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List of Abbreviations

9-BBN	9-borabicyclo[3.3.1]nonane
Ac	acetyl
ACA	asymmetric conjugate addition
ATR	attenuated total reflection
AIBN	2,2'-azo <i>bis</i> isobutyronitrile
BARF	sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
Bn	benzyl
Binol	1,1'-bi-2,2'-naphthol
BOC	<i>t</i> -butoxycarbonyl
Bu (<i>n</i> Bu)	butyl
CDI	carbonyl diimidazole
Cp	cyclopentadienyl
D.A.	Diels-Alder reaction
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DIBAL	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DMAP	<i>N,N</i> -4-dimethylaminopyridine
DMF	<i>N,N</i> -dimethylformamide
DMP	Dess-Martin periodinane
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dppf	1,1'- <i>bis</i> (diphenylphosphino)ferrocene
dr	diastereomeric ratio
ee	enantiomeric excess
EE	ethyl acetate
FG	functional group
GGPP	geranylgeranyl diphosphate
HRMS	high resolution mass spectrometry
IBX	<i>o</i> -iodoxybenzoic acid
IMDA	intramolecular Diels-Alder reaction
ImH	imidazole

IPC	isopinocampheyl
IR	infrared spectroscopy
KHMDS	potassium <i>bis</i> (trimethylsilyl)amide
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LHMDS	lithium <i>bis</i> (trimethylsilyl)amide
<i>m</i> CPBA	<i>meta</i> chloroperbenzoic acid
MOM	methoxymethyl
Ms	mesyl (methanesulfonyl)
MS	mass spectrometry
NBS	<i>N</i> -bromosuccinimide
NHK	Nozaki-Hiyama-Kishi
NHMDS	sodium <i>bis</i> (trimethylsilyl)amide
NMO	<i>N</i> -methylmorpholine oxide
NMR	nuclear magnetic resonance
Nu	nucleophile
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PIDA	phenyliodonium diacetate
Piv	pivaloyl
py.	pyridine
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBDPS	<i>t</i> -dibutyldiphenylsilyl
TBS	<i>t</i> -dibutyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
<i>o</i> -tol	<i>ortho</i> tolyl
TPAP	tetra- <i>n</i> -propylammonium perruthenate
<i>p</i> -Ts (Tos)	<i>p</i> -toluenesulfonyl

1. Introduction

Sea whips, sea fangs, sea fans, and sea plumes of the genus *Pseudopterogorgia* are remarkable dwellers of the Caribbean reefs. During the last two decades many ambitious efforts have been committed to the exploration of the natural product chemistry of the West Indian gorgonian octocoral *Pseudopterogorgia elisabethae* (Bayer, 1961).¹ These chemical studies have shown that this species possesses an astounding source of a large variety of secondary metabolites, mainly diterpenoids, sesquiterpenoids, and steroids.² The compounds are of current interest as a source of unique metabolites due to their interesting biological activities.³ Some pseudopterogens for example are potent anti-inflammatory and analgesic compounds that have been licensed for medical use as potential anti-inflammatory drugs. Investigations from the Rodríguez group on the chemical constituents of a specimen of *Pseudopterogorgia elisabethae* (Bayer) collected near San Andrés Island, Colombia, resulted in the isolation of many structurally interesting diterpenoids. Some of these components are elisabethin A, elisabanolide and elisapterosin, possessing the uncommon elisabethane, elisabane and elisapterane carbon skeleton respectively. These natural products stood out having the most complex structures.⁴ Also rearranged terpenoids of the nor-sandresane skeletal class in addition to amphilectane- and serrulatane-based diterpenes are found.^{5,6,7} Some of these exciting natural products are presented on the following pages.

2. Octocoral *Pseudopterogorgia Elisabethae*



Figure 1: *Pseudopterogorgia Elisabethae*

2.1. Occurrence and Isolation

The Caribbean sea whip *Pseudopterogorgia Elisabethae* (Figure 1) was discovered in the reefs of the West Indian region, the Bahamas and the Florida Keys.⁸ The natural habitat of this octocoral is generally on deeper reef communities as well as on fore reef zones. The systematic classification within the animal kingdom is: phylum Cnidaria, class Anthozoa, order Gorgonacea, family Gorgoniidae, genus *Pseudopterogorgia*, species *Pseudopterogorgia Elisabethae*.

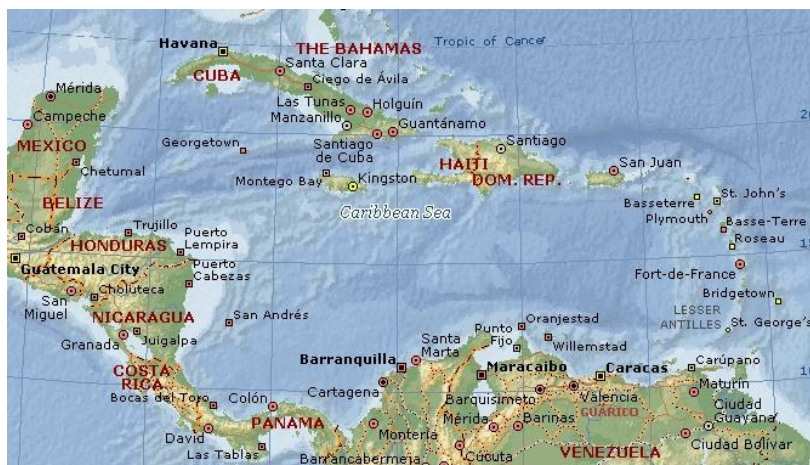


Figure 2: Map of the Caribbean Sea

Rodríguez and coworkers collected a small sample of this animal in deep waters near San Andrés Island (Columbia) for chemical investigations (Figure 2). The freshly collected animals (1.0 kg) were sun dried and stored frozen. The dried *P. elisabethae*

was extracted subsequently with MeOH/CHCl₃ (1:1). The organic suspension was filtrated and the solvent was removed under reduced pressure. The residue was partitioned between hexane and water. The hexane layer was separated and concentrated *in vacuo* to an oil. A portion was dissolved in a small volume of toluene fractionated by successive size exclusion chromatography (Bio-Beads SX-3 in toluene), silica gel chromatography, and HPLC. Thereby it was possible to explore the natural product chemistry of *P. elisabethae* to a concentration range of 0.0001 wt.% according to the dry weight.⁹

2.2. Carbon skeleton structures

This gorgonian species alone is responsible for the production of over twenty different skeletal classes of terpenes with unique substitution patterns and functionalities. This chapter gives a short overview about several carbon skeleton classes of some diterpenes isolated from *P. elisabethae*. All of the following compounds were determined by spectral analyses and if possible by X-ray crystallographic analysis.

2.2.1. The serrulatane class

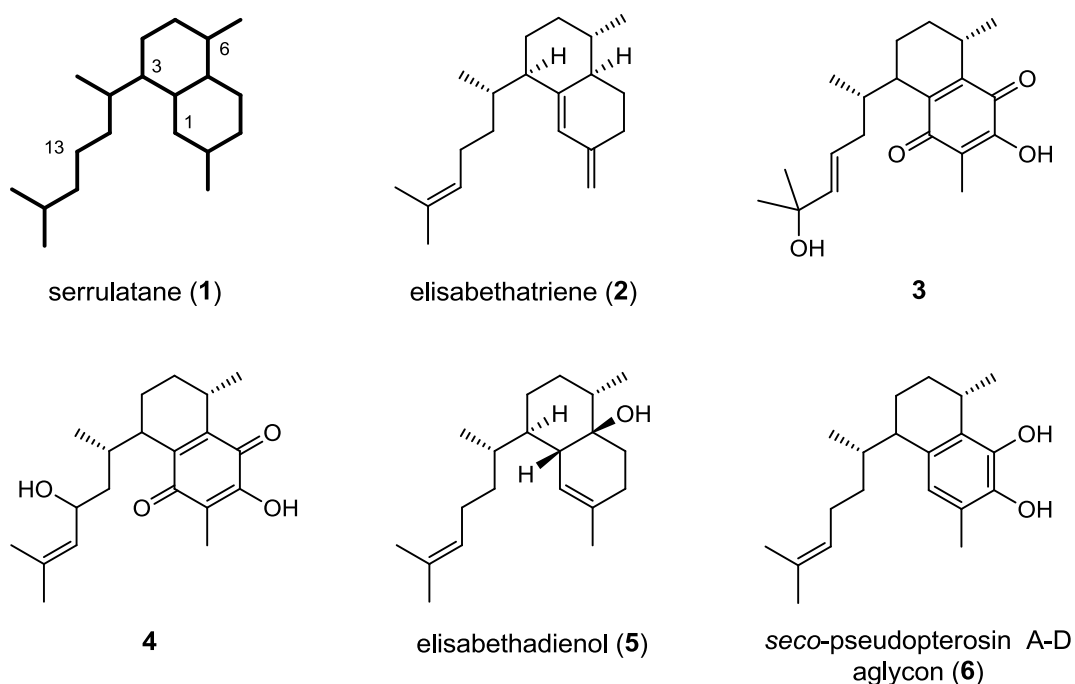


Figure 3: Compounds of the serrulatane class

Figure 3 shows some compounds of the serrulatane class. This carbon skeleton class is structurally simple. It's features are the two annulated cyclohexane rings with one methyl group on each ring and the branched eight-carbon side chain at position 3. Elisabethatriene (**2**) is the simplest compound of this family. Compound **3** is a higher oxygenated serrulatane and possesses a full substituted quinone system. Compound **4** is one of the more common molecules. Structural features of this metabolite are the quinone system and the allylic hydroxyl group on the side chain. It was first isolated by Fenical and coworkers.¹⁰ Elisabethadienol (**5**) is a more recent metabolite and was found by Rodríguez and coworkers.⁹ A good known serrulatane is seco-pseudopterisin A-D aglycon (**6**). This natural product exhibits an aromatic ring with two hydroxy groups. Glycosylation of the hydroxy groups generates the corresponding seco-pseudopterisins.

2.2.2. The amphilectane class

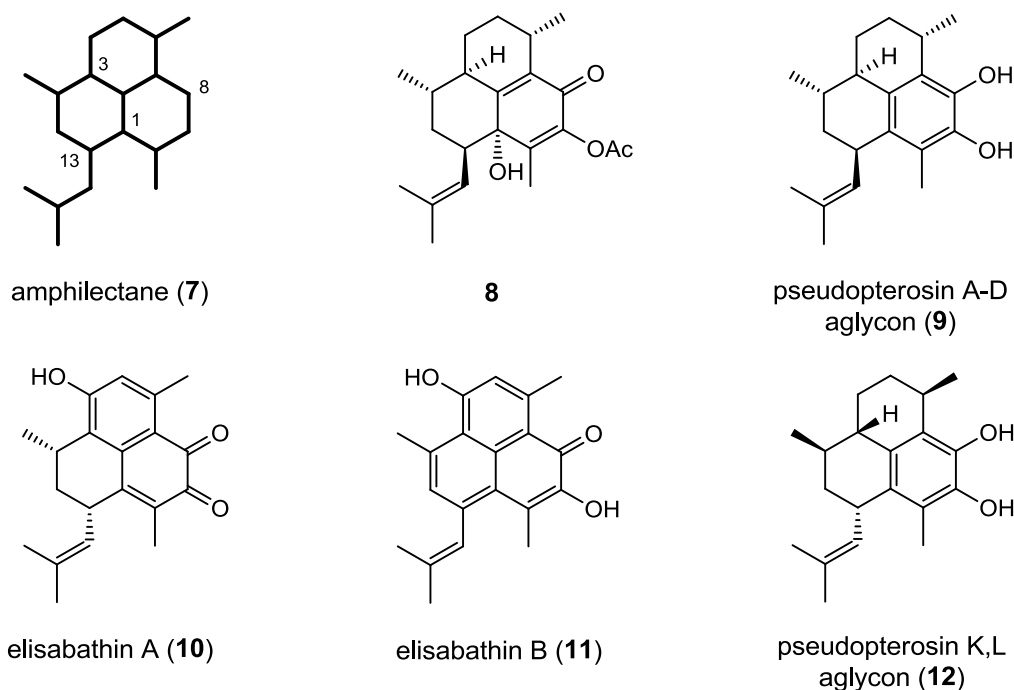


Figure 4: Compounds of the amphilectane class

The amphilectane class is structurally related to the serrulatane class. The only difference in the amphilectane class is the additional C-C bond between the C1 and C13 carbon atom which closes the third ring. Structural features of this class are the three annulated six membered rings, the three methyl groups on each ring and the

very common isobutenyl sidechain. Compound **8** was first isolated by Fenical and coworkers and is a possible intermediate in the pseudopterosin synthesis.¹⁰ Compound **9** is pseudopterosin A-D aglycon. The indices belong to the different sugar moieties (*D*-xylose and their derivatives) at position eight. Noteworthy is that pseudopterosin K,L aglycon (**12**), the enantiomer of pseudopterosin A-D aglycon (**9**) was isolated from the same *P. elisabethae* species collected by the Bahamas Islands. Apparently both enantiomers have a biological function. Elisabethin A (**10**) and B (**11**) are unique among the amphilectane class because they possess an unusually high aromatic conjugation. They were discovered a little bit later based on the low concentration in the extracts by Rodríguez and coworkers (Figure 4).⁶

2.2.3. The elisabethane and elisapterane class

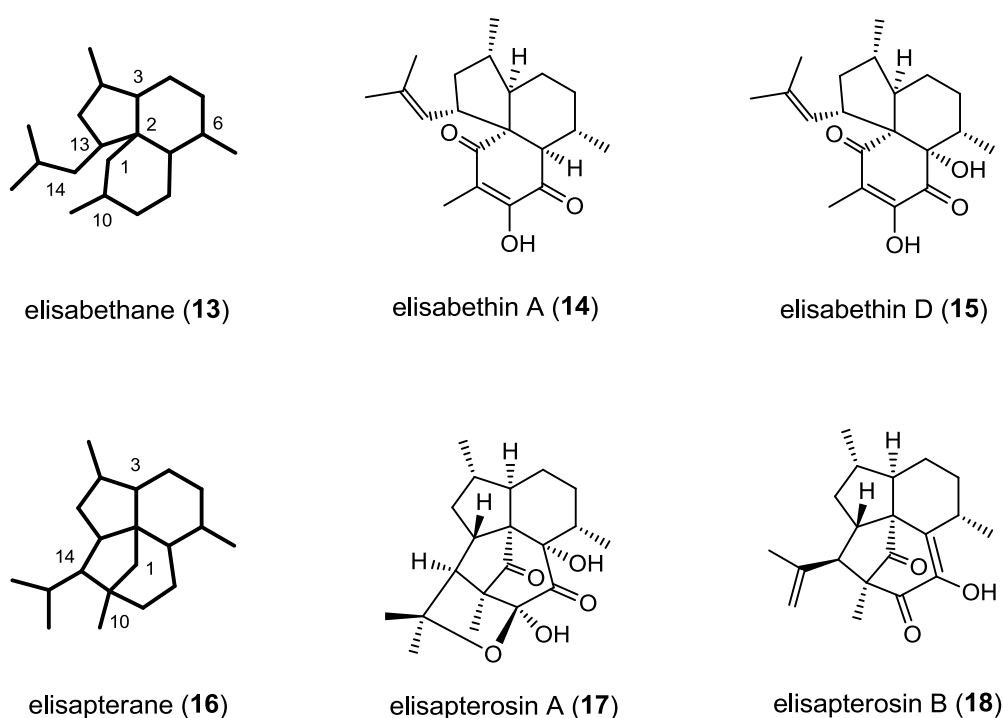


Figure 5: Compounds of the elisabethane class and the elisapterane class

Like the amphilectane class, the elisabethane class also possesses three rings. But in this case there are two annulated six membered rings and one five membered ring annulated to a six membered ring. Thus, a quaternary carbon atom is generated at position 2. Additionally, the isobutenyl side chain is still present. Two examples of this class are elisabethin A (**14**) and D (**15**). The difference between the two compounds is the hydroxy group of elisabethin B (**18**) at position 7 (Figure 5).

The next more complex carbon skeleton class is the elisapterane class. The only difference of these two carbon classes is the additional carbon bond between C10 and C14 in the elisapterane structure. Hence, a new five membered ring is generated. Structural features are the bicyclo[3.2.1]octane system and the five and six membered rings annulated to each other and to this bicycle. Still present are the three methyl groups on the different rings. The isobutenyl side chain has now changed into an isopropenyl moiety. Furthermore, there are two quaternary carbon atoms at positions 2 and 10 in the skeleton structure. Examples of this carbon skeleton class are elisapterosin A (**17**) and B (**18**). Noteworthy is that elisapterosin A (**17**) is the more oxidized compound and possesses an additional five membered ring, which generates a hemiacetal moiety at position 9.

2.2.4. The colombiane, elisabane and *bisnorseco*-elisabethane class

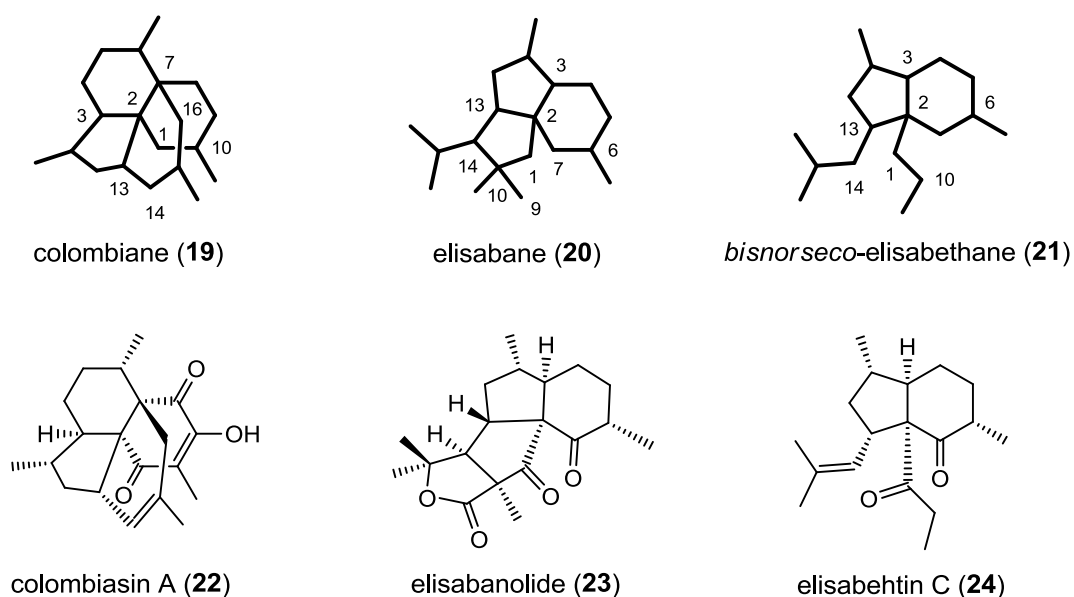


Figure 6: Compounds of the colombiane, elisabane and *bisnorseco*-elisabethane class

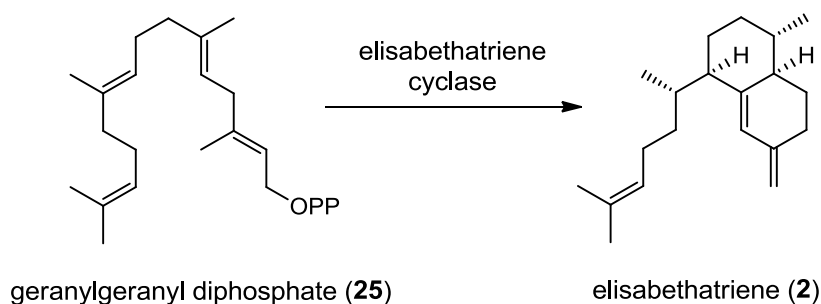
Another intricate carbon class is the colombiane family. This carbon skeleton class is closely related to the elisabethane class. The only difference is the additional carbon bond between C7 and C16, which concurrently builds up the fourth ring. Structural features are the three six membered rings and the five membered ring which are annulated to each other. Additionally, each ring has a methyl substituent. An example of this class is colombiasin A (**22**). It was first isolated by Rodríguez and coworkers.¹¹

The next carbon skeleton class is the elisabane class. It is actually a *nor*-diterpene because it possesses only 19 carbon atoms. A closer look on this carbon skeleton reveals that carbon atom 8, between C7 and C9, is missing. This leads to the assumption that the elisabane class is a derivative of the elisapterane class. Structural features of this family are the two annulated five membered rings and one six membered ring annulated to a five membered ring. Also the two quaternary carbon atoms and the isopropyl side chain are worth mentioning. Elisabanolide (**23**) is one example of this terpenoid class.

The last carbon skeleton class in Figure 6 is also not a diterpene. It is a *bisnor*-diterpene, which means it possesses only 18 carbon atoms. It is a further derivative of the elisabethane class. Structural features are the annulated five and six membered ring, again the isobutenyl side chain and the propyl side chain. Moreover, the molecule holds one quaternary carbon atom and a methyl group on each ring. An example of this carbon family is Elisabethin C (**24**).

2.3. Biosynthesis and biological activity

2.3.1. Biosynthesis

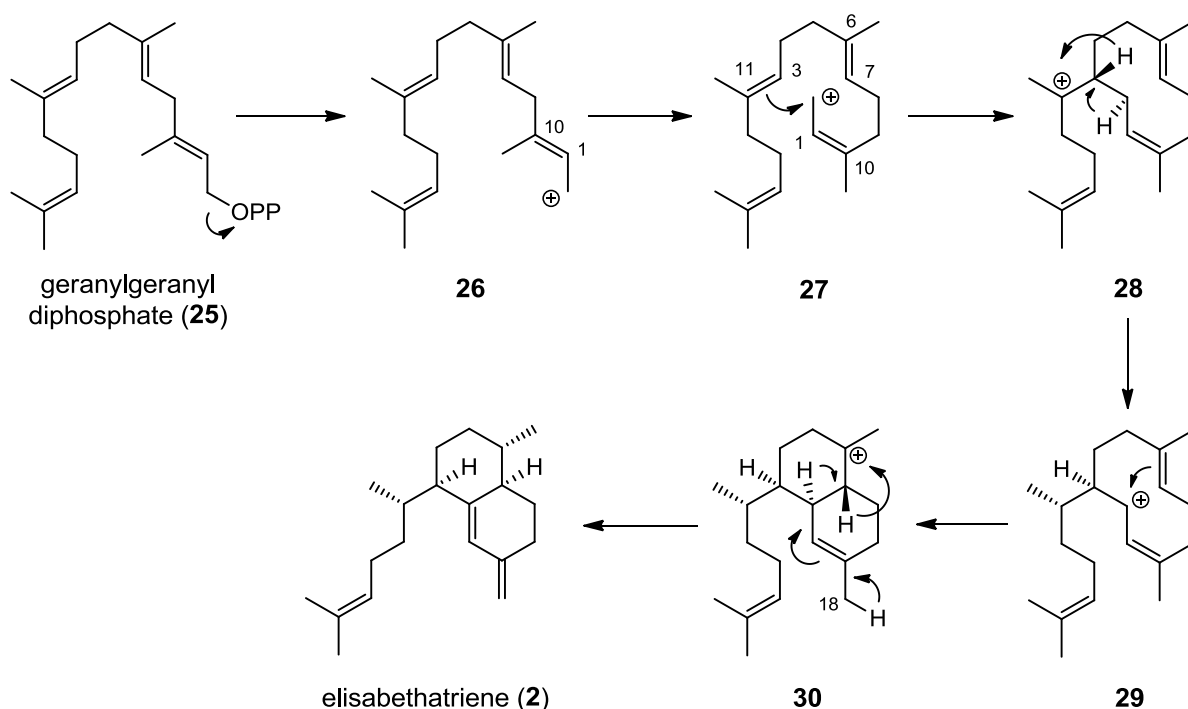


Scheme 1: Diterpene cyclase to elisabethatriene (**2**)

The biosynthesis starts from geranylgeranyl diphosphate (**25**) (GGPP). GGPP is a diterpene from the terpene biosynthesis called mevalonate pathway^{12,13}. A closer look at GGPP reveals that each carbon atom that is required for the diterpene skeleton is still present. Hence, just functional group manipulations, insertions and cyclizations reactions are outstanding. The first step in the biosynthesis is a cyclisation of GGPP catalyzed by the enzyme elisabethatriene cyclase. This terpene

cyclase is one of the key enzymes in the biosynthesis, as these generally assemble the entire carbon skeleton in a single step to elisabethatriene (**2**) (Scheme 1).

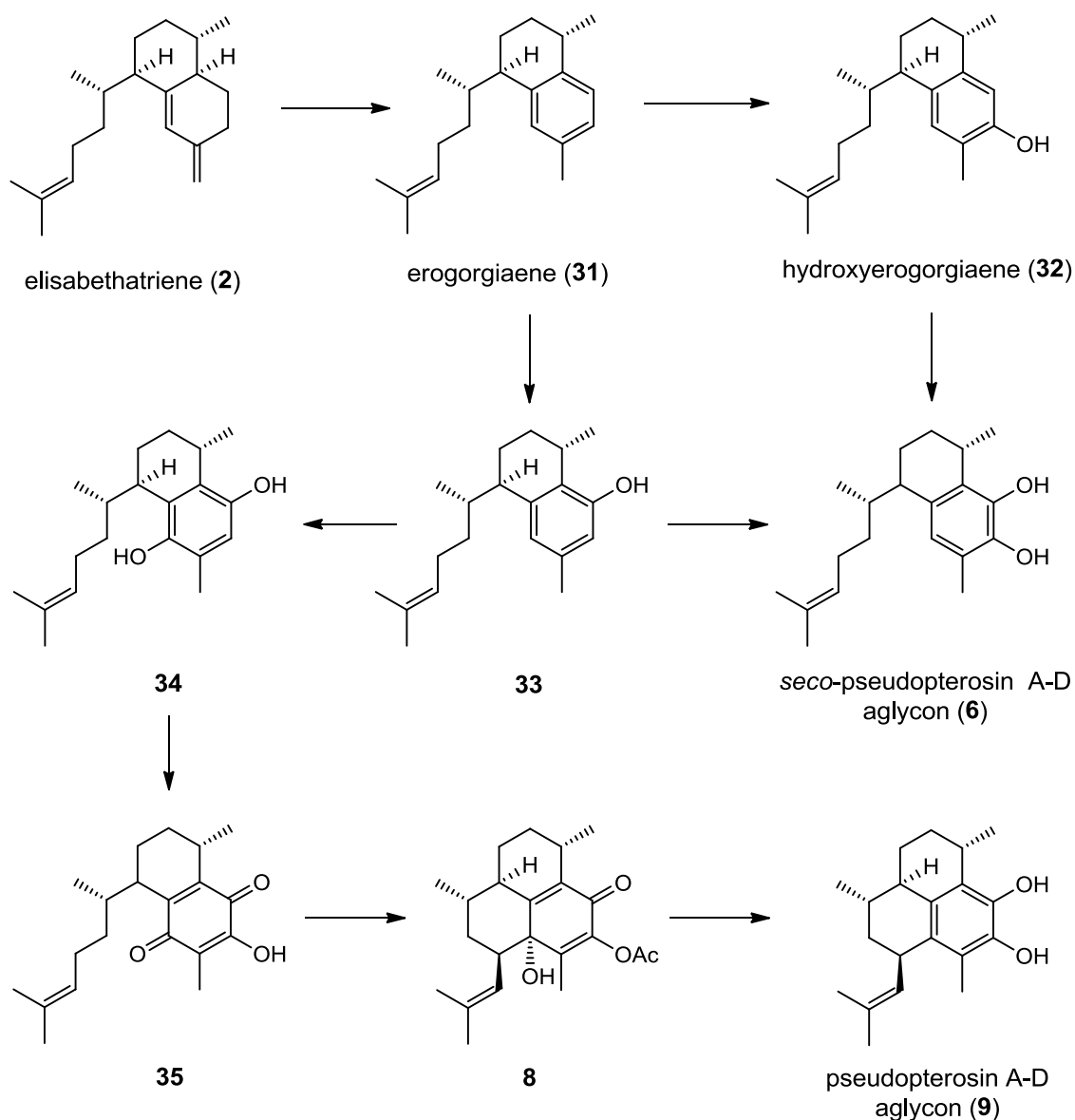
Elisabethatriene cyclase is a monomer with a molecular mass of 47 kDa. This molecular mass is quite different compared to terrestrial diterpene cyclases (e.g. taxydiene synthase, kaurene synthases A and B have molecular masses of approx. 80 kDa). This suggests that the structure of the elisabethatriene cyclase is might be different from those isolated from terrestrial organisms. The enzyme was first isolated and characterized by Kohl and coworkers.¹⁴



Scheme 2: Possible biosynthetic pathway for the elisabethatriene (**2**) synthesis

One possible mechanism for the formation of elisabethatriene (**2**) from geranylgeranyl diphosphate (**25**) is described in Scheme 2. The first step is the loss of the pyrophosphate group from GGPP. The stabilized allylic cation undergoes isomerization from *E* to *Z* to intermediate **27**. The double bond between C3 and C11 attacks the allylic cation to form a ten membered ring and a tertiary cation respectively. Subsequently two hydride shifts occur to introduce the stereochemistry at position C3 and C11. After attack of the C6-C7 double bond to the allylic cation, the ten membered ring is divided in two annulated six membered rings. Two further hydride shifts initiates the stereochemistry at position C6 and C7. Subsequently

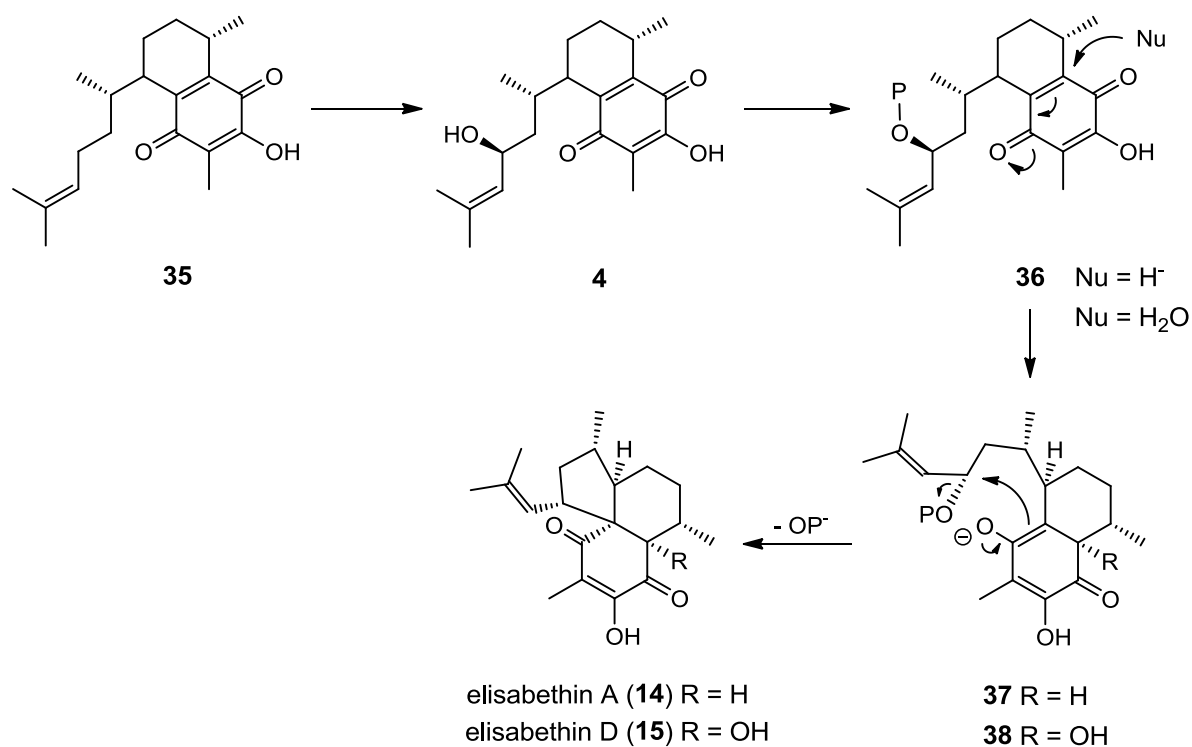
abstraction of a proton at C18 generates the third double bond to elisabethatriene (2).



Scheme 3: Biosynthetic pathway to *seco*-pseudopterosin and pseudopterosin

In the biosynthetic analysis outlined in Scheme 3, pseudopterosins co-occur with *seco*-pseudopterosins, suggesting that these two classes of diterpenes are produced through a single cyclase product.¹⁵ Next step in the biosynthesis is an aromatization to erogorgiaene (31).¹⁶ This intermediate can be hydroxylated *ortho* or *meta* to the methyl group to provide compound 32 or 33 respectively. A second hydroxylation in *ortho*-position to the existing hydroxy group of compound 32 or 33 respectively affords *seco*-pseudopterosin A-D aglycon (6). Hydroxylation of compound 33 at the *para*-position delivers intermediate 34. The next postulated step is oxidation of

intermediate **34** to compound **35**. A subsequent ring closure forms compound **8**. A following reduction with elimination of water yields pseudopterosin A-D aglycon (**9**). Additional installation of a sugar moiety at aglycon **6** and **9** delivers the corresponding *seco*-pseudopterosin and pseudopterosin.¹⁵

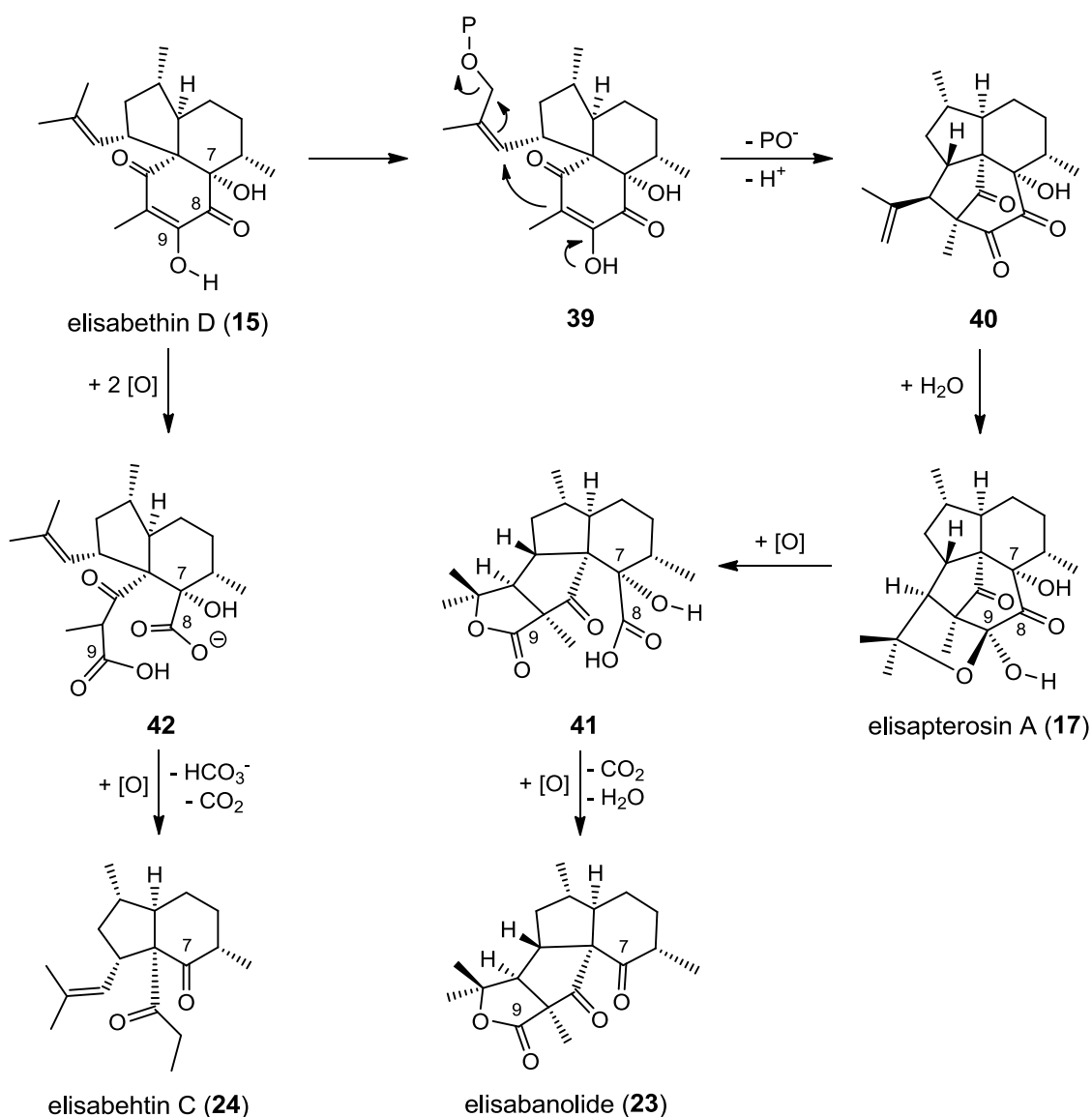


Scheme 4: Biosynthetic pathway to elisabethin A (**14**) and D (**15**)

The possible biosynthesis of elisabethin A (**14**) and D (**15**) starts with an allylic oxidation at the side chain of quinone **35** to compound **4** (Scheme 4). The generated hydroxy group is subsequently phosphorylated to compound **36**. The following step is a nucleophilic attack in a Michael fashion of a hydride or water at the quinone system to intermediate **37** or **38** respectively. The resulting enol intermediate immediately substitutes the phosphate to build up the five membered ring of elisabethin A (**14**) or D (**15**).

These two elisabethin metabolites **14** and **15** offer the way to other natural products. Based on this biosynthetic proposal, elisabethin A (**14**) and D (**15**) are two key intermediates to generate other metabolites on different pathways. Possible metabolites of elisabethin D (**15**) are elisapterosin A (**17**), elisabanolide (**23**) and elisabethin C (**24**) (Scheme 5). The synthesis of elisapterosin A (**17**) starts with an allylic oxidation and subsequent phosphorylation of elisabethin D (**15**) at the

isobutenyl side chain to intermediate **39**. The phosphorylated hydroxy group acts again as a leaving group to enable the ring closure to compound **40**. Another possibility is the direct oxidation of the enedione system to a carbocation intermediate, at position 10, which is immediately attacked by the isobutenyl double bond to compound **40**. Addition of water to the isopropenyl double bond generates a tertiary alcohol, which attacks the carbonyl at position 9 to build up a five membered hemi acetal ring to complete the biosynthesis of elisapterosin A (**17**).

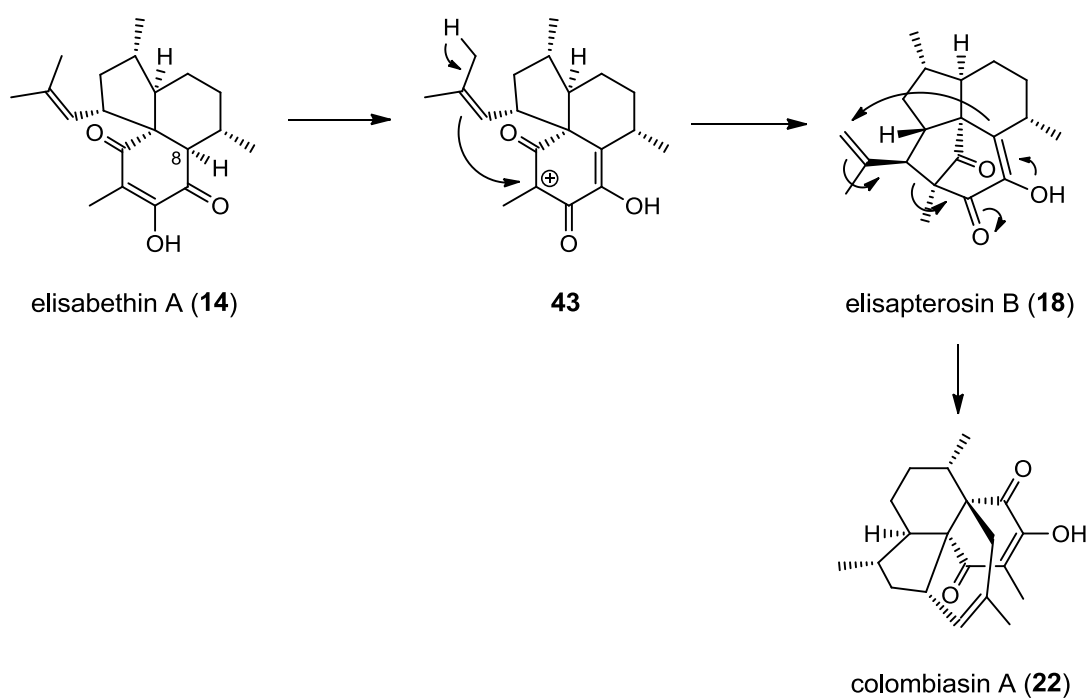


Scheme 5: Biosynthetic pathway of elisabethin C (**24**), elisapterosin A (**17**) and elisabanolide (**23**)

The biosynthesis of elisabanolide (**23**) demands cleavage of the oxidized six membered ring and the carbon atom at position 8 must be removed. This suggests an oxidative bond cleavage between position 8 and 9 to generate a five membered

lactone and a carboxylic acid. A second oxidative fragmentation between position 7 and 8 release carbon dioxide and water to generate a ketone moiety at the six membered ring to yield the *nor*-diterpene elisabanolide (**23**).¹⁷

The biosynthesis of elisabethin C (**24**) also requires a cleavage of the oxidized six membered ring and a removal of the carbon atom at position 9. Thus, the reaction mechanism should be quite similar to the elisabanolide pathway. The first step is again an oxidative cleavage of the carbon bond between position 8 and 9 to intermediate **42**. A second oxidative cleavage between position 7 and 8, releases bicarbonate to generate the ketone functionality at the remaining six membered ring. The decarboxylation reaction free up the second carbon atom completes the biosynthesis of the *bisnor*-diterpene elisabethin C (**24**).⁴



Scheme 6: Biosynthetic pathway of elisapterosin B (**18**) and colombiasin A (**22**)

The biosynthetic pathway of elisapterosin B (**18**) out of elisabethin A (**14**) is suggested quite similar to the biosynthesis of elisapterosin A (**17**).¹⁸ Scheme 6 shows the direct oxidation of the enedione system to a carbocation intermediate, at position 10, which is instantly attacked by the isobutenyl double bond to elisapterosin B (**18**). But also an allylic oxidation at the isobutenyl side chain to the primary alcohol followed by phosphorylation and subsequently substitution via an intramolecular aldol reaction to elisapterosin B (**18**) is possible. A nucleophilic attack of the enol

functionality at the isopropylene double bond generates a six membered ring and simultaneously fragment the five membered ring, which was build up in the previous step, to colombiasin A (**22**).

2.3.2. Biological activity

Some *seco*-pseudopterosins and pseudopterosins of *Pseudopteroergorgia elisabethae* collected from several locations throughout the Caribbean region exhibits strong anti-inflammatory and analgesic activity that exceed the potencies of existing drugs such as indomethacin.¹⁹ Unprocessed pseudopterosin extracts currently being used as an additive to prevent irritation caused by exposure to sun or chemicals of the skin.²⁰

Some compounds of the serrulatane, amphilectane, elisabethane and elisapterane class show *in vitro* antituberculosis activity against *Myobacterium tuberculosis* H37Rv. Especially erogorgiaene (**31**), elisapterosin B (**18**) and pseudopteroxazole (**44**) (Figure 7) have a strong growth inhibitory activity against *M. tuberculosis* (96%, 79% and 97% respectively). Also Elisabanolide (**23**) and Elisabethin C (**24**) possess a moderate inhibitory activity of 39% and 42% against *M. tuberculosis*.²¹

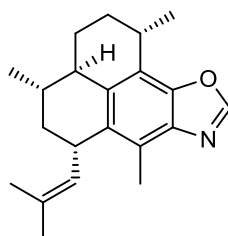


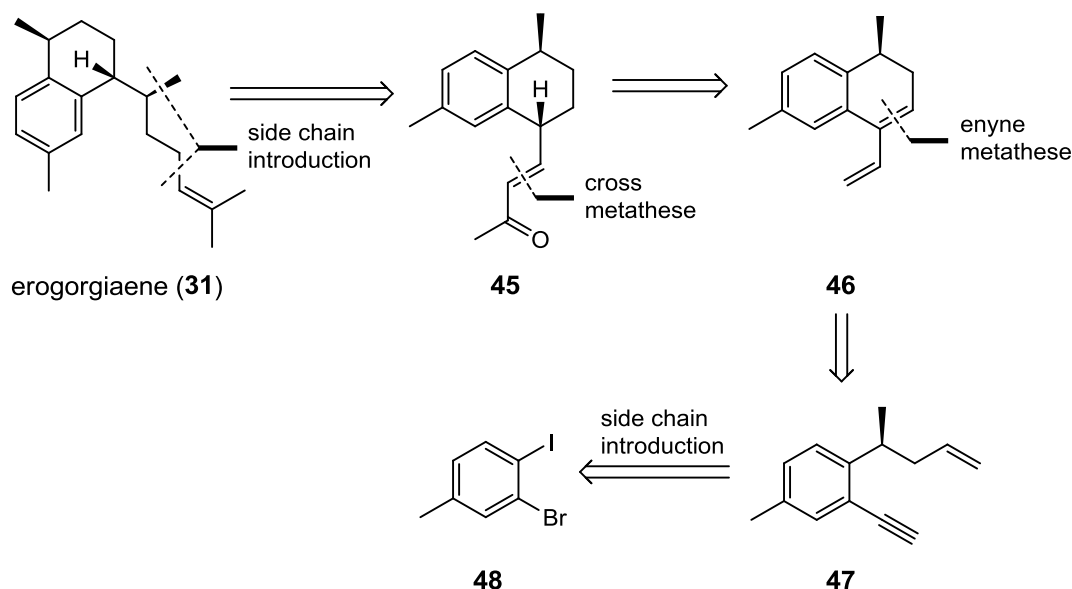
Figure 7: Pseudopteroxazole (**44**)

Several diterpenes of *P. elisabethae* indicate also cancer cell cytotoxicity. For example, Elisabethin D (**15**) show significant *in vitro* cell toxicity with concentrations of 10^{-5} M, which reveal significant differential responses at the GI₅₀ level from all the renal, CNS, and leukemia cancer cell lines.²² Also elisabethin A (**10**) shows weak *in vitro* cancer cell toxicity.

3. Previously reported partial and total synthesis of *P. elisabethae* diterpenes

3.1. Total synthesis of (+)-erogorgiaene by Hoveyda *et al.* 2004

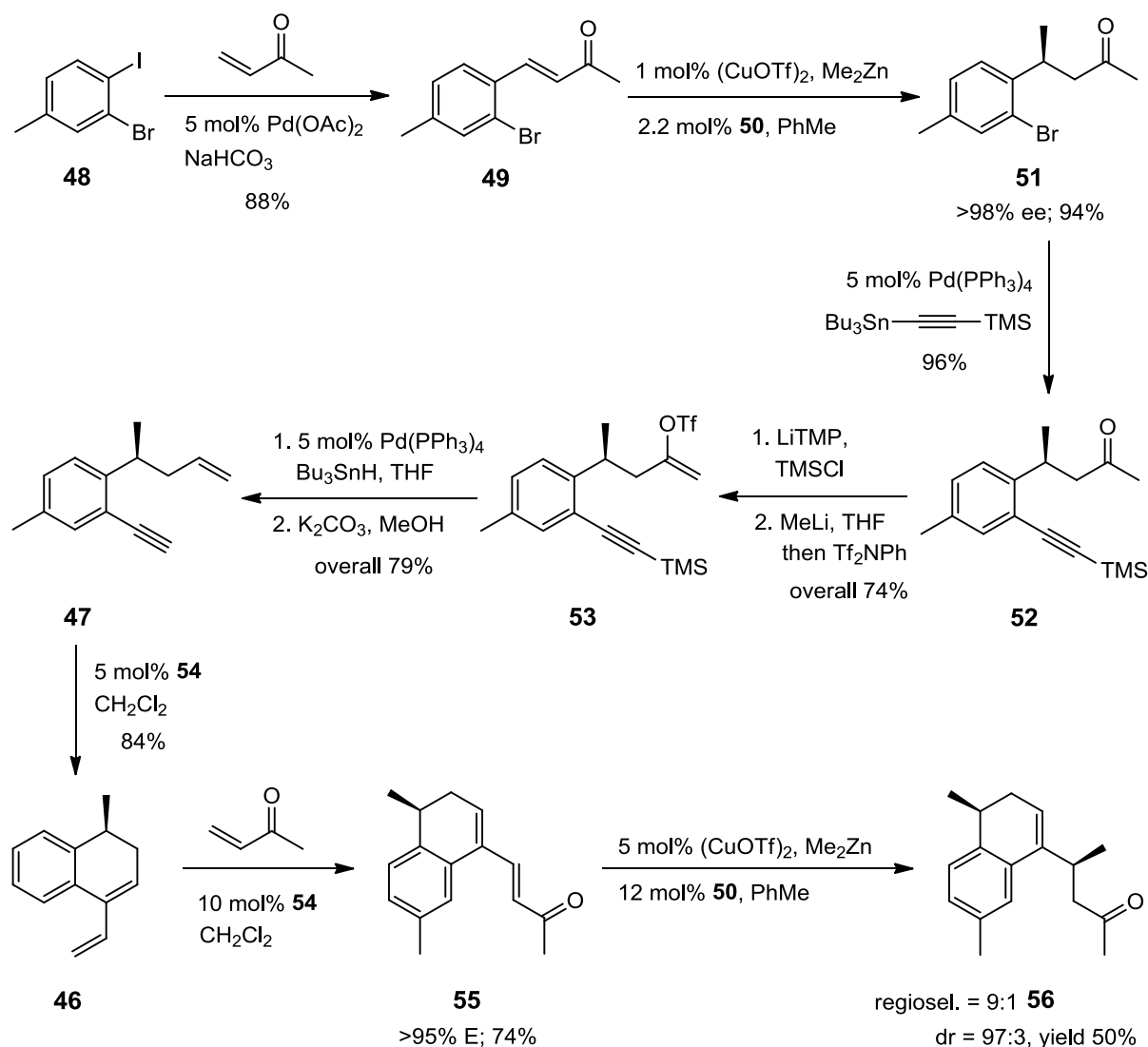
Hoveyda's retrosynthetic strategy based on a copper catalyzed asymmetric conjugate addition (ACA) of a methyl group to an α,β -unsaturated ketone. The side chain was installed via cross metathesis with methyl vinyl ketone. The ring closing was accomplished through an enyne metathesis with the same catalyst used in the cross metathesis. Functionalization of the commercially available aromatic compound **48** was done under standard palladium coupling conditions (Scheme 7).



Scheme 7: Retrosynthetic analysis of (+)-erogorgiaene (**31**)

The total synthesis starts with a Heck coupling reaction of commercially available aromatic compound **48** under Jeffery conditions to afford α,β -unsaturated ketone **49** (Scheme 8).²³ Asymmetric conjugate addition of Me_2Zn with $\text{Cu}(\text{OTf})_2$ and ligand **50** delivers β -methyl ketone **51**. The next step is a Stille coupling reaction to alkyne **52**. Enolization with LiTMP gives the kinetically favored TMS enol ether with a regioselectivity of $>25:1$. Treatment with MeLi and Tf_2NPh delivers the enol triflate **53**.²⁴ Conversion of the enol triflate into a double bond was accomplished by a palladium catalyzed reduction.²⁵ Cleavage of the TMS group with K_2CO_3 generates the enyne precursor **47**. Treatment of compound **47** with Ru-catalyst **54** (Scheme 9) affords dihydronaphthalene **46** after a ring closing enyne methathesis reaction. The

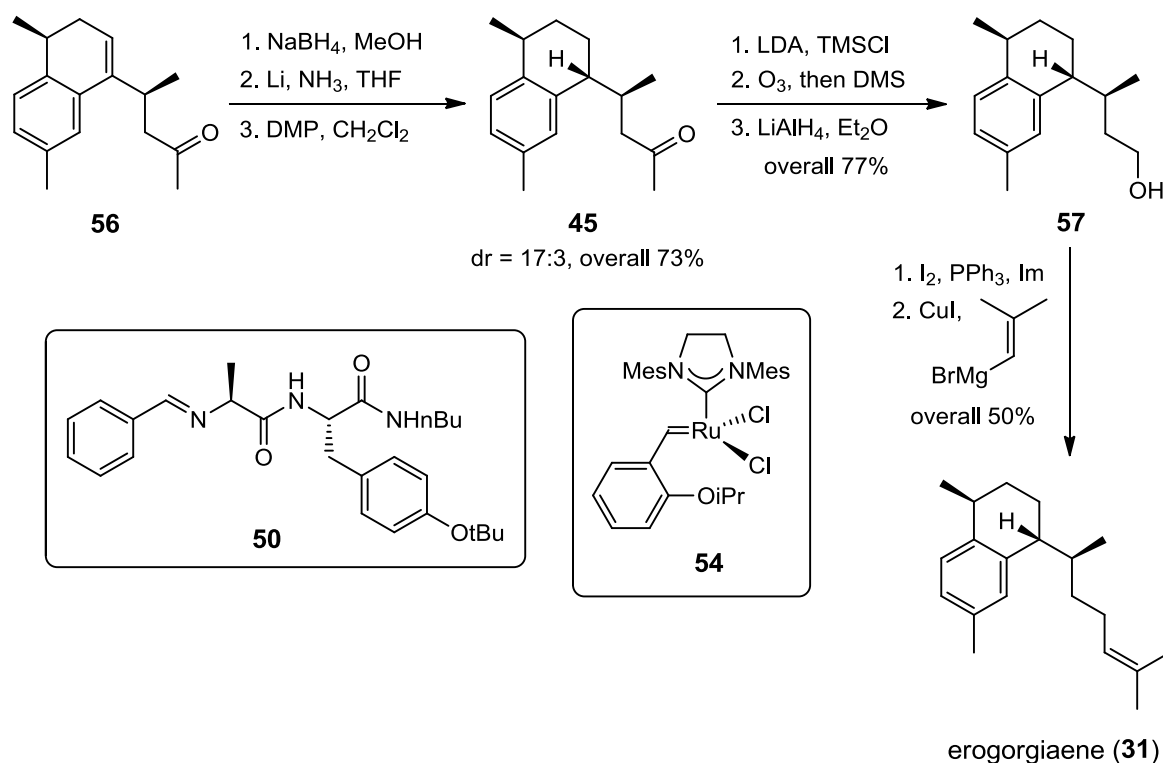
generated exomethylene group is converted into an α,β -unsaturated methyl ketone via cross metathesis with Ru-catalyst **54** and methyl vinyl ketone to enone **55**. The next step is a diastereoselective conjugate addition of Me_2Zn with $\text{Cu}(\text{OTf})_2$ and ligand **50** (Scheme 9) to intermediate **56**.



Scheme 8: Total synthesis of (+)-erogorgiaene (**31**) part 1

Direct hydrogenation of compound **56** under various conditions first affords the undesired diastereoisomer. Thus, the ketone moiety must be reduced with NaBH_4 to the secondary alcohol. Hydrogenation of the double bond with lithium in liquid ammonia and subsequent oxidation at the secondary alcohol with DMP delivers compound **45** with the desired stereochemistry. Next step is a transformation of the ketone moiety into the kinetically favored TMS enol ether with LDA and TMS-Cl. Oxidative cleavage of the TMS enol ether with ozone and subsequent treatment with

DMS delivers the aldehyde intermediate. Reduction of the aldehyde generates the primary alcohol **57**. The alcohol is transformed into an iodide under Appel conditions. Nucleophilic substitution of the alkyl iodide with an isobutenyl cuprate affords the natural product erogorgiaene (**31**).



