TECHNISCHE UNIVERSITÄT WIEN

DIPLOMARBEIT

TOWARDS THE TOTAL SYNTHESIS OF ELISABETHIN A

AUSGEFÜHRT ZUM ZWECKE DER ERLANGUNG DES AKADEMISCHEN GRADES EINES
DIPLOM-INGENIEURS UNTER DER LEITUNG VON

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EINGEREICHT AN DER TECHNISCHEN UNIVERSITÄT WIEN
FAKULTÄT FÜR TECHNISCHE CHEMIE

VON

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TAUBSTUMMENGASSE 13/8
1040 WIEN

WIEN. 15.12.2016

_____
(David Schönbauer)

_____
(Valentin Enev)

Wenn du nicht mehr weiterweißt

Denk an Kolumbus

Der hat Amerika entdeckt

Und es nicht einmal gemerkt

Der Depp

Es geht nicht immer um das Weiterwissen

Sondern um das Weitermachen

SEBASTIAN 23

Acknowledments

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Abstract

The following thesis describes a second generation synthesis of a main intermediate of the total synthesis of elisabethin A. During the route two Claisen rearrangements and diastereoselective ring closing metathesis are conducted. The sequence proceeds with a diastereoselective conjugate addition of an unsaturated ester. Furthermore, the route is altered and furnishes a regioselective silyl ether cleavage and a formation of a seven membered ring *via* ring closing metathesis.

The stereochemistry of all products is evaluated through extensive NMR studies, chemical derivatization and/ or XRD experiments.

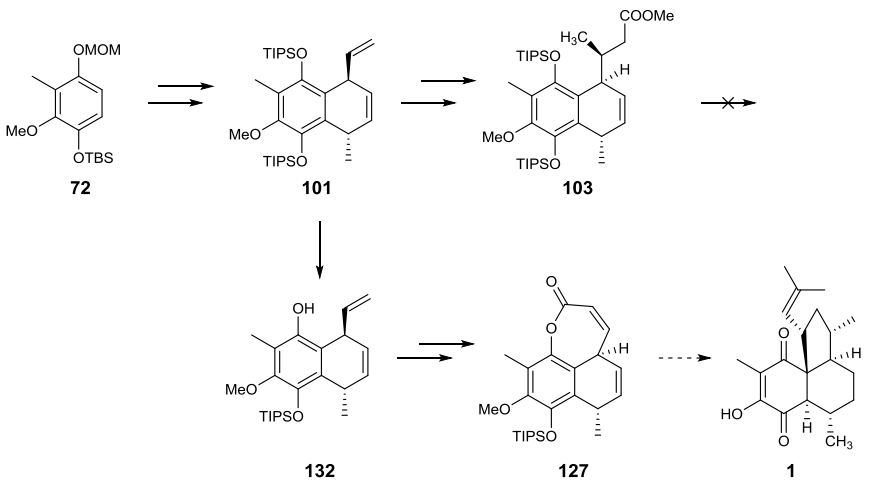
Kurzfassung

In der folgenden Diplomarbeit wird eine Synthese der zweiten Generation eines Haupintermediates der Totalsynthese von Elisabethin A beschrieben. Dabei sind insbesondere zwei Claisen Umlagerungen und eine diastereoselektive Ringschlussmetathese hervorzuheben.

Im weiteren Verlauf wird eine diastereoselektive konjugierte Addition eines Metallorganyls an einen ungesättigten Ester beschrieben. Aufgrund neuer Erkenntnisse wird die Route angepasst und durch eine regioselektive Silyletherspaltung und die Synthese eines siebengliedrigen Laktones erweitert.

Die Stereochemie der erhaltenen Produkte wird durch ausführliche NMR Spektroskopie, Derivatisierung und/ oder Röntgenbeugung bestimmt.

Graphical Abstract



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A Introduction

Since the last decades marine organisms are in focus of chemists and biologists. Among others, chemically rich gorgonians are especially interesting. These sea whips, sea fans or sea plumes occur mainly in the West Indian Sea and represent about 38 % of the known fauna in the region. Their metabolites often differ from terrestrial sources and are therefore subject to biomedical testing and chemical total synthesis projects[1]. The genus *Pseudopterogorgia* is one of the most common of these organisms and fifteen species are so far documented. Its metabolites have promising biological properties: Several are anti-inflammatory, analgetic[2], antibacterial[3] (e.g. anti tuberculosis[4]) and/ or cytotoxic[5]. From the organic extract of the sea plume *P. elisabethae* several new metabolites were isolated.[3,6–11] Interestingly, most of the terpenoid substances lacked a sugar moiety and possessed an unusual and unknown carbon framework. One of these substances is elisabethin A (**1**)[11].

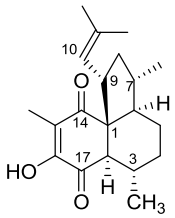
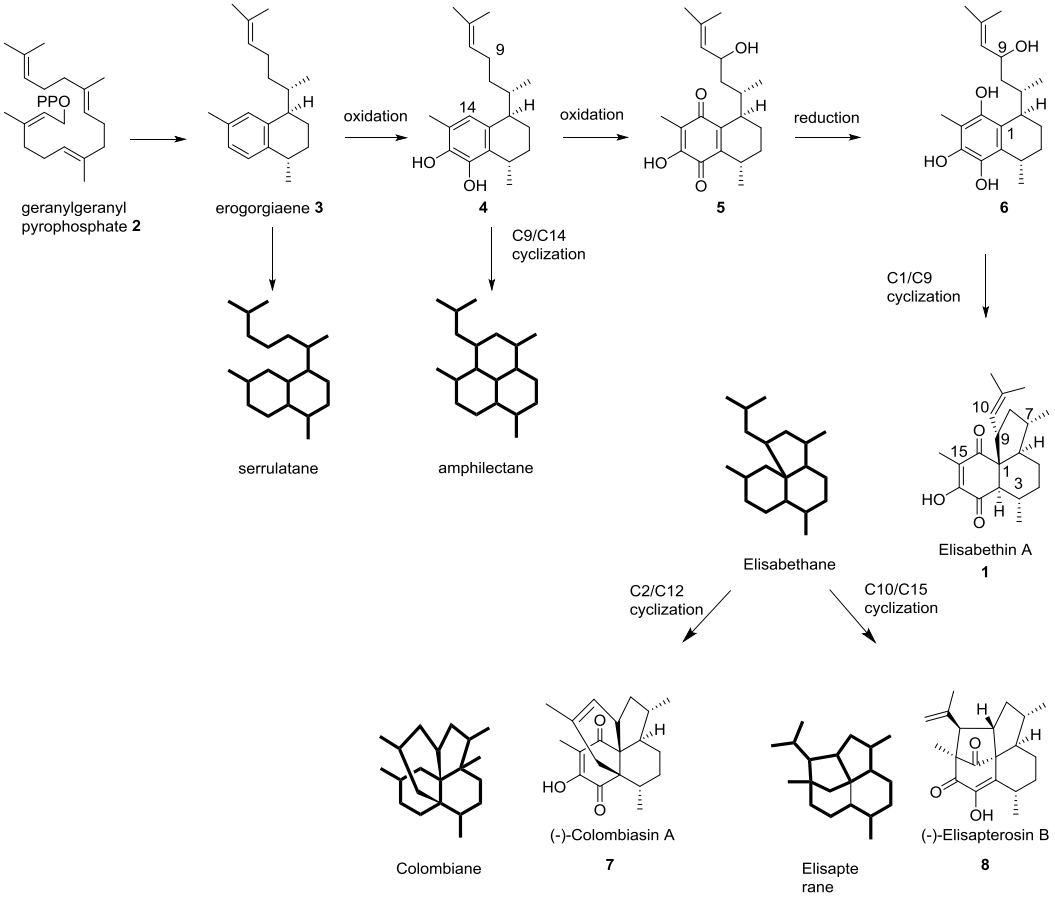


Figure 1 Elisabethin A (**1**)

Due to its low abundance (0.05 w%), only 25 mg of the substance were isolated, which was enough material to determine its relative structure by NMR, IR and X-ray measurements. However, it was not possible to deduce its absolute configuration. Furthermore, its biological activity could not be tested. This gives reason to obtain more material by means of chemical synthesis. Additionally, the development of a total synthesis is interesting because of its unusual carbon framework from an academic point of view. The molecule is a tricyclic 6,6,5-fused fully substituted enedione. Elisabethin A has five contiguous stereocenters. One is located on a quartery carbon atom. Its structure is shown in Figure 1.

The biosynthetic pathway for elisabethin A has not yet been fully investigated. However, a plausible biosynthesis for pseudopterosins has been suggested in 2005[12] and can be seen in Scheme 1.

The proposed biological formation starts with a geranylgeranylpyrophosphate, which cyclizes to intermediate **3**. With the tetrahydronaphtyl moiety already in place, this compound is perceived as one key intermediate for the synthesis of many different triterpenes deriving from *Pseudopterogorgians.* As seen in Scheme 1, oxidation and cyclization form the structure of the amphilictanes (**4**). Further transformations enable a C1/C9 cyclization to the elisabethane carbon framework. A cyclization of this structure between C10/C15 or C2/C12 forms the carbon skeletons of colombiasin A (**7**) or elisapterosin B (**8**). Both triterpenes were isolated from *P. elisabethae*.[6][10] The isolation of these substances supports the suggestion of this biosynthesis additionally, since those triterpenes are metabolites from elisabethin A.



Scheme 1 Possible Biosynthetic Pathway for the Formation of the Carbon Skeleton of Elisabethans and other Triterpenes found in *Pseudopterogorgians*

Although the structure of elisabethin A has been known since 1998 only three attempts of its total synthesis are reported.[13–15] None of those approaches were accomplished without difficulties and the majority has been rerouted towards different natural products, since elisabethin A could not be reached. The interesting structure, its obvious challenging synthesis and the possible physiological properties of the molecule are the reasons to engage its synthesis furthermore.

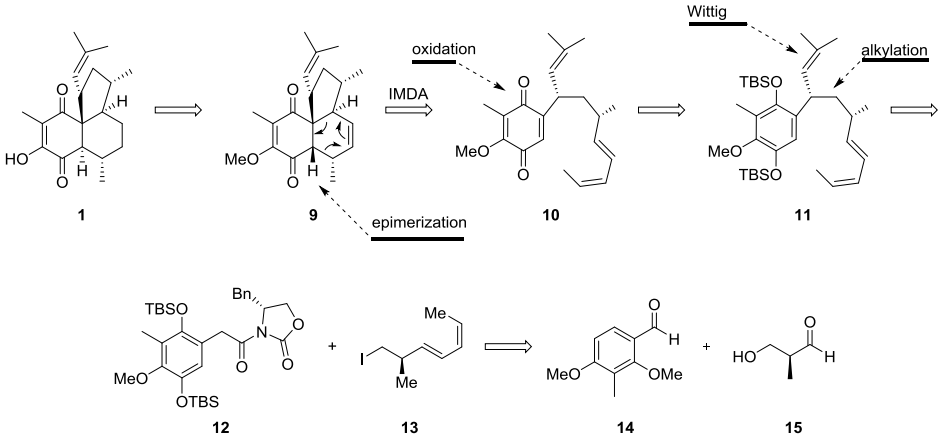
B State of the Art

As mentioned, only three groups have tackled the synthesis of elisabethin A. Every single attempt had its difficulties and limits, which will be discussed in detail in this chapter. In short, the first synthesis was published in 2003 by Mulzer. However, the stereochemical assignment was criticized[16], which led to a second approach by this group ten years later. Also in 2003, Rawal published another synthesis, which was designed to give *ent*-elisabethin A. Furthermore, the work done by Kaiser and Steiner from our group is also discussed in short, focusing especially on the impact on this work.

In all synthesis the installation of one or more stereocenters was crucial and set the end to one or the other route. 2003, Mulzer and Rawal were both relying on the stereogenic outcome of an intramolecular Diels - Alder reaction (IMDA) at the near end of their synthesis. On the other hand, Mulzer's second approach in 2014 installed more stereogenic centers earlier in the synthesis by an *inter*molecular Diels - Alder reaction and assigned the remaining centers step by step. Steiner and Kaiser abandoned the Diels - Alder reaction generally, installing each stereocenter on its own by means of both reagent and substrate controlled reactions during the synthesis.

B I Heckrodt and Mulzer

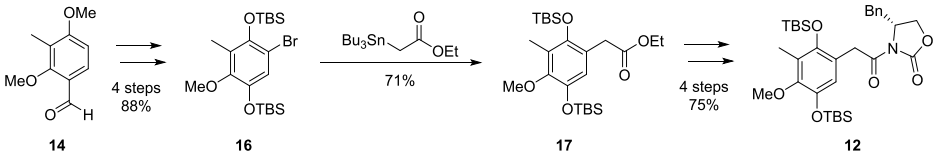
This synthesis was the first to be reported in 2003[13]. According to the retrosynthetic analysis shown in Scheme 2 the main intermediate is quinone **10**, which would be synthesized from two building blocks by asymmetric alkylation. The halide **13** and the Evan's oxazolidinone **12** would be both accessible from the aldehydes **14** and **15.** Obviously, this synthesis relies on the correct outcome of the IMDA reaction and the epimerization of the proton at C2 at the end of the synthesis. As seen later on, a synthesis that is depending on the installation of several stereocenters in one reaction can either be elegant or rather problematic, because rerouting the whole sequence could be difficult or even impossible.



Scheme 2 Retrosynthetic Analysis by Mulzer

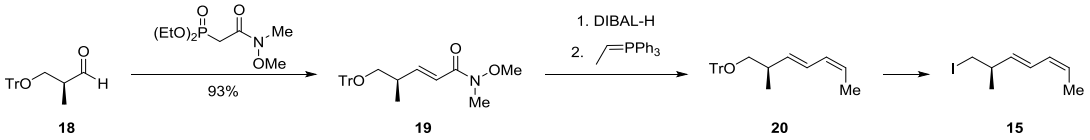
The synthesis to the oxazolidinone **12** (Scheme 3) started by converting the 2,4 dimethoxy-3-methyl benzaldehyde (**14**) to the phenol using the Dakin reaction. Then the methoxy group was cleaved and the resulting hydroquinone was protected with silyl groups. After bromination, compound **16** was synthesized in four steps with 88% yield. The side chain was installed by a Negishi-Reformatsky coupling. Interestingly, the

following hydrolysis to the carboxylic acid was not possible and the cleavage of the ethyl group could only be reached in a three step reduction/ oxidation sequence. The carboxylic acid at hand allowed the synthesis of the Evans oxazolidinone (**12**).



Scheme 3 Synthesis of the Oxazolidinone Fragment **12**

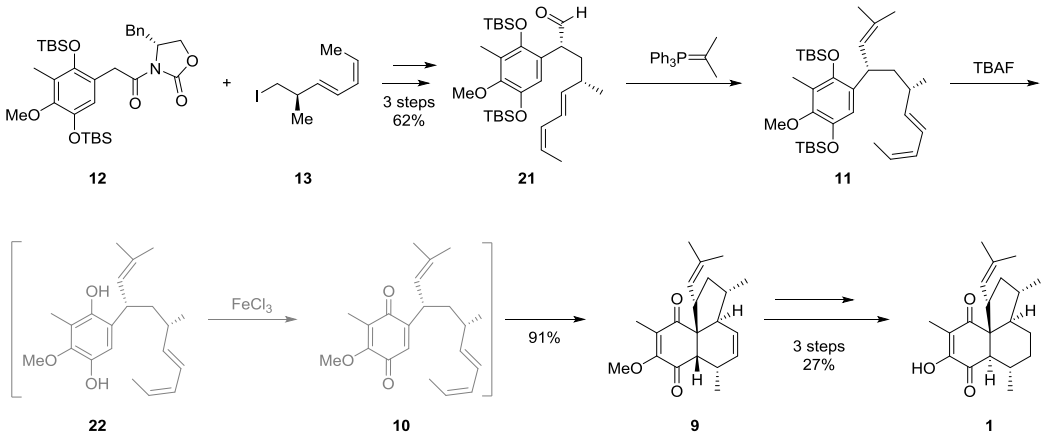
The other building block that was necessary for the asymmetric alkylation was synthesized according to Scheme 4. The first double bond was introduced *via* a Wittig reaction to the Troc protected alcohol **15** giving the Weinreb enamide (**19**). Reduction with DIBAL-H afforded the aldehyde and another Wittig reaction installed the second olefin (**20**). To ensure *Z* configuration, a salt free protocol was used. With the *E-Z* diene at hand, iodine **15** was reached in two additional steps.



Scheme 4 Synthesis of Diene **15**

The endgame (Scheme 5) was initiated by the reaction of iodine **15** with either ester **17** or oxazolidinone **12**. Because the reagent controlled alkylation gave only moderate diastereomeric excess (*de*) of 42%, the authors decided to enhance the selectivity with an Evans alkylation. This improved the *de* significantly to 86%. However, the conversion decreased and the yield could be determined after recovery of the starting material with 69%. The diastereomers could be separated after the reduction to the alcohol with $LiBH_4$. To reach the IMDA precursor, the alcohol was oxidized to aldehyde **21**. This compound was further subjected to a Wittig olefination furnishing triene **11**. At last the TBS groups were cleaved with TBAF to give hydroquinone **22**, which was oxidized *in situ* to quinone **10** (with a tenfold $FeCl_3$ in the reaction mixture). This crucial compound could only be detected by TLC and NMR, as the quinone cyclized immediately to give the tricyclic enedione **9**

. The synthesis could be completed with three further transformations. First the double bond at C4/C5 was reduced. Then the configuration at C2 was inverted under basic conditions (NaOH) and the cleavage of the methoxy group gave the final molecule. The yield of the last three steps is with 27% rather moderate.



Scheme 5 Mulzer's Endgame

The optical rotation of the final product was similar to the one determined by Rodriguez 1998[11]. However, a closer look at the NMR spectra reveals minor discrepancies in both ^{13}C and ^{1}H-NMR (Figure 2). Furthermore X-ray studies to determine the structure beyond any doubt were not published. Possible reasons for these discrepancies will be discussed in full detail later together with matching problems emerging from Rawal's synthesis.

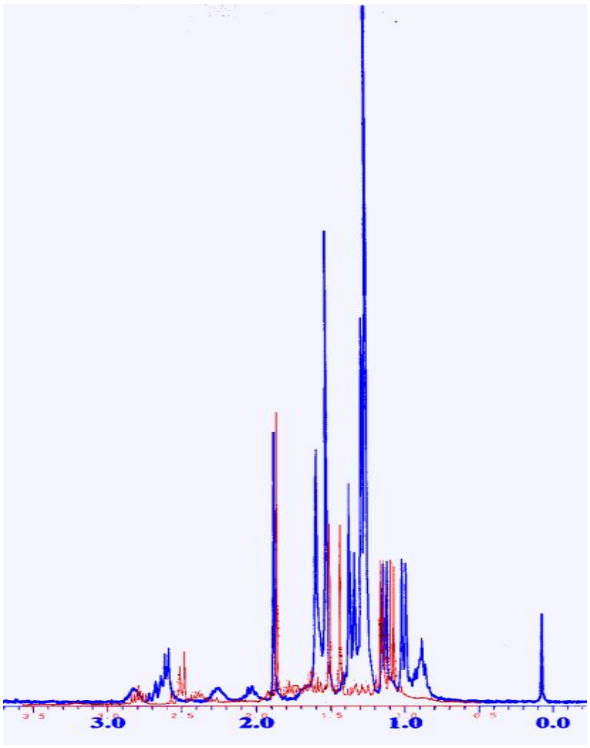
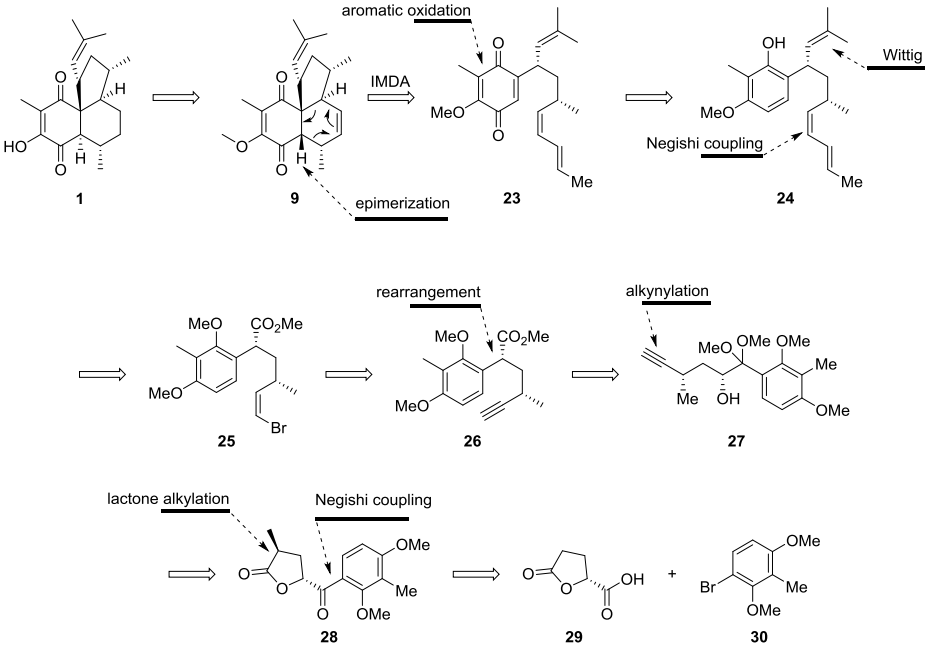


Figure 2 Montage of the ^{1}H Spectra Supplied by Mulzer[17] (blue) and Rodríguez[11] (red)

B II Waizumi and Rawal

A few months after Mulzer, Rawal also published a synthesis for *ent*-elisabethin A[15]. However, he was not able to reach the final molecule. The crucial endpoint was the epimerization at C2 towards the end of the synthesis. The retrosynthesis is quite similar to Mulzer's and will be described in the following.

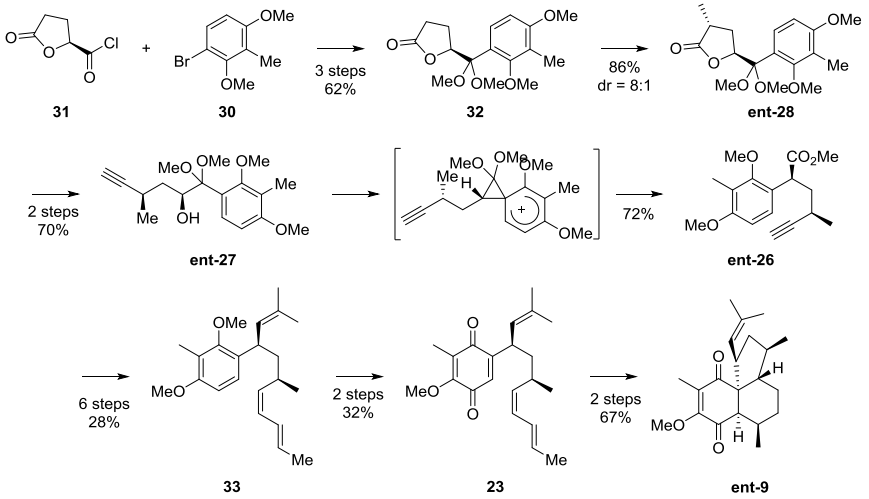
According to Scheme 6 the six and five membered rings should be fused in an IMDA reaction to give compound **9**, which would be the same key intermediate as in Mulzer's synthesis. The strategy relies again on the correct assembly of the remaining stereocenters during the IMDA and the epimerization at C2. Interestingly, the IMDA precursor differs from the one in Mulzer's approach. Instead of the *E-Z* diene (**11**), Rawal targeted a *Z-E* diene (**23**). As seen in Scheme 6, the quinoide structure should be reached by an aromatic oxidation. The isoprenyl moiety would be installed *via* a Wittig reaction and the *Z*-olefin through a Negishi coupling.



Scheme 6 Retrosynthetic Analysis by Rawal

Rawal's synthesis started from commercially available 1-bromo-2,4-dimethoxy-3-methylbenzene (**30**) and 5-oxo-2-tetrahydrofurancarboxylic acid (**29**). The carboxylic acid was formed from glutamic acid. Unfortunately, the D enantiomer is necessary for the synthesis of the target molecule, which is significantly more expensive than the naturally occurring compound. This purely economic reason led to the decision to synthesize *ent*-elisabethin A instead of the natural product.

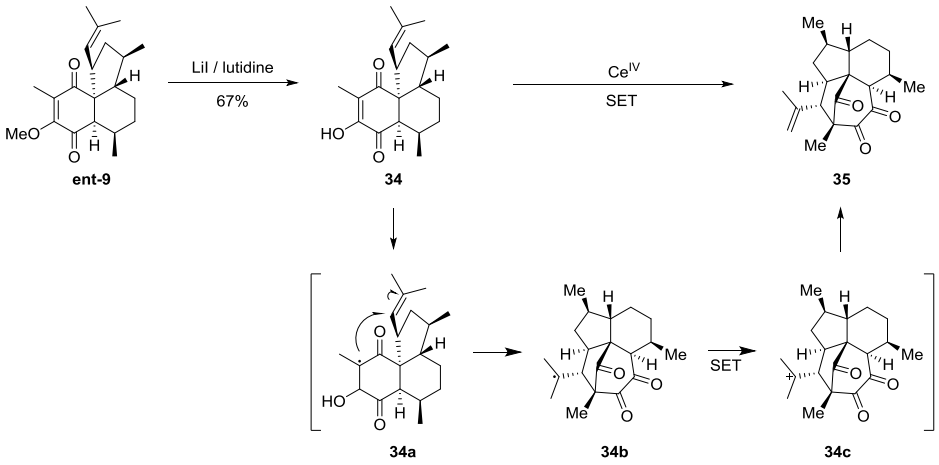
A Negishi coupling between arylcompound **30** and acid chloride **31** resulted in the corresponding ketone, which was immediately protected as ketal with orthoformiate under acidic conditions (Scheme 7). The desired product (lactone **32)** was not stable under the reaction conditions during the esterification and hydrolyzed to the corresponding open chain compound. To cyclize the compound again, it was treated immediately with potassium *t*-butoxide. Lactone **32** could be reached in 62% over these three steps. This sequence was followed by the methylation at C7 (elisabethin A numbering) *via* the lithium enolate, which furnished the desired *trans* product with a diastereoselectivity of 8:1.



Scheme 7 Rawal's Synthesis

The alkyne moiety was installed in two steps. First the lactone (***ent*-28**) was reduced with DIBAL-H and the resulting lactol was elongated *via* a Seyfert-Gilbert reaction to give compound ***ent*-27** in 70% yield. After the rearrangement, the methyl ester was installed and the triple bond was simultaneously placed in the correct position (***ent*-26**). Then the molecule was brominated with NBS and reduced with diimine. A second Negishi coupling afforded the *Z-E* moiety in 46% yield over three steps. Then the methyl ester at C10 was reduced with DIBAL-H and a Wittig reaction furnished the isoprenyl moiety (**33**). Now the more hindered methoxy group was cleaved with NaSEt and the aromatic ring was oxidized to the IMDA precursor ***ent*-23** by a Salcomine catalyzed oxidation in moderate yield (49%). The IMDA, the most crucial step of the synthesis, proceeded under heating (80 °C) in toluene with 67% yield. The resulting *endo* product (***ent*-9**) was characterized by NOE experiments and its relative configuration met the expectations. The double bond at C4/C5 was reduced quantitatively using Wilkinson catalyst. Unfortunately, only two steps away from the natural product, the epimerization at C2 was not possible and the final molecule could not be reached.

Nevertheless, the authors rerouted the synthesis towards *ent*-elisapterosin B (**3**) according to Scheme 8. The methoxy group was cleaved with LiI and lutidine. Then the molecule was cyclized oxidatively with CAN. The presumed diketone (**35**) could be enolized and gave the desired product, whose NMR data perfectly matched with the isolated product[10]. The synthesis of the natural product was not only successful, but also proved the proposed configuration of the IMDA product (***ent*-9**) indirectly.

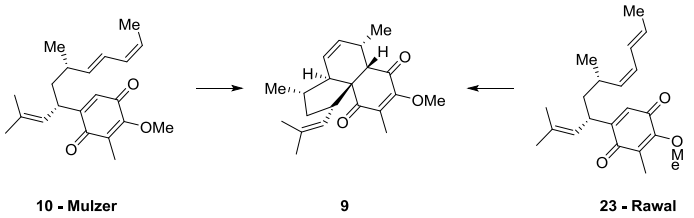


Scheme 8 Rerouting the Synthesis Towards *ent*-Elisapterosin B

B III The Troublesome IMDA Reaction

Both described syntheses rely on an IMDA reaction and as especially Mulzer's synthesis was criticized later on, a more detailed consideration regarding this crucial step is made in the following chapter. Reasons for the failure during the reaction were given by Zanoni et al 2004[16]. In their review the authors are focusing especially on the precursors and possible transition states during the IMDA reaction.

In Scheme 9 both precursors for the IMDA are illustrated. As previously stated, both syntheses postulate the same product. However, the configuration of the starting material is different. Mulzer used a *E-Z* diene, whereas Rawal constructed a *Z-E* configuration. (In fact Rawal tried to synthesize *ent*-elisabethin A and therefore as well the enantiomer of the IMDA product.)

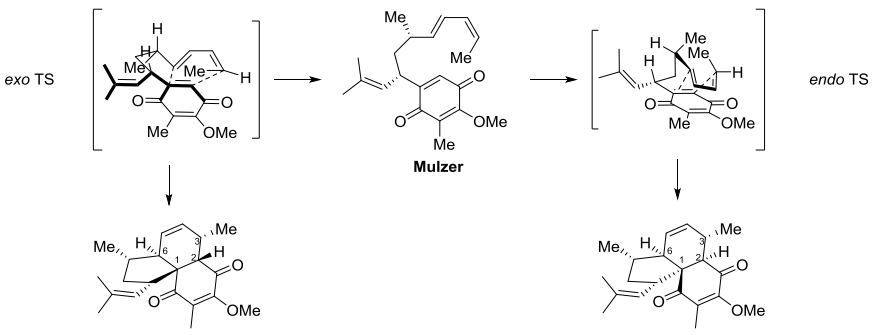


Scheme 9 Comparison of the IMDA Precursors **10** and **23**

Nevertheless, their NMR spectra are not the same, which should be the case if the compounds were indeed enantiomers. The only possibility is that one or the other configuration differs from the postulated structures and they are actually diastereomers. Rawal was able to isolate the IMDA precursor and characterized it with extensive NMR measurements. Additionally, the compound was used for the synthesis of *ent*-Elisapterosin B, whose NMR signals are in perfect correlation with the natural product. Hence, it can be safely assumed that the postulated configuration in Rawal's synthesis is correct.

However the question remains, for which reasons Mulzer's reaction proceeded differently and which stereoisomer was synthesized. Generally, a few possibilities are probable. First, every Diels - Alder reaction can proceed *via* either an *endo* or an *exo* transition state. The *endo* transition state is generally the kinetic product and is favored by Lewis acid (LA) catalyses, low temperature and electron withdrawing groups at the dienophil. Furthermore, the configuration of the diene can be also changed due to isomerization of the double bonds.

B III.1 *E-Z* Diene as Precursor

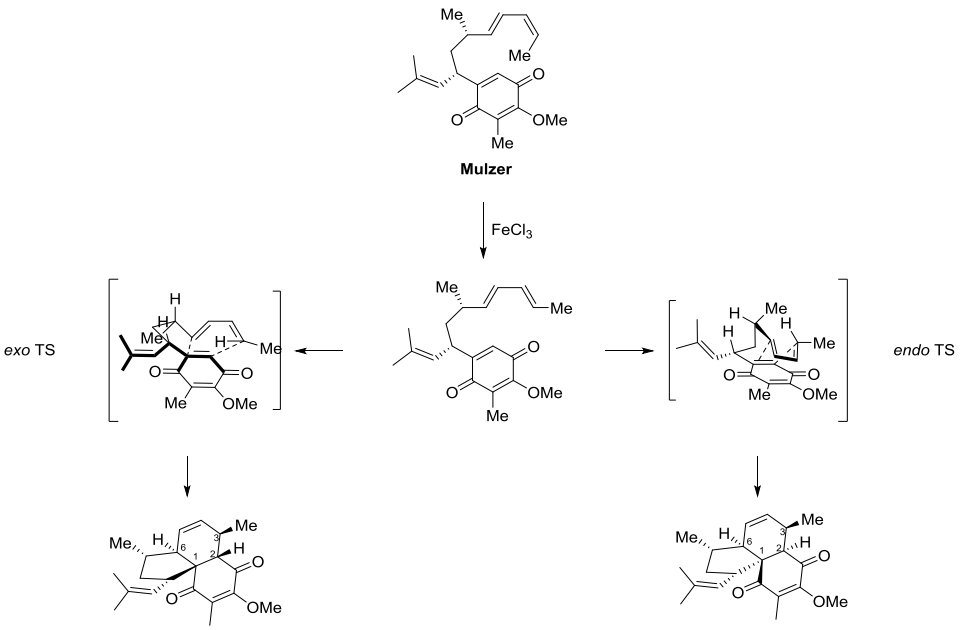


Scheme 10 Pathways for the *E-Z* Diene

If the reaction proceeds *via* the *exo* transition state (TS), the configurations at C1, C3 and C6 are the same as in the natural product. The configuration at C2 is opposed to the desired one and requires epimerization. As C2 is in α position to the carbonyl, it was postulated to epimerize the center through basic enolization rather easily. However, Rawal failed to finalize his synthesis at exactly this stage. Meanwhile, Mulzer postulated in his second attempt in 2014, that the configuration at C2 in elisabethin A might be the energetically disfavored and the isomerization of the 6-6-5 tricylic is not possible[14]. On the other hand, if the *endo* TS is more favored, the configurations at C1 is inverted, whereas C2 is already correctly assigned. The inversion of the stereocenter at C1 is impossible, since it is a quartery carbon.

After a short analysis of the reaction conditions, the *endo* transition state is more likely. As previously stated, this reaction mechanism is favored through low temperatures and is catalyzed by Lewis acids. Since the reaction mixture contains a tenfold of $FeCl_3$ (for the oxidation of the hydroquinone), this is very probable. Additionally, an *endo* TS also reduces the allylic strain between the isoprenyl unit and one of the carbonyl groups. In fact, Mulzer did suggest the *endo* transition state for his synthesis at first. A few month later he corrected himself and suggested the *exo* TS, since it would lead to correct product[17]. However the reaction conditions argue against this transition state.

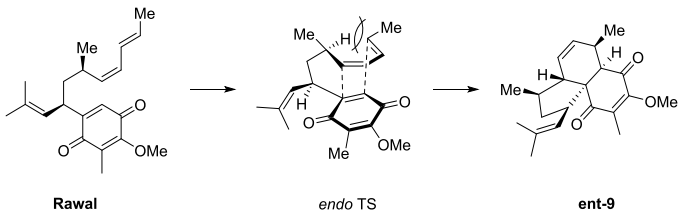
B III.2 *E-E* Diene as Precursor



Scheme 11 Pathways for the *E-E* Diene

This pathway would be possible if the terminal *Z* olefin of the precursor isomerizes to the corresponding *E* olefin. This could be possible under LA catalysis *via* a 1,5 hydrogen shift.[18–20] Therefore, two additional products are reasonable. The product emerging from the *exo* TS would result in an epimer of elisabethin A, because the inversion of C3 appears almost impossible. The *endo* transition state would give the last of the four possible stereoisomers. Here, the centers at C1, C3 and C2 would be different to the proposed structure. Again epimerization at C1 and C3 is not possible and only an epimer of elisabethin A could be reached.

B III.3 *Z-E* Diene as Precursor



Scheme 12 *Endo* TS proposed by Rawal

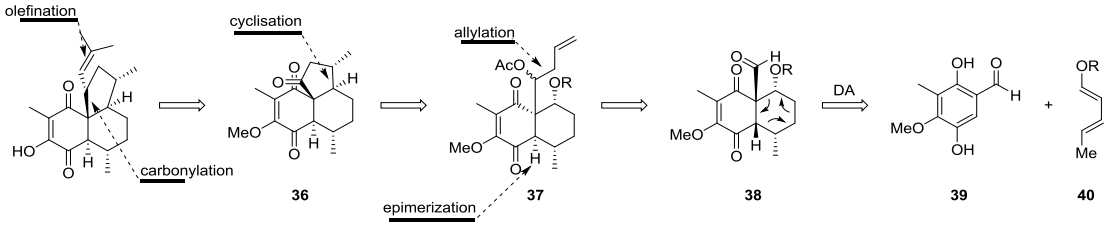
Rawal decided to conduct his synthesis with a *Z-E* diene. Instead of Mulzer's synthesis an isolation of this precursor was possible after the oxidation of the phenol and the IMDA reaction was conducted without any LA under moderate heating (80°C) in toluene. The postulated *endo* transition reduces possible allylic strain and leads to the expected product (***ent*-9**). Its configuration could be assigned by NOE-NMR measurements. Additionally, the compound was further converted to *ent*-Elisapterosin B, which proves the assumed relative configuration.

B III.4 Conclusions

Mulzer's compound (**9**) and Rawal's compound (***ent*-9**) are supposed to be enantiomers. For the reasons stated at the beginning of this chapter they are very likely diasteromers: Compound ***ent*-9** could not be epimerized at C2, whereas **9** could and their NMR spectra are not identical. Apart from the correct conversion of Rawal's intermediate to *ent*-Elisapterosin B, a few further irregularities are pointing towards compound **9** as the wrongly assigned isomer. For instance, the proposed *exo* transition state is not very likely to occur. Furthermore, under the reaction conditions an isomerization to the more reactive *E-E* diene seems very likely. Unfortunately it was not possible to isolate the IMDA precursor **22** to deduce its structure. Finally, the NMR of the synthetic final product is not superimposable with elisabethin A.

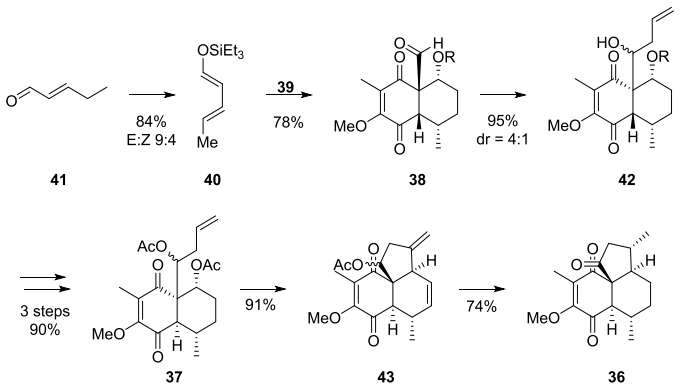
B IV Preindl and Mulzer

As his first synthesis was "met with criticism from outside" for the reasons elucidated above, Mulzer started a second approach, which was published two years ago[14]. The general concept was to discard the problematic IMDA and try to install the stereocenters step by step. According to the retrosynthetic plan (see Scheme 13), the five membered ring would be installed *via* a Heck type cyclization. The decalin system should be formed during a Diels – Alder reaction, installing the quartery asymmetric carbon at the same time. They were relying on a similar epimerization/ enolization at C2 as in their and Rawal's previous synthesis, which they mentioned might be problematic.



