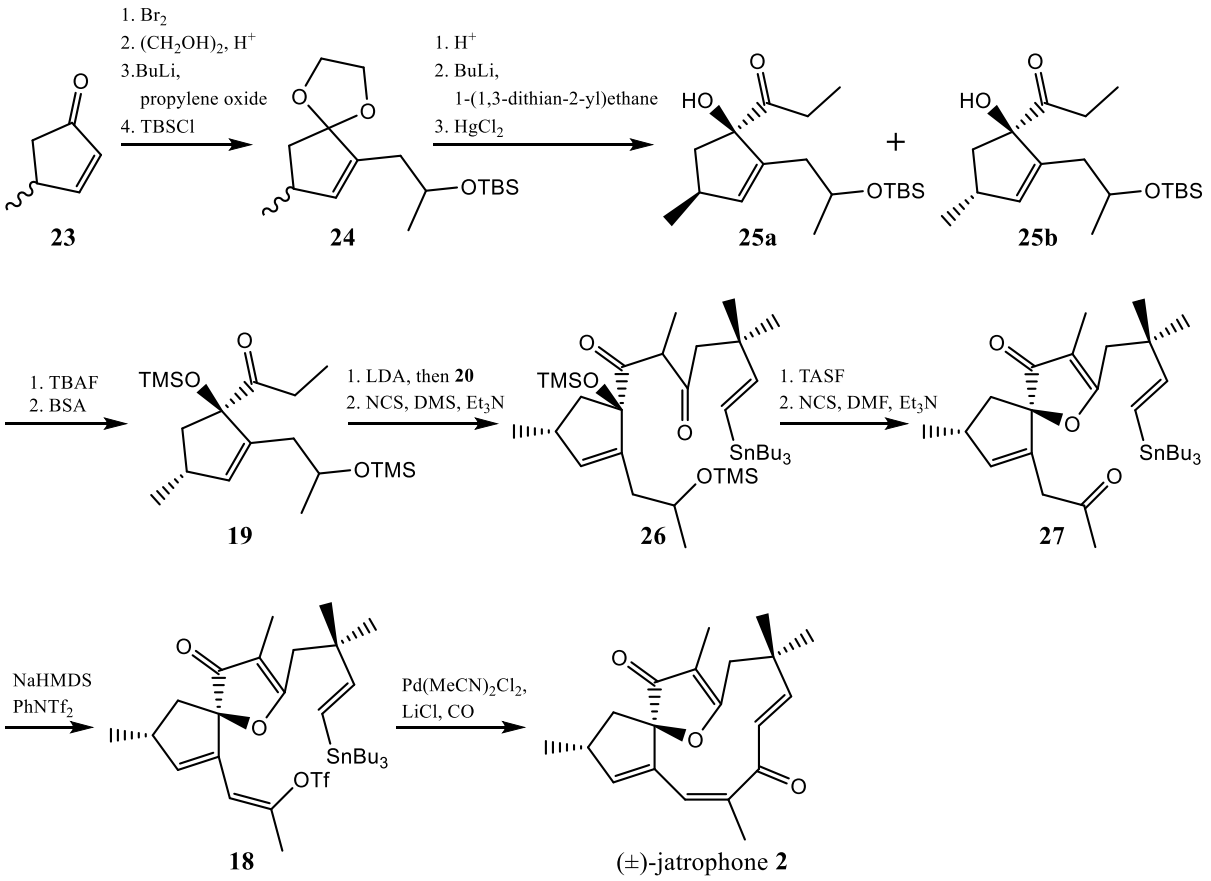

Figure 2.6

Cleavage of silyl protecting groups initiated intramolecular cyclisation, subsequent oxidation of the secondary alcohol provided ketone **27**. Said compound was then converted into vinyltriflate **18**. The stage was now set for the crucial intramolecular carbonylative coupling reaction, catalyzed by palladium in an atmosphere of carbon monoxide, to give desired (±)-jatrophone **2**.

2.1.3 *Han and Wiemer* 1992

The first enantioselective synthesis of (+)-jatrophone was done by *Han and Wiemer* in 1992.[15] Their retrosynthetic considerations included an intramolecular addition of an acetylene moiety to an aldehyde group to form the macrocycle. The authors took advantage of (+)-pulegone, an easily available substance from the chiral pool, to secure enantiomerically pure outcome of (+)-jatrophone **2**.

Required intermediate **28** was planned to be accessible from tin-organyle **29** and alkyne **30** *via* a Stille cross coupling. Mentioned compound **30** was intended to be elaborated out of ester **31** by the means of a Horner-Wadsworth-Emmons reaction. Compound **31** was considered to be accessible *via* esterification of acid chloride **32** with vinyltriflate **33**, which could be formed from available (+)-pulegone **34**.

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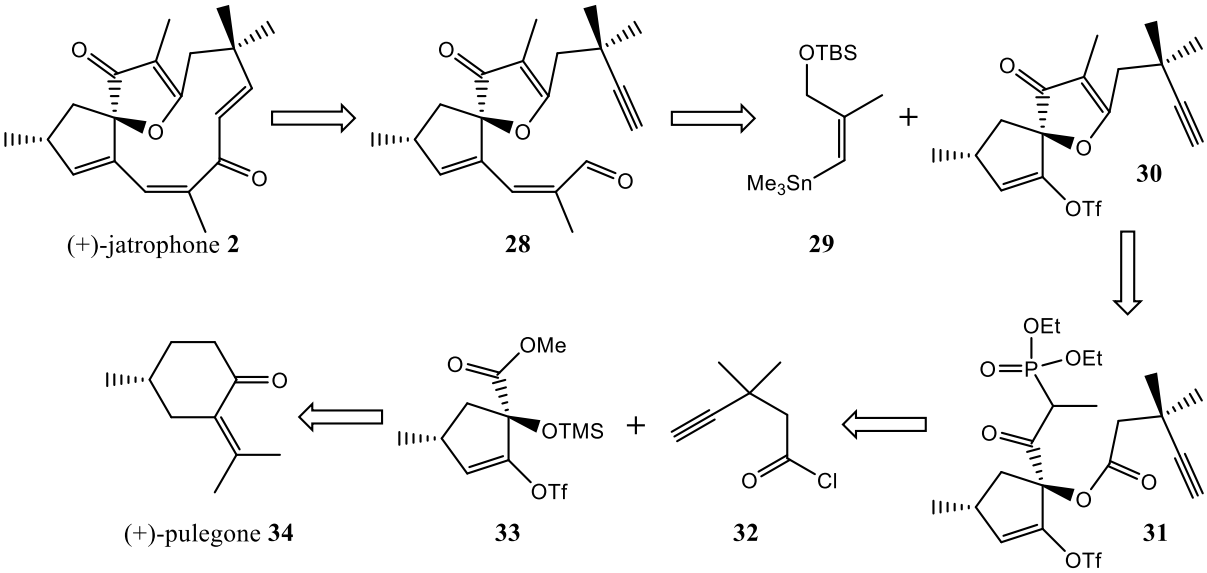

Figure 2.7

As already mentioned, the forward synthesis started with (+)-pulegone **34**, which was converted into diester **35** in a multistep reaction. Treatment with potassium permanganate caused dihydroxylation. Further oxidation formed diacid, which was converted into methyl diester subsequently. Base initiated cyclization after alpha deprotonation, addition of TBAF and trimethylsilyl protected enolate **36** provided intermediate **37**. After protection, Upjohn-dihydroxylation yielded ketone **38**, which was further elaborated to vinyltriflate **33** *via* enolization. Treatment with base and **39** installed the phosphoryl moiety, subsequent addition of lewis acid enabled its reaction with acid chloride **32** to give alkyne **31**.

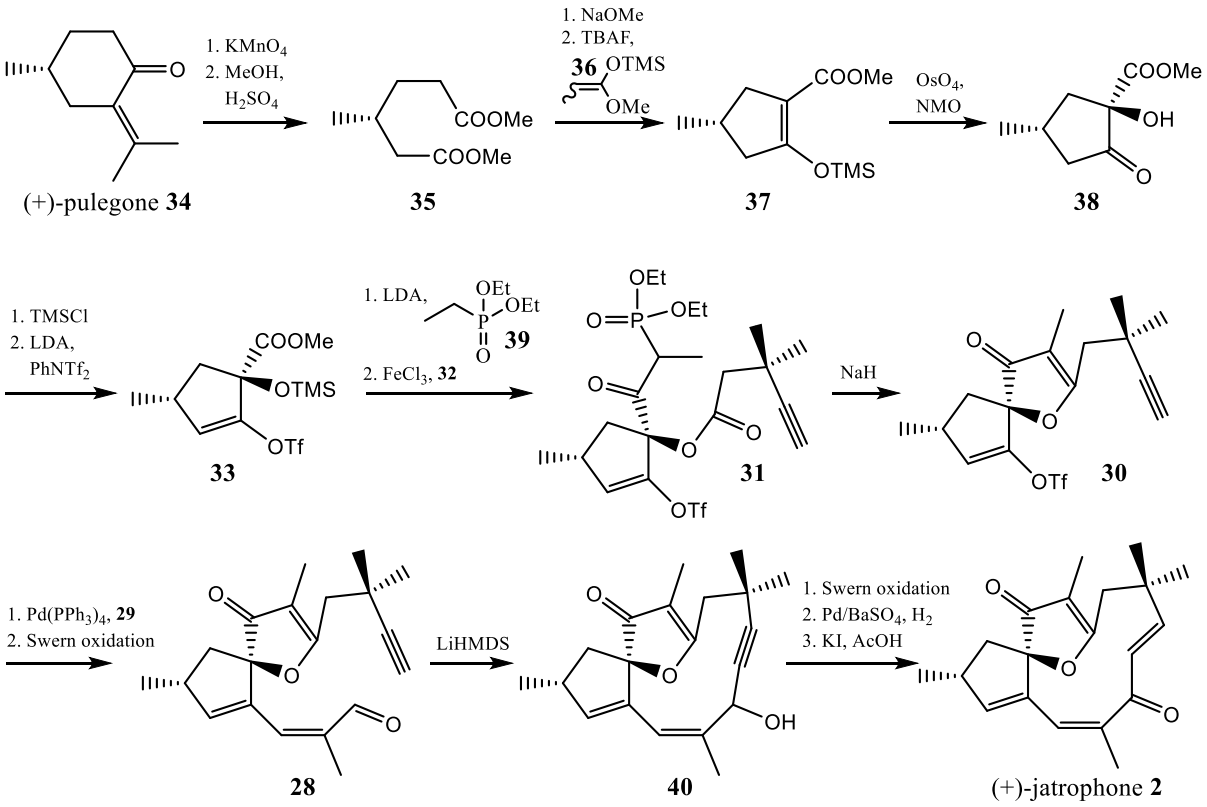

Figure 2.8

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Sodiumhydride triggered intramolecular Horner-Wadsworth-Emmons reaction to provide compound **30**. Said intermediate was further transformed into aldehyde **28** by a Stille-coupling reaction and subsequent oxidation of the primary alcohol. Treatment with base initiated the macrocycle building step to afford intermediate **40**, of which the triple bond was reduced after oxidation of the alcohol moiety. Iodine mediated isomerization of *cis*-product finally yielded enantiomerically pure (+)-jatrophone **2**.

2.1.4 *Hiersemann et al.* 2006

In 2006, *Hiersemann et al.*[16] published the synthesis of unnatural jatrophane derivative (-)-15-O-Acetyl-3-O-propionyl-17-norcharaciol **41**.

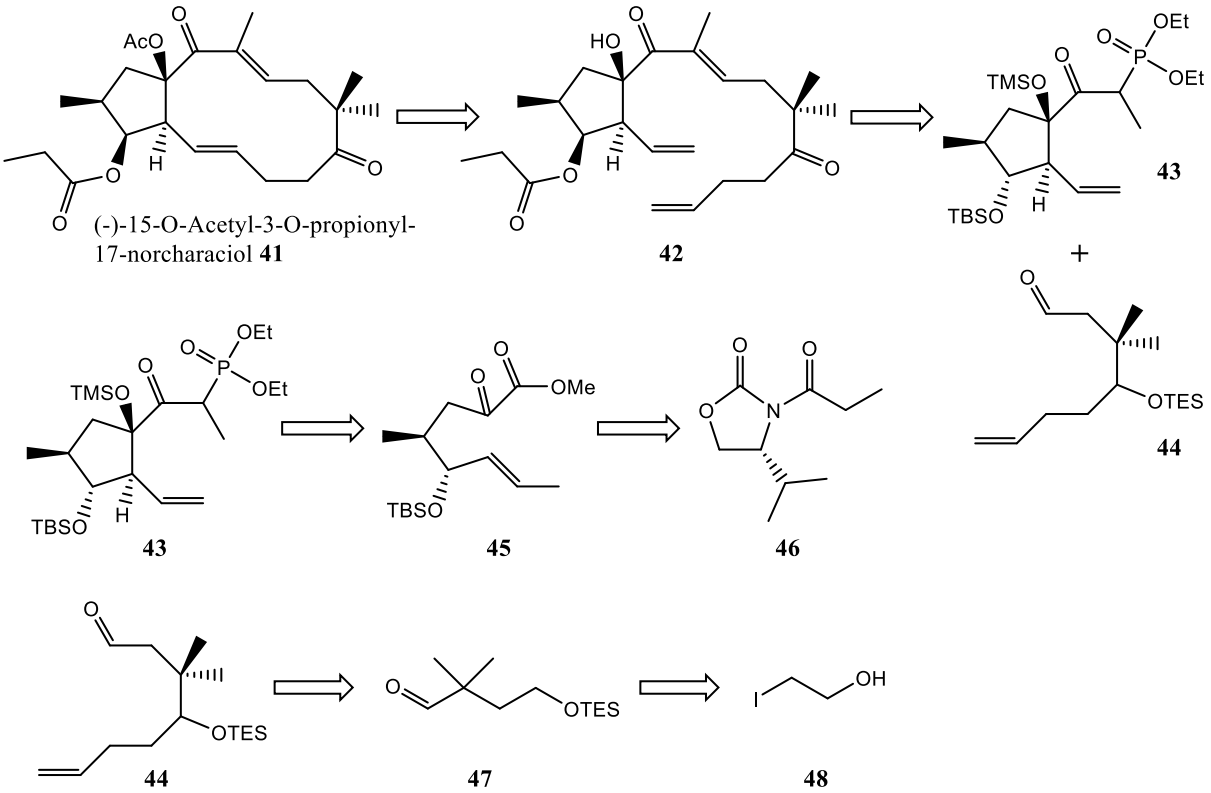

Figure 2.9

Their synthesis relied on a late-step RCM reaction of compound **42**, which was intended to be derived out of phosphoryl species **43** and aldehyde **44**.
Mentioned intermediate **43** was planned to be prepared from a-keto ester **45**, which in turn could originate in *N*-acylated Evan's auxillary **46**.

Aldehyde **44**, of which the synthesis was preliminary, was intended to be synthesized from compound **47** and iodide **48**.

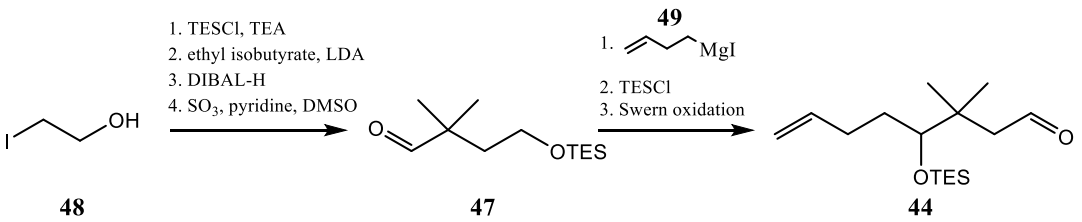

Figure 2.10

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In a four-step procedure iodide **48** was converted into intermediate **47** *via* protection, followed by substitution of iodine with alpha deprotected ethyl isobutyrate. Formed ester was reduced and immediately reoxidized. Furnished aldehyde **47** was then treated with Grignard reagent **49**, resulting secondary alcohol was protected, whereas primary protected alcohol was oxidized to aldehyde **44**.

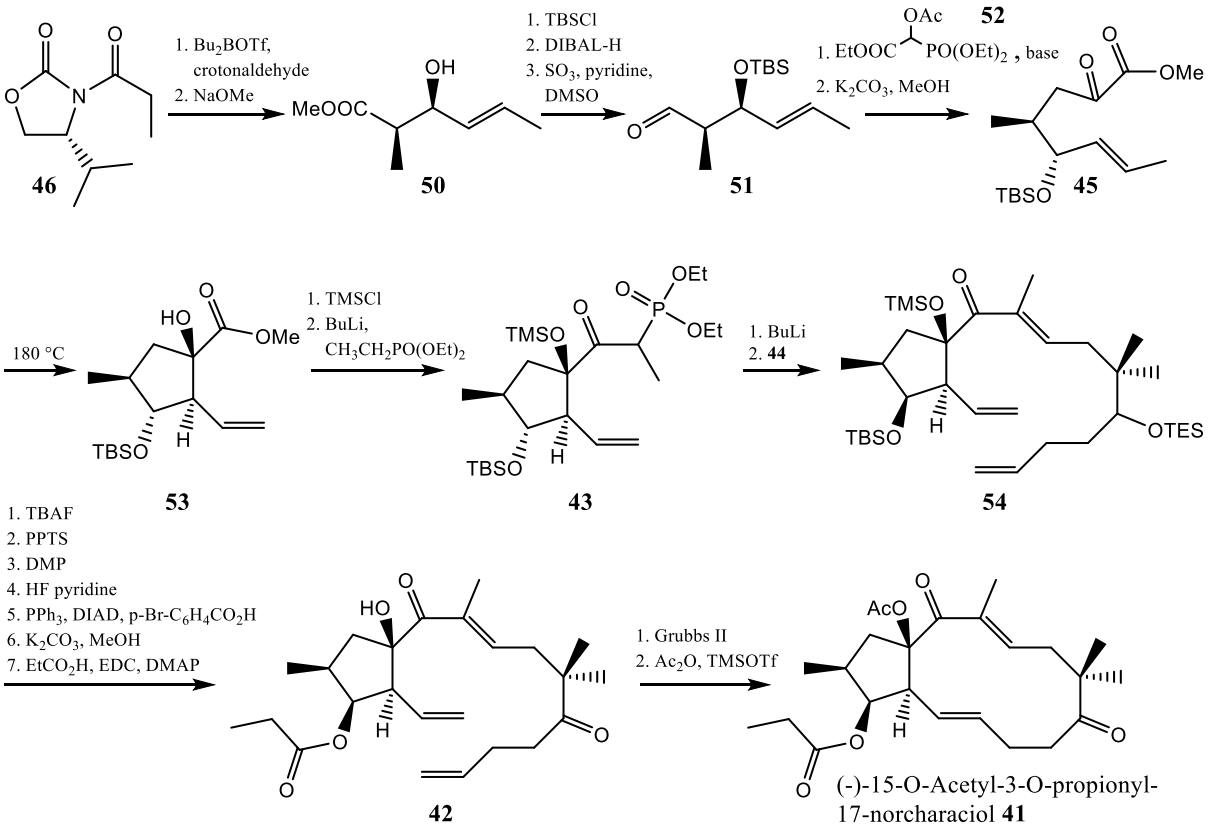

Figure 2.11

The forward synthesis commenced with Evan's aldol reaction of oxazolidinone **46** and crotonaldehyde, followed by cleavage of the chiral auxiliary to yield ester **50**. Protection of secondary alcohol and subsequent reduction followed by reoxidation gave aldehyde **51**, which was converted into a-keto ester **45** by means of a Horner-Wadsworth-Emmons olefination. Heating mentioned compound **45** initiated pivotal cyclization to afford intermediate **53** as main diastereomer.

The synthesis was continued with a Claisen-type condensation, which provided phosphoryl compound **43.** Said intermediate was deprotonated subsequently and treated with aldehyde **44** to afford the a,β-unsaturated ketone **54**. The trimethylsilyl and triethylsilyl groups were cleaved and the secondary hydroxyl group was oxidized employing Dess-Martin periodinane. Next, the TBS group was cleaved and the configuration of attached carbon could be inverted by means of a Mitsunobu reaction to provide the corresponding benzoate. Subsequent transesterification facilitated the acylation of the secondary hydroxyl group in the presence of EDC and DMAP affording crucial intermediate **42**. The stage was now set for the RCM reaction exploiting Grubbs II catalyst, followed by acetylation of the tertiary hydroxyl moiety to give (-)-15-O-Acetyl-3-O-propionyl-17-norcharaciol **41**.

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It has to be pointed out that the authors additionally planned the synthesis of (-)-15-O-Acetyl-3-O-propionylcharaciol **56**. Unfortunately, the crucial RCM reaction of prepared intermediate **55** did not work in all their attempts.

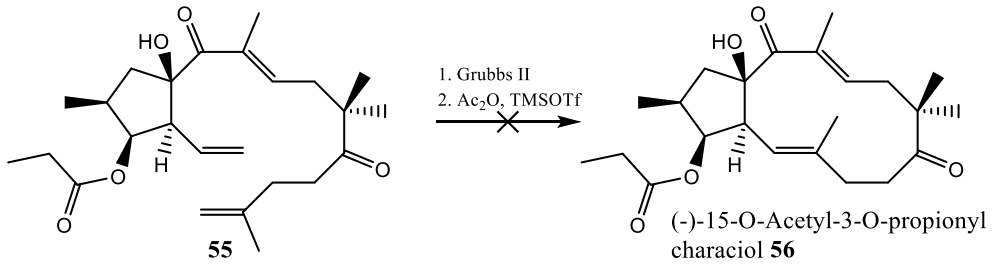

Figure 2.12

However, they successfully accomplished the total synthesis of **56** three years later in a modified approach.[17]

2.2 Partial Syntheses

2.2.1 *Yamamura et al.* 1993

In 1993, *Yamamura et al.*[18] published a synthesis of cyclopentane building block **58** en route to euphoscopin A **57**.