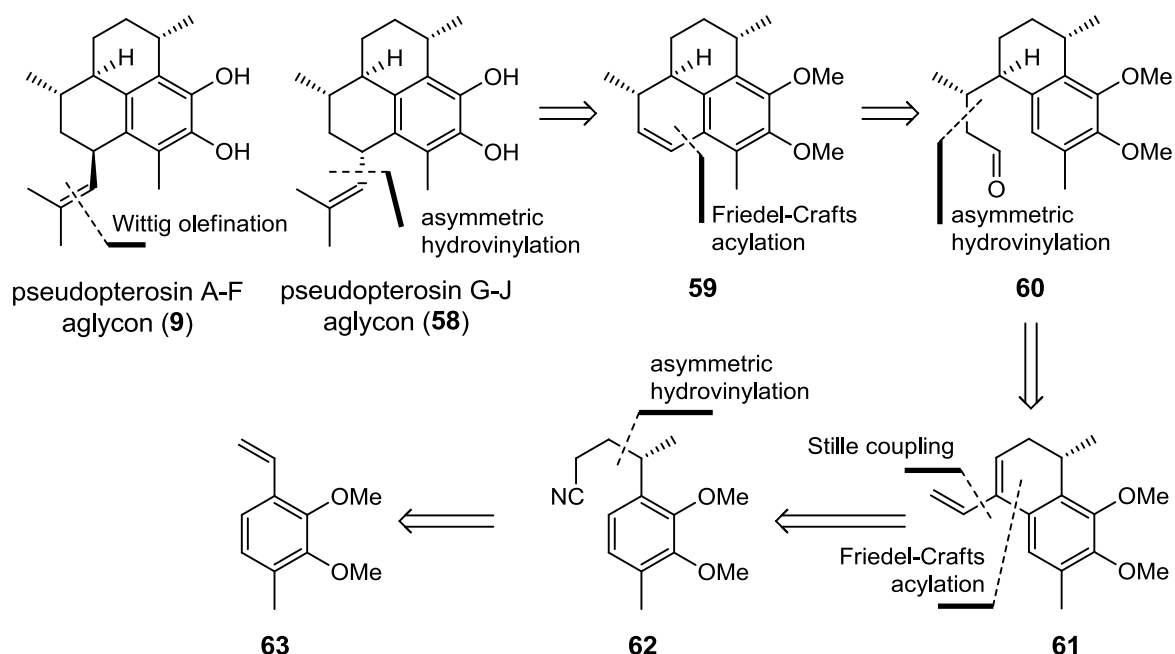
Scheme 9: Total synthesis of (+)-erogorgiaene (**31**) part 2

In summary, the enantioselective total synthesis of erogorgiaene (**31**) has been reported with an overall yield of 4% in 18 steps starting from commercially available aromatic compound (**48**).²⁶

3.2. Total synthesis of Pseudopterosins by RajanBabu *et al.* 2011

In contrast to some other total synthesis of pseudopterosins, RajanBabu used an aromatic compound instead of optically pure starting material for his synthesis.^{27,28,29} He initially synthesized the pseudopterosin core and installed the isobutenyl side chain afterwards. Thus, he could control the stereochemistry of the isobutenyl side chain via an asymmetric hydrovinylation reaction. Furthermore he was able to synthesize the aglycon of pseudopterosin A-F and G-J only by changing a few steps. Moreover he was able to invert all stereocenters introduced by hydrovinylation to

synthesize the aglycon of pseudopterosin K and L. Other key steps are the two ring closing reactions through an intramolecular Friedel-Crafts acylation of the aromatic ring (Scheme 10).



Scheme 10: Retrosynthetic analysis of pseudopterosin aglycons A-J

The synthesis starts with a Ni-catalyzed asymmetric hydrovinylation of compound **63**, using ligand **64** (Figure 8). This reaction delivers intermediate **65** with the desired stereochemistry in quantitative yield (Scheme 11). Starting material **63** is available from 2,3-dimethoxy toluene via regioselective formylation with *t*-BuLi and DMF followed by Wittig olefination.

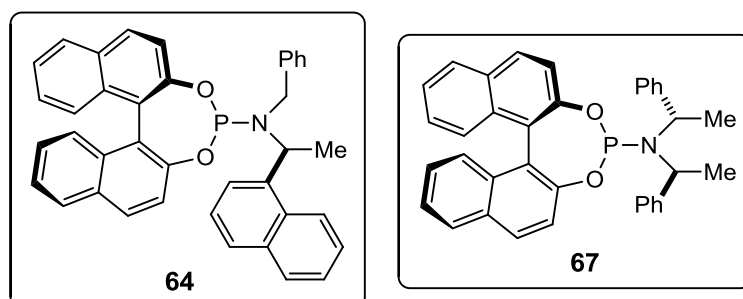
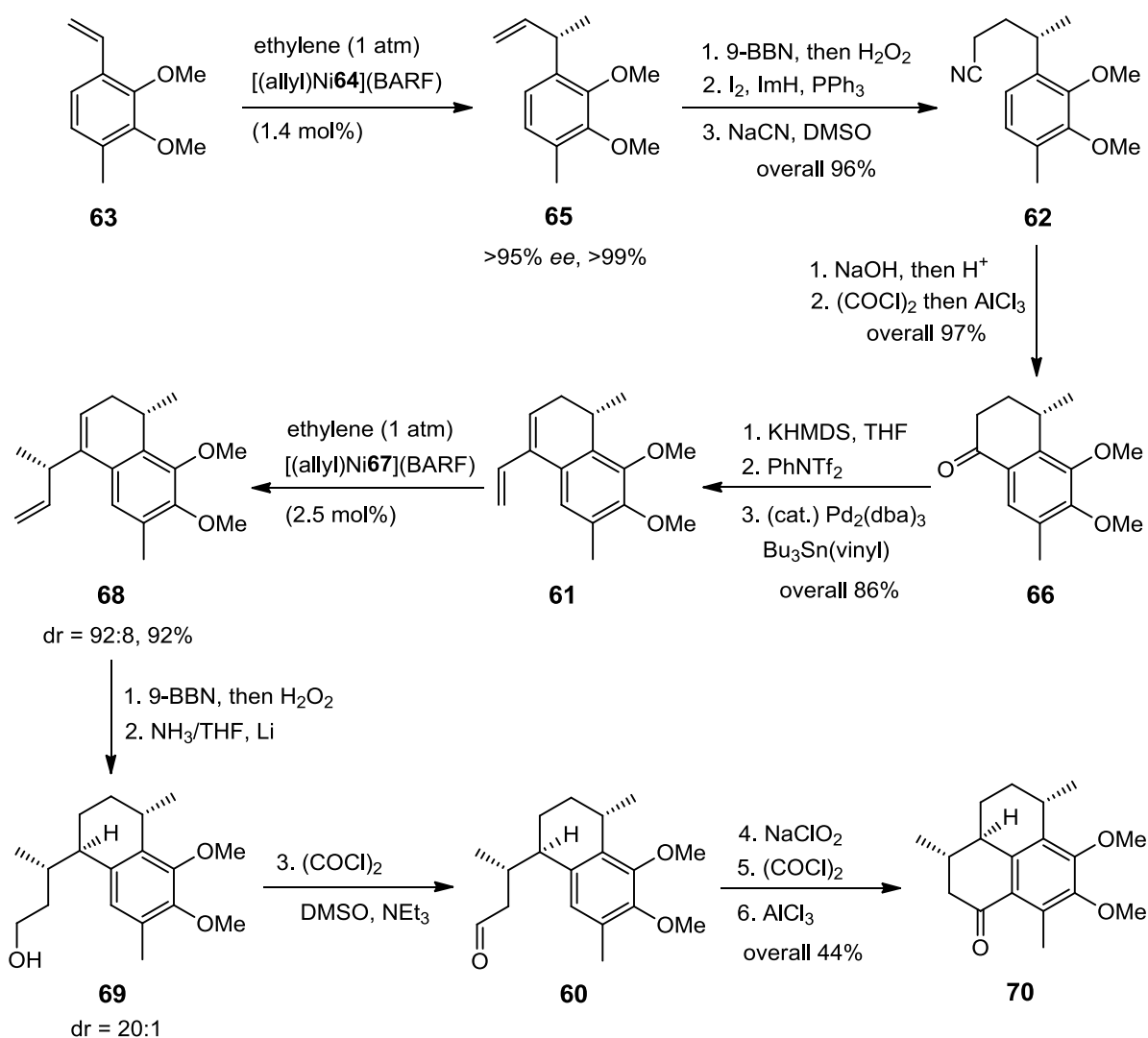


Figure 8: Ligands for the Ni-catalyzed asymmetric hydrovinylation

The next step is a regioselective hydroboration with 9-BBN and subsequent oxidation to the primary alcohol.³⁰ Substitution of the alcohol under Appel conditions delivers

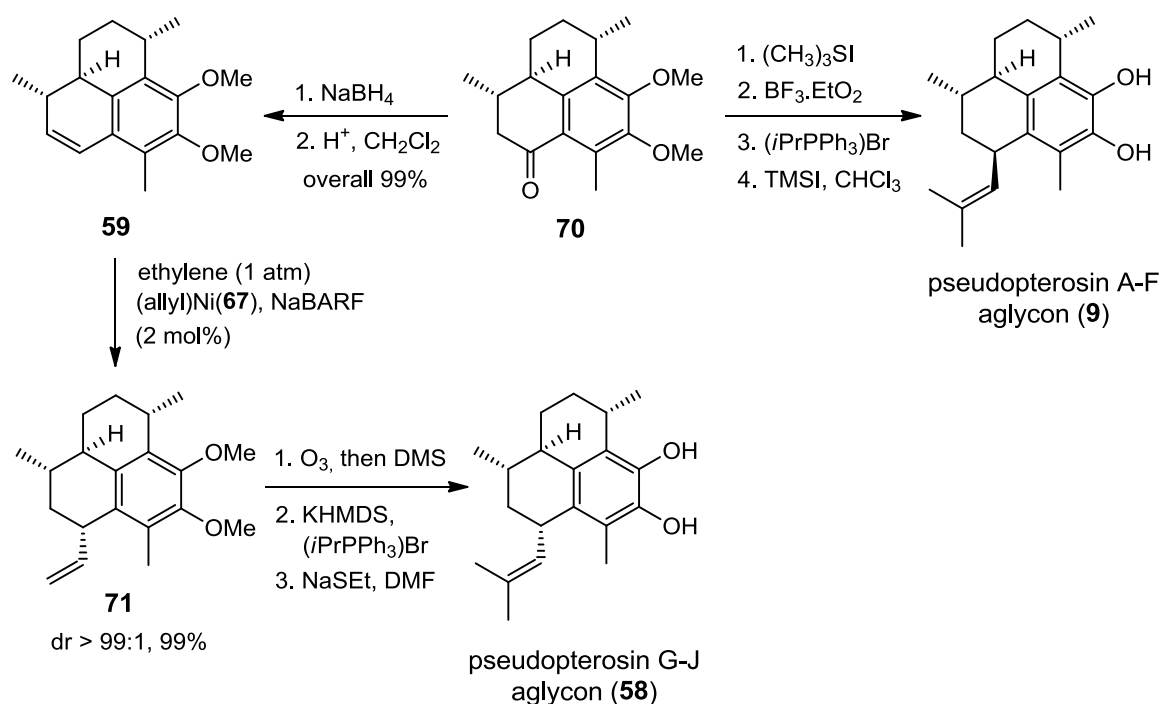
the alkyl iodide. A second displacement with sodium cyanide generates the primary cyanide **62**. Hydrolysis of cyanide **62** and subsequent treatment with oxalyl chloride affords the acid chloride. Cyclization under Friedel-Crafts conditions delivers tetralone **66**. Treatment of the ketone with KHMDS and PhNTf₂ generates the enol triflate. Stille coupling of the enol triflate with tributyl vinyl stannane affords diene **61**.³¹ A second Ni-catalyzed asymmetric hydrovinylation using ligand **67** provides the second stereogenic center in excellent diastereoselectivity.



Scheme 11: Total synthesis of pseudopterosin aglycons A-J part 1

In the next step the exomethylene group is transformed into a primary alcohol by treatment with 9-BBN and hydrogen peroxide. The remaining double bond is hydrogenated with lithium in liquid ammonia to give alcohol **69** with a diastereomeric ratio of 20:1.²⁶ Oxidation of the primary alcohol under Swern conditions affords aldehyde **60**. Pinnick oxidation of the aldehyde and treatment with oxalyl chloride

provides the acid chloride. A second Friedel-Crafts acylation reaction closes the third ring to key intermediate **70**. Out of compound **70** both series of aglycons, pseudopterosin A-F (**9**) and G-J (**58**) respectively are available. The first series of pseudopterosin aglycons A-F (**9**) are synthesized by transformation of the ketone into an epoxide moiety (Scheme 12). Subsequent opening of the epoxide with boron trifluoride affords the aldehyde. Olefination with an isopropenyl Wittig reagent and cleavage of the methoxy ether with TMS-I delivers pseudopterosin aglycon A-F (**9**). This endgame was done by Corey and coworkers.³²

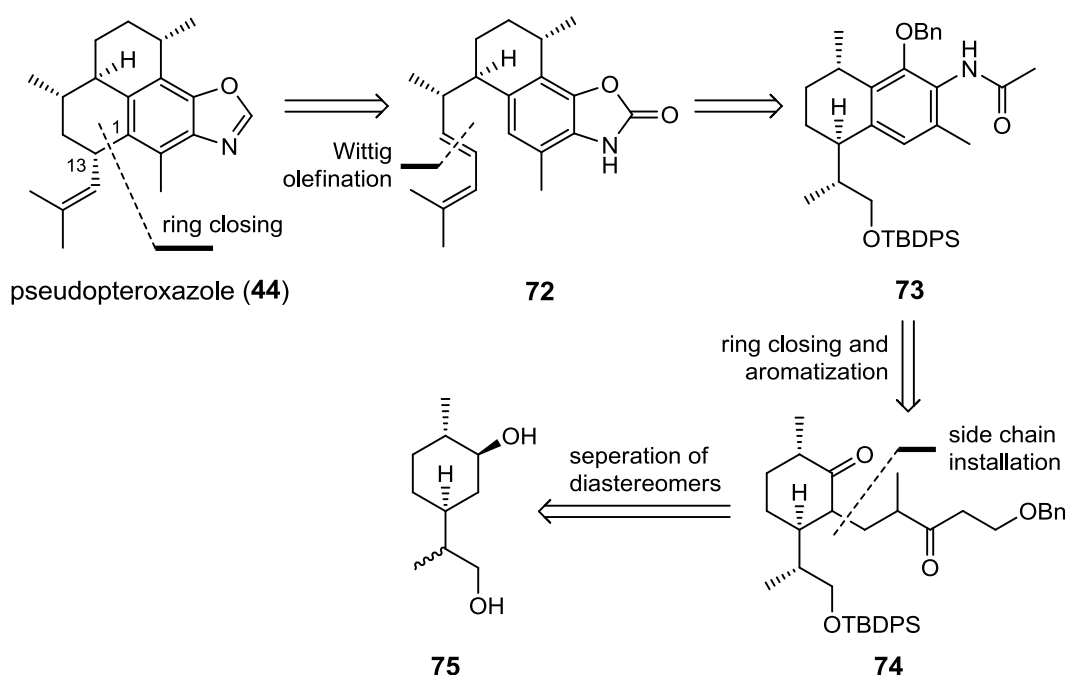


Scheme 12: Total synthesis of pseudopterosin aglycons A-J part 2

The second series of pseudopterosin aglycons G-J (**58**) are synthesized by reduction of the ketone to the alcohol. Elimination of the alcohol under acidic conditions delivers compound **59**. A third Ni-catalyzed asymmetric hydrovinylation, using ligand **67**, provides the last stereogenic center in excellent yield and diastereoselectivity. Oxidative cleavage of the double bond and work up with DMS generates the aldehyde moiety. Olefination of the aldehyde with an isopropenyl Wittig reagent and cleavage of the methoxy ether with sodium thioethanolate provides pseudopterosin aglycon G-J (**58**). In summary, the synthesis is due to the asymmetric hydrovinylation reaction very flexible. Based on this synthetic tool it is possible to synthesize all pseudopterosin aglycons.³³

3.3. Total synthesis of (+)-pseudopteroxazole by Corey *et al.* 2003

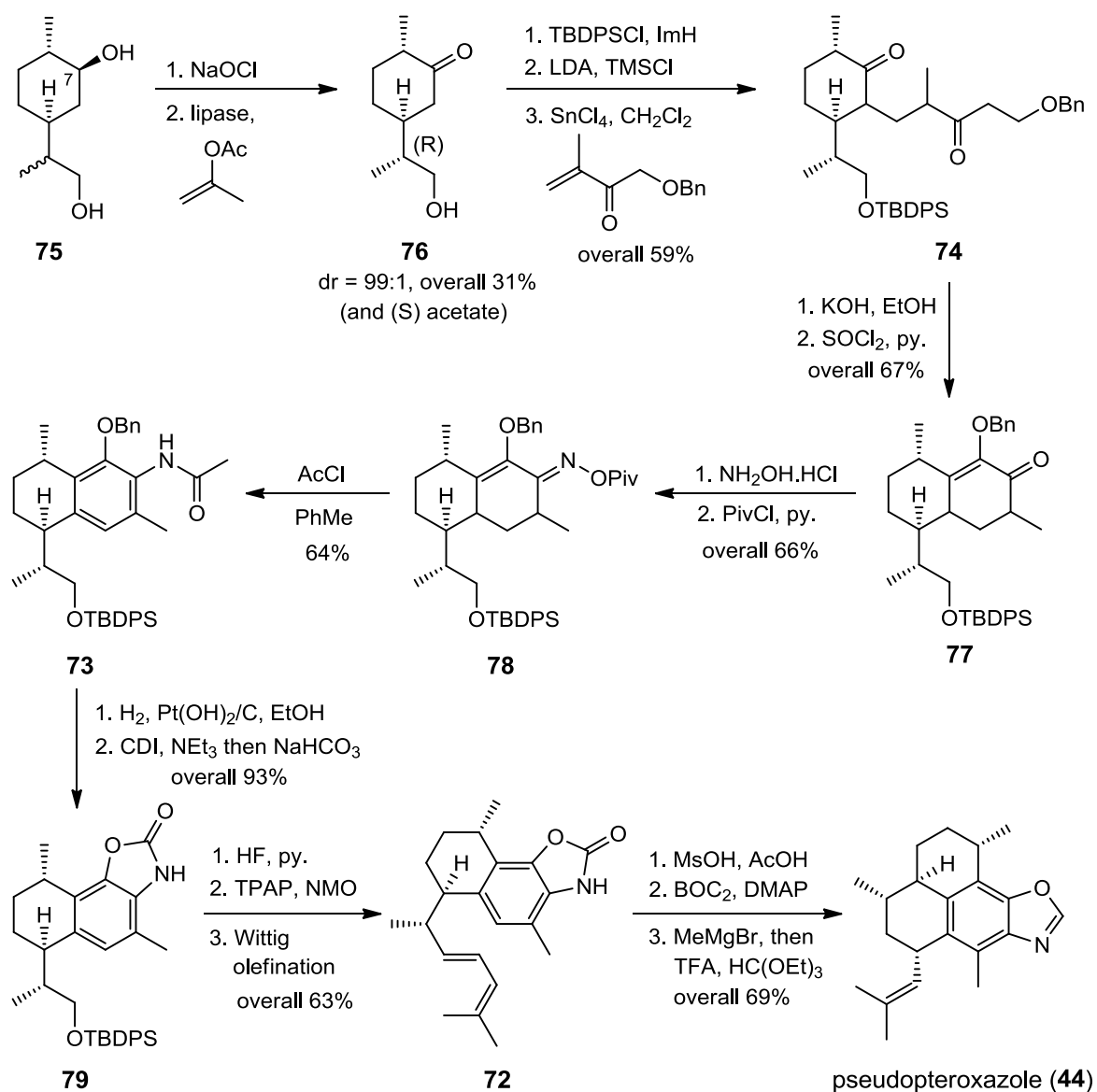
Corey's synthesis started from an optically pure (*S*)-(-)-limonene derivative which includes three out of four stereogenic centers of the final molecule. Thus, an important key step in the retrosynthetic analysis was the stereocontrolled ring closing reaction between position 1 and 13. A second key step was a modified Wolff-Semmler reaction to build up the aromatic ring (Scheme 13).



Scheme 13: Retrosynthetic analysis of (+)-pseudopteroxazole (44)

The synthesis outlined in Scheme 14 starts with the diol mixture **75** which can be obtained in almost quantitative yield from (*S*)-(-)-limonene by cyclic hydroboration and alkaline peroxide oxidation.³⁴ The nearly 1:1 mixture of diastereomers underwent selective oxidation with sodium hypochlorite at position to the corresponding hydroxy ketones.³⁵ Exposure of this mixture to isopropenyl acetate and Amano PS lipase as catalyst generates in selective acetylation the (*8R*)-alcohol **76** and the acetylated (*8S*)-ketone. Next step is the protection of the primary alcohol with TBDPS-Cl. Kinetic deprotonation with LDA and trapping of the enol with TMS-Cl provides the TMS enol ether. A Mukaiyama-Michael reaction with tin tetrachloride and α,β -unsaturated ketone delivers compound **74** in a 1:1 mixture of diastereomers. Cyclization of the 1,5-diketone with potassium hydroxide and subsequent treatment with thionyl chloride in pyridine affords bicyclic ketone **77**. Hydroxylamine hydrochloride and

pivaloyl chloride in toluene delivers the *O*-pivaloyl protected oxime **78**. The next step is a modified Wolff-Semmler reaction with acetyl chloride in toluene to yield product **73**. Hydrogenolysis of the benzyl ether followed by cyclization with carbonyldiimidazole and cleavage of the acetate group with sodium bicarbonate delivers intermediate **79**.



Scheme 14: Total synthesis of (+)-pseudopteroxazole (**44**)

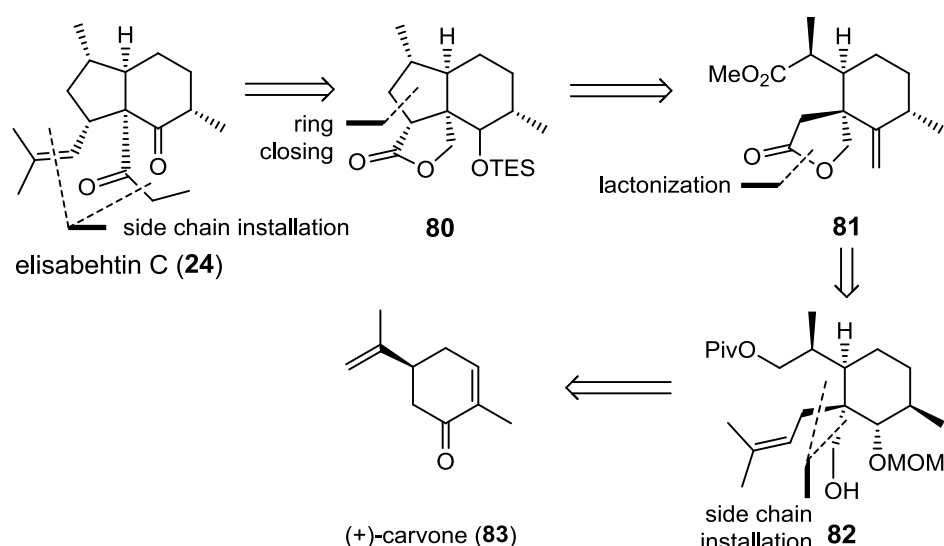
Next steps are cleavage of the TBDPS group with hydrofluoric acid-pyridine complex and mild oxidation with tetrapropylammonium perruthenate to the aldehyde. A following Wittig-Vedjez *E*-selective olefination affords the cyclization precursor **72**.³⁶ Treatment of compound **72** with methane sulfonic acid in acetic acid generates an allylic cation which undergoes an aromatic electrophilic substitution reaction. Hence,

the third six membered ring is closed to give a 4:1 mixture of diastereomers favoring the desired tetracycle. Next steps are acetylation of the free NH group with di-*tert*-butyl dicarbonate, cleavage of the carbamate group with excess of methylmagnesium bromide and subsequent treatment of the dianion with a mixture of triethylorthoformate and trifluoroacetic acid to provide the natural product pseudopteroxazole (**44**).

In summary, the enantioselective total synthesis of (+)-pseudopteroxazole (**44**) has been reported with an overall yield of approx. 2% in 20 steps starting from commercially available (*S*)-(-)-limonene.³⁷

3.4. Total synthesis of (-)-elisabethin C by Yamada *et al.* 2001

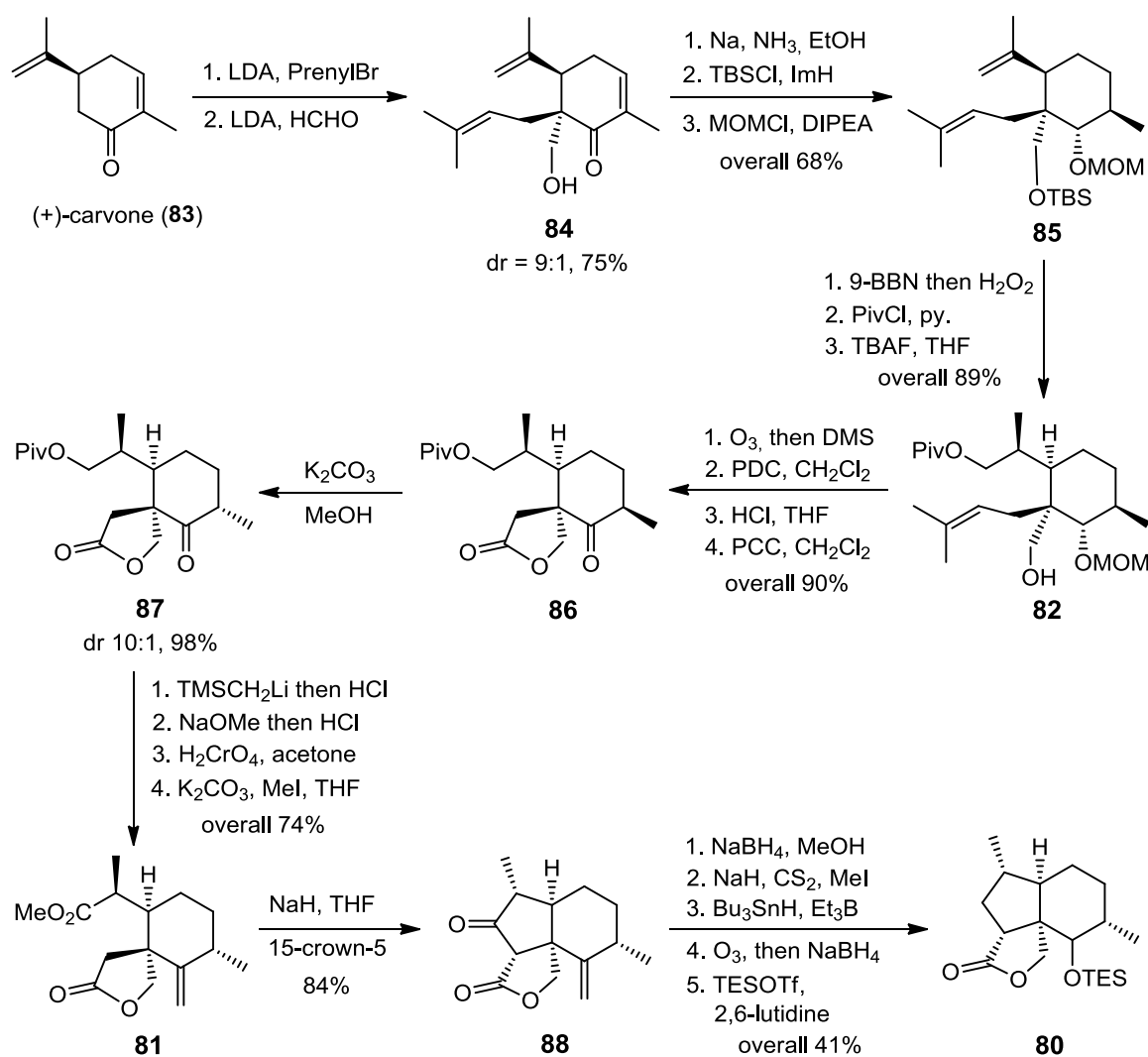
A key step in Yamada's retrosynthetic strategy was an intramolecular Dieckmann condensation to build up the five membered ring. Hence, he generated a spirolactone to introduce the correct stereochemistry for the later isobutenyl side chain. Special attention in the synthesis requires the quaternary carbon atom. Yamada generated this quaternary center in a very early stage through a double aldol reaction. Therefore, he used (+)-carvone to get an acceptable stereoisolation for the introduced side chains (Scheme 15).



Scheme 15: Retrosynthetic analysis of (-)-elisabethin C (**24**)

The synthesis starts (Scheme 16) with an aldol reaction, using LDA and prenyl bromide to introduce the first side chain. A second aldol reaction with LDA and

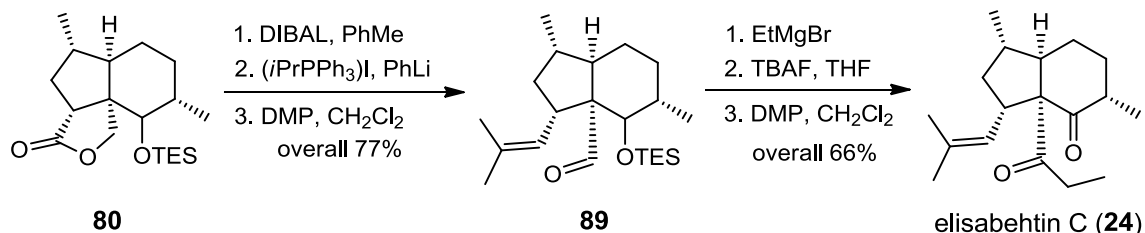
formaldehyde in THF generates the quaternary stereocenter of compound **84** in a 9:1 mixture of diastereomers. Reduction of the double bond and the ketone moiety with lithium in liquid ammonia, followed by protection of the primary alcohol with TBS-Cl and a second protection of the secondary alcohol with MOMCl provides intermediate **85** as a single product. Regio- and stereoselective hydroboration of the exomethylene double bond using 9-BBN and subsequently oxidation with hydro peroxide generates the primary alcohol. ³⁸



Scheme 16: Total synthesis of (-)-elisabethin C (**24**) part 1

Protection of the primary alcohol with pivaloyl chloride and cleavage of the TBS group with tetrabutylammonium fluoride affords alcohol **82**. Ozonolysis of the remaining double bond and work up with dimethyl sulfide provides a five membered lactol. Oxidation of the lactol to the lactone with PDC, cleavage of the MOM group with hydrochloric acid and subsequent oxidation with PCC delivers spiro lactone **86**.

Epimerization of the methyl group *alpha* to the ketone moiety with potassium carbonate affords intermediate **87** in a 10:1 mixture favoring the desired diastereomer. Next step is a transformation of the ketone moiety to an exomethylene double bond with TMSCH_2Li followed by treatment with hydrochloric acid.³⁹ Deprotection of the pivaloyl group with sodium methanolate in methanol affords the primary alcohol. Oxidation of this alcohol under Jones conditions and subsequent esterification of the carboxylic acid with methyl iodide and potassium carbonate generates methyl ester **81**. Enolization of the spirolactone using sodium hydride and 15-crown-5 initiates the Dieckmann condensation to the tricyclic intermediate **88** as a single product. It is noteworthy that the methyl group at the five membered ring epimerizes under these conditions concomitantly to the desired stereomer. Next steps are reduction of the ketone to an alcohol with sodium borohydride, transformation of the alcohol into a xanthate using carbon disulfide, NaH and methyl iodide followed by radical reduction of the xanthate with tributyltin hydride.⁴⁰ Ozonolysis of the double bond and reductive work up with sodium borohydride followed by protection of the secondary alcohol with TES-Cl provides compound **80**.

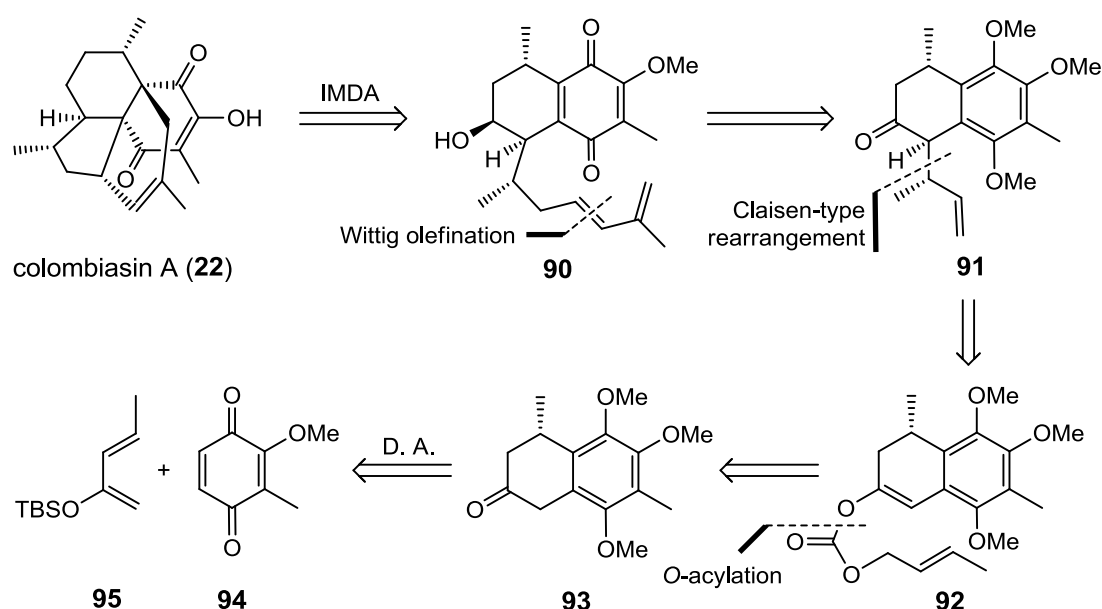


Scheme 17: Total synthesis of (-)-elisabethin C (**24**) part 2

Reduction of the lactone to the lactol with DIBAL and subsequent opening of the lactol with a Wittig reagent generates the isobutenyl side chain. Oxidation of the alcohol with Dess-Martin periodinane affords the aldehyde **89**.⁴¹ Introduction of the second side chain with ethylmagnesium bromide, cleavage of the TES group with tetrabutylammonium fluoride and oxidation of the two alcohol groups with DMP provides the natural compound elisabethin C (**24**) (Scheme 17). In summary, the enantioselective synthesis of (-)-elisabethin C (**24**) has been reported with an overall yield of approx. 4% in 29 steps starting from commercially available (+)-carvone.⁴²

3.5. Total synthesis of (–)-colombiasin A by Nicolaou *et al.* 2001

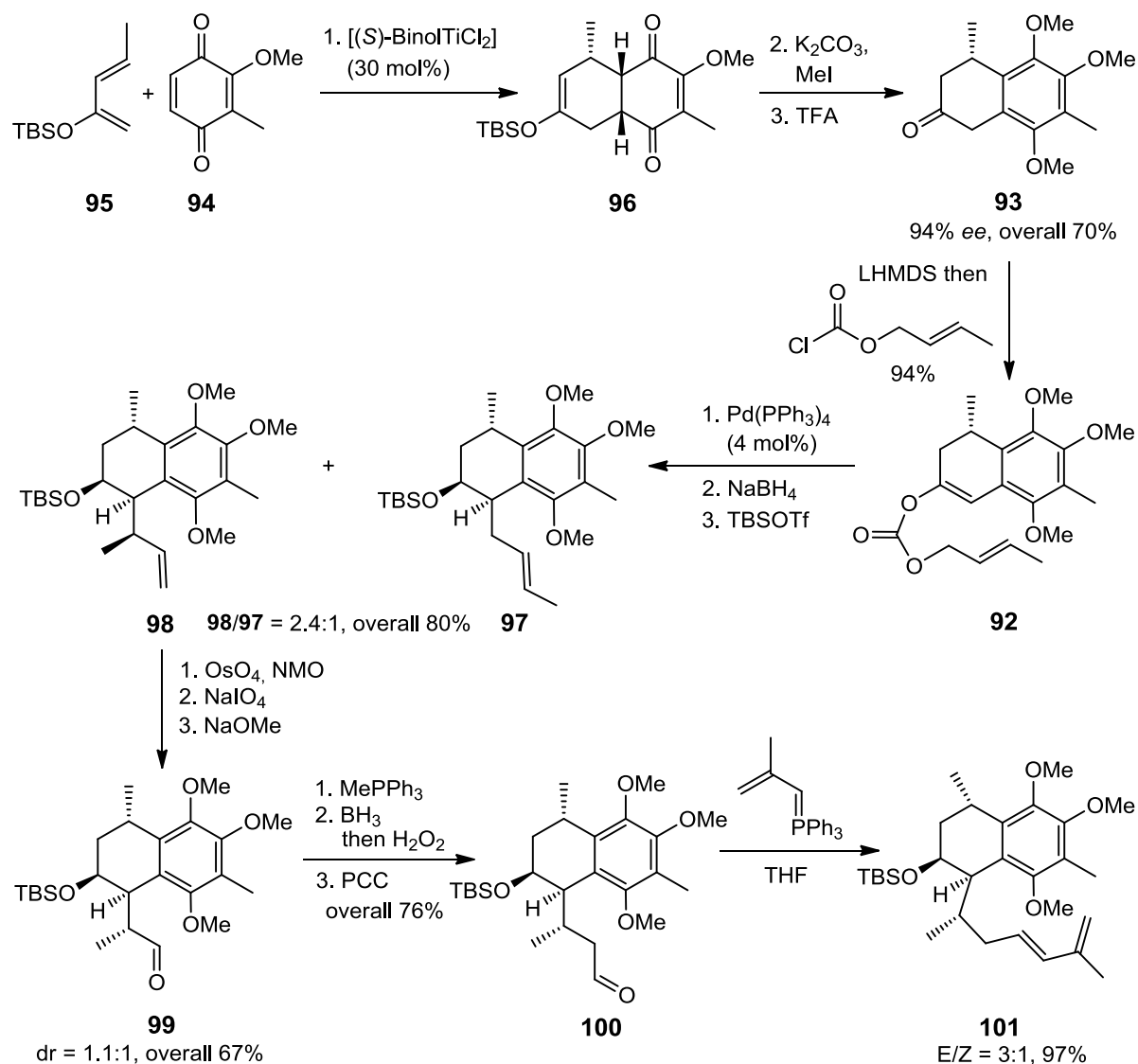
Colombiasin A (**22**) consists of three six membered rings and one five membered ring, which are annulated to each other. This ring arrangement generates two vicinal quaternary carbon atoms in the center of the molecule. Nicolaou's retrosynthetic strategy is based on an intramolecular Diels-Alder reaction, which generated two rings and the two quaternary carbon atoms in one step. A further key step was the side chain introduction via a palladium catalyzed Claisen-type rearrangement. The aromatic ring was used as a kind of protecting group for the quinone system. Moreover, he utilized a second Diels-Alder reaction and a chiral catalyst to get optically pure material (Scheme 18).



Scheme 18: Retrosynthetic analysis of (–)-colombiasin A (**22**)

The synthesis starts (Scheme 19) with an asymmetric Diels-Alder reaction with diene **95** and quinone **94** in the presence of the Mikami catalyst for chiral induction.⁴³ Quinone **94** is prepared by *ortho*-methylation of 1,2,4-trimethoxybenzene followed by oxidative cleavage of the methoxy groups with AgO and nitric acid.^{44,45} Aromatization by a double enolization of the ketones with potassium carbonate and subsequent methylation with methyl iodide delivers the aromatic system. Cleavage of the TBS ether with trifluoroacetic acid affords the bicyclic ketone **93**. Enolization of the ketone with LHMDS and treatment with crotyl chloroformate delivers compound **92**.⁴⁶ The next step is a palladium catalyzed Claisen-type rearrangement to introduce the side

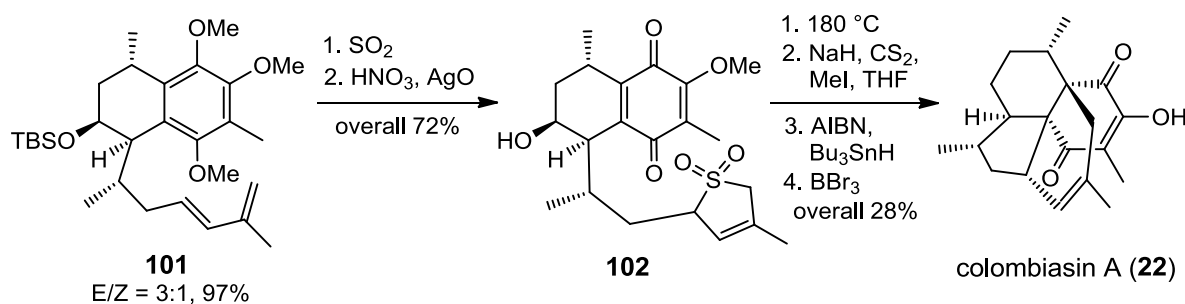
chain in α -position to the ketone. This reaction generates two products in a 2.4:1 mixture. The mixture is reduced with sodium borohydride followed by protection with TBSOTf to compounds **97** and **98**. Dihydroxylation with osmium tetroxide and subsequent cleavage of the diol with sodium periodate delivers the aldehyde moiety.⁴⁷ Epimerization in α -position to the aldehyde with sodium methanolate provides aldehyde **99** in a 1.1:1 mixture of diastereomers favoring the desired one.



Scheme 19: Total synthesis of (-)-colombiasin A (**22**) part 1

Next steps are Wittig olefination, followed by hydroboration with diborane and oxidation with hydrogen peroxide to a primary alcohol. Oxidation of the primary alcohol with PCC provides compound **100**. A further Wittig reaction affords intermediate **101** in a 3:1 mixture of double bond isomers. Protection of the diene system by treatment with sulfur dioxide delivers a cyclic sulfone.⁴⁸ Cleavage of two

methoxy groups and the TBS group with AgO and nitric acid by concomitant oxidation of the dihydroquinone affords quinone **102**. Heating of compound **102** opens the cyclic sulfone to the diene and enables the intramolecular Diels-Alder reaction to close the five- and six membered rings. The next step is a transformation of the alcohol into a xanthate using carbon disulfide, NaH and methyl iodide. A followed radical reduction of the xanthate with tributyltin hydride completes the deoxygenation. Cleavage of the methoxy group with boron tribromide affords the natural product colombiasin A (**22**) (Scheme 20).

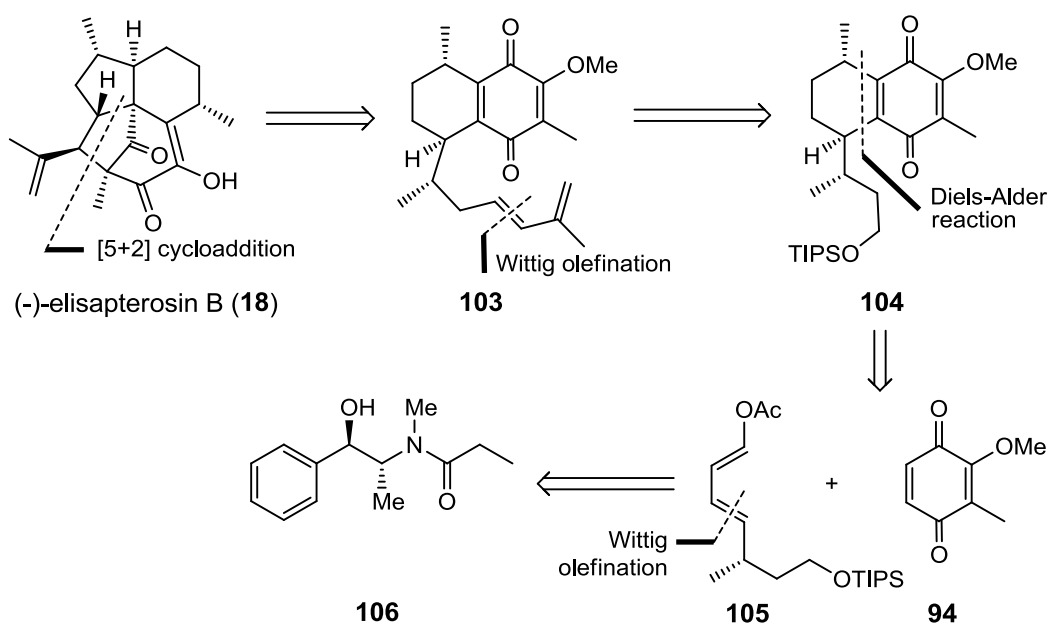


Scheme 20: Total synthesis of (-)-colombiasin A (**22**) part 2

In summary, Nicolaou used two Diels-Alder reactions to build up the main part of the colombiane system. The first Diels-Alder reaction generated the decaline system and the second closed the other two rings to the complete carbon skeleton. Intelligent manipulation of the functional groups and minimum use of protecting groups allowed him a short total synthesis in only 20 steps.⁴⁹

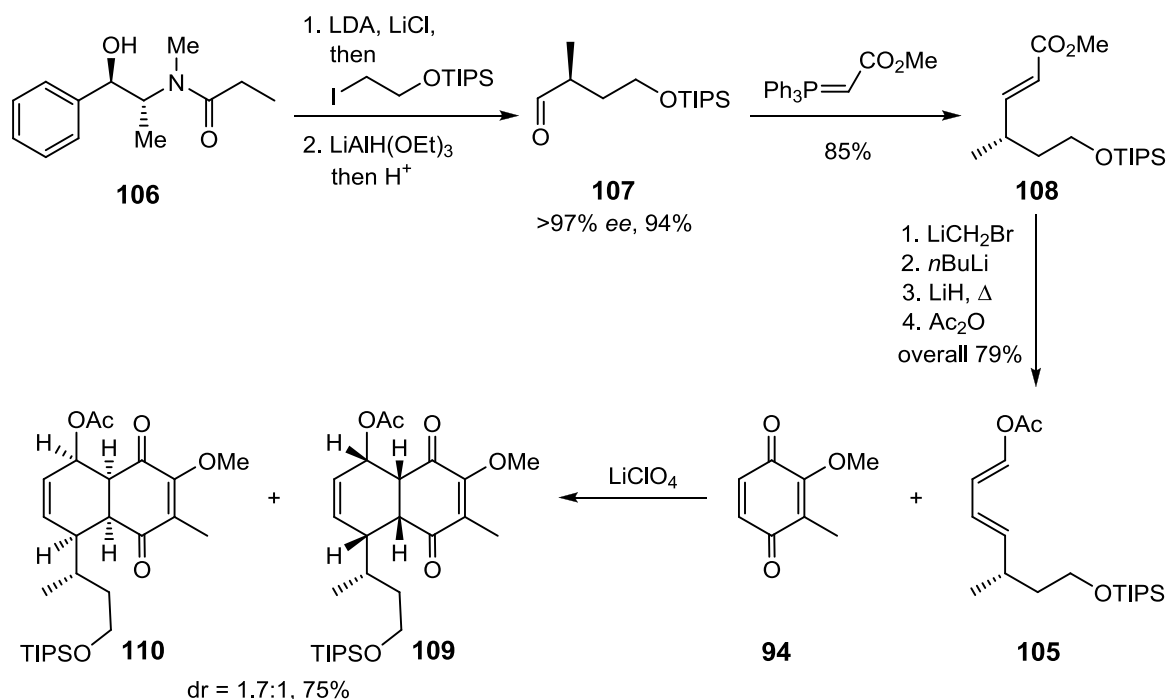
3.6 Total synthesis of (-)-elisapterosin B and (-)-colombiasin A by Rychnovsky *et al.* 2003

Rychnovsky tried to synthesize a late stage precursor molecule for both natural products. Based on previous work of other groups, he thought it might be possible to synthesize elisapterosin B (**18**) by an intramolecular [5+2] cycloaddition and colombiasin A (**22**) per intramolecular Diels-Alder reaction of compound **103**.^{49,50} He also used a Diels-Alder reaction to build up the decaline system and to introduce the desired stereochemistry of the side chain. The required enantiomer was prepared by asymmetric alkylation with pseudoephedrine as an auxiliary (Scheme 21).



Scheme 21: Retrosynthetic analysis of (-)-pseudopterosin B (**18**) and (-)-colombiasin A (**22**)

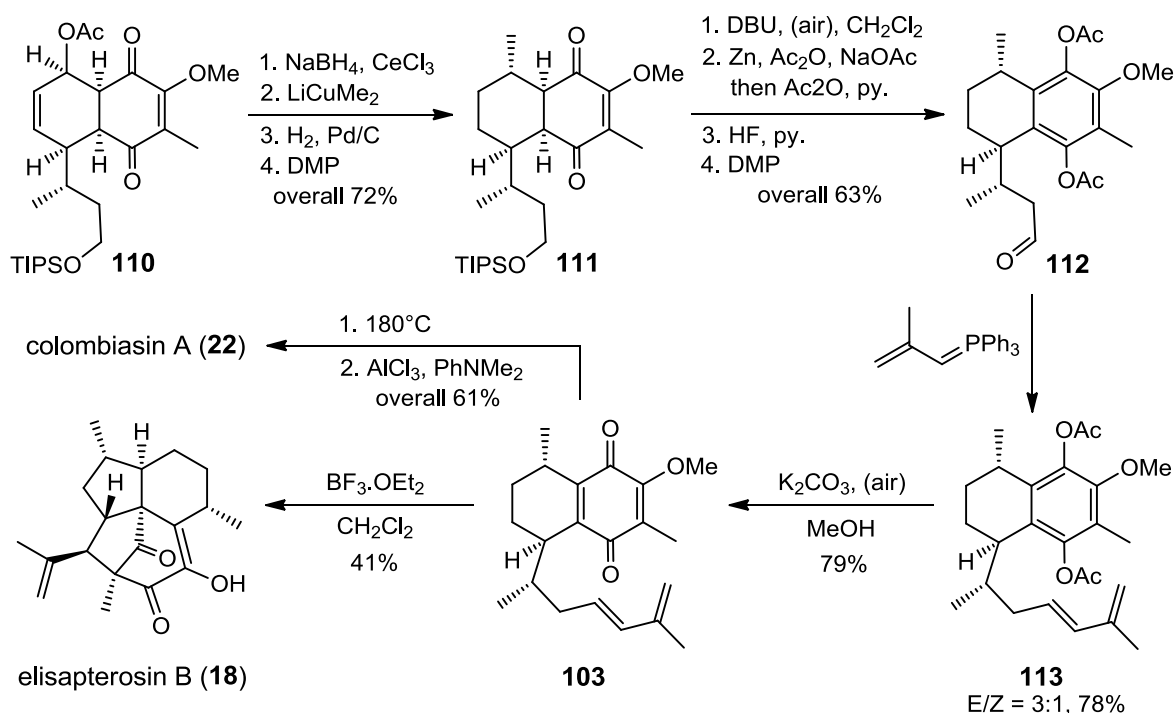
The synthesis starts with an asymmetric alkylation using Myers pseudoephedrine auxiliary for chiral induction.⁵¹ Reduction of the amide affords aldehyde **107** with excellent enantioselectivity (Scheme 22).



Scheme 22: Total synthesis of (-)-pseudopterosin B (**18**) and (-)-colombiasin A (**22**) part 1

The next step is a Wittig olefination to the α,β -unsaturated ester **108**. Transformation in the lithium ynoate followed by treatment with LiH and acetylation with acetic

anhydride provides diene **105** as a single isomer.⁵² A Diels-Alder reaction with dienophile **94**, prepared from commercially available 2,6-dimethoxytoluene,⁵³ and diene **105** in presence of lithium perchlorate generates compounds **109** and **110** in a 1:1.7 mixture of diastereomers.⁵⁴



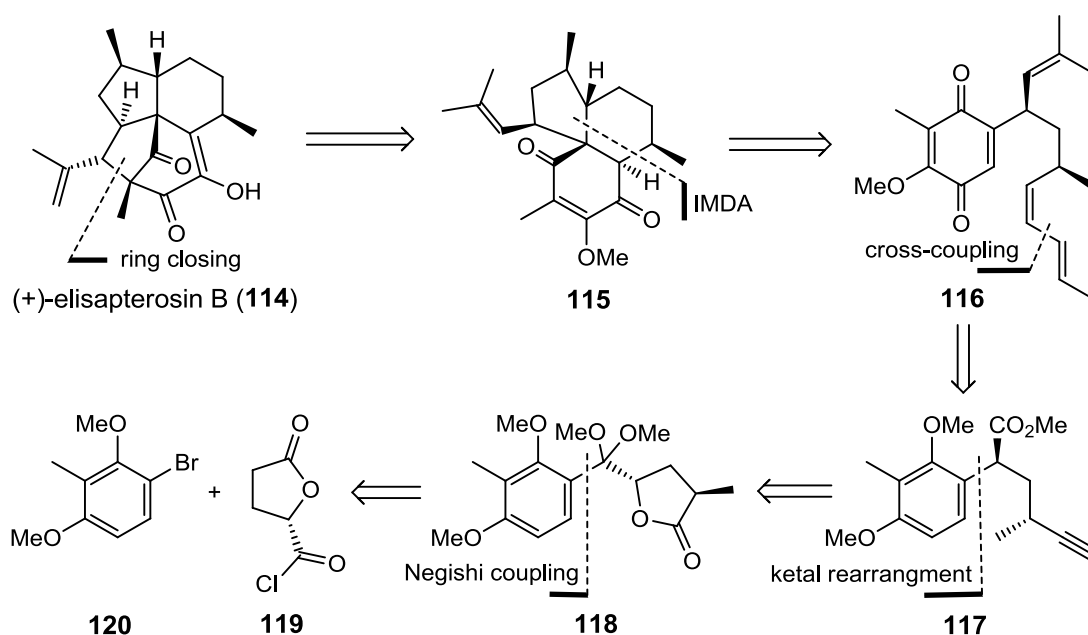
Scheme 23: Total synthesis of (-)-pseudopterosin B (**18**) and (-)-colombiasin A (**22**) part 2

Selective reduction of the ketone next to the methoxy group with sodium borohydride affords an allylic alcohol. Treatment with lithium dimethylcuprate smoothly substitutes the acetate group. Hydrogenation followed by oxidation of the alcohol with DMP delivers enedione **111** (Scheme 23). Enolization with DBU and oxidation with air gives the corresponding quinone. Reduction of the quinone with zinc and acetylation with acetic anhydride delivers the hydroquinone diacetate. Cleavage of the TIPS group with hydrofluoric acid and subsequent oxidation with Dess-Martin periodinane generates aldehyde **112**. A Wittig olefination produces diene **113** in a 3:1 mixture of double bond isomers. Cleavage of the two acetate groups and oxidation with air provides the key precursor **103**. Treatment with boron trifluoride at 0°C initiates the [5+2] cycloaddition and cleaves the methoxy group to the natural compound elisapterosin B (**18**). Heating of compound **103** enables the Diels-Alder cycloaddition and generates the colombiane carbon skeleton. Subsequent cleavage of the methoxy group provides the natural product colombiasin A (**22**).

