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MASTERARBEIT

Titel der Masterarbeit

„Synthetic Efforts towards a Total Synthesis of Elisabethin A“

Verfasser

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für meine Eltern, Geschwister und Freunde

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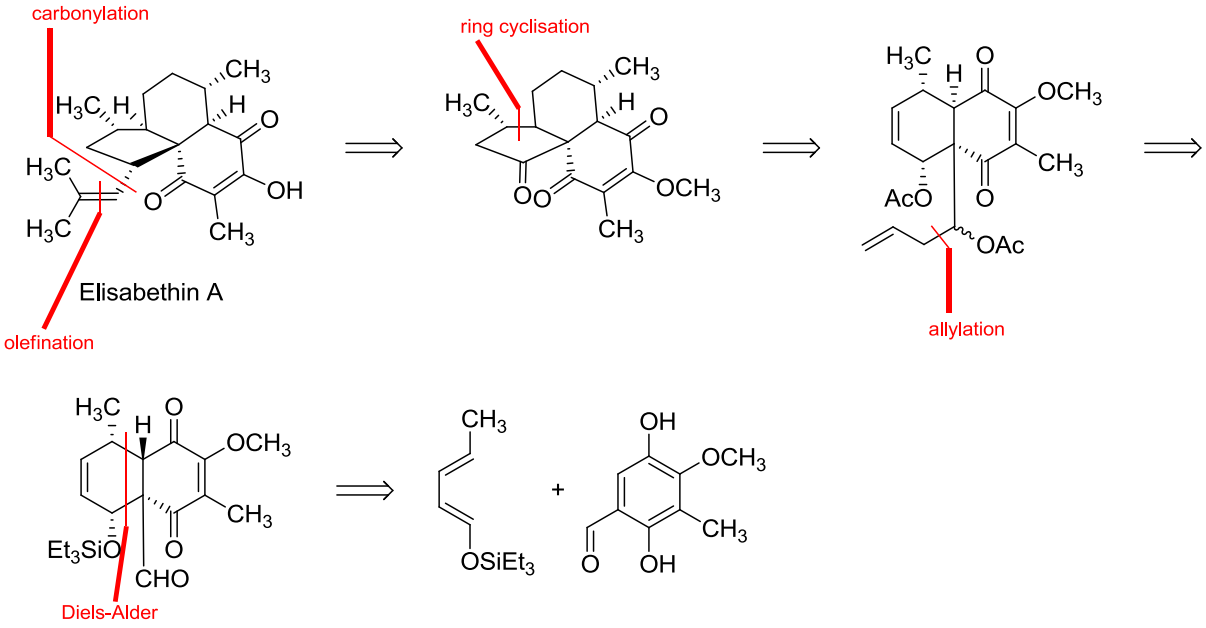
Graphic Abstract



Abstract

Many natural occurring substrates extracted from compounds gorgonian *Pseudopterogorgia elisabethae* exhibit high anti-inflammatory, anti-tuberculosis and anti-cancer activity. Fermentation of these substrates without endangering the existence of this invertebrate is not feasible. Elisabethin A (**1**) is a marine diterpenoid which was isolated in 1998 by Rodriguez *et al.* The relative configuration has already been revealed in 1998, but so far this natural product has not been synthesized yet.

We are able to present a highly stereoselective synthesis of an advanced intermediate of elisabethin A (**1**). Our intermediate contains the tricyclic system of elisabethin A (**1**) and has the desired stereochemistry at the generated stereogenic centers. We developed a new method for the selective allylation of an aldehyde in the presences of the quinone system, and we were able to close the five membered ring via a metallo-ene reaction.

As depicted by this thesis it is really hard to introduce the side chain at an advanced intermediate via coupling reactions. Nevertheless we were able to introduce a C1 fragment via a palladium catalyzed carbonylation. Unfortunately, we were not able to convert this appendage to the desired isobutenyl rest. All attempts to introduce the side chain at an earlier stage of the synthesis proofed unsuccessful, presumably because of disadvantageous electronic effects.

Zusammenfassung

Viele natürliche Verbindungen, aus der Gorgonie *Pseudopterogorgia elisabethae* isoliert, zeigen eine hohe entzündungshemmende anti-Tuberculose und anti-Krebs Aktivität. Die Isolierung der Verbindungen, für weitere medizinische Untersuchungen, ist nicht möglich ohne den Bestand an Gorgonie *Pseudopterogorgia elisabethae* völlig aufzubrauchen. Elisabethin A (**1**) ist ein marines Diterpenoid welches im Jahr 1998 von Rodriguez isoliert wurde. Die relative Konfiguration wurde bereits im Jahr 1998 bestimmt, bisher konnte dieser Naturstoff jedoch noch nicht synthetisch hergestellt werden.

Wir waren in der Lage eine hoch stereoselektive Synthese, einer fortgeschrittenen Zwischenstufe von Elisabethin A (**1**), zu entwickeln. Unsere Zwischenstufe enthält das trizyklische Gerüst von Elisabethin A (**1**) und die gewünschte Konfiguration der erzeugten Stereozentren. Wir entwickelten eine neue Methode für die selektive Allylierung von einem Aldehyd in der Anwesenheit eines Chinon-Systems. Der fünfgliedrige Ring konnte durch eine Metallo-En-Reaktion geschlossen werden. Wie sich im Laufe dieser Arbeit zeigte, ist es sehr schwierig die Seitenkette bei einer fortgeschrittenen Zwischenstufe einzuführen. Dennoch konnten wir ein C1-Fragment über eine Palladium-katalysierte Carbonylierung einführen. Leider waren wir nicht in der Lage, dieses Derivat in den gewünschten Isobutenyl-Rest zu konvertieren. Alle Versuche die Seitenkette in einem früheren Stadium der Synthese einzuführen blieben erfolglos, vermutlich wegen den nachteiligen elektronischen Effekten.

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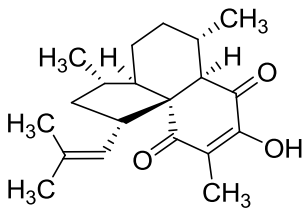
1 Introduction

Total Synthesis is an important and one of the most challenging parts of organic chemistry. It deals with the synthesis of natural products and the development of new drugs. For the verification of the relative and absolute configuration of the natural products, total synthesis is also really important and many targets of total synthesis show high pharmacological activity. A source for natural compounds with high pharmacological activity is the octocoral fauna of the West Indian Sea, which contains many gorgonian corals. A great number of these interesting structures are not isolable in sufficient quantities, therefore it is hard to determine their full biological activity. This makes a synthethic access for these biologically active substances necessary. In this master thesis we describe the synthetic efforts towards a total synthesis of elisabethin A. It is a marine diterpenoid isolated from the gorgonian octocoral *Pseudopterogorgia elisabethae* in the southern Caribbean Sea. [1]



Elisabethin A (**1**)

Figure 1. Structure of Elisabethin A

2 Natural Products from *Pseudopterogorgia elisabethae*

Since the eighties the interest in natural compounds form *Pseudopterogorgia elisabethae* raised, because some of these isolated terpenes show high inflammatory activity. The first Pseudopterosins were isolated by the Schmitz[2] and Fenical[3] group. A lot of other terpenes from the *Pseudopterogorgia elisabethae* were isolated when other research groups joined this research area like the Rodríguez[4] group from Puerto Rico and the Kerr[5] group.

2.1 Occurrence and Isolation

The gorgonian soft corals are one of the most common octocorals in the warm waters of the Caribbean Sea. More than 195 species belong to them and they can be split into two mayor families.[6] In 1968 chemical investigations of *Pseudopterogorgia* began Hossain and coworkers discovered *β*-Gorgonene from the *Pseudopterogorgia Americana* which is one of the most common of the genus *Pseudopterogorgia*rose.[7] In 1998 extensive concentration was given to chemically rich species *Pseudopterogorgia elisabethae.* In Figure **2** the classification and the system of the animal kingdom is shown.

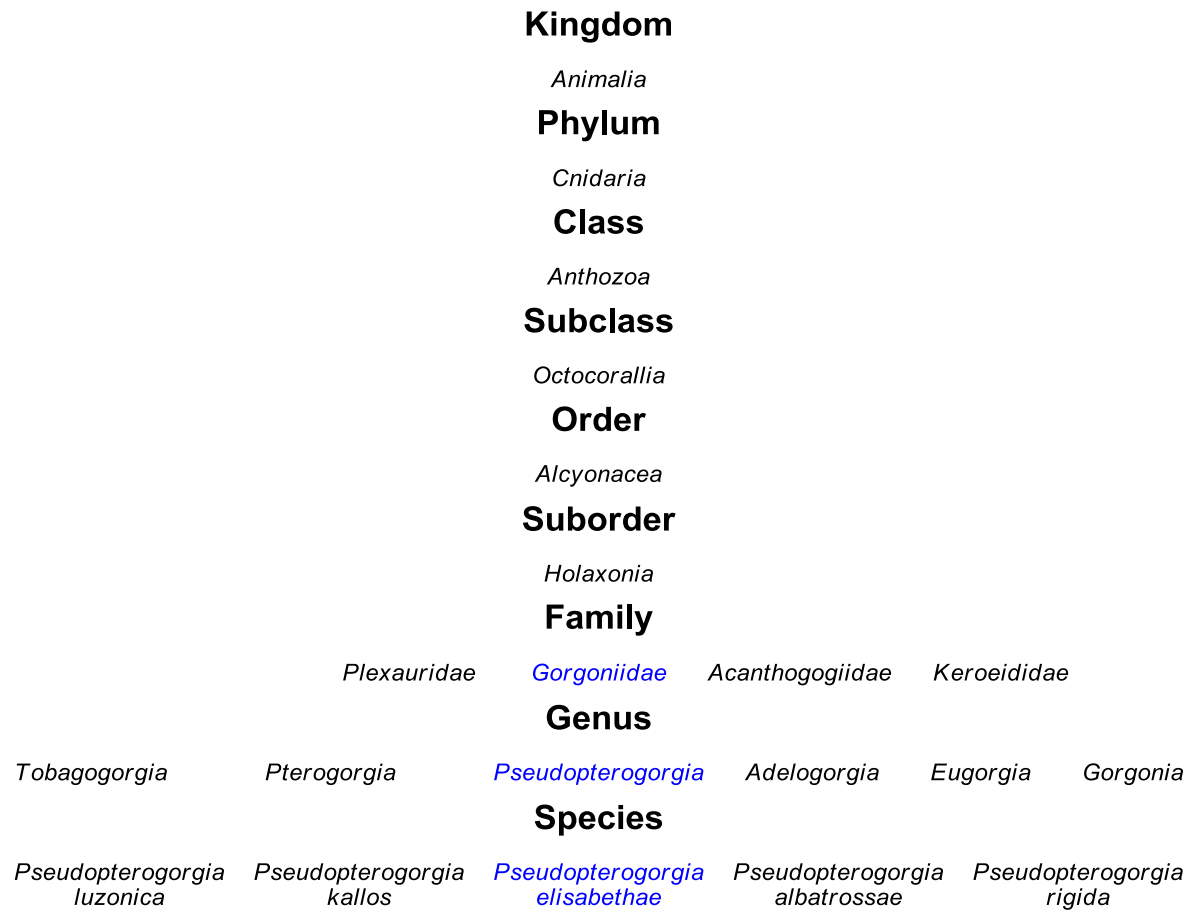


Figure 2. *Pseudopterogorgia elisabethae* within the Animal Kingdom[8]

Pseudopterogorgia elisabethae lives in the tropical western Atlantic Sea near Bahamas, Jamaica, Honduras, Mexico, Florida and Belize. The animal feeds on plankton and symbiodinium. Under good conditions, which means temperaturs from 22 °C - 28 °C it can reach a size up to 20cm. In the Caribbean Sea *Pseudopterogorgia elisabethae* lives in a depth range about 40 meters. The animal contains antibacterial bioactive compounds that have anti-inflammatory properties. Among other things, these bioactive compounds are used in cancer treatment.[9]

2.2 Structures

There are many natural products isolated from *Pseudopterogorgia elisabethae.* This chapter should give a short overview when these compounds have been isolated and its structures have been determined. The structures were proposed through:

- spectral analyses
- chemical transformations
- X-ray crystallographic analyses

The compounds from *Pseudopterogorgia elisabethae* can be divided into seven main groups by their carbon skeleton:

- serrulatane-
- amphilectane-
- elisabethane-
- cumbiane-
- colombiane-
- ileabethane-diterpenes

Until now, fifteen carbon skeletons which are derived from the serrulatane skeletons have been identified. Through different cyclizations reactions of the serrulatane skeletons, new polycyclic structures are built up. These structures can be the starting point for new degradation products. Figure **3** shows compounds possessing the serrulatane carbon skeleton. In 2001 the Rodríguez group isolated Erogorgiaene (**2**) and Hydroxyerogorgiaene (**3**), which is hydroxylated at C-17.[10] In 1987 the Fenical group isolated *seco*-pseudopterosins A-D (**4**, aglycone) and Rodríguez isolated *seco*-Pseudopterosins H-I (**4**) in 2004.[11,12] These compounds are more oxygenated than Hydroxyerogorgiaene at C-17 and C-16 and they have all the same aglycone structure. At the C-17 oxygen, *seco*-pseudopterosins A-D are glycosylated with *α*-arabinose and *seco*-pseudopterosins E-G with *β*-L-fucose at C-16. *Seco*-pseudopterosins H-I are linked at the position of C-16 with *α*-arabinose.[13] In 2003 the Jacobs group published the structure of Elisabethadione (**5**). This structure is hydroxylated at C-16 and contains a *para*-quinone system.[14] There are two hydroxylated froms of this backbone type, *tert*-Hydroxyelisabethadione which is hydroxylated at C-11 (**6**)[15] and *sec*-hydroxyelisabethadione at C-9 (**7**).[16] Kerr reported the isolation of Elisabethamine (**8**), a diterpene alkaloid with a serrulatane type skeleton in 2000.[17] Elisabethamine contains a

methylamino functionality at C-16. *Seco*-pseudopteroxazole (**9**), another diterpene alkaloid, contains a benzoxazole moiety.[18] In 2001 the Rodríguez published hydroxyerogorgiaene *bis*-diterpene (**10**) that belongs to this group. Compound **10** is produced by the dimerization of two Hydroxyerogorgiaene units.[19]

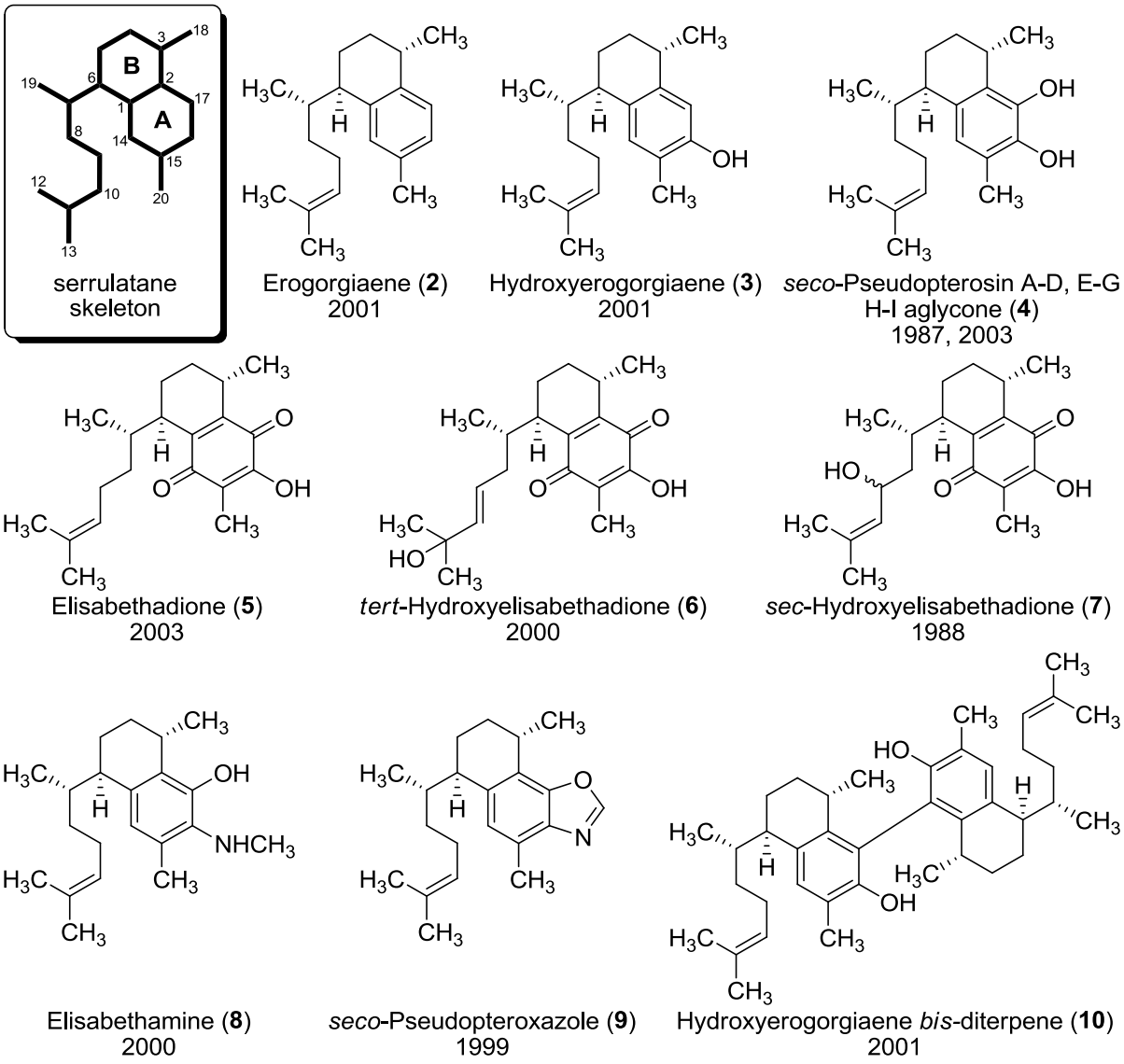


Figure 3. Compounds derived from the Serrulatane Skeleton and their year of Isolation

Figure **4** shows diterpenes with the amphilectane skeleton. Through a C-9 and C-14 cyclization the ring C is formed and this is the amphilectane skeleton. In 1986 Fenical reported the isolation of pseudopterosins A-D (**11**, aglycone) and in 1990 the isolation of Pseudopterosins E-F (**11**) which belong to this group.[20,21] At the C-17 oxygen Pseudopterosins A-D are glycosilated with *β*-D-xylopyranose, but number and position of the

acetate groups differ between the molecules. Pseudopterosin E is linked at the C-16 oxygen with an *α*-L-fucopyranoside unit and Pseudopterosin F is linked with an D-fucopyranoside unit. In 2000 Corey proved the absolute configuration of Pseudopterosins G-J (**12**, aglycon) by a total synthesis.[22] He showed that aglycon pseudopterosins G-J is not the C-3 epimer of pseudopterosins A-F, but the C-9. In 2003 pseudopterosins M-O (**12,** aglycon) were isolated.[23] The aglycone structures are identical with those of pseudopterosins G-J. At the C-16 oxygen they are linked with derivative D-arabinose. The aglycone structures of pseudopterosins K-L (**13**) are entantiomers of the aglycone structures of pseudopterosins A-F (**11**). Pseudopterosin K is linked at the C-17 oxygen to L-fucose and Pseudopterosin L is a mono-acetate derivative at the sugar.[24] Until now have also been isolated pseudopterosins P-Y (**12,** aglycon) and pseudopterosin Z (**11**, aglycon). In 2003 the isolation of elisabethol (**14**) was reported.[25] This substance shows the same stereochemistry as the aglycone structure of pseudopterosins A-F (**11**). Elisabathins A-C (**15**, **16**, **17**) have the same backbone as the aglycone structures of the pseudopterosins. They have a high number of unsaturated bonds, which leads to an extended aromatic conjugation.[2627]

Pseudopteroxazole (**18**) and Homopseudopteroxazole (**19**) are two other members with an amphilectane skeleton.[2829] They have an uncommon benzocazole fraction. Acetyl-amphilectolide (**20**) belongs to the class of the *nor*-amphilectane and has a rearranged nor-diterpene backbone.[30] From a biosynthetic viewpoint this molecule can be seen as a precursor to amphilectolide (**21**) via a deacetylation with concomitant loss of two carbon atoms.[31] Amphilectolide belongs to the *trisnor*-amphilectane class. It misses three carbon atoms in relation with the amphilectane backbone. Amphiphenalone (**22**) belongs to the *tetrisnor*-amphilectane class. In relation with the amphilectane backbone it lacks the isobutenyl side chain. The stereochemistry is the same as the one in the aglycone structures of the pseudopterosins A-F. Instead of the side chain there is a carbonyl function at C-9, and a hydroxyl function at C-8.

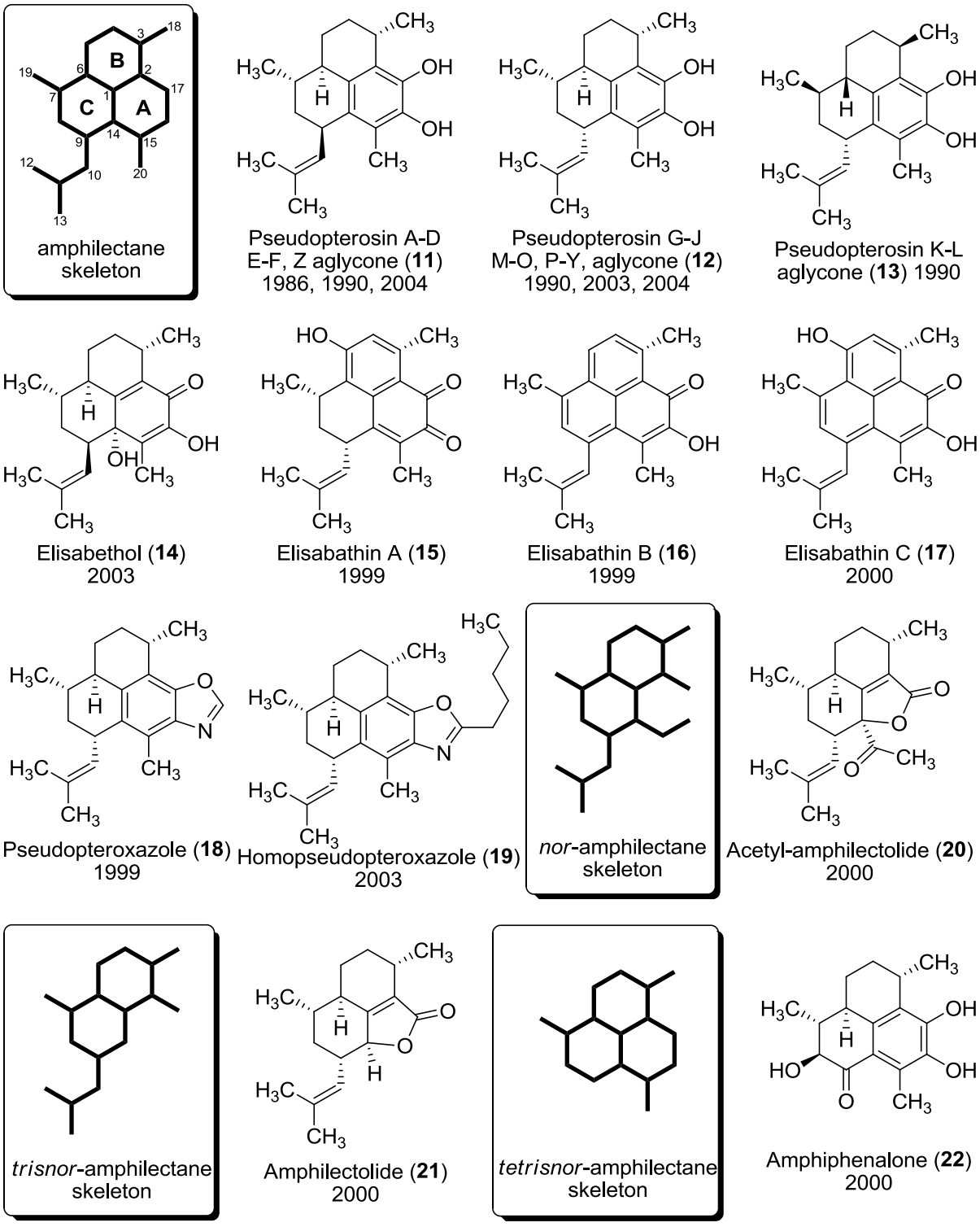


Figure 4. Compounds derived from different Amphilectane Diterpenes and Year of Isolation

Figure **5** shows the elisabethin based compound class. A new tricyclic diterpene ring-system is built up through cyclizations between C-1 and C-9 of a serrulatane based precursor. In 1998 the Rodríguez group focused on terpenoid metabolites from

pseudopterogorgia elisabethae. They collected *Pseudopterogorgia elisabethae* from the Caribbean sea in front of San Andrés Island. The isolated terpenoid metabolites are missing the sugar moiety compared to the known pseudopterosins. The new tricycle Elisabethin A (**1**) was isolated from 1 kg *Pseudopterogorgia elisabethae* 0,05 % yield. Rodríguez and co-workers were able to crystallize elisabethin A (**1**) from chloroform after normal- and reversed-phase column chromatography. They were able to determine the relative configuration by a single crystal X-ray diffraction experiment.[32] Elisabethin D (**23**) shows the same configuration as Elisabethin A and is hydroxylated at the C-2 position.[33] This structure could be a possible precursor of the *seco*-elisabethane backbone. Elisabethin E (**24**) and Elisabethin F (**25**) don't show the same *para*-quinone system as compound **1** and **23**. They also have a different configuration at C-9 and an additional hydroxyl-function at the C-4 carbon. Elisabetholide (**26**) has a *seco*-elisabethane backbone.[34] Loss of either one or two carbons leads to the *nor*-elisabethan class like Elisabethin B (**27**) or to *bisnor*-elisabethane backbone like Elisabethin C (**28**).[35] Trough a total synthesis the absolute configuration of compound **28** was determined.

Figure **6** showes the tetracyclic elisapterane backbone. In 2000 Elisapterosin A (**29**) and Elisapterosin B (**30**) were isolated from Rodríguez and co-workers from *Pseudopterogorgia elisabethae.*[36] The tetracyclic ring system could be formed out of the elisabethane backbone by a C-10/C-15 cyclisation. Through oxidation and cyclization processes it should be possible to produce elisapterosin C (**31**), elisapterosin D (**32**), elisapterosin E (**33**) and elisapterosin F (**34**) out of compound **30.**[37] In 2003 the isolation of compounds **32** and **33** was reported and in 2009 the last compound **34** of this backbone group was published.[38,39] Elisabanolide (**35**) and *3-epi*-elisabanolide (**36**) belong to the *nor*-elisapterane skeleton class. Compounds **35** and **36** have been isolated in 1998 and compound **36** in 2000.[40,41] The difference between the elisabethane and *nor*-elisapterane backbone class is the missing of the C-17 carbon. The cumbiane is backbone is build up through a cyclization between C-10 and C-16. Cumbiasin A (**37**) and cumbiasin B (**38**) belong to this new class of diterpenes. Compound **38** has two additional hydroxyl-functionalities compared to compound **37** at the C-2 and C-15 Carbons.[42] Cumbiasin C (**39**) belongs to the *seco*-cumbiane class.[43] This tricylic ring system, has no connection between C-15 and C-16. The last class with a tetracylic ring system in Figure **6** is

the colombiane skeleton. Ring D of this class arises from a cyclization between carbons C-12 and C-2. Until now colombiasin A (**40**) is the only synthesized of this class.[44]

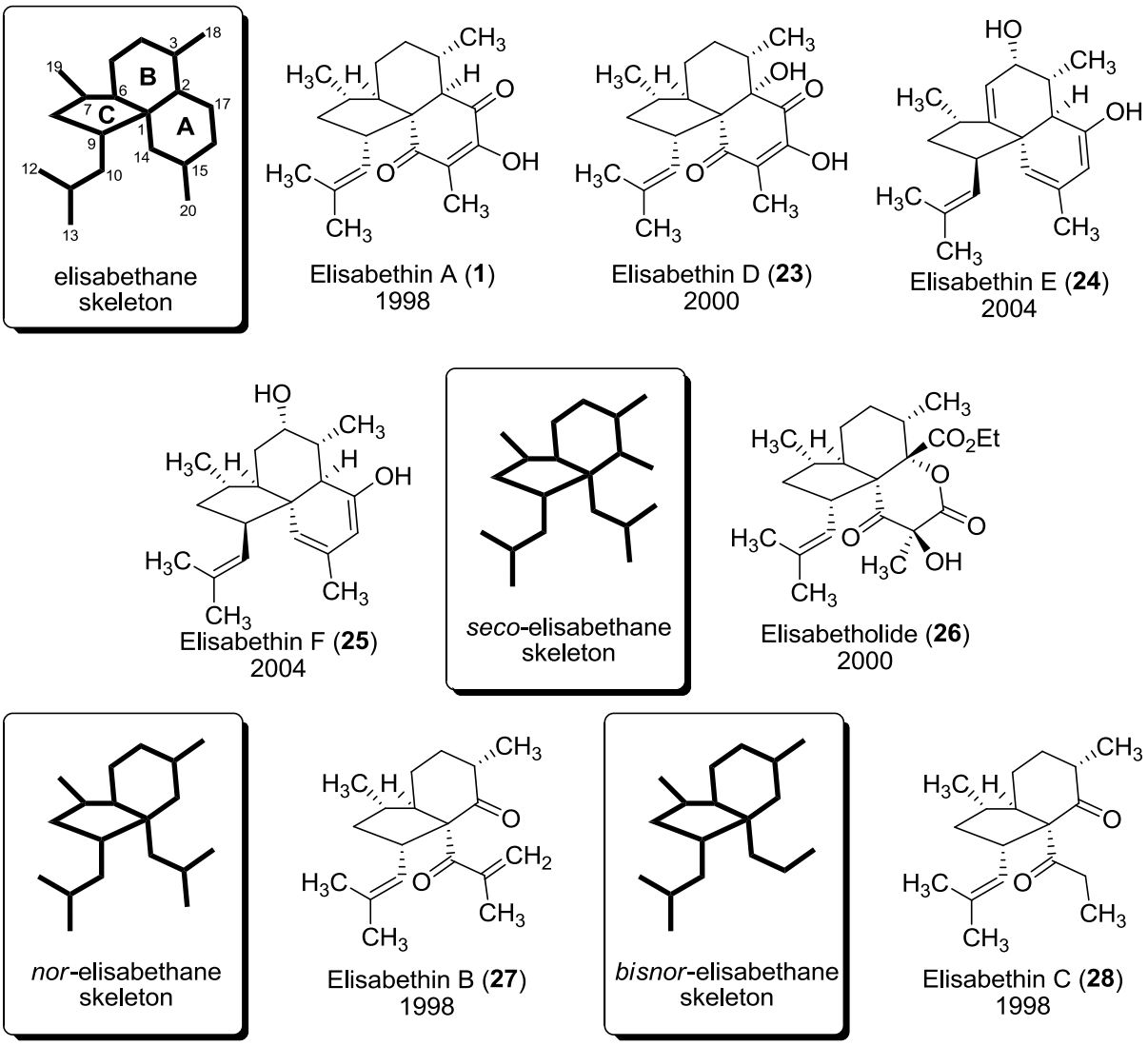


Figure 5. Elisabethin-based Compound Class and Year of Isolation

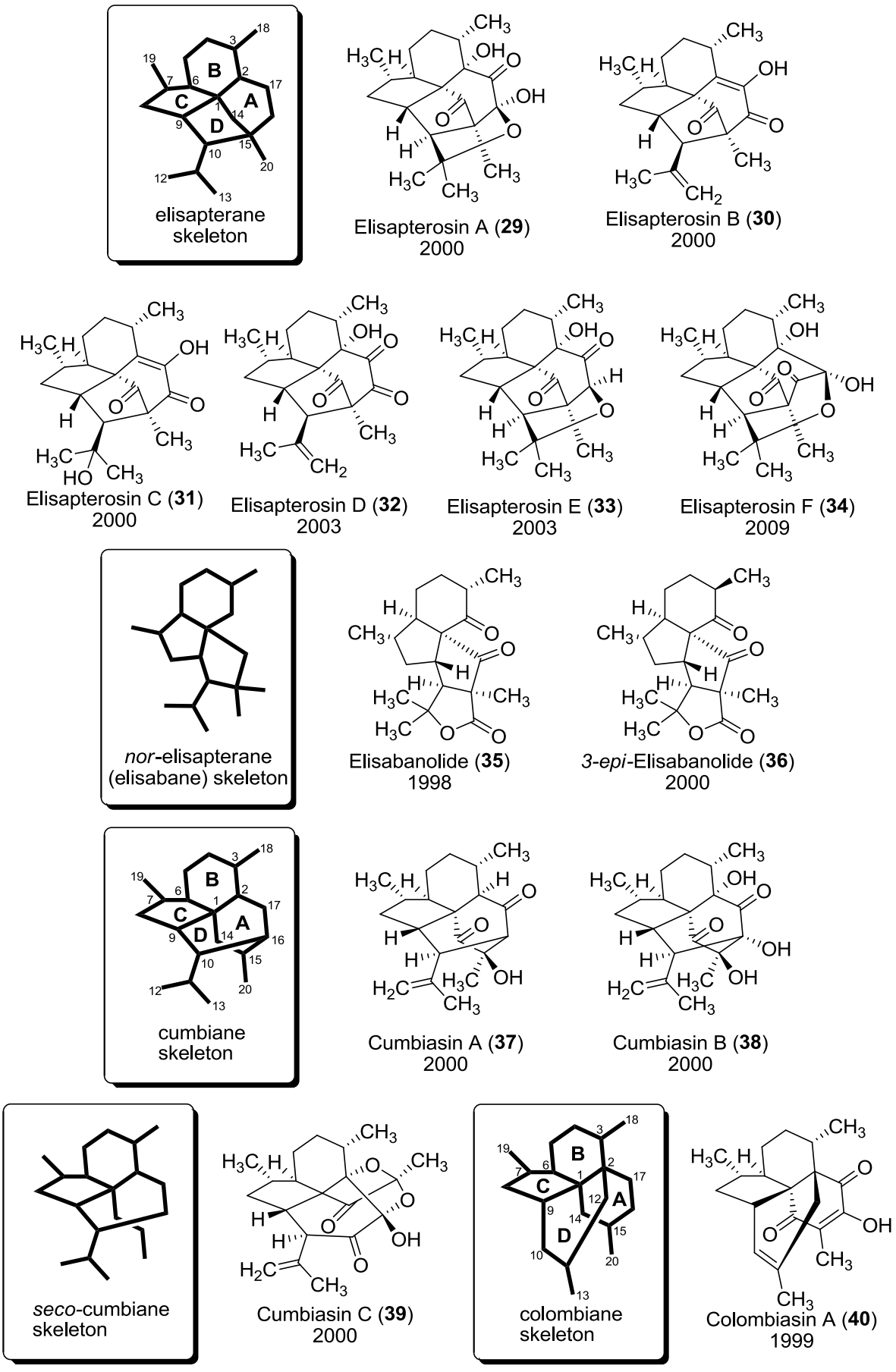


Figure 6. Compounds based on the Backbone of *Elisapterane*, *Cumbiane* and *Colombiane and Year of Isolation*

Figure **7** shows the tricyclic ileabethane skeleton. The ring C has been formed by cyclization between C-8 and C-14 from the serrulatane skeleton. Ileabethin (**41**) has been isolated by Rodríguez and co-workers in 2002.[45] Compound **41** shows an unusual structural feature, the isobutenyl side chain is masked as a spiro *gem*-dimethyl dihydrofuran moiety. The *nor*-sandresane skeleton is lacking the C-16 carbon and ring B is fused with the seven membered ring C. Members of that backbone are sandresolide A (**43**) and sandresolide B (**44**).[46] In sandresolide B there is an additional hydroxyl-funcionality at carbon C-14. The isolation of 12-Acetoxypseudopterolide (**42**) has been published in 1999.[47] Compound **42** belongs to the pseudopterane skeleton. It differs significantly from all the described backbones sofar. There is no structural and biosynthetical relationship between compound **42** and the previously described structures.

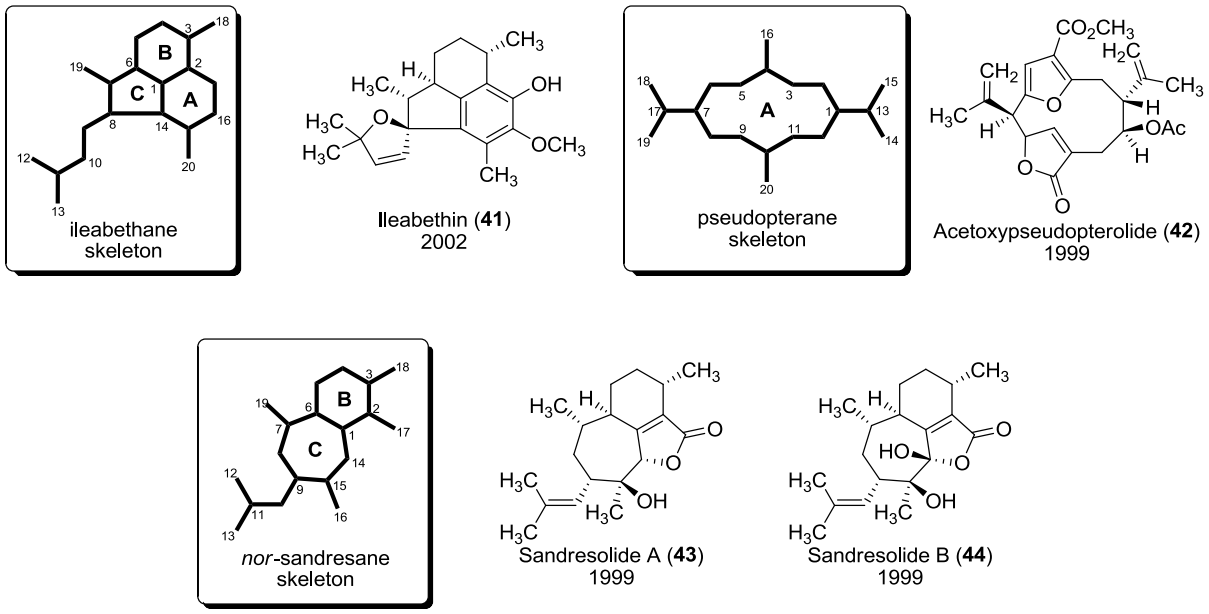


Figure 7. Compounds based on the Backbone of *Ileabethane*, *Pseudopterane* and *nor-Sandresane and Year of Isolation*

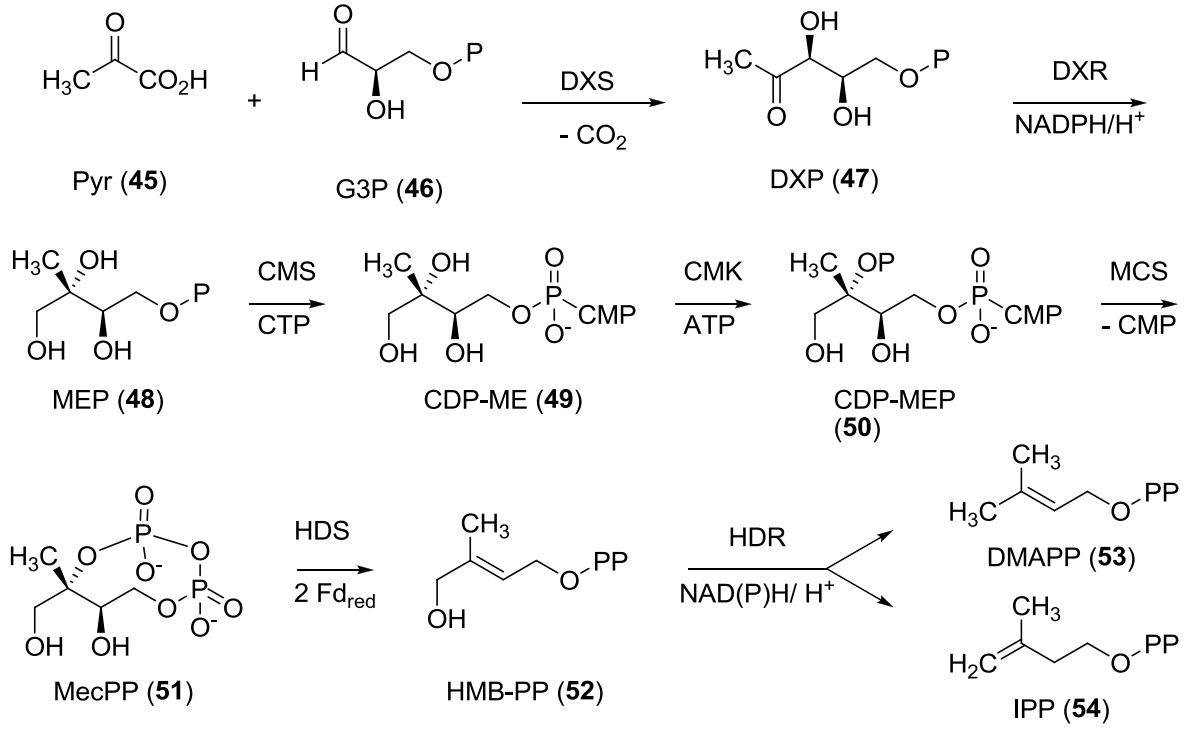
3 Biosynthetic Pathways

Terpenes are a large and diverse class of organic compounds. Normally they occur as secondary metabolites in plants. Many terpenes are aromatic hydrocarbons and thus may have had a protective function. The difference between terpenes and terpenoids is that terpenes are hydrocarbons, whereas terpenoids contain oxygen. They can be divided, in hemi-, mono-, sesqui-, di-, tri- and tetraterpenes with C_5-, C_{10}-, C_{15}-, C_{20}-, C_{30}- and C_{40}-frame works., according their number of carbon atoms. They all can be divided in isoprene units. The isoprene units can be connected head to tail or head to head. There are two different biogenetic pathways to produce terpenes, the Rohmer pathway and the Mevalonate pathway. The resulting products dimethylallyl pyrophosphate (DMAPP, **53**) and isopentenyl pyrophosphate (IPP, **54**) are the starting materials for more complex terpenes.

3.1 The Rohmer Pathway and the Mevalonate Pathway

3.1.1 The Rohmer pathway[48,49]

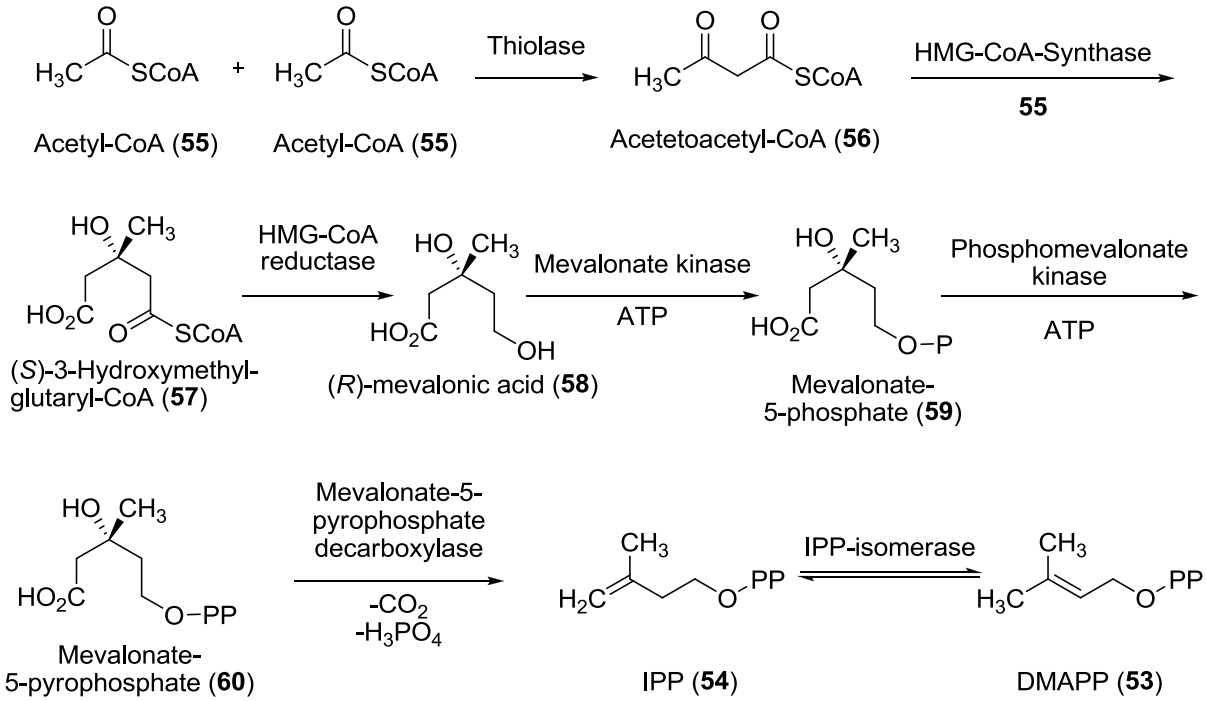
This metabolic pathway shown in Scheme **1**, leeds to the synthesis of DMAPP (**53**) and IPP (**54**). It occurs in the plastids of plants, algae and various bacteria and has been described for the unicellular parasites. The metabolic pathway starts with condensation of glycerinaldehyde-3-phosphate and pyruvate. This reaction is catalyzed by 1-deoxy-D-xylulose-5-phosphate synthase to produce 1-deoxy-xylulose-5-phosphate (DXP, **47**). DXP is reduced by DXP-reduktase to 2*C*-methyl-D-erythritol-4-phosphate (MEP, **48**), which forms the cyclic diphosphate MecPP after repeated phosphorylation. DMAPP (**53**) and IPP (**54**) are formed through an unknown biosynthetic mechanism by reduction of MecPP.



