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MASTERARBEIT

Titel der Masterarbeit

„Concise and flexible synthesis of the five-membered ring synthon of highly oxygenated jatrophane diterpenes“

Verfasser

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Abbreviations

9-BBN	9-borabicyclo[3.3.1]borane
Ac	acetyl
Ang	angeloyl
ATR	attenuated total reflection
Bn	benzyl
BSA	*N*,*O*-bis(trimethylsilyl) acetamide
Bu	butyl
Bz	benzoyl
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
Cy	cyclohexyl
D -(-)-DIPT	D -(-)-diisopropyl tartrate
DBU	1,8-diazabicyloundec-7-ene
DCE	1,2-dichloroethane
DCM	dichlormethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DIPA	diisopropylamine
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMP	Dess-Martin periodinane
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dppf	1,1'-Bis(diphenylphosphino)ferrocen
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
Et	ethyl
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hydrpr	3-hydroperoxy-2-methylene-butyryl
*i*Bu	isobutyl
IBX	2-iodoxybenzoic acid
*i*Pr	isopropyl
IR	infrared
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
M	molar (concentration)
*m*CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl

Mes	2,4,6-trimethylphenyl
MOM	methoxy methyl
MPLC	medium pressure liquid chromatography
Ms	mesyl
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NCS	*N*-chlorosuccinimide
Nic	nicotinoyl
NMO	*N*-methylmorpholine *N*-oxide
PDC	pyridinium dichromate
PG	protective group
Ph	phenyl
PMB	paramethoxybenzyl
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
Pyr	pyridine
RCM	ring closing metathesis
TASF	tris(dimethylamino)sulfur (trimethylsilyl)difluoride
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
*t*Bu	*tert*-butyl
TES	triethylsilyl
THF	tetrahydrofuran
Tig	tigloyl
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Tol	toluene
Ts	*para*-toluenesulfonyl

1. General Part

1.1 Introduction

Euphorbiaceae are widely spread all over the world. Mainly they occur in tropical regions as the Indomalayan ecozone and the tropical regions of Central and South America. A smaller variety can be found in tropical Africa, but also more moderate climate zones are well known to be habitat of *Euphorbiaceae* as the Mediterranean Basin, the Middle East, South Africa and southern USA.

Genus *Euphorbia* is only one of around 300 genera of *Euphorbiaceae* and contains more than 2,100 species. It is believed to be one of the most diverse genera in the whole plant kingdom.[1] Some of these species have been used in many cultures to treat constipation, remove warts, heal breast ailments or as general tonic. For instance *Euphorbia pithyusa,* a species endemic to the central and western Mediterranean region, is known as medical plant since ancient times in Greece, the Roman Empire and later in medieval times.[2-4] Another example is *Euphorbia mongolica*, endemic to southeastern parts of Asia, which is traditionally used to treat inflammation, warts and tumors.[5]

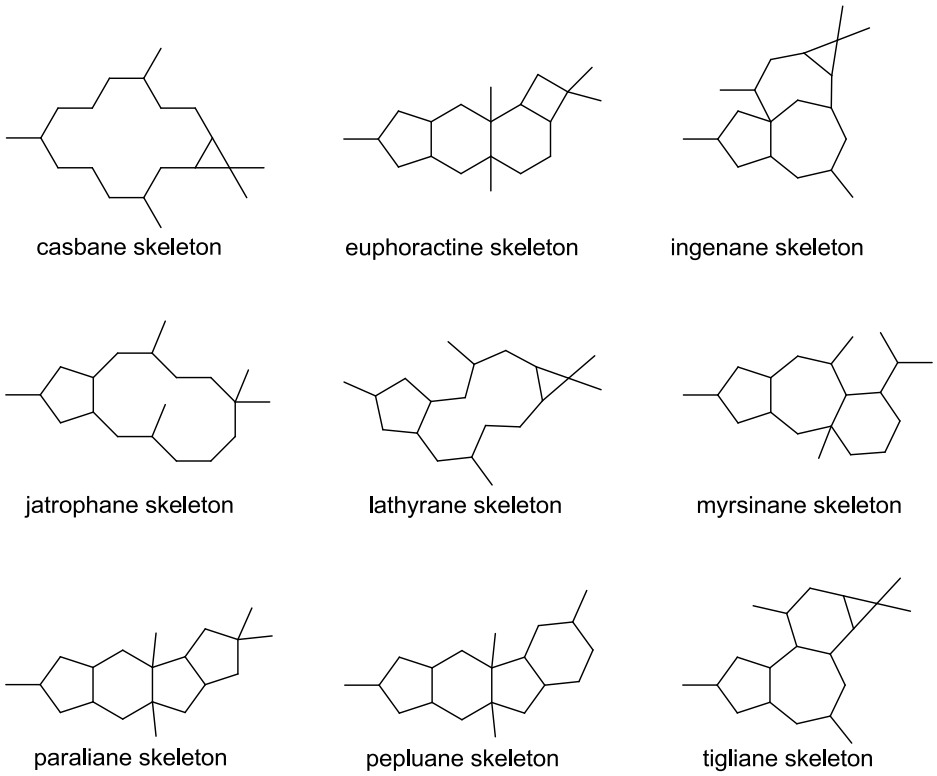


Fig. 1 Carbon skeletones of *Euphorbiaceae* diterpenes.

When jatrophone (**1**) was isolated in 1970 from *Jatropha gossypiifolia*, which belongs to the *Euphorbiaceae* family, the interest of chemists began to grow, since this natural compound seemed to be one of the active compounds of the different traditional folk remedies in several countries.[6-9]

The carbon skeleton of various diterpenes of the casbane, jatrophane, lathyrane, myrsinane, tigliane, ingenane, segetane, paraliane, pepluane and euphoractine families are shown in Fig. 1. Diterpenes that feature these skeletons are known as *Euphorbiaceae* diterpenoids.

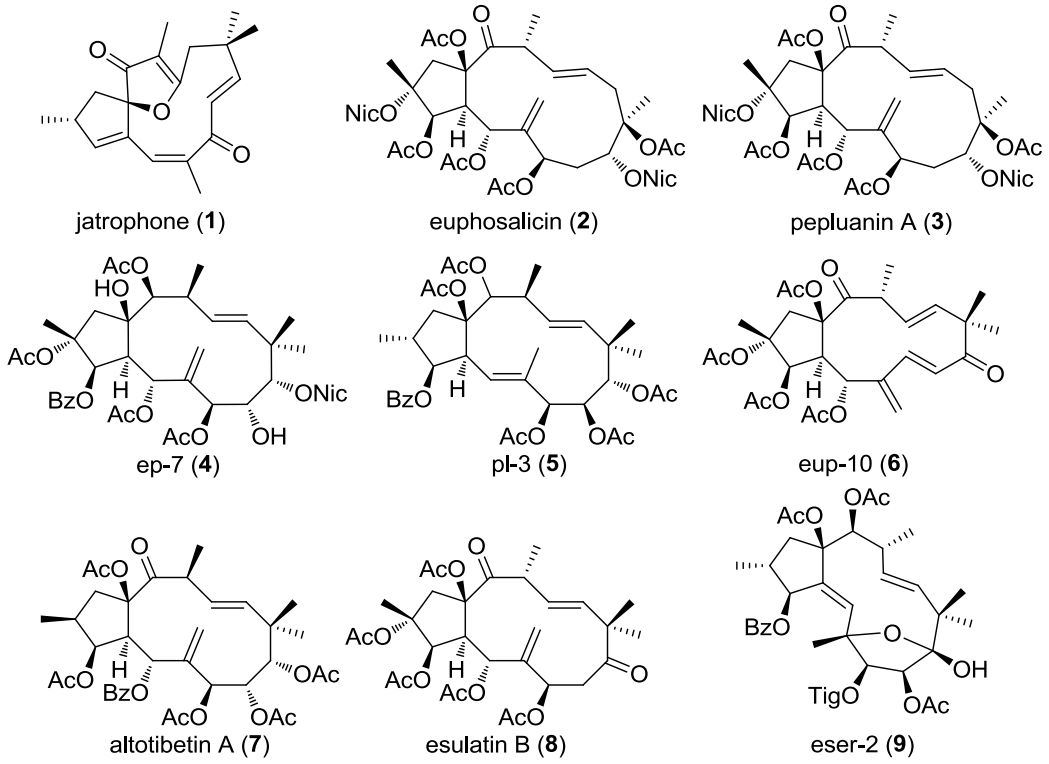


Fig. 2 Various jatrophane *Euphorbiaceae* diterpenes.

The *Euphorbiaceae* diterpenes shown in Fig. 2 show a huge variety of functional groups and also differ in the oxygenation patterns. Due to the circumstance that they are diversely substituted with various acyl groups, such as acetyl, benzoyl, nicotinoyl or tigloyl, to name a few, the name “jatrophane polyesters” is also commonly used.[10]

The skeleton of euphosalicin (**2**) and pepluanin A (**3**) differs from the common jatrophane skeleton. Structure elucidation of euphosalicin (**2**) led to an abeojatrophane skeleton, see Fig. 3, suggesting that one of the geminal methyl groups is incorporated in the ring which implicates a 13-membered macrocycle.[11]

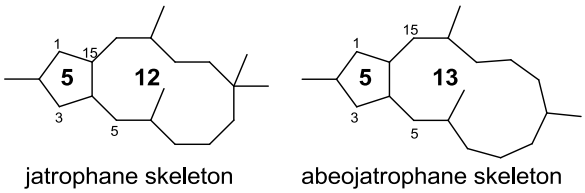


Fig. 3 Jatrophane and abeojatrophane skeleton.

Euphorbiaceae constituents have much to offer to researchers of different areas. Phytochemists are intrigued by the structural complexity of natural products obtained from these wide-spread plants. The high level of biological activity raises interest within the medicinal community, and last but not least, diterpenes isolated from plants of the *Euphorbiaceae* family offer a fascinating play-ground to synthetic chemists. The synthetic aspect becomes even more pronounced as insufficient quantities of diterpenes are available from natural sources for extensive biological evaluation.[12-15]

1.2 Aim of the Synthetic Work

The goal of the present master thesis was the preparation of highly oxygenated five-membered ring synthons, namely **16**-**19** shown in Fig. 4, required for the preparation of various jatrophane diterpenes such as ep-7 (**4**), eup-10 (**6**), euphosalicin (**2**) or pepluanin A (**3**), shown in Fig. 2. The strategy was based on previous studies by Lentsch and Rinner[16] as described in section 1.4.1.5 of this document. The highly flexible route gives access to both high oxygenated patterns. Compounds **16**-**19** were envisaged to be synthesized based on the same methodology in a stereoselective manner.

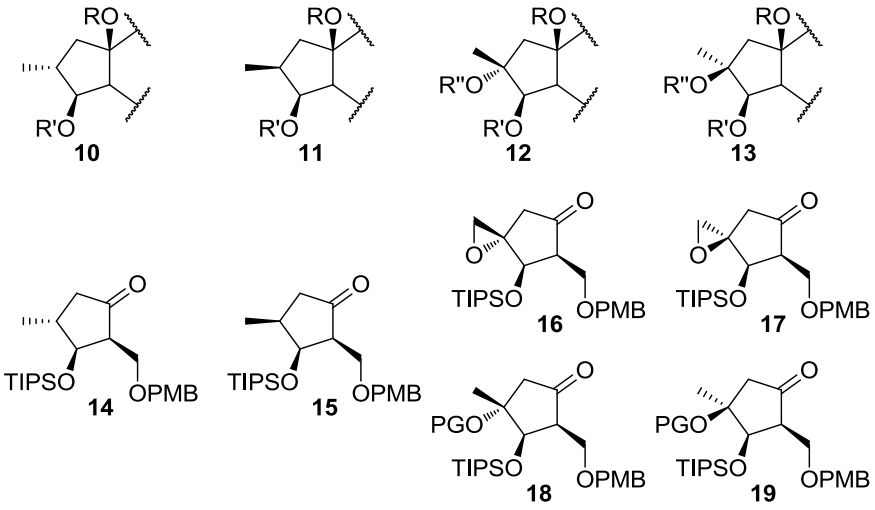


Fig. 4 Natural substitution patterns and their synthetic equivalents.

The retrosynthetic analysis is discussed in detail in chapter 2.1 of this document. The envisaged key steps in the preparation of the five-membered ring synthon (**16**) were a Sharpless asymmetric epoxidation reaction[17], a stereoselective aldol reaction[18], a ring closing metathesis and a hydroboration/oxidation sequence[16].

1.3 Isolation and Biological Activities of Jatrophane Diterpenes

In 1970, Kupchan *et al.* isolated jatrophone (**1**) from *Jatropha gossypiifolia* and the carbon skeleton was named "jatrophane skeleton" after its botanical origin.[8] After the isolation of jatrophone (**1**) only 4 more diterpenes with jatrophane skeleton (Fig. 5) were isolated from the genus *Jatropha*. 2α-Hydroxyjatrophone (**20**), 2β-hydroxyjatrophone (**21**), 2β-hydroxy-5,6-isojatrophone (**22**) were isolated by Taylor *et al.* 1983, and japodagrone (**23**) was isolated from *Jatropha podagrica* by Aiyelaagbe *et al.* in 2007.[19,20]

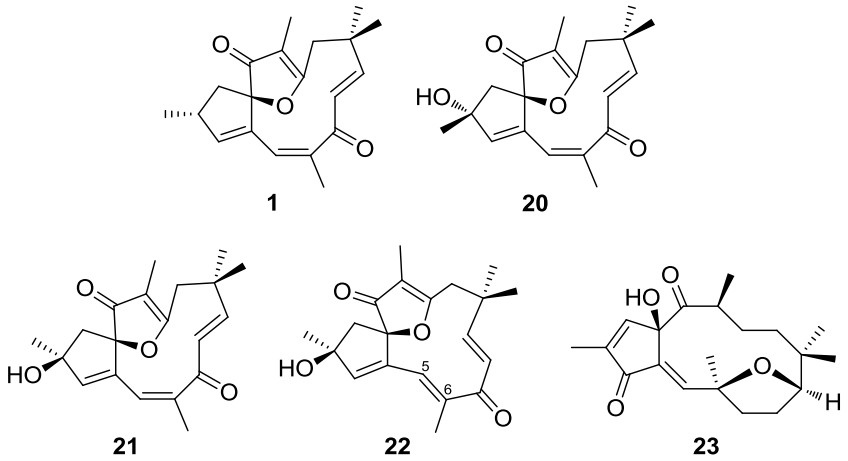


Fig. 5 Jatrophanes isolated from the genus *Jatropha*.

Table 1 Antineoplastic activity of jatrophone and derivatives.[19]

		P-388		KB
no.	**name**	***in vivo* [T/c], [mg/kg]**	**ED_{50} [μg/mL]**	***in vitro* ED_{50}, [μg/mL]**
1	jatrophone	145, 12.0	0.01	0.000087
20	2α-hydroxyjatrophone	125, 6.0	0.03	0.16
21	2β-hydroxyjatrophone	132, 10.0	0.06	0.07
22	2β-hydroxy-5,6-isojatrophone	no activity	2.2	0.03

The isolation of jatrophone (**1**) is best described by Kupchan *et al.* (1976).[7] Dried ground roots of *Jatropha gossypiifolia* L. (11.7 kg) were extracted continuously with hot ethanol. The dark brown gum received after evaporation of the solvent was triturated with benzene. The benzene fraction was evaporated and triturated with hexane. Treatment of the hexane fraction with activated carbon gave a light yellow oil from which jatrophone (**1**, 1.37 g, 0.012%) was isolated after two chromatographic steps.

Another isolation of jatrophone (**1**) from *J. gossypiifolia* was reported by Taylor *et al.*, along with three new hydroxyjatrophanes **20**-**22**.[19] After Kupchan showed that jatrophone (**1**) was

soluble in hexane, Taylor reasoned that a preliminary fractionation with hexane, followed by chloroform would obtain jatrophone (**1**) and related compounds.[7,8,19]

Starting from 25 kg dried and milled roots of *J. gossypiifolia,* several chromatographical steps were needed to isolate jatrophone (**1**, 2.31 g, 0.009%) and the two hydroxyjatrophanes (**21**, as colorless gum, 0.14 g, 0.0005%; and **22**, as white crystals, 0.048 g, 0.0002%).
From the $CHCl_3$ fraction hydroxyjatrophane (**20**, 0.095 g, 0.001%) was obtained as colorless gum after five chromatographic steps. These compounds were tested for their antineoplastic activity in P-388 and the Eagle's carcinoma of the nasopharynx test system (KB). The results of these tests are shown in Table 1.[19]

Japodagrone (**23**) showed activity in standard disk assays against *Bacillus subtilis* (ATCC 6051) giving a zone of 12 mm at 20 µg/disk., whereas no activity against *Staphylococcus aureus* was observed.[20]

A review published by Shi *et al.* in 2008 provides a good overview about the *Euphorbiaceae* diterpenes isolated from the genus *Euphorbia*.[10] In this article, 154 *Euphorbiaceae* diterpenes possessing the jatrophane skeleton are listed. In comparison to the 5 jatrophanes isolated from the name giving genus *Jatropha*, *Euphorbia* seems to be a much more important source of jatrophanes.
Within the following section of this master thesis, all newly isolated jatrophane diterpenes are listed, along with compounds which have not been discussed in Shi's review article.

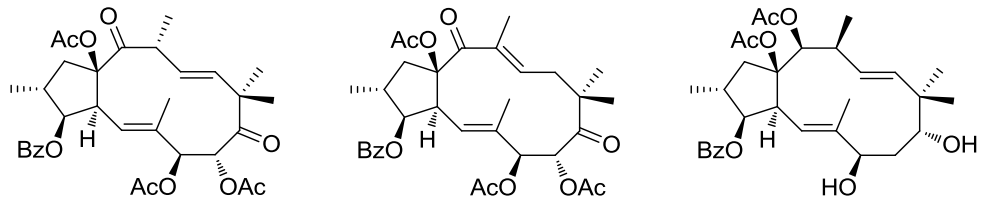


Fig. 6 Jatrophanes isolated by Barile *et al.*

Euphoscopin M (**24**), euphoscopin N (**25**) and euphornin L (**26**), shown in Fig. 6, were isolated by Barile *et al.* in 2008 from an ethyl acetate extract of *E. helioscopia* using a combination of chromatographic techniques (MPLC and HPLC). Euphoscopin M (**24**) and euphoscopin N (**25**) were found to inhibit P-glycoprotein-mediated mitoxantrone efflux. [21]

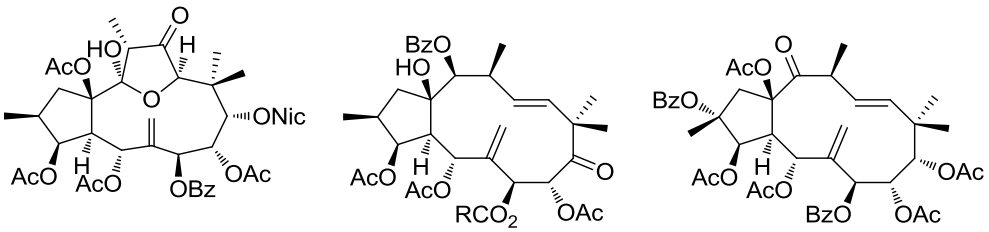


Fig. 7 Jatrophanes isolated by Chen *et al.* and Duarte *et al.*, respectively.

Chen *et al.* reported the isolation of kansuinin D1 (**27**),see Fig. 7, from *E. kansui* in 2008.[22] Tuckeyanol A (**28**), tuckeyanol B (**29**) and euphotuckeyanol (**30**), also shown in Fig. 7, were isolated from *E. tuckeyana* by Duarte *et. al*.[23]

The isolation of 7β,9α,14β-triacetoxy-3β-benzoyloxy-12β,15β-epoxy-11-hydroxyjatropha-5*E*-ene (**31**) was reported by Lu *et al.* in 2008 (Fig. 8). The natural product (**31**) did not express cytotoxic activity against HeLa (human cervical carcinoma cells) and MDA-MB-231 (breast tumor cells). **31** was isolated along with known jatrophanes from an ethanolic extract of *E. helioscopia* after multiple chromatographic steps.[24] Two years later, in 2010, Geng *et al.* reported the isolation of another jatrophane diterpene, shown in Fig. 8, named euphornin N (**32**), from *E. helioscopia*.[25]

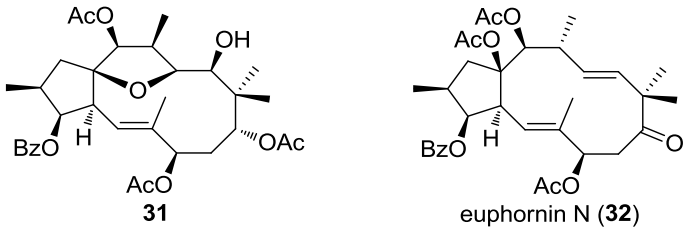


Fig. 8 Newly isolated jatrophanes from *E. helioscopia* by Lu and Geng, respectively.

In 2010 Huang *et al.* reported the isolation of nine novel jatrophane diterpenes, shown in Fig. 9 and Table 2, from *E. sororia* in two independent papers.[26,27] The structure of the sororianolides (**39**-**41**), which is called 17-bishomojatrophane, is remarkable, because of the 8-membered lactone ring and the unusual substituents at C-1. Remarkably, compounds **33–38** are reported with a *cis*-bicyclo[10.3.0]pentadecane skeletone, whereas usually a *trans*-fused-bicyclo[10.3.0]pentadecane skeleton is found in jatrophane diterpenes.

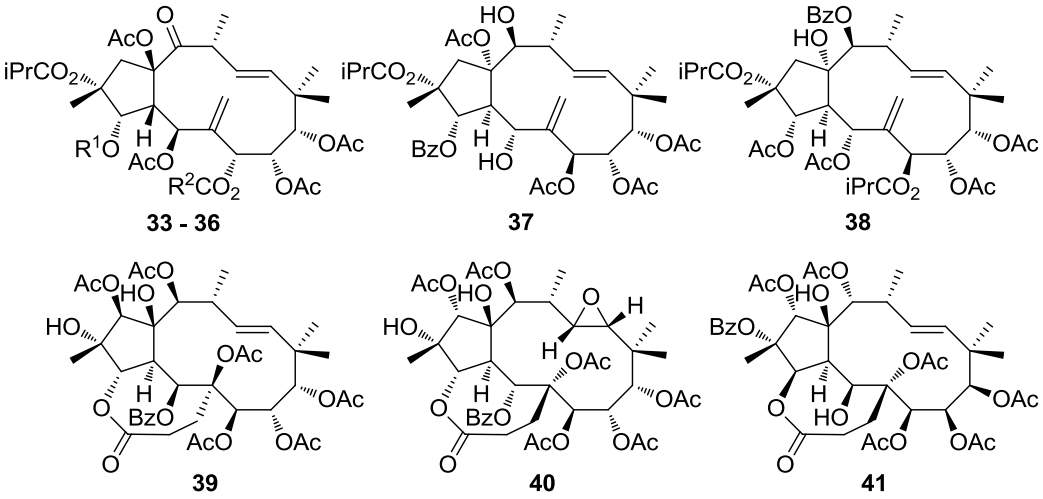


Fig. 9 Jatrophanes and bishomojatrophanes from *E. sororia*.

Table 2 Jatrophanes and bishomojatrophanes from *E. sororia*.

no.	name	R^1	R^2	ref
33	2α,7α-diisobutyroyloxy-3α-nicotinoyloxy-5β,8α,9α,15β-tetraactoxyjatropha -6(17),11E-diene-14-one	Nic	Me	24
34	2α-isobutyroyloxy-3α-nicotinoyloxy-5β,7α,8α,9α,15β-pentaactoxyjatropha-6(17),11E-diene-14-one	Nic	*i*Pr	24
35	3α-benzoyloxy-2α,7α-diisobutyroyloxy-5β,8α,9α,15β-tetraactoxyjatropha-6(17),11E-diene-14-one	Bz	*i*Pr	24
36	3α-benzoyloxy-2α-isobutyroyloxy-5β,7α,8α,9α,15β-pentaactoxyjatropha-6(17),11E-diene-14-one	Bz	Me	24
37	3α-benzoyloxy-5β,14β-dihydroxy-2α-isobutyroyloxy-7α,8α,9α,15β-tetraactoxyjatropha-6(17),11E-diene	-	-	24
38	14β-benzoyloxy-2α,7β-diisobutyroyloxy-15α-hydroxy-3β,5α,8α,9α-tetraactoxyjatropha-6(17),11E-diene	-	-	24
39	sororianolide A	-	-	25
40	sororianolide B	-	-	25
41	sororianolide C	-	-	25

Euphopeplin A (**42**) was isolated by Song *et al.* in 2010 from *E. peplus* together with two already known compunds.[28] Hegazy and co-workers isolated guyonianins E (**43**) and F (**44**) after repetitive chromatographic steps of the dichlormethane/methanol extract of *E. guyoniana*. Guyonianins E (**43**) and F (**44**) showed a moderate activity (IC_{50} = 70 and 100 µM, respectively) against human embryonic kidney cells (HKE293) in a test for their cytotoxic activities.[29] Their structures and the structure of euphopeplin A (**42**) are shown in Fig. 10.

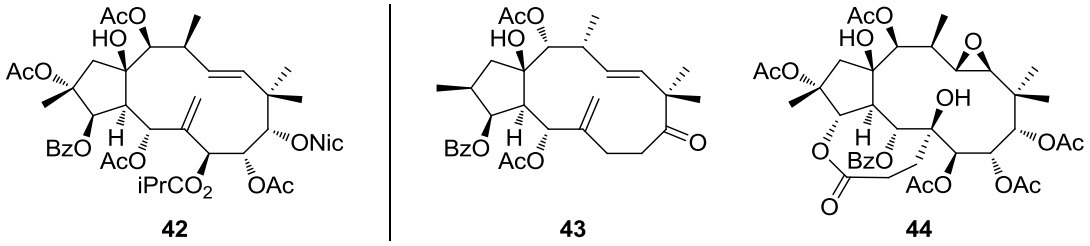


Fig. 10 Euphopeplin A (42**) and guyonianins E (**43**) & F (**44**).**

Aljancic *et al.* isolated six jatrophanes (euphodendrines A-F, **45**-**50**, see Fig. 11) from the Montenegrin spurge *E. dendroides* in 2011.[30] The euphodendrines A,B,D and E (**45**, **46**, **48**, **49**,) only differ in the ester functionalities, euphodendrine C (**47**) is the only one of these compounds that has no alcohol moiety, whereas euphodendrine F (**50**) has no exocyclic but a second endocyclic double bond. Fig. 11 and Table 3 show the structures of the newly isolated compounds and selected data of their biological evaluation.[30]

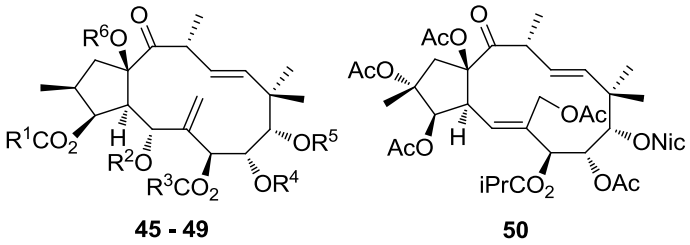


Fig. 11 Euphodendrines A-F (45-50**).**

Table 3 Euphodendrines A-F (45-50**) and their growth inhibitory effects on different cancer cell lines.**

no.	name	R^1	R^2	R^3	R^4	R^5	R^6	NCI-H460*	NCI-H461*	DLD-1*	U-87 MG*
45	euphodendrine A	Et	Ac	*i*Pr	Ac	Nic	H	46.6	44.8	59.3	155.3
46	euphodendrine B	*i*Pr	Ac	*i*Pr	Ac	Nic	H	16.2	17.2	22.1	107.7
47	euphodendrine C	Et	Ac	*i*Pr	Ac	Nic	Ac	-	-	-	-
48	euphodendrine D	*i*Pr	Ac	Me	Bz	Ac	H	21.3	30.1	42.7	52.6
49	euphodendrine E	Et	Ac	*i*Pr	Bz	Ac	H	21.9	49.8	37.9	73.1
50	euphodendrine F	-	-	-	-	-	-	14.8	90.8	75.3	65.5

*** The values presented here are IC_{50} [µM]**

Jatrophanes **51** and **52** (Fig. 12) were isolated in Iran by Shokoohinia *et al.* in 2011.[31] Several chromatographic steps were needed to yield compounds **51** and **52** from an acetone extract of *E. bungei* Boiss.