In summary, the enantioselective synthesis of (–)-elisapterosin B (**18**) has been reported with an overall yield of approx. 3% in 19 steps starting from compound **106**. The enantioselective synthesis of (–)-colombiasin A (**22**) has been reported with an overall yield of approx. 5% in 20 steps starting from compound **106**.⁵⁵

3.7 Total synthesis of (+)-elisapterosin B by Rawal *et al.* 2003

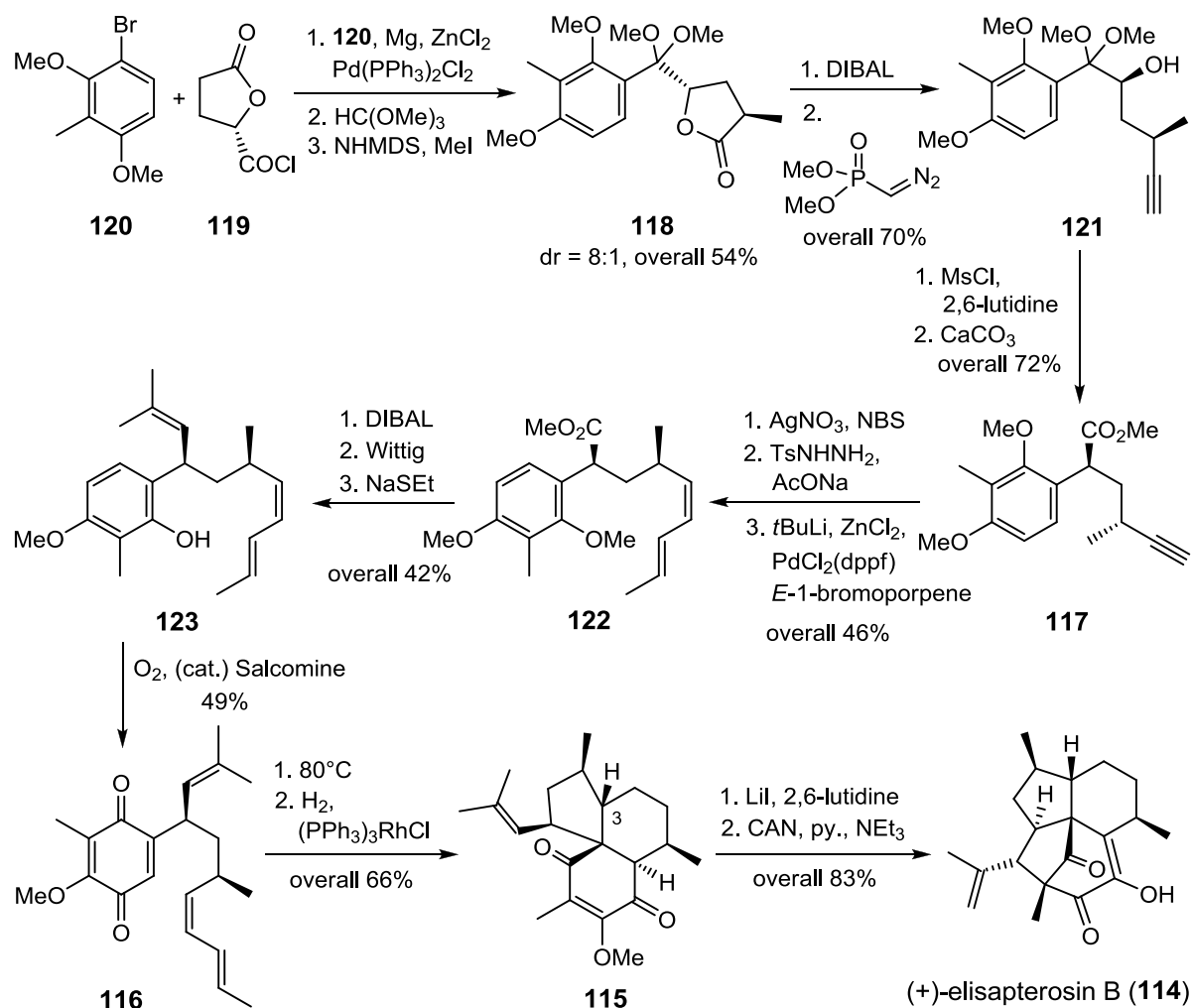
Rawal's retrosynthetic strategy based of an oxidative ring closing reaction out of an elisabethin derivative. This ring closing reaction could also be a possible biosynthetic pathway to elisapterosin B. After due considerations, he synthesized an elisabethin derivative which underwent oxidative cyclization to the desired target molecule. The elisabethane carbon skeleton was generated via an intramolecular Diels-Alder reaction. Further coupling reactions and functional group manipulations led back to optical pure material **119** and the aromatic compound **120** (Scheme 24).



Scheme 24: Retrosynthetic analysis of (+)-elisapterosin (**114**)

The optical pure starting material (S)-(+)-tetrahydro-5-oxo-2-furanacyl chloride **119** is prepared from inexpensive *L*-glutamic acid.⁵⁶ The first step is a zinc chloride mediated and palladium catalyzed Grignard reaction of the aromatic compound **120**, prepared via bromination out of 2,5-dimethoxytoluene,⁵⁷ and the optical pure material **119** (Scheme 25).⁵⁸ Acetalization with trimethyl orthoformate under acidic conditions

provides the dimethyl ketal. Alkylation with NHMDS and methyl iodide affords compound **118** in a 8:1 mixture of diastereomers. Reduction of the lactone with DIBAL and subsequent treatment of the crude lactol intermediate with the Seyferth reagent delivers the terminal alkyne **121**.⁵⁹ Mesylation of the free hydroxy group and subsequent treatment with calcium carbonate initiates the pinacol-type rearrangement to methyl ester **117**.⁶⁰



Scheme 25: Total synthesis of (+)-elisapterosin B (**114**)

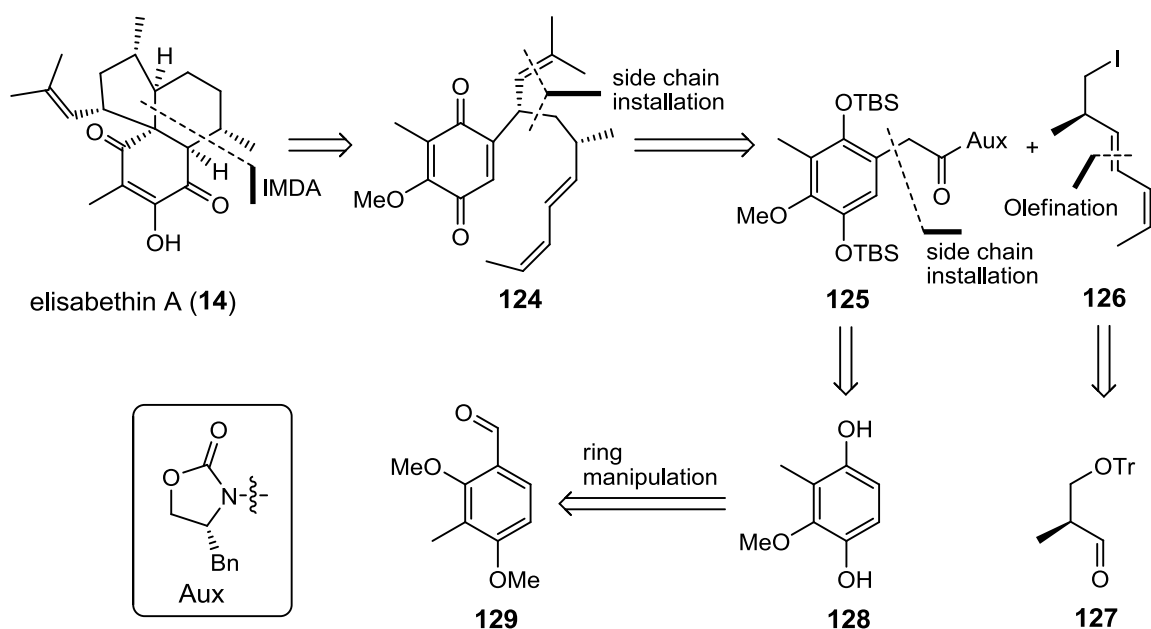
Treatment of **117** with NBS and catalytic amounts of silver nitrate delivers the terminal bromo alkyne. Hydrogenation with *in situ* generated diimide, prepared from tosyl hydrazine and sodium acetate, provides the terminal vinyl bromide exclusively *Z*-selective. A palladium catalyzed coupling reaction with *E*-1-bromopropene, *t*-BuLi and zinc chloride affords diene **122**.⁶¹ Reduction of the ester moiety with DIBAL to the aldehyde followed by Wittig olefination generates the isobutenyl side chain. Regioselective demethylation of the more hindered methoxy group with sodium

ethanethionate affords phenol **123**.⁶² Salcomine-catalyzed oxidation with oxygen delivers the quinone **116**.⁶³ The next step is an intramolecular Diels-Alder reaction followed by Wilkinson catalyzed hydrogenation of the double bond to 3-*epi*-elisabethin **115**. Cleavage of the methoxy group with lithium iodide and 2,6-lutidine followed by oxidative cyclization with CAN afford (+)-elisapterosin B (**114**).

In summary, the enantioselective synthesis of (+)-elisapterosin B (**114**) has been reported with an overall yield of approx. 1% in 18 steps starting from compound **120**. Rawal could also demonstrate that it is possible to synthesize elisapterosin B out of an elisabethin derivate. Furthermore, he reported that he was not able to epimerize 3-*epi*-elisabethin **115** to gain elisabethin A.¹⁸

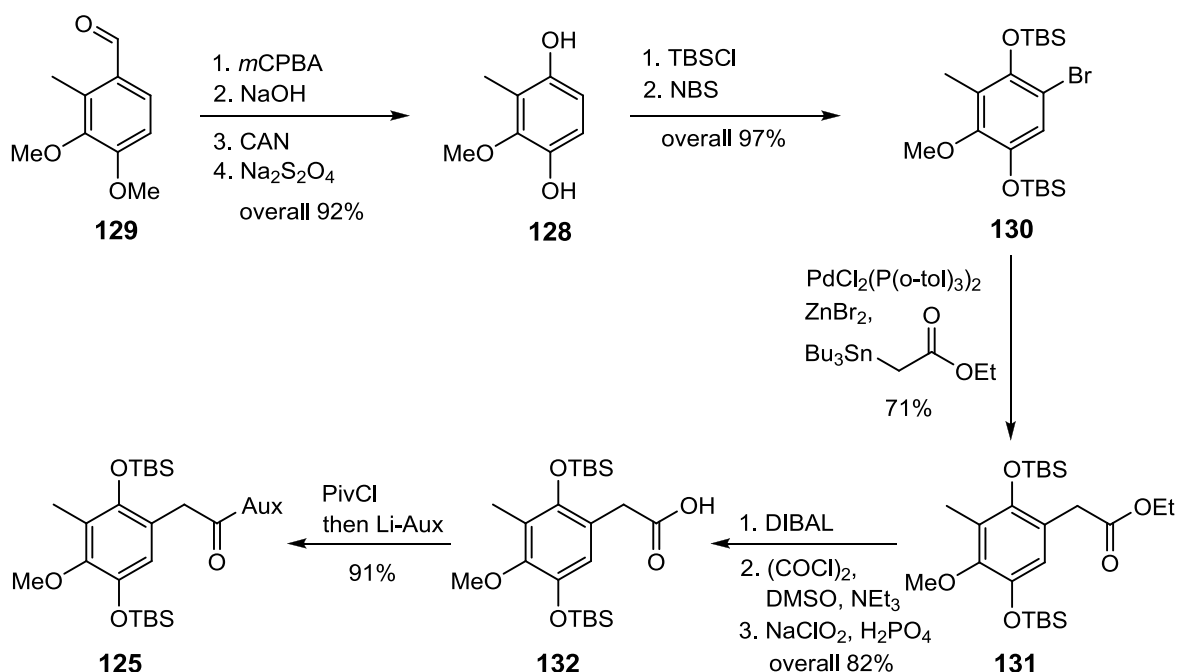
3.8. Partial synthesis of elisabethin A by Mulzer *et al.* 2003

Mulzer's retrosynthetic strategy was based on an intramolecular Diels-Alder reaction. This powerful key step allowed him to close two rings and introduce four out of six stereogenic centers in one step. Further he decided to divide the molecule in two parts to achieve a highly convergent synthesis (Scheme 26).



Scheme 26: Retrosynthetic analysis of elisabethin A (**14**)

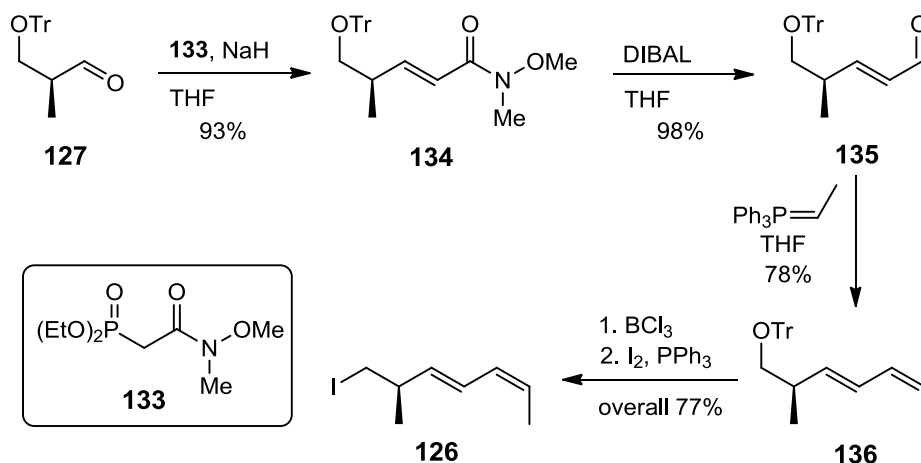
Hence, two different fragments were synthesized. On the one side the aromatic compound **129** for the quinone system and on the other the optically pure compound **127** to prepare the diene side chain.



Scheme 27: Synthesis of elisabethin A (**14**) part 1

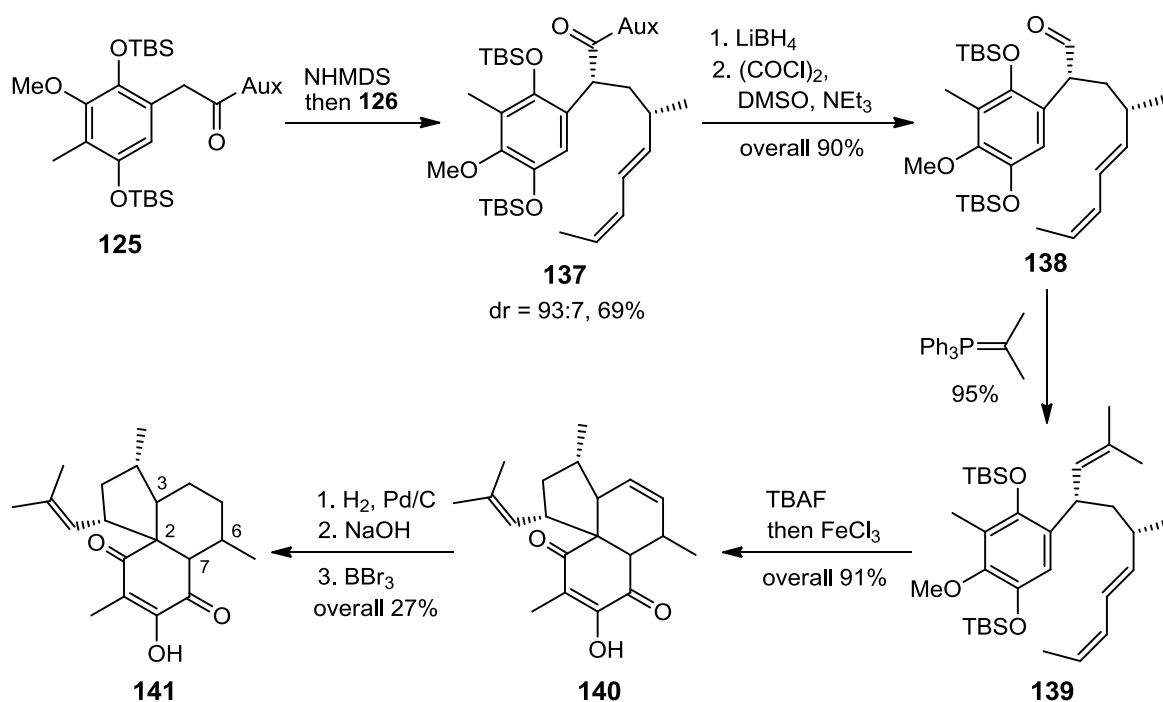
The synthesis starts with commercially available aldehyde **129** which is converted into a phenol by Baeyer-Villiger oxidation and subsequent saponification of the formic acid ester. Selective oxidation to the *para*-quinone followed by reduction with sodium hydrosulfite delivers the hydroquinone **128**. Protection of the hydroxy groups with TBS-Cl and regioselective bromination with NBS affords compound **130**. A palladium catalyzed Negishi-Reformatsky reaction with ethyl tributyltin acetate and zinc bromide delivers ethyl ester **131**.⁶⁴ Reduction of the ester moiety with DIBAL provides the primary alcohol. Oxidation of the alcohol under Swern conditions to the aldehyde and a further Pinnick oxidation afford the carboxylic acid **132**. Treatment with pivaloyl chloride generates a mixed acid anhydride which is subsequently attacked by the lithium auxiliary to imide **125** (Scheme 27).

Preparation of the diene side chain starts with an olefination reaction between aldehyde **127**⁶⁵ and the phosphor component **133**. Reduction of the Weinreb amide with DIBAL affords the α,β -unsaturated aldehyde **135**. Wittig olefination of the aldehyde generates the *cis* double bond. Cleavage of the trityl group with boron trichloride and subsequent substitution under Appel conditions provides the desired diene fragment **126** (Scheme 28).



Scheme 28: Synthesis of elisabethin A (**14**) part 2

Assembling of the two fragments via an alkylation reaction delivers compound **137** (Scheme 29). Reductive cleavage of the auxiliary with lithium borohydride followed by oxidation under Swern conditions generates aldehyde **138**.



Scheme 29: Synthesis of elisabethin (**14**) part 3

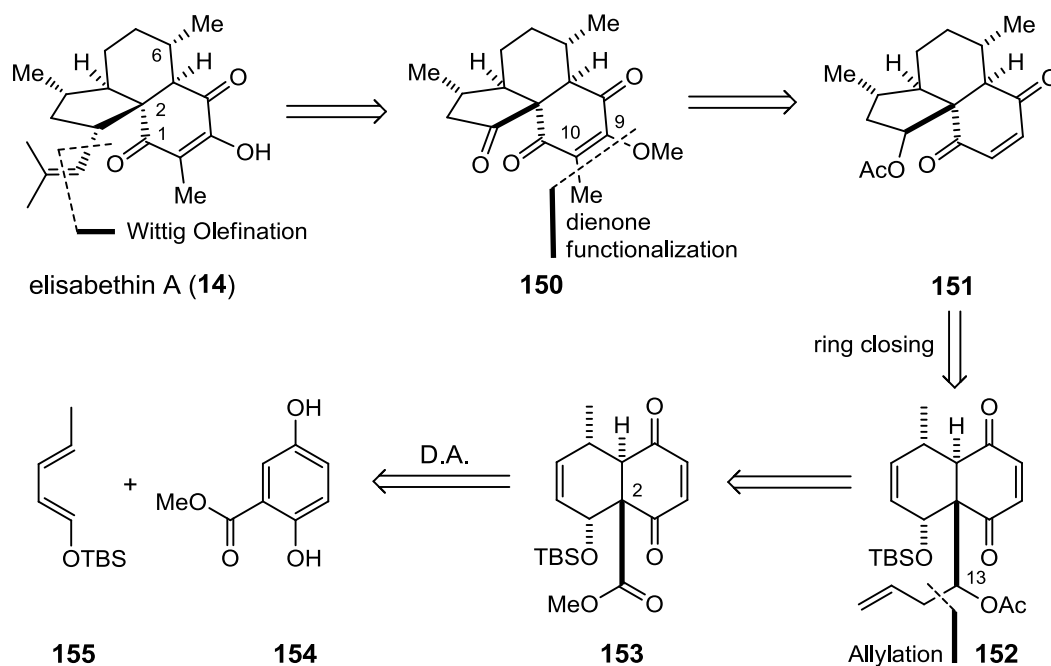
A further Wittig olefination generates the isobutenyl side chain. Cleavage of the TBS groups with tetrabutylammonium fluoride and subsequent oxidation of the hydroquinone to the quinone with iron trichloride initiates the intramolecular Diels-Alder reaction to compound **140**. Unfortunately, the stereochemistry of this tricycle at

position 2,3,6 and 7 is not absolutely clear.⁶⁶ Next steps are hydrogenation of the double bond, epimerization at position 7 with sodium hydroxide and cleavage of the methoxy group with boron tribromide to postulated final compound **141**.

In summary, the synthesis of postulated compound **141** has been reported with an overall yield of approx. 7% in 21 steps along the longest linear sequence.⁶⁷ A problem of this approach is the unknown transition state and the product of the intramolecular Diels-Alder reaction, respectively. Furthermore, the epimerization at position 7 should also be impossible.¹⁸ In consideration of these facts, a totally different approach for the total synthesis of elisabethin is required.

4. Results and Discussion

4.1. Retrosynthetic Analysis

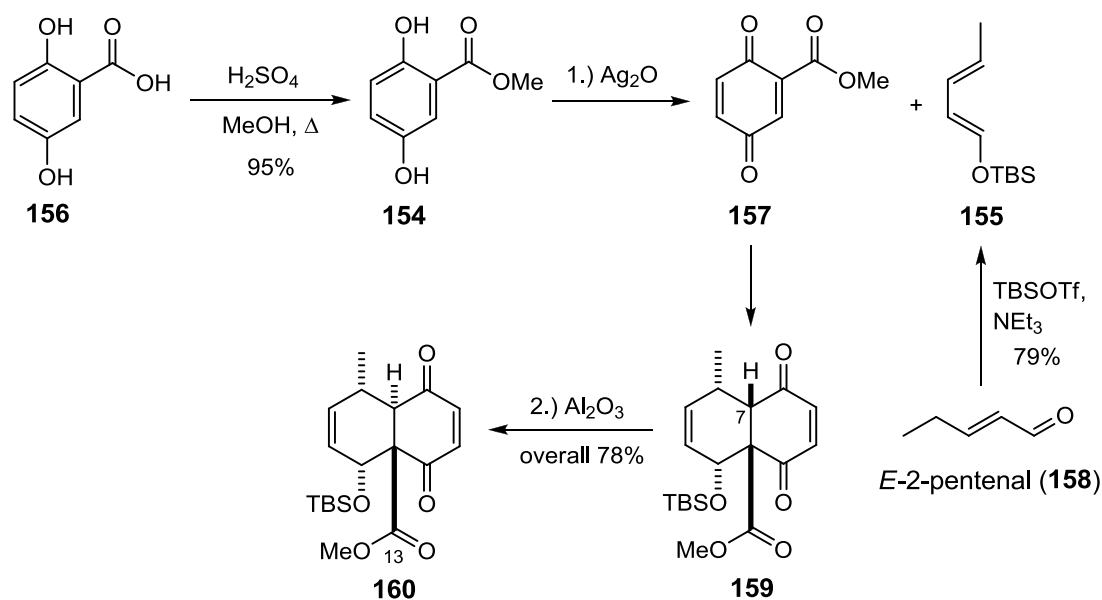


Scheme 30: Retrosynthetic analysis of elisabethin A (14)

Our retrosynthetic strategy based on an early regioselective Diels-Alder reaction to generate the decaline system and the quaternary carbon atom at position 2. Furthermore, this reaction provides four stereogenic centers which are required later in the synthesis. Moreover, this step could be catalyzed by a chiral ligand or auxiliary at the aromatic compound to establish an enantioselective total synthesis. Functional group manipulation of the ester moiety enables the homoallylic side chain introduction. A subsequent ring closing reaction generates the 5 membered ring to complete the elisabethin core with the correct stereochemistry. Functionalization of the enedione system with a methyl- and a methoxy group delivers intermediate **150**. Two different Wittig olefination reactions generate the isobutenyl side chain. A following cleavage of the methoxy group provides the natural product elisabethin A (**14**) (Scheme 30).

4.2. Preliminary Studies towards elisabethin A

First target of our preliminary studies was literature known compound **160**.⁶⁸ The synthesis started with commercially available 2,5-dihydroxybenzoic acid (**156**). Esterification with sulfuric acid in methanol under reflux conditions afforded methyl ester **154**. Diene **155** was prepared from commercially available *E*-2-pentenal (Scheme 31). Enolization with triethylamine and protection of the enol with TBSOTf delivered a mixture of double bond isomers which contains 25-30% of the *E,E*-isomer **155**. Next step was a Diels-Alder reaction with *in situ* oxidized hydroquinone **154** and diene **155** to bicycle **159**. Epimerization at position 7 with aluminum oxide provided the desired enedione **160**.

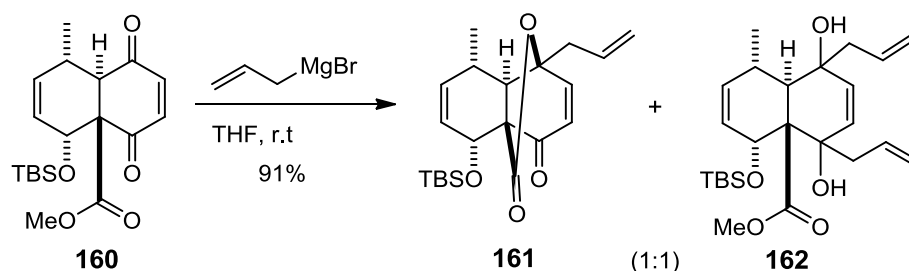


Scheme 31: Preliminary studies, preparation of enedione **160**

Our next ambition was to install the homoallylic side chain at position 13. Installation of the homoallylic side chain via direct allylation with allylmagnesium bromide was unsuccessful. Just the expected allylation at the ketone moiety to compounds **161** and **162** in a 1:1 mixture were obtained (Scheme 32). Noteworthy is the instant generation of the five membered lactone ring in compound **161**.

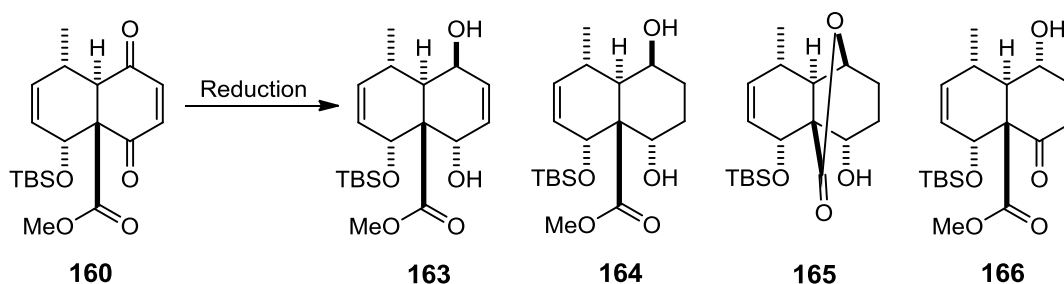
At that point it was clear that the ketone moieties have to be converted into other functional groups. The first attempt was to generate ketal moieties with methanol or ethylene glycol under reflux and different acidic conditions. Unfortunately, the ketones did not react at all. Experiments under more harsh conditions just resulted in

decomposition of the starting material. A second attempt was the reduction of the two ketones to the corresponding alcohols.



Scheme 32: Direct allylation of enedione **160**

Therefore different reducing agents were tested (see Scheme 33 and Tab. 1). Reduction of enedione **160** with sodium borohydride in methanol delivered diol **164**. This reaction condition also afforded small amounts of the lactone **165** (Entry 1). Reduction under Luche conditions also reduced the double bond and provided diol **164** as main product (Entry 2). Reduction with DIBAL in methylene chloride afforded the desired allylic diol **163** in moderate yield (Entry 3). It is noteworthy that the ester moiety was stable under these conditions. A Meerwein-Ponndorf-Verley reduction of enedione **160** with aluminum triisopropoxide in isopropanol generated compound **166** with inverse stereochemistry at the alcohol position (Entry 4).

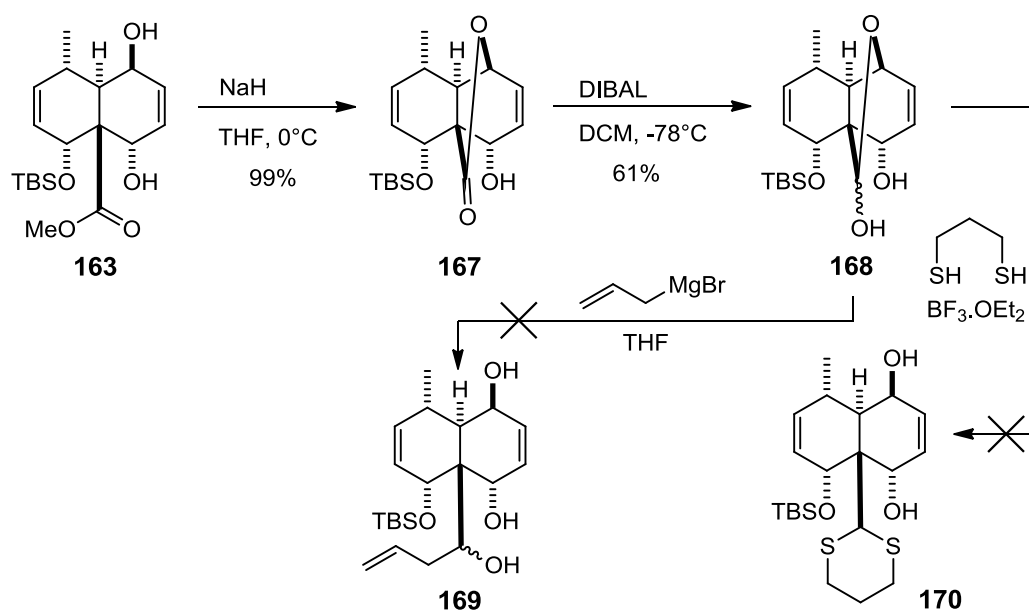


Scheme 33: Reduction of enedione **160**

Tab. 1: Reduction of enedione **160**

Entry	Reagents	Solvent	Temp.	Yield
1	NaBH ₄	MeOH	0 °C	73% (164) + (165)
2	NaBH ₄ , CeCl ₃ •7H ₂ O	MeOH	0 °C	78% (164) + s. p.
3	DIBAL	DCM	-78 °C	45% (163)
4	Al(O <i>i</i> Pr) ₃	<i>i</i> PrOH	70 °C	52% (166)

Next problem was to find an accurate protection group for the two alcohols in allylic diol **163**. Protection of the allylic diol **163** with MOMCl was not successful. Only an inseparable mixture of mono- and diprotected product was obtained. Using more equivalents of MOMCl did not improve the yield. These results indicated that it is quite complicated to protect the diol **163**. Especially the alcohol at the isopentenyl position was very hard to protect, probably because of steric hindrance at this position. On the other side, lactonization to a five membered lactone under basic conditions occurred very easily. Selective reduction of the lactone **167** with DIBAL provided lactol **168** as a 1:1 mixture of diastereomers. Attempts to open the lactol with an excess of allylmagnesium bromide at room temperature or even under reflux conditions in THF gave no reaction. Opening with 1,3-propanedithiol and boron trifluoride to the corresponding thioacetal resulted in decomposition (Scheme 34).



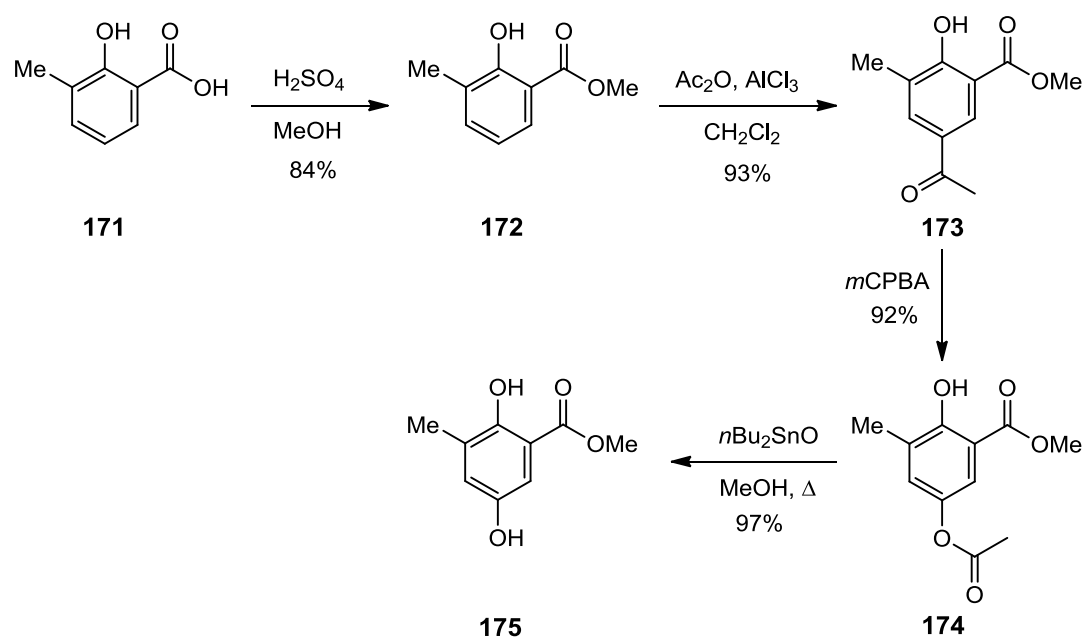
Scheme 34: Attempt to lactol opening of compound **168**

4.2.1. Conclusion of the Preliminary Studies

The synthesis of the literature known enedione **160** worked fine. A direct allylation at the ester moiety was not possible. Also the conversion of the ketone moieties into the corresponding ketals was unsuccessful. Reduction of the ketones was possible but the protection of the resulting alcohols was difficult. Furthermore, the synthesis of lactol **168** worked in good yields, but opening of this lactol under different conditions was not possible.

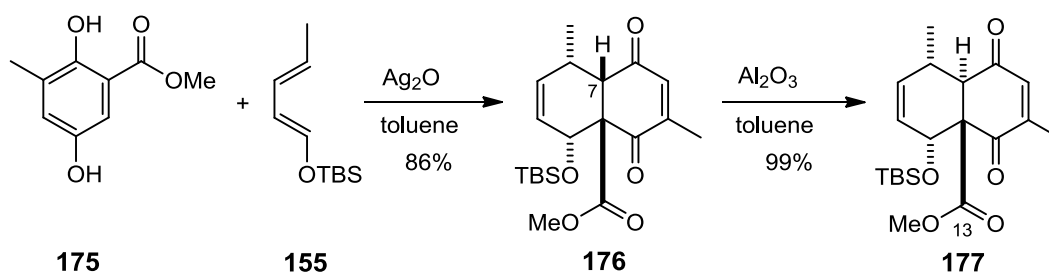
4.3. Advanced Studies towards elisabethin A

At that point, two major problems occurred. The first problem was how to install the homoallylic side chain at position 13. The second problem was how to get the correct regioselectivity in the methylation- and hydroxylation reaction at the enedione system later in the synthesis. Fortunately, the solution for the regioselectivity problem by the methylation- and hydroxylation reaction simultaneously solved the allylation problem at position 13. The answer was to install more substituents at the aromatic precursor for the Diels-Alder reaction.



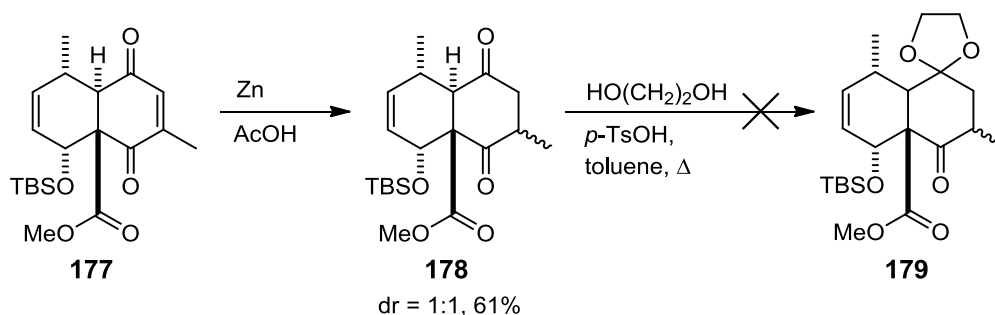
Scheme 35: Synthesis of the aromatic compound **175**

The synthesis started by esterification of inexpensive 3-methylsalicylic acid **171** under acidic conditions in methanol (Scheme 35). The next reaction was a Fries rearrangement with acetic anhydride and aluminum trichloride to methyl ketone **173**. A subsequent Baeyer-Villiger oxidation using $m\text{CPBA}$ as oxidant delivered intermediate **174**. Cleavage of the acetate group with dibutyltin oxide in methanol under reflux conditions provided the desired Diels-Alder precursor **175**. Next step was a Diels-Alder reaction with *in situ* oxidized hydroquinone **175**, using Ag_2O as oxidant, and diene **155** to bicycle **176**. Epimerization at position 7 with aluminum oxide in toluene provided the desired *trans* decaline system **177** (Scheme 36).



Scheme 36: Synthesis of enedione **177**

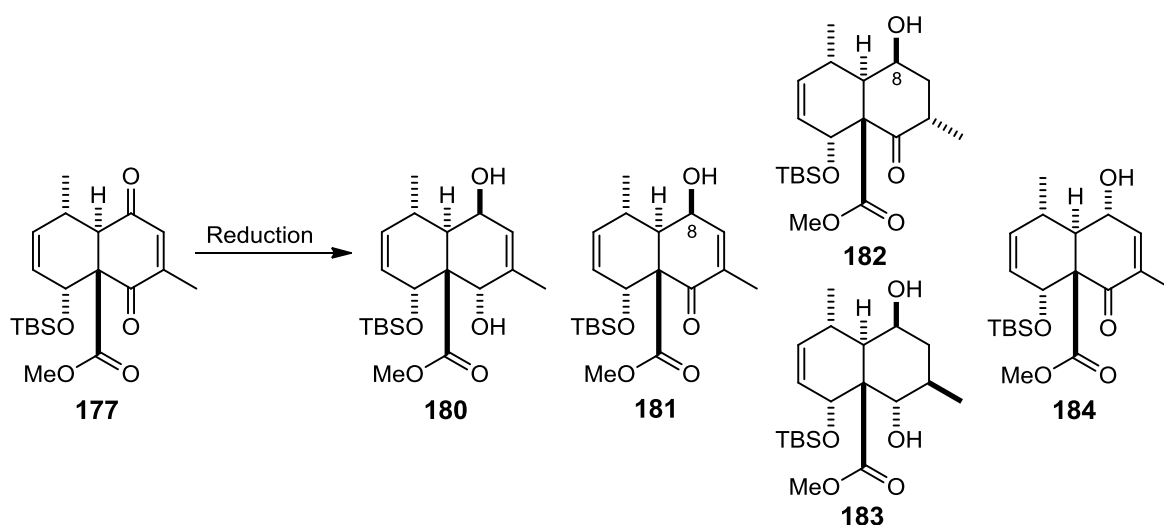
Experiments to generate ketals of enedione **177** with methanol or ethylene glycol under different acidic conditions and reflux conditions were unsuccessful, similar to enedione **160**. An explanation for the missing acetalization could be the stable enedione system. Therefore reduction of the double bond with zinc in acetic acid delivered diketone **178** as an inseparable 1:1 mixture of diastereoisomers. The mixture was treated with ethylene glycol and catalytic amounts of *para*-toluenesulfonic acid to get the desired ketal **179**. However, the starting material was not affected (Scheme 37). After this attempt we decided to dismiss the ketal strategy to focus on the reduction reaction.



Scheme 37: Attempt to generate a ketal moiety

Therefore the two ketone moieties of enedione **177** were reduced under different conditions (see Scheme 38 and Tab. 2). Reduction of enedione **177** with sodium borohydride in methanol (Entry 1) delivered alcohol **182** and diol **183** in a 1:1.2 mixture. Noteworthy is that the methyl group of compound **182** is *trans* to the alcohol at position 8, whereas the methyl group of diol **183** is *cis* to the alcohol. Reduction under Luche conditions afforded alcohols **181** and **184** in a 1:1 mixture of diastereoisomers (Entry 2). It is noteworthy that only the less hindered ketone at position 8 is reduced. Reduction with DIBAL in methylene chloride provided the desired allylic diol **180** in moderate yield (Entry 3). A Meerwein-Ponndorf-Verley

reduction of enedione **177** with aluminum triisopropoxide in isopropanol generated compound **184** (Entry 4).



Scheme 38: Reduction of enedione **177**

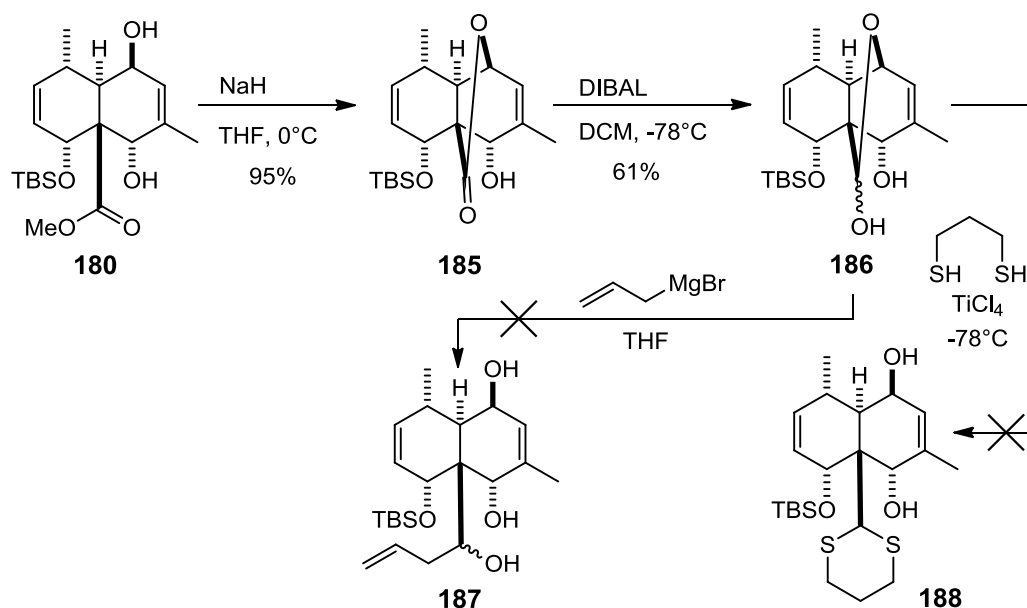
Tab. 2: Reduction of enedione **177**

Entry	Reagents	Solvent	Temp.	Yield
1	NaBH ₄	MeOH	0 °C	55% (182) + (183)
2	NaBH ₄ , CeCl ₃ •7H ₂ O	MeOH	0 °C	93% (181) + (184)
3	DIBAL	DCM	-78 °C	51% (180)
4	Al(O <i>i</i> Pr) ₃	<i>i</i> PrOH	70 °C	41% (184)

Based on these results a second attempt was made to alkylate the lactol **186** (Scheme 39). Hence, the next step in the synthesis was a lactonization reaction with sodium hydride in THF to give a five membered lactone. A following selective reduction of the lactone **185** with DIBAL delivered lactol **186** as a 1:1 mixture of diastereomers. Opening of the lactol with an excess of allylmagnesium bromide at room temperature or even under reflux conditions in THF was again unsuccessful, only unaffected starting material was recovered. The attempt to open the lactol with 1,3-propanedithiol and titanium tetrachloride as Lewis acid in methylene chloride to the corresponding thioacetal resulted in decomposition of the starting material.

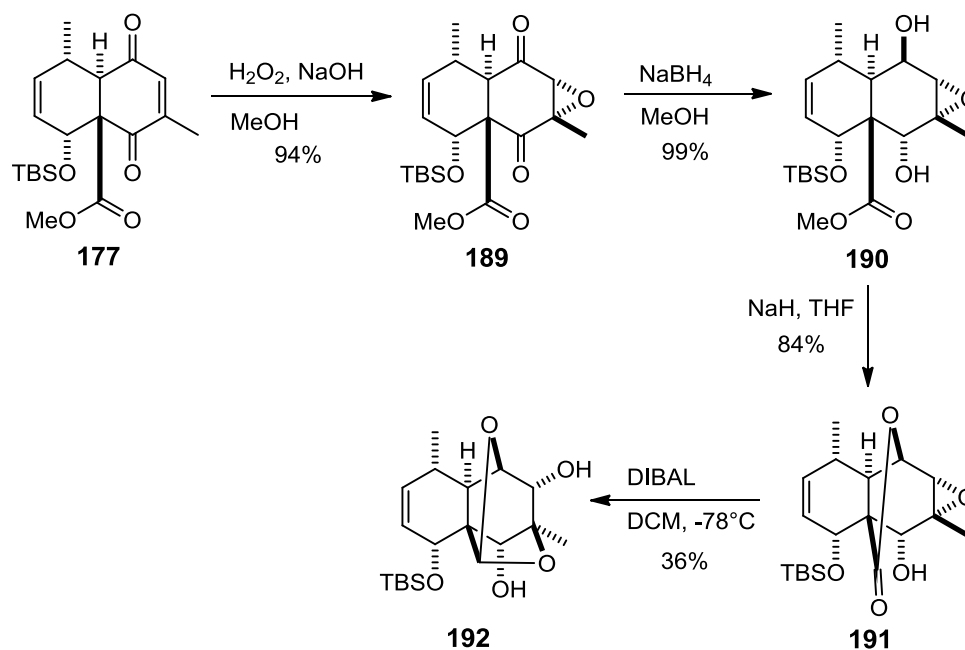
Thereby we reached another dead end in the synthesis. At that point we decided to create a new synthesis out of enedione **177**. Due to the unrequested reduction of the enedione double bond we determined to replace this functionality. Based on results from enedione systems, we decided to epoxidize the double bond.^{69,70} This epoxide

should be opened regioselectively to the desired 1,2-diketone system of elisabethin A (**14**) later in the synthesis.



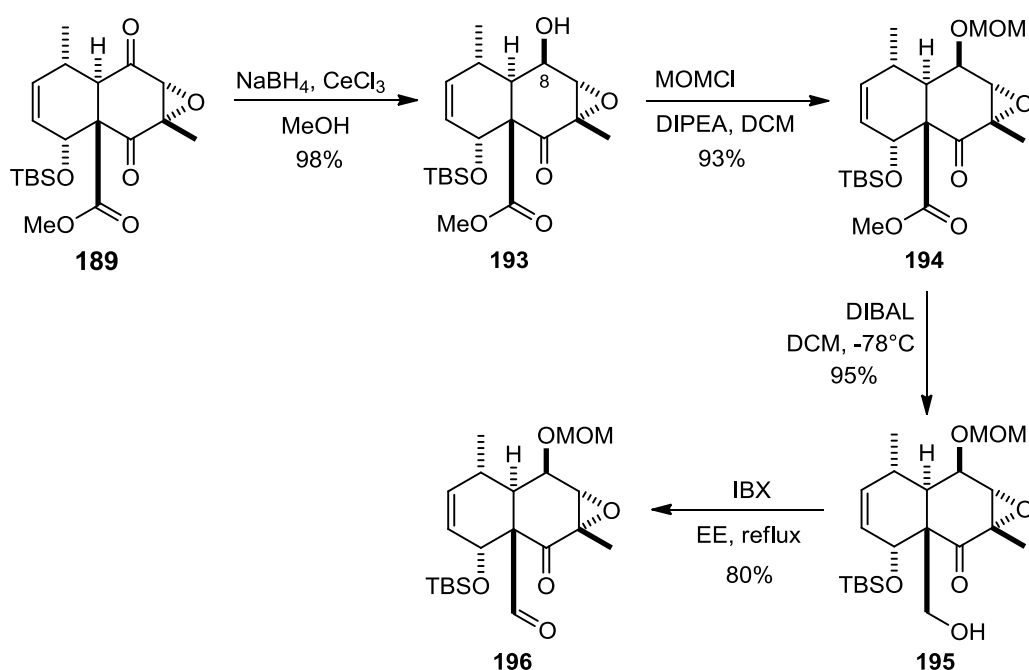
Scheme 39: Attempt to lactol opening of compound **186**

Compound **177** was treated with hydrogen peroxide and a catalytic amount of sodium hydroxide in methanol to provide epoxide **189** as single product. Reduction with sodium borohydride in methanol afforded diol **190** in excellent yield.



Scheme 40: Reduction of lactone **191**

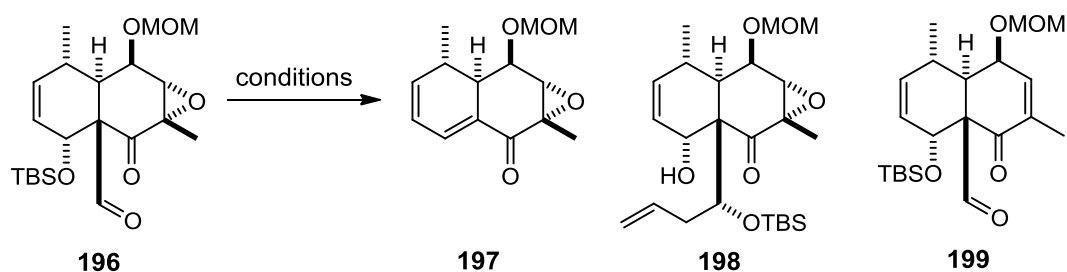
Worth mentioning is that reduction of epoxide **189** with DIBAL delivered only undesired product mixtures. A subsequent lactonization with sodium hydride in THF provided lactone **191**. Reduction of lactone **191** with DIBAL generated an alcoholate which attacked the epoxide and closed a new five membered ring to the undesired full acetylated tetracycle **192** as single product (Scheme 40). Due to the undesired epoxide opening and simultaneous generation of a full acetal we decided to dismiss this approach.



Scheme 41: Synthesis of aldehyde compound **196**

Parallel to this effort epoxide **189** was reduced under Luche conditions and revealed a regio- and stereoselective reduction of the ketone at position 8 to alcohol **193** in excellent yields. It is noteworthy that lactonization of alcohol **193** to the corresponding five membered lactone with sodium hydride was not possible even under reflux conditions. According to previous synthetic efforts, protection of the hydroxy function at position 8 with MOMCl and diisopropylethylamine in methylene chloride worked fine. Reduction of the ester moiety with DIABL afforded the primary alcohol **195**. Several attempts to get directly the aldehyde by changing the solvents, equivalents of DIBAL or the reaction temperature failed. Subsequent oxidation of the primary alcohol with IBX generated aldehyde **196**. The next goal was the installation of the homoallylic side chain to the aldehyde moiety. Therefore several allylation reactions were tested (see Scheme 42 and Tab. 3). Allylation of aldehyde **196** with

allylmagnesium bromide provided undesired bicycle **197** as major product (Entry 1). Treatment with *in situ* generated allylzinc chloride from allylmagnesium chloride and zinc chloride in diethyl ether delivered a mixture of bicycle **197** and allylic alcohol **198**, whereas **198** is a single diastereoisomer (Entry 2). A Sakurai allylation with allyl-TMS and tin tetrachloride at -78 °C gave no reaction (Entry 3). Another Sakurai allylation by the use of the same reagents at -10°C led to decomposition of the starting material (Entry 4). Allylation under Brown conditions did not affect the starting material (Entry 5). Treatment of aldehyde **196** with allyl tributyltin and magnesium bromide as Lewis acid at room temperature afforded allylic alcohol **198** as single product (Entry 6). Worth mentioning is that the TBS protection group underwent a 1,5-migration to the generated alcohol at the side chain.



Scheme 42: Allylation of aldehyde **196**

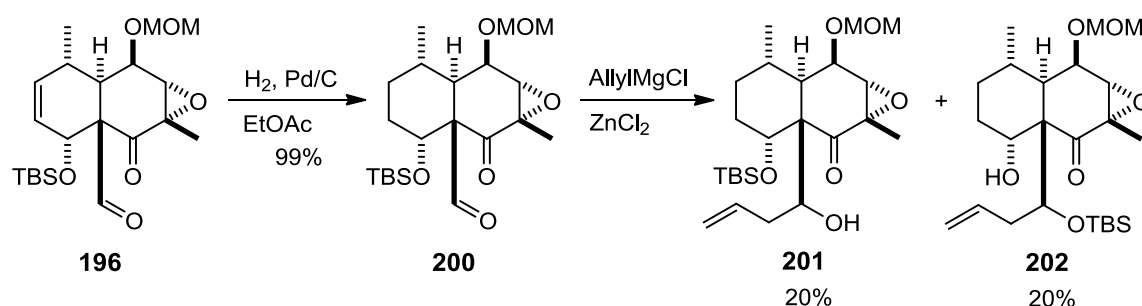
Tab. 3: Allylation of aldehyde **196**

Entry	Reagents	Solvent	Temp.	Yield
1	Allyl-MgBr	THF	-10 °C	46% (197) + side prod.
2	Allyl-ZnCl	THF	-78 °C	73% (197) +24% (198)
3	Allyl-TMS, SnCl ₄	DCM	-78 °C	no reaction
4	Allyl-TMS, SnCl ₄	DCM	-10 °C	decomposition
5	Allyl-B(IPC) ₂	Et ₂ O	-100 °C	no reaction
6	Allyl-Sn(Bu) ₃ , MgBr ₂	DCM	r.t.	40% (198)
7	Allyl-Sn(Bu) ₃ , BF ₃ •OEt ₂	DCM	-78 °C → 0 °C	48% (198)
8	Allyl-Br, CrCl ₂	DMF	r.t.	80% (199)

Allylation with allyl tributyltin and boron trifluoride as Lewis acid also provided allylic alcohol **198** with slightly better yields (Entry 7). It is noteworthy that this reaction only worked with 0.5-0.6 equivalents of boron trifluoride with respect to the starting material. One or more equivalents of boron trifluoride led to decomposition of the

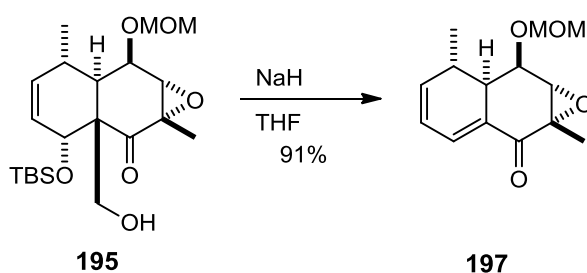
starting material. A NHK coupling by the use of chromium dichloride and allylbromide in DMF only eliminated the epoxide to α,β -unsaturated ketone **199** (Entry 8).

In summary, all of the allylation reactions were not really satisfying due to their moderate yields. Hence, further experiments were made to improve the yield. An attempt to improve the yield was to inhibit the elimination reaction. Therefore we decided to eliminate the double bond to get a more flexible six membered ring system and to avoid a 1,5-conjugated dienone system in the undesired product **197**. Based on this consideration, aldehyde **196** was hydrogenated with molecular hydrogen and palladium on charcoal in ethyl acetate to saturated bicycle **200**, but subsequent allylation of the aldehyde by *in situ* generated allylzinc chloride delivered compounds **201** and **202** as main products with unknown stereochemistry in poor yields (Scheme 43). Although the configuration at the newly formed center could not have been assigned, only one diastereomer was formed.