Scheme 13 Retrosynthesis for Mulzer's Second Synthesis

After extensive work and drawbacks, it was possible to prepare the Diels - Alder adduct **38** in good yields. The authors pointed out that the following allylation required specific conditions and the correct protection group for the enolate (**40**) to avoid the regioselectivity problems due to presence of three carbonyl groups. They prepared the diene from *E*-pent-2-enal (**41**) by formation of the TES ether (*E*:*Z* 9:4).

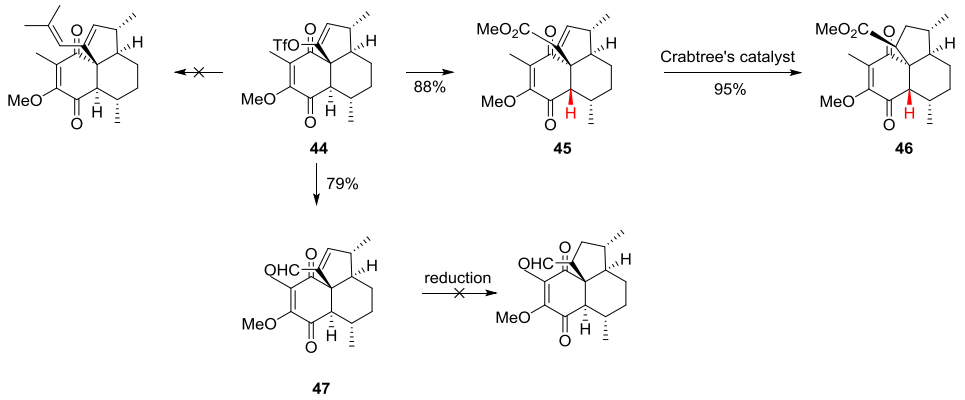


Scheme 14 Preparation of the Elisabethin A Framework by Mulzer 2014

The Diels - Alder reaction was performed *in situ* by adding aldehyde **39** and silver(I)oxide. The allylation proceeded with $ZnCl_2$ as additive rather well as 95 % yield and a *dr* = 4:1 were achieved. After acetylation of the addition product, the stereogenic center at C2 was easily inverted. The epimerization was possible at this stage, because the *trans* configuration (C1 to C2) in the decalin system was favored, which is apparently not the case in the 6,6,5-fused tricyclic system of Rawal's synthesis. Then the TES ether was cleaved and the free phenol acetylated, giving the precursor for the palladium catalyzed cyclization (**37**). The five membered ring was formed easily and in excellent yield (91%). The stereocenter at C7 was correctly installed after hydrogenation with H_2 on Pd/C (**36**). The authors assume that although the hydrogen needs to attack the exocyclic double bond from the more hindered side, the axial position of the carbonyl at C14 directs the hydrogen in the appropriate way. The synthesis of this main intermediate (**36**) can also be seen in Scheme 14.

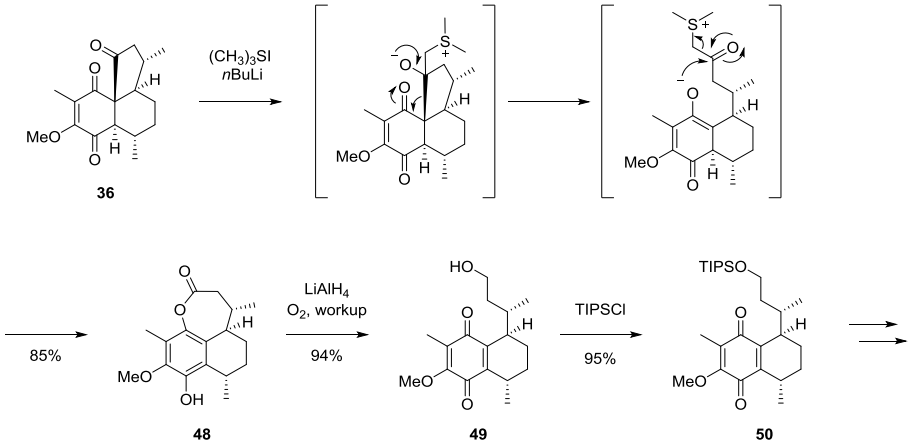
At last the isoprenyl moiety and its correct configuration at C9 needed to be established. As hydrolysis of the acetate led to decomposition of the starting material, the same oxidation/ reduction strategy as in their previous synthesis was applied. Finally, the enolate was trapped as triflate (**44**). Unfortunately, all attempts to install the isoprenyl group by coupling chemistry failed. Hence a detour was necessary (Scheme 15). The authors installed the carbonyl group first and wanted to introduce the double bond *via* olefination. As the carbonylation with methanol lead to epimerization at the C2 (ester **45**), a protocol without methanol in the reaction mixture afforded aldehyde **47**. This compound proved to be inert towards any hydrogenation attempts.

On the other hand it was possible to reduce the double bond of ester **45**. However the next step, the olefination, was not possible and the synthesis attempts were stopped at this point. Furthermore with compound **46** at hand, epimerization at C2 would have been necessary, which Rawal could not achieve ten years before.



Scheme 15 Failed Endgame 2014

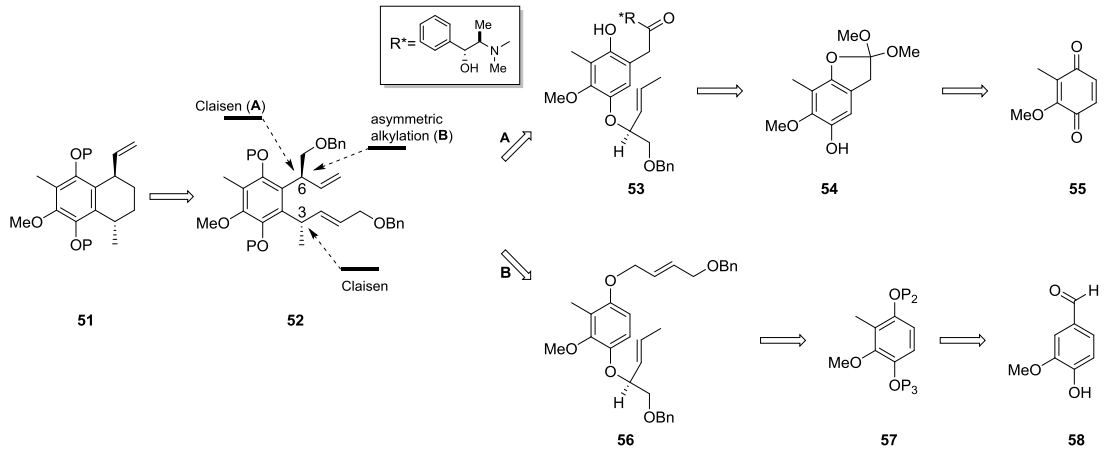
At last, the sequence was changed towards a formal synthesis of elisapterosin B and colombiasin A (Scheme 16). The authors assumed that ketone **36** would readily undergo a Grob-Eschenmoser fragmentation like Claisen cleavage[21], which proceeded with treatment of trimethylsulfonium methylide to lactone **48**. The cyclus underwent reduction to quinone **49**. After protection of the primary alcohol with TIPS (**50**), a comparison of its spectral data proved its identity. As this quinone was previously used in the synthesis of elisapterosin B and colombiasin A by Rychnovsky[22] its formal synthesis was established and the correct configuration of intermediate **36** was also proven.



Scheme 16 Retro-Claisen Cleavage and Formal Synthesis of Eliapterosin B and Colombiasin A

B V Approaches in our Research Group

Both Steiner and Enev[23] and Kaiser and Enev[24] were targeting elisabethin A *via* intermediate **52**, although by different strategies. The retrosynthetic analysis of the endgame is shown in Scheme 28 in the next chapter. Since their work set the basis for my own studies, the key steps and problems will be described in the following. The decalin intermediate **51** would be synthesized by a ring closing metathesis (RCM) of diene **52** according to Scheme 17. Its reductive deprotection would simultaneously hydrogenate the double bond between C4/C5. Then oxidation to the aldehyde and Wittig reaction should give the bicyclic olefin **51**. The RCM precursor **52** was presumed to be accessible through two different routes according to Scheme 17.

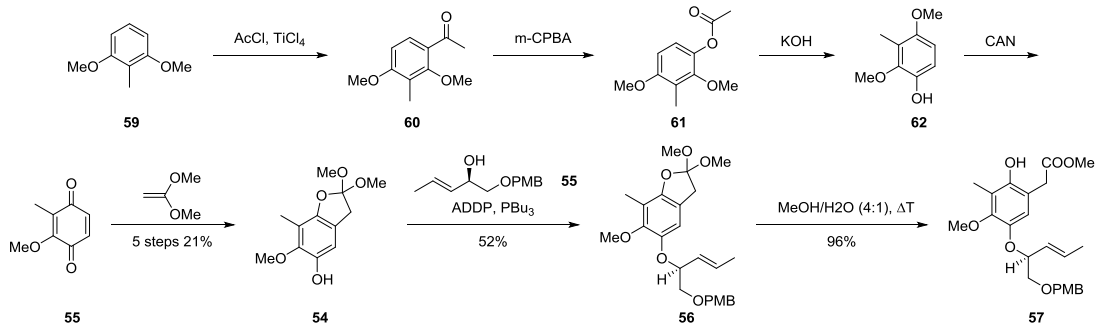


Scheme 17 Retrosynthetic Analysis Kaiser (**A**) and Steiner (**B**)

Route **A** was conducted by Kaiser. The aim was to install the stereocenter at C6 through asymmetric alkylation using *R,R* pseudoephedrine as chiral auxiliary. The lower part of the molecule with the stereocenter at C3 would be introduced *via* a Mitsunobu reaction of a chiral alcohol and the phenol. A Claisen rearrangement would then install the methyl group at the correct position.

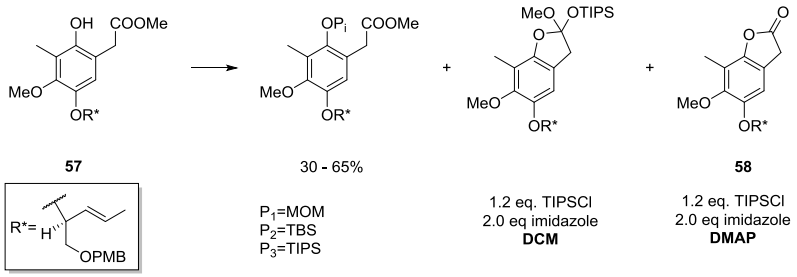
Route **B** on the other hand would rely on a different concept: In short, Steiner's strategy pursued the idea of a double alkylated hydroquinone **56**, which could be converted to diene **52** by two Claisen rearrangements. The southern ether would again be introduced by a Mitsunobu reaction and the northern part by a Williamson ether synthesis. The stereocenter at C6 would be adjusted after the RCM through epimerization. Both routes have an orthogonally protected hydroquinone (**54** or **57**) as a key intermediate, which allows a parallel development of either southern or northern approaches.

B V.1 Enantioselective Approach by Kaiser and Enev



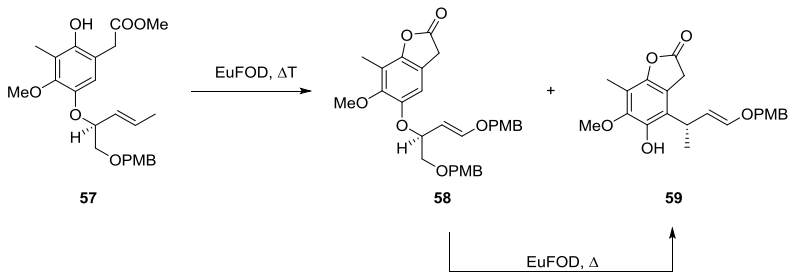
Scheme 18 Synthesis of Orthoester **54** and further Transformation to free Phenol

The synthesis started from commercially available 2,6 dimethoxy toluene (**59**), which gave ketone **60** in a Friedel-Crafts acylation. Then a Bayer-Villiger oxidation gave the acetate **61**, which was cleaved under basic conditions to give free phenol **62**. Another oxidation with cerium ammonium nitrate gave quinone **55**, which underwent a Michael addition with a ketal to furnish othoester **54** in 21% yield over five steps. The free phenol was immediately converted to chiral ether **56** with a yield of 52%..Then the orthoester was hydrolyzed to furnish methyl ester **57**. The protection of the free phenol proved to be laborious and yielded either low yields (30-65%) and/ or side products as seen in Scheme 19. This led to termination of this approach in favor of a slightly different one.



Scheme 19 Protection of Phenol **57**. Conditions for the Formation of the Side Products are given.

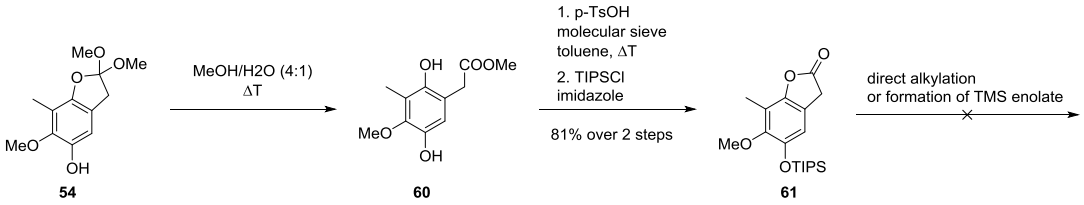
The unexpected behavior of the southern Claisen rearrangement of the free phenol **57** according to Scheme 20 gave reason to this alternative sequence. This experiment was merely executed as proof of concept, to see if the rearrangement of the southern ether proceeded as planned. However, under the Lewis acidic conditions, the formation of lactone **58** and the desired rearrangement were both catalyzed, which resulted in a product mixture of 3:2.



Scheme 20 Claisen Rearrangement of Unprotected Phenol **57**

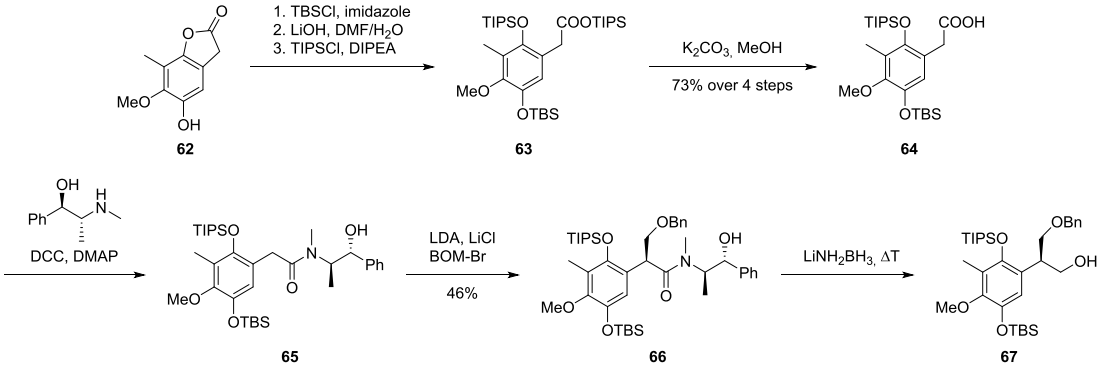
To take advantage of this undesired side reaction and to avoid the unsatisfying protection of the northern phenol, the route was changed to achieve both goals. The idea was to mask the phenol as a lactone

and alkylate it directly. Lactone **61** was formed from the methyl ester (**60**) under acidic (TsOH) conditions in the presence of molecular sieves (Scheme 21). Now the phenol was protected with TIPS instead of conducting the Mitsunobu reaction. Unfortunately, lactone **61** proved to be inert towards any alkylation protocol. Furthermore, it was not possible to convert it to the TMS enol ether to try selective alkylation using a chiral ligand.



Scheme 21 Lactone Alkylation Approach

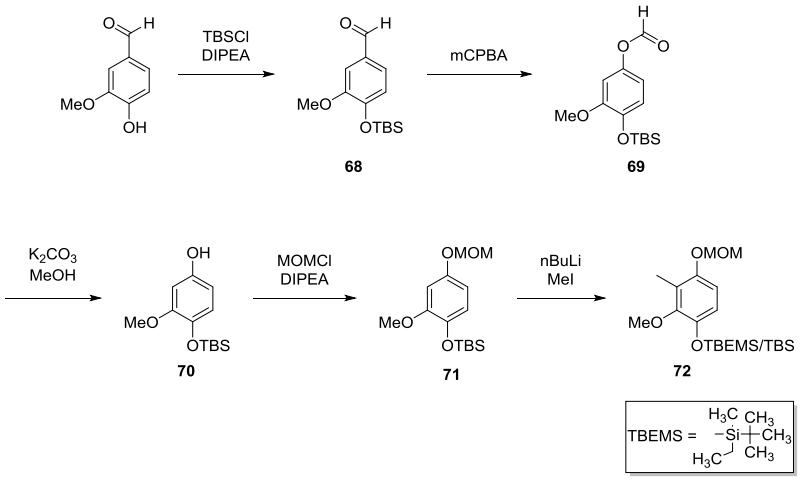
As this strategy did not work as expected, another approach was tried according to Scheme 22. Lactone **62** was TBS protected (instead of installing the chiral alcohol directly). This was done to avoid the problematic protection of phenol **57**. Additionally, the chiral alcohol was modified, bearing an allyl group, which would eventually isomerize due to the strong basic conditions needed for the alkylation. The reasons for the modification of the alcohol and its synthesis will be discussed later on. To avoid these problems, the Mitsunobu reaction would be performed after the assignment of the stereocenter at C6. The sequence proceeded with hydrolysis of the lactone and protection of the free phenol with TIPS to give compound **63**. Then the carboxylic acid was liberated by selective cleavage of the silyl ester under mild conditions (MeOH, cat. K_2CO_3). Interestingly, this reaction proceeded very cleanly with high yield (76 % over two steps) compared to the troublesome protection of phenol **57**. Now the chiral auxiliary (*R,R* pseudoephedrine) could be installed *via* DCC in the presence of DMAP (**65**). The crucial asymmetric alkylation gave 46 % at 70 % conversion (**66**). The amide was reduced to alcohol **67** with $LiNH_2BH_3$ and the *ee* was determined to be excellent (> 99 %). The approach was stopped at this point. However, a possible route to key compound **51** was established, since diene **52** was only a few transformations away.



Scheme 22 Successful Asymmetric Alkylation

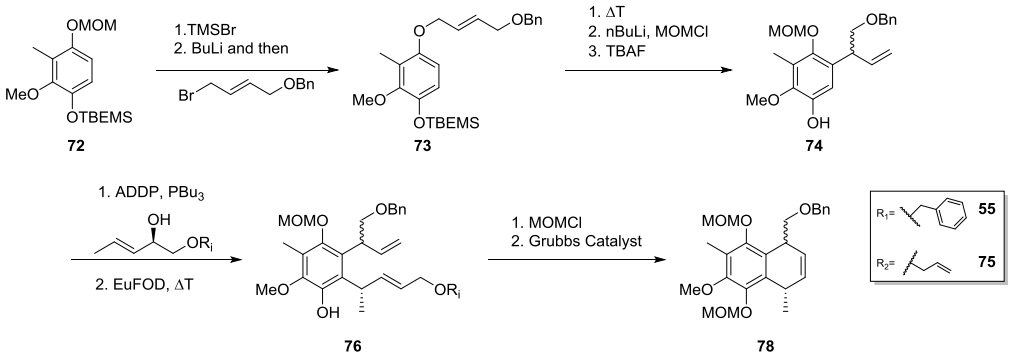
B V.2 Approach by Steiner and Enev

The double protected phenol **57** was established in a quick and high yielding literature known procedure[25] according to Scheme 23. Vanillin was protected with TBSCl and then oxidized to furnish acetate **69**. After basic hydrolysis, the free phenol was protected with MOM. The methyl group was installed with MeI and *n*-BuLi. Interestingly, a certain amount of the *tert*-butyl groups on the silyl ether were methylated as well, resulting in a *tert*-butyl, methyl, ethyl silyl (TBEMS) group. This five step procedure yielded 76 % of a mixture of TBEMS/TBS ether **72** after purification.



Scheme 23 Synthesis of the Protected Hydrochinone **72**

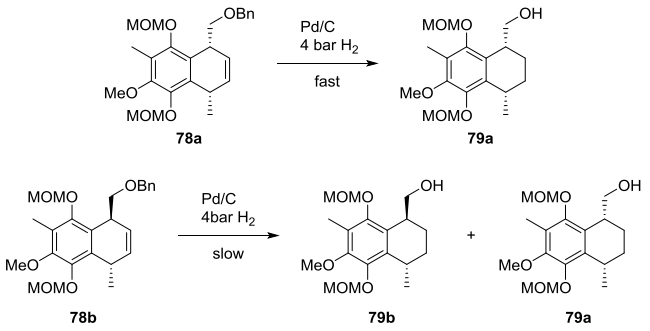
According to Scheme 24 the MOM group was cleaved again with TMSBr and allowed the first installation of the ether group with *n*-BuLi and (*E*)-((4-bromobut-2-en-1-yl)methyl)benzene. A thermally induced Claisen rearrangement furnished the free phenol, which was again protected with MOMCl to allow the cleavage of the TBEMS group with TBAF resulting in phenol **74**. The Mitsunobu reaction of phenol **74** and the chiral alcohol **55** allowed the installation of the second ether. The southern Claisen rearrangement was catalyzed by a Lewis acid (EuFOD) giving precursor **76** for the RCM reaction as diastereomeric mixture, since C6 was not installed enantioselectively. The free phenol was again protected with MOMCl and the metathesis allowed the formation of the bicyclus **78**. However, the last step was not suitable for scale-up since it gave only 51% yield with a catalyst* loading of 17%.



Scheme 24 Synthesis of Bicyclus **78**

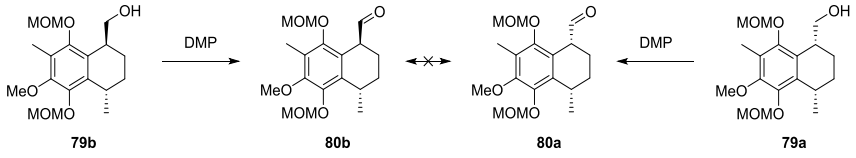
* Dichloro[1,3-Bis(2-methylphenyl)-2-imidazolidinylidene](benzylidene)(tricyclohexylphosphine)ruthenium(II)

To improve the conversion rate, chiral alcohol **55** was modified by exchanging the benzylic moiety with an allyl group (R_2, **75**). (Its synthesis will be discussed later.) The installation of the allyl group allowed the ring closure as a relay ring closing metathesis (RRCM)[26], which proceeded significantly faster and better, giving 83 % yield, with a reduced loading of 8 % catalyst. The reaction was achieved directly with the unprotected diene **76** and was catalyzed with Grubbs II. Hence, the protection of the southern phenol was done after the RRCM. However, both diastereomers were separated and their relative configuration could be confirmed by NOESY experiments. Both stereoisomers were catalytically hydrogenated to cleave the benzyl group and reduce the double bond at C4/C5 according to Scheme 25. The *cis* diastereomer (**78a**) was converted quickly, while the *trans* diastereomer (**78b**) generated a few issues: First, the hydrogenation took four times longer than with the *cis* isomer. This can be explained due to the conformational hindrance of the substrate. However, the main problem was a partial epimerization at C6 to the unwanted *cis* isomer. Additionally, both diastereomers underwent cleavage of the northern protecting group to a certain extent.



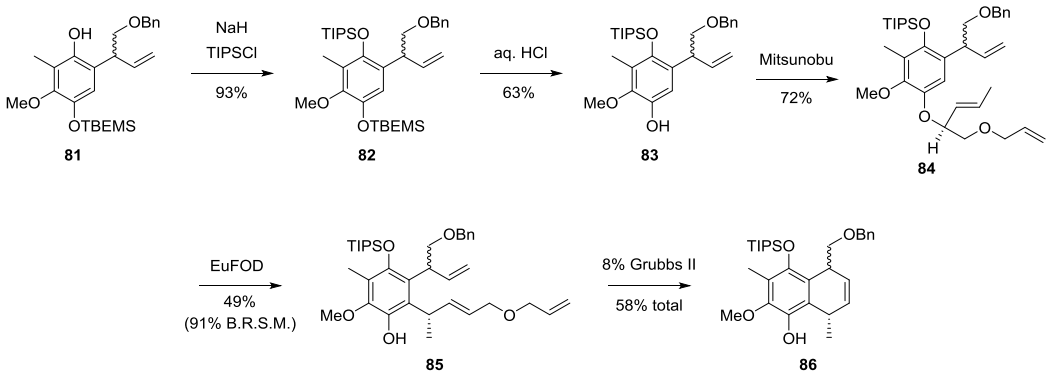
Scheme 25 Catalytic Hydrogenation

Nevertheless, both diastereomers were oxidized to the corresponding aldehydes (**80a** and **80b**) using Dess-Martin periodinane (DMP) and the crucial epimerization was tried (Scheme 26). However, the strong base KO*t*Bu led to partial epimerization, but not full conversion. On the other hand, longer reaction times led only to decomposition. Using milder conditions, such as triethylamine in dichloromethane for several days led only to a 1:1 mixture of the diastereomers. In conclusion, this approach led to the wanted diastereomer **80b**, but with low yields, since the epimerization of C6 was not successful.



Scheme 26 Failed Isomerization of Aldehyde **80**

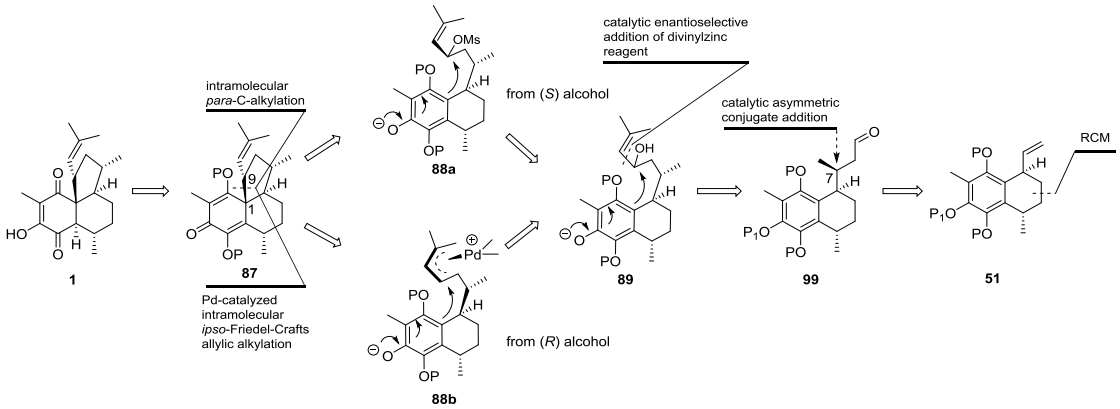
Additionally, another strategy was pursued to overcome the instability of the MOM protecting group during dehydrogenation of the decalin (**78)**. Instead of installing the northern MOM group, the phenol was protected with a TIPS silyl ether (**82**) according to Scheme 27. The TBEMS group was cleaved using HCl in MeCN/THF (phenol **83**). Here, the protocol was altered, because selective deprotection of the TBEMS group with TBAF was not successful, as the TIPS ether was also cleaved partially. The introduction of the chiral alcohol by Mitsunobu reaction and Claisen rearrangement did proceed as described above (compounds **84** and **85**). The RRCM yielded only a fair yield of 58 % (8 % Grubbs II catalyst). However, a closer examination of the reaction revealed interesting circumstances. As the reaction was stopped at 50 %, different reaction rates for both diastereomers were discovered. Under the kinetic resolution the *trans* isomer was slightly favored (1.4:1). This fact enables the possibility to access the bicyclus by a different route, using the chiral induction of the substrate itself.



Scheme 27 TIPS Protection Strategy

C Own Synthesis

C I Retrosynthetic Analysis



Scheme 28 Initial Retrosynthetic Analysis

Our own endgame of the synthesis follows in principle the proposed biological synthesis and is therefore biomimetically inspired. As suggested in the biological pathway, the five membered ring would be closed at last. We suggest either with an intramolecular *para*–C-alkylation[27,28] or a palladium catalyzed *ipso*-Friedel-Crafts allylic alkylation[29–31]. Compound **88a** and **88b** resemble alcohol **6** in the biosynthesis of elisabethin A, which supports the claim of a biomimetic route. The problematic stereocenter at C2 would be formed after the cyclization through global deprotection and oxidation at the end of the synthesis under kinetic conditions. The isoprenyl moiety should be installed through enantioselective addition of an organometal alkyl to the aldehyde. The methyl group at C7 would be introduced *via* an asymmetric conjugate addition at an α,β-unsaturated system, which should be accessible through a cross metathesis at olefin **51** with methyl acrylate.

C II Cross Metathesis Approach

C II.1 Preliminaries

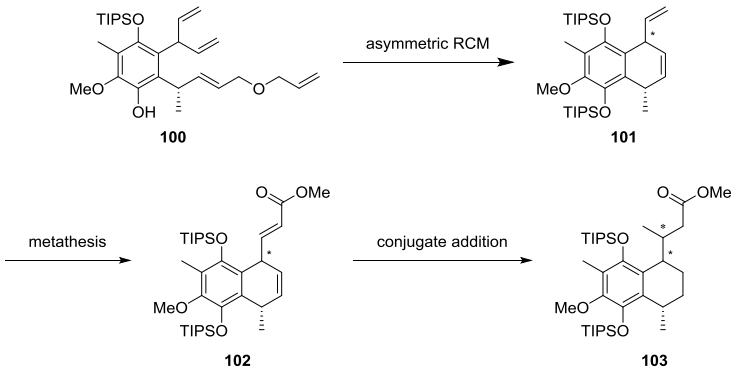
Steiner and Kaiser's work brought insights to the second generation of the synthesis, which follows mainly Steiner's TIPS strategy. Our main concern was the correct configuration at C6 and our considerations are summed up in the following.

- Epimerization of aldehyde **80** at C6 did not favor one stereoisomer over the other, as the energy difference between the two isomers is very small according to MM2.
- The asymmetric alkylation proved to be of relatively low yield and the route towards the bicyclus was not fully established.
- The RCM appeared to favor one transition state over the other.

These facts envisioned the idea to use the different reactivity of the transition states during the RRCM to our benefit. First the precursor for the RCM would be altered to substrate **100**, which has a prochiral center

at C6 (Scheme 29). If the *trans* transition state is favored, the corresponding product should be formed at a higher probability. Therefore, diastereomeric excess should be achievable during the RCM. Depending on the extent of this asymmetric induction, a chiral metathesis catalyst could be used to gain the *trans* isomer in an even higher *de*.

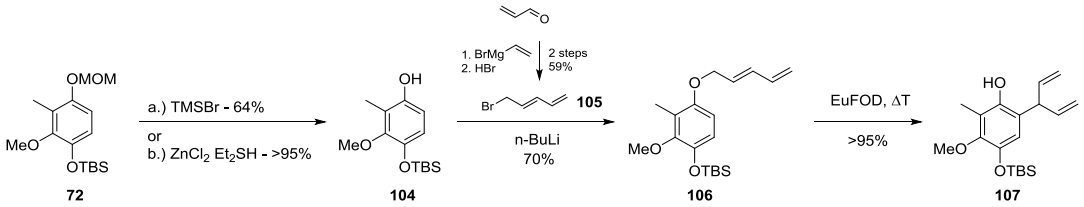
Then the unsaturated ester (**102)** would be installed by cross metathesis to enable the introduction of the methyl group at C7 by an asymmetric conjugate addition. The double bond at C4/C5 should be reduced after the conjugate addition.



Scheme 29 Second Generation Route Towards Intermediate **99**

C II.2 Ring Closing Metathesis

C II.2.1 Installation of the Prochiral Center and Synthesis of Diene 105



Scheme 30 Introduction of the Prochiral Center at C6 and Synthesis of Building Block **105**

To install the prochiral center, (*E*)-((4-bromobut-2-en-1-yl)methyl)benzene had to be altered to bromodiene **105** and was introduced by a Williamson ether synthesis according to Scheme 30. The route aligns with the sequence conducted by Steiner.

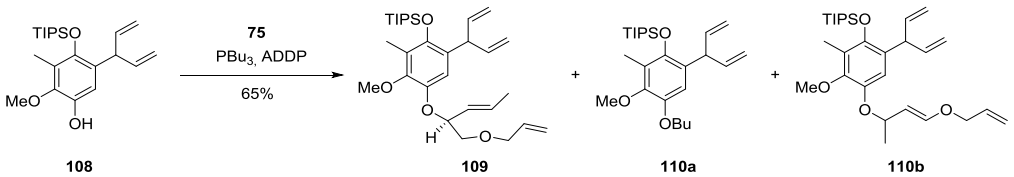
The deprotection of MOM ether **72** with TMSBr[32] required purification with rather large amounts of silica and above that proceeded not to our full satisfaction regarding the yields (up to 70%) and side product formation (TMSEther). Therefore, we cleaved the ether with ethanthiol and $ZnCl_2$ using an alternative protocol[33]. The high yield (>95%) and the very fast reaction rate (10 min) outweighed the unpleasant odor of this protocol, which is clearly disadvantageous. The following etherification proved to be more troublesome than expected. As a side reaction, the free phenol also reacts with the silyl ether. This results in regioisomers as side products. Additional issues were caused by the starting material: As previously explained, due to the methylation prior in the sequence, a certain amount of TBEMS ether was also present. The etherification

caused a slight shift in certain NMR signals, which did not appear at MOM ether **72** or the starting material (**104**). Additionally, a slight difference in the R_f values disturbed us. Only after deprotection of the silyl ethers with TBAF and careful comparison of the NMR spectra, regioisomers were ruled out as a cause of those shifts. To reduce the possibility of side product formation, the reaction was performed generally in high dilution, giving 70 to 75 % yield during this step.

The building block (*E*-*E*)-1-bromo-2,4-pentadiene (**105**) was synthesized by addition of acrolein to vinyl Grignard and consecutive substitution with HBr. The initially used procedure for divinylcarbinol[34] gave only very moderate yields of about 60 % (calculated from NMR) and a relatively high amount of remaining solvent in the product, which could not be removed without further loss of the product. The following substitution with HBr was also not very satisfying, very likely due to impurities of the starting material. For these reasons it was also tried to produce vinyl Grignard *in situ* and add methylformiate. Unfortunately, the synthesis of the Grignard reagent did not proceed according to the literature and the yield was below our expectations[35–38]. We assume that losses of material are caused by the low boiling point of vinylbromid of 16 °C. However, the synthesis of the alcohol and the following substitution could be improved by several factors. First, to ensure full addition of methylformiate to the Grignard reagent, the solution was allowed to stir overnight. Additionally, the workup was as well slightly altered. The mixture was quenched with saturated ammonium chloride solution and extracted several times with the solution to assure full distribution of the product in the organic phases. Due to the low boiling point of the product, the solvents were removed over a Vigreux distillation apparatus. Then the product was distilled and a yield of 62 % pure material was achieved. To prevent oxidation, hydroquinone was also added. This procedure can obviously also be used by addition of acrolein to the Grignard reagent. The now pure material assured better premises for the second step of the synthesis. The addition of HBr was conducted very slowly and carefully, as the exothermic reaction caused carbonization of the material at faster rates. This resulted in a yield of 95 %, without the need of another purification step.

Having diene **106** at hand, the first Claisen rearrangement could be conducted and the prochiral center established. The similar step in Steiner's synthesis was achieved by thermal induction only (*vide supra*). However, the altered substrate required the addition of EuFOD as catalyst. The high conversion and yield of more than 95 % is noteworthy, since the rearrangement under purely thermal conditions has been observed only as a byproduct compared to a [5;5] sigmatropic rearrangement[39].

C II.2.2 Mitsunobu Reaction and Synthesis of Chiral Alcohol 75

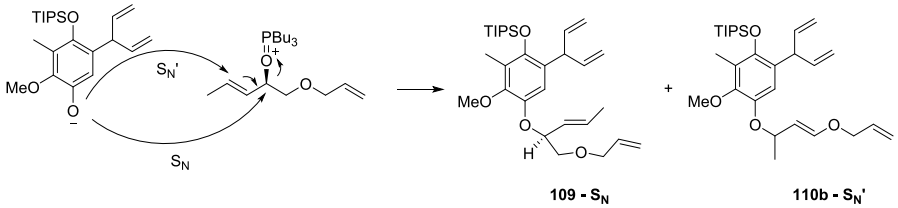


108 **109** **110a** **110b**

Scheme 31 Mitsunobu Reaction

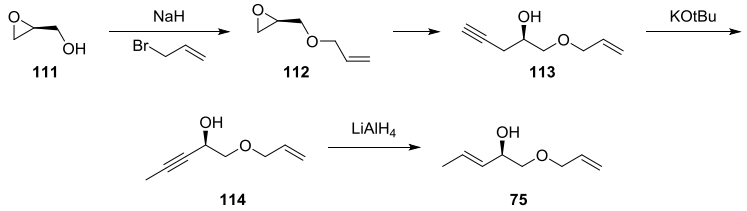
After the first Claisen rearrangement, the synthesis aligns with Steiner's route. Now the protection groups of the hydroquinone needed to be exchanged and the southern ether installed by a Mitsunobu reaction. First, the northern phenol was protected with TIPS using NaH to deprotonate in order to enhance the reactivity of the substrate. Then the southern phenol could be deprotected by TBS ether cleavage under acidic conditions (using the protocol established by Steiner). As the TIPS group was unstable under these conditions, the reaction was stopped as soon as more polar spots were visible on TLC. (This indicated the cleavage of the northern silyl group). After separation of the components by chromatography, phenol **108** was subjected to a

Mitsunobu reaction with chiral alcohol **75** yielding 65% of ether **109**. As side products, butyl ether **110a** (10%) and S_N' product **110b** (10%) were formed as well. While formation of ether **110b** can easily be explained as a conjugate substitution (Scheme 32), the formation of the butyl ether is yet unknown and would require further investigation.



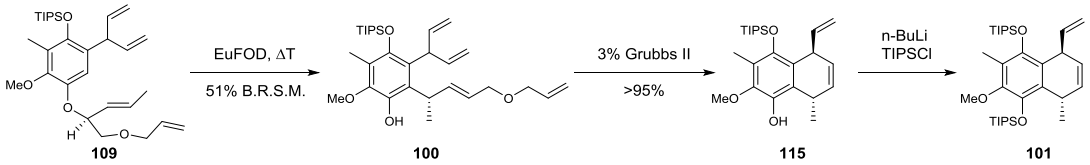
Scheme 32 Formation of Mitsunobu Ether **109** and Side Product **110b**

The chiral alcohol **75** was synthesized from *S*-glycidol (**111**) in a four step synthesis very similar to Steiner according to Scheme 33. First, glycidol was allylated to install the relay arm for the RRCM. The very hygroscopic product **112** was purified after workup *via* Kugelrohr distillation. Then the epoxide was opened with lithium acetylide ethylenediamin complex giving a mixture of **113** and isomerized product **114**. To accomplish full migration of the triple bond, the isolated mixture was treated with an equimolar amount of potassium *tert*-butoxide. Then the alkyne was reduced selectively to the *E* alkene (**75**) using LAH. Here, the unexpectedly low yield of only 50% can be explained by the cleavage of the allyl group. This reaction is known to take place in boiling solvent for aryl allyl ethers[40]. The overall yield was determined with moderate 20% and can be clearly improved by a more careful monitoring during the reduction.