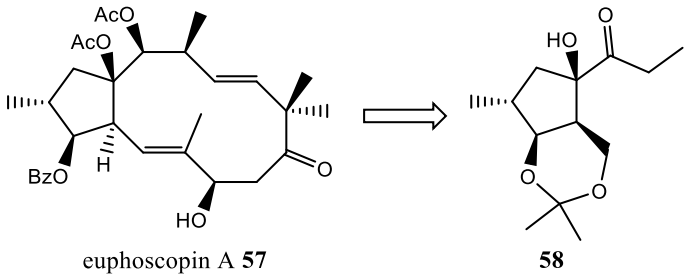

Figure 2.13

Chiral cyclopentene derivative **59** was chosen as starting material, assuming that the chiral information already present could control the formation of the remaining stereogenic centers.

Said fragment **59** was first protected, subsequent dihydroxylation employing OsO_4, and protection of formed diol gave intermediate **60**. Four additional steps were needed to convert **60** into enone **61**. The missing methyl group was installed by means of an 1,4-addition, reduction of formed ketone with L-selectride and following protection afforded compound **62**.

The acetal was then cleaved under acidic conditions, protection and Dess-Martin oxidation yielded ketone **63**. Methenylation employing Petasis' reagent and subsequent oxidative hydroboration formed a 1,3-diol, which was protected to furnish dimethyl acetal **64**.

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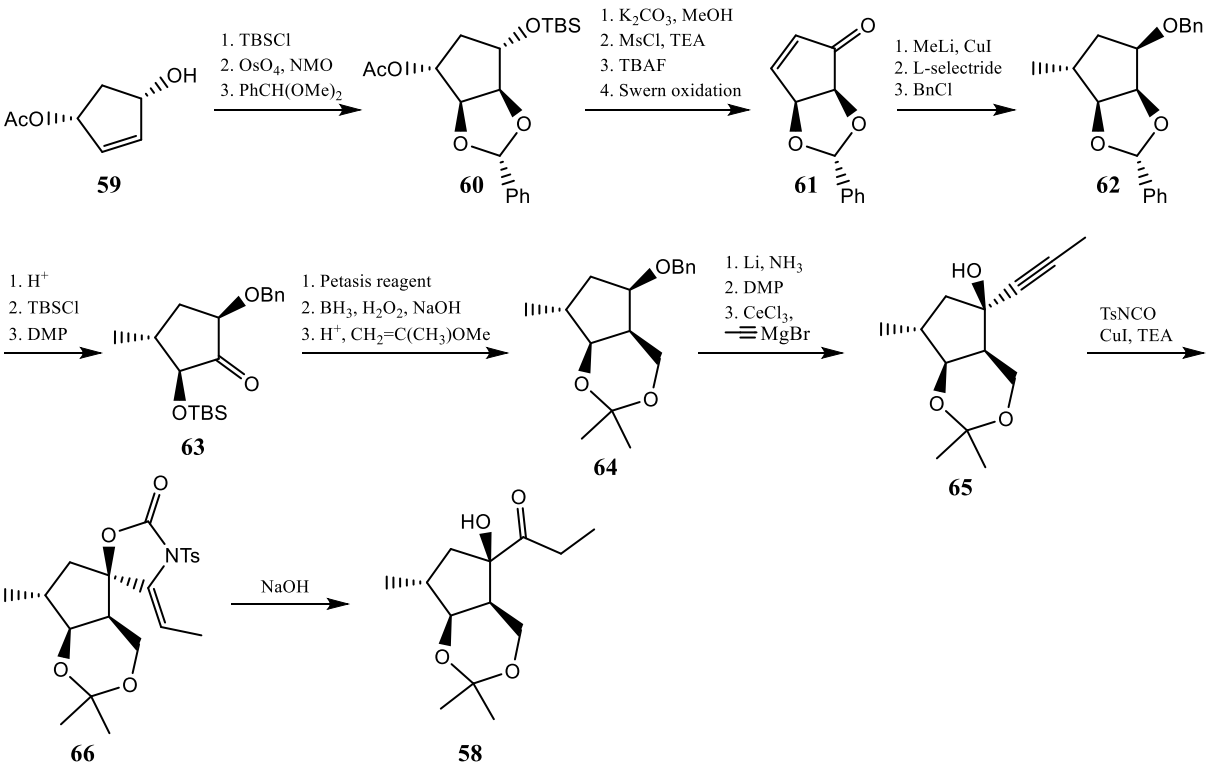

Figure 2.14

Intermediate **64** was then treated with lithium and ammonia to cleave the benzyl group, the ketone furnished by subsequent oxidation was then treated with 1-propynylmagnesiumbromide in the presence of cerium(III) chloride to give ynol **65**. Said compound **65** was further elaborated to cyclic carbamate **66** employing tosyl isocyanate, final hydrolysis provided desired cyclopentane fragment **58**.

2.2.2 *Mulzer et al.* 2004

In 2004, *Mulzer et al.*[19] published a synthesis of cyclopentane fragment **68** as building block for preparation of euphosalicin **67**. Up to the present day their work is the only known synthesis to such a highly substituted cyclic synthon with *trans* 1,2-diol moiety.

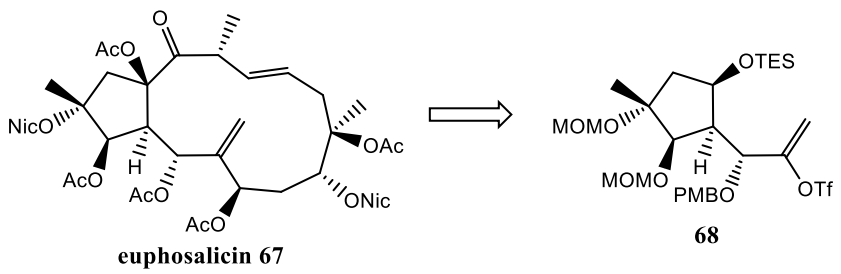

Figure 2.15

The synthesis commenced with deprotection-oxidation of cyclopentene **69** to furnish enone **70**, which was further elaborated to tertiary alcohol **71**. Amide **72** was then produced *via* substrate controlled Eschenmoser-Claisen rearrangement. Said compound was then treated with *in situ* generated DMDO to give an epoxide, which in the course of purification underwent regioselective opening to form lactone **73**.

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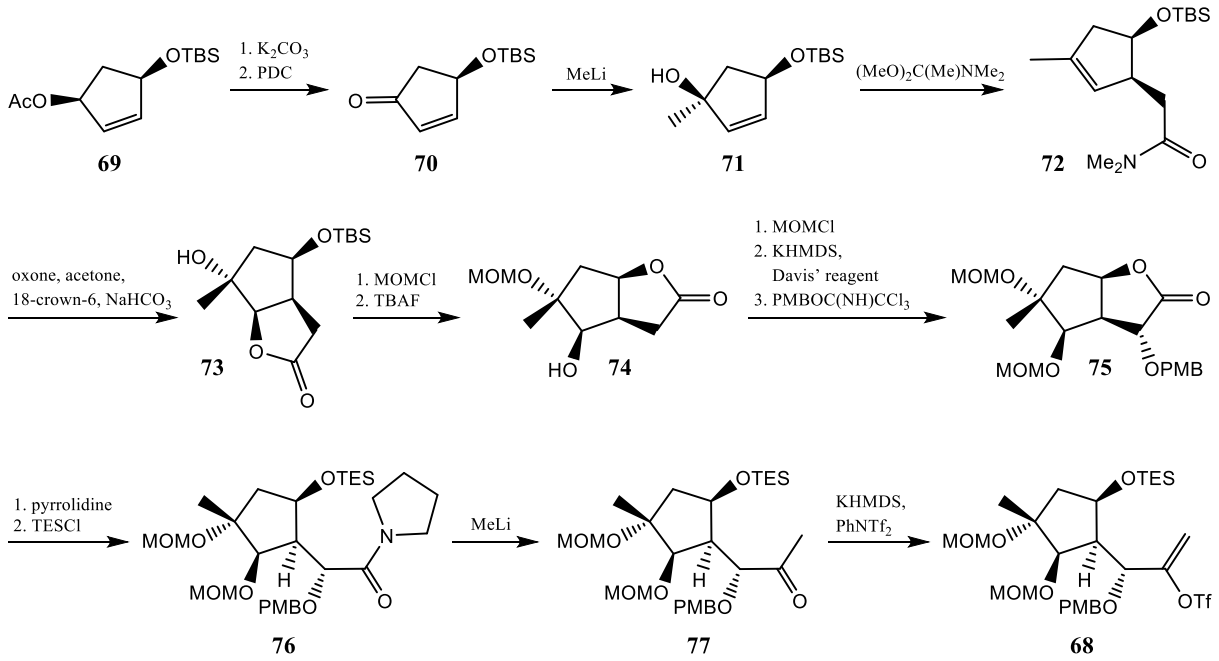
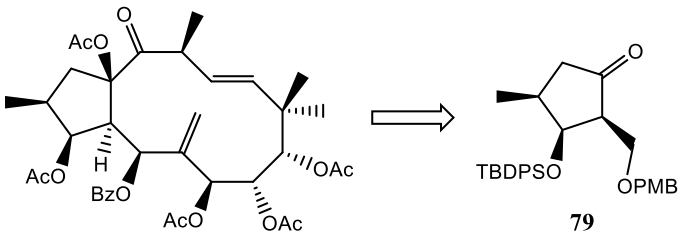


Figure 2.16

Routine protecting group manipulations triggered intramolecular *trans*-lactonization to afford lactone **74**. Said intermediate was then converted into compound **75** in a three-step procedure employing Davis' reagent for a-oxidation. Treatment with pyrrolidine and subsequent protection furnished amide **76**, which was further converted to ketone **77** employing methyl lithium. Finally, enolization with base and enolate trapping with phenyl triflimide gave desired vinyl triflate **68**.

2.2.3 *Rinner et al.* 2009

Rinner et al. reported an RCM based synthesis of cyclopentanone synthon **79** en route to altotibetin A **78** in 2009.[20]



altotibetin A **78**

Figure 2.17

Starting with chiral alcohol **80**, the synthesis proceeded with oxidation and subsequent stereoselective C2-elongation to afford β-hydroxyester **81**. Transesterification gave corresponding methyl ester, which was further transformed into intermediate **82** *via* hydroxymethylation.

Conversion of the formed primary alcohol into the corresponding tosylate and following elimination yielded a,β-unsaturated ester. Subsequent protection provided compound **83**.

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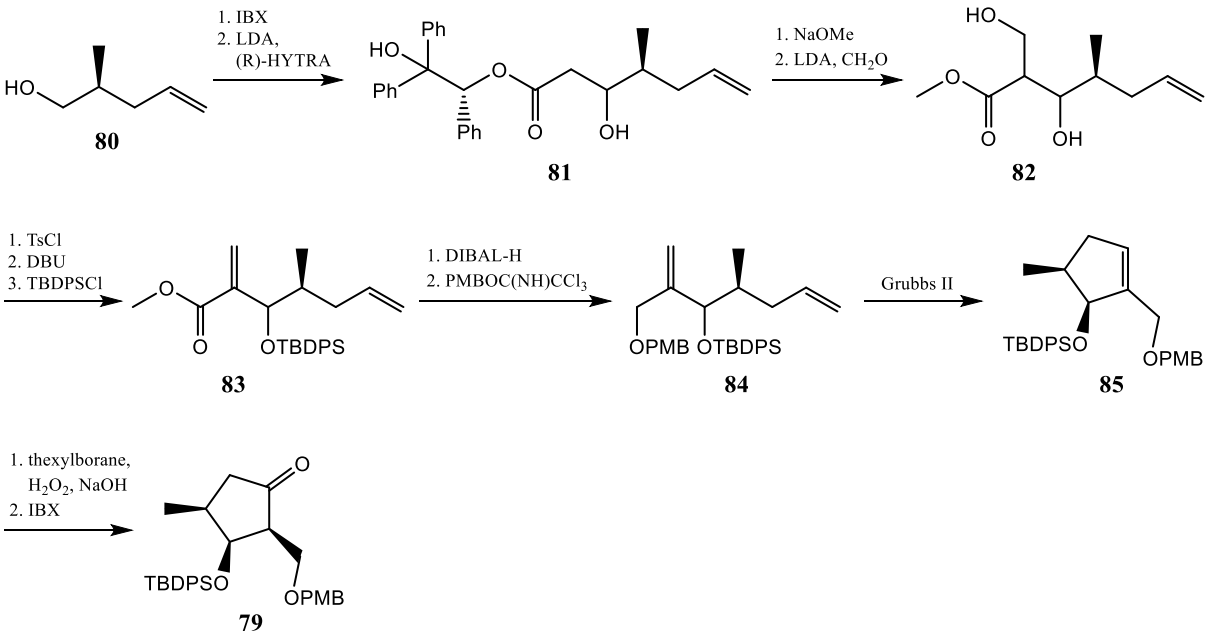

Figure 2.18

The ester functionality was further reduced and then converted to PMB-ether **84**, which was then treated with Grubbs 2nd generation catalyst to undergo the crucial RCM reaction affording cyclopentene **85**. Oxidative hydroboration and subsequent oxidation provided desired cyclopentanone fragment **79**.

A few years later, *Rinner et al.* published two approaches to the structurally similar compounds **86** and **87**.[21,22]

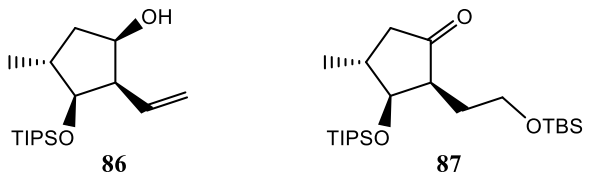

Figure 2.19

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3 Synthetic Work

3.1 Retrosynthetic analysis

In the course of this approach to the total synthesis of euphosalicin **67**, said compound is planned to be synthesized *via* a late-stage ring-closing metathesis elaborating the macrocycle. The necessary diene **88** could be accessible *via* Seebach reaction of ketone **89** with thioacetal-protected chiral 2-methyl-3-butenal **90**.

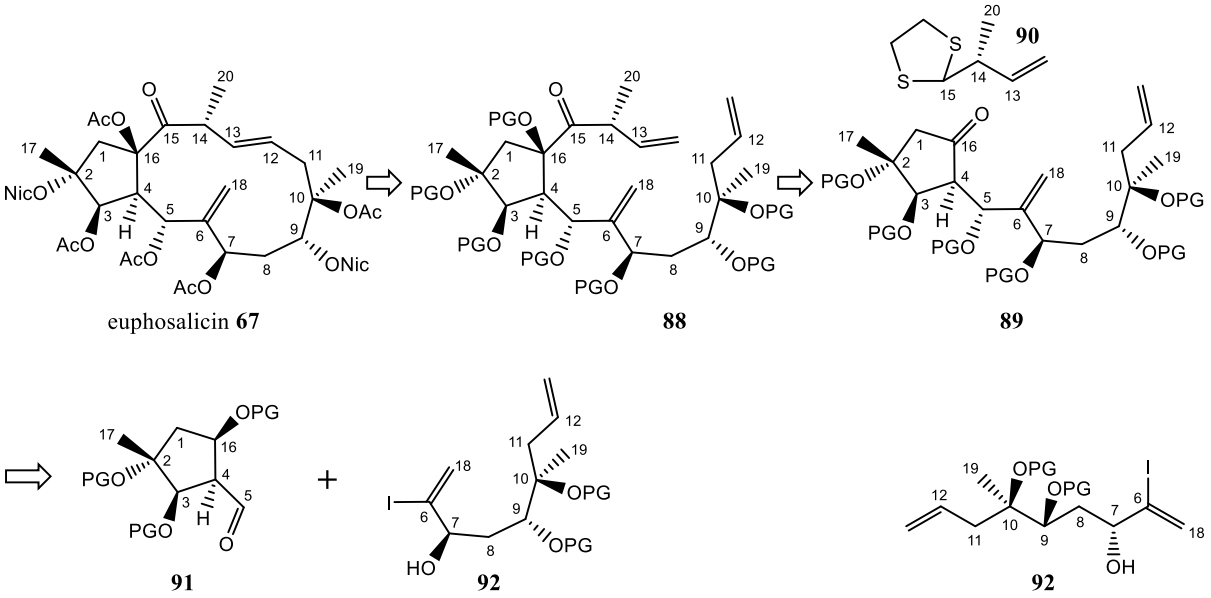

Figure 3.1

Intermediate **89** in turn is intended to be synthesized *via* addition of vinyl iodide **92** to aldehyde **91**, including the cyclopentane moiety. It is now apparent that this approach relies on the combination of the two key fragments **91** and **92**.

In the course of this diploma thesis the emphasis has been set on the synthetic route towards key structure **92**, of which the retrosynthetic analysis is shown in the following schemes.

Vinyl iodide **92** could be accessible *via* Wittig olefination of aldehyde **93**, which itself is planned to be elaborated from primary protected alcohol **94**. The vinyl iodide moiety is intended to be synthesized out of terminal alkyne **95**, which in turn could be available from aldehyde **96** *via* enantioselective C2 elongation.

At this point, different pathways are planned to be investigated. Whereas in approach A, mentioned aldehyde **96** may be constructed *via* asymmetric dihydroxylation of olefin **97**, approaches B and C rely on reduction of ester **98** and anti-Markovnikov addition of water to alkyne **99**, respectively.

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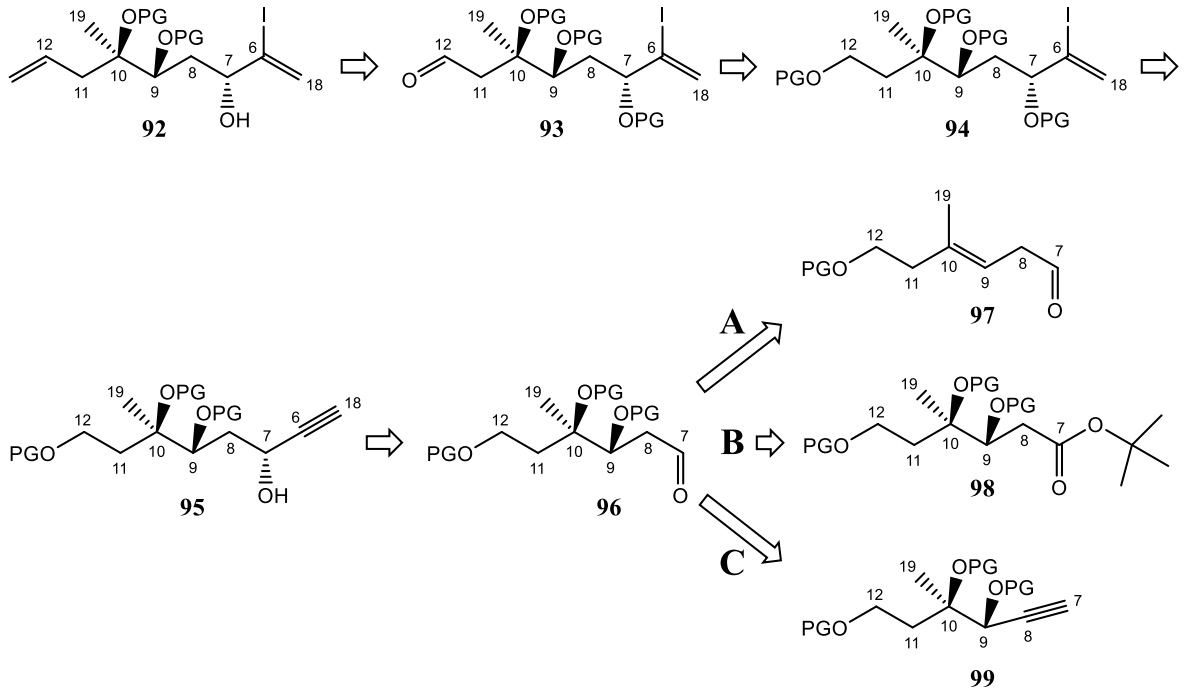

Figure 3.2

3.1.1 Approach A

Approach A is split up into two subpathways, A1 and A2. In approach A1, desired olefin **97** is planned to originate from enol ether **100** *via* acidic cleavage. Said compound **100** is intended to be constructed out of vinyliodide **101** applying a Stille cross-coupling reaction.

In approach A2, however, intermediate **97** could be accessible from free alcohol **102** through oxidation, the primary hydroxyl functionality is planned to be installed using oxidative hydroboration conditions on conjugated diene **103**. Said intermediate could be formed out of vinyliodide **101** *via* Kumada cross-coupling.

