ASYMMETRIC DIHYDROXYLATION AND JACOBSEN'S HYDROLYTIC KINETIC RESOLUTION METHODS TO THE SYNTHESIS OF NATURALLY OCCURING AMINO ALCOHOLS AND LACTONES

A THESIS

SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

(IN CHEMISTRY)

TO

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BY

S. VASUDEVA NAIDU

ORGANIC CHEMISTRY: TECHNOLOGY

NATIONAL CHEMICAL LABORATORY

PUNE-411008

March 2008

DEDICATED

TO MY BELOVED

PARENTS

CANDIDATE'S DECLARATION

I here by declare that the thesis entitled "**Asymmetric dihydroxylation and Jacobsen's Hydrolytic Kinetic resolution methods to the synthesis of naturally occurring amino alcohols and lactones**" submitted for the degree of Doctor of Philosophy in Chemistry to the University of Pune has not been submitted by me to any other university or Institution. This work was carried out at the National Chemical Laboratory, Pune, India.

Sagi. Vasudeva Naidu
Senior Research Fellow (CSIR)
Division of Organic Chemistry: Technology
National Chemical Laboratory
Pune-411008

March 2008

NATIONAL CHEMICAL LABORATORY

Dr. Homi Bhabha Road, PUNE. 411 008, INDIA.

Dr. Pradeep Kumar
Scientist F
Division of Organic Chemistry: Technology

Telephone and Fax: + 91-20-25902627
+ 91-20-25902629
E-mail: pk.tripathi@ncl.res.in
Website: http://www.ncl-india.org

CERTIFICATE

The research work presented in thesis entitled "**Asymmetric dihydroxylation and Jacobsen's Hydrolytic Kinetic resolution methods to the synthesis of naturally occurring amino alcohols and lactones**" has been carried out under my supervision and is a bonafide work of **Mr. S. Vasudeva Naidu**. This work is original and has not been submitted for any other degree or diploma of this or any other University.

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March 2008

(Dr. Pradeep Kumar)
Research Guide

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ABBREVIATIONS

Ac	-	Acetyl
AcOH	-	Acetic acid
Ac_2O	-	Acetic anhydride
AIBN	-	2,2'-Azobisisobutyronitrile
Bn	-	Benzyl
BnBr	-	Benzyl bromide
$BH_3 \cdot Me_2S$	-	Boron dimethyl sulfide complex
Boc	-	*tert*-Butoxy carbonyl
$(Boc)_2O$	-	Di-*tert*-butyl dicarbonate
BuLi	-	Butyl Lithium
DCM	-	Dichloromethane
DDQ	-	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
de	-	Diastereomeric excess
ds	-	Diastereoselectivity
DIBAL-H	-	Diisobutylaluminiumhydride
DHP	-	Dihydropyran
$(DHQ)_2PHAL$	-	1,4-Bis(dihydroquinin-9-*O*-yl)phthalazine
$(DHQD)_2PHAL$	-	1,4-Bis(dihydroquinidin-9-*O*-yl)phthalazine
DMP	-	Dess–Martin periodinane
DMP	-	2,2-Dimethoxypropane
DMF	-	*N, N'*-Dimethylformamide
DMAP	-	*N,N'*-Dimethylaminopyridine
DMSO	-	Dimethyl sulfoxide
ee	-	Enantiomeric excess
eq. or equiv	-	Equivalents
EtOH	-	Ethanol
Et	-	Ethyl

Et_2O	-	Diethyl ether
EtOAc	-	Ethyl acetate
Et_3N	-	Triethylamine
h	-	Hours
Hz	-	Hertz
IBS	-	Iodoxybenzoic Acid
Im	-	Imidazole
i-Pr	-	Isopropyl
IR	-	Infrared
LDA	-	Lithium diisopropylamide
m-CPBA	-	*m*-Chloroperbenzoic acid
MeOH	-	Methanol
MsCl	-	Methanesulfonyl chloride
Ms	-	Methanesulfonyl
Me	-	Methyl
MeI	-	Methyl iodide
$NaBH_4$	-	Sodiumborohydride
NaH	-	Sodium hydride
NOE	-	Neuclear Overhauser Effect
Ph	-	Phenyl
Py	-	Pyridine
PDC	-	Pyridiniumdichromate
p-TSA	-	*para*-Toluenesulfonic acid
RCM	-	Ring closing metathesis
TEA	-	Triethylamine
TBAI	-	Tetra-*n*-butylammonium iodide
TBAF	-	Tetra-*n*-butylammonium fluoride
TBDMSCl	-	*tert*-Butyldimethyl chlorosilane
TBDMS	-	*tert*-Butyldimethyl silyl
THF	-	Tetrahydrofuran
TPP	-	Triphenylphosphine
*P*TSA	-	*p*-Toluenesulphonic acid

TsCl - *p*-Toluenesulphonyl chloride

GENERAL REMARKS

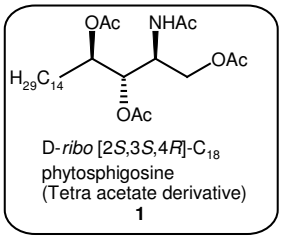
- ^{1}H NMR spectra were recorded on AC-200 MHz, MSL-300 MHz, and DRX-500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- ^{13}C NMR spectra were recorded on AC-50 MHz, MSL-75 MHz, and DRX-125 MHz spectrometer
- EI Mass spectra were recorded on Finngan MAT-1020 spectrometer at 70 *eV* using a direct inlet system.
- Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm^{-1}.
- Optical rotations were measured with a JASCO DIP 370 digital polarimeter.
- Melting points were recorded on Buchi 535 melting point apparatus and are uncorrected.
- All reactions are monitored by Thin Layer chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F-254) with UV light, I_2 and anisaldehyde in ethanol as development reagents.
- All solvents and reagents were purified and dried by according to procedures given in Vogel's Text Book of Practical Organic Chemistry. All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.
- All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 40 °C.
- Silica gel (60–120) used for column chromatography was purchased from ACME Chemical Company, Mumbai, India.

ABSTRACT

The thesis entitled **"Asymmetric dihydroxylation and Jacobsen's hydrolytic kinetic resolution methods to the synthesis of naturally occurring amino alcohols and lactones"** consists of four chapters. First chapter describes the double diastereodifferentiation in asymmetric dihydroxylation: Application to the diastereoselective synthesis of D-ribo-(2*S*,3*S*,4*R*)-C_{18}-phytosphingosine. The second chapter deals with the enantio- and diastereocontrolled total synthesis of (+)-boronolide. The third chapter discusses the total synthesis of microcarpalide, sapinofuranone B, (–)-pinellic acid and α- and β-dimorphecolic acid. Final chapter describes a simple and efficient approach to 1,3-polyols and its application to the synthesis of (+)-strictifolione, lactone moiety of HMG-CoA reductase inhibitor: compactin and mevinolin and (+)-negamycin.

CHAPTER 1:

Double Diastereodifferentiation in Asymmetric Dihydroxylation: Application to the Diastereoselective Synthesis of D-ribo-(2*S*,3*S*,4*R*)-C_{18}-Phytosphingosine.



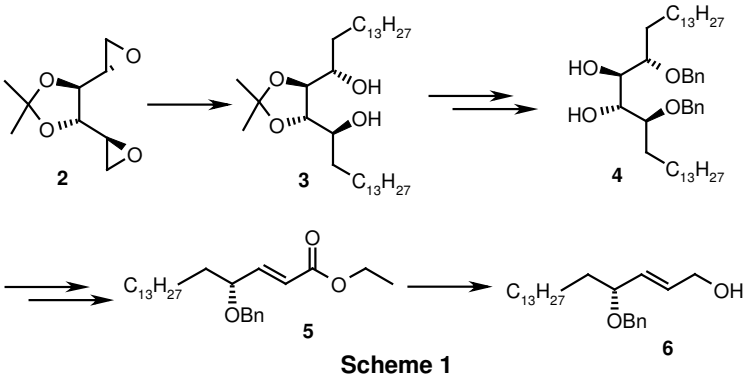
D-*ribo* [2*S*,3*S*,4*R*]-C_{18} phytosphigosine (Tetra acetate derivative)
1

Figure 1.

Sphingolipids constitute a class of widely ranging natural products. Sphingosine, phytosphingosine and their biosynthetic precursor, sphinganine, are long chain amino alcohols, generally possessing 18 or 20 carbon atoms. They are building blocks of sphingolipids such as sphingomyelins, glycosphingolipids, and phosphosphingolipids, which are important membrane constituents playing vital roles in cell regulation and signal transduction. D-*ribo*-C_{18}-Phytosphingosine ((2*S*,3*S*,4*R*)-2-amino-octa-decane-1,3,4-triol) and its related C_{20}-homologues are widely distributed as amides of α-hydroxy long chain acids in

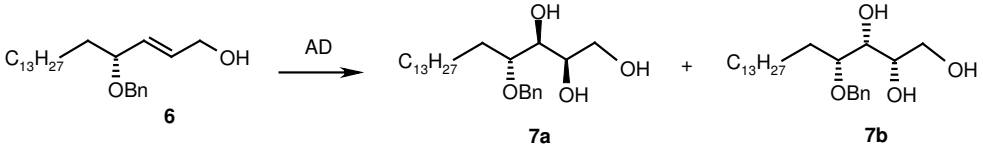
plant sphingolipids.[1] Various methods for the synthesis of phytosphingosine **1** either racemic[2] or enantiomerically enriched[3] have been described in literature.

Like many other reactions including the Sharpless asymmetric epoxidation and the Sharpless asymmetric dihydroxylation of olefins, the pre-existing chiral information in the substrate has a marked influence on the stereoselective outcome of the reaction. With a view to exploit the concept of double stereodifferentiation, the olefinic ester **5** was subjected to the Sharpless asymmetric dihydroxylation (AD) conditions.[4] However, the reaction proceeded much more slowly with a poor diastereoselectivity probably as a consequence of the electron-withdrawing properties of the ester group. While the Sharpless asymmetric dihydroxylation on the allylic alcohols with different long alkyl chains has been exploited to a large extent, the reaction on allylic alcohols having chiral centers remains still unexplored. The enantioselectivity of an asymmetric dihydroxylation reaction can be modulated by the size of the allylic substituent and the configuration at the allylic position.



Scheme 1

The dihydroxylation of allylic alcohol **6** under the AD conditions using $(DHQD)_2PHAL$ and $(DHQ)_2$ PHAL ligands gave diols **7a, 7b** (Scheme 2) with diastereomeric ratios 9:1 and 1:2 respectively as given in the table 1.

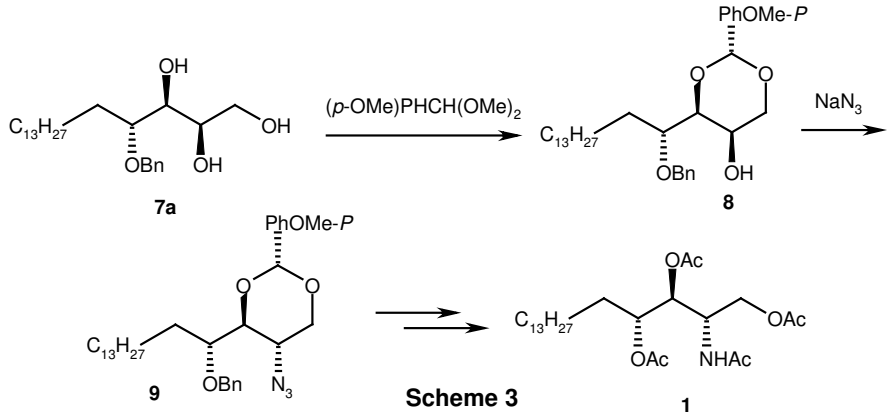


Scheme 2

Table 1

Ligand	**7a**	**7b**	Yield (%)
$(DHQD)_2PHAL$	9	1	92
$(DHQ)_2PHAL$	1	2	89

In order to achieve the synthesis of target compound **1** from **7a**, we required the transformation of the hydroxy group into azide at the C-2 position. To this end protection of **7a** as *p*-methoxybenzylidene derivative **8** and its conversion into an *O*-mesyl followed by azide substitution furnished the azide **9** with the desired stereochemistry at C-2. Deprotection of benzyl, cleavage of 1,3-benzylidene protecting group and reduction of azide to amine were carried out in one-pot reaction by hydrogenation followed by acetylation to furnish the target compound as the tetra-acetate derivative (**1**).



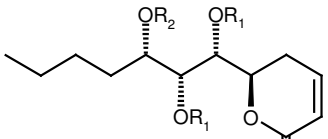
Scheme 3

Thus, a highly enantioselective synthesis of D-*ribo*-C_{18}-phytosphingosine has been achieved from a readily available carbohydrate precursor by using the Sharpless asymmetric dihydroxylation procedure. The concept of double diastereoselection was employed for the first time on a chiral allylic alcohol in AD reaction. The merits of this synthesis are high diastereoselectivity and high yielding reaction steps. The other isomer L-*lyxo*-C_{18}-phytosphingosine can be synthesized from *S*-diepoxide using the chiral ligand $(DHQ)_2PHAL$ in the dihydroxylation step and following the reaction sequence shown above.

CHAPTER 2:

Enantio- and Diastereocontrolled Total Synthesis of (+)-Boronolide

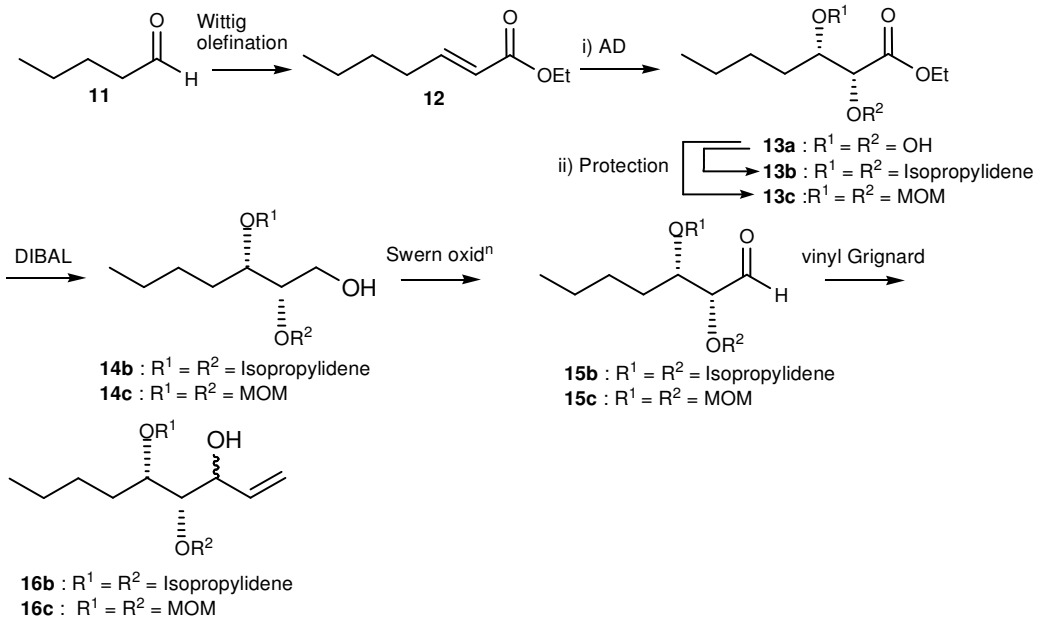
α-Pyrones (5,6-dihydro-2*H*-pyran-2-ones) possessing polyhydroxy or polyacetoxy side chains have attracted much attention from synthetic and medicinal chemists due to their broad range of biological activities.[5] Examples of such compounds include (+)-boronolide **10**, and its deacetylated **10a** and dideacetylated derivative **10b** (Fig. 2).



10 : $R_1 = R_2 = Ac$
10a : $R_1 = R_2 = H$
10b : $R_1 = H; R_2 = Ac$

Figure 2

We have accomplished a stereoselective total synthesis of (+)-boronolide **10** from commercially available valeraldehyde **11** employing Sharpless asymmetric dihydroxylation, a chelation controlled Grignard reaction, hydrolytic kinetic resolution (HKR), Sharpless asymmetric epoxidation and ring closing metathesis.

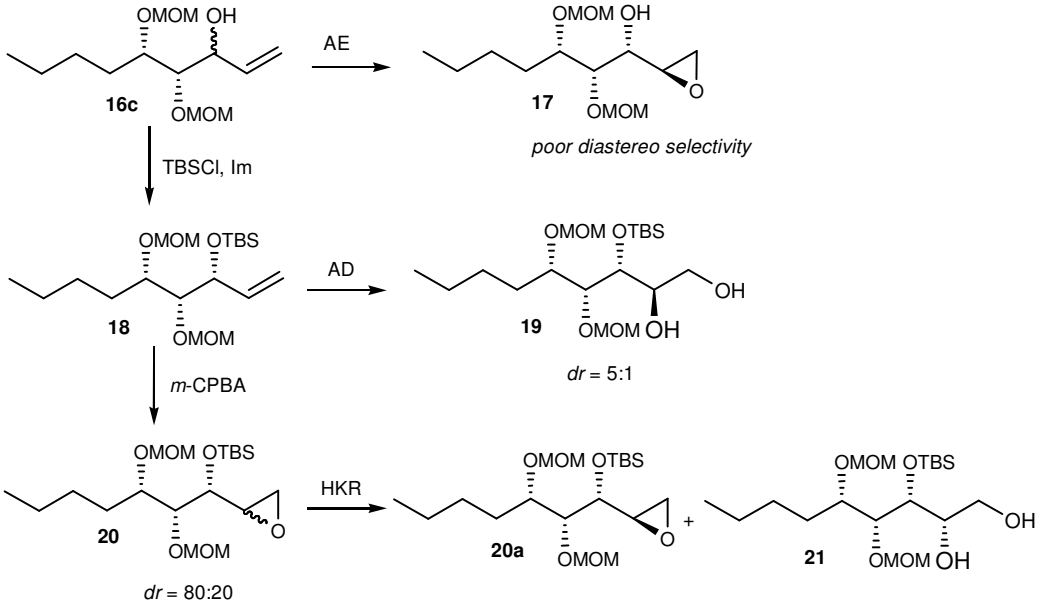


Scheme 4

Wittig Horner-Emmons olefination of aldehyde **11** to **12**, asymmetric dihydroxylation of olefin **12** to **13**, dihydroxyl protection **13a** to **13b/13c**, ester reduction followed by oxidation of alcohol **14b** provided the aldehyde **15b**. Chelation controlled vinyl Grignard reaction of aldehyde **15b** using $MgBr_2.Et_2O$[6] provided the allyl alcohol **16b** with moderate diastereomeric selectivity (*dr* = 75:25; *syn*:*anti*) as a non separable mixture of diastereomers. In order to explore the possibility of achieving a better *syn*-selectivity in vinylation reaction, diol was protected as MOM **13c**, ester reduction followed by oxidation of alcohol **14c** provided aldehyde **15c**. The aldehyde was subjected to chelation controlled vinylation to furnish the allylic alcohol **16c** with an excellent diastereoselectivity. After protection of hydroxyl group

with TBSCl, Sharpless asymmetric epoxidation was employed to afford the epoxide **17** only in low yield and with less selectivity.

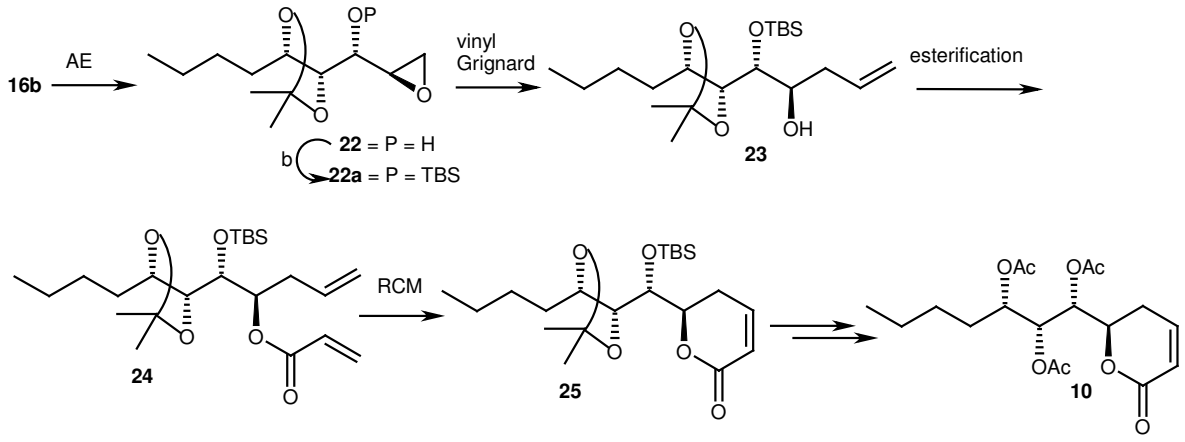
As a next alternative, when the Sharpless asymmetric dihydroxylation was employed on olefin **18**, it furnished the diol **19** with moderate diastereomeric selectivity. In an another attempt, we then carried out the epoxidation of olefin using *m*-CPBA in various solvent systems in the presence of Na_2HPO_4 as the base to afford the epoxide **20** (*dr* = 80:20; *anti*:*syn*). In order to get the diastereomerically pure epoxide the HKR was performed on epoxide **20**. Thus epoxide **20** was resolved with *R*,*R*-salen-Co(OAc) complex (0.5 mol%) and water (0.4 eq) to yield the epoxide **20a** and diol **21**.



Scheme 5

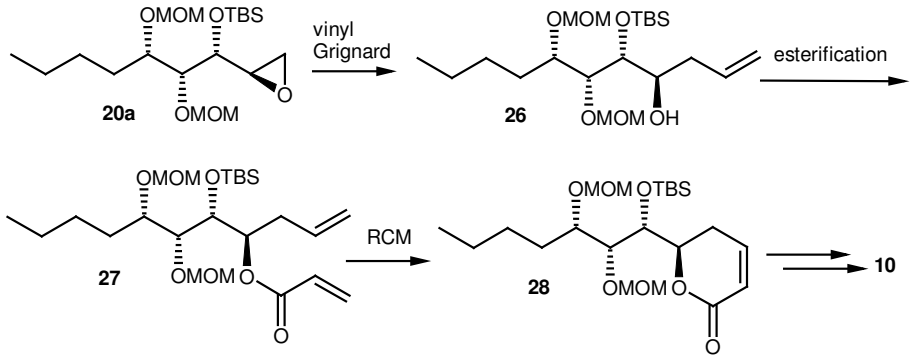
While asymmetric epoxidation of **16c** gave rather low yield of the product, the treatment of allylic alcohol **16b** under the Sharpless asymmetric epoxidation conditions[7] furnished the desired epoxide **22** in good yield and high diastereomeric excess. After the protection of the hydroxyl group as the *tert*-butyldimethylsilyl ether, epoxide **22a** was opened with vinylmagnesium bromide to give homoallylic alcohol **23**. The subsequent esterification of **23** with acryloyl chloride and ring closing metathesis with commercially available Grubbs' I[st] generation catalyst[8] (10 mol %) in the presence of Ti(OPr-*i*)$_4$ in refluxing CH_2Cl_2 afforded the

α,β-unsaturated δ-lactone **25**. Finally all protecting groups in compound **25** were deprotected and the resulting triol was acetylated with acetic anhydride to give (+)-boronolide **10**.



Scheme 6

In the same manner ring opening of the epoxide **20a** with vinylmagnesium bromide followed by esterification with acryloyl chloride and ring closing metathesis afforded the α,β-unsaturated lactone **28**. Finally all protecting groups in compound **28** were deprotected and the resulting triol was acetylated with acetic anhydride to give (+)-boronolide **10**.



Scheme 7

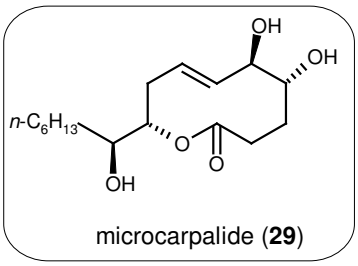
CHAPTER 3:

Enantioselective syntheses of naturally occurring lactones microcarpalide, sapinofuranone B, (–)-pinellic acid, α- and β-Dimorphecolic Acid.

The vicinal diol, polyene (with *E*- and *Z*-geometry) in the macrolactones or simple lactones are key structural features in variety of bioactive molecules. This chapter summarizes our

studies on the asymmetric synthesis of microcarpalide and sapinofuranone B; (–)-pinellic acid, α- and β-dimorphecolic acid and is divided into four sections.

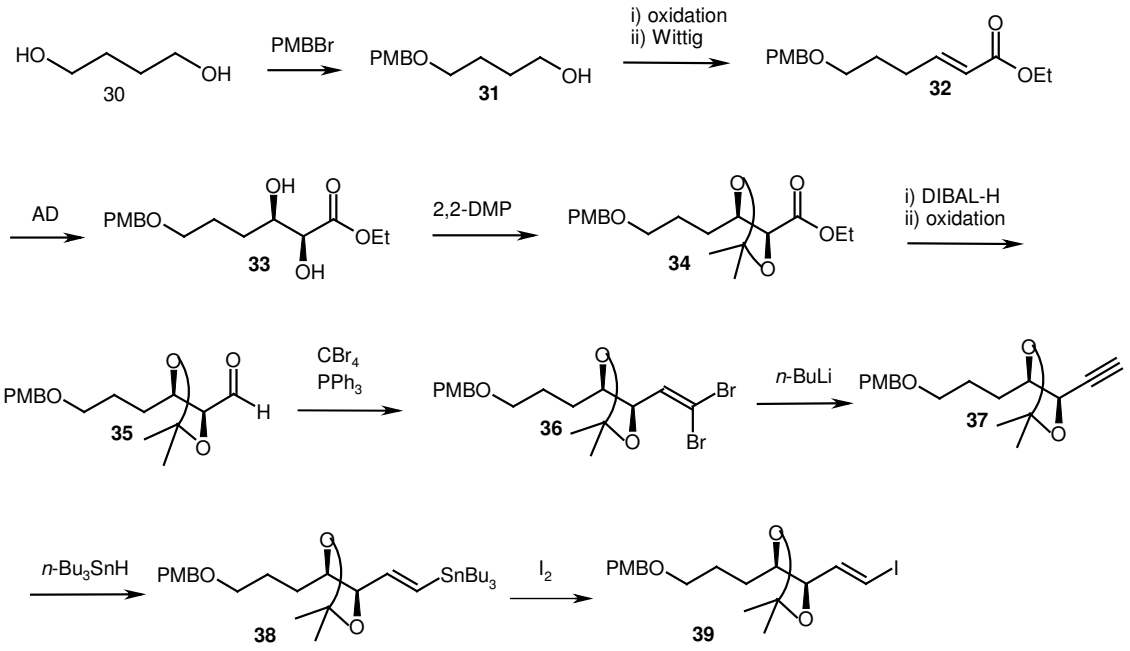
<u>Section A:</u> Total Synthesis of Microcarpalide



microcarpalide (**29**)

Figure 3

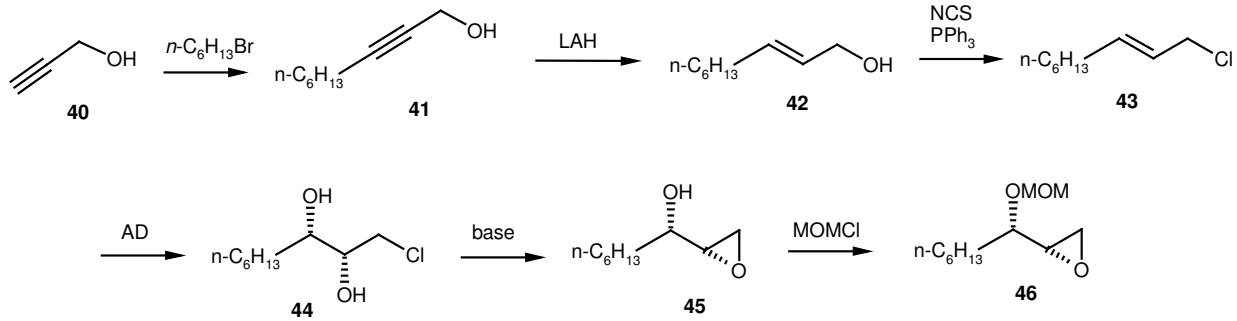
Microcarpalide **29**, a new alkyl-substituted nonenolide, was isolated by Hemscheidt and co-workers in 2001 from fermentation broths of an unidentified endophytic fungus growing on the bark of *Ficus microcarpa* L.[9] This compound acts as a strong anti-microfilament disrupting agent and displayed a weak cytotoxicity to mammalian cells, thus making it an attractive tool for studying cell motility and metastasis, and a potential lead structure to develop new anti-cancer drugs. So far five total syntheses of microcarpalide have been reported in the literature.[10] Most of the approaches described are based on ring closing metathesis for the key macrocyclization to construct the olefin with selectivities between 2:1 to 10:1 in favor of the desired (*E*)-isomer. The synthesis of microcarpalide **29** started from commercially available 1,4-butanediol and propargyl alcohol.



Scheme 8

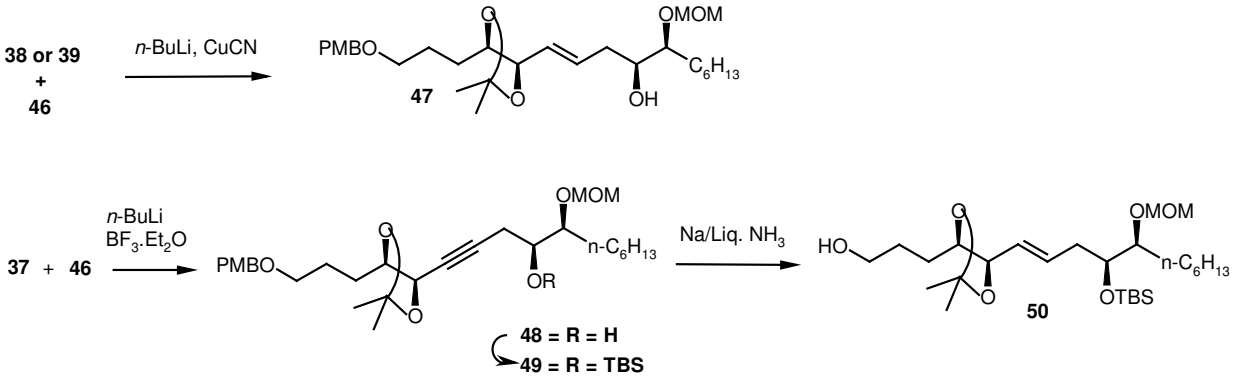
Synthesis of acetylene fragment 37. The synthesis of acetylene component **37** started from commercially available 1,4-butanediol **30**. Monoprotection of 1,4-butanediol, oxidation, Wittig olefination of aldehyde followed by asymmetric dihydroxylation provided the diol **33**. The diol **33** was protected as acetonide **34**, reduction-oxidation followed by dibromomethylenation afforded the dibromo olefin **36**. Treatment of **36** with excess of *n*-BuLi furnished acetylene fragment **37**[11], which was readily converted into (*E*)-vinyl stannane **38**, which was further replaced with iodine to furnish vinyl iodide **39**.

Synthesis of epoxy fragment. The synthesis of epoxy component **46** commenced from propargyl alcohol **40**. Alkylation with hexyl bromide, LAH reduction, followed by chlorination provided allyl chloride **43**. Asymmetric dihydroxylation of allyl chloride[12] provided the chloro diol **44**. The chloro diol **44** was converted into epoxide followed by MOM protection to furnish the epoxide fragment **46**.



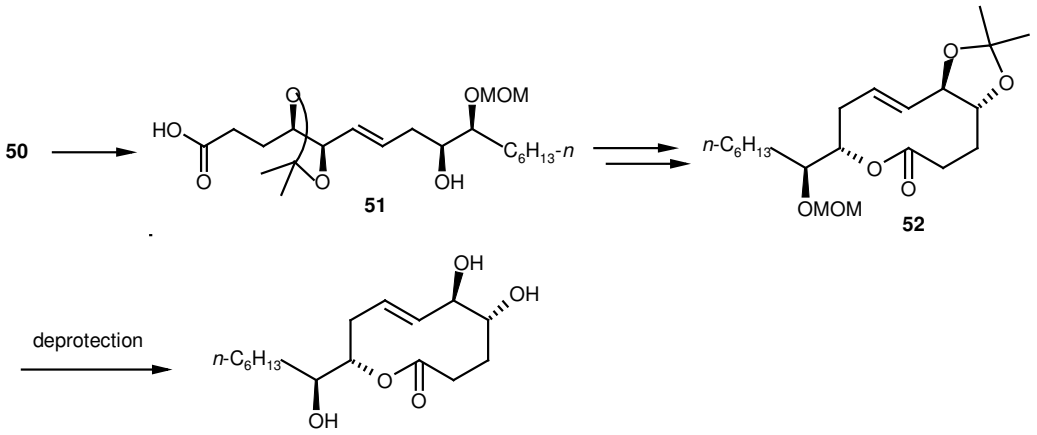
Scheme 9

Coupling of two fragments was effected with the regioselective opening of epoxide with different nucleophiles such as **37**, **38**, and **39**. Thus, the cuprate derived from vinyl stannane **38** was treated with **46** to furnish the coupled product **47**.[13] In the same way compound **39** was coupled with **46** to give **47**. In both these reactions 3 eq. of cuprate was utilized. In order to circumvent this problem, the acetylene **37** was finally coupled with epoxide **46** via Yamaguchi method[14] to afford the coupled product **48**. The free hydroxy group of **48** was protected as its TBS ether **49** followed by Birch reduction[15] to give the *E*-olefin **50**.



Scheme 10

Oxidation of primary alcohol to the corresponding acid[16] followed by TBS deprotection provided the seco-acid **51** for lactonization. Macrolactonization of **51** under Yamaguchi conditions[17] provided the macrocyclic lactone **52**, which on subsequent cleavage of the protective groups afforded the target molecule **29**.



Scheme 11

Section B: An Efficient Total Synthesis of Sapinofuranone B

An efficient enantioselective synthesis of sapinofuranone B (**53**) using Sharpless asymmetric dihydroxylation, Sonogashira coupling and Wittig olefination as the key steps, is described.

During a screening program for inhibition of benzodiazepine binding to the $GABA_A$ receptor, xenovulene A was isolated from submerged cultures of the fungus *Acremonium strictum*.[18] While optimizing the production of xenovulene A in the preliminary fermentation work, Simpson and co-workers isolated a novel metabolite from fermentation extracts and they named it as (4*S*, 5*S*, 6*Z*, 8*E*)-5-hydroxydeca-6,8-dien-4-olide [(*S*,*S*)-Sapinofuranone B] **53**.[19] Both the structures and stereochemistry of sapinofuranones were determined by spectroscopic methods.

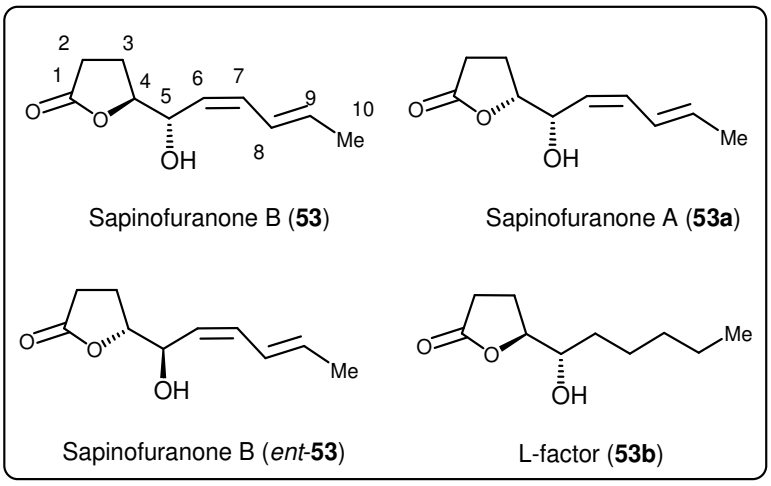
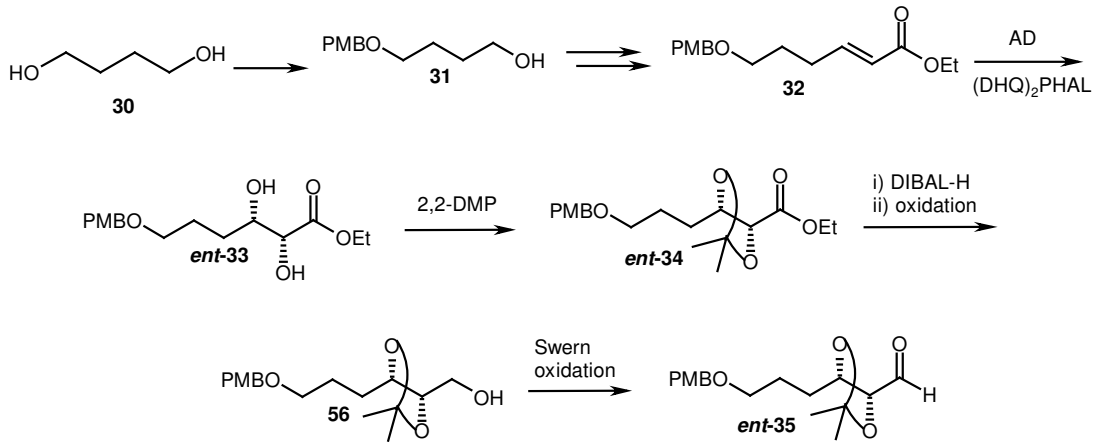


Figure 4. Structures of sapinofuranones and L- factor

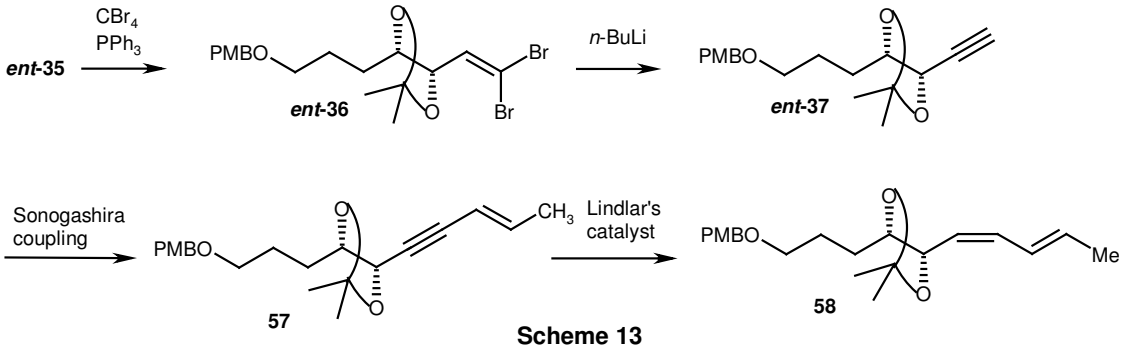
The synthesis of sapinofuranone B **53** started from commercially available 1,4-butanediol as illustrated in Scheme 12.

Monoprotection of 1,4-butanediol **30**, oxidation, Wittig olefination of aldehyde followed by aymmetric dihydroxylation provided the diol ***ent*-33**. The diol ***ent*-33** was protected as its acetonide ***ent*-34**, reduction-oxidation followed by dibromomethylenation afforded the dibromo olefin ***ent*-36**. Treatment of ***ent*-36** with excess of *n*-BuLi furnished the acetylene fragment ***ent*-37**.



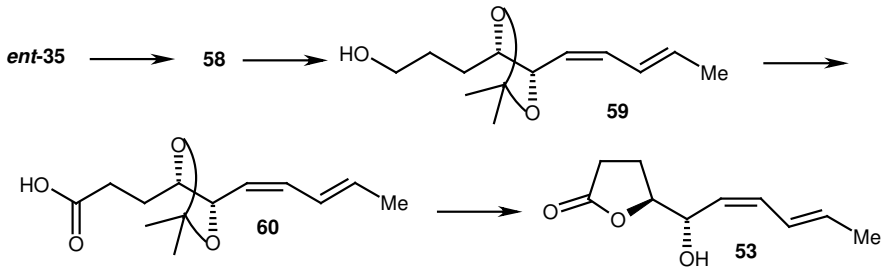
Scheme 12

The Sonogashira coupling[20] of ***ent*-37** with commercially available *trans*-1-bromopropene **37a** was successfully carried out with $Pd(PPh_3)_2Cl_2$ and CuI in triethylamine to furnish the 1,3-enyne product **57**. The partial hydrogenation of triple bond furnished the desired compound **58**.[21]



Scheme 13

Alternatively the diene **58** was also obtained by the Wittig olefination of the aldehyde ***ent*-35** in the presence of LiHMDS (*Z*:*E* = 80:20). The subsequent deprotection of the *p*-methoxybenzyl group followed by oxidation of the resulting alcohol **59** to the corresponding aldehyde and further oxidation afforded the acid **60**. Finally, the deprotection of acetonide as well as cyclisation was achieved in one-pot by using cat. conc. HCl in methanol to furnish the target molecule **53**.



Scheme 14

Section C: Enantioselective synthesis of (–)-pinellic acid

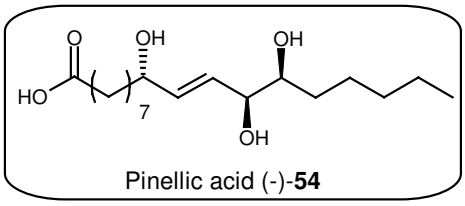
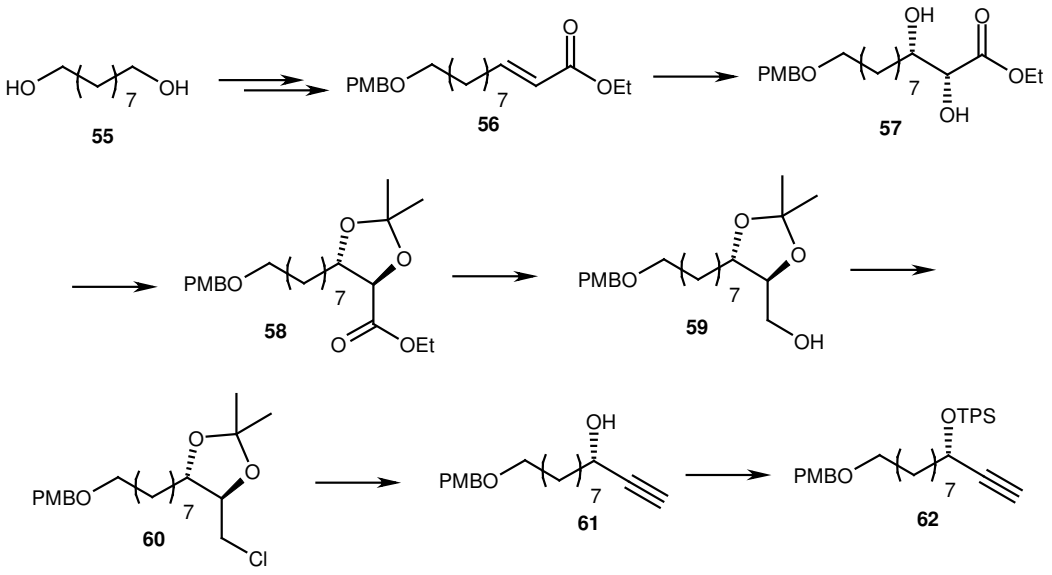


Figure 5

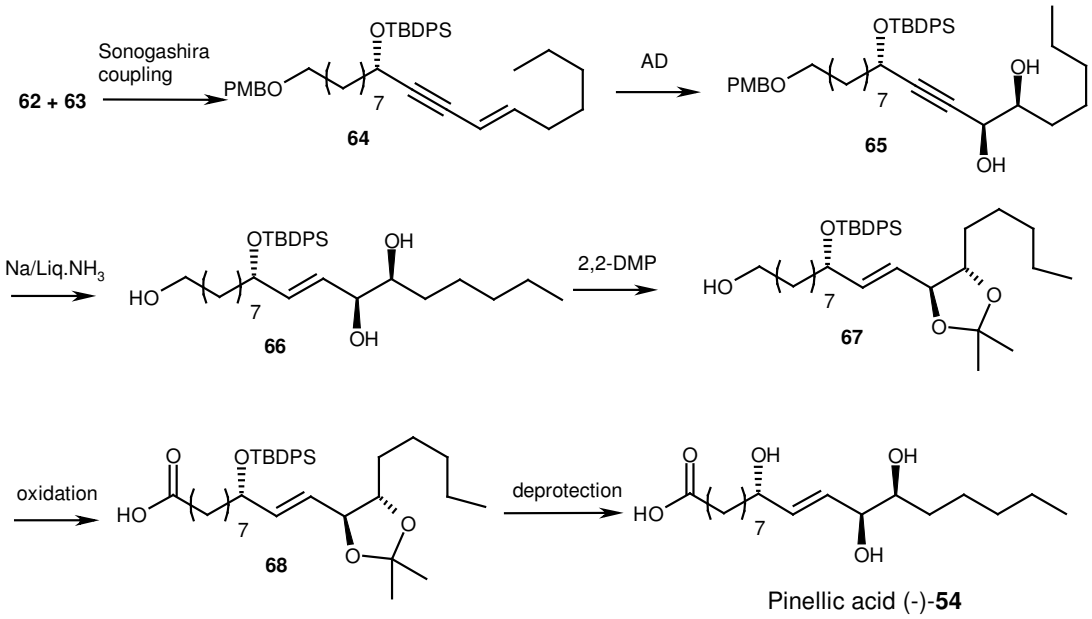
Influenza, commonly known as the flu, is an infectious disease of birds and mammals caused by an RNA virus of the family Orthomyxoviridae (the influenza viruses). In people, common symptoms of influenza are fever, sore throat, muscle pains, severe headache, coughing, and weakness and fatigue.[22] Pinellic acid (9*S*, 12*S*, 13*S*-trihydroxy-10*E*-octadecenoic acid, Fig. 5) was isolated from the tuber of *P. ternata*, one of eight component herbs of the Kampo formula, Sho-seiryu-to (SST). Pinellic acid is a novel and potentially useful oral adjuvant when used in conjunction with intranasal inoculation of influenza HA vaccines.[23]

The synthesis of pinellic acid (–)-**54** started from commercially available 1,9-nonane diol **55** as illustrated in Scheme 15. Thus, selective mono hydroxyl protection of **55** with *p*-methoxybenzyl bromide followed by oxidation and Witiig olefination gave *trans*-olefin **56** in good yield. Sharpless asymmetric dihydroxylation of olefin under AD conditions in the presence of $(DHQ)_2PHAL$ ligand furnished the diol **57** in 96% yield with 99% ee. Treatment of diol **57** with 2,2-dimethoxy propane in the presence of *p*-TSA followed by reduction using DIBAL-H and chlorination by Mitsunobu conditions[24] gave chloro-compound **60** in good yield. Propargylic alcohol **61** was obtained by treatment of **60** with *n*-BuLi in the presence of HMPA[25] in 82% yield. The free hydroxy group of **61** was protected with TBDPSCl to furnish compound **62**.



Scheme 15

In order to generate the *trans*-olefin to execute the second Sharpless asymmetric dihydroxylation, acetylene was coupled with *trans*-vinyliodide **63** using Sonogashira conditions with $Pd(PPh_3)_2Cl_2$ and CuI in triethylamine to furnish the 1,3-enyne product **64** in excellent yield. Enantioselective AD reaction of 1,3-enyne **64** under standard conditions gave the acetylene diol **65** in good yield with high diastereomeric excess (de = >96%) as judged by ^1H and ^{13}C NMR spectral analysis. Reduction of alkyne **65** to the *E*-alkene and concomitant removal of the PMB group proceeded smoothly under Birch conditions using Na/liq NH_3 to afford **66** in good yield. The diol **66** was protected as its isopropylidene derivative followed by oxidation of primary alcohol to the corresponding aldehyde and further oxidation afforded the acid **68**. Finally, acetonide and TBDPS groups were deprotected under acidic conditions (catalytic amount of HCl in MeOH) to furnish the target molecule (–)-**54**.



Scheme 16

Section D: Enantioselective total synthesis of α- and β-Dimorphecolic Acid

Unsaturated hydroxy fatty acids play important role in biological systems and were isolated from both animals and plants. β-Dimorphecolic acid (**69**) (It can also called as 9-HODE) is a unique hydroxydienoid fatty acid, which was first isolated from the seed oil of *Dimorphothecu auruntiaca*.[26] It was also isolated from *Osteospermum aurantiaca* Compositae A. DC[27] and *Osteospermum ccklonis* D. C. Compositae.[28] Owing to their lipid nature, long-chain fatty acids play a vital role in maintaining cellular properties[29] and consequently can elicit a variety of biological responses.

However, its diene congener α-dimorphecolic acid **70** was isolated from the plant *Glechoma hederacea* L. Labiatae[30] (commonly known as *'lierre terrestre',* 'ground ivy' or 'creeping Charlie), which has been demonstrated to be a calcium specific ionophore,[31] an inhibitor of acetylcholine esterase (ACE)[32] and aromatase,[33] and as well as being implicated in the pathogenesis of familial Mediterranean fever.[34]

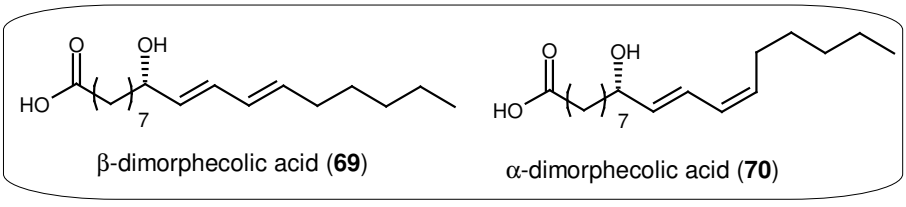
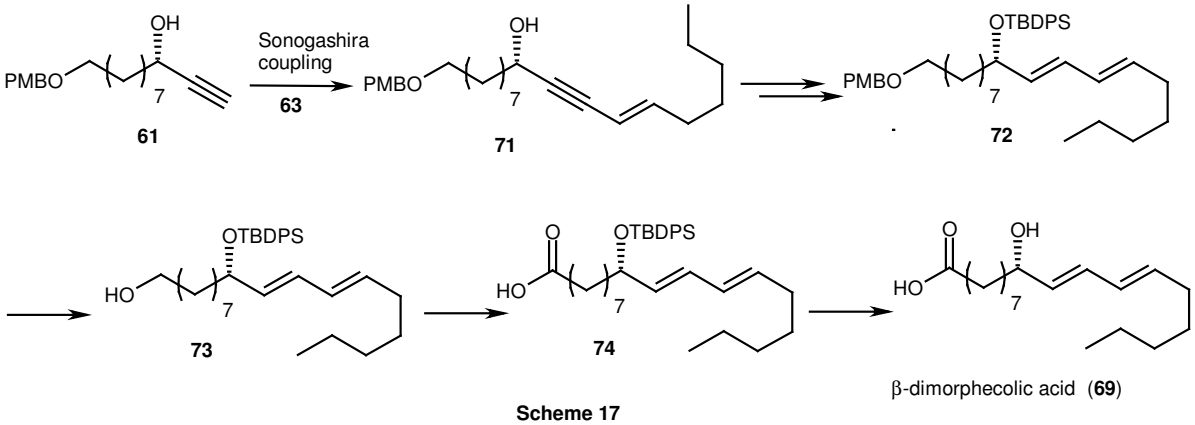


Figure 6

Synthesis of β-dimorphecolic acid

Propargylic alcohol was used as starting material to synthesize the α- and β-dimorphecolic acids. Sonogashira coupling of chiral propargylic alcohol **61** with *trans*-vinyliodide **63** using $Pd(PPh_3)_2Cl_2$ and CuI in triethylamine furnished the 1,3-enyne product **71** in excellent yield. Reduction of **71** proceeded smoothly with the required *E*-geometry of the alkyne under



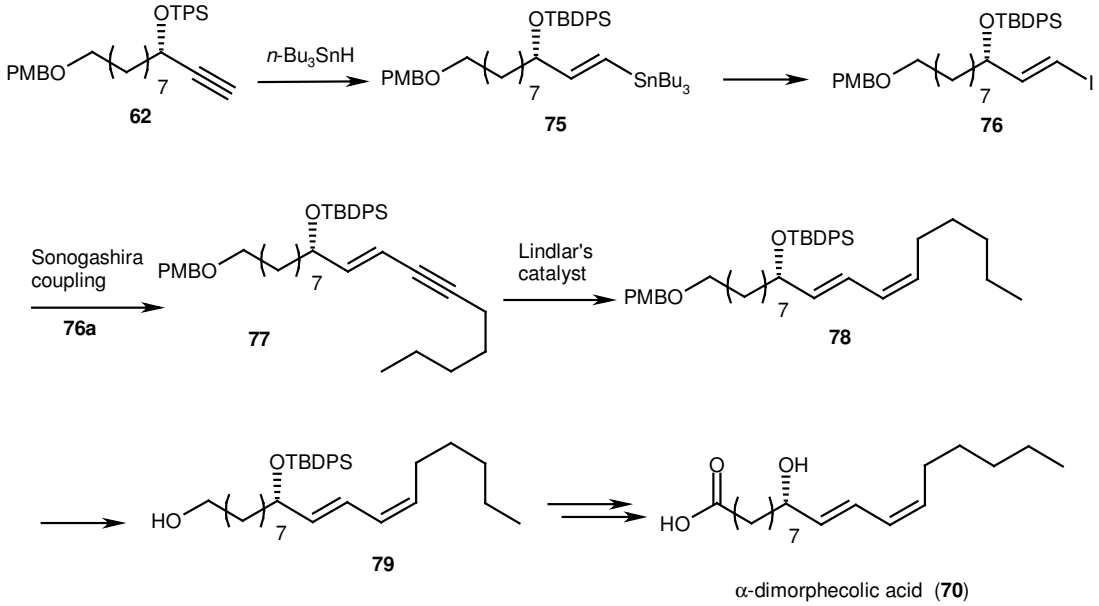
Scheme 17

reduction conditions using LAH in refluxing THF to afford **72** in good yield. The free hydroxy group of **72** was protected with TBDPSCl followed by deprotection of PMB group with DDQ to furnish compound **73** in good yield. Oxidation of primary alcohol in **73** to the corresponding aldehyde using Swern conditions and further oxidation using $NaClO_2$ in DMSO under buffer conditions afforded the acid **74**. Finally, TBDPS group was deprotected using TBAF to afford the target molecule **69** in 89% yield.

Synthesis of α-dimorphecolic acid

To achieve the synthesis of α-dimorphecolic acid, chiral propargylic alcohol **62** was converted into (*E*)-vinyl iodide through vinyl stannane. Thus, acetylene was readily converted into (*E*)-vinyl stannane **75** by reaction with tri-*n*-butyltin hydride and AIBN in refluxing benzene in 99% yield. Tributyltin was then replaced with iodide by using I_2 in CH_2Cl_2 to afford the corresponding iodo compound **76** in excellent yield. The Sonogashira coupling of **76** with commercially available 1-heptyne **76a** was successfully carried out using $Pd(PPh_3)_2Cl_2$ and CuI in triethylamine to furnish the 1,3-enyne product **77** in good yield. The partial

hydrogenation of the triple bond in **77** proved to be challenging. Irrespective of whether catalytic quantities or several molar equivalents of quinoline were present, the mixture of **78** and over hydrogenated product was formed. The use of 1-octene as a co-solvent along with EtOAc in the presence of pyridine (EtOAc/pyridine/1-octene = 10:1:1) furnished the diene **78** as a single product. The subsequent deprotection of the *p*-methoxybenzyl group with DDQ furnished the alcohol **79** in 94% yield.



Scheme 18

Oxidation of the resulting alcohol to the corresponding aldehyde using Swern conditions and further oxidation using sodium chlorite in DMSO under buffer conditions afforded the acid. Finally, TBDPS group was deprotected using TBAF to afford the target molecule **70** in good yield. The physical and spectroscopic data of **70** were identical with those reported.

CHAPTER 4:

A simple and efficient approach to 1,3-polyols: application to the synthesis of strictifolione, compactine lactone and (+)-negamycin and is divided into two sections.

Section A: Total synthesis of strictifolione and compactin lactone.

(+)-Strictifolione **80** (Fig. 7) has been isolated by Aimi *et al*. from the stem bark of *Cryptocaria strictifolia* in West Kalimantan, Indonesia.[35] Later, Takayama *et al.* were able to determine its absolute configuration by an 'exchiral-pool' synthesis.[36] The main structural features of (+)-strictifolione (**80**) are an *anti*-1,3-diol and a 6-substituted 5,6-dihydro-α-pyrone subunit, which are present in various natural products with important biological activities.

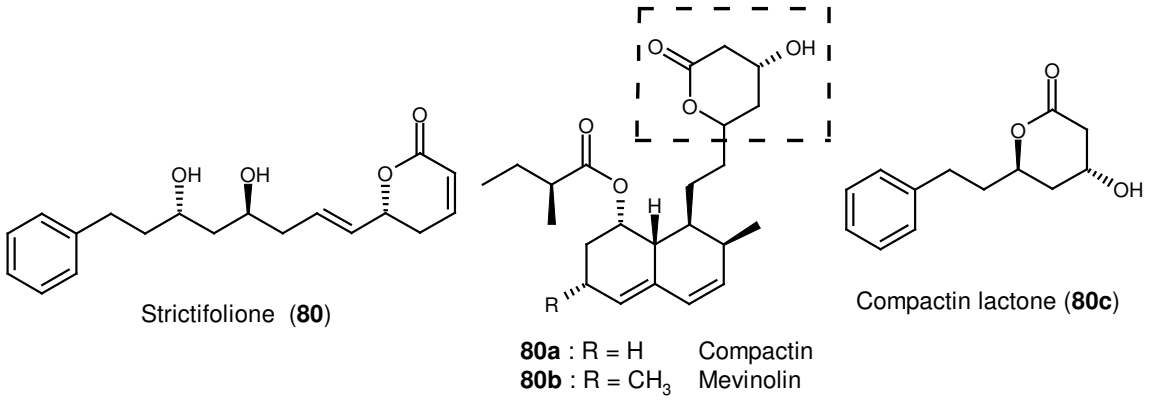
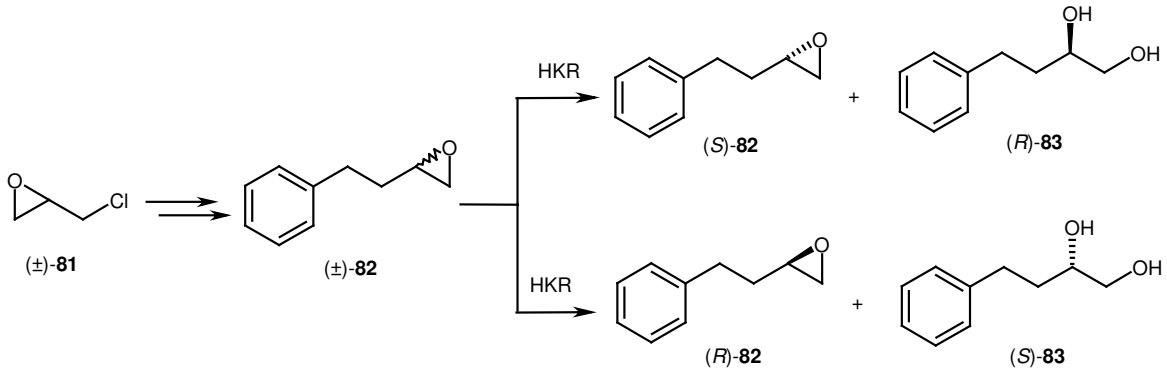


Figure 7

Synthesis of enantio pure epoxides (Scheme 19):

In designing a route to **80**, we chose epichlorohydrin as an appropriate starting material. Our synthesis of **80** requires iterative Jacobsen's hydrolytic kinetic resolution to install the stereogenic centers, cross-olefin metathesis to establish the *trans* geometry and ring-closing metathesis to construct the α,β-unsaturated δ-lactone.

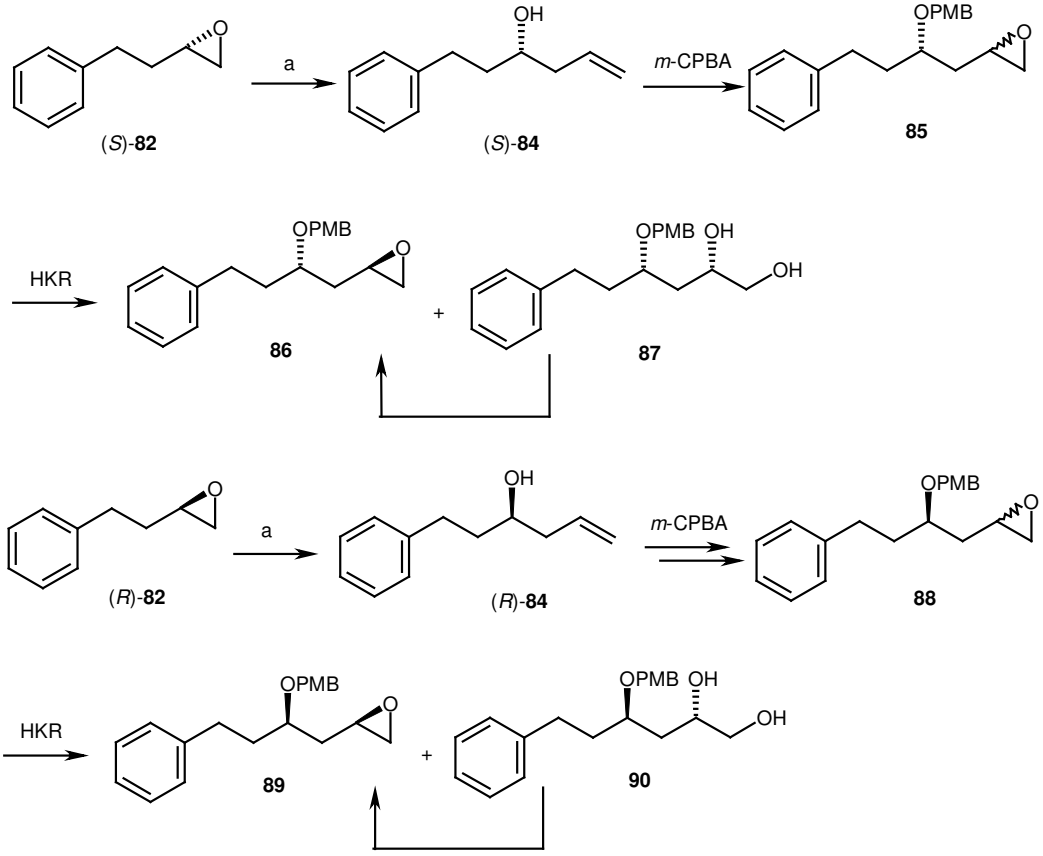
The chiral allyllic alcohols (*S*)-**84** and (*R*)-**84** were obtained from the epoxides (*S*)-**82** and (*R*)-**82** respectively by opening with vinyl Grignard. Thus, the stereogenic centre in (*S*)-**84** and (*R*)-**84** was derived from the epoxides (*S*)-**82** and (*R*)-**82**, which in turn were prepared by the hydrolytic kinetic resolution of the racemic epoxide (±)-**82**.



Scheme 19

Synthesis of diastereomerically pure epoxide (Scheme 20):

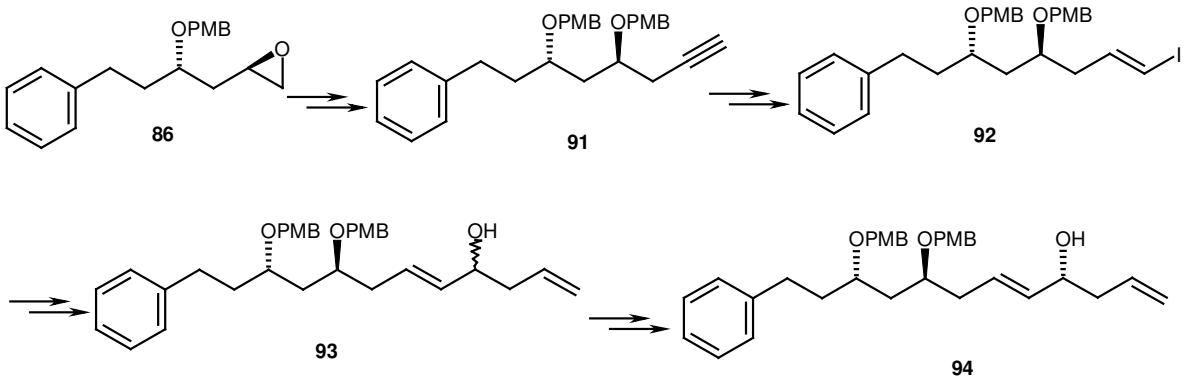
With substantial amount of homoallylic alcohol in hand we then further proceeded to explore the stereoselective outcome of epoxidation reaction with hydroxyl group protection. Towards this end, the hydroxyl group of homoallylic alcohol **(*S*)-84** was first protected as the PMB ether, followed by epoxidation with *m*-CPBA. The epoxide **85** thus obtained was found to be a mixture of two diastereomers (*anti : syn* = 2.2:1). The desired *anti* isomer of **85** was obtained as a major component.



Scheme 20

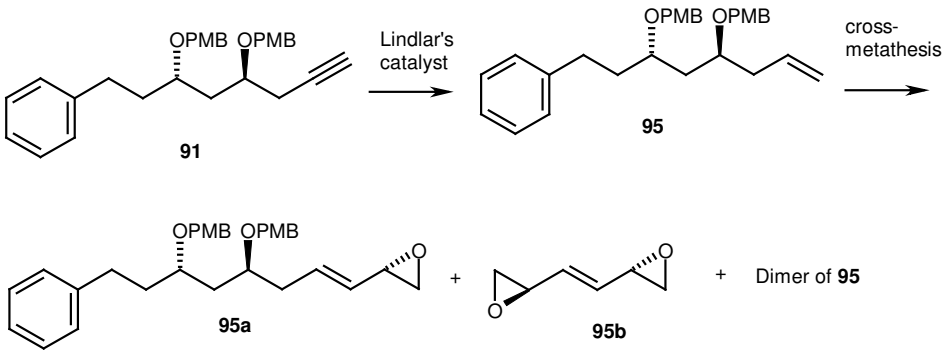
In order to improve the diastereoselectivity, we next attempted the Jacobsen's hydrolytic kinetic resolution (HKR). With epoxides **85** (*anti : syn* = 2.2:1) and **88** (*syn* : *anti* = 1.2:1) in hand, our next aim was to synthesize the diastereomerically pure epoxides through the Jacobsen's hydrolytic kinetic resolution method. Thus, epoxide **85** was treated with (*R*,*R*)-Salen-Co-OAc complex (0.5 mol%) and water (0.55 eq) in THF (0.55 eq) to afford the epoxide **86** as a single diastereoisomer in 46% yield and the diol **87** in 45% yield. In the same manner, epoxide **88** was resolved to the diastereopure epoxide **89** and diol **90** in good yields.

With substantial amount of **86** in hand, we required to generate the *trans*-olefin and carry out the subsequent reactions to complete the synthesis of (+)-strictifolione. We, then further proceeded for the synthesis of **1** by opening of the epoxide **86** with an excess of lithium acetylide followed by PMB protection to furnish compound **91**. Acetylene **91** was converted into (*E*)-vinyl stannane and further stannane was replaced with iodine to give iodo compound **92** in excellent yield. Vinyl iodide **92** was treated with *n*-BuLi in THF at –78 ^{o}C for 1 h and further treated with CuCN followed by addition of but-3-enal to form the coupling product **93** in 68% yield.[19] The oxidation of secondary hydroxy group using IBX followed by asymmetric reduction using chiral BINAL-H[37] in THF proceeded in a stereoselective fashion to give the allylic alcohol **94** in substantially high enantiomeric excess (91% ee, determined from the ^{1}H and ^{13}C NMR spectral analysis).



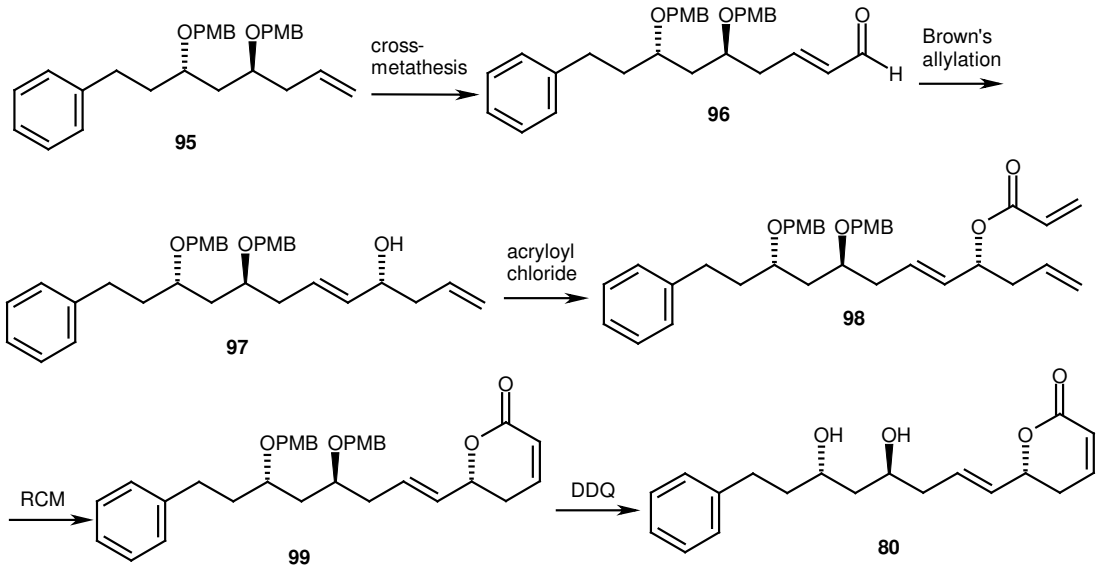
Scheme 21

Alternatively, it was thought worthwhile to convert the acetylene into the olefin and study the cross-olefin metathesis to construct *trans*-olefin with chiral epoxide. Thus, acetylene **91** was converted into homoallylic alcohol by partial hydrogenation using Lindlar's catalyst followed by cross-olefin metathesis with 3 equivalents of (*S*)-butadiene mono-epoxide using Grubbs' 2nd generation catalyst to furnish compound **95a** in only 16% yield as a 6:1 mixture of *E*/*Z* isomers along with homodimer of **95**, homodimer of (*S*)-butadiene mono-epoxide **95b** and unreacted **95**.



Scheme 22

In another attempt, to improve the selectivity and yield, we examined the cross-olefin metathesis of olefin **95** and by treatment with 3 equivalents of acrolein using 10 mol% Grubbs' 2nd generation catalyst to afford the α,β-unsaturated aldehyde **96** in good yield with an *E*/*Z* ratio of >30:1. Aldehyde **96** was transformed to the desired homoallylic alcohol **97** by using brown allyl boration. Alcohol **97** was esterified with acryloyl chloride in the presence of Et_3N and catalytic amount of DMAP to afford the acryloyl ester **98**. Subsequent ring closing metathesis of ester **98** with commercially available Grubbs' 1st generation catalyst afforded the lactone **99**. Finally, global deprotection of **99** produced (+)-strictifolione **80**.

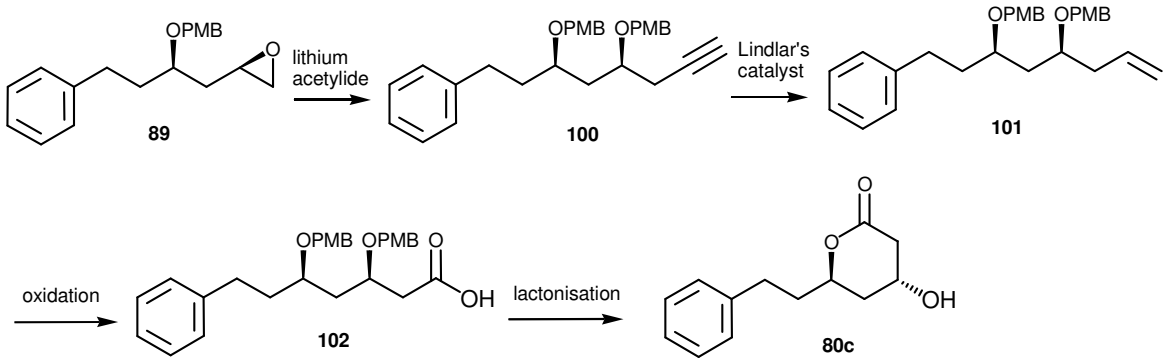


Scheme 23

Synthesis of the Lactone moiety of HMG-CoA Reductase Inhibitor: Compactin and Mevinolin.

In 1976, Endo *et al*.[38] at the Sankyo Co. and Brown *et. al.*[39] at Beecham Pharmaceuticals isolated a potent competitive inhibitor of hydroxymethylglutaryl coenzyme A reductase (HMGCoA reductase) from the metabolites of *Penicillium citrinum* and *Penicillium brevicompactum*, respectively. The new compound, shown to have structure **80a**, was named ML 236B by the Japanese group and 'compactin' by the British workers. In 1980, Alberts *et al*.[12] at Merck, Sharp and Dohme, reported the isolation of a relative of compactin from *Aspergillus terrus*.

To prepare the lactone moiety of compactin and mevinolin, we chose epoxide **89** as starting material. Thus, epoxide **89** was opened with lithium acetylide followed by PMB protection and partial hydrogenation using Lindlar's catalyst to give olefin **101** in good yield. Olefinic oxidation of **101** using $RuCl_3$ furnished the acid **102**, which was cyclised under acidic conditions (catalytic amount of HCl in MeOH) to give the lactone **80c** in good yield.



Scheme 24

<u>Section B</u>: A simple and efficient Approach to 1,3-aminoalcohol: Application to the synthesis of (+)-negamycin

(3*R*,5*R*)-3,6-Diamino-5-hydroxyhexanoic acid (**103**), is the core fragment of the pseudo-peptide antibiotics negamycin (**104**), (-)-5(*S*)-epi-negamycin **105** and sperabillin A and C (**106a** and **106c**, respectively (Figure 8). (+)-Negamycin **104** is an unusual antibiotic which contains a hydrazine peptide linkage, which was isolated[40] by Umezawa *et al*. in 1970 from the culture filtrate of three strains, related to *Streptomyces purpeofuscus*. It exhibits very low acute toxicity (LDm-400-500 mg/kg) and has considerable activity toward multiple drug resistant enteric Gram-positive and Gram-negative bacteria including *Pseudomonas*

aerginosa.[40] Negamycin also exhibits genetic miscoding activity[41] on bacterial ribosome systems and is a specific inhibitor of protein synthesis in *Escherichia coli* K12.[42]

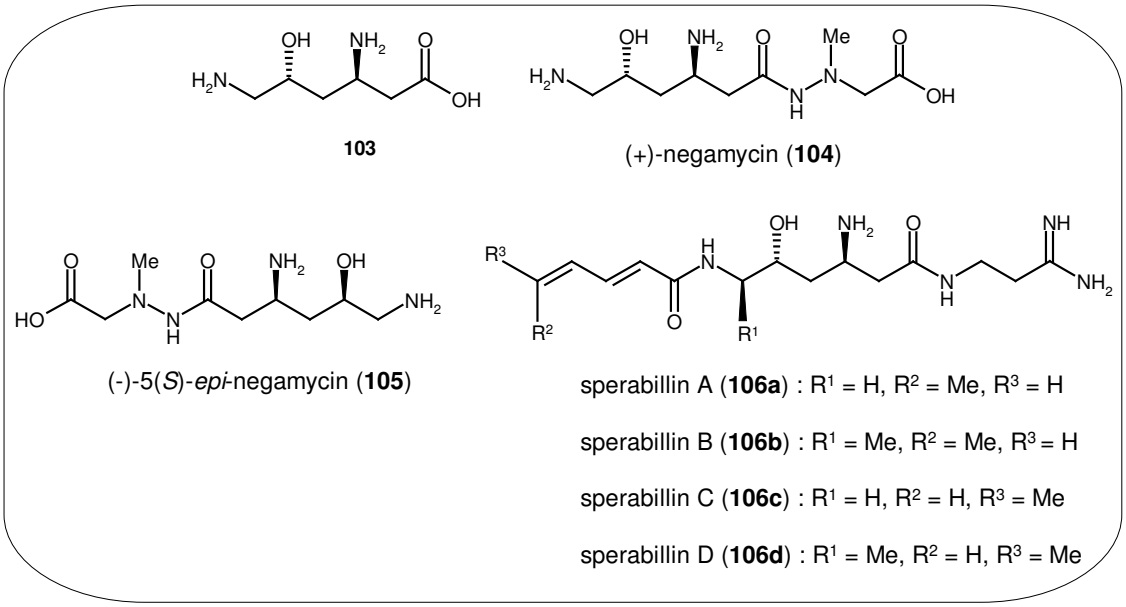
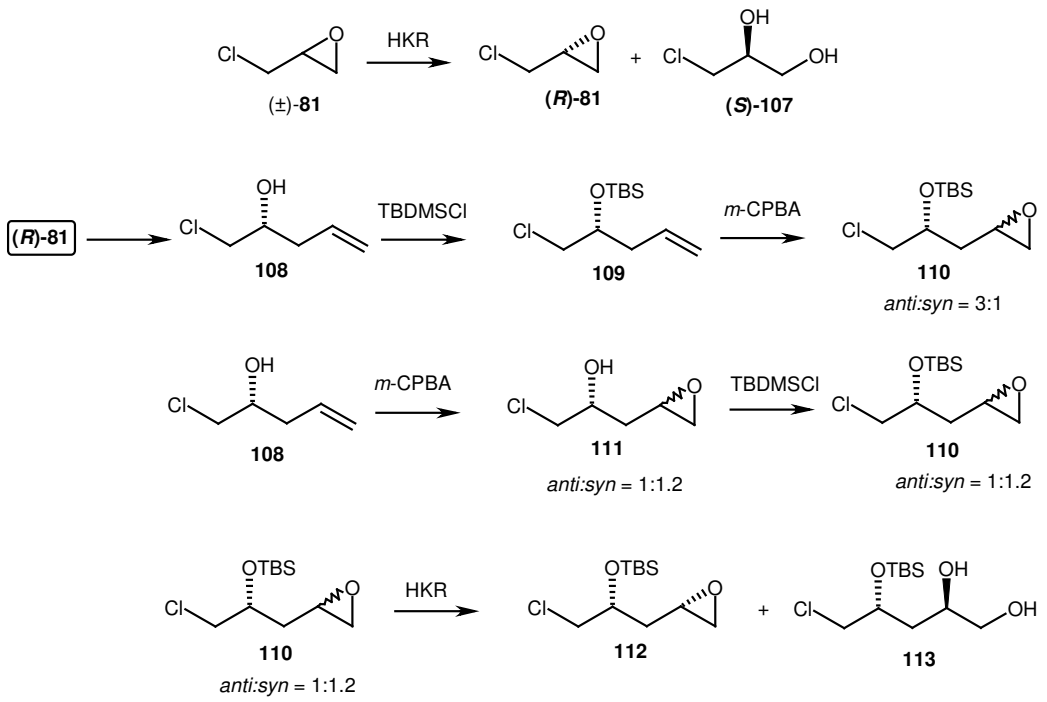


Figure 8

In designing a route to **104**, we chose racemic epichlorohydrin as an appropriate starting material. Thus, commercially available epichlorohydrin (±)-**81** was subjected to Jacobsen's HKR by using (*S*,*S*)-Salen-Co-OAc catalyst to give *R*-epichlorohydrin[13] (*R*)-**81** as a single isomer, which was easily isolated from the more polar diol (*S*)-**107** by distillation. *R*-epichlorohydrin (*R*)-**81** was treated with vinylmagnesium bromide in the presence of CuI to give the homoallylic alcohol **108** in excellent yield.

The free hydroxyl group of homoallylic alcohols was first protected as TBS ether, followed by epoxidation with *m*-CPBA. The epoxide **110**, thus obtained was found to be a mixture of two diastereomers (*anti:syn*/3:1).

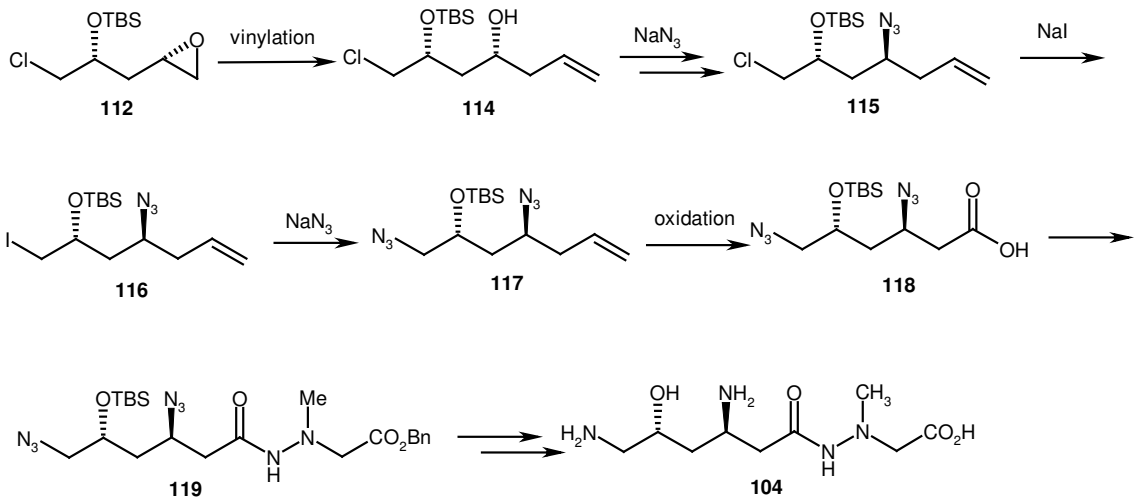
The desired *syn* isomer of **110** was obtained only as a minor component. However, when epoxidation was carried out on alcohol **108** followed by hydroxy protection as a TBDMS-ether, the epoxide **110** were formed in favor of the desired *syn* isomer (*syn*: *anti*/1.2:1).[14]



Scheme 25

In order to improve the diastereoselectivity, we next attempted the Jacobsen's hydrolytic kinetic resolution (HKR). The epoxide **110** was treated with (*S*,*S*)-salen-Co-OAc complex (0.5 mol%) and water (0.55 eq) in THF (0.55 eq) to afford the epoxide **112** as a single stereoisomer (determined from the ^{1}H and ^{13}C NMR spectral analysis) in 46% yield and the diol **113** in 47% yield.

Opening of epoxide **112** with vinylmagnesium bromide in the presence of CuI in THF at –20 ^{o}C gave the homoallylic alcohol **114** in good yield. Compound **114** was then converted into an *O*-mesylated derivative, which on treatment with sodium azide in DMF furnished the azide **115** with the desired stereochemistry at C-3. Treatment of **115** with large excess of NaI in 2-butanone gave iodo-azide **116** in quantitative yield, which was then treated with NaN_3 to give bis-azide **117** in good yield. Oxidation of olefinic bond in **117** using $RuCl_3/NaIO_4$ furnished the corresponding acid **118** in moderate yield.



Scheme 25

The hydrazide **119** was prepared in good yield from **118** by formation of its mixed anhydride[43] with ethyl chloroformate and subsequent reaction of the activated carbonyl with benzyl (1-methylhydrazino)acetate. In the final step, the azides were reduced to amino groups by catalytic hydrogenation over Pd/C in CH_3OH, acetic acid and H_2O, with concomitant removal of the benzyl and silyl protecting groups to produce the acetate salt of (+)-negamycin, which was further purified by ion-exchange chromatography (Amberlite CG-50, NH_4^+ form) to afford (+)-Negamycin **104** as white powder in 72% yield from **119**.

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Publications

1. Enantioselective Synthesis of D-*ribo*-(2*S*,3*S*,4*R*)-C18-phytosphingosine using Double Stereo differentiation. **S. Vasudeva Naidu** and Pradeep Kumar, *Tetrahedron Lett*. **2003**, *44*, 1035–1037.
2. A Practical Enantioselective Synthesis of Massoialactone via Hydrolytic Kinetic Resolution. Priti Gupta, **S. Vasudeva Naidu** and Pradeep Kumar, *Tetrahedron Lett*. **2004**, *45,* 849–851.
3. An Efficient total Synthesis of Sulfobacin A. Priti Gupta, **S. Vasudeva Naidu** and Pradeep Kumar, *Tetrahedron Lett.* **2004**, *45*, 9641–9643.
4. Stereoselective Synthesis of (+)-boronolide, **S. Vasudeva Naidu**, Priti Gupta and Pradeep Kumar, *Tetrahedron Lett.* **2005**, *46*, 2129–2131.
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6. Total Synthesis of Microcarpalide. Pradeep Kumar and **S. Vasudeva Naidu**.
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7. Enantio- and Diastereocontrolled Total Synthesis of (+)-Boronolide. Pradeep Kumar and **S. Vasudeva Naidu**. *J. Org. Chem*, **2006**, *71*, 3935-3941.
   (This is one of the most accessed articles during April-June 2006, http://pubs.acs.org/journals/joceah/promo/most_accessed/index.html)
   (This is also one of the most accessed articles during 2006 Full year, http://pubs.acs.org/journals/joceah/promo/most_accessed/index.html)
8. A Simple and Efficient Approach to 1,3-Polyols: Application to the Synthesis of Cryptocarya diacetate. Pradeep Kumar, Priti Gupta and **S. Vasudeva Naidu**. *Chemistry-A European Journal*, **2005**, *12*, 1397-1402.
9. Enantioselective Synthesis of Tarchonanthuslactone via Iterative Hydrolytic Kinetic Resolution. Priti Gupta, **S. Vasudeva Naidu** and Pradeep Kumar. *Tetrahedron Lett*. **2005**, *46*, 6571–6573

10. Enantioselective synthesis of (–)-pinellic acid. **S. Vasudeva Naidu** and Pradeep Kumar. *Tetrahedron Lett.* **2007**, *48*, 2279-2282.
11. A simple and efficient approach to 1,3-aminoalcohols: Application to the synthesis of (+)-negamycin. **S. Vasudeva Naidu** and Pradeep Kumar. *Tetrahedron Lett*. **2007**, *48,* 3793.
12. Enantioselective syntheses of (−)-pinellic acid, α- and β-dimorphecolic acid. **S. Vasudeva Naidu**, Priti Gupta and Pradeep Kumar. *Tetrahedron* **2007**, *63*, 7624-7633.
13. An efficient total Syntheses of (+)-Strictifolione and Compactin. **S. Vasudeva Naidu** and Pradeep Kumar. (*J. Org. Chem*., *Manuscript under preparation*)

REVIEWS:

1. Application of hydrolytic kinetic resolution (HKR) in the synthesis of bioactive compounds.

   Pradeep Kumar, **S. Vasudeva Naidu** and Priti Gupta

   (*Tetrahedron* Report, *Tetrahedron* **2007**, *63*, 2745–2785.

Symposia/ Conferences Attended

1. Stereoselective total synthesis of phytosphingosine and its analogues from D-mannitol. Presented at NSC-4 in NCL, Pune, India in Feb 2002.
2. A novel one-pot synthesis of coumarin employing triphenyl(α-carboxymethylene)phosphorane imidazolide as C-2 synthon. Presented at NSC-5 in CLRI Chennai, India in Feb 2003.
3. An asymmetric synthesis of Tarchonanthuslactone and Kurzilactone by Jacobsen's hydrolytic kinetic resolution. Presented at NSC-5 in CLRI Chennai, India in Feb 2003.
4. Enantioselective total synthesis of Microcarpalide. Presented at NSC-6 in IIT Kanpur, India in Feb 2004.
5. An enantioselective total synthesis of sulfobacin A. Presented at NSC-6 in IIT Kanpur, India in Feb 2004.
6. A Simple and Efficient Approach to 1,3-Polyols: Application to the Syntheses of Tarchonanthuslactone, Cryptocarya diacetate and (+)-Strictifolione. Presented at ACS-CSIR in NCL, Pune, India in January 2006.

Awards

1. The "**Keerti Sangoram Endowment Award**" for Best Research Scholar of the Year **2005** (*Chemical Sciences*), NCL Research Foundation. **S. Vasudeva Naidu**

CHAPTER -I

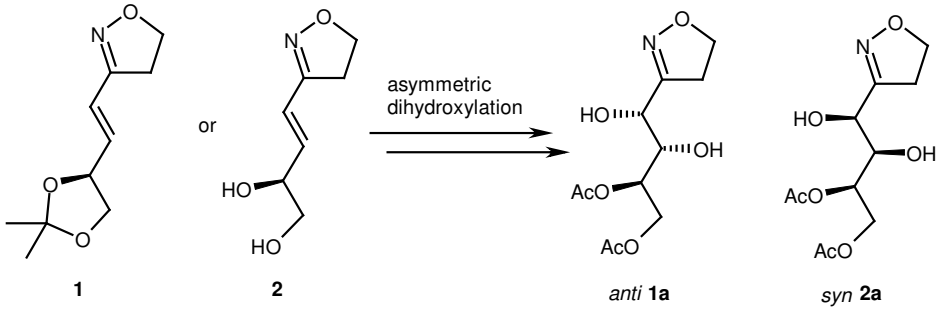
Double Diastereodifferentiation in Asymmetric Dihydroxylation: Application to the Diastereoselective Synthesis of D-ribo-(2S,3S,4R)-C18-Phytosphingosine

1.1. INTRODUCTION

1.1.1. Double Diastereodifferentiation in Asymmetric Dihydroxylation

Asymmetric dihydroxylation of pro-chiral olefins gives high levels of enantioselectivities with the recent developments in reaction conditions and ligands. But, what about asymmetric dihydroxylation of chiral olefins? For a given case, a determination of the intrinsic diastereofacial selectivity of a chiral substrate is helpful in order to estimate the likelihood of success, especially in the "mismatched" pairing.[1] This is most easily accomplished by carrying out the osmylation in the absence of chiral ligand. A few examples of matched and mismatched double diastereoselection in the asymmetric dihydroxylation of chiral olefins have been reported and are summarized in the following paragraphs.

In his studies on the stereoselective synthesis of amino sugars, Wade[2] investigated asymmetric dihydroxylation of 4,5-dihydroisoxazoles **1** and **2**, shown in Table 1. The reactions employing the phthalazine class of ligands displayed useful levels of matched and mismatched diastereoselectivity (entries 6-9). Thus, in the mismatched reaction (entries 7 and 9), the reagent was able to strongly override the intrinsic diastereofacial bias of the olefin substrate.



Scheme 1

Morikawa and Sharpless[3] carried out a similar set of experiments on carbohydrate-derived olefin **3** shown in Table 2. These experiments were performed to assess the relative ability of

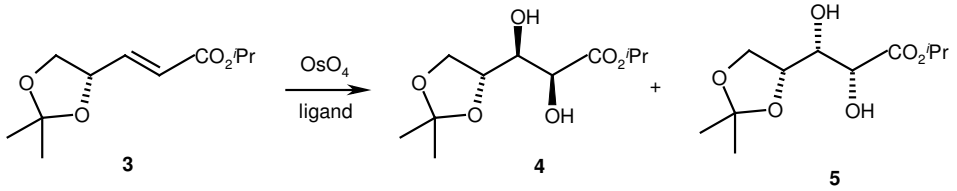
several different ligands in the context of matching and mismatching in the asymmetric dihydroxylation reaction.

Table 1.

Entry	Substrate	Ligand	Condition	Anti/Syn	Yield (%)
1	**1**	None	Cat. achiral[a]	77:23	85
2	**2**	None	Cat. achiral[a]	76:24	83
3	**1**	DHQD-MEQ	Cat. achiral[a,b]	89:11	52
4	**1**	DHQD-MEQ	Stoich. chiral[c]	78:22	48
5	**2**	DHQ-MEQ	Cat. achiral[d]	52:48	66
6	**1**	$(DHQD)_2PHAL$	Cat. achiral[d]	96:4	53
7	**1**	$(DHQ)_2PHAL$	Cat. achiral[d,c]	11:89	62
8	**2**	$(DHQD)_2PHAL$	Cat. achiral[d]	98:2	82
9	**2**	$(DHQ)_2PHAL$	Cat. achiral[d]	5:95	85

[a]0.1 eq. of OsO_4, 3 eq. NMO, THF/H_2O, 9:1, 20 °C. [b]0.4 eq. of chiral aux, [c]3 eq. of chiral aux, 1 eq. OsO_4, $PhCH_3$, 20 °C. [d]0.08 eq. of $K_2OsO_4.2H_2O$, 3 eq. $K_3Fe(CN)_6$, 3 eq. of K_2CO_3, 0.4 eq. of chiral aux, 1 eq. $MeSO_2NH_2$, *t*-BuOH/H_2O, 1:1, 20°C. [e]Use of AD-mix-α under recommended conditions gave only 20% reaction after 22 h.

For this substrate, it was found that the phthalazine ligand $(DHQD)_2PHAL$ was the ligand of choice for the matched reaction (entry 4). Whereas, inspite of their poor performance in the matched reactions, the pyrimidine derivatives $(DHQ)_2PYR$ and $(DHQ)_2PYR(OMe)_3$ gave the best results in the mismatched examples (entries 7 and 9).



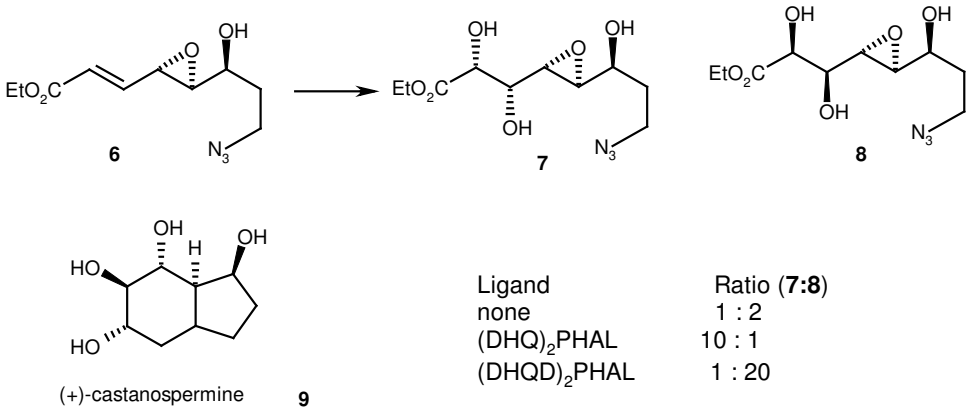
Scheme 2

Table 2.

Entry	Ligand (mol%)	Ratio (**4**:**5**)	Yield (%)
1	Quinuclidine (10)	2.6:1	85%
2	DHQD-CLB (10)	10:1	87%
3	DHQ-CLB (10)	1:10	85%
4	$(DHQD)_2$-PHAL (1)	39:1	84%
5	$(DHQ)_2$-PHAL (1)	1:1.3	52%
6	$(DHQ)_2$-PYR (5)	6.9:1	90%
7	$(DHQD)_2$-PYR (5)	1:4.1	86%

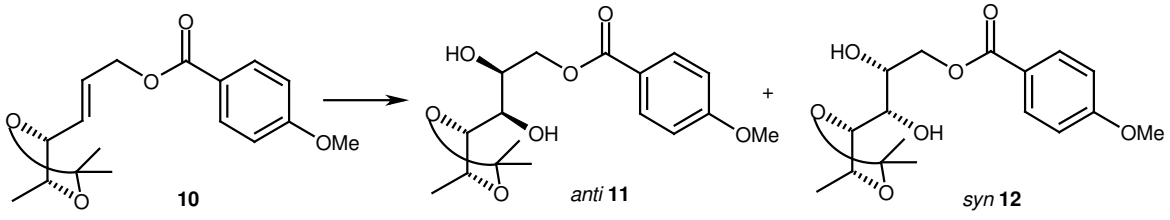
8	$(DHQD)_2$-PYR$(OMe)_3$ (5)	12:1	89%
9	$(DHQ)_2$-PYR$(OMe)_3$ (5)	1:7	90%

A mismatched double diastereoselective asymmetric dihydroxylation played a key role in the synthesis of polyhydroxylated indolizidine alkaloid castanospermine[4] (Scheme 3). In the asymmetric dihydroxylation of epoxy ester **6**, Cha[4] observed 10:1 preference for the *syn* diastereomer **7** in reactions employing the $(DHQ)_2$-PHAL ligand. A complete reversal of selectivity was observed in the matched case, as the *anti* product **8** was the major product with >20:1 diastereoselectivity. The major product **7** from the mismatched reaction was subsequently converted into (+)-castanospermine.



Scheme 3

Several more examples of double diastereoselection in asymmetric dihydroxylation are reported in the literature. Among them are the synthesis of brassinosteroid analogs,[5] synthesis of immunosuppressant FK-506,[6] preparation of intermediates in the synthesis of mycalamide B,[7] insect juvenile hormone bisepoxide,[8] and the preparation of modified pyrimidine nucleobases.[9] Corey *et al.*[10] have carried out the stereocontrolled total syntheses of several *vic*-polyols through double diastereoselective asymmetric dihydroxylation. Olefin **10** with the $(DHQ)_2$PHAL ligand in the matched case gave excellent diastereoselectivity in favor of *anti* product **11**, while use of $(DHQD)_2$PYDZ ligand also resulted (mismatched case) in good diastereoselection in favor of *syn* product **12** (Table 3).

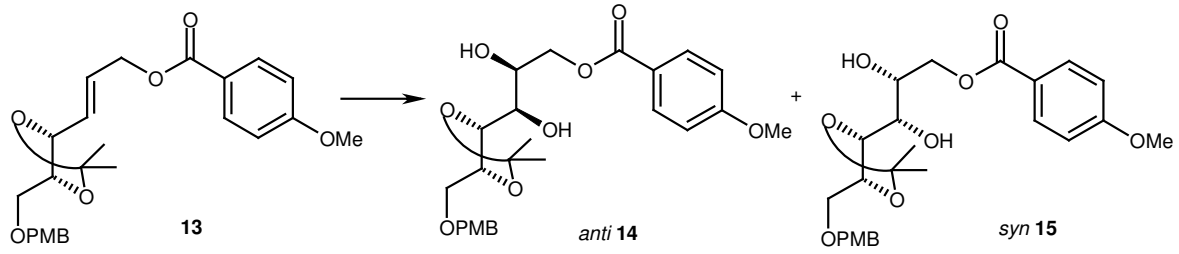


Scheme 4

Table 3.

Dihydroxylation conditions	Isolated Yield	Ratio of *anti*:*syn*
OsO_4, NMO, Acetone-H_2O (10:1)	88% of *anti* and *syn*	1.9:1
$(DHQ)_2$-PHAL (matched case)	86% of *anti*	54:1
$(DHQD)_2$PYDZ (mismatched case)	86% of *syn*	1:35

Similarly, the asymmetric dihydroxylation of olefin **13** in the matched case with $(DHQ)_2$PHAL ligand gave excellent diastereoselectivity in favor of *anti* product **14**, while the mismatched case with $(DHQD)_2$PHAL ligand favored the *syn* product **15** (Table 4).



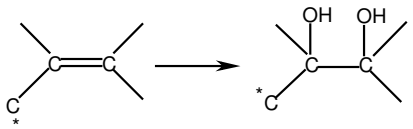
Scheme 5

Table 4.

Dihydroxylation conditions	Isolated Yield	Ratio of *anti*:*syn*
OsO_4, NMO, Acetone-H_2O (10:1)	96% of *anti* and *syn*	2.5:1
$(DHQ)_2$-PHAL (matched case)	93% of *anti*	200:1
$(DHQD)_2$PYDZ (mismatched case)	90% of *syn*	1:90

1.1.2. On stereoselectivity of osmium tetroxide oxidation of allylic alcohol system: Empirical rule- *by Kishi*

Kishi group[11] has examined the stereochemical outcome of the osmium tetroxide oxidation of allylic alcohols, generalized as in scheme 7.[12] Olefins **16-43** were subjected to osmium tetroxide oxidation under stoichiometric and catalytic conditions. Judging from their previous experiments based on the conformational analysis of the sp^3-sp^2 single bond systems, they expected this process might be stereoselective.[13]



Scheme 6

Comments over stereoselective outcome of osmium tetroxide oxidation of allylic alcohol systems:

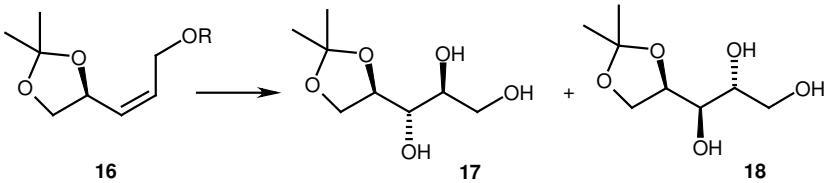
- Stoichiometric procedure provided slightly higher stereoselectivity than the catalytic procedure.

- Protecting groups of the hydroxyl at the chiral center, except acyl groups, were found to have only a limited effect in determining the stereochemical course of the oxidation. For the cases of acyl derivatives, however, the stereoselectivity diminished noticeably or completely.

- The hydroxyl or alkoxyl oxygen seems to play the importance in obtaining a high degree of stereoselectivity.

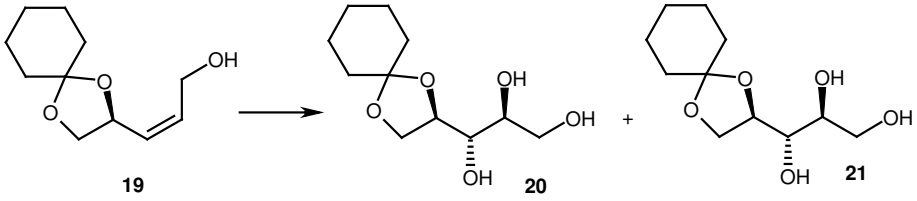
- The degree of stereoselectivity observed for the *cis*-olefins is higher than that for corresponding *trans*-olefins, which may be attributed to the different degrees of preference of one eclipsed conformation over the others.[4]

- The relative stereochemistry between the pre-existing hydroxyl or alkoxyl group and the adjacent newly introduced hydroxyl group of the major product in all cases is *erythro*.



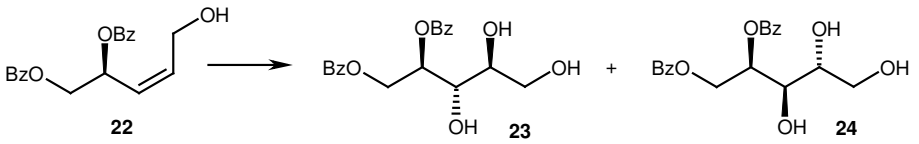
16 **17** **18**

16a : R = H	stoichiometric	6.3 : 1.0
	catalytic	6.0 : 1.0
16b : R = COC(Me)3	stoichiometric	6.3 : 1.0
	catalytic	6.0 : 1.0
16c : R = TBDPS	stoichiometric	8.3 : 1.0
	catalytic	7.2 : 1.0



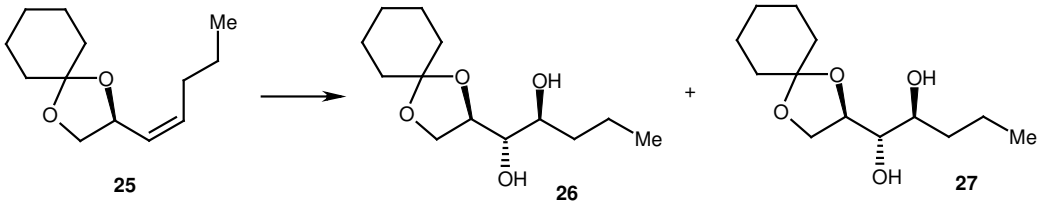
19 **20** **21**

stoichiometric	6.2 : 1.0
catalytic	6.0 : 1.0



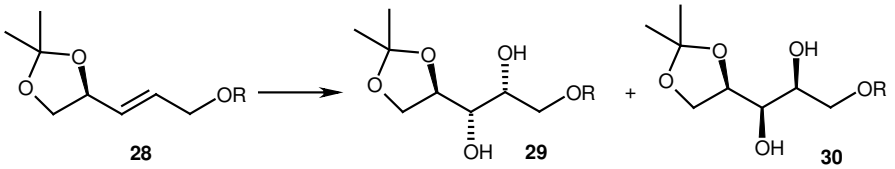
22 **23** **24**

stoichiometric	8.0 : 1.0
catalytic	7.0 : 1.0

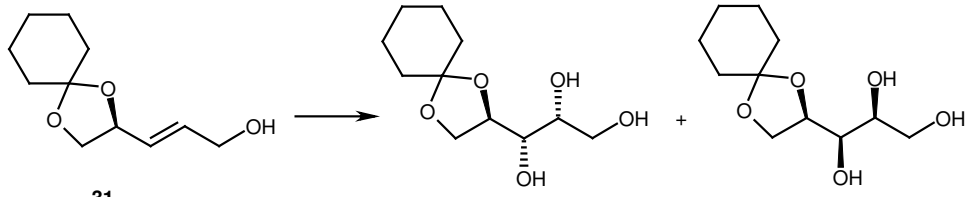


25 **26** **27**

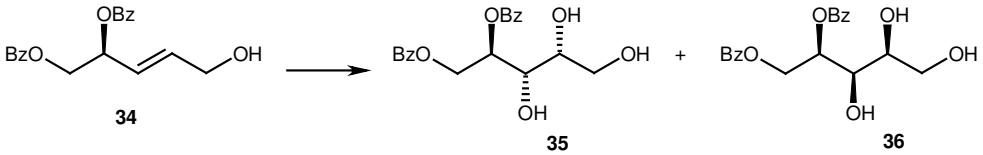
stoichiometric	11.0 : 1.0
catalytic	8.1 : 1.0



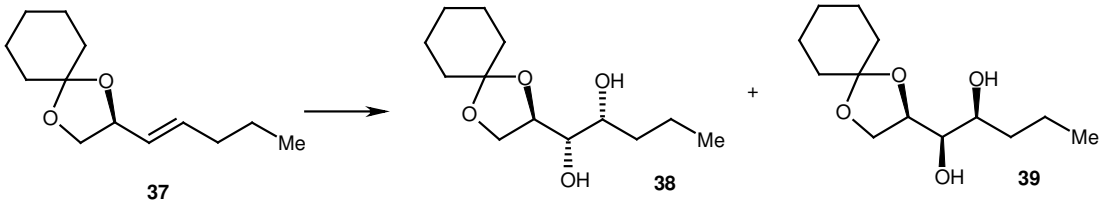
28a : R = H	stoichiometric	3.3 : 1.0
	catalytic	3.0 : 1.0
28b : R = $COC(Me)_3$	stoichiometric	4.2 : 1.0
	catalytic	4.0 : 1.0
28c : R = TBDPS	stoichiometric	3.3 : 1.0
	catalytic	3.1 : 1.0



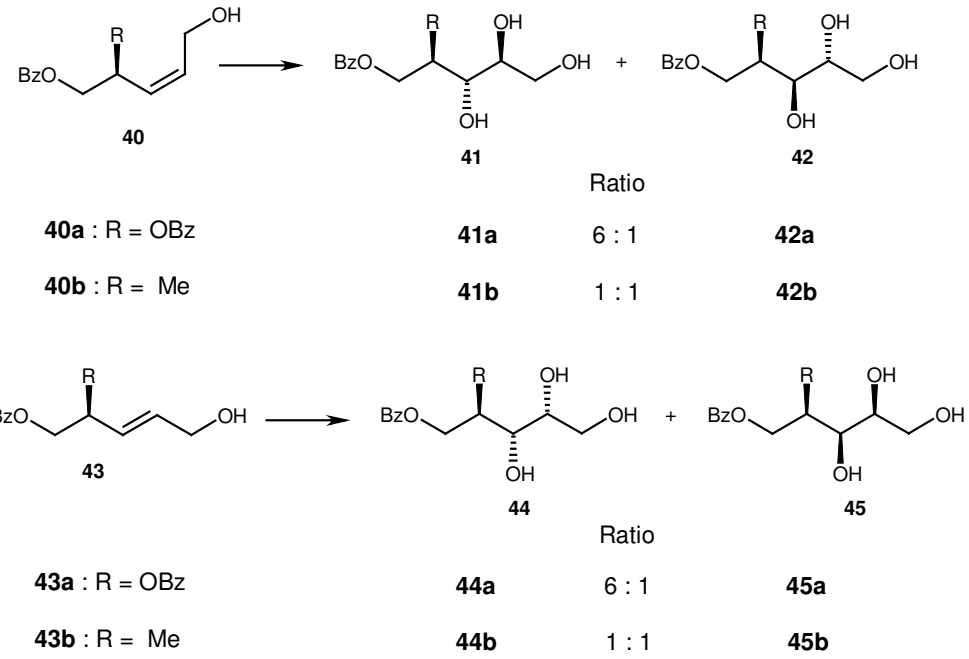
stoichiometric	4.6 : 1.0
catalytic	3.1 : 1.0



stoichiometric	4.3 : 1.0
catalytic	3.7 : 1.0



stoichiometric	4.3 : 1.0
catalytic	3.7 : 1.0



Scheme 7

1.1.3. Phytosphingosines

Sphingolipids are structurally diverse constituents of membranes in mammals, plants, fungi, yeast, and in some prokaryotic organisms and viruses.[14] More than 300 different types of complex sphingolipids have been isolated, and new examples from a variety of sources continue to be isolated and characterized.[15] The prevalent backbone (sphingoid base: see Figure 1) in sphingolipids is sphingosine, (2*S*, 3*R*, 4*E*)-2-amino-1,3-dihydroxy-4-octadecene, although there are numerous variations in chain length, degree of unsaturation, branching and in the number and position of hydroxyl groups. The majority of these sphingoid bases are *N*-acylated with long-chain fatty acids to provide a group of compounds called ceramides. These fatty acids also vary in chain length, unsaturation and number and position of the hydroxyl groups. Most sphingolipids contain a polar head group, such as a phosphate (phosphosphingolipid) or sugar residue (glycosphingolipid), at position 1 of the sphingoid base. Although the sphingolipids were first described in the late 1800's, interest in them has intensified in recent years with the realization that they modulate cell behavior via cell-surface receptors and intracellular signal transduction. For example, glycosphingolipids mediate, among other things, cell-cell interactions and immune responses.

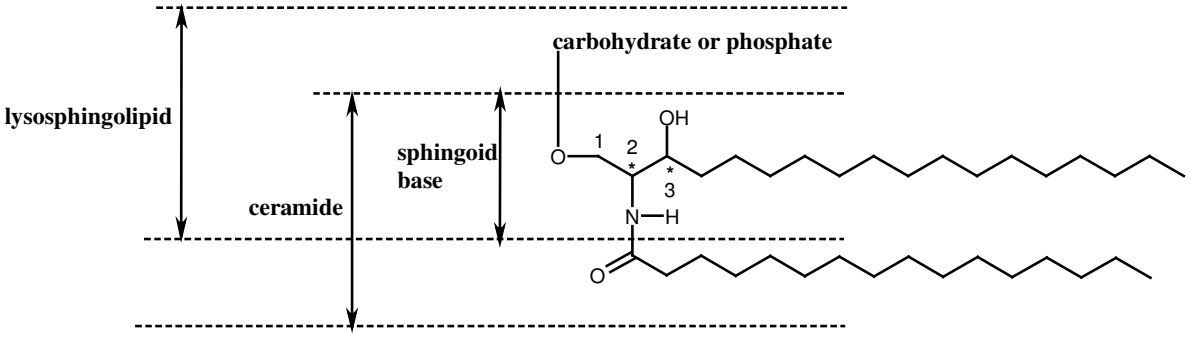


Figure 1

Phytosphingosines constitute a group of related long chain aliphatic 2-amino-1,3,4-triols of which D-*ribo*-C18-phytosphingosine ((2*S*, 3*S*, 4*R*)-2-aminooctadecane-1,3,4-triol) is the most predominant. D-*ribo*-Phytosphingosine was first isolated from the mushroom *Amanita muscaria* in 1911 by Zellner as a nitrogen-containing substance "fungus cerebrin."[16] Due to its plant origin and its structural similarity to sphingosine, the name "phytosphingosine" was coined for this base.[17] However, it is now evident that plants are not the only preserve for phytosphingosines; they are widely distributed as a structural component of sphingolipids in yeast, fungi, mammalian tissues and marine organisms.[18] The long-chain base of the majority of the phytosphingolipids has 18-carbons; minor amounts of other chain lengths, especially C20, are also found, depending on the origin.

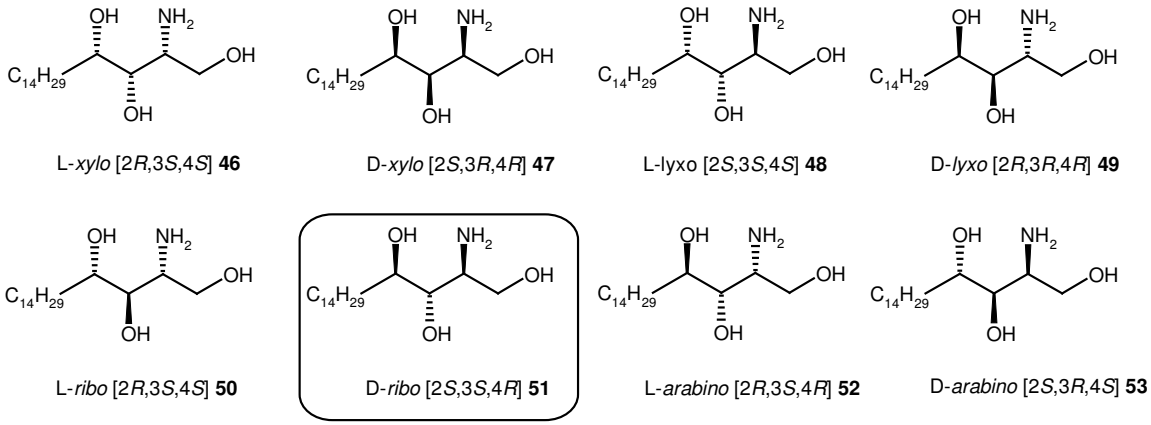


Figure 2. General structure of phytosphingosines

1.1.4. BIOLOGICAL IMPORTANCE OF PHYTOSPHINGOSINES

In addition to its structural function as the long-chain base of sphingolipids in membranes, D-*ribo*-phytosphingosine itself is a bioactive lipid. It has been reported to be a potential heat stress signal in yeast cells.[19] This finding has led to the investigation of the possible role of phytosphingosines in heat-induced cell cycle arrest and subsequent recovery.[20] Thus, a sphingolipid deficient yeast strain was found to lack the cell cycle arrest seen in the isogenic wild type. Moreover, strains lacking sphingoid base kinases were found to display cell cycle arrest. Temporary arrest was also seen upon treatment with exogenous *ribo*-phytosphingosine. *ribo*-Phytosphingosine has been shown to inhibit raynodine binding to both skeletal and cardiac sarcoplasmic reticulum membranes and to modulate the activity of the Ca+2 release channel.[21] Strong inhibition of calf thymus DNA primase by *ribo*-phytosphingosine has also been demonstrated, and it also inhibited the growth of human leukemic cell line HL-60, showing strong cytotoxicity.[22]

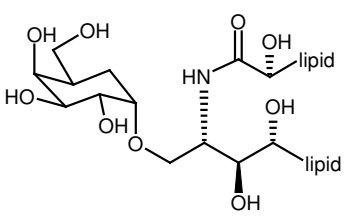
It is the derivatives of the phytosphingosines, exhibiting a wide range of biological activities, which are particularly fascinating. Natural products isolated from a variety of species have proven to be particularly fertile sources of phytosphingosine containing glycosphingolipids (GSL's). Thus, GSL's isolated from the sea cucumbers, *Holothuria leucospilota* and *Stichopus japonicus*, showed neuritogenic activity toward the rat heochromocytoma cell line, PC-12, in the presence of nerve growth factor.[23] A mixture of phytosphingosine-containing 1-*O*-β-D-glucopyranosideceramides isolated from *Phytolaccae radix* (poke-weed) inhibited the cyclooxygenase-2-dependent phase of prostaglandin D2 generation in bone marrow-derived mast cells in a concentration dependent manner.[24]

A number of a-galactosyl ceramides isolated from the *Agelus* genus of sponge have been shown to have immunostimulatory properties. Agelasphin-9b, a potent, immunostimulatory compound, has been utilized as a lead in structure activity studies by Kirin Brewery Company (Japan) to determine a novel, potent, cytotoxic agent. Their investigations identified KRN7000, currently in clinical trials as a chemotherapeutic agent for treating liver tumors. Although the identification of a potential new cancer chemotherapeutic agent was significant, the discovery of the novel mode of action of this compound has even greater implications.

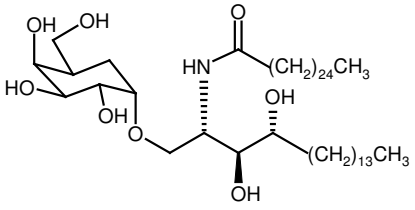
Recent studies have identified the CD1 family of proteins as novel, antigen-presenting molecules encoded by genes located outside of the major histocompatibility complex (MHC) families.[25] The human CD1 family contains five members, which are divided into two groups,

based on amino-acid sequence homologies.[26] Group I proteins are designated CD1a-c, and Group 2 is comprised of CD1d, which has significant homology with mouse CD. CD1e has been shown to be transcribed, but no protein product has yet been identified. Significantly, identification of naturally occurring antigens presented by CD1 has revealed that, unlike the proteins presented by the MHC's, CD1 predominantly presents lipids and glycolipids.[27]

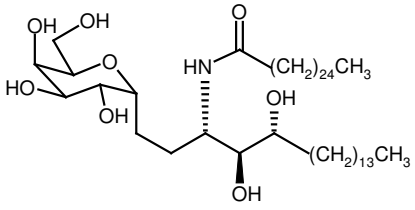
Structural and biological studies suggest that CD1 proteins bind the hydrophobic alkyl portions of the lipid antigens and position their polar head groups to interact with T cell antigen receptors.[28] Recently, several groups have independently demonstrated that one class of CD1 proteins, CD1d, are antigen presenting molecules for the T cell receptors (TCR's) of natural killer T (NKT) cells.[29] Most of the CD1d studies have utilized the a-galactosylceramide, KRN7000. The Kirin group demonstrated that KRN7000 selectively activated Va14 NKT cells which appeared to kill target tumor cells by an NK-like mechanism.[30] In addition, monoclonal antibodies against CD1d suppressed the immunostimulatory properties of KRN7000 (**B**), implicating CD1d as the antigen presenting protein.



agelasphins (**A**)



KRN7000 (**B**)



C-glycoside analogue (**C**)

It has been shown that, upon intravenous injection of KRN7000 (**B**), the immediate activation of NKT cells results in a cascade of cellular activation events that include the release of cytokines, the activation of NK cells and dendritic cells and ultimate stimulation of B and CD8 cells.[31] The myriad of events induced by KRN7000 suggests that the role of the CD1d family is quite complex. More recent reports have shown that NKT cell activiation by

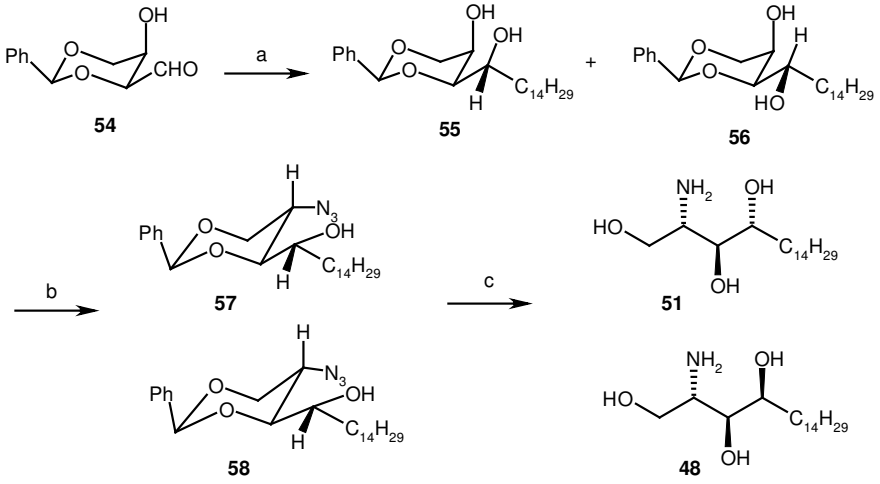
KRN7000 inhibits hepatitis B virus (HBV) replication *in vivo*.[32] The abolishment of HBV replication by a direct injection of KRN7000 into transgenic mouse liver appeared to be mediated by the NK cell-released cytokines IFN-a/b and IFN-g. These results suggest that the viral inhibition triggered by KRN7000 occurs by direct activation of NKT cells and secondary activation of NK cells which secrete antiviral cytokines in the liver. Another recent study supports the importance of NK cell cytokines.[33] When sporozite-inoculated mice were administered KRN7000, a rapid, stage dependent antimalarial response, mediated by IFN-g, was observed. Moreover, suboptimal immunizing dosing of *P. yoelii* sporozoites concomitant with administration of KRN7000 induced complete protection against malaria in the mice, suggesting a possible adjuvant effect of the galactosyl ceramide. Indeed, there is growing support for the concept that glycolipids, such as KRN7000, may demonstrate their greatest promise as adjuvants. Adjuvants are substances that, when mixed with an antigen and co-injected, enhance the immunogenecity of that antigen.

1.2. Review of Literature

Due to the variety of their biological activity and their scarcity in nature, it is little wonder that phytosphingosines have become important synthetic targets. To provide homogenous material for use in biophysical, biochemical and pharmacological studies, a variety of synthetic methods has been developed. The vast majority of reported preparations of phytosphingosine are asymmetric.[34] In general these approaches can be placed into three main categories. The first two rely on the chiral pool of amino acids and carbohydrates as the source of asymmetry. The third category of syntheses is based on asymmetric reactions. Various methods for the synthesis of phytosphingosines either racemic[35] or enantiomerically enriched[36] have been described in literature. Reported syntheses of phytosphingosines have burgeoned in recent years because of increasing recognition of their biological relevance. A few interesting syntheses of phytosphingosine are described below.

Schmidt *et al*.[36j] (1988)

Schmidt *et al*. employed 2,4-*O*-benzylidene-D-threose **54**, derived in two steps from D-galactose, in their syntheses of *ribo*- and *lyxo*-phytosphingosines (Scheme 8). Grignard reaction of **54** provided **55** and **56** as a separable 1:1 mixture of diastereomers.

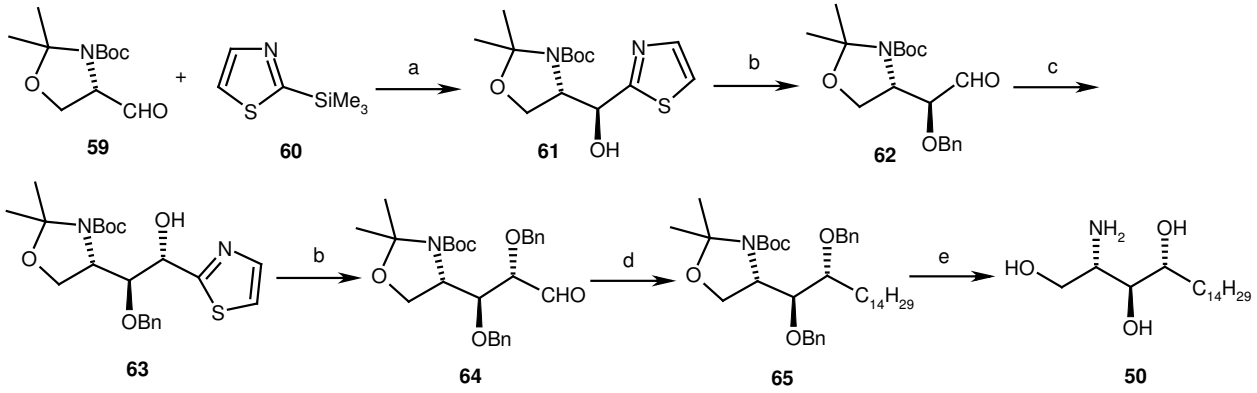


Scheme 8. *Reagents and conditions*: (a) $C_{14}H_{29}MgBr$, THF, 35% (**55**), 36% (**56**). (b) (i) MsCl, pyridine, -30 °C, 12 h, 75%, (ii) DMF, NaN_3, 90 °C, 2 days, 63%. (c) (i) MeOH, conc. HCl, 15 h, 65%, (ii) $LiAlH_4$, THF, rt, 30 min, 1 h, reflux, 95%.

Compound **55** was ultimately converted to *ribo*-phytosphingosine, as shown in Scheme 8, while **56** was converted to the *lyxo*-isomer by the same sequence. Compound **56** could be selectively procured as a single diastereomer in 76% by using a mixed solvent system in the presence of catalytic $TiCl_4$. Serendipitously, it was found that compound **55** could be selectively activated for azide displacement at the axial hydroxyl moiety of the dioxane. Acetal removal, followed by reduction of the azide provided *ribo*-phytosphingosine (Scheme 8).

Dondoni *et al*.[37] (1990)

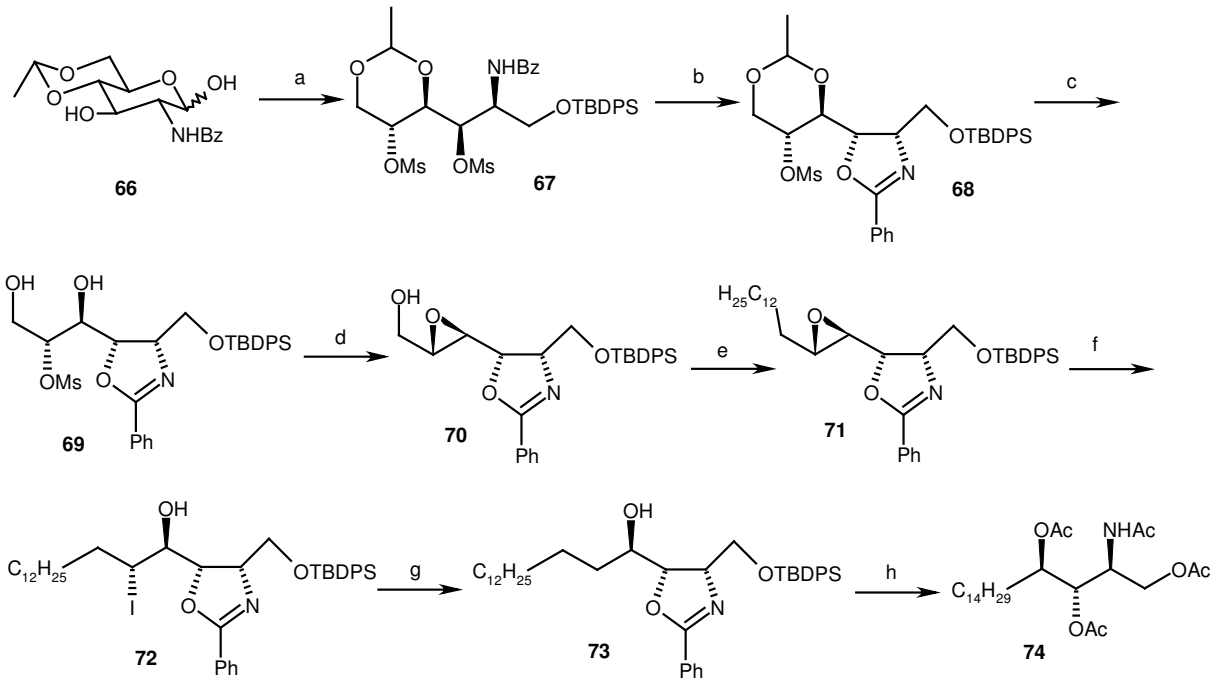
Dondoni *et al*. were the first to report the exploitation of **59** for the preparation of phytosphingosines. Homologation with 2-TMS-thiazole (2-TST) **60** proceeded with high *anti*-selectivity (92:8) to give **61**. Compound **61** was converted in a 3 stage-one pot process into **62** in 73% yield. A second homologation again proceeded in a stereoselective manner (~6:1 ratio of *anti:syn*), and after hydroxyl protection, the aldehyde was unmasked as before to give **64**. Aldehyde **64** was subjected to Wittig reaction; subsequent Raney nickel reduction, followed by treatment with TFA, afforded *ribo*-phytosphingosine (Scheme 9).



Scheme 9. *Reagents and conditions*: (a) CH_2Cl_2, rt, 20 h, then *n*-Bu_4NF, 1 h, 85%. (b) (i) NaH, reflux, 20 min then BnBr, THF, *n*-Bu_4NI, 12 h, 73%, (ii) MeI, CH_3CN, reflux, 12 h then $NaBH_4$, MeOH, −10°C, 30 min then $HgCl_2$, CH_3CN, H_2O, 15 min, 73%. (c) 2-TST, THF, 0 °C, 63%. (d) (i) $C_{13}H_{27}P^+Ph_3Br^-$, *n*-BuLi, $PhCH_3$, rt, 2 h, 66%, (ii) Raney Ni, EtOH, 8 h, reflux, 70%. (e) CF_3CO_2H, H_2O, 15 min, 95%.

Murakami *et al.*[36h] (1994)

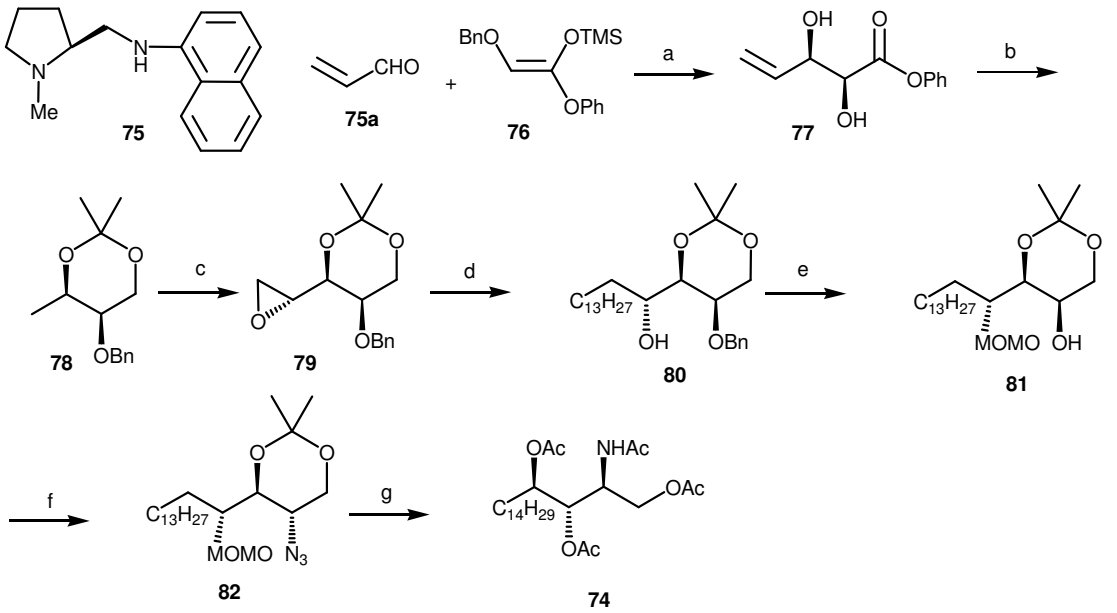
Murakami *et al*. synthesized D-*ribo*-phytosphingosine from D-glucosamine by utilizing its whole carbon skeleton and functional groups. 4,6-*O*-Ethylidene-*N*-benzoyl-D-glucosamine **66** (readily prepared from D-glucosamine)[38] was reduced to give the triol. Selective protection of the primary hydroxyl and mesylation gave the dimesylate **67**, which was further converted into phenyl oxazoline **68**. Deprotection of acetal followed by base treatment gave the epoxide **70**. Conversion of the free hydroxyl into tosylate and displacement with dodecyl magnesium bromide gave rise the epoxide **71**, which was subjected to ring opening with iodide to furnish **72**. Deiodination, hydrolysis of phenyloxazoline and TBDPS group deprotection followed by acetylation afforded the tetraacetate derivative of D-*ribo*-phytosphingosine **74** (Scheme 10).



Scheme 10. *Reagents and conditions*: (a) (i) $NaBH_4$, *i*-PrOH, H_2O, 0 ^oC, 1 h, 95%, (ii) *t*-$BuPh_2SiCl$, pyridine, CH_2Cl_2, rt, 24 h then MsCl, Et_3N, CH_2Cl_2, 0 ^oC, 2 h. (b) pyridine, Et_3N, toluene, 110 ^oC, 24 h, 90%. (c) $TiCl_4$, PhSH, CH_2Cl_2, 0 ^oC, 2 h, 83%. (d) K_2CO_3, MeOH, 0 ^oC, 2 h. (e) (i) *p*-TsCl, DMAP, Et_3N, CH_2Cl_2, 0 ^oC, 2 h, 88%, (ii) $C_{12}H_{25}MgBr$, CuBr, THF, –30 ^oC to 0 ^oC, 4 h, 84%. (f) NaI, Me_3SiCl, H_2O, CH_3CN, 0 ^oC to 10 ^oC, 2 h. (g) *n*-Bu_3SnH, AIBN, $PhCH_3$, 60 ^oC, 30 min, 88%, (h) (i) 4N HCl, THF, rt, 24 h, (ii) aq. NaOH, rt, (iii) aq. NaOH, EtOH, 95 ^oC, 12 h, (iv) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 75%.

Kobayashi *et al*.[39](1994)

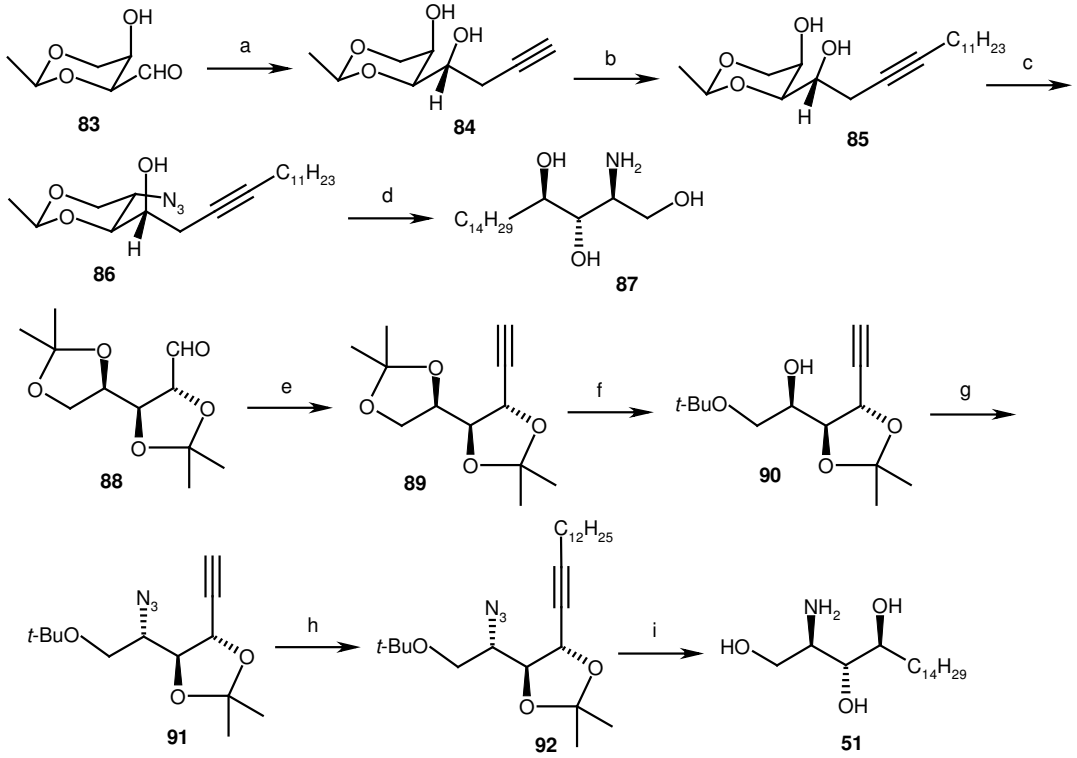
Kobayashi employed Lewis acid catalyzed asymmetric Aldol reaction of acrolein **75a** with ketene silyl acetal **76** in presence of diamine **75** to give **77** (*syn*/*anti* = 98:2, 96% ee for *syn*). Reduction of **77** and diol protection gave **78**, which on epoxidation and subsequent alkylation with Grignard reagent furnished compound **80**. The subsequent protection/deprotection of hydroxyl groups followed by its conversion into azide eventually led to the formation of compound **82**. Removal of MOM and acetonide groups followed by azide reduction and subsequent acetylation gave the tetraacetate derivative of D-*ribo*-phytosphingosine **74** (Scheme 11).



Scheme 11. *Reagents and conditions*: (a) $Sn(OTf)_2$, SnO, **76**, propionitrile, 80%. (b) (i) DIBAL-H, (ii) *p*-TsOH, 2,2-DMP, 92%. (c) *m*-CPBA, 96% (74/26). (d) CuI, $C_{13}H_{27}MgBr$, 97%. (e) (i) MOMCl, *i*-Pr_2NEt, 93%, (ii) H_2, Pd-C, 100%. (f) (i) MsCl, pyridine, 96%, (ii) NaN_3, 83%. (g) (i) AcOH, H_2O, (ii) Ph_3P/H_2O-pyridine, (iii) Ac_2O, Et_3N, DMAP, 48%.

Wu *et al.*[40] (1995)

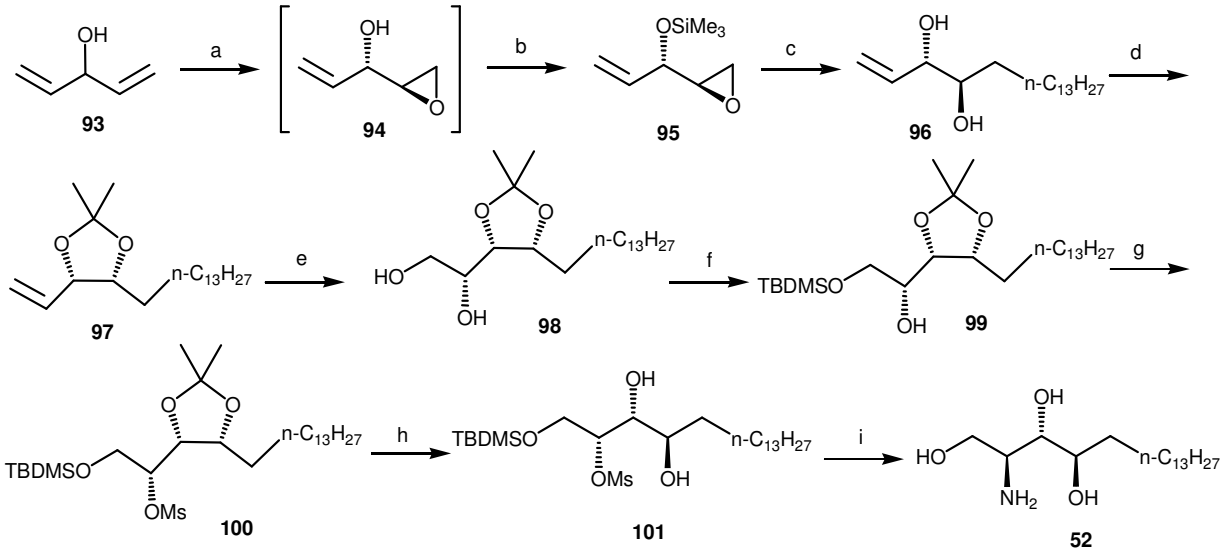
In Wu's approach, the reaction of 2,4-*O*-ethylidene-D-threose **83** (prepared from D-galactose[41]) with prop-2-ynyl bromide/Zn gave **84** (*erythro*:*threo*, 11.7:1). Alkyne substitution, triflation of 2-OH and azide displacement furnished **86**. Deprotection of acetal and hydrogenation of azide and alkyne gave D-*ribo*-phytosphingosine **87**. In order to synthesize L-*lyxo*-phytosphingosine, **88** (prepared from D-xylose[42]) was first converted into the alkyne **89**. Conversion of terminal acetonide into *t*-butyl ether gave **90**. Mesylation of hydroxyl and azide displacement followed by alkyne substitution furnished **92**. Deprotection of acetonide and hydrogenation afforded L-*lyxo*-phytosphingosine **51** (Scheme 12).



Scheme 12. *Reagents and conditions*: (a) prop-2-ynyl bromide, Zn, DMF-Et_2O, 85%; (b) *n*-BuLi, $C_{11}H_{23}Br$, THF-HMPA, 74%; (c) (i) Tf_2O, Py, CH_2Cl_2, -78 ^oC to rt; (ii) NaN_3, DMF, rt, 82%; (d) (i) 90% CF_3CO_2H; (ii) 10% Pd-C, MeOH; (e) (i) CBr_4, Ph_3P, Zn, CH_2Cl_2, 62%; (ii) *n*-BuLi, THF, 89%; (f) MeMgI, Et_2O-PhMe, reflux, 52%; (g) (i) MsCl, pyridine, DMAP, CH_2Cl_2 (ii) NaN_3, DMF, *n*-BuLi, 110 ^oC, 68%; (h) LDA, $C_{12}H_{25}Br$, THF-HMPA, 82%; (i) (i) CF_3CO_2H, 66%, (ii) 10% Pd-C, MeOH, 77%.

Lin *et al.* [43a] **(1996)**

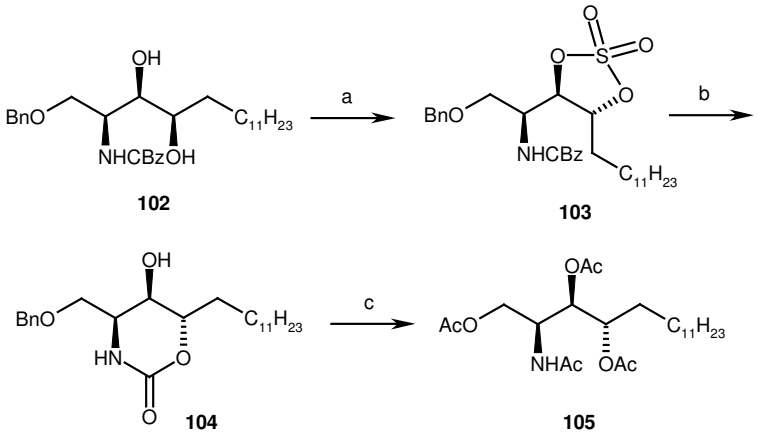
Lin and Shi used a combination of Sharpless asymmetric epoxidation and Sharpless asymmetric dihydroxylation in their synthesis of *ribo*-phytosphingosine. Thus, divinylcarbinol **93** was converted to the corresponding epoxide **94** with excellent diastereo- and enantioselectivity; protection as the TMS-ether provided **95**. Copper-catalyzed ring opening with tridecylmagnesium bromide and protection of the diol provided alkene **97**. Sharpless AD with $(DHQ)_2PHAL$ proceeded with modest diastereoselectivity. The primary hydroxyl of the resulting diol **98** was selectively protected, and the remaining hydroxyl was mesylated, resulting in **100**. Double deprotection gave **101**, which was converted by a literature procedure to *ribo*-phytosphingosine (Scheme 13).



Scheme 13. *Reagents and conditions*: (a) L-(+)-DIPT, TBHP, $Ti(OPr^i)_4$, 4Å molecular sieves, CH_2Cl_2, -20 ^oC, 10 days, (b) Me_3SiCl, DMAP, Et_3N, CH_2Cl_2, 0 °C 65%, (c) *n*-$C_{13}H_{27}MgBr$, CuI, (10 mol%), THF, –l0 ^oC, 85%; (d) $(CH_3)_2C(OMe)_2$, *p*-TSA, CH_2Cl_2, rt, 98%; (e) OsO_4, $K_3Fe(CN)_6$, K_2CO_3, $(DHQ)_2PHAL$, *t*-BuOH/ H_2O = 1:1, rt, 92% (dr = 4:1); (f) TBDMS-Cl, imidazole, DMF, 0 ^oC, 91%; (g) MsCl, pyridine, CH_2Cl_2, rt, 90%: (h) *p*-TSA/MeOH, 10% aq. HCl, 85%, (i) Ref. 43b.

Pedersen *et al.*[44] (1996)

In Pedersen's approach, the *syn*,*syn*-diol **102** obtained by Pinacol coupling[45] was converted into cyclic sulfate **103**.

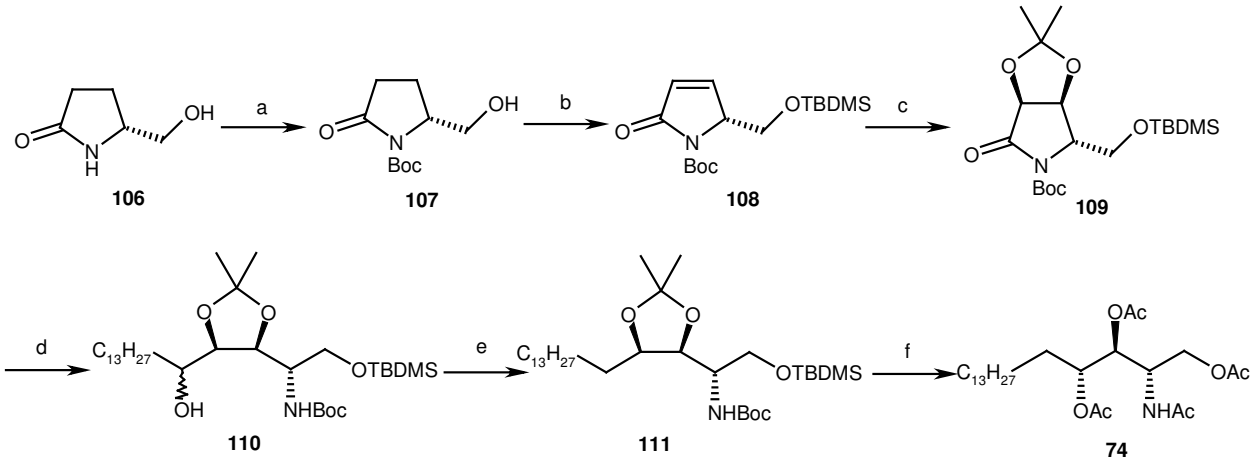


Scheme 14. *Reagents and conditions*: (i) (a) $SOCl_2$, Et_3N, (b) $RuCl_3$, $NaIO_4$, 89%. (ii) (a) CH_3CN, reflux, (b) THF, 2% H_2SO_4. (iii) (a) HCO_2H, 10% Pd/C, (b) LiOH, EtOH, H_2O, (c) Ac_2O, pyridine.

Compound **103** on heating in CH_3CN at reflux gave the cyclic carbonate **104**. Removal of benzyl protection, saponification of carbonate and acetylation afforded the D-*arabino*-phytosphingosine tetraacetate **105** (Scheme 14).

Yoda *et al*.[36f] (1996)

In Yoda's approach, the hydroxylactam **106**[46] on successive TBDMS and BOC protection followed by unsaturation gave **108**. Dihydroxylation and acetonide protection followed by treatment with tridecyl magnesium bromide and reduction afforded **110**, which on deoxygenation *via* thioimidazolide led to compound **111**. Deprotection of acetonide, BOC, TBDMS and subsequent acetylation gave D-*ribo*-phytosphingosine tetraacetate **74** (Scheme 15).

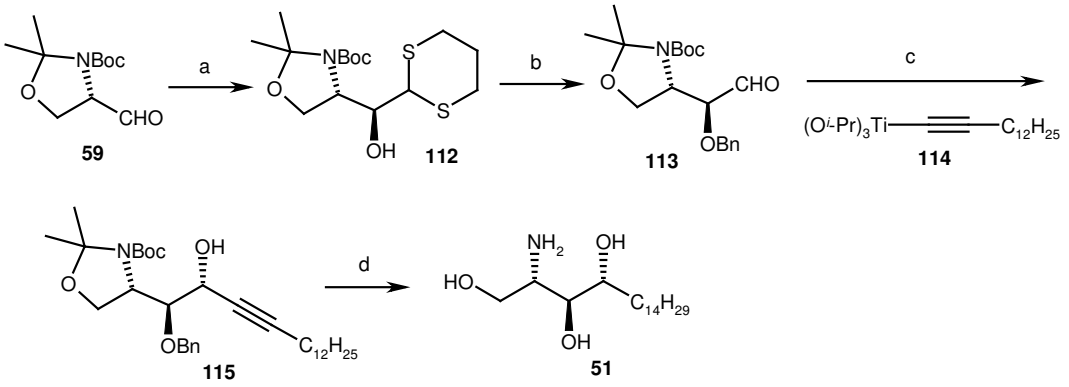


Scheme 15. Reaction conditions: (a) (i) *t*-$BuMe_2SiCl$, imidazole, DMF, 88%, (ii) $(BOC)_2O$, Et_3N, DMAP, CH_2Cl_2, 90%. (b) (i) LDA, THF, PhSeBr, −78 °C, (ii) *m*-CPBA, −78°C. (c) (i) OsO_4, NMO, acetone-H_2O, 55%, (ii) 2,2-DMP, *p*-TsOH, 100%. (d) (i) $C_{13}H_{27}MgBr$, −78°C, 60%. (ii) $NaBH_4$, EtOH, 88%. (e) (i) (thiocarbonyl)diimidazole, 50 °C, 98%, (ii) *n*-Bu_3SnH, AIBN, toluene, 100°C, 87%. (f) (i) CF_3CO_2H, H_2O then KOH, MeOH, 100%, (ii) Ac_2O, pyridine, DMAP, 70%.

Fujisawa *et al*.[47] (1997)

Fujisawa carried out the diastereoselective addition of dithianide to Garner aldehyde **59** with high *anti*-diastereoselectivity to give **112**. Protection of hydroxyl and selective dithiane hydrolysis furnished the aldehyde **113**. Dodecylacetylide **114** addition to aldehyde **113** at

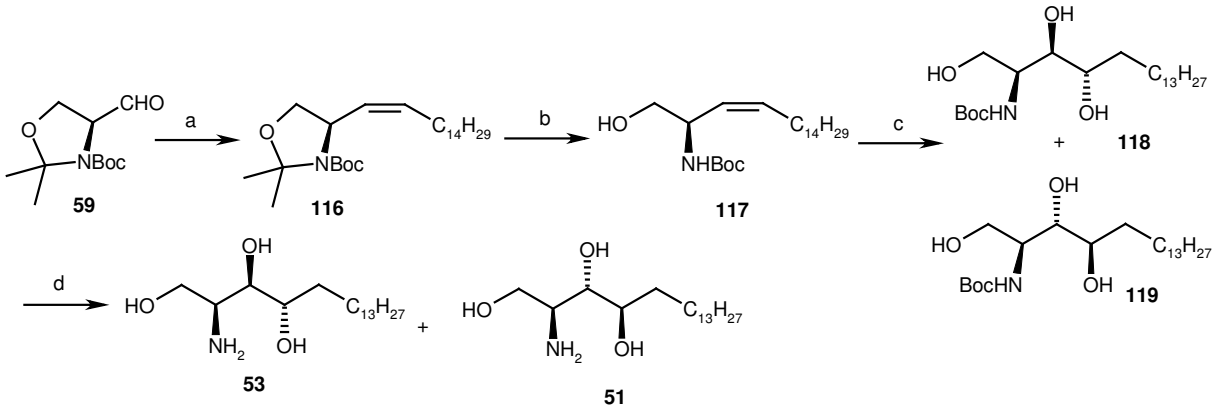
lower temperature gave **115** in high *anti*-diastereoselectivity (95% de). Hydrogenation of **115** followed by deprotection of acetonide and BOC groups eventually led to D-*ribo*-phytosphingosine **51** (Scheme 16).



Scheme 16. *Reagents and conditions*: (a) Li-dithianide, $BF_3.Et_2O$, CuI, −50 °C-rt, THF, 70%. (b) (i) KHMDS, BnBr, 92%, (ii) NBS, 67%. (c) **114**, −110 °C to rt, THF. (d) (i) 10% Pd-C, H_2, EtOH, 92%, (ii) CF_3CO_2H, H_2O, 68%.

Horikawa *et al*.[48] (1998)

Horikawa employed Wittig olefination of **59** to give separable alkene (**116**) diastereomers with good Z-selectivity. The authors found in a related system that the yield and diastereoselectivity were better if the acetonide group was removed prior to dihydroxylation.



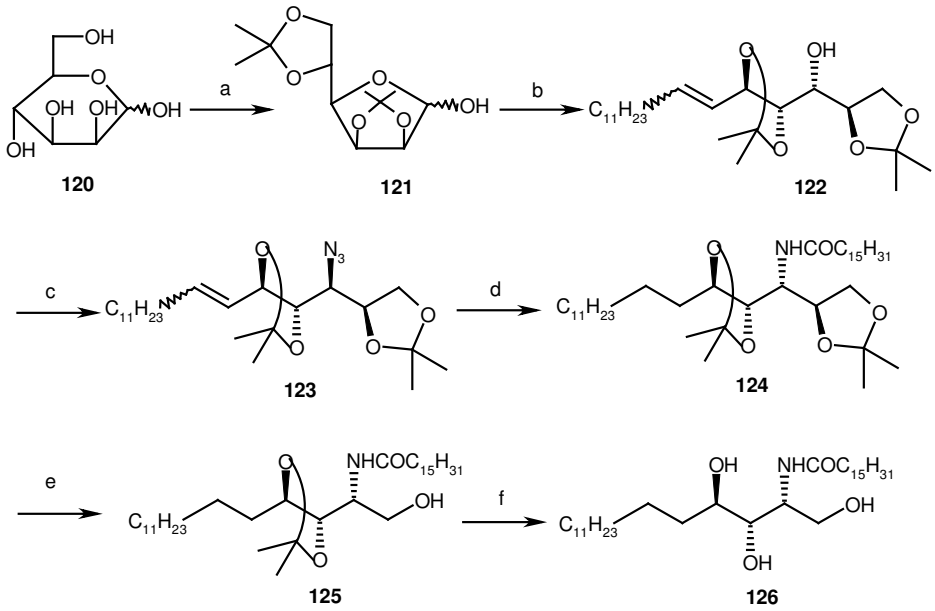
Scheme 17. *Reagents and conditions*: (a) $C_{14}H_{29}CH{=}PPh_3$, 71%. (b) Amberlite IR-120, 93%. (c) AD-mix-α or AD-mix-β, 86-89%. (d) (i) CF_3CO_2H, (ii) aq. $NaHCO_3$, 96-100%.

Moreover, it was observed that enhanced diastereoselectivities were possible with the Sharpless AD catalysts. Thus, **116** was deprotected, and **116** was dihydroxylated in the presence of AD-mix-β to give **118** and **119** in 89% yield and with high 2,3-*anti* selectivity

(83:17). Reaction in the presence of AD-mix-α proceeded in similar yield and with high 2,3-*syn* selectivity (83:17). Compounds **118** and **119** were converted to *ribo*- and *arabino*-phytosphingosine, respectively (Scheme 17).

Suryawanshi *et al*.[49] (1998)

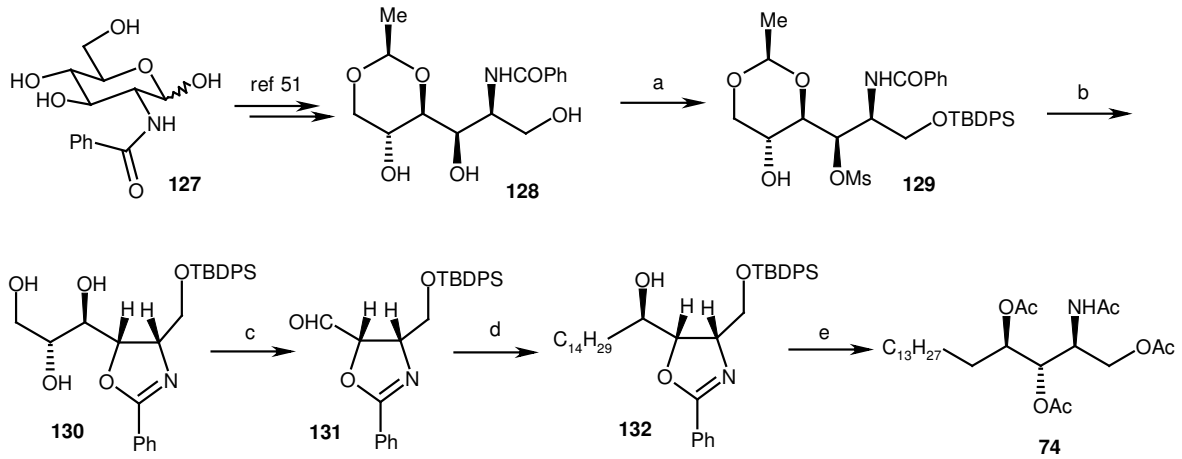
Suryawanshi *et al*. employed diacetone mannose **120** in Wittig reaction to give the olefin **121**. Triflation of hydroxyl and azide displacement gave **123**, which on reduction followed by acylation furnished the palmitate **124**. Deprotection of terminal acetonide and periodic oxidation followed by reduction gave the alcohol **125**, which on subsequent deprotection of acetonide group led to D-*ribo*-ceramide **126** (Scheme 18).



Scheme 18. Reaction conditions: (a) Acetone, H^+. (b) $C_{12}H_{25}P^+Ph_3Br^-$, *t*-BuOK, $PhCH_3$, 80%. (c) (i) Tf_2O, pyridine, (ii) NaN_3, DMF, 80%. (d) (i) 10% Pd-C, H_2, EtOAc, 65%, (ii) $C_{15}H_{31}CO_2C_6H_4pNO_2$, pyridine, 100%. (e) (i) H_5IO_6, EtOAc, (ii) $NaBH_4$, EtOH, 60%. (f) 70% CH_3CO_2H, 100%.

Murakami *et al*.[50] (1999)

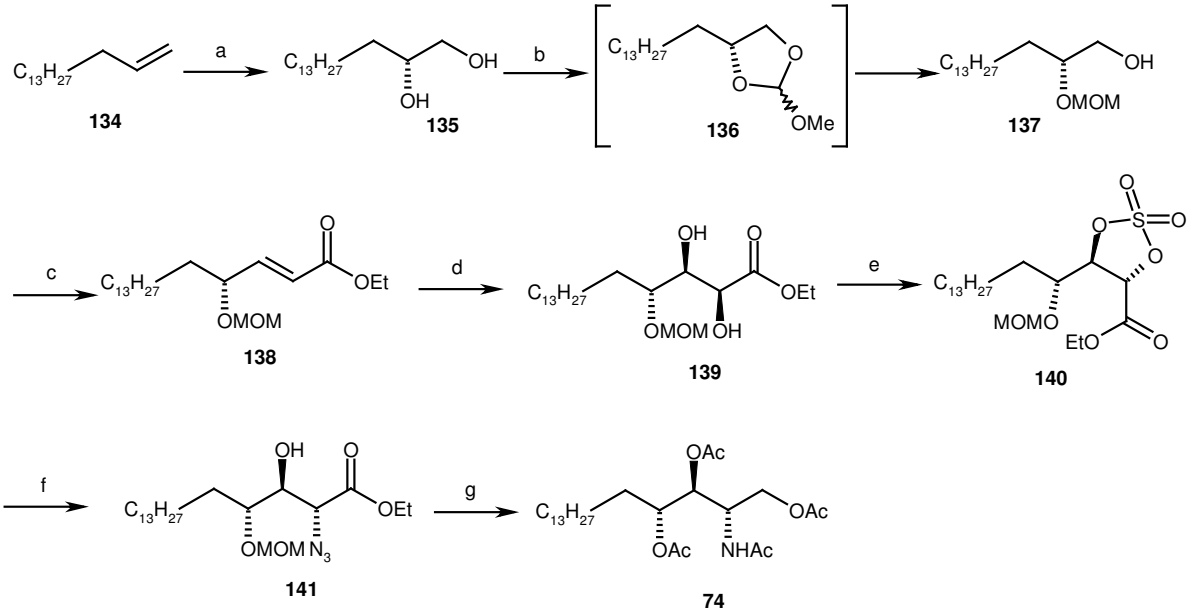
Murakami and Taguchi reported an improved preparation of **132** from **127**. After TBDPS protection of the primary alcohol, *in-situ* reaction with methanesulfonyl chloride gave predominantly the *mono*-mesylate **129**. Oxazoline formation, acetal removal and periodate cleavage provided aldehyde **131**. Nucleophilic addition with tetradecylmagnesium bromide provided **74** as the major diastereomer (Scheme 19).



Scheme 19. *Reagents and conditions:* (a) *t*-$BuPh_2SiCl$, pyridine, CH_2Cl_2, rt, 24 h; then $MeSO_2Cl$, 0 to 5 °C, 5 h; (b) pyridine, toluene, 110 °C, 24 h; (c) (i) $TiCI_4$, PhSH, CH_2Cl_2, -10 °C, 1 h; (ii) $NaIO_4$, aq. MeOH, 5 °C, 2 h; (d) (i) *n*-$C_{14}H_{29}MgCl$, THF, -70 to -20 °C; (e) (i) 2 M aq. HCI, THF, r. t., 5 h, then NaOH, aq. EtOH, 95 °C, 12 h; (ii) Ac_2O, pyridine, DMAP, CH_2Cl_2.

Bittman *et al.*[36d] (2000)

In Bittman's approach, asymmetric dihydroxylation and cyclic sulfate methodology was employed in the synthesis of **74**.