Scheme 1. Rohmer pathway

3.1.2 The Mevalonate Pathway[50]

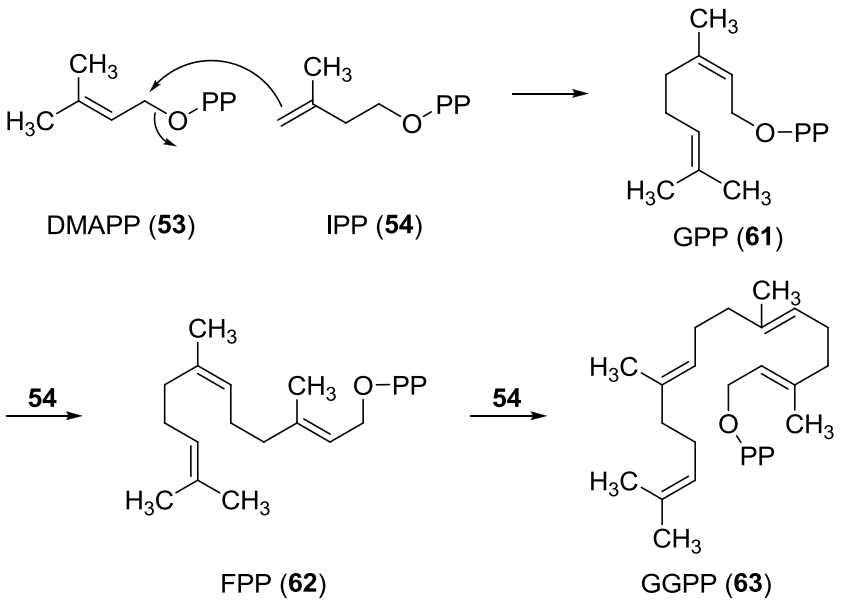
The mevalonate pathway (Scheme **2**) is an important cellular metabolic pathway present in all higher eukaryotes and many bacteria. This metabolic pathway also leads to the synthesis of DMAPP (**53**) and IPP (**54**). In this case two molecules of Acetyl-CoA (**46**) are condensed to Acetoacetyl-CoA via Acetyl-CoA transferase. Acetoacetyl-CoA is condensed with another unit Acetyl-CoA to form (*S*)-3-hydroxy-3-methylglutaryl-CoA. HMG-CoA (**57**) is reduced to the corresponding acid (**58**) by NADPH. (R)-Mevalonic acid is transformed through several steps to compound **54.** This can be isomerized to DMAPP (**53**).



Scheme 2. Mevalonate pathway

3.1.3 Biosynthetic Formation of GGPP[51]

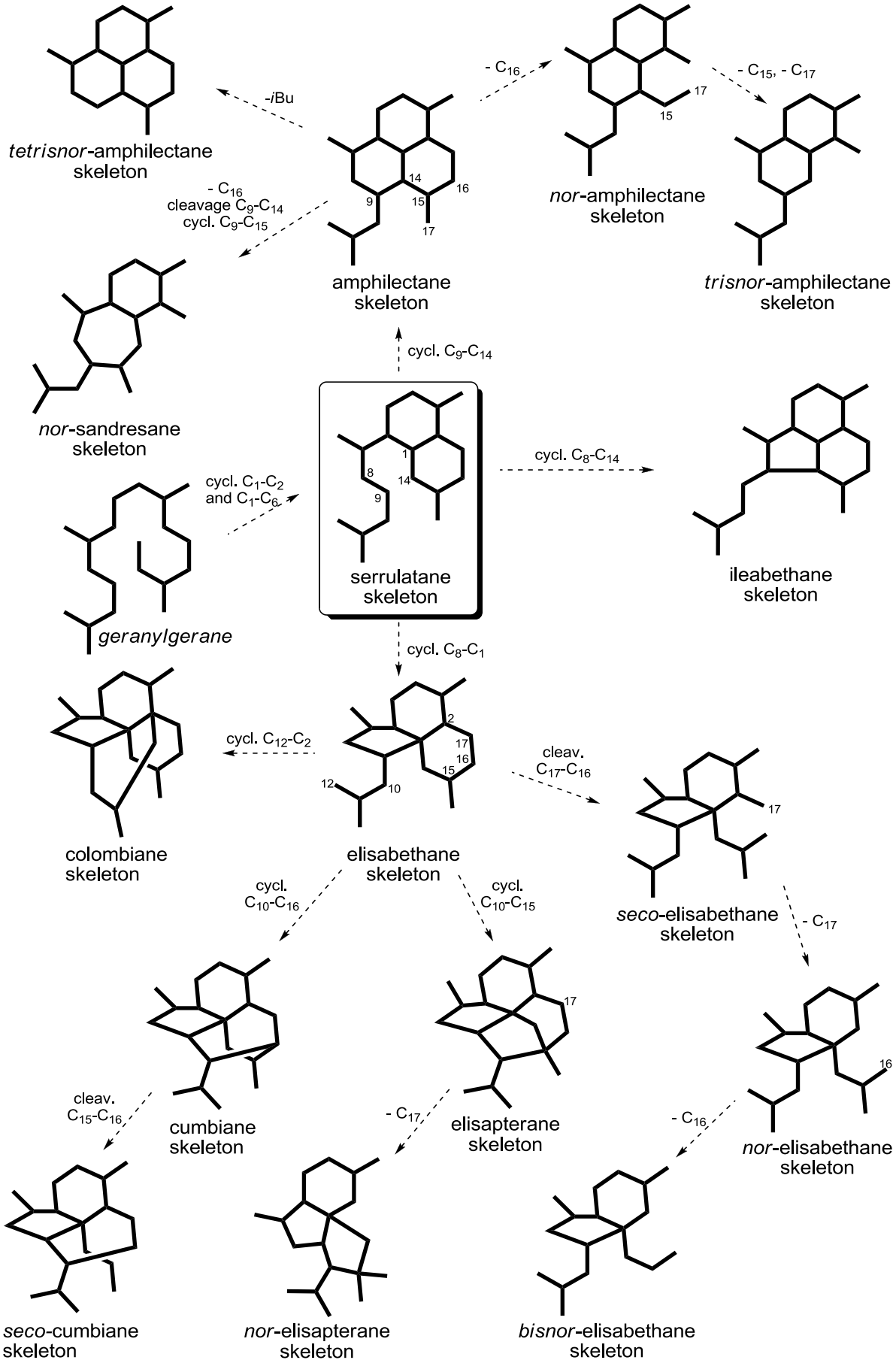
In 1914, Wallach formulated the ”isoprene rule”, which postulates that most terpenoids be hypothetically construced by a repetitive joining of isoprene units. The concept was refined by Ruzicka in 1953 when he formulated the “biogentic isoprene rule”. It ignores the precise character of the biological precursors and assumes only that they are “isoprenoid” in structure. Scheme **3** shows the biosynthetic formation of GGPP. The terminal methylene-group of IPP (**54**) attacks the electrophilic CH_2-group of DMAPP (**53**) and forms geranyl-diphosphate, GPP (**61**). Another elongation with IPP (**54**) leads to farnesyl-diphosphate (FPP, **62**) and finally to geranylgeranyl-diphosphate (GGPP, **63**). GGPP looks quite similar to the serrulatane skeleton.



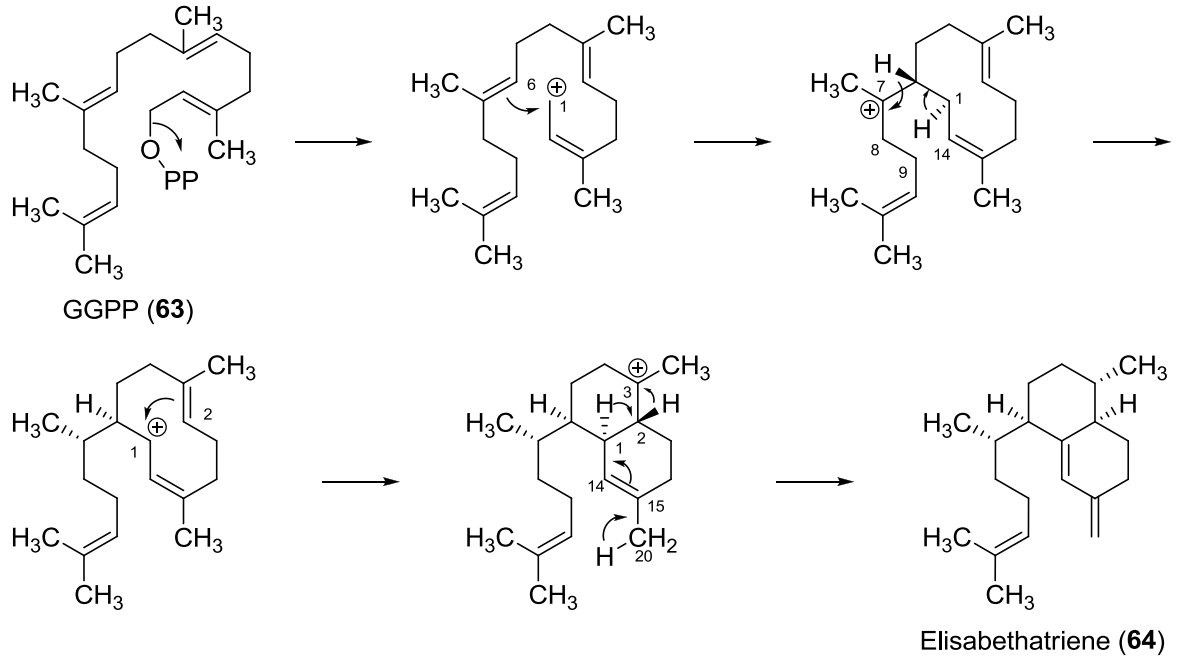
Scheme 1. Formation of GGPP

3.2 Biosynthetic Pathways of Diterpenes isolated from *Pseudopterogorgia Elisabethae*

There are many diterpenes isolated from *Pseudopterogorgia elisabethae*. The structural diversity is enormous. Scheme **4** shows a way how the carbon backbones could be built from geranylgerane skeleton. The geranylgerane skeleton seems to be a precursor for the serrulatane skeleton and this could be a biogentic precursor for a lot of this carbon backbones. The serrulatane skeleton is formed from GGPP (**63**) with elisabethatriene cyclase. Scheme **5** shows a possible mechanism for the transformation of GGPP (**63**) to elisabethatriene (**64**) via the elisabethatriene cyclise. First a carbocation at C-1 is generated through the loss of the pyrophosphate group. A 10 membered carbon ring-system is formed by cyclisation. The tertiary position is located at the tertiary carbon C-7. Hydride shift at C-1 and C-7 generates an allylic carbocation at C-1. This initiates a ring closure, generating a second ring and relocating the positive charge to C-3. After two 1,2 hydride shifts and the loss of a proton at C-20 elisabethatriene(**64**) is formed.[52]

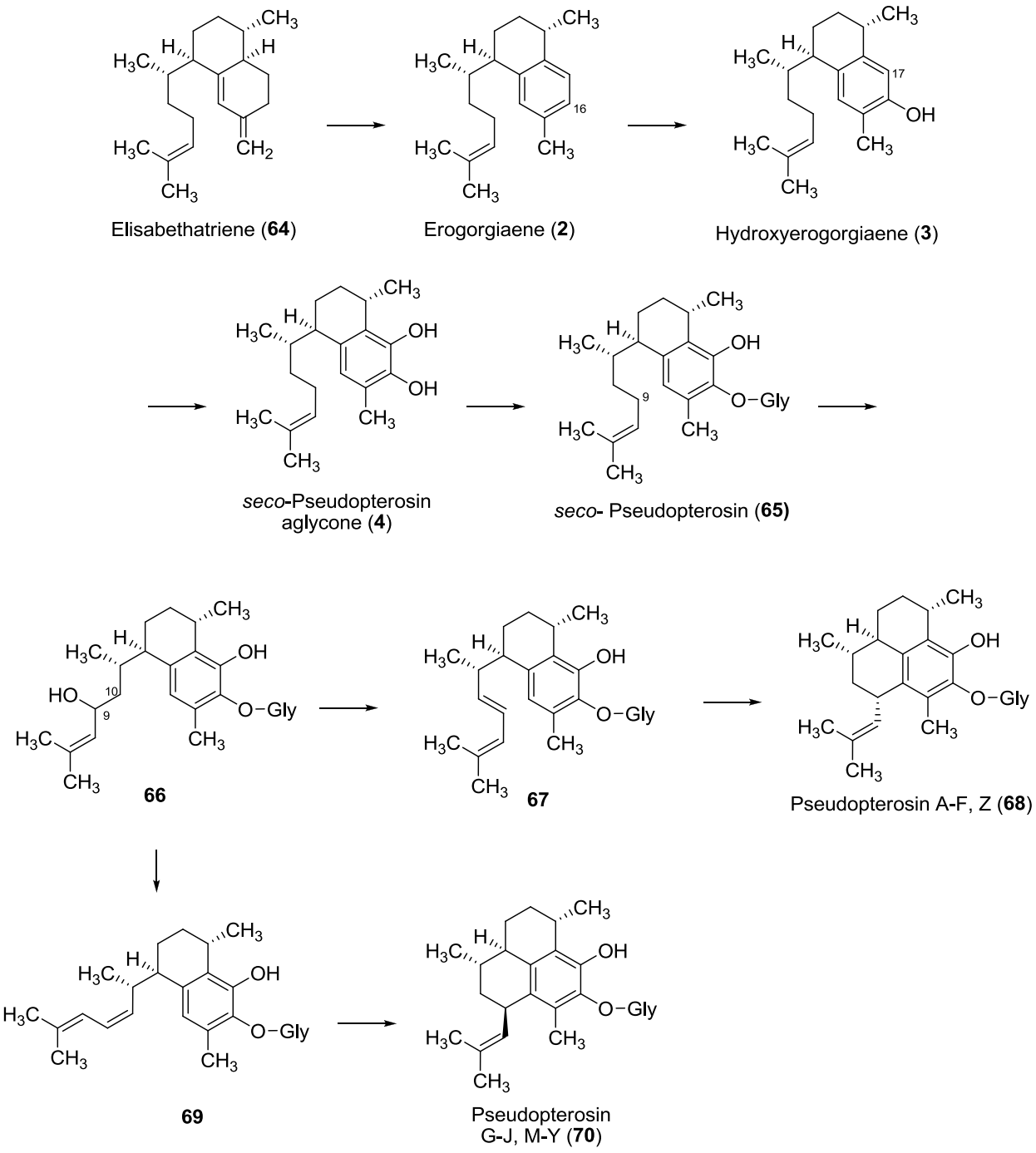


Scheme 4. Biosynthetic Pathway to Carbon Backbones produced by *Pseudopterogorgia Elisabethae*



Scheme 5. Formation of Elisabethatiene

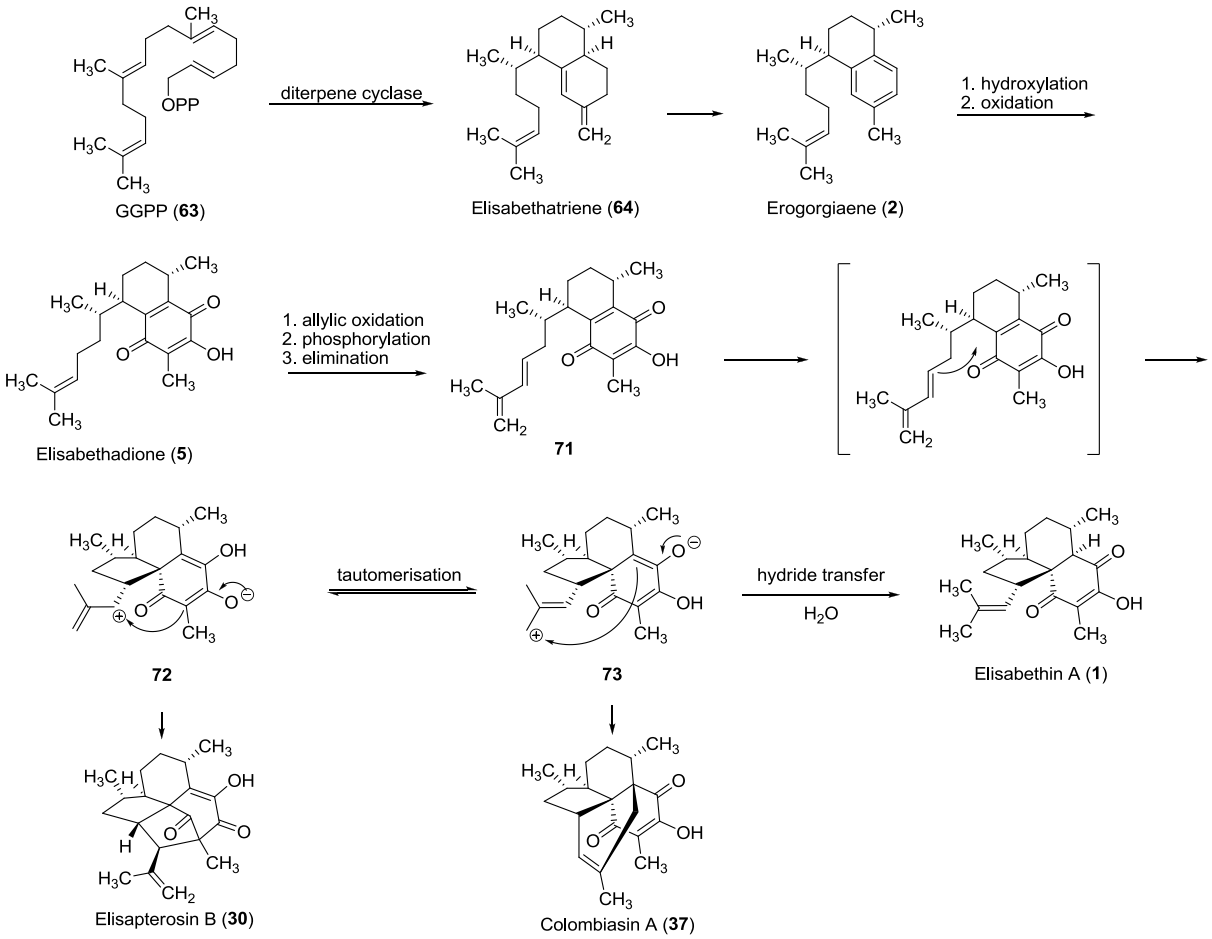
A possible biosynthesis for the pseudopterosins is shown in Scheme **6**. Elisabethatriene (**64**) undergoes aromatization to erogorgiaene (**2**). Oxidation at C-16 leads to hydroxyerogorgiaene (**3**) and another oxidation at C-17 leads to *seco*-pseudopterosin-aglycone (**4**). *Seco*-pseudopterosins (**65**) is produced through gylcosidation of the hydroxyl group at C-16. Hydroxylation at C-9 leads to compound **66**. Phosphorylation and elimination of the hydroxyl moiety from C-9 leads to two different compounds **67** and **69**, **67** with a new (*E)*-double bound and **69** with a (*Z)*-double bond. Ring closure of **67** leads to pseudopterosin A-F, Z (**68**) and the ring closure of **69** leads to pseudopterosin G-J, M-Y (**70**). The ring closure is acid promoted.[53]



Scheme 6. Proposed biosynthesis of Pseudopterosins

The following scheme **7** shows a possible biosynthesis of elisabethin A (**1**). Erogorgiaene (**2**) is formed as reported before. Three time oxidation of erogorgiaene (**2**) and oxidation to the *para*-quinone gives elisabethadione (**5**). Allylic oxidation, phosphorylation and elimination affords compound (**71**). This compound can undergo a ring closure to form a five-membered ring to compound **72**, which can now form Elisapterosin B (**30**) or tautomerise to **73**.

Elisabethin A (**1**) can be formed with a hydride transfer from **73**, or **73** can be trapped to form Colombiasin A (**37**).[54]



Scheme 7. Proposed Biosynthesis of *Elisabethin A, Colombiasin A, Elisapterosin B*

4 Pharmacological Properies

4.1 *Anti*-inflammatory activity

The *seco*-pseudopterosins, pseudopterosins and elisabethadione isolated from *Pseudopterogorgia elisabethae* shows shows strong anti-inflammatory and analgesic activity in *in-vivo* mice ear tests.[55] They act in a different modes compared to the common non-steroidal anti-inflammatory drugs.[56] Commercially they are applied in skin creams.[57]

4.2 *Anti*-tuberculosis activity

A lot of compounds of the serrulatane, amphilectane, elisabethane and elisapterane class and derivates show a high *anti*-tuberculosis activity. Typical values for growth inhibition of *Mycobacterium tuberculosis* range between 20 % and 60 % with concentration of 12 µg/mL. Elisapterosin B shows a growth inhibition of 79 %, pseudoteroxazole 97 %, erogorgiaene 96 % and Homopseudopteroxazole 80%.[58,59]

4.3 *Anti*-cancer activity

Elisapterosin A and elisabatin A show a non selective cell cytotoxicity in the NCI's 60 cell-line tumor panel.[60,61] Two structures show interesting anti-cancer activity. Elisabethin B shows significant *in vitro* cancer cell cytotoxicity. Elisabethamin was found to have high activity against prostate cancer and lung cancer cell lines. Also acetoxypseudopterolide shows mild *anti*-cancer activity against prostate cancer cell lines.[62]

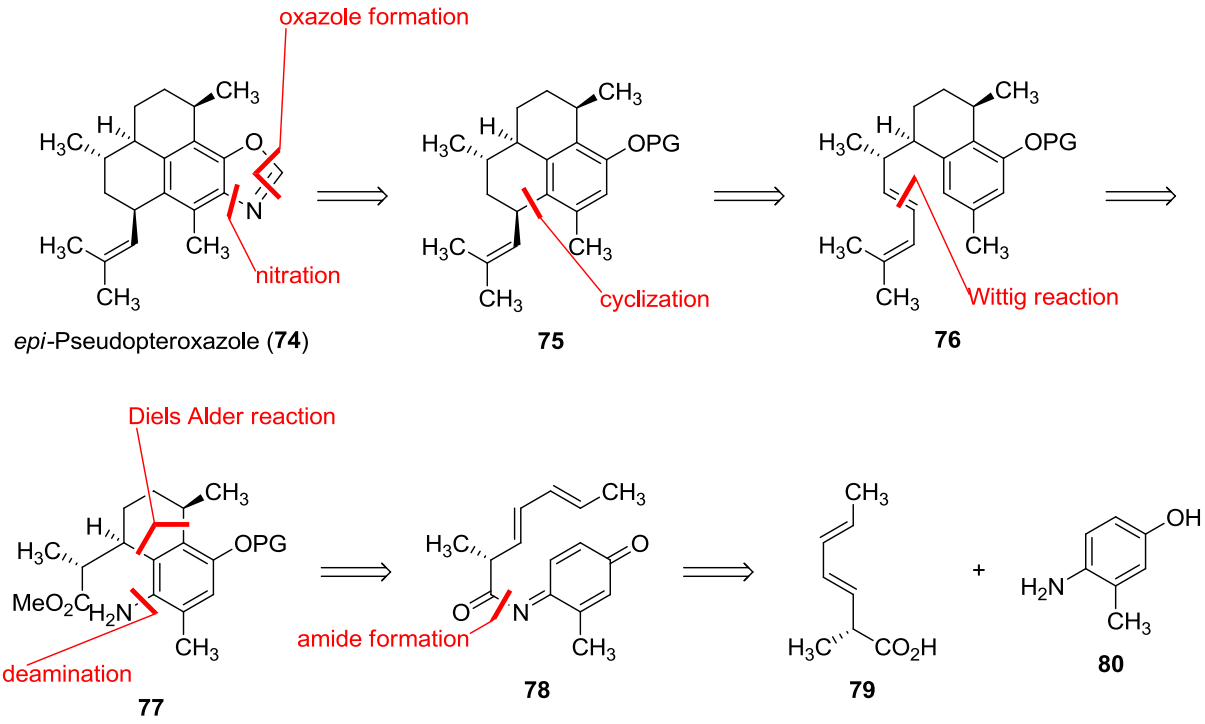
4.4 *Anti*-plasmodial activity

Elisapterosin A shows strong *anti*-plasmodial activity against *Plasmodium falciparum*. This parasite is responsible for the most forms of malaria.[63]

5 Recent Total Syntheses

5.1 Total Synthesis of 3,9-*epi*-Pseudopteroxazole: Corey`s Approach[54]

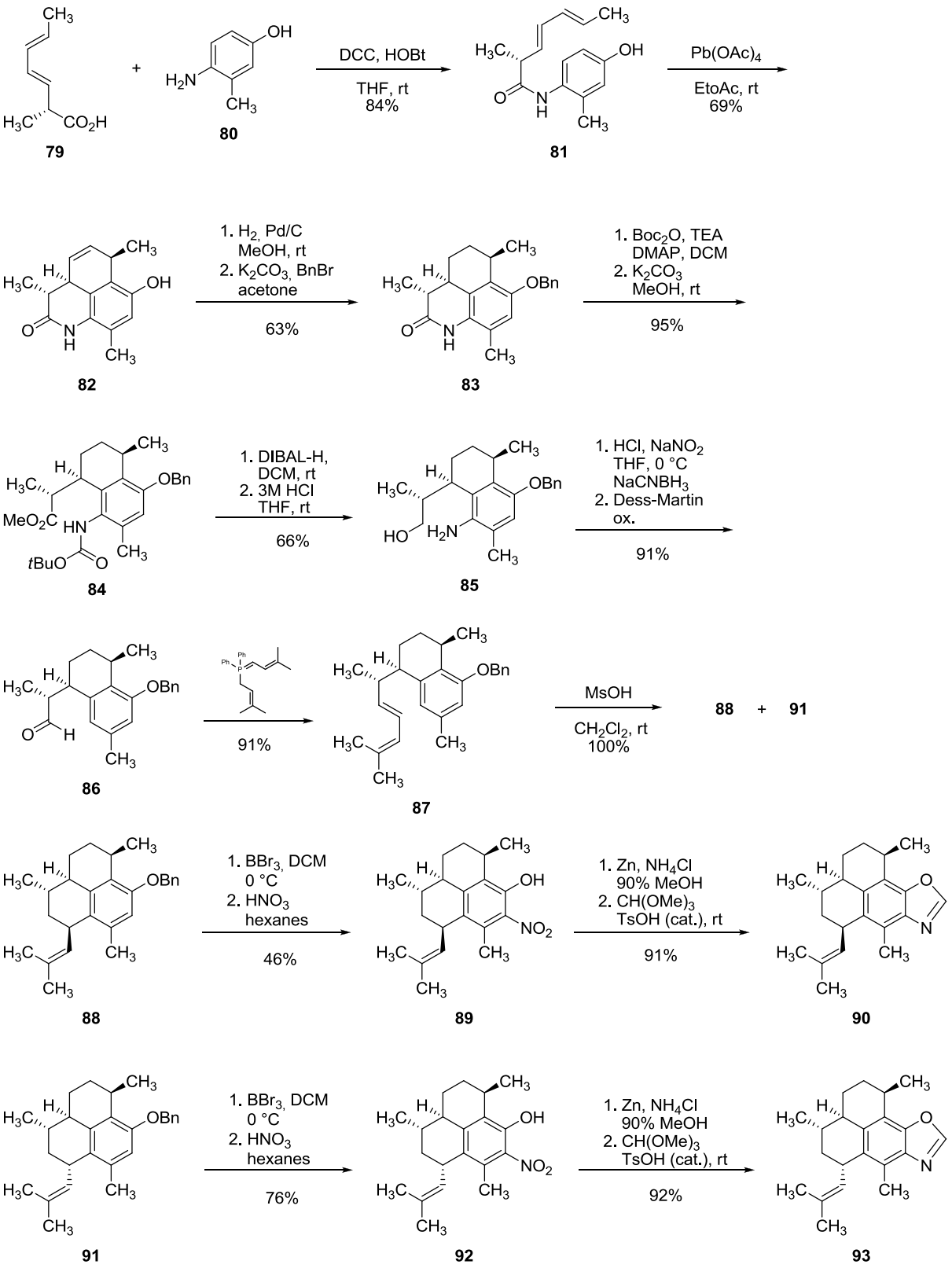
The retrosynthetic plan is showen in Scheme **8.** It is based on two key steps, a cationic cyclization and an intramolecular Diels-Alder reaction. *Epi*-pseudopteroxazole (**74**) should be build up via a nitration and oxazole formation from **75.** A cationic cyclization from **76** should give precursor **75**. Compound **76** would be obtained by deamination and Wittig reaction from **77**. A stereocontrolled intramolecular Diels-Alder reaction of quinone imide **78** should from compound **77**. Precursor **78** could be accessible by amide coupling of compounds **79** and **80** followed by an oxidation to produce the quinone imide system.[64]



Scheme 8. Corey's Retrosynthetic Analysis of *epi*-Pseudopteroxazole (**74**)

Scheme **9** shows the total synthesis from Corey and his coworkers. They start with a coupling of compounds **79** and **80** moderated by DCC and HOBt to produce **81**, which was oxidized to the quinone imide system and an intramolecular Diels-Alder reaction to obtain compound **82** (8:1 mixture of endo/exo-adducts), followed by hydrogenation and benzylic protection of the free alcohol functionality to yield substance **83**. Boc-protection and methanolyis of the

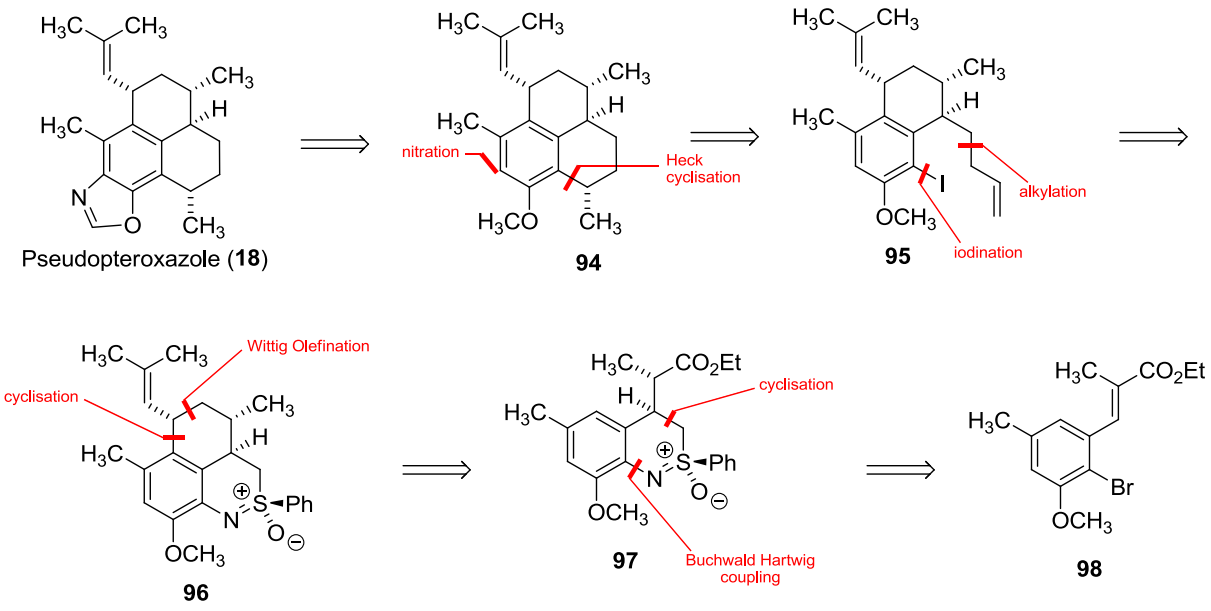
amide afforded methyl ester **84.** Compound **85** was produced through reduction of the ester functionality and cleavage of the Boc-protection group. Deamination and oxidation of the alcohol yielded aldehyde **86.** The conjugated diene **87** was obtained by a Wittig chain elongation. Cationic cyclization with methanesulfonic acid as catalyst gave a mixture of diastereomers in a ratio of about 1:2. They were able to separate the diastereomers **88** and **91** by chromatography. The diastereomers were converted by parallel processes to the isomeric pseudopteroxazole structures **90** and **93** by cleavage of the benzyl ether and nitration to nitro phenols **89** and **92**. **90** and **93** were produced *via* reduction of the nitro moiety and formation of the desired tetracyclic pseudopteroxazole structures **90** and **93.** 16 linear steps achieved an overall yield of 3.2% of 3,9-*epi*-Pseudopteroxazole.



Scheme 9. Corey's Total Synthesis of *epi*-Pseudopteroxazole (**74**)

5.2 Total Synthesis of Pseudopteroxazole: Harmata's Approach [66,67]

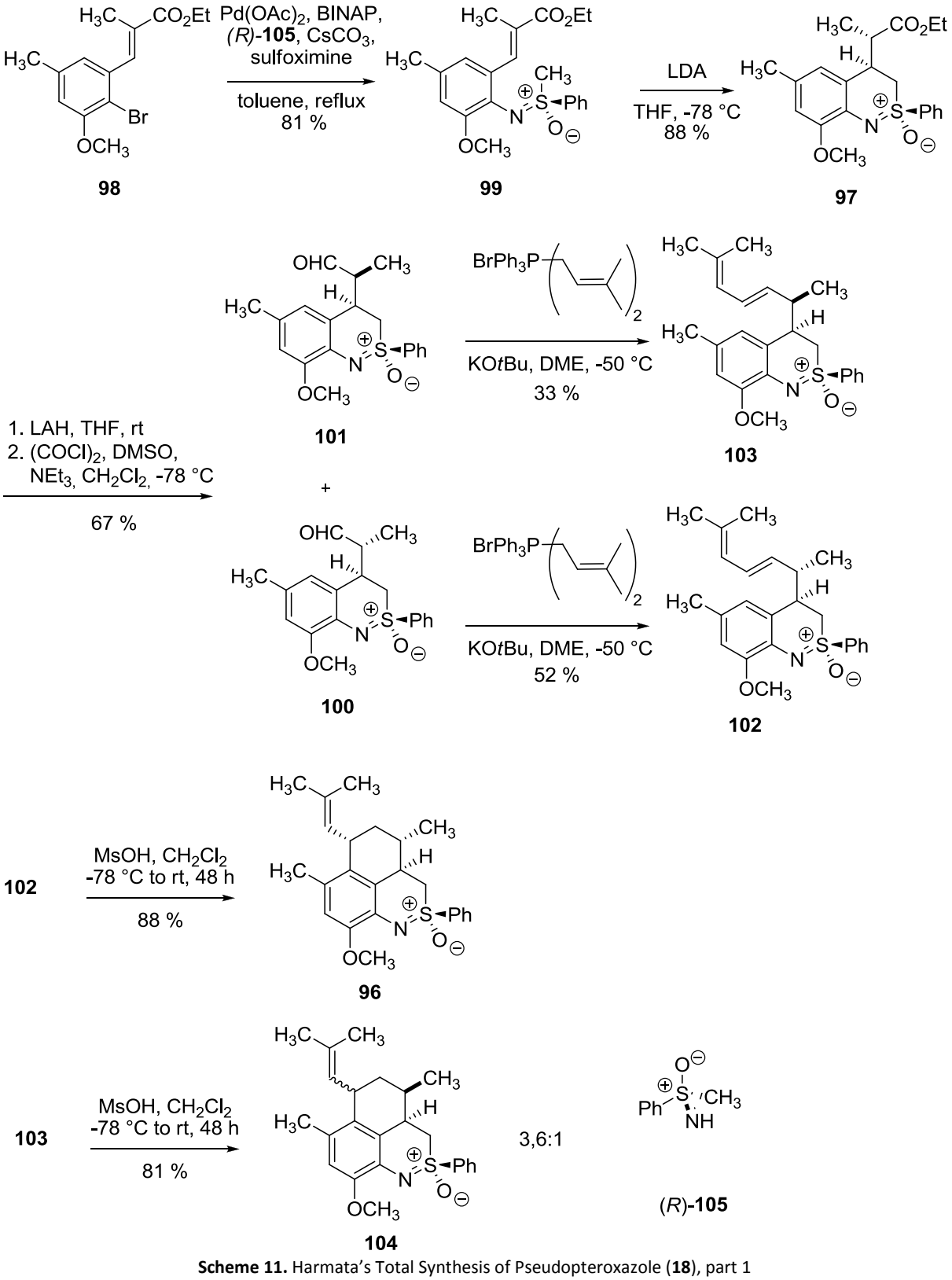
Scheme **9** shows the retrosynthetic plan of Harmata and his group for the synthesis of pseudopteroxazole, reported in 2004. The oxazole 5 membered ring should be built up through a nitration of the aromatic ring and cleavage of the ether out of compound **94.** This precursor for pseudopteroxazole should be built up through a Heck cyclisation from **95** to form the tricyclic system. Intermediate **95** should be built up through allylation of the sulfoximine and reduction to the corresponding amine followed by an iodination. Through a cationic cyclisation the second six-membered ring system should be build up after Wittig chain elongation. The precursor for that should be built up by a Buchwald-Hartwig coupling with a chiral sulfoximine and cyclisation from compound **98.**



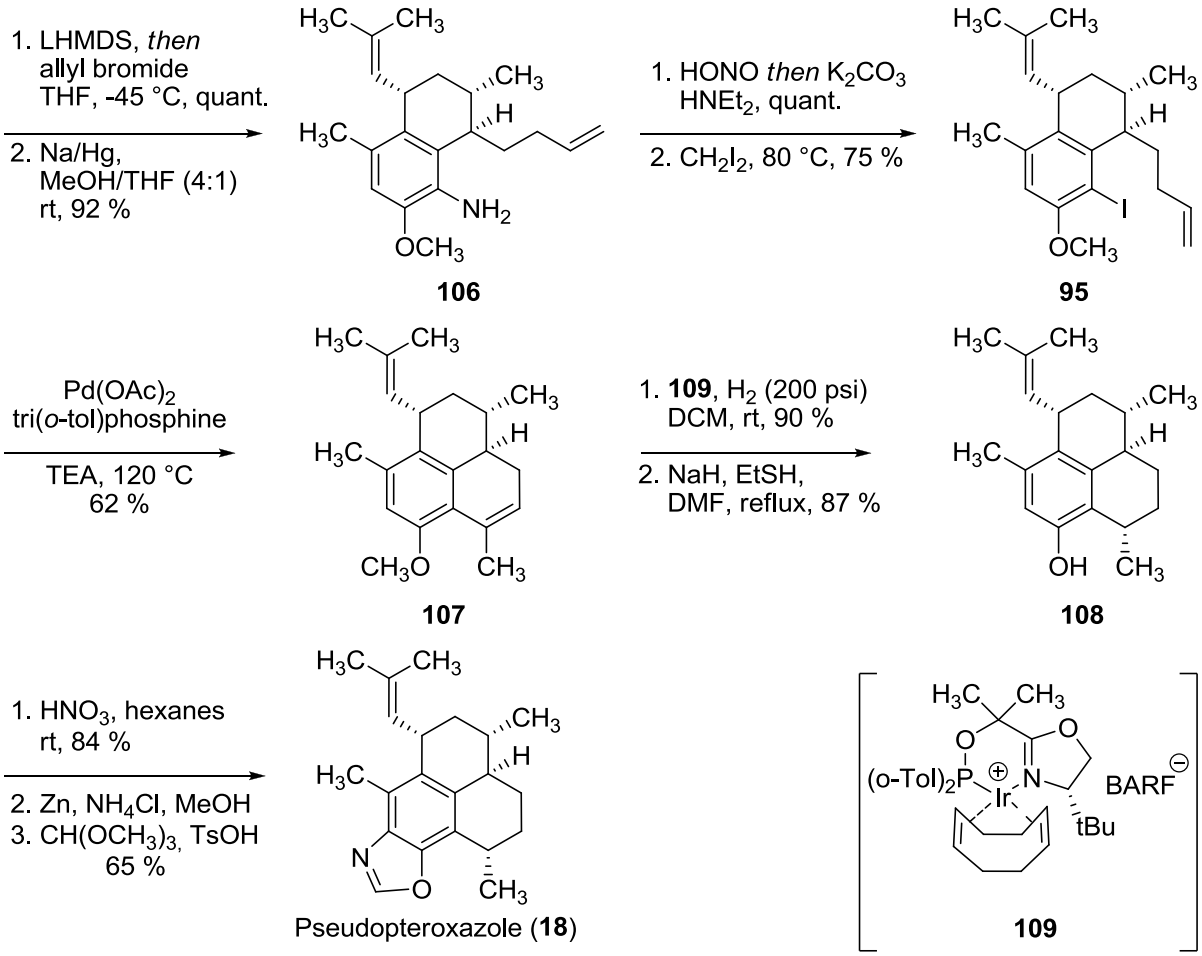
Scheme 10. Harmata's Retrosynthetic Analysis of Pseudopteroxazole (**18**)

Scheme **11** and **12** show the first part of the total synthesis of Pseudopteroxazole (**18**). Harmata and co-workers started from compound **98.**[65] Buchwald-Hartwig coupling with a chiral sulfoximine under reflux conditions gave **99.** Deprotonation with LDA of the methylene group at the sulfur ended in the desired 6-membered ring system **97.** Reduction of the ester moiety followed by a Swern oxidation gave a mixture of diastereomers **101** and **100** in ratio of about 1.6:1, which couldn't be sepearated chromatographically. After a Wittig olefination with the mixture of diastereomers, they were able to separate the mixture

chromatographically. Only the diastereomer **102** was needed for the total synthesis of Pseudopteroxazole (**18**). A cationic cyclisation to **96** under acid conditions gave the desired product. Allylation of the sulfoximine and reductive cleavage with Na/Hg provided aniline **106**. Treatment with triazene followed by addition of diiodomethane gave iodide **97.** With a intramolecular Heck cyclization the third ring was closed, followed by hydrogenation with compound **109** as catalyst. They split up the methyl ester to afford **108.** Nitration to nitro phenols of **108** and reduction of the nitro moiety and formation of the desired tetracyclic yield pseudopteroxazole (**18**) Harmata and coworkers accomplished a total synthesis of Pseudopteroxazole (**18**) in 16 steps with an overall yield of 4%.[66,67]



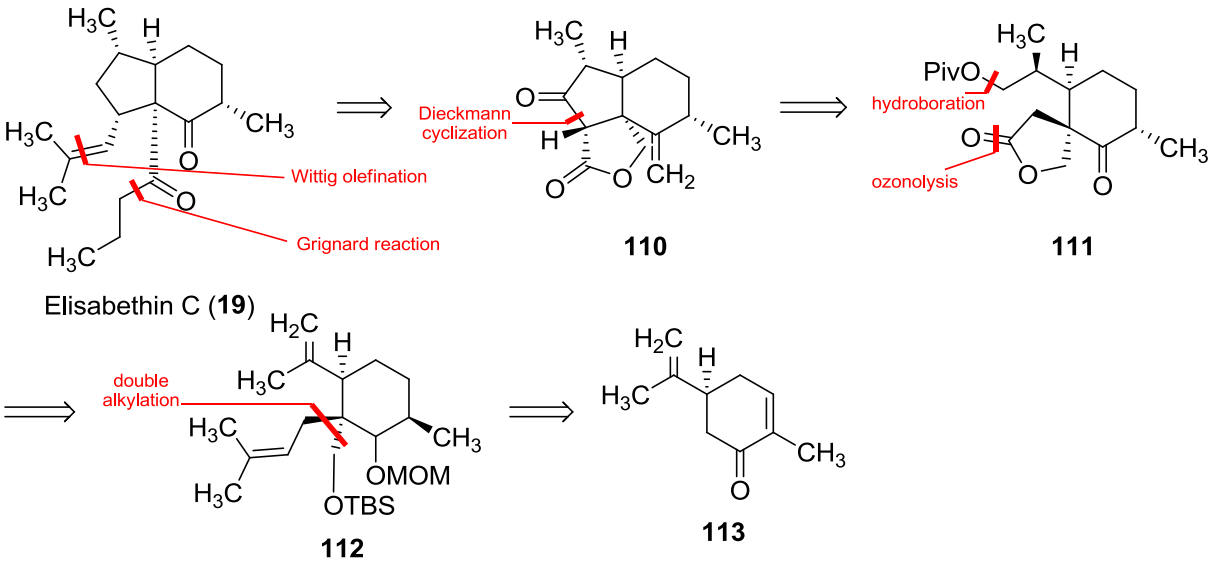
Scheme 11. Harmata's Total Synthesis of Pseudopteroxazole (**18**), part 1



Scheme 12. Harmata's Total Synthesis of Pseudopteroxazole (**18**), part 2

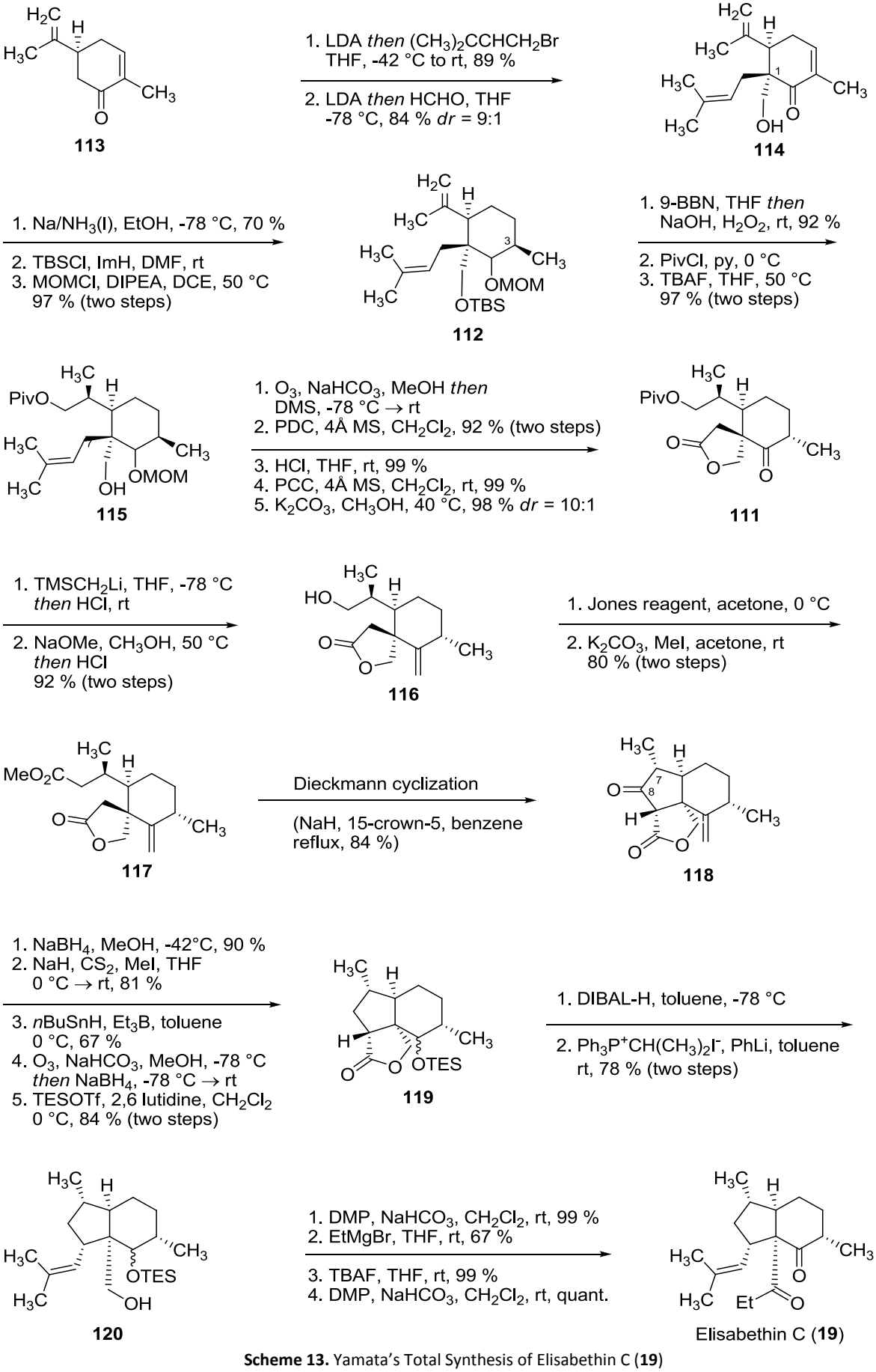
5.3 Total Synthesis of Elisabethin C: Yamada's Approach[68]

In 2002 Yamada and co-workers published the total syntehesis of Elisabethin C (**17**). The retrosynthetic plan is shown in Scheme **13**. The two side chains should be introduced through a Wittig and a Gringnard reaction from precursor **110**. The key step of Yamada's plan is a stereoselective Dieckmann cyclization to yield compound **110** from precursor **111**. This precursor should be build up through a series of oxidation reactions from **112.** This would lead to commercially available (+)-carvone (**113**) as starting material for this synthesis which can be easily turned into **112** through a double alkylation.