Scheme 33 Synthesis of Chiral Alcohol **75**

C II.2.3 Second Claisen Rearrangement and Ring Closing Metathesis



Scheme 34 Southern Claisen Rearrangement and Ring Closing Metathesis

With ether **109** at hand, the Claisen rearrangement of the southern ether was again catalyzed with EuFOD. This resulted in partial cleavage of the ether to phenol **108**. Based on recovery of the starting material, 51% yield could be achieved, however. Column chromatography with DCM as eluent revealed the possibility to

separate the product (**100)** easily from the starting material (**109**) and phenol **108**. The latter could be subjected directly to the Mitsunobu reaction without further separation, producing the same yields as with pure starting material. This process allowed faster synthesis. Further experiments using HoFOD[41] as Lewis acid or conducting the reaction under microwave heating did not alter the results. In fact, cleavage of the ether appeared to be faster under radiation.

The formation of the six membered ring (**115**) was achieved with a RRCM using Grubbs II ruthenium catalyst (Scheme 34). The reaction proceeded very cleanly and quantitatively with a relative low loading of catalyst (3 to 5 mol%) under mild conditions (35 °C). Furthermore and most importantly, only one of the two possible diastereomers was formed. As assumed, NOESY experiments confirmed the desired *trans* identity of the product. The free phenol could be protected with TIPS (**101**). Surprisingly, it was necessary to use *n*-BuLi to deprotect the southern phenol instead of NaH as in the silylation of the northern phenol prior in the sequence.

Olefin **101** is a starting point of several approaches throughout this work. This route facilitates the synthesis towards the decalin olefin essentially, as it was not only four steps shorter (deprotection of the benzyl group, oxidation to the aldehyde, epimerization at C6 and Wittig reaction) but also diastereoselective. For further prove of the stereochemistry, the TIPS protected product (**101**) was recrystallized and its structure was confirmed by X-ray measurements (Figure 3).

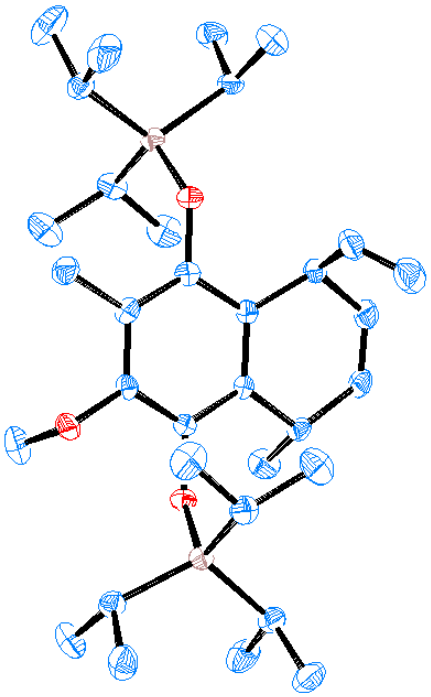


Figure 3 Structure of Decalin Compound **101** determined by X-Ray

The high stereochemical induction during the reaction can be explained by the comparison of the two different conformations at the prochiral center of the RRCM precursor (**100**, Figure 4). On the left side the relay arm is in proximity to one of the vinyl groups. The other vinyl group is *trans* to the methyl group at C3. Both circumstances facilitate the RCM compared to the other structural possibility shown on the right side. Here, the methyl group and one of the vinyl groups are closer together, which results in a higher strain. MM2 calculations show a difference of approximately 33 kcal/mol. Additionally, the RCM with the other vinyl group would be more difficult, since both double bonds are rather far apart.

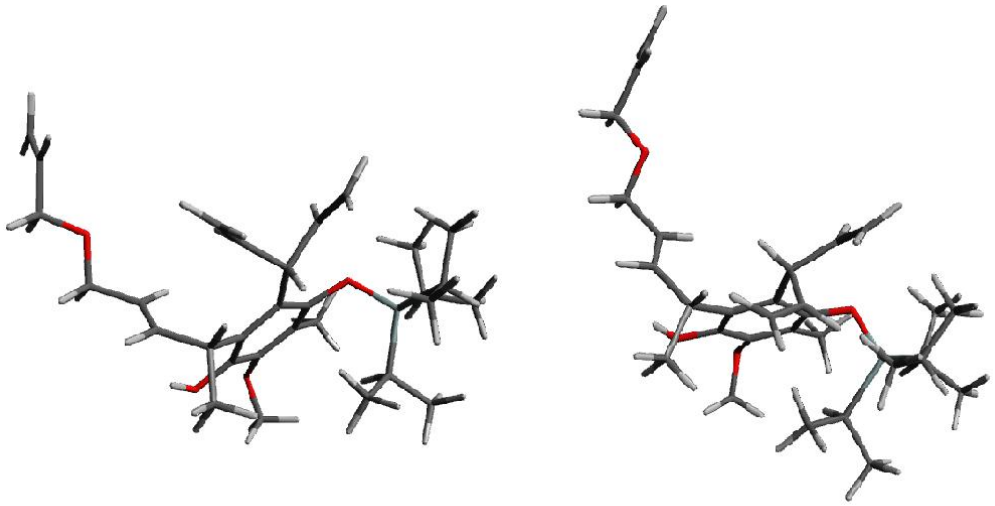
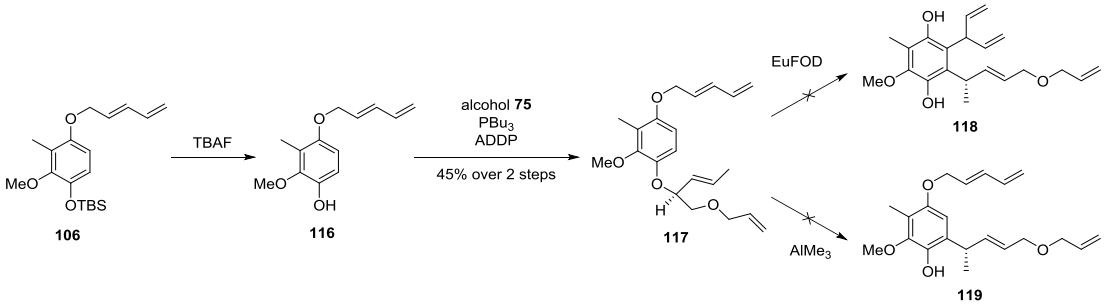


Figure 4 Comparison of both Conformations of Prochiral RRCM Precursor **100**.
The Structure on the Left Leads to the *Trans* Product, the one on the Right to the *Cis* Product

C II.3 Double Claisen Rearrangement Approach

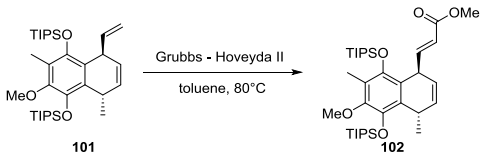


Scheme 35 Double Claisen Rearrangement Approach

To improve and facilitate the synthesis, it was attempted to conduct both Claisen rearrangements simultaneously. For this approach ether **106** was treated with TBAF to deprotect the phenol according to Scheme 35. Then the chiral alcohol (**75**) was introduced by the same protocol as used before to give 46 % yield of compound **117** over these two steps. The product was subjected to the rearrangement in toluene at 110°C using EuFOD (5.0 mol%) as catalyst. Unfortunately, a complex mixture of several compounds was detected by TLC. This led to the assumption that apart from both rearrangements, cleavage of the southern ether (and probably the northern as well) also took place. This material could not be recovered and the reaction was stopped. As it was not possible to rearrange both ethers simultaneously, another approach was tried. This

time, $AlMe_3$ was used to rearrange the southern part of the molecule first. The rearrangement was performed by Steiner at a similar substrate. However, no product (**119**) was obtained after several days of reaction. As these attempts towards a quicker synthesis were not successful, this approach was terminated.

C II.4 Conjugate Addition



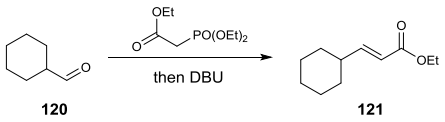
Scheme 36 Cross Metathesis

The α,β - unsaturated system was installed by a cross metathesis with methyl acrylate and Grubbs-Hoveyda II catalyst. Based on the recovery of starting material, the yield was determined with 84 %. Otherwise the reaction proceeded very cleanly, giving only *E* – isomer **102** (Scheme 36).

The installation of the methyl group at C7 proved to be troublesome for mainly three reasons. First, the nucleophilicity of the methyl reagent is relatively low compared to bigger groups. Secondly, the cyclic system in γ-position to the carbonyl is rather flexible and more importantly sterically very demanding. Thirdly, the reactivity of conjugate esters towards conjugate addition is relatively low compared to more common systems like ketones.

At first we tried a protocol from Wang[42] in which the addition of MeMgBr was catalyzed with copper(I)iodide and could be controlled stereochemically with BINAP as catalytic additive. Unfortunately, at low temperature no conversion and on higher temperature direct addition to the ester was also observed.

To save time and material, we developed a working protocol for a test substrate (**121)** first. It was synthesized *via* Horner-Wadsworth-Emmons olefination of cyclohexanecarbaldehyde (**120**) with triethyl phosphonacetate with DBU as base (Scheme 37)[43].

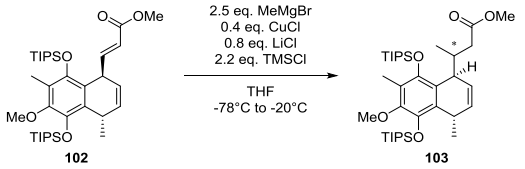


Scheme 37 Synthesis of the Test Substrate **121**

As the reactions with the Grignard reagent did not give satisfying results, we changed the alkylsource and used Gilman cuprates. Addition of TMSCl to enhance reactivity was also investigated[44]. Although some protocols gave results with the test substrate, none gave any reaction with ester **102**. The next protocol we tried, used copper (I) bromide dimethyl sulfide complex, MeMgBr and a chiral Josiphos catalyst†. To the best of our knowledge this is the only protocol reported that is both enantioselective and works with a hexyl group in γ-position with *Et*MgBr[45]. Unfortunately, it was only possible to achieve low conversion at the test substrate and no conversion at all with ester **102**. At last the addition with CuCl as copper source and TMSCl and LiCl as additives was successful[46] (Scheme 38). Table 1 summarizes the results of the different protocol for the model substrate **121** and ester **102**.

† (*R*)-1-[(*SP*)-2-(Diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine

Apparently, the different copper(I) salt in combination with the additives was successfully enhancing the reactivity of the substrate and the conjugate addition proceeded almost at full conversion with a yield of 80 %. To our surprise the chiral induction of the substrate was so strong, that only one diastereomer was formed. As free rotation around C6/C7 is possible, the determination of the configuration was only feasable through derivatisation and XRD experiments.



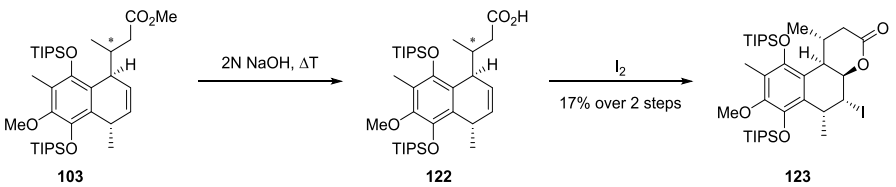
Scheme 38 Successful Conjugate Addition of Ester **102** to Product **103** (see also Entry 10 in **Table 1**)

Table 1 Conjugate Addition of Model **121** and Ester **102**

							Result	
	Solvent	**Cu(I) - Salt**	**Methylsource**	**Additive**	**T [°C]**	**t [h]**	**Model**	**Substrate**
1	Et_2O	CuI (4 mol%)	MeMgBr (5 equiv.)	-	-20 to r.t.	16	-	d.a.‡
2	MTBE/DCM	CuI (4 mol%)	MeMgBr (5 equiv.)	-	-20	20	-	d.a.
3	MTBE/DCM	CuI (4 mol%)	MeMgBr (2 equiv.)	-	-20 to +4	16	n.c.§	-
4	MTBE	CuI (4 mol%)	TMSMeMgCl (2 equiv.)	-	-40 to r.t.	16	n.c.	-
5	MTBE	CuI (1.0 equiv.)	MeLi (2 equiv.)	-	0	16	c.a.**	-
6	MTBE	CuI (1.5 equiv.)	MeLi (3 equiv.)	-	0	2.5	c.a.	n.c.
7	MTBE	CuI (1.5 equiv.)	MeLi (3 equiv.)	TMSCl (1.0 equiv)	-78	3.5	n.c.	-
8	MTBE	CuBr x SMe_2 (5 mol%)	MeMgBr (1.1 equiv.)	Josiphos (5 mol%)	-78 to +4	16	c.a.††	n.c.
9	MTBE	CuBr x SMe_2 (5 mol%)	TMSMeMgBr (1.1 equiv.)	Josiphos (5 mol%)	-78	16	-	n.c.
10	THF	CuCl (40 mol%)	MeMgBr (2.5 equiv.)	TMSCl (2.2 equiv.), LiCl (80 mol%)	-78 to -20	3	c.a.	c.a.

‡ direct addition
§ no conversion
** conjugate addition
††very low conversion

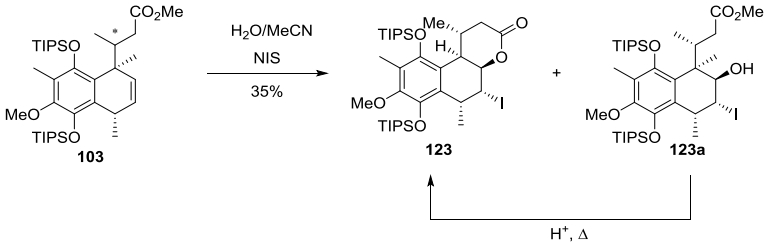
C II.4.1 Configuration of the New Chiral Center



Scheme 39 Iodolactonization *via* Carboxylic Acid

A possibility to determine the configuration at C7 is to enhance rigidity of the molecule through cyclization, namely through iodolactonisation. Treatment of ester **103** with iodine in MeCN did not give any conversion[47]. Therefore we decided to cleave the methyl ester and form the lactone with the free acid **122** (Scheme 39). The hydrolysis proved to be more troublesome than expected, since K_2CO_3 in methanol or LiOH in DMF did not cleave the methyl group. Only stirring the ester in a 1:1 mixture of dioxane and 1 N NaOH at 40 °C

over several days gave results. As full conversion was not reached and the lactonization was performed with the mixture, only a yield of 17 % over these two steps was achieved for the iodolactone.
Concurrently, cyclization was also possible with the ester with NIS in water/MeCN[48]. However, this reaction was accompanied by side product formation. After confirmation of the structure *via* NMR, it was possible to convert the halohydrine **123a** easily to the iodolactone by slightly elevated temperatures under acidic conditions. (Scheme 40).



Scheme 40 Direct Lactonization and Formation of Halohydrine

NOESY experiments of the gained iodolactone revealed that the conformation of the methyl group was opposite to the one in the natural product as seen in Figure 5.

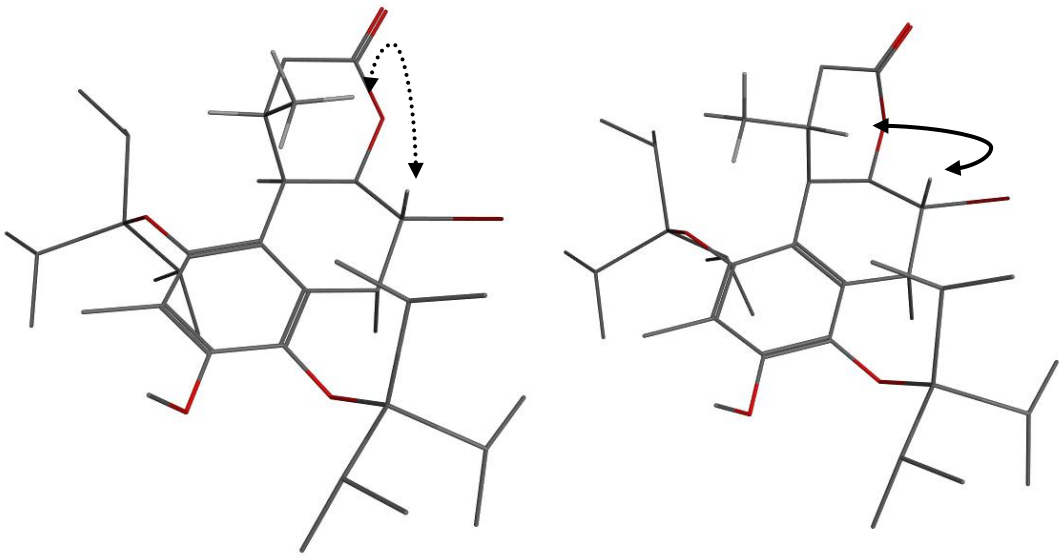


Figure 5 Expected NOE for Iodolactone **123** (Dotted Line). Measured NOE for 7-epi-Iodolactone **123** (Solid Line)

Furthermore, the addition product **103** was also crystallized and the resulting XRD experiments confirmed the undesired results. At C7 the methyl group is clearly pointing away from the viewer. A picture of the structure can be seen in Figure 6.

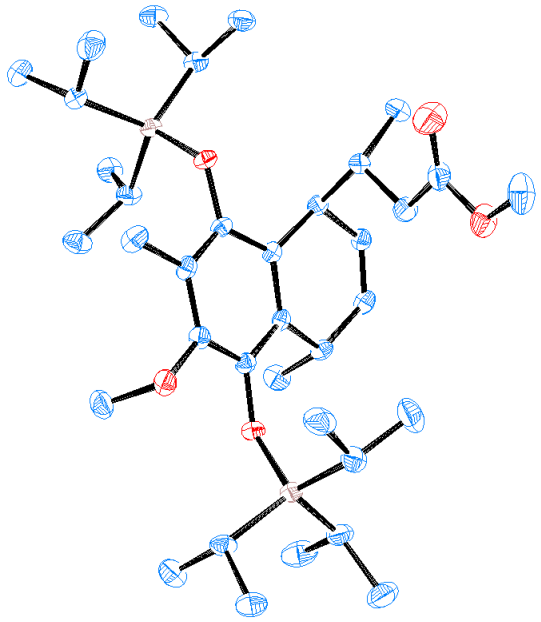
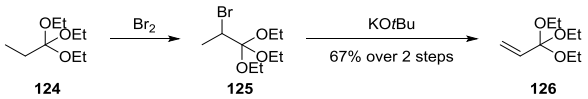


Figure 6 X-Ray of 7-*epi*-Ester **103**

Since it is very unlikely to synthesize the other diastereomer by addition of a chiral catalyst, due to the strong substrate control, we thought of different methods to synthesize the now necessary *Z* – olefin. Among other possibilities we aimed for a *Z* selective cross metathesis, which would be the fastest and easiest way. Additionally, a second route *via* a seven membered lactone *via* RCM was in development at the same time.

C II.5 *Z* Selective Cross Metathesis

This approach relies on rather recent work mainly from Grubbs[49]. The most promising protocol is merging allylic acetals with terminal olefins using a ruthenium catalyst[‡‡][50]. We hoped it might be possible to achieve similar results with orthoesters such as **126**. The latter was synthesized using a literature protocol[51] (Scheme 41). Bromination of triethylorthopropionate and successive elimination with potassium butoxide provided the orthoester in good yield (67%) over these two steps.



Scheme 41 Synthesis of Orthoester **126**

The cross metathesis itself was conducted with both orthoester **126** and methyl acrylate under different temperatures. THF and toluene were used as solvents. All experiments are summarized in Table 2. Unfortunately, at our hands it was not possible to convert any material, which led to termination of this approach.

Table 2 *Z* – Selective Cross Metathesis

Entry	Olefin	Equiv.	Catalyst	Solvent	T [°C]	t [h]	Product
1	methyl acrylate	4.0	2mol%	THF	35	16	-
2	methyl acrylate	-	5mol%	neat	25 to 40	16	-
3	orthoester	2.0	5mol%	THF	35	16	-
4	orthoester	3.0	5mol%	toluene	80	16	-
5	orthoester	3.0	5mol%	toluene	80	24	*E*

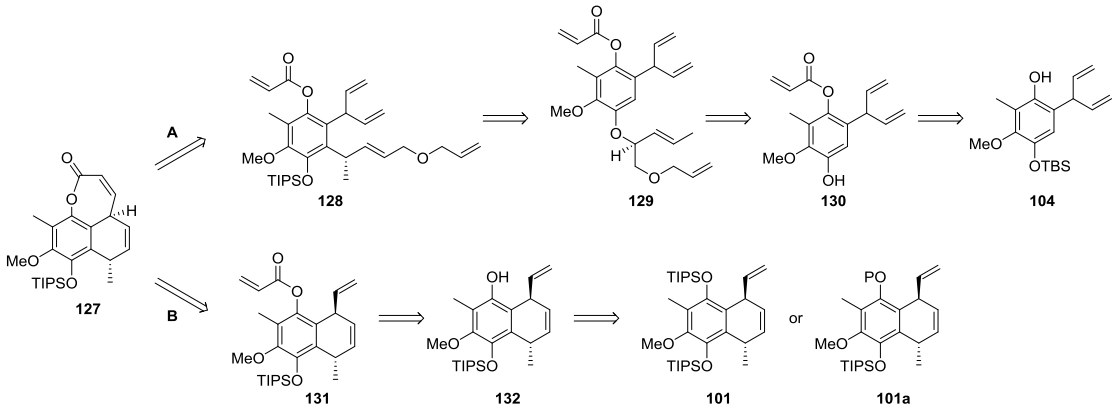
C III Lactone Formation

As mentioned above, another possibility to access the necessary *Z* conjugate ester moiety is to synthesize a cyclic structure, namely lactone **127**. Mainly two possibilities appear feasible to reach the molecule as seen in Scheme 42.

First, starting from rearranged product **104**, a rather quick approach should be possible (path **A**). At first, the acryloyl ester would be formed and then the TBS ether could be cleaved to install the southern ether with the already developed Mitsunobu reaction. Then a Claisen rearrangement of this southern ether should give phenol **128** a precursor for a double ring closing metathesis, during which both rings should be formed simultaneously. This approach is flexible, since either the northern ester or the southern ether can be installed first.

[‡‡] [2-(1-Methylethoxy-O)phenylmethyl-C](nitrato-O,O')[rel-(2R,5R,7S)-tricyclo[3.3.1.13,7]decane-2,1-diyl[3-(2,4,6-trimethylphenyl)-1-imidazolidinyl-2-ylidene]}ruthenium

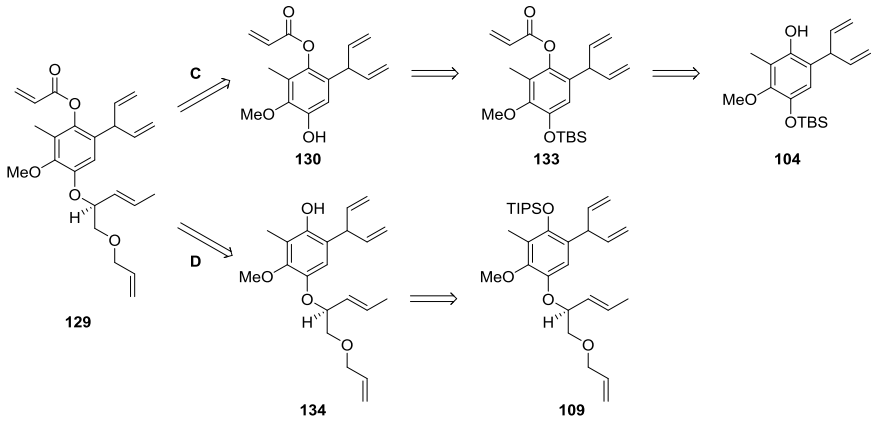
The other possibility is to form the six membered ring first and cyclize the lactone in a separate RCM (path **B**). For this approach the northern protecting group of the decalin compound **101** or **101a** should be cleaved selectively and the seven membered ring would be formed after esterification and ring closing metathesis. Since we had rather much material of **101** at hand, this appeared to be an attractive approach. Furthermore, it should be possible to protect the hydroquinone orthogonally earlier in the sequence, as the selective cleavage of one of the silyl ethers seems to be a major difficulty and is clearly a detour.



Scheme 42 Possible Routes Towards Lactone **127**

C III.1.1 Towards Double Ring Closing Metathesis (Route A)

The precursor **129** for the southern Claisen rearrangement (**128**) was tried to be reached *via* mainly two compounds (Scheme 43).

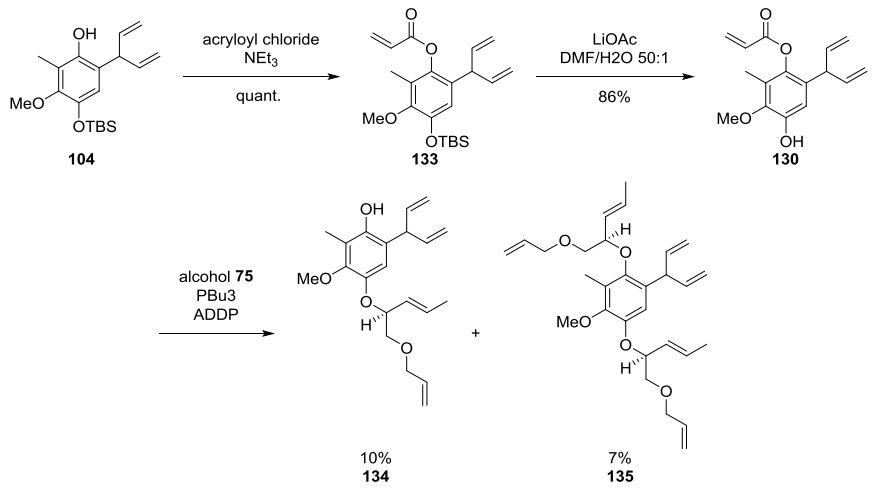


Scheme 43 Approaches towards Precursor **129** for the Second Claisen Rearrangement

Both substances required the cleavage of either TIPS (northern, compound **109**) or TBS (southern, compound **133**) ethers. The routes differ mainly in the order of events. On route **C** the ester would be introduced first. Then the southern phenol is deprotected and the chiral alcohol (**75**) is installed. The other possibility (**D**) would be to conduct the Mitsunobu reaction first and then install the ester after deprotection of the TIPS group at the northern site of the molecule. Route **C** would be more direct and faster, while route **D** would avoid eventual difficulties regarding the Mitsunobu reaction with acryloyl ester **130**.

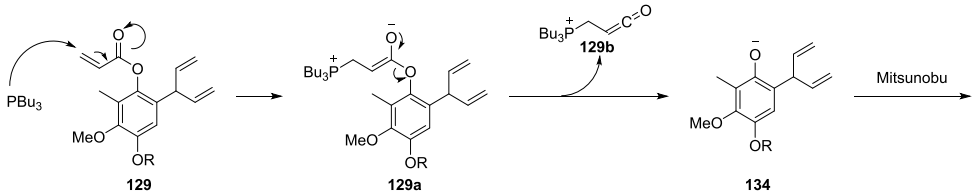
Pursuing route **A**, ester **133** was synthesized quantitatively with acryloyl chloride and triethylamine as base. All attempts to cleave the silyl ether at compounds **133** (TBS) or **109** (TIPS) with TBAF in THF at low temperatures lead to either isomerization of the double bonds or decomposition of material. Presumably, this was caused by the high basicity of the reagent. Alternative protocols were investigated to avoid these problems. First, HF buffered in pyridine as a solution in THF was tried. Although silyl ether cleavage was observed *via* NMR, full conversion was only reached after several days with huge excess of reagent. Furthermore, for TIPS ether **109**, the chiral alcohol was also cleaved partially. If less equivalents of the reagent were used, the reaction time increased significantly beyond practicability. Those experiments were stopped after several days without significant cleavage of the silyl moiety. Reactions with TBS ether **133** gave similar results as prolonged reaction times led only to small amounts of free phenol **130**. Nevertheless, a different approach led to very satisfying results: The deprotection proceeded with good yields *via* hydrolysis, which was mediated with lithium acetate.[52]

After the deprotection, the next step was the introduction of the southern ether using the established Mitsunobu protocol. Unfortunately, the reaction did not proceed as expected. Apart from the very low recovery of material after purification by column chromatography (15%), only two different side products were obtained (**134** and **135**). The whole sequence can be seen in Scheme 44.



Scheme 44 Route **C**: Esterification, TIPS Deprotection and Failed Mitsunobu Reaction

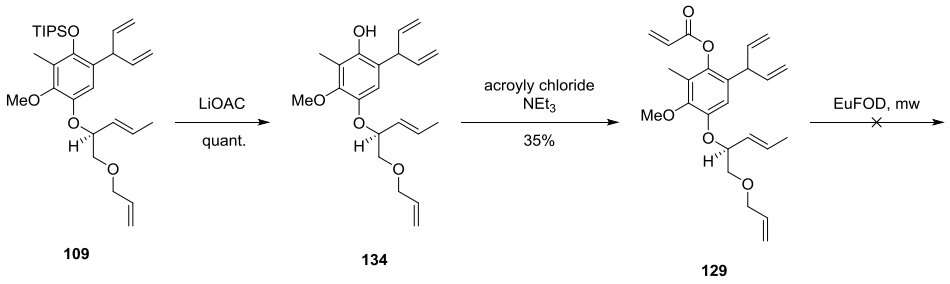
Possibly, the acryloyl ester was also cleaved by a nucleophilic attack of the phosphine to the double bond. This resulted in ketene **129a** and phenol **134**, which underwent another Mitsunobu reaction and the ether was therefore as well installed on the northern site of the molecule (Scheme 45). Apparently, the etherification is therefore not usable and this route met a dead end. Now the second possibility (**D**) was pursued.



Scheme 45 Possible Side Reaction during the Mitsunobu Reaction with Acryloyl Ester **130**

The northern ester was installed after the Mitsunobu reaction and the precursor for the Claisen rearrangement (**129**) could be synthesized. The acrylate was introduced directly at phenol **134** using the same

protocol as described above. Interestingly, the reaction was only very low yielding (35%), which is clearly not suitable for scale-up, but allowed the testing of the southern Claisen rearrangement (Scheme 46). The reaction was conducted under microwave heating and was monitored by TLC. As after two hours mainly two more polar substances were formed and one of which was the undesired side product **130**, the reaction was stopped. Although the rearrangement was basically possible, this approach was still aborted, as the cleavage of the ether led to phenol **130**, which is not reusable due to the side reaction during the Mitsunobu reaction. Again, the sequence met its dead end and the double metathesis approach was terminated.

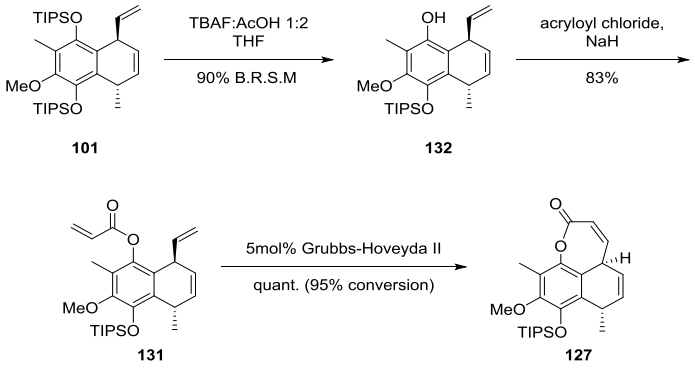


Scheme 46 Route **D**: Deprotection, Esterification and Failed Claisen Rearrangement

C III.1.2 Separate Ring Closing Metathesis Reactions (Route B)

As explained above, another possibility to approach lactone **127** is *via trans* decalin compound **131**. The northern phenol would be deprotected and then the acryloyl ester installed to form the lactone in a RCM (Scheme 42, Route **B**). The first approach required the cleaving of one of the two TIPS groups of compound **101** selectively, since a lot of material from the cross metathesis approach was still present. The route can be seen in Scheme 47. Only later, different protecting groups were used to facilitate the resynthesis.

C III.1.2.1 Regioselectively Deprotection of TIPS Ethers



Scheme 47 Regioselective Deprotection of Compound **101** and Synthesis of Lactone **127**

The regioselective cleavage of one of the two TIPS ethers proved to be difficult. First attempts with TBAF led only to decomposition of the material and HF buffered in pyridine led to no product whatsoever. The hydrolysis with LiOAc was as well unsuccessful. Here, even prolonged reaction times and slightly elevated temperatures did not give any conversion of the material. Finally, treatment with TBAF which was buffered with acetic acid, gave positive results. The reaction was carefully monitored *via* TLC and showed a significant

selectivity towards one of the two possible products. The reaction was stopped after 1 h at 60% conversion. After purification, 90% of the desired phenol **132** and 10% of phenol **115** were isolated (based on the recovery of starting material) and the structure was clarified by NOESY-NMR experiments. Interestingly, the northern phenol was substantially more difficult to work with than the southern pendant (**115**). The product is not bench stable, requires storage under argon and decomposes at standard laboratory manipulations such as evaporating the solvents at mild temperatures (40 °C) *in vacuo*.

The esterification was first conducted in methylenchloride and triethylamine. Suprisingly, the reaction required purification over silica due to unspecific side reactions and gave only 50% of isolated product. After decreasing the reaction temperature, full conversion could not be reached, even after adding additional portions of acryloyl chloride and base. In order to increase the yields, other protocols were investigated. First, the reaction was conducted in pyridine as solvent. DBU was also added to deprotonate the phenol. However, the same problems occurred and the reaction did not proceed to full conversion. A Steglich esterification led to a significant loss of material and incomplete conversion. At the end, the reaction was optimized using NaH as base in THF. The amount of hydride was carefully adjusted to achieve full conversion and a yield of 83% after purification.

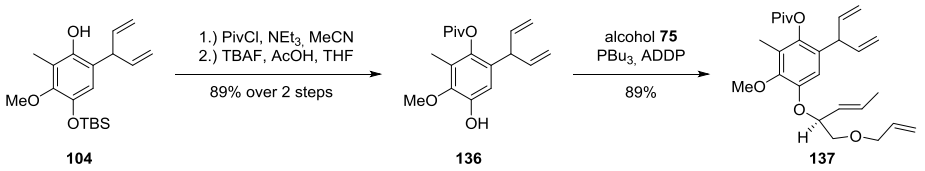
The RCM was conducted with Grubbs-Hoveyda II catalyst using a similar protocol as with the cross metathesis. The catalyst was added over three hours to a diluted solution of the substrate. Reaction overnight gave 90 to 95% conversion. The addition of more catalyst did not increase the conversion and the reaction was stopped at this point. The crude material could not be purified *via* conventional column chromatography, as the product isomerized during the separation from the substrate. Therefore, the crude product was only filtered very quickly over a plug of silica and used directly. Furthermore, the lactone was unstable and decomposed very quickly, even if stored under argon and lower temperatures.

C III.1.2.2 Resynthesis with Orthogonally Protected Phenol

To avoid the unnecessary regioselective deprotection steps and facilitate the resynthesis, the northern phenol was protected as pivalate instead of TIPS. However, the introduction of the pivalate at phenol **104** was not as straight forward as expected. The formation under standard conditions using pivaloyl chloride in pyridine in the presence of DMAP did not lead to any product. At the same time a reaction with NaH in DMF and acid chloride did only cleave the TBS group and no product was formed. Esterification in DCM either with triethylamine or DIPEA as base was only partially successful: Although the desired product was formed relatively fast in each case, it was not possible to convert all of the substrate to the desired ester. Prolonged stirring, elevating the reaction temperature and further addition of reagent did not improve the results. To control the reactivity of the mixture, a test substrate was added to the reaction. To our puzzlement the hydroxy group of this test substrate was easily converted to the corresponding pivalate, while no further reaction took place at the substrate itself. Under these circumstances, it was very satisfying, when the reaction proceeded very cleanly and with full conversion when the solvent was changed to MeCN. 89% yield were achieved after filtration over a small plug of silica. For the next step, the deprotection of the southern phenol, the insights of previous experiments led to a quick determination of a protocol. Again a solution of TBAF in THF in the presence of AcOH yielded the corresponding phenol **136** quantitatively without the isomerization of any double bond.

The installation of the southern ether exceeded our expectations. The Mitsunobu reaction proceeded faster and cleaner than with the substrate used previously. We assume that the ester pivalate decreases

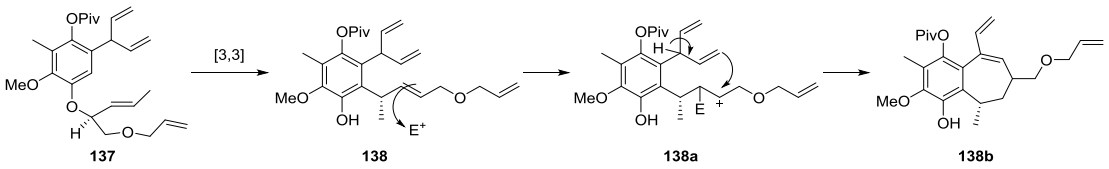
electron charge in the aromatic ring and therefore facilitates the reaction. This resulted in substantially higher yields and surprisingly as well in less amounts of side products. After purification with silica, 89% ether **137** and only 6% S_N' product were isolated. Additionally, no butyl ether was formed, which made the purification of the crude material significantly faster and easier. The synthesis of ether **137** starting from the first Claisen rearrangement is summarized in Scheme 48.



104 **136** **137**

Scheme 48 Pivalate Protection Strategy

The southern Claisen rearrangement on the other hand was more difficult due to the same reason why the Mitsunobu reaction was facilitated. The pivalate reduces electron charge, which decreases the reaction rate compared to the silylated substrate. Treating the substrate (**137**) with 15 mol % EuFOD in degassed toluene and heating for 24 h at 110 °C gave only 13 % of rearranged product (**138**) and about 50 % recovered starting material (**137**). To improve the conversion rate, xylene was used as solvent. The higher boiling point of the solvent allowed elevating the reaction temperature to 130 °C. However, only phenol **136** (33 %) and an unknown side product were isolated. After extensive NMR analysis, the structure of this side product could be determined (**138b**). We assume that the cyclization is possible because an electrophile seems to be present in the reaction mixture. This could either be Eu^{3+} or a proton that is present in the reaction mixture. The free proton could derive from the free phenol, which could be deprotonated at the reaction conditions (Scheme 49).