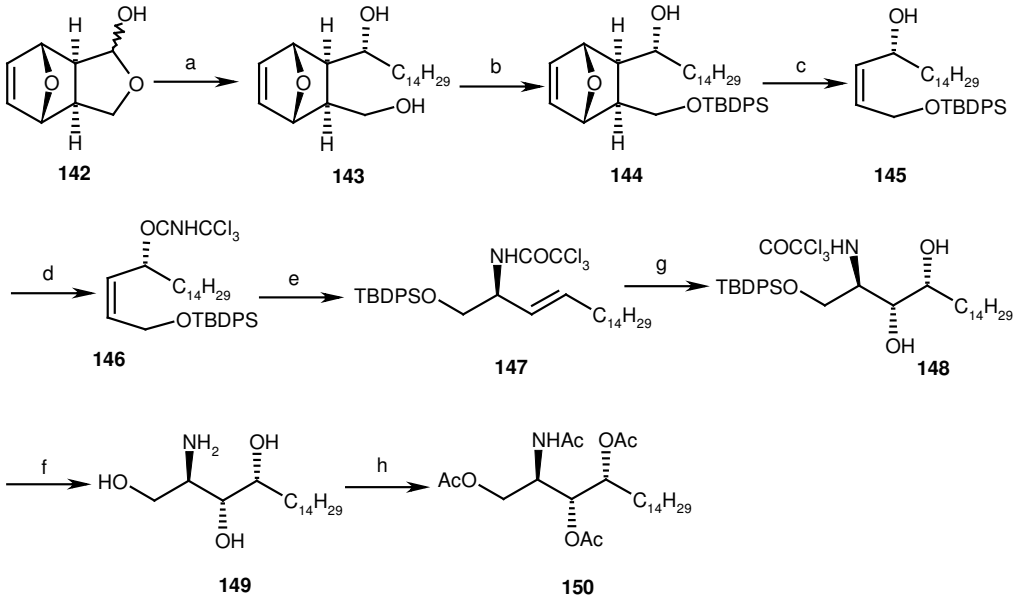
Scheme 20. *Reagents and conditions*: (a) (i) AD-mix-β, *t*-$BuOH/H_2O$,1:1, 0 °C; (b) $CH(OMe)_3$, CH_2Cl_2, D-10-camphorsufonic acid, rt; then DIBAL-H, -78 °C, (c) (i) $(COCl)_2$,

DMSO, Et_3N, CH_2Cl_2, –78 to –46 °C; (ii) $(i\text{-PrO})_2P(O)CH_2CO_2Et$, LiBr, Et_3N, THF, rt; (d) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH/H_2O 1:1, 0 °C; (e) (i) $SOCl_2$, py, CH_2Cl_2, 0 °C; (ii) $NaIO_4$, $RuCl_3$ (cat.), MeCN/H_2O 1:1, rt; (f) (i) NaN_3, Me_2CO/H_2O 1:1, rt (ii) 20% H_2SO_4 (aq)/Et_2O, rt, (g) (i) concd. HCl/MeOH 3:25, rt; (ii) $LiAlH_4$, THF, 65 °C; (iii) Ac_2O, DMAP (cat.), py, rt.

Asymmetric dihydroxylation of terminal olefin **134** gave the diol **135**. Selective conversion of secondary hydroxyl into MOM ether *via* orthoacetate and DIBAL-H cleavage furnished **137**. Oxidation of alcohol **137** and Wittig reaction gave the olefin **138** that was subjected to a second asymmetric dihydroxylation to furnish the diol **139** in 91% de. The diol was converted into the cyclic sulfate **140**, which on opening with azide gave **141**. Removal of MOM protection, reduction of azide and ester followed by acetylation furnished D-*ribo*-phytosphingosine tetraacetate **74** (Scheme 20).

Martin *et al*.[36k] (2000)

Martin *et al*. utilized the lactol **142**[52] in Grignard reaction to give the diol **143** 90% de. Primary hydroxyl protection and retro Diels-Alder reaction gave (*Z*)-allylic alcohol **145**, which on reaction with trichloroacetonitrile in presence of DBU gave the unstable trichloroacetamide **146**.



Scheme 21. *Reagents and conditions*: (a) $C_{14}H_{29}MgBr$, THF, 80%. (b) *t*-$BuMe_2SiCl$, imidazole, DMF, 70%. (c) Microwaves, 100%. (d) CCl_3CN, DBU, CH_2Cl_2. (e) xylenes, 140 °C, 7 h, 81% from **146**. (f) AD-mix-β, 1% $K_2OsO_2(OH)_4$, $CH_3SO_2NH_2$, H_2O/*t*-BuOH, 4 h,

80%. (g) (i) *n*-Bu_4NF, THF, 4 h, (ii) NaOH, H_2O/C_2H_5OH, 100 °C, 16 h, 67%. (h) Ac_2O, pyridine, DMAP, CH_2Cl_2, 6 h, 74%.

The subsequent thermal rearrangement afforded (*E*)-allylic trichloroacetamide **147**, which on asymmetric dihydroxylation with AD-mix-β gave **148** in 94% de. Deprotection of TBDPS and hydrolysis of trichloroacetamide, followed by acetylation eventually led to D-*lyxo*phytosphingosine tetraacetate **150** (Scheme 21).

Shiozaki *et al*.[36e] (2001)

Tartaric acid was converted to *lyxo*-phytosphingosine as reported by Nakamura and Shiozaki. The key synthon was β-lactam **151**, derived by a literature procedure from tartaric acid.[53] Reduction of the ester and protection of the resulting alcohol and the amide gave **153**.

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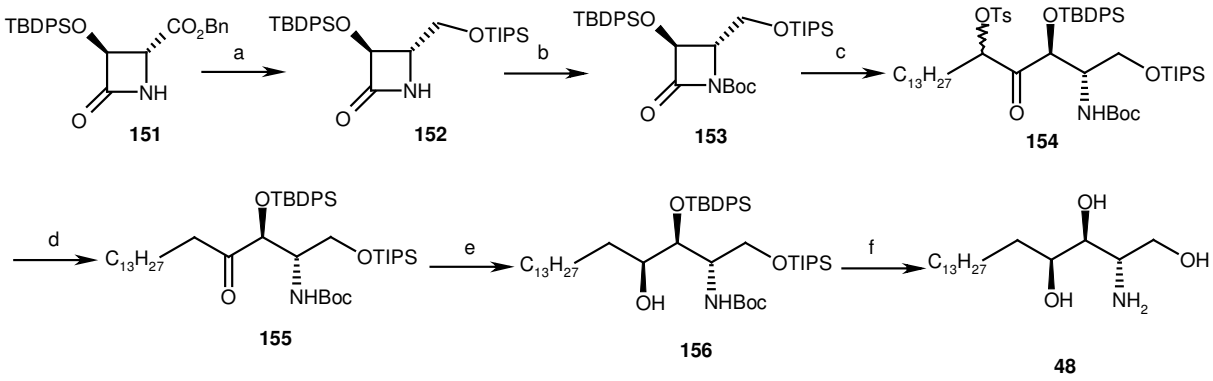
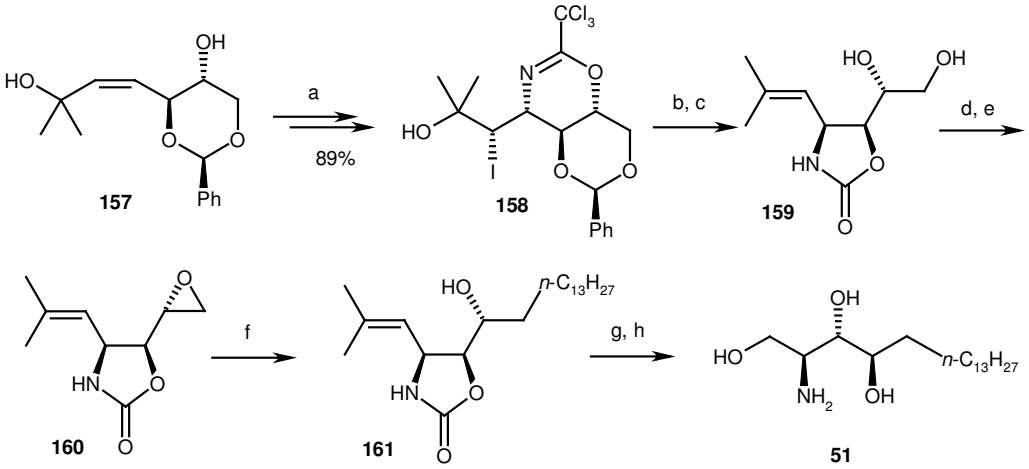


Scheme 22. *Reagents and conditions*: (a) (i) $NaBH_4$, EtOH, rt, 1 h, 73%, (ii) *i*-Pr_3SiCl, imidazole, DMF, rt, 4 h, 95%. (b) $(BOC)_2O$, Et_3N, DMAP, CH_2Cl_2, rt, 1 h, 100%. (c) $C_{14}H_{29}SO_2C_6H_4Me$, *n*-BuLi, THF, −78 °C, 1 h, 88%. (d) Li-naphthalenide, THF, −78 °C, 20 min, 93%. (e) $LiEt_3BH$, THF, −78 °C, 1 h, 86%. (f) (i) *n*-Bu_4NF, THF, rt, 2 h, (ii) 10% HCl in MeOH, 40 °C, 9 h, 96%.

Treatment of **153** with tetradecyl *p*-toluenesulfonate and *n*-butyllithium yielded a mixture of diastereomers **154**. Reductive cleavage of the sulfone, followed by a highly stereoselective reduction of the ketone with $LiEt_3BH$ furnished **156** in 92% ds. The subsequent removal of silyl groups and BOC deprotection afforded L-*lyxo*-phytosphingosine **48** (Scheme 22).

Kang *et al.*[54] (2002)

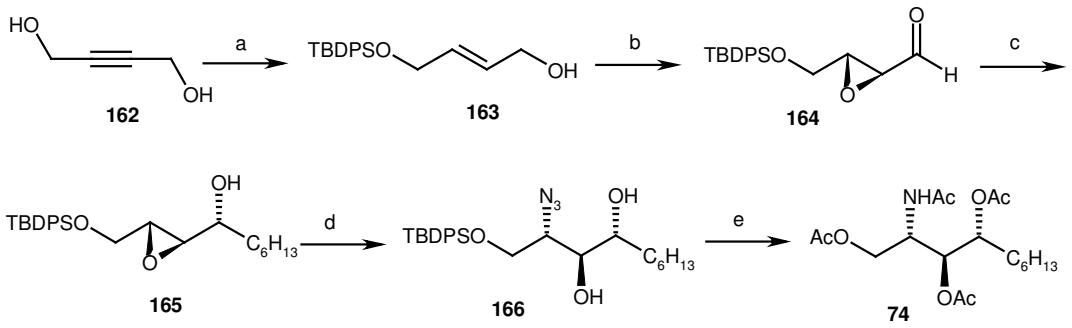
To synthesize D-*ribo*-phytosphingosine **51**, Kang *et al*. utilized dihydro-1,3-oxazine **158**, which was secured in 2 steps and 89% yield from diol **157**, was reductively eliminated, exhaustively hydrolyzed, and the resulting amine was protected to render carbamate **159** in 75% overall yield. Regioselective sulfonation of **159** followed by cyclization gave epoxy oxazolidinone **160**. The epoxy group of **160** was opened with tridecylmagnesium bromide in the presence of lithium tetrachlorocuprate[55] to afford oxazolidinone **161**. Sequential subjection of **161** to ozonolysis, $NaBH_4$ reduction and basic hydrolysis produced D-*ribo*-phytosphingosine **51** in 68% yield (Scheme 23).



Scheme 23. *Reagents and conditions*: (a) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2, -20 ^oC, then NaI, DMF, 0 ^oC; (b) 6 N HCl, MeOH, rt; (c) CbzCl, K_2CO_3, MeOH, 0 ^oC; (d) 2,4,6-$Me_3C_6H_2SO_2Cl$, DMAP, Et_3N, CH_2Cl_2, 0 ^oC to rt; (e) NaH, THF, 0 ^oC; (f) *n*-$C_{13}H_{27}MgBr$, Li_2CuCl_4, Et_2O, -20 ^oC; (g) O_3, MeOH, –78 ^oC, then $NaBH_4$, 0 ^oC; (h) 2 N KOH, MeOH, reflux.

Génisson *et al.*[56] (2003)

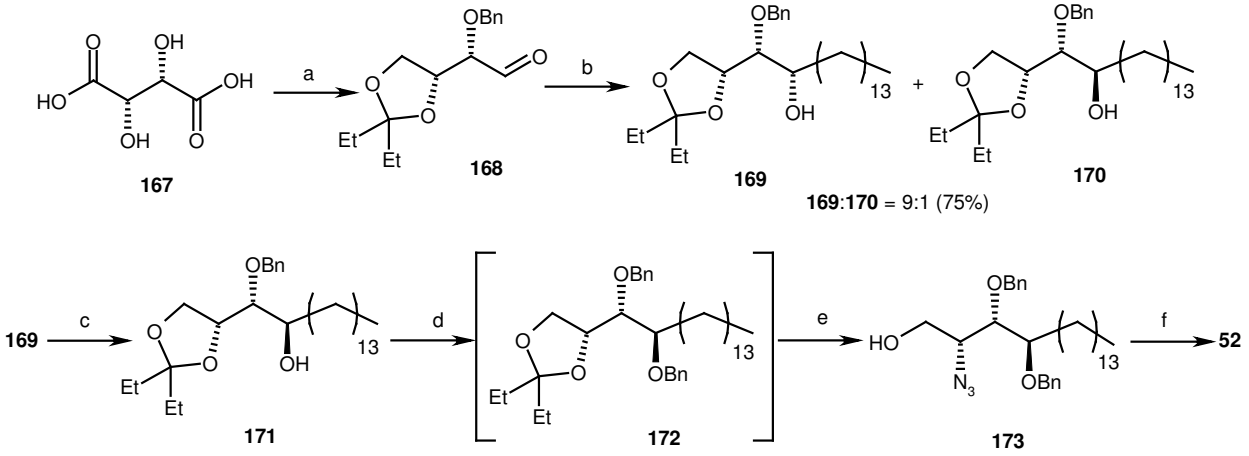
Génisson *et al*. utilized the α,β-epoxyaldehyde **164**, which was synthesized from *t*-butyldiphenylsilyl derivative via a Sharpless asymmetric epoxidation and a Doering oxidation.[57] The highly stereoselective alkylation of the aldehyde **164** with a diorganozinc reagent furnished **165**. Treatment of the *anti*-epoxyalcohol **165** under Sharpless conditions gave the two expected regioisomeric azidodiols (75/25 ratio) in 80% yield. Separation of major C-2 opening product and subsequent desilylation of the primary alcohol and hydrogenolysis of the azido group furnished **74** in good yield (Scheme 24).



Scheme 24. *Reagents and conditions*: (a) (i) LAH (2.2 equiv.), THF, reflux, 18 h, 80%; (ii) TBDPSCl (1 equiv., addition over 12 h), imidazole (2.5 equiv.), DMF, rt, 20 h, 56% based on the chlorosilane; (b) (i) Sharpless epoxidation, (ii) Doering oxidation (Ref. 57); (c) (1*S*,2*S*)-1,2-*N*,*N*´-bis(trifluoromethanesulfonylamino)cyclohexane, Ti(O*i*-Pr)$_4$, $(C_6H_{13})_2Zn$, degassed toluene, −10 °C, 20 h, 40% , 100% de; (d) NaN_3, NH_4Cl, methoxyethanol/H_2O, 120°C, 5 h, C-2/C-3 opening ratio 75/25; (e) (i) $Et_3N{\cdot}3HF$, THF, rt, 24 h; (ii) 10% Pd/C (cat.), MeOH, rt, 18 h; (iii) Ac_2O/pyridine (1/1), rt, 24 h, 85% (three steps).

Bittman *et al*.[58a] (2005)

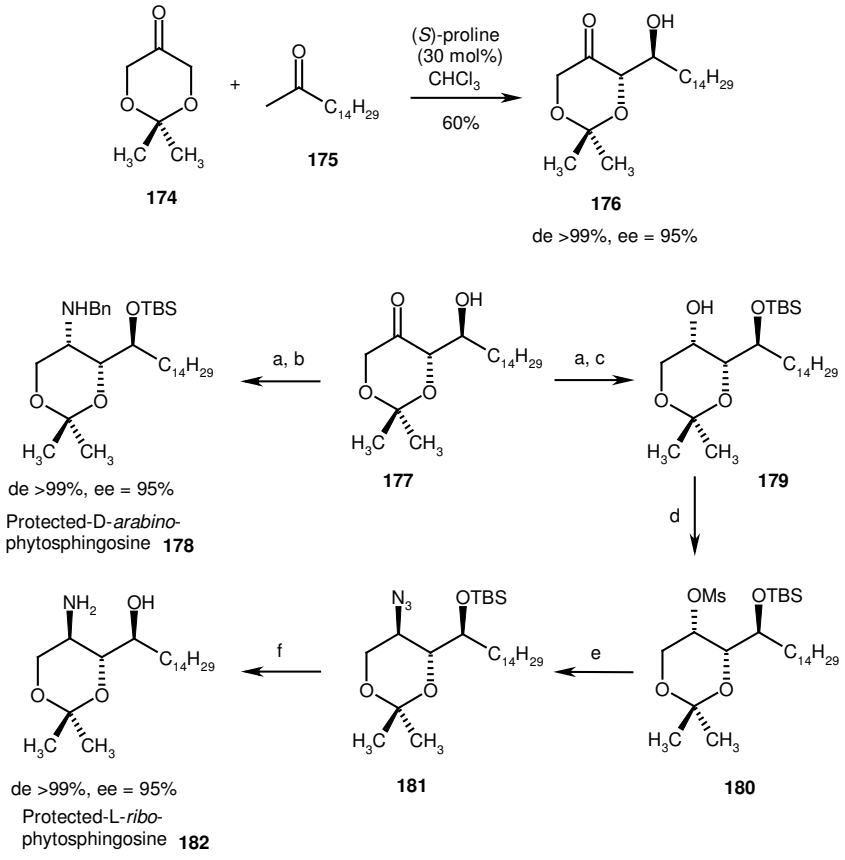
Bittman *et al*. employed chelation-controlled addition of tetradecylmagnesium bromide to pentylidene-protected D-threitol aldehyde, **168** to give a 9:1 mixture of compounds **169** and **170**. The hydroxy group of **169** was protected as benzyl ether followed by deprotection of acetonide group to furnish 1,2-diol. One pot conversion of diol to azido alcohol and simultaneous reduction of the azido group and hydrogenolysis of the benzyl groups furnished **52** (Scheme 25).



Scheme 25. *Reagents and conditions*: (a) Ref. 58b; (b) $C_{14}H_{29}Br$, Mg, $BrCH_2CH_2Br$, Et_2O; (c) (i) DIAD, PPh_3, *p*-nitrobenzoic acid, CH_2Cl_2; (ii) NaOMe, MeOH; (d) BnBr, NaH, THF; (d) 5% H_2SO_4, MeOH; (e) (i) PPh_3, DIAD, CH_2Cl_2, 0 ^oC, (ii) $TMSN_3$, 0 ^oC–rt, (iii) TBAF, THF; (f) $Pd(OH)_2/C$, H_2, MeOH.

Enders *et al*.[59] (2006)

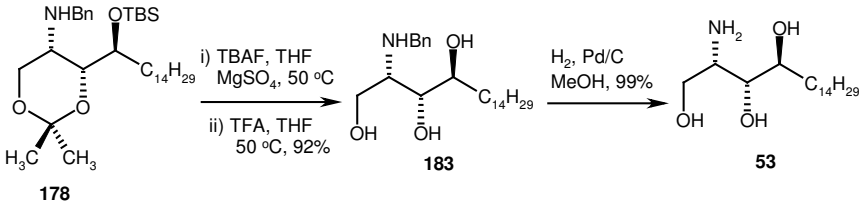
Organocatalytic asymmetric synthesis was employed by Enders *et al*. to the syntheses of D-*arabino*- and L-*ribo*-phytosphingosine. Thus, the simple (*S*)-proline catalyzed aldol reaction of the dioxanone **174** with pentadecanal **175** directly delivered gram amounts of the selectively acetonide protected ketotriol **176** precursor of the core unit of phytosphingosines in excellent stereoisomeric purity.



Scheme 26. Diastereoselective reductive amination and ketone–amine conversion. *Reagents and conditions:* (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, –20 ^oC, 95%, de > 99%; (b) $BnNH_2$, $NaBH(OAc)_3$, AcOH, CH_2Cl_2, -20 ^oC, 94%, de > 99%; (c) L-Selectride, THF, –78 ^oC, 93%,

de > 99%; (d) MsCl, DMAP, CH_2Cl_2, –10 to 0 ^oC, 91%, de > 99%; (e) NaN_3, 18-crown-6, DMF, 100 ^oC, 80%, de > 99%; (f) LAH, THF, 0 ^oC, 98%, de > 99%.

Protection of hydroxy as TBS ether followed by reductive amination of **177** gave 1,3-aminoalcohol **178** in good yield. For the synthesis of *syn*-1,3-aminoalcohol **177**, was first transformed to the corresponding anti-1,3-diol **179** by a highly diastereoselective reduction with L-Selectride followed by mesylation and subsequent azidation to furnish **181** with complete inversion of the stereogenic centre. Subsequent reduction of the azide **181** and deprotection the silyl- and acetonide group followed by hydrogenation afford D-*arabino*-phytosphingosine **53** in 99% yield (Scheme 26 and 27).



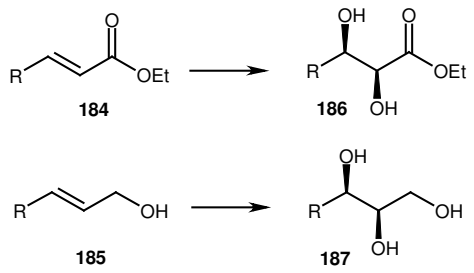
Scheme 27. Deprotection of **178** to D-*arabino*-phytosphingosine **53**.

1.3. PRESENT WORK

1.3.1. Objective

Given the vast chemistry, structural modifications and biological activities associated with the sphingolipids, the synthesis of this class of vicinal amino alcohols has aroused considerable interest among several research groups around the world. Although a few syntheses are reviewed above, several more are documented in the literature. This explains the importance of research work in sphingolipid chemistry.

The AD reaction of *trans*-α,β-unsaturated esters[60a] (**184**) and long chain terminal *trans*-allylic alcohols[60b] (**185**) is reported to give the corresponding dihydroxy esters (**186**) and 1,2,3-trihydroxy compounds (**187**) respectively in high enantiomeric purity. With a view to investigate the double diastereoselection in asymmetric dihydroxylation of chiral olefins, i.e. the influence of substrate chirality and the ligand induction, we synthesized the allylic alcohol **193**.

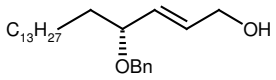


Scheme 28

According to literature, the factors affecting the Sharpless asymmetric dihydroxylation are following.

- Internal olefins give more diastereoselection than olefins.
- Electron withdrawing groups reduce the diastereoselectivity.
- Pro-chiral olefinic esters give more diastereoselectivity than pre-chiral ones.
- Pro-chiral allyl alcohols give more diastereoselectivity than olefinic esters.
- Protecting group on the hydroxy α- to olefin plays important role on the AD reaction.

Keeping above factors in mind, the starting material allylic alcohol **193** derived from mannitol diepoxide was found to be more suitable and appropriate for double diastereo differentiation in AD reaction. Thus the allylic alcohol **193** was envisaged as chiral building block from which D-*ribo*-C18-phytosphingosine and related analogs can be synthesized.

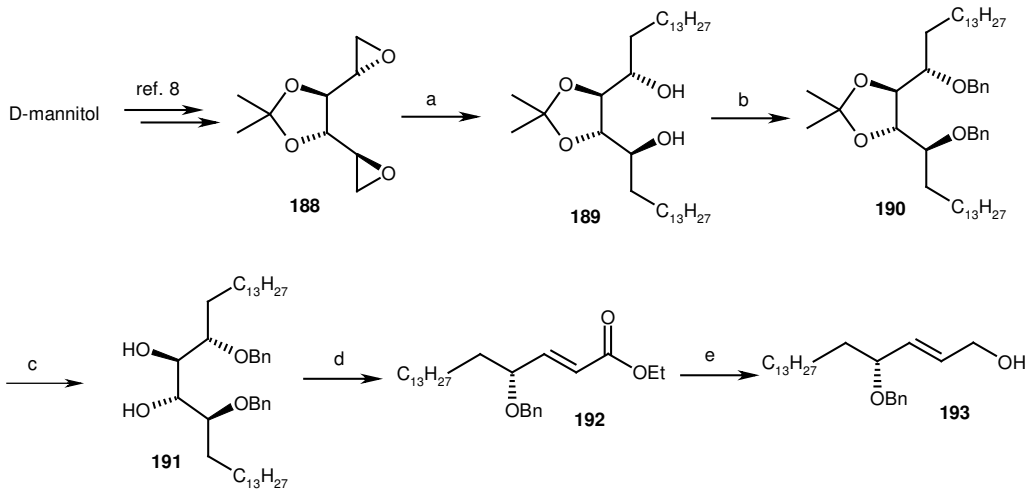


193

1.3.2. Results and Discussion

Sharpless asymmetric dihydroxylation was envisaged as a powerful tool to the chiral dihydroxy compounds offering considerable opportunity for synthetic manipulations. We developed a new and enantioselective synthesis of D-*ribo*-(2*S*,3*S*,4*R*)-C18-phytosphingosine from D-mannitol employing the Sharpless asymmetric dihydroxylation as a key step.

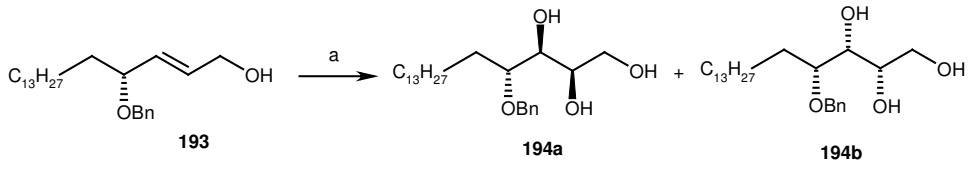
The chiral building block **193** was synthesized from D-mannitol. Thus, D-mannitol was first converted to diepoxide **188** following a literature procedure.[8] The opening of diepoxide **188** was carried out regioselectively using tridecylmagnesium bromide in the presence of CuI to afford compound **189** in 86% yield, $[\alpha]_D^{25}$ = +21.33 (*c* 0.36, $CHCl_3$). In the IR spectrum, hydroxyl absorption appeared at 3322 cm^{-1}. The ^1H NMR spectrum showed disappearance of epoxide peaks at δ 2.71 (dd, 2H), 2.81 (triplet, 2H) and presence of chiral protons at δ 3.55-3.76 (multiplet, 4H). Protection of hydroxyl groups in **189** with benzyl bromide furnished the corresponding 2,5-*O*-dibenzylated product **190** in essentially quantitative yield.



Scheme 29. *Reagents and conditions*: (a) *n*-$C_{13}H_{27}MgBr$, CuI, THF, 45 °C to rt, 1 h, (86%); (b) BnBr, NaH, *n*-Bu_4NI, THF, rt, 4 h, (95%); (c) *p*-TSA, MeOH, rt, 32 h, (90%); (d) (i) $NaIO_4$ adsorbed on silica gel, DCM, rt, 30 min (95%); (ii) $(EtO)_2P(O)CH_2COOEt$, LiBr, Et_3N, THF, rt, overnight, (89%); (e) DIBAL-H, Et_2O, 0 °C to rt, 2 h, (91%).

The IR spectrum of **190** indicated absence of hydroxyl groups. Subsequent deprotection of the isopropylidene group with a catalytic amount of *p*-TSA afforded compound **191** in excellent yield. The acetonide methyl protons at δ 1.43 (singlet) disappeared in the ^{1}H NMR spectrum and the typical quaternary carbon of acetonide appeared at δ 110.82 in the ^{13}C NMR spectrum. Oxidative cleavage of **191** with $NaIO_4$ adsorbed on silica gel gave the corresponding aldehyde in 95% yield, which was subsequently treated with $(EtO)_2P(O)CH_2COOEt$ under the Wittig–Horner reaction conditions to afford the α,β-unsaturated ester **192** in 89% yield. The IR spectrum of **192** gave carbonyl absorption at 1723 cm^{-1} and C=C stretching at 1656 cm^{-1}. The ^{1}H NMR spectrum gave olefin peaks at δ 6.05 (doublet) and 6.90 (doublet of doublet) with the coupling constant J = 16 Hz indicating *trans*-olefin.

In the asymmetric dihydroxylation of an olefin, the stereoselective outcome of the reaction is affected by the presence of pre-existing chiral information in the substrate. With a view to exploiting the concept of double diastereoselection, the olefinic ester **192** was subjected to the Sharpless asymmetric dihydroxylation (AD) conditions.[62] However, the reaction proceeded much more slowly with a poor diastereoselectivity probably as a consequence of the electron-withdrawing properties of the ester group.[62] While the Sharpless asymmetric dihydroxylation on the allylic alcohols with different long alkyl chains has been exploited to a large extent,[63] the reaction on allylic alcohols having chiral centers remains still unexplored. The enantioselectivity of an asymmetric dihydroxylation reaction can be modulated by the size of the allylic substituent and the configuration at the allylic position. Therefore, in order to explore the possibility of achieving a good diastereoselectivity, it was thought worthwhile to convert ester **192** into the allylic alcohol **193** for AD reaction. Thus, DIBAL-H reduction of ester **192** furnished the corresponding allyl alcohol **193** in 91% yield, which was then subjected to the Sharpless asymmetric dihydroxylation reaction (Scheme 30).



193 **194a** **194b**

Scheme 30. *Reagents and conditions*: (a) ligand, OsO4, $MeSO_2NH_2$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH:H_2O (1:1), 24 h, 0 °C (89–92%).

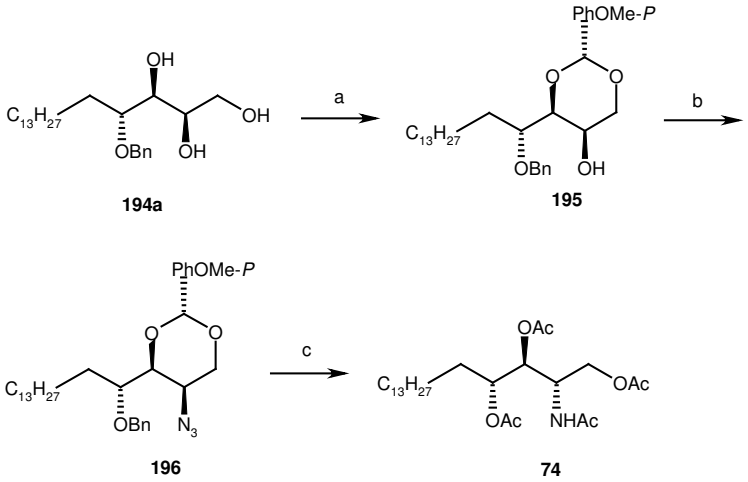
The IR spectrum of **193** gave hydroxyl absorption at 3440 cm^{-1} and the ester carbonyl group was absent. The results of double diastereoselection are given in Table 5.

Table 5.

Ligand	194a	194b	Yield %
$(DHQD)_2PHAL$	9	1	92
$(DHQ)_2PHAL$	1	2	89

The dihydroxylation of allyl alcohol **193** under the Sharpless asymmetric dihydroxylation conditions using $(DHQD)_2PHAL$ ligand afforded the diastereomeric mixture **194a**:**194b** in a 9:1 ratio. The stereochemical purity of **194a** was easily enriched to 90% by recrystallization twice from acetone. The compound **194a** was fully characterized by analytical and spectroscopic data. The use of $(DHQ)_2PHAL$ ligand under similar conditions gave a diastereomeric ratio **194a**:**194b** (1:2). In the IR spectrum, the olefin absorption was absent. The ^1H NMR spectrum showed chiral protons at δ 3.75–3.80 (multiplet, 2H). The high diastereoselectivity obtained in the former case could be regarded as a matched case where the chirality information of the reagent and the substrate probably act synergistically while the poor degree of diastereoselection observed in the latter case may be because of opposite influences of the chiral reagent and substrate (mismatched case). It should be mentioned here that the dihydroxylation of allylic alcohols and their derivatives using OsO_4 (stoichiometric or catalytic) and NMO is reported to give only poor to moderate diastereoselectivity.[64]

In order to achieve the synthesis of target compound **74** from **194a** (Scheme 31), we required the transformation of the hydroxy group into azide at the C-2 position. To this end protection of **194a** as *p*-methoxybenzylidene derivative was effected using 4-methoxybenzaldehyde dimethyl acetal in the presence of a catalytic amount of *p*-TSA to afford a mixture of 1,3- and 1,2-benzylidene compounds in a 19:1 ratio. The desired major 1,3-benzylidene compound **195** was separated by silica gel column chromatography. Compound **195** showed acetal proton at δ 5.92 (doublet) and *p*-methoxy protons at 3.91 (singlet) in the ^1H NMR spectrum.



Scheme 31. *Reagents and conditions*: (a) *p*-MeO-PhCH(OMe)$_2$, *p*-TSA, CH_2Cl_2, rt, overnight (70%); (b) (i) $MeSO_2Cl$, Et_3N, DMAP (Cat), CH_2Cl_2, rt, overnight; (ii) NaN_3, DMF, 80 °C, 24 h (81%); (c) (i) Pd/C, H_2, EtOH; (ii) Ac_2O, Py, DMAP, CH_2Cl_2, rt, 24 h (69%).

Compound **195** was then converted into an *O*-mesylated derivative, which on treatment with sodium azide in DMF furnished the azide **196** with the desired stereochemistry at C-2. Compound **196** showed absence of hydroxyl absorption in the IR spectrum and strong azide absorption at 2104 cm^{-1}. Deprotection of benzyl, cleavage of 1,3-benzylidene protecting group and reduction of azide to amine were carried in one-pot reaction by hydrogenation in the presence of 10% Pd/C in ethanol followed by acetylation to furnish **74** in 69% yield, $[\alpha]_D^{25}$: +29 (*c* 0.31, $CHCl_3$) [lit $[\alpha]_D^{23}$ +26.2 (*c* 0.1, $CHCl_3$)].[47] The IR spectrum of **74** gave amine absorption at 3297-3290 cm^{-1}, acetyl carbonyls at 1740 cm^{-1} and amide carbonyl at 1667 cm^{-1}. The ^{1}H NMR spectrum of **74** gave acetyl methyl protons at d 2.03 (singlet, one methyl), 2.05 (singlet, two methyl) and 2.08 (singlet, one methyl), the chiral protons at δ 4.46 (multiplet, one proton), 4.93-5.14 (multiplet, two potons) and the amide proton at δ 6.02 (doublet with *J* =10 Hz). The ^{13}C NMR spectrum gave the chiral carbons at δ 62.8, 71.9 and 72.9 and four carbonyl carbons at δ 169.7, 170.1, 170.8 and 171.2.

1.3.4. Conclusion

In summary, a highly enantioselective synthesis of D-*ribo*-C_{18}-phytosphingosine has been achieved from a readily available carbohydrate precursor by using the Sharpless asymmetric dihydroxylation procedure. The concept of double diastereoselection was employed for the first time on a chiral allylic alcohol in AD reaction. The merits of this synthesis are high

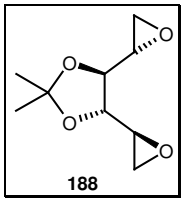
diastereoselectivity and high yielding reaction steps. The other isomer L-*lyxo*-C18-phytosphingosine can be synthesized from *S*-diepoxide using the chiral ligand $(DHQ)_2PHAL$ in the dihydroxylation step and following the reaction sequence shown above.

1.4. Experimental Section

1.4.1. General information

Solvents were purified and dried by standard procedures before use. Petroleum ether of boiling range 60-80°C was used. Melting points are uncorrected. Optical rotations were measured using sodium D line on a JASCO P-1020 microprocessor based polarimeter. Infrared spectra were recorded on ATI MATTSON RS-1 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AC-200 spectrometer. In the ^{13}C NMR data, peaks of only the major diastereomer (in case of a mixture) are given. Mass spectra were obtained with a TSQ 70, Finningen MAT mass spectrometer. Elemental analyses were carried out on a Carlo Erba CHNSO analyzer.

1,2:5,6-Dianhydro-3,4-*O*-isopropylidene-D-mannitol (188):



188

Yield: 4.82 g, 95%

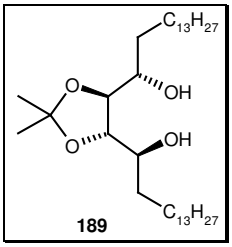
Mol. Formula: $C_9H_{14}O_4$

$[\alpha]_D^{25}$: -2.6 (*c* 0.90, $CHCl_3$); [lit.[8] $[\alpha]_D^{25}$: -2.3 (*c* 1.1, $CHCl_3$)]

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.41 (s, 6H), 2.71 (dd, *J* = 4.2, 2.0 Hz, 2H), 2.81 (t, *J* = 6.0 Hz, 2H), 3.04-3.06 (m, 2H), 3.82 (dd, *J* = 4.3, 1.9 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 26.6, 42.3, 51.4, 79.0, 110.4

Diol (189).



189

A round bottom flask was charged with copper(I)iodide (0.51 g, 2.68 mmol), gently heated under vaccum and slowly cooled with a flow of argon and THF (20 mL) was added. This

suspension was cooled to –45 °C, stirred and *n*-tridecylmagnesium bromide [prepared from Mg (0.522 g, 24.31 mmol and *n*-tridecyl bromide (7.069 g, 26.85 mmol) in THF] was added to it. A solution of epoxide **188** (1.0 g, 5.37 mmol) in THF (10 mL) was added to the above reagent and the mixture was stirred at –20 °C for 1 h. After consumption of starting material, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl. The water layer was extracted with EtOAc (3 x 100 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated. Purification of crude product by silica gel column chromatography using pet ether/EtOAc (9:1) as eluent afforded **189** as a colorless solid.

Yield: 2.56 g, 86%

Mol. Formula: $C_{35}H_{70}O_4$

M.P: 91-92 °C

$[\alpha]_D^{25}$: +21.33 (*c* 0.36, $CHCl_3$)

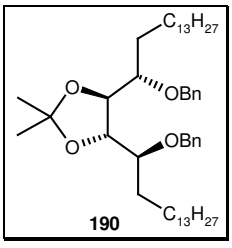
IR (neat, cm^{-1}): ν_{max} 3322, 3142, 2926, 1465, 1215, 669.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.1 Hz, 6H), 1.26 (br s, 48H), 1.43 (s, 6H), 1.65-1.88 (m, 4H), 2.41 (br s, 2H), 3.55-3.76 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.8, 23.8, 26.6, 29.6, 29.7, 29.8, 30.1, 30.4, 31.8, 32.3, 68.8, 81.6, 111.6.

Analysis: Calcd.: 75.75; H, 12.71%; **Found:** C, 75.87; H, 12.48%.

(4*S*,5*S*)-4,5-Bis((*S*)-1-(benzyloxy)pentadecyl)-2,2-dimethyl-1,3-dioxolane (190).



190

To a suspension of NaH (374 mg, 7.78 mmol) in dry THF (75 mL) was added diol **189** (1.8 g, 3.24 mmol) in THF (10 mL) under nitrogen atmosphere at 0 °C. After the mixture was stirred for 30 min at room temperature, benzyl bromide (1.33 g, 7.78 mmol) was added followed by TBAI at 0 °C. The reaction mixture was stirred for 5 h at room temperature and then quenched with saturated aqueous NH_4Cl solution (100 mL). The organic solvent was removed and the aqueous solution was extracted with EtOAc (3 x 100 mL). The organic layer was washed with brine, concentrated, dried (Na_2SO_4). The residual oil was purified by silica gel

column chromatography using petroleum ether/EtOAc (9.5:0.5) as eluent to furnish the dibenzyl protected alcohol **190** as colourless oil.

Yield: 2.27 g, 95%

Mol. Formula: $C_{49}H_{82}O_4$

$[\alpha]_D^{25}$: +8.77 (*c* 0.70, $CHCl_3$)

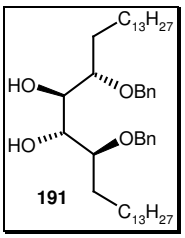
IR (neat, cm^{-1}): ν_{max} 3028, 2974, 2768, 1455, 1090, 1074, 751.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.1 Hz, 6H), 1.29 (br s, 48H), 1.43 (s, 6H), 1.55-1.71 (m, 4H), 3.54 (m, 2H), 4.09 (m, 2H), 4.60 (s, 4H), 7.32 (m, 10H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.8, 24.6, 25.1, 26.6, 29.1, 29.6, 29.7, 30.4, 31.9, 33.9, 73.1, 78.3, 79.7, 111.6, 127.5, 128.4, 128.7, 137.5.

Analysis: Calcd.: C, 80.05; H, 11.24%; **Found:** C, 80.34; H, 11.01%.

(15*S*,16*R*,17*R*,18*S*)-15,18-bis(benzyloxy)dotriacontane-16,17-diol (190).



To a stirred solution of compound **190** (2.5 g, 3.596 mmol) in MeOH was added catalytic amount of *p*-TSA at room temperature and reaction mixture was stirred for 32 h at the same temperature. The mixture was filtered through a filter paper and washed with MeOH to remove excess *p*-TSA, concentrated to give compound **191** as white solid.

Yield: 2.13 g, 90%

Mol. Formula: $C_{46}H_{78}O_4$

M.P: 63-64 ^oC

$[\alpha]_D^{25}$: –5.31 (*c* 0.64, $CHCl_3$)

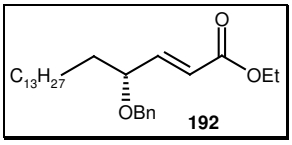
IR (neat, cm^{-1}): ν_{max} 3446, 3019, 2927, 2854, 1215, 669.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.1 Hz, 6H), 1.26 (br s, 48H), 1.65-1.72 (m, 4H), 2.41 (s, 2H), 2.68 (q, *J* = 4.0 Hz, 2H), 3.85 (m, 2H), 4.63 (s, 4H), 7.33 (m, 10H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1, 22.8, 24.6, 25.1, 26.7, 29.2, 29.6, 29.7, 30.4, 31.9, 33.9, 73.1, 73.2, 80.2, 127.6, 127.9, 128.7, 137.6.

Analysis: Calcd.: C, 79.48; H, 11.31%; **Found:** C, 79.65; H, 11.22%.

(*R*,*E*)-Ethyl 4-(benzyloxy)octadec-2-enoate (192).



To a vigorously stirred suspension of silica gel supported $NaIO_4$ reagent (7.22 g) in CH_2Cl_2 (50 mL) in 100 mL r.b flask was added a solution of vicinal diol (2.0 g, 2.88 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 30 min and filtered through a sintered funnel and washed with CH_2Cl_2 (4 x 50 mL) and concentrated to give the crude aldehyde, which was used without further purification.

To a nitrogen-flushed solution of LiBr (2.50 g, 28.81 mmol) in 50 mL of freshly distilled THF was injected $(EtO)_2P(O)CH_2CO_2Et$ (1.55 g, 6.91 mmol) at room temperature. After the solution was stirred at room temperature for 10 min, Et_3N (1.17 g, 1.60 mL, 11.52 mmol) of was injected, and stirring was continued for another 15 min. The solution of thoroughly dried above crude aldehyde (2.0 g, 5.76 mmol) prepared as above in 10 mL of dry THF was injected. A white precipitate was formed several minutes after the addition of the aldehyde. The reaction mixture was stirred vigorously at room temperature until the full consumption of the aldehyde was observed (TLC). The precipitate was removed by passing the reaction mixture through a pad of silica gel in a sintered glass funnel. The pad was washed with 400 mL of hexane/EtOAc 6:1 and concentrated. Silica gel column chromatography using petroleum ether/EtOAc (9.0:1) as eluent furnished the α,β-ester **192** as colourless oil.

Yield: 4.53 g, 95%

Mol. Formula: $C_{27}H_{44}O_3$

$[\alpha]_D^{25}$: +22.69 (*c* 0.84, $CHCl_3$)

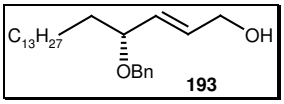
IR ($CHCl_3$, cm^{-1}): ν_{max} 2924, 2853, 1723, 1656, 1464, 1267, 1174, 1095.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.0 Hz, 3H), 1.26 (br s, 27H), 1.51-1.81 (m, 2H), 3.96 (dd, *J* = 8.0, 4.1 Hz, 1H), 4.25 (q, *J* = 12.1 Hz, 2H), 4.45 (d, J = 12 H, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 6.05 (d, *J* = 16.0 Hz, 1H), 6.90 (dd, *J* = 16.1, 6.0 Hz, 1H), 7.31-7.36 (m, 5H)

^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.6, 24.7, 25.1, 29.1, 29.1, 29.6, 30.5, 31.8, 33.8, 59.8, 70.3, 80.3, 127.2, 127.6, 128.6, 133.4, 134.3, 138.2, 171.4

Analysis: Calcd.: C, 77.83; H, 10.64%; **Found:** C, 78.11; H, 10.38%.

(*R*,*E*)-4-(Benzyloxy)octadec-2-en-1-ol (193).



193

To a solution of **192** (1.0 g, 2.40 mmol) in dry CH_2Cl_2 (80 mL) at 0 ^oC was added dropwise DIBAL-H (1.97 mL, 5.53 mmol, 2.8 M sol. in toluene) through a syringe. The reaction mixture was allowed to warm to room temperature over 2 h, then re-cooled to 0 ^oC and treated with saturated sodium/potassium tartrate. The solid material was filtered through a pad of celite and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (8:2) as eluent gave **193** as a colorless oil.

Yield: 819 mg, 91%

Mol. Formula: $C_{25}H_{42}O_2$

$[\alpha]_D^{25}$: +24.89 (*c* 0.54, $CHCl_3$).

IR (neat, cm^{-1}): 3372, 2924, 2853, 2450, 1464.

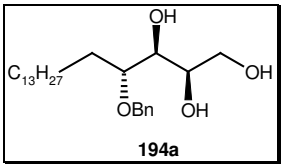
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.90 (t, *J* = 6 Hz, 3H), 1.27 (m, 24H), 1.81 (m, 2H), 3.80 (dd, *J* = 6, 8 Hz, 1H), 4.19 (d, *J* = 6 Hz, 2H), 4.35 (d, *J* = 10 Hz, 1H), 4.57 (d, *J* = 10 Hz, 1H), 5.44-5.68 (m, 1H), 5.81 (dt, *J* = 6, 16 Hz, 1H), 7.34 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 22.64, 25.1, 29.3, 29.66, 30.5, 31.90, 31.97, 35.6, 58.92, 63.1, 70.3, 127.36, 127.8, 128.31, 131.7, 132.61, 133.6, 138.12

MS (EI) *m*/*z* (%) 374 (M+).

Analysis: Calcd.: 80.15; H, 11.30%; **Found:** C, 79.95; H, 11.31%.

(2*R*,3*S*,4*R*)-4-(Benzyloxy)octadecane-1,2,3-triol (194a).



194a

To a mixture of $K_3Fe(CN)_6$ (4.75 g, 14.42 mmol), K_2CO_3 (1.99 g, 14.42 mmol) and $(DHQ)_2PHAL$ (24 mg, 1 mol%), in *t*-BuOH-H_2O (1:1, 50 mL) cooled at 0 ^oC was added OsO_4 (0.192 mL, 0.1 M sol in toluene, 0.4 mol%) followed by methane sulfonamide (253 m g, 4.81 mmol). After stirring for 5 min at 0 ^oC, the olefin **193** (1.8 g, 4.81 mmol) was added in one portion. The reaction mixture was stirred at 0 ^oC for 24 h and then quenched with solid sodium sulfite (10 g). The stirring was continued for 45 min and the solution was extracted

with EtOAc (3 x 50 mL). The combined organic phases were washed (10% KOH, then brine), dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (4:6) as eluent gave the diastereomeric mixture **194a**:**194b** in a 9:1 ratio. The stereochemical purity of **194a** was easily enriched to 90% by recrystallization twice from acetone.

Yield: 1.806 g, 92%

Mp = 77 °C

Mol. Formula: $C_{25}H_{44}O_4$

$[\alpha]_D^{25}$: −7.60 (*c* 0.86, $CHCl_3$).

IR (neat, cm^{-1}): 3422, 2926, 1458, 1370, 1215, 765, 668

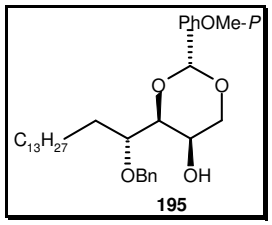
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6 Hz, 3H), 1.27–1.30 (m, 26H), 3.32 (br s, 3H), 3.65 (s, 2H), 3.75–3.80 (m, 2H), 3.95–4.10 (m, 1H), 4.62 (s, 2H), 7.34 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.03, 22.60, 25.17, 29.29, 29.62, 29.80, 30.57, 31.86, 64.88, 70.39, 72.67, 72.78, 81.98, 127.80, 127.85, 128.36, 138.18.

MS (EI) *m*/*z* (%) 408 (M+), 393 (M+ −15).

Analysis: Calcd.: C, 73.48; H, 10.85%; **Found:** C, 73.21; H, 10.52%.

(2*R*,4*S*,5*R*)-4-((*R*)-1-(Benzyloxy)pentadecyl)-2-(4-methoxyphenyl)-1,3-dioxan-5-ol (195).



195

To a solution of **194a** (850 mg, 2.09 mmol) in dry CH_2Cl_2 (30 mL) was added *p*-TsOH (60 mg) and *p*-methoxy benzaldehyde dimethylacetal (457 mg, 2.51 mmol). The reaction mixture was stirred at room temperature overnight. Subsequently it was neutralized with saturated aq. $NaHCO_3$ (10 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extracts were washed with aq. $NaHCO_3$, brine, dried (Na_2SO_4) and concentrated. Column chromatography over silica gel using petroleum ether:acetone (9.2:0.8) as eluent furnished **195**, the major product as a pale yellowish oil.

Yield: 770 mg, 70%

Mol. Formula: $C_{33}H_{50}O_5$

$[\alpha]_D^{25}$: +8.5 (*c* 1.1, $CHCl_3$).

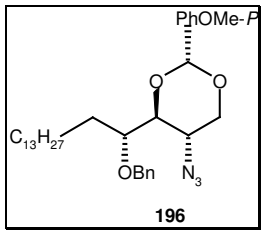
IR ($CHCl_3$, cm^{-1}): ν_{max} 3423, 2917, 2849, 1605, 1451, 1215, 1079, 1025, 699.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.4 Hz, 3H), 1.27 (br s, 24H), 1.53-1.72 (m, 2H), 2.48 (br s, 1H), 3.62-3.67 (m, 1H), 3.64-3.77 (m, 2H), 3.91 (s, 3H), 4.01-4.06 (m, 1H), 4.21-4.32 (m, 1H), 4.59-4.81 (m, 2H), 5.92 (d, *J* = 6.3 Hz, 1H), 6.90 (d, *J* = 8.6 Hz, 2H), 7.36-7.41 (m, 7H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1, 22.8, 24.1, 25.1, 29.3, 29.6, 29.7, 29.8, 30.6, 31.9, 55.9, 60.8, 71.1, 73.2, 77.7, 82.4, 101.9, 114.2, 127.6, 127.9, 128.5, 128.7, 129.6, 137.5, 159.9.

Analysis: Calcd.: C, 75.25; H, 9.57%; **Found:** C, 75.57; H, 9.23%.

(2*R*,4*R*,5*S*)-4-((*R*)-1-(Benzyloxy)pentadecyl)-5-azido-2-(4-methoxyphenyl)-1,3-dioxane (196).



196

To a solution of **195** (640 mg, 1.21 mmol) in dry CH_2Cl_2 (20 mL) at 0°C was added methanesulfonyl chloride (0.254 g, 2.18 mmol), Et_3N (0.5 mL) and DMAP (cat). The reaction mixture was stirred at room temperature overnight and then poured into Et_2O-H_2O mixture. The organic phase was separated and the aqueous phase extracted with Et_2O (3 x 20 mL). The combined organic phases were washed with water, brine, dried (Na_2SO_4) and concentrated to a yellow waxy solid, which was used as such in the next step.

To the solution of above mesylate in dry DMF (20 mL) was added sodium azide (157 mg, 2.42 mmol) and the reaction mixture stirred at 80 °C for 24 h. It was cooled and poured into water and extracted with ethyl acetate (4 x 20 mL). The organic extracts were washed with water, brine, dried (Na_2SO_4) and concentrated. Column chromatography on silica gel column using petroleum ether: ethyl acetate (9.5:0.5) as eluent gave **196** as a white solid.

Yield: 543 mg, 81%

Mol. Formula: $C_{33}H_{49}N_3O_4$

$[\alpha]_D^{25}$: –6.9 (*c* 0.36, $CHCl_3$)

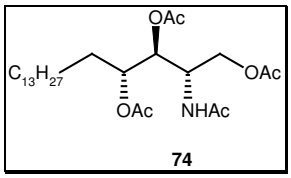
IR (neat, cm^{-1}): ν_{max} 2924, 2853, 2104, 1615, 1463, 1372, 1109, 1074, 1029, 745, 693.

^{1}H NMR (200 MHz, $CDCl_3$): δ δ 0.92 (t, *J* = 6.8 Hz, 3H), 1.30 (br s, 24H), 1.55-1.72 (m, 2H), 3.38-3.47 (m, 1H), 3.64-3.77 (m, 2H), 3.85 (s, 3H), 4.02-4.08 (m, 1H), 4.30-4.42 (m, 1H), 4.59-4.74 (m, 2H), 5.95 (d, *J* = 6.3 Hz, 1H), 7.07 (d, *J* = 8.8 Hz, 2H), 7.33-7.47 (m, 7H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 22.8, 24.2, 25.2, 29.3, 29.7, 29.8, 30.5, 31.8, 55.1, 68.2, 73.1, 78.8, 85.1, 101.6, 113.9, 127.5, 127.9, 128.5, 128.7, `29.7, 137.6, 159.8

Analysis: Calcd.: 75.75; H, 12.71; N, 7.62%; **Found:** C, 75.87; H, 12.48; N, 7.91%.

D-*ribo*-Phytosphingosine tetraacetate (74).



74

A mixture of compound **196** (98 mg, 0.178 mmol) and Pd–C 10% (0.1 g) in EtOH (10 mL) was stirred under a H_2 atmosphere at rt for 12 h. The mixture was filtered, concentrated. The resulting syrup was then subsequently acetylated with pyridine (5 mL), DMAP (cat) and Ac_2O (3 mL) in CH_2Cl_2 (5 mL). After stirring for 12 h at room temperature the reaction mixture was quenched with water (10 mL). The aqueous layer was extracted with EtOAc (4 x 20 mL). The combined organic extracts were washed (water and then brine), dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petrol ether:EtOAc (3:2) as eluent gave **74** as a waxy white solid.

Yield: 60 mg, 69%

Mol. Formula: $C_{35}H_{70}O_4$

M.P: 35-38 ^oC

$[\alpha]_D^{25}$: +29 (*c* 0.31, $CHCl_3$) [lit $[\alpha]_D^{23}$ +26.2 (*c* 0.1, $CHCl_3$)].

IR ($CHCl_3$, cm^{-1}): ν_{max} 3356, 3317, 3297-3290, 2926, 1740, 1667, 1239, 468.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.86 (t, *J* = 6.8 Hz, 3H), 1.26 (br s, 24H), 1.65-1.74 (m, 2H), 1.65 (m, 2H), 2.03 (s, 3H), 2.05 (s, 6H), 2.08 (s, 3H), 3.95-4.01 (m, 2H), 4.29 (m, 1H), 4.46 (m, 1H), 4.93-5.14 (m, 2H), 6.02 (d, *J* = 9.4 Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 20.6, 20.83, 22.6, 23.3, 25.5, 29.25, 29.47, 29.5, 30.5, 31.8, 62.8, 71.9, 72.8, 169.7, 170.1, 170.8, 171.2.

1.4.3. Spectra

1] ^{1}H NMR Spectrum of **188**

2] ^{13}C NMR Spectrum of **188**

3] ^{13}C NMR Spectrum of **189**

4] ^{1}H NMR Spectrum of **190**

5] ^{13}C NMR Spectrum of **192**

6] ^{1}H NMR Spectrum of **193**

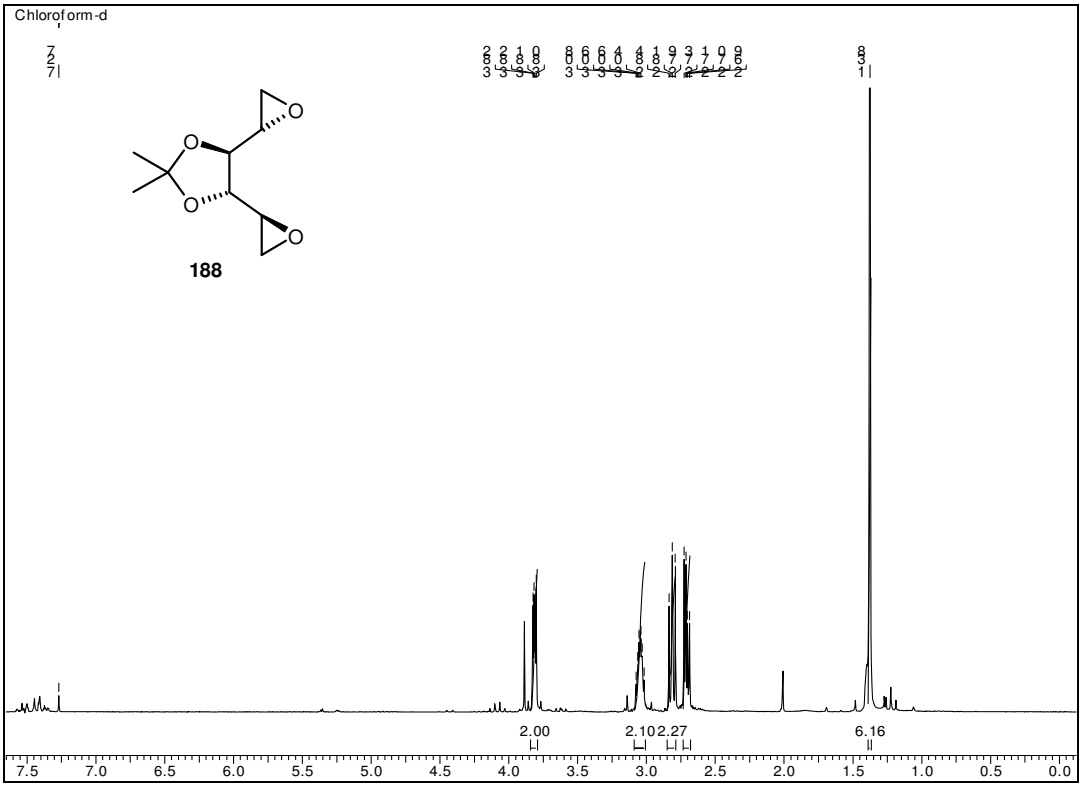
7] ^{13}C NMR Spectrum of **193**

8] ^{1}H NMR Spectrum of **194a**

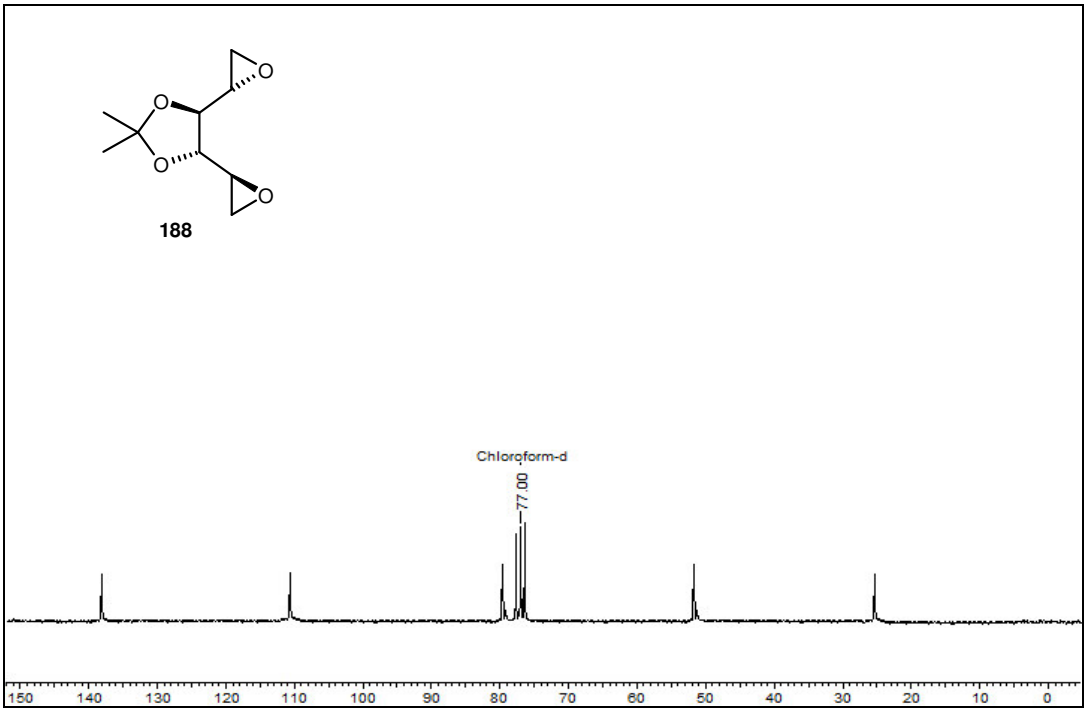
9] ^{13}C NMR Spectrum of **194a**

10] ^{1}H NMR Spectrum of **74**

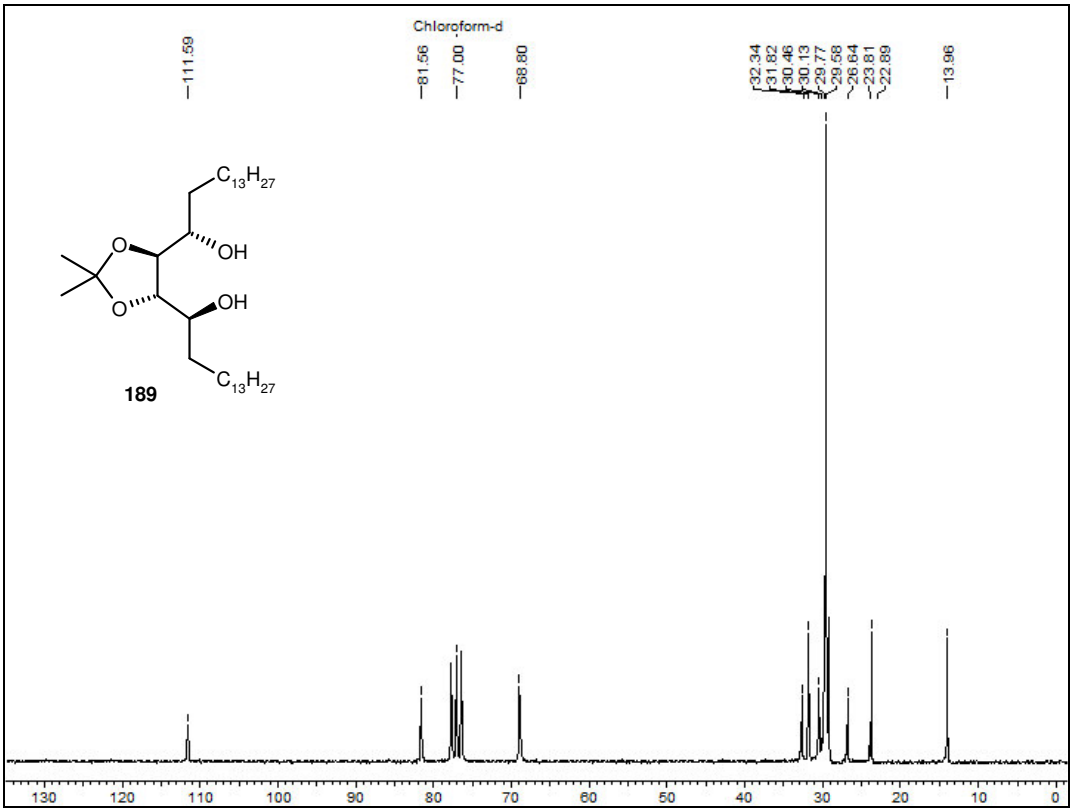
11] ^{13}C NMR Spectrum of **74**



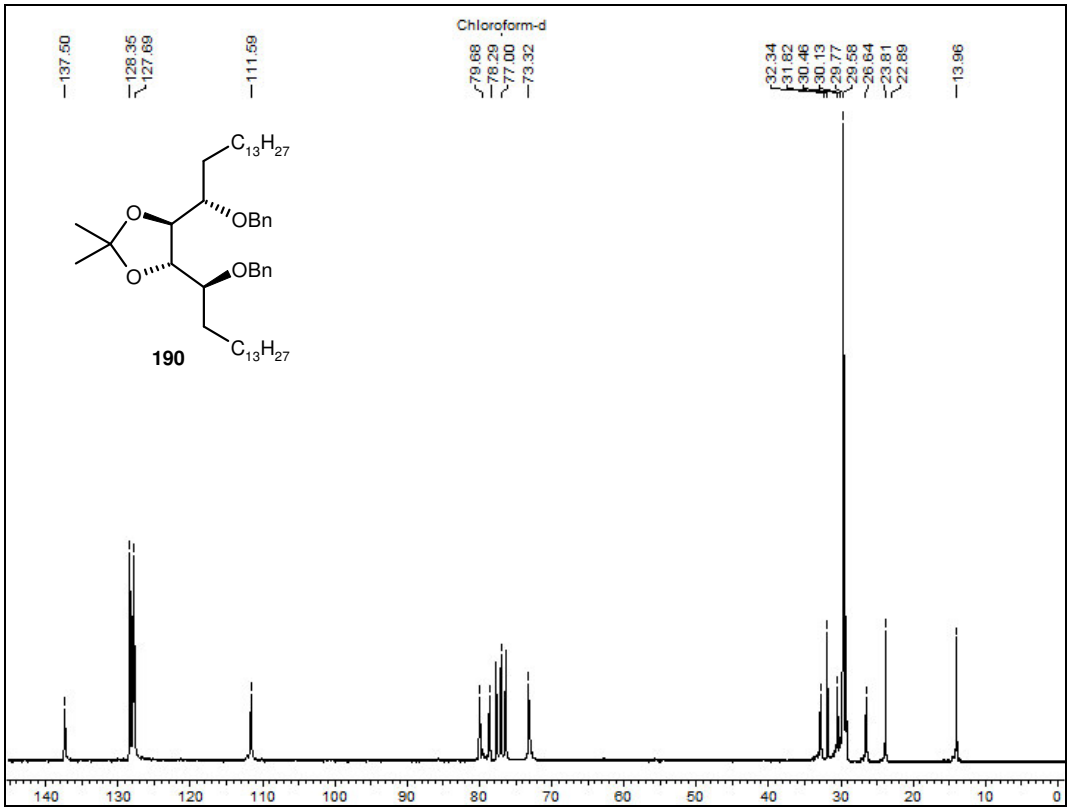
^{1}H NMR Spectrum of **188**



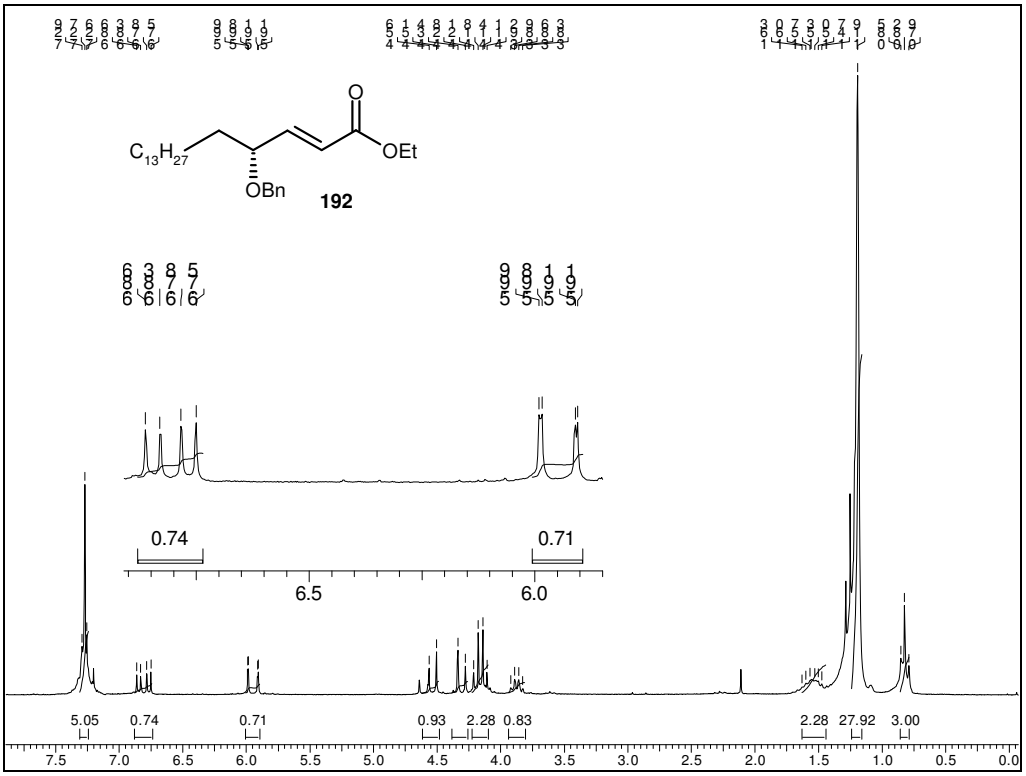
^{13}C NMR Spectrum of **188**



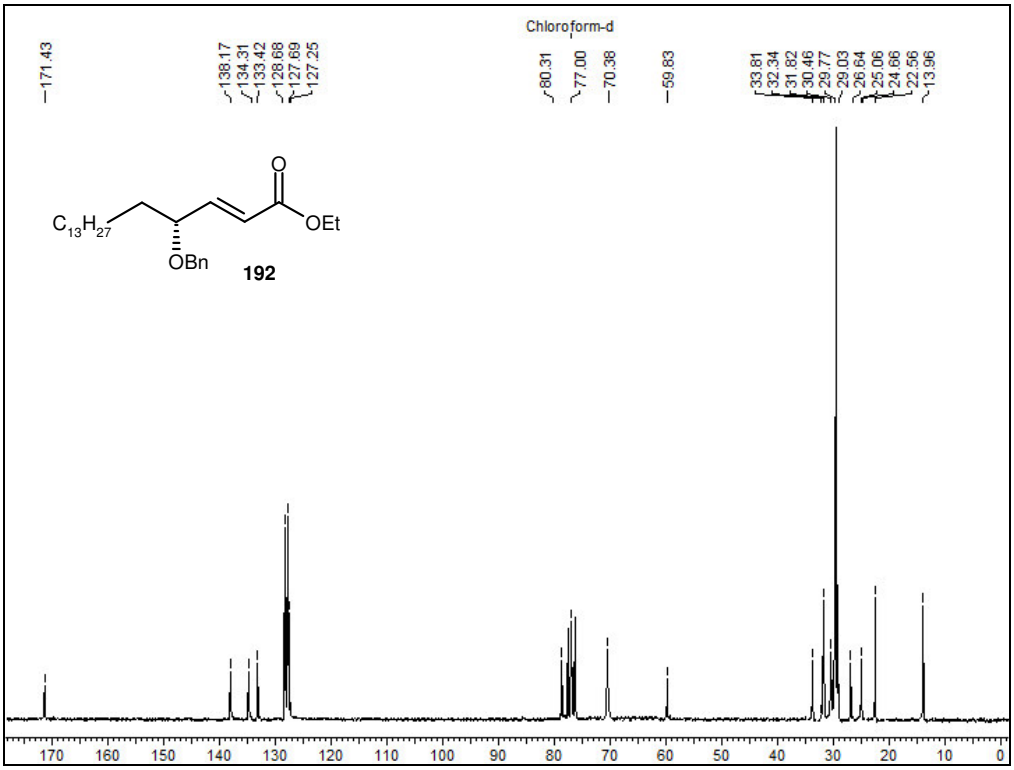
^{13}C NMR Spectrum of **189**



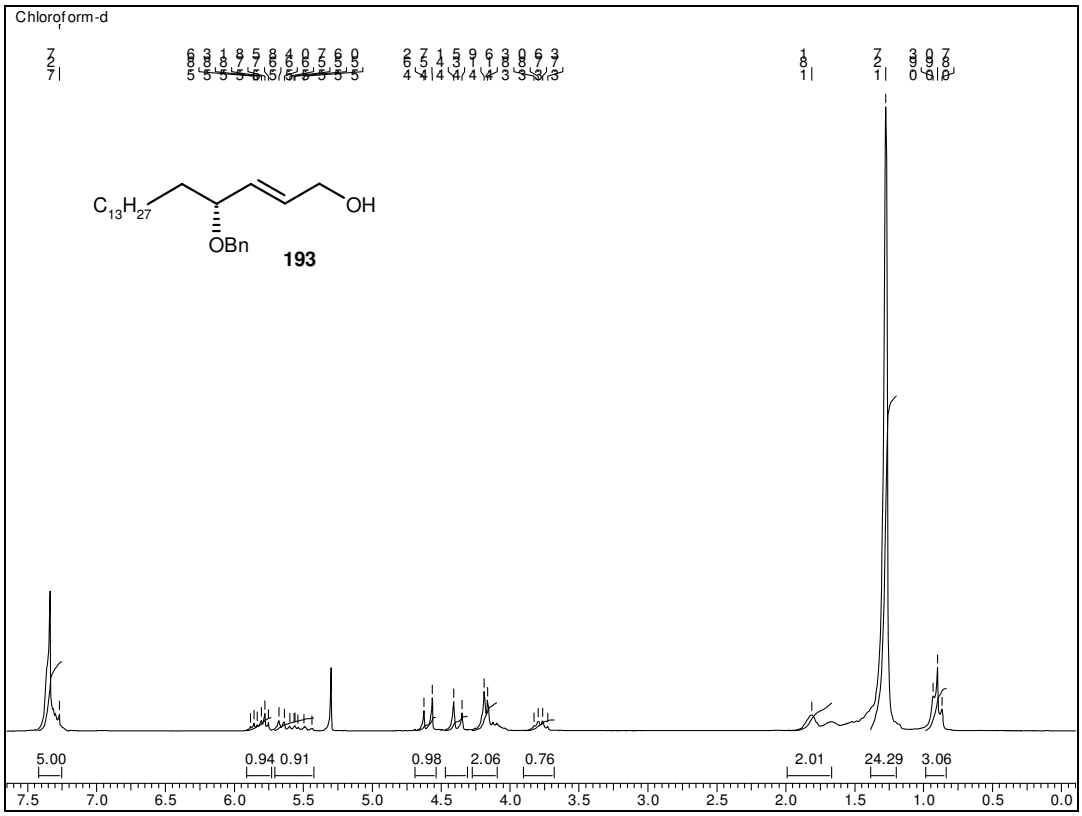
^{1}H NMR Spectrum of **190**



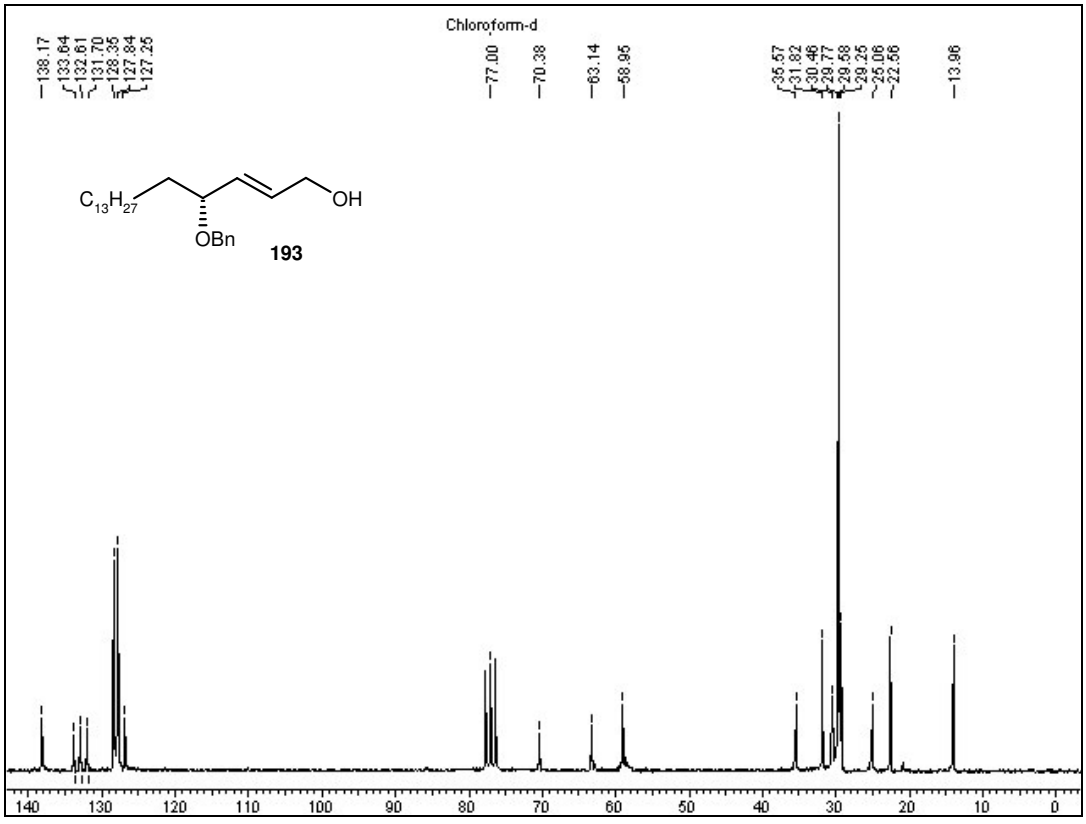
^{1}H NMR Spectrum of **192**



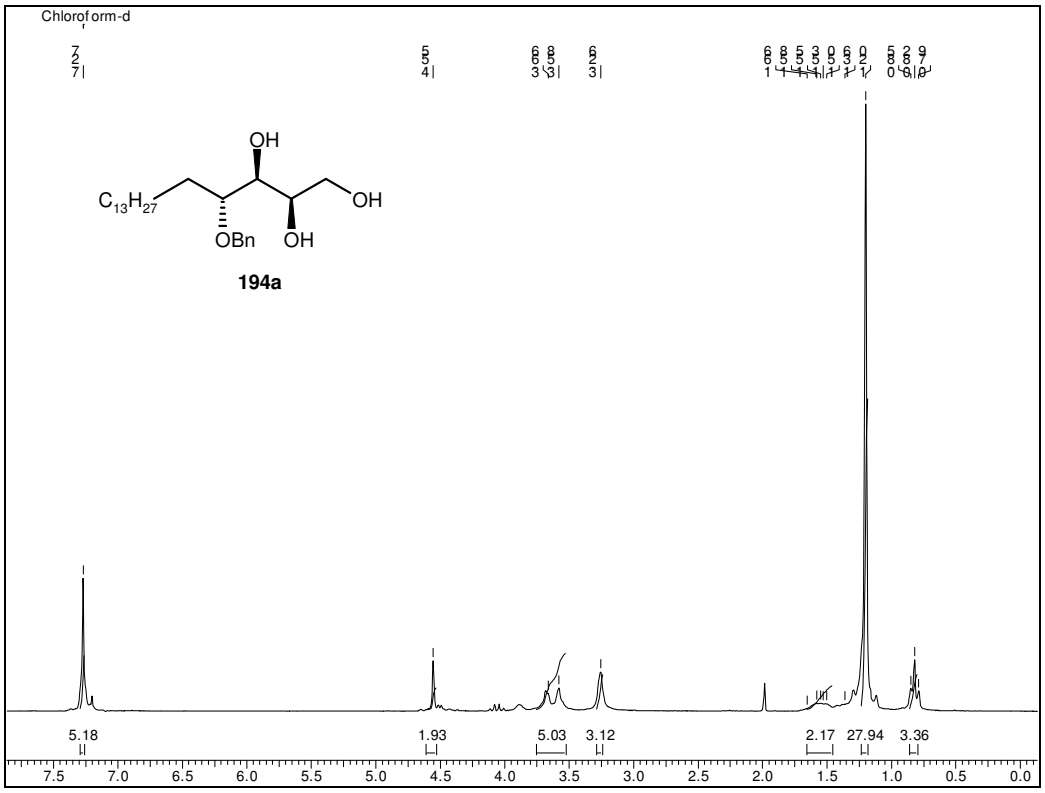
^{13}C NMR Spectrum of **192**



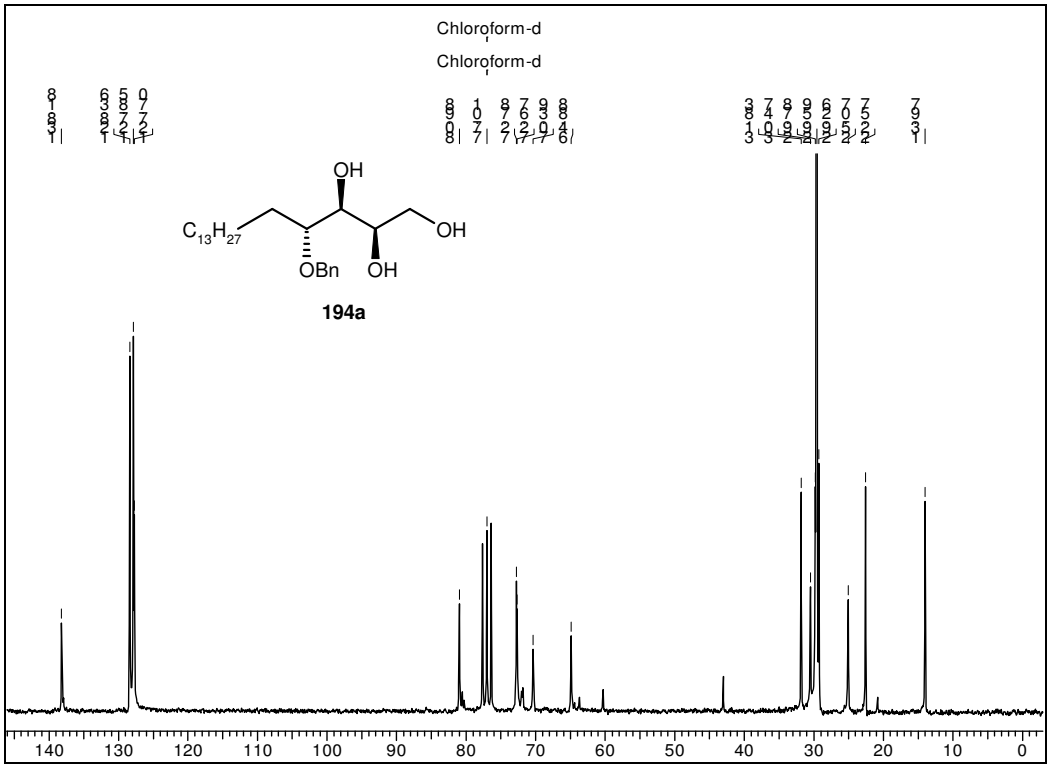
^{1}H NMR Spectrum of **193**



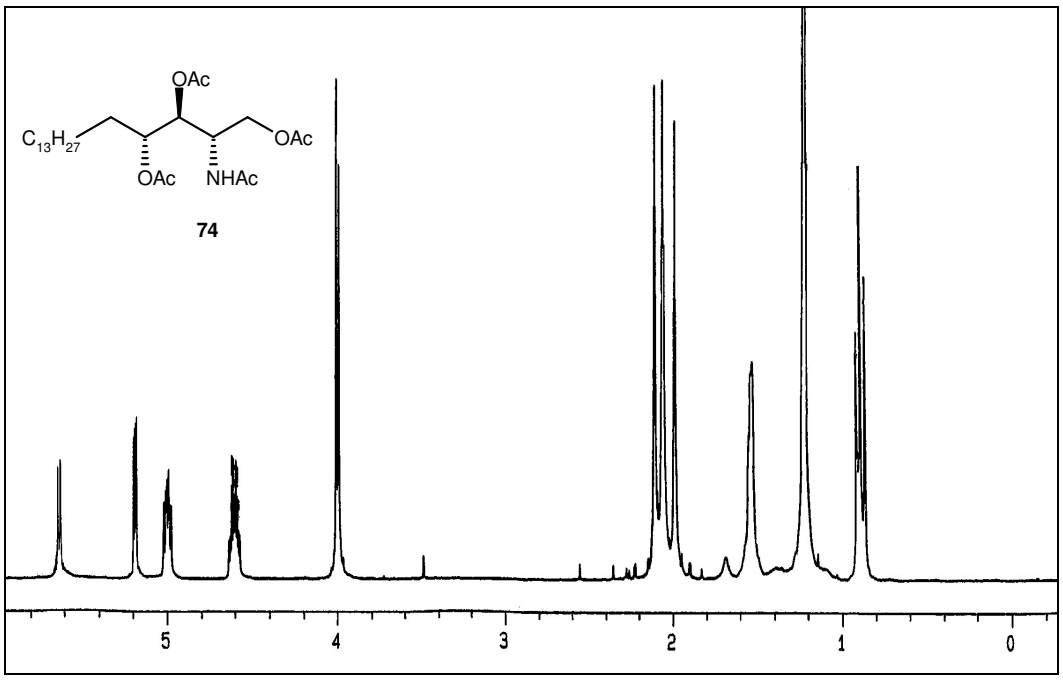
^{13}C NMR Spectrum of **193**



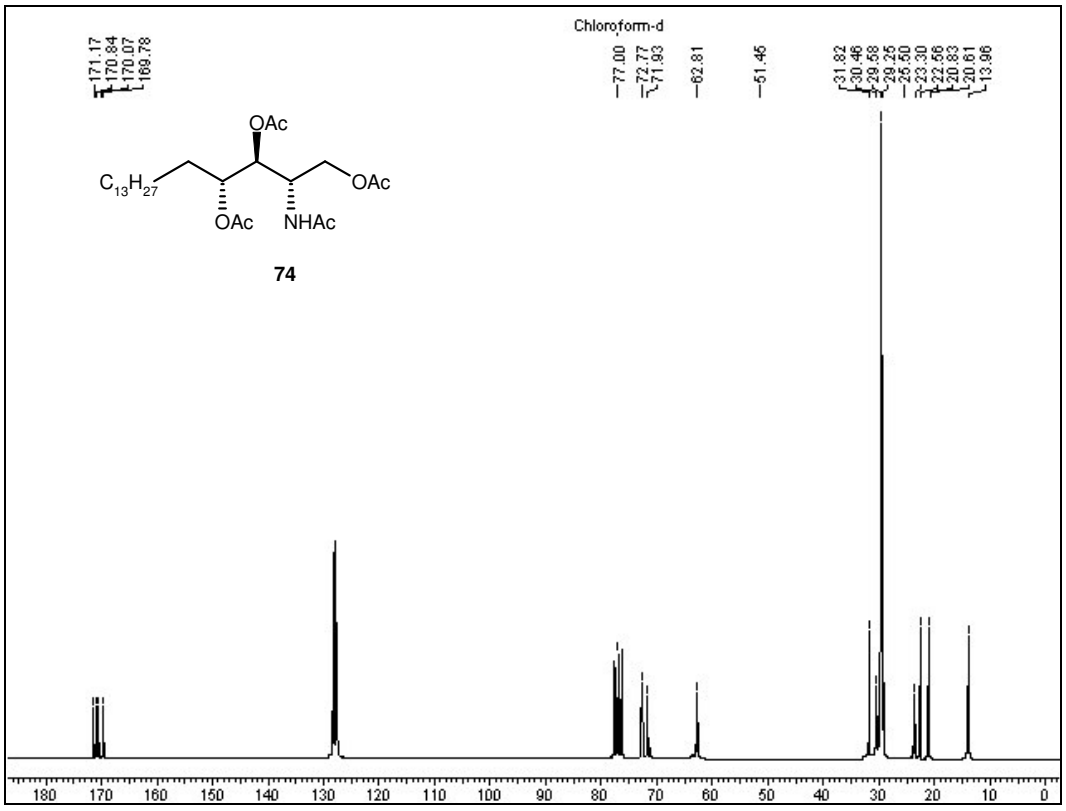
^{1}H NMR Spectrum of **194a**



^{1}H NMR Spectrum of **194a**



^{1}H NMR Spectrum of **74**



^{13}C NMR Spectrum of **74**

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CHAPTER -II

Enantio- and Diastereocontrolled Total Synthesis of (+)-Boronolide

2.1. INTRODUCTION

Many natural products with different biological activities such as insect growth inhibition, antitumor, antibacterial, antifungal or immunosuppressive properties, possess α,β-unsaturated δ-lactone moiety as an important structural feature. α,β-Unsaturated δ-lactone[1] functionality is presumed to be responsible for biological activities due to its ability to act as a Michael acceptor enabling these molecules to bind to a target enzyme. The pyrone units are widely distributed in all parts of plants (Lamiaceae, Piperaceae, Lauraceae, and Annonaceae families) including leaves, stems, flowers and fruits. α-Pyrones possessing polyhydroxy or polyacetoxy side chains have attracted much attention from synthetic and medicinal chemists due to their broad range of biological activities such as plant-growth inhibition, as well as antifeedant, antifungal, antibacterial, and antitumor properties.[2] Examples of such compounds include (+)-boronolide **1** and its deacetylated **1a** and dideacetylated derivative **1b** (Fig. 1). Boronolide **1** is an α,β-unsaturated C-12 lactone isolated from the leaves and branches of *Tetradenia*

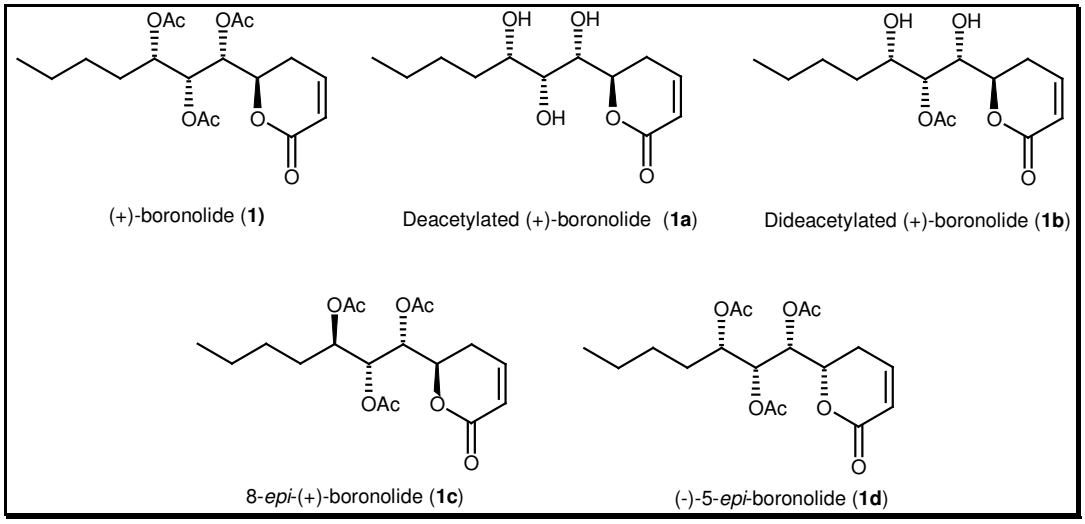


Figure 1. Structure of (+)-boronolide and its derivatives

fruticosa[3] and from the leaves of *Tetradenia barberae*,[4] which has been used as a local folk medicine in Madagascar and South Africa.[5] Deacetylated **1a** and dideacetylated boronolide **1b** have been obtained from *Tetradenia riparia*,[6] a Central African species typically employed by the Zulu as an emetic, which is an infusion of the leaf has also been reported to be effective against malaria. The relative stereochemistry of **1** was determined by X-ray analysis.[7] The *R*-

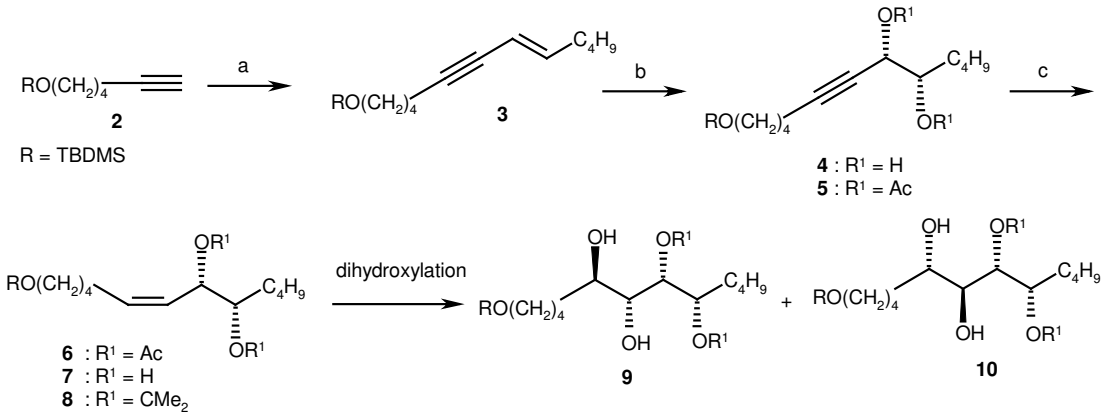
configuration at the C-6 position was proposed by application of Hudson's lactone rule to the molecular rotation. Later, the stereochemistry at the C-6 position was confirmed by chemical degradation.

2.2. Review of Literature

The first synthesis of **1** was reported from an acrolein derivative[8a] in racemic form. Most of the enantioselective syntheses known for boronolide derive the asymmetry from chiral pool starting materials such as glucose,[8b] mannitol,[8e,i] tartaric acid,[8d,j] D-glucono-δ-lactone[8j] and L-erythrulose[8f] etc. However synthetic approaches involving achiral substrate as starting material are rather scarce.[8c,h,k-l] A detailed report of these synthesis is described below.

Honda *et al.* (1996)[8c]

Honda and co-workers employed iterative Sharpless asymmetric dihydroxylation (AD) approach for the synthesis of boronolide. As shown in Scheme 1, 1,3-enyne **3**, prepared by Pd-catalyzed cross-coupling reaction of (*E*)-1-iodo-1-hexane with acetylene **2**, was subjected to the AD reaction using AD-mix-α to give the diol **4** with 94% ee. To achieve high diastereoselectivity for the second dihydroxylation, they prepared three substrates by protection of diol as acetate and isopropylidene followed by partial hydrogenation to give substrates **6**, **7** and **8**, which were subjected to second dihydroxylation under the conditions shown in Table 1. Finally, hydrolysis of TBDPS, oxidation, cyclisation, elimination and subsequent acetylation gave boronolide **1** (Scheme 2).

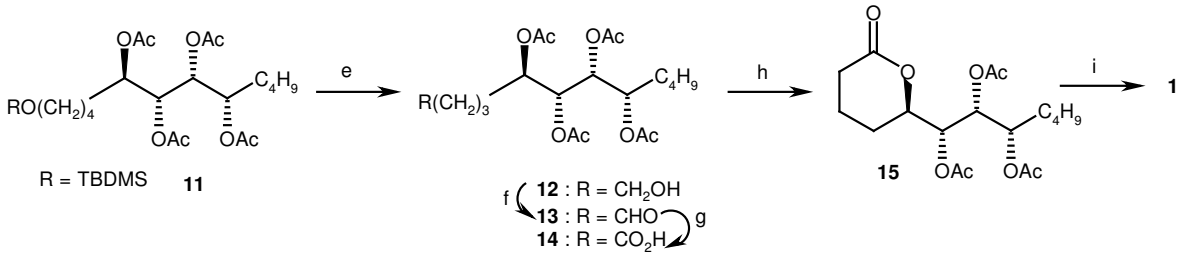


Scheme 1. *Reagents and conditions*: (a) (*E*)-1-iodo-1-hexene, $(Ph_3P)_2PdCl_2$, CuI, Et_2NH, rt (95%); (b) (i) AD-mix-α, $CH_3SO_2NH_2$, *t*-BuOH-H_2O, 0 °C (96%, 94% ee); (ii) Ac_2O, Py, rt (99%); (c) (i) Lindlar catalyst, H_2, AcOEt, rt (quant); (ii) K_2CO_3, MeOH, 0 °C to rt (99%);

(iii) PPTS, CH_2Cl_2, 2,2-dimethoxypropane, 0 °C to rt (86%); (d) [a]AD-mix reagent (14 g/mmol of substrate) was used in 50% aqueous *t*-BuOH (50 mL/mmol of substrate). [b]OsO_4 (35 mol %), 4-methylmorpholine *N*-oxide (NMO) (3 mol equiv) in 75% aqueous *t*-BuOH (30 mL/mmol of substrate). [c]Yield was that of the corresponding tetraacetate after treatment with acetic anhydride in pyridine.

Table 1. Dihydroxylation of (*Z*)-olefin.

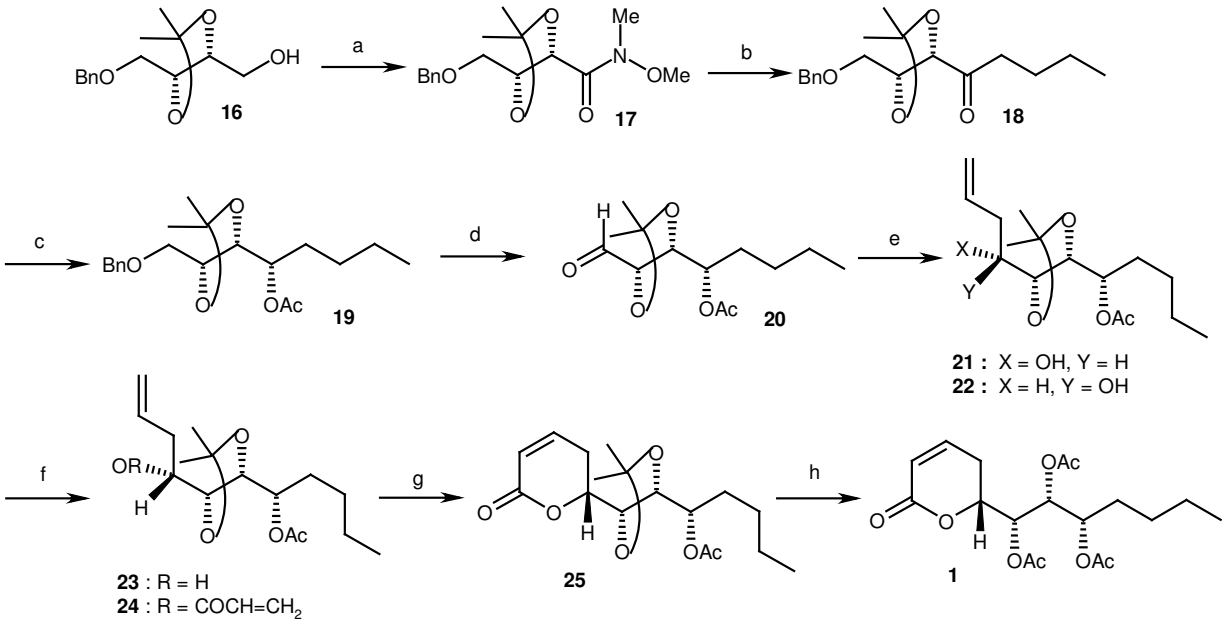
Entry	Substrate	Oxidant	Product (yield %)	
1	**7** (R^1 = H)	AD-mix-β[a]	**9A** (53)[c]	**10A** (25)[c]
2	**7** (R^1 = H)	AD-mix-α[a]	**9A** (27)[c]	**10A** (41)[c]
3	**7** (R^1 = H)	OsO_4-NMO[b]	**9A** (46)[c]	**10A** (45)[c]
4	**6** (R^1 = Ac)	OsO_4-NMO[b]	**9A** (46)[c]	**10A** (42)[c]
5	**6** (R^1 = $CNMe_2$)	OsO_4-NMO[b]	**9A** (19)	**10A** (74)



Scheme 2. *Reagents and conditions*: (e) AcOH-H_2O-THF (3:1:1), rt (97%); (f) PCC, AcONa, rt (76%); (g) $NaClO_2$, 2-methyl-2-butene, *t*-BuOH-H_2O, rt (95%); (h) NaOMe, MeOH, rt, then 2N HCl; *p*-TsOH, benzene-THF, reflux; Ac_2O, Py, rt (79%); (i) $[PhSe(O)]_2O$, chlorobenzene, reflux (63%).

Ghosh *et al.* (2000)[8d]

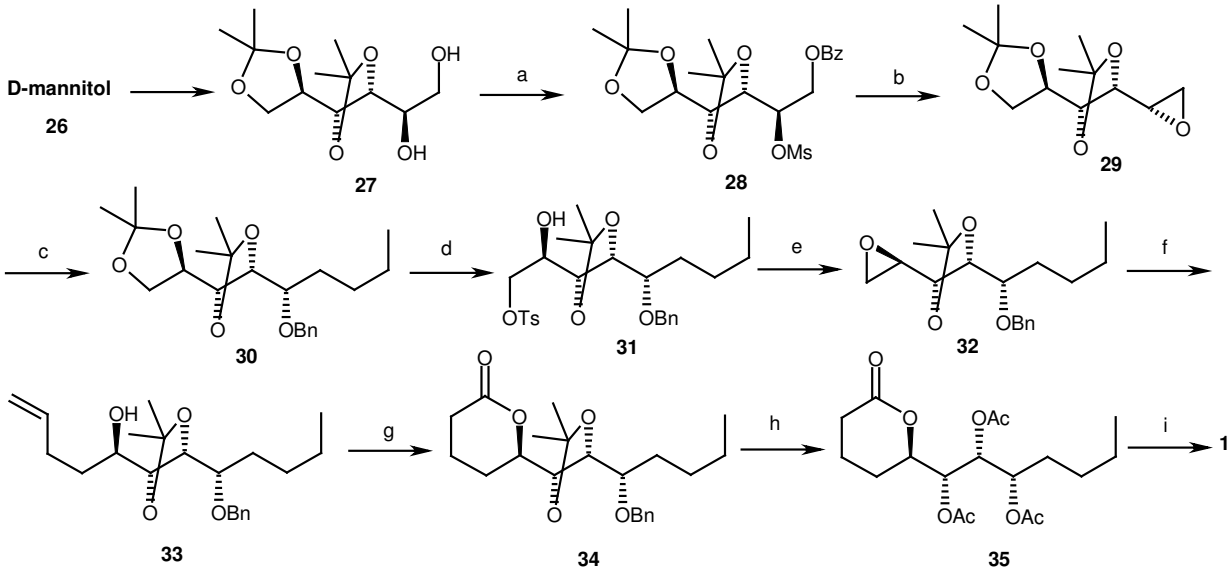
Ghosh and co-workers employed 1-*O*-benzyl-2,3-*O*-isopropylidene-D-threitol **16** as the starting material which can be easily prepared from tartaric acid. Isopropylidene derivative **16** was converted into the Weinreb amide **17**, which was further treated with butylmagnesium bromide to afford the ketone **18**. Reduction of ketone **18** with L-selectride followed by acetyl protection provided the acetate derivative **19**. Benzyl deprotection and subsequent oxidation followed by allylation with diallyl zinc furnished the homoallylic alcohol **21**. α,β-Unsaturated-δ-lactone **25** was constructed by RCM of the acrylated derivative of **24**, which was subsequently converted into the target molecule **1**.



Scheme 3. *Reagents and conditions*: (a) (i) CrO_3, H_2SO_4, Me_2CO–H_2O, 0°C, 68%; (ii) Me_2CHCH_2OCOCl, *N*-methylpiperidine, CH_2Cl_2–THF (10:1); (MeO)NHMe**.**HCl, *N*-methylpiperidine, CH_2Cl_2, 83%; (b) $CH_3(CH_2)_3MgBr$, THF, -20 °C, 96%; (c) (i) L-selectride, THF, -78 °C, 99%; (ii) Ac_2O, Et_3N, DMAP (cat), CH_2Cl_2, 98%; (d) (i) H_2, $Pd(OH)_2$ (cat), EtOAc–MeOH (4:1), quant.; (ii) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78 °C; (e) allylmagnesium bromide, $ZnCl_2$, THF, -78 °C; (f) CH_2=CHCOCl, Et_3N, 0 ^oC to 23 ^oC, CH_2Cl_2, 80%; (g) $PhCH=RuCl_2(ChX_3P)_2$, (10 mol%), $Ti(OiPr)_4$ (30 mol%), CH_2Cl_2, 40 ^oC, (84%); (h) (i) Dowex 50 W-X8 (H^+), H_2O, 70 ^oC; (ii) Ac_2O, Et_3N, DMAP (cat), CH_2Cl_2, 0 ^oC, quant.

Singh *et al.* (2000)[8e]

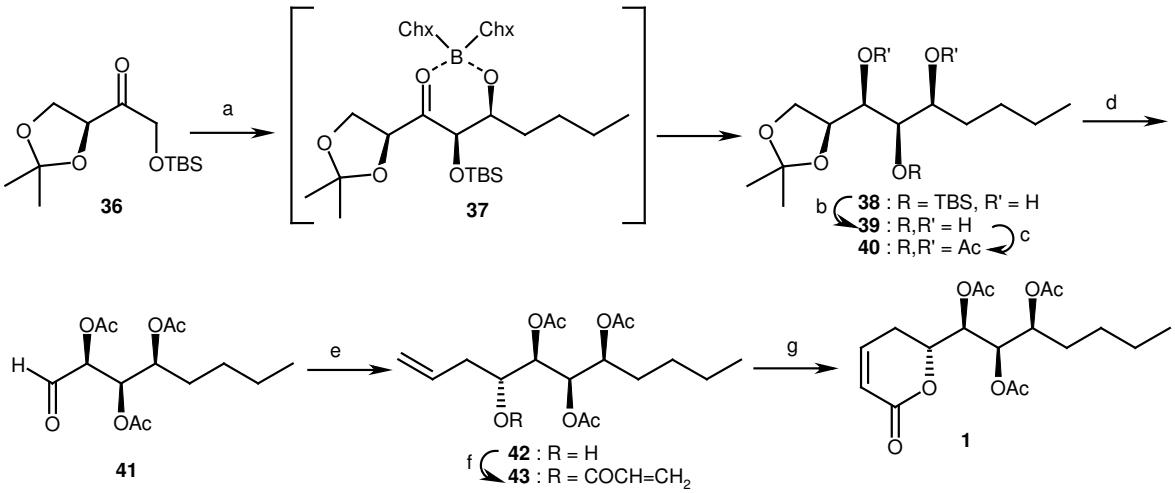
Singh and co-workers synthesized (+)-boronolide using D-mannitol **26** as starting material. 1,2,3,4-*O*-Diisopropylidene-D-mannitol was converted into epoxide **29** with inverted stereochemistry by selective hydroxyl protection followed by mesylation of secondary hydroxyl group of **28** and saponification with K_2CO_3. Ring opening of the epoxide **29** with *n*-propylmagnesium bromide followed by hydroxyl protection with BnBr provided **30**. The other acetonide was converted into epoxide **32** with retention of configuration and opened with allylcuprate followed by hydroboration and oxidation to provide **33**, which was lactonized and converted into the target molecule **1** by known methods.[8a-c]



Scheme 4. *Reagents and conditions*: (a) (i) PhCOCl, Py, DCM, -80 to -20 ^{o}C, 4 h (83%); (ii) $MeSO_2Cl$, Et_3N, DCM, -80 to -20 ^{o}C, 12 h (95%); (b) K_2CO_3, MeOH, rt, 2 h (85%); (c) (i) *n*-PrLi, CuCN, THF, -80 ^{o}C, 12 h (95%); (ii) $PhCH_2Br$, NaH, THF, rt, 16 h (90%); (d) (i) $CuCl_2.2H_2O$, MeOH, 0 ^{o}C, 40 min (80%); (ii) TsCl, Py, DMAP (cat.), 0 ^{o}C, 14 h (65%); (e) K_2CO_3, MeOH, 0 ^{o}C, 1 h (90%); (f) Allyl magnesium bromide, CuBr.DMS, -80 ^{o}C, 8 h (80%); (g) (i) BH_3.DMS, 0 ^{o}C, 12 h, PhH followed by 30% aq. H_2O_2, NaOH, EtOH, 0 ^{o}C (75%); (ii) $AgCO_3$ on Celite, PhH, reflux, 12 h (75%); (h) (i) $CuCl_2.2H_2O$, MeCN, rt, 36 h (80%); (ii) H_2, 10% Pd/C, EtOH, rt, 24 h (95%); (iii) Ac_2O, Py, rt, (i) Ref. 8a-c

Carda *et al*. (2002)[8f,g]

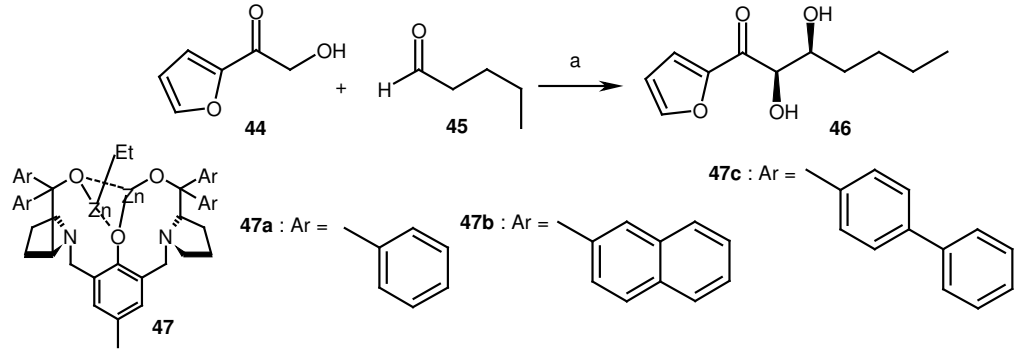
Carda and co-workers employed ketone **36**, a functionalized d^3 (homoenolate) synthon as a starting material which can be prepared from L-erythrulose. Thus, enolization of **36** with ChX_2BCl/Et_3N (Chx = cyclohexyl) followed by addition of pentanal generated a boran aldolate intermediate **37**, which was reduced in situ with $LiBH_4$ to give all-*syn* acetonide **38** as a single stereoisomer. Protection of hydroxyl groups with Ac_2O followed by oxidative cleavage of acetonide moiety of **40** and allylation of the resulting aldehyde **41** in the presence of indium metal afforded the homoallylic alcohol **42** with 91:9 diastereomeric ratio. Esterification followed by ring-closing metathesis and deprotection provided the target molecule **1**.



Scheme 5. *Reagents and conditions*: (i) Chx_2BCl, Et_3N, $CH_3(CH_2)_3CHO$, Et_2O, from -78 to 0 °C, 5 h, then $LiBH_4$, 2 h (83%); (ii) TBAF, THF, 15 min (96%); (iii) Ac_2O, Et_3N, cat. DMAP, CH_2Cl_2, rt, 12 h (90%); (iv) H_5IO_6, AcOEt, rt, 1 h (85%); (v) allyl bromide, In powder, THF/H_2O (1:1), rt, 18 h; (vi) acryloyl chloride, Et_3N, cat. DMAP, CH_2Cl_2, rt, 12 h (50% overall of two steps); (vii) $PhCH{=}RuCl_2(Chx_3P)_2$, $Ti(OiPr)_4$, CH_2Cl_2, reflux, 24 h (71%).

Trost *et al.* (2002)[8h]

Trost and co-workers synthesized **46** stereoselectively from hydroxyacetylfuran **44** and valeraldehyde **45** using a novel dizinc aldol catalyst **47**. Aldol reaction of **44** and **45** gave the *syn*-diol **46**, which was protected as its corresponding acetonide followed by reduction of ketone under Felkin-Anh control using L-selectride[9] to furnish the alcohol with excellent diastereoselectivity (98:2).



Scheme 6. Asymmetric Aldol

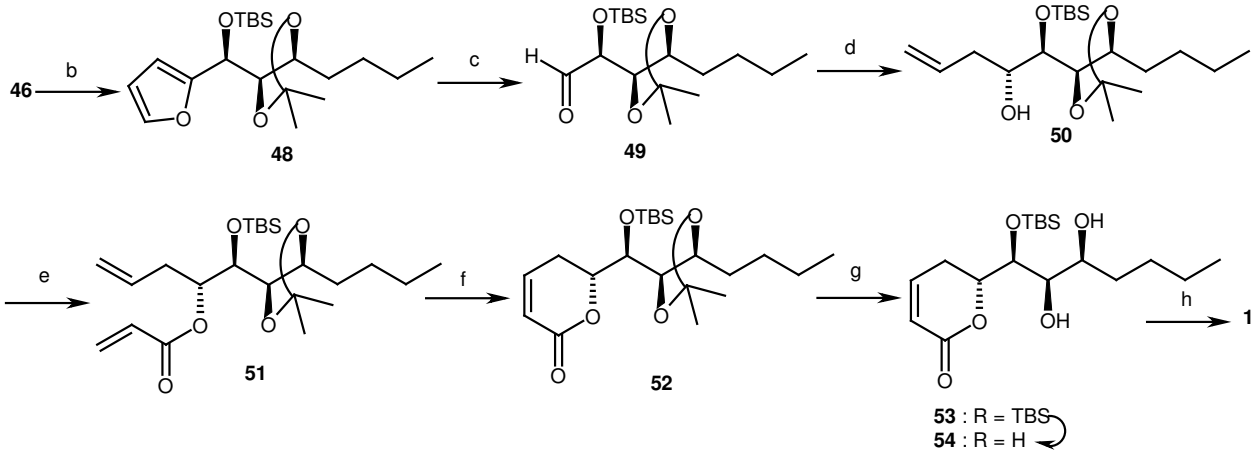
Protection of secondary alcohol as its TBS ether **48** followed by oxidative cleavage of furan, esterification and reduction furnished the aldehyde **49**. Brown's chiral allylboration[10] (8:1 dr)

of aldehyde followed by esterification, ring-closing metathesis[11] and deprotection led to target molecule **1**.

Table 1. Optimization of the Aldol Reaction[a]

Entry	ligand	isolated yields *ee* syn/anti	dr[b]	*syn/anti*[c]
1[d]	**47a**	56/14	4.3:1	97/84
2	**47a**	78/16	4.6:1	97/84
3	**47a**[e]	58/13	3.5:1	95/81
4	**47b**	77/15	4:1	93/83
5	**47c**	78/12	6:1	97/86
6[f]	**47a**	76/17	4.2:1	96/83

[a]All reactions were carried out on 2 mmol scale using 5 mol % catalyst, 1.1 equiv of ketone and 100 mg of 4 Å molecular sieves in 0.33 M of THF solution at -35 °C for 12 h unless noted otherwise. [b]Determined by NMR of the crude reaction isolate. [c]Determined by chiral HPLC using Chirapak AD column; [d]This reaction was run for 4 h. [e]2.5 mol % catalyst was used. [f]This reaction was done on a 16 mmol scale of valeraldehyde **45**.

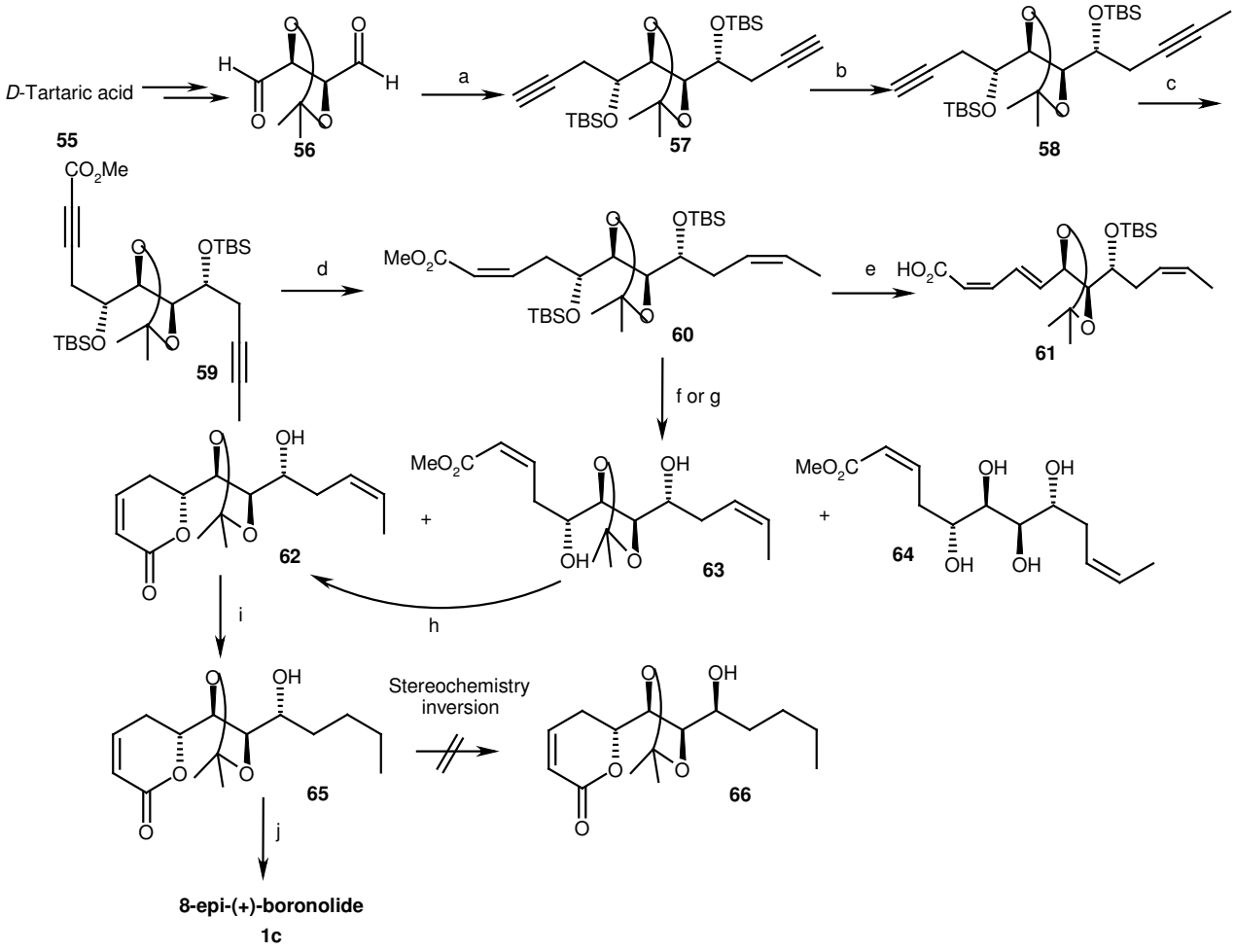


Scheme 7. *Reagents and conditions*: (b) (i) DMP, Amberlyst 15, CH_2Cl_2, rt, 98%; (ii) L-selectride, THF, -100 °C; H_2O_2, NaOH, 89%, dr 98:2; (iii) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 98%; (c) (i) $RuCl_3$ (cat.), $NaIO_4$, CCl_4, CH_3CN, H_2O, CH_2N_2, Et_2O, 70%; (ii) $LiBH_4$, Et_2O, MeOH, 0 °C, 98%; (iii) Dess-Martin periodinane, CH_2Cl_2, rt, 100%; (d) (+)-$(Ipc)_2$B-allyl, Et_2O, 100 °C; H_2O_2, NaOH, 85%, dr 8:1; (e) acryloyl chloride, *i*-Pr_2NEt, CH_2Cl_2, 0 °C,

89%; (f) 2 mol % Grubbs' cat., CH_2Cl_2, 40 ^oC, 92%; (g) aq HF, CH_3CN, 65%; (h) Ac_2O, DMAP, *i*-Pr_2NEt, CH_2Cl_2, 0 ^oC, 86%.

Wu *et al.* (2004)[8j]

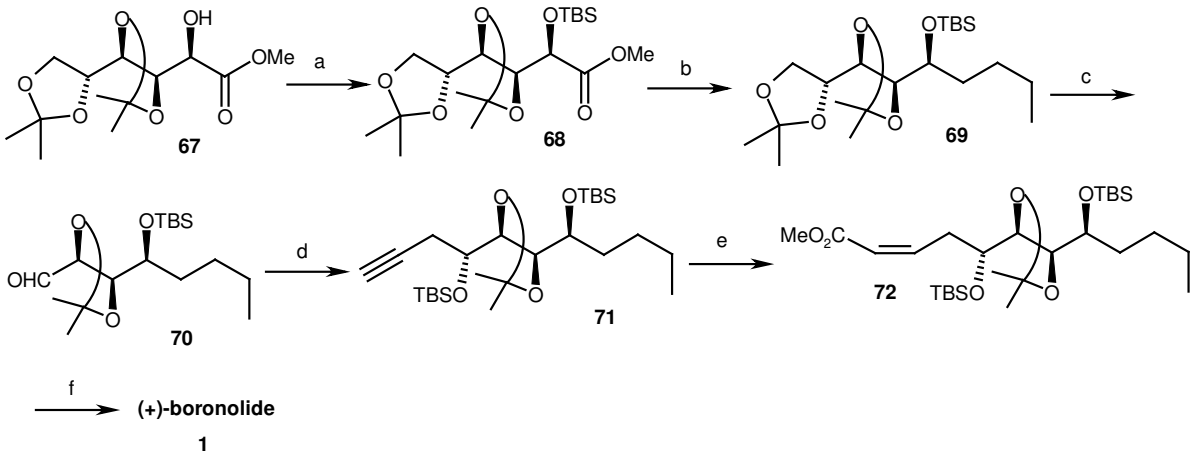
Wu and co-workers synthesized 8-epi-(+)-boronolide **1c** and (+)-boronolide **1**, starting form readily available carbohydrates such as D-tartaric acid **55** and D-glucano-δ-lactone derivative **67** respectively.



Scheme 8. *Reagents and conditions*: (a) (i) Propargyl bromide, Zn powder, DMF–Et_2O. (ii) TBSCl, DMF, imidazole. DMAP, rt, 44% for three steps. (iii) BuLi (1.15 eq, 1.6 M in hexane), CH_3I, THF, −78 °C to rt, 83%. (c) *n*-BuLi (1.5 eq, 1.6 M in hexane), $ClCO_2Me$, THF, −78 °C to rt, 81.3%. (d) H_2, Lindlar's cat., quinoline, ethyl acetate, 50–60 °C, 91%, (e) TBAF, THF, 72%, (f) HF (40%)–acetonitrile (16 : 1), **62**: 21%, **63**: 37%, **64**: 32%. (g) NH_4F, MeOH, 60 °C, 2 days, **62**: 70%; **63**: 24%, (h) PPTS (cat.) or *p*-TSOH (cat.), toluene, 50–60

°C, 88%, (i) H_2, $(Ph_3P)RhCl$, benzene–EtOH (6 : 1), rt, 86%, (j) $CuCl_2 \cdot 2H_2O$, MeCN–MeOH (6 : 1), rt to 50 °C. (ii) Ac_2O, Py, DMAP, CH_2Cl_2, 77% for two steps.

Dialdehyde **56** prepared from diethyl (2*S*,3*S*)-2,3-*O*-isopropylidenetartrate[13] was subjected to two-directional propargylation[12] with propargylzinc bromide followed by TBS protection to give **57**, which was desymmetrised by selective methylation followed by methoxycarbonylation to furnish the intermediate **59**. Partial hydrogenation of **59** with Lindlar catalyst afforded *cis*,*cis*-diene **60**. TBS deprotection-ring closing with NH_4F followed by regioselective hydrogenation with Wilkinson's catalyst and global deprotection furnished 8-*epi*-(+)-boronolide **1c** (Scheme 8). (+)-boronolide was synthesized from D-glucano-δ-lactone derivative **67** as described in Scheme 9.

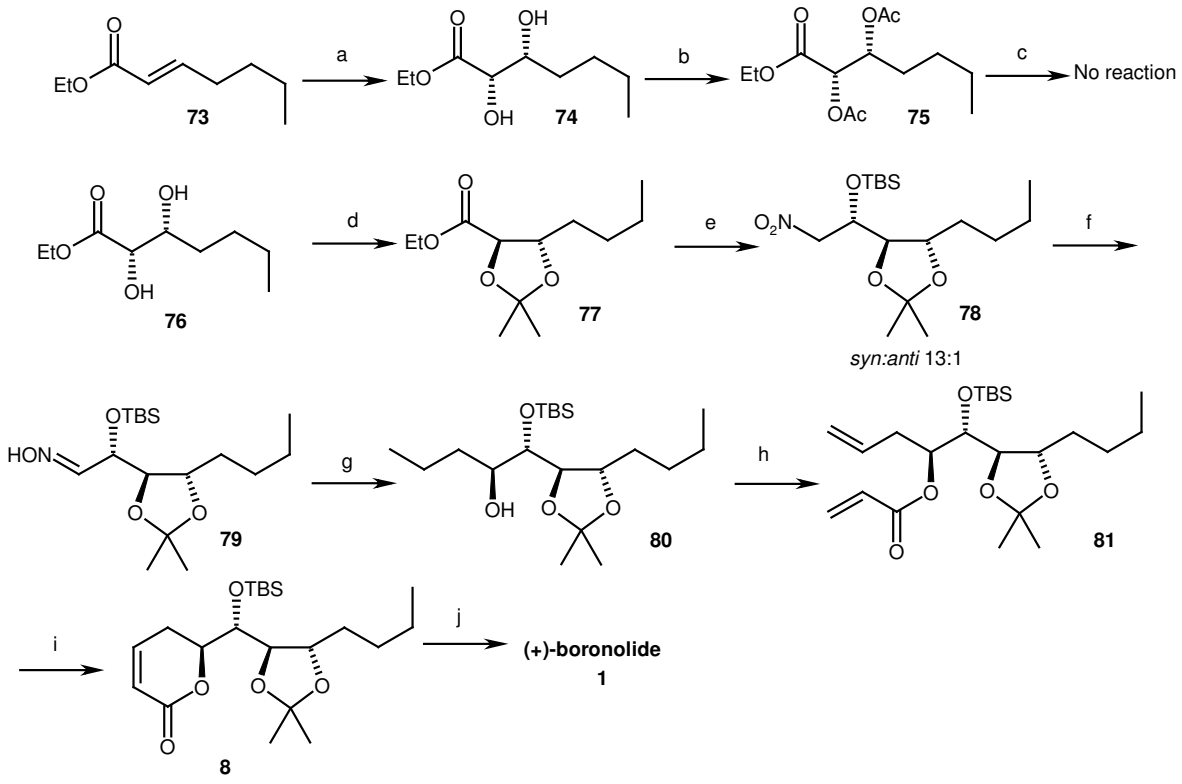


Scheme 9. *Reagents and conditions*: (a) TBSCl, Im, DMAP(cat.), CH_2Cl_2, 94%. (b) (i) DIBAL-H (1 M solution in toluene), toluene, −78 °C. (ii) $Ph_3PC_3H_7Br$, *n*-BuLi (1.6 M solution in hexanes), −40 to 0 °C; (iii) Pd/C, H_2, 35 atm, EtOAc–CH_3OH (5 : 1), 58% for three steps; (c) H_5IO_6, ether, rt. (d) (i) Propargyl bromide, DMF–Et_2O, Zn powder, total yield 59% for two steps. (ii) TBSCl, DMF, Im., DMAP, rt, 92%; (e) *n*-BuLi (1.2 eq, 1.6 M in hexanes), $ClCO_2Me$, THF, −78 °C to rt, 87%; (f) Lindlar cat., quinoline, ethyl acetate, 91.2%; (i) 6 M HCl–THF (1 : 2), rt; (j) Ac_2O, Py, DMAP, CH_2Cl_2, 73% for two steps.

Barua *et al.* (2006)[81]

Barua and co-workers synthesized (+)-boronolide starting from (*E*)-α,β-unsaturated ester **73** employing Sharpless asymmetric dihydroxylation, Shibasaki's asymmetric Henry reaction,[14]

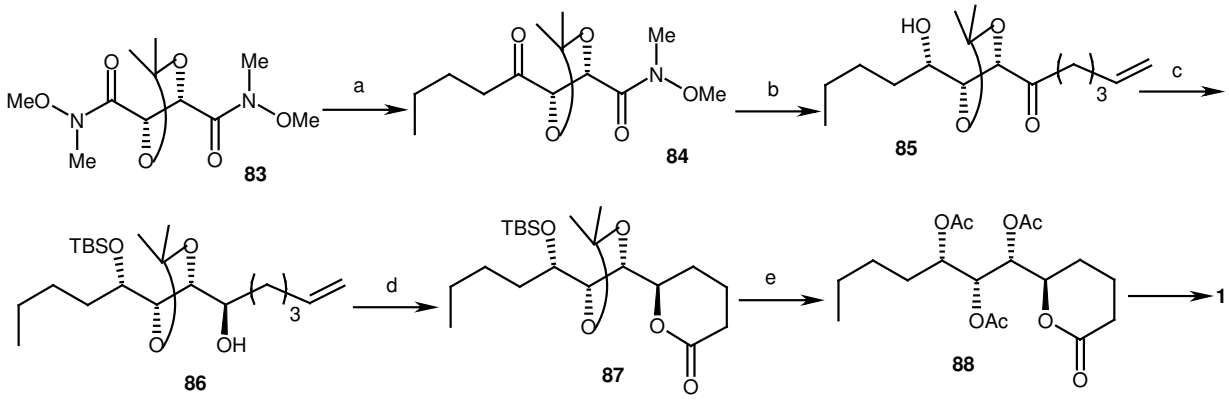
asymmetric allylation and ring-closing metathesis as key steps. Thus, AD reaction of **73** and subsequent isopropylidene protection followed by reduction and nitro aldol reaction under the influence of La-(*S*)-BINOL catalyst gave the nitro alcohol **78** with 13:1 (*syn:anti*) diastereomeric ratio. The oxime **79** derived from nitro alcohol **78** by Nef reaction[15] was converted into aldehyde, which was then subjected to asymmetric allylation and ring-closing metathesis to give the target molecule **1**.



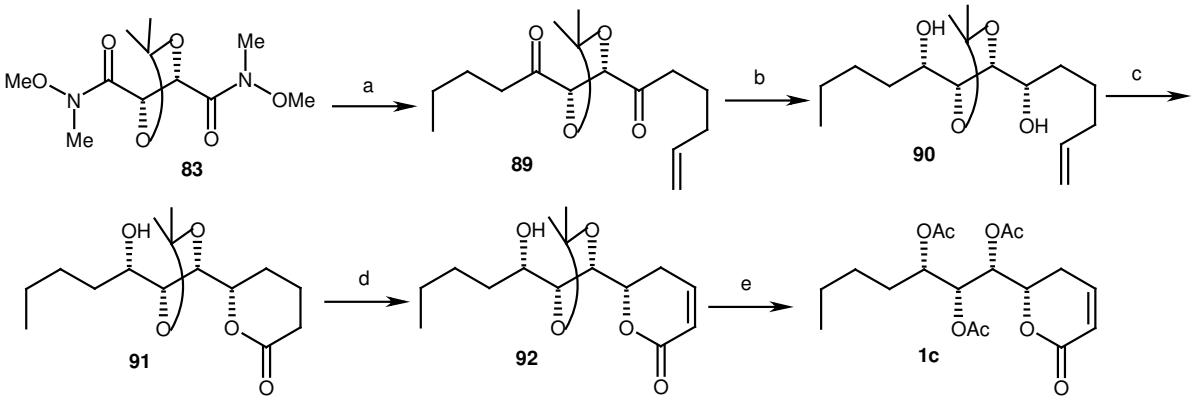
Scheme 10. *Reagents and conditions*: (a) $(DHQ)_2PHAL$, OsO_4, $K_3[Fe(CN)_6]$, K_2CO_3, *t*-BuOH–H_2O (1/1), 0 ^oC, 18 h; (b) acetic anhydride, iodine, rt, 10 min; (iii) DIBAL, toluene, -78 to 0 ^oC; (c) $LiBH_4$, ether, 0 ^oC to rt; (d) 2,2-DMP, Amberlyst 15, CH_2Cl_2, rt, 30 min; (e) (i) DIBAL, toluene, -78 ^oC, 2 h; (ii) nitromethane, La(*S*)-BINOL, THF, -50 ^oC, 60 h; (iii) TBSCl, imidazole, DMF, rt, 16 h; (f) anhydride $SnCl_2$, Et_3N, PhSH, MeCN, rt, 30 min; (g) (i) PCC, 30% H_2O_2, acetone, rt, 30 min; (ii) (*S*)-BINOL, $Ti(O\text{-}iPr)_4$, allyltributyltin, CH_2Cl_2, -78 to -20 ^oC, 36 h; (h) acryloyl chloride, Et_3N, DMAP, CH_2Cl_2, 0 ^oC to rt; (i) Grubb's catalyst, CH_2Cl_2, 40 ^oC, 14 h; (j) (i) aq HF, CH_3CN, rt, 12 h; (ii) acetic anhydride, pyridine, DMAP, rt, 3 h.

Prasad *et al.* (2006)[8m]

Prasad and co-workers employed bis-Weinreb amide **83** as starting material for the synthesis of (+)-boronolide **1** and (–)-5-*epi*-boronolide **1d**. As depicted in Scheme 11, mono substitution of bis-Weinreb amide **83**[16] with butylmagnesium bromide followed by reduction with L-selectride.



Scheme 11. *Reagents and conditions*: (i) ^{n}BuMgBr, THF, -15 ^{o}C, 92%; (ii) (a) L-Selectride, THF, -78 ^{o}C, 83%, (b) pentenylmagnesium bromide, THF, 0 ^{o}C, 2 h, 94%; (c) (i) TBSCl, DMF, Im, DMAP, 80 ^{o}C, 4 h, 93%, (ii) DIBAL-H, toluene, -50 ^{o}C, 1.5 h, 82%; (d) O_3/O_2, Me_2S, $NaHCO_3$, DCM:MeOH, -78 ^{o}C to rt, 5 h, (ii) PCC, NaOAc, celite, DCM, rt, 2 h, 89% for 2 steps; (e) (i) $FeCl_3$, $6H_2O$, DCM, rt, 4 h, 75%, (ii) Ac_2O, Et_3N, DMAP, DCM, rt, 8 h, 90%.



Scheme 12. *Reagents and conditions*: (a) (i) pentenylmagnesium bromide, THF, 0 ^{o}C, 0.5 h, (ii) *n*-BuLi, THF, 0 ^{o}C, 1 h, 83%; (b) L-selectride, THF, -78 ^{o}C, 2.5 h, 89%; (c) (i) O_3/O_2, Me_2S, $NaHCO_3$, DCM:MeOH, -78 ^{o}C to 0 ^{o}C, 5.5 h, 87%, (ii) Ag_2CO_3 on celite, toluene, Δ,

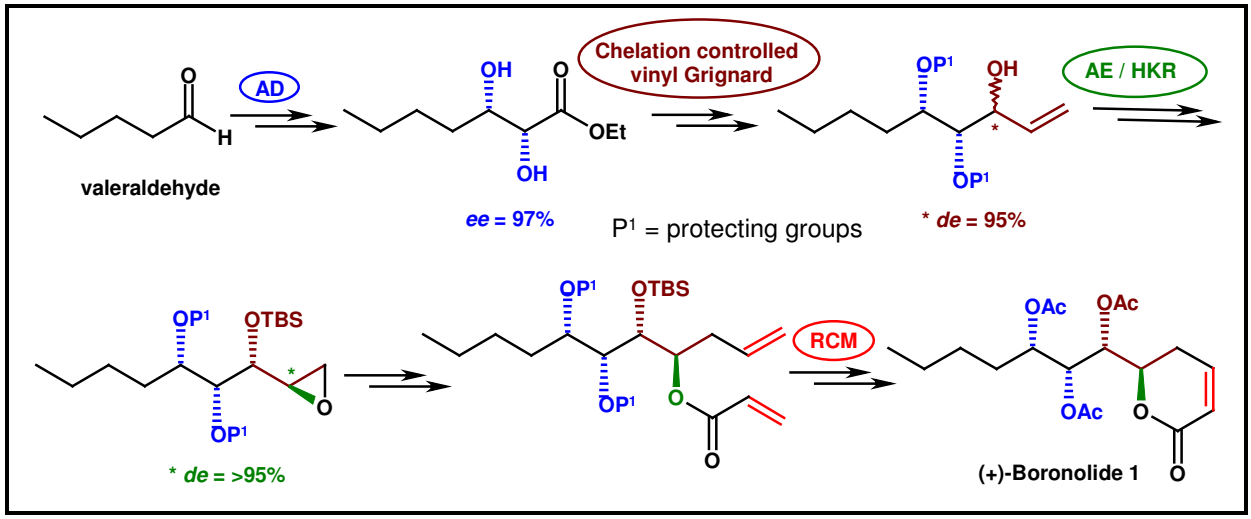
1.5 h, 98%; (d) LDA/PhSeBr, THF, -78 ^{o}C to -30 ^{o}C, 4 h, (ii) H_2O_2, DCM, rt, 1 h, 34%; (e) (i) $FeCl_3.6H_2O$, DCM, 0.5 h, rt, (ii) Ac_2O, Py/DMAP, rt, 10 h, 76% for two steps.

The other amide was substituted with 4-pentenylmagnesium bromide followed by stereoselective reduction with DIBAL-H to afford the required alcohol **86**. Ozonolysis of **86**, followed by PCC oxidation of resultant lactol afforded the lactone **87**. Global deprotection followed acetylation and elimination afforded the target molecule **1**. Reaction of bis-Weinreb amide **83** successively with 4-pentenylmagnesium bromide and *n*-butyllithium in one-pot afforded the diketone **89**, which was reduced stereoselectively by L-selectride to furnish the diol **90** as a single diastereomer. Ozonolysis of **90**, followed by PCC oxidation of resultant lactol afforded the lactone **91**, which was converted into 5-*epi*-boronolide **1d** (Scheme 12).

2.3. PRESENT WORK

2.3.1. Objective

Our synthetic strategy for the synthesis of boronolide **1** is outlined in Scheme 13. We envisioned that the lactone ring could be constructed by the ring closing metathesis of an acrylate ester, which in turn would be obtained from an epoxide. The enantio pure epoxide could be prepared either by the Sharpless asymmetric epoxidation of an allylic alcohol or by hydrolytic kinetic resolution of a racemic epoxide. The chelation-controlled vinylation of an aldehyde would install the third stereogenic centre, while the initial two stereo centers could easily be established by the Sharpless asymmetric dihydroxylation of an olefin.

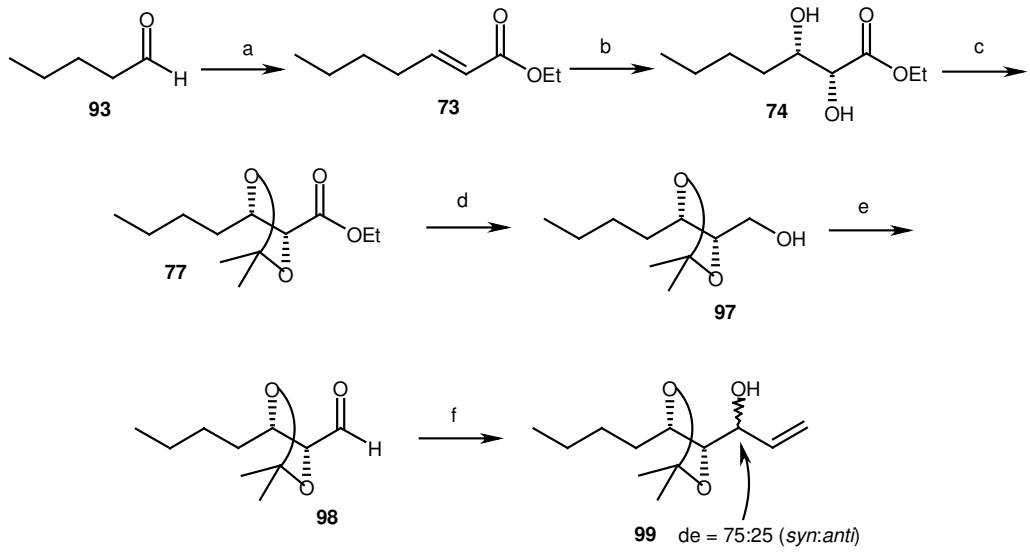


Scheme 13. Retrosynthetic analysis for (+)-boronolide

2.3.2. Results and Discussion:

The synthesis of boronolide started from commercially available valeraldehyde **93** as illustrated in Scheme 14. Thus, valeraldehyde **93** was subjected to Horner-Emmons olefination with triethyl phosphonoacetate to furnish the (*E*)-α,β-unsaturated ester **73** in 89% yield. The IR spectrum of **73** showed the ester carbonyl absorption at 1724 cm^{-1} and olefin C=C stretching at 1655 cm^{-1}. The ^1H NMR spectrum gave olefin protons at δ 5.76 (doublet of doublet) and 6.95 (doublet of triplet) with the coupling constant J = 15.76 Hz indicating *trans*-olefin. The ester **73** was treated with osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of $(DHQ)_2PHAL$ ligand under AD conditions[17] to give the diol (2*R*, 3*S*)-**74** in 96% yield having $[\alpha]_D^{25}$ –8.8 (*c* 0.9, $CHCl_3$) with 97% ee.[18, 8k,l] The IR spectrum gave hydroxyl absorption at 3400-3300 cm^{-1} and ester carbonyl at 1732 cm^{-1}. The ^1H NMR indicated absence of olefin protons. The chiral protons appeared at δ 3.85 (doublet

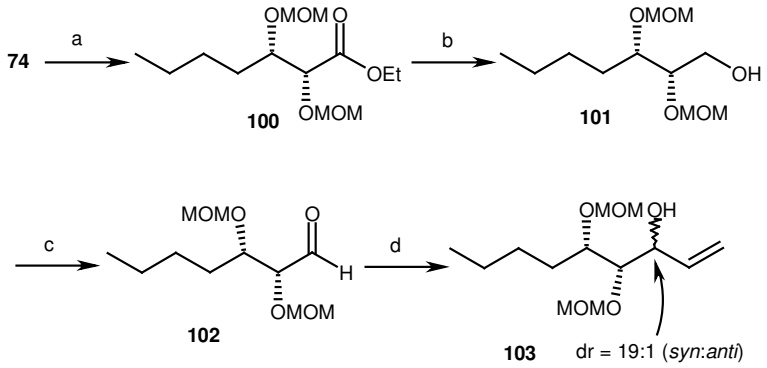
of triplet) and 4.06 (doublet) in proton NMR spectrum. The chiral carbons appeared at δ 72.4 and 73.2 in the ^{13}C NMR spectrum. Treatment of diol **74** with 2,2-dimethoxypropane in the presence of *p*-TSA gave the acetonide ester (2*R*, 3*S*)-**77** in 95% yield. The IR spectrum of **77** indicated absence of hydroxyl groups. The acetonide methyl protons appeared at δ 1.42 (singlet) and 1.44 (singlet) in the ^{1}H NMR spectrum and typical quaternary carbon of acetonide appeared at 110.5 in the ^{13}C NMR spectrum. The reduction with DIBAL-H furnished the alcohol (2*S*, 3*S*)-**97** in 91% yield. The IR spectrum of **97** gave hydroxyl absorption at 3440 cm^{-1} and the ester carbonyl group was found to be absent. The resulting alcohol **97** was subjected to oxidation under Swern conditions[19] to give the aldehyde **98** in excellent yield.



Scheme 14. *Reagents and conditions*. (a) $(EtO)_2P(O)CH_2CO_2Et$, LiBr, Et_3N, THF, rt, overnight, 89%; (b) $(DHQ)_2PHAL$, K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, *t*-BuOH/H_2O 1:1, 0 ^oC, 24 h, 96%; (c) *p*-TSA, 2,2-DMP, CH_2Cl_2, 95%; (d) DIBAL-H, CH_2Cl_2, 0 ^oC to rt, 2 h, 91%; (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^oC to -60 ^oC, 95%. (f) CH_2=CHMgBr, $MgBr_2.Et_2O$, THF or CH_2Cl_2, -78 ^oC, 6 h, 92%.

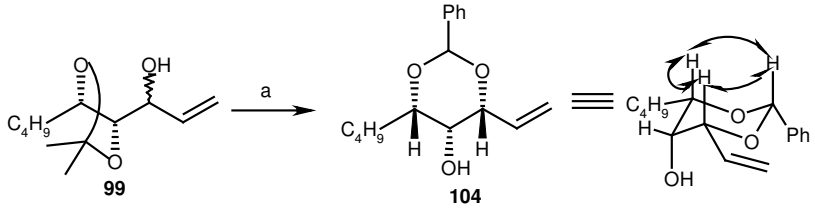
To establish the third stereogenic centre with the required stereochemistry, it was thought worthwhile to examine stereoselective vinylation. Thus, treatment of aldehyde **98** with vinylmagnesium bromide in THF in the presence of $MgBr_2.Et_2O$[20] at –78 ^oC furnished the allylic alcohol **99** in 92% yield with moderate diastereomeric selectivity (*dr* = 3:1; *syn*:*anti*) as an inseparable mixture of diastereomers. The IR spectrum of **99** gave broad hydroxyl

absorption at 3358-3250 cm^{-1}. The ^1H NMR spectrum of **99** gave olefin peaks at δ 5.81-5-91 (multiplet, one proton) and 5.26-5.34 (multiplet, two protons). The hydroxyl proton appeared at δ 2.42 (broad singlet) and the diastereomeric protons at δ 3.61 (doublet of doublet, minor diastereomer) and δ 3.69 (doublet of doublet, major diastereomer) with coupling constants *J* = 7.5, 4.5 and 7.9, 3.9 Hz respectively in ^1H NMR spectrum.



Scheme 15. *Reagents and conditions*. (a) MOM chloride, DIPEA, CH_2Cl_2, 0 ^oC to rt, overnight, 91%; (b) (i) DIBAL-H, CH_2Cl_2, 0 ^oC to rt, 2 h, 89%, (ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^oC to -60 ^oC, 95%; (c) CH_2=CHMgBr, $MgBr_2.Et_2O$, THF or CH_2Cl_2, -78 ^oC, 6 h, 90%.

Even after protection of the hydroxy group of **99** with different protecting groups such as TBS, MOM, Ac, PMB, we were unable to separate the diastereomers by flash chromatography. In order to determine the stereochemistry of newly generated third stereocentre, compound **99** was subjected to acid treatment followed by 1,3-dihydroxy protection as the benzylidene derivative. The required major isomer **104** could easily be separated by silica gel column chromatography. The newly generated stereocentre in **99** was assigned *syn* configuration which was based on the NOE studies as strong NOE correlations were observed between the 1,3-diaxial protons of the cyclic derivative **104** (Scheme 16).



Scheme 16. *Reagents and conditions*. (a) (i) HCl, MeOH, rt, 12 h; (ii) $PhCH(OMe)_2$, *p*-TSA, CH_2Cl_2, rt, overnight.

Subsequently several attempts were made to achieve better selectivity with the use of additives such as $ZnCl_2$ or $TiCl_4$ and employing addition of vinyl lithium as alkylating reagent with different solvent systems (CH_2Cl_2 or diethyl ether). However, the required *syn*-selectivity could not be improved. In order to explore the possibility of achieving a better *syn*-selectivity in vinylation reaction, it was thought worthwhile to change the protecting group. We assumed that the chelation between MOM and aldehyde would be more effective as compared to other protecting groups. Thus the diol **74** was treated with MOMCl in the presence of diisopropylethylamine to afford compound (2*R*, 3*S*)**-100** in excellent yield (Scheme 15). The IR spectrum of **100** indicated absence of hydroxyl groups. The methylene and methyl protons of MOM group appeared at δ 4.70, 4.62 and 3.37, 3.31 respectively in ^1H NMR spectrum. Subsequent reduction of ester **100** with DIBAL-H followed by Swern oxidation gave the aldehyde **102**, which was used immediately in the next reaction without any further purification.

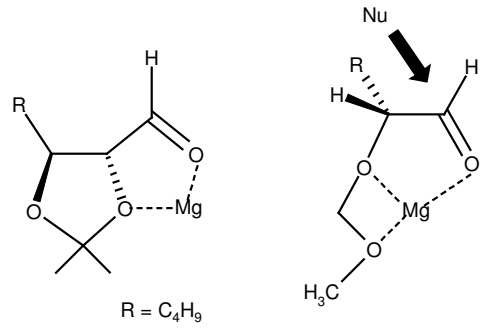


Figure 2. Chelation controlled transition models

Thus when **102** was subjected to chelation controlled vinylation in CH_2Cl_2 at –78 ^oC with $MgBr_2.Et_2O$,[20] it furnished the allylic alcohol **103** in 90% yield with an excellent diastereoselectivity (*dr* = 19:1; *syn*:*anti*) as determined by ^1H and ^{13}C NMR spectral analysis. The formation of major *syn*-diastereomer can be explained by the chelated five membered transition state as depicted in Fig. 2.

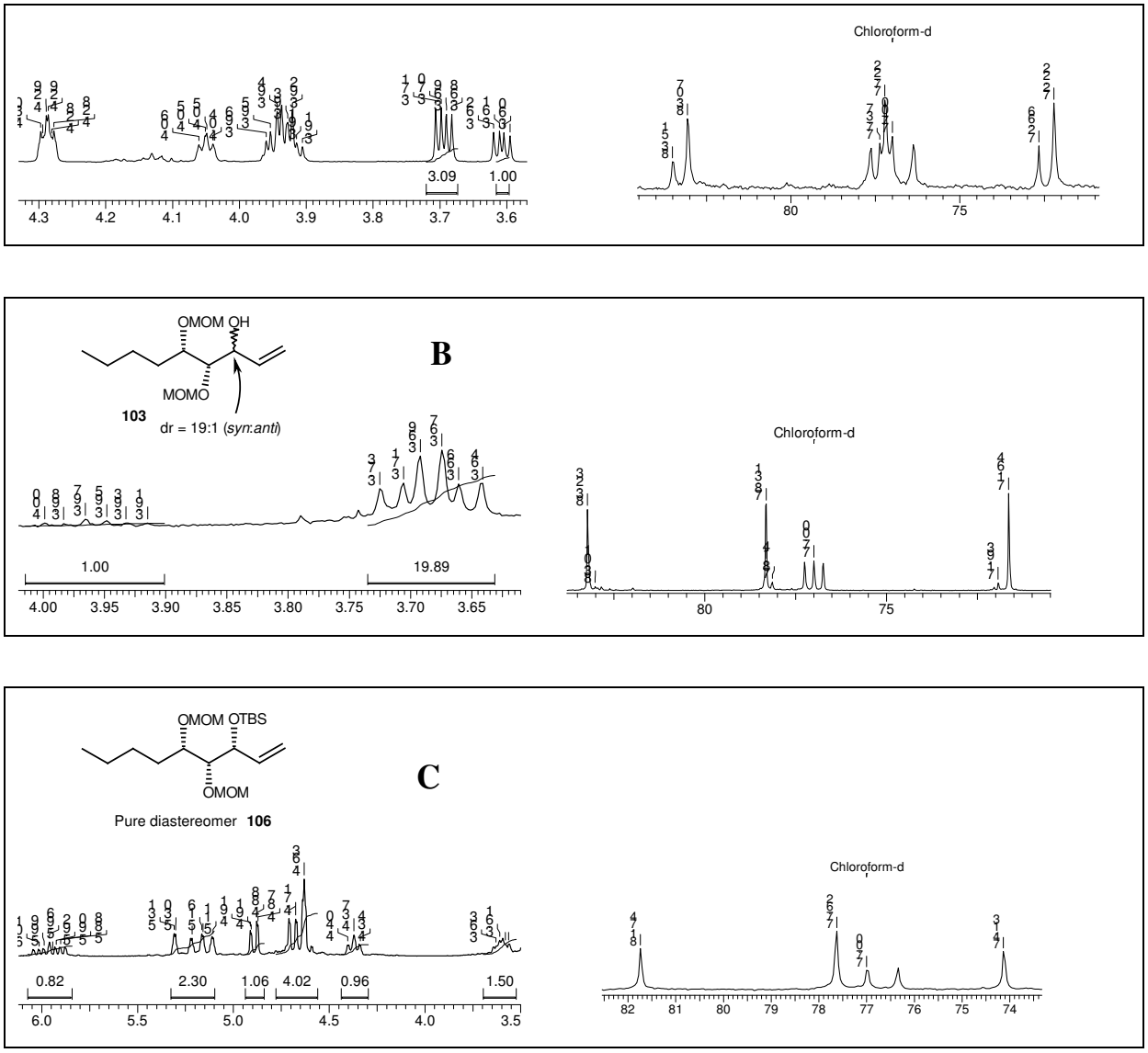
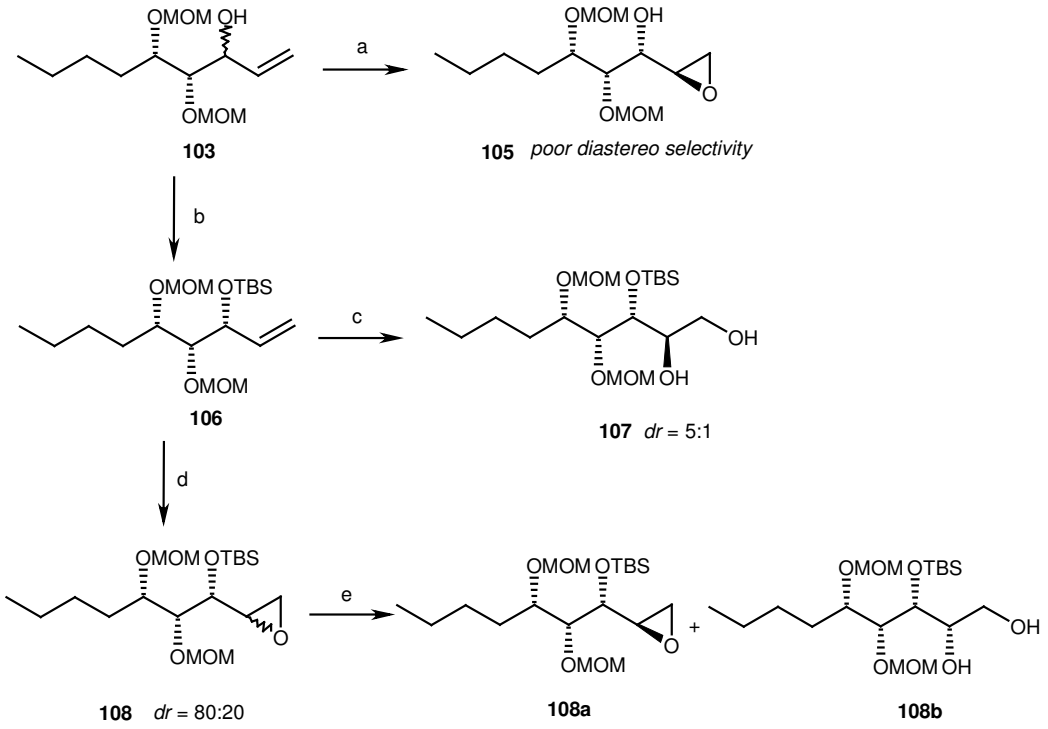


Figure 3: (**A**) Partial ^{1}H NMR and ^{13}C NMR spectra of diastereomeric mixture (3:1) **99**. (**B**) Partial ^{1}H NMR and ^{13}C NMR spectra of diastereomeric mixture (19:1) **103**. (**C**) Partial ^{1}H NMR and ^{13}C NMR spectra of pure diasteomer **106**.

The improvement in the *syn*-selectivity in case of **103** (19:1) as compared to **99** (3:1) could probably be attributed to the extra chelation by MOM protecting group with magnesium as illustrated in Fig.2. After protection of hydroxyl group in compound **103** with TBSCl, the required *syn*-diastereomer (3*R*, 4*R*, 5*S*)-**106** could easily be separated by flash chromatography.

In order to generate the final stereogenic centre with an appropriate functionality, a Sharpless asymmetric epoxidation was employed in the next step (Scheme 17). Thus, treatment of allylic alcohol **103** with titanium tetra-isopropoxide and *t*-butyl hydroperoxide in the presence of (+)-DIPT for 4 days under Sharpless asymmetric epoxidation conditions[21] provided the epoxide **105** albeit in low yield and poor diastereoselectivity. The extra chelation of titanium-tetra isopropoxide with MOM might be possible reason for retarding the rate of epoxidation reaction. As a next alternative, it was thought worthwhile to prepare first the diol **107** by the Sharpless asymmetric dihydroxylation of olefin **106**, which could further be converted easily into the required epoxide **108a** by standard transformations. Accordingly, the olefin **106** was treated with osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of $(DHQ)_2AQN$ ligand under AD conditions[10] to give the diol **107** in 91% yield with moderate diastereomeric selectivity (*dr* = 5:1; *anti:syn*) as an inseparable mixture of diastereomers. The IR spectrum of **107** gave broad hydroxyl absorption at 3400 cm^{-1}. The hydroxyl protons appeared at δ 1.73 and 1.59 as two broad singlets. In another attempt, to improve the selectivity and to examine the stereochemical outcome of the epoxidation reaction, we carried out epoxidation of olefin **106** using *m*-CPBA in various solvent systems in the presence of Na_2HPO_4. Addition of phosphate could be effective in avoiding the unfavorable acid catalyzed ring opening of epoxide once formed.[22] Thus compound **106** was treated with *m*-CPBA/Na_2HPO_4 in CH_2Cl_2 to afford the epoxide **108** in 92% yield (*dr* = 4:1; *anti*:*syn*) as a non separable mixture of diastereomers. Even with the use of different solvent systems, we could not improve the selectivity. The ^1H NMR spectrum of **108** showed absence of olefin protons and epoxide protons appeared at δ 2.67-2.76 (multiplet, two protons) and 3.27 (multiplet, one proton). The ^{13}C NMR spectrum of **108** showed upfield carbons of epoxide at δ 44.5, 43.5 and 52.3, 51.8 as a diastereomeric mixture.



Scheme 17. *Reagents and conditions*. (a) Ti(OPr-*i*)$_4$, (+)DIPT, *t*-BuOOH, dry CH_2Cl_2, -20 ^oC, 4 days, 15%; (b) TBSTf, 2,6-lutidine, CH_2Cl_2, 0 ^oC, 30 min, 98%; (c) $(DHQ)_2AQN$ (1 mol%), 0.1M OsO_4 (0.4 mol%), K_2CO_3, $K_3Fe(CN)_6$, *t*-BuOH/H_2O 1:1, 0 ^oC, 24 h, 91%; (d) *m*-CPBA, Na_2HPO_4, CH_2Cl_2, over night, 91%; (e) (*R*,*R*)-salen-Co-(OAc) (0.5 mol %), dist H_2O, 42 h, (94% for **108a**, 90% for **108b** according to the ratio of the starting material).

In order to get the diastereomerically pure epoxide, we next attempted at the hydrolytic kinetic resolution method (HKR) developed by Jacobsen. The HKR method uses readily accessible cobalt-based chiral salen complexes as catalyst and water as the only reagent to afford the chiral epoxide and diol of high enantiomeric excess in excellent yields. These advantages have made it a very attractive asymmetric synthetic tool. While the HKR was successfully employed for the resolution of simple epoxides of small molecular weight,[23] mono functional unbranched alkyl substituted epoxides[24] and bis-epoxides,[25] its application to the multi functional epoxides has not been fully explored. Therefore, we decided to use this method for the resolution of epoxide **108**, which would further extend the scope of this protocol for the multifunctionalized large molecules having olefin with pre-existing adjacent chiral centre. Thus epoxide **108** was resolved with *R*,*R*-salen-Co(OAc) complex (0.5 mol%) and water (0.4 eq) to yield the epoxide (2*R*, 3*R*, 3*R*, 5*S*)-**108a** in 94% yield (as calculated from

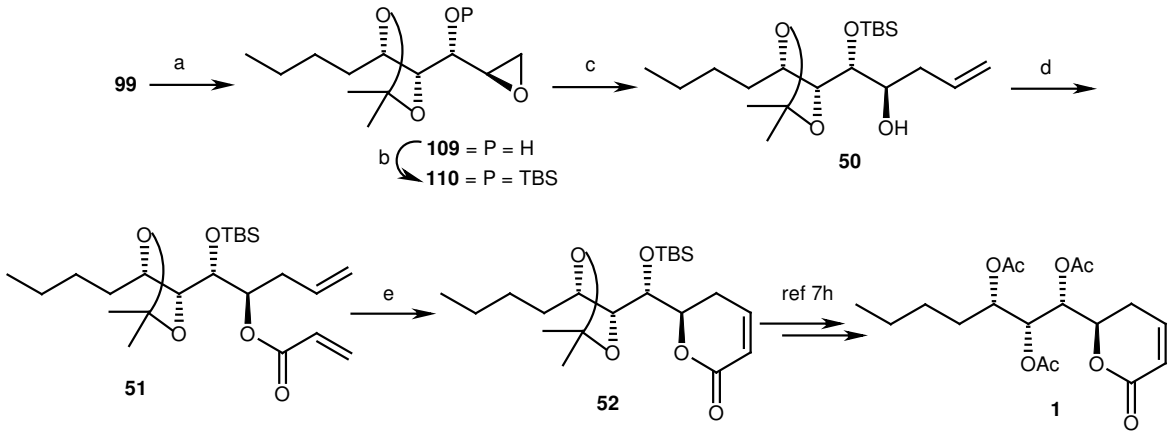
80% epoxide) and diol (2*S*, 3*R*, 3*R*, 5*S*)-**108b** in 90% yield (as calculated from 20% other epoxide). The diol **108b** can be converted into the required epoxide by conventional method.