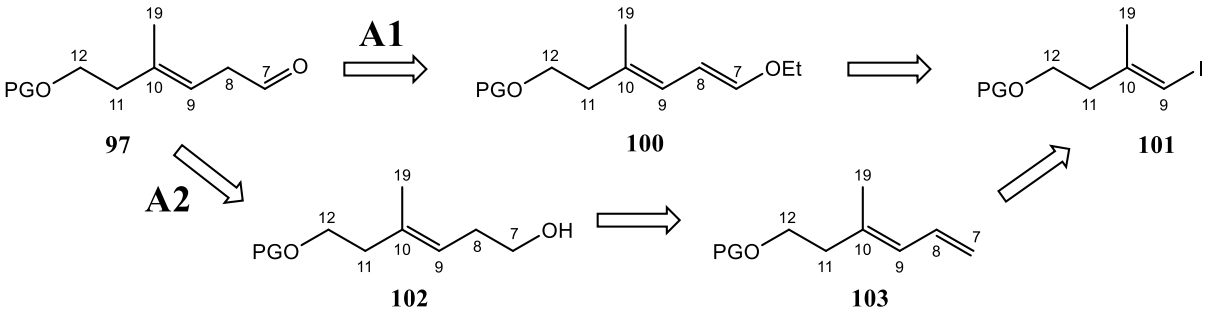

Figure 3.3

3.1.2 Approaches B & C

Both intermediates, **98** and **99**, could originate from the corresponding olefins **104** and **105** applying asymmetric dihydroxylation. Said compounds could be constructed from crucial intermediate **101** *via* Negishi and Sonogashira cross coupling, respectively.

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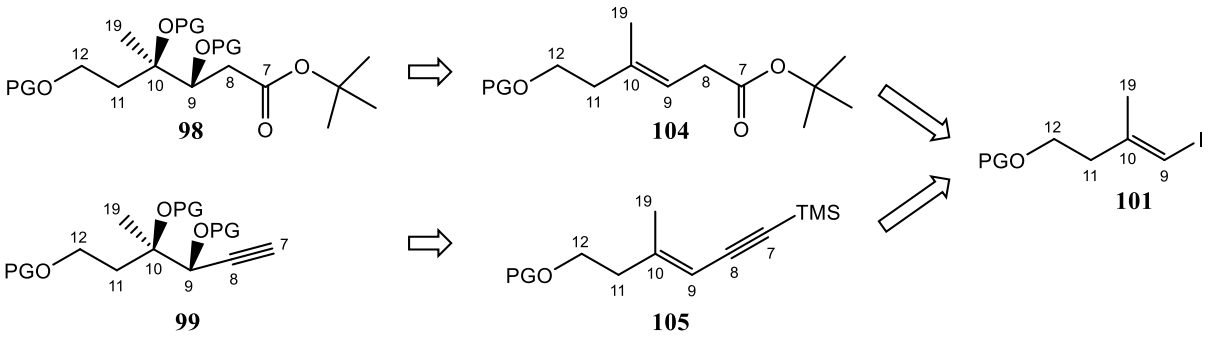

Figure 3.4

Mentioned vinyl iodide **101**, which is planned to be the starting point of all different approaches, could be accessible from commercially available 3-Butyn-1-ol **106** *via* carboalumination.

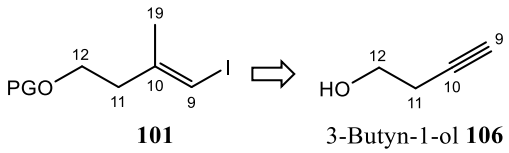

Figure 3.5

3.2 Syntheses

3.2.1 First steps – Preparation of crucial vinyl iodide

The synthesis commenced with the protection of the primary hydroxyl functionality of 3-Butyn-1-ol. *tert*.-Butyldimethylsilyl group (TBS) was chosen to mask the alcohol as silyl ether due to its expected stability towards all conditions of the following steps.

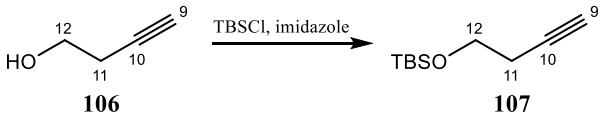

Figure 3.6

The standard procedure of silyl protections was applied, using TBS chloride and imidazole in DMF.

Subsequently, the triple bond was converted to *trans*-alkene **101**, introducing a vicinal methyl-iodide group based on the methylation-iodination conditions developed by *Negishi et al.*[23,24]

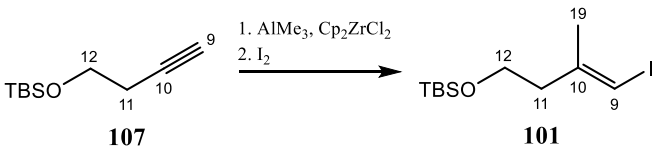

Figure 3.7

In addition to trimethyl aluminum, these conditions involve a zirconium catalyst facilitating Al-C bond formation. Resulting *in situ* generated (*E*)-2-methyl-1-alkenylalane **108** can easily be transformed into vinyl iodide by adding iodine.

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The reaction can be significantly accelerated by addition of water. By doing so, an oxo-bridged active species is generated *in situ*, which outperforms the chloro-bridged species significantly.[24]

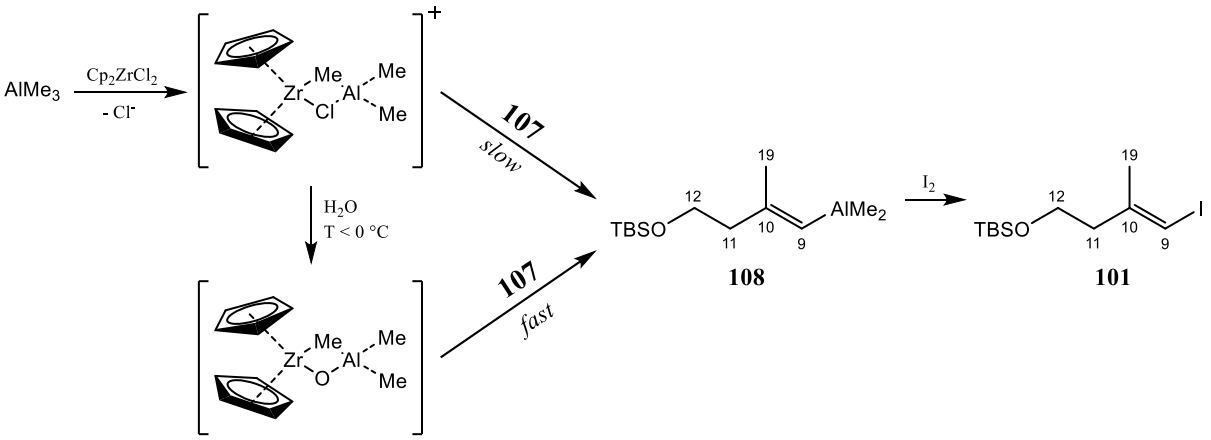

Figure 3.8

3.2.2 Approach A1

In approach A1, vinyl iodide **101** should be joined with stannane **109** in a palladium catalyzed Stille cross-coupling reaction, following a procedure of *Kwon et al.*[25]

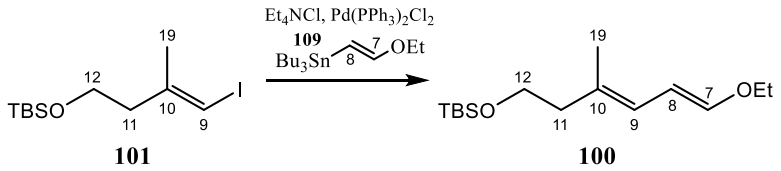

Figure 3.9

Unfortunately, the yields of this reaction did not exceed 35%. With this fact being unsatisfactory, further investigations were conducted and it was found out that an occurring side reaction had been responsible for the low yields.

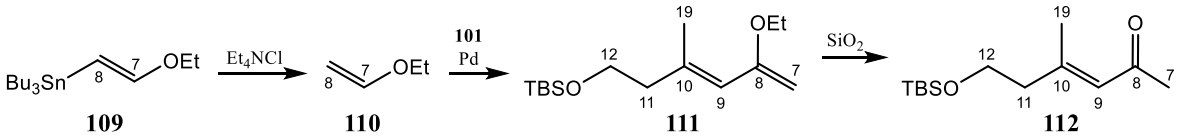

Figure 3.10

Tetraethylammonium chloride was capable of cleaving stannane **109** to form vinyl ethyl ether **110**, which, under the presence of palladium, underwent a Heck reaction with vinyl iodide **101**. Then, the acidity of Silica was powerful enough to cleave formed enol ether **111** to corresponding enone **112**. Up to 30% of the starting material was converted to undesired compound **112**, decreasing yields of the desired product significantly. Nevertheless, the synthesis was continued and the cleavage of enol ether **100** was investigated.

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Unfortunately, treatment with aqueous hydrochloric acid led to decomposition of the material. With the yield of the previous step being already unsatisfactory, approach A1 was discarded at this point.

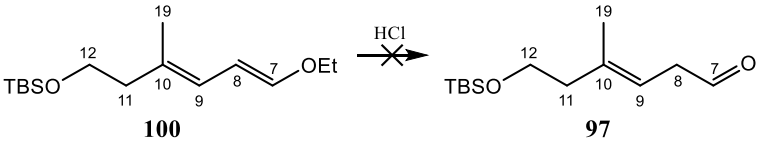

Figure 3.11

3.2.3 Approach A2

Approach A2 commenced with a palladium catalyzed Kumada cross-coupling reaction, elaborating diene **103** from vinyl iodide **101**.

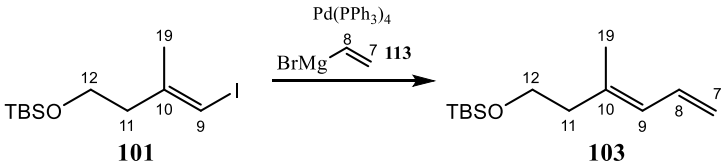

Figure 3.12

On the basis of a procedure from *Cazes et al.*[26], using vinylmagnesium bromide **113** and tetrakis(triphenylphosphin)palladium, this transformation was accomplished in high yields.

To introduce the primary hydroxyl functionality on position 7, the conversion of diene **103** to alcohol **102** was investigated, applying common hydroboration conditions.

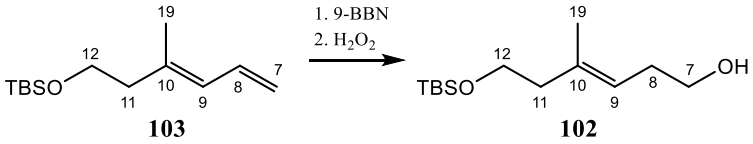

Figure 3.13

9-BBN was chosen as sterically hindered hydroborating agent to ensure addition to the terminal double bond with high regioselectivity. Oxidative workup adding hydrogen peroxide furnished desired primary alcohol **102**, but yields did not exceed 40% in all attempts. Unfortunately, all efforts to optimize the yields by increasing the added amounts of 9-BBN and H_2O_2 failed.

Despite low yields in this hydroboration reaction, synthesis was carried over to the next step. The approach continued with the oxidation of primary alcohol **102** to aldehyde **97**. The standard procedure of Dess-Martin oxidation was applied.

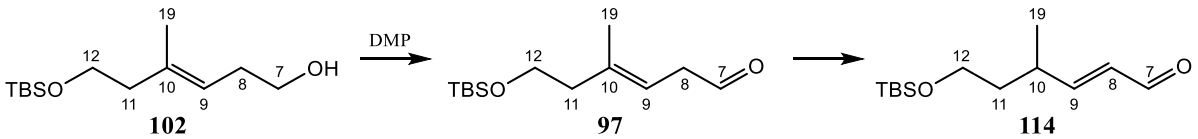

Figure 3.14

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However, desired product **97** was not stable, particularly the double bond migrated, forming the a,β-unsaturated carbonyl compound **114**. This process could already be observed during the reaction and was even accelerated by exposure to acidic Silica. Considering the low yields of the hydroboration reaction and the stability issues of desired product **97**, approach A2 was also discarded.

3.2.4 Approach B

A new approach was then started, stepping back to vinyl iodide **101** and converting it to *tert*. butyl ester **104**. Therefore, a palladium catalyzed Negishi cross-coupling was carried out, modifying procedures from *Huang et al.*[27] and *Tomooka et al.*[28]

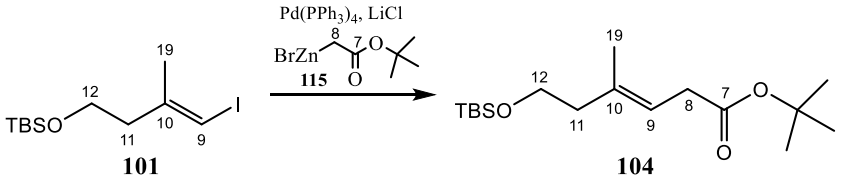

Figure 3.15

Tert.-butyl bromoacetate served as precursor for preparation of zinc-organyle **115**, according to Huang's protocol.[27] In addition to the procedure published by *Tomooka et al.*[28] lithium chloride was added to enhance the reactivity of the palladium. With these conditions applied, the reaction proceeded smoothly.

Considering the tendency of the double bond to migrate to the a,β-unsaturated carbonyl compound, it was decided to do the essential dihydroxylation at this point.

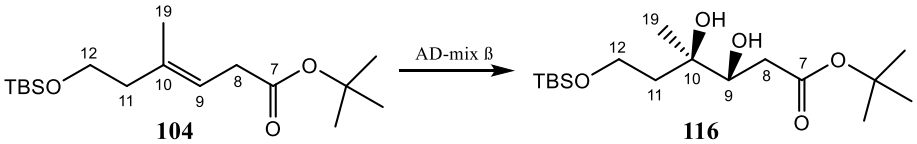

Figure 3.16

Carrying out a Sharpless asymmetric dihydroxylation, a procedure of *Kobayashi et al.* was investigated, using a three-times more concentrated AD-mix in a 1:1 mixture of *tert*-butanol/H_2O.[29]

According to the mnemonic device developed by *Sharpless et al.*[30], AD-mix-β (containing dehydroquinidine ligand) was chosen because an *R,R* configuration of the formed *cis*-vicinal diol **116** has been desired.

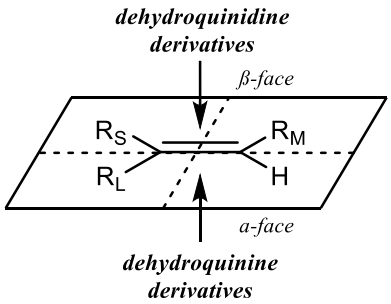

Figure 3.17 Mnemonic decive developed by Sharpless et al. [30]

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Achieving enantioselectivity was the sole challenge of this reaction. In the first attempts, only a 3:1 mixture in favor of the desired enantiomer could be synthesized. While decreasing the concentration of the substrate by the factor two did not lead to significant improvements, enhancement of the concentration in combination with modifying the style of stirring could improve the selectivity significantly.

Table 3.1 Optimization of the Sharpless Dihydroxylation

No.	molarity [mol/L]	style of stirring	ratio (*R*/*R* : *S*/*S*)	*ee* [%]
1	0.10	magnetic	3:1	50
2	0.05	magnetic	3:1	50
3	0.30	mechanically	9:1	80

The enantiomeric excess (*ee*) of performed dihydroxylations was determined *via* Steglich esterification with Mosher's acid to ester **117**. By doing so, diastereomers were obtained, which could be distinguished and quantified in recorded ^{1}H and ^{19}F NMR spectra.

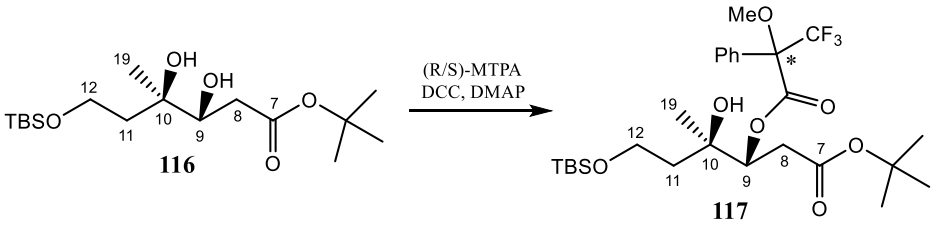

Figure 3.18

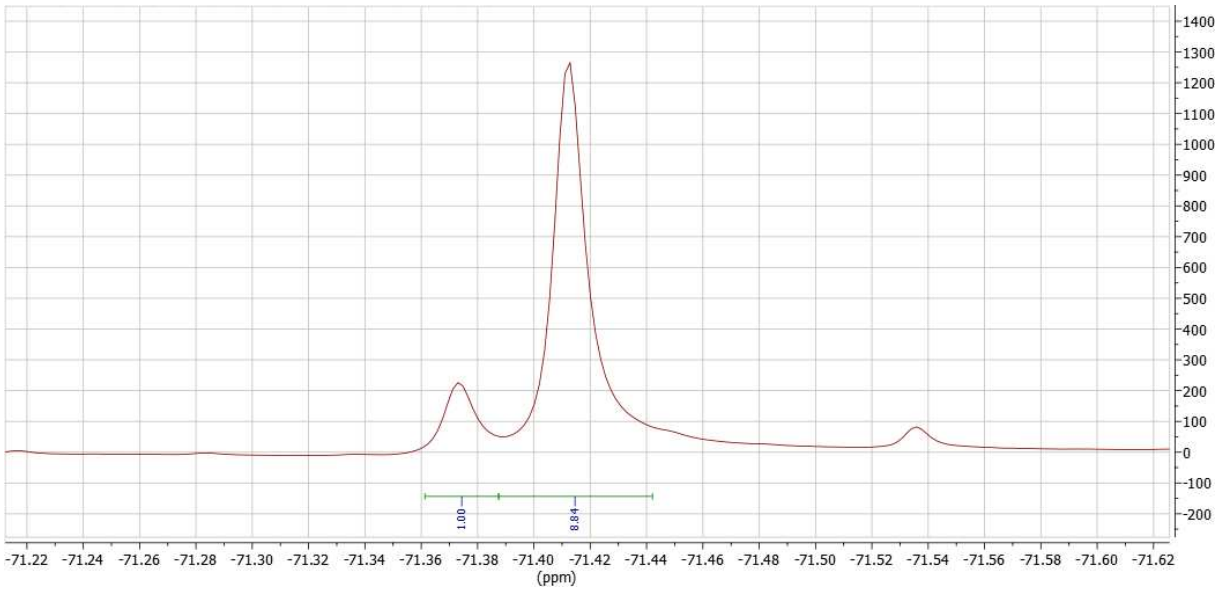

Figure 3.19

Understanding the influence of the intensity of stirring requires a deeper insight in the mechanism of the Sharpless AD, which has been extensively studied.[31,32]
After addition of the ligand and the alkene to osmium tetroxide, the osmylate ester intermediate is oxidized before it is hydrolyzed, giving the *cis*-vicinal diol and reforming the osmium tetroxide. While the addition takes place in the organic phase, the hydrolysis happens in the aqueous phase of the biphasic mixture. (see *Figure 3.20*)

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It is known that a secondary catalytic cycle can also occur where the oxidized osmylate ester intermediate may dihydroxylate another alkene.[33] Dihydroxylations resulting from this secondary pathway generally suffer lower enantioselectivities than those resulting from the primary pathway.

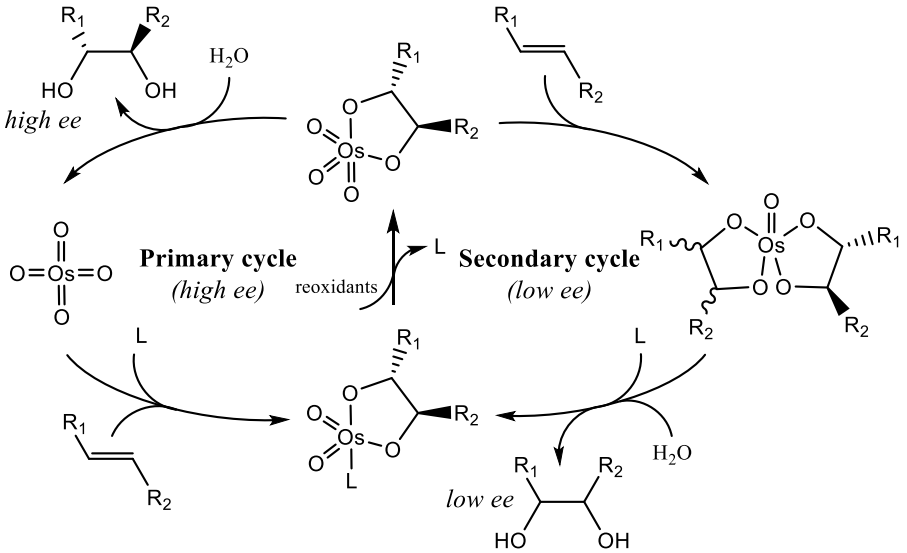

Figure 3.20 Primary and Secondary cycle of the asymmetric dihydroxylation [33]

The distribution between the two cycles is determined by the rate difference between hydrolysis and addition. By increasing the rate of hydrolysis, occurrence of the secondary cycle can be avoided.

A high rate of hydrolysis can be achieved by a quick transfer of the oxidized osmylate ester to the aqueous phase. Apparently, magnetic stirring only provides insufficient phase transfer, which explains the significantly higher enantioselectivity, if mechanical stirring is applied. (see *Table 3.1*)

In continuation, transformation of the formed diol **116** to acetal **98** was carried out. Said compound was obtained *via* treatment of **116** with 2,2-dimethoxypropane **118** under acidic conditions.

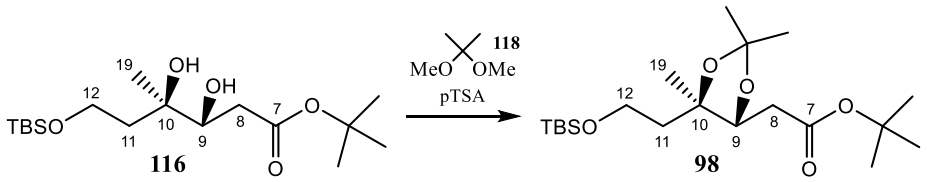

Figure 3.21

To complete approach B, ester **98** was reduced to aldehyde **96** applying a routine procedure employing DIBAL-H.