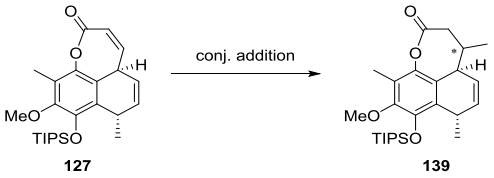


137 **138** **138a** **138b**

Scheme 49 Side Product Formation during the Southern Claisen Rearrangement with Ether **137**

To avoid further overreaction of the product, the next experiments were conducted again at lower temperatures and prolonged reaction times in xylene (115 °C). However, the difficulties remained, as the rearranged product cyclized readily to give again side product **138b**. This approach of the resynthesis was stopped at this point. However, it was shown that this sequence is faster and more convenient than the previous route due to mainly two reasons: First the TBS deprotection and the Mitsunobu reaction are more efficient regarding yield and workup. Especially the improvement of the etherification is noteworthy, since about 25 % more yield have been achieved compared to the reaction conducted with the TIPS protected substrate. After optimization of the southern rearrangement the sequence will be faster than previously.

C III.1.3 Conjugate Addition with Lactone 127



Scheme 50 Desired Introduction of the Methyl Group at C7

Having lactone **127** at hand, the introduction of the methyl group proved to be even more troublesome than with *E* - conjugate ester **102** (Scheme 50). The application of the same protocol that enabled the conjugate addition in the *E* - substrate before, led to partial isomerization of the isolated double bond of the hexyl ring. Other attempts to install the methyl group with the addition of HMPA or a variation of the addition of the reagents did not yield any product.

Regardless of these reactivity issues, problems concerning the recovery of starting material emerged additionally. We encountered loss of mass and impurification of the substrate after the reaction. These circumstances, however, could not only be explained by side reactions during the reaction but also by inadequate workup of the mixture. Although the conditions appeared to be very mild[§§], we observed decomposition of the material *via* TLC. Hence, other different protocols for the workup were attempted. At first, carefully quenching with 1.1 equivalent dry pyridine and sodium bicarbonate led only to further decomposition. The only protocol with which at least most of lactone **127** could be recovered was a fast quench by pouring the mixture in saturated aqueous bicarbonate solution, extract it with ethyl acetate and treat the combined organic with ammon chloride solution. As further purification with silica was not possible due to isomerization of the material, the development of a working protocol was impeded. At the end it was discovered by happenstance, that the substrate was not stable in the solvent THF, but decomposed over the reaction time even at low temperatures. This approach was also stopped at this point, since resynthesis of the material was necessary and time issues complicated further investigation of this reaction.

To avoid the problematic instability of the product and furthermore eliminate the probability of the isomerization of the double bond, an attempt was made to reduce the isolated double bond between C3/C4 selectively[53]. However, NMR of the crude product indicated full reduction of the more electron rich double bond at C7/C8. Due to the small quantities of material available, only this protocol could be tried.

The instability of the substrate could be explained by the very high strain between C1 and C6. The conjugate lactone moiety should align in a plain line. Furthermore the aromatic system is also plain and the lone double bond (C4/C5) is as well in one level. For these reasons lactone **127** might be under a high strain that could be released under decomposition or unspecific fragmentation. The other issue that troubled us was obviously the reactivity towards the conjugate addition itself. A closer look at the ^{1}H NMR and comparison with similar but reactive substrates gives a possible explanation for the poor reactivity of the substrate (Figure 7).

[§§] The solution was quenched with bicarbonate solution and the slowly warmed up to r.t. Then ammon chloride was added to achieve complexation of the copper species.

The conjugated double bond of lactone **127** is situated at about 6.5 ppm (bottom), whereas the corresponding proton of lactone **140**[***], is more deshielded (middle, 0.35 ppm). A further comparison with the NMR spectrum of conjugated ester **107** (top) reveals an even bigger discrepancy of the shifts in question (0.6 ppm). Additionally, the signal of the proton is situated in between the conjugated and unconjugated double bond of lactone **140**. These circumstances give reason to assume that the double bond of lactone **127** is actually not in full conjugation with the carbonyl group. This could again be explained by the very high strain of the molecule and therefore a certain twist of the moiety in question. If this is indeed the case, a conjugate addition would be simply not possible.

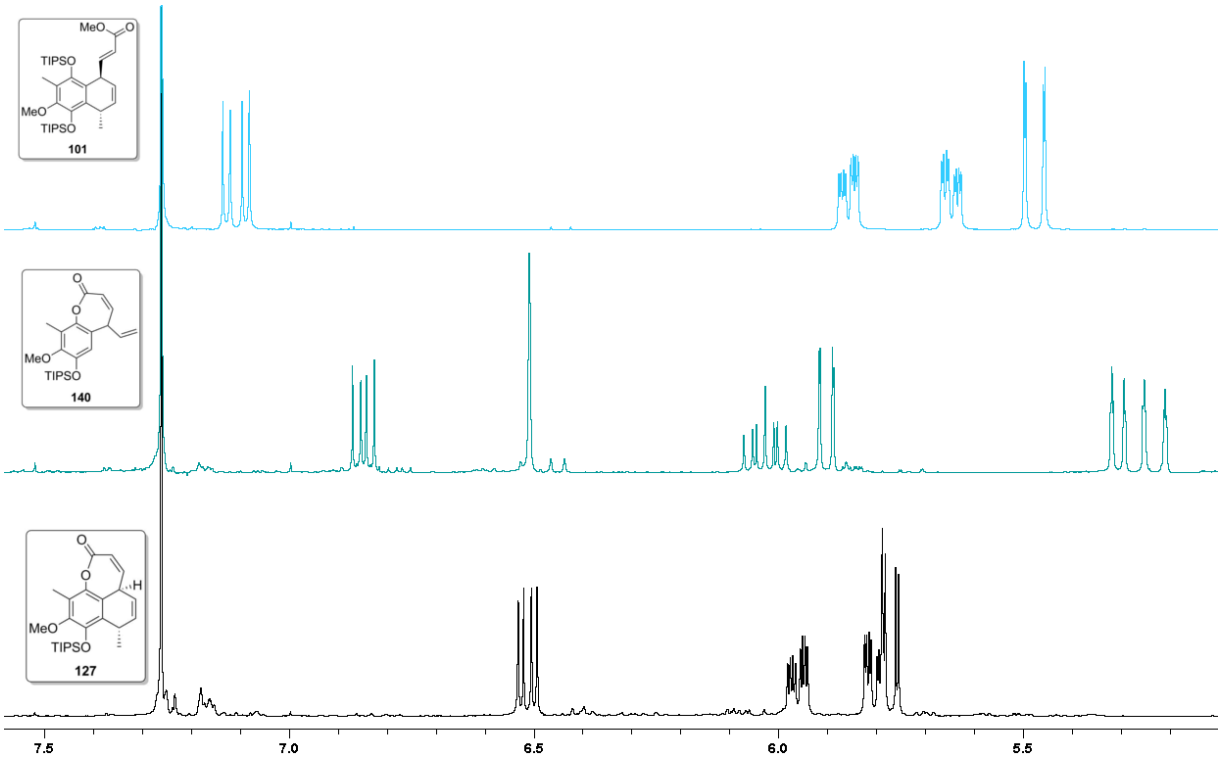
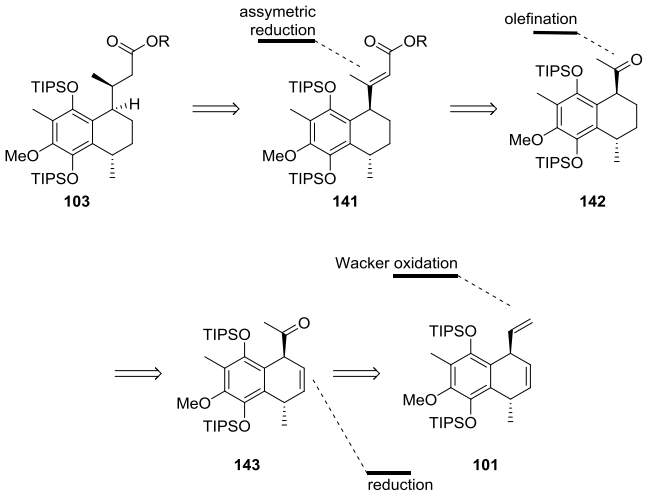


Figure 7 Comparison of ^{1}H Spectra of Lactone **127** (bottom), Lactone **140** (middle) and Conjugated Ester **102** (top)

[***] This compound was synthesized by Maximilian Kaiser at the same time and showed an excellent reactivity towards the conjugate addition reaction.

C IV Reduction Approach

In order to have another strategy at hand if the conjugate addition approach was not feasible, preliminary experiments towards another route were conducted. The general concept was to introduce the methyl group directly after the RRCM by a Wacker oxidation. Then a Wittig like olefination should elongate the chain and the introduced double bond could be reduced asymmetrically[54] (Scheme 51).



Scheme 51 Concept of the Alternative Reduction Approach

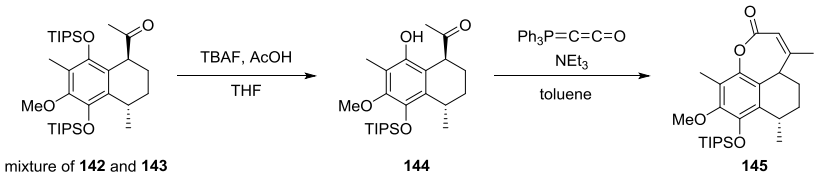
The main difficulty of this approach seems to be the Wittig olefination for two reasons. The first and most crucial difficulty appears to be the proton at C6, which is α to the carbonyl and can enolize under the conditions applied at the Wittig olefination. Therefore protocols developed for base sensitive substances would be used.[55–57] Additionally, the probability of enolization would be decreased, if the double bond between C4/C5 would be reduced prior to the olefination, since the enol would be stabilized due to the conjugation with this double bond. The second problem would be the *E/Z* selectivity of the olefination itself and the loss of material due to possible low selectivity.

The oxidation of olefin **101** proceeded cleanly with bis(acetonitrile)dichloropalladium(II) as catalyst and *para* - quinone as oxidation agent and yielded 88 % of ketone **143**. The following catalytic hydrogenation was troublesome as it was not possible to reduce the whole amount of material at once. The reaction was always performed in EtOAc and 10 w% palladium on charcoal. Table 3 summarizes all experiments and its conversion of the material. The ratio between starting material and product was determined by NMR and the mixture was subjected again to hydrogenation as it was not separable by chromatography. As shown, full conversion could not be reached even under higher pressure and prolonged stirring. Since palladium is known to catalyze isomerizations of double bonds[58], further experiments under higher pressure and prolonged reaction times were not investigated further, though they might lead to full conversion.

Table 3 Catalytic Hydrogenation of Ketone **143**

Entry	H_2 [bar]	time [h]	Conversion [%]	Remarks
1	3.5 - 2.4	3	66	test reaction with 10 mg scale
2	3.5 - 2.5	8	22	160 mg scale
3	3.5 - 2.5	16	29	
4	10.9	18	50	15 mol% Pd/C

Instead, a different approach was tested due to the parallel conducted conjugate addition of ester **102**. At this point of the research it was clear, that the synthesis of a *Z*-olefin and its reduction would very likely lead to the correct stereocenter at C7. Therefore, lactonization using a Bestmann ylide was pursued[59] (Scheme 52). For this very preliminary testing a mixture of ketone **143** and the hydrogenated ketone **142** was used. The northern TIPS group was selectively cleaved using TBAF that was buffered with AcOH. After separation by column chromatography phenol **144** was isolated and subjected to the cyclization. Due to the low amount of material that was used and probable instabilities regarding the lactone **145** (similar to lactone **127**), no product could be obtained. However, basic transformations towards this approach were made and further investigations would be necessary in the future.



mixture of **142** and **143** — **144** — **145**

Scheme 52 Selective Deprotection and Cyclization of Ketone **144**

D Conclusion

During this work the synthesis of the *trans* decalin compound **101** was achieved. Its formation relies on previous research already done in this group. However, the synthesis was accelerated in means of time and yield. Furthermore, the decalin intermediate is the desired diastereomer and was synthesized exclusively.

Additionally, a lot of insight towards the installation of a methyl group was gained. A successful conjugate addition to an unsaturated ester proved to be diastereoselective. However, the methyl group was installed on the wrong side compared to the natural product. Due to this unexpected selectivity a *Z* unsaturated ester moiety - a lactone - could be synthesized. This substrate proved to be rather unstable and certain issues are causing doubts of the conjugation of the double bond.

Additionally, another approach was also investigated. Here preliminary results were achieved.

During all the approaches, the resynthesis of the material was additionally gradually improved to ensure the ongoing synthesis of elisabethin A.

E Experimental Part

E I Materials and General Methods

The following general procedures were used in all reactions unless otherwise noted. Glassware was oven-dried at 110 °C and assembled while still hot. Schlenk flasks were flame-dried under argon. Oxygen- and moisture sensitive reactions were carried out under a slight argon overpressure using Schlenk techniques and in dry solvents. Residual water in the substrates was removed via aceotropic distillation with toluene. Sensitive liquids and solutions were transferred *via* double tipped cannula or syringes through rubber septa. All reactions were stirred magnetically.

The solvents used were purified and dried according to common procedures as follows.

- **Dry methylene chloride and diethyl ether** were retrieved from an Innovative Technologies PureSolv system.
- **Dry tetrahydrofurane** was pre-dried using an Innovative Technologies PureSolv system, refluxed over sodium/benzophenone ketyl and freshly distilled.
- **Toluene, xylene, ethyl acetate and acetonitrile** were p.a. and HPLC grade. If noted they were additionally dried as stated.
- **Dry DMF and DMSO** were used as purchased.
- **Dry MeCN** were distilled over CaH_2 and stored over activated molecular sieves (4 Å).

All other solvents used were p.a. or HPLC grade.

All reagents were used as received, except diisopropylethylamine and triethylamine which were freshly distilled from CaH_2.

$^{[1]}$H and $^{[13]}$C NMR spectra were recorded on a Bruker AC 400 at 400 MHz and 100 MHz or on a Bruker AC 600 at 600 MHz and 150 MHz, using the solvent peak as reference. $^{[13]}$C NMR spectra were run in proton-decoupled mode and multiplicities from DEPT or APT were referred to as s (singlet), d (doublet), t (triplet), q (quartet). Multiplicities of $^{[1]}$H signals were referred to as s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sext (sextet), sept (septet) and m (multiplet).

TLC analysis was done with precoated aluminium-backed plates (Silica gel 60 F_{254}, Merck). Compounds were visualized by submerging in an acidic phosphomolybdic acid/ ceric sulphate solution and heating. Column chromatography was carried out with silica gel Merck 60.

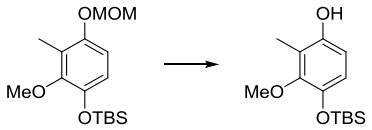
Melting points of crystalline compounds were determined with a Kofler hot-stage apparatus and are uncorrected.

Specific rotations were measured on an Anton Parr MCP 500 polarimeter in methylenchloride at 20 °C and 589 nm. Concentrations are given in [g/100 mL]

HR/MS: HR/MS analysis was carried out from solutions in acetonitrile (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 Agilent 6230 AJS ESI–TOF mass spectrometer (Agilent Technologies, Palo Alto, United States).

E II Cross Metathesis Approach

E II.1 4-((*Tert*-butyldimethylsilyl)oxy)-3-methoxy-2-methylphenol



Procedure A (TMSBr)

A solution of MOM ether **72** (525.0 mg, 1.7 mmol) in dry DCM (10 mL) was cooled to -30 °C. TMSBr (643 mg, 4.2 mmol) was added slowly *via* syringe and the solution was stored at 4 °C o.n. until TLC (PE/EE 4:1) showed full conversion of the starting material. The solution was quenched with 10 mL sat. sodium bicarbonate solution, causing a change of color to yellow. The aqueous layer was extracted with DCM two times (á 15 mL). The organic layers were combined, washed with brine (10 mL) and dried over sodium sulphate. The solvent was removed *in vacuo*, giving 477.0 mg of crude product **104**. The crude dark orange oil was purified *via* column chromatography yielding 191.0 mg (43 %) of product **104** and 234.0 mg (39 %) of TMS protected product.

The latter was dissolved in 2.0 mL MeOH and 0.1 mL water and K_2CO_3 (44.6 mg, 0.32 mmol) were added. The solution was stirred for 15 min at r.t. until TLC (PE/EE 20:1) showed full conversion. The mixture was diluted with water and diethyl ether. The organic phase was washed with brine and dried over sodium sulphate. The solvent was removed *in vacuo* yielding 154 mg (89 %) of crude product, which was used without further purification.

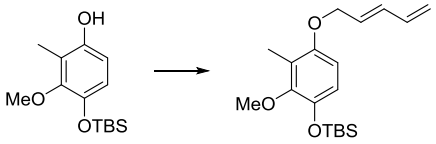
The combined yield after TMS cleavage of the side-product was determined with 77 % (345.0 mg, 1.29 mmol).

Procedure B (Et_2S, $ZnCl_2$)

A flame dried flask was charged with a solution of MOM ether **72** (1.0 g, 3.06 mmol) in dry DCM (10 mL). $ZnBr_2$ (689.7 mg, 3.06 mmol) and ethanthiole (380.6 mg, 6.13 mmol) was added at r.t. After 25 min TLC confirmed complete conversion of the starting material and the solution was diluted with 50 mL DCM and quenched with 10 mL sat. NH_4Cl solution. The mixture was filtrated over Celite® and the aqueous layer was extracted with DCM (three times). The combined organic phases were washed two times with water and brine. Then the solvent was dried over sodium sulphate. The solvent was removed *in vacuo*. The byproduct was removed in high vacuum o.n. and product **104** was yielded quantitatively.

Spectroscopical data were identical to that reported in literature.

E II.2 (*E*)-*Tert*-butyl(2-methoxy-3-methyl-4-(penta-2,4-dien-1-yloxy)phenoxy)dimethylsilane



Phenol **104** (4.64 g, 17.3 mmol) was separated in two batches. The following experimental description is per batch:

A solution of phenol **104** in THF (320 mL) was cooled to -20 °C in a three necked flask. *n*-BuLi (5.4 mL, 1.0 equiv.) was added and the mixture was stirred for 10 min. Then a solution of 5-bromo-1,3-pentadiene (1.27 equiv.) in DMF (10 mL) was added slowly *via* syringe. The solution was allowed to warm to r.t. and stirred o.n. The reaction was quenched with sat. NH_4Cl solution and the mixture was diluted with 30 mL water. The solution was extracted three times with diethyl ether. The combined organic phases were washed with water, brine and dried over sodium sulphate. The solvents were removed *in vacuo* giving crude product that was purified *via* column chromatography. 71 % (4.13 g, 12.35 mmol) product **106** and 11 % (511.4 mg, 1.91 mmol) starting material were isolated.

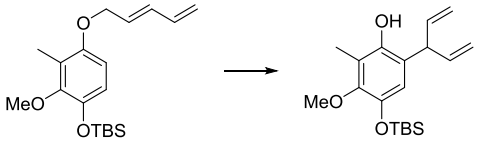
R_f = 0.53 (PE:EA 20:1), 0.61 (PE:EA 30:1)

[1]H-NMR (400 MHz, $CDCl_3$): δ_H = 6.63 (1H, d, *J*=8.68 Hz), 6.48 (1H, dd, *J*=2.02 Hz, 8.82 Hz), 6.42 - 6.32 (2H, m), 5.96 - 5.85 (1H, m) 5.24 (1H, d, *J*=13.04 Hz), 5.13 (1H d, *J*=9.36 Hz), 4.49 (2H, d, *J*=5.48 Hz), 3.75 (3H, s), 2.17 (3H, s), 1.01 (9H, s), 0.98 (3H, t, *J*=8.00 Hz), 0.83-0.67 (2H, m), 0.17 (3H, s).

[13]C-NMR (100 MHz, $CDCl_3$): δ_C = 151.8 (s); 150.2 (s); 143.2 (s); 136.4 (d), 133.0 (d), 129.3 (d), 121.7 (s), 118.0 (t), 117.4 (d), 107.8 (d), 69.0 (t), 60.0 (q), 26.4 (q, 3C), 18.9 (s), 9.9 (q), 7.9 (q), 5.0 (t).

HR/MS for $C_{19}H_{30}O_3Si$: $[M+NH_4]^+$ calcd. 352.2302, found: 352.2304

E II.3 4-((*Tert*-butyldimethylsilyl)oxy)-3-methoxy-2-methyl-6-(penta-1,4-dien-3-yl)phenol



A Schlenk flask was charged with ether **106** (4.6 g, 12.17 mmol) in 120 mL toluene (puriss.) and the solution was degassed *via* Schlenk technique (four cycles). EuFOD (427.0 mg, 3.3 mol%) was added and the mixture was heated to 110 °C for 3 h. Then another 0.3 mol% EuFOD were added and the mixture was heated for another 30 min until TLC confirmed full conversion of the starting material. The reaction mixture was diluted with toluene (100 mL), extracted three times with water (15 mL each portion) and washed with brine two times. After removing the solvent *in vacuo*, the crude product was gained quantitatively and was used without further purification.

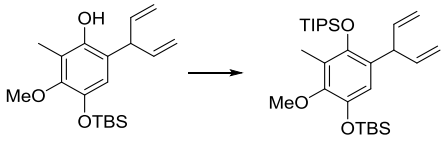
R_f = 0.38 (PE:EA 10:1), 0.29 (PE:EA 20:1)

$^{[1]}$H-NMR (400 MHz, $CDCl_3$): δ_H = 6.49 (1H, s), 6.04 (2H, ddd, *J*=6.83 Hz, 10.05 Hz, 16.70 Hz), 5.24 (2H, td, *J*=1.35 Hz, 10.30 Hz), 5.14 (2H, td, *J*=1.54 Hz, 17.45 Hz), 4.74 (1H, s), 4.02-4.13 (1H, m), 3.74 (3H, s), 2.15 (3H, s), 0.97 (9H; s), 0.96 (3H, t, *J*=7.80 Hz), 0.82-0.61 (m, 2H), 0.14 (9H, s).

$^{[13]}$C-NMR (100 MHz, $CDCl_3$): δ_C = 148.8 (s), 146.6 (s), 142.5 (s), 138.7 (d), 122.2 (s), 119.6 (s), 118.2 (d), 116.5 (t), 60.2 (q), 47.7 (q), 26.4 (q), 18.9 (s), 9.4 (q), 7.5 (q), 4.9 (t).

HR/MS for $C_{19}H_{30}O_3Si$: $[M- C_6H_{15}OSi +NH_4]^+$ calcd. 222.1489, found: 222.1487

E II.4 *Tert*-butyl(2-methoxy-3-methyl-5-(penta-1,4-dien-3-yl)-4-((triisopropylsilyl)oxy)phenoxy)dimethylsilane



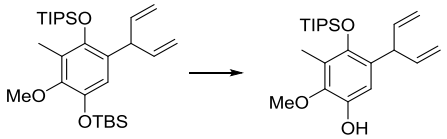
A solution of phenol **107** (4.07 g, 12.17 mmol) DMF (220 mL) was charged with TIPSCl (3.36 g, 15.82 mmol). Then NaH (630 mg, 15.82 mmol as 60% suspension in mineral oil) was added portionwise over a period of 5 min. The solution was stirred at r.t. for 5 h until TLC showed full conversion of the starting material. The reaction mixture was diluted with diethyl ether and quenched with sat. NH_4Cl solution. The aqueous phase was extracted with dietyhl ether three times and the combined organic phases were washed three times with water and brine. After drying over sodium sulphate, the solvent was removed *in vacuo*. The crude product was purified *via* column chromatography yielding 5.16 g of colorless oil (86 %).

R_f =0.72 (PE:EA 10:1)

$^{[1]}$H-NMR (400 MHz, $CDCl_3$): δ_H = 6.48 (1H, s), 5.12 (2H, td, *J*=1.14 Hz, 10.76 Hz), 5.92 (2H, ddd, *J*=6.12 Hz, 10.56 Hz, 16.97 Hz), 4.99 (2H, d, *J*=17.21 Hz), 4.47 -4.40 (1H, m), 3.73 (3H, s), 2.18 (3H, s), 1.34 – 1.22 (3H, m), 1.10 (18H, d, *J*=7.40 Hz), 0.99 (9H, s), 0.93 (3H, t, *J*=7.84 Hz), 0.80 -0.58 (2H, m), 0.14 (3H, s).

$^{[13]}$C-NMR (100 MHz, $CDCl_3$): δ_C = 148.3 (s), 147.1 (s), 142.9 (s), 140.2 (d), 127.1 (s), 122.9 (s), 118.4 (d), 115.3 (t), 59.9 (q), 44.7 (q), 26.7 (q), 18.9 (s), 18.1 (q), 14.5 (q), 11.5 (q), 7.5 (q), 4.8 (t).

E II.5 2-Methoxy-3-methyl-5-(penta-1,4-dien-3-yl)-4-((triisopropylsilyl)oxy)phenol



Due to the large amounts of solvents necessary the reaction was done in two separate identical flasks. Amounts stated below are per batch. The yield is given for the whole material, because the purification was performed at once.

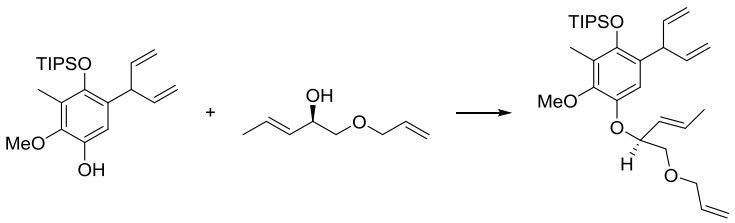
A flask was charged with TBS ether (2.59 g, 5.27 mmol), MeCN and 3.0 mL of 1 N HCl. The precipitate was dissolved by adding MeCN dropwise until the solution cleared up again. The mixture was stirred at r.t. for 21 h until TLC confirmed also small amounts of byproduct. The reaction mixture was quenched by adding a spatula of sodium bicarbonate and most of the MeCN was removed by rotary evaporation. Then diethyl ether and water were added. For better phase separation, the emulsion was salted out with small amounts of brine. The aqueous phase was extracted three times with diethyl ether and was dried with brine and sodium sulphate. Then the solvents were evaporated. After purification per column chromatography, 70 % (2.83 g, 7.51 mmol) product and 14 % (762.9 mg, 1.55 mmol) of starting material were separated.

R_f = 0.30 (PE:EA 10:1)

[1]H-NMR (400 MHz, $CDCl_3$): δ_H =6.59 (1H, s), 5.93 (2H, ddd, *J*=6.18 Hz, 10.70 Hz, 17.17 Hz). 5.23 (1H, s), 5.12 (2H, td, *J*=1.16 Hz, 9.76 Hz), 5.01 (2H, td, *J*=1.56 Hz, 17.17 Hz), 4.47-4.40 (1H, m), 3.73 (3H, s), 2.21 (3H, s), 1.36-1.24 (3H, m), 1.11 (18H, d, *J*=7.68 Hz).

[13]C-NMR (100 MHz, $CDCl_3$): δ_C = 146.2 (s), 144.3 (s), 142.9 (s), 140.0 (d), 128.5 (s), 121.8 (s), 115.5 (t), 112.6 (d), 60.8 (q), 44.9 (q), 18.3 (q), 14.5 (q), 11.6 (q).

E II.6 (*E*)-(4-((1-(Allyloxy)pent-3-en-2-yl)oxy)-3-methoxy-2-methyl-6-(penta-1,4-dien-3-yl)phenoxy)triisopropylsilane



Toluene was freshly distilled over sodium.

A solution of phenol **108** (2.49 g, 6.62 mmol) and alcohol **75** (1.22 g, 8.61 mmol) in toluene (40 mL) was cooled to 0°C and tributylphosphine (2.15 g, 9.93 mmol) was added at once. Then a solution of ADDP (2.50 g, 9.92 mmol) in toluene (10 mL) was added at a moderate speed. After complete addition, a preticipate was formed and the solution was allowed to warm up to r.t. The mixture was stirred for 36 h until TLC confirmed full conversion of the starting material. After dilution with 100 mL diethyl ether, the solution was filtered over Celite® and the solvents were removed *in vacuo*. The crude product (6.67 g) was filtrated over silica using PE:EA 9:1 as eluent. The phosphate free crude product (3.16 g) was further purified *via* column chromatography (MPLC, 180 g silica) yielding 65 % product **109** as a colorless oil (2.15 g, 4.31 mmol). Additionally, 9 % (302 mg, 0.62 mmol) S_N' product **104b** and 10 % (297 mg, 0.67 mmol) of butyl ether **104a** were isolated.

R_f = 0.62 (PE:EA 10:1)

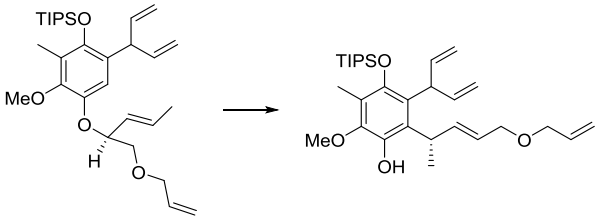
$^{[1]}$H-NMR (400 MHz, $CDCl_3$): δ_H = 6.55 (1H, s), 5.97 -5.86 (3H, m), 5.70-5.60 (1H, m), 5.46 (1H, qdd, *J*=0.99 Hz, 6.84 Hz, 14.62 Hz), 5.28 (1H, qd, *J*=1.39 Hz, 16.41 Hz), 5.17 (1H, qd, *J*=1.18 Hz, 9.82 Hz), 5.10 (2H, tdd, *J*=1.59 Hz, 6.58 Hz, 10.15 Hz), 4.97 (2H, tdd, *J*=1.67 Hz, 8.33 Hz, 17.32 Hz), 4.86-4.60 (1H, m), 4.46-4.39 (1H, m), 4.07 (2H, td, *J*=1.46 Hz, 5.66 Hz), 3.79 (3H, s), 3.69 (1H, dd, *J*=6.44 Hz, 10.36 Hz), 3.59 (1H, dd, *J*=4.40 Hz, 10.36 Hz), 2.17 (3H, s), 1.64 (3H, dd, *J*=1.42 Hz, 6.46 Hz), 1.28 (4H, q, *J*=7.50 Hz), 1.09 (18H, d, *J*=7.41 Hz).

$^{[13]}$C-NMR (100 MHz, $CDCl_3$): δ_C = 148.2 (s), 147.4 (s), 144.8 (s), 140.22 (d), 140.19 (d), 135.0 (d), 130.6 (d), 128.2 (d), 126.6 (s), 122.7 (s), 117.1 (t), 116.8 (d), 115.3 (t), 115.2 (t), 79.9 (q), 73.0 (t), 72.5 (t), 60.4 (q), 44.7 (q), 18,3 (q), 14.4 (t).

HR/MS for $C_{30}H_{48}O_4Si$: $[M+Na]^+$ calcd. 523.3226, found: 523.3214

$[\alpha]^{20}_D$ = 15.403° (c 2.65, CH_2Cl_2)

E II.7 (*S*,*E*)-2-(5-(Allyloxy) pent-3-en-2-yl)-6-methoxy-5-methyl-3-(penta-1,4-dien-3-yl)-4-((triisopropylsilyl)oxy)phenol



A solution of ether **109** (2.7 g, 5.43 mmol) in toluene (80 mL) was degassed *via* Schlenk technique four times. EuFOD (562.5 mg, 0.54 mmol) was added and the mixture was heated to 110°C and stirred o.n. Then another portion of EuFOD (5 mol%) was added and the solution was stirred for another 7 h at 110°. The reaction was stopped at approximately 90 % conversion (judging from TLC). The reaction mixture was diluted with toluene, extracted two times with water and washed with brine. After removing the solvent *in vacuo* the crude material (3.32g) was obtained as a mixture of product **100**, starting material and phenol **108**. After separation by column chromatography (90 g silica, DCM), 52 % (1.4 g, 2.8 mmol) product could be isolated.

Starting material and phenol **108** were additionally obtained as a mixture that contained 25 % (519 mg, 1.38 mmol) of phenol **108** and 9 % (234 mg, 0.48 mmol) of starting material. (Yields were determined by NMR). This mixture was directly subjected to a Mitsunobu reaction (see above).

R_f = 0.42 (PE:EA 10:1)

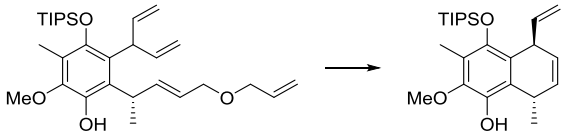
$^{[1]}$H-NMR (400 MHz, $CDCl_3$): δ_H = 6.19–6.02 (3H, m), 5.97-5.84 (1H, m), 5.58-5.48 (1H, m), 5.40 (1H, s), 5.24 (1H, dd, *J*=0.78 Hz, 16.43 Hz), 5.18-5.11 (3H, m), 5.05 (1H, dd, *J*=13.64 Hz, 15.24 Hz), 4.88-4.81 (1H, m), 3.95 (3H, t, *J*=6.20 Hz), 3.73 (3H, s), 2.18 (3H, s), 1.35 (3H, d, *J*=7.00 Hz), 1.32-1.22 (3H, m), 1.09 (18H, d, *J*=7.32 Hz).

$^{[13]}$C-NMR (100 MHz, $CDCl_3$): δ_C = 146.5 (s), 145.2 (s), 142.8 (s), 140.7 (d), 140.4 (d), 138.2 (d), 135.2 (d), 128.1 (s), 127.0 (s), 125.3 (d), 119.2 (s), 117.0 (t), 115.5 (t), 115.0 (t), 71.1 (t), 70.6 (t), 60.7 (q), 43.3 (q), 37.1 (q), 18.7 (d), 18.4 (q), 14.4 (d), 11.80 (q).

HR/MS for $C_{30}H_{48}O_4Si$: $[M+Na]^+$ calcd. 523.3211, found: 523.3214

$[\alpha]^{20}_D$ = -0.1138° (c 1.18, CH_2Cl_2)

E II.8 (S,*E*)-2-(5-(Allyloxy) pent-3-en-2-yl)-6-methoxy-5-methyl-3-(penta-1,4-dien-3-yl)-4-((triisopropylsilyl)oxy)phenol



A flame dried three-necked flask was charged with phenol **100** (102.8 mg, 0.21 mmol) and dry DCM (100 mL). The solution was degassed *via* freeze-pump-thaw cycle (three times). After adding Grubbs 2 catalyst (8.7 mg, 5mol%), the solution was stirred at 35 °C o.n. Full conversion was confirmed *via* TLC.

The reaction was quenched by bubbling air through the solution for 20 min and the solution was filtered over silica. To ensure complete filtration the plug was washed thoroughly several times with DCM. The solvent was removed with rotary evaporation, yielding 99% (82.80 mg, 0.20 mmol,) of crude product, which was used without further purification.

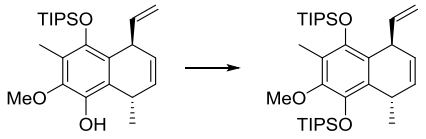
R_f = 0.57 (PE:EA 10:1) and 0.16 (PE:EA 40:1)

$^{[1]}$H-NMR (400 MHz, $CDCl_3$): δ_H = 6.11 (1H, ddd, *J*=5.49 Hz, 10.35 Hz, 17.30 Hz), 5.84 (1H, ddd, *J*=1.46 Hz, 3.42 Hz, 10.28 Hz), 5.74 (1H, ddd, *J*=1.74 Hz, 4.16 Hz, 10.24 Hz), 5.45 (1H, s), 4.91 (1H, d, *J*=10.24 Hz), 4.85 (1H, d, *J*=17.37 Hz), 4.21-4.14 (1H, m), 3.73 (3H, s), 3.58-3.48 (1H, m), 2.19 (3H, s), 1.34-1.21 (3H, m), 1.28 (3H, d, *J*=6.88 Hz), 1.11 (9H, d, *J*=7.48 Hz), 1.06 (9H, d, *J*=7.48 Hz).

$^{[13]}$C-NMR (100 MHz, $CDCl_3$): δ_C = 145.9 (s), 143.8 (s), 141.8 (d), 141.0 (s), 130.6 (s), 124.1 (d), 123.8 (2C, s), 119.1 (s), 113.0 (t), 60.8 (q), 38.5 (d), 29.9 (q), 23.3 (d), 18.2 (q), 14.6 (q), 11.1 (d).

$[\alpha]^{20}_D$ = 192.840° (c 1.65, CH_2Cl_2)

E II.9 (((5*S*,8*S*)-2-Methoxy-3,8-dimethyl-5-vinyl-5,8-dihydronaphthalene 1,4-diyl)bis(oxy))bis(triisopropylsilane)



A solution of phenol **115** (417.2 mg, 1.04 mmol) in THF (20 mL) was cooled to -80 °C and *n*-BuLi (1.6 M in THF, 0.72 mL, 1.15 mmol) was added *via* syringe. The solution was stirred for 20 min. DMF (20 mL, over a period of appr. 10 min) and TIPSCl (303.46 mg, 1.57 mmol) were added. The mixture was allowed to warm up slowly o.n. to r.t.

After confirmation of full conversion *via* TLC, the solution was quenched with sat. bicarbonate solution and was extracted with diethyl ether. The aqueous phase was reextracted with diethyl ether once. The combined organic phases were washed with water (2x3 mL) and brine (10 mL). Remaining water was removed with sodium sulfate. After concentrating the crude product, it was purified by column chromatography (PE:EA 100:1) yielding 93% (537.0 mg, 0.96 mmol) of pure product.

R_f = 0.85 (PE:EA 24:1) and 0.49 (PE:EA 40:1)

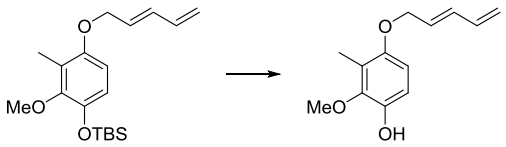
$^{[1]}$H-NMR (400 MHz, $CDCl_3$): δ_H = 6.01 (1H, ddd, *J*=6.09 Hz, 10.53 Hz, 16.96 Hz), 5.80 (1H, ddd, *J*=1.56 Hz, 3.38 Hz, 10.14 Hz), 5.69 (1H, ddd, *J*=1.79 Hz, 4.05 Hz, 10.13 Hz), 4.86 (1H, td, *J*=1.32 Hz, 10.20 Hz), 4.74 (1H, td, *J*=1.44 Hz, 17.33 Hz), 4.21-4.30 (1H, m), 3.63 (2H, s), 3.54-3.47 (1H, m), 2.17 (3H, s), 1.35-1.24 (6H, m), 1.22 (3H, d, *J*=6.80 Hz), 1.13-1.01 (36H, m).

$^{[13]}$C-NMR (100 MHz, $CDCl_3$): δ_C = 148.5 (s), 147.1 (s), 142.2 (d), 141.7 (s), 130.1 (d), 129.7 (s), 124.4 (d), 123.2 (s), 120.2 (s), 112.7 (t), 60.5 (q), 39.0 (d), 31.0 (q), 24.6 (d), 18.3 (q), 18.2 (q), 14.6 (q), 14.1 (q), 11.3 (d).