It is interesting to note that while asymmetric epoxidation of **103** gave rather low yield of the product, the treatment of allylic alcohol **99** with titanium tetra-isopropoxide and *t*-butyl hydroperoxide in the presence of (+)-DIPT under the Sharpless asymmetric epoxidation conditions[21] furnished the desired epoxide (2*R*, 3*R*, 3*R*, 5*S*)-**109** in good yield and high diastereomeric excess (*de* = >95%) as judged by ^{1}H and ^{13}C NMR spectral analysis (Scheme 18). The ^{1}H NMR spectrum of **109** showed absence of olefinic protons and epoxide protons appeared at δ 2.77-2.89 (multiplet, two protons) and 3.28 (multiplet, one proton). The ^{13}C NMR spectrum of **109** showed upfield carbons of epoxide at δ 44.57 and 52.33. As expected the Sharpless kinetic resolution in the epoxidation reaction has pronounced effect in enhancing the diastereomeric purity of the desired product. The free secondary hydroxyl group was protected with TBSCl in the presence of imidazole and catalytic amount of DMAP to furnish compound **110** in excellent yield. The ring opening of the epoxide **110** with vinylmagnesium bromide in the presence of catalytic amount of CuI in THF at -20 ^{o}C furnished the homoallylic alcohol **50** in excellent yield having $[\alpha]_D^{25}$ –10.1 (*c* 0.64, $CHCl_3$). The IR spectrum of **50** gave broad hydroxyl absorption at 3475 cm^{-1}. The ^{1}H NMR spectrum of **50** gave olefin peaks at δ 5.91 (multiplet, one proton) and 5.10-5.20 (multiplet, two protons). Treatment of **50** with acryloyl chloride and Et_3N in the presence of a catalytic amount of DMAP in CH_2Cl_2 provided the acrylate **51** in 88% yield having $[\alpha]_D^{25}$ –2.86 (*c* 0.64, CH_2Cl_2). The IR spectrum of **51** indicated absence of hydroxyl group, acryloyl carbonyl appeared at 1726 cm^{-1}. The carbonyl carbon appeared at δ 165.7 in the ^{13}C NMR spectrum. Olefin metathesis of **51** with commercially available Grubbs' Ist generation catalyst[26] (2 mol %) in the presence of Ti(OPr-*i*)$_4$ (0.3 eq) in refluxing CH_2Cl_2 afforded the α,β-unsaturated δ-lactone **52** in 90% yield having $[\alpha]_D^{25}$ +71.6 (*c* 0.44, CH_2Cl_2). The IR spectrum of **52** showed characteristic carbonyl group absorption of α,β-unsaturated δ-lactone at 1644 cm^{-1}. The olefin protons appeared at δ 5.99 (doublet of doublet of doublet) with *J* = 8.2, 6.3, 2.0 Hz and 5.92 (doublet of doublet) with *J* = 9.7, 2.3 Hz in the ^{1}H NMR spectrum. The olefinic carbons appeared at δ 146.84 and 120.67 in ^{13}C NMR spectrum.

Global deprotection[8h] of **52** using aqueous HF in CH_3CN occurred slowly. Deacetyboronolide **1a** was recovered in 65% after stirring 5 days at room temperature. Silyl ether was also

recovered in 30% yield and could be recycled under the same deprotection conditions to give **1a** and the resulting triol was acetylated with acetic anhydride to give (+)-boronolide **1**.

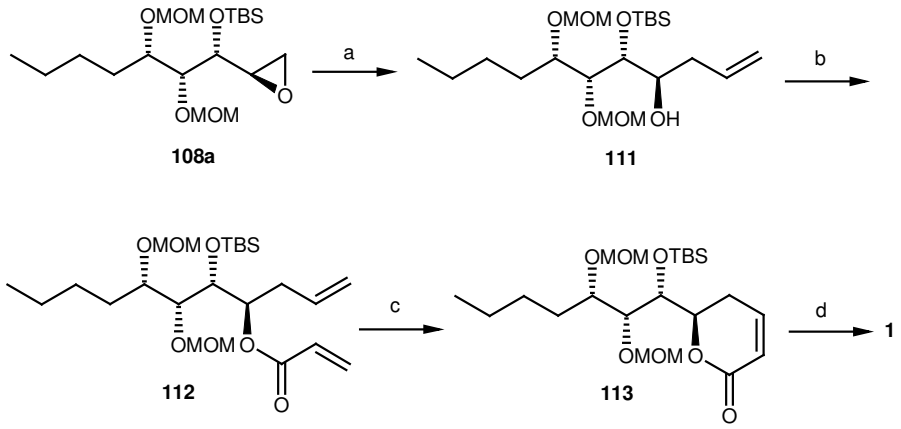
In the same manner, the ring opening of epoxide **108a** was carried out with vinylmagnesium bromide in the presence of catalytic amount of CuI in THF at –20 ^{o}C to furnish the homoallylic alcohol **111** in excellent yield (Scheme 19). Reaction of **111** with acryloyl chloride and Et_3N in the presence of catalytic amount of DMAP in CH_2Cl_2 provided the acrylate ester **112** in 91% yield.



Scheme 18. *Reagents and conditions*. (a) Ti(OPr-*i*)$_4$, (+)DIPT, *t*-BuOOH, dry CH_2Cl_2, -20 ^{o}C, 48 h, 78% (yield based on 75% of s*yn* compound); b) TBSCl, imidazole, cat. DMAP, CH_2Cl_2, 0 ^{o}C to rt, 98%; (c) CH_2=CHMgBr, CuI, THF, -30 ^{o}C, 90%; d) Acryloyl chloride, Et_3N, cat. DMAP, CH_2Cl_2, 0 ^{o}C to rt, 88%; e) 2 mol% $(PCy_3)_2$ $Ru(Cl)_2$=CH-Ph, CH_2Cl_2, reflux, 16 h, 90%.

Olefin metathesis of **112** with commercially available Grubbs' Ist generation catalyst[26] (2 mol%) in the presence of Ti(*i*-PrO)$_4$ (0.3 eq) in refluxing CH_2Cl_2 afforded the α,β-unsaturated lactone **113** in 89% yield having $[\alpha]_D^{25}$ +51.4 (*c* 1.18, $CHCl_3$). All protecting groups such as MOM and TBS were deprotected in the presence of $BF_3.SMe_2$ and aq. HF to afford triol **1a**, which was acetylated with acetic anhydride in the presence of Et_3N and catalytic amount of DMAP to give (+)-boronolide **1** in 50% overall yield having m.p 101 ^{o}C, [lit.[8h] mp 99-100 ^{o}C and $[\alpha]_D^{25}$ +57.4 (*c* 0.71, EtOH); lit.[8h] $[\alpha]_D^{25}$ +56 (*c* 0.07, EtOH). The IR spectrum of **1** showed presence of acetyl carbonyls at 1744 cm^{-1}. The ^{1}H NMR spectrum of **1** gave acetyl methyl protons at δ 2.11 (singlet, one methyl), 2.05 (singlet, one methyl), 2.03 (singlet, one methyl), the chiral protons at δ 5.33-5.38 (multiplet, two protons), 5.01 (quartet with *J* = 6.01

Hz, one proton), 4.55 (doublet of triplet with J = 12.1, 4.5 Hz, one proton). The ^{13}C NMR spectrum gave chiral carbons at δ 75.1, 71.6, 70.6 and 70.5 and four carbonyl carbons at δ 170.5, 169.8, 169.5 and 162.5. The physical and spectroscopic data were identical with those reported.[8h]



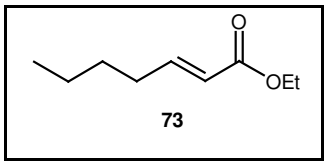
Scheme 19. *Reagents and conditions*. (a) CH_2=CHMgBr, CuI, THF, -30 ^oC, 86%, (b) Acryloyl chloride, Et_3N, cat. DMAP, CH_2Cl_2, 0 ^oC to rt, 91%; (c) 2 mol% $(PCy_3)_2$ $Ru(Cl)_2$=CH-Ph, CH_2Cl_2, reflux, 8 h, 89%; (d) $BF_3.SMe_2$, -30 ^oC, then aq HF, CH_3CN, rt, then Ac_2O, Et_3N, cat DMAP, CH_2Cl_2, rt, (50% overall).

2.3.3. Conclusion

In conclusion, a practical and stereoselective total synthesis of (+)-boronolide **1** has been achieved in 13 steps from commercially available valeraldehyde **93** in a overall yield of 18% using the Sharpless asymmetric dihydroxylation, chelation controlled addition of vinyl Grignard, epoxidation, Jacobson's hydrolytic kinetic resolution and ring closing metathesis as the key steps. The HKR on the multifunctional terminal olefin having chiral centers was successfully utilized for the synthesis of boronolide. We believe our new approach is thus the most efficient route to (+)-boronolide reported so far and would permit maximum variability in product structure with regard to stereochemical diversity which is particularly important for making various synthetic analogues required for screening of biological activity.

2.4.1. Experimental Section

Hept-2-enoic acid ethyl ester (73).



73

To a nitrogen flushed solution of LiBr (35.29 g, 406.40 mmol) in dry THF (150 mL) was added $(EtO)_2P(O)COOEt$ (21.87 g, 97.53 mmol) dropwise at room temperature for 15 min and followed by addition of Et_3N (22.65 mL, 162.56 mmol). The stirring was continued for another 15 min. To this was added the solution of aldehyde **93** (7 g, 81.28 mmol) in dry THF (20 mL). A white precipitate was formed several minutes after the addition of aldehyde. The reaction was stirred vigorously at room temperature until the full consumption of the aldehyde was observed (TLC). The precipitate was removed by passing the reaction mixture through a pad of silica gel in sintered glass funnel. The pad was washed with 400 mL of hexane/EtOAc 6:1. Concentration gave a colorless oil. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (19:1) as eluent gave compound 7**3**[81] as a colorless oil.

Yield: 11.30 g (89%).

Mol. Formula: $C_9H_{16}O_2$

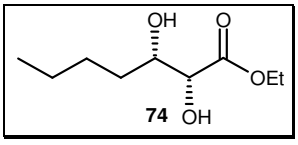
IR (neat, cm^{-1}): ν_{max} 2924, 2856, 1724, 1655, 1466, 1366, 1310, 1178, 1128, 1045, 980, 721.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.95 (dt, *J* = 15.7, 7.1 Hz, 1H), 5.76 (dt, *J* = 15.7, 1.3 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.17 (q, *J* = 8 Hz, 2H), 1.37-1.40 (m, 4H), 1.27 (t, *J* = 7.6 Hz, 3H), 0.91 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 165.9, 148.5, 132.0, 59.4, 31.4, 21.7, 13.7.

Analysis: Calcd.: C, 69.19; H, 10.32%; **Found:** C, 69.34; H, 10.12%.

(2*R*, 3*S*)-2,3-Dihydroxyheptanoic acid ethyl ester (74):



74

To a mixture of $K_3Fe(CN)_6$ (18.98 g, 57.67 mmol), K_2CO_3 (7.96 g, 57.69 mmol) and $(DHQ)_2PHAL$ (149 mg, 1 mol%), in *t*-BuOH-H_2O (1:1, 75 mL) cooled at 0 ^oC was added OsO_4 (0.769 mL, 0.1 M sol in toluene, 0.4 mol%) followed by methane sulfonamide (1.826 g, 19.23 mmol). After stirring for 5 min at 0 ^oC, the olefin 7**3** (3 g, 19.23 mmol) was added in one portion. The reaction mixture was stirred at 0 ^oC for 24 h and then quenched with solid sodium sulfite (25 g). The stirring was continued for 45 min and the solution was extracted with EtOAc (3 x 50 mL). The combined organic phases were washed (10% KOH, then brine),

dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (3:2) as eluent gave diol **74**[81] as a colorless syrupy liquid.

Yield: 3.51 g (96%).

Mol. Formula: $C_9H_{18}O_4$

$[\alpha]_D^{25}$: –8.8 (*c* 0.9, $CHCl_3$).

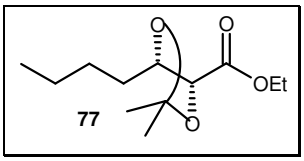
IR (neat, cm^{-1}): ν_{max} 3400, 3133, 3018, 2926, 2854, 1732, 1460, 1401, 1215, 760, 667.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.3 Hz, 3H), 1.24-1.37 (m, 6H), 1.59 (t, *J* = 13.6 Hz, 3H), 3.20 (brs, 2H), 3.85 (dt, *J* = 6.8, 2.4 Hz, 1H), 4.06 (d, *J* = 2.4 Hz, 1H), 4.25 (q, *J* = 7.2 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.7, 13.81, 22.3, 27.6, 32.9, 61.5, 72.4, 73.2, 173.5.

Analysis: Calcd.: C, 56.82; H, 9.54%; **Found:** C, 56.95; H, 9.33%.

(2*R*, 3*S*)-5-Butyl-2,2-dimethyl-[1,3]dioxolane-4-carboxylic acid ethyl ester (77):



To a solution of the diol 7**4** (2.45 g, 12.90 mmol), *p*-TSA (100 mg) in CH_2Cl_2 (75 mL) was added 2,2-dimethoxypropane (2.02 g, 19.35 mmol) and mixture stirred overnight. Solid $NaHCO_3$ (1 g) was added and stirred for 30 min. The reaction was filtered through a pad of neutral alumina and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) gave 77[81] as a colorless liquid.

Yield: 2.52 g (95%).

Mol. Formula: $C_{12}H_{22}O_4$

$[\alpha]_D^{25}$: –13.2 (*c* 3.22, $CHCl_3$);

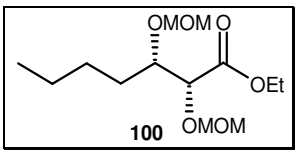
IR (neat, cm^{-1}): ν_{max} 3400, 3133, 3018, 2926, 2854, 1732, 1460, 1401, 1215, 760, 667.

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.20 (q, *J* = 8.0 Hz, 2H), 4.09 (m, 2H), 1.62 (t, *J* = 8.2 Hz, 3H), 1.44 (s, 3H), 1.42 (s, 3H), 1.27-1.35 (m, 6H), 0.89 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 170.7, 110.5, 79.1, 60.9, 33.0, 27.0, 25.5, 22.3, 13.9, 13.6.

Analysis: Calcd.: C, 62.58; H, 9.63%; **Found.** C, 62.72; H, 9.48%.

(2*R*, 3*S*)-2,3-Bis-methoxymethoxyheptanoic acid ethyl ester (100).



To a solution of the diol 7**4** (2.10 g, 11.04 mmol) and diisopropylethyl amine (4.99 g, 38.64 mmol) in dry CH_2Cl_2 (50 mL) was added MOMCl (2.13 g, 26.49 mmol), under argon over 5 min at 0 ^oC and mixture allowed to warm to room temperature overnight. After cooling to 0 ^oC, the reaction mixture was quenched with water and extracted with CH_2Cl_2 (3 x 50 ml). The combined organic extracts were washed with water (3 x 50 mL), brine, dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (8:2) gave **100** as a colorless liquid.

Yield: 2.80 g (91%).

Mol. Formula: $C_{13}H_{26}O_6$

$[\alpha]_D^{25}$: +59.2 (*c* 2.21, $CHCl_3$).

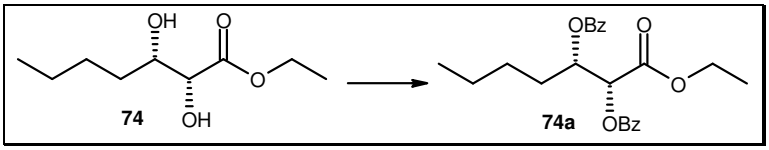
IR ($CHCl_3$, cm^{-1}): ν_{max} 3016, 2955, 2824, 2402, 1726, 1466, 1382, 1215, 1102, 1036.

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.70 (s, 2H), 4.62 (s, 2H), 4.19 (m, 3H), 3.91 (m, 1H), 3.37 (s, 3H), 3.31 (s, 3H), 1.64 (t, *J* = 8.2 Hz, 3H), 1.22-1.30 (m, 6H), 0.88 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.6, 13.8, 22.3, 27.2, 30.2, 55.4, 55.8, 60.5, 76.9, 77.3, 78.1, 96.3, 170.4.

Analysis: Calcd for.: C, 56.10; H, 9.42%; **Found:** C, 56.44; H, 9.12%.

2,3-Dibenzoylheptanoic acid ethyl ester (74a).



To a solution of the diol 7**4** (101 mg, 0.53 mmol) and dry pyridine (5 mL) was added benzoyl chloride (184 mg, 1.31 mmol) at 0 ^oC and mixture stirred over night at room temperature. The reaction mixture was quenched with 6N HCl (10 mL) and aqueous layer was extracted with diethyl ether. The combined organic extracts were washed with water, saturated aqueous $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9.5:0.5) gave 7**4a** as a colorless liquid.

Yield: 190 mg (90%).

Mol. Formula: $C_{23}H_{26}O_6$

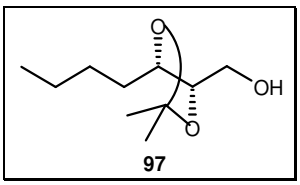
$[\alpha]_D^{25}$: 67.7 (*c* 1.03, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (dd, *J* = 12.4, 8.1 Hz, 4H), 7.38-7.63 (m, 6H), 5.51 (d, *J* = 4.5 Hz, 1H), 5.25 (m, 1H), 4.20 (q, *J* = 8.0 Hz, 2H), 1.86-1.90 (m, 2H), 1.52 (m, 4H), 1.15 (t, *J* = 12.0 Hz, 3H), 0.89 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 167.3, 165.7, 133.4, 133.0, 129.8, 129.6, 129.1, 128.4, 128.3, 73.1, 72.7, 61.6, 30.2, 27.2, 22.2, 13.9, 13.7.

Analysis: Calcd.: C, 69.33; H, 6.58%; **Found:** C, 69.01, H, 6.84%.

(2*S*, 3*S*)-(5-Butyl-2,2-dimethyl-[1,3]dioxolan-4-yl)-methanol (97).



97

To a solution of **77** (2.40 g, 10.42 mmol) in dry CH_2Cl_2 (80 mL) at 0 ^oC was added drop wise DIBAL-H (25.8 mL, 25.8 mmol, 1M in toluene) through a syringe. The reaction mixture was allowed to warm to room temperature over 2 h, then re-cooled to 0 ^oC and treated with saturated sodium/potassium tartrate. The solid material was filtered through a pad of celite and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (7:3) as eluent gave **97** as a colorless oil.

Yield: 1.79 g (91%).

Mol. Formula: $C_{10}H_{20}O_3$

$[\alpha]_D^{25}$: –21.5 (*c* 1.08, $CHCl_3$).

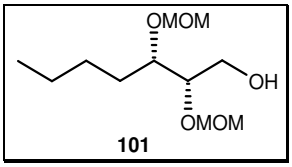
IR (neat, cm^{-1}): ν_{max} 3440, 2926, 1460, 1361, 1216, 764, 667.

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.75 (m, 2H), 3.58 (dd, *J* = 11.3, 3.9 Hz, 2H), 2.17 (s, 1H), 1.44-1.62 (m, 2H), 1.42 (s, 3H), 1.41 (s, 3H), 1.37-1.42 (m, 4H), 0.91 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.7, 22.5, 26.8, 27.1, 27.9, 32.6, 62.0, 77.00, 81.6, 108.3.

Analysis: Calcd.: C, 63.80; H, 10.71%; **Found:** C, 64.09; H, 10.58%.

2,3-Bis-methoxymethoxyheptan-1-ol (101).



101

Compound **101** was prepared following the procedure as described for compound **97** as colorless oil.

Yield: 89%.

Mol. Formula: $C_{11}H_{24}O_5$

$[\alpha]_D^{25}$: +7.69 (*c* 1.04, $CHCl_3$).

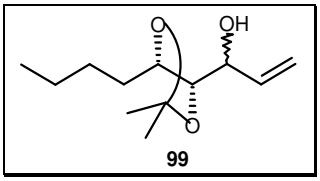
IR ($CHCl_3$, cm^{-1}): ν_{max} 3453, 30.17, 2956, 2826, 2401, 1467, 1381, 1216, 1150, 1035, 918, 756.

^{1}H NMR (200 MHz, $CDCl_3$): 4.73 (d, *J* = 8.0 Hz, 2H), 4.66 (d, *J* = 6.1 Hz, 2H), 3.60-3.70 (m, 4H), 3.41 (s, 3H), 3.39 (s, 3H), 2.80 (s, 1H), 1.30-1.61 (m, 6H), 0.89 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9, 22.6, 27.8, 29.9, 55.6, 55.8, 62.3, 78.2, 81.9, 96.7, 97.5.

Analysis: **Calcd.:** C, 55.91; H, 10.24%; **Found:** C, 55.69; H, 10.56%.

1-(5-Butyl-2,2-dimethyl-[1,3]-dioxolan-4-yl)-prop-2-en-1-ol (99).



99

To a solution of oxalyl chloride (1.405 g, 0.966 mL, 11.074 mmol) in dry CH_2Cl_2 (100 mL) at -78 ^oC was added dropwise dry DMSO (1.730 g, 1.57 mL, 22.15 mmol) in CH_2Cl_2 (20 mL). After 30 min, alcohol **97** (1.39 g, 7.382 mmol) in CH_2Cl_2 (20 mL) was added over 10 min giving a copious white precipitate. After stirring for 1 h at -78 ^oC the reaction mixture was brought to -60 ^oC and Et_3N (2.988 g, 2.169 mL, 29.53 mmol) was added slowly and stirred for 30 min allowing the reaction mixture to warm to room temperature. The reaction mixture was poured into water (150 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL) and combined organic layers were washed with water (3 x 50 mL), brine (50 mL), dried (Na_2SO_4) and passed through short pad of silica gel. The filtrate was concentrated to give the aldehyde **98** (1.31 g) as pale yellow oil, which was used as such for the next step without purification.

The crude aldehyde **98** dissolved in CH_2Cl_2 under argon was added via cannula to a stirred suspension of $MgBr_2.Et_2O$ in a 250 mL round bottom flask at 0 ^oC. After stirring for 10 min, the flask was cooled to -78 ^oC and treated with vinylmagnesium bromide (14.94 mL, 14.94 mmol) (purchased from Aldrich as 1.0 M solution in THF); the solvent was removed in *vacuo* and diluted with CH_2Cl_2 three times) over 30 min and allowed to warm to 0 ^oC. The reaction mixture was diluted with saturated NH_4Cl and extracted with CH_2Cl_2 (3 x 50 mL). Combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) as eluent gave the allylic alcohol **99** as an inseparable mixture of diastereomers (*syn*:*anti* = 3:1) as a pale yellowish oil.

Yield: 1.39 g (92%).

Mol. Formula: $C_{12}H_{22}O_3$

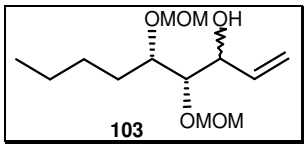
IR (neat, cm^{-1}): ν_{max} 3358-3250, 2924, 2855, 1466, 1372, 1220, 761, 669.

^{1}H NMR (200 MHz, $CDCl_3$): δ 5.81-5.91 (m, 1H), 5.34-5.39 (m, 1H), 5.26 (m, 1H), 4.28 - 4.30 (m, 1H), 3.91-3.96 (m, 1H), 3.69 (dd, *J* = 7.9, 3.9 Hz, 1H), 3.61 (dd, *J* = 7.5, 4.5 Hz, 1H, minor diastereomer), 1.49-1.60 (m, 3H), 1.39 (s, 6H), 1.31-1.36 (m, 3H), 0.89 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 137.1, 136.3, 116.7, 116.3, 108.6, 108.3, 83.51, 83.0, 77.37, 77.2, 72.7, 72.2, 33.7, 33.0, 28.0, 27.3, 26.9, 22.5, 13.7 (mixture of diastereomers).

Analysis: **Calcd.:** C, 67.26; H, 10.35%, **Found:** C, 67.51; H, 10.11%.

4,5-Bis-methoxymethoxynon-1-en-3-ol (103).



103

Compound **103** was prepared following the procedure as described for compound **99** as an inseparable mixture of diastereomers (*syn*:*anti* = 19:1) as a pale yellowish oil. **Yield**: 90%.

Mol. Formula: $C_{13}H_{26}O_5$

$[\alpha]_D^{25}$: +26.43 (*c* 0.8, $CHCl_3$).

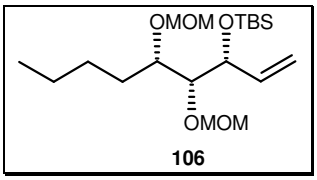
^{1}H NMR (200 MHz, $CDCl_3$): δ 5.87-6.04 (m, 1H), 5.36 (td, *J* = 23.8, 17.2 Hz, 2H), 4.79 (d, *J* = 6.7 Hz, 1H), 4.70 (d, *J* = 6.7 Hz, 1H), 4.68 (s, 2H), 4.32 (tt, *J* = 5.5, 1.6 Hz, 1H), 3.64-3.73

(m, 1H), 3.44 (s, 3H), 3.39 (s, 3H), 2.97 (br s, 1H), 1.58-1.68 (m, 2H), 1.26-1.35 (m, 4H), 0.88 (t, J = 7 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.8, 22.6, 27.3, 27.7, 30.1, 30.4, 55.7, 56.0, 71.6, 71.9, 78.1, 78.3, 83.0, 83.2, 96.6, 96.9, 97.9, 98.3, 115.9, 116.5, 137.3, 137.7.

Analysis: **Calcd.:** C, 59.52; H, 9.99%; **Found:** C, 59.86; H, 9.63%.

[1-(1,2-Bis-methoxymethoxy-hexyl)-allyloxy]-tert-*butyl-dimethyl-silane (106).*



106

To a stirred solution of allylic alcohol *103* ***(1.20 g, 4.57 mmol) in CH_2Cl_2 (50 mL) and 2,6-lutidine (2.94 g, 3.175 mL, 27.44 mmol) was added TBSTf (1.33 g, 5.031 mmol) at 0 ^oC and mixture was stirred at the same temperature for 30 min. The reaction mixture was quenched with water and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (3:1) as eluent gave compound*** *106* ***as a colorless oil.***

Yield: 1.69 g (98%).

Mol. Formula: $C_{19}H_{40}O_5Si$

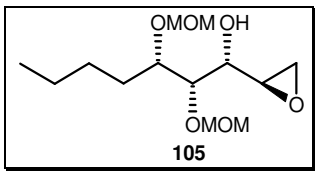
$[\alpha]_D^{25}$***: +31.90 (c 0.9, $CHCl_3$).***

^{1}H NMR ***(200 MHz, $CDCl_3$): δ 5.88-6.04 (m, 1H), 5.16 (dd, J = 27.3, 17.8 Hz, 2H), 4.91 (d, J = 7.04 Hz, 1H), 4.71 (d, J = 7.04 Hz, 2H), 4.63 (s, 2H), 4.37 (t, J = 6.7 Hz, 1H), 3.56-3.64 (m, 1H), 3.40 (s, 3H), 3.38 (s, 3H), 1.51-1.74 (m, 2H), 1.26-1.33 (m, 4H), 0.89 (s, 12H), 0.06 (s, 3H), 0.03 (s, 3H).***

^{13}C NMR ***(50 MHz, $CDCl_3$): δ 138.1, 115.4, 98.3, 96.9, 81.7, 77.6, 74.1, 55.8, 55.7, 30.9, 27.5, 25.7, 22.7, 17.9, 13.9, -4.8, –4.9.***

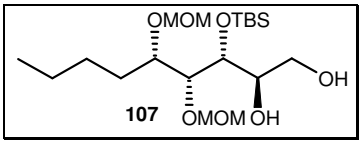
Analysis: Calcd.: ***C, 60.60; H, 10.71;*** *Found:* ***C, 60.89, H, 10.42%.***

2,3-Bis-methoxymethoxy-1-oxiranyl-heptan-1-ol (105).



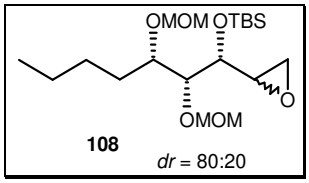
To a solution of titanium (IV) isopropoxide (475 mg, 1.67 mmol) (-)-diisopropyl-D-tartrate (0.46 g, 1.97 mmol) in CH_2Cl_2 (20 mL) at -20 ^oC was added the olefin *103* ***(399 mg, 1.52 mmol) in CH_2Cl_2 (4 mL) followed by* tert*-butyl hydroperoxide (273 mg, 3.03 mmol). The reaction mixture was stirred for 4 days at -20 ^oC and then diluted with ether and saturated sodium sulphate. The mixture was stirred vigorously for 2 h at room temperature and filtered. The filtrate was concentrated and residue was chromatographed over silica gel to give epoxide*** *105* ***(63 mg, 15%) as a colorless oil.***

3-(*tert*-Butyl-dimethylsilanyloxy)-4,5-bis-methoxymethoxynonane-1,2-diol (107).



To a mixture of $K_3Fe(CN)_6$ (915 mg, 2.78 mmol), K_2CO_3 (384 mg, 2.78 mmol) and $(DHQ)_2AQN$ (7.8 mg, 1 mol %), in *t*-BuOH-H_2O (1:1, 5 mL) cooled at 0 ^oC was added OsO_4 (0.79 mL, 0.1 M soln in toluene, 0.4 mol %). After stirring for 5 min at 0 ^oC, the olefin **106** (346 mg, 0.92 mmol) was added in one portion. The reaction mixture was stirred at 0 ^oC for 24 h and then quenched with solid sodium sulfite (2 g). The stirring was continued for 45 min and the solution was extracted with EtOAc (3 x 50 mL). The combined organic phases were washed (10% KOH, then brine), dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (3:2) as eluent gave diol **107** (347mg, 91%) as an inseparable mixture of diastereomers (5:1) in form of a colorless syrupy liquid.

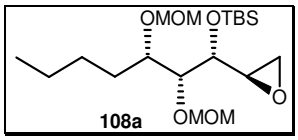
(2,3-Bis-methoxymethoxy-1-oxiranylheptyloxy)-*tert*-butyldimethylsilane (108).



To a stirred solution of olefin **106** (0.940 g, 2.49 mmol) and Na_2HPO_4 (709 mg, 4.99 mmol) in THF (30 mL) was added *m*-CPBA (1.72 g, 4.99 mmol) at 0 ^oC. The mixture was stirred for

1 h and then overnight at room temperature. The solution was treated with saturated aqueous $NaHCO_3$ and $Na_2S_2O_3$ and extracted with CH_2Cl_2. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. Silica gel column chromatography using pet ether/EtOAc (9:1) as eluent gave the epoxide **108** (0.89 g, 91%) as an inseparable mixture of diastereomers (*anti*:*syn* = 4:1) as a colorless syrupy liquid.

Hydrolytic kinetic resolution of epoxide 108.



108a

A solution of epoxide **108** (0.574 g, 1.46 mmol) and (*R,R*)-salen-Co(III)-OAc (4 mg, 0.007 mmol) in THF (10 μL) was stirred at 0 ^oC for 5 min, and then distilled water (10 μL, 0.584 mmol) was added. After stirring for 42 h, it was concentrated and purified by silica gel column chromatography using pet ether/EtOAc (8:2) to afford **108a** as a colorless syrupy liquid as a single diastereomer. (Determined by ^1H NMR and ^{13}C NMR analysis). Continued chromatography with pet ether/EtOAc (3:2) provided the diol **108b** as a brown color liquid as a single diastereomer.

Data of compound 108a.

Yield: 431 mg (94%).

Mol. Formula: $C_{19}H_{40}O_6Si$

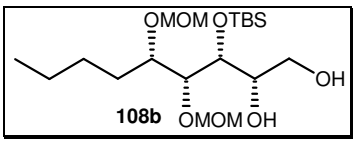
$[\alpha]_D^{25}$: –7.1 (*c* 1.28, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 2954, 2932, 2893, 2859, 1471, 1376, 1361, 1252, 1215, 1102, 1042, 919, 839, 776, 759.

^1H NMR (200 MHz, $CDCl_3$): δ 4.80 (d, *J* = 6.1 Hz, 1H), 4.74 (d, *J* = 6.3 Hz, 2H), 4.65 (d, *J* = 6.5 Hz, 1H), 3.81 (m, 1H), 3.62 (dd, *J* = 6.2, 4.0 Hz, 1H), 3.57 (m, 1H), 3.39 (s, 3H), 3.37 (s, 3H), 3.27 (m, 1H), 2.67-2.76 (m, 2H), 1.61-1.66 (m, 2H), 1.25-1.36 (m, 4H), 0.91 (s, 12 H), 0.08 (s, 3H), 0.06 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 96.6, 96.3, 83.3, 79.9, 55.6, 55.2, 52.9, 44.2, 28.5, 25.7, 22.9, 17.9, 13.9, -4.86, -5.33.

Data of compound 108b.



108b

Yield: 103 mg (90%).

Mol. Formula: $C_{19}H_{42}O_7Si$

$[\alpha]_D^{25}$: +19.6 (*c* 1.03, $CHCl_3$).

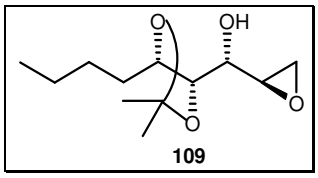
IR (neat, cm^{-1}): ν_{max} 3400, 2933, 2862, 1473, 1367, 1214, 1179, 1027, 929, 874, 638, 758.

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.79 (d, *J* = 6.6 Hz, 1H), 4.74 (d, *J* = 6.3 Hz, 1H), 4.71 (d, *J* = 6.4 Hz, 2H), 3.91 (m, 2H), 3.86 (m, 2H), 3.63 (m, 2H), 3.44 (s, 3H), 3.42 (s, 3H), 1.73 (br s, 1H), 1.59 (br s, 1H), 1.26-1.39 (m, 6H), 0.91 (t, *J* = 7.1 Hz, 3H), 0.89 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 97.8, 96.7, 80.5, 77.0, 72.6, 70.6, 63.3, 56.1, 55.8, 30.8, 27.6, 25.7, 22.6, 22.5, 17.8, 13.8, -4.3, -5.0.

Analysis: **Calcd.:** C, 55.58; H, 10.31%; **Found:** C, 55.69; H, 10.12%.

(5-Butyl-2,2-dimethyl-[1,3]-dioxolan-4-yl)-oxiranylmethanol (109).



109

To a solution of titanium (IV)isopropoxide (729 mg, 2.56 mmol), (-)-diisopropyl-D-tartrate (710 mg, 3.03 mmol) in CH_2Cl_2 (20 mL) at -20 ^oC was added olefin **99** (500 mg, 2.33 mmol) in CH_2Cl_2 (4 mL) followed by *tert*-butyl hydroperoxide (420 mg, 0.52 mL, 4.66 mmol). After 48 h at -20 ^oC, the reaction mixture was diluted with ether and saturated sodium sulphate. The mixture was stirred vigorously for 2 h at room temperature and filtered. The filtrate was concentrated and residue was chromatographed over silica gel to give epoxide **109**[7k] as a colorless oil.

Yield: 314 mg (78%); yield based on 75% of s*yn* compound.

Mol. Formula: $C_{12}H_{22}O_4$

$[\alpha]_D^{25}$: –3.7 (*c* 0.9, $CHCl_3$).

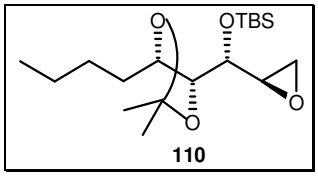
IR (neat, cm^{-1}): ν_{max} 3453, 2956, 2931, 2893, 2859, 1379, 1254, 1192.

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.02-4.09 (m, 1H), 3.83-3.90 (m, 1H), 3.68 (t, *J* = 7.13 Hz, 1H), 3.22-3.28 (m, 1H), 2.77-2.89 (m, 2H), 2.09 (s, 1H), 1.46-1.66 (m, 3H), 1.42 (s, 3H), 1.39 (s, 3H), 1.26-1.36 (m, 3H), 0.91 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 108.9, 81.3, 79.5, 71.5, 52.3, 44.6, 33.8, 28.2, 27.4, 27.0, 22.7, 13.9.

Analysis: **Calcd.:** C, 62.58; H, 9.63%; **Found:** C, 62.78; H, 9.41%.

***tert*-Butyl-[(5-butyl-2,2-dimethyl-[1,3]-dioxolan-4-yl)-oxiranylmethoxy]dimethyl-silane (110).**



110

To a stirred solution of epoxy alcohol **109** (0.40 g, 1.737 mmol) and imidazole (260 mg, 3.82 mmol) in CH_2Cl_2 (50 mL) was added TBSCl (0.392 g, 2.61 mmol) at 0 ^oC and the reaction mixture was stirred at the same temperature for 30 min. The reaction mixture was quenched with water and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) as eluent gave compound **110** as a colorless oil.

Yield: 586 mg (98%).

Mol. Formula: $C_{18}H_{36}O_4Si$

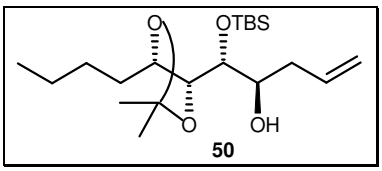
$[\alpha]_D^{25}$: –18.1 (*c* 0.8, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.91-4.12 (m, 2H), 3.68 (t, *J* = 7.2 Hz, 1H), 3.24 (m, 1H), 2.72-2.88 (m, 2H), 1.48-1.66 (m, 2H), 1.43 (s, 3H), 1.39 (s, 3H), 1.24-1.37 (m, 4H), 0.91 (s, 12H), 0.08 (s, 3H), 0.06 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 108.7, 81.4, 78.9, 72.3, 53.4, 43.9, 33.7, 28.3, 27.4, 27.0, 24.5, 22.8, 16.2, 13.86, -4.8, -4.9;

Analysis: **Calcd.:** C, 62.74; H, 10.53%; **Found.** C, 62.46; H, 10.87%.

1-(5-Butyl-2,2-dimethyl-[1,3]dioxolan-4-yl)-1-(*tert*-butyldimethylsilanyloxy)-pent-4-en-2-ol (50).



50

A round bottom flask was charged with copper(I)iodide (0.011 g, 0.06 mmol), gently heated under vacuum and slowly cooled with a flow of argon. After the addition of THF (20 mL), this suspension was cooled to –20 ^{o}C, stirred and vinylmagnesium bromide (1.22 mL, 1.21 mmol, 1M in THF) was added to it. A solution of epoxide **110** (0.21 g, 0.609 mmol) in THF (5 mL) was added to the above reagent and the mixture was stirred at –20 ^{o}C for 1 h. After consumption of starting material, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl. The water layer was extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated. Purification of crude product by silica gel column chromatography using pet ether/EtOAc (8:2) as eluent afforded **50**[8h] as a colorless liquid.

Yield: 204 mg (90%).

Mol. Formula: $C_{20}H_{40}O_4Si$

$[\alpha]_D^{25}$: –10.1 (*c* 0.64, $CHCl_3$), lit.[3] -9.10 (*c* 0.17, CH_2Cl_2).

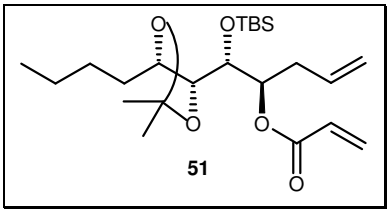
IR (neat, cm^{-1}): ν_{max} 3475, 2858, 1608.

^{1}H NMR (200 MHz, $CDCl_3$): δ 5.91 (m, 1H), 5.10-5.20 (m, 2H), 4.07 (m, 1H), 3.75-3.86 (m, 2H), 3.69 (dd, *J* = 4.6, 2.8 Hz, 1H), 1.44-1.56 (m, 4H), 1.43 (s, 3H), 1.42 (s, 3H), 1.32-1.41 (m, 2H), 0.95 (s, 9H), 0.92 (t, *J* = 7.2 Hz, 3H), 0.12 (s, 3H), 0.11 (3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 134.0, 117.2, 108.5, 81, 32, 73.4, 71.9, 38.5, 32.8, 28.3, 27.3, 26.8, 25.9, 22.8, 18.2, 13.9, -4.4, -4.5.

Analysis: **Calcd.:** C, 64.47; H, 10.82; **Found:** C, 64.62; H, 10.71%.

Acrylic acid 1-[(5-butyl-2,2-dimethyl-[1,3]dioxolan-4-yl)-(*tert*-butyldimethylsilanyloxy)-methyl]-but-3-enyl ester (51).



Acryloyl chloride (0.034 g, 0.376 mmol) was added drop wise under argon to a solution of **50** (140 mg, 0.376 mmol) and triethylamine (0.152 g, 1.50 mmol) in dry CH_2Cl_2 (10 mL) at 0 ^oC. The mixture was stirred overnight at room temperature. The resulting mixture was filtered through a pad of celite and poured into water and organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL) and combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated. Purification of crude product by silica gel column chromatography using pet ether/EtOAc (19:1) as eluent afforded **51** as a yellowish syrupy liquid.

Yield: 173 mg (88%).

Mol. Formula: $C_{23}H_{42}O_5Si$

$[\alpha]_D^{25}$: –2.86 (*c* 0.64, CH_2Cl_2); lit.[3] $[\alpha]_D^{25}$: –2.46 (*c* 0.65, CH_2Cl_2).

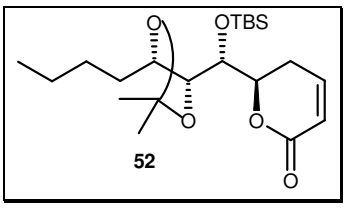
IR (neat, cm^{-1}): ν_{max} 3029, 2956, 2931, 2859, 1644, 1464, 1255, 1102, 1036, 918, 873, 837, 776.

^{1}H NMR (200 MHz, $CDCl_3$): δ 5.83-6.04 (m, 1H), 5.07-5.17 (m, 2H), 4.78 (d, *J* = 6.7 Hz, 1H), 4.73 (t, *J* = 1.96 Hz, 3H), 3.60-3.88 (m, 1H), 3.75 (t, *J* = 3.52 Hz, 1H), 3.61-3.68 (m, 1H), 3.43 (s, 3H), 3.41 (s, 3H), 1.55-1.76 (m, 2H), 1.21-1.36 (m, 6H), 1.21 (s, 12H), 0.12 (s, 3H), 0.10 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 116.2, 99.1, 96.4, 85.8, 79.3, 73.6, 70.1, 55.7, 37.2, 29.4, 28.6, 25.8, 22.7, 18.0, 14.1, -4.4, -4.9.

Analysis: **Calcd.:** C, 64.75; H, 9.92%; **Found:** 64.94%; H, 9.72%.

6-[(5-Butyl-2,2-dimethyl-[1,3]dioxolan-4-yl)-(*tert*-butyldimethylsilanyloxy)-methyl]-5,6-dihydropyran-2-one (52).



Grubb's catalyst (5 mg, 0.0056 mmol) dissolved in CH_2Cl_2 (10 mL) was added drop wise to a refluxing solution of acrylate **51** (120 mg, 0.281 mmol), Ti(*i*-PrO)$_4$ (24 mg, 0.08 mmol) in dry CH_2Cl_2 (60 mL). Refluxing was continued for 16 h by which time all the starting material was consumed. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography using pet ether/EtOAc (9:1) as eluent to afford **52** as a yellowish syrupy liquid.

Yield: 91 mg (90%).

Mol. Formula: $C_{21}H_{38}O_5Si$

$[\alpha]_D^{25}$: +71.6 (*c* 0.44, CH_2Cl_2); lit.[3] +69.2 (c 0.30, CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.13 (s, 3 H), 0.14

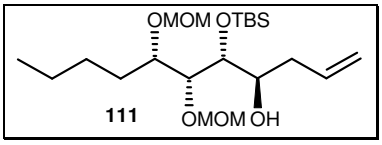
(s, 3 H), 0.91 (t, *J* = 7.3 Hz, 3 H), 0.92 (s, 9 H), 1.30-1.41 (m, 3 H), 1.38 (s, 6 H), 1.46-1.56 (m, 3 H), 2.56 (ddd, *J* = 19.3, 5.4, 4.0 Hz, 1 H), 2.75 (ddd, *J* = 18.8, 12.6, 2.7 Hz, 1 H), 3.61 (dd, *J* = 8.1, 2.4 Hz, 1 H), 3.96-4.04 (m, 2 H), 4.54 (dd, *J* = 12.6, 4.0, 2.0 Hz, 1 H), 5.99 (dd, *J* = 9.8, 3.1 Hz, 1 H), 6.95 (ddd, *J* = 8.7, 6.3, 2.1 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.5, -3.4, 14.2, 18.7, 23.0, 24.5, 26.3, 27.1, 27.8, 28.6, 33.0, 72.2, 76.8, 81.2, 82.4, 108.9, 120.6, 146.8, 164.1.

Analysis: **Calcd.:** C, 63.28; H, 9.61%; **Found:** C, 63.44; H, 9.81%.

The spectroscopic data (IR, ^{1}H NMR, & ^{13}C NMR) were in accord with those described.[8h]

5-(*tert*-Butyldimethylsilanyloxy)-6,7-bis-methoxymethoxy-undec-1-en-4-ol (111).



Compound **111** was prepared following the procedure as described for compound **50** as a colorless liquid.

Yield: 86%.

Mol. Formula: $C_{21}H_{44}O_6Si$

$[\alpha]_D^{25}$: +26.3 (*c* 0.9, $CHCl_3$).

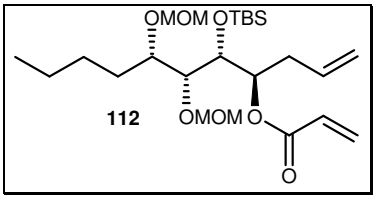
IR (neat, cm^{-1}): ν_{max} 3029, 2956, 2931, 2859, 1644, 1464, 1255, 1102, 1036, 918, 873, 837, 776.

1H NMR (200 MHz, $CDCl_3$): δ 5.83-6.04 (m, 1H), 5.07-5.17 (m, 2H), 4.78 (d, *J* = 6.7 Hz, 1H), 4.73 (t, *J* = 1.96 Hz, 3H), 3.80-3.88 (m, 2H), 3.75 (t, *J* = 3.52 Hz, 1H), 3.64-3.68 (m, 1H), 3.43 (s, 3H), 3.41 (s, 3H), 2.17-2.25 (m, 2H), 1.60-1.72 (m, 2H), 1.21-1.36 (m, 4H), 0.89 (s, 12H), 0.12 (s, 3H), 0.10 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 136.2, 116.2, 99.1, 96.4, 85.8, 79.3, 73.6, 70.1, 55.7, 37.2, 29.6, 28.6, 25.7, 22.7, 18.0, 13.9, -4.8, -4.9.

Analysis: Calcd.: C, 59.96; H, 10.54; **Found:** C, 60.11; H, 10.61.

Acrylic acid 1-[1-(*tert*-butyldimethylsilanyloxy)-2,3-bis-methoxymethoxy-heptyl]-but-3-enyl ester (112).



Compound **112** was prepared following the procedure as described for compound **51** as a yellowish syrupy liquid.

Yield: 91%.

Mol. Formula: $C_{24}H_{46}O_7Si$

$[\alpha]_D^{25}$: -42.14 (*c* 0.84, $CHCl_3$).

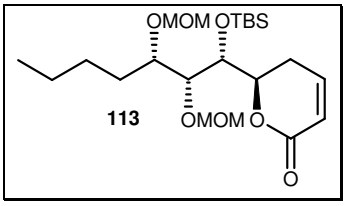
IR (neat, cm^{-1}): ν_{max} 2931, 2858, 1726, 1638, 1254, 1256, 1192.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.45 (ddd, *J* = 17.2, 1.6 Hz, 1H), 6.09 (dd, *J* = 17.2, 4.3 Hz, 1H), 5.83 (dd, *J* = 10.2, 1.5 Hz, 1H), 5.75 (dd, *J* = 11.7, 1.6 Hz, 1H), 5.18 (m, 1H), 5.01 (m, 1H), 4.67 (m, 2H), 4.54 (m, 2H), 3.64-3.66 (m, 1H), 3.92 (dt, *J* = 8.2, 1.6 Hz, 1H), 3.37-3.42 (m, 2H), 3.33 (s, 3H), 3.30 (s, 3H), 2.24-2.48 (m, 2H), 1.27-1.34 (m, 6H), 0.81 (s, 12 H), -0.04 (s, 3H), -0.05 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 165.7, 134.6, 131.7, 128.2, 117.1, 98.8, 96.9, 80.8, 79.4, 75.82, 74.4, 74.0, 56.1, 56.0, 32.8, 29.6, 29.4, 28.5, 22.7, 18.2, 14.1, -4.1, -4.7.

Analysis: **Calcd.:** C, 60.72; H, 9.77%; **Found:** C, 61.09; H, 9.62%.

6-[1-(*tert*-Butyldimethylsilanyloxy)-2,3-bis-methoxymethoxyheptyl]-5,6-dihydropyran-2-one (113).



Compound **113** was prepared following the procedure as described for compound **52** as a colorless syrupy liquid.

Yield: 89%.

Mol. Formula: $C_{22}H_{42}O_7Si$

$[\alpha]_D^{25}$: +51.4 (*c* 1.18, $CHCl_3$).

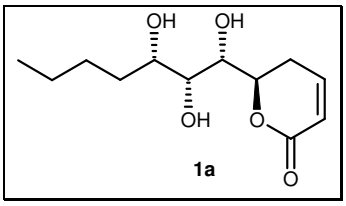
IR (neat, cm^{-1}): ν_{max} 2954, 2934, 2856, 1712, 1469, 1386, 1252, 1149, 1123, 1102, 1018, 923, 838, 779.

^{1}H NMR (200 MHz, $CDCl_3$): δ 5.92 (ddd, *J* = 8.2, 6.3, 2.0 Hz, 1H), 5.99 (dd, *J* = 9.7, 2.3 Hz, 1H), 4.58-4.82 (m, 4H), 4.21 (dd, *J* = 8.2, 1.7 Hz, 1H), 3.62-3.70 (m, 1H), 3.46-3.49 (m, 2H), 3.39 (s, 6H), 2.77 (m, 1H), 2.17 (ddd, *J* = 19.9, 5.9, 3.9 Hz, 1H), 1.31-1.42 (m, 6H), 0.88 (s, 12 H), 0.16 (s, 3H), 0.11 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 164.0, 145.6, 120.7, 98.9, 96.4, 79.2, 78.28, 78.21, 73.8, 56.1, 55.9, 29.6, 28.3, 25.9, 22.9, 22.7, 18.2, 14.0, -4.2, -4.3.

Analysis: Calcd.: C, 59.16; H, 9.48%; **Found:** C, 59.45; H, 9.34%.

Deacetylated boronolide (1a).



Lactone **113** (182 mg, 0.41 mmol) was dissolved in dimethyl sulfide (3 mL) and cooled to -10 ^oC. Then, $BF_3.Et_2O$ (1.02 mL, 8.15 mmol) was added to the solution, which was stirred at the room temperature for 30 min. The reaction mixture was quenched with water and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated to give an oily material which was dissolved in MeCN (5 mL) and treated with 45% aq HF (172 mg, 0.15 mL, 4.1 mmol) at room temperature. After stirring at room temperature for over night, the reaction mixture was quenched with $NaHCO_3$ (1 g) and the

aqueous layer was extracted with CH_2Cl_2 and organic layer was washed with brine, dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using EtOAc as eluent gave deacetylated boronolide **1a** as a white solid.

Yield: 106 mg (86%).

Mol. Formula: $C_{12}H_{20}O_5$

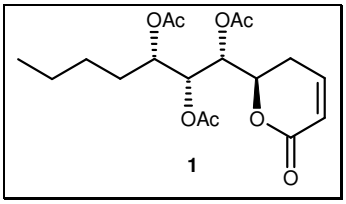
m.p: 101 ^oC, [lit.[7h] m.p 99-100 ^oC].

$[\alpha]_D^{25}$: +57.4 (*c* 0.71, EtOH); lit.[7h] $[\alpha]_D^{25}$ +56 (*c* 0.07, EtOH).

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.95 (ddd, *J* = 9.6, 6.1 Hz, 1H), 6.02 (dd, *J* = 10.1, 2.6 Hz, 1H), 4.52 (ddd, *J* = 11.5, 7.3, 4.1 Hz, 1H), 3.85 (d, *J* = 7.1 Hz, 1H), 3.64 (br s, 2H), 3.01 (br s, 3H), 2.64 (ddd, *J* = 18.7, 5.2, 4.2 Hz, 1H), 2.51 (ddd, *J* = 18.8, 11.5, 2.5 Hz, 1H), 1.46-1.66 (m, 2H), 1.26-1.34 (m, 4H), 0.89 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 163.9, 145.9, 120.9, 77.1, 76.7, 74.3, 70.1, 33.4, 27.7, 25.8, 22.6, 14.0.

boronolide (1).



Acetic anhydride (0.18 mL, 1.96 mmol) was added drop wise to a stirred and cooled (0 ^oC) solution of **1a** (48 mg, 0.196 mmol), *i*-Pr_2EtN (0.5 mL, 2.94 mmol), DMAP (catalytic amount) in CH_2Cl_2 (5 mL). The resulting mixture was allowed to stir for 6 h at room temperature. The resulting mixture was diluted with Et_2O (40 mL). The organic phase was washed with saturated NH_4Cl, water, brine, dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (7:3) as eluent gave compound **1** as a clear oil which solidified on standing.

Yield: 62 mg (85%).

Mol. Formula: $C_{18}H_{26}O_8$

m.p : 88-90 ^oC [lit.[7] mp 90 ^oC].

$[\alpha]_D^{25}$: +26.4 (*c* 0.7, EtOH); lit.[7h] $[\alpha]_D^{25}$ +25 (*c* 0.2, EtOH).

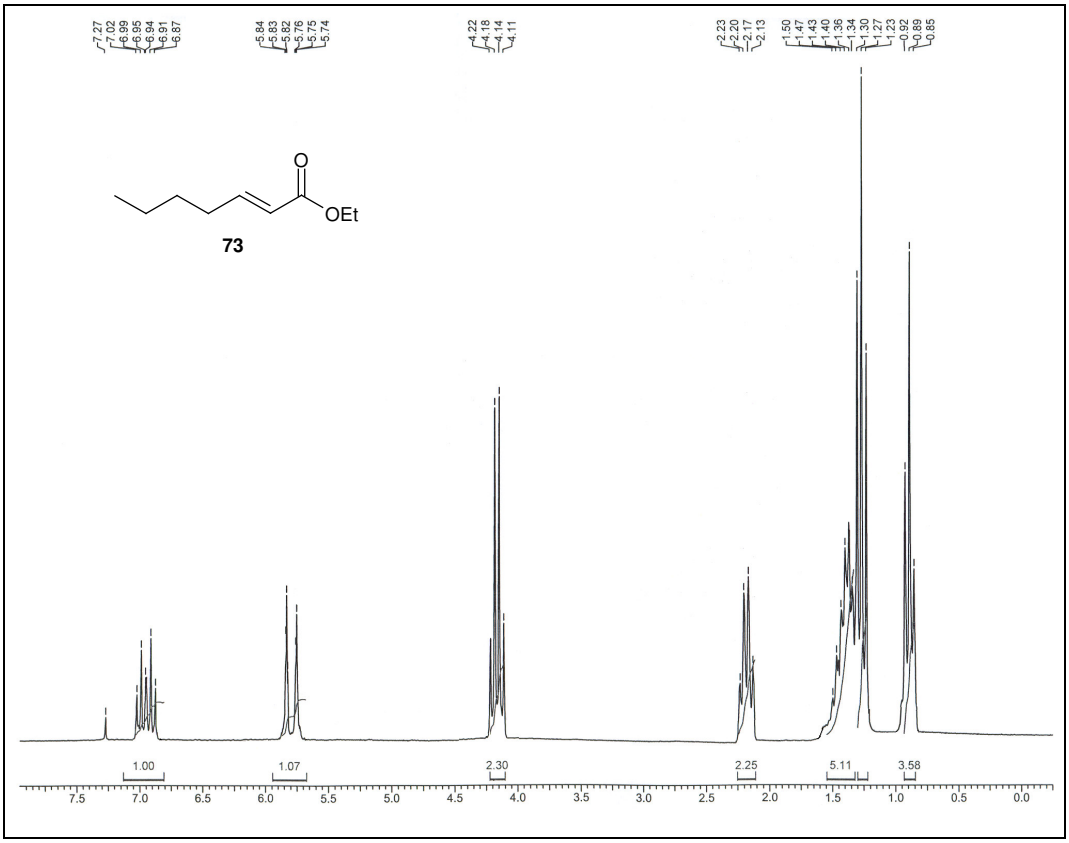
^{1}H NMR (200 MHz, $CDCl_3$): δ 6.89 (ddd, *J* = 9.7, 6.2, 2.7 Hz, 1H), 6.01 (dd, *J* = 9.8, 2.4 Hz, 1H), 5.33-5.38 (m, 2H), 5.01 (q, *J* = 6.1 Hz, 1H), 4.55 (dt, *J* = 12.1, 4.5 Hz, 1H), 2.51 (dddd,

J = 18.1, 11.8, 2.6, 2.5 Hz, 1H), 2.31 (m, 1H), 2.11 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 1.54 (m, 2H), 1.17-1.30 (m, 4H), 0.89 (t, *J* = 6.7 Hz, 3H).

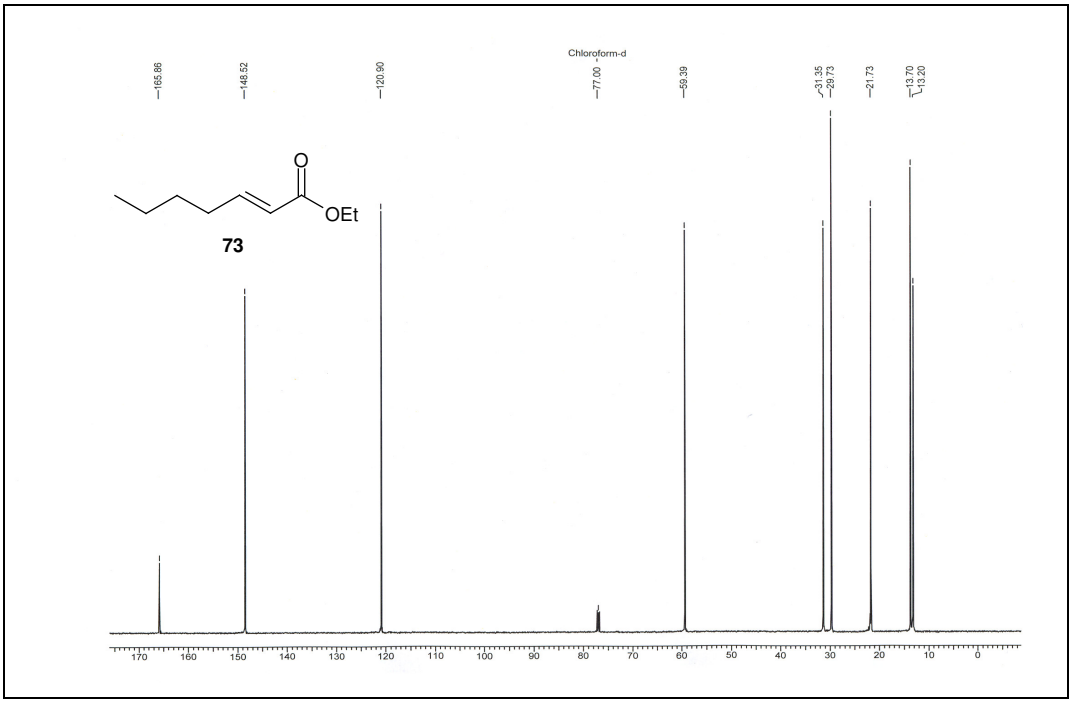
^{13}C NMR (50 MHz, $CDCl_3$): δ 170.5, 169.8, 169.5, 162.5, 144.0, 121.2, 75.1, 71.6, 70.6, 70.5, 30.1, 27.1, 25.2, 22.3, 21.1, 20.6, 13.8.

2.4.2. Spectra

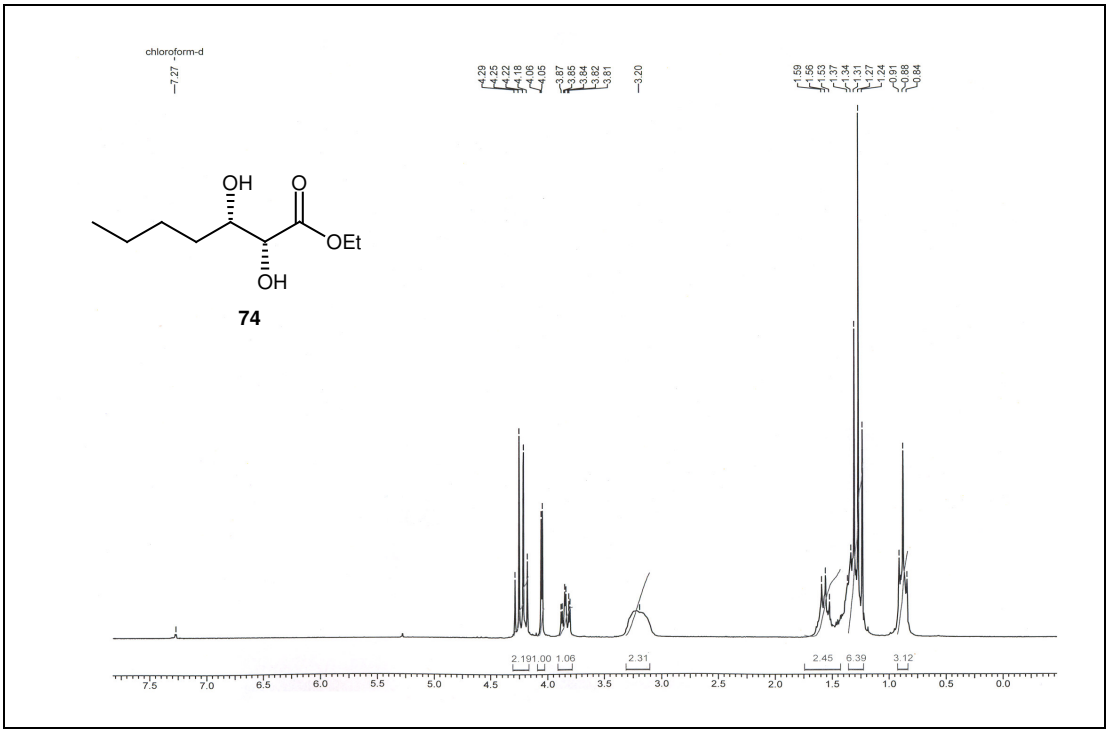
1] ^{1}H NMR Spectrum of **73**
2] ^{13}C NMR Spectrum of **73**
3] ^{1}H NMR Spectrum of **74**
4] ^{13}C NMR Spectrum of **74**
5] ^{13}C NMR Spectrum of **77**
6] ^{1}H NMR Spectrum of **100**
7] ^{13}C NMR Spectrum of **100**
8] ^{1}H NMR Spectrum of **74a**
9] ^{13}C NMR Spectrum of **74a**
10] HPLC of **74a**
11] ^{1}H NMR Spectrum of **97**
12] ^{13}C NMR Spectrum of **97**
13] ^{1}H NMR Spectrum of **101**
14] ^{13}C NMR Spectrum of **101**
15] ^{1}H NMR Spectrum of **99**
16] ^{13}C NMR Spectrum of **99**
17] NOSEY of **104**
18] ^{1}H NMR Spectrum of **103**
19] ^{13}C NMR Spectrum of **103**
20] ^{1}H NMR Spectrum of **106**
21] ^{13}C NMR Spectrum of **106**
22] ^{1}H NMR Spectrum of **108a**
23] ^{13}C NMR Spectrum of **108a**
24] ^{1}H NMR Spectrum of **108b**
25] ^{13}C NMR Spectrum of **108b**
26] ^{1}H NMR Spectrum of **109**
27] ^{13}C NMR Spectrum of **109**
28] ^{1}H NMR Spectrum of **52**
29] ^{13}C NMR Spectrum of **52**
30] ^{1}H NMR Spectrum of **111**
31] ^{13}C NMR Spectrum of **111**
32] ^{1}H NMR Spectrum of **112**
33] ^{13}C NMR Spectrum of **112**
34] ^{1}H NMR Spectrum of **113**
35] ^{13}C NMR Spectrum of **113**
36] ^{1}H NMR Spectrum of **1a**
37] ^{13}C NMR Spectrum of **1a**
38] ^{1}H NMR Spectrum of **1**
39] ^{13}C NMR Spectrum of **1**



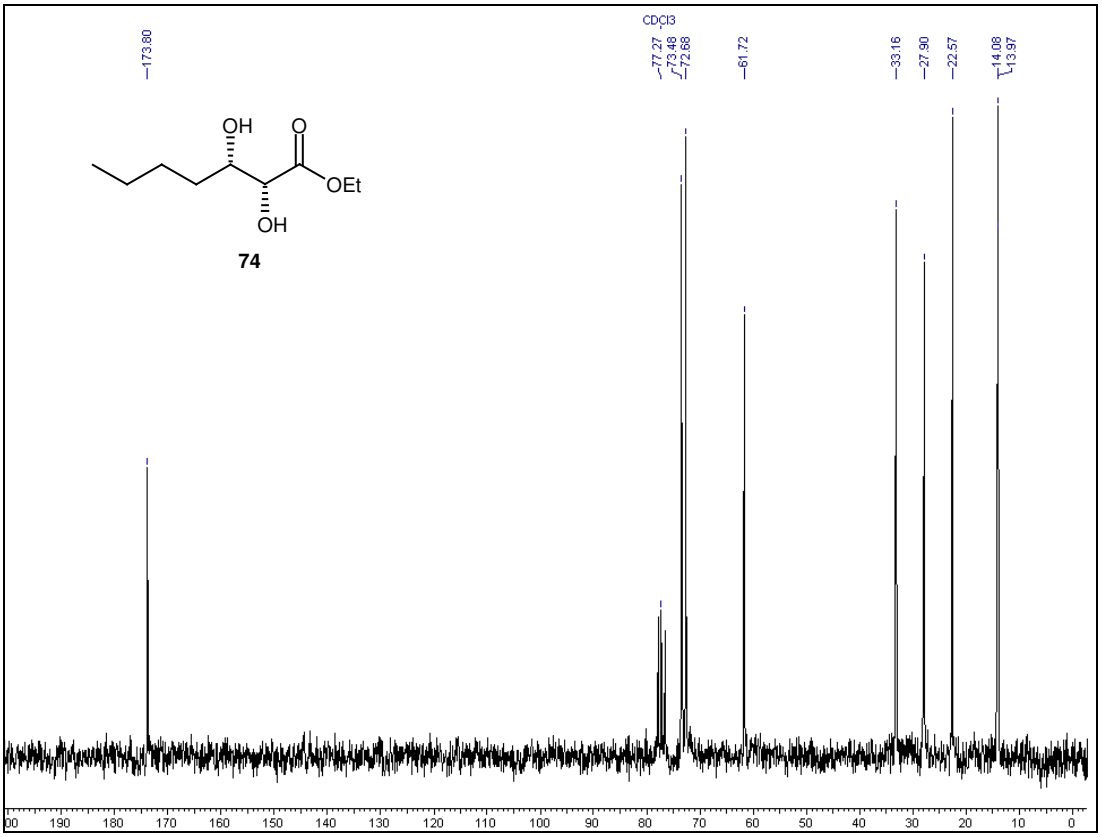
^{1}H NMR Spectrum of **73**



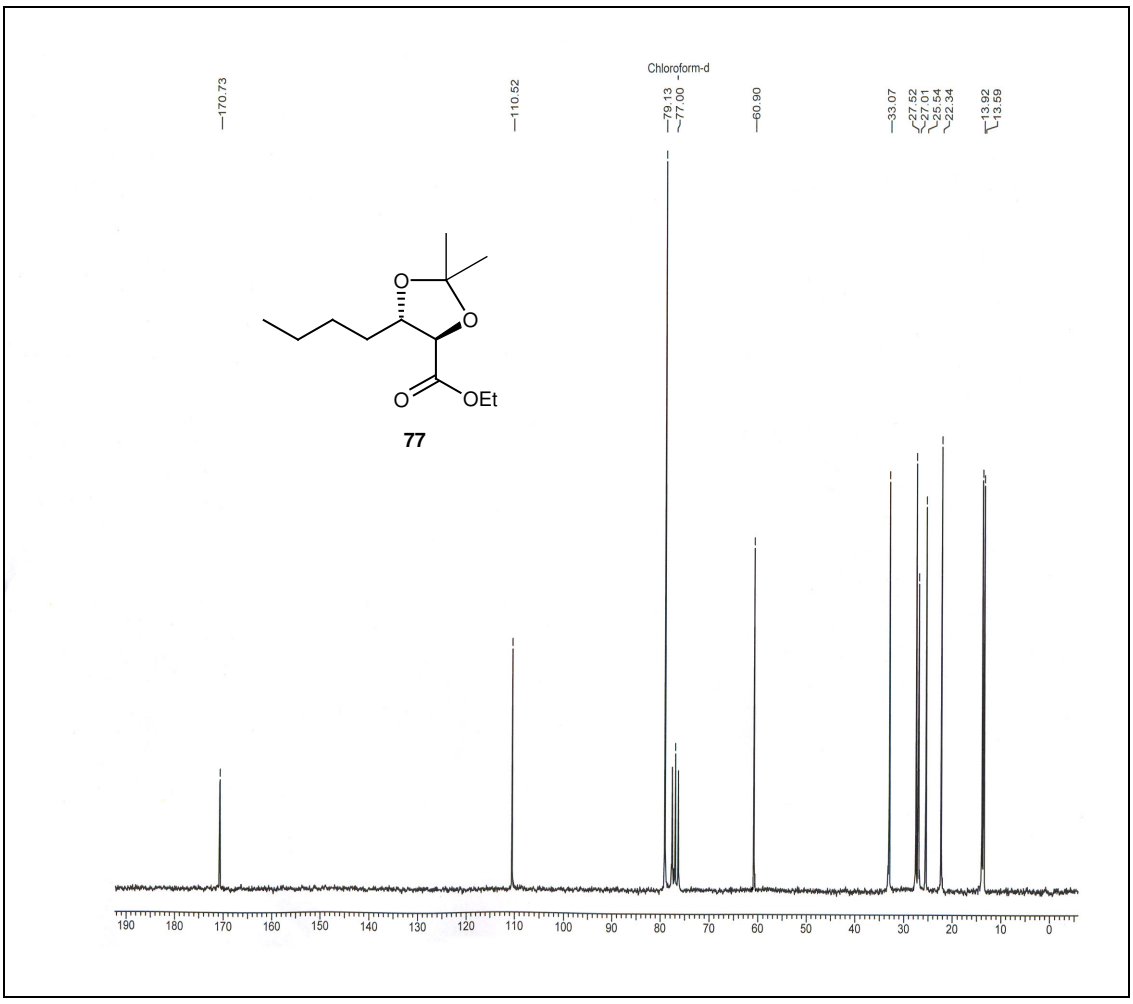
^{13}C NMR Spectrum of **73**



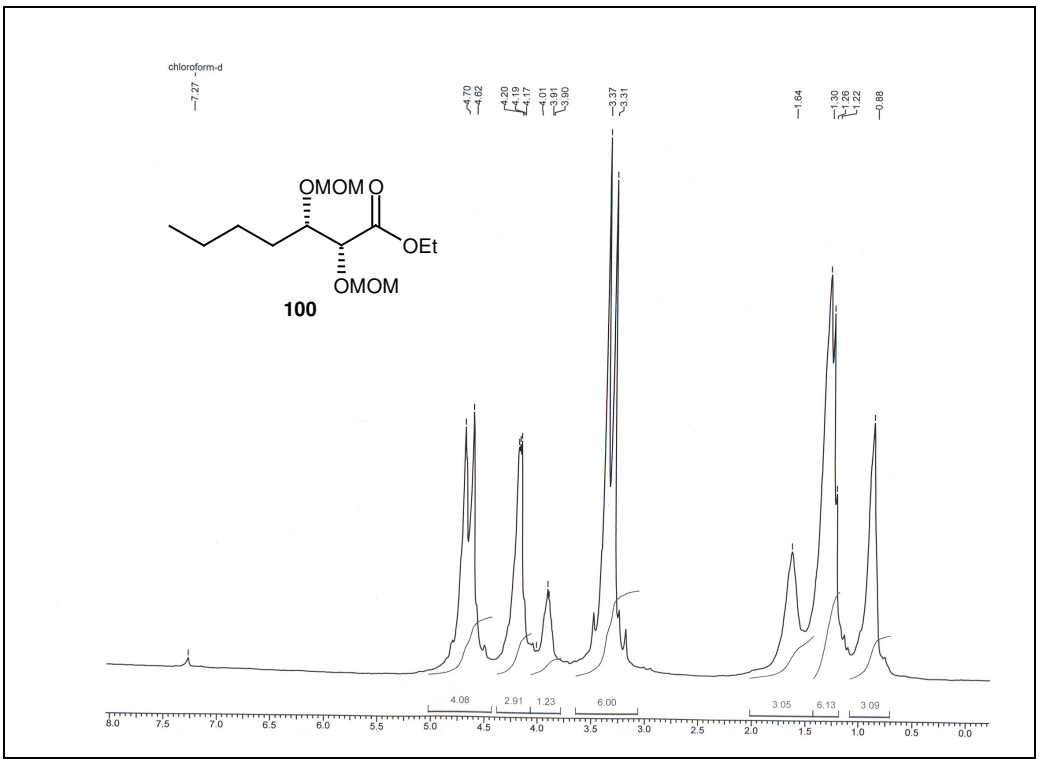
^{1}H NMR Spectrum of **74**



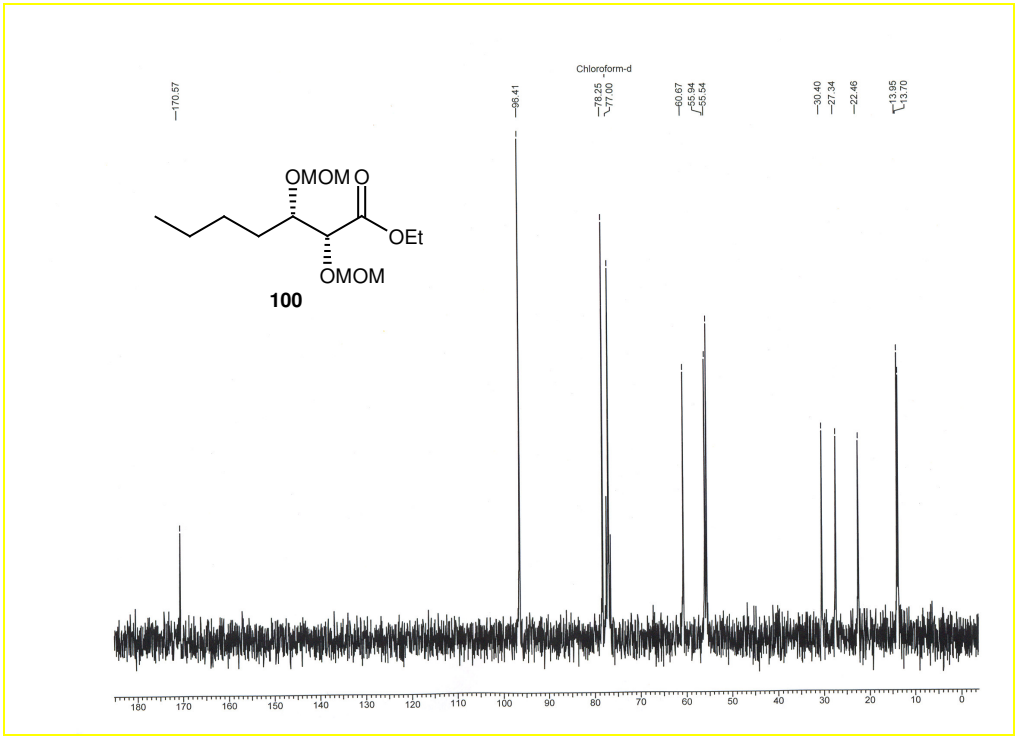
^{13}C NMR Spectrum of **74**



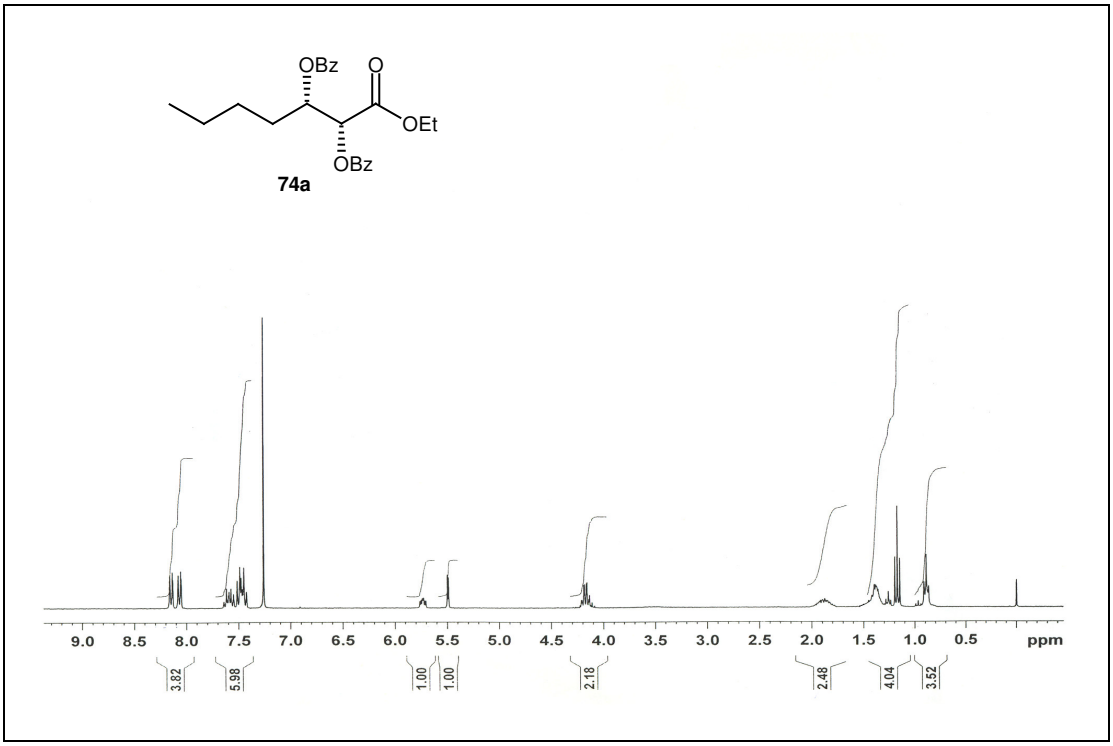
^{13}C NMR Spectrum of **77**



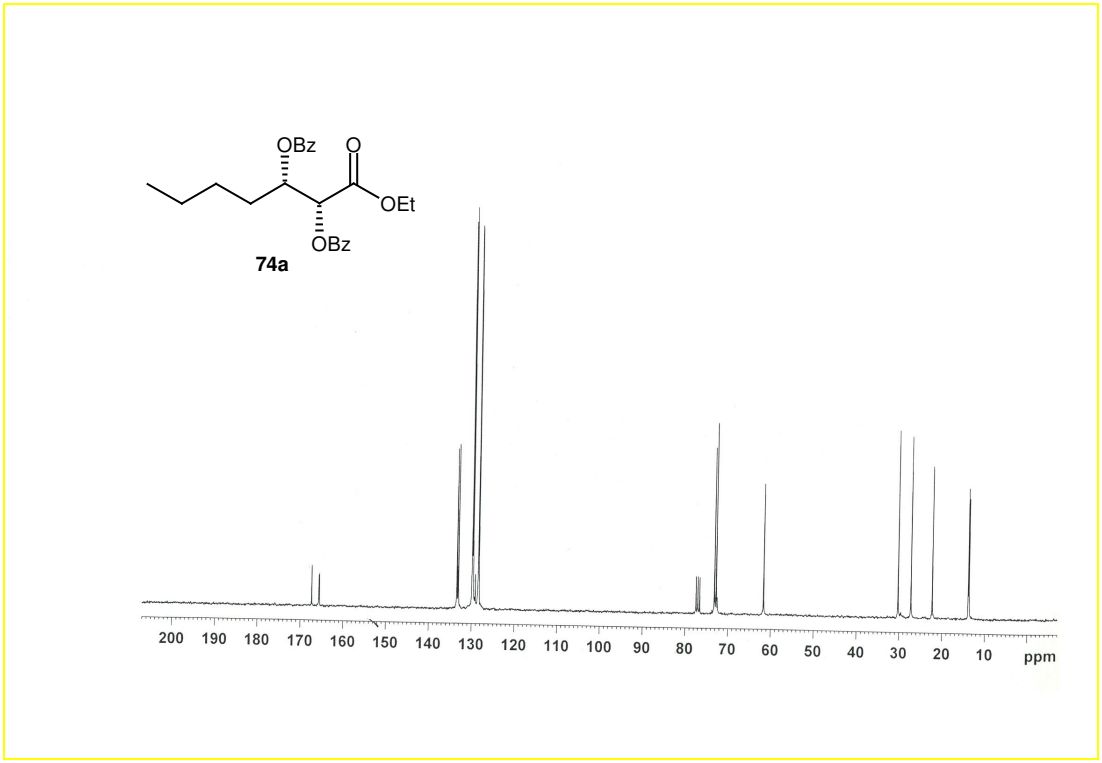
^{1}H NMR Spectrum of **100**



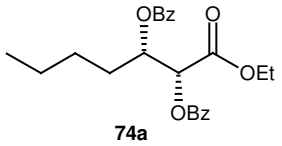
^{13}C NMR Spectrum of **100**



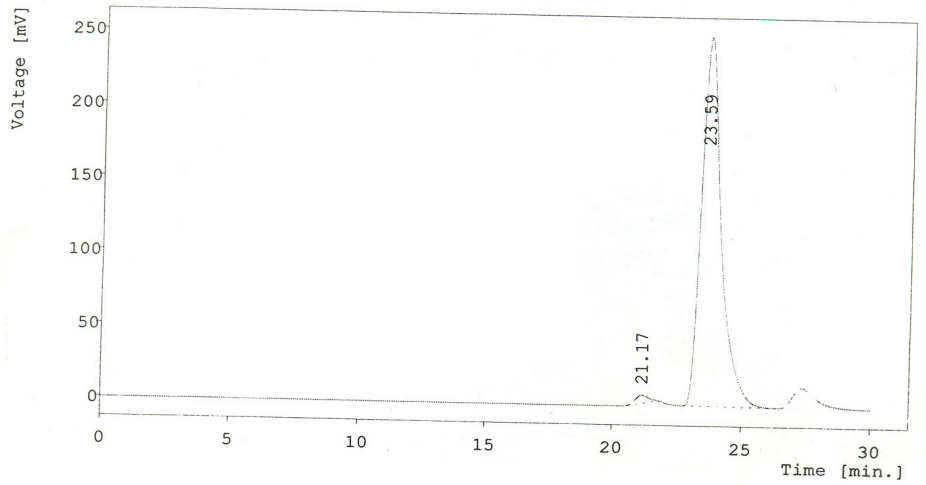
^{1}H NMR Spectrum of **74a**



^{13}C NMR Spectrum of **74a**



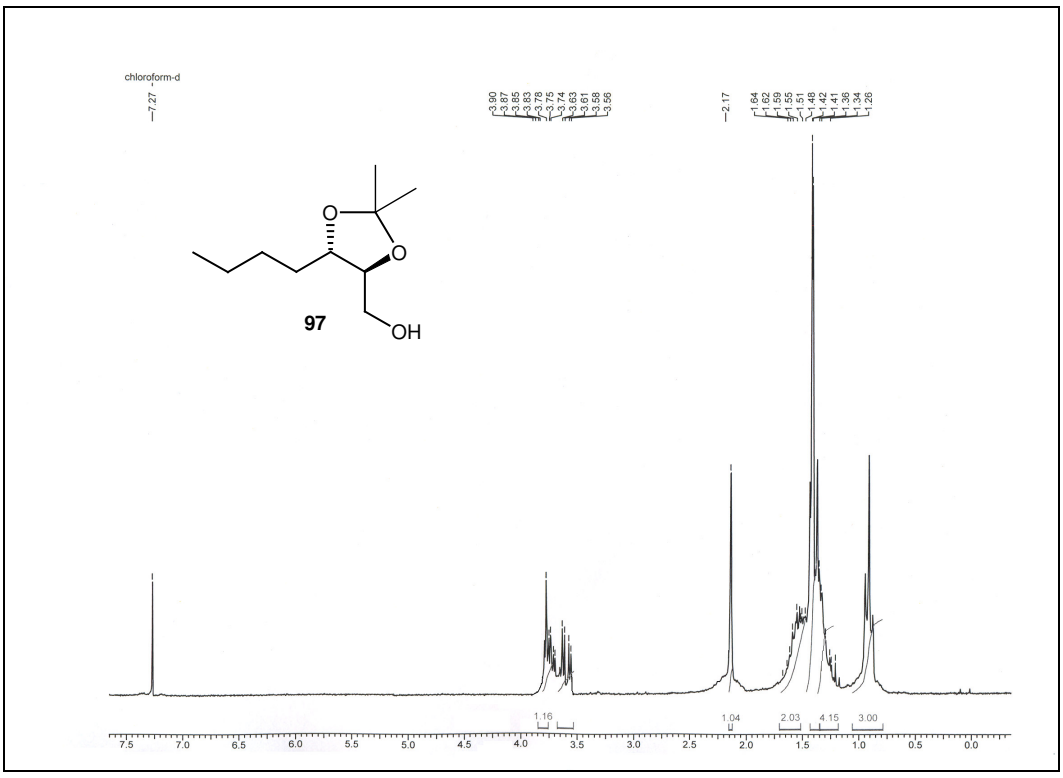
74a



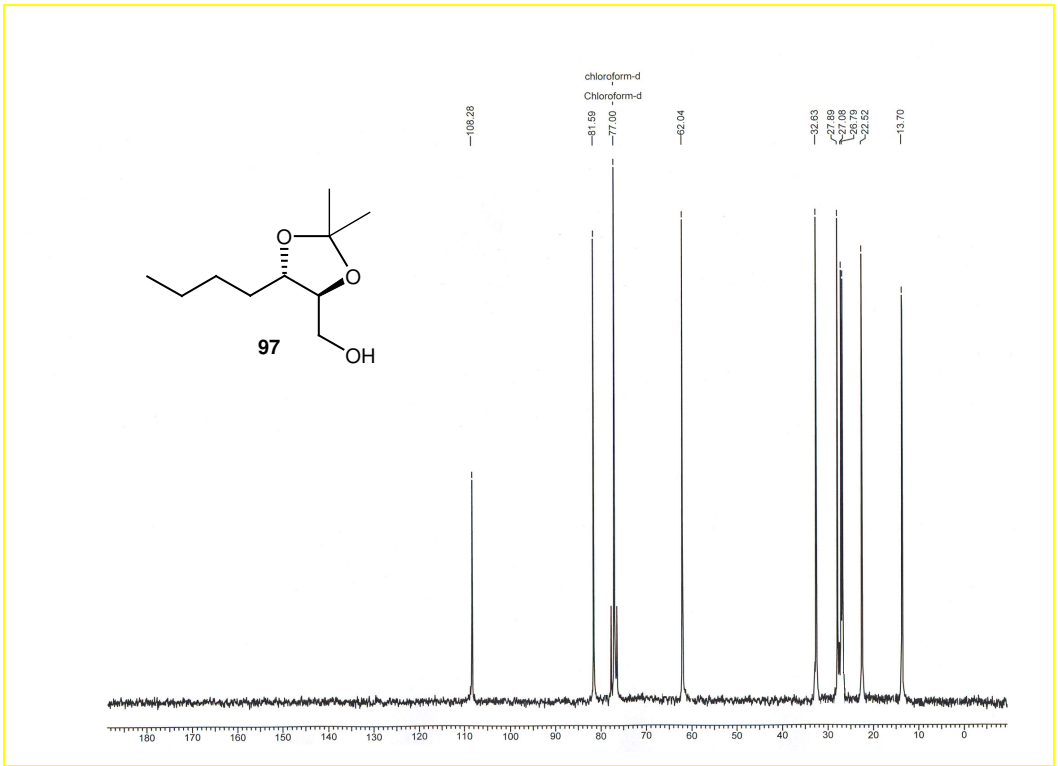
Result Table - Calculation Method Uncal

Peak No.	Reten. time	Area [mV.s]	Height [mV]	W05 [min.]	Area [%]	Height [%]
1	21.167	179.3265	5.374	0.613	1.325	2.099
2	23.593	13351.8468	250.709	0.780	98.675	97.901
-	Total	13531.1733	256.083			

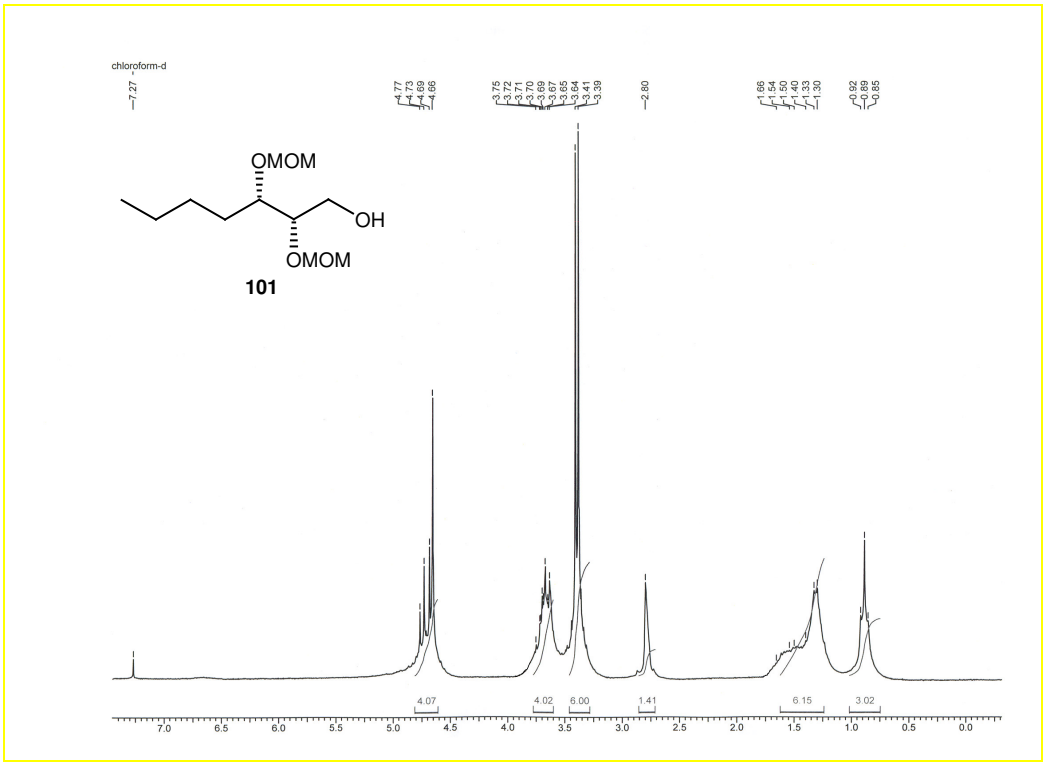
HPLC of **74a**



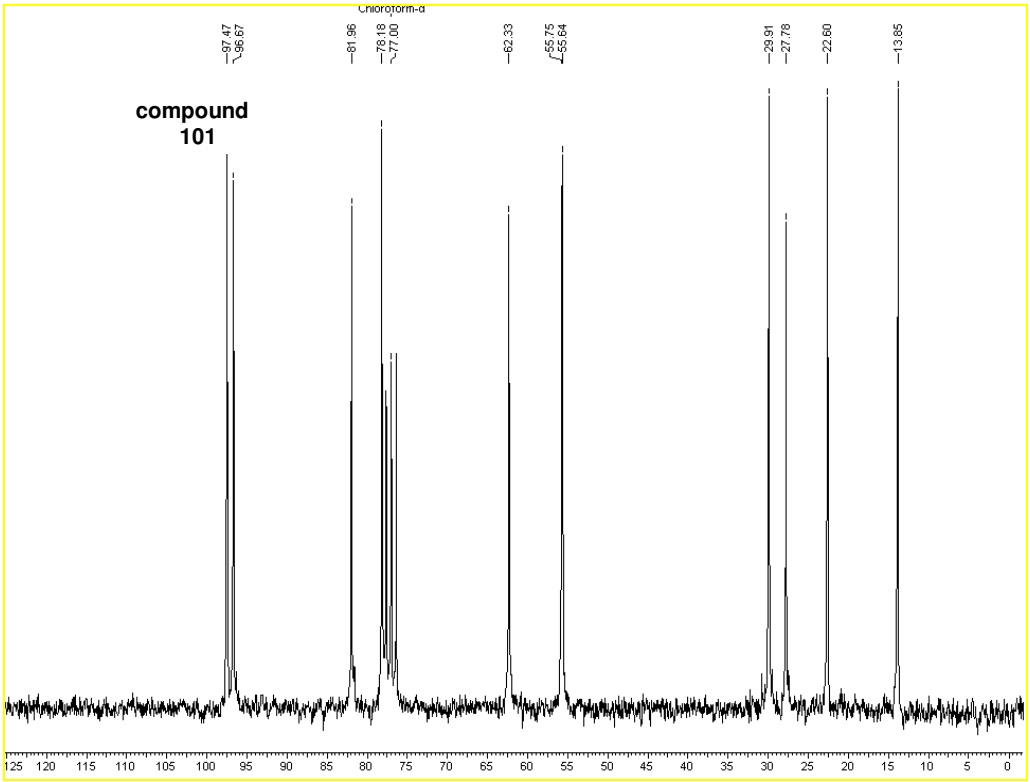
^{1}H NMR Spectrum of **97**



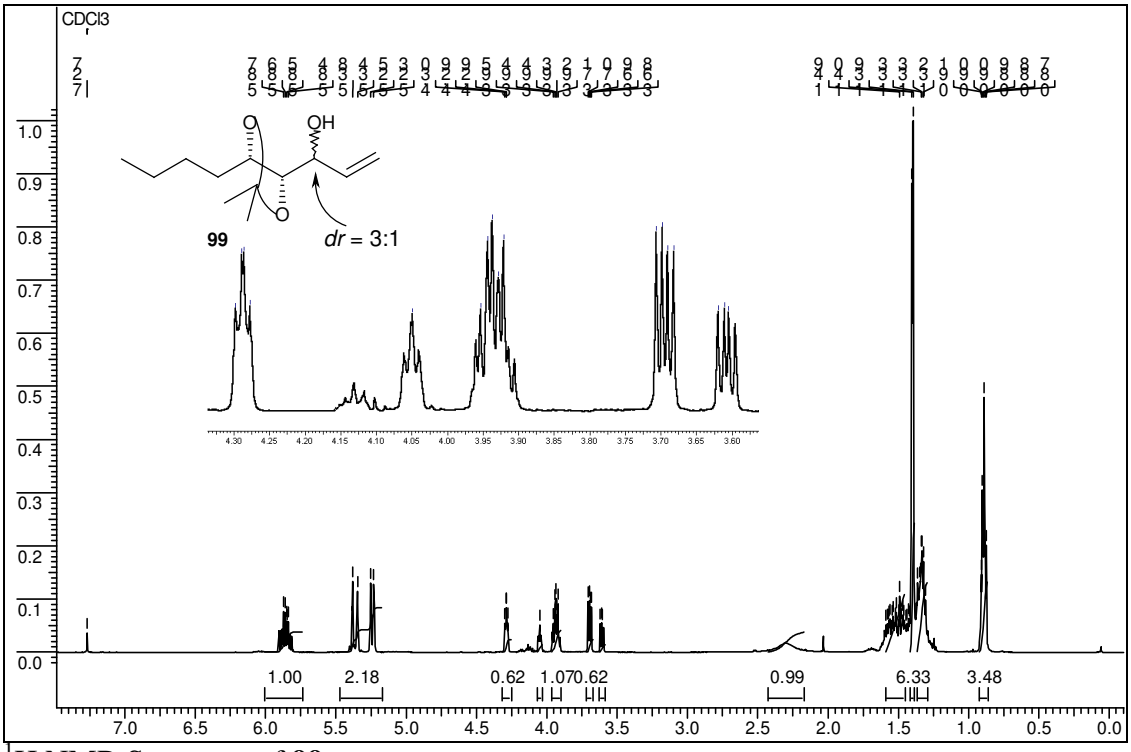
^{13}C NMR Spectrum of **97**



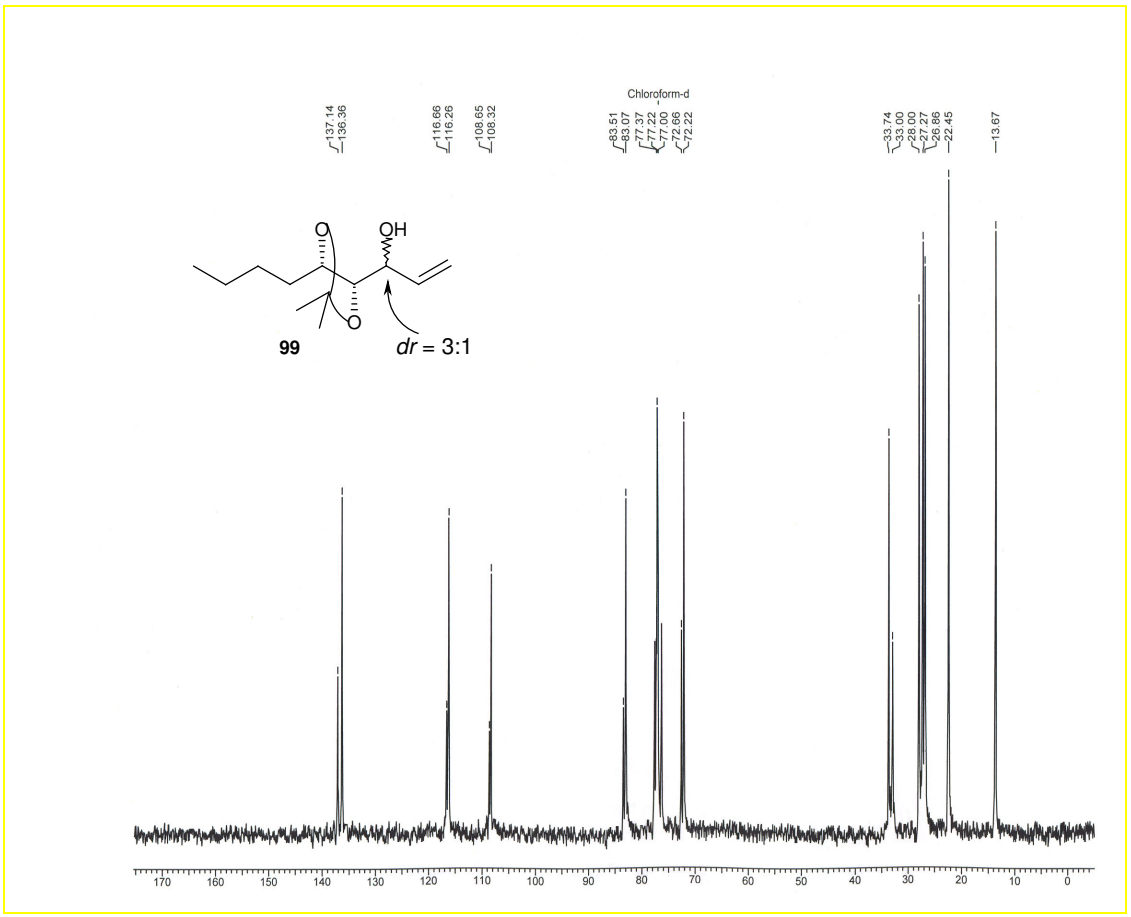
^{1}H NMR Spectrum of **101**



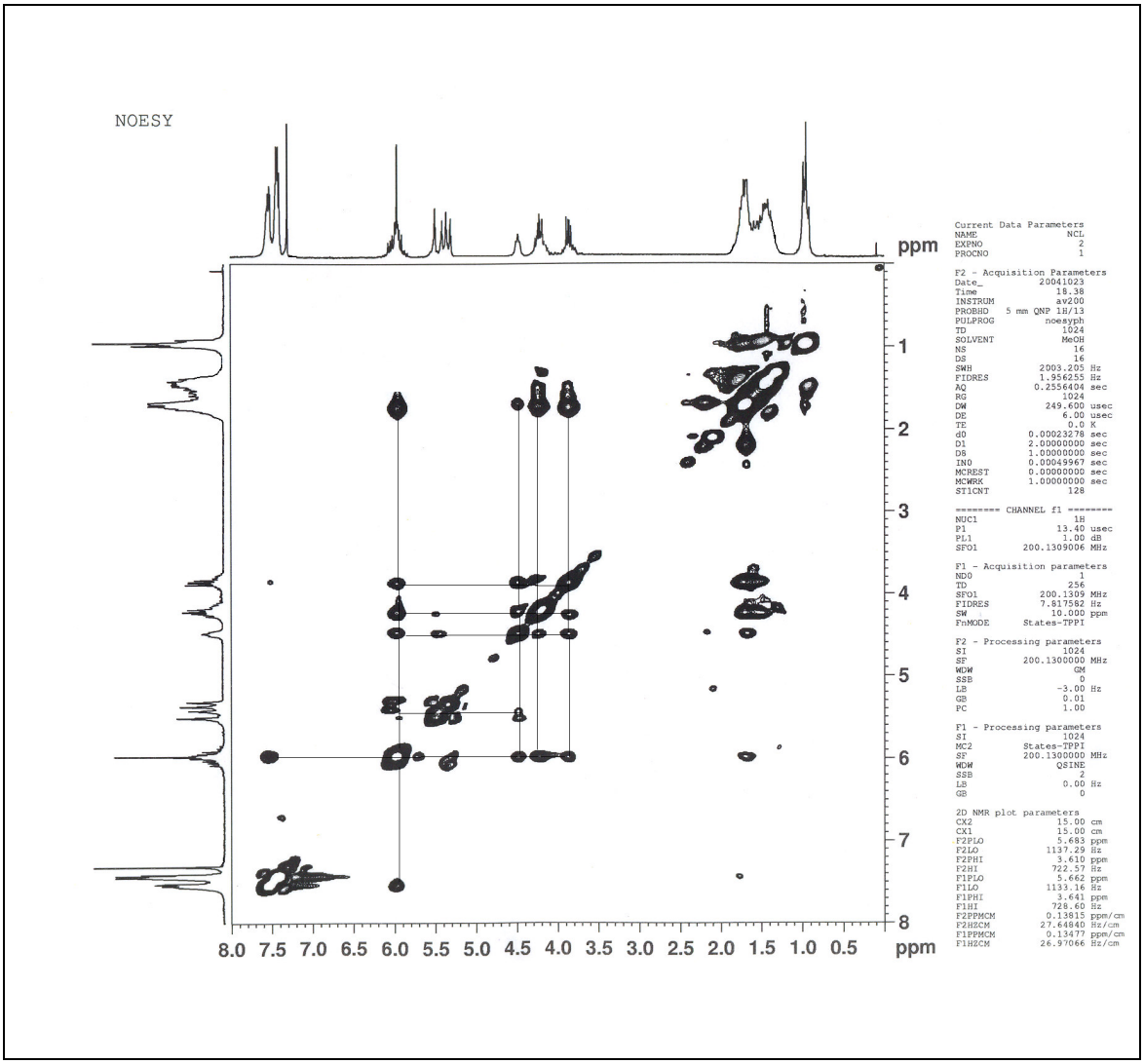
^{13}C NMR Spectrum of **101**

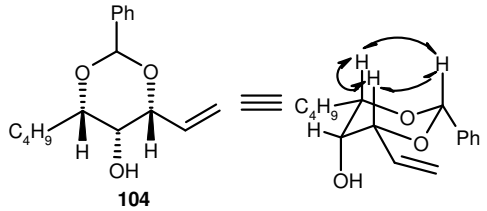


^{1}H NMR Spectrum of **99**



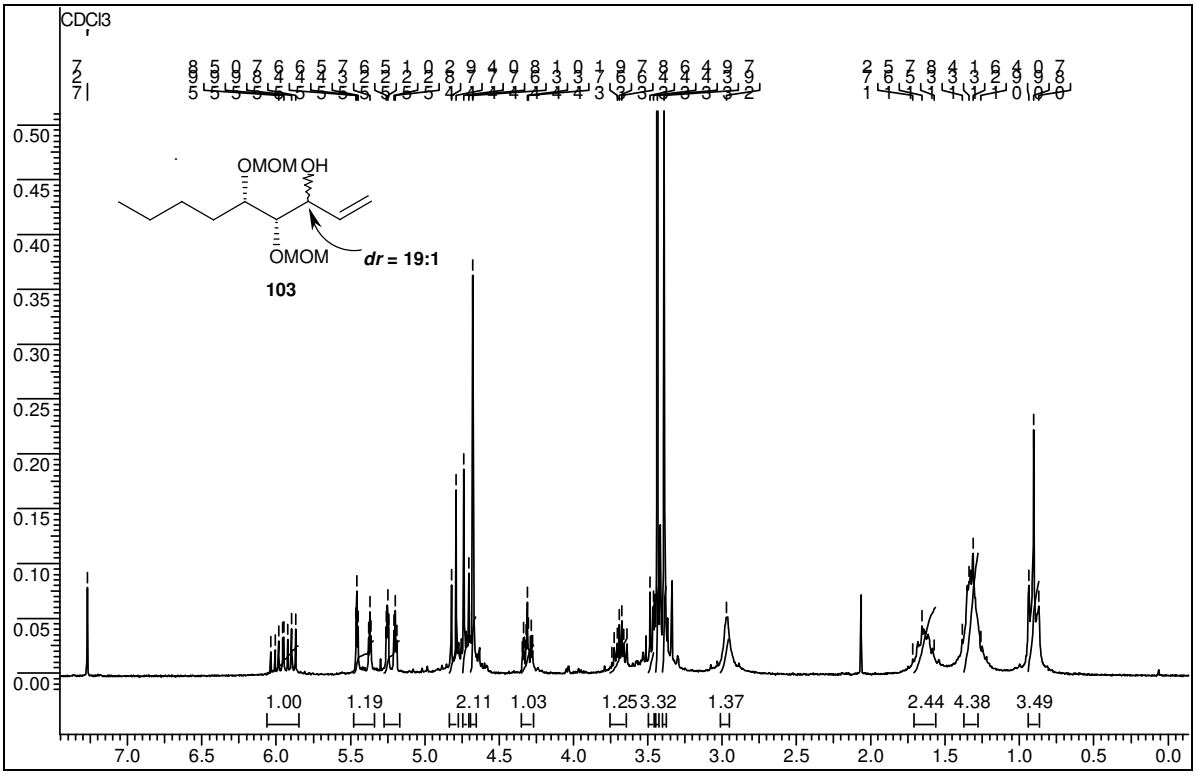
^{13}C NMR Spectrum of **99**



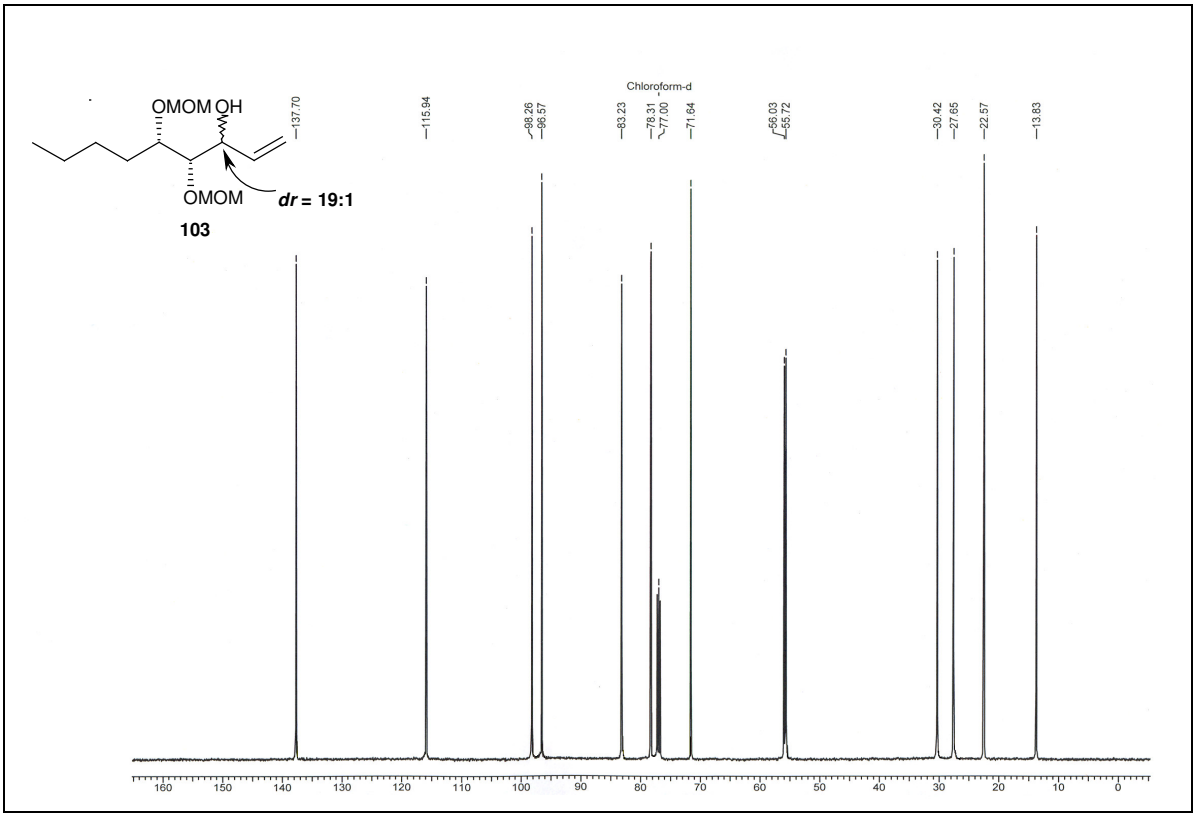


104

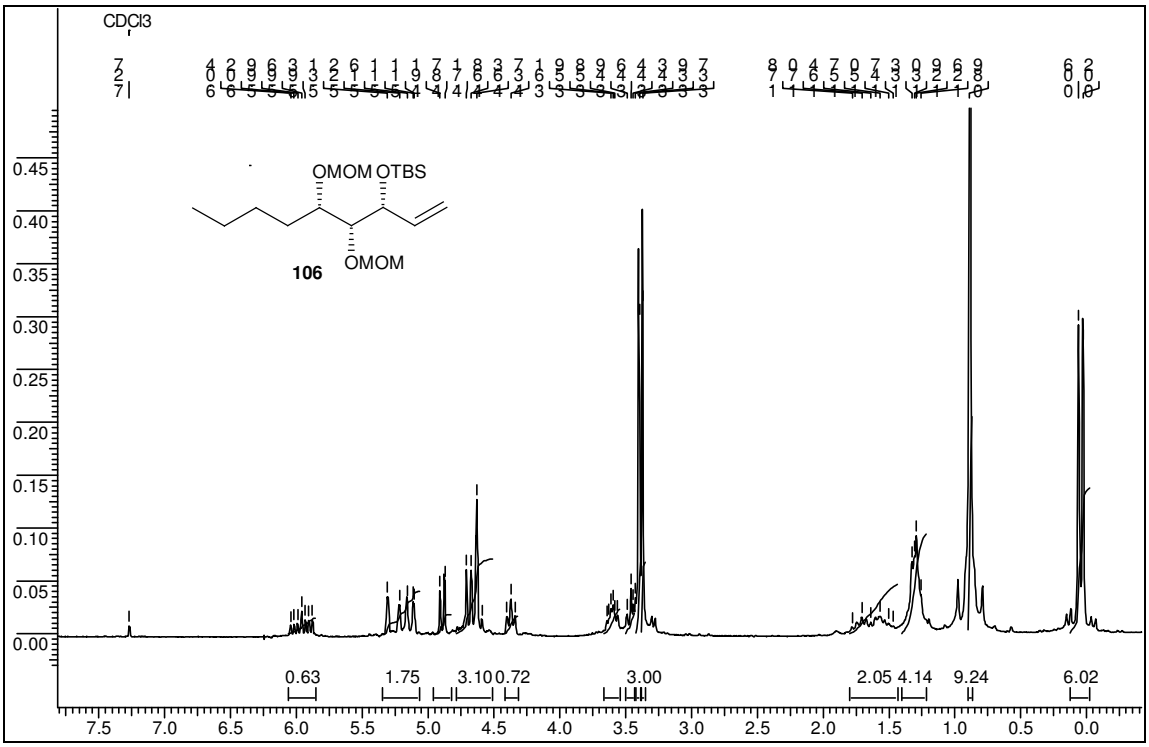
NOSEY of **104**



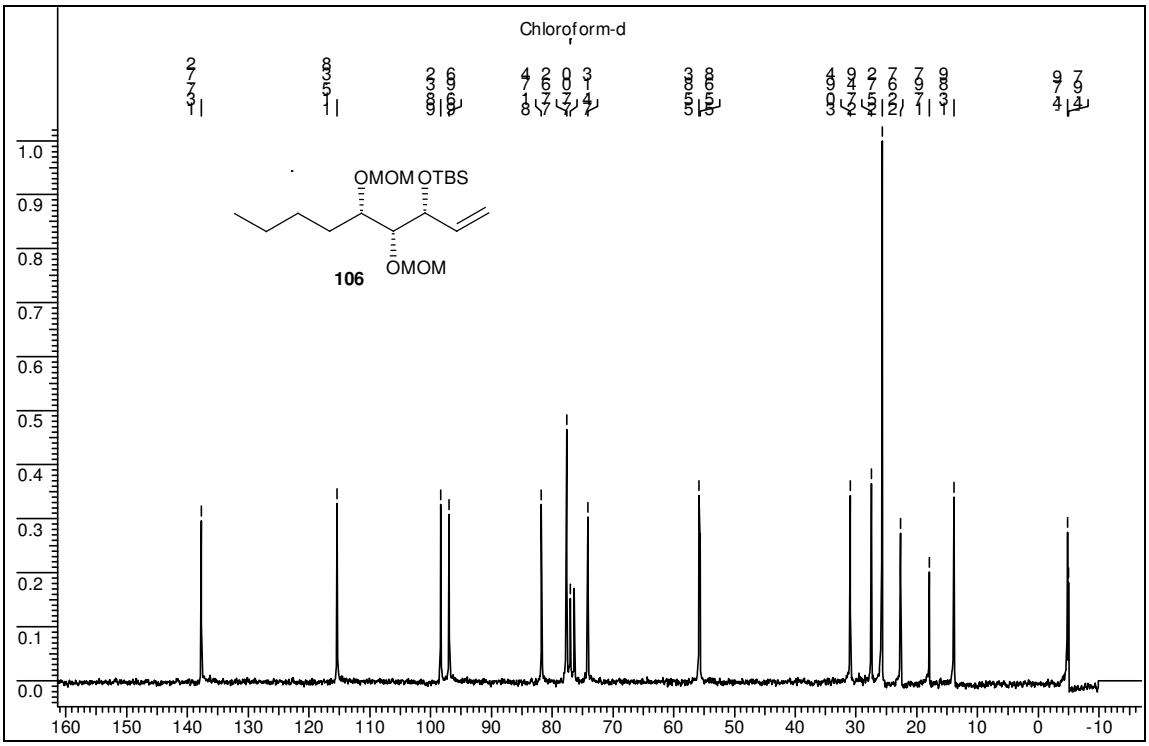
^{1}H NMR Spectrum of **103**



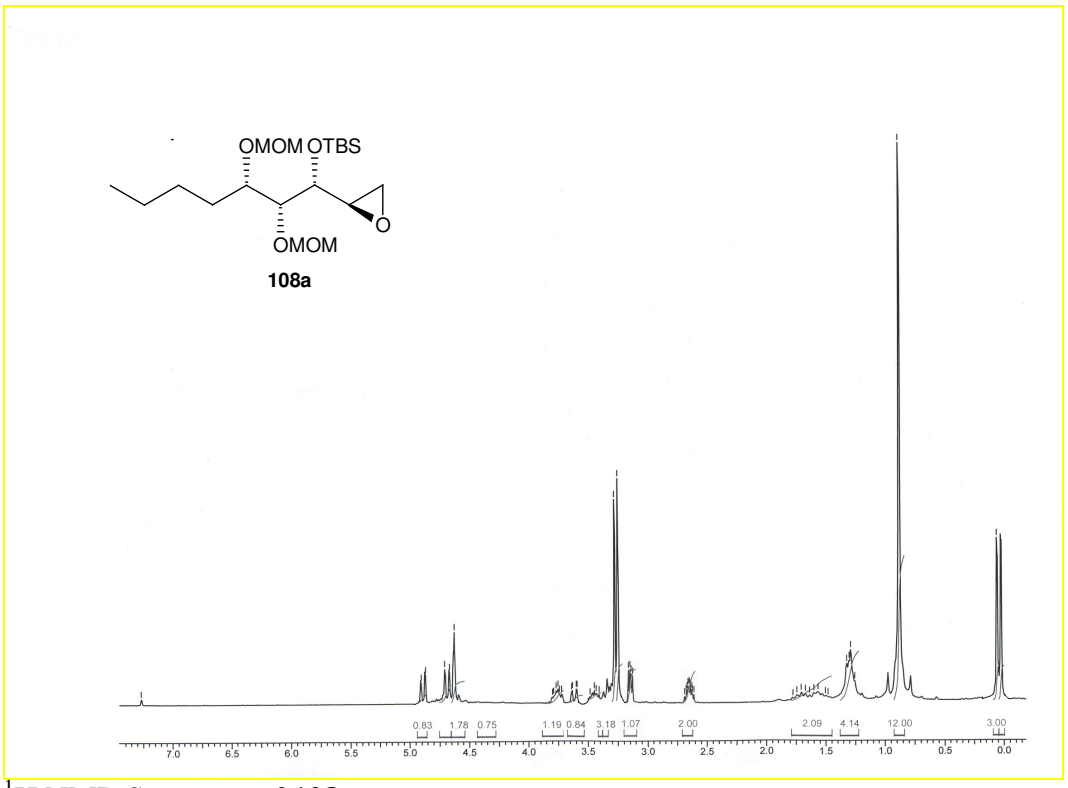
^{13}C NMR Spectrum of **103**



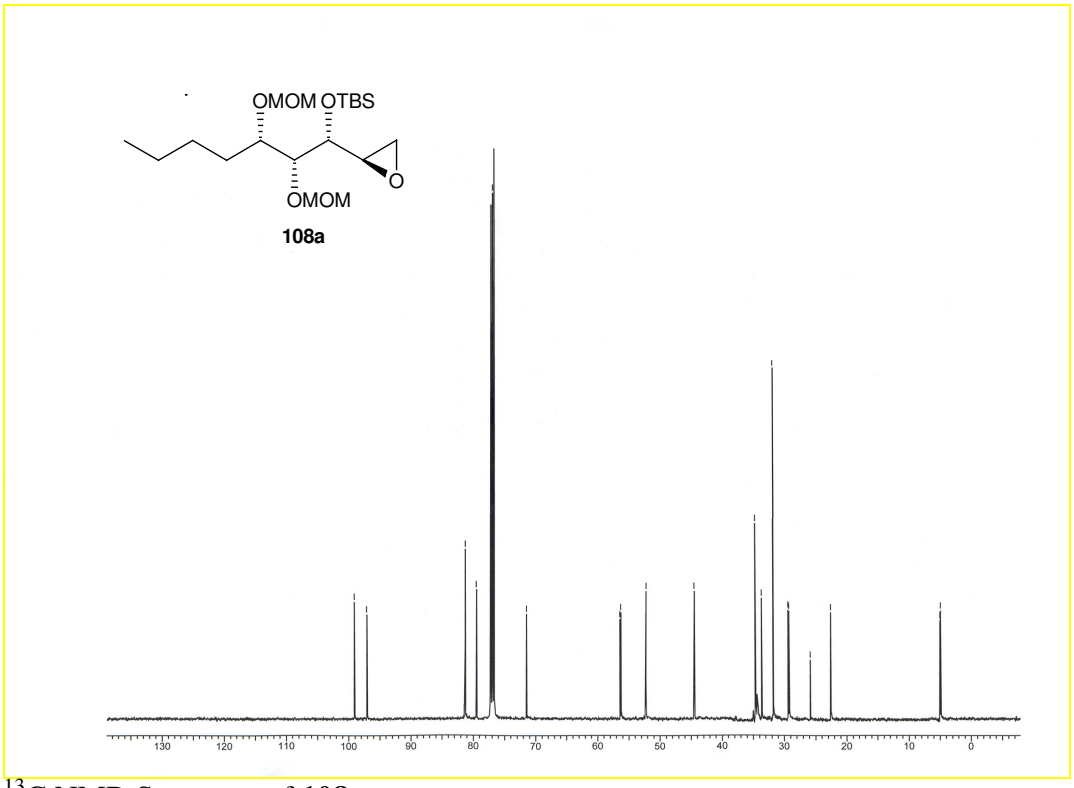
^{1}H NMR Spectrum of **106**



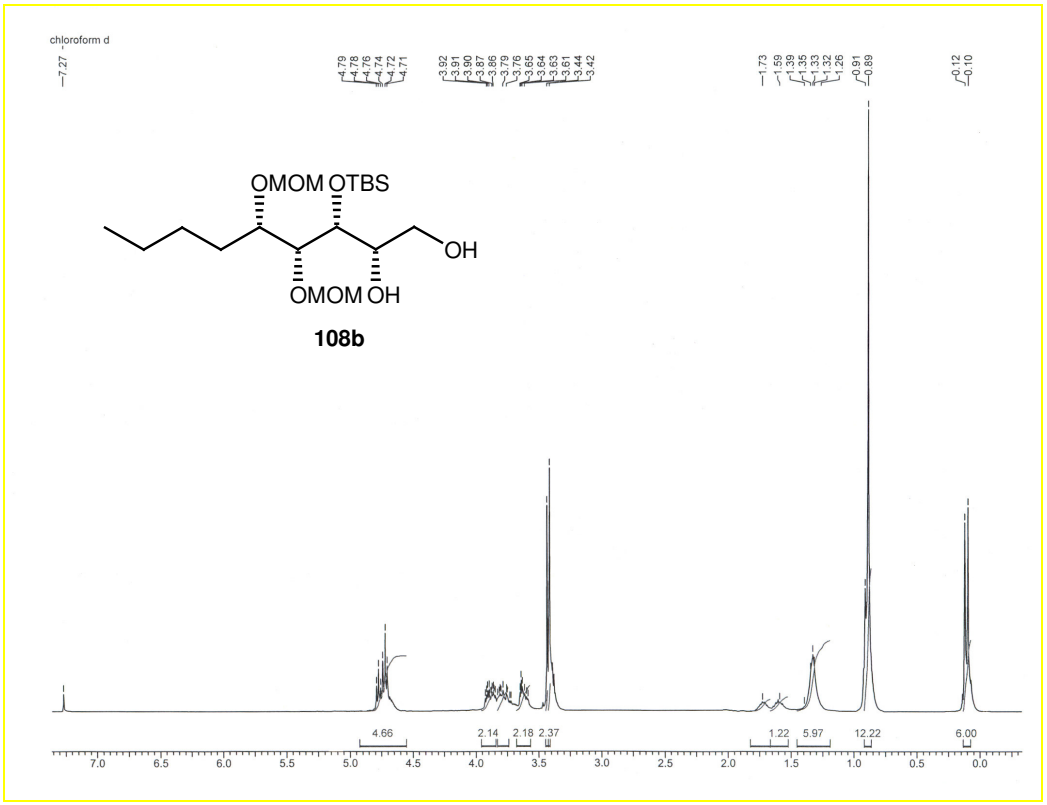
^{13}C NMR Spectrum of **106**



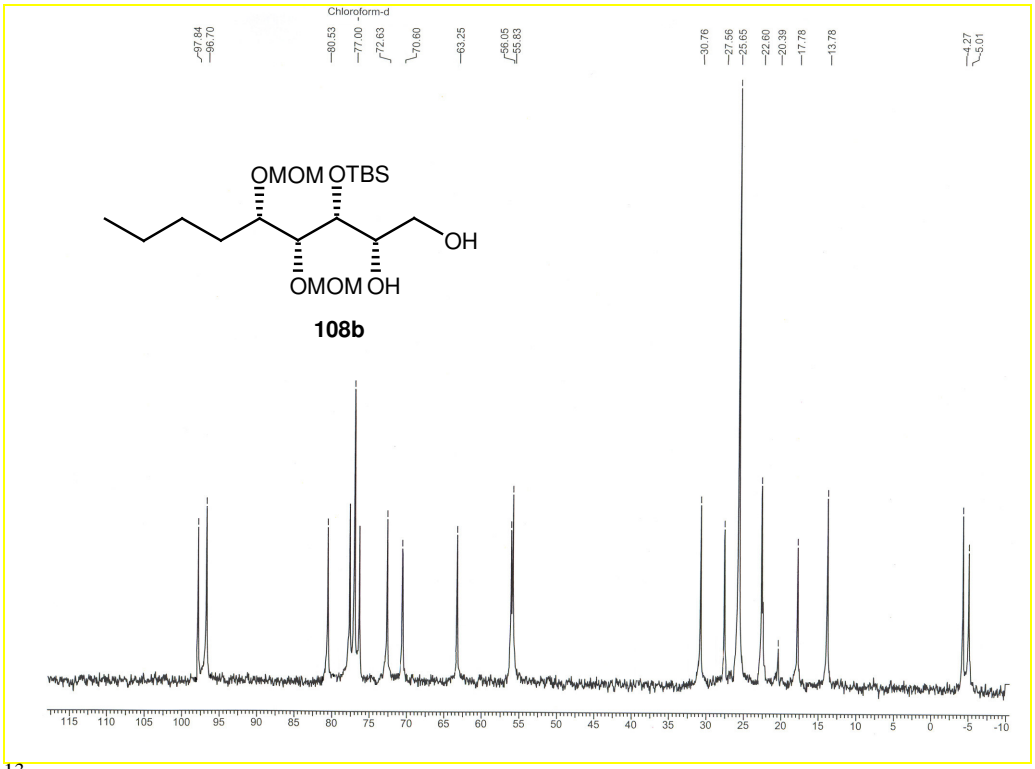
^{1}H NMR Spectrum of **108a**



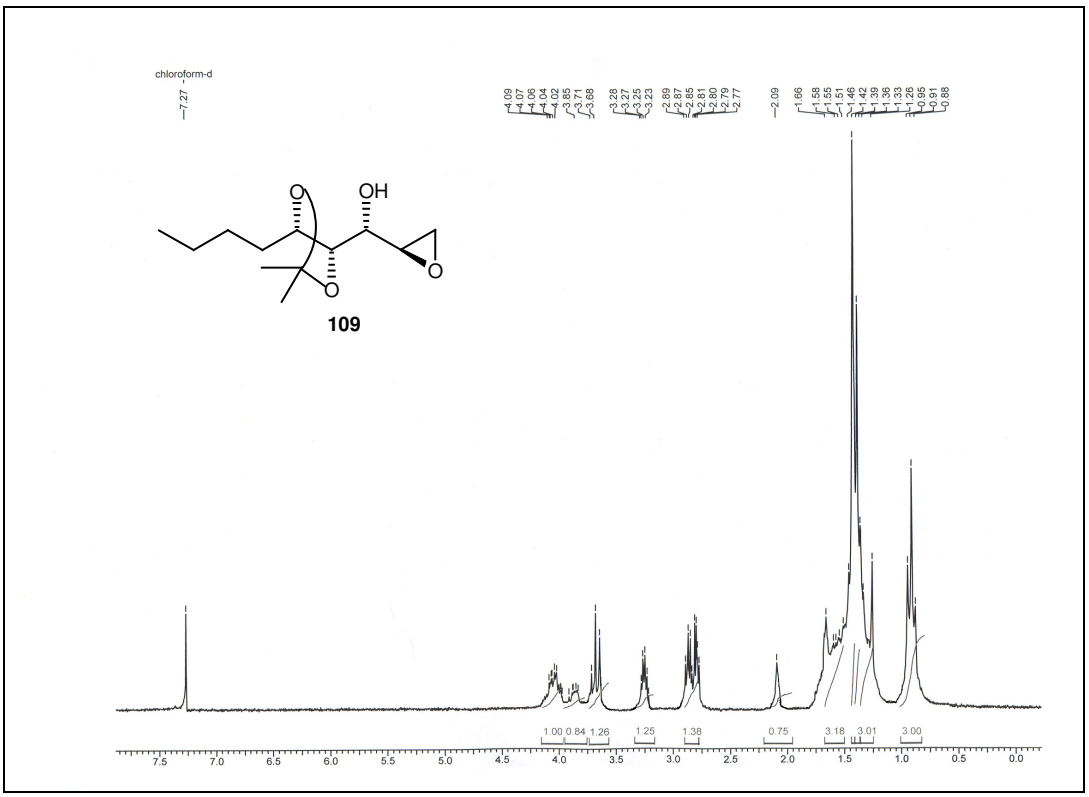
^{13}C NMR Spectrum of **108a**



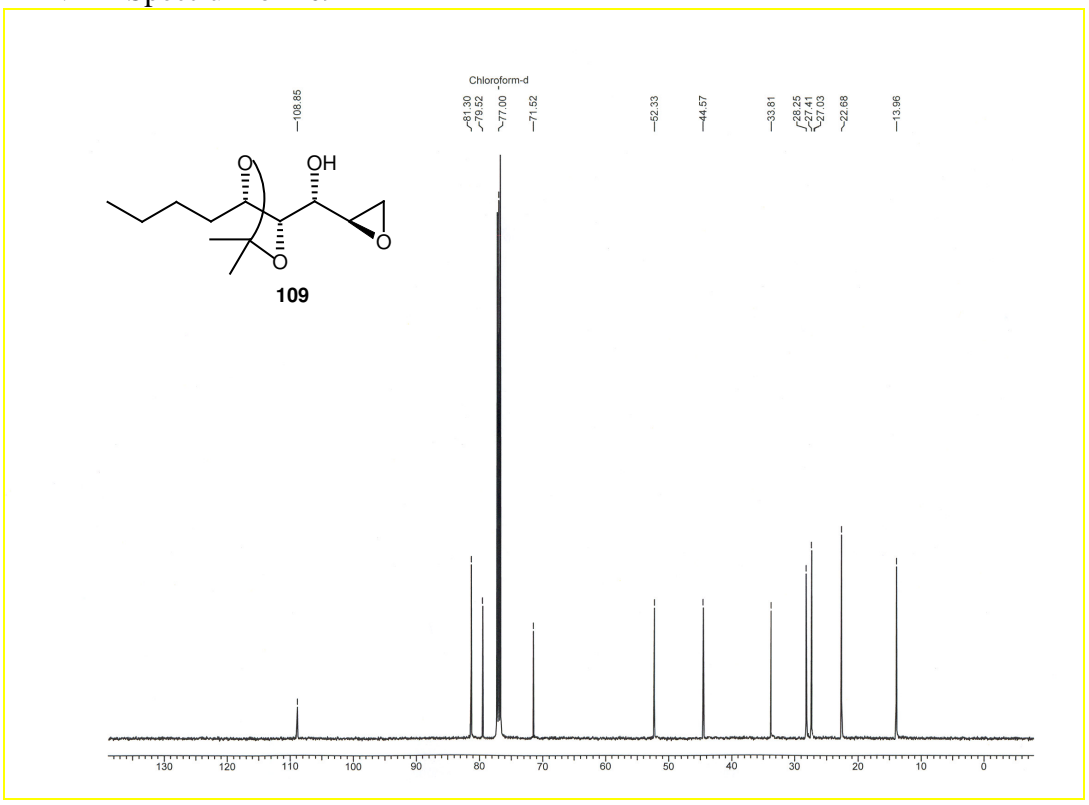
^{1}H NMR Spectrum of **108b**



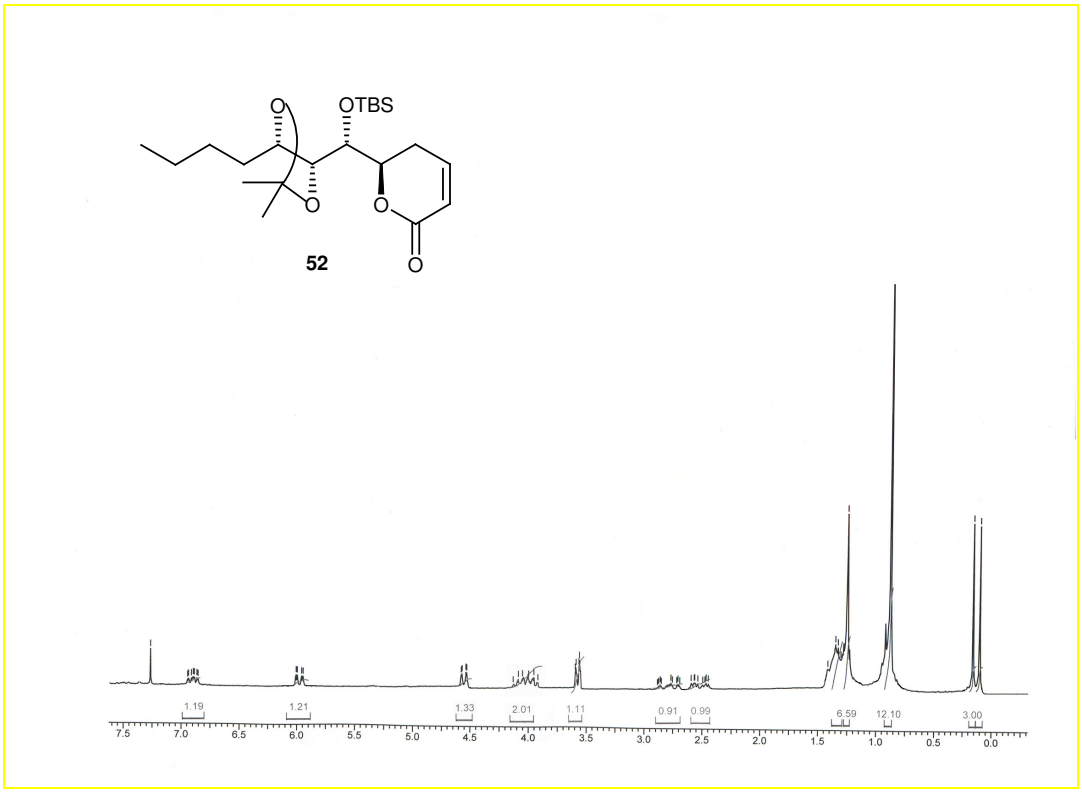
^{13}C NMR Spectrum of **108b**



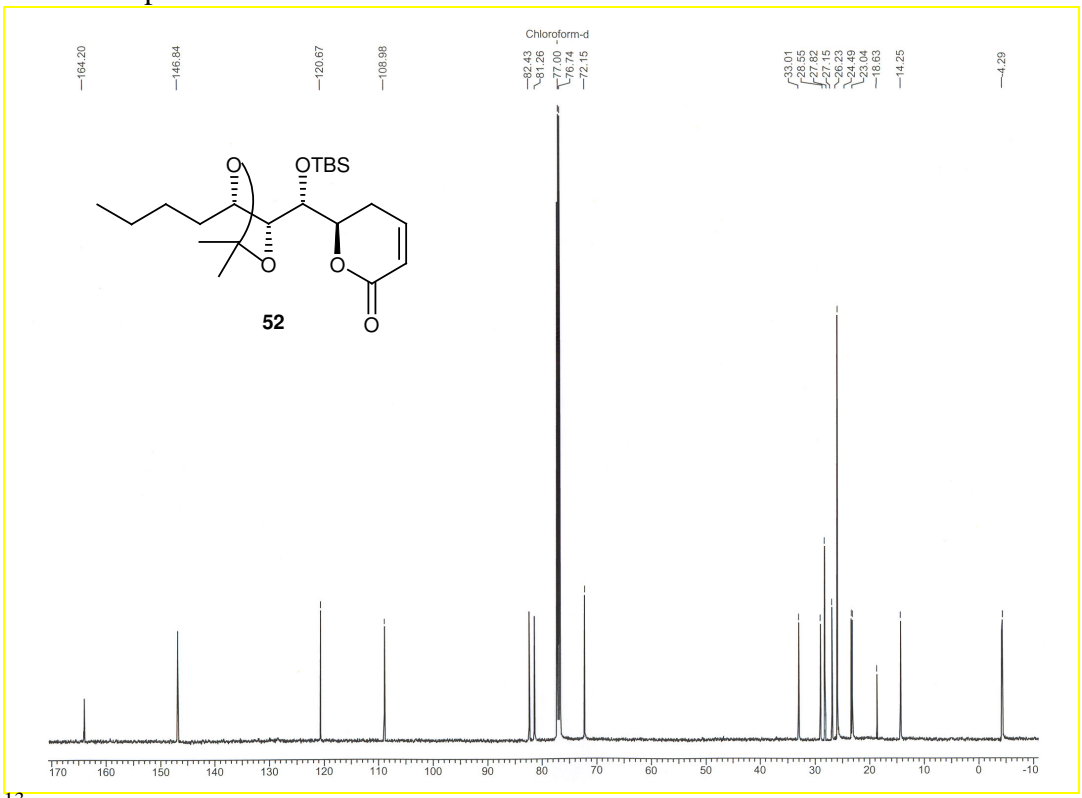
^{1}H NMR Spectrum of **109**



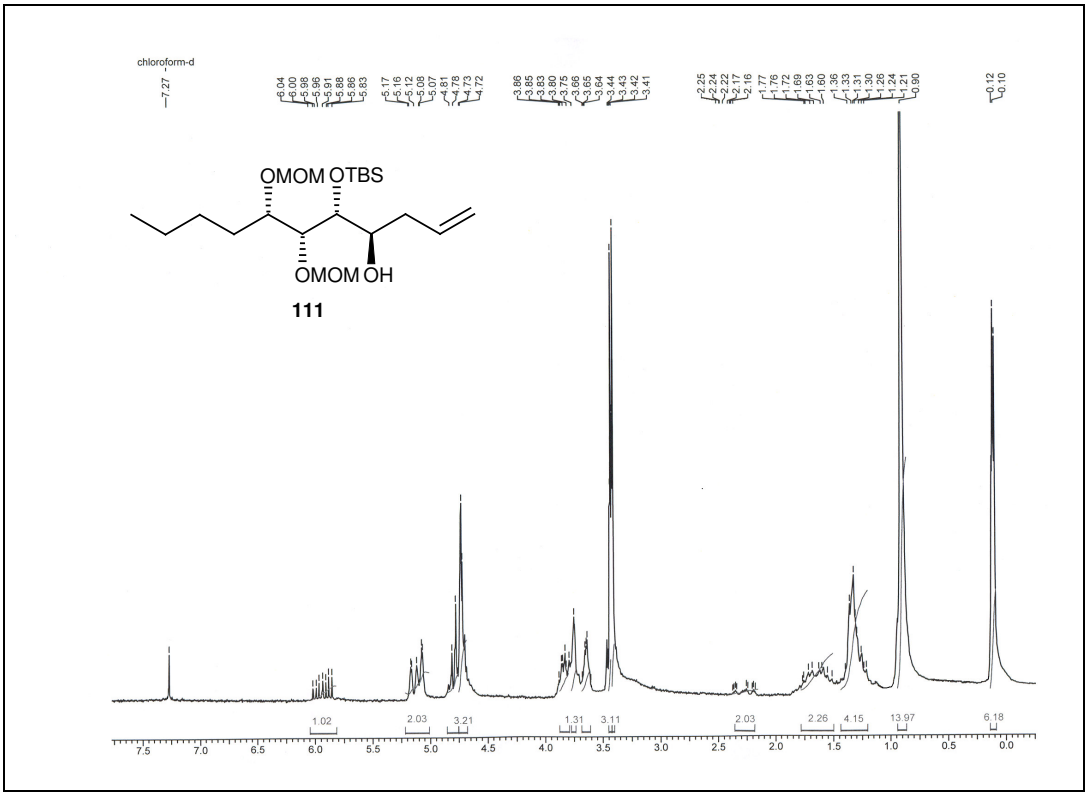
^{13}C NMR Spectrum of **109**



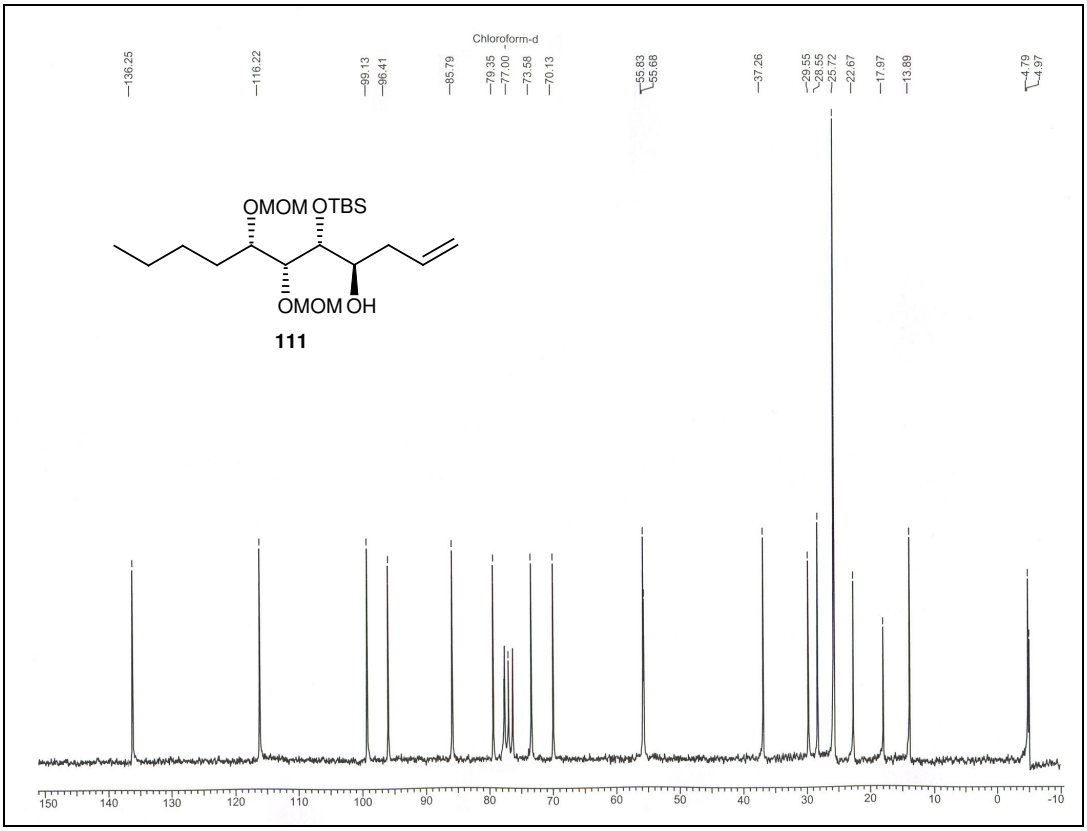
^{1}H NMR Spectrum of **52**



^{13}C NMR Spectrum of **52**



^{1}H NMR Spectrum of **111**



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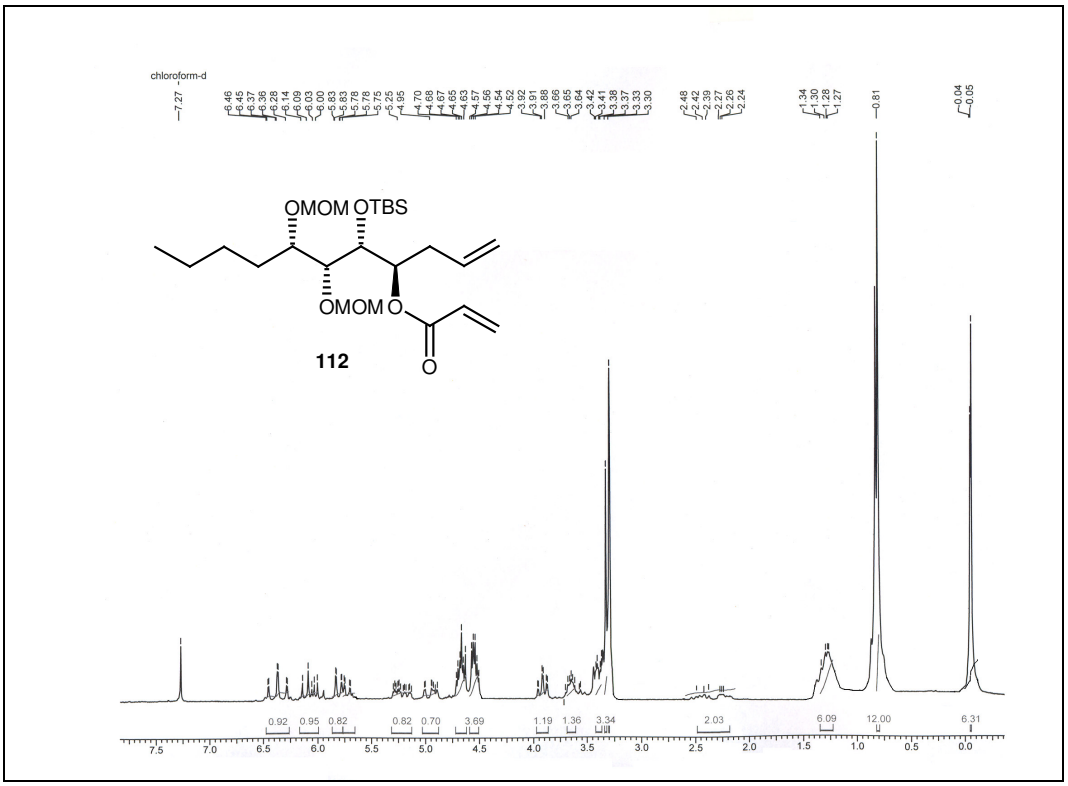

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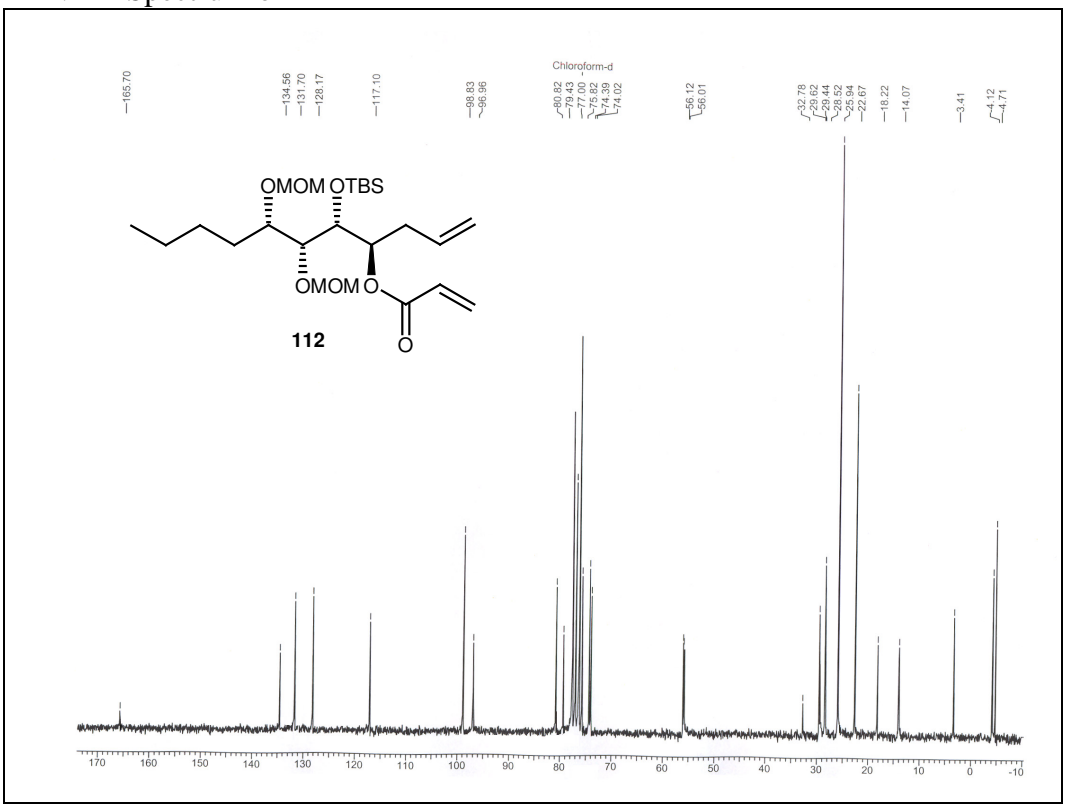

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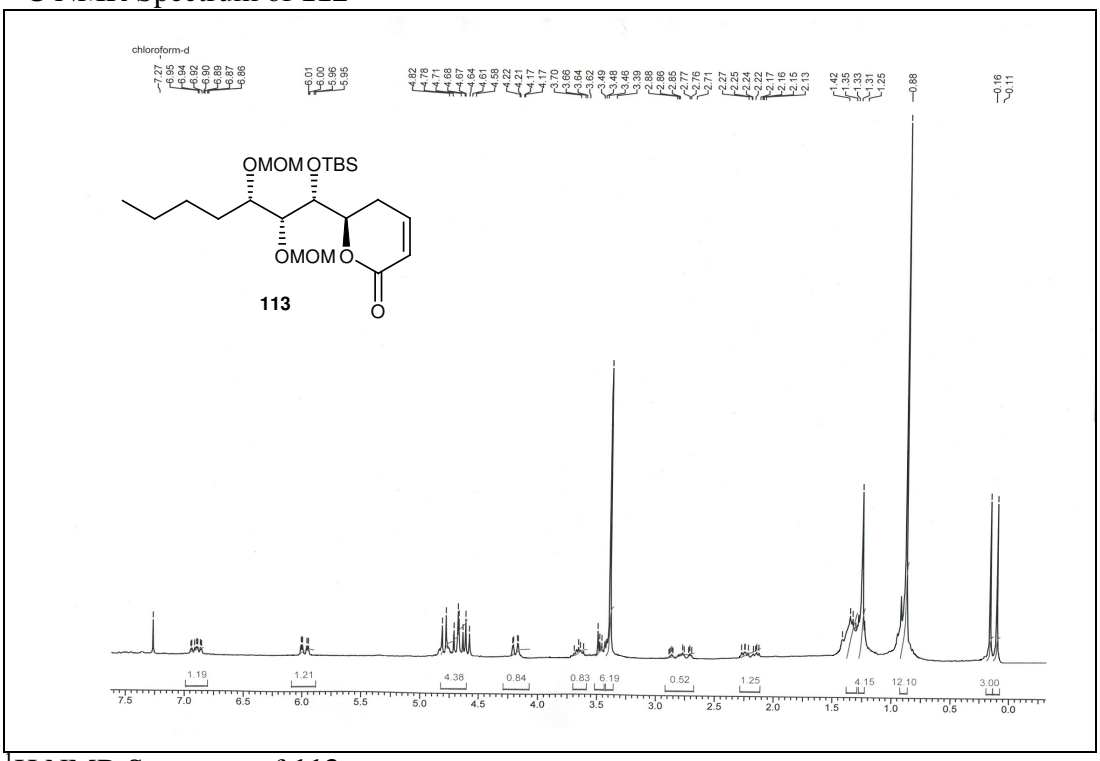

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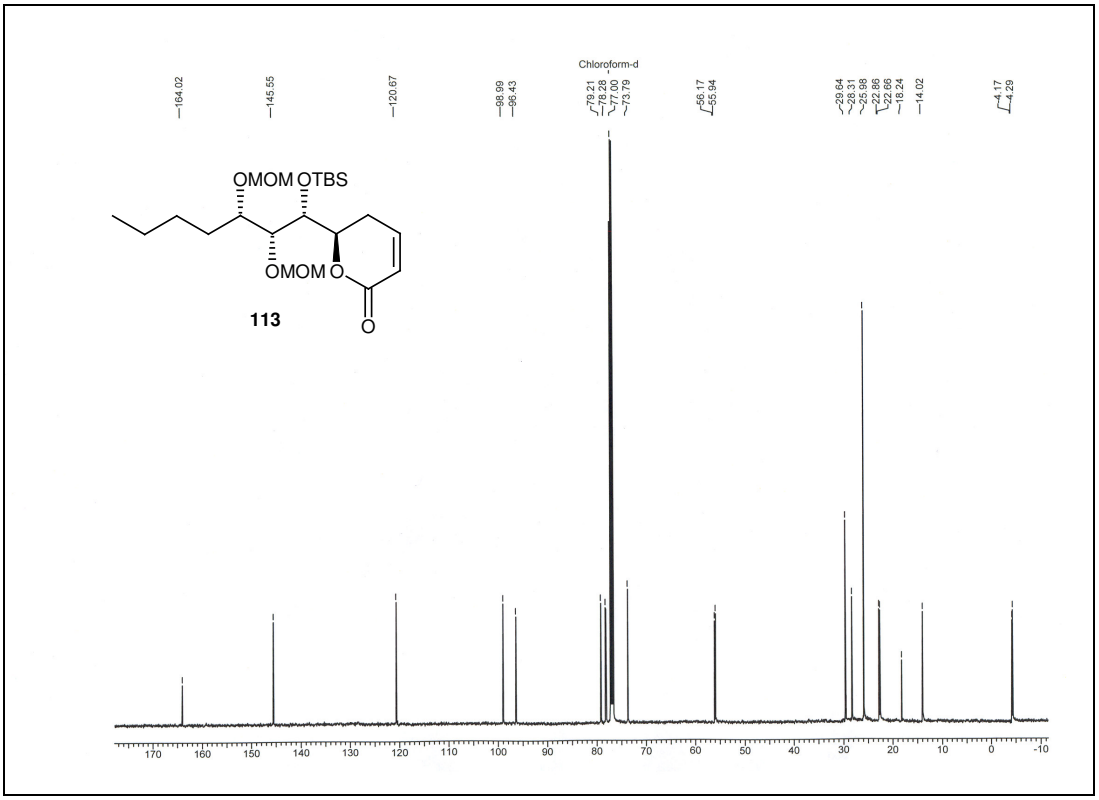

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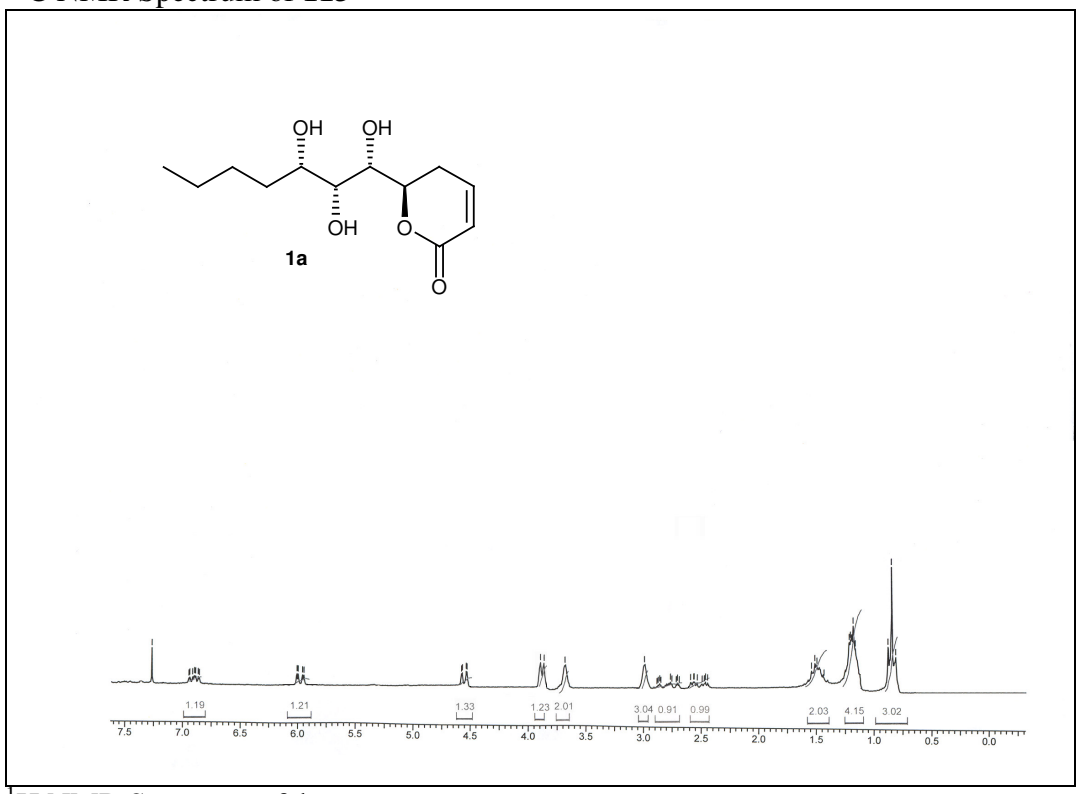
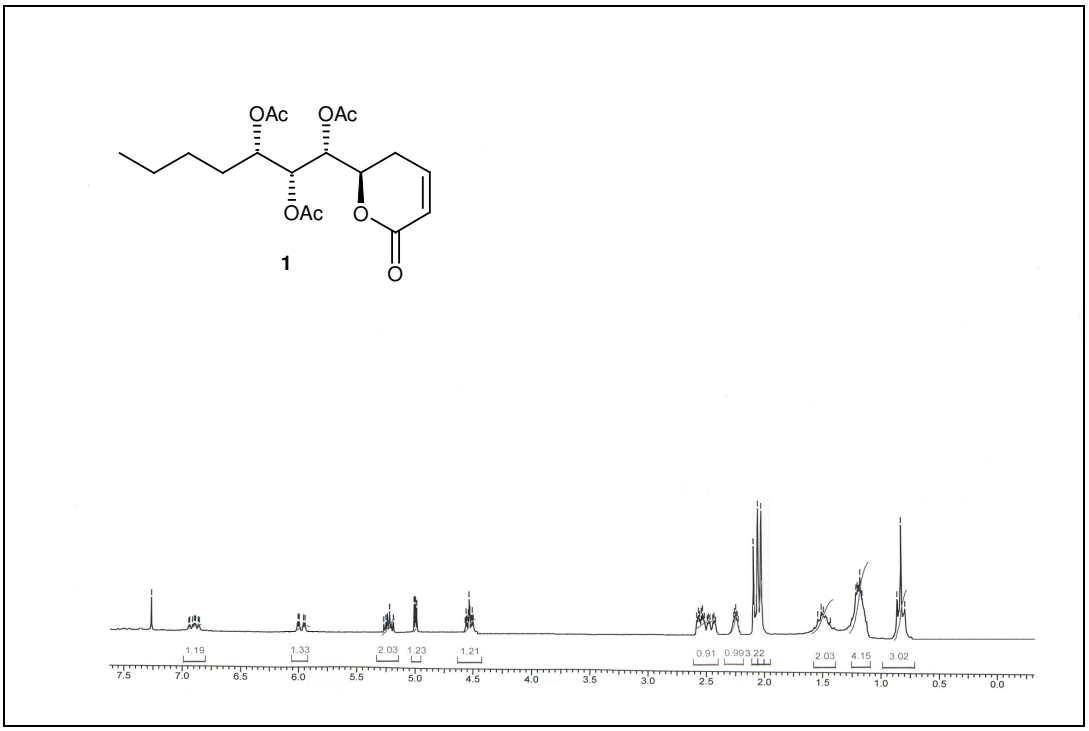


^{1}H NMR Spectrum of **1a**

^{13}C NMR Spectrum of **1a**



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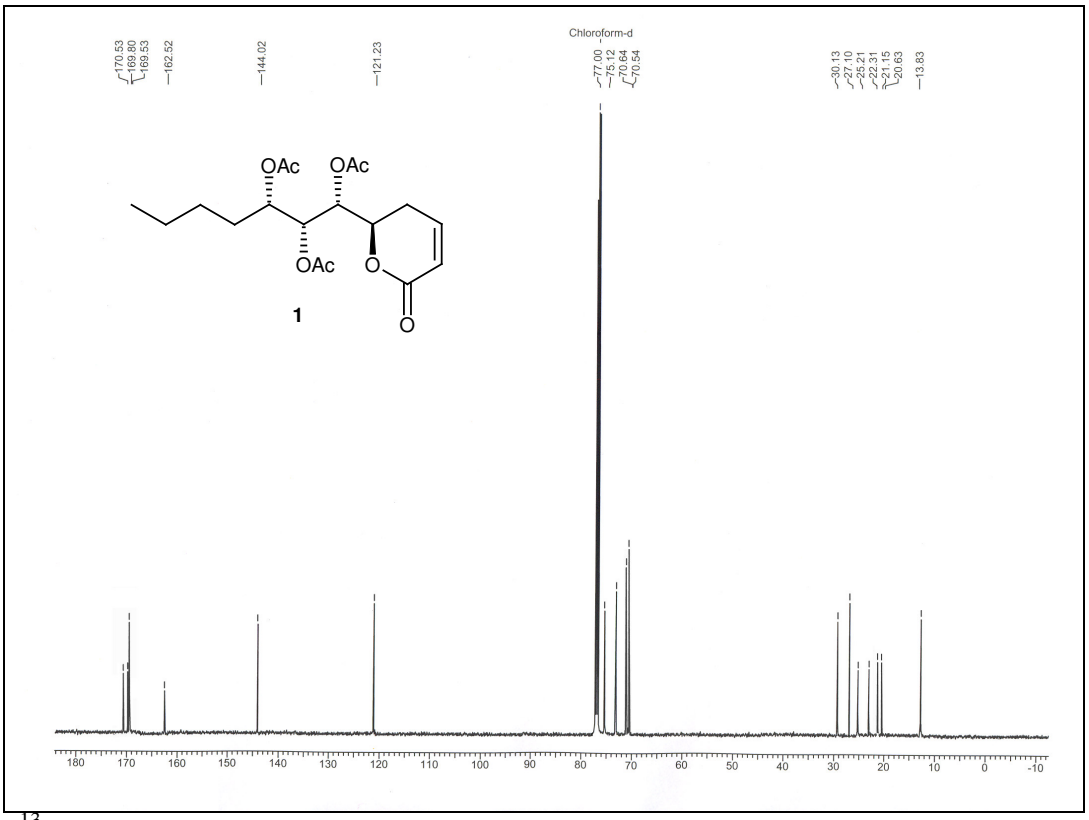

^{13}C NMR Spectrum of **1**

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CHAPTER –III

Enantioselective syntheses of naturally occurring lactones

SECTION A: Total Synthesis of Microcarpalide

SECTION B: An Efficient Total Synthesis of Sapinofuranone B

SECTION C : Enantioselective synthesis of (–)-pinellic acid

SECTION D: Enantioselective total synthesis of α- and β-Dimorphecolic Acid

3.1. SECTION A

TOTAL SYNTHESIS OF MICROCARPALIDE

3.1.1. INTRODUCTION:

Cancer[1] is the ability of some of the cells in a person's body to divide uncontrollably, form a tumor and often spread to other parts of the body through the blood stream. Cancerous cells are often significantly mixed up in their DNA structure. An entire chromosome may be linked with another, broken at odd locations or strands may be linked together incorrectly. These mutated cells often have many genetic defects. It is these defects that generally lead to uncontrolled cell growth. Over time some cells in one's body, for various reasons (may be age, environment, smoking, probably lots of things), lose the p53 gene. The p53 gene automatically commands cells to die if there is a mutation during the division process. Without the control of the p53 gene these cells are much more susceptible to further mutations later on. Over more time some cells further mutate again and begin producing growth factors such as EGF or PSA. Growth factors are simply small molecules that mutated cells are producing on a regular basis. Over even more time some of the p53 defective cells may further mutate on the Ras gene. These cells are very dangerous as Ras controls whether a cell reacts to a growth signal like EGF or PSA based on other conditions in the cell. Because of the high mortality rate involved with this disease it is very much warranted to look for new anti cancer agents, in this regard recently many new chemical entities have been isolated from one of the most abundant species Fungi.