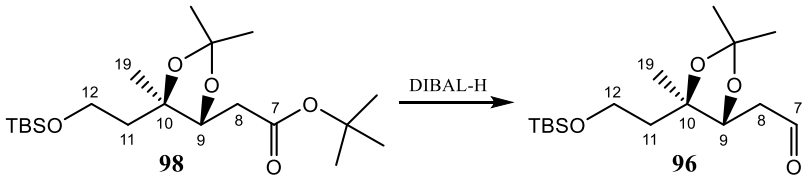

Figure 3.22

To prevent further reduction, the reaction was carried out at low temperatures and exactly one equivalent of the reducing agent was used.

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3.2.5 Approach C

Simultaneously, reactions of approach C were investigated, starting with the conversion of vinyl iodide **101** to enyne **105** by means of a Sonogashira cross-coupling.

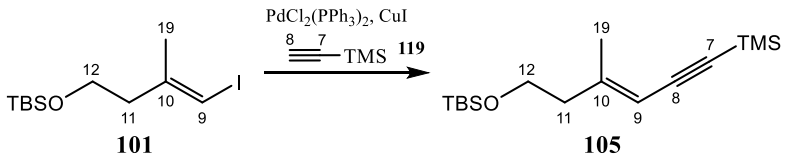

Figure 3.23

On the basis of a procedure published by *Zhang et al.*[34], diethylamine was used as solvent and bis(triphenylphosphine)palladium chloride was exploited as catalyst. Additionally, CuI served as copper(I) source.

In analogy to approach B, the Sharpless asymmetric dihydroxylation was carried out in the next step to obtain diol **120**.

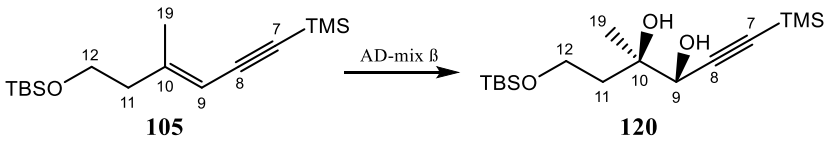

Figure 3.24

Same optimized procedure (see *Chapter 3.2.4.2*) was applied and the enantiomeric excess was as well determined *via* Mosher's esterification.

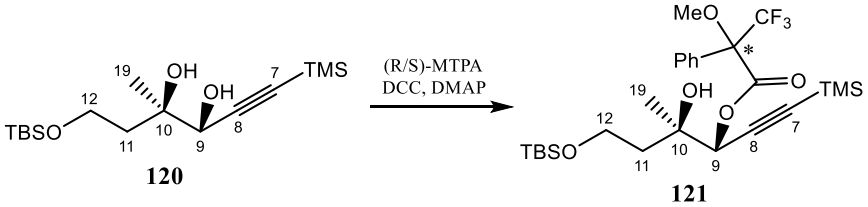

Figure 3.25

Analysis of Mosher ester **121** proved an enantiomeric excess of 82% (10:1), which is almost identical with the outcome of the dihydroxylation in approach B.

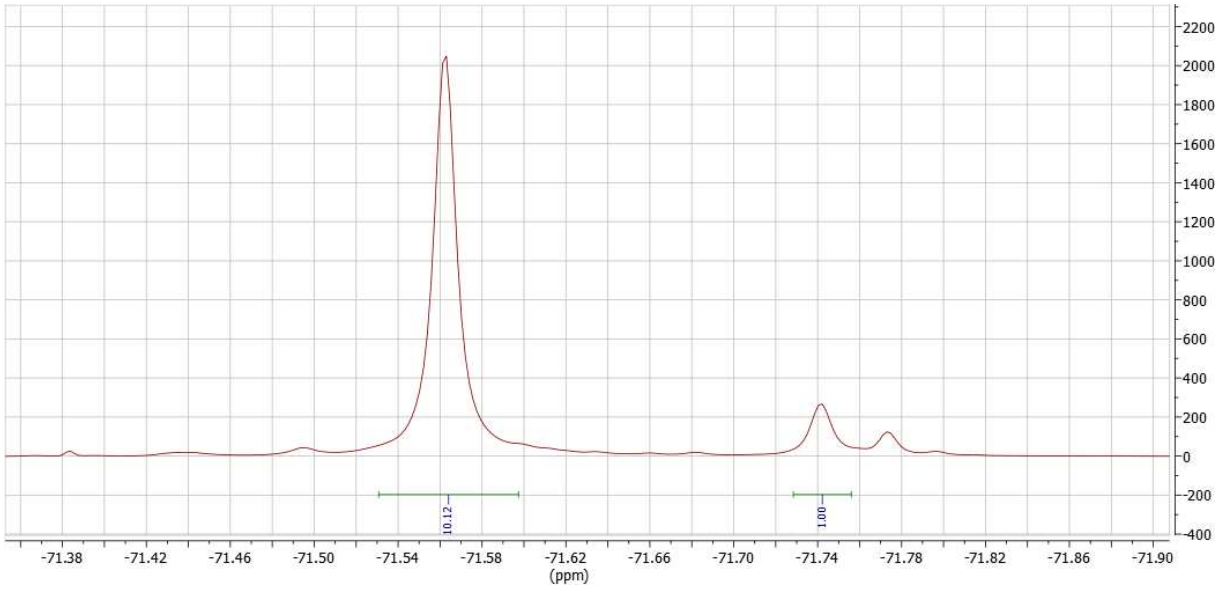

Figure 3.26

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Continuing the synthesis, the diol was protected as acetal to give compound **122**, of which the installed TMS-group was removed subsequently.

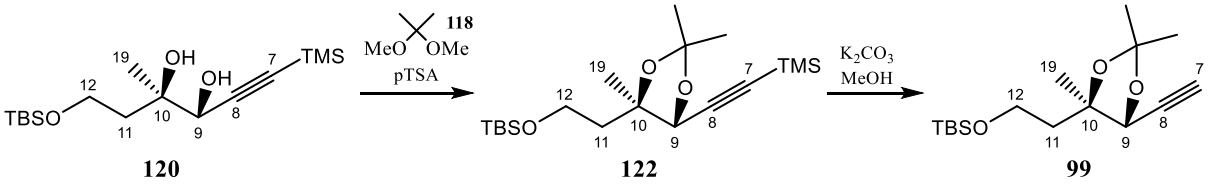

Figure 3.27

The conditions already known from approach B were applied to form the acetal. For the TMS cleavage common basic conditions in methanol were used, enabling access to terminal alkyne **99**.

Finally, the last step of approach C, namely the transformation of alkyne **99** to aldehyde **96**, was investigated. Trying said conversion with common hydroboration conditions did not lead to any success, therefore all efforts were focused on the more frequently cited anti-Markovnikov hydration of terminal alkynes, exploiting ruthenium catalysts.

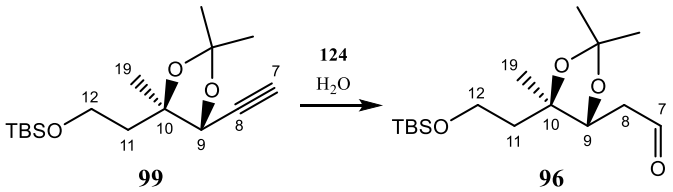

Figure 3.28

According to procedures published by *Oestreich*[35], compounds **123** and **124** were examined in terms of catalytic potential towards the hydration of **99**.
While species **123** did not show any activity, commercially available catalyst **124** reliably converted alkyne **99** to aldehyde **96**.

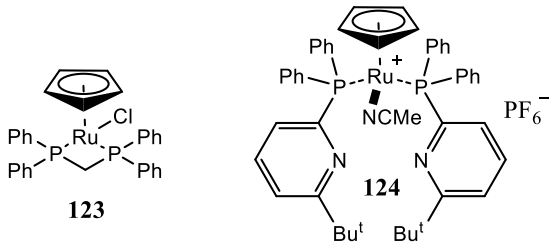

Figure 3.29

Carried out at increased temperatures and in aqueous environment, the greatest worry was the stability of the primary TBS group during the reaction. By using absolutely pure starting material to exclude any acidic residues from previous steps, this concern proved to be unfounded. Additionally, exclusion of air was crucial due to the high sensitivity of **124** to oxygen.

The catalytic cycle is generally believed to commence with protonation of the activated alkyne and proceed further over a ruthenium(IV)-vinylidene species. Next, the a-carbon is prone to nucleophilic attack and therefore readily reacts with a hydroxide anion. Formed 1-hydroxyvinyl complex instantaneously isomerizes to an acyl species, which is transformed to desired aldehyde *via* reductive elimination.[35]

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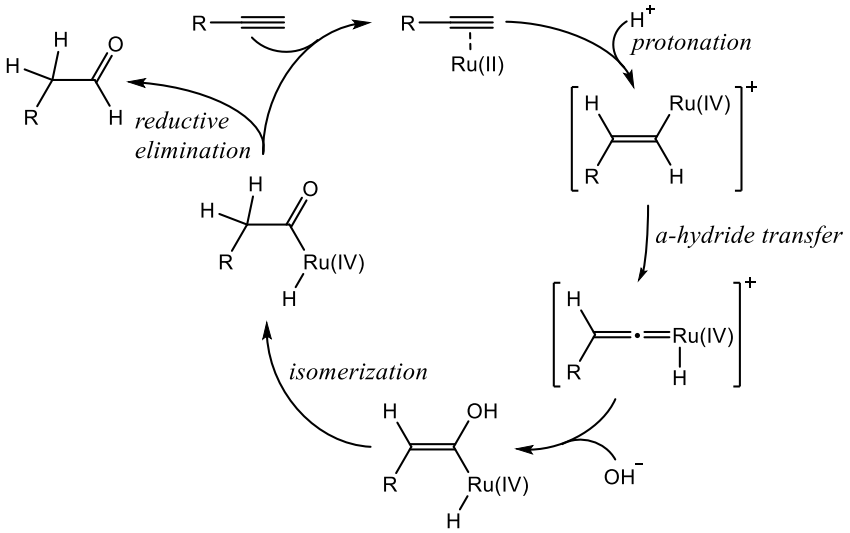

Figure 3.30 Catalytic cycle of the ruthenium catalyzed hydration[35]

3.2.6 Continuing the Synthesis – Stereoselective Acetylene Addition

With crucial aldehyde **96** in hand, synthesis could continue with the enantioselective addition of trimethylsilylacetylene to said compound. According to Carreira's protocol, desired *R*-configuration on carbon 7 could be expected, if (+)-*N*-methylephedrine was used as chiral auxiliary.[36]

In the presence of zinc triflate and base, compound **125** could be elaborated from aldehyde **96,** slightly modifying the procedure by *Carreira et al.*[36] In contrast to the published conditions, trimethylsilylacetylene **119** was used as acetylene source instead of 2-methyl-3-butyn-2-ol.

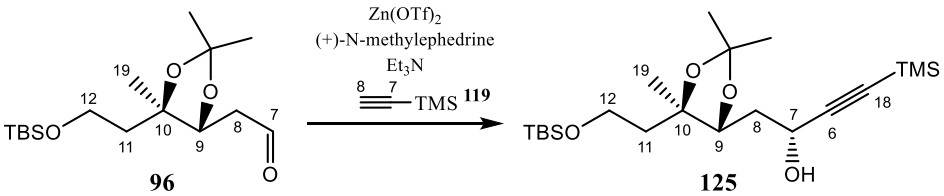

Figure 3.31

The reaction resulted in a diastereomeric ratio (*dr*) of 7:1 in favor of the desired diasteromer **125**. Considering that the enantiomeric ratio of the starting material was 9:1 (see *Chapter 3.2.4.2*), the addition alone gave a ratio of 35:1 considering solely the stereocenter at carbon 7.

Finally, the introduced TMS group was cleaved, applying the conditions already used in approach C. Intermediate **95** could be obtained in quantitative yields.

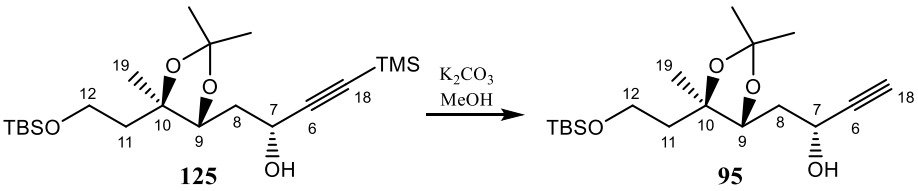

Figure 3.32

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3.2.7 Stereochemistry

To prove the stereochemistry of carbons 7, 9, and 10, the acetal as well as the TBS group were cleaved, exposing **125** to acidic conditions in methanol. The resulting tetraol **126** was then directly treated with anisaldehyde dimethylacetal **127** in the presence of zinc chloride to furnish a crude mixture containing bisacetal **128**. Additionally, other cyclic acetals originating in the formation of five and seven membered rings, as well as monoacetals, were formed.

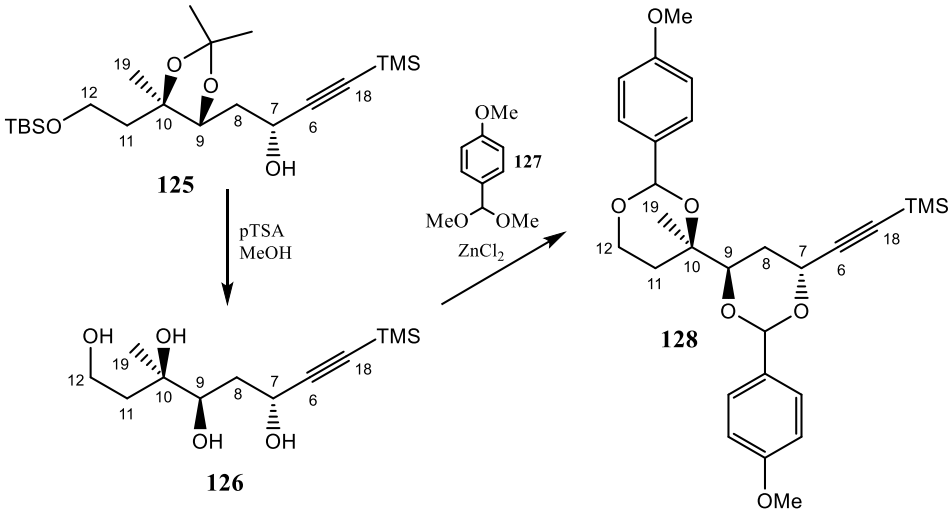

Figure 3.33

The original intention was to investigate the NOESY spectrum of **128**, which was hoped to give insight into the absolute configuration.

Luckily, however, compound **128** crystallized and was subjected to an X-RAY crystallography after recrystallization. Resulting crystallographic data proved that the configuration of all three stereocenters was in fact the desired one. (*Figure 3.36*)

Additionally, the absolute configuration of triol **130**, obtained by dihydroxylation of **129** with AD-mix-ß, had already been proven.[37]

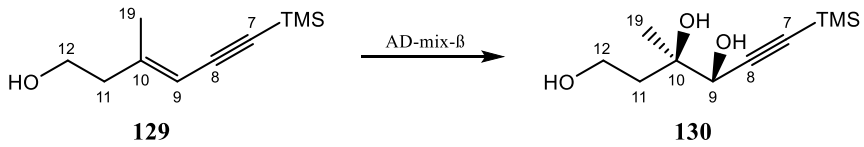

Figure 3.34

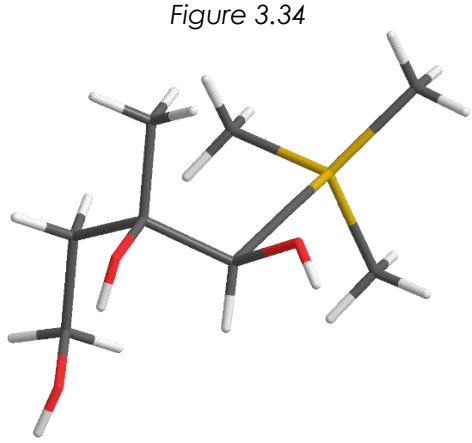

*Figure 3.35 X-Ray Structure of Triol **130**[37]*

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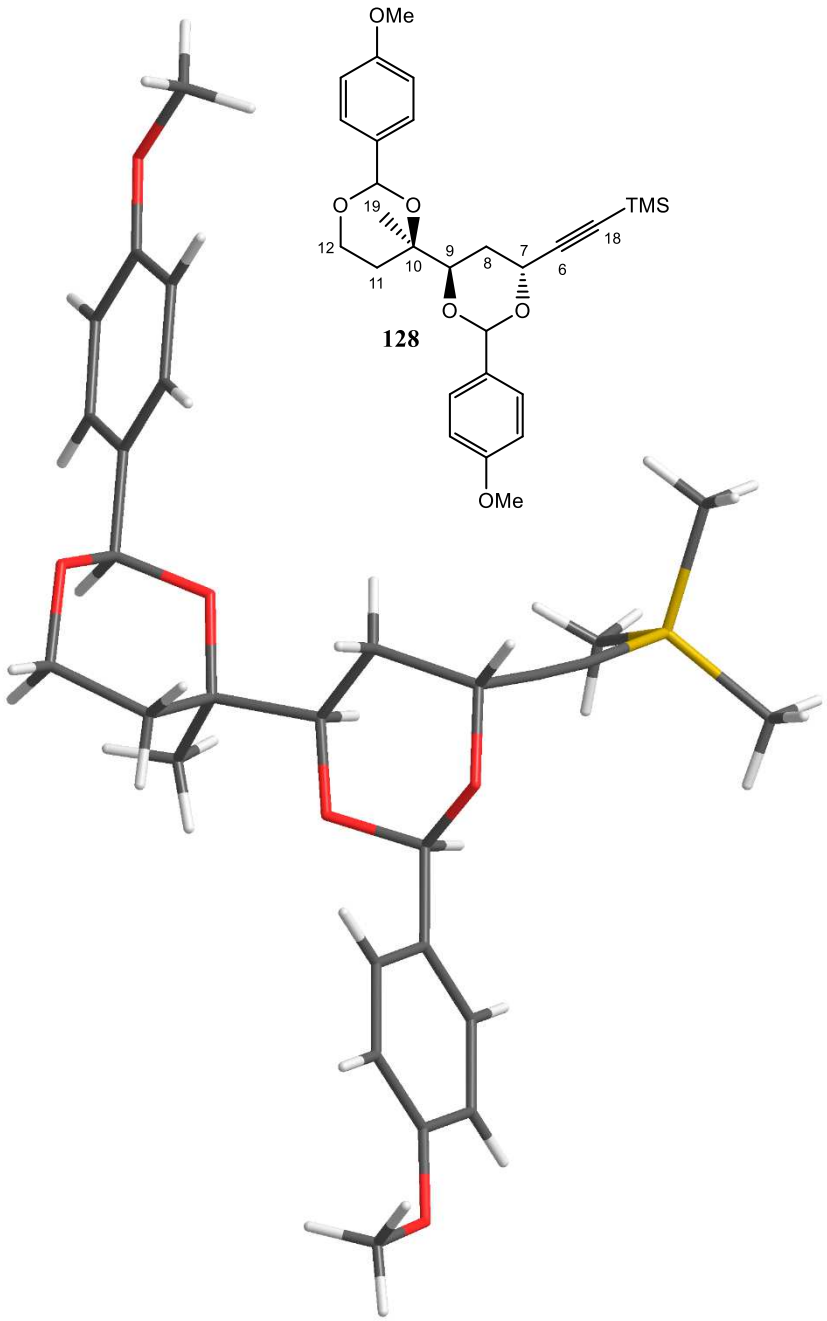

Figure 3.36 X-Ray Structure of bisacetal ***128***

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4 Conclusion and Outlook

4.1 Conclusion

In the course of this diploma thesis, a reliable route to compound **95** was elaborated, which is only a few steps away from key intermediate **92**.

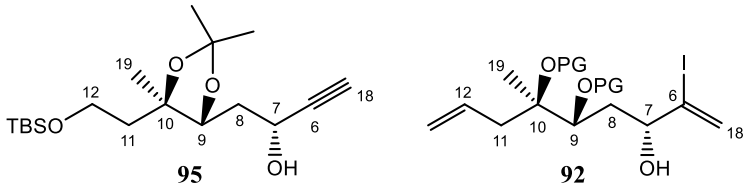

Figure 4.1

Commercially available 3-Butyn-1-ol **106** was transformed into compound **101** in two steps.

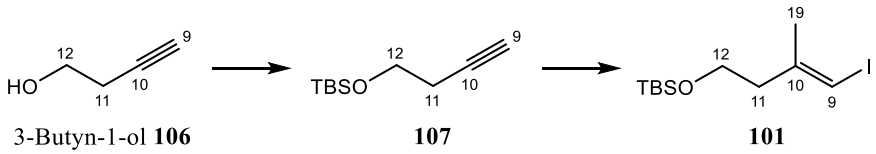

Figure 4.2

With vinyl iodide **101** in hand, different pathways to the synthesis of aldehyde **96** were investigated, of which pathways B & C were successful.