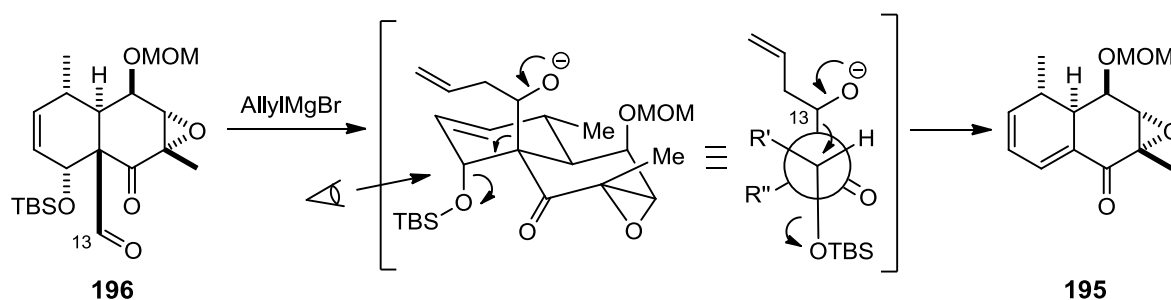
Scheme 43: Allylation of saturated bicycle **200**

Due to this result we knew that the double bond was not the driving force for the elimination reaction. In another experiment we treated the primary alcohol **195** with sodium hydride in THF and observed the same product as the elimination product **197** in the allylation reaction. Based on this result it was clear that a Grob fragmentation occurred (Scheme 44).



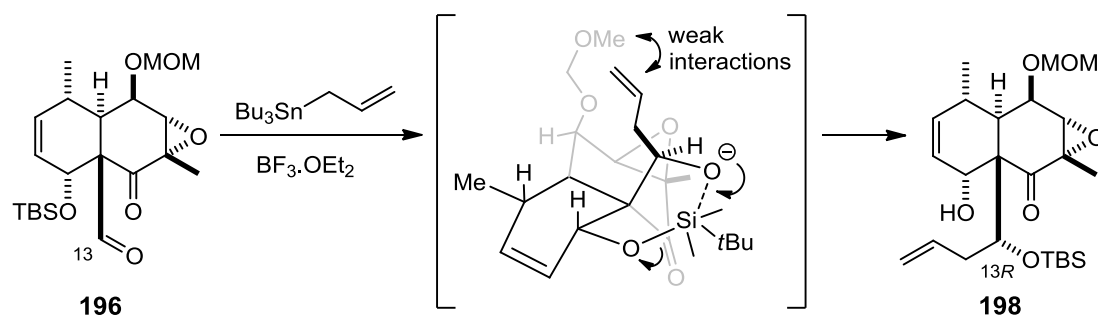
Scheme 44: Fragmentation of primary alcohol **195**

A closer look on the reaction mechanism revealed the perfect antiperiplanar configuration of the alcoholate intermediate on the side chain to the leaving group in our case the OTBS group. A further preferential of this fragmentation was may be the rigid decaline system and the 1,3-dicarbonyl arrangement (Scheme 45).



Scheme 45: Grob fragmentation mechanism

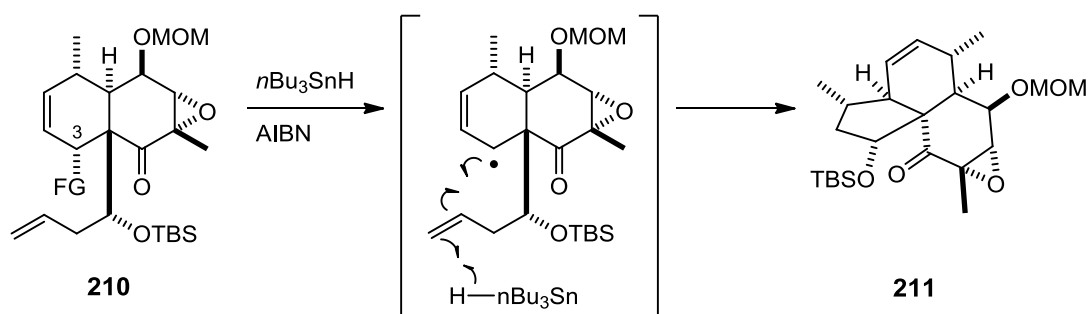
This reaction mechanism also explains the 1,5-migration of the protection group. The alcoholate intermediate interacts with the TBS group via a six membered transition state and enables a 1,5-migration (Scheme 46). The alcoholate was consequently trapped and inhibits the fragmentation reaction. This migration only occurred if the new generated chiral center at position 13 was in (*R*)-configuration. The (*S*)-configuration had maybe to strong interactions between the homoallylic side chain and the MOM group. Thus, a six membered transition state was not possible and fragmentation to product **195** occurred. This assumption would also explain the stereoselective product **198** and the maximum yield of 48%.



Scheme 46: Migration of the protection group

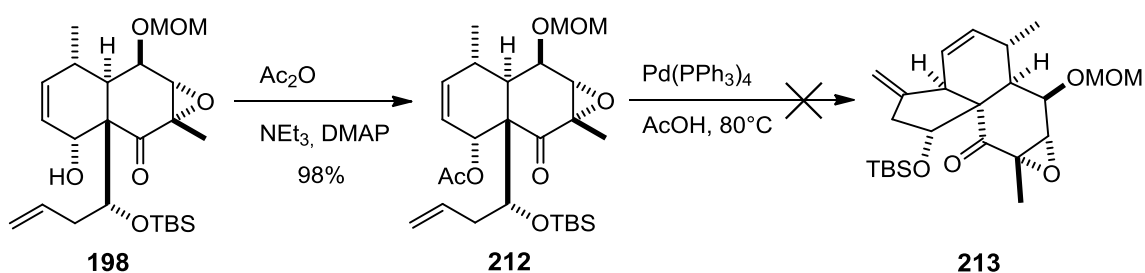
With these results in hand our next goal was to generate the five membered ring. One approach based on a reductive radical ring closing reaction (Scheme 47). The double bond in the six membered ring should stabilize the radical intermediate.

Moreover, this reaction required a functional group which is able to generate a radical at position 3. Functionalization of the hydroxy group into a xanthate with phenyl chlorothionoformate was unsuccessful. Substitution into an allyl bromide with thionyl bromide or hydrogen bromide was not possible. Only unaffected starting material was recovered.



Scheme 47: Reductive radical ring closing

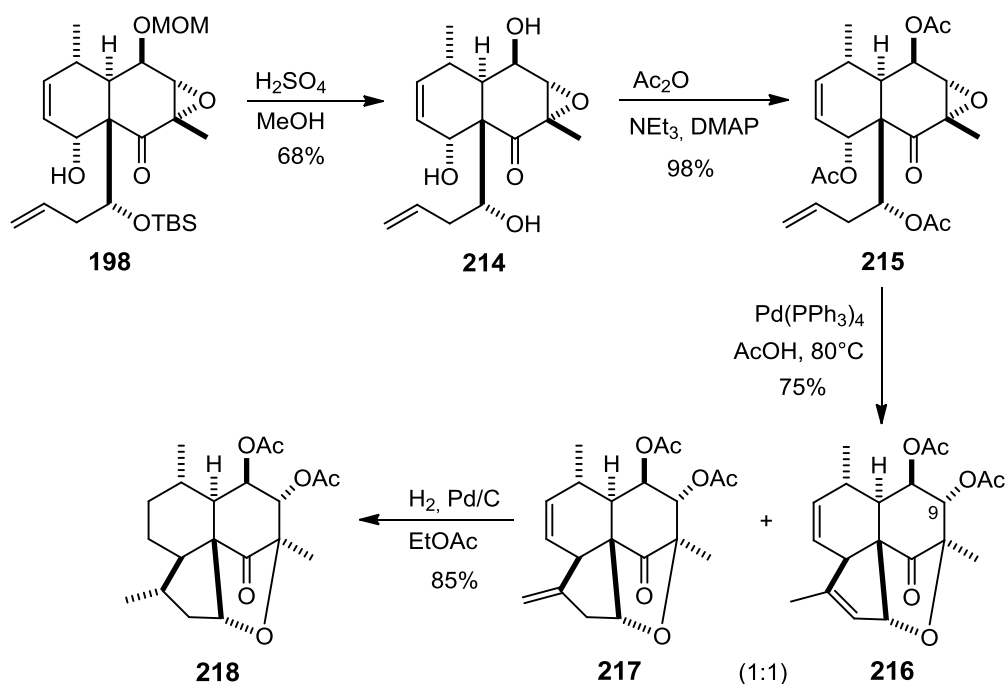
At that point we decided to try a palladium catalyzed ring closing reaction. Therefore the hydroxy group at position 3 was transformed into an acetate using acetic anhydride, DMAP and triethylamine. Unfortunately, the following palladium catalyzed ring closing reaction was unsuccessful. The starting material **212** was not affected under these conditions. The TBS group was probably too bulky and pushed the side chain away from the reactive transition state so that the reaction could not proceed (Scheme 48).



Scheme 48: Attempt to palladium catalyzed ring closing with allylic acetate **212**

Due to this consideration the TBS group and the MOM group of allylic alcohol **198** were cleaved with sulfuric acid in methanol to triol **214**. Subsequent protection of all alcohols with acetic anhydride, DMAP and triethylamine delivered triacetate **215**. The following palladium catalyzed ring closing reaction provided compounds **216** and **217** in an inseparable 1:1 mixture of double bond isomers. Unfortunately these conditions

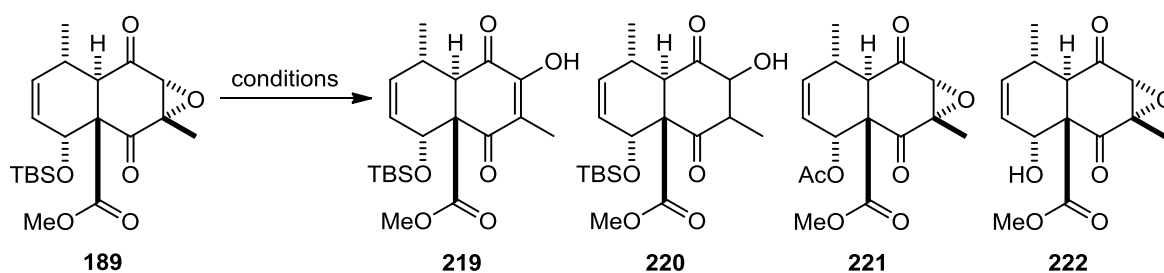
also opened the epoxide and generated an additional five membered heterocycle. A subsequent acetylation of the hydroxy group at position 9 delivered the second acetate group. Hydrogenation of the product mixture with molecular hydrogen and palladium on charcoal provided tetracycle **218** as single product (Scheme 49).



Scheme 49: Preparation of compound **218**

This preparation sequence revealed that the palladium catalyzed ring closing reaction worked. Also the hydrogenation of the double bonds delivered the product with the desired stereochemistry. The only problem was the opening of the epoxide during the ring closing reaction. According to these facts we decided to open the epoxide earlier in the synthesis. Therefore we attempted to open the epoxide of compound **189** to the desired hydroxy enedione **219** (see Scheme 50 and Tab. 4). Treatment of epoxide **189** with sulfuric acid in acetic acid delivered only the undesired allylic acetate **221** (Entry 1). These conditions only cleaved the TBS group to the alcohol. A subsequently esterification with acetic acid generated the acetate moiety. Epoxide opening with boron trifluoride cleaved the TBS group and afforded alcohol **222** (Entry 2). Hence, acidic conditions did not affect the epoxide moiety. Treatment with 30 wt.% sodium hydroxide in methanol decomposed the starting material (Entry 3). Treatment with LDA in THF led to decomposition too (Entry 4). Epoxide opening with sodium methanolate in methanol gave no reaction (Entry 5). Due to these results even under basic conditions it was not possible to open the

epoxide. After these attempts we tried some reductive epoxide opening conditions to synthesize alcohol **220**. Treatment with an excess of hydrazine in ethanol did not affect the starting material (Entry 6).⁷¹ Treatment with titanocene dichloride and zinc was unsuccessful too (Entry 7).⁷² Epoxide opening under radical conditions by the use of tributyltin hydride and AIBN gave no reaction (Entry 8).⁷³

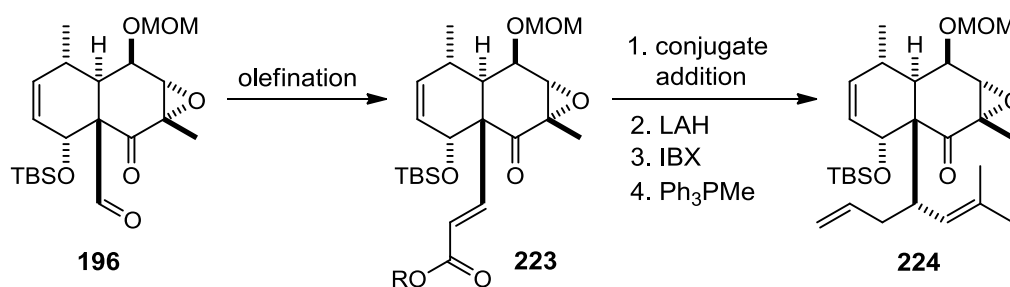


Scheme 50: Attempts to open the epoxide

Tab. 4: Attempts to open the epoxide

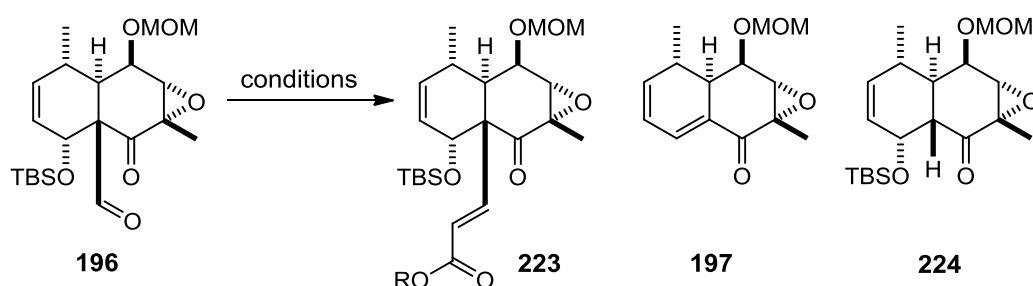
Entry	Reagents	Solvent	Temp.	Yield
1	H ₂ SO ₄	AcOH	r.t.	93% (221)
2	BF ₃ •OEt ₂	Et ₂ O	0 °C	73% (222)
3	30 wt.% NaOH	MeOH	r.t.	decomposition
4	LDA	THF	-78 °C → r.t.	decomposition
5	NaOMe	MeOH	50°C	no reaction
6	H ₂ NNH ₂	EtOH	0 °C → r.t.	no reaction
7	Cp ₂ TiCl ₂ , Zn	DCM	-78 °C	no reaction
8	<i>n</i> Bu ₃ SnH, AIBN	Toluene	100 °C	no reaction

Parallel to these efforts we attempted to install the isobutenyl side chain before we close the five membered ring. Based on this consideration we decided to generate the homoallylic side chain from an α,β -unsaturated ester and install the isobutenyl side chain via conjugate addition (Scheme 51).



Scheme 51: Attempts for isobutenyl side chain installation

First we had to generate the α,β -unsaturated ester via an olefination reaction. Therefore, several olefination reagents were tested (see Scheme 52 and Tab. 5). Olefination with the corresponding Wittig reagent in methanol at room temperature was unsuccessful (Entry 1). Heating of the reaction mixture afforded well known bicycle **197** and the deformylated bicycle **224** (Entry 2). A further reaction with the same Wittig reagent at 60 °C in toluene gave no reaction (Entry 3). These results indicated that the aldehyde moiety in the previous experiment reacted with the methanol instead of the Wittig reagent. Changing the Wittig reagent to a MOM-Wittig also did not affect the starting material (Entry 4). Olefination with the corresponding Horner reagent at room temperature or even at 0 °C also provided compounds **197** and **224** (Entry 5 and 6).



Scheme 52: Olefination of aldehyde **196**

Tab. 5: Attempts to olefinate aldehyde **196**

Entry	Reagents	Solvent	Temp.	Yield
1	MeO ₂ CCHPPh ₃	MeOH	r.t.	no reaction
2	MeO ₂ CCHPPh ₃	MeOH	60 °C	70% (197) + 20% (224)
3	MeO ₂ CCHPPh ₃	Toluene	60 °C	no reaction
4	MeOCH ₂ PPh ₃ , <i>t</i> BuOK	THF	r.t.	no reaction
5	EtO ₂ CCH ₂ PO(OEt) ₂ , NaH	THF	r.t.	77% (197) + 20% (224)
6	EtO ₂ CCH ₂ PO(OEt) ₂ , NaH	THF	0 °C	77% (197) + 19% (224)

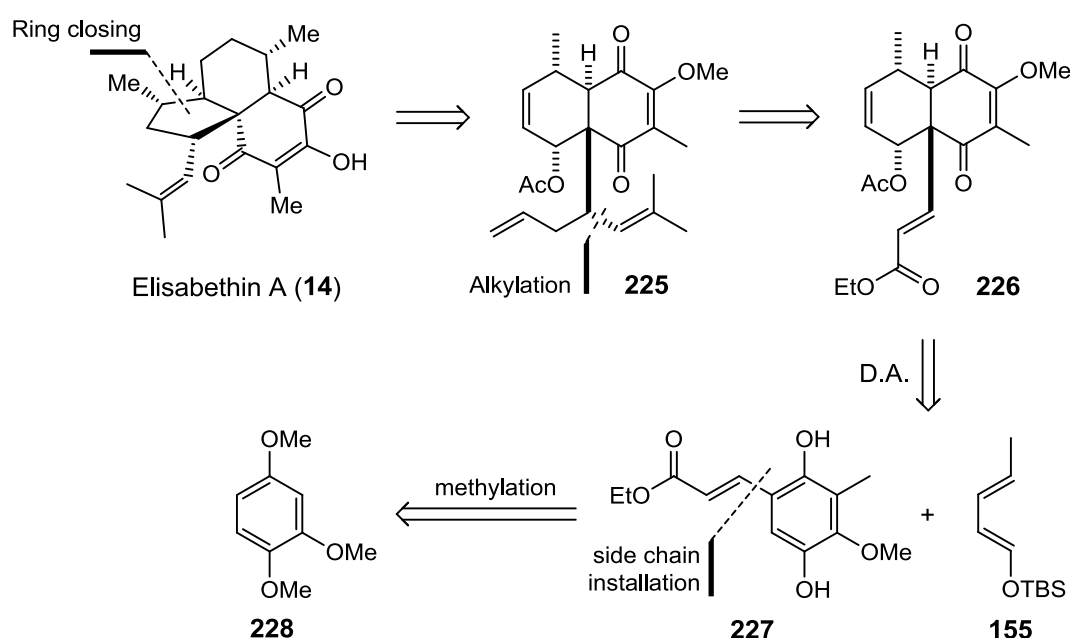
4.3.1. Conclusion of the Advanced Studies

Preparation of a more complex aromatic precursor for the Diels-Alder reaction was successful. Furthermore, it was possible to generate the aldehyde functionality at position 13. Also, the allylation reaction at the aldehyde to install the homoallylic side chain worked under moderate yields. Attempts to improve the yield of this reaction failed. Subsequent experiments revealed that a radical ring closing reaction was not

possible due to the inaccessibility of the neopentylic position. Moreover it was shown that a palladium catalyzed ring closing reaction followed by hydrogenation of the double bonds delivers the desired five membered carbon ring and simultaneously an additional undesired heterocycle. Following attempts to avoid this side reaction by opening the epoxide in an earlier stage of the synthesis were unsuccessful. Also, the synthesis of an α,β -unsaturated ester from aldehyde **196** delivered no satisfying results.

4.4. New Approach to elisabethin A

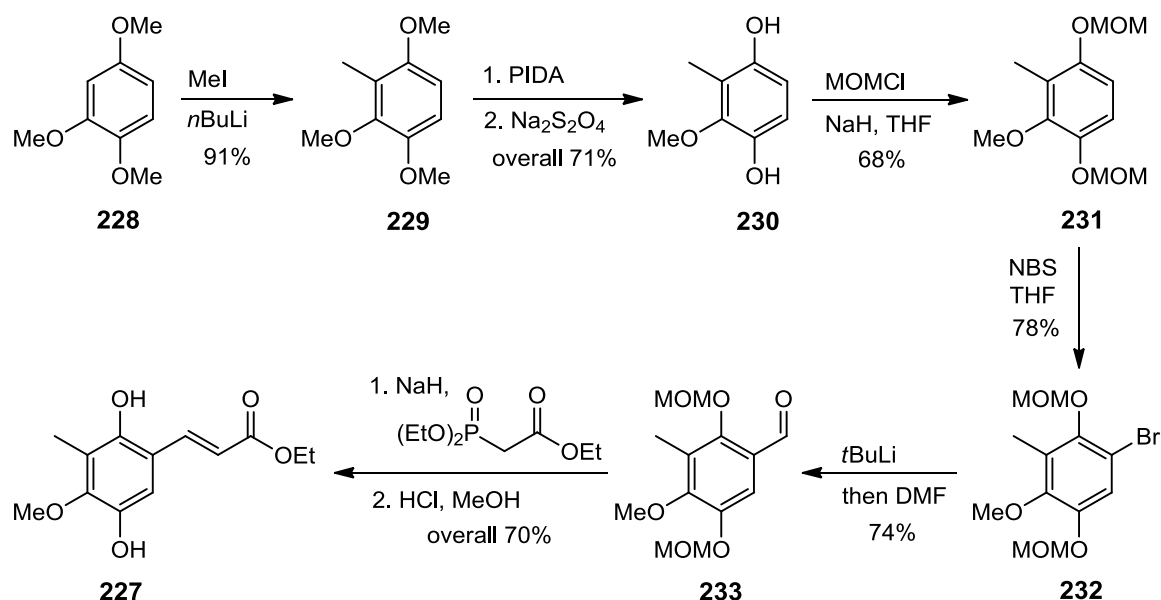
At that point we had two unanswered questions. The question was how to open the epoxide and the second how to install the side chains. After careful considerations we decided to attempt a new retrosynthetic strategy. This strategy based on a late stage palladium catalyzed ring closing. A further modification was the higher substituted aromatic compound which contained all of the required functional groups. The strategy to generate the decaline system via a Diels-Alder reaction was the same as in the first retrosynthesis.



Scheme 53: New retrosynthetic strategy to elisabethin A (**14**)

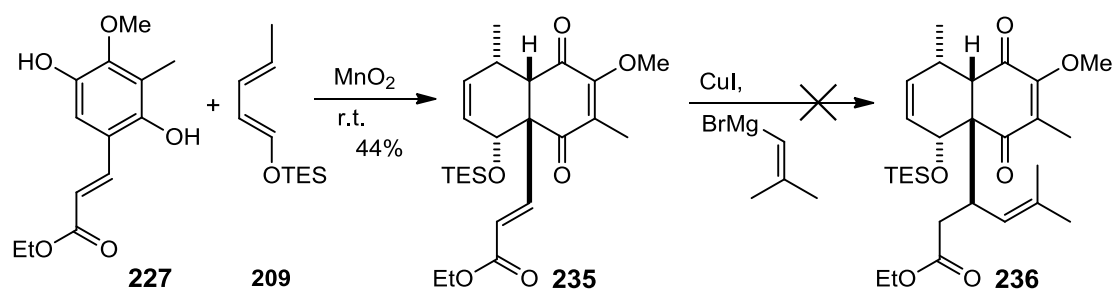
The first target of the new synthesis was α,β -unsaturated ester **227**. The synthesis started with commercially available 1,2,4-trimethoxybenzene **228** (Scheme 54).

Ortho-metalation with *n*BuLi and subsequent treatment with methyl iodide delivered 2,3,6-trimethoxytoluene **229**.⁷⁴ Regioselective oxidative demethylation of the two *para* methoxy groups with PIDA provided the quinone. Reduction of the quinone with sodium hydrosulfite afforded the hydroquinone **230**. Protection of the two hydroxy groups with MOMCl and sodium hydride delivered compound **231**. A regioselective electrophilic aromatic substitution with NBS generated arylbromide **233**. The next step was a transmetalation reaction with *t*-BuLi followed by treatment with DMF to the desired aldehyde. An *E*-selective olefination reaction with the corresponding Horner reagent delivered the α,β -unsaturated methyl ester. Cleavage of the MOM group with hydrochloric acid in methanol provided the Diels-Alder precursor **227**.



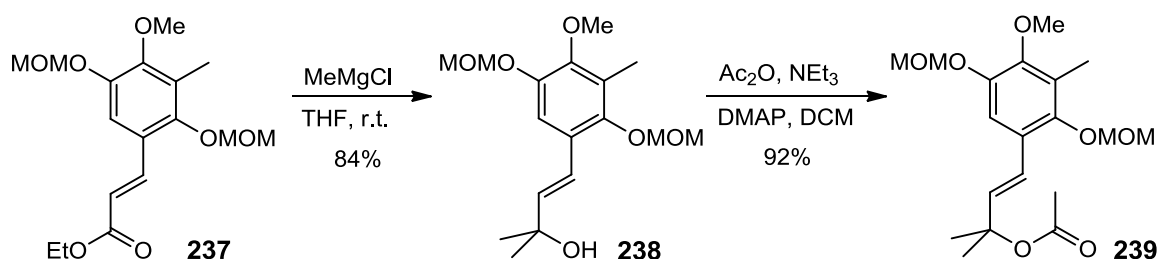
Scheme 54: Synthesis of aromatic compound **227**

The next step was a Diels-Alder reaction with *in situ* oxidized hydroquinone **154** and diene **229** generated the desired bicycle **235** as single product (Scheme 55).



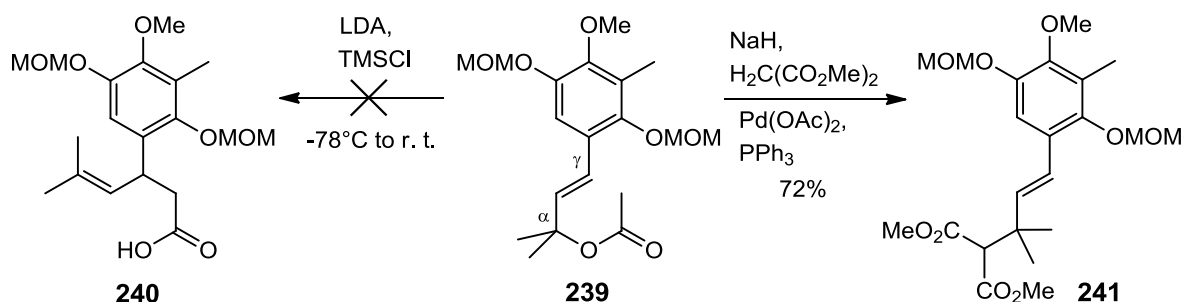
Scheme 55: Attempt for isobutenyl side chain introduction

Diene **209** was prepared from commercially available *E*-2-pentenal. Enolization with triethylamine and protection of the enol with TBSOTf delivered a mixture of double bond isomers which contains 25-30% of the *E,E*-isomer. Subsequent conjugate addition of the cuprate reagent to the α,β -unsaturated methyl ester was unsuccessful. Only unaffected starting material was recovered. The conjugate addition was maybe too hindered because of the MOM group *ortho* to the side chain. At that point we decided to install the isobutenyl side chain directly on the aromatic compound. Due to this consideration we transformed the ester moiety into the tertiary alcohol **238** by the use of methylmagnesium bromide. The resulting alcohol was esterified with acetic anhydride, triethylamine and DMAP in methylene chloride to allylic acetate **239** (Scheme 56).



Scheme 56: Modification of compound **239**

A planned Ireland-Claisen rearrangement from allylic acetate **239** to the desired acid **240** was unsuccessful. Only unaffected starting material was recovered. Heating of the reaction mixture led to decomposition. The next attempt was a Tsuji-Trost allylic alkylation with dimethylmalonate to the desired γ -alkylated compound, but unfortunately the nucleophilic attack occurred in α -position at the two methyl groups to dimethyl ester **241**. (Scheme 57)



Scheme 57: Attempts from allylic acetate **239**

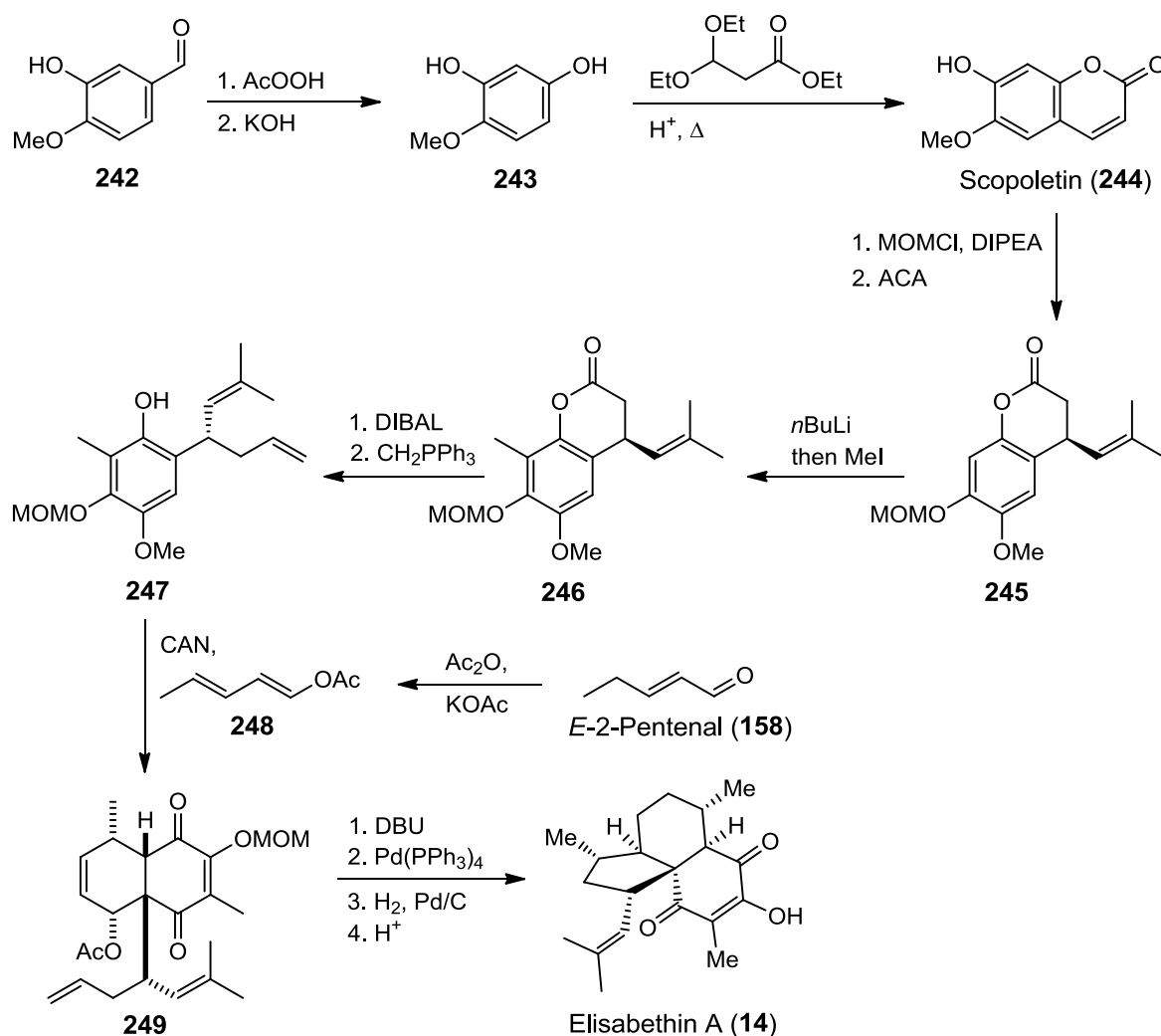
An Eschenmoser-Claisen rearrangement with *N,N*-dimethylacetamide-dimethylacetal and allylic alcohol **238** in hot xylene was also unsuccessful. The starting material was not affected under these conditions. The conjugated position of the double bond to the aromatic ring could be an explanation for the failed rearrangement. Obviously the starting material was the more stable compound in the equilibrium.

5. Conclusion and Outlook

Many complex diterpenes isolated from *Pseudopterogorgia Elisabethae* were synthesized in the last ten to fifteen years from different synthetic research groups. After all, elisabethin A is one of the few natural compounds which has not been synthesized until now. Many different approaches from several workgroups were tested but none of them were successful. This master thesis dealt with the total synthesis of elisabethin A too, but unfortunately the total synthesis could not be finished in the course of this master thesis. However, we reported a totally different route to synthesize this natural component. In contrast to other reported approaches we generated first the decaline system including the quaternary carbon atom via a highly regioselective Diels-Alder reaction. After several functional group manipulations at the enedione system we installed the homoallylic side via a tin mediated allylation. At that point we discovered the high tendency for a Grob fragmentation of this system. After several failed attempts to inhibit this fragmentation we decided to manage the ring closing reaction. Here we found that a palladium catalyzed ring closing reaction is the reaction of choice. Furthermore, we finished the elisabethin core with the correct stereochemistry via simple hydrogenation of the double bonds. Following attempts to open the epoxide which should avoid the generation of a five membered heterocycle during the carbon ring closing reaction were unsuccessful. Based on these results we decided to substitute the acetate group at the homoallylic side chain by an isobutenyl moiety. Installation of the side chain via conjugate addition to an α,β -unsaturated methyl ester was not possible. Hence, we attempted to install the isobutenyl side chain earlier in the synthesis at the aromatic compound, but it was not possible to generate the desired α -branched aromatic compound via [3,3]-sigmatropic rearrangements or a Tsuji-Trost allylation.

According to these last results we want to give a short outlook to a possible synthetic pathway (Scheme 58).

The synthesis starts from inexpensive commercially available *iso*-vanilline (**242**). Oxidation of the starting material with peracetic acid and subsequent saponification with potassium hydroxide delivers diol **243**.⁷⁵



Scheme 58: Possible synthetic way to elisabethin A (**14**)

Treatment of diol **243** with ethyl 3,3-diethoxypropionate in phosphoric acid affords literature known scopoletin (**244**).⁷⁶ The next step is a protection of the hydroxy group with MOMCl and DIPEA. A following asymmetric conjugate addition (ACA) to the α,β -unsaturated lactone with isobutenylmagnesium bromide, copper bromide and a chiral ligand provides compound **245**.⁷⁷

Regioselective *ortho*-metalation with *n*BuLi using the MOM group as directing moiety and subsequent treatment with methyl iodide delivers bicycle **246**.⁷⁸ Reduction of the

lactone with DIBAL provides the lactol. Opening of the lactol via a Wittig olefination generates the terminal double bond in phenol **247**.⁷⁹ The next step is a Diels-Alder reaction by *in situ* oxidative demethylation of phenol **247**, using cerammonium nitrate as oxidant and diene **248** to afford bicycle **249**.⁸⁰ The diene **248** is prepared from commercially available *E*-2-pentenal. Enolization with potassium acetate and protection of the enol with acetic anhydride delivered a mixture of double bond isomers which contains 25-30% of the *E,E*-isomer.⁸¹ Epimerization using DBU as base delivers the *trans*-annulated decaline system. A palladium catalyzed ring closing reaction followed by hydrogenation of the generated double bonds with molecular hydrogen delivers the correct elisabethane skeleton. Cleavage of the MOM group under acidic conditions provides elisabethin A (**14**).

6. Experimental Part

6.1. General Information

All moisture and oxygen sensitive reactions were performed in flame-dried glassware under a slight argon overpressure. All reactions were stirred magnetically. Sensitive solutions, solvents or reagents were transferred via cannula or syringe. Reactions were monitored by thin-layer chromatography (TLC) or NMR of the crude mixture. Evaporations were conducted under reduced pressure at temperatures less than 40°C, unless otherwise noted. Further dryings of the residues were accomplished using a high vacuum pump.

All solvents (except dichloromethane and methanol) were purchased as the highest available grade from Sigma-Aldrich, Acros-Organics or Fisher-Chemicals. Anhydrous dichloromethane was purified by filtration through alumina under argon immediately before use. Methanol was heated under reflux for several hours over sodium before being distilled. NEt_3 , $i\text{Pr}_2\text{NEt}$, and $i\text{PrNH}$ were distilled over CaH_2 before use. Ethyl acetate and hexane for column chromatography were distilled and used without further purification. All other reagents were used as received from Sigma-Aldrich, Acros-Organics, TCI or Fisher-Chemicals unless otherwise noted.

Thin-layer chromatographies (TLC) were carried out on pre-coated Merk silica gel 60 F254 to monitor all reactions. The detection was first performed using UV (254 nm) as a visualizing agent followed by immersion in an aqueous solution of phosphomolybdic acid (20 g), ceric(IV)sulfate (0.4 g) and 22 mL of sulfuric acid. Treatment with a heat-gun eventually revealed the state of the reaction. Preparative column chromatography was performed with silica gel 60 from Merk (0.040-0.063 μm , 240-400 mesh). The columns were packed with a suspension of gel in hexane and eluted with an appropriate solvent combination using a hand-pump overpressure.

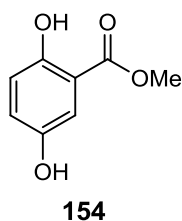
All NMR spectra were measured on a Bruker AV400 or DRX400. Chemical shifts are given in ppm and referenced to the solvent residual peaks (CDCl_3 ^1H , $\delta = 7.26$ ppm, ^{13}C , $\delta = 77.00$ ppm). Data are reported as follows: chemical shift, multiplicity (s =

singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant J , integration.

Infrared spectra were recorded as thin films of pure products on an ATR-unit on a Bruker Vertex 70. High-resolution mass spectra were measured on Bruker MaXis (ESI-TOF) with a resolution of 10.000.

6.2. Experimental Procedures

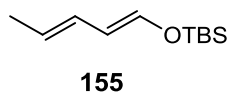
Methyl 2,5-dihydroxybenzoate **154**



To a solution of 2,5-Dihydroxybenzoic acid (**156**) (5 g, 32.45 mmol) in MeOH (40 mL) was added conc. H₂SO₄ (2 mL, 38 mmol). The reaction mixture was stirred under reflux for 20 hours. The solution was cooled to r.t. and treated with water. The organic layer was extracted with diethyl ether (3x), washed with brine and dried over MgSO₄. The solvent was removed by rotary evaporation to the crude product **154** (5.19 g, 95%) as a brown solid and was used in the next step without further purification.

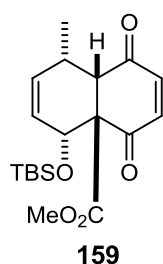
¹H NMR (400 MHz, CDCl₃): δ (ppm) 10.31 (s, 1H), 7.28 (d, $J = 3.1$ Hz, 1H), 7.0 (dd, $J = 9.0, 3.1$ Hz, 1H), 6.88 (d, $J = 9.0$ Hz, 1H), 3.94 (s, 3H), 2.89 (s, 1H).

1-(*tert*-Buthyldimethylsilyl)-oxypenta-1,3-dien **155**



To a stirred solution of *trans*-2-pentenal (9 mL, 92 mmol) and triethylamine (19 mL, 140 mmol) in CH₂Cl₂ (150 mL) was added dropwise *tert*-buthyldimethylsilyl triflate (21.7 mL, 95 mmol) at 0°C. After the addition the mixture was heated to reflux for 6 h. To the resulting mixture was added aq. NaHCO₃, and the organic layer was separated. The separated organic layer was washed with brine, dried, and concentrated *in vacuo*. Vacuum distillation (1 mbar, 45 – 52 °C) of the residue afforded 14.48 g of an oily mixture of stereoisomeric 1-(*tert*-buthyldimethylsilyl)-oxypenta-1,3-diens (**155**) which contained 25 – 30% of the (*E,E*) isomer.

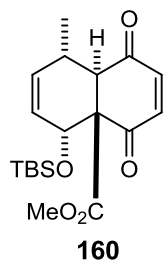
DA adduct **159**



To a suspension of **154** (740 mg, 4.4 mmol) and 1-*tert*-buthyldimethylsilyloxy-penta-1,3-diene (**155**) (2.80 g, 9.52 mmol, mixture of stereoisomers) in toluene (7.5 mL) at 10°C was added silver(I)oxide (2.04 g, 8.8 mmol) in one portion. The mixture was warmed to room temperature and stirred for 19 h, then was diluted with diethyl ether, and filtered through Celite. The Celite was washed thoroughly with diethyl ether, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc, 10:1) to give **159** (1.246 g, 78%) as clear oil.

¹H NMR (400 MHz, CDCl₃): δ (ppm) 6.77 (d, *J* = 10.2 Hz, 1H), 6.58 (d, *J* = 10.2 Hz, 1H), 5.69 (m, 2H), 4.79 (m, 1H), 3.77 (s, 3H), 3.65 (d, *J* = 4.9 Hz, 1H), 2.18 (m, 1H), 1.43 (d, *J* = 7.7 Hz, 3H), 0.75 (s, 9H), 0.02 (s, 3H), -0.07 (s, 3H).

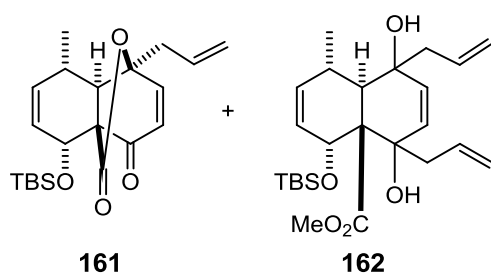
Epi-DA adduct **160**



A mixture of **159** (1.0 g, 2.75 mmol) and neutral alumina (26 g Brockman Activity II, M70 – 220) in toluene (70 mL) was stirred for 4 h at room temperature. The resulting mixture was filtered and washed with EtOAc. Concentration of the filtrate afforded **160** (0.96 g, 96%) as a white solid and was used in the next step without further purification.

¹H NMR (400 MHz, CDCl₃): δ (ppm) 6.83 (d, *J* = 10.3 Hz, 1H), 6.58 (d, *J* = 10.3 Hz, 1H), 5.81 (ddd, *J* = 9.9, 5.6, 2.0 Hz, 1H), 5.64 (dd, *J* = 9.9, 3.0 Hz, 1H), 5.01 (d, *J* = 5.6 Hz, 1H), 3.61 (s, 3H), 3.35 (d, *J* = 9.0 Hz, 1H), 2.85 (m, 1H), 1.21 (d, *J* = 6.8 Hz, 3H), 0.81 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H).

Lactone **161** and diallyl **162**



To a solution of **160** (170 mg, 0.46 mmol) in THF (4 mL) was added allylmagnesium bromide (0.47 mL, 1 M solution in diethyl ether, 0.47 mmol) dropwise at -20 °C. After stirring at room temperature for 5 h, the resulting solution was quenched with aq. ammonium chloride, extracted with CH₂Cl₂ (3x), washed with brine and dried over MgSO₄. The solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 20:1) to give **161** (43 mg, 25%) and **162** (66 mg, 32%).

Lactone **161**

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.28 (d, *J* = 9.5 Hz, 1H), 6.01 (d, *J* = 9.5 Hz, 1H), 5.98 (ddd, *J* = 10.0, 5.9, 1.8 Hz, 1H), 5.85 (m, 1H), 5.69 (dd, *J* = 10.0, 4.3 Hz, 1H), 5.35 (m, 2H), 4.85 (d, *J* = 6.0 Hz, 1H), 2.92 (d, *J* = 5.5 Hz, 1H), 2.91 (m, 1H), 2.65 (m, 1H), 2.63 (m, 1H), 1.21 (d, *J* = 7.0 Hz, 3H), 0.81 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 190.4, 171.5, 151.4, 134.5, 130.8, 128.9, 127.0, 121.7, 85.3, 69.6, 61.5, 56.4, 37.4, 29.4, 26.2, 23.1, 18.3, -3.8, -4.6 ppm.

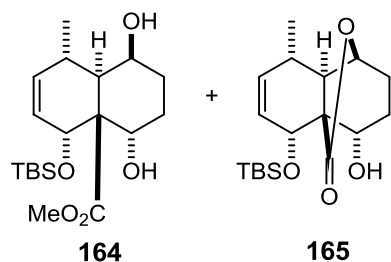
HRMS: calculated for C₂₁H₃₀O₄SiNa⁺: 397.1806; found: 397.1821

Diallyl **162**

¹H NMR (400 MHz, CDCl₃): δ (ppm) 5.90 (m, 2H), 5.74 (m, 1H), 5.64 (dd, *J* = 9.5, 4.5 Hz, 1H), 5.58 (d, *J* = 10.4 Hz, 1H), 5.47 (d, *J* = 10.4 Hz, 1H), 5.10 (m, 4H), 4.71 (d, *J* = 5.8 Hz, 1H), 4.61 (s, 1H), 3.60 (s, 3H), 3.01 (m, 1H), 2.78 (m, 1H), 2.67 (d, *J* = 7.7 Hz, 3H), 2.55 (m, 3H), 2.46 (m, 1H), 1.27 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 9H), 0.14 (s, 3H), 0.08 (s, 3H).

HRMS: calculated for C₂₅H₄₀O₅SiNa⁺: 471.2538; found: 471.2535

Diol **164** and lactone **165**



To a solution of **160** (300 mg, 0.82 mmol) in MeOH (12 mL) was added NaBH₄ (311 mg, 8.2 mmol) at 0°C. The reaction mixture was stirred for 2 h at 0 °C. The resulting mixture was quenched with aq. ammonium chloride, extracted with CH₂Cl₂ (3x), washed with brine and dried over MgSO₄. The solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 3:1) to give **164** (222 mg, 73%) as a white solid and **165** (17 mg, 6%).

Diol **164**

¹H NMR (400 MHz, CDCl₃): δ (ppm) 5.80 (dd, *J* = 9.9, 3.1 Hz, 1H), 5.70 (ddd, *J* = 9.9, 5.6, 2.1 Hz, 1H), 5.43 (d, *J* = 2.3 Hz, 1H), 5.07 (d, *J* = 9.8 Hz, 1H), 4.73 (d, *J* = 5.6 Hz, 1H), 4.30 (m, 1H), 4.10 (m, 1H), 3.67 (s, 3H), 2.84 (m, 1H), 2.21 (m, 2H), 1.71 (m, 1H), 1.60 (m, 1H), 1.51 (m, 1H), 1.10 (d, *J* = 7.0 Hz, 3H), 0.91 (s, 9H), 0.20 (s, 3H), 0.13 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 176.3, 141.1, 125.5, 71.9, 71.3, 64.5, 55.1, 53.3, 37.9, 30.4, 27.7, 25.7, 24.6, 18.9, 17.9, -3.0, -4.5 ppm.

HRMS: calculated for C₁₉H₃₄O₅SiNa⁺: 393.2068; found: 393.2063

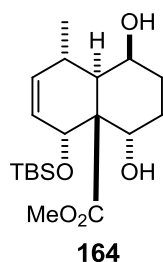
Lactone **165**

¹H NMR (400 MHz, CDCl₃): δ (ppm) 5.66 (ddd, *J* = 10.3, 3.7, 2.4 Hz, 1H), 5.61 (m, 1H), 4.58 (m, 1H), 4.55 (m, 1H), 4.14 (m, 1H), 4.11 (m, 1H), 2.41 (d, *J* = 8.7 Hz, 1H), 1.97 (m, 3H), 1.85 (m, 2H), 1.15 (d, *J* = 7.2 Hz, 3H), 0.93 (s, 9H), 0.22 (s, 3H), 0.19 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 177.1, 134.7, 127.4, 81.9, 68.8, 67.6, 54.9, 43.5, 30.3, 26.8, 25.8, 24.5, 20.1, -4.1, -4.8 ppm.

HRMS: calculated for C₁₈H₃₀O₄SiNa⁺: 361.1806; found: 361.1804

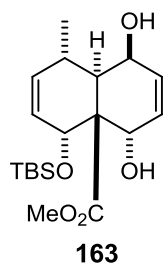
Diol **164** (using NaBH₄ and CeCl₃•7H₂O)



To a solution of **160** (100 mg, 0.27 mmol) and CeCl₃•7 H₂O (201 mg, 0.54 mmol) in MeOH (5 mL) was added NaBH₄ (97 mg, 2.57 mmol) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C. The resulting mixture was quenched with aq. ammonium chloride, extracted with CH₂Cl₂ (3x), washed with brine and dried over MgSO₄. The solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 3:1) to give **164** (78 mg, 78%) as a white solid.

(Spectroscopic data see page 63)

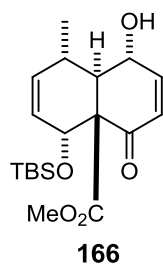
Diallylic alcohol **163**



To a solution of **160** (340 mg, 0.93 mmol) in CH_2Cl_2 (3 mL) was added DIBAL (2.8 mL, 1 M in toluene, 2.8 mmol) dropwise at $-78\text{ }^\circ\text{C}$ under an argon atmosphere. The reaction mixture was stirred at $-78\text{ }^\circ\text{C}$ for 1 h and quenched with MeOH. After 15 min the resulting mixture was warmed to room temperature, diluted with water and aq. Na,K- tartrate, extracted with diethyl ether (2x) and CH_2Cl_2 (1x), washed with brine and dried over MgSO_4 . The solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 6:1) to give **163** (160 mg, 45%) as a clear liquid.

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ (ppm) 6.04 (dd, $J = 10.0, 3.5$ Hz, 1H); 5.92 (ddd, $J = 10.0, 5.8, 1.8$ Hz, 1H); 5.86 (dd, $J = 10.0, 3.0$ Hz, 1H); 5.68 (ddd, $J = 9.8, 5.3, 2.3$ Hz, 1H), 5.40 (d, $J = 0.8$ Hz, 1H), 4.75 (d, $J = 5.2$ Hz, 1H), 4.55 (dd, $J = 5.8, 0.8$ Hz, 1H), 4.35 (m, 1H), 3.81 (d, $J = 11.8$ Hz, 1H), 3.63 (s, 3H), 2.96 (m, 1H), 2.53 (dd, $J = 9.9, 7.2$ Hz, 1H), 1.18 (d, $J = 7.0$ Hz, 3H), 0.91 (s, 9H), 0.21 (s, 3H), 0.15 (s, 3H).

Allylic alcohol **166**



To a solution of **160** (100 mg, 0.27 mmol) in *i*PrOH (1.1 mL) was added $\text{Al}(\text{O}i\text{Pr})_3$ (248 mg, 1.22 mmol). The mixture was boiled gently, and acetone and *i*PrOH were distilled slowly from the reaction mixture through a short column. From time to time *i*PrOH was added to maintain a constant volume. After 18 h the reaction mixture was concentrated under reduced pressure, treated with 1 M HCl, and extracted with CH_2Cl_2 (3x). The organic layer was washed with sat. NaHCO_3 and brine, dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc, 6:1) to give **166** (52 mg, 52%) as a white solid.

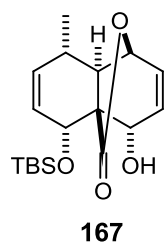
^1H NMR (400 MHz, CDCl_3): δ (ppm) 6.87 (dd, $J = 10.3, 2.1$ Hz, 1H), 5.95 (dd, $J = 10.3, 2.1$ Hz, 1H), 5.79 (ddd, $J = 9.8, 5.5, 2.0$ Hz, 1H), 5.58 (dd, $J = 9.8, 2.8$ Hz, 1H), 5.30 (s, 1H), 5.15 (tt, $J = 9.0, 2.0$ Hz, 1H), 4.95 (d, $J = 5.6$ Hz, 1H), 3.60 (s, 3H), 2.62 (m, 1H), 2.53 (t, $J = 9.2$ Hz, 1H), 1.71 (d, $J = 8.9$ Hz, 1H), 1.32 (d, $J = 7.0$ Hz, 3H), 0.80 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 192.5, 168.9, 154.0, 137.9, 127.7, 126.5, 70.9, 66.3, 64.4, 52.9, 46.3, 35.7, 26.1, 22.4, 18.3, -4.1, -5.0$ ppm.

IR: 3473, 3028, 2855, 1728, 1682, 1462, 1390, 1251, 1071, 840 cm^{-1}

HRMS: calculated for $\text{C}_{19}\text{H}_{30}\text{O}_5\text{SiNa}^+$: 389.1755; found: 389.1762

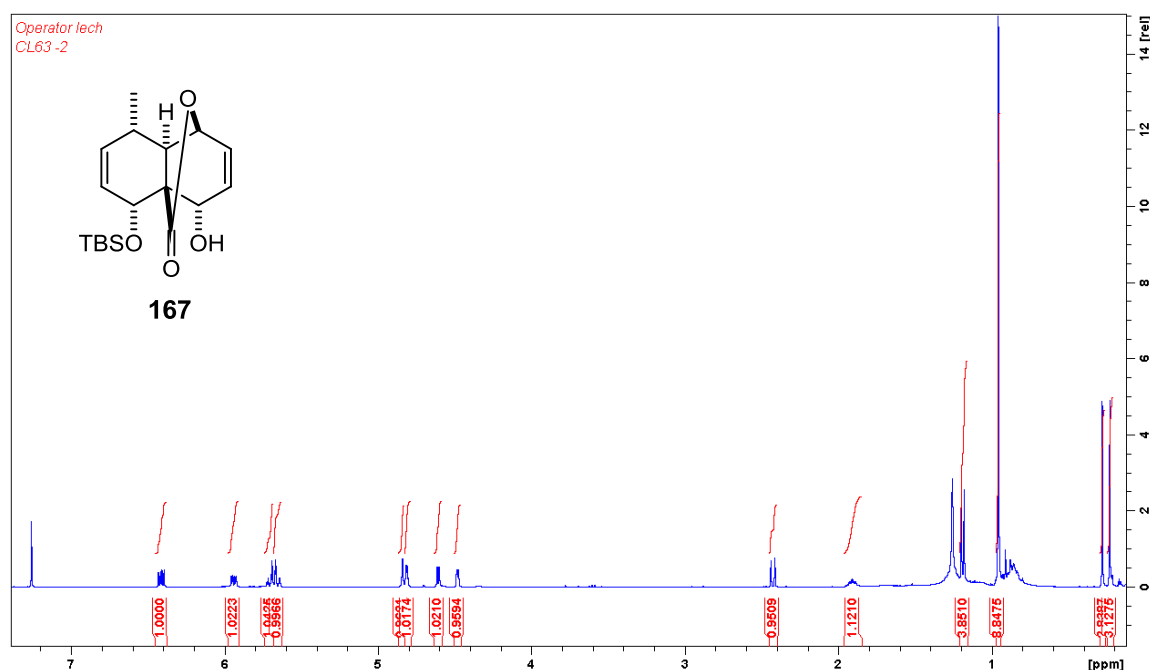
Lactone **167**



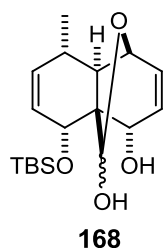
To a solution of **163** (100 mg, 0.27 mmol) in THF (4 mL) was added NaH (27 mg, 60% in mineral oil, 0.68 mmol) at 0 °C. After stirring at room temperature for 1 h, the resulting solution was quenched with aq. ammonium chloride, extracted with EtOAc (3x), washed with brine and dried over MgSO₄. The solvent was removed by rotary evaporation to the crude product **167** (90 mg, 99%) as a clear liquid and was used in the next step without further purification.

¹H NMR (400 MHz, CDCl₃): δ (ppm) 6.41 (dd, *J* = 9.3, 5.5 Hz, 1H); 5.94 (ddd, *J* = 9.3, 4.0, 1.0 Hz, 1H); 5.71 (dt, *J* = 10.2, 2.3 Hz, 1H); 5.65 (dt, *J* = 10.4, 2.0 Hz, 1H), 4.84 (d, *J* = 1.8 Hz, 1H), 4.81 (q, *J* = 2.6 Hz, 1H), 4.61 (d, *J* = 5.5 Hz, 1H), 4.48 (dd, *J* = 4.0, 1.3 Hz, 1H), 2.43 (d, *J* = 10.0 Hz, 1H), 1.91 (m, 1H), 1.19 (d, *J* = 7.0 Hz, 3H), 0.96 (s, 9H), 0.28 (s, 3H), 0.23 (s, 3H).

¹H NMR



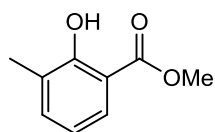
Lactol **168**



To a solution of **167** (100 mg, 0.27 mmol) in CH_2Cl_2 (1 mL) was added DIBAL (0.57 mL, 1 M in toluene, 0.57 mmol) dropwise at $-78\text{ }^\circ\text{C}$ under an argon atmosphere. The reaction mixture was stirred at $-78\text{ }^\circ\text{C}$ for 1.5 h and quenched with MeOH. After 15 min the resulting mixture was warmed to room temperature, diluted with water and aq. Na,K- tartrate, extracted with diethyl ether (2x) and CH_2Cl_2 (1x), washed with brine and dried over MgSO_4 . The solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 3:1) to give **168** (55 mg, 60%) in a 1:1 mixture of diastereomers.

^1H NMR (400 MHz, CDCl_3): δ (ppm) 6.34 (dd, $J = 9.3, 5.5$ Hz, 1H), 6.20 (dd, $J = 9.3, 5.8$ Hz, 1H), 5.94 (ddd, $J = 9.3, 4.3, 1.0$ Hz, 1H), 5.74 (m, 4H), 5.65 (m, 1H), 5.06 (m, 2H), 4.82 (d, $J = 7.8$ Hz, 1H), 4.73 (d, $J = 1.5$ Hz, 1H), 4.70 (q, $J = 2.4$ Hz, 1H), 4.67 (dd, $J = 4.3, 1.5$ Hz, 1H), 4.44 (m, 1H), 4.31 (d, $J = 5.2$ Hz, 1H), 4.26 (dd, $J = 4.3, 1.5$ Hz, 1H), 4.17 (d, $J = 5.5$ Hz, 1H), 2.86 (m, 1H), 2.71 (m, 1H), 2.23 (d, $J = 9.3$ Hz, 1H), 2.12 (d, $J = 9.6$ Hz, 1H), 2.04 (m, 2H), 1.12 (d, $J = 7.0$ Hz, 6H), 0.95 (s, 18H), 0.22 (s, 3H), 0.19 (s, 9H).

Methyl 2-hydroxy-3-methylbenzoate **172**



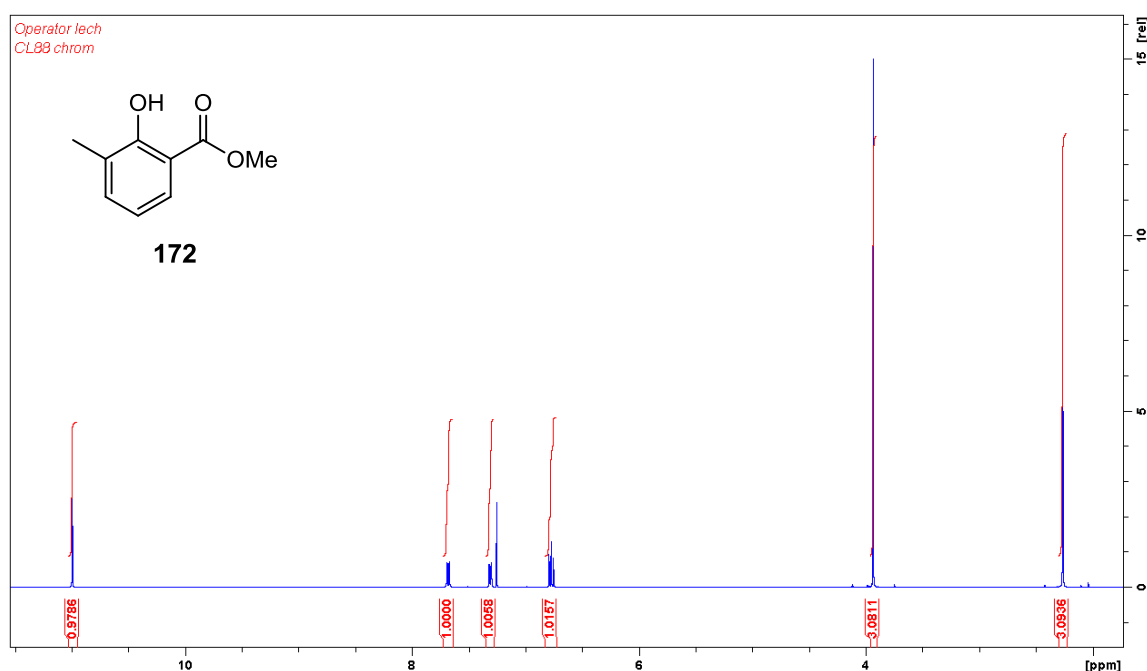
172

To a solution of 3-Methylsalicylic acid **171** (10 g, 66 mmol) in MeOH (200 mL) was added conc. H₂SO₄ (7 mL, 132 mmol). The reaction mixture was stirred under reflux for 72 hours. The solution was cooled to r.t. and neutralized with 25% NaOH and NaHCO₃. The organic layer was extracted with EtOAc (3x), washed with brine and dried over MgSO₄. The solvent was removed by rotary evaporation. The crude product was purified by flash chromatography on silica gel eluting with a mixture of hexane and EtOAc (10:1) to yield the methyl ester **172** (9.23 g, 84%) as a clear liquid.

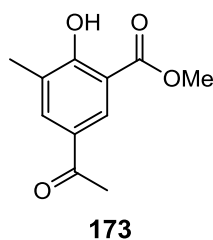
¹H NMR (400 MHz, CDCl₃): δ (ppm) 11.0 (s, 1H), 7.68 (d, *J* = 8.2 Hz, 1H), 7.31 (d, *J* = 7.3 Hz, 1H), 6.78 (dd, *J* = 7.7, 7.7 Hz, 1H), 3.94 (s, 3H), 2.27 (s, 3H).

IR: 3145, 2954, 1670, 1613, 1461, 1289, 1247, 1144, 1083, 752 cm⁻¹

¹H NMR



Methyl 5-acetyl-2-hydroxy-3-methylbenzoate **173**



To a suspension of AlCl_3 (812 mg, 6.1 mmol) in CH_2Cl_2 (2 mL) was added **172** (338 mg, 2 mmol). The reaction mixture was stirred under reflux for 30 minutes. The suspension was cooled to 0 °C and Ac_2O (0.21 mL, 2.2 mmol) was added dropwise. The solution was stirred under reflux for 6 h. The resulting mixture was quenched with water and neutralized with aq. NaHCO_3 . The organic layer was extracted with CH_2Cl_2 (3x), washed with brine and dried over MgSO_4 . The solvent was removed by rotary evaporation to the crude product **173** (389 mg, 92%) as a clear liquid and was used in the next step without further purification.

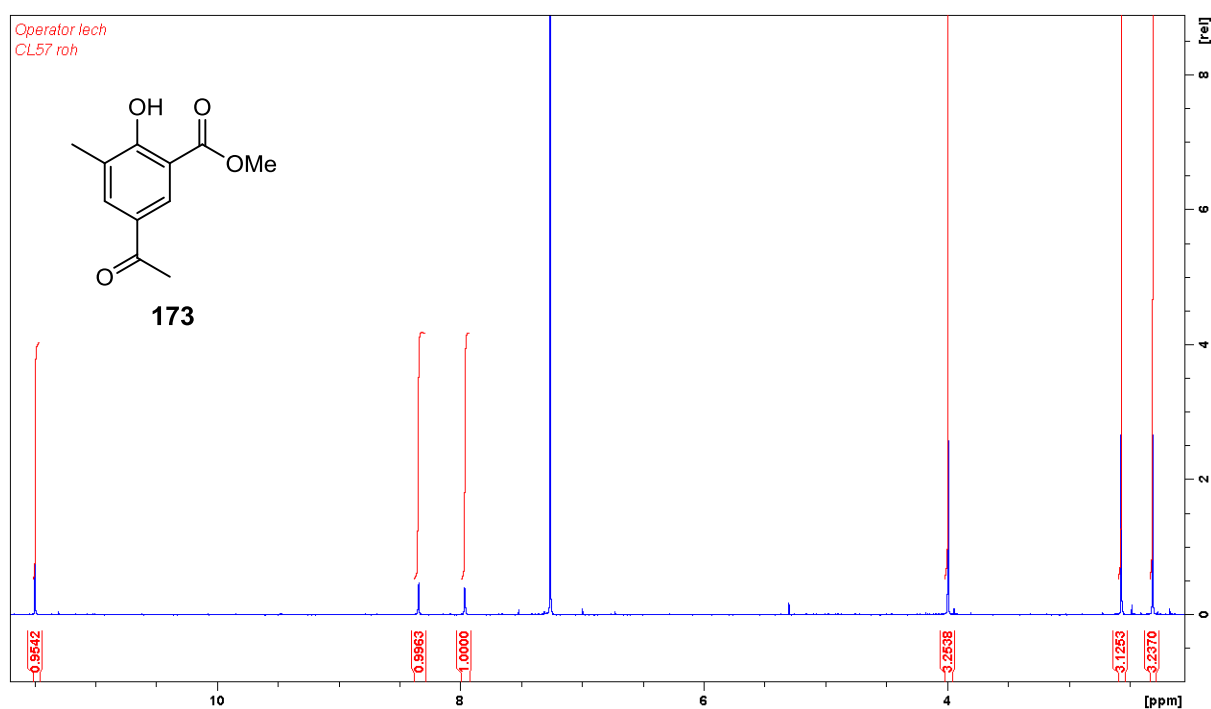
$^1\text{H NMR}$ (400 MHz, CDCl_3): δ (ppm) 11.49 (s, 1H), 8.34 (d, $J = 2.4$ Hz, 1H), 7.96 (m, 1H), 3.99 (s, 3H), 2.57 (s, 3H), 2.31 (s, 3H).

$^{13}\text{C NMR}$ (100 MHz, CDCl_3): $\delta = 196.2, 170.6, 163.9, 135.8, 129.1, 128.3, 127.3, 111.2, 52.6, 29.2, 15.7$ ppm

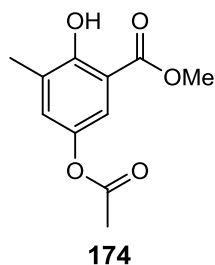
IR: 2955, 1738, 1672, 1444, 1349, 1288, 1233, 1149, 973, 745 cm^{-1}

HRMS: calculated for $\text{C}_{11}\text{H}_{12}\text{O}_4\text{Na}^+$: 231.0628; found: 231.0626

¹H NMR



Methyl 5-acetoxy-2-hydroxy-3-methylbenzoate **174**



To a solution of **173** (389 mg, 1.87 mmol) in CH₂Cl₂ (2 mL) was added pTsOH.H₂O (9 mg, 0.05 mmol) and *m*CPBA (645 mg, 3.74 mmol) in small portions. The reaction mixture was stirred under reflux for 22 h. The solution was quenched with aq. NaHCO₃, extracted with CH₂Cl₂ (3x), washed with brine and dried over MgSO₄. The solvent was removed by rotary evaporation to the crude product **174** (402 mg, 86%) as a clear liquid and was used in the next step without further purification.

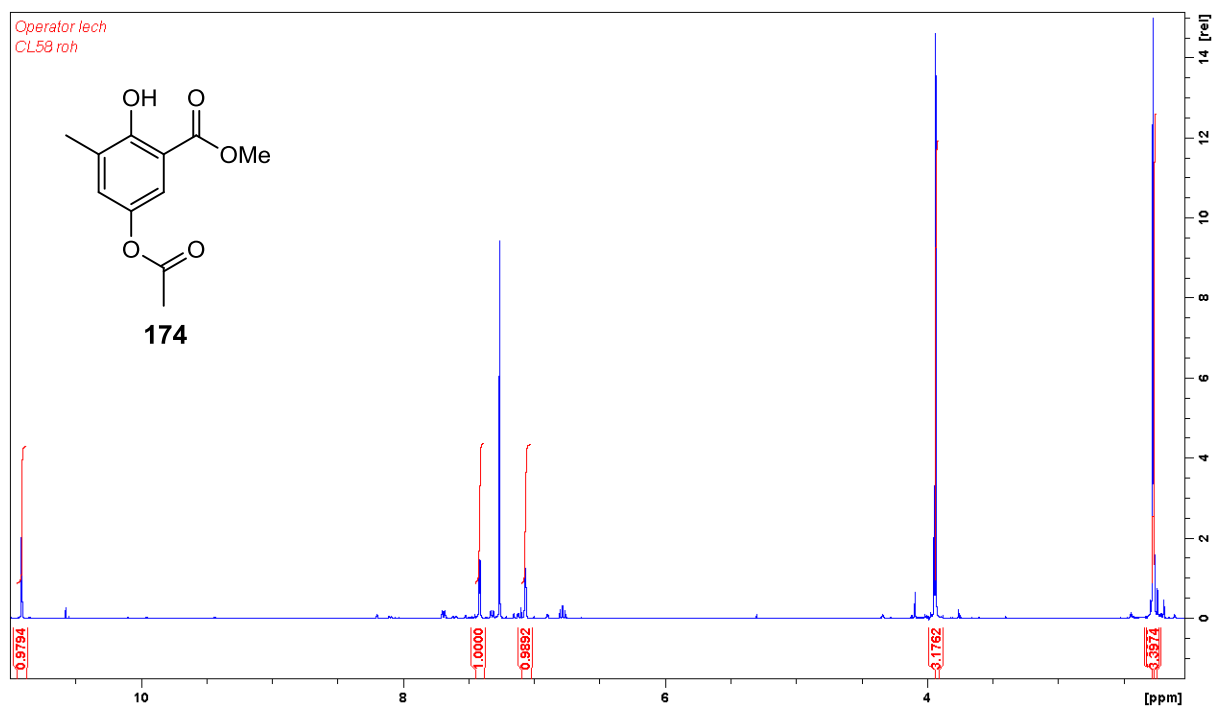
¹H NMR (400 MHz, CDCl₃): δ (ppm) 10.91 (s, 1H), 7.41 (d, *J* = 3.0 Hz, 1H), 7.06 (d, *J* = 2.7 Hz, 1H), 3.93 (s, 3H), 2.27 (s, 3H), 2.26 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 170.3, 169.9, 157.9, 141.7, 129.9, 128.2, 119.4, 111.5, 52.4, 21.0, 15.8 ppm

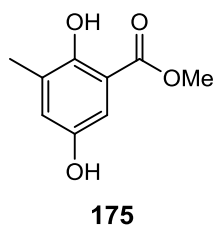
IR: 3150, 1753, 1675, 1474, 1438, 1344, 1269, 1216, 1029, 792 cm⁻¹

HRMS: calculated for C₁₁H₁₂O₅Na⁺: 247.0577; found: 247.0584

¹H NMR



Methyl 2,5-dihydroxy-3-methylbenzoate **175**

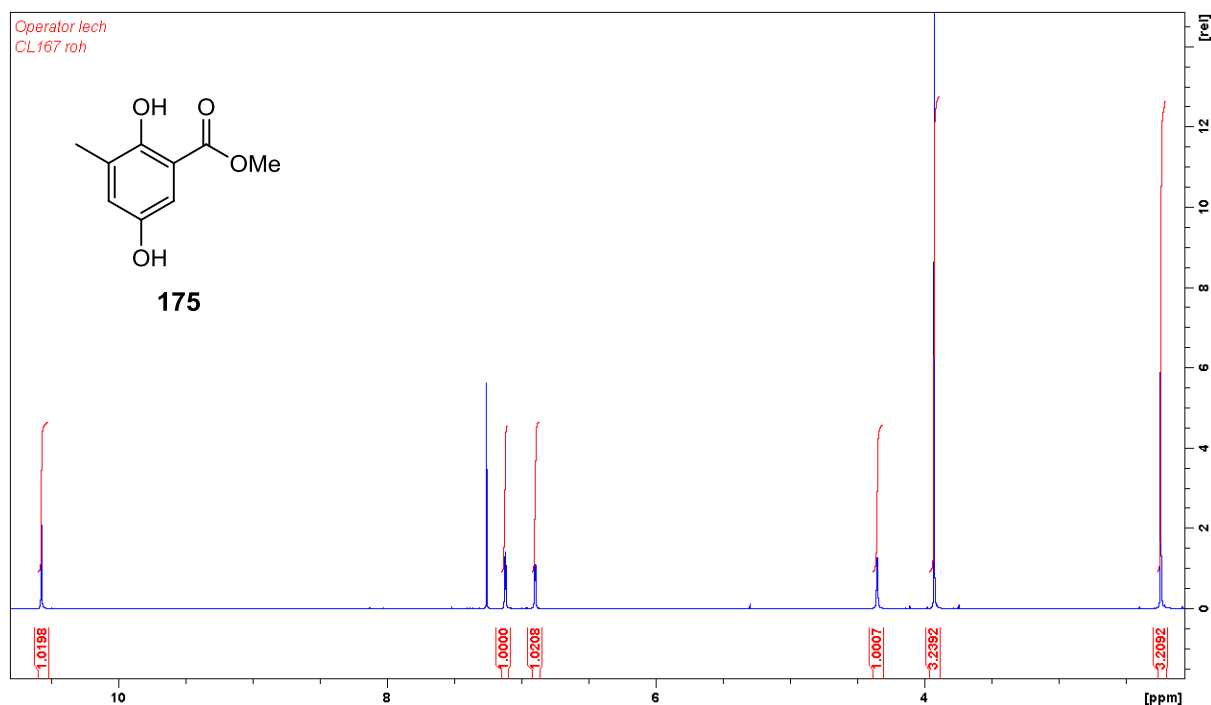


To a suspension of **174** (1.48 g, 6.61 mmol) in MeOH (66 mL) was added $n\text{Bu}_2\text{SnO}$ (164 mg, 0.66 mmol). The reaction mixture was stirred under reflux for 3 h. The solution was quenched with aq. NaHCO_3 , extracted with EtOAc (3x), washed with brine, dried over MgSO_4 and filtered through a pad of Celite. The solvent was removed by rotary evaporation to the crude product **175** (1.20 mg, 97%) as a pale yellow solid and was used in the next step without further purification.

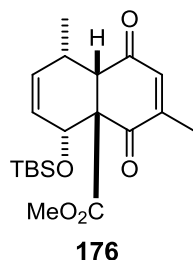
$^1\text{H NMR}$ (400 MHz, CDCl_3): δ (ppm) 10.58 (s, 1H), 7.12 (d, $J = 3.1$ Hz, 1H), 6.90 (d, $J = 3.0$ Hz, 1H), 4.35 (s, 1H), 3.93 (s, 3H), 2.24 (s, 3H).

IR: 3428, 1677, 1607, 1441, 1357, 1213, 1126, 905, 730, 668 cm^{-1}

$^1\text{H NMR}$



Methyl DA adduct **176**



To a suspension of **175** (3.3 g, 18.11 mmol) and 1-tert-butyldimethylsiloxypenta-1,3-diene (**155**) (11.5 g, 57.97 mmol, mixture of stereoisomers) in toluene (18 mL) at 10 °C was added silver(I)oxide (8.40 g, 32.2 mmol) in one portion. The mixture was warmed to room temperature and stirred for 19 h, then was diluted with diethyl ether, and filtered through Celite. The Celite was washed thoroughly with diethyl ether, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc, 10:1) to give **176** (5.91 g, 86%) of as a pale green solid.

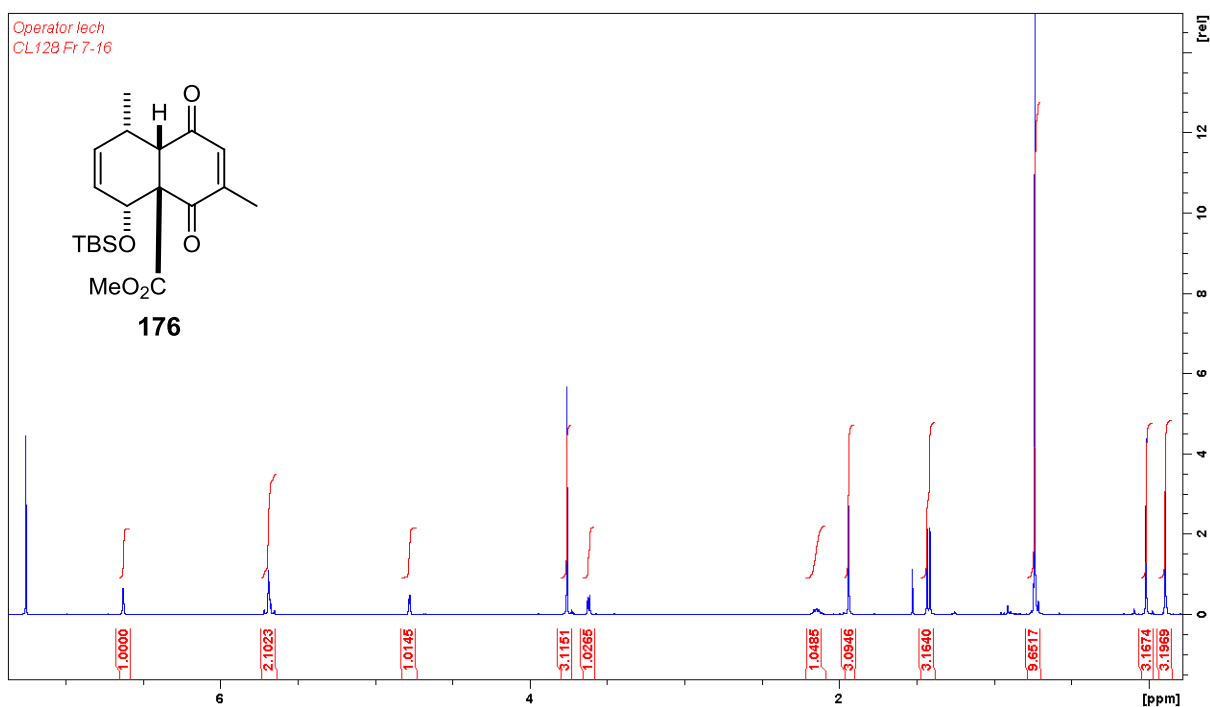
¹H NMR (400 MHz, CDCl₃): δ (ppm) 6.63 (m, 1H), 5.68 (m, 2H), 4.78 (m, 1H), 3.76 (s, 3H), 3.62 (d, *J* = 4.9 Hz, 1H), 2.15 (m, 1H) 1.94 (d, *J* = 1.5 Hz, 3H), 1.42 (d, *J* = 7.6 Hz, 3H), 0.74 (s, 9H), 0.02 (s, 3H), -0.11 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 196.5, 195.9, 169.7, 146.8, 141.5, 132.8, 126.0, 67.2, 65.8, 52.9, 50.7, 29.9, 25.5, 17.8, 17.3, 15.8, -4.7, -5.2 ppm.

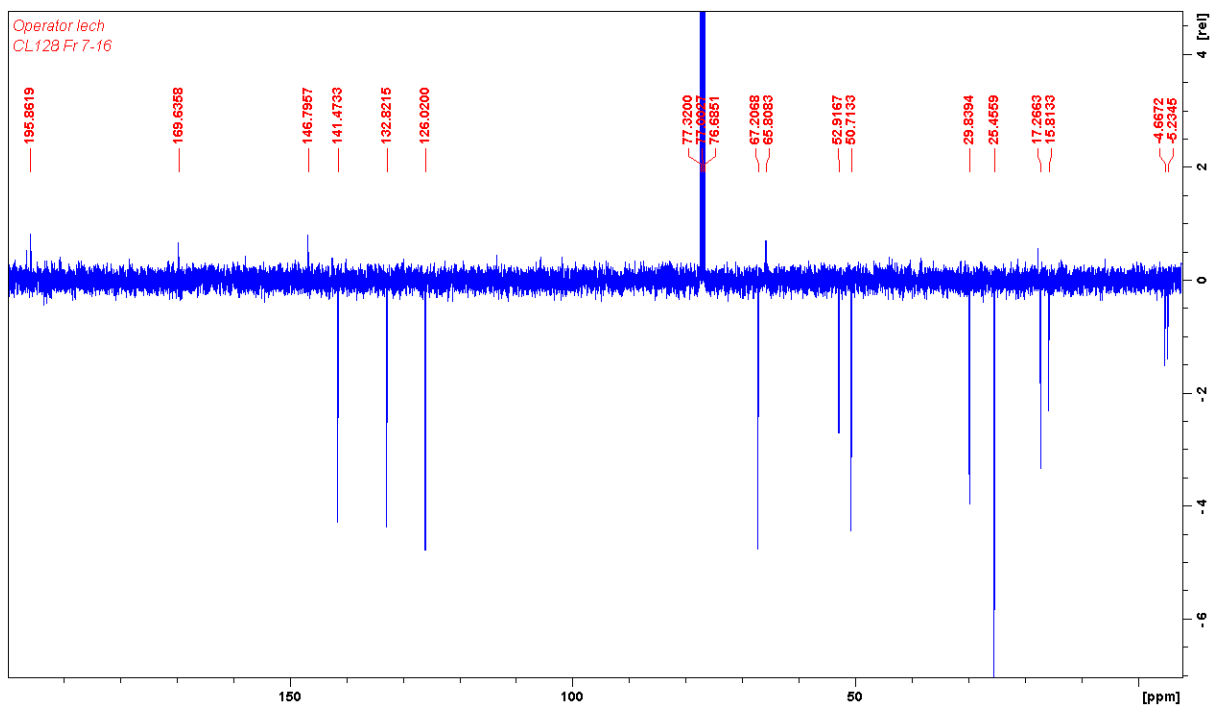
IR: 2927, 2856, 2361, 1750, 1705, 1682, 1468, 1258, 1227, 1055 cm⁻¹

HRMS: calculated for C₂₀H₃₀O₅SiNa⁺: 401.1755; found: 401.1754

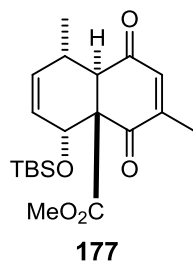
¹H NMR



¹³C NMR



Epi-methyl DA adduct **176**



A mixture of **176** (5.91 g, 15.61 mmol) and neutral alumina (156 g Brockman Activity II, M70 – 220) in toluene (470 mL) was stirred for 4 h at room temperature. The resulting mixture was filtered and washed with EtOAc. Concentration of the filtrate afforded **177** (5.71 g, 97%) of as a pale green solid and was used in the next step without further purification.

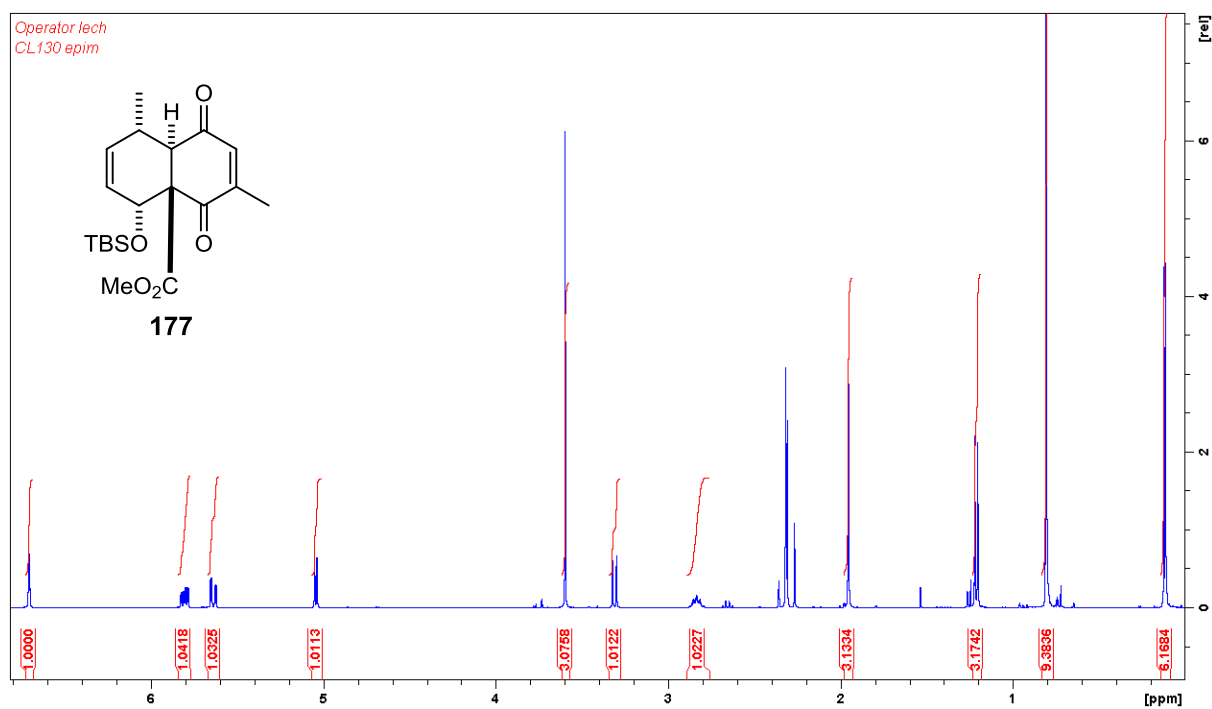
¹H NMR (400 MHz, CDCl₃): δ (ppm) 6.71 (q, *J* = 1.5 Hz, 1H), 5.81 (ddd, *J* = 10.1, 5.6, 2.0 Hz, 1H), 5.34 (dd, *J* = 9.9, 3.0 Hz, 1H), 5.04 (d, *J* = 5.5 Hz, 1H), 3.60 (s, 3H), 3.31 (d, *J* = 9.3 Hz, 1H), 2.83 (m, 1H), 1.96 (d, *J* = 1.5 Hz, 3H), 1.21 (d, *J* = 6.8 Hz, 3H), 0.81 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 197.7, 192.0, 167.4, 146.7, 139.6, 136.3, 125.8, 67.4, 65.4, 53.0, 50.4, 30.0, 25.6, 20.8, 17.8, 16.2, -4.0, -5.0 ppm.

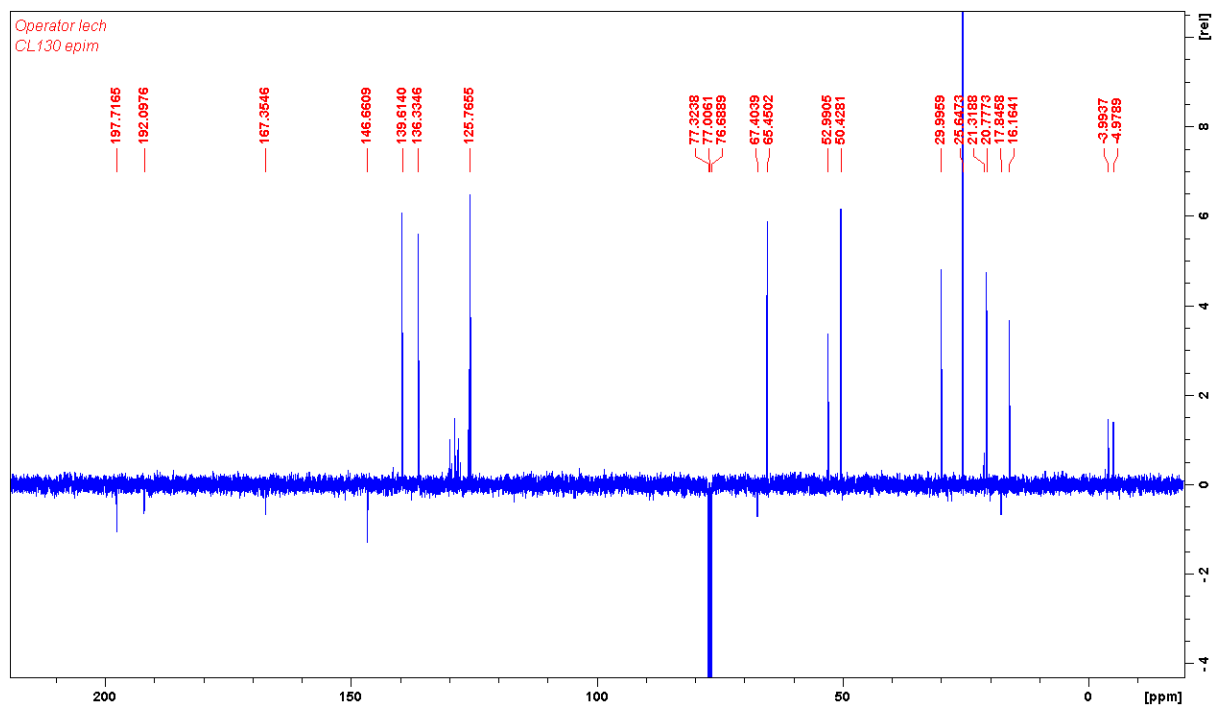
IR: 2954, 2928, 2855, 2349, 1734, 1687, 1461, 1251, 1072, 838, 632 cm⁻¹

HRMS: calculated for C₂₀H₃₀O₅SiNa⁺: 401.1755; found: 401.1747

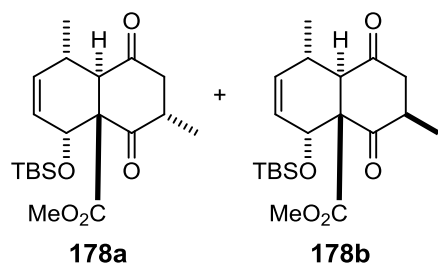
¹H NMR



¹³C NMR



Diketones **178a** and **178b**



To a solution of **177** (100 mg, 0.26 mmol) in acetic acid (95%) (1 mL) was added zinc powder (34.5 mg, 0.53 mmol). After stirring for 2 h at room temperature, the resulting solution was treated with water and aq. NaHCO₃, extracted with CH₂Cl₂ (3x), washed with brine and dried over MgSO₄. The solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 6:1) to give **178** (63 mg, 64%) as a 1:1 mixture of diastereomers.

Diketone **178a**:

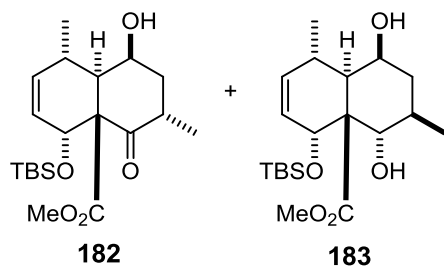
¹H NMR (400 MHz, CDCl₃): δ (ppm) 5.78 (ddd, *J* = 9.7, 5.7, 2.0 Hz, 1H), 5.60 (dd, *J* = 9.8, 3.0 Hz, 1H), 4.95 (d, *J* = 5.6 Hz, 1H), 3.62 (s, 3H), 3.19 (d, *J* = 8.8 Hz, 1H), 2.91 (m, 1H), 2.81 (m, 2H), 2.49 (dd, *J* = 16.3, 6.4 Hz, 1H), 1.26 (d, *J* = 7.1 Hz, 3H), 1.17 (d, *J* = 6.8 Hz, 3H), 0.84 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 206.5, 203.0, 167.8, 136.2, 126.0, 67.8, 65.9, 52.9, 49.9, 43.9, 42.4, 30.4, 25.8, 21.1, 17.9, 17.7, -4.3, -4.6 ppm.

IR: 3383, 2928, 2855, 1770, 1641, 1471, 1250, 1063, 836, 633 cm⁻¹

HRMS: calculated for C₂₀H₃₂O₅SiNa⁺: 403.1912; found: 403.1925

Hydroxyketone **182** and diol **183**



To a solution of **177** (100 mg, 0.26 mmol) in MeOH (3.5 mL) was added NaBH₄ (100 mg, 2.64 mmol) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C. The resulting mixture was quenched with aq. ammonium chloride, extracted with CH₂Cl₂ (3x), washed with brine and dried over MgSO₄. The solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 3:1) to give **182** (25 mg, 25%) and **183** (30 mg, 30%).

Hydroxyketone **182**

¹H NMR (400 MHz, CDCl₃): δ (ppm) 5.73 (ddd, *J* = 9.7, 5.4, 2.3 Hz, 1H); 5.62 (dd, *J* = 9.6, 2.5 Hz, 1H); 5.46 (d, *J* = 9.1 Hz, 1H); 4.91 (d, *J* = 5.6 Hz, 1H), 4.25 (m, 1H), 3.65 (s, 3H), 2.80 (m, 1H), 2.71 (m, 1H), 2.57 (dd, *J* = 10.9, 3.8 Hz, 1H), 2.27 (ddd, *J* = 13.8, 5.2, 3.4 Hz, 1H), 2.10 (d, *J* = 1.5 Hz, 1H), 1.44 (dt, *J* = 13.8, 2.5 Hz, 1H), 1.10 (d, *J* = 6.8 Hz, 3H), 1.03 (d, *J* = 6.6 Hz, 3H), 0.80 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 204.0, 172.0, 137.5, 127.1, 67.9, 66.7, 63.8, 53.5, 45.3, 41.5, 36.5, 31.4, 25.7, 18.8, 17.8, 14.4, -4.0, -4.9 ppm.

IR: 3434, 2953, 2856, 1694, 1438, 1249, 1074, 837, 774, 669 cm⁻¹

HRMS: calculated for C₂₀H₃₄O₅SiNa⁺: 405.2068; found: 405.2066

Diol **183**

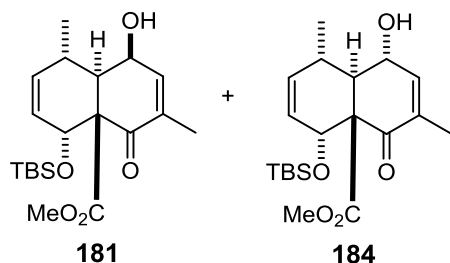
¹H NMR (400 MHz, CDCl₃): δ (ppm) 5.77 (m, 2H); 4.86 (m, 1H); 4.5 (d, *J* = 9.8 Hz, 1H); 4.20 (m, 1H), 3.70 (d, *J* = 8.8 Hz, 1H), 3.68 (s, 3H), 3.55 (t, *J* = 9.0 Hz, 1H), 2.71 (m, 1H), 2.32 (ddd, *J* = 14.6, 8.6, 4.5 Hz, 1H), 2.21 (dd, *J* = 10.4, 5.0 Hz, 1H), 1.79 (m, 1H), 1.24 (m, 1H), 1.09 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.17 (s, 3H), 0.11 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 177.6, 140.3, 125.6, 79.5, 69.5, 64.4, 55.1, 52.7, 39.8, 39.5, 33.0, 30.7, 25.8, 18.7, 18.2, 17.9, -2.7, -4.3 ppm.

IR: 3397, 2953, 2928, 2856, 1698, 1435, 1251, 1044, 835, 777 cm⁻¹

HRMS: calculated for C₂₀H₃₆O₅SiNa⁺: 407.2225; found: 407.2228

Allylic alcohol **181** and **184**



To a solution of **177** (200 mg, 0.53 mmol) and CeCl₃·7 H₂O (413 mg, 1.11 mmol) in MeOH (7.5 mL) was added NaBH₄ (60 mg, 1.59 mmol) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C. The resulting mixture was quenched with aq. ammonium chloride, extracted with CH₂Cl₂ (3x), washed with brine and dried over MgSO₄. The solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 6:1) to give **181** (108 mg, 54%) and **182** (80 mg; 39%).

Allylic alcohol **181**

¹H NMR (400 MHz, CDCl₃): δ (ppm) 6.92 (dq, *J* = 5.8, 1.3 Hz, 1H); 5.78 (ddd, *J* = 9.8, 5.3 Hz, 2.3 Hz, 1H); 5.68 (dd, *J* = 9.8, 2.3 Hz, 1H); 5.00 (d, *J* = 5.3 Hz, 1H), 4.77 (d, *J* = 11.3 Hz, 1H), 4.42 (m, 1H), 3.67 (s, 3H), 2.68 (dd, *J* = 10.8, 5.3 Hz, 1H), 2.60 (m, 1H), 1.81 (t, *J* = 1.1 Hz, 3H), 1.14 (d, *J* = 6.8 Hz, 3H), 0.77 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 192.7, 171.6, 145.6, 137.0, 134.5, 126.7, 66.7, 63.3, 61.3, 53.4, 40.2, 30.5, 25.6, 18.4, 18.0, 16.4, -4.0, -5.1 ppm.

IR: 3443, 2954, 2856, 1676, 1435, 1251, 1067, 859, 837, 778 cm⁻¹

HRMS: calculated for C₂₀H₃₂O₅SiNa⁺: 403.1912; found: 403.1922

Allylic alcohol **184**

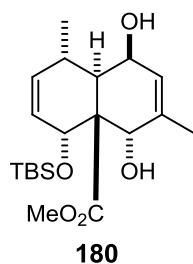
¹H NMR (400 MHz, CDCl₃): δ (ppm) 6.64 (m, 1H), 5.78 (dd, *J* = 9.9 Hz, 5.6, 2.3 Hz, 1H); 5.57 (dd, *J* = 9.9, 2.5 Hz, 1H); 5.09 (m, 1H), 4.96 (d, *J* = 5.3 Hz, 1H), 3.59 (s, 3H), 2.59 (m, 1H), 2.48 (t, *J* = 9.3 Hz, 1H), 1.78 (t, *J* = 1.5 Hz, 3H), 1.63 (d, *J* = 8.6 Hz, 1H), 1.31 (d, *J* = 6.8 Hz, 3H), 0.79 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 192.5, 168.8, 149.0, 137.4, 133.8, 126.3, 70.3, 66.3, 63.5, 52.4, 46.2, 35.3, 25.8, 22.0, 17.9, 15.9, -4.1, -5.0 ppm.

IR: 2953, 2855, 1727, 1675, 1462, 1360, 1250, 1075, 838, 631 cm⁻¹

HRMS: calculated for C₂₀H₃₂O₅SiNa⁺: 403.1912; found: 403.1904

Diallylic alcohol **180**



To a solution of **177** (100 mg, 0.26 mmol) in CH_2Cl_2 (1 mL) was added DIBAL (0.78 mL, 1 M in toluene, 0.78 mmol) dropwise at $-78\text{ }^\circ\text{C}$ under an argon atmosphere. The reaction mixture was stirred at $-78\text{ }^\circ\text{C}$ for 1 h and quenched with MeOH. After 15 min the resulting mixture was warmed to room temperature, diluted with water and aq. Na,K- tartrate, extracted with diethyl ether (2x) and CH_2Cl_2 (1x), washed with brine and dried over MgSO_4 . The solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 10:1) to give **180** (51 mg, 51%) as a white solid.

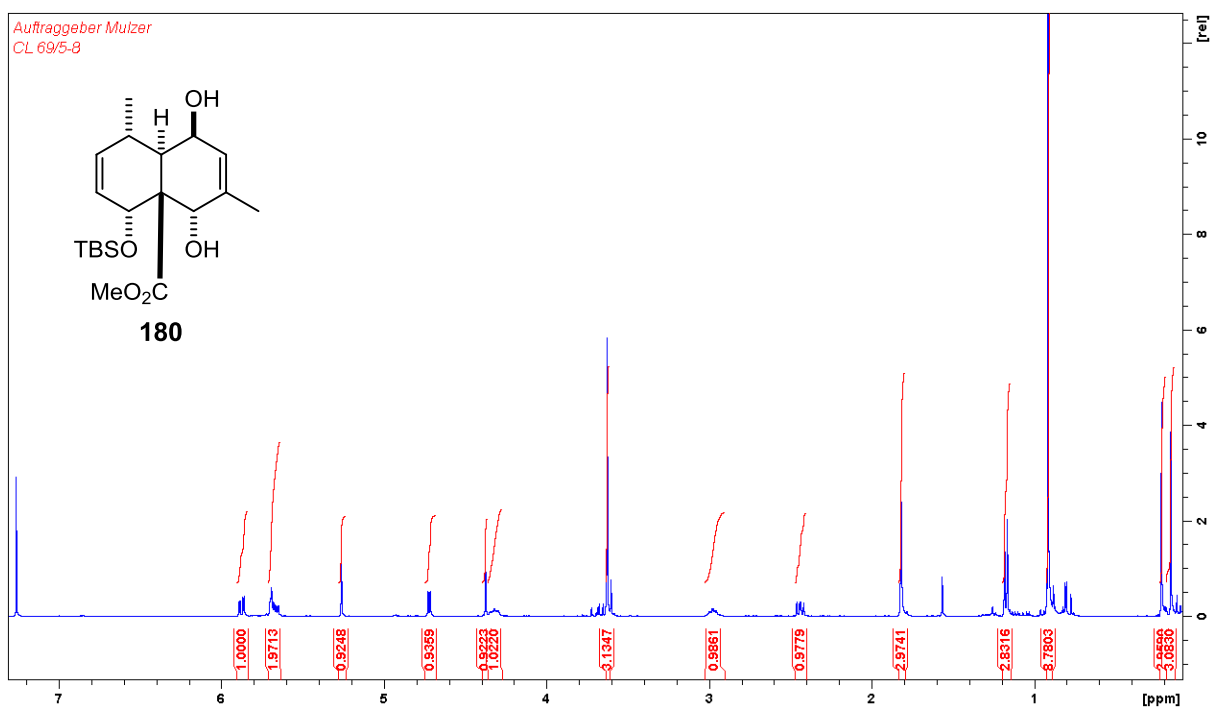
^1H NMR (400 MHz, CDCl_3): δ (ppm) 5.87 (dd, $J = 10.0, 3.16$ Hz, 1H), 5.68 (m, 2H), 5.26 (d, $J = 0.5$ Hz, 1H); 4.72 (d, $J = 5.3$ Hz, 1H), 4.37 (s, 1H), 4.32 (m, 1H), 3.63 (s, 3H), 2.97 (m, 1H), 2.44 (dd, $J = 9.8, 7.1$ Hz, 1H), 1.82 (t, $J = 1.5$ Hz, 3H), 1.17 (d, $J = 6.8$ Hz, 3H), 0.91 (s, 9H), 0.22 (s, 3H), 0.16 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 175.1, 140.3, 135.0, 128.9, 124.0, 73.1, 71.0, 63.3, 52.6, 52.5, 34.6, 28.7, 25.7, 21.8, 19.8, 17.9, -3.2, -4.5$ ppm.

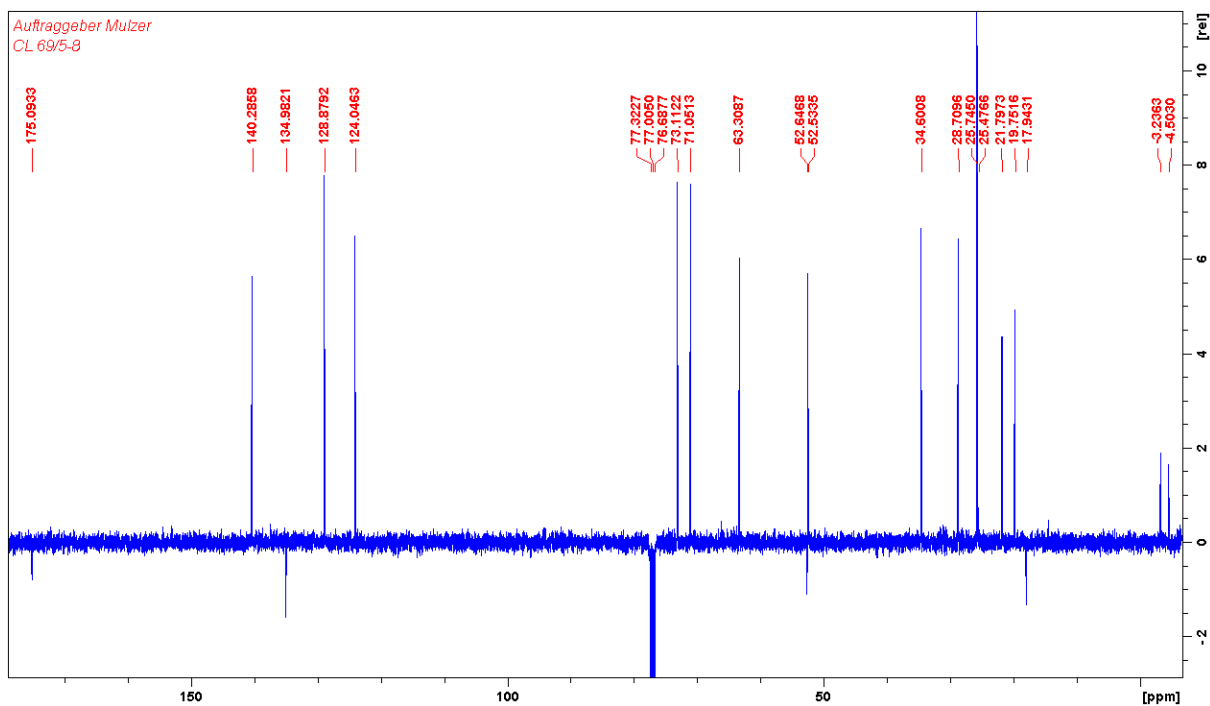
IR: 2925, 2356, 2341, 1743, 1714, 1674, 990, 753, 648, 620 cm^{-1}

HRMS: calculated for $\text{C}_{20}\text{H}_{34}\text{O}_5\text{SiNa}^+$: 405.2068; found: 420.2061

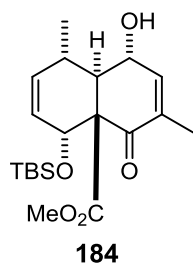
¹H NMR



¹³C NMR



Allylic alcohol **184**



To a solution of **177** (50 mg, 0.13 mmol) in *i*PrOH (0.6 mL) was added Al(O*i*Pr)₃ (120 mg, 0.59 mmol). The mixture was boiled gently, and acetone and *i*PrOH were distilled slowly from the reaction mixture through a short column. From time to time *i*PrOH was added to maintain a constant volume. After 18 h the reaction mixture was concentrated under reduced pressure, treated with 1 M HCl, and extracted with CH₂Cl₂ (3x). The organic layer was washed with sat. NaHCO₃ and brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc, 10:1) to give **184** (21 mg, 41%) as a white solid.

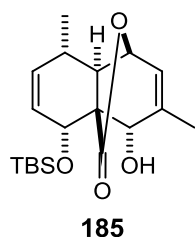
¹H NMR (400 MHz, CDCl₃): δ (ppm) 6.64 (m, 1H), 5.78 (dd, *J* = 9.9 Hz, 5.6, 2.3 Hz, 1H); 5.57 (dd, *J* = 9.9, 2.5 Hz, 1H); 5.09 (m, 1H), 4.96 (d, *J* = 5.3 Hz, 1H), 3.59 (s, 3H), 2.59 (m, 1H), 2.48 (t, *J* = 9.3 Hz, 1H), 1.78 (t, *J* = 1.5 Hz, 3H), 1.63 (d, *J* = 8.6 Hz, 1H), 1.31 (d, *J* = 6.8 Hz, 3H), 0.79 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 192.5, 168.8, 149.0, 137.4, 133.8, 126.3, 70.3, 66.3, 63.5, 52.4, 46.2, 35.3, 25.8, 22.0, 17.9, 15.9, -4.1, -5.0 ppm.

IR: 2953, 2855, 1727, 1675, 1462, 1360, 1250, 1075, 838, 631 cm⁻¹

HRMS: calculated for C₂₀H₃₂O₅SiNa⁺: 403.1912; found: 403.1904

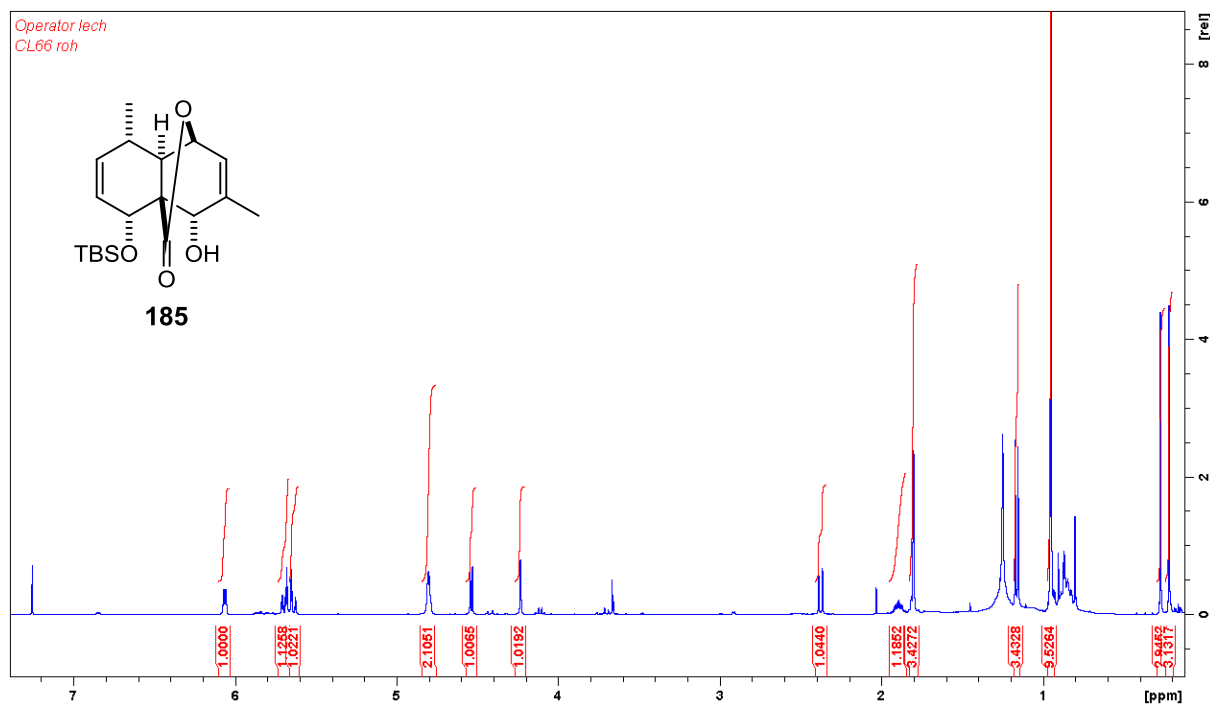
Methyl lactone **185**



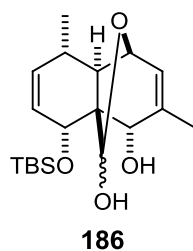
To a solution of **180** (100 mg, 0.27 mmol) in THF (4 mL) was added NaH (27 mg, 60% in mineral oil, 0.68 mmol) at 0 °C. After stirring at room temperature for 1.5 h, the resulting solution was quenched with aq. ammonium chloride, extracted with EtOAc (3x), washed with brine and dried over MgSO₄. The solvent was removed by rotary evaporation to the crude product **185** (90 mg, 95%) as a clear liquid and was used in the next step without further purification.

¹H NMR (400 MHz, CDCl₃): δ (ppm) 6.06 (dq, *J* = 5.6, 1.6 Hz, 1H), 5.70 (dt, *J* = 10.3, 2.52 Hz, 1H), 5.64 (dt, *J* = 10.3, 2.0 Hz, 1H), 4.80 (m, 2H), 4.54 (d, *J* = 5.8 Hz, 1H), 4.23 (s, 1H), 2.38 (d, *J* = 9.8 Hz, 1H), 1.90 (m, 1H), 1.80 (d, *J* = 1.5 Hz, 3H), 1.16 (d, *J* = 7.0 Hz, 3H), 0.95 (s, 9H), 0.27 (s, 3H), 0.22 (s, 3H).

¹H NMR



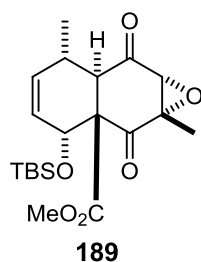
Methyl lactol **186**



To a solution of **185** (45 mg, 0.13 mmol) in CH_2Cl_2 (1 mL) was added DIBAL (0.55 mL, 1 M in toluene, 0.55 mmol) dropwise at $-78\text{ }^\circ\text{C}$ under an argon atmosphere. The reaction mixture was stirred at $-78\text{ }^\circ\text{C}$ for 1 h and quenched with MeOH. After 15 min the resulting mixture was warmed to room temperature, diluted with water and aq. Na,K- tartrate, extracted with diethyl ether (2x) and CH_2Cl_2 (1x), washed with brine and dried over MgSO_4 . The solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 3:1) to give **186** (28 mg, 61%) in a 1:1 mixture of diastereomers.

^1H NMR (400 MHz, CDCl_3): δ (ppm) 5.99 (m, 1H), 5.88 (m, 1H), 5.71 (m, 4H), 5.04 (m, 2H), 4.75 (d, $J = 8.8\text{ Hz}$, 1H), 4.68 (q, $J = 2.3\text{ Hz}$, 1H), 4.64 (d, $J = 1.5\text{ Hz}$, 1H), 4.41 (m, 1H), 4.39 (d, $J = 1.0\text{ Hz}$, 1H), 4.22 (d, $J = 5.8\text{ Hz}$, 1H), 4.11 (d, $J = 5.8\text{ Hz}$, 1H), 4.02 (d, $J = 1.0\text{ Hz}$, 1H), 2.44 (m, 1H), 2.33 (m, 1H), 2.22 (d, $J = 9.1\text{ Hz}$, 1H), 2.11 (d, $J = 9.3\text{ Hz}$, 1H), 2.03 (m, 2H), 1.84 (d, $J = 1.5\text{ Hz}$, 3H), 1.78 (d, $J = 1.5\text{ Hz}$, 3H), 1.12 (d, $J = 2.5\text{ Hz}$, 3H), 1.11 (d, $J = 2.5\text{ Hz}$, 3H), 0.95 (s, 18H), 0.23 (s, 3H), 0.20 (s, 3H) 0.20 (s, 3H), 0.19 (s, 3H).

Diketone epoxide **189**



To a solution of **177** (4.0 g, 11 mmol) in MeOH (110 mL) was added aq. NaOH 10% (2.1 mL) and H₂O₂ 30 wt.% (4.1 mL, 53 mmol) at 0°C. The reaction mixture was stirred for 1 h at 0 °C. The resulting mixture was quenched with sodium thiosulfate, extracted with diethyl ether (3x), washed with brine and dried over MgSO₄. The solvent was removed by rotary evaporation to the crude product **189** (1.20 mg, 97%) as a white solid and was used in the next step without further purification.

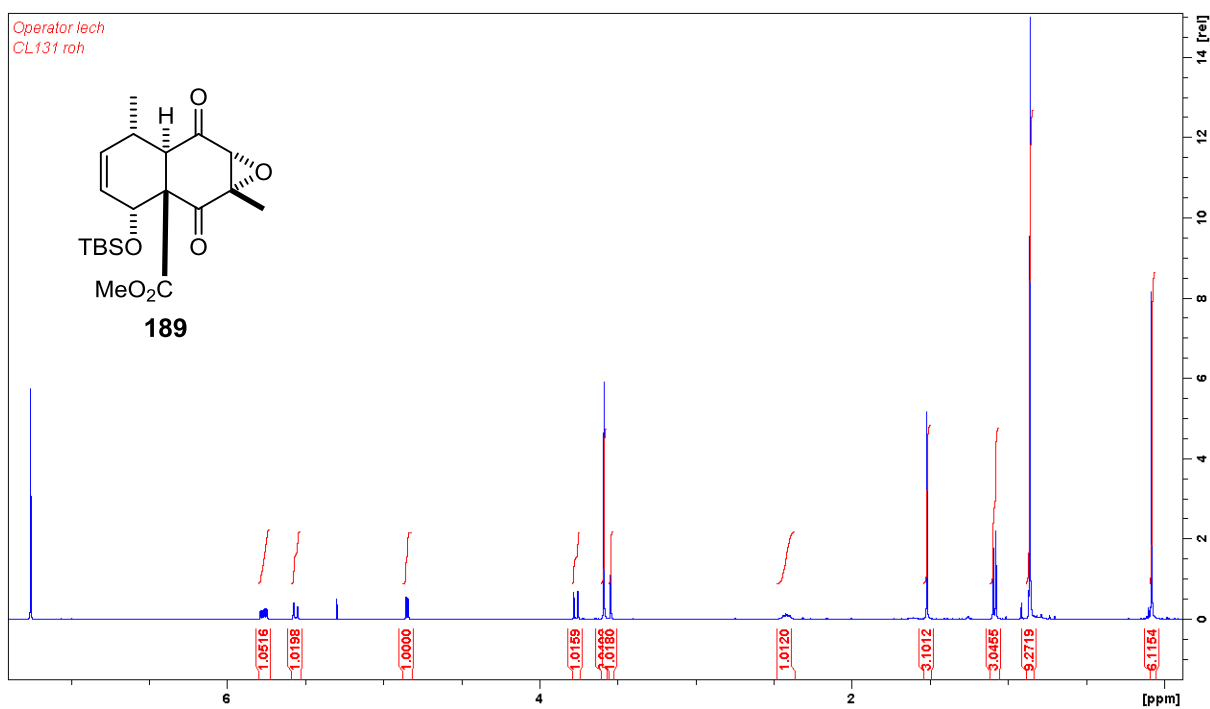
¹H NMR (400 MHz, CDCl₃): δ (ppm) 5.77 (ddd, *J* = 9.8, 5.1, 2.4 Hz, 1H), 5.56 (dd, *J* = 9.7, 2.2 Hz, 1H), 4.85 (d, *J* = 5.2 Hz, 1H), 3.77 (d, *J* = 10.3 Hz, 1H), 3.59 (s, 3H), 3.54 (s, 1H), 2.42 (m, 1H), 1.52 (s, 1H), 1.09 (d, *J* = 6.6 Hz, 3H), 0.86 (s, 9H), 0.08 (s, 6H).

¹³C NMR (100 MHz, CDCl₃): δ = 203.1, 197.4, 167.4, 134.9, 126.1, 67.3, 66.9, 66.5, 62.3, 52.7, 44.5, 28.7, 25.5, 19.6, 17.8, 16.2, -3.8, -5.3 ppm.

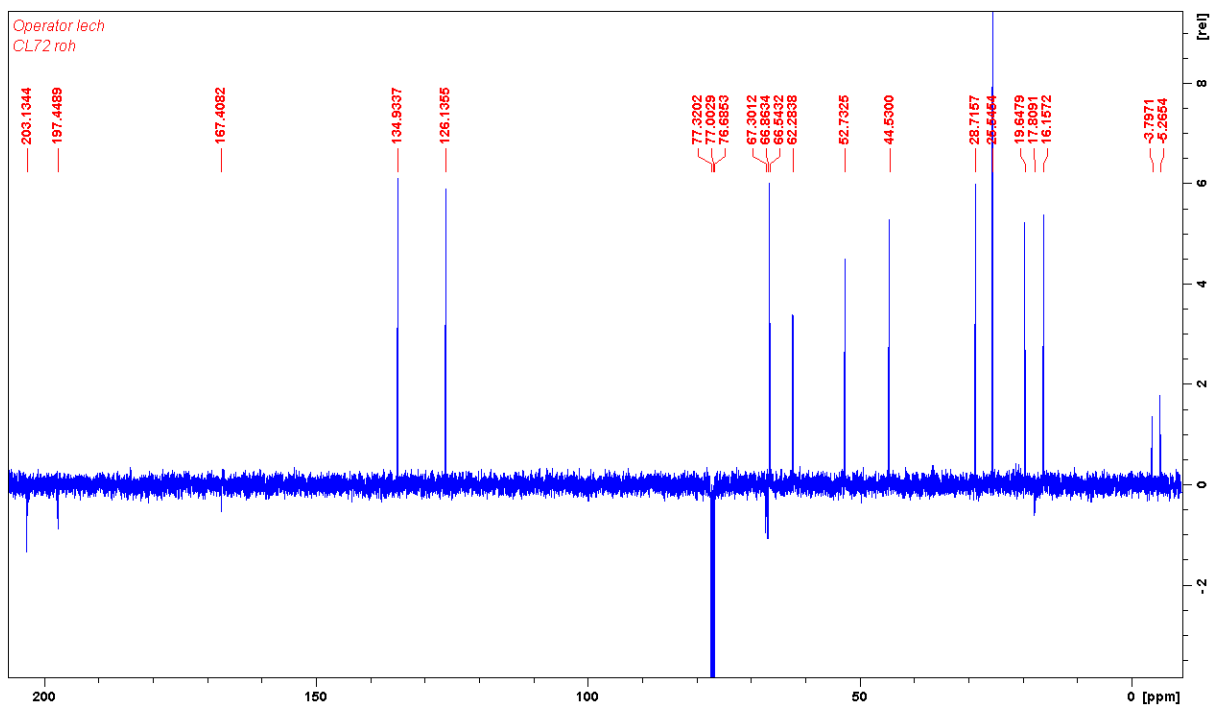
IR: 2956, 2929, 2857, 2367, 1757, 1733, 1715, 1076, 839, 778 cm⁻¹

HRMS: calculated for C₂₀H₃₀O₆SiNa⁺: 417.1704; found: 417.1706

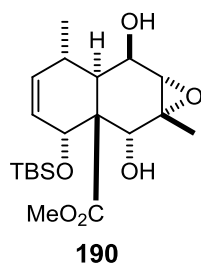
¹H NMR



¹³C NMR



Dihydroxy epoxide **190**



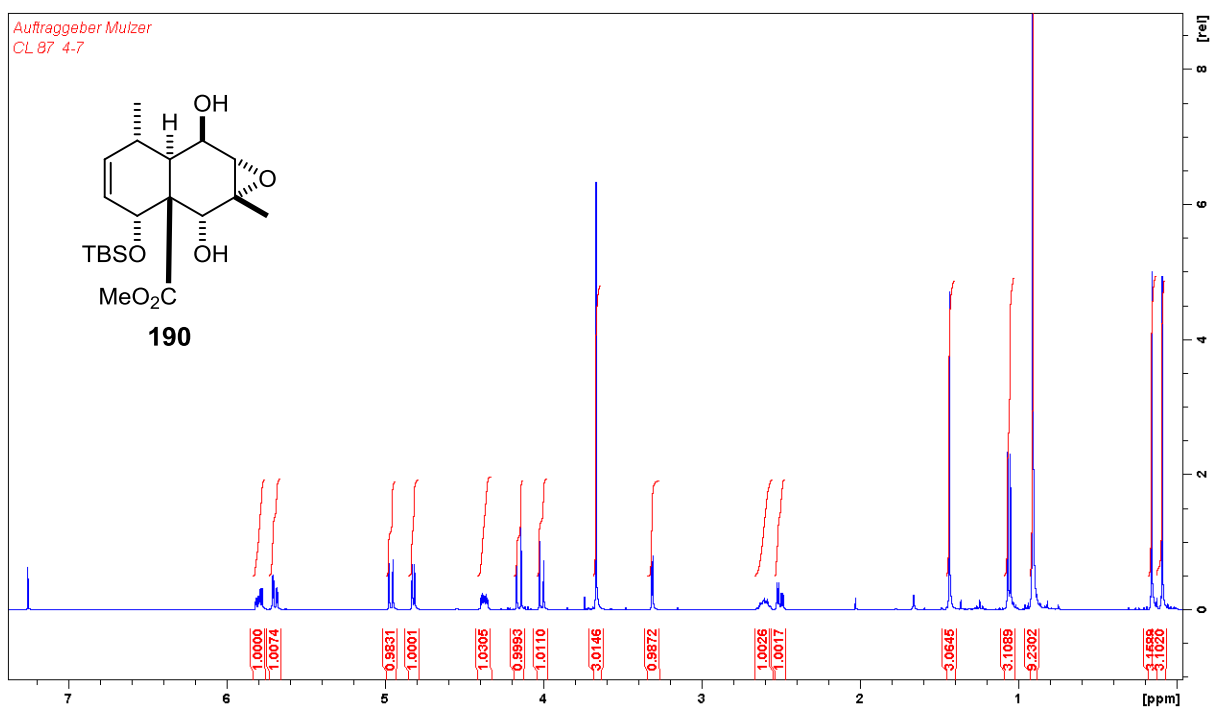
To a solution of **189** (100 mg, 0.25 mmol) in MeOH (3.6 mL) was added NaBH₄ (29 mg, 0.76 mmol) at 0 °C. The reaction mixture was stirred for 1.5 h at 0 °C. The resulting mixture was quenched with aq. ammonium chloride, extracted with diethyl ether (3x), washed with brine and dried over MgSO₄. The solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 3:1) to give **190** (100 mg, 99%) as a clear liquid.

¹H NMR (400 MHz, CDCl₃): δ (ppm) 5.80 (ddd, *J* = 9.8, 5.6, 2.0 Hz, 1H), 5.64 (dd, *J* = 9.8, 2.8 Hz, 1H), 4.97 (d, *J* = 9.8 Hz, 1H), 4.82 (d, *J* = 5.3 Hz, 1H), 4.38 (m, 1H), 4.16 (d, *J* = 10.6 Hz, 1H), 4.01 (d, *J* = 10.6 Hz, 1H), 3.67 (s, 3H), 3.31 (d, *J* = 3.0 Hz, 1H), 2.61 (m, 1H), 2.51 (dd, *J* = 10.8, 4.3 Hz, 1H), 1.44 (s, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.91 (s, 9H), 0.16 (s, 3H), 0.09 (s, 3H).

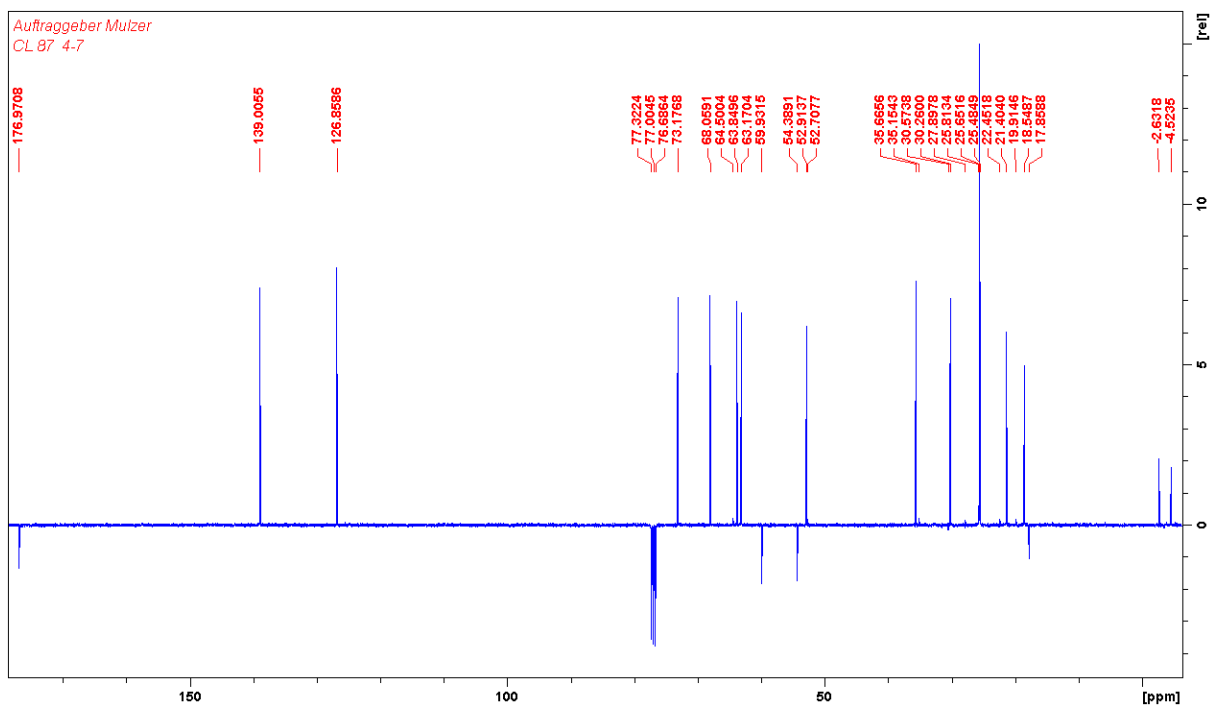
¹³C NMR (100 MHz, CDCl₃): δ = 177.0, 139.0, 126.9, 73.2, 68.0, 64.5, 63.8, 59.9, 54.4, 52.9, 35.7, 30.3, 25.7, 21.4, 18.5, 17.9, -2.6, -4.5 ppm.

HRMS: calculated for C₂₀H₃₄O₆SiNa⁺: 421.2017; found: 421.2023

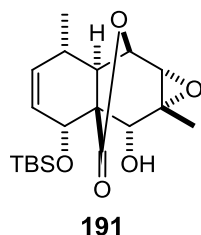
¹H NMR



¹³C NMR



Epoxy-lactone **191**



To a solution of **190** (100 mg, 0.25 mmol) in THF (2.5 mL) was added NaH (25 mg, 60% in mineral oil, 0.63 mmol) at 0 °C. After stirring for 1.5 h at 0 °C, the resulting solution was quenched with aq. ammonium chloride, extracted with CH₂Cl₂ (3x), washed with brine and dried over MgSO₄. The solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 3:1) to give **191** (76 mg, 84%) as a clear liquid.

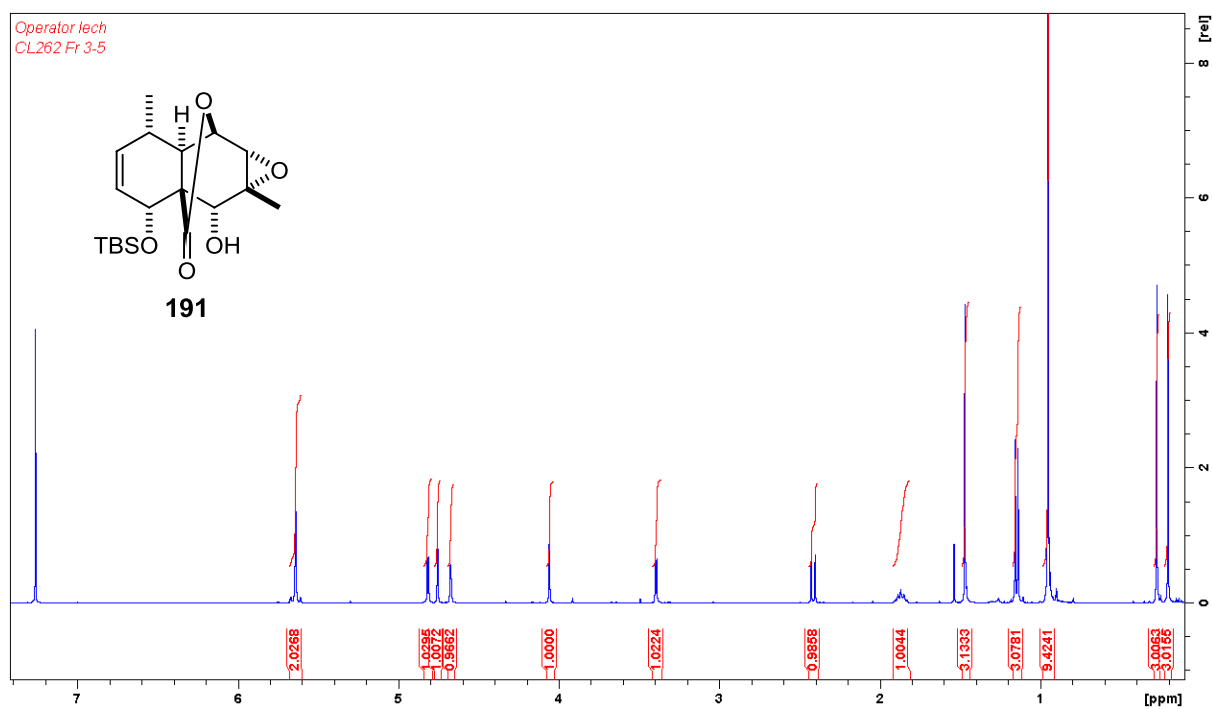
¹H NMR (400 MHz, CDCl₃): δ (ppm) 5.64 (m, 2H), 4.81 (d, *J* = 3.5 Hz, 1H), 4.75 (d, *J* = 1.8 Hz, 1H), 4.67 (m, 1H), 4.06 (d, *J* = 4.1 Hz, 1H), 3.39 (d, *J* = 3.5 Hz, 1H), 2.41 (d, *J* = 9.6 Hz, 1H), 1.87 (m, 1H), 1.47 (s, 3H), 1.15 (d, *J* = 6.8 Hz, 3H), 0.95 (s, 9H), 0.27 (s, 3H), 0.20 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 177.0, 134.2, 129.5, 79.8, 70.2, 68.2, 58.9, 58.6, 55.6, 37.6, 27.9, 25.7, 19.4, 17.9, -4.5, -4.9 ppm.

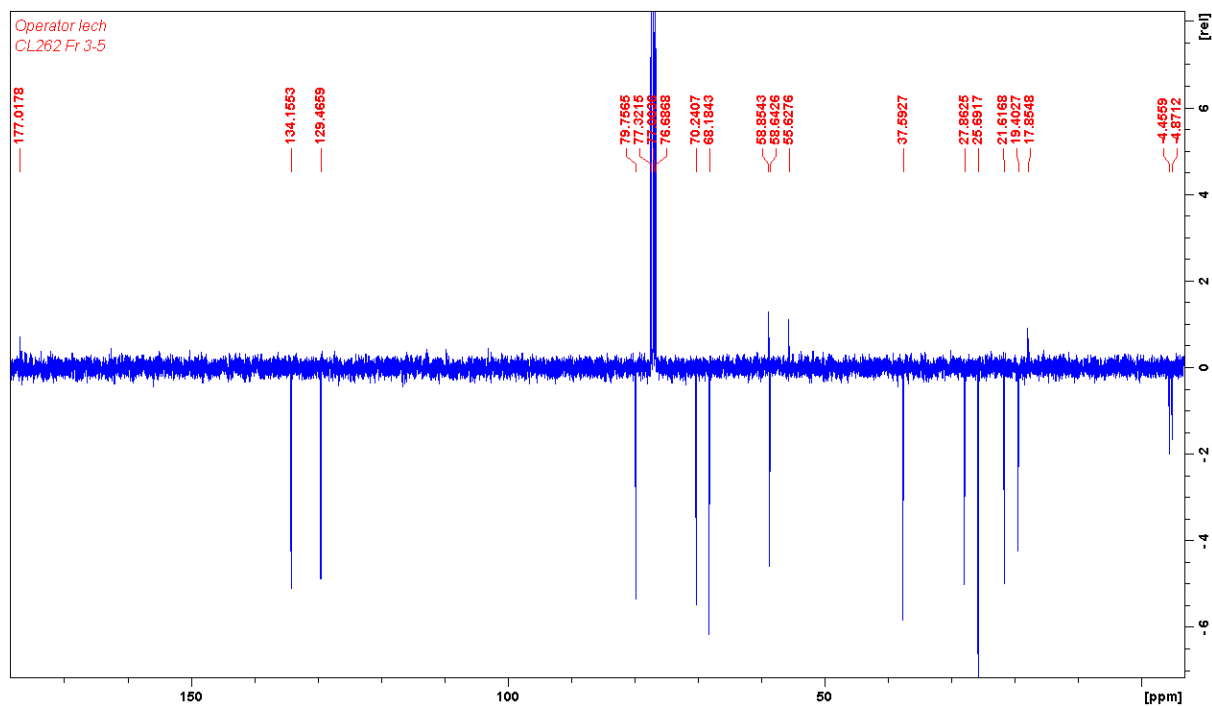
IR: 3467, 2927, 2856, 2362, 1776, 1463, 1258, 1075, 1000, 848 cm⁻¹

HRMS: calculated for C₁₉H₃₀O₅SiNa⁺: 389.1755; found: 389.1765

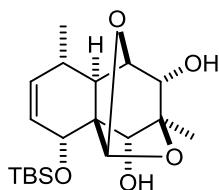
¹H NMR



¹³C NMR



Acetal **192**



192

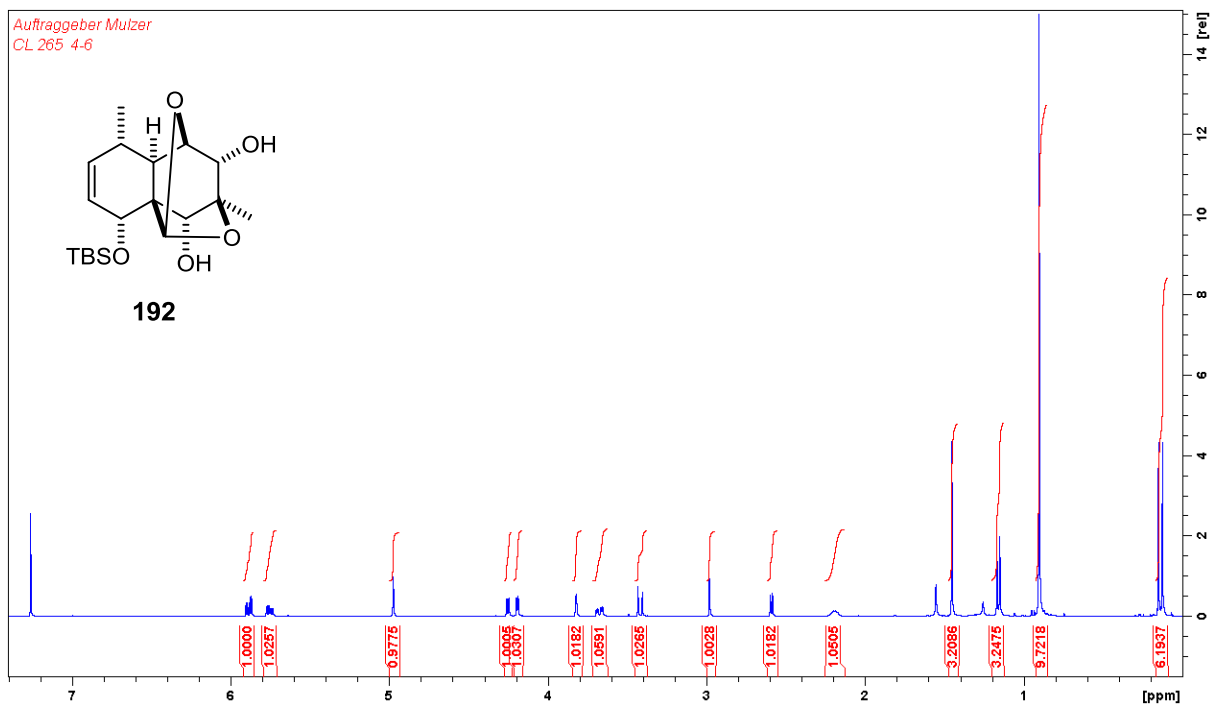
To a solution of **191** (30 mg, 0.082 mmol) in CH_2Cl_2 (0.8 mL) was added DIBAL (0.14 mL, 1.5 M in toluene, 0.20 mmol) dropwise at $-78\text{ }^\circ\text{C}$ under an argon atmosphere. The reaction mixture was stirred at $-78\text{ }^\circ\text{C}$ for 1 h and quenched with MeOH. After 15 min the resulting mixture was warmed to room temperature, diluted with water and aq. Na,K- tartrate, extracted with diethyl ether (2x) and CH_2Cl_2 (1x), washed with brine and dried over MgSO_4 . The solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 3:1) to give **192** (11 mg, 36%) as clear oil.

^1H NMR (400 MHz, CDCl_3): δ (ppm) 5.88 (dd, $J = 10.1, 3.8$ Hz, 1H), 5.75 (ddd, $J = 10.2, 5.4, 2.0$ Hz, 1H); 4.97 (s, 1H); 4.25 (d, $J = 5.2$ Hz, 1H), 4.19 (d, $J = 4.0$ Hz, 1H), 3.82 (m, 1H), 3.67 (m, $J = 11.4, 3.9, 2.3$ Hz, 1H), 3.41 (d, $J = 11.5$ Hz, 1H), 2.97 (d, $J = 1.0$ Hz, 1H), 2.59 (d, $J = 5.2$ Hz, 1H), 2.19 (m, 1H), 1.45 (s, 3H), 1.16 (d, $J = 7.2$ Hz, 3H), 0.90 (s, 9H), 0.15 (s, 3H), 0.12 (s, 3H).

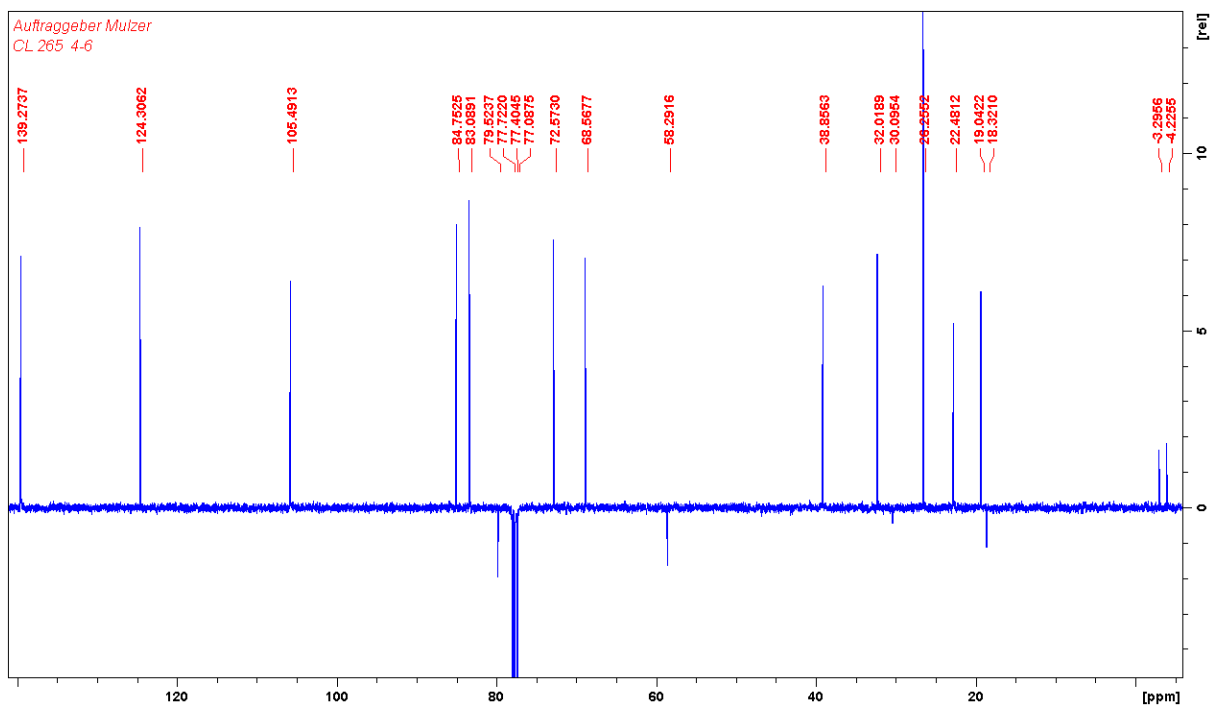
^{13}C NMR (100 MHz, CDCl_3): $\delta = 138.9, 123.9, 105.1, 84.4, 82.7, 79.1, 72.2, 68.2, 57.9, 38.5, 31.6, 25.9, 22.1, 18.6, 17.9, -3.7, -4.6$ ppm.

HRMS: calculated for $\text{C}_{19}\text{H}_{32}\text{O}_5\text{SiNa}^+$: 391.1912; found: 391.1907

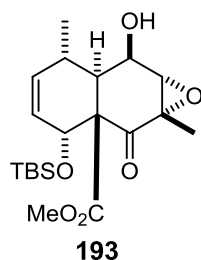
¹H NMR



¹³C NMR



Monohydroxy epoxide **193**



To a solution of **189** (4.12 g, 11 mmol) and $\text{CeCl}_3 \cdot 7 \text{H}_2\text{O}$ (8.61 g, 23.1 mmol) in MeOH (150 mL) was added NaBH_4 (1.25 g, 33 mmol) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C. The resulting mixture was quenched with aq. ammonium chloride, extracted with CH_2Cl_2 (3x), washed with brine and dried over MgSO_4 . The solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 3:1) to give **193** (3.73 g, 85%) as a white solid.

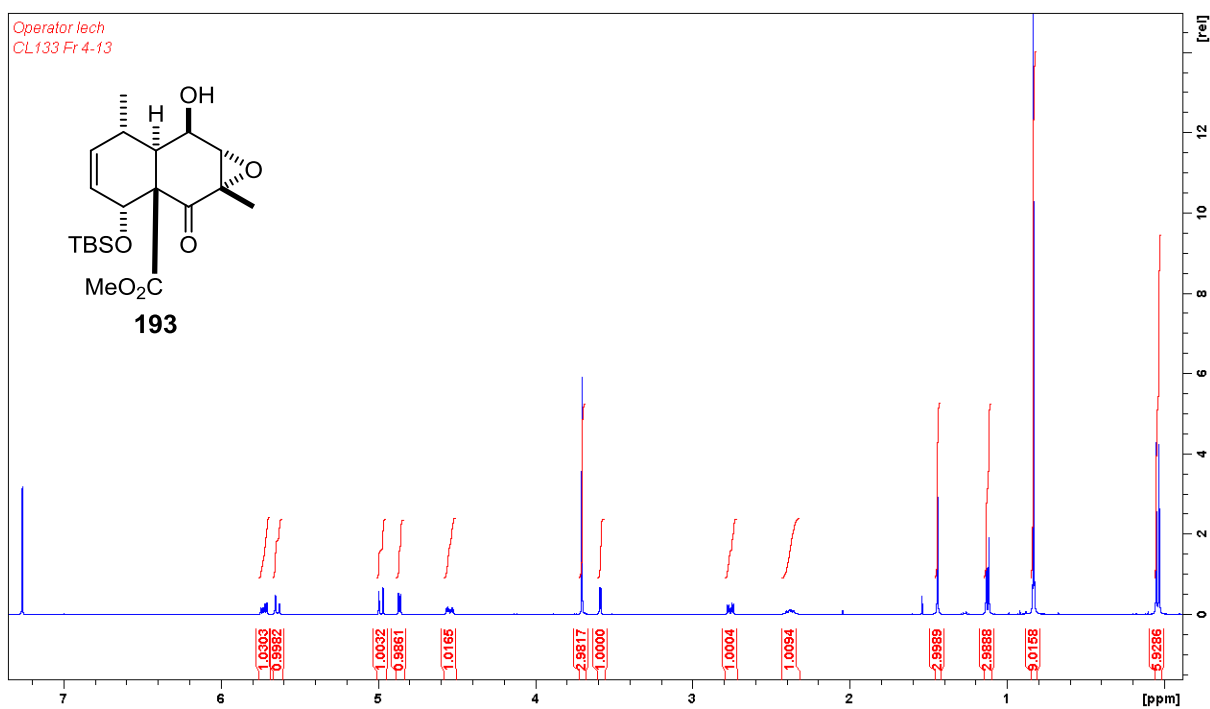
^1H NMR (400 MHz, CDCl_3): δ (ppm) 5.72 (ddd, $J = 9.8, 5.1, 2.3$ Hz, 1H), 5.64 (dd, $J = 9.8, 2.0$ Hz, 1H), 4.98 (d, $J = 11.0$ Hz, 1H), 4.86 (d, $J = 5.0$ Hz, 1H), 4.54 (m, 1H), 3.70 (s, 3H), 3.58 (d, $J = 2.9$ Hz, 1H), 2.76 (dd, $J = 11.3, 4.3$ Hz, 1H), 2.38 (m, 1H), 1.44 (s, 3H), 1.12 (d, $J = 6.9$ Hz, 3H), 0.83 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 200.8, 172.2, 137.0, 126.9, 67.9, 63.9, 63.6, 63.5, 58.8, 53.6, 37.4, 30.1, 25.5, 18.3, 17.8, 16.3, -3.9, -5.2$ ppm.

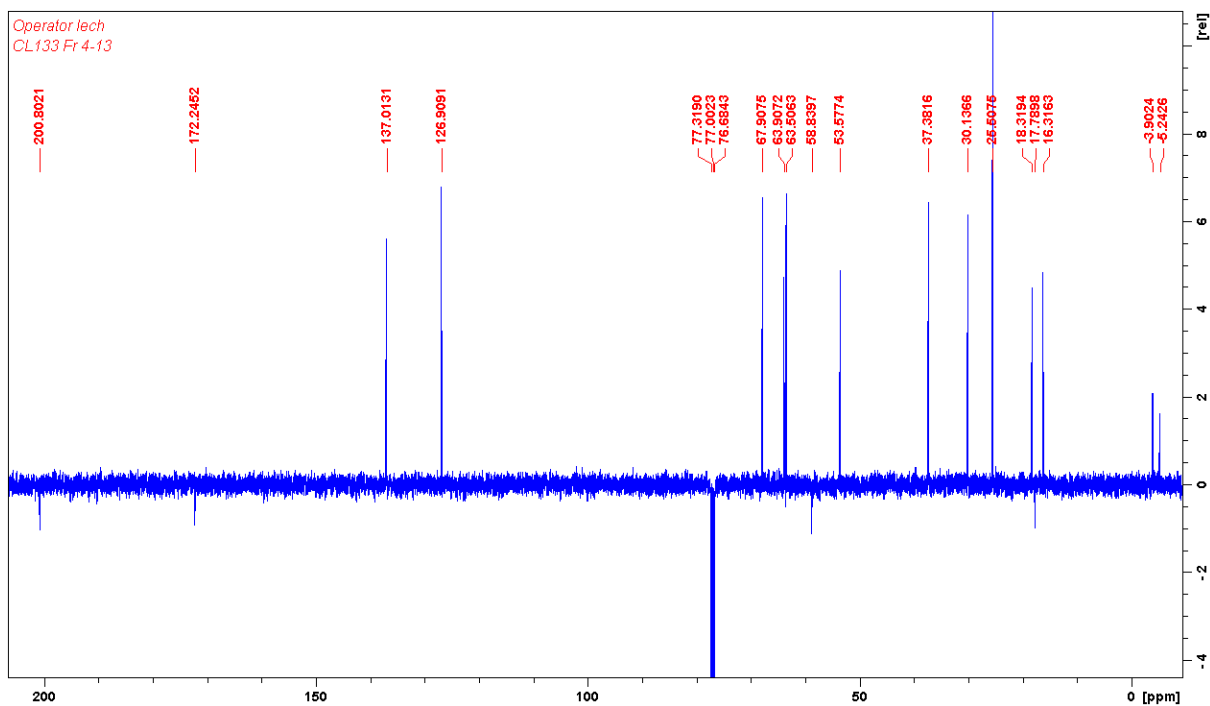
IR: 2428, 2955, 2917, 2875, 1697, 1659, 1543, 1419, 1264, 1078 cm^{-1}

HRMS: calculated for $\text{C}_{20}\text{H}_{32}\text{O}_6\text{SiNa}^+$: 419.1861; found: 419.1864

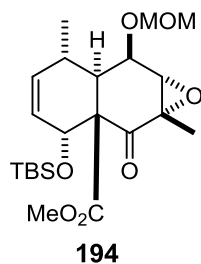
¹H NMR



¹³C NMR



MOM-epoxide **194**



To a solution of **193** (3.73 g, 9.4 mmol) in CH₂Cl₂ (9 mL) was successively added DIPEA (4 mL, 23.5 mmol) and MOMCl (3.6 mL, 47 mmol) dropwise at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 h. The resulting mixture was quenched with water, extracted with CH₂Cl₂ (3x), washed with brine and dried over MgSO₄. The solvent was removed by rotary evaporation to the crude product **194** (4.02 mg, 97%) as clear oil.

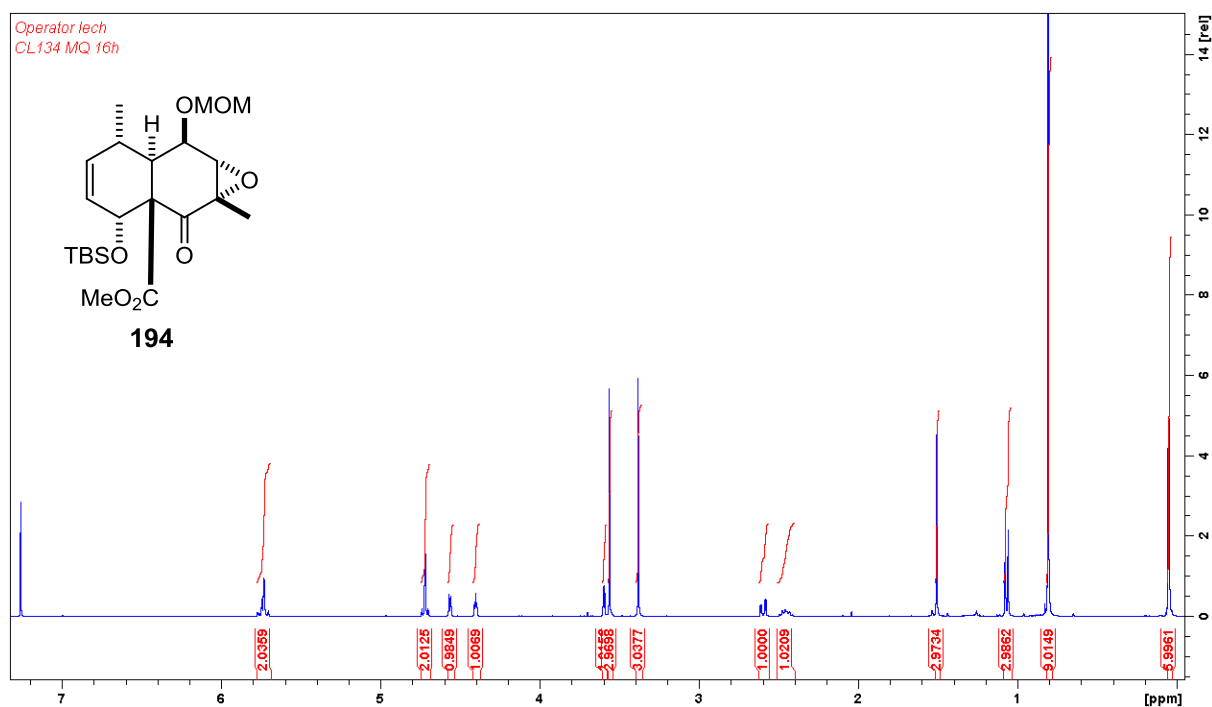
¹H NMR (400 MHz, CDCl₃): δ (ppm) 5.73 (m, 2H), 4.72 (m, 2H), 4.56 (d, *J* = 4.4 Hz, 1H), 4.40 (m, 1H), 3.59 (d, *J* = 3.2 Hz, 1H), 3.56 (s, 3H), 3.38 (s, 3H), 2.59 (dd, *J* = 10.8, 3.1 Hz, 1H), 2.45 (m, 1H), 1.51 (s, 3H), 1.07 (d, *J* = 6.9 Hz, 3H), 0.81 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 200.0, 169.8, 136.0, 125.5, 98.1, 72.3, 66.3, 60.6, 59.3, 59.2, 55.4, 51.8, 37.8, 29.1, 25.6, 18.4, 16.3, -3.7, -5.3 ppm.

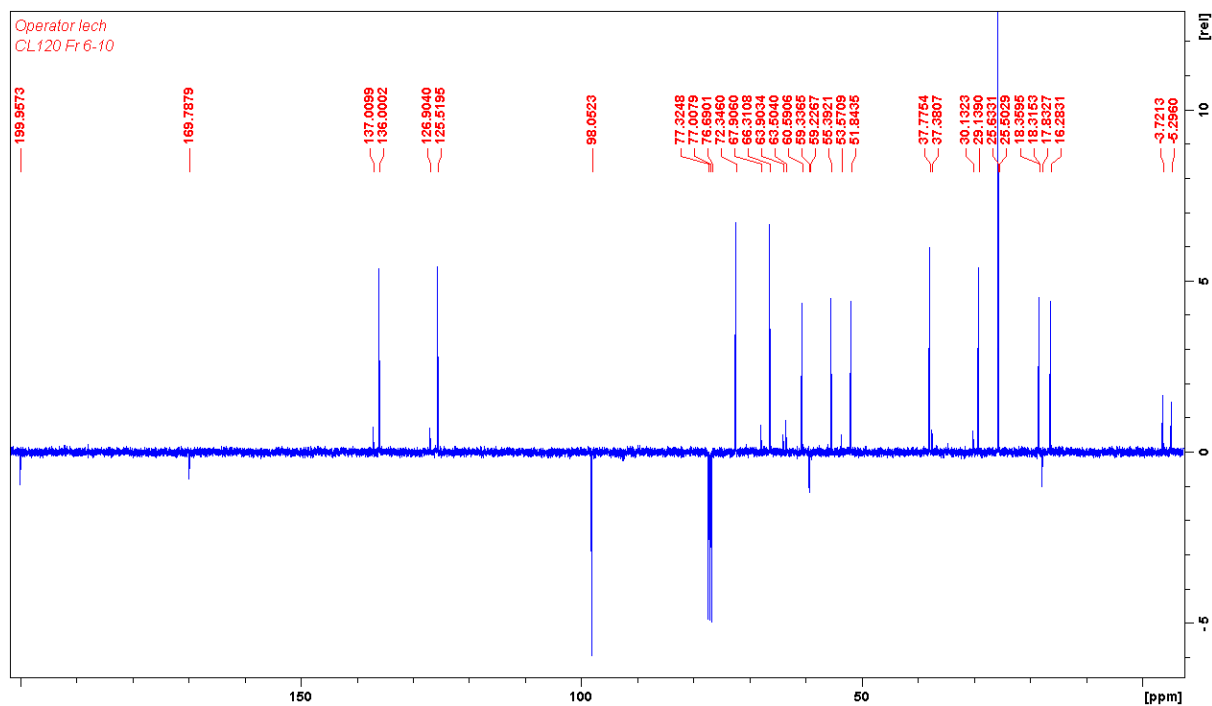
IR: 2951, 2929, 2855, 2373, 1748, 1719, 1066, 1045, 724, 630 cm⁻¹

HRMS: calculated for C₂₂H₃₆O₇SiNa⁺: 463.2123; found: 463.2113

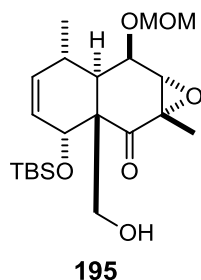
¹H NMR



¹³C NMR



Primary alcohol **195**



To a solution of **194** (1.0 g, 2.27 mmol) in CH_2Cl_2 (9 mL) was added DIBAL (4.54 mL, 1.5 M in toluene, 6.81 mmol) dropwise at $-78\text{ }^\circ\text{C}$ under an argon atmosphere. The reaction mixture was stirred at $-78\text{ }^\circ\text{C}$ for 1 h and quenched with MeOH. After 15 min the resulting mixture was warmed to room temperature, diluted with water and aq. Na,K- tartrate, extracted with diethyl ether (2x) and CH_2Cl_2 (1x), washed with brine and dried over MgSO_4 . The solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 3:1) to give **195** (880 mg, 95%) as a white solid.

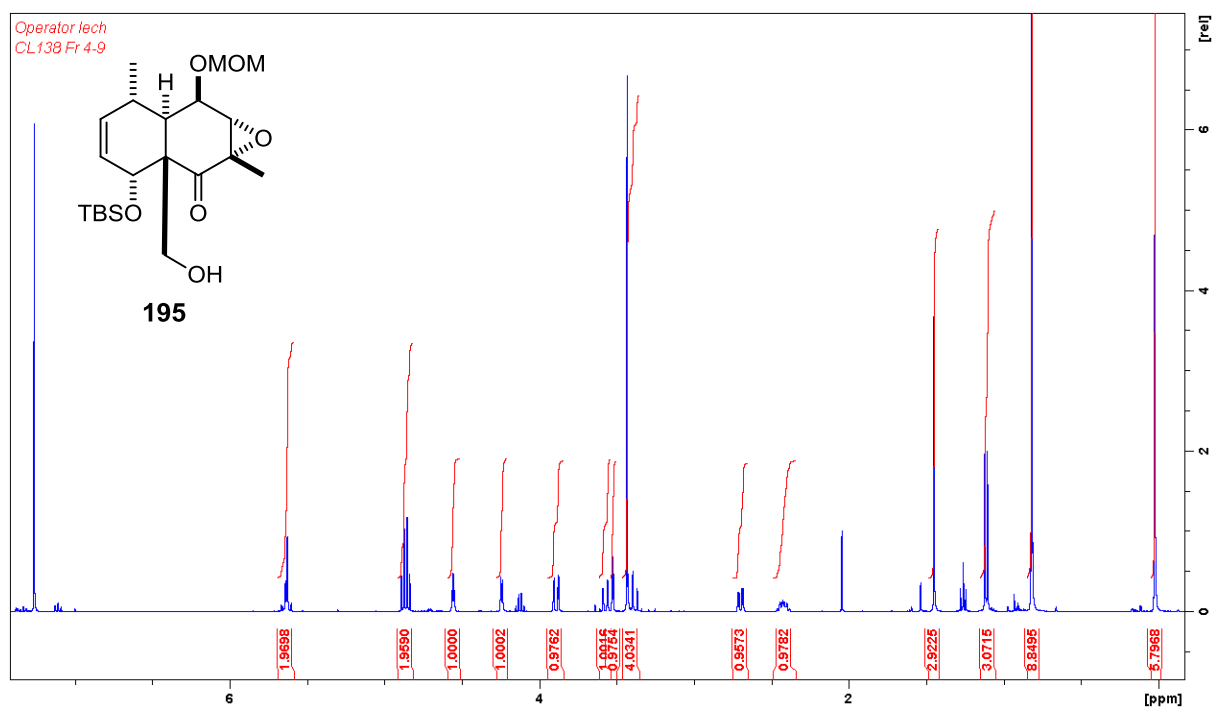
^1H NMR (400 MHz, CDCl_3): δ (ppm) 5.64 (m, 2H), 4.88 (d, $J = 7.1$ Hz, 1H), 4.84 (d, $J = 7.1$ Hz, 1H), 4.56 (m, 1H), 4.24 (m, 1H), 3.89 (dd, $J = 12.1, 2.0$ Hz, 1H), 3.57 (dd, $J = 11.5, 2.0$ Hz, 1H), 3.53 (d, $J = 3.0$ Hz, 1H), 3.43 (s, 3H), 3.40 (m, 1H), 2.70 (dd, $J = 11.1, 3.5$ Hz, 1H), 2.42 (m, 1H), 1.45 (s, 3H), 1.11 (d, $J = 6.9$ Hz, 1H), 0.82 (s, 9H), 0.02 (s, 3H), 0.02 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 206.5, 136.1, 126.3, 97.7, 72.7, 67.9, 64.7, 60.4, 60.0, 56.1, 55.4, 36.4, 28.8, 25.6, 18.2, 17.8, 15.7, -3.8, -5.2$ ppm.

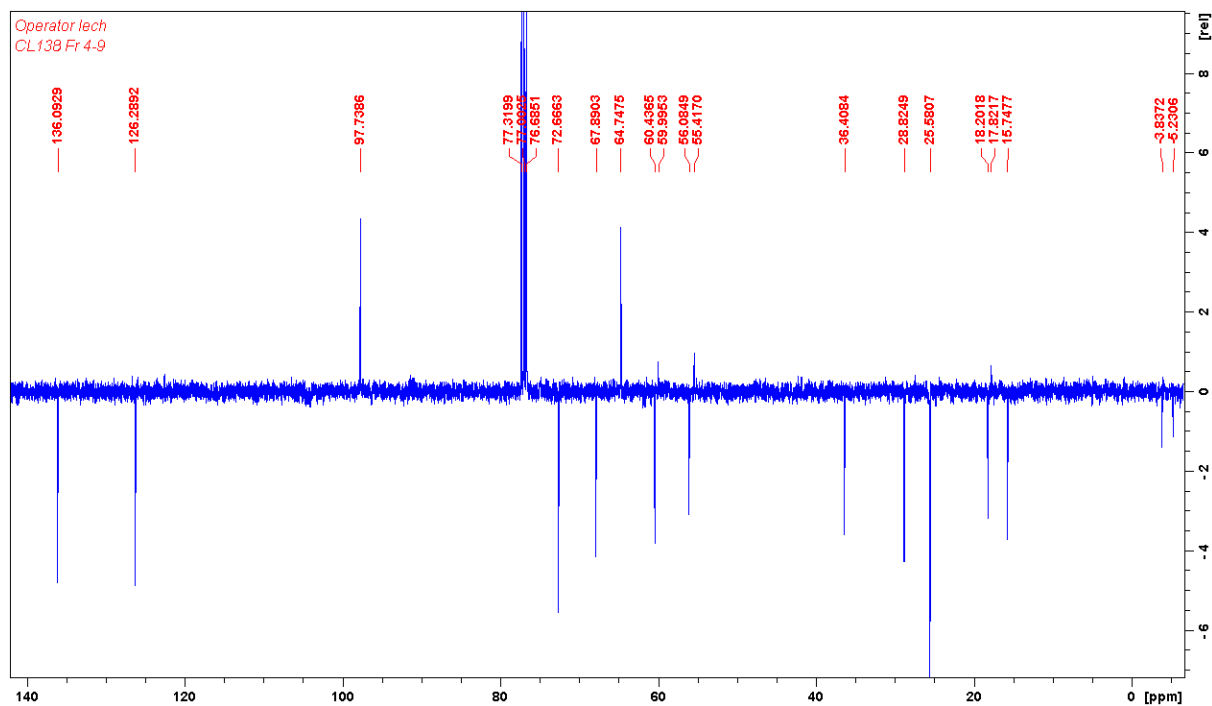
IR: 3469, 2930, 2856, 2364, 1713, 1250, 1077, 1032, 764, 630 cm^{-1}

HRMS: calculated for $\text{C}_{21}\text{H}_{36}\text{O}_6\text{SiNa}^+$: 435.2174; found: 435.2173

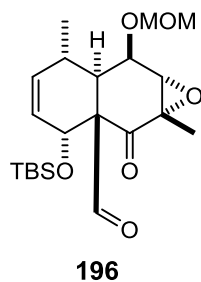
¹H NMR



¹³C NMR



Aldehyde **196**



To a solution of **195** (880 mg, 2.13 mmol) in EtOAc (21 mL) was added IBX (1.79 g, 6.40 mmol). The reaction mixture was stirred under reflux for 10 h. The resulting mixture was cooled to room temperature and filtered through a pad of Celite. The Celite was washed thoroughly with diethyl ether, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc, 3:1) to give **196** (701 mg, 80%) as a white solid.

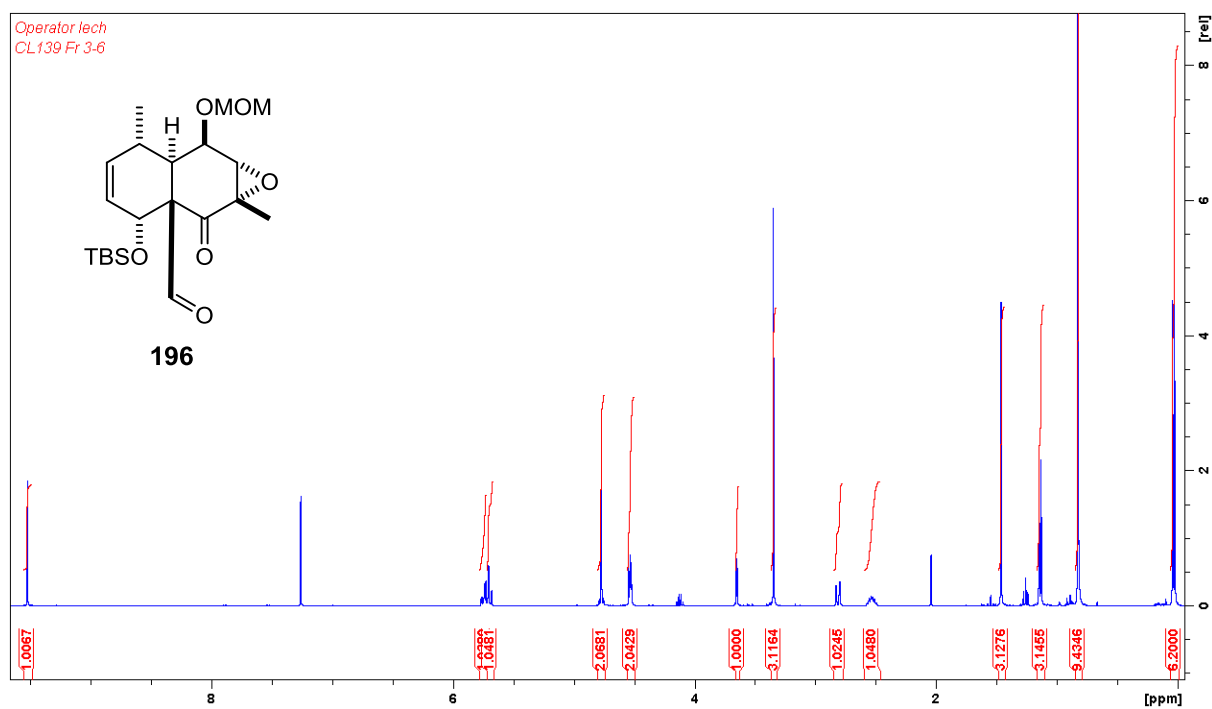
¹H NMR (400 MHz, CDCl₃): δ (ppm) 9.52 (s, 1H), 5.75 (ddd, *J* = 9.9, 5.1, 2.1 Hz, 1H), 5.69 (dd, *J* = 9.9, 1.9 Hz, 1H), 4.77 (m, 2H), 4.53 (m, 2H), 3.65 (d, *J* = 3.4 Hz, 1H), 3.35 (s, 3H), 2.81 (dd, *J* = 11.2, 2.4 Hz, 1H), 2.53 (m, 1H), 1.46 (s, 3H), 1.14 (d, *J* = 6.9 Hz, 3H), 0.82 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 200.1, 197.0, 136.0, 126.4, 97.4, 72.6, 67.2, 67.1, 61.2, 60.1, 55.7, 37.8, 29.3, 35.5, 18.9, 17.8, 15.9, -3.9, -5.3 ppm.

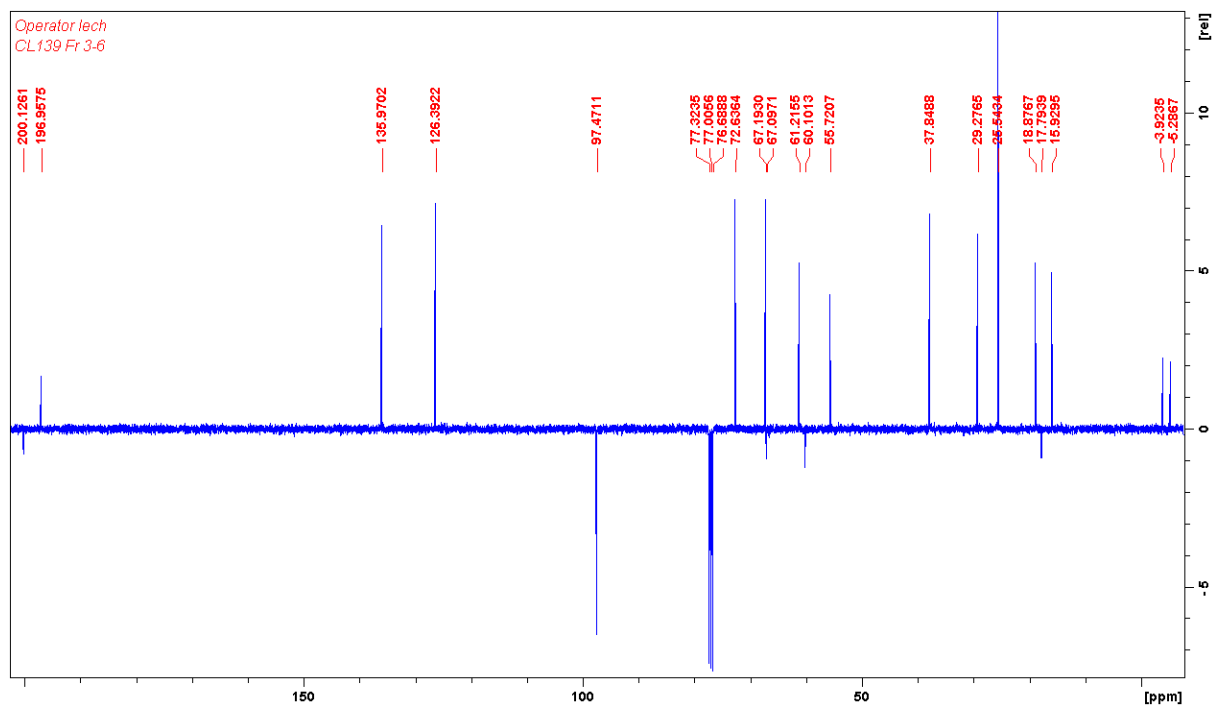
IR: 2951, 2930, 2855, 2364, 1725, 1692, 1253, 1072, 1042, 838 cm⁻¹

HRMS: calculated for C₂₁H₃₄O₆SiNa⁺: 433.2017; found: 433.2011

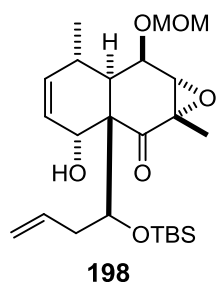
¹H NMR



¹³C NMR



Homoallylic OTBS ether **198**



To a solution of **196** (500 mg, 1.22 mmol) and AllylSnBu_3 (0.4 mL, 1.23 mmol) in CH_2Cl_2 (12 mL) was added $\text{BF}_3 \cdot \text{OEt}_2$ (190 μL , 0.73 mmol) at -78°C under an argon atmosphere. After stirring at -78°C for 1 h the reaction mixture was allowed to warm up slowly to 0°C . The resulting solution was quenched with aq. NaHCO_3 , extracted with CH_2Cl_2 (3x), washed with brine and dried over MgSO_4 . The solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/ EtOAc , 3:1) to give **198** (265 mg, 48%) of as clear oil.

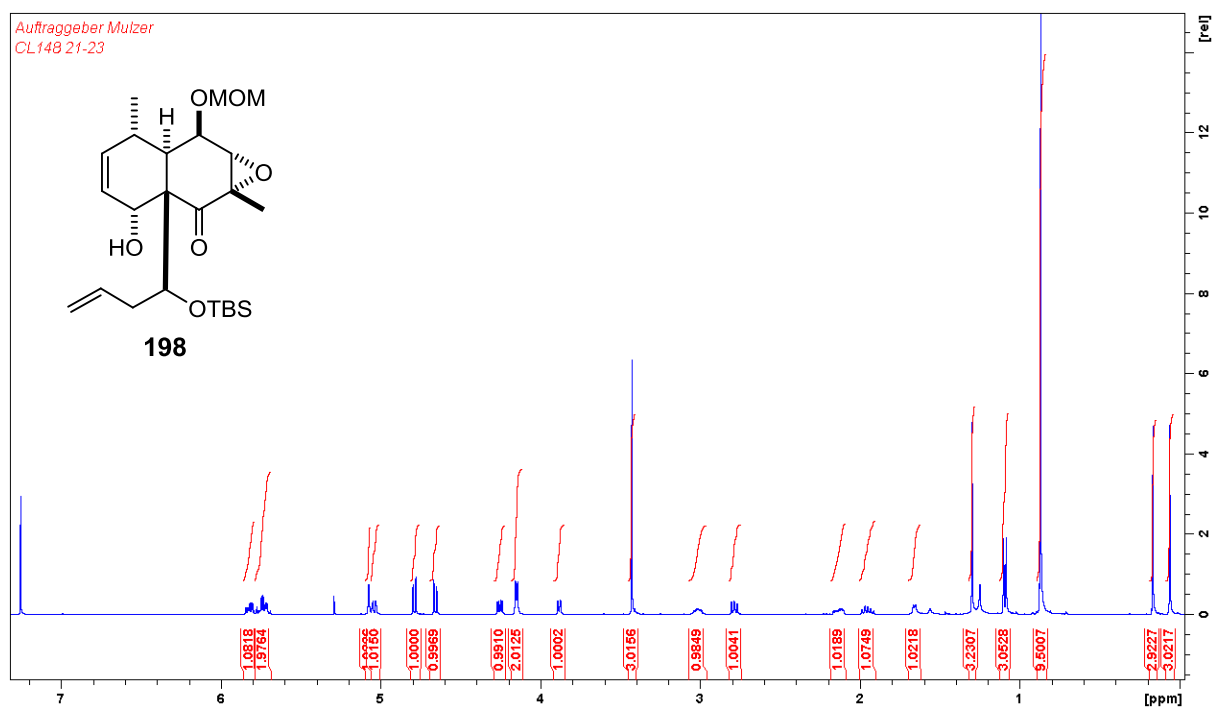
^1H NMR (400 MHz, CDCl_3): δ (ppm) 5.83 (ddd, $J = 9.7, 5.7, 2.1$ Hz, 1H), 5.74 (m, 2H), 5.08 (s, 1H), 5.05 (m, 1H), 4.79 (d, $J = 7.1$ Hz, 1H), 4.66 (d, $J = 7.1$ Hz, 1H), 4.26 (dd, $J = 8.0, 4.2$ Hz, 1H), 4.16 (d, $J = 5.7$ Hz, 1H), 3.89 (dd, $J = 6.1, 1.1$ Hz, 1H), 3.44 (s, 3H), 3.02 (m, 1H), 2.79 (dd, $J = 8.6, 6.2$ Hz, 1H), 2.14 (m, 1H), 1.96 (m, 1H), 1.60 (s, 1H), 1.31 (s, 3H), 1.10 (d, $J = 7.0$ Hz, 3H), 0.88 (s, 9H), 0.17 (s, 3H), 0.07 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 210.7, 137.0, 133.9, 125.6, 118.0, 97.0, 81.0, 78.9, 76.7, 75.6, 62.2, 56.1, 55.4, 45.6, 37.7, 28.5, 19.5, 17.0, -4.0, -4.7$ ppm.

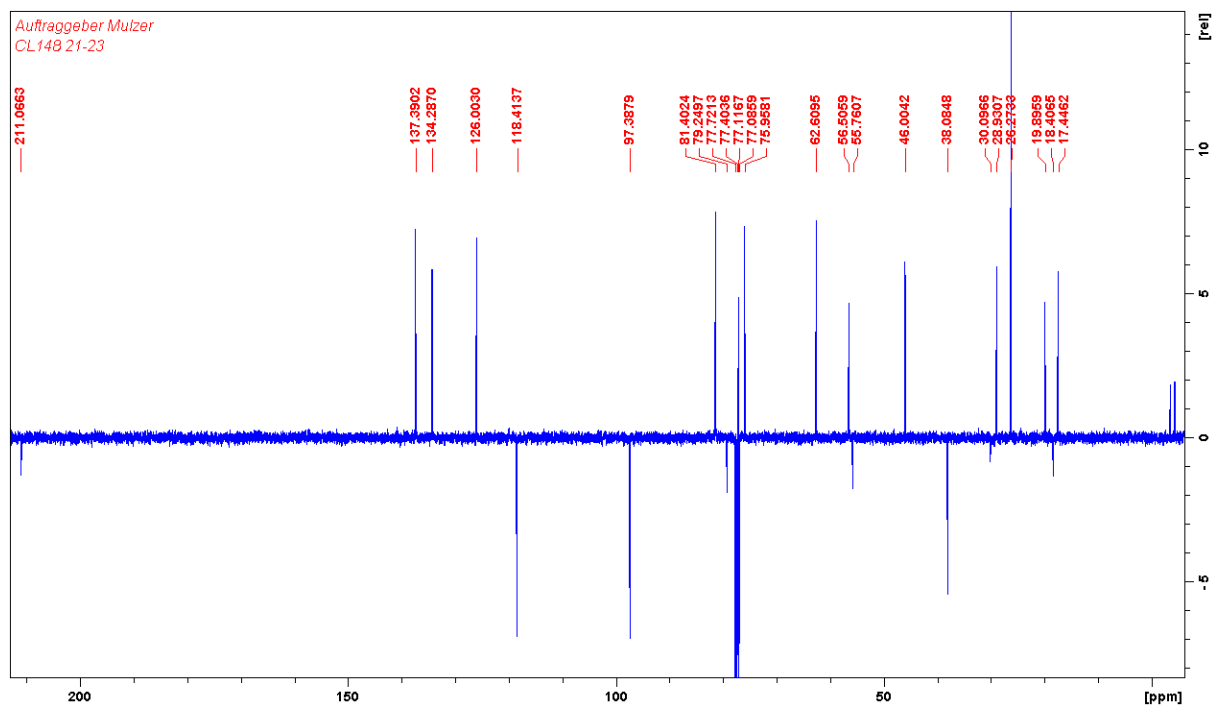
IR: 3445, 2954, 2928, 2855, 1769, 1461, 1249, 1057, 835, 775 cm^{-1}

HRMS: calculated for $\text{C}_{24}\text{H}_{40}\text{O}_6\text{SiNa}^+$: 475.2487; found: 475.2484

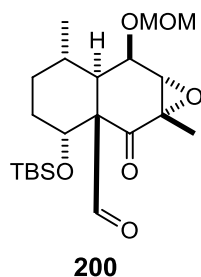
¹H NMR



¹³C NMR



Hydrated aldehyde **200**



To a solution of **196** (50 mg, 0.12 mmol) in EtOAc (1.2 mL) was added Pd/C (8 mg). The reaction mixture was stirred under hydrogen atmosphere (1 atm) for 1 h at room temperature. The resulting suspension was diluted with EtOAc and filtered through a pad of Celite. The solvent was removed by rotary evaporation to the crude product **200** (50 mg, 99%) as a white solid and was used in the next step without further purification.

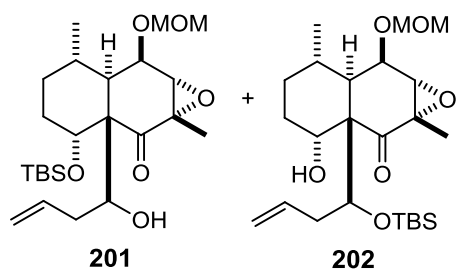
¹H NMR (400 MHz, CDCl₃): δ (ppm) 9.82 (s, 1H), 4.77 (d, *J* = 7.0 Hz, 1H), 4.74 (d, *J* = 7.0 Hz, 1H), 4.50 (m, 2H), 3.57 (d, *J* = 3.2 Hz, 1H), 3.32 (s, 3H), 2.58 (dd, *J* = 11.8, 2.2 Hz, 1H), 2.07 (m, 1H), 1.61 (m, 4H), 1.43 (s, 3H), 1.01 (d, *J* = 6.3 Hz, 3H), 0.83 (s, 9H), 0.04 (s, 3H), 0.00 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 199.6, 198.3, 97.4, 73.1, 69.6, 68.2, 60.6, 59.5, 55.7, 39.2, 29.7, 29.2, 27.6, 25.7, 19.6, 18.0, 16.0, -4.5, -5.3 ppm.

IR: 2931, 2857, 2360, 1732, 1698, 1463, 1254, 1042, 1022, 835 cm⁻¹

HRMS: calculated for C₂₁H₃₆O₆SiNa⁺: 435.2174; found: 435.2188

Homoallylic alcohol **201** and homoallylic OTBS **202**



To a solution of zinc chloride (0.19 mL, 1 M in diethyl ether 0.19 mmol) in THF (0.5 mL) was added allylmagnesium chloride at $-78\text{ }^{\circ}\text{C}$. The suspension was stirred for 5 min and **200** (50 mg, 0.11 mmol) solved in THF (0.6 mL) was added via syringe. After stirring for 1 h at $-78\text{ }^{\circ}\text{C}$ the reaction mixture was allowed to warm up to room temperature. The mixture was stirred for 1 h at room temperature, quenched with ammonium chloride, extracted with diethyl ether (3x), washed with brine, dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc, 6:1) to give **201** (11 mg, 20%) and **202** (10 mg, 20%).

Homoallyl alcohol **201**:

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ (ppm) 5.82 (m, 1H), 5.03 (m, 2H), 4.88 (d, $J = 7.0$ Hz, 1H), 4.83 (d, $J = 7.0$ Hz, 1H), 4.51 (m, 2H), 3.76 (ddd, $J = 11.0, 5.5, 1.5$ Hz, 1H), 3.49 (d, $J = 2.5$ Hz, 1H), 3.42 (s, 3H), 3.72 (dd, $J = 4.2, 1.2$ Hz, 1H), 2.54 (ddt, $J = 14.1, 6.8, 1.4$ Hz, 1H), 2.46 (dd, $J = 11.8, 3.5$ Hz, 1H), 2.21 (m, 1H), 1.95 (m, 1H), 1.86 (m, 1H), 1.58 (m, 1H), 1.52 (m, 2H), 1.40 (s, 3H), 0.93 (d, $J = 6.3$ Hz, 1H), 0.83 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H).

$^{13}\text{C NMR}$ (100 MHz, CDCl_3): $\delta = 203.9, 136.8, 116.4, 97.7, 73.7, 72.3, 67.5, 59.6, 58.8, 57.8, 56.0, 37.9, 35.6, 28.4, 28.4, 27.6, 25.8, 20.5, 18.0, 16.4, -4.2, -5.4$ ppm.

HRMS: calculated for $\text{C}_{24}\text{H}_{42}\text{O}_6\text{SiNa}^+$: 477.2643; found: 477.2647

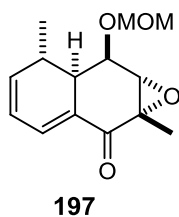
Homoallyl OTBS **202**

¹H NMR (400 MHz, CDCl₃): δ (ppm) 5.80 (m, 1H), 5.08 (m, 2H), 4.78 (d, *J* = 7.0 Hz, 1H), 4.67 (d, *J* = 7.0 Hz, 1H), 4.54 (dd, *J* = 8.2, 3.4 Hz, 1H), 4.17 (dd, *J* = 5.5, 1.5 Hz, 1H), 4.10 (d, *J* = 3.5 Hz, 1H), 3.75 (dd, *J* = 5.5, 1.2 Hz, 1H), 3.42 (s, 3H), 2.40 (dd, *J* = 10.9, 5.4 Hz, 1H), 2.25 (m, 1H), 2.12 (m, 1H), 1.95 (m, 1H), 1.64 (m, 2H), 1.57 (d, *J* = 5.5 Hz, 1H), 1.44 (m, 2H), 1.26 (s, 3H), 0.95 (d, *J* = 6.3 Hz, 1H), 0.90 (s, 9H), 0.18 (s, 3H), 0.07 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 210.4, 133.9, 118.1, 97.6, 80.1, 78.8, 78.4, 75.1, 65.6, 55.8, 55.8, 47.5, 37.3, 29.8, 27.9, 27.3, 26.1, 19.9, 18.3, 17.1, -4.2, -4.8 ppm.

HRMS: calculated for C₂₄H₄₂O₆SiNa⁺: 477.2643; found: 477.2644

Dienone **197**



To a solution of **195** (50 mg, 0.12 mmol) in THF (1.2 mL) was added NaH (10 mg, 60% in mineral oil, 0.24 mmol) at 0 °C. After stirring at room temperature for 3 h, the resulting solution was quenched with aq. ammonium chloride, extracted with EtOAc (3x), washed with brine and dried over MgSO₄. The solvent was removed by rotary evaporation to the crude product **197** (27 mg, 91%) as a clear liquid and was used in the next step without further purification.

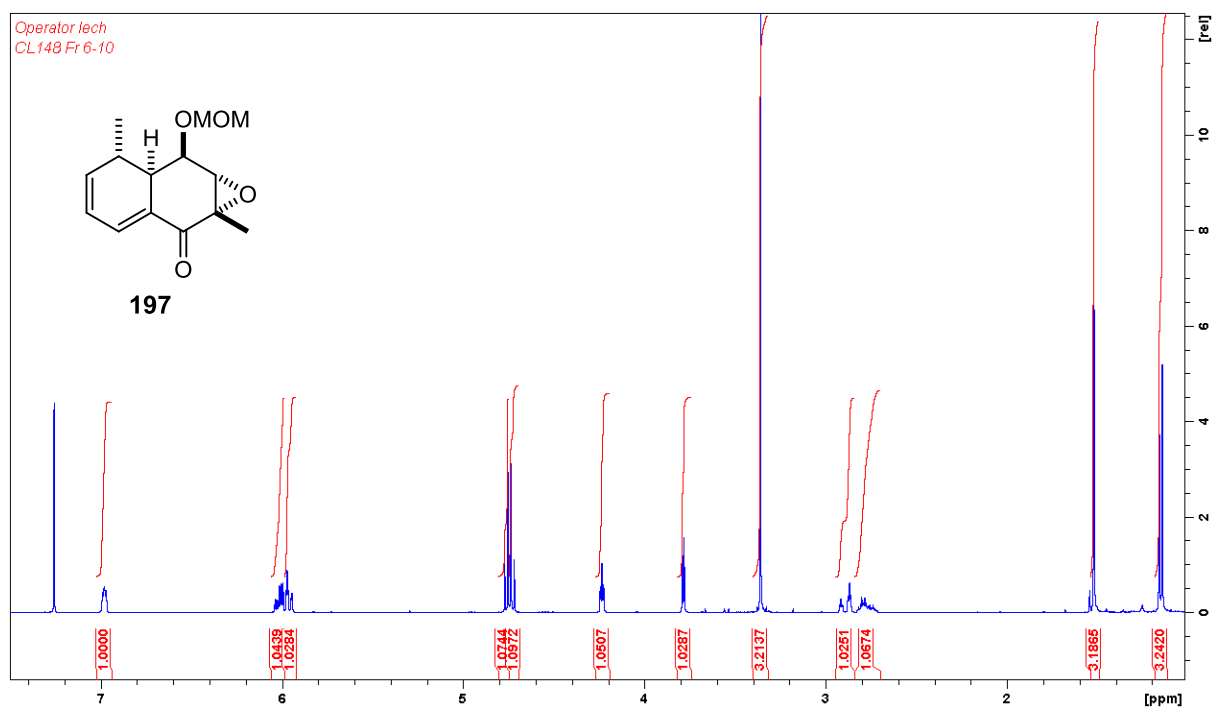
¹H NMR (400 MHz, CDCl₃): δ (ppm) 6.98 (m, 1H), 6.02 (ddd, *J* = 9.5, 5.3, 2.8 Hz, 1H), 5.96 (m, 1H), 4.76 (d, *J* = 7.0 Hz, 1H), 4.73 (d, *J* = 7.0 Hz, 1H), 4.24 (m, 1H), 3.79 (d, *J* = 4.0 Hz, 1H), 3.36 (s, 3H), 2.89 (dtd, *J* = 18.3, 3.0, 1.0 Hz, 1H), 2.77 (m, 1H), 1.52 (s, 3H), 1.15 (d, *J* = 6.8 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 195.2, 141.6, 131.8, 130.3, 122.8, 97.5, 72.5, 65.0, 60.1, 55.6, 42.4, 29.4, 18.4, 15.7 ppm.

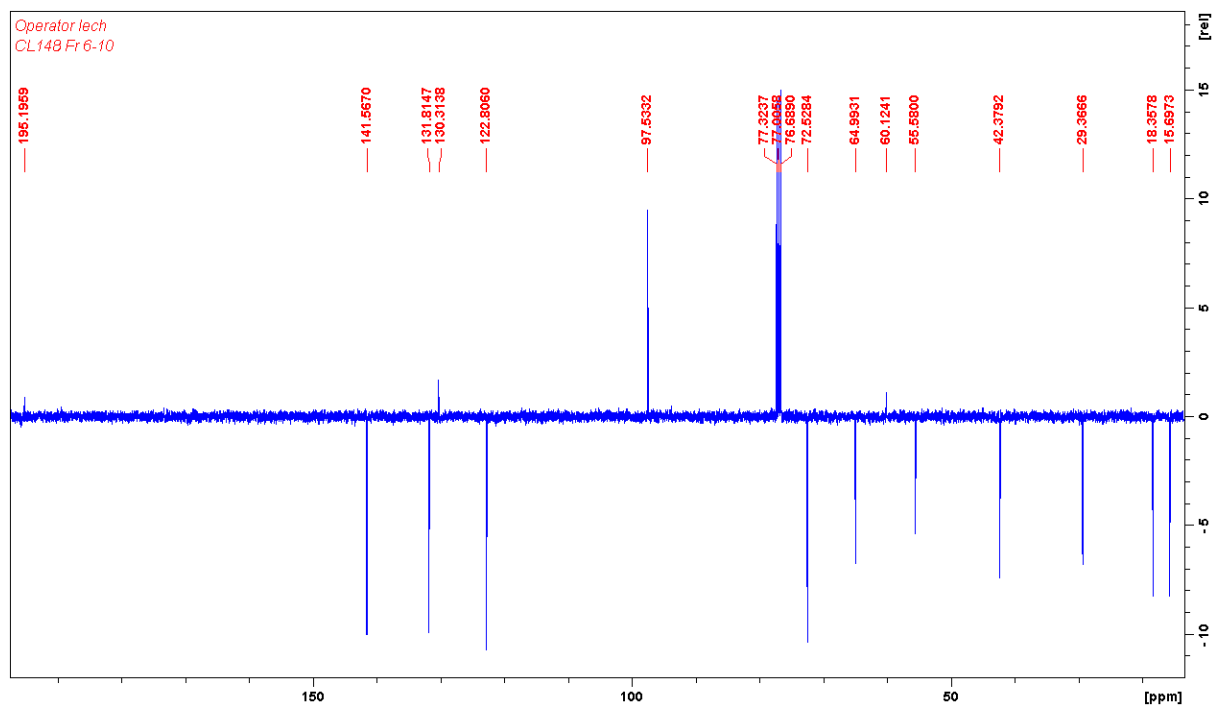
IR: 2933, 2889, 1678, 1628, 1557, 1330, 1149, 1023, 920, 852 cm⁻¹

HRMS: calculated for C₁₄H₁₈O₄SiNa⁺: 273.1098; found: 273.1099

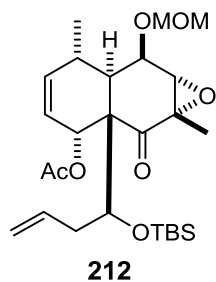
¹H NMR



¹³C NMR



Allylic acetate **212**



To a solution of **198** (20 mg, 0.044 mmol) in CH_2Cl_2 (0.4 mL) was added DMAP (0.5 mg, 0.004 mmol), acetic anhydride (42 μL , 0.44 mmol) and triethylamine (3 μL , 0.022 mmol). The reaction mixture was stirred for 18 h at room temperature. The resulting solution was quenched with water, extracted with EtOAc (3x), washed with brine and dried over MgSO_4 . The solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 6:1) to give **212** (12 mg, 55%) as a clear liquid.

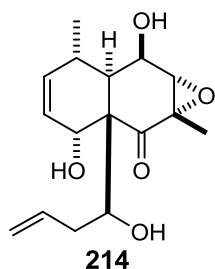
$^1\text{H NMR}$ (400 MHz, CDCl_3): δ (ppm) 5.83 (ddd, $J = 9.8, 5.8, 2.0$ Hz, 1H), 5.73 (m, 2H), 5.18 (d, $J = 1.2$ Hz, 1H), 5.05 (m, 2H), 4.93 (d, $J = 6.8$ Hz, 1H), 4.68 (d, $J = 7.0$ Hz, 1H), 4.25 (dd, $J = 8.5, 4.0$ Hz, 1H), 4.15 (d, $J = 5.8$ Hz, 1H), 3.85 (dd, $J = 6.3, 1.0$ Hz, 1H), 3.44 (s, 3H), 3.05 (m, 1H), 2.71 (dd, $J = 8.5, 6.3$ Hz, 1H), 2.11 (m, 1H), 2.01 (s, 3H), 1.95 (m, 1H), 1.89 (s, 3H), 1.09 (d, $J = 7.0$ Hz, 3H), 0.87 (s, 9H), 0.18 (s, 3H), 0.07 (s, 3H).

$^{13}\text{C NMR}$ (100 MHz, CDCl_3): $\delta = 208.5, 169.5, 137.1, 133.8, 125.5, 118.0, 96.3, 80.0, 76.5, 75.5, 73.0, 62.1, 56.4, 55.0, 45.4, 37.6, 28.5, 25.5, 20.9, 19.3, 18.0, 16.9, -3.8, -4.9$ ppm.

IR: 2924, 2852, 2364, 1771, 1744, 1644, 1224, 1028, 836, 722 cm^{-1}

HRMS: calculated for $\text{C}_{26}\text{H}_{42}\text{O}_7\text{SiNa}^+$: 517.2592; found: 517.2595

Homoallylic alcohol **214**



To a solution of **198** (77 mg, 0.19 mmol) in MeOH (1.9 mL) was added sulfuric acid (30 μ L, 0.56 mmol). The reaction mixture was stirred for 4 h at room temperature. The resulting solution was quenched with aq. NaHCO₃, extracted with diethyl ether (3x), washed with brine and dried over MgSO₄. The solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 1:1) to give **214** (38 mg, 68%) as clear oil.

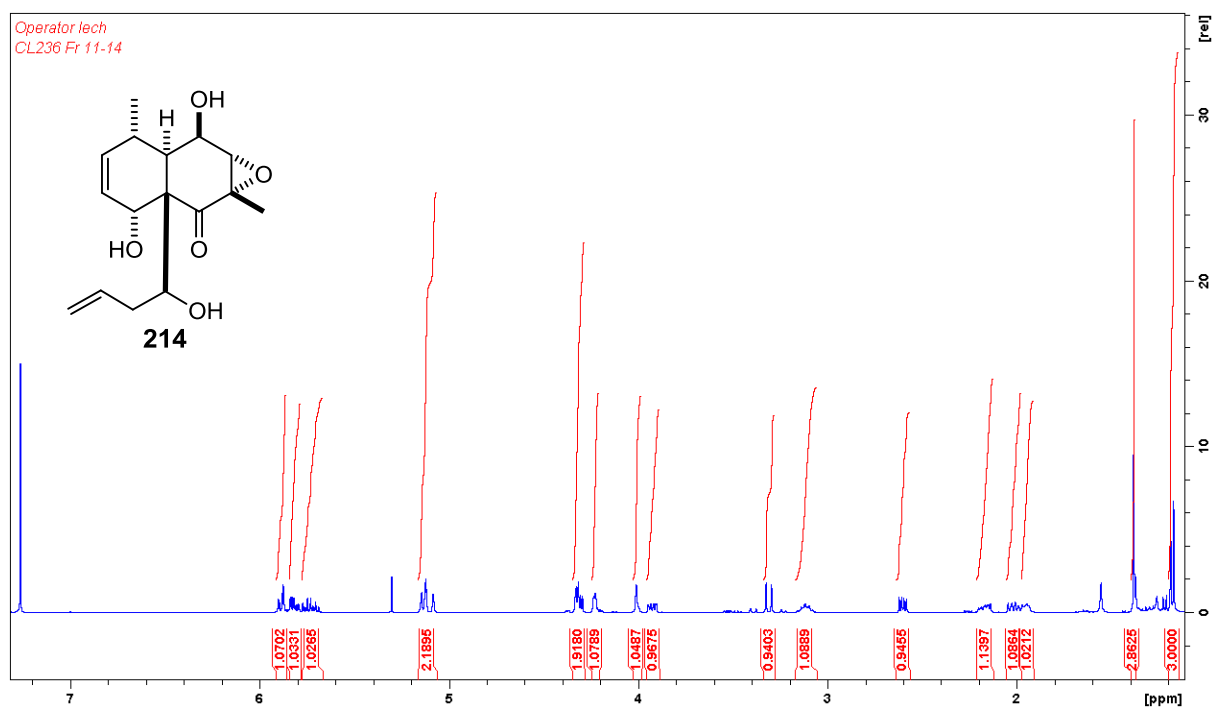
¹H NMR (400 MHz, CDCl₃): δ (ppm) 5.89 (dd, J = 10.0, 2.6 Hz, 1H), 5.81 (m, 1H), 5.73 (m, 1H), 5.12 (m, 2H), 4.31 (m, 2H), 4.00 (m, 1H), 3.92 (ddd, J = 11.4, 5.4, 1.5 Hz, 1H), 3.31 (d, J = 11.4 Hz, 1H), 3.12 (m, 1H), 2.60 (dd, J = 9.9, 5.5 Hz, 1H), 2.17 (m, 1H), 2.02 (m, 1H), 1.95 (m, 1H), 1.38 (s, 3H), 1.18 (d, J = 7.0 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 215.7, 139.2, 132.7, 123.0, 118.9, 83.3, 76.5, 70.9, 62.8, 56.1, 53.4, 45.7, 37.5, 29.2, 19.2, 16.9, ppm.

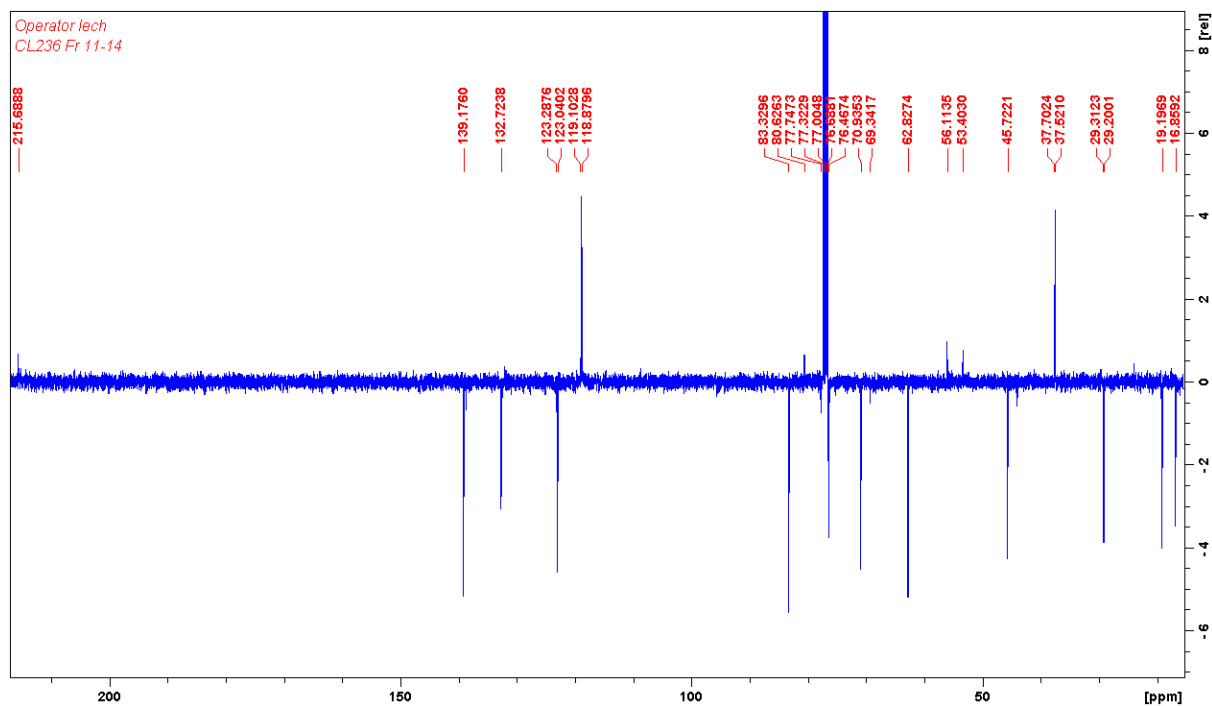
IR: 3375, 2923, 2356, 1752, 1642, 1415, 1378, 1224, 1054, 1021 cm⁻¹

HRMS: calculated for C₁₆H₂₂O₅SiNa⁺: 317.1360; found: 317.1362

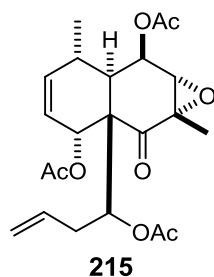
¹H NMR



¹³C NMR



Triacetate **216**



To a solution of **215** (33 mg, 0.13 mmol) in CH₂Cl₂ (1.1 mL) was added DMAP (4.1 mg, 0.03 mmol), acetic anhydride (0.16 mL, 1.68 mmol) and triethylamine (18 μ L, 0.13 mmol). The reaction mixture was stirred for 24 h at room temperature. The resulting solution was quenched with water, extracted with EtOAc (3x), washed with brine and dried over MgSO₄. The solvent was removed by rotary evaporation to the crude product **216** (56 mg, 99%) as a clear liquid.

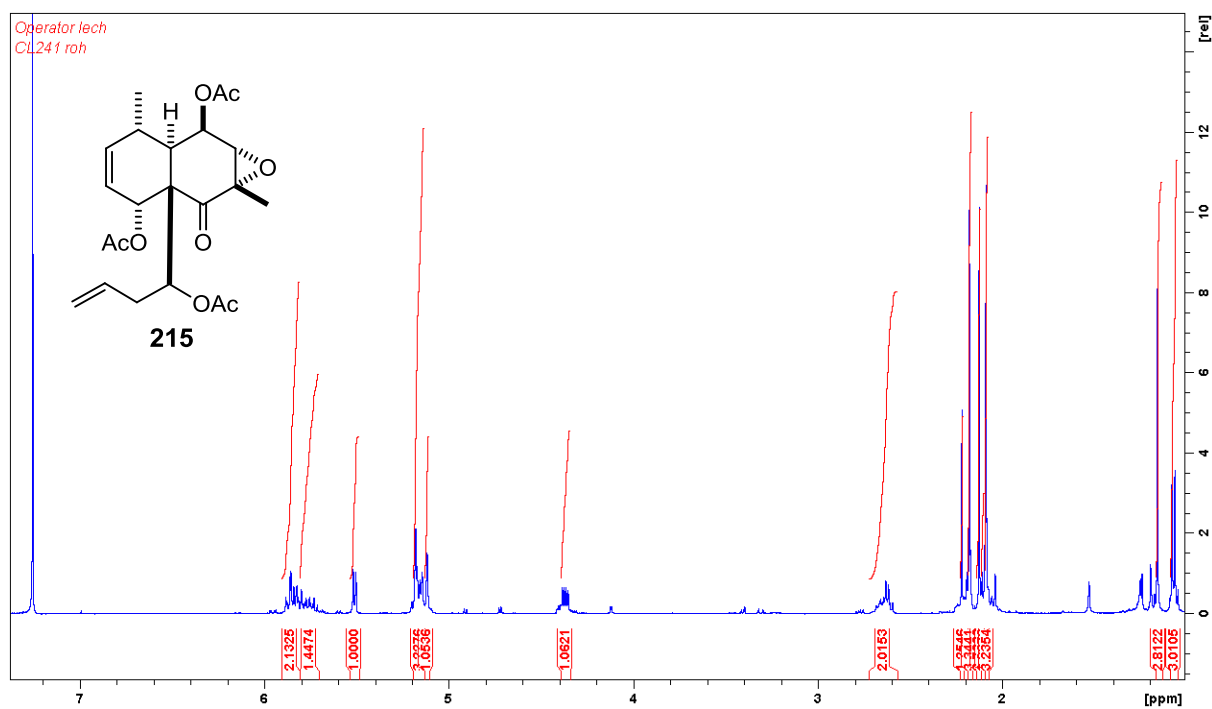
¹H NMR (400 MHz, CDCl₃): δ (ppm) 5.85 (m, 2H), 5.81 (m, 1H), 5.75 (m, 1H), 5.51 (d, J = 5.6 Hz, 1H), 5.16 (m, 3H), 5.12 (m, 1H), 4.37 (dd, J = 8.3, 4.2 Hz, 1H), 2.64 (m, 2H), 2.22 (s, 1H), 2.18 (s, 3H), 2.12 (s, 3H), 2.10 (m, 1H), 2.09 (s, 3H), 1.16 (s, 3H), 1.07 (d, J = 6.6 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 207.5, 169.6, 168.6, 168.5, 139.0, 132.6, 121.5, 119.0, 79.8, 75.7, 68.2, 63.0, 52.4, 45.9, 38.0, 29.2, 21.1, 21.0, 20.9, 19.3, 16.4 ppm. One quaternary carbon atom could not be assigned.

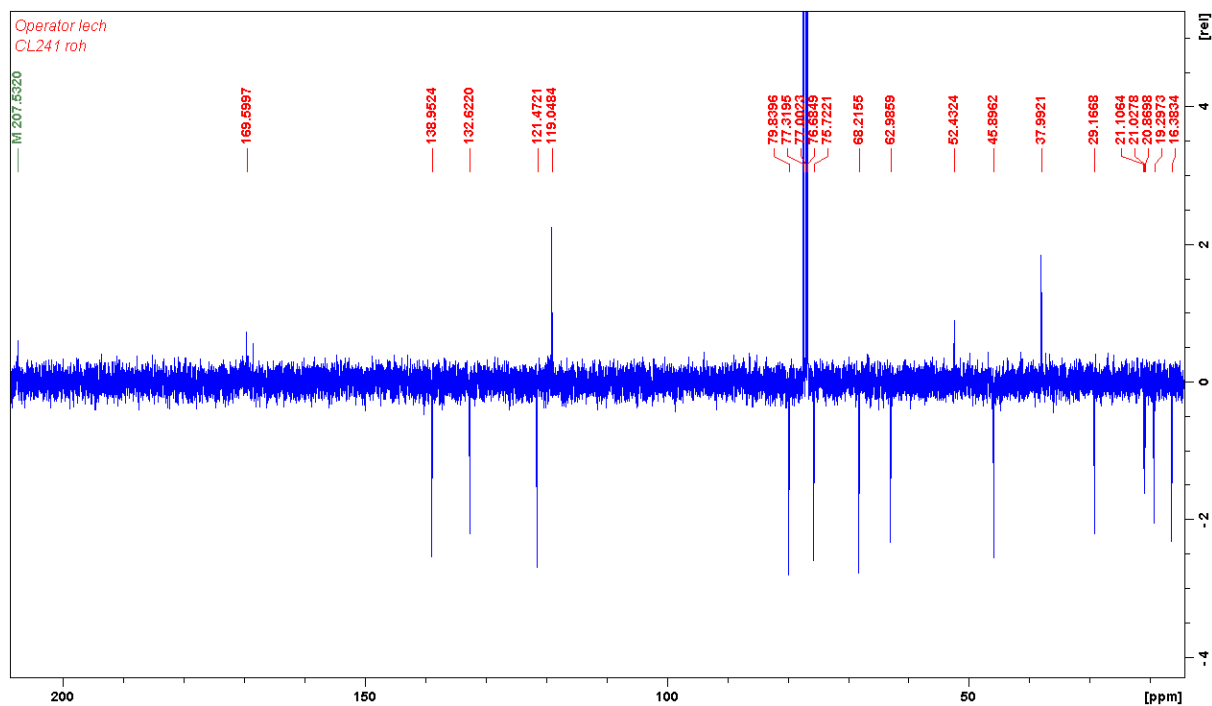
IR: 3367, 2948, 2839, 2361, 2342, 1642, 1412, 1112, 1018, 669 cm⁻¹

HRMS: calculated for C₂₂H₂₈O₈SiNa⁺: 420.1784; found: 420.1669

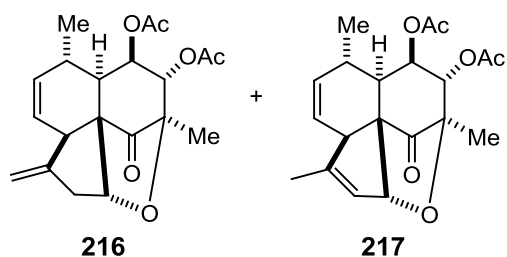
¹H NMR



¹³C NMR



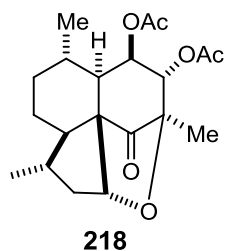
Tetracycle **216** and **217**



To a solution of **215** (56 mg, 0.13 mmol) in AcOH (3.25 mL) was added Pd(PPh₃)₄ (15 mg, 0.001 mmol) under argon atmosphere. The reaction mixture was stirred at 80 °C for 3 h. The resulting solution was diluted with water, quenched with water, extracted with diethyl ether (3x), washed with brine and dried over MgSO₄. The solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 3:1) to give **216** and **217** (35 mg, 75%) as a 1:1 mixture of double bond isomers.

HRMS: calculated for C₂₂H₂₈O₈SiNa⁺: 383.1466; found: 383.1469

Hydrogenated tetracycle **218**



To a solution of **216** and **217** (35 mg, 0.097 mmol) in EtOAc (1.1 mL) was added Pd/C (8 mg). The reaction mixture was stirred under hydrogen atmosphere (1 atm) for 6 h at room temperature. The resulting suspension was diluted with EtOAc and filtered through a pad of Celite. The solvent was removed by rotary evaporation to the crude product **218** (28 mg, 79%) as a clear liquid.

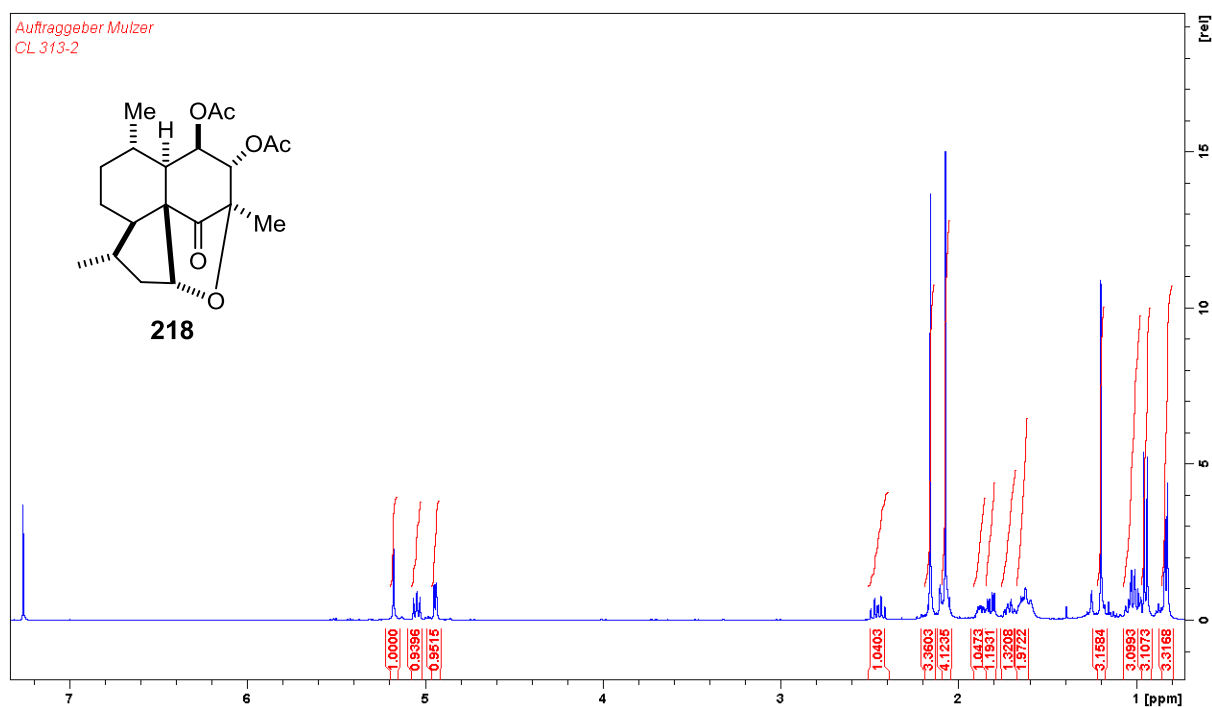
¹H NMR (400 MHz, CDCl₃): δ (ppm) 5.18 (d, *J* = 1.2 Hz, 1H), 5.05 (dd, *J* = 8.1, 6.7 Hz, 1H), 4.94 (dd, *J* = 4.8, 1.2 Hz, 1H), 2.45 (dt, *J* = 14.6, 8.6 Hz, 1H), 2.16 (s, 3H), 2.07 (s, 3H), 2.07 (m, 1H), 1.88 (m, 1H), 1.82 (dd, *J* = 10.8, 4.8 Hz, 1H), 1.71 (m, 1H), 1.64 (m, 2H), 1.20 (s, 3H), 1.02 (m, 3H), 0.95 (d, *J* = 7.2 Hz, 3H), 0.83 (d, *J* = 6.3 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 213.4, 169.6, 168.6, 80.7, 79.8, 79.5, 69.8, 60.5, 51.8, 42.0, 41.3, 38.9, 33.3, 31.0, 29.9, 22.6, 21.0, 20.9, 19.5, 16.8 ppm.

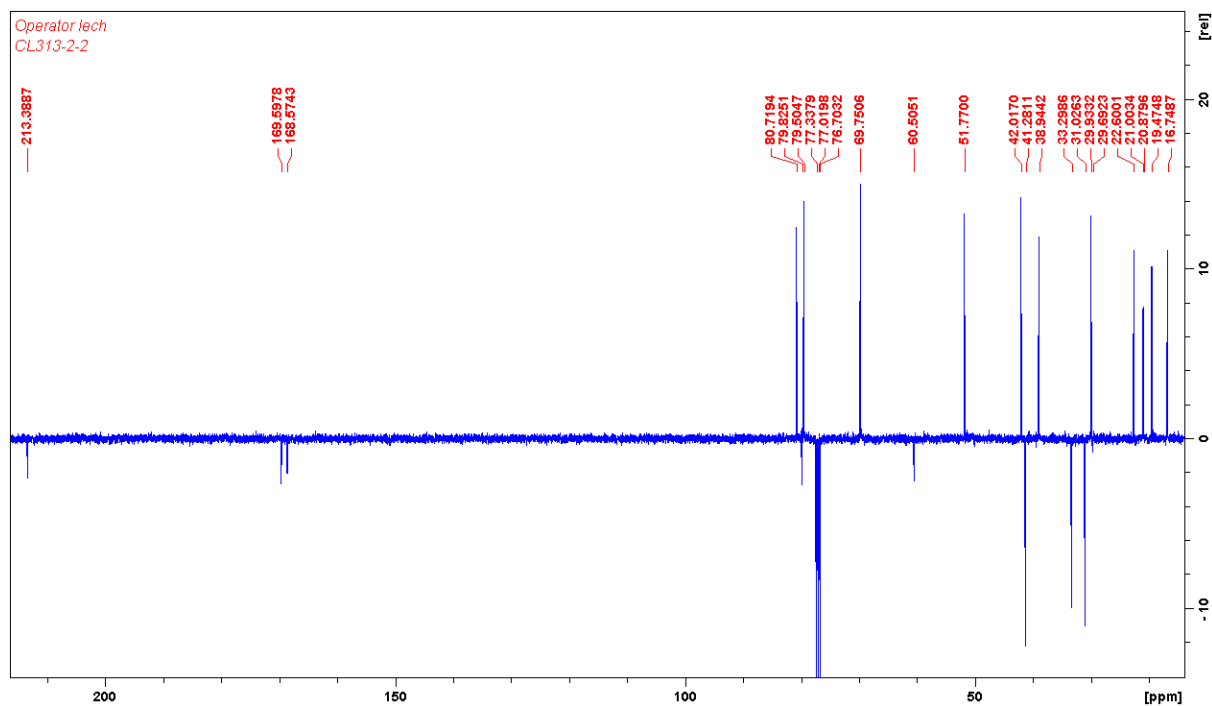
IR: 2927, 1743, 1484, 1449, 1373, 1234, 1153, 1033, 922, 861 cm⁻¹

HRMS: calculated for C₂₂H₂₈O₈SiNa⁺: 387.1779; found: 387.1779

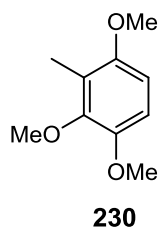
¹H NMR



¹³C NMR



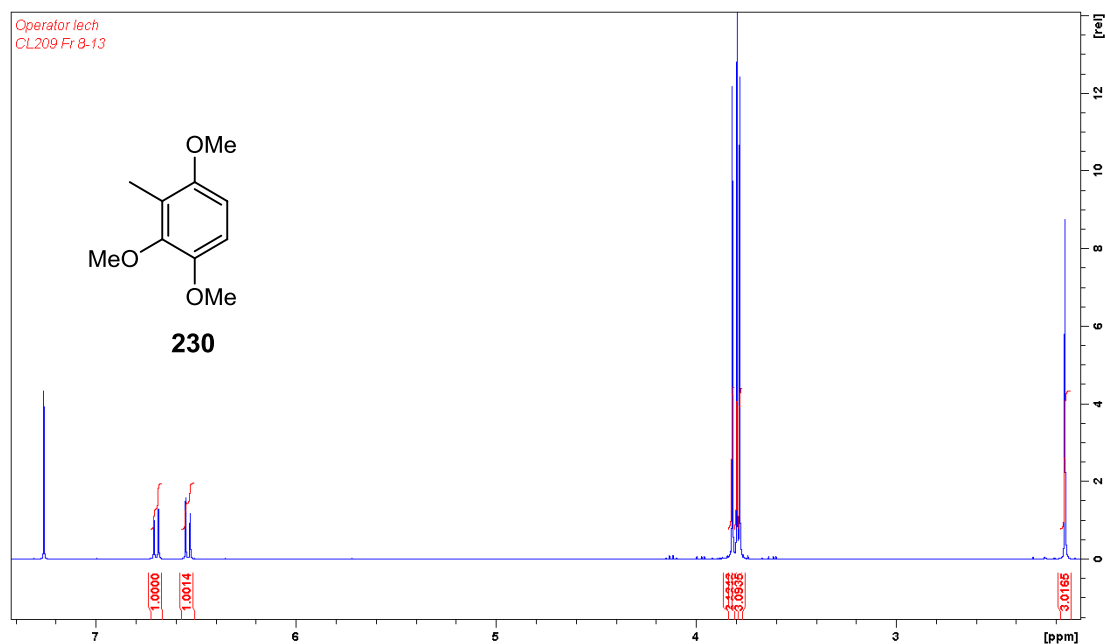
1,2,4-Trimethoxy-3-methylbenzene **230**



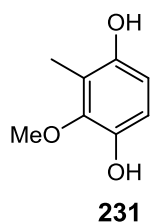
To a solution of nBuLi (11.4 mL, 2.5 M in toluene, 28.54 mmol) in THF (25 mL) was added 1,2,4-trimethoxybenzene **228** (4 g, 23.78 mmol) slowly under argon at room temperature (bubbler is required). After stirring for 1 h at room temperature, the suspension was cooled to $-78\text{ }^{\circ}\text{C}$ and methyl iodide (1.78 mL, 28.54 mmol) was added. The reaction mixture was stirred for 30 min at $-78\text{ }^{\circ}\text{C}$. The mixture was allowed to warm up slowly to room temperature. The resulting solution was quenched with aq. ammonium chloride, extracted with diethyl ether (3x), washed with brine and dried over MgSO_4 . The solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 6:1) to give **230** (3.94 g, 91%) as clear liquid.

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ (ppm) 6.70 (d, $J = 8.8$ Hz, 1H), 6.54 (d, $J = 8.8$ Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 2.16 (s, 3H).

$^1\text{H NMR}$



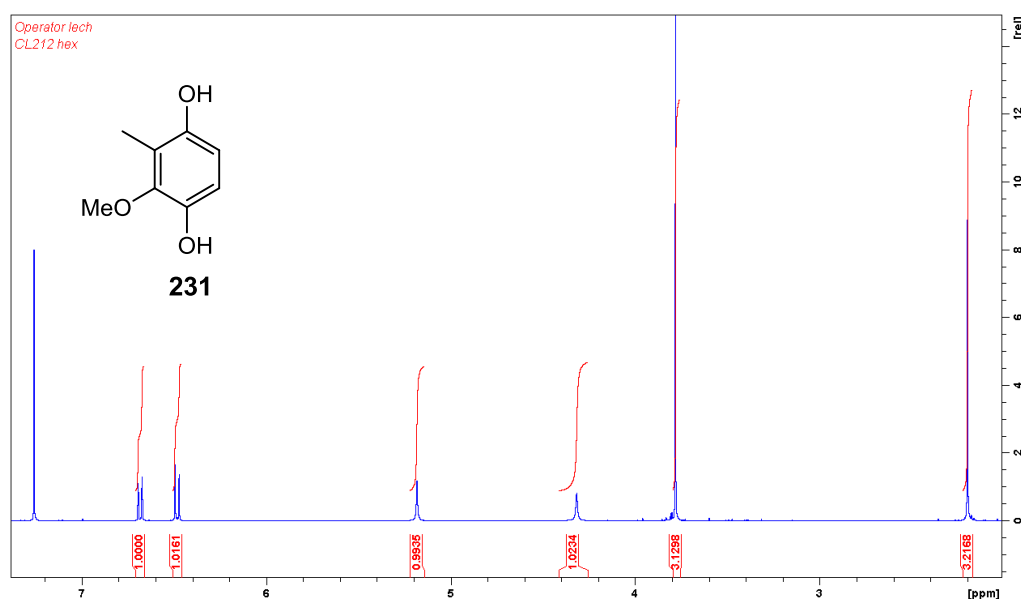
2-Methoxy-3-methylbenzene-1,4-diol **231**



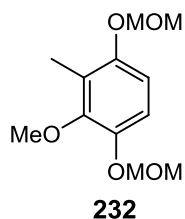
To a solution of **230** (12.58 g, 66.85 mmol) in water (25 mL) and MeOH (13 mL) was added PIDA (32.3 g, 100.3 mmol). After stirring for 16 h at room temperature, the solution was treated with aq. ammonium chloride, extracted with diethyl ether (3x) and washed with NaHCO₃. The organic layer was evaporated till approx. 100 mL. The solution was mixed with water (100 mL) and sodium hydrosulfite (46.55 g, 267 mmol) was slowly added. The reaction mixture was stirred for 1 h at room temperature. The aqueous layer was extracted with diethyl ether (3x). The combined organic layers were washed with brine, dried over MgSO₄, and the solvent was removed by rotary evaporation. The precipitate was washed with hexane to the crude product **231** (7.31 g, 71%) as a brown solid and was used in the next step without further purification.

¹H NMR (400 MHz, CDCl₃): δ (ppm) 6.68 (d, *J* = 8.5 Hz, 1H), 6.48 (d, *J* = 8.5 Hz, 1H), 5.18 (s, 1H), 4.32 (s, 1H), 3.78 (s, 3H), 2.20 (s, 3H).

¹H NMR



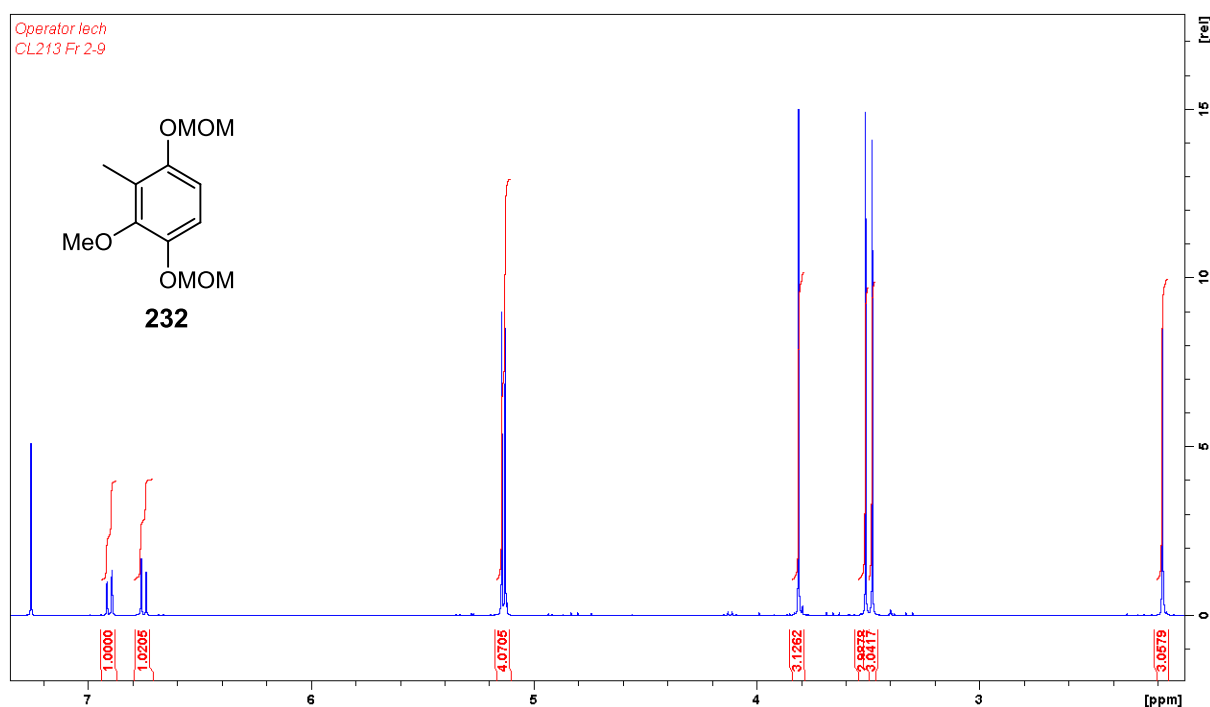
2-Methoxy-1,4-bis(methoxymethoxy)-3-methylbenzene **232**



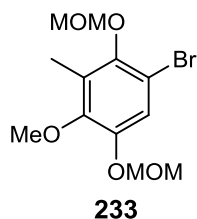
To a solution of **231** (10.38 g, 67.15 mmol) in THF (330 mL) was added NaH (9.4 g, 60% in mineral oil, 235 mmol) at 0 °C. After stirring for 1 h at room temperature, the suspension was cooled to 0 °C and MOMCl (20 mL, 269 mmol) was added. The reaction mixture was stirred for 24 h at room temperature. The suspension was quenched with water, extracted with diethyl ether (3x), washed with brine and dried over MgSO₄. The solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 4:1) to give **232** (11.06 g, 68%) as clear oil.

¹H NMR (400 MHz, CDCl₃): δ (ppm) 6.90 (d, *J* = 9.0 Hz, 1H), 6.75 (d, *J* = 9.0 Hz, 1H), 5.15 (s, 2H), 5.13 (s, 2H), 3.81 (s, 3H), 3.51 (s, 3H), 3.48 (s, 3H), 2.18 (s, 3H).

¹H NMR



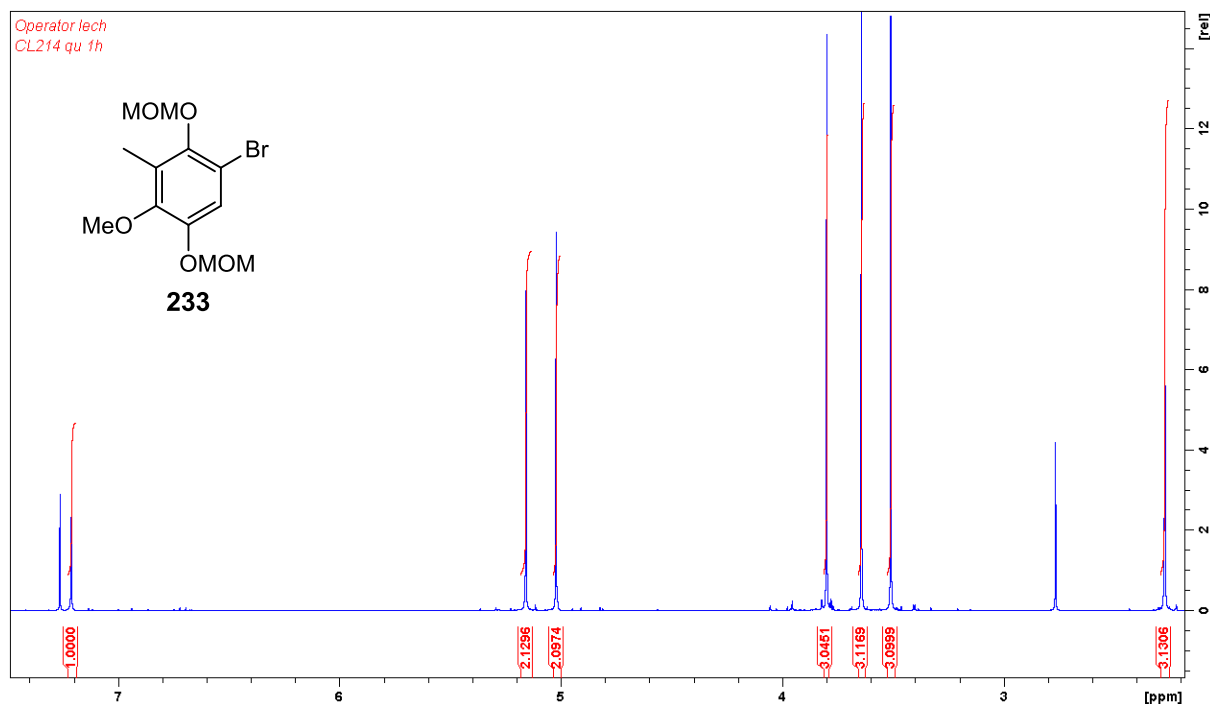
1-Bromo-4-methoxy-2,5-bis(methoxymethoxy)-3-methylbenzene **233**



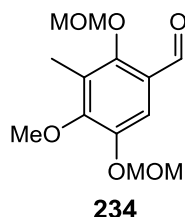
To a solution of **232** (9.7 g, 40.06 mmol) in THF (130 mL) was added NBS (8.56 g, 48.1 mmol) at 0 °C. The mixture was stirred for 16 h in the dark at 0 °C. The solution was quenched with sodium hyposulfite, extracted with diethyl ether (3x), washed with brine and dried over MgSO₄. The solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 4:1) to give **233** (10.04 g, 78%) as clear red oil.

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.21 (s, 1H), 5.16 (s, 2H), 5.02 (s, 2H), 3.80 (s, 3H), 3.64 (s, 3H), 3.51 (s, 3H), 2.27 (s, 3H).

¹H NMR



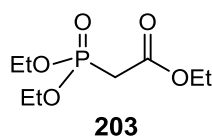
4-Methoxy-2,5-bis(methoxymethoxy)-3-methylbenzaldehyde **234**



To a solution of **233** (2.51 g, 7.91 mmol) in THF (26 mL) was added *t*-BuLi (11.6 mL, 1.7 M solution in pentane, 19.78 mmol) under argon atmosphere at -78 °C. After stirring for 30 min dry DMF (3.1 mL, 40.0 mmol) was added. The reaction mixture was stirred for 2.5 h at -78 °C. The mixture was quenched with MeOH and warmed to room temperature. The resulting solution was treated with aq. ammonium chloride, extracted with diethyl ether (3x), washed with brine and dried over MgSO₄. The solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 3:1) to give **234** (1.58 g, 74%) as clear oil.

¹H NMR (400 MHz, CDCl₃): δ (ppm) 10.22 (s, 1H), 7.46 (s, 1H), 5.22 (s, 2H), 5.02 (s, 2H), 3.91 (s, 3H), 3.59 (s, 3H), 3.51 (s, 3H), 2.23 (s, 3H).

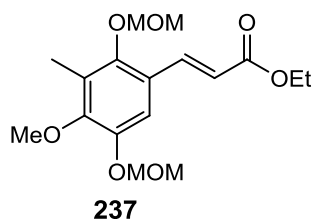
Ethyl 2-(diethoxyphosphoryl)acetate **203**



Ethyl bromoacetate (0.11 mL, 1.0 mmol) and triethyl phosphite (0.18 mL, 1.04 mmol) were mixed neat at room temperature. The reaction mixture was heated slowly to 90 °C and stirred for 22 h. The resulting solution was cooled to room temperature to afford the crude product **203** (220 mg, 98%) as clear oil and was used in the next step without further purification.

¹H NMR (400 MHz, CDCl₃): δ (ppm) 4.18 (m, 6H), 2.95 (d, *J* = 21.6 Hz, 2H), 1.34 (t, *J* = 7.0 Hz, 6H), 1.28 (t, *J* = 7.1 Hz, 3H).

(*E*)-Ethyl 3-(4-methoxy-2,5-bis(methoxymethoxy)-3-methylphenyl)acrylate **237**



To a solution of **203** (515 mg, 2.11 mmol) in THF (7 mL) was added NaH (90 mg, 60% in mineral oil, 2.25 mmol) at 0 °C. After stirring for 15 min, **234** (190 mg, 0.70 mmol) was added and the solution was stirred for 1 h at 0 °C. The resulting mixture was quenched with aq. ammonium chloride, extracted with diethyl ether (3x), washed with brine and dried over MgSO₄. The solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 4:1) to give **237** (221 mg, 92%) as a clear liquid.

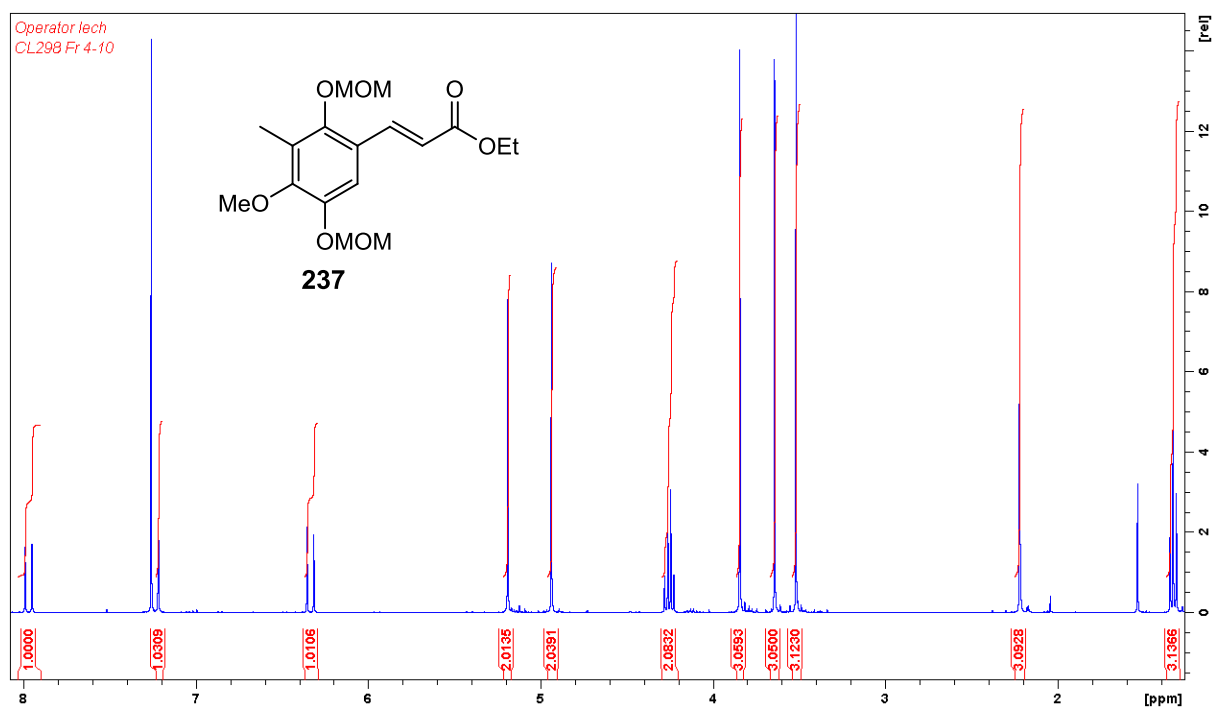
¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.97 (d, *J* = 16.1 Hz, 1H), 7.22 (s, 1H), 6.33 (d, *J* = 16.1 Hz, 1H), 5.19 (s, 2H), 4.93 (s, 2H), 4.25 (q, *J* = 7.2 Hz, 2H), 3.84 (s, 3H), 3.64 (s, 3H), 3.52 (s, 3H), 2.22 (s, 3H), 1.33 (t, *J* = 7.0 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 167.1, 153.3, 151.0, 147.4, 140.0, 126.5, 124.0, 118.0, 111.8, 100.4, 95.6, 60.5, 60.4, 57.9, 56.3, 14.3, 10.2 ppm

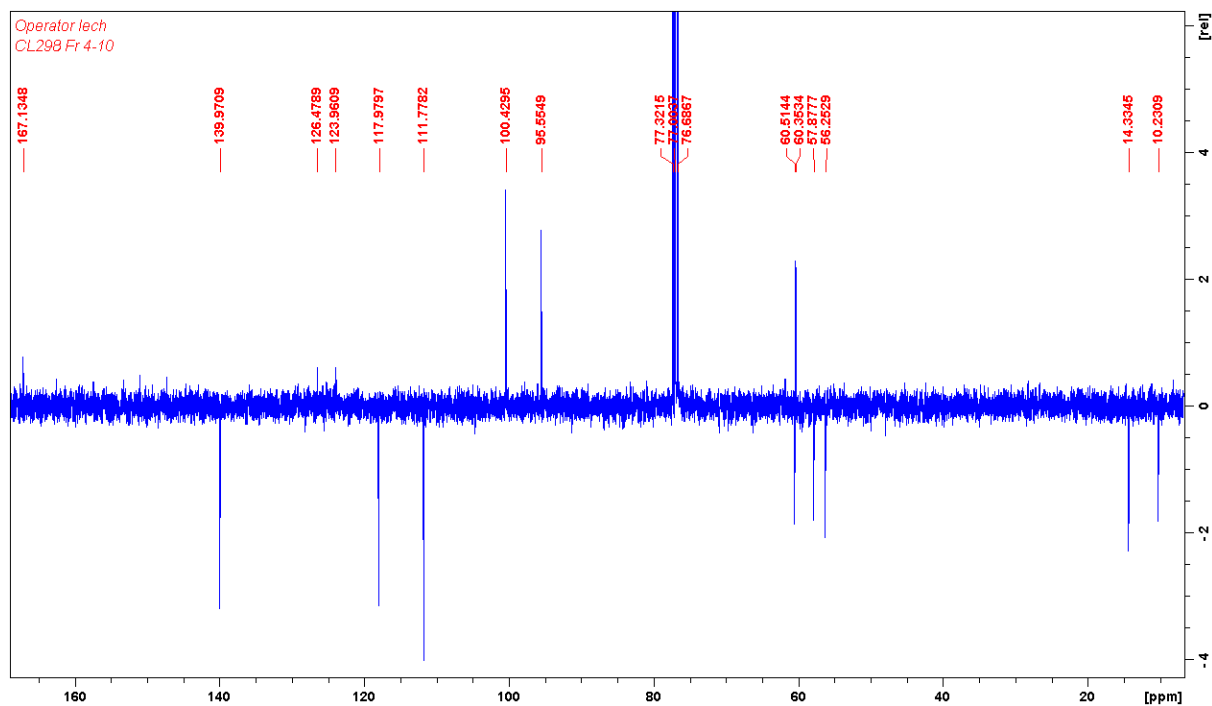
IR: 2935, 2828, 1709, 1632, 1481, 1285, 1157, 1049, 960, 858 cm⁻¹

HRMS: calculated for C₁₇H₂₄O₇Na⁺: 363.1415; found: 363.1424

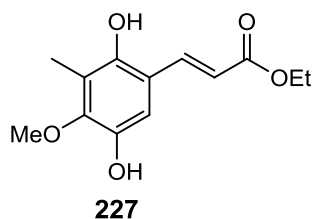
¹H NMR



¹³C NMR



(*E*)-Ethyl 3-(2,5-dihydroxy-4-methoxy-3-methylphenyl)acrylate **227**

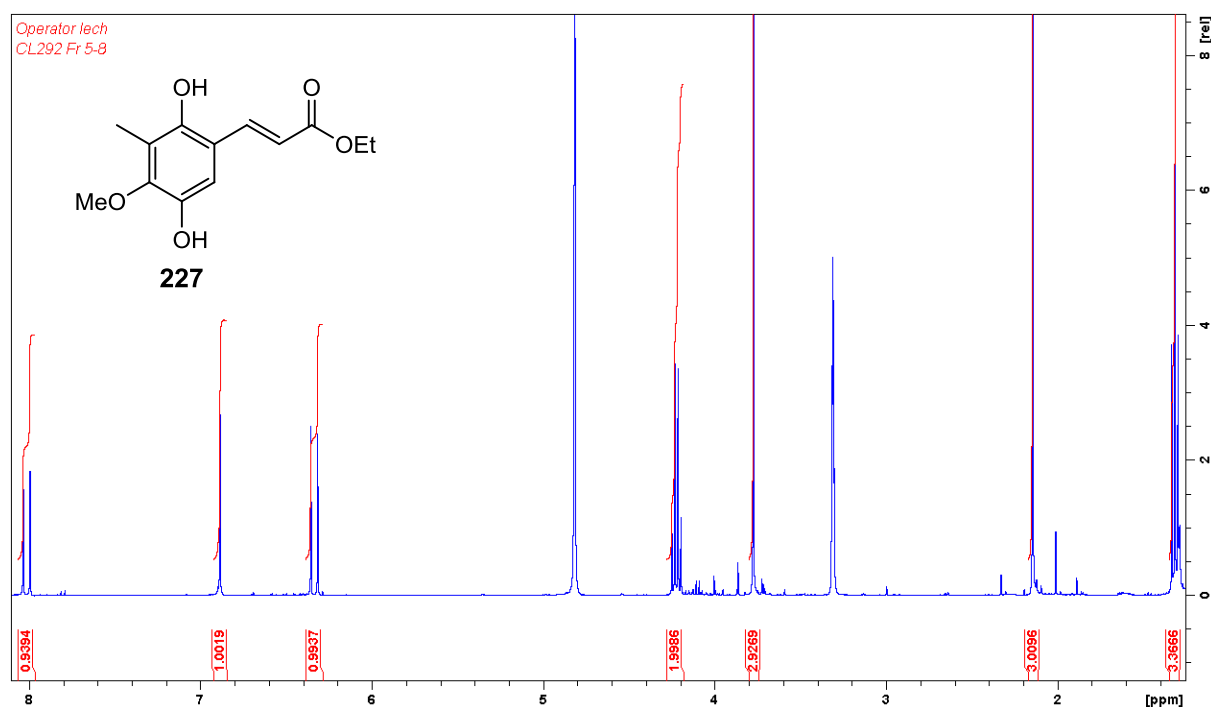


To a solution of **237** (27 mg, 0.07 mmol) in EtOH (0.75 mL) was added conc. HCl (0.08 mL, 37 wt.%). The reaction mixture was stirred for 16 h at room temperature. The resulting solution was neutralized with aq. NaHCO₃, extracted with diethyl ether (3x), washed with brine and dried over MgSO₄. The solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 2:1) to give **227** (14 mg, 75%) of as a white solid.

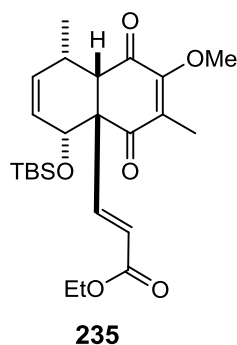
¹H NMR (400 MHz, CD₃OD): δ (ppm) 8.01 (d, *J* = 16.1 Hz, 1H), 6.89 (s, 1H), 6.34 (d, *J* = 16.1 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.77 (s, 3H), 2.14 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H).

IR: 2922, 2851, 2360, 2340, 1719, 1634, 1468, 1275, 1193, 669 cm⁻¹

¹H NMR



Cis-decaline **235**



To a suspension of **227** (14 mg, 0.056 mmol) and 1-tert-butyldimethylsiloxypenta-1,3-diene (**229**) (35 mg, 0.18 mmol, mixture of stereoisomers) in THF (0.1 mL) was added MnO₂ (9.7 mg, 0.11 mmol) at 10 °C in one portion. The mixture was warmed to room temperature and stirred for 19 h, then was diluted with diethyl ether, and filtered through Celite. The Celite was washed thoroughly with diethyl ether, and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (hexane/EtOAc, 6:1) to give **235** (11 mg, 44%) of as a white solid.

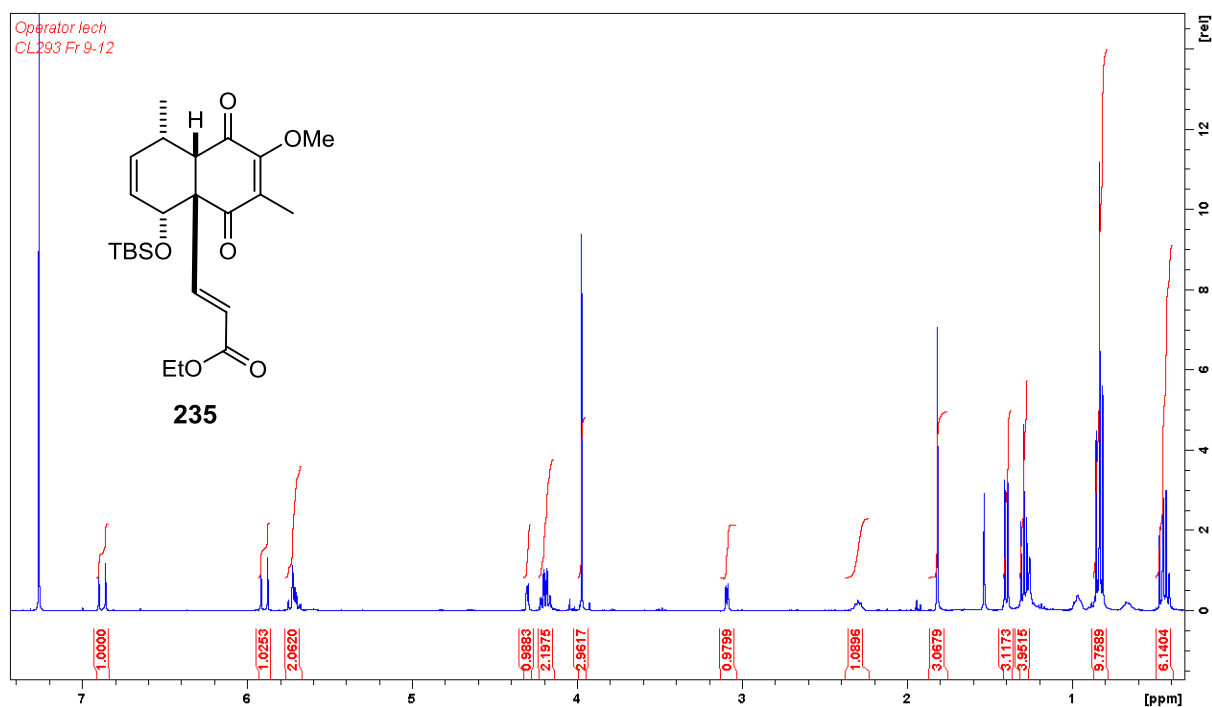
¹H NMR (400 MHz, CDCl₃): δ (ppm) 6.88 (d, *J* = 16.2 Hz, 1H), 5.89 (d, *J* = 16.2 Hz, 1H), 5.71 (m, 2H), 4.30 (m, 1H), 4.19 (dq, *J* = 6.8, 1.0 Hz, 2H), 3.97 (s, 3H), 3.09 (d, *J* = 4.8 Hz, 1H), 2.29 (m, 1H), 1.82 (s, 3H), 1.40 (d, *J* = 7.6 Hz, 3H), 1.29 (t, *J* = 7.2 Hz, 3H), 0.83 (t, *J* = 7.9 Hz, 9H), 0.44 (q, *J* = 8.2 Hz, 6H).

¹³C NMR (100 MHz, CDCl₃): δ 198.2, 192.2, 165.9, 162.8, 145.7, 133.9, 128.6, 125.0, 123.0, 68.6, 61.0, 60.7, 59.4, 52.0, 29.1, 17.1, 14.2, 8.8, 6.5, 4.8 ppm

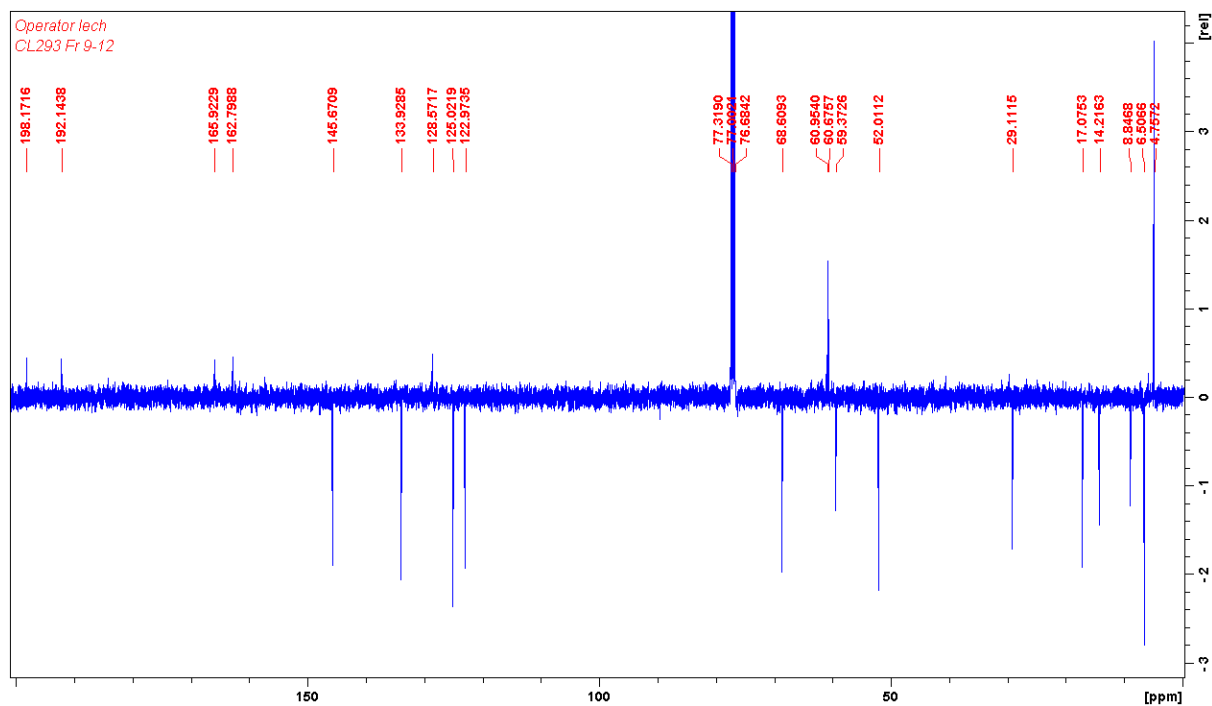
IR: 2921, 2877, 1711, 1659, 1609, 1459, 1373, 1282, 1045, 727 cm⁻¹

HRMS: calculated for C₂₄H₃₆O₆Na⁺: 471.2174; found: 471.2179

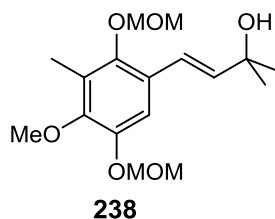
¹H NMR



¹³C NMR



Tertiary allylic alcohol **238**



To a solution of **237** (200 mg, 0.59 mmol) in THF (4.0 mL) was added methylmagnesium bromide (0.78 mL, 22 wt.% solution in THF, 2.35 mmol) dropwise at 0 °C. After stirring at room temperature for 2 h, the resulting solution was quenched with aq. ammonium chloride, extracted with diethyl ether (3x), washed with brine and dried over MgSO₄. The solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 1:1) to give **238** (175 mg, 91%) as clear liquid.

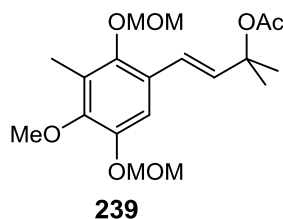
¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.09 (s, 1H), 6.83 (d, *J* = 16.1 Hz, 1H), 6.25 (d, *J* = 16.1 Hz, 1H), 5.20 (s, 2H), 4.91 (s, 2H), 3.81 (s, 3H), 3.61 (s, 3H), 3.53 (s, 3H), 2.22 (s, 3H), 1.51 (s, 1H), 1.42 (s, 6H).

¹³C NMR (100 MHz, CDCl₃): δ 149.0, 148.5, 147.2, 138.0, 126.1, 126.1, 121.6, 111.3, 99.9, 95.6, 71.2, 60.5, 57.7, 56.3, 29.9, 10.2 ppm

IR: 3428, 2967, 2930, 1479, 1229, 1151, 1045, 963, 922, 855 cm⁻¹

HRMS: calculated for C₁₇H₂₆O₆Na⁺: 349.1622; found: 349.1608

Tertiary allylic acetate **239**



To a solution of **238** (140 mg, 0.44 mmol) in CH_2Cl_2 (4.4 mL) was added DMAP (5.3 mg, 0.044 mmol), acetic anhydride (0.21 mL, 2.18 mmol) and triethylamine (31 μL , 0.22 mmol). The reaction mixture was stirred for 20 h at room temperature. The resulting solution was quenched with water, extracted with diethyl ether (3x), washed with NaHCO_3 and brine and dried over MgSO_4 . The solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexane/EtOAc, 3:1) to give **239** (147 mg, 92%) as a clear liquid.

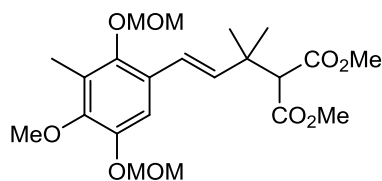
^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.06 (s, 1H), 6.77 (d, $J = 16.5$ Hz, 1H), 6.31 (d, $J = 16.3$ Hz, 1H), 5.20 (s, 2H), 4.90 (s, 2H), 3.80 (s, 3H), 3.60 (s, 3H), 3.53 (s, 3H), 2.22 (s, 3H), 2.00 (s, 3H), 1.62 (s, 6H).

^{13}C NMR (100 MHz, CDCl_3): δ 170.0, 149.0, 148.7, 147.1, 134.4, 126.1, 126.0, 123.3, 111.5, 99.9, 95.6, 80.7, 60.5, 57.7, 56.3, 27.0, 22.3, 10.2 ppm

IR: 2922, 2852, 1739, 1666, 1593, 1481, 1230, 1152, 1045, 957 cm^{-1}

HRMS: calculated for $\text{C}_9\text{H}_{10}\text{O}_3\text{Na}^+$: 391.1728; found: 391.1710

Dimethyl ester **241**



241

To a solution of Pd(OAc)₂ (1.6 mg, 0.007 mmol) and triphenylphosphine (7 mg, 0.028 mmol) in THF (0.3 mL) was added a solution of **239** (50 mg, 0.136 mmol) in THF (0.3 mL). In another flask, to a suspension of NaH (7 mg, 60% in mineral oil, 0.16 mmol) was added dimethylmalonate (31 μ l, 0.271 mmol) at 0 °C and stirred for 5 min until a clear solution obtained. It was then added to the reaction mixture and stirred for 6 h at room temperature. It was diluted with water, extracted with diethyl ether (3x), washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc, 3:1) to give **241** (43 mg, 72%) as a clear liquid.

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.02 (s, 1H), 6.60 (d, J = 16.3 Hz, 1H), 6.22 (d, J = 16.3 Hz, 1H), 5.18 (s, 2H), 4.87 (s, 2H), 3.68 (s, 6H), 3.59 (s, 3H), 3.52 (s, 3H), 3.44 (s, 1H), 2.20 (s, 3H), 1.33 (s, 6H).

¹³C NMR (100 MHz, CDCl₃): δ 168.2, 148.8, 148.4, 147.1, 137.1, 126.7, 126.0, 122.8, 111.7, 99.8, 95.7, 60.8, 60.5, 57.7, 56.3, 52.1, 39.0, 25.4, 10.2 ppm

IR: 2956, 1755, 1481, 1437, 1338, 1280, 1238, 1153, 1092, 969 cm⁻¹

HRMS: calculated for C₂₂H₃₂O₉Na⁺: 463.1939; found: 463.1925

7. Appendix

Abstract

In the last twenty years several research groups focused their attention on the chemically rich gorgonians (sea fans, sea whips and sea plumes) found in the reef habitats of the West Indian region. Especially the gorgonian octocoral *Pseudopterogorgia elisabethae*, collected from several locations throughout the Caribbean region, is of particular interest since chemical investigations have revealed these animals to contain large quantities of highly bioactive secondary terpenoid metabolites. For example some pseudopterosins which are diterpene-pentose-glycosides of the amphilectane class possess high anti-inflammatory and analgesic properties.

The unique structure and biological activity from some of these natural products motivated synthetic research groups to establish synthetic approaches. These efforts have led to many reported total synthesis of *P. elisabethae* diterpenes. A still unsolved challenge is the total synthesis of elisabethin A. Many attempts of several synthetic research groups were reported but none of them were able to establish a total synthesis of this complex molecule.

This master thesis deals with the total synthesis of elisabethin A too. In contrast to previous published approaches we focused on an early stage Diels-Alder reaction to generate the decaline system with the quaternary carbon atom. Further key steps are the side chain introduction and the five membered ring closing reaction to the desired elisabethin core.

Zusammenfassung

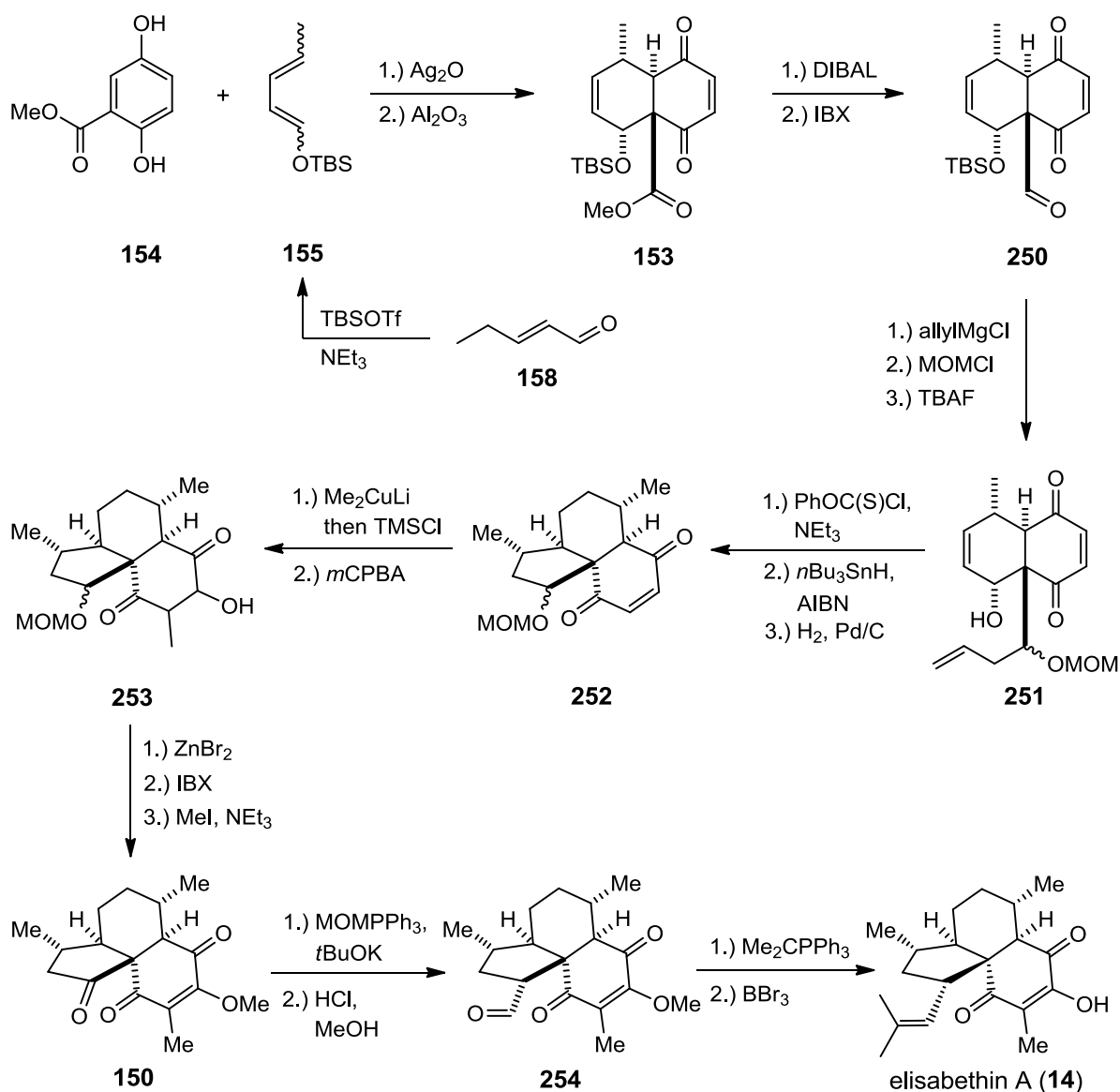
In den letzten zwanzig Jahren haben sich viele Forschungsgruppen mit Gorgonians (Korallen) aufgrund ihrer Vielfältigkeit an chemischen Verbindungen beschäftigt. Der natürliche Lebensraum dieser Korallen ist der westindische Ozean. Besondere Aufmerksamkeit erhielt dabei die Gorgonien *Octocorallia Pseudopterogorgia Elisabethae*, die an verschiedenen Orten in der Karibik vorkommt. Chemische Untersuchungen dieses Tieres zeigten ein breites Spektrum biologisch hochaktiver Terpene und Sekundärmetabolite. Ein Beispiel dafür sind einige Pseudopterose, Diterpenoid-Pentose-Glycoside der Amphilectan Klasse, die eine sehr hohe entzündungshemmende und schmerzmildernde Wirkung besitzen.

Die einzigartigen Strukturen und bemerkenswerten biologischen Eigenschaften jener Naturstoffe erweckten auch das Interesse von synthetischen Forschungsgruppen. Dadurch entstanden viele Totalsynthesen von Diterpenen, die aus *P. Elisabethae* isoliert wurden. Ein bis heute ungelöstes Problem stellt die Totalsynthese von Elisabethin A dar. Viele Ansätze von verschiedenen Forschungsgruppen wurden unternommen, um diesen komplexen Naturstoff herzustellen, doch keiner davon war erfolgreich.

Diese Masterarbeit beschäftigt sich ebenfalls mit der Totalsynthese von Elisabethin A. Im Gegensatz zu anderen Totalsynthesen wählten wir eine intermolekulare Diels-Alder Reaktion, um das Grundgerüst aufzubauen. Weitere Schlüsselschritte in der Synthese sind die Einführung der Seitenkette und der anschließende Fünfringschluss zum gewünschten Elisabethin-Grundgerüst.

Possible Approach to Elisabethin A

A possible total synthesis to elisabethin A (**14**) is outlined in Scheme 59. This route shows our envisioned strategy to the natural product.



Scheme 59: Possible approach to elisabethin A (**14**)

The first step is an intermolecular Diels-Alder reaction with *in situ* oxidized hydroquinone **154** and diene **155** which is prepared from commercially available *E*-2-pentenal **158** by enolization with triethylamine and protection of the enol with TBSOTf. Epimerization of the resulting *cis*-decalone with Aluminum oxide provides *trans*-decalone **153**. Reduction of the ester moiety with DIBAL and subsequent oxidation using IBX delivers aldehyde **250**. The side chain is introduced with

allylmagnesium chloride. Protection of the resulting alcohol with MOMCl and cleavage of the TBS group with TBAF affords allylic alcohol **251**. Functionalization of the allylic hydroxy group with phenyl chlorothionoformate generates a xanthate. A radical ring closing reaction with tributyltin hydride and AIBN provides the five membered ring. Subsequent hydrogenation of the double bond in the six membered ring with molecular hydrogen and palladium on charcoal affords tricyclic enedione **252**. The next reaction is conjugate addition to the enedione with lithium dimethylcuprate and protection of the generated enol with TMS-Cl. A subsequent Rubottom oxidation with *m*CPBA delivers alcohol **253**. Cleavage of the MOM group with zinc bromide provides the diol. Oxidation of the alcohols with IBX and subsequent oxidation of the enol with methyl iodide and triethylamine delivers compound **150**. Olefination of the ketone with a Wittig reagent provides the methyl enol ether. Cleavage of this ether with hydrochloric acid affords aldehyde **254**. A further Wittig olefination generates the desired isobutenyl side chain. Cleavage of the methyl group with boron tribromide delivers elisabethin A (**14**).

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7.4. References

- ¹ Blunt J. W., Copp B. R., Wu W.-P. *et al.*, *Nat. Prod. Rep.* **2008**, 25, 35
- ² Fenical W., *J. Nat. Prod.* **1987**, 50, 1001
- ³ Rodríguez A. D., *Tetrahedron* **1995**, 51, 4571
- ⁴ Rodríguez A. D., González E., Huang S.D., *J. Org. Chem.* **1998**, 63, 7083
- ⁵ Rodríguez A. D., Ramírez C., Rodríguez I. I., *Tetrahedron Lett.* **1999**, 40, 7627
- ⁶ Rodríguez A. D., Ramírez C., Rodríguez I. I., *J. Nat. Prod.* **1999**, 62, 997
- ⁷ Rodríguez A. D., Ramírez C., Rodríguez I. I., *Org. Lett.* **1999**, 1, 527
- ⁸ Bayer F. M., *The Shallow-Water Octocorallia of the West Indian Region*; Martinus Nijhoff; The Hague, **1961**
- ⁹ Rodríguez, A.D., Shi Y.-P., *Eur. J. Org. Chem.* **2009**, 493
- ¹⁰ W. Fenical, C. A. Harvis, M. T. Burch *Tetrahedron Lett.* **1988**, 29, 4364
- ¹¹ Rodríguez, A.D., Ramírez, C., *Org. Lett.* **2000**, 2, 507
- ¹² McGarvey J. D., Croteau R. *The Plant Cell* **1995**, 7, 1015
- ¹³ Breitmaier E., *Terpenes* **2006**, WILEY-VCH, p.3
- ¹⁴ Kerr G.R., Kohl C. A., *Archives of Biochemistry and Biophysics* **2004**, 97
- ¹⁵ Kerr G.R., Athar A., Kohl C. A., *Ind. Microbiol. Biotechnol.* **2003**, 30, 495
- ¹⁶ Rodríguez, A.D., Ramírez, C., *J. Nat. Prod.* **2001**, 64, 100
- ¹⁷ Rodríguez A.D., Ramírez C., Rodríguez I. I., *J. Org. Chem.* **2000**, 65, 1390
- ¹⁸ Rawal H. V., Stankovic R. A., Waizumi N., *J. Am. Chem. Soc.* **2003**, 125, 13022
- ¹⁹ Look S. A., Fenical W., Jacobs R. S., *J. Proc. Natl. Acad. Sci. U.S.A.* **1986**, 83, 6238
- ²⁰ A. Kijjoa, P. Sawangwong, *Mar. Drugs* **2004**, 2, 73
- ²¹ Restogi N., Goh K. S., Van Ginkel S. Z. *Res. Microbiol.* **1996**, 147, 97

- ²² Paull K. D., Shoemaker R. H., Hodes L., *J. Natl. Cancer Inst.* **1989**, *81*, 1088
- ²³ Jeffery T., *Tetrahedron* **1996**, *52*, 10113
- ²⁴ McMurry J. E., Scott W. T., *Tetrahedron Lett.* **1983**, *24*, 979
- ²⁵ Stille J. K., *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508
- ²⁶ Hoveyda H. A., Cesati R. R., Armas J., *J. Am. Chem. Soc.* **2004**, *126*, 96
- ²⁷ Broka C. A., Chan S., Peterson B., *J. Org. Chem.* **1989**, *111*, 5472
- ²⁸ Corey E. J., Carpino P., *J. Am. Chem. Soc.* **1989**, *111*, 5472
- ²⁹ Kocienski P. J., Pontiroli A., Qun L., *J. Chem. Soc., Perkin Trans 1* **2001**, 2356
- ³⁰ Zhang A., RajanBabu T. V. *Org Lett.* **2004**, *6*, 3159
- ³¹ De Riccardis F., Meo D., Izzo I, *Eur. J. Org. Chem.* **1998**, 1965
- ³² Corey E. J., Lazwewith S. E., *J. Am. Chem. Soc.* **1998**, *120*, 12777
- ³³ RajanBabu T. V., Mans J. D., Cox G. A., *J. Am. Chem. Soc.* **2011**, *133*, 5776
- ³⁴ Brown H.C., Pfafanberger C. D., *J. Am. Chem. Soc.* **1967**, *89*, 5475
- ³⁵ Stevens R. V., Chapman K.T., Stubbs C. A., *Tetrahedron Lett.* **1982**, *23*, 4647
- ³⁶ Vedejs E., Fang H. W., *J. Org. Chem.* **1984**, *49*, 210
- ³⁷ Corey E. J., Davison J. P., *J. Am. Chem. Soc.* **2003**, *125*, 13487
- ³⁸ Liotta R., Brown H. C., *J. Org. Chem.* **1977**, *42*, 2836
- ³⁹ Lebsack A. D., Overman L. E., Valentekovich R. J., *J. Am. Chem. Soc.* **2001**, *123*, 4851
- ⁴⁰ Barton D. K., Mahapatra S. N., *Tetrahedron* **1960**, *11*, 234
- ⁴¹ Dess D. B., Marin J. C., *J. Am. Chem. Soc.* **1991**, *113*, 7277
- ⁴² Yamada Y., Mitome H., Miyaoka H., *Tetrahedron Letters* **2002**, *43*, 7773
- ⁴³ Mikami K., Motoyama Y., Terada M., *J. Am. Chem. Soc.* **1994**, *116*, 2812
- ⁴⁴ Carreno M. C., García Ruano J. L., Toledo M. A., *Tetrahedron: Asymmetry* **1997**, *8*, 913
- ⁴⁵ Luly J. L., Rapoport H., *J. Org. Chem.* **1981**, *46*, 2745
- ⁴⁶ Flack-Pederson M. L., Benneche T., Undheim K., *Acto Chem. Scand.* **1993**, *47*, 63
- ⁴⁷ Zhong Y.-L., Shing T. K. M., *J. Org. Chem.* **1997**, *62*, 2622
- ⁴⁸ Yamada S., Suzuki T., Takayama H., *J. Org. Chem.* **1983**, *48*, 3483
- ⁴⁹ Nicolaou K. C., Kranich R., Mägerlein W., *Chem. Eur. J.* **2001**, *7*, 5359
- ⁵⁰ Joseph-Nathan P., Garibay M. E., Santillan R. L., *J. Org. Chem.* **1987**, *52*, 759
- ⁵¹ Myers A. G., Yang B. H., Chen H., *J. Am. Chem. Soc.* **1997**, *119*, 6496
- ⁵² Kowalski C. J., Haque M. S., *J. Am. Chem. Soc.* **1986**, *108*, 1325

- ⁵³ Knölker H.-J., Fröhner W., Reddy K. R., *Synthesis* **2002**, 557
- ⁵⁴ Grieco P. A., Nunes J. J., Gaul M. D., *J. Am. Chem. Soc.* **1990**, *112*, 4595
- ⁵⁵ Rychnovsky D. S., Kim I. A., *Angew. Chem. Int. Ed.* **2003**, *42*, 1267
- ⁵⁶ Grigore O. H., Rouessac F. P., *Org. Synth.* **1985**, *63*, 121
- ⁵⁷ Schlegel D. C., Tipton C. D., Rinehart K. L., *J. Org. Chem.* **1970**, *35*, 849
- ⁵⁸ Negishi E., Bagheri V., Chatterjee S., *Tetrahedron Lett.* **1983**, *24*, 5181
- ⁵⁹ Seyferth D., Marmor R. S., Hilbert P., *J. Org. Chem.* **1971**, *36*, 1379
- ⁶⁰ Tsuchihashi G., Kitajima K., Mitamura M., *Tetrahedron Lett.* **1981**, *22*, 4305
- ⁶¹ Negishi E., Takahashi T., Baba S., Van Horn D. E., *J. Am. Chem. Soc.* **1987**, *109*, 2393
- ⁶² Evers M., *Chem. Scr.* **1986**, *26*, 585
- ⁶³ Van Dort H. M., Greusen H. J., *Recl. Trav. Chim. Pays-Bas* **1967**, *86*, 520
- ⁶⁴ Kosugi M., Negishi Y., Kameyama M., *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3383
- ⁶⁵ Mulzer J., Dupré S., Buschmann J., *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1452
- ⁶⁶ Zanoni G., Franzini M., *Angew. Chem.* **2004**, *116*, 4942
- ⁶⁷ Mulzer J., Heckrodt T., *J. Am. Chem. Soc.* **2003**, *125*, 4680
- ⁶⁸ White D. J., Hyunik S., Tae-Seong K., *J. Am. Chem. Soc.* **1997**, *119*, 2404
- ⁶⁹ Claessens S., Habonimana P., De Kimpe N., *Org. Biomol. Chem.* **2010**, *8*, 3790
- ⁷⁰ Lockwood *et al.*, Pub. No.: US 2006/0167319 A1
- ⁷¹ Salvador R. A. J., Leitao L. J. A., Sa e Melo M. L., *Tetrahedron Letters* **2005**, *46*, 1067
- ⁷² Hardouin C., Chevallier F., Doris E., *J. Org. Chem.* **2001**, *66*, 1046
- ⁷³ Hasegawa E., Ishiyama K., Kato T., *J. Org. Chem.* **1992**, *57*, 5352
- ⁷⁴ Carreno C., Ruano G. L. J., Toledo A. M. *Tetrahedron: Asymmetry* **1997**, *8*, 913
- ⁷⁵ Crosby G. D., *J. Org. Chem.* **1961**, *26*, 1215
- ⁷⁶ Crosby G. D., Berthold V. R., *J. Org. Chem.* **1962**, *27*, 3083
- ⁷⁷ Teichert R. J., Feringa L. B., *Chem. Commun.* **2011**, *47*, 2679
- ⁷⁸ Townsend A. C., Bloom M. L., *Tetrahedron Letters* **1981**, *22*, 3923
- ⁷⁹ De Kimpe N., Demyttenaere J., Van Syngel K., *Tetrahedron* **2002**, *58*, 2163
- ⁸⁰ Rychnovsky D. S., Bahnck B. K., *J. Am. Chem. Soc.* **2008**, *130*, 13177
- ⁸¹ Fehr C., Magpantay I., Vuagnoux M., *Chem. Eur. J.* **2011**, *17*, 1257

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