Fungi[2] produce a fascinating range of structurally diverse secondary metabolites, which often possess unusual and sometimes unexpected biological activities. This structural diversity makes these marine natural products excellent molecular probes for the investigation of biochemical pathways. Recently, a number of novel and stereo chemically complex macrolides, having a large macrolactone (22-to 44-membered) ring that interacts with the actin cytoskeleton have been isolated from different fungal and marine sources. Many

molecules, which are of fungal as well as marine origin shown promising effect on the disruption of microfilaments of carcinomal cells, which consists mainly of a protein actin.

Actin,[3] like tubulin, is a major component of the cytoskeleton and has important cellular functions. Although the details of these interactions are still under investigation, these macrolides are becoming increasingly important as novel molecular probes to help elucidate the cellular functions of actin. Owing to their potent anti tumor activities, these compounds, for example the aplyronines, also have potential for preclinical development in cancer chemotherapy. Their appealing molecular structures, with an abundance of stereochemistry, and biological significance, coupled with the extremely limited availability from the fungal sources, have stimulated enormous interest in the synthesis of these compounds. Actin is one of the two major components of the cytoskeleton in eukaryotic cells.[3] The other major component, tubulin, is more familiar to the chemistry community, primarily due to the success of paclitaxel in the treatment of cancer[4] and the subsequent discovery of a number of other natural products (the epothilones, discodermolide, laulimalide,the eleutherobins, and sarcodictyins) that share paclitaxel's microtubule-stabilizing properties.[5] The actin cytoskeleton plays a critical role in the determination of cell shape, and in a variety of cellular processes, including cell motility, division, adhesion, and intracellular transportation. Actin also interacts with tubulin, although the two-cytoskeleton systems more often operate independently. Very recently, an actin dependent cell cycle checkpoint that ensures the proper orientation of microtubule spindles during metaphase has been uncovered by Gachet and Hyams *et al*.[6] Furthermore, certain bacterial and viral (e.g. HIV) pathogens have been found to exploit the actin cytoskeleton during their lifecycle of infection.[7] As a consequence, the implications of the actin cytoskeleton and the release of actin filaments into extracellular space in numerous disease states are now being recognized.[8]

In cells, actin structures are assembled and disassembled constantly in a reversible process. The dynamic polymerization/ depolymerization equilibrium between monomeric soluble globular actin (G-actin; about 43 kDa) and helical filamentous actin (F-actin), and the organization of the three dimensional architecture of actin filaments in response to intracellular and extra cellular stimulations is regulated and performed by a panoply of actin[12] binding proteins[9] (e.g. profilin, cofilin, gelsolin, filamin, actinin and Arp2/3 complex) (Figure 1).

These proteins act through a number of mechanisms, including the sequestering of Gactin, severing of F-actin, control of nucleation, and capping of the barbed or pointed ends of F-actin.[10] G-actin itself is an ATPase and this activity affects the polymerization kinetics. The ATP- and ADP-bound actin monomers dissociate from actin filaments at different rates, and are recognized by different sets of actin binding proteins. Genetic approaches are often used to study the highly complex and dynamic actin cytoskeleton and its associated cellular functions.

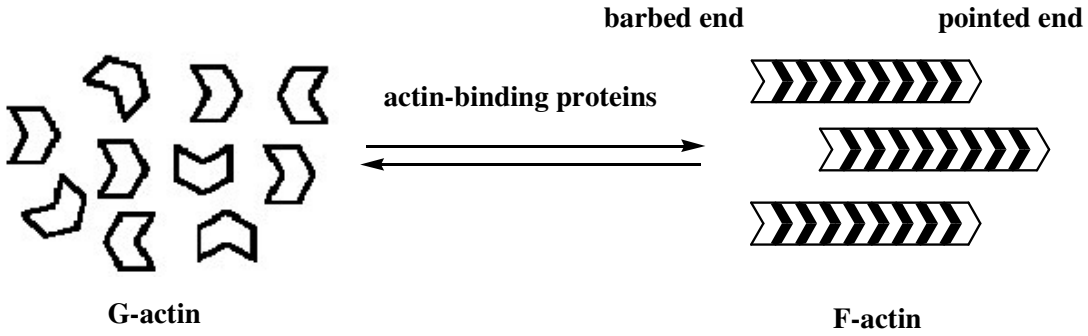


Figure 1: A simplified schematic representation

However, new and versatile molecular probe agents[11] are becoming increasingly valuable in advancing the understanding of actin organization and by unveiling important cellular functions of actin. The fungal secondary metabolites, cytochalasins (e.g. cytochalasin B (**1**) and cytochalasin D (**2**), are the earliest agents that were widely adopted as molecular probes to study the actin cytoskeleton.[12a] However, these agents exhibit nonspecific modes of actions, often complicating experiments performed with them. Latrunculin A (**3**) and latrunculin B (**4**) were the first marine macrolides identified to have well-defined actinbinding properties[12b] These 2-thiazolidinone-containing macrocycles form a 1:1 complex with G-actin, inhibiting its polymerization. They also induce F-actin depolymerization. Latrunculin B (**4**) was used in the seminal work of Gachet and Hyams *et al*.[6] that established the very important and previously unknown role of the actin cytoskeleton in spindle orientation.

In recent years the secondary metabolites from endophytic fungi have been receiving great deal of attention, because of peculiar structures with specific biological activities. Along this line, microcarpalide[12c] a nonenolide has been recently characterized as a new secondary metabolite produced by an endophytic fungus growing on the bark of *Ficus microcarpa* L. Bio-assay guided purification of fermentation broths using immunofluorescence microscopy to test anticytoskeletal activity led to the isolation of a new substance displaying a remarkable

microfilament disrupting activity,[12c] which mainly consists of protein called actin, which was first identified in non-muscle cells only about three decades ago, and at about the same time, it was found that actin filaments were disrupted in the malignant transformed cells. The actin network is a rather complex, yet important structural and functional system of all eukaryotic cells. Actin filaments provide the basic infrastructure for maintaining cell morphology and functions such as adhesion, motility, exocytosis, endocytosis, and cell division. Growing evidence from this laboratory and others show that alterations of actin polymerization, or actin remodeling, plays a pivotal role in regulating the morphologic and phenotypic events of a malignant cell. Actin remodeling is the result of activation of oncogenic actin signaling pathways (e.g., Ras and Src), or inactivation of several important actin-binding proteins that have tumor suppressor functions (e.g., gelsolin). Distinctive protein expression patterns of some of these genes in cancer and progressive carcinogenic processes have been observed. It has become evident that actin dynamics are regulated by a complex interplay of the small GTPase proteins of Ras superfamily Rac, Rho, and Cdc42, and efforts to develop specific inhibitors for these small G proteins as anticancer drug are underway. In the present context similar to the cytochalacins,[12a] microcarpalide,[12c] which was isolated from the fermentation broths of the unidentified endophytic fungus growing on the bark of *Ficus microcarpa* L. was proved to disrupt actin microfilaments in approximately 50% of A-10 cells (from rat smooth muscles) at a concentration of 0.5 μg mL^{-1}, by binding to the (+) end of the F-actin and prevents the subunit addition. Depolymeriztion at the (-) end led to the loss of the filament, moreover, it displayed a weak cytotoxicity in mammalian cells, thus making it the attractive tool for studying cell motility and cell metastasis, and a potential tool for the development of anti-cancer drugs.[12c]

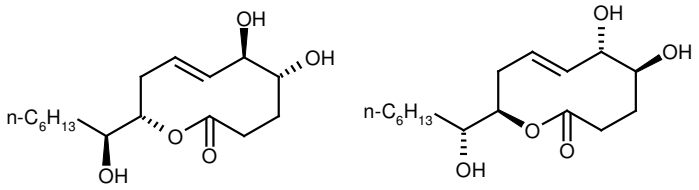


Figure 2. Structure of microcarpalide and its isomer

Microcarpalide represents a novel alkyl-substituted nonenolide structurally related to a family of phytotoxins such as achaetolide, pinolidoxin, lethalotoxin, putaminoxins, and herbarumins from which it differs in the hydroxylation pattern and the double bond position within the

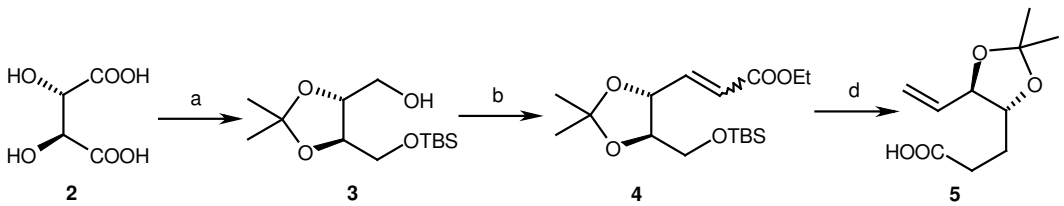
longer side chain at C-10. At concentrations of 0.5-1 μg mL^{-1}, microcarpalide was found to disrupt actin microfilaments in approximately 50% of A-10 cells (from rat smooth muscle), moreover, it displayed a weak cytotoxicity to mammalian cells, thus making it attractive tool for studying cell motility and metastasis, and a potential lead structure to develop new anticancer drugs.

3.1.2. Review of Literature

So far five total syntheses of microcarpalide have been reported in the literature.[13] Most of the approaches described are based on ring closing metathesis for the key macrocyclization to construct the olefin with selectivities between 2:1 to 10:1 in favor of the desired (*E*)-isomer. Moreover the stereogenic centers were mainly derived from chiral pool starting materials such as tartaric acid,[13a,c] (*R*)-glycidol,[13a] D-mannose[13b] and malic acid[13d] etc. Owing to such a peculiar biological activity and attracted by the structural potential of microcarpalide for structure-activity relationship studies, we became interested in developing a general route capable of providing not only the target molecule **1**, but also its congeners with desired stereo- and enantioselectivities for studies on relationship between structure and pharmacological activity. A detailed report of these synthesis is described below.

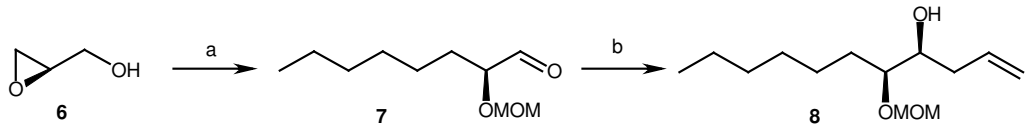
Marco *et al* . (2002).[13a]

Marco and co-workers accomplished the synthesis of microcarpalide by using the RCM reaction[14] as the key step for the ring closure (Scheme 3). The diene ester **9** required for the macrocyclization reaction was assembled via DCC mediated esterification of appropriate partners **5** and **8**, each bearing the terminal alkene group. The acid fragment **5**[15] was synthesized stating from the D-tartaric acid **2** as shown in Scheme 1. The hydroxy fragment **8** was synthesized from (*R*)-glycidol **6** by epoxide opening with a *n*-pentyl cuprate reagent[16] followed by oxidation[17] and chelation controlled Grignard reaction[18] of corresponding aldehyde **7** (Scheme 2).

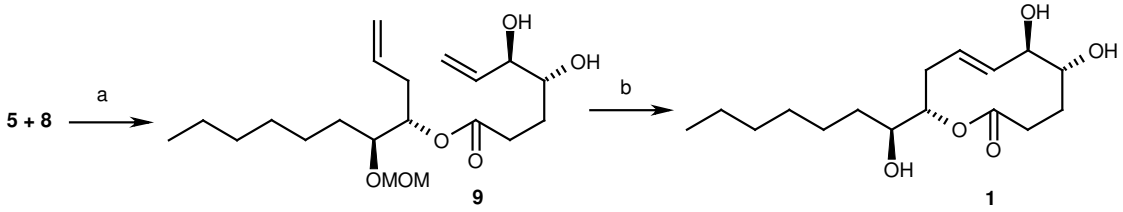


2 **3** **4** **5**

Scheme 1. *Reagents and conditions*: a) (i) 2,2-dimethoxy propane, *p*-TsOH, 91%; (ii) LAH, Et_2O, reflux, 87%; (iii) TBDMSCl, NaH, THF, 91%; (b) (i) $(COCl)_2$, DMSO, Et_3N, -70 °C, 90%; (ii) $Ph_3P{=}CHCO_2Et$, DMF, rt, 94%; (c) (i) H_2, Pd/C, EtOH, rt, 99%; (ii) TBAF, THF, rt; (iii) $(COCl)_2$, DMSO, Et_3N, -72 °C, 76%; (iv) $Ph_3P{=}CH_2$, *n*-BuLi, THF, -20 °C to rt, 42%; (v) KOH-MeOH-H_2O, rt, 81%.



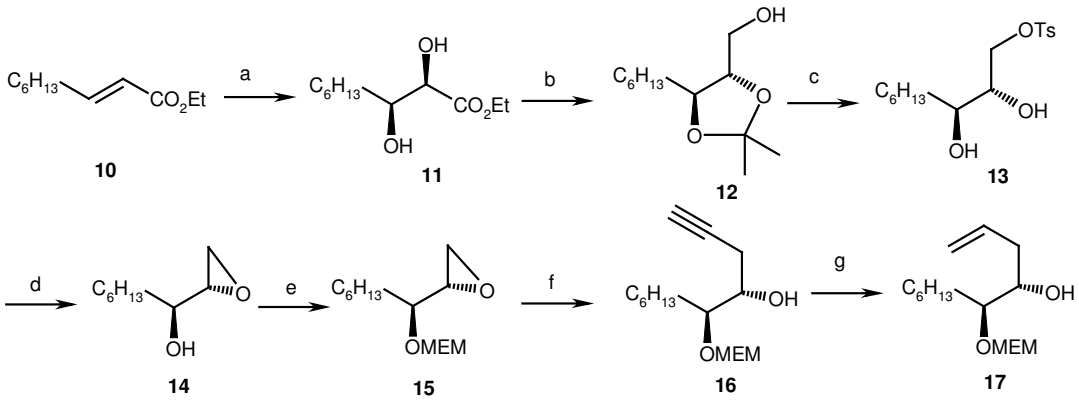
Scheme 2. *Reagents and conditions*: (a) (i) TPSCl, Et_3N, DMAP, CH_2Cl_2, rt, 18 h, 93%; (ii) $CH_3(CH_2)_4MgBr$, CuI, THF, -30 °C, 87%. (iii) MOMCl, Et_3N, DMAP, CH_2Cl_2, rt, 18 h, 87%. (iv) TBAF, THF, 5 h, rt, 93%. (v) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C, 30 min, then *N*,*N*-diisopropyl ethylamine, 2 min at -78 °C, then rt. (b) $Bu_3SnCH_2CH{=}CH_2$, $MgBr_2.Et_2O$, 3 Å MS, CH_2Cl_2, 3 h at -78 °C, then 1.5 h at -40 °C, 60% combined yield of the two last steps.



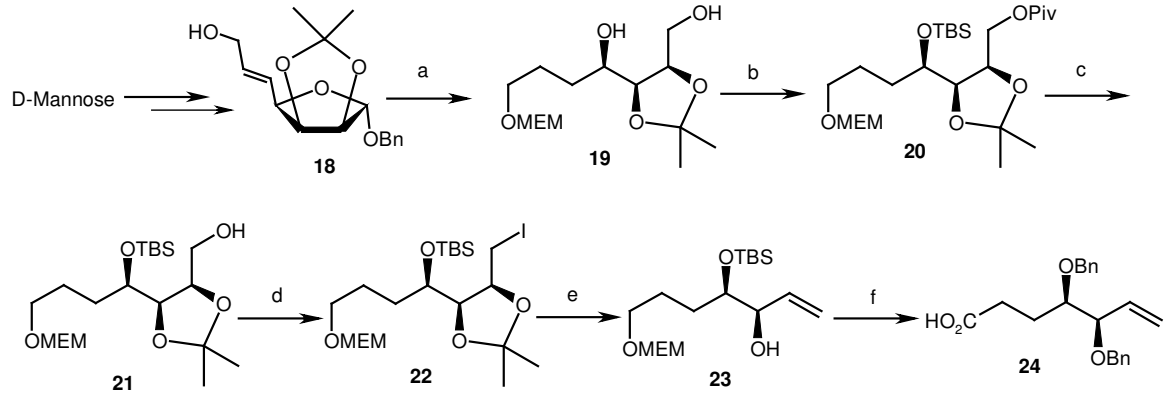
Scheme 3. *Reagents and conditions*: (a) DCC, DMAP, CH_2Cl_2, rt, 18 h, 86%; (b) (i) 20 mol % $Cl_2(PCy_3)_2Ru{=}CHPh$, CH_2Cl_2, reflux, 24 h, 67%; (ii) SMe_2, $BF_3.Et_2O$, -10 °C, 30 min, 71%; (d) $(CH_2SH)_2$, BF_3, CH_2Cl_2, 0 °C, 1 h, 66%.

Gurjar *et al.* (2003).[13b]

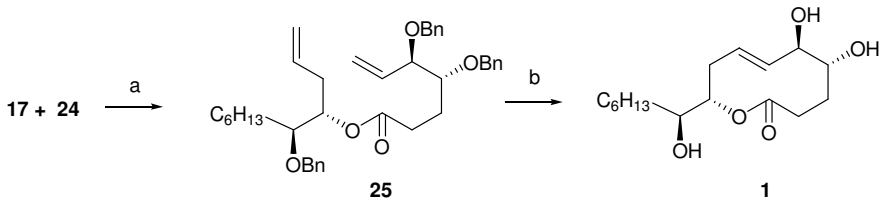
Gurjar and co-workers synthesized microcarpalide employing ring closing metathesis and Sharpless asymmetric dihydroxylation as key steps. The hydroxy fragment **17** was prepared from α,β-unsatured ester **10** via AD reaction (Scheme 4), while the acid fragment **24** was prepared from D-mannose as a chiral pool source via a Zn-mediated elimination[19] of α-iodo acetonide derivative **22** (Scheme 5). Finally, the two fragments were coupled using DCC followed by ring-closing metathesis to give the target molecule **1** (Scheme 6).



Scheme 4. *Reagents and conditions*: (a) AD-mix-α, *t*-BuOH, H_2O, 0 °C, 10 h, 94%; (b) (i) 2,2-dimethoxypropane, *p*-TsOH, CH_2Cl_2, 1.5 h, 96%; (ii) DIBAL-H, CH_2Cl_2, −78 °C, 1 h, 97%; (c) (i) *p*-TsCl, pyridine, 0°C – rt, 96%; (ii) conc. HCl (cat.), MeOH, 3 h, 87%; (d) K_2CO_3 (1.5 equiv.), MeOH, rt, 1.5 h, 85%; (e) MEM-Cl, *i*Pr_2NEt, CH_2Cl_2, rt, 4 h, 91%; (f) LiC≡CH:ethylenediamine, DMSO, rt, 12 h, 86%; (g) H_2, Pd/$BaSO_4$, quinoline, benzene, 1 bar, rt, 0.5 h, 91%.



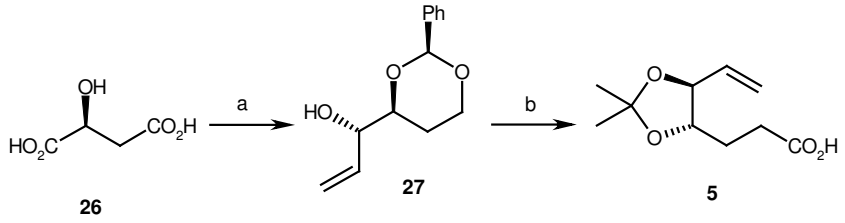
Scheme 5. *Reagents and conditions*: (a) (i) MEM-Cl, *i*Pr_2NEt, CH_2Cl_2, rt, 10 h; (ii) H_2, 10% Pd–C, MeOH, 6 bar, 60 °C, 4 h; (iii) $LiAlH_4$, THF, rt, 1 h, 71% for three steps; (b) (i) $(CH_3)_3CCOCl$, pyridine, 0°C – rt, 91%; (ii) TBSCl, DMF, imidazole, rt, 4 h, 90%; (c) DIBAL-H, CH_2Cl_2, −78 °C, 1 h, 89%; (d) I_2, PPh_3, imidazole, ether–benzene (2:1), rt, 1.5 h, 86%; (h) Zn, ethanol, reflux, 1.5 h, 96%; (e) *n*-$Bu_4N^+F^-$, THF, rt, 1 h, 85%; (f) (i) NaH, BnBr, DMF, 0°C – rt, 88%; (ii) PPTS, *t*-BuOH, 80 °C, 1.5 h, 85%; (iii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 1 h; (iv) $NaClO_2$, DMSO, NaH_2PO_4, rt, 1.5 h, 83% for two steps.



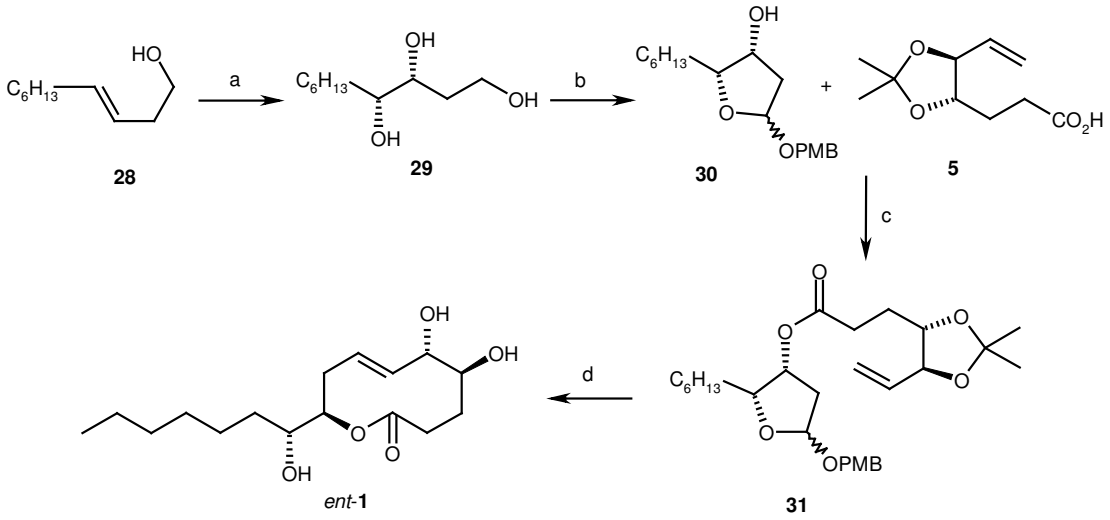
Scheme 6. *Reagents and conditions*: (a) DCC, DMAP, CH_2Cl_2, rt, 18 h, 76%; (b) (i) $(PCy_3)_2Ru(Cl)_2CH$-Ph (20 mol%), CH_2Cl_2, reflux, 28 h, 67%; (ii) $TiCl_4$, CH_2Cl_2, 0°C, 0.5 h, 76%.

Banwell *et al.* (2004).[13c]

Banwell and co-workers reported the synthesis of enantiomer of (-) microcarpalide, using RCM as the key reaction. A chiral pool approach for the preparation of the acid component **5** from (*S*)-malic acid **26** was executed using well established reactions (Scheme 7).



Scheme 7. *Reagents and conditions*: (a) (i) BH_3-DMS, $B(OMe)_3$, THF; (ii) PhCHO, $(MeO)_3CH$, TFA, CH_2Cl_2; (iii) 4-AcN-TEMPO, $PhI(OAc)_2$, CH_2Cl_2; (iv) $(CH_2{=}CH)_2Zn$, THF, -50 °C; (b) (i) 1 M aq. HCl, THF; (ii) *p*-TsCl, Py, DMAP; (iii) KCN, DMF, 60 °C; (iv) KOH, MeOH-H_2O.



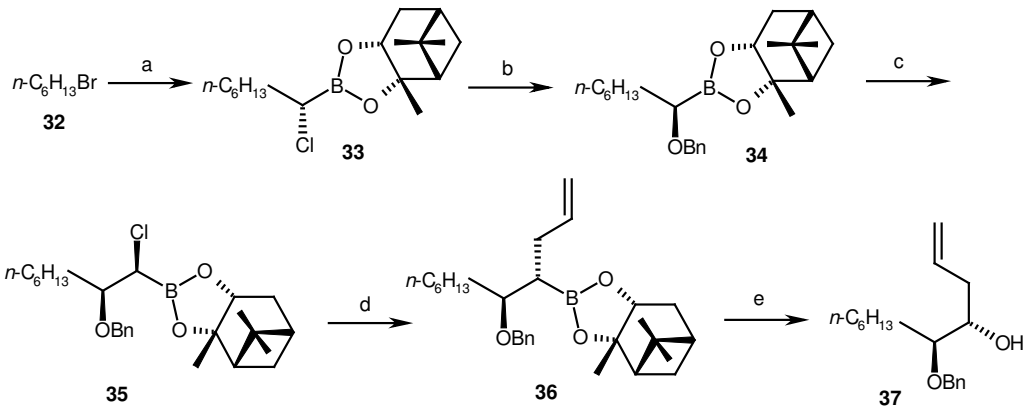
Scheme 8. *Reagents and conditions*: (a) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH-H_2O, 0 °C; (b) (i) 2,2-DMP, *p*-TsOH, CH_2Cl_2; (ii) 4-AcN-TEMPO, $PhI(OAc)_2$, CH_2Cl_2; (iii) AcOH-H_2O-THF, 50 °C; (iv) PMB-OH, *p*-TsOH, CH_2Cl_2; (c) DCC, DMAP, CH_2Cl_2; (d) (i) DDQ, THF; (ii) $Ph_3P{=}CHCO_2Me$, toluene, 0 °C; (iii) MOM-Cl, DIPEA, CH_2Cl_2; (iv) Grubbs 2nd gen. Cat., $CH_2{=}CH_2$, CH_2Cl_2; (v) ($Cl_2(PCy_3)_2Ru{=}CHPh$), CH_2Cl_2, 40 °C; (vi) $(CH_2SH)_2$, $BF_3.Et_2O$, CH_2Cl_2.

Sharpless dihydroxylation of a homoallyl alcohol **28** has been used in the preparation of the second fragment **30**. One of the difference in the approach of Banwell is that they have coupled both the fragment in advance before constructing the olefin of the alcohol fragment (Scheme 8).

Prati *et al.* (2004).[13d]

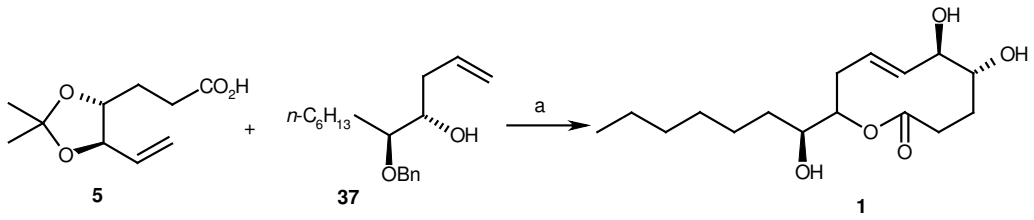
Prati and co-workers accomplished the synthesis of microcarpalide by using the RCM reaction as the key step for the ring closure (Scheme 10). The diene ester required for the macrocyclization reaction was assembled via DCC mediated esterification of appropriate partners, each bearing the terminal alkene group. The acid fragment was synthesized starting from D-tartaric acid as shown in Scheme 1.

As shown in Scheme 9, the alcohol fragment **37** was synthesized from *n*-bromohexane utilizing the stereoselective homologations of chiral boronic esters as strategic transformation for the sequential insertion of two stereocenters having *S*-configuration, using the (1*S*,2*S*,3*R*,5*S*)-(+)-pinanediol as the chiral director.[20]



Scheme 9. *Reagents and conditions*: (a) (i) Mg, Et_2O, reflux, then triethyl borate, -78 ^{o}C to rt, 72%; (ii) (1*S*,2*S*,3*R*,5*S*)-(+)-pinanediol, Et_2O, rt; (iii) Cl_2MeLi, THF, -100 °C to rt, 64%; (b)

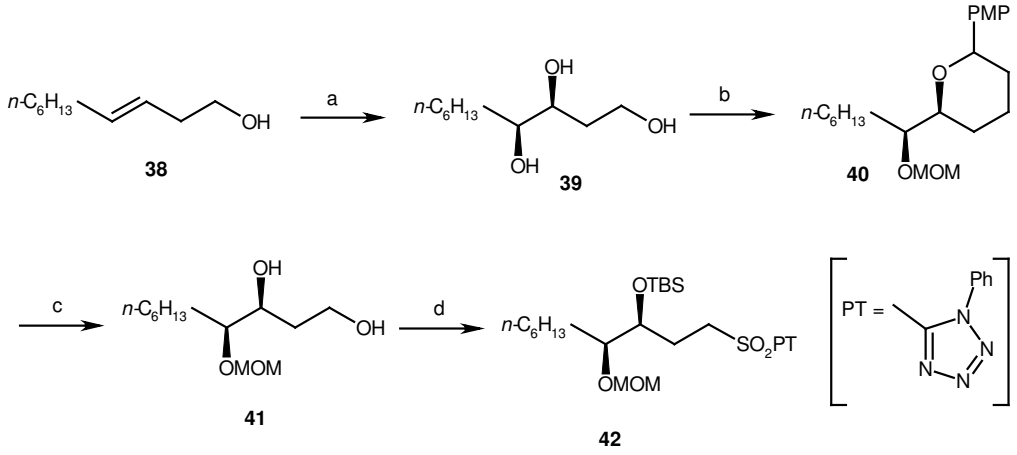
C_6H_5OH, *n*-BuLi, THF, -78 °C to rt, then reflux, 70%; (c) Cl_2MeLi, $ZnCl_2$, THF, -100 °C to rt, 61%; (d) allylMgBr, THF, -78 °C to rt, 74%; (e) H_2O_2, NaOH, THF, 0 °C to 45 °C, 90%.



Scheme 10. *Reagents and conditions*: (a) (i) DCC, DMAP, Et_2O, 85%; (ii) ($Cl_2(PCy_3)_2Ru$=CHPh), CH_2Cl_2, reflux, 92%; (iii) $TiCl_4$, CH_2Cl_2, 0 °C, 66%.

Kitahara *et al.* (2004).[13e]

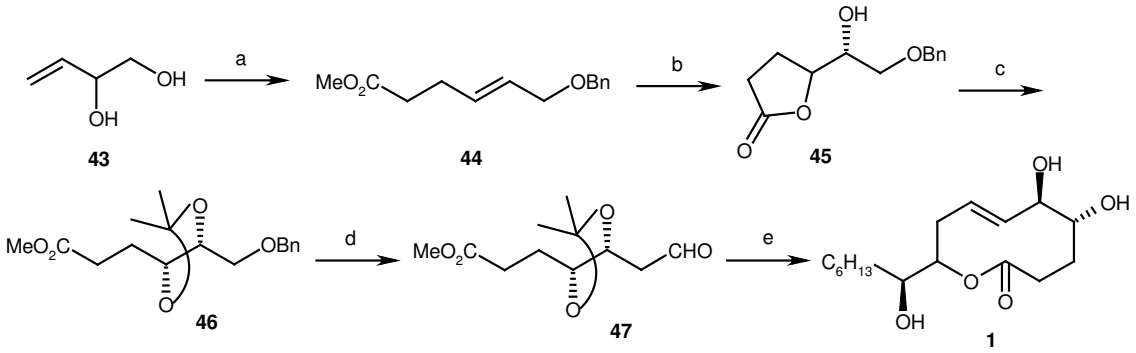
Kitahara and co-workers accomplished the synthesis of microcarpalide employing the Julia olefination and macrolactonization (Scheme 12). Synthesis of sulphone fragment **42** required for the Julia olefination reaction[21] was obtained starting from 3-decenol **38** by Sharpless asymmetric dihydroxylation as shown in the Scheme 11.



Scheme 11. *Reagents and conditions*: (a) (i) PMBCl, NaH, TBAB, THF, reflux, quant.; (ii) AD-mix-α, $MeSO_2NH_2$, *t*-BuOH, H_2O, 95% ee; recrystn., >99% ee, 74% in two steps; (b) (i) DDQ, CH_2Cl_2; (ii) MOMCl, *i*-Pr_2EtN, CH_2Cl_2; (c) AcOH, H_2O, THF, 82% in three steps; (d) (i) *p*-TSH, PPh_3, DIAD, THF; (ii) $(NH_4)_6Mo_7O_{24}.4H_2O$, H_2O_2, EtOH; (iii) TBSOTf, 2,6-lutidine, CH_2Cl_2, 91% in three steps.

As depicted in the Scheme 12, the synthesis of aldehyde fragment **47** started from diol **43**. After having the key coupling partners **42** and **47** in hand the authors employed the Julia

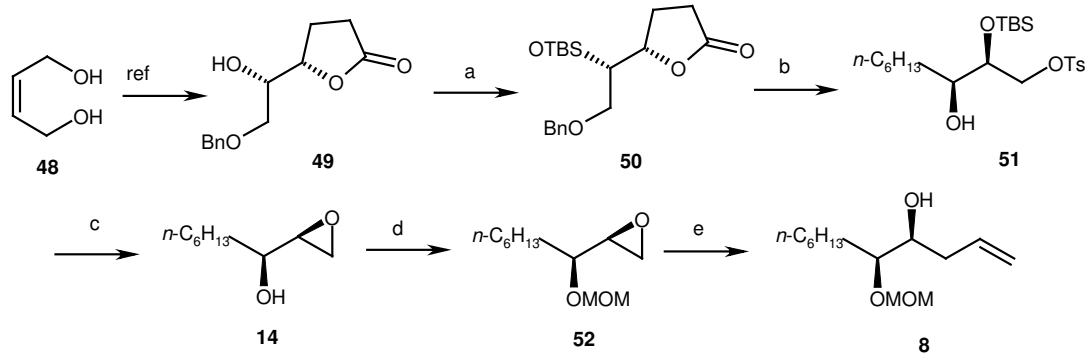
olefination reaction for the formation of *trans* olefin, followed by Yamaguchi protocol for the ring closure and the deprotection to furnish the target molecule microcarpalide **1**.



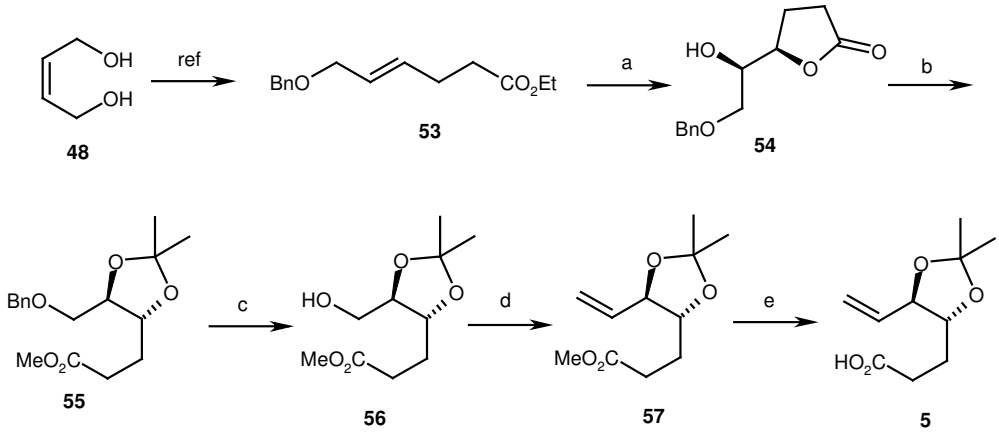
Scheme 12. *Reagents and conditions*: (a) (i) BnBr, NaH, TBAI, THF; (ii) $MeC(OMe)_3$, $EtCO_2H$, 140 ^oC, 48% in two steps; (b) (i) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH, H_2O, 95% ee, 83%; recrystn., >99% ee, 86%; (c) (i) LiOH, THF, H_2O; (ii) 2,2-dimethoxypropane, acetone; (iii) CH_2N_2, Et_2O, EtOAc, 88% in three steps; (d) (i) H_2, 10% Pd/C, *i*-PrOH, quant.; (ii) 4-MeO-TEMPO, KBr, NaOCl, $NaHCO_3$, CH_2Cl_2, H_2O, ca. 70%; (e) (i) KHMDS, 18-C-6, -108 ^oC; (ii) TBAF, THF, 99%; (ii) LiOH, THF; (iii) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, DMAP, C_6H_6, 94%; (iv) $BF_3.Et_2O$, $(CH_2SH)_2$, CH_2Cl_2, 85%.

Chavan *et al.* (2005).[13f]

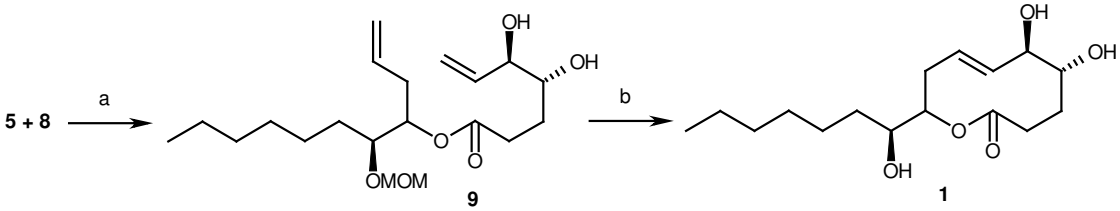
Chavan and co-workers accomplished the total synthesis of microcarpalide employing Sharpless asymmetric dihydroxylation and ring closing metathesis. As shown in Scheme 13 and 14, the key fragments **5** and **8** were obtained from enantiomeric lactones **50** and **54** respectively. Both enantiomeric lactones were readily obtained from *cis*-2-butene-1,4-diol **48** using a Claisen *ortho* ester rearrangement[22] and Sharpless dihydroxylation. Finally, the two fragments **5** and **8** were coupled using DCC followed by ring-closing metathesis to give the target molecule **1** (Scheme 15).



Scheme 13. *Reagents and conditions*: (a) (i) TBDMSCl, imidazole, DMF, 90 ^{o}C, 18 h, 98%; (b) (i) DIBAL-H, CH_2Cl_2, -78 ^{o}C, 1 h, $CH_3CH_2CH_2PPh_3^+$ Br^- LiHMDS, $^-$78 ^{o}C to 0 ^{o}C, 3 h, 72%; (ii) 10% Pd–C, H_2, rt, 4 h, 96%; (iii) Tosyl chloride, pyridine, CH_2Cl_2, 0 ^{o}C, 24 h, 92%; (c) 1M TBAF, THF, 0 ^{o}C–rt, 6 h, 86%; (d) MOMCl, DIPEA, DCM, 0 ^{o}C–rt, 92%; (e) (i) LiCCH:ethylenediamine, DMSO, rt, 12 h, 87%; (ii) H_2, Pd/$BaSO_4$, quinoline, benzene, 1 bar, rt, 0.5 h, 92%.



Scheme 14. *Reagents and conditions*: (a) AD-mix-β, $CH_3SO_2NH_2$, *t*-BuOH/H_2O (1:1), 24 h, 0 ^{o}C, 94%, 93% ee; (b) 2,2-DMP, catalytic *p*-TSA, methanol, rt, 3 h, 93%; (c) 10% Pd–C, H_2, ethyl acetate, rt, 8 h, 94%; (d) (i) oxalyl chloride, DMSO, Et_3N, DCM, $^-$78 ^{o}C, 1 h; (ii) $CH_3PPh_3^+$ I^-, *n*-BuLi, THF, $^-$20 ^{o}C, 3 h, 52%; (for 2 steps) (e) KOH, THF/methanol/water, (2:2:1), rt, 8 h, 87%.



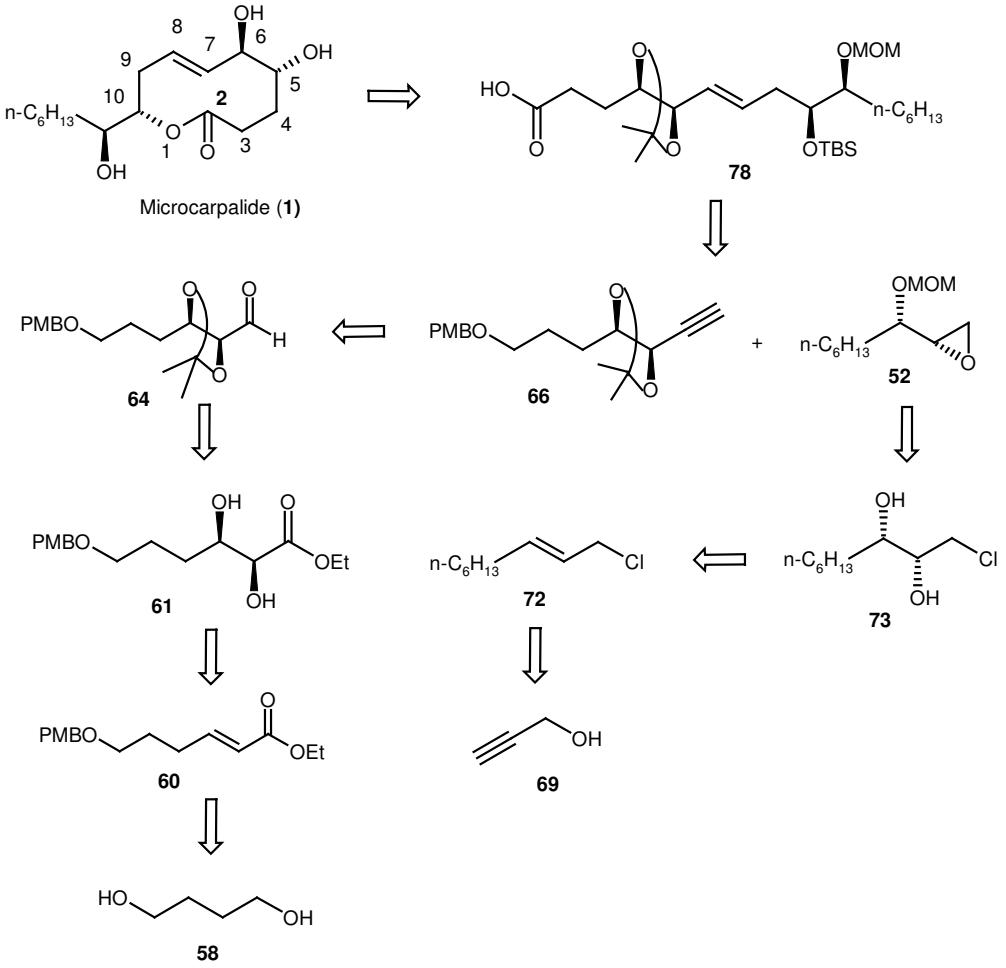
Scheme 15. *Reagents and conditions*: (a) DCC, DMAP, CH_2Cl_2, rt, 18 h, 76%; (b) (i) $(PCy_3)_2Ru(Cl)_2CH$=Ph (20 mol%), CH_2Cl_2, reflux, 28 h, 67%; (ii) BF_3:Et_2O, $(CH_2SH)_2$, CH_2Cl_2, 0 ^{o}C, 1 h, 76%.

3.1.3. PRESENT WORK

Objective

As mentioned earlier, most of the literature methods relied mainly on the ring closing metathesis of diene esters leading to a mixture of *cis* and *trans* compounds. We have employed altogether a different strategy to achieve the synthesis of target molecule in optically pure form and with exclusive E-zeometry of C7-C8 double bond.

The retrosynthetic analysis is based on convergent approach as outlined in Scheme 16. We envisioned that the ring closing could be effected *via* Yamaguchi macrolactonisation of **78**, which in turn would be obtained by Yamaguchi coupling of epoxide **52** with acetylene **66**.



Scheme 16. Retrosynthetic analysis for microcarpalide (1).

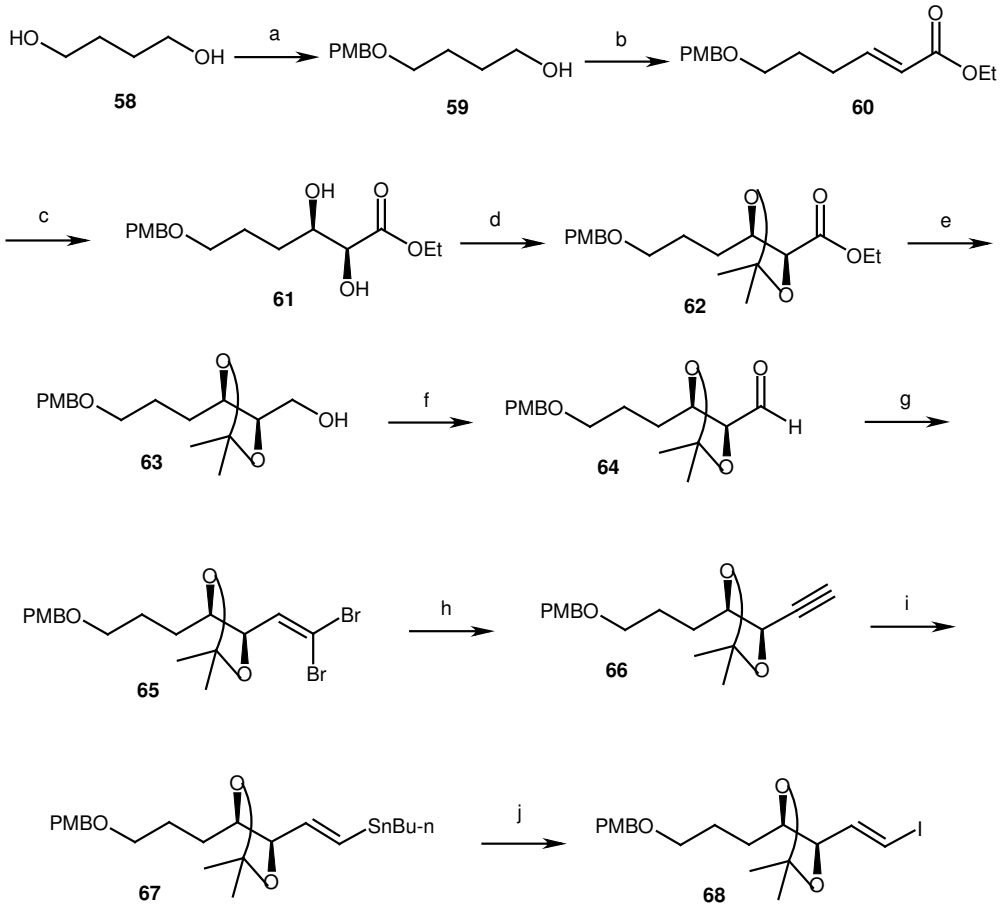
The acetylene **66** would be obtained through a Corey-Fuchs protocol from the aldehyde **64**, which in turn could be obtained from the diol **61**. In this strategy, the stereogenic centers of both the fragments were obtained through Sharpless asymmetric dihydroxylation of olefins **60** and **72**, which in turn could be obtained from the commercially available starting materials 1,4-butane diol **58** and propargyl alcohol **69.**

3.1.4. Results and Discussion

Synthesis of fragment 66 (**Scheme 17**).

The synthesis of acetylene component **66** started from commercially available 1,4-butane diol **58**. Thus selective mono hydroxyl protection of **58** with *p*-methoxybenzyl bromide in the presence of NaH gave **59** in 90% yield. The ^{1}H NMR spectrum gave benzylic protons at δ 4.45 (singlet, two protons) and aromatic protons at δ 7.26 (doublet) and 6.88 (doublet) with coupling constant J = 10.0 Hz. The IR spectrum gave hydroxyl absorption at 3400 cm^{-1}. Compound **59** was oxidized to the corresponding aldehyde under Swern conditions[23] and subsequently treated with (ethoxycarbonylmethylene)triphenylphosphorane in benzene under reflux conditions to furnish the *trans*-olefin **60**[24] in 89% yield. The IR spectrum of **60** showed the ester carbonyl absorption at 1724 cm^{-1} and olefin C=C stretching at 1654 cm^{-1}. The ^{1}H NMR spectrum gave olefin protons at δ 6.98 (doublet of triplet) and 5.86 (doublet) with the coupling constant J = 15.0 Hz indicating *trans*-olefin. The olefin **60** was treated with osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of $(DHQD)_2PHAL$ ligand under AD conditions[25] to give the diol **61** in 96% yield with 97% ee.[26] The IR spectrum gave hydroxyl absorption at 3440-3300 cm^{-1} and ester carbonyl at 1736 cm^{-1}. The ^{1}H NMR indicated absence of olefin protons. The chiral protons appeared at δ 4.06 (multiplet) and 3.91 (doublet). The chiral carbons appeared at δ 72.1 and 69.5 in the ^{13}C NMR spectrum. Treatment of diol **61** with 2,2-dimethoxypropane in the presence of catalytic amount of *p*-TSA gave compound **62** in good yield. The IR spectrum of **62** indicated absence of hydroxyl groups. The acetonide methyl protons appeared at δ 1.44 (singlet) and 1.47 (singlet) in the ^{1}H NMR spectrum and typical quaternary carbon of acetonide appeared at 110.4 in the ^{13}C NMR spectrum. Reduction of **62** using DIBAL-H provided the alcohol **63** in excellent yield. The IR spectrum of **63** gave hydroxyl absorption at 3440 cm^{-1} and the ester carbonyl group was absent. Subsequent homologation to the acetylene **66** was carried out by Corey-Fuchs

protocol[27] in a three-step sequence involving Swern oxidation, dibromomethylenation of the aldehyde and dehalogenation. Thus compound **63** was oxidized to the aldehyde **64** using standard Swern conditions followed by dibromomethylenation with CBr_4 and PPh_3 in CH_2Cl_2 at -78 ^oC to furnish the dibromo olefin **65** in essentially quantitative yield. The ^1H NMR spectrum gave olefin protons at δ 6.44 (doublet) with coupling constant J = 8.7 Hz. Treatment of **65** with excess of *n*-BuLi in THF at -78 ^oC provided the acetylene **66** in 92% yield. The ^1H NMR spectrum gave acetylenic protons at δ 2.51 (singlet).



Scheme 17. *Reagents and conditions:* (a) *p*-$CH_3OC_6H_5CH_2Br$, NaH, dry DMF, cat. TBAI, 0 ^oC to rt, 1 h, 90%; (b) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^oC to -60 ^oC; (ii) $Ph_3P{=}CHCO_2Et$, benzene, reflux, 6 h, 89%; (c) $(DHQD)_2PHAL$, K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, OsO_4 (0.1M sol. in toluene), *t*- BuOH/H_2O (1:1), 0 ^oC, 24 h, 96%; (d) *p*-TSA, 2,2-DMP, CH_2Cl_2, 95%; (e) DIBAL-H, CH_2Cl_2, 0 ^oC to rt, 2 h, 96%; (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^oC to -60 ^oC, 94%; (g) CBr_4, PPh_3, CH_2Cl_2, -78 ^oC, 2 h, 98%; (h) *n*-BuLi,

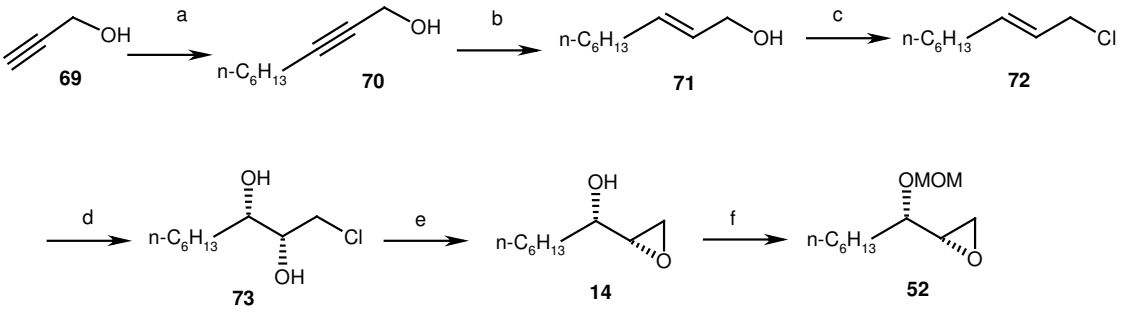
THF, -78 ^{o}C, 1 h, 92%; (i) (*n*-Bu)$_3$SnH, AIBN, C_6H_6, reflux, 4 h, 99%; (j) I_2, CH_2Cl_2, 30 min, 96%.

Acetylene was readily converted into (*E*)-vinyl stannane **67** by reaction with tri-*n*-butyltin hydride and AIBN in refluxing benzene.[28] The ^{1}H NMR spectrum gave olefin protons at δ 6.36 (doublet) and 5.95 (doublet of doublet) with the coupling constant *J* = 19.0, 5.1 Hz, indicating *trans*-olefin. Tributyltin was then replaced with iodide by using I_2 in CH_2Cl_2[29] to afford the corresponding iodo compound **68** in excellent yield. The ^{1}H NMR spectrum gave olefin protons shifted to δ 6.29 (multiplet) and tri-butyl protons were found disappeared.

Synthesis of fragment 52 (**Scheme 18**).

The synthesis of epoxy component **52** commenced from propargyl alcohol **69**. Thus, alkylation of **69** with *n*-hexyl bromide in THF gave the propargylic alcohol **70** in 95% yield. The propargyl alcohol **70** was further converted into (*E*)-allylic alcohol **71** in 96% yield by $LiAlH_4$ reduction.[30] The ^{1}H NMR spectrum gave olefin protons at δ 5.40-5.60 (multiplet, two proton). The IR spectrum of **71** gave hydroxyl absorption at 3323 cm^{-1}. Then, the allyl alcohol was converted into the chloride **72** in 89% yield using *N*-chlorosuccinimide in the presence of PPh_3 at 0 ^{o}C. The allylic chloride **72** was treated with osmium tetroxide in the presence of $(DHQ)_2PHAL$ ligand under AD conditions to afford the diol **73** in 91% yield and 95% ee having m.p. 85-86 ^{o}C and $[\alpha]_D^{25}$ 9.3 (*c* 0.42, $CHCl_3$), which are in accordance with the literature data, m.p. 82-84 ^{o}C and $[\alpha]_D^{25}$ –9.0 (*c* 1.0, MeOH).[31] To minimize the epoxide formation, the reaction was carried out under "buffered" conditions[32] (with 3 equiv. of $NaHCO_3$). The IR spectrum gave hydroxyl absorption at 3335 cm^{-1}. The ^{1}H NMR indicated absence of olefin protons. Two free hydroxyl protons appeared at δ 2.75 and 2.25 as broad singlets in ^{1}H NMR. The chiral carbons appeared at δ 73.7,and 71.52 in the ^{13}C NMR spectrum. Treatment of **73** with 2 eq. of NaOH in THF at 0 ^{o}C afforded the epoxide **14** in 90% yield having $[\alpha]_D^{25}$ -64.2 (*c* 1.0, $CHCl_3$). The IR spectrum of **14** showed strong absorption at 3400 cm^{-1}. The ^{1}H NMR spectrum of **14** showed epoxide protons upfield at δ 2.96-2.98 (multiplet, one proton), 2.81 (triplet, one proton, with coupling constant *J* = 5.2 Hz) and 2.70 (doublet of doublet, with coupling constant *J* = 4.8, 2.8 Hz). The ^{13}C NMR spectrum of **14** showed upfield carbons characteristic of epoxide at δ 55.4 and 44.9. The protection of free hydroxy group of **14** with MOMCl in CH_2Cl_2 in the presence of diisopropylethyl amine gave

the epoxy compound **52** in excellent yield. The ^{1}H NMR spectrum of **52** showed methyleneoxy protons at δ 4.71 (singlet) and methoxy protons at δ 3.42 (singlet).

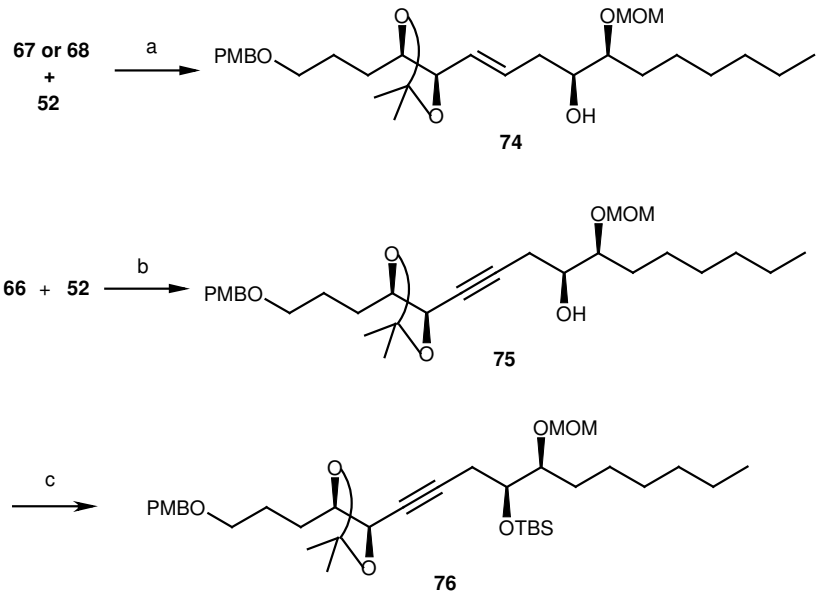


Scheme 18. Reagents and conditions: (a) Li, Liq NH_3, $Fe(NO_3)_3$, *n*-$C_6H_{13}Br$, THF, -78 ^oC, 95%; (b) $LiAlH_4$, THF, reflux, 96%; (c) *N*-chlorosuccinimide, PPh_3, CH_2Cl_2, 0 ^oC to rt, 3 h, 89%; (d) $(DHQ)_2PHAL$, K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, OsO_4 (0.1M sol. in toluene), *t*-BuOH/H_2O (1:1), 0 ^oC, 24 h, 91%; (e) NaOH, THF, 2 h, 0 ^oC to rt, 90%; (f) MOMCl, *i*-Pr_2EtN, CH_2Cl_2, 0 ^oC to rt, 6 h, 98%.

Coupling of the epoxide 52 with different nucleophiles (Scheme 19).

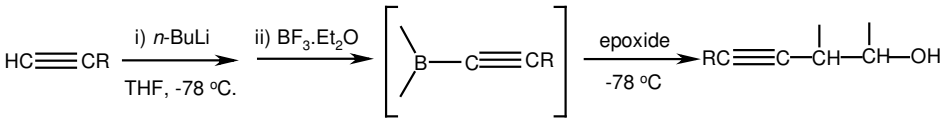
Having completed the synthesis of both fragments **66** and **52**, we required to couple two fragments by regioselective epoxide opening and carry out subsequent macrolactonisation. To this end, we studied the opening of epoxide with different nucleophiles such as **66**, **67**, and **68**. Thus, vinyl stannane **67** was treated with *n*-BuLi in THF at –78 ^oC for 1 h and further treated with CuCN followed by addition of epoxide **52** to form the coupling product **74** in 51% yield.[33] The structure of **74** was proven by the ^{1}H NMR and ^{13}C NMR spectra.

In the same way compound **68** was transformed into the corresponding cuprate by sequential treatment with *n*-BuLi and CuCN followed by addition of epoxide to give compound **74** in 78% yield. In both these reactions 2-3 eq. of cuprate was utilized. Though the compound **74** was obtained with requisite *trans*-geometry of the double bond, the drawback of this reaction was in employing 2-3 equivalents of substrates **67** or **68** with respect to the epoxide. The epoxide opening reaction did not work with the use of 1-1.5 equivalent of cuprates even in the presence of $BF_3.Et_2O$.



Scheme 19. Reagents and conditions: (a) For **67**: *n*-BuLi/**67**, -78 ^{o}C for 1 h, -50 ^{o}C for 1.5 h, then CuCN, -78 ^{o}C, 1.5 h, then epoxide **52**, 51%; for **68**: *n*-BuLi/**52**, -78 ^{o}C, CuCN, THF, 5 h, 78%; (b) *n*-BuLi, THF, -78 ^{o}C to –20 ^{o}C, 30 min, then $BF_3.Et_2O$, -78 ^{o}C, 10 min, then **52**, 30 min, 89%; (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 ^{o}C, 30 min, 98%.

Mechanism of Yamaguchi coupling



Scheme 19a

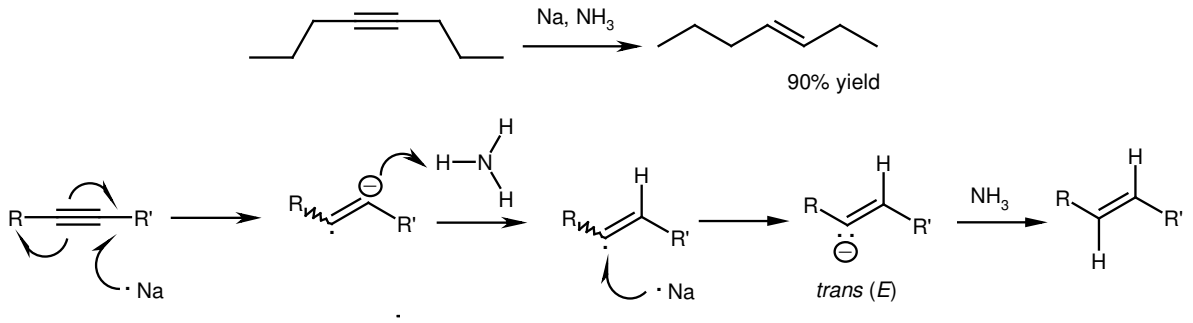
Although the precise reaction mechanism is not fully clear. The assumption of alkynyldifluoro boranes as the intermediate may account for the above mentioned reaction.

Initially we tried Yamaguchi coupling of the epoxide **52** with acetylide generated directly from the debromination of dibromoalkene **65** in the presence of $BF_3.Et_2O$ and *n*-BuLi, however the reaction was not very clean affording only a mixture of compounds which could not be separated. This may be attributed to the use of excess of *n*-BuLi in the debromination reaction. In order to circumvent these problems, the acetylide **66** (1.5 equivalent) was finally coupled with epoxide **52** (1 equivalent) via Yamaguchi method[34] in the presence of $BF_3.Et_2O$

at -78 ^{o}C to afford **75** in 89% yield. The free hydroxy group of **75** was protected with TBSCl to furnish compound **76**.

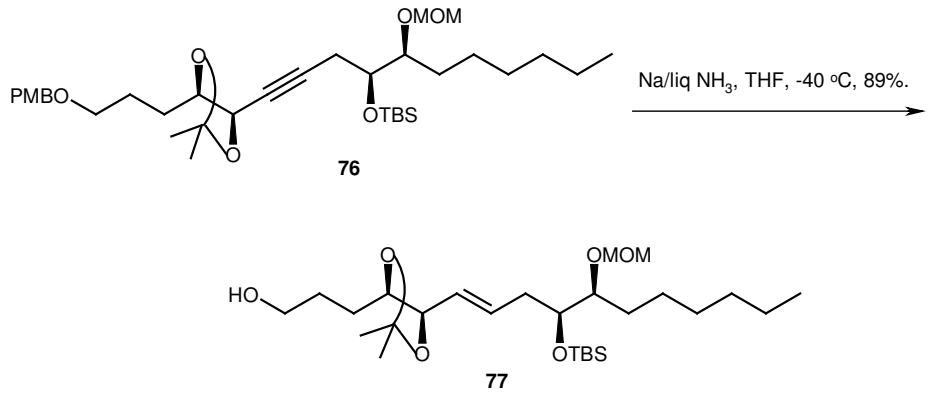
Mechanism of Birch reduction

The vinyl anion is sufficiently basic to take the proton from ammonia so no EtOH is required here- the trans (E) stereochemistry is set up at the vinyl anion stage for optimum stability.



Scheme 19b.

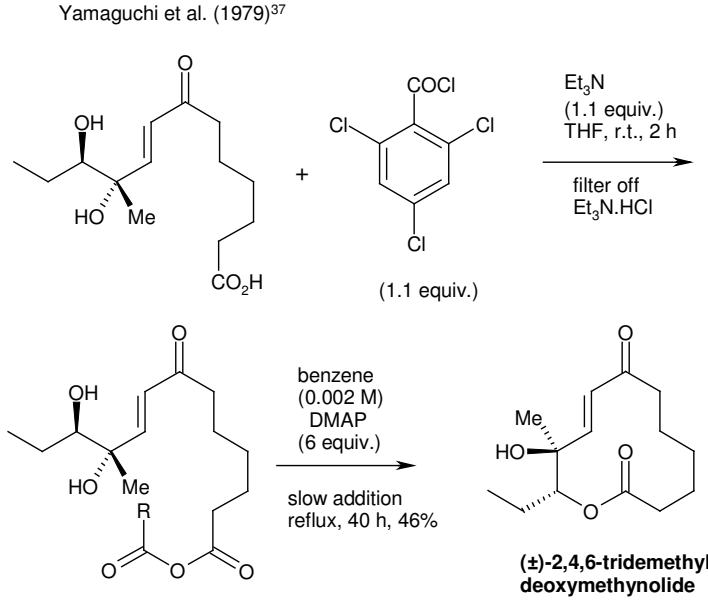
Reduction of the alkyne under Birch conditions using Na/liqNH_3[35] proceeded smoothly with the required *E*-geometry of the C7-C8 double bond and concomitant removal of the PMB group affording **77** in good yield. Thus the *E*-selective construction of C7-C8 double bond in the synthesis of target molecule **1** is a significant improvement over all the reported syntheses. The ^{1}H NMR spectrum gave olefin protons at δ 5.45-5.60 (multiplet) and 5.31 (doublet of doublet) with the coupling constant *J* = 15.7, 6.7 Hz and PMB group protons were found to be missing. It confirmed the presence of *trans*-olefin and deprotection of PMB group. ^{13}CNMR spectrum showed the presence of olefin carbons at δ 131.7 and 128.2.



Scheme 19c. Birch reduction of 76

Yamaguchi macrolactonization:

In 1979, M. Yamaguchi and co-workers[37] developed a novel procedure for the rapid preparation of esters and lactones under mild conditions via the alcoholysis of the corresponding mixed anhydrides. As a result of their thorough study, they found that 2,4,6-trichlorobenzoyl chloride/DMAP was the best reagent combination in terms both the high reaction rate as well as the high product yield. The procedure was put to the end and used for the lactonization of a very acid sensitive substrate that was known to rapidly decompose on contact with catalytic amounts of HCl. The substrate hydroxy acid was treated with 2,4,6-trichlorobenzoyl chloride in the presence of Et_3N, and the by-product triethylamine hydrochloride was removed. The resulting mixed anhydride was diluted with toluene and slowly added to a refluxing solution of DMAP in toluene under high dilution conditions (0.002 M).

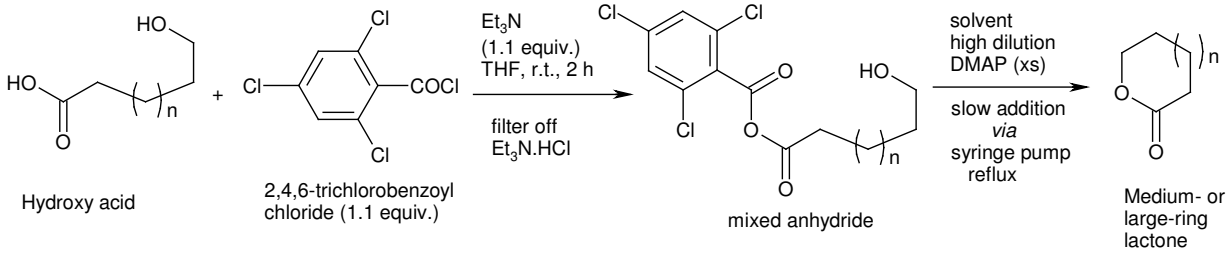


Scheme 19d. Yamaguchi macrolactonization.

The formation of medium- and large-ring lactones from hydroxyl acids using 2,4,6-trichlorobenzoyl chloride/DMAP is known as the ***Yamaguchi macrolactonization****. The general features of this transformation are: 1) the substrate is first converted to the corresponding mixed anhydride with 2,4,6-trichlorobenzoyl chloride in the presence of a tertiary amine to activate the carboxylic acid functionality; 2) aromatic hydrocarbon such as benzene and toluene are the best solvents; 3) the reaction is conducted under high-dilution conditions to minimize intermolecular coupling; 4) the mixed anhydride is dissolved and*

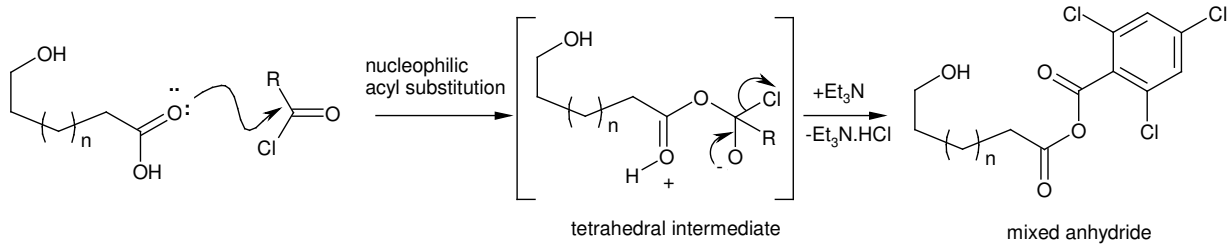
slowly added (via a syringe pump) to a refluxing solution of DMAP in benzene or toluene; and 5) usually several equivalents of DMAP, a known catalyst for acyl transfer reactions, is used. The main advantages of the Yamaguchi macrolactonization over other existing methods are its operational simplicity, its high reaction rate and the lack of by-products.

Yamaguchi macrolactonization:

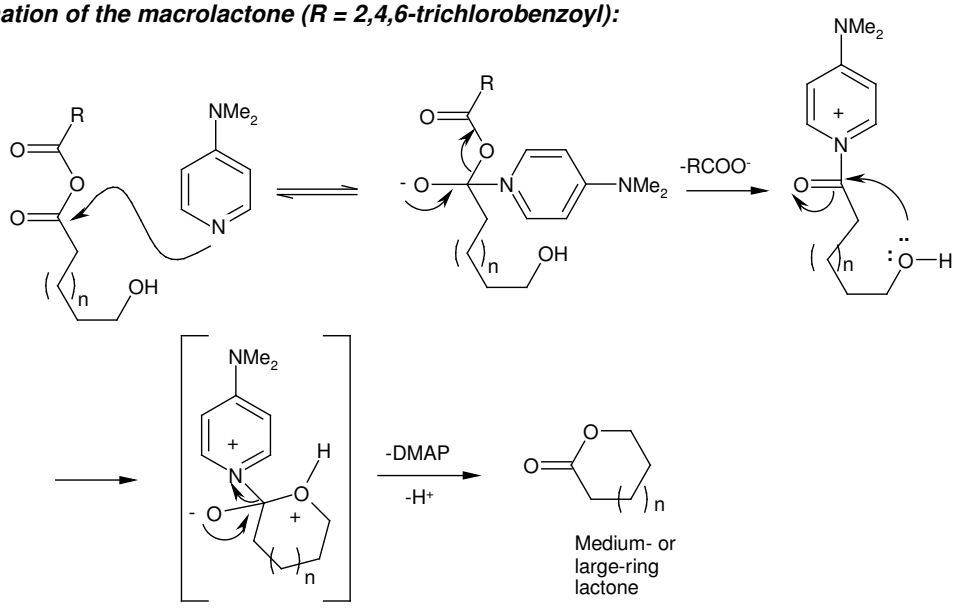


Mechanism:

Formation of the mixed anhydride (R = 2,4,6-trichlorobenzoyl):

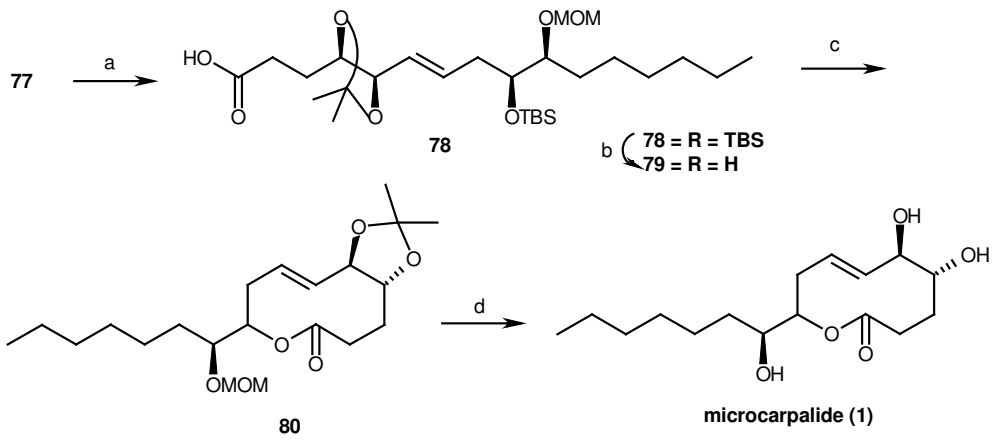


Formation of the macrolactone (R = 2,4,6-trichlorobenzoyl):



Synthesis of microcarpalide 1 (Scheme 20).

Oxidation of primary alcohol in **77** to the corresponding aldehyde using Swern conditions and further oxidation using $NaClO_2$ in DMSO under buffer conditions[36] afforded the acid **78**. The TBS group in **78** was removed with TBAF to give the seco acid **79** for lactonization. Macrolactonization of **79** under Yamaguchi conditions[37] provided the macrocyclic lactone **80** in quantitative yield, which on subsequent cleavage of the protective groups[13a] afforded the target molecule **1** in 88% yield, whose spectral data matched with those reported by Hemscheidt *et al.*[12c] for the natural product. Like the natural microcarpalide (**1**), in deuterated acetonitrile, the NMR spectrum of synthetic **1** revealed two slowly inter convertible conformers in a 76:24 ratio. The resonances due to H-10 were seen at 4.84 ppm for the major conformer and at 4.63 ppm for the minor one. This conformer ratio is identical to the 3.5:1 value reported for natural product in the same solvent.



Scheme 20. Reagents and conditions: (a) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^oC to -60 ^oC, 95%; (ii) $NaClO_2$, DMSO, H_2O, NaH_2PO_4, rt, 1.5 h, 86%; (b) TBAF, THF, rt, overnight; (c) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, then DMAP, benzene, 86% from **24**; (d) $BF_3.Et_2O$, $(CH_2SH)_2$, CH_2Cl_2, 1 h, 88%.

3.1.5. Conclusion

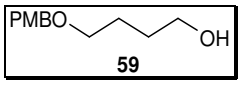
A convergent and efficient total synthesis of microcarpalide **1**, with high enantioselectivities has been developed in which all the stereocenters were established by Sharpless asymmetric dihydroxylation. Notable features of this approach include Corey-Fuchs protocol to synthesize

the acetylene fragment, various nucleophiles used in the regioselective epoxide opening to establish the C7-C8 *trans*-olefin geometry exclusively and Yamaguchi protocol in the macrocyclization step. The synthetic strategy described for **1** might be easily amenable for the preparation of either enantiomer or its double-bond isomer simply by partial hydrogenation using Lindlar's catalyst.

3.1.6. Experimental Section

All reactions were carried out under argon or nitrogen in oven-dried glassware using standard gas-light syringes, cannulas and septa. Solvents and reagents were purified and dried by standard methods prior to use. Optical rotations were measured at room temperature. IR spectra were recorded on an FT-IR instrument. ^{1}H NMR spectra were recorded on 200 MHz, 300 MHz and 500 MHz and are reported in parts per million (δ) downfield relative to $CDCl_3$ as internal standard and ^{13}C NMR spectra were recorded at 50 MHz, 75 MHz and 125 MHz and assigned in parts per million (δ) relative to $CDCl_3$. Column chromatography was performed on silica gel (100-200 and 230-400 mesh) using a mixture of petroleum ether and ethyl acetate as the eluent. Enantiomeric excess was determined using chiral HPLC.

4-(4-Methoxybenzyloxy)-butan-1-ol (59).



59

To a solution of 1,4-butanediol **58** (7.0 g, 77.67 mmol) in dry DMF (200 mL) was added sodium hydride (50%, 3.73 g, 77.70 mmol) at 0 ^{o}C. The reaction mixture was then stirred at room temperature for 30 min after which it was again cooled to 0 ^{o}C. To this was added slowly *p*-methoxybenzyl bromide (15.63 g, 77.7 mmol) and tetra *n*-butylammonium iodide (2.50 g, 6.77 mmol) with further stirring for 1 h at the same temperature. The reaction mixture was quenched with addition of cold water at 0 ^{o}C. The two phases were separated and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with water (3 x 100 mL), brine, dried (Na_2SO_4) and concentrated. The residual oil was purified by silica gel column chromatography using petroleum ether/EtOAc (8:2) as eluent to furnish the mono-PMB protected alcohol **59** as a colorless oil.

Yield: 14.71 g, 90%

Mol. Formula: $C_{12}H_{18}O_3$

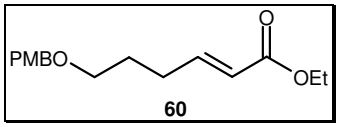
IR (neat, cm^{-1}): ν_{max}3400, 2937, 2863, 1612, 1513, 1248, 1174, 1097.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.26 (d, 2H, *J* = 10 Hz); 6.88 (d, 2H, *J* = 10 Hz), 4.45 (s, 2 H), 3.80 (s, 3 H) 3.62 (t, 2H, *J* = 5 Hz), 3.49 (t, 2H, *J* = 5 Hz), 1.64-1.71 (m, 4H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 159.2, 130.3, 129.3, 113.8, 72.5, 69.9, 62.2, 55.1, 29.6, 26.3.

Analysis: Calcd.: C, 68.54; H, 8.63%; **Found:** C, 68.33; H, 8.85%.

6-(4-Methoxybenzyloxy)-hex-2-enoic acid ethyl ester (60).



60

(a) Swern oxidation. To a solution of oxalyl chloride (9.06 g, 71.38 mmol) in dry CH_2Cl_2 (100 mL) at -78 ^oC was added dropwise dry DMSO (11.15 g, 10.12 mL, 142.71 mmol) in CH_2Cl_2 (20 mL). After 30 min, alcohol **59** (10.0 g, 47.56 mmol) in CH_2Cl_2 (20 mL) was added over 10 min giving copious white precipitate. After stirring for 1 h at -78 ^oC, the reaction mixture was brought to -60 ^oC and Et_3N (19.25 g, 26.52 mL, 190.24 mmol) was added slowly and stirred for 30 min allowing the reaction mixture to warm to room temperature. The reaction mixture was then diluted with water (150 mL) and CH_2Cl_2. The organic layer was separated and washed with water and brine, dried (Na_2SO_4) and passed through short pad of celite. The filtrate was concentrated to give the aldehyde (9.86 g, 95%) as pale yellow oil, which was used as such for the next step without purification.

(b) Wittig olefination. To a solution of (ethoxycarbonylmethylene)triphenylphosphorane (18.14 g, 52.07 mmol) in dry benzene (150 mL) was added a solution of the above aldehyde in dry benzene (100 mL). The reaction mixture was refluxed for 6 h. It was then concentrated and purified by silica gel column chromatography using petroleum ether/EtOAc (8.5:1.5) as eluent to afford the α,β-unsaturated olefin **60** as a pale yellow liquid. **Yield:** 11.73 g, 89%

Mol. Formula: $C_{16}H_{22}O_4$

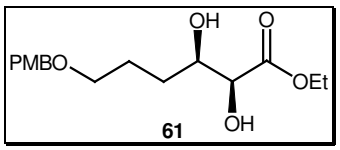
IR ($CHCl_3$, cm^{-1}): ν_{max}2956, 2858, 1724, 1654, 1038, 1300, 1204, 1100.

^{1}H NMR (500 MHz, $CDCl_3$): δ7.28 (d, 2H, *J* = 9 Hz); 6.98 (dt, 1 H, *J* = 15, 10 Hz), 6.91 (d, 2H, *J* = 9 Hz), 5.86 (d, 1H, *J* = 15 Hz), 4.45 (s, 2 H), 4.20 (q, 2H, *J* = 8 Hz), 3.83 (s, 3H), 3.48 (t, 2H, *J* = 6Hz), 2.31 (q, 2H, *J* = 7 Hz), 1.75-181 (m, 2 H), 1.31(t, 3H, *J* = 8 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.4, 158.9, 148.4, 130.2, 129.0, 121.4, 113.5, 72.3, 68.7, 59.9, 54.9, 28.7, 27.9, 14.0.

Analysis: Calcd.: C, 69.04; H, 7.97%; **Found:** C, 69.10; H, 7.75%.

2,3-Dihydroxy-6-(4-methoxybenzyloxy)-hexanoic acid ethyl ester (61).



61

To a mixture of $K_3Fe(CN)_6$ (18.45 g, 56.0 mmol), K_2CO_3 (7.74 g, 56.0 mmol) and $(DHQD)_2PHAL$ (145 mg, 1 mol%), in *t*-BuOH-H_2O (1:1, 100 mL) cooled at 0 ^oC was added OsO_4 (0.79 mL, 0.1 M solution in toluene, 0.4 mol%) followed by methanesulfonamide (1.78 g, 18.71 mmol). After being stirred for 5 min at 0 ^oC, the olefin **60** (5.20 g, 18.68 mmol) was added in one portion. The reaction mixture was stirred at 0 ^oC for 24 h and then quenched with solid sodium sulfite (25 g). The stirring was continued for an additional 45 min, and then the solution was extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with 10% KOH, and brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (3:2) as eluent gave the diol **61** as a colorless syrupy liquid.

Yield: 5.63 g, 96%

Mol. Formula: $C_{16}H_{24}O_6$

$[\alpha]_D^{25}$: +6.7 (*c* 1.6, $CHCl_3$).

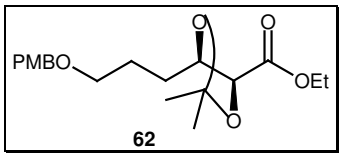
IR (neat, cm^{-1}): ν_{max} 3440, 2938, 2864, 1736, 1612, 1513, 1248, 1130, 1032.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (d, 2H, *J* = 10.1 Hz); 6.88 (d, 2H, *J* = 10.1 Hz), 4.44 (s, 2H), 4.26 (q, 2H, *J* = 5.0 Hz), 4.06 (m, 1H), 3.91(d, 1H, *J* = 5.3 Hz), 3.80 (s, 3H), 3.49 (t, 2H, *J* = 6.1 Hz), 2.82 (br s, 2H), 1.73 (m, 4H), 1.30 (t, 3H, *J* = 6.1 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ 173.2, 158.8, 130.1, 128.9, 113.4, 73.4, 72.1, 69.5, 61.2, 54.8, 42.5, 30.0, 25.6, 13.7.

Analysis: Calcd.: C, 61.52; H, 7.74%; **Found:** C, 61.78; H, 7.82%.

5-[3-(4-Methoxybenzyloxy)-propyl]-2,2-dimethyl-[1,3]dioxolane-4-carboxylic acid ethyl ester (62).



62

To a solution of the diol **61** (4.50 g, 14.41 mmol), *p*-TSA (100 mg) in CH_2Cl_2 (100 mL) was added 2,2-dimethoxypropane (2.25 g, 21.60 mmol) and reaction mixture stirred overnight at room temperature. Solid $NaHCO_3$ (1 g) was added and mixture again stirred for 30 min. The reaction mixture was filtered through a pad of neutral alumina and filtrate concentrated. Silica gel column chromatography using petroleum ether/EtOAc (9:1) as eluent gave **62** as a colorless liquid.

Yield: 4.82 g, 95%

Mol. Formula: $C_{19}H_{28}O_6$

$[\alpha]_D^{25}$: +24.2 (*c* 1.9, $CHCl_3$)

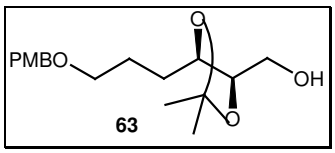
IR (neat, cm^{-1}): ν_{max} 2864, 1736, 1612, 1513, 1248, 1130, 1032

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (d, 2H, *J* = 10.0 Hz), 6.91 (d, 2H, *J* = 10.0 Hz), 4.52 (s, 2H), 4.22 (q, 2H, *J* = 7.3 Hz), 4.10-4.14 (m, 1H), 3.80 (s, 3H), 3.53 (t, 3H, *J* = 5.8 Hz), 1.72-1.93 (m, 4H), 1.47 (s, 3H), 1.44 (s, 3H), 1.29 (t, 3H, *J* = 6.8 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 158.9, 130.4, 128.8, 113.5, 110.4, 78.89, 78.71, 72.2, 69.2, 60.9, 54.9, 29.8, 26.9, 25.5, 25.4, 13.8.

Analysis: Calcd.: C, 64.75; H, 8.01%; **Found:** C, 64.86; H, 8.44%.

{5-[3-(4-Methoxybenzyloxy)-propyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-methanol (63).



63

To a solution of **62** (4.0 g, 11.35 mmol) in dry CH_2Cl_2 (80 mL) at 0 ^oC was added dropwise DIBAL-H (22.70 mL, 22.70 mmol, 1M in toluene) through a syringe. The reaction mixture was allowed to warm to room temperature over 2 h, then re-cooled to 0 ^oC and treated with saturated solution of sodium/potassium tartrate. The solid material was filtered through a pad of celite and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (7:3) as eluent gave **63** as a colorless oil.

Yield: 3.38 g, 96%

Mol. Formula: $C_{17}H_{26}O_5$

$[\alpha]_D^{25}$: +12.1 (*c* 1.9, $CHCl_3$).

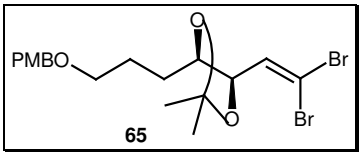
IR ($CHCl_3$, cm^{-1}): ν_{max} 3440, 2938, 2860, 1361, 1204, 1126, 1038.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (d, 2H, *J* = 8.7 Hz), 6.89 (d, 2H, *J* = 8.7 Hz), 4.44 (s, 2H), 3.90 (dt, *J* = 7.6, 4.0 Hz, 1H), 3.81 (s, 3H), 3.76 (m, 2H), 3.60 (dd, 1H, *J* = 7.5, 4.4 Hz), 3.46-3.53 (m, 2H), 2.18 (s, 1H), 1.62-1.84 (m, 4H), 1.41 (s, 3H), 1.40 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.1, 130.5, 129.1, 113.7, 108.5, 81.5, 76.7, 72.4, 69.6, 62.1, 55.1, 29.7, 27.2, 26.9, 26.0.

Analysis: Calcd.: C, 65.78; H, 8.44%; **Found:** C, 65.94; H, 8.64%.

4-(2,2-Dibromovinyl)-5-[3-(4-methoxybenzyloxy)-propyl]-2,2-dimethyl-[1,3]dioxolane (65).



65

To a solution of oxalyl chloride (2.45 g, 1.69 mL, 19.30 mmol) in dry CH_2Cl_2 (100 mL) at -78 ^oC was added dropwise dry DMSO (3.02 g, 2.74 mL, 38.65 mmol) in CH_2Cl_2 (20 mL). After 30 min, alcohol **63** (4.0 g, 12.89 mmol) in CH_2Cl_2 (20 mL) was added over 10 min giving a copious white precipitate. After stirring for 1 h at -78 ^oC the reaction mixture was brought to -60 ^oC and Et_3N (5.22 g, 7.18 mL, 51.59 mmol) was added slowly and stirred for 30 min allowing the reaction mixture to warm to room temperature. The reaction mixture was poured into water (150 mL) and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL) and combined organic layers were washed with water (3 x 50 mL), brine (50 mL), dried (Na_2SO_4) and passed through short pad of silica gel. The filtrate was concentrated to give the aldehyde **64** (3.9 g) as pale yellow oil, which was used as such for the next step without purification.

To a cooled (0 ^oC) and stirred solution of carbon tetrabromide (7.74 g, 23.34 mmol) in CH_2Cl_2 (100 mL) was added triphenylphosphine (12.25 g, 46.70 mmol) in CH_2Cl_2 (30 mL) under argon. After 10 min, the reaction mixture was cooled to -78 ^oC and a solution of the above aldehyde **64** (3.6 g, 11.66 mmol) in CH_2Cl_2 (20 mL) was introduced into the yellowish ylide solution. The mixture was stirred for 2 h at -78 ^oC, quenched with saturated $NaHCO_3$ solution

and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) as eluent gave **65** as a yellow syrup.

Yield: 5.31 g, 98%

Mol. Formula: $C_{18}H_{24}Br_2O_4$

$[\alpha]_D^{25}$: +9.7 (*c* 2.8, $CHCl_3$).

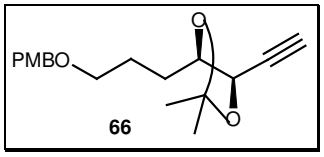
IR ($CHCl_3$, cm^{-1}): ν_{max}2938, 2864, 1613, 1514, 1248, 1130, 1032.

^{1}H NMR (500 MHz, $CDCl_3$): δ δ 7.30 (d, 2H, *J* = 8.3 Hz), 6.92 (d, 2H, *J* = 8.3 Hz), 6.44 (d, 1H, *J* = 8.7 Hz), 4.46 (s, 2H), 4.32 (t, 1H, *J* = 8.7 Hz), 3.83 (s, 3H), 3.72-3.80 (m, 1H), 3.49-3.56 (m, 2H), 1.67-1.81 (m, 4H), 1.43 (s, 3H), 1.40 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): δ 158.9, 135.6, 130.4, 129.0, 113.5, 109.1, 93.7, 80.4, 79.4, 72.2, 69.2, 55.0, 28.4, 27.0, 26.5, 25.8.

Analysis: Calcd.: C, 46.57; H, 5.21; Br, 34.43%; **Found:** C, 46.85; H, 5.38; Br, 34.48%.

4-Ethynyl-5-[3-(4-methoxybenzyloxy)-propyl]-2,2-dimethyl-[1,3]dioxolane (66).



66

To a cooled (-78 ^oC) and stirred solution of **65** (5.8 g, 12.49 mmol) in THF (50 mL) was added *n*-BuLi (1.6 M solution in hexane, 39.06 mL, 62.47 mmol) dropwise under argon. After 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (8:2) as eluent gave **66** as a yellowish oil.

Yield: 3.49 g, 92%

Mol. Formula: $C_{18}H_{24}O_4$

$[\alpha]_D^{25}$: +13.4 (*c* 1.6, $CHCl_3$)

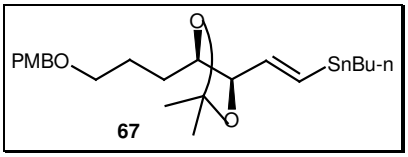
IR ($CHCl_3$, cm^{-1}): ν_{max} 2943, 2859, 1615, 1518, 1244, 1132, 1030

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (d, 2H, *J* = 8.0 Hz), 6.89 (d, 2H, *J* = 7.6 Hz), 4.44 (s, 2H), 4.22 (d, 1H, *J* = 7.9 Hz), 4.05 (dt, *J* = 7.9, 3.6 Hz, 1H), 3.80 (s, 3H), 3.47-3.52 (m, 2H), 2.51 (s, 1H), 1.70-1.81 (m, 4H), 1.45 (s, 3H), 1.40 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.0, 130.5, 129.0, 113.6, 109.8, 81.2, 80.7, 74.5, 72.4, 70.1, 69.4, 55.1, 28.9, 26.9, 26.0, 25.7.

Analysis: Calcd.: C, 71.03; H, 7.95%; **Found:** C, 71.21; H, 8.01%.

Tributyl-(2-{5-[3-(4-methoxybenzyloxy)-propyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-vinyl)-stannane (67).



To a stirred solution of **66** (0.500 g, 1.64 mmol) in benzene (25 mL) were added *n*-Bu_3SnH (0.65 mL, 2.45 mmol) and AIBN (catalytic) at room temperature under N_2. The reaction mixture was gently refluxed with stirring for 4 h. The solvent was removed and the residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1) as eluent to give **67** as yellowish oil.

Yield: 968 mg, 99%

Mol. Formula: $C_{30}H_{52}O_4Sn$

$[\alpha]_D^{25}$: +8.4 (*c* 0.9, $CHCl_3$)

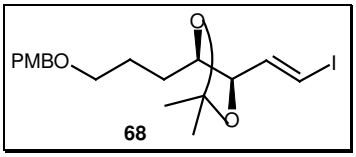
IR ($CHCl_3$, cm^{-1}): ν_{max} 3004, 2957, 2928, 2853, 1612, 1513, 1464, 1378, 1247, 1173, 1036.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.36 (d, *J* = 19.0 Hz, 1H), 5.95 (dd, *J* = 19.0, 5.1 Hz, 1H), 4.44 (s, 2H), 3.98 (t, *J* = 7.3 Hz, 1H), 3.81 (s, 3H), 3.73-3.79 (m, 1H), 3.48 (t, *J* = 5.9 Hz, 2H), 1.61-1.69 (m, 4H), 1.42-1.48 (m, 8H), 1.41 (s, 3H), 1.38 (s, 3H), 1.26-1.31 (m, 10H), 0.88-0.93 (m, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0, 144.8, 134.1, 130.6, 129.1, 113.6, 108.3, 85.3, 80.2, 80.4, 72.4, 69.7, 55.1, 29.1, 29.0, 28.5, 27.3, 27.1, 26.9, 26.1, 13.6, 11.1, 10.6, 10.1, 9.4, 8.8.

Analysis: Calcd.: C, 60.51; H, 8.80; **Found:** C, 60.73; H, 8.64.

4-(2-Iodovinyl)-5-[3-(4-methoxybenzyloxy)-propyl]-2,2-dimethyl-[1,3]dioxolane (68).



To a cooled (0 ^oC), stirred solution of **67** (250 mg, 0.42 mmol) in CH_2Cl_2 (15 mL) was added iodine (213 mg, 0.84 mmol). After 10 min at 0 ^oC**,** the reaction mixture was diluted with

CH_2Cl_2, washed with saturated $Na_2S_2O_3$ and 10% KF solutions, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9.5:0.5) as eluent gave **68** as a yellowish oil.

Yield: 174 mg, 96%

Mol. Formula: $C_{18}H_{25}IO_4$

$[\alpha]_D^{25}$: +7.6 (*c* 1.1, $CHCl_3$).

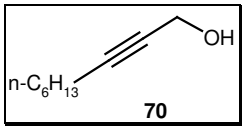
IR ($CHCl_3$, cm^{-1}): ν_{max} 2946, 2932, 2856, 1612, 1513, 1465, 1372, 1174, 1092, 947.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.29 (d, *J* = 8.6 Hz, 2H), 6.53 (d, *J* = 8.7 Hz, 2H), 6.29 (m, 2H), 4.44 (s, 2H), 3.94-4.01 (m, 1H), 3.81 (s, 3H), 3.63-3.76 (m, 1H), 3.47 (t, *J* = 5.8 Hz, 2H), 1.61-1.78 (m, 4H), 1.40 (s, 3H), 1.40 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 161.4, 147.6, 129.5, 128.6, 114.0, 101.7, 86.5, 81.6, 75.8, 74.3, 70.1, 56.2, 28.8, 26.2, 25.5.

Analysis: Calcd.: C, 50.01; H, 5.83, I, 29.36%; **Found:** C, 50.42; H, 5.75, I, 30.01%.

Non-2-yn-1-ol (70).



70

To a mechanically stirred solution of lithium (100 mg) in liquid ammonia (500 mL, under nitrogen at –35 ^oC), were added a few crystals of $Fe(NO_3)_3.9H_2O$, followed by finely cut lithium (6.45 g, 0.90 mol) in small portions over 25 min. After the mixture turned grey, it was stirred for another 30 min. Distilled propargylic alcohol **69** (25.30 g, 0.45 mol, dissolved in 26 mL of dry THF) was added over 20 min, followed by stirring for 90 min. To this solution was added *n*-bromohexane (24.83 g, 0.30 mmol), dissolved in THF (75 mL) in 1 h. The mixture was stirred overnight to evaporate ammonia. After adding water (400 mL) and ether (400 mL), and stirring for 30 min, the layers were separated and the aqueous layer was extracted with ether (3 x 100 mL) and combined organic layers were washed brine (100 mL), dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether:EtOAc (3:2) as eluent gave the propargylic alcohol **70** as a colorless syrupy liquid.

Yield: 20.25 g, 95%

Mol. Formula: $C_9H_{16}O$

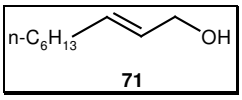
IR ($CHCl_3$, cm^{-1}): ν_{max} 3610, 3400, 2920, 2850, 2290, 2220

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.25 (t, *J* = 2.2 Hz, 2H), 2.18-2.23 (m, 2H), 1.77 (br s, 1H), 1.23-1.55 (m, 8H), 0.89 (t, *J* = 6.6 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): δ 85.7, 78.1, 50.5, 31.1, 28.37, 28.31, 22.2, 18.4, 13.7.

Analysis: Calcd.: C, 77.09; H, 11.50%, **Found:** C, 77.31; H, 11.28%.

Non-2-en-1-ol (71).



71

To a stirred solution of compound **70** (5.0 g, 35.66 mmol) in dry THF (100 mL) was added $LiAlH_4$ (1.35 g, 35.66 mmol) slowly at 0 ^oC under nitrogen atmosphere. After Stirring for 20 min, the reaction mixture was heated under reflux for 6 h. The reaction was quenched by adding 10% aqueous NaOH at 0 ^oC. The mixture was filtered, and washed with EtOAc. The organic layer was dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using petroleum ether:EtOAc (3:2) as eluent gave the **71** as a colorless syrupy liquid.

Yield: 4.86 g, 96%

Mol. Formula: $C_9H_{18}O$

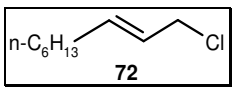
IR (neat, cm^{-1}): ν_{max} 3323, 2924, 1704, 1468

^{1}H NMR (200 MHz, $CDCl_3$): δ 5.40-5.60 (m, 2H), 4.09 (d, *J* = 4.9 Hz, 2H), 2.60-2.70 (br s, 1H), 2.01-2.10 (m, 2H), 1.26-1.40 (m, 8H), 0.87 (t, *J* = 6.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 132.8, 128.7, 63.1, 32.0, 31.5, 28.98, 28.72, 22.4, 13.8.

Analysis: Calcd.: C, 76.00; H, 12.76%; **Found:** C, 76.09; H, 12.62%.

1-Chloro-non-2-ene (72).



72

To a solution of alcohol **71** (3.5 g, 24.61 mmol) and Ph_3P (7.74 g, 29.51 mmol) in 50 mL of dry CH_2Cl_2 was added NCS (3.61 g, 27.04 mmol) at 0 ^oC under nitrogen. The reaction mixture was stirred at 0 ^oC for 1 h, then allowed to warm to room temperature, and stirred for 2 h. The mixture was diluted with 100 mL of hexane and passed through a pad of celite under

suction to remove the precipitate of Ph_3PO. The filtrate was concentrated, and resulting residue was dissolved in 100 mL of hexane and passed through a pad of celite to remove the precipitate of Ph_3PO again. Evaporation of solvent gave **72** as colorless oil.

Yield: 3.2 g, 89%

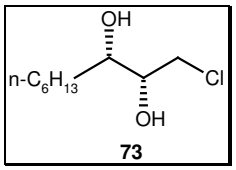
Mol. Formula: $C_9H_{17}Cl$

^{1}H NMR (200 MHz, $CDCl_3$): δ 5.73-5.83 (m, 1H), 5.56-5.66 (m, 1H), 4.05 (d, *J* = 6.1 Hz, 2H), 2.05 (q, *J* = 15.0 Hz, 2H), 1.28-1.43 (m, 8H), 0.89 (t, *J* = 6.2 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): δ 134.6, 125.9, 48.0, 32.6, 32.5, 30.3, 30.1, 23.1, 14.0.

Analysis: Calcd.: C, 67.27; H, 10.66%; **Found:** C, 67.15; H, 10.74%.

1-Chloro-nonane-2,3-diol (73).



73

To a mixture of $K_3Fe(CN)_6$ (19.68 g, 59.77 mmol), K_2CO_3 (8.26 g, 59.76 mmol), $NaHCO_3$ (5.02 g, 59.75), and $(DHQ)_2PHAL$ (155 mg, 1 mol%), in *t*-BuOH-H_2O (1:1, 100 mL) cooled at 0 ^{o}C was added $K_2OsO_2(OH)_4$ (37 mg, 0.5 mol%) followed by methanesulfonamide (1.89 g, 19.87 mmol). After being stirred for 5 min at 0 ^{o}C, the olefin **72** (3.2 g, 19.92 mmol) was added in one portion. The reaction mixture was stirred at 0 ^{o}C for 10 h and then quenched with solid sodium sulfite (25 g). The stirring was continued for 45 min and the solution was extracted with EtOAc (3 x 50 mL). The combined extracts were dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (8:2) as eluent gave the diol **73** as a white solid.

Yield: 5.63 g, 96%

Mol. Formula: $C_9H_{19}ClO_2$

M.p 85-86 ^{o}C (lit. mp 82-84 ^{o}C)

$[\alpha]_D^{25}$: 9.3 (*c* 0.42, $CHCl_3$) (lit. $[\alpha]_D^{25}$ –9.0 (*c* 1.0, MeOH).

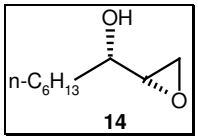
IR ($CHCl_3$, cm^{-1}): ν_{max} 3335, 2856, 2931, 1467, 1396, 1305, 1073, 1029, 937.

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.67 (d, *J* = 5.1 Hz, 2H), 3.59-3.66 (m, 2H), 2.75 (br s, 1H), 2.25 (br s, 1H), 1.47-1.55 (m, 3H), 1.29-1.37 (m, 7H), 0.89 (t, *J* = 6.1 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): δ 73.7, 71.52, 46.5, 33.4, 31.6, 29.1, 25.4, 22.5, 13.9.

Analysis: Calcd.: C, 55.52; H, 9.84%; **Found:** C, 55.64; H, 9.92%.

1-Oxiranyl-heptan-1-ol (14).



14

To a solution of diol **73** (2.5 g, 12.84 mmol) in THF (50 ml) was added pulverized NaOH (1.02 g, 25.5 mmol) at 0 ^{o}C and reaction mixture was stirred at room temperature for 2 h. The reaction mixture was quenched by addition of water (50 mL) and then extracted with diethyl ether (3 x 50 mL). The combined extracts were dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (8:2) as eluent gave the epoxide **14** as a colourless liquid.

Yield: 1.83 g, 90%

Mol. Formula: $C_9H_{18}O_2$

$[\alpha]_D^{25}$: -64.2 (*c* 1.0, $CHCl_3$).

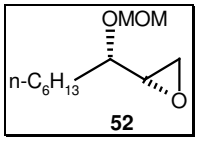
IR (neat, cm^{-1}): ν_{max} 3400, 2929, 2858, 1740, 1466, 1241, 1075.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.41 (m, 1H), 2.96-2.98 (m, 1H), 2.81 (t, *J* = 5.2 Hz, 1H), 2.70 (dd, *J* = 4.8, 2.8 Hz, 1H), 2.21 (br s, 1H), 1.55-1.63 (m, 2H), 1.43-1.49 (m, 1H), 1.26-1.37 (m, 7H), 0.89 (t, *J* = 6.0 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): δ 71.6, 55.4, 44.9, 34.0, 31.5, 29.0, 25.0, 22.3, 13.7.

Analysis: Calcd.: C, 68.31; H, 11.47%; **Found:** C, 68.28; H, 11.53%.

2-(1-Methoxymethoxyheptyl)-oxirane (52).



52

To a solution of hydroxy epoxide **14** (2.1 g, 13.27 mmol) and DIPEA (6.8 mL, 39.30 mmol) in dry CH_2Cl_2 (50 mL) was added under argon MOM chloride (1.27 g, 1.2 mL, 15.77 mmol) at 0 ^{o}C and the reaction mixture was stirred for 6 h at room temperature. The reaction was quenched by addition of water and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) as eluent gave **52** as a colorless oil.

Yield: 2.63 g, 98%

Mol. Formula: $C_{11}H_{22}O_3$

$[\alpha]_D^{25}$: +4.2 (*c* 1.1, $CHCl_3$)

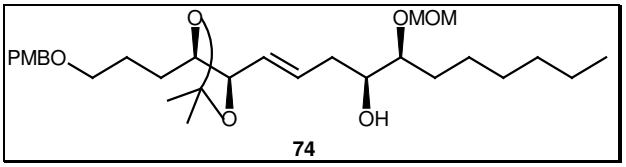
IR (neat, cm^{-1}): ν_{max} 2943, 2859, 1615, 1518, 1244, 1132, 1030

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.71 (s, 2H), 3.75-3.80 (q, *J* = 10.9 Hz, 1H), 3.64-3.71 (m, 2H), 3.57 (dd, *J* = 10.9, 5.8 Hz, 1H), 3.42 (s, 3H), 1.53-1.63 (m, 2H), 1.29-1.36 (m, 8H), 0.89 (t, *J* = 7.3 Hz, 3H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9, 22.4, 25.2, 29.2, 30.7, 31.6, 45.9, 55.8, 72.7, 79.2, 96.8.

Analysis: Calcd.: C, 65.31; H, 10.96%, **Found:** C, 65.64; H, 11.01%.

1-{5-[3-(4-Methoxybenzyloxy)-propyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-5-methoxymethoxy-undec-1-en-4-ol (74).



74

(a) Reaction with stannane 67. To a solution of **67** (641 mg, 1.08 mmol) in THF (10 mL) was added *n*-BuLi (0.93 mL, 1.48 mmol, 1.6 M solution in hexane) at -78 ^oC. After that reaction mixture was stirred at -78 ^oC for 1h and at -50 ^oC for 1.5 h. The reaction mixture was sequentially treated with cuprous cyanide (66 mg, 0.74 mmol), and epoxide **52** (100mg, 0.49 mmol) at -78 ^oC. Stirring was continued at -50 ^oC for 24 h, and -15 ^oC for an additional 24 h. The reaction mixture was quenched with aqueous NH_4Cl and aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (8.5:1.5) as eluent gave **74** as a yellow syrupy liquid.

Yield: 128 mg, 51%

Mol. Formula: $C_{29}H_{48}O_7$

$[\alpha]_D^{25}$: +14.1 (*c* 0.9, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 3426, 2938, 2867, 1610, 1514, 1467, 1242, 1092.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.47-5.52 (m, 1H), 5.39 (dd, *J* = 15.6, 6.4 Hz, 1H), 4.69 (s, 2H), 4.45 (s, 2H), 4.21 (d, *J* = 7.4 Hz, 1H), 3.98 (dt, *J* = 7.4, 4.4 Hz, 1H), 3.81 (s, 3H), 3.70-3.79 (m, 1H), 3.54 (m, 1H), 3.46-3.50 (m,

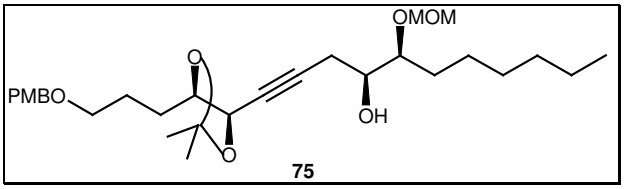
2H), 3.24 (s, 3H), 2.84 (br s, 1H), 2.24-2.36 (m, 2H), 1.67-1.79 (m, 6H), 1.44 (s, 3H), 1.39 (s, 3H), 1.23-1.39 (m, 8H), 0.89 (t, J = 6.4 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 160.1, 131.7, 131.5, 131.1, 128.1, 113.7, 109.3, 81.4, 80.7, 72.9, 72.4, 71.0, 69.6, 55.6, 55.1, 35.3, 30.7, 29.9, 28.9, 27.1, 26.3, 25.3, 24.1, 22.6, 14.1.

Analysis: Calcd.: C, 68.47; H, 9.51%; **Found:** C, 68.74; H, 9.12%.

(b) Reaction with vinyl iodide 68. To a solution of vinyl iodide **68** (500 mg, 1.15 mmol) in THF (15 mL) was added n-BuLi (0.72 mL, 1.15 mmol, 1.6M solution in hexane) at -78 ^{o}C. The yellow mixture was warmed to 0 ^{o}C for 40 minutes before recooling to -78 ^{o}C. Then, the reaction mixture was treated with CuCN (119 mg, 1.15 mmol), followed by addition of epoxide **52** (78 mg, 0.39 mmol) at -78 ^{o}C. Stirring was continued at -50 ^{o}C for 24 h and -15 ^{o}C for additional 24 h. The reaction mixture was quenched with aqueous NH_4Cl and aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (8.5:1.5) as eluent gave **74** (153 mg, 78%) as a yellow syrupy liquid.

1-{5-[3-(4-Methoxybenzyloxy)-propyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-5-methoxymethoxy-undec-1-yn-4-ol (75).



75

To a solution of acetylene **66** (0.8 g, 2.63 mmol) in THF (20 mL) was added *n*-BuLi (1.6 M solution in hexane) (1.8 mL, 2.88 mmol) at -78 ^{o}C and the reaction mixture was stirred for 10 min. Then, $BF_3.Et_2O$ (2.89 mmol, 0.36 mL) was added to the reaction mixture and stirring was continued for 10 min at –78 ^{o}C. Finally solution of epoxide **52** (354 mg, 1.75 mmol) in THF (2 mL) was added, and after stirring for 30 min at -78 ^{o}C, the reaction was quenched by adding aqueous ammonium chloride. After two layers were separated, the aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (8:2) as eluent gave compound **75** as a yellowish liquid.

Yield: 789 mg, 89%

Mol. Formula: $C_{29}H_{46}O_7$

$[\alpha]_D^{25}$: +10.3 (*c* 1.24, $CHCl_3$)

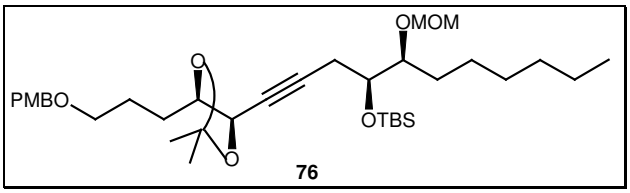
IR ($CHCl_3$, cm^{-1}): ν_{max} 3414, 3019, 2933, 2860, 2400, 1612, 1513, 1465, 1372, 1216, 1097, 757

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.2 Hz, 2H), 4.65 (s, 2H), 4.44 (s, 2H), 4.23 (d, *J* = 7.8 Hz, 1H), 3.96 (dt, *J* = 7.8, 4.6 Hz, 1H), 3.78 (s, 3H), 3.77 (dt, *J* = 5.5, 1.9 Hz, 1H), 3.64 (dt, *J* = 6.0, 1.9 Hz, 1H), 3.47-3.50 (m, 2H), 3.41 (s, 3H), 2.72 (br s, 1H), 2.44-2.49 (m, 1H), 2.39 (ddd, *J* = 15.1, 7.8, 1.4 Hz, 1H), 1.63-1.80 (m, 6H), 1.44 (s, 3H), 1.39 (s, 3H), 1.26-1.31 (m, 8H), 0.89 (t, *J* = 6.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.1, 131.5, 130.6, 129.11, 113.72, 113.54, 109.3, 96.8, 83.6, 81.4, 80.7, 78.8, 72.4, 71.6, 70.1, 69.6, 55.7, 55.1, 31.6, 30.7, 29.29, 28.97, 27.0, 26.2, 25.90, 25.24, 24.0, 22.5, 13.9.

Analysis: Calcd.: C, 68.74; H, 9.15%; **Found:** C, 68.81; H, 9.24%.

***tert*-Butyl-[4-{5-[3-(4-methoxybenzyloxy)-propyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-1-(1-methoxymethoxyheptyl)-but-3-ynyloxy]-dimethylsilane (76).**



76

To a stirred solution of compound **75** (0.76 g, 1.50 mmol) and 2,6-lutidine (1.7 mL, 14.69) in dry CH_2Cl_2 (30 mL) was treated under argon with TBSOTf (0.51 mL, 2.22 mmol) at 0 ^oC and the reaction mixture was stirred for 30 min. at the same temperature. The reaction mixture was quenched by addition of water (30 mL) and the mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined extracts were dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9.5:0.5) as eluent gave the compound **76** as a colorless syrupy liquid.

Yield: 0.91 g, 98%

Mol. Formula: $C_{35}H_{60}O_7Si$

$[\alpha]_D^{25}$: +14.7 (*c* 0.48, $CHCl_3$)

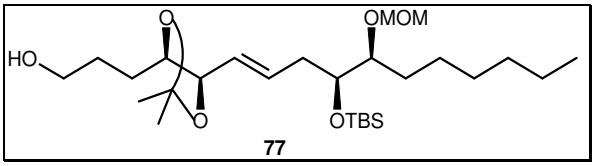
IR ($CHCl_3$, cm^{-1}): ν_{max} 3020, 2936, 2861, 2412, 1613, 1512, 1374, 1096, 758

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (d, *J* = 7.9 Hz, 2H), 6.88 (d, *J* = 7.9 Hz, 2H), 4.70 (d, *J* = 6.8 Hz, 1H), 4.63 (d, *J* = 6.8 Hz, 1H), 4.44 (s, 2H), 4.22 (d, *J* = 7.6 Hz, 1H), 3.95-4.01 (m, 1H), 3.88-3.93 (m, 1H), 3.81 (s, 3H), 3.49 (m, 2H), 3.38 (s, 3H), 2.55 (d, *J* = 16.3 Hz, 1H), 2.31 (dd, *J* = 16.3, 8.1 Hz, 1H), 1.58-1.78 (m, 6H), 1.44 (s, 3H), 1.39 (s, 3H), 1.27-1.36 (m, 8H), 0.90 (m, 12 H), 0.13 (s, 3H), 0.09 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.1, 131.5, 130.6, 129.1, 113.7, 113.5, 109.4, 96.8, 83.6, 81.4, 80.8, 78.9, 74.7, 72.5, 69.6, 55.8, 55.1, 31.7, 30.8, 29.3, 28.9, 27.0, 26.2, 25.8, 25.2, 24.0, 22.5, 18.0, 13.9, -4.5, -5.2.

Analysis: Calcd.: C, 67.70; H, 9.74%; **Found:** C, 67.91; H, 10.57%.

3-{5-[4-(tert-Butyldimethylsilanyloxy)-5-methoxymethoxy-undec-1-enyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-propan-1-ol (77).



77

To a blue solution of lithium metal (100 mg, 14.41 mmol) in 50 mL of NH_3 was added dropwise a solution of **76** (445 mg, 0.72 mmol) in THF (10 ml) at –78 ^oC. During the addition of compound, the blue color of the reaction mixture was maintained by adjusting the speed of the addition. After all of the compound had been added, the reaction mixture was stirred for 6 h at –40 ^oC. The reaction mixture was quenched by adding NH_4Cl, and the mixture was warmed to room temperature overnight, during which time the ammonia was evaporated. The mixture was then diluted with water and extracted with diethyl ether, and organic layer was dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (7:3) as eluent gave compound **77** as a brown syrupy liquid.

Yield: 327 mg, 89%

Mol. Formula: $C_{27}H_{54}O_6Si$

$[\alpha]_D^{25}$: +7.7 (*c* 0.7, $CHCl_3$)

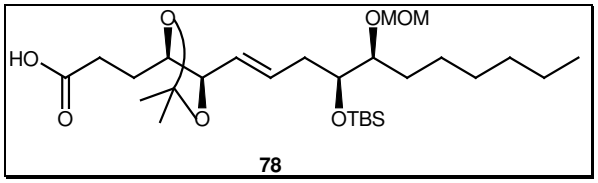
IR ($CHCl_3$, cm^{-1}): ν_{max} 3426, 1510, 1467, 1224

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.45-5.60 (m, 1H), 5.31 (dd, *J* = 15.7, 6.7 Hz, 1H), 4.72 (dd, *J* = 7.0, 2.35 Hz, 1H), 4.62 (d, *J* = 7.0 Hz, 1H), 4.22 (dt, *J* = 8.2, 1.9 Hz, 1H), 3.83-4.01 (m, 2H), 3.67 (t, *J* = 5.8 Hz, 2H), 3.46-3.54 (m, 1H), 3.39 (s, 3H), 2.23-2.36 (m, 2H), 1.68-1.84 (m, 6H), 1.45 (s, 3H), 1.40 (s, 3H), 1.29 (m, 8H), 0.91 (s, 9H), 0.89 (t, *J* = 6.8 Hz, 3H), 0.12 (s, 3H), 0.09 (s, 3H)

^{13}C NMR (75 MHz, $CDCl_3$): δ 131.7, 128.2, 109.5, 81.6, 80.9, 72.4, 71.0, 69.6, 63.4, 55.6, 55.2, 35.4, 30.8, 30.0, 28.8, 27.2, 26.4, 25.3, 24.1, 22.6, 18.1, 13.9, -4.5, -5.2.

Analysis: Calcd.: C, 64.50; H, 10.83%; **Found:** C, 64.11; H, 10.24%.

3-{5-[4-(*tert*-Butyldimethylsilanyloxy)-5-methoxymethoxy-undec-1-enyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-propionic acid (78).



78

A solution of oxalyl chloride (0.121 g, 0.083 mL, 0.95 mmol) in dry CH_2Cl_2 (20 mL) at -78 ^oC was added dropwise dry DMSO (0.149 g, 0.135 mL, 1.90 mmol) in CH_2Cl_2 (5 mL). After 30 min, alcohol **77** (320 mg, 0.64 mmol) in CH_2Cl_2 (5 mL) was added over 10 min giving a copious white precipitate. After stirring for 1 h at -78 ^oC the reaction mixture was brought to -60 ^oC and Et_3N (0.254 g, 0.35 mL, 2.51 mmol) was added slowly and stirred for 30 min allowing the reaction mixture to warm to room temperature. The reaction mixture was poured into water (50 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL) and combined organic layers were washed with water (3 x 20 mL), brine (20 mL), dried (Na_2SO_4) and passed through short pad of silica gel. The filtrate was concentrated to give the aldehyde (302 mg) as pale yellow syrup, which was used as such for the next step without further purification.

A solution of 79% $NaClO_2$ (81 mg, 0.90 mmol) in 1.0 mL of water was added dropwise to a stirred solution of above crude aldehyde (302 mg, 0.60 mmol) in 0.5 mL of DMSO and NaH_2PO_4 (54 mg, 0.45 mmol) in 1.0 mL of water in 5 min at room temperature. The mixture was left overnight at room temperature, then 5% aqueous solution of $NaHCO_3$ was added. The aqueous phase was extracted three times with CH_2Cl_2 and washed with brine, dried

(Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (6:4) as eluent gave the acid **78** as a yellow syrupy liquid.

Yield: 268 mg, 86%.

Mol. Formula: $C_{27}H_{52}O_7Si$.

$[\alpha]_D^{25}$: +8.9 (*c* 0.7, $CHCl_3$).

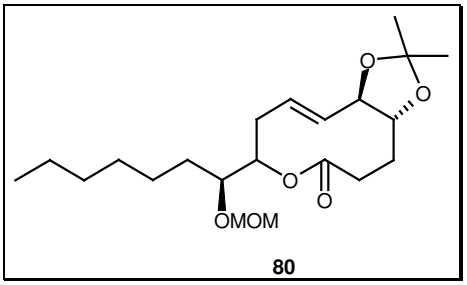
IR ($CHCl_3$, cm^{-1}): ν_{max} 3251, 1685, 1512, 1461, 1220

^{1}H NMR (200 MHz, $CDCl_3$): δ δ 5.42-5.51 (m, 1H), 5.31 (dd, *J* = 15.8, 7.5 Hz, 1H), 4.82 (d, *J* = 6.2 Hz, 1H), 4.73 (d, *J* = 6.2 Hz, 1H), 4.29 (dt, *J* = 8.4, 2.1 Hz, 1H), 3.81-4.04 (m, 2H), 3.41-3.52 (m, 1H), 3.40 (s, 3H), 2.28 (t, *J* = 7.5 Hz, 2H), 2.12-2.43 (m, 2H), 1.72-1.88 (m, 4H), 1.44 (s, 6H), 1.21-1.38 (m, 8H), 0.92 (s, 9H), 0.89 (t, *J* = 6.6 Hz, 3H), 0.09 (s, 3H), 0.06 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 176.1, 131.8, 124.3, 109.3, 97.8, 81.4, 80.6, 72.5, 71.0, 70.7, 69.4, 55.7, 55.2, 30.7, 30.3, 29.2, 29.0, 27.1, 26.2, 25.8, 25.2, 24.5, 22.5, 18.1, 14.0, -4.2, -4.7.

Analysis: Calcd.: C, 62.75; H, 10.14%; **Found:** C, 62.32; H, 10.24%.

8-(1-Methoxymethoxyheptyl)-2,2-dimethyl-3a,4,5,8,9,11a-hexahydro-1,3,7-trioxa-cyclopentacyclodecen-6-one (80).



80

Compound **78** (200 mg, 0.39 mmol) was dissolved in THF (5 mL), followed by the dropwise addition of TBAF (0.58 mL, 1M solution in THF, 0.58 mmol). The reaction mixture was stirred at room temperature for overnight and quenched by addition of water, and aqueous layer was extracted with EtOAc (3 x 30 mL) and combined EtOAc extracts were washed with brine, dried (Na_2SO_4), and concentrated to give the crude product **79**, which was used in the next step without further purification.

To a solution of above crude product **79** (155 mg, 0.39 mmol) in THF (4 mL) were added Et_3N (0.13 mL, 0.93 mmol), and 2,4,6-trichlorobenzoyl chloride (0.234 g, 0.96 mmol) and the

reaction mixture was stirred for 2 h at room temperature under argon atmosphere and then diluted with benzene (150 mL). The resulting reaction mixture was added drop wise to a solution of DMAP (352 mg, 2.88 mmol) in benzene (20 mL) at 80 ^{o}C over 1 h and the mixture was stirred for additional 1 h under reflux. The reaction mixture was washed with saturated aqueous citric acid solution and brine. The organic layer was dried over Na_2SO_4 and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (8:2) as eluent gave compound **80** as a yellow syrupy liquid.

Yield: 128 mg, 86% from **78.**

Mol. Formula: $C_{21}H_{36}O_6$

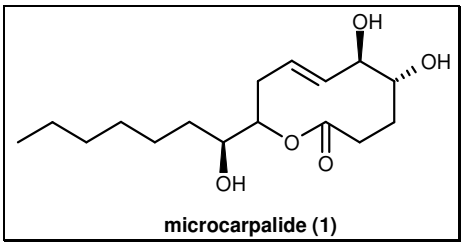
$[\alpha]_D^{25}$: -18.6 (*c* 0.8, $CHCl_3$); [lit.[13a] –18.1 (*c* 0.6, $CHCl_3$)].

IR ($CHCl_3$, cm^{-1}): ν_{max} 2955, 2932, 2888, 1732, 1452, 1372, 1238, 1167, 1038, 918, 876, 804.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.78 (ddd, *J* = 15.8, 11.6, 4.8 Hz, 1H), 5.35 (dd, *J* = 15.9, 9.5 Hz, 1H), 4.95 (ddd, *J* = 8.8, 3.9, 2.6 Hz, 1H), 4.68 (m, 2H), 3.95 (t, *J* = 8.8 Hz, 1H), 3.64 (m, 2H), 3.44 (s, 3H), 2.26-2.62 (m, 4H), 1.98-2.08 (m, 2H), 1.61 (m, 2H), 1.44 (s, 6H), 1.22-1.36 (m, 8H), 0.89 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.8, 130.2, 129.6, 108.9, 96.6, 84.6, 79.9, 79.4, 73.6, 56.1, 34.4, 31.8, 30.8, 30.4, 29.5, 27.2, 26.8, 25.6, 25.3, 22.6, 14.1.

Microcarpalide (1).



microcarpalide (1)

To an ice cooled stirred solution of compound **26** (40 mg, 0.104 mmol) in CH_2Cl_2 (5 mL) was added $BF_3.Et_2O$ (13 μL, 0.104 mmol), and ethanedithiol (38 μL, 0.45 mmol). The resulting mixture was stirred at 0 ^{o}C for 1 h, then quenched with aqueous $NaHCO_3$, and aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using EtOAc as eluent gave microcarpalide **1** as a yellow syrupy liquid and a 3.2:1 (as judged by ^{1}H NMR spectra) mixture of conformers.

Yield: 28 mg, 88%.

Mol. Formula: $C_{16}H_{28}O_5$

$[\alpha]_D^{25}$: –23.4 (*c* 0.9, MeOH); [lit.[12c, 13a] –22.0 (*c* 0.67, MeOH)].

IR (neat, cm^{-1}): ν_{max} 3370, 2922, 2863, 1711, 1430, 1226, 1153, 1067

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.69 (dd, *J* = 15.5, 2.5 Hz, 1H), 5.50 (dddd, *J* = 15.6, 9.9, 5.1, 2.1 Hz, 1H), 4.81 (ddd, *J* = 11.1, 4.8, 3.3 Hz, 1H), 4.11 (br, 1H), 3.78 (br, 1H), 3.54 (br m, 1H), 3.08 (br d, 1H), 2.85 (br m, 2H), 2.47-2.50 (m, 1H), 2.15-2.25 (m, 2H), 1.98-2.14 (m, 2H), 1.77-1.93 (m, 1H), 1.38-1.44 (m, 2H), 1.29-1.36 (m, 8H). 0.88 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (125 MHz, CD_3CN): (observed as a mixture of two conformers): δ 176.3, 174.1, 134.5, 126.6, 79.7, 73.5, 72.8, 72.3, 36.7, 34.2, 32.5, 29.9, 26.4, 26.1, 23.3, 14.4.