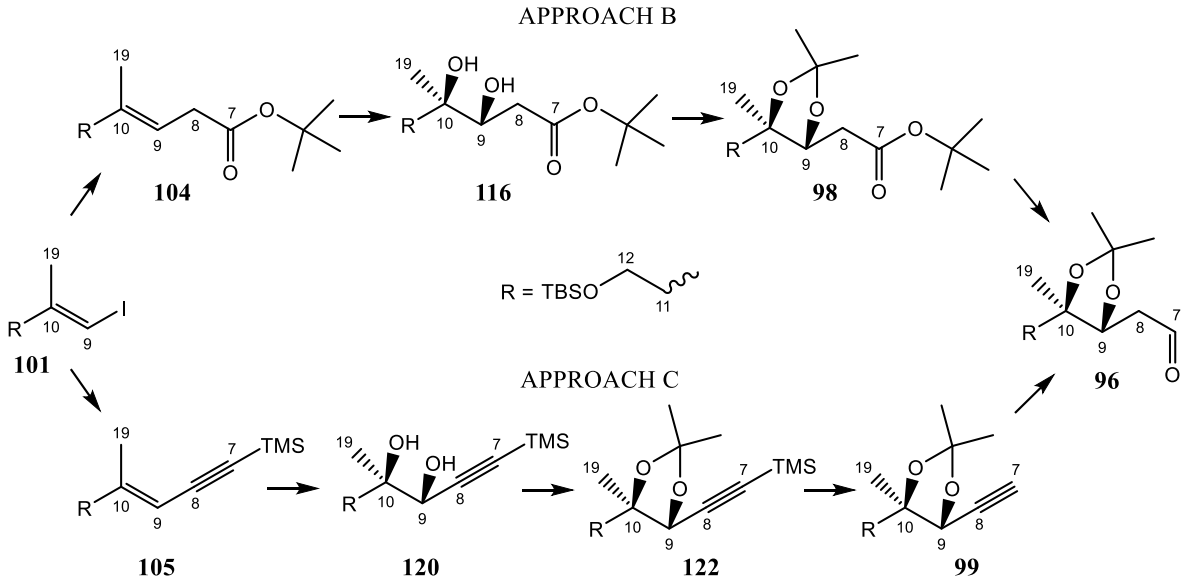

Figure 4.3

While approach B is shorter by one step and does not require an expensive catalyst, approach C could become handy in the construction of the cyclopentane fragment **91** in this approach towards the total synthesis of euphosalicin.
(see *Chapter 4.2 Outlook*)

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In continuation, terminal alkyne **95** was synthesized out of aldehyde **96** in two steps.

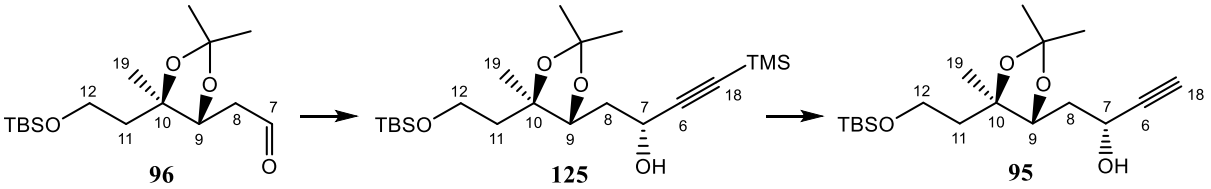

Figure 4.4

During the synthesis, several reactions and their conditions were optimized, including a significant increase of enantioselectivity for the dihydroxylation reactions. Additionally, the absolute configuration of intermediate **95** could be proven *via* the synthesis of a crystalline derivative and subsequent X-RAY crystallography.

Every step was optimized to yields of 70% and higher, therefore the developed routes provide access to compound **95** in large scale.

4.2 Outlook

Concerning the synthesis of key intermediate **92**, only a few steps are missing. First, the vinyl iodide moiety is planned to be installed *via* hydrozirconation[38] or hydrosilylation[39], followed by iodination. Then, deprotection of the primary TBS group, subsequent oxidation and Wittig olefination could provide desired product **92**.

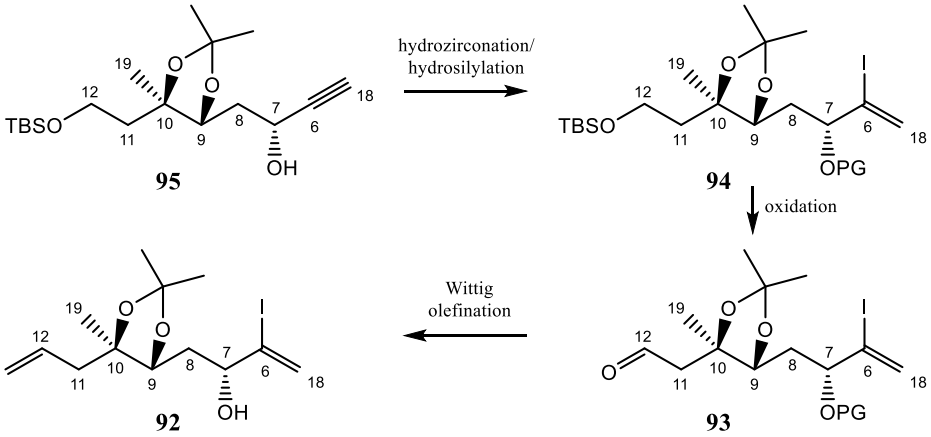

Figure 4.5

As already mentioned, intermediate **122**, which was synthesized in approach B, could give access to cyclopentane fragment **91**, the second key intermediate in this approach towards the synthesis of euphosalicin.

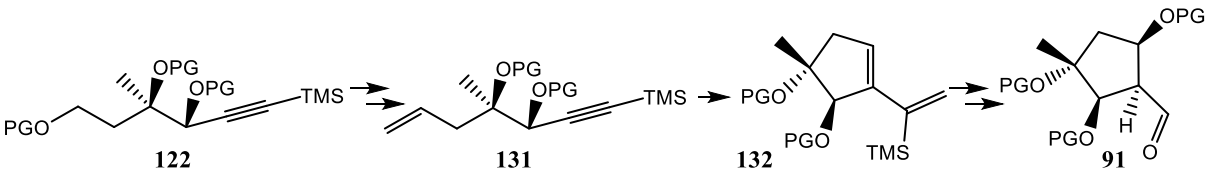

Figure 4.6

In this regard, intermediate **122** could be the starting point for construction of compound **131**, which in turn could be a potent substrate for a ring closing enyne metathesis (RCEYM) providing cyclopentene moiety in **132**.

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5 Experimental Part

5.1 General Remarks

Commercial reagents were - unless specified otherwise - used without further purification. Absolute solvents were dried by using a PURESOLV facility. Reaction flasks were either oven-dried at 110 °C or flame-dried. For oxygen- and moisture-sensitive reactions, Schlenk techniques with slight argon overpressure were used. Sensitive solutions and liquids were transferred *via* syringes through rubber septa. Unless otherwise noted, reactions were stirred magnetically.

5.1.1 Chromatography

Thin Layer Chromatography

TLC was carried out on silica gel plates on aluminum support (Merck, silica gel 60 F_{254}). The visualization of spots was obtained *via* heat staining using a solution of ceric ammonium molybdate in EtOH/H_2SO_4 or *p*-anisaldehyde in EtOH/AcOH/H_2SO_4.

Column Chromatography

Preparative column chromatography was conducted manually using glass columns packed with silica gel 60 (Merck, 40-63 µm) under slight overpressure.

5.1.2 Analysis

NMR

NMR measurements were recorded on either Bruker Avance 200 (200 MHz) or 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 $CDCl_3$ (7.26 ppm) as the internal reference.

HRMS

HRMS measurements were carried out from solutions in methanol (concentration: 10 ppm) by using an HT CPAL system autosampler (CTC Analytics AG, Zwingen, Switzerland), an Agilent 1100/1200 HPLC with binary pumps, degasser and column thermostat (Agilent Technologies, Waldbronn, Germany) and an Agilent 6230 AJS ESI–TOF mass spectrometer (Agilent Technologies, Palo Alto, United States).

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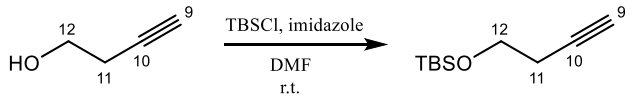
5.2 Synthesis of Compounds

5.2.1 (But-3-yn-1-yloxy)(*tert*-butyl)dimethylsilane (107)



106
C_4H_6O
70.09

107
$C_{10}H_{20}OSi$
184.35

To a stirred solution of 3-butyn-1-ol (2.90 g, 41.37 mmol, 1 eq.) in DMF (15 mL), imidazole (6.76 g, 99.30 mmol, 2.4 eq.), and chloro *tert*-butyldimethylsilane (7.48 g, 49.65 mmol, 1.2 eq.) were added. The reaction was stirred for 1 hour until TLC indicated complete conversion. The mixture was then poured into a separatory funnel containing 100 mL diethylether and was washed 10 times with 5 mL of water. The organic phase was separated, dried over Na_2SO_4, and concentrated. The residue was purified *via* flash chromatography to yield 6.41 g (84 %) of the TBS-protected alcohol **107** as colorless liquid.

R_f: 0.50 (PE:EA 40:1)

^{1}H NMR (400 MHz, chloroform-*d*): δ 3.74 (t, *J* = 7.2 Hz, 2H), 2.40 (td, *J* = 7.1, 2.7 Hz, 2H), 1.96 (t, *J* = 2.6 Hz, 1H), 0.90 (s, 9H), 0.08 (s, 6H).

^{13}C NMR (100 MHz, chloroform-*d*): δ 81.7, 69.4, 61.9, 26.0, 23.0, 18.5, -5.1.

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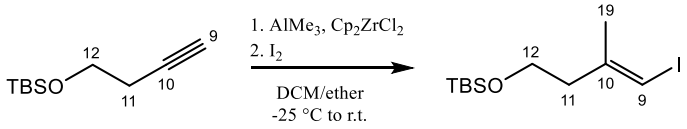
5.2.2 (*E*)-*tert*-butyl((4-iodo-3-methylbut-3-en-1-yl)oxy)dimethylsilane (101)



107
$C_{10}H_{20}OSi$
184.35

101
$C_{11}H_{23}IOSi$
326.29

Procedure according to [24]

To a stirred suspension of Cp_2ZrCl_2 (2.79 g, 9.55 mmol, 0.22 eq.) in dry DCM (120 mL) in a Schlenk flask, $AlMe_3$ (2M in toluene, 65 mL, 130 mmol, 3 eq.) was added dropwise *via* syringe at -25 °C. The resulting yellow mixture was stirred at -25 °C for 15 minutes. After dropwise addition of deion. water (1.25 mL, 69.43 mmol, 1.6 eq.), the reaction was stirred again for 20 minutes at respective temperature. Then, **107** (8 g, 43.39 mmol, 1 eq.), pretreated with $AlMe_3$ (2M in toluene, 6.51 mL, 13.02 mmol, 0.3 eq.) in dry DCM (30 mL) at 0 °C, was added dropwise *via* syringe. The reaction was allowed to reach room temperature and was stirred overnight.
The resulting yellow slurry was again cooled to -25 °C and a solution of I_2 (16.52 g, 65.09 mmol, 1.5 eq.) in dry diethyl ether (150 mL) was added dropwise *via* syringe. The mixture was allowed to reach room temperature and stirred for 4 hours. The reaction was quenched by the addition of 40 mL sat. Na–K–tartrate-solution and stirred until the aluminum was fully complexed. The organic phase was decanted off and the precipitate was washed several times with diethyl ether. The combined organic phases were washed once with sat. $Na_2S_2O_3$ solution and once with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified *via* column chromatography to afford 12.06 g (85 %) of the title compound **101** as a colorless oil.

R_f: 0.61 (PE:EA 40:1)

^{1}H NMR (400 MHz, chloroform-*d*): δ 5.93 (q, *J* = 1.1 Hz, 1H), 3.68 (t, *J* = 6.6 Hz, 2H), 2.41 (td, *J* = 6.6, 1.1 Hz, 2H), 1.85 (d, *J* = 1.2 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H).

^{13}C NMR (100 MHz, chloroform-*d*): δ 145.3, 76.5, 61.5, 42.8, 26.0, 24.4, 18.4, -5.2.

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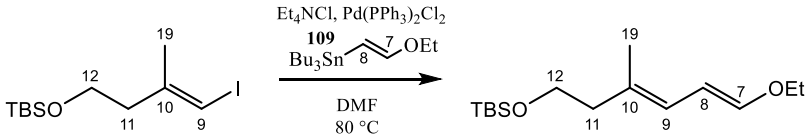
5.2.3 *tert*-butyl(((3*E*,5*E*)-6-ethoxy-3-methylhexa-3,5-dien-1-yl)oxy) dimethylsilane (100)



101
$C_{11}H_{23}IOSi$
326.29

100
$C_{15}H_{30}O_2Si$
270.49

Procedure according to [25]

To a stirred mixture of **101** (85 mg, 260 µmol, 1 eq.), tetraethylammonium chloride (45 mg, 260 µmol, 1 eq.) and bis(triphenylphosphine)palladium chloride (9.2 mg, 13 µmol, 0.05 eq.) in DMF (3 mL), stannane **109** (146 mg, 135 µL, 404 µmol, 1.55 eq.) was added in one portion. The resulting mixture was heated to 80 °C and stirred for 45 min until TLC confirmed full completion.
The reaction was quenched by addition of aqueous KF-solution (30 %) and filtered over a short plug of celite. The filtrate was poured into a separatory funnel and the aqueous phase was extracted with ethyl acetate three times. The combined organic phases were washed with water and brine, dried over Na_2SO_4 and concentrated. The residue was purified *via* column chromatography to yield 25 mg (35 %) of the title compound **100**.

R*f*: 0.46 (toluene)

^{1}H NMR (200 MHz, methylene chloride-d_2): δ 6.14 (dt, *J* = 11.3, 1.3 Hz, 1H), 5.94 (d, *J* = 6.3 Hz, 1H), 5.15 (dd, *J* = 11.3, 6.4 Hz, 1H), 3.83 (q, *J* = 7.1 Hz, 2H), 3.68 (t, *J* = 7.0 Hz, 2H), 2.26 (t, *J* = 7.1 Hz, 2H), 1.70 (d, *J* = 1.4 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H).

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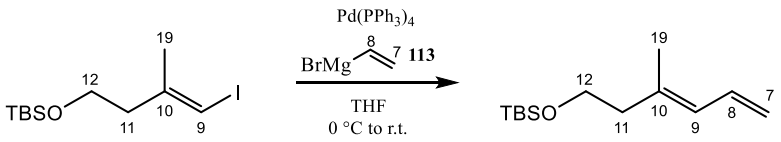
5.2.4 (*E*)-tert-butyldimethyl((3-methylhexa-3,5-dien-1-yl)oxy)silane (103)



101
$C_{11}H_{23}IOSi$
326.29

103
$C_{13}H_{26}OSi$
226.44

Procedure according to [26]

To a stirred solution of **101** (100 mg, 306 µmol, 1 eq.) in THF (1 mL) was added tetrakis(triphenylphosphine)palladium (18 mg, 15 µmol, 0.05 eq.). Then, the mixture was cooled to 0 °C and vinylmagnesiumbromide (1M in THF, 920 µL, 920 µmol, 3 eq.) was added dropwise.
The mixture was allowed to reach room temperature over a period of 15 min, which caused the formation of a brown precipitate. After 1 h, 5 mL of ether were added before the reaction was quenched with sat. NH_4Cl solution.
The aqueous phase was then extracted three times with ether, the combined organic phases were washed with water and brine. Drying over Na_2SO_4 and subsequent evaporation of the solvent furnished a crude mixture, which was purified *via* column chromatography to yield 66 mg (95 %) of the title compound **103**.

R*f*: 0.59 (PE:EA 40:1)

^{1}H NMR (200 MHz, chloroform-*d*): δ 6.57 (dt, *J* = 16.8, 10.5 Hz, 1H), 5.87 (d, *J* = 10.9 Hz, 1H), 5.05 (dd, *J* = 17.8, 15.7 Hz, 2H), 3.70 (t, *J* = 7.0 Hz, 2H), 2.27 (t, *J* = 6.8 Hz, 2H), 1.78 (d, *J* = 1.4 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H).

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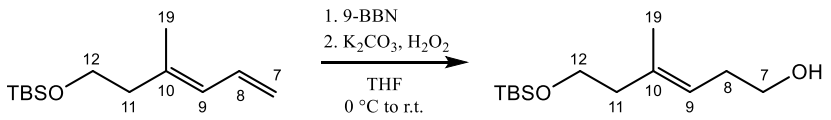
5.2.5 (*E*)-6-((*tert*-butyldimethylsilyl)oxy)-4-methylhex-3-en-1-ol (102)



103
$C_{13}H_{26}OSi$
226.44

102
$C_{13}H_{28}O_2Si$
244.45

To a stirred solution of **103** (118 mg, 395 µmol, 1 eq.) in THF (2 mL) was added 9-BBN (0.5M in THF, 3.16 mL, 1.58 mmol, 4 eq.) dropwise at 0 °C. The mixture was allowed to reach room temperature and stirred until TLC confirmed full completion after 4 h.
Then, K_2CO_3 (10% solution in water, 4 ml, 3.16 mmol, 8 eq.) was added, followed by H_2O_2 (30w%, 290 µL, 2.77 mmol, 7 eq.).
The resulting suspension was stirred for 2 h before the reaction was quenched with solid NH_4Cl. The mixture was extracted three times with ethyl acetate, washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified *via* column chromatography to give 45 mg (36 %) of the primary alcohol **102**.

R*f*: 0.44 (PE:EA 10:1)

^{1}H NMR (400 MHz, chloroform-*d*): δ 5.15 (tp, *J* = 7.3, 1.3 Hz, 1H), 3.67 (t, *J* = 6.8 Hz, 2H), 3.63 – 3.58 (m, 2H), 2.28 (dddd, *J* = 7.3, 6.5, 5.7, 0.8 Hz, 2H), 2.22 (td, *J* = 6.9, 1.0 Hz, 2H), 1.65 (d, *J* = 1.5 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H).

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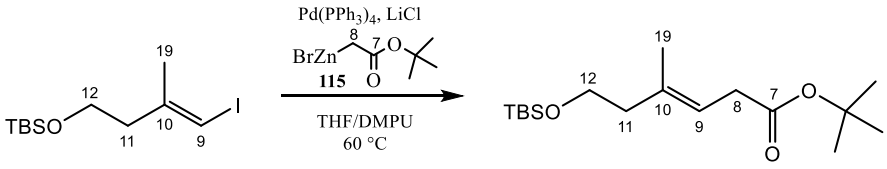
5.2.6 *tert*-butyl (*E*)-6-((tert-butyldimethylsilyl)oxy)-4-methylhex-3-enoate (104)



101
$C_{11}H_{23}IOSi$
326.29

104
$C_{17}H_{34}O_3Si$
314.54

Procedure according to [27,28]

Preparation of **115**: Zinc powder (2 g, 30.76 mmol, 1 eq.) was weighed into a three-necked round bottom flask equipped with condenser and septum and fused under argon. Next, 20 mL of dry THF were added and the resulting gray suspension was subsequently treated with trimethylsilyl chloride (400 µL, 3.08 mmol, 0.1 eq.). The mixture was then heated to 60 °C, before *tert*-butyl bromoacetate (6 g, 4.54 mL, 30.76 mmol, 1 eq.) was added dropwise. Once the addition was complete, a yellow-greenish suspension with some white precipitate was obtained.
To determine the concentration of **115** in the supernatant solution, a small equivalent was taken *via* syringe and titrated against iodine until a color change from purple to colorless was observed.

To a stirred suspension of tetrakis(triphenylphosphine)palladium (460 mg, 400 µmol, 0.04 eq.) and lithium chloride (1.27 g, 30 mmol, 3 eq.) in dry THF (4 mL) was added **101** (3.26 g, 10 mmol, 1 eq.) in dry THF (10 mL). Resulting orange suspension was treated with the prepared solution of zinc organyle (0.83M in THF, 36 mL, 30 mmol, 3 eq.), followed by addition of THF (10 mL) and freshly distilled DMPU (24 mL). It is important, that the ratio of THF/DMPU roughly equals 2.5/1.
Then, the mixture was heated to 60 °C and stirred for 45 min until TLC confirmed full conversion. The reaction was quenched with sat. NH_4Cl solution and stirred for another 30 min before the whole mixture was filtered over a plug of celite and washed with ether. The filtrate was transferred into a separatory funnel and the aqueous phase was extracted with ether (3x). The combined organic phases were washed with water (10x), dried over Na_2SO_4, filtered and concentrated. Resulting residue was purified *via* column chromatography to obtain 2.55 g (81 %) of ester **104** as a colorless oil.

R*f*: 0.66 (PE:EA 20:1)

^{1}H NMR (400 MHz, chloroform-*d*): δ 5.37 – 5.30 (m, 1H), 3.67 (t, *J* = 7.1 Hz, 2H), 2.94 (dd, *J* = 7.0, 1.0 Hz, 2H), 2.24 (td, *J* = 7.1, 1.1 Hz, 2H), 1.64 (d, *J* = 1.3 Hz, 3H), 1.44 (s, 9H), 0.88 (s, 9H), 0.04 (s, 6H).

^{13}C NMR (100 MHz, chloroform-*d*): δ 171.8, 135.9, 118.3, 80.4, 62.5, 43.0, 35.2, 28.2, 26.1, 18.5, 17.0, -5.1.