$[\alpha]^{20}_D$ = 2.839° (c 1.05, CH_2Cl_2)

E III Double Claisen Approach

E III.1 (*E*)-2-Methoxy-3-methyl-4-(penta-2,4-dien-1-yloxy)phenol



TBAF (3.44 mL, 3.44 mmol,1 M) was added slowly to a solution of ether **106** (1.0 g, 2.87 mmol) in THF (10 mL). After 5 min full conversion was determined by TLC.

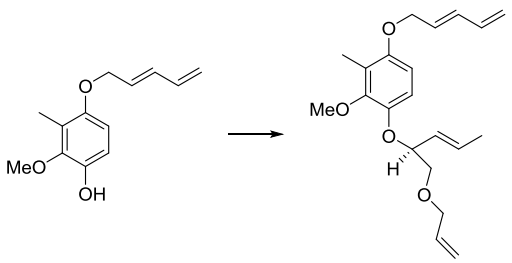
The mixture was quenched with sat. ammonium chloride solution and diethyl ether was added. The organic layer was washed with water and brine. After drying over sodium sulphate, the solvents were removed giving phenol **116** quantitatively (632 mg, 2.87 mmol).

R_f = 0.23 (PE:EA 10:1)

[1]H-NMR (400 MHz, $CDCl_3$): δ_H = 6.73 (1H, d, *J*=8.96 Hz), 6.54 (1H, d, *J*=8.84 Hz), 6.46-6.31 (2H, m), 5.96-5.87 (1H, m), 5.36 (1H, broad s), 5.29-5.20 (1H, m), 5.16-5.12 (1H, m), 4.51 (2H, d, *J*=5.52 Hz), 3.78 (3H, s), 2.21 (3H, s).

[13]C-NMR (100 MHz, $CDCl_3$): δ_C = 151.0 (s), 146.1 (s), 143.3 (s), 136.4 (d), 133.2 (d), 129.2 (d), 120.7 (s), 118.0 (t), 111.8 (d), 108.7 (d), 69.3 (t), 61.0 (q), 9.6 (q).

E III.2 1-(((*S*,*E*)-1-(Allyloxy)pent-3-en-2-yl)oxy)-2-methoxy-3-methyl-4-(((*E*)-penta-2,4-dien-1-yl)oxy)benzene



Toluene was freshly destilled over sodium before use.

A solution of phenol **116** (189.0 mg, 898 µmol) and alcohol **117** (166 mg, 1.17 mmol) in toluene (5.0 mL) was cooled to 0 °C in a flame dried Schlenk flask and PBu_3 (291.8 mg, 1.35 mmol) was added. Then a solution of ADDP (340.2 mg, 1.35 mmol) in toluene (5.0 mL) was added slowly, causing the mixture to become solid. The solution was allowed to reach r.t. and was stirred for 36 h until TLC confirmed full conversion of the starting material. After dilution with diethyl ether, the solution was filtered over Celite® and the solvents were removed *in vacuo*.

The crude product was purified *via* column chromatography. 45 % (141.0 mg, 409.4 µmol) of colorless oil were obtained as pure product.

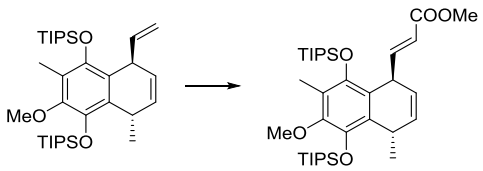
R_f = 0.61 (PE:EA 10:1)

$^{[1]}$H-NMR (400 MHz, $CDCl_3$): δ_H = 6.71 (1H, d, *J*=8.92 Hz), 6.47 (1H, d, *J*=8.92 Hz), 6.42-6.32 (2H, m), 5.97-5.85 (2H, m), 5.80-5.69 (1H, m), 5.55 (1H, qd, *J*=1.23 Hz, 6.18 Hz), 5.51 (1H, qd, *J*=1.57 Hz, 7.11 Hz), 5.33-5.08 (4H, m), 4.70-4.62 (1H, m), 4.50 (2H, d, *J*=5.12 Hz), 4.07 (2H, td, *J*=1.36 Hz, 5.44 Hz), 3.82 (3H, s), 3.70 (1H, dd, *J*=6.58 Hz, 10.38 Hz), 3.60 (1H, dd, *J*=4.36 Hz, 10.44 Hz), 2.16 (3H, s), 1.68 (3H, dd, *J*=0.94 Hz, 6.46 Hz).

$^{[13]}$C-NMR (100 MHz, $CDCl_3$): δ_C = 152.0 (s), 149.6 (s), 145.5 (s), 136.4 (d), 134.9 (d), 133.0 (d), 129.9 (d), 129.2 (d), 128.2 (d), 121.6 (s), 118.0 (t), 117.1 (t), 114.6 (d), 106.9 (d), 79.8 (d), 73.1 (t), 72.4 (t), 68.9 (t), 60.5 (q), 18.0 (q), 9.3 (q).

E IV Conjugate Addition

E IV.1 Methyl (*E*)-3-((1*R*,4*S*)-6-methoxy-4,7-dimethyl-5,8-bis((triisopropylsilyl)oxy)-1,4-dihydronaphthalen-1-yl)acrylate



A solution of Grubbs-Hoveyda Catalyst (2nd generation) (28.8 mg) in toluene (5.0 mL) was added with a syringe pump (4 h) to a solution of olefin **101** (514.0 mg, 0.920 mmol) and methyl acrylate (237.4 mg, 2.76 mmol) in toluene (10 mL) at 80°C and the mixture was stirred o.n. After 16 h another portion of catalyst (8.0 mg) and methyl acrylate (237.5mg, 2.76mmol) were added and the mixture was stirred for additional 7 h.

Then the reaction was quenched by bubbling air through the solution. The mixture was filtered through silica, which was washed with DCM. The solvents were removed *in vacuo* giving 616.6 mg crude product that was separated by column chromatography (50 g silica PE/EE as eluent) from the starting material. 53 % (302.6 mg, 0.490 mmol) of ester **102** and 36 % (185.4 mg, 0.33 mmol) of starting material were isolated.

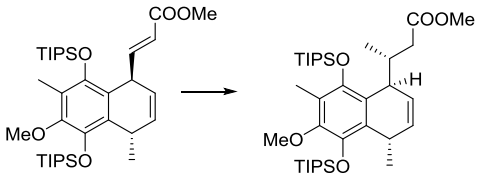
R_f = 0.47 (PE:EA 24:1) and 0.94 (Tol)

$^{[1]}$H-NMR (400 MHz, $CDCl_3$): δ_H = 7.11 (1H, dd, *J*=5.98 Hz, 15.79 Hz), 5.86 (1H, ddd, *J*=1.70 Hz, 3.72 Hz, 10.18 Hz), 5.65 (1H, ddd, *J*=1.68 Hz, 4.10 Hz, 10.10 Hz), 5.48 (1H, dd, *J*=1.38 Hz, 15.75 Hz), 4.35-4.28 (1H, m), 3.65 (3H, s), 3.63 (3H, s), 3,56-3.46 (1H, m), 2.17 (3H, s), 1.35-1.24 (9H, m), 1.14-1.02 (36H, m).

$^{[13]}$C-NMR (100 MHz, $CDCl_3$): δ_C = 167.8 (s), 152.2 (d), 149.0 (s), 147.2 (s), 141.8 (s), 131.6 (d), 129.7 (s), 122.4 (d), 121.0 (s), 120.5 (s), 119.3 (d), 60.5 (q), 51.4 (q), 38.2 (d), 30.9 (d), 24.4 (d), 18.3 (q), 18.2 (q), 18.1 (q), 14.6 (d), 14.0 (d).

$[\alpha]^{20}_D$ = 0.871° (c 0.51, CH_2Cl_2)

E IV.2 Methyl (*R*)-3-((1*S*,4*S*)-6-methoxy-4,7-dimethyl-5,8-bis((triisopropylsilyl)oxy)-1,4-dihydronaphthalen-1-yl)butanoate



A slurry of CuI (12.97 mg, 0.131 mmol) and LiCl (10.79 mg, 0.254 mmol) in THF (15mL) was stirred until only small amounts of precipitant were visible and cooled to -78 °C. MeMgBr (0.3 mL, 0.923 mmol as 3 M solution in diethyl ether) was added slowly over a period of 5 min, causing the solution to turn bright yellow. Then a solution of ester **102** (190.0 mg, 0.307 mmol) and TMSCl (0.86 mL, 0.677 mmol) in THF (1.0 mL) was added over a period of 5 min and the solution was allowed to warm up to -25 °C over 5 h.

The solution was quenched with 1.0 mL triethylamine and 3.0 mL sat. ammonium chloride solution and stirred for 15 min at r.t. The mixture was diluted with water and diethyl ether. The aqueous phase was extracted three times with diethyl ether. The combined organic phases were washed with water (three times), brine (two times) and dried over sodium sulphate.

The crude product was separated from the starting material *via* column chromatography (PE/ Et_2O), giving 122.0 mg (63 %) of pure product as colorless oil and 57.0 mg (15 %) of a 50% mixture of product and starting material (also as oil). The pure product could be crystallized from methanol.

R_f = 0.37 (PE:EA 50:1)

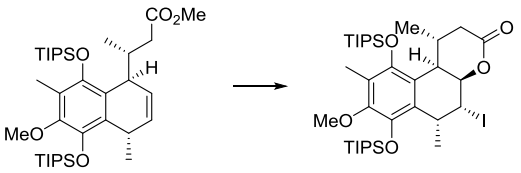
Mp = 78-79°C (crystallized from MeOH)

[1]H-NMR (400 MHz, $CDCl_3$): δ_H = 5.85 (1H, ddd, *J*=10.25 Hz, 3.41 Hz, 1.31 Hz), 5.70 (1H, ddd, *J*=10.47 Hz, 4.39 Hz, 1.69 Hz), 5.60 (3H,s), 5,60 (1H, m), 3.52 (3H, s), 3.46 (1H, m), 2.60 (1H, m), 1.76 (1H, dd, *J*=15.83 Hz, 11.62 Hz), 1.65 (1H, dd, *J*=15.51 Hz, 3.34 Hz), 1.31 (6H, m), 1.20 (1H, d, *J*=6.72 Hz), 1.07 (39H, m).

[13]C-NMR (100 MHz, $CDCl_3$): δ_C = 174.6 (s), 148.5 (s), 147.0 (s), 141.3 (s), 132.6 (d), 130.6 (s) , 123.6 (s), 121.0 (d), 120.7 (s), 60.5 (q) , 51.2 (q) , 40.9 (d), 35.9 (t), 34.2 (d), 31.4 (q), 24.5 (d), 18.4 (q), 18.3 (q), 18.2 (q), 18.1 (q), 14.6 (q), 14.0 (q) , 11.5 (d).

spec. rot.: 0.420g/100ml 345.84°

E IV.3 (1*R*,6*R*,10b*R*)-5-Iodo-8-methoxy-1,6,9-trimethyl-7,10-bis((triisopropylsilyl)oxy)-1,2,4a,5,6,10b-hexahydro-3H-benzo[f]chromen-3-one



Procedure A (via the carboxylic acid)

2N NaOH (0.3 mL) was added to a solution of ester **103** (10.0 mg, 15.80 µmol) in THF (0.3 mL). The yellow solution turned red immediately and was stirred at r.t. for 25 h. As no reaction took place the temperature was increased to 50 °C and the mixture was stirred for three more days. The reaction was quenched with acetic acid (pH 6) and extracted with chloroform. After evaporation of the solvent, NMR of the crude material (10 mg, 16.15 µmol) revealed a ratio of 1:1 starting material to product, which was dissolved in 1.0 MeCN without further purification. Although a red precipitate remained, iodine (8.13 mg, 32.03 µmol) was added and the flask was coiled with tinfoil. The solution was stirred o.n. at r.t. Then another equivalent iodine and sodium bicarbonate (1.36 mg, 16.15 mmol) were added and the reaction mixture was stirred for another night.

The solution was quenched with sodium thiosulfate and was extracted with diethyl ether. The organic phase was dried over sodium sulphate and the solvents evaporated. The crude material (11.3 mg) was purified over 0.6g silica using toluene/ ethyl acetate as eluent. 17 % (2.0 mg, 2.68 µmol) of product were isolated.

Procedure B (with NIS)

To a solution of ester **103** (9.0 mg, 14.22 µmol) in MeCN/H_2O (2/1 0.9 mL) NIS (3.84 mg, 17.06 µmol) was added and the flask was wrapped with aluminum coil. The solution was stirred o.n at r.t until TLC confirmed full conversion of the starting material.

The reaction mixture was quenched with sodium thiosulfate and two drops sat. bicarbonate solution. The clear solution was diluted with diethyl ether, the phases separated and the organic phase dried over sodium sulphate. The solvents were evaporated and the crude material (7.5 mg) was subjected to a column chromatography (250 mg silica, PE:EA 100:1) giving a mixture of two substances. The mixture could be separated using Tol:EA 50:1 as eluent. One substance was the desired product **123**.

The other was the corresponding halo-hydrine (**123a)**, which was dissolved in toluene. A crystal of p-toluenesulfonic acid was added. The solution was stirred at 40°C for 1 h until TLC confirmed full conversion of the starting material. The reaction was stopped by adding solid sodium bicarbonate. The solution was diluted with ethyl acetate and extracted with water and brine. After drying over sodium sulphate, the solvents were removed giving iodolactone **123** as single product.

The yield of 35 % (3.50 mg, 4.97 µmol) was determined for the whole amount of product obtained.

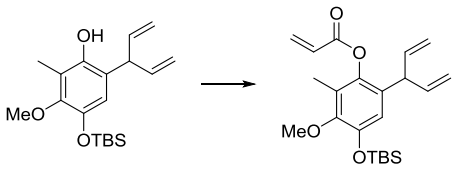
R_f = 0.42 (PE:EA 50:1)

[1]H-NMR (400 MHz, $CDCl_3$): δ_H = 4.94 (1H, dd, *J*=5.62 Hz, 11.98 Hz), 4.82 (1H, dd, *J*=5.22 Hz, 12.02 Hz), 3.64-3.61 (1H, m), 3.63 (3H, s), 3.39 (1H, dd, *J*=5.24 Hz, 11.16 Hz), 2.68 (1H, dd, *J*=5.00 Hz, 18.25 Hz), 2.26 (1H, dd, *J*=11.84 Hz, 18.41 Hz), 2.18 (3H, s), 1.93 -1.80 (1H, m), 1.36 (3H, d, *J*=6.92 Hz), 1.33 – 1.20 (6H, m), 1.12-1.03 (36H, m), 0.85 (3H, d, *J*=6.68 Hz).

[13]C-NMR (100 MHz, $CDCl_3$): δ_C = 169.4 (s), 149.2 (s), 148.6 (s), 141.3 (s), 128.7 (s), 121.4 (s), 120.5 (s), 60.5 (q), 40.2 (d),39.1 (t), 38.3 (d), 35.4 (d), 32.5 (d), 29.8 (d), 24.3 (q), 18.2 (q), 18.1 (q), 18.0 (q), 17.6 (q), 14.4 (q), 11.6 (q).

E V Double Ring Closing Metathesis Approach

E V.1 4-((*Tert*-butyldimethylsilyl)oxy)-3-methoxy-2-methyl-6-(penta-1,4-dien-3-yl)phenyl acrylate



Triethylamine (245.0 mg, 2.42 mmol) was added to a solution of phenol **104** (270.0 mg, 807.0 µmol) in DCM (5 mL) and the mixture was cooled to 0°C. Then acryloyl chloride (80 µl, 990.0 µmol) was added. The solution turned yellow immediately and was stirred for 55 min at r.t. TLC confirmed full conversion.

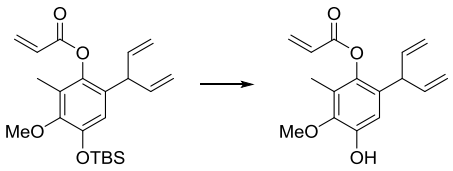
The solution was quenched with 0.8 mL sat. NH_4Cl solution and was diluted with 15 mL DCM. The phases were allowed to separate and the aqueous layer was extracted with 20 mL DCM. The combined organic phases were washed with water (15 mL) and brine (10 mL). After drying over sodium sulphate, the solvent was removed, yielding ester **130** quantitatively (313.6 mg, 807.1 µmol). The product could be used without further purification.

R_f = 0.80 (PE:EA 10:1)

$^{[1]}$H-NMR (400 MHz, $CDCl_3$): δ_H 6.60 (1H, d, *J*=16.37 Hz), 6.57 (1H, s), 6.33 (1H, dd, *J*=10.46 Hz, 17.31 Hz), 6.01 (1H, d, *J*=10.52 Hz), 5.90 (2H, ddd, *J*=6.47 Hz, 10.37 Hz, 17.02 Hz), 5.12 (2H, d, *J*=10.24 Hz), 5.01 (2H, d, *J*=17.21 Hz), 4.07-4.00 (1H, m), 3.77 (3H, s), 2.03 (3H, s), 1.06-0.92 (3H, m), 1.01 (9H, S), 0.86-0.64 (2H, m), 0.18 (3H, s).

$^{[13]}$C-NMR (100 MHz, $CDCl_3$): δ_C = 164.3 (s), 146.9 (s), 144.2 (s), 140.2 (s), 138.7 (d), 132.8 (t), 131.0 (s), 127.7 (d), 124.5 (s), 115.9 (t), 112.7 (d), 61.0 (q), 46.8 (q), 10.3 (q).

E V.2 4-Hydroxy-3-methoxy-2-methyl-6-(penta-1,4-dien-3-yl)phenyl acrylate



LiOAc (74.2 mg, 727.2 µmol) was added to a solution of TBS ether **130** (182.1 mg, 363.6 µmol) in DMF:H_2O 50:1 (3.0 mL). The solution stirred at r.t. for three days until TLC confirmed full conversion of the starting material.

The reaction mixture was diluted with ethyl acetate (20 mL) and brine. After phase separation, the aqueous layer was extracted with ethyl acetate (20 mL). The combined organic phases were washed with brine and dried over sodium sulphate. After evaporation of the solvents *in vacuo*, 134.1 mg crude product was obtained.

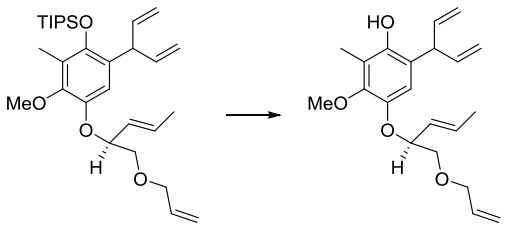
After purification by filtration over silica (PE:EA 10:1 as eluent) 86% (108.1mg, 313.8 µmol) of pure product were obtained as colorless oil.

R_f = 0.16 (PE:EA 10:1)

[1]H-NMR (400 MHz, $CDCl_3$): δ_H = 6.71 (1H, s) 6.62 (1H, dd, *J*=1.39 Hz, 17.51 Hz), 6.34 (1H, dd, *J*=10.49 Hz, 17.68 Hz), 6.02 (1H, dd, *J*=1.22 Hz, 10.50 Hz), 5.91 (2H, ddd, *J*=6.60 Hz, 10.36 Hz, 17.09 Hz), 5.77 (1H, braod s), 5.12 (2H, td, *J*=1.41 Hz, 10.2 Hz), 5.03 (2H, td, *J*=1.52 Hz, 17.17 Hz), 4.04 (1H, tt, *J*=1.34 Hz, 6.4 Hz), 3.75 (3H, s), 2.07 (3H, s).

[13]C-NMR (100 MHz, $CDCl_3$): δ_C = 164.3 (s) 146.9 (s), 144.2 (s), 140.2 (s), 138.7 (t), 132.8 (d), 131.0 (s), 127.7 (d), 124.5 (s), 115.9 (t), 112.7 (d), 70.0 (d), 46.8 (q), 10.3 (q).

E V.3 (*E*)-4-((1-(Allyloxy)pent-3-en-2-yl)oxy)-3-methoxy-2-methyl-6-(penta-1,4-dien-3-yl)phenol



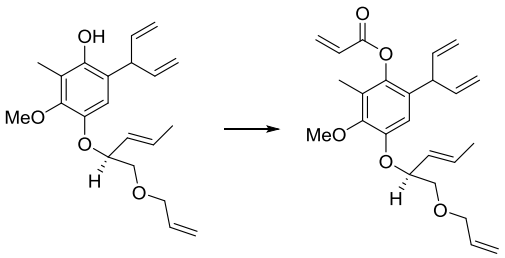
LiOAc (24.0 mg, 235.3 µmol) was added to a solution of TIPS ether **109** (60.0 mg, 119.8 µmol) in DMF:H_2O 50:1 (0.5 mL) and the solution stirred at r.t. for seven days until TLC confirmed full conversion of the starting material. The reaction mixture was diluted with 20 mL ethyl acetate and brine and the phases separated. The aqueous layer was extracted with ethyl acetate (20 mL). The combined organic phases were washed with brine and dried over sodium sulphate. After evaporation of the solvents *in vacuo*, 47.7 mg crude product (containing 7 % of starting material calculated from NMR) werre obtained and used directly without further purification.

R_f = 0.45 (PE:EA 10:1)

[1]H-NMR (400 MHz, $CDCl_3$): δ_H= 6.59 (1H, s), 6.09-5.97 (2H,m), 5.98-5.84 (1H, m), 5.76-5.66 (1H, m), 5.50 (1H, qdd, *J*=1.53 Hz, 7.34 Hz, 15.30 Hz), 5.28 (1H, qd, *J*=1.69 Hz, 17.57 Hz), 5.22 (2H, td, *J*=1.28 Hz, 10.36 Hz), 5.19-5.09 (3H, m), 4.81 (1H, broad s), 4.66-4.60 (1H, m), 4.20-4.15 (1H, m), 4.07 (2H, td, *J*=1.40 Hz, 5.56 Hz), 3.81 (1H, s), 3.71-3.57 (2H, m), 2.14 (3H, s), 1.67 (3H, dd, *J*=1.40 Hz, 6.64 Hz).

[13]C-NMR (100 MHz, $CDCl_3$): δ_C = 148.6 (s), 147.0 (s), 144.7 (s), 138.8 (t), 138.7 (t), 134.9 (t), 130.3 (t), 128.3 (t), 121.8 (s), 119.5 (s), 117.1 (d), 116.4 (d), 80.1 (d), 73.0 (t), 72.5 (t), 60.6 (q), 47.7 (d), 17.9 (q), 9.2 (q).

E V.4 (*E*)-4-((1-(Allyloxy)pent-3-en-2-yl)oxy)-3-methoxy-2-methyl-6-(penta-1,4-dien-3-yl)phenyl acrylate



NEt_3 (51.21 mg, 506.0 µmol) was added to a solution of phenol **134** (58.1 mg. 168.7 µmol) in DCM (1.0 mL). The solution was cooled to 0°C and acryloyl chloride (18.32 mg, 202.4 µmol) was also added dropwise. The temperature was increased to r.t. and the mixture was stirred for 40 min until TLC confirmed full conversion of the starting material. The reaction was quenched with water and was extracted three times with DCM. The combined organic phases were washed with water and brine. The solvent was dried over sodium sulphate and removed *in vacuo* (70.6 mg crude product). Ester **129** was isolated by column chromatography (5.6 g silica, PE:EA as eluent) in 35 % yield (23.60 mg, 59.2 µmol).

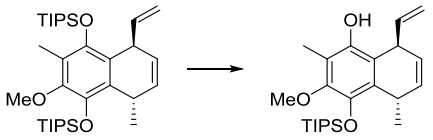
R_f = 0.32 (PE:EA 10:1)

[1]H-NMR (400 MHz, $CDCl_3$): δ_H= 6.68 (3H, s), 6.60 (1H, dd, *J*=1.17 Hz, 17.66 Hz), 6.33 (1H, dd, *J*=10.44 Hz, 17.33 Hz), 6.01 (1H, dd, *J*=1.20 Hz, 10.44 Hz), 5.96-5.83 (3H, m), 5.82-5.71 (1H, m), 5.48 (1H, qdd, *J*=0.72 Hz, 7.29 Hz, 15.60 Hz), 5.28 (1H, qd, *J*=1.52 Hz, 17.21 Hz), 5.17 (1H, qd, *J*=1.17 Hz, 10.15 Hz), 5.11 (2H, td, *J*=1.12 Hz, 9.93 Hz), 5.00 (2H, d, *J*=17.21 Hz), 4.75-4.69 (1H; m), 4.12-4.00 (3H, td, *J*=1.33 Hz, 5.65 Hz and m), 3.82 (3H, s), 3.71 (1H, dd, *J*=6.68 Hz, 10.44 Hz), 3.61 (1H, dd, *J*=4.26 Hz, 10.46 Hz), 2.03 (3H, s), 1.68 (3H, dd, *J*=1.10 Hz, 6.42 Hz).

[13]C-NMR (100 MHz, $CDCl_3$): δ_C = 164.2 (s), 149.1 (s), 147.4 (s), 141.1 (s), 138.9 (d), 134.8 (d), 132.6 (t), 130.6 (d), 129.2 (s), 127.8 (d), 125.3 (s), 117.2 (t), 115.8 (t), 115.8 (t), 114.4 (d), 79.4 (d), 73.0 (t), 72.5 (t), 60.5 (q), 46.5 (d), 17.9 (q), 10.1 (q).

E VI Consecutive RCM Approach

E VI.1 (5*S*,8*S*)-3-Methoxy-2,5-dimethyl-4-((triisopropylsilyl)oxy)-8-vinyl-5,8-dihydronaphthalen-1-ol



To prevent oxidation and decomposition of the material the reaction was performed under argon.

Acetic acid (219.66 mg, 3.66 mmol) was added to a solution of ether **101** (838 mg, 1.50 mmol) in THF (20.0 mL) and the mixture cooled to 0 °C. After addition of TBAF (1.0 M in THF, 1.50 mL, 1.50 mmol) over a period of 10 min, the solution turned yellow and was stirred at r.t. for 1 h 50 min until TLC showed formation of the hydroquinone.

The reaction was stopped by adding 5.0 mL water and 100 mL ethyl acetate. The organic phase was washed with water and brine. The solvents were removed *in vacuo*. The crude mixture (843.0 mg) was separated by column chromatography (PE:EA as eluent) giving 40 % (338.3 mg, 605.1 µmol) starting material and 54 % (324.7 mg, 806.5 µmol,) phenol **132**. 10 % (58.8 mg, 146.1 µmol) phenol **115** was also isolated as side product.

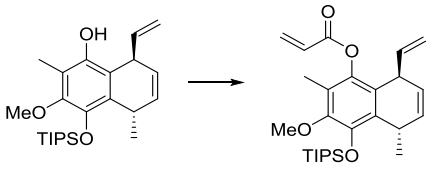
R_f = 0.45 (PE:EA 30:1)

$^{[1]}$H-NMR (400 MHz, $CDCl_3$): δ_H= 5.86 (1H, ddd, *J*=2.25 Hz, 4.25 Hz, 10.01 Hz), 5.70 (1H, ddd, *J*=9.38 Hz, 9.62 Hz, 17.37 Hz), 5.52 (1H, ddd, *J*=1.39 Hz, 3.41 Hz, 10.07 Hz), 5.35 (1H, d, *J*=17.01 Hz),), 5.22 (1H, dd, *J*=1.96 Hz, 9.36 Hz), 5.21 (1H, s), 3.99-3.92 (1H, m), 3.67 (3H, s), 3.59-3.49 (1H, m), 2.15 (3H, s), 1.18-1.28 (3H, m), 1.26 (3H, d, *J*=6.80 Hz), 1.11-1.04 (18H, m).

$^{[13]}$C-NMR (100 MHz, $CDCl_3$): δ_C = 149.2 (s), 146.9 (s), 142.5 (d), 140.9 (s), 130.8 (d), 129.1 (s),124.5 (d), 117.3 (s), 116.8 (s), 116.1 (t), 60.8 (q), 40.8 (d), 30.5 (d), 23.9 (q), 18.3 (q), 18.2 (q), 14.0 (d), 9.3 (q).

$[\alpha]^{20}_D$ = 123.184° (c 0.90, CH_2Cl_2)

E VI.2 (5*S*,8*S*)-3-Methoxy-2,5-dimethyl-4-((triisopropylsilyl)oxy)-8-vinyl-5,8-dihydronaphthalen-1-yl acrylate



A slurry of NaH (55 % in mineral oil, 17.92 mg, 410.8 µmol) in THF (3.0 mL) was cooled to -23 °C. Then phenol **132** (82.70 mg, 205.4 µmol) in THF (1.0 mL) was added slowly over 20 min and the mixture was stirred for 6 min. Then acryloyl chloride (37.18 mg, 410.8 µmol) was added dropwise over 5 min. The solution became brighter. After 1 h 10 min at -20 °C TLC confirmed full conversion of the starting material.

The reaction mixture was quenched by adding a spatula of $NaHCO_3$. Then the solution was diluted with ethyl and the phases were separated. The aqueous layer was extracted with ethyl acetate. The combined organic phases were washed with water and brine. The solution was dried over sodium sulphate and the solvents evaporated, giving 95.1 mg crude material. The crude material was purified over a plug of silica (PE:EA as eluent). 83 % (78.0 mg, 170.8 µmol) of ester **131** were isolated as clear oil.

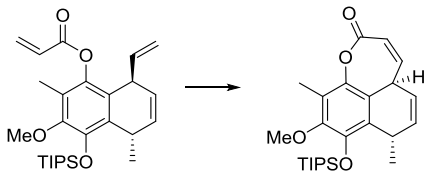
R_f = 0.27 (PE:EA 30:1) and 0.60 (PE:EA 6:1)

$^{[1]}$H-NMR (600 MHz, $CDCl_3$): δ_H= 6.57 (1H, broad d, *J*=18.24 Hz), 6.29 (1H, broad dd, *J*=9.72 Hz, 17.16 Hz), 5.98 (1H, broad d, *J*=7.62 Hz), 5.77 (1H, ddd, *J*=1.91 Hz, 3.98 Hz, 10.10 Hz), 5.71-5.53 (1H, broad m), 5.50 (2H, ddd, *J*=1.68 Hz, 3.60 Hz, 10.20 Hz), 4.91 (2H, braod d, *J*=16.98 Hz), 3-92-3.57 (1H, m), 3.69 (3H, s), 3.57-3.50 (1H, m), 2.02 (3H, broad s), 1.33 (3H, m, *J*=7.58 Hz) , 1.28 (3H, d, *J*=7.3 Hz), 1.09 (9H, d, *J*=7.62 Hz), 1.06 (9H, d, *J*=7.62 Hz).

$^{[13]}$C-NMR (125 MHz, $CDCl_3$): δ_C = 164.1 (s), 148.7 (s), 148.6 (s), 141.9 (t), 141.6 (broad d), 132.6 (broad t), 130.1 (s), 129.6 (d), 128.0 (broad d), 125.3 (d), 124.2 (broad s), 122.6 (broad s), 113.2 (broad t), 60.9 (q), 40.3 (d), 30.5 (d), 23.8 (q), 18.2 (q), 18.1 (q), 14.0 (d), 10.0 (q).

$[\alpha]^{20}_D$ = 3.746° (c 0.37, CH_2Cl_2)

E VI.3 (4a*R*,7*S*)-9-Methoxy-7,10-dimethyl-8-((triisopropylsilyl)oxy)-4a,7-dihydro-2H-naphtho[1,8-bc]oxepin-2-one



A solution of ester **131** (225.9 mg, 0.497 mmol) in degassed (freeze-pump-thaw, three cycles) toluene (30 mL) was heated to 80 °C. Then a solution of Grubbs-Hoveyda catalyst (2nd generation) (6.3 mg, 10.5 µmol) in toluene (0.5 mL) was added dropwise over 3.5 h to the starting material (syringe pump). After addition, the reaction was stirred for 15 h at 80 °C.

Then another portion of catalyst (1.5 mg) was added and the solution was stirred for additional 3 h. The reaction was quenched by bubbling air through the solution for 40 min. Then toluene was evaporated to obtain 210 mg of crude product, which was purified *via* flash chromatography using toluene and diethyl ether as eluents (very fast filtration to avoid decomposition and isomerization). 98 % (198.2 mg, 462.4 µmol) of pure product were isolated.

R_f = 0.48 (PE:EA 6:1)

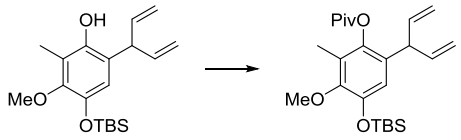
$^{[1]}$H-NMR (400 MHz, $CDCl_3$): δ_H= 6.51 (1H, dd, *J*=4.54 Hz, 10.98 Hz), 6.51 (1H, dd, *J*=4.54 Hz, 10.98 Hz), 5.95 (1H, ddd, *J*=2.21 Hz, 4.23 Hz, 10.23 Hz), 5.80 (1H, ddd, *J*=1.16 Hz, 3.54 Hz, 10.10 Hz), 5.76 (1H, dd, *J*=2.40 Hz, 10.96 Hz), 4.38-4.32 (1H, m), 3.67 (3H, s), 3.56-3.48 (1H, m), 2.26 (3H, s), 1.38-1.27 (3H, m), 1.26 (3H, d, *J*=6.64 Hz), 1.07 (9H, d, *J*=7.52 Hz), 1.04 (9H, d, *J*=7.52 Hz).

$^{[13]}$C-NMR (100 MHz, $CDCl_3$): δ_C = 164.1 (s), 154.3 (d), 148.6 (s), 144.6 (s), 143.7 (s), 131.6 (d), 128.4 (s), 124.8 (s), 122.7 (d), 119.4 (s), 60.9 (q), 34.5 (d), 29.8 (d), 23.6 (q), 18.2 (q), 18.1 (q), 14.0 (d), 10.3 (q).

Due to the instability of the product, specific rotation and HR-MS could not be measured.

E VII Pivalate Approach

E VII.1 4-((*Tert*-butyldimethylsilyl)oxy)-3-methoxy-2-methyl-6-(penta-1,4-dien-3-yl)phenyl pivalate



The reaction was performed in two separate flasks. All amounts given below were calculated for the whole amount.

A solution of phenol **104** (1.50 g, 4.48mmol) in dry MeCN (45mL, 0.1 M solution) was cooled to 0°C. Triethylamine (1.25 mL, 8.97 mmol) and then pivaloyl chloride (0.83 mL, 6.73 mmol) were added and the solution was allowed to warm up to r.t. After 1.5 h the mixture was heated at 40 °C for 6 h. The reaction mixture was stirred at r.t. over the weekend. TLC confirmed full conversion of the starting material.

The reaction was quenched with sat. NH_4Cl solution and was diluted with diethyl ether. The aqueous phase was extracted two times with diethyl ether. The combined organic phases were washed with water and brine. After drying over magnesium sulphate, the solvent was removed and product **136** was obtained quantitatively. The crude material was used without further purification.

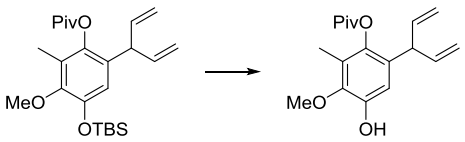
R_f =0.54 (PE:EA 30:1)

$^{[1]}$H-NMR (400 MHz, $CDCl_3$): δ_H= 6.57 (1H, s), 5.91 (2H, ddd, *J*=6.28 Hz, 10.48 Hz, 17.01 Hz), 5.14 (2H, td, *J*=1.34 Hz, 10.32 Hz), 5.00 (2H, td, *J*=1.50 Hz, 17.25 Hz), 4.02 (1H, tt, *J*=1.40 Hz, 6.05 Hz), 3.76 (3H, s), 2.02 (3H, s), 1.38 (9H, s), 1.01 (9H, s), 0.96 (3H, t, *J*=7.92 Hz), 0.84-0.63 (2H, m), 0.17 (3H, s).

$^{[13]}$C-NMR (100 MHz, $CDCl_3$): δ_C = 176.3 (s), 148.3 (s), 146.6 (s), 141.4 (s), 139.1 (d), 129.5 (s), 125.3 (s), 118.1 (d), 115.9 (t), 60.2 (q), 45.6 (q), 39.3 (s), 27.5 (q), 26.3 (d), 18.9 (s), 10.1 (q), 7.5 (q), 4.8 (t).

HR/MS for $C_{24}H_{38}O_4Si$: $[M+NH_4]^+$ calcd. 436.2878, found: 436.2876

E VII.2 4-Hydroxy-3-methoxy-2-methyl-6-(penta-1,4-dien-3-yl)phenyl pivalate



A solution of ester **136** (320.0 mg, 0.76 mmol) in THF (7 mL) was cooled down to 0°C (ice). Then acetic acid (79.0 mg, 1.32 mmol) was added quickly. After stirring for 5 min, TBAF (1.0 M in THF, 0.76 mL, 0.76 mmol) was added slowly over 5 min. The solution turned slightly yellow and the ice bath was removed.

TLC showed incomplete conversion after 15 min and additional TBAF was added until full conversion was accomplished.

The reaction mixture was diluted with 50 mL ethyl acetate and quenched with 5 mL of water. After phase separation the organic phase was washed with water and brine. After drying over magnesium sulphate and removing the solvent *in vacuo*, the yellow crude product (298 mg) was purified by filtration over silica (PE:EE 10:1), yielding 97 % (226.7 mg, 0.74 mmol) of product as colorless oil.

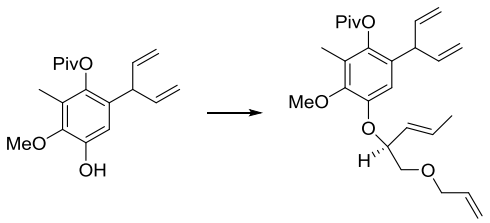
R_f = 0.10 (PE:EA 30:1)

$^{[1]}$H-NMR (400 MHz, $CDCl_3$): δ_H= 6.69 (1H, s), 5.92 (2H, ddd, *J*=7.42 Hz, 9.42 Hz, 16.03 Hz), 5.49 (1H, broad s), 5.13 (2H, td, *J*=1.38 Hz, 10.28 Hz), 5.02 (2H, td, *J*=1.54 Hz, 17.21 Hz), 4.07-3.98 (1H, m), 3.76 (3H, s), 2.05 (3H, s), 1.39 (9H, s).

$^{[13]}$C-NMR (100 MHz, $CDCl_3$): δ_C = 176.4 (s), 146.6 (s), 144.1 (s), 140.4 (s), 139.1 (broad d), 138.7 (broad d), 131.1 (s), 124.2 (s), 116.2 (broad t), 115.9 (broad t), 61.2 (q), 45.9 (d), 39.3 (s), 27.5 (q), 10.3 (q).

HR/MS for $C_{18}H_{24}O_4$: $[M+H]^+$ calcd. 305.1731, found: 305.1747

E VII.3 (*S*,*E*)-4-((1-(Allyloxy)pent-3-en-2-yl)oxy)-3-methoxy-2-methyl-6-(penta-1,4-dien-3-yl)phenyl pivalate



The reaction was conducted in two separate flasks. Amounts stated below are given for the whole material. Toluene was distilled over sodium.