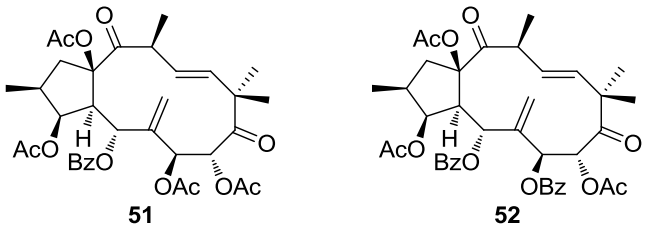


Fig. 12 Jatrophanes isolated by Shokoohinia *et al.*

After the isolation of esulatins A-F by Hohmann *et al.*, the same workgroup also reported the isolation of esulatin H-M (**53**-**58**), shown in Fig. 13.[32-36] Esulatins A-M were isolated from *E. esula*, as the name suggests. Esulatin G has a norparaliane skeleton,[37] whereas all the esulatins isolated by Hohmann and co-workers possess a jatrophane skeleton.

A set of human adherent cell lines of gynecological origin (HeLa, Ishikawa and MCF7) was used to test the esulatins isolated by Hohmann *et al.* for their antiproliferative activity using the MTT test[38]. Esulatin J (**55**) showed the highest activity of all tested compounds against all cell lines (HeLa 64.5 at 30 µg/mL, Ishikawa 98.4% at 30 µg/mL and MCF7 81.4% at 30 µg/mL). Esulatin I (**54**) and esulatin B (**8**) were also notably active against the cell growth of MCF7 (60.1% and 43.3% at 30 µg/mL each). The highest MDR-reversing activity in L5178 mouse lymphoma cells was found for esulatin J (**55**) and esulatin M (**58**). The activities were found to be two- and five-fold higher than verapamil, which was used as positive control in the tests.[32]

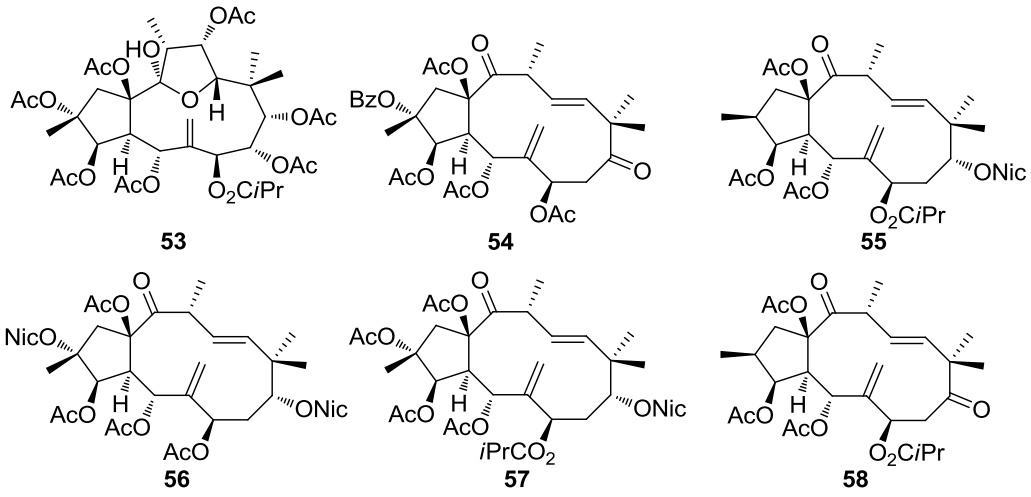


Fig. 13 Esulatins H-M (53-58**).**

Diterpenes possessing the jatrophane skeleton have also been isolated from other sources than *Jatropha* or *Euphorbia*, several novel compounds, isolated from *Pedilanthus*

tithymaloides, are outlined in Fig. 14. Compounds (**59** - **63**) were tested for antimalarial and antitubercularial effects against *Plasmodium falciparum* K1 strain and *Mycobacterium tuberculosis* H37Ra, respectively. Compounds **59**, and **61** - **63** were found to possess an antimalarial effect with LC_{50} values of 3.4 - 4.4 µg/mL. The antitubercularial effects were less pronounced, **59** was most active with 12.5 µg/mL minimum inhibitory concentration. Compounds **59**, **60** and **63** showed no activity in an additional antifungal assay against *Candida albicans* at 50 µg/mL.[39]

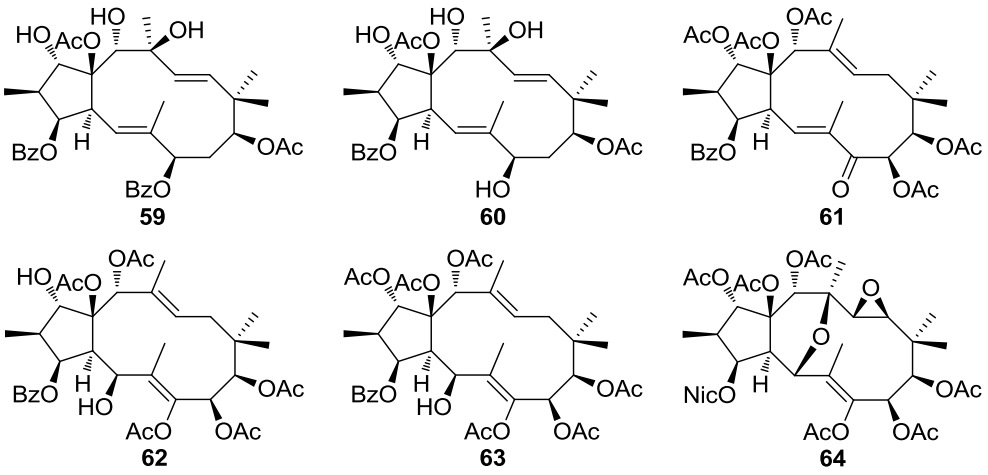


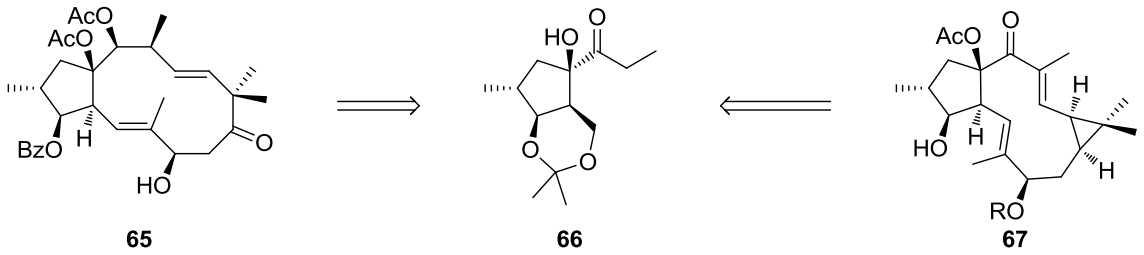
Fig. 14 Jatrophanes isolated from *P. tithymaloides.*

1.4 Previously Reported Synthetic Studies on *Euphorbiaceae* Diterpenes

1.4.1 Syntheses of Five-Membered Ring Synthons

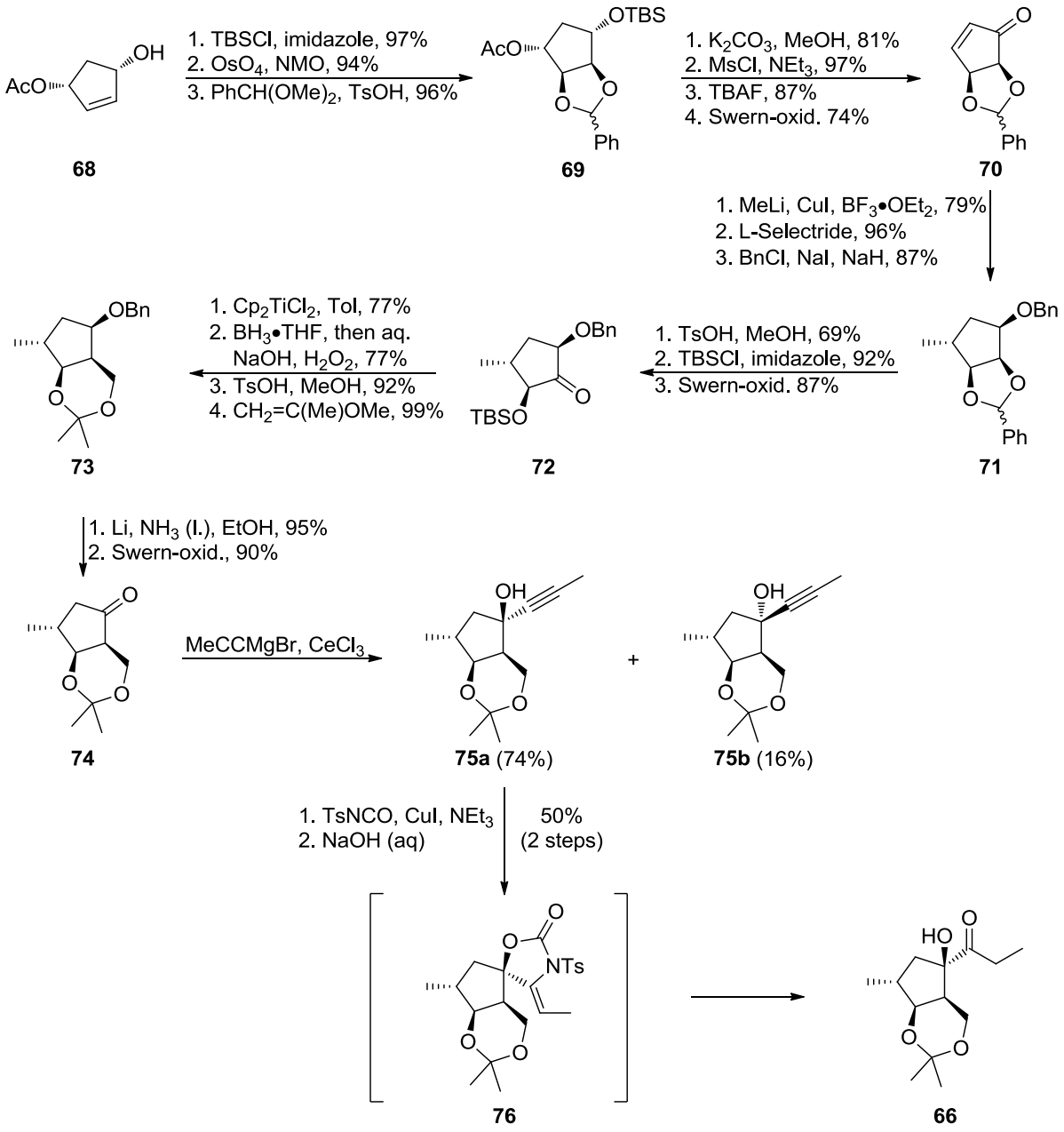
1.4.1.1 Yamamura's Cyclopentane Derivative

Yamamura *et al.* investigated the syntheses of *Euphorbiaceae* diterpenes and their biomimetic conversion. A simplified retrosynthetic analysis of *Euphorbiaceae* diterpenes is shown in Scheme 1.[40]



Scheme 1 Proposed application of Yamamura's cyclopentane derivative.

Scheme 2 shows the preparation of Yamamura's cyclopentane fragment (**66**). Silylation of literature known alcohol **68**[41] was followed by dihydroxylation of the double bond with osmium tetroxide. The resulting diol was proteceted to give benzylidene acetal **69**. After saponification of the acetyl group, mesylation of the resulting alcohol, deprotecion of the TBS group and subsequent oxidation of the free secondary alcohol, enone **70** was obtained. After conjugate addition of a methyl group the carbonyl moiety was reduced and benzylated to give **71**. Removal of the benzylidene acetal afforded a vicinal diol, selective TBS protection of the sterically less hindered hydroxy group led to a secondary alcohol which was then converted into a ketone (**72**) by a Swern oxidation. Next, Petasis methylenation and hydroboration led to the corresponding primary alcohol. **73** was obtained after desilylation and protection of the resulting diol as acetonide. Cleavage of the benzyl group *via* Birch reaction and oxidation of the alcohol under Swern conditions afforded ketone **74**. Nucleophilic addition of 1-propinylmagnesium bromide to the carbonyl function gave diastereomers **75a** and **75b**. Treatment of the main product (**75a**) with TsNCO furnished the desired cyclopentane segment **66** on a gram scale *via* cyclic intermediate **76**.

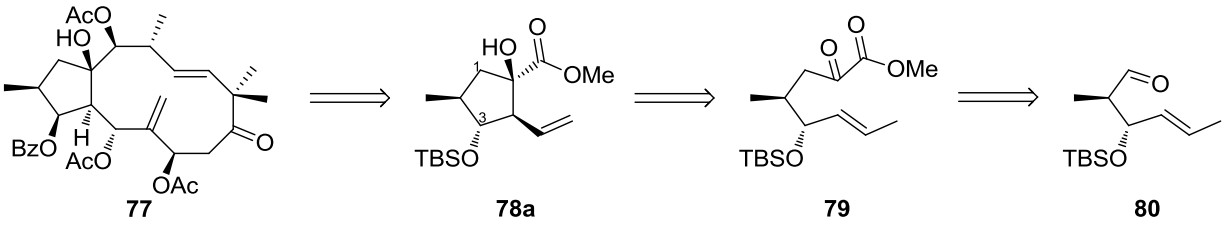


Scheme 2 Preparation of Yamamura's cyclopentane fragment (66**).**

1.4.1.2 Hiersemann's Cyclopentane Building Block

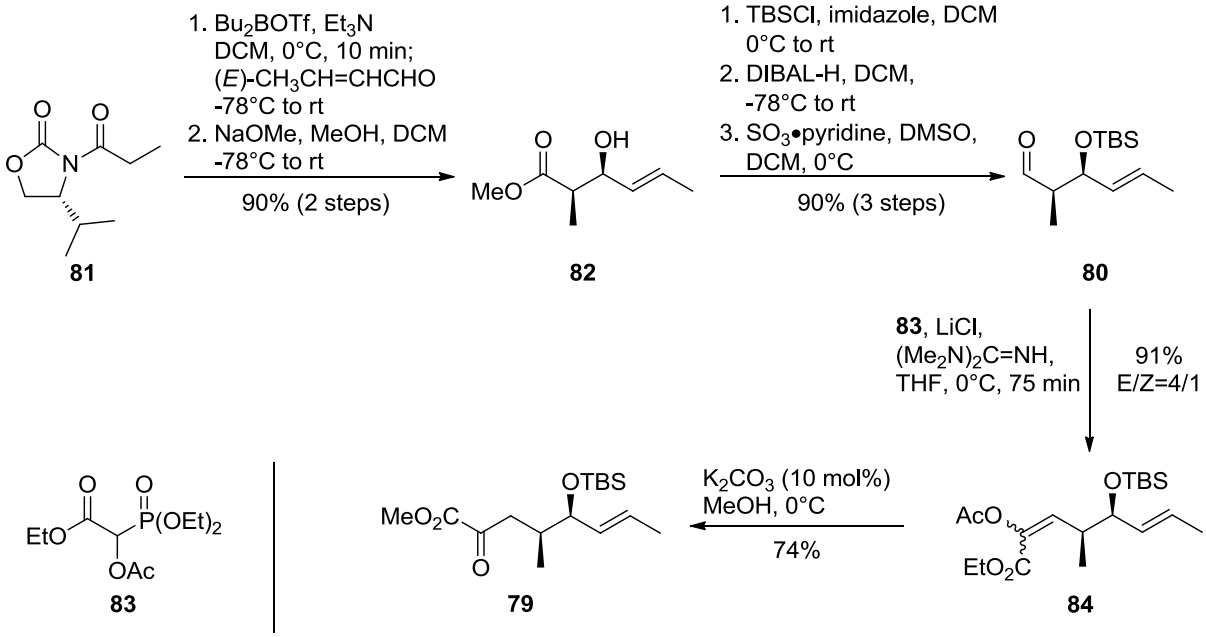
Helmboldt and Hiersemann reported a synthesis of a five-membered ring fragment of jatrophane diterpenes in 2003.[42] The key steps of their synthesis, shown in Scheme 3, are a Horner-Wadsworth-Emmons olefination and a carbonyl-ene reaction which led them to cyclopentane derivative **78a**. The diastereoselectivity of the carbonyl-ene reaction was expected to be more favorable for their desired product if the configuration of the C-3 stereocenter was *R*, whereas the configuration of the C-3 atom in natural products is *S*. Therefore, this stereogenic center has to be inverted in total syntheses of jatrophane

diterpenes. Certainly, a larger number of steps in total syntheses are necessary for this inversion but better yields in the synthesis of the cyclopentane fragment can be obtained in return.



Scheme 3 Retrosynthetic analysis of Hiersemann's cyclopentane fragment.

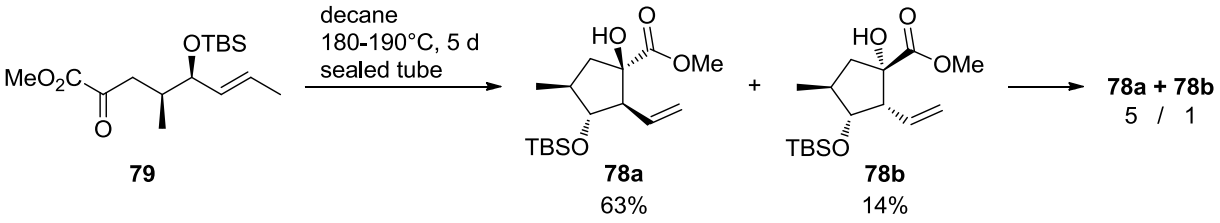
Scheme 4 outlines the first part of the synthesis of **78a** in detail. The synthesis of the five-membered ring synthon was improved and **78a** was applied to the preparation of the norjatrophane diterpene (-)-15-acetyl-3-propionyl-17-norcharaciol (**81**) by Hiersemann.[43] Evan's aldol reaction of **81** with crotonaldehyde delivered β-hydroxyester **82** after cleavage of the auxiliary with sodium methoxide. Protection of the alcohol moiety was followed by a reduction-oxidation sequence to give aldehyde **80**. Horner-Wadsworth-Emmons reaction of phosphonoacetate **83** and aldehyde **80** gave **84**, which delivered α-keto ester **79** under basic conditions.



Scheme 4 Synthesis of the cyclopentane fragment by Hiersemann - part 1.

As shown in Scheme 5, the carbonyl-ene reaction of **79** yielded the desired diastereomer **78a** in good yield. The side product **78b** could be converted in a mixture of both diastereomers

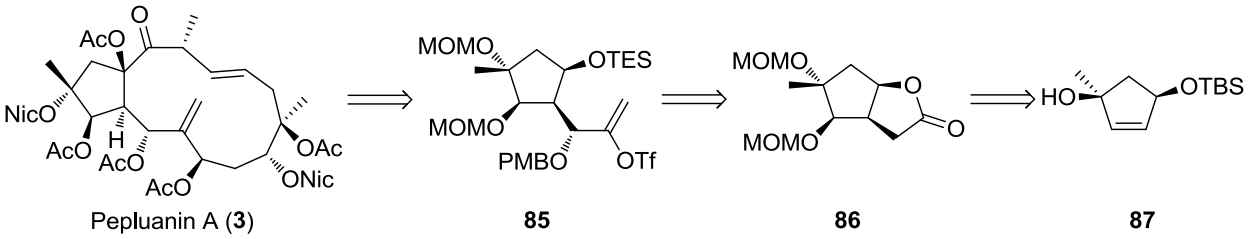
(**78a**/**78b**=5/1) again *via* a retro-ene/ene reaction under similar conditions as the original carbonyl-ene reaction. Recycling was reported with 180°C in decane and several days reaction time.[42]



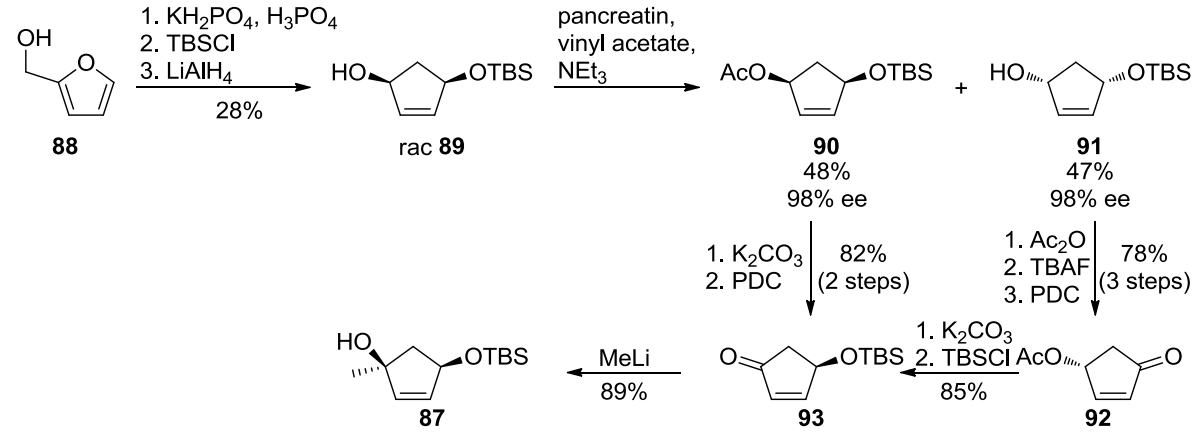
Scheme 5 Synthesis of the cyclopentane fragment by Hiersemann - part 2.

1.4.1.3 Mulzer's Cyclopentane Fragment

Mulzer reported the synthesis of a highly oxygenated cyclopentane synthon **85** for the total synthesis of jatrophane diterpenes.[44,45] Scheme 6 shows the retrosynthetic analysis which goes back to known alcohol **87**.[46]

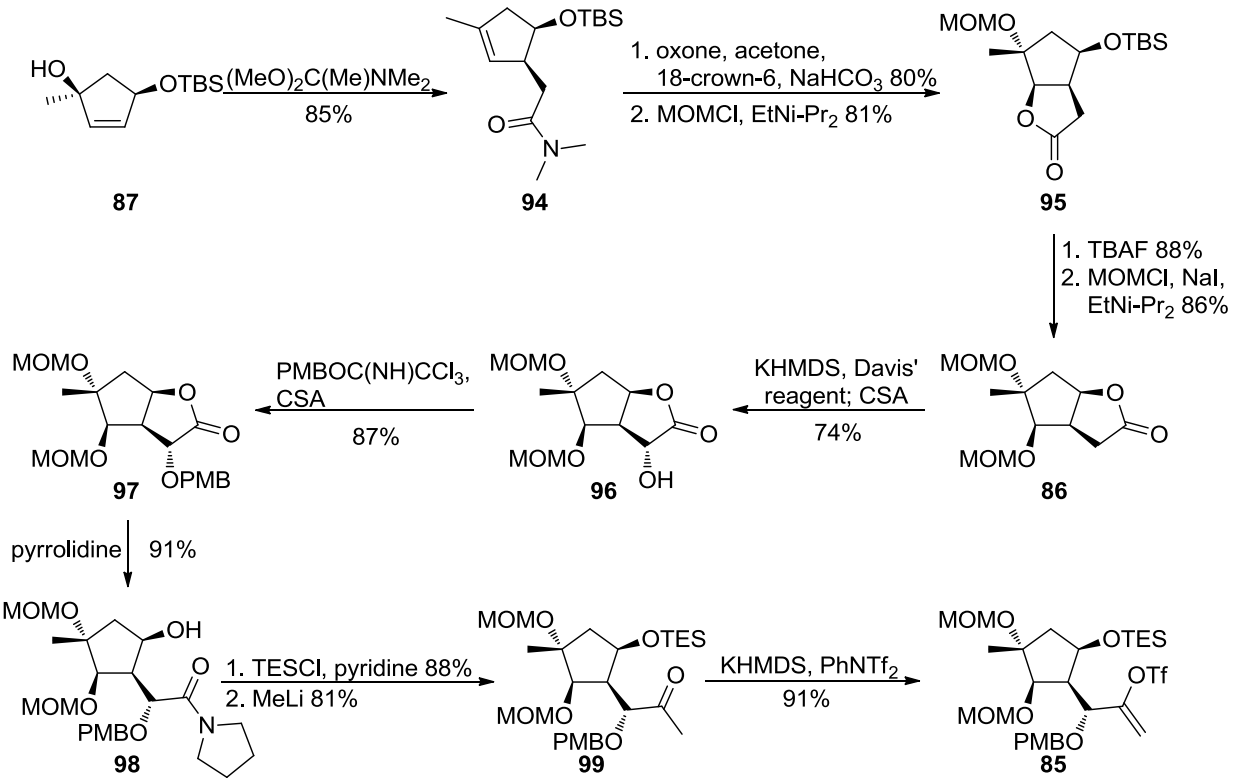


Scheme 6 Mulzer's retrosynthetic analysis.



Scheme 7 Peparation of tertiary alcohol 87**.**

An alternative preparation of alcohol **87**, shown in Scheme 7**,** was also presented. Furfuryl alcohol **88** was converted into a separable mixture of acetate **90** and alcohol **91** using a protocol reported by Curran *et al.*[47] These compounds were converted in a common intermediate, ketone **93**, using established chemistry.[48] Alcohol **87** was obtained by nucleophilic addition of methyl lithium.[46] The starting material (**68**) of the preparation of Yamamura's cyclopentane[40] can also be prepared in this fashion.



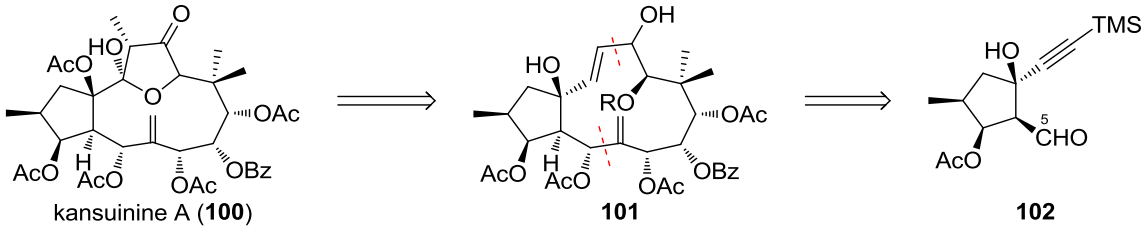
Scheme 8 Synthesis of Mulzer's cyclopentanyl vinyl triflate 85**.**

The following steps are shown in Scheme 8. Amide **94** was obtained from tertiary alcohol **87**, by a Claisen-Eschenmoser rearrangement. In the next step an epoxide was formed, which spontaneously yielded the requisite bicyclic lactone *via* intramolecular opening of the oxirane moiety with the newly installed amide during flash chromatography. The resulting tertiary alcohol was then protected as MOM ether **95**. Cleavage of the silyl ether directly gave the desired rearranged lactone. The resulting alcohol was protected as MOM ether (**86**) as well. Davis' oxidation gave the desired alcohol **96**, which was protected as PMB ether in the next step. Treatment of **97** with pyrrolidine yielded amide **98**. The free hydroxy group was TES protected before the amide group was converted to the corresponding methyl

ketone **99**. Kinetically controlled deprotonation and addition of $PhNTf_2$ to the reaction mixture finally afforded the desired synthon **85**.