HRMS: calc.: 337.2169, found: 337.2174 (M + Na)

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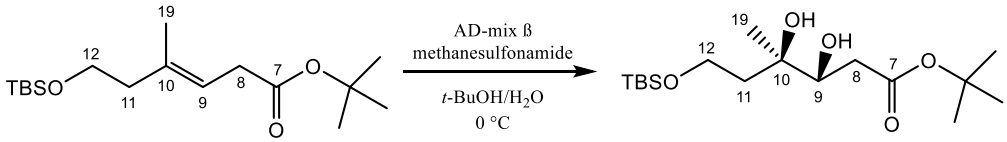
5.2.7 *tert*-butyl (3*R*,4*R*)-6-((*tert*-butyldimethylsilyl)oxy)-3,4-dihydroxy-4-methylhexanoate (116)



104
$C_{17}H_{34}O_3Si$
314.54

116
$C_{17}H_{36}O_5Si$
348.56

Procedure according to [29]

Potassiumosmate dihydrate (22 mg, 60 µmol) and $(DHQD)_2PHAL$ (234 mg, 300 µmol) were added to a mixture of powdered $K_3Fe(CN)_6$ (9.80 g, 30 mmol) and K_2CO_3 (4.12 g, 30 mmol). The resulting mixture was ground to afford 14.18 g of AD-mix-β-(x3).

To a mechanically stirred suspension of AD-mix-β-(x3) (9 g, 1.4 g/mmol) in *t*-BuOH/H_2O (10 mL each) was added methanesulfonamide (1.83 g, 19.27 mmol, 3 eq.). After 2 h of stirring, the mixture was cooled to 0 °C before compound **104** (2.02 g, 6.42 mmol, 1 eq.), dissolved in ether (5 mL), was added slowly. The orange suspension was then stirred for 48 h until TLC indicated complete conversion.

The reaction was quenched with solid Na_2SO_3 and allowed to reach room temperature. Ether was added and the mixture was stirred for 30 minutes. The product was extracted five times with ether, and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated to obtain a crude product, which was purified *via* column chromatography to yield 1.63 g (73 %) of the title compound **116** as a colorless oil.

R*f*: 0.47 (PE:EA 5:1)

^{1}H NMR (400 MHz, chloroform-*d*): δ 3.95 – 3.80 (m, 3H), 3.73 (s, 1H), 3.42 (d, *J* = 4.0 Hz, 1H), 2.50 (dd, *J* = 15.7, 3.0 Hz, 1H), 2.35 (dd, *J* = 15.6, 9.9 Hz, 1H), 1.84 (ddd, *J* = 14.6, 8.7, 4.5 Hz, 1H), 1.66 (ddd, *J* = 14.6, 5.6, 3.7 Hz, 1H), 1.45 (s, 9H), 1.17 (s, 3H), 0.89 (s, 9H), 0.08 (s, 6H).

^{13}C NMR (100 MHz, chloroform-*d*): δ 172.5, 81.0, 74.1, 73.9, 60.2, 39.2, 37.7, 28.2, 26.0, 22.8, 18.2, -5.1.

HRMS: calc.: 371.2224, found: 371.2223 (M + Na)

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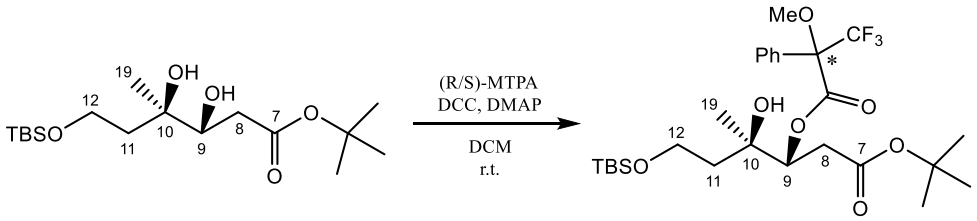
5.2.8 *tert*-butyl (3*R*,4*R*)-6-((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-4-methyl-3-((3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy) hexanoate (117)



116
$C_{17}H_{36}O_5Si$
348.56

117
$C_{27}H_{43}F_3O_7Si$
564.71

To a stirred solution of **116** (19 mg, 55 µmol, 1 eq.) in dry DCM (2 mL) were added DCC (23 mg, 109 µmol, 2 eq.) and cat. amounts of DMAP. Then, the mixture was treated with MTPA (38 mg, 164 µmol, 3 eq.), which caused the solution to become cloudy after 15 min. The suspension was stirred overnight, until TLC indicated full completion.
After addition of 1 mL sat. $NaHCO_3$-solution, the product was extracted several times with DCM, the combined organic phases were dried over Na_2SO_4, filtered, and concentrated to yield 22 mg (71 %) of the title compound **117**.

R*f*: 0.42 (PE:EA 8:1)

^{19}F NMR (376 MHz, chloroform-*d*): δ -71.41. (*S*-ester)

^{19}F NMR (376 MHz, chloroform-*d*): δ -71.37. (*R*-ester)

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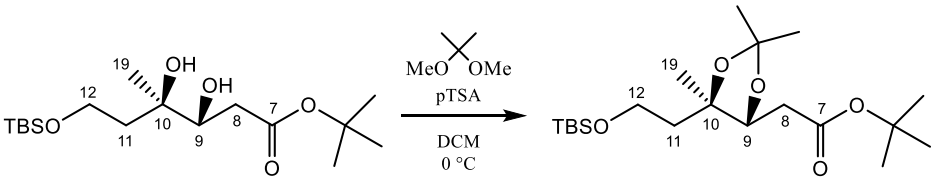
5.2.9 *tert*-butyl 2-((4*R*,5*R*)-5-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2,2,5-trimethyl-1,3-dioxolan-4-yl)acetate (98)



116
$C_{17}H_{36}O_5Si$
348.56

98
$C_{20}H_{40}O_5Si$
388.62

To a stirred mixture of **116** (300 mg, 860 µmol, 1 eq.) and molecular sieve (4 Å) in dry DCM were added pTSA (15 mg, 86 µmol, 0.1 eq.) and 2,2-dimethoxypropane (269 mg, 320 µL, 2.58 mmol, 3 eq.) at 0 °C. The resulting suspension was stirred for 12 h at respective temperature. Once TLC had indicated full completion, the reaction was quenched with sat. $NaHCO_3$-solution.
The whole mixture was filtered over a plug of celite before the product was extracted several times with DCM. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified *via* column chromatography to obtain 310 mg (93 %) of the acetal protected product **98** as a colorless oil.

R*f*: 0.69 (PE:EA 10:1)

^{1}H NMR (400 MHz, chloroform-*d*): δ 4.23 (dd, *J* = 7.2, 5.6 Hz, 1H), 3.79 – 3.65 (m, 2H), 2.41 (s, 1H), 2.39 (d, *J* = 1.7 Hz, 1H), 1.82 – 1.65 (m, 2H), 1.41 (s, 9H), 1.36 (d, *J* = 0.7 Hz, 3H), 1.30 (d, *J* = 0.7 Hz, 3H), 1.04 (s, 3H), 0.83 (s, 9H), 0.00 (s, 6H).

^{13}C NMR (100 MHz, chloroform-*d*): δ 170.1, 107.0, 81.2, 80.9, 78.1, 59.2, 42.0, 36.1, 28.6, 28.1, 26.8, 26.0, 21.8, 18.3, -5.2.

HRMS: calc.: 411.2537, found: 411.2539 (M + Na)

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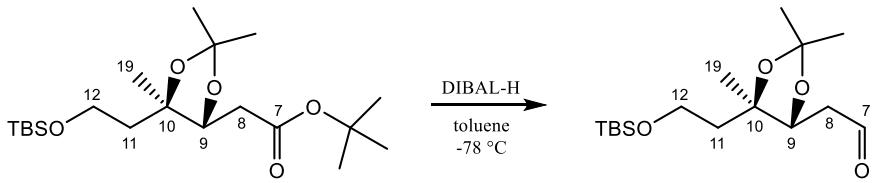
5.2.10 2-((4*R*,5*R*)-5-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2,2,5-trimethyl-1,3-dioxolan-4-yl)acetaldehyde (96)



98
$C_{20}H_{40}O_5Si$
388.62

96
$C_{16}H_{32}O_4Si$
316.51

To a stirred solution of **98** (555 mg, 1.43 mmol, 1 eq.) in dry toluene (15 mL) was added DIBAL-H (1M in heptane, 1.43 mL, 1 eq.) dropwise at -78 °C. The mixture was stirred for 1 h at respective temperature before the reaction was quenched by the addition of methanol and sat. aqueous Na-K-tartrate solution. The resulting suspension was then allowed to reach room temperature before the product was extracted three times with ether. The combined organic phases were washed with water, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified *via* column chromatography to yield 386 mg (85 %) of aldehyde **96** as a colorless oil.

R*f*: 0.53 (PE:EA 10:1)

^{1}H NMR (400 MHz, chloroform-*d*): δ 9.80 (t, *J* = 2.1 Hz, 1H), 4.48 (dd, *J* = 8.5, 4.3 Hz, 1H), 3.83 (ddd, *J* = 10.6, 6.5, 6.0 Hz, 1H), 3.71 (ddd, *J* = 10.6, 6.7, 5.9 Hz, 1H), 2.68 – 2.51 (m, 2H), 1.87 – 1.70 (m, 2H), 1.43 (d, *J* = 0.8 Hz, 3H), 1.36 (s, 3H), 1.11 (s, 3H), 0.88 (s, 9H), 0.05 (d, *J* = 1.1 Hz, 6H).

^{13}C NMR (100 MHz, chloroform-*d*): δ 200.3, 107.6, 81.6, 76.3, 59.1, 43.8, 41.8, 28.6, 27.0, 26.1, 22.2, 18.4, -5.1, -5.2.

HRMS: calc.: 317.2143, found: 317.2145 (M + H)

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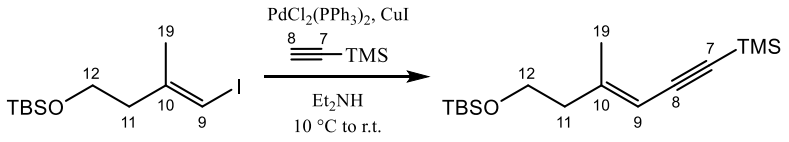
5.2.11 (*E*)-*tert*-butyldimethyl((3-methyl-6-(trimethylsilyl)hex-3-en-5-yn-1-yl)oxy)silane (105)



101
$C_{11}H_{23}IOSi$
326.29

105
$C_{16}H_{32}OSi_2$
296.60

Procedure according to [34]

To a solution of vinyl iodide **101** (500 mg, 1.53 mmol, 1 eq.) in Et_2NH (10 mL), $PdCl_2(PPh_3)_2$ (20 mg, 23 µmol, 0.015 eq.) and CuI (90 mg, 460 µmol, 0.3 eq.) were added. The reaction mixture was stirred under light protection for 30 minutes at 10 °C. After dropwise addition of TMS-acetylene (320 mg, 450 µL, 3.20 mmol, 2 eq.) at 10 °C the reaction was allowed to reach room temperature and stirred for 3 hours.
After TLC had indicated complete conversion, the reaction was quenched by the addition of 8 mL sat. NH_4Cl-solution, the organic compound was extracted three times with ether and the combined organic phases were dried over Na_2SO_4, filtered and concentrated. The crude product was purified *via* column chromatography to yield 420 mg (91 %) of the title compound **105** as an oily liquid.

R*f*: 0.52 (PE)

^{1}H NMR (400 MHz, chloroform-*d*): δ 5.33 (q, *J* = 1.2 Hz, 1H), 3.68 (t, *J* = 6.9 Hz, 2H), 2.29 (td, *J* = 6.9, 1.2 Hz, 2H), 1.92 (d, *J* = 1.2 Hz, 3H), 0.88 (s, 9H), 0.18 (s, 9H), 0.04 (s, 6H).

^{13}C NMR (100 MHz, chloroform-*d*): δ 151.1, 111.6, 106.7, 103.4, 97.1, 61.9, 42.1, 26.1, 18.5, 0.3, -5.2.

HRMS: calc.: 295.1919, found: 295.1925 (M - H)

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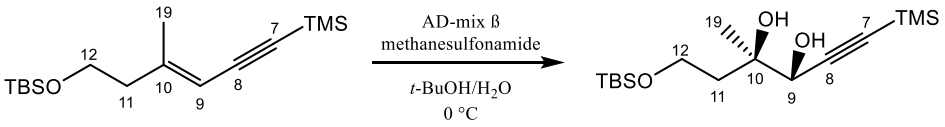
5.2.12 (3*R*,4*R*)-6-((*tert*-butyldimethylsilyl)oxy)-4-methyl-1-(trimethylsilyl)hex-1-yne-3,4-diol (120)



105
$C_{16}H_{32}OSi_2$
296.60

120
$C_{16}H_{34}O_3Si_2$
330.62

Procedure according to [29]

Potassiumosmate dihydrate (22 mg, 60 µmol) and $(DHQD)_2PHAL$ (234 mg, 300 µmol) were added to a mixture of powdered $K_3Fe(CN)_6$ (9.80 g, 30 mmol) and K_2CO_3 (4.12 g, 30 mmol). The resulting mixture was ground to afford 14.18 g of AD-mix-β-(x3).

To a mechanically stirred suspension of AD-mix-β-(x3) (9 g, 1.4 g/mmol) in *t*-BuOH/H_2O (10 mL each) was added methanesulfonamide (1.83 g, 19.27 mmol, 3 eq.). After 2 h of stirring, the mixture was cooled to 0 °C before compound **105** (1.91 g, 6.42 mmol, 1 eq.), dissolved in ether (5 mL), was added slowly. The orange suspension was then stirred for 48 h until TLC indicated complete conversion.
The reaction was quenched with solid Na_2SO_3 and allowed to reach room temperature. Ether was added and the mixture was stirred for 30 minutes. The product was extracted five times with ether and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated to obtain a crude product which was purified *via* column chromatography to yield 1.49 g (70 %) of the title compound **120** as colorless oil.

R_f: 0.39 (PE:EA 6:1)

^{1}H NMR (400 MHz, chloroform-*d*): δ 4.27 (d, *J* = 4.6 Hz, 1H), 3.90 (qdd, *J* = 10.9, 7.0, 4.2 Hz, 2H), 3.83 (s, 1H), 3.16 (d, *J* = 4.9 Hz, 1H), 1.94 – 1.78 (m, 2H), 1.31 (s, 3H), 0.90 (s, 9H), 0.17 (s, 9H), 0.10 (d, *J* = 1.8 Hz, 6H).

^{13}C NMR (100 MHz, chloroform-*d*): δ 103.8, 91.2, 75.2, 69.8, 60.4, 39.3, 26.0, 22.2, 18.2, 0.0, -5.1, -5.2.

HRMS: calc.: 353.1938, found: 353.1943 (M + Na)

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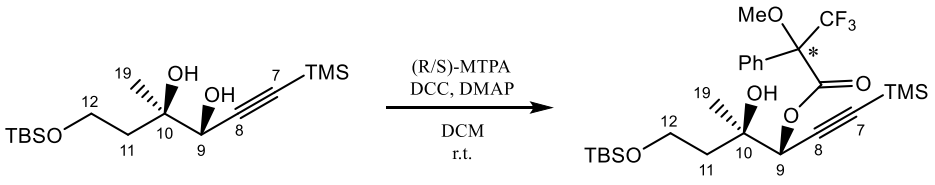
5.2.13 (3*R*,4*R*)-6-((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-4-methyl-1-(trimethylsilyl)hex-1-yn-3-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (121)



120
$C_{16}H_{34}O_3Si_2$
330.62

121
$C_{26}H_{41}F_3O_5Si_2$
546.77

To a stirred solution of **120** (14 mg, 42 µmol, 1 eq.) in dry DCM (2 mL) were added DCC (26 mg, 127 µmol, 3 eq.) and cat. amounts of DMAP. Then, the mixture was treated with MTPA (30 mg, 127 µmol, 3 eq.), which caused the solution to become cloudy after 15 min. The suspension was stirred overnight, until TLC indicated full completion.
After addition of 1 mL sat. $NaHCO_3$-solution, the product was extracted several times with DCM, the combined organic phases were dried over Na_2SO_4, filtered, and concentrated to yield 15 mg (65 %) of the title compound **121**.

R_f: 0.55 (PE:EA 8:1)

^{19}F NMR (565 MHz, chloroform-*d*): δ -71.56. (*S*-ester)

^{19}F NMR (565 MHz, chloroform-*d*): δ -71.74. (*R*-ester)

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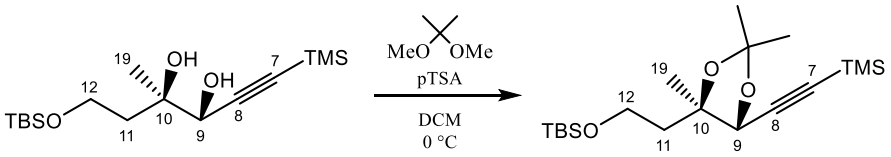
5.2.14 *tert*-butyldimethyl(2-((4*R*,5*R*)-2,2,4-trimethyl-5-((trimethylsilyl) ethynyl)-1,3-dioxolan-4-yl)ethoxy)silane (122)



120
$C_{16}H_{34}O_3Si_2$
330.62

122
$C_{19}H_{38}O_3Si_2$
370.68

To a stirred mixture of **120** (200 mg, 605 µmol, 1 eq.) and molecular sieve (4 Å) in dry DCM were added pTSA (10 mg, 60 µmol, 0.1 eq.) and 2,2-dimethoxypropane (189 mg, 220 µL, 1.81 mmol, 3 eq.) at 0 °C. The resulting suspension was stirred for 12 h at respective temperature. Once TLC had indicated full completion, the reaction was quenched with sat. $NaHCO_3$-solution.
The whole mixture was filtered over a plug of celite, before the product was extracted several times with DCM. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified *via* column chromatography to obtain 198 mg (88 %) of the acetal protected product **122** as a colorless oil.

R*f*: 0.61 (PE:EA 12:1)

^{1}H NMR (200 MHz, chloroform-*d*): δ 4.77 (d, *J* = 2.2 Hz, 1H), 3.90 – 3.67 (m, 2H), 1.85 (td, *J* = 6.5, 1.6 Hz, 2H), 1.50 (s, 3H), 1.36 (s, 3H), 1.35 (s, 3H), 0.90 (s, 9H), 0.17 (s, 9H), 0.07 (s, 6H).

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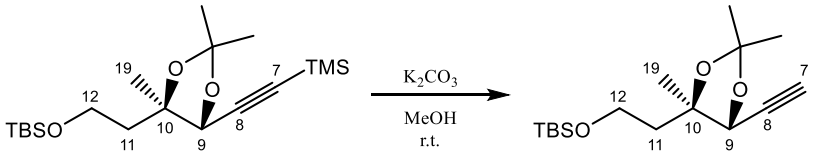
5.2.15 *tert*-butyl(2-((4*R*,5*R*)-5-ethynyl-2,2,4-trimethyl-1,3-dioxolan-4-yl)ethoxy)dimethylsilane (99)



122
$C_{19}H_{38}O_3Si_2$
370.68

99
$C_{16}H_{30}O_3Si$
298.50

To a stirred solution of **122** (114 mg, 308 µmol, 1 eq.) in methanol (2.5 mL) was added K_2CO_3 (9 mg, 62 µmol, 0.2 eq.). The mixture was stirred for 2 h until TLC confirmed full completion.
The reaction mixture was then concentrated and the residue was diluted with ether, washed with water and brine, and dried over Na_2SO_4. Filtration and evaporation of the solvent, followed by purification yielded 88 mg (96 %) of the title compound **99** as a colorless oil.

R*f*: 0.58 (PE:EA 10:1)

^{1}H NMR (200 MHz, chloroform-*d*): δ 4.76 (d, *J* = 2.2 Hz, 1H), 3.89 – 3.65 (m, 2H), 2.52 (d, *J* = 2.2 Hz, 1H), 1.85 (td, *J* = 6.5, 1.6 Hz, 2H), 1.50 (s, 3H), 1.36 (s, 3H), 1.35 (s, 3H), 0.89 (s, 9H), 0.06 (s, 6H).

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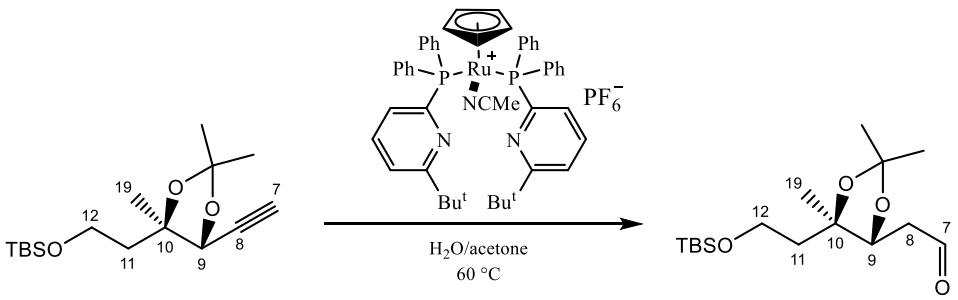
5.2.16 2-((4*R*,5*R*)-5-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2,2,5-trimethyl-1,3-dioxolan-4-yl)acetaldehyde (96)



99
$C_{16}H_{30}O_3Si$
298.50

96
$C_{16}H_{32}O_4Si$
316.51

Procedure according to [35]

A degassed mixture of H_2O/acetone (1/25) (1.5 mL) was added to a Schlenk-flask containing the catalyst (33 mg, 33 µmol, 0.05 eq.) to obtain an orange solution. The whole was then transferred to a separate Schlenk-flask containing alkyne **99** (200 mg, 670 µmol, 1 eq.), and the resulting mixture was heated to 60 °C.
After 18 h, ether was added, followed by solid Na_2SO_4, and the supernatant solution was filtered over a plug of silica. After removal of all volatiles under reduced pressure, the residue was purified *via* column chromatography to obtain 148 mg (70 %) of the aldehyde **96** as a colorless oil.

R*f*: 0.53 (PE:EA 10:1)

^{1}H NMR (400 MHz, chloroform-*d*): δ 9.80 (t, *J* = 2.1 Hz, 1H), 4.48 (dd, *J* = 8.5, 4.3 Hz, 1H), 3.83 (ddd, *J* = 10.6, 6.5, 6.0 Hz, 1H), 3.71 (ddd, *J* = 10.6, 6.7, 5.9 Hz, 1H), 2.68 – 2.51 (m, 2H), 1.87 – 1.70 (m, 2H), 1.43 (d, *J* = 0.8 Hz, 3H), 1.36 (s, 3H), 1.11 (s, 3H), 0.88 (s, 9H), 0.05 (d, *J* = 1.1 Hz, 6H).

^{13}C NMR (100 MHz, chloroform-*d*): δ 200.3, 107.6, 81.6, 76.3, 59.1, 43.8, 41.8, 28.6, 27.0, 26.1, 22.2, 18.4, -5.1, -5.2.

HRMS: calc.: 317.2143, found: 317.2145 (M + H)

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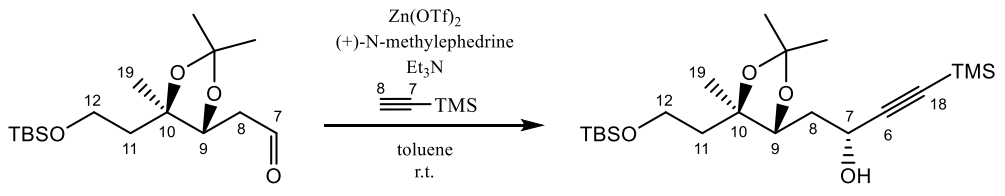
5.2.17 (*R*)-1-((4*R*,5*R*)-5-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2,2,5-trimethyl-1,3-dioxolan-4-yl)-4-(trimethylsilyl)but-3-yn-2-ol (125)



96
$C_{16}H_{32}O_4Si$
316.51

125
$C_{21}H_{42}O_4Si_2$
414.73

Procedure according to [36]

A 20 mL Schlenk-flask was charged with $Zn(OTf)_2$ (810 mg, 2.23 mmol, 3 eq.) and (+)-*N*-methylephedrine (413 mg, 2.30 mmol, 3.1 eq.) and fused under argon. To the flask dry toluene (6 mL) and triethylamine (233 mg, 319 µL, 2.30 mmol, 3.1 eq.) were added. The resulting slurry was vigorously stirred for 3 h to obtain a cloudy mixture before trimethylsilylacetylene (226 mg, 319 µL, 2.30 mmol, 3.1 eq.) was added in one portion. After 30 min of stirring, a solution of the aldehyde **96** (235 mg, 742 µmol, 1 eq.) in dry toluene (1 mL) was added *via* syringe. After stirring for 14 h at room temperature, the reaction was quenched by the addition of saturated aqueous NH_4Cl solution. The reaction mixture was poured into a separatory funnel containing ether. The layers were separated and the aqueous layer was extracted with ether three times. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*.
Purification of the residue by column chromatography afforded 226 mg (73 %) of the secondary propargylic alcohol **125**.

R*f*: 0.55 (PE:EA 10:1)

^{1}H NMR (600 MHz, chloroform-*d*): δ 4.59 (dd, *J* = 6.5, 3.2 Hz, 1H), 4.28 (dd, *J* = 10.6, 2.3 Hz, 1H), 3.84 – 3.74 (m, 2H), 2.92 (s, 1H), 1.92 (ddd, *J* = 14.0, 10.6, 3.2 Hz, 1H), 1.84 – 1.77 (m, 3H), 1.43 – 1.40 (m, 3H), 1.34 (s, 3H), 1.11 (s, 3H), 0.89 (s, 9H), 0.17 (s, 9H), 0.06 (s, 6H).

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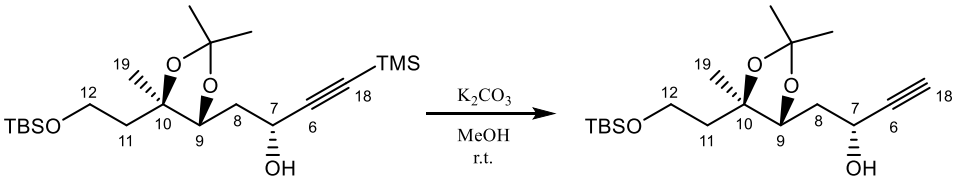
5.2.18 (*R*)-1-((4*R*,5*R*)-5-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2,2,5-trimethyl-1,3-dioxolan-4-yl)but-3-yn-2-ol (95)



125
$C_{21}H_{42}O_4Si_2$
414.73

95
$C_{18}H_{34}O_4Si$
342.55

To a stirred solution of **125** (160 mg, 386 µmol, 1 eq.) in methanol (3 mL) K_2CO_3 (11 mg, 77 µmol, 0.2 eq.) was added. The mixture was stirred for 2 h until TLC confirmed full completion.
The reaction mixture was then concentrated and the residue was diluted with ether, washed with water and brine, and dried over Na_2SO_4. Filtration and evaporation of the solvent, followed by purification, yielded 123 mg (93 %) of the title compound **95** as a colorless oil.

R_f: 0.36 (PE:EA 10:1)

^{1}H NMR (400 MHz, chloroform-*d*): δ 4.63 (dddd, *J* = 8.5, 6.3, 3.4, 2.2 Hz, 1H), 4.33 (dd, *J* = 10.6, 2.4 Hz, 1H), 3.78 (qdd, *J* = 10.3, 7.4, 6.6 Hz, 2H), 3.06 (d, *J* = 8.4 Hz, 1H), 2.48 (d, *J* = 2.2 Hz, 1H), 1.96 (ddd, *J* = 14.0, 10.5, 3.3 Hz, 1H), 1.86 – 1.76 (m, 3H), 1.42 (d, *J* = 0.7 Hz, 3H), 1.36 (d, *J* = 0.7 Hz, 3H), 1.12 (s, 3H), 0.89 (s, 9H), 0.06 (s, 6H).

^{13}C NMR (100 MHz, chloroform-*d*): δ 107.7, 84.3, 81.7, 78.8, 73.3, 60.7, 59.3, 42.0, 36.0, 28.7, 27.0, 26.1, 22.0, 18.5, -5.2.

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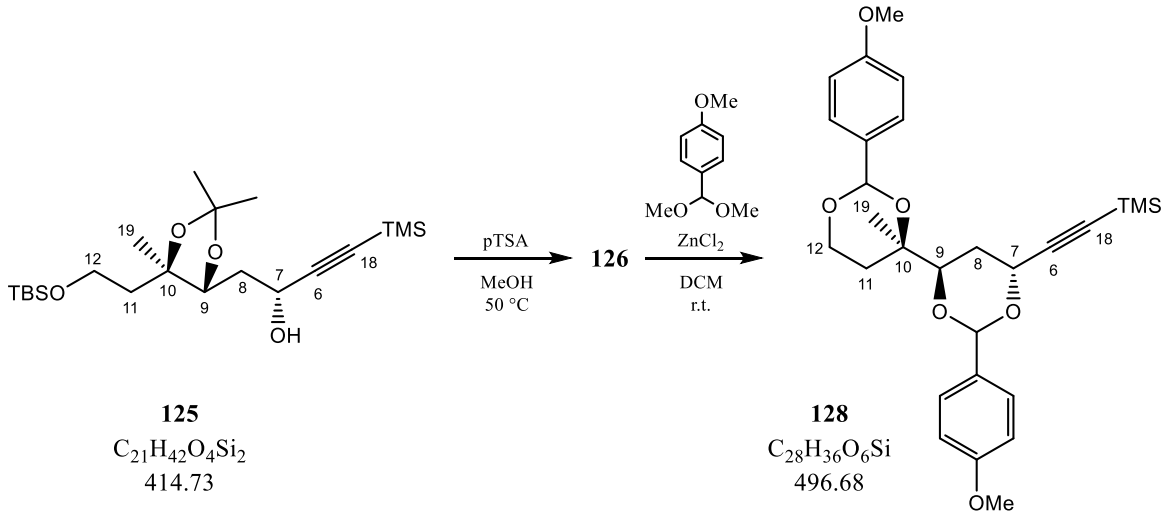
5.2.19 (((4*R*,4'*R*,6*R*)-2,2'-bis(4-methoxyphenyl)-4'-methyl-[4,4'-bi(1,3-dioxan)]-6-yl)ethynyl)trimethylsilane (128)



To a solution of **125** (30 mg, 72 µmol, 1 eq.) in MeOH (3 mL), *p*-toluenesulfonic acid (3 mg, 15 µmol, 0.2 eq.) was added in one portion. The resulting mixture was heated to 50 °C and stirred for 24 hours at respective temperature. After TLC had indicated complete conversion, the solvent was removed under reduced pressure. The residue was purified *via* flash chromatography to obtain a crude mixture containing tetraol **126**, which was directly used for the next reaction.

Mentioned crude was dissolved in dry DCM (3 mL) before anisaldehyde dimethyl acetal (29 mg, 30 µL, 160 µmol, 2.2 eq.) and zinc chloride (0.5M in THF, 436 µL, 218 µmol, 3 eq.) were added. Resulting mixture was stirred for 48 h before it was diluted with DCM (10 mL) and washed with sat. aqueous $NaHCO_3$ solution and brine. The volatiles were then removed and the residue was purified by column chromatography to obtain a white solid, which was recrystallized from hexane/ether to yield 8 mg (22 % over two steps) of bisacetal **128**.

R_f: 0.30 (PE:EA 8:1)

^{1}H NMR (600 MHz, chloroform-*d*): δ 7.42 (dd, *J* = 8.8, 6.9 Hz, 4H), 6.89 (d, *J* = 8.5 Hz, 4H), 6.04 (s, 1H), 5.75 (s, 1H), 5.08 (dd, *J* = 5.9, 1.5 Hz, 1H), 4.16 – 4.11 (m, 3H), 3.81 (d, *J* = 2.9 Hz, 6H), 2.25 (ddt, *J* = 13.3, 9.3, 6.5 Hz, 2H), 1.85 (ddd, *J* = 13.2, 2.4, 1.4 Hz, 1H), 1.57 (s, 3H), 1.33 (dt, *J* = 13.5, 2.0 Hz, 1H), 0.21 (s, 9H).

^{13}C NMR (150 MHz, chloroform-*d*): δ 160.1, 160.0, 131.7, 131.3, 127.7, 127.7, 113.8, 113.6, 102.9, 95.7, 95.1, 93.5, 79.3, 75.2, 65.0, 63.4, 55.5, 55.5, 29.0, 28.5, 18.8, 0.1.

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7 Appendices

Abbreviations

9-BBN	9-borabicyclo[3.3.1]nonane
Ac	acetyl
AD	asymmetric dihydroxylation
Bn	benzyl
BSA	bis(trimethylsilyl)acetamide
Bu	butyl
Bu^t	*tert*-butyl
Cp	cyclopentadienyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-en
DCC	*N,N'*-dicyclohexylcarbodiimide
DCM	dichloromethane
DHQD	dihydroquinidine
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DMF	dimethylformamide
DMP	Dess-Martin-Periodinan
DMPU	*N,N'*-dimethylpropyleneurea
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
EA	ethyl acetate
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
Et	ethyl
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
HRMS	high-resolution mass spectrometry
HYTRA	2-hydroxy-1,2,2-triphenylethyl acetate
IBX	2-iodoxybenzoic acid
LDA	lithium diisopropylamide
MDR	multi drug resistance

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Me	methyl
min	minutes
MOM	methoxymethyl
Ms	mesyl
MTPA	a-methoxy-a-trifluoromethylphenylacetic acid
NCS	*N*-chlorosuccinimide
Nic	nicotinoyl
NMO	*N*-methylmorpholine *N*-oxide
NOESY	Nuclear Overhauser Enhancement Spectroscopy
PDC	pyridinium dichromate
PE	petroleum ether
PG	protecting group
Ph	phenyl
PHAL	phthalazinediyl
PMB	*p*-methyoxybenzyl
ppm	parts per million
PPTS	pyridinium p-toluenesulfonate
pTSA	*p*-toluenesulfonic acid
r.t.	room temperature
RCEYM	Ring-Closing Enyne Metathesis
RCM	Ring-Closing Metathesis
R_f	retardation factor
sat.	saturated
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	tetra-n-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
TES	triethylsilyl
Tf	triflyl
THF	tetrahydrofurane
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMS	trimethylsilyl
Ts	tosyl

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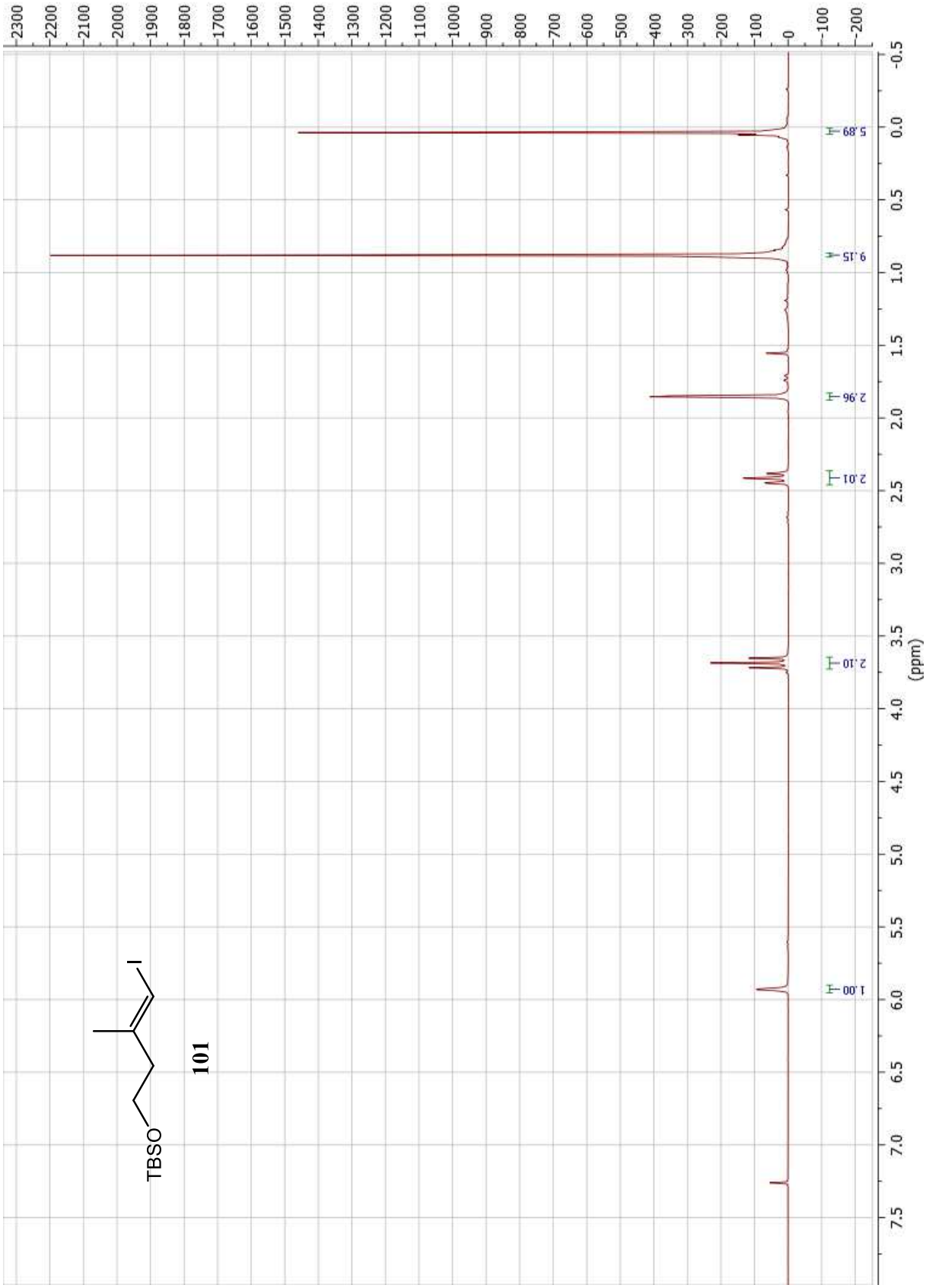
Selected Spectra



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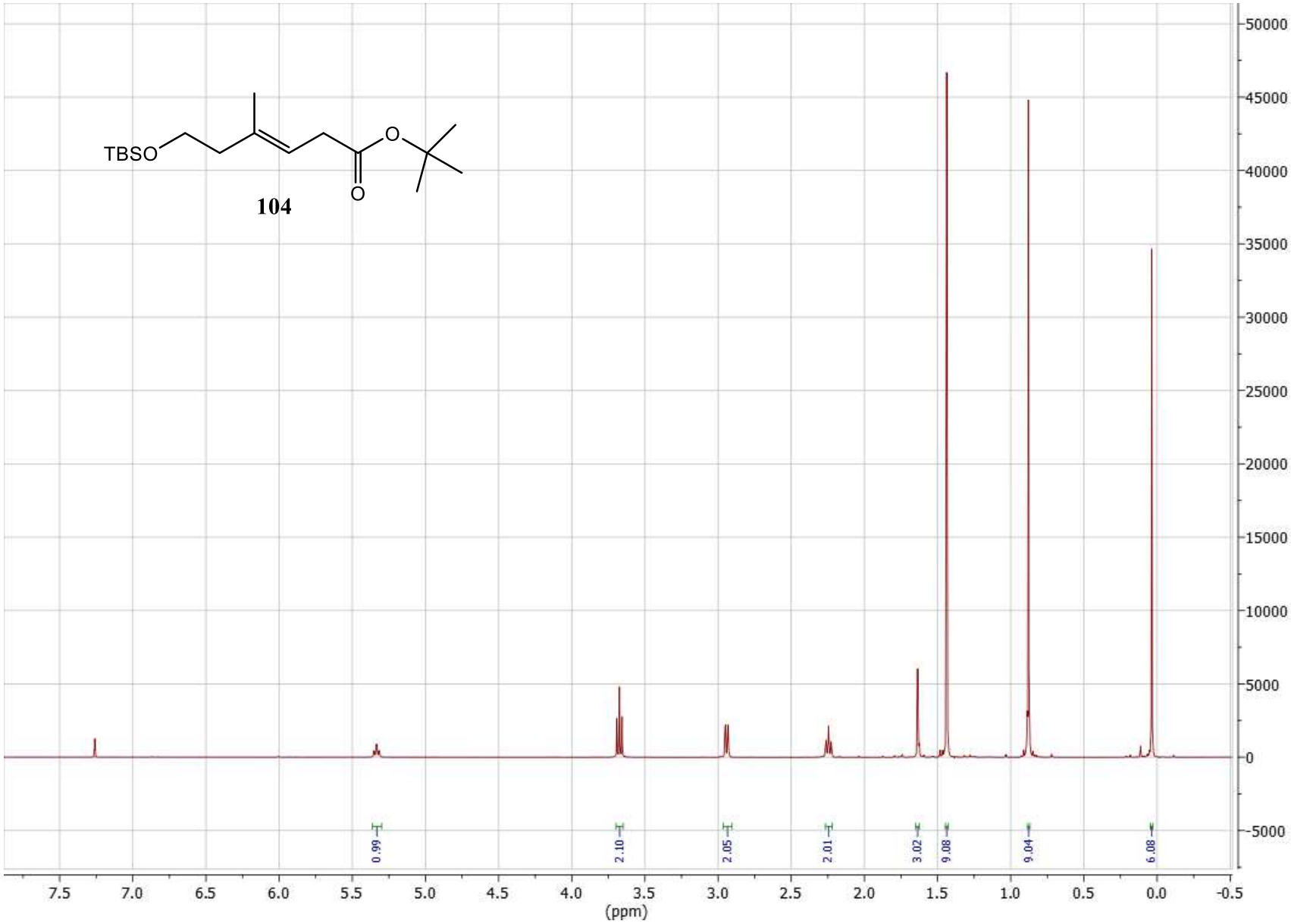

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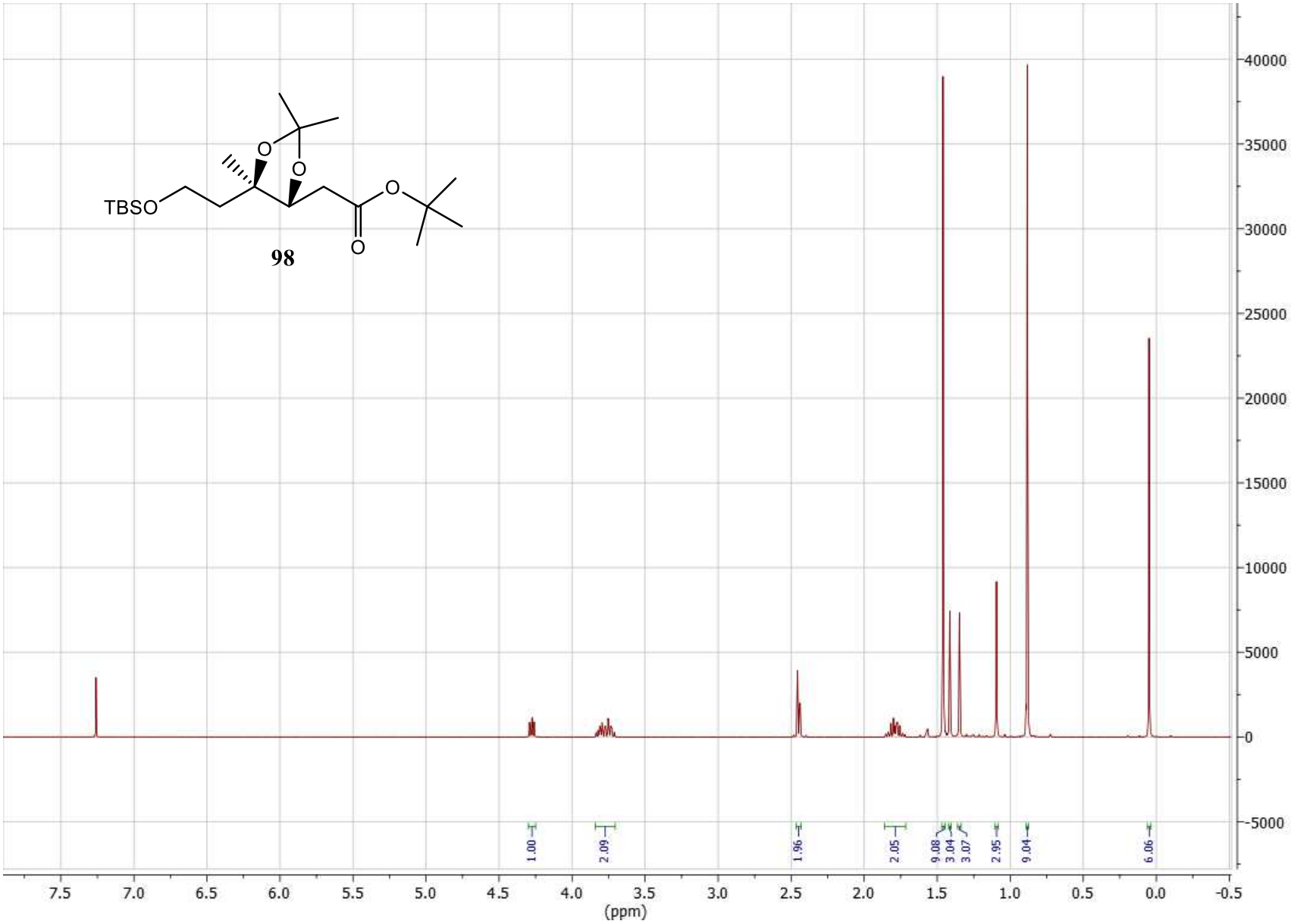

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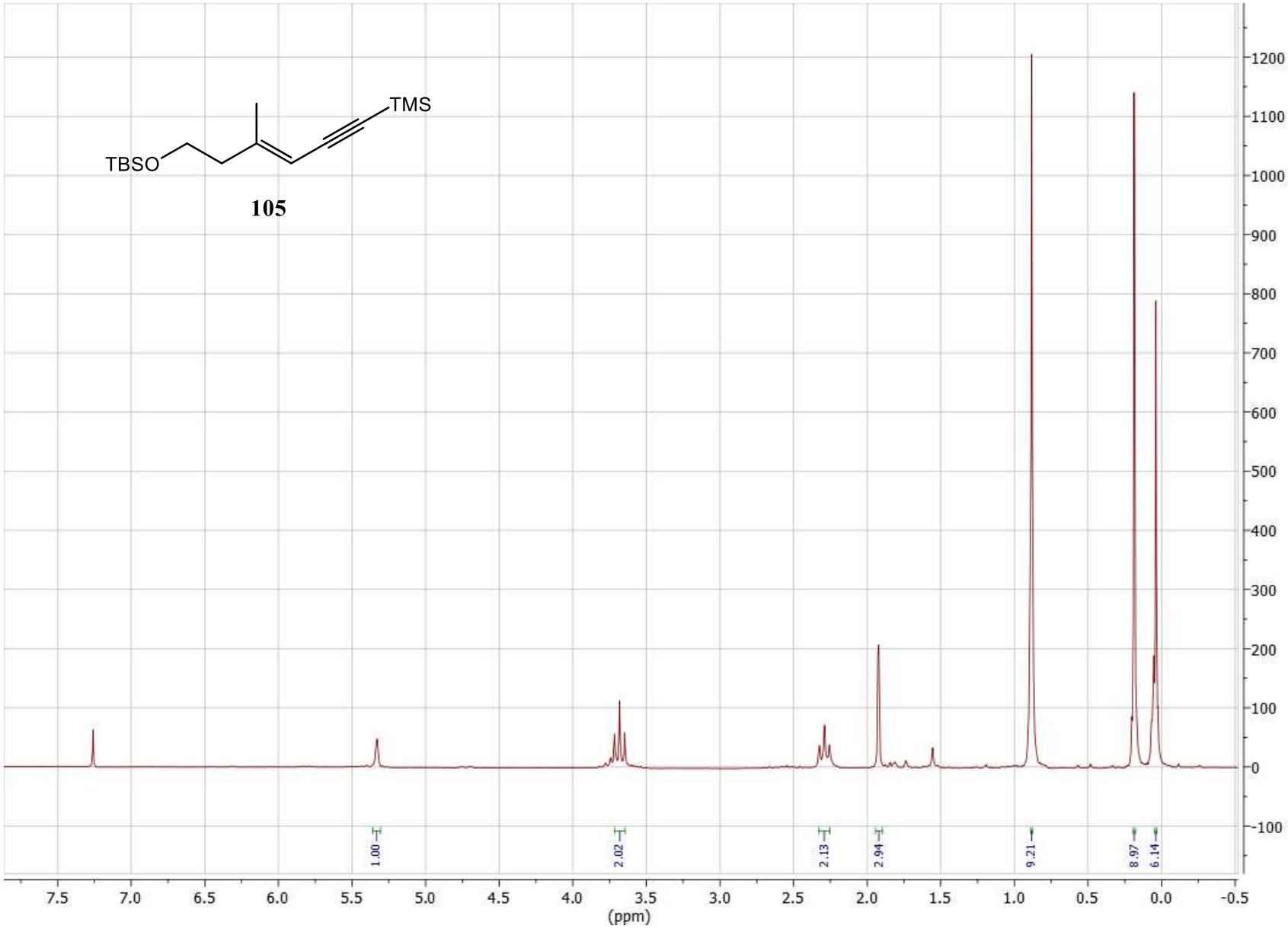

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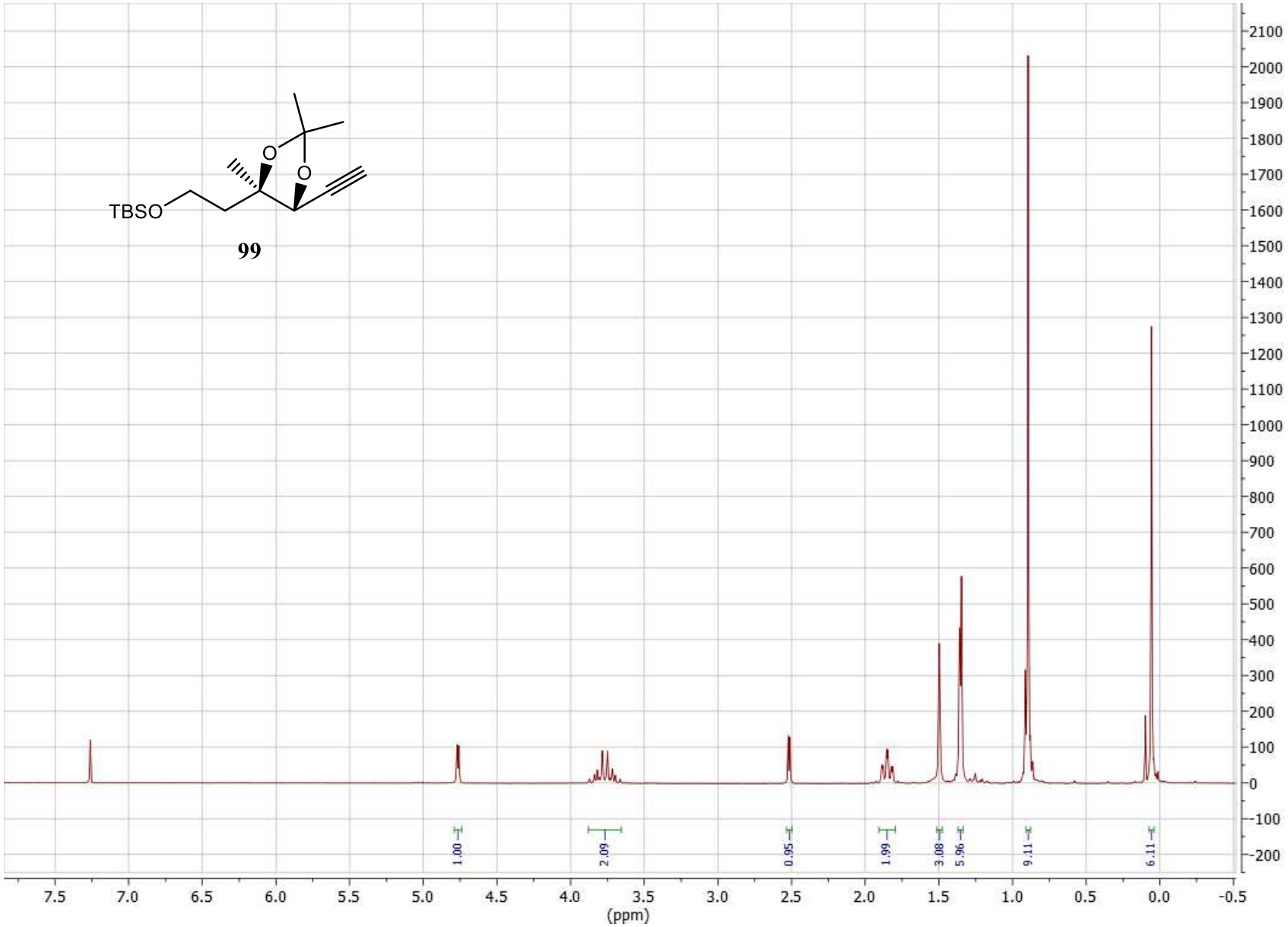

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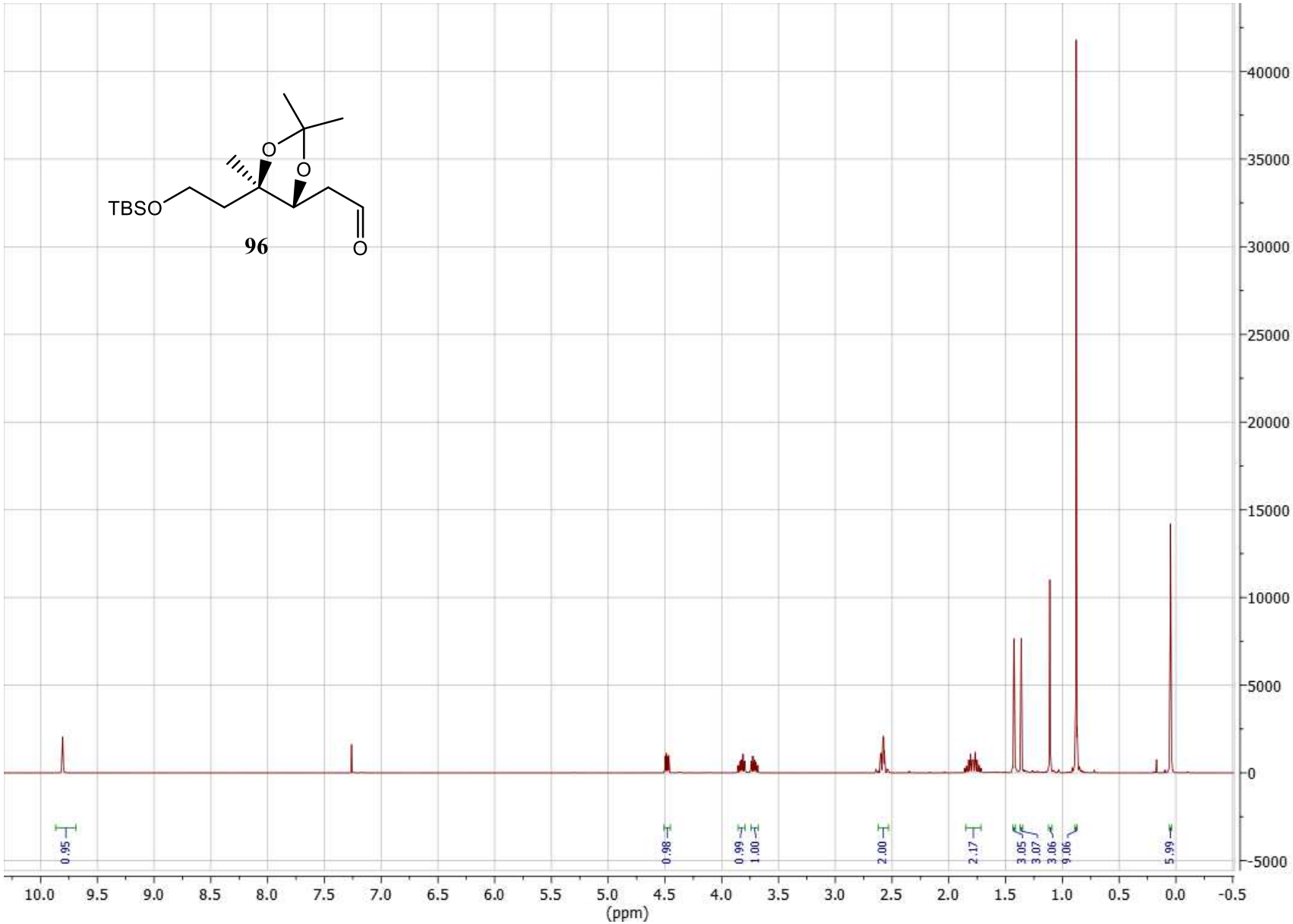

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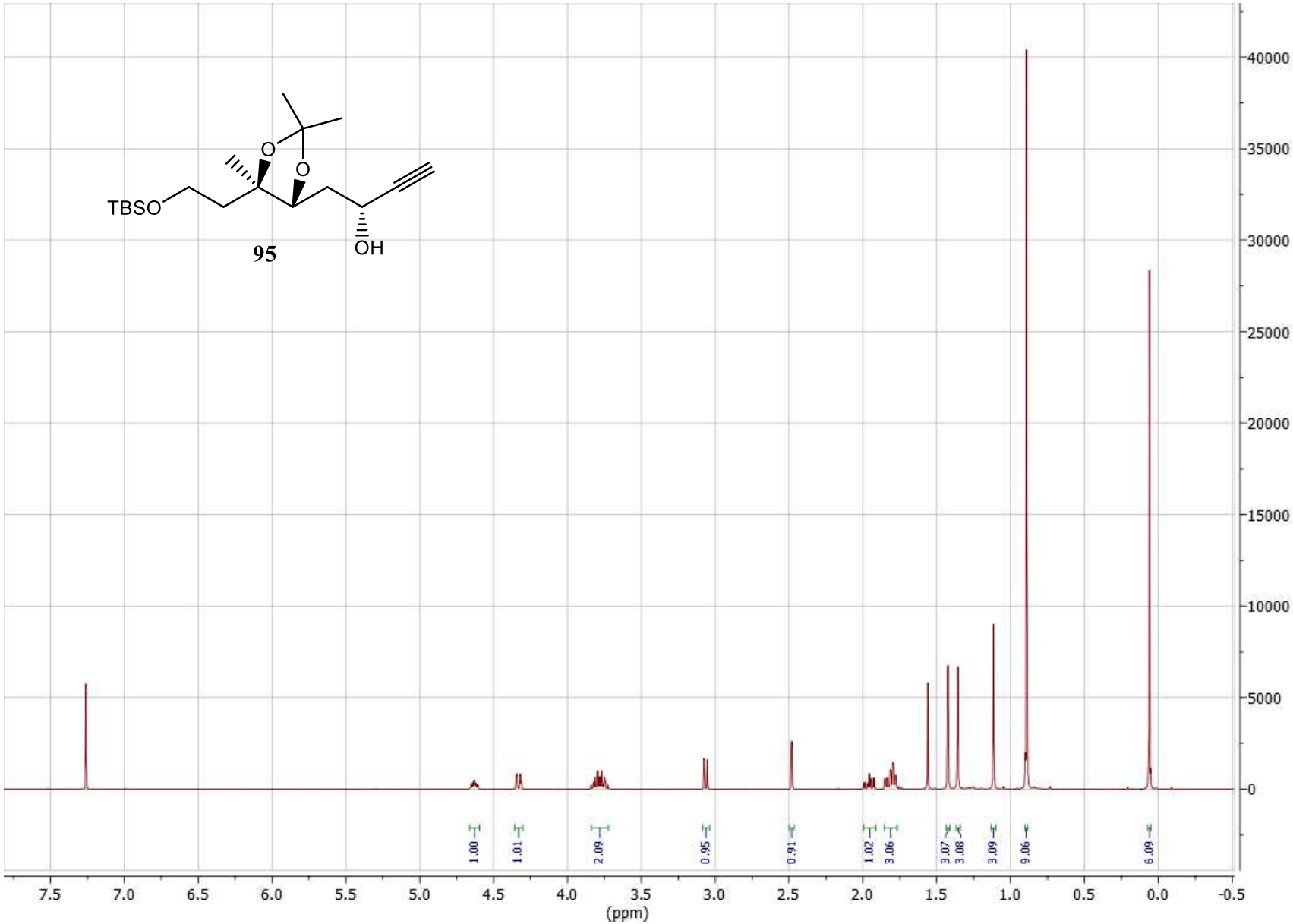
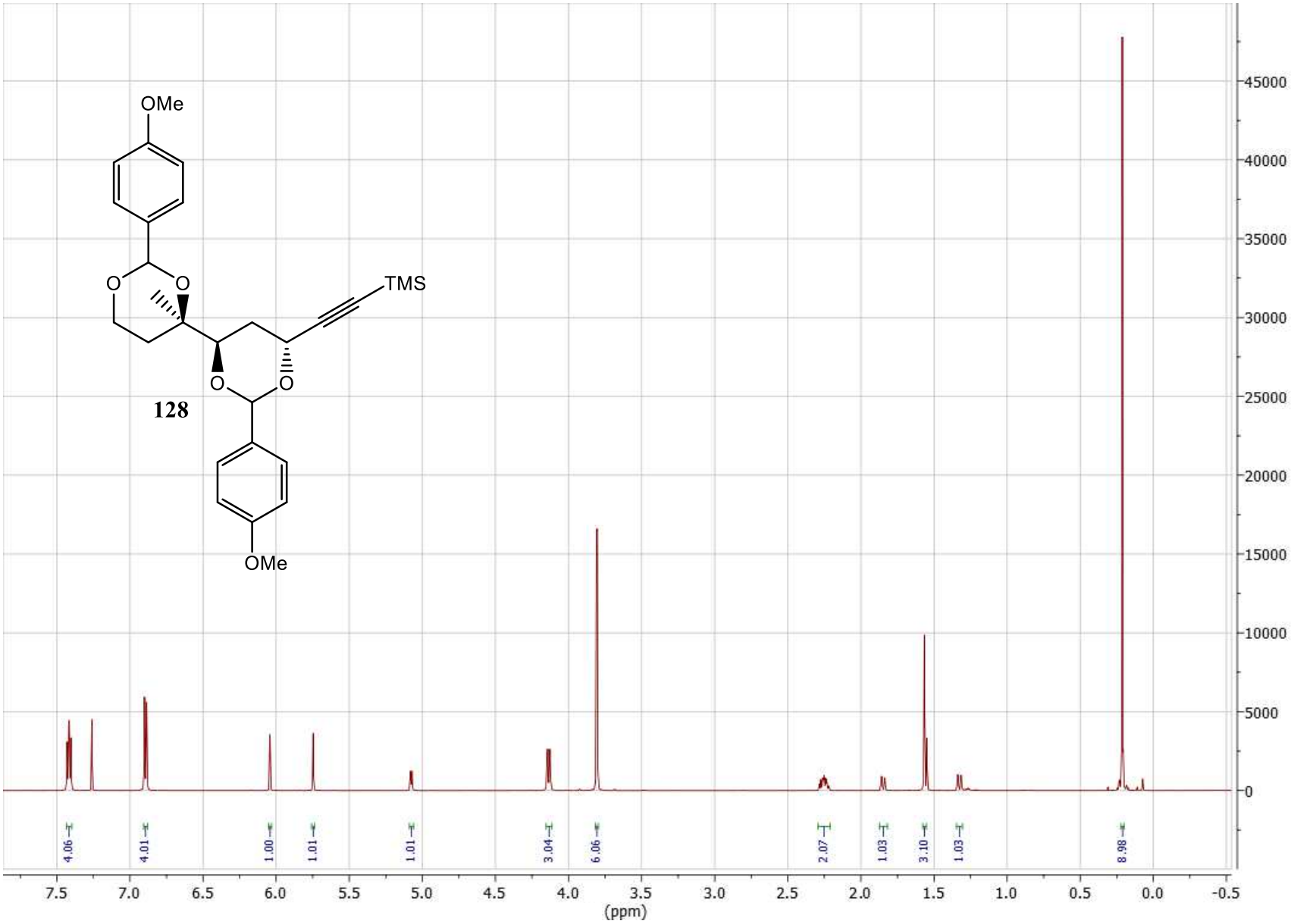
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