A solution of phenol **136** (1.21 g, 3.98 mmol) and alcohol **75** (790.26 mg, 5.1 7mmoll) in toluene (44 mL) was cooled to 0 °C and tributylphosphine (1.59 mL, 5.96 mmol) was added. Then a solution of ADDP (1.50 g, 5.96 mmol) in toluene (20 mL) was added at moderate speed. After complete addition, a preticipate was formed and the solution was stirred at r.t. o.n. until TLC confirmed full conversion of the starting material. After dilution with toluene and diethyl ether, the solution was filtered over Celite® and the solvents were removed *in vacuo*. The crude product was filtrated over 15 cm silica using PE:EA 12:1 and 10:1 as eluents. 89% (1.52 g, 3.55mmol) of pure product were isolated as colorless oil. Additionally, 7% (116 mg, 288 µmol) of a mixture of SN' product and product in a ratio of 2:3 were also isolated.

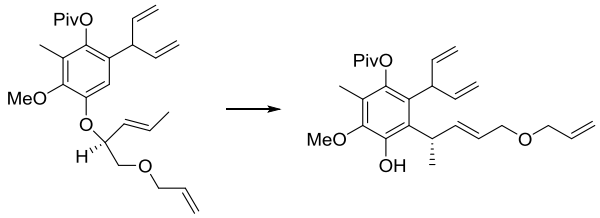
R_f = 0.45 (PE:EA 8:1)

[1]H-NMR (400 MHz, $CDCl_3$): δ_H= 6.66 (1H, s), 5.97-5.83 (2H, m), 5.80-5.69 (1H, m), 5.48 (1H, ddd, *J*=1.30 Hz, 7.34 Hz, 15.58 Hz), 5.28 (1H, qd, *J*=1.63 Hz, 17.37 Hz), 5.17 (1H, qd, *J*=1.30 Hz, 10.54 Hz), 5.12 (2H, td, *J*=1.37 Hz, 10.54 Hz), 4.99 (2H, qd, *J*=1.74 Hz, 17.23 Hz), 4.78-4.69 (1H, m), 4.08 (2H, d, *J*=5.16 Hz), 4.05-3.99 (1H, m), 3.82 (3H, s), 3.72 (1H, dd, *J*=7.18 Hz, 10.74 Hz), 3.62 (1H, dd, *J*=4.12 Hz, 10.40 Hz), 2.02 (3H, s), 1.67 (3H, dd, *J*=1.30 Hz, 6.42 Hz), 1.37 (9H, s).

[13]C-NMR (100 MHz, $CDCl_3$): δ_C = 176.3 (s), 148.8 (s), 147.5 (s), 141.3 (s), 139.1 (d), 134.8 (d), 130.7 (d), 129.1 (s), 127.8 (d), 125.1 (s), 117.2 (t), 115.8 (t), 79.4 (d), 73.0 (t), 72.5 (t), 60.6 (q), 45.7 (d), 39.3 (s), 27.5 (q), 18.0 (q), 10.1 (q).

HR/MS for $C_{26}H_{36}O_5$: $[M+Na]^+$ calcd. 451.2455, found: 451.2441

E VII.4 (*S*,*E*)-3-(5-(Allyloxy)pent-3-en-2-yl)-4-hydroxy-5-methoxy-6-methyl-2-(penta-1,4-dien-3-yl)phenyl pivalate



EuFOD (85.7 mg, 82.60 µmol) was added to a degassed solution of ether **137** (236.0 mg, 550.7 µmol) in toluene (8.5 mL). The mixture was heated to 110 °C and stirred o.n. TLC showed no conversion and another portion (5 mol%) of EuFOD was added and the reaction stirred for another 16 h.

The reaction mixture was diluted with toluene, extracted two times with water and washed with brine. After removing the solvent *in vacuo*, the crude product (316 mg) was obtained as a mixture of starting material and phenol **137**. After separation by column chromatography (27 g silica), 53 %, (126.0 mg, 294.0 µmol) starting material and 13 % (30.0 mg, 70.0 µmol) product were isolated.

R_f = 0.26 (PE:EA 10:1)

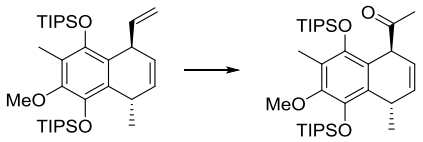
[1]H-NMR (400 MHz, $CDCl_3$): δ_H=6.19-5.83 (4H, m), 5.67 (1H, s), 5.63-5.49 (1H, m), 5.24 (1H, d, *J*=17.17 Hz), 5.18-5.07 (3H, m), 5.01 (2H, d, *J*=17.17 Hz), 4.42-4.34 (1H, m), 3.99-3.83 (5H, m), 3.75 (3H, s), 2.00 (3H, s), 1.41-1.33 (12H, m).

[13]C-NMR (100 MHz, $CDCl_3$): δ_C = 176.7 (s), 146.3 (s), 144.8 (s), 141.1 (s), 139.5 (d), 137.8 (d), 136.6 (s), 135.0 (d), 126 (d), 125.9 (d), 125.5 (d), 125.5 (s), 121.9 (s), 117.0 (t), 116.0 (t), 115.7 (t), 71.0 (t), 70.8 (t), 61.2 (q), 44.8 (d), 39.3 (s), 27.6 (q), 18.5 (d), 10.3 (q).

HR/MS for $C_{26}H_{36}O_5$: $[M+NH_4]^+$ calcd. 446.2894, found: 446.2901

E VIII Reduction Approach

E VIII.1 1-((1*S*,4*S*)-6-Methoxy-4,7-dimethyl-5,8-bis((triisopropylsilyl)oxy)-1,4-dihydronaphthalen-1-yl)ethan-1-one



A flask was charged with diene **101** (97.1 mg, 0.17 mmol), DMAc (6.0 mL) and H_2O (0.5 mL), causing the mixture to become cloudy. Dichloroethane (2.0 m) was added to clear up the solution. Bis(acetonitrile)dichloropalladium(II) (15.0 mg, 57.8 µmol) and para-quinone (200 mg, 1.85 mmol) were added at once. The dark brown solution was stirred at 36 °C for 6 h and o.n. at r.t.

The reaction mixture was diluted with diethyl ether (100 mL) and was extracted three times with sat. $NaHCO_3$ solution (in total 10 mL). After washing with brine and drying over sodium sulphate the solvent was removed *in vacuo*. The crude mixture was purified *via* column chromatography (PE:toluene as eluent) affording ketone **143** (88.2 mg, 153.4 µmol, 88 %) as white crystals.

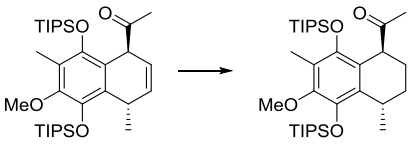
R_f = 0.67 (PE:EA 10:1) and 0.65 (Tol)

$^{[1]}$H-NMR (600 MHz, $CDCl_3$): δ_H = 5.96 (1H, ddd, *J*=2.55 Hz, 4.29 Hz, 9.99 Hz), 5.55 (1H, ddd, *J*=1.44 Hz, 3.84 Hz, 10.02 Hz), 4.30-4.26 (1H, m), 3.64 (3H, s), 3.62-3.57 (1H, m), 2.18 (3H, s), 1.63 (3H, s), 1.38-1.29 (6H, m), 1.24 (3H, d, *J*=7.08 Hz), 1.12-0.99 (36H, m).

$^{13]}$C-NMR (100 MHz, $CDCl_3$): δ_C = 208.8 (s), 149.5 (s), 148.0 (s), 141.8 (s), 133.5 (d), 129.9 (s), 121.4 (d), 120.5 (s), 119.8 (s), 60.5 (q), 52.6 (d), 30.8 (d), 25.1 (q), 24.4 (q), 18.3 (q), 18.2 (q), 18.1 (q), 14.5 (q), 14.1 (q), 11.3 (d).

$[\alpha]^{20}_D$ = 57.618° (c 1.74, CH_2Cl_2)

E VIII.2 1-((1*S*,4*S*)-6-Methoxy-4,7-dimethyl-5,8-bis((triisopropylsilyl)oxy)-1,2,3,4-tetrahydronaphthalen-1-yl)ethan-1-one

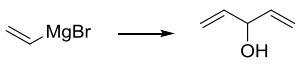


Activated palladium(0) on charcoal (23 mg) was added to a solution of ketone **143** (140.0 mg 243.5 µmol) in ethyl acetate (10.0 mL). The flask was set under H_2 atmosphere (10.9bar) and the mixture was stirred at r.t. o.n.

The reaction vessel was purged with argon, and the mixture filtrated over Celite® and the solvent evaporated. 145.0 mg of the material were recovered containing a 1:1 mixture of product and starting material according to NMR. The material was used without separation.

E IX Building Blocks

E IX.1 Penta-1,4-dien-3-ol



Procedure A (Synthesis of Vinyl Grignard and Addition to Methyl Formiate)

All glassware was either flame dried or dried at 120 °C o.n. A 250 mL three necked flask was cooled with liquid nitrogen and vinyl bromide (74.70 g, 698.5 mmol) was condensed in the flask.

A 1.0 L three necked flask equipped with an acetone/nitrogen condenser and a 250 mL dropping funnel was charged with magnesium (15.6 g, 643.0 mmol). The metal was overlayed with THF. Vinyl bromide (~1.0 mL) was added and the reaction was initiated with iodine. The dropping funnel was charged with cooled THF (170 mL) and vinyl bromide was added. This solution was added dropwise to the reaction mixture, maintaining a slightly reflux. After addition, the condenser was changed to an ordinary condenser and the mixture was refluxed for 1 h. As the reaction was not complete, the solution was poured in a separate flask and the residual magnesium was weighed (after 15 min under vacuum). 9.08 g (373.6 mmol) magnesium were converted, resulting in 58 % yield. The following addition of methyl formiate was calculated from the synthesized Grignard reagent.

A solution of methyl formiate (10.33 g, 172.0 mmol) in THF (1:1 mixture) was added dropwise to vinyl Grignard (49.0 g, 373.3 mmol) in THF at 0°C (ice bath) over a period of 1 h 20 min. During the reaction the solution turned brown. The mixture was stirred o.n. at r.t. and was quenched with sat. NH_4Cl solution, which caused the solution to turn yellow. Additionally, a precipitate was formed. The solution was decanted and the sediments were rinsed with diethyl ether. The combined organic phases were washed with sat. NH_4Cl solution. For better phase separation, water (4x10 mL) was added. The organic phase was washed with brine and dried over sodium sulphate. The solvents were distilled over a Vigreux distillation apparatus at 65 °C over several hours. A spatula hydroquinone was added to prevent oxidation and the product was distilled at 55 °C at 100 mbar giving 63 % (9.08 g, 107.9 mmol) of pure product.

Procedure B (Addition of Acrolein)

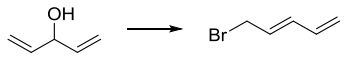
Vinyl Grignard (100 mL, 160 mmol as 1.6 M solution in THF) was cooled to 0°C and stirred in a flame dried three-necked flask. Then a solution of acrolein (8.54 g, 152.4 mmol) in THF (10 mL) was added dropwise (30 min), causing the solution to brighten up. The reaction was stirred for 3 h at 0 °C and subsequently quenched with sat. NH_4Cl solution (1.5 equiv.) It was extracted with diethyl ether three times. For better phase separation, small amounts of water were added. After washing with water and brine the solvent was removed carefully (40°C, 380 mbar) and 64 % of the product were obtained as orange oil (11,66 g, 97.0 mmol, 70% purity calculated from NMR)

R_f = 0.83 (PE:EtOAc 4:1)

[1]H-NMR (400 MHz, $CDCl_3$): δ_H= 5.87-5.99 (1H, m), 5.31 (1H, d, J= 17.2 Hz), 5.22 (1H, d, J=10.5 Hz), 4.00-4.13 (2H, m), 3.75 (1H, dd, J=11.0 Hz, 3.4 Hz), 3.43 (1H, dd, J=11.4 Hz, 5.8 Hz), 3.15-3.22 (1H, m), 2.80-2.86 (1H, m) 2.64 (1H, dd, J= 5.0 Hz, 2.6 Hz).

[13]C-NMR (100 MHz, $CDCl_3$): δ_C =134.4 (d), 117.4 (t), 72.8 (d).

E IX.2 (*E*)-5-Bromopenta-1,3-diene

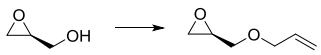


A solution of 1,4-pentadien-3-ol (9.08 g, 107.9 mmol) in pentane (140 mL) was divided in two batches, which were cooled to 0 °C. Per batch 13.0 mL HBr (48 % in water) were added dropwise over 2 h (batch 1) and 3 h (batch2). After addition the solutions were stirred for additional 2 h.

Then the phases were separated and the organic phase was washed with sat. bicarbonate solution, water and brine. After drying over sodium sulphate, both batches were combined and the solvent was removed carefully (30 °C at 900 mbar using a Vigreux column) giving the product as dark yellow liquid. NMR revealed a purity of 88 % of the residue resulting in 95 % yield (3.54 g, 24.1 mmol).

Spectroscopical data were identical to that reported in literature.

E IX.3 (*R*)-2-((Allyloxy)methyl)oxirane



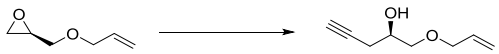
To a slurry of NaH (3.24 g as 55 % suspension in mineral oil, 74.25 mmol) DMF (120 mL) allyl bromide (8.98 g, 74.25 mmol) was added and the mixture was cooled to 0 °C. Then (*S*)-oxiran-2-ylmethanol (5.00 g, 67.50 mmol) was added dropwise over 30 min. The reaction mixture was allowed to warm up to r.t and was stirred o.n. TLC (PE:EE 10:1) showed full conversion of the starting material.

The reaction was quenched with water and the solution was poured in a mixture of 300 mL pentane and 100 mL diethyl ether. After stirring vigorously for 10 min, the phases were allowed to separate and the organic layer was washed with water (3 x 20 mL) and brine (10 mL). After drying over sodium sulphate the solvents were removed under ambient pressure (100 mbar, 40 °C). As DMF was still present in the mixture, it was poured on 100 mL pentane. After phase separation and evaporation of pentane 9.08 g of crude material were obtained.

The product was purified *via* Kugelrohr distillation at 80 °C and 5 mbar yielding 46% (3.57 g, 31.3 mmol) of pure product, which was used without any delay due to the high hygroscopicity.

Spectroscopical data were identical to that reported in literature.

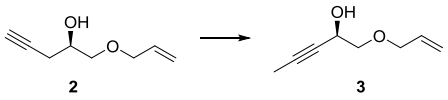
E IX.4 (*R*)-1-(Allyloxy)pent-4-yn-2-ol



A solution of epoxid **112** (3.56 g, 31.19 mmol) in dry DMSO (48 mL) was cooled to 0°C. Lithium acetilyde ethylenediamine complex (4.31 g, 47.33 mmol) was added portionwise and the reaction was stirred for 2 h at r.t. After confirmation of full conversion *via* TLC (PE:EE 10:1), the solution was poured on diethyl ether (200 mL) and the mixture was cooled to 0 °C. The solution was neutralized with 2 N HCl pH 7). After phase separation the aqueous phase was extracted with additional of 70 mL diethyl ether. The combined organic phases were washed with water (seven times 10 mL), brine (15 mL) and dried over sodium sulphate. The solvent was removed *in vacuo*, yielding 91 % (4.00 g, 28.46 mmol) of crude product, which was used without further purification.

Spectroscopical data were identical to that reported in literature.

E IX.5 (*R*)-1-(Allyloxy)pent-3-yn-2-ol



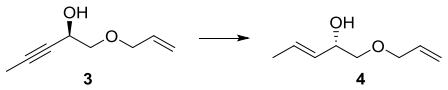
2 3

A solution of potassium *tert*-butanolat (3.19 g, 28.46 mmol) in DMSO (20 mL) was added dropwise (22 min) to a solution of alcohol **113** (3.99 g, 28.46 mmol) in DMSO (60 mL), causing the solution to turn to a deep black. The solution was stirred at r.t. for 1 h. Reaction control *via* NMR revealed full conversion of the starting material (a sample was quenched with sat. NH_4Cl solution and extracted with diethyl ether).

The mixture was poured on 400 mL diethyl ether and quenched with 2 M HCl (pH 5). After phase separation the aqueous phase was extracted several times with diethyl ether (300 mL). The combined organic phases were washed eight times with water (in total 120 mL) and dried with brine (20 mL). After drying over sodium sulphate and evaporating the solvent, 92 % (3.67 g, 26.18 mmol) of crude product were isolated as yellow oil.

Spectroscopical data were identical to that reported in literature.

E IX.6 (*R*,*E*)-1-(Allyloxy)pent-3-en-2-ol



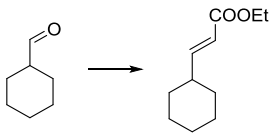
3 4

A solution of alcohol **114** (3.67 g, 26.2 mmol) in THF (45 mL) was added dropwise over 25 min to a slurry of $LiAlH_4$ (1.79 g, 47.1 mmol) in THF (30 mL). After ceasing of the initial fume, the solution was heated to 65 °C for 1.5 h. Reaction control *via* NMR confirmed full conversion.

Diethyl ether (150 mL) was added, the solution cooled down to 0° C and the reaction mixture was carefully hydrolyzed with water. Rochelle salt (35 mL) was added and the mixture was stirred o.n. After phase separation the aqueous phase was extracted with diethyl ether (4 x 50 mL). The combined organic phases were washed with sat. NH_4Cl solution, water and brine (20 mL each) and dried over sodium sulphate. The solvent was removed by rotary evaporation. The crude product (2.25 g) was purified by flash chromatography (40 g silica, diethyl ether as eluent) giving 50 % (1.85 g, 23.6mmol) of pure slightly yellow oil.

Spectroscopical data were identical to that reported in literature.

E IX.7 Ethyl (*E*)-3-cyclohexylacrylate



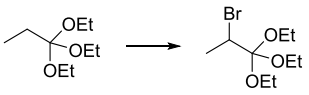
DBU (6.11 g, 40.12 mmol) was added to solution of cyclohexancarbaldehyde (3.00 g, 26.74 mmol) and ethyl-2(diethoxyphosphoryl)acetate (6.11 g, 40.12 mmol) in DCM (20 mL) and the reaction mixture was refluxed for 4 h. Reaction control *via* NMR showed 95 % conversion and the reaction was stirred at r.t. o.n.

The solution was diluted with 10 mL DCM and was quenched with sat. NH_4Cl solution. After addition of water (10 mL), the phases were separated. The aqueous phase was extracted with another portion of DCM. The combined organic phases were washed with water and brine. After drying over sodium sulphate, the mixture was filtrated over silica, yielding the product quantitatively (4.87 g, 26.74 mmol).

For further purification the product was distilled *via* Kugelrohr distillation at 85 °C and 0.44 mbar.

Spectroscopical data were identical to that reported in literature.

E IX.8 2-Bromo-1,1,1-triethoxypropane

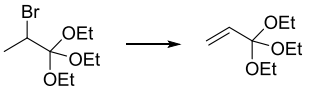


A flame dried three-necked flask was charged with triethylorthopropionate (15.10 g, 85.60 mmol) and pyridine (6.90 mL, 6.7 g, 85.60 mmol). After cooling to -25 °C, bromine (4.4 mL, 13.7 g, 85.60 mmol) was added dropwise over a period of 1.5 h. Subsequently, the mixture was stirred for 5 h at 3°C and stored o.n. in the refrigerator. Then it was stirred for 8 h at r.t. and stored o.n. in the refrigerator again.

The mixture was diluted with PE: Et_2O (3:1, 100 mL) and filtered over Celite®. The filter cake was washed with PE five times. Afterwards, it was diluted with PE up to a volume of 400 mL. Then it was washed with aq. sat. $NaHCO_3$ solution (3 x 5 mL) and brine (1 x 5 mL). The organic phase was dried over Na_2SO_4 and the solvent evaporated (200 mbar, 40°C). 2-bromo-1,1,1-triethoxypropane (**26**) (20.8 g, 81.4 mmol, 95 %) was obtained and used in the next reaction without purification.

Spectroscopical data were identical to that reported in literature.

E IX.9 3,3,3-Triethoxyprop-1-ene

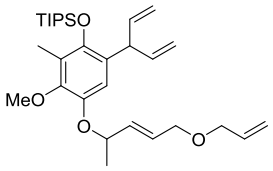


A flask was charged with 2-bromo-1,1,1-triethoxypropane (20.8 g, 81.4 mmol) and KO*t*Bu (11.06 g, 98.56 mmol) was added slowly. The suspension was heated up to 80 °C and stirred for 1 h. Then the temperature was increased to 135 °C for 2 h. The viscous yellow suspension became fluid and cloudy. The mixture was cooled down and diluted with water (15 mL) and diethyl ether (40 mL). The aqueous phase was extracted with diethyl ether (3x 40 mL) and the pooled organic phases were dried over K_2CO_3. The solvent was evaporated (300 mbar, 40 °C) and the crude product was purified through vacuum distillation (35 mbar, 68 °C) giving 3,3,3-triethoxyprop-1-ene (**27**) (10.0 g, 57.4 mmol, 70 %) as a colorless oil.

Spectroscopical data were identical to that reported in literature.

E X Analytics of Side Products

E X.1 (*E*)-(4-((5-(Allyloxy)pent-3-en-2-yl)oxy)-3-methoxy-2-methyl-6-(penta-1,4-dien-3-yl)phenoxy)triisopropylsilane

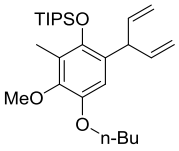


R_f = 0.59 (PE:EA 10:1)

[1]H-NMR (400 MHz, $CDCl_3$): δ_H=6.52 (1H, s), 5.98-5.83 (3H, m), 5.81-5.92 (2H, m), 5.24 (1H, qd, *J*=1.69 Hz, 17.17 Hz), 5.16 (1H, qd, *J*=1.38 Hz, 10.27 Hz), 5.10 (2H, tdd, *J*=1.57 Hz, 5.64 Hz, 10.40 Hz), 4.98 (2H, tdd, *J*=1.64 Hz, 6.14 Hz, 17.19 Hz),4.73-4.64 (1H, m), 4.47-4.40 (1H, m), 3.92 (4H, dd, *J*=5.42 Hz, 9.34 Hz), 3.78 (3H, s), 2.04 (3H, s), 1.41 (3H, d, *J*=6.28 Hz), 1.35-1.22 (6H, m), 1.10 (18H, d, *J*=7.36 Hz).

[13]C-NMR (100 MHz, $CDCl_3$): δ_C = 148.2 (s), 147.4 (s), 144.8 (s), 140.2 (d), 134.8 (d), 134.3 (d), 131.0 (d), 129.0 (d), 128.4 (d), 126.8 (s), 122.9 (s), 117.1 (t), 116.2 (d), 115.4 (t), 75.9 (q), 71.1 (t), 70.1 (t), 60.5 (t), 60.4 (q), 44.8 (q), 38.9 (q), 21.4 (d), 18.3 (q), 14.5 (q).

E X.2 (4-Butoxy-3-methoxy-2-methyl-6-(penta-1,4-dien-3-yl)phenoxy)triisopropyl silane

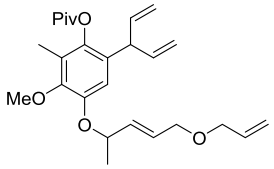


R_f = 0.74 (PE:EA 10:1)

[1]H-NMR (400 MHz, $CDCl_3$): δ_H= 6.49 (1H, s), 5.95 (2H, ddd, *J*=6.13 Hz, 10.59 Hz, 17.00 Hz), 5.12 (2H, td, *J*=1.62 Hz, 10.48 Hz), 5.01 (2H, td, *J*=1.70 Hz, 17.37 Hz), 4.52-4.44 (1H, m), 3.91 (2H, t, *J*=6.48 Hz), 3.77 (3H, s), 2.18 (3H, s), 1.81-1.71 (2H, m), 1.55-1.45 (2H, m), 1.35-1.22 (3H, m), 1.10 (18H, d, *J*=7.40 Hz), 0.97 (3H, t, *J*=7.40 Hz).

[13]C-NMR (100 MHz, $CDCl_3$): δ_C = 146.9 (s), 146.7 (s), 146.6 (s), 140.2 (d), 126.8 (s), 122.9 (s), 115.4 (t), 111.8 (d), 69.0 (t), 60.3 (q), 44.9 (d), 31.8 (t), 19.5 (t), 18.3 (q), 18.3 (q), 14.5 (q), 14.1 (d), 11.4 (q).

E X.3 (*E*)-4-((5-(Allyloxy)pent-3-en-2-yl)oxy)-3-methoxy-2-methyl-6-(penta-1,4-dien-3-yl)phenyl pivalate

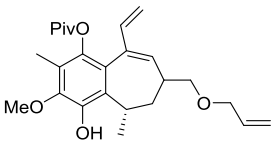


R_f = 0.42 (PE:EA 10:1)

[1]H-NMR (400 MHz, $CDCl_3$): δ_H= 6.61 (1H, s), 5.97-5.82 (3H, m), 5.80-5.74 (2H, m), 5.26 (1H, qd, *J*=1.56 Hz, 17.17 Hz), 5.17 (2H, dd, *J*=1.34 Hz, 10.4 Hz), 5.12 (3H, td, *J*=1.56 Hz, 10.24 Hz), 4.99 (3H, d, *J*=17.21 Hz), 4.80-4.72 (1H, m), 4.06-4.00 (1H, m), 3.97 (2H, d, *J*=3.92 Hz), 3.93 (2H, d, *J*=5.60 Hz), 3.80 (3H, s), 2.01 (3H, s), 1.44 (3H, d, *J*=6.32 Hz), 1.38 (9H, s).

[13]C-NMR (100 MHz, $CDCl_3$): δ_C = 176.3 (s), 148.6 (s), 147.6 (s), 141.4 (s), 139.1 (broad d), 135.1 (d), 134.8 (d), 129.3 (s), 128.6 (broad d), 125.3 (s), 117.2 (t), 116.9 (t), 116.1 (s), 75.4 (d), 71.1 (t), 70.0 (t), 60.5 (q), 45.8 (d), 39.3 (s), 27.5 (q), 21.5 (d), 10.1 (q).

E X.4 (5*S*)-7-((Allyloxy)methyl)-4-hydroxy-3-methoxy-2,5-dimethyl-9-vinyl-6,7-dihydro-5H-benzo[7]annulen-1-yl pivalate

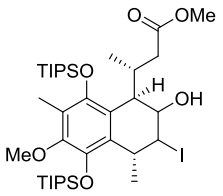


R_f = 0.32 (PE:EA 10:1)

[1]H-NMR (600 MHz, $CDCl_3$): δ_H =6.44 (1H, dd, *J*=10.50 Hz, 17.22 Hz), 5.96-5.83 (2H, m), 5.75 (1H, s), 5.23 (1H, qd, *J*=1.37 Hz, 17.02 Hz), 5.14 (1H, qd, *J*=1.27 Hz, 10.27 Hz), 5.01 (1H, broad d, *J*=9.30 Hz), 4.79 (1H, broad d, *J*=17.16 Hz), 3.95-3.87 (2H, m), 3.81 (3H, s), 3.23-3.17 (1H, m), 3.06-3.00 (1H, m), 2.94-2.86 (1H, m), 2.14-2.07 (1H, m), 2.04 (3H, s), 1.76-1.66 (2H, m), 1.43 (3H, d, *J*=7.34 Hz), 1.24 (9H, s).

[13]C-NMR (125 MHz, $CDCl_3$): δ_C = 176.8 (s), 145.4 (s), 139.6 (s), 138.5 (d), 137.4 (s), 135.2 (d), 131.0 (s), 126.2 (s), 120.8 (s), 117.0 (t), 114.2 (t), 75.8 (t), 72.2 (t), 61.3 (q), 39.0 (s), 38.3 (t), 36.7 (d), 32.8 (q), 30.0 (t), 27.4 (q), 22.1 (q), 10.1 (q).

E X.5 Methyl (3*R*)-3-((1*R*,4*R*)-2-hydroxy-3-iodo-6-methoxy-4,7-dimethyl-5,8-bis((triisopropylsilyl) oxy)-1,2,3,4-tetrahydronaphthalen-1-yl)butanoate



R_f = 0.36 (PE:EA 50:1)

[1]H-NMR (400 MHz, $CDCl_3$): δ_H = 4.99 (1H, dd, *J*=5.73 Hz, 11.97 Hz), 4.27 (1H, ddd, *J*=1.94 Hz, 5.27 Hz, 11.99 Hz), 3.60 (3H, s), 3.65 (3H, s), 3.61-3.55 (1H, m), 3.50-3.47 (1H, m), 2.99 (1H, d, *J*=2.28 Hz), 2.95-2.88 (1H, m), 2.38-2.32 (2H, m), 2.18 (3H, s), 1.38 (3H, d, *J*=6.84 Hz), 1.33-1.23 (6H, m), 1.11-1.01 (36H, m), 0.43 (3H, d, *J*=6.48 Hz).

[13]C-NMR (100 MHz, $CDCl_3$): δ_C = 174.9 (s), 148.5 (s), 148.3 (s), 140.9 (s), 129.7 (s), 123.3 (s), 121.2 (s), 69.4 (d), 60.4 (q), 51.6 (q), 46.7 (d), 44.0 (d), 43.3 (t), 38.0 (d), 30.3 (d), 24.2 (q), 18.6 (q), 18.3 (q), 18.2 (q), 18.2 (q), 18.1 (q), 14.6 (d), 11.9 (q).

F Appendices

F I List of Abbreviations

AcOH	acetic acid
ADDP	1,1'-(azodicarbonyl) dipiperidine
$AlMe_3$	trimethylaluminum
appr.	approximately
APT	attached proton test
B.R.S.M	based on the recovery of starting material
CAN	ceric ammonium nitrate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
CaH_2	calcium hydride
DCC	*N*,*N'*-dicyclohexylcarbodiimide
DCM	dichloromethane
de	diastereomeric excess
DEPT	Distortionless Enhancement by Polarization Transfer
DIBAL-H	Diisobutylaluminium hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMAc	dimethylacetamide
DMAP	4-(dimethylamino)-pyridine
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
EA	ethyl acetate
EuFOD	Europium(III)-tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionate)
equiv.	equivalent(s)
$FeCl_3$	iron(III) chloride
HBr	hydrogen bromide
HF	hydrogen fluoride
HMPA	hexamethylphosphoramide
IMDA	intramolecular Diels – Alder reaction
IR	infra-red
LA	Lewis acid
LAH	lithium aluminum hydride
$LiBH_4$	lithium boroydride
LiI	lithium iodide
LiOAc	lithium acetate
MeCN	acetonitrile
MeI	methyl iodide
MOMCl	chloromethyl methyl ether
MTBE	methyl-*tert*-butylether
n-BuLi	*n*-butyllithium
NaH	sodium hydride
NBS	*N* - bromosuccinimide
NIS	*N* - iodosuccinimide
NMR	nuclear magnetic resonance spectroscopy
NOE	nuclear Overhauser effect
NOESY	Nuclear Overhauser Enhancement Spectroscopy

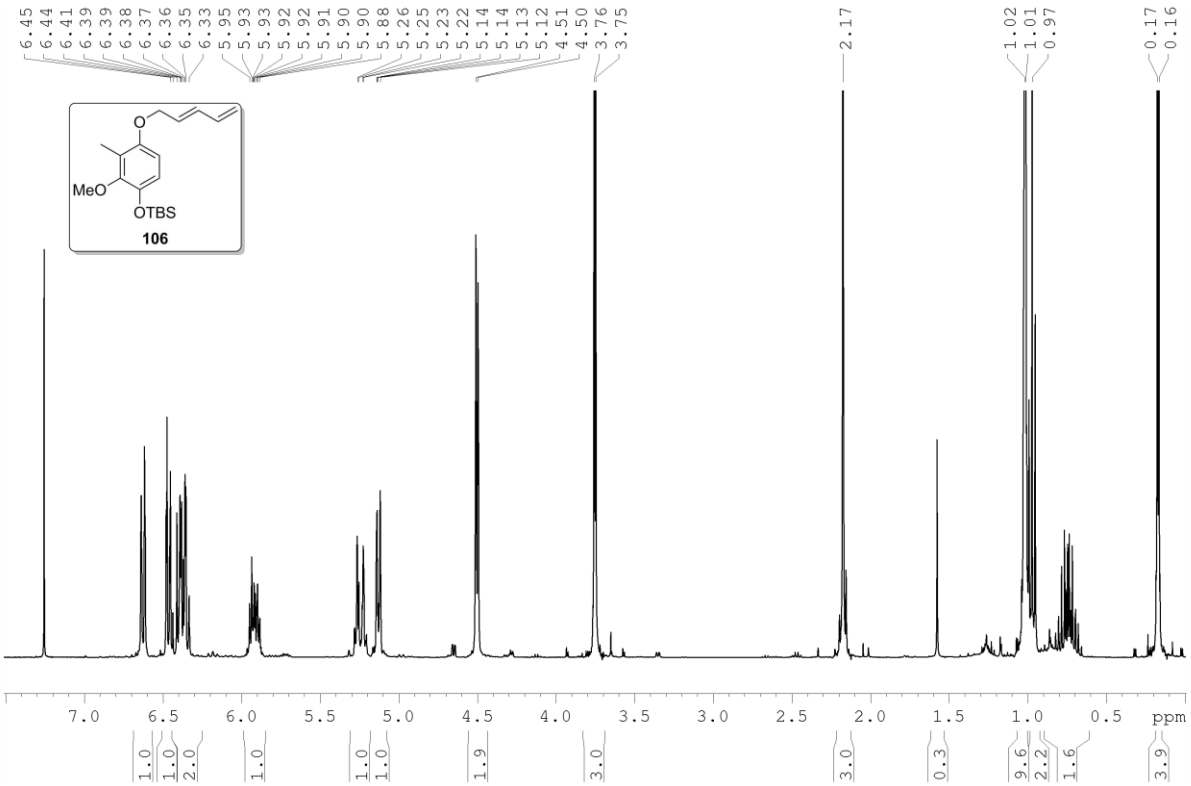
o.n.	overnight	TLC	thin layer chromatography
PE	petroleum ether	THF	tetrahydrofuran
r.t.	room temperature	Tol	toluene
RCM	ring closing metathesis	Troc	2,2,2-trichlorethoxycarbonyl-
RRCM	relay ring closing metathesis	TS	transition state
sat.	saturated	XRD	X -ray diffraction
TBAF	tetra butyl ammonium fluoride	$ZnCl_2$	zinc chloride
TBS	*tert*-butylsilyl		
TES	triethylsilyl		
TIPS	triisopropylsilyl		
TMS	trimethylsilyl		
TMSBr	trimethylsilyl bromide		