3.1.7. Spectra

1] ^{1}H NMR Spectrum of **60**

2] ^{13}C NMR Spectrum of **60**

3] ^{1}H NMR Spectrum of **61**

4] ^{13}C NMR Spectrum of **61**

5] ^{1}H NMR Spectrum of **65**

6] ^{13}C NMR Spectrum of **65**

7] ^{1}H NMR Spectrum of **66**

8] ^{13}C NMR Spectrum of **66**

9] ^{1}H NMR Spectrum of **61**

10] ^{13}C NMR Spectrum of **61**

11] ^{1}H NMR Spectrum of **73**

12] ^{13}C NMR Spectrum of **73**

13] ^{1}H NMR Spectrum of **14**

14] ^{13}C NMR Spectrum of **14**

15] ^{1}H NMR Spectrum of **52**

16] ^{13}C NMR Spectrum of **52**

17] ^{1}H NMR Spectrum of **75**

18] ^{13}C NMR Spectrum of **75**

19] ^{1}H NMR Spectrum of **76**

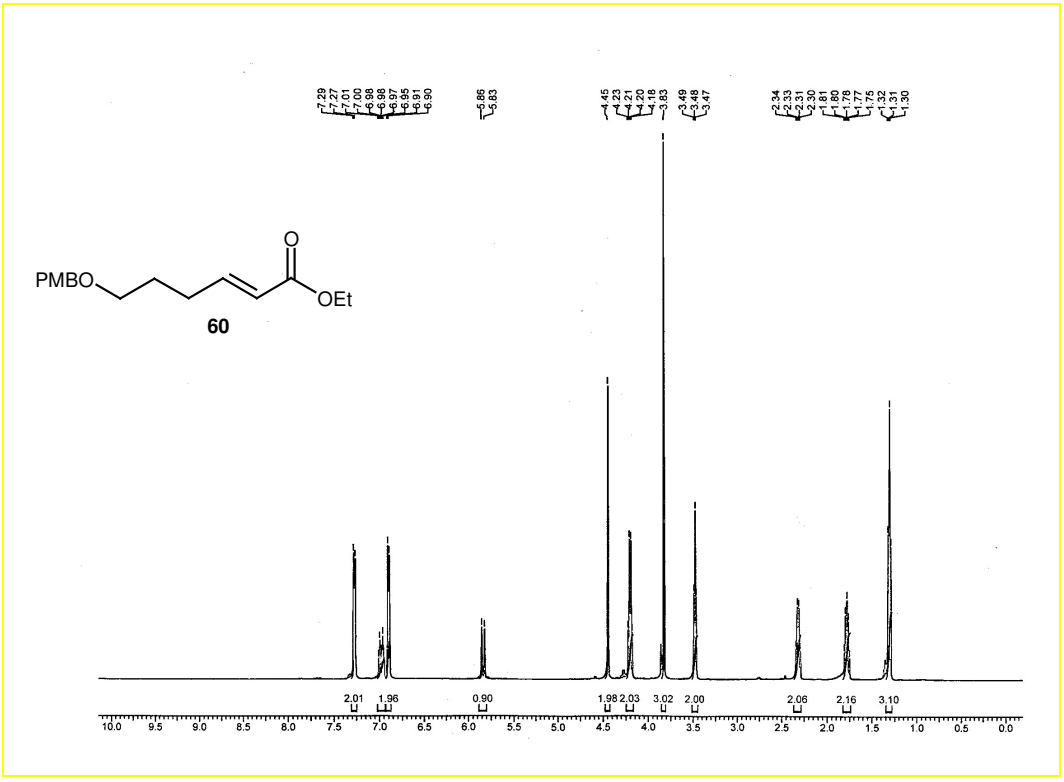
20] ^{13}C NMR Spectrum of **76**

21] ^{1}H NMR Spectrum of **80**

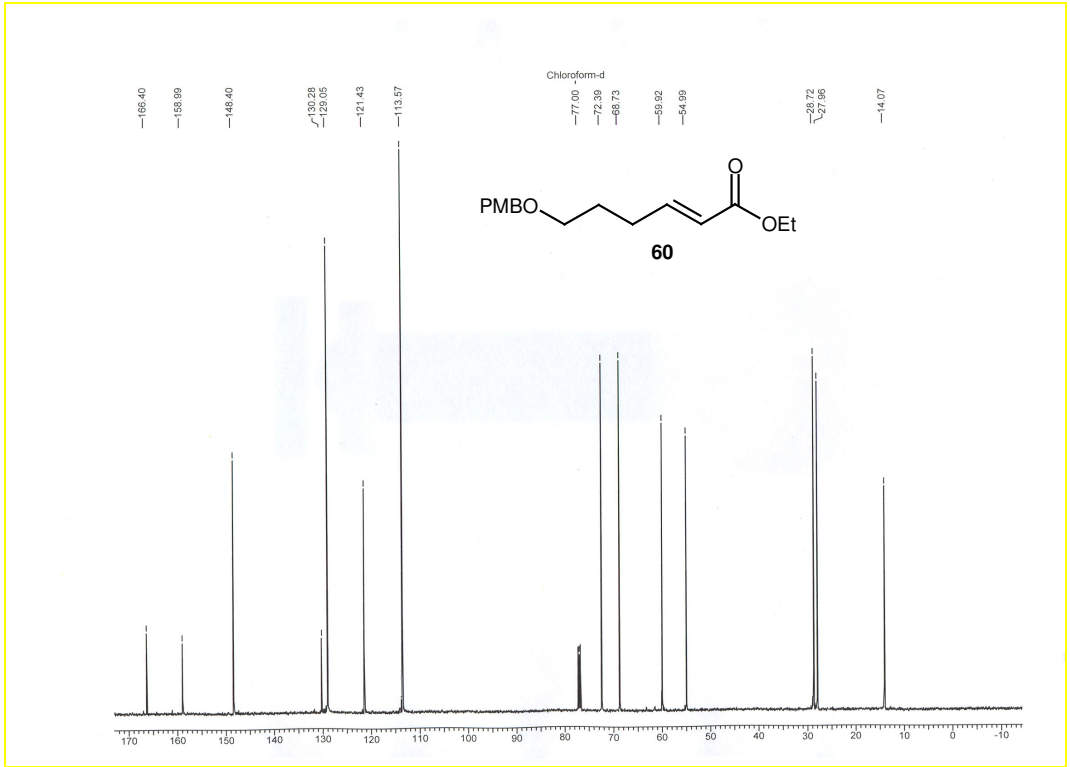
22] ^{13}C NMR Spectrum of **80**

23] ^{1}H NMR Spectrum of **1**

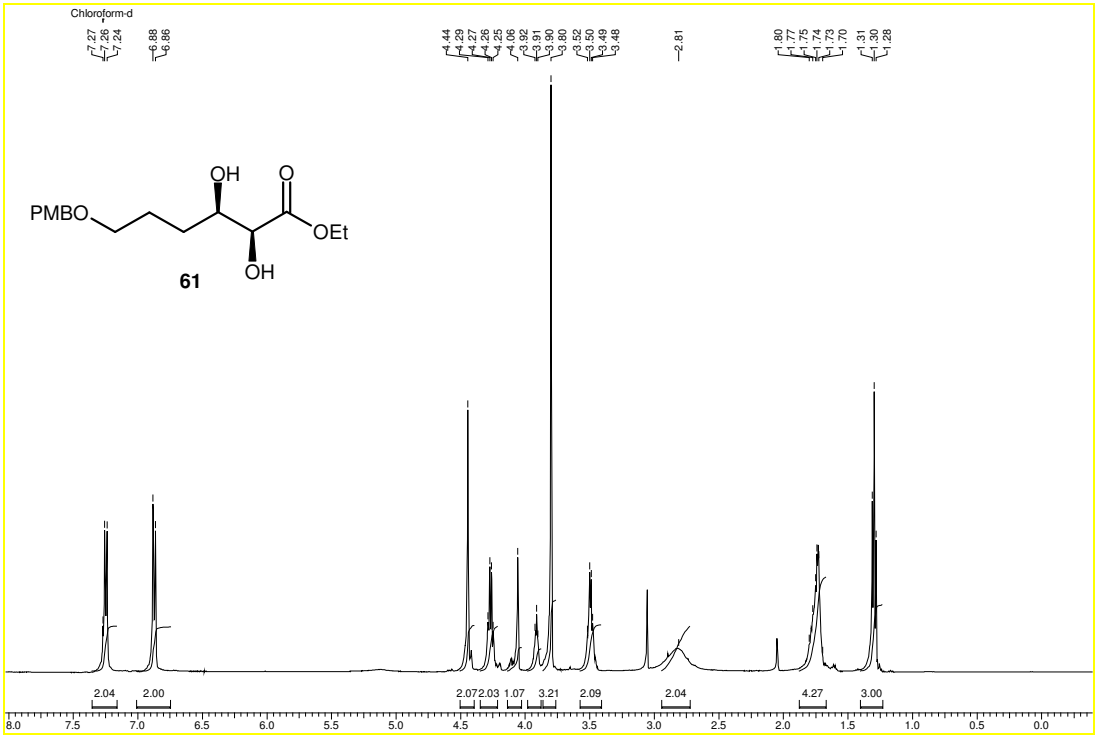
24] ^{13}C NMR Spectrum of **1**



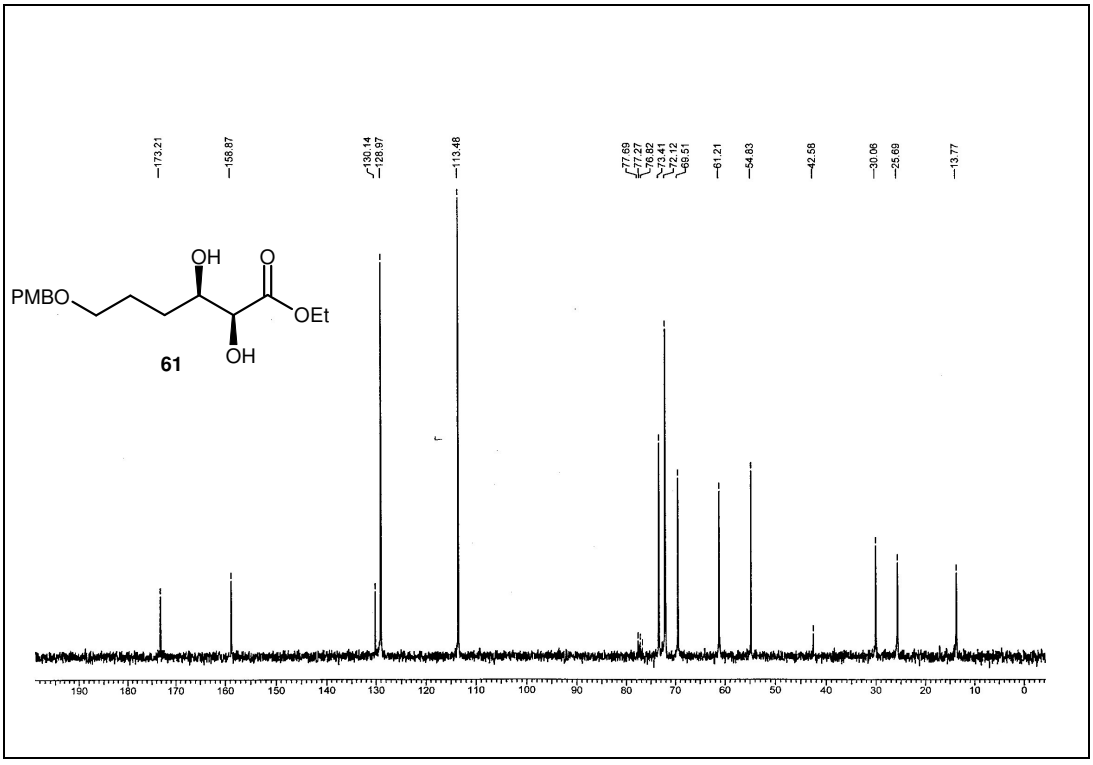
^{1}H NMR Spectrum of **60**



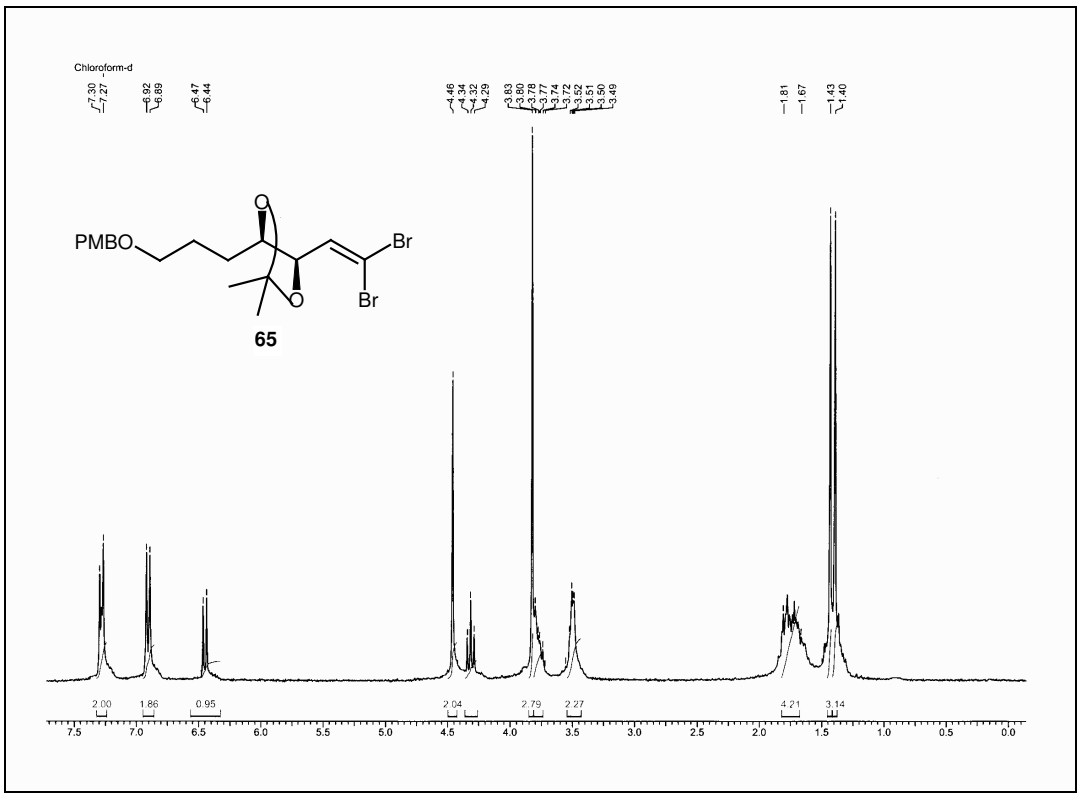
^{13}C NMR Spectrum of **60**



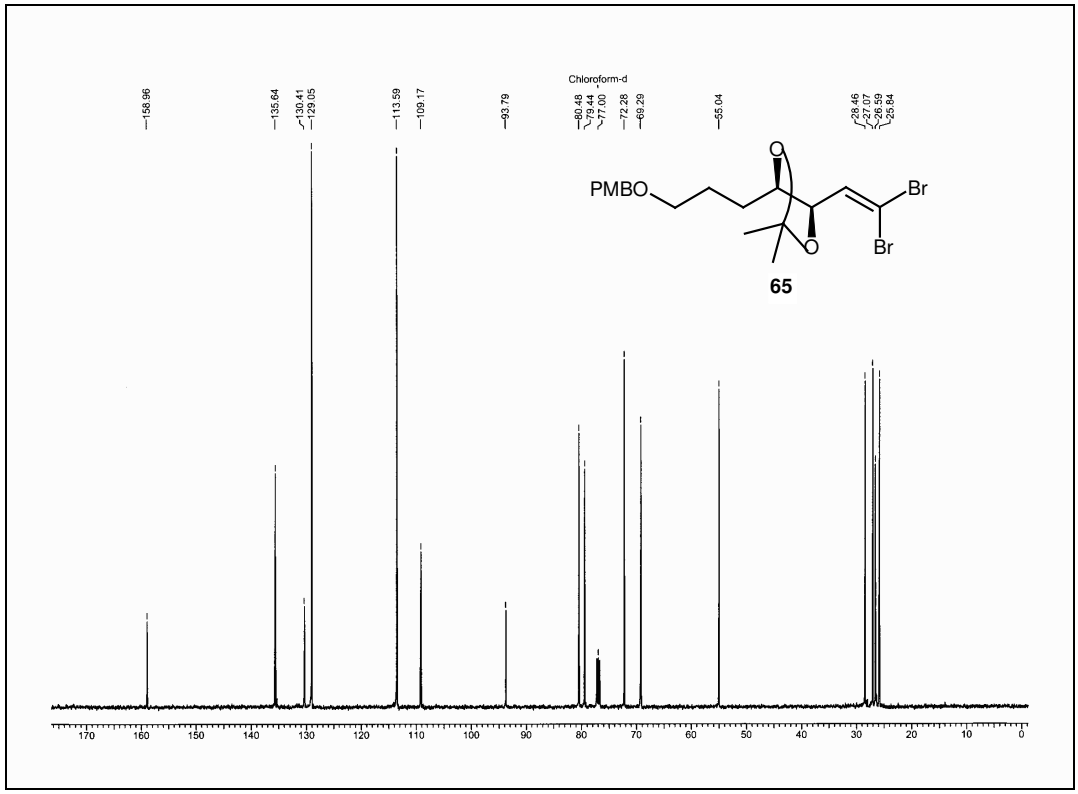
^{1}H NMR Spectrum of **61**



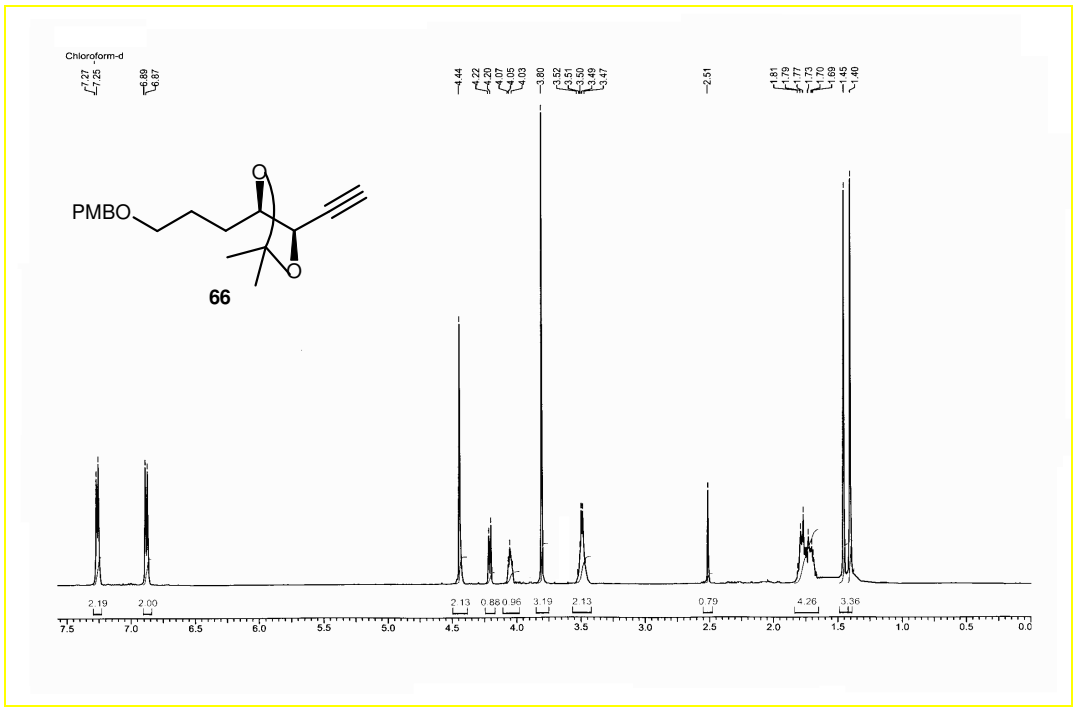
^{13}C NMR Spectrum of **61**



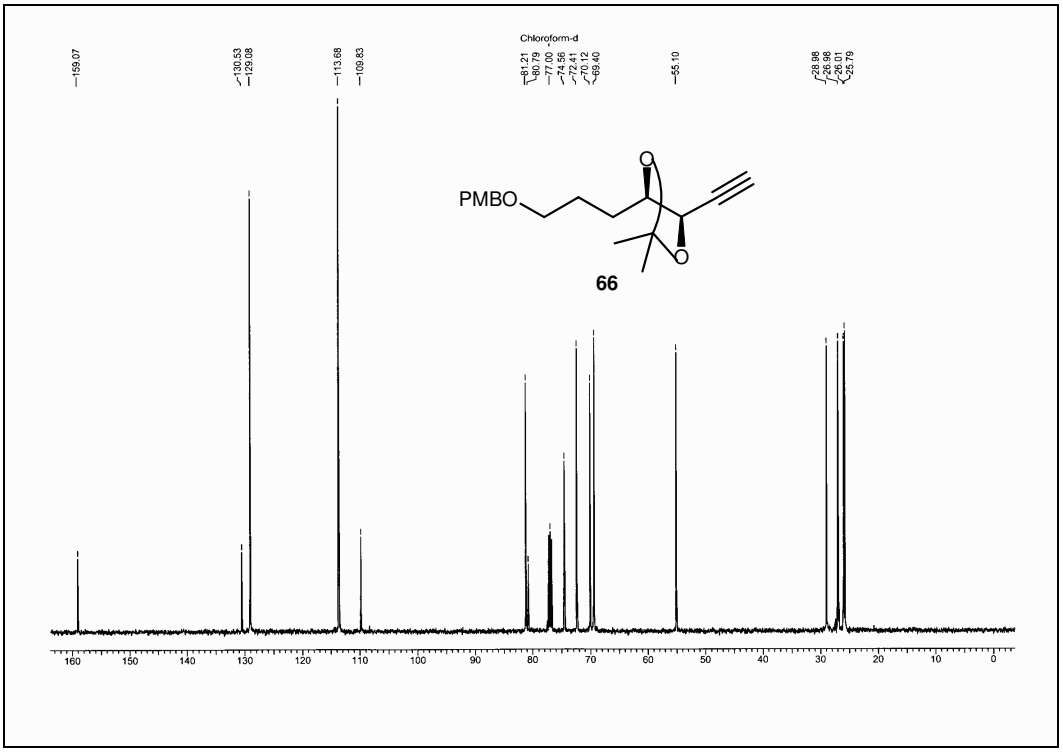
^{1}H NMR Spectrum of **65**



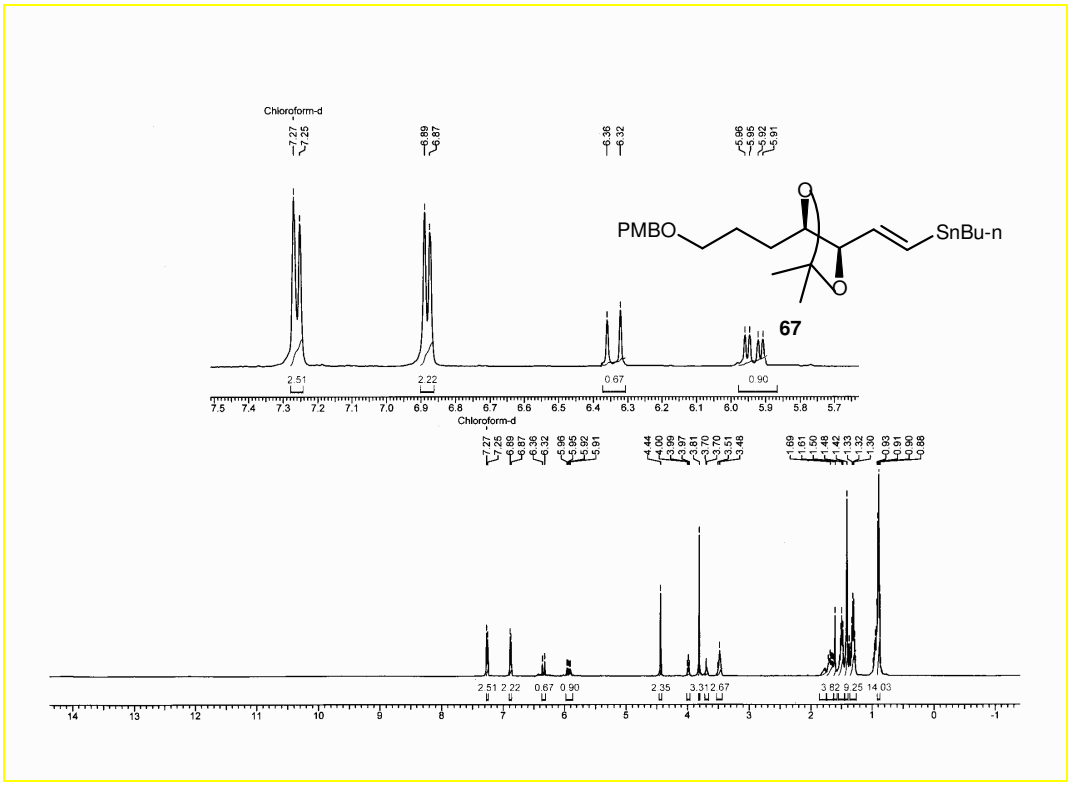
^{13}C NMR Spectrum of **65**



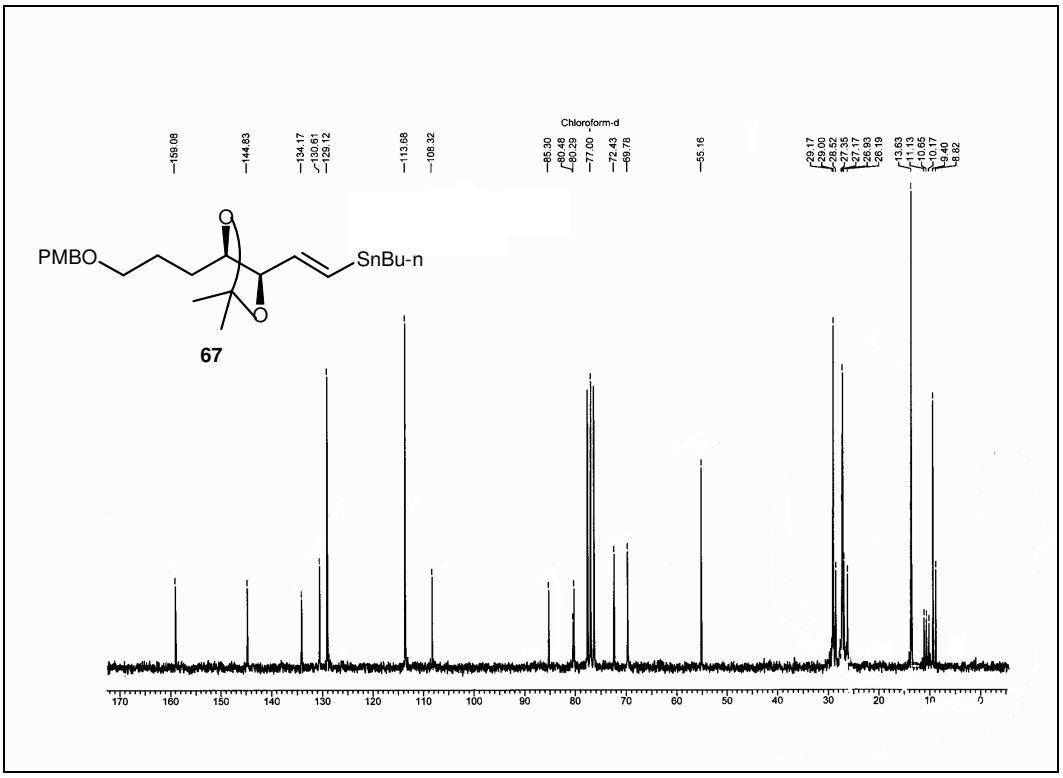
^{1}H NMR Spectrum of **66**



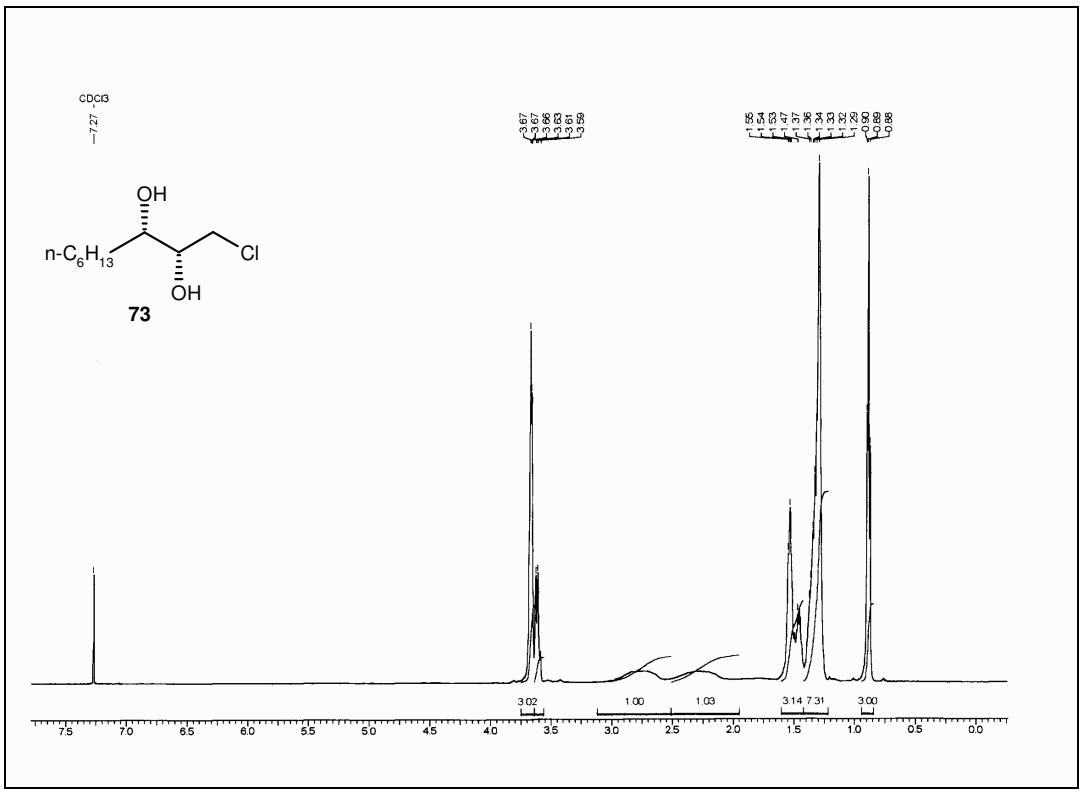
^{13}C NMR Spectrum of **66**



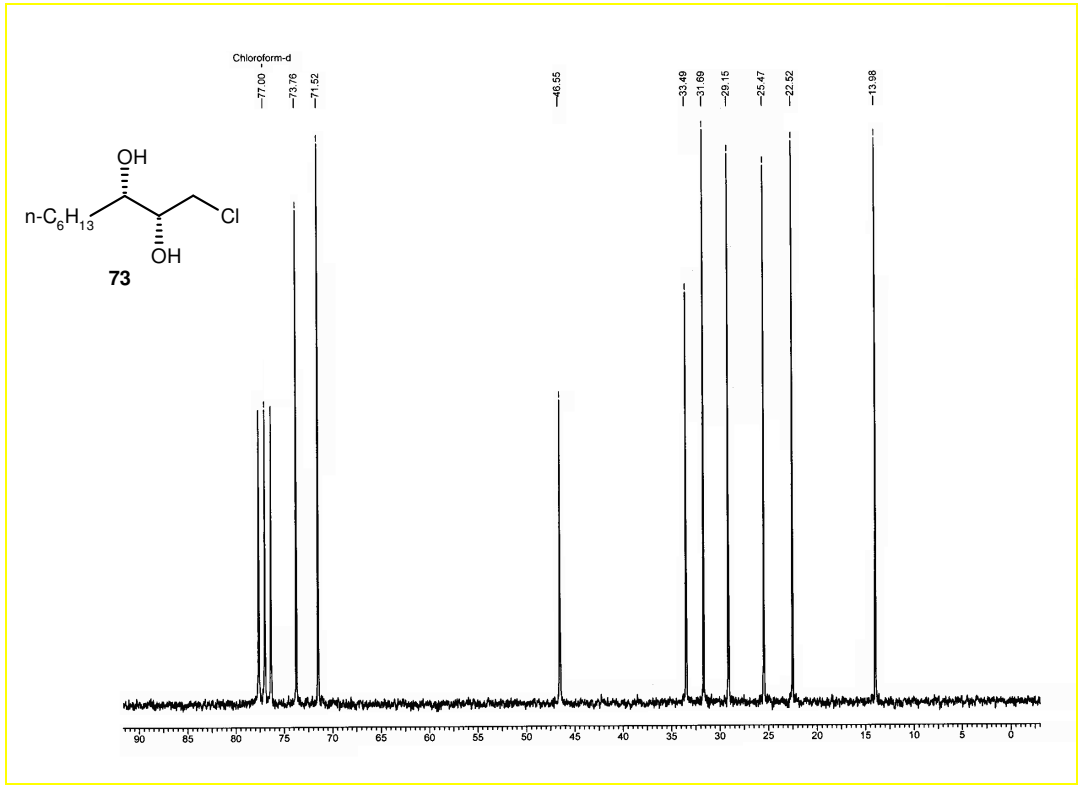
^{1}H NMR Spectrum of **67**



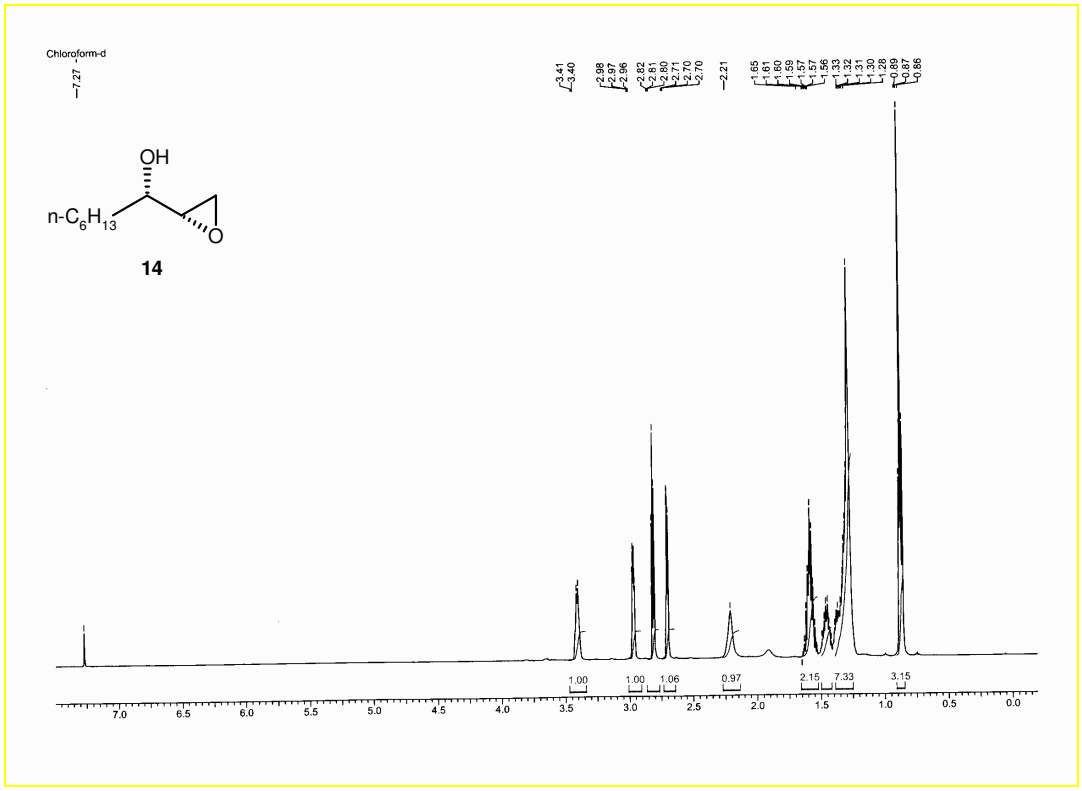
^{13}C NMR Spectrum of **67**



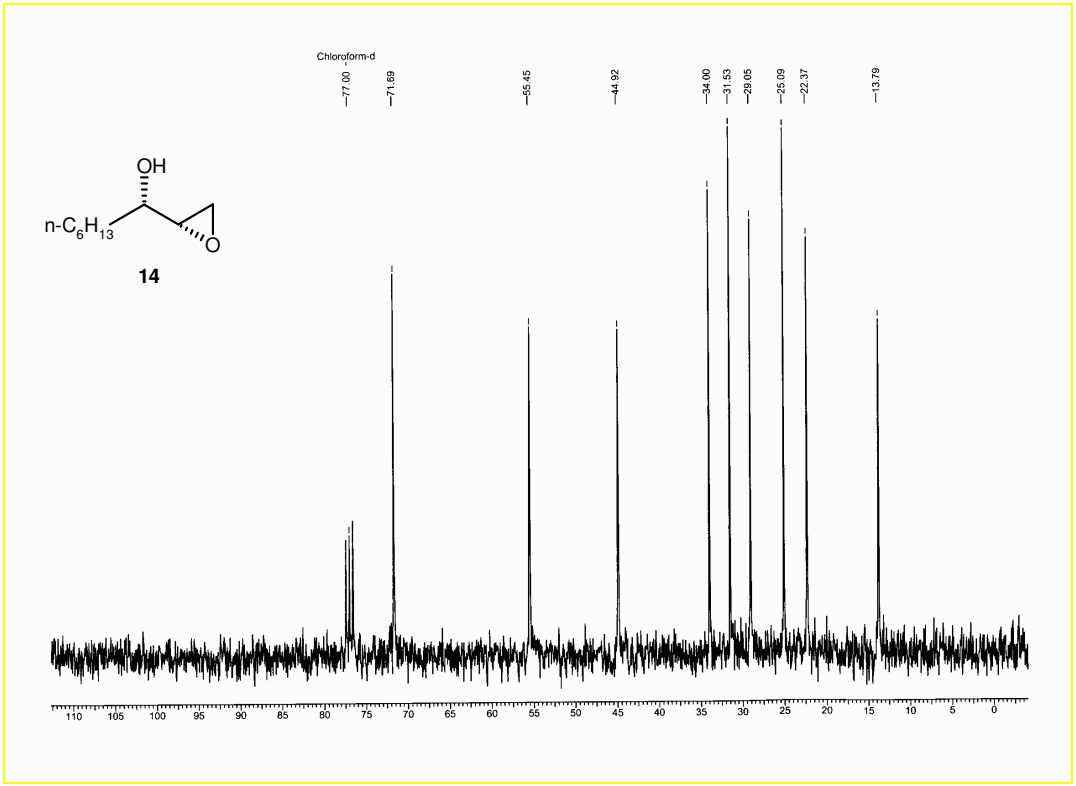
^{1}H NMR Spectrum of **73**



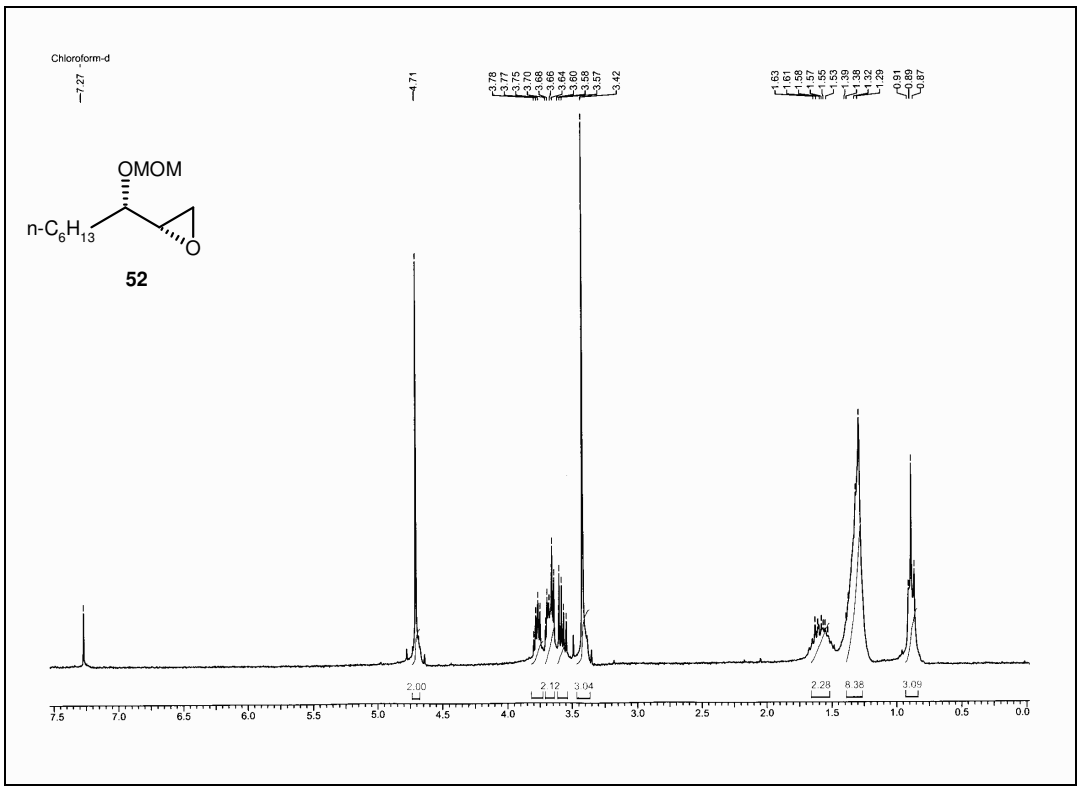
^{13}C NMR Spectrum of **73**



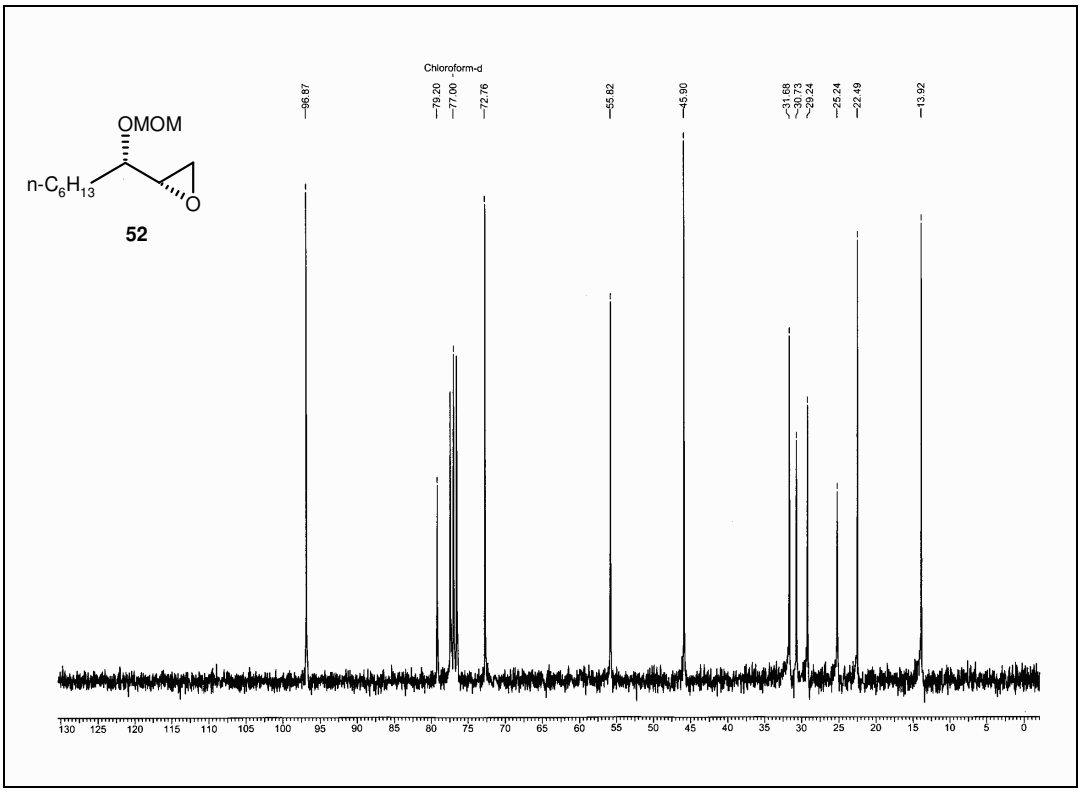
^{1}H NMR Spectrum of **14**



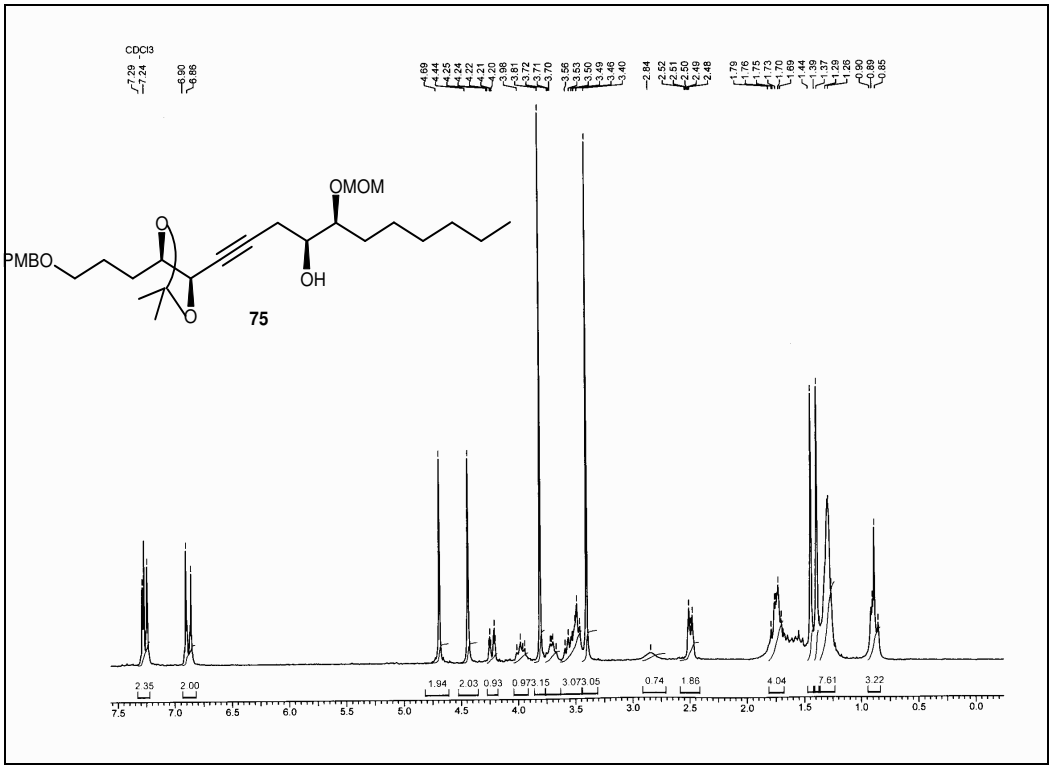
^{13}C NMR Spectrum of **14**



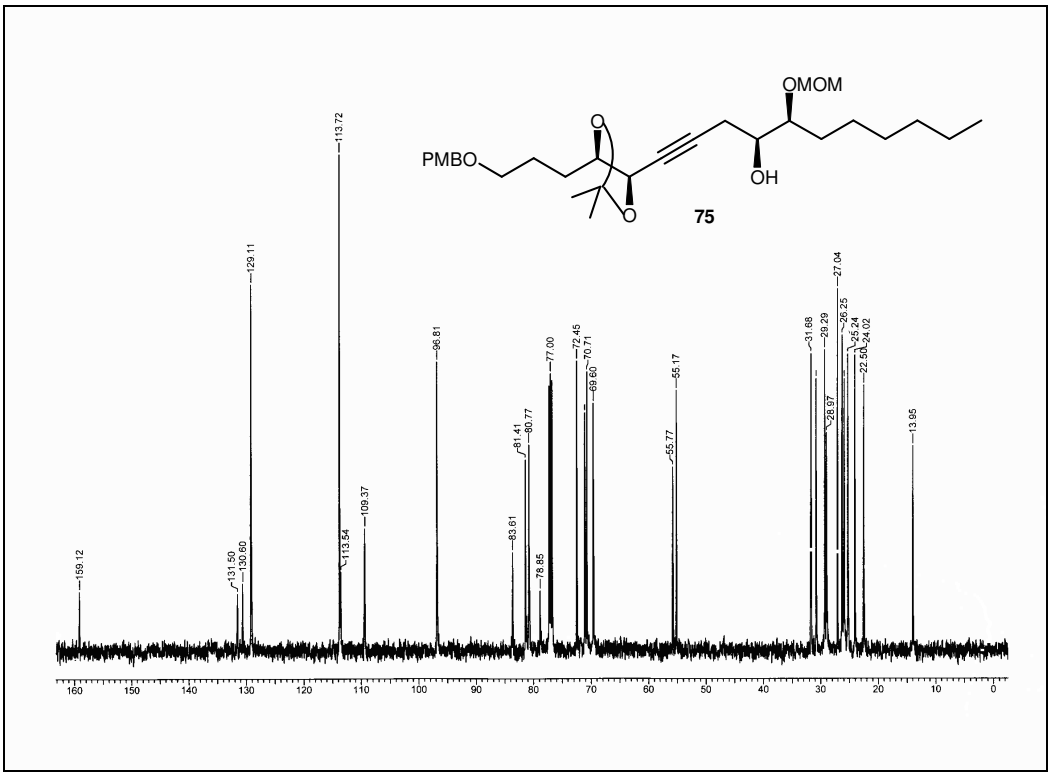
^{1}H NMR Spectrum of **52**



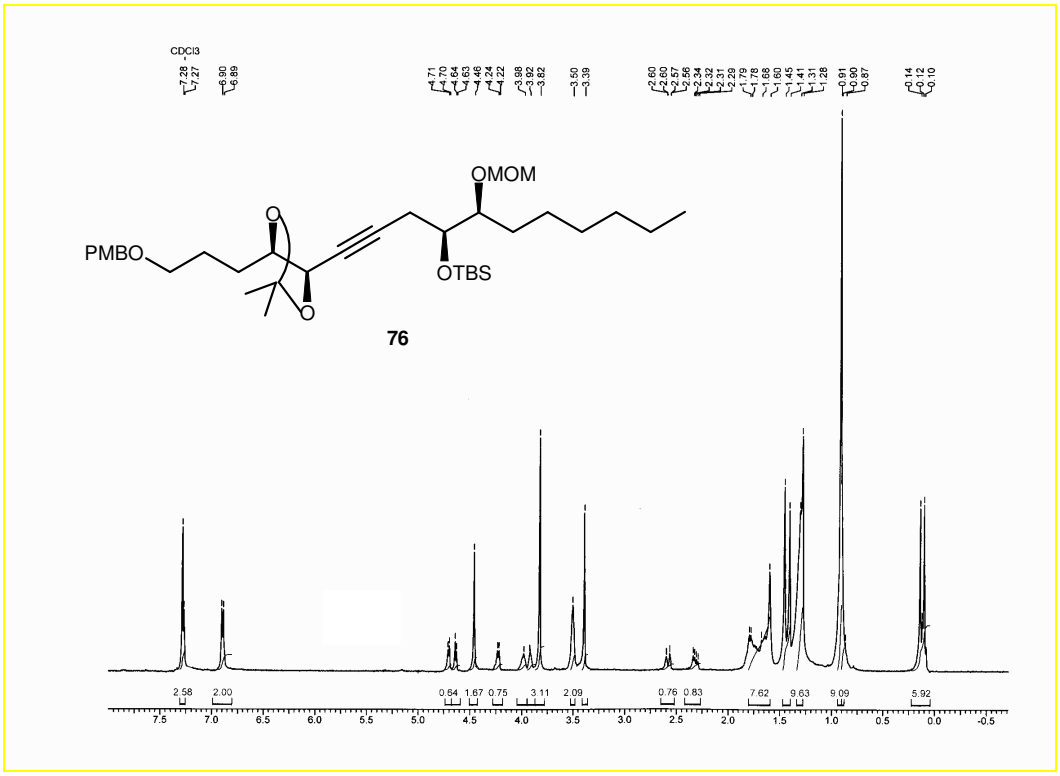
^{13}C NMR Spectrum of **52**



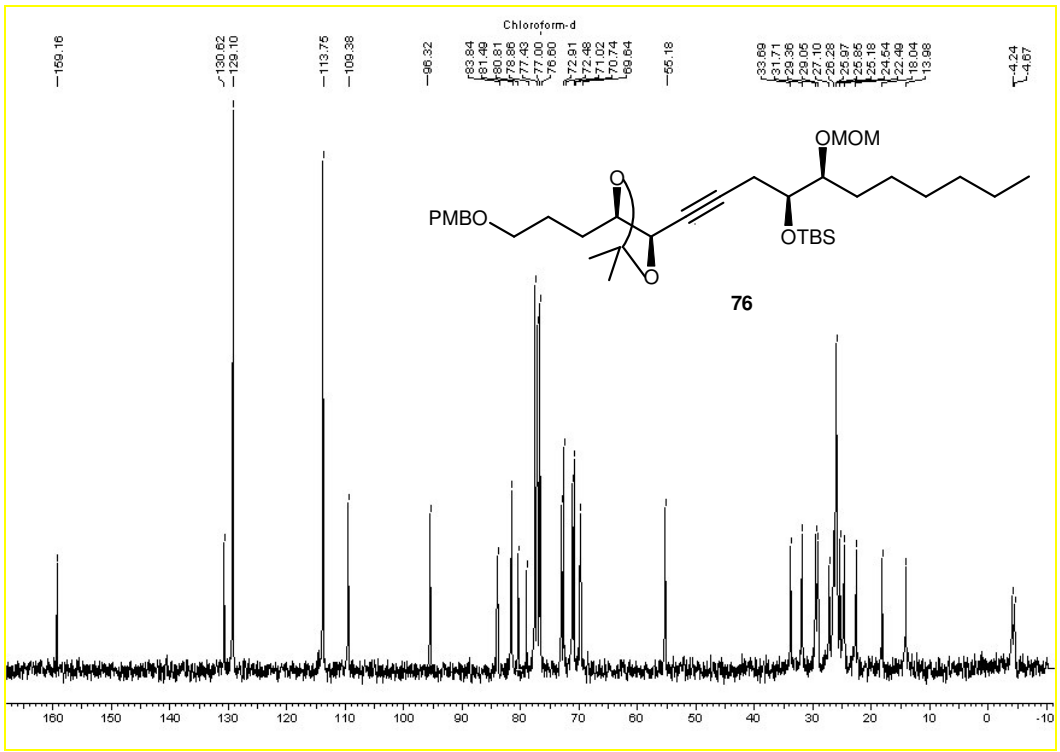
^{1}H NMR Spectrum of **75**



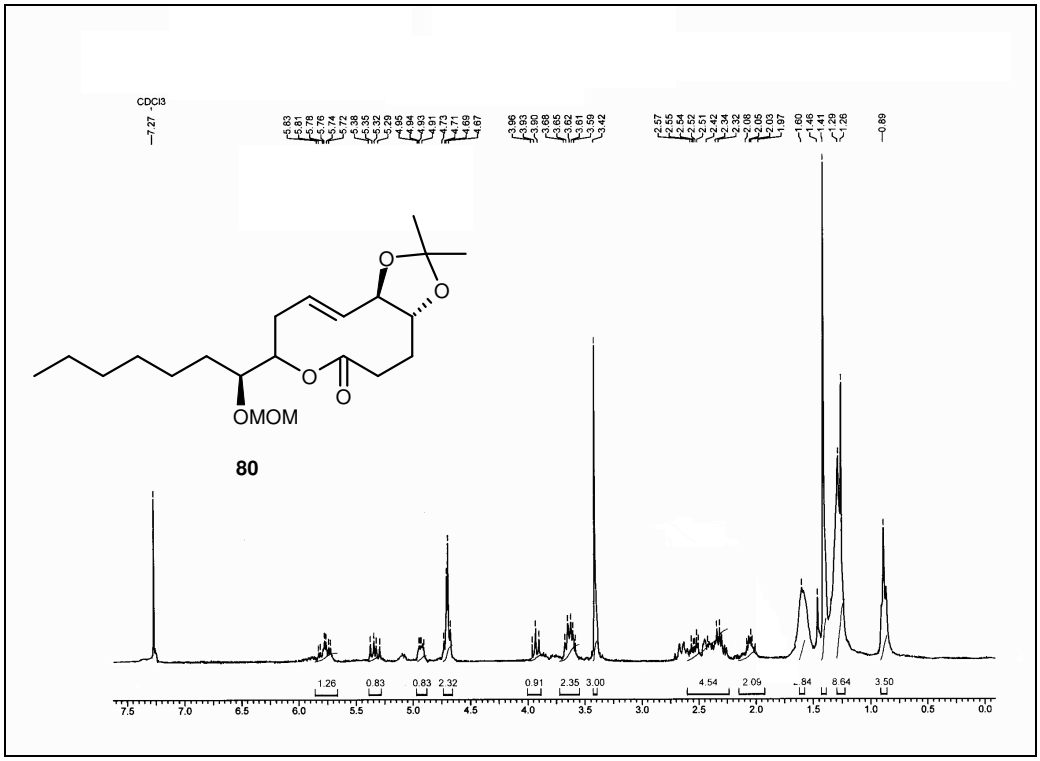
^{13}C NMR Spectrum of **75**



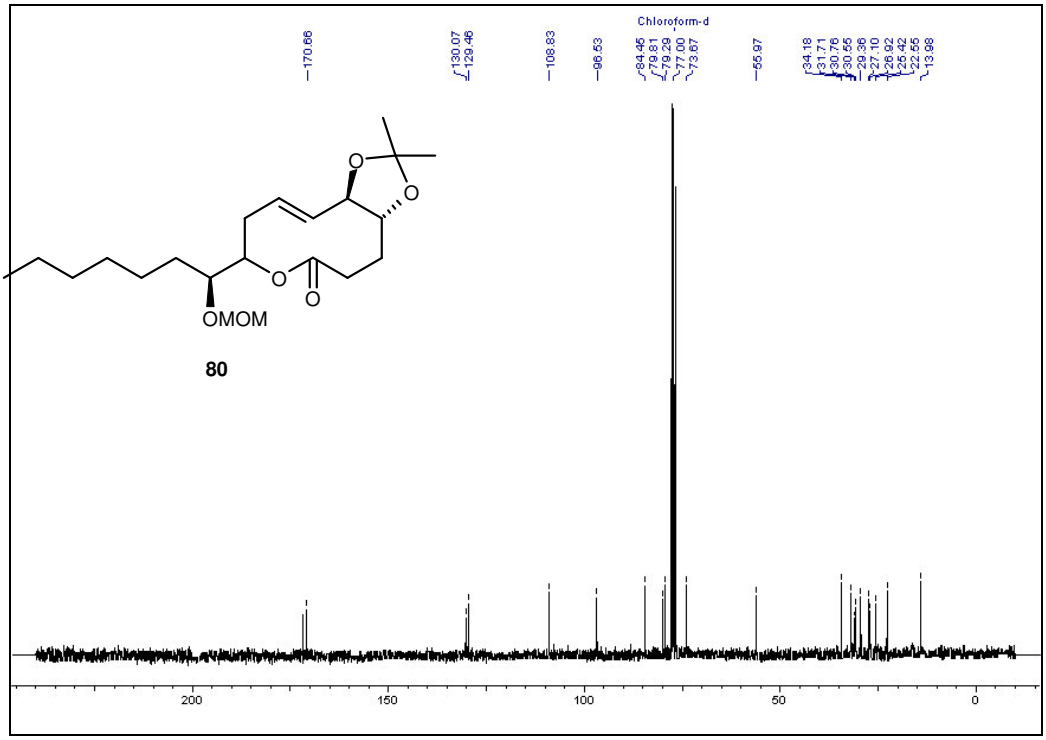
^{1}H NMR Spectrum of **76**



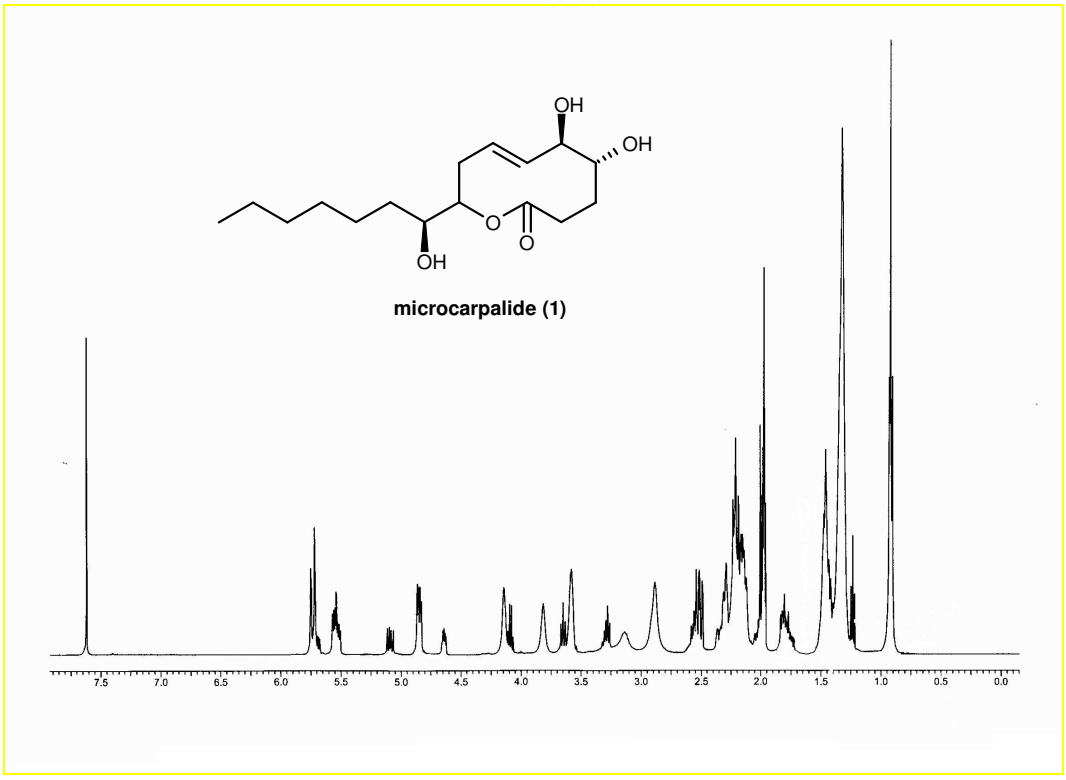
^{13}C NMR Spectrum of **76**



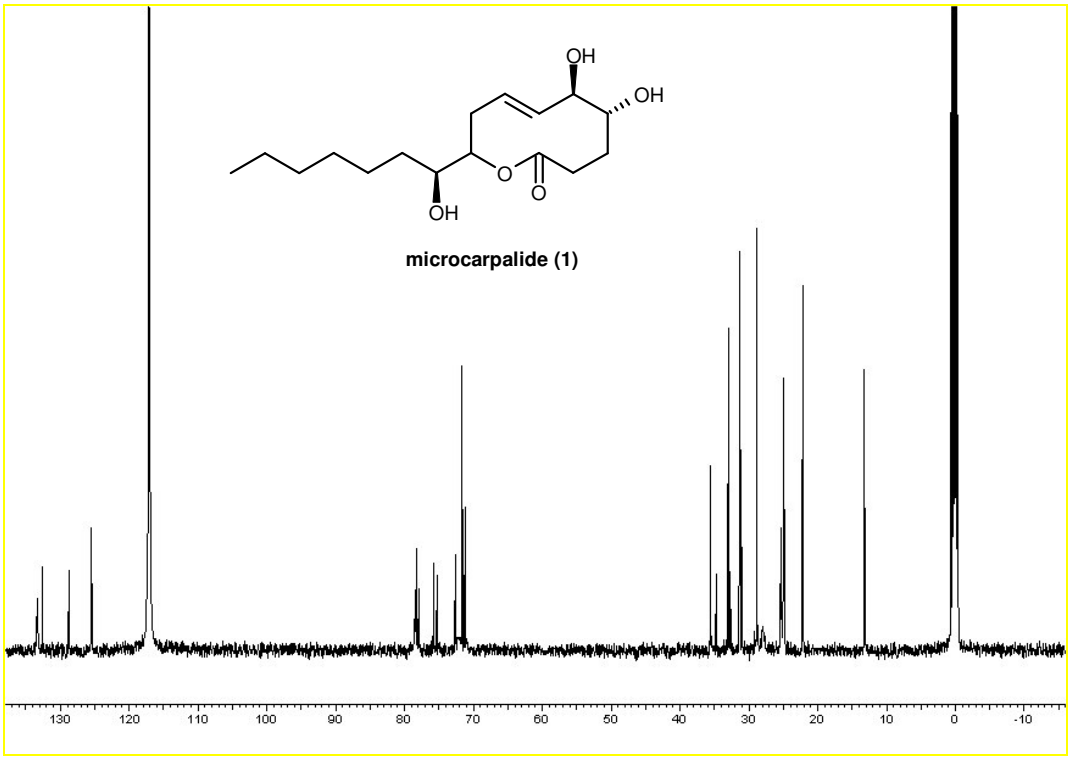
^{1}H NMR Spectrum of **80**



^{13}C NMR Spectrum of **80**



^{1}H NMR Spectrum of microcarpalide (**1**)



^{13}C NMR Spectrum of microcarpalide (**1**)

3.1.8. REFERENCES

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26. For the measurement of enantiomeric excess, the diol **61** was converted into its dibenzoate. The enantiomeric purity of the dibenzoate was estimated to be 97% by chiral HPLC analysis using Lichocart 250-4 (4 mm IDx25 cm) HPLC-Cartridge (R.R.-Whelk-01), 1% *i*PrOH in hexane, 1 mL/min.

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3.2. SECTION B

AN EFFICIENT TOTAL SYNTHESIS OF SAPINOFURANONE B

3.2.1. Introduction

Xenovulene A **81** was isolated from submerged cultures of the fungus *Acremonium strictum* during a screening programme for inhibition of benzodiazepine binding to the $GABA_A$ receptor **81**.[1] It contains an unusual polyketide-derived bicyclic cyclopentenone moiety linked *via* a furan ring to an 11-membered ring derived from the sesquiterpenoid humulene. A number of closely related metabolites have been isolated in which the cyclopentenone ring is replaced by a 6-membered phenolic ring or a 7-membered tropolone moiety. Recent biosynthetic studies[2] have shown that the cyclopentenone ring is formed by a unique ring expansion-contraction mechanism in which an intermediate methylorsellinate derivative is ring expanded to form a tropolone which is then subjected to two successive contractions to form the phenol- and cyclopentenone-containing metabolites. In the course of these studies, Simpson and co-workers isolated a novel metabolite from fermentation extracts and they named it as (4*S*, 5*S*, 6*Z*, 8*E*)-5-hydroxydeca-6,8-dien-4-olide [(*S*,*S*)-Sapinofuranone B] **86**.[3]

In preliminary fermentation work to optimise the production of xenovulene A **81** prior to labelling studies, the growth of *A. strictum* was investigated in a fermenter instead of the normal shake flasks. No xenovulene A was produced but a novel metabolite was isolated from the fermentation extracts. This metabolite was subsequently also isolated from shake flask fermentations in which xenovulene A **81** was present, and indeed was identified as a trace contaminant in ^{1}H NMR spectra of previously isolated samples of xenovulene A **81**. High resolution mass spectrometry of the new metabolite, which had an optical rotation of +19, indicated a molecular formula of $C_{10}H_{14}O_3$. The ^{1}H NMR spectrum showed the presence of only 13 protons, implying the presence of a free hydroxy group which was confirmed by the

infra-red spectrum (ν_{max} 3450 cm^{-1}). The connectivity in the ^1H NMR spectrum was evident from analysis of the coupling constants and was confirmed by a ^1H–^1H COSY experiment. The 10-methyl appeared as a doublet of doublets of doublets (1.83 ppm) which was clearly coupled to three of the four protons in the olefinic region. The four olefinic protons were mutually coupled, indicating a 1,3-diene system with a terminal methyl group. An (*E*,*Z*) geometry was assigned to the diene on the basis of the olefinic coupling constants of 15 and 11 Hz. The olefinic proton furthest from the methyl group was coupled to a proton at 4.63 ppm which was further coupled to one at 4.51 ppm, chemical shifts consistent with their being on oxygen-bearing carbons. The signals resulting from the remaining four protons were complex multiplets. The signal centered at 2.58 ppm integrated for two hydrogens and was coupled to that at 4.51 ppm and to the remaining two signals at 2.15 ppm and 2.35 ppm. The ^{13}C NMR spectrum was consistent with these observations, showing four olefinic signals, two oxygen-bearing methines, one methyl, two methylenes and a single signal in the carbonyl region at 180.2 ppm. That this was present as a γ-lactone was confirmed by the carbonyl stretch at 1772 cm^{-1} in the infra-red spectrum. These data are consistent with structure **86**. A number of related hydroxylated γ-lactones have been reported from microbial sources. The fungal lactone **83**, which has two carbons fewer than **86**, is a metabolite of a *Nigrospora* sp.,[4] whereas muricatacin **82** from the seeds of *Annona muricata*[5] has a dodecyl side chain. L-factor **84**, which is the reduced form of **86**, was isolated from *Streptomyces griseus* and was thought to have an autoregulatory role,[6] controlling the formation of aerial mycelia and production of the anthracycline antibiotic leukaemomycin, although this activity was subsequently shown[7] to be due to contamination with trace amounts of the true regulatory molecule, A-factor **85**.

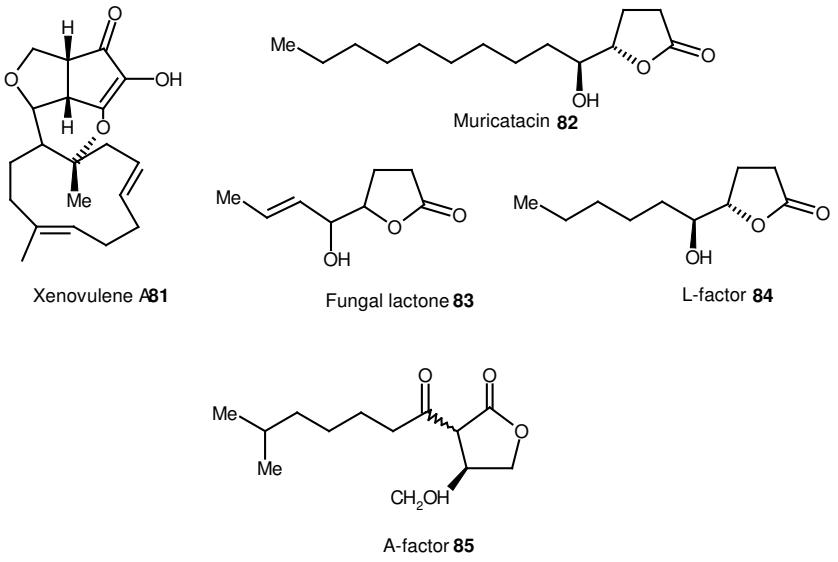


Figure 1. Structures of γ-lactone metabolites.

Almost at the same time, two closely related lactones named sapinofuranone A (**86**) and B ***ent*-86** were isolated from liquid cultures of *Saphaeropsis sapinae*, a phytopathogenic fungus causing a wide range of disease symptoms on conifers.[8] Both the structures and stereochemistry of sapinofuranones were determined by spectroscopic methods. The optical rotations of sapinofuranone A (**77**) and B (***ent*-86**) were reported to be +65.9 and –18.9 and stereochemistries at C-5 were designated as *S* and *R* respectively. Comparison of these data with those for the *A. strictum* metabolite **77** indicated that sapinofuranone A and B isolated from *S. sapinae* must be the (4*R*, 5*S*) diastereomer **77** and (4*R*, 5*R*) enantiomer (***ent*-86**) respectively. The *A. strictum* lactone **77** was therefore described as (4*R*, 5*S*)-(+)-sapinofuranone B (Figure 2).

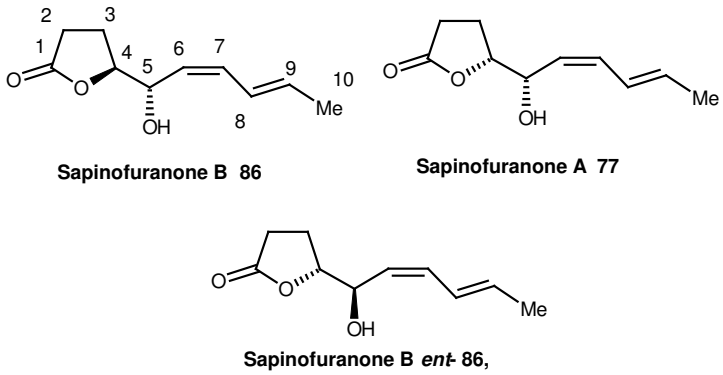
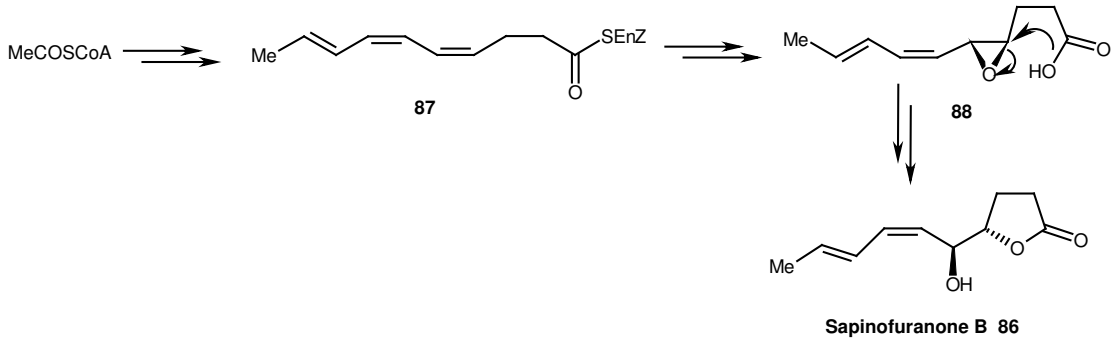


Figure 2. Structures of sapinofuranones

Lactone **86** is clearly of polyketide origin and it can be proposed to be biosynthesised (Scheme 1) *via* the pentaketide derived (*Z*,*Z*,*E*)-triene **87**. Epoxidation and opening of the epoxide **88** by the free acid formed on release from the enzyme would give the γ-lactone with inversion of stereochemistry at C-4.



Scheme 1. Proposed biosynthesis of *A. strictum* lactone 2.

86 was further established by spectroscopic studies, chemical co-relation with the known L-factor **84**. Definitive proof for the structures and stereochemistry of **86** has been provided by a stereoselective total synthesis from tartaric acid as a chiral pool material. The absolute configuration at C-4 and C-5 in **86**, isolated from *A. strictum* was further confirmed by the catalytic hydrogenation of the diene and by comparing the optical rotations of the saturated product with that of L-factor **84**.[3b]

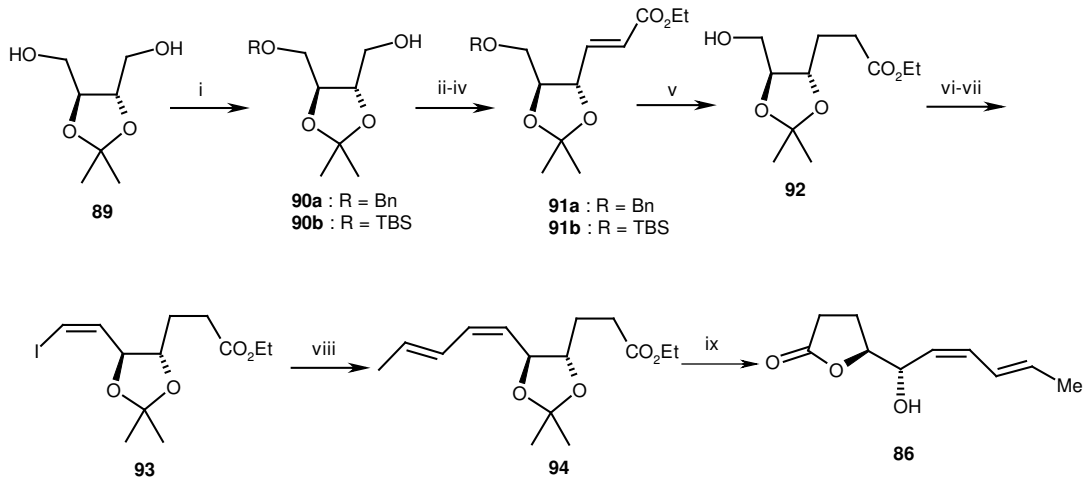
3.2.2. Review of Literature

From a synthetic point of view, there has been only one literature report on the total synthesis of **86** in which asymmetric centers at C-4 and C-5 were elaborated from dimethyl L-tartrate and the 6,8-diene moiety was introduced *via* Stille coupling of (*E*)-prop-1-enyltributyltin with a (*Z*)-vinylic iodide.[3b]

Simpson *et al.*[3b]

Simpson and co-workers confirmed the structure and stereochemistry of sapinofuranone B by its total synthesis in which the asymmetric centres at C-4 and C-5 were elaborated from dimethyl-L-tartrate and the 6,8-diene moiety was introduced *via* Stille coupling of (*E*)-prop-1-enyltributyltin with a (*Z*)-vinylic iodide. As shown in Scheme 2, selective monoprotection of

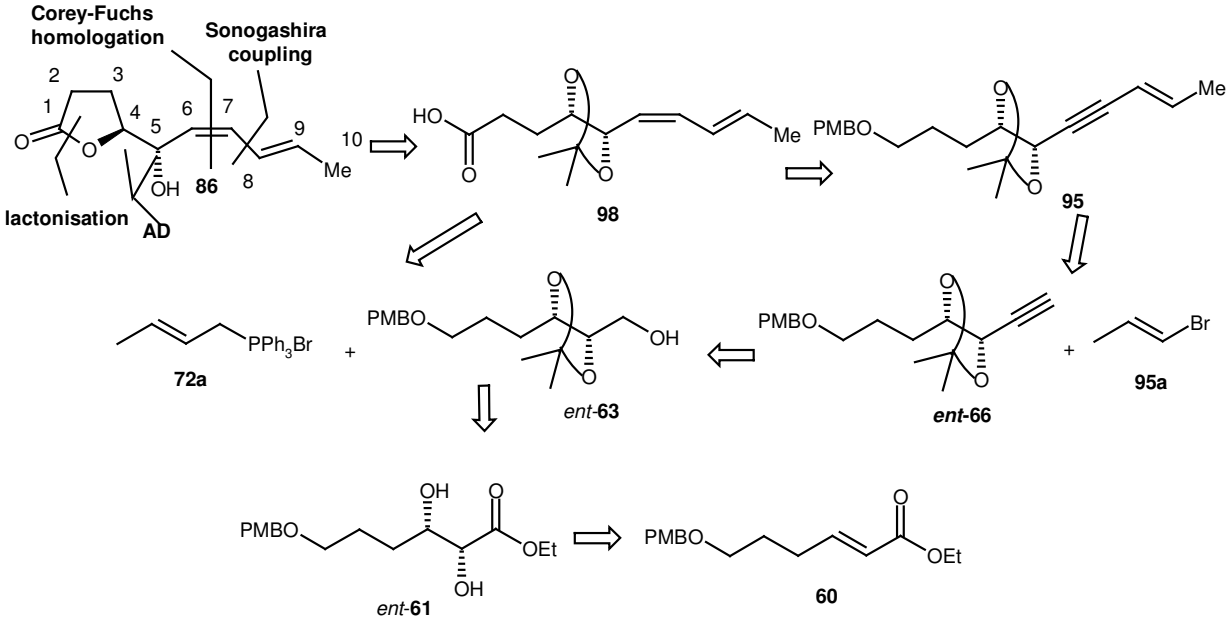
diol **89** and oxidation followed by Wittig chain extension, catalytic hydrogenation and deprotection gave the hydroxy ester **92**. Further Wittig chain extension of corresponding aldehyde gave the (*Z*)-vinylic iodide **93** (25% yield), which was coupled with stannane by Stille coupling to give the diene **94** in 57% yield. Finally, treatment of the diene with *p*-TSA led to deprotection of the diol and spontaneous lactonisation to give the target molecule **86** in 50% overall yield.



Scheme 2. *Reagents and conditions*: (i) BnCl, NaH, DMSO, 94%; (ii) TBDMSCl, NaH, DME, 86%; (iii) $Ph_3P{=}CHCO_2Et$, $C_6H_5CO_2H$, Dess–Martin periodinane, DCM, DMSO, 90%; (iv) $(COCl)_2$, DMSO, Et_3N, then $(EtO)_2POCH_2CO_2Et$, K_2CO_3, 70%; (v) H_2, 10% Pd/C, EtOH, 80%; (vi) Dess–Martin periodinane, DCM, 92%; (vii) $[Ph_3PCH_2I]^+I^-$, NaHMDS, HMPA, 25%; (viii) $(Ph_3P)_2PdCl_2$ (10 mol%), THF, 57%; (ix) TsOH, MeOH, 50%.

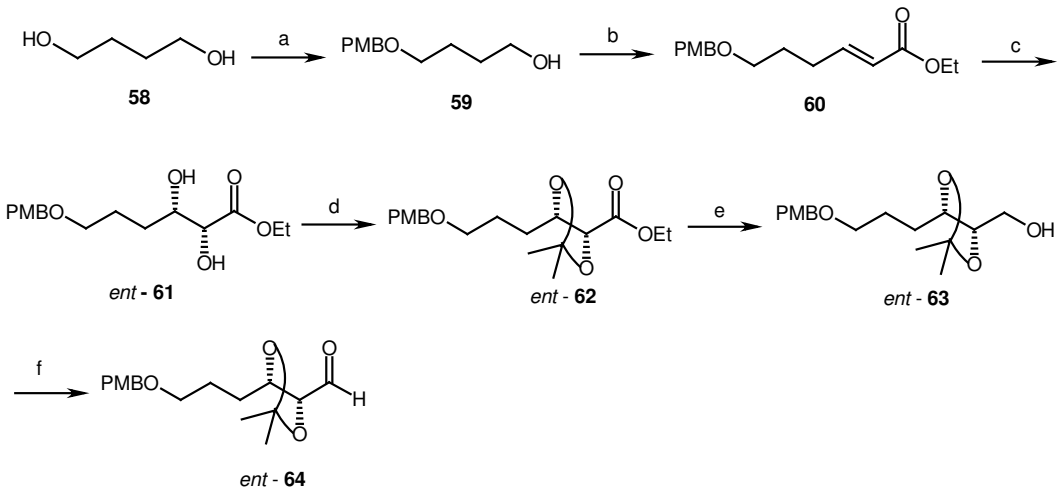
3.2.3. PRESENT WORK

As a part of our research program aimed at developing enantioselective synthesis of naturally occurring lactones[9] and amino alcohols,[10] we have accomplished the stereoselective synthesis of sapinofuranone B employing the Sharpless asymmetric dihydroxylation as the source of chirality from the commercially available starting material 1,4-butanediol.

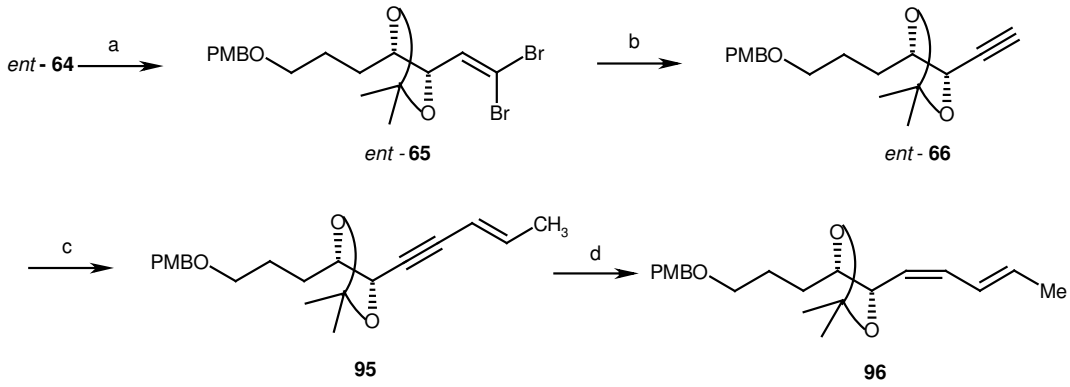


Scheme 3. Retro synthetic analysis for sapinofuranone B (1).

Our retrosynthetic strategy for the synthesis of sapinofuranone B is outlined in Scheme 3. We envisioned that the 1,3-diene system could be prepared by Wittig olefination of an aldehyde or partial hydrogenation of 1,3-enyne **95**, which in turn would be obtained from acetylene *ent*-**66** by Sonogashira coupling. The acetylene *ent*-**66** could be obtained from the alcohol *ent*-**63** through a Corey-Fuchs protocol. In this strategy, both the stereogenic centers could be obtained through Sharpless asymmetric dihydroxylation of an olefin **60**. The synthesis of sapinofuranone B **86** started from commercially available 1,4-butanediol as illustrated in Scheme 4. Selective mono hydroxyl protection of **58** with *p*-methoxybenzyl bromide in the presence of NaH gave **59** in 90% yield. Compound **59** was oxidized to the corresponding aldehyde under standard Swern conditions[11] and subsequently treated with (ethoxycarbonylmethylene)triphenylphosphorane in benzene under reflux conditions to



Scheme 4. *Reagents and conditions*: (a) *p*-$OCH_3C_6H_5CH_2Br$, NaH, dry DMF, cat. TBAI, 0 ^oC to rt, 1 h, 90%; (b) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^oC to -60 ^oC, 95%; (ii) $Ph_3P{=}CHCO_2Et$, C_6H_6, reflux, 6 h, 89%; (c) $(DHQ)_2PHAL$ (1 mol%), 0.1M OsO_4 (0.4 mol%), K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, *t*- BuOH/H_2O 1:1, 0 ^oC, 24 h, 96%; (d) *p*-TSA, 2,2-DMP, CH_2Cl_2, rt, overnight, 95%; (e) DIBAL-H, CH_2Cl_2, 0 ^oC to rt, 2 h, 96%; (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^oC to -60 ^oC, 94%.



Scheme 5. *Reagents and conditions*: (a) CBr_4, PPh_3, CH_2Cl_2, -78 ^oC, 2 h, 98%; (b) *n*-BuLi, THF, -78 ^oC, 1 h, 92%; (c) $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, **95a**, 6 h, 85%; (d) H_2, Lindlar's catalyst, EtOAc/pyridine/1-octene (10:1:1), 6 h, 95%.

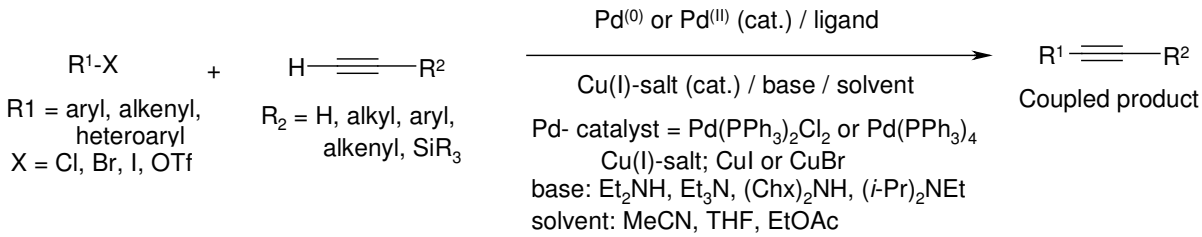
furnish the *trans* olefinic product **60**[12] in 89% yield. The olefin **60** was treated with osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of $(DHQ)_2PHAL$ ligand

under AD conditions[13] to give the diol *ent*-**61** in 96% yield with 97% ee.[14] Treatment of diol *ent*-**61** with 2,2-dimethoxy propane in the presence of *p*-TSA gave compound *ent*-**62**, which on reduction with DIBAL-H furnished the alcohol *ent*-**63** in excellent yield. Subsequent homologation to acetylene *ent*-**66** was carried out by Corey-Fuchs protocol[15] in a three-step sequence involving Swern oxidation, dibromomethylenation of the aldehyde and dehalogenation. Thus compound *ent*-**63** was oxidized to the aldehyde *ent*-**64** using standard Swern conditions followed by dibromomethylenation with CBr_4 and PPh_3 to furnish the dibromo olefin *ent*-**65** in essentially quantitative yield. Treatment of *ent*-**65** with excess of *n*-BuLi in THF at –78 ^{o}C provided the acetylene *ent*-**66** in 92% yield.

Mechanism of Sonogashira coupling:

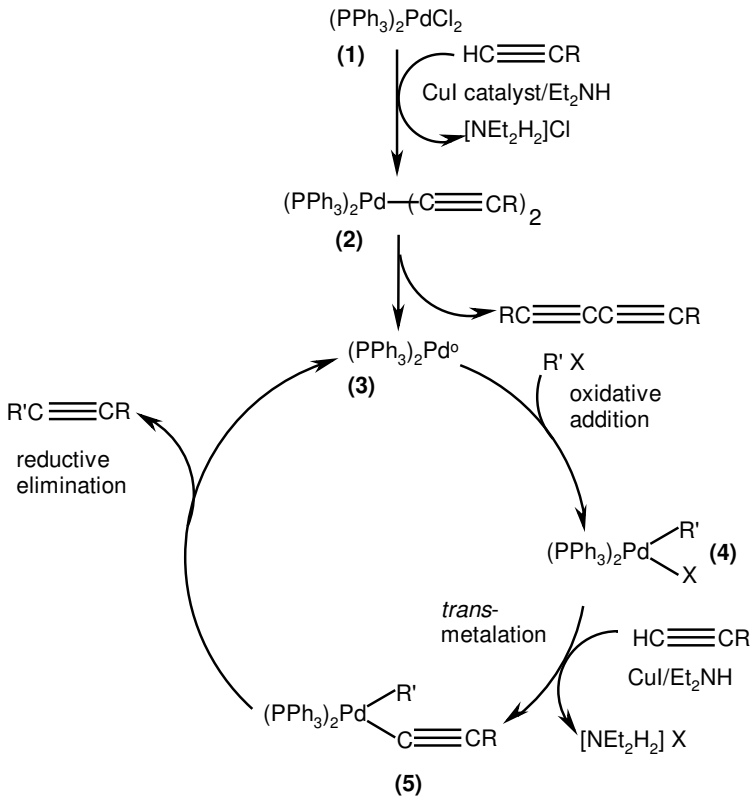
In 1975, K. Sonogashira and co-workers reported that symmetrically substituted alkynes could be prepared under mild conditions by reacting acetylene gas with aryl iodides or vinyl bromides in the presence of catalytic amounts of $Pd(PPh_3)Cl_2$ and cuprous iodide (CuI). During the same year the research groups both R. F. Heck and L. Cassar independently disclosed similar Pd-catalysed processes, but these were not using copper co-catalysis, and the reaction conditions were harsh.[16e,f] The copper-palladium catalysed coupling of terminal alkynes with aryl and vinyl halides to give enynes is known as the 'Sonogashira coupling' and can be considered as catalytic version of the Castro-Stephens coupling. The general features of the reaction are: 1) the coupling can usually be conducted at or slightly above room temperature, and this is the major advantage over the forcing conditions required for the alternative Castro-Stephenes coupling; 2) the handling of the shock-sensitive/explosive copper acetylides is avoided by the use of a catalytic amounts of copper(I)salt; 3) the copper(I) salt can be commercially available CuI or CuBr and usually applied in 0.5 -5 mol % with respect to the halide or alkyne; 4) the best palladium catalyst are $Pd(PPh_3)_2Cl_2$ or $Pd(PPh_3)_4$; 5) the solvents and the reagents do not need to be rigorously dried. However, a thorough deoxygenation is essential to maintain the activity of the Pd-catalyst; 6) often the base serves as the solvent but occasionally a co-solvent is used; 7) the reaction works well on both very small and large scale (>100 g); 8) the coupling is stereospecific; the stereochemical information of the substrates is preserved in the products; 9) the order of the reactivity for the aryl and vinyl halides is I ~ OTf > Br >> Cl; 10) the difference between the reaction rates of iodides and bromides allows selective coupling with the iodides in the

presence of bromides; 11) almost all functional groups are tolerated on the aromatic and vinyl halide substrates. However, alkynes with conjugated electron-withdrawing groups ((R^2= COOMe) give Michael addition products and propargylic substrates with electron-withdrawing groups ((R^2= COOMe or NH_2) tend to rearrange to allenes under the reaction conditions; 12) the exceptional functional group tolerance of the process makes it feasible to use this coupling for complex substrates in the late stages of a total synthesis. The coupling of sp^2-C halides with sp-C metal derivatives is also possible by using other reactions such as the Negishi-, Stille-, Suzuki-, and Kumada cross-couplings. In terms of functional group tolerance, the Negishi cross-coupling is the best alternative to the Sonogashira reaction. There are certain limitations on the Sonogashira coupling: 1) aryl halides and bulky substrates that are not very reactive require higher reaction temperature; and 2) at higher temperatures terminal alkynes undergo side reactions.

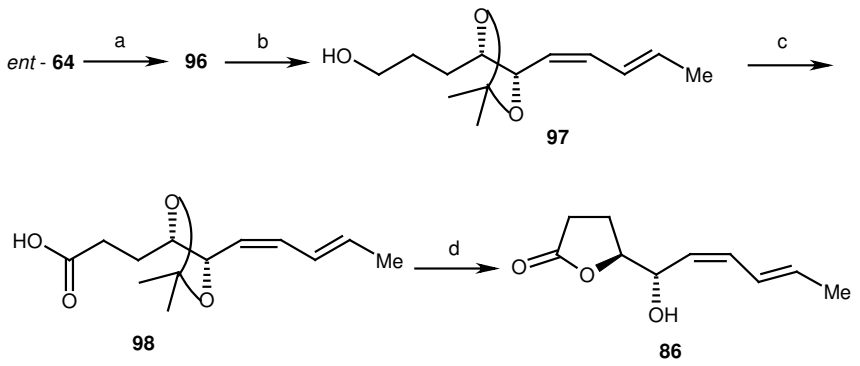


Mechanism:

*Although the detailed mechanism of the reaction is yet to be clarified, it seems likely that the substitution occurs through an initial formation of bis-(triphenylphosphine)dialkynylpalladium (II) (**2**), which gives a catalytic species, bis-(triphenylphosphine)dialkynylpalladium (0) (**3**), through a reductive elimination of 1,4-diphenylbutadiyne. Subsequent oxidative addition of vinyl halide to (**3**), followed by an alkynylation of the adduct (**4**), gives vinyl-alkynyl derivative of palladium (**5**), which easily regenerates the original bis-(triphenylphosphine)dialkynylpalladium (0) (**3**) through the reductive elimination of the substitution products. The alkynylation of the starting catalyst (**1**) or an oxidative adduct (**4**) in the catalytic cycle in scheme 1 is catalysed by cuprous iodide in the presence of diethylamine.*



The Sonogashira coupling[16] of *ent*-**66** with commercially available *trans*-1-bromopropene **95a** was successfully carried out with $Pd(PPh_3)_2Cl_2$ and CuI in triethylamine to furnish the 1,3-enyne product **95** in excellent yield. The ^1H NMR spectrum gave olefin protons at δ 6.21 (doublet) and 5.69 (doublet of quartet) with the coupling constant J = 15.7 and 14.9 Hz respectively, indicating *trans*-olefin. Methyl protons (C=C-CH_3) appeared at δ 1.84 as doublet with coupling constant J = 7.8 Hz. The partial hydrogenation of the triple bond in **95** proved to be challenging. Irrespective of whether catalytic quantities or several molar equivalents of quinoline were present, the mixture of **96** and over hydrogenated product was formed. The use of 1-octene[17] as a co-solvent along with EtOAc in the presence of pyridine (EtOAc/pyridine/1-octene = 10:1:1) furnished the diene **96** as a single product (Scheme 5). Thus, the use of Corey-Fuchs protocol and Sonogashira coupling followed by hydrogenation for the synthesis of the 1,3-diene system is an improvement over the first reported synthesis.[3b] An (*E*,*Z*) geometry was assigned to the diene system on the basis olefinic coupling constants of 14.8 and 11.2 Hz. Alternatively, the diene **96** was also obtained by the Wittig olefination (Scheme 6).



Scheme 6. *Reagents and conditions*: (a) $CH_3CH{=}CHCH_2Ph_3P^+Br^-$(**95b**), LiHMDS, THF, -80 ^oC, 2 h, 76%; (b) DDQ, CH_2Cl_2/H_2O (18:1), rt, 1 h, 94%; (c) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^oC to -60 ^oC; (ii) $NaClO_2$, DMSO, NaH_2PO_4, rt, overnight; (d) HCl (*cat*), MeOH, rt, overnight, 67% from **97**.

Thus, the aldehyde *ent*-**64** was treated with the Wittig salt **95b** in THF at –80 ^oC in the presence of LiHMDS to furnish a mixture of *cis* and *trans*-Wittig product (*Z*:*E* = 80:20). The desired *Z*-isomer **96** was easily separated by silica gel column chromatography. The subsequent deprotection of the *p*-methoxybenzyl group with DDQ furnished the alcohol **97** in 94% yield. The IR spectrum of **97** gave hydroxyl absorption at 3460 cm^{-1}. PMB group protons disappeared in ^1H NMR spectrum. Oxidation of the resulting alcohol to the corresponding aldehyde using Swern conditions and further oxidation using sodium chlorite in DMSO under buffer conditions afforded the acid **98**. Finally, the deprotection of acetonide as well as cyclisation were achieved in one-pot by using cat. conc. HCl in methanol to furnish the target molecule **86** in 67% overall yield from alcohol **97**, $[\alpha]_D^{25}$ +19.6 (*c* 1.0, $CHCl_3$), [Lit.[2] $[\alpha]_D^{20}$ +19.0 (*c* 0.77, $CHCl_3$)]. The physical and spectroscopic data of **86** were in accord with those reported for same compound obtained from natural source.[2]

3.2.4. conclusion

In conclusion, a practical and enantioselective total synthesis of sapinofuranone B has been achieved using the Sharpless asymmetric dihydroxylation, Sonogashira coupling and Wittig olefination as the key steps. The obvious advantages of our synthesis in terms of high overall

yields, ready access to 1,3-diene system and stereogenic centers, high enantioselectivity and various possibilities available for structural modifications are noteworthy.

3.2.5. Experimental Section

2,3-Dihydroxy-6-(4-methoxybenzyloxy)-hexanoic acid ethyl ester (*ent*-61): $[\alpha]_D^{25}$ -7.0 (*c* 1.6, $CHCl_3$)

5-[3-(4-Methoxybenzyloxy)-propyl]-2,2-dimethyl-[1,3]dioxolane-4-carboxylic acid ethyl ester (*ent*-62).

$[\alpha]_D^{25}$ -26.2 (*c* 2.1, $CHCl_3$).

{5-[3-(4-Methoxybenzyloxy)-propyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-methanol (9).

$[\alpha]_D^{25}$ -11.7 (*c* 1.8, $CHCl_3$).

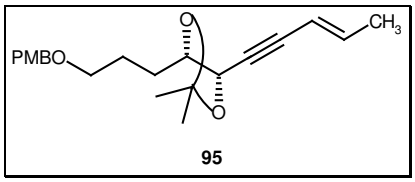
4-(2,2-Dibromovinyl)-5-[3-(4-methoxybenzyloxy)-propyl]-2,2-dimethyl-[1,3]dioxolane (11).

$[\alpha]_D^{25}$ -9.2 (*c* 2.6, $CHCl_3$)

4-Ethynyl-5-[3-(4-methoxybenzyloxy)-propyl]-2,2-dimethyl-[1,3]dioxolane (12).

$[\alpha]_D^{25}$ -12.4 (*c* 1.4, $CHCl_3$)

4-[3-(4-Methoxybenzyloxy)-propyl]-2,2-dimethyl-5-pent-3-en-1-ynyl-[1,3]dioxolane (95). (Sonogashira coupling).



95

To a stirred mixture of $Pd(PPh_3)_2Cl_2$ (738 mg, 1.05 mmol), CuI (621 mg, 3.26 mmol) in Et_3N (2 mL) were added solutions of *trans*-1-bromopropene **95a** (2.54 g, 21.0 mmol) in Et_3N (2 mL) and acetylene *ent*-**66** (3.2 g, 10.51 mmol) in Et_3N (2 mL) under argon. After 6 h, the reaction mixture was filtered through celite and filtrate was concentrated. Silica gel column chromatography of the crude product using petroleum ether:EtOAc (9:1) as eluent gave **95** as a pale yellow oil.

Yield: 3.08 g, 85%.

Mol. Formula: $C_{21}H_{28}O_4$

$[\alpha]_D^{25}$: -11.4 (*c* 0.4, $CHCl_3$).

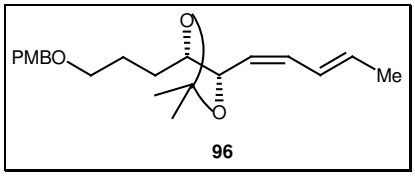
IR ($CHCl_3$, cm^{-1}): ν_{max} 2952, 2854, 1615, 1514, 1232, 1132, 1030.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.29 (d, *J* = 7.9 Hz, 2H), 6.89 (d, *J* = 7.6 Hz, 2H), 6.21 (d, *J* = 15.7 Hz, 1H), 5.69 (dq, *J* = 14.9, 7.0 Hz, 1H), 4.45 (s, 2H), 4.2 (d, *J* = 8.0 Hz, 1H), 4.01-4.08 (m, 1H), 3.82 (s, 3H), 3.50 (t, *J* = 5.4 Hz, 2H), 1.84 (d, *J* = 7.8 Hz, 3H), 1.54-1.79 (m, 4H), 1.46 (s, 3H), 1.42 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 159.1, 133.8, 132.5, 130.5, 129.0, 113.6, 109.8, 81.2, 82.1, 74.5, 72.4, 70.1, 69.4, 55.1, 28.9, 26.9, 26.0, 25.7.

Analysis: Calcd.: C, 73.23; H, 8.19%; **Found:** C, 73.42; H, 8.02.%.

4-[3-(4-Methoxybenzyloxy)-propyl]-2,2-dimethyl-5-penta-1,3-dienyl-[1,3]dioxolane (96).



96

To a solution of **95** (3.08 g, 8.94 mmol) in 5 mL of ethyl acetate/pyridine/1-octene (10:1:1) was added Lindlar's catalyst (6 mg). The reaction mixture was stirred for 6 h under a balloon of H_2 at room temperature and filtered through a celite pad. The filtrate was concentrated and the residue was purified by silica gel column chromatography using petroleum ether:EtOAc (9:1) as eluent to give **96** as a pale yellow oil.

Yield: 2.94 g, 95%.

Mol. Formula: $C_{21}H_{30}O_4$

$[\alpha]_D^{25}$: -16.7 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 2952, 2854, 1613, 1300, 1204, 1100, 1038

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.23 (d, *J* = 8.1 Hz, 2H), 6.90 (d, *J* = 10.0 Hz, 2H), 6.38 (m, 2H), 5.82 (dq, *J* = 14.8, 7.1 Hz, 1H), 4.50-4.57 (m, 1H), 4.43 (s, 2H), 3.81 (s, 3H), 3.62-3.72 (m, 1H), 3.47 (t, *J* = 6.1 Hz, 3H), 1.81 (ddd, *J* = 6.8, 1.5, 1 Hz, 3H), 1.61-1.68 (m, 4H), 1.43 (s, 3H), 1.41 (s, 3H)

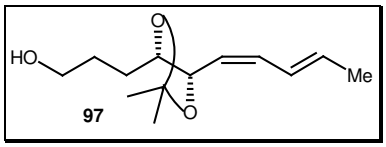
^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0, 133.9, 132.9, 130.5, 129.1, 126.2, 124.3, 113.6, 108.3, 80.7, 76.8, 72.3, 69.6, 55.2, 28.2, 27.2, 27.0, 26.1, 18.3.

Analysis: Calcd.: C, 72.80; H, 8.73,%; **Found:** C, 72.61; H, 8.82.

Wittig olefination of aldehyde *ent*-64.

To a solution of Wittig salt **95b** (3.56 g, 8.96 mmol) in THF (50 mL) was added LiHMDS (9.0 mL, 9.55 mmol, 1.06 M sol. in THF) at -80 ^{o}C over 5 min. After 1 h stirring at the same temperature the aldehyde *ent*-**64** (1.84 g, 5.92 mmol) in THF (5 mL) was added. After stirring for 1 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc (3 x 50 mL), brine, dried (Na_2SO_4), and concentrated. The required *Z*-isomer was separated by flash chromatography of the crude product using petroleum ether: EtOAc (9:1) as eluent to give **96** (1.57 g, 76%) as pale yellow oil.

3-(2,2-Dimethyl-5-penta-1,3-dienyl-[1,3]dioxolan-4-yl)-propan-1-ol (97).



97

To a solution of compound **96** (230 mg, 0.66 mmol) in CH_2Cl_2 (18 mL) and H_2O (1 mL) at 0 ^{o}C was added DDQ (180 mg, 0.79 mmol) in portions. The resultant mixture was stirred at room temperature for 1 h and then saturated aqueous $NaHCO_3$ (10 mL) was added. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether:EtOAc (6:4) as eluent afforded alcohol **97** as pale yellow oil.

Yield: 141 mg, 94%.

Mol. Formula: $C_{13}H_{22}O_3$

$[\alpha]_D^{25}$: +17.7 (*c* 0.7, $CHCl_3$).

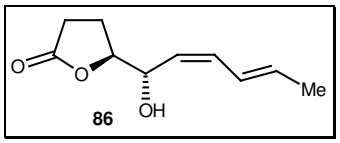
IR ($CHCl_3$, cm^{-1}): ν_{max} 3460, 2941, 2858, 1612, 1300, 1204

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.36 (m, 2H), 5.81 (dq, *J* = 15.2, 7 Hz, 1H), 5.26 (dd, *J* = 10.9, 2 Hz, 1H), 4.43-4.60 (m, 1H), 3.80-3.86 (m, 1H), 3.67 (t, *J* = 8.0 Hz, 2H), 2.64 (brs, 1H), 1.81 (ddd, *J* = 6.9, 2.0, 1.0 Hz, 3H), 1.60-1.74 (m, 4H), 1.42 (s, 3H), 1.41 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 133.8, 132.9, 126.3, 124.3, 108.3, 80.7, 72.3, 67.9, 28.8, 27.2, 27.0, 26.1, 18.3.

Analysis: Calcd.: C, 68.99; H, 9.80%; **Found:** C, 68.42; H, 9.89%.

Sapinofuranone B (**86**).



86

A solution of oxalyl chloride (0.118 g, 0.081 mL, 0.93 mmol) in dry CH_2Cl_2 (20 mL) at -78 ^oC was added dropwise dry DMSO (0.146 g, 0.132 mL, 1.87 mmol) in CH_2Cl_2 (5 mL). After 30 min, alcohol **97** (141 mg, 0.62 mmol) in CH_2Cl_2 (5 mL) was added over 10 min giving a copious white precipitate. After stirring for 1 h at -78 ^oC the reaction mixture was brought to -60 ^oC and Et_3N (0.252 g, 0.347 mL, 2.49 mmol) was added slowly and stirred for 30 min allowing the reaction mixture to warm to room temperature. The reaction mixture was poured into water (50 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL) and combined organic layers were washed with water (3 x 30 mL), brine (30 mL), dried (Na_2SO_4) and passed through short pad of silica gel. The filtrate was concentrated to give the aldehyde (140 mg) as pale yellow syrup, which was used as such for the next step without purification.

A solution of 79% $NaClO_2$ (91mg, 1.00 mmol) in 1.0 mL of water was added dropwise to a stirred solution of above crude aldehyde (140 mg, 0.62 mmol) in 0.5 mL of DMSO and NaH_2PO_4 (60 mg, 0.50 mmol) in 1.0 mL of water in 5 min at room temperature. The mixture was left overnight at room temperature, then 5% aqueous solution of $NaHCO_3$ was added. The aqueous phase was extracted 3 times with CH_2Cl_2 and washed with brine, dried (Na_2SO_4) and concentrated to give the acid **98**, which was used as such for the next step without purification.

The above crude acid was dissolved in methanol (5 mL) and catalytic amount of conc. HCl was added. The mixture was stirred at room temperature for overnight and then quenched with solid $NaHCO_3$, filtered and the filtrate was concentrated. Silica gel column chromatography of the crude product using petroleum ether:EtOAc (6:4) as eluent gave **86** as an oil.

Yield: 73 mg, 67% from **97**

Mol. Formula: $C_{10}H_{14}O_3$

$[\alpha]_D^{25}$: +19.6 (*c* 1.0, $CHCl_3$) [Lit.[2] $[\alpha]_D^{20}$ +19.0 (*c* 0.77, $CHCl_3$)].

IR ($CHCl_3$, cm^{-1}): ν_{max} 3450, 2811, 1772, 1641, 1513, 1239, 1130, 1032

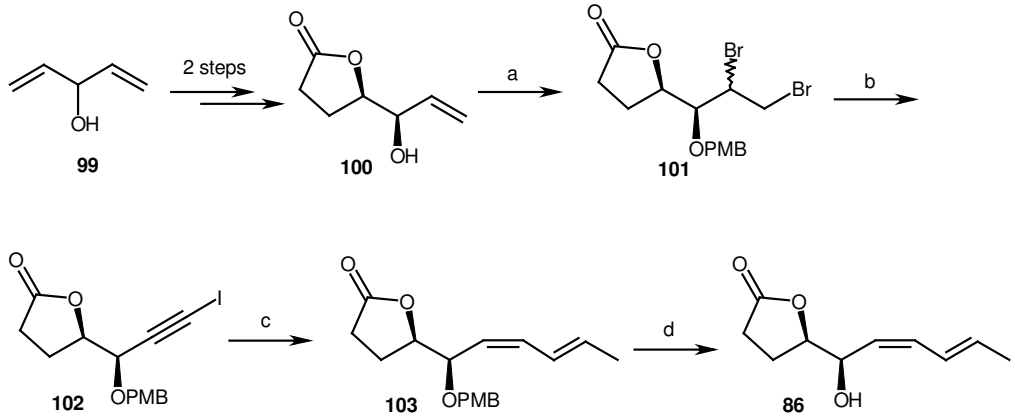
^{1}H NMR (200 MHz, $CDCl_3$): δ 6.12-6.37 (m, 2H), 5.82 (dq, 1H, *J* = 14.8, 7.0), 5.26 (dd, 1H, *J* = 10.8, 2.0 Hz), 4.65 (ddd, 1H, *J* = 8.9, 5.0, 1.5 Hz), 4.52 (ddd, 1H, *J* = 7.6, 6.9, 5.5 Hz), 2.48-2.72 (m, 3H), 2.10-2.35 (m, 2H), 1.82 (ddd, 3H, *J* = 7.1, 1.7, 1.0 Hz)

^{13}C NMR (125 MHz, $CDCl_3$): δ 180.1, 134.1, 133.1, 126.4, 125.8, 85.1, 69.8, 29.1, 24.6, 18.4.

3.2.6. Post Work: After the report of our total synthesis of sapinofuranone B, one more report of its total synthesis appeared in literature. A brief description of this total synthesis is given below.

Nishiyama *et al.* [18]

Nishiyama and co-workers developed a methodology for the synthesis of alkynes under the DBU conditions based on an elimination reaction and this protocol was applied to the synthesis of sapinofuranone B. The allyl alcohol, prepared from divinyl carbinol in two steps was initially protected as PMB and subjected to bromination, elimination and iodination to give compound **102**. Diimide reduction of acetylene iodide followed by Suzuki–Miyaura coupling with *E*-1-propeneboronic acid furnished the target molecule **86**.



Scheme 7. *Reagents and conditions:* (a) (i) *p*-methoxybenzyl trichloroacetimidate, TfOH/Et_2O (100%); (ii) Py–HBr_3/CH_2Cl_2 (93%); (b) DBU (5 equiv)/DMF, 80 ^oC (73%); (c) NIS, $AgNO_3$/acetone (80%); (d) (i) NBSH, Et_3N/THF-^{i}PrOH (100%); (ii) $PdCl_2$(dppf), *E*-1-propeneboronic acid, CsF/PhMe (87%); (iii) DDQ/CH_2Cl_2–H_2O (89%).

3.1.7. Spectra

1] ^{1}H NMR Spectrum of **95**

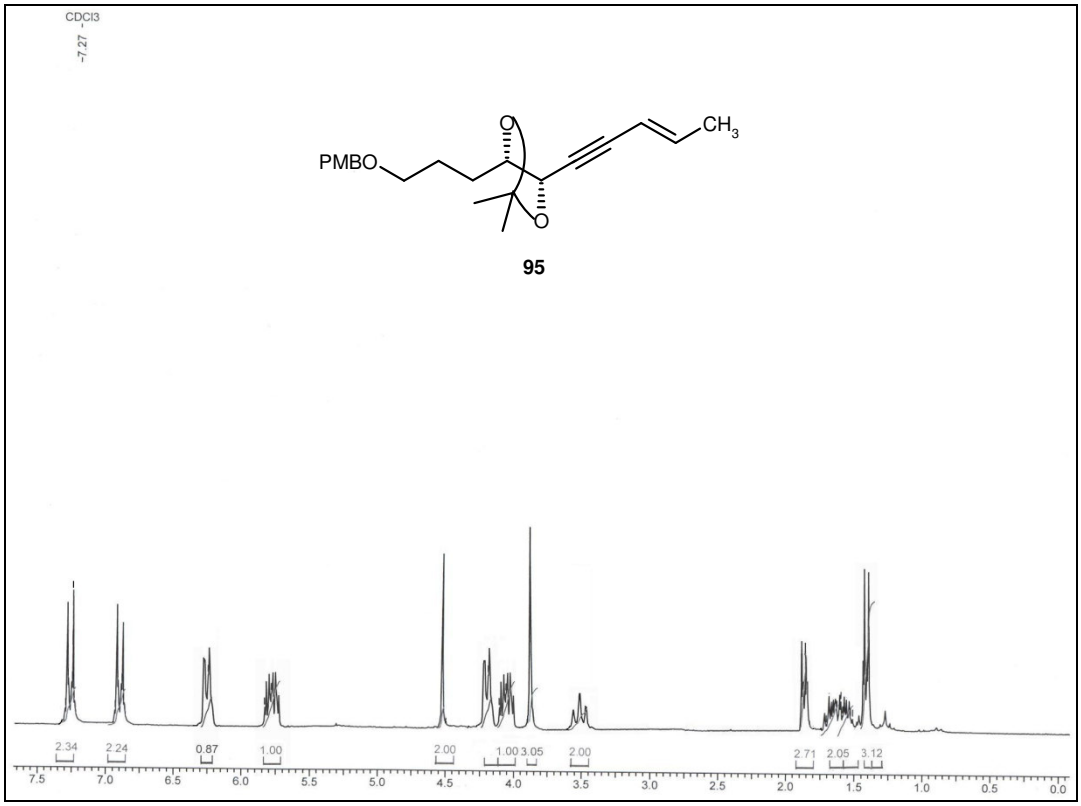
2] ^{13}C NMR Spectrum of **95**

3] ^{1}H NMR Spectrum of **96**

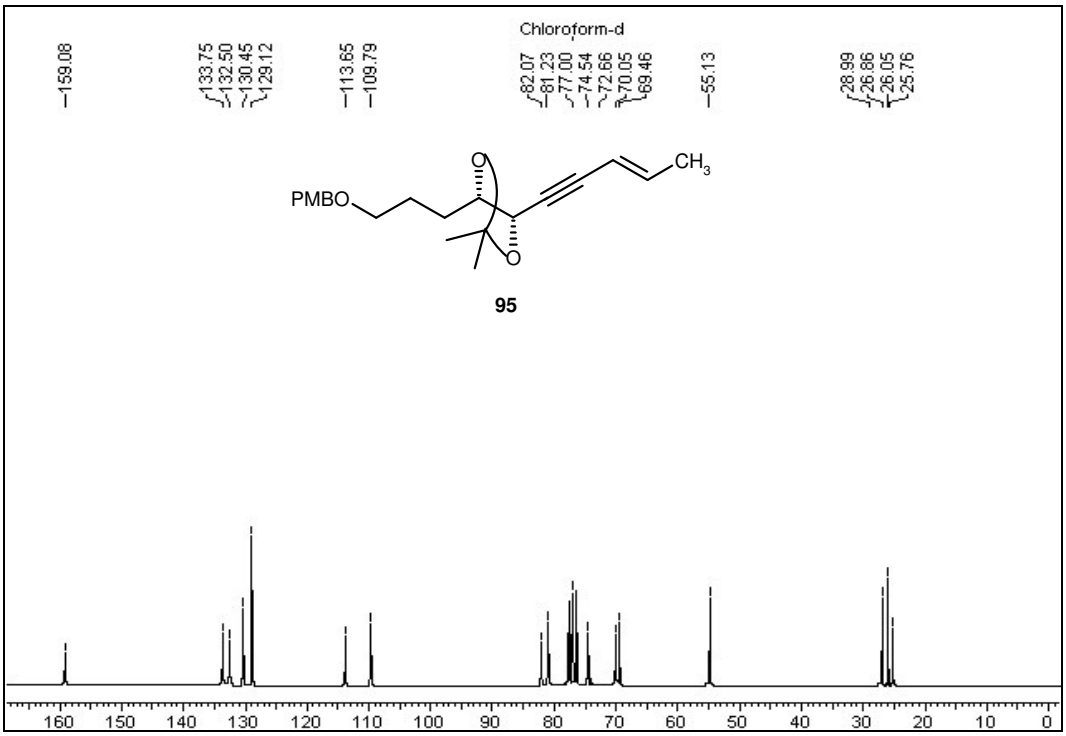
4] ^{13}C NMR Spectrum of **96**

5] ^{13}C NMR Spectrum of **86**

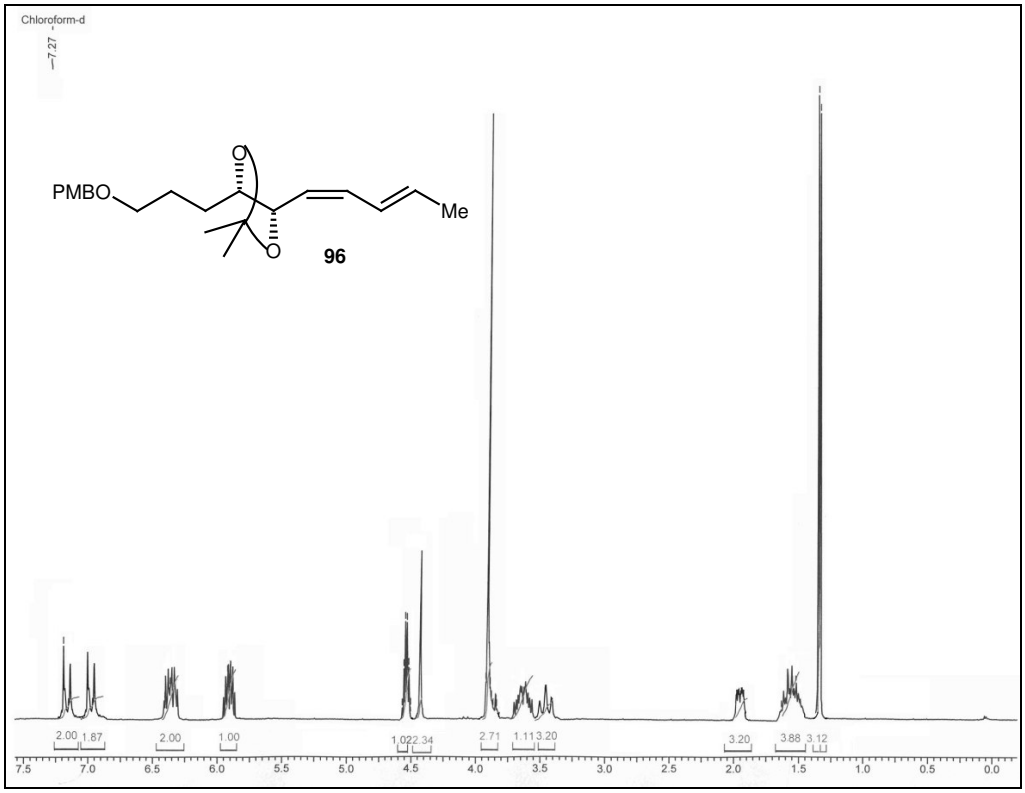
6] ^{13}C NMR Spectrum of **86**



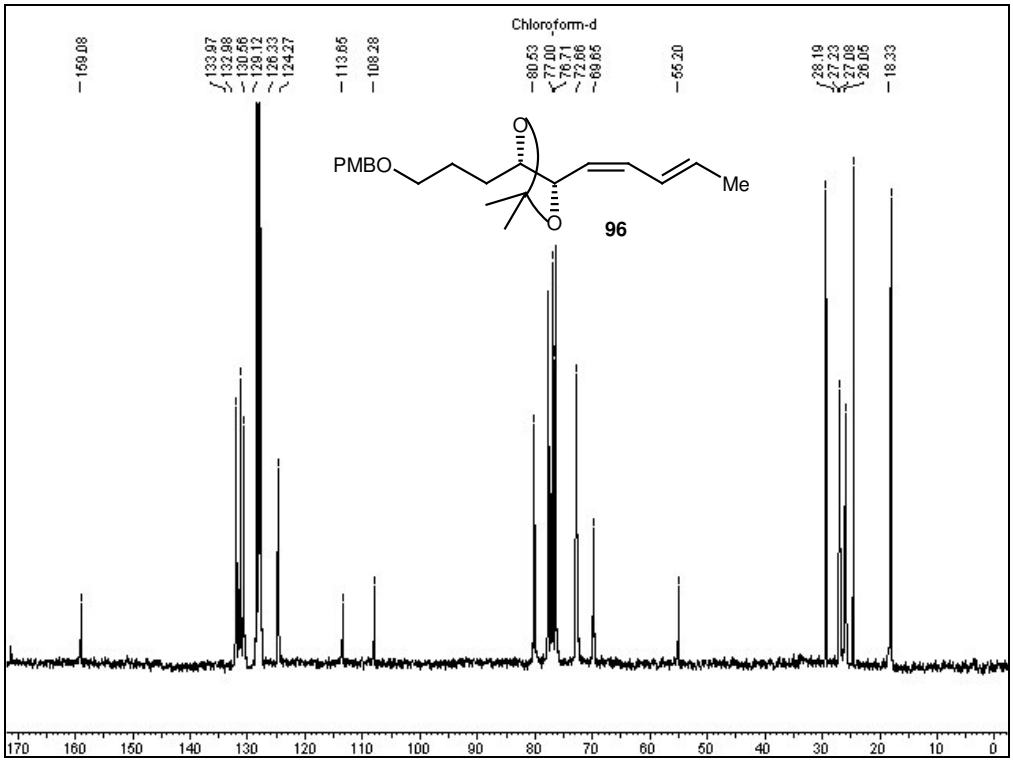
^{1}H NMR Spectrum of **95**



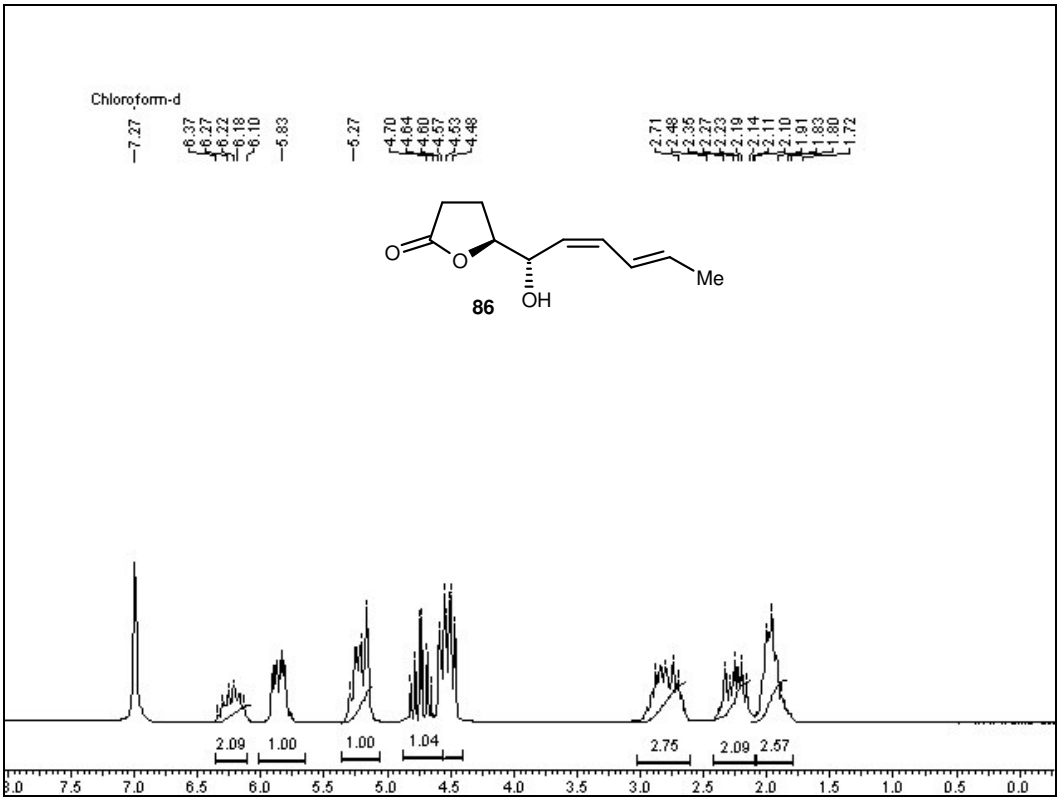
^{13}C NMR Spectrum of **95**



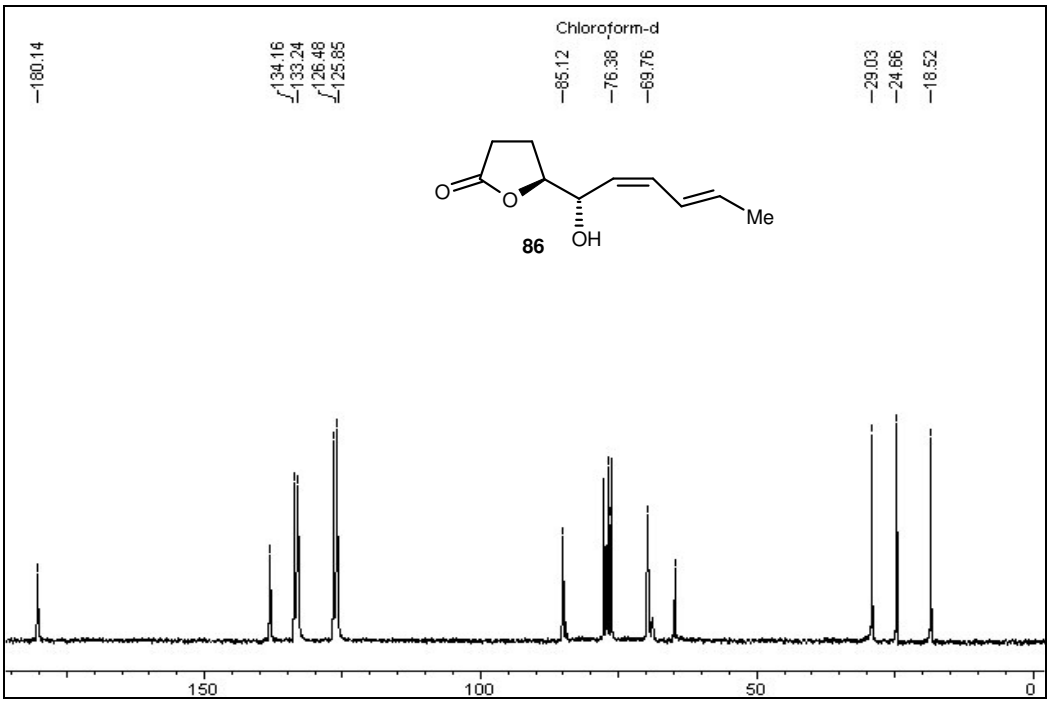
^{1}H NMR Spectrum of **96**



^{13}C NMR Spectrum of **96**



^{1}H NMR Spectrum of **86**



^{13}C NMR Spectrum of **86**

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3.3. SECTION C

ENANTIOSELECTIVE SYNTHESIS OF (–)-PINELLIC ACID

3.3.1. Introduction:

Influenza, commonly known as the flu, is an infectious disease of birds and mammals caused by an RNA virus of the family *Orthomyxoviridae* (the influenza viruses). In people, common symptoms of influenza are fever, sore throat, muscle pains, severe headache, coughing, and weakness and fatigue.[1] In more serious cases, influenza causes pneumonia, which can be fatal, particularly in young children and the elderly. Although the common cold is sometimes confused with influenza, it is a much less severe disease and caused by a different virus.[2] similarly, gastroenteritis is sometimes called "*stomach flu*" or "24-hour flu", but is unrelated to influenza.

Typically, influenza is transmitted from infected mammals through the air by coughs or sneezes creating aerosols containing the virus, and from infected birds through their droppings. Influenza can also be transmitted by saliva, nasal secretions, feces and blood. Infections either occur through direct contact with these bodily fluids, or by contact with contaminated surfaces. Flu viruses can remain infectious for over 30 days at 0°C (32°F) and about one week at human body temperature, although they are rapidly inactivated by disinfectants and detergents.[3,4]

Flu spreads around the world in seasonal epidemics, killing millions of people in pandemic years and hundreds of thousands in non-pandemic years. Three influenza pandemics occurred in the 20th century–each following a major genetic change in the virus–and killed tens of millions of people. Often, these pandemics result from the spread of a flu virus between animal species. Since it first killed humans in Asia in the 1990s a deadly avian strain of H5N1 has posed the greatest influenza pandemic threat. However, this virus has not yet mutated to spread easily between people.[5]

Vaccinations against influenza are most common in high-risk humans in industrialized countries[6] and farmed poultry.[7] The most common human vaccine is the trivalent ***flu vaccine*** that contains purified and inactivated material from three viral strains. Typically this vaccine includes material from two *influenza A virus* subtypes and one *influenza B virus* strain.[8] A vaccine formulated for one year may be ineffective in the following year, since the influenza virus changes every year and different strains become dominant. Antiviral drugs can be used to treat influenza, with neuraminidase inhibitors being particularly effective.

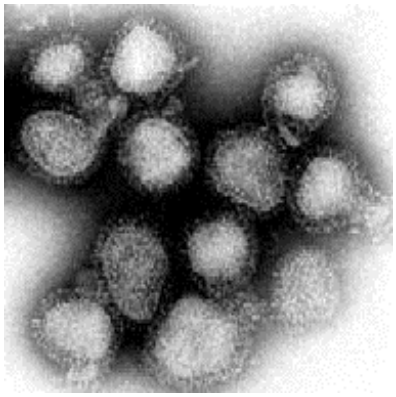


Figure 1. Influenza virus

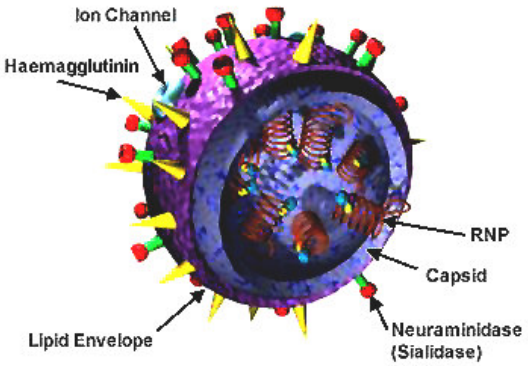
The first significant step towards preventing influenza was the discovery by Thomas Francis, Jr. in 1944 of a live vaccine for influenza. This built on work by Frank Macfarlane Burnet, who showed that the virus lost virulence when it was cultured in fertilized hen's eggs.[9] Application of this observation by Francis allowed his group of researchers at the *University of Michigan* to develop the first *flu vaccine*, with support from the U.S. army.[10] The U.S. army was deeply involved in this research due to its experience of influenza in World War I, when thousands of troops were killed by the virus in a matter of months.[11]

The influenza virus is an RNA virus of the family *Orthomyxoviridae*, which comprises the *influenzaviruses*, *Isavirus* and *Thogotovirus*. There are three types of influenza virus: *Influenzavirus A*, *Influenzavirus B* or *Influenzavirus C*. *Influenza A* and *C* infect multiple species, while *influenza B* almost exclusively infects humans.[12]

The type A viruses are the most virulent human pathogens among the three influenza types and causes the most severe disease. The *Influenza A* virus can be subdivided into different

serotypes based on the antibody response to these viruses.[12] The serotypes that have been confirmed in humans, ordered by the number of known human pandemic deaths, are

- **H1N1** caused "*Spanish Flu*".
- **H2N2** caused "*Asian Flu*".
- **H3N2** caused "*Hong Kong Flu*".
- **H5N1** is a pandemic threat in 2006-7 flu season.
- **H7N7** has unusual zoonotic potential.
- **H1N2** is endemic in humans and pigs.
- **H9N2**, **H7N2**, **H7N3**, **H10N7**.



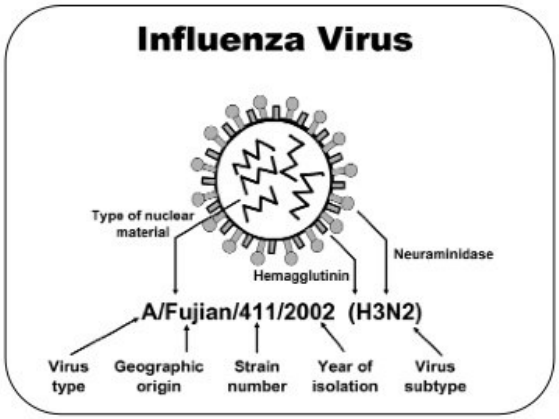


Figure 2. 3D–Influenza virus; Figure 3. CDC nip pink flu Influenza Nomenclature Diagram

Influenza B virus is almost exclusively a human pathogen, and is less common than influenza A. The only other animal known to be susceptible to influenza B infection is the seal.[13] This type of influenza mutates at a rate 2-3 times lower than type A[14] and consequently is less genetically diverse, with only one influenza B serotype.[12] As a result of this lack of antigenic diversity, a degree of immunity to influenza B is usually acquired at an early age. However, influenza B mutates enough that lasting immunity is not possible.[15] This reduced rate of antigenic change, combined with its limited host range (inhibiting cross species *antigenic shift*), ensures that pandemics of influenza B do not occur.[16]

The influenza C virus infects humans and pigs, and can cause severe illness and local epidemics.[17] However, influenza C is less common than the other types and usually seems to cause mild disease in children.[18,19]

Structure and properties:

The influenza A virus particle or *virion* is 80-120 nm in diameter and usually roughly spherical, although filamentous forms can occur.[20] Unusually for a virus, the influenza A genome is not a single piece of nucleic acid; instead, it contains eight pieces of segmented negative-sense RNA (13.5 kilobases total), which encode 11 proteins (HA, NA, NP, M1, M2, NS1, NEP, PA, PB1, PB1-F2, PB2).[21] The best-characterized of these viral proteins are *hemagglutinin* and *neuraminidase*, two large *glycoproteins* found on the outside of the viral particles. Neuraminidase is an enzyme involved in the release of progeny virus from infected cells, by cleaving sugars that bind the mature viral particles. By contrast, hemagglutinin is a lectin that mediates binding of the virus to target cells and entry of the viral genome into the target cell.[22] The hemagglutinin (HA or H) and neuraminidase (NA or N) proteins are targets for antiviral drugs.[23] These proteins are also recognised by antibodies, i.e. they are antigens.[24] The responses of antibodies to these proteins are used to classify the different serotypes of *influenza A* viruses, hence the *H* and *N* in *H5N1*.

Influenza viruses bind through *hemagglutinin* onto *sialic acid* sugars on the surfaces of *epithelial cells*; typically in the nose, throat and lungs of mammals and intestines of birds.[25] The cell imports the virus by endocytosis. In the acidic *endosome*, part of the haemagglutinin protein fuses the viral envelope with the vacuole's membrane, releasing the viral RNA (vRNA) molecules, accessory proteins and *RNA-dependent RNA transcriptase* into the cytoplasm (Stage 2).[26] These proteins and vRNA form a complex that is transported into the cell nucleus, where the RNA-dependent RNA transcriptase begins transcribing complementary positive-sense vRNA (Steps 3a and b).[27] The vRNA is either exported into the cytoplasm and translated (step 4), or remains in the nucleus. Newly-synthesized viral proteins are either secreted through the *Golgi apparatus* onto the cell surface (in the case of *neuraminidase* and *hemagglutinin*, step 5b) or transported back into the nucleus to bind vRNA and form new viral genome particles (step 5a). Other viral proteins have multiple actions in the host cell, including degrading cellular mRNA and using the released nucleotides for vRNA synthesis and also inhibiting translation of host-cell mRNAs.[28]

The virus attacks the respiratory tract, is transmitted from person to person by saliva droplets expelled by coughing or sneezing, and can cause the following symptoms:

- Body aches, especially joints and throat
- Coughing and sneezing
- Extreme coldness and fever

- Fatigue
- Headache
- Irritated watering eyes
- Nasal congestion
- Nausea and vomiting
- Reddened eyes, skin (especially face), mouth, throat and nose.

Epidemic and pandemic spread:

New influenza viruses are constantly being produced by mutation or by reassortment.[12] Mutations can cause small changes in the hemagglutinin and neuraminidase antigens on the surface of the virus. This is called *antigenic drift*, which creates an increasing variety of strains over time until one of the variants eventually achieves higher fitness, becomes dominant, and rapidly sweeps through the human population often causing an epidemic.[29] In contrast, when influenza viruses re-assort, they may acquire new antigens - for example by reassortment between avian strains and human strains. This is called *antigenic shift*. If a human influenza virus is produced with entirely novel antigens, everybody will be susceptible and the novel influenza will spread uncontrollably, causing a pandemic.[30]

Treatment

People with the flu are advised to get plenty of rest, drink a lot of liquids, avoid using alcohol and tobacco and, if necessary, take medications such as *acetaminophen* (paracetamol) to relieve the fever and muscle aches associated with the flu. Children and teenagers with flu symptoms (particularly fever) should avoid taking *aspirin* during an influenza infection (especially *influenza type B*) because doing so can lead to *Reye syndrome*, a rare but potentially fatal disease of the liver.[31]

Since influenza is caused by a virus, antibiotics have no effect on the infection, but may be prescribed if the influenza causes secondary infections such as *bacterial pneumonia*. Antiviral medication is sometimes effective, but viruses can develop resistance to the standard antiviral drugs. The *antiviral drugs* *amantadine* and *rimantadine* are designed to block a viral ion channel and prevent the virus from infecting cells. These drugs are sometimes effective against influenza A if given early in the infection, but are always ineffective against influenza B.[32] Measured resistance to *amantadine* and *rimantadine* in American isolates of H3N2 has increased to 91% in 2005.[33] Antiviral drugs such as

oseltamivir (trade name Tamiflu) and *zanamivir* (trade name Relenza) are *neuraminidase inhibitors* that are designed to halt the spread of the virus in the body.[34] These drugs are often effective against both influenza A and B.[32] Different strains of influenza virus have differing degrees of resistance against these antivirals and it is impossible to predict what degree of resistance a future pandemic strain might have.

Vaccination and hygiene

Vaccination against influenza with a flu vaccine is strongly recommended for high-risk groups, such as children and the elderly. These vaccines can be produced in several ways; the most common method is to grow the virus in fertilised hen eggs. After purification, the virus is inactivated (for example, by treatment with detergent) to produce an inactivated-virus vaccine. Alternatively, the virus can be grown in eggs until it loses virulence and the avirulent virus given as a live vaccine.[24] The effectiveness of these flu vaccines is variable. Due to the high mutation rate of the virus, a particular flu vaccine usually confers protection for no more than a few years. Every year, the World Health Organization predicts which strains of the virus are most likely to be circulating in the next year, allowing pharmaceutical companies to develop vaccines that will provide the best immunity against these strains.[35] Vaccines have also been developed to protect poultry from avian influenza. These vaccines can be effective against multiple strains and are used either as part of a preventative strategy, or combined with culling in attempts to eradicate outbreaks.[36]

It is possible to get vaccinated and still get influenza. The vaccine is reformulated each season for a few specific flu strains, but cannot possibly include all the strains actively infecting people in the world for that season. It takes about six months for the manufacturers to formulate and produce the millions of doses required to deal with the seasonal epidemics; occasionally, a new or overlooked strain becomes prominent during that time and infects people although they have been vaccinated (as by the H3N2 Fujian flu in the 2003-2004 flu season).[37] It is also possible to get infected just before vaccination and get sick with the very strain that the vaccine is supposed to prevent, as the vaccine takes about two weeks to become effective.[38]

Good personal health and hygiene habits are reasonably effective in avoiding and minimizing influenza. Since influenza spreads through aerosols and contact with

contaminated surfaces, it is important to persuade people to cover their mouths while sneezing and to wash their hands regularly.[39]

The primary method for the treatment of influenza is to use the influenza vaccine as a prophylaxis. The upper respiratory mucosa is the primary site of influenza virus infection.[40] This site provides a means of protection from viral infections of the respiratory tract. Possible defence mechanisms against infections involve immune competent cells responsible for humoral and cell-mediated immune responses, including IgA Ab-producing cells, helper T cells, cytotoxic T cells, and natural killer cells. However, it has been shown that vaccinations in the nasal cavity are less effective than subcutaneous ones and may not provide sufficient immunostimulation. In order to overcome these problems, using adjuvants for enhancement of the local mucosal immune response has been reported.[41]

Kampo medicine, 'Sho-seiryu-to' was found to possess potent adjuvant activity by oral administration on nasal influenza infection and nasal influenza vaccination.[42] Pinellic acid (9*S*, 12*S*, 13*S*-trihydroxy-10*E*-octadecenoic acid, Fig. 4) was isolated from the tuber of P. *ternata*, one of eight component herbs of the Kampo formula, Sho-seiryu-to (SST).[43] Pinellic acid is a novel and potentially useful oral adjuvant when used in conjunction with intranasal inoculation of influenza HA vaccines.[43a]

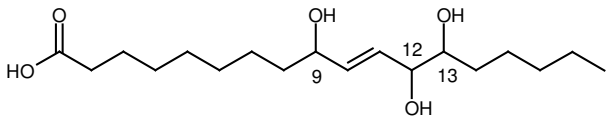


Figure 4. Structure of pinellic acid **1**

Oral administration of pinellic acid (1 Ag) to BALB/c mice given primary and secondary intranasal inoculations of influenza HAvaccine (1 Ag) enhanced antiviral IgA antibody (Ab) titers 5.2- and 2.5-fold in nasal and bronchoalveolar washes, respectively, and antiviral IgG Ab titers 3-fold in bronchoalveolar wash and serum. Intranasal administration of pinellic acid (1 Ag) with influenza HA vaccine (1 Ag) slightly enhanced antiviral IgG Ab titers in bronchoalveolar wash and serum but not antiviral IgA Ab titers in nasal and bronchoalveolar washes. Pinellic acid showed no hemolytic activity.[38a] Among the series of pinellic acid isomers, the (9*S*,12*S*,13*S*)-compound, which is a natural product, exhibited the most potent adjuvant activity.[44]

Effects of pinellic acid on hemolysis:

Some fatty acids are known to have hemolytic activity. Therefore, hemolytic activity of the pinellic acid was measured using sheep red blood cells. Pinellic acid showed no hemolytic activity at final concentrations up to 200 Ag/ml (highest concentration tested).

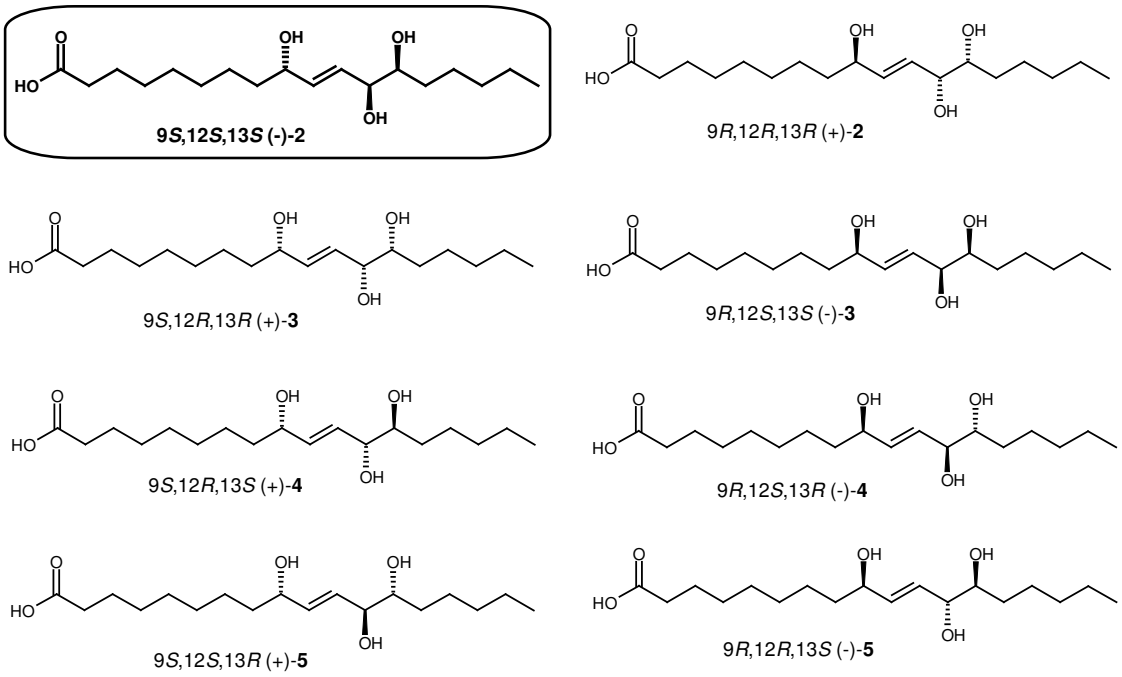
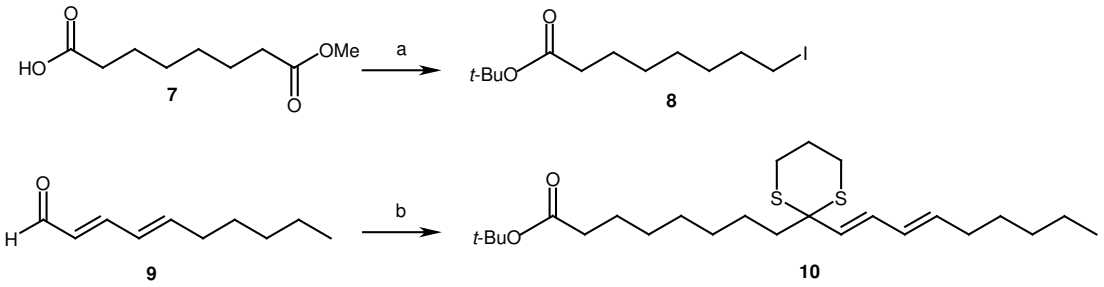


Figure 5.

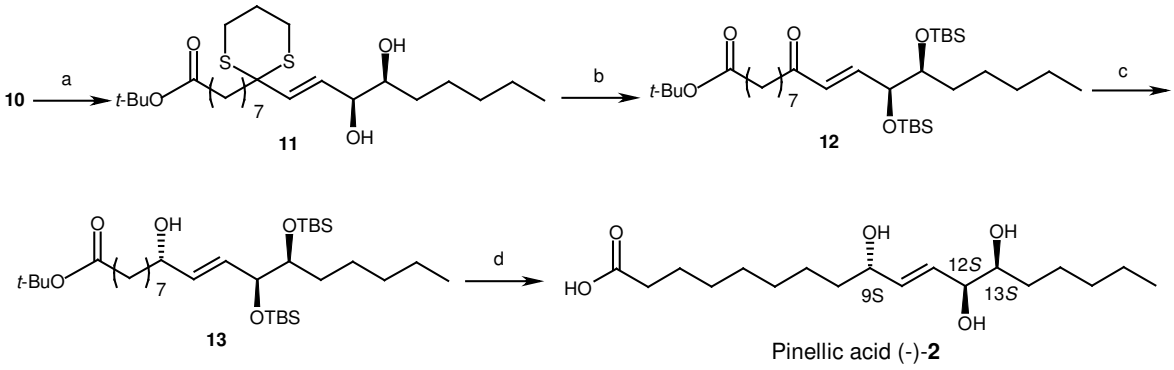
3.3.2. Review of Literature

So far only one total synthesis of pinellic acid has been reported in the literature. Ōmura *et al*. reported the first synthesis of pinellic acid **1** and determined its absolute configuration by synthesizing all isomers *via* regioselective Sharpless asymmetric dihydroxylation and stereoselective reduction.[45] The synthesis of C18 skeleton **10** utilizing dithiane coupling[46] is shown in Scheme 1.

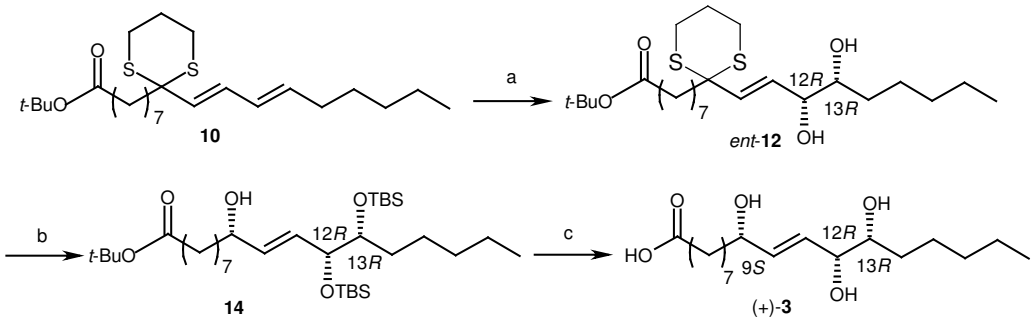


Scheme 1. *Reagents and conditions*: (a) (i) $(Boc)_2O$, DMAP, *t*-BuOH, rt, 1 h (82%); (ii) 0.1 N NaOH in THF/MeOH/H_2O (3:1:1), rt, 28 h; (iii) BH_3.THF, THF, 0 °C to rt, 24 h; (iv) I_2, PPh_3, imidazole, CH_2Cl_2, 0 °C to rt, 2 h; (b) (i) 1,3-propanedithiol, $BF_3.OEt_2$, CH_2Cl_2, 0 °C to rt, 10 h (96%); (ii) *n*-BuLi, THF, –78 °C, 1 h, then **8**, –78 °C, 1 h (85%).

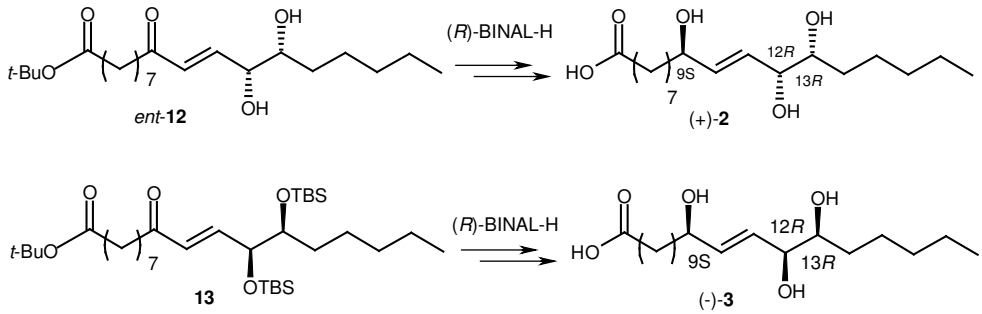
The regioselective asymmetric dihydroxylation of **10** using AD-mix containing $(DHQ)_2PHAL$ gave C12–C13 *syn*-diol (–)-**11** in disappointing yield and enantiomeric excess (55%, 80% ee). However, the use of modified Sharpless ligand [(DHQ)PHAL(DHQ)Me+.I⁻][47] for the hydroxylation resulted in 64% yield with 95% ee. The protection of the diol **11** with excess TBSOTf followed by the deprotection of dithioacetal provided enone (–)-**12**. The stereoselective reduction of enone **12** with (*S*)-BINAL-H[48] provided the (9*S*)-alcohol (diastereoselectivity >20:1). The desilylation of **13** with TBAF followed by hydrolysis of the *tert*-butyl ester with a highly concentrated alkaline solution afforded (–)-**2** (Scheme 2, 3 and 4).



Scheme 2. *Reagents and conditions*: (a) (DHQ)PHAL(DHQ)Me^+.I⁻, $K_3[Fe(CN)_6]$, K_2CO_3, $K_2OsO_4.2H_2O$, methanesulfonamide, *t*-BuOH/H_2O (1:1), 0 °C, 41 h, 64%, 95% ee; (b) (i) TBSOTf, 2,6-lutidine, –78 °C, 30 min., 89%; (ii) $Hg(ClO_4)_2$, $CaCO_3$, THF/H_2O (5:1), rt, 30 min., 83%; (c) (i) (*S*)-BINAL-H, THF, –78 °C, 1 h (diastereoselectivity >20:1); (d) (i) TBAF, THF, 70 °C, 3 h; (ii) 2.0 N KOH in EtOH/H_2O (5:1), rt, 46 h, 82%.

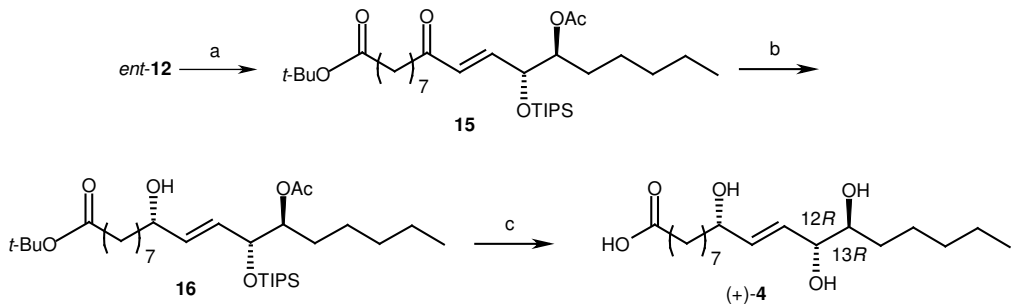


Scheme 3. *Reagents and conditions*: (a) $(DHQD)_2PHAL$, $K_3[Fe(CN)_6]$, K_2CO_3, $K_2OsO_4.2H_2O$, methanesulfonamide, *t*-BuOH/H_2O (1:1), 0 ^oC, 73 h, 75%, 92% ee; (b) TBSOTf, 2,6-lutidine, –78 ^oC, 30 min., 87%; (c) (i) $Hg(ClO_4)_2$, $CaCO_3$, THF/H_2O (5:1), rt, 30 min., 83%; (ii) (*S*)-BINAL-H, THF, –78 ^oC, 1 h (diastereoselectivity >20:1); (iii) TBAF, THF, 70 ^oC, 3 h; (iv) 2.0 N KOH in EtOH/H_2O (5:1), rt, 46 h, 76%.

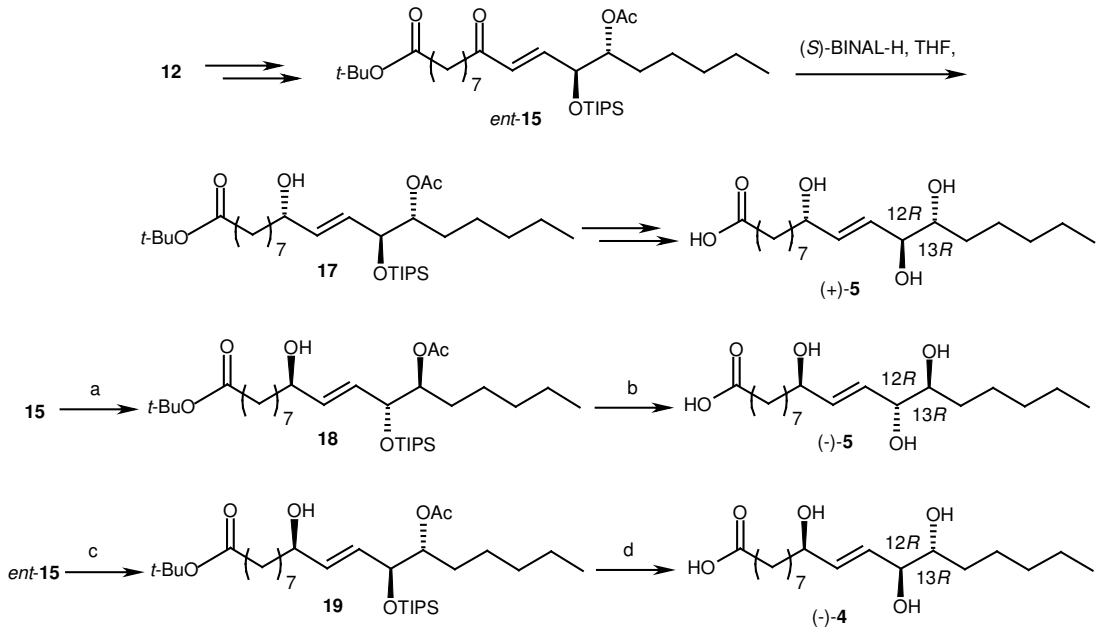


Scheme 4.

The C12–C13 *anti*-isomers were constructed *via* regioselective protection of the C12 hydroxy group with bulky TIPS in the C12–C13 *syn*-diol followed by inversion of the C13 hydroxy group by Nakata's method,[49] using a monochloromethanesulfonyl group ($ClSO_2CH_2Cl$, pyridine) and by treatment with CsOAc, gave the protected C12–C13 anti-diol **15** in good yield (Scheme 5 and 6).



Scheme 5. *Reagents and conditions*: (a) (i) TIPSOTf, 2,6-lutidine, CH_2Cl_2, –78 °C, 8 h (90%); (ii) $ClCH_2SO_2Cl$, pyridine, 0 °C, 2 h; (iii) CsOAc, 18-crown-6, benzene, 80 °C, 20 h (83%); (iv) $Hg(ClO_4)_2$, $CaCO_3$, THF/H_2O (5:1), rt, 5 min (97%); (b) (*S*)-BINAL-H, THF, –78 °C, 90 min (99%, dr >20:1); (c) (1) 1.0 N KOH in EtOH/H_2O (4:1), rt, 5 days; (2) TBAF, THF, rt, 45 h (94%).



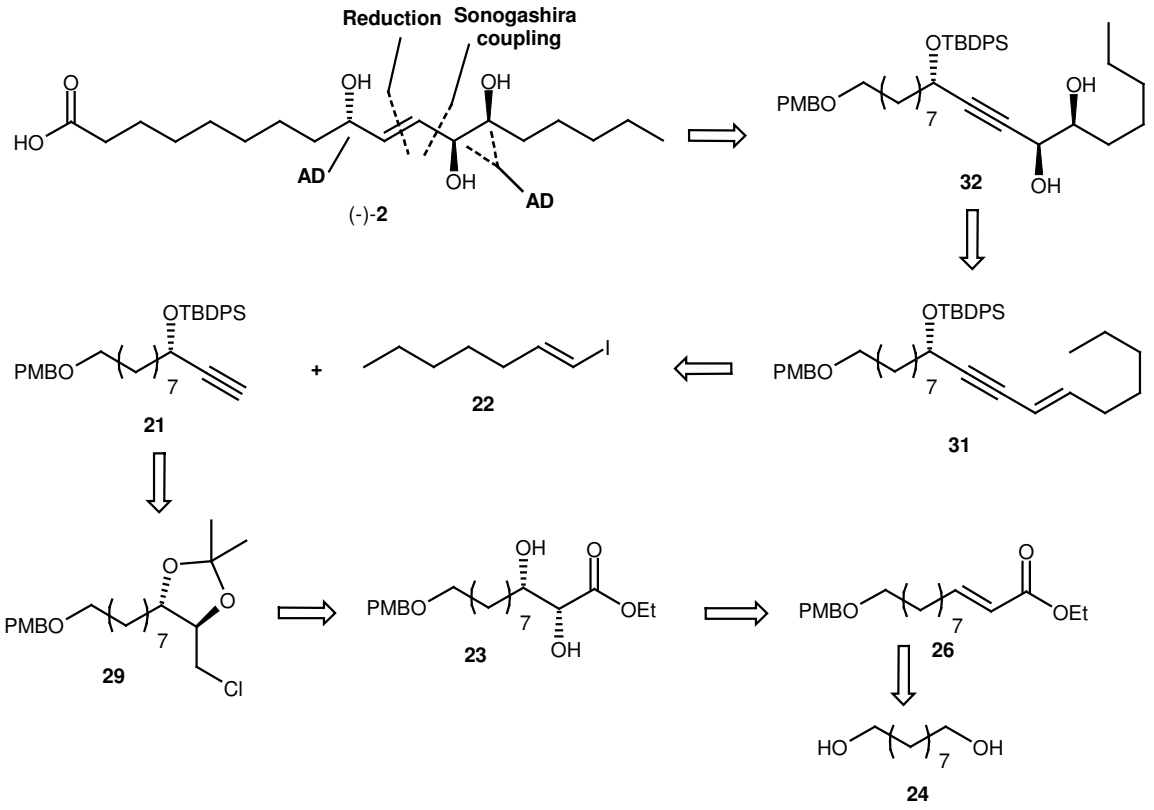
Scheme 6. *Reagents and conditions*: (a) (*R*)-BINAL-H, THF, –78 °C, 1 h, 82%, dr 13:1; (b) (i) 1.0 N KOH in EtOH/H_2O (4:1), rt, 5 days; (ii) TBAF, THF, 45 h, 94%; (c) (*R*)-BINAL-H, THF, –78 °C, 1 h, 98%, dr >20:1; (d) (i) 1.0 N KOH in EtOH/H_2O (4:1), rt, 5 days; (ii) TBAF, THF, 45 h, 18%.

3.3.3. PRESENT WORK

Objective

In foregoing section we have described the synthesis of microcarpalide and sapinofuranone B using AD and Sonogashira coupling reaction as the key steps. It was further planned to extend the same protocol towards the total synthesis of yet another interesting molecule (–)-pinellic acid.

Scheme 7 depict the synthetic route to pinellic acid (–)-**2** by employing the Sharpless asymmetric dihydroxylation as the source of chirality from the commercially available starting material 1,9-nonanediol **24**. We envisioned that the 12*S*,13*S syn* diol **32** could be prepared from 1,3-enyne **31**, which in turn could be prepared form acetylene **21** by Sonogashira coupling with vinyliodide **22**. The acetylene **21** could be obtained from the chloro compound **29**, through base induced elimination. In this strategy, 9*S* hydroxy could be obtained through Sharpless asymmetric dihydroxylation of olefin **26**, which in turn could be prepared from 1,9-nonane diol **24**.



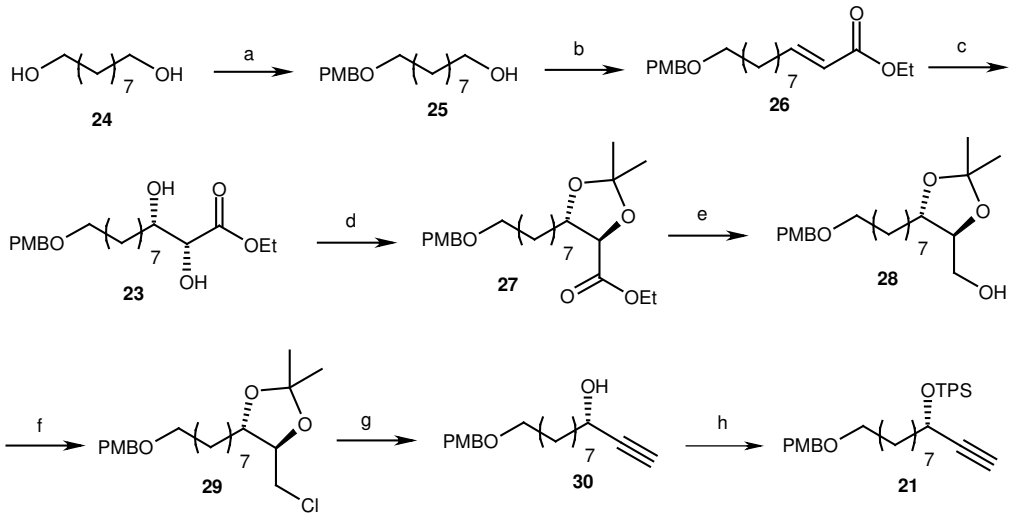
Scheme 7. Retrosynthetic analysis for pinellic acid (–)-**2**.

3.3.4. Results and Discussion:

Synthesis of acetylene fragment 21

The synthesis of pinellic acid (–)-**2** started from commercially available 1,9-nonane diol **24** as illustrated in Scheme 8. Thus, selective mono hydroxyl protection of **24** with *p*-methoxybenzyl bromide in the presence of NaH gave monoprotected diol **25** in 95% yield. The ^{1}H NMR spectrum gave benzylic protons at δ 4.48 (singlet, two protons) and aromatic protons at δ 7.26 (doublet) and 6.88 (doublet) with coupling constant J = 10.0 Hz. The IR spectrum gave hydroxyl absorption at 3400 cm^{-1}. Compound **25** was oxidized to the corresponding aldehyde under Swern conditions[50] and subsequently treated with (ethoxycarbonylmethylene)-triphenylphosphorane in benzene under reflux conditions to furnish the *trans*-olefin **26** in 91% yield. The IR spectrum of **26** showed the ester carbonyl absorption at 1724 cm^{-1} and olefin C=C stretching at 1654 cm^{-1}. The ^{1}H NMR spectrum gave olefin protons at δ 6.98 (doublet of triplet) and 5.90 (doublet) with the coupling constant J = 15.0 Hz indicating *trans*-olefin. The olefin **26** was treated with osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of $(DHQ)_2PHAL$ ligand under AD conditions[51] to give the diol **23** in 96% yield with 99% ee.[52] The IR spectrum gave hydroxyl absorption at 3440-3300 cm^{-1} and ester carbonyl at 1736 cm^{-1}. The ^{1}H NMR indicated absence of olefinic protons. The chiral protons appeared at δ 4.06-4.16 (multiplet) and 3.90 (doublet). The chiral carbons appeared at δ 72.3 and 70.0 in the ^{13}C NMR spectrum. Treatment of diol **23** with 2,2-dimethoxy propane in the presence of *p*-TSA gave compound **27**. The IR spectrum of **27** indicated absence of hydroxyl groups. The acetonide methyl protons appeared at δ 1.46 (singlet) and 1.49 (singlet) in the ^{1}H NMR spectrum and typical quaternary carbon of acetonide appeared at 110.5 in the ^{13}C NMR spectrum. Reduction of **27** with DIBAL-H furnished the alcohol **28** in excellent yield. The IR spectrum of **28** gave hydroxyl absorption at 3440 cm^{-1} and the ester carbonyl group was absent. The alcohol **28** was converted to chloride **29** in 89% yield by Mitsunobu reaction.[53] The product **29** was reliably confirmed by the analysis of the ^{1}H NMR, ^{13}C NMR and IR spectra. In the ^{1}H NMR spectrum of **29,** upfield shift of peaks belonging to methylene protons (CH_2Cl) compared to that of **28** was noticed. Propargylic alcohol **30** was obtained by treatment of **29** with *n*-BuLi in the presence of HMPA[54] in 82% yield. The IR spectrum showed hydroxyl absorption at 3400-3200 cm^{-1} and C≡C absorption at 2100 cm^{-1}. The presence of acetylenic

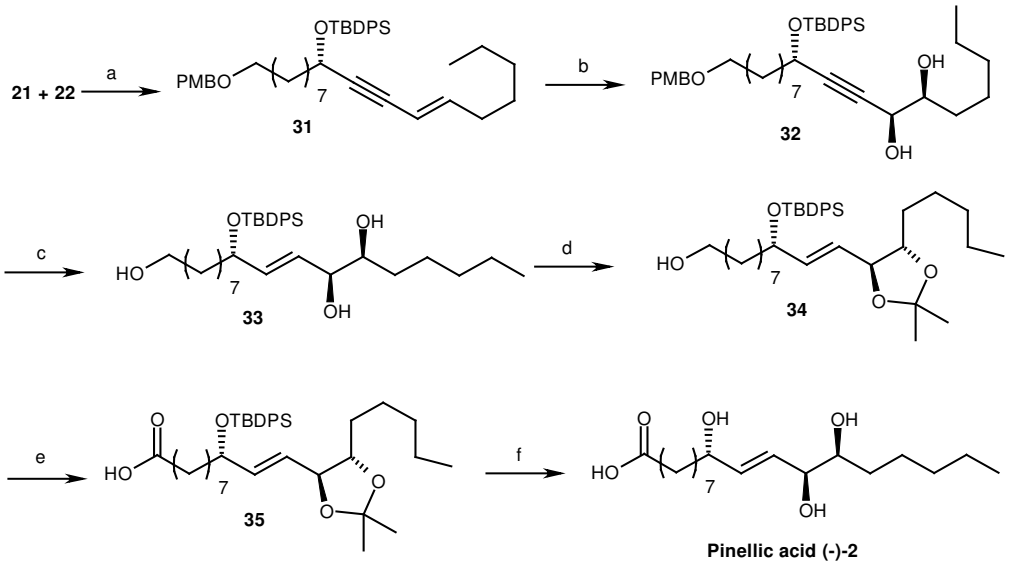
group with its proton resonating at 2.48 ppm as a doublet in the ^{1}H NMR spectrum confirmed that the substrate had indeed undergone elimination and chiral proton appeared at δ 4.39 (doublet of doublet) with coupling constant 6.6 Hz. The free hydroxy group of **30** was protected with TBDPSCl to furnish compound **21**.



Scheme 8. *Reagents and conditions*: (a) (i) *p*-$CH_3OC_6H_4CH_2Br$, NaH, dry DMF, cat. TBAI, 0 ^oC to rt, 1 h, 95%; (b) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^oC to -60 ^oC; (ii) $Ph_3P{=}CHCO_2Et$, benzene, reflux, 4 h, 91%; (c) $(DHQ)_2PHAL$, K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, OsO_4 (0.1M sol. in toluene), *t*-BuOH/H_2O (1:1), 0 ^oC, 24 h, 96%; (d) *p*-TSA, 2,2-DMP, CH_2Cl_2, overnight, 96%; (e) DIBAL-H, CH_2Cl_2, 0 ^oC to rt, 2 h, 96%; (f) *N*-chlorosuccinimide, PPh_3, CH_2Cl_2, 0 ^oC to rt, 3 h, 89%; (g) *n*-BuLi, HMPA, THF, –42 °C to rt, 30 min, 82%; (h) TBDPSCl, imidazole, CH_2Cl_2, 0 ^oC to rt, overnight, 98%.

In order to generate the *trans*-olefin to execute the second Sharpless asymmetric dihydroxylation, Sonogashira coupling[55] was employed in the next step. Thus, the coupling of **21** with *trans*-vinyliodide **22** with $Pd(PPh_3)_2Cl_2$ and CuI in triethylamine furnished the 1,3-enyne product **31** in excellent yield. The ^{1}H NMR spectrum gave olefin protons at δ 5.38 (doublet of doublet) with the coupling constant J = 15.8 Hz indicating *trans*-olefin. Enantioselective AD reaction of 1,3-enyne **31** under standard conditions gave the acetylene diol **32** in good yield with high diastereomeric excess (de = >96%) as judged by ^{1}H and ^{13}C NMR spectral analysis. The IR spectrum of **32** gave hydroxyl absorption at 3400 cm^{-1}.

Reduction of alkyne **32** to the *E*-alkene and concomitant removal of the PMB group proceeded smoothly under Birch conditions using Na/liq NH_3[17] to afford **33** in 89% yield.



Scheme 9. *Reagents and conditions*: (a) $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, **22**, 6 h, 86%; (b) $(DHQ)_2PHAL$, K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, OsO_4 (0.1M in toluene), *t*-BuOH/H_2O 1:1, 0 ^oC, 24 h, 91%; (c) Na/liq NH_3, THF, -40 °C, 89%; (d) *p*-TSA, 2,2-DMP, CH_2Cl_2, overnight, 92%; (e) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^oC to -60 ^oC; (ii) $NaClO_2$, DMSO, NaH_2PO_4, rt, overnight, 81%; (f) HCl (cat), MeOH, rt, overnight, 78%.

The ^1H NMR spectrum gave olefinic protons at δ 5.64 (doublet of doublet) and 5.85 (doublet of doublet) with the coupling constant J = 15.5 Hz and PMB group protons were found to be misiing, which confirmed the presence of *trans*-olefin and deprotection of PMB group. ^{13}C NMR showed that presence of olefin carbons at δ 131.7 and 127.4. The diol **33** was protected as its isopropylidene derivative in the presence of 2,2-dimethoxypropane and catalytic amount of *p*-TSA to furnish compound **34** in good yield. The acetonide methyl protons appeared at δ 1.41 (singlet) and 1.45 (singlet) in the ^1H NMR spectrum and the typical quaternary carbon of acetonide appeared at δ 108.6 in the ^{13}C NMR spectrum. Oxidation of primary alcohol in **34** to the corresponding aldehyde under IBX conditions and further oxidation using $NaClO_2$ in DMSO under buffered conditions[57] afforded the acid **35**. Finally, acetonide and TBDPS groups were deprotected under acidic conditions (catalytic

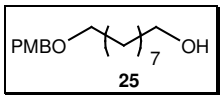
amount of HCl in MeOH) to furnish the target molecule (–)-**2** in 88% yield, $[\alpha]_D^{25}$: –7.9 (*c* 0.30, MeOH); (lit.[44] $[\alpha]_D^{28}$ –8.1 (*c* 0.32, MeOH). The IR spectrum of (–)-**2** showed presence of hydroxyl groups at 3372 cm^{-1} and acid carbonyl at 1695 cm^{-1}. The ^1H NMR spectrum of (–)-**2** gave *trans*-olefinic protons at δ 5.65 (doublet of doublet) and 5.72 (doublet of doublet) with coupling constant 15.6 Hz, chiral protons at δ 3.41 (multiplet), 3.91 (doublet of doublet) with coupling constant 5.5 and 5.0 Hz, 4.05 (multiplet). The ^{13}C NMR spectrum gave chiral carbons at δ 73.0, 75.8 and 76.4; olefinic protons at δ 136.6 and 131.2; and acid carbonyl at δ 177.6. The physical and spectroscopic data of (–)-**2** were identical with those reported.[44,45]

3.3.5. Conclusion

In conclusion, a convergent and efficient total synthesis of pinellic acid (–)-**2**, with high enantioselectivities has been developed in which all the stereocenters were established by Sharpless asymmetric dihydroxylation. Notable features of this approach include Sonogashira coupling, Birch reduction to establish the C10-C11 *trans*-olefin geometry. We believe our new approach is thus the most efficient route to pinellic acid (–)-**2**, reported so far and would permit maximum variability in product structure with regard to stereochemical diversity which is particularly important to the syntheses of other biologically active compounds for the studies of structure activity relationship.

3.3.6. Experimental Section

9-(4-Methoxybenzyloxy)nonan-1-ol (25).



25

To a solution of 1,9-nonanediol **24** (8.0 g, 49.92 mmol) in dry DMF (200 mL) was added sodium hydride (50%, 2.64 g, 77.70 mmol) at 0 ^oC. The reaction mixture was then stirred at room temperature for 30 min after which it was again cooled to 0 ^oC. To this was added slowly *p*-methoxybenzyl bromide (10.04 g, 49.92 mmol) and tetra *n*-butylammonium iodide (1.84 g, 4.99 mmol) with further stirring for 1 h at the same temperature. The reaction mixture was quenched with addition of cold water at 0 ^oC. The two phases were separated and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic

layers were washed with water (3 x 100 mL), brine, dried (Na_2SO_4) and concentrated. The residual oil was purified by silica gel column chromatography using petroleum ether/EtOAc (8:2) as eluent to furnish the mono-PMB protected alcohol **25** as colourless oil.

Yield: 13.31 g (95%).

Mol. Formula: $C_{17}H_{28}O_3$

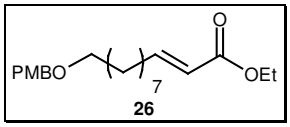
IR (neat, cm^{-1}): ν_{max} 3400, 2937, 2863, 1612, 1513, 1248, 1174, 1097.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.27-1.42 (m, 10H), 1.52-1.64 (m, 4H), 3.49 (t, *J*=5.0 Hz, 2H), 3.62 (t, *J*=5.0 Hz, 2H), 3.81 (s, 3H), 4.48 (s, 2H), 6.88 (d, *J*=10.0 Hz, 2H), 7.26 (d, *J*=10.0 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9, 26.1, 27.8, 28.9, 29.1, 29.6, 55.1, 62.2, 69.9, 72.5, 113.8, 129.2, 130.4, 159.2.

Analysis: Calcd.: C, 72.82; H, 10.06%; **Found:** C, 72.99; H, 9.87%.

(*E*)-Ethyl 11-(4-methoxybenzyloxy)undec-2-enoate (26).



26

To a solution of oxalyl chloride (4.75 g, 37.44 mmol) in dry CH_2Cl_2 (100 mL) at -78 ^oC was added dropwise dry DMSO (5.85 g, 5.31 mL, 74.89 mmol) in CH_2Cl_2 (20 mL). After 30 min, alcohol **25** (7.0 g, 24.96 mmol) in CH_2Cl_2 (20 mL) was added over 10 min giving copious white precipitate. After stirring for 1 h at -78 ^oC the reaction mixture was brought to -60 ^oC and Et_3N (10.10 g, 13.92 mL, 99.85 mmol) was added slowly and stirred for 30 min allowing the reaction mixture to warm to room temperature. The reaction mixture was then diluted with water (150 mL) and CH_2Cl_2. The organic layer was separated and washed with water and brine, dried (Na_2SO_4) and passed through short pad of celite. The filtrate was concentrated to give the aldehyde (9.86 g, 95%) as pale yellow oil, which was used as such for the next step without purification.

To a solution of (ethoxycarbonylmethylene)triphenyl-phosphorane (10.51 g, 30.17 mmol) in dry benzene (150 mL) was added a solution of the above aldehyde in dry benzene (100 mL). The reaction mixture was refluxed for 6 h. It was then concentrated and purified by silica gel column chromatography using petroleum ether/EtOAc (8.5:1.5) as eluent to afford the α,β-unsaturated ester **26** as a pale yellow liquid.

Yield: 7.92 g (91%).

Mol. Formula: $C_{21}H_{32}O_4$

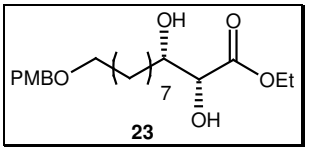
IR (neat, cm^{-1}): ν_{max} 2956, 2858, 1724, 1654,1038, 1300, 1204, 1100.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30-1.37 (m, 11H), 1.48-1.68 (m, 4H), 2.28 (q, *J*=7.0 Hz, 2H), 3.48 (t, *J*=6.0 Hz, 2H), 3.85 (s, 3H), 4.25 (q, *J*=8.0 Hz, 2H), 4.48 (s, 2H), 5.90 (d, *J*=15.0 Hz, 1H), 6.91 (d, *J*=8.0 Hz, 2H), 6.98 (dt, *J*=15.0, 10.0 Hz, 1H), 7.30 (d, *J*=8.0 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 26.0, 27.8, 28.9, 29.1, 29.6, 32.0, 54.9, 59.9, 69.9, 72.3, 113.5, 121.1, 128.9, 130.6, 149.1, 158.9, 166.5.

Analysis: Calcd.: C, 72.38; H, 9.26%; **Found:** C, 72.52; H, 9.11%.

(2*R*,3*S*)-Ethyl11-(4-methoxybenzyloxy)-2,3-dihy-droxyundecanoate (23).



23

To a mixture of $K_3Fe(CN)_6$ (17.01 g, 51.65 mmol), K_2CO_3 (7.14 g, 51.65 mmol) and $(DHQ)_2PHAL$ (134 mg, 1 mol%), in *t*-BuOH-H_2O (1:1, 175 mL) cooled at 0 ^oC was added OsO_4 (0.69 mL, 0.1 M solution in toluene, 0.4 mol%) followed by methanesulfonamide (1.64 g, 17.22 mmol). After being stirred for 5 min at 0 ^oC, the olefin **26** (6.0 g, 17.22 mmol) was added in one portion. The reaction mixture was stirred at 0 ^oC for 24 h and then quenched with solid sodium sulfite (25 g). The stirring was continued for an additional 45 min, and then the solution was extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with 10% KOH, and brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (3:2) as eluent gave the diol **23** as a colourless syrupy liquid.

Yield: 6.32 g (96%).

Mol. Formula: $C_{21}H_{34}O_6$

$[\alpha]_D^{25}$: –6.7 (*c* 1.7, $CHCl_3$)

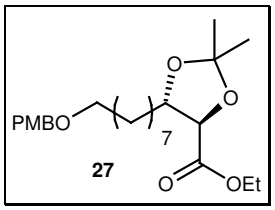
IR (neat, cm^{-1}): ν_{max} 3440, 2938, 2864, 1736, 1612, 1513, 1248, 1130, 1032.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.25-1.36 (m, 13H), 1.50-1.74 (m, 4H), 2.51 (br s, 2H), 3.46 (t, *J*=6.6 Hz, 2H), 3.82 (s, 3H), 3.90 (d, *J*=6.6 Hz, 1H), 4.06-4.16 (m, 1H), 4.32 (q, *J*=7.0 Hz, 2H), 4.46 (s, 2H), 6.93 (d, *J*=8.5 Hz, 2H), 7.31 (d, *J*=8.5 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 25.5, 26.0, 29.2, 29.3, 29.5, 33.5, 55.0, 61.6, 70.0, 72.3, 73.0, 73.1, 113.6, 128.9, 130.7, 158.9, 173.4.

Analysis: Calcd.: C, 65.94; H, 8.96%; **Found:** C, 66.09; H, 8.81%.

(4*S*,5*S*)-Ethyl-5-(8-(4-methoxybenzyloxy)octyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (27).



27

To a solution of the diol **26** (5.0 g, 13.07 mmol), *p*-TSA (100 mg) in CH_2Cl_2 (100 mL) was added 2,2-dimethoxypropane (2.04 g, 19.61 mmol) and reaction mixture stirred overnight at room temperature. Solid $NaHCO_3$ (1 g) was added and mixture again stirred for 30 min. The reaction mixture was filtered through a pad of neutral alumina and filtrate concentrated. Silica gel column chromatography using petroleum ether/EtOAc (9:1) as eluent gave **27** as a colourless liquid.

Yield: 5.19 g (94%).

Mol. Formula: $C_{24}H_{38}O_6$

$[\alpha]_D^{25}$: –23.1 (*c* 1.7, $CHCl_3$)

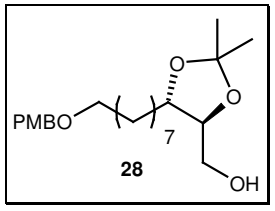
IR (neat, cm^{-1}): ν_{max} 2864, 1736, 1612, 1513, 1248, 1130, 1032.

^{1}H NMR (200 MHz, $CDCl_3$): 1.29-1.40 (m, 13H), 1.46 (s, 3H), 1.49 (s, 3H), 1.56-1.63 (m, 2H), 1.66-1.80 (m, 2H), 3.45 (t, *J*=6.6 Hz, 2H), 3.82 (s, 3H), 4.11-4.14 (m, 2H), 4.25 (q, *J*=7.32 Hz, 2H), 4.45 (s, 2H), 6.91 (d, *J*=8.8 Hz, 2H), 7.30 (d, *J*=8.8 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.8, 25.4, 25.6, 25.9, 29.2, 29.3, 29.6, 54.8, 60.9, 69.3, 72.3, 78.7, 110.5, 113.5, 128.8, 130.3, 158.9, 172.5.

Analysis: Calcd.: C, 68.22; H, 9.06%; **Found:** C, 68.01; H, 9.21%.

((4*S*,5*S*)-5-(8-(4-Methoxybenzyloxy)octyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (28).



28

To a solution of **27** (5.0 g, 11.83 mmol) in dry CH_2Cl_2 (80 mL) at 0 ^oC was added dropwise DIBAL-H (17.74 mL, 17.74 mmol, 1.0 M in toluene) through a syringe. The reaction mixture was allowed to warm to room temperature over 2 h, then re-cooled to 0 ^oC and treated with saturated solution of sodium/potassium tartrate. The solid material was filtered through a pad of celite and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (7:3) as eluent gave **28** as a colorless oil.

Yield: 4.28 g (95%).

Mol. Formula: $C_{22}H_{36}O_5$

$[\alpha]_D^{25}$: –13.05 (*c* 1.6, $CHCl_3$).

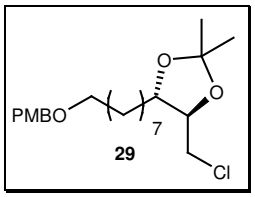
IR (neat, cm^{-1}): ν_{max} 3440, 2938, 2860, 1361, 1204, 1126, 1038.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.28-1.40 (m, 10 H), 1.41 (s, 3H), 1.42 (s, 3H), 1.51-1.63 (m, 4H), 2.18 (s, 1H), 3.46-3.54 (m, 2H), 3.61 (dd, *J*=7.5, 4.4 Hz, 1H), 3.76 (m, 2H), 3.81 (s, 3H), 3.90 (dt, *J*=7.6, 4.0 Hz, 1H), 4.44 (s, 2H), 6.89 (d, *J*=8.7 Hz, 2H), 7.25 (d, *J*=8.7 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 25.4, 25.9, 26.9, 27.2, 29.3, 29.4, 29.7, 55.2, 62.1, 69.7, 72.4, 76.7, 81.6, 108.4, 113.7, 129.1, 130.5, 159.1.

Analysis: Calcd.: C, 69.44; H, 9.54%; **Found:** C, 69.62; H, 9.33%.

(4*S*,5*R*)-4-(8-(4-Methoxybenzyloxy)octyl)-5-(chloromethyl)-2,2-dimethyl-1,3-dioxolane (29).



To a solution of alcohol **28** (5.0 g, 13.14 mmol) and Ph_3P (4.14 g, 15.77 mmol) in 50 mL of dry CH_2Cl_2 was added NCS (2.11 g, 15.77 mmol) at 0 ^oC under nitrogen. The reaction mixture was stirred at 0 ^oC for 1 h, then allowed to warm to room temperature, and stirred for 2 h. The mixture was diluted with 100 mL of hexane and passed through a pad of celite under suction to remove the precipitate of Ph_3PO. The filtrate was concentrated, and resulting residue was dissolved in 100 mL of hexane and passed through a pad of celite to remove the precipitate of Ph_3PO again. Evaporation of solvent gave **29** as colourless oil.

Yield: 4.67 g (89%).

Mol. Formula: $C_{22}H_{35}ClO_4$

$[\alpha]_D^{25}$: –5.6 (*c* 0.5, $CHCl_3$).

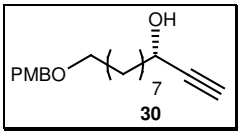
IR ($CHCl_3$, cm^{-1}): ν_{max} 2987, 2932, 2855, 1613, 1715, 1586, 1513, 1463, 1379, 1370, 1247, 1171, 1098, 1063, 1037, 821, 747.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.29 (brs, 10H), 1.40 (s, 3H), 1.41 (s, 3H), 1.52-1.61 (m, 4H), 3.42 (t, *J*=6.6 Hz, 2H), 3.57 (d, *J*=4.7 Hz, 2H), 3.79 (s, 3H), 3.84-3.88 (m, 2H), 4.42 (s, 2H), 6.88 (d, *J*=8.6 Hz, 2H), 7.23 (d, *J*=8.7 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 25.8, 26.1, 27.0, 27.5, 29.3, 29.5, 29.7, 33.5, 44.4, 55.2, 70.2, 72.5, 79.4, 80.3, 109.1, 113.8, 129.1, 130.9, 159.1.

Analysis: Calcd.: C, 66.23; H, 8.84; Cl, 8.89%; **Found:** C, 66.45; H, 8.66; Cl, 8.92%.

(*S*)-11-(4-Methoxybenzyloxy)undec-1-yn-3-ol (30).



30

To a solution of 11.43 g (70.18 mmol) of HMPA in 20 mL of dry THF was added 70.18 mL (70.18 mmol) of *n*-BuLi (a 1.0 M solution in hexane) at –42 ^oC under N_2. After 10 min, a solution of 4.0 g (10.03 mmol) of chloride 10 in 10 mL of THF was added dropwise over 5 min. 0.5 h, the reaction mixture was warmed to room temperature and stirred for another 0.5 h. Saturated aqueous NH_4Cl solution was added to quench the reaction. The product was extracted with EtOAc (3 x 30 ml), and combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (7:3) as eluent gave compound **30** as a colorless oil.

Yield: 2.50 g (82%).

Mol. Formula: $C_{19}H_{28}O_3$

$[\alpha]_D^{25}$: –1.75 (*c* 0.76, $CHCl_3$).

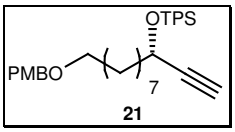
IR (neat, cm^{-1}): ν_{max} 3372, 3188, 2100, 1034, 699.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.33-1.51 (m, 10H), 1.59-1.79 (m, 4H), 1.86 (brs, 1H), 2.48 (d, *J*=2.0 Hz, 1H), 3.46 (t, *J*=6.6 Hz, 2H), 3.83 (s, 3H), 4.39 (dd, *J*=6.6, 1.8 Hz, 1H), 4.46 (s, 2H), 6.93 (d, *J*=8.2 Hz, 2H), 7.31 (d, *J*=8.5 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 24.8, 25.9, 28.9, 29.1, 29.2, 29.4, 37.4, 55.0, 61.7, 69.9, 72.2, 72.4, 85.1, 113.5, 129.1, 130.4, 158.8.

Analysis: Calcd.: C, 74.96; H, 9.27%; **Found:** C, 74.81; H, 9.39%.

((9*S*,10*E*,12*E*)-1-(4-Ethoxybenzyloxy)octadeca-10,12-dien-9-yloxy)(*tert*-butyl)diphenylsilane (21).



21

To a stirred solution of compound **30** (3.0 g, 9.85 mmol) and imidazole (1.01 g, 14.78 mmol) in dry CH_2Cl_2 (30 mL) was treated under argon with TBDPSCl (2.98 g, 10.84 mmol) at 0 ^oC and the reaction mixture was stirred overnight at the same temperature. The reaction mixture was quenched by addition of aqueous NH_4Cl (30 mL) and the mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined extracts were dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9.5:0.5) as eluent gave the compound **21** as a colourless syrupy liquid.

Yield: 5.24 g (98%).

Mol. Formula: $C_{35}H_{46}O_3Si$

$[\alpha]_D^{25}$: –22.3 (*c* 1.9, $CHCl_3$).

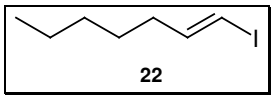
IR (neat, cm^{-1}): ν_{max} 2938, 2864, 2100, 1612, 1513, 1248, 1130, 1032.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.10 (s, 9H), 1.24 (br s, 10H), 1.53-1.72 (m, 4H), 2.33 (d, *J*=2.0 Hz, 1H), 3.44 (t, *J*=6.6 Hz, 3H), 3.82 (s, 2H), 3.35 (ddd, *J*=6.1, 1.9 Hz, 1H), 4.45 (s, 2H), 6.92 (d, *J*=8.7 Hz, 2H), 7.31 (d, *J*=8.6 Hz, 2H), 7.37-7.45 (m, 6H), 7.64-7.79 (m, 4H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 19.2, 24.3, 24.5, 26.1, 26.5, 26.8, 28.9, 29.25, 29.28, 29.65, 37.2, 38.1, 55.0, 63.6, 69.2, 70.0, 72.4, 85.0, 113.6, 117.0, 127.3, 127.5, 129.1, 129.4, 129.56, 129.65, 129.7, 130.7, 133.9, 134.7, 135.7, 135.9, 159.0.

Analysis: Calcd.: C, 77.44; H, 8.54%; **Found:** C, 77.51; H, 8.45%.

(*E*)-1-Iodohept-1-ene (22).



22

Anhydrous $CrCl_2$ (22.09 g, 179.71 mmol) is suspended in THF (150 mL) under argon atmosphere. A solution of hexanaldehyde (3.0 g, 29.95 mmol) and iodoform (23.58 g, 59.90

mmol) in THF (30 mL) is added dropwise to the suspension at 0 ^{o}C. After stirring at 0 ^{o}C for 3 h, the reaction mixture is poured into water (100 mL) and extracted with ether (3 x 100 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9.5:0.5) as eluent gave **22** with *E*:*Z* = 95:5 selectivity as a pale yellow oil.

Yield: 5.90 g, 88%

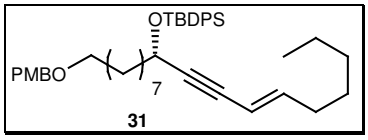
Mol. Formula: $C_7H_{13}I$

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.1 Hz, 3H), 1.26-1.43 (m, 6H), 1.62 (q, *J* = 7.4 Hz, 1H), 2.00-2.18 (m, 1H), 6.01 (d, *J* = 15.4 Hz, 1H), 6.44-6.59 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1, 22.9, 28.5, 32.1, 34.4, 141.2, 82.1.

Analysis: Calcd.: C, 37.52; H, 5.85; I, 56.63%; **Found:** C, 37.81; H, 5.72; I, 56.56%.

((*S*,*E*)-1-(4-Methoxybenzyloxy)octadec-12-en-10-yn-9-yloxy)(*tert*-butyl)diphenylsilane (31).



31

To a stirred mixture of $Pd(PPh_3)_2Cl_2$ (181 mg, 0.257 mmol), CuI (147 mg, 0.77 mmol) in Et_3N (2 mL) were added solutions of (*E*)-1-iodohept-1-ene **22** (982 mg, 4.38 mmol) in Et_3N (2 mL) and acetylene **21** (1.2 g, 3.94 mmol) in Et_3N (2 mL) under argon. After 6 h, the reaction mixture was filtered through celite and filtrate was concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) as eluent gave **31** (1.36 g, 86%) as a pale yellow oil.

Yield: 1.41 g, 86%

Mol. Formula: $C_{42}H_{58}O_3Si$

$[\alpha]_D^{25}$: +3.5 (*c* 0.51, $CHCl_3$).

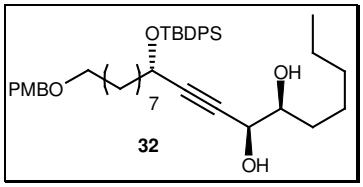
IR ($CHCl_3$, cm^{-1}): ν_{max} 2952, 2854, 1615, 1514, 1232, 1132, and 1030.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.91 (t, *J* = 6.4 Hz, 3H), 1.09 (s, 9H), 1.22-1.43 (m, 16H), 1.56-1.72 (m, 4H), 2.06 (q, *J* = 7.0 Hz, 2H), 3.44 (t, *J* = 6.6 Hz, 2H), 3.81 (s, 3H), 4.44 (s, 2H), 4.47-4.54 (m, 1H), 5.38 (dd, *J* = 15.8, 1.6 Hz, 1H), 5.76-5.97 (m, 1H), 6.91 (d, *J* = 8.7 Hz, 2H), 7.30 (d, *J* = 8.7 Hz, 2H), 7.36-7.43 (m, 6H), 7.68-7.79 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0, 19.3, 22.4, 24.9, 26.1, 27.0, 28.4, 29.2, 29.4, 29.8, 31.2, 32.9, 38.4, 55.2, 64.4, 70.2, 72.5, 83.7, 89.2, 109.1, 113.7, 134.8, 135.9, 136.1, 144.0, 159.1.

Analysis: Calcd.: C, 78.94; H, 9.15%; **Found:** C, 78.76; H, 9.33%.

(6*S*,7*S*,10*S*)-10-(*tert*-Butyldiphenylsilyloxy)-18-(4-methoxybenzyloxy)octadec-8-yne-6,7-diol (32).



32

To a mixture of $K_3Fe(CN)_6$ (1.55 g, 4.69 mmol), K_2CO_3 (649 mg, 4.69 mmol) and $(DHQ)_2PHAL$ (12 mg, 1 mol%), in *t*-BuOH-H_2O (1:1, 20 mL) cooled at 0 ^oC was added OsO_4 (0.062 mL, 0.1 M solution in toluene, 0.4 mol%) followed by methanesulfonamide (149 mg, 1.56 mmol). After being stirred for 5 min at 0 ^oC, the olefin **31** (1.0 g, 1.56 mmol) was added in one portion. The reaction mixture was stirred at 0 ^oC for 24 h and then quenched with solid sodium sulfite (25 g). The stirring was continued for an additional 45 min, and then the solution was extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (3:2) as eluent gave the diol **32** as a colourless syrupy liquid.

Yield: 941 mg, 91%

Mol. Formula: $C_{42}H_{60}O_5Si$

$[\alpha]_D^{25}$: +8.8 (*c* 0.9, $CHCl_3$).

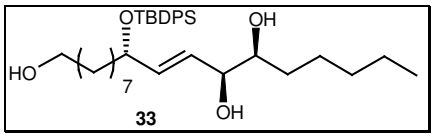
IR ($CHCl_3$, cm^{-1}): ν_{max} 3440, 2938, 2864, 1736, 1612, 1513, 1248, 1130, and 1032.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.90 (t, *J* = 6.8 Hz, 3H), 1.07 (s, 9H), 1.27 (br s, 18H), 1.57-1.73 (m, 4H), 2.34 (br s, 2H), 3.29-3.34 (m, 2H), 3.81 (s, 3H), 3.90 (t, *J* = 7.3 Hz, 2H), 4.23-4.34 (m, 1H), 4.45 (s, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 7.30 (d, *J* = 8.7 Hz, 2H), 7.35-7.49 (m, 6 H), 7.69-7.78 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 19.1, 22.5, 24.8, 25.1, 26.1, 26.8, 29.0, 29.3, 29.4, 29.7, 31.7, 32.1, 38.2, 55.2, 63.7, 65.9, 70.1, 72.4, 74.5, 83.2, 87.7, 113.7, 127.3, 127.6, 129.2, 129.6, 129.8, 130.7, 133.4, 134.1, 135.8, 135.9, 159.1.

Analysis: Calcd.: C, 74.95; H, 8.99%; **Found:** C, 75.10; H, 8.80%.

(9*S*,12*S*,13*S*,*E*)-9-(*tert*-Butyldiphenylsilyloxy)octadec-10-ene-1,12,13-triol (33).



33

To the blue solution prepared by addition of 334 mg (48.18 mmol) of lithium metal to 5 mL of liquid $EtNH_2$ was added a solution of **32** (450 mg, 0.668 mmol) in 5 ml of dry THF at -78 ^oC. After the mixture was stirred for 1 h, the reaction was quenched by addition of 2.68 g (50.14 mmol) of NH_4Cl. After removal of $EtNH_2$ by stream of N_2, the mixture was diluted with 50 mL of $CHCl_3$ and washed with water. The organic layer was dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (4:6) as eluent gave the diol **33** as a colourless syrupy liquid.

Yield: 333 mg, 90%

Mol. Formula: $C_{34}H_{54}O_4Si$

$[\alpha]_D^{25}$: +9.3 (*c* 0.42, $CHCl_3$).

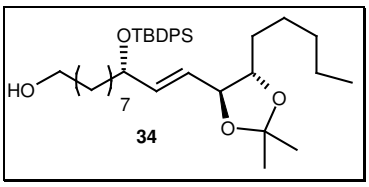
IR ($CHCl_3$, cm^{-1}): ν_{max} 3376, 1644, 1367, 1310, 1178, 1128, 1045, 980 and 721.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6.3 Hz, 3H), 1.04 (s, 9H), 1.4 (br s, 18H), 1.51-1.72 (m, 4H), 2.35 (br s, 2H), 3.38-3.48 (m, 1H), 3.61 (t, *J* = 6.6 Hz, 2H), 3.94 (t, *J* = 5.9 Hz, 1H), 4.08 (q, *J* = 6.6, 1H), 5.67 (dd, *J* = 15.5, 5.9 Hz, 1H), 5.86 (dd, *J* = 15.5, 5.6 Hz, 1H), 7.36-7.43 (m, 6H), 7.66-7.75 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0, 22.6, 25.0, 26.1, 26.9, 28.1, 27.0, 28.1, 28.9, 29.1, 29.2, 31.8, 32.8, 32.9, 55.1, 64.1, 72.1, 74.6, 75.3, 127.5, 134.0, 134.8, 135.8, 136.1, 137.8.

Analysis: Calcd.: C, 73.60; H, 9.81%; **Found:** C, 73.8; H, 9.64%.

(*S*,*E*)-9-(*tert*-Butyldiphenylsilyloxy)-11-((4*S*,5*S*)-2,2-dimethyl-5-pentyl-1,3-dioxolan-4-yl)undec-10-en-1-ol (34).



34

Yield: 5.63 g, 96%

Mol. Formula: $C_{37}H_{58}O_4Si$

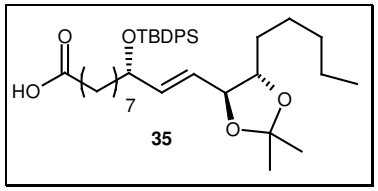
$[\alpha]_D^{25}$: +16.1 (*c* 0.57, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.90 (t, *J* = 6.3 Hz, 3H), 1.07 (s, 9H), 1.19-1.39 (br s, 18H), 1.41 (s, 3H), 1.45 (s, 3H), 1.54-1.73 (m, 4H), 2.31 (br s, 1H), 3.64 (t, *J* = 6.6 Hz, 2H), 4.09 (q, *J* = 6.6, 1H), 4.14-4.20 (m, 2H), 5.65 (dd, *J* = 15.5, 7.1 Hz, 1H), 5.85 (dd, *J* = 15.5, 5.7 Hz, 1H), 7.36-7.43 (m, 6H), 7.69-7.78 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0, 19.3, 22.5, 24.9, 26.1, 26.9, 28.3, 29.2, 29.4, 29.7, 31.2, 31.9, 32.6, 64.1, 71.7, 80.1, 81.9, 108.6, 127.4, 134.0, 134.8, 135.8, 136.1, 137.8.

Analysis: Calcd.: 74.70; H, 9.83%; **Found:** C, 75.01; H, 9.657%.

(*S*,*E*)-9-(*tert*-Butyldiphenylsilyloxy)-11-((4*S*,5*S*)-2,2-dimethyl-5-pentyl-1,3-dioxolan-4-yl)undec-10-enoic acid (35)



35

To a solution of **34** (212 mg, 0.356 mmol) in EtOAc (5 mL) in 25 mL r.b.flask was added IBX (299 mg, 1.069 mmol) in one portion and the reaction mixture was refluxed for 5 h. The reaction mixture was filtered through a pad of celite and filtrate was concentrated to give the crude aldehyde, which was used in the next step without further purification.

A solution of 79% $NaClO_2$ (48 mg, 0.53 mmol) in 1.0 mL of water was added dropwise to a stirred solution of above crude aldehyde (210 mg) in 0.5 mL of DMSO and NaH_2PO_4 (84 mg, 0.71 mmol) in 1.0 mL of water in 5 min at room temperature. The mixture was left overnight at room temperature and then 5% aqueous solution of $NaHCO_3$ was added. The aqueous phase was extracted 3 times with CH_2Cl_2 and washed with brine, dried (Na_2SO_4) and concentrated to give the acid **35**, which was used as such for the next step without purification.

Yield: 174 mg, 78%

Mol. Formula: $C_{37}H_{56}O_5Si$

$[\alpha]_D^{25}$: –9.3 (*c* 0.43, $CHCl_3$).

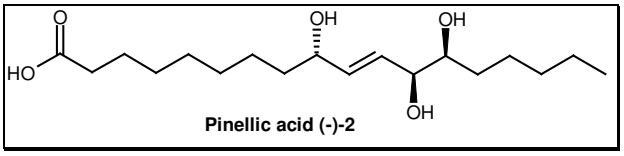
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.3 Hz, 3H), 1.07 (s, 9H), 1.19-1.39 (br s, 16H), 1.41 (s, 3H), 1.45 (s, 3H), 1.50-1.62 (m, 4H), 2.26 (t, *J* = 7.6 Hz, 2H), 3.41 (m, 1H), 4.12-4.16 (m, 2H), 5.66 (dd, *J* = 15.6, 5.2 Hz, 1H), 5.71 (dd, *J* = 15.6, 5.1 Hz, 1H); 7.36-7.43 (m, 6H), 7.69-7.78 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 177.6, 137.8, 136.1, 135.8, 134.8, 131.3, 134.0, 127.4, 108.6, 82.1, 80.3, 71.7, 38.8, 32.6, 31.9, 31.2, 29.7, 29.4, 29.2, 28.3, 26.9, 26.1, 24.9, 22.5, 19.3, 14.0.

Analysis: Calcd.: C, 72.98; H, 9.27%; **Found:** C, 73.10; H, 9.38%.

(9*S*,12*S*,13*S*)-(*E*)-9,12,13-Trihydroxy-10-octadecaenoic acid [Pinellic acid (-)-2].

To a stirred solution of compound **35** (66 mg, 0.108 mmol) in MeOH was added catalytic amount of conc. HCl at room temperature and reaction mixture was stirred for overnight at the same temperature. The mixture was filtered through celite pad and washed with MeOH and concentrated. The crude product was redissolved in CH_2Cl_2 and washed with saturated aq. $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using $CHCl_3$/MeOH (10:1) furnished the target compound pinellic acid (-)-**2** as a white solid. R_f = 0.24 (silica gel, $CHCl_3$/MeOH/AcOH = 10:1:0.1).



Pinellic acid (-)-2

Mp: 104–106 °C

Yield: 27 mg, 78%

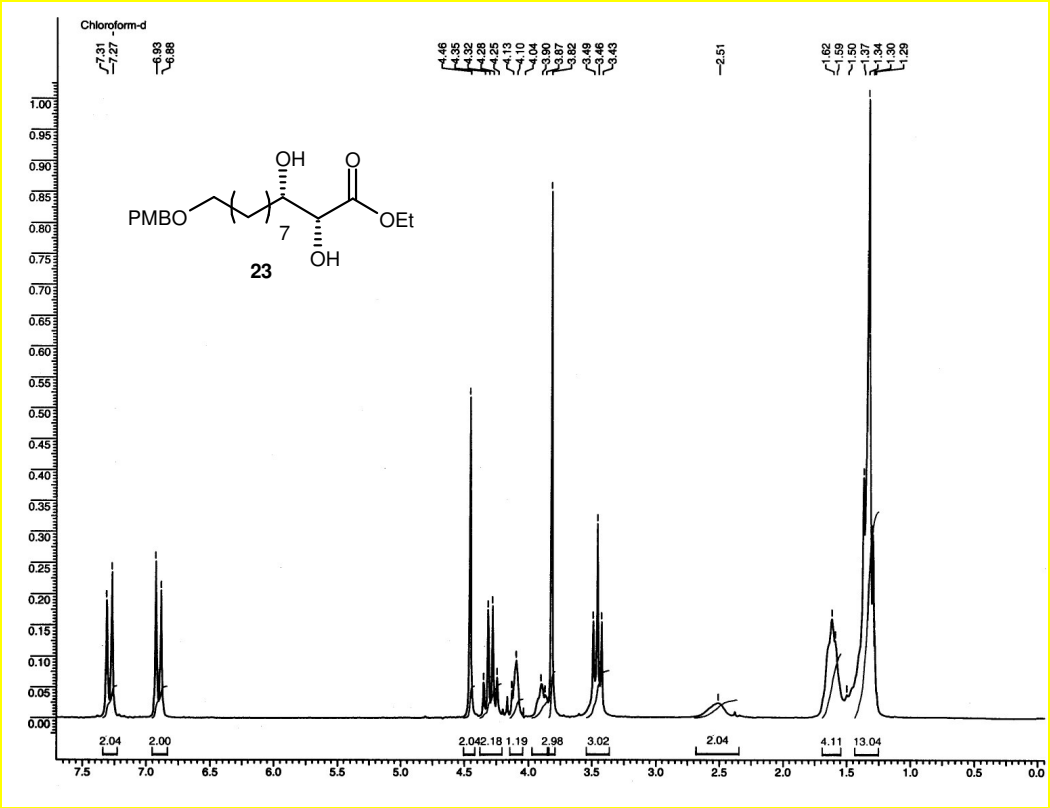
Mol. Formula: $C_9H_{34}O_5$

$[\alpha]_D^{25}$: –7.9 (*c* 0.30, MeOH); (lit.[44] $[\alpha]_D^{25}$: –8.1 (*c* 0.32, MeOH).

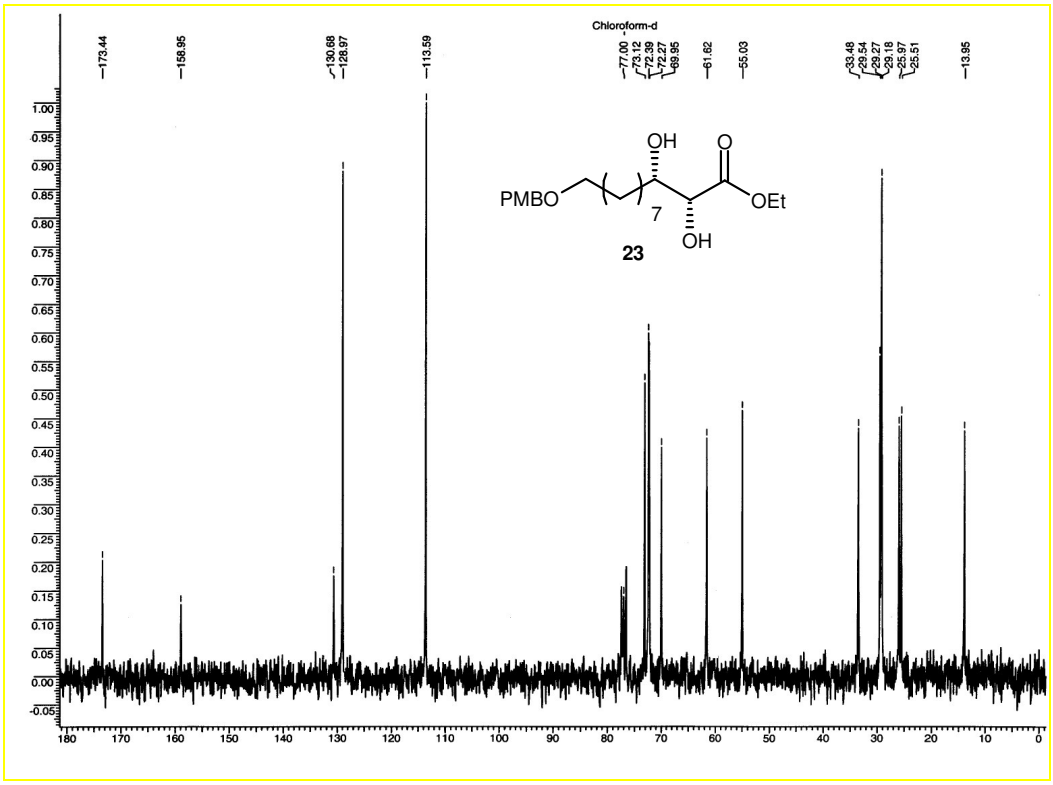
IR (KBr, cm^{-1}): ν_{max} 3376, 1694 and 1638.

^{1}H NMR (200 MHz, CD_3OD): δ 0.89 (t, *J* = 6.3 Hz, 3H), 1.45–1.25 (m, 16H), 1.50-1.62 (m, 4H), 2.27 (t, *J* = 7.6 Hz, 2H), 3.41 (m, 1H), 3.91 (dd, *J* = 5.5, 5.0 Hz, 1H), 4.05 (m, 1H), 5.65 (dd, *J* = 15.6, 5.2 Hz, 1H), 5.72 (dd, *J*=15.6, 5.1 Hz, 1H).

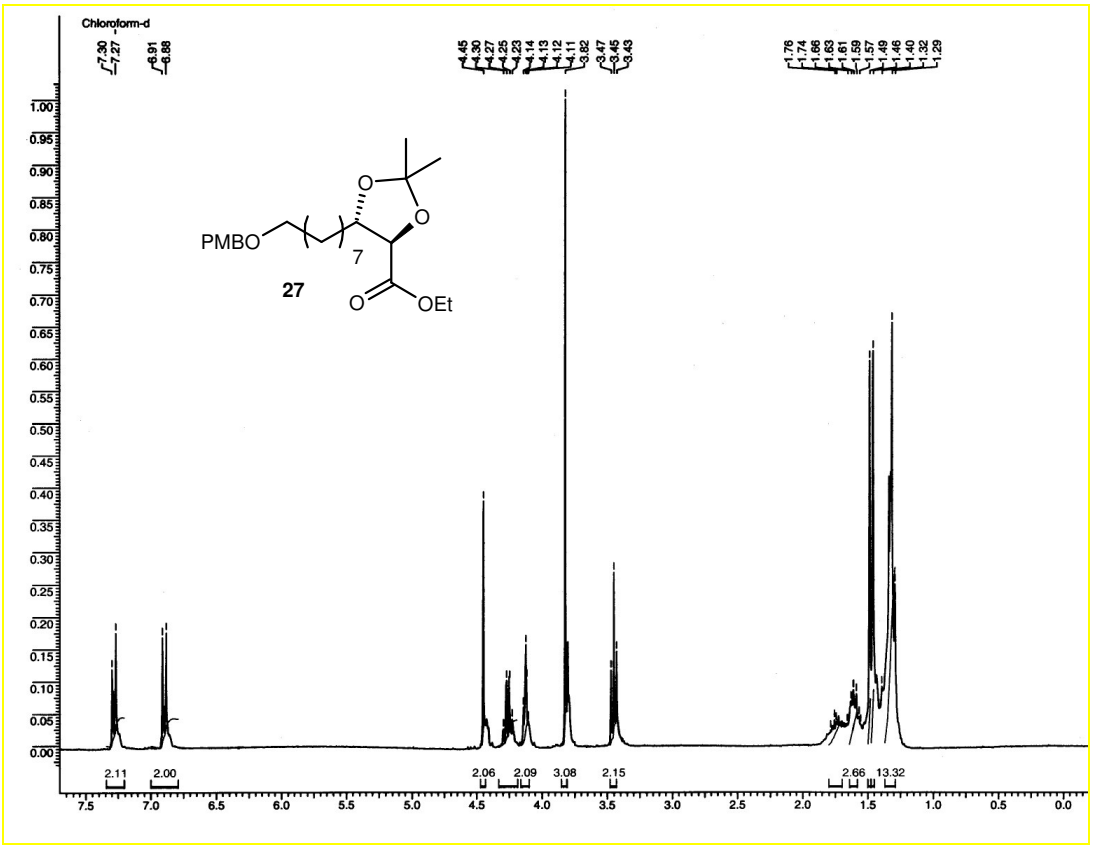
^{13}C NMR (125 MHz, CD_3OD): δ 177.6, 136.6, 131.2, 76.4, 75.8, 73.0, 38.3, 35.1, 33.6, 33.2, 30.5, 30.4, 30.1, 26.6, 26.5, 26.1, 23.7, 13.9.



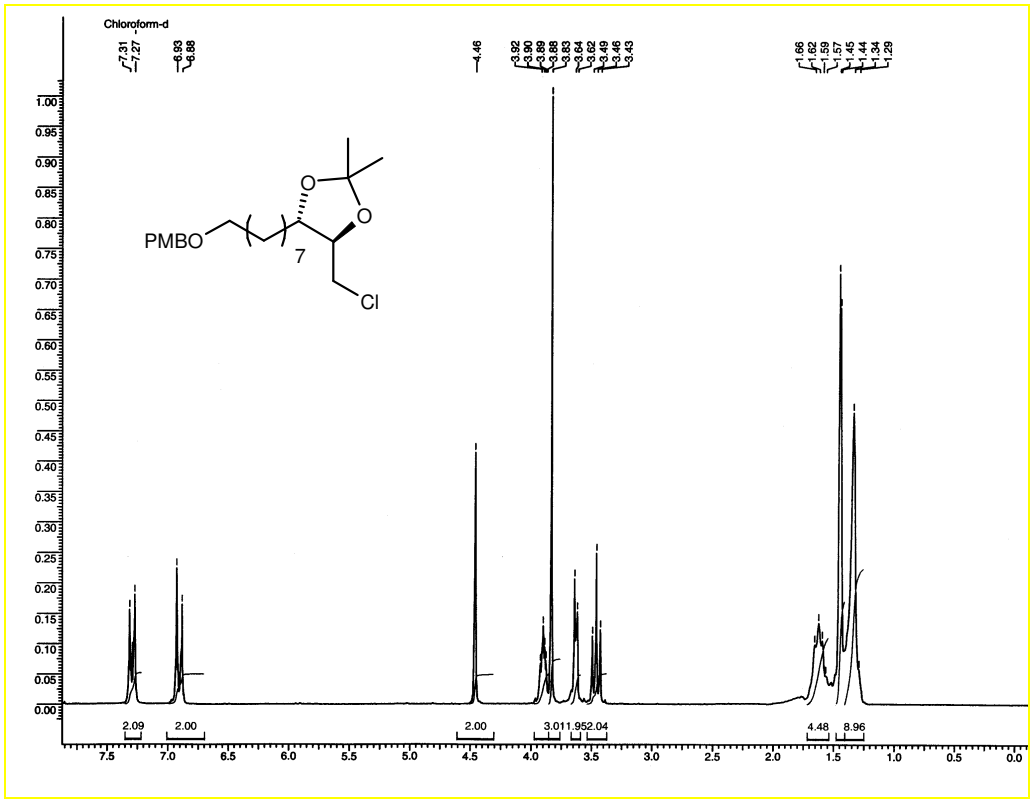
^{1}H NMR Spectrum of **23**



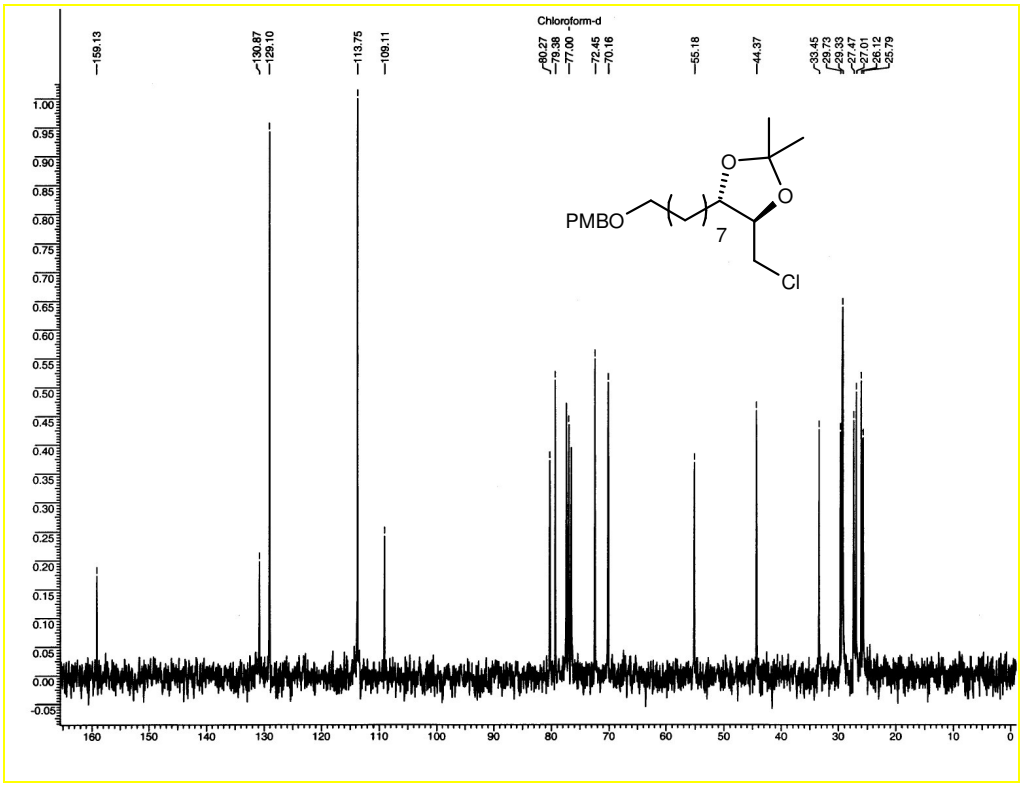
^{13}C NMR Spectrum of **23**



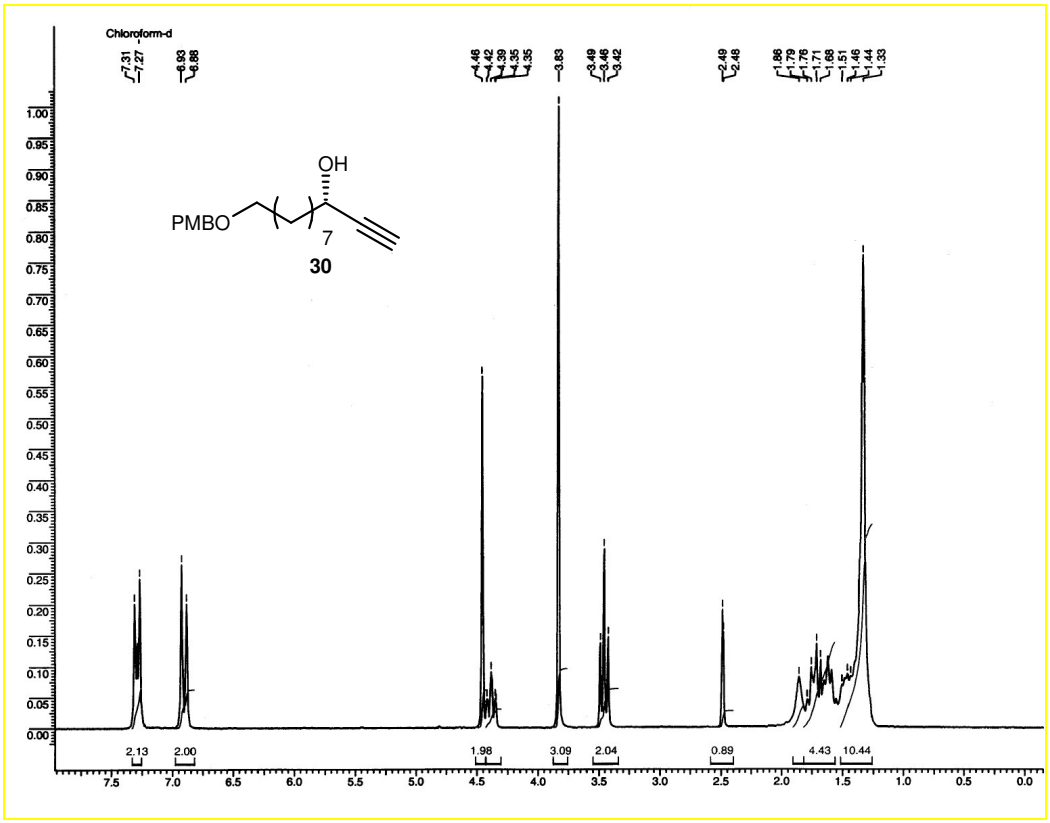
^{1}H NMR Spectrum of **27**



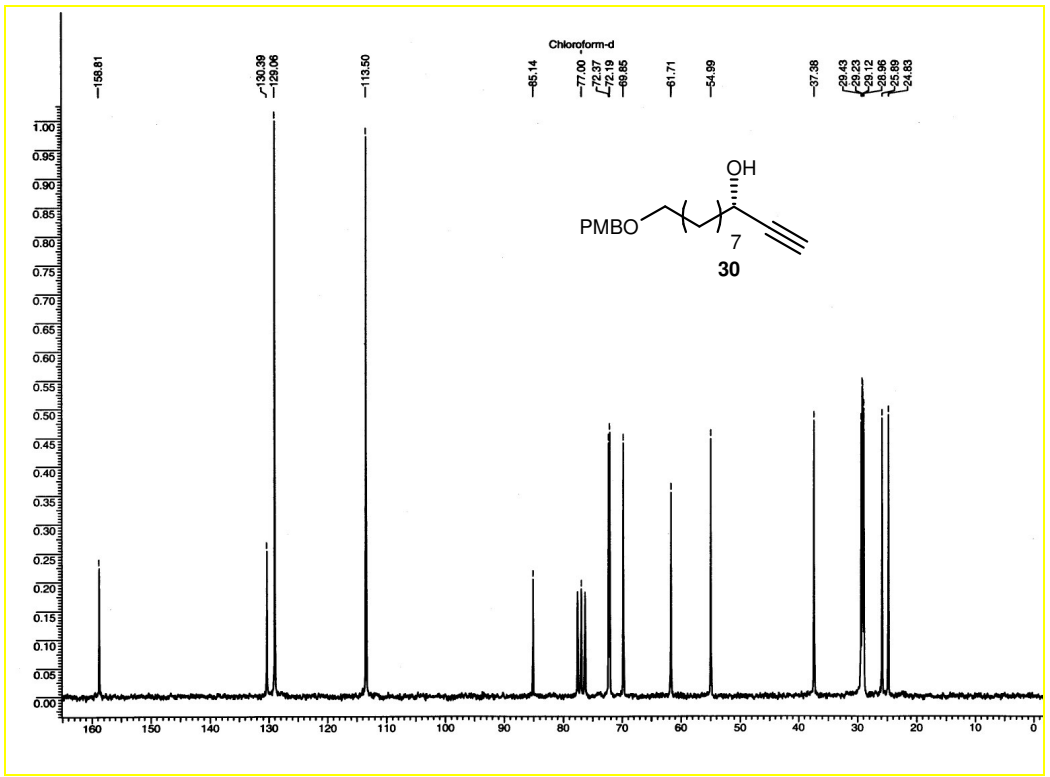
^{1}H NMR Spectrum of **23**



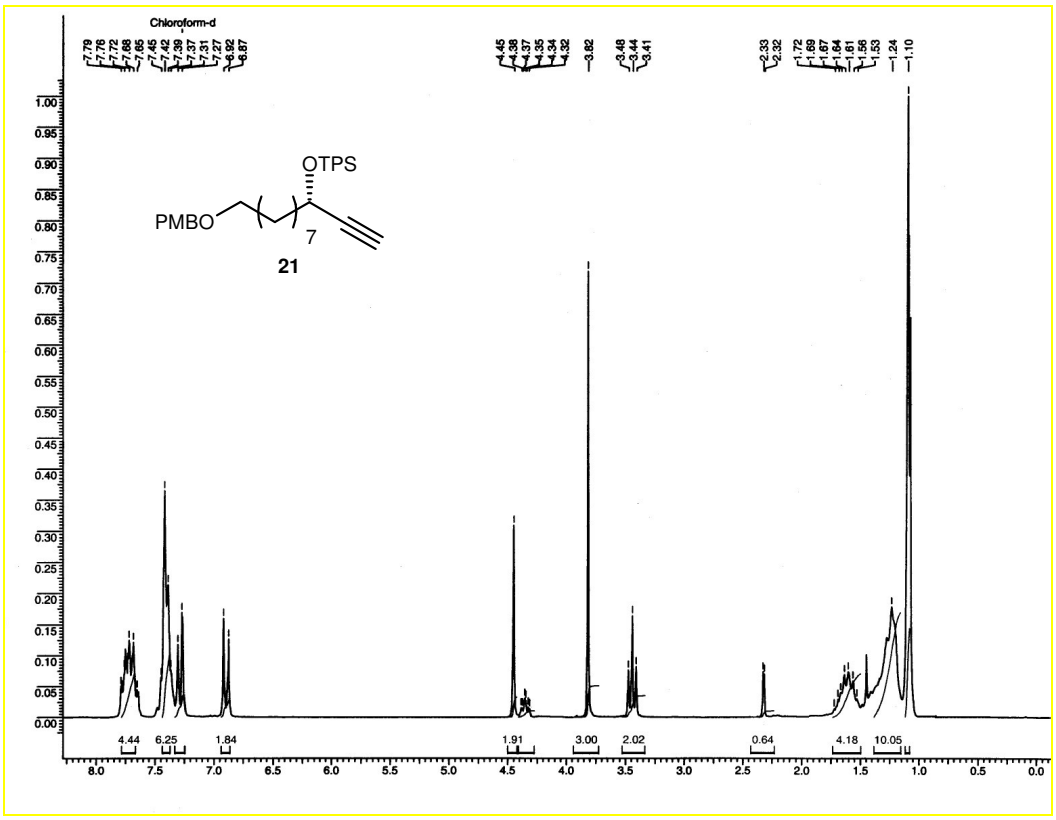
^{13}C NMR Spectrum of **23**



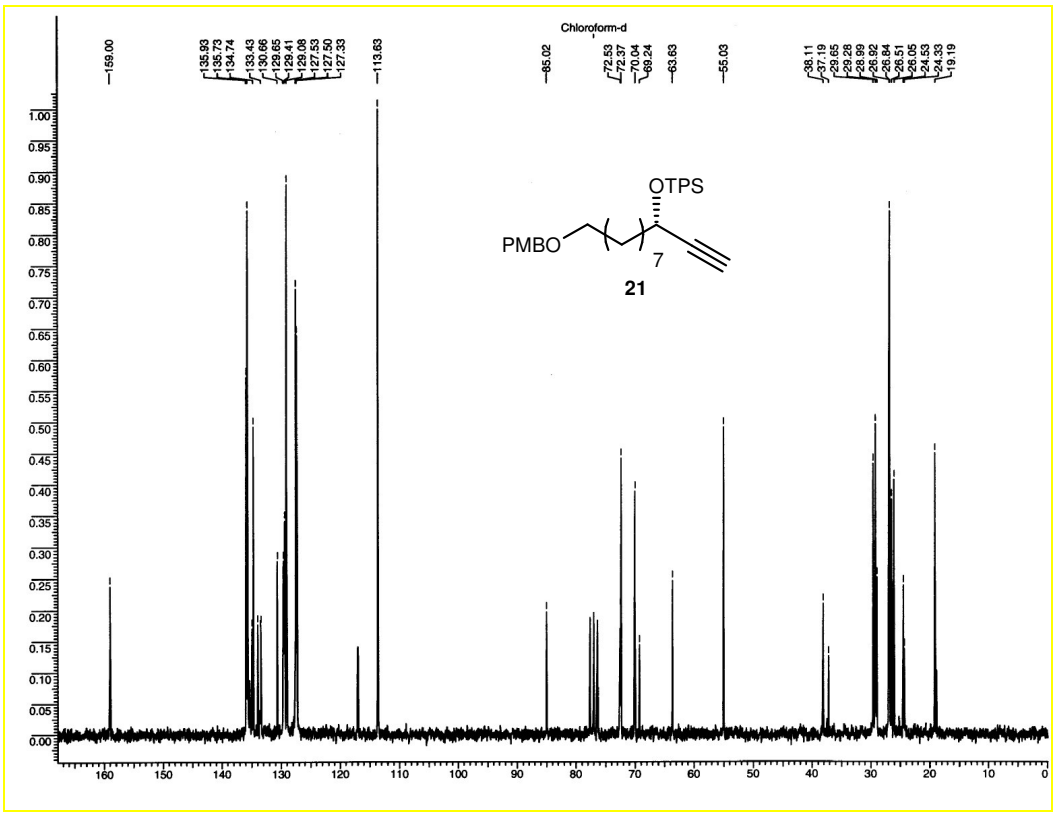
^{1}H NMR Spectrum of **30**



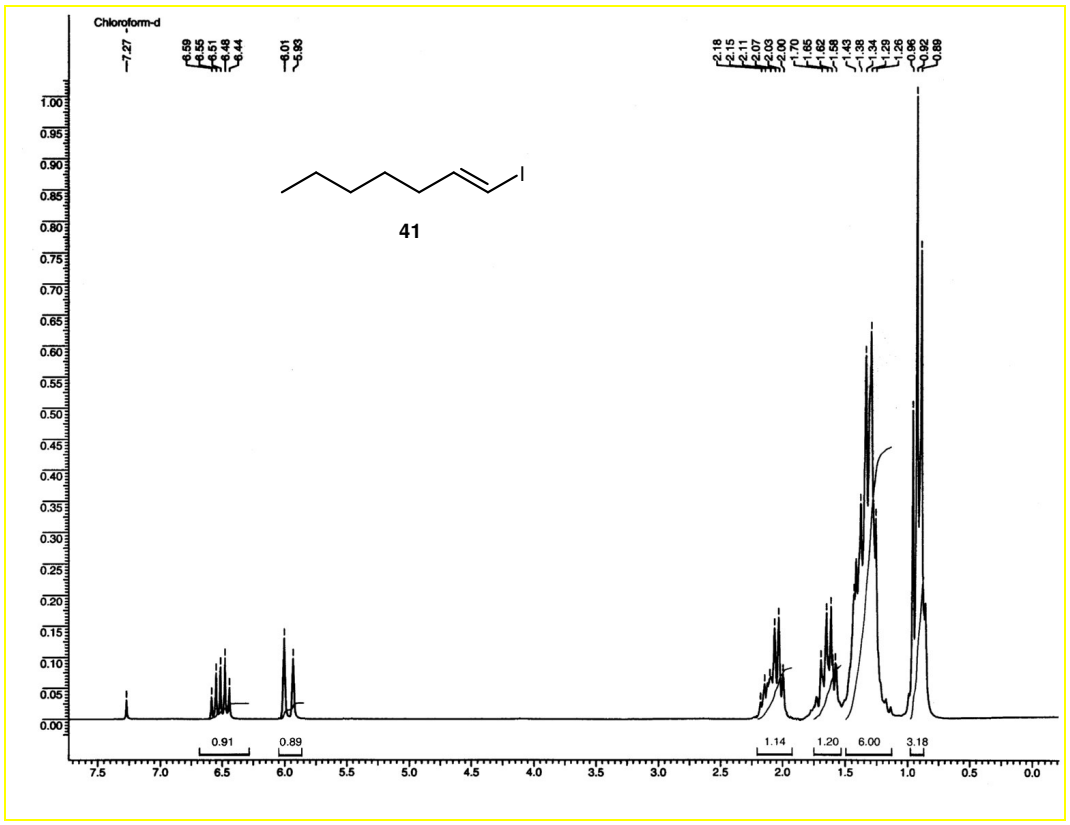
^{13}C NMR Spectrum of **30**



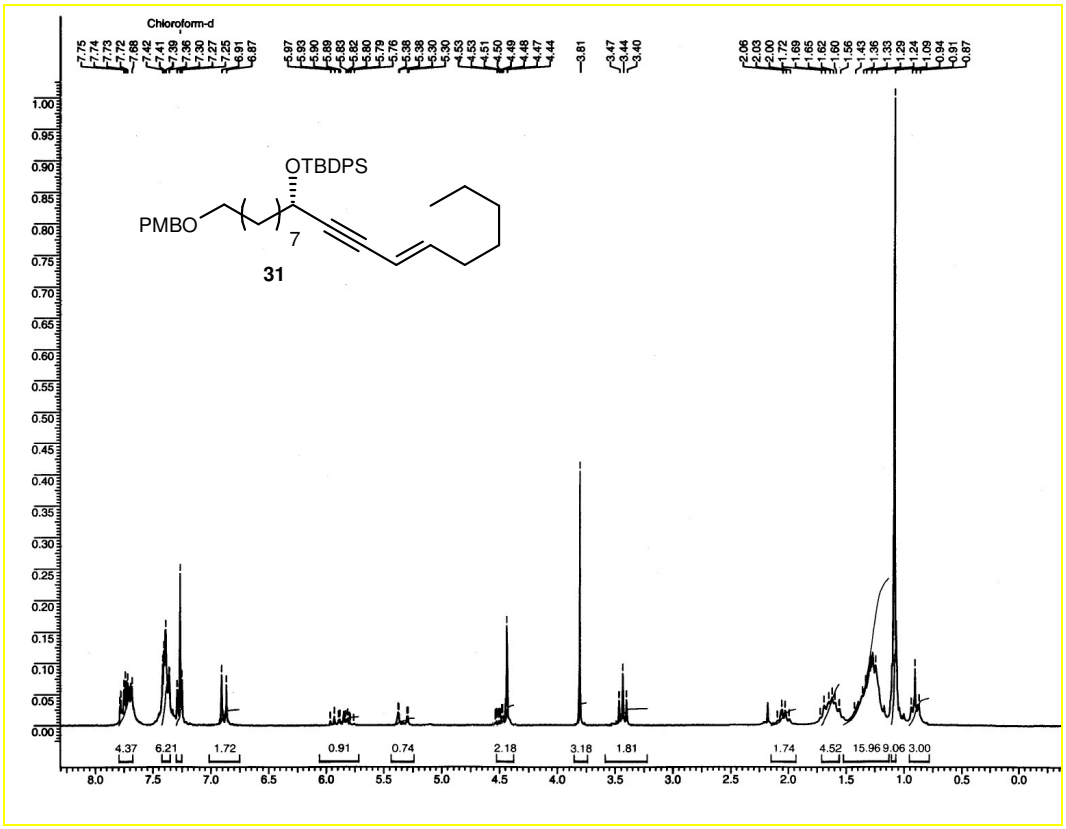
^{1}H NMR Spectrum of **21**



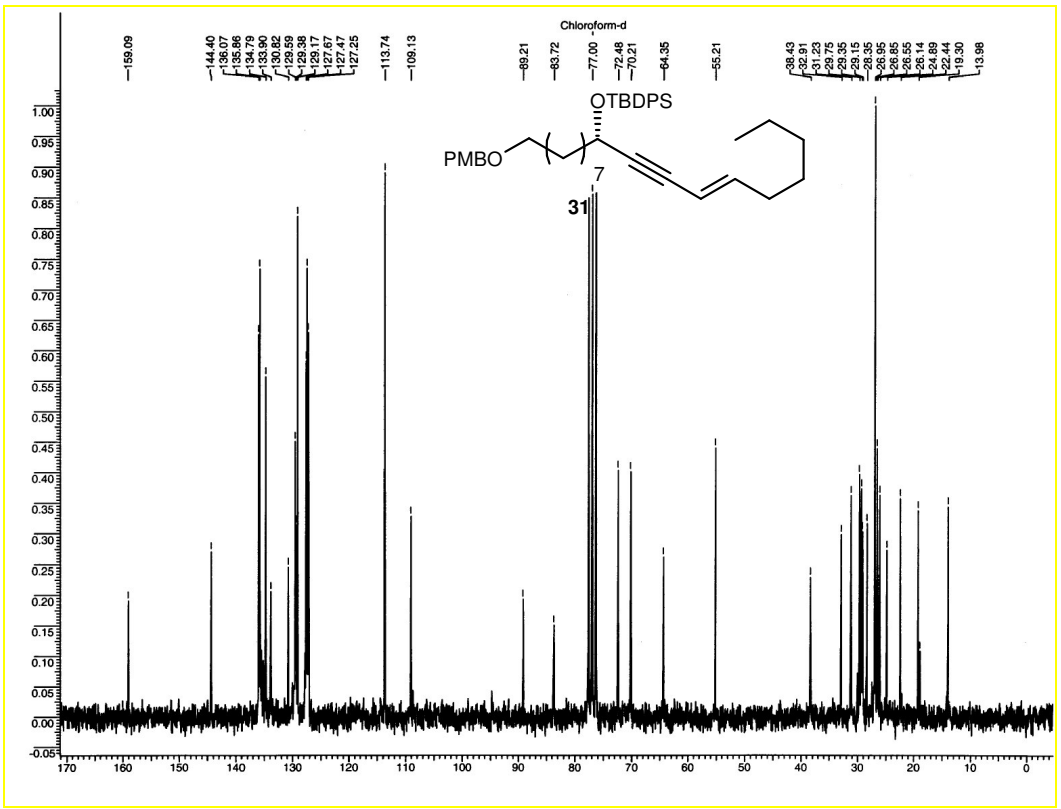
^{13}C NMR Spectrum of **21**



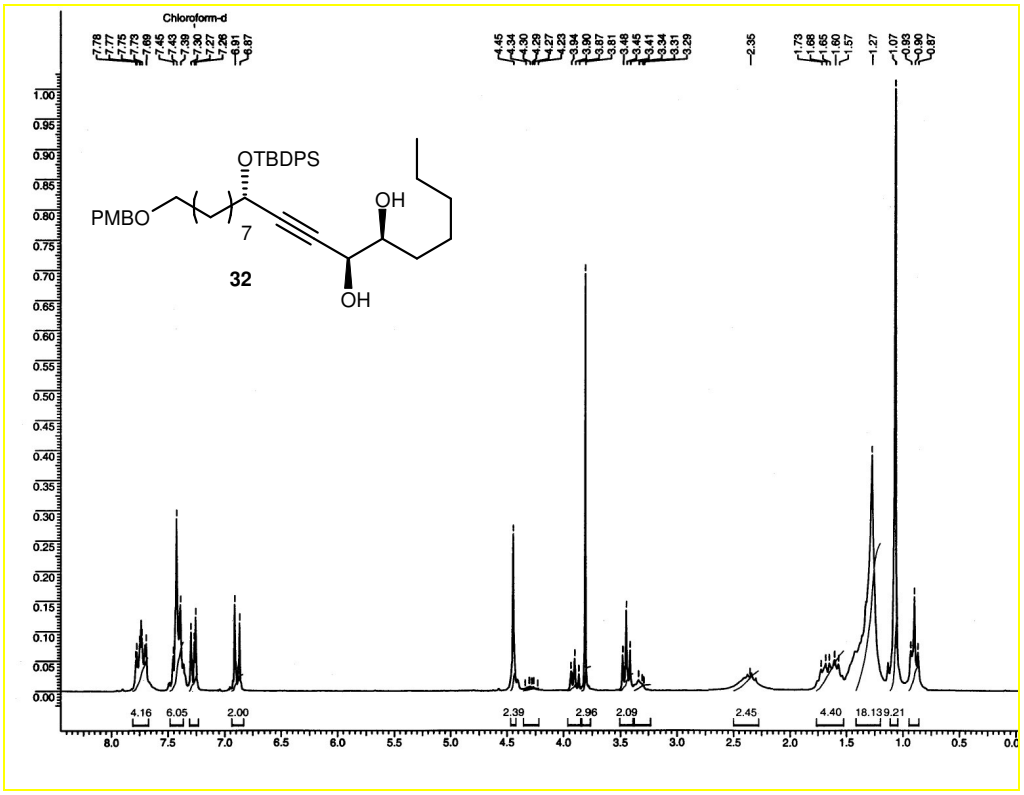
^{1}H NMR Spectrum of **41**



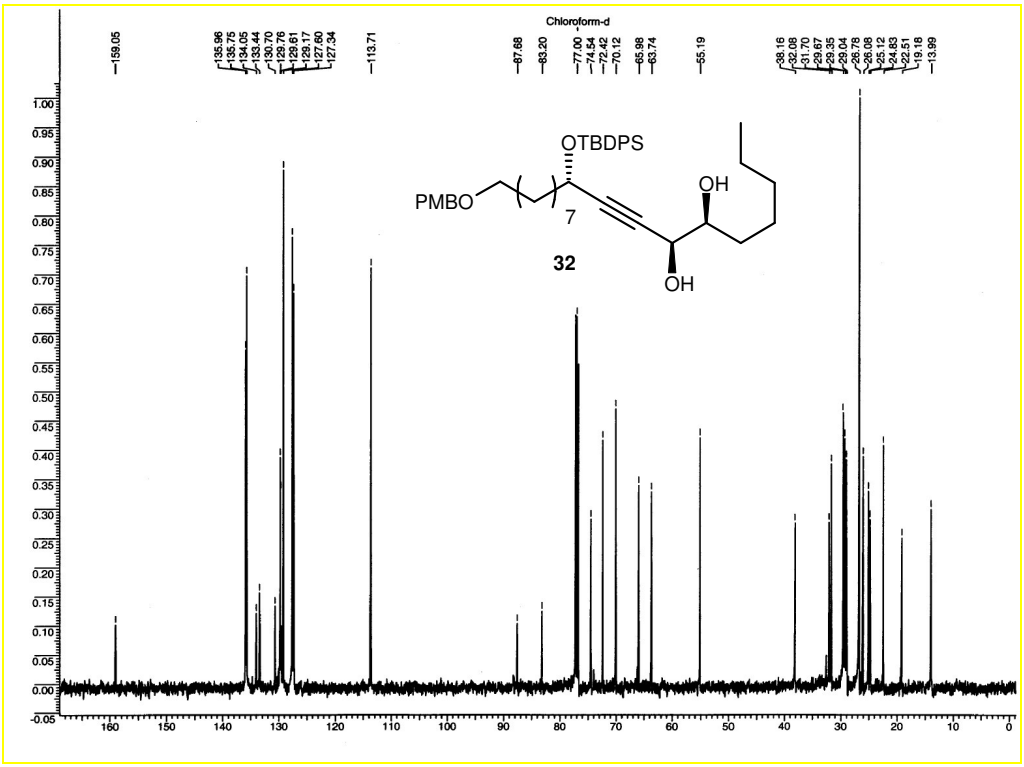
^{1}H NMR Spectrum of **31**



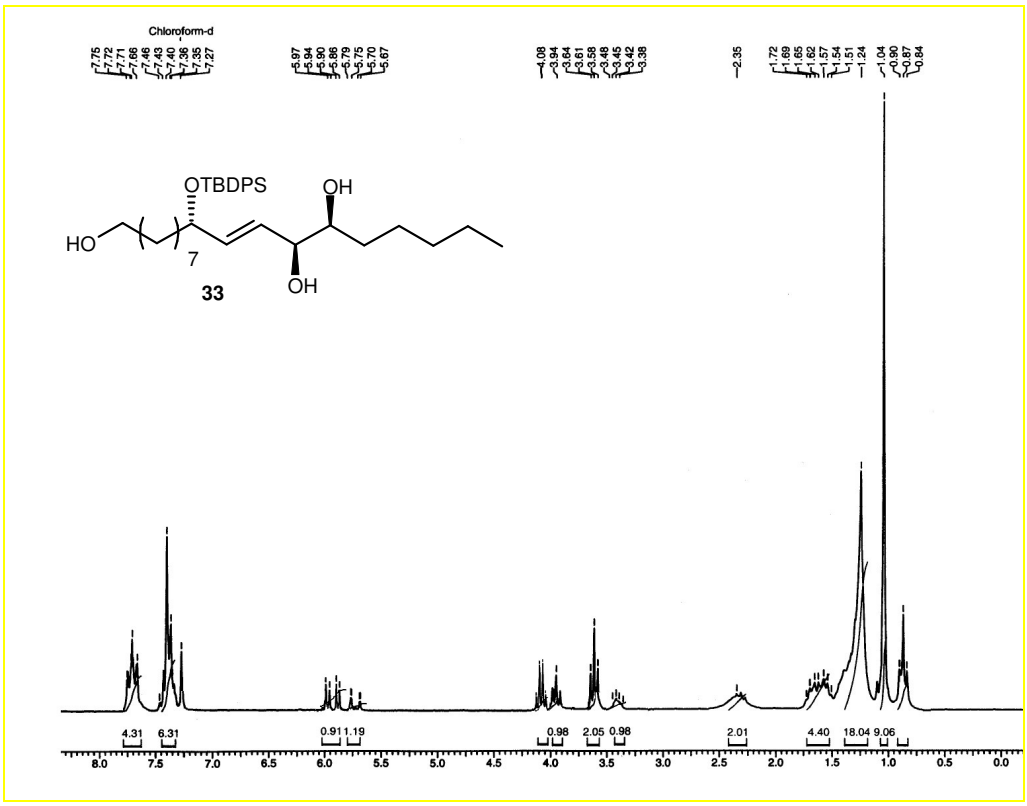
^{13}C NMR Spectrum of **31**



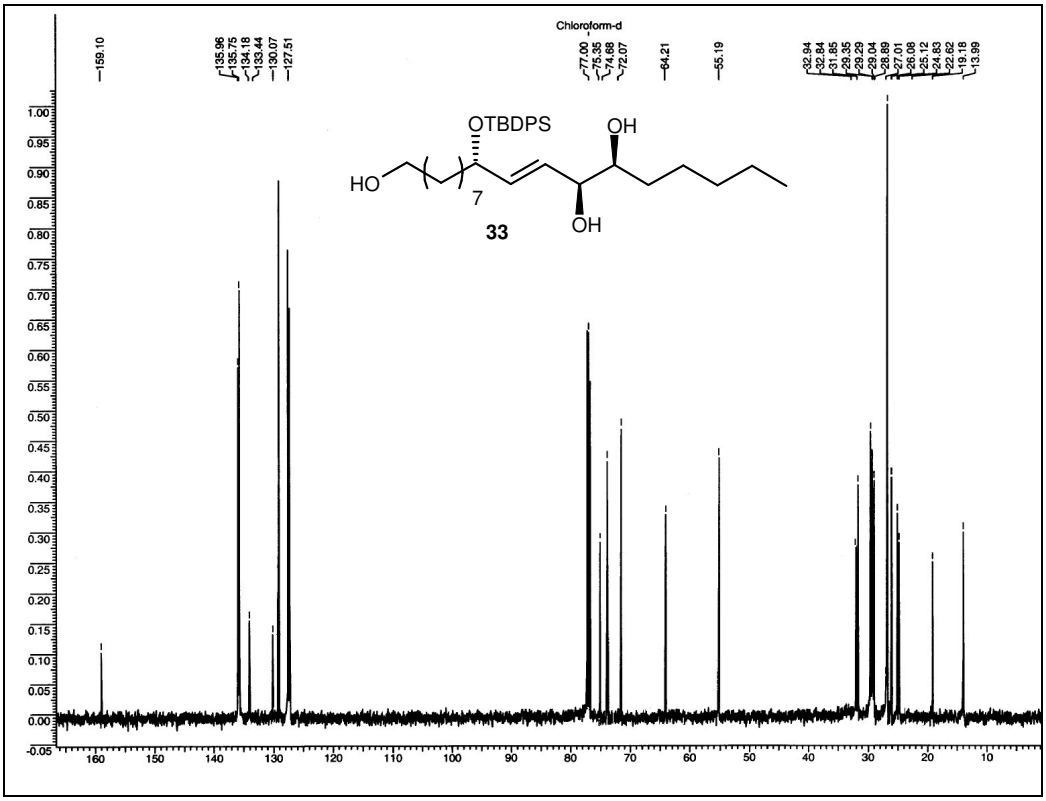
^{1}H NMR Spectrum of **32**



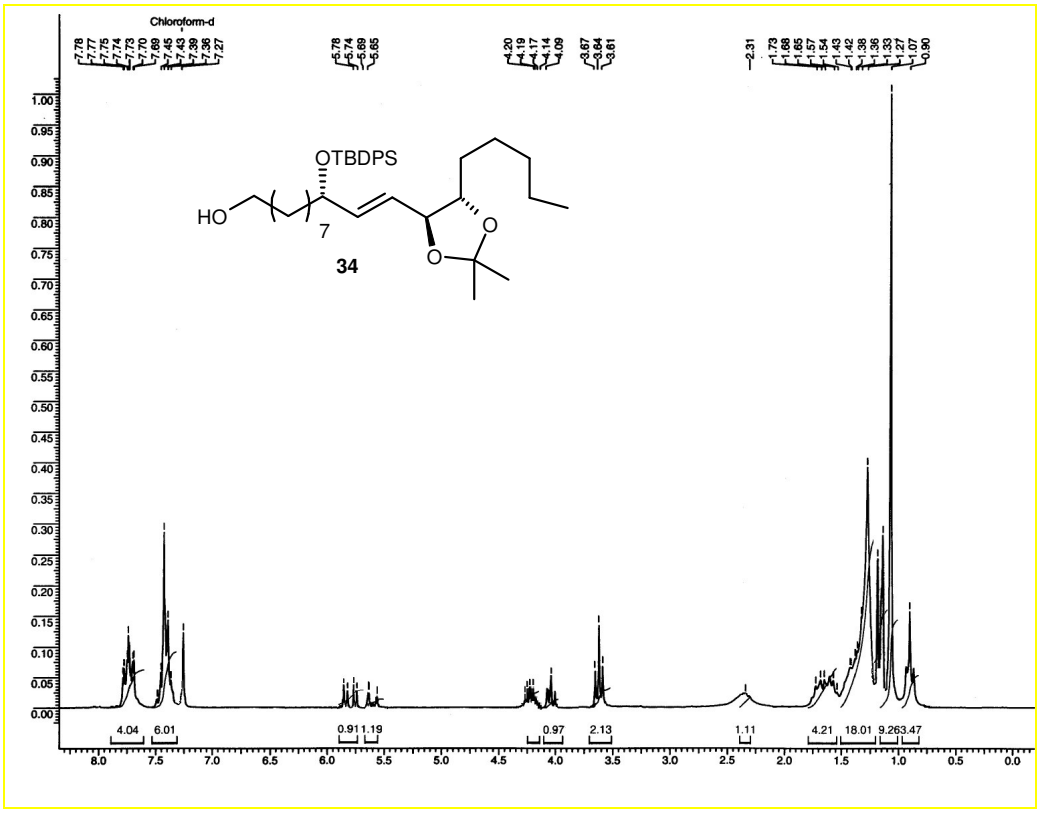
^{13}C NMR Spectrum of **32**



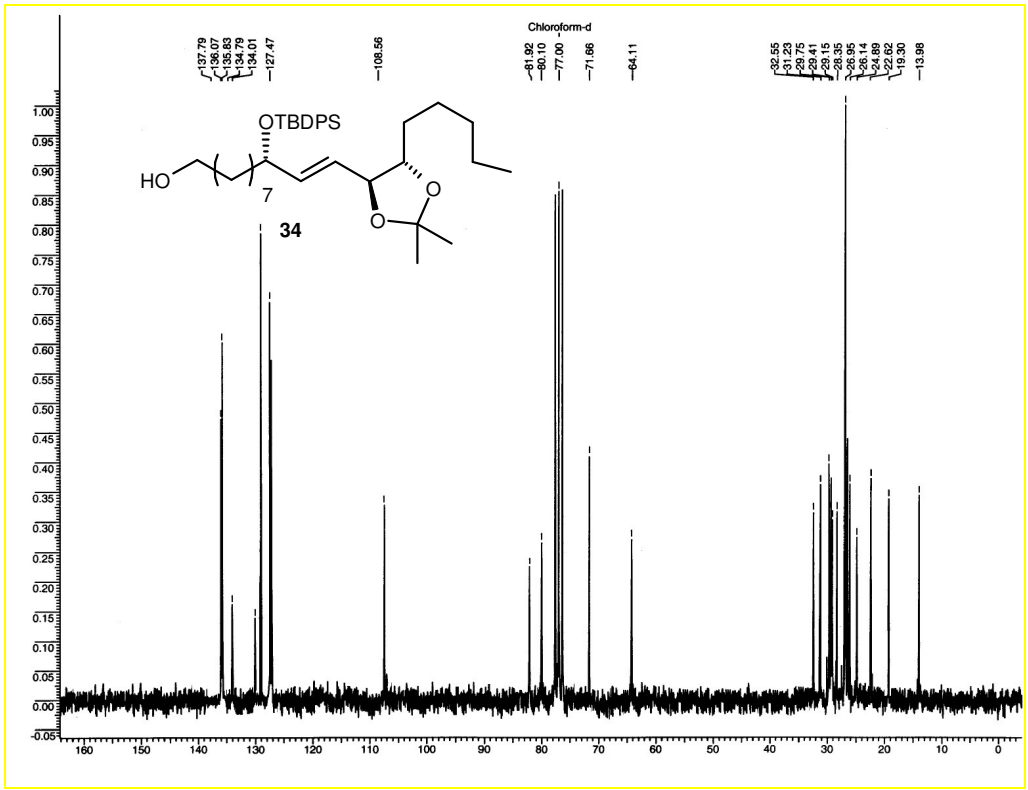
^{1}H NMR Spectrum of **33**



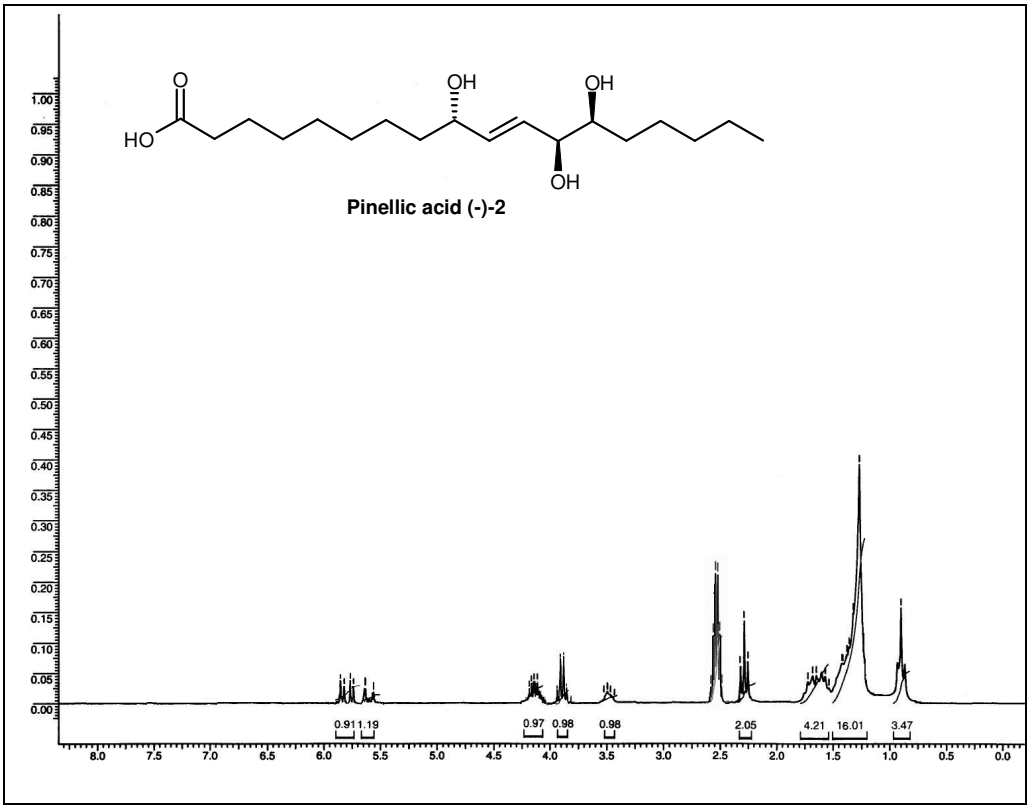
^{13}C NMR Spectrum of **33**



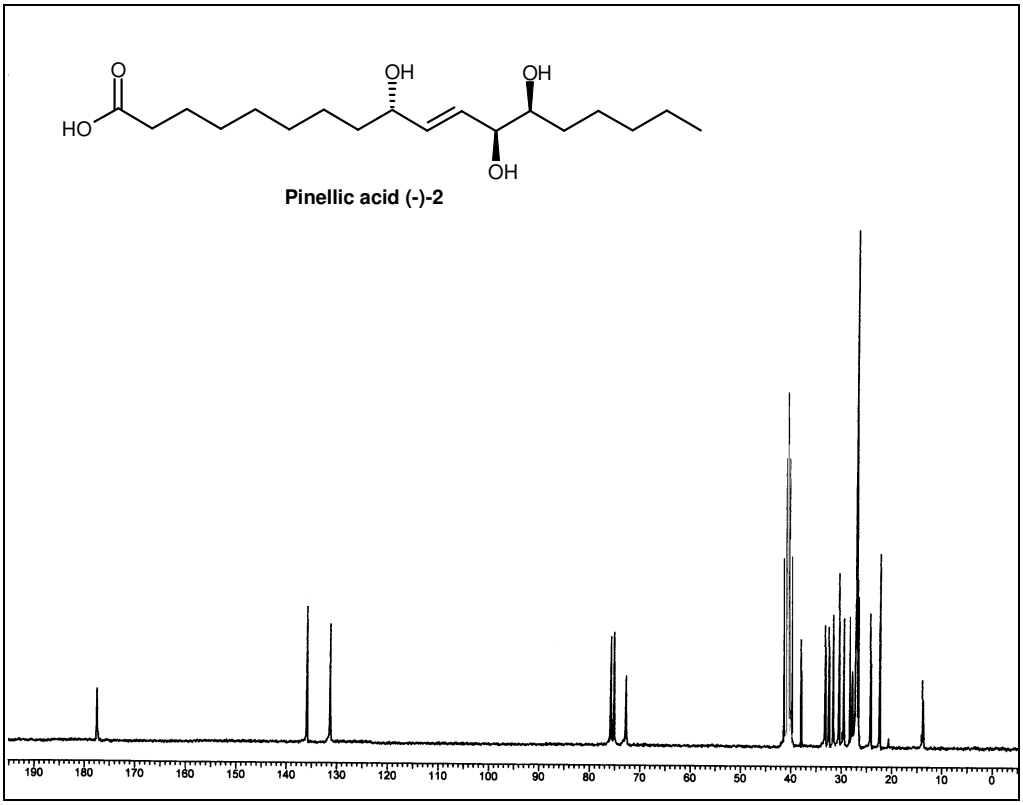
^{1}H NMR Spectrum of **34**



^{13}C NMR Spectrum of **34**



^{1}H NMR Spectrum of Pinellic acid (-)-**2**



^{13}C NMR Spectrum of Pinellic acid (-)-**2**

3.3.8. References:

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3.4. SECTION C

ENANTIOSELECTIVE TOTAL SYNTHESIS OF α- AND β-DIMORPHECOLIC ACID

3.4.1. INTRODUCTION:

Unsaturated hydroxy fatty acids (**1-3**) play important role in biological systems and were isolated from both animals and plants. β-Dimorphecolic acid (**1a**) (It can also called as 9-HODE) is a unique hydroxydienoid fatty acid, which was first isolated from the seed oil of *Dimorphothecu auruntiaca*.[1] It was also isolated from *Osteospermum aurantiaca* Compositae A. DC[2] and *Osteospermum ccklonis* D. C. Compositae.[3] Owing to their lipid nature, long-chain fatty acids play a vital role in maintaining cellular properties[4] and consequently can elicit a variety of biological responses.

However, its diene congener α-dimorphecolic acid was isolated from the plant *Glechoma hederacea* L. Labiatae[5] (commonly known as *'lierre terrestre',* 'ground ivy' or 'creeping Charlie'), which has been demonstrated to be a calcium specific ionophore,[6] an inhibitor of acetylcholine esterase (ACE)[7] and aromatase,[8] and as well as being implicated in the pathogenesis of familial Mediterranean fever.[9] It was also able to stimulate platelet adenylate cyclase activity up to several fold over basal levels and can enhance the stimulation of adenylate cyclase activity produced by forskolin and p[NH]ppG. In addition, it can competitively inhibit enzyme activity stimulated by PGE_l and PGD_2. 9-HODE acts as a partial agonist at platelet PGE_l and PGD_2 receptors. This fatty acid contains structural features that are not typically found in plant fatty acids, including a C-9 hydroxyl group and C10-C12 conjugated double bonds, which possess a wealth biological properties.[10] This fatty acid has been previously isolated from *Tragopogon porrifolius* L. Compositae[11] and *Xeranthemum annuurn* Asso Compositae.[12] It has also been found in rice plants infected with blast disease,[13] in sera of patients suffering from familial rnediterranean fever,[9] and in bovine heart mitochondria.[14] Little is known about the biological properties of β-dimorphecolic acid.

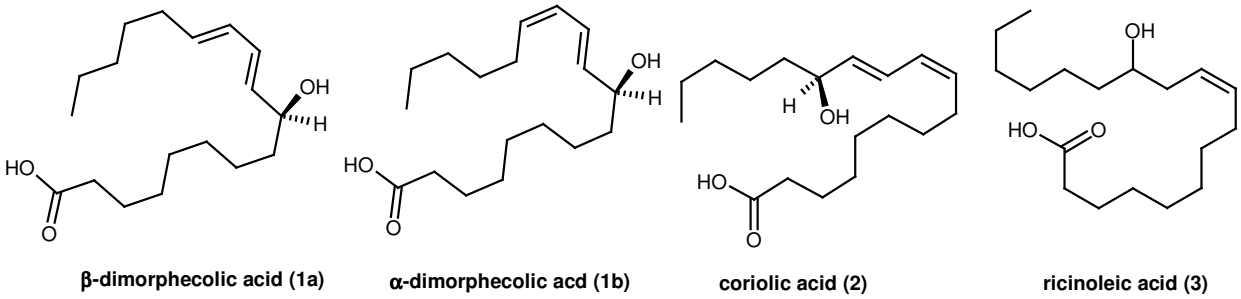


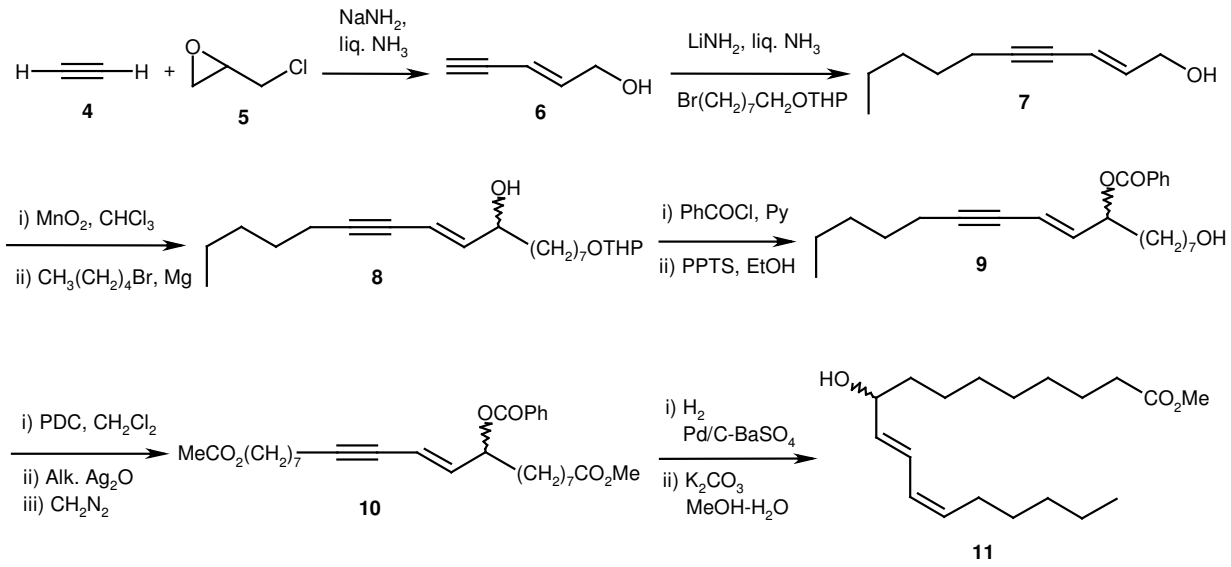
Figure 1.

3.4.2. Review of Literature

In the interest of evaluating the biological and pharmacological properties of these compounds it was necessary to obtain sufficient quantities by chemical synthesis. Ramarao and co-workers[15] reported the first total synthesis of racemic dimorphecolic acid and coriolic acid from tetrahydrofurfuryl chloride. Later, Ley and co-workers[16] synthesized β-dimorphecolic acid utilizing a π–allyltricarbonyliron lactone complex to control the formation of all the stereochemical features of the natural product. Both of these syntheses are described below in fair details.

Ramarao *et al*. (1985).[15]

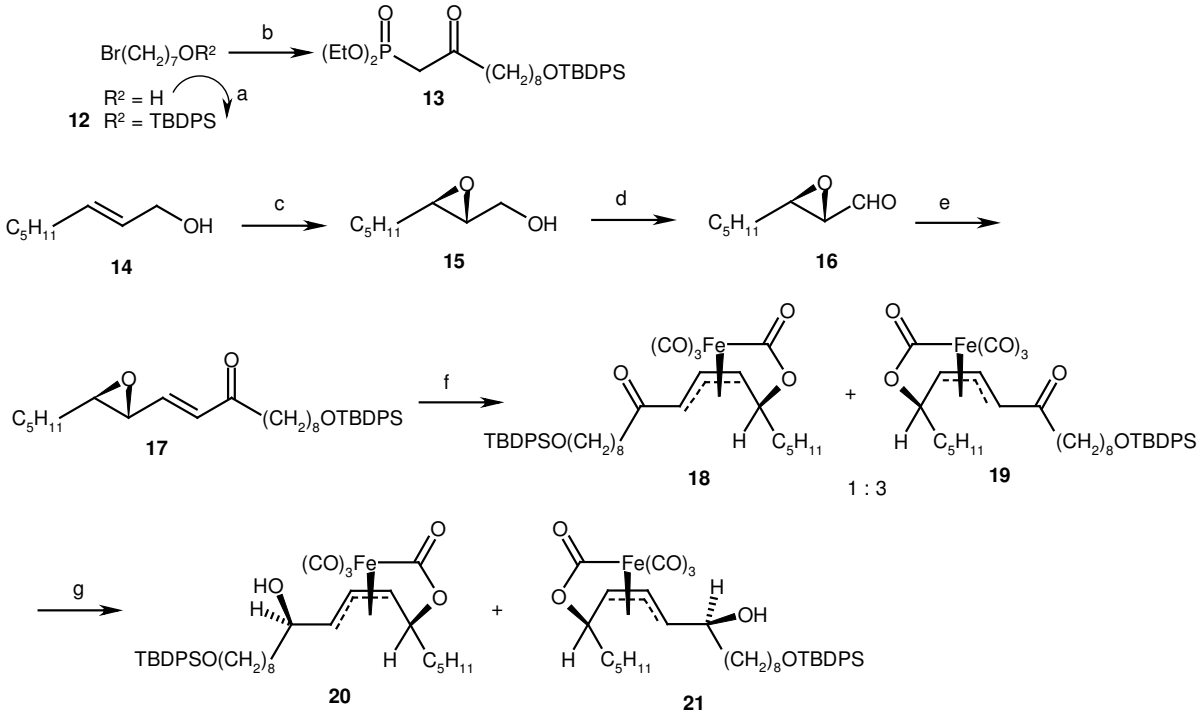
Ramarao *et al*. synthesized racemic dimorphecolic acid from (*E*)-pent-2-ene-4-1-ol. Alkylation of **6** with *n*-amyl bromide the presence of $LiNH_2$, liq. NH_3 followed by oxidation and Grignard reaction furnished the alcohol **8** in good yield. Protection of the secondary alcohol with BzCl followed by depyranylation gave the benzoate alcohol **9**. Stepwise oxidation of the alcohol **9**, esterification and partial reduction of **10** to the diene by hydrogenation using Lindlar catalyst in petroleum ether and saponification gave dimorphecolic acid.



Scheme 1

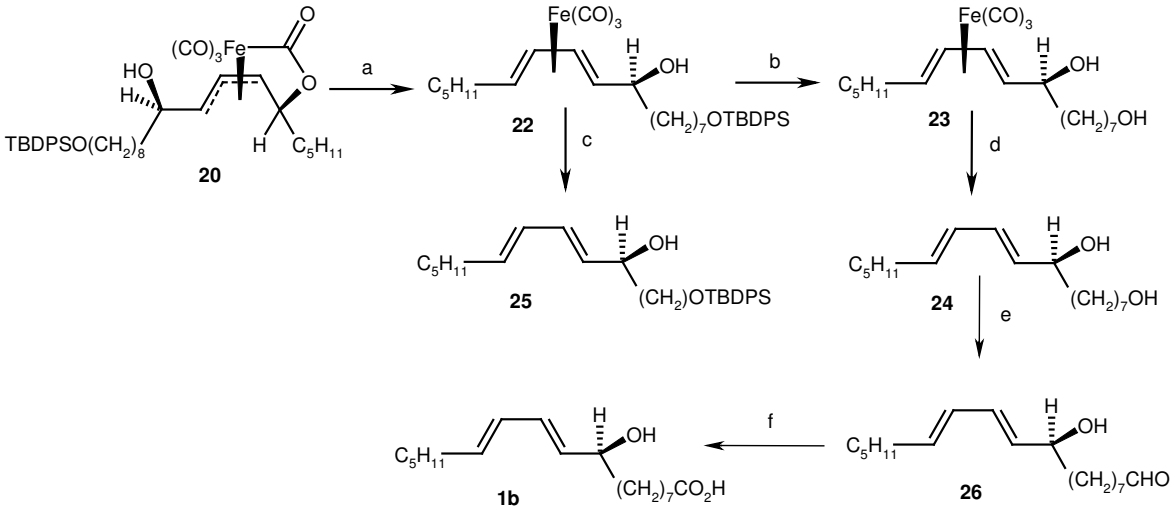
Ley *et al.* (1997).[16]

Ley *et al*. synthesized β-dimorphecolic acid from allylic alcohol **14**. Sharpless asymmetric epoxidation of allylic alcohol **14** followed by oxidation with *in situ*-generated Collins' reagent and Wittig olefination of resultant aldehyde **16** with phosphonate **13** furnished epoxy enone **17**.



Scheme 2. *Reagents and conditions:* (a) $ClSiPh_2Bu$*t*, Et_3N, DMAP (10 mol%), CH_2Cl_2, 0 °C to rt, 40 min (94%); (b) $(Et_2O)_2P(O)CH_2$-$C(O)CH_3$, NaH, THF, 0 °C to rt, 45 min, then *n*-BuLi, 0 °C, 50 min, 0 °C to rt, 16 h (70%); (c) Ti(OPr*i*)$_4$ (15 mol%), D-DET (18 mol%), *t*-BuOOH, 4 Å mol. sieves, CH_2Cl_2, –20 °C, 90 min (70%); (d) CrO_3, pyridine, CH_2Cl_2, rt, 45 min (85%); (e) **13**, KHMDS, THF, 0 °C, 40 min, then **16**, −78 °C, 50 min (66%); (f) $Fe_2(CO)_9$, THF, room temp., 3 h (64%, **18**:**19** = 3:1); (g) *i*-Bu_3Al, C_6H_6–toluene (4 : 1), 0 °C, 35 min (53% **20**, 18% **21**).

Treatment of **17** with $Fe_2(CO)_9$ in THF gave two diastereoisomeric π-allyltricarbonyliron lactone complexes, *endo*-**18** and *exo*-**19**, in 64% combined yield and in a ratio of 3:1, respectively. Reduction of the side-chain carbonyl groups of the inseparable complexes **18** and **19** with triisobutylaluminium afforded the corresponding alcohols **20** and **21**, respectively. Treatment of the required diastereoisomer **20** with barium hydroxide provided the η^4-dienetricarbonyliron complex **22** as a single diastereoisomer. Unmasking of the diene unit with basic methanolic hydrogen peroxide followed by step wise oxidation of primary alcohol **24** with $RuCl_2(PPh_3)_3$ in benzene[17] and buffered sodium hypochlorite,[18] furnished β-dimorphecolic acid (**1b**).



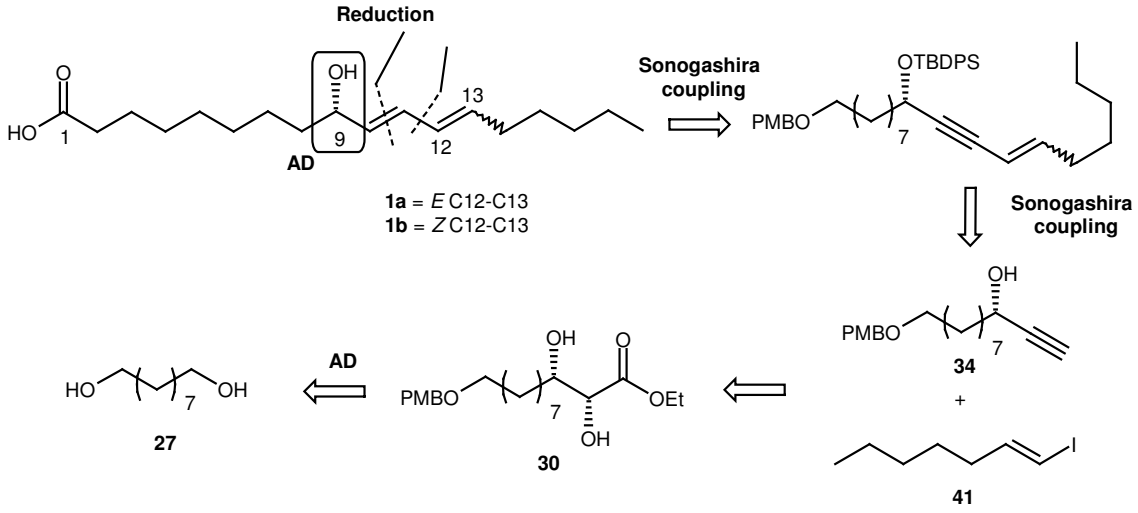
Scheme 3. *Reagents and conditions*: (a) $Ba(OH)_2$, MeOH, room temp., 5 min (78%); (b) HF.pyridine, pyridine, THF, room temp., 18 h (92%); (c) H_2O_2, NaOH, MeOH, 0 °C, 6 h (46%); (d) H_2O_2, NaOH, MeOH, 0 °C, 25 min (94%); (e) $Ru(PPh_3)_3Cl_2$, C_6H_6, room temp., 22 h (73%); (f) NaOCl, KH_2PO_4, 2-methylbut-2-ene, *t*-BuOH–H_2O (1:1), room temp., 1 h.

3.4.3. PRESENT WORK

Objective

In foregoing section we have described the synthesis of microcarpalide, sapinofuranone B and pinellic acid using AD and Sonogashira coupling reaction as the key steps. It was further planned to extend the same protocol towards the total synthesis of yet another interesting molecules α- and β-dimorphecolic acid. A very few syntheses of α- and β-dimorphecolic acid are documented in the literature either in racemic form or chiral form. Hence, a general strategy with fewer steps and higher optical purity to achieve the synthesis of all α- and β-dimorphecolic acid is still desirable.

Retrosynthetic strategy for the synthesis of α- and β-dimorphecolic acid (**1a** and **1b**) is outlined in Scheme 1. We envisioned that 1,3-enyne system can be prepared by Sonogashira coupling of chiral propargyl alcohol **11** and vinyl iodide **11a** or 1-heptyne and vinyl iodide **17**. The acetylene **11** could be obtained from 1,9-nonane diol **4**, through base induced elimination. In this strategy, 9*S* hydroxy could be obtained through Sharpless asymmetric dihydroxylation of olefin **6**, which in turn could be prepared from 1,9-nonane diol **4**.



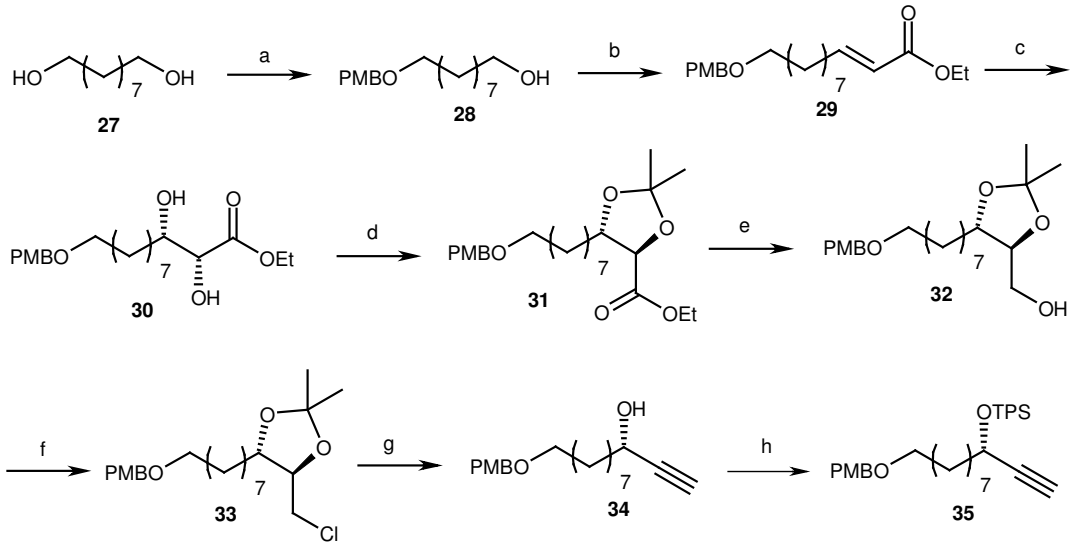
Scheme 4. Retrosynthetic analysis for α- and β-dimorphecolic acid (1a and 1b).

3.4.4. Results and Discussion:

3.4.4.1. Synthesis of chiral propargylic alcohol

The synthesis α- and β-dimorphecolic acid **1a** and **1b** started from commercially available 1,9-nonane diol **27** as illustrated in Scheme 5. Thus, selective mono hydroxyl protection of **27** with *p*-methoxybenzyl bromide in the presence of NaH gave monoprotected diol **28** in 95% yield. The ^{1}H NMR spectrum gave benzylic protons at δ 4.48 (singlet, two protons) and aromatic protons at δ 7.26 (doublet) and 6.88 (doublet) with coupling constant J = 10.0 Hz. The IR spectrum gave hydroxyl absorption at 3400 cm^{-1}. Compound **28** was oxidized to the corresponding aldehyde under Swern conditions and subsequently treated with (ethoxycarbonylmethylene)-triphenylphosphorane in benzene under reflux conditions to furnish the *trans*-olefin **29** in 91% yield. The IR spectrum of **29** showed the ester carbonyl absorption at 1724 cm^{-1} and olefin C=C stretching at 1654 cm^{-1}. The ^{1}H NMR spectrum gave olefin protons at δ 6.98 (doublet of triplet) and 5.90 (doublet) with the coupling constant J = 15.0 Hz indicating *trans*-olefin. The olefin **29** was treated with osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of $(DHQ)_2PHAL$ ligand under AD conditions to give the diol **30** in 96% yield with 99% ee. The IR spectrum gave hydroxyl absorption at 3440-3300 cm^{-1} and ester carbonyl at 1736 cm^{-1}. The ^{1}H NMR indicated absence of olefin protons. The chiral protons appeared at δ 4.06-4.16 (multiplet) and 3.90 (doublet). The chiral carbons appeared at δ 72.3 and 70 in the ^{13}C NMR spectrum. Treatment of diol **30** with 2,2-dimethoxy propane in the presence of *p*-TSA gave compound **31**. The IR spectrum of **31** indicated absence of hydroxyl groups. The acetonide methyl protons appeared at δ 1.46 (singlet) and 1.49 (singlet) in the ^{1}H NMR spectrum and typical quaternary carbon of acetonide appeared at 110.5 in the ^{13}C NMR spectrum. Reduction of **27** with DIBAL-H furnished the alcohol **32** in excellent yield. The IR spectrum of **32** gave hydroxyl absorption at 3440 cm^{-1} and the ester carbonyl group was absent. The alcohol **32** was converted to chloride **33** in 89% yield by Mitsunobu reaction. The product **33** was reliably confirmed by the analysis of the ^{1}H NMR, ^{13}C NMR and IR spectra. In the ^{1}H NMR spectrum of **33**, upfield shift of peaks belonging to methylene protons (CH_2Cl) compared to that of **28** was noticed. Propargylic alcohol **34** was obtained by treatment of **33** with *n*-BuLi in the presence of HMPA in 84% yield. The IR spectrum showed hydroxyl absorption at 3400-3200 cm^{-1} and C≡C absorption at 2100 cm^{-1}. The presence of acetylenic group with its proton resonating at 2.48 ppm as a doublet in the ^{1}H NMR spectrum confirmed that the

substrate had indeed undergone elimination and chiral proton appeared at δ 4.39 (doublet of doublet) with coupling constant 6.6 Hz. The free hydroxy group of **34** was protected with TBDPSCl to furnish compound **35**.



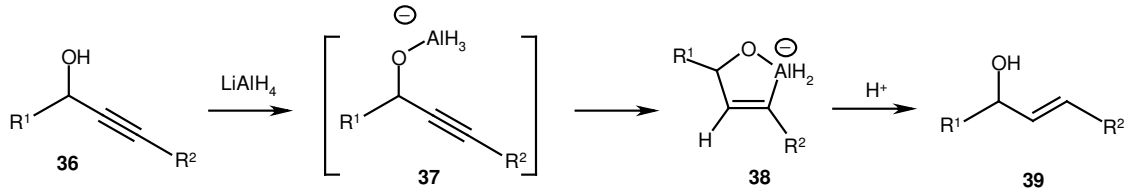
Scheme 5. *Reagents and conditions*: (a) (i) *p*-$CH_3OC_6H_5CH_2Br$, NaH, dry DMF, cat. TBAI, 0 °C to rt, 1 h, 95%; (b) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C to -60 °C; (ii) $Ph_3P{=}CHCO_2Et$, benzene, reflux, 4 h, 91%; (c) $(DHQ)_2PHAL$, K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, OsO_4 (0.1M sol. in toluene), *t*-BuOH/H_2O (1:1), 0 °C, 24 h, 96%; (d) *p*-TSA, 2,2-DMP, CH_2Cl_2, overnight, 96%; (e) DIBAL-H, CH_2Cl_2, 0 °C to rt, 2 h, 96%; (f) *N*-chlorosuccinimide, PPh_3, CH_2Cl_2, 0 °C to rt, 3 h, 89%; (g) (i) *n*-BuLi, HMPA, THF, –42°C–rt, 30 min, 82%; (ii) TBDPSCl, imidazole, CH_2Cl_2, 0 °C to rt, overnight, 98%.

A brief note on reduction of propargylic alcohols

Next, we turned our attention to the reduction of propargylic alcohol ***36*** *to the corresponding allylic alcohol. While (Z)-isomers are conveniently obtained under mild conditions by hydrogenation of carbon–carbon triple bonds, methods for their selective conversion to (E)-olefins are scarce and often not tolerant of a wide variety of functional groups.*

The most widely used methods include dissolving metal reductions (Na/NH_3), low-valent chromium salts and hydroalumination reagents.[19] *An intriguing hydrogenation catalyst was reported by Bayer and co-worker*[20] *palladium on poly(ethylenimine) support, when bound to benzonitrile, was shown to reduce 2-pentyne to (E)-2-pentene selectively.*

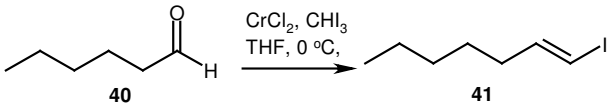
Hydroalumination of alkenes and alkynes at high temperature and high pressure has been known for a long time.[21] *A pronounced positive effect on the ease of reduction is observed when a neighboring hydroxyl group is present because of the formation of intermediate alkoxy hydridoaluminate, facilitating intramolecular hydride delivery (Scheme 6) and allowing for reduction at ambient temperature and atmospheric pressure. These reactions appear to be quite sensitive to solvent effects and THF was found to be the solvent of choice for the selective formation of (E)-olefins.*[22]



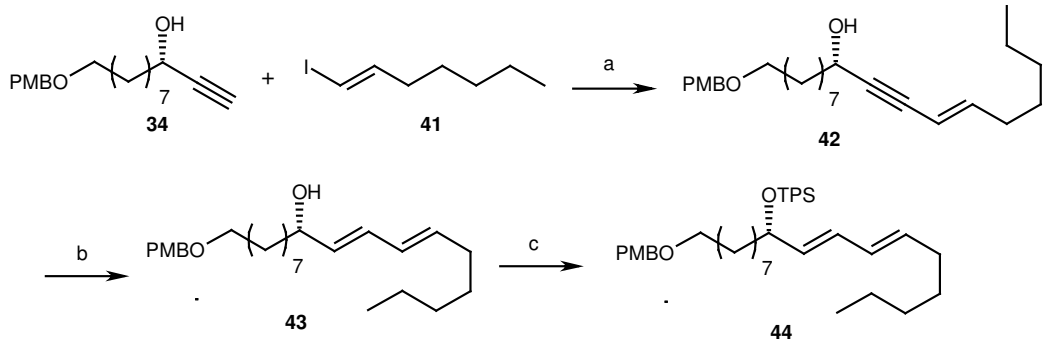
Scheme 6.

3.4.4.2. Synthesis of β-dimorphecolic acid

Trans-vinyliodide **41** was prepared through Takai olefination.[23] Thus, *n*-hexanal was treated with $Cr(II)Cl_2$ and CHI_3 to give *trans*-vinyl iodide in 87% yield with *E*:*Z* = 95:5 selectivity. The ^1H NMR spectrum gave olefin protons at δ 6.01 (doublet) and 5.90 (multiplet) with the coupling constant *J* = 15.4 Hz indicating *trans*-olefin. Having completed the synthesis of chiral propargylic alcohol **34** and *trans*-vinyliodide **41**, we required the generation of the 1,3-diene system through 1,3-dienyne and carry out subsequent reactions to get the target molecules. To this end, we employed Sonogashira coupling[24] of chiral propargylic alcohol **34** and vinyl iodide **41** in the next step. Thus, the coupling of **34** with *trans*-vinyliodide **41** using $Pd(PPh_3)_2Cl_2$ and CuI in triethylamine furnished the 1,3-enyne product **42** in excellent yield. The ^1H NMR spectrum gave olefin protons at δ 5.52 (doublet of doublet) and 6.07-6.26 (multiplet) with the coupling constant *J* = 15.9 Hz indicating *trans*-olefin. Reduction of **42** proceeded smoothly with the required *E*-geometry of the alkyne under reduction conditions using LAH in refluxing THF to afford **43** in good yield. The ^1H NMR spectrum gave olefin protons at δ 5.53 (doublet of doublet, one proton), 5.71 (multiplet, one proton), 6.01 (doublet of doublet, one proton), 6.15 (doublet of doublet, one proton) with coupling constant 15.1-15.9, 10.5 and 6.6 indicating *trans*, *trans* conjugated diene. The free hydroxy group of **43** was protected with TBDPSCl to furnish compound **44** in 96% yield.

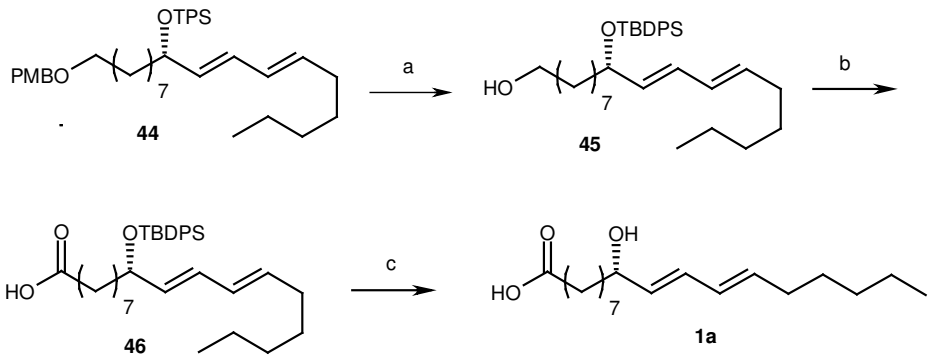


Scheme 7. Preparation of vinyl iodide (**41**).



Scheme 8. *Reagents and conditions*: (a) $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, 11a, 8 h, 86%; (b) LAH, THF, 0 °C to rt, 83%; (c) TBDPSCl, imidazole, CH_2Cl_2, 0 °C to rt, overnight, 96%.

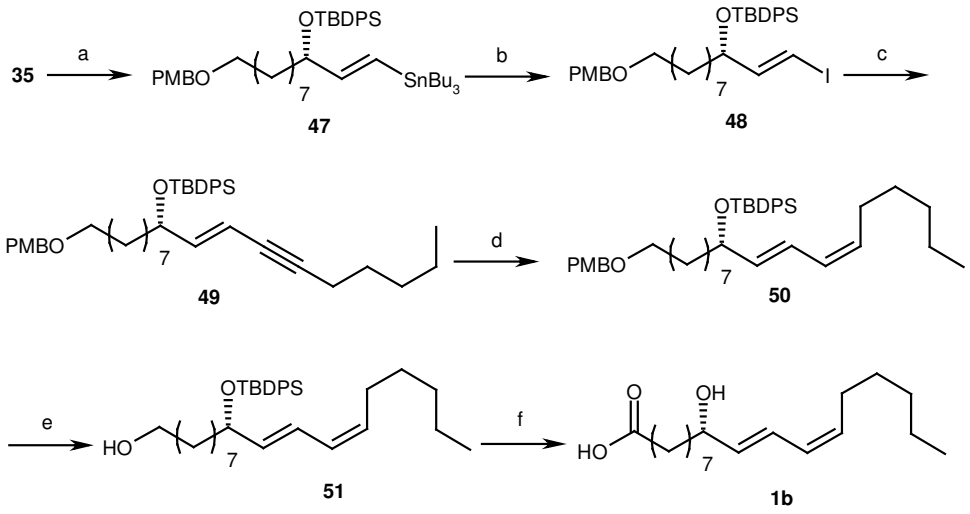
Deprotection of PMB group with DDQ proceeded smoothly to furnish compound **45** in good yield. Oxidation of primary alcohol in **45** to the corresponding aldehyde using Swern conditions and further oxidation using $NaClO_2$ in DMSO under buffer conditions afforded the acid **46**. Finally, TBDPS group was deprotected using TBAF to afford the target molecule **1a** in 89% yield. $[a]_D^{24}$ +15.1 (*c* 0.8 in MeOH) [lit.[15,16,26] $[a]_D^{24}$ +15.4 (*c* 5.0 in MeOH]. M.P: 38–40 °C (lit.[26] 39–40 °C). The IR spectrum of **1a** showed presence of hydroxyl groups at 3422 cm^{-1} and acid carbonyl and C=C at 1712-1458 cm^{-1}. The ^1H NMR spectrum of **1a** gave *trans, trans*-diene protons at δ 5.51 (doublet of doublet, one proton) with coupling constant 15.1 and 6.5 Hz; 5.66 (multiplet, one proton); 6.02 (doublet of doublet, one proton) with coupling constant 15.1 and 10.5 Hz; 6.14 (doublet of doublet, one proton) with coupling constant 15.1 and 10.5 Hz. The chiral proton appeared at δ 4.02 (quartet, one proton) with coupling constant 6.6 Hz. The ^{13}C NMR spectrum gave chiral carbon at δ 72.8; olefinic protons at δ 129.4, 131.0, 133.5, 135.6 and acid carbonyl at δ 178.5. The physical and spectroscopic data of **1b** were identical with those reported.[15, 16, 26]



Scheme 9. *Reagents and conditions*: (a) DDQ, CH_2Cl_2-H_2O (9:1), 89%; (b) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 ^oC to –60 ^oC; (ii) $NaClO_2$, DMSO, H_2O, NaH_2PO_4, rt, 1.5 h; (c) TBAF, THF, rt, overnight, 89%.

3.4.4.3. Synthesis of α-dimorphecolic acid (1b).

To achieve the synthesis of α-dimorphecolic acid (**1b)**, chiral TPS-protected propargylic alcohol was converted into (*E*)-vinyl iodide through vinyl stannane. Thus, acetylene **34** was readily converted into (*E*)-vinyl stannane **47** by reaction with tri-*n*-butyltin hydride and AIBN in refluxing benzene. The ^1H NMR spectrum of **47** gave *trans*-olefinic protons at δ 5.95 (doublet of doublet, one proton) with coupling constant 19.0, 5.1 Hz; 6.36 (doublet, one proton) with coupling constant 19.0 Hz. Tributyltin was then replaced with iodide by using I_2 in CH_2Cl_2[25] to afford the corresponding iodo compound **48** in excellent yield.



Scheme 10. *Reagents and conditions*: (a) $(n\text{-}Bu)_3SnH$, AIBN, C_6H_6, reflux, 4 h, 99%; (b) I_2, CH_2Cl_2, 30 min, 96%; (c) $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, 1-heptyne (**48a**), 6 h, 89%; (d) H_2,

Lindlar's catalyst, EtOAc/pyridine/1-octene (10:1:1), 6 h, 95%; (e) DDQ, CH_2Cl_2-H_2O (9:1), 94%; (f) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 ^oC to –60 ^oC, 95%; (ii) $NaClO_2$, DMSO, H_2O, NaH_2PO_4, rt, 1.5 h, 86%.

The Sonogashira coupling of vinyl iodide **48** with commercially available 1-heptyne **48a** was successfully carried out with $Pd(PPh_3)_2Cl_2$ and CuI in triethylamine to furnish the 1,3-enyne product **49** in excellent yield. The partial hydrogenation of the triple bond in **49** proved to be challenging. Irrespective of whether catalytic quantities or several molar equivalents of quinoline were present, the mixture of **50** and over hydrogenated product was formed. The use of 1-octene as a co-solvent along with EtOAc in the presence of pyridine (EtOAc/pyridine/1-octene = 10:1:1) furnished the diene **50** as a single product. The subsequent deprotection of the *p*-methoxybenzyl group with DDQ furnished the alcohol **51** in 94% yield. Oxidation of the resulting alcohol **51** to the corresponding aldehyde using Swern conditions and further oxidation using sodium chlorite in DMSO under buffer conditions afforded the acid **51**. Finally, TBDPS group was deprotected using TBAF to afford the target molecule **1b** in good yield. $[a]_D^{24}$ **+**13.1 (*c* 0.6 in MeOH) [lit.[15,16,26] $[a]_D^{24}$ **+**11.4 (*c* 1.9 in MeOH]. The IR spectrum of **1b** showed presence of hydroxyl groups at 3600 cm^{-1}; acid carbonyl at 1715; *cis-trans* conjugated double bonds at 950, 985 cm^{-1}. The ^1H NMR spectrum of **1b** gave *cis-trans* double bond protons at δ 5.47 (doublet of triplet, one proton) with coupling constant 11.0 and 7.1 Hz; 5.66 (doublet of doublet, one proton) with coupling constant 15.0 and 7.0 Hz; 5.98 (doublet of doublet, one proton) with coupling constant 11.0 and 11.0 Hz; 6.51 (doublet of doublet, one proton) with coupling constant 15.1 and 11.0 Hz. The chiral proton appeared at δ 4.17 (quartet, one proton) with coupling constant 7.0 Hz. The ^{13}C NMR spectrum gave chiral carbon at δ 73.03; olefinic protons at δ 126.1, 127.9, 133.2, 135.9; acid carbonyl at δ 178.6; methylene carbons at δ 22.6-37.5 and methyl carbon at δ 14.1. The physical and spectroscopic data of **1b** were identical with those reported.[15,16]

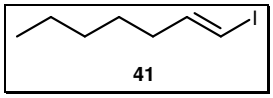
3.4.5. Conclusions

In conclusion, an efficient total synthesis of α- and β-dimorphecolic acid (**1a** and **1b**) with high enantioselectivity has been developed in which the stereocenter was established by Sharpless asymmetric dihydroxylation. Notable features of this approach include

Sonogashira coupling, reduction to establish the *trans*-and *cis*-olefin geometry. Further application of this methodology to the syntheses of other biologically active compounds for the studies of structure activity relationship is currently underway in our laboratory.

3.4.6. Experimental Section

(*E*)-1-Iodohept-1-ene (41):



Anhydrous $CrCl_2$ (22.09 g, 179.71 mmol) is suspended in THF (150 mL) under argon atmosphere. A solution of hexanaldehyde (3.0 g, 29.95 mmol) and iodoform (23.58 g, 59.90 mmol) in THF (30 mL) is added dropwise to the suspension at 0 ^oC. After stirring at 0 ^oC for 3 h, the reaction mixture is poured into water (100 mL) and extracted with ether (3 x 100 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) as eluent gave **41** (*E* : *Z* = 95:5) as a pale yellow oil. (5.90 g) 88%

Yield: 5.90 g (88%).

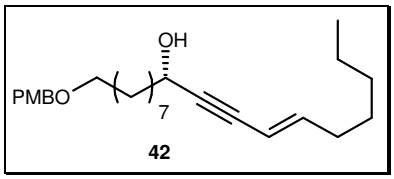
Mol. Formula: $C_7H_{13}I$

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.92 (t, *J* = 7.1 Hz, 3H), 1.26-1.43 (m, 6H), 1.62 (q, *J* = 7.4 Hz, 1H), 2.00-2.18 (m, 1H), 6.01 (d, *J* = 15.4 Hz, 1H), 6.44-6.59 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 22.9, 28.5, 32.1, 34.4, 141.2, 82.1.

Analysis: Calcd.: C, 37.52; H, 5.85; I, 56.63%; **Found:** C, 37.81; H, 5.72; I, 56.56%.

(*S*,*E*)-1-(4-Methoxybenzyloxy)octadec-12-en-10-yn-9-ol (42).



To a stirred mixture of $Pd(PPh_3)_2Cl_2$ (276 mg, 0.39 mmol), CuI (225 mg, 1.18 mmol) in Et_3N (2 mL) were added solutions of (*E*)-1-iodohept-1-ene **41** (1.50 g, 6.70 mmol) in Et_3N (2 mL) and acetylene **34** (1.2 g, 3.94 mmol) in Et_3N (2 mL) under argon. After 6 h, the reaction mixture was filtered through celite and filtrate was concentrated. Silica gel column

chromatography of the crude product using petroleum ether/EtOAc (9:1) as eluent gave **42** as a pale yellow oil.

Yield: 1.36 g (86%).

Mol. Formula: $C_{26}H_{40}O_3$

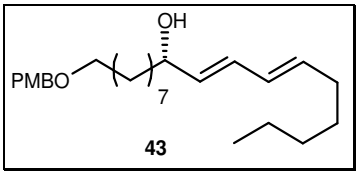
$[\alpha]_D^{25}$: +1.75 (*c* 0.8, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 3440, 2938, 2864, 1736, 1612, 1513, 1248, 1130 and 1032.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, *J*=6.7 Hz, 3H), 1.20-1.52 (m, 16H), 1.53-1.75 (m, 4H), 2.01-2.20 (m, 2H), 3.44 (t, *J*=6.6 Hz, 2H), 3.81 (s, 3H), 4.12-4.26 (m, 1H), 4.44 (s, 2H), 5.52 (dd, *J*=15.9, 1.64 Hz, 1H), 6.07-6.26 (m, 1H), 6.90 (d, *J*=8.7 Hz, 2H), 7.29 (d, *J*=8.7 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 22.5, 25.4, 25.6, 25.7, 28.3, 29.2, 29.4, 29.7, 31.2, 32.9, 38.4, 55.2, 64.4, 70.2, 72.5, 83.7, 89.2, 109.1, 113.7, 129.1, 130.9, 144.4, 159.1. **Analysis: Calcd.:** C, 77.95; H, 10.06%; **Found:** C, 78.21; H, 10.11%.

(*S*,10*E*,12*E*)-1-(4-Methoxybenzyloxy)octadeca-10,12-dien-9-ol (43).



43

To a suspension of lithium aluminum hydride (61 mg, 1.62 mmol) in THF (40 ml) was added a solution of **42** (650 mg, 1.62 mmol) in THF (40 ml) at 0 °C. The mixture was warmed to room temperature, and stirred for 10 min. The mixture was refluxed for 1 h, and then cooled to 0 °C. The reaction was quenched with saturated aqueous potassium sodium tartarate solution. After the suspension was stirred vigorously, the aqueous layer was extracted with ether. The ethereal extract was washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) as eluent gave **43** as a pale yellow oil.

Yield: 542 mg (83%).

Mol. Formula: $C_{26}H_{42}O_3$

$[\alpha]_D^{25}$: +13.1 (*c* 0.3, $CHCl_3$)

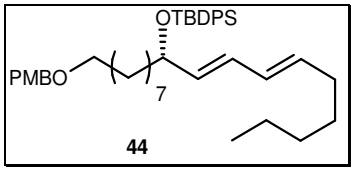
IR (neat, cm^{-1}): ν_{max} 3400, 2938, 2863, 1612, 1513, 1457, 1216, 1054, 990.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.91 (t, *J* = 6.7 Hz, 3H), 1.21-1.52 (m, 16H), 1.53-1.76 (m, 4H), 2.08 (q, *J* = 6.8 Hz, 2H), 3.46 (t, *J* = 6.6 Hz, 2H), 3.83 (s, 3H), 4.05-4.24 (m, 1H), 4.46 (s, 2H), 5.53 (dd, *J* = 15.9, 6.5 Hz, 1H), 5.71 (m, 1H), 6.01 (dd, *J* = 15.1, 6.6 Hz, 1H), 6.15 (dd, *J* = 15.2, 10.5 Hz, 1H), 6.93 (d, *J* = 8.7 Hz, 2H), 7.29 (d, *J* = 8.7 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.8, 22.5, 25.4, 25.7, 28.9, 29.3, 29.4, 29.5, 31.4, 32.6, 32.8, 37.3, 55.0, 72.9, 73.1, 113.5, 129.1, 129.5, 130.1, 131.0, 133.6, 135.8, 158.8.

Analysis: Calcd.: C, 77.56; H, 10.51%; **Found:** C, 77.62; H, 10.33%.

((*S*,10*E*,12*E*)-1-(4-Methoxybenzyloxy)octadeca-10,12-dien-9-yloxy)(*tert*-butyl)diphenylsilane (44).



44

Compound **44** was prepared following the procedure as described for compound **35** in 96% yield as a colorless liquid.

Mol. Formula: $C_{42}H_{60}O_3Si$

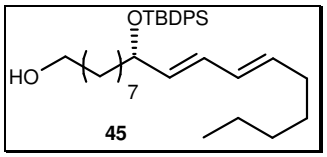
$[\alpha]_D^{25}$: +19.5 (*c* 0.7, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 2938, 2864, 1736, 1612, 1513, 1248, 1130, 1032.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, *J*=6.7 Hz, 3H),1.04 (s, 9H), 1.19-1.50 (m, 16H), 1.53-1.81 (m, 4H), 2.07 (q, *J*=7.0 Hz, 2H), 3.45 (t, *J*=6.6 Hz, 2H), 3.81 (s, 3H), 4.10 (q, *J*=6.8 Hz, 1H), 4.44 (s, 2H), 5.56 (dd, *J*=15.2, 6.6 Hz, 1H), 5.70 (m, 1H), 6.01 (dd, *J*=15.1, 6.8 Hz, 1H), 6.16 (dd, *J*=15.2, 10.5 Hz, 1H), 6.89 (d, *J*=8.7 Hz, 2H), 7.29 (d, *J*=8.7 Hz, 2H), 7.36-7.46 (m, 6H), 7.64-7.79 (m, 4H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9, 19.2, 22.5, 25.7, 25.8, 26.9, 28.9, 29.2, 29.5, 29.7, 31.4, 32.5, 32.7, 37.9, 54.9, 64.3, 70.3, 72.5, 113.8, 127.5, 127.6, 127.7, 129.1, 129.4, 129.5, 129.6, 130.1, 131.1, 133.4, 134.0, 135.7, 135.9, 159.0.

(*S*,10*E*,12*E*)-9-(*tert*-Butyldiphenylsilyloxy)octa- deca-10,12-dien-1-ol (45).



45

To a stirring solution of PMB ether **44** (380 mg, 0.59 mmol) in CH_2Cl_2/H_2O (10.5, 20:1) was added DDQ (161 mg, 0.71 mmol). The resulting mixture was stirred for 45 min at rt. The mixture was poured into saturated aqueous $NaHCO_3$ and further diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was then filtered through a pad of celite and washed with 50% EtOAc/hexanes (20 mL). The solvents were removed under reduced pressure to give the crude product mixture as yellow oil. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (7:3) as eluent gave **45** as a colorless oil

Yield: 275 mg (89%).

Mol. Formula: $C_{34}H_{52}O_2Si$

$[\alpha]_D^{25}$: +6.28 (*c* 0.9, $CHCl_3$).

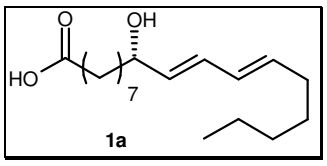
IR (neat, cm^{-1}): ν_{max} 3400, 2928, 2855, 1659, 1589, 1464, 1427, 1389, 1216, 1112, 986.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, *J*=6.7 Hz, 3H), 1.04 (s, 9H), 1.19-1.50 (m, 16H), 1.53-1.81 (m, 4H), 2.08 (q, *J*=7.0 Hz, 2H), 3.64 (t, *J*=6.6 Hz, 2H), 4.12 (q, *J*=6.6 Hz, 1H), 5.56 (dd, *J*=15.2, 6.6 Hz, 1H), 5.70 (dt, *J*=15.2, 7.1 Hz, 1H), 6.02 (dd, *J*=15.1, 10.5 Hz, 1H), 6.16 (dd, *J*=15.2, 10.4 Hz, 1H), 7.36-7.45 (m, 6H), 7.66-7.78 (m, 4H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 19.2, 22.5, 25.6, 25.8, 26.9, 28.8, 29.5, 29.7, 31.5, 32.6, 32.7, 37.4, 64.1, 73.1, 127.6, 129.4, 129.5, 131.1, 133.6, 134.3, 135.7.

Analysis: Calcd.: C, 78.40; H, 10.06; **Found:** C, 78.61; H, 9.87.

(9*S*,10*E*,12*Z*)-9-Hydroxy-10,12-octadecadienoic acid [β-Dimorphecolic acid] (1a).



1a

A solution of oxalyl chloride (76 mg, 0.053 mL, 0.60 mmol) in dry CH_2Cl_2 (20 mL) at -78 ^oC was added dropwise dry DMSO (94 mg, 0.085 mL, 1.90 mmol) in CH_2Cl_2 (5 mL). After 30 min, alcohol **45** (210 mg, 0.40 mmol) in CH_2Cl_2 (5 mL) was added over 10 min giving a copious white precipitate. After stirring for 1 h at −78 ^oC, the reaction mixture was brought to -60 ^oC and Et_3N (0.163 g, 0.22 mL, 1.61 mmol) was added slowly and stirred for 30 min allowing the reaction mixture to warm to room temperature. The reaction mixture was poured into water (50 mL) and the organic layer was separated. The aqueous layer was

extracted with CH_2Cl_2 (2 x 25 mL) and combined organic layers were washed with water (3 x 20 mL), brine (20 mL), dried (Na_2SO_4) and passed through short pad of silica gel. The filtrate was concentrated to give the aldehyde (302 mg) as pale yellow syrup, which was used as such for the next step without further purification.

A solution of 79% $NaClO_2$ (68 mg, 0. 60 mmol) in 1.0 mL of water was added dropwise to a stirred solution of above crude aldehyde (209 mg, 0.40 mmol) in 0.5 mL of DMSO and NaH_2PO_4 (97 mg, 0.81 mmol) in 1.0 mL of water in 5 min at room temperature. The mixture was left overnight at room temperature and then 5% aqueous solution of $NaHCO_3$ was added. The aqueous phase was extracted three times with CH_2Cl_2 and washed with brine, dried (Na_2SO_4) and concentrated give the crude product **46**, which was used as such for the next step without further purification.

The above crude compound **46** (215 mg, 0.40 mmol) was dissolved in THF (5 mL), followed by the dropwise addition of TBAF (0.80 mL, 1M solution in THF, 0.80 mmol). The reaction mixture was stirred at room temperature for overnight and the reaction mixture was quenched by addition of water, and aqueous layer was extracted with EtOAc (3 x 30 mL) and combined EtOAc extracts were washed with brine, dried (Na_2SO_4), and concentrated give the crude product as a cream-colored solid which was then triturated with acetone to provide the acid **1a**.

Yield: 82 mg (69% yield over three steps).

M.P: 38–40 ^oC (lit.[26] 39–40 ^oC).

Mol. Formula: $C_9H_{16}O_2$

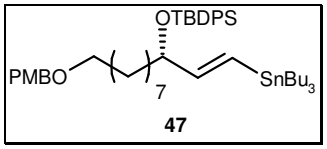
$[\alpha]_D^{25}$: **+**15.1 (*c* 0.8 in MeOH); [lit.[26] $[a]_D^{24}$ **+**15.4 (*c* 5.0 in MeOH].

IR (KBr, cm^{-1}): ν_{max} 3422, 2924, 2869, 1712, 1459, 1321, 1211, 986.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, *J*=6.8 Hz, 3H), 1.19-1.51 (m, 16H), 1.53-1.81 (m, 4H), 2.06 (q, *J*=7.0 Hz, 2H), 2.24 (t, *J*=7.5 Hz, 2H), 4.02 (q, *J*=6.6 Hz, 1H), 5.51 (dd, *J*=15.1, 6.5 Hz, 1H), 5.66 (m, 1H), 6.02 (dd, *J*=15.1, 10.5 Hz, 1H), 6.14 (dd, *J*=15.1, 10.5 Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 22.5, 24.9, 25.3, 28.9, 29.1, 29.3, 29.7, 31.4, 32.6, 34.1, 37.2, 72.8, 129.4, 131.0, 133.5, 135.6, 178.5.

((*S*,*E*)-11-(4-Methoxybenzyloxy)-1-(tributylstannyl)undec-1-en-3-yloxy)(*tert*-butyl)diphenylsilane (47).



47

To a stirred solution of **35** (1.80 g, 3.32 mmol) in benzene (30 mL) were added *n*-Bu_3SnH (1.07 mL, 3.98 mmol) and AIBN (catalytic) at room temperature under N_2. The reaction mixture was gently refluxed with stirring for 4 h. The solvent was removed and the residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1) as eluent to give **47** as colorless oil.

Yield: 2.74 g (99%).

Mol. Formula: $C_{47}H_{74}O_3SiSn$

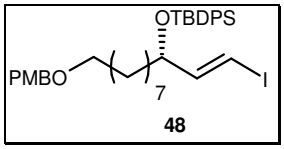
$[\alpha]_D^{25}$: –9.8 (*c* 0.64, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 3004, 2957, 2928, 2853, 1612, 1513, 1464, 1378, 1247, 1173, 1036.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88-0.93 (m, 9H), 1.10 (s, 9H), 1.24 (br s, 10H), 1.26-1.31 (m, 10H), 1.42-1.74 (m, 12 H), 3.44 (t, *J*=6.6 Hz, 2H), 3.82 (s, 3H), 4.12 (q, *J*=6.6 Hz, 1H), 4.45 (s, 2H), 5.95 (dd, *J*=19.0, 5.1 Hz, 1H), 6.36 (d, *J*=19.0 Hz, 1H), 6.92 (d, *J*=8.7 Hz, 2H), 7.31 (d, *J*=8.6 Hz, 2H), 7.37-7.45 (m, 6H), 7.64-7.79 (m, 4H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 8.9, 9.4, 10.2, 10.6, 11.2, 13.5, 19.3, 24.2, 24.5, 26.1, 26.4, 26.9, 28.9, 29.3, 29.3, 29.7, 37.2, 38.1, 55.2, 61.8, 69.9, 72.3, 113.6, 117.0, 127.2, 127.3, 127.4, 129.2, 129.5, 129.56, 129.65, 129.7, 130.8, 133.9, 134.5, 134.9, 135.7, 135.9, 144.9, 159.1.

((*S*,*E*)-11-(4-Methoxybenzyloxy)-1-iodoundec-1-en-3-yloxy)(*tert*-butyl)diphenylsilane (48).



48

To a cooled (0 ^oC), stirred solution of **47** (1.60 g, 1.92 mmol) in CH_2Cl_2 (40 mL) was added iodine (973 mg, 3.84 mmol). After 10 min at 0 ^oC, the reaction mixture was diluted with CH_2Cl_2, washed with saturated $Na_2S_2O_3$, 10% KF solutions, and brine. The organic layer

was dried (Na_2SO_4), filtered, and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9.5:0.5) as eluent gave **48** as a yellowish oil.

Yield: 1.24 g (96%).

Mol. Formula: $C_{35}H_{47}IO_3Si$

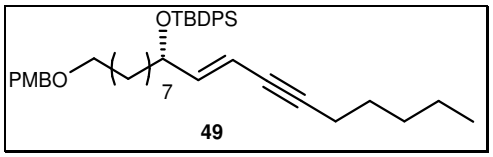
$[\alpha]_D^{25}$: −6.1 (*c* 0.48, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 2948, 2933, 2861, 1612, 1515, 1465, 1372, 1174, 1092, 948.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.10 (s, 9H), 1.24 (br s, 10H), 1.53-1.72 (m, 4H), 3.47 (t, *J*=6.1 Hz, 2H), 3.92 (s, 3H), 4.12 (q, *J*=6.6 Hz, 1H), 4.45 (s, 2H), 6.29 (m, 2H), 6.53 (d, *J*=8.7 Hz, 2H), 7.31 (d, *J*=8.6 Hz, 2H), 7.37-7.45 (m, 6H), 7.64-7.79 (m, 4H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 19.2, 24.3, 24.5, 26.1, 26.5, 26.8, 28.9, 29.25, 29.28, 29.65, 37.2, 38.1, 55.0, 62.8, 70.1, 72.2, 114.0, 117.0, 127.2, 127.3, 127.4, 128.6, 129.5, 129.6, 129.7, 130.8, 133.9, 134.5, 134.9, 135.7, 135.9, 147.6, 161.4.

((*S*,*E*)-1-(4-Methoxybenzyloxy)octadec-10-en-12-yn-9-yloxy)(*tert*-butyl)diphenylsilane (49).



49

Compound **49** was prepared following the procedure as described for compound **42** in 89% yield as pale yellow oil.

Mol. Formula: $C_{42}H_{58}O_3Si$

$[\alpha]_D^{25}$: −15.4 (*c* 0.4, $CHCl_3$).

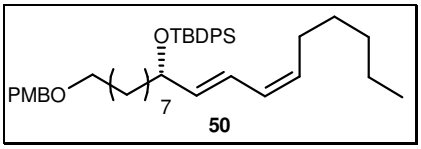
IR (neat, cm^{-1}): ν_{max} 3004, 2957, 2928, 2853, 1612, 1513, 1464, 1378, 1247, 1173, 1036.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, *J*=6.7 Hz, 3H), 1.04 (s, 9H), 1.20-1.52 (m, 16H), 1.53-1.81 (m, 4H), 2.08 (q, *J*=6.8 Hz, 2H), 3.49 (t, *J*=6.6 Hz, 2H), 3.81 (s, 3H), 4.14-4.28 (m, 1H), 4.44 (s, 2H), 5.72 (dd, *J*=15.9, 1.64 Hz, 1H), 6.03-6.24 (m, 1H), 6.91 (d, *J*=8.7 Hz, 2H), 7.29 (d, *J*=8.7 Hz, 2H), 7.36-7.45 (m, 6H), 7.66-7.78 (m, 4H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 19.2, 22.6, 25.7, 25.8, 26.9, 28.9, 29.2, 29.5, 29.7, 31.4, 32.5, 32.7, 37.9, 55.1, 64.6, 71.3, 72.5, 81.8, 82.4, 113.8, 127.5, 127.6, 127.7, 129.0, 129.4, 129.6, 130.5, 132.5, 133.8, 134.0, 135.7, 135.9, 159.1.

Analysis: Calcd.: C, 78.94; H, 9.15%; **Found:** C, 79.22; H, 9.01%

((*S*,10*E*,12*Z*)-1-(4-Methoxybenzyloxy)octadeca-10,12-dien-9-yloxy)(*tert*-butyl)diphenyl-silane (50).



50

To a solution of **49** (620 mg, 0.97 mmol) in 10 mL of ethyl acetate/pyridine/1-octene (10:1:1) was added Lindlar's catalyst (20 mg). The reaction mixture was stirred for 6 h under a balloon of H_2 at room temperature and filtered through a celite pad. The filtrate was concentrated and the residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1) as eluent to give **50** (590 mg, 95%) as a pale yellow oil.

Yield: 11.30 g (89%).

Mol. Formula: $C_{42}H_{60}O_3Si$

$[\alpha]_D^{25}$: +12.59 (*c* 0.43, $CHCl_3$)

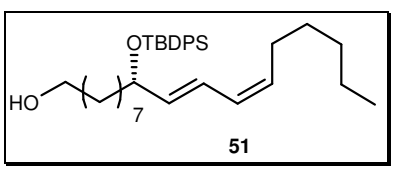
IR (neat, cm^{-1}): ν_{max} 3600, 1715, 985, 950.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.90 (t, *J*=6.8 Hz, 3H), 1.04 (s, 9H), 1.19-1.51 (m, 16H), 1.54-1.80 (m, 4H), 2.09 (q, *J*=7.1 Hz, 2H), 3.45 (t, *J*=6.6 Hz, 2H), 3.81 (s, 3H), 4.12 (q, *J*=6.9 Hz, 1H), 4.41 (s, 2H), 5.49 (dt, *J* = 11.0, 7.1 Hz, 1H), 5.64 (dd, *J* = 15.0, 7.0 Hz, 1H), 6.01 (dd, *J* = 11.0, 11.0 Hz, 1H), 6.51 (dd, *J* = 15.1, 11.0 Hz, 1H), 6.90 (d, *J*=8.7 Hz, 2H), 7.30 (d, *J*=8.7 Hz, 2H), 7.36-7.48 (m, 6H), 7.66-7.79 (m, 4H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9, 19.2, 22.5, 25.7, 25.8, 26.9, 28.9, 29.2, 29.5, 29.7, 31.4, 32.5, 32.7, 37.9, 54.9, 64.9, 70.5, 72.3, 113.8, 113.8, 126.1, 127.5, 127.6, 127.9, 129.1, 129.4, 129.5, 129.6, 130.1, 131.1, 133.4, 134.0, 135.7, 135.9, 159.0.

Analysis: Calcd.: C, 78.70; H, 9.43%; **Found:** C, 78.84; H, 9.28%.

(*S*,10*E*,12*Z*)-9-(*tert*-Butyldiphenylsilyloxy)octadeca-10,12-dien-1-ol (51).



51

Compound **51** was prepared following the procedure as described for compound **45** in 94% yield as a colorless liquid.

Mol. Formula: $C_{34}H_{52}O_2Si$

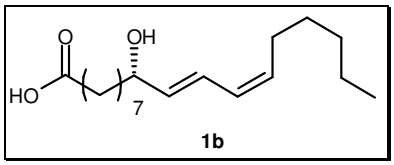
$[\alpha]_D^{25}$: +10.1 (*c* 0.39, $CHCl_3$)

IR (neat, cm^{-1}): ν_{max} 3400, 2928, 2855, 1659, 1589, 1464, 1427, 1389, 1216, 1112, 986, 950, 985.

^{1}H NMR (200 MHz, $CDCl_3$): 0.89 (t, *J*=6.7 Hz, 3H), 1.05 (s, 9H), 1.19-1.52 (m, 16H), 1.53-1.79 (m, 4H), 2.21 (q, *J*=7.0 Hz, 2H), 3.68 (t, *J*=6.6 Hz, 2H), 4.07 (q, *J*=7.1 Hz, 1H), 5.56 (dd, *J*=15.2, 6.6 Hz, 1H), 5.70 (m, 1H), 6.02 (dd, *J*=15.1, 10.5 Hz, 1H), 7.36-7.45 (m, 6H), 7.66-7.78 (m, 4H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 19.2, 22.9, 25.7, 25.8, 26.9, 28.8, 29.5, 29.7, 31.4, 32.6, 32.7, 37.8, 64.4, 73.1, 126.3, 127.6, 127.9, 129.4, 129.5, 133.2, 134.1, 135.7.

α-Dimorphecolic acid (1b). Compound **1b** was prepared following the procedure as described for compound **1a** in 89% yield as a yellow syrupy.



1b

Mol. Formula: $C_9H_{16}O_2$

$[\alpha]_D^{25}$: +2.0 (*c* 0.41, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 3600, 1715, 950, 985.

^{1}H NMR (200 MHz, $CDCl_3$): 0.90 (t, *J*=6.7 Hz, 3H), 1.19-1.50 (m, 16H), 1.52-1.79 (m, 4H), 2.20 (m, 2H), 2.36 (t, *J*=7.0 Hz, 2H), 4.17 (q, *J*=7.0 Hz, 1H), 5.47 (dt, *J*=11.0, 7.1 Hz, 1H), 5.66 (dd, *J*=15.0, 7.0 Hz, 1H), 5.98 (dd, *J*=11.0, 11.0 Hz, 1H), 6.51 (dd, *J*=15.1, 11.0 Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 22.5, 25.6, 25.8, 26.9, 28.8, 29.5, 29.7, 31.5, 32.6, 32.7, 37.4, 73.0, 126.2, 127.9, 133.2, 135.9, 178.6.

3.1.7. Spectra

1] ^{1}H NMR Spectrum of **49**

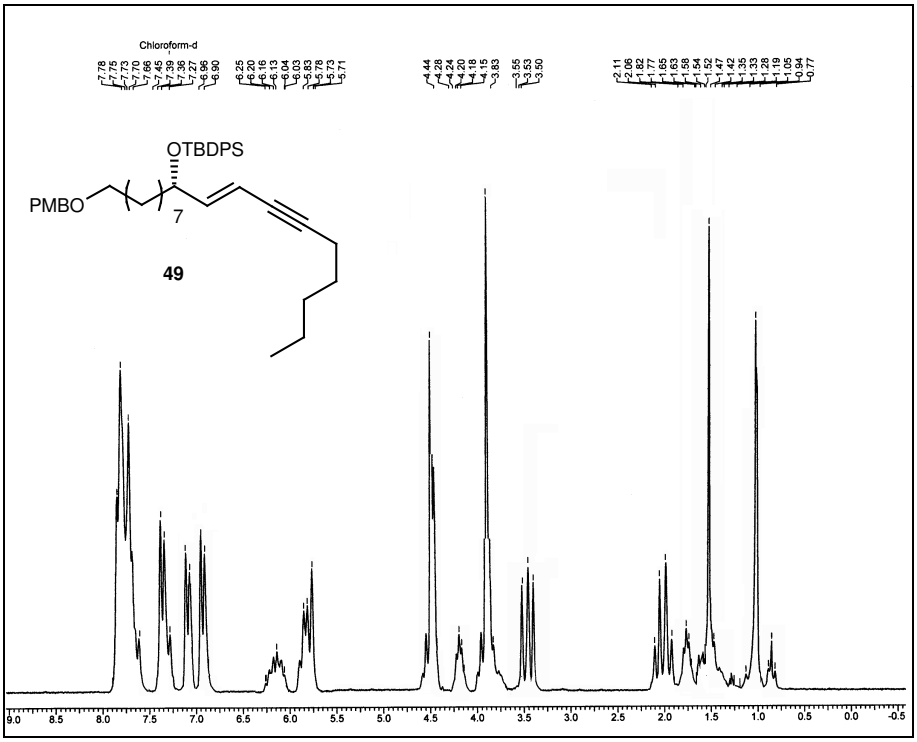
2] ^{13}C NMR Spectrum of **49**

3] ^{1}H NMR Spectrum of **1a**

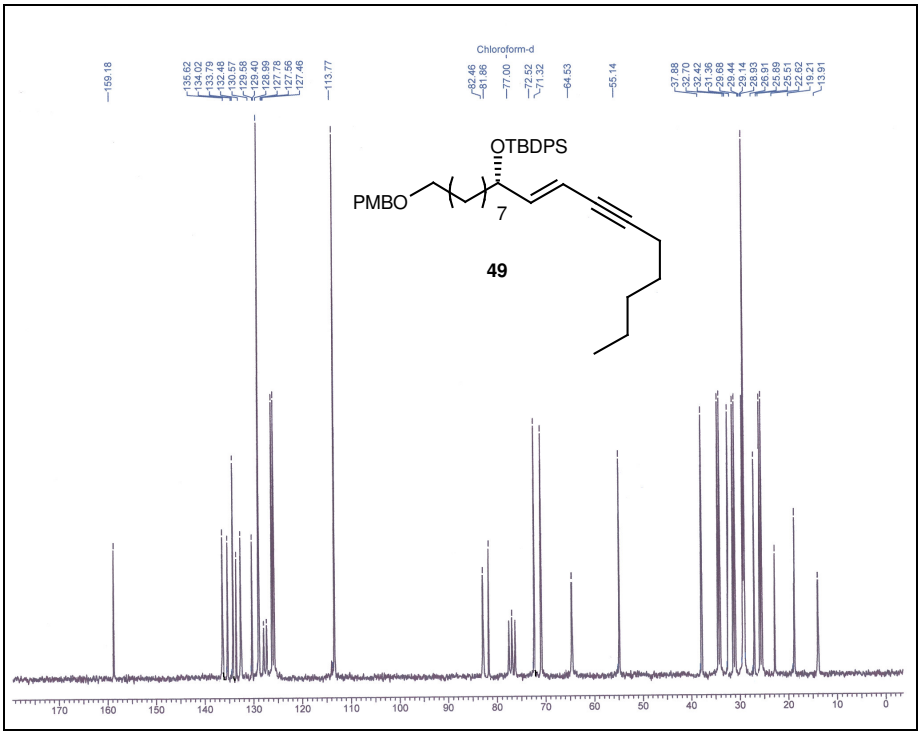
4] ^{13}C NMR Spectrum of **1a**

5] ^{1}H NMR Spectrum of **1b**

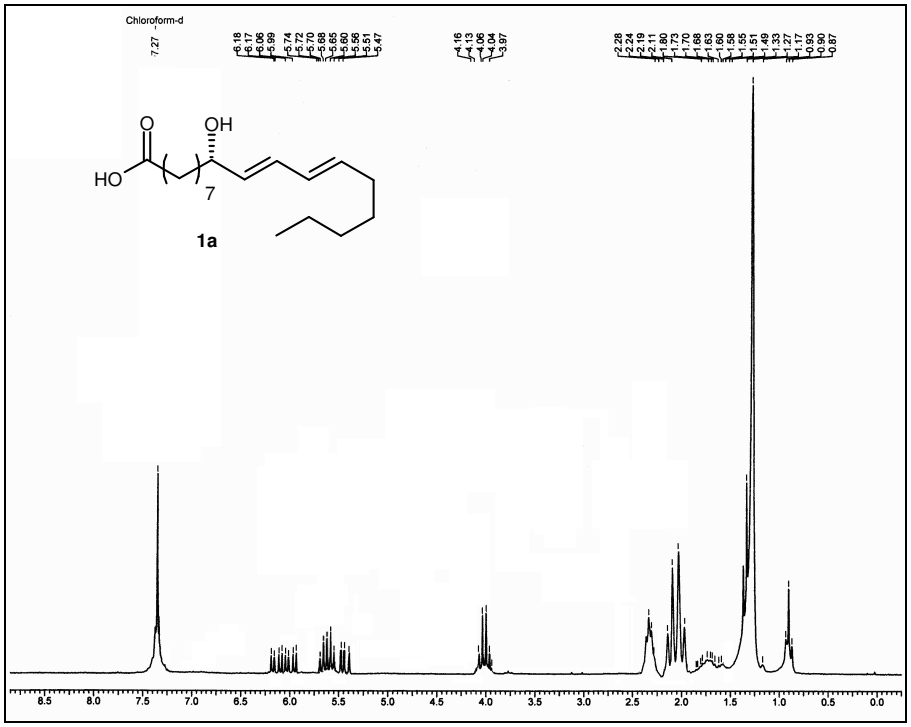
6] ^{13}C NMR Spectrum of **1b**



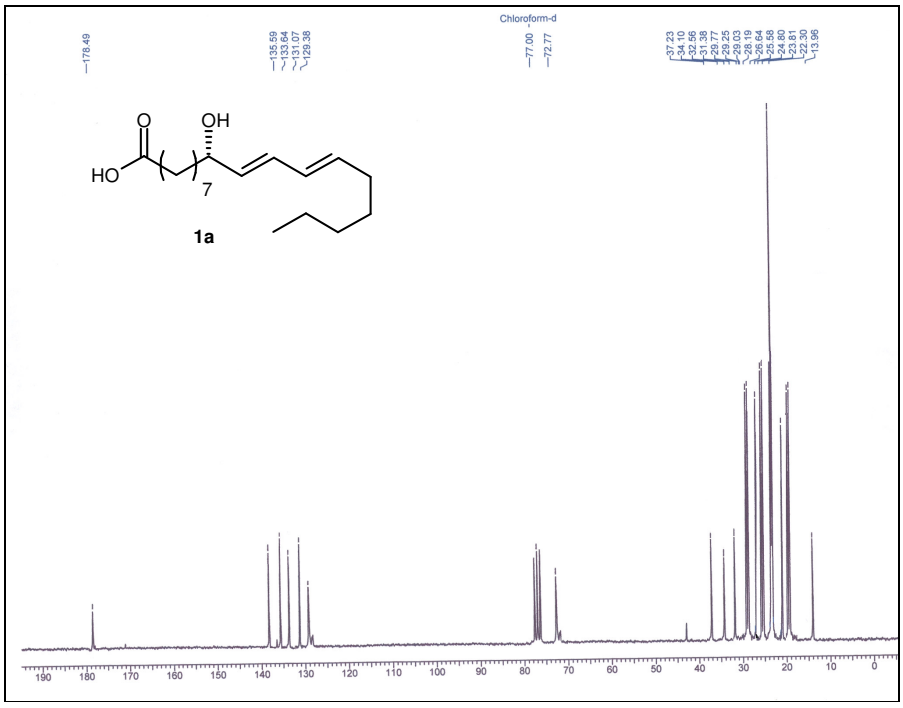
^{1}H NMR Spectrum of **49**



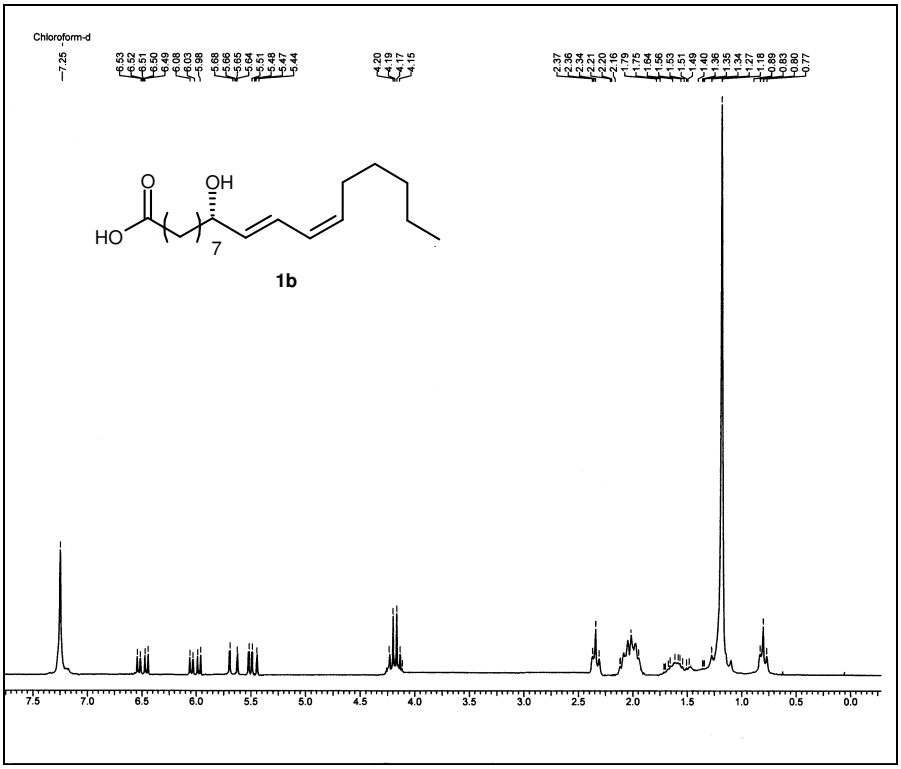
^{13}C NMR Spectrum of **49**



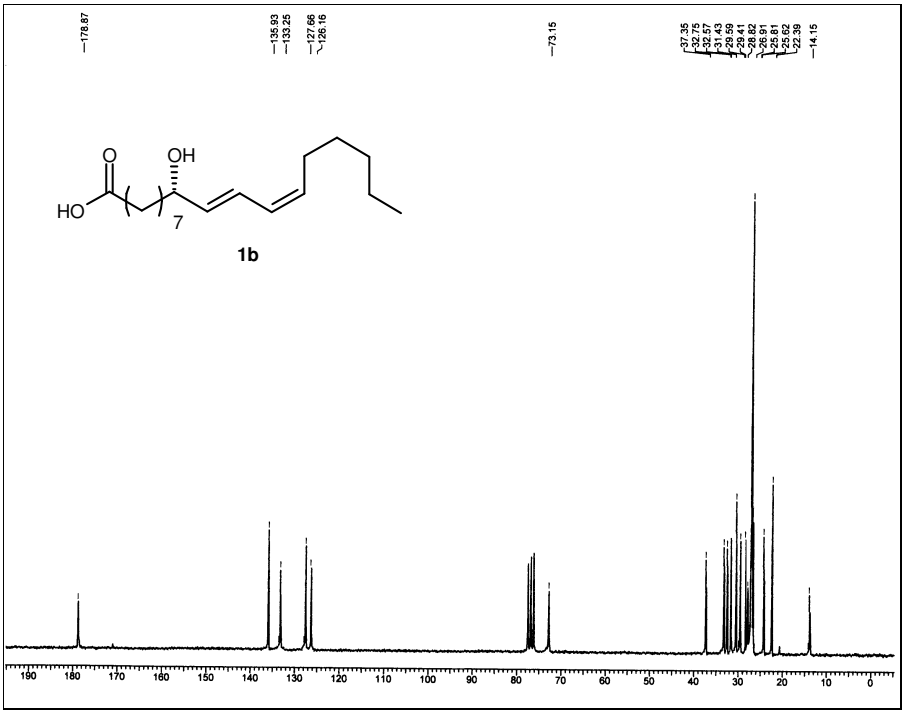
^{1}H NMR Spectrum of β-Dimorphecolic acid **(1a)**



^{13}C NMR Spectrum of β-Dimorphecolic acid **(1a)**



^{1}H NMR Spectrum of α-Dimorphecolic acid **(1b)**



^{13}C NMR Spectrum of α-Dimorphecolic acid **(1b)**

3.4.8. References:

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CHAPTER -IV

A simple and efficient Approach to 1,3-polyols.

SECTION A:

1. Total syntheses of (+)-Strictifolione and The Lactone moiety of HMG-CoA Reductase Inhibitor: Compactin and Mevinolin

SECTION B:

3. A simple and efficient Approach to 1,3-aminoalcohols: Application to the Synthesis of (+)-Negamycin

4.1. SECTION A:

TOTAL SYNTHESES OF (+)-STRICTIFOLIONE AND THE LACTONE MOIETY OF HMG-COA REDUCTASE INHIBITOR: COMPACTIN AND MEVINOLIN

4.1.1. INTRODUCTION:

4.1.1.1. (+)-Strictifolione:

Optically active *syn*-and *anti*-1,3-polyols/5,6-dihydropyran-2-ones are ubiquitous structural motifs in various biologically active compounds. α,β-Unsaturated δ-lactone[1] functionality is presumed to be responsible for biological activities as a result of its ability to act as a Michael acceptor, enabling these molecules to bind to a target enzyme. The pyrone units are widely distributed in all parts of plants (Lamiaceae, Piperaceae, Lauraceae, and Annonaaceae families) including leaves, stems, flowers, and fruits.

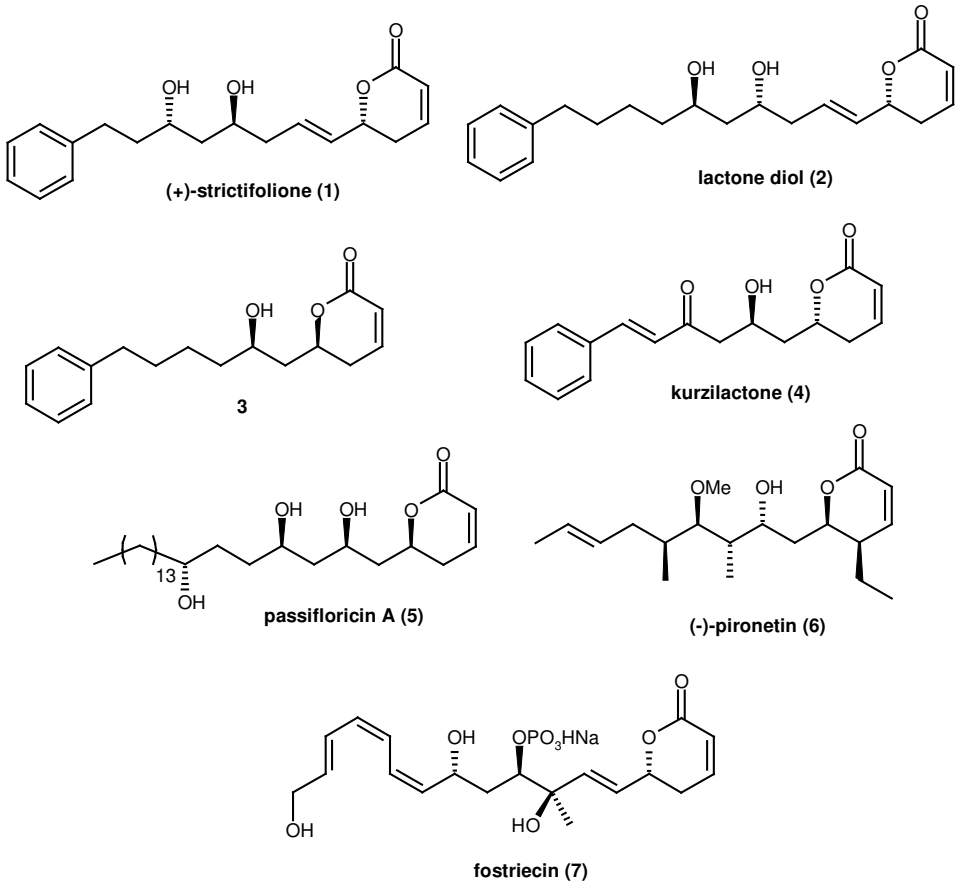


Figure 1.

(+)-Strictifolione (**1**, Figure 1) has been isolated by Aimi *et al*. from the stem bark of *Cryptocaria strictifolia* in West Kalimantan, Indonesia.[2] The main structural features of (+)-strictifolione (**1**) are an *anti*-1,3-diol and a 6-substituted 5,6-dihydro-α-pyrone[3] subunit, which are present in various natural products with important biological activities, e.g. the polyene macrolides[4] and the leptomycin family[5] of natural products, respectively. The relative stereochemistry of the 1,3-diol function at C4′ and C6′ was elucidated from the ^{1}H NMR spectrum of the acetonide derivative, and the absolute configurations of their stereogenic centers were deduced by the Mosher method. The absolute configuration at C6 was assumed based on the Cotton effect in the CD spectrum and confirmed by the synthesis of the two isomers at C6 with the (*R*)- and (*S*)-configurations.

Recently, a number of 5,6-dihydro-α-pyrone derivatives having an alkyl side chain at the C6 position, with 1,3- or 1,5-diol units, have been isolated from plants. The biological activities of these compounds have not been completely studied, but it seems that the activity depends on the substituents on the alkyl side chain. Some of these compounds have been found to exhibit antifungal activity such as passifloricin A (**5**),[6] to inhibit the cell cycle progression in the M-phase and to be an immunosuppressive agent such as (-)-pironetin (**6**),[7] an anticancer agent such as fostriecin (**7**),[8] antifungal agent such as lactone diol **2**,[9] cytotoxic agent such as kurzilactone (**4**).[10]

4.1.1.2. Lactone moiety of HMG-CoA Reductase Inhibitors: Compactin and Mevinolin:

In 1976, Endo *et al.*[11a-c] at the Sankyo Co. and Brown *et al.*[11d] at Beecham Pharmaceuticals isolated a potent competitive inhibitor of hydroxymethylglutaryl coenzyme A reductase (HMGCoA reductase) from the metabolites of *Penicillium citrinum* and *Penicillium brevicompactum*, respectively. The new compound, shown to have structure **8**, was named ML 236B by the Japanese group and 'compactin' by the British workers. In 1980, Alberts *et al.*[12] at Merck, Sharp and Dohme, reported the isolation of a relative of compactin from *Aspergillus terrus*. The Merck compound was named 'mevinolin' and shown to have the absolute stereostructure **9**. The identical fungal metabolite was isolated from Monascus rubber and named monacolin K.[13] The Merck group also discovered that the active forms of compactin and mevinolin are the respective open-chain dihydroxy acids **12** and **13**.

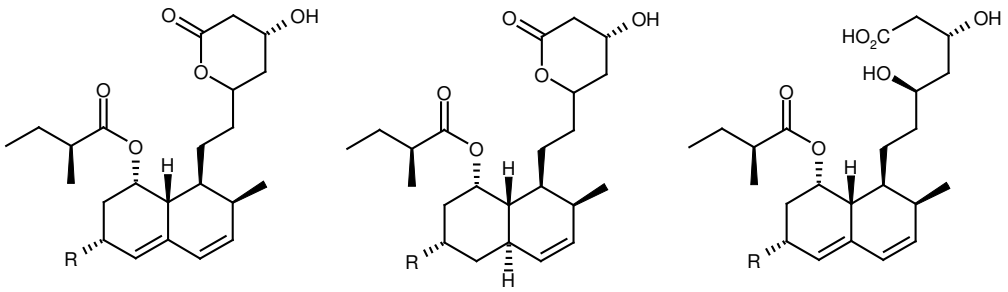
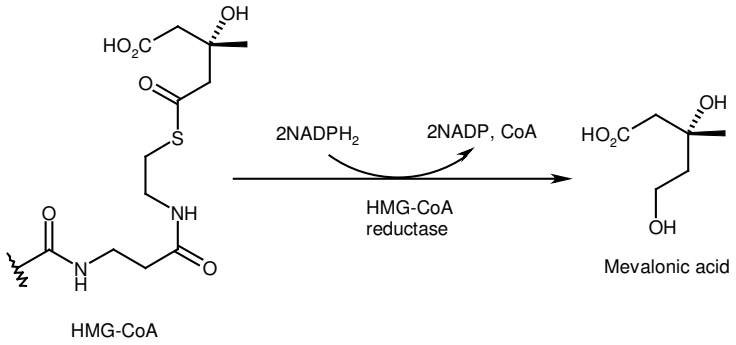


Figure 2.

In humans, more than one-half of total body cholesterol is derived from *de novo* synthesis.[14] The rate-limiting step in cholesterol biosynthesis is the reduction of HMG-CoA to mevalonic acid.[15]



Scheme 1.

Because of their potent inhibitory activity on this key enzyme, there is the attractive possibility that compactin or some related compounds might be useful as hypocholesterolemic agents. Indeed, compactin has been shown to lower serum cholesterol levels in dogs,[16] cynomolgus monkeys,[17] and humans.[18] Compactin also has been used as a tool by biochemists in elegant studies which have provided insight into the mechanism by which mammalian cells regulate HMG-CoA reductase.[19] More recently the dihydro derivatives of compactin[20] and mevinolin,[21] **10** and **11**, respectively, have been isolated. The class of compounds, distinguished by a highly functionalized decalin unit and a β-hydroxy-δ-lactone portion linked by an ethylene bridge, are collectively referred to as mevinic acids.

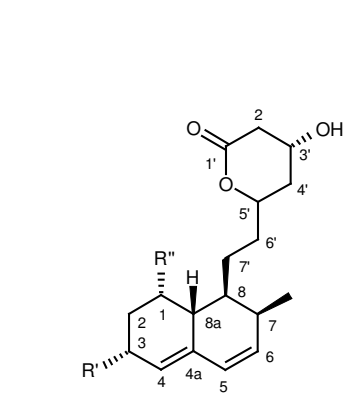
Mechanism for HMG-CoA Reductase Inhibition

The inhibition of HMG-CoA reductase by compactin and related compounds is reversible.[22] As can be expected from the structure of their acid forms, the inhibition by these compounds is competitive with respect to HMG-CoA. The K_i value for the acid form

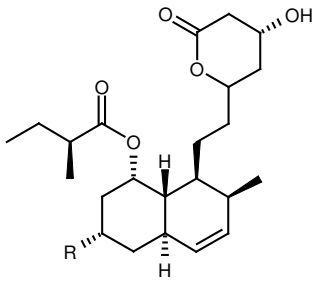
of compactin, which is determined from the partially purified rat liver enzyme, is ~10^{-9}M, while under the same conditions, the K_m value for HMG-CoA is 10^{-5}M.[23] Thus, the affinity of HMGCoA reductase for compactin is 10,000-fold higher than its affinity for the natural substrate HMG-CoA, showing compactin to be a highly potent inhibitor. Compactin does not affect other enzymes involved in cholesterol biosynthesis.[24] In addition, almost all studies on compactin with cultured cells and intact animals suggest that reductase is the only enzyme that is inhibited by compactin.

Structure Activity Relationship at Enzyme Level

Structural similarity between HMG-CoA and compactin-related compounds suggests that the active center of these agents in the inhibition of HMG-CoA reductase is at the δ-lactone moiety of the molecules. This hypothesis is supported by the data that inhibitory activity of compactin is reduced to 1/100 or less by acetylation of the hydroxyl group at either C-3′ or C-5′ and that 5′-phosphocompactin acid and 5′-phosphomonacolin K acid are 1/10 and 1/20 of compactin and monacolin K in the inhibitory activity, respectively.[25]



	R'	R''
Ml-236A (2)	H	OH
ML-236B (compactin)(50)	H	
ML-236C (10)	H	H
Monacolin J (4)	CH_3	OH
Monacolin K (mevinolin)(100)	CH_3	
Monacolin L(15)	CH_3	H
Monacolin X (20)	CH_3	



Dihydrocompactin (50)	H	
Dihydromevinolin (100)	CH_3	
Dihydromonacolin L (20)	CH_3	H

Figure 3: Compactin (ML-236B) related compounds of microbial origin. Numbers in parentheses represent relative activity to inhibit rat liver HMG-CoA reductase.

Other portions of the compactin molecule also seem to be involved in inhibitory activity (**Figure 3**). Among them, the α-methyl-butyrate ester plays a significant role, since analogues that lack such an ester (ML-236A and monacolin J) are 1/25 in the activity, as compared with their respective counterparts (compactin and monacolin K). The decalin ring of compactin-related compounds is essential to the inhibitory activity. This is shown by the data that HMG is more than 10^6 fold less active than compactin.[25] Dihydrocompactin, dihydromevinolin, and dihydromonacolin L are comparable in the activity to compactin, monacolin K and monacolin L, respectively.[20,21]

Monacolin K analogs that have a methyl group at C-3 are twice as active as their respective compactin analogs (**Figure 3**), indicating a contribution of the methyl radical to potency. However, hydroxylation at C-8a, C-3, or C-6 has no significant effect.[26, 27]

Since discovery, both compactin and mevinolin have attracted considerable world-wide attention due to their unique structural features and biological activities as inhibitors of HMGCoA reductase which is a major rate limiting enzyme responsible for the reduction of HMG-CoA to mevalonic acid[24] which is a crucial intermediate in the biosynthesis of cholesterol. Mevinolin, presently marketed under the trade name 'Mevacor' by the Merck group is one of the most clinically useful hypocholesterolemic agents. It is manufactured by the fermentation process. Dihydromevinolin, which exhibits biological activity similar to mevinolin, is produced in small quantities during fermentation; it has, therefore not been developed as a clinical candidate. The lactone moiety of the mevinic acids is essential for the inhibition because in its open form, it closely mimics mevalonic acid. The role of the decalin unit is probably hydrophobic in nature.[28]

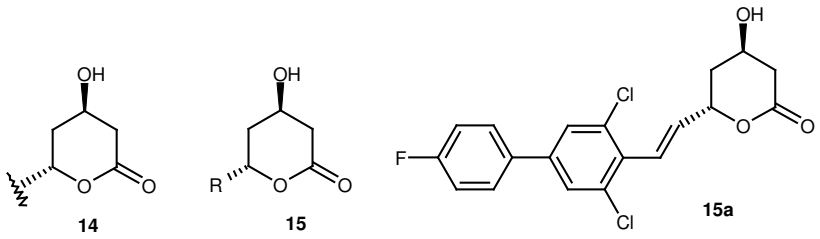


Figure 4.

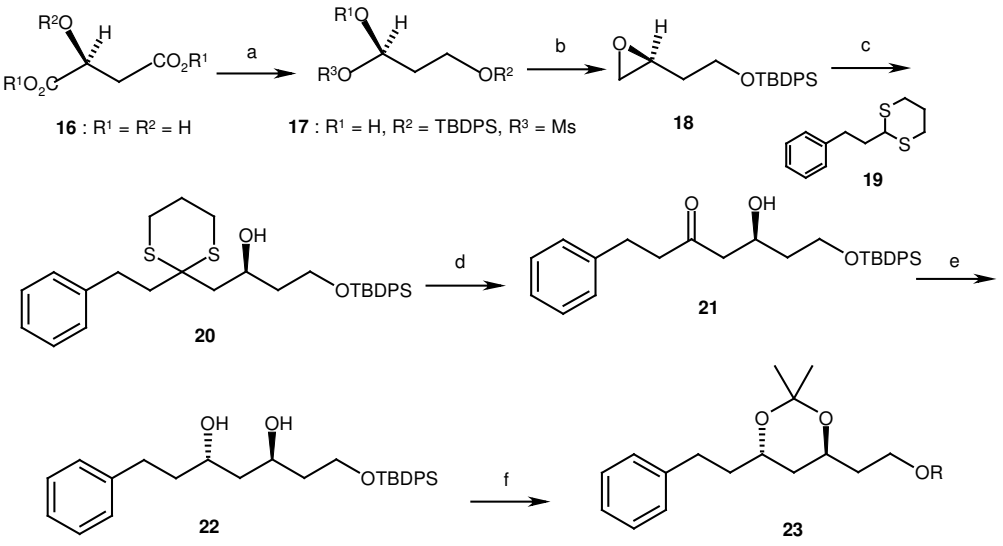
The design of the synthetic analogs of mevinic acids[29] has been governed by two major considerations, namely the requirement for a lactone function **14** and the desirability of having a much simpler array of place of the complex decalin system present in the natural products. The resulting analogs **15** of mevinic acids were generally most active when the R group was arylethyl or (*E*)-arylethenyl;[30] an example being the material **15a** which, in its dihydroxy acid form, displays 2.8 times the activity of the natural compactin **8** in

HMG-CoA reductase inhibition.[31] This unique structure-activity relation has aroused the interest of synthetic organic chemists, resulting in an onslaught of activity directed at the stereocontrolled synthesis of lactone **15** with different R substituents.[32]

4.1.2. Review of Literature.1: (+)-Strictifolione

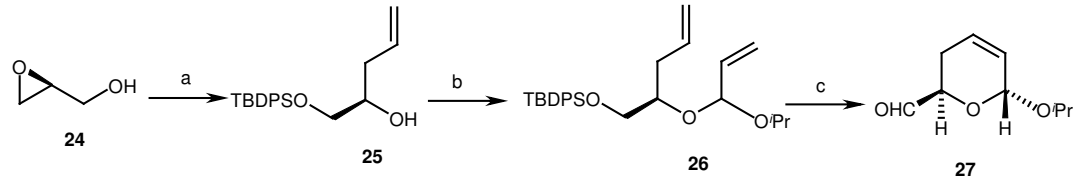
Takayama *et al*. (2002)[33]

Takayama and co-workers have employed (*S*)-malic acid **16** and (*S*)-glycidol **24** as starting materials, which features the condensation of two fragments in the last stage of the synthesis, both of which can be prepared from chiral synthons (**2** and **3**) with known absolute stereochemistry. Thus, the epoxide derived from (*S*)-malic acid **16**, was opened with dithiane followed by deprotection of dithioacetal group with I_2–$NaHCO_3$ and stereoselective reduction of keto with $Me_4NHB(OAc)_3$, in acetonitrile–acetic acid (1:1) at −20 °C to give *anti*-diol **22** with excellent *anti*-selectivity (*anti*:*syn* = 99.2:0.8). Kocienski-modified Julia olefination[34] of sulfone and pyranone aldehyde **27** prepared from (*S*)-glycidol **24** according to the procedure of Crimmins *et al*.[35] gave mixture (4:1) of isomeric *E*- and *Z*-alkenes (**30**). Hydrolysis of the acetals at C2 and of the diol function with PPTS, followed by MnO_2 oxidation of the resulting allylic alcohol moiety gave the 5,6-dihydro-α-pyrone, which was recrystallized from *n*-hexane/$CHCl_3$ to afford the pure *E*-isomer in 30% overall yield.

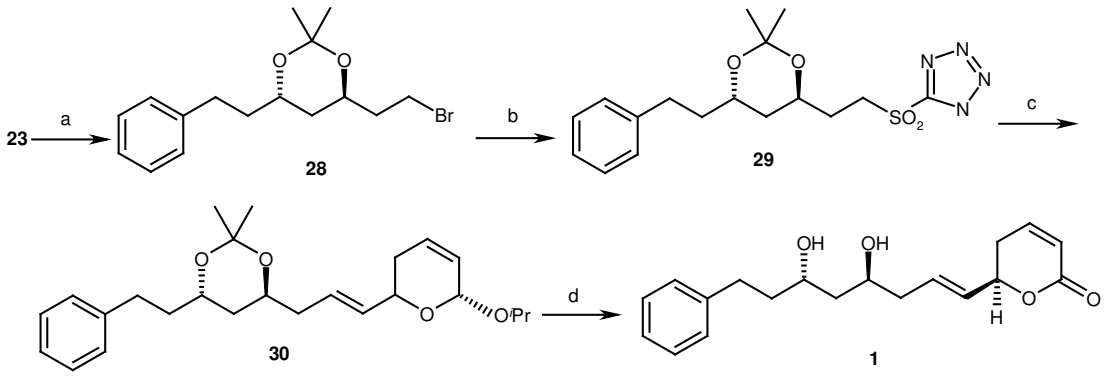


Scheme 2. *Reagents and conditions*: (a) (i) conc. H_2SO_4, EtOH, reflux, 4 h, 93%; (ii) Ph_3CCl, DBU, CH_2Cl_2, rt, 25 h, 71%; (iii) $LiAlH_4$, Et_2O, reflux, 1.5 h, 88%; (b) (i) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, −10°C, 72%; (ii) MsCl, CH_2Cl_2, rt, 12 h, quant.; (iii)

BCl_3, CH_2Cl_2, −10°C, quant.; (iv) K_2CO_3, MeOH, 0 °C, 88%; (c) **19**, *n*-BuLi, THF, rt, 98%; (d) $NaHCO_3$, I_2, aq. acetone, 0°C, 77%; (e) $Me_4NHB(OAc)_3$, MeCN–AcOH (1:1), −20°C, 25 h, 95%; (e) 2,2-dimethoxypropane, *p*-TsOH, CH_2Cl_2, rt, 3 h, 82%; (f) TBAF, 4 ^oA MS, THF, rt, 2 h, 100%.



Scheme 3. *Reagents and conditions*: (a) (i) TBDPSCl, imidazole, CH_2Cl_2, rt, 3 h, 67%; (ii) vinylmagnesium bromide, CuI, THF, −25 °C, 1 h, 88%; (b) acrolein diisopropylacetal, PPTS, 40 to 60 °C, 32 h, 74% (diastereomeric mixture 1:1); (c) (i) $RuCl_2(=CHPh)(PCy_3)_2$, CH_2Cl_2, reflux, 2 h, quant. (*trans*:*cis* 1:1, isolated *trans*-isomer 44%); (ii) TBAF, THF, rt, 1 h, 87%; (iii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 10 min, 90%.

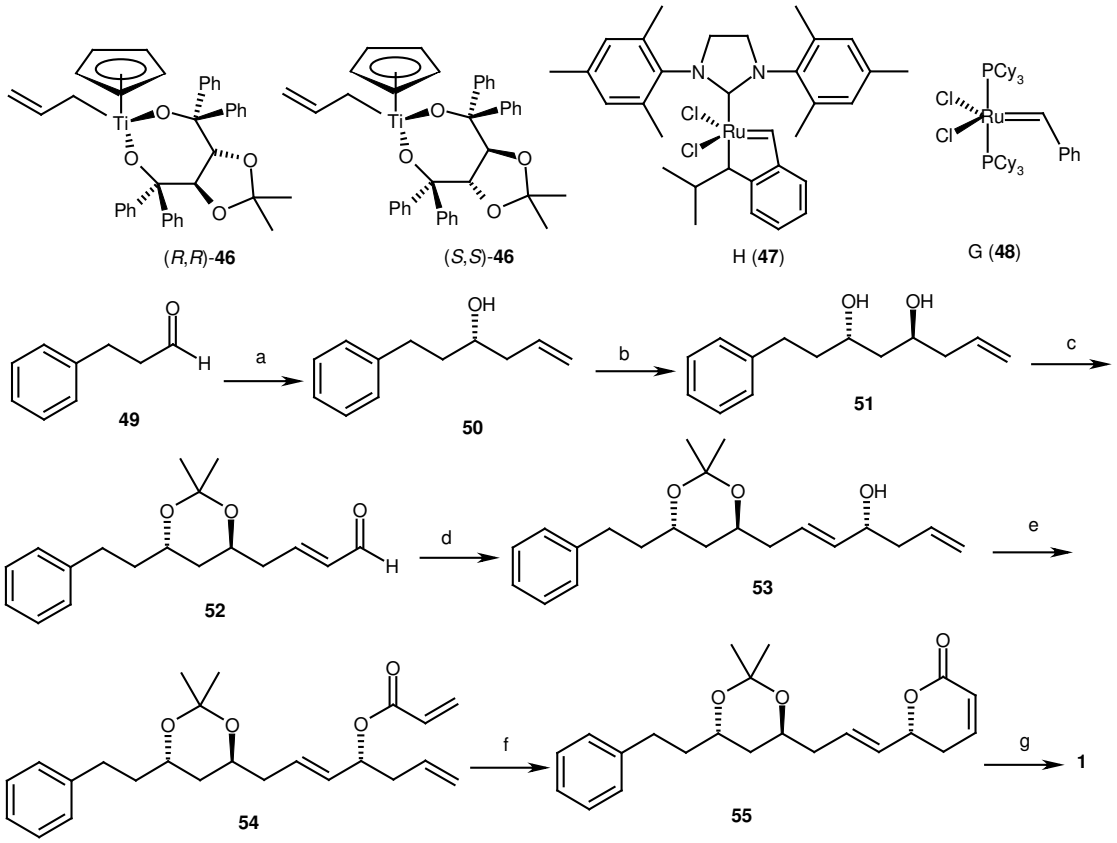


Scheme 4. *Reagents and conditions*: (a) (i) MsCl, 2,6-lutidine, CH_2Cl_2, rt, 10 h, quant.; (ii) LiBr, DMF, rt, 5 days, 86%; (b) (i) 1-phenyl-5-mercaptotetrazole, NaH, DMF, rt to 70°C, 96%; (ii) *m*-CPBA, CH_2Cl_2, rt, 24 h, 96%; (c) **27**, NaHMDS, THF, −60 °C, 1.5 h, 34% (*E*-, *Z*-isomer 4:1); (d) (i) PPTS, acetone–H_2O (6:1), rt, 1.5 h, 80%; (ii) MnO_2, pyridine, CH_2Cl_2, 24 h, 50%.

Janine Cossy *et al.*(2003).[36]

Cossy and co-workers employed three enantioselective allyltitanations to control the stereogenic centers, a cross-metathesis reaction to introduce the (*E*)-double bond at C1′-C2′[37] and a ring-closing metathesis reaction to build up the lactone ring from 3-phenylpropionaldehyde as starting material. Thus, 3-phenylpropionaldehyde **49** was treated with the allyltitanium complex (*S*,*S*)-**46** according to the reported procedure,[38] homoallylic alcohol **50** was obtained with >95% ee.[39] Oxidative cleavage of the olefin followed by second enantioselective allyltitanation with (*R*,*R*)-**46** furnished 1,3-diol **51**. (The *anti* relative stereochemistry of the 1,3-diol **51** was established by its conversion to

the corresponding acetonide.[40] The treatment of a mixture of **51** and acrolein (3 equiv) with Hoveyda's catalyst **H** (**47**) (5 mol%), in refluxing CH_2Cl_2, afforded the unsaturated aldehyde **52** (*E*/*Z* ratio > 30/1), which was transformed to the desired homoallylic alcohol **53** using the allyltitanium complex (*S*,*S*)-**46**. Esterification of allylic alcohol **53** followed by ring-closing metathesis by Grubbs' catalyst[41] and deprotection gave target molecule **1**.

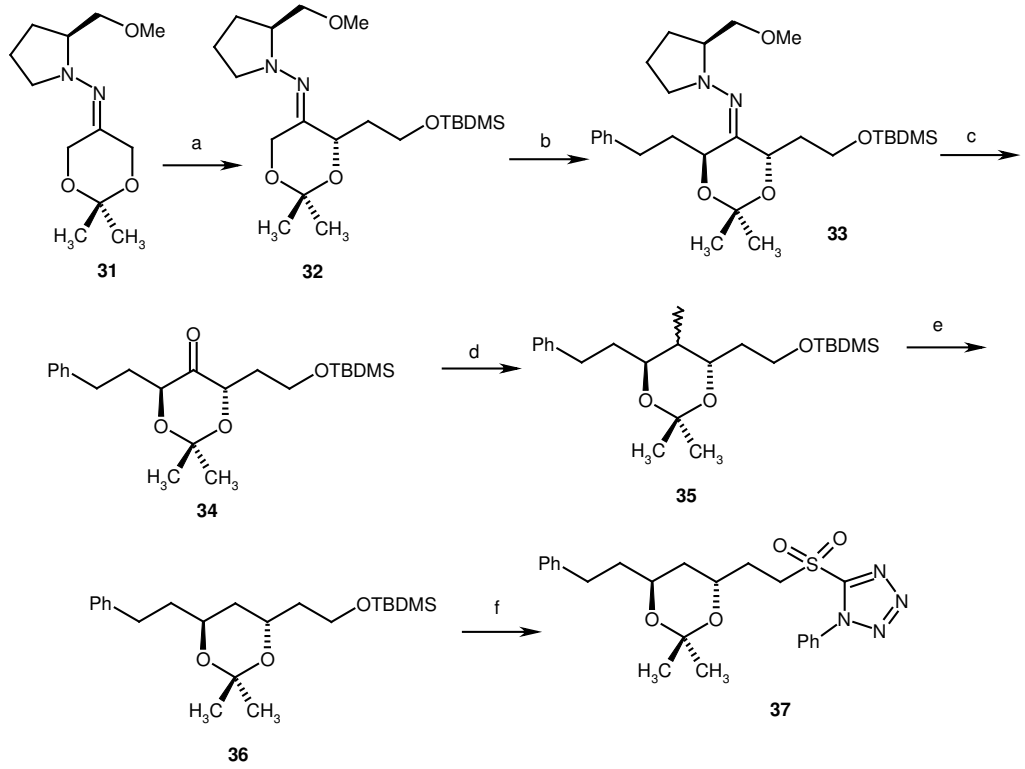


Scheme 5. *Reagents and conditions:* (a) (*S*,*S*)-**46**, ether, -78 °C, 4 h, 83%; (b) (i) OsO_4, NMO, acetone/H_2O, $NaIO_4$, 25 °C; (ii) (*R*,*R*)-**46**, ether, -78 °C, 4 h, 76% for the two steps. (c) (i) DMP/acetone, CSA, 25 °C, 95%. (ii) acrolein, catalyst **H** (**47**) (5 mol%), CH_2Cl_2, 25 °C, 70%. (d) (*S*,*S*)-**46**, ether, -78 °C, 4 h, 84%. (e) acryloyl chloride, *i*Pr_2NEt, CH_2Cl_2, -78 °C, 92%. (f) Catalyst **G** (**48**) (5 mol%), refluxing CH_2Cl_2, 82%. (g) 1 N HCl, MeOH, 40 °C, 87%.

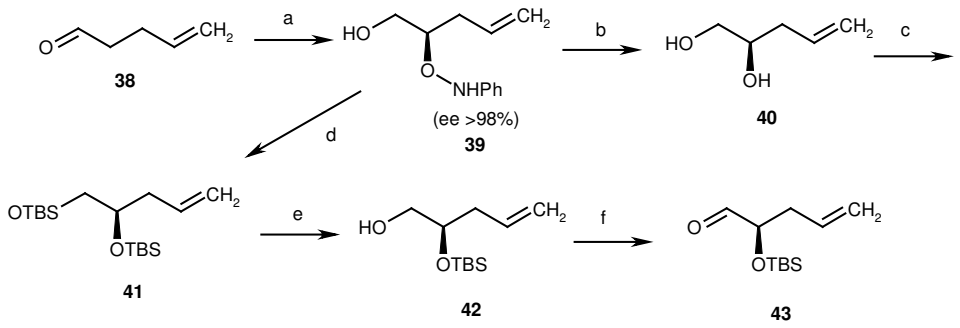
Enders *et al.* (2004)[42]

Enders and co-workers employed SAMP-hydrazone α,α′-bisalkylation/deoxygenation protocol[43] for the synthesis of sulfone moiety, an enzymatic reduction with baker's yeast/(*S*)-proline catalysed α-oxyamination of pent-4-enal (**38**)[44] for the stereocentre of the lactone unit and Julia–Kocienski olefination to create an *E*-configured alkene.

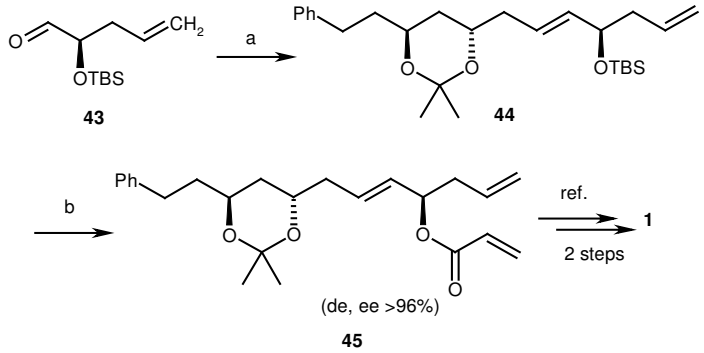
Thus, successive alkylation of hydrazone **31** with (2-bromoethoxy)-*tert*-butyldimethylsilane and (2-iodoethyl)-benzene affords the SAMP-hydrazone **33**. Cleavage of the hydrazone, reduction of keto with $NaBH_4$ and conversion of alcohol into xanthates followed by reduction with Bu_3SnH and acetonide protection yielded compound **36**. Cleavage of the TBS-protecting group and conversion of hydroxyl to the corresponding iodide, followed by a Williamson etherification gave sulfide. Finally, oxidation with *m*-CPBA yielded the desired sulfone **37**. Coupling of sulfone **37** and aldehyde **43** (Barbier-type reaction conditions; KHMDS, DME, –60 °C → r.t.) gave **44** as single isomer. Clevage of TBS group, esterification and ring-closing metathesis furnished the target molecule **1**.



Scheme 6. *Reagents and conditions:* (a) *t*-BuLi, THF, –78 °C; $Br(CH_2)_2OTBS$, –100 °C → r.t.; (b) *t*-BuLi, THF, –78 °C; $Ph(CH_2)_2I$, –100 °C → r.t., 71% over two steps; (c) sat. aq oxalic acid, Et_2O, r.t., 96%; (d) $NaBH_4$, MeOH, 0 °C; (e) (i) NaH, THF, 0 °C; CS_2; MeI, 0 °C → r.t., 99% over two steps; (ii) Bu_3SnH, AIBN (cat.), toluene, reflux; (iii) TBAF, THF, r.t., 93% over two steps; (f) (i) Ph_3P, imidazole, I_2, Et_2O–CH_3CN, 0 °C, 84%; (ii) 1-Phenyl-1*H*-tetrazole-5-thiol, NaH, THF–DMF, 0 °C; 0 °C → r.t., 99%; (iii) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, r.t., 87%.



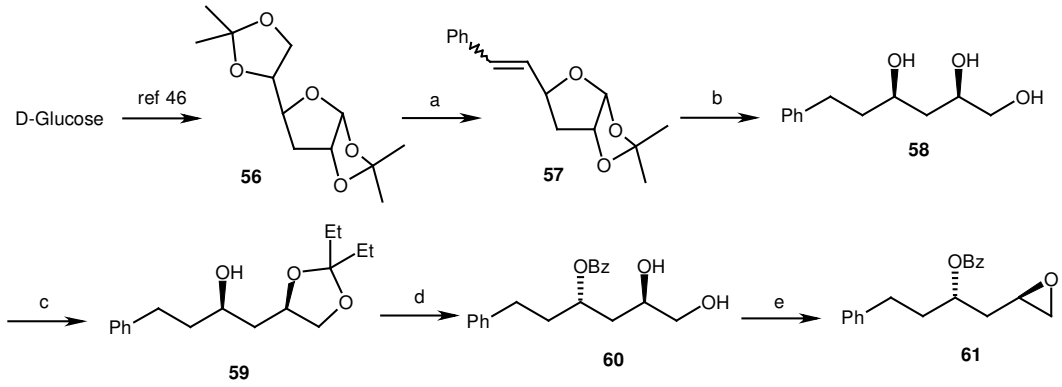
Scheme 7. *Reagents and conditions*: (a) (i) (*S*)-proline (10 mol%), PhNO, $CHCl_3$, 0 °C; (ii) $NaBH_4$, MeOH, 0 °C, 92% over two steps; (b) $CuSO_4 \cdot 5H_2O$, MeOH, 0 °C to rt, 28%; (c) (i) SmI_2, THF, rt; (ii) TBSCl, imidazole, DMF, rt, 50% over two steps; (d) TBSCl, imidazole, DMF, rt, 91%; (e) HF·pyridine, pyridine, THF, rt, 57%; (f) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C; **42**; Et_3N, 0 °C, 98%.



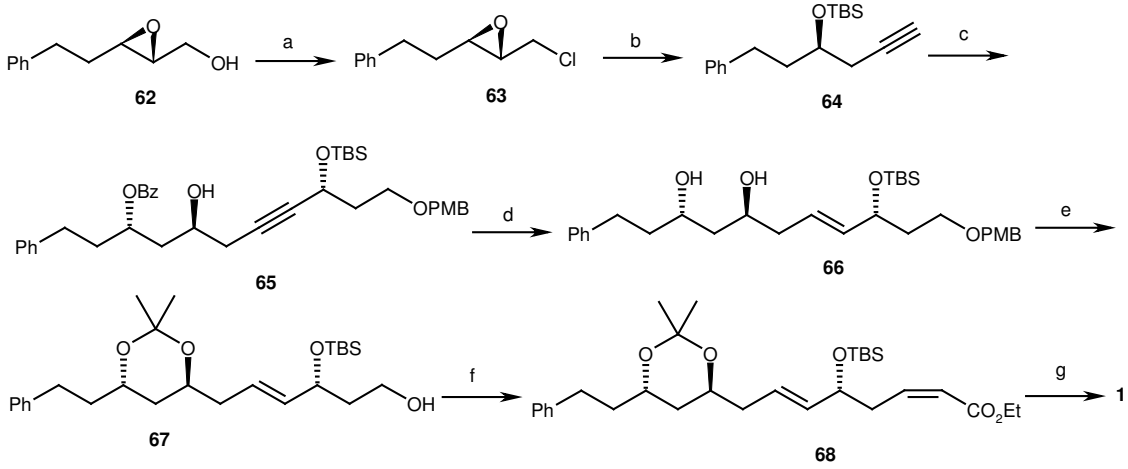
Scheme 8. *Reagents and conditions:* (a) **37**, DME, –(65–60) °C; KHMDS, –(65–60) °C → r.t., 69%; (b) (i) TBAF, THF, r.t.; (ii) acryloyl chloride, Et*i*-Pr_2N, CH_2Cl_2, –78 °C, 91% over two steps.

Ramana *et al.* (2005).[45]

Ramana and co-workers employed Yamaguchi protocol and a *Z*-selective HWE reaction followed by lactonization using D-glucose as chiral pool starting material. Thus, 3-deoxy-1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose **56**[46] prepared from D-glucose was converted into epoxide in several steps. Alkyne fragment **64** was prepared from known epoxide **62**,[47] by chlorination[48] and double elimination[49] reactions. Opening of epoxide **61** with alkyne **64** using Yamaguchi method[50] afforded the advanced intermediate **65**. The reduction of C≡C to the corresponding *E*-olefin with concomitant de-benzoylation using Red-Al[51] followed by acetonide protection, Wittig olefination, cyclization and deprotection gave the target molecule **1**.



Scheme 9. *Reagents and conditions*: (a) (i) 30% AcOH, rt, 75%; (ii) $NaIO_4$ on silica gel, CH_2Cl_2, 96%; (iii) $C_6H_5CH_2P^+Ph_3Br^-$, *n*-BuLi, THF, 0 °C to rt, 67%; (b) (i) Raney-Ni, ethanol, 60 psi, 98%; (ii) 30% AcOH, reflux, 72%; (iii) $LiAlH_4$, THF, rt, 92%; (c) 3-pentanone, CSA, 85%; (d) (i) DEAD, TPP, benzoic acid, THF, 91%; (ii) PTSA, methanol, 74%; (e) (i) TsCl, Bu_2SnO, triethylamine, CH_2Cl_2, rt, 89%; (ii) NaH, THF, 0 °C, 94%.



Scheme 10. *Reagents and conditions*: (a) TPP, CCl_4, reflux, 87%; (b) *n*-BuLi, THF, -40 °C, 79%; (c) (i) TBSCl, imidazole, CH_2Cl_2, rt, 81%; (ii) *n*-BuLi, $BF_3.Et_2O$, THF, -78 °C, then **3**, 85%; (d) Red-Al, ether, -20 °C, 73%; (e) (i) 2,4-DMP, CSA, acetone, 95%; (ii) DDQ, DCM–water (9:1), 86%; (f) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C; (ii) ethyl (di-*o*-tolylphosphono)acetate, NaH, THF, 0 °C to –78 °C, overall 81%; (g) PPTS, ethanol, 55 °C, 67%.

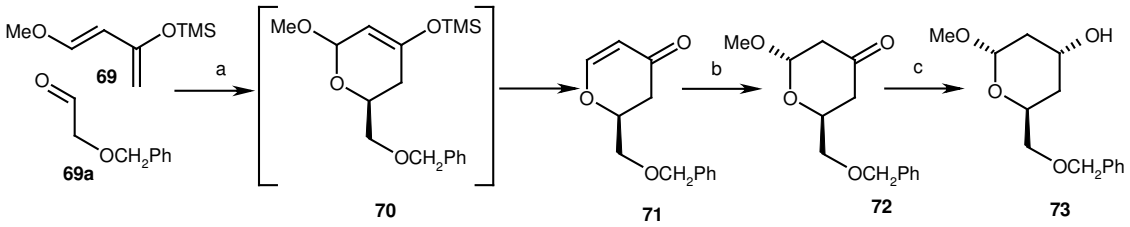
4.1.3. Review of Literature (synthesis of β-hydroxy-δ-lactone moiety)

Along with the interest generated by the biological properties of the mevinic acids, their unique structural features have aroused considerable global attention directed at the synthesis of these challenging targets. Synthetic studies in mevinic acids can be grouped into three primary sections: (1) total synthesis, (2) synthesis of the decalin units, and (3) synthesis of β-hydroxy-δ-lactone moiety.

The β-hydroxy-δ-lactone moiety in its open acid form closely mimics mevalonic acid and is of prime importance in inhibition. Hence, several research groups round the world have focused much attention in the synthesis of this δ-lactone portion.[30,32] Some of the important literature syntheses are given below.

Danishefsky *et al*. (1982)[52]

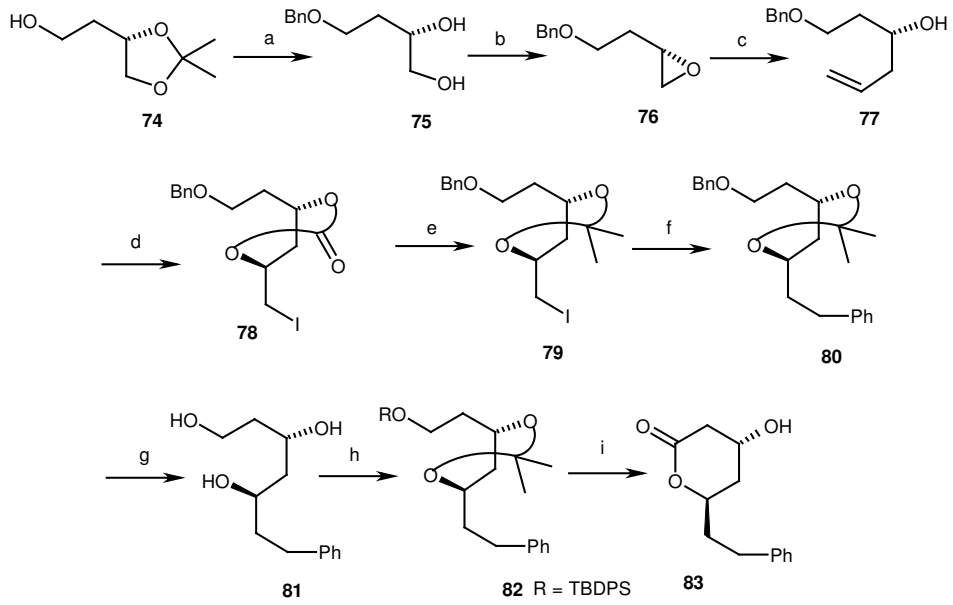
Danishefsky and co-workers have synthesized the masked pyranone segment **70** for the lactone moiety of compactin. The cyclocondensation of silyloxy diene **69** with benzyloxyacetaldehyde **69a** gave adduct **71**. Treatment of **70** with methanolic HCl produced a methylglycoside **72** with concomitant ketalization; deketalization with acetone containing a trace of HCl. Stereoselective reduction of ketone **72** gave the racemic synthon **73**. By starting with an optically active acetonide of glyceraldehyde rather than with benzyloxyacetaldehyde, the synthesis has been manipulated to provide a 100% optically active version of **73**.[53]



Scheme 11. *Reagents and conditions*: (a) (i) $ZnCl_2$, PhH, rt, 87%. (b) (i) MeOH, HCl, 69%, (b) $(CH_3)_2CO$, HCl. (c) L-Selectride, 88%.

Clive *et al*. (1984)[54]

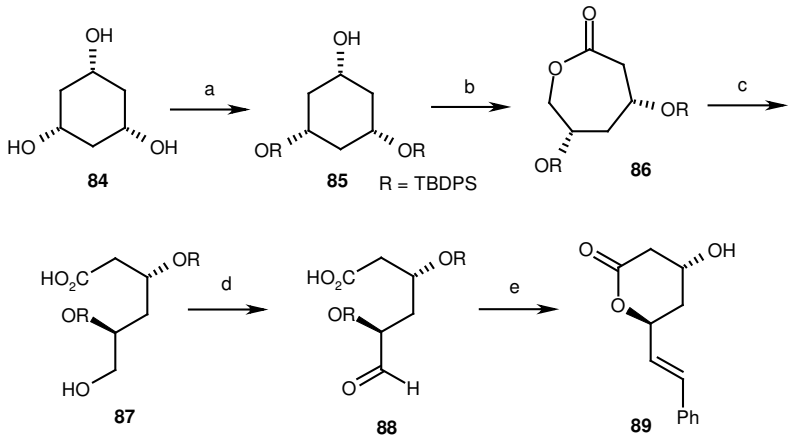
Clive and co-workers utilized L-malic acid derivative **74** as a precursor. Sequential benzylation, acetonide deprotection, mono-mesylation and base treatment gave the epoxide **76** that was opened with vinyl magnesium bromide to obtain the hydroxy olefin **77**. Treatment of alkoxide of **77** sequentially with CO_2 and I_2 gave iodocarbonate which on hydrolysis and acetonide formation furnished pure acetal **79**. Benzyl coupling of **79** gave adduct **80**. Deprotection of acetonide and benzyl and oxidation with Fetizons's reagent afforded **83** in poor yield (20%). Alternatively, **83** on selective protection of primary alcohol and acetonide formation gave **82**. Desilylation, oxidation and subsequent lactonization led to the desired lactone **83** (33% yield).



Scheme 12. *Reagents and conditions*: (a) (i) NaH, DMF, BnBr, (ii) AcOH-H_2O, 50 °C, 1 h, 86%. (b) (i) MsCl, pyridine, (ii) Triton B, 65%. (c) H_2C=CHMgBr, 92%. (d) *n*-BuLi, CO_2, I_2, 69%. (e) $(CH_3)_2CO$, *p*-TsOH. (f) (i) *p*-$MeC_6H_4SO_2CH_2Ph$, KH, DMF, rt, 3 h, (ii) 6% Na-Hg, MeOH, 78%. (g) Me_3SiI, 73% (94% with one recycling of **80**). (h) (i) *t*-$BuPh_2Si$-Cl, (ii) $(CH_3)_2CO$, *p*-TsOH. (i) (i) *n*-Bu_4NF, (ii) Collins [O], (iii) PDC, DMF, (iv) HCl, CH_2Cl_2, 33% from **81**.

Prasad *et al.* (1984)[55]

Prasad and Repic have synthesized the lactone moiety beginning with *cis*-cyclohexane-1,3,5-triol **84**. Conversion of **84** to bis silyl ether **85** followed by PCC and Baeyer-Villiger oxidations afforded the lactone **86**. Methanolysis and oxidation of the resulting hydroxyl gave the aldehyde **88**, which on Wittig coupling and desilylation furnished the unmasked lactone **89**.

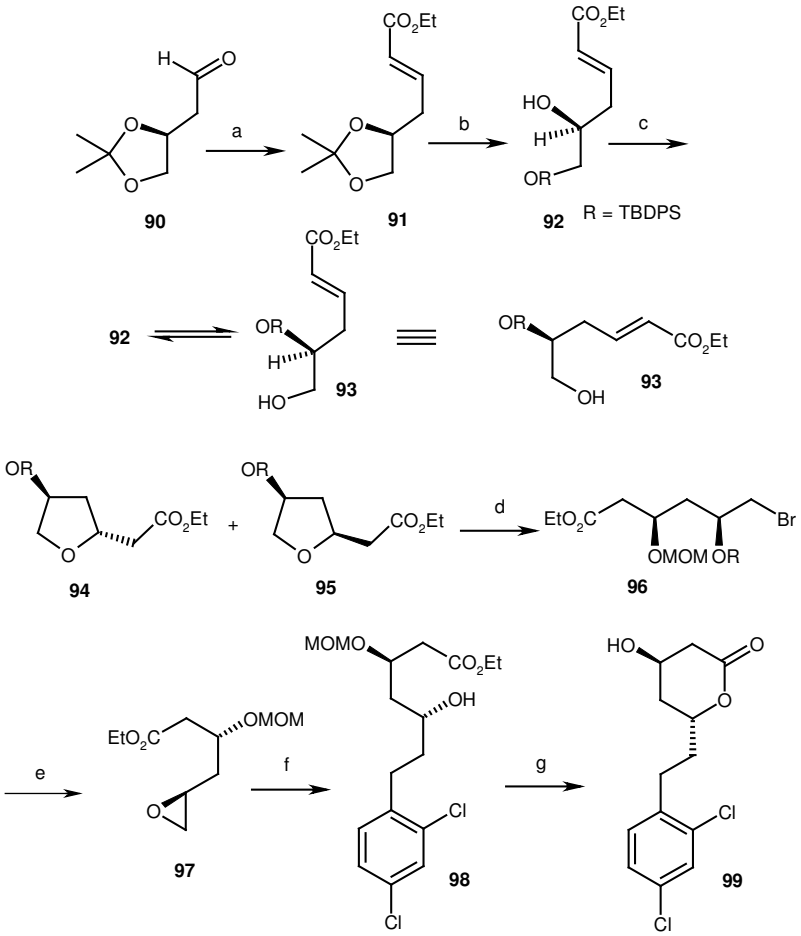


Scheme 13. *Reagents and conditions*: (a) *t*-$BuPh_2Si$-Cl, imidazole, DMF, 40%. (b) (i) PCC, 4A° molecular sieves, CH_2Cl_2, 3 h, 93%, (ii) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 18 h, 77%. (c) MeOH, F_3CCO_2H, reflux, 20 min, 95%. (d) PCC, 4A° molecular sieves, CH_2Cl_2,

4 h. (e) (i) $PhCH=PPh_3$, THF, -20 °C, 3 h, 77%, (ii) *n*-Bu_4NF, AcOH, THF, 20 °C, 18 h, 60 °C, 2 h, 45%.

Guindon *et al.* (1985)[56]

In Guidon's approach, the L-malic acid aldehyde **90** was converted into olefin ester **91**. Acetonide deprotection and selective silylation of the primary alcohol afforded the mono protected diol **92** that on treatment with catalytic NaOEt, establishes equilibrium with its isomer **93**. Ensuing intramolecular Michael reaction displaces the equilibrium and the tetrahydrofurans **94** and **95** are obtained in 2:1 ratio. Cleavage of **94** with dimethylboron bromide proceeds regiospecifically to produce, after protection, the bromide **96**. Cleavage of the silyl ether afforded the epoxide **97**, which was opened regioselectively to give **98**. Subsequent acid catalyzed cyclization and unmasking of the hydroxyl group gave the lactone **99**.

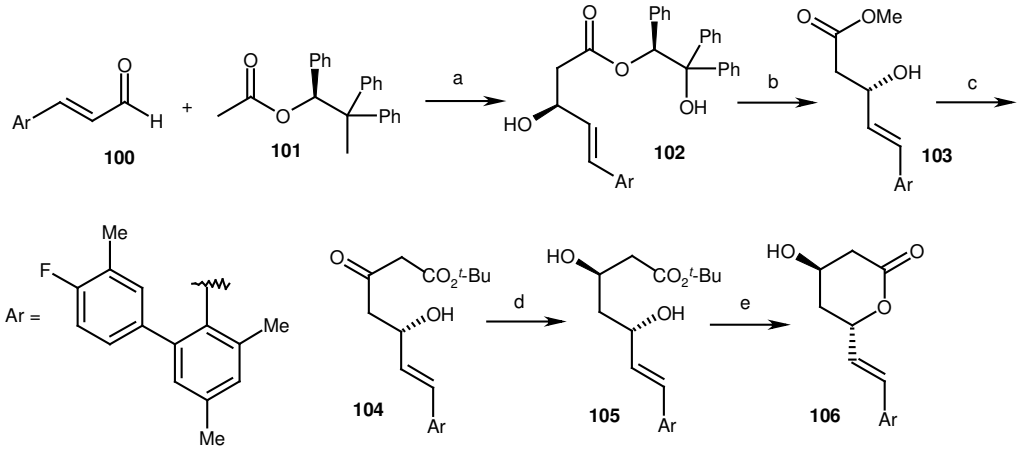


Scheme 14. *Reagents and conditions*: (a) $Ph_3P=CHCO_2Et$, 84%. (b) (i) 1N HCl, THF, (ii) *t*-$BuPh_2Si$-Cl, Et_3N, DMAP, CH_2Cl_2, rt. (c) 10 mol% NaOEt, EtOH, 87%. (d) (i) Me_2BBr, CH_2Cl_2, 82%, (ii) MOMCl, *i*-Pr_2NEt, DMAP, CH_3CN, 94%. (e) *n*-Bu_4NF, THF, 80%. (f)

$R_2CuMgBr$, Et_2O, -78 °C, then –23 °C, 1 h, 100%. (g) (i) *p*-TsOH, PhH, 90%, (ii) Me_2BBr, CH_2Cl_2, 79%.

Lynch *et al.* (1987)[57]

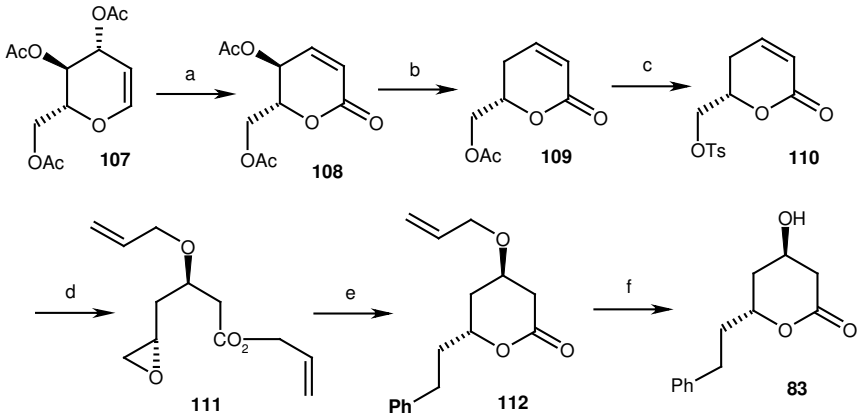
Lynch and co-workers have utilized the diastereoselective aldol reaction of **100** with Mg (II) enolate of **101** following the procedure of Braun and Devant[58] to give the diastereoisomer **102** (*SS*:*SR* = 97:3). Transesterification of **103** followed by Claisen condensation furnished **104**. The 5-(*S*)-hydroxyl directed reduction of β-keto ester **104** gave diol **105**. Subsequent saponification and acidification afforded the lactone **106**.



Scheme 15. *Reagents and conditions*: (a) (i) LDA, THF, (ii) $MgBr_2$, 93%. (b) NaOMe, MeOH, 95%. (c) lithio *t*-butylacetate, THF, -40 °C to –30 °C, 90%. (d) Et_3B, $NaBH_4$, THF-MeOH, –78 °C, 93%. (e) H^+, pH 3.8, 85%.

Roth *et al.* (1988)[59]

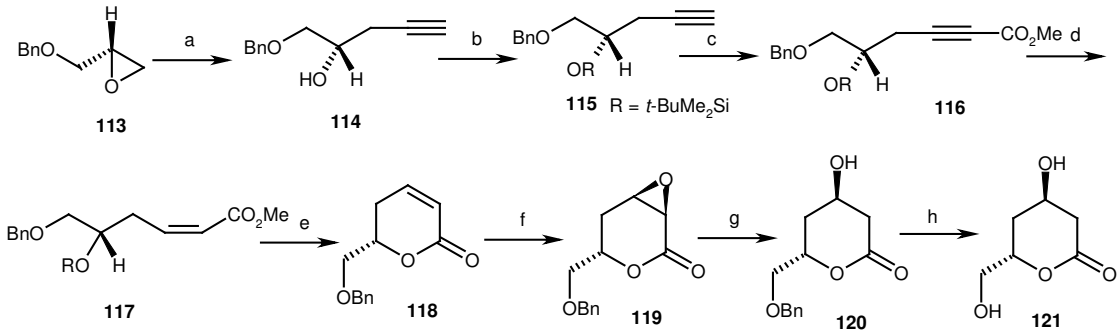
Roth and Roark have used the commercially available glucal **107**. PCC oxidation of **107** afforded the unsaturated lactone **108**. Reductive deconjugation with Zn-AcOH followed by reconjugation with Et_3N produced the 5-deoxygenated lactone **109**. Hydrolysis and tosylation gave **110**, which on reaction with sodium allyl alcoholate produced the epoxide **111**. Reaction of **111** with dibenzylcuprate followed by allyl deprotection gave the lactone **83**.



Scheme 16. *Reagents and conditions*: (a) PCC, 85%. (b) Zn-AcOH and then Et_3N, 92%. (c) (i) 2N HCl, (ii) *p*-TsCl, 92%. (d) CH_2=$CHCH_2ONa$, allyl alcohol, 87%. (e) $PhCH_2MgCl$, CuBr-Me_2S, 73%. (f) 10% Pd/C, dioxane:H_2O (2:1), 50%.

Takano *et al.* (1989)[60]

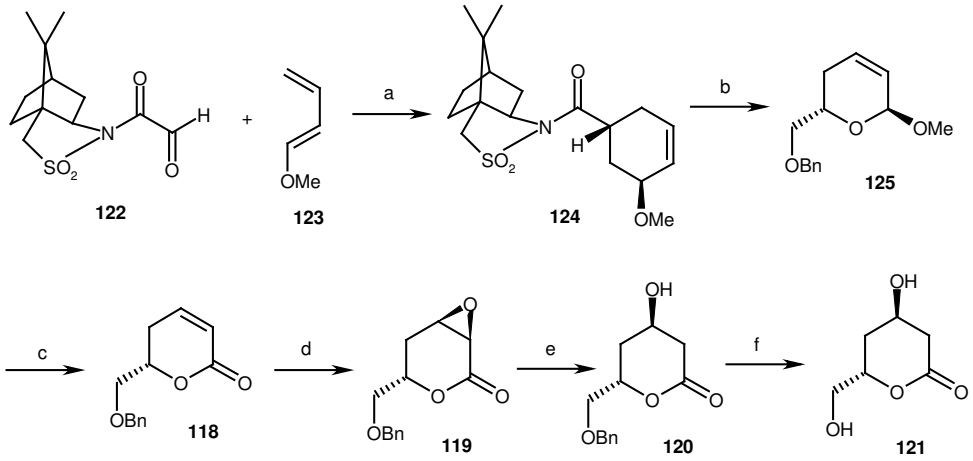
In Takano's approach, (*R*)-*O*-benzylglycidol **113** is opened with sodium acetylide to give **114**. Silyl protection of the hydroxyl group followed by sequential lithiation and methoxy carbonylation gave ester **116**. Alkyne reduction to (*Z*)-olefin and exposure to acid furnished the α,β-unsaturated lactone **118**. Epoxidation of **118** stereoselectively gave the epoxide **119**. Regioselective cleavage of the oxirane and debenzylation furnished the lactone **121**.



Scheme 17. *Reagents and conditions*: (a) NaH, DMSO, acetylene, 87%. (b) *t*-$BuMe_2Si$-Cl, imidazole, 99%. (c) (i) *n*-BuLi, THF, -72 °C, (ii) $ClCO_2Me$, -50 °C, 87%. (d) H_2, Lindlar cat. PhH, quinoline, rt, 99%. (e) conc. HCl, MeOH, rt, 86%. (f) 30% H_2O_2, 6N NaOH, MeOH, rt, 73%. (g) $(PhSe)_2$, $NaBH_4$, AcOH, *i*-PrOH, rt, 87%. (h) H_2, $Pd(OH)_2$, EtOAc, rt, 81%.

Jurczak *et al*. (1990)[61]

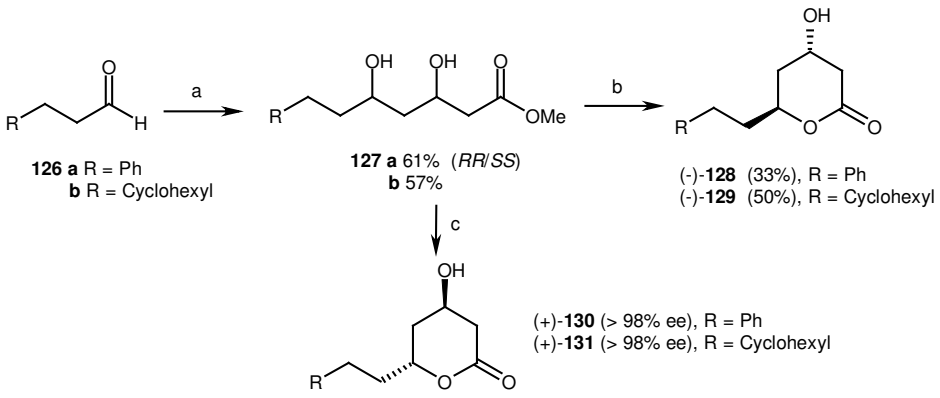
In Jurczak's approach the asymmetric hetero Diels-Alder reaction of 1-methoxybuta-1,3-diene **123** with (2*R*)-*N*-glyoxyloylbornane-10,2-sultam **122** furnished the adduct **124**. Reduction of **124** and benzylation of hydroxyl gave **125**. Anomeric oxidation[62] of **125** afforded **118**. Compound **118** is transformed into the lactone **121** as shown in **Scheme 17**.



Scheme 18. *Reagents and conditions*: (a) (i) 2 mol% $Eu(fod)_3$, (ii) PPTS. (b) (i) $LiAlH_4$, (ii) NaH, BnBr. (c) (i) 30% H_2O_2, MoO_3 (cat), (ii) Ac_2O, pyridine. (d)-(e) as in **Scheme 17**.

Bonini *et al*. (1991)[63] **Scheme 35**

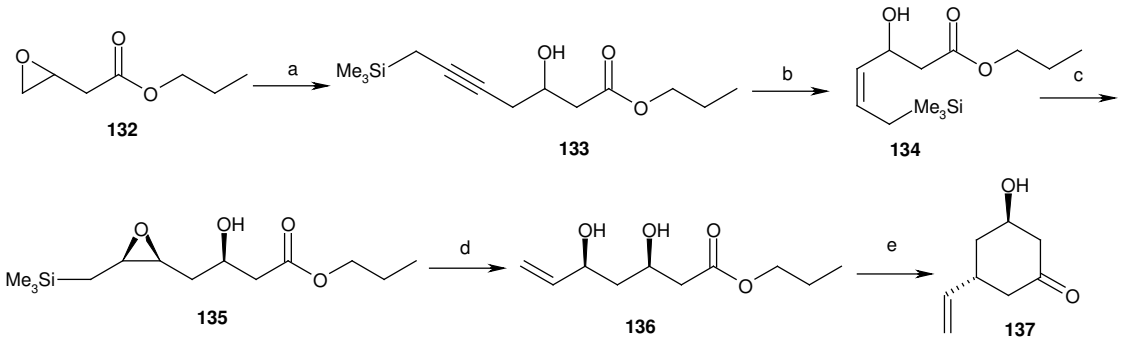
Bonini and co-workers employed biocatalytic lactonization of *syn*-3,5-dihydroxy esters **127** which were obtained by the diastereoselective reduction of the aldol derived from dianion of acetoacetate with an appropriate aldehyde **126**. Biocatalytic lactonization of **127a/b** with pig liver esterase (PLE) afforded the unnatural mevinic acid analogs (-)-**128** and (-)-**129** respectively. However, when porcine pancreatic lipase (PPL) is used to perform lactonization of the dihydroxy esters **127a/b**, natural analogs of the mevinic acid (+)-**130** and (+)-**131** are obtained in good yield and high enantiomeric excess.



Scheme 19. *Reagents and conditions*: (a) (i) $H_3CCOCH_2CO_2Me$, 2LDA, (ii) $Ti(O\textit{i}\text{-}Pr)_4$, $NaBH_4$. (c) PLE, 80%. (d) PPL, 70%.

Mohr *et al.* (1992)[64]

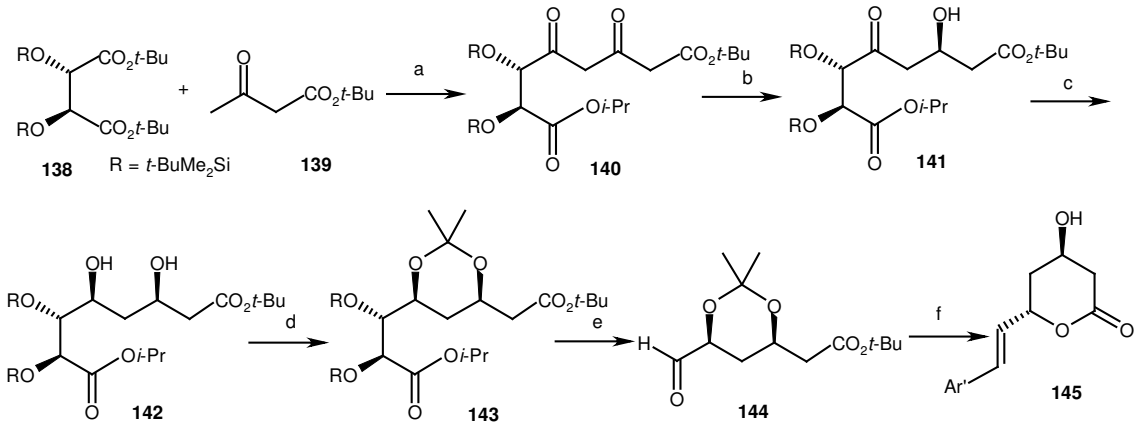
Mohr and co-workers employed the *Z*-allyl silane **134** in an epoxidation reaction with V^{5+}/*t*-BuOOH with high *erythro*-selectivity to give **135**. Subsequent HF or TBAF induced fragmentation afforded *syn*-1,3-diol **136** which is then transformed into the lactone **137**.



Scheme 20. *Reagents and conditions*: (a) Propargyl trimethylsilane, *n*-BuLi, THF, $BF_3.Et_2O$. (b) Lindlar catalyst, H_2. (c) *t*-BuOOH (1.5 eq.), $VO(acac)_2$, -15 °C-rt, 15 h, (d) *n*-Bu_4NF, THF, 57% from **134**. (e) camphor sulfonic acid.

Hiyama *et al.* [65] **(1993) Scheme 37**

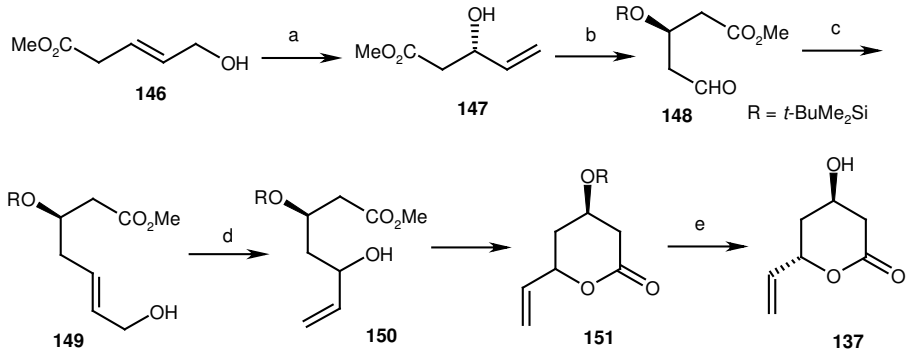
Hiyama and co-workers employed stereoselective reductions of a β,δ-diketo ester **140** derived from D-tartaric acid to give chiral β,δ-*syn* dihydroxyester **141**. Protection of 1,3-diol as acetonide and removal of silyl groups gave diol **143**. Oxidative cleavage of **143** afforded the desired aldehyde **144**. Wittig olefination with the carbanion of $Ar'CH_2P(O)Ph_2$ gave various types of HMG-CoA reductase inhibitors **145**.



Scheme 21. *Reagents and conditions*: (a) NaH, *n*-BuLi, -78 °C, 20 h, 74%. (b) DIBAL-H, THF, hexane, 78 °C, 4 h, 60%. (c) Et_2BOMe, $NaBH_4$, THF, MeOH, -78 °C-rt, 12 h, 76%. (d) (i) 2,2-DMP, *p*-TsOH, rt, 2 h, 98%, (ii) *n*-Bu_4NF, THF, rt, 3 h, 99%. (e) $NaIO_4$, Et_2O, H_2O, rt, 2 h, 85%. (f) (i) Ar′$CH_2P(O)Ph_2$, lithium 2,2,6,6-tetramethylpiperazide, (ii) CF_3CO_2H.

Dittmer *et al.*[66] (1994)

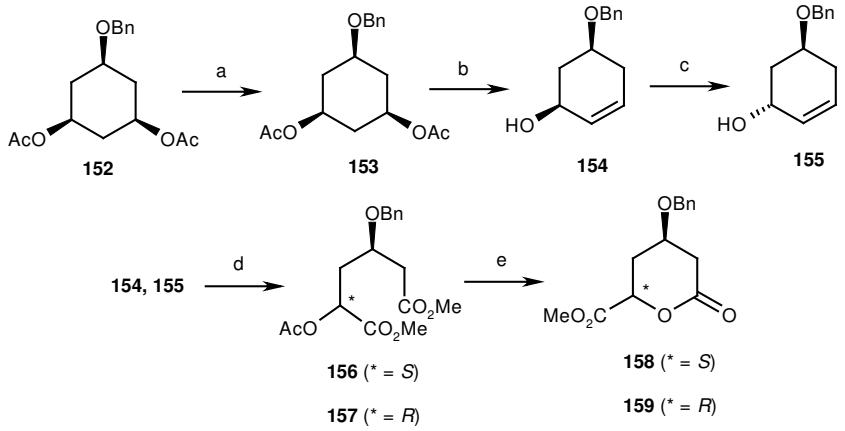
In Dittmer's approach, the AE of allylic alcohol **146** and conversion of hydroxyl into tosylate gave glycidyl sulfonate which on tellurium-induced nucleophilic reduction afforded the allylic alcohol **147**. Sequential protection of hydroxyl, hydroboration and PCC oxidation gave aldehyde **148**. Subsequent Wittig reaction and borohydride reduction furnished the allylic alcohol **149**. The SAE-Te transposition sequence on **149** gave **150** which spontaneously lactonized to afford **151**. Silyl group deprotection gave **137**.



Scheme 22. *Reagents and conditions*: (a) (i) *t*-BuOOH, (+)-DIPT, Ti(O*i*-Pr)$_4$, (ii) *p*-TsCl, Et_3N, CH_2Cl_2, (iii) Te_2- (Te, $NaBH_4$, DMF). (b) (i) *t*-$BuMe_2Si$-Cl, imidazole, DMF, (ii) $(Me_2CHCHMe)_2BH$, THF, -12 °C, (iii) PCC, CH_2Cl_2, 63% from **147**. (c) (i) Ph_3P=CHCHO, PhH, THF, (ii) $NaBH_4$, MeOH, -50 °C, 60% from **148**. (d) *n*-Bu_4NF.

Suemune *et al.*[67] (1992)

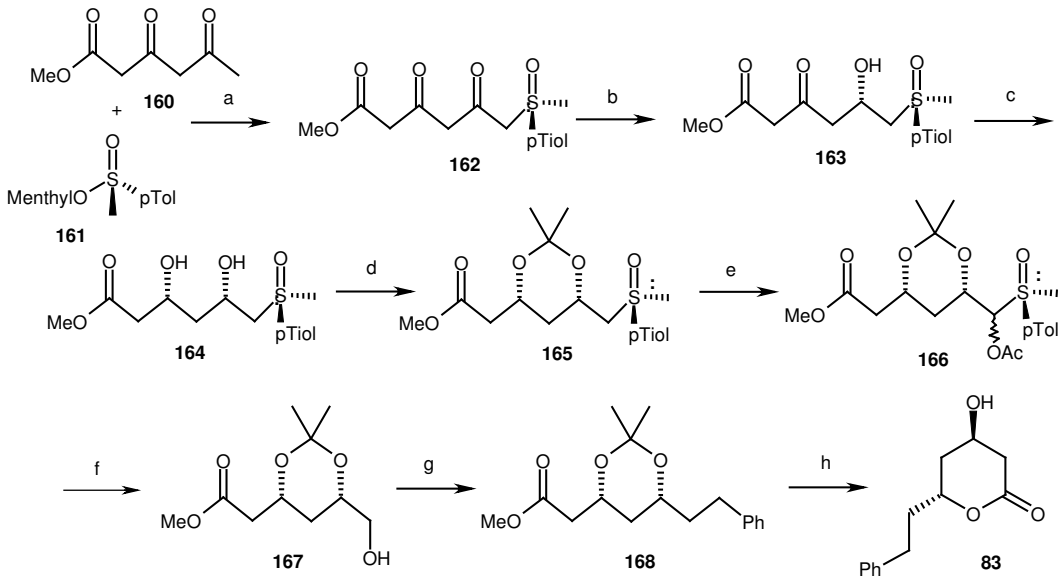
Suemune and co-workers used porcine liver esterase (PLE) in desymmetrization of **152** to give **153**. Subsequent oxidation and stereoselective reduction gave **154**. Mitsunobu's inversion of **154** gave the epimeric material **155**. Ozonolysis followed by Jones oxidation of **154/155** and subsequent esterification gave **156/157**. Solvolysis of **156/157** and subsequent lactonization afforded the lactone moiety of compactin **158** and its epimer at C-5, **159**.



Scheme 23. *Reagents and conditions*: (a) PLE, pH 7, 62%. (b) (i) Swern oxidation, 92%, (ii) $NaBH_4$, $CeCl_3$, MeOH, 90%. (c) (i) Ph_3P, DEAD, AcOH, THF, 87%, (ii) K_2CO_3, MeOH, 82%. (d) (i) O_3, (ii) Jones oxidation, (iii) CH_2N_2, 69%. (e) (i) K_2CO_3, MeOH, 78%, (ii) *p*-TsOH, PhH, 65%.

Solladie *et al.*[68] (1995)

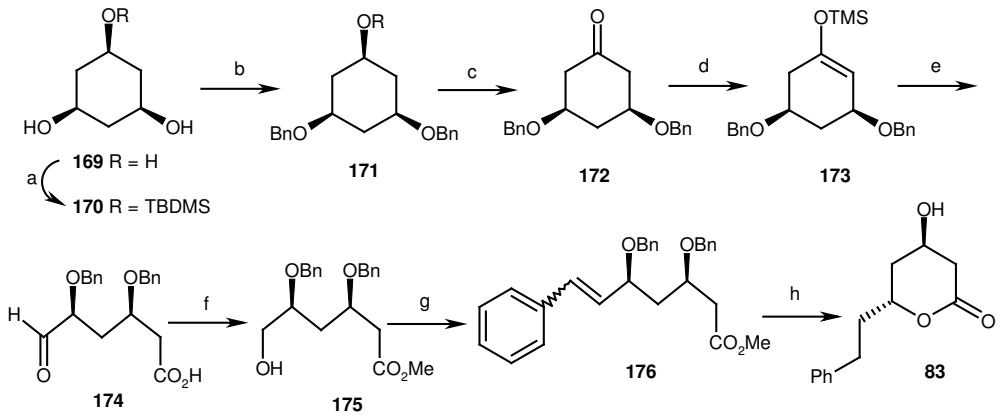
In Solladie's approach, reaction of the trianion of methyl-3,5-dioxahexanoate **160** with (-)-menthyl (*S*)-*p*-toluenesulfinate **161** gave the diketosulfoxide **162**. DIBAL-H reduction of **162** gave only one diastereomer **163**. Reduction of δ-keto group in **163** with $NaBH_4$ and Et_2BOMe gave the *syn*-diol **164** in greater than 98% diastereoselectivity. Protection of 1,3-dihydroxy function, Pummerer reaction, desulfurization and acetate hydrolysis furnished **167**. Oxidation of primary alcohol, Wittig olefination and subsequent reduction of olefin gave ester **168**. Acetic acid hydrolysis afforded the lactone **83**.



Scheme 24. *Reagents and conditions*: (a) NaH, *t*-BuLi, 0 °C, 68%. (b) DIBAL-H, THF, 44%. (c) $NaBH_4$, Et_2BOMe, 99%. (d) 2,2-DMP, *p*-TsOH. (e) Pummerer, 97%. (f) (i) Raney Ni, 73%, (ii) K_2CO_3, 78%. (g) (i) Swern oxidation, 81%, (ii) Ph_3P=CHPh, 65%. (iii) H_2, Pd/C, AcOEt, 96%. (h) AcOH/H_2O, rt, 81%.

Honda *et al.* (1997)[69]

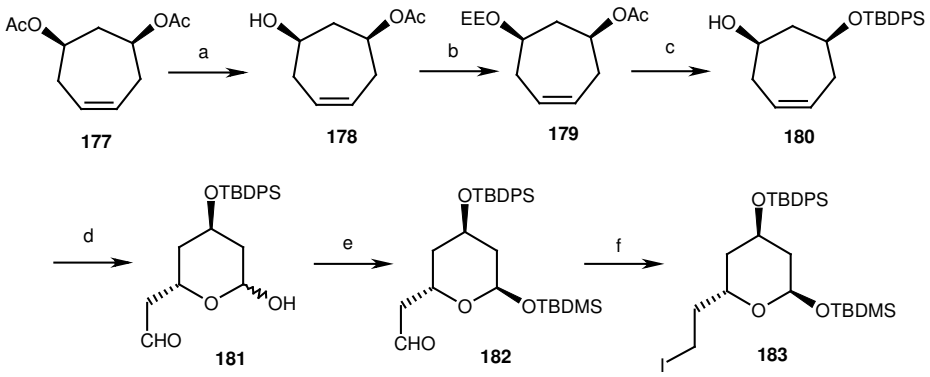
In Honda's approach, the reaction of mono-sodium salt derived from *cis*,*cis*-1,3,5-trihydroxy cyclohaxane **169** with 1 equivalent of *t*-BuMe_2Si-Cl gave **170**, which on further alkylation with BnBr furnished **171**. Desilylation, followed by oxidation afforded ketone **172**. Enantioselective deprotonation reaction of **172** with lithium (*S,S*)-α,α′-dimethyldibenzylamide as the chiral base and TMSCl gave the silyl ether **173**. Ozonolysis, aldehyde reduction and esterification of acid furnished **174**. Swern oxidation and Wittig reaction led to 1:4 mixture of *E*:*Z* isomers **176**. Benzyl ether deprotection, olefin reduction and lactonization eventually afforded **83**.



Scheme 25. *Reagents and conditions*: (a) NaH, pyridine, rt, *t*-$BuMe_2Si$-Cl, THF, 0 °C, 84%. (b) NaH, BnBr, *n*-Bu_4NI, THF, rt, 100%. (c) (i) *n*-Bu_4NF, THF, rt, (ii) PCC, NaOAc, celite, CH_2Cl_2, rt, 76%. (d) lithium (*S,S′*)-α,α′-dimethyldibenzylamide, TMSCl, THF, -100 °C, 62%. (e) O_3, CH_2Cl_2, −78 °C, then PPh_3, 71%. (f) (i) $NaBH_4$, MeOH, rt, 68%, (ii) MeI, K_2CO_3, DMF, rt, 90%. (g) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to -45 °C, (ii) $PhCH_2P^+Ph_3Cl^-$, *n*-BuLi, THF, 0 °C-rt, 95%. (h) (i) H_2, $Pd(OH)_2$, EtOH, rt, (ii) *p*-TsOH, PhH, rt, 67%.

Suemune *et al*. (1997)[70]

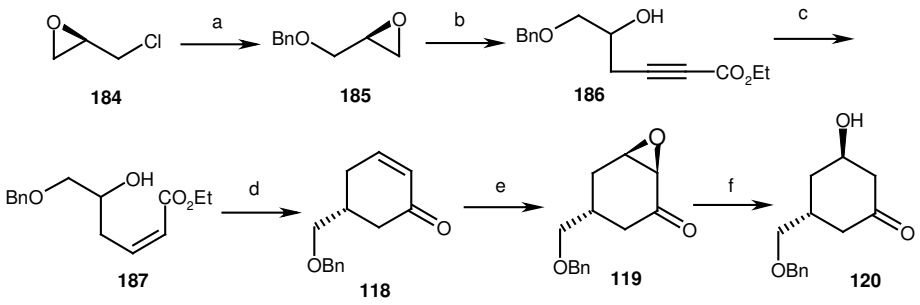
Suemune and co-workers desymmetrized meso-1,3-diacetoxy-5-cycloheptene **177** enzymatically using *Pseudomonas fluorescence* lipase (PFL) to afford the monoacetate **178**. Sequential protection of hydroxyl as ethoxy ethyl ether, solvolysis of acetate and protection as TBDPS followed by deprotection of ethoxy ethyl ether gave **180**. Reductive ozonolysis of **180** furnished the hemiacetal **187** as a 1:1 diastereomeric mixture at the C-2 position. Protection of the hemiacetal function as a TBDMS ether gave the sole product **182**. $NaBH_4$ reduction of **182** and iodination afforded **183**, a synthetic equivalent of the lactone moiety in mevinic acids.



Scheme 26. *Reagents and conditions*: (a) PFL, phosphate buffer, pH 7, 44 h, 72%. (b) Ethyl vinyl ether, PPTS, 79%. (c) (i) K_2CO_3, MeOH, 82%, (ii) *t*-$BuPh_2Si$-Cl, imidazole, 91%, (iii) 5% aq. AcOH, $(CH_3)_2CO$, 89%. (d) (i) O_3, CH_2Cl_2, (ii) Zn, AcOH, 60%. (e) *t*-$BuMe_2Si$-Cl, imidazole, 70%. (f) (i) $NaBH_4$, 74%, (ii) I_2, Ph_3P, pyridine, 95%.

Ogasawara *et al*. (1997)[71]

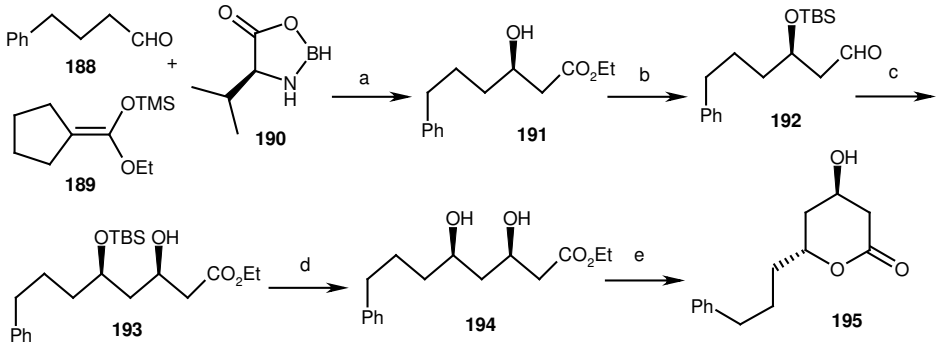
Ogasawara and co-workers have employed chiral epichlorohydrin **184**, which is transformed into (*S*)-*O*-benzylglycidol **185** by literature procedure.[72] Epoxide opening with ethyl 3-lithiopropiolate, partial hydrogenation of alkyne and acid-treatment gave the lactone **118** which on epoxidation with 30% H_2O_2 furnished single diastereomer **119**. Regioselective cleavage of the epoxide with aluminium amalgam gave **120**, the lactone equivalent of mevinic acid.



Scheme 27. *Reagents and conditions*: (a) Ref. 72. (b) Ethyl propiolate, *n*-BuLi, $BF_3.Et_2O$, THF, -78 °C, 89%. (c) H_2, Lindlar cat., $PhCH_3$, rt, 91%. (d) *p*-TsOH, $PhCH_3$, reflux, 88%. (e) 30% H_2O_2, 6N NaOH, MeOH, 0 °C, 89%. (f) Al-Hg, Na_2HPO_4, *i*-PrOH, 70%.

Kiyooka *et al*. (1997)[73]

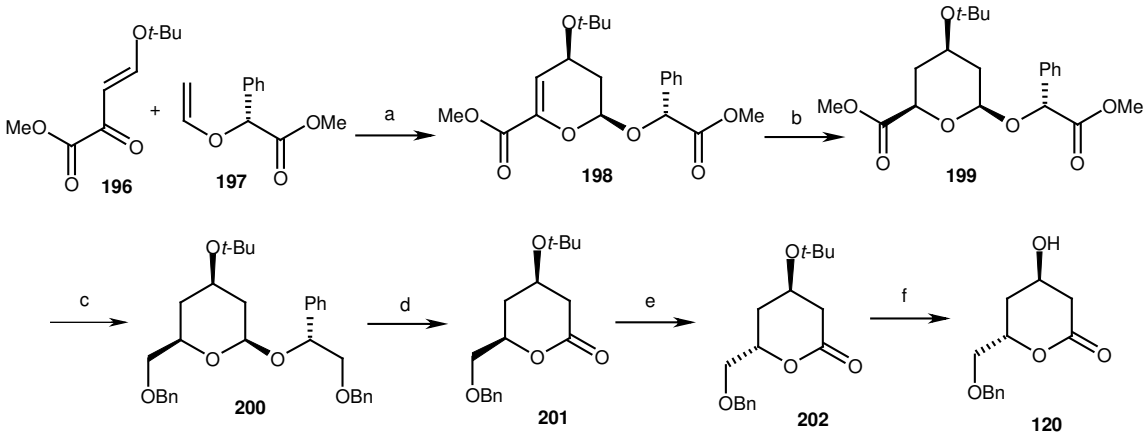
Kiyooka and coworkers employed the chiral oxazaborolidinone **190** catalyzed Aldol reaction of a silyl ketene involving a dithiolane moiety **189** with 4-phenylbutanal **188** to give **191**. Protection of hydroxyl and ester reduction afforded aldehyde **192**. A second aldol reaction on **192** with **189** in the presence of **190** gave *syn*-1,3-diol **193**. Deprotection of TBS group and lactonization furnished the lactone **195**.



Scheme 28. *Reagents and conditions*: (a) (i) Nitroethane, -78 °C, 1 h, 86%, (ii) Ni_2BH_2, 96%. (b) (i) TBSCl, (ii) DIBAL-H, 85%. (c) (i) Nitroethane, **189**, **190**, -78 °C, 1 h, (ii) Ni_2BH_2, 77%. (d) *n*-Bu_4NF. (e) *p*-TsOH, 70%.

Dujardin *et al*. (1998)[74]

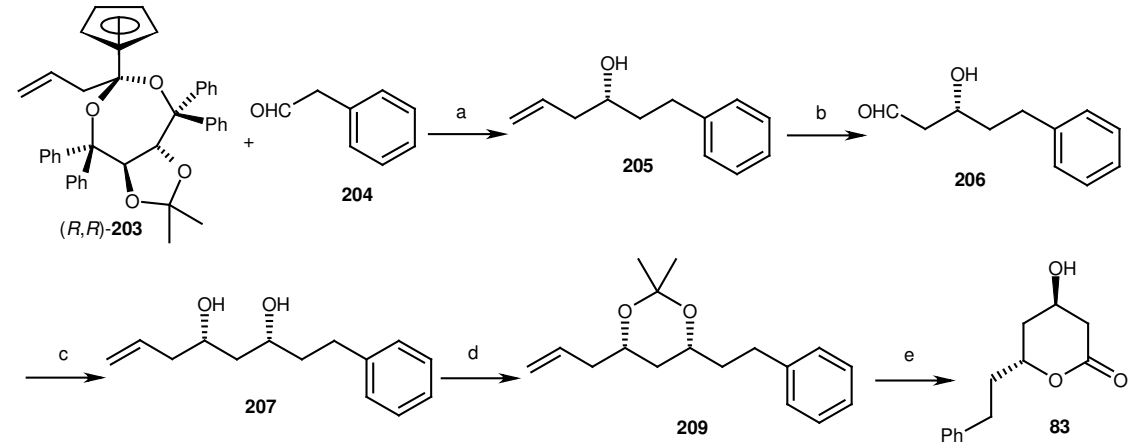
Dujardin and co-workers employed a hetero Diels-Alder reaction of oxabutadiene **196** with enolether **197** in the presence of $Eu(fod)_3$ to give the *endo*-heterocycloadduct **198** in 96% de. Catalytic hydrogenation of **198** and reduction of ester groups followed by benzylation gave **200**. Subsequent acidic hydrolysis and PCC oxidation afforded **201**. Hydrolysis of lactone and Mitsunobu inversion at C-5 center followed by *tert*-butyl deprotection furnished lactone **120**.



Scheme 29. *Reagents and conditions*: (a) 5% $Eu(fod)_3$, hexane, reflux, 70%. (b) H_2/Pd-C, EtOH, 88%. (c) (i) $LiAlH_4$, Et_2O, 93%, (ii) NaH, BnBr, DMF, 94%. (d) (i) 3N HCl, THF, 96%, (ii) PCC, 3A° molecular sieves, CH_2Cl_2, 89%. (e) (i) NaOH, THF, (ii) NH_4Cl, (iii) DIAD, Ph_3P, CH_2Cl_2, 42%. (f) CF_3CO_2H, CH_2Cl_2, 72%.

Bouzbouz *et al.* (2000)[75]

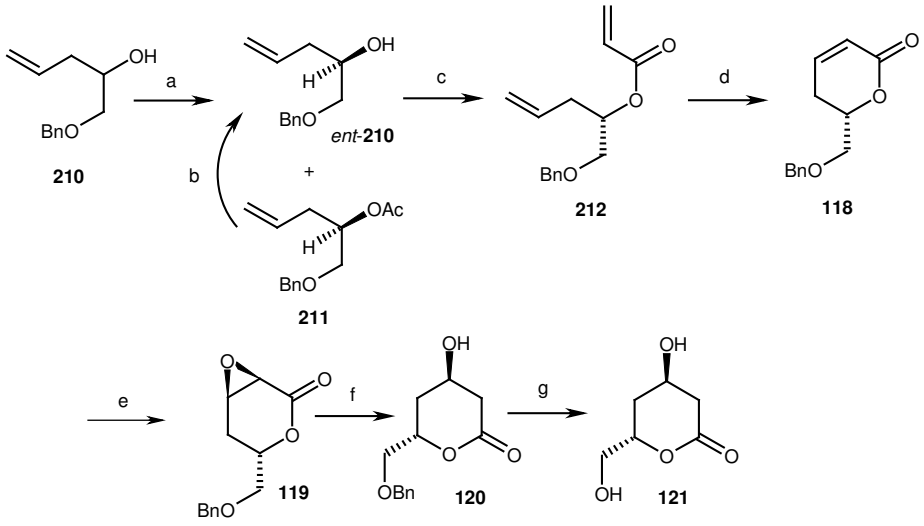
Bouzbouz and Cossy employed two consecutive enantioselective allytitanation with cyclopentadienyldial-ketoxyallytitanium complex (*R*,*R*)-**203**, first on **204** to give **205** and second on aldehyde **206** to give the *syn* 1,3-diol **207** in 95% diastereoselectivity. 1,3-Hydroxyl groups protection of **207** and $RuCl_3$ oxidation followed by acid treatment furnished the lactone **83**.



Scheme 29. *Reagents and conditions*: (a) -78 °C, 4 h, H_2O, 12 h, 90%. (b) OsO_4, $NaIO_4$, Et_2O:H_2O, 90%. (c) (*R*,*R*)-**203**, -78 °C, 4 h, H_2O, 12 h, 80%. (d) 2,2-DMP, $(CH_3)_2CO$, CSA, 0 °C, 94%. (e) $RuCl_3.3H_2O$, AcOH, THF, 48%.

Ghosh *et al.* (2000)[76]

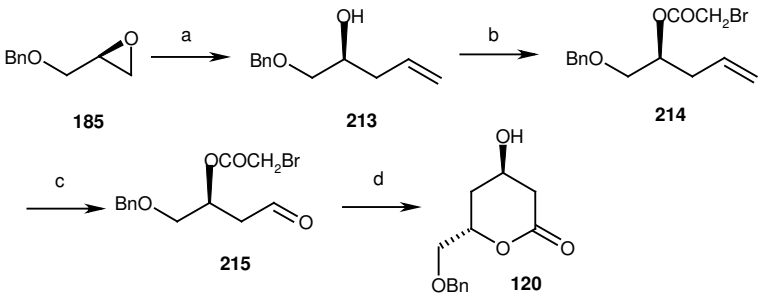
Ghosh and Lei carried out enzymatic acylation of racemic alcohol (±)-**210** with immobilized lipase PS-30 in presence of isopropenyl acetate to afford optically active *ent*-**210** and the acylated alcohol **211**. Compound **211** was converted to *ent*-**210** through saponification and Mitsunobu inversion. Reaction of *ent*-**210** with acryloyl chloride gave acrylate ester **212**. Olefin metathesis of **212** with Grubbs catalyst in the presence of Ti(O*i*-Pr)$_4$ furnished the α,β-unsaturated-δ-lactone **118**. Sequential epoxidation, reductive opening of epoxide and debenzylation produced the mevinic acid lactone **121**.



Scheme 30. *Reagents and conditions*: (a) Immobilized lipase PS-30, CH_2=C(Me)OAc, DME, 37 °C, 36 h. (b) (i) LiOH, THF-H_2O, 23 °C, 12 h, (ii) *p*-NO_2PhCO_2H, Ph_3P, DEAD, 23 °C, 12 h, 91%, (iii) LiOH, THF-H_2O. (c) CH_2=CHCOCl, Et_3N, DMAP (cat), -15 °C, 30 min, 75%. (d) Grubbs catalyst, Ti(Oi-Pr)$_4$, CH_2Cl_2, 40 °C, 15 h, 91%. (e) aq. NaOH, H_2O_2, MeOH, 23 °C, 81%. (f) $(PhSe)_2$, $NaBH_4$, *i*-PrOH, 0 °C, 93%. (g) H_2, Pearlman's cat., EtOAc, 5 h, 23 °C, 70%.

Uang *et al.* (2002)[77]

Uang and co-workers employed the SmI_2 mediated intramolecular Reformatsky reaction in the synthesis of the lactone moiety of compactin. Vinyl magnesium bromide reaction on the glycidyl ether **185** furnished **213**. Reaction of **213** with bromoacetyl bromide gave **214**. Ozonolysis of **214** furnished the aldehyde **215** which on intramolecular Reformatsky reaction mediated by SmI_2 afforded the lactone **120** in >95:5 ratio.



Scheme 31. *Reagents and conditions*: (a) CH_2=CH-MgBr, CuCN, -10 °C, 94%. (b) $BrCOCH_2Br$, 2,6-lutidine, 0 °C, 89%. (c) O_3, CH_2Cl_2-MeOH, DMS. (d) SmI_2, THF, 0 °C, 2 h, 91%.

4.1.4. PRESENT WORK

Objective

The stereoselective synthesis of 1,3-polyol arrays is one of the most important topics in organic chemistry because of the ubiquity of 1,3-polyols in various biologically active natural products and drugs, such as polyene macrolide antibiotics.[78] Thus, numerous strategies for their synthesis have been developed with great success.[79] The synthesis of 1,3-polyol arrays starts with the introduction of the first chiral center to the molecule. For this purpose, with the majority of chiral pool strategy,[80] a wide variety of synthetic methods are utilized[81] and the following asymmetric reactions are mainly used for 1,3-polyol syntheses: chiral auxiliary controlled aldol reaction,[82] allylboration using chiral borane reagents,[83] catalytic asymmetric epoxidation of allylic alcohols[84] or unfunctionalized olefins,[85] catalytic asymmetric hydrogenation,[86] catalytic asymmetric Mukaiyama type aldol reaction,[87] and catalytic asymmetric dihydroxylation.[88] The second stage of the synthesis is the elongation of 1,3-polyol arrays by stereoselective construction of the next chiral center. Chirality in the vicinity of the substrate reaction site makes this process very challenging and attractive in terms of the diversity of diastereocontrol. Thus, organic chemists have developed a variety of strategies, which can be classified into three approaches according to the structure relation between the chiral source and chiral products: a) substrate control synthesis (employing intramolecular chirality transfer); b) reagent control synthesis (employing stoichiometric amounts of the chiral source); and c) catalyst control synthesis (employing catalytic amounts of the chiral source). The majority

of the strategies use the substrate controlled asymmetric induction (category a). Many highly stereocontrolled 1,3-asymmetric induction reactions[89] have been developed that mainly rely on 1,3-syn[90]- or anti[91]- selective ketone reduction using borane reagents, intramolecular addition of the acetal to olefins,[92] inter- or intramolecular addition of silyl reagents to olefins such as hydrosilylation,[93] and intramolecular allylsilylation to carbonyl groups.[94] In contrast to the diversity of asymmetric reactions that are employed for the introduction of the first chirality, only a few chiral reagents (category b) or chiral catalysts (category c) are applied for stereoselective elongation of 1,3-polyol arrays due to crucial matched or mismatched effects caused by the substrate chirality. Among the above-mentioned asymmetric reactions, chiral auxiliary controlled aldol reaction (category b),[95] allyl addition using chiral borane or titanium reagents (category b),[96] and catalytic asymmetric epoxidation of allylic alcohols (category c)[97] are commonly used for 1,3-polyol synthesis. Employing these strategies, many polyene macrolide antibiotics, such as amphotericin B,[98] mycoticin A,[99] roxaticin,[100] roflamycoin,[101] dermostatin,[102] and 1,3-polyol/a-pyrones[103] were synthesized in a highly stereocontrolled manner.[104]

To synthesize not only 1,3-polyol natural products, but also their analogues, a highly versatile synthetic method that makes all possible stereoisomers freely accessible with the same efficiency is required. Herein we describe our successful endeavors towards development of a general and practical route for 1,3-polyols and its subsequent application for the stereoselective total synthesis of strictifolione and compactin employing hydrolytic kinetic resolution (HKR),[105] nucleophilic addition,[106] cross-olefin metathesis,[107] and ring closing metathesis[108] as the key steps.

Scheme 32 shows our general synthetic strategy to construct the *syn*-and *anti*-1,3-polyol system which is based on a three-step reaction sequence employing iterative epoxidation, hydrolytic kinetic resolution and vinylation. Accordingly, the racemic epoxide can easily be derived from the corresponding olefin by oxidation. In order to install the first stereogenic centre, the hydrolytic kinetic resolution (HKR) can be performed on the racemic epoxide **217** using Jacobsen's catalyst **216a**, **216b** (Fig. 5).

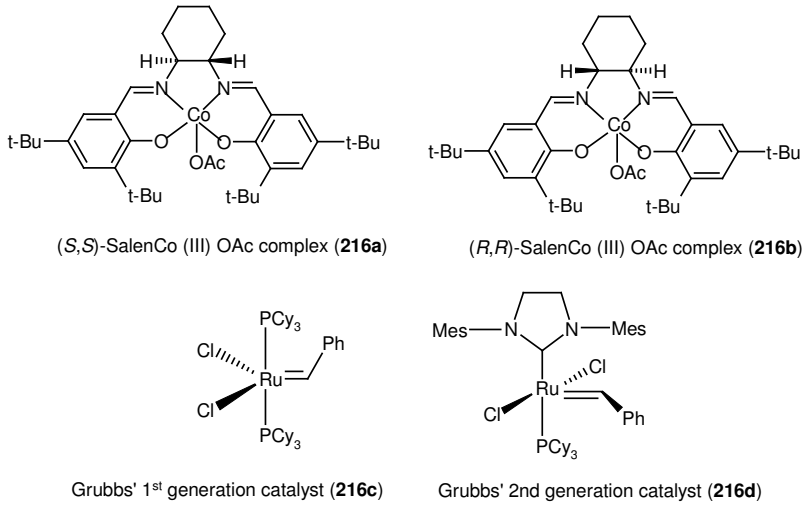
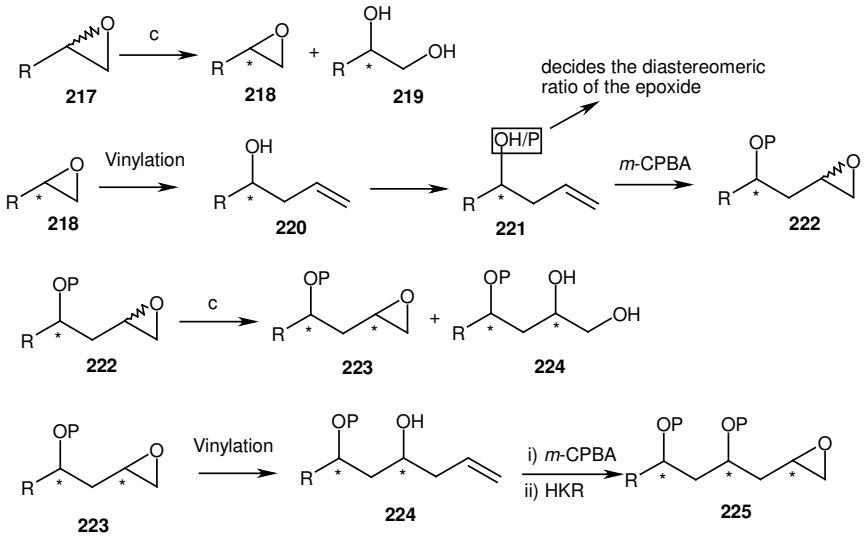


Figure 5.

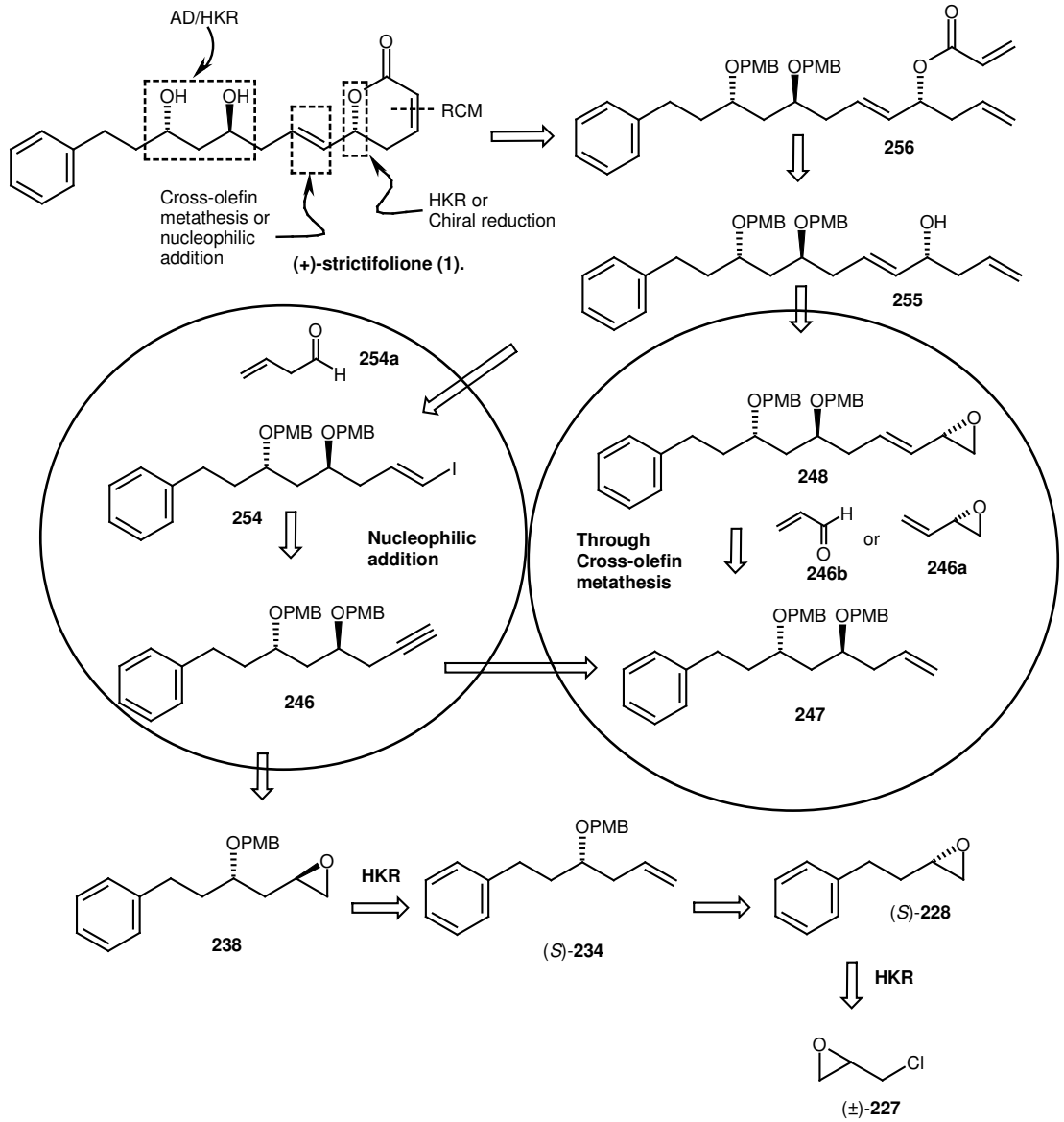
The ring opening of chiral epoxide **218** thus obtained with vinylmagnesium bromide would provide the homoallylic alcohol **220** as precursor for the epoxide and subsequent HKR. The homoallylic alcohol **220** can then be subjected to epoxidation with *m*-CPBA to get a mixture of diastereomeric epoxide **222**. The diastereomeric ratio in epoxidation reaction would depend on whether the hydroxyl group is free or protected. The HKR can subsequently be performed on the diastereomeric epoxide to obtain the enantiopure epoxide **223** which by iterative vinylation and epoxidation would eventually lead to the 1,3-polyol system. The *syn*-and *anti*-configuration of 1,3-polyol moiety can be manipulated simply by changing the Jacobsen's catalyst in the hydrolytic kinetic resolution step.



Scheme 32. General synthetic strategy to the synthesis of 1,3-polyols.

4.1.5. Result and discussion

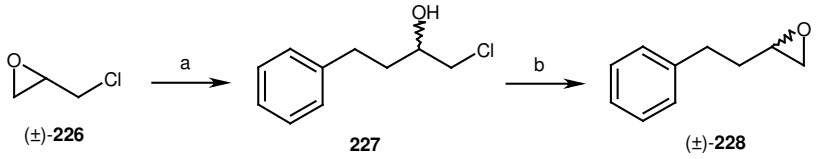
Our synthetic strategy for the synthesis of **1** is outlined in Scheme 33. We envisioned that the lactone ring could be constructed by the ring-closing metathesis of an acrylate ester **256**, which in turn could be obtained from homoallylic alcohol **255**. Homoallylic alcohol could be derived either from **247** *via* cross-olefin metathesis with acrolin **247a** or vinyl epoxide **247b**, or from vinyl iodide **254**. Vinyl iodide **254** and olefin **247** can be derived from terminal acetylene *via* nucleophilic addition and partial hydrogenation respectively. Initial two stereogenic centers can easily be established by iterative hydrolytic kinetic resolution and vinylation form commercially available epichlorohydrin.



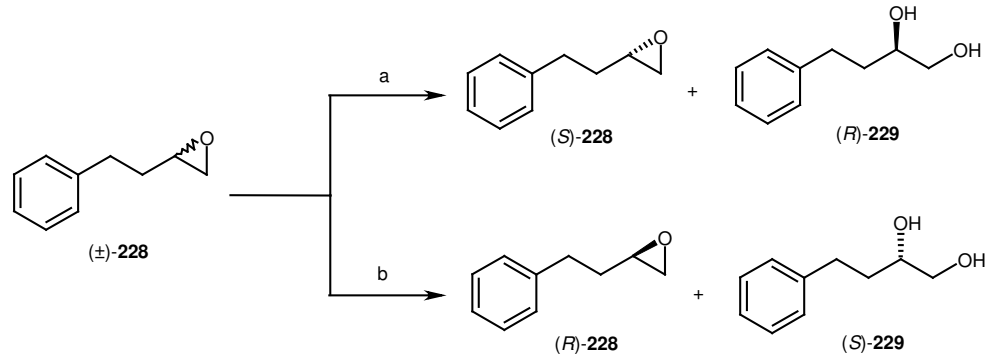
Scheme 33. Retrosynthetic analysis of strictifolione (1).

Synthesis of chiral epoxides (*S*)-228 and (*R*)-228: In designing a route to **1**, we chose epichlorohydrin as an appropriate starting material. Our synthesis of **1** requires three major reactions, Jacobsen's hydrolytic kinetic resolution, BINAL-H mediated chiral reduction to install the stereogenic centers, and ring-closing metathesis to construct the δ-lactone moiety.

As shown in Scheme 34, commercially available epichlorohydrin (±)-**226** was treated with benzylmagnesium bromide to give the chlorohydrin **227**, which was subsequently treated with pulverized NaOH in diethyl ether to furnish the rac-epoxide (±)-**228** in excellent yield. The epoxide peaks appeared at δ 2.96-3.30 (multiplet, one proton), 2.75-2.88 (m, three protons, *two protons from epoxide*), in ^{1}H NMR spectrum. The ^{13}C NMR spectrum of (±)-**228** showed upfield carbons of epoxide at δ 51.4, 46.7. Jacobsen's hydrolytic kinetic resolution of rac-epoxide (±)-**228** with (*S*,*S*)-Salen-Co-OAc catalyst **216a** gave (*S*)-epoxide (*S*)-**228** as a single isomer [detected by chiral HPLC (5 μ chiracel OD column, 95:5 hexane-EtOAc, 10.8 min.) analysis] in excellent yield, which was easily isolated from the more polar diol (*R*)-**239** by silica gel column chromatography. Analogously epoxide (*R*)-**228** was prepared using (*R*,*R*)-Salen-Co-OAc in 48% yield and diol (*S*)-**229** in 49% yield.



Scheme 34. *Reagents and conditions*: (a) Benzylmagnesium bromide, diethyl ether, (±)-**226**, 0 °C to rt, 5 h, 89%; (b) KOH, diethyl ether, 0 °C to rt, 4 h, 96%.

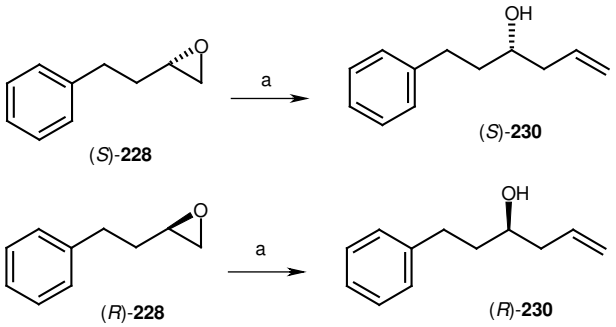


Scheme 35. *Reagents and conditions*: (a) *S*,*S*-salen-Co-(OAc) (0.5 mol%), dist. H_2O (0.6 eq), 0 °C, 10 h, (48% for (*S*)-**228**, 46% for (*R*)-**229**); (b) *R*,*R*-salen-Co-(OAc) (0.5 mol%), dist. H_2O (0.6 eq), 0 °C, 10 h, (47% for (*R*)-**228**, 46% for (*S*)-**229**).

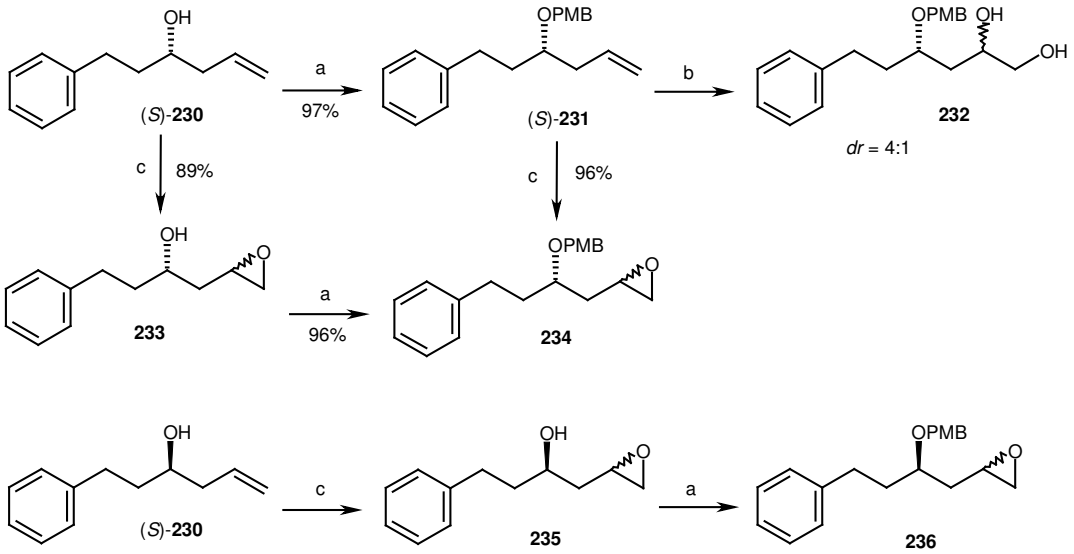
Synthesis of diastereomeric mixtures of epoxides

With enantiomerically pure epoxides (*S*)-**228** and (*R*)-**228** in hand, our next aim was to construct the *syn*- or *anti*-1,3-diol. To establish the second stereogenic center with required stereochemistry, we then examined the stereoselective dihydroxylation or epoxidation of homoallylic alcohols. Thus, epoxide (*S*)-**228** was treated with vinylmagnesium bromide in the presence of CuI to give the homoallylic alcohol (*S*)-**230** in excellent yield. The IR spectrum of (*S*)-**230** gave broad hydroxyl absorption at 3386-3250 cm^{-1}. The ^1H NMR spectrum of (*S*)-**230** gave olefin peaks at δ 5.14-5.24 (multiplet, two protons) and 5.80-5.97 (multiplet, one proton). In a similar manner, epoxide (*R*)-**228** gave the homoallylic alcohol (*R*)-**230**. Initially, it was thought worthwhile to prepare first the diol **232** by the Sharpless asymmetric dihydroxylation of olefin (*S*)-**231**, which could further be converted easily into the required epoxide by standard transformations. Accordingly, the olefin (*S*)-**231** was treated with osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of $(DHQD)_2AQN$ ligand under AD conditions[10] to give the diol **232** in 91% yield with moderate diastereomeric selectivity (*dr* = 4:1; *anti:syn*) as an inseparable mixture of diastereomers. In another attempt, to improve the selectivity and to examine the stereochemical outcome of the epoxidation reaction, we carried out epoxidation of olefins (*S*)-**231** and (*R*)-**231** using *m*-CPBA. We initially protected the hydroxyl group of homoallylic alcohols as PMB ether, followed by epoxidation with *m*-CPBA. The epoxide obtained was found to be a mixture of two diastereomers (*anti:syn*; 2.1:1)) as determined by ^1H and ^{13}C NMR spectral analysis. The ^1H NMR spectrum of **234** showed absence of olefin protons at δ 5.14-5.24 and 5.80-5.97. The diastereomeric epoxide peaks appeared at δ 2.48-2.50 (multiplet, 1/3 proton), 2.53-2.54 (multiplet, one proton); 2.78 (triplet, 1/3 proton), 2.82 (triplet, one proton) and 3.03-3.06 (multiplet, one proton), 3.07-3.10 (multiplet, 1/3 proton) in ^1H NMR spectrum. The ^{13}C NMR spectrum of **234** showed upfield carbons of epoxide at δ 46.6, 47.4; 49.3, 49.4 and other stereocentre at δ 73.0, 73.1 as a diastereomeric mixture. The *syn* isomer of (*S*)-**231** was obtained only as minor component. However, when epoxidation was carried out on the alcohol (*S*)-**230** and (*R*)-**230** followed by hydroxy protection as a PMB-ether, the epoxides **234** and **236** were formed in favor of the desired *syn* isomer (*syn*: *anti*; 1.2:1). The two diastereomers could not be differentiated on TLC. In order to improve the diastereoselectivity, we next attempted the Jacobsen's hydrolytic kinetic resolution (HKR). In the structure of

strictifolione the 1,3-diol is arranged in an *anti*-fashion, therefore the epoxide **234**, rich in anti-isomer was chosen as substrate for further resolution by HKR method.



Scheme 36. *Reagents and conditions*: Vinylmagnesium bromide, THF, CuI, –20 ^{o}C, 16 h, 88%.

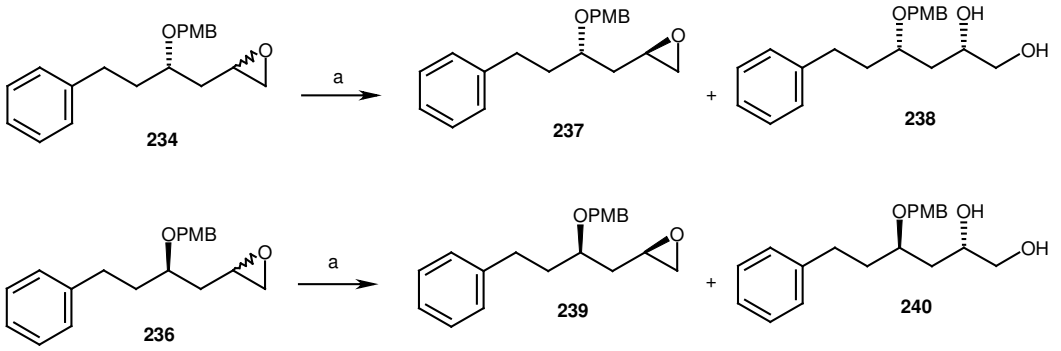


Scheme 37. *Reagents and conditions*: (a) NaH, PMBBr, THF, TBAI, 0 ^{o}C to rt, overnight; (b) $(DHQD)_2AQN$ (1 mol%), 0.1M OsO_4 (0.4 mol%), K_2CO_3, $K_3Fe(CN)_6$, *t*-BuOH/H_2O 1:1, 0 ^{o}C, 24 h, 92%; (c) *m*-CPBA, CH_2Cl_2, 0 ^{o}C to rt, 10 h.

Synthesis of diastereomerically pure epoxides (**Scheme 38**).

With racemic epoxides **234** (*anti*: *syn*; 2.1:1) and **236** (*syn*: *anti*; 1.2:1) in hand, our next aim was to synthesize the chiral epoxides through the Jacobsen's hydrolytic kinetic resolution method. Towards this end the epoxide **234** was treated with (*R*,*R*)-salen-Co-OAc complex (0.5 mol%) and water (0.7 eq) in THF (0.7 eq) to afford the epoxide **237** as a single stereoisomer (determined from the ^{1}H and ^{13}C NMR spectral analysis) in 45% yield and the diol **238** in 47% yield. Epoxide **237** could easily be separated from the more polar diol **238** through silica gel column chromatography. In a similar manner, HKR

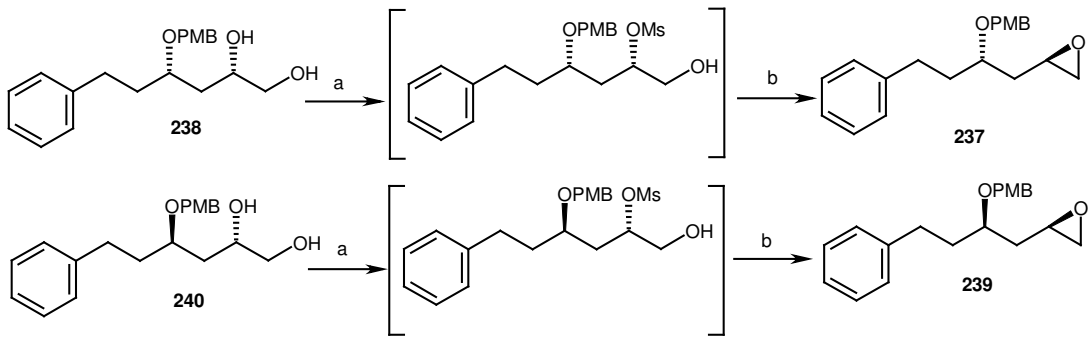
performed on the racemic epoxide **236** by using (*R*,*R*)-salen-Co-OAc catalyst afforded the chiral epoxide **239** as a single stereoisomer in 46% yield and diol **240** in 45% yield.



Scheme 38. *Reagents and conditions*: (a) *R*,*R*-Salen-Co-(OAc) (0.5 mol%), dist. H_2O (0.55 eq), THF, 0 ^oC, 24 h, (45% for **237**, 47% for **238**; 46% for **239**, 45% for **240**).

Conversion of diols (238, 240) into epoxides (237, 239) (**Scheme 39**)

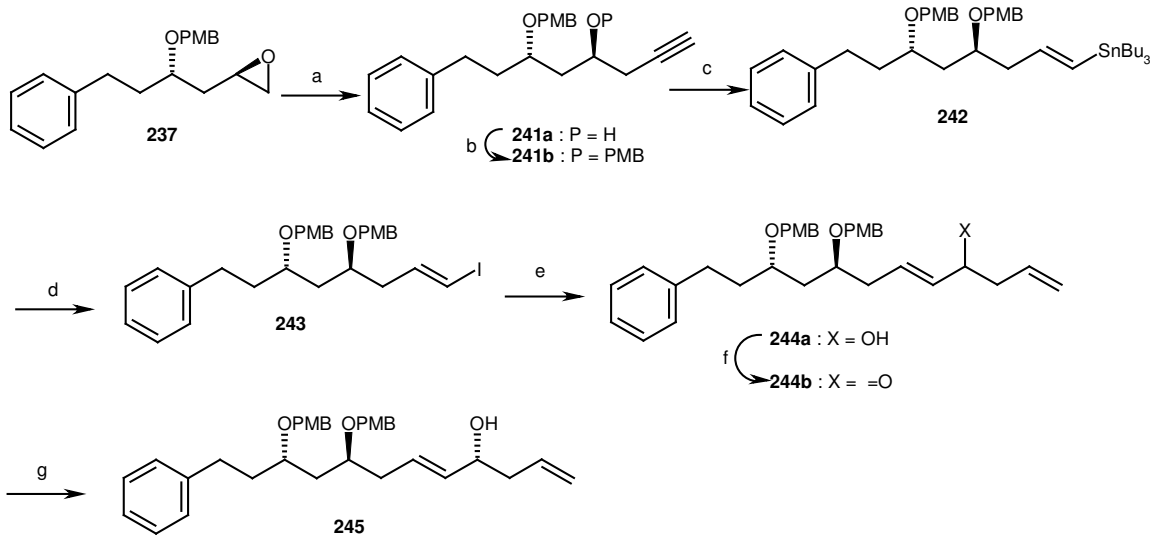
In order to achieve the synthesis of target molecule **1**, we required epoxides **237** and **239** in substantial amount. As the HKR method provided the desired epoxide **237** along with unwanted diol **238** in almost equal amounts, we thought it would be appropriate to convert the diol into the required epoxide *via* internal nucleophilic substitution of a secondary mesylate.[109] The diols **238** and **240** can be easily converted into the required epoxides **237** and **239** respectively *via* internal nucleophilic substitution in a secondary mesylate. Thus, the chemoselective pivalation of diols with pivaloyl chloride followed by mesylation of secondary hydroxy and treatment of the crude mesylate product with K_2CO_3 in methanol led to deprotection of the pivaloyl ester to hydroxy group. The concomitant ring closure *via* intramolecular S_N2 displacement of the mesylate furnished the epoxides **237** and **239** in 61% overall yield.



Scheme 39. *Reagents and conditions*: (a) (i) PivCl, Et_3N, Cat. DMAP, rt; (ii) MsCl, Et_3N, DMAP, 0 ^oC to rt; (b) K_2CO_3, MeOH, rt (60-65% for three steps).

Synthesis of (+)-strictifolione:

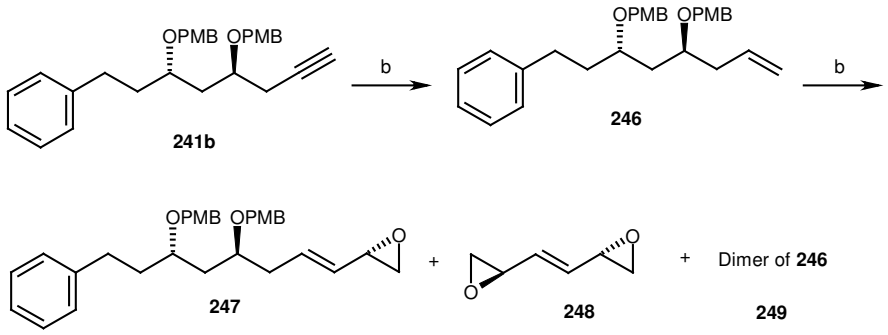
With substantial amount of **237** in hand, we required to generate the *trans*-olefin and carry out the subsequent reactions to complete the synthesis of (+)-strictifolione. We, then further proceeded for the synthesis of **1** by opening of the epoxide **237** with an excess of lithium acetylide to furnish acetylene **241** in 86% yield. The free hydroxy group of **241** was protected as its PMB ether to give **241b** in excellent yield. Acetylene **241b** was treated with tri-*n*-butyltin hydride and AIBN in refluxing benzene[110] to give (*E*)-vinyl stannane **242** in 96% yield. The ^1H NMR spectrum gave olefin protons at δ 5.85 (doublet of doublet of doublet) with the coupling constant J = 16.7, 7.1 Hz, and 5.15 (doublet) with the coupling constant J = 15.5 Hz, indicating *trans*-olefin. Tributyltin was then replaced with iodide by using I_2[111] in CH_2Cl_2 to afford the corresponding iodo compound **243** in excellent yield. Vinyl iodide **243** was treated with *n*-BuLi in THF at –78 ^oC for 1 h and further treated with CuCN followed by addition of but-3-enal **243a** to form the coupling product **244a** in 68% yield in 1:1 diastereomeric ratio. The secondary hydroxy was further oxidized using IBX to give keto product **244b** in good yield.



Scheme 40. *Reagents and conditions*: (a) LiC≡C.EDA, DMSO, 0 ^oC to rt, 5 h, 86%; (b) NaH, PMBBr, THF, TBAI, 0 ^oC to rt, overnight, 97%; (c) $(n\text{-}Bu)_3SnH$, AIBN, C_6H_6, reflux, 4 h, 96%; (d) I_2, CH_2Cl_2, 30 min, 94%; (e) *n*-BuLi, THF, -78 ^oC for 1 h, -50 ^oC for 1.5 h, then CuCN, -78 ^oC, 1.5 h, then but-3-enal **31a**, 68%; (f) IBX, EtOAc, reflux, 6 h; (g) BINAL-H, THF, −100 ^oC for 1 h, −78 ^oC 3 h, 75%.

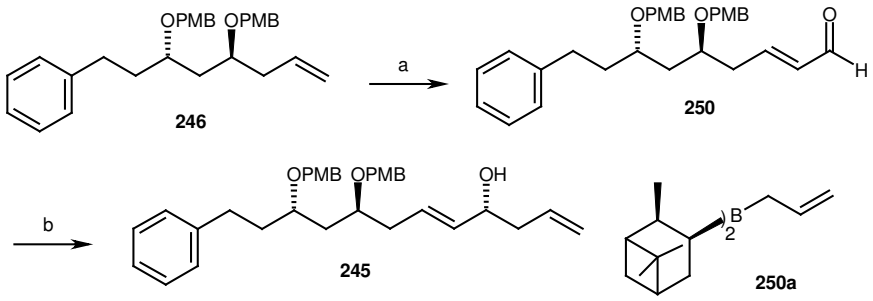
With the desired allylic ketone **244** in hand, we turned our attention to the installation of the pyranone portion of the natural product (+)-strictifolione. Thus, asymmetric reduction of **244** using chiral BINAL-H[112] in THF proceeded in a stereoselective fashion to give the allylic alcohol **245** in substantially high enantiomeric excess (91% ee, determined from the ^{1}H and ^{13}C NMR spectral analysis).

Alternatively, it was thought worthwhile to convert the acetylene into the olefin and study the cross-olefin metathesis to construct *trans*-olefin with chiral epoxide. Thus, acetylene **241** was converted into homoallylic alcohol by partial hydrogenation using Lindlar's catalyst in excellent yield. Olefin **246** was subjected to the cross-olefin metathesis with 3 equivalents of (*S*)-butadiene mono-epoxide[113] using Grubbs' 1st generation catalyst (**216c**), in refluxing CH_2Cl_2 or in benzene; however formation of desired product **247** could not be observed. Use of Grubbs' 2nd generation catalyst (**216d**) in refluxing CH_2Cl_2 furnished compound **247** in only 16% yield as a 6:1 mixture of E/Z isomers along with homodimer of **246**, homodimer of (*S*)-butadiene mono-epoxide and unreacted **246**.



Scheme 41. *Reagents and conditions*: (a) H_2, Pd-$BaSO_4$, quinoline, EtOAc, 1 h, 98%; (b) $RuCl_2$(=CHPh)(PCy_3)(IEMS) (**216d**), (*S*)-2-vinyloxirane (**246a**), CH_2Cl_2, reflux, 18 h, 16% of **248**.

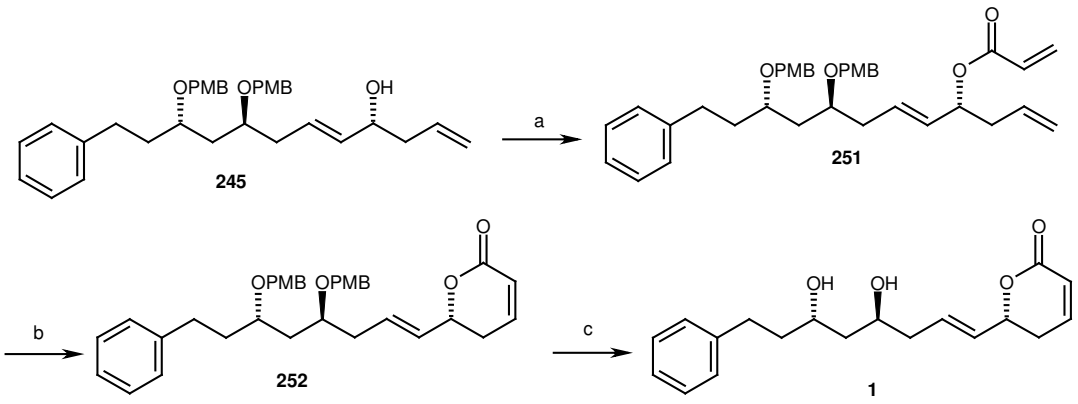
In another attempt, to improve the selectivity and yield, we examined the cross-olefin metathesis of olefin **246** and by treatment with 3 equivalents of acrolein using 10 mol% Grubbs' 2nd generation catalyst (**216d**) in refluxing CH_2Cl_2 to afford the α,β-unsaturated aldehyde in 89% yield with an *E*/*Z* ratio of >30:1. With the desired aldehyde **250** in hand, we turned our attention to the installation of the pyranone portion of the natural product (+)-strictifolione. Asymmetric allylation of the α,β-unsaturated aldehyde **250** was unsuccessful with Keck's methodology.[114]



Scheme 42. *Reagents and conditions*: (a) acrolein (**246b**), $RuCl_2$(=CHPh)(PCy_3)(IEMS) (**216d**) 10 mol%, CH_2Cl_2, rt, 76%; (b) (−)-DIP-Cl, allylmagnesium bromide, Et_2O-pentane, −100 ^oC, 2 h, 74%.

However, Brown's protocol[115] proved useful here. Thus, an allylating reagent (allylBIpc$_2$), prepared from allylmagnesium bromide and (−)-DIP-Cl (diisopinocampheylboron chloride), was reacted with **250** at −100 ^oC to afford the homoallylic alcohol **245** in good yield with diasteromeric ratio 96:4 (determined from the ^1H and ^{13}C NMR spectral analysis).

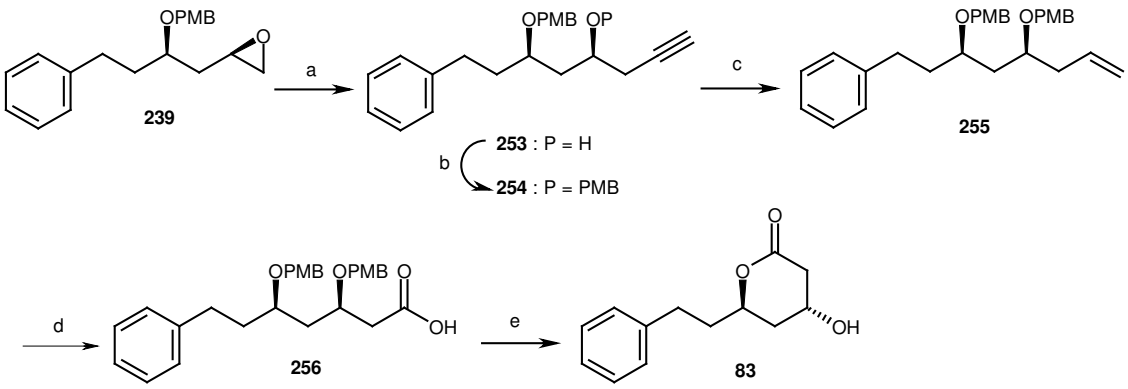
Alcohol **245** was esterified with acryloyl chloride in the presence of Et_3N and catalytic amount of DMAP to afford the acryloyl ester **251** in 82% yield. Subsequent ring-closing metathesis of ester **251** with commercially available Grubbs' 1st generation catalyst **216c** in the presence of Ti(*i*-PrO)$_4$ (0.03 eq) in refluxing CH_2Cl_2 for 6 h afforded the α,β-unsaturated δ-lactone **252** in 87% yield. In the absence of Ti(*i*-PrO)$_4$, the reaction was found to be sluggish. In contrast to this, the reaction proceeded well in almost comparable yield with the use of 5 mol% Grubbs' 2nd generation catalyst **216d** without addition of any Ti(*i*-PrO)$_4$. Now all that remained to complete the synthesis was to remove the PMB groups. Thus, debenzylation of **252** in the presence of DDQ gave (+)-strictifolione **1** in 89% yield. $[\alpha]_D^{25}$ +72 (*c* 0.6, $CHCl_3$); lit.[2] $[\alpha]_D^{25}$ +81.5 (*c* 0.52, $CHCl_3$); lit.[42] $[\alpha]_D^{25}$ +54.1 (*c* 0.33, $CHCl_3$)}. The physical and spectroscopic data of **1** were in full agreement with the literature data.



Scheme 43. *Reagents and conditions*: (a) Acryloyl chloride, Et_3N, CH_2Cl_2, 0 ^oC to rt, 5 h, 82%; (b) $(PCy_3)_2Ru(Cl)_2$=CH-Ph (20 mol%), CH_2Cl_2, Ti(*i*-PrO)$_4$ (0.03 eq.), reflux, 6 h , 87%; (c) DDQ, CH_2Cl_2-H_2O (9:1), 91%.

4.1.6. Synthesis of the Lactone moiety of HMG-CoA Reductase Inhibitor: Compactin and Mevinolin.

To prepare the lactone moiety of compactin and mevinolin, we chose epoxide **239** as starting material. Thus, epoxide **239** was opened with lithium acetylide to furnish acetylene **241** in 86% yield. The free hydroxyl group of **253** was protected as its PMB ether to give compound **254** in excellent yield. Acetylene **254** was converted into protected homoallylic alcohol **255** by partial hydrogenation using Lindlar's catalyst in excellent yield. Olefinic oxidation of **255** using $RuCl_3$ furnished the acid, which was cyclised under acidic conditions (catalytic amount of HCl in MeOH) to give the lactone **83** in good yield. mp: 109 ^oC, lit.[83, 59, 68] mp: 106–107 ^oC; $[\alpha]_D^{25}$ = +66.9 (*c* = 0.7, $CHC1_3$); lit.[59] $[\alpha]_D^{25}$ + 68.88 (*c* 2.29 $CHCl_3$); lit.[4c] $[\alpha]_D^{25}$ + 68.88 (*c* 2.29 $CHCl_3$). The physical and spectroscopic data of **83** were in full agreement with the literature data.



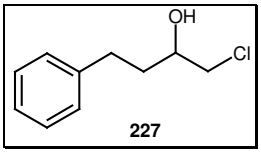
Scheme 44. *Reagents and conditions*: (a) LiC≡C.EDA, DMSO, 0 ^{o}C to rt, 5 h, 86%; (b) NaH, PMBBr, THF, TBAI, 0 ^{o}C to rt, overnight, 95%; (c) H_2, Pd-$BaSO_4$, quinoline, EtOAc, 1 h, 98%; (d) $RuCl_3 \cdot 3H_2O$, $NaIO_4$, CCl_4-H_2O-CH_3CN = 4:1:1, 5 h, 44%, (e) cat. HCl, MeOH, overnight, 79%.

4.1.7. Experimental Section

General information:

All reactions were carried out under argon or nitrogen in oven-dried glassware using standard gas-light syringes, cannulas and septa. Solvents and reagents were purified and dried by standard methods prior to use. Optical rotations were measured at room temperature. IR spectra were recorded on an FT-IR instrument. ^{1}H NMR spectra were recorded on 200 MHz, 300 MHz and 500 MHz and are reported in parts per million (δ) downfield relative to $CDCl_3$ as internal standard and ^{13}C NMR spectra were recorded at 50 MHz, 75 MHz and 125 MHz and assigned in parts per million (δ) relative to $CDCl_3$. Column chromatography was performed on silica gel (100-200 and 230-400 mesh) using a mixture of petroleum ether and ethyl acetate as the eluent. Enantiomeric excess was determined using chiral HPLC.

1-Chloro-4-phenylbutan-2-ol (227).



227

A round bottomed flask was charged with Mg (9.19 g, 378.38 mmol), gently heated under vacuum, and slowly cooled with a flow of argon, and dry diethyl ether (100 mL) was added. To this was added slowly benzyl bromide (55.77 g, 302.70 mmol) in diethyl ether (50 mL) slowly at room temperature and stirred vigorously. After 50% addition of benzyl bromide the reaction mixture was cooled to 0 ^{o}C followed by addition of epichlorohydrin (14.0 g, 151.35 mmol) in diethyl ether (25 mL) slowly with simultaneous addition of remaining amount of benzyl bromide. After the completion of addition of both the reagents, the reaction mixture was stirred at the room temperature for 5 h. The reaction mixture was quenched by pouring into a saturated aqueous solution of NH_4Cl at 0 ^{o}C and then aqueous layer was extracted with diethyl ether (3 x 50 mL). The organic layer was washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (8:2) as eluent gave the chlorohydrin **227** as a colourless liquid.

Yield: 24.87 g (89%).

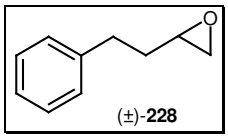
Mol. Formula: $C_{10}H_{13}ClO$

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.85-1.96 (m, 2H), 2.52 (dd, *J* = 5.2, 2.2 Hz, 2H), 3.55 (d, *J* = 8.1 Hz, 2H), 3.83-3.91 (m, 1H), 7.25-7.41 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 140.9, 128.0, 125.7, 70.4, 48.8, 33.8, 31.9.

Analysis: Calcd.: C, 65.04; H, 7.10; Cl, 19.20%; **Found:** C, 65.21; H, 7.06; Cl, 18.97%.

2-Phenethyloxirane [(±)-228].



(±)-**228**

To a solution of chlorohydrin **227** (15.0 g, 81.49 mmol) in diethyl ether (100 ml) was added pulverized KOH (9.14 g, 162.98 mmol) at 0 ^{o}C and reaction mixture was stirred at room temperature for 4 h. The reaction mixture was quenched by addition of water (50 mL) and then extracted with diethyl ether (3 x 50 mL). The combined extracts were dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) as eluent gave the epoxide (±)-**228** as a colourless liquid.

Yield: 11.56 g (96%).

Mol. Formula: $C_{10}H_{12}O$

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.86-1.95 (m, 2H), 2.52 (dd, *J* = 5.2, 2.2 Hz, 1H), 2.75-2.88 (m, 3H), 2.96-3.30 (m, 1H), 7.25-7.41 (m, 5H).

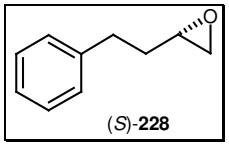
^{13}C NMR (50 MHz, $CDCl_3$): δ 140.9, 128.0, 125.6, 51.4, 46.7, 33.9, 31.8.

Analysis: Calcd.: C, 81.04; H, 8.16%; **Found:** C, 81.24; H, 8.01%.

Compound (*S*)-228 and (*R*)-229.

Racemic epoxide **(±)-228** (8.0 g, 54.02 mmol), THF (583 μL) were added to (*S*,*S*)-Salen-Co-OAc catalyst (179 mg, 0.27 mmol, 0.5 mol%) and the solution was cooled to 0 ^{o}C. Every 5 min, H_2O (117 μL) was added until 583 μL (0.6 equiv., 32.41 mmol) had been added; after another 5 min the ice bath was removed and the reaction was stirred at room temperature for 10 h. The reaction mixture was concentrated and purified through silica gel column chromatography using petroleum ether/EtOAc (9:1) as eluent to furnish the epoxide (*S*)-**228** as a single stereoisomer as a yellow color liquid. Continued chromatography with petroleum ether/EtOAc (4:6) provided the diol (*R*)-**239** as a brown color liquid as a single diastereomer.

(2-Phenethyloxirane): Epoxide (*S*)-228

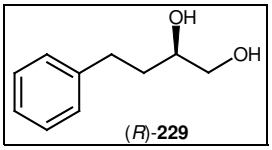


Yield: 3.84 g (48%).

Mol. Formula: $C_{10}H_{12}O$

$[\alpha]_D^{25}$: –13.8 (*c* 0.7, $CHCl_3$)

((*R*)-4-Phenylbutane-1,2-diol). Diol (*R*)-229



Yield: 4.13 g (46%).

Mol. Formula: $C_{10}H_{14}O_2$

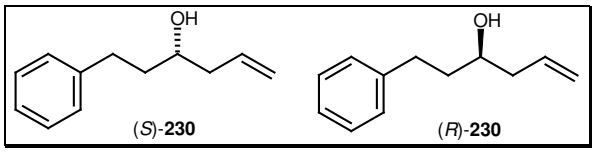
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.83 (q, *J* = 14.0 Hz, 2H), 2.64-2.93 (m, 2H), 3.57-3.69 (m, 1H), 3.82-3.89 (m, 1H), 3.91-4.12 (m, 1H), 7.17-7.41 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 141.7, 128.3, 125.8, 71.1, 66.1, 32.3, 31.8.

Analysis: Calcd.: C, 72.26; H, 8.49%; **Found:** C, 72.41; H, 8.32%.

Compound (*R*)-**228** and (*S*)-**229** were prepared by using (*R,R*)-Salen-Co(III)-OAc following the procedure as described for compounds (*S*)-**228 and** (*R*)-**239** in 47% and 46% yield respectively. All spectroscopic data for (*R*)-**228** and (*S*)-**229** (^{1}H NMR, ^{13}C NMR and IR) were identical to the epoxide (*S*)-**228** and diol (*R*)-**239** respectively, except optical rotation. **Epoxide** (*R*)-**228:** $[\alpha]_D^{25}$: +14.6 (*c* 0.9, $CHCl_3$).

(*S*)-1-Phenylhex-5-en-3-ol (*S*)-230 and (*R*)-1-Phenylhex-5-en-3-ol (*R*)-230:



A round bottomed flask was charged with copper(I)iodide (39 mg, 0.20 mmol), gently heated under vacuum and slowly cooled with a flow of argon and THF (20 mL) was added. This suspension was cooled to –20 ^oC, stirred and vinylmagnesium bromide (1M in THF, 40.5 mL, 40.51 mmol) was added to it. A solution of epoxide (*S*)-**228** (3.0 g, 20.25 mmol) in THF (15 mL) was added to the above reagent and the mixture was stirred at –20 ^oC for 1 h. After consumption of starting material, the reaction mixture was quenched with

a saturated aqueous solution of NH_4Cl. The water layer was extracted with EtOAc (3 ×50 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated. Purification of crude product by silica gel column chromatography using petroleum ether/EtOAc (8.5:1.5) as eluent afforded (*S*)-**230** as a colorless liquid.

Yield: 3.14 g (88%).

Mol. Formula: $C_{12}H_{16}O$

$[\alpha]_D^{25}$: –19.98 (*c* 2.06, $CHCl_3$)

IR (neat, cm^{-1}): ν_{max} 3386, 1640, 1603, 1493, 1453

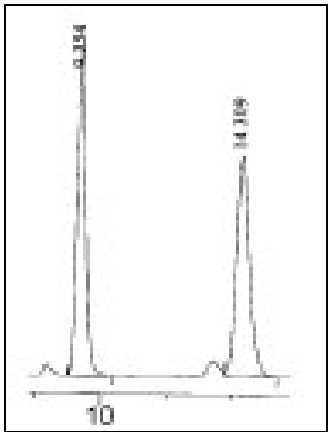
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.71 (s, 1H), 1.78-1.82 (m, 2H), 2.22-2.35 (m, 2H), 2.72-2.87 (m, 2H), 3.66-3.78 (m, 2H), 5.14-5.24 (m, 2H), 5.80-5.97 (m, 1H), 7.23-7.37 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 141.9, 134.5, 128.2, 125.6, 117.8, 69.8, 41.8, 38.2, 31.8.

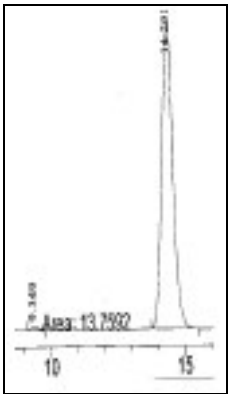
Analysis: Calcd.: C, 72.26; H, 8.49%; **Found:** C, 72.41; H, 8.32%.

Compound (*R*)-**230** was prepared following the procedure as described for compound (*S*)-**230** in 90% yield as a colorless liquid. IR, ^{1}H NMR and ^{13}C NMR spectra were essentially identical to those of (*S*)-**230**.

$[\alpha]_D^{25}$: +19.90 (*c* 1.9, $CHCl_3$).



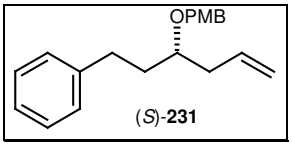
Peak #	RetTime [min]	Type	Width [min]	Area mAU	Area *s	Area %
1	9.354	BP	0.2732	622.39453		49.4276
2	14.309	VB	0.4280	636.80902		50.5724



Peak #	RetTime [min]	Type	Width [min]	Area mAU	Area *s	Area %
1	9.349	MM	0.3861	13.75921		0.8198
2	14.291	BB	0.4375	1664.57983		99.1802

HPLC conditions: Chiralcel OD, Hexane/*i*-PrOH 95:5, 1mL/min.

1-((*S*)-3-(4-Methoxybenzyloxy)hex-5-enyl)benzene: (*S*)-**231**



To a solution of (*S*)-**230** (4.0 g, 22.69 mmol) in dry DMF (100 mL) was added sodium hydride (50%, 1.53 g, 31.77 mmol) at 0 ^{o}C. The reaction mixture was then stirred at room temperature for 30 min after which it was again cooled to 0 ^{o}C. To this was added slowly *p*-methoxybenzyl bromide (5.02 g, 24.96 mmol) and tetra *n*-butylammonium iodide (838 mg, 2.26 mmol) with further stirring for overnight at the same temperature. The reaction mixture was quenched with addition of cold water at 0 ^{o}C. The two phases were separated and the aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with water (3 x 50 mL), brine, dried (Na_2SO_4) and concentrated. The residual oil was purified by silica gel column chromatography using petroleum ether/EtOAc (9.5:0.5) as eluent to furnish the PMB protected homoallylic alcohol (*S*)-**231** as colourless oil.

Yield: 6.52 g (97%).

Mol. Formula: $C_{20}H_{24}O_2$

$[\alpha]_D^{25}$: –27.41(*c* 1.66, $CHCl_3$)

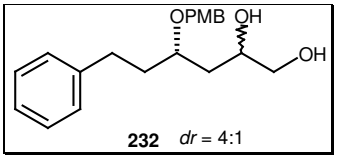
IR (neat, cm^{-1}): ν_{max} 1641, 1606, 1491, 1462.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.78-1.86 (m, 2H), 2.37 (t, *J* = 5.7 Hz, 2H), 2.55-2.86 (m, 2H), 3.39-3.54 (m, 1H), 3.81 (s, 3H), 4.45 (dd, *J* = 24.8, 11.2 Hz, 2H), 5.05-5.18 (m, 2H), 5.71-5.96 (m, 1H), 6.91 (d, *J* = 8.2 Hz, 2H), 7.08-7.31 (m, 7H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 31.7, 35.7, 38.2, 55.3, 70.6, 113.8, 117.0, 125.7, 128.4, 129.3, 129.7, 130.9, 134.8, 142.4, 159.1.

Analysis: Calcd.: C, 81.04; H, 8.16%; **Found:** C, 81.29; H, 8.31%.

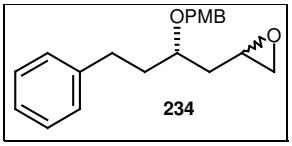
(2*R*,4*S*)-4-(4-Methoxybenzyloxy)-6-phenylhexane-1,2-diol (232).



232 *dr* = 4:1

To a mixture of $K_3Fe(CN)_6$ (666 mg, 2.02 mmol), K_2CO_3 (280 mg, 2.02 mmol) and $(DHQ)_2AQN$ (6 mg, 0.007 mmol, 1 mol %), in *t*-BuOH-H_2O (1:1, 8 mL) cooled at 0 °C was added OsO_4 (26 μL, 0.1 M solution in toluene, 0.003 mmol, 0.4 mol %). After stirring for 5 min at 0 °C, the olefin **231** (346 mg, 0.92 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 24 h and then quenched with solid sodium sulfite (2 g). The stirring was continued for 45 min and the solution was extracted with EtOAc (3 x 50 mL). The combined organic phases were washed brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (3:2) as eluent gave diol **232** (205 mg, 92%) as an inseparable mixture of diastereomers (4:1) in form of a colorless syrupy liquid.

Diastereomeric epoxide (234).



234

To a solution of PMB ether (*S*)-**231** (4.6 g, 15.51 mmol) in CH_2Cl_2 (150 mL), *meta*-chloroperbenzoic acid (6.43 g, 18.62 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 10 h, then diluted with saturated aqueous Na_2SO_3 at 0 °C, stirred for 30 min, neutralized with saturated $NaHCO_3$ and extracted with CH_2Cl_2. Combined organic fractions were dried (Na_2SO_4), filtered, concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (8:2) as eluent provided **234** (an approximately 2.2:1 mixture of diastereomers) as a colorless liquid .

Yield: 4.65 g (96%).

Mol. Formula: $C_{20}H_{24}O_3$

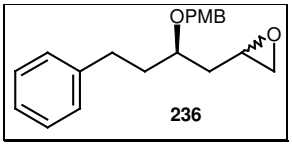
$[\alpha]_D^{25}$: –38.6 (*c* 1.0, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 2960, 2860, 1470, 1410, 1340, 1250, 1095, 1035, 840, 780.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.64-1.77 (m, 2H), 1.83-2.10 (m, 2H), 2.47-2.54 (m, 1H), 2.62-2.84 (m, 3H), 3.04-3.10 (m, 1H), 3.66-3.76 (m, 1H), 3.80 (s, 3H), 4.53 (s, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 7.17-7.35 (m, 7H).

^{13}C NMR (50 MHz, $CDCl_3$): (Mixture of diastereomers, dr (*anti*:*syn*) = 2.2:1) δ 31.1, 31.3, 35.9, 37.2, 46.4, 47.2, 49.5, 54.9, 70.1, 70.7, 75.4, 75.6, 113.5, 125.5, 128.1, 129.1, 130.3, 141.8, 158.9.

Epoxide (236).



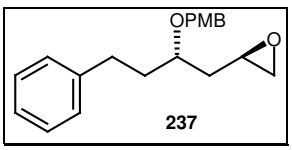
236

Analogously epoxide **236** was prepared by *m*-CPBA epoxidation followed by PMB protection in 85% yield (over two steps, from (*S*)-**230**) as an approximately 1.1:1 (*syn*:*anti*) mixture of diastereomers following procedure as described for (*S*)-**231** and **234**. $[\alpha]_D^{25}$: +42.1 (*c* 0.9, $CHCl_3$). IR, ^{1}H NMR & ^{13}C NMR spectra were essentially identical to those of **234**.

Hydrolytic kinetic resolution of 234 with Jacobsen cobalt catalyst.

A solution of epoxide **234** (2.4 g, 7.68 mmol) and (*S,S*)-Salen-Co(III)-OAc (26 mg, 0.038 mmol) in THF (83 μL) was stirred at 0 ^oC for 5 min, and then distilled water (83 μL, 4.6 mmol) was added. After stirring for 24 h, it was concentrated and purified by silica gel column chromatography using petroleum ether/EtOAc (8:2) to afford **237** as a yellow color liquid. Continued chromatography with petroleum ether/EtOAc (6:4) provided the diol **238** as a brown color liquid as a single diastereomer.

***(R)*-2-((*S*)-2-(4-Methoxybenzyloxy)-4-phenylbutyl)oxirane (237).**



237

Yield: 1.46 g (45%).

Mol. Formula: $C_{20}H_{24}O_3$

$[\alpha]_D^{25}$: –49.4 (*c* 0.9, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 2960, 2860, 1470, 1410, 1340, 1250, 1095, 1035, 840, 780.

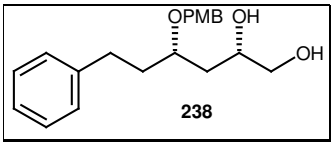
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.60-1.72 (m, 1H), 1.82-2.0 (m, 3H), 2.52 (dd, *J* = 5.1, 2.8 Hz, 1H), 2.63-2.77 (m, 2H), 2.82 (dd, *J* = 4.9, 4.0 Hz, 1H), 3.03-3.13 (m, 1H), 3.61-3.76

(m, 1H), 3.82 (s, 3H), 4.46-4.49 (m, 1H), 4.53 (s, 1H), 6.92 (d, *J* = 8.7 Hz, 2H), 7.17-7.32 (m, 7H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 31.3, 36.1, 37.4, 47.2, 49.5, 54.9, 70.9, 75.8, 113.7, 125.6, 128.2, 129.2, 130.6, 141.7, 159.1.

Analysis: Calcd.: C, 81.04; H, 8.16%; **Found:** C, 81.29; H, 8.31%.

(2*S*,4*S*)-4-(4-Methoxybenzyloxy)-6-phenylhexane-1,2-diol (238).



238

Yield: 0.769 g (47%).

Mol. Formula: $C_{20}H_{26}O_4$

$[\alpha]_D^{25}$: –50.9 (*c* 0.8, $CHCl_3$)

IR (neat, cm^{-1}): ν_{max} 3354, 2961, 2896, 2861, 1478, 1411, 1251, 1105, 1022, 978, 847, 780.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.26-1.52 (m, 2H), 1.81-2.16 (m, 4H), 2.74 (m, 2H), 3.51-3.61 (m, 1H), 3.85 (br s, 6H), 4.42-4.63 (m, 2H), 6.96 (d, J = 7.7 Hz, 2H), 7.33 (m, 7H).

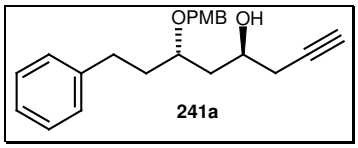
^{13}C NMR (50 MHz, $CDCl_3$): δ 31.3, 36.1, 37.4, 54.9, 66.3, 70.9, 71.4, 75.6, 113.8, 125.6, 128.1, 129.2, 130.5, 141.8, 159.2.

Analysis: Calcd.: C, 81.04; H, 8.16%; **Found:** C, 81.29; H, 8.31%.

Compound 239 and 240. Analogously **239** and **240** were prepared from epoxide **236** by using (*R*,*R*)-salen-Co-OAc catalyst in 46% and 45% yield respectively. All data (IR, ^{1}H NMR and ^{13}C NMR) were identical to **237** and **248** respectively except rotations.

239: $[\alpha]_D^{25}$ +39.1 (*c* 0.9, $CHCl_3$); **240:** $[\alpha]_D^{25}$ +59.4 (*c* 0.9, $CHCl_3$).

(4*S*,6*S*)-6-(4-Methoxybenzyloxy)-8-phenyloct-1-yn-4-ol (241a).



241a

To a solution of **237** (1.8 g, 5.76 mmol) in DMSO (5 mL) at 0 °C was added lithium acetylide-EDA complex (0.778 g, 8.64 mmol) in one portion. The reaction mixture was stirred at 0 °C for 30 min and 5 h at room temperature. The excess of reagent was quenched with 0.3 N H_2SO_4 and extracted with diethylether, washed with water, brine,

dried (Na_2SO_4) and concentrated. The residue was purified by silica gel chromatography by eluting with light petroleum: EtOAc (8:2) to afford the alkyne product **241a** as a colorless liquid.

Yield: 1.677 g (86%).

Mol. Formula: $C_{22}H_{26}O_3$

$[\alpha]_D^{25}$: +21.24 (*c* 1.0, $CHCl_3$)

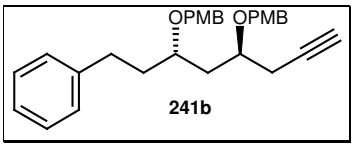
IR (neat, cm^{-1}): ν_{max} 3454, 2957, 2898, 2861, 2214, 1466, 1390, 1360, 1257, 1100, 1005, 980, 835, 777.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.83-1.92 (m, 2H), 2.08 (t, *J* = 2.6 Hz, 2H), 2.40 (dd, *J* = 2.5, 1.3 Hz, 1H), 2.43 (dd, *J* = 2.7, 1.1 Hz, 1H), 2.72 (t, *J* = 8.0 Hz, 2H), 3.09 (br s, 1H), 3.73-3.81 (m, 1H), 3.85 (s, 3H), 4.07-4.20 (m, 1H), 4.53 (d, *J* = 2.5 Hz, 2H), 6.94 (d, *J* = 7Hz, 2H), 7.20-7.38 (m, 7H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 27.2, 31.46, 35.2, 38.7, 55.1, 66.9, 70.5, 70.8, 75.6, 80.9, 113.8, 125.8, 128.3, 129.5, 130.1, 141.8, 159.2.

Analysis: Calcd.: C, 78.07; H, 7.74%; **Found:** C, 78.22; H, 7.61%.

1-(((3*S*,5*S*)-5-(4-Methoxybenzyloxy)-1-phenyloct-7-yn-3-yloxy)methyl)-4-methoxybenzene (241b).



241b

Compound **241b** was prepared following the procedure as described for compound (*S*)-**230** in 97% yield as a colorless liquid.

Mol. Formula: $C_{30}H_{34}O_4$

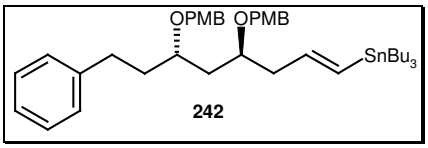
$[\alpha]_D^{25}$: +19.4 (*c* 1.1, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.66-1.79 (m, 2H), 1.83-1.91 (m, 2H), 2.04 (d, *J* = 2.2 Hz, 1H), 2.47 (dd, *J* = 5.3, 2.7 Hz, 2H), 3.49-3.75 (m, 2H), 3.79 (s, 3H), 3.82 (s, 3H), 4.20-4.63 (m, 4H), 6.88 (d, *J* = 8.6 Hz, 4H), 7.11-7.32 (m, 9H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 29.2, 31.4, 38.6, 39.2, 55.1, 70.1, 70.5, 71.1, 71.3, 75.6, 80.1, 103.9, 113.7, 114.2, 125.7, 128.3, 129.3, 130.8, 131.8, 142.4, 158.6, 159.1.

Analysis: Calcd.: C, 78.57; H, 7.47%; **Found:** C, 78.63; H, 7.28%.

((*E*,4*S*,6*S*)-4,6-Bis(4-methoxybenzyloxy)-8-phenyloct-1-enyl)tributylstannane (242).



242

To a stirred solution of **241b** (1.10 g, 2.40 mmol) in benzene (40 mL) were added *n*-Bu_3SnH (0.768 g, 0.71 mL, 2.64 mmol) and AIBN (79 mg, 0.48 mmol) at room temperature under N_2. The reaction mixture was gently refluxed with stirring for 4 h. The solvent was removed and the residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1) as eluent to give **242** as yellowish oil.

Yield: 1.73 g (96%).

Mol. Formula: $C_{42}H_{62}O_4Sn$

$[\alpha]_D^{25}$: +8.8 (*c* 0.7, $CHCl_3$)

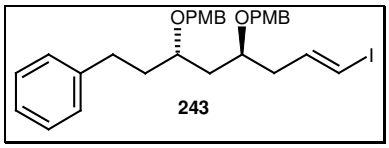
IR (neat, cm^{-1}): ν_{max} 2958, 2929, 2853, 1612, 1513, 1464, 1378, 1249, 1171, 1035.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.94 (dt, *J* = 7.2, 2.3 Hz, 9H), 1.27-1.43 (m, 10H), 1.59-1.74 (m, 10H), 1.82-2.02 (m, 2H), 2.23 (t, *J* = 7.0 Hz, 2H), 2.69 (ddd, *J* = 6.6, 2.3 Hz, 2H), 3.69-3.77 (m, 1H), 3.79 (s, 3H), 3.81 (s, 3H), 3.97-4.04 (m, 1H), 4.36-4.63 (m, 4H), 5.15 (d, *J* = 15.5 Hz, 1H), 5.85 (ddd, *J* = 16.7, 7.1 Hz, 1H), 6.91 (d, *J* = 8.6 Hz, 4H), 7.17-7.31 (m, 9H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.4, 16.2, 17.3, 26.6, 26.8, 27.6, 30.7, 31.5, 35.0, 35.3, 39.3, 42.0, 54.9, 70.0, 70.3, 75.4, 75.7, 113.7, 114.2, 117.3, 125.6, 128.2, 129.4, 130.2, 131.6, 134.8, 141.8, 158.6, 159.1.

Analysis: Calcd.: C, 67.29; H, 8.34; Sn, 15.84%; **Found:** C, 67.43; H, 8.17; Sn, 16.09%.

1-(((*E*,3*S*,5*S*)-5-(4-Methoxybenzyloxy)-8-iodo-1-phenyloct-7-en-3-yloxy)methyl)-4-methoxybenzene (243).



243

To a cooled (0 ^oC), stirred solution of **242** (1.3 g, 1.73 mmol) in CH_2Cl_2 (40 mL) was added iodine (484 mg, 1.91 mmol). After 30 min at 0 ^oC, the reaction mixture was diluted with CH_2Cl_2, washed with saturated $Na_2S_2O_3$ and 10% KF solutions, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. Silica gel column

chromatography of the crude product using petroleum ether/EtOAc (9.5:0.5) as eluent gave **243** as a yellowish oil.

Yield: 956 mg (94%).

Mol. Formula: $C_{30}H_{35}IO_4$

$[\alpha]_D^{25}$: +6.6 (*c* 0.7, $CHCl_3$).

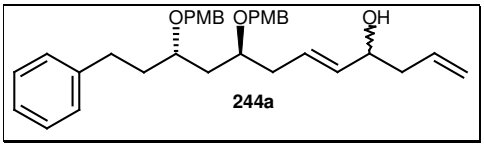
IR (neat, cm^{-1}): ν_{max} 2936, 2937, 2858, 1614, 1511, 1467, 1379, 1171, 1092, 948.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.29-1.39 (m, 2H), 1.71 (t, *J* = 6.2 Hz, 1H), 1.81-1.93 (m, 1H), 2.36 (dd, *J* = 6.8, 5.8 Hz, 2H), 2.65 (t, *J* = 8.5 Hz, 2H), 3.69-3.77 (m, 1H), 3.79 (s, 3H), 3.81 (s, 3H), 3.97-4.04 (m, 1H), 4.36-4.63 (m, 4H), 6.19 (m, 2H), 6.89 (d, *J* = 8.8 Hz, 4H), 7.17-7.31 (m, 9H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 31.3, 35.8, 38.4, 39.7, 55.1, 70.1, 70.4, 75.3, 75.8, 113.7, 114.5, 117.2, 125.8, 128.2, 129.5, 130.2, 131.6, 134.8, 141.8, 158.6, 159.1.

Analysis: Calcd.: C, 61.44; H, 6.01; I, 21.64%; **Found:** C, 61.68; H, 6.22; I, 21.81%.

(*E*,8*S*,10*S*)-8,10-Bis(4-methoxybenzyloxy)-12-phenyldodeca-1,5-dien-4-ol (244a).



244a

To a solution of vinyl iodide **243** (540 mg, 0.927 mmol) in THF (15 mL) was added *n*-BuLi (0.58 mL, 1.0 mmol, 1.6M solution in hexane) at –78 ^oC. The yellow mixture was warmed to 0 ^oC for 30 minutes before recooling to –78 ^oC. Then, the reaction mixture was treated with CuCN (96 mg, 1.38 mmol), followed by addition of but-3-enal **243a** (78 mg, 0.39 mmol) at –78 ^oC. Stirring was continued at –50 ^oC for 1.5 h. The reaction mixture was quenched with aqueous NH_4Cl and aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (8:2) as eluent gave **244a** as a yellow syrupy liquid.

Yield: 332 mg (68%).

Mol. Formula: $C_{34}H_{42}O_5$

$[\alpha]_D^{25}$: –31.8 (*c* 1.1, $CHCl_3$)

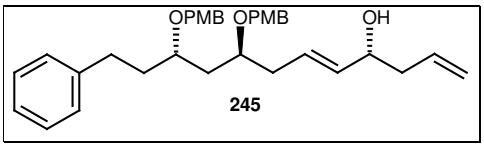
IR (neat, cm^{-1}): ν_{max} 3443, 3064, 3028, 2938, 2864, 1949, 1870, 1710, 1641, 1603, 1496, 1454, 1350, 1067

^{1}H NMR (200 MHz, $CDCl_3$): (as a diastereomeric mixture, dr = 2:1) δ 1.62-1.76 (m, 2H), 1.78-1.94 (m, 2H), 2.05 (bs s, 1H), 2.23-2.41 (m, 4H), 2.59-2.79 (m, 2H), 3.41-3.58 (m, 1H), 3.65-3.74 (m, 2H), 3.78 (s, 3H), 3.79 (s, 3H), 3.82 (m, 3H), 4.16 (d, *J* = 6.1 Hz, 1H), 4.19 (d, *J* = 11.1 Hz, 1H), 4.43 (d, *J* = 8.3 Hz, 1H), 4.48 (d, *J* = 8.0 Hz, 1H), 5.10-5.18 (m, 2H), 5.51-5.92 (m, 3H), 6.83 (d, *J* = 8.7 Hz, 4H), 7.17-7.34 (m, 9H).

^{13}C NMR (50 MHz, $CDCl_3$): (as a diastereomeric mixture, dr = 2:1) δ 29.9, 31.2, 31.3, 31.5, 35.8, 36.83, 36.89, 39.9, 41.9, 55.2, 70.3, 70.6, 71.6, 71.69, 74.64, 74.88, 74.96, 113.7, 117.98, 118.0, 125.7, 127.4, 127.5, 128.32, 128.37, 129.33, 129.36, 129.42, 129.48, 130.76, 130.79, 130.86, 134.39, 134.86, 134.90, 134.94, 142.31, 159.02, 159.11.

Analysis: Calcd.: C, 76.95; H, 7.98%; **Found:** C, 77.16; H, 7.83%.

(*E*,4*R*,8*S*,10*S*)-8,10-Bis(4-methoxybenzyloxy)-12-phenyldodeca-1,5-dien-4-ol:



245

To a solution of **244a** (280 mg, 0.528 mmol) in EtOAc (5 mL) in 25 mL R.B. was added IBX (443 mg, 1.583 mmol) in one portion and the reaction mixture was refluxed for 6 h. The reaction mixture was filtered through a pad of celite and filtrate was concentrated to give the crude enone product **244**, which was pure enough and used in the next step without further purification.

To a solution of above crude product **244** (349.0 mg, 0.570 mmol) in THF (10 mL) was added (*R*)-BINAL-H (0.5 M solution in THF, 7.52 mL, 3.76 mmol) at –78 ^oC. The reaction mixture was stirred at –78 ^oC for 3 h. The resultant mixture was treated with 1.0 N HCl (10 mL) and extracted with $CHCl_3$ (3 x 20 mL). The organic layer was washed with 1.0 N NaOH (20 mL), brine (20 mL), dried (Na_2SO_4), filtered, and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (8:2) as eluent gave **245** as a colorless oil.

Yield: 210 mg (75%).

Mol. Formula: $C_{34}H_{42}O_5$

$[\alpha]_D^{25}$: +7.9 (*c* 1.1, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 3522, 2935, 2857, 1454, 1342, 1104, 1026, 914, 752, 698.

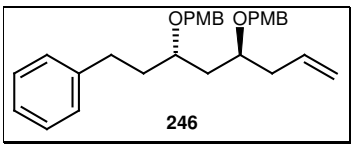
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.69 (t, *J* = 5.8 Hz, 2H), 1.81-1.94 (m, 2H), 2.05 (br s, 1H), 2.23-2.41 (m, 4H), 2.67 (t, *J* = 7.9 Hz, 2H), 3.43-3.58 (m, 1H), 3.65-3.70 (m, 2H), 3.78 (s, 3H), 3.79 (s, 3H), 4.25 (d, *J* = 11.1 Hz, 2H), 4.47 (d, *J* = 8.4 Hz, 2H), 5.10-5.18

(m, 2H), 5.51-5.71 (m, 2H), 5.75-5.92 (m, 1H), 6.88 (d, *J* = 8.7 Hz, 4H), 7.17-7.34 (m, 9H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 31.2, 35.8, 36.8, 39.9, 41.9, 55.2, 70.5, 70.7, 71.7, 74.6, 74.9, 113.8, 118.0, 125.7, 127.4, 128.3, 129.4, 130.8, 134.3, 134.9, 142.3, 159.3, 159.1.

Analysis: Calcd.: C, 76.95; H, 7.98%; **Found:** C, 77.21; H, 7.91%.

1-((3*S*,5*S*)-3,5-Bis(4-methoxybenzyloxy)oct-7-enyl)benzene:



246

To a solution of **241b** (1.60 g, 3.49 mmol) in ethyl acetate (40 mL) was added Lindlar's catalyst (20 mg). The reaction mixture was stirred for 1 h under a balloon of H_2 at room temperature and filtered through a celite pad. The filtrate was concentrated and the residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1) as eluent to give **246** (590 mg, 95%) as a pale yellow oil.

Yield: 1.57 g (98%).

Mol. Formula: $C_{30}H_{36}O_4$

$[\alpha]_D^{25}$:+16.1 (*c* 0.9, $CHCl_3$)

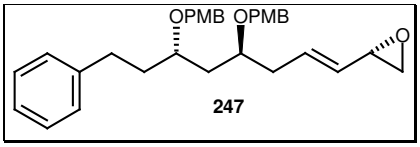
IR (neat, cm^{-1}): ν_{max} 2938, 2864, 1949, 1870, 1710, 1641, 1603, 1496, 1454, 1350, 1067.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.22-1.29 (m, 1H), 1.34-1.39 (m, 1H), 1.71 (t, *J* = 6.2 Hz, 1H), 1.81-1.93 (m, 1H), 2.36 (dd, *J* = 6.8, 5.8 Hz, 2H), 2.67 (t, *J* = 8.5 Hz, 2H), 3.61-3.74 (m, 2H), 3.78 (s, 3H), 3.81 (s, 3H), 4.25 (dd, *J* = 10.9, 4.3 Hz, 1H), 4.47 (s, 3H), 5.03-5.15 (m, 2H), 5.76-5.93 (m, 1H), 6.87 (t, *J* = 8.8 Hz, 4H), 7.17-7.31 (m, 9H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 31.1, 35.7, 38.4, 39.8, 55.0, 70.3, 70.5, 74.5, 74.7, 113.6, 114.2, 117.1, 125.6, 128.3, 129.3, 130.3, 130.7, 131.8, 142.2, 158.9, 159.0.

Analysis: Calcd.: C, 78.23; H, 7.88%; **Found:** C, 78.31; H, 7.67%.

(*S*)-2-((*E*,4*S*,6*S*)-4,6-Bis(4-methoxybenzyloxy)-8-phenyloct-1-enyl)oxirane



247

Olefin **246** (0.218 g, 0.47 mmol) was diluted with CH_2Cl_2 (10 mL) and degassed for fifteen minutes. Vinyl epoxide (0.099 g, 1.42 mmol) was then added to the reaction flask

followed by catalyst (40 mg, 0.047 mmol). The reaction was allowed to reflux for twenty-four hours under argon, at which time, it was allowed to oxidize by opening the reaction to air and stirring overnight. The dark brown solution was then concentrated and purified by flash column chromatography to give the product.

Yield: 38 mg (16%).

Mol. Formula: $C_{32}H_{38}O_5$

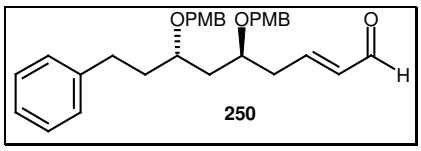
$[\alpha]_D^{25}$: +11.6 (*c* 0.6, $CHCl_3$)

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.58 (dd, *J* = 7.6, 7.8 Hz, 2H), 1.73-1.84 (m, 2H), 2.24 (m, 2H), 2.61-2.81 (m, 3H), 2.88 (dd, *J* = 5.9, 4.0 Hz, 1H), 3.07-3.13 (m, 1H), 3.61-3.74 (m, 2H), 3.79 (s, 3H), 3.82 (s, 3H), 4.25-4.47 (m, 4H), 5.58 (dd, *J* = 15.6, 6.4 Hz, 1H), 5.74 (ddd, *J* = 15.5, 7.3, 7.3 Hz, 1H), 6.88 (t, *J* = 8.8 Hz, 4H), 7.17-7.31 (m, 9H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 29.6, 31.2, 36.9, 38.9, 48.1, 51.6, 55.2, 70.7, 71.9, 74.6, 74.8, 113.8, 118.0, 125.7, 127.4, 128.3, 129.6, 130.8, 131.5, 134.4, 134.8, 141.9, 159.0, 159.1

Analysis: Calcd.: C, 76.46; H, 7.62%; **Found:** C, 76.59; H, 7.41%.

(*E*,5*S*,7*S*)-5,7-Bis(4-methoxybenzyloxy)-9-phenylnon-2-enal



250

Olefin **246** (0.810 g, 1.75 mmol) was diluted with CH_2Cl_2 (10 mL) and degassed for fifteen minutes. Acrolein (394 mg, 7.03 mmol) was then added to the reaction flask followed by catalyst (149 mg, 0.175 mmol, 10 mol%). The reaction was allowed to stir for 4 days under argon, at which time, it was allowed to oxidize by opening the reaction to air and stirring overnight. The dark brown solution was then concentrated and purified by flash column chromatography to give the product as brown color liquid.

Yield: 653 mg (76%).

Mol. Formula: $C_{31}H_{36}O_5$

$[\alpha]_D^{25}$: +26.1 (*c* 1.5, $CHCl_3$).

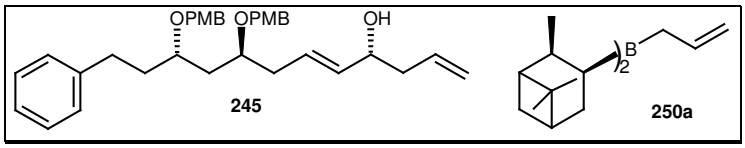
IR (neat, cm^{-1}): ν_{max} 2920, 2939, 2862, 1690, 1513, 1248, 1130, 1032.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.22-1.29 (m, 1H), 1.34-1.39 (m, 1H), 1.71 (t, *J* = 6.2 Hz, 1H), 1.81-1.93 (m, 1H), 2.36 (dd, *J* = 6.8, 5.8 Hz, 2H), 2.67 (t, *J* = 8.5 Hz, 2H), 3.61-3.74 (m, 2H), 3.78 (s, 3H), 3.81 (s, 3H), 4.25 (dd, *J* = 10.9, 4.3 Hz, 1H), 4.47 (s, 3H), 5.03-5.15 (m, 2H), 5.76-5.93 (m, 1H), 6.87 (t, *J* = 8.8 Hz, 4H), 7.17-7.31 (m, 9H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 31.1, 35.7, 38.4, 39.8, 70.3, 70.5, 74.5, 74.7, 113.6, 114.2, 117.1, 125.6, 128.3, 129.3, 130.3, 130.7, 131.8, 142.2, 158.9, 159.0.

Analysis: Calcd.: C, 76.20; H, 7.43%; **Found:** C, 76.33; H, 7.28%.

(*E*,4*R*,8*S*,10*S*)-8,10-Bis(4-methoxybenzyloxy)-12-phenyldodeca-1,5-dien-4-ol:

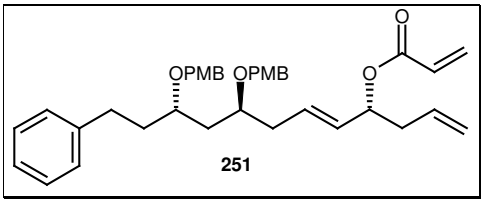


Allylmagnesium bromide (0.78 mL, 1.0 M, 0.78 mmol) was added dropwise to a well-stirred solution of (+)-DIP-chloride (251 mg, 0.78 mmol) in Et_2O (5 mL) at −78 °C. The mixture was then stirred for 0.5 h at −78 °C, allowed to warm to room temperature, and stirred for 4 h. The solvent was removed under aspirator vacuum, and the residue was extracted with pentane (3 X 10 mL) filtered and concentrated to afford $^{I}Ipc_2BAll$ (**250a**) in essentially quantitative yield. The reagent was dissolved in pentane to make a 1 M solution. A 0.57 mmol (0.57 mL) amount of the above $^{I}Ipc_2BAll$ was dissolved in Et_2O (0.6 mL) and cooled to −100 °C. A solution of aldehyde **250** (255 mg, 0.52 mmol) in anhydrous Et_2O (0.5 mL) was added dropwise, and the reaction mixture was stirred at −100 °C for 2 h. Addition of methanol (0.5 mL) to this intermediate, followed by the usual workup with NaOH and H_2O_2, afforded the crude product which was extracted with Et_2O, washed with brine, and dried (Na_2SO_4). Purification of crude product by silica gel column chromatography using petroleum ether/EtOAc (9:1) as eluent afforded **245** as a yellowish syrupy liquid.

Yield: 207mg (74%).

All data (IR, ^{1}H NMR, ^{13}C NMR and rotation) were identical to **245**.

(*E*,4*R*,8*S*,10*S*)-8,10-Bis(4-methoxybenzyloxy)-12-phenyldodeca-1,5-dien-4-yl acrylate:



Acryloyl chloride (0.029 g, 0.025 mL, 0.317 mmol) was added drop wise under argon to a solution of **245** (112 mg, 0.211 mmol) and triethylamine (0.053 g, 0.074mL, 0.528 mmol) in dry CH_2Cl_2 (10 mL) at 0 ^{o}C. The mixture was stirred overnight at room temperature. The resulting mixture was filtered through a pad of celite and poured into water and

organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL) and combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated. Purification of crude product by silica gel column chromatography using petroleum ether/EtOAc (19:1) as eluent afforded **251** as a yellowish syrupy liquid.

Yield: 101 mg (82%).

Mol. Formula: $C_{37}H_{44}O_6$

$[\alpha]_D^{25}$: +29.1 (*c* 1.1, $CHCl_3$).

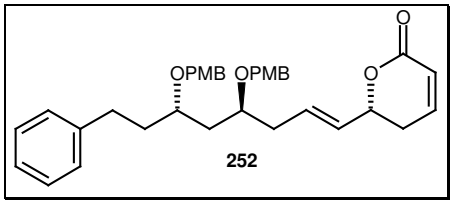
IR ($CHCl_3$, cm^{-1}): ν_{max} 3068, 3025, 2985, 2934, 2857, 1721, 1639, 1494, 1454, 1404, 1296, 1224, 1194, 1117, 1041, 971, 917, 810, 750, 699, 500.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.18-7.31 (m, 9H), 6.89 (t, *J* = 8.7 Hz, 4H), 6.43 (dd, *J* = 17.3, 1.8 Hz, 1H), 6.14 (dd, *J* = 17.3, 10.3 Hz, 1H), 5.82 (dd, *J* = 10.2, 1.5 Hz, 1H), 5.68-5.79 (m, 2H), 5.55 (ddt, *J* = 15.4, 7.1, 1.1 Hz, 1H), 5.37 (q, *J* = 6.7 Hz, 1H), 5.02-5.11 (m, 2H), 4.25-4.47 (m, 4H), 3.81 (s, 3H), 3.78 (s, 3H), 3.62-3.75 (m, 2H), 2.71-2.79 (m, 1H), 2.56-2.64 (m, 1H), 2.44 (m, 2H), 2.26 (m, 2H), 1.68-1.92 (m, 2H), 1.60 (t, *J* = 7.6 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 31.7, 37.5, 38.1, 38.5, 39.0, 55.0, 70.1, 70.6, 73.9, 74.5, 74.7, 117.9, 125.8, 128.3, 128.5, 128.8, 130.1, 130.5, 133.3, 142.0, 158.9, 159.0, 165.4.

Analysis: Calcd.: C, 76.00; H, 7.58%; **Found:** C, 76.22; H, 7.41%.

(*R*)-6-((*E*,4*S*,6*S*)-4,6-Bis(4-methoxybenzyloxy)-8-phenyloct-1-enyl)-5,6-dihydropyran-2-one:



252

Grubb's catalyst (13 mg, 0.01 mmol) dissolved in CH_2Cl_2 (10 mL) was added drop wise to a refluxing solution of acrylate **251** (94 mg, 0.01 mmol), Ti(*i*-PrO)$_4$ (14 mg, 0.05 mmol) in dry CH_2Cl_2 (60 mL). Refluxing was continued for 6 h by which time all the starting material was consumed. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1) as eluent to afford **252** as a yellowish syrupy liquid.

Yield: 78 mg (87%).

Mol. Formula: $C_{35}H_{40}O_6$

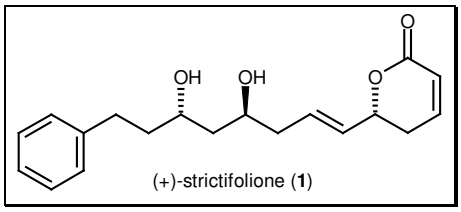
$[\alpha]_D^{25}$: –49.2 (*c* 0.7, $CHCl_3$)

IR (neat, cm^{-1}): ν_{max} 2929, 2857, 1730, 1245, 1119, 1026, 699.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.61 (dd, *J* = 7.6, 7.9 Hz, 2H), 1.73-1.91 (m, 2H), 2.24-2.29 (m, 2H), 2.41-2.46 (m, 2H), 2.60-2.2.67 (m, 1H), 2.74-2.85 (m, 1H), 3.61-3.75 (m, 2H), 3.79 (s, 3H), 3.82 (s, 3H), 4.25-4.47 (m, 4H), 4.86-5.01 (m, 1H), 5.64 (ddd, *J* = 10.3, 2.4, 1.8 Hz, 1H), 5.81 (ddd, *J* = 15.5, 7.2, 7.2 Hz, 1H), 6.04 (ddd, *J* = 10.3, 2.4, 1.8 Hz, 1H), 6.87 (ddd, *J* = 9.7, 4.1, 4.1 Hz, 1H), 6.87 (t, *J* = 8.8 Hz, 4H), 7.17-7.31 (m, 9H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 29.7, 31.6, 37.4, 38.1, 38.4, 55.0, 70.3, 70.5, 74.5, 74.7, 77.9, 113.6, 121.6, 125.6, 125.7, 128.3, 128.4, 129.1, 130.3, 131.0, 134.8, 141.9, 144.6, 158.9, 159.0. 163.9.

(+)-Strictifolione



(+)-strictifolione (**1**)

To a stirring solution of PMB ether **252** (35 mg, 0.062 mmol) in CH_2Cl_2/H_2O (20:1) was added DDQ (43 mg, 0.19 mmol). The resulting mixture was stirred for 45 min at rt. The mixture was poured into saturated aqueous $NaHCO_3$ and further diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The solvents were removed under reduced pressure to give the crude product mixture as yellow oil. Silica gel column chromatography of the crude product using MeOH/EtOAc (1:9) as eluent gave **1** as a colourless solid.

Yield: 18 mg (91%).

Mol. Formula: $C_{19}H_{24}O_4$

M.P: 111–114 ^oC; lit.[2]: 119–121 ^oC.

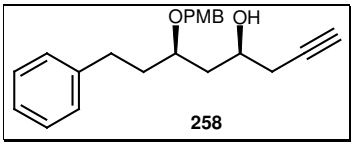
$[\alpha]_D^{25}$: +72 (*c* 0.6, $CHCl_3$); lit.[2] $[\alpha]_D^{25}$: +81.5 (*c* 0.52, $CHCl_3$); lit.[42] $[\alpha]_D^{25}$: +54.1 (*c* 0.33, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 1048, 1238, 1380, 1437, 1724, 2934 and 3328.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.64 (t, *J* = 5.6 Hz, 2H), 1.73-1.91 (m, 2H), 2.29 (t, *J* = 6.6 Hz, 2H), 2.41-2.46 (m, 2H), 2.55 (d, *J* = 4.5 Hz, 1H), 2.64-2.86 (m, 3H), 3.98-4.03 (m, 1H), 4.90 (m, 1H), 5.69 (dd, *J* = 15.5, 6.6 Hz, 1H), 5.88 (ddt, *J* = 15.6, 7.3 Hz, 1H), 6.05 (dt, *J* = 99.8, 1.8 Hz, 1H), 6.90 (ddd, *J* = 9.7, 4.8, 3.6 Hz, 1H), 7.21-731 (m, 5H).

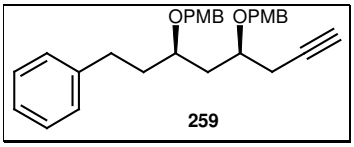
^{13}C NMR (50 MHz, $CDCl_3$): 29.7, 32.1, 38.9, 40.3, 42.1, 68.29, 68.78, 77.73, 121.4, 125.57, 128.36, 128.37, 129.46, 131.0, 141.8, 144.6, 163.8.

(4*S*,6*R*)-6-(4-Methoxybenzyloxy)-8-phenyloct-1-yn-4-ol (258).



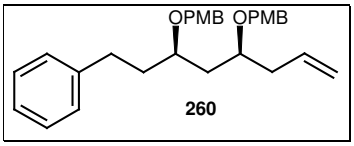
Compound **258** was prepared following the procedure as described for compound **241a** in 86% yield as a colorless liquid. IR, ^{1}H NMR & ^{13}C NMR spectra were essentially identical to those of **241a**. $[\alpha]_D^{25}$: +16.1 (*c* 0.5, $CHCl_3$).

1-(((4*S*,6*R*)-6-(4-Methoxybenzyloxy)-8-phenyloct-1-yn-4-yloxy)methyl)-4-methoxybenzene (259).



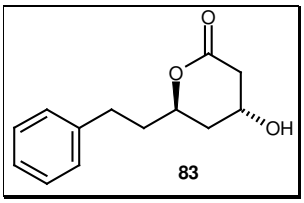
Compound **259** was prepared following the procedure as described for compound **241b** in 98% yield as a colorless liquid. IR, ^{1}H NMR & ^{13}C NMR spectra were essentially identical to those of **241b**. $[\alpha]_D^{25}$: +21.6 (*c* 0.7, $CHCl_3$).

1-(((4*S*,6*R*)-6-(4-Methoxybenzyloxy)-8-phenyloct-1-en-4-yloxy)methyl)-4-methoxybenzene (260).



Compound **260** was prepared following the procedure as described for compound **246** in 98% yield as a colorless liquid. IR, ^{1}H NMR & ^{13}C NMR spectra were essentially identical to those of **246**. $[\alpha]_D^{25}$: +9.9 (*c* 0.6, $CHCl_3$).

(4*R*,6*R*)-Tetrahydro-4-hydroxy-6-phenethylpyran-2-one (83).



83

Acid (34 mg, 0.071 mmol) was dissolved in methanol (5 mL) and catalytic amount of conc. HCl was added. The mixture was stirred at room temperature for overnight and then quenched with solid $NaHCO_3$, filtered and the filtrate was concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (6:4) as eluent gave **83** as an oil.

Yield: 12 mg (79%).

Mol. Formula: $C_{35}H_{40}O_6$

$[\alpha]_D^{25}$: + 66.9 (*c* = 0.7, $CHC1_3$); lit.[59] $[\alpha]_D^{25}$ + 68.88 (*c* 2.29 $CHCl_3$); lit.[4c] $[\alpha]_D^{25}$ + 68.88 (*c* 2.29 $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 3405, 2935, 1720.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.09-7.44 (m, 5H), 4.71 (m, lH), 4.37 (m, lH), 2.96-2.64 (m, 4H), 2.17-1.69 (m, 4H), 2.46 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 171.3, 141.7, 129.2, 129.1, 126.8, 75.7, 63.3, 41.7, 39.3, 38.0, 31.8.

4.1.8. Spectra

1] ^{1}H NMR Spectrum of (*S*)-**228**

2] ^{13}C NMR Spectrum of (*S*)-**228**

3] ^{1}H NMR Spectrum of (*S*)-**230**

4] ^{13}C NMR Spectrum of (*S*)-**230**

5] ^{1}H NMR Spectrum of (*S*)-**231**

6] ^{13}C NMR Spectrum of (*S*)-**231**

7] ^{1}H NMR Spectrum of **238**

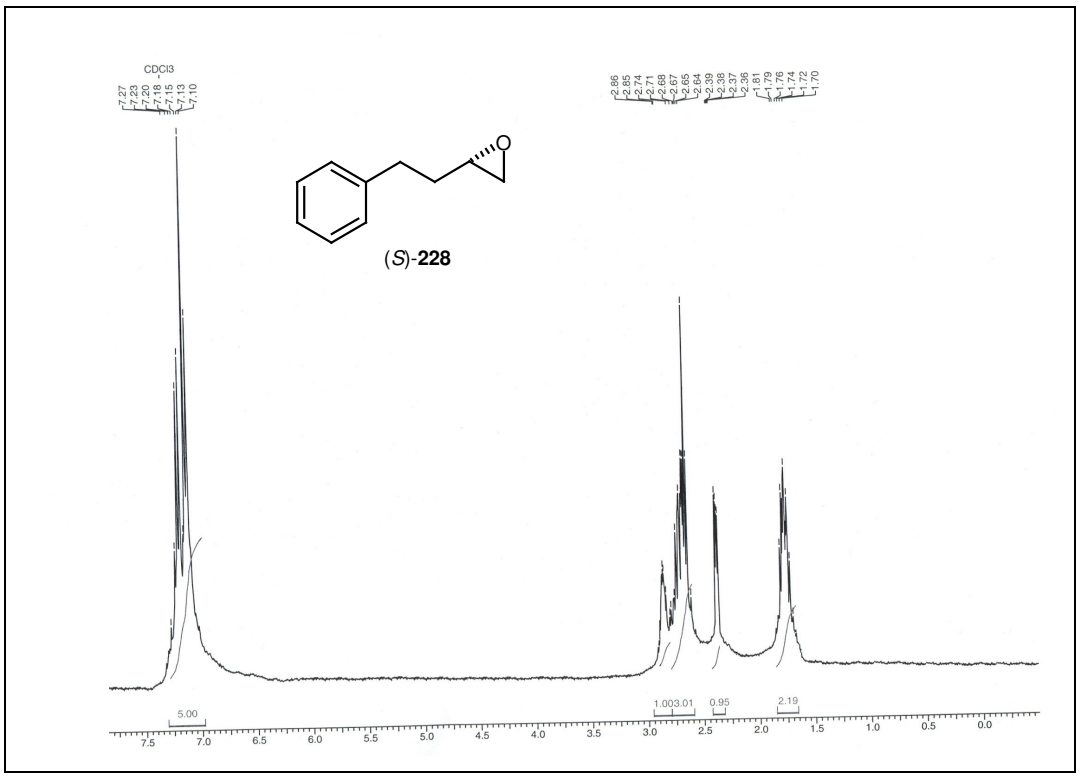
8] ^{13}C NMR Spectrum of **238**

9] ^{13}C NMR Spectrum of **234**

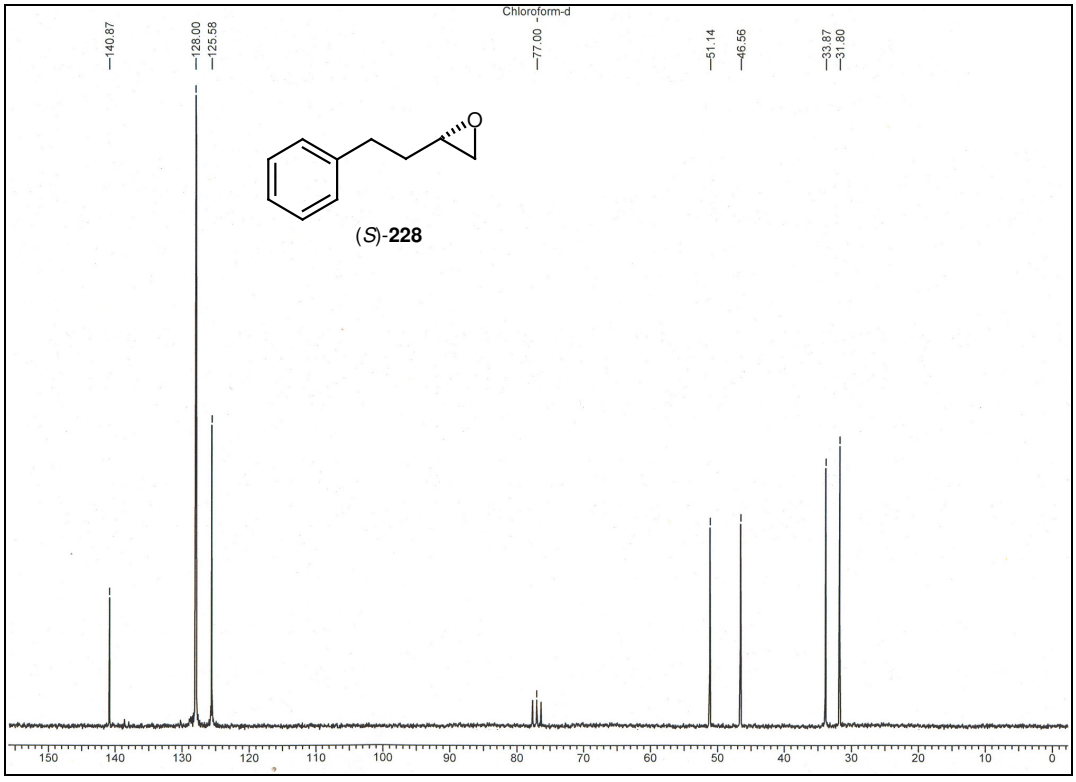
10] ^{13}CNMR-DEPT Spectrum of **234**

11] ^{1}H NMR Spectrum of **237**

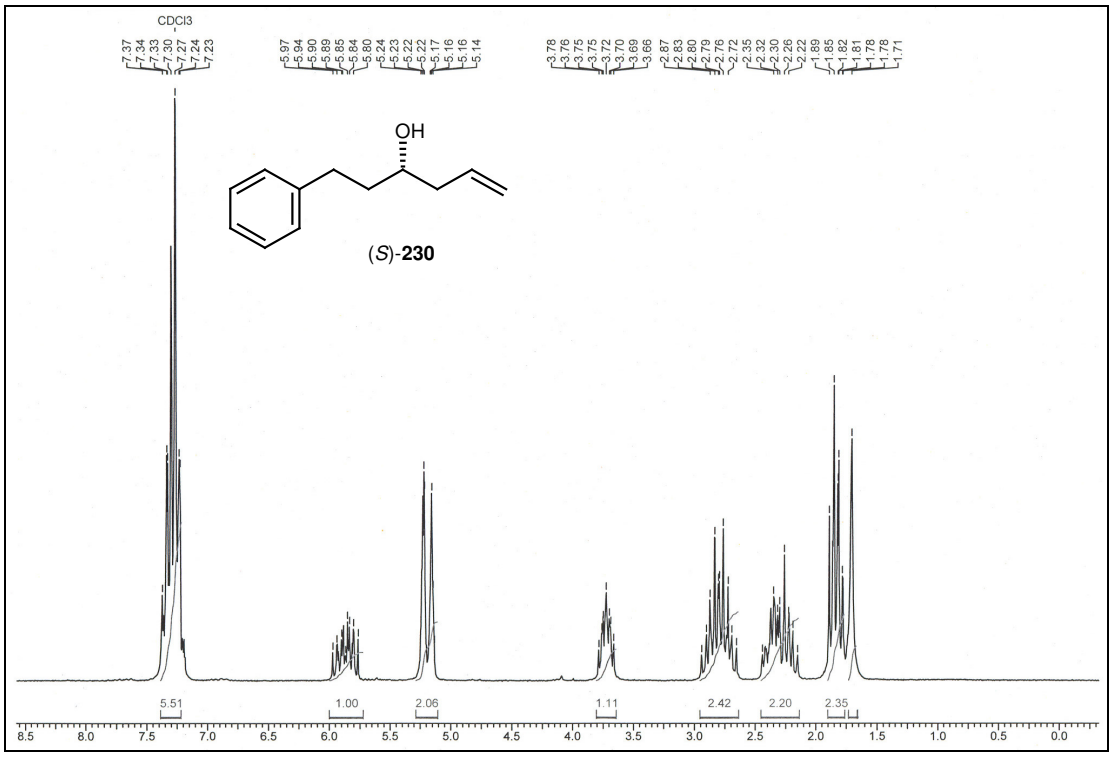
12] ^{13}C NMR Spectrum of **237**



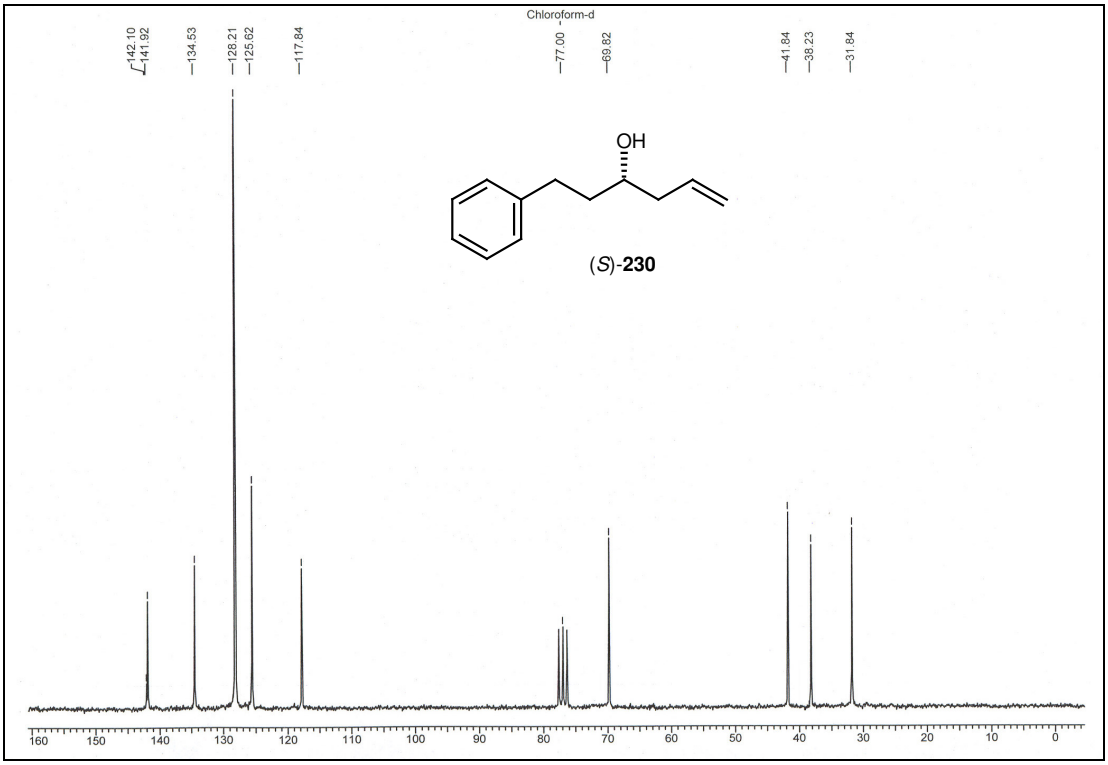
^{1}H NMR Spectrum of (*S*)-**228**



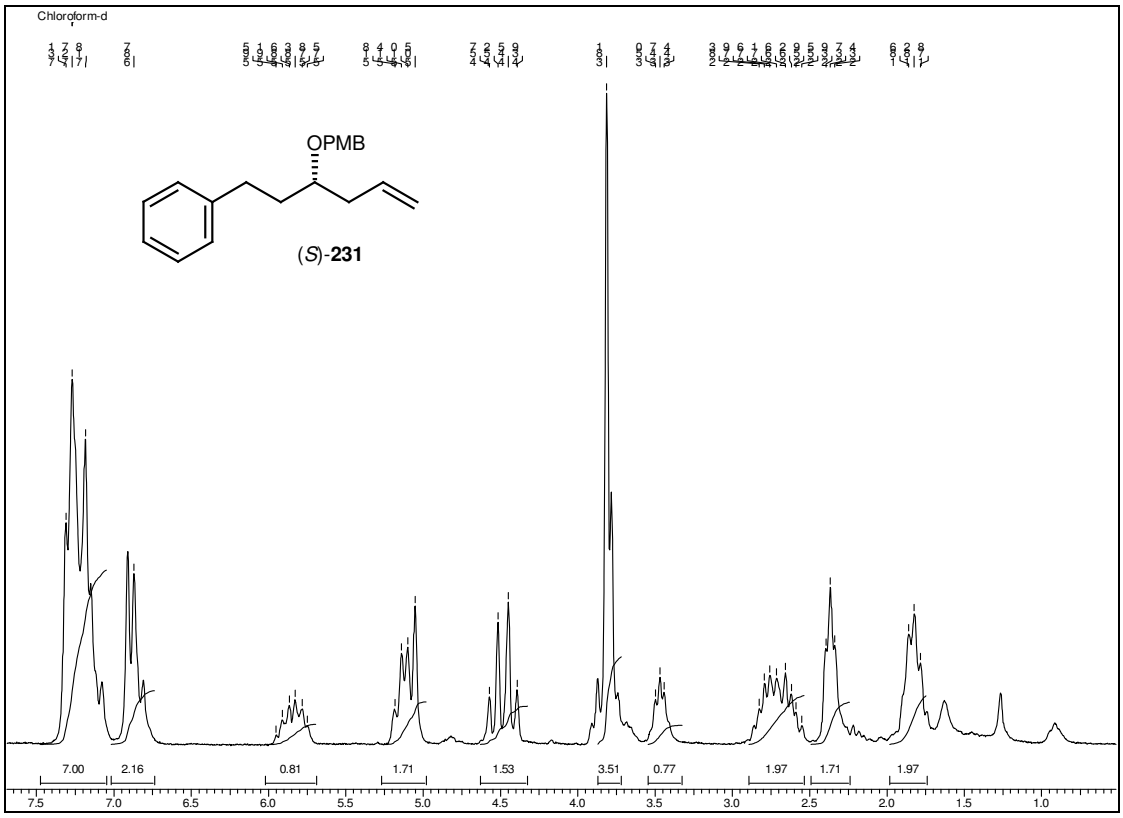
^{13}C NMR Spectrum of (*S*)-**228**



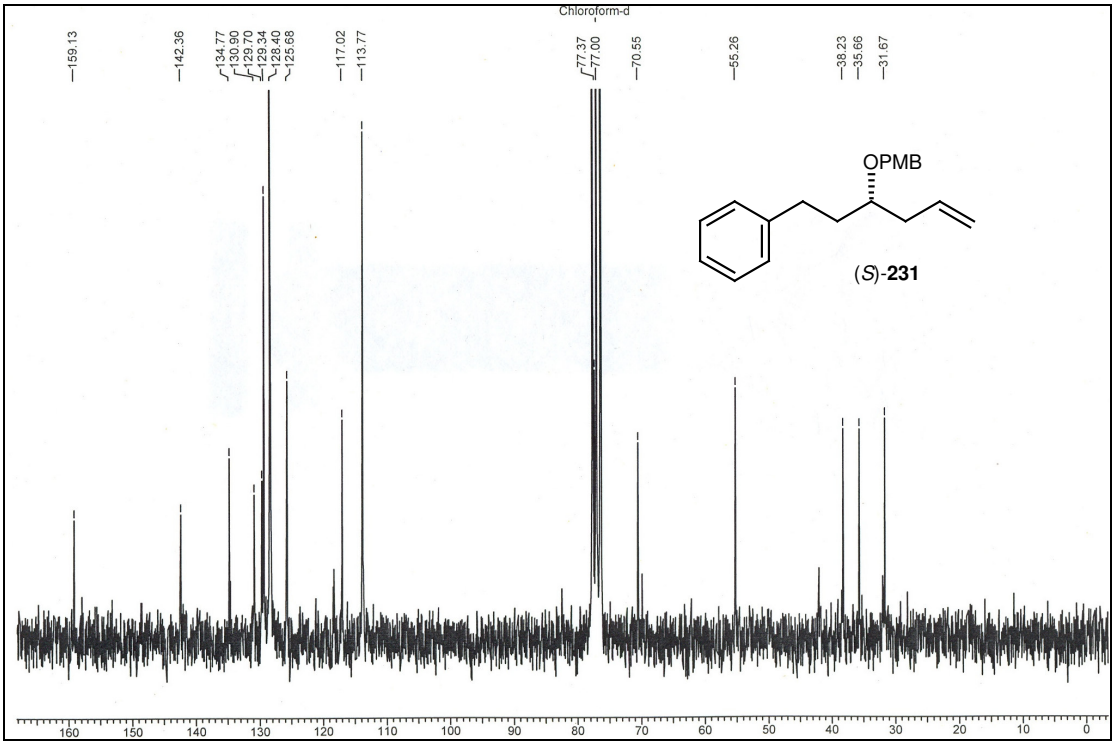
^{1}H NMR Spectrum of (*S*)-**230**



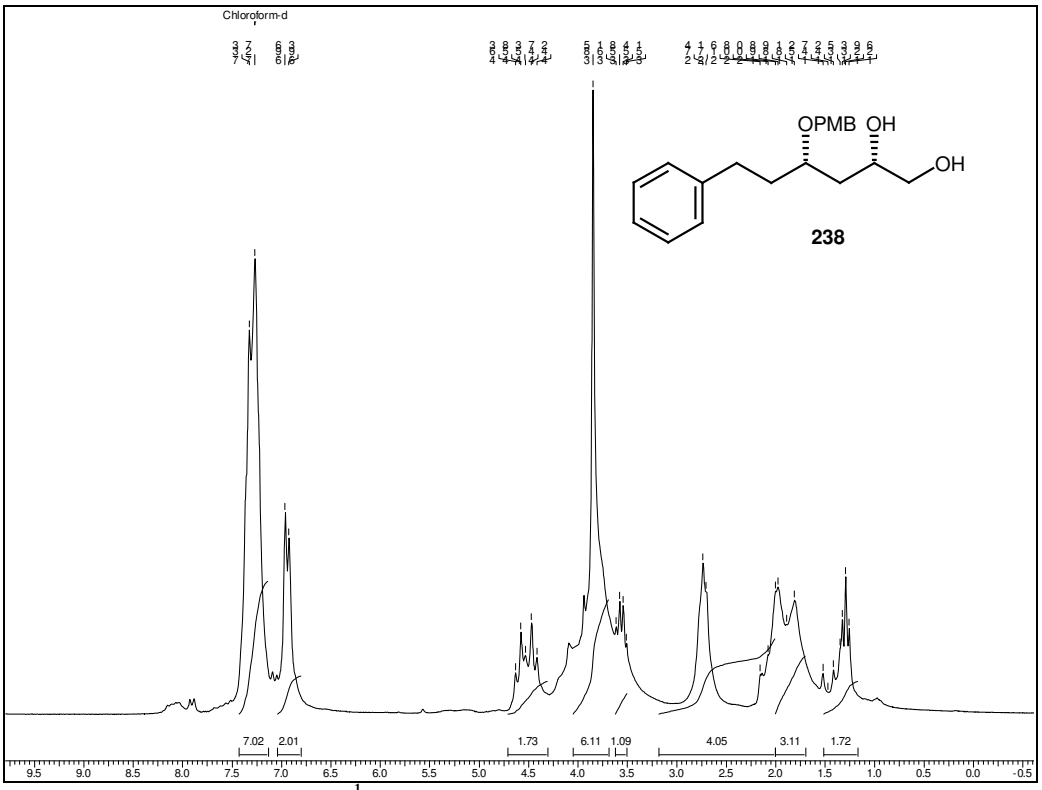
^{13}C NMR Spectrum of (*S*)-**230**



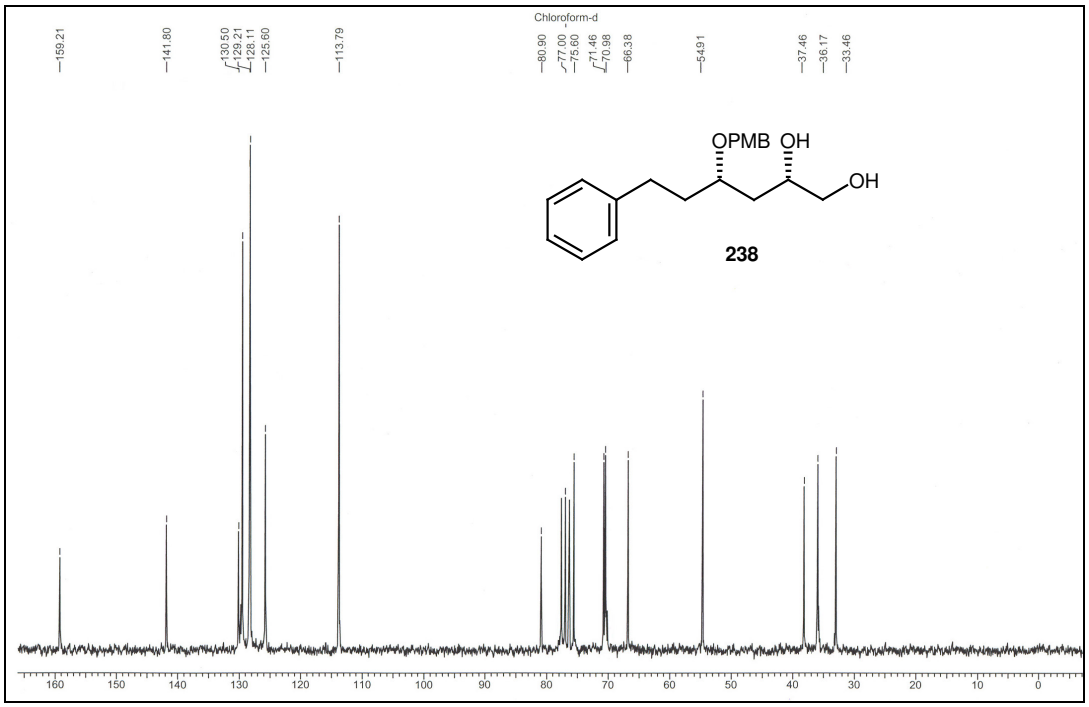
^{1}H NMR Spectrum of (*S*)-**231**



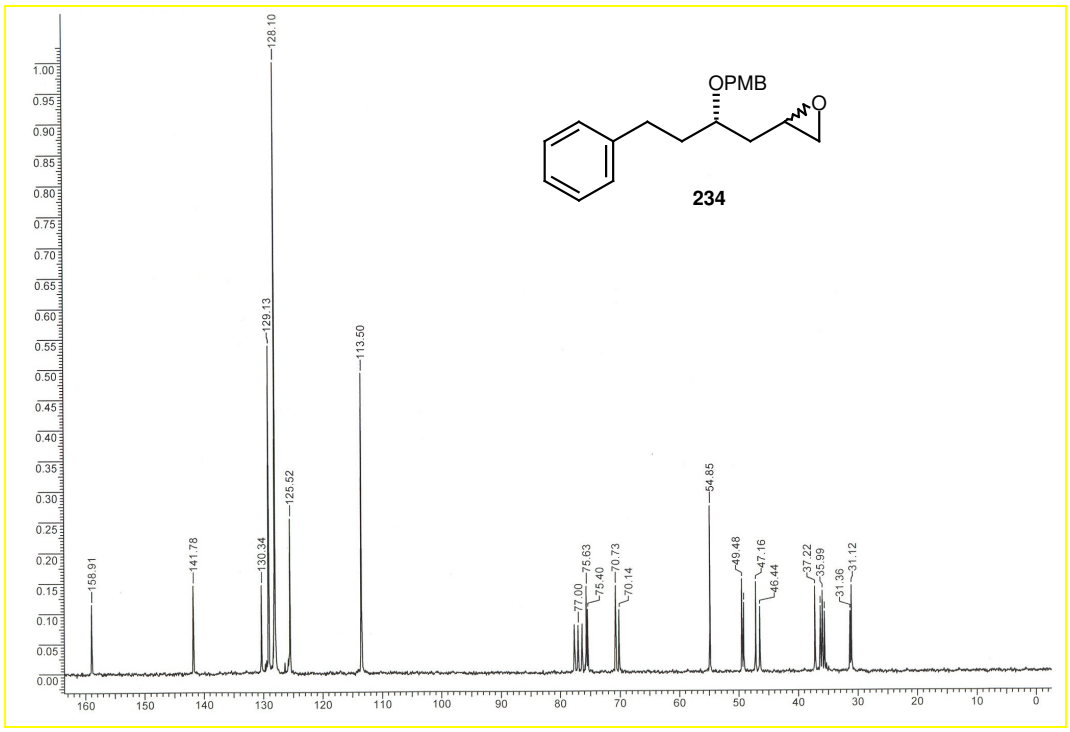
^{13}C NMR Spectrum of (*S*)-**231**



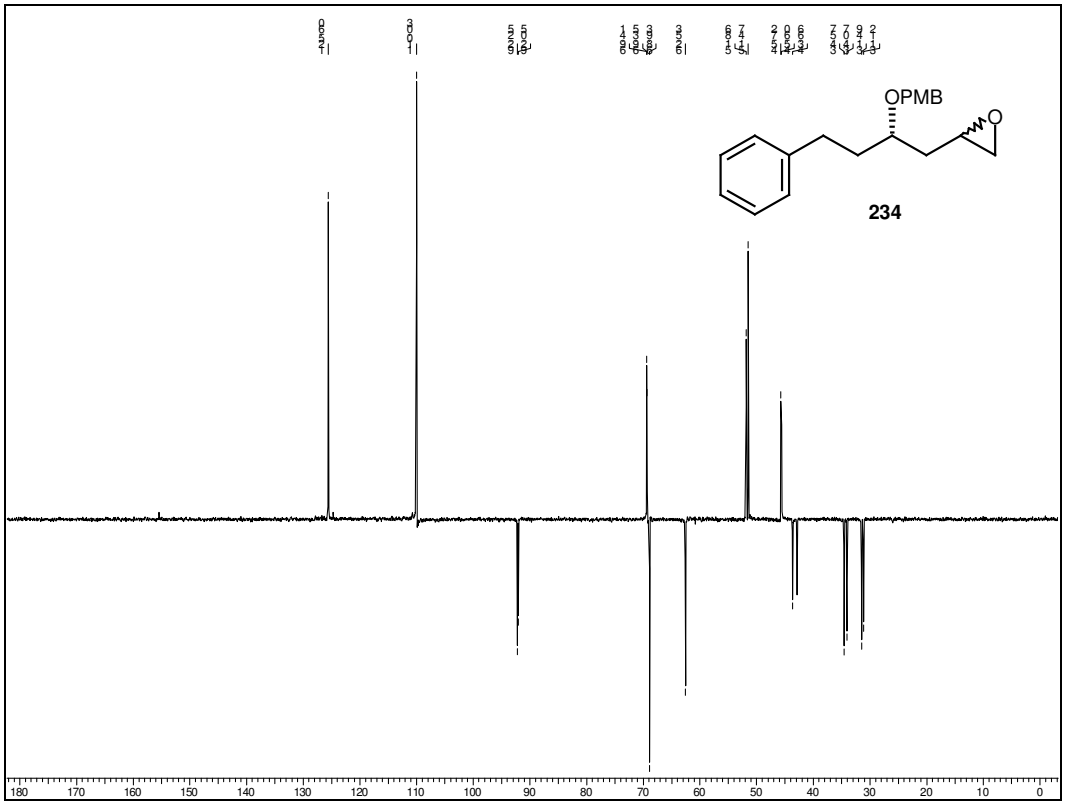
^{1}H NMR Spectrum of **238**



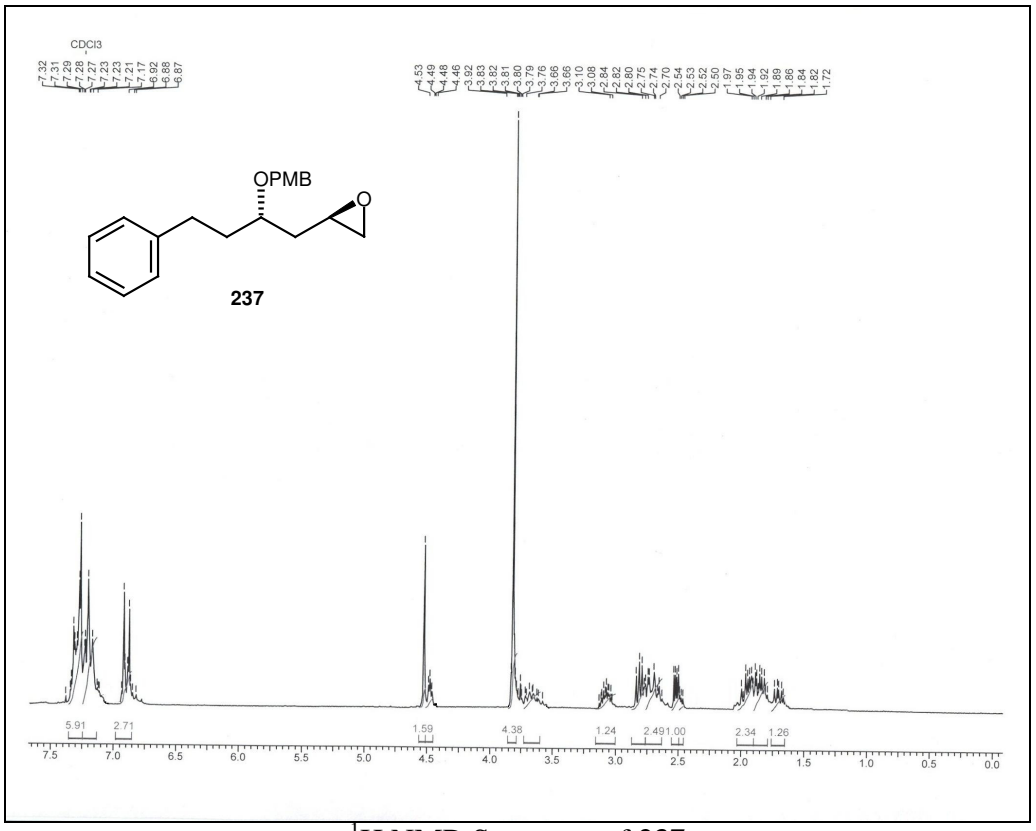
^{13}C NMR Spectrum of **238**



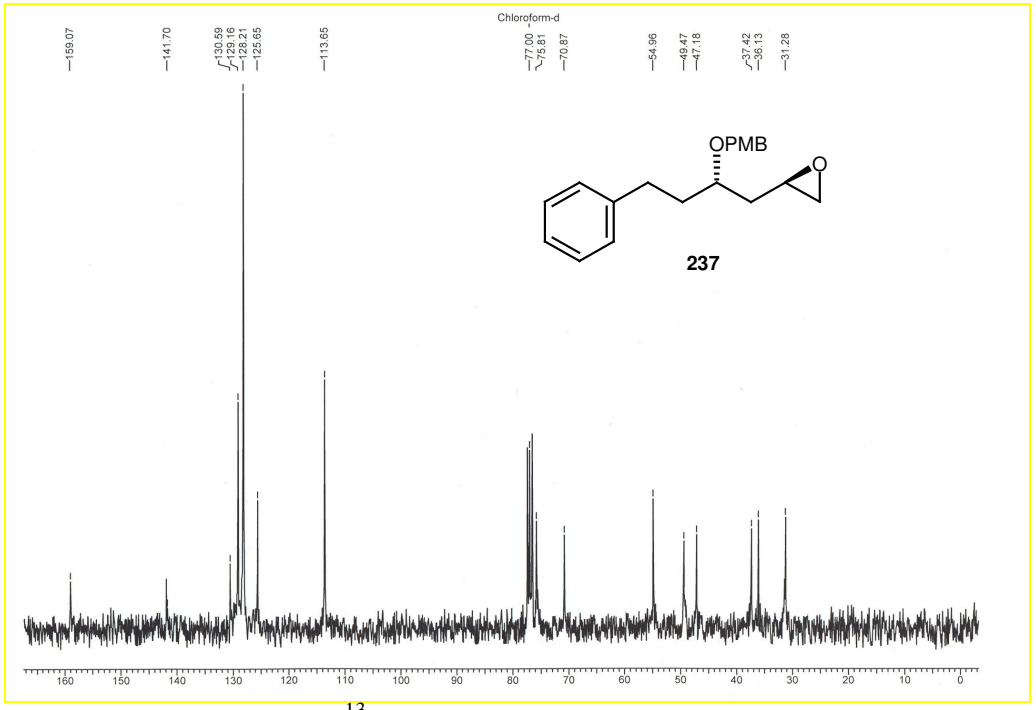
^{1}H NMR Spectrum of **234**



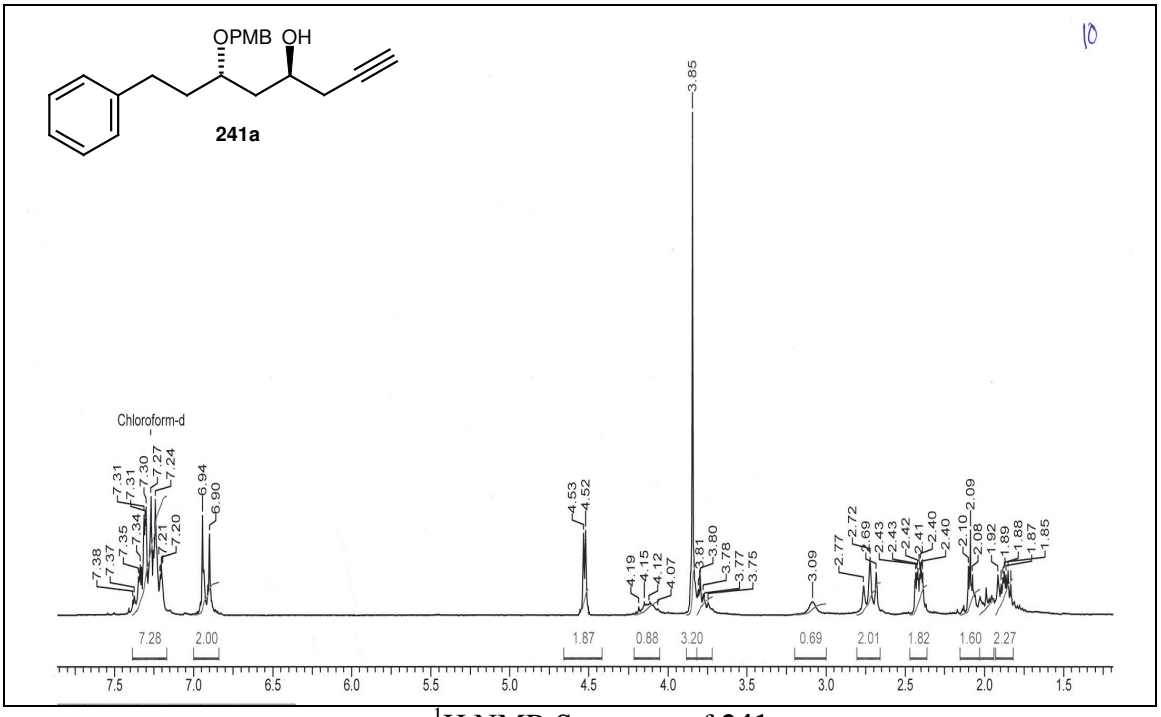
^{13}C NMR-DEPT Spectrum of **234**



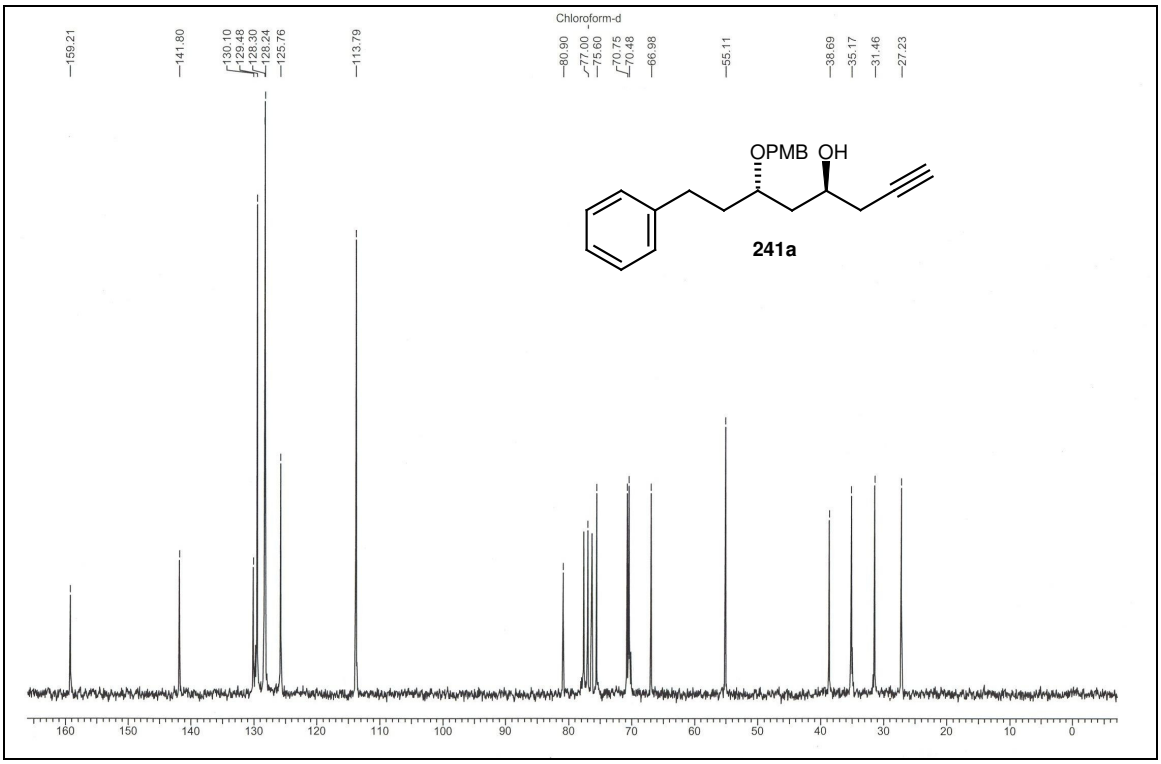
^{1}H NMR Spectrum of **237**



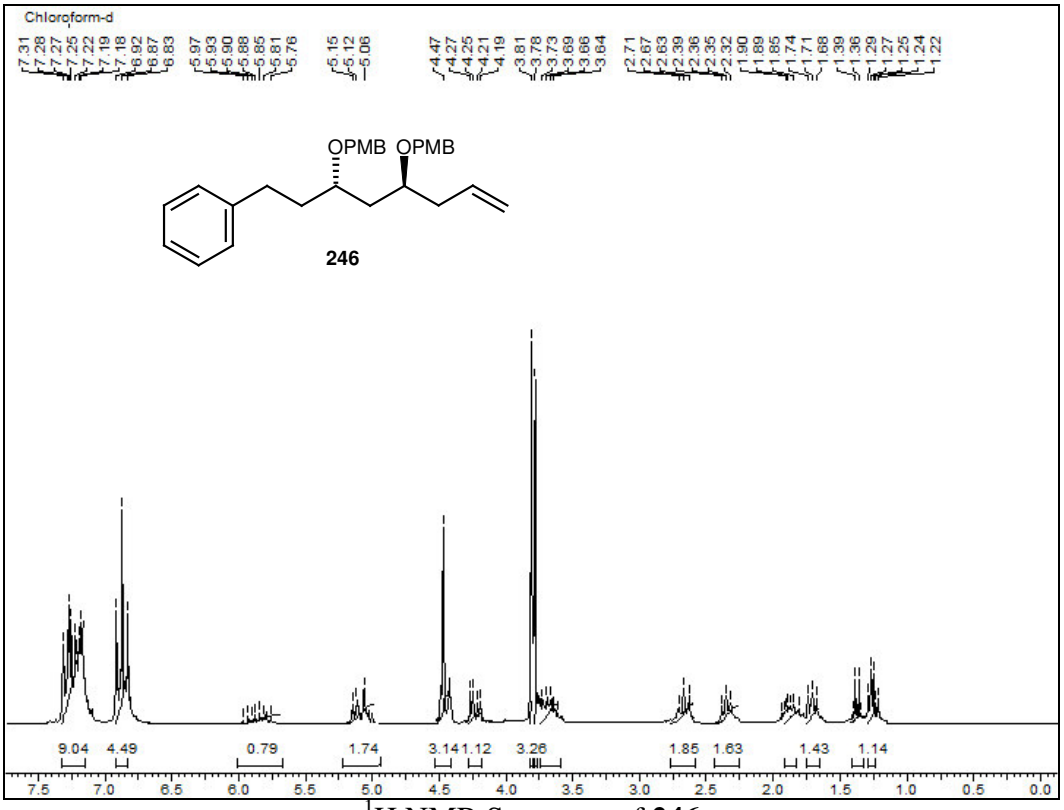
^{13}C NMR Spectrum of **237**



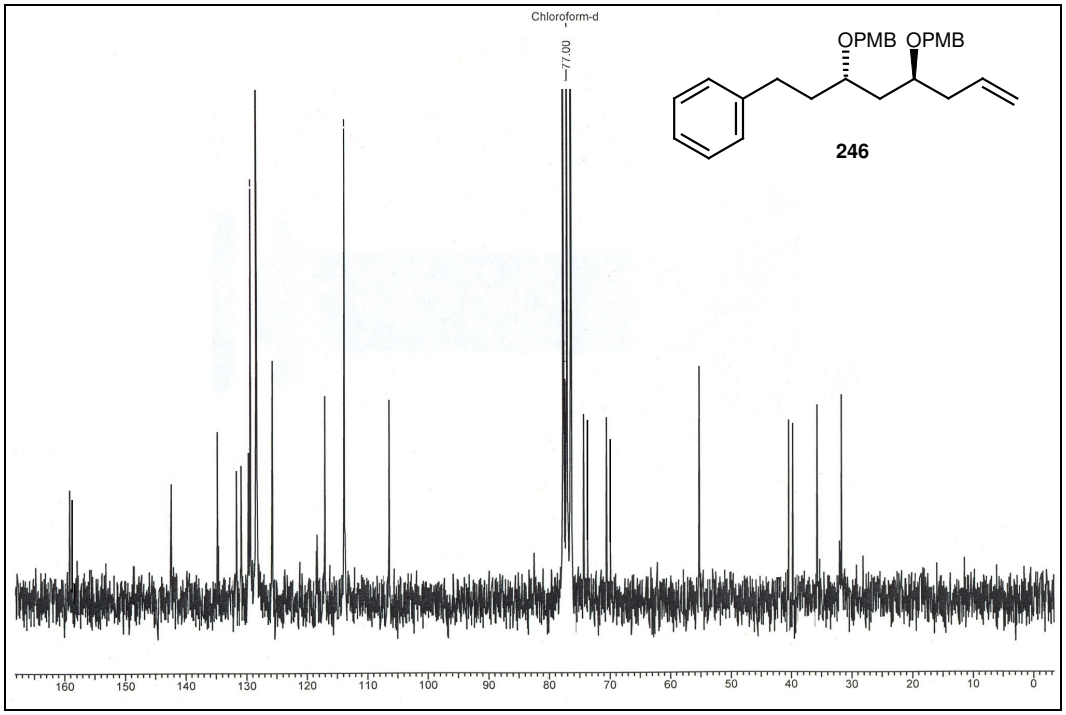
^{1}H NMR Spectrum of **241a**



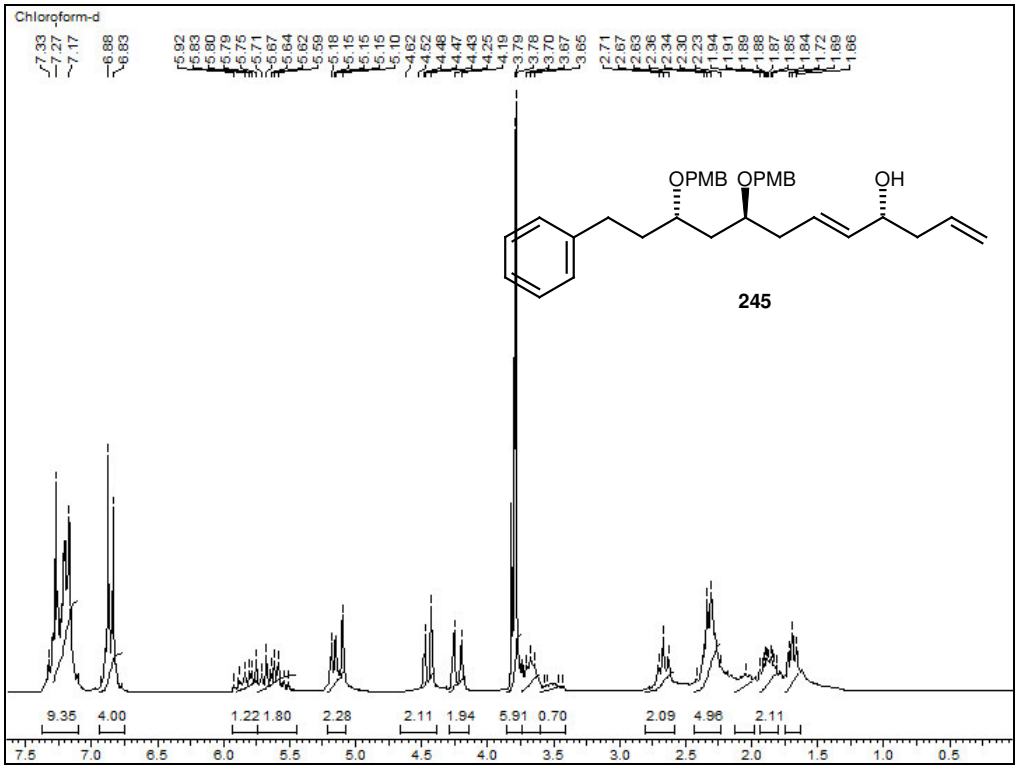
^{13}C NMR Spectrum of **241a**



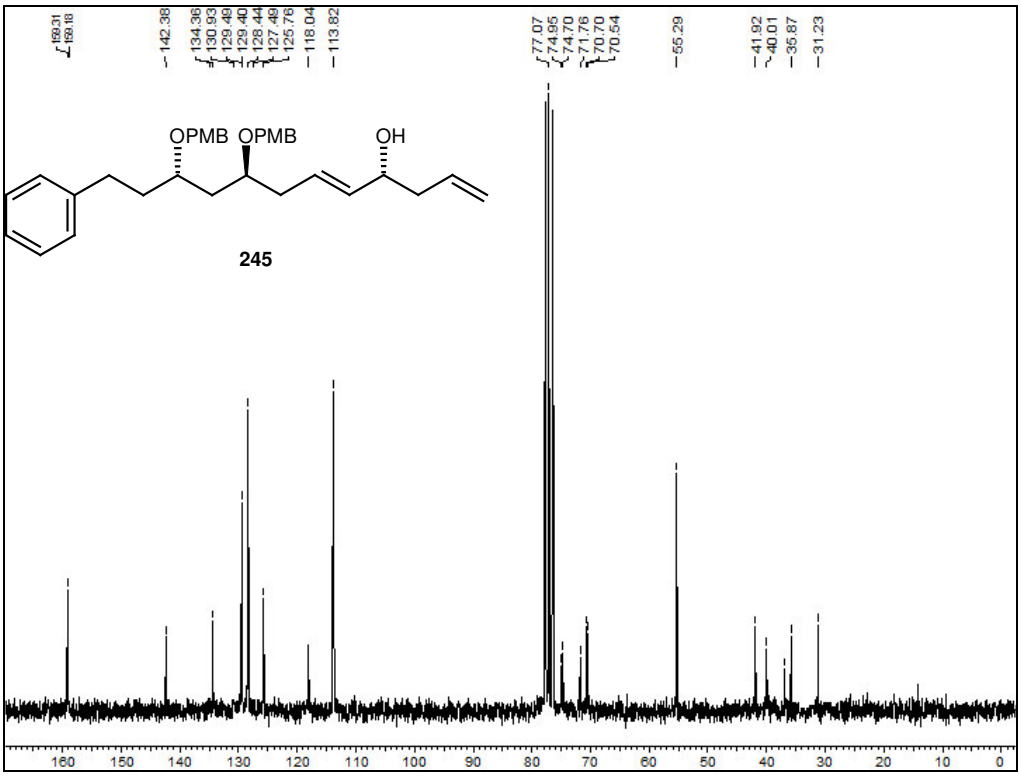
^{1}H NMR Spectrum of **246**



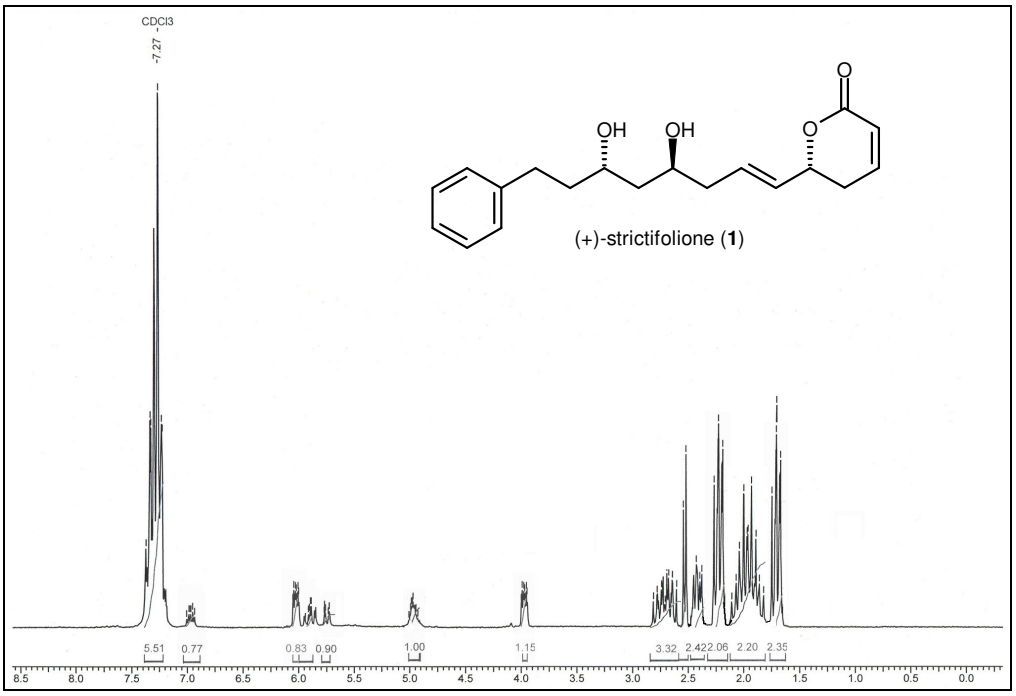
^{13}C NMR Spectrum of **246**



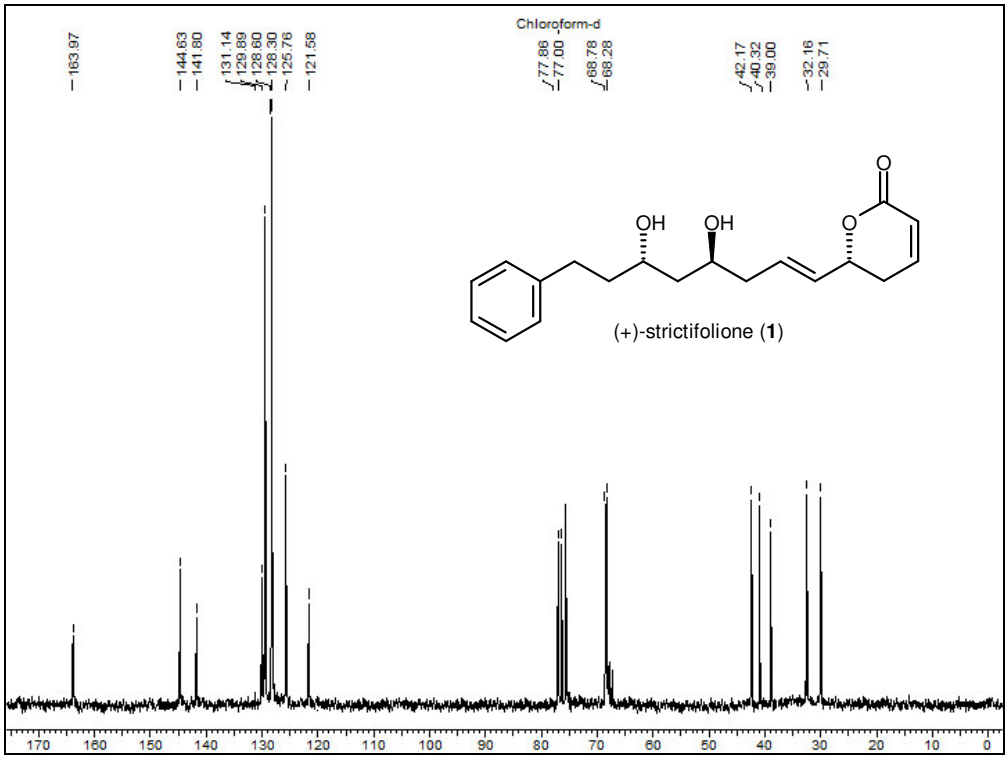
^{1}H NMR Spectrum of **245**



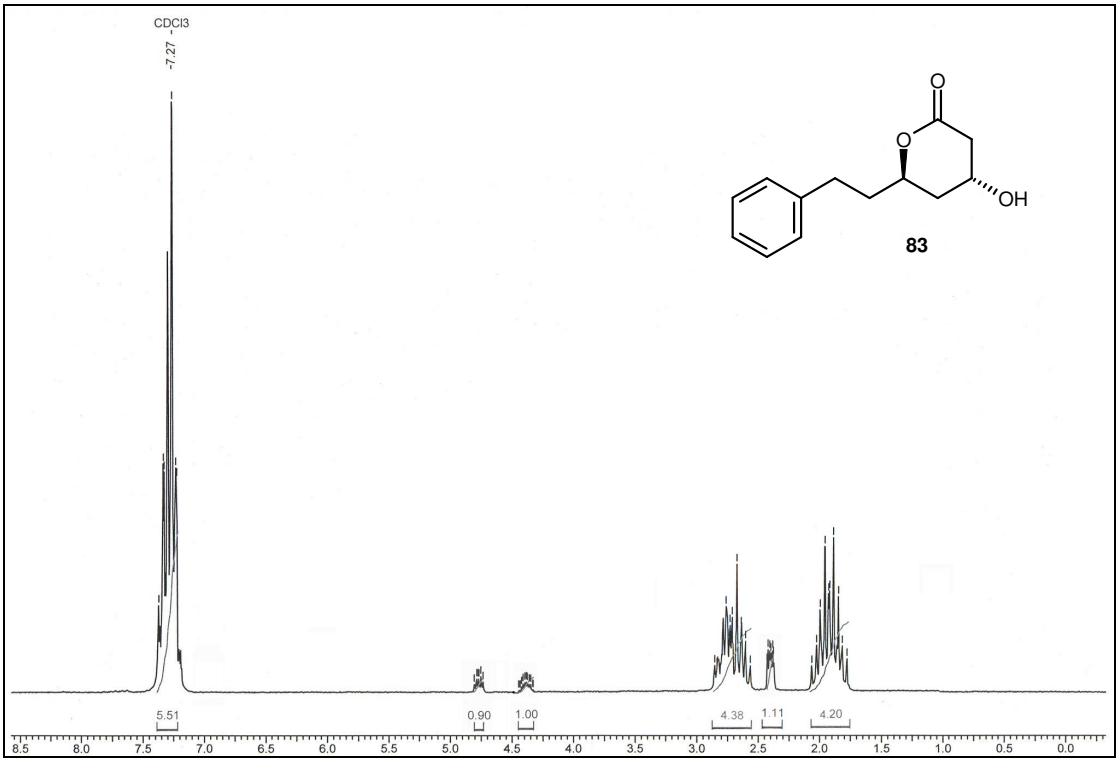
^{13}C NMR Spectrum of **245**



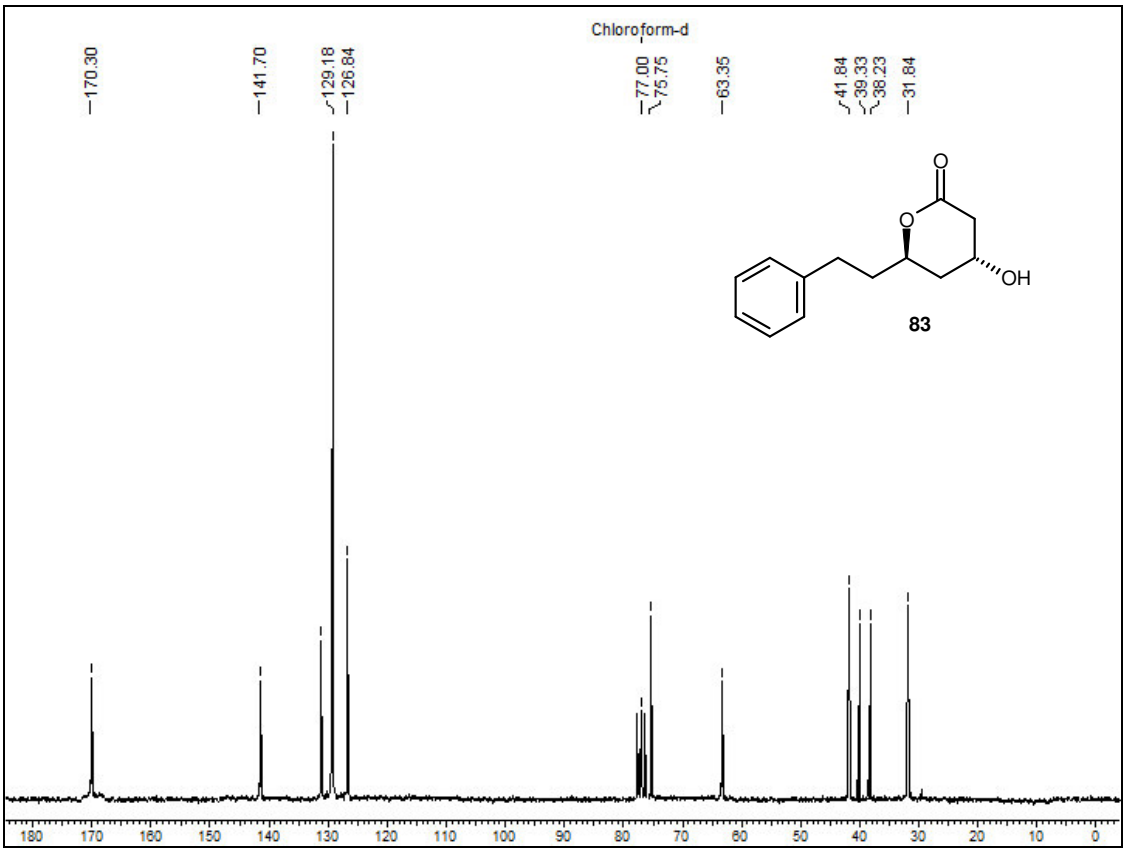
^{1}H NMR Spectrum of (+)-strictifolione **(1)**



^{13}C NMR Spectrum of (+)-strictifolione **(1)**



^{1}H NMR Spectrum of **83**



^{13}C NMR Spectrum of **83**

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4.2. SECTION B

A SIMPLE AND EFFICIENT APPROACH TO 1,3-AMINOALCOHOLS: APPLICATION TO THE SYNTHESIS OF (+)-NEGAMYCIN

4.2.1. INTRODUCTION:

(3*R*,5*R*)-3,6-Diamino-5-hydroxyhexanoic acid (**1**), is the core fragment of the pseudo-peptide antibiotics negamycin (**2**), (-)-5(*S*)-epi-negamycin **2a** and sperabillin A and C (**3a** and **3c**, respectively (Figure 1). (+)-Negamycin **2** is an unusual antibiotic which contains a hydrazine peptide linkage, which was isolated[1] by Umezawa *et al*. in 1970 from the culture filtrate of three strains, related to *Streptomyces purpeofuscus*.

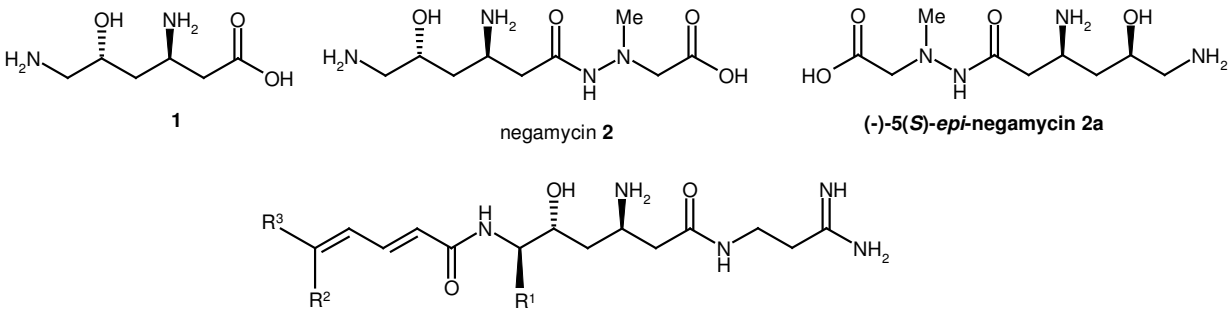


Figure 1.

It exhibits very low acute toxicity (LDm-400-500 mg/kg) and has considerable activity toward multiple drug resistant enteric Gram-positive and Gram-negative bacteria including *Pseudomonas aerginosa*.[1] Negamycin also exhibits genetic miscoding activity[2] on bacterial ribosome systems and is a specific inhibitor of protein synthesis in *Escherichia coli* K12.[3] The

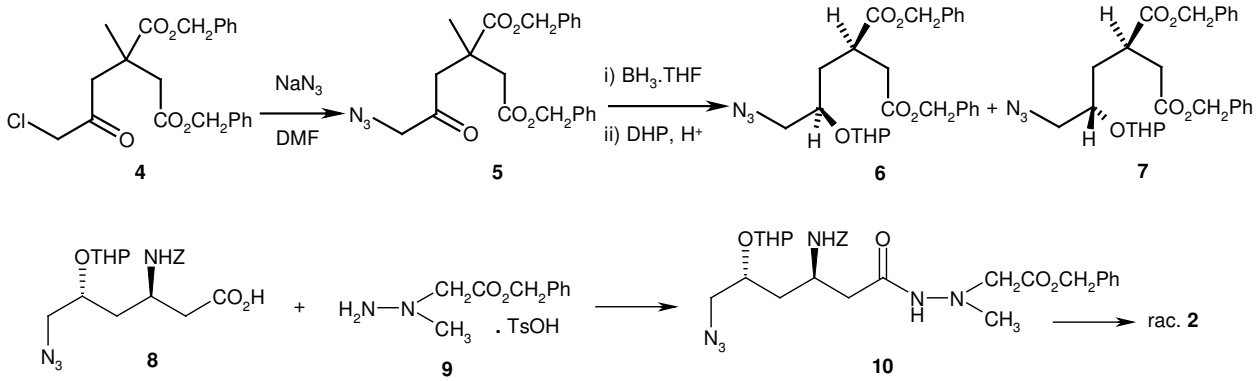
structure of negamycin was elucidated via degradation studies[4] and confirmed in 1972 by total synthesis from D-galacturonic acid.[5] The sperabillin family of antibiotics isolated from the culture broth of Pseudomonas fluoresens YK-437,[6] shows potential in vitro and in vivo antibacterial activity especially against Gram-positive pathogens, including multi-resistant strains of *Staphylococcus aureus*. Sperabillin polymers have also been shown to have antitumour activity.[7]

4.2.2. Review of Literature

Several approaches have been reported in the literature for the synthesis of racemic[8] as well as optically active negamycin.[9] Most of the enantioselective syntheses known for negamycin derive the asymmetry by an enzymatically derived chiral building block[9a] or form chiral pool starting materials, such as D-galacturomic acid, 3*R*,6-diacetamido-5*R*-hydroxy-hexano lactone, amino acid, D-glucose, malic acid, etc. Reported syntheses of negamycin have burgeoned in recent years because of increasing recognition of their biological relevance. However synthetic approaches involving achiral substrate as starting material are rather scarce. A few interesting syntheses of negamycin are described below.

Pilgrim *et al*. (1980).[8b]

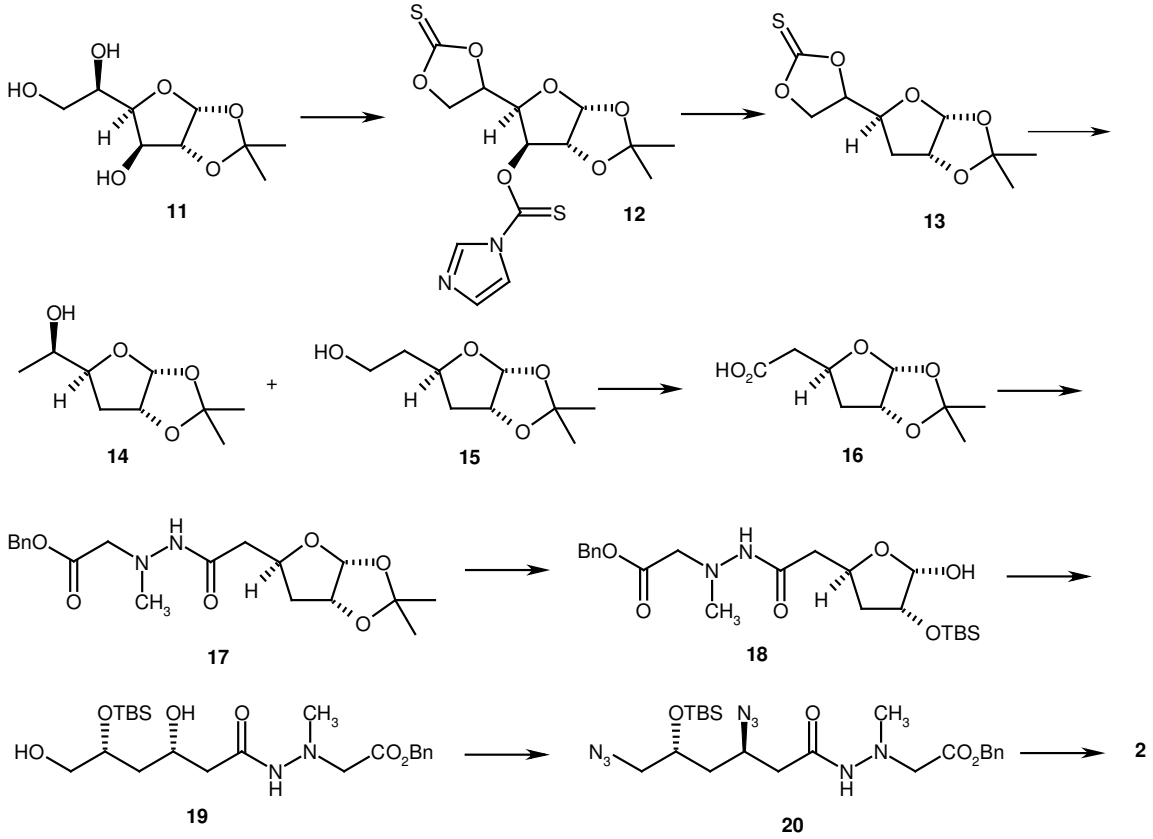
Pilgrim and co-workers accomplished the synthesis of negamycin and its diastereomer in racemic form. Thus, benzyl *N*-carbobenzoxy-dl-3-amino-5-oxo-6-chlorohexanoate **4**[11] was converted to the azidoketone **5** followed by reduction with 50% excess borane-THF to give the azido-alcohol **6**. Saponification of the benzyl ester **6** gave the free acid **8**, which was coupled with α-methylhydrazinoacetic acid protected as the benzyl ester, using the mixed anhydride method to give the fully protected *rac*-negamycin. Finally deprotection of all protecting groups led to negamycin **2** (Scheme 1).



Scheme 1.

Weigele *et al*. (1988).[9e]

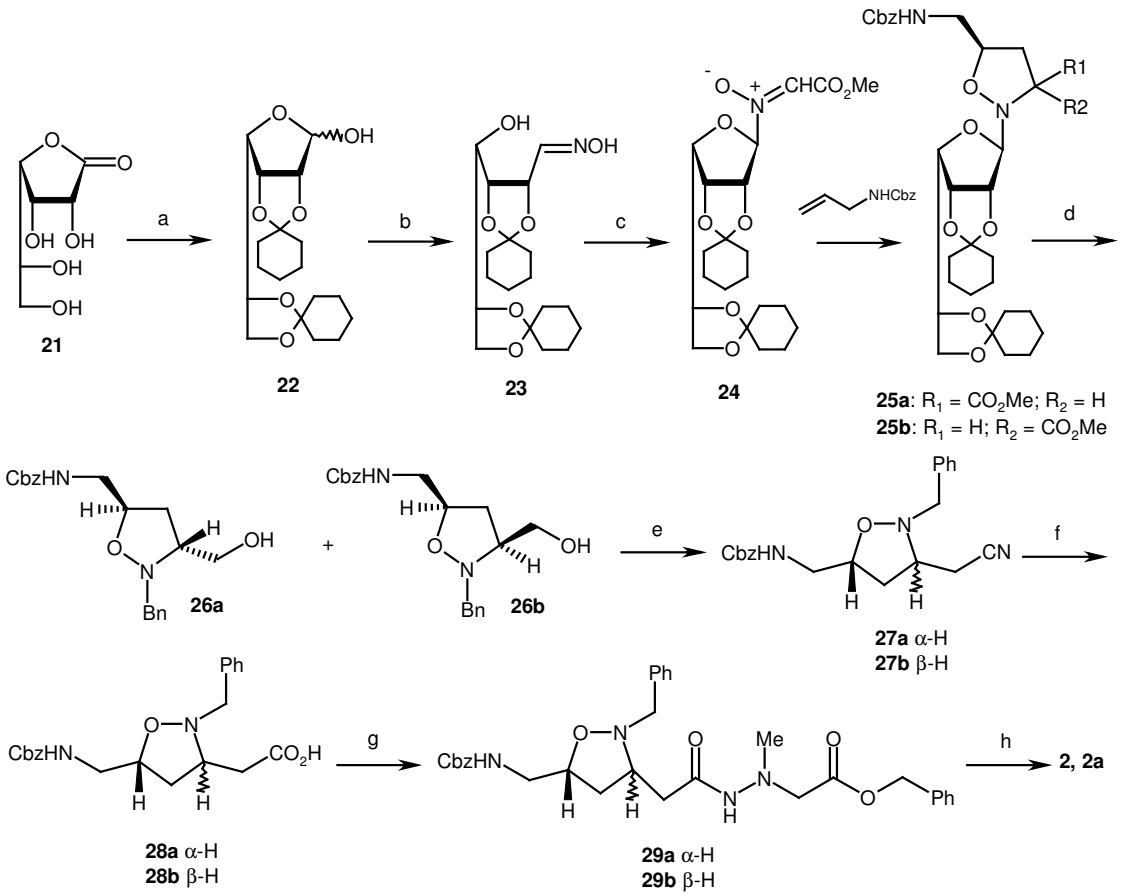
Weigele and co-workers accomplished the synthesis of (+)-negamycin from 1,2-*O*-isopropylidene-D-glucose **11**. Formation of a cyclic thiocarbonate involving the 5- and 6-oxygen functions, along with thiocarbamation of *O*-3 (**12)** and reduction with Bu_3SnH gave the desired 3,5-dideoxy sugar derivative **13**. Oxidation of **13** gave the corresponding hexuronic acid **16**. The hydrazide **17** was then prepared from **16** with benzyl 2-hydrazinoacetate by the mixed anhydride method employing isobutyl chloroformate and *N*-methylmorpholine in THF. Removal of the isopropylidene protecting group with acidic ion exchange resin, and subsequent conversion led to (+)-negamycin **2** (Scheme 2).



Scheme 2.

Kibayashi *et al*. (1986).[9b]

Kibayashi and co-workers accomplished the synthesis of (+)-negamycin **2** and (-)-3- *epi*-negamycin by the introduction of asymmetry through 1,3-dipolar cycloaddition with chiral nitrone **24** modified with carbohydrates, (*N*-D-gulosyl nitrone D-**24**), which proceeds in stereocontrolled and predictable manner with a high degree of enantioselectivity. Tosylation of (3*R*,5*R*)-**26a-b** followed by substitution with NaCN gave the nitrile (3*S*,5*R*)-**27a-b**, which was converted to the carboxylic acid (3*R*,5*R*)-**28a-b** *via* ethanolysis followed by saponification. Condensation of (3*R*,5*R*)-**28a-b** with benzyl (1-methylhydrazino)acetate was carried out by using the mixed anhydride method leading to the hydrazide (3*R*,5*R*)-**29a-b**. Deprotection followed by purification by silica gel chromatography provided (+)-negamycin **2** and (-)-3- *epi*-negamycin (Scheme 3).

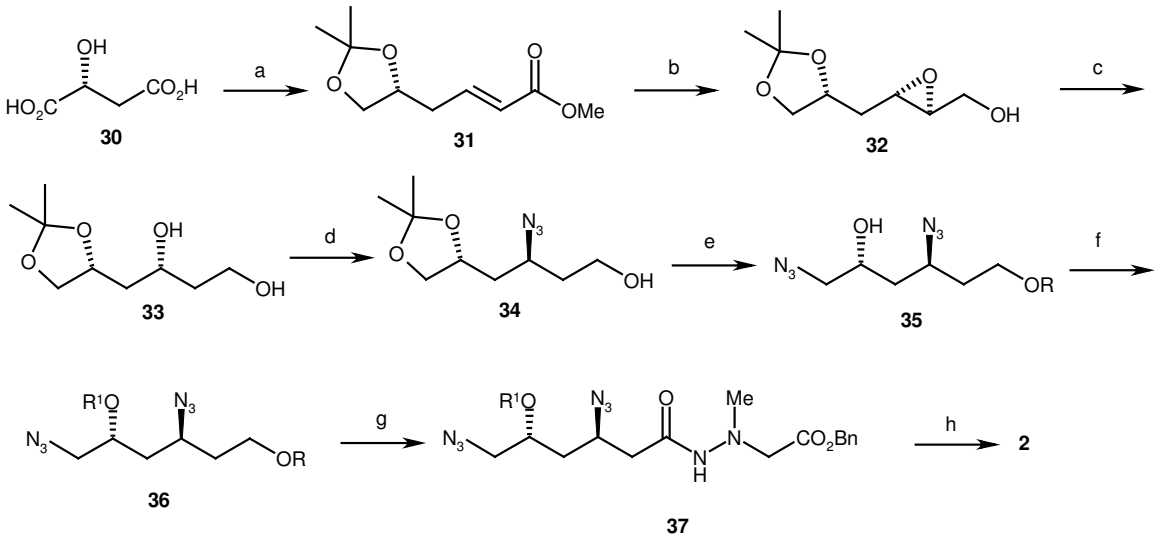


Scheme 3. *Reagents and conditions*: (a) (i) Dimethoxycyclohexane, TsOH, benzene, reflux; (ii) DIBAL, toluene, −78 ^{o}C; (b) $NH_2OH.HCl$, pyridine, rt; (c) methyl glyoxylate, toluene, reflux; (d) (i) 10% HC1, MeOH, 40 ^{o}C; (ii) BnBr, K_2CO_3, DMF, 50 ^{o}C; (iii) $LiAlH_4$, Et_2O, 0 ^{o}C – rt; (e) (i) TsCl, EtN(*i*-Pr)$_2$, CH_2Cl_2, 0 ^{o}C – rt; (ii) NaCN, Me_2SO, 80 ^{o}C ; (f) HC1, EtOH, rt; (g) (i) 4% aq. NaOH, MeOH, rte; (ii) EtOCOCl, Et_3N, toluene, 0 ^{o}C, then $H_2NN(Me)CO_2Bn$, toluene, 0 ^{o}C to rt; (h) H_2 (3 atm), 10% Pd-C, MeOH-10% aqueous AcOH.

Tanner *et al*. (1988).[9d]

Tanner and co-workers accomplished the synthesis of negamycin from malic acid. Thus, commercially available (*R*)-(+)- malic acid **30** was converted into *trans*-α,β-unsaturated ester **31** using standard chemistry. DIBAL-H reduction of ester and Sharpless asymmetric epoxidation of allyl alcohol gave the epoxide **32**. Regioselective (C-2) ring-opening of this epoxy alcohol with Red-Al gave the relevant 1.3-diol **33**. The primary hydroxy was protected selectively as the *t*-butyldiphenylsilyl ether and the free secondary hydroxyl was then

mesylated and substituted with NaN_3 to furnish **34**. Deprotection of acetonide and selective tosylation followed by azidation gave bis-azide **35**. The remaining secondary alcohol was protected as the benzyloxymethyl (BOM) ether. Deprotection of TBS followed by oxidation and hydrazine coupling using the mixed anhydride method gave **37**. Global deprotection by hydrogenolysis furnished negamycin **2** (Scheme 4).

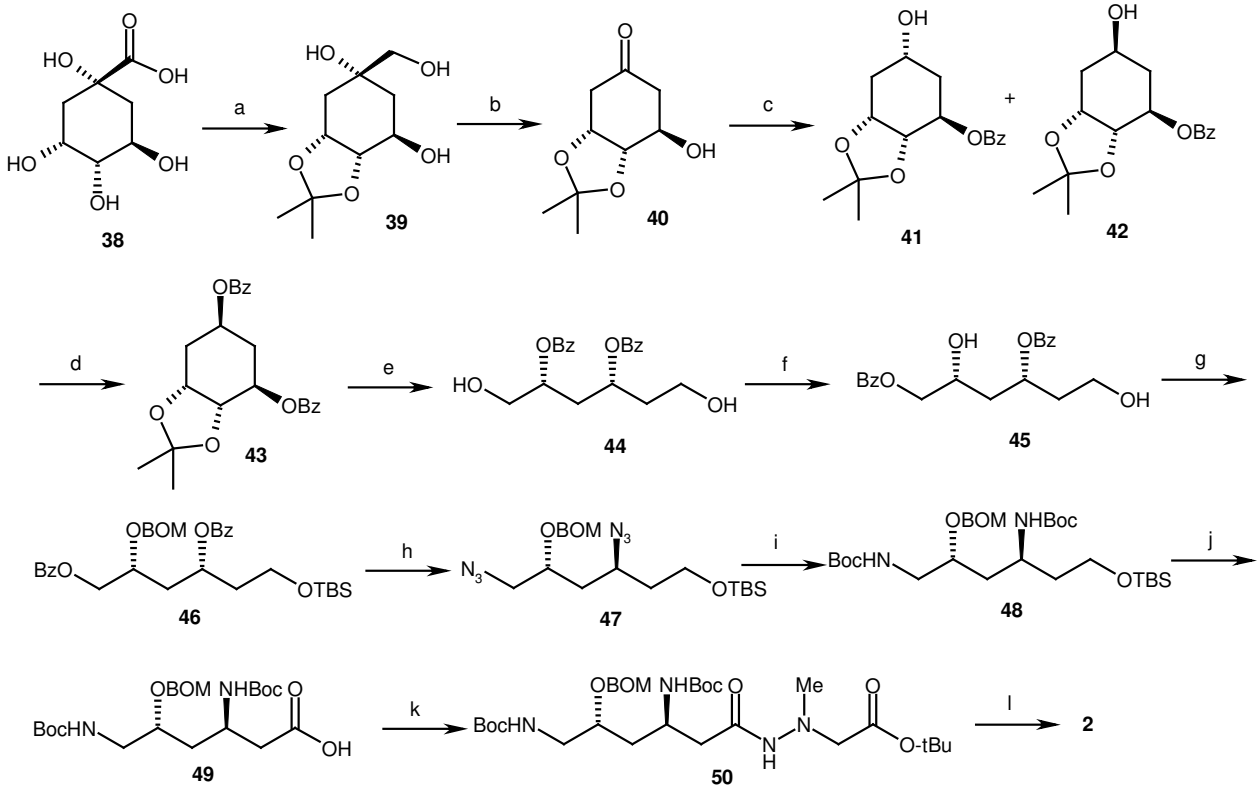


Scheme 4. *Reagents and conditions*: (a) See refs. 5,6,7. (b) DIBAL-H, CH_2Cl_2,–78 ^oC, 96%; (c) (+)-DET, Ti(O*i*Pr$_4$), TBHP, CH_2Cl_2, –20 ^oC, 92%. (d) Red-Al, THF, –40 ^oC to rt, 98%; (e) ^{t}BuPh$_2$SiCl, DMAP, NEt_3, CH_2C1_2, 89%; (f) MsC1,THF,0 ^oC, 100%; (g) NaN_3, 15-crown-5 (cat.), DMF, 50 ^oC, 99 %; (h) $CuC1_2.2H_2O$, EtOH, rt, 87%; (i) *p*-TsCl, pyridine, –20 °C 92%; (j) as for (g), 91%; (k) BOMCl, ^{i}Pr$_2$NEt, CH_2C1_2, rt, 93%; (1) Bu_4NF.THF, 94%; (m) $RuC1_3$ (cat.), $NaIO_4$, $CH_3CN/CC1_4/H_2O$, rt, 67%; (n) $C1CO_2Et$, NEt_3, toluene, –5 ^oC, then benzyl(l-methylhydrazino)-acetate, 63%; (o) H_2, Pd-C, MeOH/aq. AcOH, 89%.

Maycock *et al*. (1992).[9g]

Maycock and co-workers accomplished the synthesis of (+)-negamycin from quinic acid. Compound **38** was prepared from quinic acid using literature method.[12] Diol **39** was converted into ketone **40** followed by hydroxyl protection with benzylchloride and reduction of ketone to afford a 3: I mixture of the diastereoisomers **41** and **42**, which were easily separated by chromatography. The isomer **41** was benzoylated and converted into the corresponding diol **44**. 1,4-Migration of the benzoyl group was effected by treatment of diol **44** with diisopropylethylamine. Subsequent selective protection of primary hydroxyl group with the TBDMS group, and the secondary hydroxyl with BOM group afforded compound **47**.

Hydrolysis of the benzoate esters followed by dimesylation and diazidation furnished **50**. Compound **50** was converted into (+)-negamycin over several steps (Scheme 5).

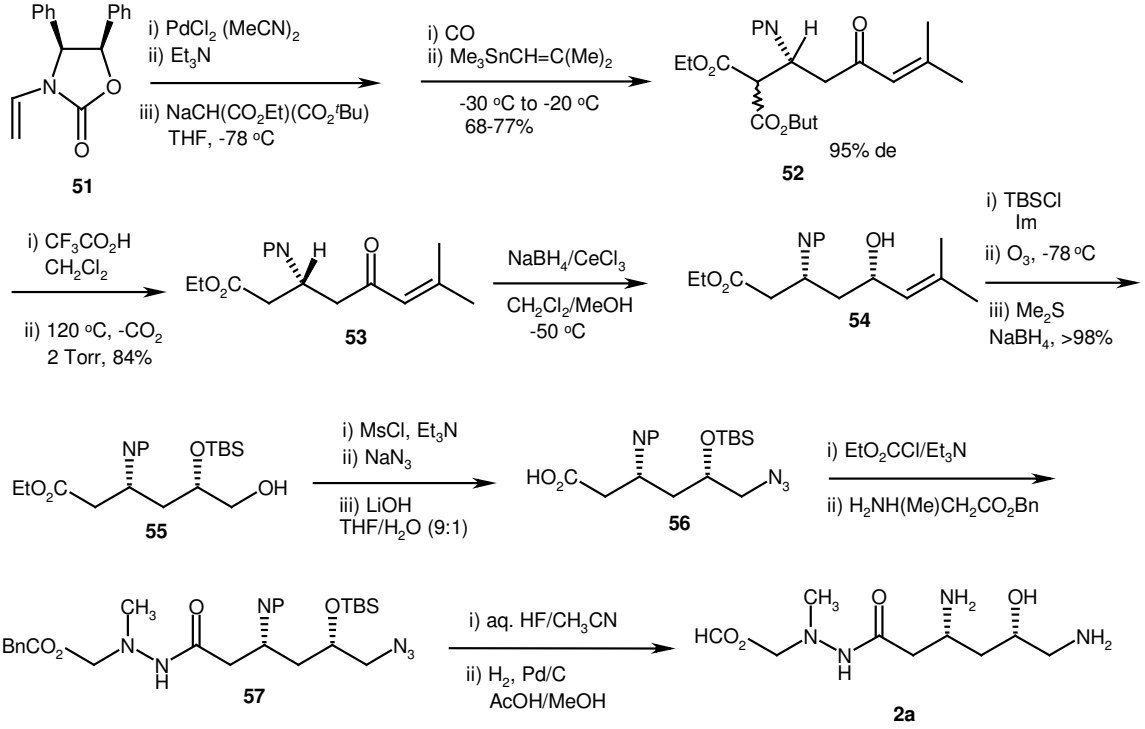


Scheme 5. *Reagents and conditions*: (a) ref. 9m (b) $NaIO_4$, H_2O, 25 ^oC, pH 5-6, 95%; (c) (i) BzCl, pyridine, DMAP, 0 ^oC, 90%; (ii) $NaBH_4$, EtOH, 25 ^oC; (d) BzOH, DEAD, TPP, THF, 25 ^oC, 50%; (e) (i) BzCl, pyridine, DMAP, 0 ^oC, 90%; (ii) 1,2-ethanethiol, $BF_3.Et_2O$, CH_2Cl_2, 25 ^oC, 99%, $Pb(OAc)_4$, CH_2Cl_2, 0 ^oC, 98%; (iii) $NaBH_4$, EtOH, 25 ^oC, 97%; (f) $(i\text{-}Pr)_2NEt$, CH_2Cl_2, 25 ^oC, 88%; (g) (i) TBDMSCl, $(i\text{-}Pr)_2NEt$, DMAP, CH_2Cl_2, 25 ^oC; (ii) BOMCl, $(i\text{-}Pr)_2NEt$, DMAP, 79%; (h) (i) KOH, MeOH, 25 ^oC, 92%; (ii) MsCl, DMAP, pyridine, CH_2Cl_2; (iii) NaN_3, DMF, 80 ^oC, 88%; (i) (i) H_2, Pd/C, EtOH, 25 ^oC, (ii) Boc_2O, $(i\text{-}Pr)_2NEt$, $CHCl_3$, reflux, 84%; (j) (i) TBAF, THF, 25 ^oC, 97%; (ii) $NaIO_4$, $RuCl_3$, CH_3CN, CCl_4, H_2O, 25 ^oC, 82%; (k) $ClCO_2Et$, Et_3N, *t*-butylhydrazineacetate, CH_2Cl_2, -10 ^oC to -5 ^oC, 98%; (l) (i) 10% Pd/C-H_2, (ii) CF_3COOH.

Hegedus *et al*. (1993).[9h]

Hegedus and co-workers accomplished the synthesis of (+)-negamycin **2** and (-)-5-*epi*-negamycin **2a** by a process involving the palladium-(II)-assisted alkylation with of an

optically active ene carbamate **51** using $PdC1_2(MeCN)$ followed by carbonylative coupling to a trialkylvinyltin to give difunctionalized product **52** in 95% de.



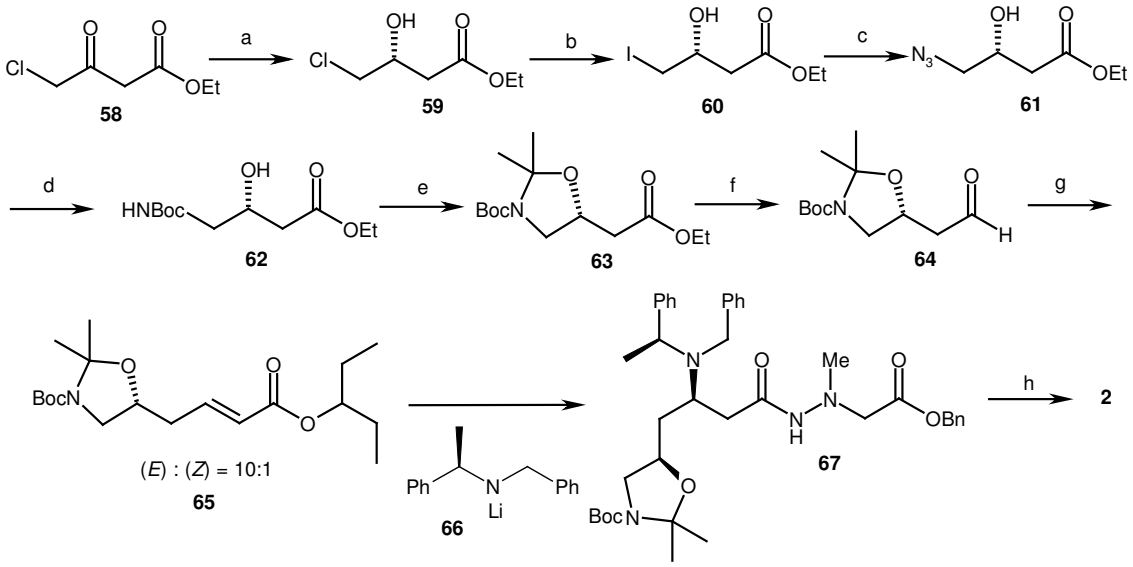
Scheme 6.

Hydrolysis of the *tert*-butyl ester followed by decarboxylation gave **53**. Diastereoselective reduction of the 5-keto group, using cerium trichloride and sodium borohydride furnished allylic alcohol **54** in 89% de. Isobutenyl group of **54** was converted into amine by ozonolysis, reduction, mesylation and azidation. Peptide bond formation and deprotection gave (-)-5-*epi*-negamycin **2a** (Scheme 6).

Ichihara *et al*. (1996).[9j]

Ichihara and co-workers accomplished the synthesis of (+)-negamycin by employing the highly diastereoselective conjugate addition of lithium (α-methylbenzyl)benzylamide as the key step. The synthesis was initiated with the asymmetric reduction of the commercially available ethyl 4-chloroacetoacetate **58**. The hydrogenation of **58** using (*S*)-BINAP-Ru(II) complex afforded γ-chloro-3-hydroxy ester **59** with excellent enantioselectivity (96%). Displacement of chloro with iodo using NaI followed by further displacement with azide followed by hydrogenation of azide and *N*-BOC protection gave *N*-Boc protected amino ester **62**. Protection of **62** as acetonide and subsequent synthetic conversion led to the formation of α,β-unsaturated ester **65**. The α,β-unsaturated ester **65** was reacted with lithium amide at −78

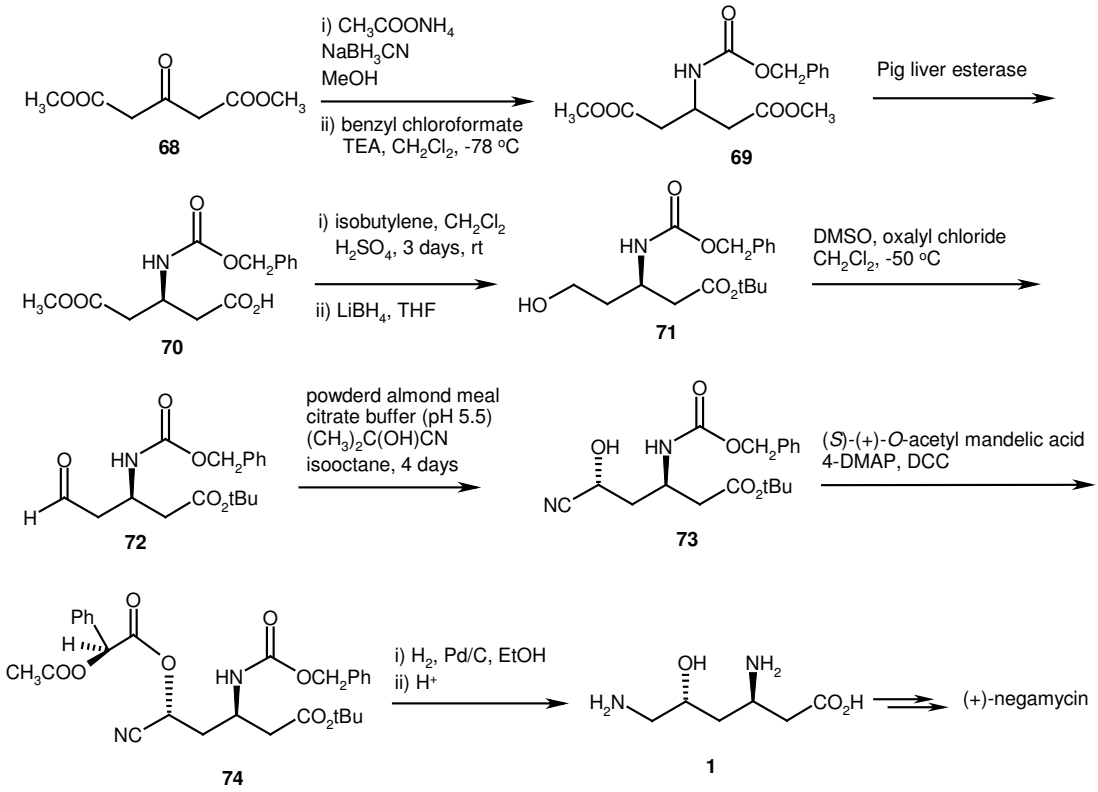
°C to afford the Michael adduct **67**. LiOH-mediated hydrolysis of the bulky ester moiety followed by coupling and deprotection gave (+)-negamycin **2** (Scheme 7).



Scheme 7. *Reagents and conditions*: (a) H_2, (*S*)-Ru[BINAP]CI_2; (b) NaI; (c) NaN_3; (c) H_2, Pd/C, $(Boc)_2O$; (d) $(CH_3O)_2C(CH_3)_2$, CSA; (e) sodium bis(2-methoxyethoxy)aluminium hydride; (f) DMSO, oxalyl chloride, $(iPr)_2EtN$; (g) 3-pentyl-(triphenylphosphoranylidcae)acetate; (h) (i) LiOH, MeOH/THF/Water; (ii) benzyl (1-methylhydrazino)acetate *p*-TSA salt, DCC, Et_3N, HOBt; (iii) TFA, THF/Water, (iv) H_2, $Pd(OH)_2/C$.

Ahn *et al*. (1997).[10]

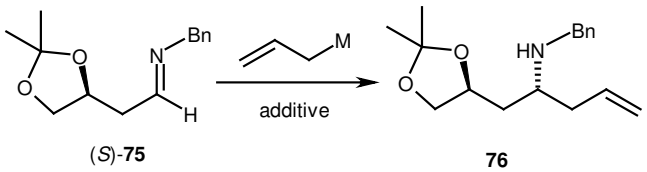
Ahn and co-workers accomplished the synthesis of (+)-negamycin by chemoenzymatic method. Reduction of dimethyl β-oxoglutarate **68** with $CH_3COONH_4/NaBH_3CN$ using Borch's method and protection of amine with benzyloxycarbonyl gave compound **69**. Porcine liver esterase hydrolyzed monomethyl ester **70** was formed to give the alcohol **71**, which was oxidized and second stereocentre **73** was introduced by mendalonitrile lyase. Finally, deprotection and coupling gave (+)-negamycin (Scheme 8).



Scheme 8.

Fujisawa *et al*. (1998).[91]

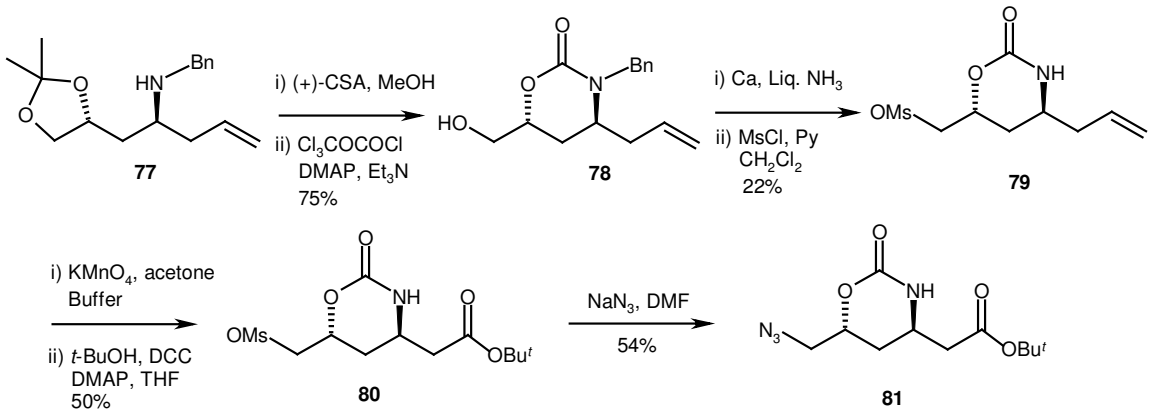
Fujisawa and co-workers accomplished the synthesis of negamycin from optically active imine, derived from malic acid (*S*)-**75**. Thus, stereoselective addition of allyl metals to imine under variety of conditions (Table 1) furnished homoallylic amine **76** with different ratios. The best stereoselectivity was obtained when the addition was carried out using allyltributylstannane in the presence of $AlCl_3$ and *anti*-product was obtained as a sole product. Hydrolysis of acetonide followed by oxazolidinone formation and debenzylation and mesylation afforded compound **79**. Oxidation of olefinic bond and esterification followed by azidation gave the known intermediate **81** (Scheme 9 and 10).



Scheme 9.

Table 1. Addition of allyl metal reagents to imine (*S*)-**1**

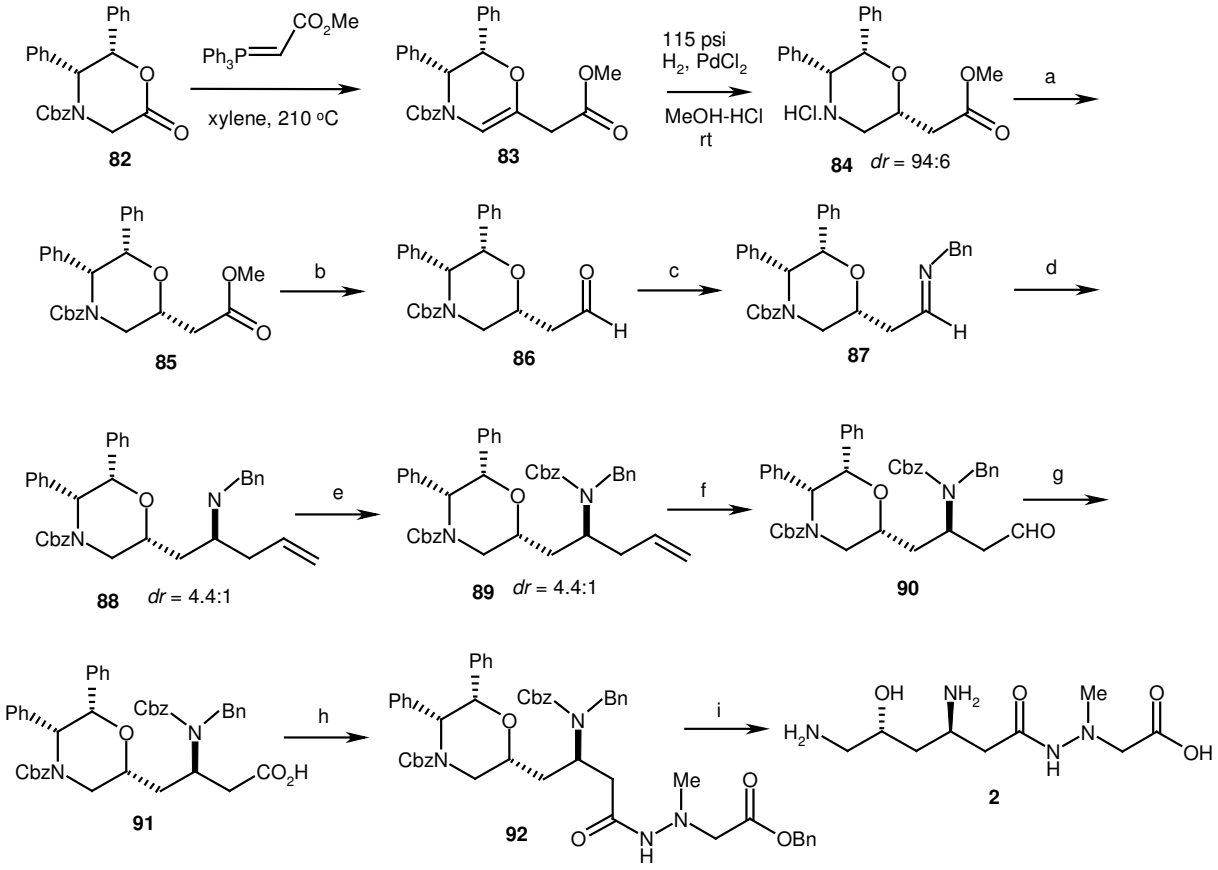
Entry	Metal	Additive	Solvent	Temp.(^{o}C)	Yield (%)	*anti* : *syn*
1	MgCl	None	Et_2O	–78 to –30	62	67 : 33
2	MgCl	$CeCl_3$	THF	–78 to rt	54	89 : 11
3	MgBr	None	Et_2O	–78 to –55	19	52 : 48
4	$SnBu_3$	$AlCl_3$	CH_2Cl_2	–78 to 0	33	99 : <1
5	$SnBu_3$	$AlCl_3$	CH_2Cl_2	–78 to 0	54	99 : <1
6	$SnBu_3$	$TiCl_4$	CH_2Cl_2	–78 to rt	Trace	- : -
7	Li	none	Et_2O	–78 to rt	46	29 : 71



Scheme 10.

Williams *et al*. (2002).[9k]

Williams and co-workers accomplished an asymmetric synthesis of (+)-negamycin (**1**), starting from commercially available (5*R*,6*S*)-4-(benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (**82**). The synthesis involved the stabilized Wittig olefination of the lactone carbonyl group of **82** and subsequent asymmetric hydrogenation to generate the corresponding all-*syn* oxazine **84** with excellent diastereoselectivity (94:6). Conversion of **84** into β-alkoxy imine **87** and subsequent $CeCl_3$-promoted chelation-controlled allylation of **87** generated the corresponding homoallylamine **88** with good diastereoselectivity, which was readily converted into (+)-negamycin (**2**) in 25% overall yield over 11 steps (Scheme 11).



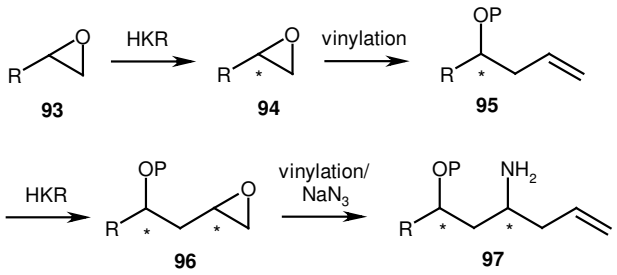
Scheme 11. *Reagents and conditions*: (a) Cbz-Cl, Et_3N, DMAP, CH_2Cl_2, rt, 96%; (b) DIBAL-H, CH_2Cl_2, −78 °C, 85%; (c) $BnNH_2$, Al_2O_3, CH_2Cl_2, 0 °C, 98%; (d) $CeCl_3$, THF, −40 °C, $BrZnCH{=}CH_2$; (e) Cbz-Cl, 1 M NaOH, dioxane, 0-5 °C, 80%; (f) O_3, CH_2Cl_2, MeOH, −78 °C, 73%; (g) PDC, DMF, rt, 97%; (h) benzyl (1-methylhydrazino)acetate-PTSA salt, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, Et_3N, HOBT, CH_2Cl_2, rt, 80%; (i) 40 psi of H_2, 10% Pd/C (25 mol %), MeOH, H_2O, AcOH, 75 °C, 75%.

4.2.3. PRESENT WORK

Objective

Given the vast chemistry, structural modifications and biological activities associated with the negamycin, the synthesis of this class of 1,3-amino alcohols has aroused considerable interest among several research groups round the world. Although a few syntheses are reviewed above, several more are documented in the literature.[9] This explains the importance of research work in negamycin synthesis. With the development of an efficient approach to the synthesis of 1,3-polyols and its subsequent application towards the synthesis of strictifolione through HKR, our attention was further focused to extrapolate the above knowledge to the synthesis of naturally occurring 1,3-aminoalcohol such as negamycin.

Scheme 12 shows our general synthetic strategy to construct the *syn*-and *anti*-1,3-aminoalcohol system which is based on a three-step reaction sequence employing iterative epoxidation, hydrolytic kinetic resolution (HKR)[13] and vinylation. The diastereomeric ratio in the *m*-CPBA epoxidation reaction would depend on whether the hydroxyl group is free or protected.



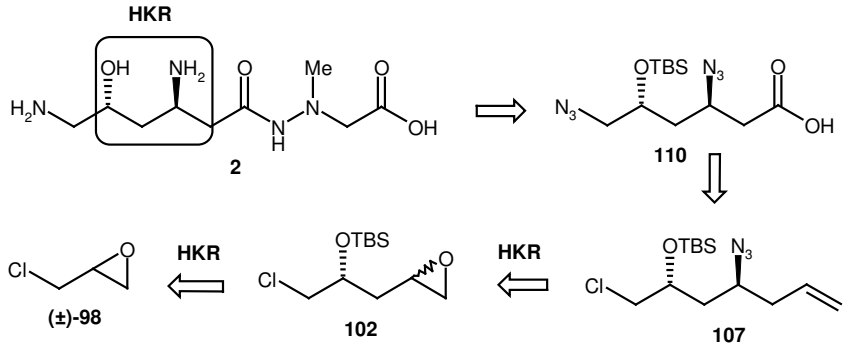
Scheme 12. General synthetic strategy to the synthesis of 1,3-aminoalcohol.

Thus, the objective of the present investigation is the construction of 1,3-aminoalcohol through 1,3-diol by stereoselective epoxide ring opening and its further application to the synthesis of negamycin. The *syn*-and *anti*-configuration of 1,3-polyol/aminoalcohol moiety can be manipulated simply by changing the Jacobsen's catalyst in the hydrolytic kinetic resolution step.

4.2.4. Result and discussion

Our synthetic strategy for the synthesis of **2** is outlined in Scheme 13. We envisioned that the (+)-negamycin **2** can be synthesized by peptide formation of **110** with the l-methylhydrazineacetic acid. The bis-azido compound **110** can be derived by regioselective

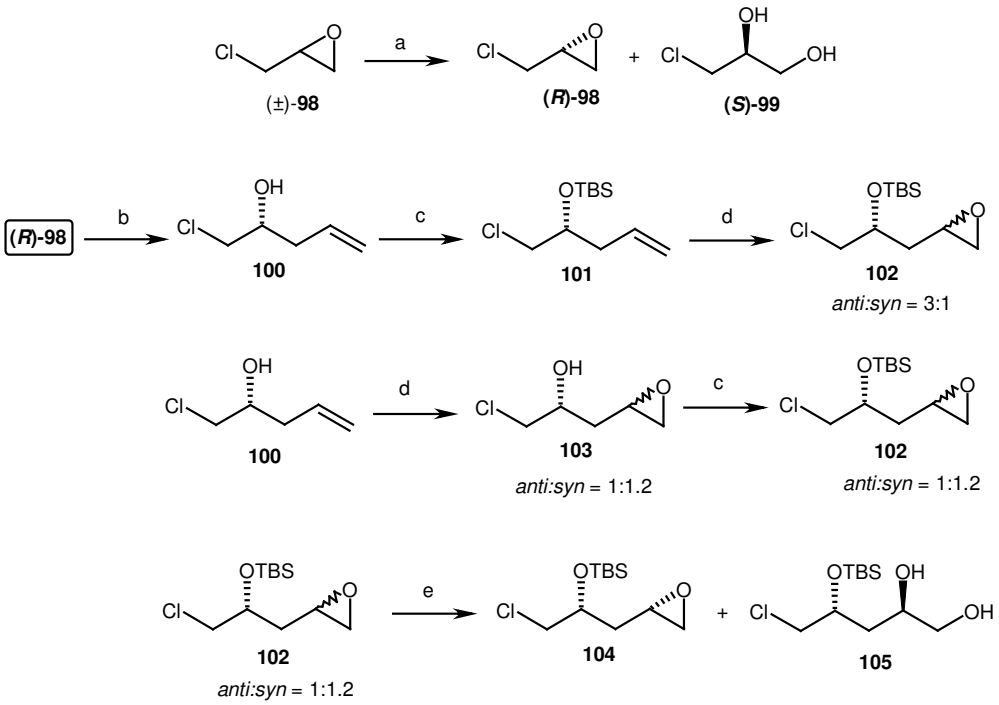
opening of epoxide **104**, which in turn could be obtained *via* hydrolytic kinetic resolution of epoxide **102**. Olefin **100**, the precursor for racemic epoxide **102**, would be prepared



Scheme 13. Retrosynthetic analysis for negamycin (2).

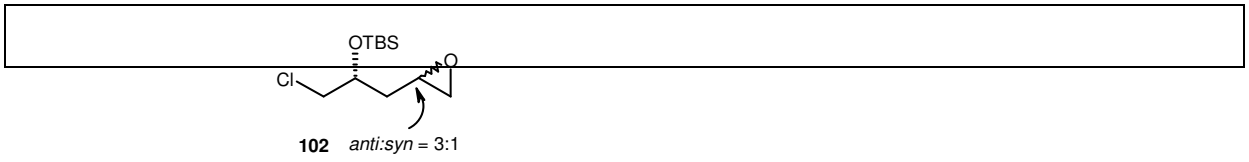
from chiral epichlorohydrin, which in turn, could be derived from racemic epichlorohydrin (±)-**98**[13] *via* hydrolytic kinetic resolution. In designing a route to **2**, we chose racemic epichlorohydrin as an appropriate starting material. Thus, commercially available epichlorohydrin (±)-**98** was subjected to Jacobsen's HKR by using (*S*,*S*)-Salen-Co-OAc catalyst to give *R*-epichlorohydrin[13] (*R*)-**98** as a single isomer, which was easily isolated from the more polar diol **99** by distillation. With enantiomerically pure epoxide **102** in hand our next aim was to construct the *anti* 1,3-amino alcohol. To establish the subsequent stereogenic centre with the required stereochemistry, it was thought worthwhile to examine stereoselective epoxidation of a homoallylic alcohol. Thus, *R*-epichlorohydrin (*R*)-**98** was treated with vinylmagnesium bromide in the presence of CuI to give the homoallylic alcohol **100** in excellent yield. The IR spectrum of **100** gave broad hydroxyl absorption at 3358-3250 cm^{-1}. The ^1H NMR spectrum of **100** gave olefin peaks at δ 5.08-5.19 (multiplet, two protons) and 5.74-5.87 (multiplet, one proton). We then further proceeded to explore the stereoselective outcome of the epoxidation reaction with and without hydroxyl group protection. Towards this end, the hydroxyl group of homoallylic alcohols was first protected as TBS ether, followed by epoxidation with *m*-CPBA. The epoxide **102**, thus obtained was found to be a mixture of two diastereomers (*anti:syn*/3:1) as determined by ^1H and ^{13}C NMR spectral analysis. The ^1H NMR spectrum of **102** showed absence of olefin protons at δ 5.08-5.19 and 5.74-5.87. The diastereomeric epoxide peaks appeared at δ 2.48-2.50 (multiplet, 1/3 proton), 2.53-2.54 (multiplet, one proton); 2.78 (triplet, 1/3 proton), 2.82 (triplet, one proton)

and 3.03-3.06 (multiplet, one proton), 3.07-3.10 (multiplet, 1/3 proton) in ^{1}H NMR spectrum. The ^{13}C NMR spectrum of **102** showed upfield carbons of epoxide at δ 49.68, 49.36; 47.31, 46.40; 42.59, 42.13 and other stereocentre at δ 66.28; 66.07 as a diastereomeric mixture.



Scheme 14. *Reagents and conditions*: (a) *S*,*S*-salen-Co-(OAc) (0.5 mol%), dist. H_2O (0.55 eq), 0 ^{o}C, 14 h, [46% for (*S*)-**98**, 45% for (*R*)-**99**]; (b) vinylmagnesium bromide, ether, CuI, −73 to −40 ^{o}C, 19 h, 70%; (c) TBDMS-Cl, imidazole, CH_2Cl_2, 0 ^{o}C to rt, 4 h, 98%; (d) *m*-CPBA, CH_2Cl_2, 0 ^{o}C to rt, 10 h, 88%; (e) *S*,*S*-salen-Co-(OAc) (0.5 mol%), dist. H_2O (0.55eq), 0 ^{o}C, 24 h, (46% for **104**, 45% for **105**).

The desired *syn* isomer of **102** was obtained only as a minor component. However, when epoxidation was carried out on alcohol **100** followed by hydroxy protection as a TBDMS-ether, the epoxide **102** were formed in favor of the desired *syn* isomer (*syn*: *anti*/1.2:1).[14] In order to improve the diastereoselectivity, we next attempted at the Jacobsen's hydrolytic kinetic resolution (HKR).



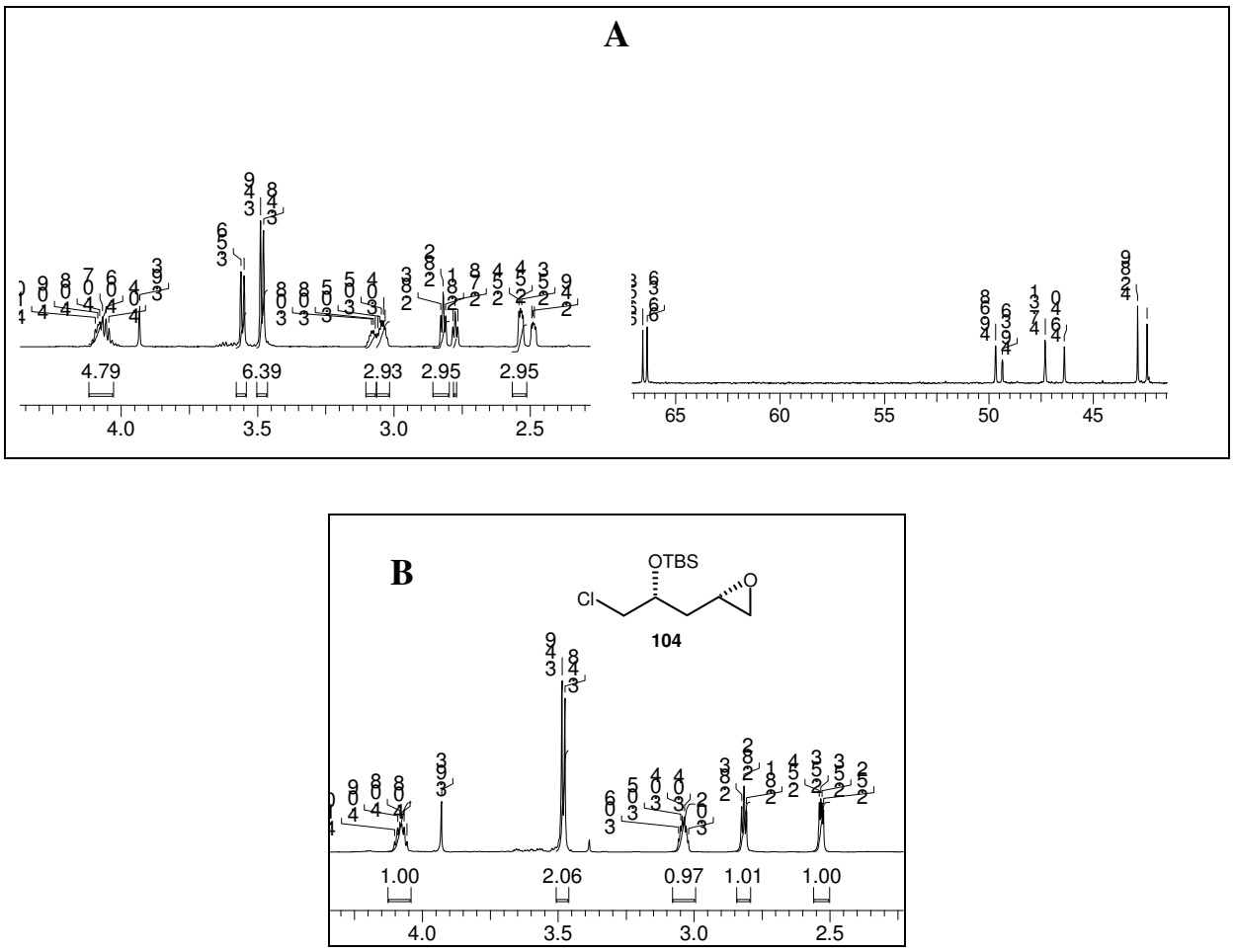
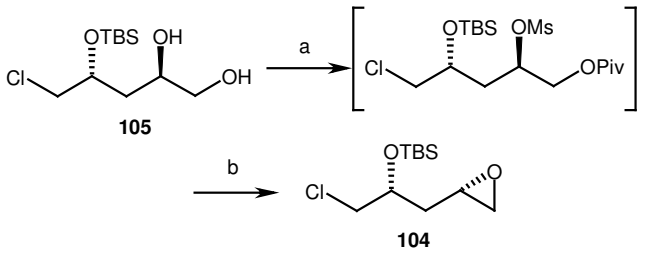


Figure 1: (**A**) Partial ^{1}H NMR and ^{13}C NMR spectra of diastereomeric mixture (3:1) **102**. (**B**) Partial ^{1}H NMR and ^{13}C NMR spectra of pure diasteomer **104**.

With racemic epoxide **102** (*syn*: *anti*/1.2:1) in hand, our next aim was to synthesize the chiral epoxide through the Jacobsen's hydrolytic kinetic resolution method, which could further be elaborated to *anti*-1,3-aminoalcohol moiety. Towards this end, the epoxide **102** was treated with (*S*,*S*)-salen-Co-OAc complex (0.5 mol%) and water (0.55 eq) in THF (0.55 eq) to afford the epoxide **104** as a single stereoisomer (determined from the ^{1}H and ^{13}C NMR spectral analysis) in 46% yield and the diol **105** in 47% yield.

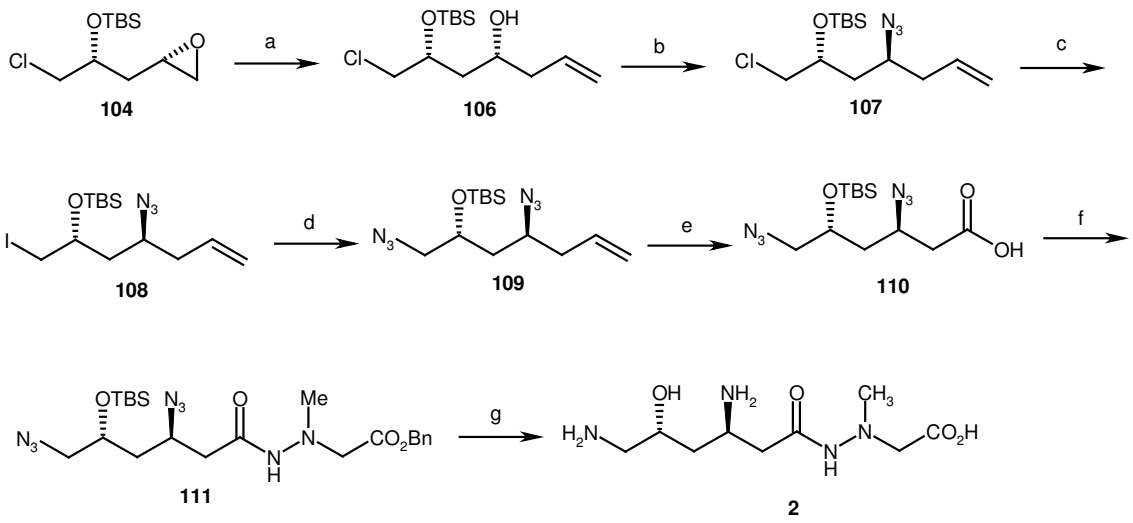
Epoxide **104** could easily be separated from the more polar diol **105** through silica gel column chromatography.



Scheme 15. *Reagents and conditions*: (a) (i) PivCl, Et_3N, Cat. DMAP, rt, 2h; (ii) MsCl, Et_3N, DMAP, 0 ^oC to rt, 1h; (b) K_2CO_3, MeOH, rt, overnight, (62% for three steps).

In order to achieve the synthesis of target molecule **2**, we required epoxide **104** in substantial amount. As the HKR method provided the desired epoxide **104** along with equal amount of diol **105**, we therefore thought it would be appropriate to convert unwanted diol into the required epoxide. Thus, the diol **105** was smoothly converted into the desired epoxide **104** *via* internal nucleophilic substitution in a secondary mesylate[15] (Scheme 15). Accordingly, the chemoselective pivalation of diol **105** with pivaloyl chloride followed by mesylation of secondary hydroxy and treatment of the crude mesylate product with K_2CO_3 in methanol led to deprotection of the pivaloyl ester to hydroxy group. The concomitant ring closure *via* intramolecular S_N2 displacement of the mesylate furnished the epoxide **104** in overall 62% yield. With substantial amount of **104** in hand, we further proceeded for the synthesis of **2** by opening of epoxide **104** with vinylmagnesium bromide in the presence of CuI in THF at –20 ^oC to give the homoallylic alcohol **106** in 86% yield. The IR spectrum of **106** gave broad hydroxyl absorption at 3460 cm^{-1}. The ^1H NMR spectrum of **106** gave olefin peaks at δ 5.03–5.06 (multiplet, two protons), 5.71–5.77 (multiplet, one proton). Compound **106** was then converted into an *O*-mesylated derivative, which on treatment with sodium azide in DMF furnished the azide **107** with the desired stereochemistry at C-3. The IR spectrum of **107** showed strong azide absorption at 2150 cm^{-1}. Treatment of **107** with large excess of NaI in 2-butanone gave iodoazide **108** in quantitative yield. The bis-azide **109** was obtained by the smooth displacement of the iodo group in **108** with sodium azide. Oxidation of olefinic bond in **109** using $RuCl_3/NaIO_4$ furnished the corresponding acid **110** in 67% yield. The hydrazide **111** was prepared in good yield from **110** by formation of its mixed anhydride[16] with ethyl chloroformate and subsequent reaction of the activated carbonyl with benzyl (1-methylhydrazino)acetate.[9h] In the final step, the azides were reduced to amino groups by catalytic hydrogenation over Pd/C in CH_3OH, acetic acid and H_2O, with concomitant removal

of the benzyl and silyl protecting groups to produce the acetate salt of (+)-negamycin, which was further purified by ion-exchange chromatography (Amberlite CG-50, NH_4^+ form) to afford (+)-Negamycin **2** as white powder in 72% yield from **111**. $[\alpha]_D^{25}$ +2.1 (*c* 0.72, H_2O); lit.[9h] $[\alpha]_D^{25}$ +1.7 (*c* 0.6, H_2O); lit.[9b] +2.3 (*c* 4.07, H_2O). The IR spectrum of **2** showed C=O of amide at 1662 and NH, OH, COOH at 3650-2500 cm^{-1} respectively.



Scheme 16. *Reagents and conditions*: (a) Vinylmagnesium bromide, THF, CuI, –20 ^oC, 1 h, 86%; (b) (i) MsCl, Et_3N, DMAP, 0 ^oC to rt, 1.5 h; (ii) NaN_3, DMF, 70 ^oC, 9 h, 89%; (c) NaI, acetone, reflux, 6 h; (d) NaN_3, DMF, 70 ^oC, 4 h; (e) $RuC1_3.3H_2O$ (cat.), $NaIO_4$, $CH_3CN/CCl_4/H_2O$, rt, 69%; (f) $C1CO_2Et$, NEt_3, toluene, –5 ^oC, then benzyl(l-methylhydrazino)-acetate, 65%; (g) H_2, Pd–C, MeOH, H_2O, AcOH, rt, 89%.

The ^1H NMR spectrum of **2** gave the chiral protons at δ 3.86-3.78 (multiplet, C*H*NH_2) and 3.30-3.18 (multiplet, C*H*OH). The methylene protons appeared at δ 3.21 (singlet, two protons of N*CH*$_2$$CO_2H$); 2.87 (doublet of doublet with *J* = 12.9 and 3.3 Hz, one proton of C*H*$_2$$NH_2$), 2.70 (doublet of doublet, with *J* = 12.0 and 9.0 Hz, one proton of C*H*$_2$$NH_2$); 2.20 (doublet with *J* = 6.3 Hz, two protons of C*H*$_2$CONH); 1.46-1.39 (multiplet, two protons of CHC*H*$_2$CH) and methyl protons appeared at δ 2.45 (singlet, three protons of NC*H*$_3$) in the ^1H NMR spectrum. The ^{13}C NMR spectrum gave chiral carbons at δ 65.6, 45.0; methylene carbons at δ 60.9, 45.2, 41.1, 39.5; *N*-methyl carbon at δ 43.9; acid carbon (*C*OOH) at δ 177.2 and amide

carbon (*C*ONH) at δ 170.9. The physical and spectroscopic data of **2** were in full agreement with the literature data.[9]

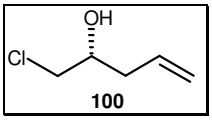
4.2.5. Conclusions

In conclusion, a practical and efficient strategy has been developed for the syntheses of 1,3-aminoalcohol. The synthetic strategy is amenable to both *syn*-and *anti*-1,3- aminoalcohol with high degree of enantio- and diastereoselectivities. The desired stereocentres can simply be achieved by changing the catalyst at HKR step. The synthetic protocol has been well utilized for the syntheses of (+)-negamycin **2**, in which both the stereocentres were established by hydrolytic kinetic resolution. Further application of this methodology to the syntheses of all the isomers of negamycin with variations at *C*-terminal as well as at *N*-terminal and other biologically active compounds for the studies of structure activity relationship is currently underway in our laboratory.

4.2.6. Experimental Section

(*R*)-Epichlorohydrin [(*R*)-98]: The racemic epichlorohydrin (±)-**98** was resolved to chiral epoxide (*R*)-**98** in high enantiomeric excess by the HKR method following a literature procedure.[13b] $[\alpha]_D^{25} = -11.3$ (neat); lit.[13b] $[\alpha]_D^{25} = -11.6$ (neat).

(*R*)-1-Chloropent-4-en-2-ol (100):



100

A round bottom flask was charged with copper (I) iodide (205 mg, 1.08 mmol), gently heated under vacuum, and slowly cooled with a flow of argon, and to this dry diethyl ether (50 mL) was added. This suspension was cooled to –20 ^{o}C and vigorously stirred, and vinylmagnesium bromide (1M in THF, 216 mL, 216.16 mmol) was injected to it. A solution of epichlorohydrin **(±)-98** (10 g, 108.08 mmol) in diethyl ether (20 mL) was added slowly to the above reagent, and the mixture was stirred at –73 ^{o}C to –40 ^{o}C for 19 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated to afford the crude homoallylic alcohol **100** which on vacuum distillation provided homoallylic alcohol **100** as a colorless liquid.

Yield: 9.12 g (70%).

Mol. Formula: C_5H_9ClO

B.P: 66-69 ^oC/21 mm of Hg

$[\alpha]_D^{25}$: –2.2 (*c* 0.47, CH_2Cl_2);

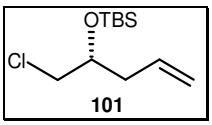
IR (neat, cm^{-1}): ν_{max} 3400, 3078, 2931, 2975, 1562, 1457, 1432, 1243, 1071, 914.

^{1}H NMR (200 MHz, $CDCl_3$): 2.34 (t, *J* = 8.1 Hz, 2H), 3.54 (d, *J* = 8.1 Hz, 2H), 3.85-3.90 (m, 1H), 5.08-5.19 (m, 2H), 5.74-5.87 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 38.4, 48.9, 70.4, 118.1, 133.2.

Analysis: Calcd.: C, 49.80; H, 7.52; Cl, 29.40%; **Found:** C, 49.91; H, 7.38; Cl, 29.56%.

((*R*)-1-Chloropent-4-en-2-yloxy)(*tert*-butyl)dimethylsilane (101):



101

To a stirred solution of alcohol **100** (1.0 g, 8.29 mmol) in CH_2Cl_2 (25 mL) was added imidazole (790 mg, 11.61 mmol). To this solution *t*-butyldimethylchlorosilane (1.37 g, 9.12 mmol) was added at 0 ^oC and reaction was stirred at room temperature for 4 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2 (3 × 50 mL). The extract was washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using pet ether/EtOAc (19:1) as eluent provided **101** as a colorless liquid.

Yield: 1.53 g (98%).

Mol. Formula: $C_{11}H_{23}ClOSi$

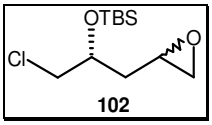
$[\alpha]_D^{25}$: –14.97 (*c* 0.42, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): 0.10 (s, 3H), 0.11 (s, 3H), 0.90 (s, 9H), 2.32-2.41 (m, 2H), 3.44 (d, *J* = 5.1 Hz, 2H), 5.10-5.14 (m, 2H), 5.81-5.85 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ –4.6, 18.1, 25.8, 39.5, 47.9, 72.2, 117.9, 133.6.

Analysis: Calcd.: C, 56.26; H, 9.87; Cl, 15.10 %; **Found:** C, 56.51; H, 9.62; Cl, 15.22%.

1-Chloro-3-oxiran-2-yl(propan-2-yloxy)(*tert*-butyl)dimethylsilane (101).



102

To a stirred solution of olefin **101** (1.0 g, 4.25 mmol) in CH_2Cl_2 (50 mL) at 0 ^oC was added *m*-CPBA (50%) (2.20 g, 6.38 mmol). The reaction mixture was stirred at room temperature for 10 h and quenched by saturated $NaHCO_3$ solution, extracted with CH_2Cl_2, washed with sat. $NaHCO_3$ and brine, dried (Na_2SO_4), concentrated and purified by silica gel column chromatography using pet ether/EtOAc (9:1) as eluent to yield the epoxide **102** as a colorless liquid in diastereomeric mixture (*anti*:*syn* = 3.0:1).

Yield: 1.01 g (88%).

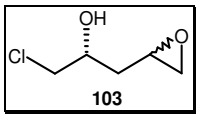
Mol. Formula: $C_{11}H_{23}ClO_2Si$

$[\alpha]_D^{25}$: −8.89 (*c* 0.5, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.12 (s, 3H), 0.14 (s, 3H), 0.92 (S, 9H), 1.27-1.31 (m, 2H), 1.70-1.78 (m, 1H), 1.82-1.92 (m, 1H), 2.48-2.54 (m, 1H), 2.77-2.83 (m, 1H), 3.03-3.08 (m, 1H), 4.04-4.10 (m, 1H) (mixture of diastereomers).

^{13}C NMR (50 MHz, $CDCl_3$): δ −5.1, −4.6; 13.9, 17.9; 23.6, 24.3; 25.7, 26.9; 31.6, 31.9; 42.4, 42.9; 46.4, 47.3; 49.4, 49.7; 66.4, 66.6 (mixture of diastereomers).

(*R*)-1-Chloro-3-(oxiran-2-yl)propan-2-ol (103):



103

Compound **103** was prepared following the procedure as described for compound **101** in 88% yield as a colorless liquid in diastereomeric mixture *anti*:*syn* = 1.0:1.2).

Mol. Formula: $C_5H_9ClO_2$

IR (neat, cm^{-1}): ν_{max} 3436, 3192, 2968, 2932, 2852, 1471, 1379, 1265, 1206, 1101, 944, 878

^{1}H NMR (200 MHz, $CDCl_3$): 4.06-4.10 (m, 1H), 3.46 (d, *J* = 5.4 Hz, 2H), 3.02-3.05 (m, 1H), 2.81-2.84 (m, 1H), 2.52-2.54 (m, 1H), 1.82-1.86 (m, 1H), 1.71-1.74 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 66.5, 66.3, 49.6, 49.3, 48.2, 46.3, 42.9, 42.3, 25.7, 24.2 ppm (both the diastereomers).

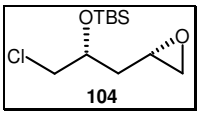
Analysis: Calcd.: C, 43.97; H, 6.64; Cl, 25.96%; **Found:** C, 44.21; H, 6.57; Cl, 25.88%.

Compound 104 and 105.

A solution of epoxide **103** (4 g, 15.94 mmol) and (*S,S*)-Salen-Co(III)-OAc (0.052 g, 0.08 mmol) in THF (0.2 mL) was stirred at 0 ^oC for 5 min, and then distilled water (172 μL, 9.56 mmol) was added. After stirring for 24 h, it was concentrated and purified by silica gel

column chromatography using pet ether/EtOAc (9:1) to afford **104** as a yellow color liquid. Continued chromatography with pet ether/EtOAc (3:2) provided the diol **105** as a brown color liquid as a single diastereomer.

Epoxide 104.



104

Yield: 1.84 g (46%)

Mol. Formula: $C_{11}H_{23}ClO_2Si$

$[\alpha]_D^{25}$: +24.0 (*c* 0.52, $CHCl_3$).

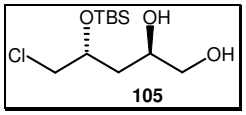
IR (neat, cm^{-1}): ν_{max} 3020, 2959, 2930, 1858, 1472, 1463, 1379, 1256, 1218, 1104, 1008, 940, 879, 760.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.12 (s, 3H), 0.13 (s, 3H), 0.91 (s, 9H), 0.69 (ddd, *J* = 7.3, 3.9 Hz, 1H), 1.85 (ddd, *J* = 7.3, 4.4 Hz, 1H), 2.53 (q, *J* = 5.3 Hz, 1H), 2.82 (t, *J* = 4.4 Hz, 1H), 3.02–3.06 (m, 1H), 3.49 (d, *J* = 5.4 Hz, 2H), 4.06–4.10 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.9, -4.6, 17.9, 25.7, 38.3, 47.5, 48.5, 49.1, 70.4.

Analysis: Calcd.: C, 52.67; H, 9.24; Cl, 14.13%.; **Found:** C, 52.74; H, 9.11; Cl, 14.31%.

Diol 105.



105

Yield: 1.92 g (45%)

Mol. Formula: $C_{11}H_{25}ClO_3Si$

$[\alpha]_D^{25}$: –34.9 (*c* = 0.94, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 3430, 3018, 2957, 2931, 2859, 1652, 1471, 1379, 1256, 1212, 1101, 1036, 971, 869, 758.

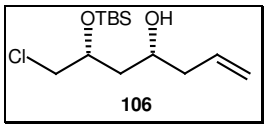
^{1}H NMR (200 MHz, $CDCl_3$): = 0.13 (s, 3H), 0.12 (s, 3H), 0.91 (s, 9H), 1.32-1.50 (m, 2H), 1.67-1.81 (m, 2H), 3.45 (d, *J* = 5.5 Hz, 2H), 3.46-3.71 (m, 2H), 4.02-4.16 (m, 1H), 4.24-4.32 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ -5.1, -4.7, 17.7, 25.6, 41.1, 47.8, 66.3, 66.7, 68.9.

Analysis: Calcd.: C, 49.14; H, 9.37; Cl, 13.19%; **Found:** C, 49.28; H, 9.19; Cl, 13.26%.

Conversion of 105 into 104: Diol **105** (2 g, 7.43 mmol) was dissolved under argon in dry CH_2Cl_2 (25 mL) and treated with pivaloyl chloride (0.986 g, 8.13 mmol), Et_3N (0.903 g, 8.92 mmol) and catalytic amount of DMAP. The mixture was stirred at room temperature for 2 h, then worked up (extraction with CH_2Cl_2). Removal of volatiles under reduced pressure gave an oily crude mono pivalate. The crude compound was then dissolved under argon in dry CH_2Cl_2 (30 mL) and treated with MsCl (0.937 g, 8.18 mmol), Et_3N (1.50 g, 14.87 mmol) and catalytic amount of DMAP. The reaction mixture was stirred at room temperature for 1 h and then quenched with water. The water layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated to give a crude product which was dissolved in MeOH (20 mL) and treated with K_2CO_3 (2.26 g, 16.36 mmol). The reaction mixture was then stirred overnight at room temperature and filtered through Celite. Removal of volatile under reduced pressure and column chromatography on silica gel using pet ether/EtOAc (19:1) as eluent gave the epoxide **104** (1.15 g, overall yield 62%) as a yellow color liquid.

(4*R*,6*R*)-6-(*tert*-Butyldimethylsilyloxy)-7-chlorohept-1-en-4-ol (106):



106

A round bottom flask was charged with copper (I) iodide (15 mg, 0.08 mmol), gently heated under vacuum, and slowly cooled with a flow of argon, and dry THF (20 mL) was added. This suspension was cooled to –20 ^oC and vigorously stirred, and vinylmagnesium bromide (1M in THF, 15.9 mL, 15.9 mmol) was injected to it. A solution of propylene oxide **104** (2.0 g, 7.97 mmol) in THF (10 mL) was added slowly to the above reagent, and the mixture was stirred at –20 ^oC for 12 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using pet ether/EtOAc (8:2) as eluent provided **106** as a colorless liquid.

Yield: 1.91 g (86%).

Mol. Formula: $C_{13}H_{27}ClO_2Si$.

$[\alpha]_D^{25}$: +31.9 (*c* 0. 71, $CHCl_3$).

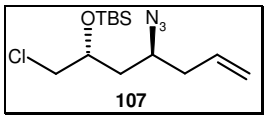
IR (neat, cm^{-1}): ν_{max} 3460, 2959, 2857, 1640, 1448, 1376, 1255, 1078.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.80 (s, 9H), 1.61–1.95 (m, 2H), 2.13 (t, *J* = 10.1 Hz, 2H), 3.43 (d, *J* = 5.2 Hz, 2H), 3.81-3.83 (m, 1H), 4.03-4.08 (m, 1H), (5.03–5.06 (m, 2H), 5.71–5.77 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ –5.1, –4.8, 13.9, 17.7, 25.5, 42.3, 47.9, 66.9, 70.2, 117.4, 134.2.

Analysis: Calcd.: C, 55.99; H, 9.76; Cl, 12.71%; **Found:** C, 56.21; H, 9.58; Cl, 12.91%.

((2*R*,4*S*)-4-Azido-1-chlorohept-6-en-2-yloxy)(*tert*-butyl)dimethylsilane (107):



107

The homoallylic alcohol **106** (0.95 g, 3.40 mmol) was dissolved under argon in dry CH_2Cl_2 (30 mL) and treated with MsCl (0.468 g, 4.08 mmol), Et_3N (0.689 g, 6.81 mmol) and catalytic amount of DMAP. The reaction mixture was stirred at room temperature for 1.5 h and then quenched with water. The water layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated to give a crude product, which was dissolved in dry DMF and treated with NaN_3 (0.551 g, 8.47 mmol) at room temperature. The reaction mixture was heated up to 80 ^oC and continued stirring for 9 h. The reaction mixture was quenched by addition of water at room temperature and the aqueous layer was extracted with EtOAc (3 × 40 mL). The combined organic extracts were washed with water (3 × 40 mL), brine, dried (N_2SO_4) and concentrated. Silica gel column chromatography of the crude product using pet ether/EtOAc (9:1) as eluent provided **107** as a yellowish syrupy liquid.

Yield: 0.921 g (89%).

Mol. Formula: $C_{13}H_{26}ClN_3OSi$

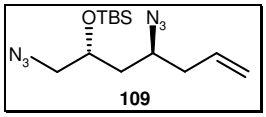
$[\alpha]_D^{25}$: +41.1 (*c* 0.51, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.80 (s, 9H), 1.62–1.97 (m, 2H), 2.13 (t, *J* = 10.1 Hz, 2H), 2.42 (m, 1H), 3.46 (d, *J* = 5.2 Hz, 2H), 4.02-4.10 (m, 1H), (5.03–5.06 (m, 2H), 5.71–5.77 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ –5.1, –4.8, 13.9, 17.7, 25.5, 42.3, 47.9, 54.8, 70.2, 117.6, 133.9.

Analysis: Calcd.: C, 51.38; H, 8.62; Cl, 11.67; N, 13.83%; **Found:** C, 51.53; H, 8.47; Cl, 11.66; N, 13.77%.

((2*R*,4*R*)-1,4-Diazidohept-6-en-2-yloxy)(*tert*-butyl)dimethylsilane (109):



109

Compound **106** (0.91 g, 2.99 mmol) was dissolved under argon in dry 2-butanone (8 mL) and was treated with NaI (0.897 g, 5.98 mmol). The reaction mixture was refluxed and was continued for further 6 h. After cooling to room temperature the volatiles were removed under reduced pressure to give an oily crude iodide (**108**). The crude compound was then dissolved under argon in dry DMF (30 mL) and treated with NaN_3 (0.389 g, 5.98 mmol) at room temperature. The reaction mixture was heated up to 80 ^oC and continued stirring for 4 h. The reaction mixture was then quenched by addition of *water* at room temperature and the aqueous layer was extracted with EtOAc (3 × 40 mL). The combined organic extracts were washed with water (3 × 40 mL), brine, dried (N_2SO_4) and concentrated. Silica gel column chromatography of the crude product using pet ether/EtOAc (8.5:1.5) as eluent provided **109** as a yellowish syrupy liquid.

Yield: 827 mg (89%).

Mol. Formula: $C_{13}H_{26}N_6OSi$

$[\alpha]_D^{25}$: +8.83 (*c* 0.61, $CHCl_3$).

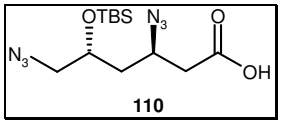
IR (neat, cm^{-1}): ν_{max} 2154, 1744, 1696.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.01 (s, 3H), 0.03 (s, 3H), 0.91 (s, 9H), 1.36-1.48 (m, 2H), 2.13 (t, *J* = 10.1 Hz, 2H), 3.29 (dd, *J* = 13.0, 4.1 Hz, 1H), 3.52 (dd, *J* = 13.0, 4.0 Hz, 1H), 3.74 (m, 1H), 3.89 (m, 1H), 5.03–5.06 (m, 2H), 5.71–5.77 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ –4.9, –4.6, 18.0, 25.8, 37.3, 42.3, 48.7, 55.9, 70.7

Analysis: Calcd.: C, 50.29; H, 8.44; N, 27.07%; **Found:** C, 50.45; H, 8.19; N, 27.01%.

(3*R*,5*R*)-3,6-Diazido-5-(*tert*-butyldimethylsilyloxy)hexanoic acid (110):



110

Compound **109** was dissolved in 14 ml of 2:2:3 CCl_4–CH_3CN–H_2O, $NaIO_4$ (323 mg, 1.51 mmol) and $RuCl_3.3H_2O$ (10 mg, 0.027 mmol) was then added. The resulting mixture was stirred vigorously at room temperature for 3 h. The mixture was extracted with CH_2Cl_2 (3 X 30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using pet ether/EtOAc (9:1) as eluent provided **110** as a brown color syrupy liquid.

Yield: 312 mg (69%).

Mol. Formula: $C_{12}H_{24}N_6O_3Si$

$[\alpha]_D^{25}$: +34.2 (*c* 0.51, $CHCl_3$)

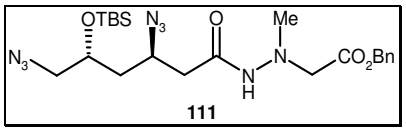
IR (neat, cm^{-1}): ν_{max} 3420, 2150, 1715, 1698.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.01 (s, 3H), 0.03 (s, 3H), 0.91 (s, 9H), 1.36-1.48 (m, 2H), 1.93-1.86 (m, 1H), 2.10-1.98 (m, 1H), 2.67 (d, *J* = 7.2 Hz, 2H), 3.29 (dd, *J* = 13.0, 4.1 Hz, 1H), 3.52 (dd, *J* = 13.0, 4.0 Hz, 1H), 3.74 (m, 1H), 3.89 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ –4.9, –4.6, 17.9, 25.7, 36.2, 37.3, 48.7, 55.8, 70.7, 176.2.

Analysis: Calcd.: C, 43.88; H, 7.37; N, 25.59%; **Found:** C, 44.01; H, 7.27; N, 25.76%.

Benzyl 2-(2-((3*R*,5*R*)-3,6-diazido-5-(*tert*-butyldimethylsilyloxy)hexanoyl)-1-methylhydrazinyl)acetate (111):



111

To an ice-cold stirred mixture of **110** (289 mg, 0.88 mmol) and triethylamine (124 mg, 1.23 mmol) in toluene (10 mL) was added dropwise a solution of ethyl chloroformate (134 mg, 1.23 mmol) in toluene (3 mL). After being stirred for 30 min at 0 ^oC, a solution of benzyl (1-methylhydrazino)acetate (205 mg, 1.05 mmol) in toluene (3 mL) was added dropwise to the reaction mixture with stirring at 0 ^oC. The stirring was continued for 2 h at 0 ^oC and then 10 h at room temperature. The reaction mixture was diluted with benzene (10 mL), and the resulting precipitates (triethylamine hydrochloride) were filtered. The filtrate was washed with water and then with saturated aqueous solution of $NaHCO_3$, and dried (Na_2SO_4). After evaporation of the solvent, the crude product was purified by chromatography on silica gel with pet ether/EtOAc (1:2) to provide **111** as pale yellow oil.

Yield: 292 mg (65%).

Mol. Formula: $C_{22}H_{36}N_8O_4Si$

$[\alpha]_D^{25}$: +32.0 (*c* 0.41, $CHCl_3$).

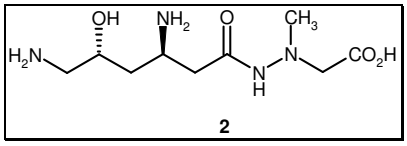
IR (neat, cm^{-1}): ν_{max} 3246, 2102, 1751, 1676, 1605, 1585.

^{1}H NMR (200 MHz, $CDCl_3$): 0.11 (s, 3/2 H), 0.12 (s, 3H), 0.13 (s, 3/2 H), 0.90 (s, 9H), 1.40-1.54 (m, 1H), 1.54-1.72 (m, 1H), 2.31 (d, *J* = 7.0 Hz, 1H), 2.42-2.73 (br m, 1H), 2.55 (s, 3/2 H, NMe), 3.17 (dt, *J* = 13.0, 5.0, 5.0 Hz, 1H), 3.48 (dt, *J* = 13.0, 4.0, 4.0 Hz, 1H), 3.53 (br d, 1H), 3.74 (d, *J* = 18.5 Hz, 1H), 3.87-4.04 (br m, 2H), 5.12 (s, 1H), 5.13 (br s, 1H), 7.26-7.44 (m, 5H), 8.46 (br s, ½ H, NH), 9.33 (s, ½ H, NH).

^{13}C NMR (50 MHz, $CDCl_3$): δ –4.9, –4.6, 17.9, 25.7, 34.0, 36.6, 37.6, 44.1, 45.0, 48.3, 48.5, 49.1, 55.6, 55.8, 57.7, 58.4, 66.5, 66.8, 127.7, 127.8, 128.0, 128.1, 169.7, 169.8, 170.1, 170.2, 174.1, 174.2.

Analysis: Calcd.: C, 52.36; H, 7.19; N, 22.20%; **Found:** C, 52.48; H, 7.03; N, 22.43%.

(+)-Negamycin:



2

To a solution of **111** (0.2 g, 0.22 mmol, 1 equiv) in methanol (15 mL) were added acetic acid (1.2 g, 20 mmol) and water (4 mL). To this clear solution was added in portions 10% Pd/C (0.06 g, 0.056 mmol, 0.25 equiv), and the mixture was hydrogenated under H_2 and at 75 °C for 5-5.5 h. The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure. The residue was dissolved in water and purified on Amberlite CG-50 resin (NH_4^+ form), eluting with 1.5% aq NH_4OH. The eluents were concentrated under reduced pressure to furnish 0.043 g (75%) of **2** as a white powder.

Yield: 11.30 g (89%).

Mol. Formula: $C_9H_{20}N_4O_4$

$[\alpha]_D^{25}$ +2.1 (*c* 0.72, H_2O); lit.[9h] $[\alpha]_D^{25}$ +1.7 (*c* 0.6, H_2O); lit.[8b] +2.3 (*c* 4.07, H_2O).

IR (neat, cm^{-1}): ν_{max} 3650-2500, 1662, 1602, 1450, 1401, 1315, 1131.

^{1}H NMR (50 MHz, D_2O): ^{1}H NMR 3.86-3.78 (m, 1H), 3.30-3.18 (m, 1H), 3.21 (s, 2H), 2.87 (dd, 1H, J = 12.9, 3.3 Hz), 2.70 (dd, 1H, J = 12.9, 9.0 Hz), 2.45 (s, 3H), 2.20 (d, 2H, J = 6.3 Hz), 1.46-1.39 (m, 2H).

^{13}C NMR (50 MHz, D_2O): δ 177.2, 170.9, 65.6, 60.9, 45.2, 45.0, 43.9, 41.1, 39.5.

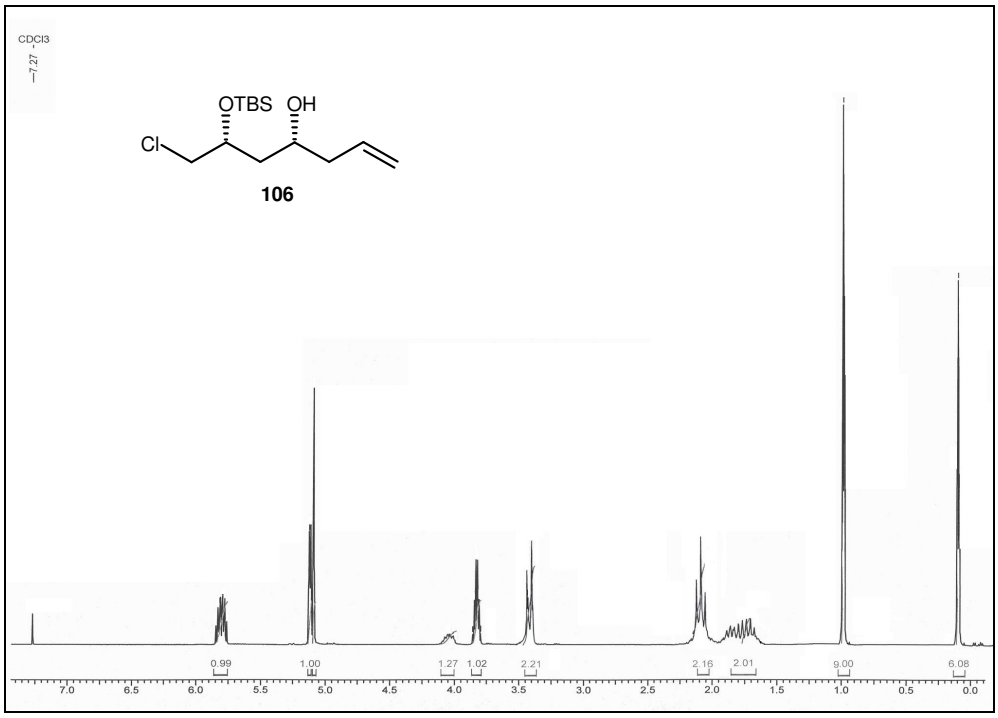
4.2.7. Spectra

1] ^{1}H NMR Spectrum of **106**

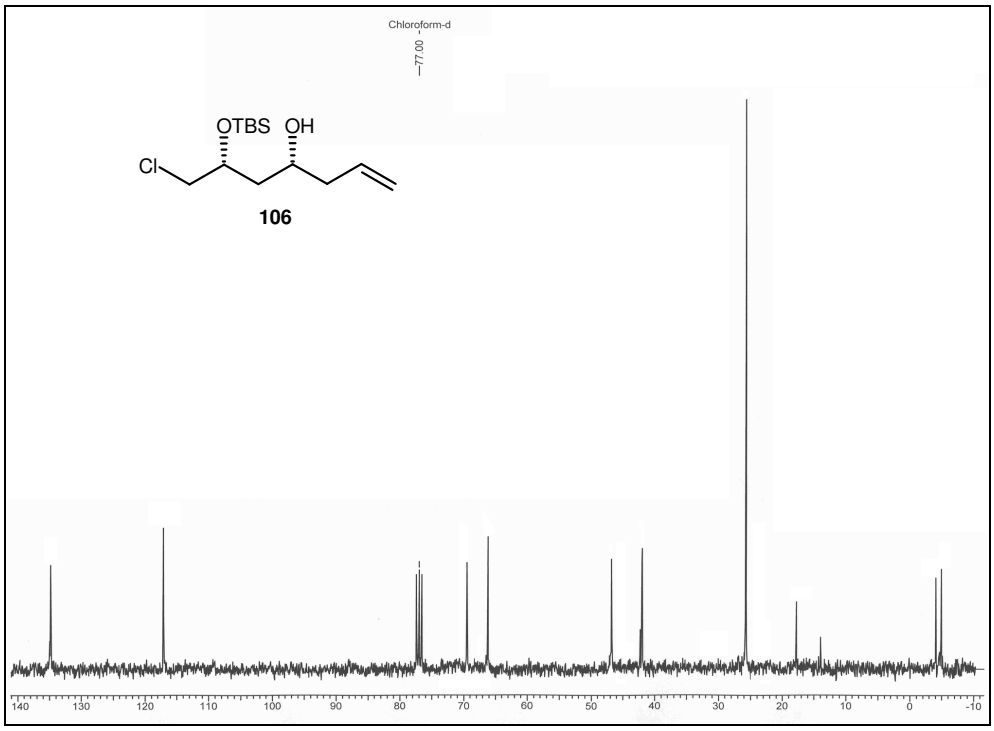
2] ^{13}C NMR Spectrum of **106**

3] ^{1}H NMR Spectrum of **2**

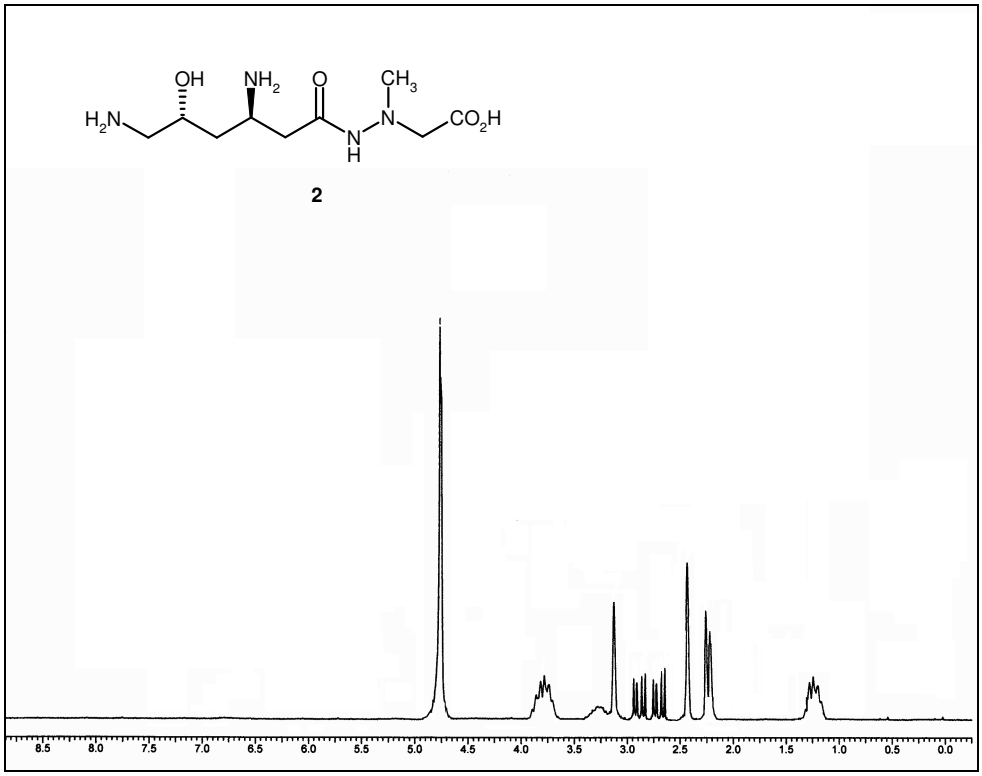
4] ^{13}C NMR Spectrum of **2**



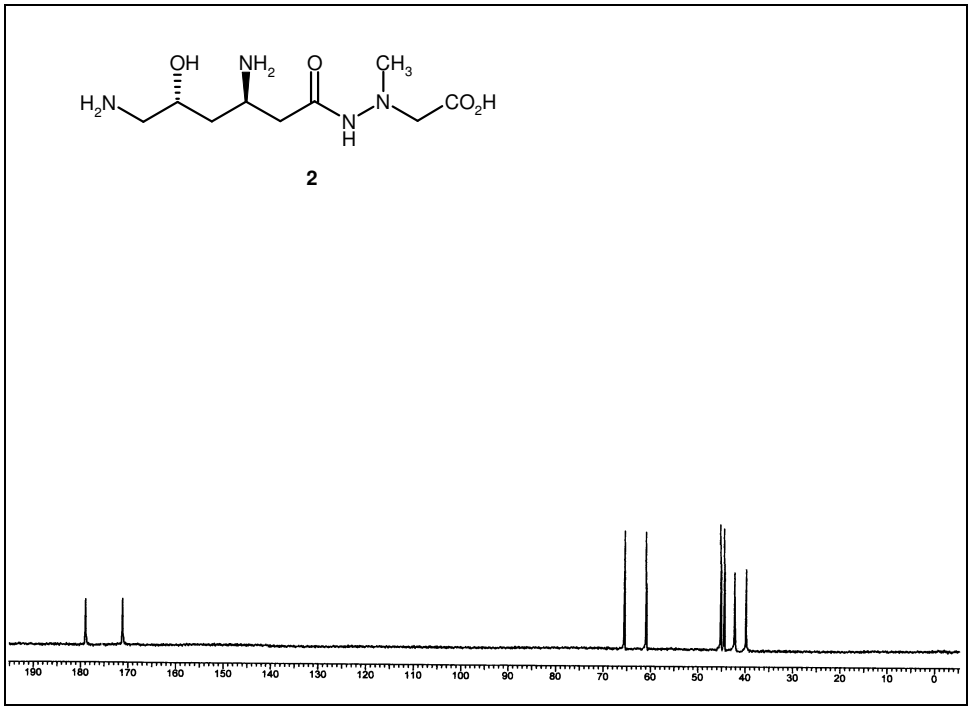
^{1}H NMR Spectrum of **106**



^{13}C NMR Spectrum of **106**



^{1}H NMR Spectrum of **2**



^{13}C NMR Spectrum of **2**

4.2.8. References:

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