1.4.1.4 Uemura's Cyclopentane Segment

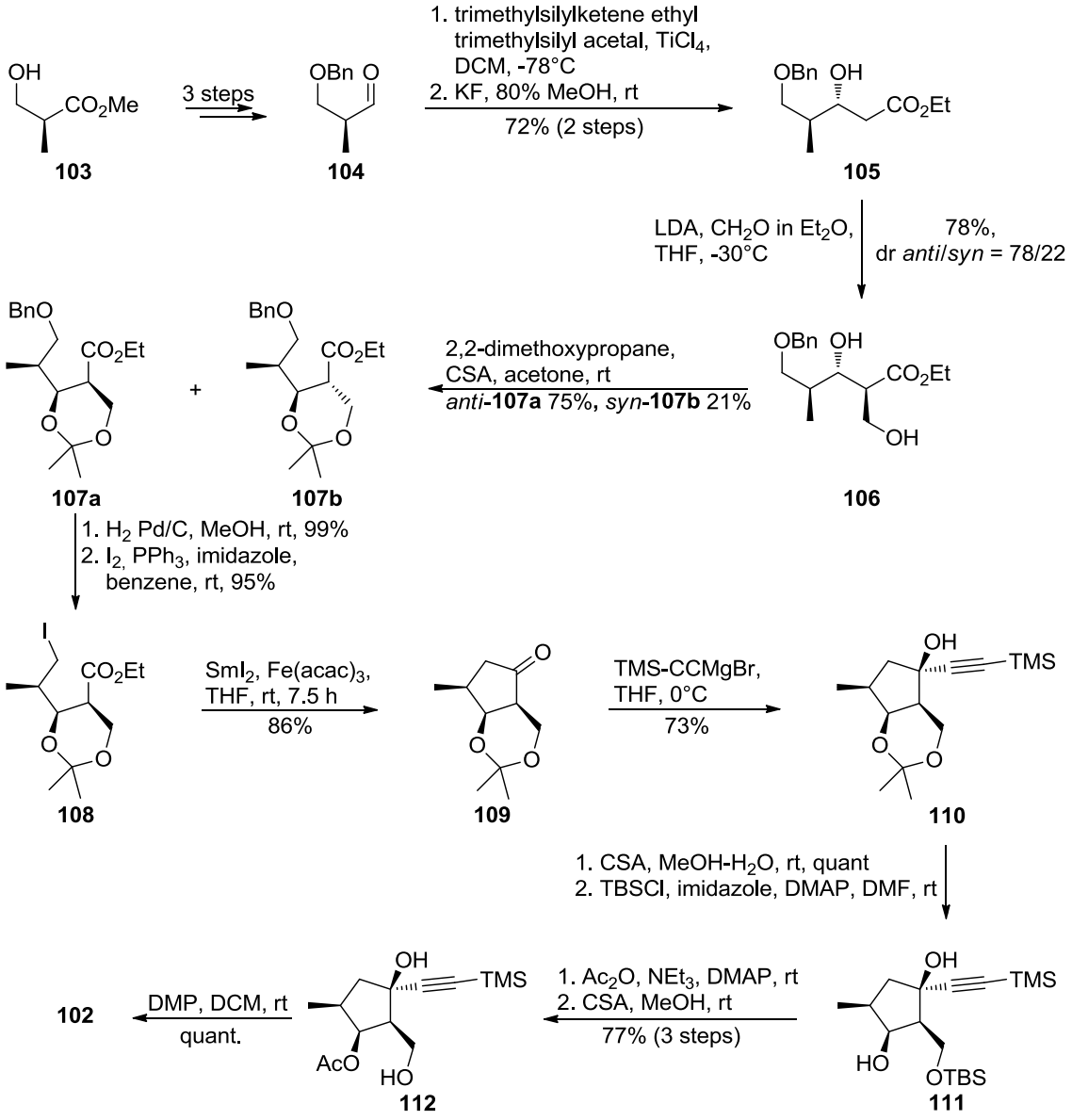
The synthesis of cyclopentane segment **102** was reported by Shimokawa, Takamura and Uemura in 2007.[49] As shown in Scheme 9, Uemura *et al.* envisaged the construction of the macrocycle of kansuinine A (**100**) *via* two NHK coupling reactions as key steps. Following their retrosynthetic rationale, the exocyclic double bond should be constructed via coupling of the C-5 aldehyde in cyclopentane-segment **102** with the requisite vinyl halide while final ring closing reaction should become feasible via reaction of TMS-alkyne derived vinyl halide with the corresponding aldehyde.



Scheme 9 Retrosynthetic analysis of kansuinine A (100**).**

The synthesis, shown in Scheme 10, starts with Mukaiyama aldol reaction of trimethylsilylketene ethyl trimethylsilyl acetal and aldehyde **104**[50,51], derived from β-hydroxyester **103**,[50,51] and sequential desilylation to give β-hydroxyester **105**. Diol **106** was obtained by treatment of **105** with LDA and a formaldehyde solution. After protection of the diol as acetonide, *anti*- and *syn*-**107** were separable by chromatography. Cleavage of the benzyl group and iodination under Appel conditions led to iodoester **108**. A variety of reaction conditions were tried for the intramolecular SmI_2-mediated nucleophilic acyl substitution. Intermediate **109** was obtained with 86% yield as best reported result. Noteworthy, protective groups other than the isopropylidene group or reaction of the unprotected diol tended to deliver protonated acyclic species as well as the cyclopentanes. Next, Grignard reaction of trimethylsilylethynylmagnesium bromide and cyclopentanone **109** gave tertiary alcohol **110** as single stereoisomer. Acid mediated deprotection and subsequent selective TBS protection of the primary alcohol delivered **111** before acetylation of the secondary alcohol and selective deprotection of the TBS group led to primary alcohol

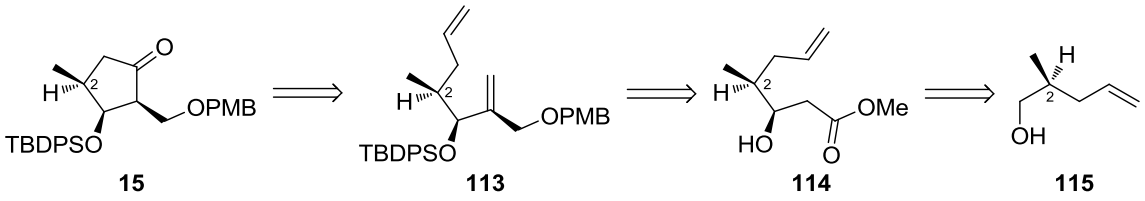
112. The preparation of the cyclopentane segment (**102**) was concluded by Dess-Martin oxidation of the requisite alcohol.



Scheme 10 Synthesis of Uemura's cyclopentane segment 102**.**

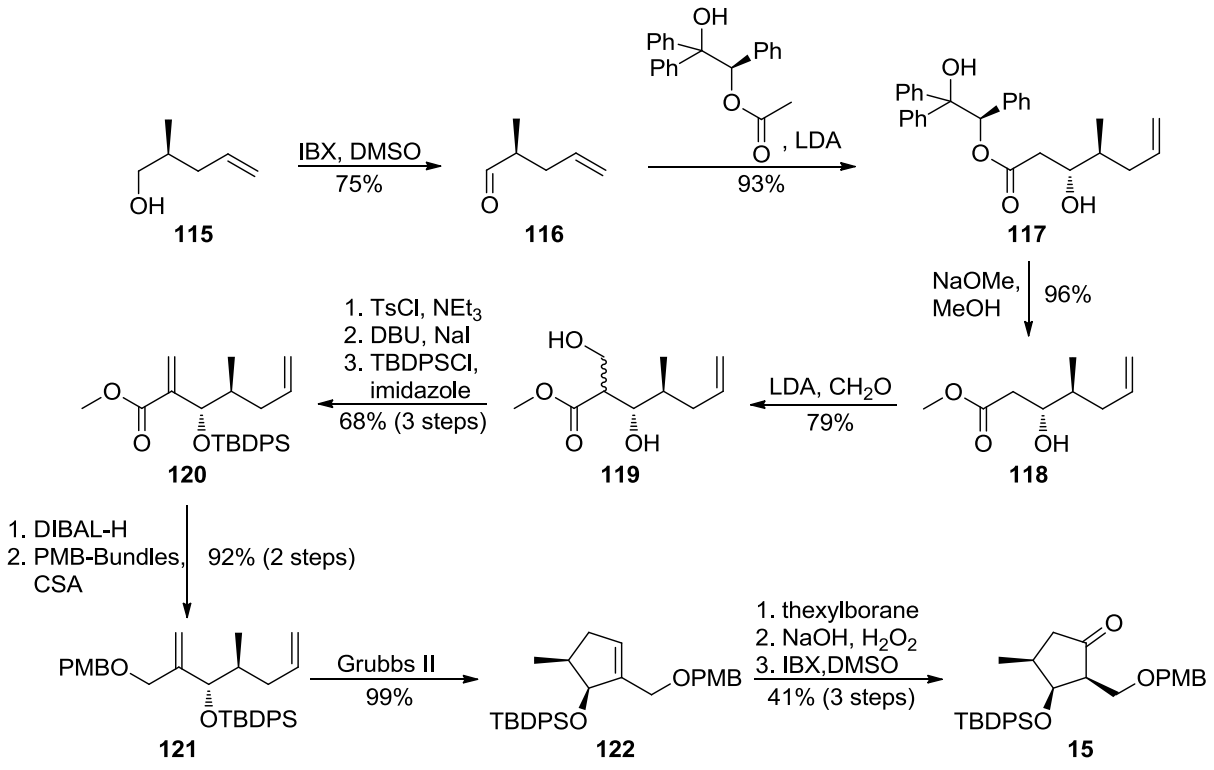
1.4.1.5 General Cyclopentane Segments of Lentsch and Rinner

The retrosynthesis of a cyclopentane segment (**15**) reported by Lentsch and Rinner is shown in Scheme 11.[16] The corresponding diastereomer with inverted configuration at C-2 (**14**) was also accessed via the same route. However, as the synthesis of this material is identical to the route towards **15**, further discussion is omitted at this point.



Scheme 11 Retrosynthesis of the cyclopentane segments by Lentsch and Rinner.

Alcohol **115** was obtained by Myers' alkylation of the corresponding pseudoephedrine propionamide with allyl iodide, followed by a lithium aminoborohydride reduction.[52] As shown in Scheme 12, oxidation of alcohol **115** with IBX gave aldehyde **116**. Stereoselective aldol reaction with (*R*)-HYTRA afforded **117** in a diasteriomeric ratio of at least 10:1 (ratio was determined by NMR analysis after transformation to the methyl ester **118**). The introduction of an exomethylene group was achieved *via* aldol reaction of **118** with formaldehyde, tosylation of the primary alcohol, and subsequent DBU-mediated elimination. Next, TBDPS protection of the remaining secondary hydroxy group afforded **120**. The ester function was reduced to the primary alcohol using DIBAL-H, and the primary hydroxy moiety was protected with PMB-Bundles reagent. Ring closing metathesis, mediated by Grubbs II catalyst, gave cyclopentene **122**. A hydroboration/oxidation sequence delivered cyclopentanone **15**.

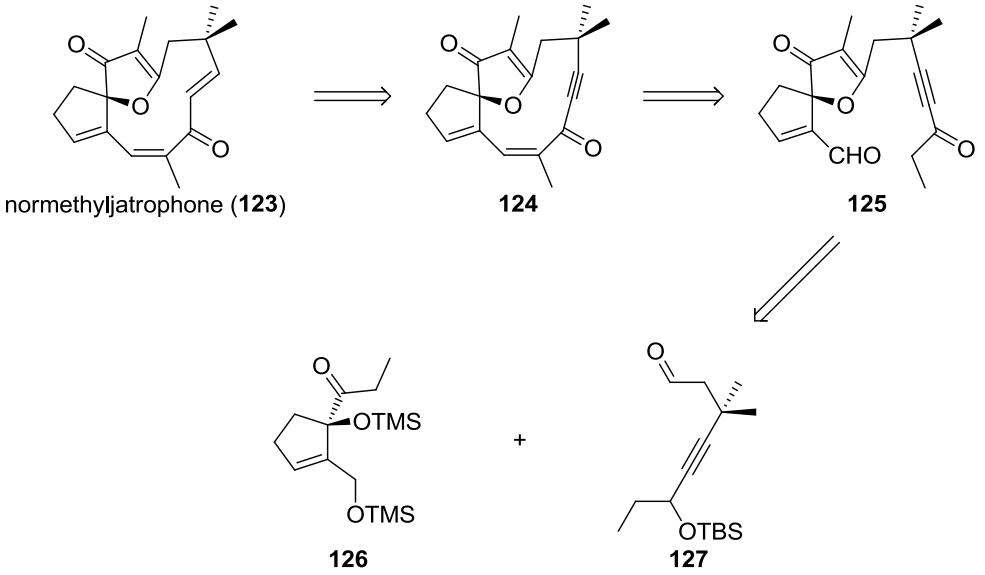


Scheme 12 Preparation of cyclopentane fragment 15 **by Lentsch and Rinner.**

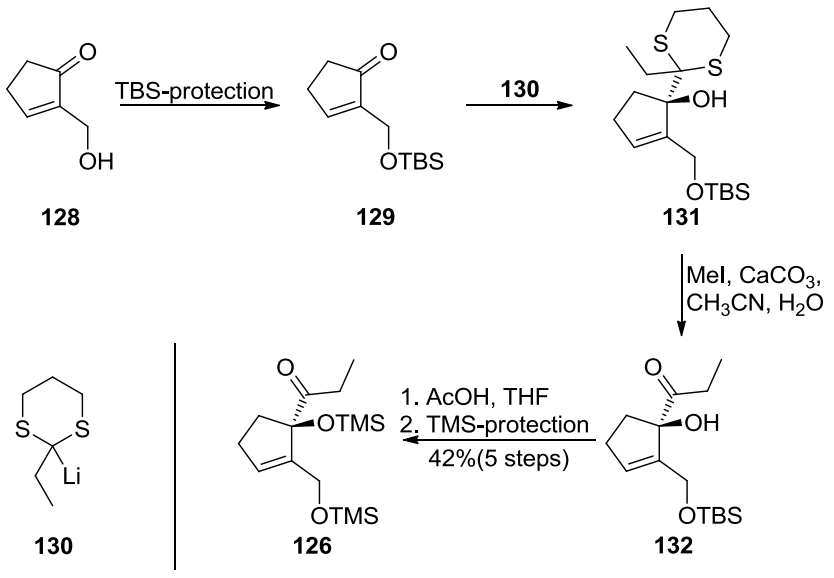
1.4.2 Total Syntheses of Jatrophane Diterpenes

1.4.2.1 Total Synthesis of (±) Normethyljatrophone by Smith et al. *1981*

With the synthesis of **123**, Smith *et al.* were the first to complete a total synthesis of a jatrophane diterpene.[12] The strategy, see Scheme 13, relied on a general method for the construction of a 3-(2H)-furanone ring system they had developed in the first place. Later, a Mukaiyama aldol reaction closes the macrocyclic ring before the conversion of acetylene (**124**) to a *trans*-fused double bond concludes the synthesis of normethyljatrophone (**123**).



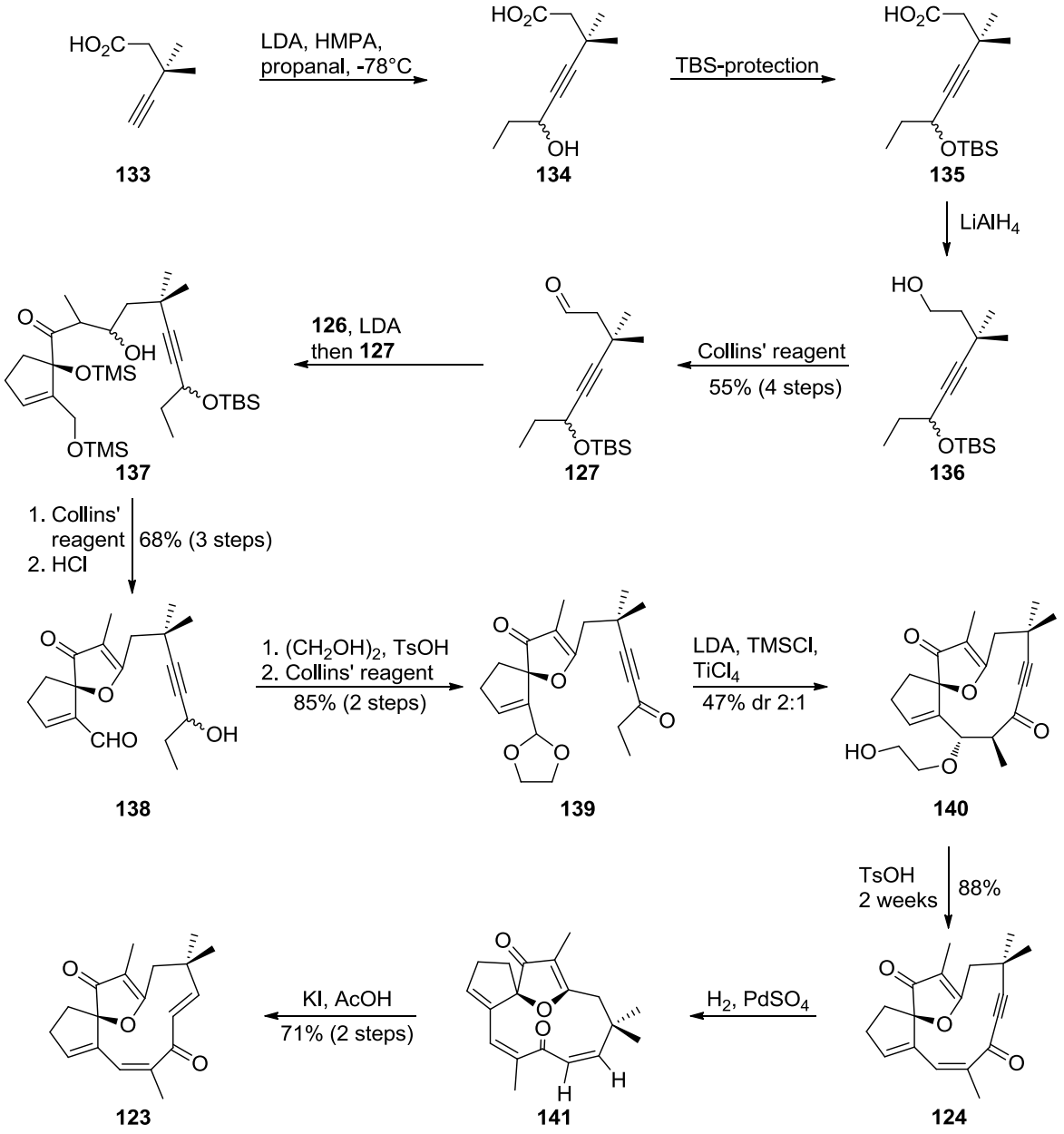
Scheme 13 Retrosynthetic analysis of normethyljatrophone (123**).**



Scheme 14 Smith's cyclopentene building block.

Ketone (**126**) was built from α-hydroxymethylcyclopentenone (**128**), as outlined in Scheme 14.[53,54] Silylation of **128** was followed by treatment with lithiodithiane (**130**) and gave **131**, which was then hydrolyzed to give ketone **132**. Cleavage of the TBS group and subsequent TMS protection of both free hydroxy groups delivered desired ketone **126** with an overall yield of 42%.

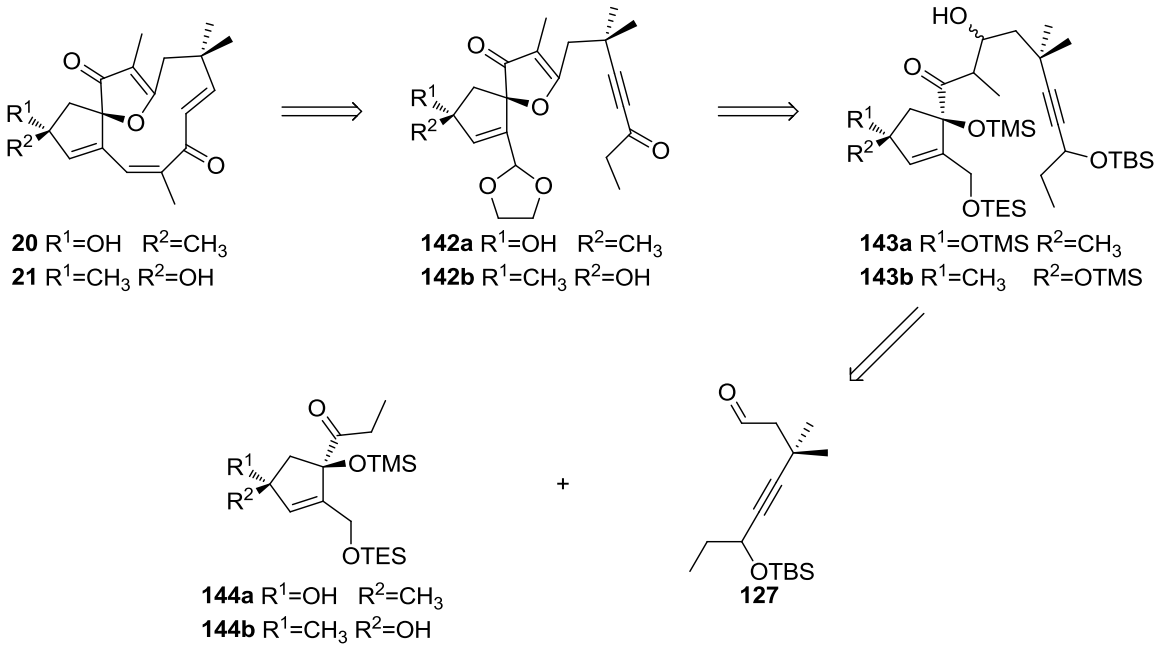
As shown in Scheme 15, aldehyde (**127**) was prepared from 3,3-dimethyl-4-pentynoic acid (**133**). The hydroxy acid (**134**) was obtained by treatment of the dianion of **133** with propanal. TBS protection led to **135**, which was reduced with lithium aluminum hydride to give the primary alcohol **136**. Treatment with Collins' reagent[55] gave aldehyde **127** in 55% yield over 4 steps. Following the protocol to construct the spirofuranone array which was developed prior to the synthesis, aldehyde **127** was added to the deprotonated ketone **126** to give the β-hydroxy ketone **137**. Spirofuranone (**138**) was obtained in an overall yield of 68% after oxidation, acid catalyzed deprotection and cyclization/dehydration. Protection of the aldehyde as acetal and the oxidation of hydroxy group with Collins reagent[55] gave ketone **139**. Direct aldol cyclization failed, but an attempt of Mukaiyama aldol reaction with the silyl enol ether and the acetal was successful and delivered **140** as major diastereomer. Both diastereomers were found to eliminate ethylene glycol upon treatment with *p*-toluenesulfonic acid and gave **124** after sufficiently long reaction times. The long reaction time was necessary to achieve isomerization of the less stable *E*-isomer. In the final steps of this synthesis, the acetylene had to be converted into the *trans* olefin. A direct approach failed, probably due to transannular interactions, but selective *cis* hydrogenation led to **141**, which could be isomerized to normethyljatrophone (**123**). In summary, the total synthesis of racemic normethyljatrophone (**123**) has been reported with an overall yield of 5.6% in 15 steps starting from cyclopentenone (**128**).



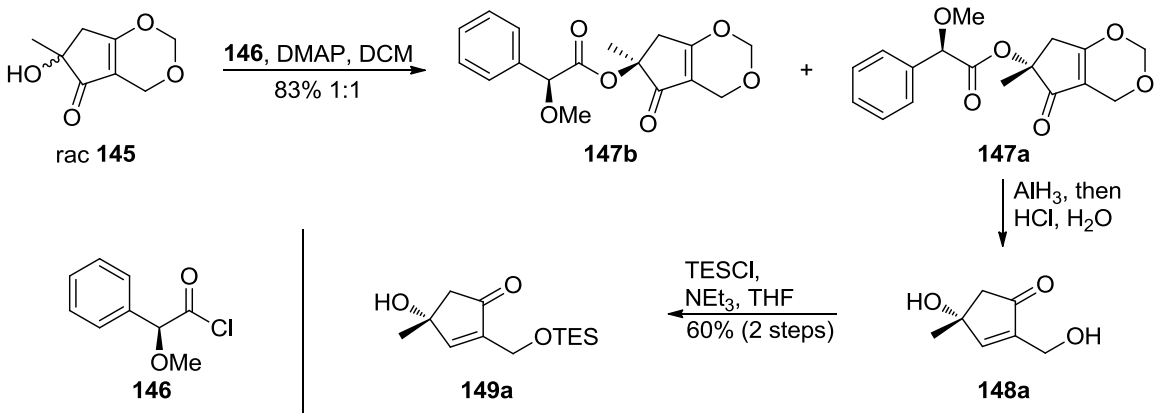
Scheme 15 Synthesis of normethyljatrophone (123**).**

1.4.2.2 Total Synthesis of (+)-Hydroxyjatrophone A and (+)-Hydroxyjatrophone B by Smith et al. *1989*

In close analogy to the earlier published total synthesis of normethyljatrophone,[12] Smith *et al.* reported the total synthesis of the diastereomers (+)-hydroxyjatrophone A (**20**) and(+)-hydroxyjatrophone B (**21**) in 1989.[15] An intramolecular Mukaiyama acetal-aldol reaction was envisaged to construct the 11-membered macrocycle as key step, as shown in Scheme 16. The 3(2H)-spirofuranone was built up from acid-promoted cyclization. Early stage synthons are ketones **144a**/**144b** and aldehyde **127** that are used in an aldol reaction to synthesize intermediates **143a** and **143b**.

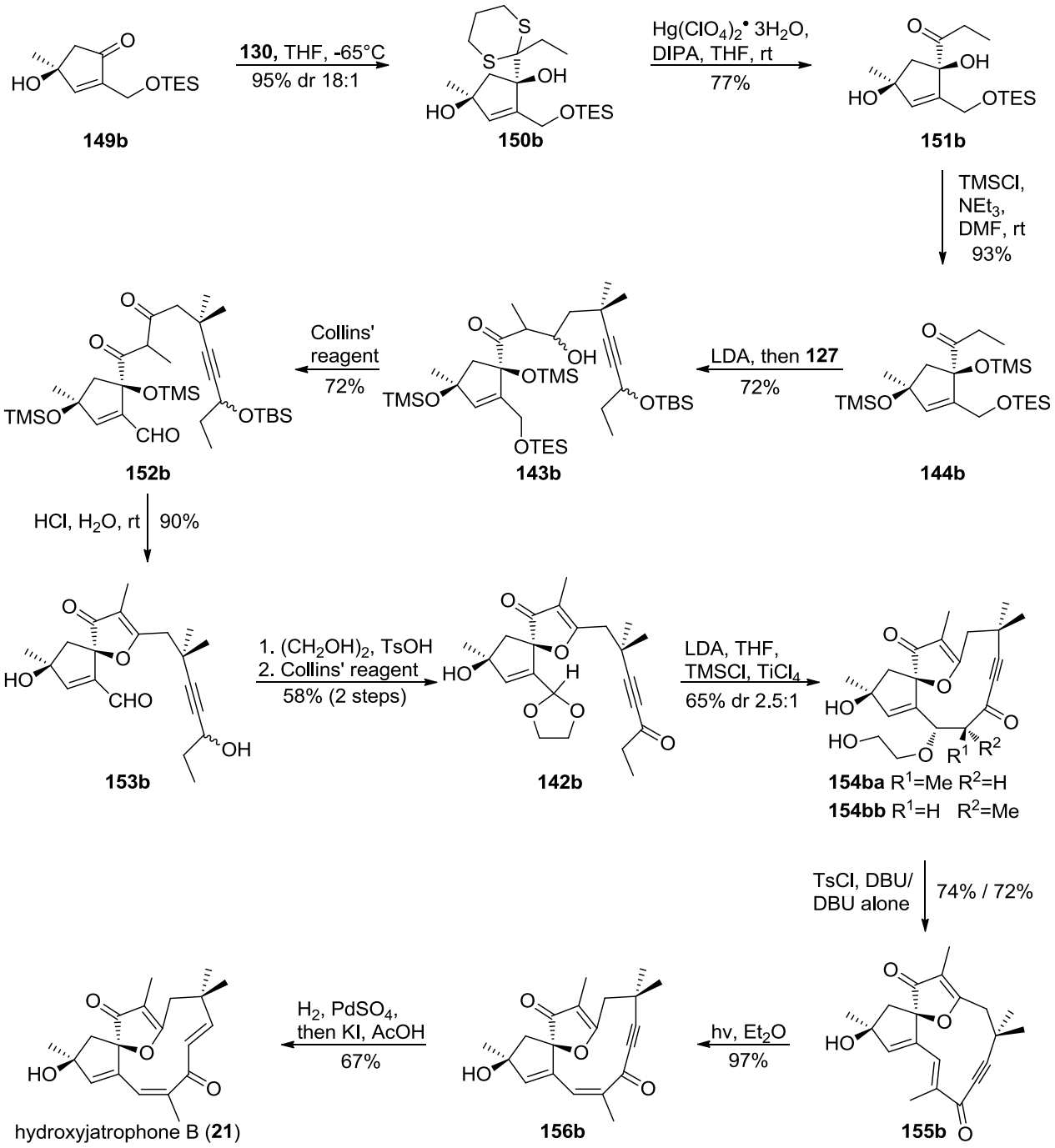


Scheme 16 Retrosynthetic analysis of (+)-hydroxyjatrophone A (20**) and (+)-hydroxyjatrophone B (**21**).**



Scheme 17 Synthesis of (+)-hydroxyjatrophone A (20**) and (+)-hydroxyjatrophone B (**21**) – part 1.**

Racemic tertiary alcohol **145**, which is available from 1,3-cyclopentenetione in three steps[56], was treated with (+)-*O*-methylmandeloyl chloride (**146**) to give diastereomeric esters **147a** and **147b**, as shown in Scheme 17. After separation of the diastereomers by flash chromatography, the ester moiety in **147a** was cleaved with aluminum hydride. From the resulting diol **148a** the desired ketone (-)-**149a** was obtained after protection as triethyl silyl ether. (+)-**149b** was obtained from ester **147b** in the same fashion in a yield of 63%, thus discussion within the scheme is omitted.



Scheme 18 Synthesis of (+)-hydroxyjatrophone A (20**) and (+)-hydroxyjatrophone B (**21**) – part 2.**

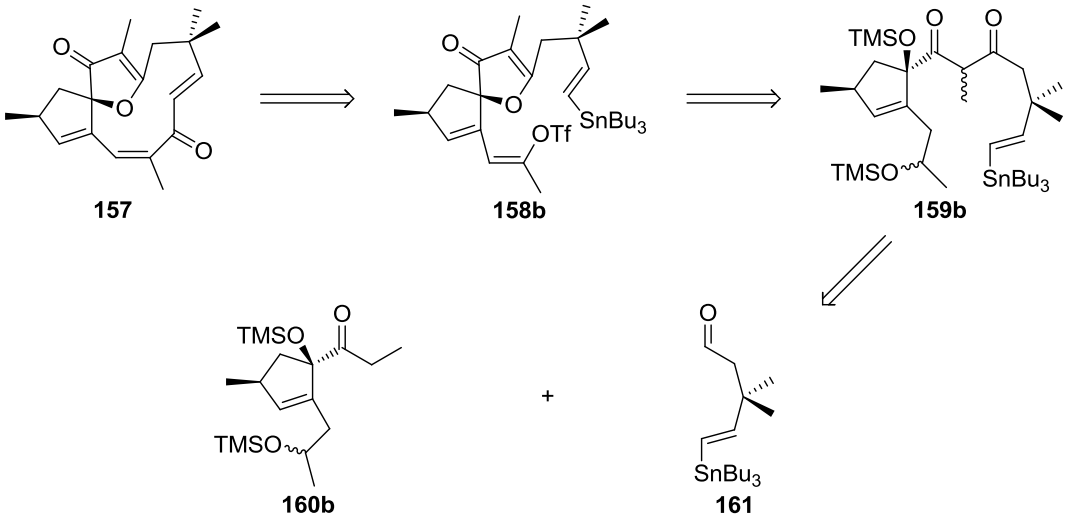
Scheme 18 shows the synthesis of (+)-hydroxyjatrophone A (**20**) and (+)-hydroxyjatrophone B II (**21**). Addition of dithiane **130** to ketone **149b** provides **150b** in good yield and diastereomeric ratio. Hydrolysis of the dithiane moiety with mercury (II) perchlorate yields diol-ketone **151b**. Protection leads to key intermediate **144b**. After deprotonation and addition of the racemic aldehyde **127** that was already used in the synthesis of normethyljatrophone (**123**), a diastereomeric mixture of β-hydroxyketones **143b** was

obtained. Treatment with Collins' reagent gave enal-dione **152b**. Acid promoted cyclization and desilylation led to the furanone array in **153b**. Ketalization of **153b** and subsequent oxidation gave advanced intermediate **142b**, which reacts under the known Mukaiyama aldol conditions to give a diastereomeric mixture of products (**154ba**/**154bb**). The major diastereomer **154ba** (R^1=Me, R^2=H) gave the corresponding *trans* olefin **155b** after treatment with *p*-toluenesulfonyl chloride and DBU. However, the minor diastereomer **154bb** (R^1=H, R^2=Me) eliminated ethylene glycol efficiently under treatment with DBU to give **155b**, without the prior conversion into a tosylate. Photoisomerization converted the *trans* double bond into a *cis* double bond (**156b**). The final step was hydrogenation of the alkyne and isomerization to the desired *trans* double bond in (+)-hydroxyjatrophone B (**21**).

(+)-Hydroxyjatrophone A (**20**) was synthesized in a similar fashion with a slightly changed order of reactions. The C-2 TMS protected derivative of **149a** was used instead of using the free hydroxy group in the lithio dithiane (**130**) addition step. Hydrolysis of the dithiane moiety followed by silylation of the tertiary alcohol leads to *tris*-protected triol **144a** in 20% overall yield starting from **149a**. The remaining steps are identical to the shown synthesis of (+)-hydroxyjatrophone B (**21**) shown in Scheme 18.

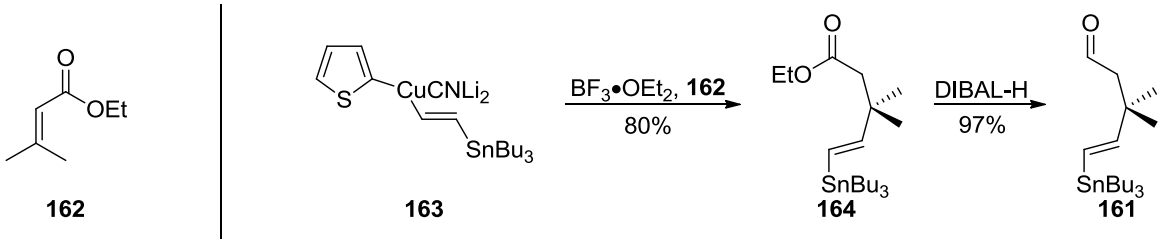
*1.4.2.3 Total Synthesis of (±)-***epi-***Jatrophone and (±)-Jatrophone by Hegedus* **et al.** *1990*

After Smith *et al.* synthesized racemic jatrophone, Hegedus *et al.* reported the total synthesis of racemic-*epi*-jatrophone (**157**) and racemic jatrophone (**1**) using palladium-catalysis.[13] Stille *et al.* developed a palladium-catalyzed carbon-carbon bond-forming process of vinylic triflates and organostannanes, the so called "Stille carbonylative cross-coupling".[57-59] This technique was used in the final steps of the synthesis as shown in the retrosynthetic analysis (Scheme 19).



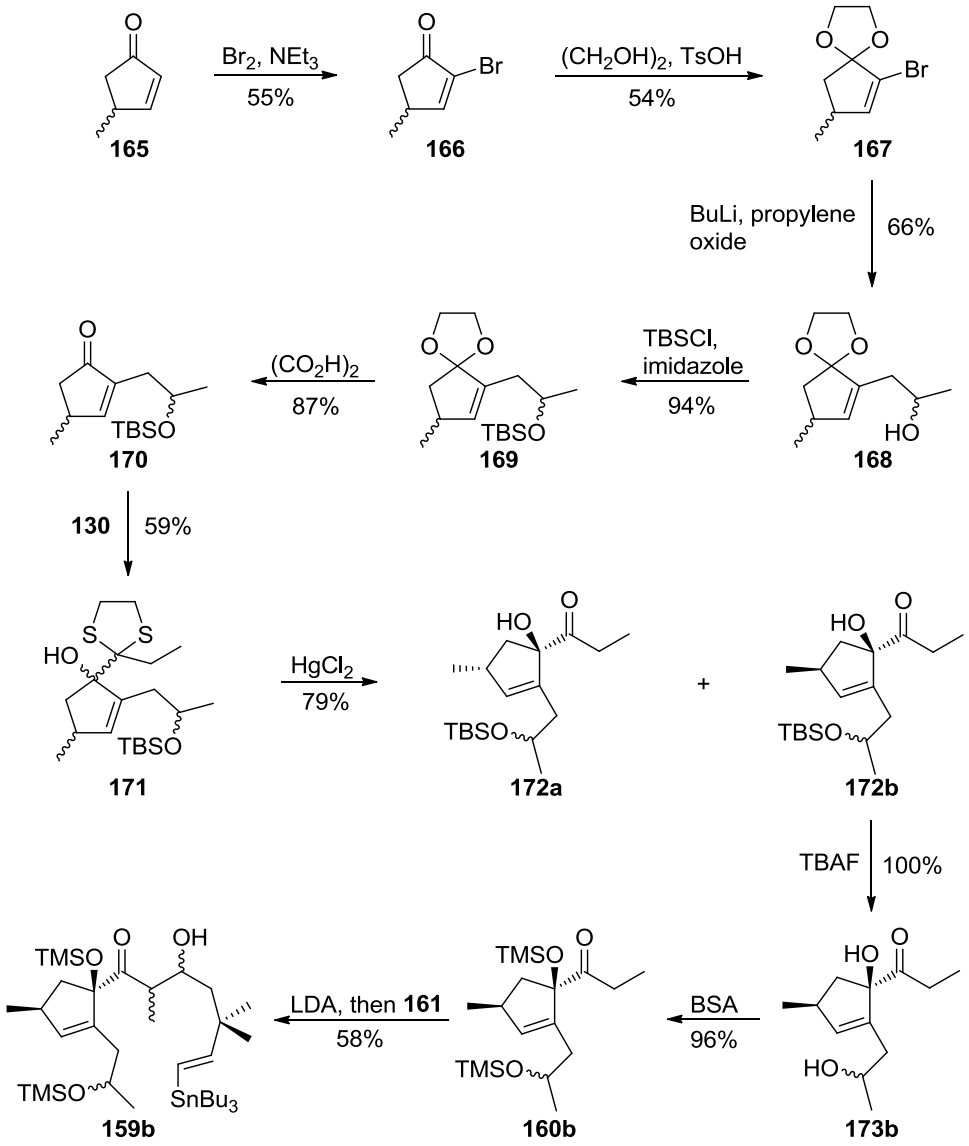
Scheme 19 Hegedus' retrosynthetic analysis of (±)-*epi*-jatrophone (157**).**

3(2H)-spirofuranone **158b** was accessible through acid-mediated cyclization dehydration as reported by Smith *et al.*[12] Its precursor 1,3-diketone **159b** was synthesized by aldol reaction of ketone **160a** and vinyltin-bearing aldehyde **161**.



Scheme 20 Hegedus' synthesis of (±)-*epi*-jatrophane (157**) - part 1.**

Conjugate addition of thiophene derived vinyltin **163** to ethyl 3,3-dimethylacrylate (**162**) afforded **164**. Reduction of the ester with DIBAL-H provided the vinyltin bearing aldehyde **161**, as shown in Scheme 20.



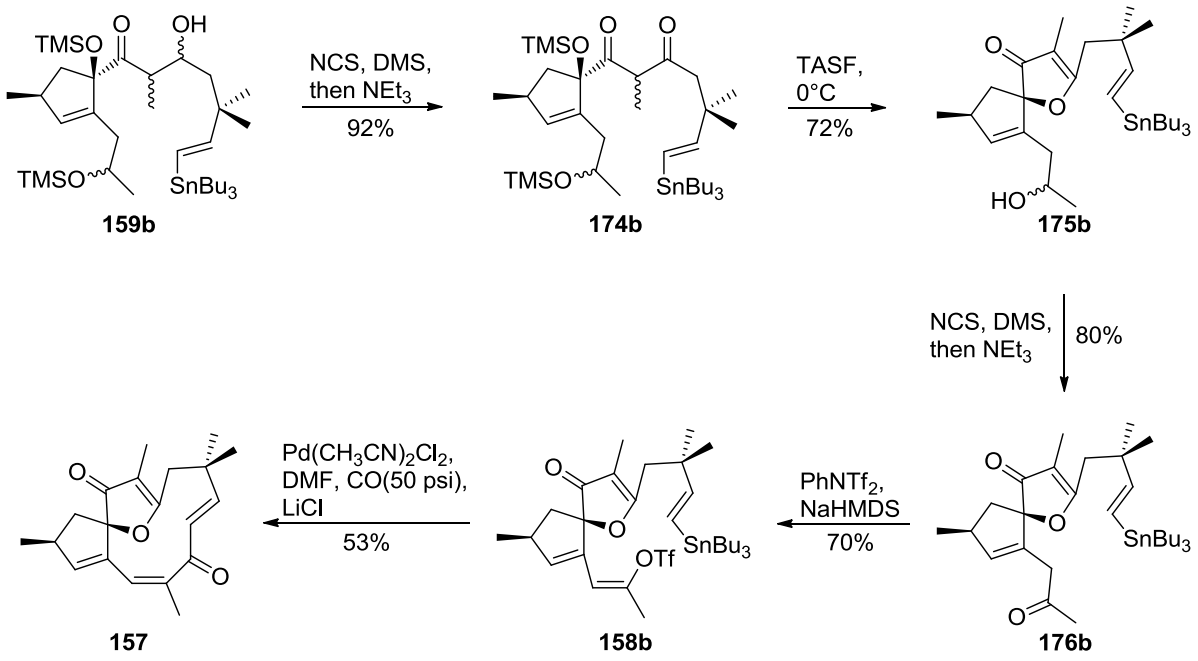
Scheme 21 Hegedus' synthesis of (±)-*epi*-jatrophane (157**) - part 2.**

The approach to compound **159b**, shown in Scheme 21 started with a bromination/dehydrobromination sequence to afford **166**.[60,61] Ketalization provided **167**, which was converted to the diastereomers **168** after halogen-metal exchange and addition of propylene oxide.[62] Protection of the hydroxy group as a TBS ether gave **169**, which was converted to α,β-unsaturated ketone **170** (16% yield for the overall sequence) under acidic conditions.

Through addition of lithio-dithiane **130**, a complex mixture of diastereomers (**171**) was obtained.[63] The dithiane moiety was removed with mercury (II) chloride to give target molecule **172b** and its stereoisomer **172a** (47% for both steps, 1:9 ratio). The major product (diastereomer **172b**) was used to synthesize (±)-*epi*-jatrophone (**157**), whereas the minor product **172a** was used in the synthesis of (±)-jatrophone (**1**). The TBS ether was cleaved

with TBAF, the resulting diol **173b** was protected as TMS ether **160b** on both hydroxy groups. Intermediate **159b** was accessible *via* an aldol reaction of ketone **160b** and aldehyde **161**.

Scheme 22 shows further oxidation of hydroxyketone **159b** which provided 1,3-diketone **174b**. The cyclization was accomplished *via* treatment of **174b** with TASF, an anhydrous fluoride source. Because other approaches failed, it was necessary to conduct the cyclization under aprotic conditions. Conveniently this method also cleaved the other TMS ether, so oxidation of the secondary hydroxy group led to diketone **176b**. This could be done without the need for another deprotection step. Conversion of the newly generated ketone into Z-vinylic triflate gave key intermediate **158b**. In the final step *epi*-jatrophane (**157**) was obtained by a reaction that is known today as Stille carbonylative cross-coupling.[59]

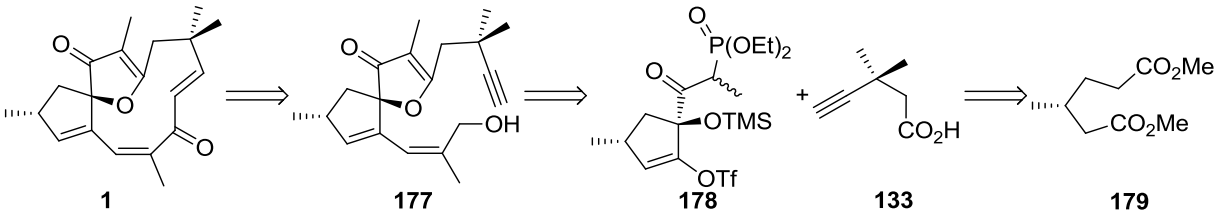


Scheme 22 Hegedus' synthesis of (±)-*epi*-jatrophane (157**) – part 3.**

(±)-Jatrophone (**1**) was synthesized following exactly the same route from the minor occurring diastereomer **172a** after addition of dithiane **130**.

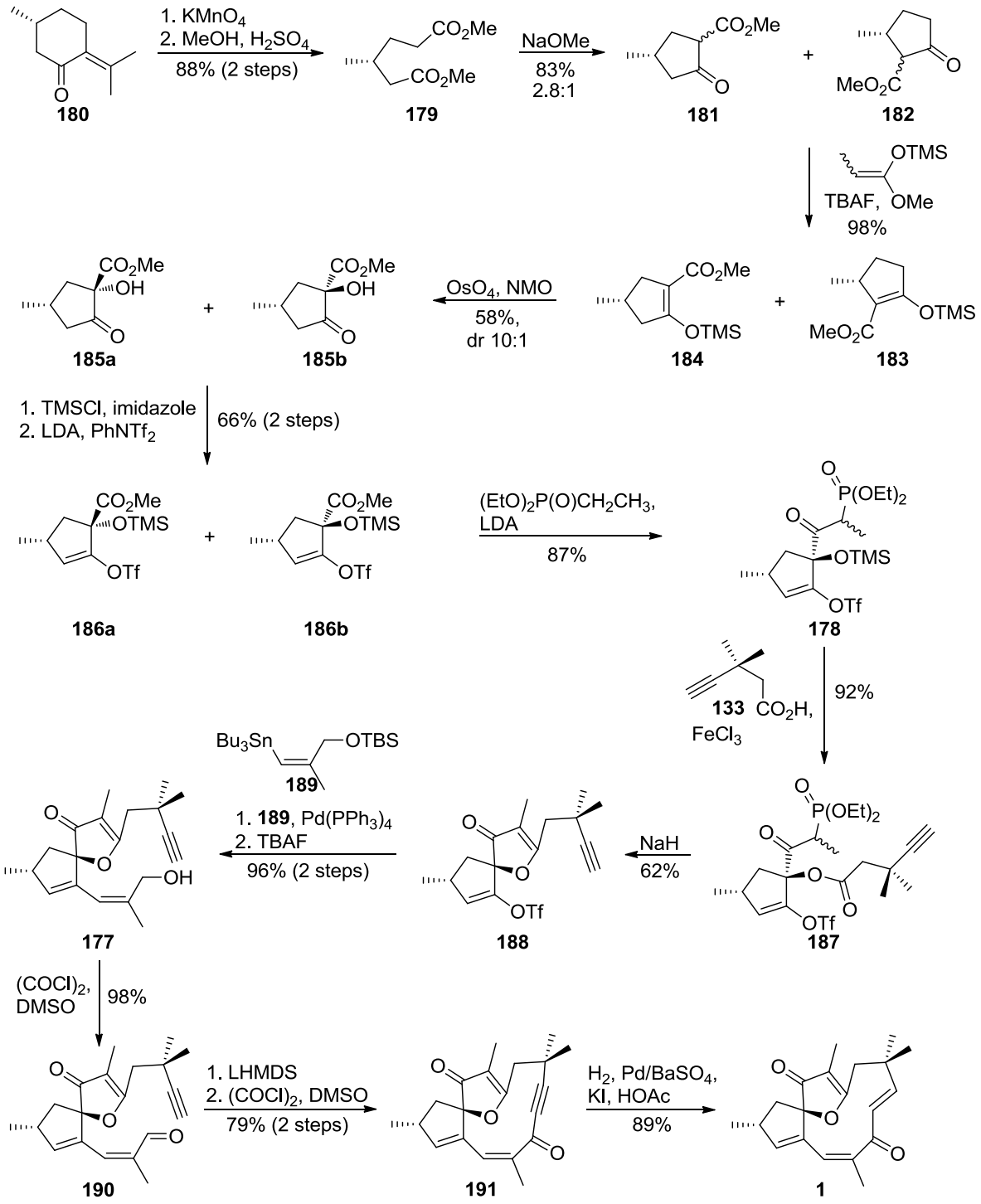
1.4.2.4 Total Synthesis of (+)-Jatrophone 1992 by Wiemer et al.

In 1992, Han and Wiemer were the first to report an enantiopure synthesis of (+)-jatrophone.[14] The retrosynthetic analysis of (+)-jatrophone (**1**) is shown in Scheme 23.



Scheme 23 Wiemer's retrosynthetic analysis of (+)-jatrophone (1).

The synthesis of (+)-jatrophone (**1**) is shown in Scheme 24 in detail. (*R*)-Pulegone (**180**) was used as a chiral source in this synthesis as an optical pure starting material. Oxidation of the starting material with $KMnO_4$ and subsequent esterification yielded 3-methyl diadipate (**179**).[64] Regioisomers **181** and **182** were obtained after a Dieckmann condensation.[65] Separation of these regioisomers was postponed after the introduction of an α-hydroxy substituent.[66] Both regioisomers **181** and **182** were converted to the corresponding silyl enol ethers **183** and **184**. Diastereomers **185a** and **185b** were obtained by treatment of silyl enol ethers **183**, which was left primarily unreacted, and **184** with OsO_4 and NMO and removal of the undesired regioisomers. The next two steps provided triflates **186a** and **186b**, which is referred to as starting material in the publication that reports on the synthesis of (+)-jatrophone (**1**).[14] However, reaction of triflate **186b** and diethyl ethylphosphonate gave β-keto phosphonate **178**.[67] Acetylenic acid **133** was converted into the corresponding acid chloride, and was then reacted with β-keto phosphonate **178** in a $FeCl_3$-catalyzed acylation reaction yielding intermediate **187**. Furanone **188** was obtained through an intramolecular Horner-Wadsworth-Emmons reaction by treatment of **187** with NaH in DME. In previous studies Wiemer *et al.* investigated this method, whereas they originally expected better yields from treatment with K_2CO_3 than NaH.[68,69] Coupling of organostannane **189** and triflate **188** and subsequent deprotection afforded advanced primary alcohol **177**, which was oxidized to the corresponding aldehyde (**190**) in the next step using Swern conditions. Macrocyclization of acetylenic aldehyde **190** was accomplished by treatment with LHMDS under strictly anhydrous conditions. Subsequent Swern oxidation afforded acetylene **191**, which was converted to optical active (+)-jatrophone (**1**) following Smith's procedure for the reduction of ynone **191** to the natural product.[12,15] Optical rotation of synthetic (+)-jatrophone was +289°, nearly identical to natural (+)-jatrophone (+292°). Impurities of this grade were expected since (+)-pulegone (**180**, *ee* 98%) was used as starting material.

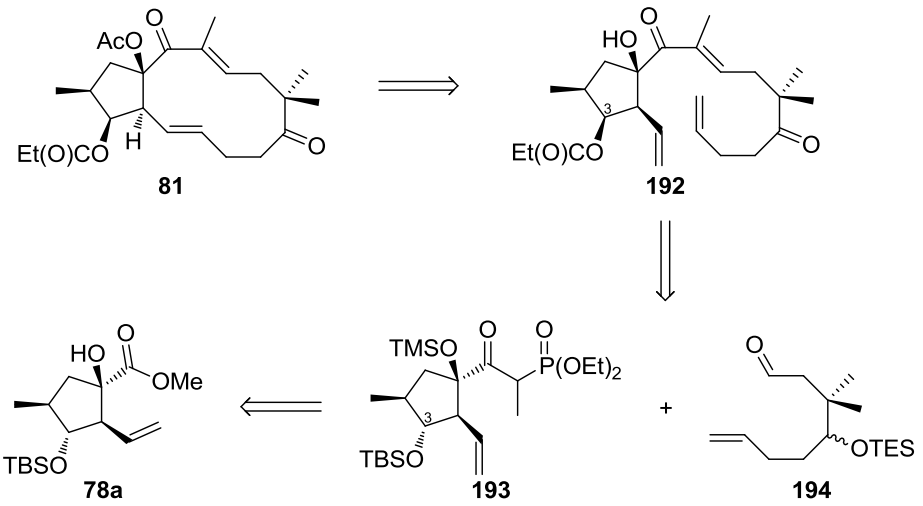


Scheme 24 Wiemer's synthesis of (+)-jatrophone (1).

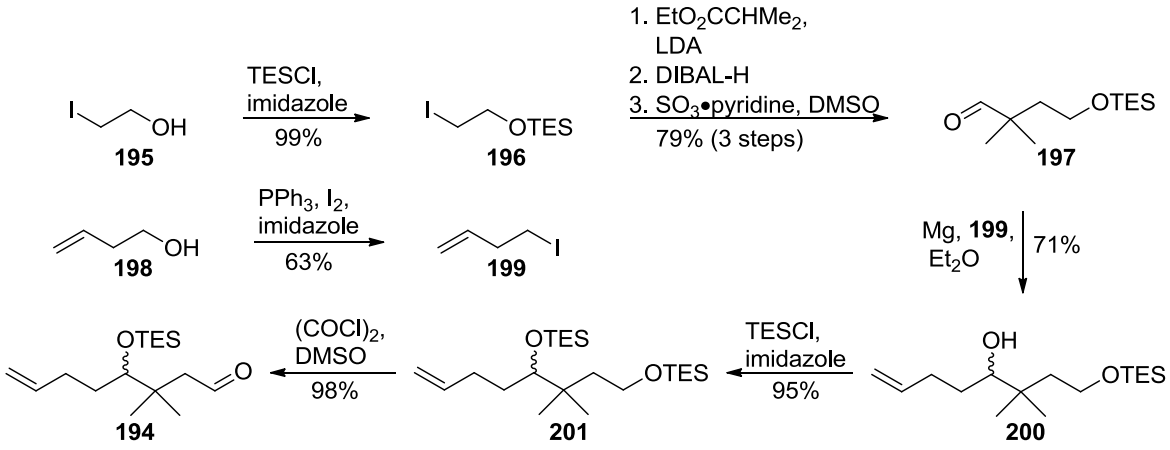
1.4.2.5 Synthesis of the Norjatrophane Diterpene (-)-15-Acetyl-3-propionyl-17-norcharaciol

The report of the synthesis of the norjatrophane diterpene (-)-15-acetyl-3-propionyl-17-norcharaciol (**81**) by Hiersemann *et al.* was the first application of his methodology to build a five membered ring synthon *via* an ene-reaction.[42,43,70] The retrosynthetic analysis (Scheme

25) envisaged a late stage ring closing metathesis of **192**. A Horner-Wadsworth-Emmons olefination of aldehyde **194** with β-keto phosphonate **193** afforded a precursor of the advanced intermediate **192**, which was only accessible through an inversion of the stereocenter on C-3 on the synthetic path. β-Keto phosphonate **192** was derived from Hiersemann's five-membered ring synthon **78a**.



Scheme 25 Retrosynthetic analysis of (-)-15-acetyl-3-propionyl-17-norcharaciol (81**).**

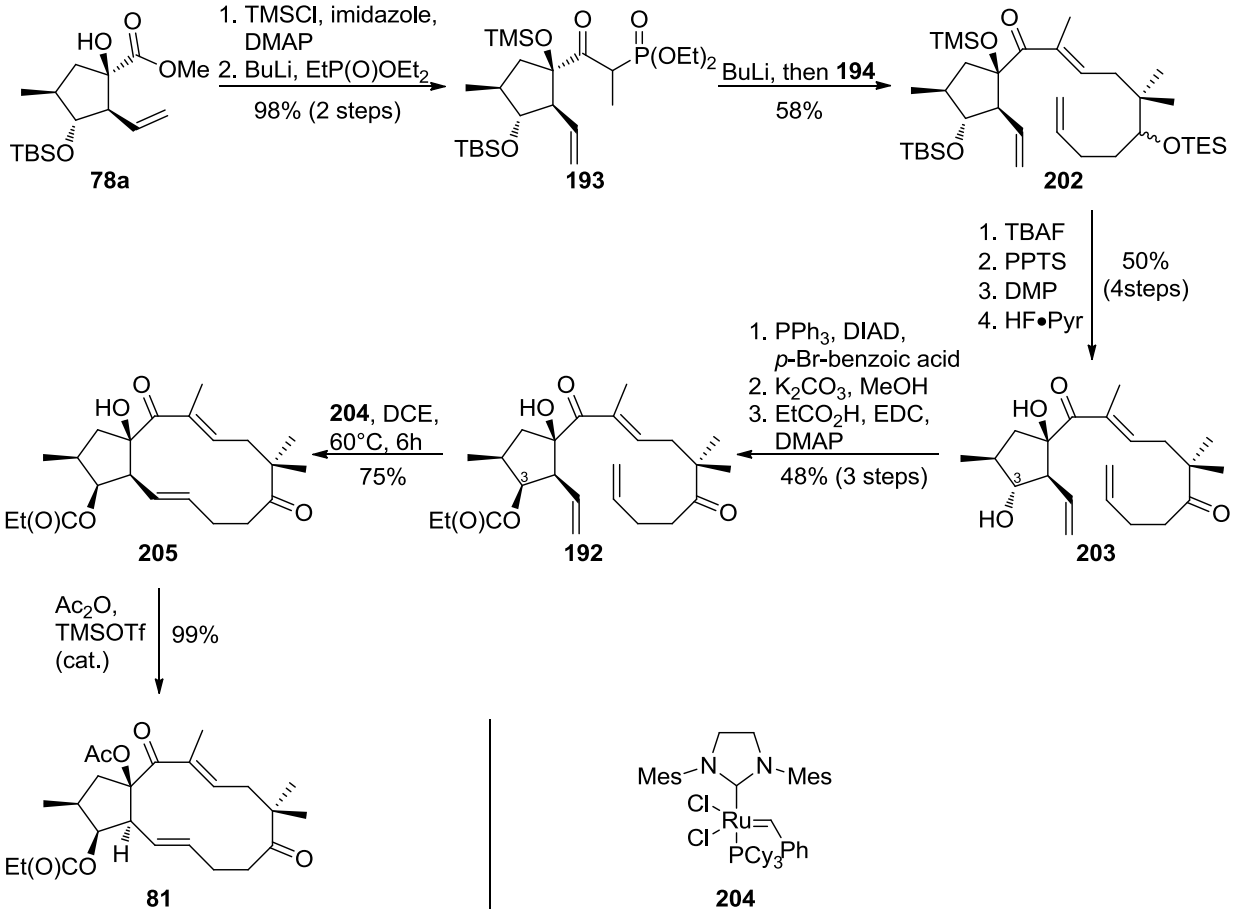


Scheme 26 Synthesis of aldehyde 194.

The synthesis of the five-membered ring synthon **78a** was already shown in Scheme 4 and Scheme 5 (chapter 1.4.1.2), respectively. In Scheme 26 the synthesis of aldehyde **194** is shown in detail. TES protection of 2-iodo ethanol (**195**) gave silyl ether **196**. Reaction with deprotonated ethyl isobutyrate, followed by reduction and subsequent Parikh-Doering oxidation afforded aldehyde **197**. Addition of a Grignard reagent derived from iodine **199**, which was obtained in moderate yield from but-3-en-1-ol (**198**), gave racemic secondary

alcohol **200**. Protection gave disilyl ether **201**, which was converted to aldehyde **194** by selective oxidation of the primary hydroxy group.

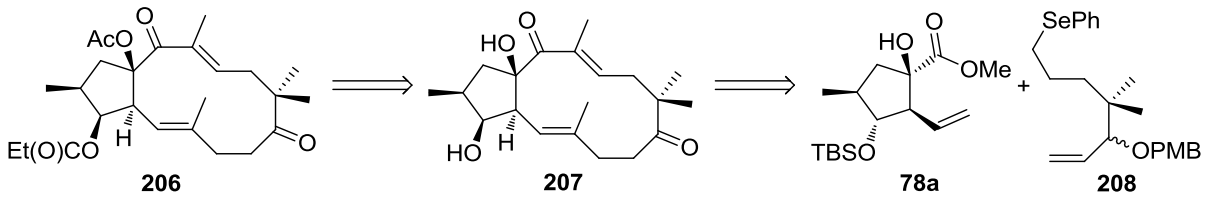
Scheme 27 shows how the synthesis of (-)-15-acetyl-3-propionyl-17-norcharaciol (**81**) was concluded. By TMS protection of the free hydroxy group in the five-membered ring synthon **78a** and subsequent treatment with deprotonated diethyl ethylphosphonate β-keto phosphonate **193** was obtained. A Horner-Wadsworth-Emmons olefination of aldehyde **194** provided **202**. TBAF and PPTS removed the TMS and the TES groups, respectively. Oxidation of the secondary hydroxy group to the corresponding ketone and cleavage of the remaining TBS group afforded diketone-diol **203**. Inversion of the stereocenter at C-3, which occurred in 3 steps by a Mitsunobu reaction and transesterification sequence, provided advanced intermediate **192**. A ring closing metathesis mediated by Grubbs II catalyst (**204**) led to tertiary alcohol **205**. Acetylation of the free hydroxy group in the final step yielded target molecule (-)-15-acetyl-3-propionyl-17-norcharaciol (**81**).



Scheme 27 Synthesis of (-)-15-acetyl-3-propionyl-17-norcharaciol (81**).**

1.4.2.6 Synthesis of (-)-15-O-Acetyl-3-O-propionylcharaciol by Hiersemann et al. *2009*

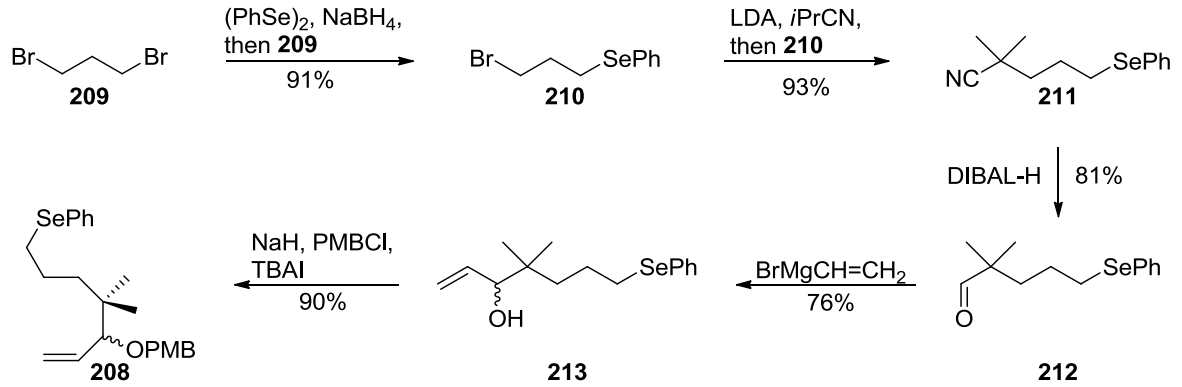
In 2009 Hiersemann *et al.* reported the total synthesis of (-)-15-*O*-Acetyl-3-*O*-propionylcharaciol (**206**), a jatrophane diterpene originally isolated from *Euphorbia characias*.[71,72] An earlier attempt using the same reactions as in the synthesis of (-)-15-acetyl-3-propionyl-17-norcharaciol (**81**) was not successful.[43]



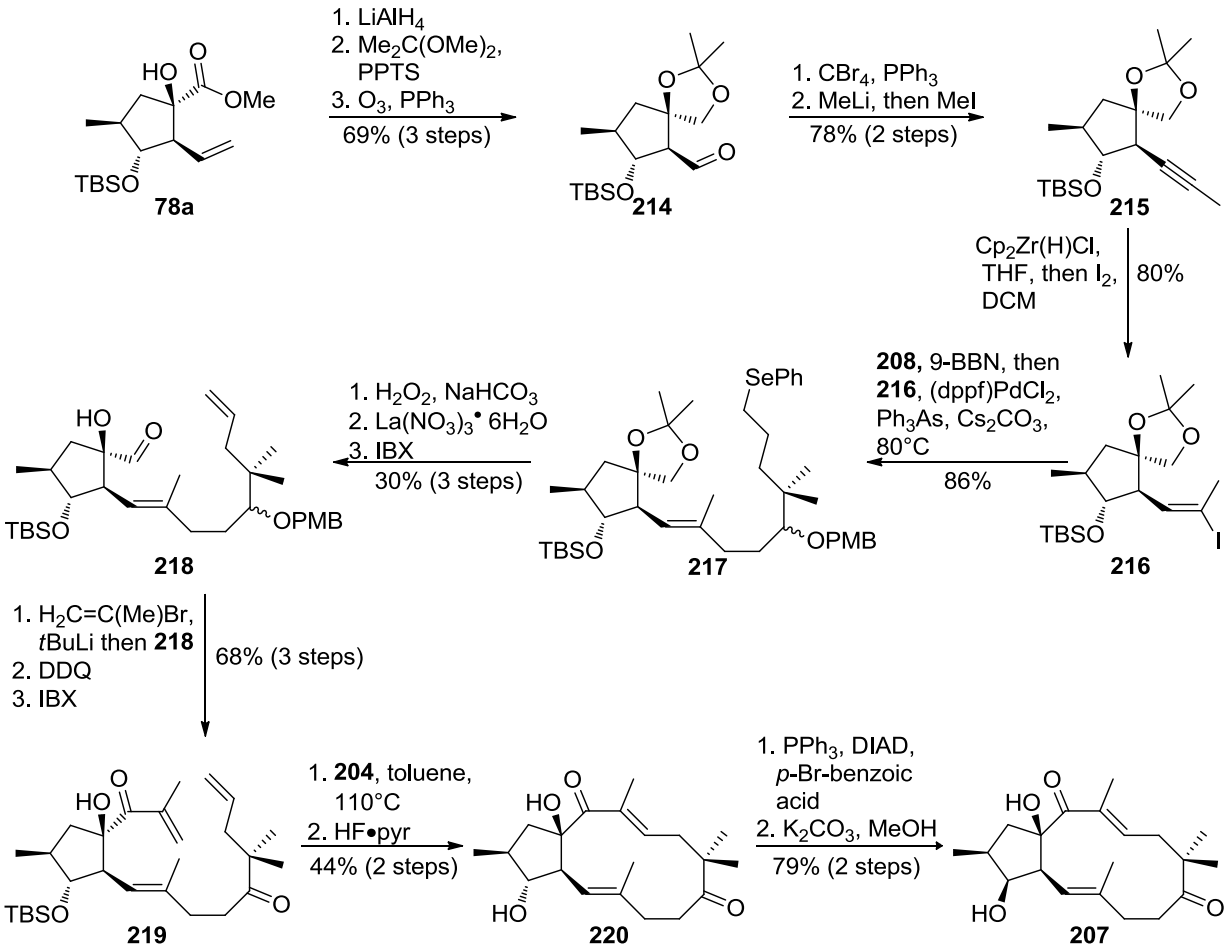
Scheme 28 Retrosynthetic analysis of (-)-15-*O*-acetyl-3-*O*-propionylcharaciol (206**).**

The retrosynthetic analysis (Scheme 28) shows that characiol (**207**) was envisaged as suitable advanced intermediate in this synthesis. Hiersemann's five membered ring synthon (**78a**) was considered as precursor of this diol (**207**).

Scheme 29 illustrates how selenide **208** was made. An *in situ* generated phenylselenide anion reacted with dibromide **209** and afforded **210.** A subsequent alkylation of the anion of isobutyronitrile delivered nitrile **211**. Reduction with DIBAL-H afforded aldehyde **212**. Allylic alcohol **213** was obtained after addition of vinylmagnesium bromide to the aldehyde (**212**) generated before. Protection as PMB ether yielded intermediate **208**.



Scheme 29 Synthesis of (-)-15-*O*-acetyl-3-*O*-propionylcharaciol (206**) – part 1.**

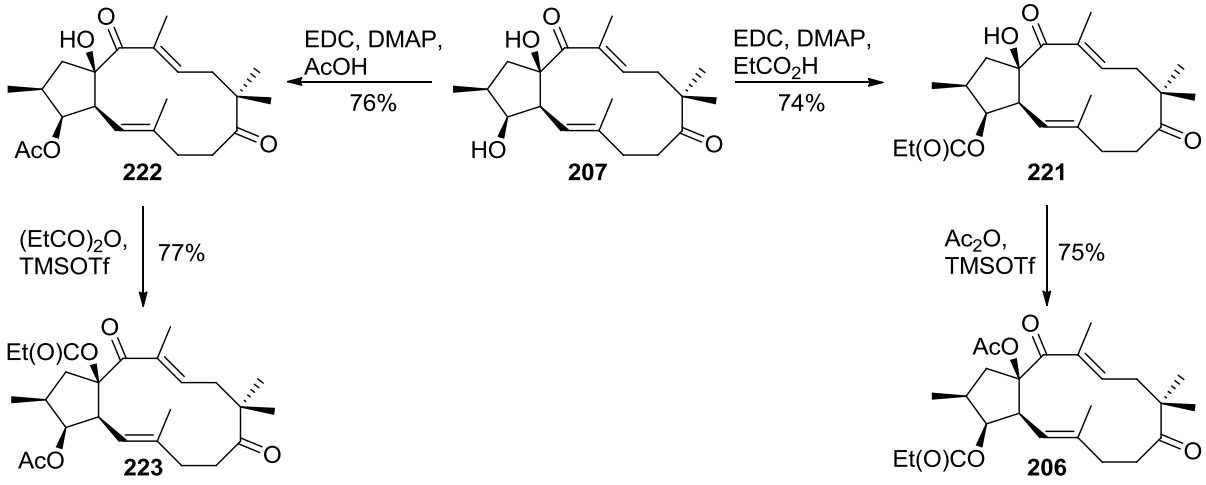


Scheme 30 Synthesis of (-)-15-*O*-acetyl-3-*O*-propionylcharaciol (206**) – part 2.**

Characiol (**207**) was synthesized as shown in Scheme 30. Hiersemann's five-membered ring synthon (**78a**) was considered as advanced starting material. The synthesis of this fragment is shown, as pointed out above, in Scheme 4 and Scheme 5 (chapter 1.4.1.2), respectively. Reduction of the starting material (**78a**), gave a vicinal diol, which was protected with an isopropylidene moiety. Ozonolysis of the double bond with reductive workup gave aldehyde **214**. Aldehyde **214** was converted to alkyne **215** in two steps. Hydrozirconation of the alkyne gave vinyl iodide **216** as single isomer. B-alkyl Suzuki-Miyaura cross-coupling of **208** and **216** provided **217** as mixture of diastereomers. The installation of the double bond *via* oxidation/elimination of phenyl selenide was followed by removal of the isopropylidene moiety (lanthanum(III) nitrate hexahydrate was found not to affect the other protecting groups in the molecule), before the resulting primary alcohol was oxidized to aldehyde **218**. Addition of isopropenyl lithium, cleavage of the PMB ether and subsequent oxidation of the newly generated secondary alcohol groups delivered corresponding diketone **219**. RCM

mediated by Grubbs II catalyst (**204**) and a deprotection step gave diol **220**. Inversion of the C-3 stereocenter gave characiol (**207**) in two steps.

Regioselective esterifications of the jatrophone core (Scheme 31) proved that the original assignment by Seip and Hecker[72] of (-)-15-*O*-acetyl-3-*O*-propionylcharaciol (**206**) was correct. With the preparation of **206**, Hiersemann *et al.* were the first to synthesize a jatrophane diterpene isolated of the genus Euphorbia in enantioselective fashion.



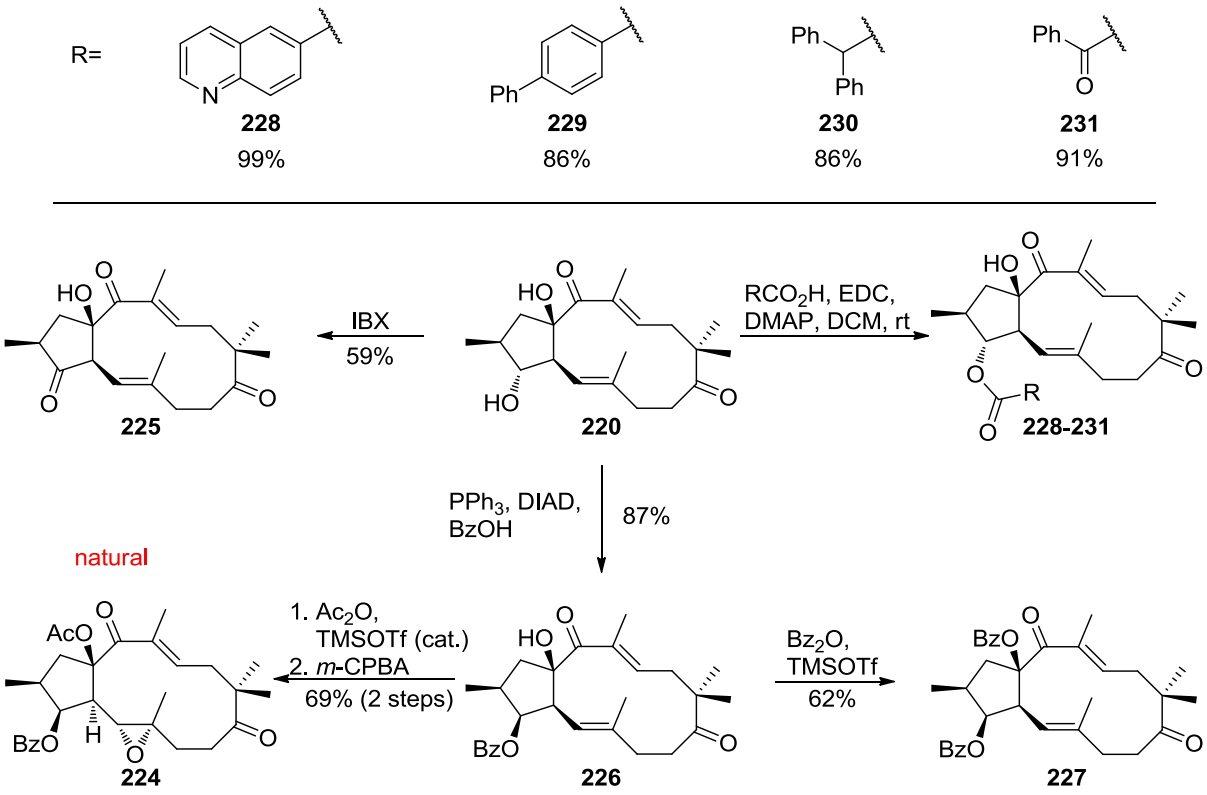
Scheme 31 Synthesis of (-)-15-*O*-acetyl-3-*O*-propionylcharaciol (206**) - part 3.**

1.4.2.7 Total Synthesis of Natural and Non-Natural Δ5,6Δ12,13-Jatrophane Diterpenes by Hiersemann et al. *2011*

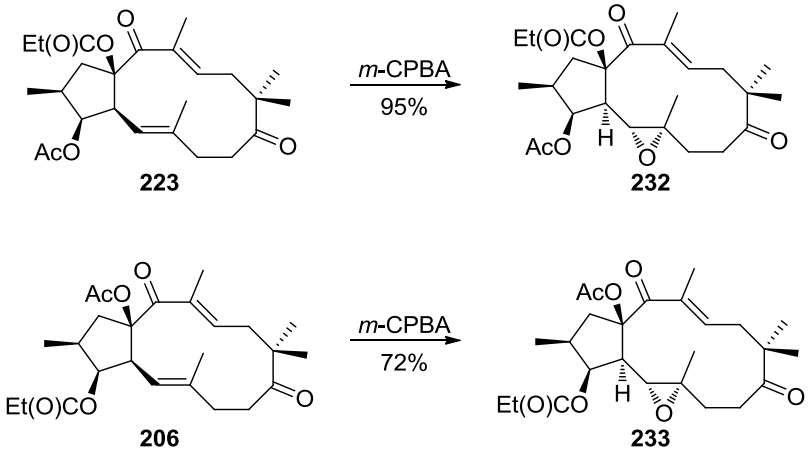
Building on prior syntheses, Hiersemann *et al.* reported the synthesis of natural 15-*O*-acetyl-3-*O*-benzoylcharaciol (5*R*, 6*R*)-oxide (**224**) as well as a collection of non-natural jatropha-5,12,-dienes.[73] Scheme 32 outlines how 15-*O*-acetyl-3-*O*-benzoylcharaciol (5*R*, 6*R*)-oxide (**224**) was available from previously reported diol **220**[71] in three steps. There had been controversial statements about the configuration of the epoxide moiety by Uemura, who proposed a (5*R*, 6*R*) configuration[74], and Seip and Hecker who depicted a (5*S*, 6*S*) configuration[72] in this natural compound. Hiersemann *et al.* agreed to Uemuras assignment which was validated in two independent NOE studies.[75,76]

A total of 18 synthetic natural and non-natural jatrophane diterpenes, some examples are depicted in Scheme 32 and Scheme 33, were tested concerning their MDR modulating activity. **228** was found to possess an inhibitory potency comparable to that of standard inhibitor verapamil towards ABCB1 (p-glycoprotein).[73,77] Inhibitory activity of the same

compound was also found against ABCG2. Similar compounds with lipophilic residues were also found to be active against ABCB1.



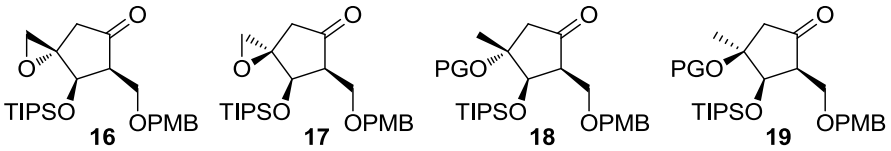
Scheme 32 Synthesis of 15-*O*-acetyl-3-*O*-benzoylcharaciol (5*R*, 6*R*)-oxide (224) and non-natural jatrophane diterpenes by Hiersemann *et al.* – part 1.



Scheme 33 Synthesis of non-natural jatrophane diterpenes by Hiersemann *et al.* - part 2.

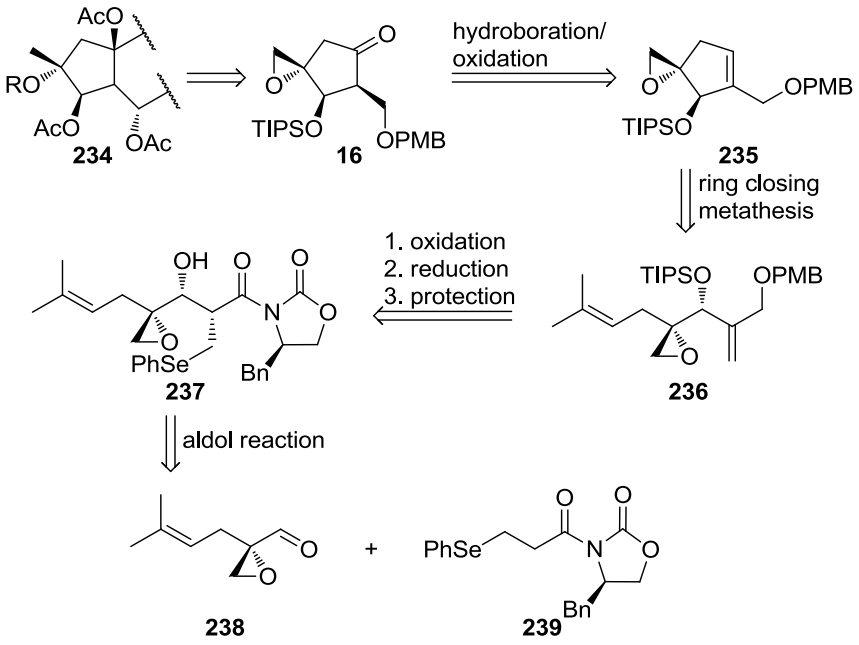
2. Results and Discussion

2.1 Retrosynthethic Analysis



Scheme 34 Synthetic equivalents to highly oxygenated five-membered rings in jatrophane diterpenes.

As outlined in the introduction (chapter 1.2) the preparation of synthons **16–19** (Scheme 34) was considered as goal of this master thesis.

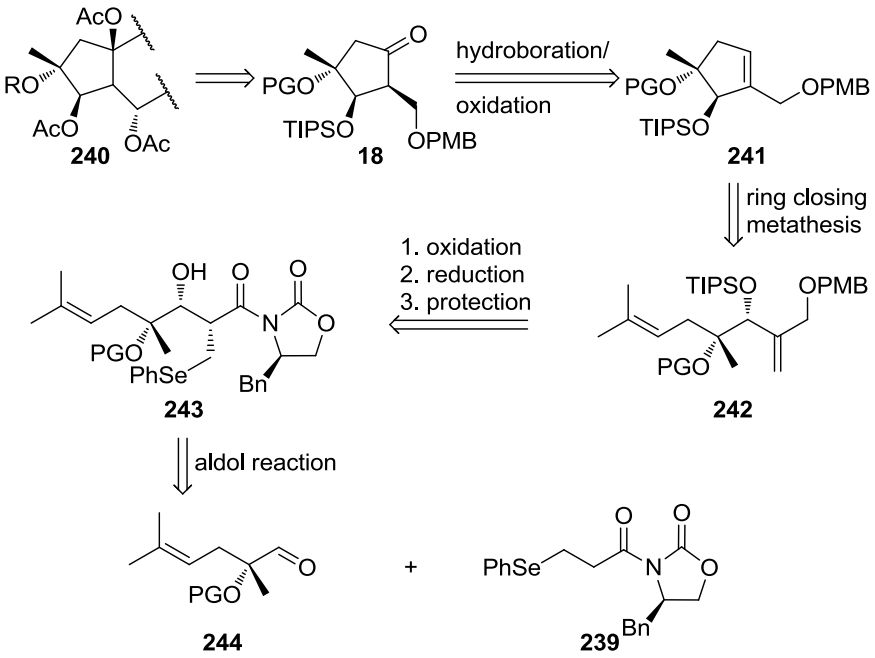


Scheme 35 Initial retrosynthetic analysis.

Scheme 35 shows the proposed retrosynthetic analysis of synthon **16**. It contains several steps that are envisaged in close analogy to previous work done in our laboratory, described in detail in chapter 1.4.1.5 of this document.[16] We considered five-membered ring synthon **16** as possible precursor to a variety of natural products (**234**), since the epoxide can be opened to deliver the desired C-2 pattern. The ketone functionality in **16** can be used in a vast number of C-C bond forming reactions, for instance a pinacol coupling reaction, and the primary hydroxy group, here protected as PMB ether, was meant to be converted to an aldehyde to perform a Nozaki–Hiyama–Kishi coupling in later steps of a total synthesis of *Euphorbiaceae* diterpenes. Compound **16** was envisaged to be prepared by a

hydroboration/oxidation sequence from cyclopentene **235**, which was thought to be accessible through a RCM. Both of these steps have been key steps in the preparation of the cyclopentane fragment of Lentsch and Rinner.[16] Imide **237** should have served as precursor to diene **236** in our plans. Oxidation was meant to eliminate the selenium phenyl residue and afford a diene, subsequent reduction was planned to provide an alcohol and protection to finally give **237** as product in three steps. Imide **237** was considered to be accessible through aldol reaction of epoxy aldehyde **238** and imide **239**.

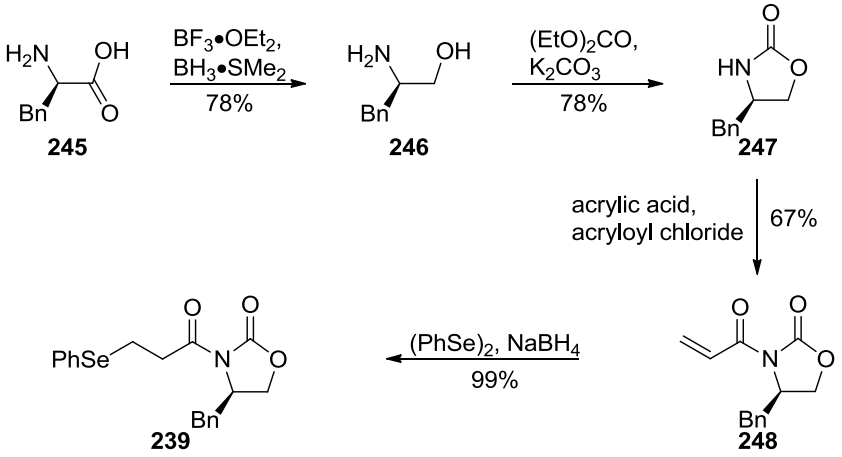
We considered to prepare synthon **17** through the same route, starting with the enantiomer of epoxide **238**.



Scheme 36 Revised retrosynthetic analysis.

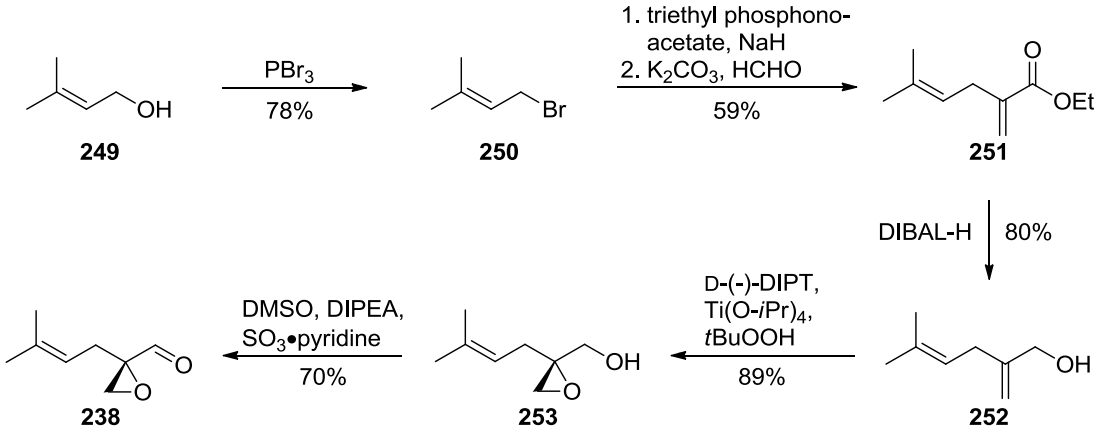
After we found that intermediate **237** was unstable (see below) a different route (Scheme 36) was envisaged avoiding intermediates with an epoxide moiety and an amide function in the same molecule. This revised route starts with aldol reaction of protected tertiary alcohol **244** and auxiliary **239**. All other steps remained the same.

2.2 Approach Towards Euphosalicin and Related Diterpenes



Scheme 37 Preparation of chiral auxiliary 239**.**

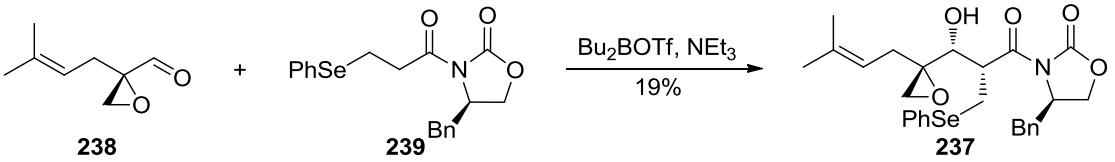
The preparation of chiral auxiliary **239** is shown in Scheme 37. Commercially available D-phenylalanine (**245**) was reduced to give hydroxy amine **246**. Condensation of hydroxy amine **246** with diethyl carbonate furnished oxazolidinone **247**.[78] Both of these reactions gave good yields. Next, oxazolidinone **247** was acylated to give imide **248** in fair yield. Auxiliary **239** was obtained by 1,4-addition of phenyl selenide to imide **248** in nearly quantitative yield.



Scheme 38 Preparation of chiral epoxy aldehyde 238**.**

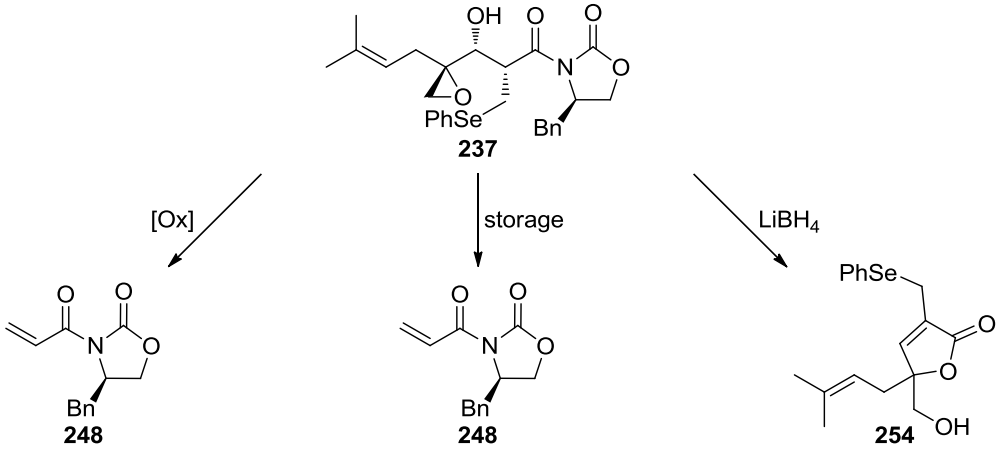
Scheme 38 shows the preparation of chiral epoxy aldehyde **238**. Commercially available prenyl alcohol (**249**) was converted to prenyl bromide (**250**) in good yield with PBr_3.[79] Conversion of **250** to a phosphonate and subsequent Horner-Wadsworth-Emmons olefination furnished ester **251** in moderate yield. Reduction of **251** with diisobutyl aluminum hydride gave allylic alcohol **252** in good yield. This reduction was also tried with

$LiAlH_4$ and $NaBH_4$, but no method worked as well as the reduction with diisobutyl aluminum hydride. Sharpless epoxidation of allylic alcohol **252** gave epoxide alcohol **253** in excellent yield.[17] Epoxy aldehyde **238** was obtained by oxidation under Parikh-Doering conditions.[18]



Scheme 39 Aldol reaction of epoxy aldehyde 238 **and chiral auxiliary** 239**.**

Scheme 39 shows the aldol reaction of epoxy aldehyde **238** and chiral auxiliary **239**, which delivered the desired product in only low yields.[18] Purification of the crude product of this reaction was a difficult task, but *via* HPLC the desired product could be isolated, and characterized. Due to the low yield of the reaction several large scale reactions were carried out to provide multigram quantities of aldol adduct **237**.

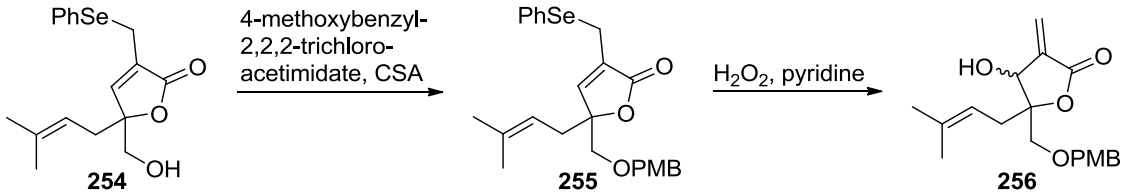


Scheme 40 Reactions of aldol adduct 237**.**

Unfortunately, no successful subsequent reaction could be performed with aldol adduct **237**, as shown in Scheme 40. A large variety of reaction conditions (including: sodium periodate, hydrogen peroxide/ pyridine, hydrogen peroxide/ ammonium chloride, tributyl borane/ oxygen[80], isobutyraldehyde/ oxygen[81], *tert*-butyl hydroperoxide and mCPBA) were tried to achieve selenoxide elimination without success. The only isolated compound from these reactions was retro aldol product **248**.

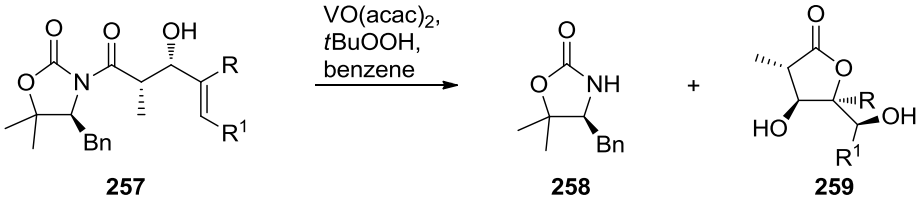
Decomposition of aldol adduct **237** was shown after three weeks of storage at -20°C. Until decomposition had been observed, several of the above mentioned reactions had been carried out. So no clear statement can be made if the oxidation reactions may have

decomposed the aldol adduct **237**, or if it already decomposed while storage. Interestingly a try to convert the imide to the corresponding alcohol led to 2-furanone **254**.



Scheme 41 Reactions performed with 2-furanone 254**.**

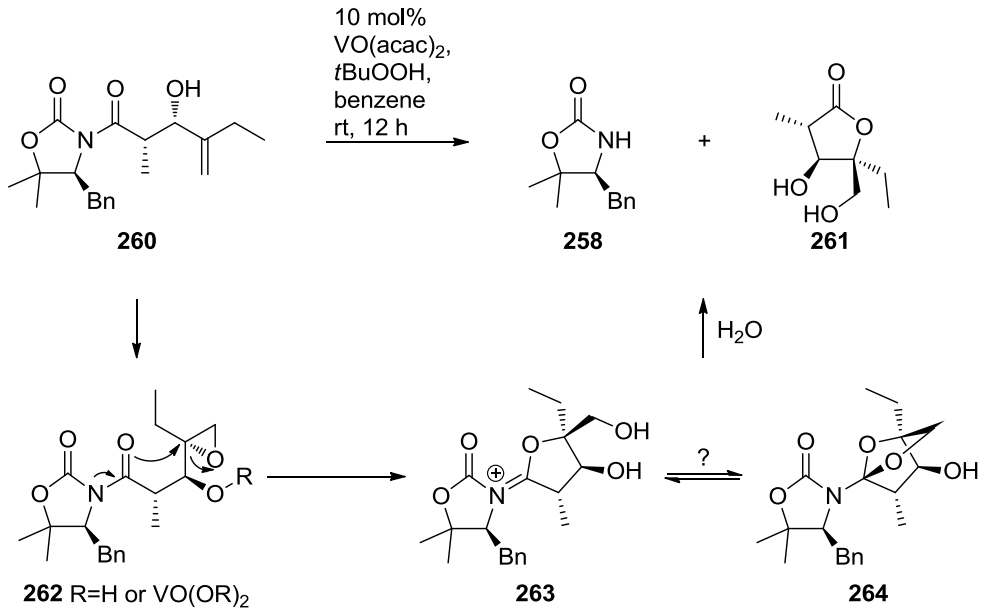
As shown in Scheme 41, the primary hydroxy group of **254** was protected as PMB ether **255**, in the next step selenoxide elimination led to intermediate **256**. After derivatization of **254** to **256** the structures of the single intermediates were easily replicable *via* spectroscopic methods.



Scheme 42 Synthesis of hydroxy-γ-butyrolactones.[82]

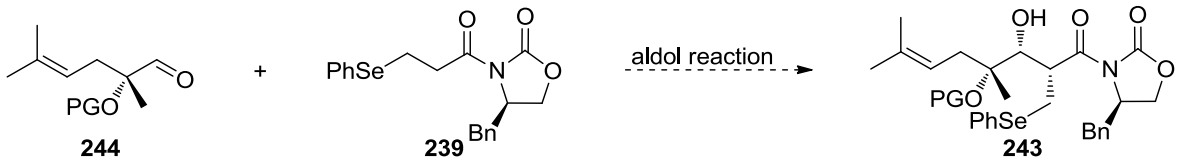
Literature research led to an article[82] that described rearrangement of intermediates (**257**) similar to aldol adduct **237**. A generalized reaction presented in this article is shown in Scheme 42.

Epoxidation of imide **260** lead directly to γ-butyrolactone **261**. A mechanism proposed by Davies *et al.* is shown inScheme 43. Epoxide **262** was suggested to be built *via* hydroxy-directed epoxidation. Ring-opening of the epoxide by intramolecular nucleophilic attack of the exocyclic carbonyl oxygen leads to the unstable iminium species **263**, which may be stabilized by the reversible formation of *N*,*O*,*O*-orthoester **264**. Hydrolytic workup gives oxazolidinone **258** and γ-butyrolactone **261**.



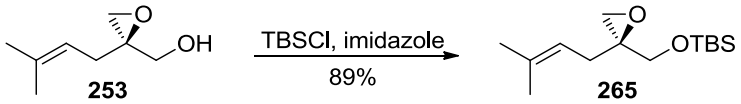
Scheme 43 Proposed mechanism of the rearrangement by Davies *et al.*[82]

This made clear that our aldol reaction must not include molecules having an epoxide moiety since intermediates generated in such a reaction would again be prone to a rearrangement.



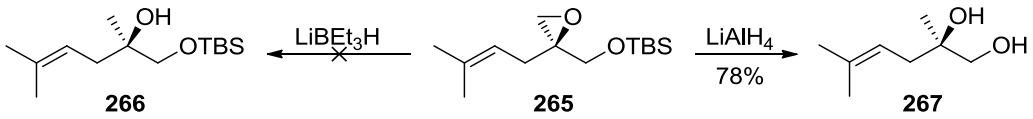
Scheme 44 Proposed epoxide free aldol reaction.

It was envisaged that aldol adduct **243**, which cannot perform the rearrangement may be a suitable intermediate on the route to a five-membered ring synthon. As depicted in Scheme 44, an aldehyde containing a protected tertiary hydroxy group (**244**) had to be prepared.



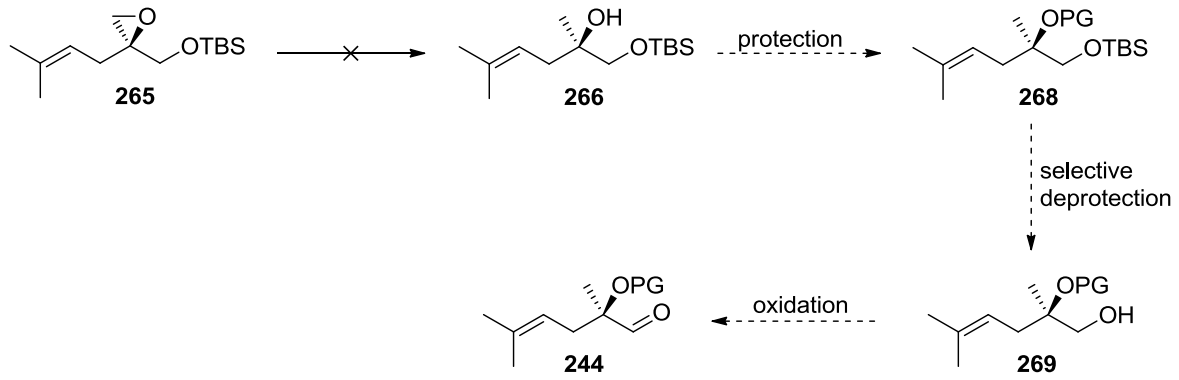
Scheme 45 TBS protection of epoxy alcohol 253**.**

In order to prepare a tertiary alcohol from already prepared epoxy alcohol **253**, it was protected as its TBS ether in excellent yield, see Scheme 45.



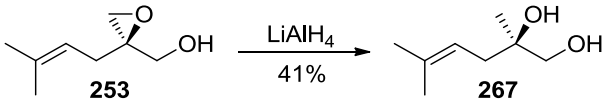
Scheme 46 Nucleophilic opening of the epoxide.[83,84]

The next step was a nucleophilic ring opening which was tried with two different reducing agents, namely superhydride[83] and lithium aluminum hydride[84], as shown in Scheme 46. Both of these reactions could not furnish the desired product **266**. Only starting material was isolated after treatment of **265** with superhydride, whereas treatment with lithium aluminum hydride afforded diol **267** in good yield.



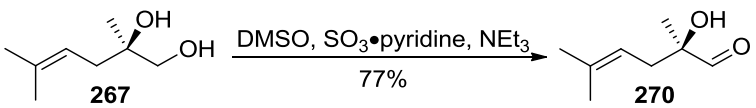
Scheme 47 Initially envisaged route to aldehyde 244**.**

The initially envisaged route, shown in Scheme 47, would have featured a protection of the tertiary hydroxy group, a selective cleavage of the TBS group and an oxidation reaction to give the desired aldehyde **244**. Unfortunately monoprotected diol **266** could not be derived from epoxy TBS ether **265**, so the route to aldehyde **244** had to be changed.



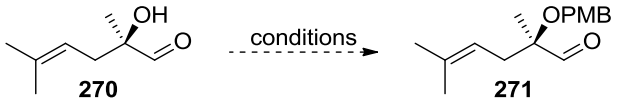
Scheme 48 Direct epoxide opening of 253**.**

After epoxide opening of epoxy TBS ether **265** gave diol **267**, a direct epoxide opening of epoxy alcohol **253** was considered. Treatment of epoxy alcohol **253** with lithium aluminum hydride gave expected diol **267** in low yield, as Scheme 48 shows. In comparison, epoxide opening after protecting with TBSCl gave a better yield of the desired material (69% over two steps).



Scheme 49 Oxidation of diol 267**.**[18]

Diol **267**, either from direct epoxide opening shown in Scheme 48 or from epoxide opening of epoxy TBS ether, was oxidized under Parikh-Doehring conditions, shown in Scheme 49, in good yield.[18]

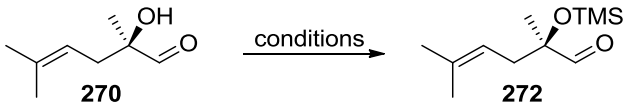


Scheme 50 PMB protection of 270**.**

Table 4 PMB protection of 270**.**

conditions	yield
PMB-Bundles, CSA	traces
PMB-Cl, NaH	-
PMB-Cl, NaH, TBAI	-

The PMB-moiety was identified as suitable protecting group. Scheme 50 and Table 4 show that the performed reactions did not furnish the desired product (**271**). Only traces of the PMB ether aldehyde **271** were found after HPLC, but the reaction conditions could not be optimized.

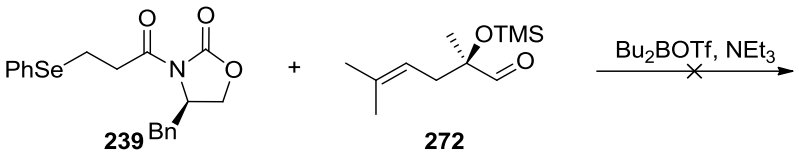


Scheme 51 TMS protection of 270**.**

Table 5 TMS protection of 270**.**

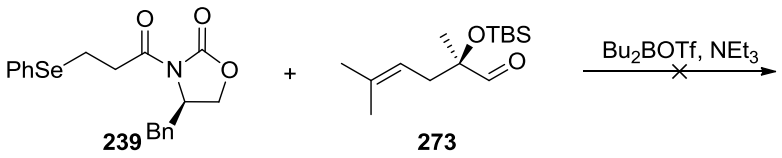
conditions	yield
TMS-Cl, LDA	-
TMS-Cl, imidazole	-
TMS-OTf, 2,6-lutidine	33%

Another protecting group that was considered as suitable for the aldol reaction was the trimethyl silyl group. The TMS-protection was carried out under different conditions as shown in Scheme 51 and Table 5, respectively. A reason for the low yield in the protection step with trimethyl silyl triflate is the competing elimination reaction which was observed.



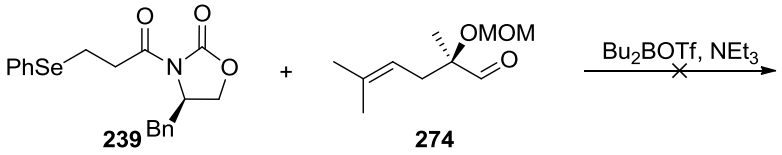
Scheme 52 Attempted aldol reaction with TMS protected hydroxy aldehyde 272**.**

With trimethyl silyl protected α-hydroxy aldehyde **272** in hands an aldol reaction as described by Barth and Roush[18] was performed without success, as shown in Scheme 52.



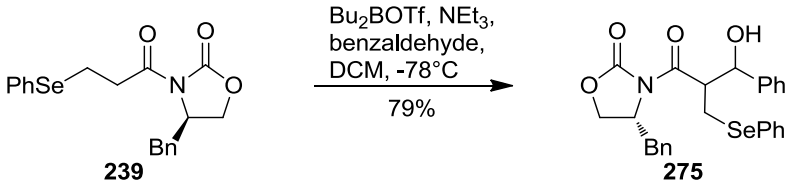
Scheme 53 Attempted aldol reaction with TBS protected hydroxy aldehyde 273**.**

Scheme 53 shows that a further aldol reaction with racemic *tert*-butyl dimethyl silyl protected α-hydroxy aldehyde **273** and auxiliary **239** was unsuccessful as well.



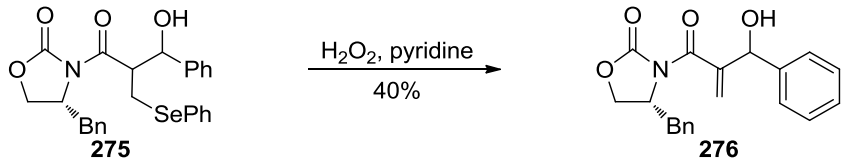
Scheme 54 Attempted aldol reaction with MOM protected hydroxy aldehyde 274**.**

When racemic methoxymethyl protected α-hydroxy aldehyde **274** was tried to be reacted (Scheme 54) in the same manner as above, again no desired product could be isolated.



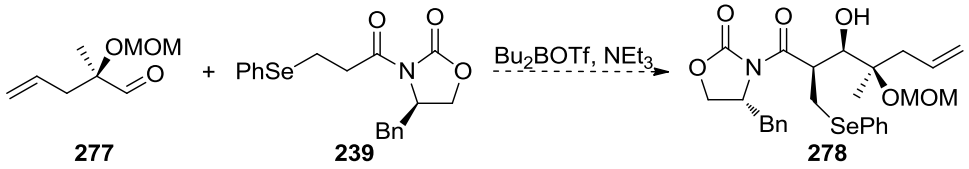
Scheme 55 Attempted aldol reaction with benzaldehyde.

In order to exclude doubts about wrong handling, the reaction was carried out with benzaldehyde as described in the original literature. This attempt, shown in Scheme 55, gave aldol adduct **275** in good yield. In literature this intermediate was not isolated, but directly converted to compound **276**.[18]



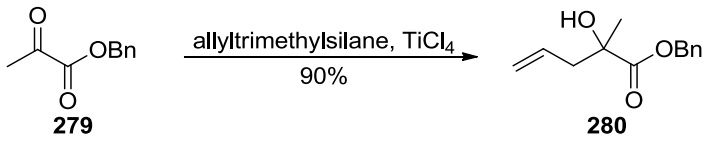
Scheme 56 Oxidative elimination of -SePh from compund 275**.**

To identify **275** as desired product of the aldol reaction, the selenyl phenyl group was eliminated by treatment of **275** with hydrogen peroxide and pyridine which gave **276** (Scheme 56). The NMR data of the product of this reaction were in agreement with the data from the literature.



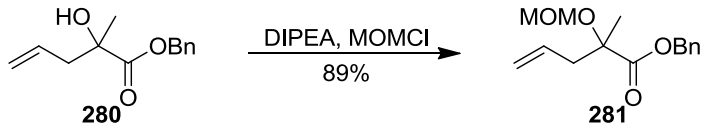
Scheme 57 Intended aldol reaction of MOM protected α-hydroxy aldehyde 277 **and auxiliary** 239.

The next investigations intended to perform this delicate aldol reaction with aldehyde **277**, as shown in Scheme 57.



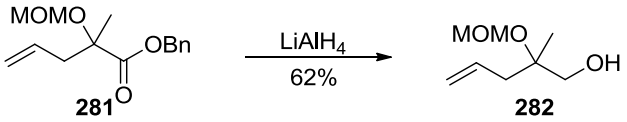
Scheme 58 Sakurai allylation of benzyl pyruvate 279**.**

Scheme 58 shows how benzyl pyruvate (**279**) was reacted with allyltrimethylsilane and $TiCl_4$ to give α hydroxy ester **280** in excellent yield, in order to prepare aldehyde **277** which is needed for the aldol reaction discussed above.



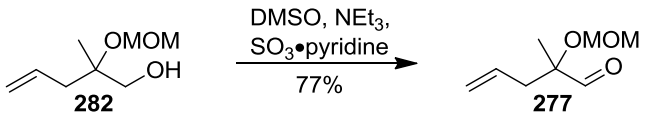
Scheme 59 MOM protection of α-hydroxy benzyl ester 280**.**

The previously prepared α-hydroxy benzyl ester (**280**) was protected as the corresponding methoxymethyl ether **281**, as shown in Scheme 59, in excellent yield *via* a procedure that generates MOM-Chloride *in situ*.[85]



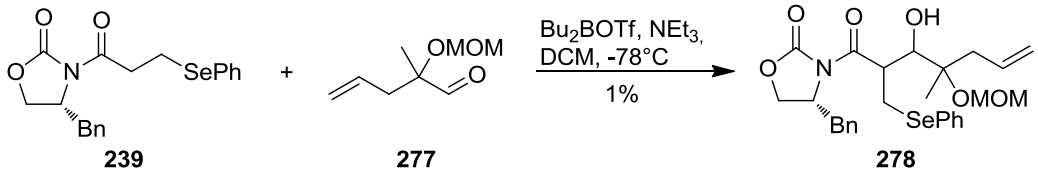
Scheme 60 Reduction of MOM protected α-hydroxy benzyl ester 281**.**

The reduction of the ester moiety of methoxymethyl protected α-hydroxy benzyl ester **281** was performed with lithium aluminum hydride, as outlined in Scheme 60, to give mono MOM-protected diol **282** in moderate yield.



Scheme 61 Oxidation of mono MOM protected diol 282**.**

As shown in Scheme 61, racemic methoxymethyl protected α-hydroxy aldehyde **277** was prepared by oxidation of mono methoxymethyl protected diol **282** under Parikh-Doering conditions in good yield.

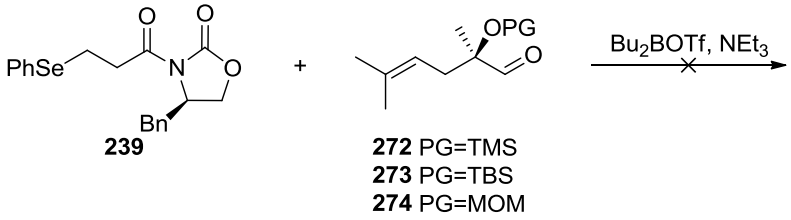


Scheme 62 Aldol reaction of MOM protected α-hydroxy aldehyde 277 **and auxiliary** 239.

With racemic methoxymethyl protected α-hydroxy aldehyde **277** in hands, the aldol reaction as shown in Scheme 62 delivered only minor amounts of the desired material (**278**). Although this result is in disagreement with previous findings, the delicate nature of the aldol addition does not guarantee reproducible yields of the expected material.

3. Conclusion and Outlook

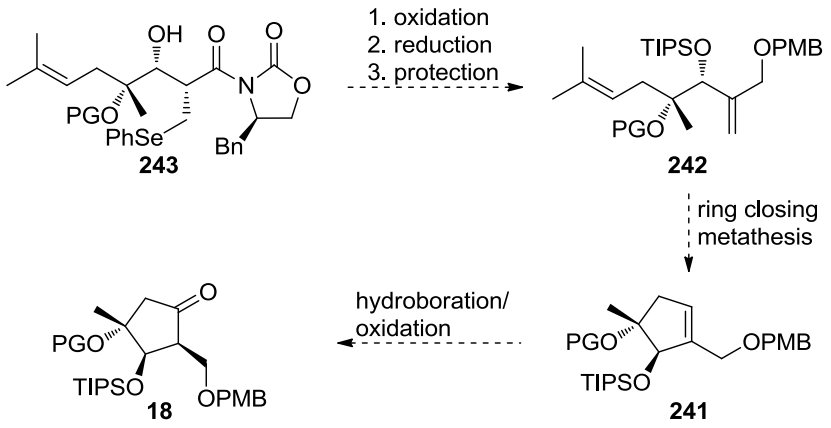
The synthesis of *Euphorbiaceae* diterpenes has been a center of interest in many synthetic workgroups. Though only a handful of syntheses (see chapter 1.4.2) were reported, names of famous synthetic chemists are related to *Euphorbiaceae* diterpenes in literature. One reason may be the biological activities of the isolated compounds, another reason the challenging structures of *Euphorbiaceae* diterpenes. All successful approaches reported so far use a substituted five-membered ring synthon in early stages of the syntheses. A total of five independent syntheses of cyclopentane segments have been reported.



Scheme 63 Aldol reaction with protected α-hydroxy aldehydes (272-274**).**

Despite great effort, the flexible preparation of highly oxygenated five-membered ring synthons required for the preparation of various jatrophane diterpenes such as ep-7 (**4**), esulatin B (**8**), eup-10 (**6**), euphosalicin (**2**) or pepluanin A (**3**), shown in Fig. 2 (chapter 1.1 of this document) could not be finished in the course of this master thesis. The strategy of previous studies by Lentsch and Rinner[16] (described in 1.4.1.5 of this document) could not be adapted to the highly oxygenated five membered ring synthons. The aldol reaction, which was in the end crucial to the failure of the synthesis, gave instable products with epoxy aldehyde (**238**). After changing the tactic, protected α-hydroxy aldehydes (**272**-**274**) were used instead of an epoxide, but these could not give desired aldol adducts as shown in Scheme 63. In comparison to the aldehydes reported as suitable by Barth[18], the used protected α-hydroxy aldehydes (**272**-**274**) had much more steric hindrance. This could be a reason why the reaction was unfavored and therefore not observed.

If it was possible to find another synthetic pathway to intermediate **243**, the envisaged strategy could still be pursued, as outlined below. Otherwise it might be fruitful to reconsider the whole strategy.



Scheme 64 Route to five-membered ring synthon 18 **from hypothetical aldol adduct** 243**.**

In Scheme 64 the synthetic route to target molecule **18** is outlined starting from inaccessible aldol adduct **243**. This hypothetic route is based on previous synthetic work done by Lentsch and Rinner[16]. Oxidation eliminates the phenyl selenyl group, introducing an exomethylene to the molecule. Reduction cleaves the imide and leaves behind a primary hydroxy function. Selective protection of the primary hydroxy group as *para*-methoxy benzyl ether and selective protection of the secondary hydroxy group as triisopropyl silyl ether leads to diene **242**. Cyclopentene **241** is accessible through ring closing metathesis of diene **242**. In the final step a hydroboration/oxidation protocol leads to the highly oxygenated five-membered ring synthon **18**.

4. Experimental Part

4.1 General Information

Reactions

All air and moisture sensitive reactions were performed in vessels dried by repeated heating under vacuum (heat gun) followed by purging with dry argon. Reaction procedures were carried out under slight overpressure of argon (balloon) in dry solvents. Sensitive reagents or solutions were transferred *via* syringe or cannula through rubber septa.

TLC was performed on Merck silica gel 60-F_{254} glass plates, or on ALUGRAM Xtra SIL G/UV 254 foil. The plates were developed with mixtures of hexane/ethyl acetate or toluene/ethyl acetate. UV active spots were detected at long wave UV (254 nm). Most plates were additionally treated with the following visualization reagent: CAN [H_2SO_4 (conc., 22 mL), phosphomolybdic acid (20 g), $Ce(SO_4)_2$ (0.5 g), 378 mL H_2O)].

Solvents and Reagents

Methylene chloride (DCM) was purified by distillation and dried by distillation from P_2O_5 and passage over aluminum oxide (aluminum oxide 90 active basic, obtained from Merck). Diethyl ether (Et_2O) was freshly distilled from sodium/benzophenone under argon. Dimethyl sulfoxide (DMSO) was dried by distillation from calcium hydride under reduced pressure. Tetrahydrofuran (THF) was distilled from potassium under argon. Diisopropylamine (DIPA), diisopropylethylamine (DIPEA) and triethylamine (NEt_3) were distilled from CaH_2. Toluene was refluxed over sodium and freshly distilled. Hexane and ethyl acetate were distilled and used without further purification.

Chromatography

Preparative column chromatography and flash chromatography was performed with silica gel 60 from Merck (0.040-0.063 µm, 240-400 mesh). For HPLC separations on analytical scale module systems from Jasco (PU-980, UV-975 detector, RI-930 RI detector, 250 x 4 mm column) were used. The adsorbent was 74 Superphere Si 60 (40 µm, Merck) or Nucleosil 50

(4µm, Macherey-Nagel). The semipreparative and preparative scale was covered by module systems from Dynamax (SD-1 pump, UV-1 UV detector), Knauer (RI detector) and Shimadzu (LC-8A, SPD-20A UV/VIS Detector, LC-20AT Bus Module).

NMR-Spectroscopy

NMR spectra were recorded either on a Bruker Avance AV 400, DRX 400, or DRX 600 MHz spectrometer. All NMR spectra were measured in $CDCl_3$ solutions and referenced to the residual $CHCl_3$/$CDCl_3$ signal (^1H, d=7.26, ^{13}C, d=77.16). All ^1H and ^{13}C shifts are given in ppm (s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, t = triplet, q = quartet, m = multiplet). Coupling constants *J* are given in Hz. Assignments of proton resonances were confirmed, when possible, by correlated spectroscopy (COSY, HSQC, HMBC, TOCSY, NOESY).

Mass Spectroscopy

All spectra are HRMS (High Resolution Mass Spectra), these were taken with a Maxis Bruker spectrometer. The kind of ionization was ESI (electron spray ionization) and a TOF (time of flight) analyzer was used in all cases.

Infrared Spectra

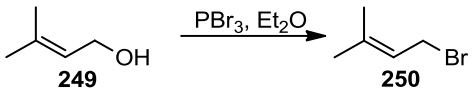
IR spectra were recorded using a Bruker Vertex 70 FTIR spectrometer and are reported in wave numbers (cm-1). All compounds were measured using ATR (attenuated total reflection) sampling technique.

Optical Rotation

Optical rotation was measured on a Perkin Elmer Polarimeter 341 in combination with a Julabo 5 thermostat. The measured temperature is stated in all cases. The wavelength of the light used is 589 nm (sodium D line) in all cases.

4.2 Experimental Procedures

1-Bromo-3-methylbut-2-ene[79]



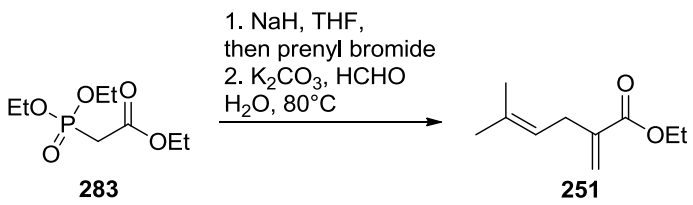
249 **250**

A solution of prenyl alcohol (**249**, 88 mL, 864 mmol) in 1100 mL ether was cooled to 0°C, and PBr_3 (42.4 mL, 438 mmol) was added *via* dropping funnel. The solution was stirred at 0°C for three hours.

Then 1000 mL saturated NaCl were added. The etheral layer was separated, dried, and distillated under vacuum to give prenyl bromide (**250,** 102 g, 79 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.53 (m, 1 H), 4.02 (d, *J* = 8.5 Hz, 2 H), 1.78 (s, 3 H), 1.73 (s, 3 H).

Ethyl 5-methyl-2-methylenehex-4-enoate[17]



283 **251**

Commercial available ethyl 2-(diethoxyphosphoryl)acetate (**283**, 66 mL, 333 mmol) was dissolved in THF (320 mL) and cooled to 0°C. Sodium hydride (9.82 g, 246 mmol) was added over a period of 20 min. The reaction mixture was stirred for 20 min at 0°C, then prenyl bromide (**250**, 38.0 g, 255 mmol) was added over a period of 20 min and the reaction mixture was stirred for six hours at room temperature.

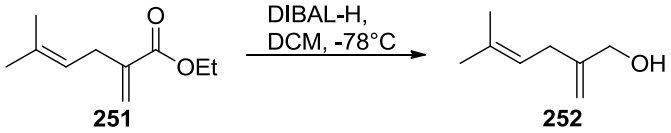
Afterwards, potassium carbonate (73.9 g, 535 mmol), formaldehyde (76 mL, 1.02 mol) and water (40.7 mL,) were added and the reaction mixture was stirred for additional two hours at 80°C.

After cooling to room temperature the aqueous layer was washed twice with diethyl ether. The combined organic extracts were washed with water and brine, dried over magnesium sulfate and the solvent was removed by rotary evaporation.

The residue was purified by column chromatography (hexane/ethyl acetate: 19/1) to give ethyl 5-methyl-2-methylenehex-4-enoate (**251**, 25.2 g, 59% yield) as a colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.11 (dd, *J* = 2.8, 1.6 Hz, 1 H), 5.49 (dd, *J* = 3.6, 2.0 Hz, 1 H), 5.15 (m, 1 H), 4.18 (dd, *J* = 14.4, 7.2 Hz, 2 H), 2.96 (d, *J* = 7.2 Hz, 2 H), 1.71 (s, 3 H), 1.61 (s, 3 H), 1.28 (t, *J* = 7.2 Hz, 3 H).

5-Methyl-2-methylenehex-4-en-1-ol[17]



251 **252**

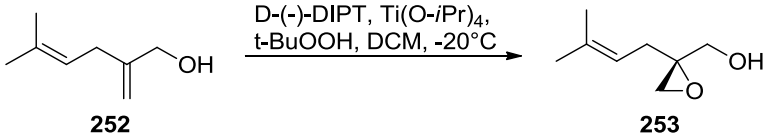
Ethyl 5-methyl-2-methylenehex-4-enoate (**251**, 0.203 g, 1.207 mmol) was dissolved in CH_2Cl_2 (11 mL) and cooled to -78 °C. DIBAL-H (2.65 mL, 2.65 mmol, 1.0 M in heptane) was slowly added *via* syringe and the reaction mixture was stirred for two hours.

Ethyl acetate (4.5 mL) was added dropwise to quench the reaction. Next, saturated solutions of NH_4Cl and Rochelle salt were added (4.5 mL each) and the mixture was stirred for ten hours.

The aqueous phase was extracted three times with ethyl acetate. The combined organic fractions were washed with H_2O and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate: 5/1) and furnished 5-methyl-2-methylenehex-4-en-1-ol (**252**, 0.121 g) in 80% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.14 (m, 1 H), 4.97 (d, *J* = 1.2 Hz, 1 H), 4.84 (d, *J* = 1.2 Hz, 1 H), 4.03 (s, 2 H), 2.72 (d, *J* = 7.6 Hz, 2 H), 1.94 (broad s, 1 H), 1.69 (s, 3 H), 1.60 (s, 3 H).

(*R*)-(2-(3-Methylbut-2-en-1-yl)oxiran-2-yl)methanol



252 **253**

Powdered 4 Å molecular sieves (1.86 g) were dispersed in CH_2Cl_2 (25 mL). Then, D-(-)-DIPT (0.131 g, 0.559 mmol) was added, and the mixture was cooled to -40 °C. After 10 min, titanium(IV) isopropoxide (0.142 mL, 0.485 mmol) was added, and the mixture was stirred at -40 °C for 15 min. After that time, 5.0-6.0 M *t*-BuOOH in decane (1.69 mL, 8.45 – 10.14 mmol) was introduced, and the mixture was stirred at -40 °C for further 30 min. Then 5-methyl-2-methylenehex-4-en-1-ol (**252**, 0.588 g, 4.66 mmol) in CH_2Cl_2 (5 mL) was added. The mixture was warmed to -20 °C and kept at this temperature for 12 hours. The reaction was quenched by addition of acetone containing 2% H_2O (10 mL). After warming to room temperature the mixture was stirred for additional three hours. After filtering through a pad of celite, the filtrate was dried ($MgSO_4$) and the solvent was removed by rotary evaporation. The crude product was purified by column chromatography (hexane/ethyl acetate: 9/1) to furnish (*R*)-(2-(3-methylbut-2-en-1-yl)oxiran-2-yl)methanol (**253**, 0.592 g, 89% yield) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.06 (t, *J* = 7.8 Hz, 1 H), 3.71 (d, *J* = 12.0 Hz, 1 H), 3.56 (d, *J* = 12.0 Hz, 1 H), 2.81 (d, *J* = 4.8 Hz, 1 H), 2.63 (d, *J* = 4.2 Hz, 1 H), 2.45 (dd, *J* = 14.4, 7.8 Hz, 1 H), 2.18 (dd, *J* = 15.6, 7.2 Hz, 2 H), 1.67 (s, 3 H), 1.58 (s, 3 H).

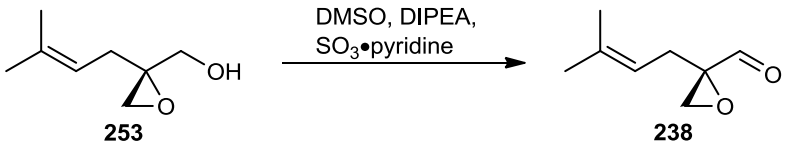
^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.4, 118.2, 63.6, 60.0, 49.6, 30.0, 26.0, 18.1.

HRMS: $[M+Na]^+$: calcd.: 165.0891 found: 165.0880.

IR: v= 3427 (br), 3051, 2970, 2918, 1449, 1378, 1232, 1104, 1043, 967, 945, 883, 843, 810, 773, 703.

$[\alpha]_D^{19,5}$= +41.7°

(*S*)-2-(3-Methylbut-2-en-1-yl)oxirane-2-carbaldehyde[18]



253 238

A solution of sulfur trioxide-pyridine complex (1.39 g, 8.7 mmol) in DMSO (5.3 mL, 74.7 mmol) was added over a period of 5 min to a stirred solution of (*R*)-(2-(3-methylbut-2-en-1-yl)oxiran-2-yl)methanol (**253**, 4.49 g, 31.6 mmol) and DIPEA (4.4 mL, 25.3 mmol) in CH_2Cl_2 (24.2 mL) at 0 °C. The reaction mixture was stirred for 90 min before being diluted with 11 mL of a saturated solution of NH_4Cl. The aqueous phase was separated and the organic layer was washed with 22 mL of a 1.0 M solution of $KHSO_4$.

The combined aqueous layers were extracted twice with ethyl acetate and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was flushed through a column filled with silica gel. (hexane/ethyl acetate: 9/1) to give (*S*)-2-(3-methylbut-2-en-1-yl)oxirane-2-carbaldehyde (**238**, 0.517 g, 70% yield) as a slightly yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.93 (s, 1 H), 5.05 (m, 1 H), 3.00 (dd, *J* = 9.3, 4.8 Hz, 2 H), 2.59 (dd, *J* = 7.4 Hz, 2 H), 1.71 (s, 3 H), 1.64 (s, 3 H).

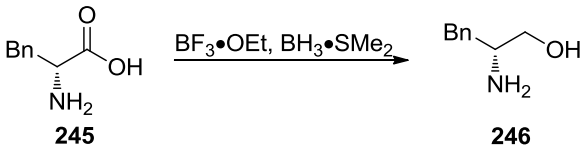
^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.2, 136.3, 116.3, 61.4, 48.8, 25.9, 25.7, 18.1.

HRMS: $[M+Na]^+$: calcd.: 163.0735 found: 163.0730.

IR: v= 2923, 2855, 1728, 1450, 1378, 1219, 1110, 1035, 1008, 963, 873, 861, 811, 784.

$[\alpha]_D^{20}$= -7.0°

(*R*)-2-Amino-3-phenylpropan-1-ol[78]



245 **246**

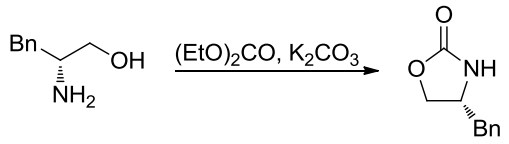
Boron trifluoride etherate (18.68 mL, 151 mmol) was added dropwise to a stirred solution of (*R*)-2-amino-3-phenylpropanoic acid (**245**, 25 g, 151 mmol) in THF (76 mL) over a period of 30 min. The mixture was heated to reflux for two hours before the borane methyl sulfide complex (16.53 mL, 174 mmol) was carefully added to the refluxing solution over a period of 100 min, afterwards the solution was again heated to reflux for 12 hours.

The reaction mixture was cooled to ambient temperature before 23 mL of a 1:1 mixture of tetrahydrofuran-water was added slowly followed by 115 mL of 5 M aqueous sodium hydroxide. The resulting biphasic mixture was again heated to reflux for approximately 20 hours, cooled to room temperature and filtered through a coarse fritted funnel. The residual solids were washed with two portions of THF (7.5 mL), and the filtrate was concentrated on a rotary evaporator.

The concentrated filtrate was extracted once with 60 mL and three times with 30 mL portions of CH_2Cl_2. Pentaerythritol was used to avoid an emulsion. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated by rotary evaporation, to give a white crystalline solid which was recrystallized from ca. 94 mL of ethyl acetate to give (*R*)-2-amino-3-phenylpropan-1-ol (**246,** 17.724 g, 78%)) as white needles in two crops.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.17–7.34 (m, 5 H), 3.64 (dd, *J* = 10.5, 4.1 Hz, 1 H,), 3.38 (dd, *J* =10.5, 7.0 Hz, 1 H), 3.12 (m, 1 H), 2.80 (dd, *J* =13.5, 5.3 Hz, 1 H), 2.53 (dd, *J* = 13.5, 8.5 Hz, 1 H), 1.3–1.9 (broad s, 3 H).

(*R*)-4-Benzyloxazolidin-2-one[78]



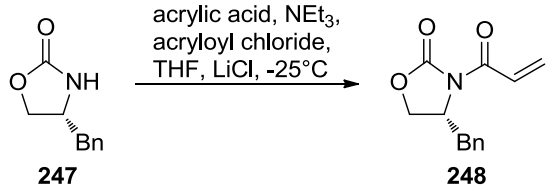
246 **247**

(*R*)-2-Amino-3-phenylpropan-1-ol (**246**, 35.45 g, 234 mmol), potassium carbonate (4.19 g, 30.3 mmol), and diethyl carbonate (76 mL, 627 mmol) were heated to 135°C. A Vigreux column fitted with a distillation head and a distillation receiver was connected to the reaction vessel. The reaction mixture was stirred for 2.5 hours until collection of ethanol (27 mL) in the distillation receiver was finished.

The reaction mixture was diluted with 180 mL of CH_2Cl_2, and washed with 180 mL of water. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to afford white crystals. Recrystallization from 102 mL of a mixture of ethyl acetate and hexane (2/1) gave 32.596 g (79%) of (*R*)-4-(phenylmethyl)-2-oxazolidinone (**247**).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.16–7.38 (m, 5 H), 4.91 (broad s, 1 H), 4.49 (t, *J* = 8.3 Hz, 1 H), 4.16 (dd, *J* = 8.4, 5.5 Hz, 1 H), 4.08 (m, 1 H), 2.87 (m, 2 H).

(*R*)-3-Acryloyl-4-benzyloxazolidin-2-one[18]

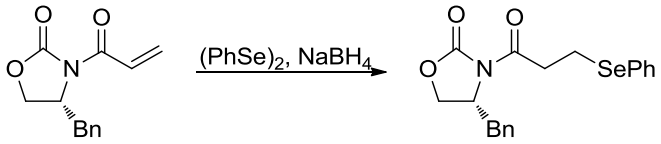


Triethylamine (20.69 mL, 148 mmol) was added to a stirred solution of acrylic acid (5.14 mL, 74.9 mmol) in THF (292 mL) at -25 °C. Then acryloyl chloride (6.52 mL, 80 mmol) was added slowly *via* syringe. The reaction mixture was stirred for 40 min at -20 °C. Lithium chloride (3.30 g, 78 mmol) was added, followed by the addition of (*R*)-4-benzyloxazolidin-2-one (**247**, 10.0 g, 56.4 mmol). The reaction mixture was allowed to warm to room temperature and was stirred for further 36 h until 0.2 M HCl (117 mL) was added. The mixture was concentrated on the rotary evaporator and poured into ethyl acetate (235 mL). The organic layer was separated and the aqueous phase was extracted twice with ethyl acetate. The combined organic layers were washed with a saturated solution of $NaHCO_3$ (235 mL), dried over Na_2SO_4 and concentrated under reduced pressure.

The crude product was purified by flash column chromatography (hexane/ ethyl acetate gradient from 5/1 to 2/1) and re-crystallized (hexane/ethyl acetate: 8/1). (*R*)-3-Acryloyl-4-benzyloxazolidin-2-one (**248,** 8.706 g, 67% yield) was obtained as colorless needles.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.52 (m, 1 H), 7.19-7.37 (m, 5 H), 6.61, (dd, *J* = 17.1, 1.8 Hz, 1 H), 5.94 (dd, *J* = 10.3, 1.8 Hz, 1 H), 4.75 (m, 1 H), 4.22 (m, 2 H), 3.36 (dd, *J* = 13.4, 3.5 Hz, 1 H), 2.82 (dd *J* = 13.5, 9.5 Hz, 1 H).

(*R*)-4-Benzyl-3-(3-(phenylselanyl)propanoyl)oxazolidin-2-one[18]



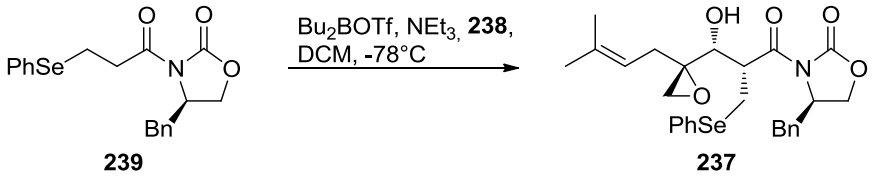
248 **239**

$NaBH_4$ (2.71 g, 71.7 mmol) was added in small portions to a stirred suspension of diphenyl diselenide (10.73 g, 34.4 mmol) in ethanol (295 mL) at room temperature over 10 min. After stirring for 5 min, acetic acid (3.11 mL, 54.3 mmol) was added dropwise and stirring was continued for 5 min. This prepared reaction mixture was then added slowly to a vigorously stirred solution of (*R*)-3-acryloyl-4-benzyloxazolidin-2-one (**248**, 13.05 g, 56.4 mmol) in THF (191 mL) at -35 °C with a cannula over 15 min. After complete addition the reaction mixture was allowed to warm to -20 °C over a period of 40 min.

The reaction was quenched by addition of a saturated solution of NH_4Cl (240 mL) and the resulting mixture was poured into CH_2Cl_2 (690 mL). The organic phase was separated and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting yellow solid was recrystallized from 170 mL hexane and 6.9 mL dichloromethane. The solid product was filtered, washed twice with cold hexane and dried under vacuum to give (*R*)-4-benzyl-3-(3-(phenylselanyl)propanoyl)oxazolidin-2-one (**239**, 21.901 g, 100% yield) as white crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.55 (m, 2 H), 7.17 – 7.35 (m, 8 H), 4.66 (m, 1 H), 4.20 (m, 2 H,), 3.41 (m, 2 H,), 3.29 (dd, *J* = 13.4, 3.3 Hz, 1 H,), 3.19 (t, *J* = 6.9 Hz, 2 H,), 2.78 (dd, *J* = 13.3, 9.6 Hz, 1 H,).

(*R*)-4-Benzyl-3-((2*R*,3*R*)-3-hydroxy-3-((*S*)-2-(3-methylbut-2-en-1-yl)oxiran-2-yl)-2-((phenylselanyl)methyl)propanoyl)oxazolidin-2-one[18]

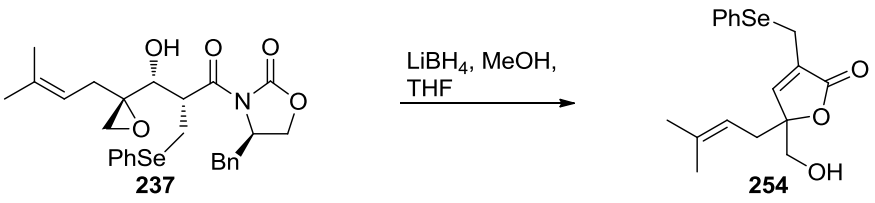


239 **237**

Dibutylboron triflate (1.0 M, 5.73 mL, 5.7 mmol) was slowly added to a stirred solution of (*R*)-4-benzyl-3-(3-(phenylselanyl)propanoyl)oxazolidin-2-one (**239**, 1.62 g, 4.2 mmol) in CH_2Cl_2 (9.8 mL) at -78°C. The mixture was stirred for 10 min before NEt_3 (1.47 mL, 10.6 mmol) was added dropwise. After stirring at -78°C for 75 min, the mixture was warmed to 0°C. After 15 min, the solution was re-cooled to -78°C before freshly prepared (*S*)-2-(3-methylbut-2-en-1-yl)oxirane-2-carbaldehyde (**238**, 0.60 g, 4.3 mmol) in CH_2Cl_2 (2.7 mL) was added slowly. The reaction mixture was stirred at -78 °C for five hours and allowed to warm to room temperature over a period of 12 hours before being quenched with 40 mL of a saturated solution of NH_4Cl. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and solvents were removed on the rotary evaporator. The crude product was purified by flash column chromatography (hexane/ ethyl acetate gradient from 19/1 to 2/1) to give (*R*)-4-benzyl-3-((2*R*,3*R*)-3-hydroxy-3-((*S*)-2-(3-methylbut-2-en-1-yl)oxiran-2-yl)-2-((phenylselanyl)methyl)propanoyl)oxazolidin-2-one(**237**, 0.418 g, 19% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53-7.63 (m, 2 H), 7.26-7.38 (m, 8 H), 5.23 (m, 1 H), 4.39 (m, 1 H), 4.31 (d, *J* =6.4 Hz, 1 H), 4.2 (t, *J* = 8.8 Hz, 1 H), 4.08 (dd, *J* = 8.9, 6.5 Hz, 1 H), 3.97 (dd, *J* = 3.1, 1.5 Hz, 1 H), 3.66 (dd, *J* =12.3, 3.8 Hz, 1 H), 3.45 – 3.51 (m, 2 H), 2.86 (dt, *J* = 12.8, 3.5 Hz, 1 H), 2.74 (dd, *J* = 13.5, 10.2 Hz, 1 H), 2.58 (d, *J* =7.6 Hz, 2 H), 2.47 (t, *J* =12.5 Hz, 1 H), 1.76 (s, 3 H), 1.65 (s, 3 H).

5-(Hydroxymethyl)-5-(3-methylbut-2-en-1-yl)-3-((phenylselanyl)methyl)furan-2(5H)-one[86]

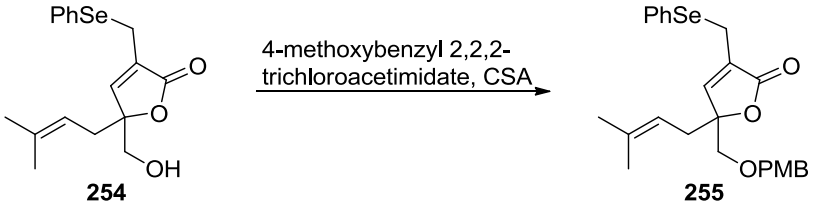


A solution of (*R*)-4-benzyl-3-((2*R*,3*R*)-3-hydroxy-3-((*S*)-2-(3-methylbut-2-en-1-yl)oxiran-2-yl)-2-((phenylselanyl)methyl)propanoyl)oxazolidin-2-one (**237**, 98 mg, 0.18 mmol) in THF (5.1 mL) was cooled to -20°C. MeOH (7 µL, 0.18 mmol) and 2 M $LiBH_4$ solution (0.37 mL, 0.74 mmol) were added subsequently. The mixture was stirred for one hour at -20°C. The reaction was quenched by addition of saturated ammonium chloride solution. The aqueous layer was extracted three times with diethyl ether (10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (hexane/ ethyl acetate gradient from 5/1 to 3/1) to give 5-(hydroxymethyl)-5-(3-methylbut-2-en-1-yl)-3-((phenylselanyl)methyl)furan-2(5H)-one (**254**, 14 mg, 22% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49-7.53 (m, 2 H), 7.27-7.29 (m, 3 H), 6.69 (s, 1 H) 4.85 (m, 1 H), 3.66 (d, *J* = 11.7 Hz, 1 H), 3.65 (t, *J* = 1.3 Hz, 2 H), 3.53 (d, *J* = 11.7 Hz, 1 H), 2.38 (m, 2 H), 1.66 (s, 3 H), 1.55 (s, 3 H).

HRMS: $[M+Na]^+$: calcd.: 375.0475 found: 375.0486.

5-(((4-Methoxybenzyl)oxy)methyl)-5-(3-methylbut-2-en-1-yl)-3-((phenylselanyl)methyl)furan-2(5H)-one



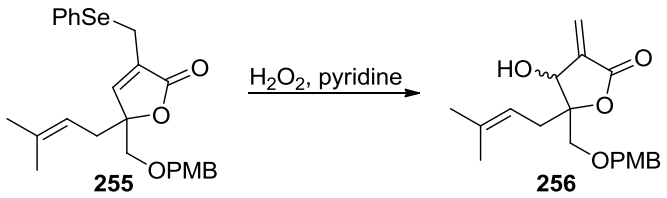
254 **255**

Camphorsulfonic acid (1 mg) was added to a solution of 5-(hydroxymethyl)-5-(3-methylbut-2-en-1-yl)-3-((phenylselanyl)methyl)furan-2(5H)-one (**254**, 19 mg, 0.05 mmol) and 4-methoxybenzyl 2,2,2-trichloroacetimidate (0.1 mL, 0.12 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was stirred for 12 h at room temperature. Though complete consumption of the starting materials could not be observed, the reaction was quenched with a saturated solution of sodium bicarbonate. The aqueous layer was extracted with DCM three times. The combined organic layers were dried over $MgSO_4$ and solvent was removed *via* rotary evaporation. The crude product was purified by flash column chromatography (hexane/ ethyl acetate gradient from 9/1 to 3/1) to give 5-(((4-methoxybenzyl)oxy)methyl)-5-(3-methylbut-2-en-1-yl)-3-((phenylselanyl)methyl)furan-2(5H)-one (**255**, 11 mg, 42% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47-7.50 (m, 2 H), 7.28-7.32 (m, 3 H), 6.85-6.92 (m, 4 H), 6.78 (s, 1 H), 4.86 (m, 1 H), 4.40 (s, 2 H), 3.82 (s, 3 H), 3.65 (s, 2 H), 3.47 (d, *J* = 10.1 Hz, 1 H), 3.34 (d, *J* = 10.1 Hz, 1 H), 2.37 (m, 2 H), 1.64 (s, 3 H), 1.54 (s, 3 H).

HRMS: $[M+Na]^+$: calcd.: 495.1051 found: 495.1054.

4-Hydroxy-5-(((4-methoxybenzyl)oxy)methyl)-5-(3-methylbut-2-en-1-yl)-3-methylenedihydrofuran-2(3H)-one[18]

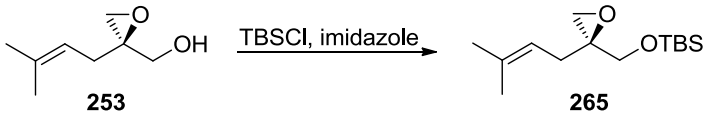


To a stirred solution of 5-(((4-methoxybenzyl)oxy)methyl)-5-(3-methylbut-2-en-1-yl)-3-((phenylselanyl)methyl)furan-2(5H)-one (**255**, 10 mg, 0.02 mmol) and pyridine (1µL, 0.01mmol) in CH_2Cl_2 (0.2 mL) was added hydrogen peroxide (30%, 3.5 µl, 0.03mmol) at 0°C. The mixture was stirred for 30 min at 0°C, and additional 90 min at room temperature. Then, 2 mg Na_2SO_3 were added and the aqueous layer was extracted with DCM three times. The combined organic layers were washed three times with water, dried over $MgSO_4$ and concentrated through rotary evaporation. Purification by flash column chromatography (hexane/ ethyl acetate 5/1) gave 4-hydroxy-5-(((4-methoxybenzyl)oxy)methyl)-5-(3-methylbut-2-en-1-yl)-3-methylenedihydrofuran-2(3H)-one (**256**, 1 mg, 14% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16 (d, *J* = 8.6 Hz, 2 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 6.31 (d, *J* = 2.7 Hz, 1 H), 5.82 (d, *J* = 2.7 Hz, 1 H), 5.15 (m, 1 H), 4.56 (dt, J = 11.2, 2.7 Hz, 1 H), 4.49 (d, *J* =11.5 Hz, 1 H), 4.39 (d, *J* =11.5 Hz, 1 H), 3.83 (d, *J* = 10.6 Hz, 1 H), 3.81 (s, 3 H), 3.59 (d, *J* = 10.6 Hz, 1 H), 3.09 (d, *J* = 10.9 Hz, 1 H), 2.39 (d, *J* =7.4 Hz, 2 H), 1.72 (s, 3 H), 1.64 (s, 3 H).

HRMS: $[M+Na]^+$: calcd.: 355.1521 found: 355.1520.

(*S*)-*Tert*-butyldimethyl((2-(3-methylbut-2-en-1-yl)oxiran-2-yl)methoxy)silane



253 **265**

Imidazole (0.124 g, 1.83 mmol) was added to a solution of (*R*)-(2-(3-methylbut-2-en-1-yl)oxiran-2-yl)methanol (**253**, 0.13 g, 0.91 mmol) in CH_2Cl_2 (1.3 mL) at 0°C. Then, TBSCl (0.152 g, 1.01 mmol) was added.

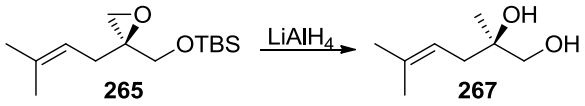
After complete consumption of the starting materials as indicated by TLC, a saturated solution of NH_4Cl was added and the aqueous layer was extracted with CH_2Cl_2 twice. The combined organic layers were dried over $MgSO_4$ and concentrated on the rotary evaporator. The crude product was purified by flash column chromatography (hexane/ ethyl acetate: 40/1) to give (*S*)-*tert*-butyldimethyl((2-(3-methylbut-2-en-1-yl)oxiran-2-yl)methoxy)silane (**265**, 0.208 g, 89% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ =5.12 (m, 1 H), 3.65 (dd, *J* = 23.0, 11.2 Hz, 2 H), 2.69 (d, *J* = 5.1 Hz, 1 H), 2.61 (d, *J* = 5.1 Hz, 1 H), 2.48 (dd, *J* = 15.5, 8.0 Hz, 1 H), 2.26 (dd, *J* = 15.5, 8.0 Hz, 1 H), 1.71 (s, 3 H), 1.62 (s, 3 H), 0.90 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ =132.8, 118.4, 66.0, 65.3, 49.6, 30.3, 29.0, 26.0, 25.9, 17.5, -5.3.

HRMS: $[M+Na]^+$: calcd.: 279.1756 found: 279.1749.

(*R*)-2,5-Dimethylhex-4-ene-1,2-diol[84]



265 **267**

To a stirred suspension of $LiAlH_4$ (58 mg, 1.54 mmol) in dry THF (2.7 mL) was added a solution of of (*S*)-*tert*-butyldimethyl((2-(3-methylbut-2-en-1-yl)oxiran-2-yl)methoxy)silane (**265**, 0.789 g, 3.08 mmol) in dry THF (2.7 mL) and the mixture was stirred for 2 h. After TLC showed incomplete consumption of the starting material further $LiAlH_4$ (0.058 g, 1.54 mmol) was added.

After TLC showed complete consumption of the starting material, excess $LiAlH_4$ was destroyed by addition of saturated potassium sodium tartrate, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated on the rotary evaporator. The residue was purified by flash column chromatography (hexane/ ethyl acetate: 3/1) yielding(*R*)-2,5-dimethylhex-4-ene-1,2-diol (**267**, 0.345 g, 78%).

^{1}H NMR (400 MHz, $CDCl_3$): δ =5.15 (m, 1 H), 3.38 (dd, *J* = 25.1, 10.9 Hz, 2 H), 2.76 (broad s, 1 H), 2.49 (broad s, 1 H), 2.16 (m, 2 H), 1.68 (s, 3 H), 1.59 (s, 3 H), 1.09 (s, 3 H).

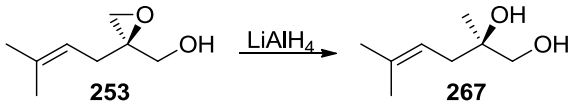
^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.6, 118.8, 73.4, 69.0, 36.7, 25.5, 22.4, 17.2.

HRMS: $[M+Na]^+$: calcd.: 167.1048 found: 167.1037.

IR: ν= 3375 (br), 2971, 2925, 2861, 1452, 1378, 1130, 1051, 904, 849, 766.

$[\alpha]_D^{19,5}$= +6.6°

(*R*)-2,5-Dimethylhex-4-ene-1,2-diol[84]



253 **267**

To a suspension of $LiAlH_4$ (0.676 g, 17.82 mmol) in dry THF (31 mL) was added a solution of (*R*)-(2-(3-methylbut-2-en-1-yl)oxiran-2-yl)methanol (**253**, 5.000 g, 35.6 mmol) in dry THF (31 mL) and the mixture was stirred for 2 h. Excess $LiAlH_4$ was destroyed by addition of saturated potassium sodium tartrate, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated on the rotary evaporator. The residue was purified by flash column chromatography (hexane/ ethyl acetate: 1/1) yielding(*R*)-2,5-dimethylhex-4-ene-1,2-diol (**267**, 2.110 g 41% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ =5.15 (m, 1 H), 3.38 (dd, *J* = 25.1, 10.9 Hz, 2 H), 2.76 (broad s, 1 H), 2.49 (broad s, 1 H), 2.16 (m, 2 H), 1.68 (s, 3 H), 1.59 (s, 3 H), 1.09 (s, 3 H).

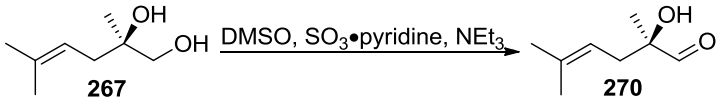
^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.6, 118.8, 73.4, 69.0, 36.7, 25.5, 22.4, 17.2.

HRMS: $[M+Na]^+$: calcd.: 167.1048 found: 167.1037.

IR: v= 3375 (br), 2971, 2925, 2861, 1452, 1378, 1130, 1051, 904, 849, 766.

$[\alpha]_D^{19,5}$= +6.6°

(*R*)-2-Hydroxy-2,5-dimethylhex-4-enal[87]



267 **270**

To a solution of (*R*)-2,5-dimethylhex-4-ene-1,2-diol (**267**, 3.102 g, 14.65 mmol) in DCM (83 mL), DMSO (3.64 mL, 51.3 mmol), Et_3N (7.15 mL, 51.3 mmol) and pyridine sulfur trioxide (5.84 g, 36.7 mmol) were added at 0 °C and the reaction mixture was stirred at 0 °C for 3 hours. The solution was poured into sat. NH_4Cl, the organic layer was separated and the aqueous phase was extracted twice with diethyl ether. The combined organic layers were subsequently washed with water and brine, dried over anhydrous $MgSO_4$ and concentrated on the rotary evaporator. The crude product was purified by flash column chromatography (hexane/ ethyl acetate gradient from 9/1 to 5/1) to give (*R*)-2-hydroxy-2,5-dimethylhex-4-enal (**270**, 1.60 g, 77% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ =9.54 (s, 1 H), 5.08 (m, 1 H), 3.03 (broad s, 1 H), 2.39 (m, 2 H), 1 H), 1.72 (s, 3 H), 1.64 (s, 3 H), 1.33 (s, 3 H).

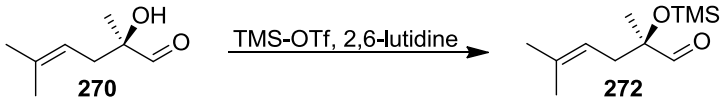
^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.3, 136.8, 116.1, 78.4, 36.2, 26.4, 22.4, 17.8.

HRMS: $[2M+Na]^+$: calcd.: 307.1885 found: 307.1892.

IR: v= 3457 (br), 2971, 2925, 2857, 2339, 1734, 1456, 1376, 1217, 1092, 806.

$[\alpha]_D^{20}$= -29.1°

(*R*)-2,5-Dimethyl-2-((trimethylsilyl)oxy)hex-4-enal



270 **272**

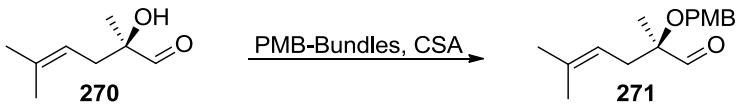
2,6-Lutidine (0.65 mL, 5.57 mmol) was added to a solution of (*R*)-2-hydroxy-2,5-dimethylhex-4-enal (**270**, 0.501 g, 2.78 mmol) in DCM (2.78 mL), followed by TMS-OTf (0.755 mL, 4.18 mmol). As the reaction did not proceed to completion additionally 0.13 mL TMS-OTf (0.696 mmol) and 0.16 mL 2,6-lutidine (1.392 mmol) were added.

The reaction was quenched with NH_4Cl and the aqueous layer was washed with DCM twice. The combined organic layers were washed with water and brine, and dried over Na_2SO_4. Solvents were removed under reduced pressure and the residue was purified by flash chromatography (hexane/ethyl acetate: 19/1) to furnish (*R*)-2,5-dimethyl-2-((trimethylsilyl)oxy)hex-4-enal (**272**, 0.191 g, 33% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.53 (s, 1 H), 5.11 (m, 1 H), 2.30 (m, 2 H), 1.71 (s, 3 H), 1.60 (s, 3 H), 1.27 (s, 3 H), 0.17 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): 204.7, 134.4, 117.5, 80.9, 37.2, 25.1, 21.9, 18.0, 2.3.

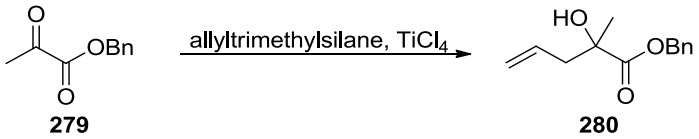
(*R*)-2-((4-Methoxybenzyl)oxy)-2,5-dimethylhex-4-enal



270 **271**

CSA (1 mg) was added to a solution of (*R*)-2-hydroxy-2,5-dimethylhex-4-enal (**270**, 0.033 g, 0.231 mmol) and 4-methoxybenzyl 2,2,2-trichloroacetimidate (1.0 M, 0.255 mL, 0.255 mmol) in CH_2Cl_2 (4.3 mL). The reaction mixture was stirred for 13 hours at 50°C in a sealed tube. Because TLC showed incomplete consumption of the starting material further 0.231 mL 4-methoxybenzyl 2,2,2-trichloroacetimidate (1.0 M, 0.231 mmol) were added, but, despite further addition, complete consumption of the starting materials could not be observed. The reaction was quenched with sat. $NaHCO_3$. The aqueous layer was extracted with DCM. The combined organic layers were dried over Na_2SO_4, and concentrated on the rotary evaporator. Purification of the crude material *via* HPLC could only give a non-quantifying trace of (*R*)-2-((4-methoxybenzyl)oxy)-2,5-dimethylhex-4-enal (**271**).

Benzyl 2-hydroxy-2-methylpent-4-enoate



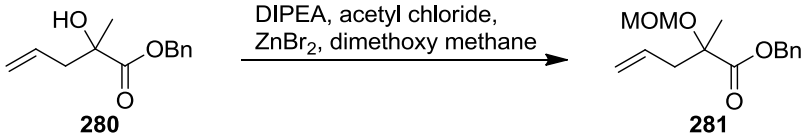
279 **280**

Titanium(IV) chloride (2.98 mL, 27.0 mmol) was slowly added to a solution of benzyl 2-oxopropanoate (**279**, 4.81 g, 27.0 mmol) in DCM (56 mL) in a three-necked 250 mL flask, which was cooled *via* a methanol/CO_2 cooling bath to -80°C. Allyltrimethylsilane (10.12 mL, 63.4 mmol) in DCM (56 mL) was added drop wise over a period of 30 min. The reaction mixture was stirred for 30 min at -80°C.

After complete consumption of the starting material as indicated by TLC, 70 mL of water were added. The aqueous layer was washed three times with 25mL diethyl ether. The combined organic layers were dried over $MgSO_4$ and the solvents were removed *in vacuo*. Flash chromatography (hexane/ethyl acetate gradient from 19:1 to 9:1) of the crude product furnished benzyl 2-hydroxy-2-methylpent-4-enoate (**280**, 5.326 g, 90% yield).

^{1}H NMR (400 MHz, $CDCl_3$): 7.31-7.42 (m, 5 H), 5.74 (m, 1 H), 5.19 (s, 2 H), 5.06 (m, 2 H), 3.11 (s, 1 H), 2.52 (dd, *J* = 14.1, 7.3 Hz, 1 H), 2.40 (dd, *J* = 14.1, 7.3 Hz, 1 H), 1.44 (s, 3 H).

Benzyl 2-(methoxymethoxy)-2-methylpent-4-enoate[85]



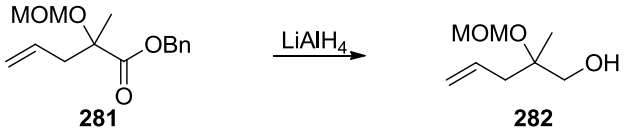
Zinc bromide (0.019 g, 0.084 mmol) was added to a solution of dimethoxymethane (8.62 mL, 96 mmol) in DCM (10.4 mL). The reaction mixture was stirred until $ZnBr_2$ was dissolved, then acetyl chloride (6.84 mL, 96 mmol) was added *via* dropping funnel over a period of 15 min. The exothermic reaction warmed slowly to 40-45 °C and re-cooled to ambient temperature over a period of three hours. Afterwards the purity and conversion was determined by NMR spectroscopy. This solution of MOMCl was used in the next step without further manipulation in the next step.

First benzyl 2-hydroxy-2-methylpent-4-enoate (**280**, 5.3 g, 24.06 mmol) was added *via* syringe, then DIPEA (33.6 mL, 192 mmol) was added to the reaction mixture dropwise *via* the addition funnel over a period of 30 min at 0°C. The reaction mixture was allowed to warm to ambient temperature and was stirred for 12 h.

After dilution with ethyl acetate and addition of saturated NH_4Cl solution the biphasic mixture was stirred vigorously for 15 minutes. The aqueous layer was washed with three times with DCM and twice with ethyl acetate. The combined organic layers were washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (hexane/ethyl acetate: 9/1) to give benzyl 2-(methoxymethoxy)-2-methylpent-4-enoate (**281**, 5.66 g, 89% yield).

^{1}H NMR (400 MHz, $CDCl_3$): 7.29-7.39 (m, 5 H), 5.77 (m, 1 H), 5.15 (s, 2 H), 5.06 (m, 2 H), 4.76 (dd, *J* = 12.3, 7.3 Hz, 2 H), 3.35 (s, 3 H), 2.55 (m, 2 H), 1.48 (s, 3 H).

2-(Methoxymethoxy)-2-methylpent-4-en-1-ol



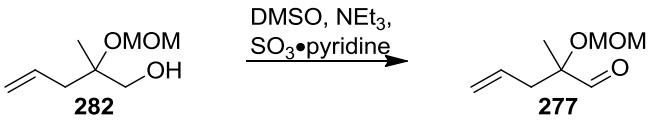
281 **282**

Benzyl 2-(methoxymethoxy)-2-methylpent-4-enoate (**281**, 9.65 g, 36.5 mmol) inTHF (105 mL) was added to a stirred solution of $LiAlH_4$ (0.915 g, 24.10 mmol) in THF (89 mL). The reaction mixture was heated to 70°C.

After TLC showed complete consumption of the starting materials, 11 mL aqueous KOH (10 w%) were added at 0°C. The mixture was stirred for 12 hours, filtered through Celite, and dried over $MgSO_4$. After rotary evaporation the crude product was purified by flash chromatography (toluene/ethyl acetate: 19:1) to give 2-(methoxymethoxy)-2-methylpent-4-en-1-ol (**282**, 3.653 g, 62% yield).

^{1}H NMR (400 MHz, $CDCl_3$): 5.82 (m, 1 H), 5.10 (m, 2 H), 5.06 (m, 2 H), 4.74 (dd, *J* = 10.1, 7.5 Hz, 2 H), 3.45 (m, 2 H), 3.43 (s, 3 H) 2.33 (m, 2 H), 1.17 (s, 3 H).

2-(Methoxymethoxy)-2-methylpent-4-enal[87]

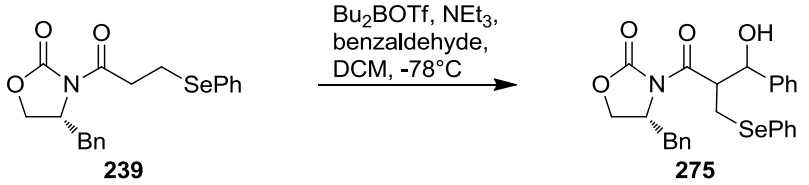


282 **277**

2-(methoxymethoxy)-2-methylpent-4-en-1-ol (**282**, 1 g, 6.24 mmol) was dissolved in DCM (35 mL), then DMSO (1.6 mL, 21.9 mmol), Et_3N (3.0 mL, 21.9 mmol) and pyridine sulfur trioxide (2.49 g, 15.7 mmol) were added at 0 °C. The reaction mixture was stirred at 0 °C for three hours until it was poured into sat NH_4Cl (4 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product by flash chromatography (hexane/ ethyl acetate gradient from 9/1 to 5/1) gave 2-(methoxymethoxy)-2-methylpent-4-enal (**277**, 0.764 g, 77% yield).

^{1}H NMR (400 MHz, $CDCl_3$): 9.55 (s, 1 H) 5.78 (m, 1 H), 5.14 (m, 2 H), 4.76 (d, *J* = 7.3 Hz, 1 H), 4.70 (d, *J* = 7.3 Hz, 1 H), 3.41 (m, 3 H), 2.48 (dd, *J* = 14.4, 7.1 Hz, 1 H), 2.37 (dd, *J* = 14.4, 7.1 Hz, 1 H), 1.29 (s, 3 H).

(4*R*)-4-Benzyl-3-(3-hydroxy-3-phenyl-2-((phenylselanyl)methyl)propanoyl)oxazolidin-2-one[18]

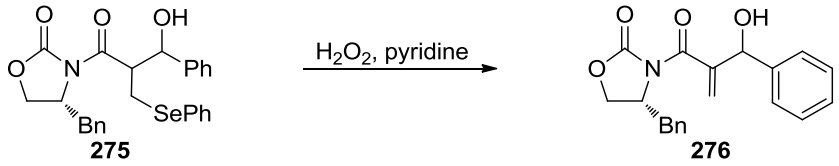


239 **275**

Dibutylboron triflate (3.18 mL, 3.18 mmol, 1.0 M solution in CH_2Cl_2) was added slowly to a solution of (*R*)-4-Benzyl-3-(3-(phenylselanyl)propanoyl)oxazolidin-2-one (**239**, 0.900 g, 2.318 mmol) in CH_2Cl_2 (5. 5 mL) at -78 °C. The mixture was stirred for 10 min, then NEt_3 (0.82 mL, 5.86 mmol) was added drop wise. The resulting mixture was stirred at -78 °C for 75 min, then warmed to 0 °C for 15 min, before it was recooled to -78 °C. A solution of freshly distilled benzaldehyde (0.24 mL, 2.38 mmol) in CH_2Cl_2 (1.5 mL) was added slowly in two portions. The reaction mixture was slowly warmed from -78°C to 0°C over a period of 13 hours and warmed to 40°C for additional 2 hours. After addition of 5 mL NH_4Cl the organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 three times. The combined organic layers were dried over Na_2SO_4 and solvents were removed on the rotary evaporator. The crude product was purified through flash chromatography (hexane/ ethyl acetate gradient from 5:1 to 1:1) to give (4*R*)-4-benzyl-3-(3-hydroxy-3-phenyl-2-((phenylselanyl)methyl)propanoyl)oxazolidin-2-one (**275**, 0.294 g, 79%).

^{1}H NMR (400 MHz, $CDCl_3$): 7.18 – 7.39 (m, 15 H), 5.05 (m, 1 H), 4.70 (m, 1 H), 4.49 (m, 1 H), 4.05 (dd, *J* = 8.9, 2.5 Hz, 1 H), 3.87 (t, *J* = 8.5 Hz, 1 H), 3.41 (dd, *J* = 12.4, 10.6 Hz, 1 H), 3.23 (m, 2 H), 2.72 (dd, *J* = 13.6, 9.7 Hz, 1 H).

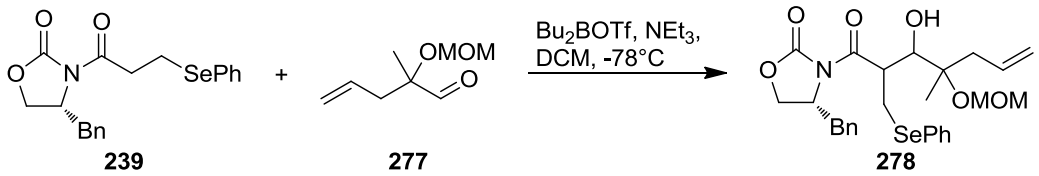
(4*R*)-4-Benzyl-3-(2-(hydroxy(phenyl)methyl)acryloyl)oxazolidin-2-one[18]



To a solution of (4*R*)-4-benzyl-3-(3-hydroxy-3-phenyl-2-((phenylselanyl)methyl)propanoyl)oxazolidin-2-one (**275**, 0.968 g, 1.96 mmol) in CH_2Cl_2 (9.8 mL) was added pyridine (0.32 mL, 3.92 mmol) followed by the addition of hydrogen peroxide (30%, 0.62 mL, 6.07 mmol) and the reaction mixture was stirred vigorously at room temperature. As TLC showed incomplete consumption of the starting material an additional amount of hydrogen peroxide (0.30 mL, 2.94 mmol) was added. The reaction mixture was poured into aqueous layer of ChDa-128 (preparation of (4*R*)-4-benzyl-3-(3-hydroxy-3-phenyl-2-((phenylselanyl)methyl)propanoyl)oxazolidin-2-one (**275**)). The organic layer was extracted twice with DCM. The combined organic layers were dried over Na_2SO_4 and concentrated on the rotary evaporator. The crude product was purified by flash chromatography (hexane/ethyl acetate gradient from 5/1 to 1/1) and recrystallization (hexane/ethyl acetate 1:1) to give (4*R*)-4-benzyl-3-(2-(hydroxy(phenyl)methyl)acryloyl)oxazolidin-2-one (**276**, 0.260 g, 40 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): 7.27 – 7.46 (m, 8 H), 7.13 – 7.17 (m, 2 H), 5.61 (m, 1 H) 5.59 (m, 2 H), 4.67 (m, 2 H), 4.21 (m, 2 H), 3.21 (dd, *J* = 13.6, 3.4 Hz, 1 H), 3.12 (d, *J* = 5.3 Hz, 1 H), 2.73 (dd, *J* = 13.6, 9.2 Hz, 1 H).

(4*R*)-4-Benzyl-3-(3-hydroxy-4-(methoxymethoxy)-4-methyl-2-((phenylselanyl)methyl)hept-6-enoyl)oxazolidin-2-one[18]



Dibutylboron triflate (3.63 mL, 3.63 mmol, 1.0 M solution in CH_2Cl_2) was added slowly to a solution of (*R*)-4-Benzyl-3-(3-(phenylselanyl)propanoyl)oxazolidin-2-one (**239**, 1.029 g, 2.65 mmol) in CH_2Cl_2 (6.9 mL) at -78 °C. The mixture was stirred for 10 min, then NEt_3 (0.93 mL, 6.70 mmol) was added drop wise. The resulting mixture was stirred at -78 °C for 75 min, then at 0 °C for 15 min and afterwards it was re-cooled again to -78 °C. A solution of freshly prepared 2-(methoxymethoxy)-2-methylpent-4-enal (**277**, 0.429 g, 2.71 mmol) in CH_2Cl_2 (1 mL) was added slowly in two portions *via* syringe. The reaction mixture was slowly warmed from -78°C to 12°C over a period 14 hours. Then, the reaction was quenched with NH_4Cl and the aqueous layer was washed with CH_2Cl_2 three times. The combined organic layers were dried over Na_2SO_4 and concentrated on the rotary evaporator.

Purification *via* flash column chromatography (hexane/ethyl acetate: 2/1) furnished (4R)-4-benzyl-3-(3-hydroxy-4-(methoxymethoxy)-4-methyl-2-((phenylselanyl)methyl)hept-6-enoyl)oxazolidin-2-one (**278**, 7.4 mg, 1% yield).

^{1}H NMR (400 MHz, $CDCl_3$): 7.56 – 7.59 (m, 2 H), 7.23 – 7.35 (m, 8 H), 5.74 (m, 1 H), 5.08 (m, 2 H), 4.68 (m, 2 H), 4.17 (m, 2 H), 3.86 (m, 1 H), 3.44 (m, 2 H), 3.35 (s, 3 H), 3.26 (m, 2 H), 3.09 (d, *J* = 9.0 Hz, 1 H), 2.75 (dd, *J* = 13.5, 9.9 Hz, 1 H), 2.44 (m, 2 H), 1.14 (s, 3 H).

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Abstract

The spurge family (*Euphorbiaceae*) is phytopharmacologically important since ancient times. A broad range of biological activities have been reported for plant extracts. Particularly, jatrophane diterpenes are potent P-glycoprotein modulators. Efflux pumps, such as P-glycoprotein, are responsible for multidrug resistance (MDR) effects of cancer cells which might result in the failure of cancer chemotherapy. Thus, jatrophane diterpenes are considered as co-therapuetics in cancer chemotherapy.

Several synthetic studies have been reported so far because of the fascinating structures and the promising biological activities. However, only few total syntheses of natural jatrophane diterpenes and non-natural jatrophane diterpenes were reported.

Within this thesis the synthetic efforts towards highly oxygenated five-membered ring synthons are reported. The route is based on previous studies on less oxygenated cyclopentane derivatives from our laboratory. Key steps are a Sharpless asymmetric epoxidation, an aldol reaction, a ring closing metathesis and a hydroboration/oxidation sequence.

Zusammenfassung

Die Wolfsmilchgewächse (*Euphorbiaceae*), sind seit jeher phytopharmakologisch von großer Bedeutung. Extrakte von Wolfsmilchgewächsen besitzen verschiedenste biologische Aktivitäten. Effluxpumpen, wie P-Glykoprotein, sind verantwortlich für multidrug resistance (MDR) Effekte, die zum Scheitern von Chemotherapie bei Krebserkrankungen führen. Nachdem in Untersuchungen von Jatrophan Diterpenen die Inhibierung solcher Effluxpumpen erreicht werden konnte ist es denkbar Jatrophan Diterpene in Chemotherapien zu verwenden um MDR Effekten vorzubeugen.

Dass bereits einige Synthesearbeiten publiziert wurden lässt sich auf die faszinierenden Strukturen und vielversprechenden biologischen Aktivitäten von Jatrophanen zurückführen. Darüber hinaus wurden auch einige wenige Totalsynthesen, sowohl von natürlichen als auch unnatürlichen Jatrophan Diterpenen mit Jatrophan Struktur, veröffentlicht.

In dieser Masterarbeit sind die synthetischen Arbeiten an höher oxygenierten fünfgliedrigen Syntheseintermediaten dokumentiert. Der gewählte Syntheseweg orientiert sich stark an vorhergehenden synthetischen Arbeiten an weniger oxygenierten fünfgliedrigen Ringfragmenten, die in unserer Arbeitsgruppe durchgeführt wurden. Geplante Schlüsselschritte der Synthese umfassen unter anderem eine asymmetrische Epoxidierung nach Sharpless, eine Aldol Reaktion, eine Ringschlussmetathese sowie einer Sequenz aus einer Hydroborierung und einer Oxidation.

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