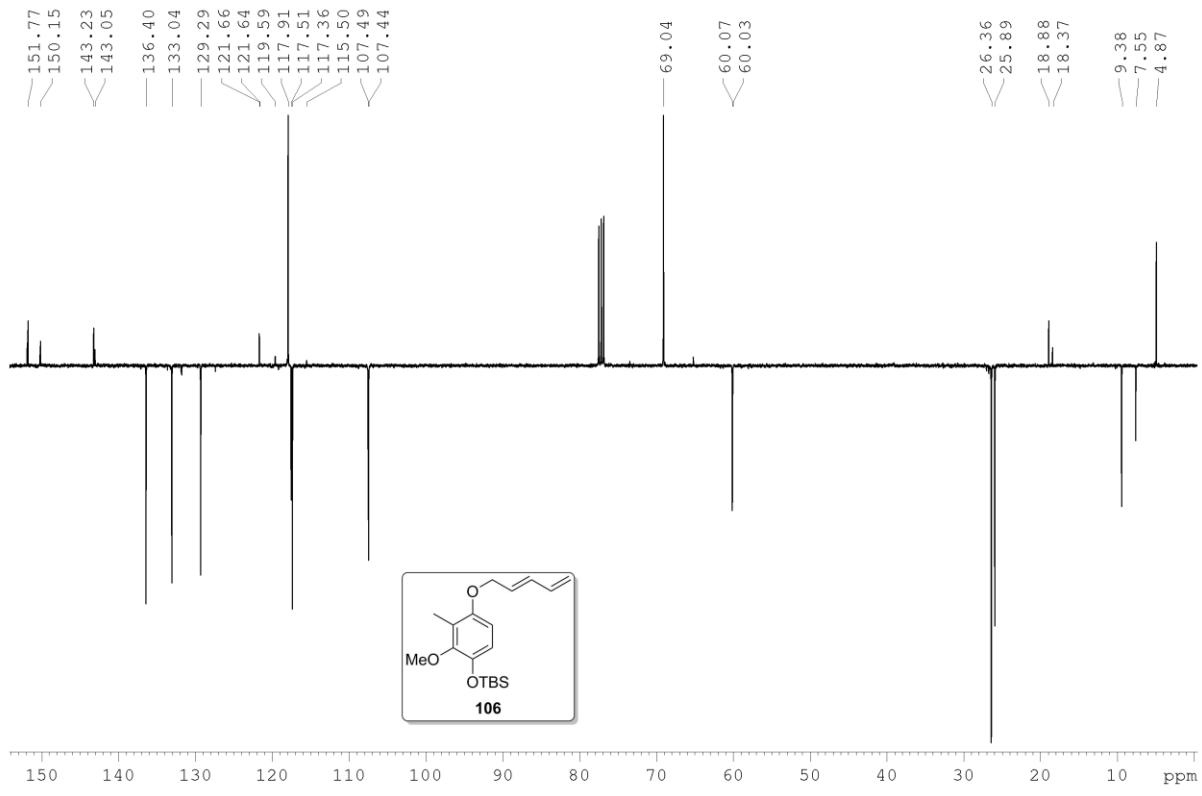
F II References

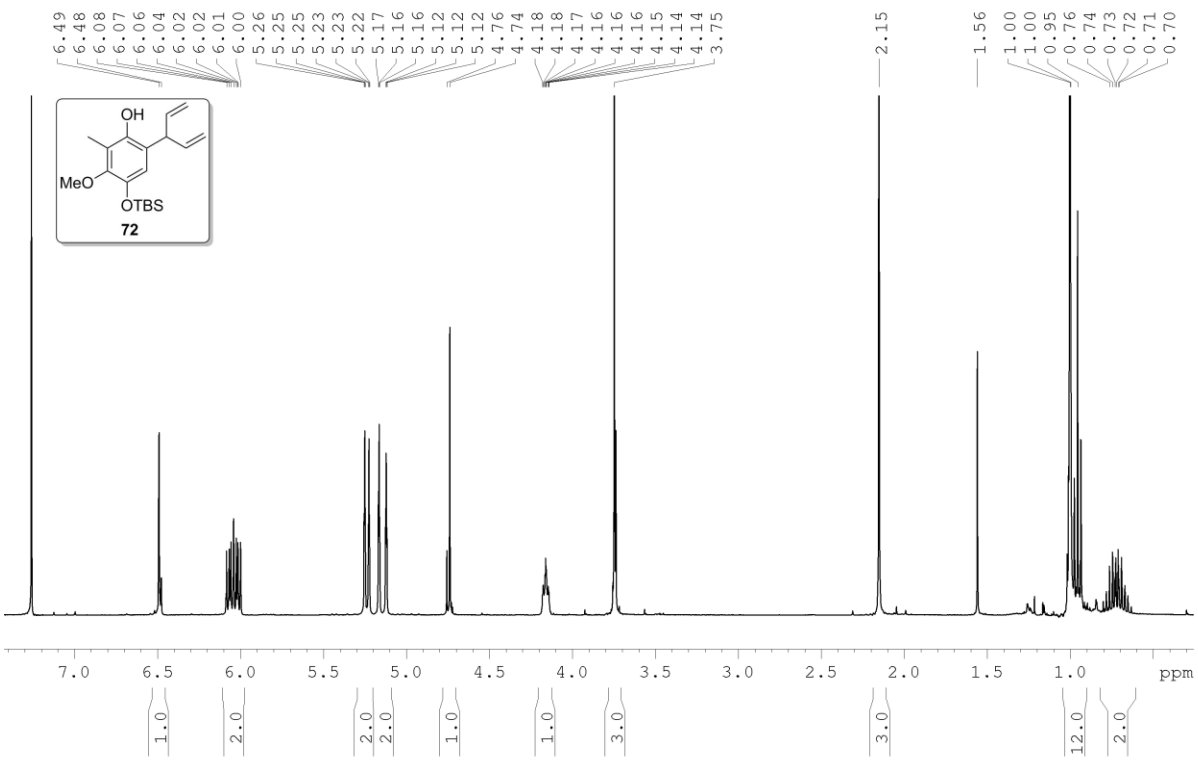
[1] A. D. Rodríguez, *Tetrahedron* **1995**, *51*, 4571–4618.
[2] S. A. Look, W. Fenical, R. S. Jacobs, J. Clardy, *Proc. Natl. Acad. Sci. U. S. A.* **1986**, *83*, 6238–40.
[3] A. Ata, H. Y. Win, D. Holt, P. Holloway, E. P. Segstro, G. S. Jayatilake, *Helv. Chim. Acta* **2004**, *87*, 1090–1098.
[4] A. M. S. Mayer, A. D. Rodríguez, R. G. S. Berlinck, M. T. Hamann, *Comp. Biochem. Physiol. Part C Toxicol. Pharmacol.* **2007**, *145*, 553–581.
[5] H. Correa, F. Aristizabal, C. Duque, R. Kerr, *Mar. Drugs* **2011**, *9*, 334–344.
[6] A. D. Rodríguez, C. Ramírez, *Org. Lett.* **2000**, *2*, 507–510.
[7] I. I. Rodríguez, A. D. Rodríguez, *Tetrahedron Lett.* **2009**, *50*, 5493–5496.
[8] Y.-P. Shi, X. Wei, I. I. Rodríguez, A. D. Rodríguez, A. M. S. Mayer, *Eur. J. Org. Chem.* **2009**, *2009*, 493–502.
[9] A. D. Rodríguez, C. Ramírez, V. Medina, Y.-P. Shi, *Tetrahedron Lett.* **2000**, *41*, 5177–5180.
[10] A. D. Rodríguez, C. Ramírez, I. I. Rodríguez, C. L. Barnes, *J. Org. Chem.* **2000**, *65*, 1390–1398.
[11] A. D. Rodriguez, E. Gonzalez, S. D. Huang, *J. Org. Chem.* **1998**, *63*, 7083–7091.
[12] T. Ferns, R. G. Kerr, *Tetrahedron* **2005**, *61*, 12358–12365.
[13] T. J. Heckrodt, J. Mulzer, *J. Am. Chem. Soc.* **2003**, *125*, 4680–4681.
[14] J. Preindl, C. Leitner, S. Baldauf, J. Mulzer, *Org. Lett.* **2014**, *16*, 4276–4279.
[15] N. Waizumi, A. R. Stankovic, V. H. Rawal, *J. Am. Chem. Soc.* **2003**, *125*, 13022–13023.
[16] G. Zanoni, M. Franzini, *Angew. Chem. Int. Ed.* **2004**, *43*, 4837–4841.
[17] T. J. Heckrodt, J. Mulzer, *J. Am. Chem. Soc.* **2003**, *125*, 9538–9538.
[18] J. Matikainen, S. Kaltia, M. Hamalainen, T. Hase, *Tetrahedron* **1997**, *53*, 4531–4538.
[19] N. A. Yakelis, W. R. Roush, *Org. Lett.* **2001**, *3*, 957–960.
[20] H. P. Kalmode, D. K. Maity, P. M. Bhate, *RSC Adv* **2016**, *6*, 63445–63462.
[21] K. Prantz, J. Mulzer, *Chem. Rev.* **2010**, *110*, 3741–3766.
[22] A. I. Kim, S. D. Rychnovsky, *Angew. Chem. Int. Ed.* **2003**, *42*, 1267–1270.
[23] S. Steiner, P. Gärtner, V. S. Enev, *Tetrahedron* **2016**, *72*, 4536–4542.
[24] M. Kaiser, P. Gärtner, V. S. Enev, *Monatshefte Für Chem. - Chem. Mon.* **2016**.
[25] J. Chen, X. Chen, M. Willot, J. Zhu, *Angew. Chem. Int. Ed.* **2006**, *45*, 8028–8032.
[26] T. R. Hoye, C. S. Jeffrey, M. A. Tennakoon, J. Wang, H. Zhao, *J. Am. Chem. Soc.* **2004**, *126*, 10210–10211.
[27] T. Ritter, P. Zarotti, E. M. Carreira, *Org. Lett.* **2004**, *6*, 4371–4374.
[28] S. R. Jackson, M. G. Johnson, M. Mikami, S. Shiokawa, E. M. Carreira, *Angew. Chem. Int. Ed.* **2001**, *40*, 2694–2697.
[29] G. Helmchen, A. Dahnz, P. Dübon, M. Schelwies, R. Weihofen, *Chem Commun* **2007**, 675–691.
[30] T. Nemoto, Y. Ishige, M. Yoshida, Y. Kohno, M. Kanematsu, Y. Hamada, *Org. Lett.* **2010**, *12*, 5020–5023.
[31] T. Nemoto, Y. Hamada, *Synlett* **2016**, *27*, 2301–2313.
[32] S. Hanessian, D. Delorme, Y. Dufresne, *Tetrahedron Lett.* **1984**, *25*, 2515–18.
[33] J. H. Han, Y. E. Kwon, J.-H. Sohn, D. H. Ryu, *Tetrahedron* **2010**, *66*, 1673–1677.
[34] N. L. Bauld, J. T. Aplin, W. Yueh, S. Endo, *J. Phys. Org. Chem.* **1998**, *11*, 825–830.
[35] A. K. Ghosh, D. D. Anderson, *Org. Lett.* **2012**, *14*, 4730–4733.
[36] T. Hudlicky, F. F. Koszyk, T. M. Kutchan, J. P. Sheth, *J. Org. Chem.* **1980**, *45*, 5020–5027.
[37] K. Schank, S. Bügler, H. Folz, N. Schott, *Helv. Chim. Acta* **2007**, *90*, 1606–1649.
[38] *Org. Synth.* **1959**, *39*, 10.
[39] K. Maruyama, N. Nagai, Y. Naruta, *Tetrahedron Lett.* **1985**, *26*, 5149–5152.
[40] V. Tweedie, M. Cuscurida, *J. Am. Chem. Soc.* **1957**, *79*, 5463–5466.
[41] B. M. Trost, G. M. Schroeder, *J. Am. Chem. Soc.* **2000**, *122*, 3785–3786.
[42] S.-Y. Wang, T.-K. Lum, S.-J. Ji, T.-P. Loh, *Adv. Synth. Catal.* **2008**, *350*, 673–677.
[43] K. Ando, K. Yamada, *Tetrahedron Lett.* **2010**, *51*, 3297–3299.
[44] F. Benoit-Marquie, A. G. Csaky, G. Esteban, M. E. Martinez, J. Plumet, *Tetrahedron Lett.* **2000**, *41*, 3355–3358.
[45] F. López, S. R. Harutyunyan, A. Meetsma, A. J. Minnaard, B. L. Feringa, *Angew. Chem. Int. Ed.* **2005**, *44*, 2752–2756.
[46] K. I. Booker-Milburn, A. Barker, W. Brailsford, B. Cox, T. E. Mansley, *Tetrahedron* **1998**, *54*, 15321–15344.
[47] M. S. Oderinde, H. N. Hunter, S. W. Bremner, M. G. Organ, *Eur. J. Org. Chem.* **2012**, *2012*, 175–182.
[48] S. Ma, L. Lu, *J. Org. Chem.* **2005**, *70*, 7629–7633.

[49] M. B. Herbert, R. H. Grubbs, *Angew. Chem. Int. Ed.* **2015**, *54*, 5018–5024.
[50] B. L. Quigley, R. H. Grubbs, *Chem Sci* **2014**, *5*, 501–506.
[51] H. Stetter, W. Uerdingen, *Synthesis* **1973**, 207–8.
[52] B. Wang, H.-X. Sun, Z.-H. Sun, *J. Org. Chem.* **2009**, *74*, 1781–1784.
[53] R. A. Roberts, V. Schuell, L. A. Paquette, *J. Org. Chem.* **1983**, *48*, 2076–84.
[54] T. Ohta, H. Takaya, M. Kitamura, K. Nagai, R. Noyori, *J. Org. Chem.* **1987**, *52*, 3174–3176.
[55] M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masamune, W. R. Roush, T. Sakai, *Tetrahedron Lett.* **1984**, *25*, 2183–6.
[56] M. W. Rathke, M. Nowak, *J. Org. Chem.* **1985**, *50*, 2624–2626.
[57] L. K. Blasdel, A. G. Myers, *Org. Lett.* **2005**, *7*, 4281–4283.
[58] K. Borszeky, T. Mallat, A. Baiker, *Catal. Lett.* **1999**, *59*, 95–97.
[59] G. Stork, F. West, H. Y. Lee, R. C. A. Isaacs, S. Manabe, *J. Am. Chem. Soc.* **1996**, *118*, 10660–10661.

F III Selected Spectra



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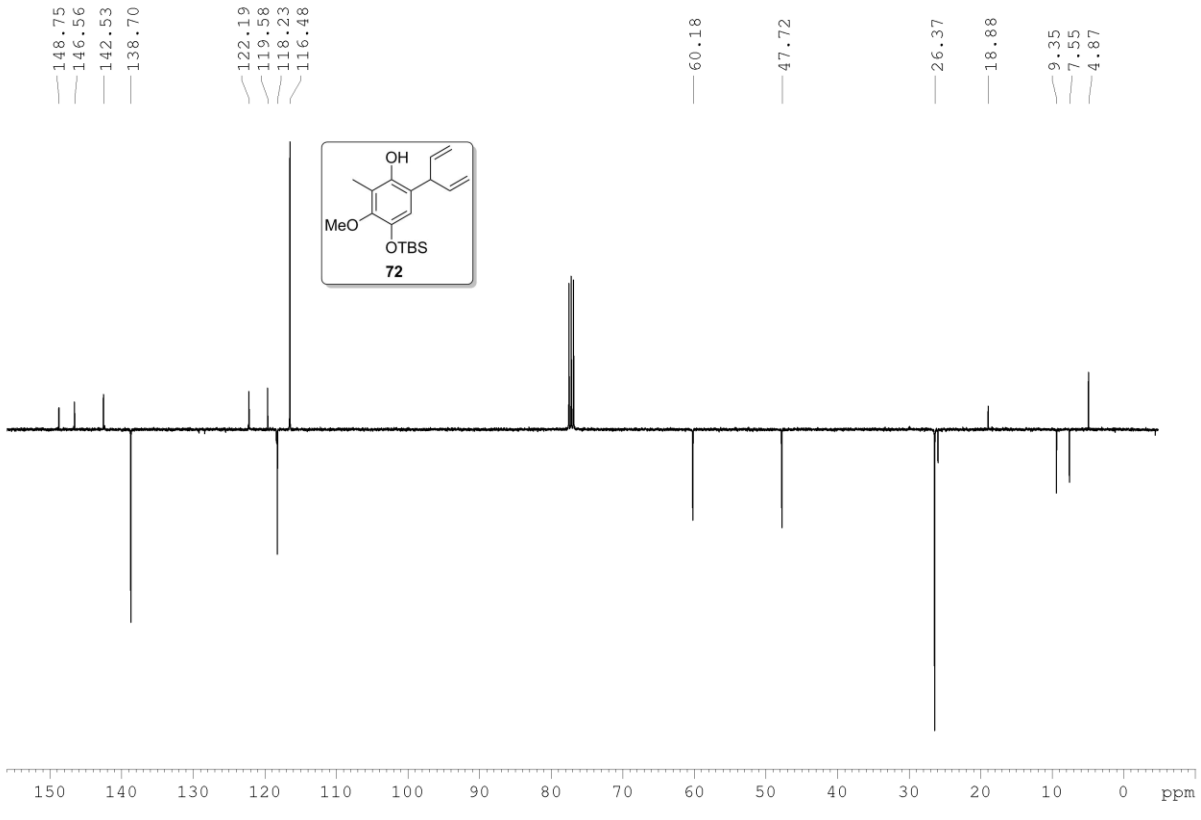
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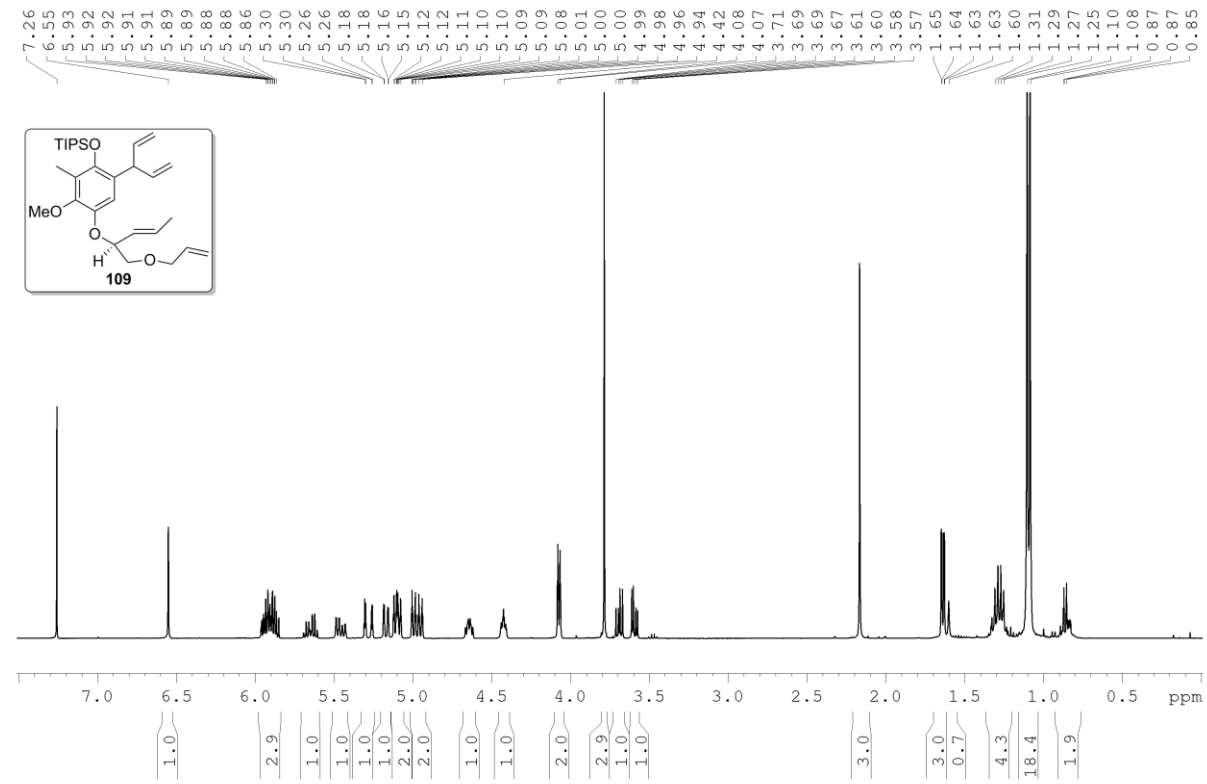
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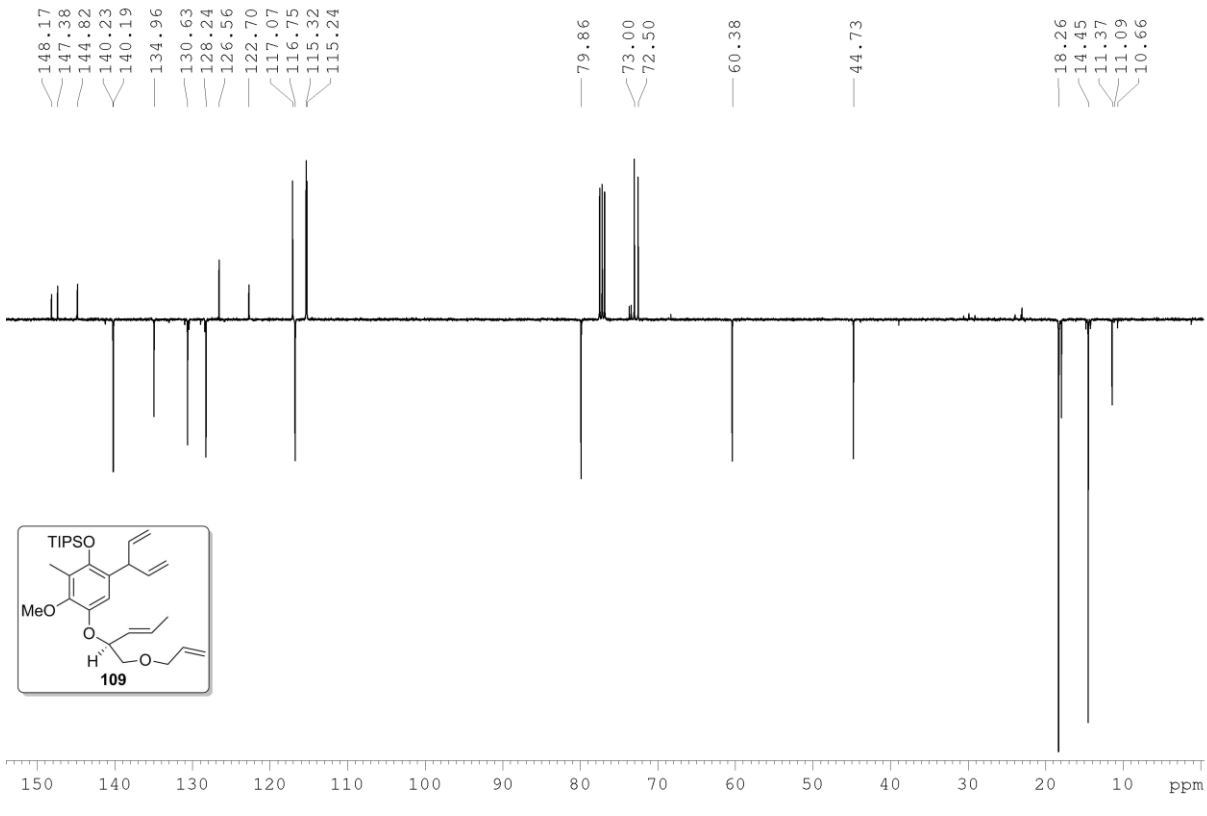
148.17 147.38 144.82 140.23 140.19 134.96 130.63 128.24 126.56 122.70 117.07 116.75 115.32 115.24 79.86 73.00 72.50 60.38 44.73 18.26 14.45 11.37 11.09 10.66
TIPSO
MeO
O
H
O
109
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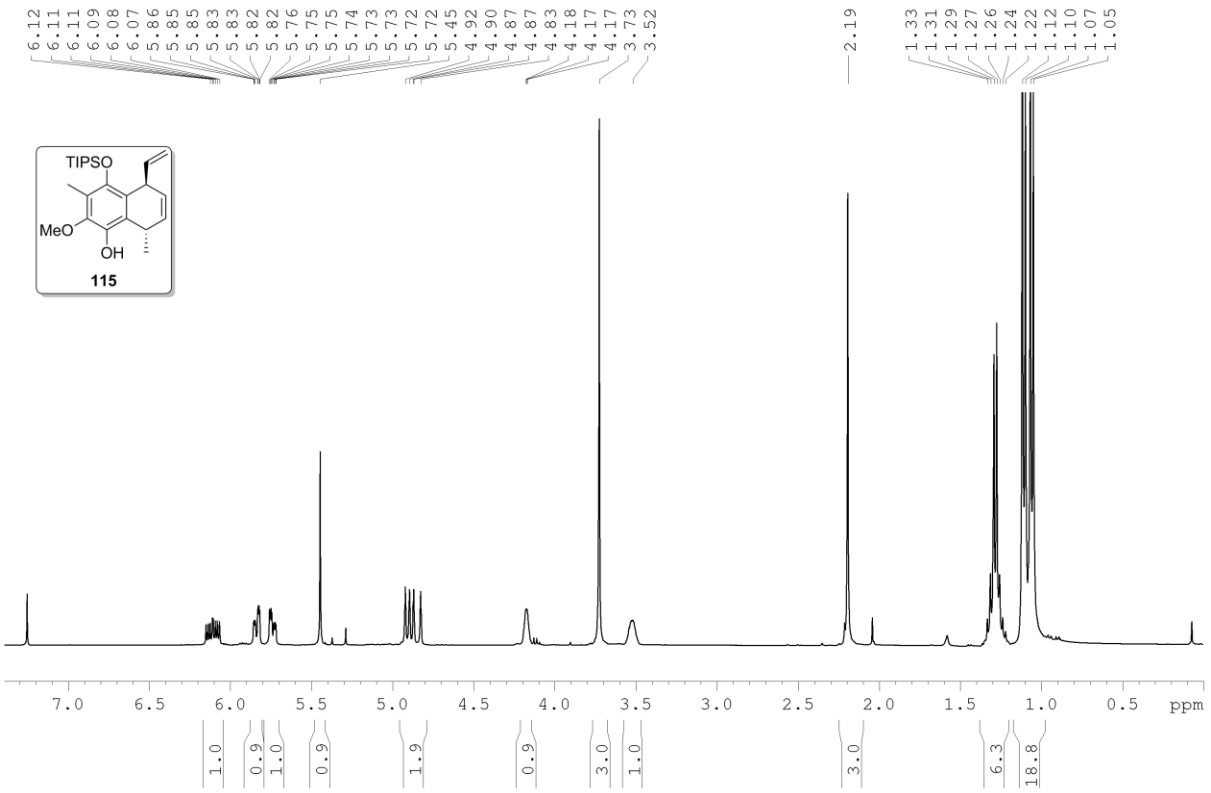
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6.11
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6.08
6.07
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5.85
5.85
5.83
5.83
5.82
5.82
5.76
5.75
5.75
5.74
5.73
5.73
5.72
5.72
5.45
4.92
4.90
4.87
4.87
4.83
4.18
4.17
4.17
3.73
3.52
2.19
1.33
1.31
1.29
1.27
1.26
1.24
1.22
1.12
1.10
1.07
1.05
TIPSO
MeO
OH
115
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
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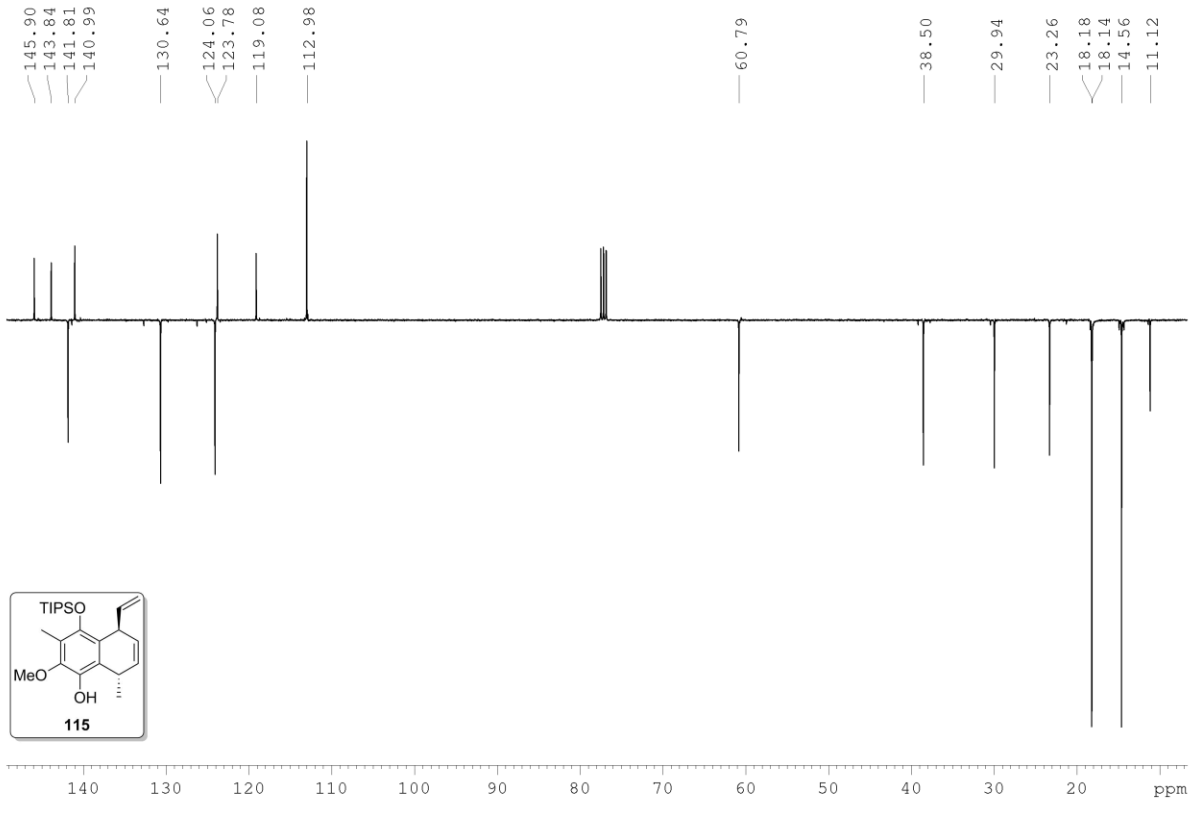
1.9
0.9
3.0
1.0
3.0
6.3
18.8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124.06
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119.08
112.98
60.79
38.50
29.94
23.26
18.18
18.14
14.56
11.12
TIPSO
MeO
OH
115
140
130
120
110
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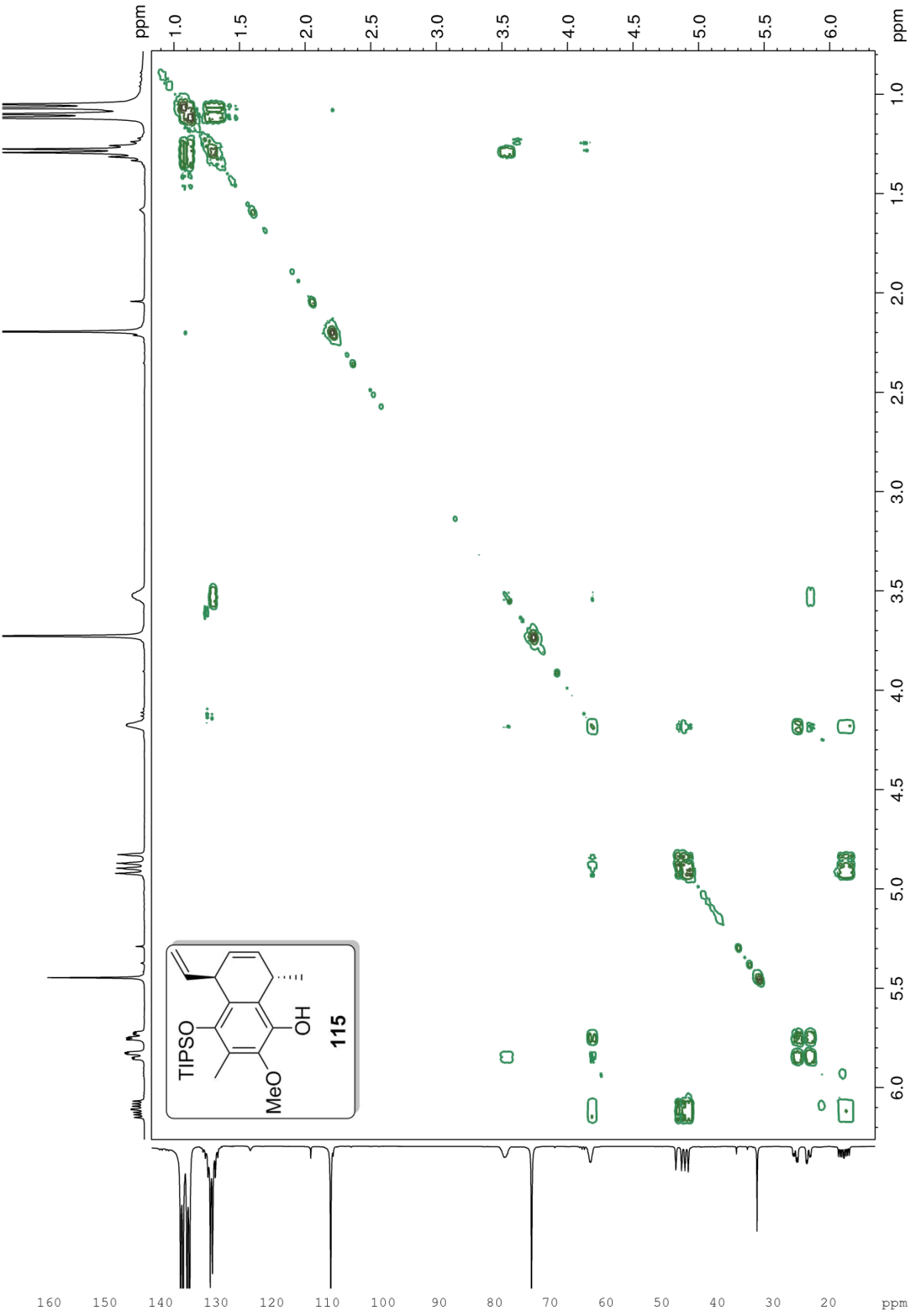
90
80
70
60
50
40
30
20
ppm