Scheme 13. Yamada's Retrosynthetic Plan of Elisabethin C (**19**)

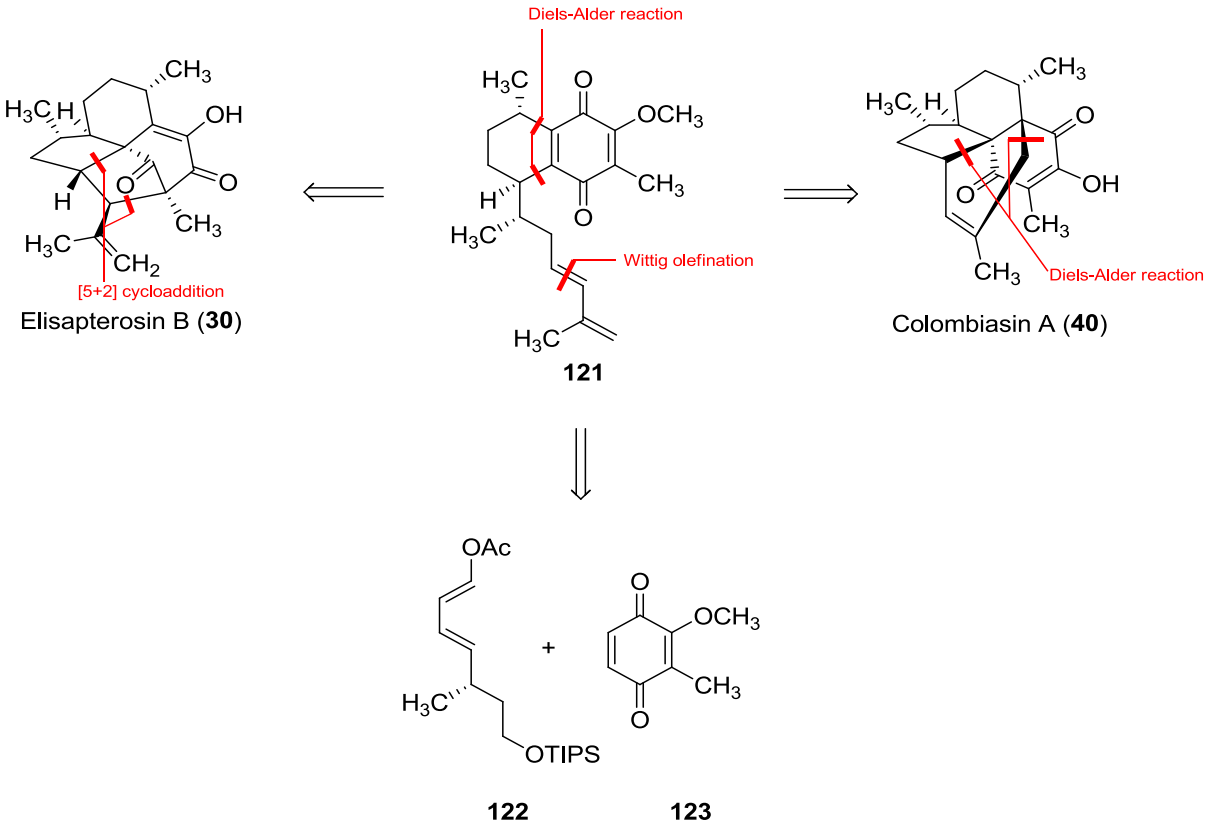
As starting martial Yamada and co-workers have choosen (+)-carvone (**113**). Double enolization and alkylation gave compound **114** in a diastereomeric mixture of 9:1. After separation of those alcohols, enone **114** was reduced under Birch conditions followed by TBS protection of the primary alcohol and MOM protection of the secondary alcohol to **112**. But the resulting product shows the undesired stereochemistry at C-3 according to Elisabethin C. Compound **112** was converted into **115** with a regio- and stereoselective hydroboration followed by a pivaloyl protection of produced alcohol and cleavage of TBS protecting group. After ozonolyis of the double bond of the ispropenyl group and oxidation they gained the five membered lactone ring of compound **111**. Cleavage of the MOM-protecting group and oxidation and epimerisation of the methyl group at C-3 gave **111**. The keto-functionality was protected as a methylene group and followed by a cleavage of the pivaloyl-ester. The primary hydroxyl group of **116** was oxidised under Jones conditions and transformed to the methylester **117**. This compound was the precursor for the Dieckmann cyclisation. Through a Dieckmann condensation they gained compound **118** with the right stereochemistry of the methyl group at C-7**.** Reduction and deoxygenation of the keto-functionality at C-8, ozonolysis of the methylene moiety and reductive workup followed by TES orotection gave intermediate **119**. The five membered lactone was reduced with DIBAL-H to provide the corresponding lactol followed by a Wittig olefination to afford **120.** The remaining alcohol was oxidized, followed by a formation of the secondary alcohol with ethylmagnesium bromide. Cleavage of the TES protecting group and oxidation of the alcohols gave Elisabethin C (**19**) in 29 steps with an overall yield of 6%.[68]



Scheme 13. Yamata's Total Synthesis of Elisabethin C (**19**)

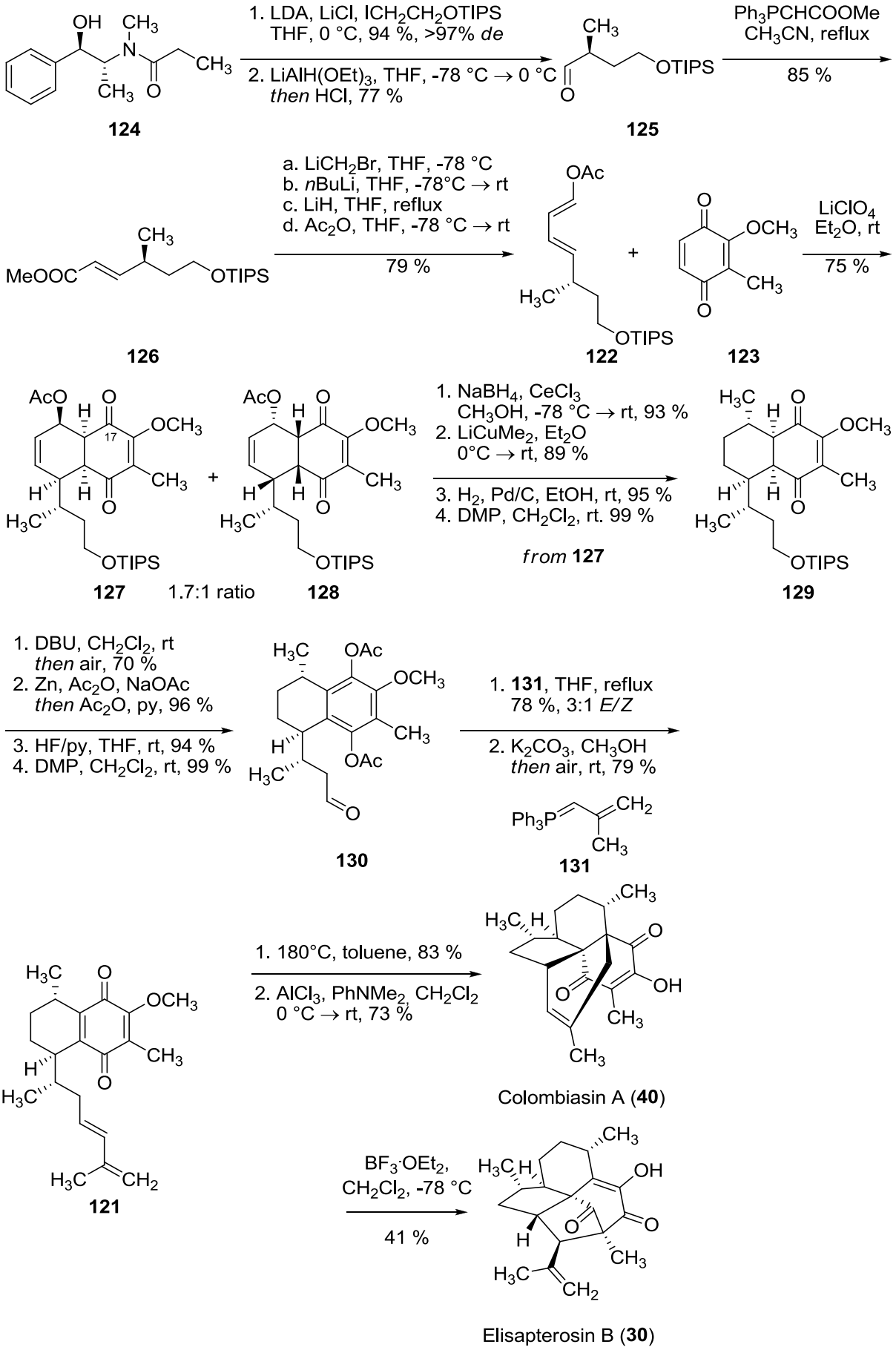
5.4 Total Synthesis of Elisapterosin B and Colombiasin A: Rychnowsky's Approach

In 2003 Rychnowsky and co-workers reported the total synthesis of elisapterosin B (**30**) and Colombiasin A (**40**). Elisapterosin B should be formed out of precursor **121** through a [5+2]-cycloaddition. Colombiasin A (**30**) should also be formed out of the same precursor **121** with a Diels Alder reaction. The side chain of intermediate **121** was planned to be built up by a Wittig reaction and the decaline system should be formed by a Diels Alder reaction out of compounds **122** and **123**. The retrosynthetic plan is shown in Scheme **14**.



Scheme 14. Rychnowsky's Retrosynthetic Plan of Elisapterosin B (**30**) and Colombiasin A (**40**)

The total synthesis of elisapterosin B (**30**) and colombiasin A (**40**) is shown in Scheme **15.** The synthesis started with a stereoselective alkylation of **124** followed by reductive cleaveage of the auxiliary to give compound **125**. A Wittig reaction gave desired product **126**. Using Kowalski's one carbon homologation protocol gave diene **122**.[69] Diels Alder reaction of **122** and **123** was successful but gave an inseparable mixture of diastereomers **128** and **129** in a ratio of 1.7:1. The mixture was carried through the rest of the synthesis and separated in the

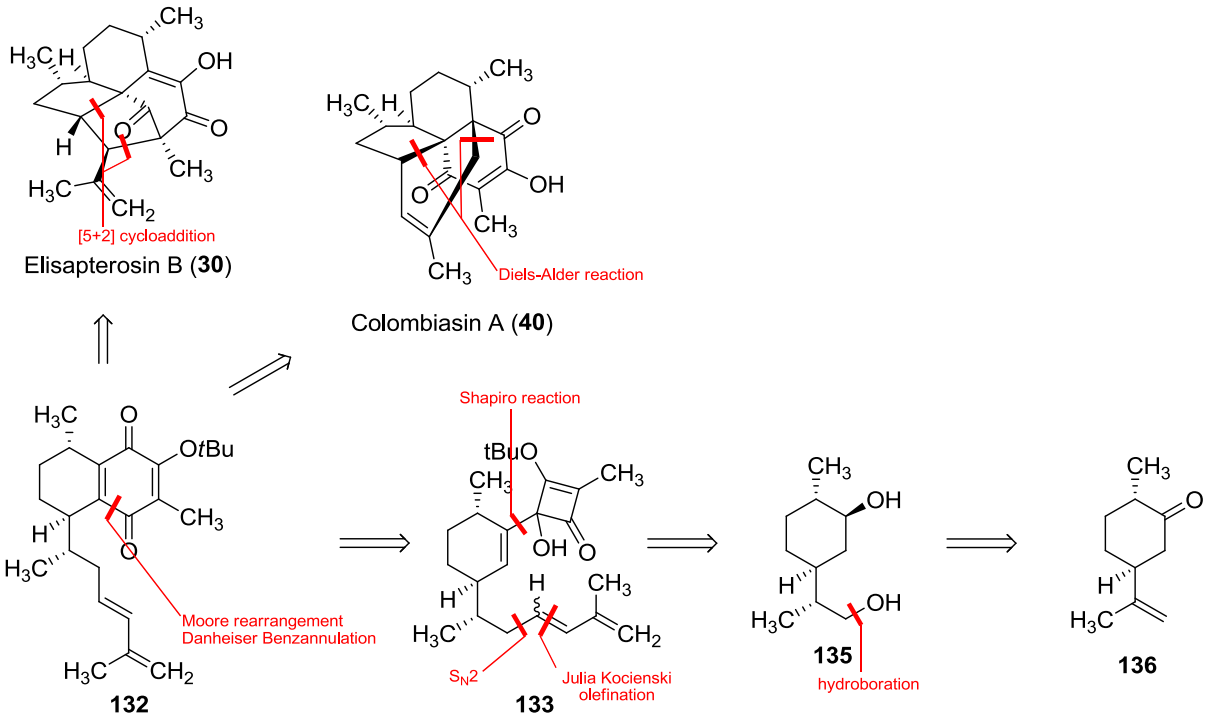


Scheme 15. Rychnowsky's Total Synthesis of Elisapterosin B (**30**) and Colombiasin A (**40**)

final step. Reduction of the carbonyl group under Luche conditions at C-17 was necasseary to prevent aromatization in the following steps. The acetate group was exchanged with Lithium dimethylcuprate through a S_N2 reaction, followed by hydrogenation of the double bond. Oxidation with DMP gave compound **129** with the desired quinone system. Treatment with DBU and interruption with air followed by treatment with Zn-dust and protection gave the desired product. Cleavage of the TIPS protecting group with HF/py and oxidation afforded **130**. Wittig reaction of **131** with **130** gave the side chain with an E/Z-ratio of 3:1. Deprotection with potassium carbonate and oxidation with air gave precursor **121.** Elisapterosin B (**30**) was gained upon treatment of **121** with boron trifluoride which reacted in a 5+2 cycloaddition. Elisapterosin B (**30**) was synthesised in 16 steps with an overall yield of 2 %. The same precursor was used to produce Colombiasin A (**40**) through an intramolecular Diels-Alder reaction and cleavage of the methyl ester with aluminium chloride and dimethylaniline. Colombiasin A (**40**) was synthesized in 17 steps with an overall yield of 3 %.[70]

5.5 Total Synthesis of Elisapterosin B and Colombiasin A: Harrowven's Approach

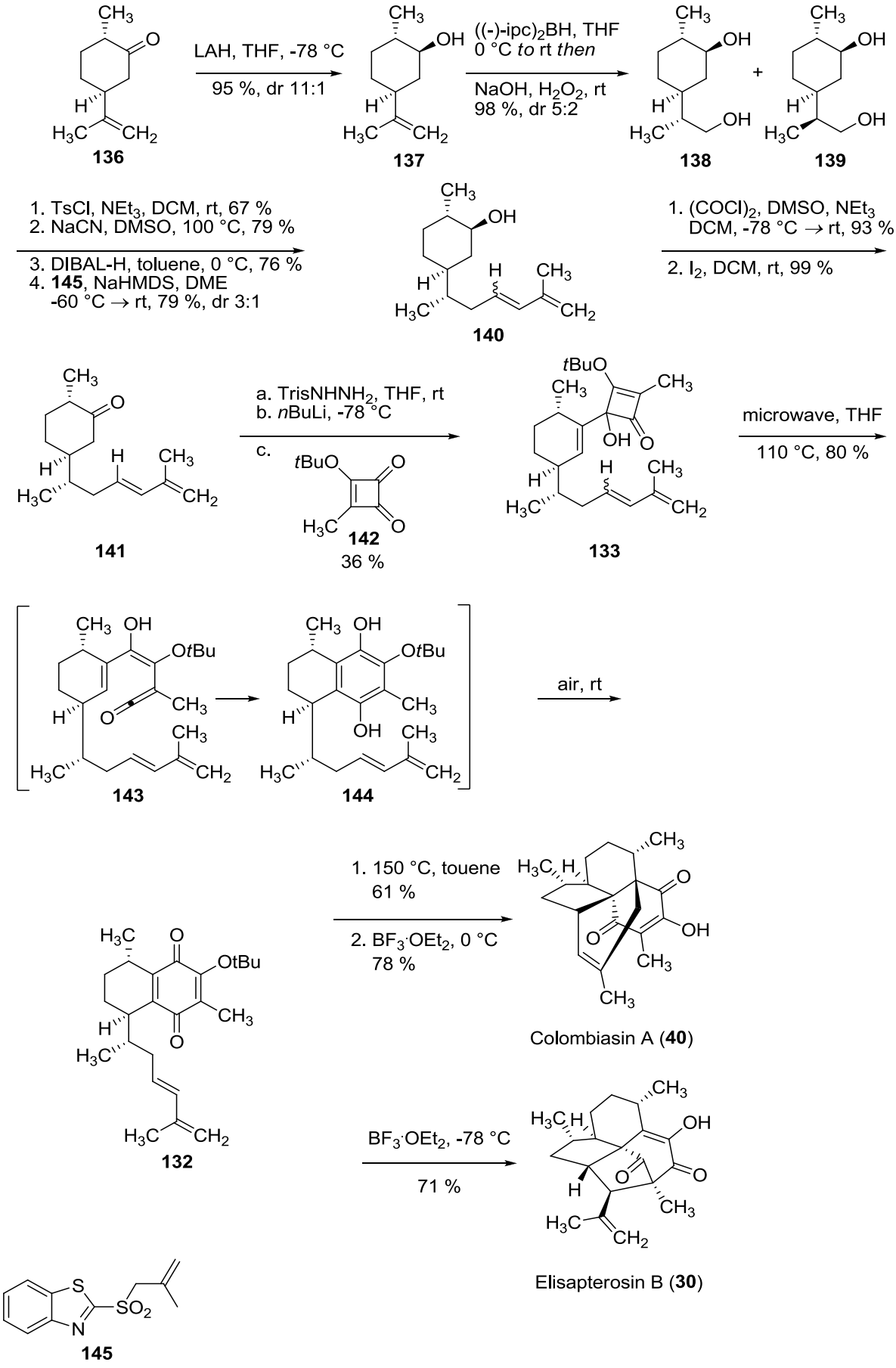
In 2005 Harrowven's and co-workers also reported the total synthesis of Elisapterosin B (**30**) and Colombiasin A (**40**). The retrosynthetic plan is shown in Scheme **16**. Harrowven also wanted to produce Elisapterosin B through a [5+2]-cycloaddition and Colombiasin A (**30**) through a Diels Alder reaction like Rychnowsky did but from a diffrent precursor. Precursor **132** should be formed by a Moore rearrangement followed by a Danheiser Benzannulation. Intermediate **133** should be built up by a Shapiro reaction and a Julia-Kocienski olefination out of **135**. This compound should be available from dihydrocarvone (**136**) through a hydroboration reaction.



Scheme 16. Harrovwen's Retrosynthetic Plan of Elisapterosin B (**30**) and Colombiasin A (**40**)

The total synthesis of Harrowven is shown in Scheme **17**. As starting material Harrowven and co-workes have chosen commercially available (–)-dihydrocarvone (**136**). Reduction of the keto moiety with LAH gave alcohol **137**, followed by a hydroboration to give a disteromeric mixture of alcohols **138** and **139** in ratio of 5:2. Conversion of the primary alcohol to a cyanide and reduction with DIBAL-H followed by Julia-Kocienski olefination lead to compound **140** with an E/Z ratio of 3:1. The secondary alcohol was oxidised by a Swern oxidation and the E/Z mixture was converted to the E–double bond by treatment with iodine. Intermediate **141** was transferred to **133** through a Shapiro reaction, followed by a Moore rearrangement to **143.** This compound cyclized to the desired product **144**. Oxidation prompted by air gave quinone **132**. This compound was the precursor to produce Elisapterosin B (**30**) and Colombiasin A (**40**). It differs from the Rychnowsky's intermediate **121** by the *t*Bu protecting group.

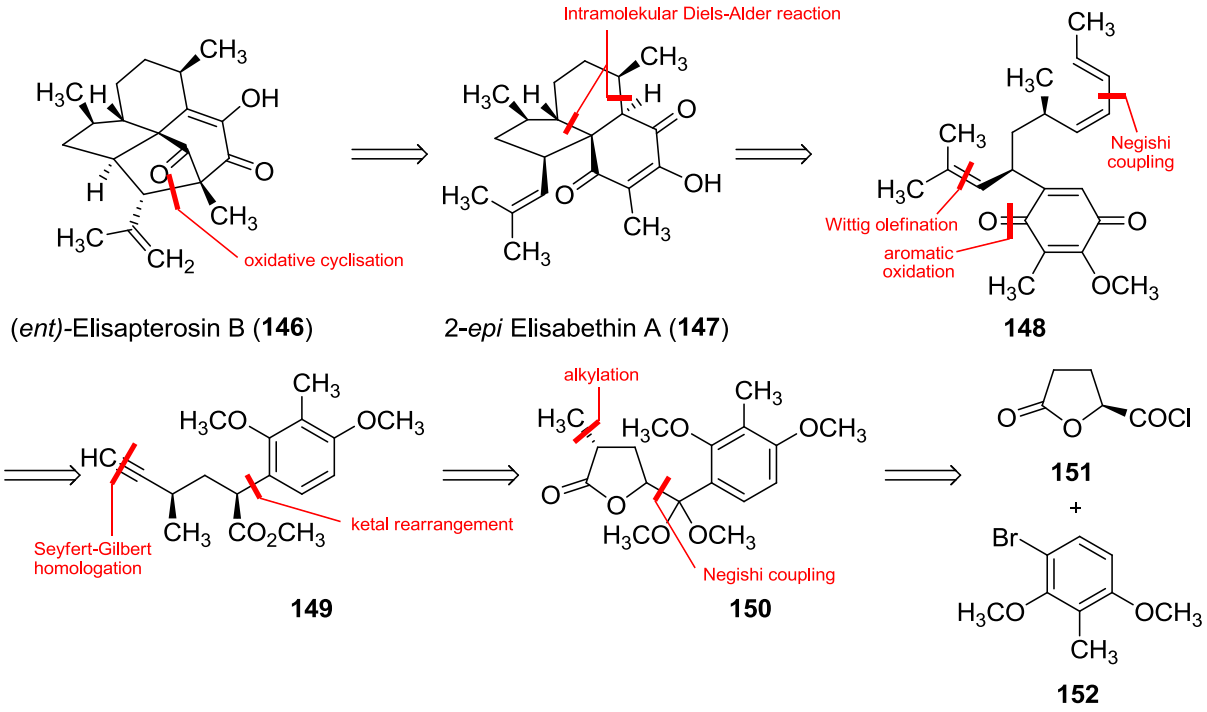
Elisapterosin B (**30**) was obtained through treatment of **132** with boron trifluoride which reacted in a 5+2 cycloaddition. Elisapterosin B (**30**) was synthesized in 11 steps with an overall yield of 4%. The same precursor was used to produce colombiasin A (**40**) through an intramolecular Diels-Alder reaction and cleavage of the *t*Bu protecting group with boron trifluoride. Colombiasin A (**40**) was synthesized in 12 steps with an overall yield of 3%.[71]



Scheme 17. Harrovwen's Total Synthesis of Elisapterosin B (**30**) and Colombiasin A (**40**)

5.6 Total Synthesis of (*ent*)-Elisapterosin B: Rawal's Approach

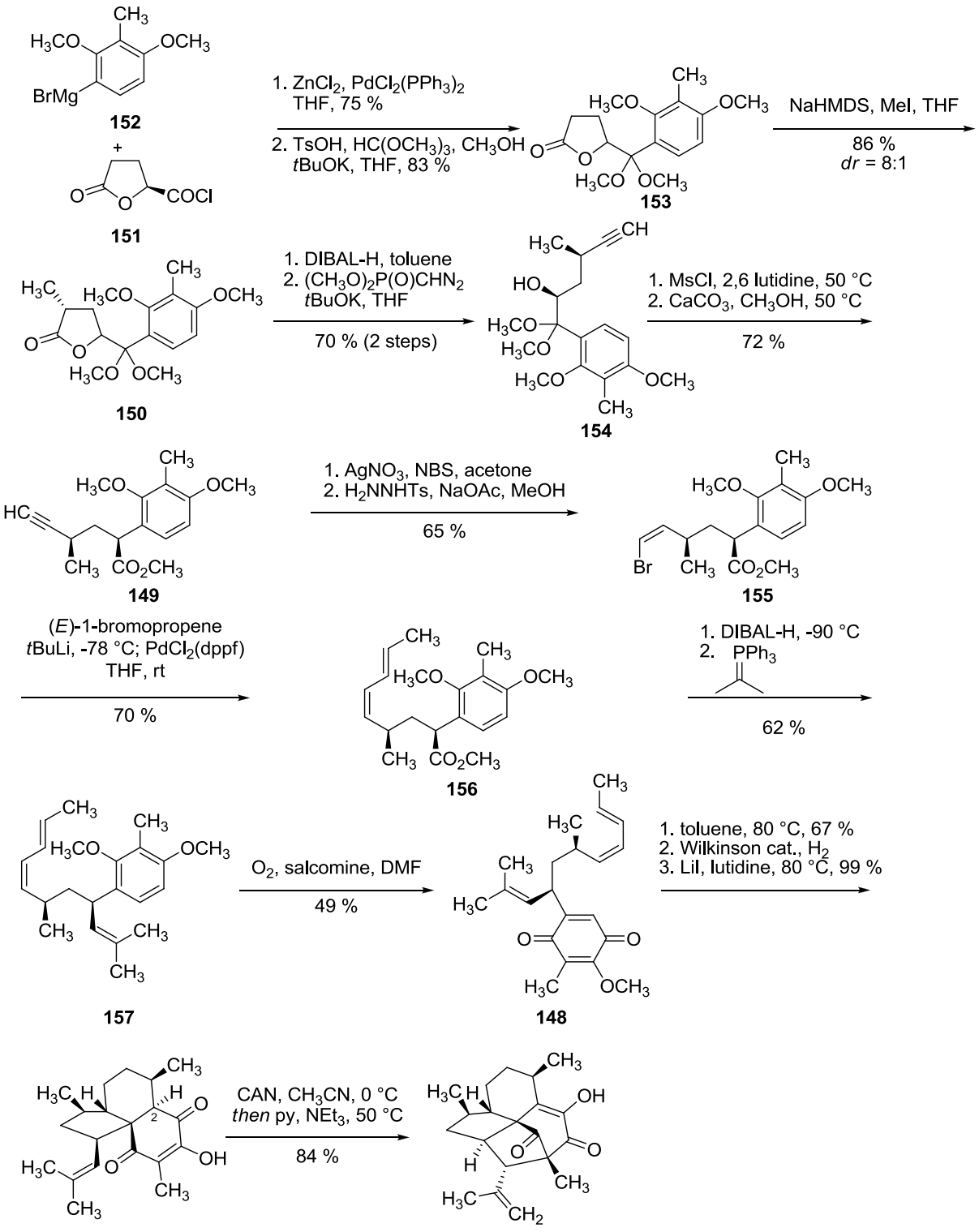
In 2003 Rawal and co-workers published the total synthesis of (*ent*)-elisapterosin B (**146**). The tetracyclic system should be formed through an oxidative cyclization from precursor 2-*epi* Elisabethin A (**147**).This precursor should be formed by a Diels-Alder cycloaddition out of intermediate **148**. The isopropenyl group of this compound could be introduced through an olefination reaction. The diene for the Diels-Alder cycloaddition could be built up by a Negishi reaction. A Seyfert-Gilbert homologation should built up the alkyne moiety. The side chain of **149** should be built up through a Ketal rearrangement. Precursor **150** should be produced through a Negishi-coupling of **151** and **152** followed by a α-alkylation.



Scheme 18. Rawal's Retrosynthetic Plan of (*ent*)-Elisapterosin B (**146**)

The total synthesis of (*ent*)-elisapterosin B (**146**) is shown in Scheme **19**. Rawal has chosen commercially available *S*-(+)-tetrahydro-5-oxo-2-furancarboxylic acid chloride (**151**) and aromatic compound **152.** Those reagents were coupled under Negishi conditions. Treatment with trimethylorthoformate led to compound **153.** Enolization of intermediate **153** with NaHMDS and treatment with methyliodide yielded a diastereomeric mixture of compound **150** in a ratio of 8:1. Reduction of the lactone and opening by Seyfert-Gilbert homologation gave alkyne **154.** Mesylation of the secondary hydroxyl group followed by basic conditions

led to a pinacol type ketal rearrangement of the produced carbocation and formed compound **149**. Terminal bromination followed hydrogenation of the alkyne afforded alkene **155**. The bromoalkene **155** was cross-coupled with (*E*)-1-bromopropene. The ester functionality was reduced to the aldehyde followed by a Wittig olefination to afforded compound **157.** Oxidation with salcomine and oxygen gave desired quinone **148.** Heating the diene in toluene led to a intramolecular Diels Alder reaction followed by hydrogenation with Wilkinson's catalyst and demethylation to generat 2-*epi*-Elisabethin A (**147**). Treatment with CAN led to an oxidative cyclization and treatment with base gave (*ent*)-Elisapterosin B (**146**). They were able to produce (*ent*)-Elisapterosin B (**146**) in 17 steps with an overall yield of 2%.[72]

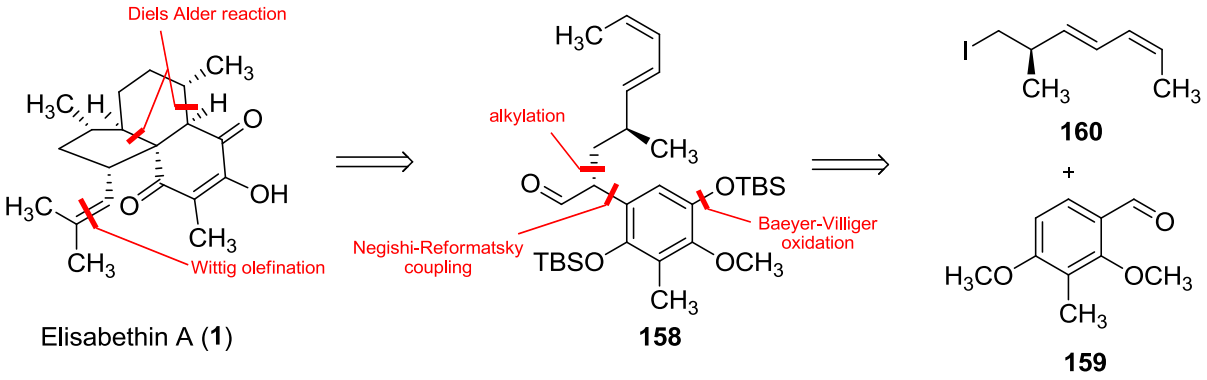


Scheme 19. Rawal's Total Synthesis of (*ent*)-Elisapterosin B (**146**)

6 Previous Approaches in the Mulzer group

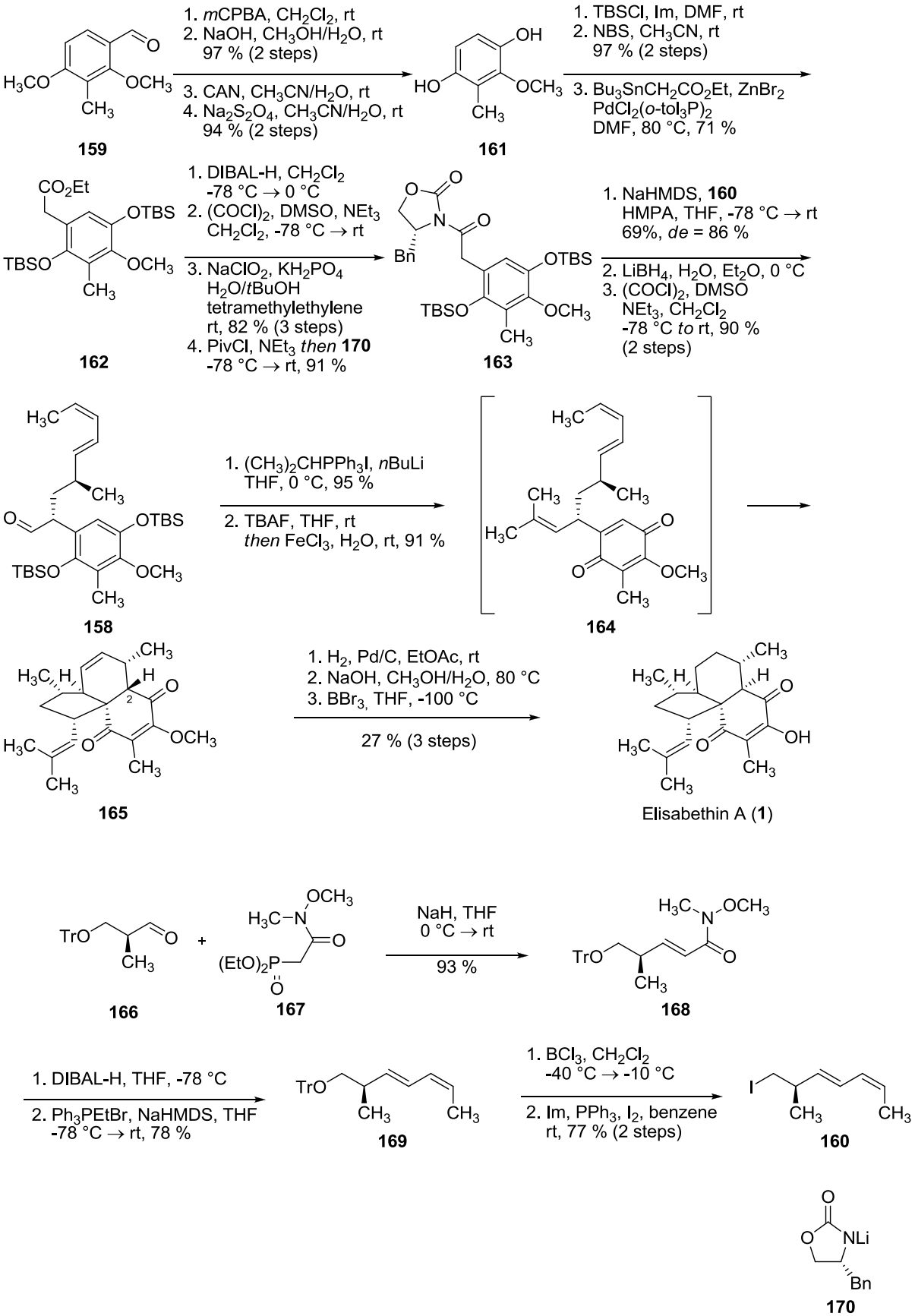
6.1 A biomatic Diels-Alder-Approach toward a Total Synthesis of Elisabethin A

Mulzer and Heckrodt published in 2003 the total synthesis of elisabethin A (**1**). Their retrosynthetic plan is shown in Scheme **20**. The finale system should be built up through an Intramolecular Diels-Alder cyclization. The isopropyl side chain should be introduced through a Wittig olefination. Precursor **158** should be produced with a stereocontrolled α-alkylation with intermediate **160** and a Negishi-Reformatsky coupling. As starting point for their synthesis they used compound **159.** The retrosynthic plan is shown in Scheme **20.**



Scheme 20. Mulzer's Retrosynthetic Plan of Elisabethin A (**1**)

Mulzer and co-workers started their synthesis from commercially available aldehyde **159**. Baeyer-Villiger oxidation of compound **159** followed by hydrolysis gave the desired phenol. An oxidation/reduction sequence led to hydroquinone **161**. TBS-protection of the free alcohols and bromination with NBS followed by a Negishi-Refomatsky coupling yielded intermediate **162**.[73] Reduction with DIBAL-H and oxidation led to the corresponding acid which was transformed to Evans oxazolidinone **163.** Enolization and treatment with **160** led to a stereoselective alkylation product. Reductive cleavage of the auxiliary and oxidation afforded aldehyde **158**. Treatment with Wittig reageant and deprotection of the TBS-ethers gave the intramolecular Diels-Alder precursor. The free alcohols were immediately oxidized to the quinone system and afforded tricycle **165**. The transition state of the Diels-Alder reaction first was published as *endo* and then corrected in an *exo*-transition state.



Scheme 21. Mulzer's Total Synthesis of Elisabethin A (**1**)

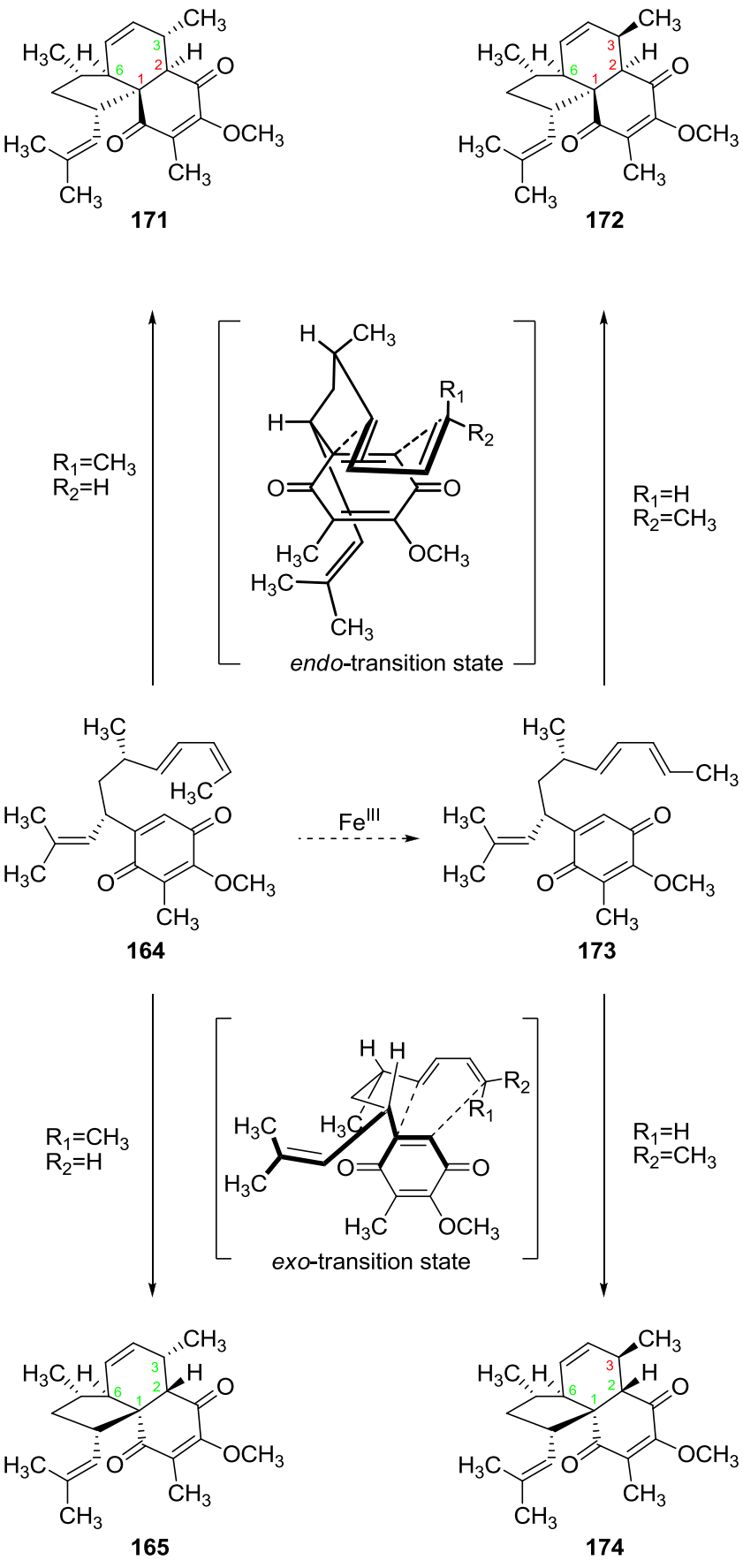
Treatment with Pd on activated charcoal and molecular hydrogen reduced the less hindered double bound. Epimerization of C-2 and cleavage of the methyl-ether with boron tribromide gave Elisabethin A (**1**).

Compound **160** for stereoselective *α*-alkylation was produced out of aldehyde **166.** Desired (*E*)-alkene **168** was obtained with a HWE-olfination followed by selective reduction of the Weinreb amide with DIBAL-H and Wittig reaction afforded compound **154**. Cleavage of the trityl-protecting group with boron trichloride and Appel-reaction gave diene **160.**

Mulzer and co-workers reported the total synthesis of elisabethin A (**1**) in 19 steps and 7 % overall yield over the longest linear sequence.[74]

6.2 Doubt about the Correctness of the Synthesis of Elisabethin A

Prof. Zanoni expressed his doubt about the accuracy of Prof. Mulzer and Heckrodt`s synthesis of Elisabethin A (**1**) because the published ^{13}C-spectra don't fit with the natural ones. To his opinion its necessary to take a closer look to the intramolecular Diels Alder reaction, because it didn't react in the way as published. There are only a few examples in literature for involvement of acyclic terminal (*Z)*-dienes,[75] because they like to undergo a thermally induced [1,5] H shift[76] or/and a thermal *Z* or *E* isomerisation[77].In literature there are much more examples for failed attempts to produce a intramolecular Diels Alder reaction with (*E,Z)* and (*Z,Z)* dienes than successful ones.[78] Generally Lewis acid and low temperature conditions prefer an *endo*-transition state and also an electron-withdrawing group at the dienophile prefer an *Endo*-transition state.[79] Therefore iron trichloride which has been shown to be a great oxidation reagent for TBS deprotected hydroquinone **158**, should help to prefer an *endo*-transition state and also polarize the carbonyl π-bonds in the quinone **164.**[80] Prof Mulzer described the *endo*-transition as an exo-transition state in a correction, but the HOMO/LUMO interaction of the (*E,Z)*-diene and the quinoid dienophile, looks really challenging because of the steric situation. From literature it is known that a *Z* to *E* isomerization of terminal olefins could occur with iron trichloride,[81] which would lead to stereoisomeric products. [82] The possible products from the intramolecular Diels Alder reaction are shown in Scheme **22.**



Scheme 21. Possible Products from the intramolecular Diels Alder Reaktion[82]

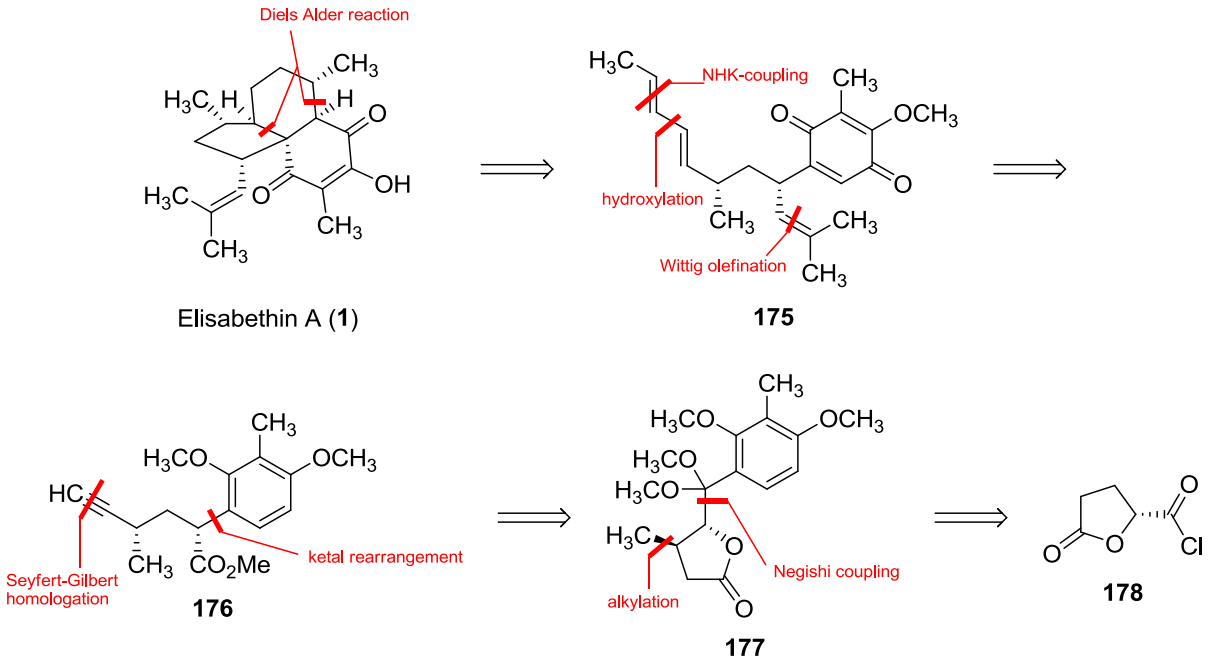
7 Results and Discussion

Because of the doubts about the total synthesis of Elisabethin A (**1**), we wanted to prove the synthesis by a new one and new spectral data.

7.1 First rout to produce Elisabethin A

7.1.1 First retrosynthetic plan

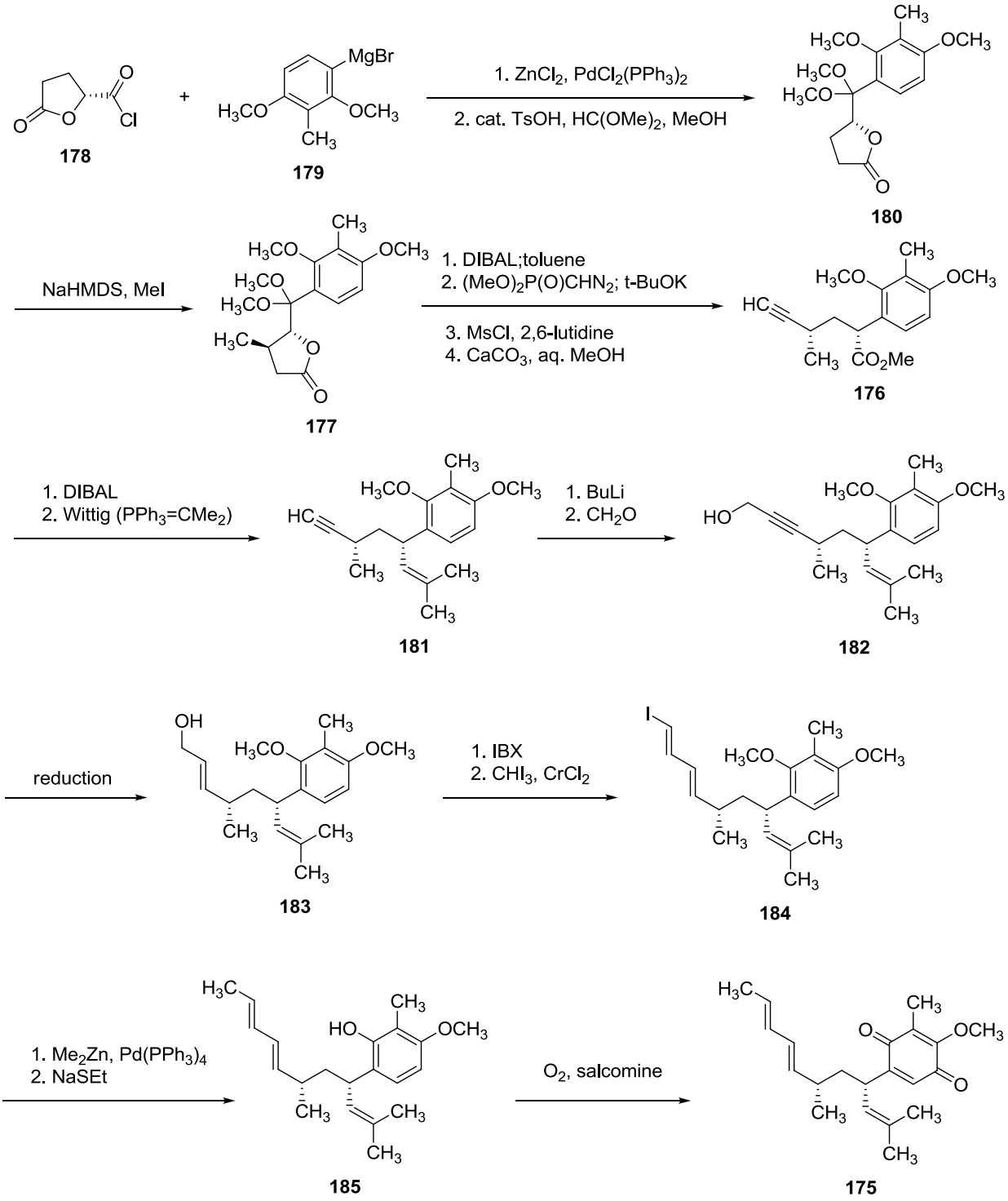
Our retrosynthetic plan is shown in Scheme **22**. The finale backbone should be built up through an Intramolecular Diels-Alder cyclisation. The isopropenyl side chain in precursor **175** should be introduced through a Wittig olefination. The diene system should be built up through a hydroxylation followed by a NHK-coupling from precursor **175**. Intermediate **175** could be formed through a Seyfert-Gilbert homologation reaction and the appendix should be built up through a rearrangement reaction. Precursor **177** should be produced through a Negishi-coupling of **178** and **179** followed by an alkylation.



Scheme 22. First retrosynthetic plan

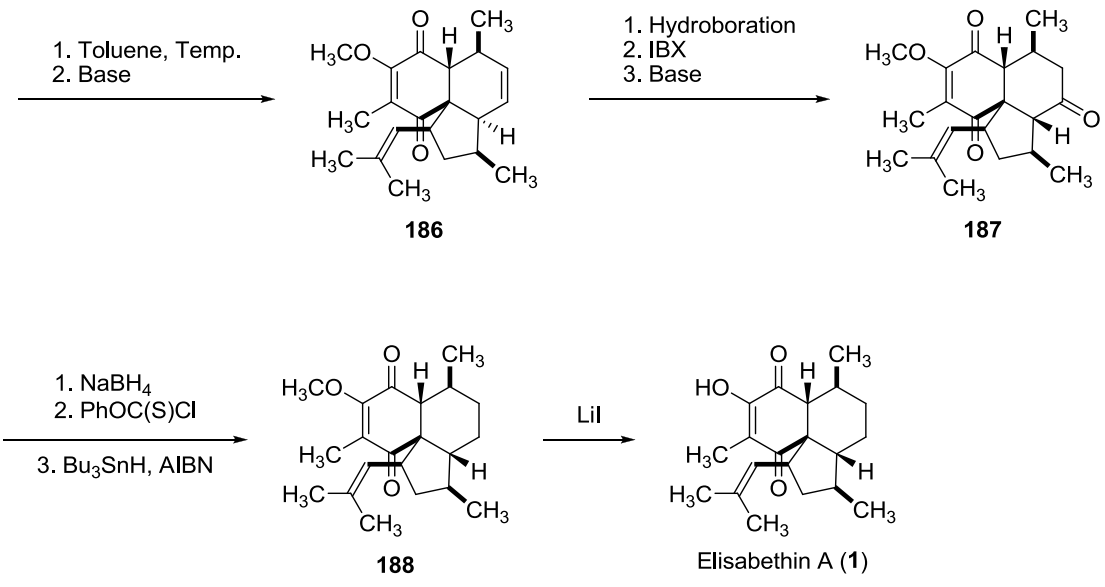
7.1.2 First synthesis plan

Our first synthesis plan is shown in schemes **23** and **24.** As starting materials for our synthesis we have chosen compounds **178** and **179.** Those reagents should be coupled under Negishi conditions. Treatment with trimethylorthoformate should lead to compound **180.**



Scheme 23. First Synthesis Plan (part 1)

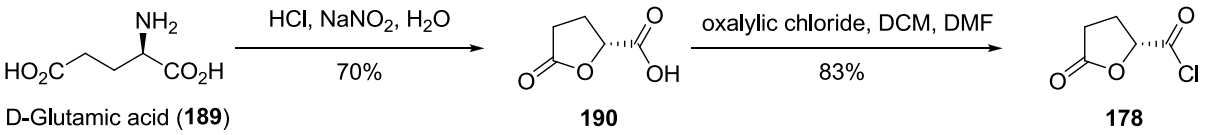
Enolization of the intermediate **180** with NaHMDS and treatment with methyl iodide should form compound **177**. Reduction of the lactone and opening by Seyfert-Gilbert homologation followed by mesylation of the secondary hydroxyl group and basic conditions should lead to a pinacol type ketal rearrangement of the produced carbocation and form compound **176**. Reduction of the ester moiety and treatment of the aldehyde with Wittig reagent should give intermediate **181.** Deprotonation with BuLi and treatment with formaldehyde should give compound **182.** Reduction of the triple bond with molecular hydrogen should afford **183.** Oxidation with IBX of the primary hydroxyle group and treatment with iodoform under NHK conditions should give compound **184.** Transformation of the iodide into a methyl group and deprotection followed by Salcomine oxidation should afford quinone **175.** Heating in toluene an intramolecular Diels-Alder reaction should occur and epimerization under basic conditions should give compound **186** (Scheme **24**). Hydroboration of the less hindered double bound, followed by oxidation with IBX and epimerization should lead to compound **187**. Reduction of the keto moiety and cleavage of hydroxyl group and demethylation hould afford elisabethin A (**1**).



Scheme 24. First Synthesis Plan (part 2)

7.1.3 Failure of the first synthesis plan

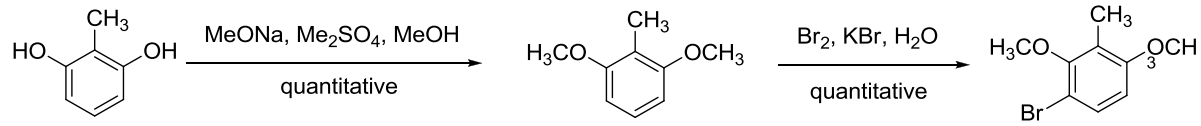
As starting material to produce precursor **178** we have chosen *D*-Glutamic acid. Treatment with hydrochloric acid and sodium nitrite gave intermediate **190** with a double inversion. The free acid was turned into the corresponding acid chloride **178** with oxalylic chloride. The synthesis of intermediate **178** is shown in Scheme **25**.



D-Glutamic acid (**189**) **190** **178**

Scheme 24. Synthesis of Intermediate **178**

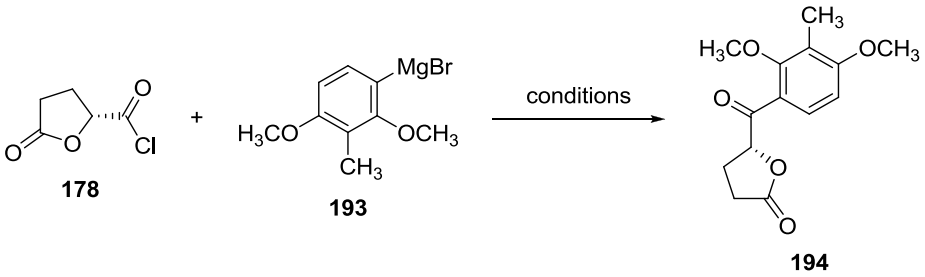
As starting material for **179** we have chosen commercially available 2-methylbenzene 1,3-diol (**191**). Treatment with commercially available sodium methoxide and dimethyl sulphate gave intermediate **192** in excellent yield. Electrophilic aromatic substitution of **192** with bromine and potassium bromide gave **179** also in quantitative yield.



2-methylbenzene-1,3-diol (**191**) **192** **179**

Scheme 25. Synthesis of intermediate **179**

With compound **178** and **179** in hand we tried to produce precursor **193** under the same conditions as Rawal and co-workers did in his total synthesis of (*ent*)-elisapterosin B with the other enantiomer.[83] Treatment of **179** with activated magnesium did not work very well, to give our desired intermediate. Compound **178** has shown to be quite unstable and needed to be distilled directly before use. Unfortunately all attempts to perform the Negishi coupling did not work and gave an inseparable mixture of products. There was no trace of the desired product in mass spectra and we were only able to re-isolate protonated **193**. At this point we decided to quit this synthetic plan and switched to different one.



Scheme 26. Negishi coupling of intermediate **178** and **193**

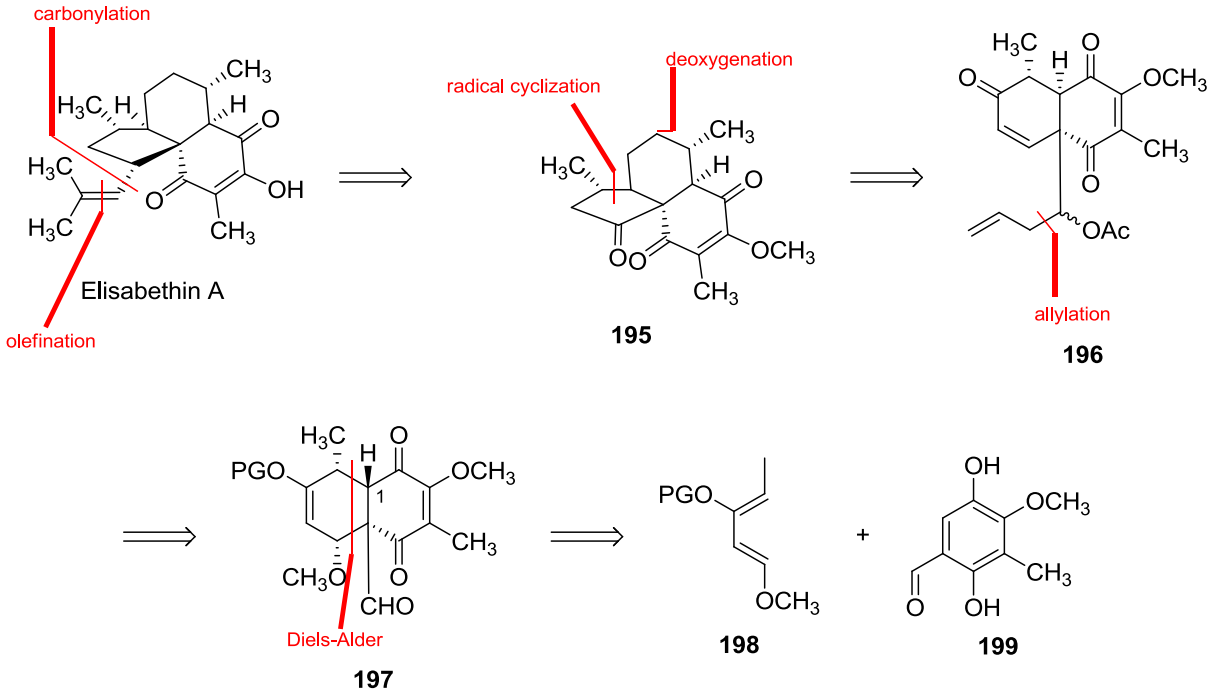
Reaction conditions	Temperature	Yield
$ZnCl_2$, $PdCl_2(PPh_3)_2$, THF	rt	decomposition
$ZnCl_2$, $PdCl_2(PPh_3)_2$, THF	0°C	decomposition
$ZnCl_2$, $PdCl_2(PPh_3)_2$, THF	-20°C	decomposition
$ZnCl_2$, $PdCl_2(PPh_3)_2$, THF	-78°C	decomposition
$ZnCl_2$(0,1M), $PdCl_2(PPh_3)_2$, THF	rt	decomposition
$ZnCl_2$(0,1M), $PdCl_2(PPh_3)_2$, THF	-78°C	decomposition

Table 1. Negishi coupling of intermediate **178** and **193**

7.2 Second Route to Produce Elisabethin A

7.2.1 Second Retrosynthetic Plan

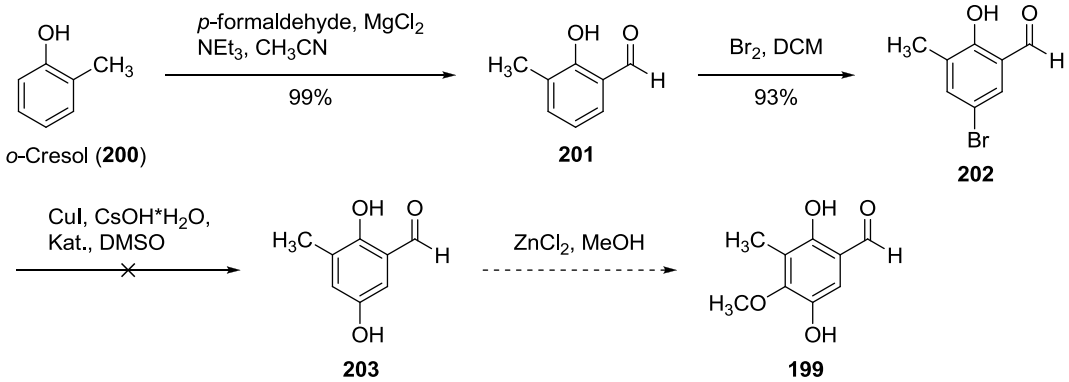
Our second retrosynthetic plan of Elisabethin A (**1**) has the advantage to build up the six stereocenters step by step, which should allow us to prove the stereochemistry of every single carbon atom. The first steps are adapted of the work of J.D. White's, where he used a Diels-Alder reaction to build up the decaline system.[84] He has also shown a way to epimerize C-2 after the Diels-Alder reaction, where Rawal wasn't able to epimerise. Our retrosynthetic plan is shown in Scheme **27**. We wanted to build up the side chain by a carbonylation reaction, followed by a Wittig olefination. Precursor **195** should be produced through a radical cyclisation and deoxygenation of the keto moiety. Intermediate **196** is planned to be built up through a chemoselective allylation of aldehyde **197** and generation of the double bound for the radical ring cyclisation. The bi cyclic backbone of **197** should be build up through a Diels Alder Reaction from precursors **198** and **199**.



Scheme 27. Second Retrosynthetic Plan

7.2.2 Route to Hydroquinone 199

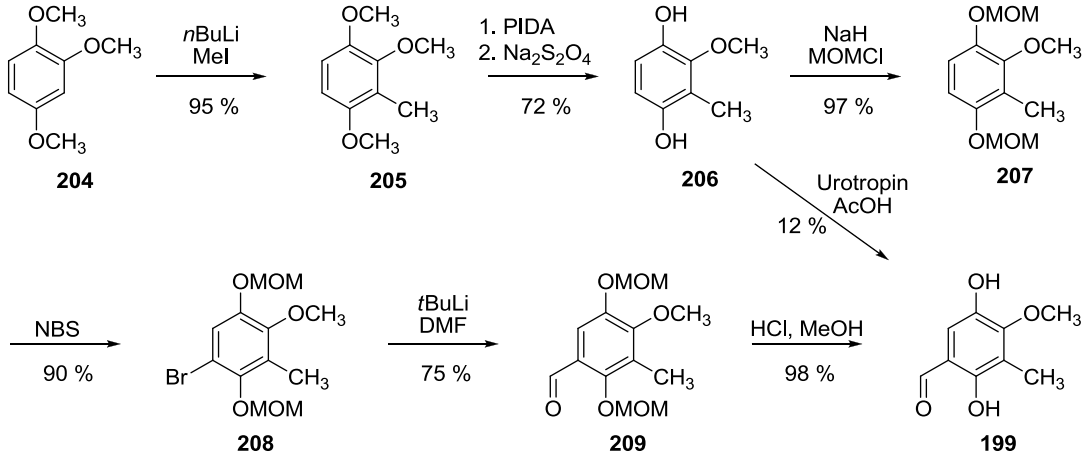
From earlier results from our group we knew how to produce hydroquinone **199**. While trying to reproduce the synthesis we discovered that it is really difficult to obtain the given yields. So we decided to find another route to afford hydroquinone **199.**[85] Our plan to build up **199** is shown in Scheme **28**. As starting material for the synthesis we chose commercially available *o*-Cresol (**200**). Treatment with *p*-formaldehyde and magnesium chloride gave compound **201** in perfect yield. Bromination with bromine afforded intermediate **202.**



Scheme 28. Plan to Synthesize Compound **199**

Since all attempts to transform **202** into **203** failed, we switched to another route to produce compound **199** developed from other members from our group.[86]

As starting material for the synthesis of intermediate **199** we chose commercially available 1,2,4-Trimethoxybenzene. Methylation with *n*BuLi and iodomethane gave compound **205** in perfect yield.[87] Oxidation with (diacetoxyiodo)benzene afforded only the para-quinone and reduction with sodium dithionite gave the corresponding hydroquinone.[88] Deprotonation with sodium hydride followed by addition of chloromethyl methyl ether afforded compound **207.**[89] Electrophilic aromatic bromination gave **208.**[90] Metalation with *t*BuLi and quenching with DMF yielded compound **209**. Deprotection under acid conditions afforded precursor **199** (Scheme **28**)**.**



Scheme 28. Rout to hydroquinone **199**

All attempts to modify the step **208** to **209** led to poorer yields.

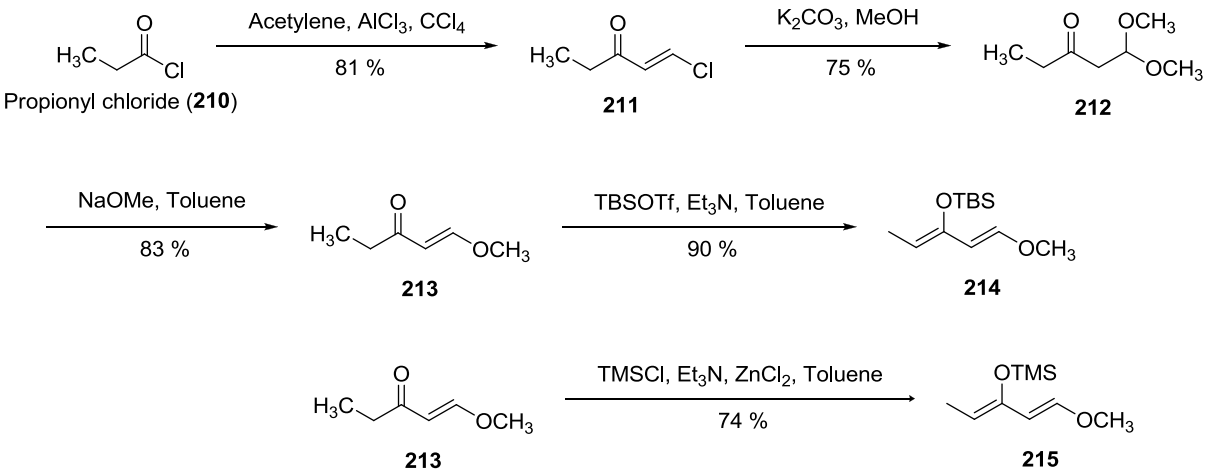
Reaction conditions	Temperature	Yield
*t*BuLi, DMF	rt	decomposition
*t*BuLi, DMF	-20°C	decomposition
*t*BuLi, DMF	-78°C	75 %
*t*BuLi, DMF	-100°C	71 %
*s*BuLi, DMF	-20°C	decomposition
*s*BuLi, DMF	-80°C	69 %

Table 2. Conditions of Transmetalation and Formylation to Compound **209**

We were able to develop an alternative access to precursor **199**. The synthesis contains 7 steps with an overall yield of 44 %.

7.2.3 Production of the Dienes for the Diels-Alder Reaction

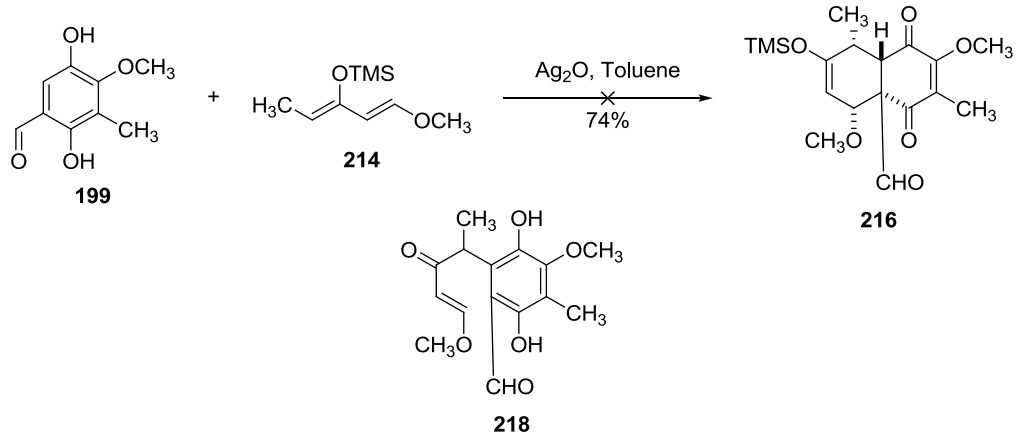
We wanted to use Danishefsky dienes **214** and **215** for the Diels-Alder reaction to produce **197**. The synthesis of these dienes is known from literature and it is shown in Scheme **29.**[96] Treatment of **210** with acetylene and aluminum chloride gave compound **211**, through addition of potassium carbonate and methanol afforded intermediate **212**. The first double bond was built up with sodium methanolate and the second double bond by enolization and protection.



Scheme 29. Synthesis of Danishefsky dienes **214** and **215**

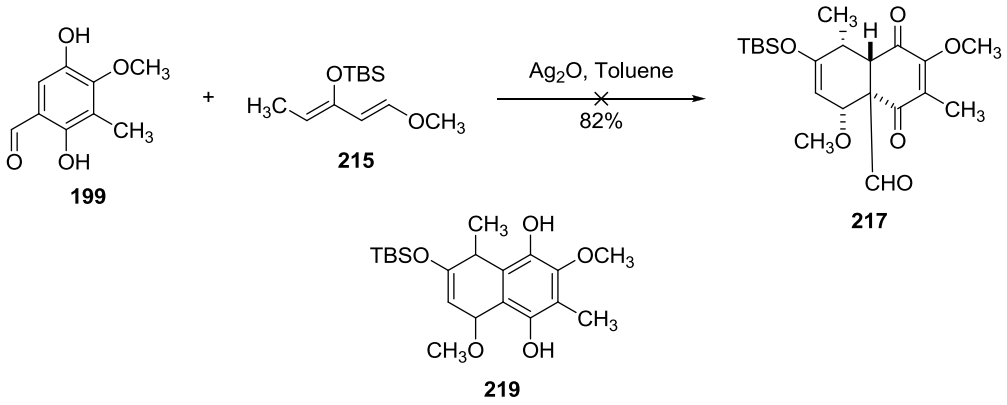
7.2.4 Formation of the decaline system

Treatment of compounds **199** and **215** with silver(I) oxide led to an *in situ* oxidation of hydroquinone **199** to the corresponding quinone. Unfortunately there were no traces of our desired decaline system, but a not expected main product in 74% yield. Spectral analysis showed that not a Diels-Alder reaction took place. The diene reacted in a Mukaiyama Aldol addition to **218** (Scheme **30**). Therefore we switched from TMS protected diene **215** to corresponding TBS protected **214**.



Scheme 29. Reaction of Compounds **214** and **199**

Treatment of **199** and **215** with silver(I) oxide also didn't lead to our desired product **217**. In this case the diene **215** reacted with the *in situ* oxidized hydroquinone in a Diels-Alder reaction and formed the decaline system. The reaction only afforded compound **219**. So we decided to modify compound **199**.



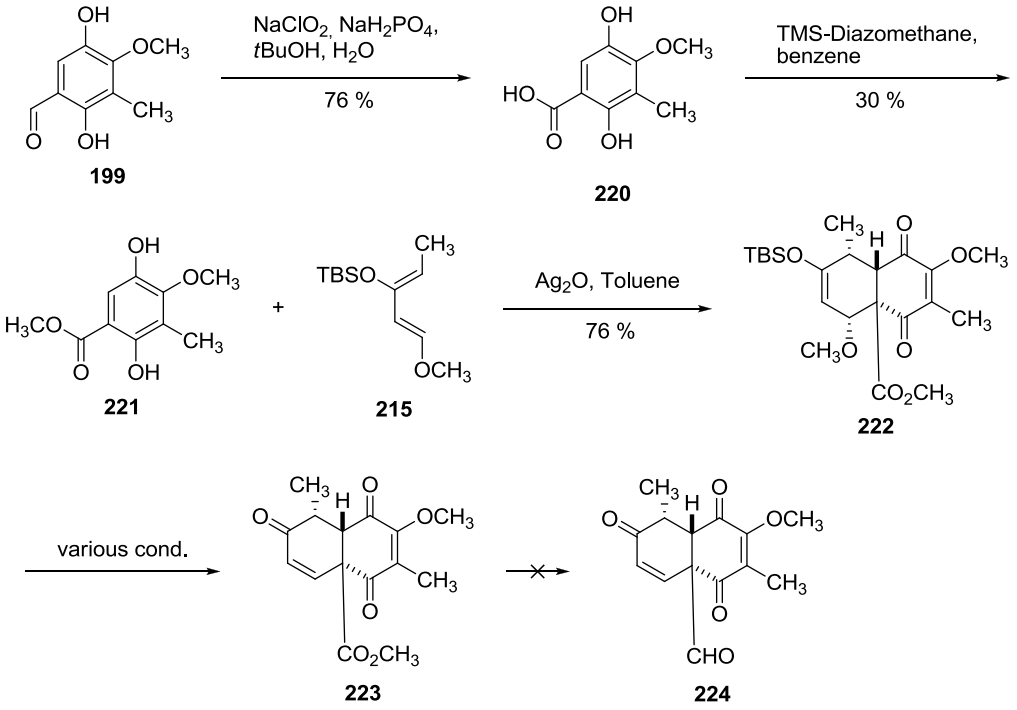
Scheme 30. Reaction of Compounds **215** and **199**

To prevent a deformylation reaction we decided to convert aldehyde **199** into the corresponding ester (Scheme **31**). Through Pinnick oxidation we were able to obtain compound **220** in good yield. Treatment with TMS-Diazomethane gave ester **221**, unfortunately we were not able to get better yields than 30 % at this step. Diels-Alder reaction with diene **215** and *in situ* oxidation with silver(I) oxide gave desired intermediate **222**. Cleavage of the TBS protecting group gave desired compound **223**. The reaction conditions for this step are shown in table **3**.

Reaction conditions	Temperature	Yield
HF in pyridine 70 %, THF	rt	21 %
HF in pyridine 35 %, THF	rt	27 %
H_2SO_4, acetone	rt	quantitive

Table 2. Conditions to produce Compound **223**

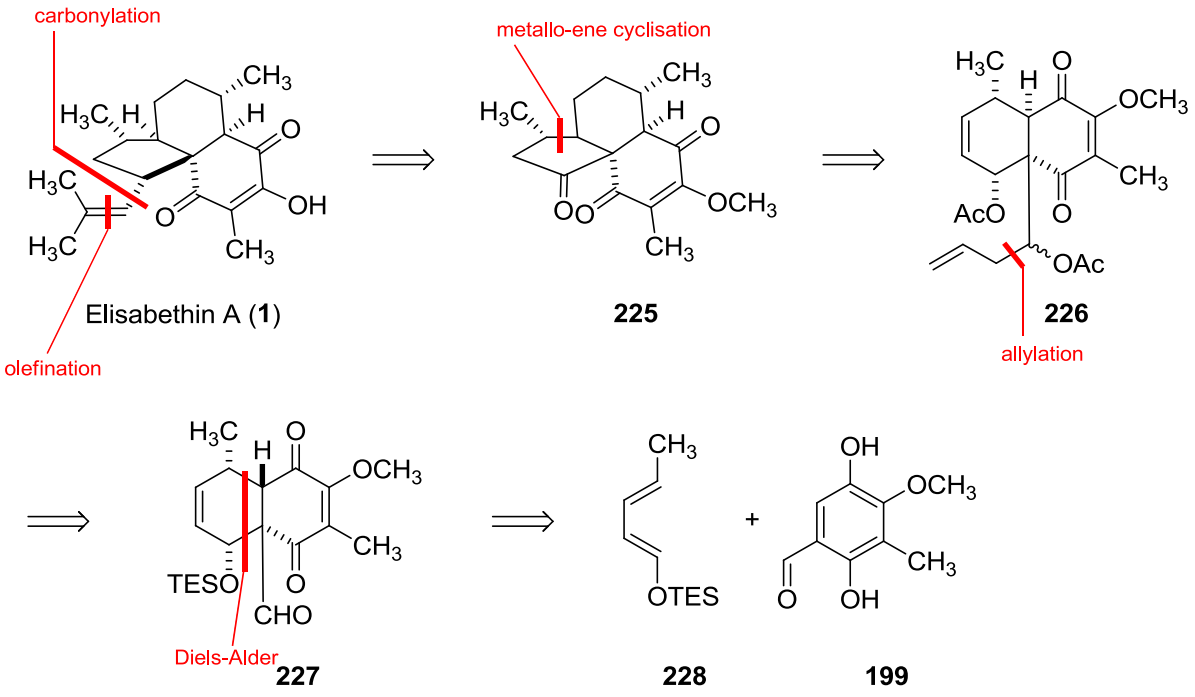
All attempts to reduce the ester moiety selectively to the corresponding aldehyde **224** failed. An oxidation reduction circle also didn't lead to the desired precursor, only decomposition was observed. At this point we decided to switch to an alternative route because without the aldehyde there was no possibility to produce precursor **196** through allylation.



Scheme 31. Conversion of **199** into the Corresponding Ester

7.3 Third Route to produce Elisabethin A

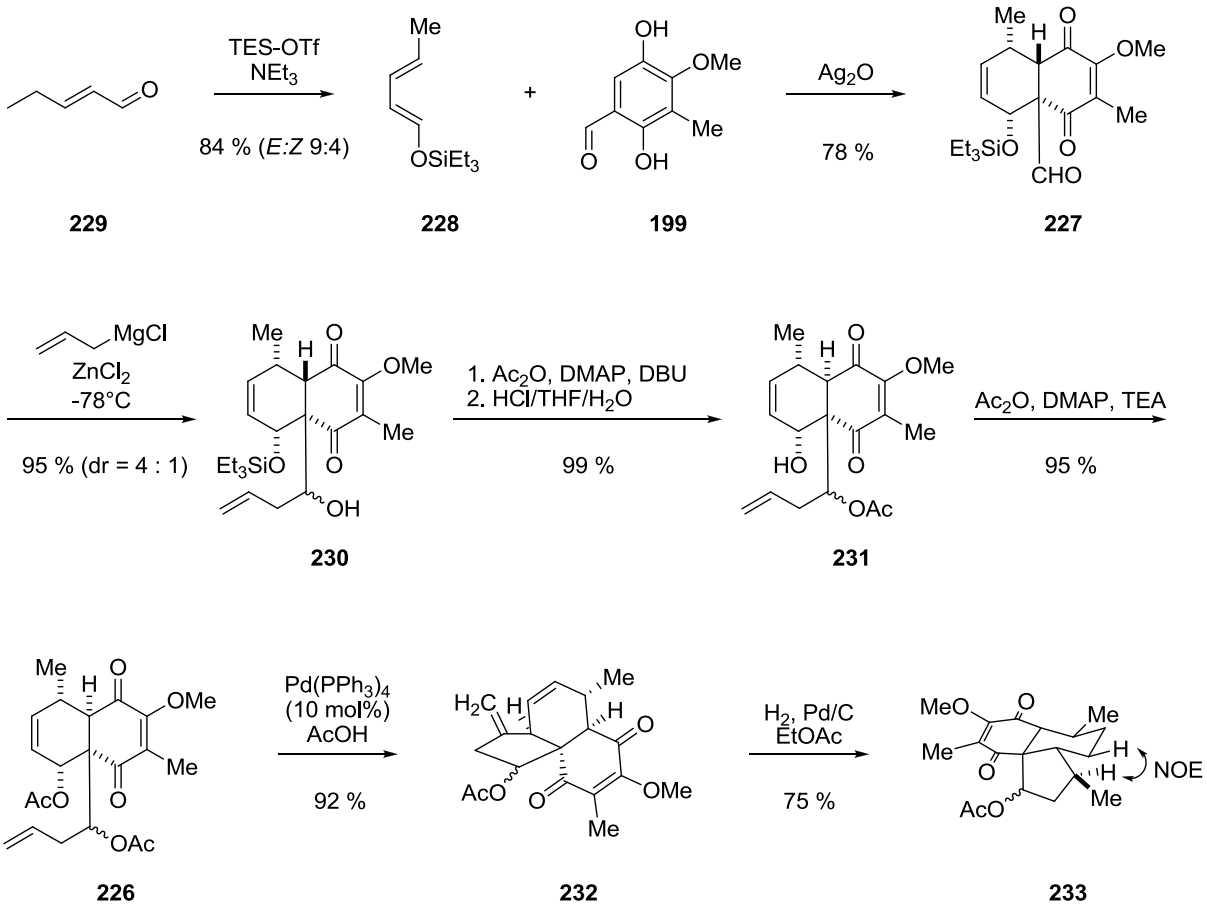
Our third retrosynthetic plan of elisabethin A (**1**) has also the advantage to build up the six stereocenters step by step, which should allow us to prove the stereochemistry of every single carbon atom. The first steps are adapted of the work of J.D. White's work, where he used a Diels-Alder reaction to build up the decaline system.[91] He has also shown a way to epimerise C-2 after the Diels-Alder reaction, where Rawal wasn't able to epimerise. Our retrosynthetic plan is shown in Scheme **32**. We wanted to build up the side chain by a carbonylation reaction, followed by a Wittig olefination. Precursor **225** showen be produced through a metallo-ene cyclisation. Intermediate **226** is planned to be built up through a chemoselective allylation of aldehyde **227**. The two cyclic backbone of **227** should be build up through a Diels-Alder reaction from precursors **228** and **199**.



Scheme 32. Third Retrosynthetic Plan

The synthesis of compound **233** is shown in scheme **33**. As starting material for our third synthesis we also used hydroquinone **199** and diene **228**. The synthesis of **199** is shown in Scheme **28**. Diene 228 was produced by a *γ*-Deprotonation of **229** and trapment of the enolate with triethylsilyl trifluoromethanesulfonate. This reaction yieled an inseparable mixture of isomers with 30- 35% of the requested (E/E) diene. Treatment of **199** with the

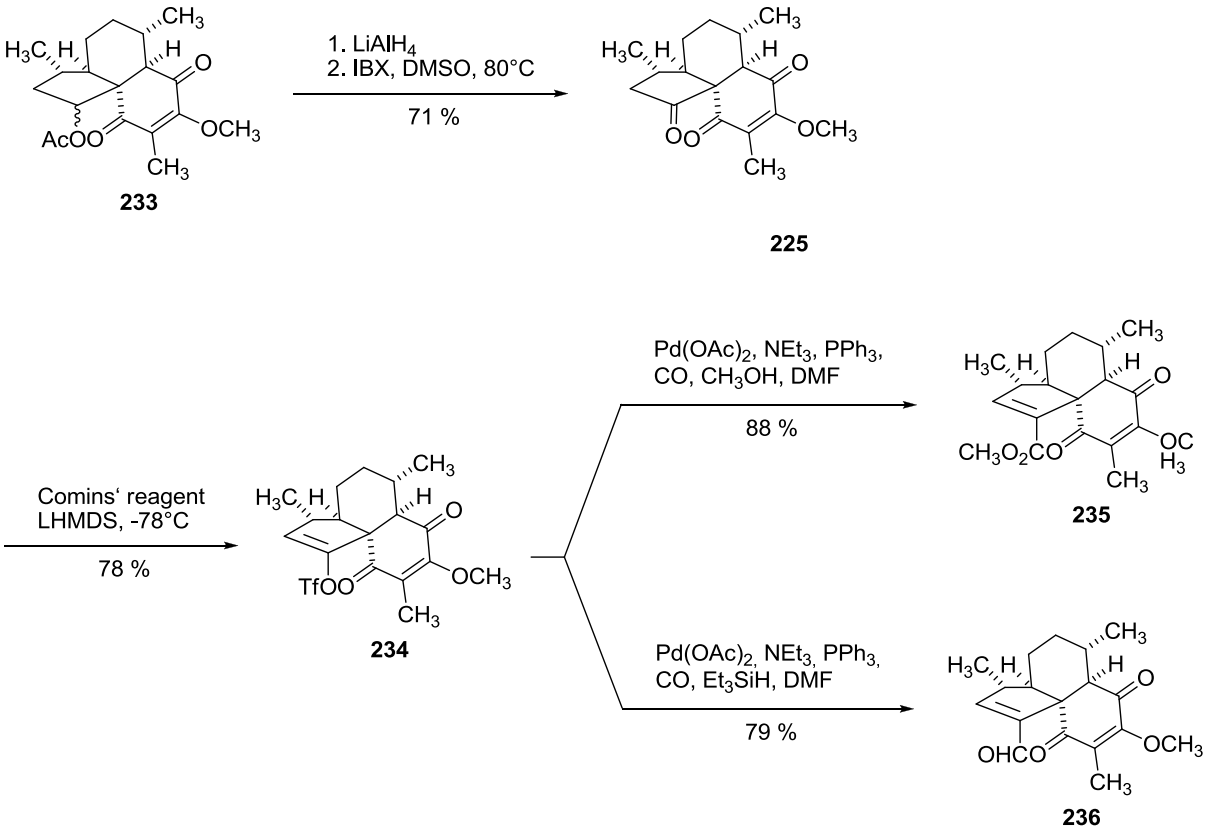
mixture of dienes with silver(I) oxide lead to our desired product **227**. Only the (E/E) diene reacted with the *situ* oxidized hydroquinone **199** in a Diels-Alder reaction. The other dienes were removed through flash chromatography. Treatment of allyl Gringnard with $ZnCl_2$ and addition of **227** after transmetallation led to two diastereomeric homoallylic alcohols in a ratio of 4:1 in good yield. The ratio can be explained by a chelate which deforms compound **227** and prefers one side for the nucleophilic addition. Protection of the homoallylic alcohols with acetic anhydride, epimerization with DBU and cleavage of the silyl ether afforded intermediate **231** in good yield. The precursor for the metallo-ene cyclization was build up through protection of the allylic alcohol with acetic anhydride. The metallo-ene cyclisation with tetrakis(triphenylphosphine)palladium gave the desired product **232.** Treatment with palladium and molecular hydrogen yieled compound **233** with the desired stereochemistry.



Scheme 33. Synthesis of Compound **233**

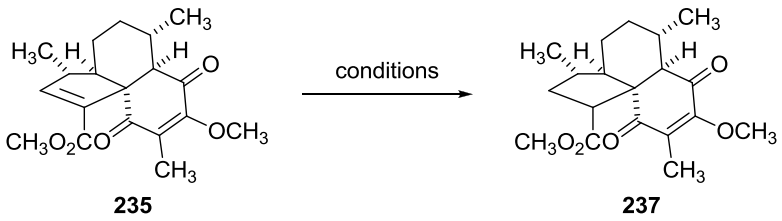
Reduction of the diastereomeric mixture of **233** with lithium aluminium hydride and reoxidation with IBX gave our desired product **225.** Transformation of the keto moiety of **225**

into the corresponding triflate **234** worked smoothly. All attempts to couple the isbutenyl side chain failed, but we were able to transform the triflate into the corresponding ester **235** and aldehyde **236**. (Scheme **34**).



Scheme 34. Synthesis of α,β unsaturated Aldehyde **236** and Ester **235**

With ester **235** and aldehyde **236** in hand we tried to reduce the α,β unsaturated double bond. Only the reduction of the α,β unsaturated double bond of ester **235** using Crabtree's catalyst and molecular hydrogen was successful all other attempts failed. The conditions we tried to reduce fort the ester are shown in table **4**.

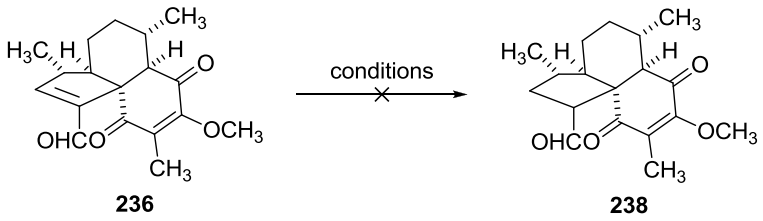


Scheme 35. Reduction of the α,β usaturated double bond of ester **235**

Reaction conditions	Temperature	Yield
H-Cube different catalysts and solvents	rt	decomposition
Raney nickel, H_2	rt	decomposition
Wilkinson's catalyst, H_2, DCM	rt	no reaction
Wilkinson's catalyst, H_2, DCM	40°C	no reaction
Adam‘s catalyst, H_2, EtOH	rt	decomposition
Crabtree‘s catalyst, H_2, DCM	rt	no reaction
Crabtree‘s catalyst, H_2, DCM	40°C	95%

Table 4. Reduction Conditions for the α,β unsaturated Double Bond of ester **235**

All conditions we tried to reduce the α,β usaturated double bond of aldehyde **236** failed. So we decided to introduce the side chain earlier in the synthesis because all attempts to transform compound **237** into the corresponding aldehyde also failed. The conditions we tried for the reduction of aldehyde **236** are shown in table **5.**



236 **238**

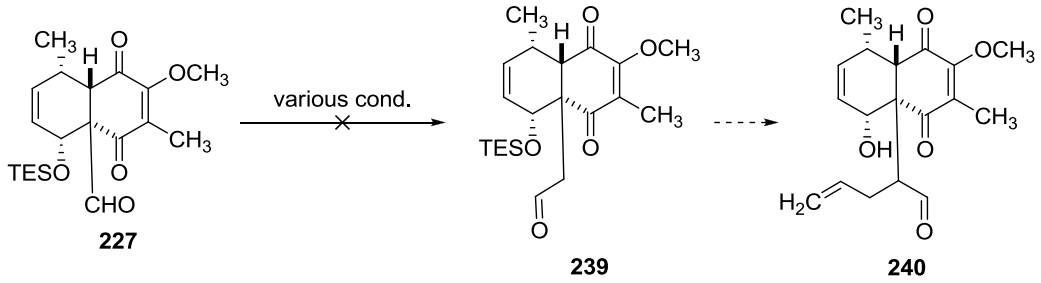
Scheme 36. Reduction of the α,β unsaturated Double Bond of aldehyde **236**

Reaction conditions	Temperature	Yield
Diphenylsilane, $Pd(PPh_3)_4$, $ZnCl_2$, DCM	0°C	decomposition
Wilkinson's catalyst, Et_3SiH, toluene	70°C	decomposition
Et_3SiH, $Pd(PPh_3)_4$, $ZnCl_2$, DCM	rt	no reaction
LAH, Et_2O and IBX, DMSO	rt and 40°C	decomposition
$NiCl_2*6H_2O$, $NaBH_4$, MeOH	0°C	no reaction
Strykers reagent, toluene	rt	no reaction
H-Cube different catalysts and solvents	rt	decomposition
Raney nickel, H_2	rt	decomposition
Wilkinson's catalyst,H_2, DCM	rt	no reaction
Wilkinson's catalyst,H_2, DCM	40°C	no reaction
Adam‘s catalyst, H_2, EtOH	rt	decomposition
Crabtree‘s catalyst, H_2, DCM	rt	no reaction
Crabtree‘s catalyst, H_2, DCM	40°C	no reaction
Crabtree’s catalyst, H_2, $CHCl_3$	60°C	no reaction

Table 5. Reduction conditions for the α,β unsaturated Double Bond of aldehyde **236**

7.3.1 First attempt to introduce the side chain earlier

We discovered that it is really hard to introduce the side chain at the tricyclic system. So we decided to go a few steps back and introduce the side chain earlier. We thought that the best intermediate to install the side chain is compound **227**. Our plan is shown in scheme **37**.



Scheme 37. First attempt to introduce the side chain earlier

Through an introduction of another carbon between the aldehyde moiety and decaline system we wanted to gain a precursor for the allylation (scheme **37**). Unfortunately all experiments to introduce the carbon failed. The reaction conditions are shown in table **6**.

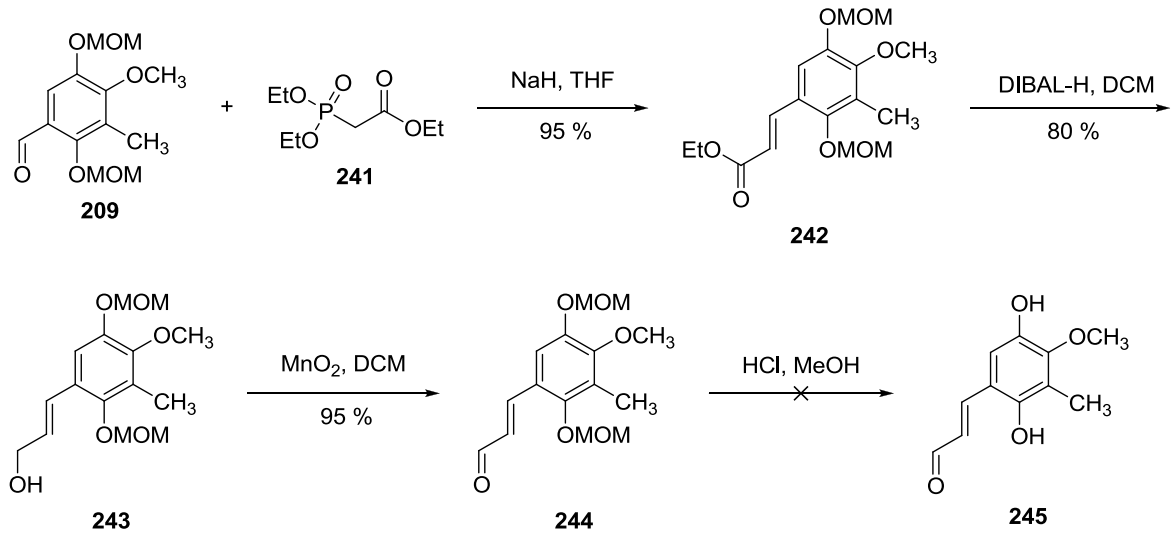
Reaction conditions	Temperature	Yield
(Methoxymethyl)triphenylphosphonium chloride, THF	rt	no reaction
(Methoxymethyl)triphenylphosphonium chloride,THF/Et_2O	rt	no reaction
Methoxytrimethysilylmethan, *s*BuLi, THF	rt	no reaction
Tebbe-Reagent, toluene	rt	no reaction
Triethyl phosphonoacetate, NaH, THF	rt	no reaction

Table 6. Conditions to produce aldehyde **236**

All the olefination reactions we tried failed. To our opinion the aldehyde moiety can't be transformed because of steric effects. So we decided to try to introduce the side chain even earlier.

7.3.2 Second attempt to introduce the side chain earlier

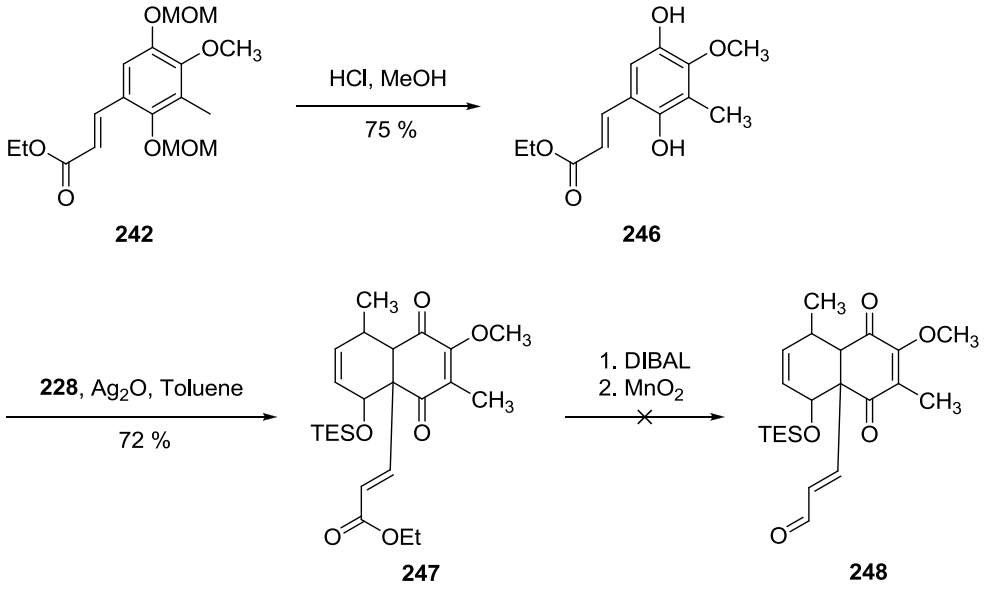
Our second approach to install the side chain featured a modified MOM protected hydroquinone **209**. With this compound we wanted to try the Diels Alder reaction. Unfortunately all attempts to transform the aldehyde by a Wittig reaction failed, only a Wittig Horner reaction with compound **241** worked smoothly and yielded compound **242.** Reduction with DIBAL-H gave the corresponding allylic alcohol **243**. Allylic oxidation with manganese(IV) oxide worked smoothly and yielded compound **244**. At this point we did several experiments to introduce the side chain by a 1,4 addition at vinylic aldehyde. All attempts failed because the benzylic position seems to be too deactivated for nucleophilic attack, because of the electron-rich nature of the hydroquinone. Therefore we wanted to try a Diels-Alder reaction with the deprotected hydroquinone, but the cleavage of the MOM protecting group always afforded only decomposition (Scheme **38**). At this point we tried the cleavage of the MOM ether at compound **242**.



Scheme 38. Second Attempt to introduce the Side Chain earlier at the Monocycle

Treatment of compound **242** with HCl in methanol afforded product **246**. Intermediate **246** reacted under the same Diels-Alder conditions as always smoothly with diene **228** and afforded compound **247**. We wanted to reduce the ester moiety under the same conditions as above with compound **242** (Scheme **37**), but the reduction with the decaline backbone did not work. Attempts with other reducing agents also failed (Scheme **39**). At this point we

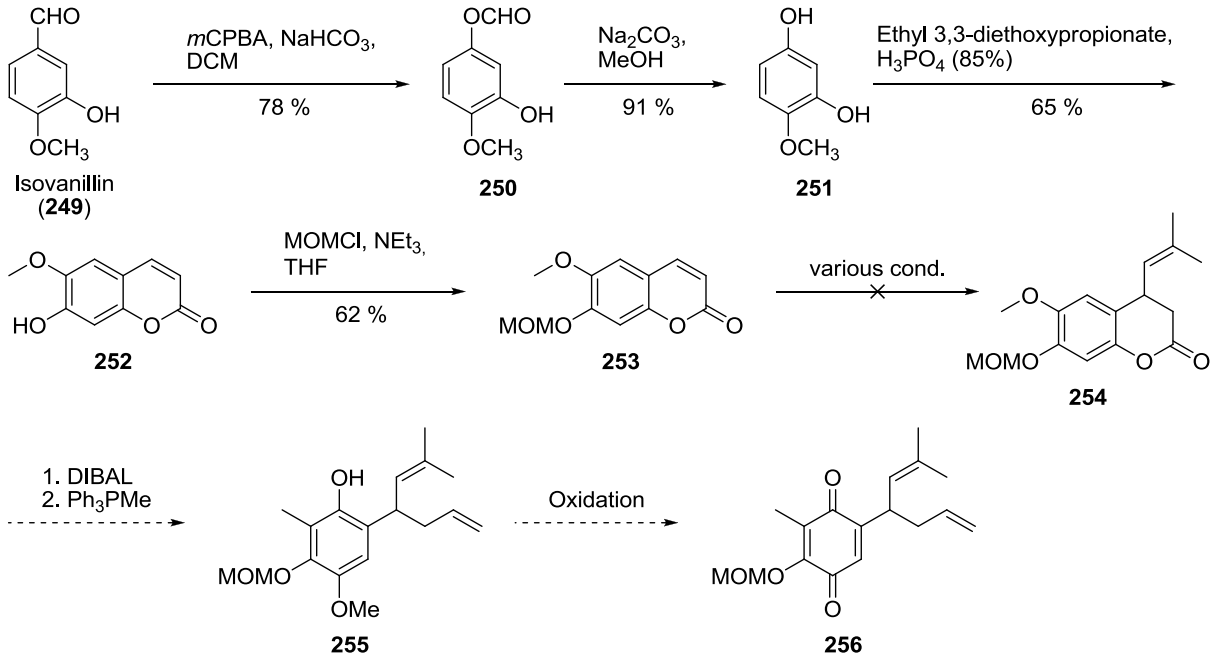
decided to switch to another route to produce the hydroquinone precursor for the Diels Alder-reaction.



Scheme 38. Second Attempt to introduce the Side Chain earlier at the Decaline System

7.3.3 Third Attempt to introduce the Side Chain earlier

Our third approach to introduce the side chain earlier was to produce a new precursor for the Diels-Alder reaction. This approach featured a later introduction of the side chain. As starting material we have chosen isovanillin (**249**). Baeyer-Villiger oxidation of isovanillin afforded intermediate **250**. Treatment with sodium carbonate gave the corresponding phenol **251.** Addition of ethyl 3,3-diethoxypropionate in phosphoric acid (85 %) yielded compound **252**. The free alcohol was MOM protected. With compound **253** in hand we tried to install the side chain by 1,4 addition. All attempts to introduce the side chain by nucleophilic addition also failed. In our opinion the system is too electron rich to be attacked with a nucleophile (Scheme **39**).

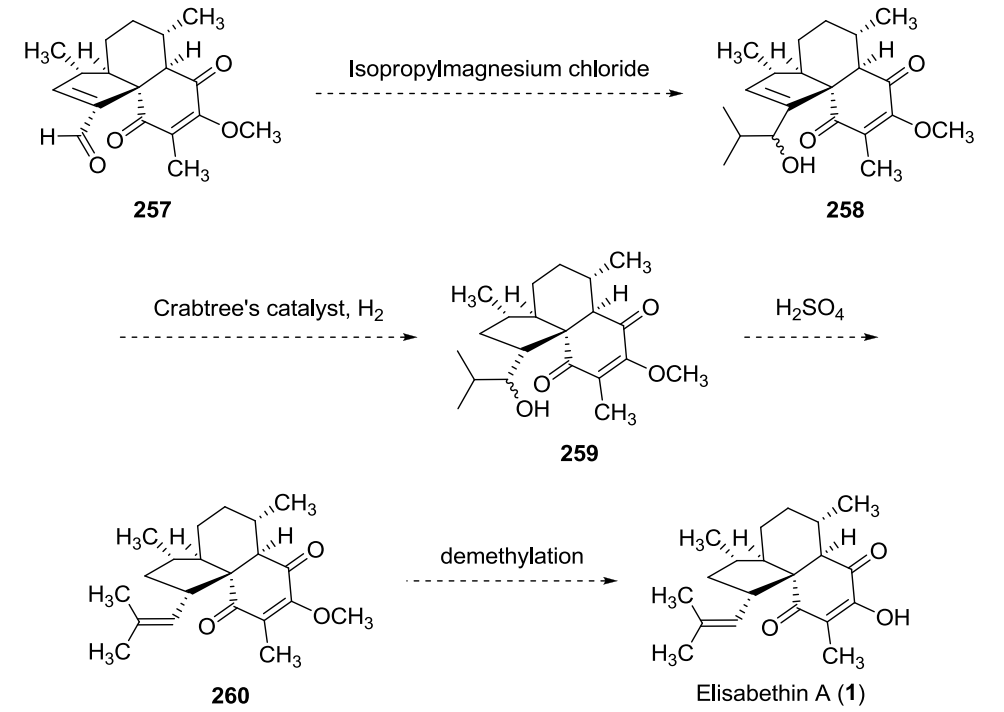


Scheme 39. Third attempt to introduce the side chain earlier

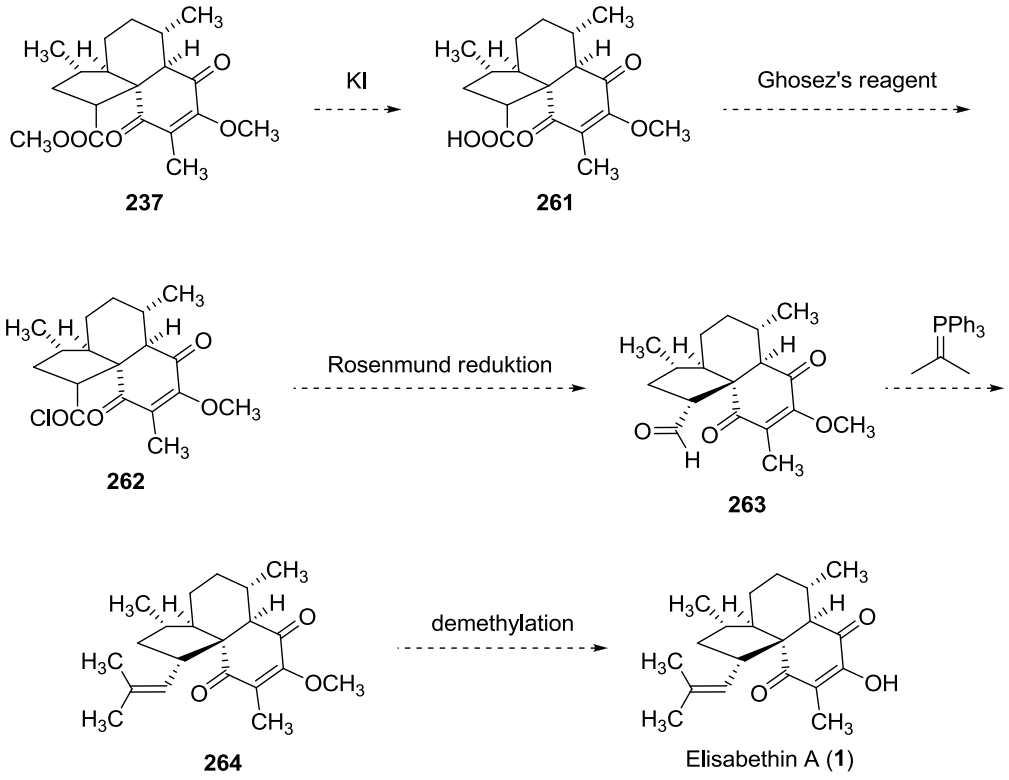
7.4 Future work

There would be two different hypothetical endgames to produce elisabethin A (**1**), one from compound **257** and one from the reduced ester **237.** Treatment of aldehyde **257** with isopropylmagnesium chloride should give the corresponding alcohol **258**. The hydroxyl group close the undesired double bond should act as an anchor group for Crabtree's catalyst and should allow us to reduce the double bond to afford intermediate **259**. Dehydration should lead to the intermediate **260** with the desired side chain and cleavage of the methyl ether should afford elisabethin A (**1**) (Scheme **40**).

The other possible endgame could start from the reduced ester **237**. Treatment with potassium iodide should give the corresponding acid **261**. Conversion of the acid to the corresponding acid chloride **262** and Rosenmund reduction should lead to aldehyde **263**. A Wittig olefination followed by cleavage of the methyl ether should give elisabethin A (**1**)



Scheme 40. Endgame to produce Elisabethin A (**1**) from Compound **257**



Scheme 41. Endgame to produce Elisabethin A (**1**) from Compound **237**

8 Summary

Finally we are able to present a highly stereoselective synthesis of an advanced intermediate of elisabethin A (**1**). Our intermediate contains the tricyclic backbone of Elisabethin A (**1**) and has the desired stereochemistry at the produced stereogenic centers.

To produce intermediate **230** we developed a new method for the selective allylation of the aldehyde in the presences of the quinone system, and to close the five membered ring we used a metallo-ene reaction.

As it has been shown, that it is not possible to introduce the side chain in intermediate **234** through coupling reactions, but we were able to introduce carbon monoxide through an insertion reaction. Untill now were not able to transform aldehyde **238** or ester **237** into the desired side chain. All attempts to introduce the side chain earlier in the synthesis failed because the system was to electronic rich.

A main problem of our approach is that the Diels-Alder reaction is missing the enantioselectivity, but all attempts to catalyze the reaction in an enantioselctive fashion in our group failed.

9 Experimental Part

9.1 General

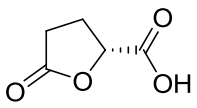
The chemical reactions were conducted under a soft argon overpressure. The glassware was always used dry and the reactions were controlled by TLC and NMR. The solvent was always removed under reduced pressure at temperatures less than 40 °C or otherwise noted and further dryings of the intermediates were completed by drying with a high vacuum pump.

The solvents were bought as the highest available grade from Sigma-Aldrich, Acros-Organics and Fischer-Chemicals. NEt_3 was distilled over CaH_2 before use. All reagents were used as received from TCI, Acros-Organics, Sigma-Aldrich, Fischer-Chemicals or ABCR. Reactions were monitored by thin-layer chromatographies (TLC) and were carried out on pre-coated Merk silica gel 60 F254. The detection was carried out by using UV (254 nm) and as a visualizing agent an aqueous solution of phosphomolybdic acid (20 g), ceric(IV)sulfate (0.4 g) and 22 mL of H_2SO_4 was used followed by heat-gun developing. Column chromatography was performed with silica gel (0.040-0.063 µm, 240-400 mesh) with the appropriate solvent.

NMR spectra were gauged on a Bruker AV400, DRX400 or DRX600. The chemical shifts are given in ppm and referenced to the solvent residual peaks ($CDCl_3$, ^1H, δ = 7.26 ppm; ^{13}C, δ = 77.16 ppm). Data is reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant *J*, integration.

High-resolution mass spectra were measured on Bruker MaXis (ESI-TOF) with a resolution of 10,000.

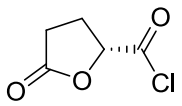
9.2 Practical implementation



190

(*R*)-5-Oxotetrahydrofuran-2-carboxylic acid. D-Glutamic acid (971 mg, 6.59 mmol) was dissolved in H_2O (4 mL, 1.6 M) and HCl (2 mL, 3.3 M). The solution was cooled to 0 °C and $NaNO_2$ (679 mg, 9.9 mmol, 1.5 Eq) in H_2O (2 mL, 5 M) was added slowly. The reaction mixture was allowed to warm up to room temperature and was stirred over night. The solvent was removed in vacuo at 40 °C. The recess was redissolved in AcOEt and filtered over a plug of celite and the solvent was evaporated and afforded pure **190** (459 mg, 3.52 mmol, 53 %)

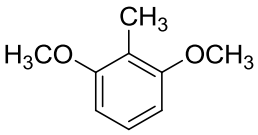
The obtained spectral data were identical to those reported in literature. [92]



178

(*R*)-5-Oxotetrahydrofuran-2-carbonyl chloride. Oxalyl chloride (0.25 mL, 2.98 mmol, 2.5 Eq) was added to acid **190** (155 mg, 1.19 mmol) in DCM (3 mL, 0.4 M) and DMF (0.1 mL, 12 M) at 0 °C. The mixture was allowed to warm up to room temperature and was stirred for two hours. The solution was concentrated in vacuo and was coevaprorated three times with dichloromethane (9 mL). The recess was distilled under vacuum at 86-89°C at 1 Torr to afford pure **178** (118.4 mg, 0.8 mmol, 67%).

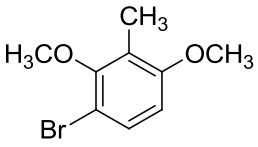
The obtained spectral data were identical to those reported in literature. [93]



192

1,3-Dimethoxy-2-methylbenzene. 2-Methylresorcinol (3 g, 24.17 mmol) was dissolved in methanol (16 mL, 1.5 M) and dimethyl sulfate (9.17 mL, 96.67 mmol, 4 Eq) was added. The solution was stirred at room temperature and a solution of sodium methoxide (5.23 g, 96.67 mmol, 4 Eq) in methanol (25 mL, 3.9 M) was added over a period of one hour. The reaction was heated to reflux for one hour and stopped by the addition of sat. aq. NH_4Cl.
The phases were separated, the aqueous layer extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuum to give the product which was purified by chromatography to afford **192** (3.47 g, 22.8 mmol, 94 %).

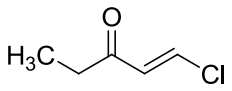
The obtained spectral data were identical to those reported in literature.



179

1-Bromo-2,4-dimethoxy-3-methylbenzene. Intermediate **192** (1.17 g, 7.7 mmol) was dissolved in distilled H_2O (32 mL, 0,25 M) and KBr (3.07 g, 25.8 mmol, 3,4 Eq) and Br_2 (0.44 mL, 8.5 mmol, 1.1 Eq) were added. The mixture was stirred over night at room temperature and quenched by the addition of sat. aq. $Na_2S_2O_3$. The phases were separated, the aqueous layer extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuum to give the product which was purified by chromatography to afford **179** (1,73 g, 7.47 mmol, 97 %).

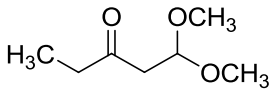
The obtained spectral data were identical to those reported in literature.[94]



211

(*E*)-1-Chloropent-1-en-3-one. Propionyl chloride (15 mL, 171.69 mmol) was dissolved in CCl_4 (100 mL, 1.7 M) and $AlCl_3$ (21 g, 157.42 mmol, 0.92 Eq) was added and the mixture was cooled to 0 °C. The reaction mixture was flushed with argon for a half hour and than ethyne was bubbled through the mixture at 0 °C for five hours. The reaction mixture was quenched with H_2O at 0 °C. The phases were separated and the aqueous phase was extracted with DCM. The combined organic extracts were washed with HCl (10 %), H_2O, sat. aq. $NaHCO_3$ and brine. Dried ($MgSO_4$) and concentrated in vacuum to give the product which was purified by vacuum distillation (58-60 °C, 15 mbar) to gave **211** (9.2 g, 77.6 mmol, 45 %).

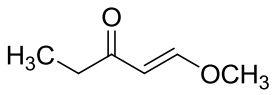
The obtained spectral data were identical to those reported in literature.[95]



212

1,1-Dimethoxypentan-3-one. Freshly powdered anhydrous potassium carbonate (55.2 g, 400 mmol, 2 Eq) was dissolved in dry methanol (300 mL, 0.7 M) under argon atmosphere. Intermediate **211** (23.6 g, 200.1 mmol) was dissolved in methanol (25 mL) and added dropwise to the reaction mixture. The reaction mixture was stirred at room temperature over night until TLC showed no more starting material. The solution was diluted with water. The phases were separated, the aqueous layer extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuum to give the product which was purified by vacuum distillation (64-65 °C, 15 mbar) to afford **212** (19.8 g, 135.44 mmol, 67 %).

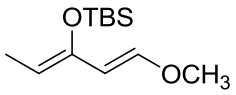
The obtained spectral data were identical to those reported in literature.[95]



213

(*E*)-1-Methoxypent-1-en-3-one. 212 (19.08g, 135.44 mmol) was dissolved in toluene (30 mL, 4.5 M) and sodium methoxide (250 mg, 4.65 mmol, 0.03 Eq) was added under argon atmosphere. The mixture was heated to 170 °C and methanol was distilled off from the reaction. After four hours the mixture was cooled to room temperature. The solution was diluted with water. The phases were separated, the aqueous layer extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuum to give the product which was purified by vacuum distillation (92-93 °C, 40 mbar) afforded pure **213** (13.8 g, 120.9 mmol, 89 %).

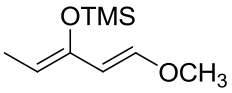
The obtained spectral data were identical to those reported in literature.[95]



214

Tert-butyl((1*E*,3*Z*)-1-methoxypenta-1,3-dien-3-yloxy)dimethylsilane. Intermediate **213** (6 g, 52,57 mmol) was dissolved in Et_2O (100 mL, 0.5 M) and cooled to -78 °C under argon atmosphere. NEt_3 (20 mL, 144.2 mmol, 2.7 Eq) was added and the mixture was stirred for 20 minutes. Trifluoromethanesulfonic acid tert-butyldimethylsilyl ester (14 mL, 77.35 mmol, 1.5 Eq) was added dropwise and the solution was stirred for two hours at -78 °C and three hours at 0 °C. The reaction mixture was diluted with hexane (100 mL) and quenched with sat. aq. $NaHCO_3$. The phases were separated, the aqueous layer extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuum to give the product which was purified by vacuum distillation (104-105 °C, 1 mbar) afforded **214** (9 g, 39.42 mmol, 75 %).

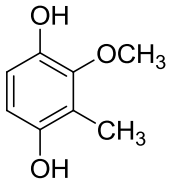
The obtained spectral data were identical to those reported in literature.[95]



215

((1*E*,3*Z*)-1-Methoxypenta-1,3-dien-3-yloxy)trimethylsilane. Anhydrous zinc chloride (101 mg, 0.75 mmol, 0.03 Eq) was added to NEt_3 (6 mL, 43.3 mmol, 1.74 Eq) and the reaction mixture was stirred for one hour at room temperature. Intermediate **213** (2.85 g, 24,9 mmol) was dissolved in benzene (6 mL, 4 M) and added to the reaction mixture. The reaction mixture was stirred for 20 minutes at room temperature. Trimethyl chlorosilane (6.37 mL, 49.9 mmol, 2 Eq) was added and the solution was stirred over night at 40 °C. The mixture was cooled to room temperature and poured into ether (100 mL). The solid was filtered off and the solvent was evaporated. Purification by vacuum distillation (45-49 °C, 5 mbar) afforded **215** (2.83 g, 15.19 mmol, 61 %).

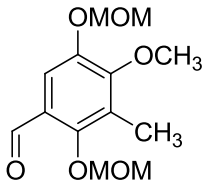
The obtained spectral data were identical to those reported in literature.[96]



206

2-Methoxy-3-methylbenzene-1,4-diol 186.[97] Intermediate **205** (12 g, 65 mmol) was dissolved in a solution of H_2O and CH_3OH in a ratio of 4:1 (45 mL). The solution was cooled to 0 °C and PIDA (31.8 g, 98 mmol, 1.5 Eq.) was added. The solution was allowed to warm up to room temperature and was stirred over night. The aqueous phase was extracted with ether three times (300 mL). The combined organic phases were combined and the solvent was evaporated at 20 °C. The remaining solution was diluted with water (200 mL) and sodium hydrosulfite (45.26 g, 260 mmol, 4 Eq.) was admitted. The reaction was stirred for 12 hours at ambient temperature. The phases were separated, the aqueous layer extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuum to give the product which was coevaported three times with toluene. The recess was mixed with hexane and filtered off two times to afforded pure **206** (7.14 g, 46.15 mmol, 71%)

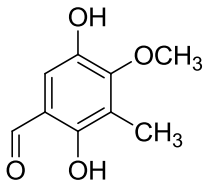
The spectral data were identical to those reported in literature.[98]



209

4-methoxy-2,5-*bis*(methoxymethoxy)-3-methylbenzaldehyde190.[97] Intermediate **206** (23 g, 149.2 mmol) was dissolved in THF (500 mL, 0.3 M) and cooled to 0 °C. Sodium hydride 60 % dispersion in mineral oil (26.85 g, 671 mmol, 4.5 Eq), was added over one hour at 0 °C and stirred for 30 minutes. MOMCl (34 mL, 447 mmol, 3 Eq) was added at 0 °C and the reaction mixture was allowed to warm up to room temperature and was stirred over night. The reaction mixture was quenched with H_2O at 0 °C. The phases were separated, the aqueous layer extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuum to give the product which was purified by chromatography to afford **207** (25 g, 103 mmol, 69 %). Intermediate **207** (25 g, 103 mmol) was dissolved in THF (500 mL, 0.2 M) and NBS (19.29 g, 1,08 mol) was added at 0 °C. The reaction mixture was stirred for 12 hours and stopped by addition of sat. aq. $Na_2S_2O_4$. The phases were separated, the aqueous layer extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuum to give the product which was purified by chromatography to afford **208** (30 g, 94.8 mmol, 92 %). The product was diluted in Et_2O (300 mL, 0.1 M) and cooled to -85 °C and *tert*-butyllithium (138 mL, 1.7 M in pentane, 234 mmol, 2.5 Eq) was dropped to the reaction slowly over a period of one hour. The reaction mixture was stirred for one hour and DMF (36 mL, 468 mmol, 5 Eq) was added slowly. The solution was stirred for another 2 hours and quenched at -85°C by addition of ethyl acetate followed by sat. aq. NH_4Cl. The solution was allowed to warm to room temperature and the phases were separated. The combined organic phases were washed with brine and dried over $MgSO_4$. After filtration the solvent was evaporated. Purification by column chromatography afforded pure **209** (18.7 g, 69.25 mmol, 73 %).

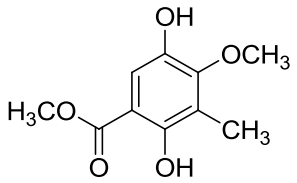
The spectral data were identical to those reported in literature.[97]



199

2,5-Dihydroxy-4-methoxy-3-methylbenzaldehyde 174.[97] Intermediat **209** (18.7 g, 69.26 mmol) was dissolved in dry methanol (117 mL, 0.6 M) and cooled to 0 °C. Then aq. HCl (36.57 mL, 8 M, 346.1 mmol, 5 Eq) was added and the reaction was allowed to warm to room temperature. The solution was stirred over night and then diluted with ether. The phases were separated. The combined organic phases were washed with brine and dried over $MgSO_4$. After filtration the solvent was removed under reduced pressure and afforded pure **199** (12.06 g, 66.09 mmol, 95 %).

The spectral data were identical to those reported in literature.[98]



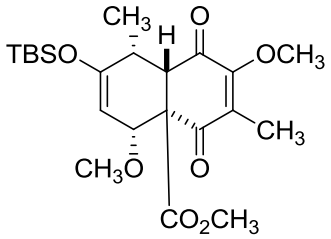
221

Methyl 2,5-dihydroxy-4-methoxy-3-methylbenzoate. Compound **199** (100 mg, 0.55 mmol) was dissolved in in *t*BuOH (4 mL), H_2O (2.25 mL) and 2-methylbutene (1 mL). The solution was cooled to 0 °C. $NaClO_2$ (248 mg, 2.7 mmol, 5 Eq) and NaH_2PO_4 (454 mg, 3.3 mmol, 6 Eq) was dissolved in H_2O (2 mL) and added dropwise to the reaction mixture at 0 °C. The reaction was allowed to warm to room temperature and was stirred over night. Treatment with sat. aq. ammonium chloride stopped the experiment and the water phase was leached with Et_2O three times. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuum. The recess was taken up in a mixture of benzene and methanol in a ratio of 3:2 (4 mL) and cooled to 0 °C. (Trimethylsilyl)diazomethane (0.28 mL, 2 M in hexane, 0.55 mmol, 1 Eq) was added and the reaction was stirred for two hours at 0 °C. Treatment with sat. aq. ammonium chloride stopped the reaction. The phases were separated, the aqueous layer extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuum to give the product which was purified by chromatography to afford **221** (72,36 mg, 0.34 mmol, 62 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.75 (s, 1H); 7.27 (s, 1H); 5.19 (s, 1H); 3.92 (s, 3H); 3.84 (s, 3H); 2.21 (s, 3H) ppm.

HRMS: m/z calcd. for $C_{10}H_{12}O_5Na^+$: 335.0577; found: 335.0582;

R_f: 0.33 (SiO_2, Hex:EE 3:1)



222

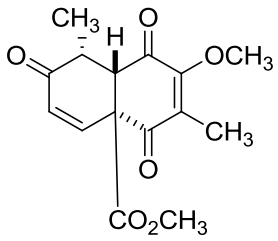
(4a*R*,5*R*,8*R*,8a*S*)-Methyl 7-(*tert*-butyldimethylsilyloxy)-2,5-dimethoxy-3,8-dimethyl-1,4-dioxo-1,4,4a,5,8,8a-hexahydronaphthalene-4a-carboxylate. 221 (100 mg, 0.55 mmol) was dissolved in toluene (2 mL, 0.2M) and diene **214** (0.251 g, 1.1 mmol, 2 Eq) was added. The combination of the reaction compounds was treated with Ag_2O (0.254 g, 1.1 mmol, 2 Eq) at 0 °C and stirred for 24 hours at ambient temperature. Ag_2O was removed through filtration over celite. Concentration in vacuum and purification by column chromatography afforded **222** (190 mg, 0.43 mmol, 79 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.14 (m, 1H); 4.66 (d, *J* = 6.0 Hz 1H); 4.07 (s, 3H); 3.60 (s, 3H); 3.33 (d, *J* = 9.1 Hz 1H); 2.83 (m, 1H); 1.87 (s, 3H); 1.27 (d, *J* = 6.9 Hz 1H), 0.93 (s, 9H); 0.16 (s,3H); 0.10 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.71; 191.26; 167.83; 161.78; 159.42; 130.05; 101.32; 73.91; 67.12; 60.62; 56.83; 53.43; 51.36; 33.69; 25.99 (3C); 18.89; 18.44; 9.78; -3.92; -4.71 ppm.

HRMS: m/z calcd. for $C_{22}H_{34}O_7NaSi^+$: 461.1966; found: 461.1969;

R_f: 0.59 (SiO_2, Hex:EE 3:1)



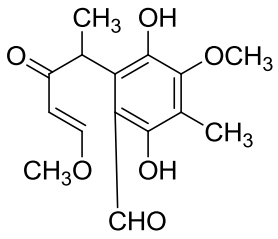
223

(1*R*,4a*S*,8a*S*)-Methyl 7-methoxy-1,6-dimethyl-2,5,8-trioxo-1,2,4a,5,8,8a-hexahydronaphthalene-4a-carboxylate. 222 (20 mg, 0.05 mmol) was dissolved in acetone (2 mL, 0.025 M) and H_2SO_4 (2.5 µL, 18 M, 0.05 mmol) was added at 0 °C. The reaction was allowed to warm up to room temperature and was stirred for 12 hours. Treatment with sat. aq. $NaHCO_3$ stopped the reaction. The phases were separated, the aqueous layer extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuum to give the product which was purified by chromatography to afford **223** (15 mg, 0.05 mmol, 99 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 10.2Hz 1H); 6.14 (d, *J* = 10.1 Hz 1H); 4.10 (s, 3H); 3.67 (s, 3H); 3.67 (m, 2H); 1.93 (s, 3H); 1.43 (d, *J* = 6.2 Hz 3H)ppm.

HRMS: m/z calcd. for $C_{15}H_{16}ONa^+$: 315.0834; found: 315.0831

R_f: 0.49 (SiO_2, Hex:EE 3:1)



218

(*E*)-2,5-Dihydroxy-4-methoxy-6-(5-methoxy-3-oxopent-4-en-2-yl)-3-methylbenzaldehyde.

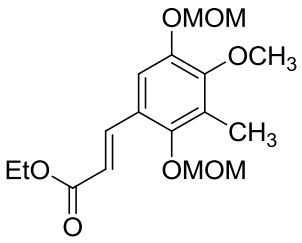
199 (100 mg, 0.55 mmol) was dissolved in toluene (2 mL, 0.2 M) and diene **215** (0.409 g, 2.2 mmol, 4 Eq) was added. The combination of the reaction compounds was treated with Ag_2O (0.254 g, 1.1 mmol, 2 Eq) at 0 °C and stirred for 24 hours at ambient temperature. Ag_2O was removed through filtration over celite. Concentration in vacuum and purification by column chromatography afforded **218** (122 mg, 0.41 mmol, 74 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.45 (s, 1H); 10.05 (s, 1H); 7.65 (d, *J* = 12.6 Hz 1H); 6.03 (s, 1H); 5.52 (d, *J* = 12.4 Hz 1H); 4.50 (m, 1H); 3.90 (s, 3H); 3.63 (s, 3H); 2.20 (s, 3H); 1.53 (s, 1H); 1.52 (d, *J* = 7.0 Hz, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.5; 194.5; 163.7; 158.2; 153.5; 139.9; 126.0; 118.4; 114.1; 103.5; 61.1; 58.0; 42.9; 17.1; 8.9; ppm.

HRMS: m/z calcd. for $C_{15}H_{18}O_6Na^+$: 315.0996; found: 315.1001;

R_f: 0.23 (SiO_2, Hex:EE 10:1)



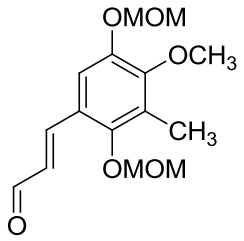
242

(*E*)-Ethyl 3-(4-methoxy-2,5-bis(methoxymethoxy)-3-methylphenyl)acrylate. Horner reagent **241** (540 mg, 2.22 mmol, 3 Eq) was dissolved in THF (8 mL, 0.1 M) and the solution was cooled to 0 °C. At this temperature NaH (95 mg, 24 mmol, 3.2 Eq) was added. The mixture was allowed to warm to room temperature and was stirred 15 minutes at this temperature. Then the solution was cooled again to 0 °C and compound **209** (200 mg, 0.74 mmol) in THF (2 mL) was added dropwise. The solution was stirred over night and stopped by addition of water. The phases were separated, the water layer extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuum to give the product which was purified by chromatography to afford **242** (240 mg, 0.71 mmol, 96 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 16.5 Hz 1H); 7.22 (s, 1H); 6.33 (d, *J* = 16.5 Hz 1H); 5.19 (s, 2H); 4.93 (s, 2H); 4.25 (m, 2H); 3.84 (s, 3H); 3.64 (s, 3H); 3.52 (s, 3H); 2.22 (s, 3H); 1.33 (t, *J* = 7.5 Hz, 3H) ppm.

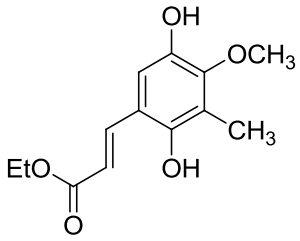
HRMS: m/z calcd. for $C_{17}H_{24}O_7Na^+$: 363.1409; found: 363.1424;

R_f: 0.23 (SiO_2, Hex:EE 3:1)



244

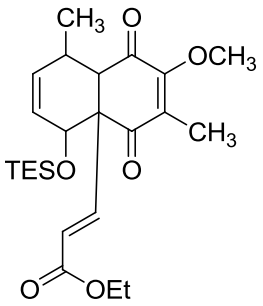
(*E*)-3-(4-Methoxy-2,5-bis(methoxymethoxy)-3-methylphenyl)acrylaldehyde. Ester **242** (800 mg, 2.35 mmol) was dissolved in DCM (25 mL, 0.1M) and cooled to -78 °C. DIBAL-H (11.8 mL, 1 M in THF, 11.8 mmol, 5 Eq) was added dropwise at -78 °C. The reactionmixture was allowed to warm to room temperature and was stirred overnight. The reaction was stopped with H_2O. The phases were separated, the water layer extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuum. The crude product was used without further purification. The recess was dissolved in DCM (40 mL, 0.06M) and cooled to 0 °C. Then MnO_2 (817 mg, 9.4 mmol, 4 Eq) was added and the reaction was warmed up to room temperature and was stirred overnight. The reaction was filtered over celite and concentrated. Purification by column chromatography afforded pure **244** (620 mg, 2.1 mmol, 89 %).



246

(*E*)-Ethyl 3-(2,5-dihydroxy-4-methoxy-3-methylphenyl)acrylate. Intermediat **242** (177 mg, 0.52 mmol) was dissolved in dry methanol (2 mL, 0.3 M) and Et_2O (5 mL, 0.1 M). The mixture was cooled to 0 °C. Then aq. HCl (0.65 mL, 4 M, 2.6 mmol, 5 Eq) was added and the reaction was allowed to warm to room temperature. The solution was stirred over night and then diluted with ether. The phases were separated. The combined organic phases were washed with brine and dried over $MgSO_4$. After filtration the solvent was removed under reduced pressure and afforded pure **199** (102 mg, 0.43 mmol, 80 %).

^{1}H NMR (400 MHz, CD_3OD): δ = 8.06 (d, *J* = 16.4 Hz 1H); 6.93 (s, 1H); 6.38 (d, *J* = 16.4 Hz 1H); 4.27 (m, 2H); 3.82 (s, 3H); 3.64 (s, 3H); 3.52 (s, 3H); 2.19 (s, 3H); 1.36 (t, *J* = 7.0 Hz, 3H) ppm.
HRMS: m/z calcd. for $C_{13}H_{16}O_5Na^+$: 275.0884; found: 275.0887
R_f: 0.19 (SiO_2, Hex:EE 1:1)



247

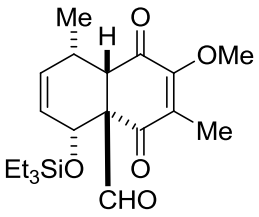
(*E*)-Ethyl 3-(2-methoxy-3,8-dimethyl-1,4-dioxo-5-(triethylsilyloxy)-1,4,4a,5,8,8a-hexahydronaphthalen-4a-yl)acrylate. Compound **199** (50m g, 0.20 mmol) was dissolved in THF (2 mL, 0.1 M). Diene **228** (134 mg, 0.67 mmol, 3.4 Eq.) was given to the mixture. The mixture was cooled to 0 °C and manganese (IV) oxide (7.54 g, 32.5 mmol, 2 Eq.) was added. The reaction was stirred at ambient temperature for 14 hours and then filtered over celite The solvent was removed under reduced pressure and column chromatography afforded clean **247** (59.2 mg, 0.13 mmol, 66 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.87 (d, *J* = 16.1 Hz 1H); 5.89 (d, *J* = 16.3 Hz 1H); 5.71 (m, 2H); 4.29 (m, 1H); 4.17 (m, 2H); 3.96 (s, 3H); 3.08 (d, *J* = 4.5 Hz 1H); 2.29 (m, 1H); 1.81 (s, 3H); 1.39 (d, *J* = 7.5 Hz 3H); 1.29 (t, *J* = 7.13 Hz, 3H); 0.82 (t, *J* = 8.1 Hz 9H); 0.43 (m, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.59; 192.55; 166.33; 163.20; 146.07; 134.32; 128.97; 125.42; 123.36; 69.99; 61.35; 61.08; 59.78; 52.40; 29.5; 17.49; 14.61; 9.25; 6.91 (3C); 5.15 (3C) ppm.

HRMS: m/z calcd. for $C_{24}H_{36}O_6NaSi^+$: 471.2173; found: 471.2179

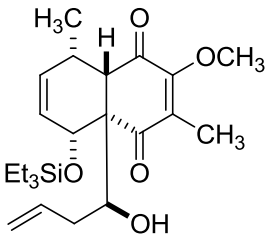
R_f: 0.43 (SiO_2, Hex:EE 4:1)



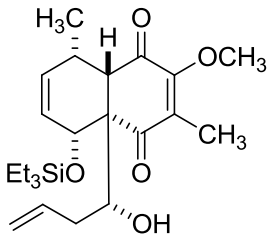
227

(4a*S*,5*R*,8*S*,8a*S*)-2-methoxy-3,8-dimethyl-1,4-dioxo-5-((triethylsilyl)oxy)-1,4,4a,5,8,8a-hexahydronaphthalene-4a-carbaldehyde195.[97] Compound **199** (50m g, 0.20 mmol) was dissolved in THF (2 mL, 0.1 M) and diene **228** (134 mg, 0.67 mmol, 3.4 Eq.) was added. The solution was cooled to 0 °C. Thereafter manganese (IV) oxide (7.54 g, 32.5 mmol, 2 Eq.) was added and the suspension was stirred at ambient temperature for 14 hours. The suspension was filtered over celite. Concentration under reduced pressure and column chromatography afforded clean **227** (59.2 mg, 0.13 mmol, 66 %).

The spectral data were identical to those reported in literature.[97]



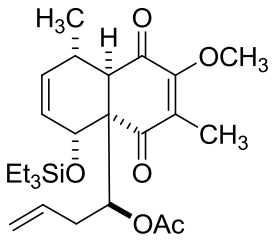
230a



230b

(4a*R*,5*R*,8*S*,8a*S*)-4a-((*S*)-1-hydroxybut-3-en-1-yl)-2-methoxy-3,8-dimethyl-5-((triethylsilyl)oxy)-4a,5,8,8a-tetrahydronaphthalene-1,4-dione 230a and **(4a*R*,5*R*,8*S*,8a*S*)-4a-((*R*)-1-hydroxybut-3-en-1-yl)-2-methoxy-3,8-dimethyl-5-((triethylsilyl)oxy)-4a,5,8,8a-tetrahydronaphthalene-1,4-dione 230b.**[97] In dry THF (200 mL, 0.1 Eq), $ZnCl_2$ (60.32 mL, 1 M in Et_2O, 60.3 mmol, 3 Eq) was dissolved and allylmagnesium chloride (25.63 mL, 2 M in THF, 51.3 mmol, 2.55 Eq) was added dropwise. The reaction was stirred for one hour at ambient temperature and then cooled to -78 °C. Compound **227** (7.6 g, 20.1 mmol) was dissolved in tetrahydrofuran (100 mL) and added dropwise to the solution at -78 °C. The mixture was stirred for four hours at -78 °C and then stopped by addition of sat. aq. ammonium chloride. The phases were separated, the water layer extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuum to give the product which was purified by chromatography to afford **230a** (5,11 g, 12.15 mmol, 60 %) and **230b** (2.24 g, 5.33 mmol, 26.5%)

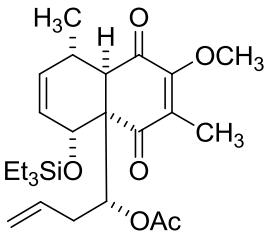
The spectral data were identical to those reported in literature.[97]



230.1a

(*S*)-1-((4a*R*,5*R*,8*S*,8a*R*)-2-Methoxy-3,8-dimethyl-1,4-dioxo-5-((triethylsilyl)oxy)-1,4,4a,5,8,8ahexahydronaphthalen-4a-yl)but-3-en-1-yl acetate 230.1a.[97] Compound **230a** (5.11 g, 12 mmol) was dissolved in DCM (40 mL, 0.3 M) and cooled to 0 °C. Then NEt_3 (0.84 mL, 6.08 mmol, 0.5 Eq.), Ac_2O (5.74 mL, 60 mmol, 5 Eq) and DMAP (0.74 mg, 0.61 mmol, 0.5 Eq.) were added. The reaction was allowed to warm to ambient temperature and was stirred for 15 hours. After DBU (9.1 mL, 60 mmol, 5 Eq) was added and the solution was stirred again for 20 hours, sat. aq. ammonium chloride was added to stop the reaction. The phases were separated, the water layer extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuum to give the product which was purified by chromatography to afford **230.1a** (.5.39 g, 11.64 mmol, 97 **%**).

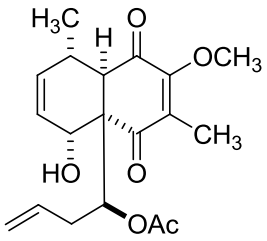
The spectral data were identical to those reported in literature.[97]



230.1b

(*R*)-1-((4a*R*,5*R*,8*S*,8a*R*)-2-methoxy-3,8-dimethyl-1,4-dioxo-5-((triethylsilyl)oxy)-1,4,4a,5,8,8a-hexahydronaphthalen-4a-yl)but-3-en-1-yl acetate 230.1b.[97] This compound was prepared according to the procedure of **230.1a** with 96 % yield from intermediate **230b**.

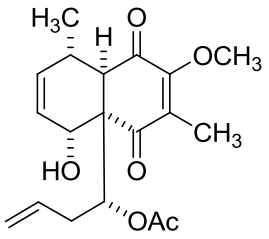
The spectral data were identical to those reported in literature.[97]



231a

(*S*)-1-((4a*S*,5*R*,8*S*,8a*R*)-5-Hydroxy-2-methoxy-3,8-dimethyl-1,4-dioxo-1,4,4a,5,8,8a-hexahydronaphthalen-4a-yl)but-3-en-1-yl acetate 231a.[97] **230.1a** (9.76 g, 21.12 mmol) was dissolved in THF (60 mL, 0.35 M) and cooled to 0 °C. Then aq. HCl (105.6 mL, 1 M, 5 Eq.) was added. The reaction was allowed to warm up to ambient temperature and stirred for 16 hours at ambient temperature. The reaction was stopped with sat. aq. sodium hydrogen carbonate. The phases were separated, the water layer extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuum to give the product which was purified by chromatography to afford **231a** (7.06 g, 20.27 mmol, 96 **%**).

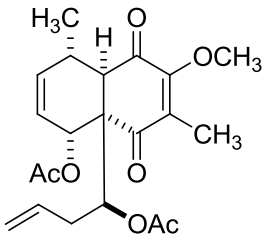
The spectral data were identical to those reported in literature.[97]



231b

(*R*)-1-((4a*S*,5*R*,8*S*,8a*R*)-5-hydroxy-2-methoxy-3,8-dimethyl-1,4-dioxo-1,4,4a,5,8,8a-hexahydronaphthalen-4a-yl)but-3-en-1-yl acetate 231b.[97] This compound was prepared according to procedure of **231a** with 96 % yield from intermediate **230.1b**.

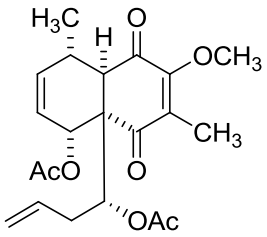
The spectral data were identical to those reported in literature.[97]



226a

(*S*)-1-((4a*R*,5*R*,8*S*,8a*R*)-5-Acetoxy-2-methoxy-3,8-dimethyl-1,4-dioxo-1,4,4a,5,8,8a-hexahydronaphthalen-4a-yl)but-3-en-1-yl acetate 226a.[97] Intermediate **231a** (8.46 g, 24.27 mmol) was dissolved in DCM (150 mL, 0.25 M) and cooled to 0 °C. Then NEt_3 (0.34 mL, 2.4 mmol, 0.1 Eq), Ac_2O (3 mL, 31.55 mmol, 1.3 Eq) and DMAP (0.3 mg, 2.4 mmol, 0.1 Eq) were added. The reaction mixture was allowed to warm to room temperature and was stirred for 15 hours and sat. aq. ammonium chloride was added to stop the reaction. The phases were separated, the water layer extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuum to give the product which was purified by chromatography to afford **226a** (8.8 g, 22.57 mmol, 93 **%**).

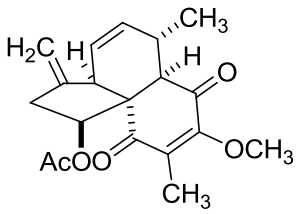
The spectral data were identical to those reported in literature.[97]



226b

(*R*)-1-((4a*R*,5*R*,8*S*,8a*R*)-5-Acetoxy-2-methoxy-3,8-dimethyl-1,4-dioxo-1,4,4a,5,8,8a-hexahydronaphthalen-4a-yl)but-3-en-1-yl acetate 226b.[97] This compound was prepared according to procedure of **226a** with 91 % yield from **231b**.

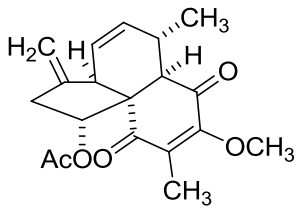
The spectral data were identical to those reported in literature.[97]



232a

(1*S*,3a*R*,6*S*,6a*R*,10a*R*)-8-Methoxy-6,9-dimethyl-3-methylene-7,10-dioxo-1,2,3,3a,6,6a,7,10-octahydrocyclopenta[d]naphthalen-1-yl acetate 232a.[97] Compound **226a** (6.1 g, 15.6 mmol) was diluted in CH_3COOH (390 mL, 0.04 M). The solution was degassed three times by pump and freeze and $Pd(PPh_3)_4$ (1.8 g, 10 mol%) was added. The solution was heated to 80 °C for 4 hours, thereafter cooled to ambient temperature and concentrated under reduced pressure. The recess was quenched with sat. aq. sodium hydrogen carbonate. The phases were separated, the water layer extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuum to give the product which was purified by chromatography to afford **232a** (3.5 mg, 10.61 mmol, 68 %).

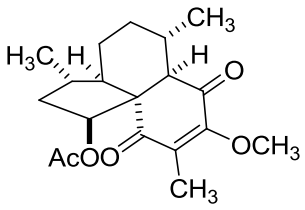
The spectral data were identical to those reported in literature.[97]



232b

(1*R*,3a*R*,6*S*,6a*R*,10a*R*)-8-methoxy-6,9-dimethyl-3-methylene-7,10-dioxo-1,2,3,3a,6,6a,7,10-octahydrocyclopenta[d]naphthalen-1-yl acetate 232b.[97] This compound was prepared according to procedure of **232a** with 89 % from **226b**.

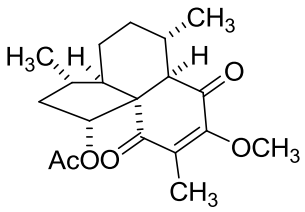
The spectral data were identical to those reported in literature.[97]



233a

(1*S*,3*S*,3a*R*,6*S*,6a*R*,10a*R*)-8-Methoxy-3,6,9-trimethyl-7,10-dioxo-1,2,3,3a,4,5,6,6a,7,10-decahydrocyclopenta[d]naphthalen-1-yl acetate 233a.[97] Compound **232a** (110 mg, 0.33 mmol) was dissolved in DCM (30mL, 0.1 M). Then Pd/C (11 mg, 10% w/w) was added. The atmosphere of the reaction was three times evacuated and flushed with molecular hydrogen. The reaction was stirred under hydrogen atmosphere for one hour. Filtration over a short plug of celite and removement of solvent, followed by column chromatography yielded pure **233a** (69 mg, 0.20 mmol 63 %).

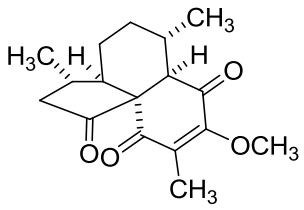
The spectral data were identical to those reported in literature.[97]



233b

(1*R*,3*S*,3a*R*,6*S*,6a*R*,10a*R*)-8-methoxy-3,6,9-trimethyl-7,10-dioxo-1,2,3,3a,4,5,6,6a,7,10-decahydrocyclopenta[d]naphthalen-1-yl acetate 233b.[97] This compound was prepared according to the procedure of **233a** with 65 % yield from **232b**.

The spectral data were identical to those reported in literature.[97]

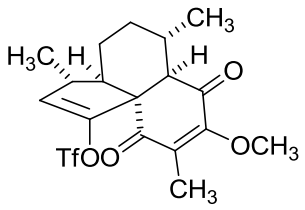


225

(3*S*,3a*R*,6*S*,6a*R*,10a*R*)-8-Methoxy-3,6,9-trimethyl-3,3a,4,5,6,6a-hexahydrocyclopenta[d]naphthalene-1,7,10(2H)-trione 225.[97] Compound **232a** (110 mg, 0.32 mmol) was dissolved in Et_2O (2 mL, 0.16 M) and cooled to 0 °C. Then LAH (3.28 mL, 1 M in THF, 3.28 mmol, 10 Eq.) was added and the reaction was allowed to warm up to ambient temperature. The reaction mixture was stirred at ambient temperature for 1 hour. The reaction was slowly quenched with H_2O. The phases were separated, the water layer extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuum to give the product which was used without further purification. The recess was dissolved in DMSO (8 mL, 0.04 M) and IBX (0.91g, 3.28 mmol, 10 Eq) was added. The solution was then heated to 80 °C for 6 hours, then cooled to room temperature and diluted with H_2O and Et_2O. The phases were separated, the water layer extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuum to give the product which was purified by chromatography to afford **225** (51 mg, 0.18 mmol, 55 %).

Applying this procedure to **232b** leaded to the same product with 45 % yield.

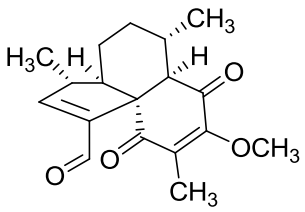
The spectral data were identical to those reported in literature.[97]



234

(3*R*,3a*R*,6*S*,6a*R*,10a*R*)-8-Methoxy-3,6,9-trimethyl-7,10-dioxo-3,3a,4,5,6,6a,7,10-octahydrocyclopenta[d]naphthalen-1-yl trifluoromethanesulfonate 234.[97] Compound **225** (82.9 mg, 0.29 mmol) was dissolved in THF (5 mL, 0.06 M) and cooled to -78 °C. Then LHMDS (0.43 mL, 1 M in toluene, 0.43 mmol, 1.5 Eq) was added slowly and the reaction was stirred at -78 °C for 30 minutes. Comin's reagent (336 mg, 0.89 mmol, 3 Eq.) was dissolved in tetrahydrofuran (1 mL) and added to the reaction. The reaction was stirred for another two hours and quenched by addition of sat. aq. ammonium chloride at -78°C. After warming to ambient temperature the phases were separated. The water layer extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuum to give the product which was purified by chromatography to afford **213** (99 mg, 0.23 mmol, 81 %).

The spectral data were identical to those reported in literature.[97]



236

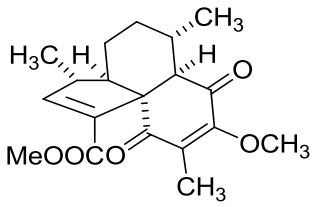
(3*S*,3a*R*,6*S*,6a*R*,10a*R*)-8-Methoxy-3,6,9-trimethyl-7,10-dioxo-3,3a,4,5,6,6a,7,10-octahydrocyclopenta[*d*]naphthalene-1-carbaldehyde 257. Triflate **234** (50 mg, 0.12 mmol), NEt_3 (33 µL, 0.24 mmol, 2 Eq.) and PPh_3 (9 mg, 0.04 mmol, 0.3 Eq.) were dissolved in DMF (1.2 mL,0.1 M) and the solution was degassed three times by pump and freeze with CO as return gas. Palladium (II) acetate (4 mg, 0.02 mmol, 15 mol%) was added to the mixture and then heated to 55°C. Et_3SiH (114 µL, 0.72 mmol, 6 Eq.) was dissolved in DMF (6 mL) and the solution was degassed 3 times by pump and freeze before it was dropped to the reaction mixture within 24 hours via a syringe pump. Et_2O and water was added and the phases were separated. The water layer extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuum to give the product which was purified by chromatography to afford **236** (29 mg, 0.09 mmol, 80 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.53 (s, 1H);6.93 (d, *J* = 3.0 Hz, 1H); 4.13 (s, 3H); 2.79 (m, 1H); 2.67 (m, 1H); 2.63 (d, *J* = 10.5, 1H); 2.11 (m, 1H); 1.83 (s, 3H); 1.69 (ddd, *J* = 13.9, 6.0, 2.5 Hz, 1H); 1.59 (m, 1H); 1.43 (d, *J* = 7.3 Hz, 3H); 1.37 (m, 1H); 1.23 (d, *J* = 6.6 Hz, 3H); 1.09 (m, 1H); ppm.

^{13}C NMR (100°MHz, $CDCl_3$): δ = 199.9; 193.8; 188.9; 165.6; 162.1;144.9; 128.6; 64.9; 60.4; 52.9; 48.3; 48.3; 26.2; 25.6; 24.9; 22.7;18.7;9.6 ppm.

HRMS: m/z calcd. for $C_{19}H_{24}O_5Na^+$: 325.1410; found: 324.1404;

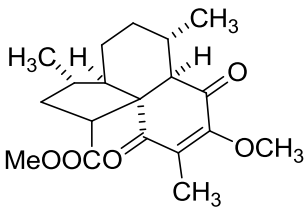
R_f: 0.48 (SiO_2, Hex:EE 3:1)



235

(3*S*,3a*R*,6*S*,6a*R*,10a*R*)-Methyl 8-methoxy-3,6,9-trimethyl-7,10-dioxo-3,3a,4,5,6,6a,7,10-octahydrocyclopenta[d]naphthalene-1-carboxylate 224.[97] Compound **234** (104 mg, 0.25 mmol), triphenylphosphine (9 mg, 0.04 mmol, 0.3 Eq), dimethylformamide (0.6 mL,0.4 M), MeOH (2.4 mL) and NEt_3 (54 µL, 0.49 mmol, 2 Eq) were mixed. The solution was degassed with carbon monoxide as return gas. Then palladium (II) acetate (8 mg, 0.04 mmol, 0.15 mol%) was added and the mixture was heated to 55°C. The reaction was stirred for 16 hours at 55°C, by addition of water and ether the reaction was stopped. The phases were separated, the water layer extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuum to give the product which was purified by chromatography to afford **235** (70 mg, 0.21 mmol, 84 %).

The spectral data were identical to those reported in literature.[97]



237

(3S,3aR,6S,6aR,101R)-Methyl 8-methoxy-3,6,9-trimethyl-7,10-dioxo-1,2,3,3a,4,5,6,6a,7,10-decahydrocyclopenta[d]naphthalene-1-carboxylate 237. Compound **235** (10 mg, 0.03 mmol) was dissolved in DCM (2mL, 0.15 M). Then Crabtree's catalyst (0.6 mg, 5% w/w) was added. The atmosphere of the reaction was three times evacuated and flushed with molecular hydrogen. The reaction was stirred under hydrogen atmosphere and heated to 40 °C for 20 hour. Removal of the solvent, followed by column chromatography yielded pure **237** (10 mg, 0.03 mmol, 99 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.03 (s, 3H); 3.52 (s, 3H); 3.11 (d, *J* = 5.4 Hz 1H); 2.66 (t, *J* = 9.3 Hz 1H); 2.42 (m, 1H); 2.37 (m, 1H); 2.29 (m, 1H); 2.18 (m, 1H); 1.94 (s, 3H); 1.78 (m, 1H); 1.66 (m, 1H); 1,51 (m, 1H); 1.45 (m, 1H); 1.35 (m, 1H); 1.04 (d, *J* = 6.4 Hz 3H); 0.65 (d, *J* = 7.4 Hz 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.67; 196.44; 174.20; 159.65; 134.50; 60.69; 60.12; 54.31; 51.96; 49.85; 46.52; 35.29; 34.40; 32.48; 27.01; 20.63; 18.24; 16.20; 10.31 ppm.

HRMS: m/z calcd. for $C_{19}H_{26}O_5Na^+$: 357.1672; found: 257.1676

R_f: 0.53 (SiO_2, Hex:EE 10:1)

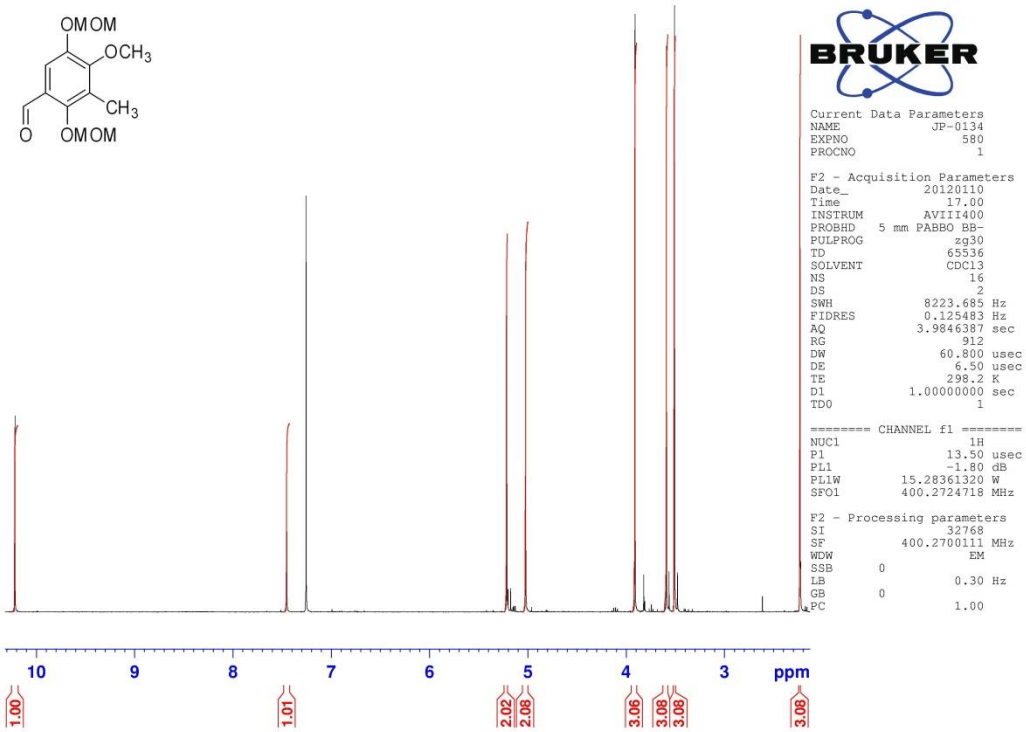
10 Appendix

10.1 Abbreviations

Acetyl CoA	Acetyl-Coenzyme A
AcOH	Acetic acid
allyl-TMS	Allyl-trimethylsilane
ATP	Adenosine triphosphate
CDP-ME	4-Diphosphocytidyl-2*C*-methylerythritol
CDP-MEP	4-Diphosphocytidyl-2*C*-methyl-*D*-erythritol 2-phosphate
CMK	4-Diphosphocytidyl-2*C*-methyl-*D*-erythritol kinase
CMS	4-Diphosphocytidyl-2*C*-methyl-*D*-erythritol synthase
DBU	1,8-Diazabicycloundec-7-ene
DCE	1,2 Dichloroethane
DCM	Dichloromethane
DIBAL-H	Diisobutyl aluminium hydride
DIPEA	Diisopropylethyl amine
DMAP	4-Dimethylaminopyridine
DMP	Dess Martin periodinane
DMS	Dimethylsulfide
DMSO	Dimethylsulfoxide
DXP	1-Deoxy-*D*-xylulose 5-phosphate
DXR	1-Deoxy-*D*-xylulose 5-phosphate reductase
DXS	1-Deoxy-*D*-xylulose 5-phosphate synthase
EtOAc	Ethylacetate
FPP	Farnesyl diphosphate
G3P	Glyceraldehyde 3-phosphate
GGPP	Geranylgeranyl diphosphate
GPP	Geranyl diphosphate
HDR	*(E)*-4-Hydroxy-3-methyl-but-2-enyl- pyrophosphate reductase
HMB-PP	*(E)*-4-Hydroxy-3-methyl-but-2-enyl- pyrophosphate
HMDS	*Bis*(trimethylsilyl)amine
HMG CoA	3-Hydroxy-3-methyl-glutaryl-Coenzyme A
HMG-CoA-reductas	3-Hydroxy-3-methyl-glutaryl-Coenzyme A reductase
HMG-CoA-synthase	3-Hydroxy-3-methyl-glutaryl-Coenzyme A synthase
IBX	2-Iodoxybenzoic acid
IPP	(hydroxy-(3-methylbut-3-enoxy)phosphoryl)Oxyphosphonic acid
IPP-isomerase	Isopentenyl pyrophosphate isomerase
LAH	Lithium aluminium hydride
LDA	Lithium diisopropylamide
LHMDS	Lithium *bis*(trimethylsilyl)amide

*m*CPBA	*meta* Chloroperoxybenzoic acid
MCS	2-*C*-methyl-*D*-erythritol 2,4-cyclodiphosphonate synthase
Mec-PP	2-*C*-methyl-*D*-erythritol 2,4-cyclopyrophosphonate
MEP	2-*C*-methyl-*D*-erythritol 4-phosphate
MeOH	Methanol
MOMCl	Chloromethyl methyl ether
MsCl	Methanesulfonyl chloride
NADH	Nicotinamide adenine dinucleotide
NADPH	Nicotinamide adenine dinucleotide phosphate
NaHMDS	Sodium *bis*(trimethylsilyl)amide
NBS	*N*-Bromosuccinimide
*n*BuLi	*n*-Butyllithium
PCC	Pyridinium chloro chromate
Pd/C	Palladium on activated charoal
PDC	Pyridinium dichromate
P_i	Phosphate group
PIDA	Phenyl iodo diacetate
PivCl	Pivaloyl chloride
PPh_3	Triphenylphosphine
ppm	Parts per million
py	Pyridine
Pyr	Pyruvate
*s*BuLi	*sec*-Butyllithium
TBAF	Tetrabutylammonium fluoride
TBSCl	*Tert*-butyl dimethylsilyl chloride
*t*BuLi	*tert*-Butyllithium
TCDI	Thiocarbonyl diimidazole
TESOTf	Triethylsilyl trifluoromethanesulfonate
THF	Tetrahydrofurane
TLC	Thin layer chromatography
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
TPP	Thiamine pyrophosphate
Tris	2-Amino-2-hydroxymethyl-propane-1,3-diol

10.2 Spectra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D1 1.00000000 sec
TD0 1
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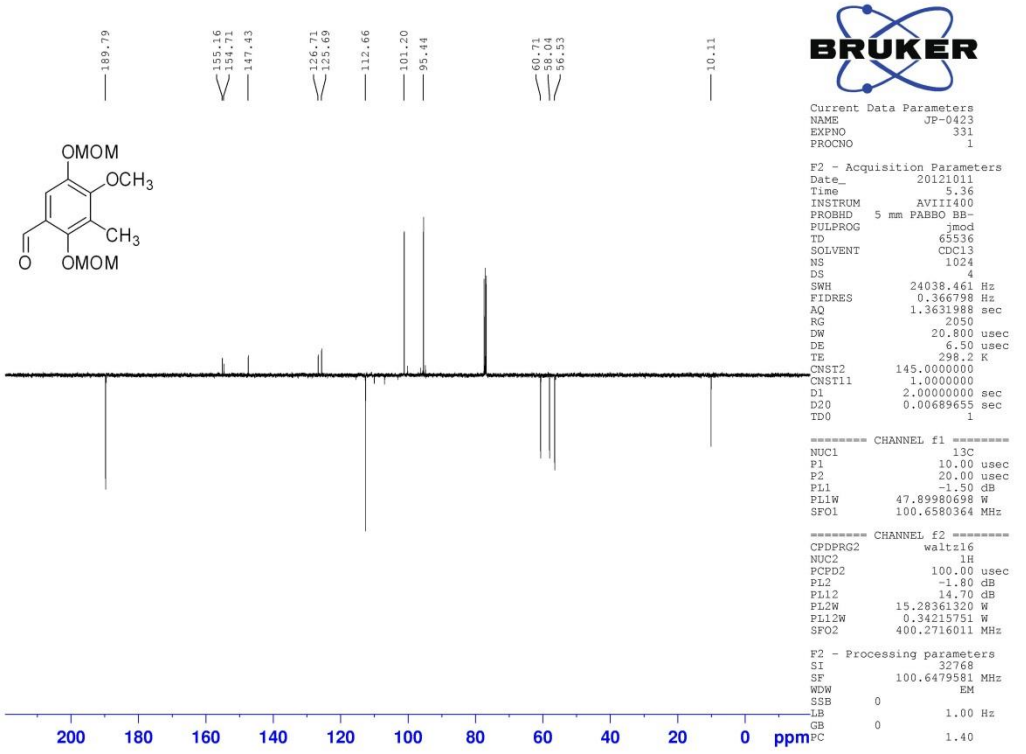
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60.71
58.04
56.53
10.11
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OCH3
CH3
O
OMOM
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160
140
120
100
80
60
40
20
0
ppm
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FIDRES 0.366798 Hz
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RG 2050
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DE 6.50 usec
TE 298.2 K
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CNST11 1.0000000
D1 2.00000000 sec
D20 0.00689655 sec
TD0 1
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P2 20.00 usec
PL1 -1.50 dB
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SFO1 100.6580364 MHz
======== CHANNEL f2 ========
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NUC2 1H
PCPD2 100.00 usec
PL2 -1.80 dB
PL12 14.70 dB
PL2W 15.28361320 W
PL12W 0.34215751 W
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F2 - Processing parameters
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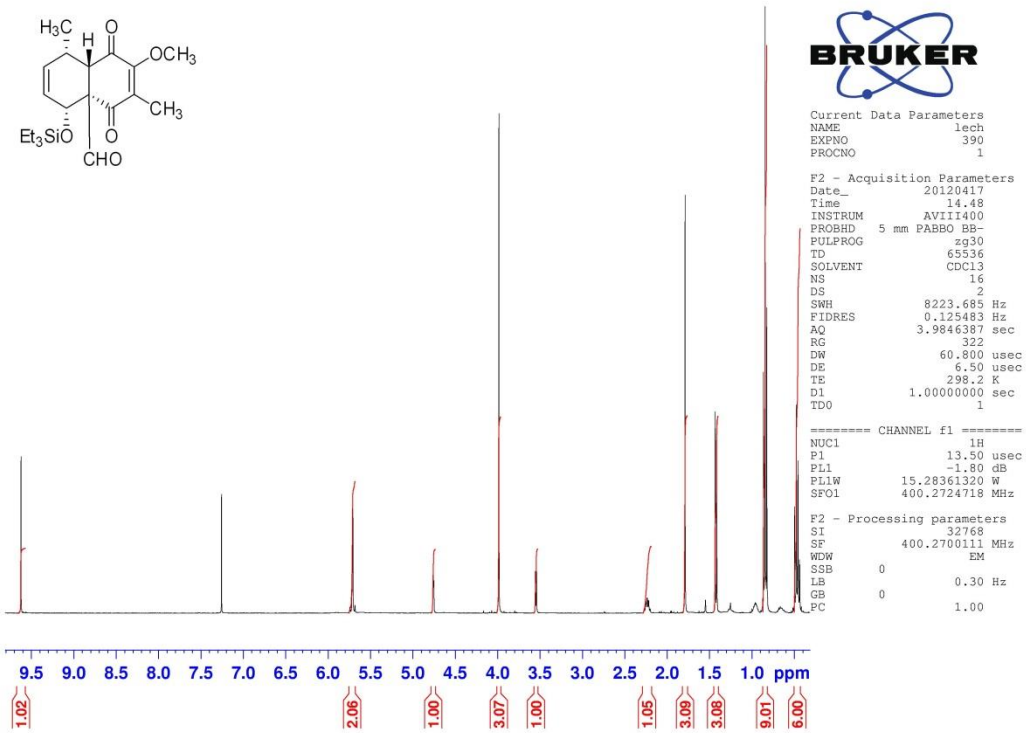
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LB 0.30 Hz
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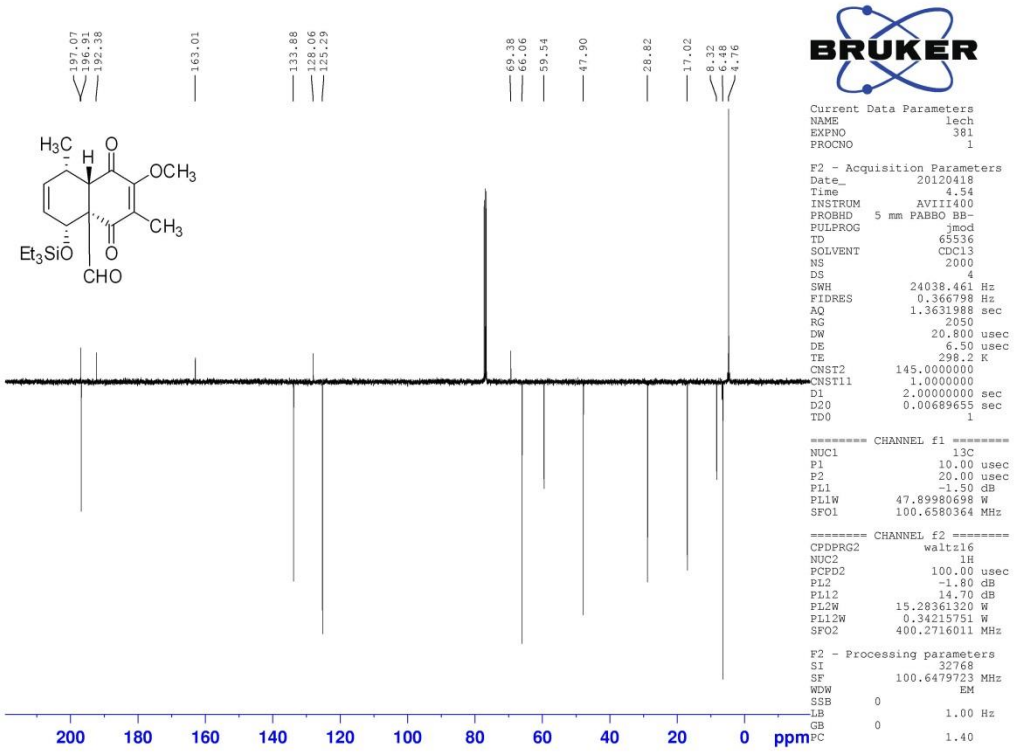
1.05
3.09
3.08
9.01
6.00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CNST11 1.0000000
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P2 20.00 usec
PL1 -1.50 dB
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SFO1 100.6580364 MHz
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NUC2 1H
PCPD2 100.00 usec
PL2 -1.80 dB
PL12 14.70 dB
PL2W 15.28361320 W
PL12W 0.34215751 W
SFO2 400.2716011 MHz
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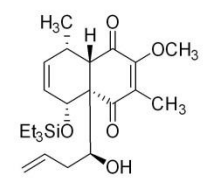


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TE                   298.2 K
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SFO1            400.2724718 MHz

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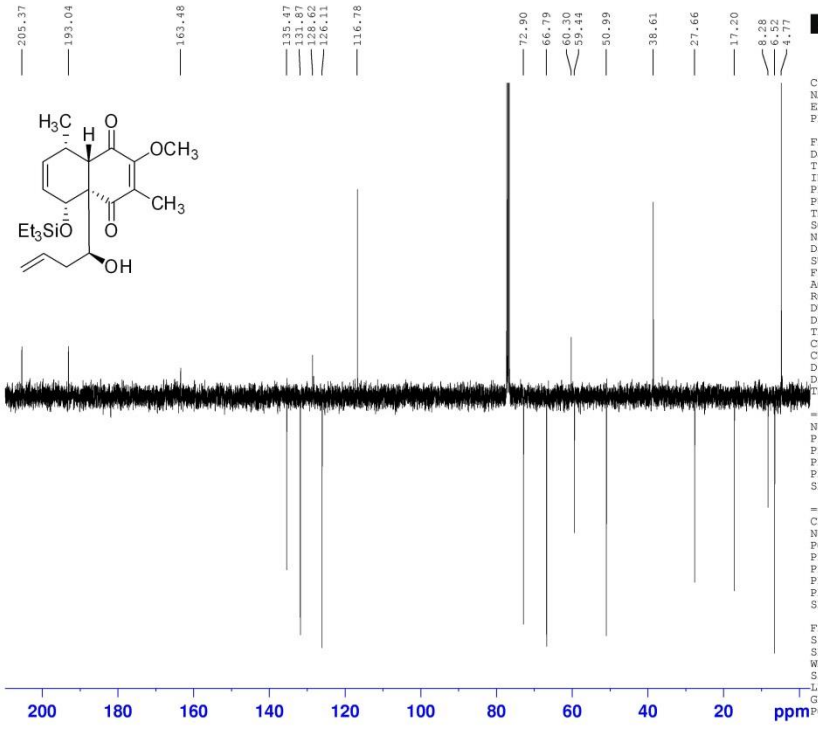


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D20               0.00689655 sec
TD0                         1

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PL1                     -1.50 dB
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SFO1            100.6580364 MHz

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NUC2                       1H
PCPD2                 100.00 usec
PL2                     -1.80 dB
PL12                    14.70 dB
PL2W             15.28361320 W
PL12W             0.34215751 W
SFO2            400.2716011 MHz

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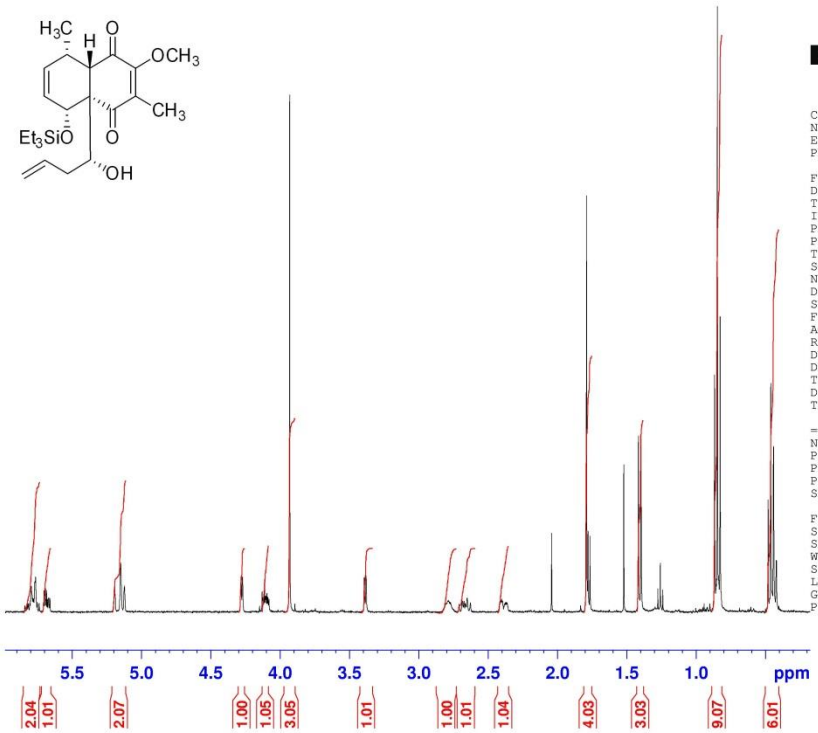

BRUKER

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TE                   298.2 K
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P1                     13.50 usec
PL1                    -1.80 dB
PL1W            15.28361320 W
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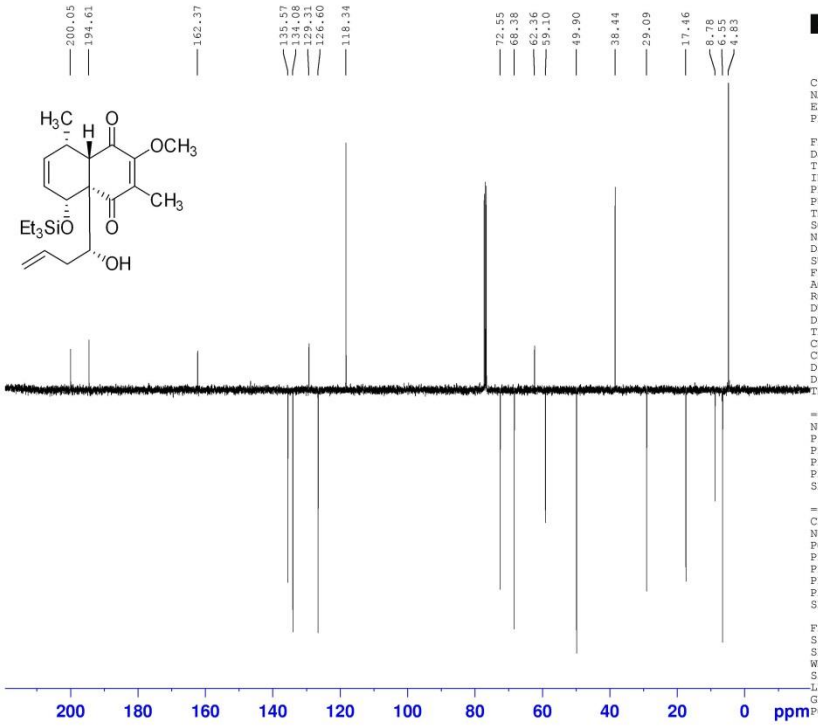

BRUKER

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TE                   298.2 K
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P1                    10.00 usec
P2                    20.00 usec
PL1                   -1.50 dB
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NUC2                      1H
PCPD2                100.00 usec
PL2                   -1.80 dB
PL12                  14.70 dB
PL2W           15.28361320 W
PL12W           0.34215751 W
SFO2           400.2716011 MHz

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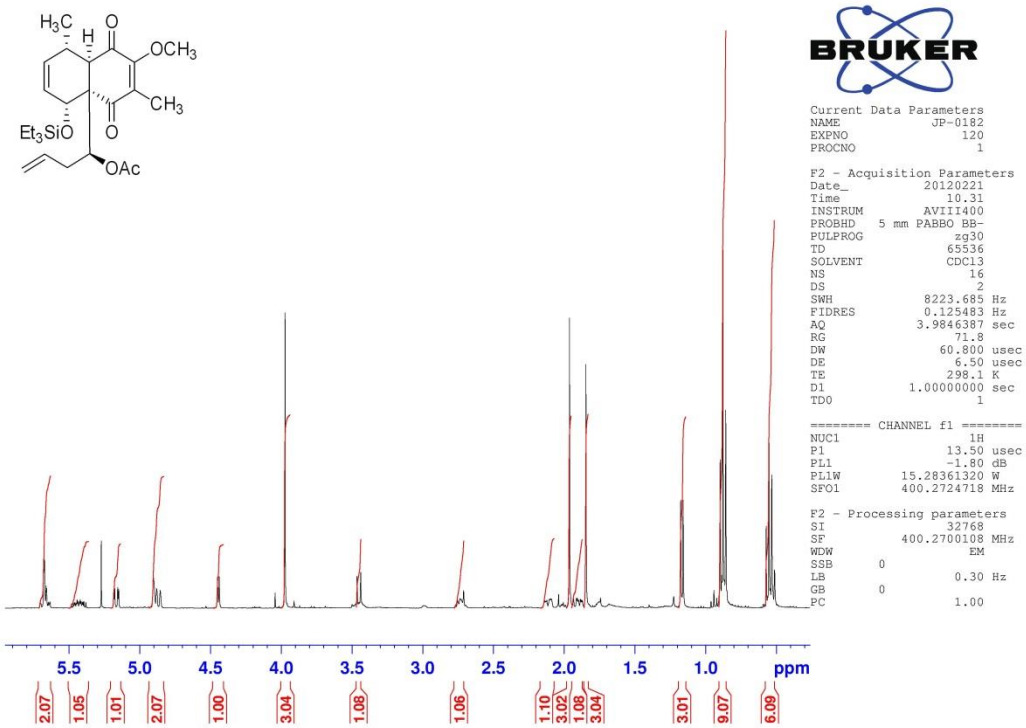
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FIDRES 0.125483 Hz
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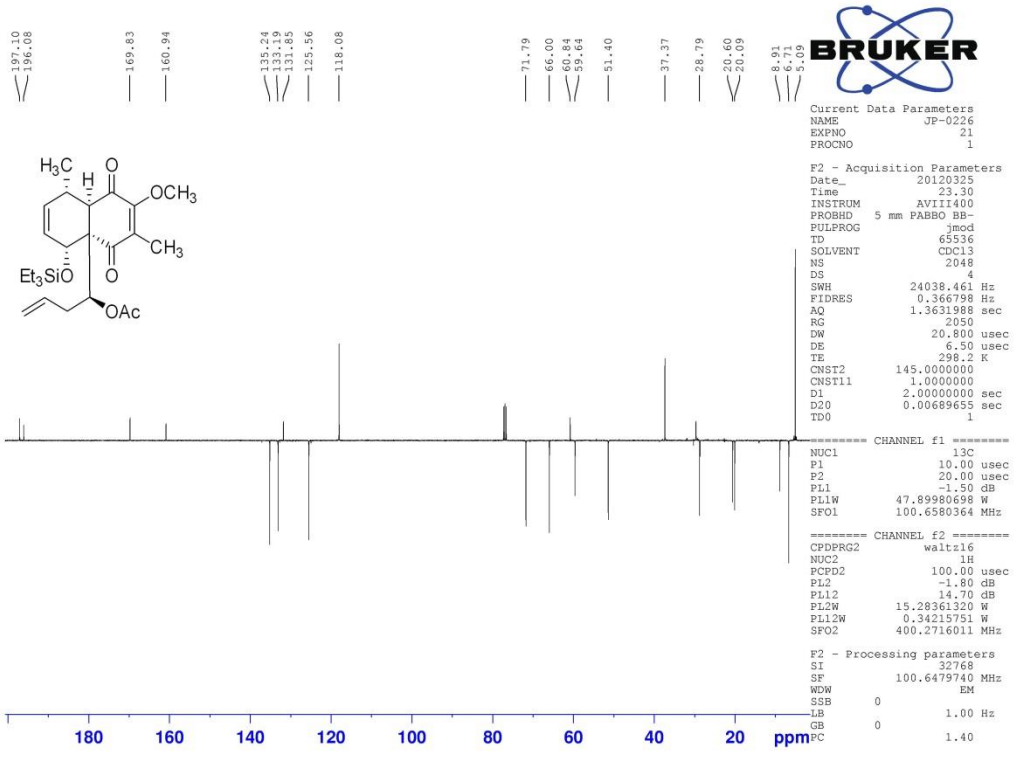
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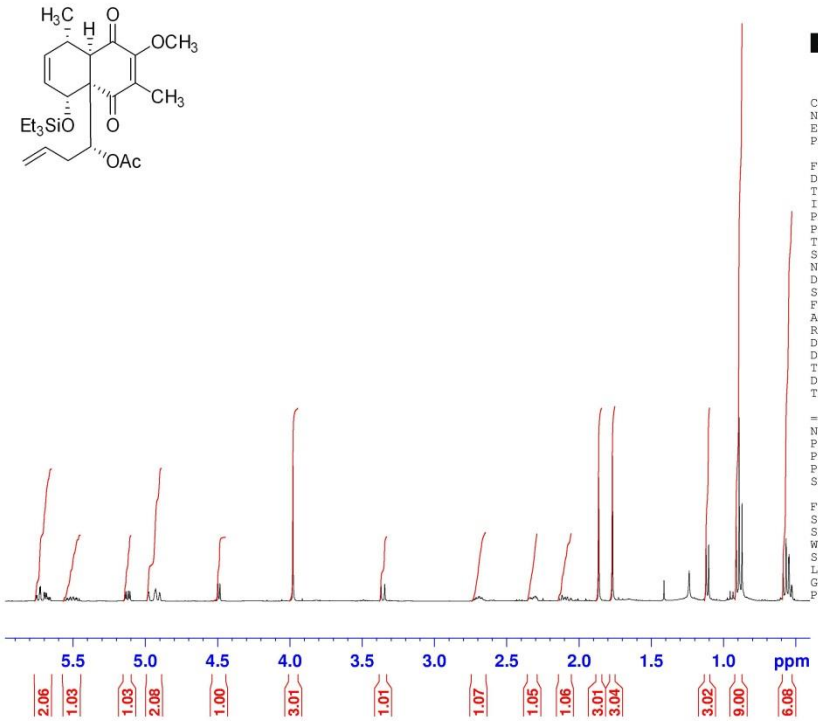
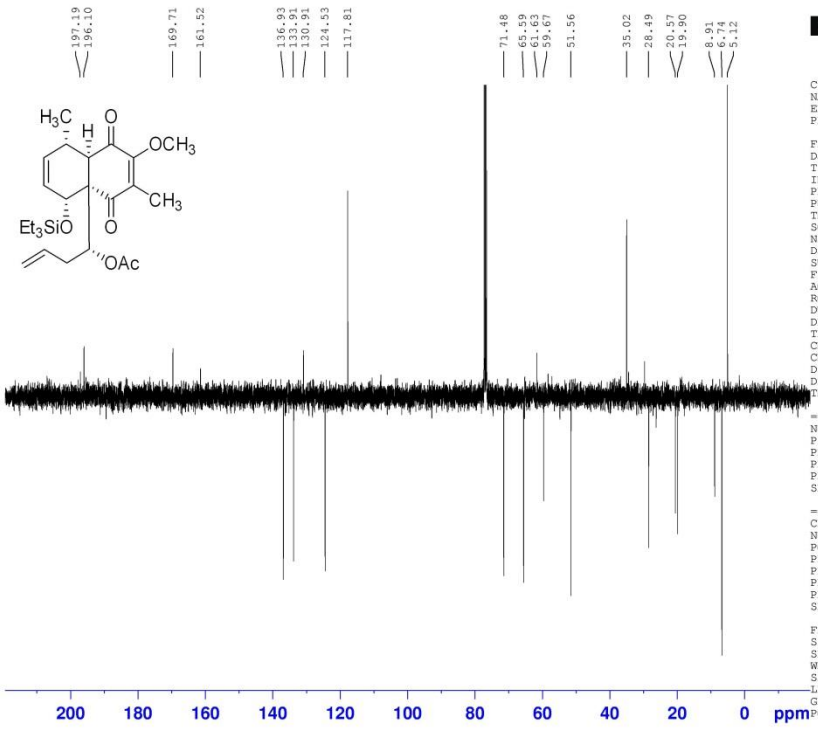
Date_ 20120325
Time 23.30
INSTRUM AVIII400
PROBHD 5 mm PABBO BB-
PULPROG jmod
TD 65536
SOLVENT CDCl3
NS 2048
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631988 sec
RG 2050
DW 20.800 usec
DE 6.50 usec
TE 298.2 K
CNST2 145.0000000
CNST11 1.0000000
D1 2.00000000 sec
D20 0.00689655 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 10.00 usec
P2 20.00 usec
PL1 -1.50 dB
PL1W 47.89980698 W
SFO1 100.6580364 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 -1.80 dB
PL12 14.70 dB
PL2W 15.28361320 W
PL12W 0.34215751 W
SFO2 400.2716011 MHz
F2 - Processing parameters
SI 32768
SF 100.6479740 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
180
160
140
120
100
80
60
40
20
ppm



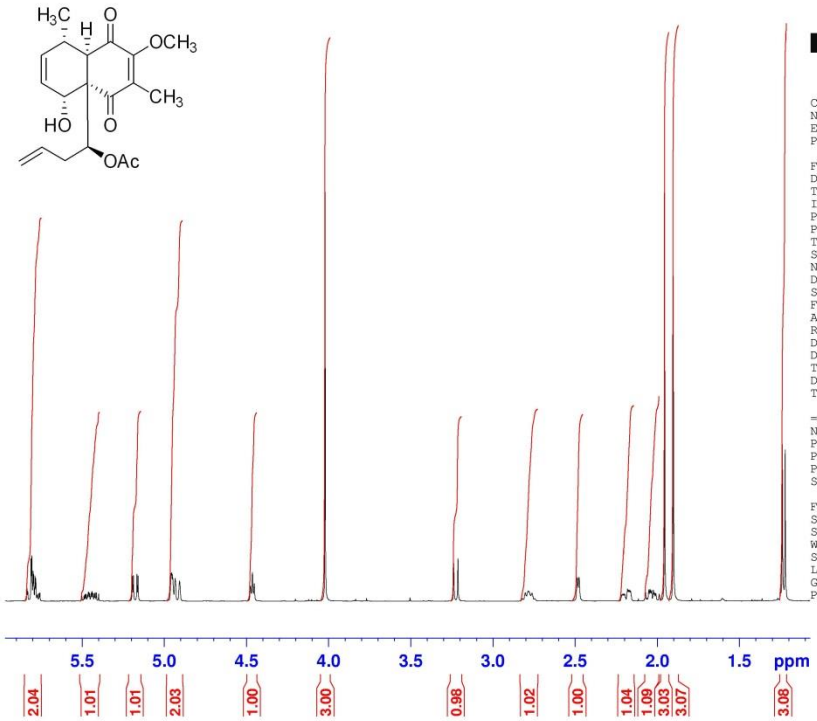
BRUKER

```
Current Data Parameters
NAME                  JP-0219
EXPNO                     160
PROCNO                      1

F2 - Acquisition Parameters
Date_              20120322
Time                  12.05
INSTRUM            AVIII400
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH                8223.685 Hz
FIDRES             0.125483 Hz
AQ                 3.9846387 sec
RG                      80.6
DW                   60.800 usec
DE                    6.50 usec
TE                   298.2 K
D1                1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       1H
P1                      13.50 usec
PL1                     -1.80 dB
PL1W             15.28361320 W
SFO1            400.2724718 MHz

F2 - Processing parameters
SI                        32768
SF               400.2700110 MHz
WDW                          EM
SSB          0
LB                      0.30 Hz
GB           0
PC                      1.00
```



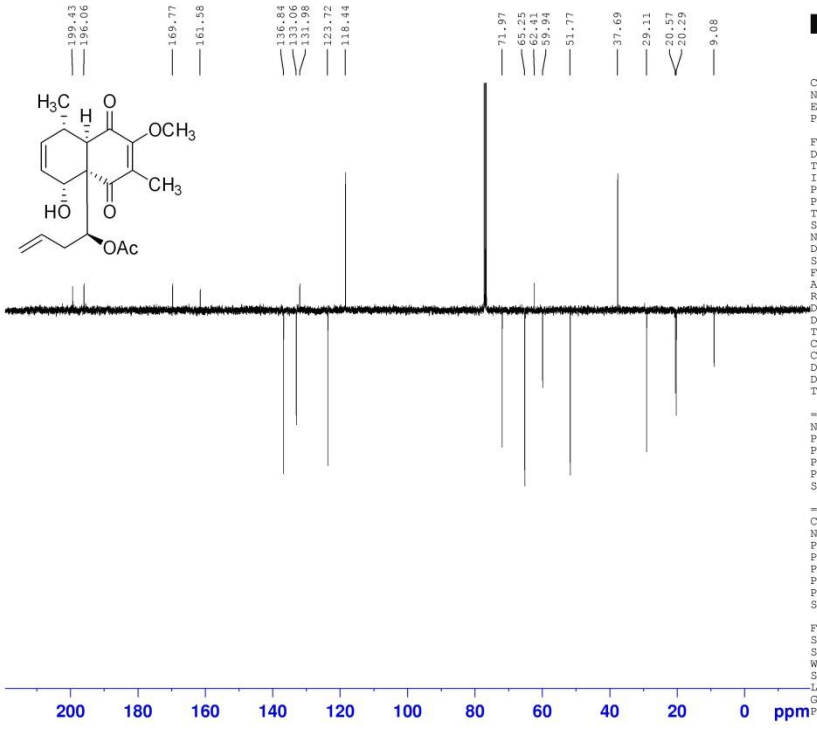
BRUKER

```
Current Data Parameters
NAME                  JP-0264
EXPNO                     101
PROCNO                      1

F2 - Acquisition Parameters
Date_              20120510
Time                   0.24
INSTRUM            AVIII400
PROBHD    5 mm PABBO BB-
PULPROG                jmod
TD                    65536
SOLVENT               CDCl3
NS                     4000
DS                        4
SWH               24038.461 Hz
FIDRES             0.366798 Hz
AQ                 1.3631988 sec
RG                      2050
DW                   20.800 usec
DE                    6.50 usec
TE                   298.2 K
CNST2             145.0000000
CNST11              1.0000000
D1                2.00000000 sec
D20               0.00689655 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                      13C
P1                      10.00 usec
P2                      20.00 usec
PL1                     -1.50 dB
PL1W             47.89980698 W
SFO1            100.6580364 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                       1H
PCPD2                 100.00 usec
PL2                     -1.80 dB
PL12                    14.70 dB
PL2W             15.28361320 W
PL12W             0.34215751 W
SFO2            400.2716011 MHz

F2 - Processing parameters
SI                        32768
SF               100.6479720 MHz
WDW                          EM
SSB          0
LB                      1.00 Hz
GB           0
PC                      1.40
```



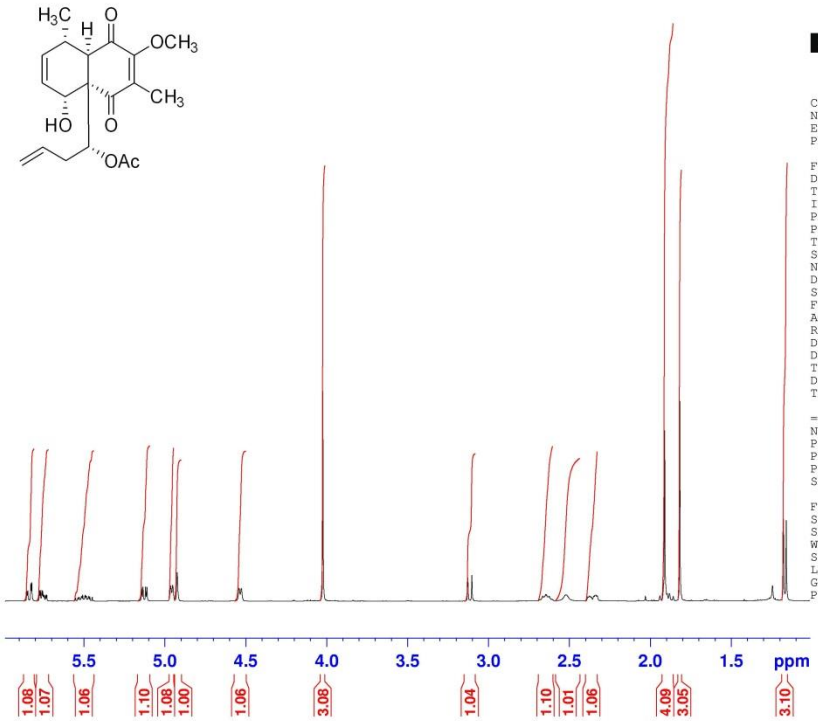
BRUKER

```
Current Data Parameters
NAME                  JP-0163
EXPNO                     470
PROCNO                      1

F2 - Acquisition Parameters
Date_              20120130
Time                   16.57
INSTRUM             AVIII400
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH                8223.685 Hz
FIDRES             0.125483 Hz
AQ                 3.9846387 sec
RG                      287
DW                   60.800 usec
DE                    6.50 usec
TE                   298.1 K
D1                1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       1H
P1                      13.50 usec
PL1                     -1.80 dB
PL1W             15.28361320 W
SFO1            400.2724718 MHz

F2 - Processing parameters
SI                        32768
SF               400.2700107 MHz
WDW                          EM
SSB          0
LB                      0.30 Hz
GB           0
PC                      1.00
```



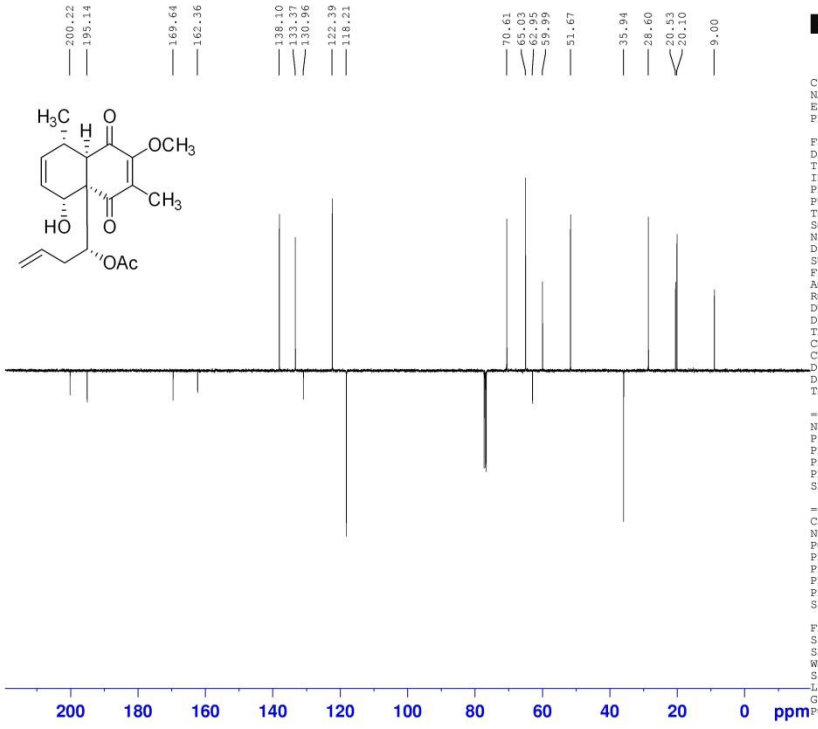
BRUKER

```
Current Data Parameters
NAME                  JP-0347
EXPNO                     151
PROCNO                      1

F2 - Acquisition Parameters
Date_              20120703
Time                    0.57
INSTRUM             AVIII400
PROBHD    5 mm PABBO BB-
PULPROG                jmod
TD                    65536
SOLVENT               CDCl3
NS                     2048
DS                        4
SWH               24038.461 Hz
FIDRES             0.366798 Hz
AQ                 1.3631988 sec
RG                      2050
DW                   20.800 usec
DE                    6.50 usec
TE                   298.2 K
CNST2             145.0000000
CNST11              1.0000000
D1                2.00000000 sec
D20               0.00689655 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                      13C
P1                      10.00 usec
P2                      20.00 usec
PL1                     -1.50 dB
PL1W             47.89980698 W
SFO1            100.6580364 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                       1H
PCPD2                 100.00 usec
PL2                     -1.80 dB
PL12                    14.70 dB
PL2W             15.28361320 W
PL12W             0.34215751 W
SFO2            400.2716011 MHz

F2 - Processing parameters
SI                        32768
SF               100.6479734 MHz
WDW                          EM
SSB          0
LB                      1.00 Hz
GB           0
PC                      1.40
```



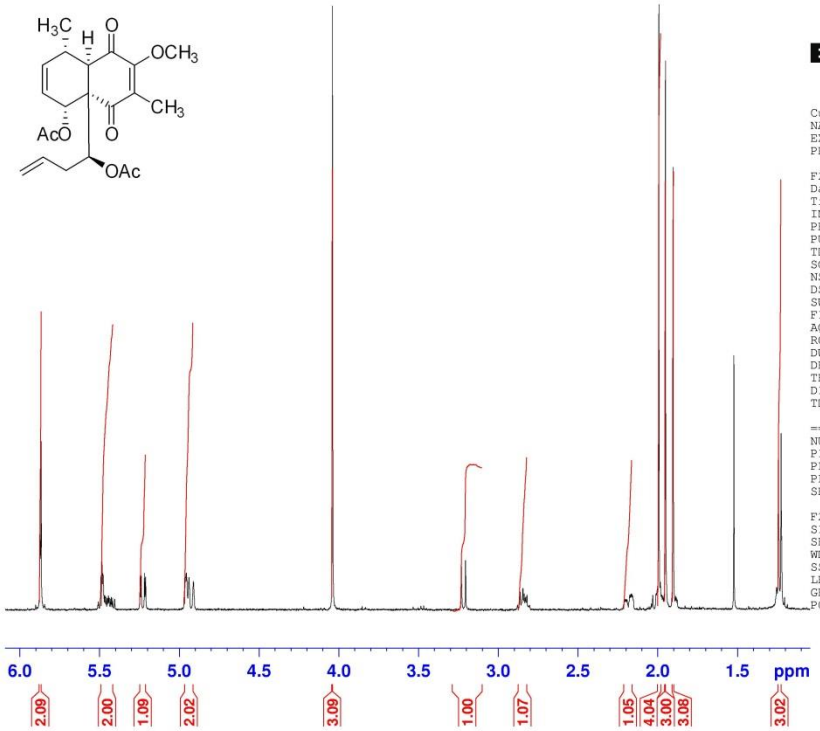
BRUKER

```
Current Data Parameters
NAME                  JP-0162
EXPNO                     460
PROCNO                      1

F2 - Acquisition Parameters
Date_               20120130
Time                   16.52
INSTRUM              AVIII400
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH                8223.685 Hz
FIDRES             0.125483 Hz
AQ                 3.9846387 sec
RG                      144
DW                   60.800 usec
DE                    6.50 usec
TE                   298.1 K
D1                1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       1H
P1                      13.50 usec
PL1                     -1.80 dB
PL1W             15.28361320 W
SFO1            400.2724718 MHz

F2 - Processing parameters
SI                        32768
SF               400.2700111 MHz
WDW                          EM
SSB          0
LB                      0.30 Hz
GB           0
PC                      1.00
```



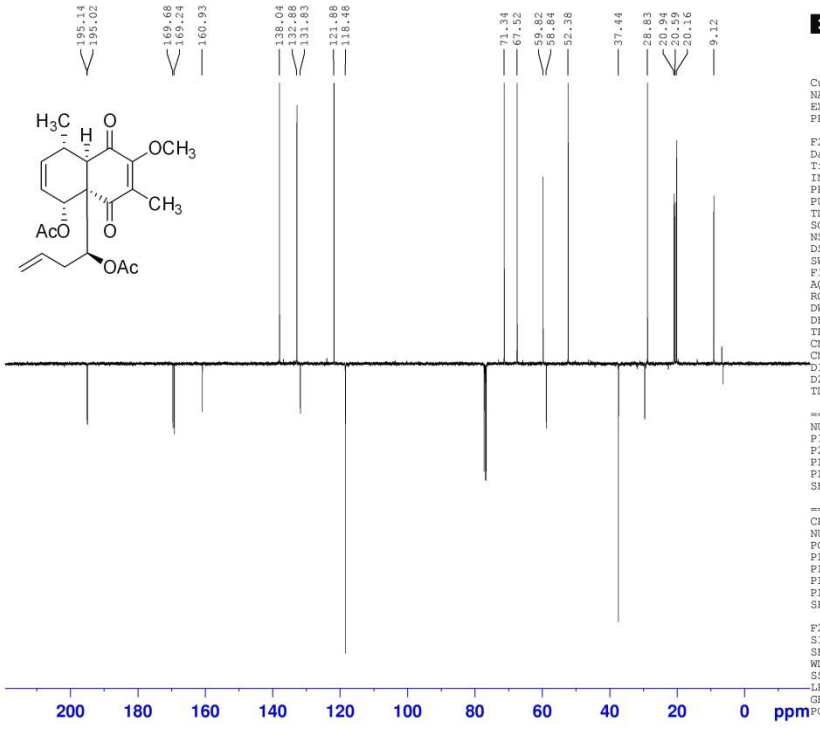
BRUKER

```
Current Data Parameters
NAME                  JP-0310
EXPNO                     281
PROCNO                      1

F2 - Acquisition Parameters
Date_               20120629
Time                    5.18
INSTRUM              AVIII400
PROBHD    5 mm PABBO BB-
PULPROG                jmod
TD                    65536
SOLVENT               CDCl3
NS                     2048
DS                        4
SWH               24038.461 Hz
FIDRES             0.366798 Hz
AQ                 1.3631988 sec
RG                      2050
DW                   20.800 usec
DE                    6.50 usec
TE                   298.2 K
CNST2            145.0000000
CNST11             1.0000000
D1                 2.00000000 sec
D20                0.00689655 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                      13C
P1                      10.00 usec
P2                      20.00 usec
PL1                     -1.50 dB
PL1W             47.89980698 W
SFO1            100.6580364 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                       1H
PCPD2                 100.00 usec
PL2                     -1.80 dB
PL12                    14.70 dB
PL2W             15.28361320 W
PL12W             0.34215751 W
SFO2            400.2716011 MHz

F2 - Processing parameters
SI                        32768
SF               100.6479720 MHz
WDW                          EM
SSB          0
LB                      1.00 Hz
GB           0
PC                      1.40
```



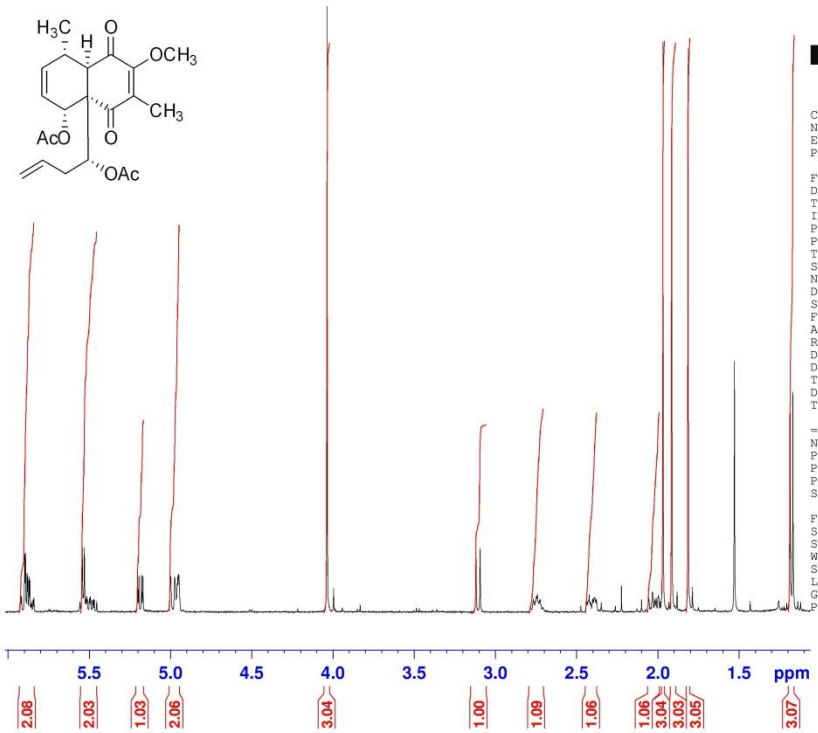
BRUKER

```
Current Data Parameters
NAME                  JP-0231
EXPNO                     270
PROCNO                      1

F2 - Acquisition Parameters
Date_               20120328
Time                   16.30
INSTRUM              AVIII400
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH                8223.685 Hz
FIDRES             0.125483 Hz
AQ                 3.9846387 sec
RG                      1150
DW                   60.800 usec
DE                    6.50 usec
TE                    298.2 K
D1                 1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       1H
P1                      13.50 usec
PL1                     -1.80 dB
PL1W              15.28361320 W
SFO1             400.2724718 MHz

F2 - Processing parameters
SI                        32768
SF                 400.2700112 MHz
WDW                          EM
SSB                 0
LB                        0.30 Hz
GB                  0
PC                        1.00
```



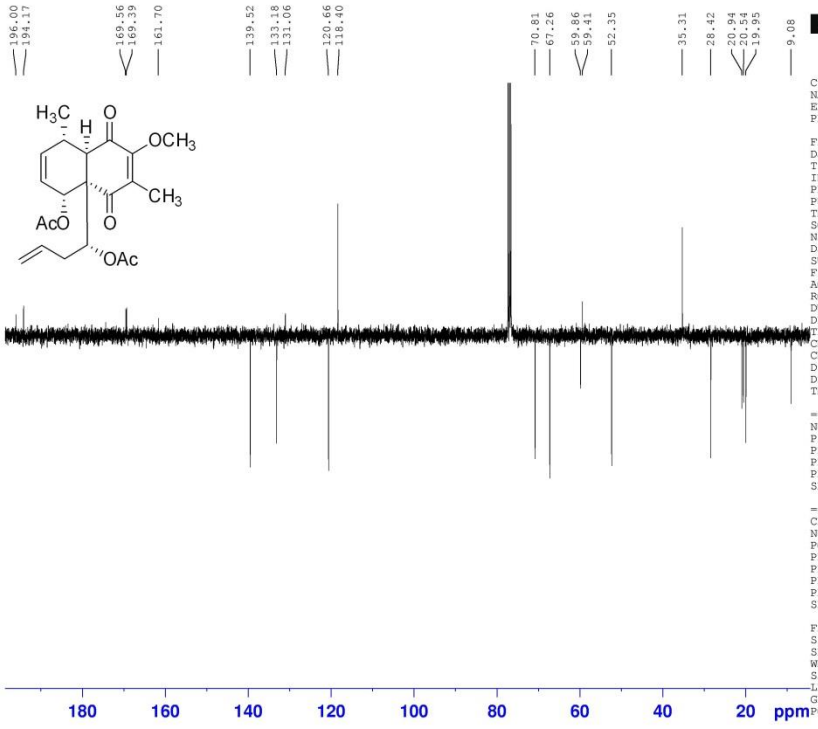
BRUKER

```
Current Data Parameters
NAME                  JP-0255
EXPNO                      31
PROCNO                      1

F2 - Acquisition Parameters
Date_               20120421
Time                   22.29
INSTRUM              AVIII400
PROBHD    5 mm PABBO BB-
PULPROG                jmod
TD                    65536
SOLVENT               CDCl3
NS                     2048
DS                        4
SWH               24038.461 Hz
FIDRES             0.366798 Hz
AQ                 1.3631988 sec
RG                      2050
DW                   20.800 usec
DE                    6.50 usec
TE                    298.2 K
CNST2             145.0000000
CNST11              1.0000000
D1                 2.00000000 sec
D20                0.00689655 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                      13C
P1                      10.00 usec
P2                      20.00 usec
PL1                     -1.50 dB
PL1W              47.89980698 W
SFO1             100.6580364 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                       1H
PCPD2                 100.00 usec
PL2                     -1.80 dB
PL12                    14.70 dB
PL2W              15.28361320 W
PL12W              0.34215751 W
SFO2             400.2716011 MHz

F2 - Processing parameters
SI                        32768
SF                 100.6479740 MHz
WDW                          EM
SSB                 0
LB                        1.00 Hz
GB                  0
PC                        1.40
```



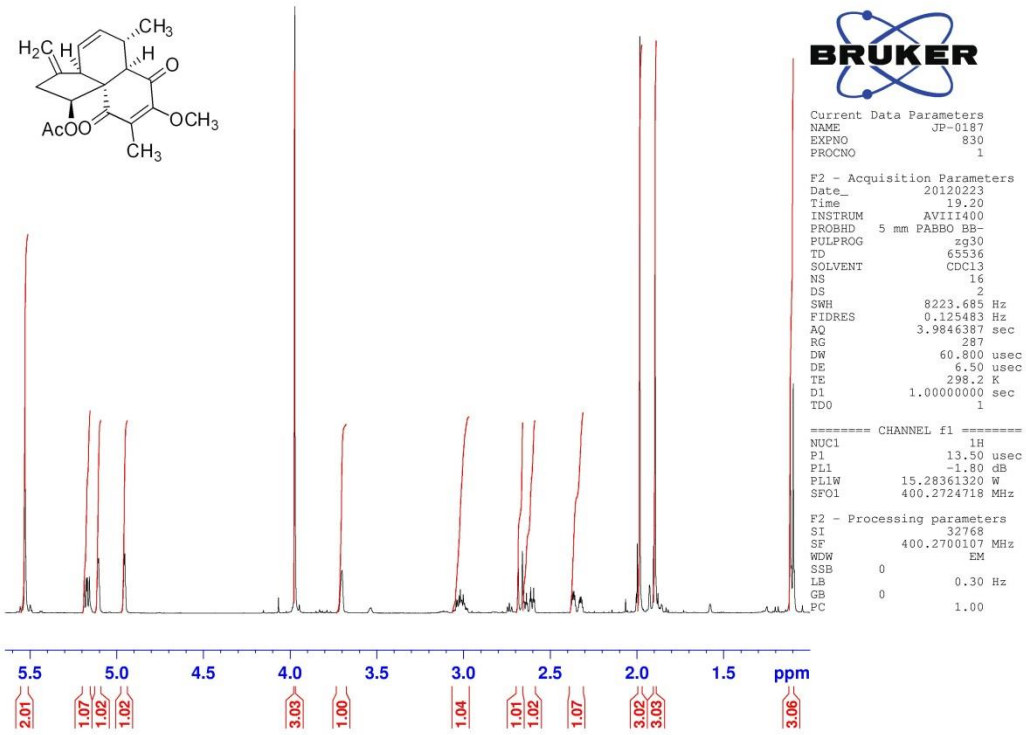
BRUKER

```
Current Data Parameters
NAME                  JP-0312
EXPNO                      60
PROCNO                      1

F2 - Acquisition Parameters
Date_              20120604
Time                   11.17
INSTRUM             AVIII400
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH                8223.685 Hz
FIDRES             0.125483 Hz
AQ                 3.9846387 sec
RG                      1150
DW                   60.800 usec
DE                    6.50 usec
TE                   298.2 K
D1              1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       1H
P1                      13.50 usec
PL1                     -1.80 dB
PL1W            15.28361320 W
SFO1           400.2724718 MHz

F2 - Processing parameters
SI                      32768
SF             400.2700110 MHz
WDW                        EM
SSB          0
LB                      0.30 Hz
GB           0
PC                      1.00
```



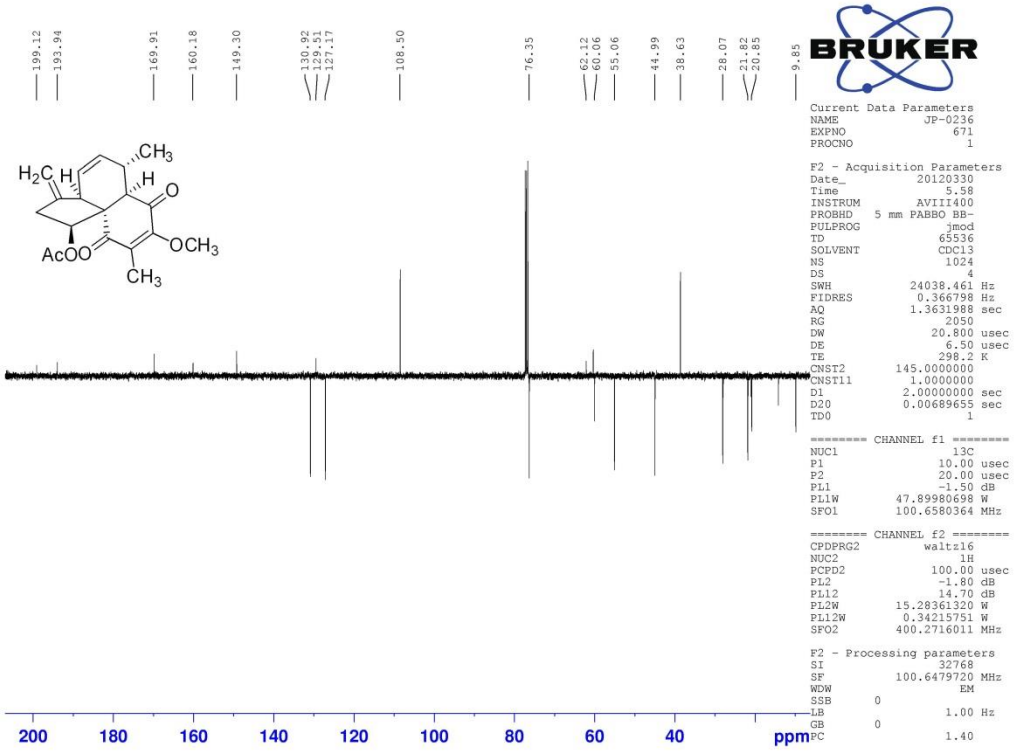
BRUKER

```
Current Data Parameters
NAME                  JP-0312
EXPNO                     390
PROCNO                      1

F2 - Acquisition Parameters
Date_              20120608
Time                    2.17
INSTRUM             AVIII400
PROBHD    5 mm PABBO BB-
PULPROG                jmod
TD                    65536
SOLVENT               CDCl3
NS                       6000
DS                          4
SWH               24038.461 Hz
FIDRES             0.366798 Hz
AQ                 1.3631988 sec
RG                      2050
DW                   20.800 usec
DE                    6.50 usec
TE                   298.2 K
CNST2          145.0000000
CNST11           1.0000000
D1               2.00000000 sec
D20              0.00689655 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                      13C
P1                      10.00 usec
P2                      20.00 usec
PL1                     -1.50 dB
PL1W            47.89980698 W
SFO1           100.6580364 MHz

======== CHANNEL f2 ========
CPDPRG2              waltz16
NUC2                       1H
PCPD2                 100.00 usec
PL2                     -1.80 dB
PL12                    14.70 dB
PL2W            15.28361320 W
PL12W            0.34215751 W
SFO2           400.2716011 MHz

F2 - Processing parameters
SI                      32768
SF             100.6479720 MHz
WDW                        EM
SSB          0
LB                      1.00 Hz
GB           0
PC                      1.40
```



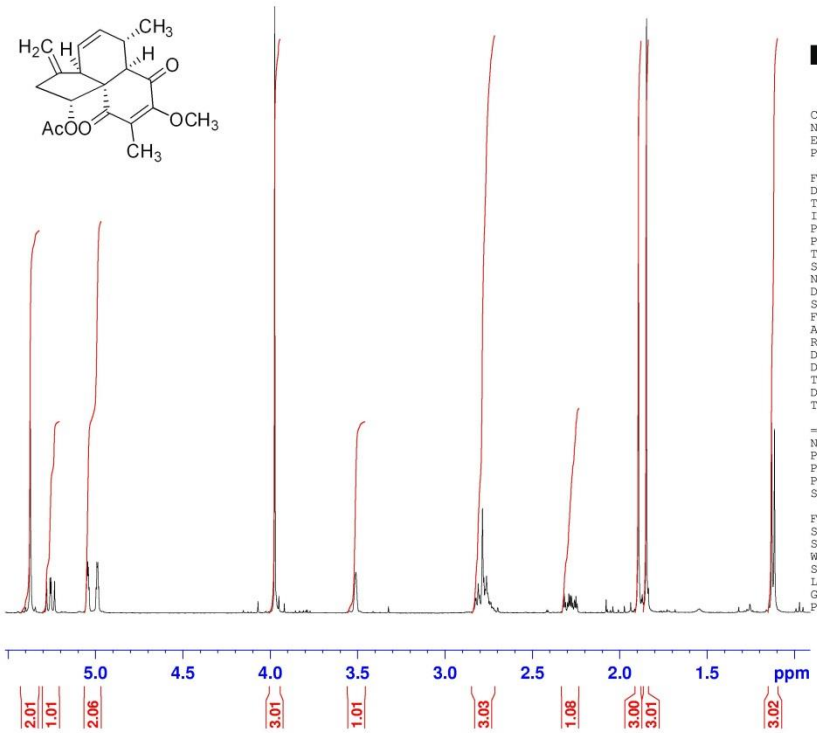
BRUKER

```
Current Data Parameters
NAME                  JP-0187
EXPNO                     830
PROCNO                      1

F2 - Acquisition Parameters
Date_              20120223
Time                  19.20
INSTRUM            AVIII400
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH                8223.685 Hz
FIDRES             0.125483 Hz
AQ                 3.9846387 sec
RG                      287
DW                   60.800 usec
DE                    6.50 usec
TE                   298.2 K
D1              1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       1H
P1                      13.50 usec
PL1                     -1.80 dB
PL1W            15.28361320 W
SFO1           400.2724718 MHz

F2 - Processing parameters
SI                      32768
SF             400.2700107 MHz
WDW                        EM
SSB          0
LB                      0.30 Hz
GB           0
PC                      1.00
```



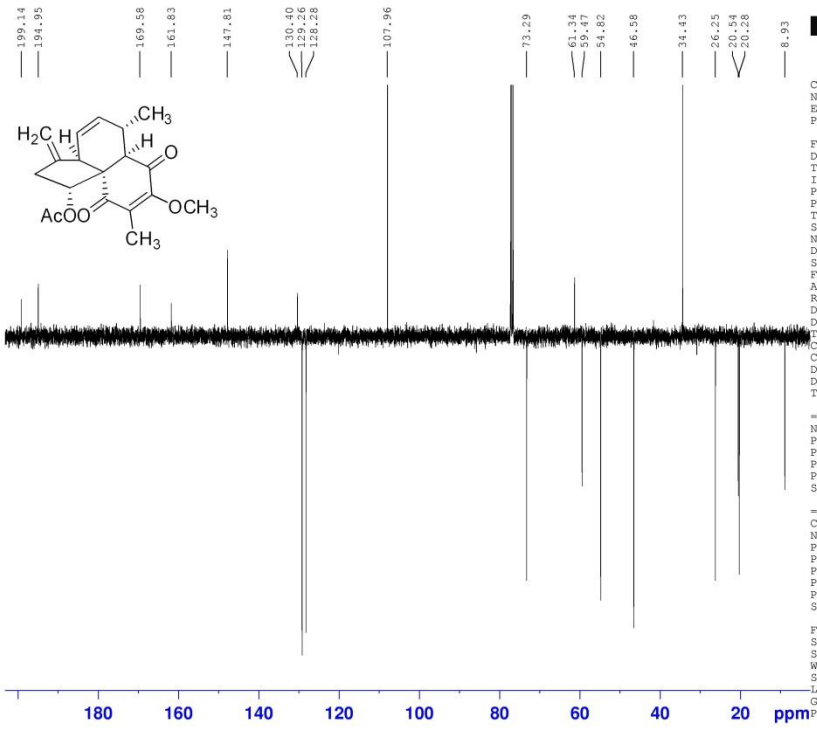
BRUKER

```
Current Data Parameters
NAME                  JP-0236
EXPNO                     671
PROCNO                      1

F2 - Acquisition Parameters
Date_              20120330
Time                   5.58
INSTRUM            AVIII400
PROBHD    5 mm PABBO BB-
PULPROG                jmod
TD                    65536
SOLVENT               CDCl3
NS                     1024
DS                        4
SWH               24038.461 Hz
FIDRES             0.366798 Hz
AQ                 1.3631988 sec
RG                     2050
DW                   20.800 usec
DE                    6.50 usec
TE                   298.2 K
CNST2             145.0000000
CNST11              1.0000000
D1              2.00000000 sec
D20             0.00689655 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                      13C
P1                      10.00 usec
P2                      20.00 usec
PL1                     -1.50 dB
PL1W            47.89980698 W
SFO1           100.6580364 MHz

======== CHANNEL f2 ========
CPDPRG2               waltz16
NUC2                       1H
PCPD2                 100.00 usec
PL2                     -1.80 dB
PL12                    14.70 dB
PL2W            15.28361320 W
PL12W            0.34215751 W
SFO2           400.2716011 MHz

F2 - Processing parameters
SI                      32768
SF             100.6479720 MHz
WDW                        EM
SSB          0
LB                      1.00 Hz
GB           0
PC                      1.40
```



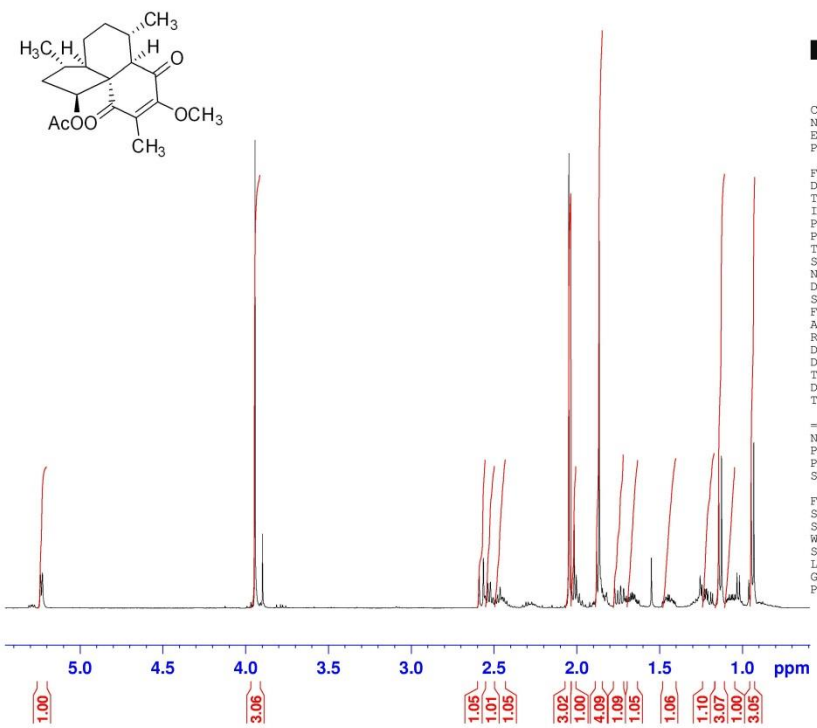
BRUKER

```
Current Data Parameters
NAME                  JP-0271
EXPNO                     260
PROCNO                      1

F2 - Acquisition Parameters
Date_              20120508
Time                  16.18
INSTRUM           AVIII400
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH                8223.685 Hz
FIDRES             0.125483 Hz
AQ                 3.9846387 sec
RG                      645
DW                  60.800 usec
DE                   6.50 usec
TE                   298.2 K
D1              1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       1H
P1                    13.50 usec
PL1                   -1.80 dB
PL1W           15.28361320 W
SFO1          400.2724718 MHz

F2 - Processing parameters
SI                        32768
SF               400.2700109 MHz
WDW                          EM
SSB          0
LB                     0.30 Hz
GB           0
PC                     1.00
```



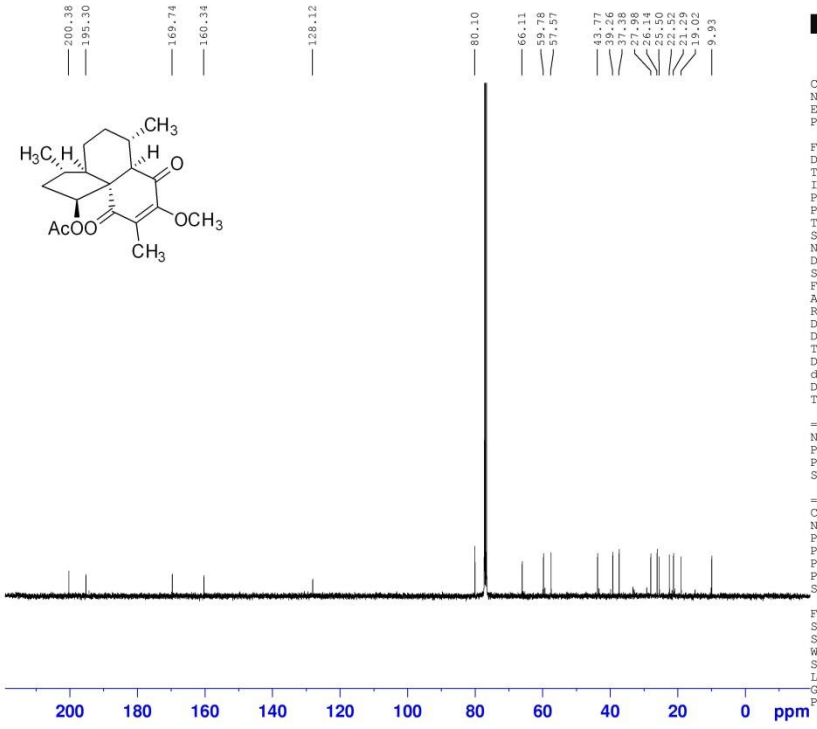
BRUKER

```
Current Data Parameters
NAME                  JP-0271
EXPNO                     261
PROCNO                      1

F2 - Acquisition Parameters
Date_              20120509
Time                   1.32
INSTRUM           AVIII400
PROBHD    5 mm PABBO BB-
PULPROG                jmod
TD                    65536
SOLVENT               CDCl3
NS                     1024
DS                        4
SWH               24038.461 Hz
FIDRES             0.366798 Hz
AQ                 1.3631988 sec
RG                      2050
DW                  20.800 usec
DE                   6.50 usec
TE                   298.2 K
CNST2          145.0000000
CNST11           1.0000000
D1              2.00000000 sec
D20             0.00689655 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                      13C
P1                    10.00 usec
P2                    20.00 usec
PL1                   -1.50 dB
PL1W           47.89980698 W
SFO1          100.6580364 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                       1H
PCPD2                100.00 usec
PL2                   -1.80 dB
PL12                  14.70 dB
PL2W           15.28361320 W
PL12W           0.34215751 W
SFO2          400.2716011 MHz

F2 - Processing parameters
SI                        32768
SF               100.6479731 MHz
WDW                          EM
SSB          0
LB                     1.00 Hz
GB           0
PC                     1.40
```



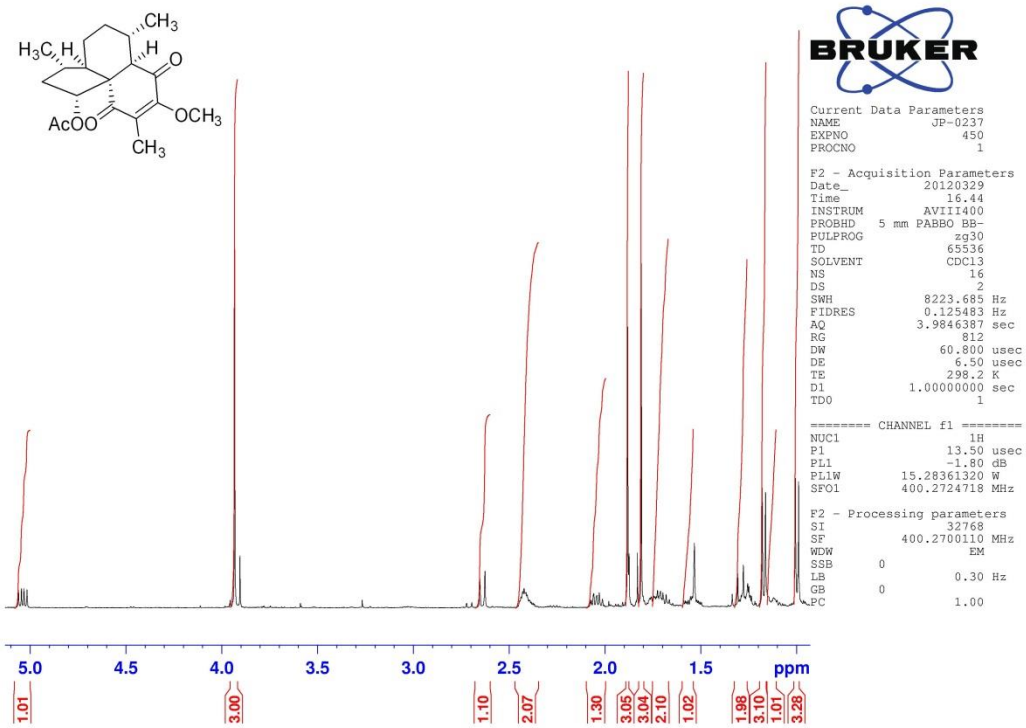
BRUKER

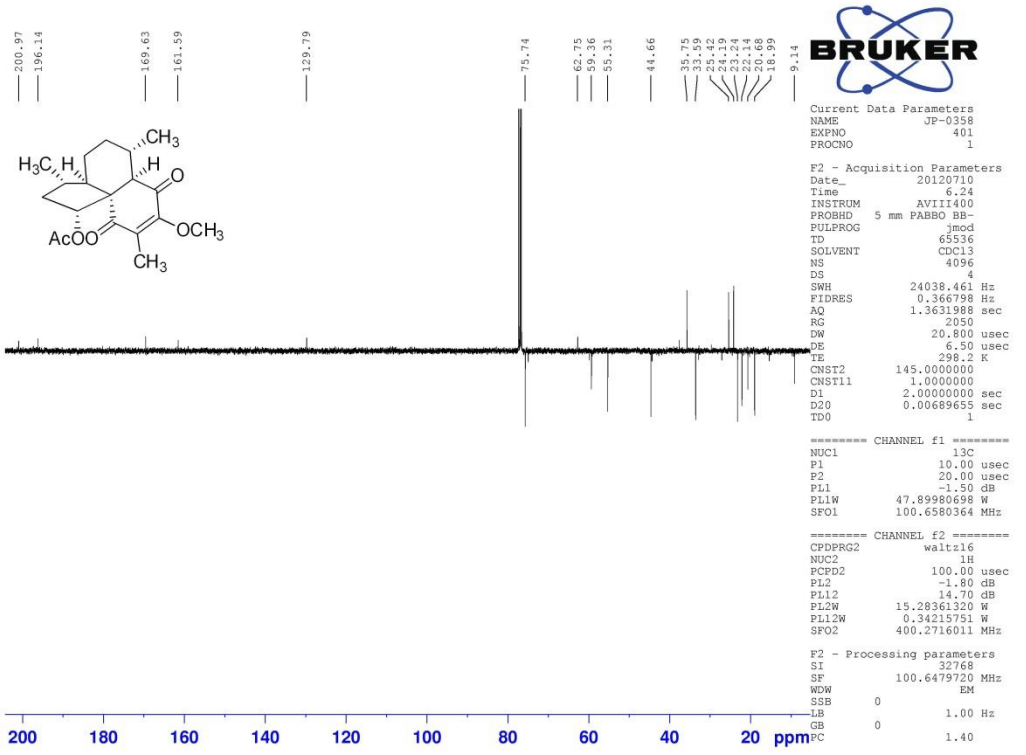
```
Current Data Parameters
NAME                  JP-0204
EXPNO                      47
PROCNO                      1

F2 - Acquisition Parameters
Date_               20120308
Time                    8.29
INSTRUM              avance400
PROBHD    5 mm BBO BB-1H
PULPROG                 zg30
TD                     65536
SOLVENT                CDCl3
NS                        64
DS                         2
SWH                 8278.146 Hz
FIDRES              0.126314 Hz
AQ                  3.9584243 sec
RG                       362
DW                    60.400 usec
DE                     6.00 usec
TE                     300.2 K
D1                1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       1H
P1                      8.75 usec
PL1                    -3.00 dB
SFO1           400.1324710 MHz

F2 - Processing parameters
SI                      32768
SF             400.1300090 MHz
WDW                        EM
SSB          0
LB                      0.30 Hz
GB           0
PC                      1.00
```

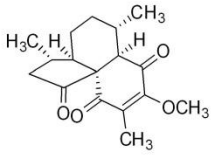


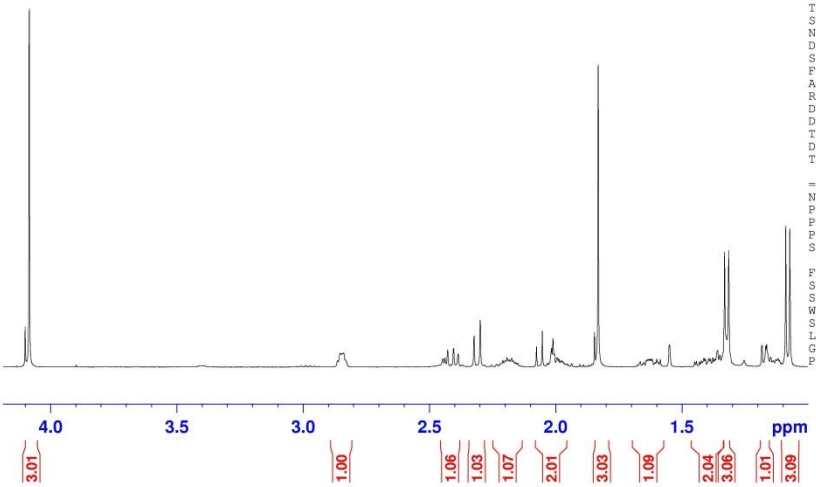
BRUKER

```
Current Data Parameters
NAME                  JP-0204
EXPNO                      46
PROCNO                      1

F2 - Acquisition Parameters
Date_               20120308
Time                    8.20
INSTRUM              avance400
PROBHD    5 mm BBO BB-1H
PULPROG             zgpg30
TD                     65536
SOLVENT                CDCl3
NS                      1977
DS                         4
SWH                23980.814 Hz
FIDRES              0.365918 Hz
AQ                  1.3664756 sec
RG                      4096
DW                    20.850 usec
DE                     6.00 usec
TE                     300.2 K
D1                2.00000000 sec
d11               0.03000000 sec
DELTA             1.89999998 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                      13C
P1                     10.30 usec
PL1                    -1.00 dB
SFO1           100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                       1H
PCPD2                 100.00 usec
PL2                    -3.00 dB
PL12                   16.00 dB
PL13                   20.00 dB
SFO2           400.1316005 MHz

F2 - Processing parameters
SI                      32768
SF             100.6127692 MHz
WDW                        EM
SSB          0
LB                      1.00 Hz
GB           0
PC                      1.40
```


CH3
H3C
H
O
AcOO
OCH3
CH3
BRUKER
Current Data Parameters
NAME JP-0237
EXPNO 450
PROCNO 1
F2 - Acquisition Parameters
Date_ 20120329
Time 16.44
INSTRUM AVIII400
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9846387 sec
RG 812
DW 60.800 usec
DE 6.50 usec
TE 298.2 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 13.50 usec
PL1 -1.80 dB
PL1W 15.28361320 W
SFO1 400.2724718 MHz
F2 - Processing parameters
SI 32768
SF 400.2700110 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
1.01
3.00
1.10
2.07
1.30
3.05
3.04
2.10
1.02
1.98
3.10
1.01
3.28


200.97
196.14
169.63
161.59
129.79
75.74
62.75
59.36
55.31
44.66
35.75
33.59
25.42
24.29
23.24
22.14
20.68
18.99
9.14
CH3
H3C
H
O
AcOO
OCH3
CH3
BRUKER
Current Data Parameters
NAME JP-0358
EXPNO 401
PROCNO 1
F2 - Acquisition Parameters
Date_ 20120710
Time 6.24
INSTRUM AVIII400
PROBHD 5 mm PABBO BB-
PULPROG jmod
TD 65536
SOLVENT CDCl3
NS 4096
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631988 sec
RG 2050
DW 20.800 usec
DE 6.50 usec
TE 298.2 K
CNST2 145.0000000
CNST11 1.0000000
D1 2.00000000 sec
D20 0.00689655 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 10.00 usec
P2 20.00 usec
PL1 -1.50 dB
PL1W 47.89980698 W
SFO1 100.6580364 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 -1.80 dB
PL12 14.70 dB
PL2W 15.28361320 W
PL12W 0.34215751 W
SFO2 400.2716011 MHz
F2 - Processing parameters
SI 32768
SF 100.6479720 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
200
180
160
140
120
100
80
60
40
20
ppm





BRUKER

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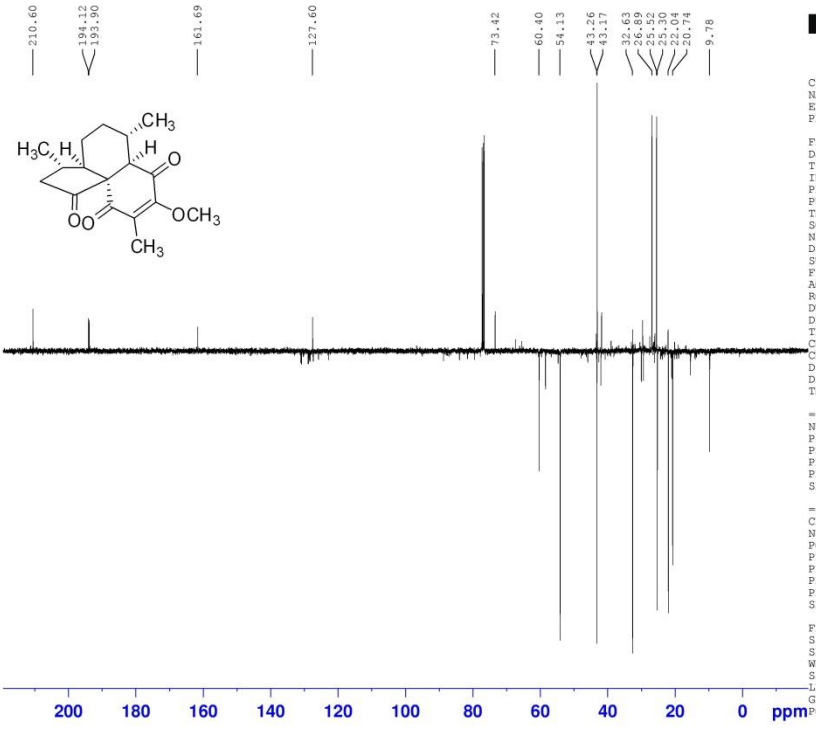
Current Data Parameters
NAME                  JP-0259
EXPNO                     500
PROCNO                      1

F2 - Acquisition Parameters
Date_                20120504
Time                    17.50
INSTRUM              AVIII400
PROBHD    5 mm PABBO BB-
PULPROG                 zg30
TD                     65536
SOLVENT                CDCl3
NS                        16
DS                         2
SWH                 8223.685 Hz
FIDRES              0.125483 Hz
AQ                  3.9846387 sec
RG                       512
DW                    60.800 usec
DE                     6.50 usec
TE                     298.2 K
D1                1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       1H
P1                      13.50 usec
PL1                     -1.80 dB
PL1W             15.28361320 W
SFO1            400.2724718 MHz

F2 - Processing parameters
SI                       32768
SF                400.2700108 MHz
WDW                         EM
SSB          0
LB                      0.30 Hz
GB           0
PC                      1.00
```



BRUKER

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Current Data Parameters
NAME                  JP-0360
EXPNO                     541
PROCNO                      1

F2 - Acquisition Parameters
Date_                20120713
Time                     7.53
INSTRUM              AVIII400
PROBHD    5 mm PABBO BB-
PULPROG                 jmod
TD                     65536
SOLVENT                CDCl3
NS                        2048
DS                           4
SWH                24038.461 Hz
FIDRES              0.366798 Hz
AQ                  1.3631988 sec
RG                        2050
DW                    20.800 usec
DE                     6.50 usec
TE                     298.2 K
CNST2             145.0000000
CNST11              1.0000000
D1                2.00000000 sec
D20               0.00689655 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                      13C
P1                     10.00 usec
P2                     20.00 usec
PL1                     -1.50 dB
PL1W             47.89980698 W
SFO1            100.6580364 MHz

======== CHANNEL f2 ========
CPDPRG2              waltz16
NUC2                       1H
PCPD2                100.00 usec
PL2                     -1.80 dB
PL12                    14.70 dB
PL2W             15.28361320 W
PL12W             0.34215751 W
SFO2            400.2716011 MHz

F2 - Processing parameters
SI                       32768
SF                100.6479747 MHz
WDW                         EM
SSB          0
LB                      1.00 Hz
GB           0
PC                      1.40
```
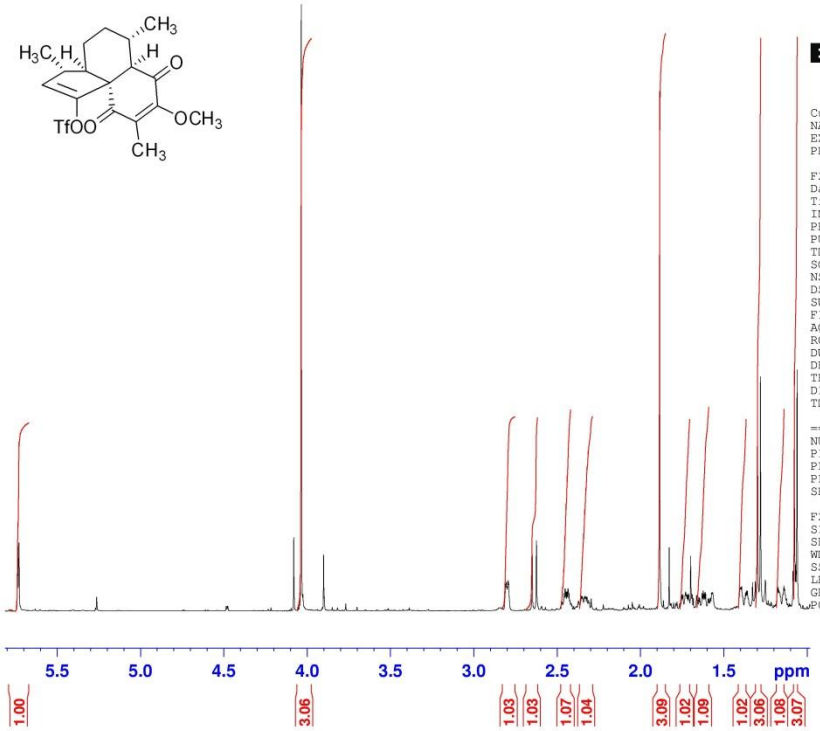
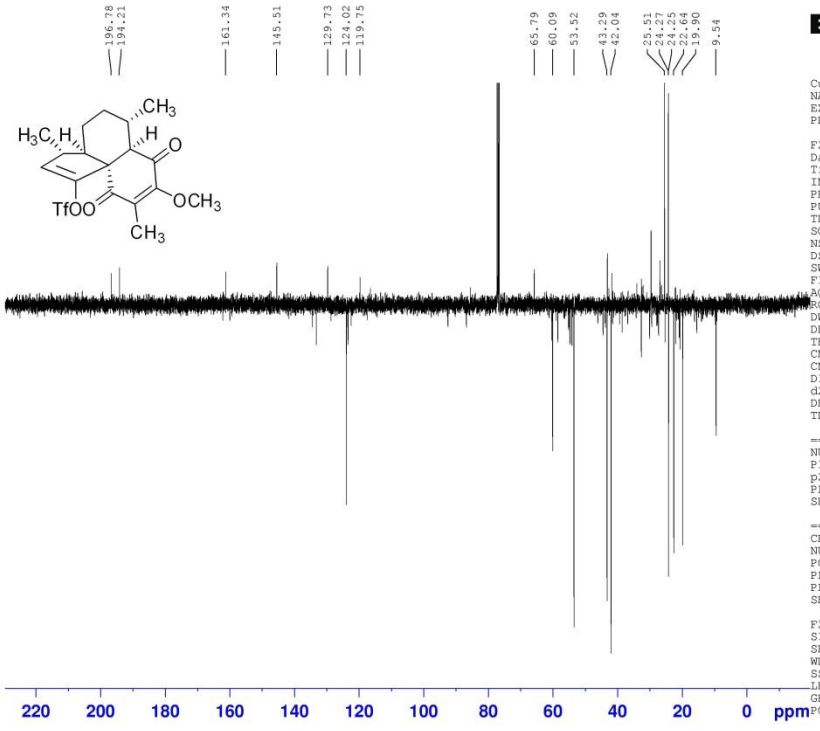



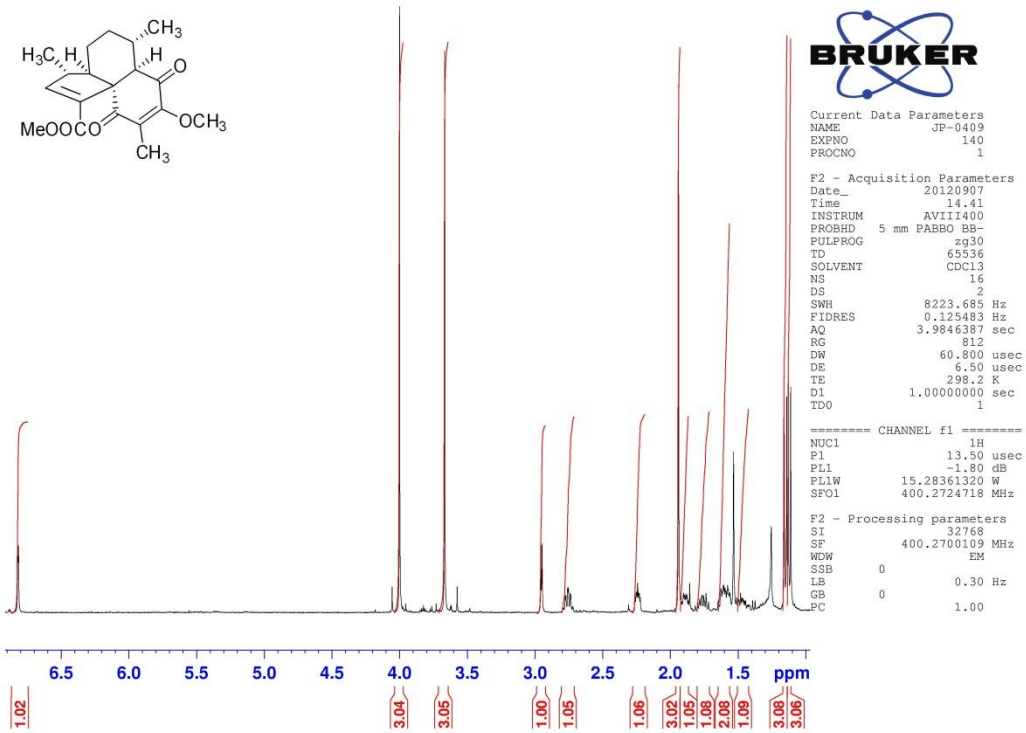
BRUKER

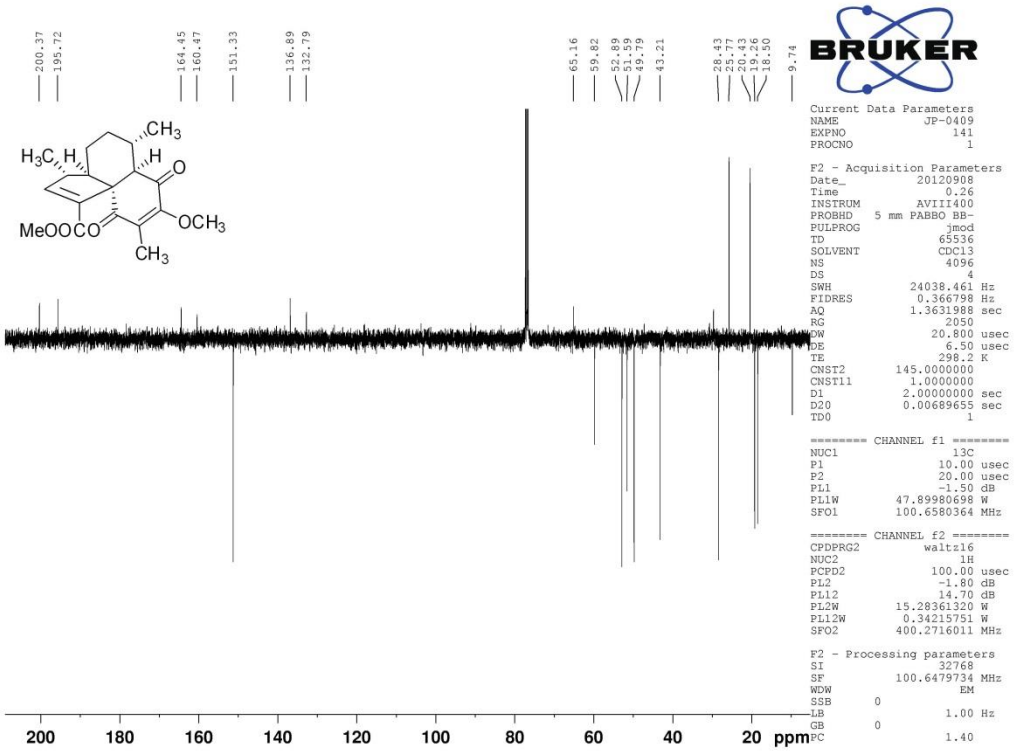
```
Current Data Parameters
NAME                  JP-0403
EXPNO                     100
PROCNO                      1

F2 - Acquisition Parameters
Date_               20120829
Time                   10.14
INSTRUM              AVIII400
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH                8223.685 Hz
FIDRES             0.125483 Hz
AQ                 3.9846387 sec
RG                       203
DW                  60.800 usec
DE                   6.50 usec
TE                   298.2 K
D1                1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       1H
P1                      13.50 usec
PL1                     -1.80 dB
PL1W             15.28361320 W
SFO1            400.2724718 MHz

F2 - Processing parameters
SI                        32768
SF               400.2700109 MHz
WDW                          EM
SSB          0
LB                      0.30 Hz
GB           0
PC                      1.00
```

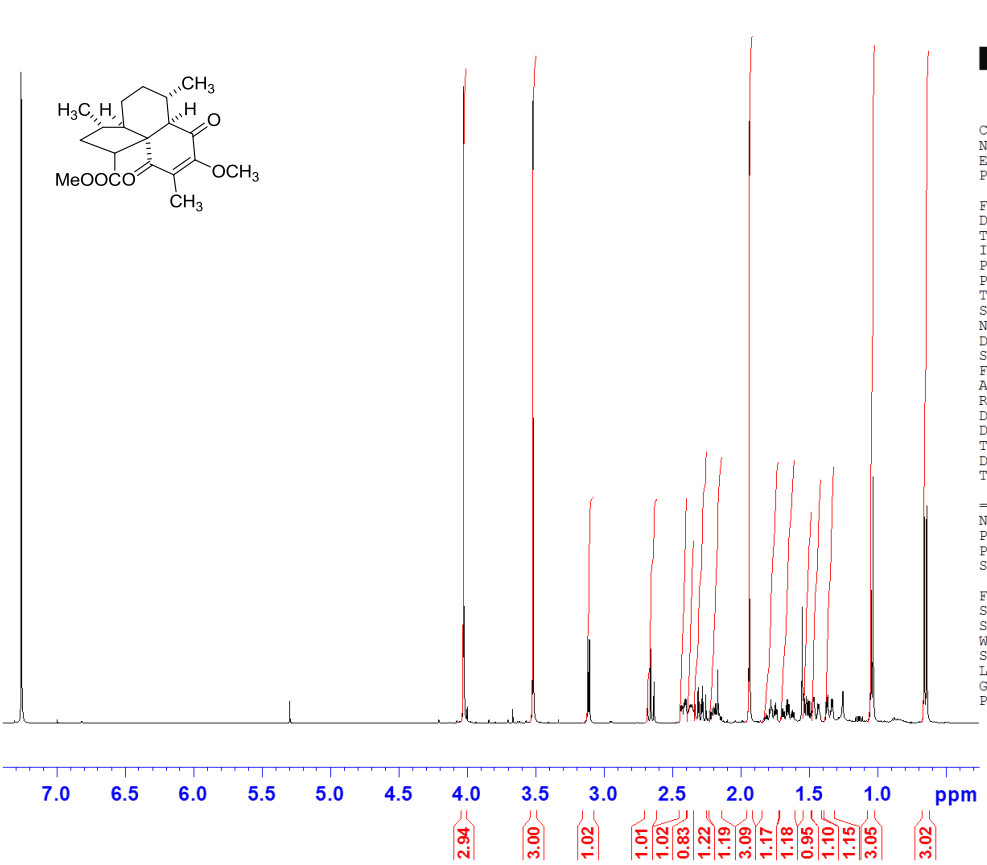


BRUKER

```
Current Data Parameters
NAME                  JP-0367
EXPNO                     100
PROCNO                      1

F2 - Acquisition Parameters
Date_               20120722
Time                   23.48
INSTRUM            avance400
PROBHD    5 mm BBO BB-1H
PULPROG                jmod
TD                    65536
SOLVENT               CDCl3
NS                     8000
DS                        2
SWH               25062.656 Hz
FIDRES             0.382426 Hz
AQ                 1.3074932 sec
RG                    7298.2
DW                  19.950 usec
DE                   6.00 usec
TE                   300.2 K
CNST2            145.0000000
CNST11             1.0000000
D1                 2.00000000 sec
d20                0.00689655 sec
DELTA              0.00001311 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                      13C
P1                      10.30 usec
p2                      20.60 usec
PL1                     -1.00 dB
SFO1            100.6233329 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                       1H
PCPD2                 100.00 usec
PL2                     -3.00 dB
PL12                    16.00 dB
SFO2            400.1316005 MHz

F2 - Processing parameters
SI                        32768
SF               100.6127696 MHz
WDW                          EM
SSB          0
LB                      1.00 Hz
GB           0
PC                      1.40
```

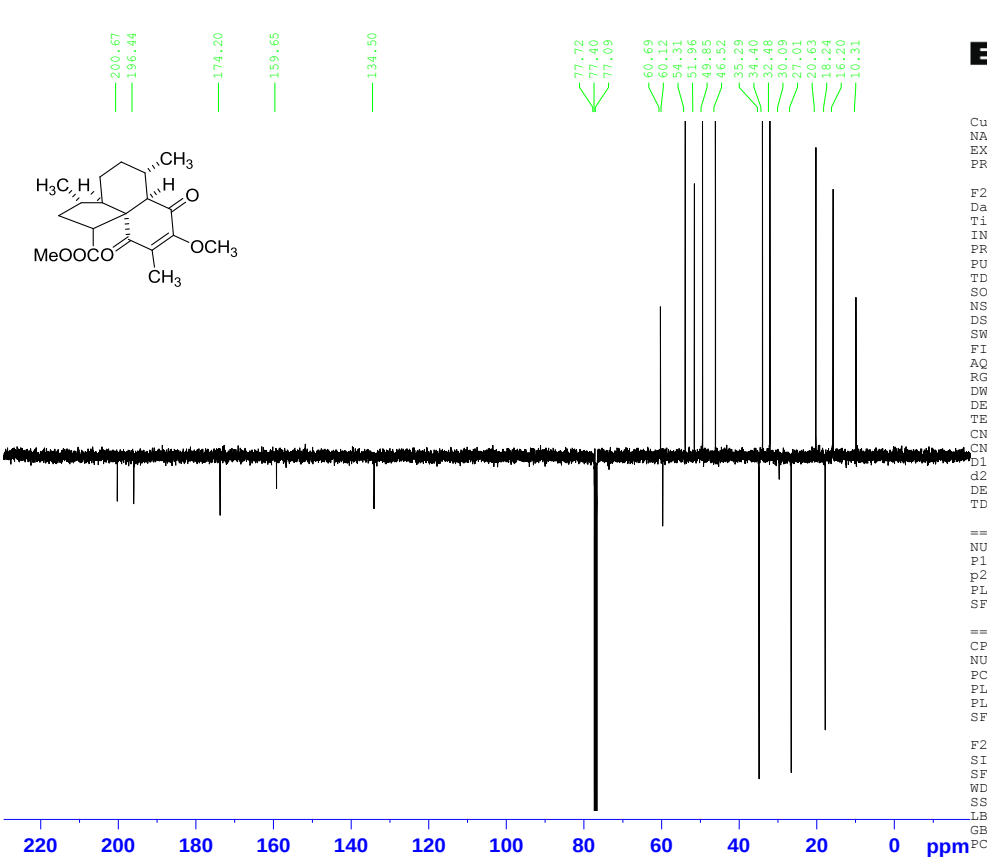

BRUKER
Current Data Parameters
NAME JP-0409
EXPNO 140
PROCNO 1
F2 - Acquisition Parameters
Date_ 20120907
Time 14.41
INSTRUM AVIII400
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9846387 sec
RG 812
DW 60.800 usec
DE 6.50 usec
TE 298.2 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 13.50 usec
PL1 -1.80 dB
PL1W 15.28361320 W
SFO1 400.2724718 MHz
F2 - Processing parameters
SI 32768
SF 400.2700109 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 ppm
1.02 3.04 3.05 1.00 1.05 1.06 3.02 1.05 1.08 2.08 1.09 3.08 3.06


200.37 195.72 164.45 160.47 151.33 136.89 132.79 65.16 59.82 52.89 51.59 49.79 43.21 28.43 25.77 20.43 19.26 18.50 9.74
BRUKER
Current Data Parameters
NAME JP-0409
EXPNO 141
PROCNO 1
F2 - Acquisition Parameters
Date_ 20120908
Time 0.26
INSTRUM AVIII400
PROBHD 5 mm PABBO BB-
PULPROG jmod
TD 65536
SOLVENT CDCl3
NS 4096
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631988 sec
RG 2050
DW 20.800 usec
DE 6.50 usec
TE 298.2 K
CNST2 145.0000000
CNST11 1.0000000
D1 2.00000000 sec
D20 0.00689655 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 10.00 usec
P2 20.00 usec
PL1 -1.50 dB
PL1W 47.89980698 W
SFO1 100.6580364 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 -1.80 dB
PL12 14.70 dB
PL2W 15.28361320 W
PL12W 0.34215751 W
SFO2 400.2716011 MHz
F2 - Processing parameters
SI 32768
SF 100.6479734 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
200 180 160 140 120 100 80 60 40 20 ppm



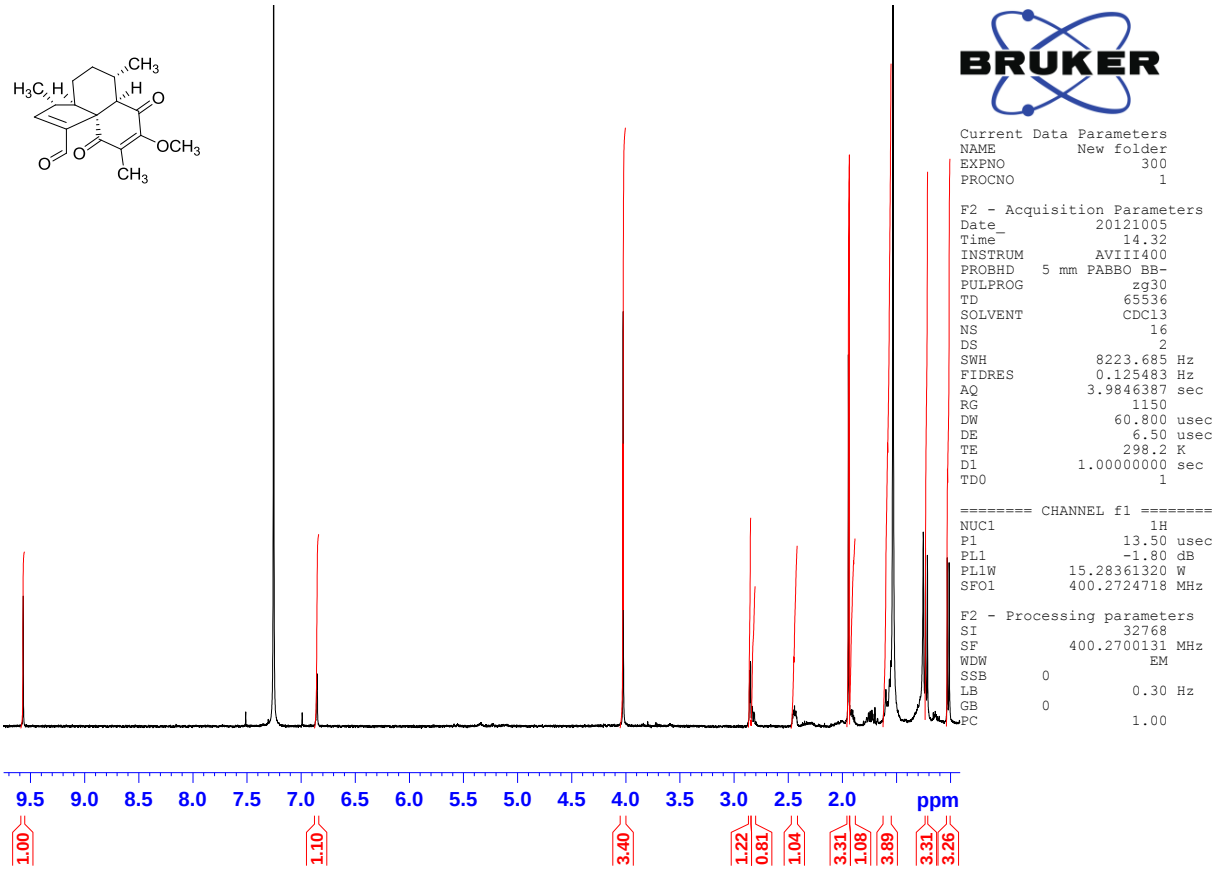
BRUKER

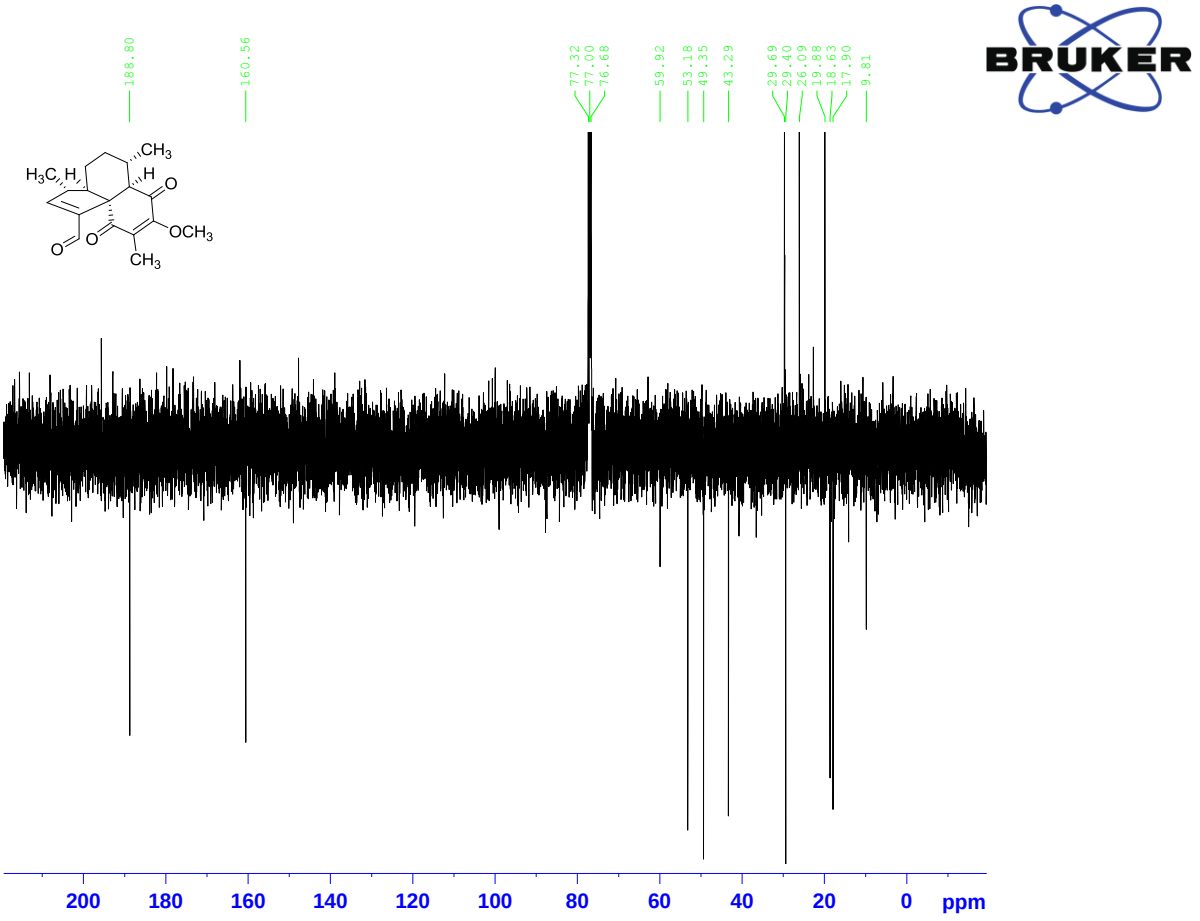
```
Current Data Parameters
NAME          New folder
EXPNO                 10
PROCNO                 1

F2 - Acquisition Parameters
Date_           20130215
Time              16.03
INSTRUM         avance400
PROBHD   5 mm BBO BB-1H
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    64
DS                     2
SWH            8278.146 Hz
FIDRES         0.126314 Hz
AQ             3.9584243 sec
RG                406.4
DW               60.400 usec
DE                6.00 usec
TE                300.2 K
D1           1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                 8.75 usec
PL1               -3.00 dB
SFO1        400.1324710 MHz

F2 - Processing parameters
SI                 32768
SF          400.1300093 MHz
WDW                   EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```



BRUKER

```
Current Data Parameters
NAME          New folder
EXPNO                 16
PROCNO                 1

F2 - Acquisition Parameters
Date_           20130216
Time              12.54
INSTRUM         avance400
PROBHD   5 mm BBO BB-1H
PULPROG             jmod
TD                 65536
SOLVENT            CDCl3
NS                  8000
DS                     2
SWH           25062.656 Hz
FIDRES         0.382426 Hz
AQ             1.3074932 sec
RG                10321.3
DW               19.950 usec
DE                6.00 usec
TE                300.2 K
CNST2        145.0000000
CNST11         1.0000000
D1           2.00000000 sec
d20          0.00689655 sec
DELTA        0.00001311 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                10.30 usec
p2                20.60 usec
PL1               -1.00 dB
SFO1        100.6233329 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2            100.00 usec
PL2               -3.00 dB
PL12              16.00 dB
SFO2        400.1316005 MHz

F2 - Processing parameters
SI                 32768
SF          100.6127691 MHz
WDW                   EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```


BRUKER
Current Data Parameters
NAME New folder
EXPNO 300
PROCNO 1
F2 - Acquisition Parameters
Date_ 20121005
Time 14.32
INSTRUM AVIII400
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9846387 sec
RG 1150
DW 60.800 usec
DE 6.50 usec
TE 298.2 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 13.50 usec
PL1 -1.80 dB
PL1W 15.28361320 W
SFO1 400.2724718 MHz
F2 - Processing parameters
SI 32768
SF 400.2700131 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 ppm
1.00 1.10 3.40 1.22 0.81 1.04 3.31 1.08 3.89 3.31 3.26


BRUKER
188.80
160.56
77.32
77.00
76.68
59.92
53.18
49.35
43.29
29.69
29.40
26.09
19.88
18.63
17.90
9.81
200 180 160 140 120 100 80 60 40 20 0 ppm

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