ppm
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2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
TIPSO
OH
MeO
115
160
150
140
130
120
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100
90
80
70
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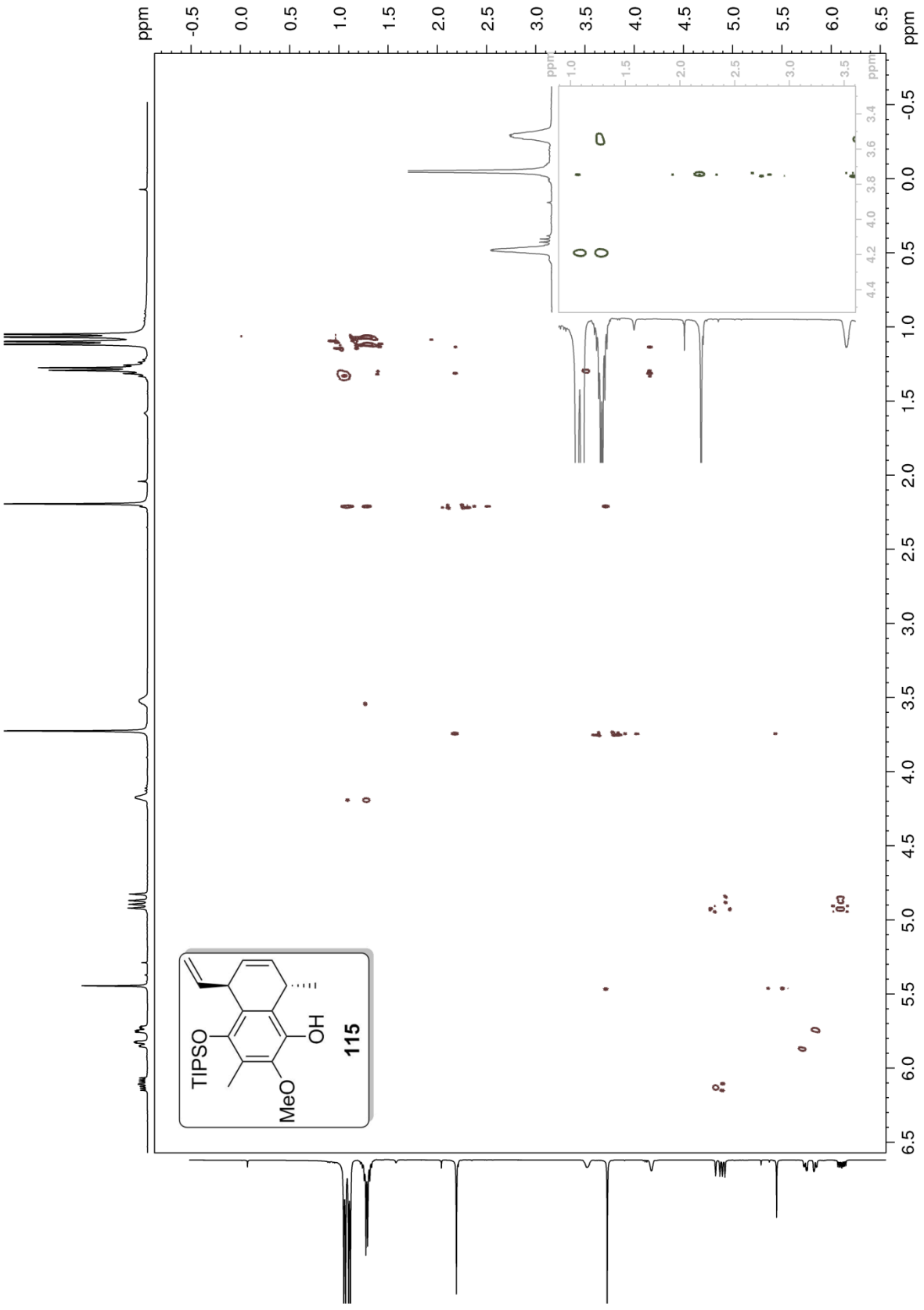
50
40
30
20
ppm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MeO
OH
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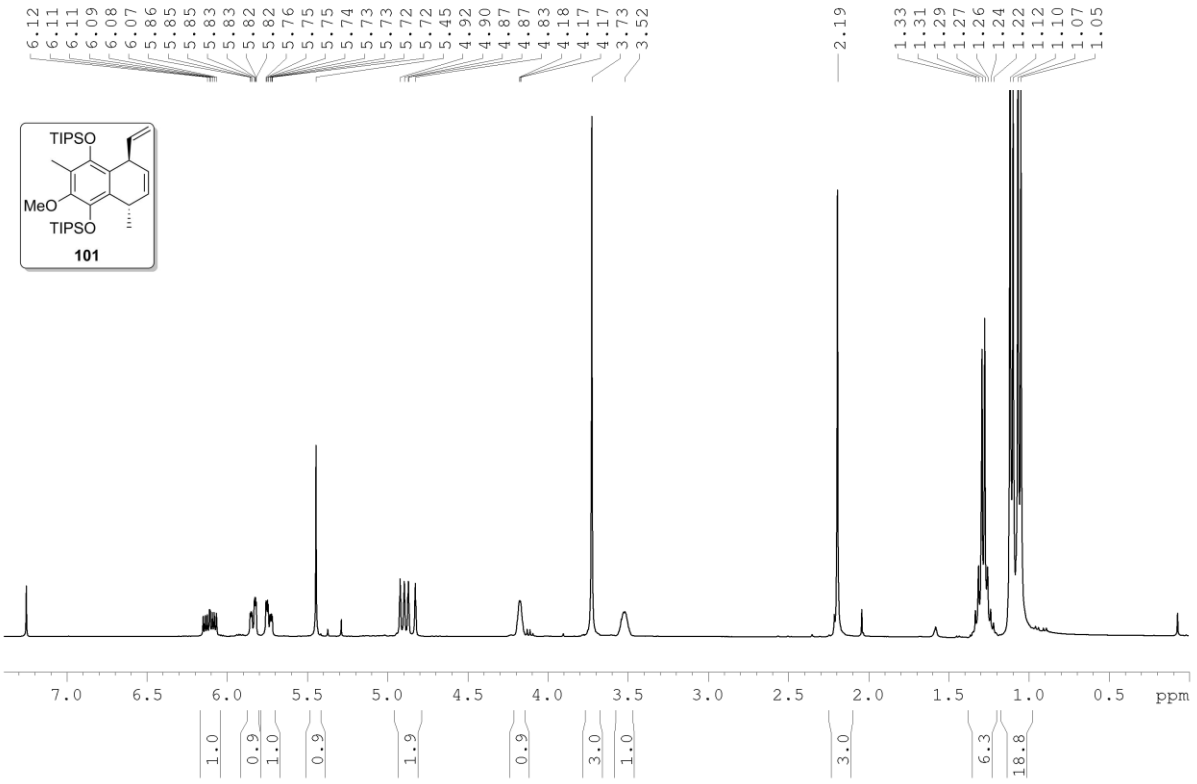
ppm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6.11
6.09
6.08
6.07
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5.85
5.83
5.83
5.82
5.82
5.76
5.75
5.75
5.74
5.73
5.73
5.72
5.72
5.45
4.92
4.90
4.87
4.87
4.83
4.18
4.17
4.17
3.73
3.52
2.19
1.33
1.31
1.29
1.27
1.26
1.24
1.22
1.12
1.10
1.07
1.05
TIPSO
MeO
TIPSO
101
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
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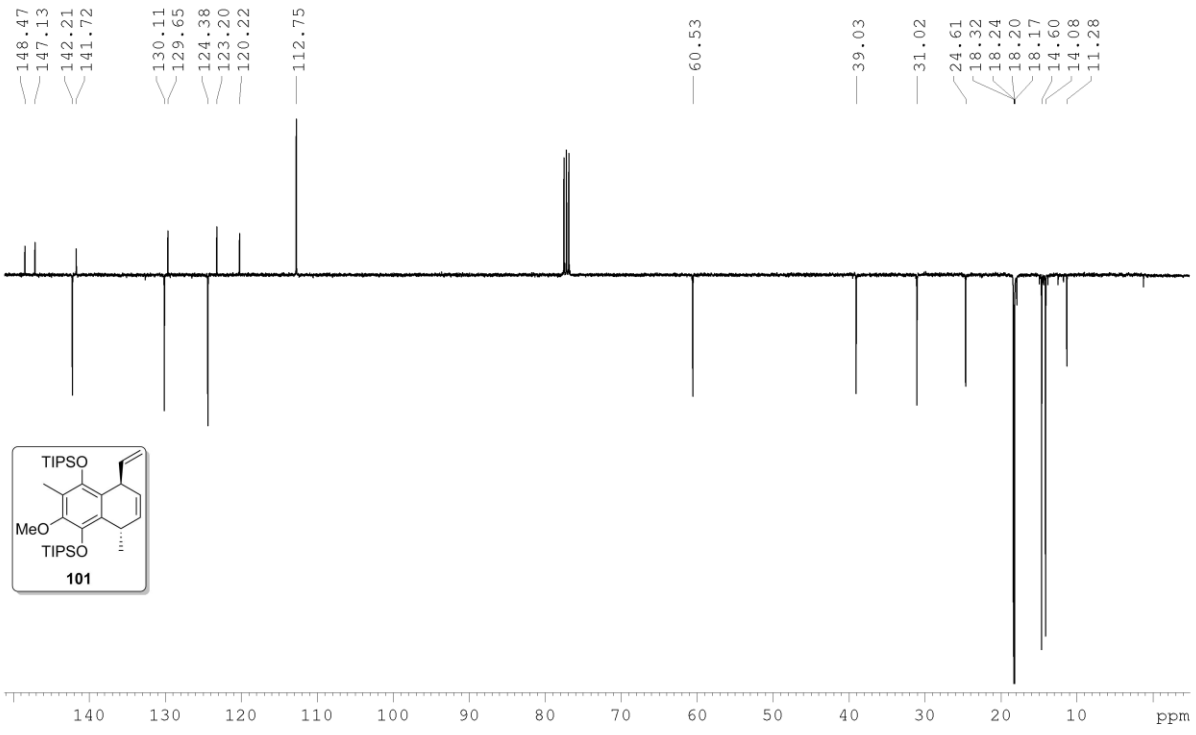
0.9
1.0
0.9
1.9
0.9
3.0
1.0
3.0
6.3
18.8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142.21
141.72
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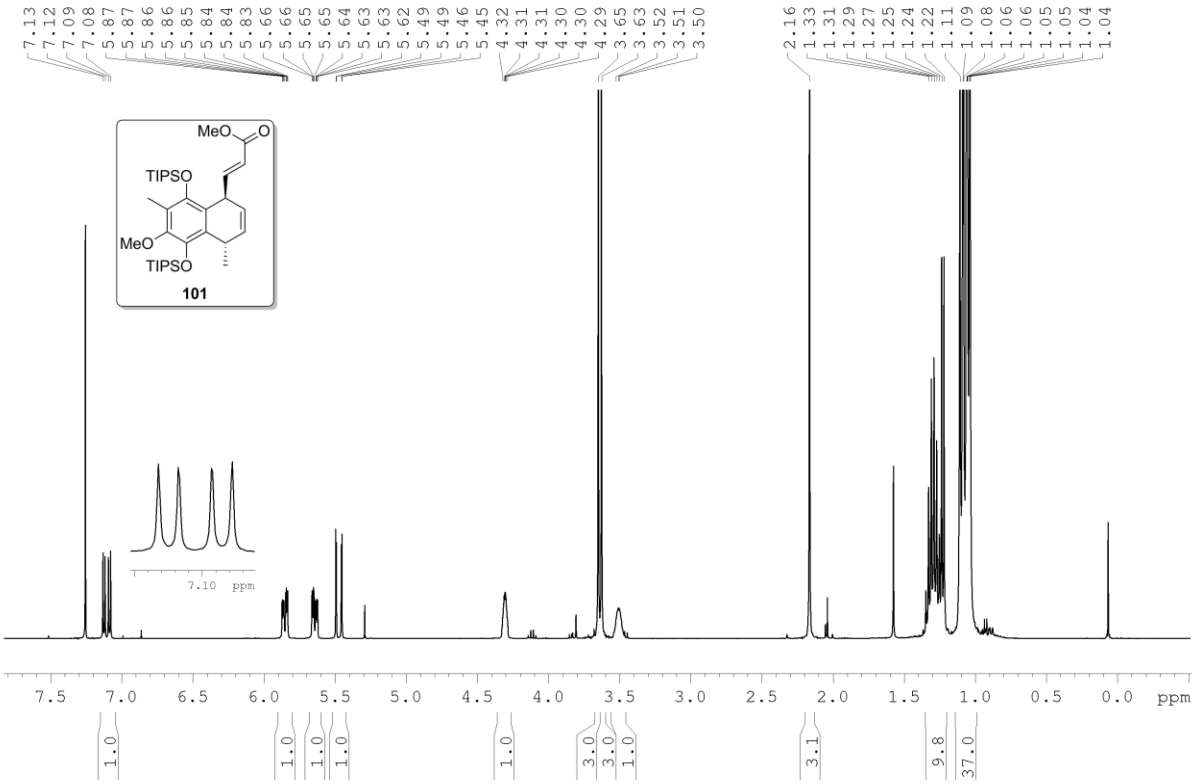
129.65
124.38
123.20
120.22
112.75
60.53
39.03
31.02
24.61
18.32
18.24
18.20
18.17
14.60
14.08
11.28
TIPSO
MeO
TIPSO
101
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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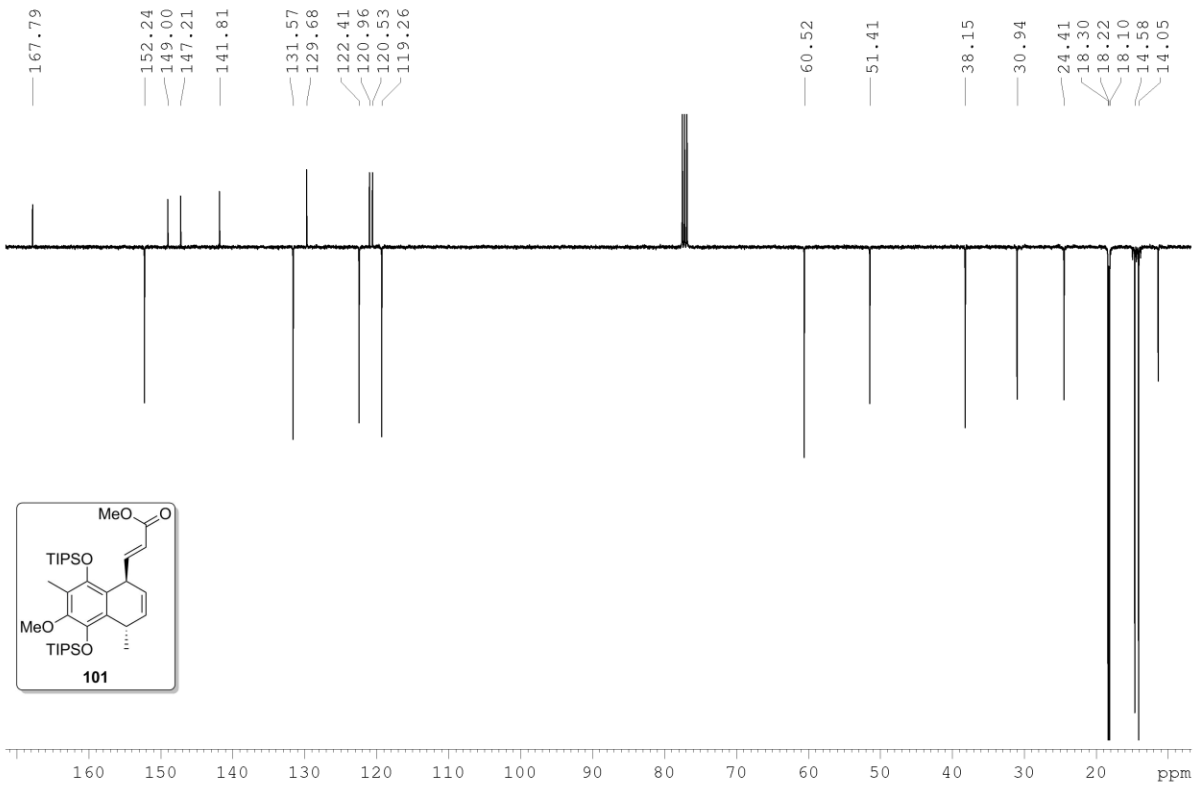
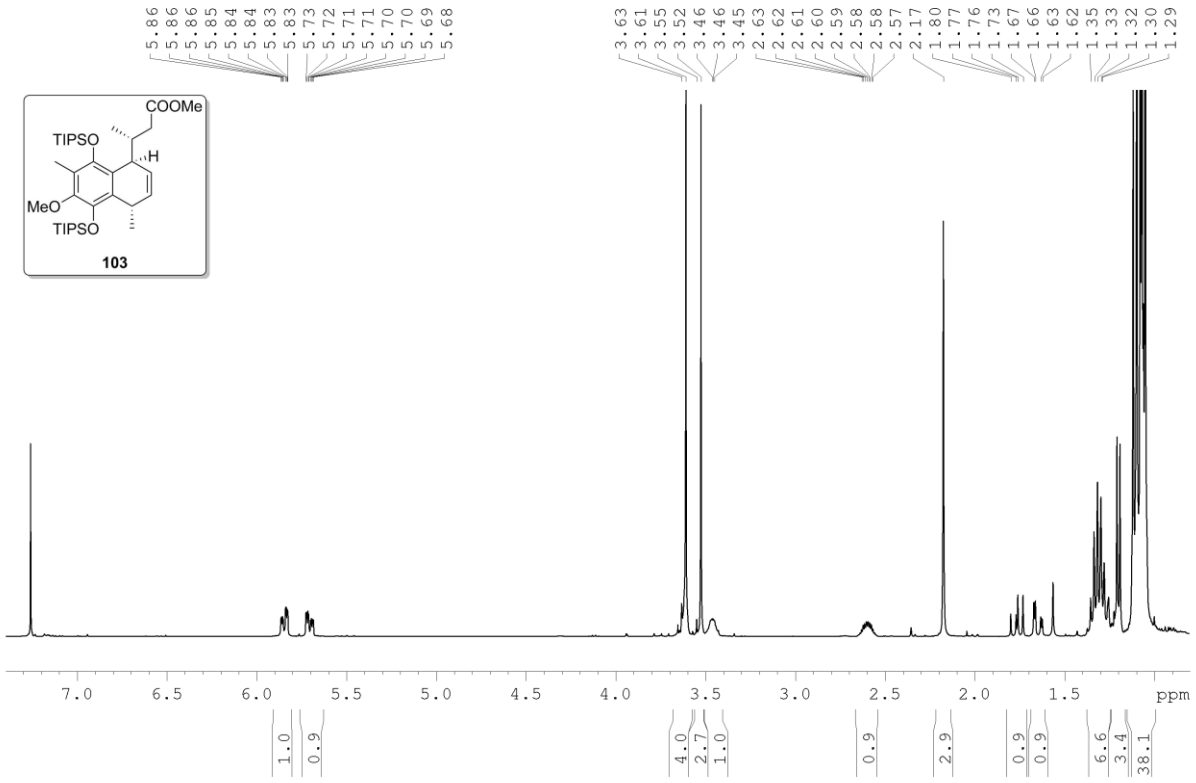
2.16 1.33 1.31 1.29 1.27 1.25 1.24 1.22 1.11 1.09 1.08 1.06 1.06 1.05 1.05 1.04 1.04
MeO
O
TIPSO
MeO
TIPSO
101
7.10 ppm
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.0 1.0 1.0 1.0 1.0 3.0 3.0 1.0 3.1 9.8 37.0


167.79
152.24 149.00 147.21 141.81 131.57 129.68 122.41 120.96 120.53 119.26
60.52 51.41 38.15 30.94 24.41 18.30 18.22 18.10 14.58 14.05
MeO
O
TIPSO
MeO
TIPSO
101
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm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5.86
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5.84
5.83
5.83
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5.72
5.71
5.71
5.70
5.70
5.69
5.68
3.63
3.61
3.55
3.52
3.46
3.46
3.45
2.63
2.62
2.61
2.60
2.59
2.58
2.58
2.57
2.17
1.80
1.77
1.76
1.73
1.67
1.66
1.63
1.62
1.35
1.33
1.32
1.30
1.29
COOMe
TIPSO
H
MeO
TIPSO
103
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
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0.9
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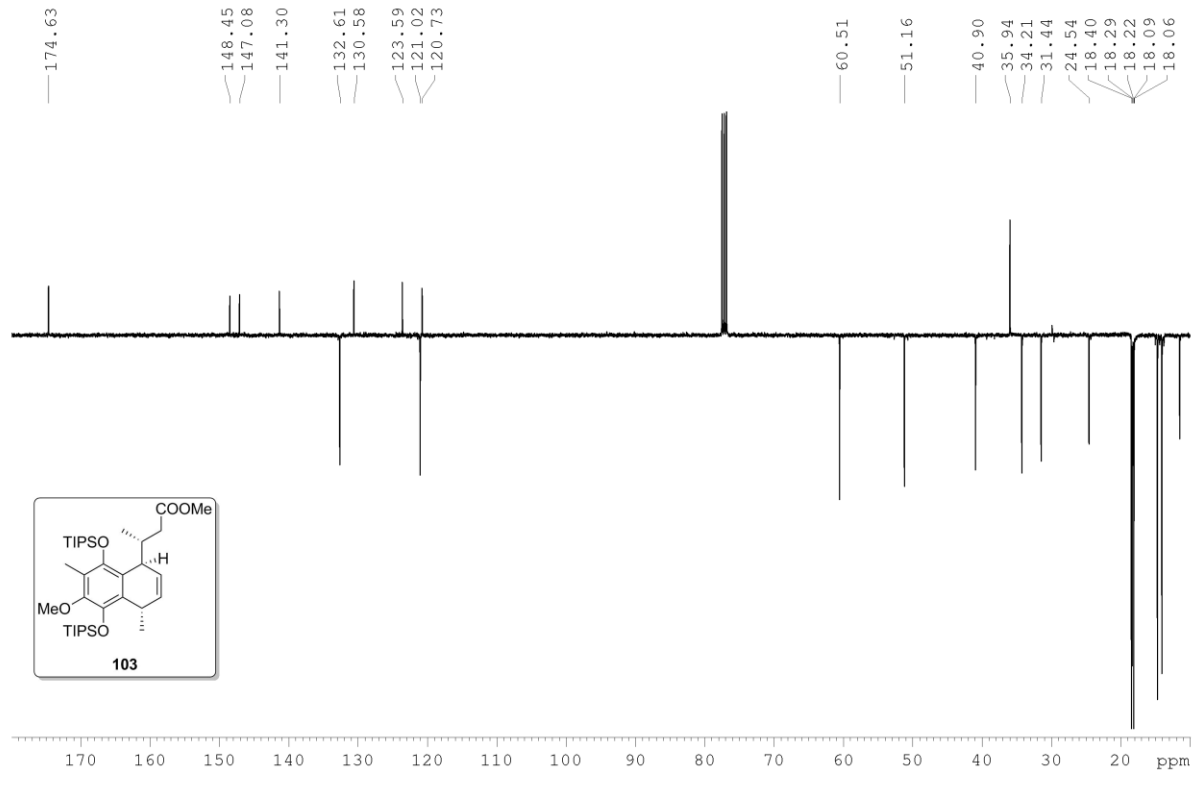
3.4
38.1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123.59
121.02
120.73
60.51
51.16
40.90
35.94
34.21
31.44
24.54
18.40
18.29
18.22
18.09
18.06
COOMe
TIPSO
H
MeO
TIPSO
103
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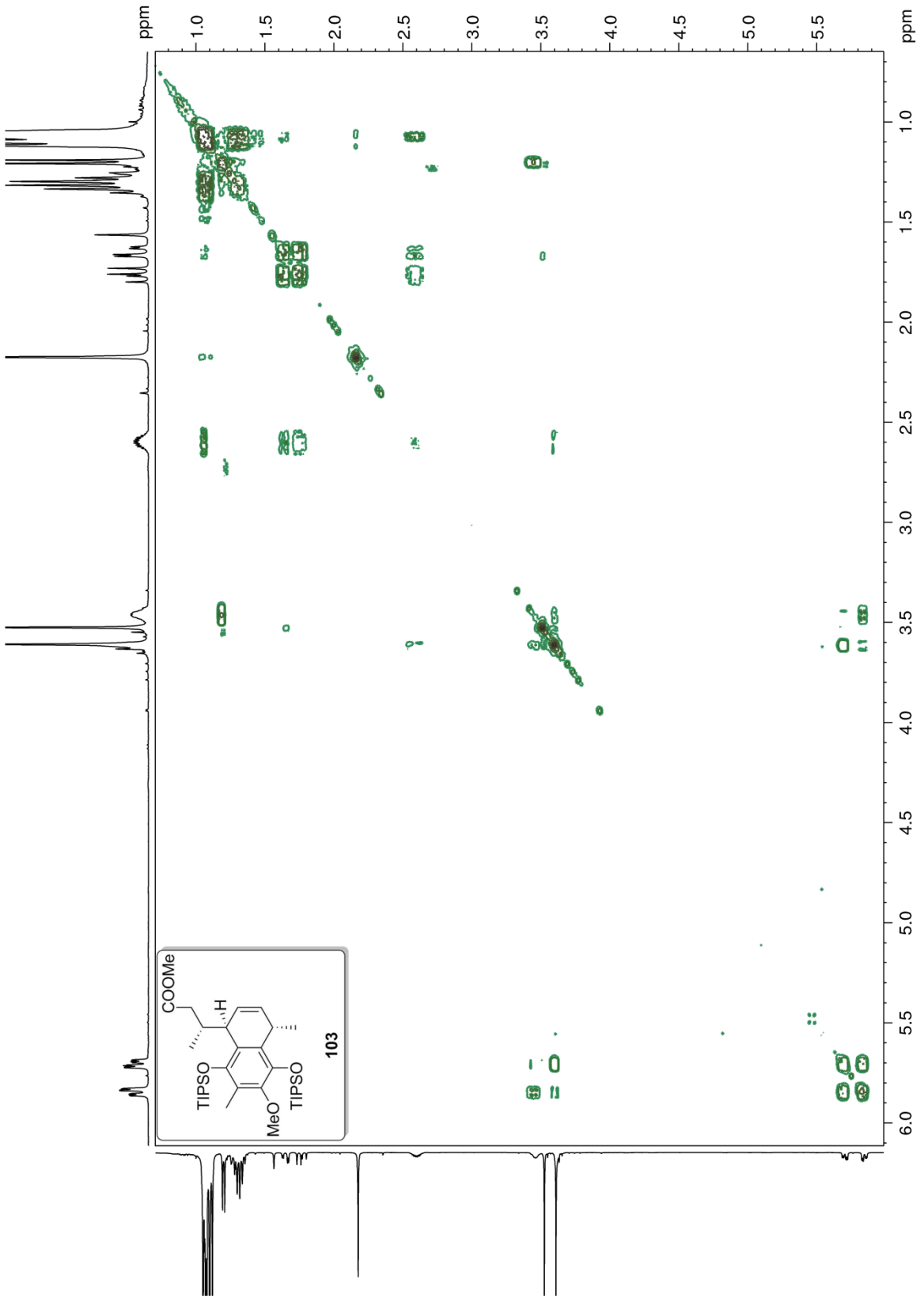
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


ppm
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2.5
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COOMe
H
TIPSO
MeO
TIPSO
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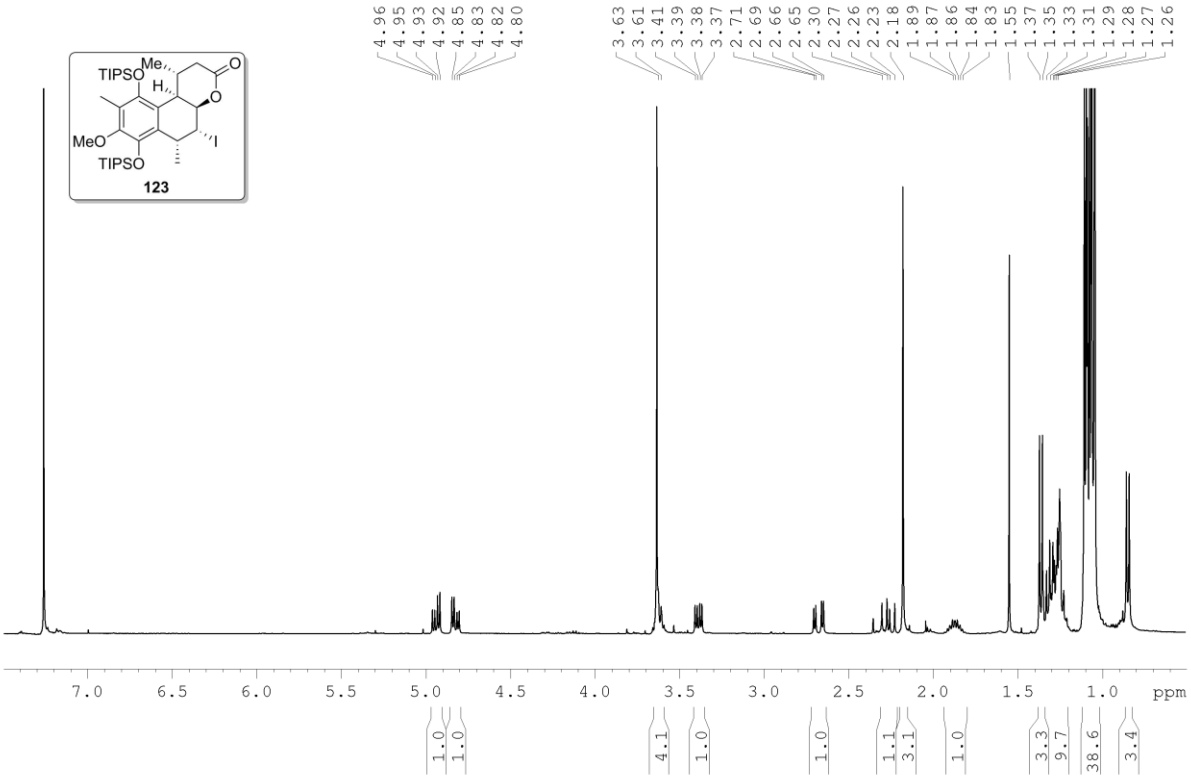
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4.80
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3.61
3.41
3.39
3.38
3.37
2.71
2.69
2.66
2.65
2.30
2.27
2.26
2.23
2.18
1.89
1.87
1.86
1.84
1.83
1.55
1.37
1.35
1.33
1.31
1.29
1.28
1.27
1.26
TIPSO
Me
H
O
O
I
MeO
TIPSO
123
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
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1.0
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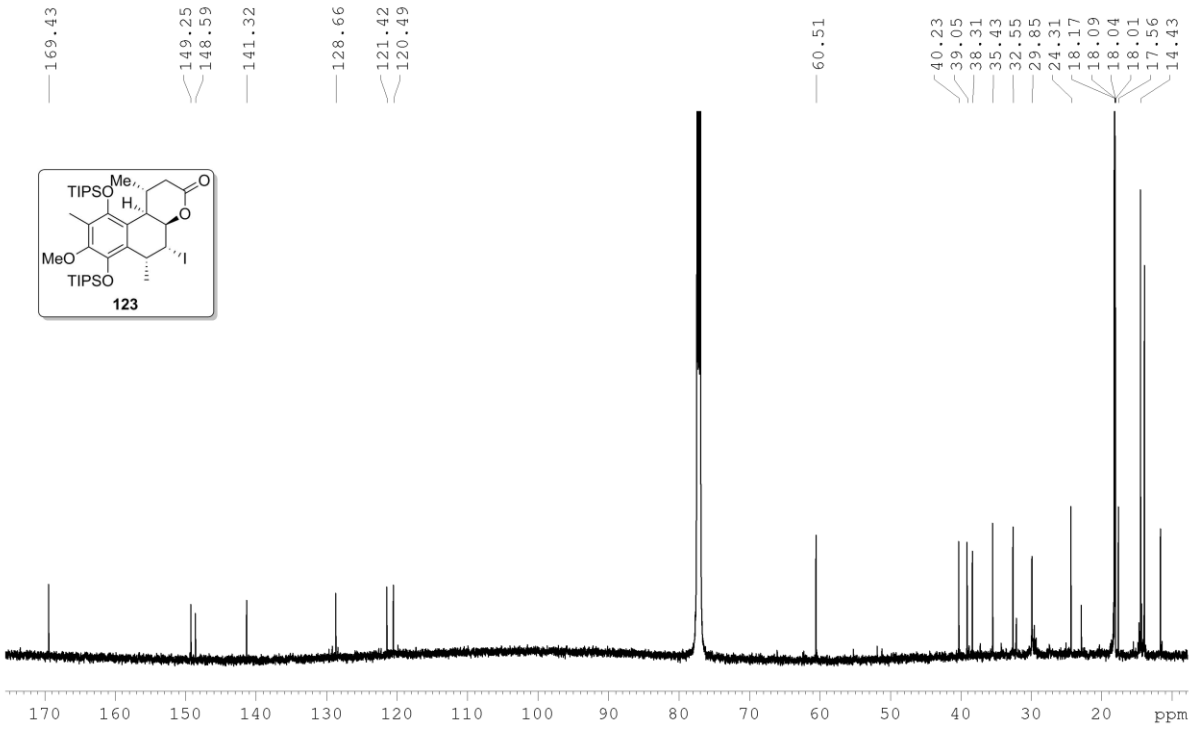
9.7
38.6
3.4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121.42
120.49
60.51
40.23
39.05
38.31
35.43
32.55
29.85
24.31
18.17
18.09
18.04
18.01
17.56
14.43
TIPSO
Me
H
O
O
I
MeO
TIPSO
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160
150
140
130
120
110
100
90
80
70
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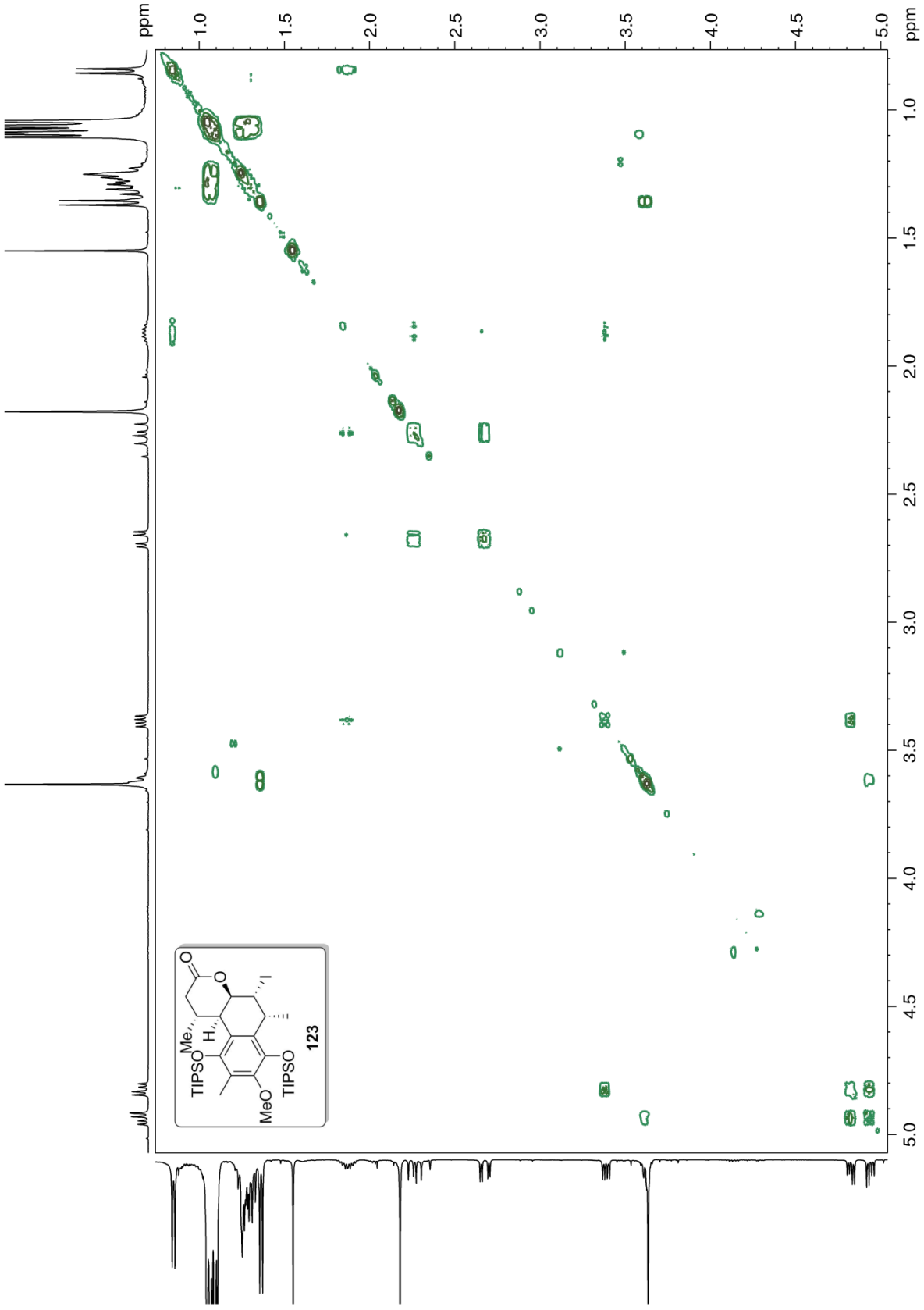
50
40
30
20
ppm


ppm
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2.5
3.0
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4.5
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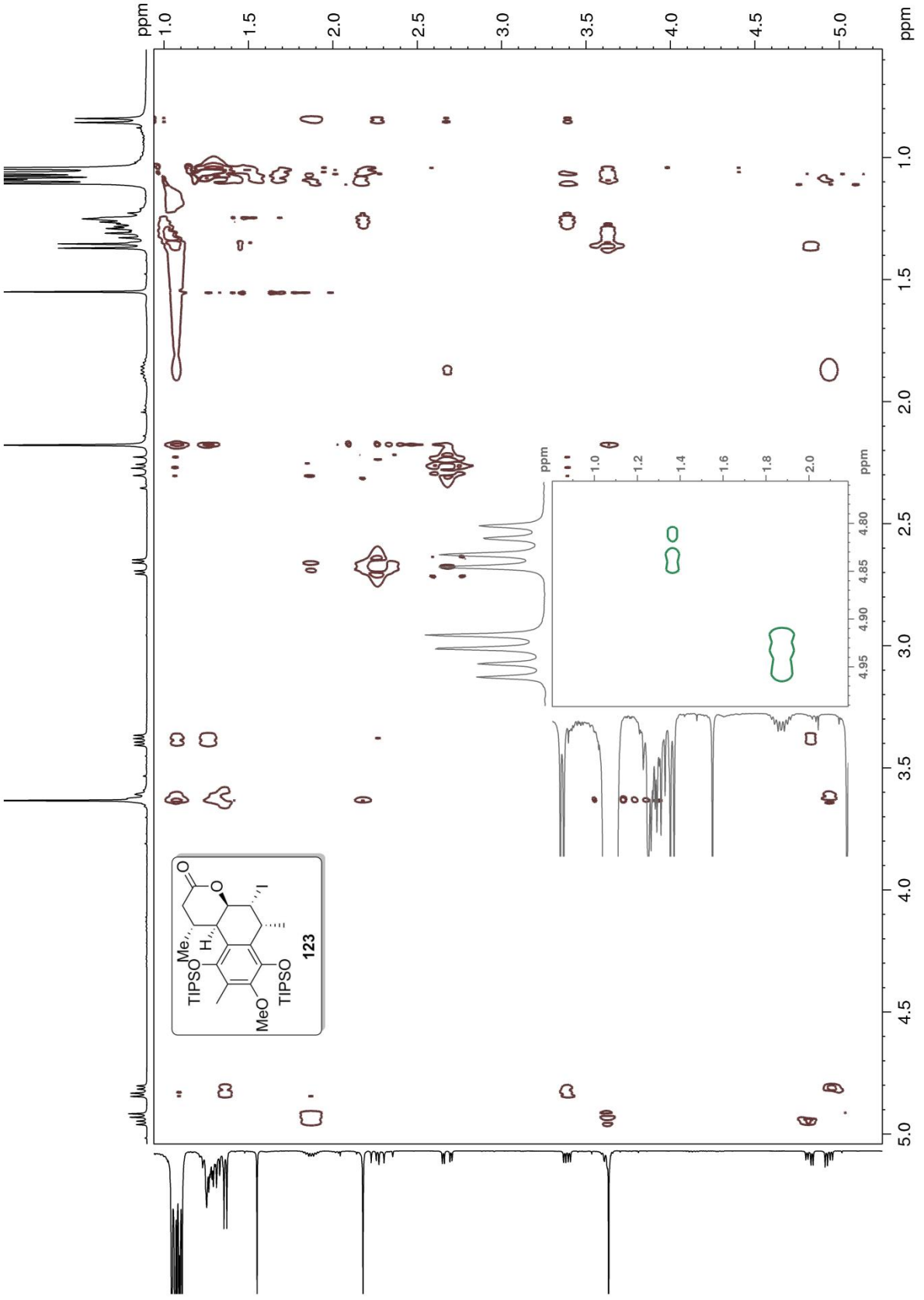
TIPSO
Me
H
MeO
TIPSO
I
O
O
123


ppm
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3.5
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TIPSO
Me
H
MeO
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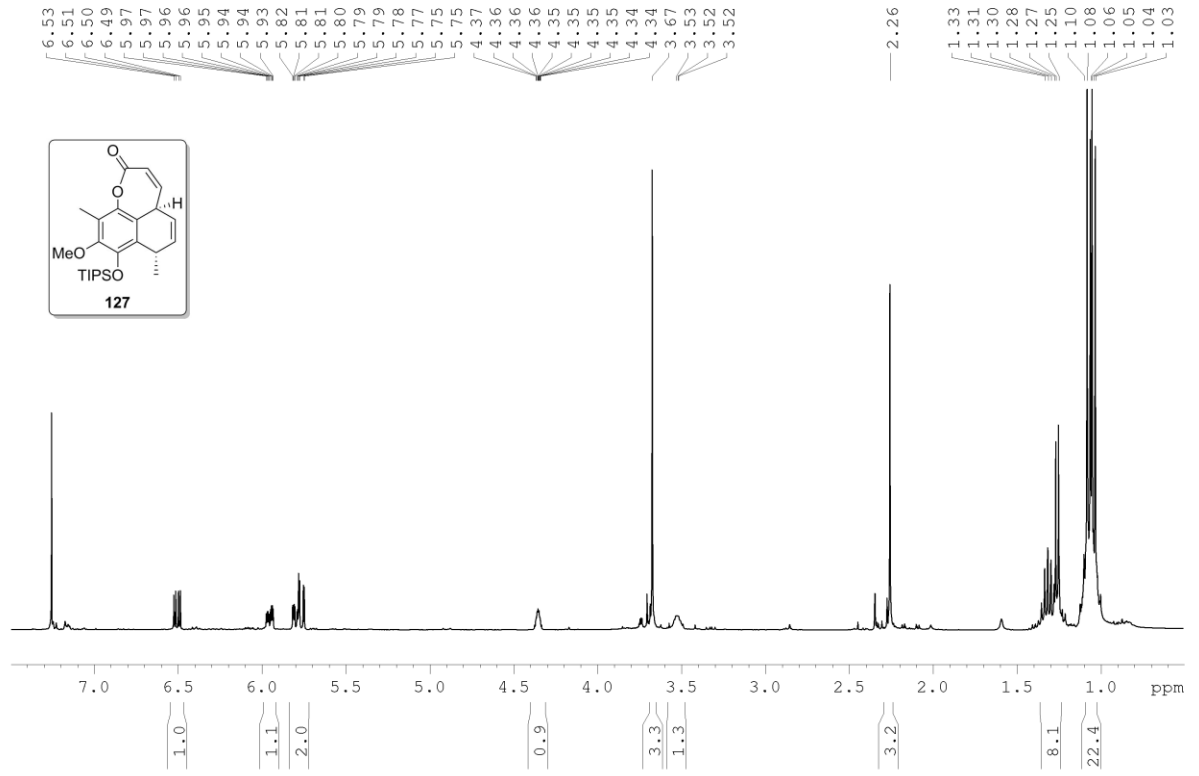
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4.36
4.35
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4.35
4.34
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3.53
3.52
3.52
2.26
1.33
1.31
1.30
1.28
1.27
1.25
1.10
1.08
1.06
1.05
1.04
1.03
MeO
TIPSO
127
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6.0
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5.0
4.5
4.0
3.5
3.0
2.5
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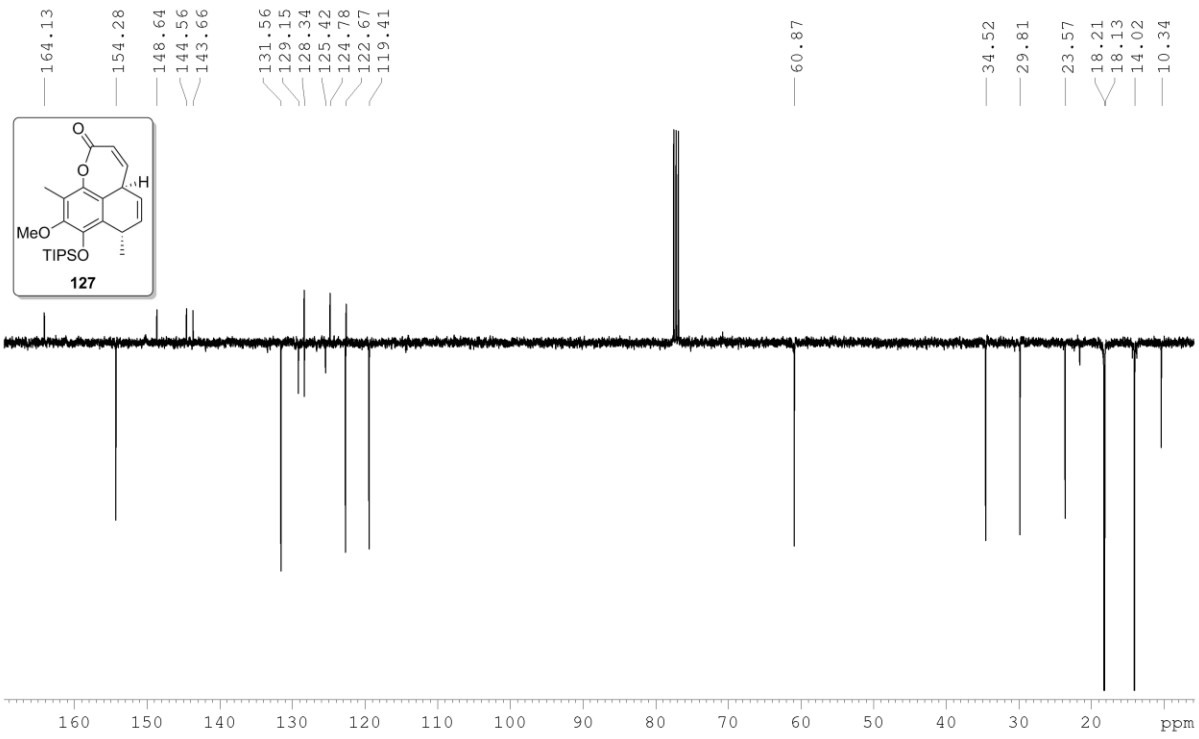
22.4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124.78
122.67
119.41
60.87
34.52
29.81
23.57
18.21
18.13
14.02
10.34
MeO
TIPSO
127
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm