ASYMMETRIC SYNTHESIS OF BIOACTIVE MOLECULES USING SHARPLESS ASYMMETRIC DIHYDROXYLATION, AMINO HYDROXYLATION AND JACOBSEN'S HYDROLYTIC KINETIC RESOLUTION

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BY

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CERTIFICATE

This is to certify that the work presented in the thesis entitled "**ASYMMETRIC SYNTHESIS OF BIOACTIVE MOLECULES USING SHARPLESS ASYMMETRIC DIHYDROXYLATION, AMINO HYDROXYLATION AND JACOBSEN'S HYDROLYTIC KINETIC RESOLUTION**" submitted by **Priti Gupta** was carried out by the candidate at National Chemical Laboratory, Pune under my supervision. Such materials as obtained from other sources have been duly acknowledged in the thesis.

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September 2007

CANDIDATE'S DECLARATION

I hereby declare that the thesis entitled "**ASYMMETRIC SYNTHESIS OF BIOACTIVE MOLECULES USING SHARPLESS ASYMMETRIC DIHYDROXYLATION, AMINO HYDROXYLATION AND JACOBSEN'S HYDROLYTIC KINETIC RESOLUTION**" 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 National Chemical Laboratory, Pune, India.

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September 2007

DEDICATED

TO MY

HUSBAND

Acknowledgements

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Priti Gupta

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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
Cat.	-	Catalytic
$CDCl_3$	-	Deuterated chloroform
DCM	-	Dichloromethane
DHP	-	Dihydropyran
$(DHQ)_2PHAL$	-	1,4-Bis(dihydroquinin-9-*O*-yl)phthalazine
$(DHQD)_2PHAL$	-	1,4-Bis(dihydroquinindin-9-*O*-yl)phthalazine
DDQ	-	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	-	Diisobutylaluminiumhydride
DMP	-	2,2-Dimethoxypropane
DMF	-	*N, N′*-Dimethylformamide
DMAP	-	*N,N′*-Dimethylaminopyridine
DMSO	-	Dimethyl sulfoxide
ee	-	Enantiomeric excess
equiv.	-	Equivalents
EtOH	-	Ethanol
Et	-	Ethyl
Et_2O	-	Diethyl ether
EtOAc	-	Ethyl acetate
Et_3N	-	Triethylamine
Hz	-	Hertz
IBX	-	Iodoxybenzoic Acid
Im	-	Imidazole
LDA	-	Lithium diisopropylamide
m-CPBA	-	*m*-Chloroperbenzoic acid
MeOH	-	Methanol
mg	-	Milligram

min	-	Minutes
mL	-	Millilitre
mmnol	-	Millimole
M. p.	-	Melting point
Ms	-	Methanesulfonyl
Me	-	Methyl
MeI	-	Methyl iodide
MEM	-	Methoxyethoxymethyl
$NaBH_4$	-	Sodiumborohydride
NaH	-	Sodium hydride
Ph	-	Phenyl
Py	-	Pyridine
PMB	-	*para*-Methoxy benzyl
p-TSA	-	*par*a-Toluenesulfonic acid
RCM	-	Ring closing metathesis
TEA	-	Triethylamine
TBAI	-	Tetra-*n*-butylammonium iodide
TBAF	-	Tetra-*n*-butylammonium fluoride
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, ninhydrin 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 synthesis of bioactive molecules using Sharpless asymmetric dihydroxylation, amino hydroxylation and Jacobsen's hydrolytic kinetic resolution"** is divided into five chapters.

Chapter 1: Describes a brief introduction to Sharpless asymmetric dihydroxylation (AD), aminohydroxylation and Jacobsen's hydrolytic kinetic resolution (HKR).

Chapter 2: Deals with the asymmetric synthesis of vicinal diols and amino alcohols and is further divided into two sections.

Chapter 3: Summarizes a simple and efficient approach to 1,3-polyols and its application to the synthesis of lactones.

Chapter 4: Constitutes the enantioselective synthesis of lactones.

Chapter 5: Covers the enantioselective total synthesis of two naturally occurring macrolactones and is divided into two sections.

Chapter 1: Introduction to Sharpless asymmetric dihydroxylation, aminohydroxylation and Jacobsen's hydrolytic kinetic resolution (HKR).

This chapter gives a brief introduction to Sharpless asymmetric dihydroxylation (AD),[1] asymmetric aminohydroxylation (AA)[2] and Jacobsen's hydrolytic kinetic resolution (HKR).[3]

The oxidation of olefins is considered as the single most versatile, powerful and reliable class of transformation in organic synthesis. The pioneering work of K. B. Sharpless on "Chirally catalyzed oxidation reactions" viz. the asymmetric epoxidation (AE) developed in early 1980 and the asymmetric dihydroxylation (AD) in early 1990 and newly developed asymmetric aminodihydroxylation (AA) in 1995, bagged him the 'Nobel Prize' (in part) in chemistry in 2001.

The hydrolytic kinetic resolution (HKR) of terminal epoxides catalyzed by chiral (salen) Co(III)OAc complex affords both recovered epoxides and 1,2-diol products in highly

enantio-enriched form. In many cases there exist no practical alternatives for accessing these valuable chiral building blocks from inexpensive racemic materials.

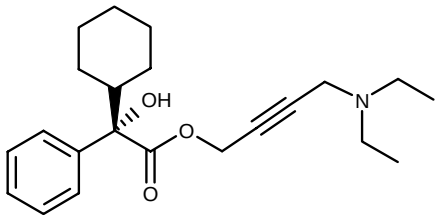
These methods have contributed to more advances in research not only in chemistry but also in material science, biology and medicine. This work gave access to new molecules needed to investigate hitherto undiscovered and unexplained phenomena in the molecular world.

In this chapter, we have described aforementioned catalytic reactions. During the course of our research work we have prepared chiral diols, amino alcohols and epoxides and successfully employed these synthetic intermediate towards the synthesis of oxybutynin, sulfobacin A and B, 1,3-polyols and macrolactones.

Chapter 2: Asymmetric synthesis of vicinal diols and amino alcohols.

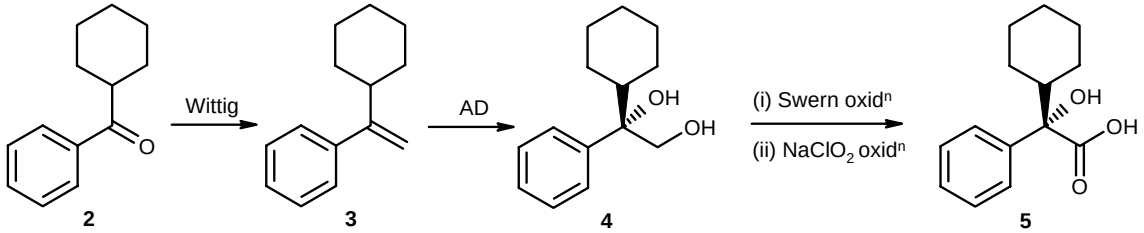
This chapter is further divided into two sections.

Section A: Asymmetric synthesis of (*S*)-oxybutynin



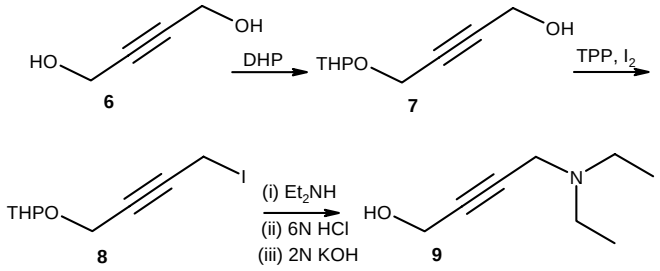
(*S*)-Oxybutynin **1**

(*S*)-Oxybutynin **1** is a widely prescribed muscarinic receptor antagonist used in the treatment of urinary frequency, urgency and urge incontinence.[4] Like the majority of muscarinic receptor antagonists, it is composed of a *tert*-α-hydroxy acid as a key component.[5] The chiral *tert*-α-hydroxy acid **5**, one of the components of the target molecule, was obtained by the Sharpless asymmetric dihydroxylation of α-cyclohexylstyrene **3** and subsequent oxidation of the 1^{o} hydroxy group to acid **5**.

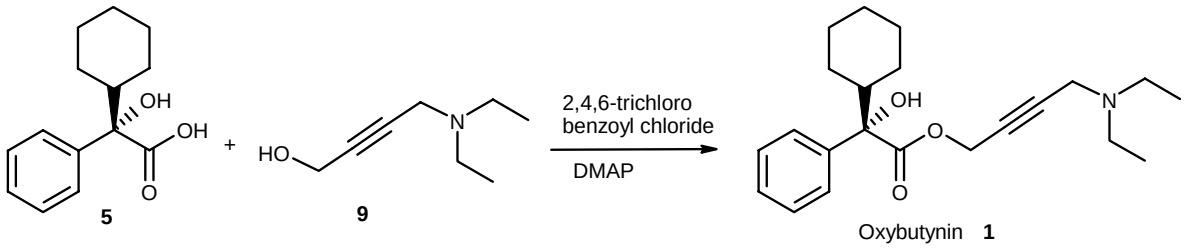


2 **3** **4** **5**

The other amino alcohol fragment **9** required for the oxybutynin synthesis was easily derived from 2-butyne-1,4-diol **6** by monoprotection as THP ether, substitution of hydroxyl with iodide and its subsequent displacement with amine followed by acid and base treatment.

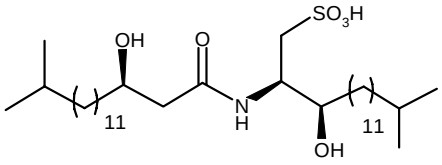


The final step involved the coupling of acid **5** with amino alcohol **9** which was performed by activating acid **5** as mixed anhydride and condensation with amino alcohol **9** to obtain the target molecule (*S*)-oxybutynin **1.**

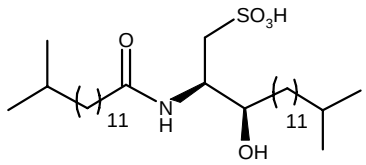


<u>Section B:</u> Total synthesis of sulfobacin A, sulfobacin B, topostin B567 and topostin D654

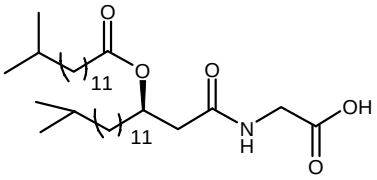
Sulfobacins A and B were isolated for the first time in 1995 by Kamiyama *et al.* from the culture broth of *Chryseobacterium* sp. NR 2993, a strain isolated from a soil sample collected on Iriomote Island.[6] These compounds are novel sulfonolipids and are unusual sphingosine derivatives. Biological studies of these compounds revealed to inhibit the binding of von Willebrand factor to the GPIb/IX receptors in a competitive manner with IC_{50s} of 0.47 μM for sulfobacin A and 2.2 μM for sulfobacin B, respectively. These compounds were also found to exhibit inhibitory activity against DNA polymerase α. Topostins were isolated from the culture broth of *Flexibacter topostinus* sp.[7] They have proved to be structurally novel inhibitors of mammalian DNA topoisomerase I.[8]



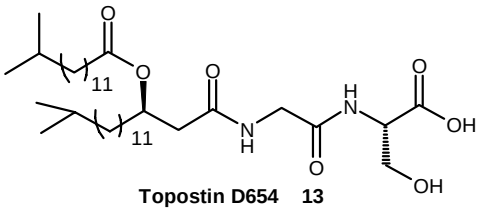
Sulfobacin A 10



Sulfobacin B 11

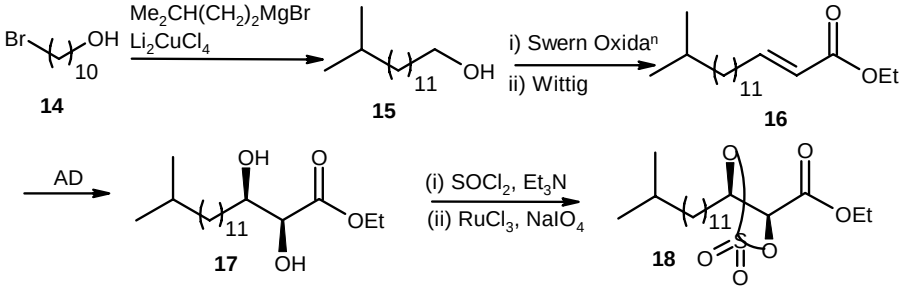


Topostin B567 12

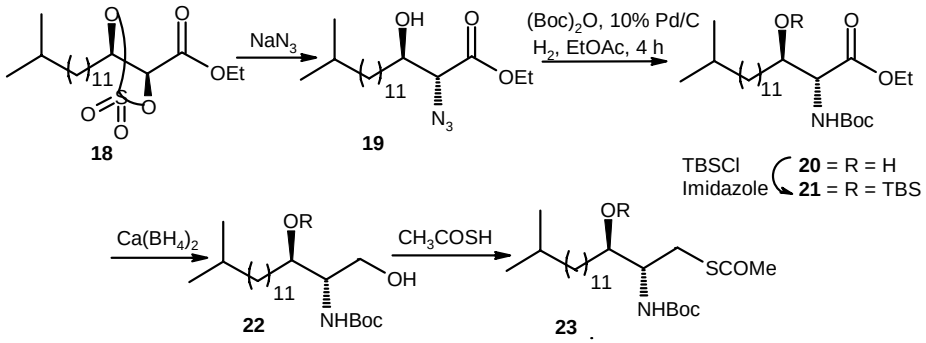


Topostin D654 13

We have accomplished the total synthesis of sulfobacin A, sulfobacin B, topostin B567 and topostin D654 from commercially available 1-bromodecanol **14**, employing Sharpless asymmetric dihydroxylation and regioselective opening of cyclic sulfate as the key steps. Thus Grignard reaction, Swern oxidation[9] and Wittig olefination followed by AD provided the diol **17**, which was further converted into cyclic sulfate[10] **18**, as a common intermediate for constructing both the fragments.

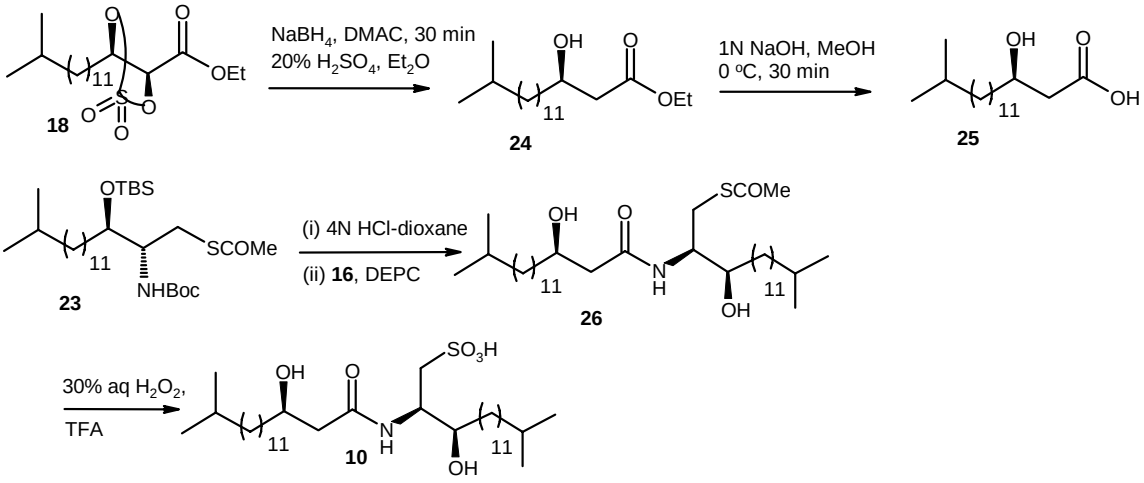


For the synthesis of thioester fragment **23**, cyclic sulfate **18** was opened with NaN_3 in a regioselective manner at α-position to give the azido alcohol **19** which was subjected to hydrogenation, reduction and Mitsunobu reaction to furnish the required thioester fragment **23**, which is common for both sulfobacin A and sulfobacin B.

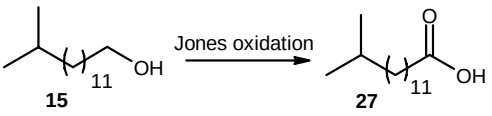


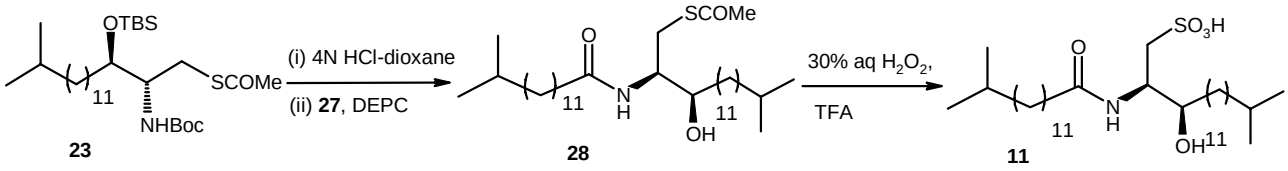
Synthesis of sulfobacin A: For the synthesis of β-hydroxy fragment **25**, the cyclic sulfate **18** was opened with hydride[11] followed by base treatment.

After deprotection of TBS and Boc protecting groups in **23**, coupling of both the fragments was easily achieved by DEPC to give **26** which on oxidation gave sulfobacin A **10**.

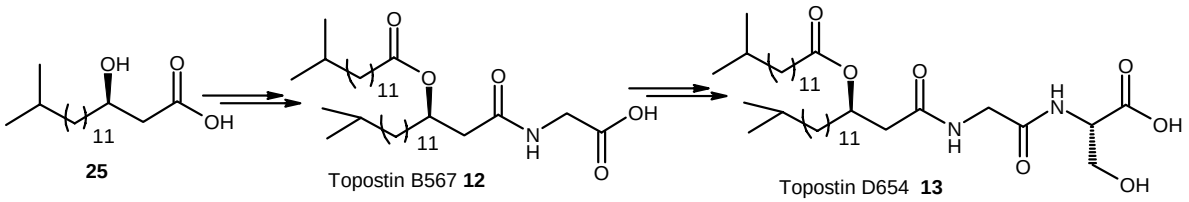


Synthesis of sulfobacin B: For the synthesis of required fragment **28**, alcohol **15** was converted into acid **27** by Jones oxidation. After deprotection of TBS and Boc protecting groups in **23**, coupling of both the fragments was easily achieved by DEPC followed by oxidation to give sulfobacin B **11**.





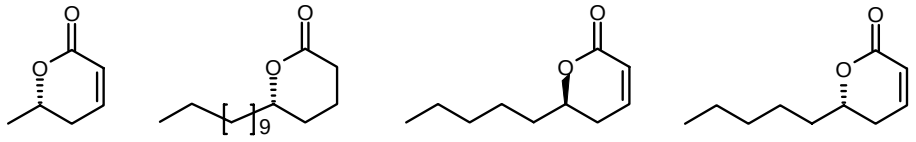
Synthesis of topostin B567 and topostin D654: Condensation of hydroxy acid **25** with glycine *tert*-butyl ester hydrochloride gave amine which on *O*-acylation with acid **27** afforded ester. Finally acidic deprotection of ester furnished the topostin B567 **12**. The coupling of topostin B567 with L-serine benzyl ester trifluoroacetate followed by benzyl deprotection provided topostin D654 **13**.



<u>Chapter 3:</u> Simple and efficient approach to 1,3-polyols: synthesis of massoialactone and kurzilactone.

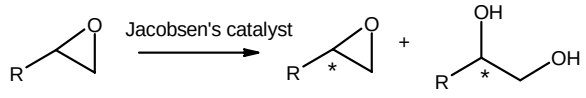
<u>Section A:</u> Enantioselective synthesis of massoialactone, parasorbic acid and hexadecanolide.

Chiral lactenones and lactones are functionalities commonly present in a number of natural products that function as pheromones or medicinal compounds. They often act as intermediates for the synthesis of other natural products. For example, (*S*)-(+)-5,6-dihydro-6-methyl-2*H*-pyran-2-one (parasorbic acid, **29**), a natural product isolated from mountain ash berries (*Sorbus aucuparia*), is an intermediate for the synthesis of several carbohydrate derived antibiotics.[12] Similarly, (*R*)-(–)-5,6-dihydro-6-pentyl-2*H*-pyran-2-one (massoialactone, **31**), isolated from bark oil of *Cryptocarya massoia*[13] and jasmine flowers[14] is also found in the defense secretion of two species of formicin ants of the genus *Camponotus*.[15] (*S*)-(–)-6-Undecyltetrahydropyran-2-one (hexadecanolide, **30**), isolated from the[16] mandibular glands of the oriental hornet *Vespa orientalis*, also contains a δ-valerolactone moiety.



Parasorbic acid **29** Hexadecanolide **30** (*R*)-Massoialactone **31** (*S*)-Massoialactone **32**

Racemic epoxides **33-35** were resolved using Jacobsen's catalyst to get the enantiopure epoxides and diols.

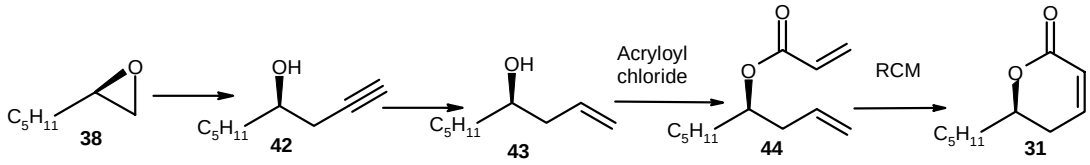


33: R= CH3
34: R=C11H23
35: R= C5H11

36: R= CH3
37: R=C11H23
38: R= C5H11

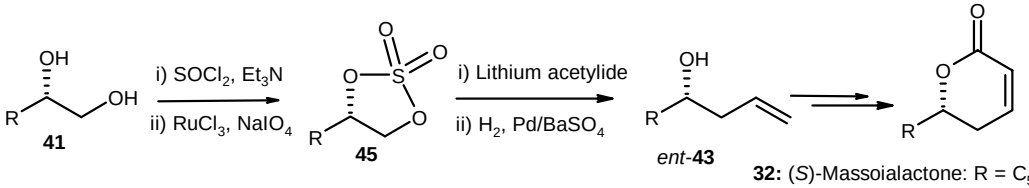
39: R= CH3
40: R=C11H23
41: R= C5H11

The epoxide **38** was opened with lithium acetylide followed by partial hydrogenation to get the homoallylic alcohol **43** which was esterified with acryloyl chloride followed by ring-closing metathesis[17] to get the lactones **31**.



38 **42** **43** **44** **31**

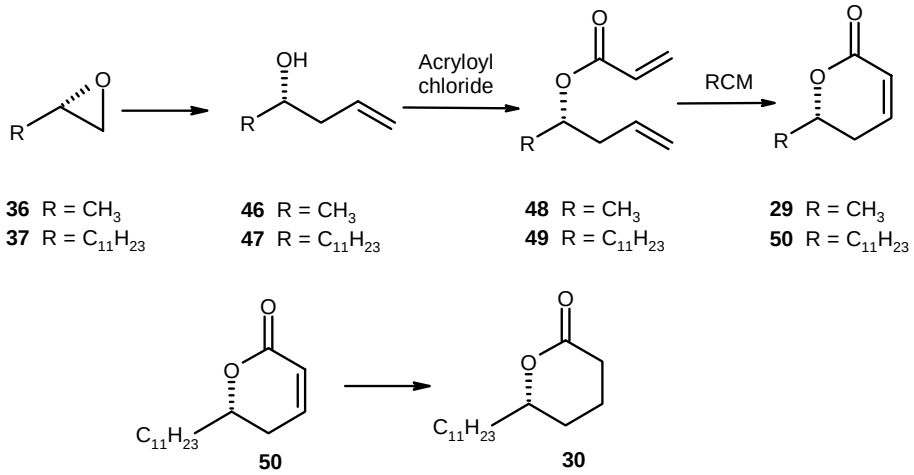
Similarly (*S*)-massoialactone was synthesized from diol **41**. Thus diol **41** was coverted into homoallylic alcohol ***ent*-43** *via* cyclic sulfate **45**, homoallylic alcohol ***ent*-43** was esterified followed by ring-closing metathesis[17] to obtain (*S*)-massoialactone.



41 **45** *ent*-**43**

32: (*S*)-Massoialactone: R = C_5H_{11}

For the synthesis of parasorbic acid and hexadecanolide epoxide **36** and **37** were opened with vinylmagnesium bromide to get the homoallylic alcohols **46** and **47** respectively, which were esterified with acryloyl chloride followed by ring-closing metathesis to get the lactones **29** and **50**. **50** was hydrogenated to get the naturally occurring hexadecanolide **30.**

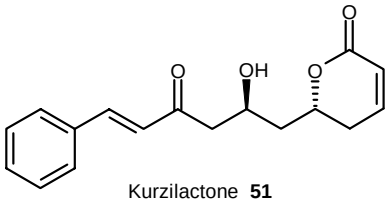


36 R = CH_3 **46** R = CH_3 **48** R = CH_3 **29** R = CH_3
37 R = $C_{11}H_{23}$ **47** R = $C_{11}H_{23}$ **49** R = $C_{11}H_{23}$ **50** R = $C_{11}H_{23}$

50 **30**

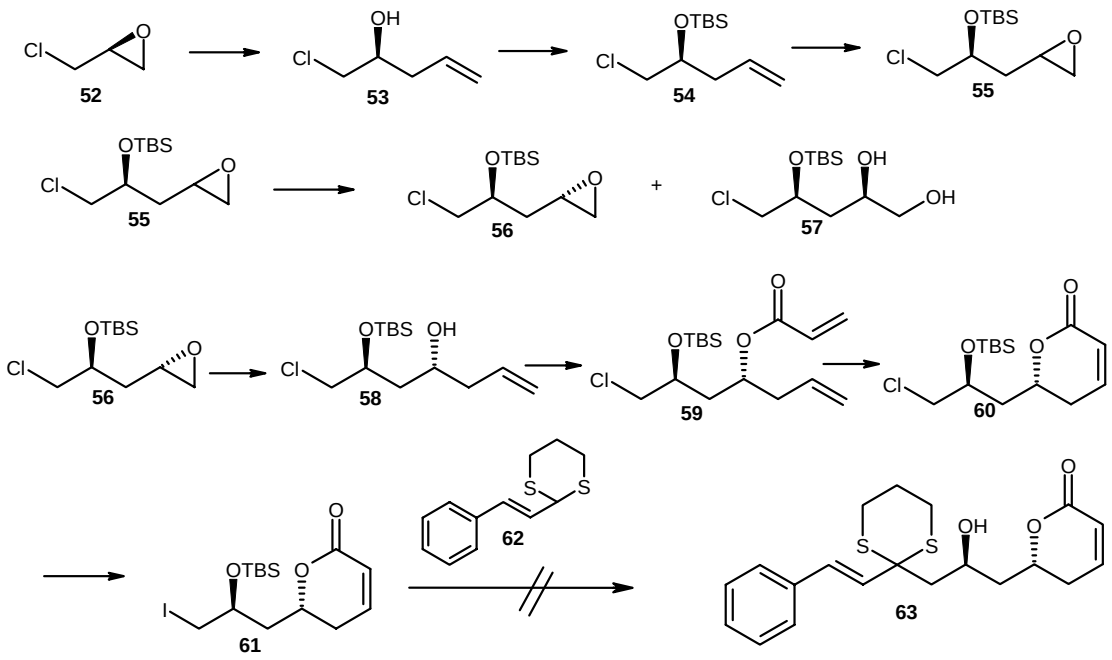
Section B: Attempted synthesis of kurzilactone

Kurzilactone **1**, a new Kawa-type lactone[18] was isolated from leaves of *Cryptocarya kurzii*, a plant which is indigenous to Malaysia. Kurzilactone shows remarkable cytotoxicity against KB cells (IC_{50} = μg/mL).[18a]



Kurzilactone **51**

The synthesis of kurzilactone **51** started with commercially available epichlorohydrin 5**2**, which was opened with vinylmagnesium bromide to give the homoallylic alcohol 5**3** which was protected as TBS ether followed by epoxidation to give the epoxide 5**5**. In order to prepare the diastereomerically pure epoxide, the epoxide 5**5** was resolved using (*S*,*S*)-salen Co(III)-OAc and water in THF to give the diastereomerically pure epoxide 5**6** as well as diol 5**7**. The epoxide was opened with vinylmagnesium bromide, esterified followed by ring-closing metathesis to furnish the lactone **60**. The chloro was substituted with iodo to get the lactone **61**. Our efforts to substitute iodo with dithiane **62** was a total failure and inspite of several attempts by using different reaction conditions, the reaction did not lead to the required compound **63**.

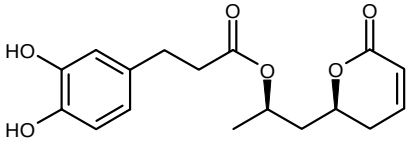


<u>Chapter 4:</u> Enantioselective synthesis of 1,3-polyols/5,6-dihydropyran-2-one: tarchonanthuslactone and cryptocarya diacetate

Optically active *syn*-and *anti*-1,3-polyols/5,6-dihydropyran-2-one are ubiquitous structural motifs in various biologically active compounds.[19] This chapter covers the synthesis of tarchonanthuslactone and cryptocarya diacetate and is divided into two sections**.**

<u>Section A:</u> Enantioselective synthesis of tarchonanthuslactone

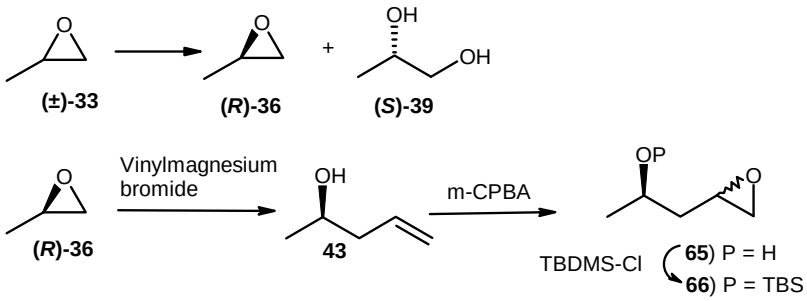
Tarchonanthualactone was isolated by Bohlmann from *Tarchonanthustrilobus compositae*.[20] It displays pharmacological properties of interest such as plant growth inhibition as well antifeedant, antifungal properties.[21]



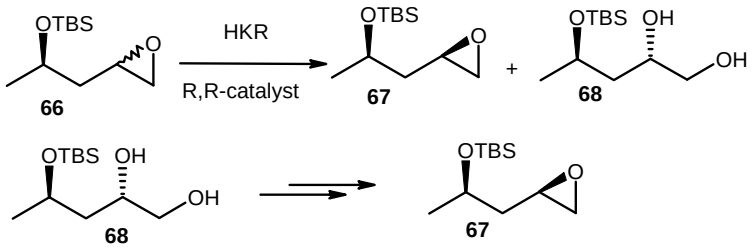
Tarchonanthuslactone **64**

In designing a route to **64**, we choose propylene oxide as an appropriate starting material. Our synthesis of **64** requires Jacobsen's hydrolytic kinetic resolution to install the stereogenic centers and ring-closing meathesis to construct the lactone moiety.

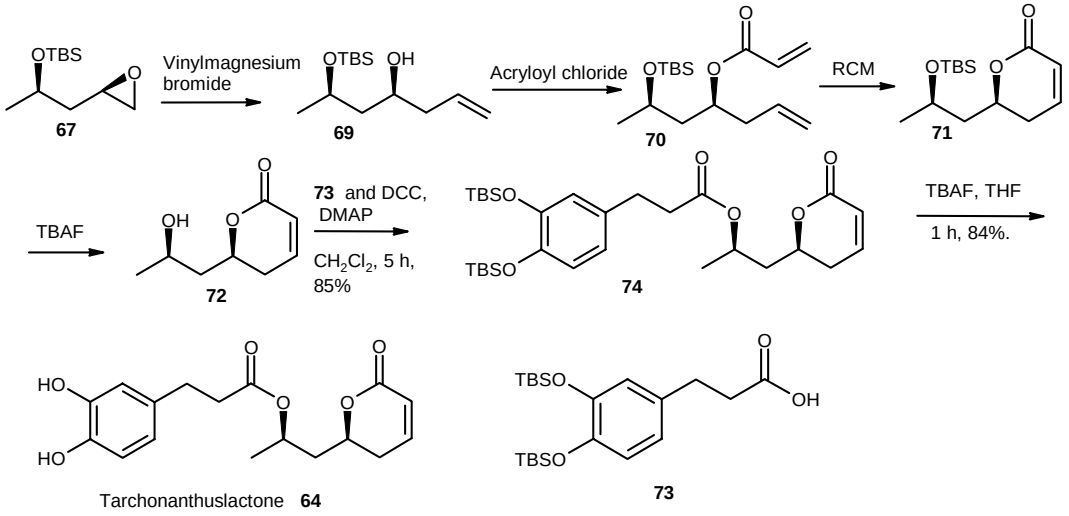
Thus racemic propylene oxide **(±)-33** was resolved by HKR method to give the enantiopure epoxide **(*R*)-36** and diol **(*S*)-39**. The epoxide **(*R*)-36** was opened with vinylmagnesium bromide followed by epoxidation and TBS protection to give the epoxide **66** as a mixture of *syn* and *anti* compounds.



In order to get the diastereomerically pure epoxide, the epoxide **66** was resolved using (*R*,*R*)-salen Co(III)-OAc and water in THF to give the diastereomerically pure epoxide **67** as well as diol **68**. This diol **68** was also converted to the required epoxide **67** via internal nucleophilic substitution of a secondary mesylate.[22]

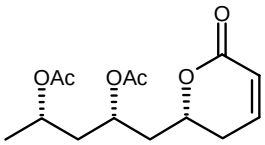


With substantial amount of epoxide **67** in hand we further proceeded for the synthesis of **64** by opening of epoxide with vinylmagnesium bromide followed by esterification and ring-closing metathesis to get the lactone moiety **71**. Further TBS was deprotected and lactone **72** was coupled with acid **73** followed by desilylation to furnish tarchonanthuslactone **64**.



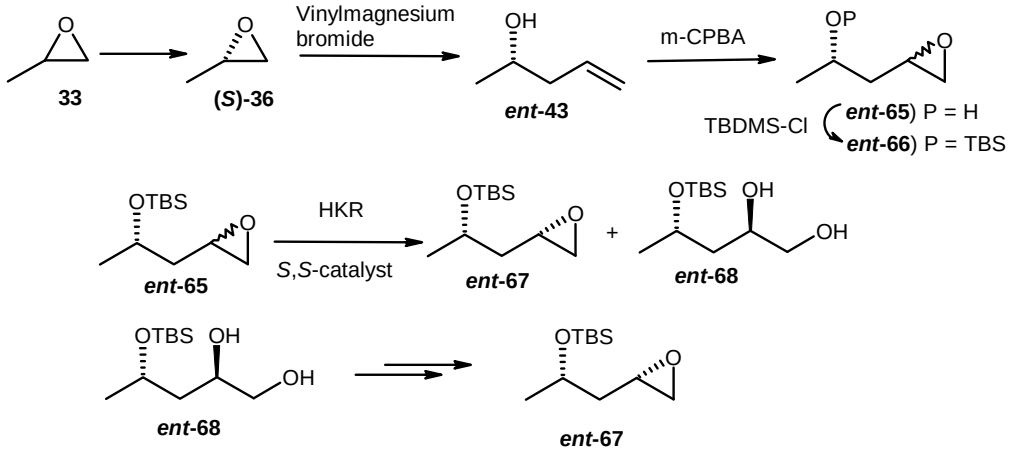
Section B: Enantioselective total synthesis of cryptocarya diacetate

Cryptocarya diacetate **75** was isolated from the leaves and bark of the South African plant *Cryptocayra latifolia*. Medicinal properties of this compounds range from the treatment of headaches and morning sickness to that of cancer, pulmonary diseases, and various bacterial and fungal infections.[23]

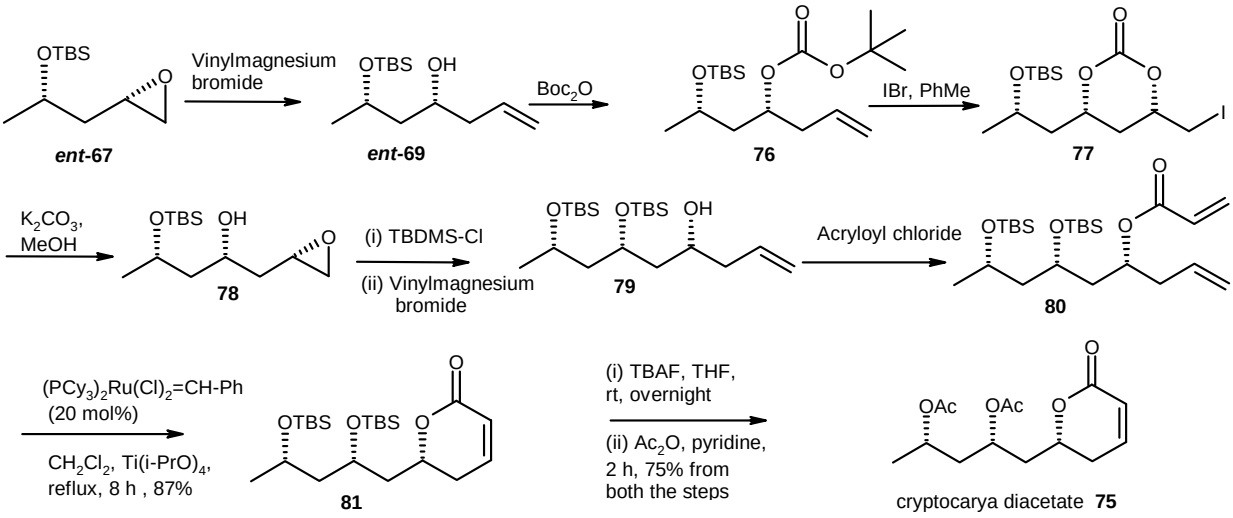


cryptocarya diacetate **75**

The epoxide **36** was prepared from propylene oxide **33** by using (*S*,*S*)-salen Co(III)-OAc catalyst in a similar manner as discussed earlier in foregoing section.



For generating third stereocentre, the epoxide ***ent*-67** was opened with vinyl Grignard followed by diastereoselective iodine induced electrophilic cyclization[24] and base treatment to afford the epoxide **78**, which was opened with vinyl Grignard, esterified and subjected to ring-closing metathesis to furnish the lactone **81**. Finally desilylation of lactone **81** followed by acylation gave cryptocarya diacetate **75**.

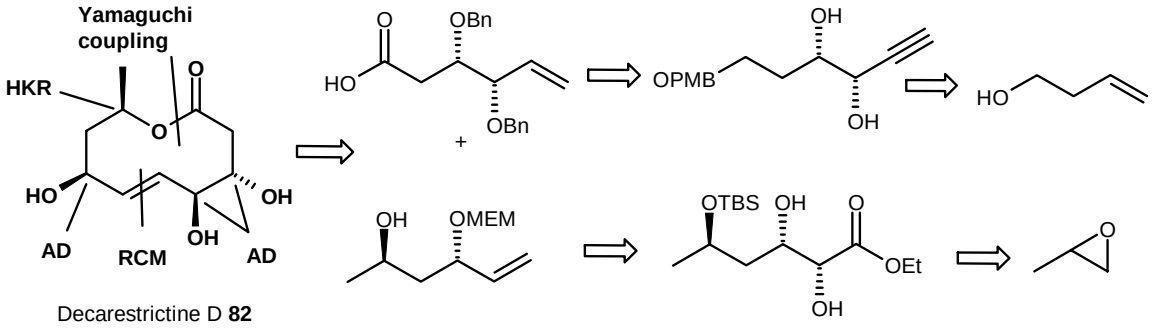


<u>Chapter 5:</u> Enantioselective total synthesis of macrolactones: decarestrictine D, herbarumin III.

This chapter is further divided into two section.

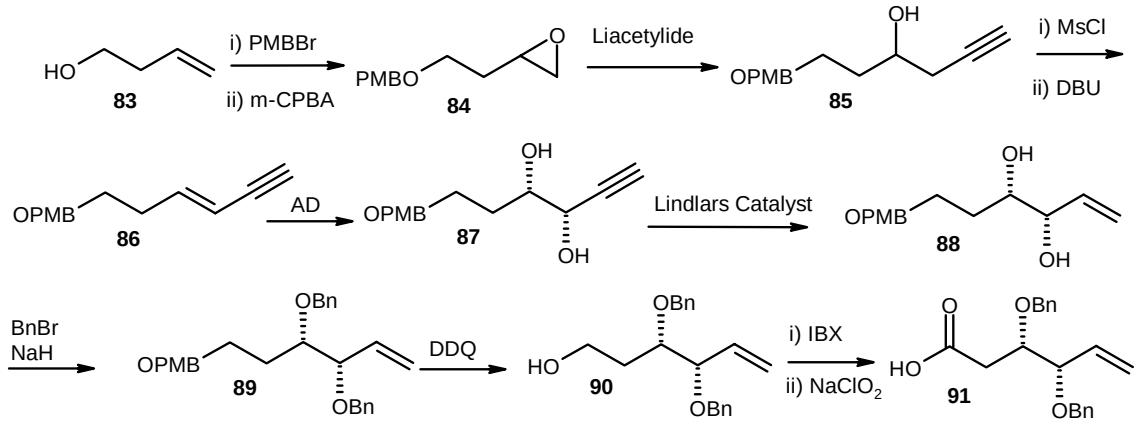
<u>Section A:</u> Total synthesis of decarestrictine D

Decarestrictine D **82**, isolated from *Penicillium corylophilum, simplicissimum*[25] is an important new member of a growing class of 10-membered lactone natural products.[25] A general panel of whole cell screens demonstrated that decarestrictine D (tuckolide) potently inhibits liver cell cholesterol biosynthesis (HEP cells, IC50 of 100 nm).[26] In addition, it appears that tuckolide is highly selective in that it exhibits no significant antibacterial, antifungal, antiprotozoal, or antiviral activity. Toxicity studies further revealed that tuckolide exhibits good tolerability, showing a lack of change in a standard set of defined safety parameters.

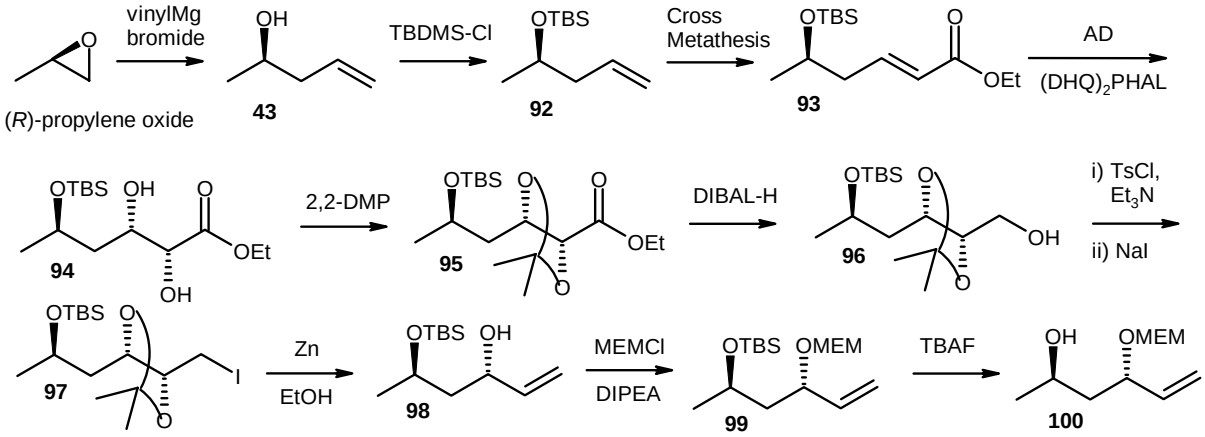


The synthesis of Decarestrictine D **82** started from commercially available propylene oxide and homoallylic alcohol.

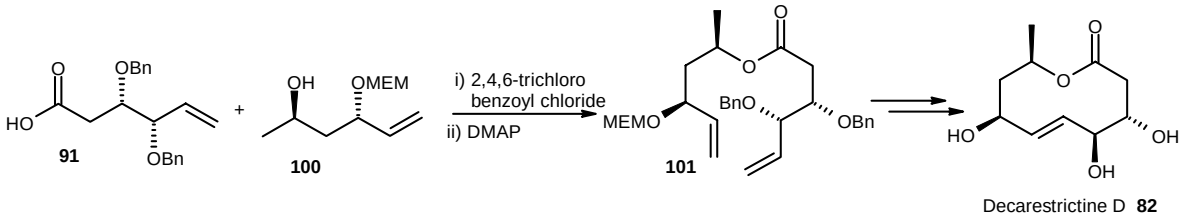
Synthesis of acid fragment: The synthesis of acid fragment **91** started from homoallylic alcohol **83**. Protection of alcohol, epoxidation followed by opening with lithium acetylide gave the homopropargylic alcohol **85**. Alcohol was converted into mesylate followed by elimination to give the ene-yne moiety **86** as the precursor for AD. **5** was subjected to AD, followed by partial hydrogenation, dibenzylation, PMB deprotection and oxidation to afford the acid fragment **91**.



Synthesis of alcohol fragment: The synthesis of alcohol fragment **100** started from racemic propylene oxide which on HKR gave (*R*)-propylene oxide. Opening of epoxide with vinyl Grignard followed by cross metathesis with acrylate ester gave the α,β-unsaturated ester which was subjected to AD to give the diol **94**. The diol **94** was protected as acetonide, followed by reduction, substitution of alcohol as iodo and elimination with Zn/HCl to afford the hydroxy olefin **98**. The hydroxyl group was protected as MEM ether followed by TBS deprotection to furnish the desired alcohol fragment **100**.

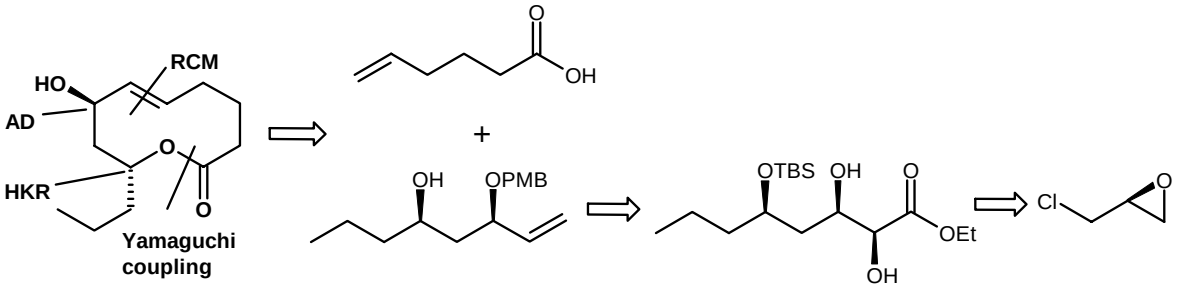


Coupling of the fragments: Both the fragments **91** and **100** were coupled using Yamaguchi protocol[27] followed by ring-closing metathesis to give the α,β-unsaturated lactone with olefin ratio (8:1) in favour of *E*-isomer, which were separable on column chromatography. Finally deprotection of all the protecting groups gave the target molecule decarestrictine D **82**.



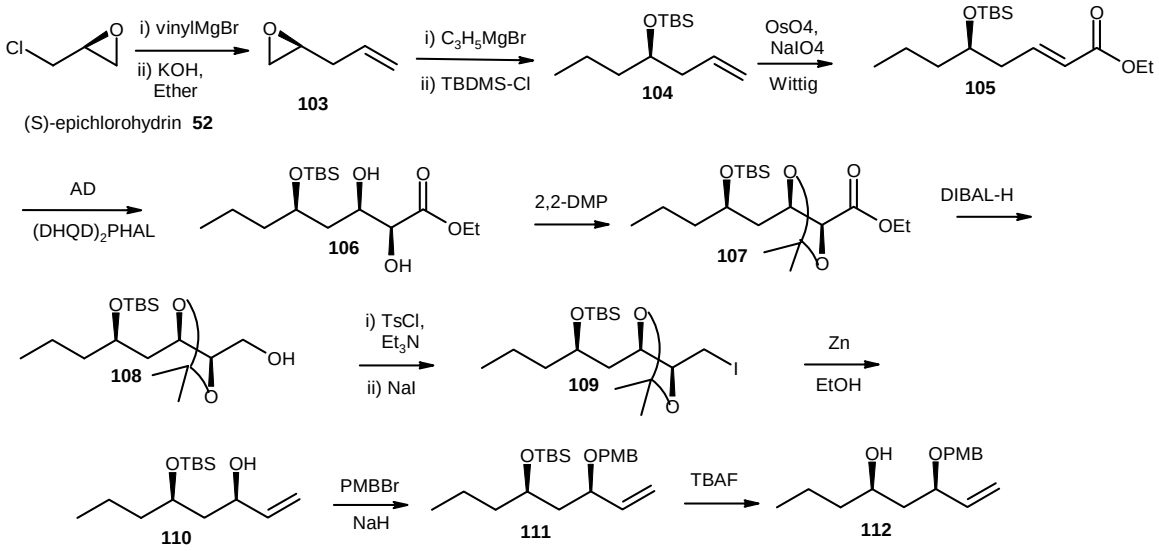
<u>Section B:</u> Asymmetric total synthesis of herbarumin III

Herbarumin III **102** was isolated from the fermentation broth and mycelium of the fungus *Phoma herbarum*[28] along with herbarumin I and II. The structure of **102** was elucidated by spectroscopic methods combined with molecular modelling. It interacted with bovine-brain calmodulin and inhibited the activation of the calmodulin-dependent enzyme camp phosphodiesterase.

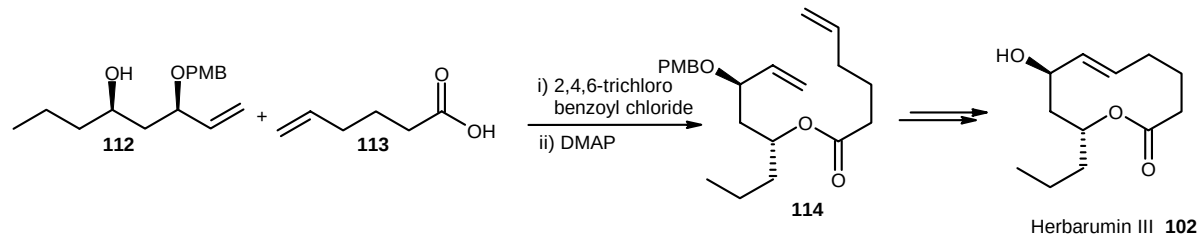


Herbarumin III **102**

Synthesis of herbarumin III **102** started from (*S*)-epichlorohydrin **52**. It was opened with vinylmagnesium bromide followed by base treatment to give the epoxide **103**. Epoxide **103** was opened with propylmagnesium bromide, followed by TBS protection, dihydroxylation, chopping and Wittig olefination to give the α,β-unsaturated ester **105**. The olefinic ester **105** was subjected to AD, followed by acetonide protection, reduction, conversion of alcohol to iodo and elimination to afford the allylic alcohol **110**. The hydroxyl group was protected as PMB, TBS was deprotected to furnish the alcohol **112**.



Alcohol **112** was coupled with hexenoic acid **113** followed by PMB deprotection and ring-closing metathesis to furnish the target molecule herbarumin III **102**.



Herbarumin III **102**

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CHAPTER-1

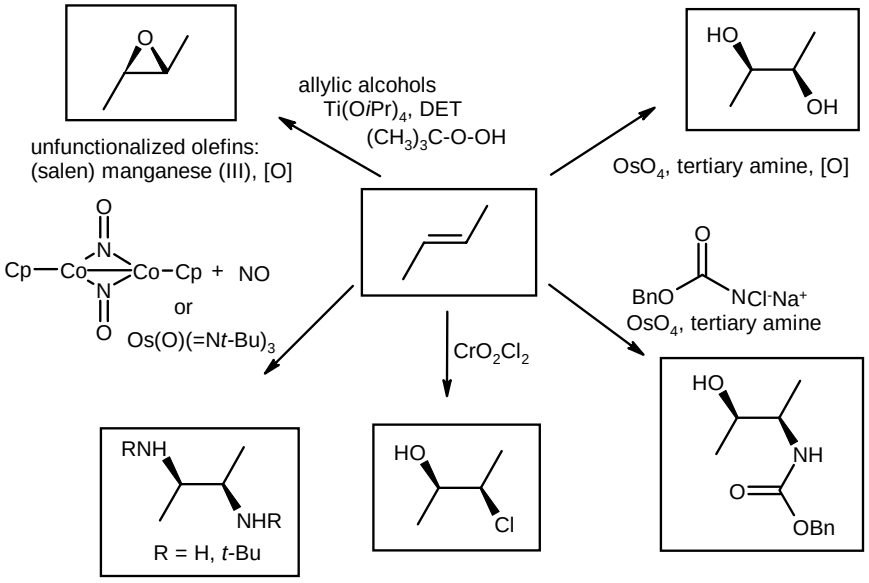
INTRODUCTION TO SHARPLESS ASYMMETRIC DIHYDROXYLATION, AMINOHYDROXYLATION AND JACOBSEN'S HYDROLYTIC KINETIC RESOLUTION

1.1. ASYMMETRIC DIHYDROXYLATION (AD)

1.1.1. Introduction

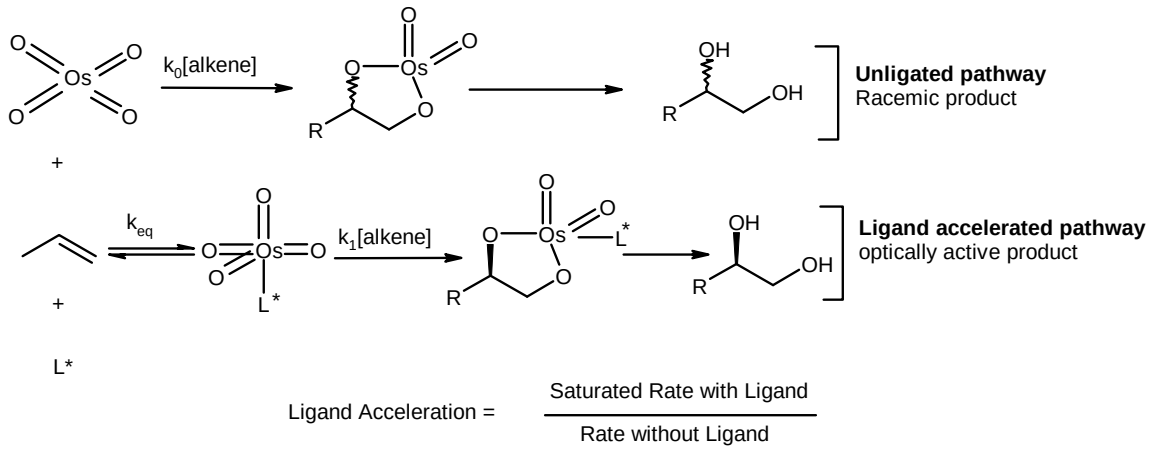
Asymmetric synthesis of bioactive molecules is in the forefront of synthetic organic chemistry due to its varied applications in drug and pharmaceutical industries and biotechnologies. The goal of asymmetric synthesis-whether it is done in an academic or an industrial setting-is to prepare stereochemically-enriched compounds in the most efficient and practical manner possible.

In the last two decades, many powerful asymmetric reactions have emerged as a result of the growing need to develop efficient and practical syntheses of biologically active compounds. Catalytic asymmetric reactions provide an especially practical entry into the chiral world due to their economical use of asymmetric inducing agents.[1] Especially useful is the carbon-heteroatom bond forming reaction, since the resulting functionality can be readily manipulated to produce many important classes of compounds. It is not surprising, therefore, that the oxidative addition of heteroatoms to olefins has been a fruitful area in recent years (**Scheme 1**).



Scheme 1. Transition metal mediated suprafacial 1,2-difunctionalization of olefins.

A number of transition metal-mediated methods for the epoxidation,[2] oxidative cyclization,[3] halohydrin formation,[4] dihydroxylation[5] and aminohydroxylation[6] have emerged. A common feature of most of these processes is the phenomenon of *ligand acceleration*,[7] wherein a metal catalyzed process turns over faster in the presence of a coordinating ligand (**Scheme 2**). This causes the reaction to be funneled through the ligated pathway with the additional consequence that the ligand may leave its 'imprint' on the selectivity determining step. Hence, the ligand can influence the chemo-, regio-, and stereoselectivity of the reaction in a profound way.



Scheme 2. Ligand accelerated catalysis-dihydroxylation of olefins.[7]

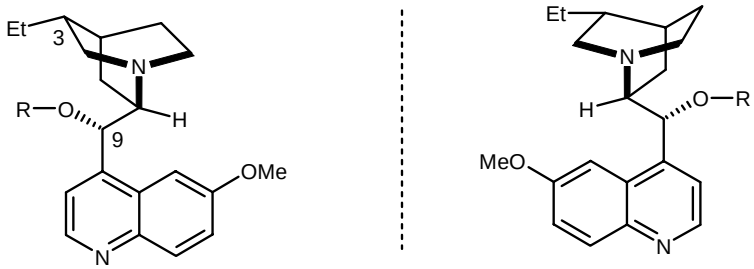
The osmium tetroxide-catalyzed asymmetric dihydroxylation (AD) of olefins, embedding two hydroxyl groups in a hydrocarbon framework is perhaps one of the most reliable and selective transformations in organic chemistry. In his pioneering work on the stoichiometric reaction of OsO_4 with olefins, Criegee[8] showed that pyridine accelerated the reaction considerably. However, cost considerations made the stoichiometric osmylation uneconomical. Not surprisingly, catalytic variants of the reaction, which employ relatively inexpensive reagents for the re-oxidation of the osmium (VI) glycolate products, greatly enhance its synthetic utility.[5b] Inorganic co-oxidants such as sodium or potassium chlorate[9a] or hydrogen peroxide,[9b,c] were among the first to be introduced, but in some cases diminished yields resulted due to over-oxidation. Much better results were obtained with alkaline *t*-BuOOH, introduced by Sharpless and Akashi,[10] or *N*-methylmorpholine *N*-oxide (NMO) (Upjohn Process).[11] Tsuji *et al.*[12] demonstrated that $K_3Fe(CN)_6$ in the

presence of K_2CO_3 provides a powerful system for the osmium-catalyzed dihydroxylation of olefins.

Initial efforts by Sharpless and Hentges to induce enantioselectivity in the osmylation with chiral pyridine derivatives failed due to the low affinity of these ligands for OsO_4.[13] It was found that the binding constant of a ligand is extremely sensitive to the steric hindrance near the reacting center. Consequently, quinuclidine derivatives were used instead of pyridines for further investigations due to their intrinsically higher affinity for OsO_4.[14] Moderate to good enantiomeric excess using acetate esters of cinchona alkaloids as chiral ligands was obtained.[13]

Apart from the cinchona alkaloid catalyzed AD, there are a number of methods employing chiral monodentate[15] and bidentate diamine[16] ligands. Despite the good to excellent enantioselectivities that can be obtained with diamine ligands, a serious drawback results from their bidentate nature, that they form very stable chelate complexes with Os (VI) glycolate products and as a consequence prevent *in situ* recycling of the Os and the ligand. Thus, all the reactions involving bidentate ligands are stoichiometric in both OsO_4 and the chiral ligand[16] (**Figure 1**).

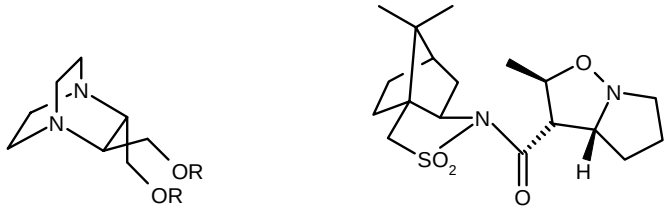
(a) Cinchona Alkaloid Ligands for AD under Catalytic Conditions



Dihydroquinidine (R = H)
DHQD

Dihydroquinine (R = H)
DHQ

(b) Monodentate Ligands for AD under Catalytic Conditions



(c) Chiral Diamine Ligands for AD under *Stoichiometric* Conditions

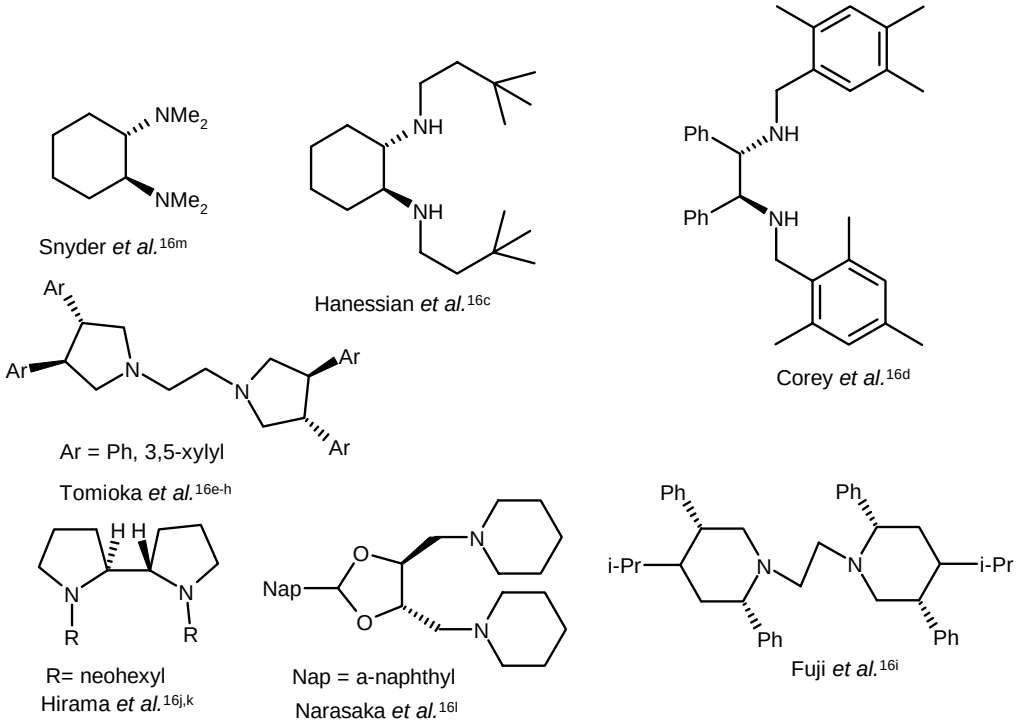


Figure 1. Some ligands for AD reaction.[13,16]

Initially, the asymmetric dihydroxylation using the derivatives of cinchona alkaloids was performed under stoichiometric conditions, but in 1987 Marko and Sharpless[17] found that the process became catalytic when NMO was employed as the co-oxidant. However, the enantiomeric excess of the diol products obtained under these catalytic conditions was initially lower than that produced by the *stoichiometric* reaction. The origin of this discrepancy was found to be the presence of a second catalytic cycle,[18] (**Figure 2**) which exhibited only low or no enantioselectivity. Wai[18] discovered a partial remedy in slow addition of the olefin. Kwong[19] found that the participation of second catalytic cycle can be virtually eliminated by performing the reaction under two-phase conditions with

$K_3Fe(CN)_6$ as the stoichiometric re-oxidant. Under these conditions there is no oxidant other than OsO_4 in the organic layer, in contrast to the homogeneous NMO conditions. Since the actual osmylation takes place in this layer, the resulting osmium (VI) monoglycolate ester undergoes hydrolysis, releasing the diol and the ligand to the organic layer and Os (VI) to the aqueous layer before its regeneration can occur, and consequently entry of the osmium glycolate into the second cycle is prevented (**Figure 3**).

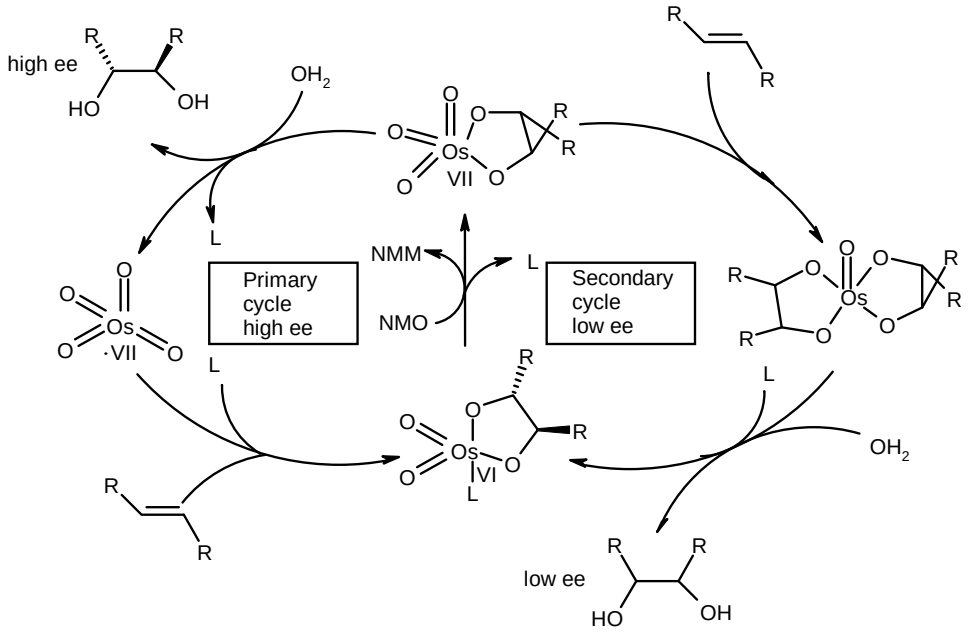


Figure 2. Two catalytic cycle for the AD reaction using NMO as the Co-oxidant

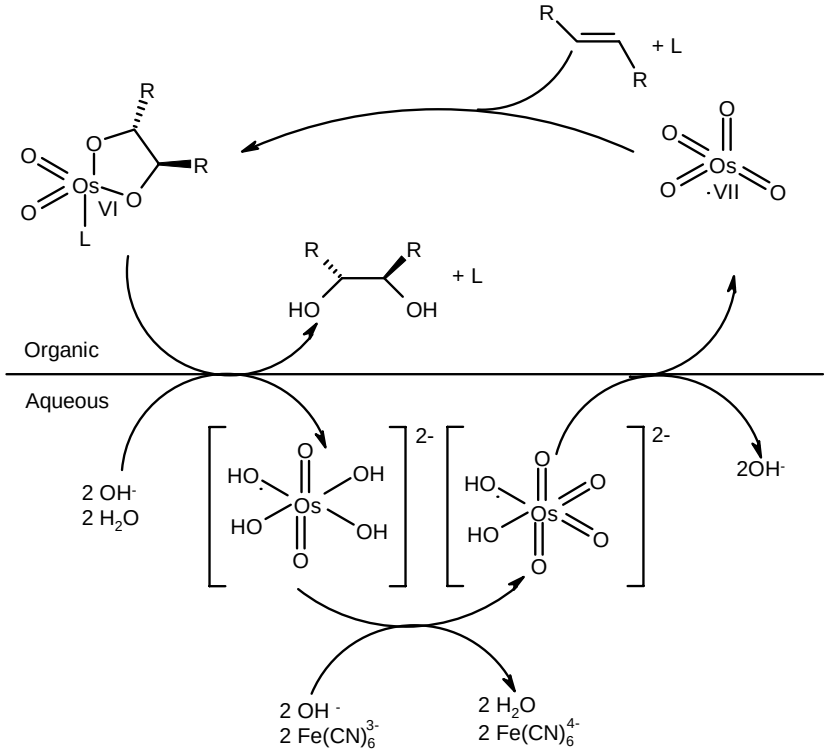


Figure 3. Catalytic cycle of the AD reaction with $K_3Fe(CN)_6$ as the Co-oxidant

Sharpless *et al*.[20] found that the hydrolysis of the osmium (VI) glycolate product could be accelerated considerably by using $MeSO_2NH_2$. The reaction time can be as much as 50 times shorter in the presence of this additive. This allows high catalytic turnover even with sterically encumbered substrates, and tetra substituted olefins are now within the scope of the reaction. Due to this "sulfonamide effect", most AD reactions can be carried out at 0°C rather than at room temperature, which may have beneficial influence on the selectivity.[21] For terminal olefins, $MeSO_2NH_2$ is not recommended. Surprisingly, terminal olefins actually react slower in the presence of $MeSO_2NH_2$. However this weak inhibitory effect is noticeable only if very small amount of OsO_4 (0.2 mol%) is employed.

The discovery of ligands with two independent cinchona alkaloid units by Hartung[20] (phthalazine core) and Crispino[22] (diphenylpyrimidine core) attached to a heterocyclic spacer, has led to a considerable increase in both the enantioselectivity and the scope of the reaction (**Figure 4**).

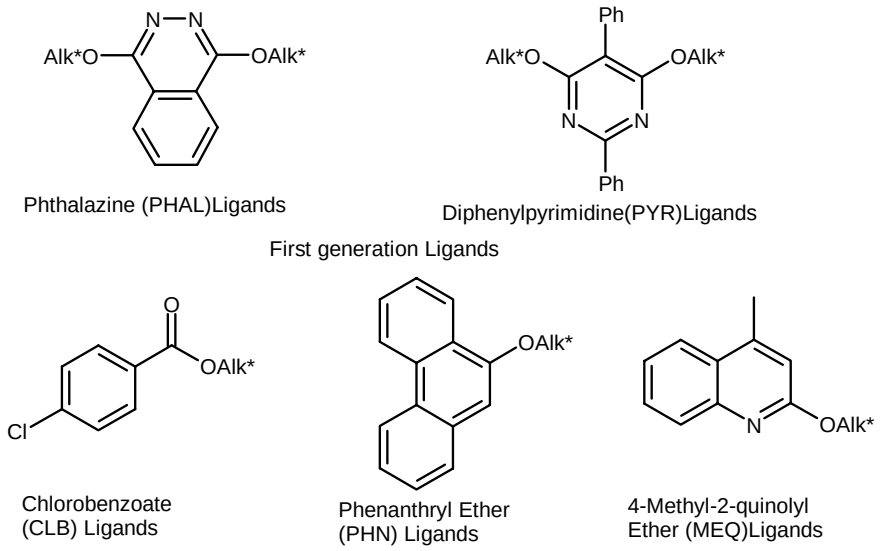
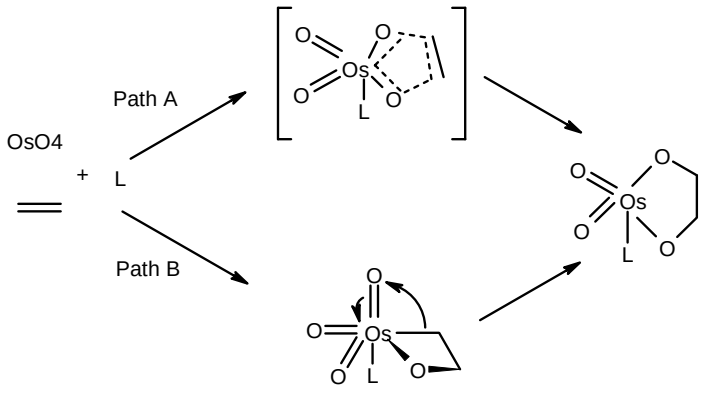


Figure 4. The latest generation of "dimeric" PHAL and PYR ligands and their predecessors (Alk* = DHQD or DHQ, see Fig. 1)

1.1.2. The Mechanism of Asymmetric Dihydroxylation (AD)

The osmium-catalyzed dihydroxylation reaction has been the center of extensive mechanistic investigations and two different mechanisms have been suggested. Boseken[23a] and Criegee[8] originally proposed a concerted [3+2] pathway, (**Scheme 3**, **Path A**) while Sharpless *et al*.[23b] and Jorgensen *et al*.[23c] suggested a stepwise reaction which is initiated by a [2+2] like addition of the olefin across an Os=O bond (**Path B**), followed by rearrangement of the resulting osmaoxetane intermediate to the glycolate product.

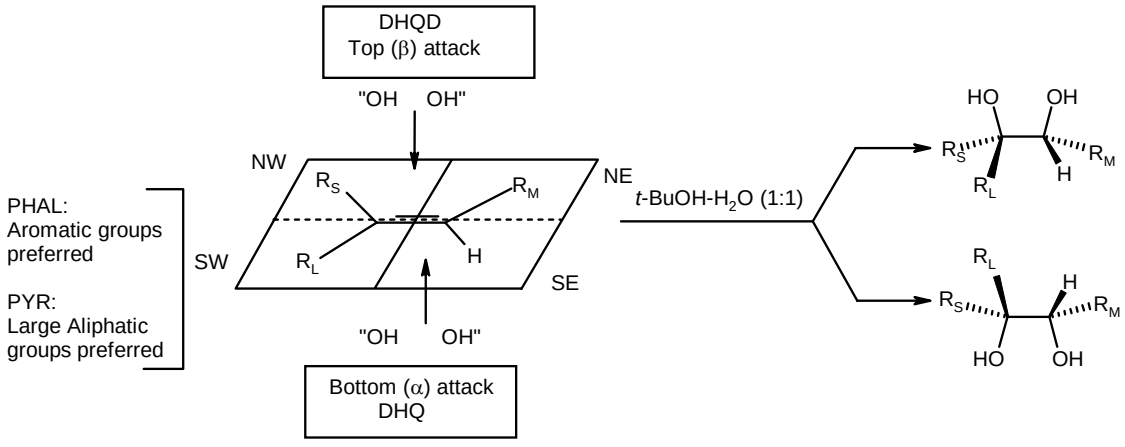


Scheme 3. Schematic presentation of the corrected [3+2] mechanism[23a] (Path A) and the stepwise osmaoxetane mechanism (Path B).[23b,c]

The recent observation of a nonlinear Erying relationship between enantiomeric excess and temperature[21] is in consistent with Criegee's one-step [3+2] mechanism, but it can be explained by a reaction pathway with at least two selectivity determining steps which are weighted differently according to temperatures owing to their different activation parameters, ΔH and ΔS. Hence, this observation suggests that the stepwise [2+2]-like mechanism is operative. High level *ab initio* calculations have indeed shown that osmaoxetanes are energetically accessible minima on the potential energy surface.[24]

1.1.3 Empirical rules for predicting the face selectivity

Despite the mechanistic investigations, the face selectivity of the dihydroxylation can reliably be predicted using an empirical 'mnemonic device' (Scheme 4).[25] The plane of the olefin is divided into the four quadrants according to a simple set of rules. The SE quadrant is sterically inaccessible and, with few exceptions, no substituent other than hydrogen can be placed here. The NW quadrant, lying diagonally across from the SE quadrant, is slightly more open and the NE quadrant appears to be quite spacious. The SW quadrant is special in that its preferences are ligand dependent. Even though this SW quadrant normally accepts the largest group, especially in the case of PYR ligands, it is especially attractive for aromatic groups in the case of PHAL ligands.[25c] An olefin which is placed into this olefin according to the above constraints receives the two OH groups from above, i.e. from the β-face, in the case of DHQD derived ligands and from the bottom, i.e. from the α-face, in the case of DHQ derivatives (**Scheme 4**).



Scheme 4. The mnemonic device for predicting the face selectivity

1.1.4 Reaction Conditions

The catalytic asymmetric dihydroxylation is performed in a 1:1 mixture of water and *t*-BuOH and the olefin concentration is usually 0.1 M.[20] The key reagents are 3 equivalents of $K_3Fe(CN)_6$ as the re-oxidant, 0.2-0.4 mol% osmium, 1 mol% of ligand, 3 equivalents of K_2CO_3 and 1 equivalent of $CH_3SO_2NH_2$. Additionally, the ligand can be recovered especially when large scale reactions are carried out. For PHAL ligand, the combined organic layers are extracted with 3% aq. H_2SO_4 satuarated with K_2SO_4 (ca. 40 mL/1g of ligand). The ligand enters the aqueous phase as the hydrogen sulphate salt and the solution can be reused directly for the subsequent AD reaction without further purification. However, the amount of K_2CO_3 in the subsequent reaction should be increased in order to neutralize excess H_2SO_4 and also to release the ligand salt as its free base, and the volume of aqueous ligand solution added to the reaction mixture.

1.1.5 The cinchona alkaloid ligands and their substrate preferences

Phthalazine (PHAL) ligands

Due to the ready availability of second generation ligands i.e. PHAL[26] (Phthalazine) ligands are widely used and this ligand class reacts especially when aromatic groups are present, and remarkably high enantioselectivities were observed when the aromatic substituents appear in certain optimal locations[27] like in *trans*-stilbene for which the enantioselectivity is as high as 99.8%.[28] However, PHAL ligands give inferior results with aliphatic olefins, especially if they are branched near the double bond or if they have very small substituents.

Anthraquinone (AQN) ligands

The anthraquinone ligands are well suited for almost all olefins having aliphatic substituents[29] and diols derived from allyl halides or allyl alcohols can be obtained with satisfactory enantiomeric purity, thereby giving access to valuable chiral building blocks. The AQN derivatives are the ligands of choice for the AD reaction, except for olefins with aromatic or sterically demanding substituents.

Pyrimidine (PYR) ligands

The pyrimidine ligands are the ligands of choice for olefins with sterically demanding substituents.[30]

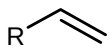
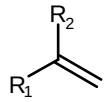
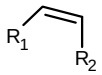
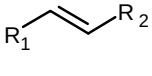
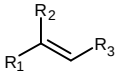
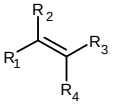
Diphenyl pyrazinopyridazine (DPP) and diphenyl phthalazine (DP-PHAL) ligands

These ligands give improved enantioselectivities for almost all olefins except for terminal alkyl olefins which are better served by the AQN or PRY ligands.[31] The DPP ligand is normally slightly superior to the DP-PHAL ligand. The DPP derivatives are the optimal ligands for aromatic olefins and for certain *cis*-1,2-disubstituted olefins.

Indoline (IND) ligands

Cis-1,2-disubstituted olefins generally are poor substrates for the AD reaction and the IND derivatives are normally the ligands of choice.[32] However, in certain cases better results are obtained with the new second generation ligands.[33]

Table 1. Recommended ligands for each olefin class

Olefin Class						
Preferred Ligands	<u>R=Aromatic</u> DPP, PHAL <u>R=Aliphatic</u> AQN <u>R=Branched</u> PYR	<u>R_1, R_2 =Aromatic</u> DPP, PHAL <u>R_1, R_2 =Aliphatic</u> AQN <u>R_1, R_2 = Branched</u> PYR	<u>Acyclic</u> IND <u>Cyclic</u> PYR, DPP, AQN	<u>R_1, R_2 = Aromatic</u> DPP, PHAL <u>R_1, R_2 = Aliphatic</u> AQN	PHAL, DPP, AQN	PYR, PHAL

1.2. HYDROLYTIC KINETIC RESOLUTION (HKR)

1.2.1. Introduction

Enormous advances have been made over the past several years in asymmetric synthesis, with particular emphasis having been placed on the development of enantioselective catalytic reactions.[34] Different factors influence the practicality of an asymmetric reaction.[35] A list of the features that would describe the ideal enantioselective transformation is necessarily subjective, but it could include:

· Products are obtained in quantitative yield.

· Reaction provides product in 100% enantiomeric excess (ee).

· Starting materials are inexpensive.

· Reaction times are short.

· Large amounts of product can be obtained with available glassware/equipment (high volumetric throughput).

· The chiral catalyst, reagent, or auxiliary is inexpensive and available, and does not contribute to the overall cost.

· Products are easily isolated, with little-or-no purification necessary.

· There is minimal generation of byproducts and waste.

· The reaction can be applied reliably and reproducibly on any scale.

· The reaction displays broad substrate scope, including high functional group compatibility.

· There is no better way to make the product in question.

Arguably no reactions discovered to date meet all of these criteria. To the extent that no enantioselective process is perfect, it is interesting to compare asymmetric reactions to the

best methods for synthesizing the corresponding products in racemic form. In a few cases, e. g., for the laboratory synthesis of 1,2-diols, epoxy alcohols, and certain hydrogenation products, asymmetric catalytic methodologies do in fact exist that make it as easy to prepare highly enantio-enriched materials as it is to prepare racemic mixtures. However, in a far greater number of cases, it is still much easier and less expensive to access racemates. As a result, despite what they might lack in "elegance", resolution strategies must always be evaluated carefully against any asymmetric process.[36]

Resolutions fall broadly into three classes. Classical resolutions involve the use of a stoichiometric amount of a chiral resolving agent.[37] The resolving agent is associated to the substrate, either covalently or non-covalently, to generate a pair of diastereomers. The diastereomers are separated and, through a separate chemical transformation, the substrate is released from the resolving agent. This approach has proven to be especially useful if salt formation is straightforward, as in the case of amines and carboxylic acids.[38] Chiral chromatography generally relies on the use of a chiral stationary phase to resolve enantiomers contained in a mobile phase, and in principle it can be carried out on analytical or preparative scale. In reality, the large solvent volumes, long separation times, and relatively high costs of chiral chromatography supports often limit the scale at which chromatographic separations can be carried out. Kinetic resolution involves using a chiral catalyst or reagent to promote selective reaction of one enantiomer over the other giving a mixture of enantio-enriched starting material and product, and the desired component is then isolated.[39]

As noted above, the theoretical yields for such resolutions are usually 50%. If the "undesired" resolution byproduct can be racemized or otherwise converted back to the desired enantiomer, then this can improve the yield, and therefore the practicality, of the resolution process, provided the additional cost in time and materials does not eclipse the cost of the initial resolution. In some special circumstances, it is possible to induce substrate racemization under the conditions of resolution. It then becomes possible in principle to convert essentially 100% of the racemate to the desired product (see Section 2.2). Such processes constitute a very special subclass of kinetic resolution reactions known as dynamic kinetic resolutions.

For the most part, however, racemization is not readily effected and the issue of a maximum yield of 50% holds. This applies equally to parallel kinetic resolutions, an additional subclass of kinetic resolution reactions. However, given that racemates can often be much less than half as expensive than their enantiopure counterparts, it is clearly simplistic to consider resolutions as being inherently inelegant or impractical. Indeed, the fact that resolution remains so widely used is probably the best evidence that it can in fact be the most attractive option for accessing enantioenriched compounds. Catalytic kinetic resolutions are particularly attractive, at least in principle, because of the need for only small amounts of chiral "resolving agent". However, kinetic resolution has been used very little in a commercial context compared to classical or even chromatographic resolution. The following conditions must be met in order for kinetic resolution to be practical:

· The racemate is cheap and no good enantioselective, chiral pool, or classical resolution route to the product exists.

· The catalyst is highly selective for one enantiomer and is effective at low loadings.

· The catalyst is inexpensive or it can be recycled efficiently.

· The reaction is economical and safe (i. e., inexpensive stoichiometric reagents, no undue dangers associated with the reagents, high volumetric throughput, and a minimum of waste generated).

· The resolved starting material and converted product are easily separated.

· In the ideal case, both the product and the resolved substrate are valuable and recoverable in highly enantio-enriched form.

The importance of epoxides in organic synthesis arises partly from the occurrence of the strained three-membered ring unit in a number of interesting natural products[39] but more so because the ring opening of epoxides allows straightforward elaboration to useful new functionality, often with generation of new carbon-carbon bonds. Indeed, reactions of epoxides with nucleophiles, Lewis acids, radicals, reducing agents, oxidizing agents, acids, and bases have all been well documented and utilized in synthesis.[40] Further, the

stereospecific manner in which epoxides generally react renders these compounds attractive chiral building blocks for asymmetric synthesis.

Since those epoxides that are produced naturally are typically complex compounds available only in limited amounts, Nature's chiral pool has not proven to be a useful direct source of optically active epoxides for use in organic synthesis. Instead, enantio-enriched epoxides have been accessed indirectly from the chiral pool via multistep procedures.[41] These, however, tend to be inherently inefficient, and the range of epoxides available by this approach is also quite limited. As a consequence, the preparation of enantio-enriched epoxides has long stood as a most significant target for asymmetric synthesis. In particular, the identification of catalytic asymmetric olefin oxidation methods has been an area of active research for several decades, and the advances made in this field have increased greatly the number of enantiomerically enriched epoxides available for use in organic synthesis.

Among available methods for the preparation of enantio-enriched epoxides, the Sharpless epoxidation reaction has arguably had the most profound impact of any asymmetric catalytic reaction discovered thus far, providing general access to highly enantio-enriched epoxyalcohols.[42] More recently, the epoxidation of unfunctionalized conjugated olefins by chiral (salen)MnIII complexes has enabled the practical synthesis of certain classes of enantiomerically enriched epoxides.[43] A highly complementary strategy for epoxidation of simple olefins involving chiral dioxirane intermediates has expanded the range of chiral epoxides now accessible in enantio-enriched form to a significant extent.[44] Indirect routes to enantiopure epoxides involving asymmetric catalytic dihydroxylation or reduction reactions have also proven highly valuable in specific contexts.[45] Despite these considerable advances in asymmetric catalytic synthesis of epoxides, no general methods have been identified for the direct preparation of highly enantio-enriched 1-oxiranes, arguably the most valuable class of epoxides for organic synthesis.[46] The utility of terminal epoxides as chiral building blocks is perhaps best illustrated by the fact that the few examples for which effective catalytic approaches exist have found extensive use in asymmetric synthesis. In particular, glycidol and a number of its derivatives are available in enantiomerically enriched form using the Sharpless epoxidation technology[47] or by enzymatic kinetic resolution methods,[48] and these compounds have become widely used

starting materials for target-oriented synthesis.[49] Epichlorohydrin has been rendered commercially available in bulk by microbial resolution of ((±)-2,3-dichloro-1-propanol, and it, too, has found widespread application.

Recently Jacobsen had discovered the (salen)Co complex **1** catalyzed efficient hydrolytic kinetic resolution (HKR) of a variety of terminal epoxides (Scheme 1).[50-52] This new method appeared to hold considerable promise with regard to meeting all of the criteria outlined above for kinetic resolution to be practical. Racemic 1,2-epoxides are generally available directly from commercial suppliers at low cost or are obtainable in one step from inexpensive olefins or aldehydes. In fact, certain racemic epoxides, such as propylene oxide, epichlorohydrin, styrene oxide, and butadiene monoepoxide, are commodity chemicals and are no more expensive than common organic solvents. Second, the ligands for catalyst **1** had previously been commercialized and manufactured on a ton scale in the context of (salen)Mn epoxidation catalysts.[53] The cobalt analogues (*R*,*R*)-**1** and (*S*,*S*)-**1** proved equally accessible, and these are also now available in bulk.[54] Third, water is perhaps the ideal reagent for effecting the resolution reaction: it is inexpensive and safe, and the rate of the ring-opening reaction can be controlled simply by modulating the rate of addition of water to the epoxide-catalyst mixture.[55] Fourth, for those examples that were described in the preliminary report, highly enantio-enriched epoxides were recovered from the HKR. Finally, the HKR provided useful enantio-enriched 1,2-diols, including many that are otherwise not readily accessible using existing asymmetric dihydroxylation methods.[56]

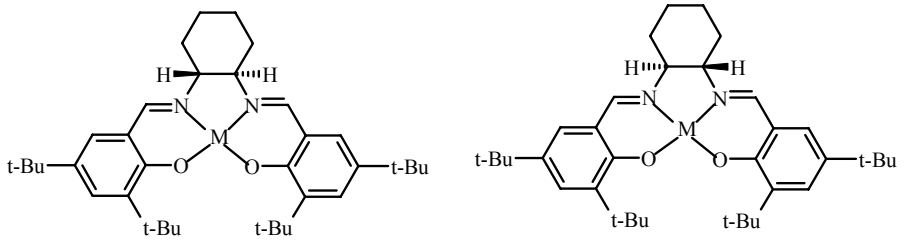
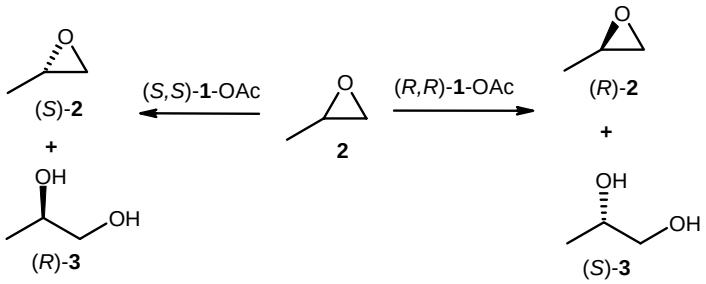


Figure 5. Jacobsen catalyst



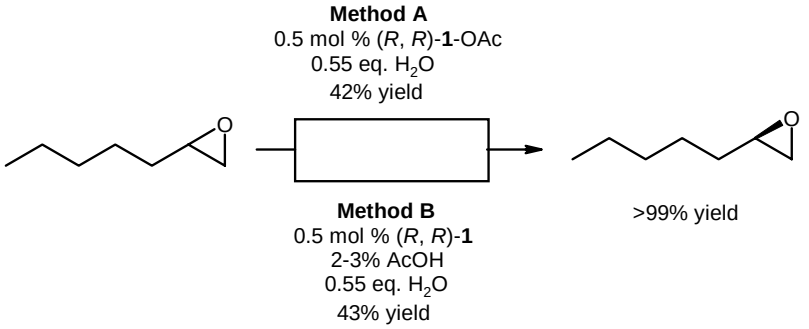
Scheme 5. Hydrolytic kinetic resolution reaction

The HKR has seen rapid adoption as the method of choice for the preparation of a variety of terminal epoxides in enantio-enriched form, and a number of applications in target oriented synthesis have been reported already.[57] In addition, the commercial manufacture of enantio-enriched propylene oxide, epichlorohydrin, and styrene oxide using HKR methodology has been implemented, thereby reducing the cost of these useful chiral building blocks.[54] Jacobsen has discovered that the HKR is an extraordinarily general reaction, allowing efficient kinetic resolution of virtually any type of terminal epoxide.

1.2.2 Preparation of Catalyst and General Experimental Considerations

Both enantiomers of the (salen)CoII complex **1** are available commercially on research or commercial scale,[54] or they can be prepared from the commercially available ligands using $Co(OAc)_2$. The Co(II) complex **1** is catalytically inactive, however, and it must be subjected to one-electron oxidation to produce a (salen)CoIIIX complex (X) anionic ligand) prior to the HKR. This may be done conveniently by aerobic oxidation in the presence of a mild Brönsted acid. Water alone was found not to mediate the oxidation reaction, but a screen of additives revealed that acetic acid was effective and that the corresponding Co(III) precatalyst **1**.OAc is convenient for use in HKR reactions both in terms of its preparation and reactivity (eq 1). Two useful methods for the generation of complex **1**.OAc have been developed. Method A involves isolation of **1**.OAc as a crude solid prior to the HKR. The Co(II) complex **1** is dissolved in toluene to generate a ca. 1 M solution, and acetic acid (2 equiv) is added. The resulting solution is stirred open to air at room temperature for 30 min, during which time the color of the mixture changes from orange to dark brown. All volatile materials are removed in vacuo, affording **1**.OAc as a brown solid residue that can be used without further purification. Method B involves in

situ generation of **1**.OAc under HKR conditions by suspension of the Co(II) complex **1** in epoxide or epoxide/solvent and addition of HOAc under an aerobic atmosphere. Catalyst obtained by both methods was examined for each of the epoxides described in this study. For certain substrates such as 1-hexene oxide, catalyst prepared by either method leads to essentially identical results. In these situations, in situ catalyst generation (method B) is preferable since the procedure avoids an extra solvent removal step. On the other hand, catalyst prepared by method A was found to be more effective with less reactive substrates (vide infra) and was applicable to all substrates examined. Therefore, if HKR did not afford epoxide in >99% ee with catalyst prepared by method B after optimization of solvent and catalyst loading, then catalyst prepared by method A was employed.



Scheme 6.

Aside from the method of generation of **1**.OAc, the only reaction parameters in the HKR that required optimization for individual substrates were catalyst loading and choice of solvent. With few exceptions, epoxide of >99% ee could be obtained using 0.55 equiv of water relative to racemate. Relatively small epoxides with some degree of water solubility could be resolved effectively without added solvent. However, the HKR of more lipophilic substrates did benefit from inclusion of a water miscible organic solvent such as tetrahydrofuran (THF), 2-propanol, or 1,2-hexanediol. In general, one volume of solvent relative to racemic epoxides was sufficient to allow efficient HKR. Catalyst loadings of 0.5 mol % or lower relative to racemic epoxide were effective for many substrates, but epoxides bearing sterically hindered or unsaturated substituents often required more catalyst (up to 2 mol %) to attain complete resolution. Reactions were initiated at 0 °C and then allowed to warm to room temperature with continued stirring for 12- 18 h.

[(*R,R*)-*N,N*'-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminato(2-)]cobalt(II) ((*R,R*)-1). A solution of cobalt(II) acetate tetrahydrate (5.98 g, 24.0 mmol) in MeOH (80 mL was added to a solution of ligand [(*R,R*)-*N,N*'-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine] (10.9 g, 20.0 mmol) in CH_2Cl_2 (80 mL) via cannula under an atmosphere of N_2 with careful exclusion of air. A brick-red solid began to precipitate before addition was complete. The sides of the reaction flask were rinsed with MeOH (20 mL), and the mixture was allowed to stir for 15 min at room temperature and then 30 min at 0 °C. Precipitated solids were isolated by vacuum filtration and rinsed with cold (0 °C) MeOH (2 x 75 mL). The red solid was collected and dried in vacuo to yield [(*R,R*)-*N,N*'-bis(3,5-di-*tert*butylsalicylidene)-1,2-cyclohexanediaminato(2-)]cobalt(II) ((*R,R*)-**1**) (11.6 g, 19.2 mmol, 96%).

1.2.3. Representative Procedures for the HKR of Terminal Epoxides

(a) Method A. (*S*)-Propylene Oxide. A 100 mL flask equipped with a stir bar was charged with (*S,S*)-**1** (242 mg, 400 μmol, 0.002 equiv). The catalyst was dissolved in 5 mL of PhMe and treated with AcOH (240 μL, 4.2 mmol). The solution was allowed to stir at room temperature open to air for 30 min over which time the color changed from orange-red to a dark brown. The solution was concentrated in vacuo to leave a crude brown solid. The resulting catalyst residue was dissolved in propylene oxide (14.0 mL, 11.6 g, 200 mmol) at room temperature, the reaction flask was cooled to 0 °C, and H_2O (1.98 mL, 110 mmol, 0.55 equiv) was added dropwise over 5 min. The reaction was allowed to warm to room temperature and stir 14 h at which time (*S*)-propylene oxide (5.35 g, 92.1 mmol, 46%) was isolated by distillation from the reaction mixture at atmospheric pressure and 36 °C. Propylene diol was removed by vacuum distillation (65 °C, 0.25 Torr). The catalyst was recovered by suspension in MeOH and collection by vacuum filtration. The ee of the propylene oxide was determined to be 99.7% by chiral GC analysis of the 1-azido-2-trimethylsiloxypropane derivative obtained by opening the epoxide with $TMSN_3$ (Cyclodex-B, 55 °C, isothermal, *t*R(minor)) 12.29 min, *t*R(major)) 12.57 min). $[R]_{23}^{D}$ -11.6° (neat).

(b) Method B. (*R*)-1,2-Epoxy-5-hexene. A 100 mL flask equipped with a stir bar was charged with (*R,R*)-**1** (302 mg, 500 μmol, 0.005 equiv). The catalyst was treated with ((±)-

1,2-epoxy-5-hexene (11.3 mL, 9.81 g, 100 mmol), AcOH (120 μL, 2.1 mmol, 0.02 equiv), and 1 mL of THF. The reaction flask was cooled to 0 °C, and H_2O (1.0 mL, 55 mmol, 0.55 equiv) was added in one portion. The reaction was allowed to warm to room temperature and stir 16 h at which time the volatile materials were isolated by vacuum transfer at 0.25 Torr into a cooled (-78 °C) receiving flask. The recovered epoxide was filtered through a silica plug to remove residual water, and the THF was removed by rotary evaporation to yield (*R*)-1,2-epoxy-5-hexene (4.23 g, 43.1 mmol). The diol was distilled under reduced pressure (56 °C, 0.25 Torr). The catalyst was recovered by suspension in MeOH and vacuum filtration. The ee of the recovered epoxide was determined to be 99.5% by chiral GC analysis of the 1-azido-2-trimethylsiloxy-5-hexene derivative obtained by opening the epoxide with $TMSN_3$ (Cyclodex-B, 70 °C, isothermal, *t*R(minor), 38.00 min, *t*R(major), 39.06 min). $[\alpha]_D^{25}$ +9.36° (neat)

1.2.4. Catalyst Recycling

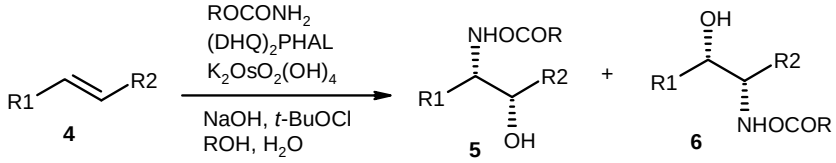
The possibility of recycling a catalyst has obvious practical appeal, particularly in cases where the catalyst is precious due to cost or limited availability. Catalyst **1** is prepared in bulk from low-cost components, and as a result it is quite inexpensive relative to most chiral catalysts. On the other hand, the HKR employs reactants (racemic epoxide, water, minimal if any solvent) that impact the cost of the overall process to an almost negligible extent in many cases, and as a result the catalyst is a significant contributor to the material costs. Accordingly, efforts were directed toward identifying practical methods for effecting catalyst recovery and recycling. The HKR reaction of propylene oxide presents an especially straightforward scenario with respect to catalyst recovery because both the epoxide and the diol are relatively volatile and can be removed by distillation. The solid residue remaining in the reaction vessel after product separation was found to have the characteristic red-brick color of the reduced (salen)CoII complex **1**. Reoxidation to **1**.OAc with air and AcOH led to catalyst with undiminished levels of reactivity and selectivity.

Thus The HKR provides a straightforward method for the preparation of a wide assortment of terminal epoxides in highly enantio-enriched form. Given that in many cases there exist no practical alternatives for accessing the valuable chiral building blocks, it is hoped that the HKR will have a beneficial and enabling effect on the field of organic synthesis.

1.3. ASYMMETRIC AMINOHYDROXYLATION (*AA*)

1.3.1. Introduction

Asymmetric aminohydroxylation[58] is the very versatile as it facilitates a single step introduction of two functional groups viz amino (protected) and hydroxy group, from a wide range of simple alkene starting materials. The significance of this invention was immediately apparent to many researchers[59] as the AA reaction provides straightforward access to the amino alcohol array and in a wide variety of biologically active agents and natural products.[60] As a result, the reaction rapidly gained the prominence of its forerunners, the AE and AD processes. The reaction typified by the conversion shown in Scheme 7, employs catalyst constituting of cinchona alkaloid derived ligands and an osmium species in combination with a stoichiometric nitrogen source that also functions as the oxidant. The chiral ligands give rise to the observed enantioselectivity by favouring addition to one enantiotopic face of the prochiral alkene substrate. In this way, the 1,4-bis-(9-*O*-dihydroquininyl)-phthalazine [$(DHQ)_2PHAL$] ligand directs addition to the α-face of an alkene **4** to form amino alcohol products such as **5** or **6** (Scheme 7). Alternatively, the 1,4-bis-(9-*O*-dihydroquinidinyl)-phthalazine [$(DHQD)_2PHAL$] ligand directs addition to the β-face of **4**.



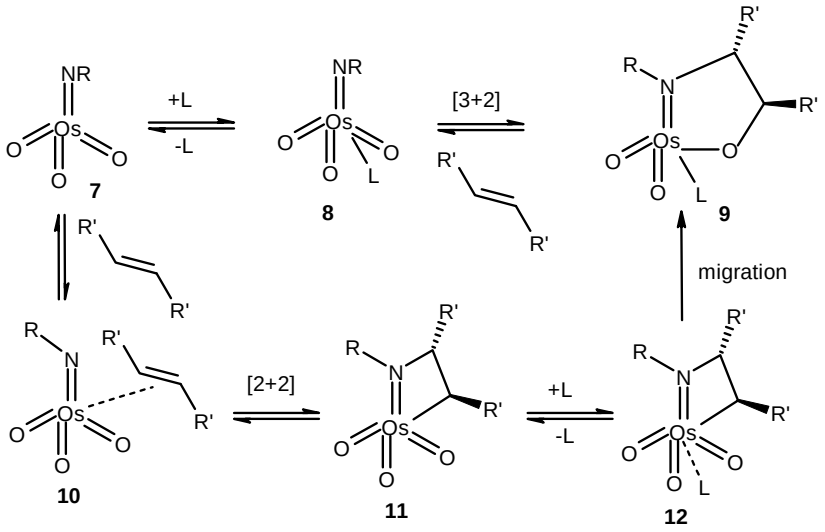
Scheme 7

An additional complexity that is not manifested in the AD process involves the regioselectivity of the AA reaction. The oxidation of unsymmetrical alkene such as **4** (R1≠R2) can, in principle, give rise to two regioisomeric amino alcohol products **5** and **6**. In many cases, the conditions or the aromatic linker of the chiral ligand, for example phthalazine (PHAL) or anthraquinone (AQN), strongly influence the regioselectivity of the reaction.[61]

1.3.2 Mechanism

The proposed mechanism for the asymmetric aminohydroxylation is closely based on mechanistic studies of its forerunner, the AD reaction. The intermediate implicated in the key bond forming step is the imidotrioxoosmium (VIII) species **7**, which adds with '*syn*' stereospecificity to the alkene to give the azaglycolate complex **9**. Like in AD, two different mechanisms have been proposed, both of which addresses the preferences of **7** to effect aminohydroxylation rather than dihydroxylation and other key aspects such as enantio-and regioselectivity.

The first mechanism involves a formed [2+2] cycloaddition of the alkene to the imidotrioxoosmium species **7** to give the osmaazetidine **11**, followed by ligand co-ordination to form **12** and 1,2 migration of the carbon-osmium bond to give the osmium azaglycolate addition product **9**. This mechanism uses electronic arguments to account for the frequently observed preference for the nitrogen to add regioselectivity to the β-carbon of alkenes bearing an electron withdrawing group.[62] The beneficial effects of the ligand on the enantio-and regioselectivity of the reaction occur by influencing the position of the equilibrium thereby favouring one of the diastereomeric complexes represented by **12** or by controlling the relative rate of final bond migration to give **11**.[63]



Scheme 8

The second mechanism is [3+2] cycloaddition of ligand-bound complex **7** to the alkene, analogous to the Criegee mechanism for osmium-mediated dihydroxylation. In this, ligand co-ordination with imidotrioxo osmium (VIII) followed by [3+2] cycloaddition with olefin gives **9** (**Scheme 8**). Based on these results, a mechanistic scheme has been proposed in which two catalytic cycles, give different results for selectivity of the transformation (**Fig. 6**). The primary cycle is mediated by the alkaloid derived ligand and in all but one of the AA methods reported to date,[64] the ligand is observed to improve catalytic turnover relative to the non-ligand-mediated reaction. Ligand mediated addition of imidotrioxoosmium(VIII) species **7** to the alkene gives azaglycolate species **9**. Reoxidation of **9** by the nitrogen source gives **13**, which can undergo hydrolysis to regenerate the initial osmium species and liberate product. The oxidized azaglycolate species **13** may also enter the secondary cycle and add to a second alkene to give the bis(azaglycolate)osmium species **14**.

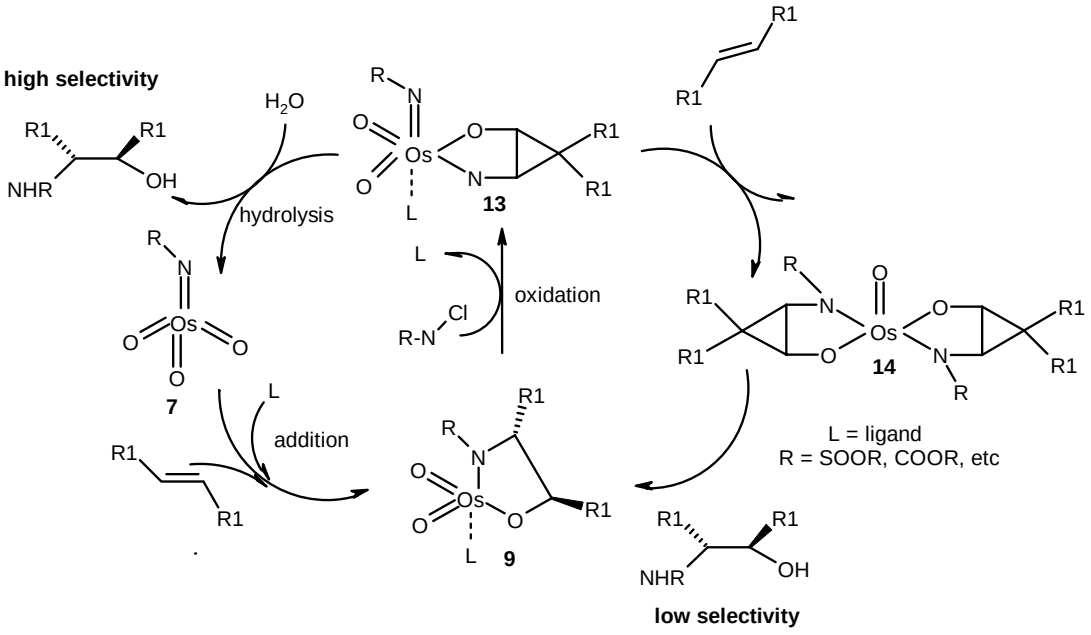


Figure 6

The addition step of this cycle is independent of the *Cinchona* alkaloid derived ligand and as a result, gives addition products with low enantio and regio-selectivity. Hydrolysis of **14** leads back to **9**, which can then reenter either the primary or secondary cycle. The turnover-limiting step in both catalytic cycles is the hydrolysis of azaglycolate complexes

13 or **14**.[65] Control of the oxidation pathway is achieved by conducting the reaction in aqueous solvent mixtures, thereby favouring hydrolysis of **13**[65a] and dominance of the primary cycle. In comparison, all of the AA processes reported to date have been carried out under homogeneous conditions and suppression of the secondary cycle relies on effective hydrolysis.

1.3.3 Nitrogen sources

There are three main classes of nitrogen source that have been used to date in the AA reaction. The *N*-halogenated species derived from (i) sulfonamides (ii) carbamates and (iii) amides. All are converted into the respective alkali metal salt prior to addition to the alkene (**Fig. 7**).

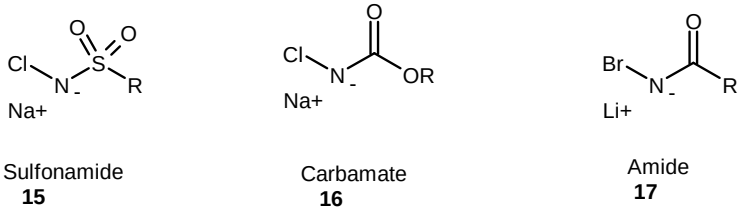


Figure 7

(i) Sulfonamide variant : The sulfonamide method was first to be developed, stemming directly from the use of chloramine-T [TsN(Na)Cl] in the catalytic but non-asymmetric forerunner to the AA.[66] Chloramine-T remains the most frequently used reagent, due to its low cost and commercial availability. Subsequent studies have revealed that the size of the sulfonamide group has a tremendous influence on the outcome of the reaction, the smaller the residue the better the results.[67] Thus the methane sulfonamide based chloramine-M reagent generally gives superior results in terms of enantio and regioselectivity, catalytic turnover, and yield, compared to chloramine-T. Additionally, the chloramine-M system shows ligand acceleration, while the toluene sulfonamide based system is ligand deaccelerated. The robust nature of the sulfonamide product requires harsh deprotection condition such as reductive cleavage of sulfonamides under Birch conditions[68] or with Red-Al.[69] In addition, 33% HBr/CH_3COOH has been used to cleave toluene sulfonamides.[70] Sulfonamide method is limited in its substrate scope, encompassing α, β-

unsaturated esters, phosphonates and amides, as well as some terminal and trisubstituted alkenes, but excluding alkenes such as styrenes and vinyl arenes.[71]

(ii) Carbamate variant: The discovery of carbamate based nitrogen sources[72] greatly expanded the scope of the AA reaction to include many styrenes and terminal alkenes. This coupled with the facile deprotection of carbamates under milder conditions,[73] gave the AA much greater synthetic utility than was the case using the original sulfonamide based approach. The commonly used carbamates include ethyl, benzyl, *tert*-butyl and 2-(trimethylsilyl) ethyl carbamate (Teoc). All except Teoc are commercially available, and all can be used without purification. The carbamate is typically converted, *in situ*, into the corresponding chloramine salt by reaction with sodium hydroxide and 3 mol equiv. of *tert*-butyl hypochlorite.[74] One frequently encountered difficulty with the carbamate variant of the AA is the removal of unreacted from the reaction mixture, with extensive column chromatography often being required.[75] As with sulfonamides, carbamates with less sterically demanding N-substituents were found to give better results.

(iii) Amide variant : The most recent major variant of the AA reaction is based on *N*-halogenated amides.[76] This variant is comparable in scope to the carbamate based method and works well with cinnamates, acrylates, styrenes, and terminal alkenes. It is advantageous in that only one equivalent of the *N*-haloamide is required, greatly simplifying isolation of the AA products. As alkali metal salts of *N*-chlorocarbamides are susceptible to Hoffmann rearrangement,[77] the lithium salt of commercially available *N*-bromoacetamide was found to be the most viable alternative. By carrying out the reaction at 4 ^{o}C, complete suppression of the Hoffmann rearrangement was achieved.[78]

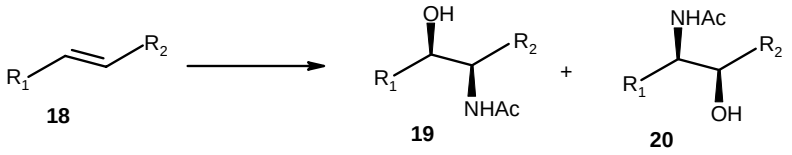
1.3.4 Regioselectivity

Control of regioselectivity in the AA is arguably the single greatest challenge when applying the reaction in synthesis. Greater understanding of the factors responsible for controlling regioselectivity would significantly expand the scope of the AA reaction and assist in the development of synthetic strategies that centre on this transformation. The problem of regioselectivity is a complex one and many factors have been invoked to explain one and many observed trends, such as alkene substitution, alkene polarisation and ligand-substrate interactions.

Alkene substitution

The AA of the homoallylic alcohol derivatives shown in **Scheme 9** explains the general trend that the nitrogen prefers to add to the less substituted end of the alkene.

The above observation may be explained by the steric demand of the substituted imidoosmium (Os = NR) relative to the unsubstituted oxo-counterpart (Os = O) in the reactive complex, which favours approach of the former to the less substituted olefinic carbon.



Substrate	**R_1**	**R_2**	**19:20**
18a	$TBDPSOCH_2CH_2$	H	>20:1
18b	*p*-OMe-$C_6H_4OCH_2CH_2$	H	1.2:1
18c	$TBDPSOCH_2CH_2$	Et	2.0 :1
18d	*p*-OMe-$C_6H_4OCH_2CH_2$	Et	1: 3.5

Scheme 9

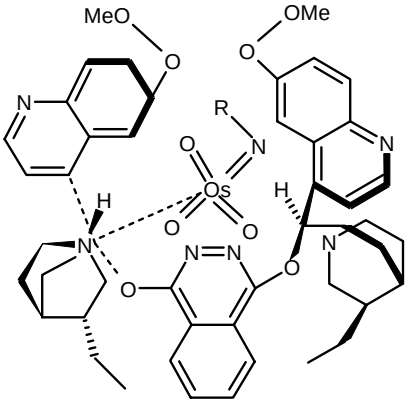
Alkene polarisation

Polarisation of the alkene has been suggested as a contributing influence on the preference of α, β-unsaturated esters to afford the β-amino product with phthalazine derived ligands. Though the precise rationale varies depending on whether the formal [2+2] or [3+2] cycloaddition is invoked as the preferred mechanistic path way, it has been suggested that the β-amino isomer predominates due to the greater nucleophilic character of the imidoosmium grouping (Os=NR) relative to (Os=O) which favours addition to the more electrophilic carbon of the alkene. However changing the aromatic linker of the chiral ligand to an anthraquinone unit results, for a range of α, β-unsaturated esters, in a reversal

in regioselectivity such that the α-aminated products are now favoured. This fact speaks against a strong electronic bias.

Ligand-substrate interaction

The most comprehensive study of ligand-substrate interactions has been reported by Janda and coworkers.[67] They proposed a model for the AA reaction with phthalazine derived ligands analogous to that proposed by Corey[77] for the AD reaction. As shown in **Fig. 8** in the putative active complex, the osmium lies at the centre of a distorted trigonal bypyramid composed of equatorial oxygens, with the nitrogens from both the quiniclidine ring and the nitrogen source occupying axial positions.[67] Assuming the proposed geometry of the OsO_3N_2 species, the regioselectivity of the AA then arises from the mode in which the alkene binds to the catalyst. It is clear that an unsymmetrically substituted alkene could orient in two different ways with regarding to the binding cleft of the catalyst (mode A and mode B) to produce two different regioisomeric products. It follows that ligand-substrate interactions will be important in determining the mode in which an alkene will approach the catalyst.



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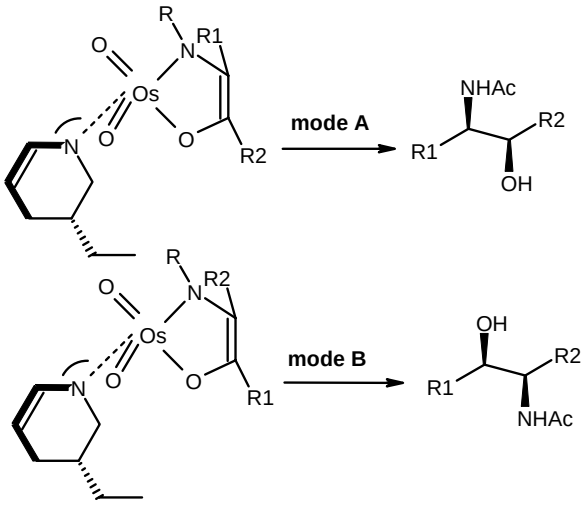
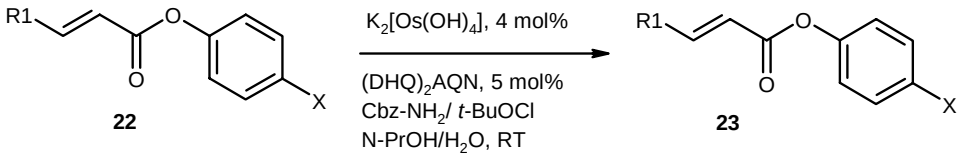


Figure 8. Proposed structure of the AcN=OsO_3-$(DHQD)_2PHAL$ catalyst 21, and alternative alkene binding modes A and B

Panek protocol:

Asymmetric synthesis of β-hydroxy-α-amino acid can be performed, by making aryl ester substrates **22** successfully using Panek protocol. The reversal of regioselection may arise from a conformational change induced by the aryl ester functionality.[78]



Scheme 10

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CHAPTER-2

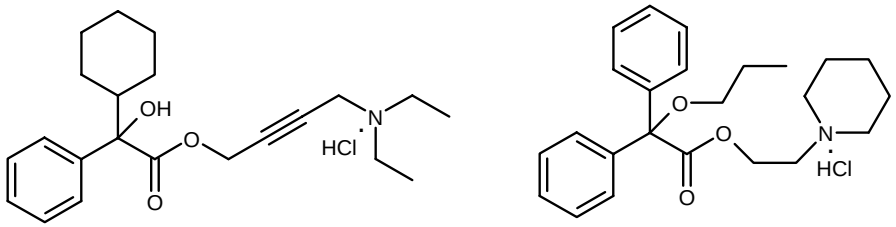
ASYMMMETRIC SYNTHESIS OF VICINAL DIOLS AND AMINO ALCOHOL

2.1 SECTION A

ASYMMETRIC SYNTHESIS OF (*S*)-OXYBUTYNIN

2.1.1. Introduction

Recently, there has been much interest in the treatment of urinary dysfunction, such as urinary incontinence, owing to the rapid increase in the proportion of aged people in the population. Urinary incontinence is a pathological condition frequently affecting the elderly; epidemiological investigations indicate that 5-15% of the adult populations are affected and the prevalence, particularly of urge incontinence, increases with age. The symptoms of an unstable bladder comprise urge incontinence, urgency, and frequency. Urge urinary incontinence is the complaint of involuntary urine loss, accompanied by or immediately preceded by urgency (sudden, compelling desire to pass urine, which is difficult to defer). Bladder instability is considered to be caused by uncontrolled detrusor contractions,[1] which are believed to be mediated by muscarinic acetylcholine receptors.[2] Consequently, muscarinic acetylcholine receptor antagonists, such as oxybutynin.HCl[3] and propiverine.HCl[4] (Fig. 1), have for years been the drugs of choice for the treatment of urinary incontinence associated with bladder muscle instability.



Oxybutynin.HCl **1** Propiverin.HCl **2**

Figure 1

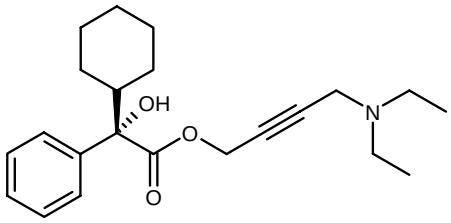
Muscarinic acetylcholine receptors, members of the huge superfamily of G protein-coupled receptors,[5-7] are heterogeneous, and have been classified into at least three pharmacologically distinct receptor subtypes (M_1- M_3).[8] The M_1 receptor is found at high density in neuronal tissues,[9] whereas M_2 and M_3 receptors are mainly present in peripheral effector organs, such as heart (M_2) and smooth muscle (M_3).[10] On the other hand, a

molecular cloning study indicated that muscarinic acetyl-choline receptors are composed of at least five molecularly distinct receptor proteins (M_1-M_5).[11] The pharmacologically defined M_1-M_3 receptors are thought to correspond to the cloned M_1-M_3 subtypes. In situ hybridization[12] and immunoprecipitation[13] studies on the human urinary bladder have revealed the presence of M_2 and M_3 receptor subtypes. In spite of the predominant presence of the M_2 receptor in the bladder, the muscarinic receptor(s) responsible for the contraction of the bladder is the M_3 subtype.[14]

Oxybutynin (Ditropan) is widely prescribed in racemic form for the treatment of urinary frequency, urgency and urge incontinence. Unfortunately it exhibits classical muscarinic side effects, such as dry mouth, accommodation paralysis and tachycardia.[15] Like the majority of muscarinic receptor antagonists, oxybutynin is composed of tertiary α-hydroxy acid as a key component.[16] Oxybutynin is extensively metabolized in the liver and undergoes marked first-pass metabolism upon oral administration.[17] This generates two main metabolites among which phenylcyclohexylglycolic acid is considered to be pharmacologically inactive. The pharmacologically active *R*- and *S*-enantiomers of *N*-desethyl-oxybutynin (DEOB)[18] are formed by liver and gut CYP3A4.[19] Accordingly, co-administration of the 3A4 inhibitor itraconazole moderately increased serum concentrations of oxybutynin but not those of DEOB. Differences in plasma concentrations of the *R*- and *S*-enantiomers of both oxybutynin and DEOB, following administration of racemic oxybutynin, indicate a stereo-specific metabolism.[20] Both isomers of oxybutynin and DEOB bind comparably to α_1-acid glycoprotein.[21] Oxybutynin is moderately selective for M_3 over M_2 receptors (Ki values at M_1, M_2, M_3, M_4 and M_5 receptors: 2.4, 6.7, 0.7, 2.0 and 11.0 nM, respectively).[22]

The effectiveness of this agent is attributed to a combination of M_3[23-25] selective muscarinic receptor subtype antagonism and antispasmodic,[26, 27] local anesthetic, and calcium channel blocking actions.[28, 29] The duration of action of **3** in man is about 6 h. In rats, it reaches a peak blood level about 2 h after dosing and a minimally detectable amount is present for 72 h.[30] The recommended clinical dosing regimen is 5 mg two to four times a day.[31]

Preliminary biological results suggest that (*S*)-oxybutynin displays an improved therapeutic profile compared to its racemic counterpart, and it is currently in phase III clinical trials.



(*S*)-Oxybutynin **3**

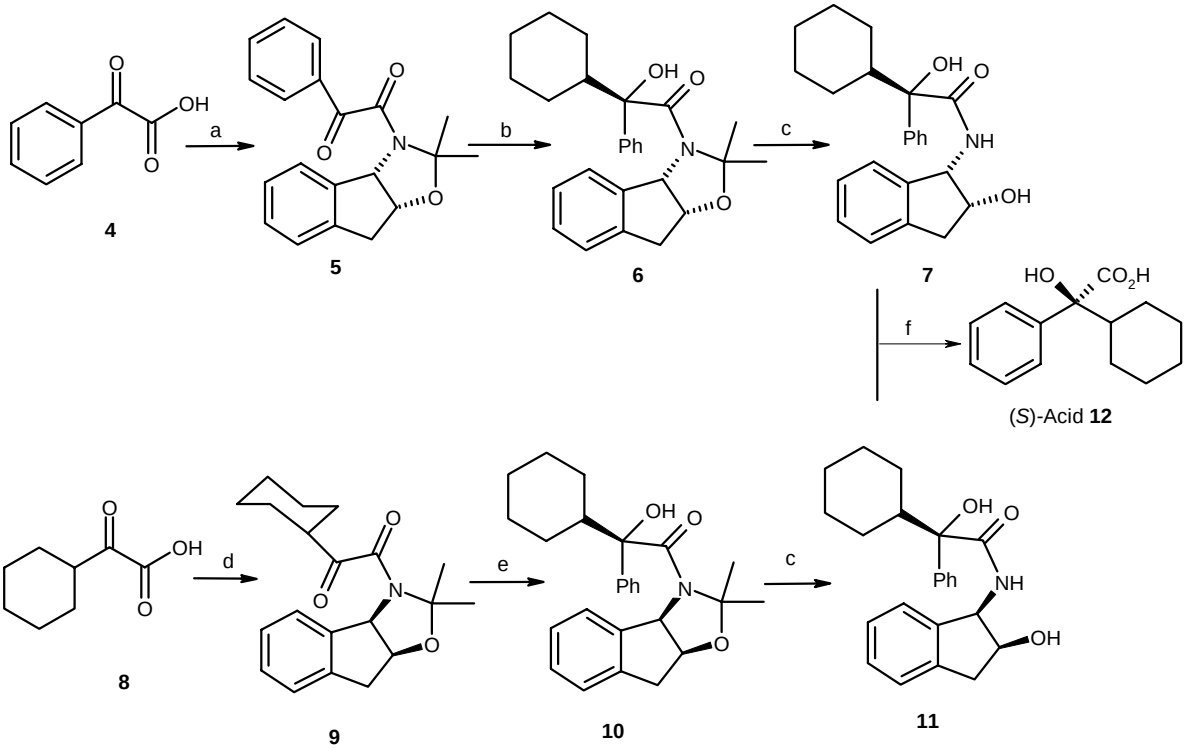
Figure 2

2.1.2. Review of Literature

A few reports have appeared on asymmetric synthesis of (*S*)-acid[32-36] and (*S*)-oxybutynin.[37] These involve the use of carbohydrate systems which contain an asymmetric benzylic center, the application of *cis* -aminoindanol or related constrained amino alcohols as highly defined chiral handle,[32] a chiral mandelic acid template,[33] catalytic chiral cyanosilylation of a ketone,[34] proline catalyzed asymmetric aldol reaction.[35] or chiral template-driven Grignard reaction[36] for the preparation of an enantiopure tertiary α-hydroxy acid. A detailed report of these syntheses is described below.

Senanayake *et al* . (1999).[32]

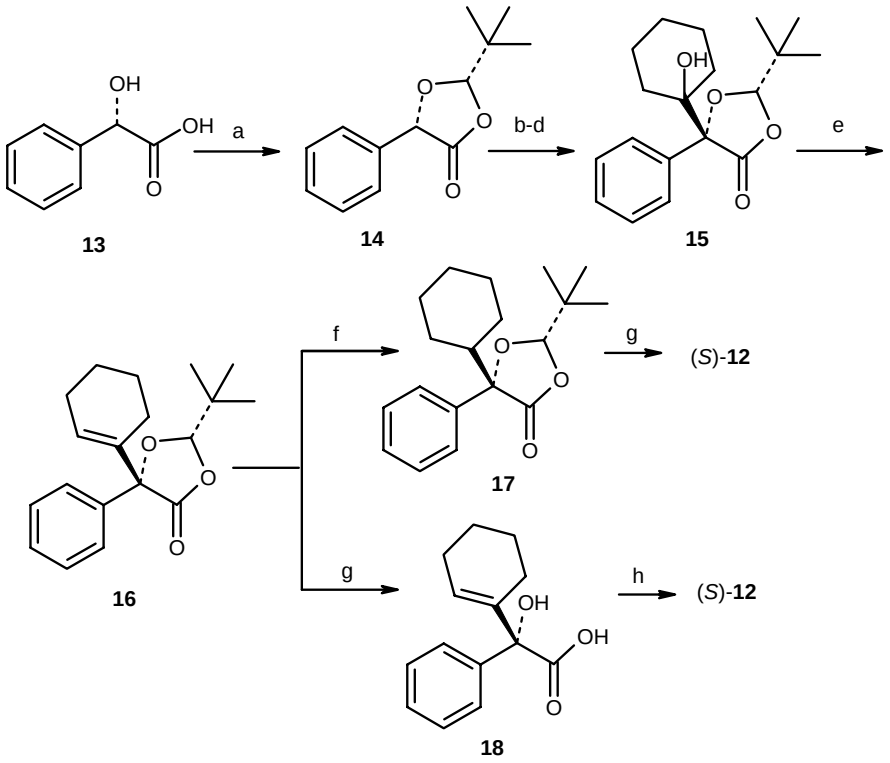
Senanayake and co-workers accomplished the synthesis of α-hydroxy acid of oxybutynin by using the C-1 amine or C-2 alcohol of cis-aminoindanol as a chiral handle and examined the diastereoselective cyclohexyl or phenyl Grignard addition process to the appropriate keto-moiety for generation of (*S*)-acid. Thus substrate **5** and **9** were prepared as depicted in scheme 1. Addition of cyclohexyl Grignard to **5** in presence of $ZnCl_2$ provides the acetonide **6** with high selectivity. Acetonide **6** was subjected to acidic hydrolysis to afford amino alcohol **7**. On the other hand **9** was subjected to phenylmagnesium chloride at -78 ^{o}C to afford **10** which on acetonide deprotection afforded amino alcohol **11**. Finally exposure of **7** and **11** to polyglycol in the presence of KOH afforded (*S*)-acid **12** (Scheme 1).



Scheme 1. *Reagents and conditions*: (a) (i) $(COCl)_2$, CH_2Cl_2, 95%; (ii) (1*S*,2*R*)-aminoindanol, TEA, THF; (iii) 2-methoxypropene, PPTS, 80%; (b) cyclohexylmagnesium chloride, THF, $ZnCl_2$, 22 ^oC, 50%; (c) (i) 6N HCl, THF, 97%; (ii) crystallization; (d) (i) $(COCl)_2$, CH_2Cl_2, 95%; (ii) (1*R*,2*S*)-aminoindanol, TEA, THF; (iii) 2-methoxypropene, PPTS, 80%; (e) phenylmagnesium chloride, THF, -78 ^oC, 80%; (f) polyglycol, KOH, 60%.

Senanayake *et al*. (2000).[33]

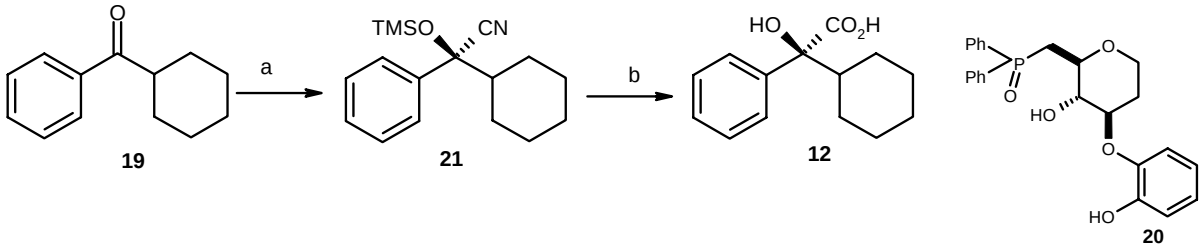
Senanayake and co-workers synthesized (*S*)-acid **12** by utilizing the readily available and inexpensive starting material (*S*)-mandelic acid **13** and cyclohexanone. Thus as shown in scheme 2, (*S*)-mandelic acid **13** was acetalized using pivaldehyde to give (*S*,*S*)-**14** with >97% cis selectivity. Stereocontrolled aldol reaction between the enolate of (*S*,*S*)-**14** with cyclohexanone afforded the aldolate **15**, in excellent diastereoselectivity, which on elimination of tertiary alcohol gave lactone (*S*,*S*)-**16**. Finally acid (*S*)-**12** could be prepared either by hydrolysis of lactone (*S*,*S*)-**16**, then hydrogenation of (*S*)-**17** or hydrogenation of a double bond of (*S*,*S*)-**16** followed by hydrolysis of (*S*,*S*)-**18**.



Scheme 2. *Reagents and conditions*: (a) pivaldehyde, cat. TfOH, pentane, >97% dr; (b) crystallization in heptane, >95%, >99.5% de; (c) LiHMDS, THF, -78 °C, 1 h then cyclohexanone, 85%, 98:2 dr; (d) crystallization in heptane, >90%; (e) $SOCl_2$, pyridine, THF, >98%; (f) KOH, MeOH, then HCl, 96%; (g) H_2, Pd/C, MeOH, 95% (h) KOH, MeOH, then HCl, 95%.

Shibasaki *et al.* (2002).[34]

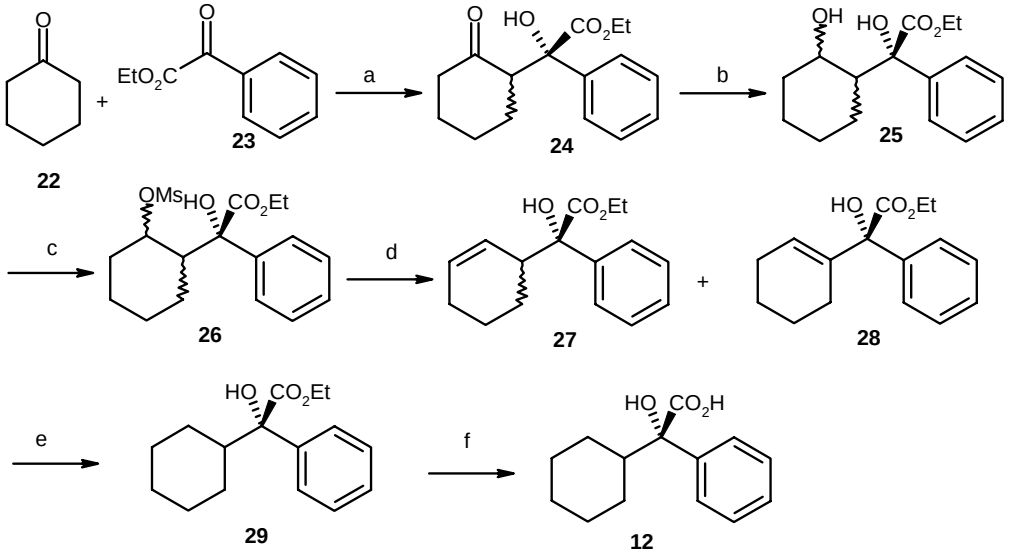
Shibasaki and co-workers synthesized the (*S*)-acid using catalytic enantioselective cyanosilylation[38] of cyclohexyl phenyl ketone as a key step. Thus, catalytic cyanosilylation of cyclohxyl phenyl ketone **19** using a chiral gadolinium (Gd)- catalyst **20** afforded **21** in 96% yield with 95% ee. Reduction of **21** with DIBAL-H in toluene, followed by desilylation and further oxidation with $NaClO_2$ afforded the (*S*)-acid **12** (Scheme 3).



Scheme 3. *Reagents and conditions*: (a) $Gd(O^iPr)_3$, **20**, TMSCN, CH_3CH_2CN, -40 ^oC, 40 h; (b) (i) DIBAL-H, toluene; (ii) aq. HCl, THF; (iii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, H_2O-*t*BuOH, 80%.

Maruoka *et al.* (2005).[35]

Maruoka and co-workers have synthesised (*S*)- acid **12** by using proline catalyzed asymmetric reaction as the key step. Thus as shown in scheme 4, proline catalyzed direct asymmetric reaction between cyclohexanone **22** and ethyl phenylglyoxalate **23** afforded aldol adduct **24** in good yield. Treatment of **24** with BH_3-Me_2S in THF at room temperature and subsequent addition of methanol afforded **25**, which was reacted with methanesulfonyl chloride followed by elimination of methanesulfonyloxy group using LiCl in HMPA to give **27** and **28**. The resulting olefin were hydrogenated followed by hydrolysis of **29** to afford (*S*)-acid, which on recrystallization yielded optically pure (*S*)-**12**.

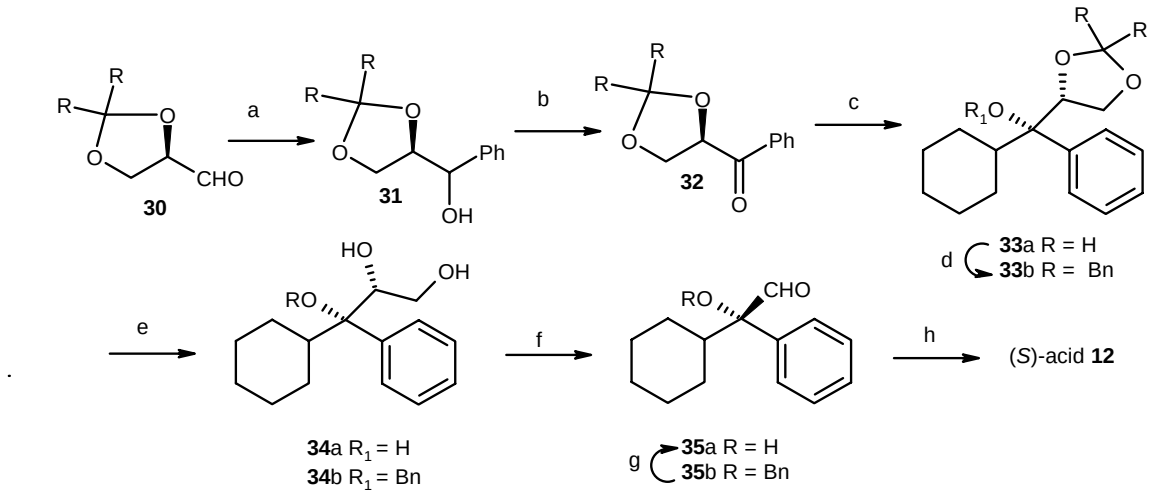


Scheme 4. *Reagents and conditions*: (a) L-proline, DMSO, rt, 72 h; (b) BH_3-Me_2S, THF, rt, 2 h; (c) MsCl, Et_3N, CH_2Cl_2, 0 ^oC, 1 h; (d) LiCl, HMPA, 80 ^oC, 4 h, 81%; (e) H_2 (1 atm), Pd-C (10%), EtOH, 24 h, 94%; (f) (i) 1 M NaOH, MeOH, reflux, 6 h; (ii) recryst., 83%.

Chattopadhyay *et al.* (2006).[36]

Chattopadhyay and co-workers have synthesised (*S*)-acid starting from (*R*)-cyclohexylidene glyceraldehyde by using chiral template-driven Grignard addition as the

key step. Thus reaction of **30** with phenylmagnesium bromide afforded **31** in excellent yield, which on oxidation with PCC[39] followed by reaction with cyclohexylmagnesium bromide furnished tertiary alcohol **33a**. Hydrolysis of acetal of **33a** followed by chopping of diol **34a** gave aldehyde **35a** which on further oxidation afforded (*S*)-acid **12**. Alternatively to improve the yield, alcohol **33a** was benzylated followed by conversion to diol **34b**. Chopping of diol **34b** followed by debenzylation and oxidation afforded (*S*)-acid **12** (Scheme 5).



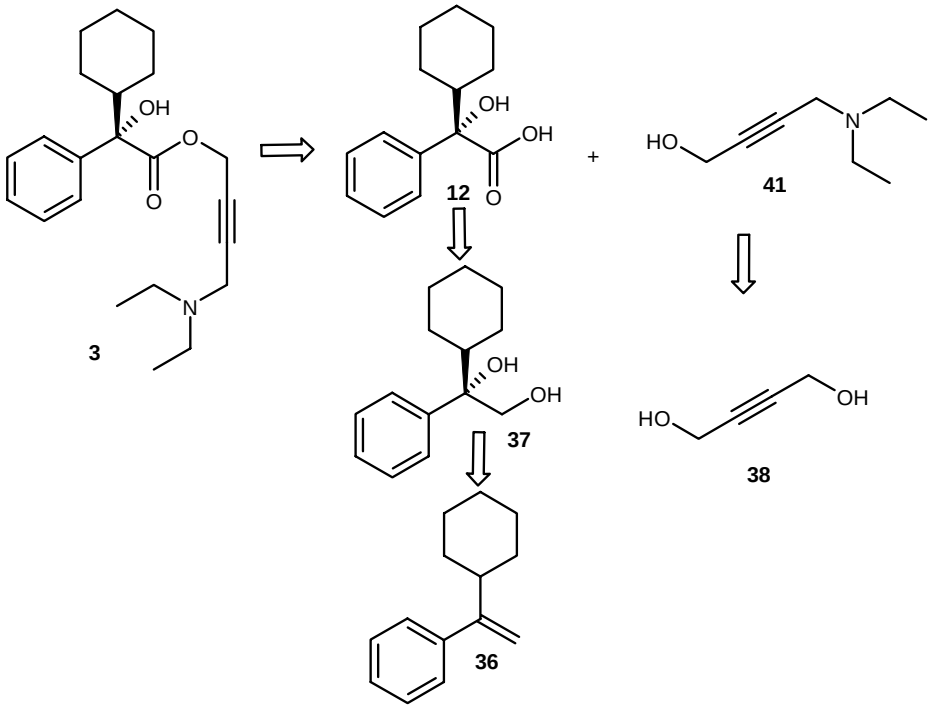
Scheme 5. *Reagents and conditions*: (a) PhMgBr, THF, 88%; (b) PCC, NaOAc, CH_2Cl_2, 84%; (c) cyclohexylmagnesium bromide, THF, 87%; (d) BnBr, NaH, THF, Δ, 88%; (e) 1% HCl–MeOH, (77% and 92% from **33a** and **33b**, respectively); (f) $NaIO_4$, MeCN, H_2O, (45% and 81% from **34a** and **34b**, respectively); (g) DDQ, CH_2Cl_2, 45 ^oC, 88%; (h) $NaClO_2$, 68%.

2.1.3 Present work:

Objective:

The medicinal properties of (*S*)-oxybutynin has attracted a great deat of interest among various chemists. Although some of the synthesis of oxybutynin were reported previously, but the major drawbacks of these methods are multistep synthesis, high cost of chiral material employed, complicated reagents and longer reaction time. Thus, in view of above mentioned disadvantages, it was desirable to develop an improved, efficient and enantioselective process for the synthesis of oxybutynin.

Our synthetic strategy for the synthesis of (*S*)-oxybutynin **3** was envisioned through the retrosynthetic route shown in Scheme 6. The chiral *tert*-α-hydroxy acid **12**, one of the components of the target molecule, could be obtained by the Sharpless asymmetric dihydroxylation of α-cyclohexylstyrene **36** and subsequent oxidation of the primary hydroxyl group. The other component **41** required for the oxybutynin synthesis could be easily derived from 2-butyne-1,4-diol **38**, a readily available starting material.

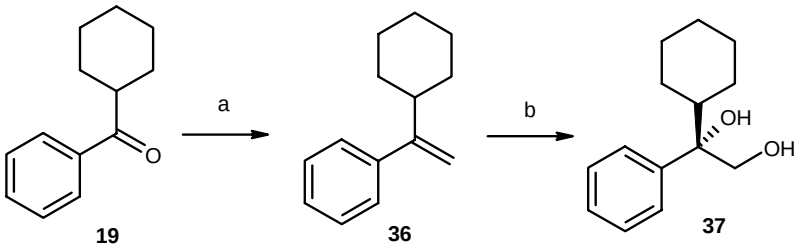


Retrosynthetic route to oxybutynin (Scheme 6).

2.1.4. Results and Discussion:

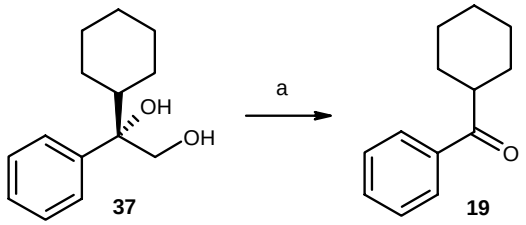
Synthesis of *tert*-α-hydroxy acid

The synthesis of *tert*-α-hydroxy acid **12** started from cyclohexyl phenyl ketone **19** as illustrated in Scheme 7. Compound **19** was treated with methylene triphenylphosphorane to give the Wittig product **36** in 92% yield. The ^{1}H NMR spectrum of **36** gave olefin peaks at 5.06-5.20 (singlet, two proton). The IR spectrum showed the olefin C=C stretching at 1625 cm^{-1}. The asymmetric dihydroxylation of olefin **36** with osmium tetroxide and potassium ferricyanide as cooxidant in the presence of $(DHQ)_2$-PHAL as the chiral ligand under Sharpless asymmetric dihydroxylation conditions[40,41] gave the crude product which on recrystallisation twice from EtOAc/pet. ether afforded the pure diol **37** in 70% yield with 92% ee. The IR spectrum of **37** showed hydroxyl absorption at 3424 cm^{-1}. The ^{1}H NMR indicated absence of olefin protons. The enantiomeric excess of diol **37** was determined by converting it into the mono-Mosher and analyzing the ^{19}F spectrum.

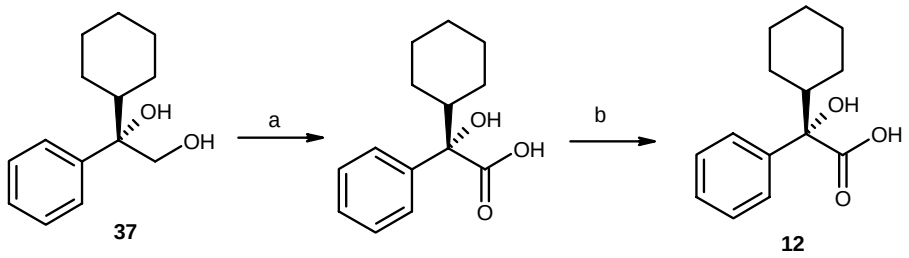


Scheme 7. *Reagents and conditions:* (a) $Ph_3P^+CH_3I^-$, *n*-BuLi, THF, 0 °C–rt, 8 h, 92%; (b) OsO_4, $(DHQ)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH:H_2O (1:1), OsO_4, 0 °C, 18 h, 70%.

The subsequent Jones' oxidation[42] of primary alcohol in **37** in order to obtain the acid **12** was unsuccessful resulting in cleavage of the diol affording the starting ketone **19** in a quantitative yield (Scheme 8). Hence we attempted a two-step process in the following way. As shown in Scheme 9, the alcohol **37** was first oxidized to the corresponding aldehyde under standard Swern oxidation conditions[43] followed by further oxidation with $NaClO_2$ and $NaH_2PO_4{\cdot}2H_2O$ to furnish the acid **12** in 70% yield. The IR spectra of **12** showed hydroxyl absorption at 3396 cm^{-1} and acid carbonyl at 1704 cm^{-1}. The ^{1}H NMR and ^{13}C NMR spectra of **12** were compatible with the assigned structure. $[\alpha]_D^{20} = +23.3$ (*c* 1, EtOH) [lit.[32] $[\alpha]_D^{20} = +22.6$ (*c* 1.4, EtOH)].



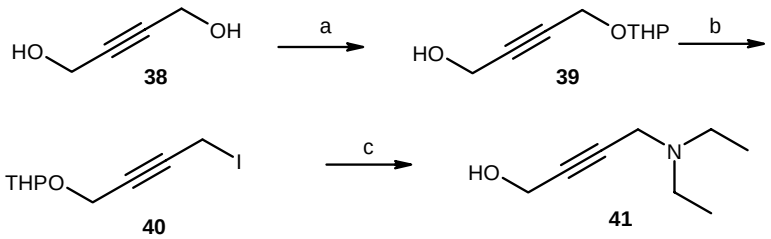
Scheme 8. *Reagents and conditions:* (a) Jones' CrO_3, acetone, 95%.



Scheme 9. *Reagents and conditions:* (a) $(COCl)_2$, DMSO, −78 °C, Et_3N, CH_2Cl_2 (b) $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, 2-methyl-2-butene, *t*-BuOH, rt, 4 h, 70%.

Synthesis of amino alcohol fragment

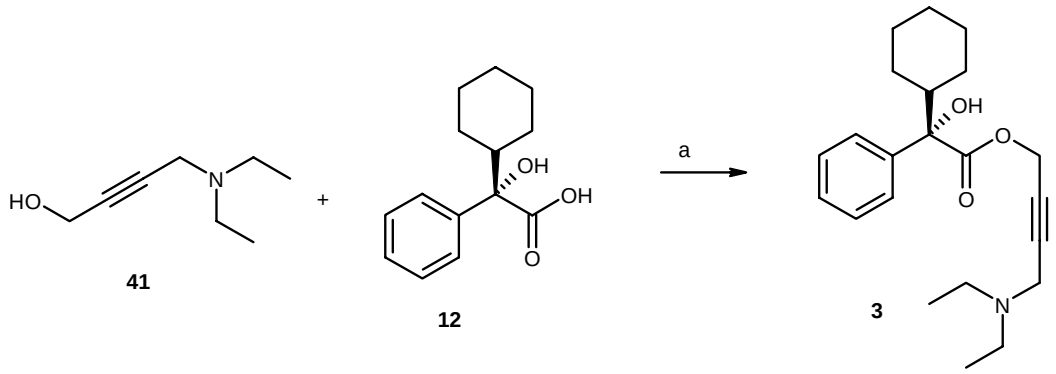
Scheme 10 summarizes the synthesis of 4-*N*,*N*-diethyl aminobut-2-yn-1-ol **41** from the commercially available 2-butyne-1,4-diol **38**. The mono hydroxyl protection of **38** by using DHP, *p*-TsOH (cat.) in CH_2Cl_2 afforded the THP ether in 60% yield. Conversion of the free hydroxyl group into the iodide afforded iodo compound **40** in good yield. In the ^1H NMR spectrum of **40** the resonances due to CH_2I were located at 3.45-4.1 as a multiplet. Displacement of iodide with diethylamine and subsequent acid treatment resulted in the formation of the hydrochloride salt of **41** with concomitant deprotection of the THP ether. Subsequent neutralization with base furnished the desired compound **41** in 70% yield. The ^1H and ^{13}C NMR spectra of **41** were compatible with the assigned structure.



Scheme 10. *Reagents and conditions:* (a) DHP, *p*-TsOH (cat.), CH_2Cl_2, rt, 60%; (b) PPh_3, I_2, imidazole, CH_2Cl_2, 0 °C–rt, 90%; (c) (a) Et_2NH, EtOH, $NaHCO_3$ (b) 6N HCl, Et_2O (c) 2N KOH, CH_2Cl_2, 70%.

Coupling of fragments

Coupling of acid **12** with amino alcohol **41** could readily be performed by activating the acid as a mixed anhydride and condensation with **41** as previously described.[37]



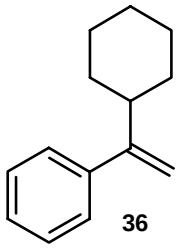
Scheme 11. *Reagents and conditions:* (a) 2,4,6-trichlorobenzoyl chloride, DMAP, Et_3N, THF, 0 ^oC - rt, 20 h, 72%

2.1.5. Conclusion

In conclusion, a practical and short synthesis of (*S*)-oxybutynin has been realized employing the Sharpless asymmetric dihydroxylation of α-cyclohexylstyrene for the first time as the key step. The synthetic strategy can be further extended to the asymmetric synthesis of (*R*)-oxybutynin and other related analogs.

2.1.6. Experimental Section

(1-Cyclohexylvinyl)benzene (36).



To a suspension of methyl triphenylphosphonium iodide (28.34 g, 70.11 mmol) in dry THF (75 mL) was added *n*-BuLi (36 mL, 72 mmol, 2 M soln in hexane) dropwise at 5-10 ^oC. The reaction mixture was stirred for 1 h and allowed to settle. The yellow supernatant

liquid was added via a syringe to a solution of cyclohexyl phenyl ketone **19** (12 g, 63.74 mmol) in THF (50 mL). The reaction mixture was stirred for 8 h at room temperature and then quenched with 5% aq. NH_4Cl soln. The organic layer was separated and aq. layer was extracted with EtOAc (2 x 50mL). The combined org. extracts were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using pet ether: EtOAc (49:1) as eluent to give α-cyclohexyl styrene **36** as colorless oil.

Yield: 10.92 g, 92%

Mol. Formula: $C_{14}H_{18}$

IR ($CHCl_3$, cm^{-1}): ν_{max} 2926, 1625, 1493, 1447, 1027, 815, 775, 604.

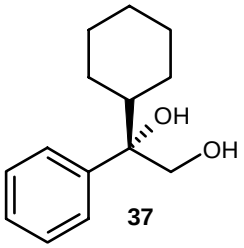
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.19-1.49 (m, 6H), 1.76-1.93 (m, 4H), 2.49 (brt, *J* = 10.7 Hz, 1H), 5.07 (d, *J* = 1.5 Hz, 1H), 5.19 (d, *J* = 1.5 Hz, 1H), 7.33-7.42 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.4, 26.8, 32.7, 42.7, 110.2, 126.6, 126.8, 127.9, 142.9, 154.

EIMS (m/z,relative intensity) : 186[M+] (40.5), 171 (39.2), 157 (7.8), 143 (12.0), 129 (100), 115 (58.8), 104 (61.4), 91 (48.36), 77 (77.1), 65 (28.7), 55 (61.4).

Analysis Calcd.: C, 90.26 ; H, 9.74%; **Found:** C, 90.42 ; H, 9.81%.

(*S*)-1-Cyclohexyl-1-phenylethane-1,2-diol (37).



37

To a mixture of $K_3Fe(CN)_6$ (10.56 g, 32.2 mmol), K_2CO_3 (4.45 g, 32.2 mmol) and $(DHQ)_2PHAL$ (83.58 mg, 0.11 mmol, 1mol%) in *t*-BuOH:H_2O (1:1, 100 mL) was added OsO_4 (434 μL, 0.1M soln in toluene, 0.4 mol%). The reaction mixture was stirred at 0 ^oC for 5 min and the olefin **36** (2 g, 10.73 mmol) was added in one portion. After stirring for 18 h at 0 ^oC the reaction mixture was quenched by adding solid Na_2SO_3 (2 g) and stirred for 15 min. The aq layer was separated and extracted with EtOAc (3x100mL). The combined organic layer was washed (brine), dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using pet ether: EtOAc (7:3) to give diol

37 in quantitative yield as a white solid. This was further recrystallised twice in EtOAc/pet ether to give diol **37**.

Yield: 1.65 g, 70%

Mol. Formula: $C_{14}H_{20}O_2$

m.p.- 98-99 ^oC

$[\alpha]_D^{25}$: -3.25 (*c* 1, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3424, 2931, 1447, 1215, 668.

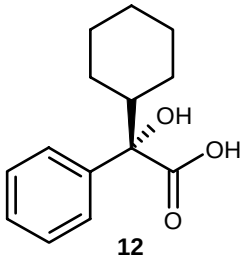
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.97-1.27 (m, 6H), 1.63-1.87 (m, 5H), 2.03 (brs, 2H), 3.88 (d, *J* = 10Hz, 1H), 4.05 (d, *J* = 10Hz, 1H), 7.29-7.45 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.3, 26.4, 26.6, 26.8, 27.2, 45.5, 68.0, 79.1, 126.1, 126.9, 128.1, 143.0.

EIMS (m/z, relative intensity): 220 [M+] (1.3), 219 [M+-1] (2.6), 203 (1.3), 189 (100), 171 (6.6), 137 (42.4), 107 (35.1), 91 (70.2), 77 (31.8), 65 (11.3), 55 (42.4).

Analysis Calcd.: C, 76.32; H, 9.15 %; **Found:** C, 76.51; H, 9.11%.

(*S*)-2-Cyclohexyl-2-hydroxy-2-phenylacetic acid (12)



12

To a soln of $(COCl)_2$ (2.59 g, 1.76 mL, 20.43 mmol) in CH_2Cl_2 (40 mL) at –78 ^oC was added a soln of DMSO (2.9 mL, 40.85 mmol) in CH_2Cl_2 (5 mL) dropwise. The reaction mixture was stirred for 30 min and then a soln of alcohol **37** (3 g, 13.62 mmol) in CH_2Cl_2 (10 mL) was added dropwise when a copious white ppt was obtained. The reaction mixture was stirred at –78 ^oC for 1 h. Et_3N (6.5 mL) in CH_2Cl_2 (10mL) was added dropwise at –60 ^oC and the reaction mixture was allowed to warm at room temperature (2 h). The reaction mixture was poured into 2N HCl (100 mL) and organic layer separated. The aq layer was extracted with CH_2Cl_2 (2 x 50mL). The combined organic layer was washed with water, brine, dried (Na_2SO_4) and filtered through a pad of neutral alumina. The filtrate was

concentrated to afford a virtually pure aldehyde which was used without further purification.

To a soln of above aldehyde in *t*-BuOH (50 mL) was added 2-methyl-2-butene (91.28 g, 18.32 mmol). A soln of $NaClO_2$ (3.31 g, 36.64 mmol) and $NaH_2PO_4.2H_2O$ (4.39 g, 28.12 mmol) in water (20 mL) was added at 0 ^oC. The reaction mixture was stirred for 4 h at room temperature. The reaction mixture was quenched by adding solid Na_2SO_3 (2 g) and acidified to acidic pH. The organic layer was separated and the aq layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layer was washed (brine), dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using $CHCl_3$:MeOH (4:1) as eluent to give **12** as a white solid.

Yield: 2.23 g, 70%

Mol. Formula: $C_{14}H_{18}O_3$

$[\alpha]_D^{25}$: = +23.3 (*c*, 1.0, EtOH)] [lit[32] $[\alpha]_D^{25}$ = + 22.6 (*c*, 1.4, EtOH)]

IR ($CHCl_3$, cm^{-1}): ν_{max} 3396, 2934, 1704, 1448, 1216, 758.

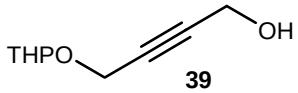
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.07-1.45 (m, 6H), 1.47-1.84 (m, 4H), 2.18-2.32 (m, 1H), 7.29-7.41 (m, 3H), 7.64-7.68 (d, *J* = 8 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 25.4, 26.1, 26.2, 27.3, 45.7, 81.0, 126.0, 127.7, 128.2, 140.0, 180.6.

EIMS: 234[M+] (1.3), 23 (1.9), 189 (68.4), 171 (5.2), 152 (85.2), 104 (100), 90 (27.1), 77 (68.4), 55 (69.0).

Analysis Calcd.: C, 71.76; H, 7.74%; **Found:** C, 71.94; H, 7.65%.

4-(Tetrahydro-2*H*-pyran-2-yloxy)but-2-yn-1-ol (39).



39

To a stirred solution of 1,4-but-2-yne-diol **38** (5 g, 58.07 mmol) and catalytic *p*-TsOH in CH_2Cl_2 (200 mL) was added 3,4-dihydro-2*H*-pyran (4.89 g, 5.27 mL, 58.07 mmol). The reaction mixture was stirred for 12 h at room temperature. A pinch of $NaHCO_3$ was added and stirred for 10 min. The reaction mixture was filtered through neutral alumina and the filtrate concentrated. The residue was purified by silica gel column chromatography using pet ether: EtOAc (85:15) as eluent to give **39** as a colorless liquid.

Yield: 5.93 g, 60%

Mol. Formula: $C_9H_{14}O_3$

IR (neat, cm^{-1}): ν_{max} 3386, 2941, 1728, 1453, 1348, 1130.

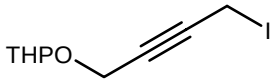
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.52-1.76 (m, 6H), 3.29 (brs, 1H), 3.48-3.52 (m, 1H), 3.75-3.85 (m, 1H), 4.2-4.4 (m, 4H), 4.75-4.8 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 21.1, 25.4, 30.4, 50.1, 52.0, 63.5, 84.6, 86.7, 104.9.

EIMS (m/z,relative intensity) : 170 [M+] (2), 169 [M+-1] (6), 111 (6.7), 101 (23.3), 97 (14.7), 85 (100), 67 (22.7), 55 (67.3).

Analysis Calcd.: C, 63.51; H, 8.29%; **Found** C, 63.35; H, 8.21%.

2-(4-Iodobut-2-ynyloxy)-tetrahydro-2*H*-pyran (40).



40

To a stirred solution of triphenyl phosphine (3.7 g, 14.1 mmol) in CH_2Cl_2 (100 mL) was added I_2 (3.58 g, 14.1 mmol) at 0 ^oC. To the orange precipitate was added drop wise a solution of alcohol **39** (2 g, 11.75 mmol) and imidazole (0.96 g, 14.1 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature for 1.5 h. The reaction mixture was quenched with water (100 mL) and the organic layer separated. The aq. layer was extracted with CH_2Cl_2 (2 x 100mL) and the combined organic layer was washed with 5% aq. Na_2HSO_3 solution followed by brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using pet ether:EtOAc (49:1) as eluent to afford **40** as a colourless oil

Yield: 3.0 g, 90%

Mol. Formula: $C_9H_{13}IO_2$

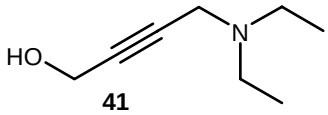
IR (neat, cm^{-1}): ν_{max} 2939, 2236, 1729, 1523, 1120, 866.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.48-1.79 (m, 6H), 3.45-4.1 (m, 4H), 4.22-4.3 (m, 2H), 4.75-4.8 (m,1H).

EIMS (m/z, relative intensity): 279 [M^+ -1] (1.3), 254 (11.05), 209 (5.26), 164 (11.8), 127 (63.1), 85 (49.3), 67 (26.3), 55 (100).

Analysis Calcd.: C, 38.59; H, 4.68; I, 45.31; **Found:** C, 38.31; H, 4.55; I, 45.45.

4-(Diethylamino)but-2-yn-1-ol (41)



41

To a solution of **40** (1.7 g, 6.07 mmol) in EtOH (10 mL) was added $NaHCO_3$ (0.51 g, 6.07 mmol) and diethyl amine (1.33 g, 18.21 mmol) at room temperature. The reaction mixture was concentrated and the residue was diluted with ether (20 mL). To this was added 6N HCl till acidic pH. The ether layer was discarded and aq layer extracted with ether (2 x 10mL).The aq. layer was basified with 2N KOH until alkaline pH to release the free amino alcohol which was extracted with CH_2Cl_2 (4 x 20 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography using $CHCl_3$:MeOH (9:1) as eluent to give **41** as a thick yellow oil.

Yield: 0.6 g, 70%

Mol. Formula: $C_8H_{15}NO$

IR (neat, cm^{-1}): ν_{max} 3357, 2972, 2333, 1462, 1106, 1024.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.04 (t, *J* = 7Hz, 6H), 2.54-2.58 (q, *J* = 7Hz, 4H), 3.41 (s, 2H), 4.21 (s, 2H), 4.40 (s, 1H).

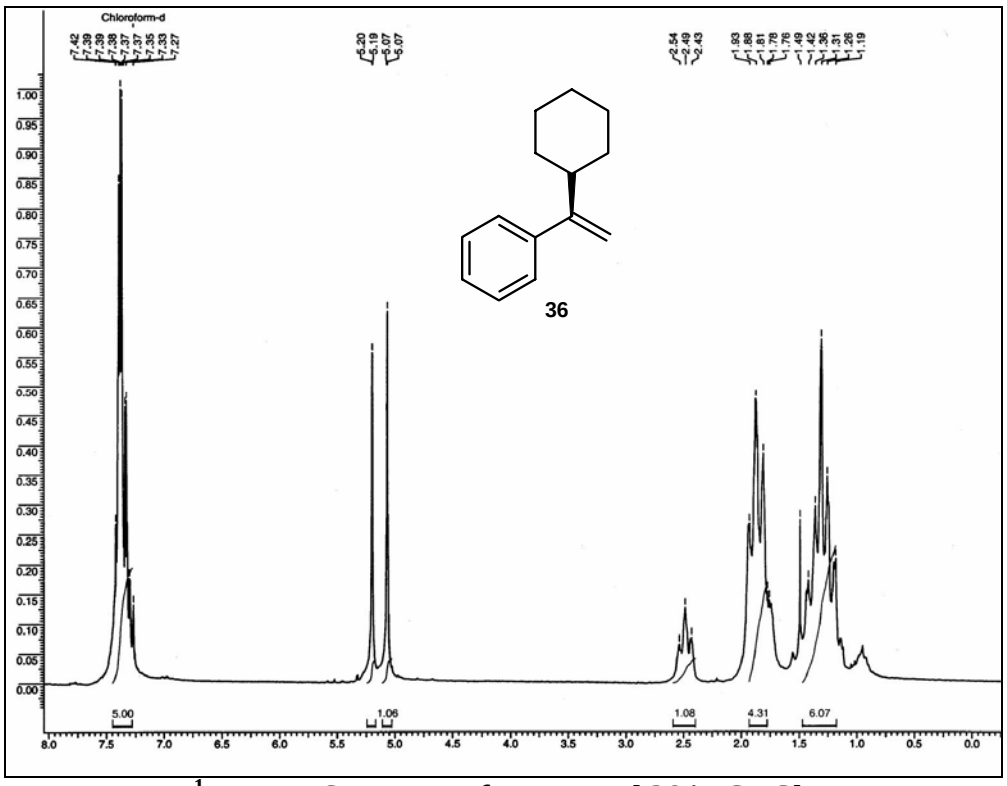
^{13}C NMR (50 MHz, $CDCl_3$): δ 12.0, 42.6, 47.2, 51.9, 82.4, 86.7.

EIMS (m/z, relative intensity): 141 [M^+] (10.4), 140 [M^+-1] (4.6), 126 [M^+-CH_3] (98.6), 108 (2.6), 94 (2.6), 86 (11.1), 68 (13.1) 58 (100), 53 (27.4).

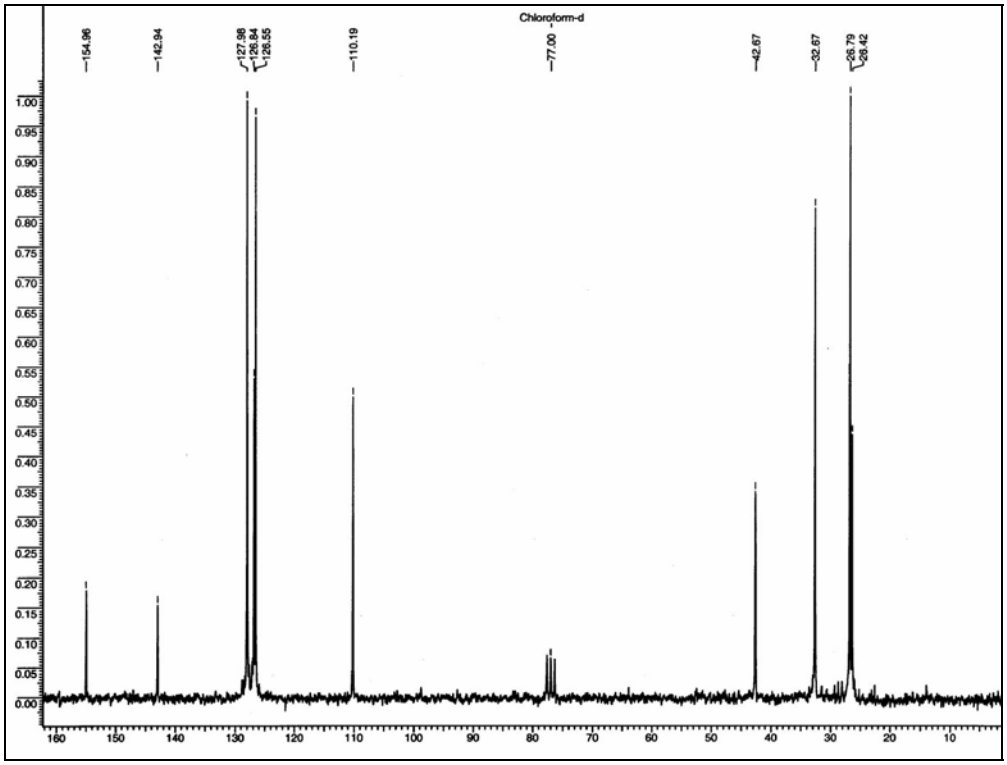
Analysis Calcd.: C, 68.04; H, 10.71; N, 9.92%; **Found:** C, 68.27; H, 10.69; N, 9.81%.

2.1.7 Spectra

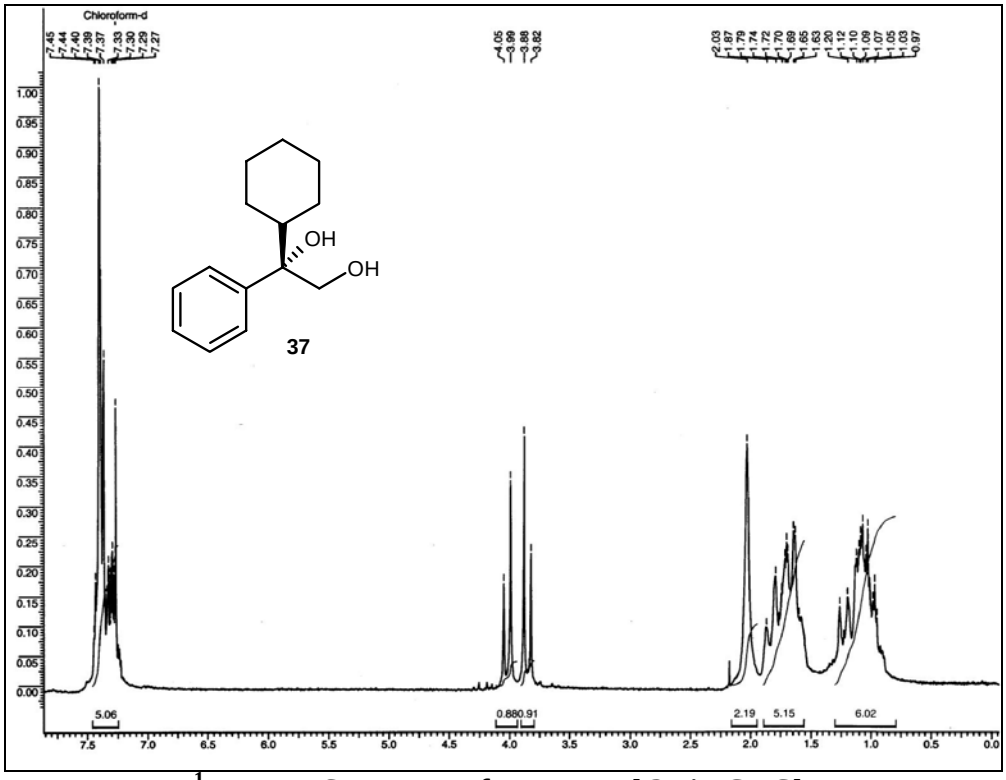
1. ^{1}H and ^{13}C NMR spectra of 36
2. ^{1}H and ^{13}C NMR spectra of 37
3. ^{1}H and ^{13}C NMR spectra of 12
4. ^{1}H and ^{13}C NMR spectra of 41



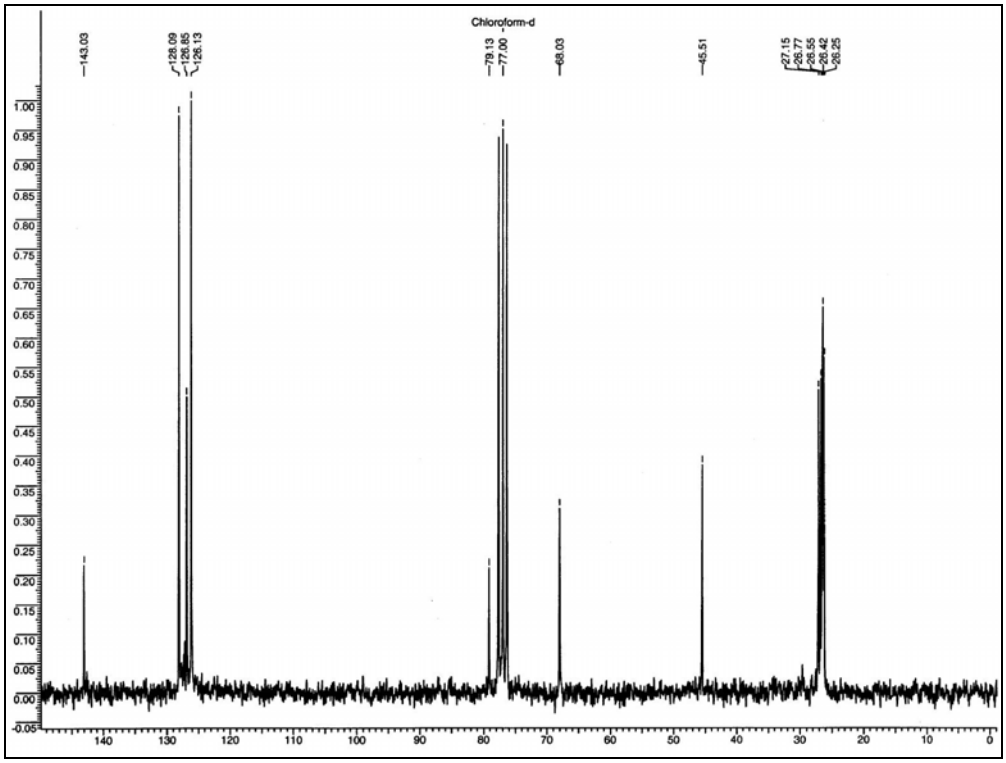
^{1}H NMR Spectrum of compound 36 in $CDCl_3$



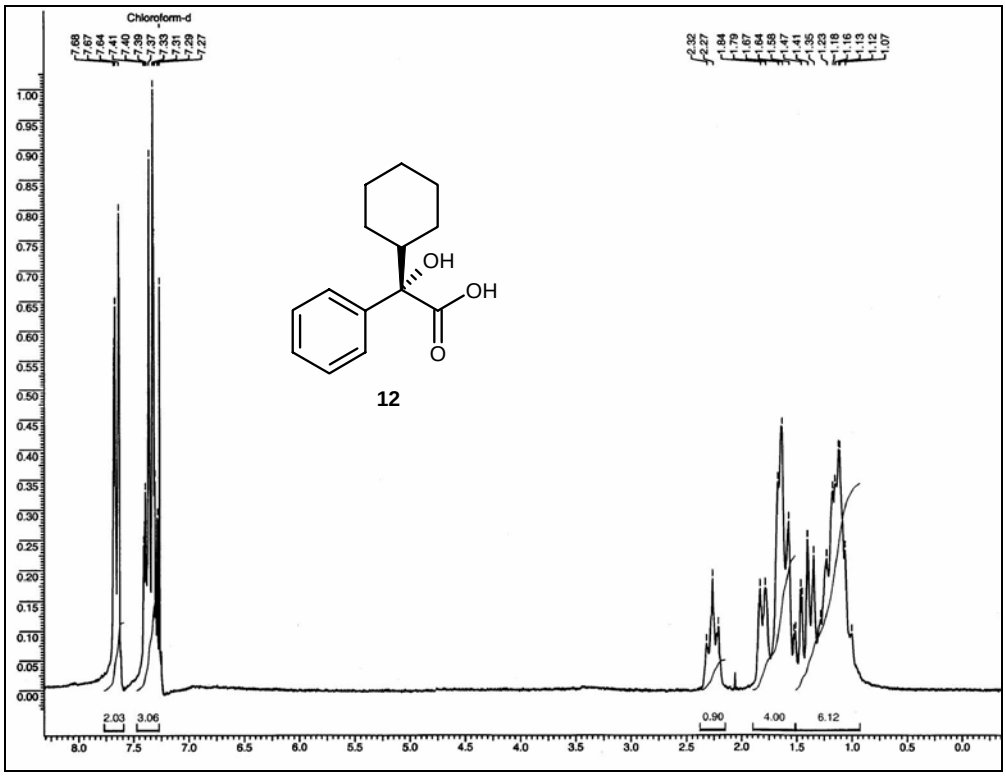
^{13}C NMR Spectrum of compound 36 in $CDCl_3$



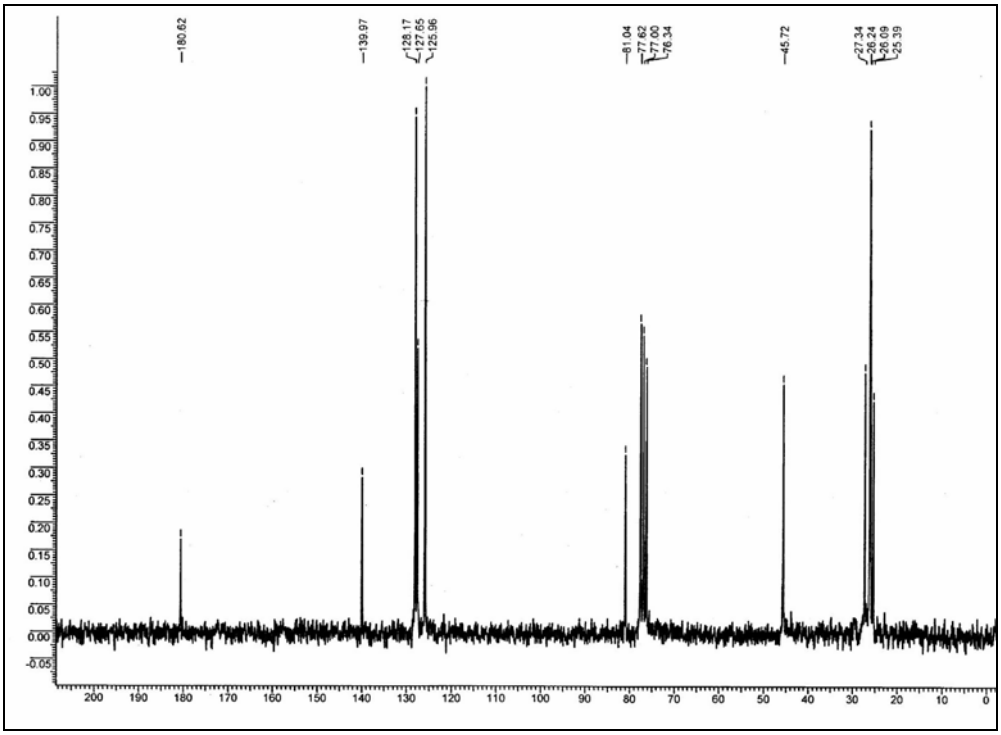
^{1}H NMR Spectrum of compound 37 in $CDCl_3$



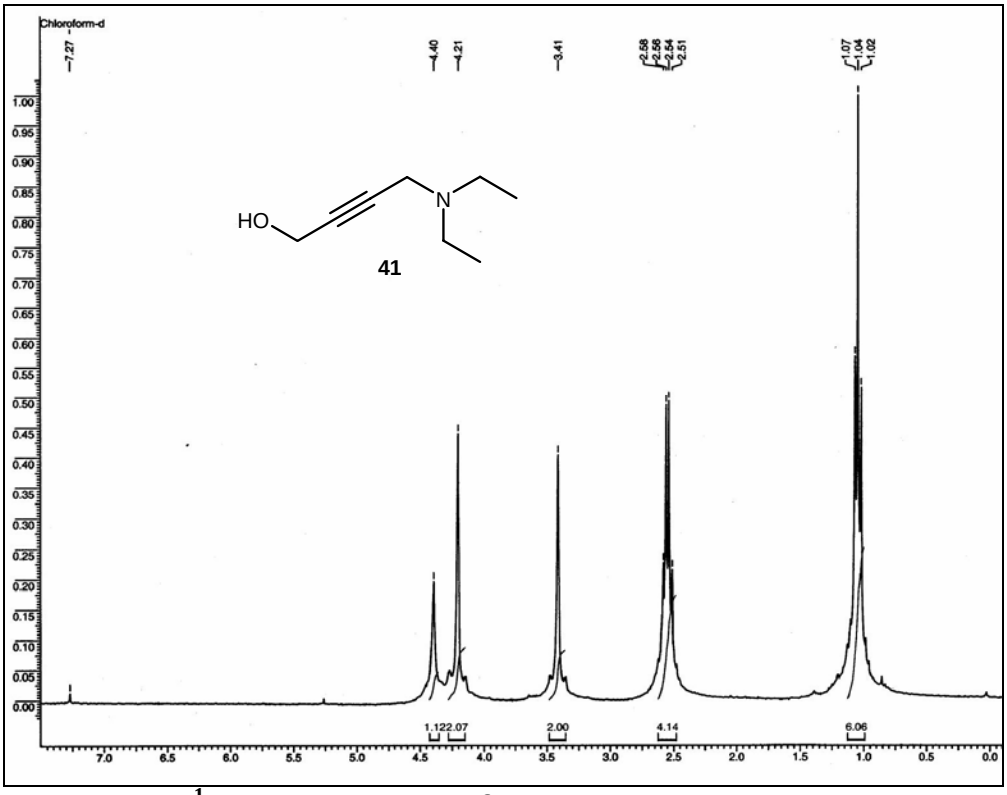
^{13}C NMR Spectrum of compound 37 in $CDCl_3$



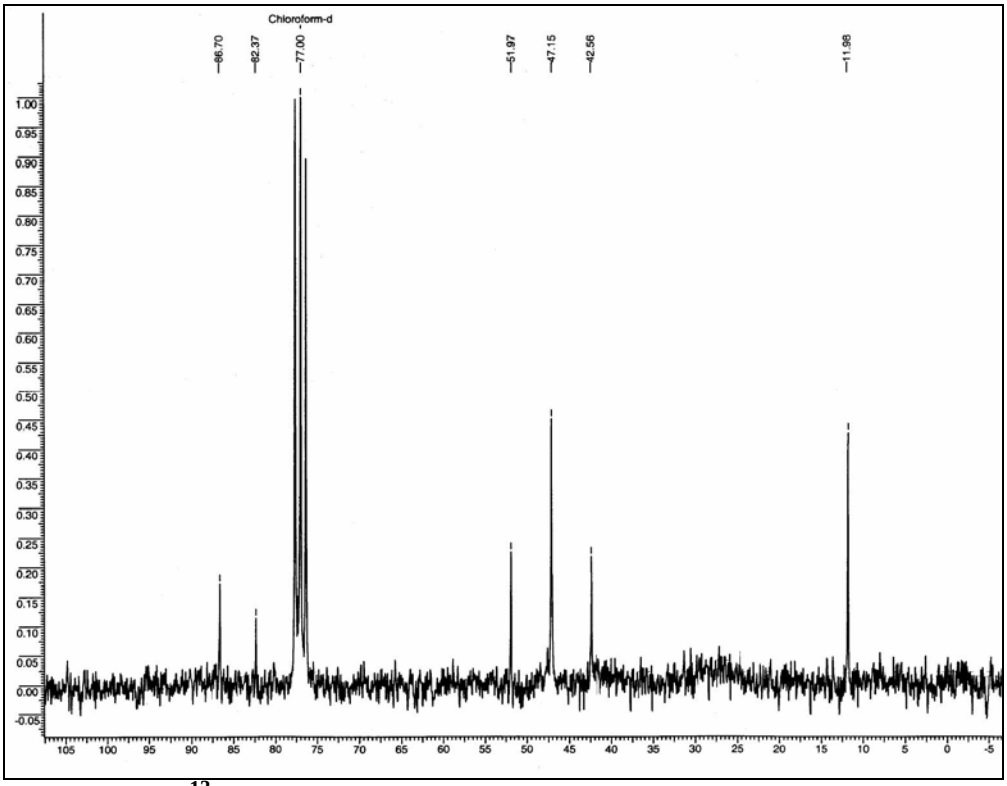
^{1}H NMR Spectrum of compound 12 in $CDCl_3$



^{13}C NMR Spectrum of compound 12 in $CDCl_3$



^{1}H NMR Spectrum of compound 41 in $CDCl_3$



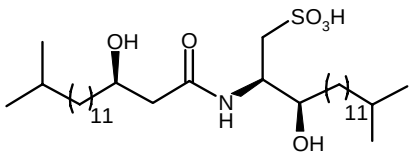
^{13}C NMR Spectrum of compound 41 in $CDCl_3$

2.2 SECTION B

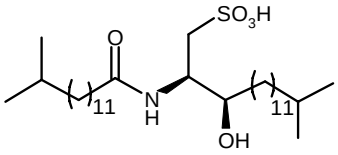
TOTAL SYNTHESIS OF SULFOBACIN A, SULFOBACIN B, TOPOSTINS B567 AND D654

2.2.1. Introduction

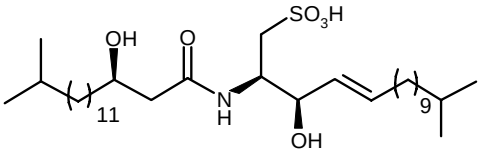
Sulfobacins A and B were isolated for the first time in 1995 by Kamiyama et al. from the culture broth of *Chryseobacterium* sp. NR 2993, a strain isolated from a soil sample collected on Iriomote Island (Fig. 3).[44] Almost simultaneously, Kobayashi and co-workers[45] isolated flavocristamide A and sulfobacin A from the cultured mycelium of *Flavobacterium* sp. These compounds are novel sulfonolipids and are unusual sphingosine derivatives. Biological studies of these compounds were revealed to inhibit the binding of von Willebrand factor to the GPIb/IX receptors in a competitive manner with IC_{50}'s of 0.47 μM for sulfobacin A and 2.2 μM for sulfobacin B, respectively. These compounds were also found to exhibit inhibitory activity against DNA polymerase α.



Sulfobacin A **42**



Sulbobacin B **43**



Flavocristamide A **44**

Figure 3

Topostins were isolated from the culture broth of *Flexibacter topostinus* sp. nov., B-572, by Andoh and co-workers.[46] They have proved to be structurally novel inhibitors of mammalian DNA topoisomerase I. Topostin B comprises two components with the molecular weights of 553 and 567 in an equimolecular ratio, and were reported to be most active. Recently, Ojika and co-workers[47] reinvestigated the isolation and structures of

topostins, and conclusively determined the structures of original topostins B, B553 **45** and B567 **46**, as well as new analogs named topostins D, D640 **47** and D654 **48**, as shown in Fig. 4. Among them, the gross structure of topostin B567 **46** was found to be identical with that of cytolipin[48] isolated from *Cytophagajohnsonae* while topostin D654 was identical with WB-3559D[49] isolated from *Flavobacterium* sp. No. 3559 and flavolipin[50] isolated from *Flavobacterium meningosepticum*. Furthermore, the western fragment of topostins B567 **46** and D654 **48**, the (3*R*)-l*S*-methyl-3-(13-methyltetradecanoyloxy)hexadecanoyl group, was found to be quite similar to the western fragment of sulfobacin A **42**.

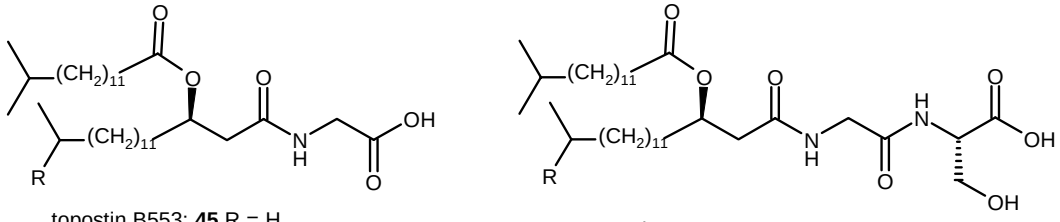


Figure 4

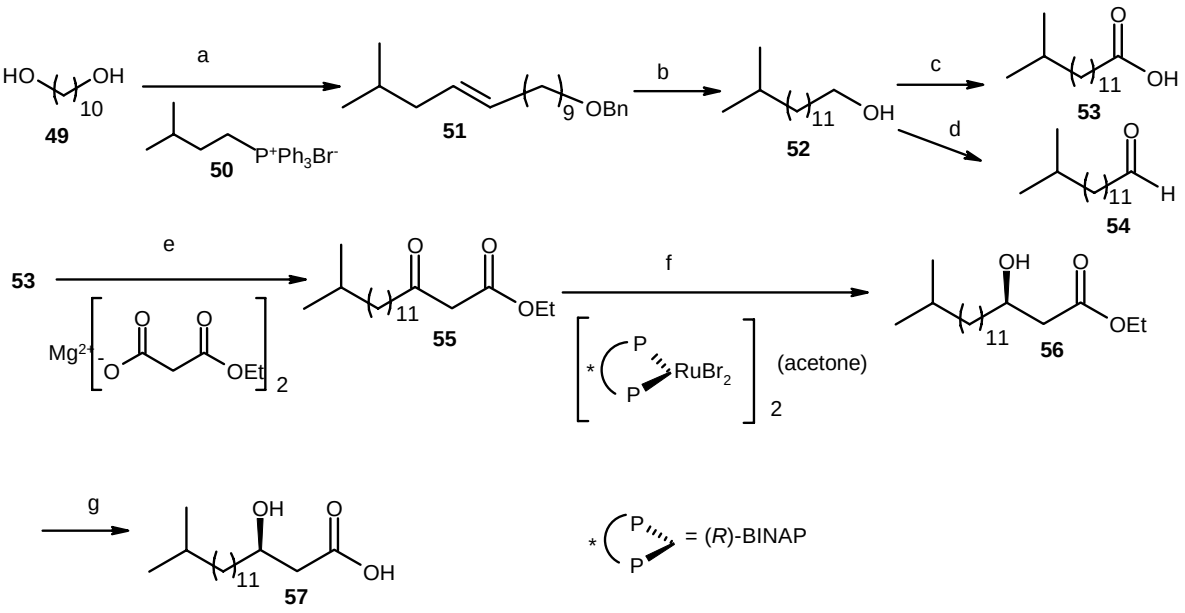
2.2.2. Review of Literature

In the literature, the three different synthetic approaches reported so far for sulfobacin A involve either a chiral building block or a chiral auxiliary to establish one or more of the stereogenic centres present in the molecule. The asymmetric aldol reaction of a Schiff's base derived from glycine ethyl ester and (+)-2-hydroxy-3-pinanone has been utilized as the key step by Shioiri et al.[51] In another approach, the title compound was synthesized in a stereoselective manner using L-cysteine as a chiral buiding block.[52] Genet et al.[53] have employed a ruthenium-catalyzed asymmetric hydrogenation and diastereoselective electrophilic amination for the construction of the three stereogenic centres. A detailed report of these syntheses is described below.

Shioiri *et al.* (1998).[51]

Shioiri and co-workers accomplished the synthesis of sulfobacin A by asymmetric aldol reaction of a Schiff's base derived from glycine ethyl ester and (+)-2-hydroxy-3-pinanone. Thus, as shown in scheme 12, 1,10-decanediol **49** was monoprotected as benzyl ether

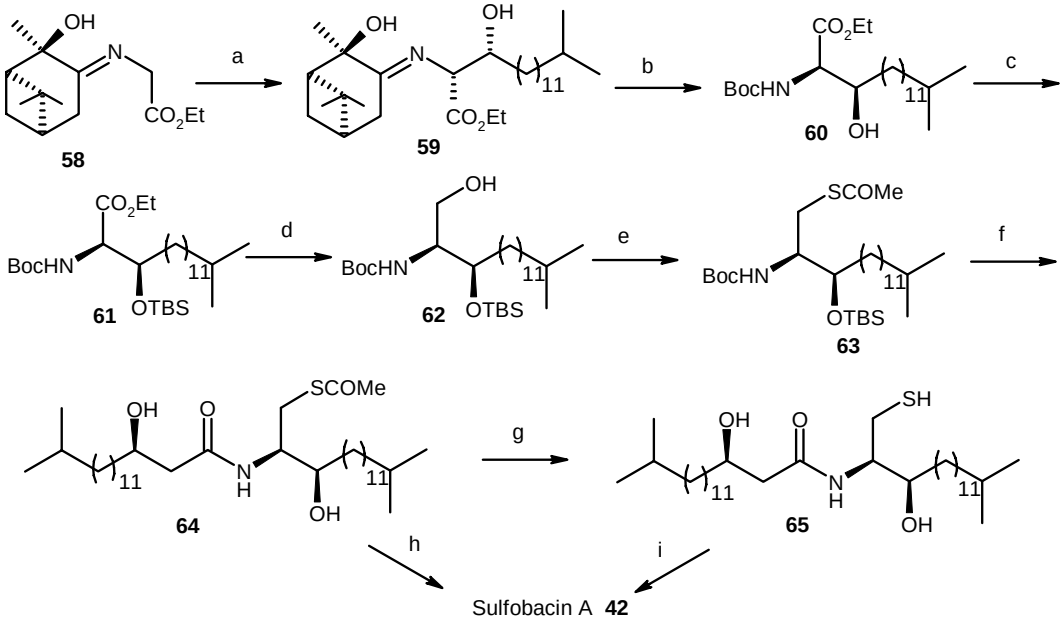
followed by Swern oxidation and Wittig olefination to afford the olefin **51**. Reduction of the double bond and hydrogenolytic deprotection afforded alcohol **52**, which on Jones oxidation furnished acid **53**. Aldehyde **54** was also obtained from alcohol **52** by oxidation with PCC. Acid **53** was converted into β-keto ester **55** which on asymmetric hydrogenation according to Genet's method[54] gave β-hydroxy ester **56**, which was further converted into β-hydroxycarboxylic acid **57** by alkaline treatment.



Scheme 12. *Reagents and conditions*: a) (i) BnBr, NaH, rt, 4 h, 50%; (ii) Swern oxidation, 100%; (iii) **50**, *n*-BuLi, rt, 1 h, 85%; (b) H_2, 5%Pd/C, EtOAc, rt, 3 h, 100%; (c) Jones reagent, rt, 1 h, 96%; (d) PCC, rt, 2 h, 87%; (e) (i) carbonyl diimidazole, THF, reflux, 6 h; (ii) rt, 4 h; (f) H_2 (1atm), EtOH, reflux, 6 h; (g) 1N aq. NaOH, 95%.

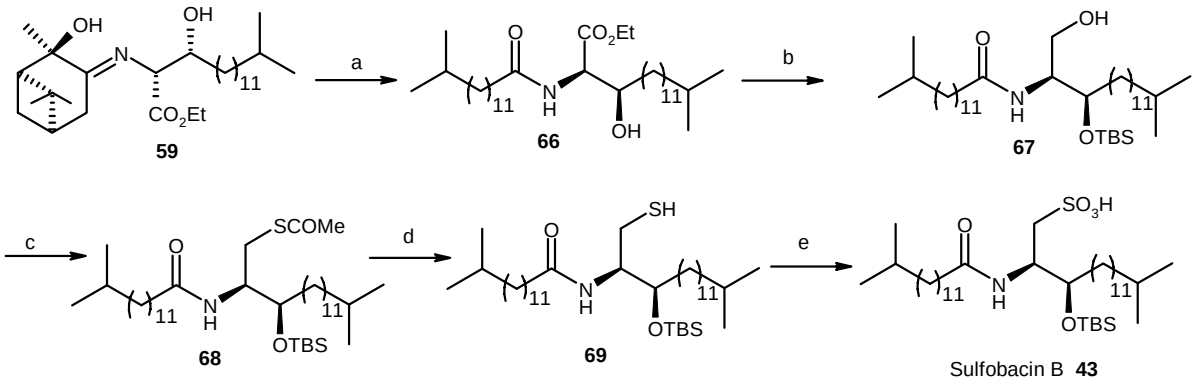
Another fragment was prepared from aldehyde **54** and the chiral Schiff base of (+)-2-hydroxy-3-pinanone **58** using the Solladie methodology.[55] Thus the asymmetric aldol reaction of **54** and the Schiff base **58** gave the erythro aldol adduct **59**. Removal of the chiral auxiliary followed by treatment with Boc_2O, and TBSCl afforded the ester **61**, which was reduced to give the primary alcohol **62**. Alcohol **62** was converted to the thioacetate **63** via mesylate. After deprotection of the Boc and TBS group in thioacetate **63**, the coupling of the deprotected right fragment with left fragment **57** was achieved with DEPC.[56] The thioacetate **64** was subjected to pertrifluoroacetic acid oxidation to afford the

sulfobacin A **42**. Alternatively, the thioacetate **64** was reduced with $LiAlH_4$ to give the corresponding thiol **65** which on pertrifluoroacetic acid oxidation yielded sulfobacin A **42** (Scheme 13).



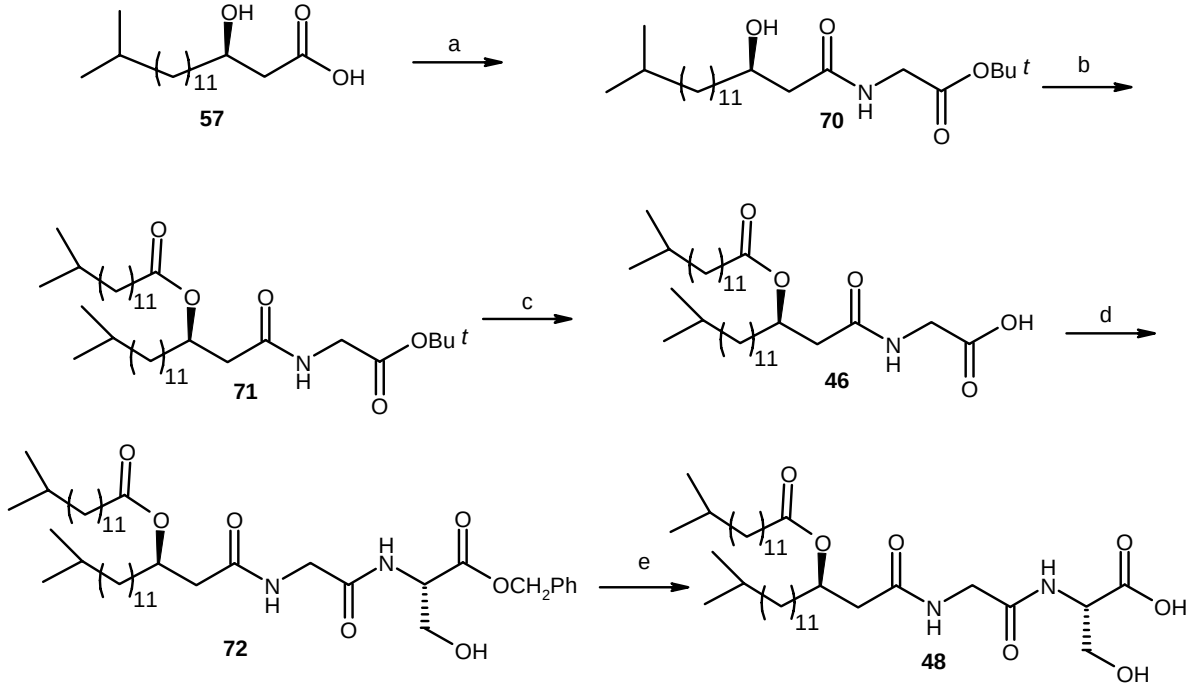
Scheme 13. *Reagents and conditions*: (a) $TiCl(OEt)_3$, $(CH_3)_2CH(CH_2)_{11}CHO$, Et_3N, CH_2Cl_2, 0 ^oC, 5 h, 92%; (b) (i) 1N aq. HCl, THF, rt, 68 h; (ii) Boc_2O, Et_3N, DMF, rt, 20 h, 87%; (c) TBSCl, imidazole, DMF, rt, 18 h, 96%; (d) $NaBH_4$, LiCl, THF, EtOH, -10 ^oC, 1 h, rt, 19 h, 100%; (e) (i) MsCl, Et_3N, benzotrifluoride, 0 ^oC, 1 h; (ii) CH_3COSK, DMF, rt, 20 h; (f) (i) 4N HCl-dioxane, rt, 3 h; (ii) **57**, DEPC, Et_3N, DMF, -10 ^oC, 1 h, rt, 20 h, 82%; (g) $LiAlH_4$, Et_2O, 0 ^oC, 0.5 h; (h) 30% aq. H_2O_2, TFA, rt, 1 h, 32%; (i) 30% aq. H_2O_2, TFA, rt, 0.5 h, 46%.

For synthesis of sulfobacin B **43**, chiral auxiliary was removed from adduct, followed by condensation with acid **53** to get the amide **66**. Protection of hydroxy of **66** as TBS ether followed by reduction afforded alcohol **67** which was converted into thioacetate **68** via Mitsunobu reaction. Thioacetate **68** was subjected to either the pertrifluoroacetic acid oxidation or the reduction followed by treatment with pertrifluoroacetic acid to give sulfobacin B.



Scheme 14. *Reagents and conditions*: a) (i) 1N aq. HCl, THF, rt, 68 h; (ii) **53**, DEPC, Et_3N, DMF, -10 ^oC, 1 h, rt, 16 h, 92%; (b) (i) TBSCl, imidazole, DMF, rt, 63 h, 95%; (ii) $NaBH_4$, LiCl, THF, EtOH, -10 ^oC, 1 h, rt, 22 h, 97%; (c) CH_3COSH, DIAD, TPP, THF, 0 ^oC, 1 h, rt, 22 h, 99%; (d) $LiAlH_4$, Et_2O, 0 ^oC, 15 min., 85%; (e) 30% aq. H_2O_2, TFA, rt, 0.5 h, 42%.

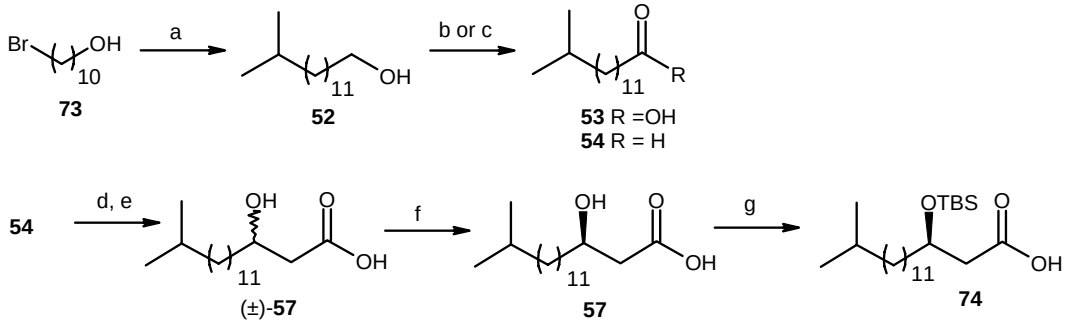
For the synthesis of topostin B567 and topostin D654, hydroxy acid **57** was condensed with glycine *tert*-butyl ester hydrochloride (H-Gly-OBu^t.HCl) to give amide **70**, which underwent the *O*-acylation with carboxylic acid **53** to afford the ester **71**. Finally, acidic deprotection of **71** furnished topostin B567 **46**, which on coupling with L-serine benzyl ester trifluoroacetate, followed by benzyl deprotection afforded topostin D654 **48**.



Scheme 39. *Reagents and conditions*: (a) H-Gly-OBu^t.HCl, DEPC, Et_3N, DMF, rt, 8 h, 96%; (b) **53**, EDCl.HCl, DMAP, CH_2Cl_2, 0 ^oC, 5 h, 90%; (c) TFA, $CHCl_3$, rt, 5 h, 97%; (d) H-L-Ser-OCH_2Ph.TFA, DEPC, TEA, DMF, rt, 20 h, 81%; (e) H_2, 5% Pd/C, EtOH, rt, 5 h, 67%.

Mori *et al.* (1998).[52]

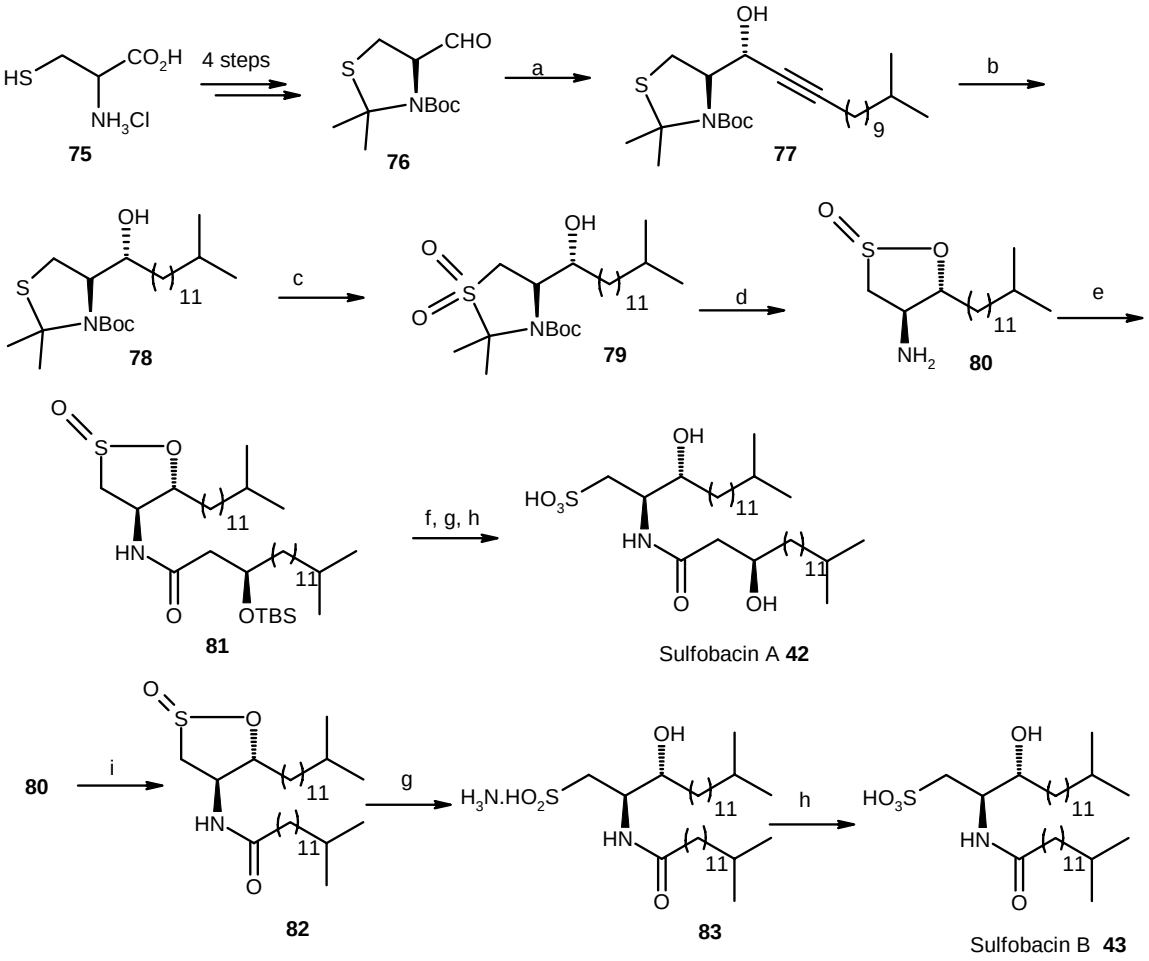
Mori and co-workers accomplished the synthesis of sulfobacin A from L-cysteine as a chiral building block. Thus Grignard coupling of bromo alcohol **73** with isoamylmagnesium bromide gave alcohol **52** which was oxidized to the corresponding aldehyde **53** and acid **54**. As shown in scheme 16, aldehyde **53** was treated with lithio enolate of ethyl acetate followed by hydrolysis to give (±)-**57**, which was resolved by lipase PS in the presence of vinyl acetate to afford desired (*R*)-**57**[57] which was further converted to the corresponding *t*-butyldimethylsilyl (TBS) ether **74**.



Scheme 16. *Reagents and conditions*: (a) $Me_2CH(CH_2)_2MgBr$, Li_2CuCl_4, THF, 96%; (b) PCC, MS 4A^o, CH_2Cl_2, 78%; (c) (Jones' oxidation) CrO_3, acetone, 70%; (d) EtOAc, LDA, THF, 79%; (e) LiOH, aq MeOH-THF, 86%; (f) lipase PS, vinyl acetate, BHT, 60 °C, 28%; (g) TBSC1, imidazole., DMF, then dil. HC1, 82%.

Synthesis of other fragment started from L-cysteine hydrochloride, which was converted into the known aldehyde **76**.[58] Diastereoselective addition of lithium acetylide derived from 12-methyl-1-tridecyne to **76** was performed by Fujisawa's procedure[58] to give the desired *anti*- adduct **77** which after reduction and further oxidation with *m*-CPBA afforded the key intermediate **79**. The cleavage of Boc and acetonide protecting group afforded aminosultine **80**.[59] For the synthesis of sulfobacin A, **80** was acylated with **74** to give **81** which on TBS deprotection, hydrolysis and oxidation furnished sulfobacin A **42** (Scheme 17).

For the synthesis of sulfobacin B, **80** was acylated with **53** to give **82** which on hydrolysis and oxidation afforded sulfobacin B **43** (Scheme 17).



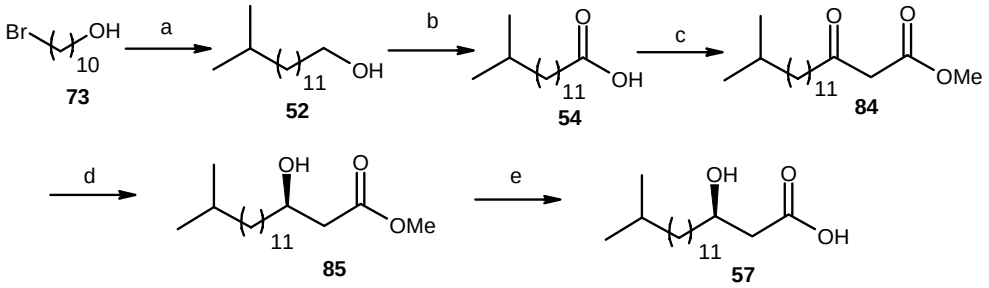
Scheme 17. *Reagents and conditions*: (a) *n*-BuLi, 12-methyl-l-tridecyne, HMPA/THF (82%, and 70%); (b) PtO_2, H_2, EtOAc (98%); (c) *m*-CPBA, $CHCI_3$, 99%; (d) 6M HCl, MeOH, 99%; (e) **74**, DCC, DMAP/$CHCl_3$, 78%; (f) TBAF, THF, 69%; (g) aq NH_3/$CHCI_3$-MeOH; (h) aq H_2O_2 (90% for 1, 94% for 2, 2 steps); (i) **54**, DCC, DMAP/$CHCl_3$ (74%);

Genet *et al.* (2003).[53]

Genet and co-workers synthesized sulfobacin A by using ruthenium-catalysed asymmetric hydrogenation and diastereoselective electrophilic amination as the key steps.

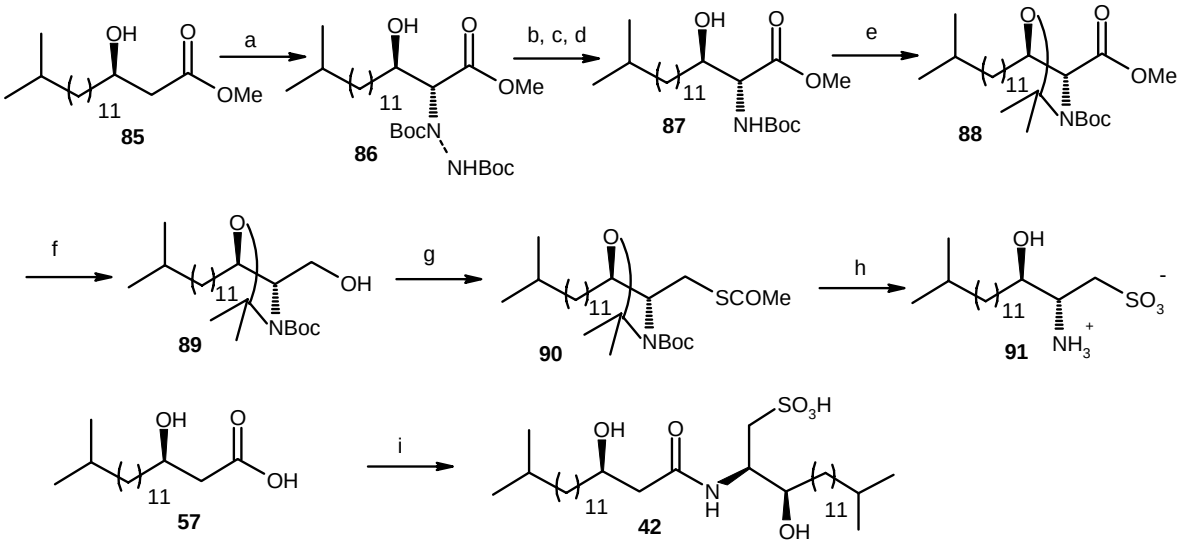
The synthesis of desired β-hydroxy ester **57** began with the commercially available 10-bromodecan-1-ol **73** which was converted into alcohol **52** via Grignard exchange followed by oxidation to afford acid **54**. Acid **54** was converted into ester **84**, using Masamune's

procedure,[60] which on asymmetric hydrogenation[61] followed by alkaline treatment furnished β-hydroxy acid **57** (Scheme 18).



Scheme 18. *Reagents and conditions*: (a) $Me_2CH(CH_2)_2MgBr$, Li_2CuCl_4 (1 mol%), THF, −78 °C to rt, 12 h, 95%; (b) Jones' reagent, acetone, rt, 1 h, 88%; (c) carbonyl diimidazole, THF, rt, 6 h; $Mg(O_2CCH_2CO_2Me)_2$, THF, rt, 16 h, 81%; (d) H_2 (6 bar), $RuCl_3$/(*R*)-MeO-BIPHEP (1 mol%), MeOH, 80 °C, 23 h, 96%; (e) 1N NaOH, MeOH, 0 °C, 30 min, then rt, 3 h, 89%.

The synthesis of another fragment **91** started from **85** which was converted into *anti*-*N*,*N*-Boc-α-hydrazino-β-hydroxy ester **86** by electrophilic amination with DTBAD.[62, 63, 64] After deprotection of the hydrazine function, the N-N bond was cleaved followed by protection of the resulting amine with di-*tert*-butyl dicarbonate to furnish compound **87**. Protection of **87** with acetonide followed by reduction afforded alcohol **89**, which on Mitsunobu reaction[65, 66] with thioacetic acid gave thioester **90** which on subsequent oxidation afforded fragment **91**. Coupling of fragment **91** with **57** followed by treatment with Amberlite IR-120B furnished sulfobacin A **42** (Scheme 19).



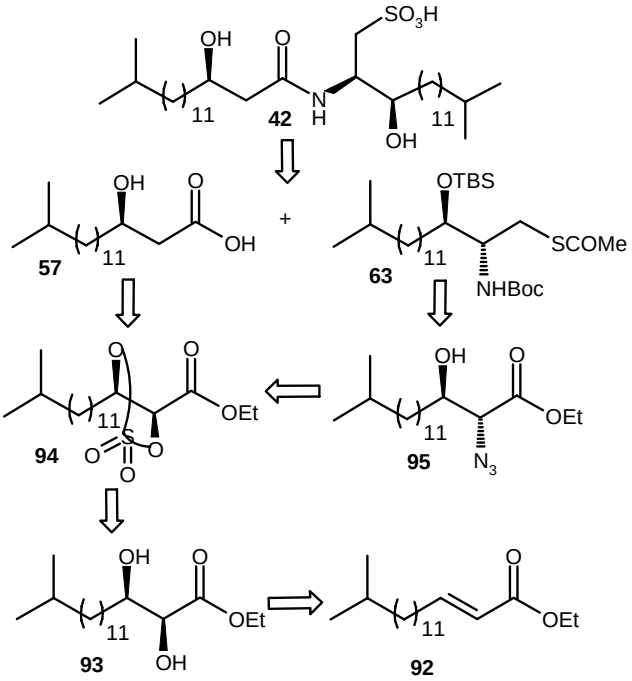
Scheme 19. *Reagents and conditions*: (a) MeZnBr (1 equiv.), 0 °C, 1 h; LDA (2 equiv.), −78 °C, 1 h; DTBAD (2 equiv.), −78 °C, 2 h, 72%; (b) TFA, CH_2Cl_2, rt, 3 h; (c) H_2 (1 atm), Raney Ni, MeOH, ultrasound, rt, 14 h; (d) Boc_2O, $NaHCO_3$, MeOH, ultrasound, rt, 3.5 h, 80% from **86**; (e) $Me_2C(OMe)_2$, $Et_2O{\cdot}BF_3$, CH_2Cl_2, rt, 1 h, 93%; (f) $Ca(BH_4)_2$, THF, EtOH, −15 °C to rt, 22 h, 94%; (g) CH_3COSH, $^{i}PrO_2CN{=}NCO_2{}^{i}Pr$, PPh_3, THF, 0 °C, 1 h, then rt, 16 h, 95%; (h) H_2O_2, TFA, rt, 1 h; (i) HONB, DCC, THF/ dioxane, 0 °C, 40 min, rt, 24 h then **91**, $NaHCO_3$, dioxane/ H_2O, rt, 20 h, 20%.

2.2.3. Present work:

Objective:

The structure of sulfobacins is related to sulfonolipids having an aminosulfonic acid moiety and is analogous to sphingosine. Their structural uniqueness as well as intriguing biological activities led us to synthesize them in a suitable manner. As a part of our ongoing research program aimed at developing enantioselective synthesis of naturally occurring amino alcohol, the Sharpless asymmetric dihydroxylation (AD) and subsequent transformation of diols formed via cyclic sulfites/sulfates were envisaged as powerful tools offering considerable opportunities for synthetic manipulation.

Our synthetic approach for the synthesis of sulfobacin A was envisioned via the retrosynthetic route as shown in Scheme 20. The cyclic sulfate **94** was visualized as a common intermediate for the synthesis of both fragments **63** and **57**, which in turn could be obtained from the diol **93**. The diol **93** could be derived from olefin **92** through asymmetric dihydroxylation. The β-hydroxy acid **57** would be obtained by nucleophilic opening of cyclic sulfate **94** with hydride and subsequent hydrolysis, while **63** would be prepared by the nucleophilic opening of cyclic sulfate **94** with azide followed by a Mitsunobu reaction with thioacetic acid.

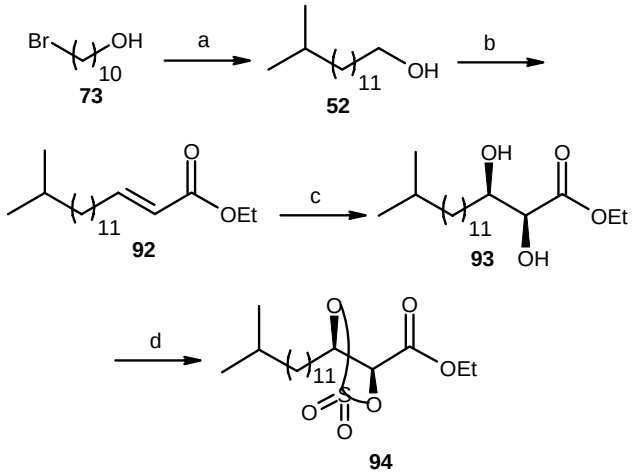


Scheme 20. Retrosynthetic route to sulfobacin A

2.2.4. Results and Discussion:

Synthesis of cyclic sulfate

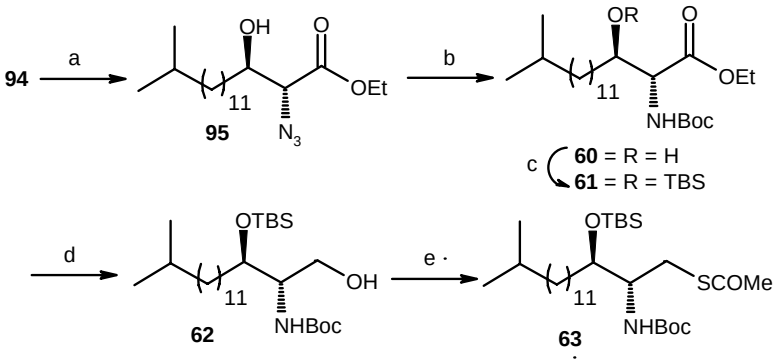
The synthesis of cyclic sulfate **94** commenced from 10-bromodecan-1-ol **73**, a commercially available material, as illustrated in Scheme 21. Thus treatment of **73** with isoamylmagnesium bromide in the presence of dilithium tetrachlorocuprate gave the alcohol **52** in excellent yield. Compound **52** was oxidised to the corresponding aldehyde under standard Swern conditions[43] followed by Horner–Wadsworth–Emmons olefination with triethyl phosphonoacetate to give the (*E*)-α,β-unsaturated ester **92** in 86% yield. The IR spectrum of **92** showed the ester carbonyl absorption at 1724 cm^{-1} and olefin C=C stretching at 1655 cm^{-1}. The ^{1}H NMR spectrum gave olefin protons at δ 5.97 (doublet of triplet) with the coupling constant J = 15.7, 6.9, 1.7 Hz and δ 5.84 (doublet of triplet) with the coupling constant J = 15.5, 6.9, 1.5 indicating *trans*-olefin. The dihydroxylation of **92** with osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of $(DHQD)_2PHAL$ ligand under the AD conditions[40] gave the diol **93** in 95% yield with >96% ee. The IR spectrum of **92** showed hydroxyl absorption at 3493 cm^{-1} and ester carbonyl at 1732 cm^{-1}. The ^{1}H NMR indicated absence of olefin protons. The chiral protons appeared at δ 4.08 (multiplet) and 3.68 (multiplet). The chiral carbons appeared at δ 73.2 and 72.5 in the ^{13}C NMR spectrum. For the measurement of enantiomeric excess, the diol **93** was converted into its dibenzoate derivative. The enantiomeric purity of the dibenzoate was estimated to be >96% by chiral HPLC analysis using Lichocart 250-4 (4mmID x 25cm) HPLC-Cartridge (R.R.-Whelk-01), 1% *i*-PrOH in hexane, 1mL/ min. $[\alpha]_D^{25}$ +7.91 (*c* 1.34, $CHCl_3$). Treatment of diol **93** with thionyl chloride and triethylamine in CH_2Cl_2 gave the cyclic sulfite, which was further oxidized using $NaIO_4$ and a catalytic amount of ruthenium trichloride to furnish the corresponding cyclic sulfate **94**[67] in quantitative yield. The IR spectrum of **94** indicated the absence of hydroxyl groups. A downfield shift in the ^{1}H NMR spectra of CH_2-SO_2- protons to δ 4.84-4.96 as multiplet was observed in comparison to the same proton of **93** at 4.08 (m, 1H) and 3.68 (m,1H).



Scheme 21. *Reagents and conditions:* (a) $Me_2CH(CH_2)_2MgBr$, Li_2CuCl_4 (1mol%), THF, -78 ^oC to rt, 12 h, 94%; (b) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^oC to -60 ^oC, (ii) $(EtO)_2P(O)CH_2CO_2Et$, LiBr, Et_3N, THF, rt, overnight, 86%; (c) $(DHQD)_2PHAL$ (1mol%), 0.1M OsO_4 (0.4mol%), K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, *t*-BuOH/H_2O (1:1), 0 ^oC, 24 h, 95%; (d) (i) $SOCl_2$, Et_3N, CH_2Cl_2, 0 ^oC, 20 min; (ii) $RuCl_3$, $NaIO_4$, CCl_4–MeCN–H_2O; 2:2:3, 0 ^oC, 2 h, 100%.

Synthesis of thioester fragment

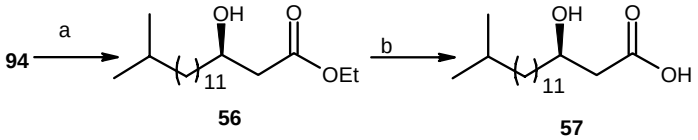
Scheme 22 summarises the synthesis of thioester **63** from **94**, a common intermediate for both fragments **57** and **63**. The essential feature of our strategy was based on the presumption that the nucleophilic opening of the cyclic sulfate **94** would occur in a regioselective manner at the α-carbon. Indeed the cyclic sulfate **94** on treatment with NaN_3 furnished the azido alcohol **95** with apparent complete selectivity for attack at the α-position. The carbonyl group must be responsible for the increased activity at the α-position.[68] Compound **95** on hydrogenation in the presence of $(Boc)_2O$ gave the Boc protected amino alcohol **60** in essentially quantitative yield. The free hydroxyl group of **60** was protected with TBSCl to give **61**. Reduction of the ester group with calcium borohydride produced the alcohol **62** in excellent yield. Finally Mitsunobu reaction[65, 66] of **62** with thioacetic acid afforded the desired thioester **63** in 92% yield.



Scheme 22. *Reagents and conditions:* (a) NaN_3, H_2O–acetone (1:10), 1.5 h, then 20% aq H_2SO_4, Et_2O, 24 h, 92%; (b) $(Boc)_2O$, 10% Pd/C, H_2, EtOAc, 4 h, 98%; (c) TBSCl, imidazole, DMF, rt, 20 h, 98%; (d) $Ca(BH_4)_2$, THF, EtOH, -15 ^oC to rt, 20 h, 96%; (e) CH_3COSH, $^iPrOCON = NCO_2{}^iPr$, PPh_3, THF, 0 ^oC, 1 h, then rt, 16 h, 92%.

Synthesis of β-hydroxy fragment

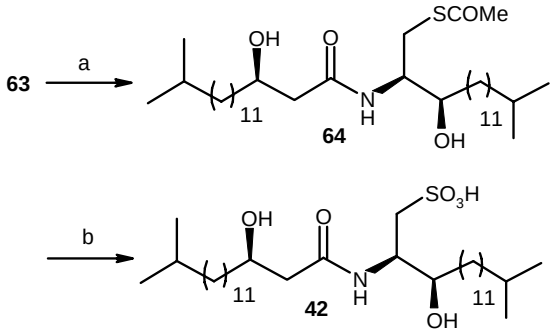
For the synthesis of β-hydroxy acid **57**, the cyclic sulfate **94** was opened similarly with hydride in a regioselective manner to give the β-hydroxy ester **56**, which on alkaline treatment furnished the corresponding β-hydroxy carboxylic acid **57** in excellent yield (Scheme 23).



Scheme 23. *Reagents and conditions:* (a) $NaBH_4$, DMAC, 25 ^oC, 30 min, then 20% aq H_2SO_4, Et_2O, 12 h, 90%; (b) 1N NaOH, MeOH, 0 ^oC, 30 min, then rt, 4 h, 90%.

Synthesis of sulfobacin A

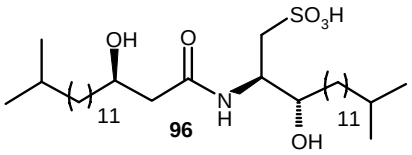
After deprotection of Boc and TBS groups of **63** with hydrogen chloride in dioxane, the coupling of both the fragments **57** and **63** was smoothly achieved with diethyl phosphonocyanidate (DEPC).[56] The thioacetate **64** thus obtained was subjected to pertrifluoroacetic acid oxidation to achieve the target molecule **42** in moderate yield (Scheme 24). The physical and spectroscopic data of **42** were in full agreement with the literature data.



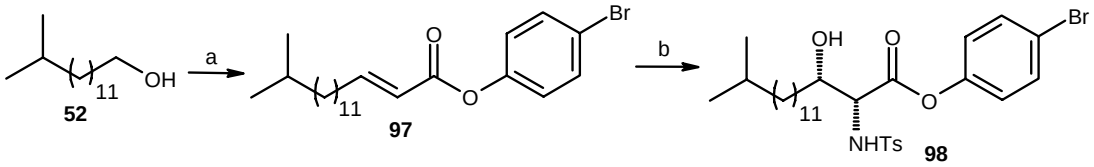
Scheme 24. *Reagents and conditions:* (a) (i) 4N HCl–dioxane, rt, 3h, (ii) **57**, DEPC, Et_3N, DMF, -10 ^oC, 1 h, then rt, 20 h, 84%; (b) 30% aq H_2O_2, TFA, rt, 1 h, 30%.

Synthesis of other isomer of sulfobacin A via Sharpless asymmetric aminohydroxylation

After successfully completing the synthesis of sulfobacin A, we thought to prepare the other isomer of sulfobacin A **96** for structure activity relationship.



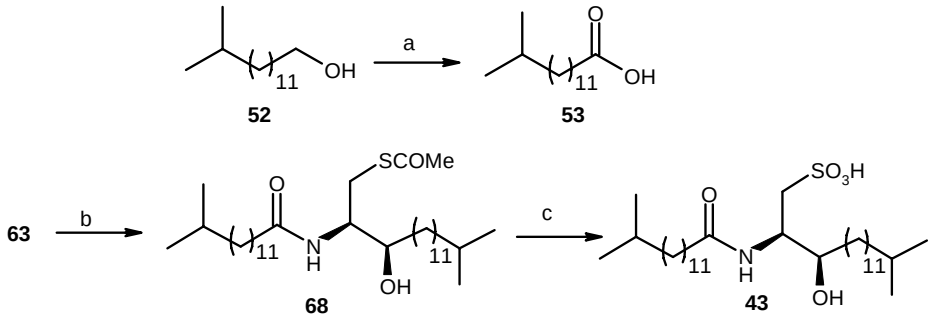
Towards this end, the alcohol **52** was subjected to Swern oxidation followed by Wittig-Horner reaction with diethyl-(p-bromophenyl)-phosphonate to afford the requisite olefin **97**. Following the Panek protocol[69] which describes the preparation of α-amino-β-hydroxy systems by using aryl esters instead of aliphatic esters, the olefin **97** was subjected to asymmetric aminohydroxylation using chloramine-T as nitrogen source, potassium osmate as oxidant and $(DHQ)_2AQN$ as chiral ligand to give the desired amino alcohol **98**. The ^1H NMR and ^{13}C NMR spectrum showed the formation of product, but isolated yield of aminohydroxy product **98** was only 18% along with byproduct *p*-toluenesulfonamide. To improve the yield, we attempted this reaction using several nitrogen sources such as chloramine-M, N-bromoacetamide and benzyl carbamate but in all these cases the yield was very poor. Therefore, the synthesis of **96** could not be accomplished (Scheme 25).



Scheme 25. *Reagents and conditions:* (a) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^oC to -60 ^oC, (ii) *p*-(bromophenyl)-diethylphosphonoacetate, NaH, 0 ^oC-rt, 5 h, 70%; (b) chloramine-T, $(DHQ)_2AQN$, potassium osmate, *t*-BuOH:H_2O (1:1), 3 h, 18%.

Synthesis of sulfobacin B

For the synthesis of acid fragment **53** of sulfobacin B, alcohol **52** was subjected to Jones oxidation. Thus treatment of alcohol **52** with Jones reagent in acetone afforded the acid. After deprotection of Boc and TBS groups of **63** with hydrogen chloride in dioxane, the coupling of both the fragments **63** and **53** was smoothly achieved with diethyl phosphonocyanidate (DEPC). The thioacetate **68** thus obtained was subjected to pertrifluoroacetic acid oxidation to achieve the target molecule **43** in moderate yield (Scheme 26). The physical and spectroscopic data of **43** were in full agreement with the literature data.[51]

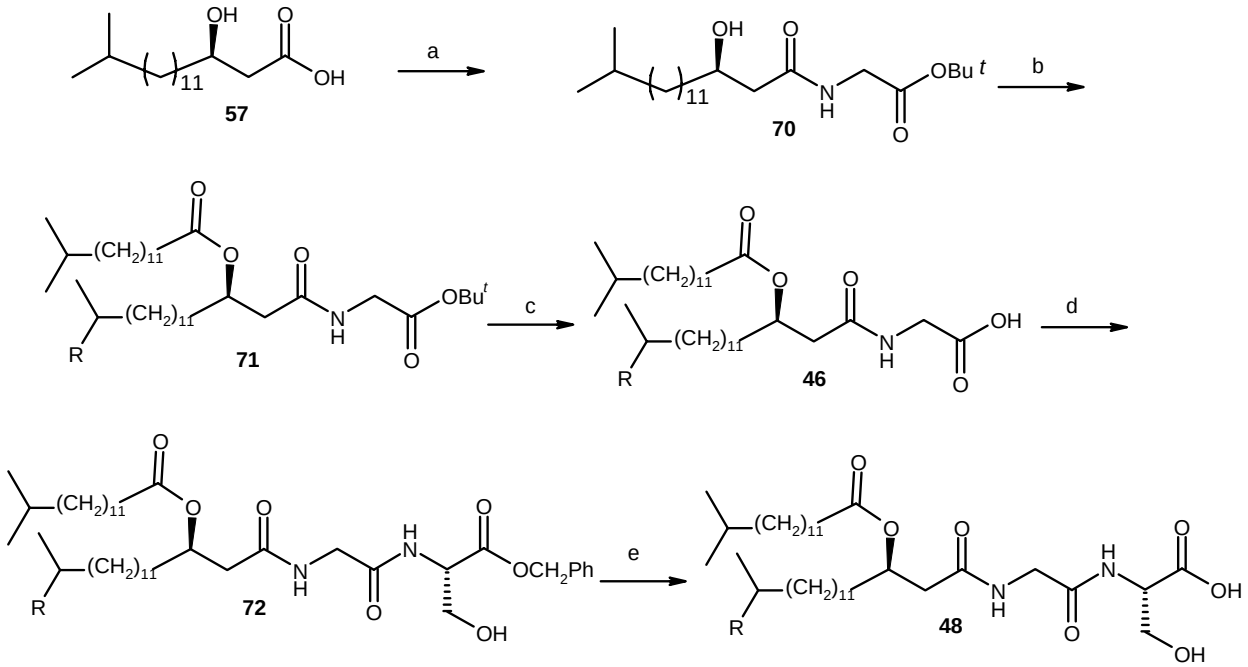


Scheme 26. *Reagents and conditions:* (a) (Jones' oxidation) CrO_3, acetone, 70% (b) (i) 4N HCl–dioxane, rt, 3h, (ii) **53**, DEPC, Et_3N, DMF, -10 ^oC, 1 h, then rt, 22 h, 80%; (c) 30% aq H_2O_2, TFA, rt, 1 h, 40%.

Synthesis of topostin B567 and topostin D654

Condensation of the hydroxy acid **57** with glycine *tert*-butyl ester hydrochloride (H-GIy-OBu^t .HCl) smoothly proceeded by use of diethyl phosphorocyanidate (DEPC, $(EtO)_2P(O)CN$) in the presence of triethylamine (TEA) to give the amide **70**, which underwent the *O*-acylation with the carboxylic acid **53** using l-(3-dimethylaminopropyl)-3--ethylcarbodiimide hydrochioride (EDCI.HCI) in the presence of 4-(*N*,*N*-dimethylamino) pyridine (DMAP) to afford the ester **71**. Final acidic deprotection of **71** with trifluoroacetic acid (TFA) produced topostin B567 **46**. Furthermore, coupling of topostin B567 **46** with *L*-serine benzyl ester trifluoroacetate (H-L-Ser-OCH2Ph-TFA) by use of DEPC furnished the

benzyl ester **72** of topostin D654, which underwent the removal of the benzyl group by catalytic hydrogenolysis to give topostin D654 **48** (Scheme 27).



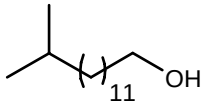
Scheme 27. *Reagents and conditions*: (a) H-Gly-OBu^t.HCl, DEPC, Et3N, DMF, rt, 8 h, 85%; (b) **53**, EDCl.HCl, DMAP, CH_2Cl_2, 0 ^oC, 5 h, 90%; (c) TFA, $CHCl_3$, rt, 5 h, 92%; (d) H-L-Ser-OCH_2Ph.TFA, DEPC, TEA, DMF, rt, 20 h, 81%; (e) H_2, 5% Pd/C, EtOH, rt, 5 h, 67%.

2.2.5. Conclusion

In conclusion, an enantioselective synthesis of sulfobacin A has been realised for the first time using the Sharpless asymmetric dihydroxylation as the source of chirality. Thus the results described herein constitute a short, efficient and highly enantioselective route to sulfobacin A. The synthetic strategy described here has significant potential for further extension to the synthesis of other analogues.

2.2.6. Experimental Section

13-Methyltetradecan-1-ol (52).



52

To a stirred solution of 10-bromo-decan-1-ol **73** (10.0 g, 21.1 mmol) in THF (50 mL) at -78 ^{o}C was added dropwise a solution of $(Me)_2CH(CH_2)_2MgBr$ in THF (80.7 mL, 0.98 M, 78.1 mmol) followed by a solution of Li_2CuCl_4 in THF (2.5 mL, 0.1M, 0.25 mmol). The reaction mixture was allowed to warm to room temperature with stirring for 12 h, then quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate. The combined organic layers were washed with water, saturated aqueous $NaHCO_3$, and brine, then dried over $MgSO_4$ and concentrated. Silica gel column chromatography of the crude product using pet ether/EtOAc (9:1) as eluent provided the alcohol **52** as a light yellow colour liquid.

Yield: 9.1 g, 94%

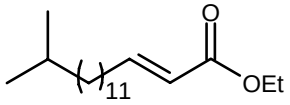
Mol. Formula: $C_{15}H_{32}O$

IR ($CHCl_3$, cm^{-1}): ν_{max} 3392, 2926, 2854, 1437, 1212, 1076, 927.

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.63 (t, 2H, *J* = 6.6 Hz), 1.44–1.60 (m, 4H), 1.26 (br s, 18H), 1.16 (m, 2H), 0.86 (d, 6H, *J* = 6.6 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 62.9, 39.0, 32.7, 29.8, 29.6, 29.5, 29.3, 27.9, 27.3, 25.6, 22.5.

(*E*)-Ethyl 15-methylhexadec-2-enoate (92):



92

To a solution of oxalyl chloride (4.17 g, 2.84 mL, 32.84 mmol) in dry CH_2Cl_2 (100 mL) at -78 ^{o}C was added dropwise dry DMSO (5.13 g, 4.65 mL, 65.67 mmol) in CH_2Cl_2 (20 mL). After 30 min, alcohol **52** (5.0 g, 21.89 mmol) in CH_2Cl_2 (20 mL) was added over 10 min giving copious white precipitate. After stirring for 1 h at -78 ^{o}C the reaction mixture was brought to -60 ^{o}C and Et_3N (9.97 g, 13.73 mL, 98.51 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 as pale yellow oil, which was used as such for the next step without purification.

To a nitrogen flushed solution of LiBr (9.59 g, 110.42 mmol) in dry THF (150 mL) was added $(EtO)_2P(O)CH_2COOEt$ (5.59 g, 26.49 mmol) dropwise at room temperature for 15 min followed by addition of Et_3N (6.16 mL, 44.17 mmol). The stirring was continued for another 15 min. To this was added the solution of above aldehyde (5 g, 22.08 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 for overnight. 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 colorless oil. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (49:1) as eluent gave compound **92** as a colorless oil.

Yield: 5.58 g, 86%

Mol. Formula: $C_{19}H_{36}O_2$

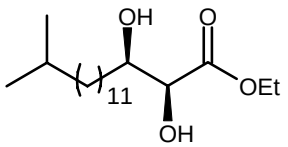
IR ($CHCl_3$, cm^{-1}): ν_{max} 2924, 2856, 1724, 1655, 1466, 1366, 1310, 1178, 1128, 1045, 980, 721.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.97 (dt, *J* = 15.7, 6.9, 1.7 Hz, 1H), 5.84 (dt, *J* = 15.5, 6.9, 1.5 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.21 (q, *J* = 6.9 Hz, 2H), 1.45-1.54 (m, 3H), 1.26 (brs, 19 H), 1.13-1.19 (m, 2H), 0.85 (d, *J* = 6.6 Hz, 6 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 166.7, 149.4, 121.2, 60.0, 39.0, 32.2, 29.9, 29.6, 29.5, 29.4, 29.1, 28.0, 27.9, 27.4, 22.6, 14.2.

Analysis Calcd.: C, 76.97; H, 12.24%; **Found:** C, 77.11; H,12.29%.

(2*S*,3*R*)-Ethyl 2,3-dihydroxy-15-methylhexadecanoate (93)



93

To a mixture of $K_3Fe(CN)_6$ (16.67 g, 50.63 mmol), K_2CO_3 (6.99 g, 50.63 mmol) and $(DHQD)_2PHAL$ (131 mg, 1 mol%), in *t*-BuOH-H_2O (1:1, 85 mL) cooled at 0 ^oC was added OsO_4 (0.06 mL, 0.1 M sol in toluene, 0.4 mol%) followed by methane sulfonamide (1.61 g, 16.88 mmol). After stirring for 5 min at 0 ^oC, the olefin **92** (5 g, 16.88 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 with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (4:1) as eluent gave diol **93** as a colorless syrupy liquid.

Yield: 5.23 g, 95%.

Mol. Formula: $C_{19}H_{38}O_4$

$[\alpha]_D^{25}$: +7.91 (*c* 1.34, $CHCl_3$)

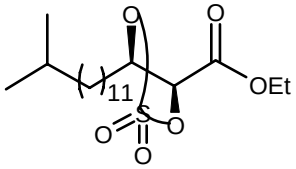
IR ($CHCl_3$, cm^{-1}): ν_{max} 3493, 3019, 2927, 2855, 2400, 1732, 1467, 1401, 1368, 1216, 1135, 1086, 1026.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.27 (q, *J* = 7.2 Hz, 2H), 4.09-3.86 (m, 1H), 3.70-3.64 (m, 1H), 1.60 (t, *J* = 7.2 Hz, 3H), 1.26 (brs, 21H), 1.17-1.20 (m, 2H), 0.85 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 173.6, 73.2, 72.5, 61.7, 39.0, 33.6, 29.9, 19.6, 19.5, 27.9, 27.3, 25.7, 22.5, 14.0.

Analysis Calcd.: C, 69.05; H, 11.59%; Found C, 68.96; H, 11.64%.

Cyclic sulfate (94).



94

To a stirred solution of diol **93** (5.1 g, 15.43 mmol) in dry CH_2Cl_2 (40 mL) cooled at 0 ^oC were added Et_3N (4.3 mL, 3.1 g, 30.86 mmol) and a solution of $SOCl_2$ (2.2 g, 1.35 mL, 18.52 mmol) in CH_2Cl_2 (5 mL) over a period of 10 min. Stirring was continued for 20 min at 0 ^oC and then the solution was quenched by adding water and extracted with CH_2Cl_2. The organic layer was separated, washed with water followed by brine, dried (Na_2SO_4) and

filtered through a pad of silica gel. The filtrate was concentrated to give cyclic sulfite as a yellow liquid.

To a solution of above cyclic sulfite (5.81 g, 15.43 mmol) in CCl_4-MeCN-H_2O (2:2:3, 10: 10: 15 mL), $RuCl_3.H_2O$ (0.21 g, 0.79 mmol) was added followed by addition of $NaIO_4$ (5.87 g, 27.46 mmol). The mixture was stirred at 0 ^oC for 2 h and then extracted with EtOAc. The combined organic phase were washed with water, brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (10:1) as eluent gave cyclic sulfate **94** as a colorless syrupy liquid.

Yield: 6.01 g, 100 %.

Mol. Formula: $C_{19}H_{36}O_6S$

$[\alpha]_D^{25}$: +8.41 (*c* 1.0, $CHCl_3$).

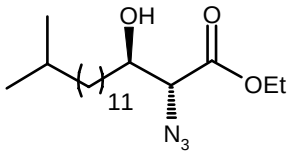
IR (neat, cm^{-1}): ν_{max} 3025, 2952, 2924, 2899, 1714, 1463, 1446, 1369, 1258, 1178, 1086, 1047, 998.

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.84-4.96 (m, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 1.90-2.01 (m, 2H), 1.46-1.58 (m, 3H), 1.33 (t, *J* = 7.0 Hz, 3H), 1.27 (brs, H), 1.10-1.19 (m, 2H), 0.88 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 164.7, 84.1, 79.9, 63.1, 38.9, 32.8, 29.8, 29.5, 29.3, 29.1, 28.8, 27.9, 27.3, 24.6, 22.5, 13.8.

Analysis Calcd.: C, 58.13; H, 9.24%; **Found** C, 58.35; H, 9.28%.

(2*R*,3*R*)-Ethyl 2-azido-3-hydroxy-15-methylhexadecanoate (95).



95

To a solution of cyclic sulfate **94** (4 g, 10.19 mmol) in acetone:water (10:1, 11 mL) at room temperature was added NaN_3 (3.97 g, 6.11 mmol). The reaction mixture was stirred for 1.5 h and the solvent removed in vacuo. The solid residue was treated with 20% aq. H_2SO_4 (2 mL) and ether (10 mL) and vigorously stirred at rt for 24 h. The ether layer was separated and the aqueous layer was further extracted with ether. The combined organic phases were washed with water, brine, dried (Na_2SO_4) and concentrated. Silica gel column

chromatography of the crude product using petroleum ether/EtOAc (17:3) as eluent gave azide **95** as a light yellow colour oil.

Yield: 3.33 g, 92%

Mol. Formula: $C_{19}H_{37}N_3O_3$

$[\alpha]_D^{25}$: +27.72 (*c* 1.24, $CHCl_3$).

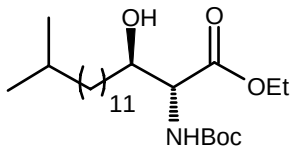
IR (neat, cm^{-1}): ν_{max} 3469, 2926, 2855, 2111, 1736, 1466, 1370, 1216, 1038, 758, 668, 521.

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.32 (q, *J* = 7.0 Hz, 2H), 3.95-3.89 (m, 1H), 2.21-.2.18 (m, 1H), 2.06 (brs, 1H), 1.55-1.48 (m, 3H), 1.26 (brs, 21H), 1.17-1.12 (m, 2H), 0.85 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 168.9, 71.8, 66.2, 61.9, 52.9, 38.9, 32.9, 29.8, 29.5, 29.4, 29.3, 27.8, 27.3, 25.9, 25.3, 22.5, 14.0

Analysis Calcd.: C, 64.19; H, 10.49; N, 11.82; Found C, 64.31; H, 10.55; N, 11.93.

(2*R*,3*R*)-Ethyl 2-(*tert*-butoxycarbonylamino)-3-hydroxy-15-methylhexadecanoate (60)



60

A solution of azido alcohol **95** (3.2 g, 9.00 mmol), Boc_2O (2.48 mL, 2.36 g, 10.80 mmol) and 10% Pd-C (20 mg), in 10 mL of EtOAc was hydrogenated (1atm) for 4 h. The solid was removed by filtration and the solution was concentrated in vacuo. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (5:1) as eluent gave **60** as a pale yellow colour oil.

Yield: 3.79 g, 98%

Mol. Formula: $C_{24}H_{47}NO_5$

$[\alpha]_D^{25}$: –16.9 (*c* 1.0, $CHCl_3$)

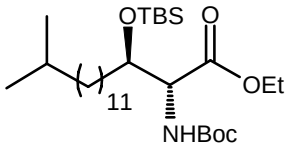
IR (neat, cm^{-1}): ν_{max} 3432, 2982, 2926, 1722, 1699, 1505, 1468, 1368, 1252, 1167, 1028.

^{1}H NMR (200 MHz, $CDCl_3$): δ 5.48 (brs, 1H), 4.31-4.37 (m, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.84-3.90 (m, 1H), 2.80 (brs, 1H), 1.51-1.56 (m, 3H), 1.45 (s, 9H), 1.25 (brs, 21H), 1.14-1.17 (m, 2H), 0.85 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 170.3, 154.4, 79.4, 78.4, 72.4, 60.7, 51.1, 50.8, 38.7, 33.1, 31.2, 29.5, 29.2, 28.0, 27.9, 27.5, 27.3, 26.9, 25.4, 22.2, 13.7.

Analysis Calcd.: C, 67.09; H, 11.03; N, 3.26%; **Found** C, 67.27; H, 11.09; N, 3.23%.

(2*R*,3*R*)-Ethyl 2-(*tert*-butoxycarbonylamino)-3-(*tert*-butyldimethylsilyloxy)-15-methylhexadecanoate (61)



61

To a stirred solution of the alcohol **60** (3 g, 6.98 mmol) in DMF (15 ml) was added imidazole (1.43 g, 20.95 mmol) and TBSCl (1.58 g, 10.47 mmol). The mixture was stirred at room temperature for 20 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 (10:1) as eluent provided **61** as a colorless liquid.

Yield: 3.72 g, 98%

Mol. Formula: $C_{30}H_{61}NO_5Si$

$[\alpha]_D^{25}$: –22.4 (*c* 1.10, $CHCl_3$).

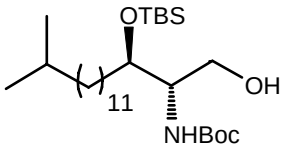
IR ($CHCl_3$, cm^{-1}): ν_{max} 3445, 2930, 1744, 1718, 1497, 1368, 1256, 1165, 1059, 1030, 837, 776.

^{1}H NMR (200 MHz, $CDCl_3$): δ 5.26 (d, *J* =7.3 Hz, 1H), 4.30-4.35 (m, 1H), 4.20 (q, *J* = 7.1 hz, 2H), 3.86-3.95 (m, 1H), 1.51-1.60 (m, 3H), 1.44 (s, 9H), 1.25 (brs, 21H), 1.10-1.18 (m, 2H), 0.87 (s, 9H), 0.84 (d, *J* = 6.6 Hz, 6H), 0.07 (s, 3H), 0.04 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 172.4, 156.7, 128.3, 127.1, 126.8, 109.3, 103.9, 95.5, 78.1, 75.0, 73.8, 71.8, 67.1, 61.5, 58.9, 57.2, 37.4, 34.9, 29.6, 25.6, 25.1, 24.0, 23.7, 18.0, 14.6, -4.61.

Analysis Calcd.: 66.25; H, 11.30; N, 2.58%; **Found** C, 66.42; H, 11.27; N, 2.56%.

***tert*-Butyl (2*S*,3*R*)-3-(*tert*-butyldimethylsilyloxy)-1-hydroxy-15-methylhexadecan-2-ylcarbamate (62)**



62

To a dispersion of $CaCl_2$ (1.43 g, 12.87 mmol), in THF (10mL) was added a solution of ester **61** (3.5 g, 6.44 mmol) in EtOH (18 mL). After cooling to -15 ^oC, $NaBH_4$ (0.97 g, 25.74 mmol) was added and the mixture was stirred for 15 min. at 15 ^oC and 20 h at room temperature. Saturated aq. Na_2SO_4 was added and the mixture was filtered on celite, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (5:1) as eluent gave alcohol compound **62** as a pale yellow oil.

Yield: 3.1 g, 96%

Mol. Formula: $C_{28}H_{59}NO_4Si$

$[\alpha]_D^{25}$: –13.4 (*c* 1.0, $CHCl_3$).

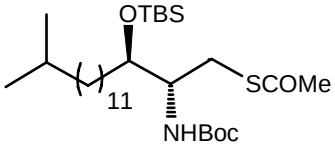
IR ($CHCl_3$, cm^{-1}): ν_{max} 3451, 2928, 1700, 1499, 1464, 1366, 1255, 1173, 1055, 837, 776.

^{1}H NMR (200 MHz, $CDCl_3$): δ 5.33 (d, *J* = 7.4 Hz, 1H), 4.01-4.08 (m, 1H), 3.92-3.97 (m, 1H), 3.62-3.63 (m, 1H), 3.55-3.58 (m, 1H), 1.50-1.59 (m, 5H), 1.46 (s, 9H), 1.26 (brs, 18 H), 0.90 (s, 9H), 0.86 (d, *J* = 6.6 Hz, 6H), 0.11 (s, 3H), 0.09 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 155.5, 78.7, 74.2, 61.3, 59.8, 54.1, 38.8, 34.1, 29.6, 29.5, 29.3, 29.2, 29.18, 28.1, 27.6, 27.1, 25.5, 25.0, 22.3, 17.6, 13.8, -4.9, -5.1.

Analysis Calcd.: C, 67.01; H, 11.85; N, 2.79%; **Found** C, 67.23; H, 11.88; N, 2.82%.

_S_-(2_R_,3_R_)-2-(_tert_-Butoxycarbonylamino)-3-(_tert_-butyldimethylsilyloxy)-15-methylhexadecyl ethanethioate (63)



63

To a solution of PPh_3 (3.29 g, 12.55 mmol), in THF (25 mL) at 0 ^oC was added diisopropylazodicarboxylate (2.42 g, 2.35 mL, 11.96 mmol). After stirring at 0 ^oC for 4 h, a solution of alcohol **62** (3g, 5.98 mmol) and thioacetic acid in THF (15 mL) was added. The yellow mixture was then stirred for 1h at 0 ^oC and 16 h at room temperature. The

reaction mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using pet ether/EtOAc (4:1) as eluent provided **63** as a pale yellow oil.

Yield: 3.08 g, 92%

Mol. Formula: $C_{30}H_{61}NO_4SSi$

$[\alpha]_D^{25}$: +7.8 (*c* 1.0, $CHCl_3$)

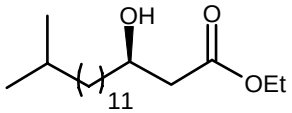
IR ($CHCl_3$, cm^{-1}): ν_{max} 3374, 2906, 1716, 1698, 1499, 1366, 1252, 1171, 1113, 837, 776.

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.70 (d, *J* = 8.6 Hz, 1H), 3.80-3.55 (m, 2H), 3.13 (dd, *J* = 14.0, 3.3 Hz, 1H), 2.96-2.90 (m, 1H), 2.33 (s, 3H), 1.59-1.50 (m, 5H) and 1.46 (s, 9H), 1.17-1.15 (m, 2H), 1.26 (brs, 16H), 0.91 (s, 9H), 0.86 (d, *J* = 6.6 Hz, 6H), 0.11 (s, 3H), 0.09 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 195.1, 156.1, 80.4, 78.8, 55.7, 54.6, 39.2, 34.5, 30.1, 29.8, 29.6, 28.5, 28.1, 27.5, 25.9, 25.4, 22.9, 17.9, -4.5, -4.7.

Analysis Calcd.: C, 64.35; H, 10.98; N, 2.50%; **Found** C, 64.49; H, 11.03; N, 2.52%.

(*R*)-Ethyl 3-hydroxy-15-methylhexadecanoate (56).



56

To a solution of cyclic sulfate **94** (2 g, 5.09 mmol) in dimethyl acetamide (10 mL) at room temperature was added $NaBH_4$ (0.19 g, 5.09 mmol). The reaction mixture was stirred for 0.5 h and the solvent removed in vacuo. The solid residue was treated with 20% aq. H_2SO_4 (mL) and ether (mL) and vigorously stirred at rt for 12 h. The ether layer was separated and the aqueous layer was further extracted with ether. The combined organic phases were washed with water, brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (3:1) as eluent gave β-hydroxy ester **56** as a light yellow colour oil.

Yield: 1.44 g, 90%

Mol. Formula: $C_{19}H_{38}O_3$

$[\alpha]_D^{25}$: –13.4 (*c* 1.0, $CHCl_3$).

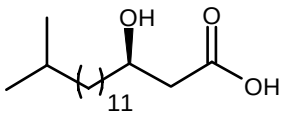
IR ($CHCl_3$, cm^{-1}): ν_{max} 3450, 2926, 1736, 1466, 1374, 1302, 1181, 1032.

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.16 (q, *J* = 7.2 Hz, 2H), 3.99-4.04 (m, 1H), 2.48 (dd, *J* = 16.5, 3.3 Hz, 1H), 2.37 (dd, *J* = 16.5, 8.6 Hz, 1H), 1.52-1.58 (m, 3H), 1.14-1.31 and 1.26 (m and brs, 23 H), 0.85 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 172.7, 67.9, 60.4, 41.4, 38.9, 36.6, 29.8, 29.5, 27.8, 27.3, 25.4, 22.5, 14.0.

Analysis Calcd.: C, 72.56; H, 12.18%; **Found** C, 72.71; H, 12.08%.

(*R*)-3-Hydroxy-15-methylhexadecanoic acid (57).



57

To a solution of methyl (*R*)-3-hydroxy-15-methyl-hexadecanoate **56** (1.3 g, 4.13 mmol) in methanol (2 mL) at 0 ^oC was added dropwise a 1N aqueous solution of NaOH (4 mL). The reaction mixture was stirred at 0 ^oC for 0.5 h, then 4 h at room temperature, and concentrated in vacuo. The residue was acidified with 0.1M aqueous HCl and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (2:1) as eluent gave β-hydroxy acid **57** as colorless crystals.

Yield: 1.1 g, 90%

Mol. Formula: $C_{17}H_{34}O_3$

M.p. 46-47 ^oC; lit[51] 46-48 ^oC

$[\alpha]_D^{25}$: -12.20 (*c* 1.0, $CHCl_3$).

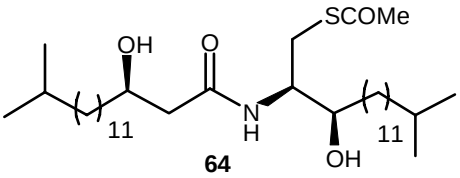
IR ($CHCl_3$, cm^{-1}): ν_{max} 3100, 2920, 2830, 1700, 1460, 1380, 1360.

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.97-4.09 (m, 1H), 2.56 (dd, *J* = 16.8, 3.1 Hz, 1H), 2.46 (dd, *J* = 16.8, 8.7 Hz, 1H), 1.40-1.56 (m, 3H), 1.26 (brs, 18 H), 1.14-1.19 (m, 2H), 0.85 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 177.60, 68.1, 41.1, 39.0, 36.5, 29.9, 29.7, 29.5, 27.9, 27.4, 25.4, 22.6.

Analysis Calcd.: C, 71.28; H, 11.96%; **Found** C, 71.36; H, 11.85%.

***S*-(2*R*,3*R*)-3-Hydroxy-2-[(*R*)-3-hydroxy-15-methylhexadecanamido]-15-ethylhexadecanyl thioacetate (64).**



64

The thioacetate **63** (0.500 g, 0.89 mmol) was treated with 4N HCl-dioxane at room temperature for 3 h. Removal of the solvent under reduced pressure afforded the crude hydrochloride salt as a pale yellow solid. To a solution of the above crude solid and β-hydroxycarboxylic acid **57** (0.22 g, 0.76 mmol) in DMF (1 ml) at -10 ^{o}C was added dropwise DEPC (0.02 ml, 0.132 mmol) and then Et_3N (0.055 ml, 0.395 mmol). The reaction mixture was stirred at -10 ^{o}C for 1 h, and then at room temperature for 20 h. After dilution with EtOAc-benzene (2:1, 60 ml), the reaction mixture was washed with saturated aqueous $NaHCO_3$, water, brine, dried (Na_2SO_4), and concentrated in vacuo. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (1:1) as eluent gave thioacetate **64** as a white solid.

Yield: 0.461 g, 84%

Mol. Formula: $C_{36}H_{71}NO_4S$

$[\alpha]_D^{25}$: -2.71 (*c* 0.5, $CHCl_3$).

M.p. 85-87 ^{o}C

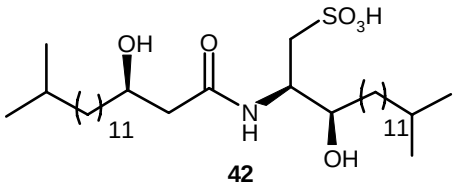
IR (nujol, cm^{-1}): ν_{max} 3291, 2922, 1694, 1643, 1539, 1377, 1134, 1036.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.20 (d, *J* = 8.9 Hz, 1H), 3.94-4.07 (m, 2H), 3.62 (brs, 1H), 3.31 (brs, 1H), 3.22-3.04 (m, 2H), 2.56 (brs, 1H), 2.39-2.35 (m, 1H), 2.31 (s, 3H), 2.28-2.18 (m, 1H), 1.55-1.43 (m, 6H), 1.25 (brs, 36 H), 1.19-1.14 (m, 4H), 0.85 (d, *J* = 6.6 Hz, 12H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 195.5, 173.5, 75.5, 67.1, 54.3, 46.9, 39.0, 32.7, 29.9, 29.6, 29.5, 29.3, 29.1, 27.9, 27.4, 26.8, 25.2, 22.6.

Analysis: Calcd.: C, 70.42; H, 11.65; N, 2.28%; **Found** C, 70.30; H, 11.61; N, 2.27%.

Sulfobacin A (42).



42

To a stirred solution of the thioacetate **64** (0.70 mg, 0.12 mmol) in TFA (0.3 ml) was added dropwise 30% aqueous H_2O_2 (0.1 ml). After being stirred at room temperature for 1 h, removal of the solvent under reduced pressure afforded the crude residue. Silica gel column chromatography of the crude product using $CHCl_3$-MeOH-H_2O (65:25:3) as eluent gave sulfobacin A **42** as a white solid.

Yield: 21 mg, 30%.

Mol. Formula: $C_{34}H_{69}NO_6S$

$[\alpha]_D^{25}$: -34.8 (*c* 0.15, MeOH), Lit[44a] $[\alpha]_D^{24}$: -35 (*c* 0.14, MeOH)

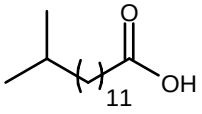
M.p. 220-222 ^oC

IR ($CHCl_3$, cm^{-1}): ν_{max} 3291, 2922, 1647, 1553, 1466, 1168, 1059.

^{1}H NMR (200 MHz, DMSO D_6): δ 7.66 (d, 1H, *J* = 8.8 Hz), 4.78 (d, 1H, *J* = 5.6 Hz), 4.66 (d, 1H, *J* = 4.4 Hz), 3.95-3.88 (m, 1H), 3.75-3.69 (m, 1H), 3.45-3.50 (m, 1H), 2.78-2.58 (m, 2H), 2.09-2.03 (m, 2H), 1.52-1.42 (m, 2H), 1.38-1.35 (m, 2H), 1.24 (m, 38H), 1.14-1.12 (m, 4H), 0.83 (d, 12H, *J* = 6.6 Hz).

^{13}C NMR (125 MHz, DMSO D_6): δ 170.4, 155.5, 72.1, 67.8, 52.0, 51.3, 45.0, 36.8, 3.5, 33.5, 29.6, 29.3, 29.2, 27.6, 27.1, 25.8, 25.5, 22.8.

13-Methyltetradecanoic Acid (53).



53

To a stirred solution of the alcohol **11** (404 mg, 1.77 mmol) in acetone (7 ml) at 0 ^oC was added dropwise Jones reagent (1.70 ml, 3.26 mmol). After stirring at room temperature for 1 h, water (50 ml) was added, and the mixture was extracted with H_2O (80 ml). The extracts were washed with saturated aqueous NaC1, and dried over $MgSO_4$. Concentration in vacuo gave the crude product, which was purified by silica gel column chromatography (with pet ether-EtOAc (2 : 1) to give the carboxylic acid **53** as a white solid.

Yield: 411 mg, 96%

Mol. Formula: $C_{15}H_{30}O_2$

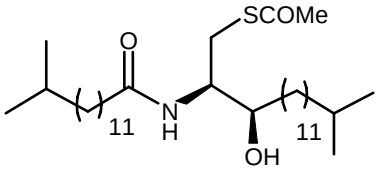
M.p. 46-48 ^oC

IR (nujol, cm^{-1}): ν_{max} 2918, 1700, 1408, 1286, 932, 750.

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.36 (t, *J* = 7.2 Hz, 2 H), 1.43-1.67 (m, 3H), 1.26 (16 H, brs), 1.14-1.19 (m, 2H), 0.85 (d, *J* = 6.6 Hz, 6 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 180.4, 39.1, 34.1, 29.9, 29.7, 29.6, 29.6, 29.4, 29.2, 29.1, 27.9, 27.4, 24.7, 22.6.

Thioester of Sulfobacin B (68).



68

The thioacetate **63** (0.5 g, 0.89 mmol) was treated with 4N HCl-dioxane at room temperature for 3 h. Removal of the solvent under reduced pressure afforded the crude hydrochloride salt as a pale yellow solid. To a solution of the above crude solid and carboxylic acid **53** (0.18 g, 0.76 mmol) in DMF (1 ml) at -10 ^oC was added dropwise DEPC (0.14 ml, 0.92 mmol) and then Et_3N (0.37 ml, 2.68 mmol). The reaction mixture was stirred at -10 ^oC for 1 h, and then at room temperature for 22 h. After dilution with EtOAc-benzene (2:1, 60 ml) it was washed with saturated aqueous $NaHCO_3$, water, brine, dried (Na_2SO_4), and concentrated in vacuo. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (4:1) as eluent gave thioacetate **68** as a white solid.

Yield: 348 mg, 82%

Mol. Formula: $C_{34}H_{67}NO_3S$

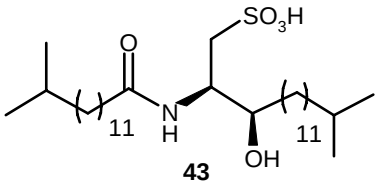
$[\alpha]_D^{25}$: -3.72 (*c* 0.4, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 3303, 2946, 2925, 1699, 1648, 1464, 1178, 1119, 984, 837.

^{1}H NMR (200 MHz, $CDCl_3$): δ 5.74 (d, *J* = 8.6 Hz, 1H), 4.11- 4.03 (m, 1H), 3.76-3.69 (m, 1H), 3.14 (dd, *J* = 10.9, 14.2 Hz, 1H), 2.98 (dd, *J* = 3.6, 14.2 Hz, 1H), 2.30 (s, 3H), 2.02-2.10 (m, 2H), 1.58-1.45 (m, 6H), 1.25 (brs, 36H), 1.19-1.13 (m, 2H), 0.85 (d, *J* = 6.6 Hz, 12H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 195.0, 172.0, 75.6, 53.4, 40.5, 38.9, 36.8, 30.9, 29.6, 27.9, 27.3, 25.5, 22.6.

(2*R*,3*R*)-3-Hydroxy-15-methyl-2-(13-methyltetradecanamido)hexadecane-1-sulfonic acid (43).



43

To a stirred solution of the thioacetate **68** (95 mg, 0.139 mmol) in TFA (0.35 ml) was added dropwise 30% aqueous H_2O_2 (0.12 ml). The reaction mixture was stirred at room temperature for 1 h. Removal of the solvent under reduced pressure afforded residue, which was purified by silica gel column chromatography with $CHCl_3$/MeOH/ H_2O (65:10:1- 65:25:3) to give sulfobacin B **43** as a white solid.

Yield: 38 mg, 40%.

Mol. Formula: $C_{32}H_{65}NO_5S$

M.p. 217-218 ^{o}C, (lit.[51] 218-220 ^{o}C)

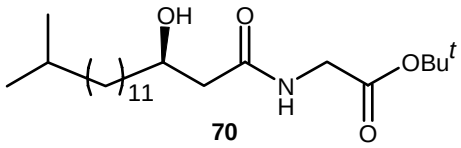
$[\alpha]_D^{25}$: -18.7 (*c* 0.14, MeOH).

IR (KBr, cm^{-1}): ν_{max} 3300, 2925, 1655, 1550, 1470, 1220, 1060.

^{1}H NMR (200 MHz, DMSO D_6): δ 7.60 (d, *J* = 8.5 Hz, 1H), 4.83 (d, *J* = 5.5 Hz, 1H), 3.80-3.84 (m, 1H), 3.52 (brs, 1H), 2.82-2.56 (m, 2H), 2.02 (t, *J* = 7.3 Hz, 2H), 1.41-1.56 (m, 4H), 1.26 (brs, 36H), 1.12-1.18 (m, 4H), 0.85 (d, *J* = 6.7 Hz, 12H).

^{13}C NMR (50 MHz, DMSO D_6): δ 171.6, 71.8, 51.9, 51.2, 33.3, 29.5, 29.3, 29.2, 28.9, 28.6, 27.5, 26.6, 25.6, 25.3, 22.6.

***N*-[(3*R*)-3-Hydroxy-15-methylhexadecanoyl]glycine *tert*-butyl ester (70).**



70

To a solution of the carboxylic acid **57** (2 g, 6.98 mmol) in DMF (30 ml) was added H-GIy-OBu^t .HCI (1.4 g, 8.34 mmol), DEPC (1.25 ml, 8.34 mmol), and then TEA (2.34 ml,

16.76 mmol) at 0 °C, and the mixture was stirred at room temperature for 8 h. The mixture was diluted with Et_2O and washed with 1 M aqueous $KHSO_4$, dried over $MgSO_4$ and concentrated in vacuo. Silica gel column chromatography of the crude product using petroleum ether/ EtOAc (2:1) as eluent afforded amide as a white wax.

Yield: 2.65 g, 95%.

Mol. Formula: $C_{23}H_{45}NO_4$

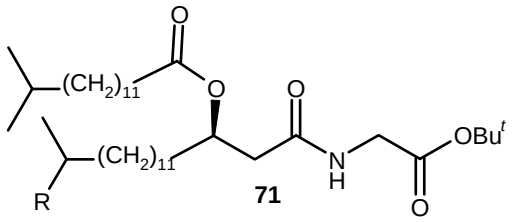
$[\alpha]_D^{25}$: –10.6 (*c* 1.1, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 3350, 2926, 2855, 1730, 1651, 1556, 1468, 1370, 1215, 1157, 758.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.46 (brs, 1H), 3.86-4.02 (m, 3H), 2.41 (dd, *J* = 15.4, 2.8 Hz, 1H), 2.29 (dd, *J* = 15.4, 8.9 Hz, 1H), 1.16-1.58 (m, 31 H), 0.85 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 173.0, 169.5, 82.5, 68.8, 42.8, 41.9, 38.9, 36.8, 29.9, 29.6, 29.5, 27.9, 27.3, 25. 5, 22.6, 20.7.

***N*-[(3*R*)-15-Methyl-3- (13-methyltetradecanoyloxy) hexadecanoyl]glycine *tert*-butyl ester (22).**



71

To a solution of the carboxylic acid **54** (0.25 g, 5.15 mmol) in CH_2Cl_2 (10 ml) was added EDCI.HCI (1.44 g, 7.51 mmol), DMAP (61 mg, 0.50 mmol) and the hydroxy amide **70** (2 g, 5.0 mmol) at 0 °C, and the mixture was stirred at 0 ^oC for 5 h. The mixture was diluted with Et_2O and successively washed with H_2O, saturated aqueous $NaHCO_3$, and saturated brine, and then dried over $MgSO_4$ and concentrated in vacuo. Silica gel column chromatography of the crude product using petroleum ether: EtOAc (5:1) as eluent afforded compound **71** as pale yellow oil.

Yield: 2.81 g, 90%

Mol. Formula: $C_{38}H_{73}NO_5$

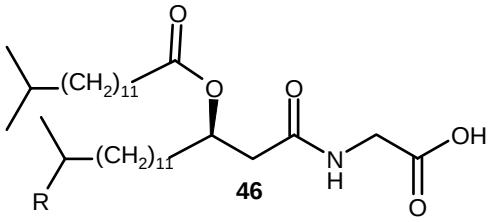
$[\alpha]_D^{25}$: +1.90 (*c* 1.0, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 3320, 2924, 2855, 1738, 1732, 1651, 1468, 1367, 1159, 848.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.27 (brs, 1H), 5.11-5.23 (m, 1H), 3.91 (d, *J* = 4.7 Hz, 2H), 2.49-2.52 (m, 2H), 2.31 (t, *J* = 7.3 Hz, 2H), 1.52-1.64 (m, 6H), 1.47 (s, 9H), 1.25 (brs, 34 H), 1.14-1.19 (m, 4H), 0.85 (d, *J* = 6.6 Hz, 12 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 173.47, 170.04, 169.07, 82.28, 71.11, 42.03, 41.29, 39.01, 35.36, 34.45, 34.00, 32.66, 31.64, 31.54, 29.90, 29.61, 29.47, 29.27, 29.11, 28.05, 27.92, 27.39, 26.85, 26.37, 25.18, 24.92, 24.7, 22.6, 20.7, 14.0

***N*-[(3*R*)-15-Methyl-3-(13-methyltetradecanoyloxy)hexadecanoyl]glycine (topostin B567, 46).**



46

To a solution of **71** (0.8 g, 1.28 mmol) in $CHCl_3$ (5 ml) was added drop wise TFA (5 ml) at 0 ^oC and the mixture was stirred at room temperature for 5 h. After addition of toluene, the mixture was concentrated in vacuo. This work-up was repeated three times to remove the excess of TFA completely. Silica gel column chromatography of the crude product using $CHCl_3$: MeOH (5 : 1) gave **46** as a colorless powder.

Yield: 0.69 g, 92%.

Mol. Formula: $C_{34}H_{65}NO_5$

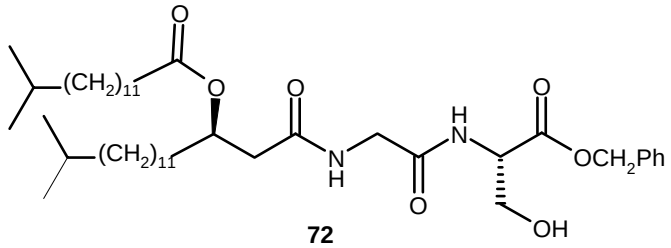
$[\alpha]_D^{25}$: +1.6 (*c* 0.3, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 3427, 2928, 2855, 1732, 1667, 1531, 1468, 1215, 758.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.62 (brs, 1H), 5.12-5.24 (m, 1H), 4.03 (brs, 2H), 2.48-2.62 (m, 2H), 2.30 (t, *J*= 7.5 Hz, 2H), 1.45-1.60 (m, 6H), 1.25 (brs, 34 H), 1.10-1.19 (m, 4H), 0.85 (d, *J* = 6.6 Hz, 12 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 173.74, 172.83, 170.72, 71.09, 45.9, 41.1, 39.0, 34.5, 34.1, 29.9, 29.7, 29.5, 29.3, 29.1, 27.9, 27.4, 25.2, 24.9, 22.6.

***N*- [*N*- [(3*R*)- 15-Methyi-3-(13-methyltetradecanoyloxy)hexadecanoyl]glycyl]-L.serine benzyl Ester (72).**



72

To a suspension of **46** (267 mg, 0.47 mmol) in DMF (6 ml) was added H-L-Ser-OCH_2Ph.TFA (139 mg, 0.71 mmol), DEPC (84 μL, 0.56 mmol), and then TEA (156 μL, 1.12 mmol) at 0 ^oC, and the mixture was stirred at room temperature for 20 h. The mixture was diluted with Et_2O and washed with 1 M aqueous $KHSO_4$, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography using pet ether : EtOAc (1 : 2) to give **72** as a colorless wax.

Yield: 275 mg, 81%.

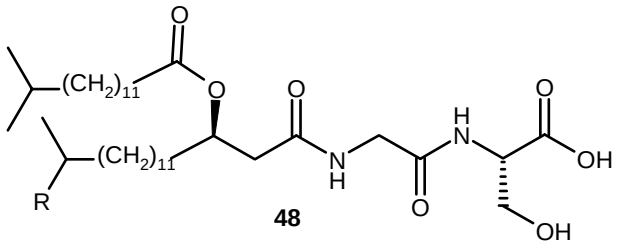
Mol. Formula: $C_{44}H_{76}N_2O_7$

$[\alpha]_D^{25}$: +15.2 (*c* 0.60, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 3360, 2953, 2926, 2855, 1738, 1732, 1660, 1653, 1520, 1468, 1215, 1080, 756.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.34-7.37 (m, 5H), 7.06 (d, *J* = 7.3 Hz, 1H), 6.51 (t, *J* = 5.3 Hz, 1H), 5.13-5.22 (m, 2H), 4.66-4.77 (m, 1H), 3.92-4.09 (m, 3H), 2.50 (d, *J* = 5.6 Hz, 2H), 2.28 (t, *J* = 7.6 Hz, 2H), 1.40-1.58 (6H, m), 1.23 (brs, 34 H), 1.11-1.17 (m, 4H), 0.86 (d, *J* = 6.6 Hz, 12 H).

_N_- [(3_R_)- 15-Methyl-3-(13-methyltetradecanoyloxy)hexadecanoyl]glycyI-L-serine (topostin D654, 48).



48

A mixture of **72** (262 mg, 0.36 mmol) and 5% Pd-C (400 mg) in EtOH (18 ml) was stirred at room temperature for 5 h under H_2. The mixture was filtered through the pad of celite, and the precipitates were washed with EtOH. The combined filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography using $CHCl_3$:

MeOH (3 : 1) to give a colorless powder. The powder was dissolved in $CHCl_3$ and the insoluble materials were filtered. The filtrate was concentrated in vacuo to give topostin D654 (**48**) as a colorless powder.

Yield: 151 mg, 65%

Mol. Formula: $C_{37}H_{70}N_2O_7$

$[\alpha]_D^{25}$: +18.2 (*c* 1, $CHCl_3$)

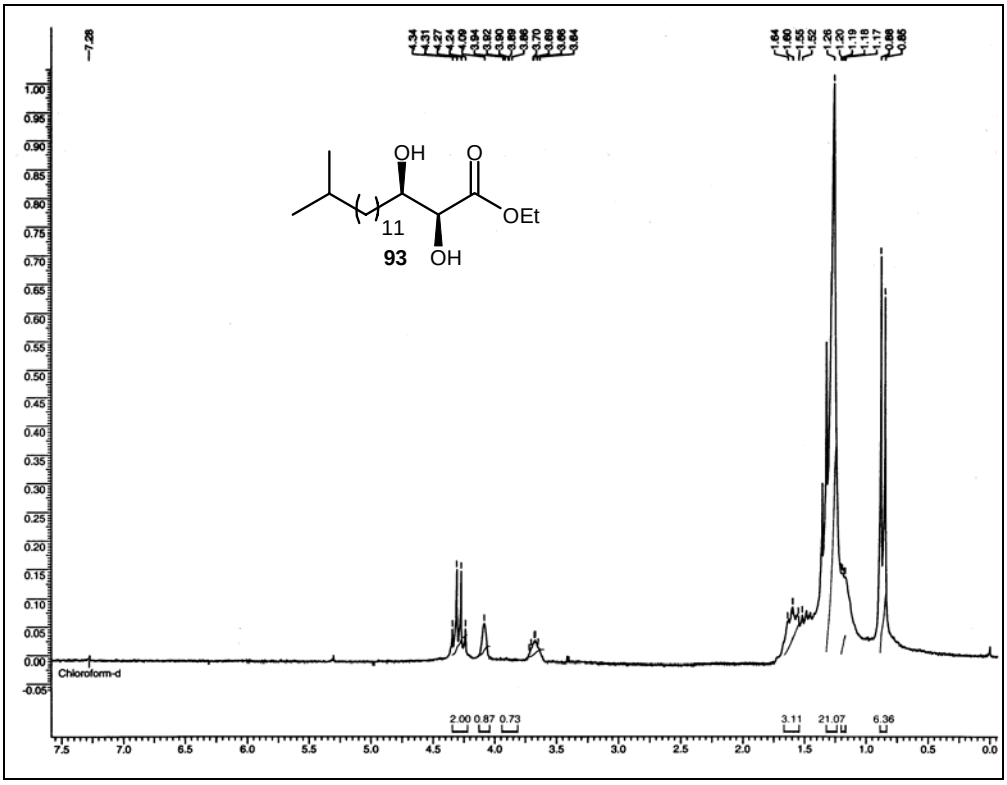
IR ($CHCl_3$, cm^{-1}): ν_{max} 3345, 2953, 2926, 2855, 1728, 1651, 1531, 1468, 1215,762.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.63 (brs, 1H), 7.15 (brs, 1H), 5.20-5.15 (m, 1H), 4.70 (brs, 1H), 4.11-3.91 (m, 4H), 2.52 (brs, 2H), 2.30 (t, *J* = 7.3 Hz, 2H), 1.61-1.45 (m, 6H), 1.25 (brs, 34H), l.19-1.13 (m, 4H), 0.85 (d, *J* = 6.6 Hz, 12H).

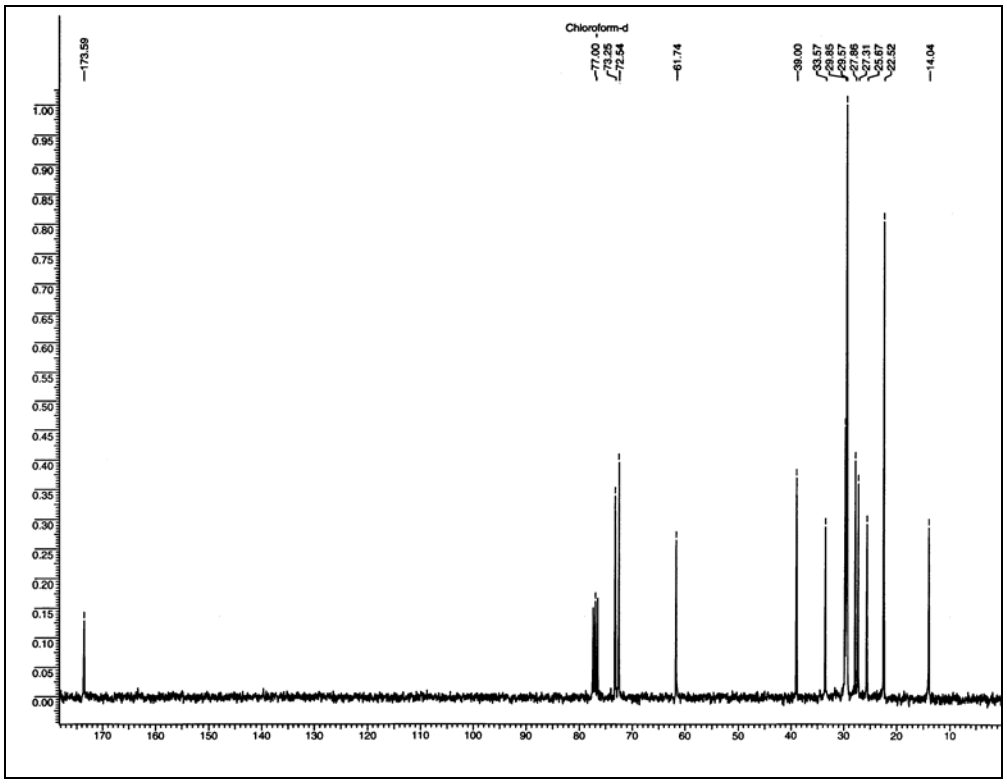
^{13}C NMR (50 MHz, $CDCl_3$): δ 173.8, 172.9, 170.8, 169.8, 71.1, 62.6, 54.7, 42.8, 41.2, 39.0, 34.5, 34.3, 31.9, 30.0, 29.7, 29.6, 29.5, 29.3, 29.1, 27.9, 27.4, 25.2, 25.1, 22.6.

2.2.7 Spectra

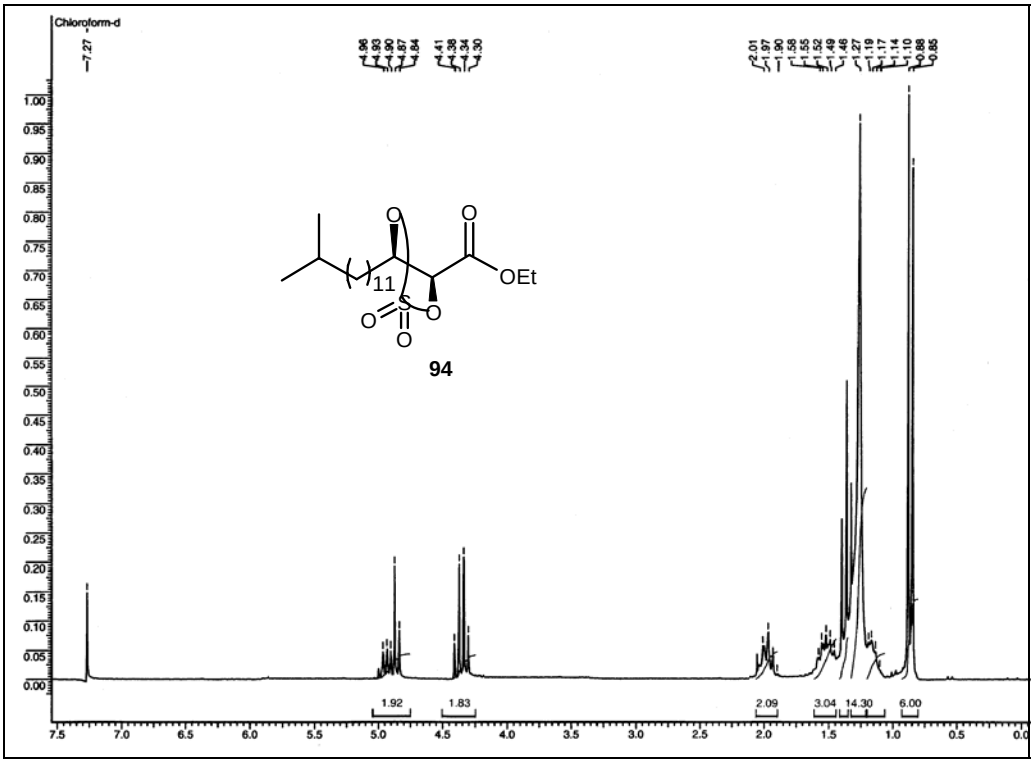
1. ^{1}H and ^{13}C NMR spectra of 93
2. ^{1}H and ^{13}C NMR spectra of 94
3. ^{1}H and ^{13}C NMR spectra of 95
4. ^{1}H and ^{13}C NMR spectra of 60
5. ^{1}H and ^{13}C NMR spectra of 62
6. ^{1}H and ^{13}C NMR spectra of 63
7. ^{1}H and ^{13}C NMR spectra of 56
8. ^{1}H and ^{13}C NMR spectra of 57
9. ^{1}H and ^{13}C NMR spectra of 64
10. ^{1}H and ^{13}C NMR spectra of 42
11. ^{1}H and ^{13}C NMR spectra of 68
12. ^{1}H and ^{13}C NMR spectra of 43
13. ^{1}H and ^{13}C NMR spectra of 70
14. ^{1}H and ^{13}C NMR spectra of 46
15. ^{1}H and ^{13}C NMR spectra of 48



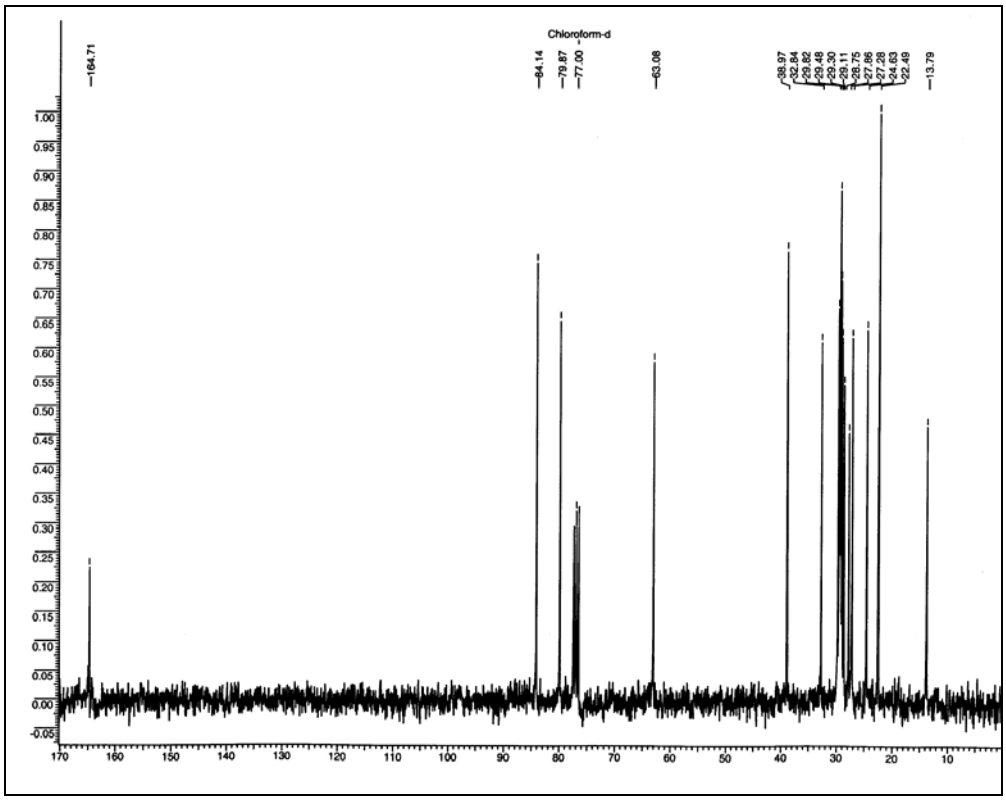
^{1}H NMR Spectrum of compound 93 in $CDCl_3$



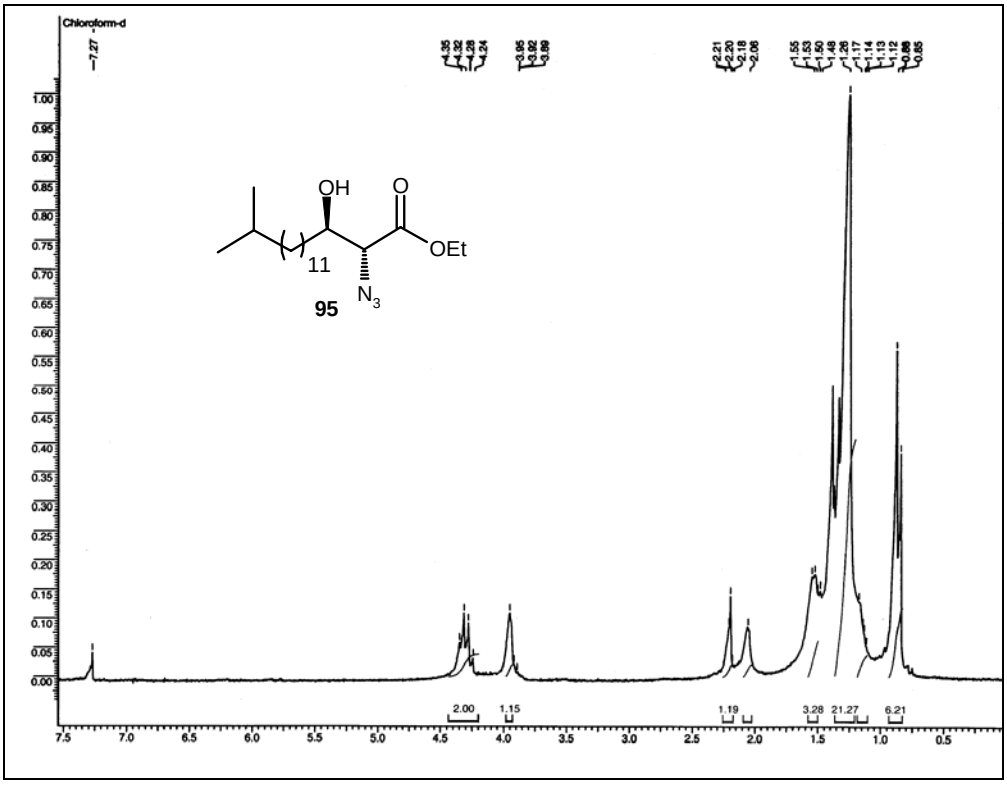
^{13}C NMR Spectrum of compound 93 in $CDCl_3$



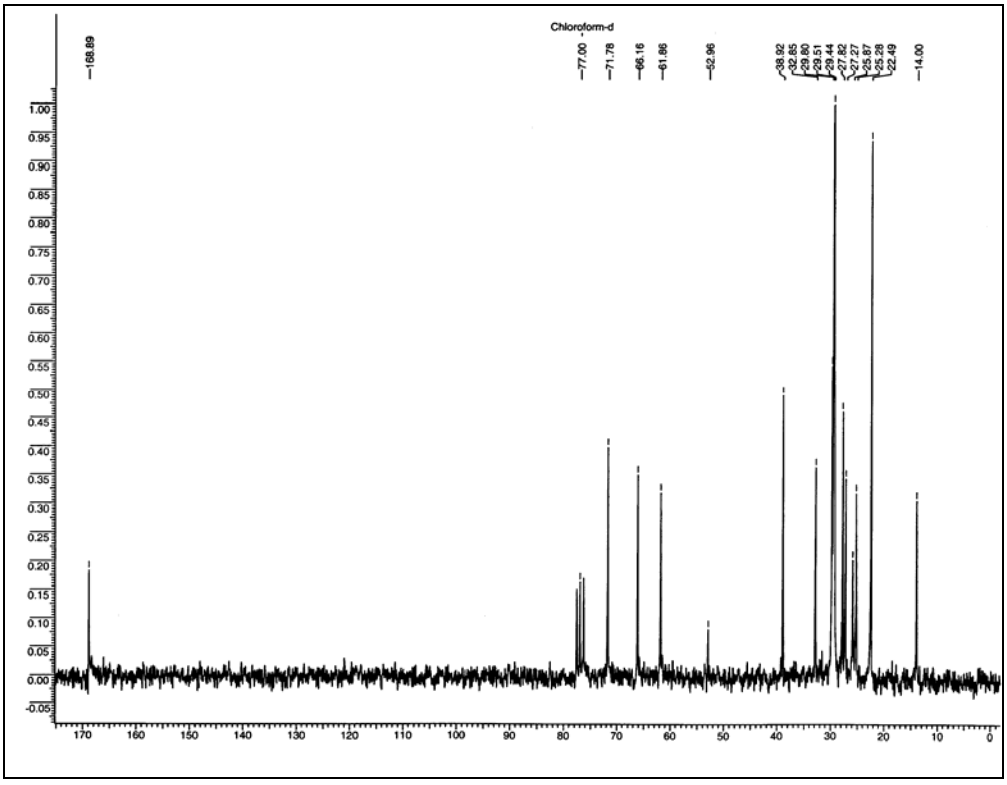
^{1}H NMR Spectrum of compound 94 in $CDCl_3$



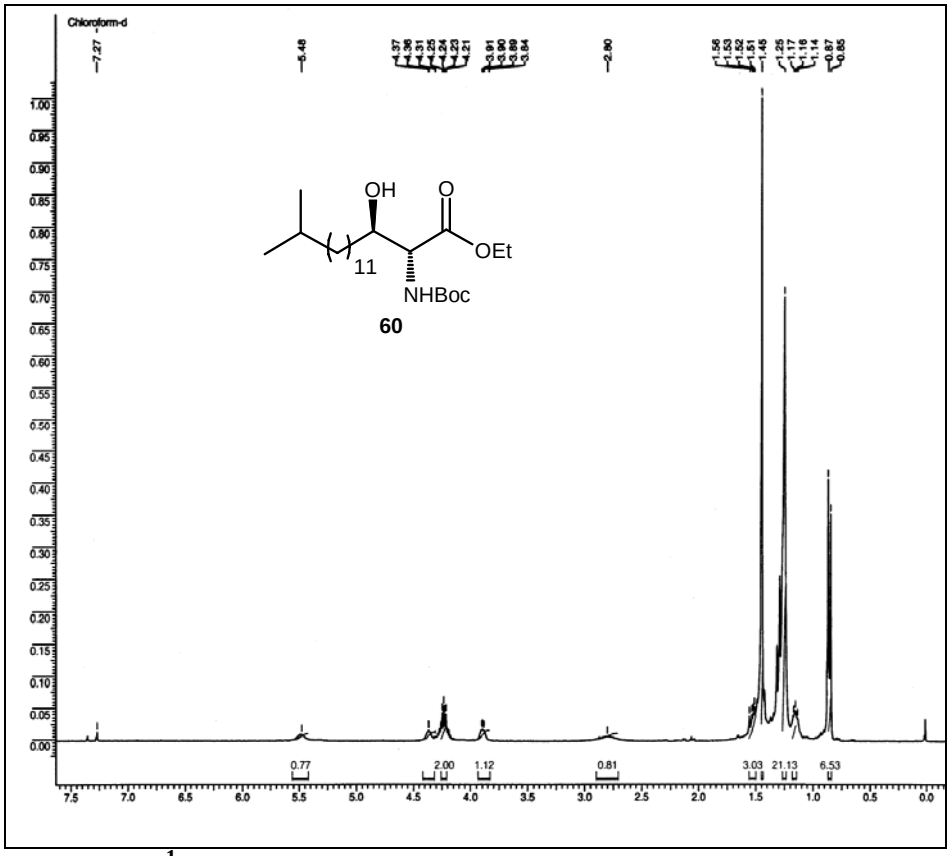
^{13}C NMR Spectrum of compound 94 in $CDCl_3$



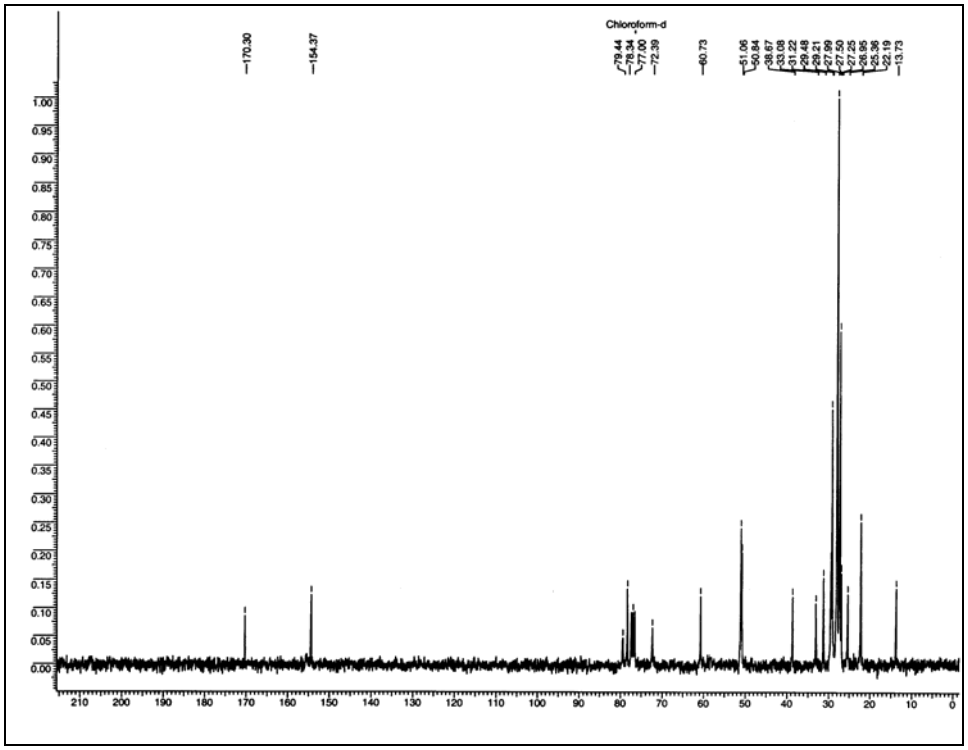
^{1}H NMR Spectrum of compound 95 in $CDCl_3$



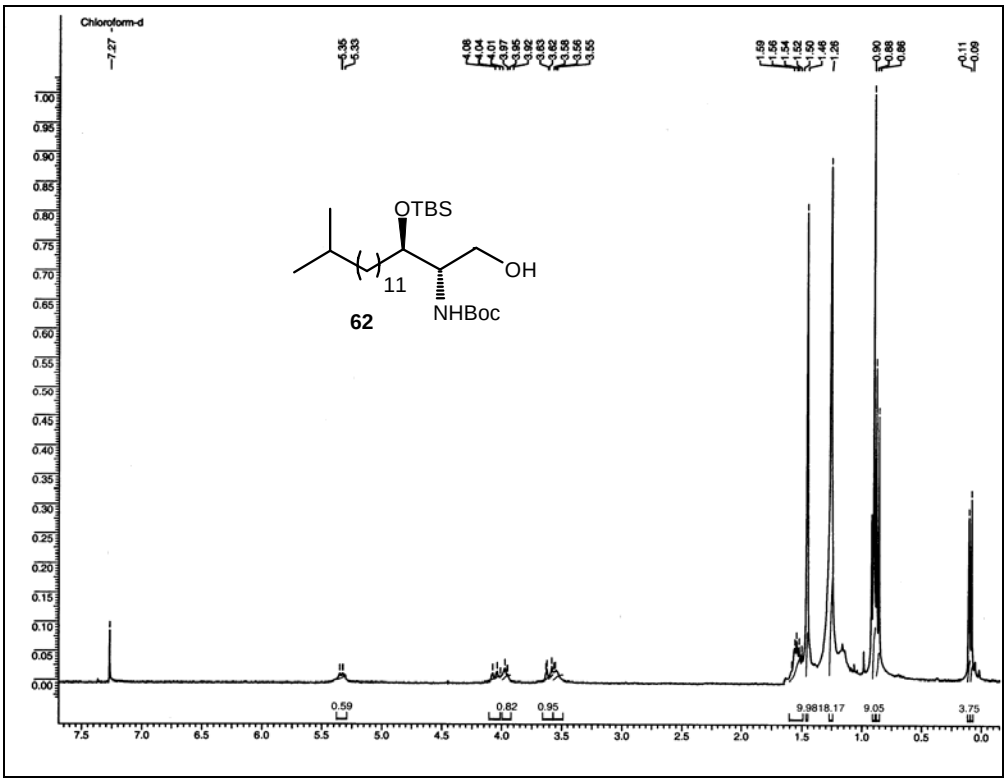
^{13}C NMR Spectrum of compound 95 in $CDCl_3$



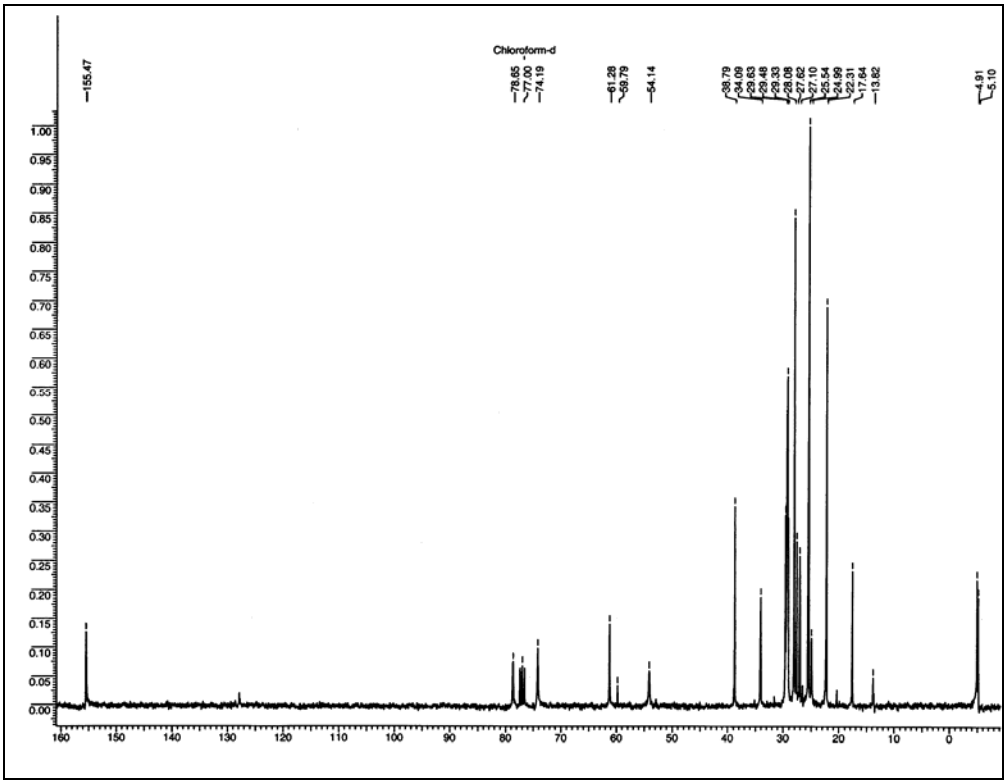
^{1}H NMR Spectrum of compound 60 in $CDCl_3$



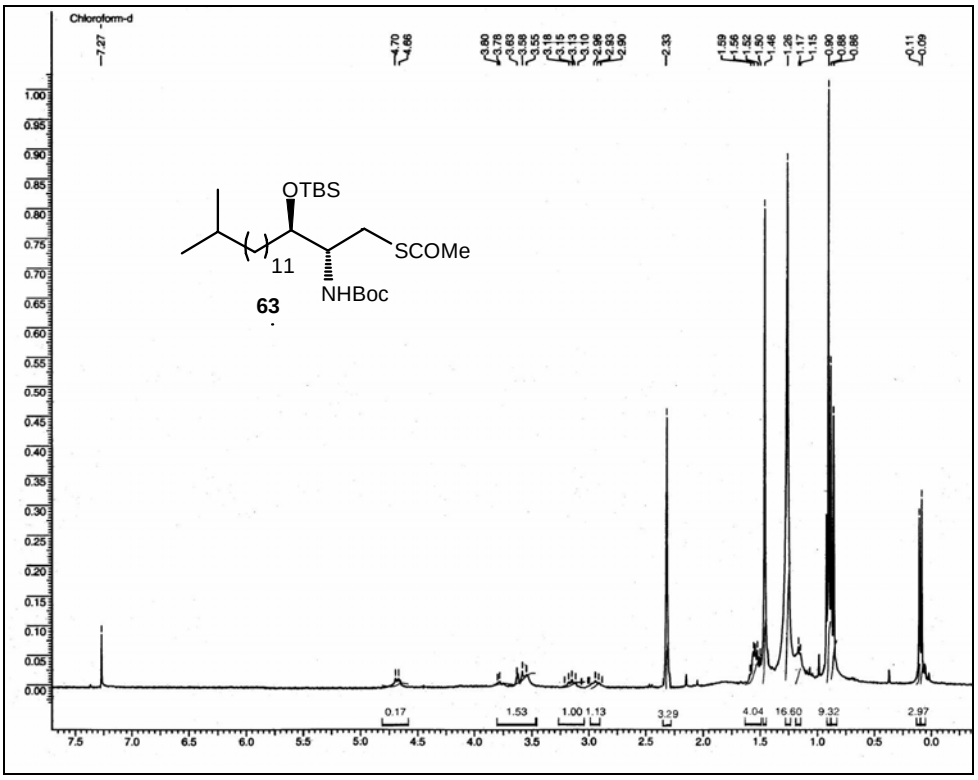
^{13}CNMR Spectrum of compound 60 in $CDCl_3$



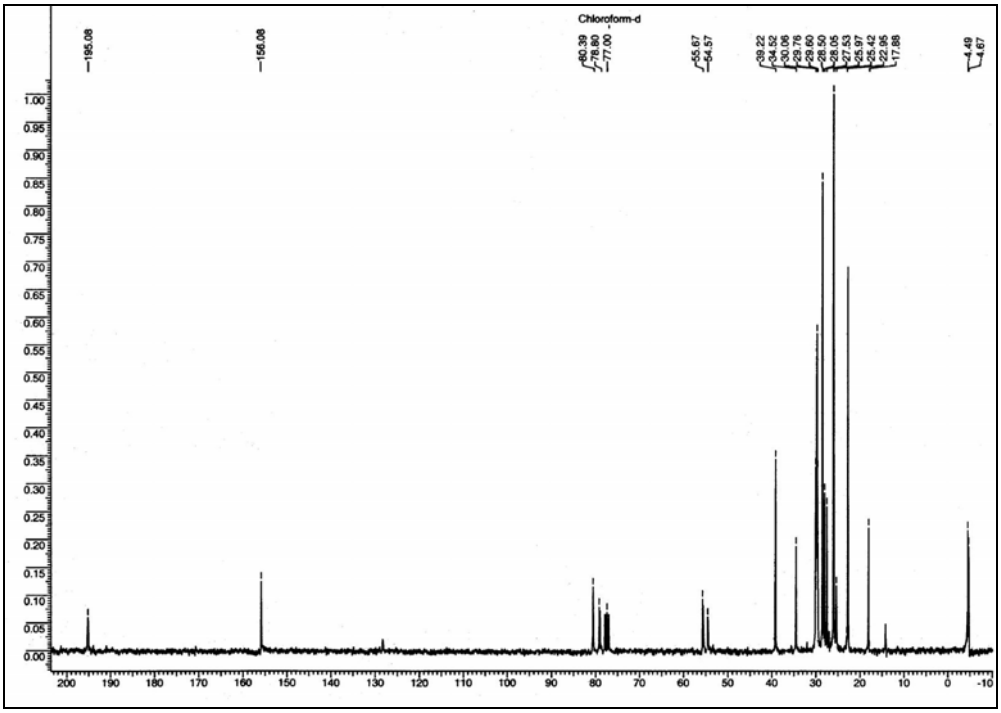
^{1}H NMR Spectrum of compound 62 in $CDCl_3$



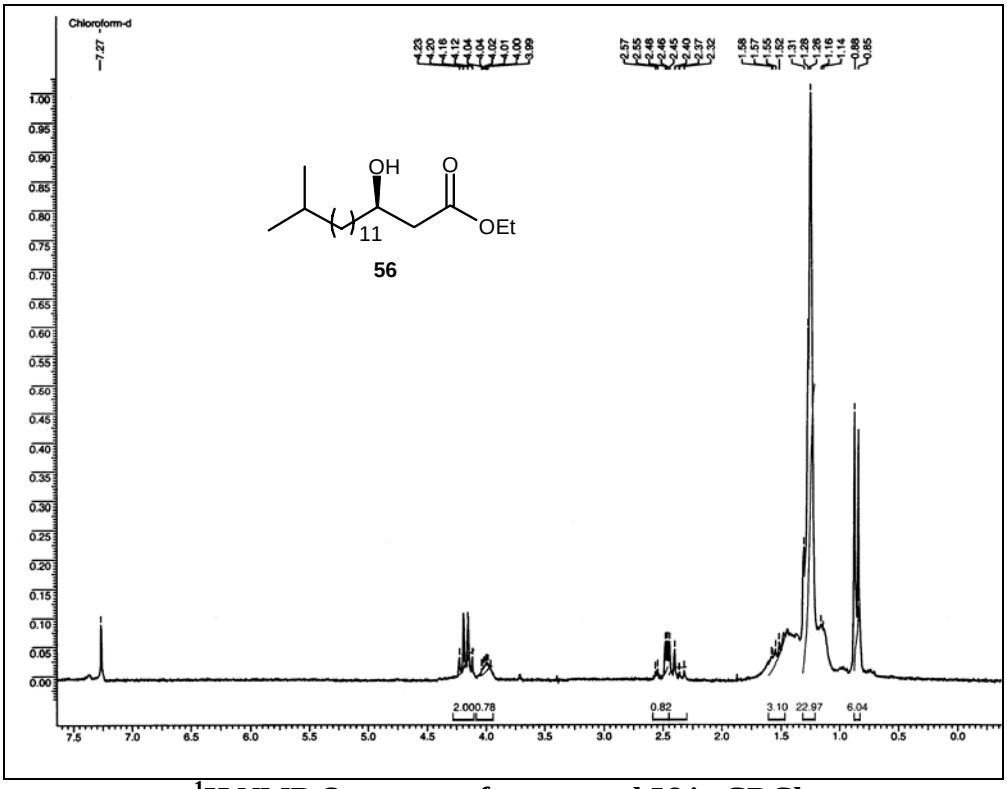
^{13}C NMR Spectrum of compound 62 in $CDCl_3$



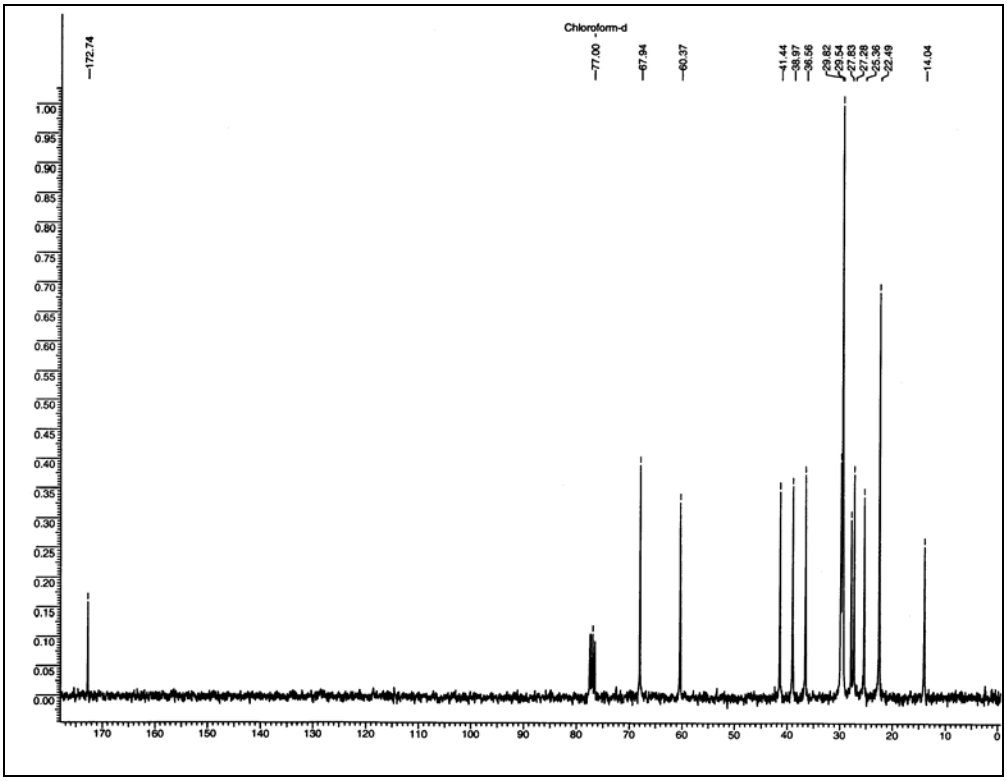
^{1}H NMR Spectrum of compound 63 in $CDCl_3$



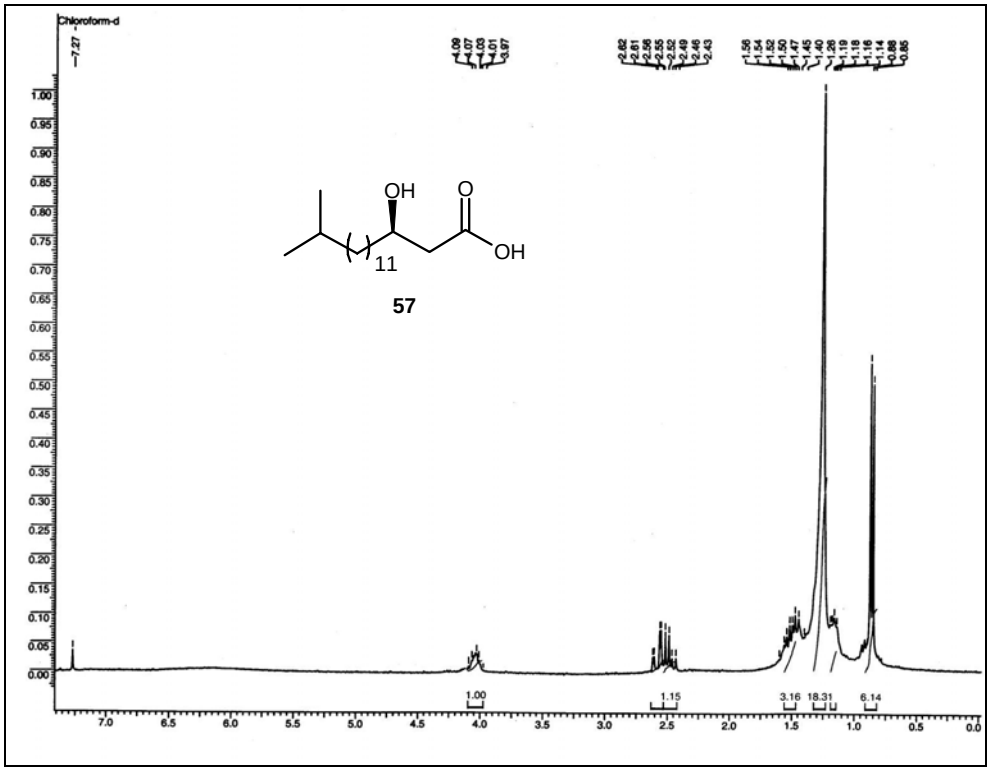
^{1}H NMR Spectrum of compound 63 in $CDCl_3$



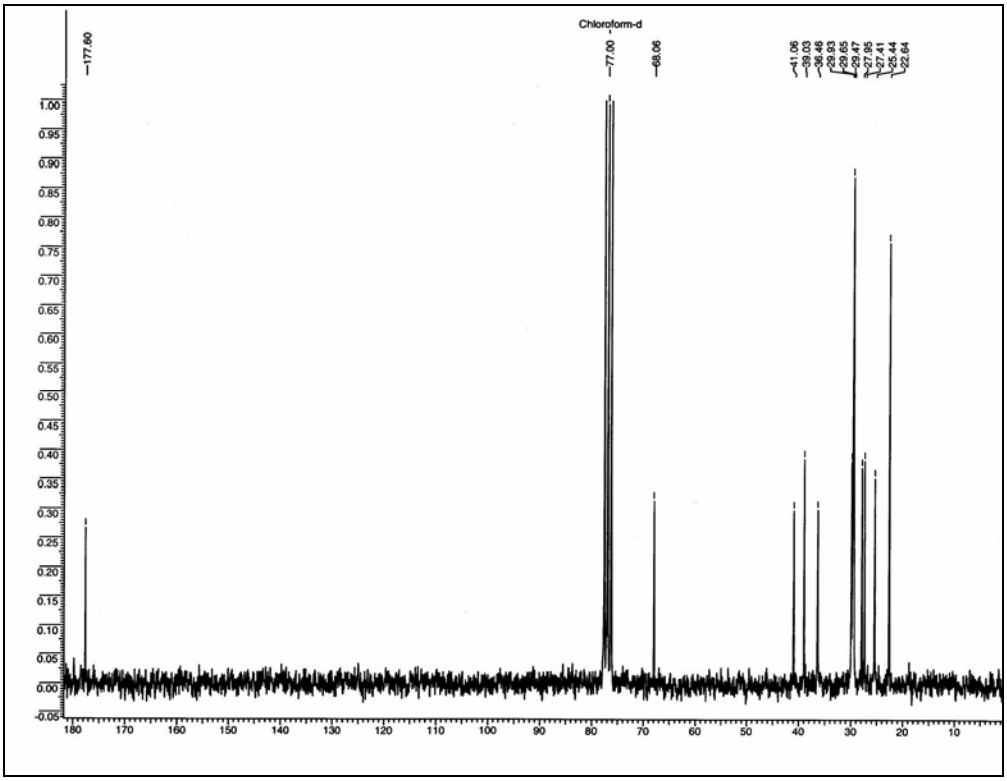
^{1}H NMR Spectrum of compound 56 in $CDCl_3$



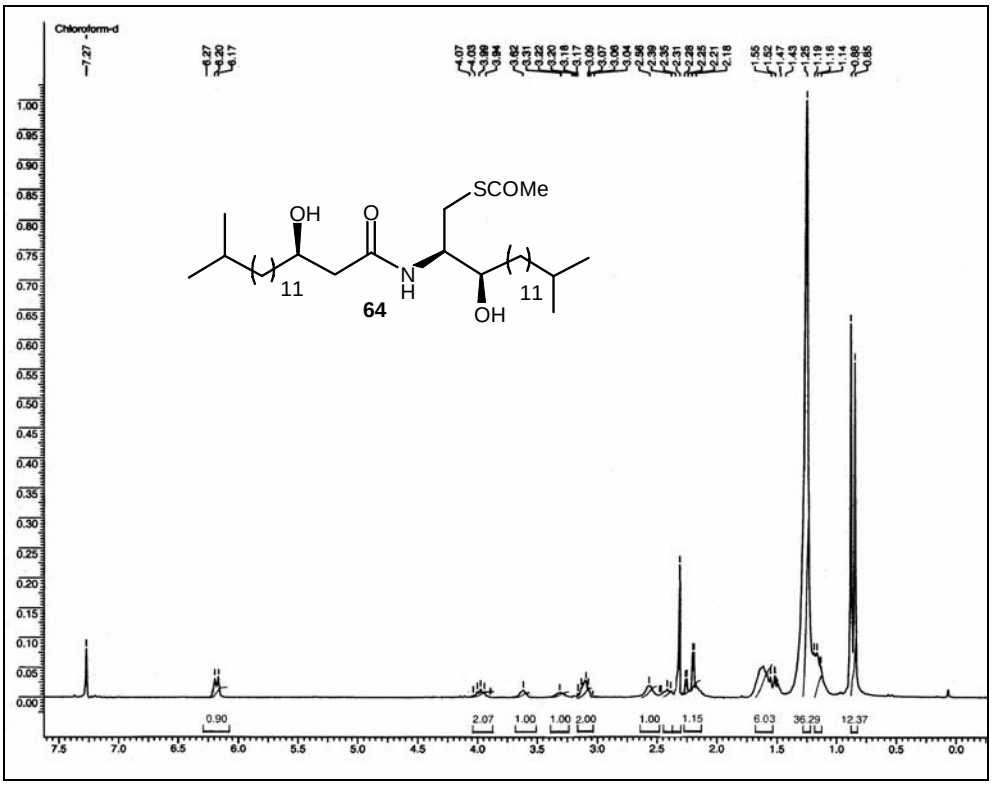
^{13}C NMR Spectrum of compound 56 in $CDCl_3$



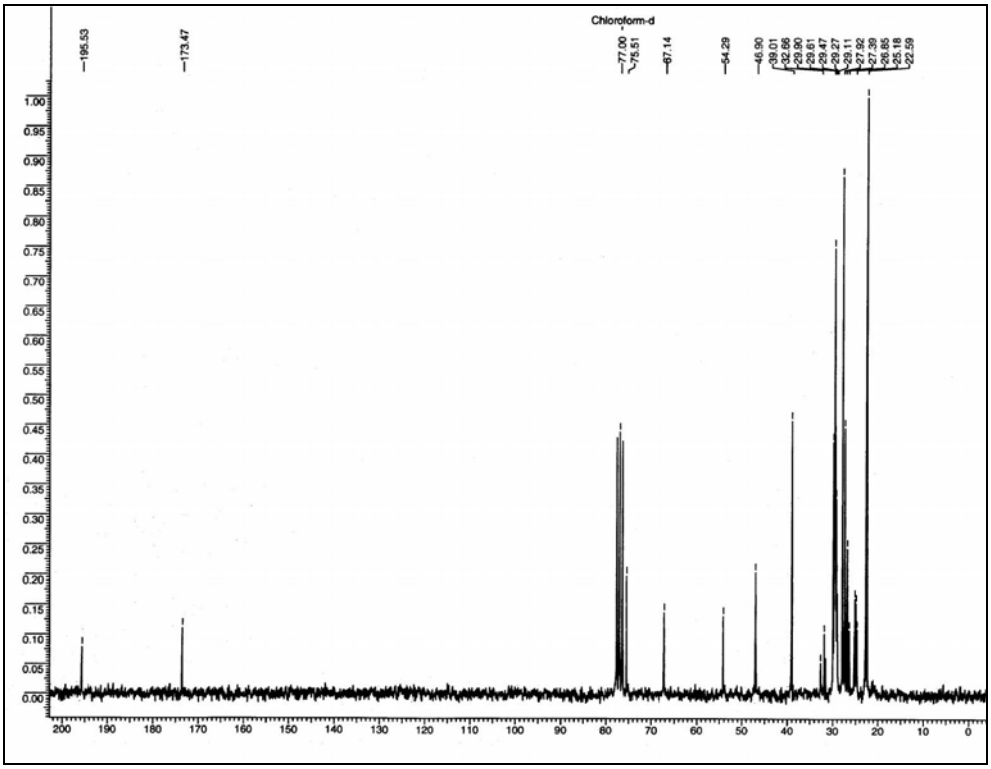
^{1}H NMR Spectrum of compound 57 in $CDCl_3$



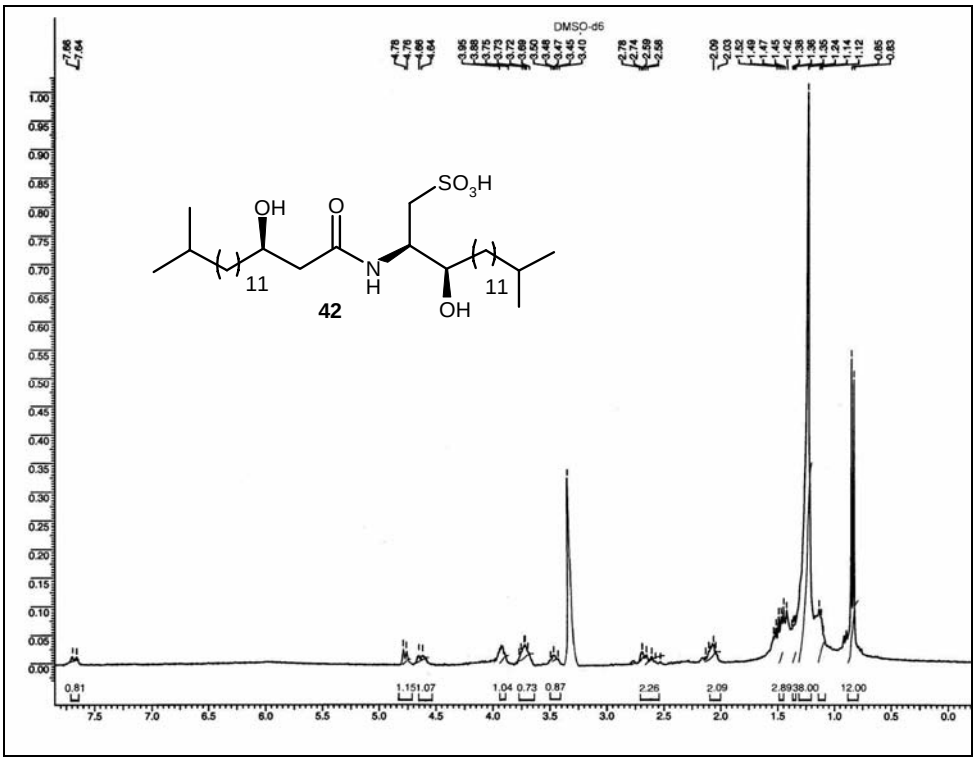
^{13}C NMR Spectrum of compound 57 in $CDCl_3$



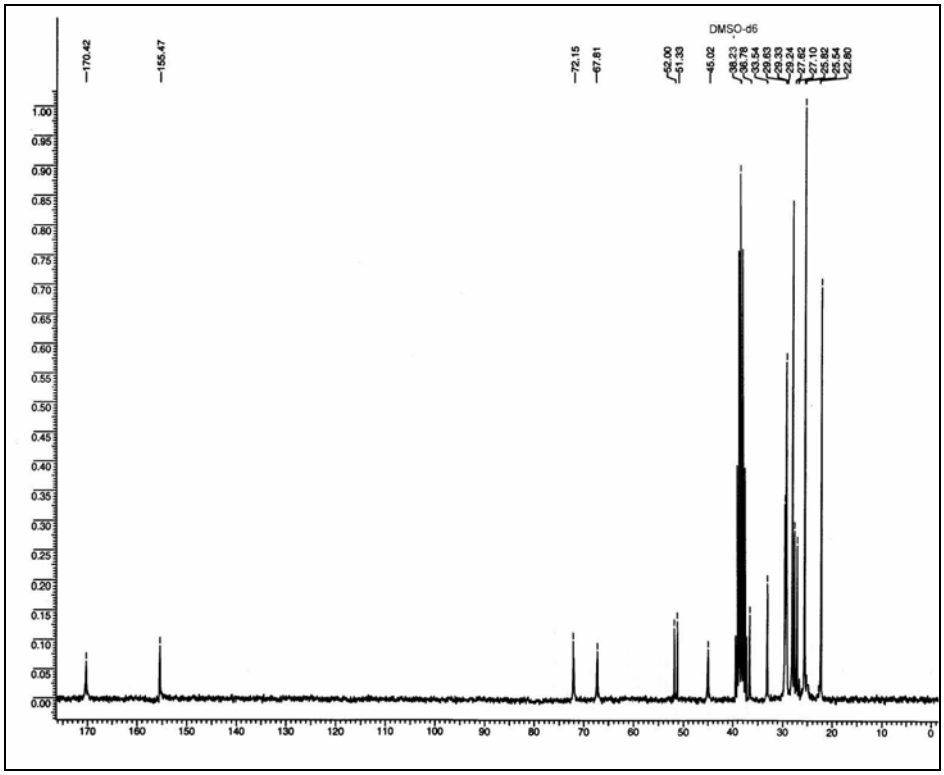
^{1}H NMR Spectrum of compound 64 in $CDCl_3$



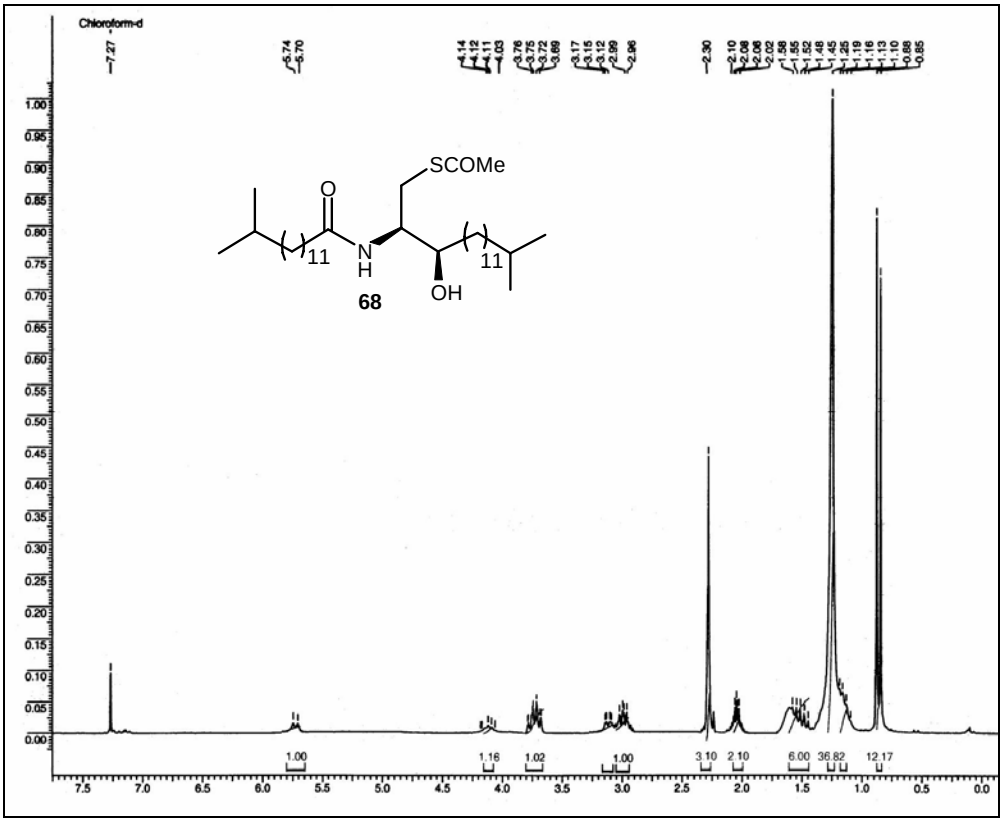
^{13}C NMR Spectrum of compound 64 in $CDCl_3$



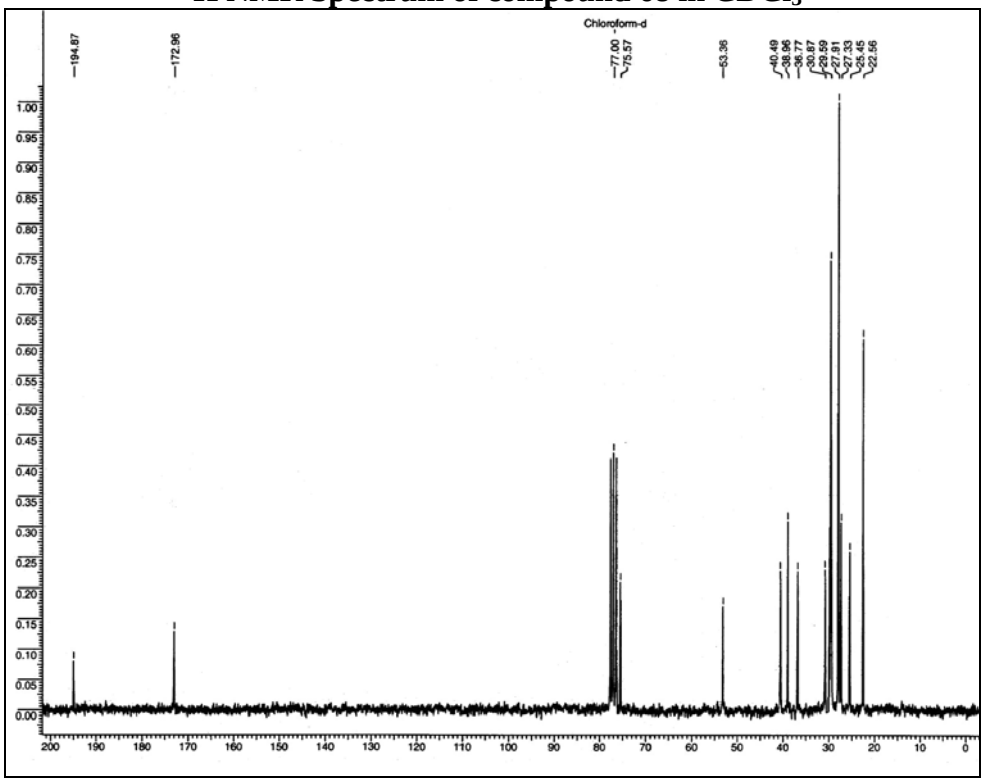
^{1}H NMR Spectrum of compound 42 in DMSO D6



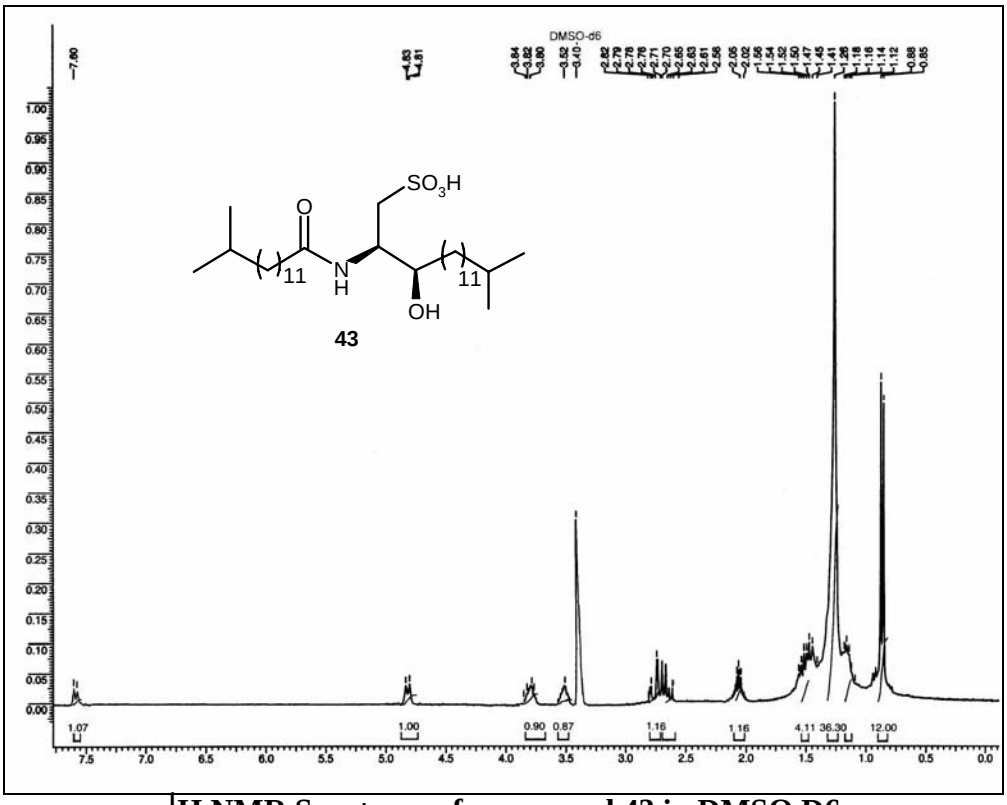
^{13}C NMR Spectrum of compound 42 in DMSO D6



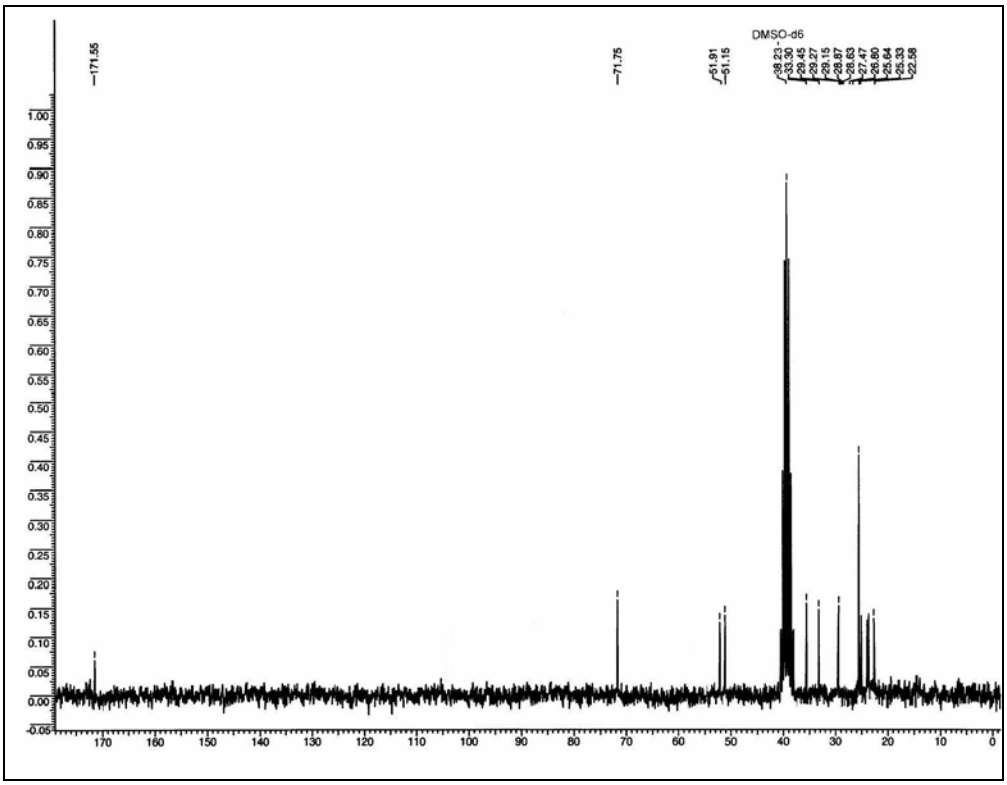
^{1}H NMR Spectrum of compound 68 in $CDCl_3$



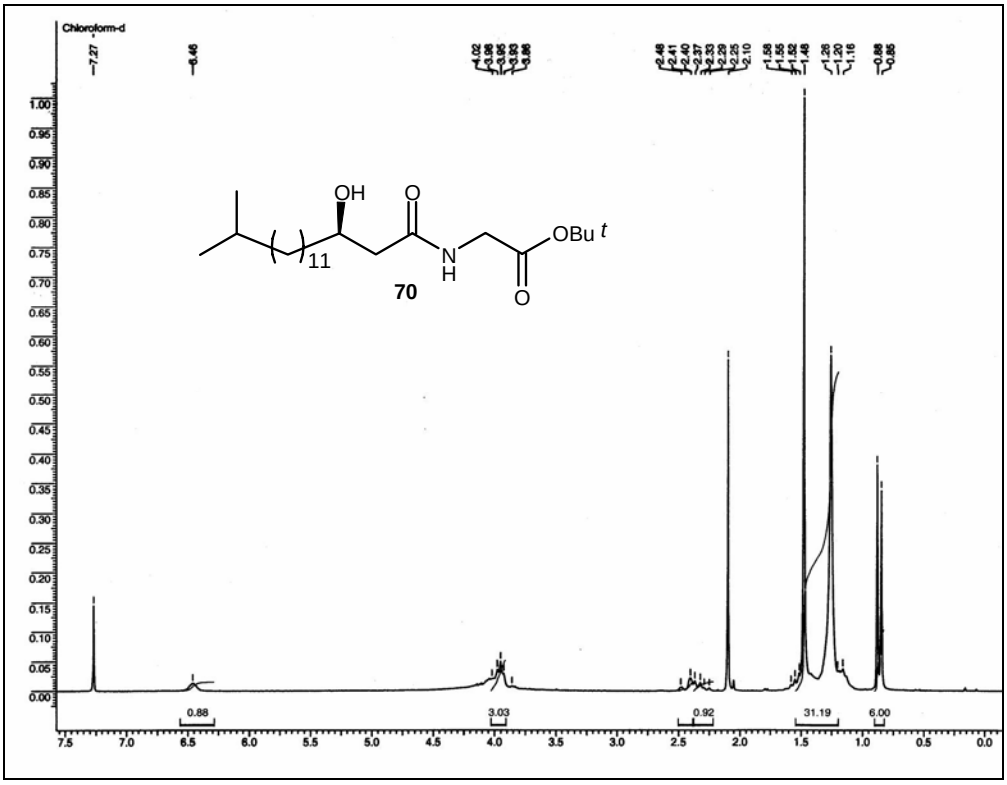
^{13}C NMR Spectrum of compound 68 in $CDCl_3$



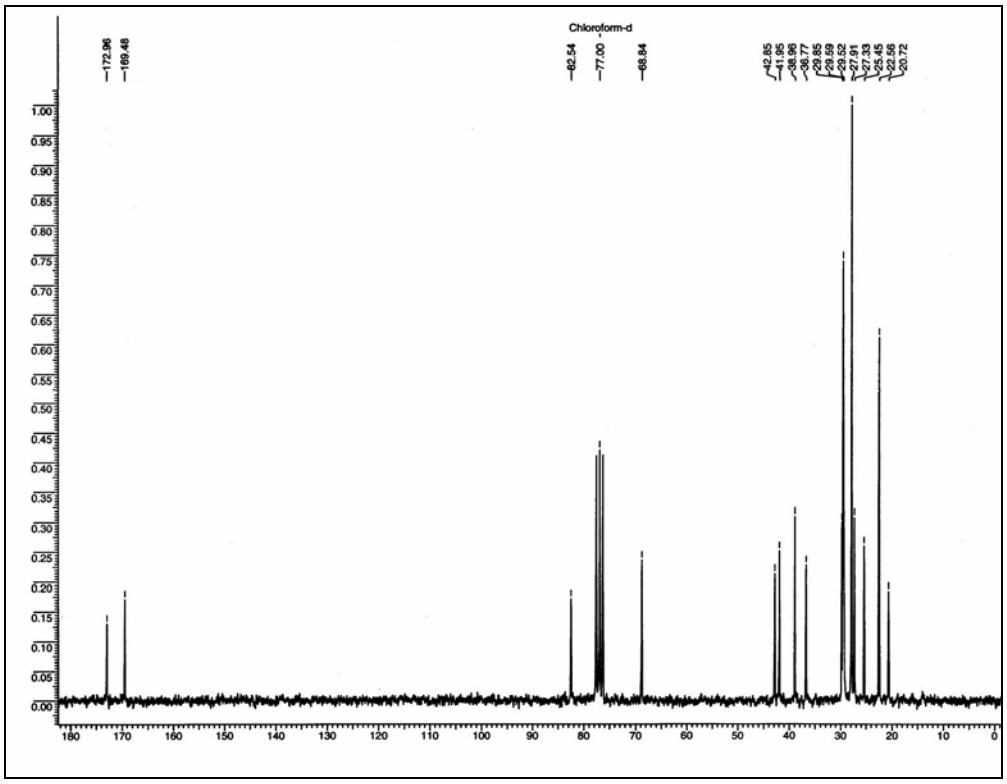
^{1}H NMR Spectrum of compound 43 in DMSO D6



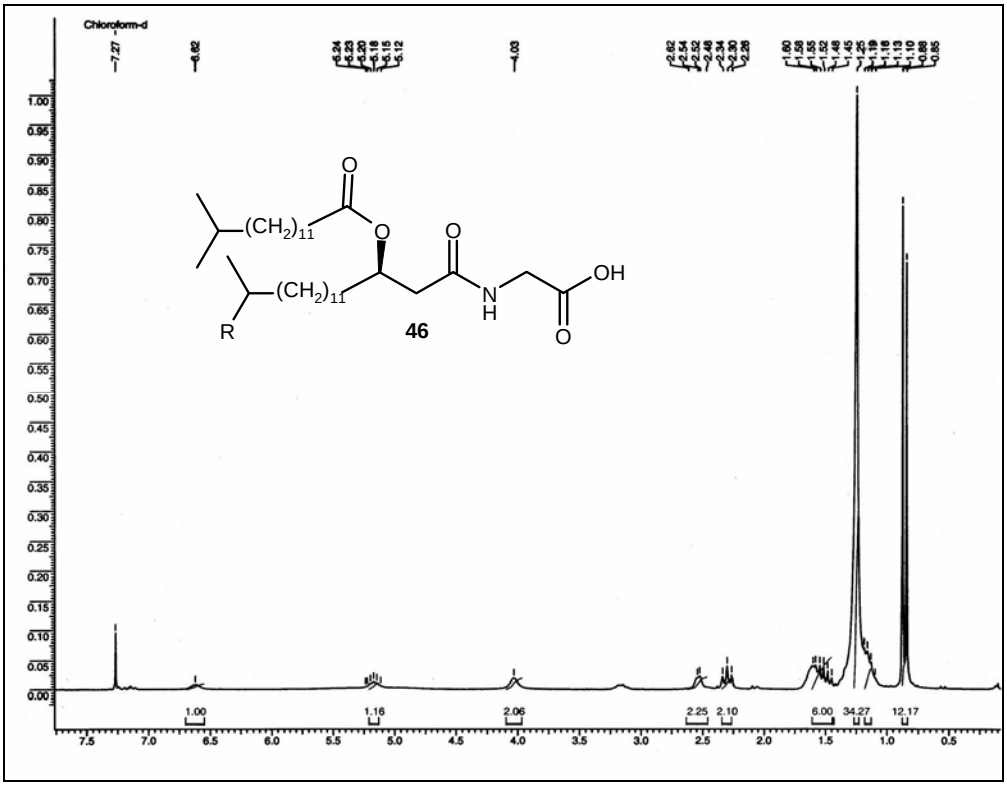
^{13}C NMR Spectrum of compound 43 in DMSO D6



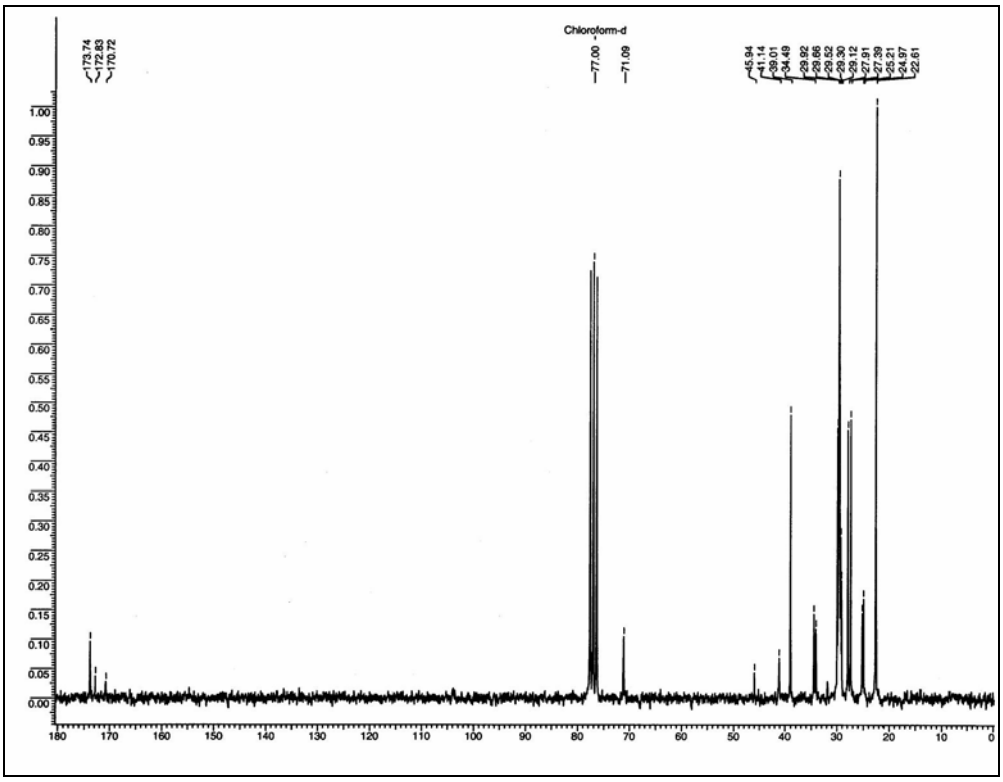
^{1}H NMR Spectrum of compound 70 in $CDCl_3$



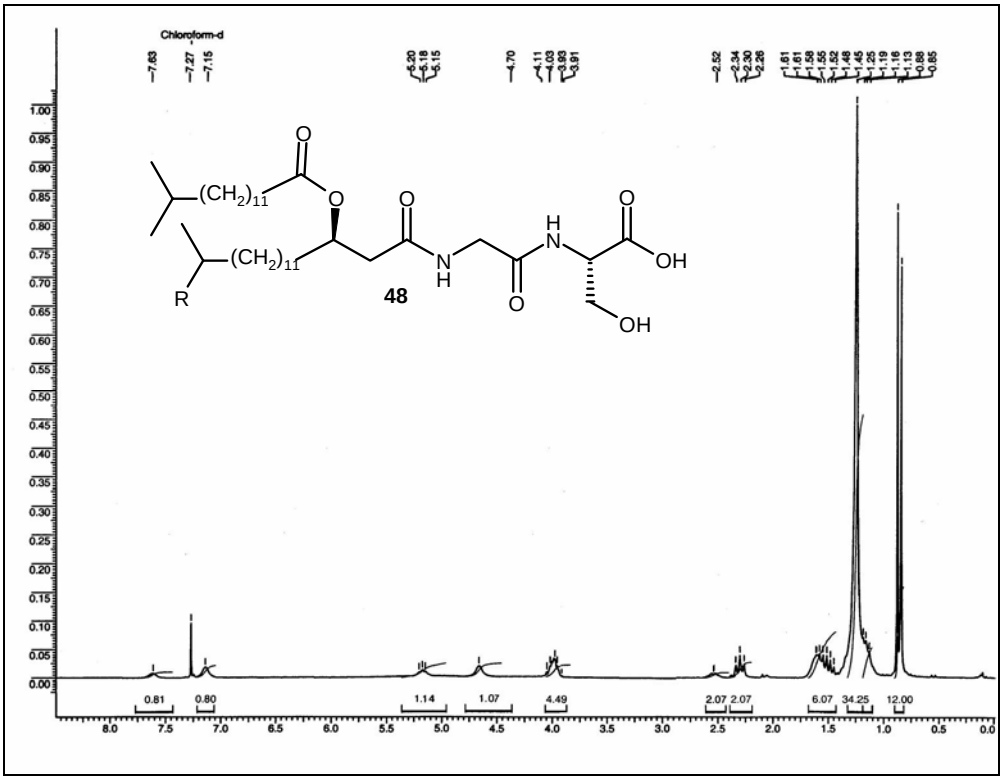
^{13}C NMR Spectrum of compound 70 in $CDCl_3$



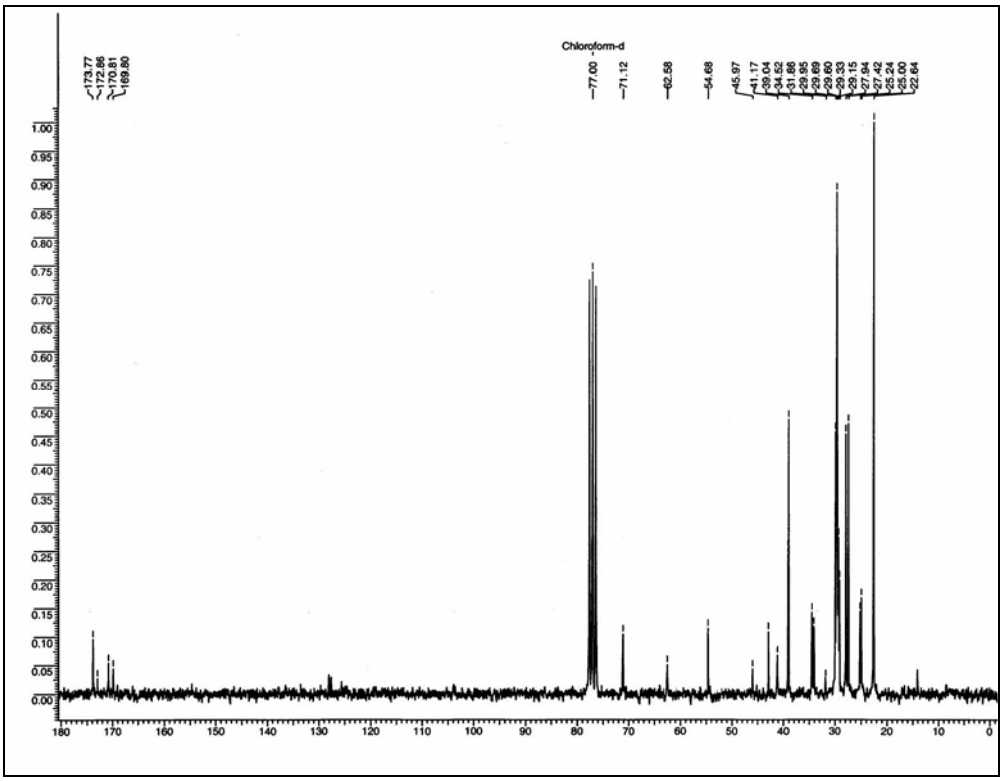
^{1}H NMR Spectrum of compound 46 in $CDCl_3$



^{13}C NMR Spectrum of compound 46 in $CDCl_3$



^{1}H NMR Spectrum of compound 48 in $CDCl_3$



^{13}C NMR Spectrum of compound 48 in $CDCl_3$

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CHAPTER-3

SIMPLE AND EFFICIENT APPROACH TO 1,3-POLYOLS: SYNTHESIS OF MASSOIALACTONE AND KURZILACTONE

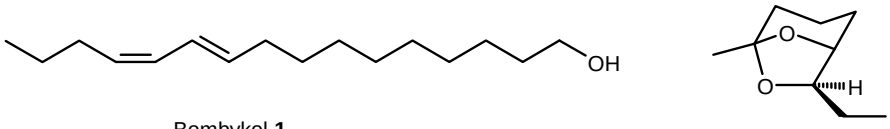
3.1 SECTION A

ENANTIOSELECTIVE SYNTHESIS OF MASSOIALACTONE, PARASORBIC ACID AND HEXADECANOLIDE

3.1.1. Introduction

In 1930's, investigations have been made into various active substances which, though they resemble hormones in some respects, can not be included among them. Unlike hormones the substance is not secreted into the blood but outside the body; it does not have hormonal evolution within the organism but communication between individuals. Karlson and Luscher[1] coined the word 'pheromones" to this group of active substances. The name is derived from the Greek *Pherin*, to transfer, *hormone*, to excite. Thus, pheromones are secreted by an individual bio-organism and are received by a second individual of the same species and produce a specific reaction, e.g. a definite behaviour or a developmental process. Compounds used for interspecific communication are called allomones (favoring the producer) and kairomones (favoring their receivers). Pheromones, allomones and kairomones are the chemical substances that deliver messages. The term semiochemicals is used as a generic name for the signal substances such as pheromones, allomones and kairomones.[2]

The first isolation of pheromones was announced in 1959 by Butendant *et al.* from the silkworm moth, *Bombyx mori*.[3] The pheromone was named bombykol **1** and was identified as an achiral olefinic alcohol as shown in Fig. 1. In the late 1960's Silverstein *et al.* isolated several chiral pheromones from beetles. An example is exo-brevicomin **2**, the aggregation pheromone of the western pine beetle, *Dendroctonus brevicomis*.[4] Since then over 100 chiral pheromones have been isolated and identified.



Bombykol **1** exo-brevicomin **2**

Figure 1

Since the quantity of pheromones isolated from natural sources is often less than a milligram, it has frequently been impossible for certain whether or not the components are optically active. However, two complementary general methods have recently been set up in order to determine the enantiomeric compositions of sub-milligram quantities of chiral pheromones.[5] First method is based on NMR studies of a chiral component in the presence of optically active lanthanide shift reagents.[6] The second one concerns the derivatisation of a chiral component with an enantiomerically pure component and the NMR study of the thus obtained diastereotopic derivatives.[7,8]

The problem of the stereochemical assignment of optically active pheromone components for which the sign of the rotatory power is known was resolved for the first time in 1973 by synthesizing stereospecifically one of the possible stereoisomer starting from a compound of known absolute configuration and optical purity, and then by comparing the optical purity data of the synthetic material with those of the natural product.[9]

On the other hand, in the case of the chiral pheromone components having unknown optical purity and / or enantiomeric composition, but supposed to be optically active, the criterion recently followed to establish their absolute stereochemistry consists of (a) synthesizing stereospecifically all the possible stereoisomers starting from optically pure compounds of known absolute configuration, (b) determining the relationship between the stereochemistry and biological activity and then (c) comparing these biological activity data with those of the natural product.[10-12]

Chemical significance of synthesizing optically active pheromones:

Pheromones are often obtained only in small amounts as volatile oil in many cases. This makes the stereochemical studies of natural pheromones very difficult. This can be overcome by an enantioselective synthesis of the target molecule starting from a compound of known absolute configuration. If chirooptical properties such as $[\alpha]_D$ value and ORD/CD spectrum of the natural pheromone are recorded then we can compare these with corresponding data for the synthetic material. The absolute configuration of the natural pheromone will thus be clarified.

Biological significance of synthesizing optically active pheromones:

Among chiral compounds there are many cases in which only one enantiomer is bioactive. For example, (+)-estrone (+)-**3** is bioactive as a female sex pheromone, but the (-)-isomer is inactive (Fig. 2). The correct perception of pheromones is essential in the successful life of insects. Incorrect perception will lead to the death of that insect.

In 1976 Wood *et al*.[12] showed that pheromone perception is enantioselective, but some pheromones are more active in racemic mixture.[13]

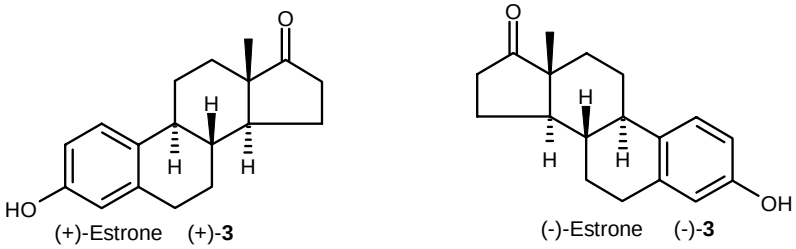


Figure 2

General Synthetic Methodologies:

Synthesis of pheromone enantiomers can be achieved[14] by one of the following three methods: (a) derivation from optically active natural products such as α-amino acids, hydroxyl-acids, terpenes and carbohydrates, (b) optical resolution of an intermediate or final product, (c) chemical or biochemical asymmetric synthesis.

Pheromones as sex attractants:

Pheromones are employed by a large number of insects in bringing the sexes together. These pheromones are known as sex pheromones. They are widespread amongst *Lipidoptera* and also in some *Dictyoptera caleoptera*, Hymenoptera and some other orders.[15] In most cases the pheromone is produced by the female to attract the male, while less frequently a male pheromone attracts the female or both sexes may be lured by the odour.[16]

Manipulation of insect pests:

Considerable progress has been made over the past decades in the application of insect sex pheromones to pest control programs. The development of food attractants and their incorporation into traps for survey and detection and into bait sprays for control has had great impact on the management of these pests. Similarly, specific male attractants have been discovered and utilized in trapping and control through annihilation. An old adage runs like this "An attractant in the bush may be worth two in the hands."

Manipulation of insect pests of stored product:

More effective control of storage pests in large granaries, small form storage, ships, warehouses, stores, houses and apartments could mean an immediate increase in the world's edible grain and food without any change in agricultural productivity. Biologically active agents such as pheromones might provide a new way of manipulating the pests. The development of simple traps baited with insect pheromones or attractants to lure the pests from their hiding places may enable us to determine the proper time for efficient control of stored-product pests, to minimize the number of applications of pesticide, to estimate population levels, and to aid in the identification of problem species. Sex pheromones often elicit extremely high levels of response by insects and provide a powerful means of fraying them into trapping devices. Food attractants are likewise useful in trapping, but the competition of the stored food lessens their effectiveness. Large traps too are useful, and their effectiveness could undoubtedly be enhanced by the use of pheromones. Accounts of pheromone concerning stored-product pests in the families dermestidae, anobiidae and pyralidae, were presented by Burkholder,[17,18] Nakajima[19] and Levinson.[20]

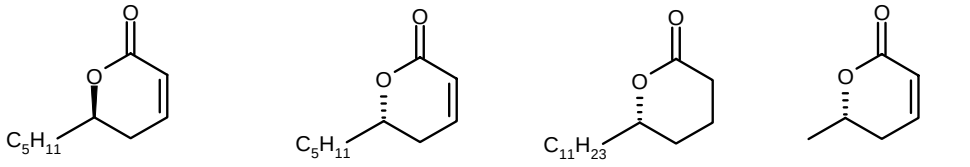
Manipulation of insect pests of stored product:

The pheromones that appear to have the greatest utility in the pest-management programs on agricultural crops are those that stimulate conspecifics from a distance. A large class of such chemicals consists of the sex pheromones.

Two main strategies are emerging for the use of pheromones in pest management. One involves the use of a pheromone for stimulation of the normal approach response of the responding insects, that the response is manipulated in such a way that the insects end up

in a location that is disadvantageous for them and advantageous for men. The other strategy involves the disruption of the normal chemical communication behavior of insects. In this case male moths might be rendered incapable of responding to or locating the source of a natural pheromone, the female would remain unmated.[21]

(-)- Massoialactone[22-23] **4a** is the major constituent of the bark oil of *Cryptocarya massoia*, isolated for the first time by Abe[24] in 1937. It is a powerful skin irritant and produces systolic standstill in frog heart muscle.[22] (-)- Massoialactone is the allomone of the two species of formicin ants[25] belonging to the *Camponotus* genus collected in Western Australia. This lactone has also been isolated from cane molasses[26] and jasmine blossoms[27] as flavour substance. Its absolute configuration was determined as *R* by comparing its ORD curve with that of (*S*)-(+)-2-hexen-5-olide.[28] Later Mori has further confirmed it by its synthesis.[29] 5-hexadecanolide **5** was isolated from the mandibular glands of the oriental hornet (*Vespa orientalis*)[30] as the pheromone for the workers to stimulate the construction of queen cells. The lactone **5** could induce the worker wasps to make queen cells even in the absence of a queen. Similarly (*S*)-(+)-5,6-dihydro-6-methyl-2*H*-pyran-2-one (parasorbic acid) **6**, a natural product isolated from the mountain ash berries (*Sorbus aucuparia*), is an intermediate for the synthesis of several carbohydrate derived antibiotics.[31] This intermediate has been converted into cis-3,6-dimethyltetrahydropyran-2-one, the major component of the male carpenter bee pheromone.[32]



(*R*)-Massoialactone **4a** (*S*)-Massoialactone **4b** Hexadecanolide **5** Parasorbic acid **6**

Figure 3

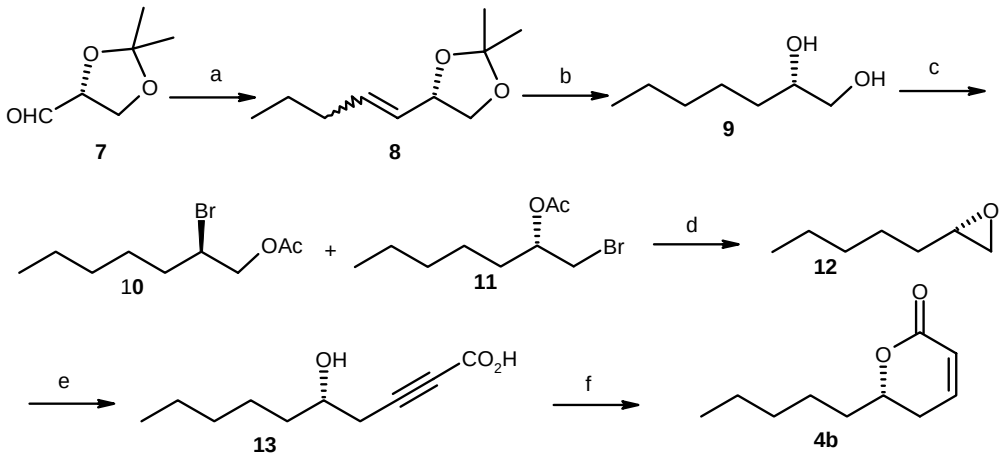
3.1.2. Review of Literature.1: Massoialactone

Various methods for the synthesis of massoialactone (Fig. 1) have been described. The asymmetric syntheses reported in the literature for the natural **4a** and unnatural **4b** isomers of massoialactone either utilize the chiral pool as a starting material or the

chromatographic resolution of the diastereomeric derivative of the lactone precursor. A recent report describes the synthesis via asymmetric allylboration of an aldehyde with *B*-allyldiisopinocampheylborane. A detailed report of these syntheses is described below.

Mori *et al.* (1976).[29]

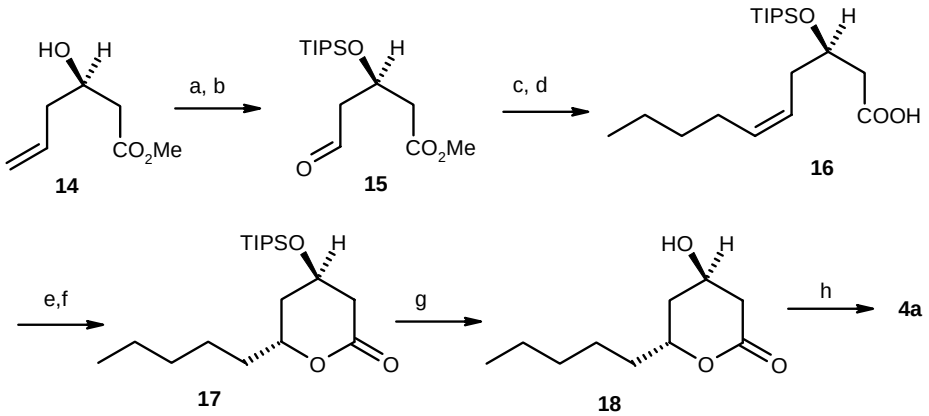
Mori and co-workers[29] confirmed the absolute configuration of massoialactone by synthesizing it from (*R*)-(+)-glyceraldehyde acetonide.[33] Thus, Wittig reaction between **7** and butylidene triphenylphosphorane afforded olefin **8**, which was hydrogenated followed by acetonide deprotection to give glycol **9**. This was treated with a saturated solution of hydrogen bromide in AcOH according to the procedure of Golding *et al*.[34] to give a mixture of **10** and **11**, which was smoothly converted into the required epoxide **12** with potassium hydroxide. Opening of epoxide **12** with dianion derived from propiolic acid[35] afforded hydroxy acid **13**, which on hydrogenation followed by lactonization afforded target molecule **4b**. The material thus obtained was identified as (*S*)-massoialactone by comparing its data with those of published one. This (*S*)-isomer was dextrorotatory, and the natural one was reported to be levorotatory.[25] It was, therefore, confirmed that the absolute configuration of the natural product was *R* as represented by **4a** (Scheme 1).



Scheme 1. *Reagents and conditions*: (a) *n*-$C_4H_9P^+Ph_3Br^-$, NaH, DMSO, 65%; (b) (i) Raney Ni, EtOH, H_2, 2 h, 77%; (ii) Conc. HCl, MeOH:H_2O (10:1), 0.5 h, 77%; (c) (i) HBr in AcOH, 0.5 h; (d) KOH, ethylene glycol, H_2O, 71%; (e) LDA, HMPA, HC≡CCO_2H then **12**, -10 ^oC-15 ^oC, 3 days; (f) (i) Pd-BaSO4, quinoline, H_2, THF, 1 h; (ii) 1N HCl, 0.5 h, 10%.

Knight *et al.* (1989).[36]

Knight and co-workers reported the enantioselective synthesis of (6*R*)-(-)-massoialactone starting from the yeast reduction product, methyl-(3*R*)-3-hydroxy-hexenoate by using trans selective kinetic iodolactonization of the unsaturated acid. Thus, as shown in scheme 2, **14** was protected as its tri-isopropylsilyl ether with subsequent ozonolysis to provide the aldehyde **15** which on Wittig olefination with *n*-pentyltriphenylphosphorane followed by saponification gave the acid **16**. The crucial lactonization step occurred smoothly when acid **16** was treated with three equivalents of iodine and an excess of sodium bicarbonate in acetonitrile[37] followed by subsequent de-iodination to afford valerolactone **17**. Deprotection of TIPS ether followed by dehydration of lactone afforded natural (-)-massoialactone **4a**.

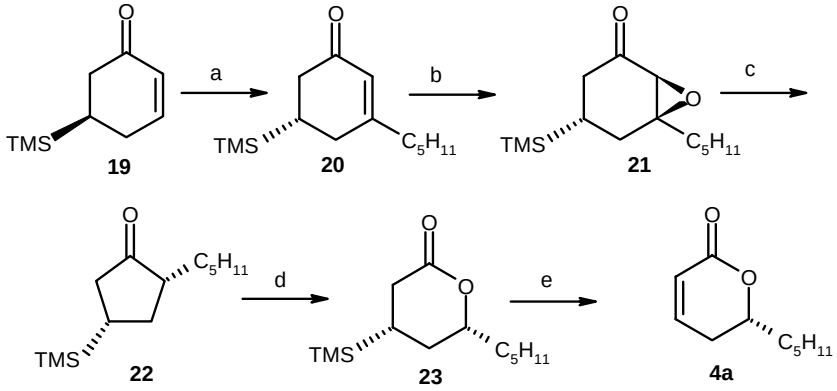


Scheme 2. *Reagents and conditions*: (a) *i*-Pr_3SiCl, imidazole, DMF, 20 ^oC, 48 h, 87%; (b) (i) O_3, CH_2Cl_2, -78 ^oC, (ii) Me_2S, 40 ^oC, 40 h, 91%; (c) *n*-$C_5H_{11}P^+Ph_3Br^-$, *n*-BuLi, THF, 20 ^oC, 0.5 h, 85%; (d) KOH, MeOH, 20 ^oC, 16 h, 86%; (e) I_2, $NaHCO_3$, CH_3CN, 0 ^oC, 3 h, 93%; (f) *n*-Bu_3SnH, THF, reflux, 3 h, 80%; (g) 40% HF, CH_3CN, 0 ^oC, 7 h, 85%; (h) $POCl_3$, pyridine, 65 ^oC, 5 h, 92%.

Asaoka *et al.* (1990).[38]

Asaoka and co-workers synthesized massoialactone by employing ring contraction by $BF_3.Et_2O$ catalyzed epoxide rearrangement of 3-substituted 5-trimethylsilyl-2,3-epoxycyclohexanone as a key step. Thus, **19** was converted into enone **20** by the reported method,[39] which on epoxidation afforded epoxide **21**. The Lewis acid ($BF_3.Et_2O$) catalyzed epoxide rearrangement of **21** followed by base treatment[40] afforded 2-substituted 4-(trimethylsilyl)cyclopentanone **22** with high diastereoselectivity. **22** was subjected to

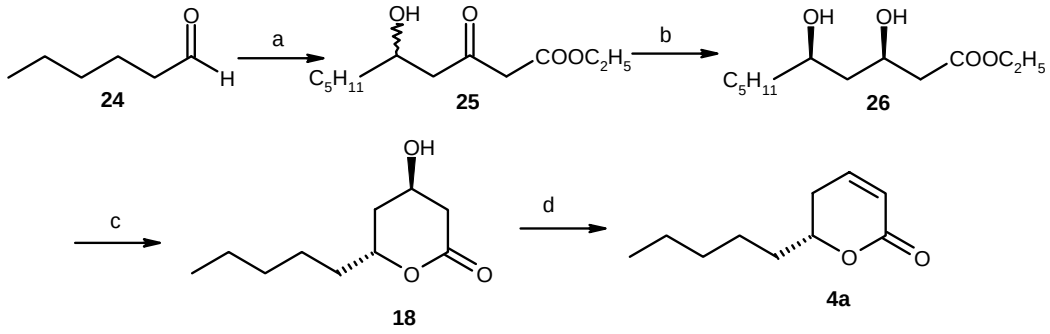
Baeyer-Villiger oxidation followed by bromination and debromosilylation to furnish target molecule (-)-massoialactone **4a** (Scheme 3).



Scheme 3. *Reagents and conditions*: (a) Ref 39; (b) H_2O_2, cat. Base; (c) $BF_3.Et_2O$; (d) NaOH; (e) *m*-CPBA; (f) LDA, Br_2; (g) TBAF.

Bonini *et al.* (1992).[41]

Bonini and co-workers reported the synthesis of massoialactone by enzyme-catalyzed lactonisation of racemic 3,5-dihydroxy esters with PPL in dry Et_2O. The dianion of ethyl acetoacetate was added to the aldehyde **24** to obtain the aldol product **25**, which was diastereoselectively reduced[42] to the *syn*-1,3-diol ester **26**. Enzymatic lactonization of **26** in presence of crude PPL[43] afforded **18** after 12 days with a chemical yield of 25% and an ee of 86%, which on dehydration afforded target molecule (-)-massoialactone **4a** (Scheme 4).

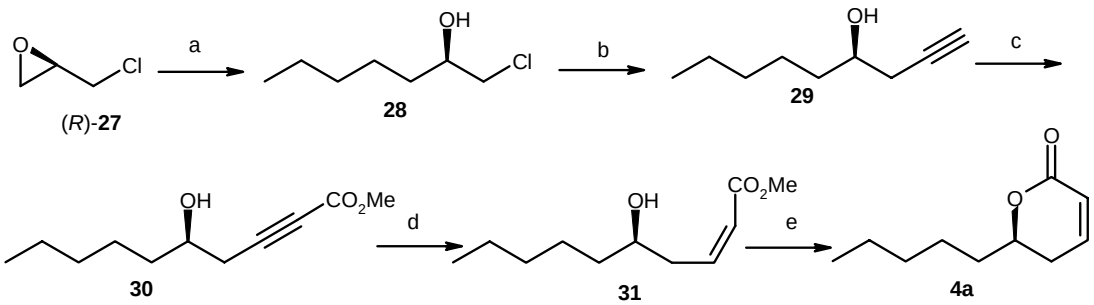


Scheme 4. *Reagents and conditions*: (a) $CH_3COCH_2COOC_2H_5$, NaH, *n*-BuLi, 0 ^oC; (b) $NaBH_4$, $B(OEt)_3$, -78 ^oC, 51%; (c) PPL, Et_2O, 25%; (d) $POCl_3$, CH_2Cl_2, rt.

Takano *et al.* (1992).[44]

Takano and co-workers accomplished the synthesis of (*R*)-(-)-massoialactone by using (*R*)-epichlorohydrin as a chiral starting material. Thus, treatment of (*R*)-epichlorohydrin (*R*)-**27**

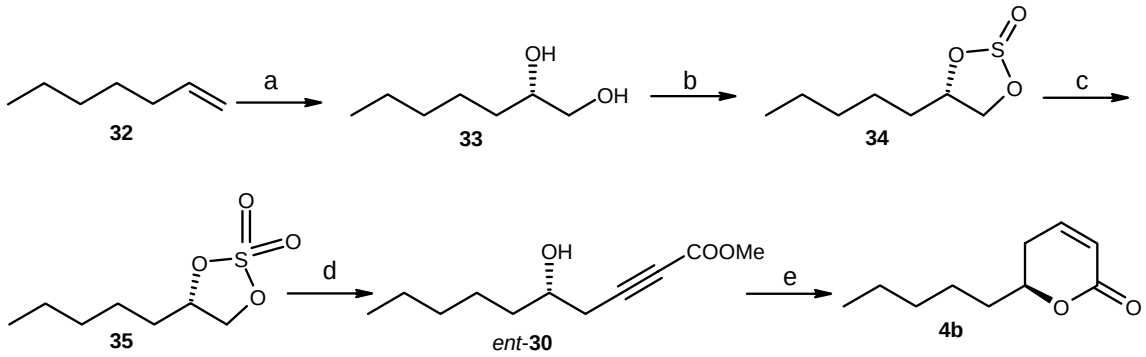
with lithium dibutylcuprate afforded the chlorohydrin **28**, which on reaction with an excess amount of lithium acetylide ethylenediamine complex furnished the β-hydroxyacetylene **29**. Treatment of **29** with catalytic amount of palladium chloride and copper chloride under atmospheric pressure of carbon monoxide[45] afforded the propiolate ester **30** which on partial hydrogenation followed by acid catalyzed cyclization afforded the target molecule (6*R*)-(-)-massoialactone **4a** (Scheme 5).



Scheme 5. *Reagents and conditions*: (a) *n*-BuLi, CuI, THF, -30 ^{o}C, 73.7%; (b) lithium acetylide.EDA complex, DMSO, rt, 94.8%; (c) CO, $PdCl_2$, $CuCl_2$, AcONa, MeOH, rt, 85.1 %; (d) H_2, Lindlar catalyst, quinoline, AcOEt, rt; (e) conc. HCl-MeOH (1:3), rt; 75.7%.

Kumar *et al.* (1999).[46]

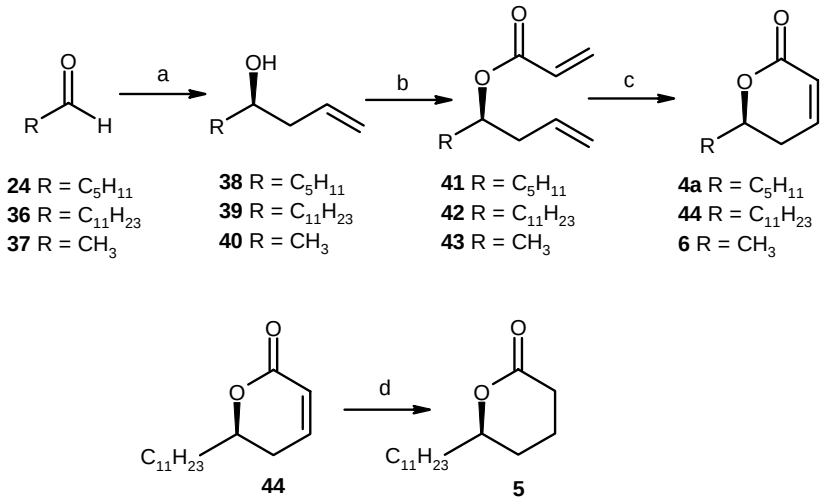
Kumar and co-workers accomplished the synthesis of (*S*)-massoialactone **4b** employing the Sharpless asymmetric dihydroxylation and the regioselective opening of cyclic sulfate as the key steps. Thus, the dihydroxylation[47] of 1-heptene **32** gave the diol **33**, which was converted into cyclic sulfite **34** followed by further oxidation to give cyclic sulfate **35**.[48] Cyclic sulfate **35** on treatment with the anion of methyl propiolate furnished the desired alcohol *ent*-**30**, which on hydrogenation followed by subsequent lactonisation afforded the target molecule **4b** (Scheme 6).



Scheme 6. *Reagents and conditions*: (a) $(DHQ)_2$-Pyr, $K_3[Fe(CN)_6]$, K_2CO_3, OsO_4(cat), *t*-BuOH-H_2O (1:1), RT, overnight, 80%; (b) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 20 min, 99%; (c) $RuCl_3$, $NaIO_4$, CCl_4-MeCN-H_2O, 2:2:3, 0 °C, 2 h, 100%; (d) *n*-BuLi, methyl propiolate, THF, -78 °C, 20 min, then RT, overnight, 75%; (e) Pd-$BaSO_4$, Quinoline, H_2 (1 atm), EtOAc, 1 h, RT, then NaOH, EtOH: H_2O (2:1), HCI, 80 ^oC, 60%.

Ramachandran *et al.* (2000).[49]

Ramachandran and co-workers accomplished the asymmetric synthesis of massoialactone, parasorbic acid and hexadecanolide via asymmetric allylboration as the key step. Thus, allylboration of aldehydes **24**, **36**, **37** with *B*-allyldiisopinocampheylborane[50] afforded homoallylic alcohols **38**, **39**, **40** respectively, which on esterification followed by ring-closing metathesis[51] furnished lactones (**4a** and **44** and **6**). Lactone **44** on hydrogenation afforded hexadecanolide **5** (Scheme 7).



24 R = C_5H_{11}
36 R = $C_{11}H_{23}$
37 R = CH_3

38 R = C_5H_{11}
39 R = $C_{11}H_{23}$
40 R = CH_3

41 R = C_5H_{11}
42 R = $C_{11}H_{23}$
43 R = CH_3

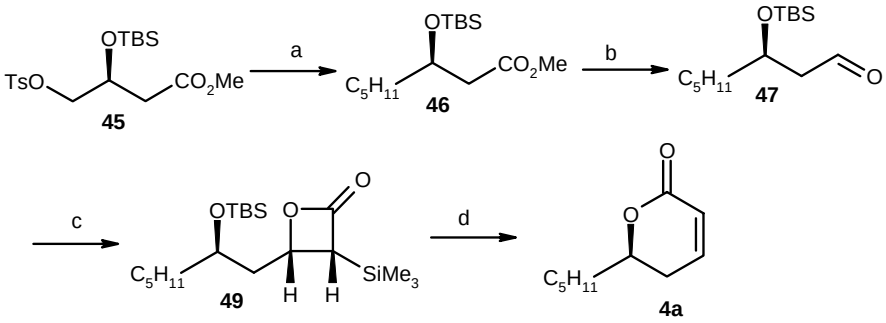
4a R = C_5H_{11}
44 R = $C_{11}H_{23}$
6 R = CH_3

Scheme 7. *Reagents and conditions*: (a) $^{I}Ipc_2BAll$, ether-pentane, NaOH, H_2O_2; (b) Acryloyl chloride, Et_3N; (c) $(PCy_3)_2Ru(Cl)_2$=CH-Ph (20 mol%), CH_2Cl_2; (d) H_2, Pd/C.

Pons *et al.* (2004).[52]

Pons and co-workers accomplished the asymmetric synthesis of massoialactone, HF-induced translactonization of 2'-silyloxy-3-trimethylsilyl-2-oxetanones starting from (2)-dimethyl malate. Thus, (2)-dimethyl malate was transformed into ester **45** followed by treatment with the lithium dialkylcuprate generated from *n*-BuLi and CuI to give ester **46**

which was reduced with Dibal-H to the corresponding aldehyde **47**. The [2+2]-cycloaddition of aldehyde **47** with trimethylsilylketene **48** gave a diastereoisomeric mixture of four β-lactones **49** which were then treated with aq. HF in alcohols, to give (-)-massoialactone **4a** (Scheme 8).

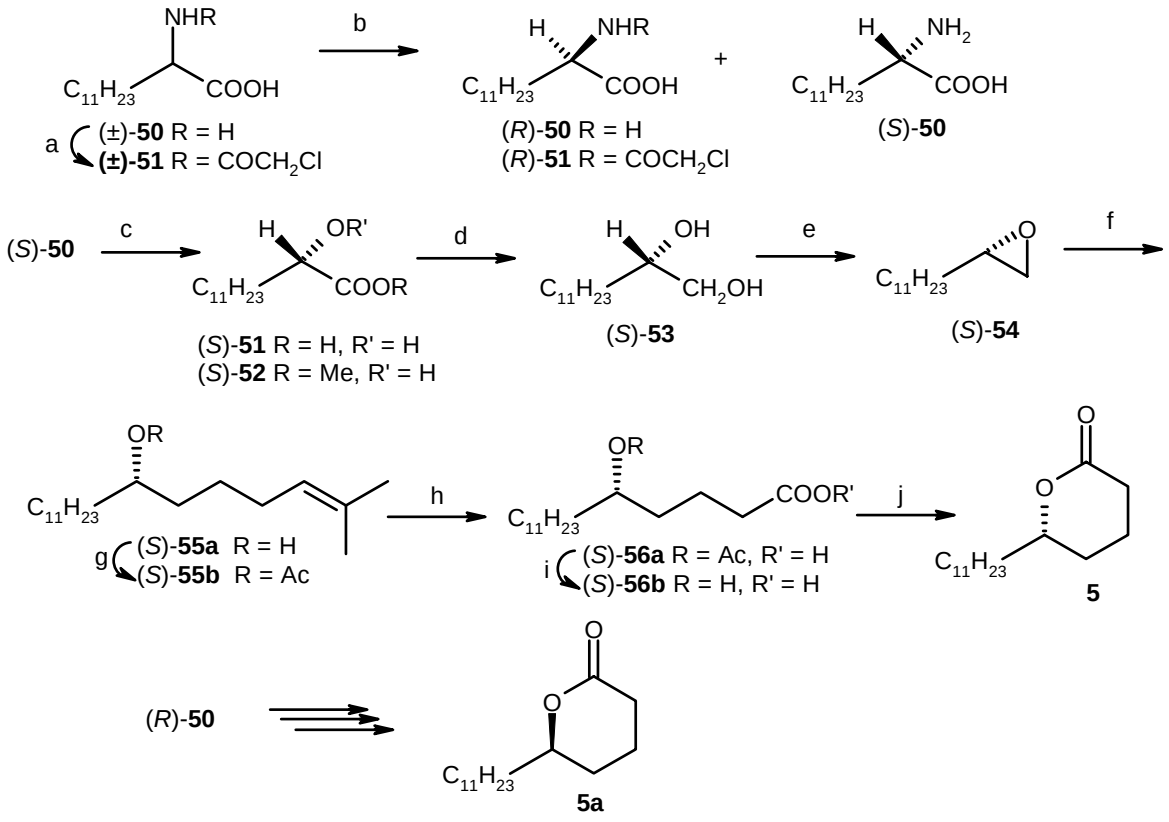


Scheme 8. *Reagents and conditions*: (a) Bu_2CuLi, Et_2O, -35 ^oC, 79%; (b) DIBAL-H, PhMe, -85 ^oC, 98%; (c) Trimethyl silyl ketene **48**, $EtAlCl_2$, Et_2O, -50 ^oC, 2 h; (d) aq. HF, MeCN, 50 ^oC, 3 h, 61% from both the steps.

3.1.3. Review of Literature.2: Hexadecanolide

Mori *et al.* (1985).[53]

Mori and co-workers accomplished the asymmetric synthesis of hexadecanolide **5** by resolution of an unnatural long-chain α-amino acid using amino acylase of *Aspergillus* spp. Thus, (±)-2-aminotridecanoic acid (±)-**50** was acylated with chloroacetyl chloride to give (±)-**51**, which was treated with the Aspergillus amino acylase to give (*S*)-**50** and unhydrolyzed (*R*)-**51**. Deamination of (*S*)-**50** followed by esterification gave (*S*)-**52**, which on reduction afforded diol (*S*)-**53**. This was converted into epoxide (*S*)-**54** according to the general method of Golding et al. Epoxide (*S*)-**54** was opened with 4-methyl-3-pentenyl bromide followed by ozonolysis, Jones oxidation, alkaline hydrolysis and lactonisation to furnish the target compound **5**. Similarly (*R*)-**50** was converted into another isomer **5a** (Scheme 9).

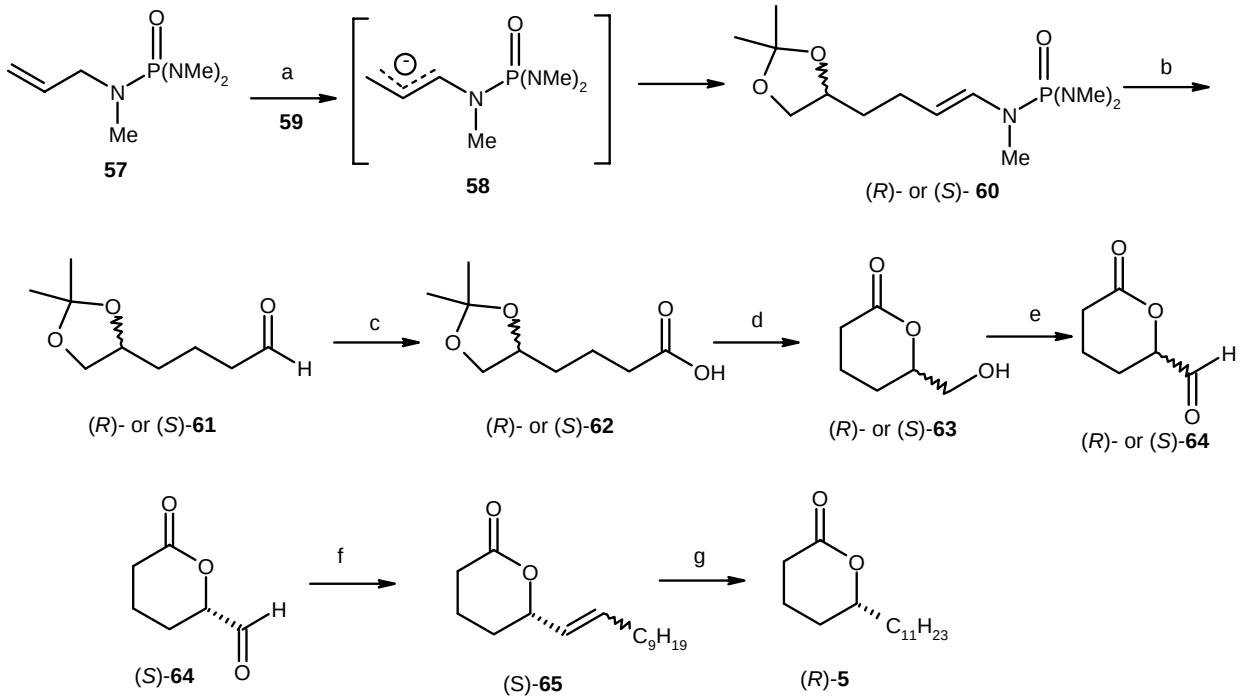


Scheme 9. *Reagents and conditions*: (a) $ClCH_2COCl$, NaOH, DME, 45%; (b) Amino acylase, $CoCl_2$, 2 days; (c) (i) H_2SO_4, $NaNO_2$, 90-93 ^oC; (ii) MeOH, Cat. HCl, C_6H_6; (d) LAH, THF, 2.5 h, 99.5 %; (e) (i) HBr-AcOH, 3 h; (ii) NaOMe, MeOH, 20 min., 85.6%; (f) $Me_2C{=}CH(CH_2)_2MgBr$, Cu_2Br_2, 2 h, 98.3%; (g) Ac_2O, Pyridine, DMAP, 85.6%; (h) (i) O_3, Acetone; (ii) Jones CrO_3, acetone, 82%; (i) KOH, THF, 1 h, then 6N HCl, 92.8%; (j) *p*-TSOH, C_6H_6, 64.3%.

Coutrot *et al.* (1994).[54]

Coutrot and co-workers accomplished the asymmetric synthesis of hexadecanolide **5** by reaction between the lithiated *N*-allyl-*N*-methyl-(bisdimethylamino)phosphoramide anion and the triflate derivative of (*R*)-(-) or (*S*)-(+)-2,3-*O*-isopropylideneglycerol. Thus, treatment of *N*-allyl-*N*-methyl-(bisdimethylamino)phosphoramide **57** with *n*-butyllithium gave the ambident anion **58**, which upon addition of (*R*)-(-) or (*S*)-(+)-2,3-*O*-isopropylideneglycerol triflate derivative **59**, yielded the enephosphoramide **60**. Hydrolysis of **60** followed by oxidation afforded acid **62**, which upon acetonide deprotection and

oxidation afforded 5-formyl-δ-valerolactone **63**. Wittig reaction of lactone **63** with decyl triphenylphosphonium bromide followed by hydrogenation afforded target molecule hexadecanolide **5** (Scheme 10).

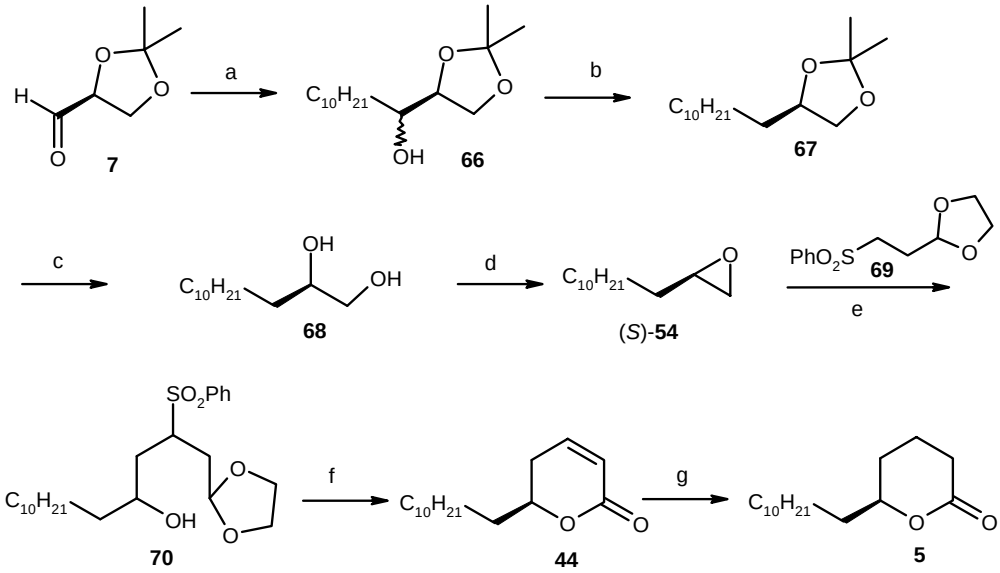


Scheme 10. *Reagents and conditions*: (a) *n*-BuLi, THP, -50 °C 1.5 h. then **59**, -50°C, 1 h, 98%; (b) H_2SO_4, H_2O, ether, pH = 2.5, 87%; (c) $AgNO_3$, NaOH, 5 °C, 1 h ; then saturated $(COOH)_2$, H_2O to pH 3.7, 70%; (d) Amberlyst 15 ; 4 x molecular sieves, 4A^o, 6 h, 75%, (34-36% overall yield from commercially available (*R*)-or (*S*)-2,3-*O*-isopropylideneglycerol); (e) PDC (pyridinium dichromate), 4x molecular sieves, 20% 2h, 60% yield in crude product; (f) $Ph_3P^+C_{10}H_{21}$ Br^-, *t*-BuOK, THF, 0 °C then 20 ^{o}C, 47%; g) H_2 , 5% Pd, 98%.

Singh *et al.* (1996).[55]

Singh and co-workers accomplished the synthesis of 5-hexadecanolide **5** from a chiral epoxide. (*R*)-Isopropylidene glyceraldehyde **7**, synthesized from the mannitol, was treated with 1-bromodecane to furnish the addition product **66**. Deoxygenation of the hydroxyl group followed by acetonide deprotection, tosylation and base treatment afforded epoxide (*S*)-**54**. The epoxide (*S*)-**54** was opened with sulphone reagent **69**[56] to provide hydroxyl acetal **70** which, on treatment with $BF_3.OEt_2$ and *m*-CPBA gave a mixture of sulphone δ-

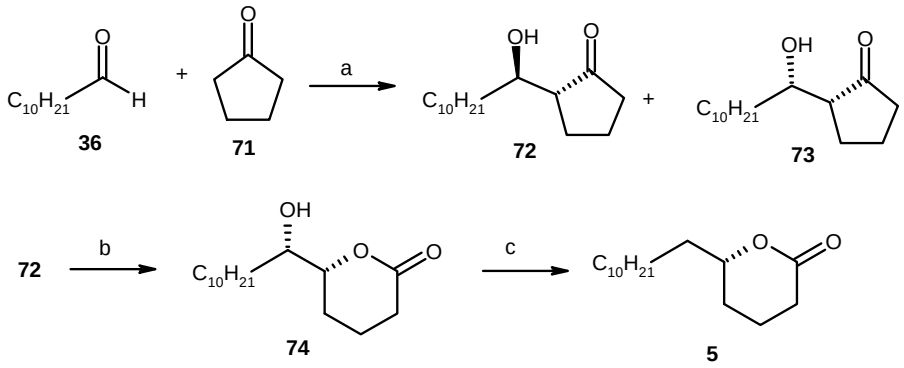
lactone and unsaturated δ-lactone **44** in the ratio 9:1. The crude mixture without purification was treated with DBU in order to have complete conversion into unsaturated δ-lactone **44**.[57] Finally hydrogenation of the double bond furnished target molecule **5** (Scheme 11).



Scheme 11. *Reagents and conditions*: (a) *n*-$C_{10}H_{21}Br$, Li, naphthalene (cat.), THF, -78 ^oC, 65%; (b) (i) TsCl, Pyridine, Et_3N, rt, 24 h; (ii) $NaBH_4$, DMSO, 160 ^oC, 7 min., 65%; (c) DDQ, CH_3CN-H_2O, 45 ^oC, 1 h, 95%; (d) (i) *p*-TsCl, pyridine, CH_2Cl_2, -20 ^oC, 24 h; (ii) K_2CO_3, MeOH, 20 ^oC, 1 h, 59%; (e) **69**, *n*-BuLi, THF, -78 ^oC, 94%; (f) (i) *m*-CPBA, $BF_3.OEt_2$, CH_2Cl_2, 0 ^oC to rt, 10 h; (ii) DBU, THF-H_2O, rt, 1 h, 65%; (g) H_2, 10% Pd-C, EtOAc, 98%.

Ying *et al.* (2005).[58]

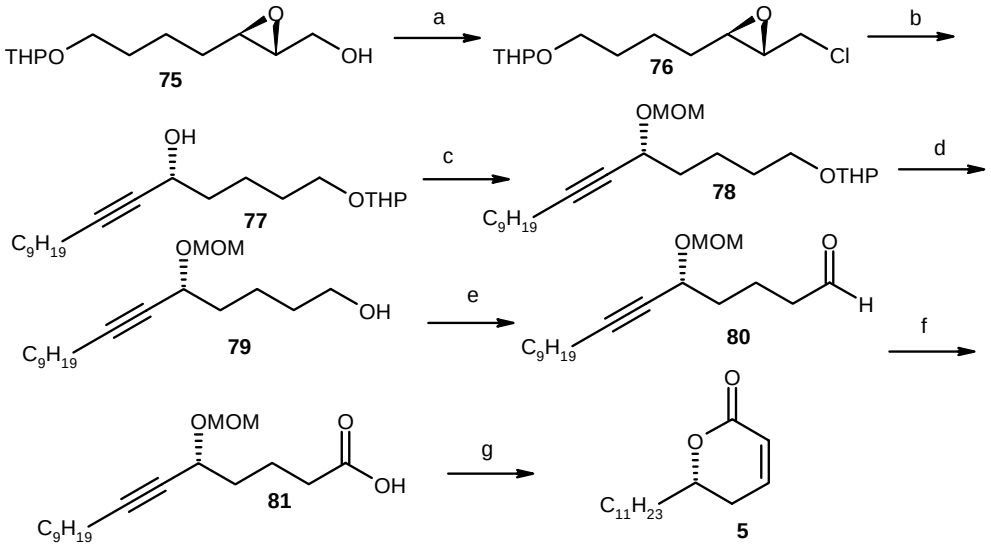
Ying and co-workers accomplished the synthesis of 5-hexadecanolide **5** using L-proline catalyzed asymmetric aldol reactions as the key step. Thus the synthesis commenced from the aldehyde **36** and cyclopentanone **71** catalyzed by L-proline[59] to give the *syn*-aldol **72** along with its *anti*-isomer **73** in a ratio of 85:15. Baeyer-Villiger oxidation of the ketone **72** followed by deoxygenation using the Barton protocol[60] gave target molecule **5** (Scheme 12).



Scheme 12. *Reagents and conditions*: (a) L-proline (30 mol%), $CHCl_3$, 24 h, 80%; (b) *m*-CPBA, CH_2Cl_2, $NaHCO_3$, 6 h, 82%; (c) (i) NaH, CS_2, MeI; (ii) Bu_3SnH, AIBN, toluene, 54%.

Sabitha *et al.* (2006).[61]

Sabitha and co-workers accomplished the synthesis of 5-hexadecanolide starting from 2,3-epoxy alcohol **75** (Scheme 13). The alcohol **75** was converted into the corresponding epoxy chloride **76** which was subjected to base-induced opening with lithium amide in liquid ammonia at –33 °C and further treated with nonyl bromide leading to the chiral acetylenic alcohol **77** directly in a one-pot procedure (Scheme 13). The secondary hydroxy group of compound **77** was protected as its methoxymethyl ether followed by reduction of the triple bond and subsequent deprotection of the tetrahydropyranyl group to give **79** in 80% yield. The alcohol **79** was oxidized to the aldehyde **80** which was further oxidized to afford the corresponding acid **81**. Finally in situ deprotection of the methoxymethyl group and subsequent cyclization afforded target molecule **5** in 80% yield.

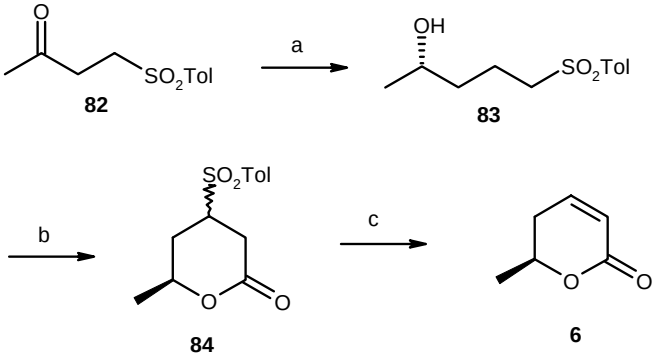


Scheme 13. *Reagents and conditions*: (a) Ph_3P, $NaHCO_3$, CCl_4, reflux, 4 h, 80%; (b) Li/liq NH_3, $Fe(NO_3)_3$ (cat.), anhyd THF, $C_9H_{19}Br$, 8 h, 60%; (c) MOMCl, *i*-Pr_2NEt, 0 °C to rt, 2 h, 98%; (d) 10% Pd/C, H_2, EtOH, rt, 6 h, 80%; (e) IBX, anhyd DMSO, anhyd CH_2Cl_2, rt, 2 h, 77%; (f) $NaClO_2$, NaH_2PO_4, aq DMSO, rt, 1 h, 71%; (g) *p*-TSA, MeOH, rt, 12 h, 80%.

Review of Literature.3: Parasorbic acid

Gopalan *et al.* (1990).[62]

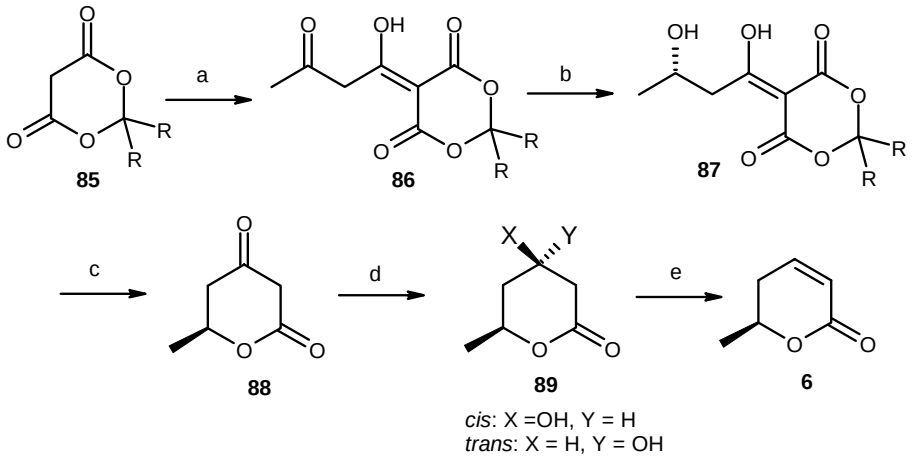
Gopalan and co-workers accomplished the synthesis of parasorbic acid **6** employing Baker's yeast reduction of γ-ketosulfones as the key steps. Thus, γ-ketosulfone **82** was reduced by bakers' yeast[63,64] to alcohol **83** with high enantiomeric excess. Alkylation of the dianion of sulfone **83** followed by lactonisation afforded **84** which on elimination with DBU furnished target molecule (*S*)-(+)-parasorbic acid **6** (Scheme 14).



Scheme 14. *Reagents and conditions*: (a) Bakers yeast; (b) (i) *n*-BuLi, THF, TMEDA, -78 ^{o}C-10 ^{o}C; (ii) $ICH_2CO_2^-Na^+$, -78 ^{o}C - rt; (iii) *p*-TSOH, benzene, reflux; (c) DBU, CH_2Cl_2, rt.

Sato *et al.* (1990).[65]

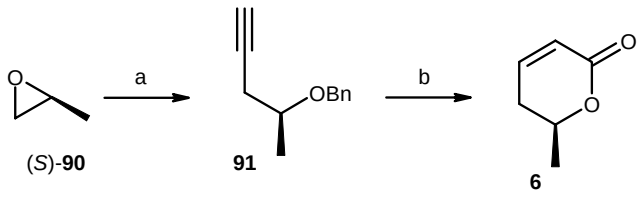
Sato and co-workers synthesized the parasorbic acid **6** by enantioselective reduction of acetoacetylated Meldrum's acid with fermenting baker's yeast. Acetoacetylated Meldrum's acid **85**,[66] readily prepared from Meldrum's acid, and diketene **86** was reduced with fermenting yeast to furnish the alcohol **87** which was further converted into keto hexanolide **88**. It was converted to the hydroxyl lactone (*cis* : *trans*, 4:1) **89**, which on dehydration afforded target molecule **6** (Scheme 15).



Scheme 15. *Reagents and conditions*: (a) Diketene, Et_3N, (b) baker's yeast, 30-32 ^{o}C, (c) MeOH or toluene, 80%, (d) H_2, Raney Ni, EtOH, 41%, (e) TsOH, benzene, 90%.

Dupont *et al.* (1998).[67]

Dupont and co-workers synthesized the parasorbic acid **6** by using hydrozirconation of *O*-protected homopropargyl alcohols followed by carbonylation and quenching with iodine. Thus, addition of the lithium acetylide ethylene diamine complex to a solution of (*S*)-(-)-propylene oxide (*S*)-**90** afforded (*S*)-(-)-4-pentyn-2-ol, that has been transformed into (*S*)-(-)-**91** by reaction with benzyl bromide which was subjected to hydrozirconation-carbonylation-demetallation to afford the target molecule **6** (Scheme 16).



Scheme 16. *Reagents and conditions*: (a) (i) CH≡C-Li.EDA complex, DMSO, 30 h; (ii) BnBr, NaH, THF, 2 h, 60 %; (b) (i) $Cp_2Zr(H)Cl$, benzene; (ii) CO; (iii) I_2, benzene.

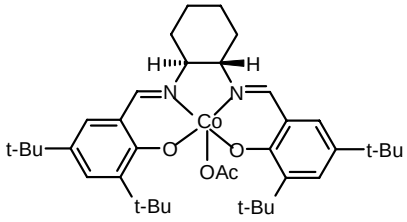
3.1.3. Present work:

Objective

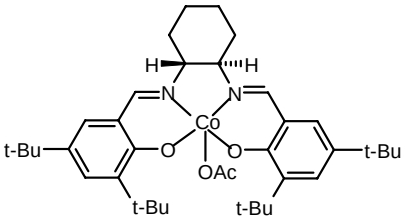
As the commercial applications of pheromones have expanded, the demand for larger quantities of these compounds has increased. But the quantity of pheromones isolated from the natural source is often less than a milligram. Further, the study of the relationship between stereochemistry and biological activity of the chiral component represents a recent development of the interdisciplinary research carried out by chemists and biologists in order to increase the basic knowledge of insect behavior and, in particular, to develop novel pest control methods. Thus a general strategy for all these lactones is still highly desirable.

3.1.4. Results and discussions:

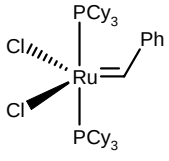
Our synthesis of lactones requires two major reactions, Jacobsen's hydrolytic kinetic resolution[68] to install the stereogenic centres and ring- closing metathesis[51] to construct the δ-lactone moiety.



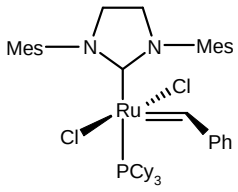
(*S*,*S*)-SalenCo (III) OAc complex (**92a**)



(*R*,*R*)-SalenCo (III) OAc complex (**92b**)



Grubbs' 1st generation catalyst (**93a**)

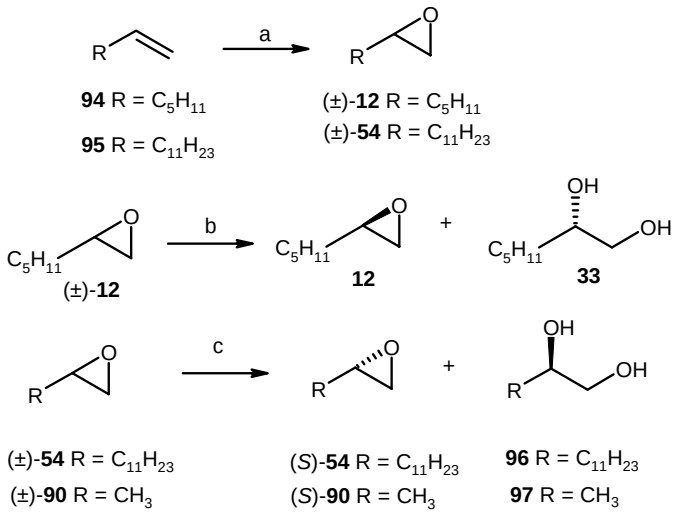


Grubbs' 2nd generation catalyst (**93b**)

Figure 4

The racemic epoxide (±)-**12** and (±)-**54**, substrates for HKR was prepared from commercially available 1-heptene **94** and 1-dodecene **95** respectively using *m*-CPBA. The HKR was performed on (±)-**12**, (±)-**54** and (±)-**90** with (*R*,*R*)-salen–Co-(OAc) complex

92b (0.5 mol %) and water (0.55 equiv) to give the *R*-epoxides **12**, **54** and **90** and the *S*-diols **33**, **96** and **97** respectively (Scheme 17).

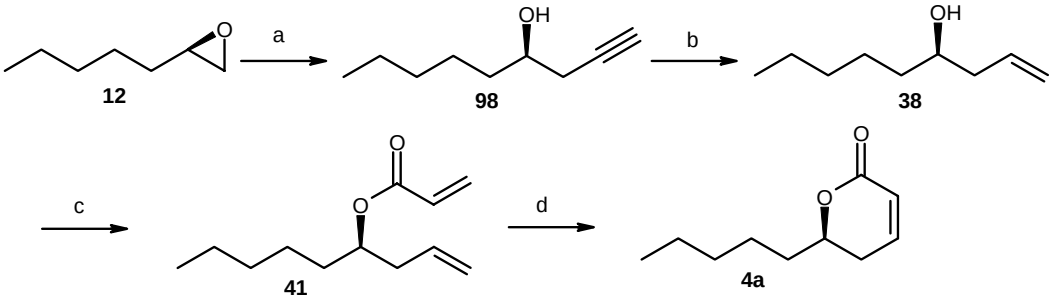


Scheme 17. *Reagents and conditions*: (a) *m*-CPBA, CH_2Cl_2, 0 ^oC to rt, 10 h, 92%; (b) *R*,*R*-salen–Co-(OAc) (0.5 mol %), distd H_2O (0.55 equiv), 0 ^oC; (c) *S*,*S*-salen–Co-(OAc) (0.5 mol %), distd H_2O (0.55 equiv), 0 ^oC.

Synthesis of (*R*)-massoialactone.

The synthesis of (*R*)-massoialactone **4a** started from the enantiomerically enriched epoxide **12** as illustrated in Scheme 18. Opening of epoxide with vinylmagnesium bromide could not afford the required product, instead some chloro or iodo substituted product was formed. Thus we have used a two step reaction sequence. The epoxide **12** was opened with an excess of lithium acetylide in presence of DMSO to afford acetylide **98**. IR spectrum of **98** showed hydroxyl absorption at 3446 cm^{-1}. In the ^1H NMR spectrum of **98** a singlet at δ 2.47 was attributed to acetylenic proton. Partial hydrogenation of the acetylene **98** with Lindlar's catalyst furnished the homoallylic alcohol **38**. The terminal olefinic group showed peaks at δ 5.91-5.77 (multiplet, 1H) and 5.16-5.12 (m, 2H). All other protons resonated at the expected chemical shift. The ^{13}C spectrum displayed peaks at 117.6 and 134.9 corresponding to olefinic carbons. Compound **38** was esterified with acryloyl chloride in the presence of triethylamine to afford **41** in 89% yield. The IR spectrum of **41** indicated absence of hydroxyl group, acryloyl carbonyl appeared at 1742 cm^{-1}. The carbonyl carbon appeared at δ 165.4 in the ^{13}C NMR spectrum. The subsequent ring-closing metathesis[51] of **41** in dichloromethane under reflux in high dilution conditions

using the first generation Grubbs' catalyst, bis(tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride and catalytic amount of Ti(*i*-PrO)$_4$ afforded (*R*)-massoialactone **4a** in 84% yield, $[\alpha]_D^{25}$ -115.2 (*c* 1, $CHCl_3$) [lit.[49] $[\alpha]_D^{29}$ -113.6 (*c* 1.36, $CHCl_3$)]. The IR spectrum of **4a** showed characteristic carbonyl group absorption of α,β-unsaturated δ-lactone at 1725 cm^{-1}. The olefin protons appeared at 6.90-6.87 (multiplet) and 6.04 (doublet) with J = 10 Hz in the ^{1}H NMR spectrum. The olefinic carbons appeared at δ 144.9 and 121.1 in ^{13}C NMR spectrum. The physical and spectroscopic data were in full agreement with the literature.[36]

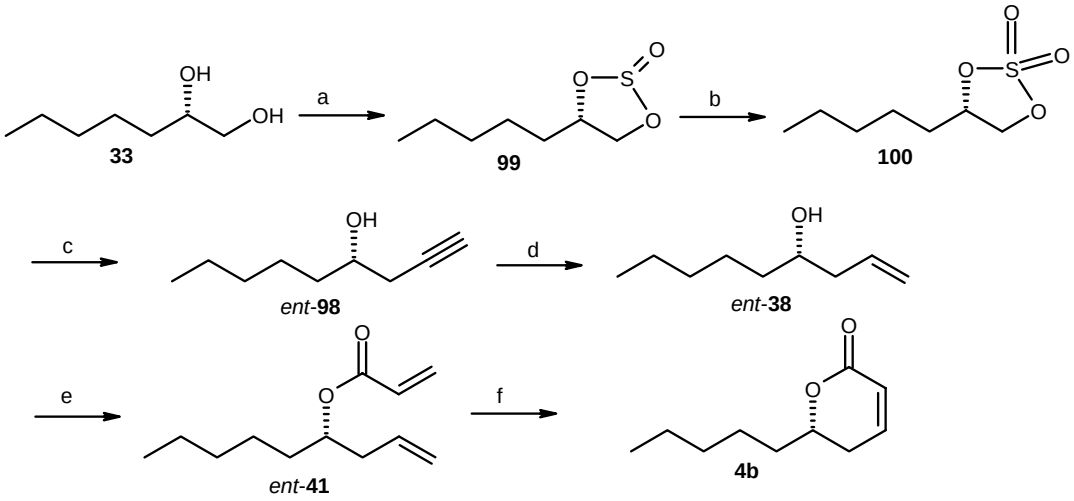


Scheme 18. *Reagents and conditions*: (a) LiC≡CH–ethylene diamine, DMSO, rt, 12 h, 86%; (b) H_2, Pd/$BaSO_4$, quinoline, benzene, 1 bar, rt, 0.5 h, 92%; (c) acryloyl chloride, Et_3N, CH_2Cl_2, 0 ^oC, 5–6 h, 89%; (d) $(PCy_3)_2$ $Ru(Cl)_2$=CH–Ph (20 mol %), CH_2Cl_2, Ti(*i*-PrO)$_4$, reflux, 12 h, 84%.

Synthesis of (*S*)-massoialactone.

Scheme 19 summarizes the synthesis of (*S*)-massoialactone **4b** from the diol **33**. Thus treatment of **33** with thionyl chloride in the presence of triethylamine gave the cyclic sulfite **99**, which was further oxidized using $NaIO_4$ and a catalytic amount of ruthenium trichloride to furnish the corresponding cyclic sulfate **100** in essentially quantitative yield.[48] The IR spectrum of **100** indicated the absence of hydroxyl groups. A downfield shift in the ^{1}H NMR spectra of CH_2-SO_2- protons to δ), 4.70–4.73 (m, 1H), 4.33–4.37 (m, 1H), was observed in comparison to the same proton of **33** at 3.65-3.71 (m, 2H). The essential feature of our synthetic strategy shown in Scheme 19 was based on the presumption that the nucleophilic opening of the cyclic sulfate **100** would occur in a regioselective manner at the terminal carbon. Indeed the

cyclic sulfate **100** on treatment with lithium acetylide furnished the desired alcohol *ent*-**98**, which on hydrogenation with Lindlar's catalyst in presence of catalytic amount of quinoline afforded homoallylic alcohol *ent*-**38**. The terminal olefinic group showed peaks. All protons resonated at the expected chemical shift. The ^{13}C spectrum displayed peaks at δ 117.6 and δ 134.9 corresponding to olefinic carbons. Esterification of alcohol *ent*-**38** with acryloyl chloride in presence of triethyl amine followed by ring-closing metathesis by using Grubbs Ist generation catalyst afforded the target molecule **4b**, $[\alpha]_D^{25}$ +110.1 (*c* 2.0, $CHCl_3$) [lit.[36] $[\alpha]_D^{22.6}$ +109.6 (*c* 2, $CHCl_3$)]. The physical and spectroscopic data were in full agreement with the literature.[36]

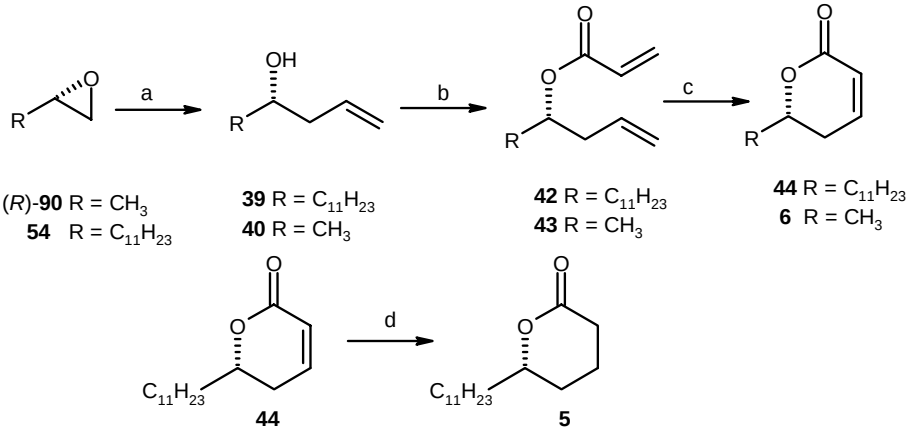


Scheme 19. *Reagents and conditions*: (a) (i) $SOCl_2$, Et_3N, CH_2Cl_2, 0 ^oC, 20 min, 99%; (ii) $RuCl_3$, $NaIO_4$, CCl_4–MeCN–H_2O; 2:2:3, 0 ^oC, 2 h, 100%; (iii) LiC≡CH-ethylene diamine, DMSO, 0 ^oC to rt, 10 h, 80%; (iv) H_2, Pd/BaSO4, quinoline, benzene, 1 bar, rt, 0.5 h, 86%; (v) acryloyl chloride, Et_3N, CH_2Cl_2, 0 ^oC, 5–6 h, 84%; (vi) $(PCy_3)_2Ru(Cl)_2$=CH–Ph (20 mol %), CH_2Cl_2, Ti(*i*-PrO)$_4$, reflux, 12 h, 85%.

Synthesis of hexadecanolide and parasorbic acid

For the synthesis of hexadecanolide and parasorbic acid, epoxides **54** and **90** were opened with vinylmagnesium bromide to give the homoallylic alcohols **39** and **40** respectively. In ^{1}HNMR spectra the terminal olefinic group of **39** showed peaks at δ 5.19-5.17 (multiplet, 1H) and 5.10-5.11 (m, 2H). All other protons resonated at the expected chemical shift. The ^{13}C spectrum displayed peaks at δ 117.7 and δ 134.9 corresponding to olefinic carbons and the terminal olefin group of **40** showed peaks at δ 5.77-5.85 (m, 1H), 5.12 (d, *J* = 6.6 Hz,

1H) in ^{1}H NMR spectrum. The ^{13}C spectrum displayed peaks at 116.6 and 134.6 corresponding to olefinic carbons. The alcohols **39** and **40** were esterified using acryloyl chloride in presence of triethyl amine in dry CH_2Cl_2 to afford esters **42** and **43**. The IR spectrum of **42** indicated absence of hydroxyl group, ester carbonyl appeared at 1741 cm^{-1}. The carbonyl carbon of **42** appeared at δ 165.8 in ^{13}C NMR spectrum. Ring closing metathesis of **42** and **43** by using Grrubs' I'st generation catalyst afforded lactone **44** and parasorbic acid **6a** respectively. Finally **44** was hydrogenated to furnish the hexadecanolide **5a** (Scheme 20). The physical and spectroscopic data were in full agreement with the literature.



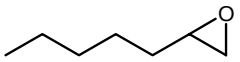
Scheme 20. *Reagents and conditions*: (a) vinylmagnesium bromide, CuI, THF, 82% for **39**, 89% for **40**; (b) acryloyl chloride, Et_3N, CH_2Cl_2, 0 ^{o}C, 5–6 h, 91% for **42**; (c) $(PCy_3)_2Ru(Cl)_2$=CH–Ph (20 mol %), CH_2Cl_2, Ti(*i*-PrO)$_4$, reflux, 89% for **44**, 82% for **6**; (d) H_2, 10% Pd-C, EtOAc, 12 h, 94%.

3.1.5. Conclusion

In conclusion, a short and efficient synthesis of (*R*)–massoialactone, (*S*)–massoialactone, hexadecanolide and parasorbic acid has been achieved using hydrolytic kinetic resolution and ruthenium catalyzed ring-closing metathesis (RCM) as the key steps. The synthetic strategy described here has significant potential to synthesise a variety of other biologically important substituted 5,6-dihydropyran-2-one-containing natural products.

3.1.6 Experimental Section

2-Pentyloxirane ((±)-12).



(±)- **12**

To a stirred solution of olefin **94** (4 g, 40.74 mmol) in CH_2Cl_2 (50 mL) at 0 ^oC was added *m*-CPBA (50%) (21.09 g, 61.11 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 to afford the crude epoxide **32** which on distillation provided **(±)-12** as a colorless liquid.

Yield: 4.28 g, 92%

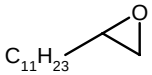
Mol. Formula: $C_7H_{14}O$

IR ($CHCl_3$, cm^{-1}): ν_{max} 3016, 2959, 2931, 2860, 1478, 1467, 1410, 1379, 1260, 1130, 1022, 916, 850, 828.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.91-2.89 (m, 1H), 2.75 (t, *J* = 5 Hz, 1H), 2.47 (d, *J* = 5 Hz, 1H), 1.55-1.51 (m, 2H), 1.49-1.46 (m, 2H), 1.45-1.33 (m, 4H), 0.90 (t, *J* = 7 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 52.2, 46.8, 32.3, 31.5, 25.5, 22.4, 13.8.

2-Undecyloxirane ((±)-54).



(±)-**54**

Prepared in a similar way as described above for (±)-**12.**

Yield: 94%.

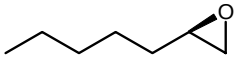
Mol. Formula: $C_{13}H_{26}O$

IR ($CHCl_3$, cm^{-1}): ν_{max} 3018, 2952, 2929, 2862, 1472, 1466, 1379, 1260, 1022, 916, 828.

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.93-2.89 (m, 1H) 2.76 (dd, *J* = 7.4 Hz, 1H), 2.47 (dd, *J* = 8.7 Hz, 1H), 1.54-1.48 (m, 2H), 1.27 (brs, 18 H), 0.89 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 52.3, 46.9, 32.4, 31.6, 29.6, 29.5, 29.4, 29.3, 26.8, 25.9, 22.6, 13.9.

(*R*)-2-Pentyloxirane (12).



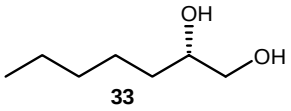
12

A solution of epoxide **(±)-12** (4 g, 35.03 mmol) and (*R,R*)-Salen-Co(III)-OAc (0.11 g, 0.18 mmol) in THF (0.3 mL) was stirred at 0 ^{o}C for 5 min, and then distilled water (346 μL, 19.3 mmol) was added. After stirring for 24 h, it was concentrated and purified by silica gel column chromatography using pet ether/EtOAc (19:1) to afford epoxide **12** as a yellow color liquid. Continued chromatography with pet ether/EtOAc (3:2) provided the diol **33** as a brown color liquid as a single diastereomer.

Yield: 1.8 g, 45%.

$[\alpha]_D^{25}$: + 9.6 (*c*, 1.0, $CHCl_3$); lit.[69] $[\alpha]_D^{24}$ +9.84 (*c* 1.0 , $CHCl_3$)

(*S*)-Heptane-1,2-diol (33)



33

Yield: 1.99 g, 43%

Mol. Formula: $C_7H_{16}O_2$

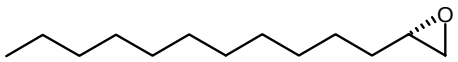
$[\alpha]_D^{25}$: -15.9 (*c*, 1.67, EtOH)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3391, 2957, 2932, 2861, 1466, 1216, 1069, 869.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.69-3.65 (m, 2H), 3.46-3.40 (m, 1H), 2.97 (brs, 2H), 1.42-1.30 (m, 8H), 0.89 (t, *J* = 7 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 71.7, 63.5, 45.7, 31.7, 25.2, 22.5, 13.9.

(*S*)-2-Undecyloxirane ((*S*)-54).



(*S*)-**54**

A solution of epoxide **(±)-54** (4 g, 20.17 mmol) and (*S,S*)-Salen-Co(III)-OAc (0.063 g, 0.11 mmol) in *i*-PrOH (0.2 mL) was stirred at 0 ^{o}C for 5 min, and then distilled water (181 μL, 10.1 mmol) was added. After stirring for 24 h, it was concentrated and purified by

silica gel column chromatography using pet ether/EtOAc (19:1) to afford epoxide (*S*)-**54** as a light yellow color liquid.

Yield: 1.68 g, 42%.

$[\alpha]_D^{25}$: -11.5 (*c*, 1.1, THF); lit[55] -11.0 (*c*, 1.0, THF).

(*S*)-Propylene oxide (*S*-90).

(*S*)-**90**

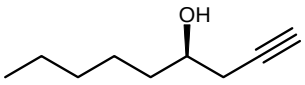
The racemic propylene oxide **90** was resolved to chiral epoxide ***S*-90** in high enantiomeric excess by the HKR method following a literature procedure.[68a]

Yield: 14.71 g, 90%

Mol. Formula: C_3H_6O

$[\alpha]_D^{25}$: +11.3 (neat); lit.[68a] $[\alpha]_D^{25}$ -11.6 (neat).

(*R*)-Non-1-yn-4-ol (98).



98

To a solution of **12** (1.6 g, 14.01 mmol) in DMSO (5 mL) at 0 °C was added lithium acetylide-EDA complex (3.23 g, 35.03 mmol) in one portion. The reaction mixture was stirred at 0 ^oC for 30 min and 12 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 (9:1) to afford the alkyne product **98** as a colorless liquid.

Yield: 1.69g, 86%

Mol. Formula: $C_9H_{16}O$

$[\alpha]_D^{25}$: -27.9 (*c* 1.74, $CHCl_3$).

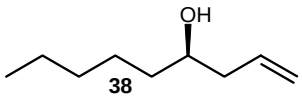
IR ($CHCl_3$, cm^{-1}): ν_{max} 3446, 3018, 2958, 2830, 2232, 1474, 1382, 1257, 1242, 1100, 1005.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.78-3.69 (m, 1H), 2.36 (s, 1H), 2.05-1.98 (m, 2H), 1.24-1.40 (m, 8H), 0.88 (t, *J* = 6.4 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 80.9, 70.6, 69.8, 36.0, 31.6, 27.2, 25.1, 22.5, 13.9.

Analysis Calcd.: C, 77.09; H, 11.50%; **Found:** C, 77.22; H, 11.48%.

(*R*)-Non-1-en-4-ol (38).



38

To a solution of **98** (2 g, 14.26 mmol) in ethyl acetate (20 mL) was added Lindlar's catalyst (20 mg). The reaction mixture was stirred for 0.5 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 **38** (590 mg, 95%) as a pale yellow oil.

Yield: 1.87 g, 92%

Mol. Formula: $C_9H_{18}O$

$[\alpha]_D^{25}$: = + 12.5 (*c*, 0.9, $CHCl_3$)

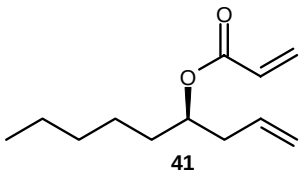
IR ($CHCl_3$, cm^{-1}): ν_{max} 3351, 2926, 2854, 1641, 1589, 1457, 1378, 1259, 1156, 999, 836.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.91-5.77 (m, 1H), 5.16-5.12 (m, 2H), 3.69-3.65 (m, 1H), 2.35-2.27 (m, 1H), 2.19-2.09 (m, 1H), 1.70 (brs, 1H), 1.47-1.26 (m, 8H), 0.89 (t, *J* = 6.4 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 134.9, 117.6, 70.7, 41.8, 36.7, 31.8, 25.2, 22.5, 13.9.

Analysis Calcd.: C, 76.00; H, 12.76%; **Found:** C, 76.12; H, 12.81%.

(*R*)-Non-1-en-4-yl acrylate (41).



41

Acryloyl chloride (0.95 g, 0.86 mL, 10.55 mmol) was added drop wise under argon to a solution of **38** (1.5 g, 10.55 mmol) and triethylamine (4.27 g, 5.9 mL, 42.18 mmol) in dry CH_2Cl_2 (15 mL) at 0 ^oC. The mixture was stirred for 5-6 h 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 **41** as a colorless liquid.

Yield: 1.84 g, 89%

Mol. Formula: $C_{12}H_{20}O_2$

$[\alpha]_D^{25}$: +19.93 (*c*, 1.1, $CHCl_3$).

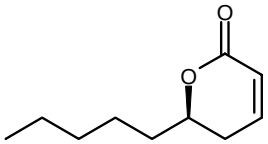
IR ($CHCl_3$, cm^{-1}): ν_{max} 2956, 2930, 2859, 1742, 1725, 1640, 1620, 1549, 1406, 1296, 1271, 1195, 1048, 986, 917, 809.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.42 (d, *J* = 18 Hz, 1H), 6.10 (dd, *J* = 15 Hz, 1H), 5.83-5.72 (m, 2H), 5.11-4.96 (m, 3H), 2.37-2.33 (m, 2H), 1.29-1.18 (m, 8H), 0.88 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 165.4, 132.7, 130.0, 128.9, 117.5, 73.6, 38.6, 33.5, 31.6, 24.9, 22.5, 13.9.

Analysis Calcd.: C, 73.43; H, 10.27%; **Found:** C, 73.32; H, 10.07%.

(*R*)-5,6-Dihydro-6-pentylpyran-2-one (4a).



4a

Grubb's catalyst (0.169 g, 0.20 mmol) dissolved in CH_2Cl_2 (10 mL) was added dropwise to a refluxing solution of acrylate **41** (0.200 g, 1.02 mmol), Ti(*i*-PrO)$_4$ (86 mg, 0.03 mmol) in dry CH_2Cl_2 (50 mL). Refluxing was continued for 12 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 (4:1) as eluent to afford **4a** as a colorless oil.

Yield: 0.144 g, 84%

Mol. Formula: $C_{10}H_{16}O_2$

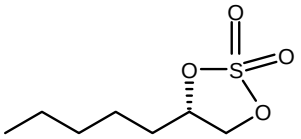
$[\alpha]_D^{25}$: -115.2 (*c* 1, $CHCl_3$) [lit.[49] $[\alpha]_D^{29}$ -113.6 (*c* 1.36, $CHCl_3$)

IR (neat, cm^{-1}): ν_{max} 2931, 2860, 1725, 1630, 1466, 1388, 1251, 1155, 1118, 1059, 1039, 955, 815.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.90-6.87 (m, 1H), 6.04 (d, *J* = 10Hz, 1H), 4.45-4.41 (m, 1H), 2.38-2.32 (m, 2H), 1.82-1.64 (m, 3H), 1.34-1.26 (m, 5H), 0.90 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 164.4, 144.9, 121.5, 78.0, 34.8, 31.5, 29.4, 24.5, 22.4, 13.9.

Cyclic sulfate (100).



100

To a stirred solution of diol **33** (1.7 g, 12.86 mmol) in dry CH_2Cl_2 (25 mL) cooled at 0 ^oC were added Et_3N (2.6 g, 3.6 mL, 25.72 mmol) and a solution of $SOCl_2$ (1.84 g, 1.13 mL, 15.43 mmol) in CH_2Cl_2 (5 mL) over a period of 10 min. Stirring was continued for 20 min at 0 ^oC and then the solution was quenched by adding water and extracted with CH_2Cl_2. The organic layer was separated, washed with water followed by brine, dried (Na_2SO_4) and filtered through a pad of silica gel. The filtrate was concentrated to give cyclic sulfite **99** as a yellow liquid.

To a solution of above cyclic sulfite **99** (2.27 g, 12.73 mmol) in CCl_4-MeCN-H_2O (2:2:3, 5: 5: 7.5 mL), $RuCl_3.H_2O$ (0.17 g, 0.64 mmol) was added followed by addition of $NaIO_4$ (4.84 g, 22.67 mmol). The mixture was stirred at 0 ^oC for 2 h and the extracted with EtOAc. The combined organic phase were washed with water, brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) as eluent gave cyclic sulfate **100** as a colorless syrupy liquid.

Yield: 2.47 g, 99%

Mol. Formula: $C_7H_{14}O_4S$

$[\alpha]_D^{25}$: -13.67 (*c*, 0.56, MeOH)

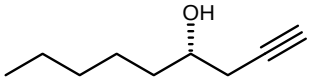
IR (neat, cm^{-1}): ν_{max} 3027, 3019, 2979, 2932, 1447, 1390, 1211, 1124, 1091, 1084, 954.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.01- 4.97 (m, 1H), 4.73-4.703 (m, 1H), 4.35 (t, *J* = 10.2 Hz, 1H), 1.98-1.95 (m, 1H), 1.78-1.75 (m, 1H), 1.60-1.54 (m, 2H), 1.53-1.34 (m, 4H), 0.91 (t, *J* = 6.6 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 83.0, 72.8, 32.1, 31.0, 24.1, 22.2, 13.70.

Analysis Calcd.: C, 43.28; H, 7.26%. **Found:** C, 43.39; H, 7.32%.

(*S*)-Non-1-yn-4-ol (*ent*-98).



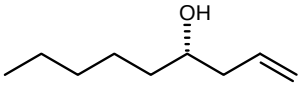
ent-**98**

To a stirred solution of cyclic sulfate **100** (2 g, 10.3 mmol) in DMSO (4 mL) at 0 ^{o}C was added lithium acetylide-EDA complex (3.23 g, 35.03 mmol). The mixture was stirred at r.t. for 10 h. To the mixture were added 50 mL of 20% aq. H_2SO_4 and 50 mL of ether. After the biphasic mixture was stirred overnight, the product was extracted with ether. The organic layer was washed with water, brine, dried (Na_2SO_4), concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (8:2) as eluent gave acetylide *ent*-**98** as a colorless syrupy liquid.

Yield: 1.15 g, 80%

$[\alpha]_D^{25}$: +25.6 (*c* 1.6, $CHCl_3$).

(*S*)-Non-1-en-4-ol (*ent*-38).

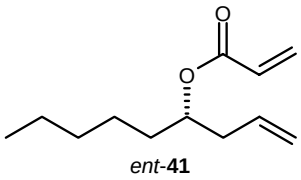


ent-**38**

Prepared in a similar way as described for **38**.

$[\alpha]_D^{25}$: -12.8 (*c*, 1.0, $CHCl_3$)

(*S*)-Non-1-en-4-yl acrylate (*ent*-41).

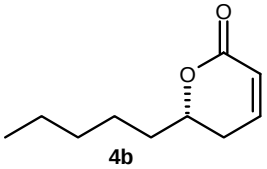


ent-**41**

Prepared in a similar way as described for **41**.

$[\alpha]_D^{25}$: -19.90 (*c*, 1.1, $CHCl_3$).

(*S*)-Massoialactone (4b).

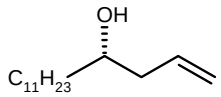


4b

Prepared in a similar way as described for **4b**

$[\alpha]_D^{25}$: +110.1 (*c* 2.0, $CHCl_3$) [lit.[32a] $[\alpha]_D^{22.6}$ +109.6 (*c* 2, $CHCl_3$)].

(*S*)-Pentadec-1-en-4-ol (39).



39

A round bottomed flask was charged with copper (I) iodide (0.14 g, 0.75 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, 15.13 mL, 15.13 mmol) was injected to it. A solution of epoxide (*S*)-**54** (1.5 g, 7.56 mmol) in THF (10 mL) was added slowly to the above reagent, and the mixture was stirred at –20 ^oC for 5 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 petroleum ether/EtOAc (9:1) as eluent gave **39** as a colorless syrupy liquid.

Yield: 1.4 g, 82%

Mol. Formula: $C_{15}H_{30}O$

$[\alpha]_D^{25}$: -15.8 (*c* 0.8, $CHCl_3$).

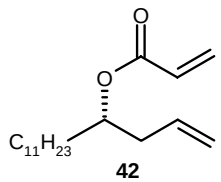
IR ($CHCl_3$, cm^{-1}): ν_{max} 3412, 2932, 2868, 1652, 1584, 1451, 1243, 1187, 1126, 837.

^{1}H NMR (200 MHz, $CDCl_3$): δ 5.95-5.74 (m, 1H), 5.19-5.17 (m, 1H), 5.11-5.10 (m, 1H), 3.71-3.62 (m, 1H), 2.36-2.27 (m, 1H), 2.21-2.10 (m, 1H), 1.50-1.37 (m, 2H), 1.27 (brs, 18 H), 0.89 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 134.9, 117.7, 70.7, 41.9, 36.8, 36.6, 31.9, 29.8, 29.5, 29.3, 25.6, 13.98, 22.6.

Analysis Calcd.: C, 79.58; H, 13.36 %; **Found:** C, 79.73; H, 13.39%.

(*S*)-Pentadec-1-en-4-yl acrylate (42).



42

Prepared in a similar way as described for **41**

Yield: 91%

Mol. Formula: $C_{18}H_{32}O_2$

$[\alpha]_D^{25}$: +14.2 (*c* 0.7, $CHCl_3$).

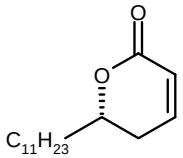
IR ($CHCl_3$, cm^{-1}): ν_{max} 2945, 2921, 2864, 1741, 1719, 1645, 1622, 1554, 1421, 1283, 1249, 1065.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.41-6.35 (m, 1H), 6.11 (dd, *J* = 10.3, 7.3 Hz, 1H), 5.75 (dd, *J* = 10.3, 8.8 Hz, 2H), 5.10-5.01 (m, 2H), 4.99-4.95 (m, 1H), 2.34 (t, *J* = 6.6 Hz, 2H), 1.59-1.57 (m, 2H), 1.25 (brs, 18 H), 0.88 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.8, 133.7, 129.9, 128.9, 117.50, 73.61, 38.58, 33.57, 31.86, 29.57, 29.30, 25.24, 22.61, 13.98.

Analysis Calcd.: C, 77.09; H, 11.50%, **Found:** C, 77.28; H, 11.54%.

(*S*)-5,6-Dihydro-6-undecylpyran-2-one (44).



44

Prepared in a similar way as described for **4a**

Yield: 89%

Mol. Formula: $C_{16}H_{28}O_2$

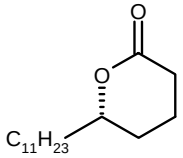
$[\alpha]_D^{25}$: -78.2 (*c*, 0.9, THF), lit.[55] $[\alpha]_D^{25}$ –78.7 (*c* 1.0, THF).

IR ($CHCl_3$, cm^{-1}): ν_{max} 3060, 1720, 1256, 1187, 1040, 875.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.85 (dt, *J* = 10, 4.0 Hz, 1H), 6.00 (dt, *J* =10, 1.5 Hz , 1H), 4.44-4.37 (m, 1H), 2.31-2.35 (m, 2H), 1.83-1.60 (m, 2H), 1.26 (brs, 18 H), 0.88 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 164.51, 145.0, 121.3, 77.9, 34.8, 31.8, 29.5, 29.3, 29.2, 24.7, 22.6, 14.0.

(*S*)-Tetrahydro-6-undecylpyran-2-one (5).



5

To a solution of **44** (0.2 g, 0.79 mmol) in ethyl acetate (5 mL) was added catalytic amount of 10% Pd/C. The reaction mixture was stirred for 12 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 **5** as a pale yellow oil.

Yield: 190 mg, 94%

Mol. Formula: $C_{16}H_{30}O_2$

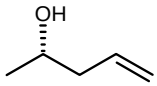
$[\alpha]_D^{25}$: -42.2 (*c*, 1.2, THF), lit.[55] $[\alpha]_D$ –40.2 (*c* 1.5, THF).

IR ($CHCl_3$, cm^{-1}): ν_{max} 1740, 1240, 1050.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.13-3.97 (m, 1H), 2.55-2.21 (m, 2H), 1.63-1.27 (m, 6H), 1.17 (brs, 18H), 0.89 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.2, 80.5, 31.9, 29.5, 29.4, 29.2, 29.0, 26.9, 22.7, 18.0, 14.1.

(*S*)-Pent-4-en-2-ol (40).



40

A round bottomed flask was charged with copper (I) iodide (1.64 g, 8.6 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, 172 mL, 172.4 mmol) was injected to it. A solution of propylene oxide (*S*)-**90** (5 g, 86.09 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 to afford the crude homoallylic alcohol which on distillation provided alcohol **40** (6.6 g, 89%) as a colorless liquid (bp 115 ^oC)

Yield: 6.6 g, 89%

B.P.: 115 ^oC

Mol. Formula: $C_5H_{10}O$

$[\alpha]_D^{25}$ **:** +10.86 (*c* 3.2 in Et_2O).

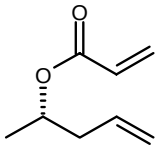
IR ($CHCl_3$, cm^{-1}): ν_{max} 3400, 3078, 2931, 2975, 1562, 1457, 1432, 1243, 1071, 914.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.85-5.77 (m, 1H), 5.12 (d, *J* = 6.6 Hz, 1H), 5.09 (d, *J* = 2.4 Hz, 1H), 3.86-3.80 (m, 1H), 2.38-2.22 (m, 2H), 1.82 (s, 1H), 1.18 (d, *J* = 6.1, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 134.6, 116.6, 66.5, 43.2, 22.1.

Analysis Calcd.: C, 69.72; H, 11.70%; **Found:** C, 69.61; H, 11.75%.

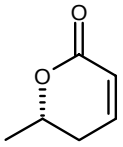
(*S*)-Pent-4-en-2-yl acrylate (43).



43

Acryloyl chloride (0.21 g, 0.19 mL, 2.32 mmol) was added dropwise under argon to a solution of **40** (0.2 g, 2.32 mmol) and triethylamine (0.94 g, 1.3 mL, 9.29 mmol) in dry CH_2Cl_2 (15 mL) at 0 ^oC. The mixture was stirred for 5-6 h 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 30mL) and combined organic layer was washed with brine, dried (Na_2S0_4), concentrated and was used as such for the next step without further purification.

(S)-5,6-Dihydro-6-methylpyran-2-one (6).



6

Grubb's catalyst (0.384 g, 0.46 mmol) dissolved in CH_2Cl_2 (100 mL) was added dropwise to a refluxing solution of acrylate **43** (0.325 g, 2.32 mmol), Ti(*i*-PrO)$_4$ (20 mg, 0.06 mmol) in dry CH_2Cl_2 (50 mL). Refluxing was continued for 12 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 (7:3) as eluent to afford **6** as a colorless oil

Yield: 0.213 g, 82%

Mol. Formula: $C_6H_8O_2$

$[\alpha]_D^{25}$: +221.6 (*c* 1.0, $CHCl_3$), lit.[67] $[\alpha]_D^{25}$ +219.2 (*c* 0.96, $CHCl_3$).

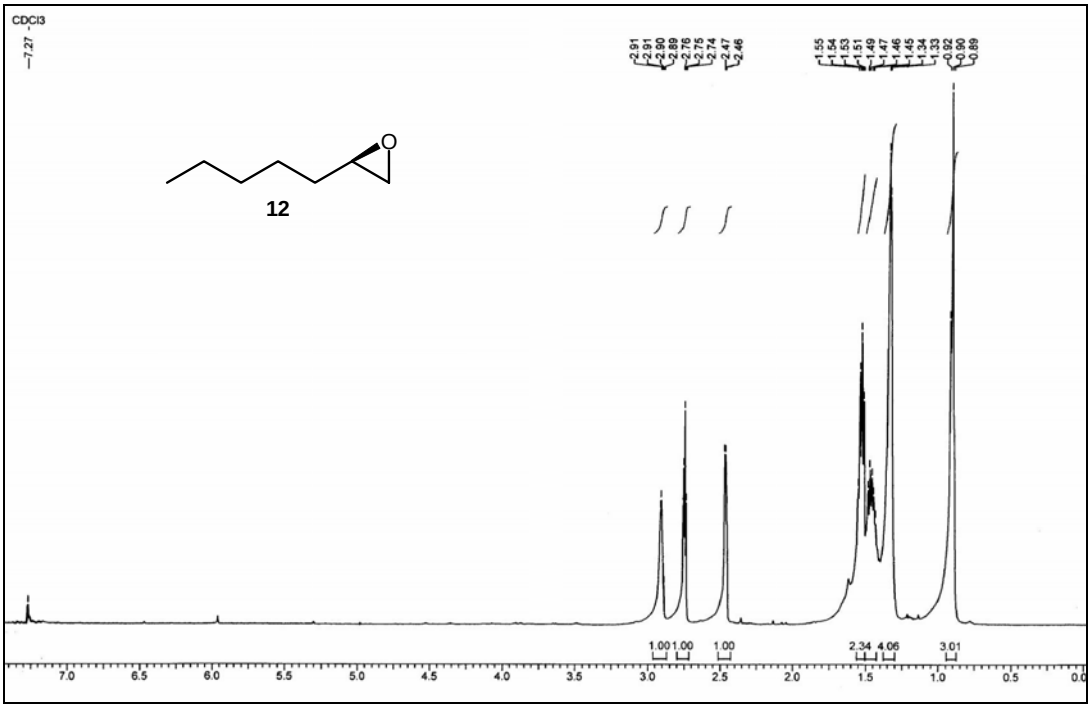
IR ($CHCl_3$, cm^{-1}): ν_{max} 2956, 2931, 2858, 1730, 1605, 1576, 1511, 1472, 1421.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.31-5.99 (m, 1H), 5.75 (d, *J* = 8.8 Hz, 1H), 4.29-4.09 (m, 1H), 2.49-2.33 (m, 2H), 1.41 (d, *J* = 6.6 Hz, 3H).

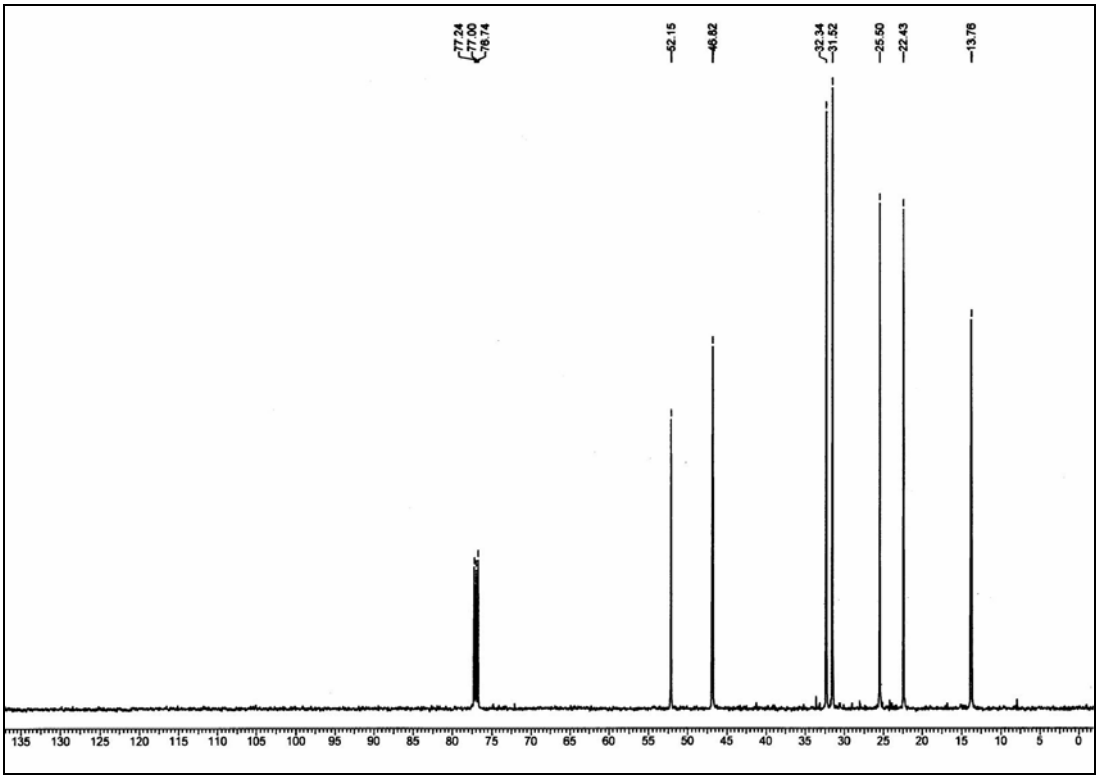
^{13}C NMR (125 MHz, $CDCl_3$): δ 162.7, 141.8, 121.1, 86.2, 34.1, 21.5.

3.1.7 Spectra

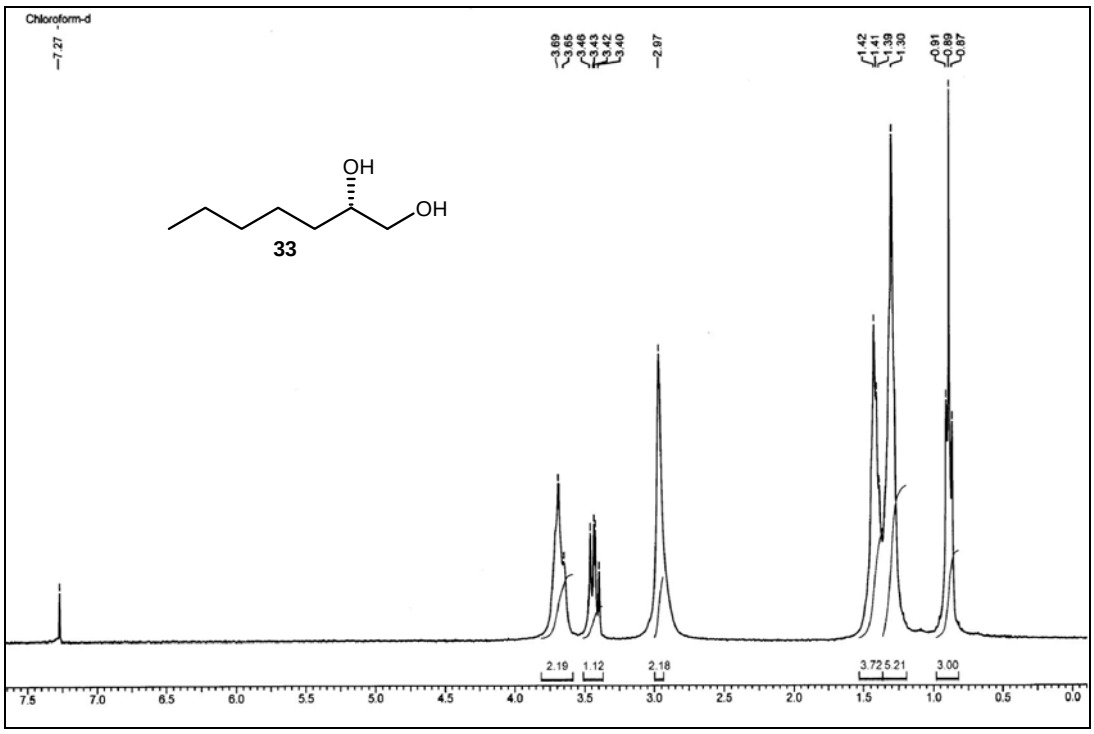
1. ^{1}H and ^{13}C NMR spectra of 12
2. ^{1}H and ^{13}C NMR spectra of 33
3. ^{1}H and ^{13}C NMR spectra of 98
4. ^{1}H and ^{13}C NMR spectra of 38
5. ^{1}H and ^{13}C NMR spectra of 100
6. ^{1}H and ^{13}C NMR spectra of 41
7. ^{1}H and ^{13}C NMR spectra of (*S*)-54
8. ^{1}H and ^{13}C NMR spectra of 39
9. ^{1}H and ^{13}C NMR spectra of 42
10. ^{1}H and ^{13}C NMR spectra of 44
11. ^{1}H and ^{13}C NMR spectra of 5
12. ^{1}H and ^{13}C NMR spectra of 6



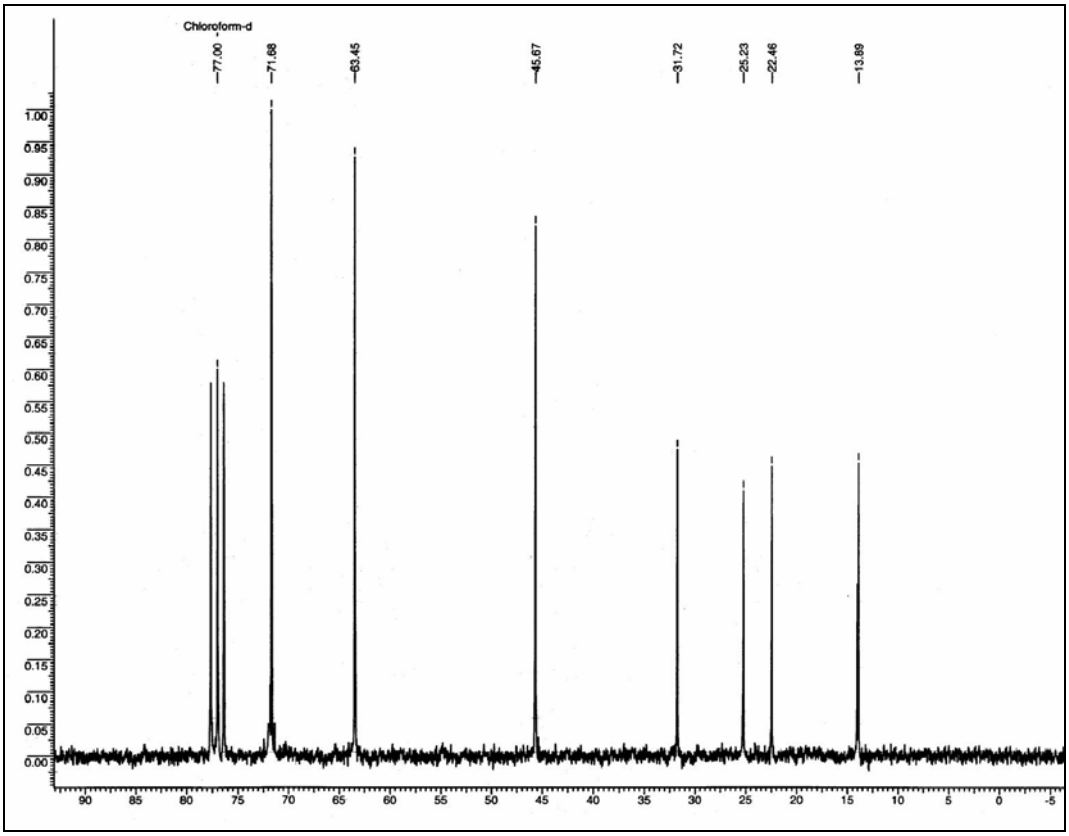
^{1}H NMR Spectrum of compound 12 in $CDCl_3$



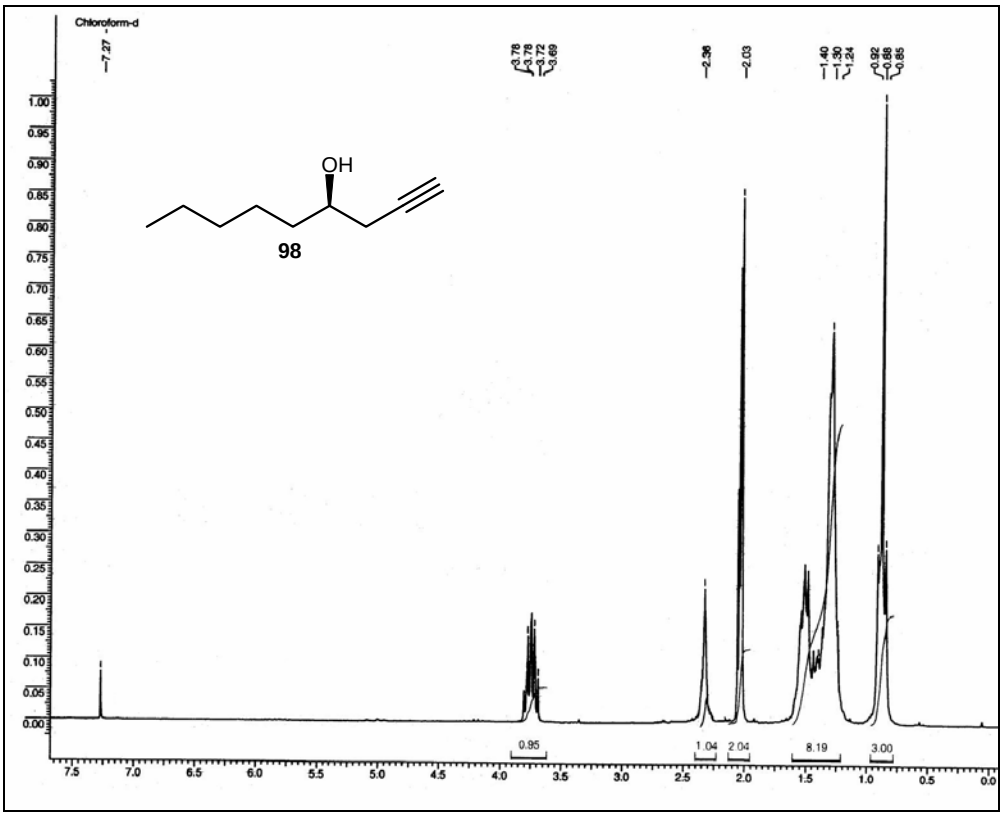
^{13}C NMR Spectrum of compound 12 in $CDCl_3$



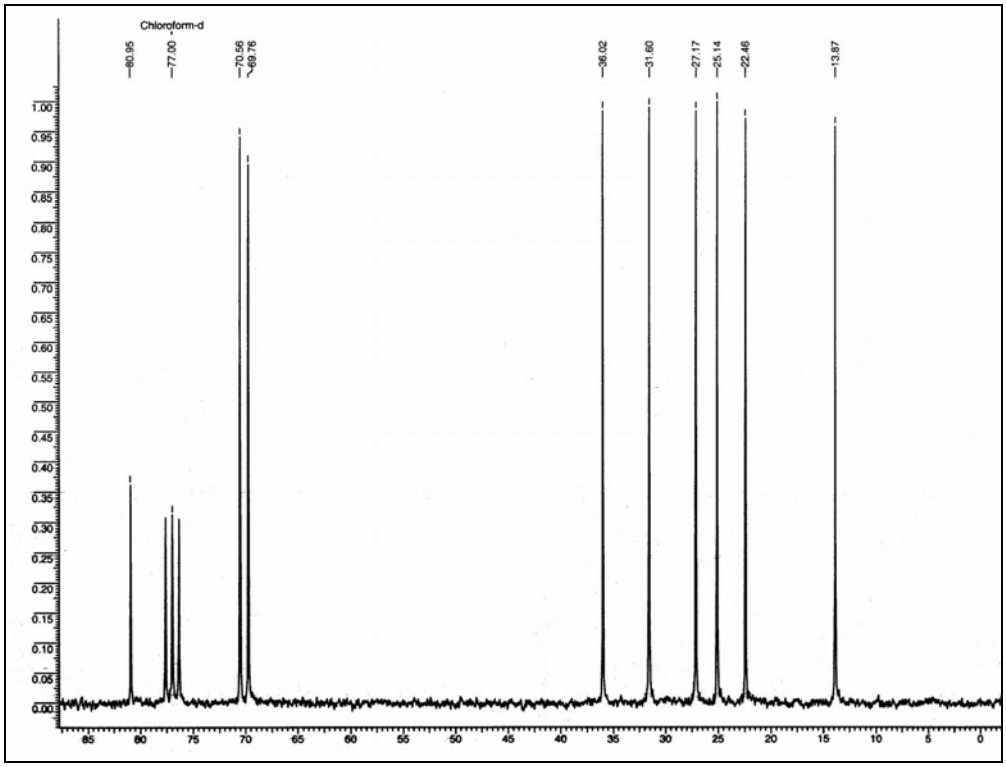
^{1}H NMR Spectrum of compound 33 in $CDCl_3$



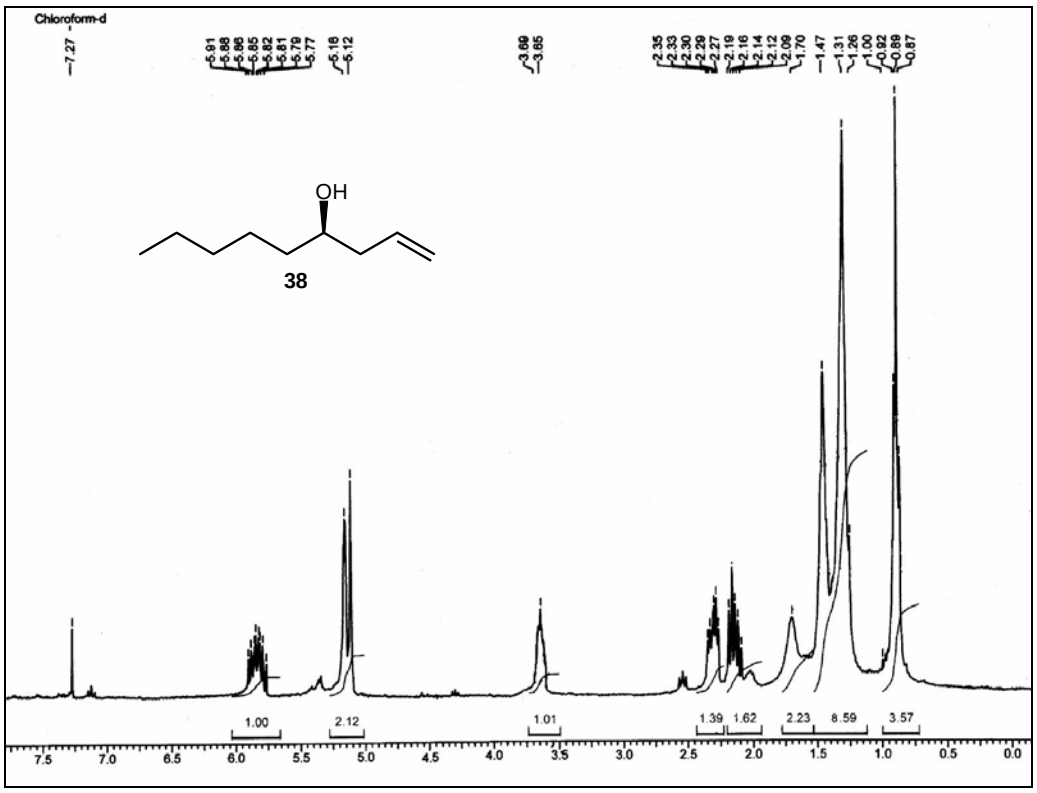
^{13}C NMR Spectrum of compound 33 in $CDCl_3$



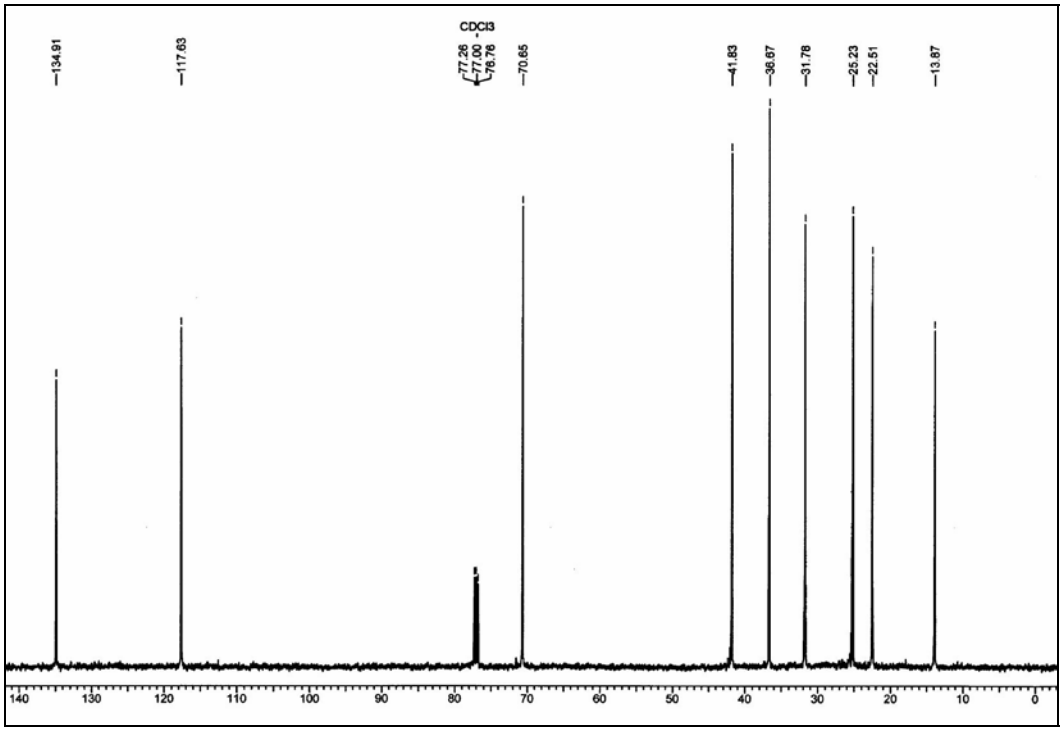
^{1}H NMR Spectrum of compound 98 in $CDCl_3$



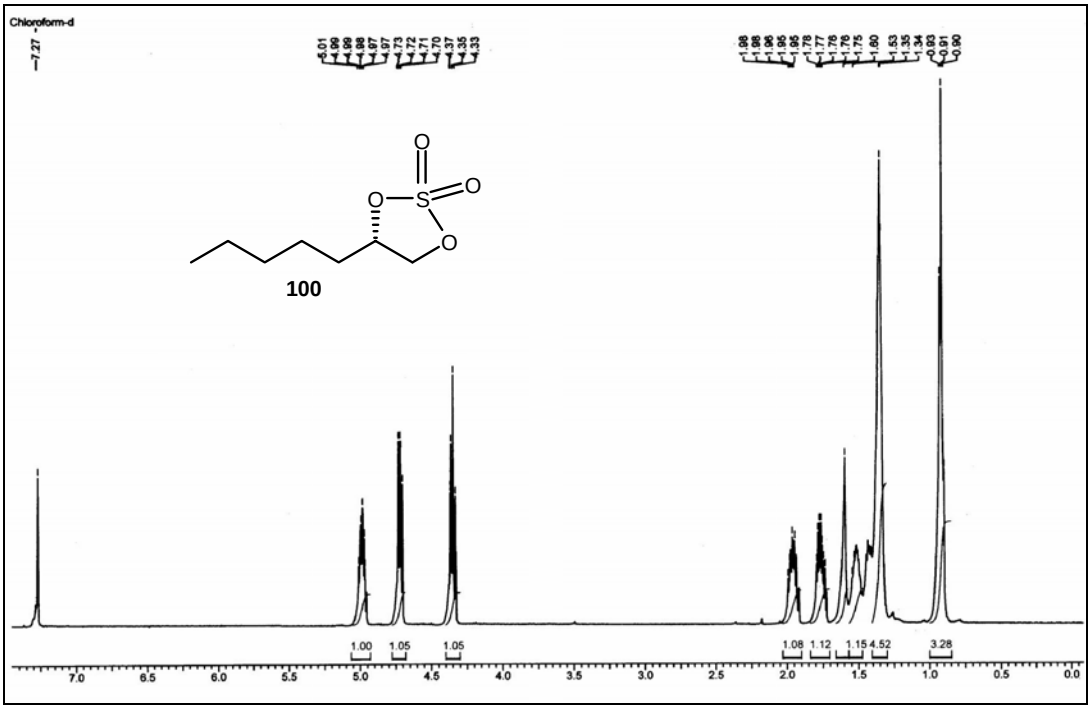
^{13}C NMR Spectrum of compound 98 in $CDCl_3$



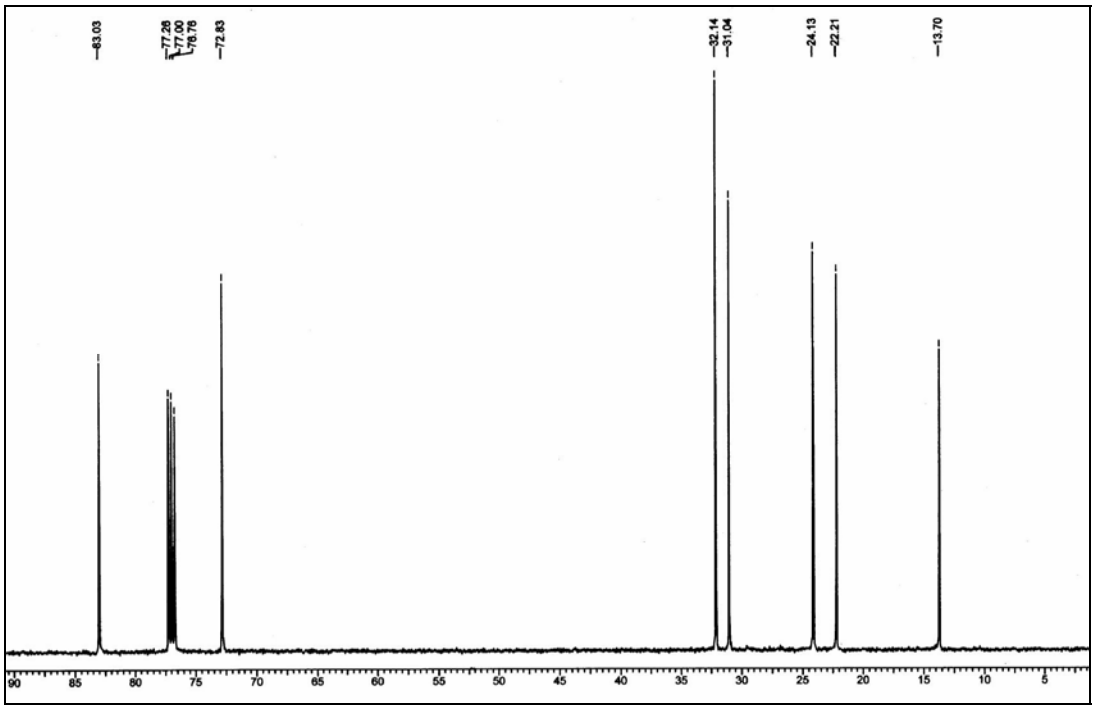
^{1}H NMR Spectrum of compound 38 in $CDCl_3$



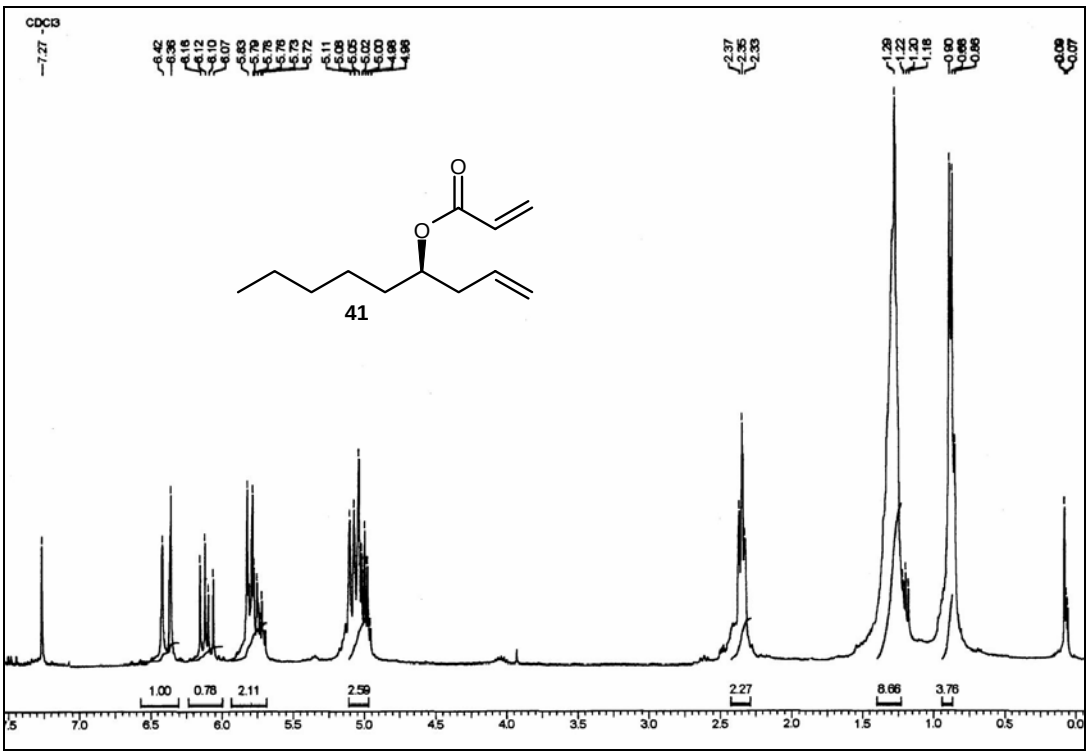
^{13}C NMR Spectrum of compound 38 in $CDCl_3$



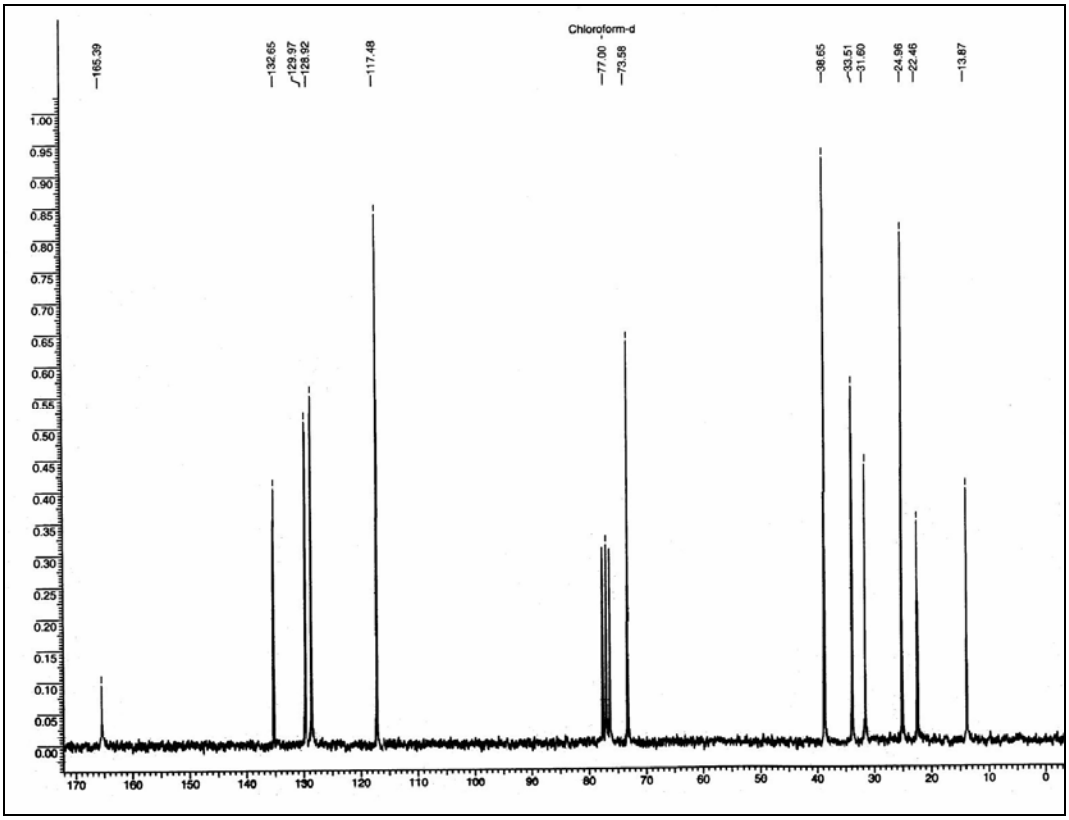
^{1}H NMR Spectrum of compound 100 in $CDCl_3$



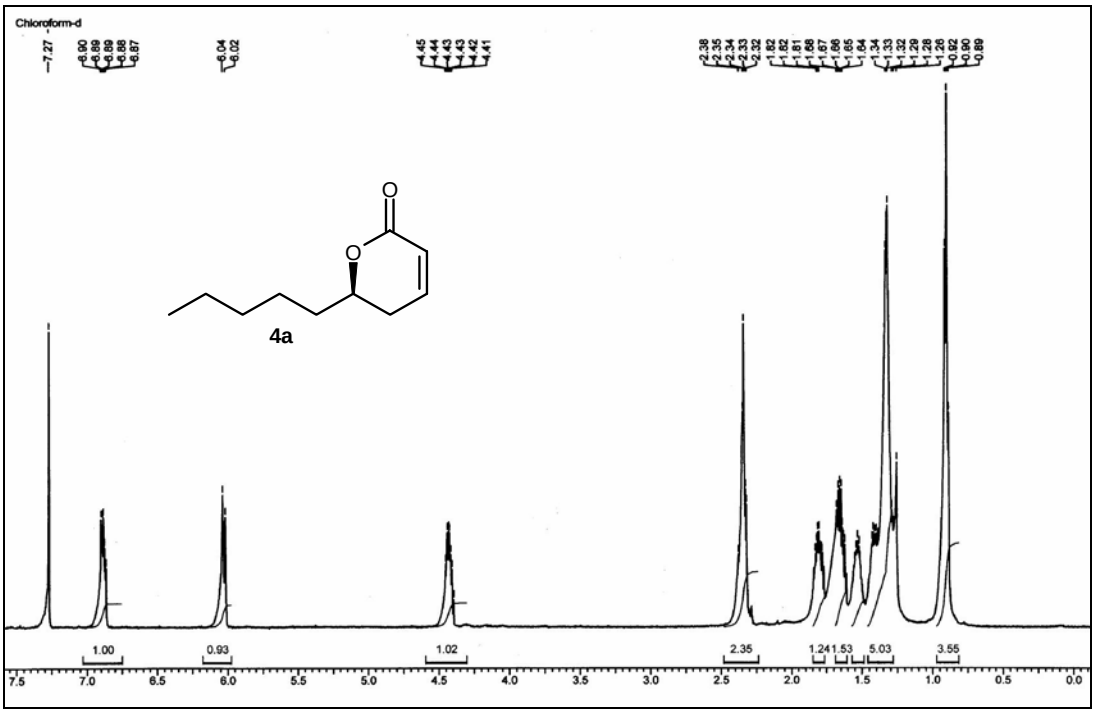
^{13}C NMR Spectrum of compound 100 in $CDCl_3$



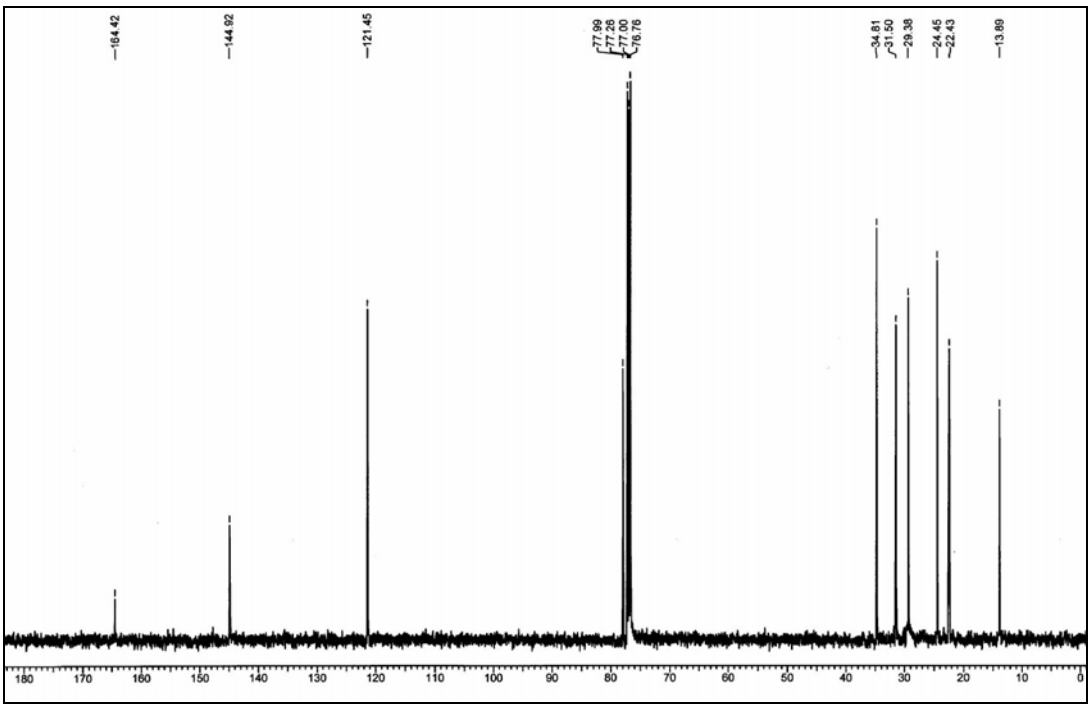
^{1}H NMR Spectrum of compound 41 in $CDCl_3$



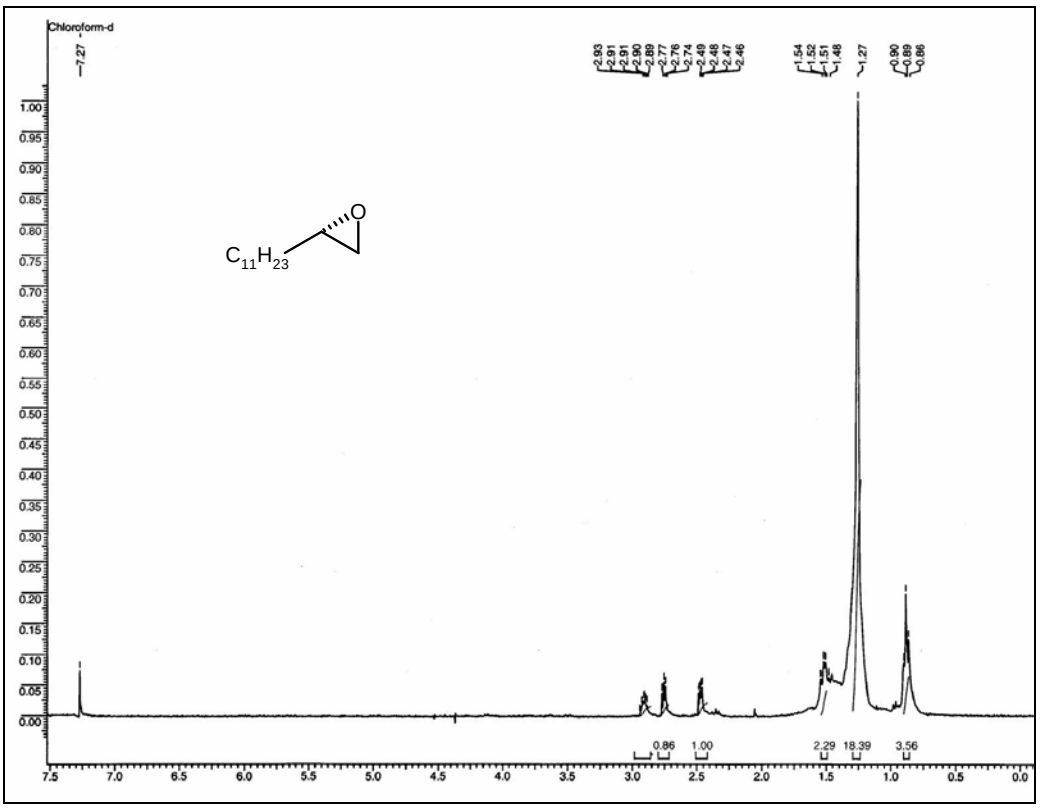
^{13}C NMR Spectrum of compound 41 in $CDCl_3$



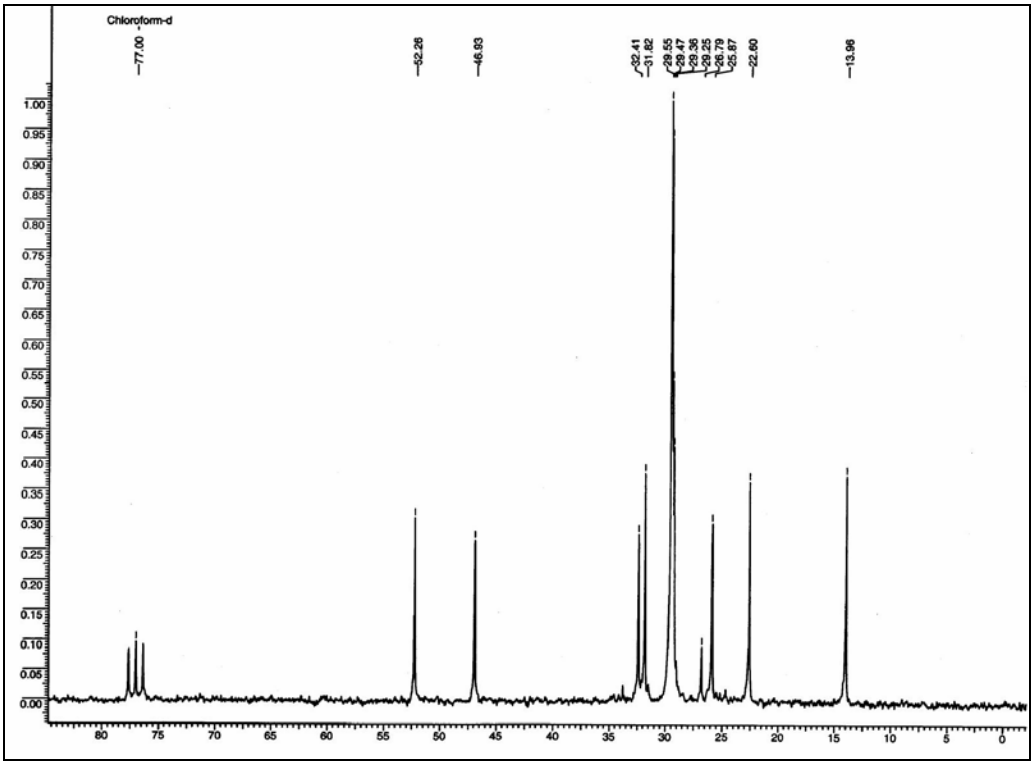
^{1}H NMR Spectrum of compound 4a in $CDCl_3$



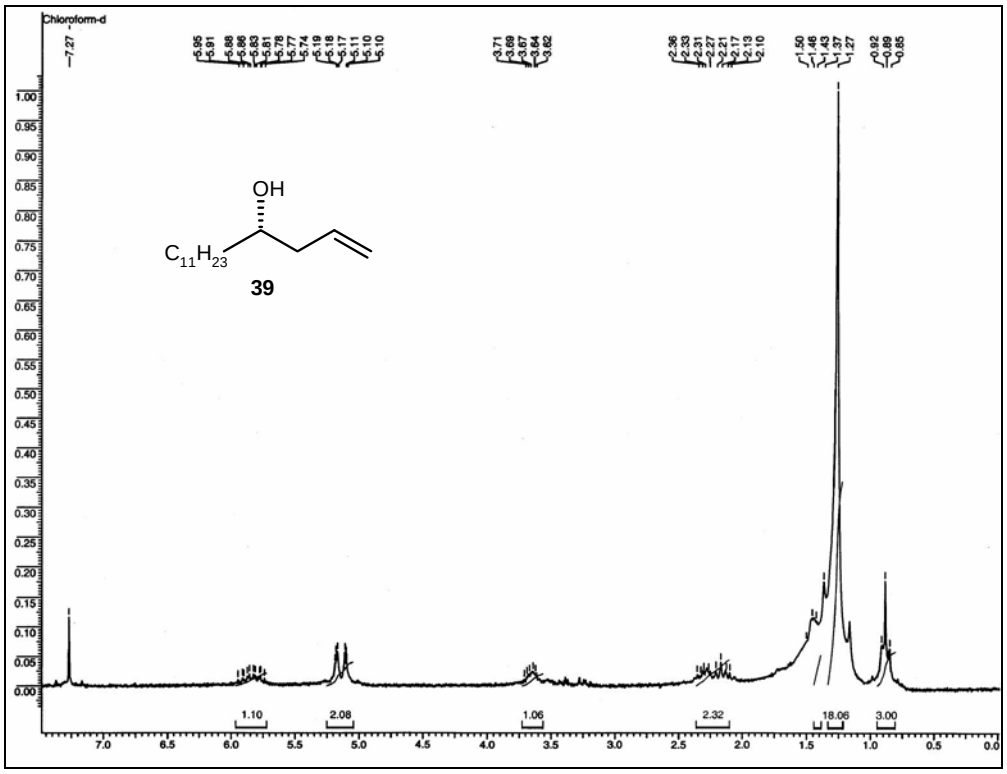
^{13}C NMR Spectrum of compound 4a in $CDCl_3$



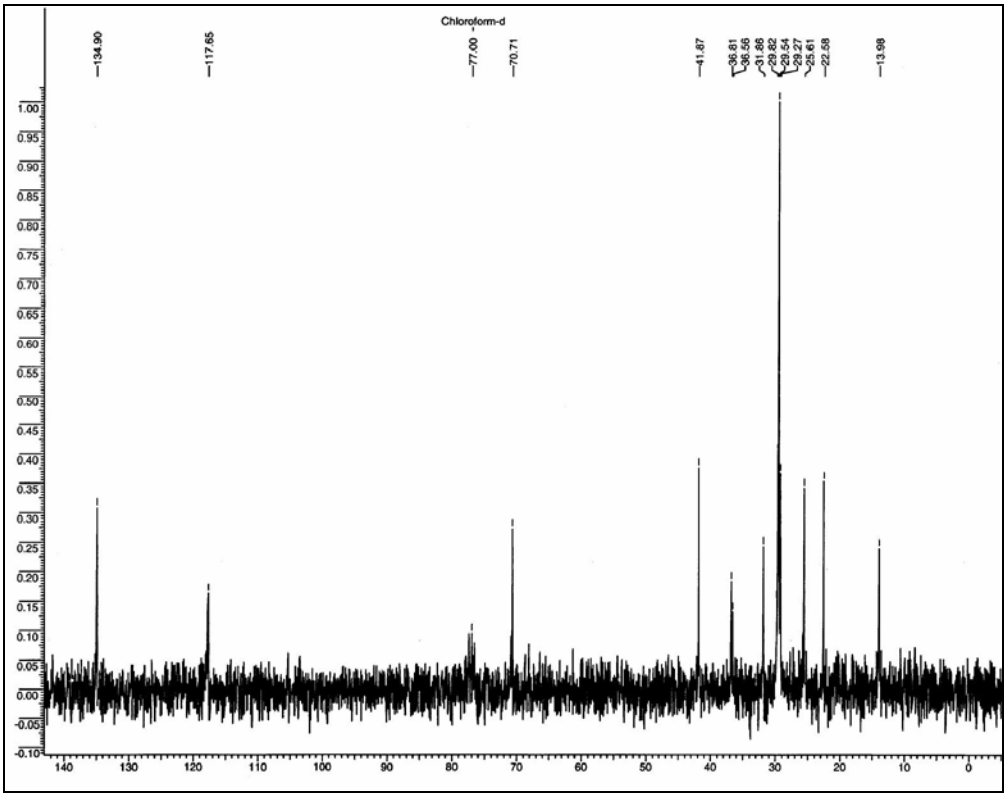
^{1}H NMR Spectrum of compound (*S*)-54 in $CDCl_3$



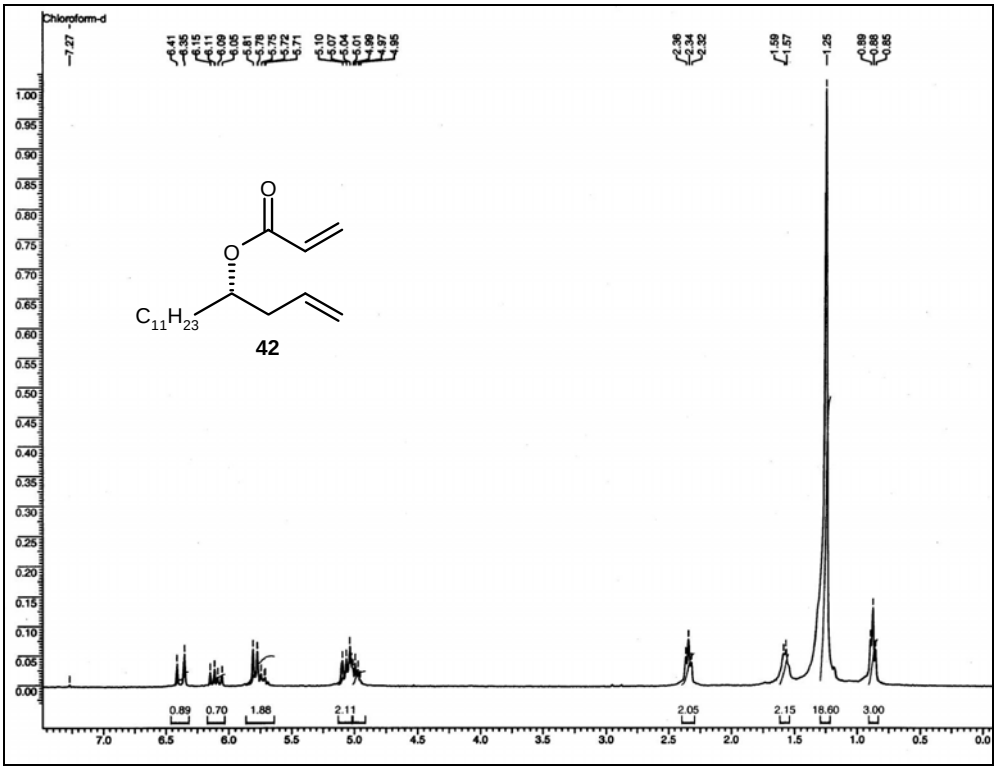
^{13}C NMR Spectrum of compound (*S*)-54 in $CDCl_3$



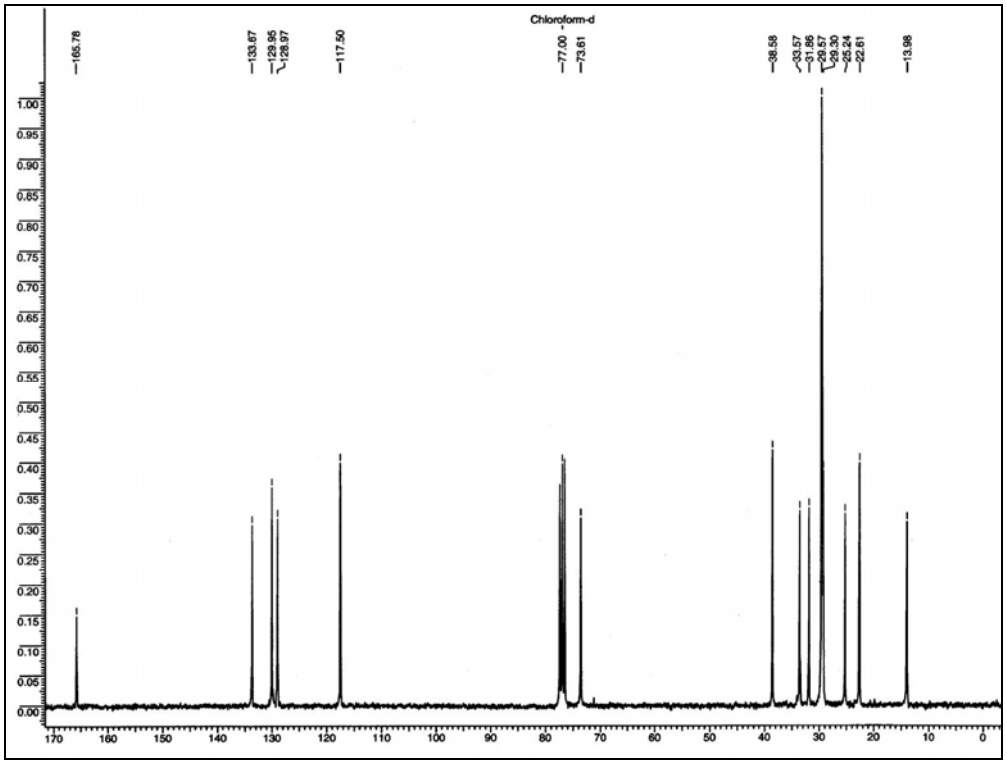
^{1}H NMR Spectrum of compound 39 in $CDCl_3$



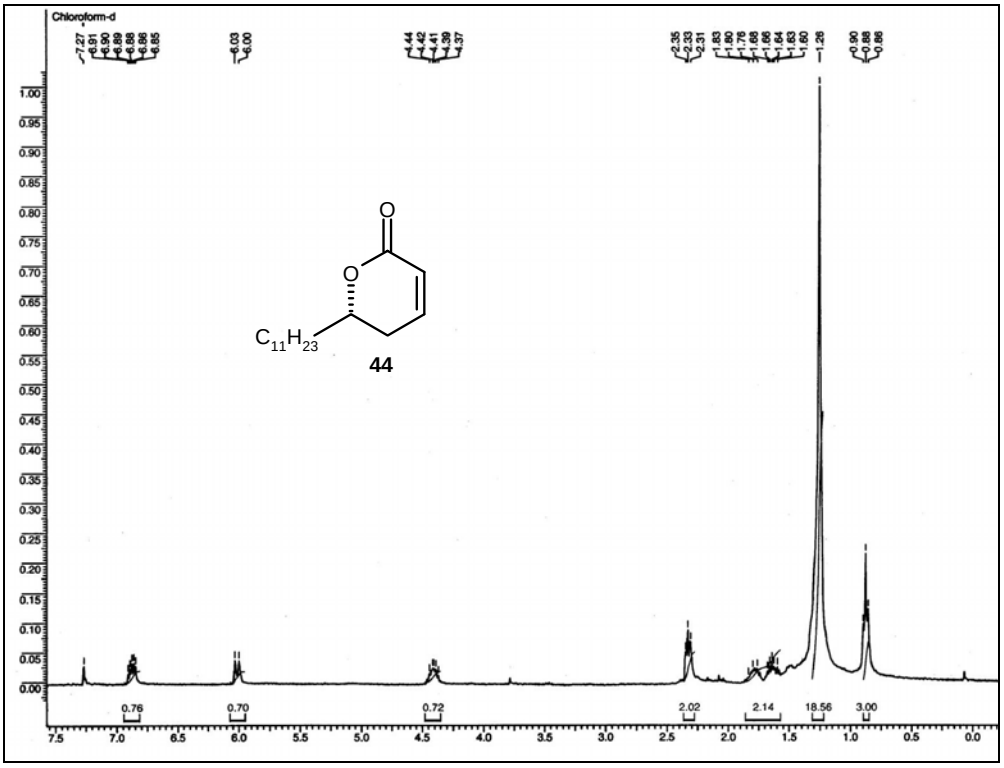
^{13}C NMR Spectrum of compound 39 in $CDCl_3$



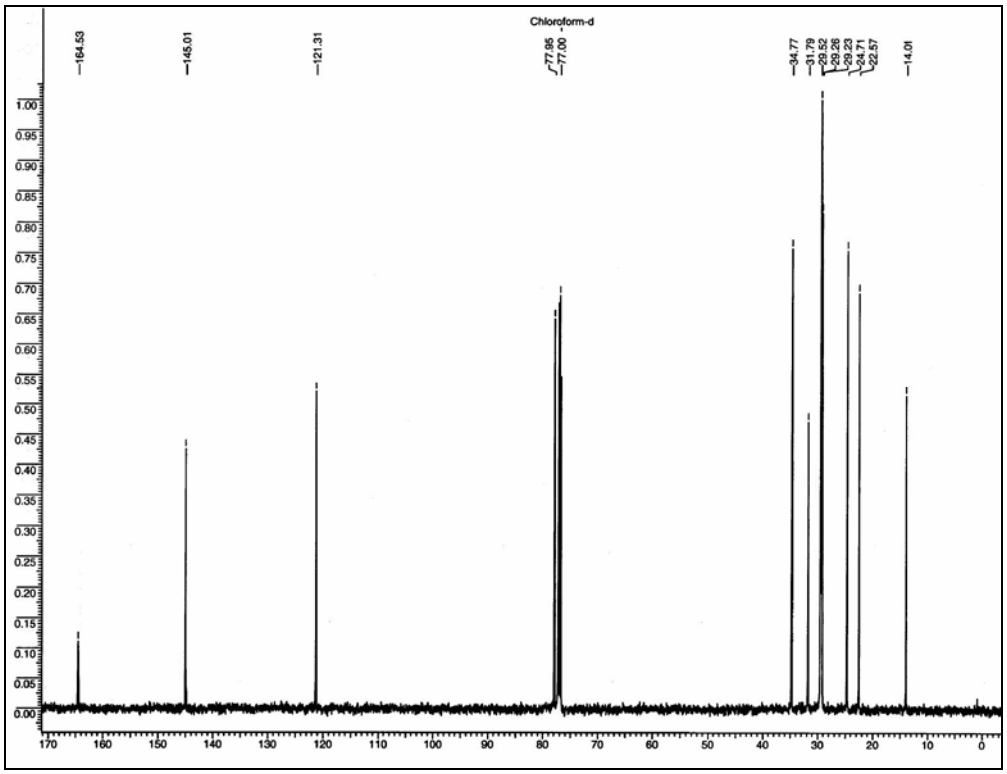
^{1}H NMR Spectrum of compound 42 in $CDCl_3$



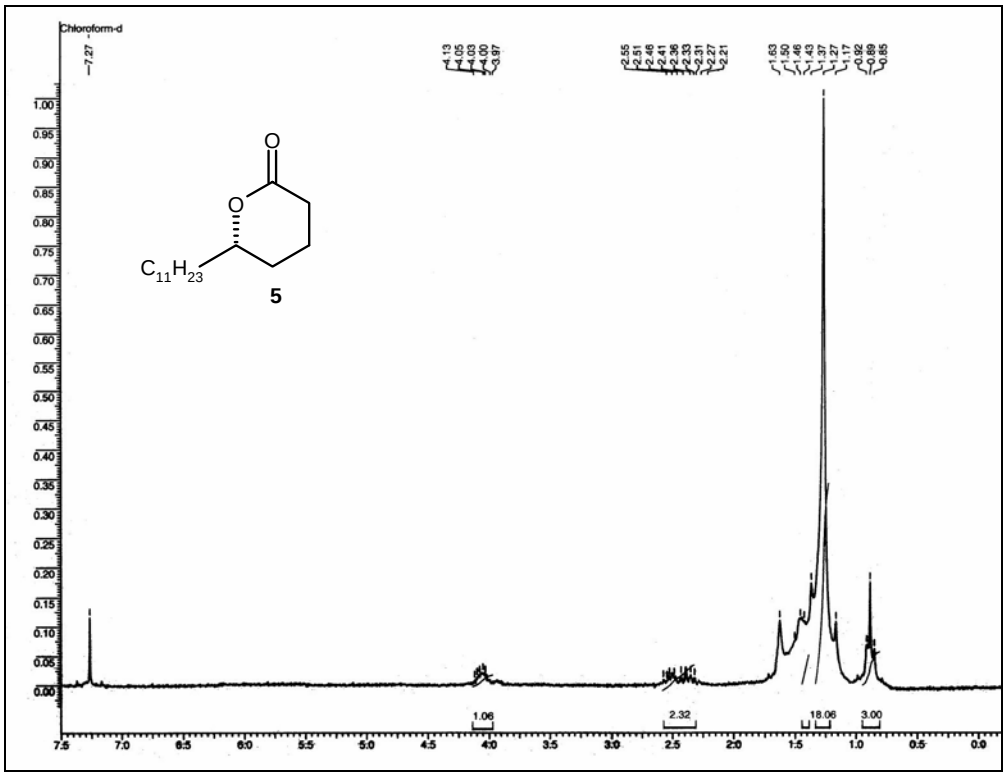
^{13}C NMR Spectrum of compound 42 in $CDCl_3$



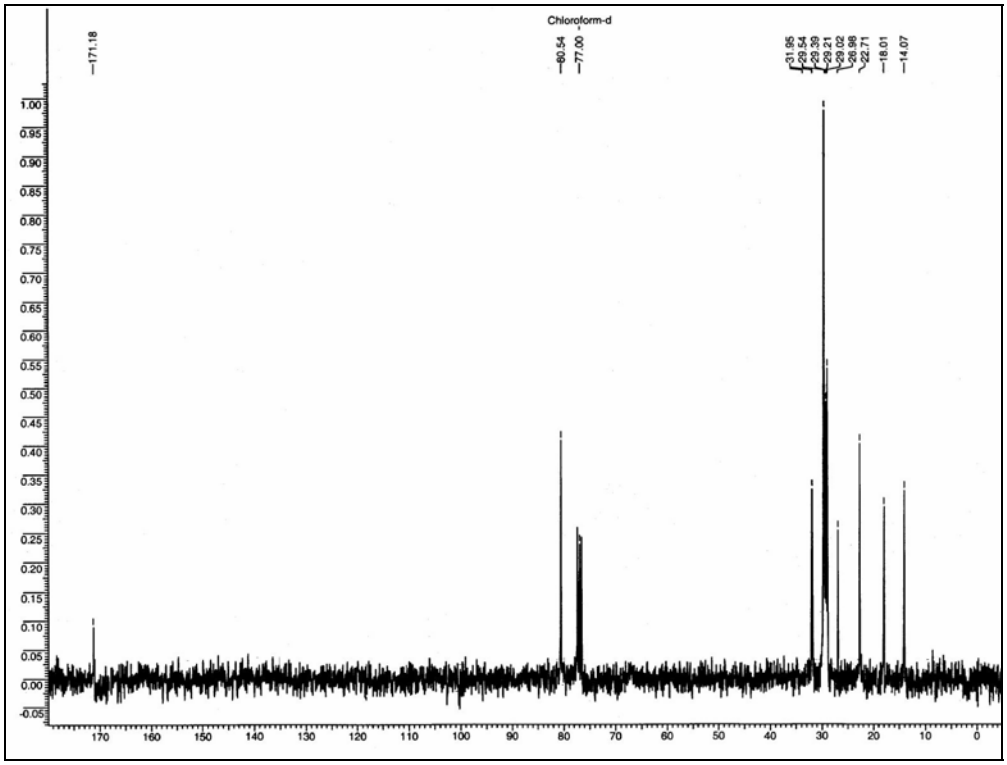
^{1}H NMR Spectrum of compound 44 in $CDCl_3$



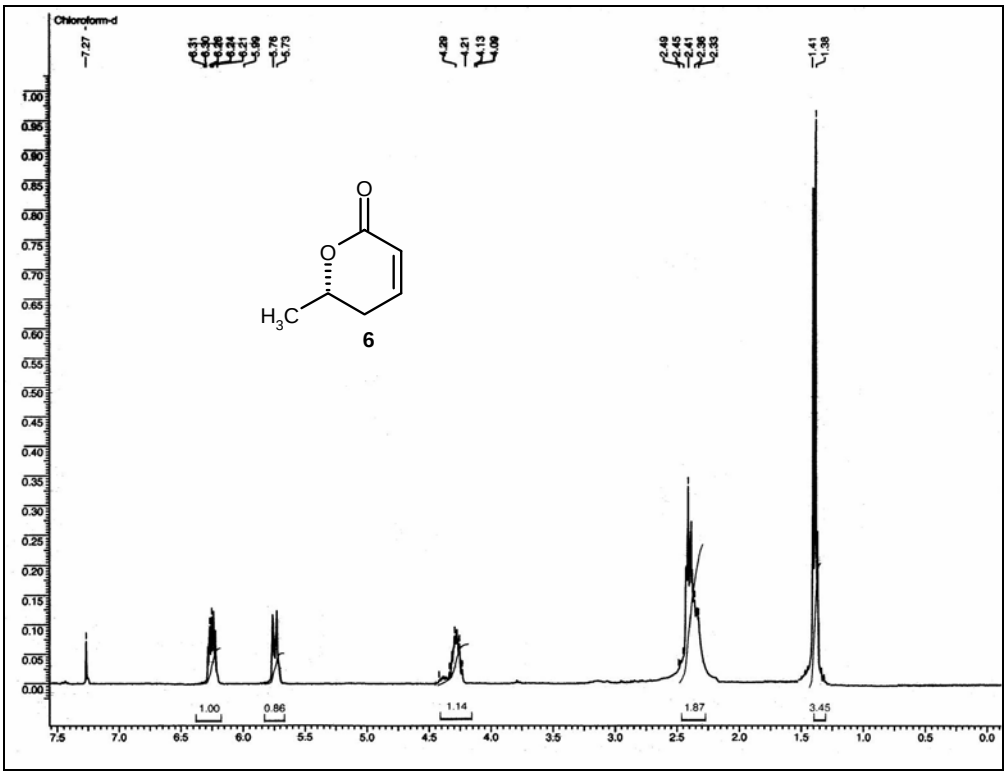
^{13}C NMR Spectrum of compound 44 in $CDCl_3$



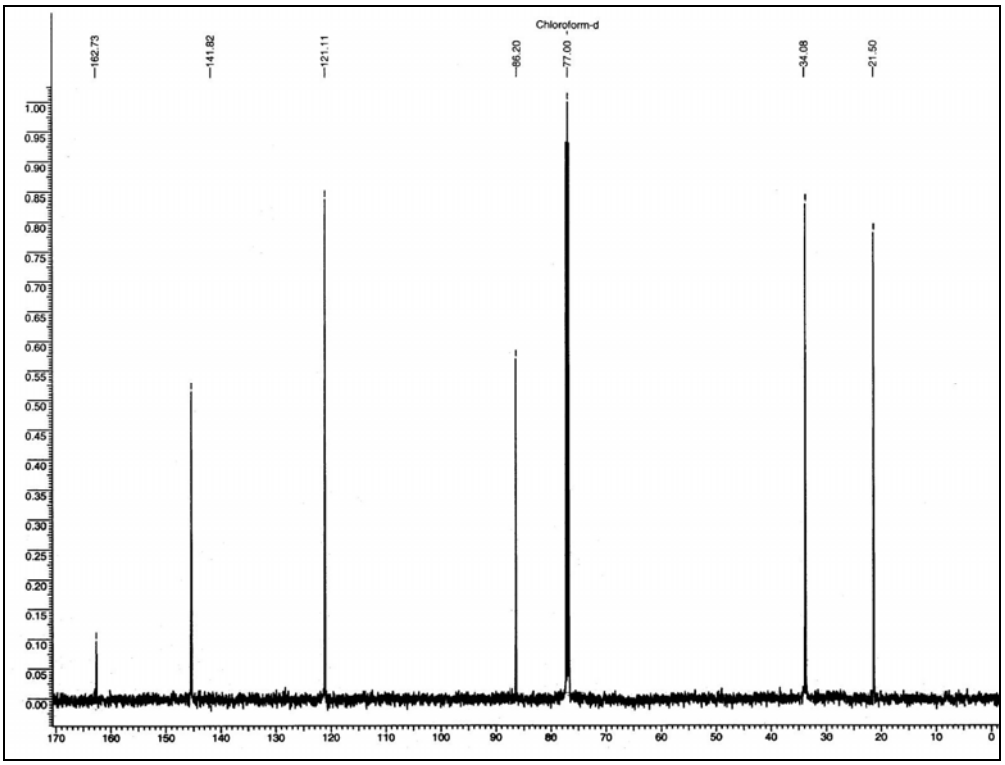
^{1}H NMR Spectrum of compound 5 in $CDCl_3$



^{13}C NMR Spectrum of compound 5 in $CDCl_3$



^{1}H NMR Spectrum of compound 6 in $CDCl_3$



^{13}C NMR Spectrum of compound 6 in $CDCl_3$

3.2 SECTION B

ATTEMPTED SYNTHESIS OF KURZILACTONE

3.2.1. Introduction

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 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. Recently, a number of 5,6-dihydro-α-pyrone derivatives having an alkyl side chain at the C_6 position, with 1,3- or 1,5-diol units, have been isolated from plants.

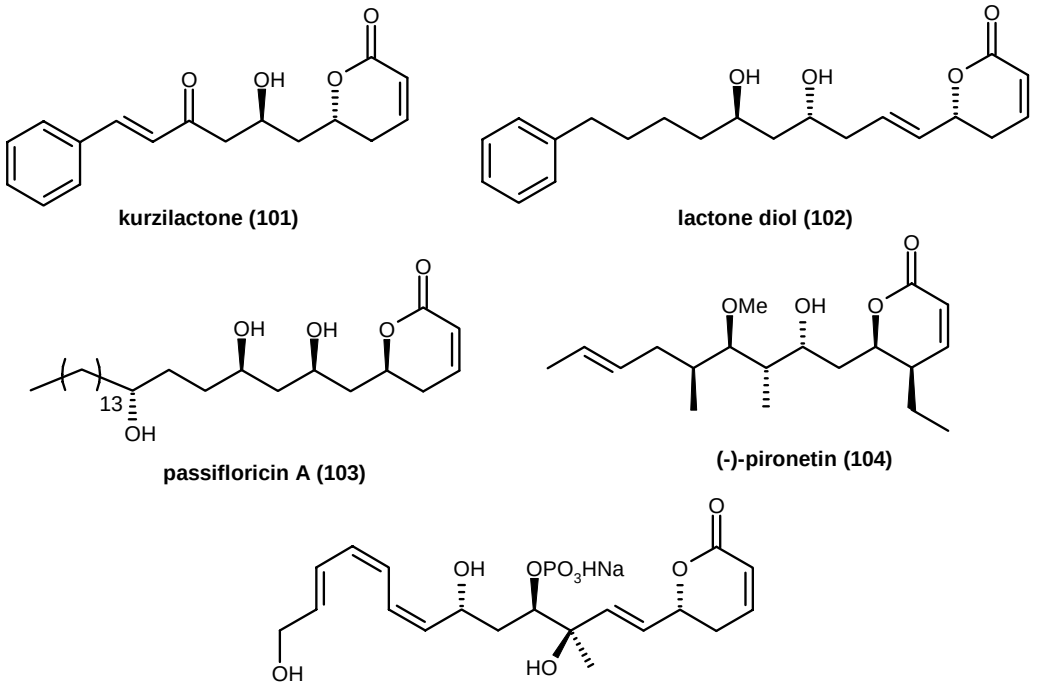


Figure 5

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

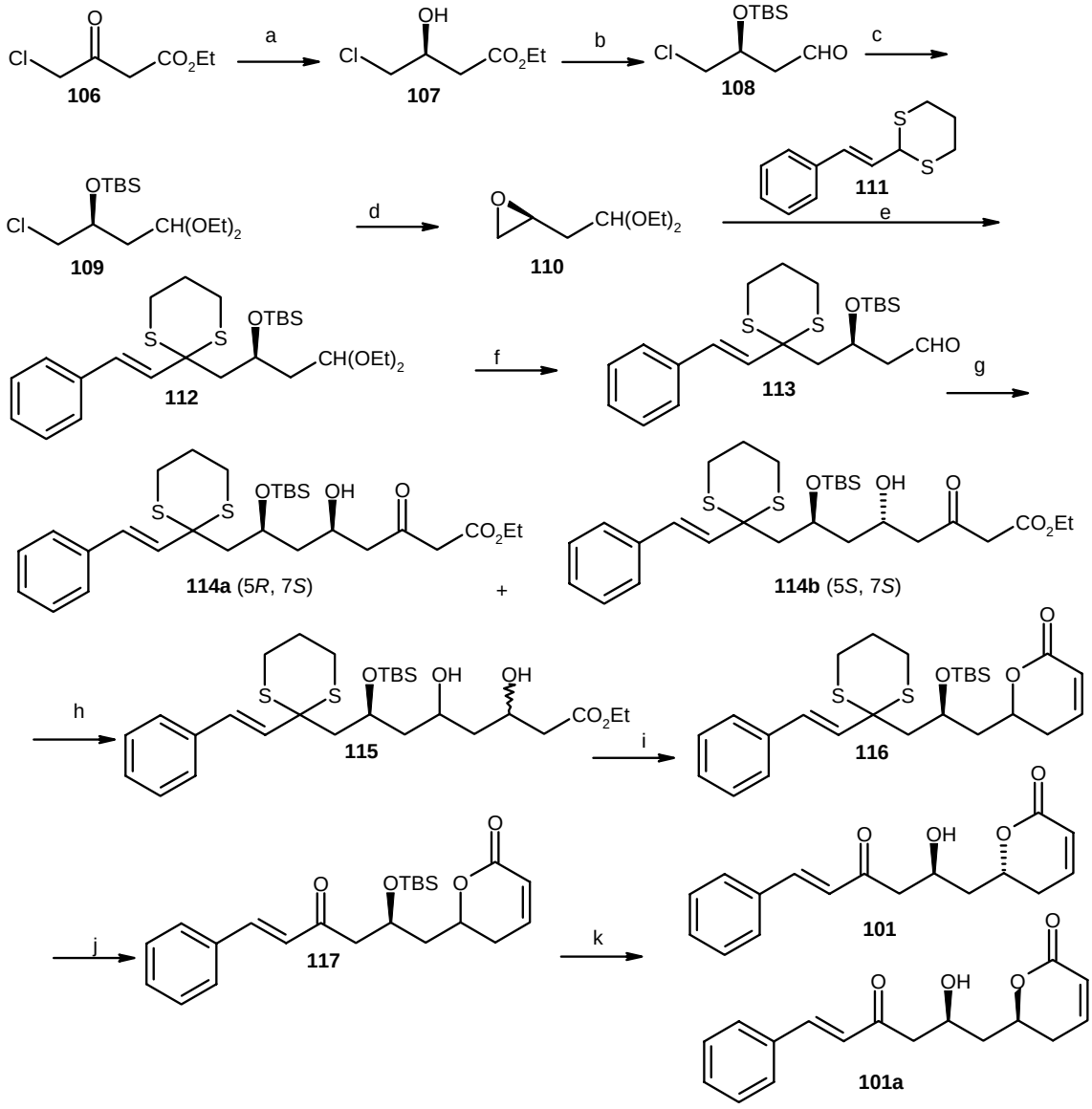
compounds have been found to exhibit antifungal activity such as passifloricin A (**103**),[70] to inhibit the cell cycle progression in the M-phase and to be an immunosuppressive agent such as (-)-pironetin (**104**),[71] an anticancer agent such as fostriecin (**105**),[72] antifungal agent such as lactone diol (**102)** (Figure 5)**.** Kurzilactone **101**, a Kawa-type lactone,[73] was isolated from leaves of *Cryptocarya kurzii*, a plant which is indigenous to Malaysia. A preliminary report included a tentative stereochemical assignment established through an NMR experiment; both stereogenic centers bearing hydroxyl groups in the side chain were assigned a *syn*-relationship. Kurzilactone shows remarkable cytotoxicity against KB cells (IC_{50}=1 μg/ mL).[73a] The relative C(5)-C(7) stereochemistry of this substance was incorrectly assigned as *syn* initially and then corrected to be *anti* by using total synthesis. Ziang and co-workers corrected the absolute configuration of kurzilactone by synthesizing both the isomers.[74]

3.2.2. Review of Literature

So far only two asymmetric synthesis of kurzilactone was reported. A detailed report of these syntheses is described below.

Jiang *et al* . (2001).[74]

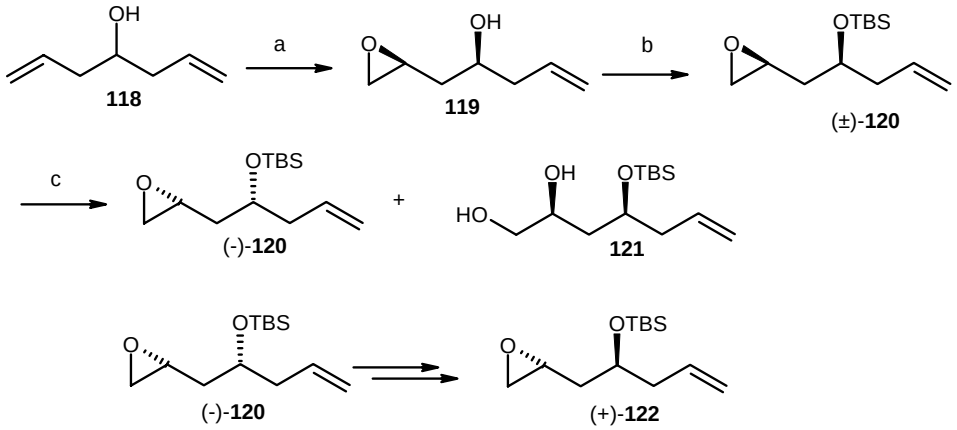
Jiang and co-workers synthesized both the isomers of kurzilactone from a chiral epoxy-aldehyde synthon through the coupling of an acyl anion equivalent and the dianion of acetoacetate. Thus, the desired epoxy synthon **110** was prepared from ethyl (*S*)-4-chloro-3-hydroxy butanoate **107**, which was obtained from the commercial 4-chloroacetate **106** by asymmetric hydrogenation. The chlorohydrin **107** was protected as TBS ether followed by reduction and Swern oxidation to give aldehyde **108**, which was converted to diethyl acetal followed by TBS deprotection to afford the desired chiral epoxy aldehyde synthon equivalents **110**.[75] The epoxide **110** was coupled with acyl anion equivalent **111** followed by TBS protection of free hydroxyl group to furnish **112** which was converted into aldehyde **113**. Coupling of aldehyde **113** with the dianion of ethylacetoacetate gave the 5,7-*cis*-dihydroxy ketone **114a** along with its *trans* isomer **114b**. Reduction of compound **114** followed by cyclization, mesylation and elimination gave lactone **116** which after dithiane and TBS deprotection afforded both isomers (**101**, **101a**) of target molecule (Scheme 21).



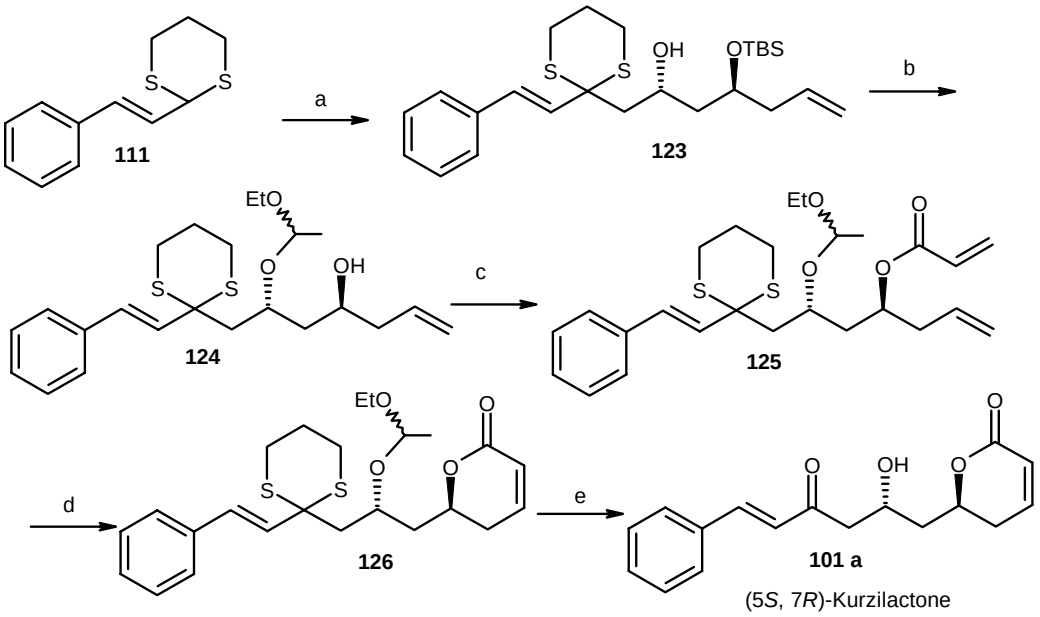
Scheme 21. *Reagents and conditions*: (a) H_2,$Ru(OAc)_2$[(*R*)-BINAP], EtOH, 40 kg/cm^2, 100 °C, 1.5 h, 94%; (b) (i) TBDMSCl, imidazole, DMAP, CH_2Cl_2, 24 h, 98%; (ii) $LiAlH_4$, Et_2O, 0 °C, 2 h, 91%; (iii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −60°C, 92%; (c) $HC(OEt)_3$, Amberlyst-15, CH_2Cl_2, rt, 48 h, 74%; (d) *n*-Bu_4NF, THF, 24 h, 60%; (e) (i) *n*-BuLi, $BF_3.Et_2O$, THF, 58%; (ii) TBSCl, imidazole, CH_2Cl_2, 81%; (f) 50% CF_3COOH, $CHCl_3$, 95%; (g) (i) ethylacetoacetate, NaH, THF; (ii) *n*-BuLi, -10 ^oC then -50 ^oC (h) $NaBH_4$, THF, 92%; (i) (i) *p*-TSOH, CH_2Cl_2, 53%; (ii) MsCl, Et_3N, CH_2Cl_2; (j) $HgClO_4$, $CaCO_3$, THF/H_2O, 5:1; (k) HF, CH_3CN, 58%.

Tae *et al.* (2006).[76]

Tae and co-workers synthesized kurzilactone **101** by using Jacobsen's hydrolytic kinetic resolution[69] as the key step. Thus epoxidation of 1,6-heptadien-4-ol **118** followed by TBS protection afforded compound (±)-**120** as a substrate for resolution. Epoxide (±)-**120** was resolved by using (*R*,*R*)-(-)-Co(salen) catalyst to get the epoxide (-)-**120** in high enantiomeric excess which was converted into the required epoxide (-)-**122** by using a four step sequence (Scheme 22). Reaction of (-)-**122** with acyl anion equivalent **111** afforded **123** which was protected as ethylvinyl ether (EVE) to give **124**. Removal of the TBS group followed by esterification with acryloyl chloride and ring-closing metathesis[51] afforded lactone **126** which on global deprotection furnished target molecule (5*S*, 7*R*)-kurzilactone **101** (Scheme 23).



Scheme 22. *Reagents and conditions*: (a) (i) *n*-BuLi, THF, CO_2 then I_2; (ii) 1N KOH, THF, *n*-Bu_4NI, 99%; (b) TBSCl, imidazole, DMF, 97%; (c) **92b**, H_2O.



Scheme 23. *Reagents and conditions*: (a) (+)-**122**, *n*-BuLi, $BF_3.Et_2O$, THF, -78 ^oC, 54%; (b) (i) EVE, PPTS, CH_2Cl_2, 84%; (ii) TBAF, THF, 99%; (c) Acryloyl chloride, Et_3N, CH_2Cl_2, 75%; (d) Grubbs' 2nd generation catalyst, CH_2Cl_2, 8 h, 95%; (e) (i) 0.5 N HCl-THF (1:1), rt, 1 h, 99%; (ii) $AgNO_2$, I_2, THF-H_2O (5:1), 4 h, 62%.

3.2.3. Present work:

Objective:

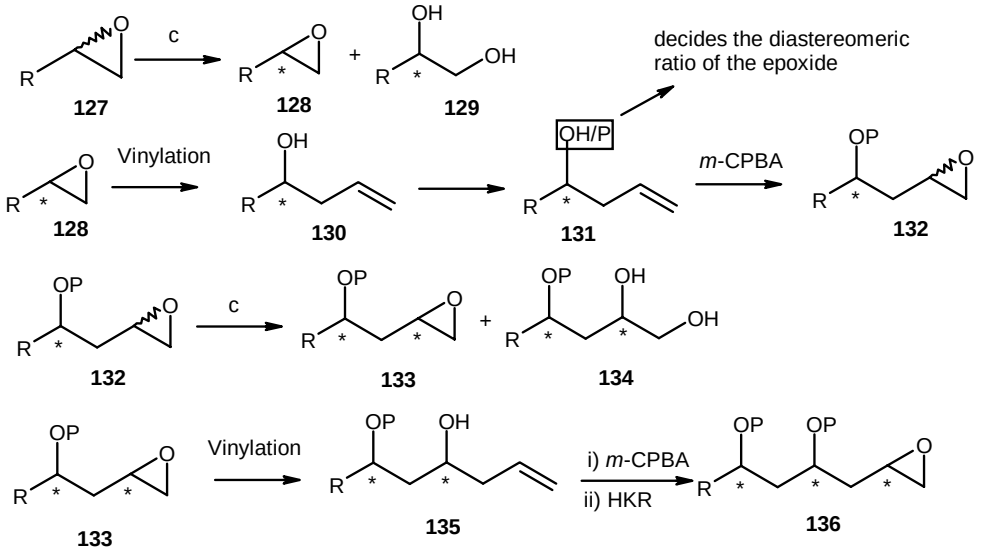
1,3-Diol subunits are present in numerous biologically active natural products and pharmaceuticals.[77] As a result, a large effort has been devoted to the development of methods for the stereoselective synthesis of 1,3-diols.[78] Common procedures developed to date rely on chiral pool strategies or asymmetric reaction methodologies for the introduction of the first asymmetric centers in these substances. Installation of the second asymmetric centers is typically orchestrated by the initial hydroxyl group by using various 1,3-*syn*- or *anti*-selective ketone reduction methods.

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,[79] a wide variety of synthetic methods are utilized[80] and the following asymmetric reactions are mainly used for 1,3-polyol syntheses: chiral auxiliary controlled aldol reaction,[81] allylboration using chiral borane reagents,[82] catalytic asymmetric epoxidation of allylic alcohols[83] or unfunctionalized olefins,[84] catalytic asymmetric hydrogenation,[85] catalytic asymmetric Mukaiyama type aldol reaction,[86] and catalytic asymmetric dihydroxylation.[87] 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[88] have been developed that mainly rely on 1,3-syn[89]or anti[90]-selective ketone reduction using borane reagents, intramolecular addition of the acetal to olefins,[91] inter- or intramolecular addition of silyl reagents to olefins such as hydrosilylation,[92] and intramolecular allylsilylation to carbonyl groups.[93] 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),[94]allyl addition using chiral borane or titanium reagents (category b),[95] and catalytic asymmetric epoxidation of allylic alcohols (category c)[96] are commonly used for 1,3-polyol synthesis. Employing these strategies, many polyene macrolide antibiotics, such as amphotericin B,[97] mycoticin A,[98] roxaticin,[99] roflamycoin,[100] dermostatin,[101] and 1,3-polyol/a-pyrones[102]were synthesized in a highly stereocontrolled manner.[103]

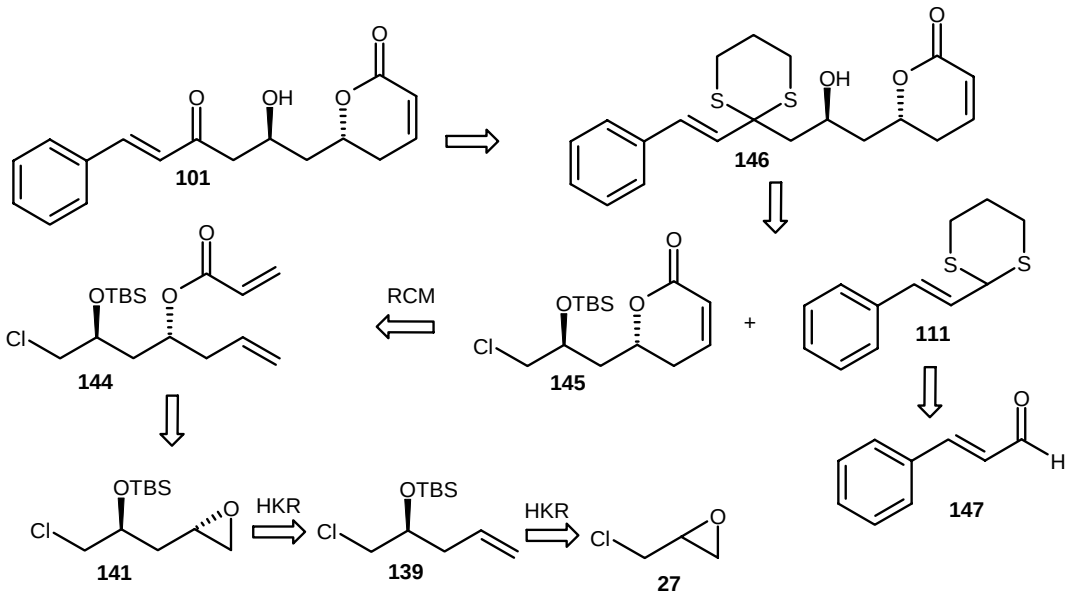
To synthesize not only 1,3-polyol natural products, but also their analogues, a highly versatile synthetic method that makes all possible stereoisomers freely accessible with the same efficiency is required. Herein we describe our successful endeavors towards development of a general and practical route for 1,3-polyols.

Scheme 24 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[69] 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 **127** using Jacobsen's catalyst **92a**, **92b** (Fig. 4). The ring opening of chiral epoxide **128**, thus obtained, with vinylmagnesium bromide would provide the homoallylic alcohol **130** as precursor for the epoxidation and subsequent HKR. The homoallylic alcohol **130** can then be subjected to epoxidation with *m*-CPBA to get a mixture of diastereomeric epoxide **132**. 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 **133** 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 24. General synthetic strategy to the synthesis of 1,3-polyols.

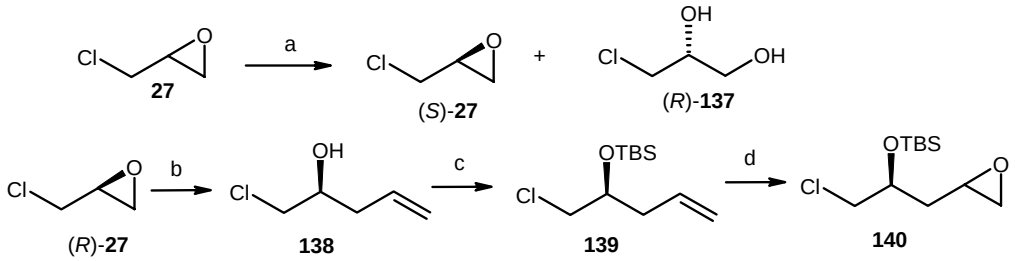
Our retrosynthetic strategy for the synthesis of **101** is outlined in Scheme 25. We envisioned that introduction of keto fragment could be achieved by opening of epoxide or substitution of halide by an acyl anion equivalent. The lactone moiety could be constructed by ring closing metathesis of an acrylate ester **144**, which in turn could be obtained from epoxide **141**. The epoxide **141** could be prepared from homoallylic alcohol **139** via hydrolytic kinetic resolution which in turn could be prepared from epichlorohydrin **27**.



Scheme 25. Retrosynthetic analysis for Kurzilactone

3.2.4. Results and Discussion:

Our synthesis of **101** requires two major reactions, Jacobsen's hydrolytic kinetic resolution, to install the stereogenic centers, and ring-closing metathesis to construct the δ-lactone moiety. As shown in Scheme 26, commercially available epichlorohydrin **27** was subjected to Jacobsen's HKR by using (*R*,*R*)-Salen-Co-OAc catalyst **92a** (Figure 4) to give (*S*)-epichlorohydrin[104] **(*S*)-27** as a single isomer, $[\alpha]_D^{25}$: +30.6 (*c* 1.2, MeOH); lit.[68a] for (*R*)-epichlorohydrin $[\alpha]_D^{25}$: –32.8 (*c* 1.27, MeOH), which was easily isolated from the more polar diol **(*R*)-137** by distillation.

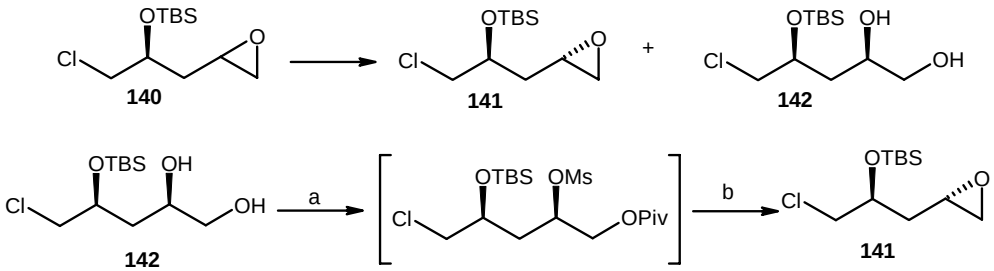


Scheme 26. *Reagents and conditions*: (a) *R*,*R*-salen-Co-(OAc) (0.5 mol%), dist. H_2O (0.55 eq), 0 ^oC, 14 h, [46% for (*R*)-**137**, 45% for (*S*)-**27**]; (b) vinylmagnesium bromide, ether, CuI, −73 to −40 ^oC, 19 h, 70%; (c) TBDMS-Cl, imidazole, CH_2Cl_2, 0 ^oC to rt, 4 h, 98%; (d) *m*-CPBA, CH_2Cl_2, 0 ^oC to rt, 10 h, 88%.

Epoxide (*S*)-**27** was opened with vinylmagnesium bromide in presence of cuprous iodide to give the homoallylic alcohol **138**. The ^1H NMR spectrum of **138** indicated absence of epoxide peakes, peaks due to olefinic protons appeared at δ 5.08-5.19 (multiplet, two protons) and 5.74-5.87 (multiplet, one proton). The IR spectrum of **138** gave broad hydroxyl absorption at 3400 cm^{-1}. Protection of hydroxyl group of **138** as TBS ether by using TBSCl and imidazole afforded **139**. The IR spectrum of **139** showed absence of hydroxy absorption. Epoxidation of olefin **139** with *m*-CPBA afforded epoxide **140** with a mixture of diastereomers. The ^1H NMR spectrum of **140** 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), 3.07-3.08 (multiplet, 1/3 proton) in ^1H 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. With epoxide **140** (*syn*: *anti*/1:3) 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-diol moiety. Towards this end, the epoxide **140** 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 **141** as a single stereoisomer (determined from the ^{1}H and ^{13}C NMR spectral analysis) (Figure 6) in 46% yield and the diol **142** in 45% yield. Epoxide **141** could easily be separated from the more polar diol **142** through silica gel column chromatography.

In order to achieve the synthesis of target molecule **101**, we required epoxide **141** in substantial amount. As the HKR method provided the desired epoxide **141** along with diol **142** 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.[104,] Accordingly, chemoselective pivalation of diol **142** with pivaloyl chloride followed by mesylation of the secondary hydroxyl and treatment of the crude mesylate product with K_2CO_3 in methanol led to deprotection of the pivaloyl ester. Concomitant ring closure via intramolecular S_N2 displacement of the mesylate furnished the epoxides **141** in 62% overall yield (Scheme 27).



Scheme 27. (a) *S*,*S*-Salen-Co-(OAc) (0.5 mol%), dist. H_2O (0.55 eq), THF, 0 ^{o}C, 24 h, (46% for **141**, 45% for **142**); (b) (i) PivCl, Et_3N, Cat. DMAP, rt, 2 h; (ii) MsCl, Et_3N, DMAP, 0 ^{o}C to rt, 1h; (c) K_2CO_3, MeOH, rt, overnight, (62% for three steps).

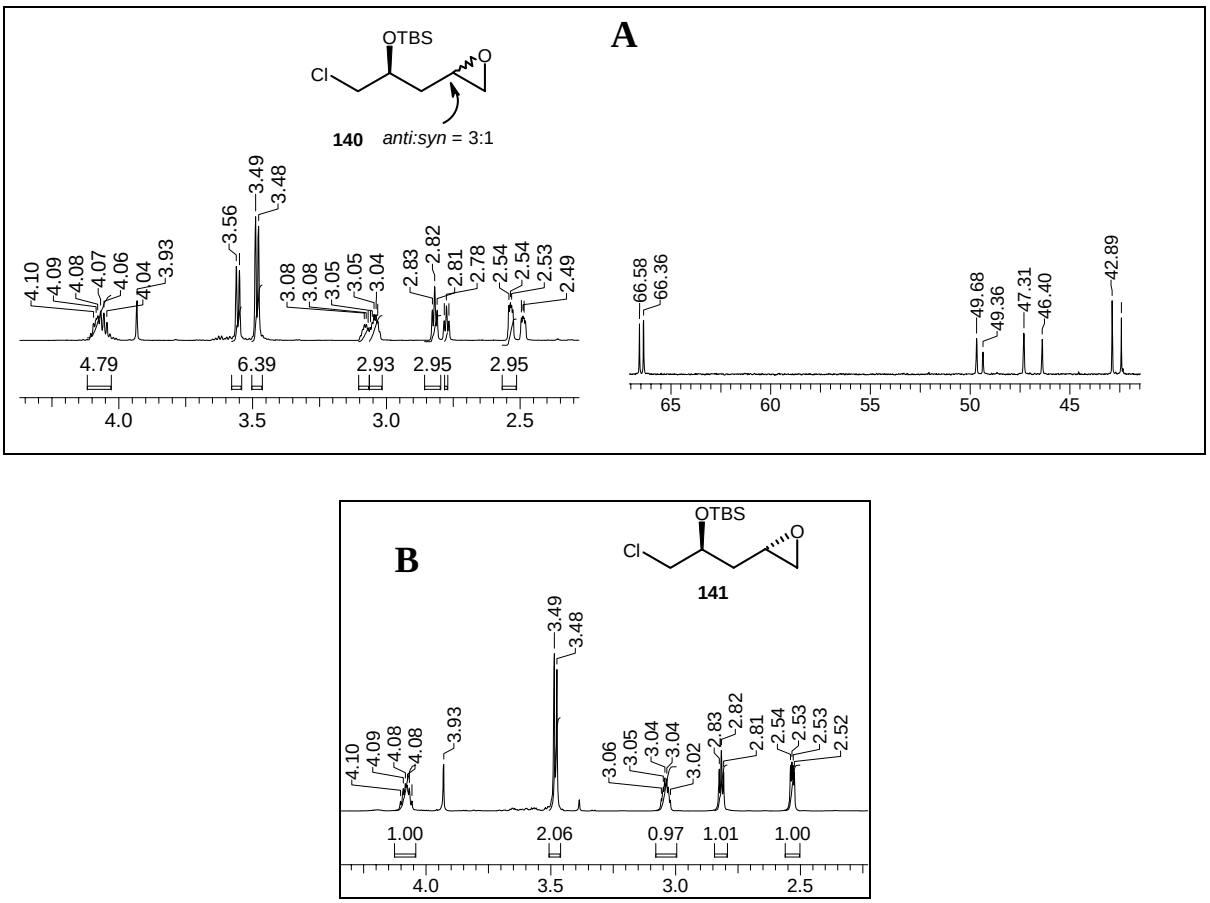
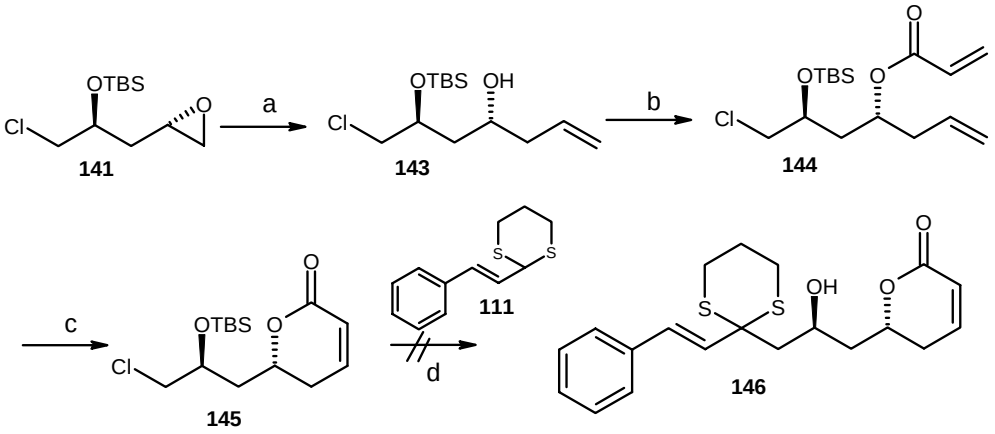


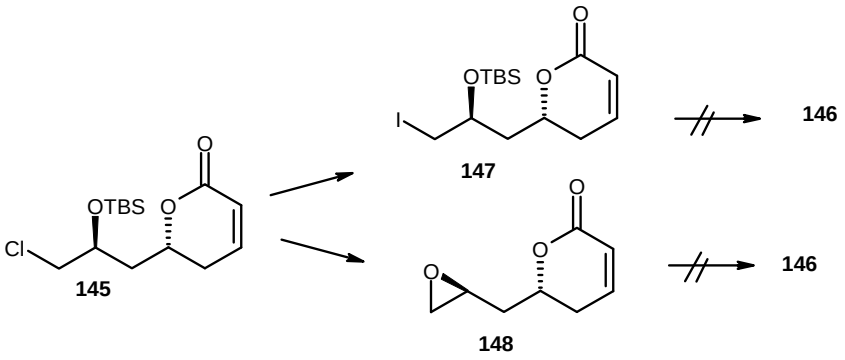
Figure 6: (**A**) Partial ^{1}H NMR and ^{13}C NMR spectra of diastereomeric mixture (3:1) **140**. (**B**) Partial ^{1}H NMR spectra of pure diastereomer **141**.

With substantial amount of **141** in hand, we further proceeded for the synthesis of **101** by opening of epoxide **141** with vinylmagnesium bromide in the presence of CuI in THF at –20 ^{o}C to give the homoallylic alcohol **143** in 82% yield. The IR spectrum of **143** gave broad hydroxyl absorption at 3460 cm^{-1}. Alcohol **143** was then esterified with acryloyl chloride to afford the acryloyl ester **144** in 86% yield. The IR spectrum of **144** indicated absence of hydroxyl group, acryloyl carbonyl appeared at 1718 cm^{-1}. The carbonyl carbon appeared at δ 165.4 in the ^{13}C NMR spectrum. Subsequent ring closing metathesis of the ester with commercially available Grubbs' 1st generation catalyst[69] (10 mol%) in the presence of Ti(*i*-PrO)$_4$ (0.03 eq) in refluxing CH_2Cl_2 for 8 h afforded the α,β-unsaturated δ-lactone **145** in 80% yield, $[\alpha]_D^{25}$ –92.6 (*c* 0.84, $CHCl_3$). The IR spectrum of **145** showed characteristic carbonyl group absorption of α,β-unsaturated δ-lactone at 1722 cm^{-1}. The

olefin protons appeared at 6.92 (doublet of triplet) with J = 9.6, 2.1 Hz and 6.02 (doublet of triplet) with J = 9.6, 1.6 Hz in the ^{1}H NMR spectrum. The olefinic carbons appeared at δ 145.0 and 121.3 in ^{13}C NMR spectrum. After completing the synthesis of lactone moiety our next aim was to substitute chloride with the acyl anion equivalent. The reaction of lactone **145** with acyl anion equivalent, generated from the thioacetal **111** in presence of *n*-BuLi could not afford the required product **146** to complete the synthesis of target molecule (Scheme 28). All efforts to get the required product by changing substrate (iodo, epoxide) and reaction conditions were unsuccessful (Scheme 29).

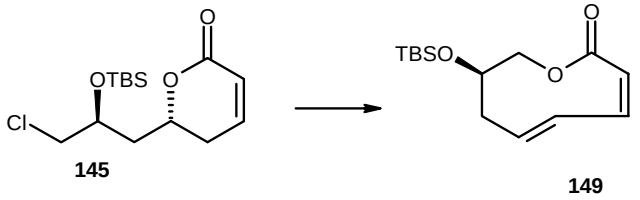


Scheme 28. (a) Vinylmagnesium bromide, THF, CuI, -20 ^{o}C, 1 h, 82%; (b) Acryloyl chloride, Et_3N, CH_2Cl_2, 0 ^{o}C to rt, 5 h, 86%; (c) $(PCy_3)_2Ru(Cl)_2$=CH-Ph (20 mol%), CH_2Cl_2, Ti(*i*PrO)$_4$ (0.03 eq.), reflux, 6 h , 80%; (d) **111**, *n*-BuLi, $BF_3.Et_2O$, THF.



Scheme 29.

On careful examination of the spectroscopic data we found that the product obtained was the rearrangement product **149** as shown below in Scheme 30.



145 149

Scheme 30. (a) *n*-BuLi, $BF_3.Et_2O$, THF.

3.2.5. Conclusion

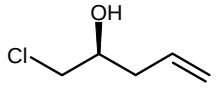
In conclusion, a practical and efficient strategy has been developed for the syntheses of 1,3-polyols/5,6-dihydropyran-2-ones. The synthetic protocol has been utilized for the synthesis of kurzilactone in which all the stereocenters were established by hydrolytic kinetic resolution and lactone moiety has been achieved by ring closing metathesis. The introduction of lactone moiety was a failure. Thus completion of the synthesis of kurzilactone could not be achieved.

3.2.6. Experimental Section

(*S*)-Epichlorohydrin [(*S*)-27]. The racemic epichlorohydrin (±)-**27** was resolved to chiral epoxide (*S*)-**27** in high enantiomeric excess by the HKR method following a literature procedure.[11d]

$[\alpha]_D^{25}$: +30.6 (*c* 1.2, MeOH); lit.[68a] for (*R*)-epichlorohydrin $[\alpha]_D^{25}$ –32.8 (*c* 1.27, MeOH)

(*S*)-1-Chloropent-4-en-2-ol (138).



138

A round bottomed 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 ^oC and vigorously stirred, and vinylmagnesium bromide (1M in THF, 216 mL, 216.16 mmol) was injected to it. A solution of (*S*)-epichlorohydrin (*S*)-**27** (10 g, 108.08 mmol) in diethyl ether (20 mL) was added slowly to the above reagent, and the mixture was stirred at –73 ^oC to –40 ^oC 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 **138** which on vacuum distillation provided homoallylic alcohol **138** as a colorless liquid.

Yield: 9.12 g (70%).

Mol. Formula: C_5H_9ClO

B.P: 66-69 ^oC/21 mm of Hg

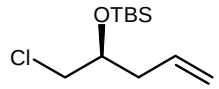
$[\alpha]_D^{25}$: +5.2 (*c* 1.4, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 3400, 3078, 2931, 2975, 1562, 1457, 1432, 1243, 1071, 914.

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.34 (t, *J* = 8.1 Hz, 2H), 3.50 (dd, *J* = 12.4, 7.1 Hz, 1H), 3.60 (dd, *J* = 12.1, 7.0 Hz, 1H), 3.85-3.90 (m, 1H), 5.08-5.19 (m, 2H), 5.74-5.87 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 38.4, 48.9, 70.4, 118.1, 133.2.

((*S*)-1-Chloropent-4-en-2-yloxy)(*tert*-butyl)dimethylsilane (139).



139

To a stirred solution of alcohol **138** (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 **139** as a colorless liquid.

Yield: 1.53 g (98%).

Mol. Formula: $C_{11}H_{23}ClOSi$

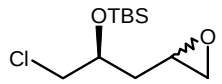
$[\alpha]_D^{25}$: +14.97 (*c* 0.42, $CHCl_3$).

^{1}H NMR (500 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), 3.88-3.91 (m, 1H), 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%.

(*S*)-1-Chloro-3-oxiran-2-yl(propan-2-yloxy)(*tert*-butyl)dimethylsilane (140).



140

To a stirred solution of olefin **139** (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 **140** as a colorless liquid in diastereomeric mixture (*anti*:*syn* = 3.0:1).

Yield: 1.01 g (88%).

Mol. Formula: $C_{11}H_{23}ClO_2Si$

$[\alpha]_D^{25}$: −8.79 (*c* 0.5, $CHCl_3$).

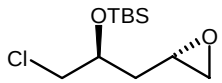
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.12 (s, 3H), 0.14 (s, 3H), 0.92 (S, 9H), 1.27-1.31 (m, 2H), 1.70-1.78 (m, 1H), 1.82-1.92 (m, 1H), 2.48-2.54 (m, 1H), 2.77-2.83 (m, 1H), 3.03-3.08 (m, 1H), 4.04-4.10 (m, 1H) (mixture of diastereomers).

^{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).

Compound 141 and 142.

A solution of epoxide **140** (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 **141** as a yellow color liquid. Continued chromatography with pet ether/EtOAc (3:2) provided the diol **142** as a brown color liquid as a single diastereomer.

((*S*)-1-Chloro-3-((*S*)-oxiran-2-yl)propan-2-yloxy)(*tert*-butyl)dimethylsilane (141).



141

Yield: 1.84 g (46%)

Mol. Formula: $C_{11}H_{23}ClO_2Si$

$[\alpha]_D^{25}$: −24.0 (*c* 0.52, $CHCl_3$).

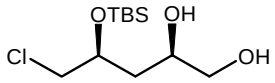
IR (neat, cm^{-1}): ν_{max} 3020, 2959, 2930, 1858, 1472, 1463, 1379, 1256, 1218, 1104, 1008, 940, 879, 760.

^{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 142.



142

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).

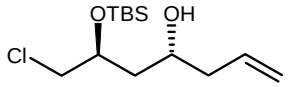
^{13}C NMR (50 MHz, $CDCl_3$): δ -5.1, -4.7, 17.7, 25.6, 41.1, 47.8, 66.3, 66.7, 68.9.

Analysis Calcd.: C, 49.14; H, 9.37; Cl, 13.19%; **Found:** C, 49.28; H, 9.19; Cl, 13.26%.

Conversion of 142 into 141: Diol **142** (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 **141** (1.15 g, overall yield 62%) as a yellow color liquid.

(4*R*,6*S*)-6-(*tert*-Butyldimethylsilyloxy)-7-chlorohept-1-en-4-ol (143).



143

A round bottomed flask was charged with copper (I) iodide (0.152 g, 0.8 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, 16.0 mL, 16.0 mmol) was injected to it. A solution of epoxide **141** (2.0 g, 7.99 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 **143** as a colorless liquid.

Yield: 1.83 g, 82%

Mol. Formula: $C_{13}H_{27}ClO_2Si$.

$[\alpha]_D^{25}$: −31.9 (*c* 0. 71, $CHCl_3$).

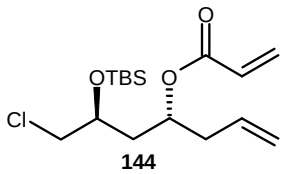
IR (neat, cm^{-1}): ν_{max} 3460, 2959, 2857, 1640, 1448, 1376, 1255, 1078.

^{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%.

Acrylic acid 1-[2-(*tert*-butyldimethylsilanyloxy)-3-chloropropyl]-but-3-enyl ester (144).



144

Acryloyl chloride (0.36 g, 0.32 mL, 3.94 mmol) was added dropwise under argon to a solution of **143** (1.1 g, 3.94 mmol) and triethylamine (1.6 g, 2.2 mL, 15.8 mmol) in dry CH_2Cl_2 (15 mL) at 0 ^oC. The mixture was stirred for 5 h 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 × 40 mL) and combined organic layer was washed with brine and dried (Na_2SO_4) and concentrated. Purification of the crude product by silica gel column chromatography using pet ether/EtOAc (19:1) as eluent afforded the acrylate **144** as a colorless oil.

Yield: 1.13 g, 86%

Mol. Formula: $C_{16}H_{29}ClO_3Si$

$[\alpha]_D^{25}$: +35.15 (*c* = 0.80 in $CHCl_3$)

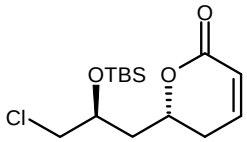
IR ($CHCl_3$, cm^{-1}): ν_{max} 3072, 2968, 2922, 2897, 2850, 2710, 2401, 1718, 1641, 1614, 1472, 1421, 1386, 1294, 1213, 1199, 911, 760.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.42 (dd, *J* = 17.3, 1.8 Hz, 1H), 6.16-6.08 (m, 1H), 5.85 (dd, *J* = 10.3, 2.1 Hz, 1H), 5.74-5.79 (m, 1H), 5.08-5.12 (m, 2H), 3.97-3.92 (m,1H), 3.51-3.35 (m, 3H), 2.43-2.37 (m, 1H), 2.11-1.58 (m, 3H), 0.89 (s, 9 H), 0.07 (s, 3H), 0.04 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.4, 132.9, 130.5, 128.6, 118.1, 70.4, 68.6, 48.6, 38.9, 25.7, 17.8, -4.53.

Analysis Calcd.: C, 57.72; H, 8.78; Cl, 10.65%; **Found:** C, 57.58; H, 8.64; Cl, 10.22%.

6-[2-(*tert*-Butyldimethylsilanyloxy)-3-chloropropyl]-5,6-dihydro-pyran-2-one (145).



145

Ist generation Grubbs' catalyst **92c** (0.124 g, 0.15 mmol) dissolved in CH_2Cl_2 (10 mL) was added dropwise to a refluxing solution of **144** (0.50 g, 1.50 mmol), Ti(*i*PrO)$_4$ (13 mg, 0.045 mmol) in dry CH_2Cl_2 (100 mL). Refluxing was continued for 8 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 (8:2) as eluent to afford **145** as a colorless oil.

Yield: 0.366 g, 80%

Mol. Formula: $C_{14}H_{25}ClO_3Si$

$[\alpha]_D^{25}$: +22.53 (*c* 0.68, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 3022, 2965, 2936, 2887, 2854, 1722, 1471, 1465, 1427, 1387, 1255, 1215, 1064, 975.

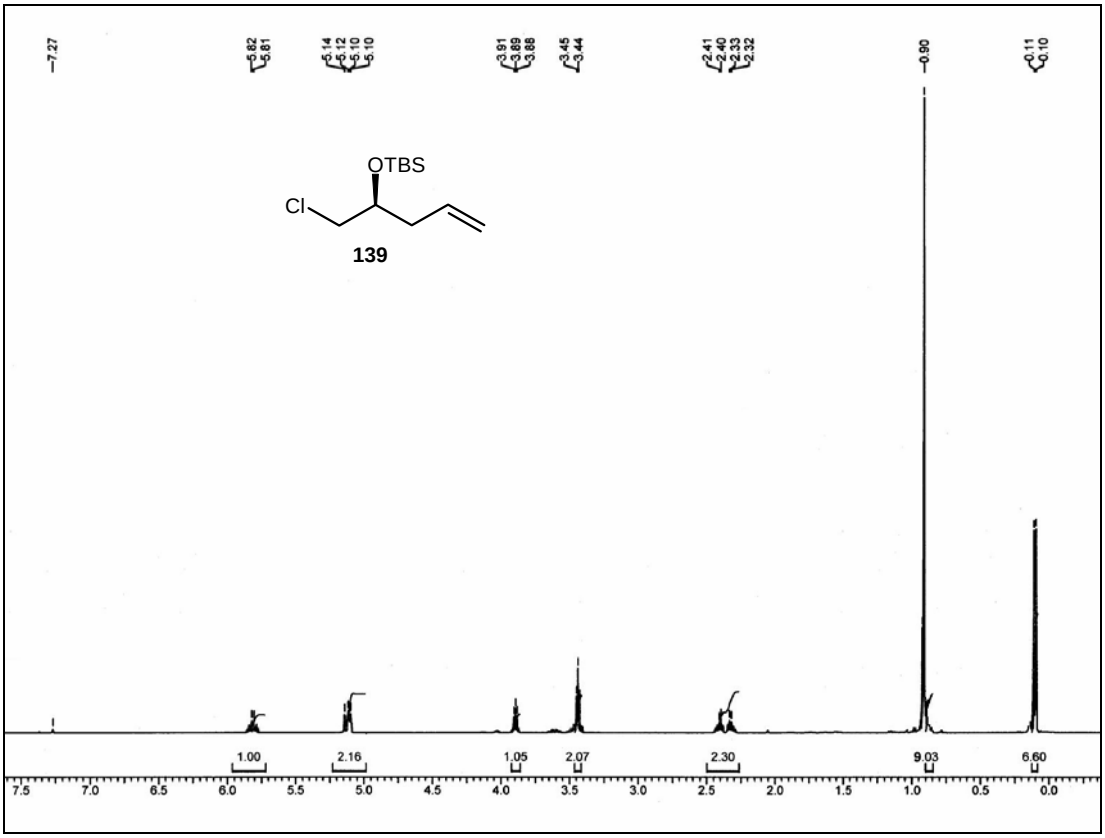
^{1}H NMR (200 MHz, $CDCl_3$): δ 6.92 (dt, *J* = 9.6, 2.1 Hz, 1H), 6.02 (dt, *J* = 9.6, 1.6 Hz, 1H), 4.53-4.68 (m, 1H), 4.25-4.31 (m, 1H), 3.41-3.51 (m, 2H), 2.33-2.39 (m, 2H), 1.85-2.07 (m, 1H), 1.74-1.84 (m, 1H), 0.89 (s, 9 H), 0.13 (s, 3H), 0.09 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 163.7, 145.0, 121.3, 73.9, 67.4, 48.9, 40.2, 29.8, 25.6, 17.8, -4.7, -4.95.

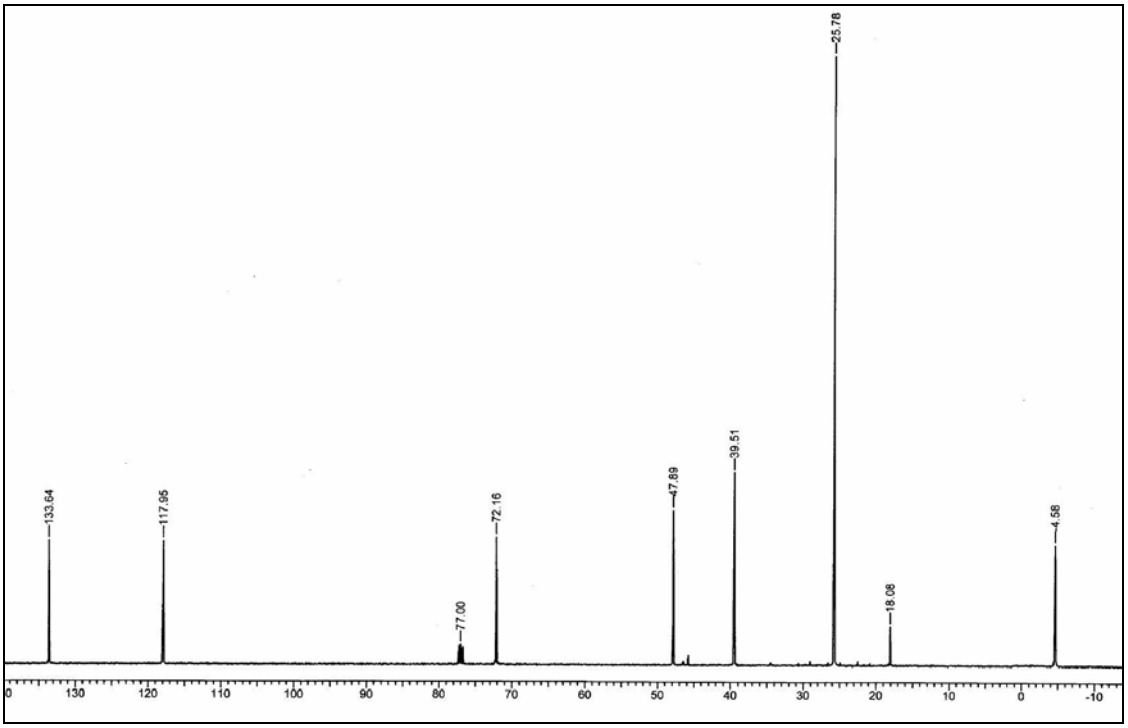
Analysis Calcd.: C, 55.15; H, 8.26; Cl, 11.63%; **Found:** C, 55.02; H, 8.36; Cl, 11.71.

3.2.7 Spectra

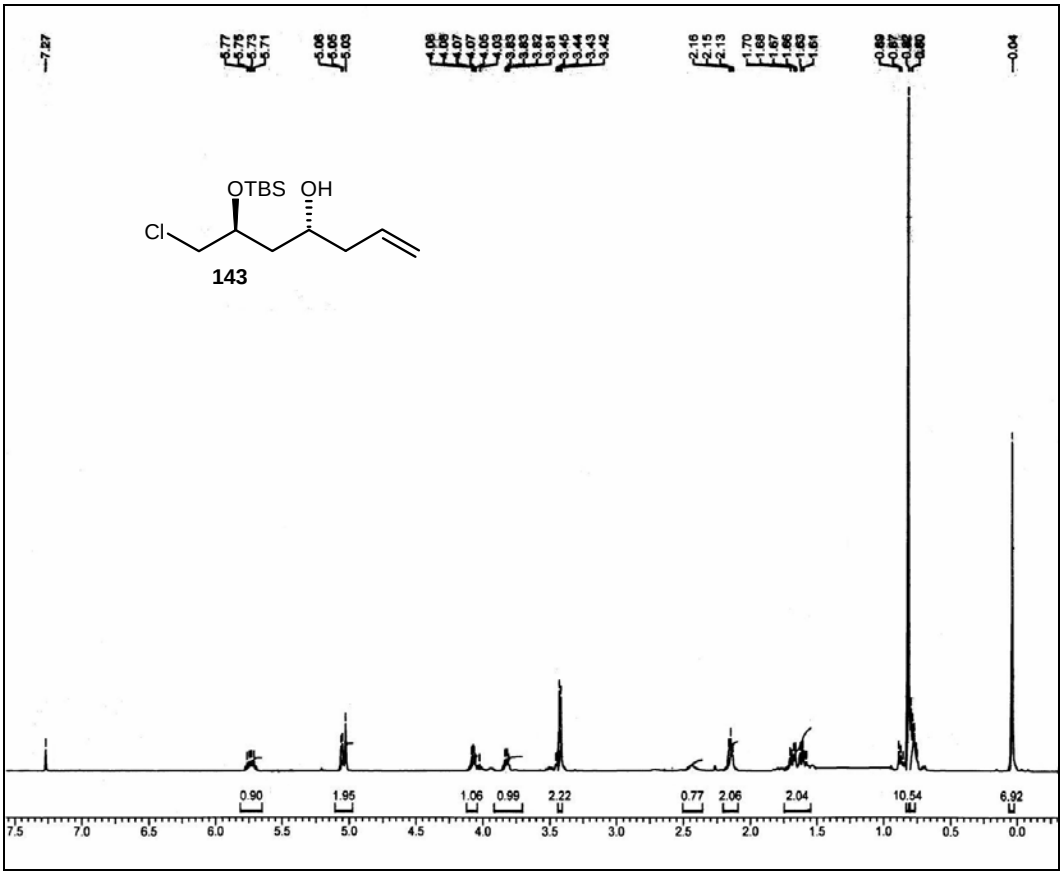
1. ^{1}H and ^{13}C NMR spectra of 139
2. ^{1}H and ^{13}C NMR spectra of 143
3. ^{1}H and ^{13}C NMR spectra of 144
4. ^{1}H and ^{13}C NMR spectra of 145



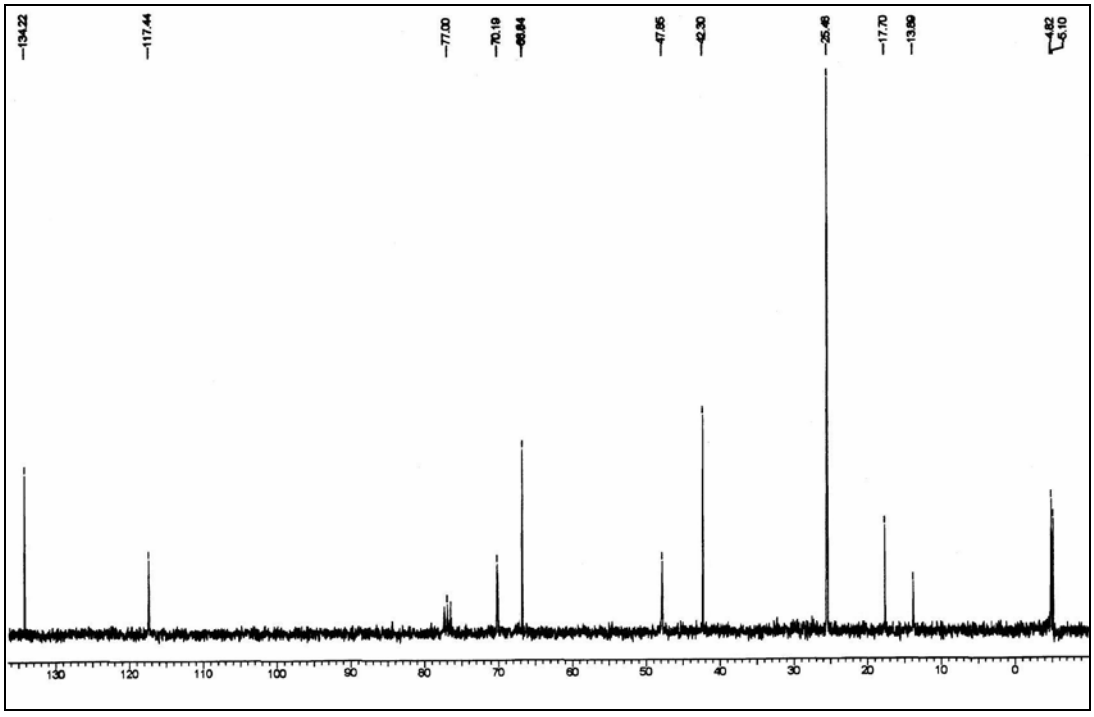
^{1}H NMR Spectrum of compound 139 in $CDCl_3$



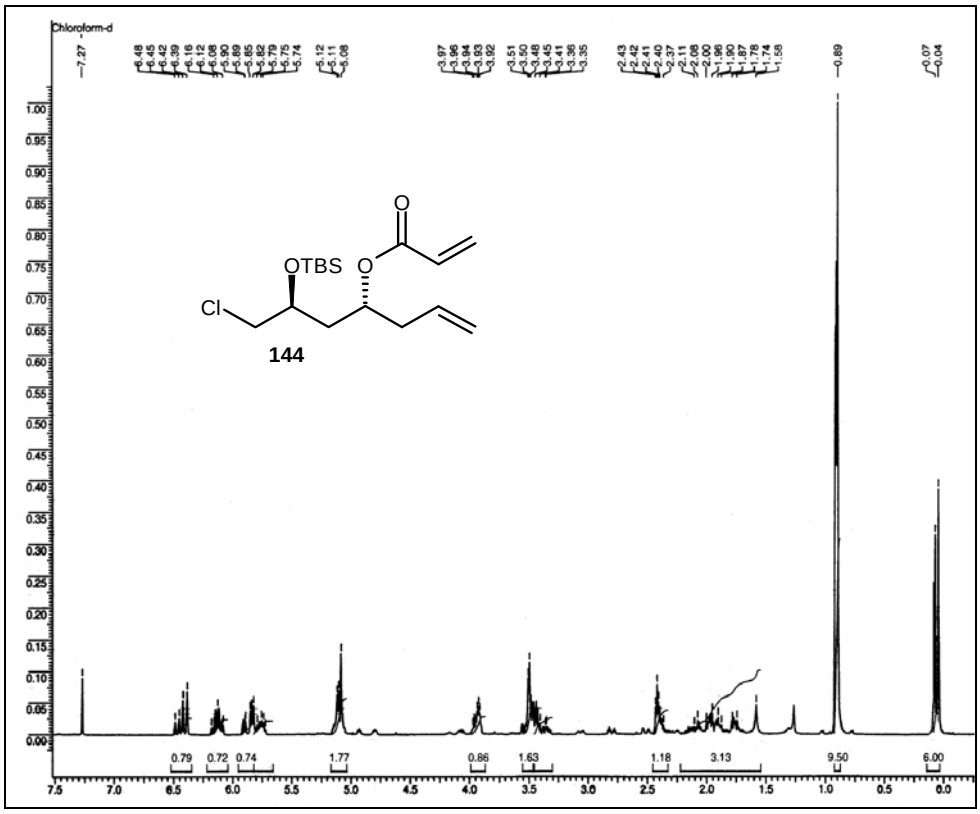
^{13}C NMR Spectrum of compound 139 in $CDCl_3$



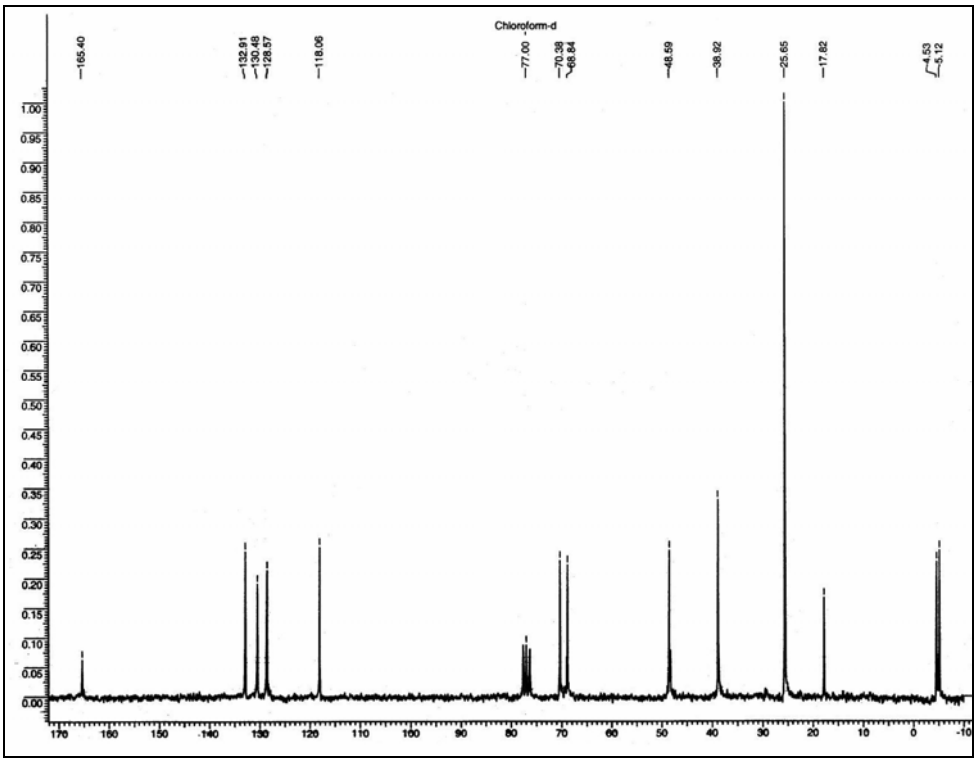
^{1}H NMR Spectrum of compound 143 in $CDCl_3$



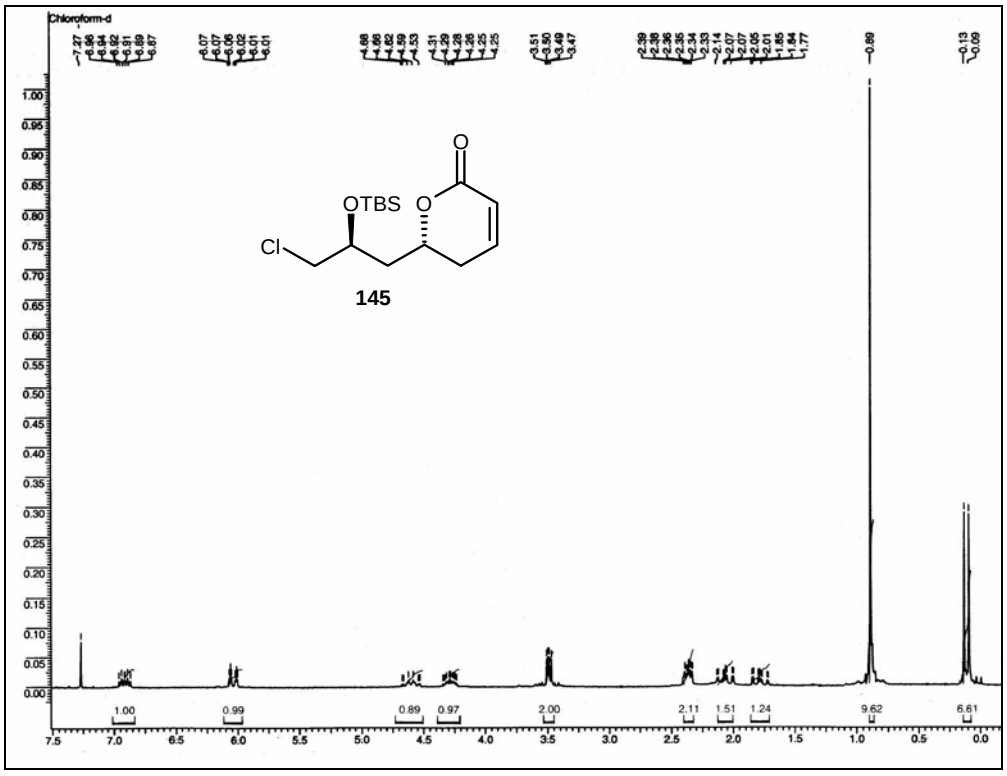
^{13}C NMR Spectrum of compound 143 in $CDCl_3$



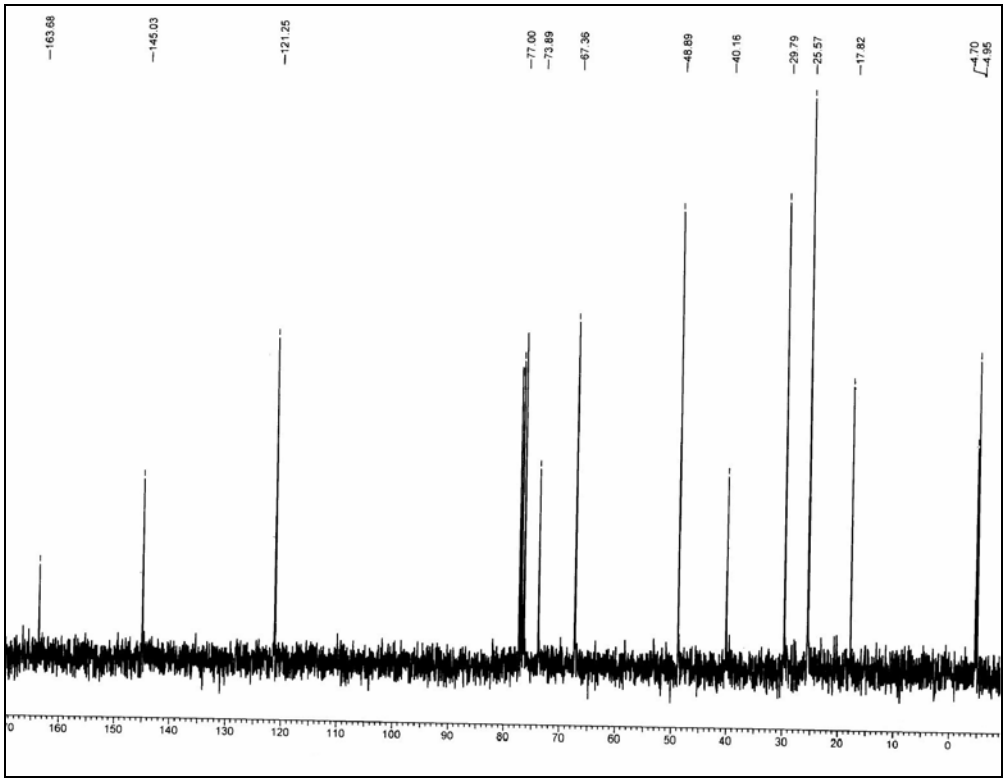
^{1}H NMR Spectrum of compound 144 in $CDCl_3$



^{13}C NMR Spectrum of compound 144 in $CDCl_3$



^{1}H NMR Spectrum of compound 145 in $CDCl_3$



^{13}C NMR Spectrum of compound 145 in $CDCl_3$

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CHAPTER 4

ENANTIOSELECTIVE SYNTHESIS OF 1,3-POLYOLS/5,6-DIHYDROPYRAN-2-ONE: TARCHONANTHUSLACTONE AND CRYPTOCARYA DIACETATE

4.1 SECTION A

ENANTIOSELECTIVE SYNTHESIS OF TARCHONANTHUSLACTONE

4.1.1. Introduction

Optically active *syn*- and *anti*-1,3-polyols/5,6-pyrones are ubiquitous structural motifs in various biologically active compounds[1] (Fig. 1). Fascinated by their broad range of biological activity and structural diversity in compounds ranging from simple carbohydrate to complex alkaloid and polyketides, synthetic chemists continue to pursue their synthesis[2] and the development of new methodologies. The lactone ring constitutes a structural feature of many natural products, particularly those that are Michael acceptors (α,β-unsaturated). They display pharmacological properties of interest such as plant growth inhibition as well as antifeedant, antifungal, antibacterial, and antitumor properties.[3,4] The simplest structure isolated which possesses a *syn*-1,3- diol/5,6-dihydropyran-2-one motif is the dihydrocaffeic ester, tarchonanthuslactone **1**. Some more complex examples of these structures are cryptocarya diacetate **2**, cryptocarya triacetate **3**, and passifloricin A **4**.

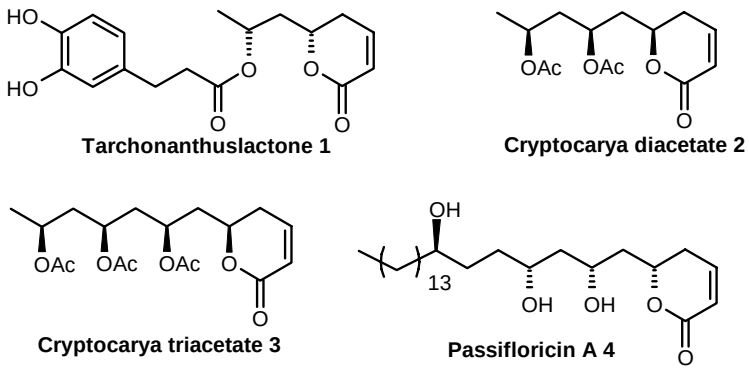


Figure 1

Tarchonanthuslactone was isolated by Bohlmann from *Tarchonanthustrilobus compositae*.[5] Caffeic acid has been established as an active principle, which lowers plasma glucose in diabetic rats.[6] The main structural features of tarchonanthuslactone (**1**) are a *syn*-1,3-diol and a 6-substituted 5,6-dihydro-α-pyrone subunit, which are present in various

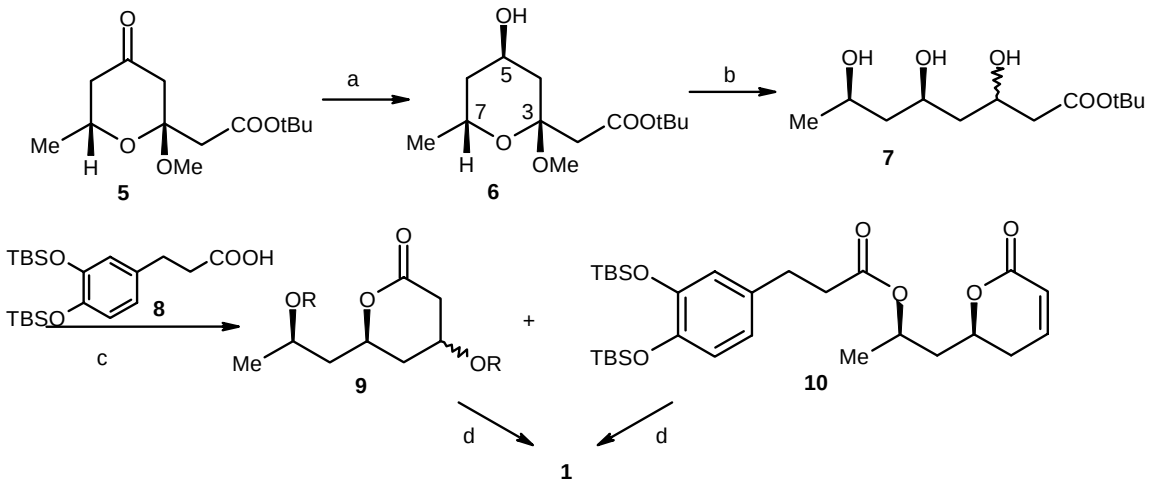
natural products with important biological activities. The absolute and relative stereochemistry of tarchonanthuslactone has been established by a combination of Mosher ester analysis and Rychnovsky ^{13}C NMR/acetonide analysis.[7] Later Nakata and co-workers confirmed its absolute configuration by carrying out its first asymmetric synthesis.[8]

4.1.2 Review of Literature

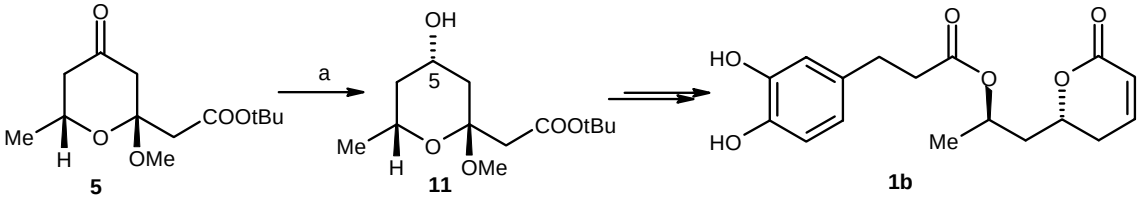
Various methods for the synthesis of tarchonanthuslactone **1** have been described in the literature. Nakata *et al.*[8] confirmed the stereochemistry of **1** via a multistep synthesis, starting with optically active 1,3-butanediol. Most of the approaches to the 1,3-diol system are based on either asymmetric methods such as 1,3-asymmetric reduction,[9] use of a chiral sulfoxide to induce the chirality,[10] chiral allylboration[11] and Sharpless asymmetric dihydroxylation[12] or enzymatic procedures.[13] A detailed report of these syntheses is described below.

Nakata *et al*. (1987).[8]

Nakata and co-workers assigned absolute configuration of tarchonanthuslactone by synthesizing both the isomers. Hydrolysis of hemiacetal group in **6**, prepared by **5** and successive reduction gave triol **7**, which after lactone formation was condensed with dihydrocaffeic acid **8**, yielded a mixture of **9** and **10**. Treatment of **10** with *n*-Bu_4NF gave the tarchonanthuslactone **1** (Scheme 1). To synthesize other isomer 5α-alcohol **11** was obtained by reduction of **5** with *n*-Bu_4NBH_4, followed by the similar transformation as discussed previously (Scheme 2).



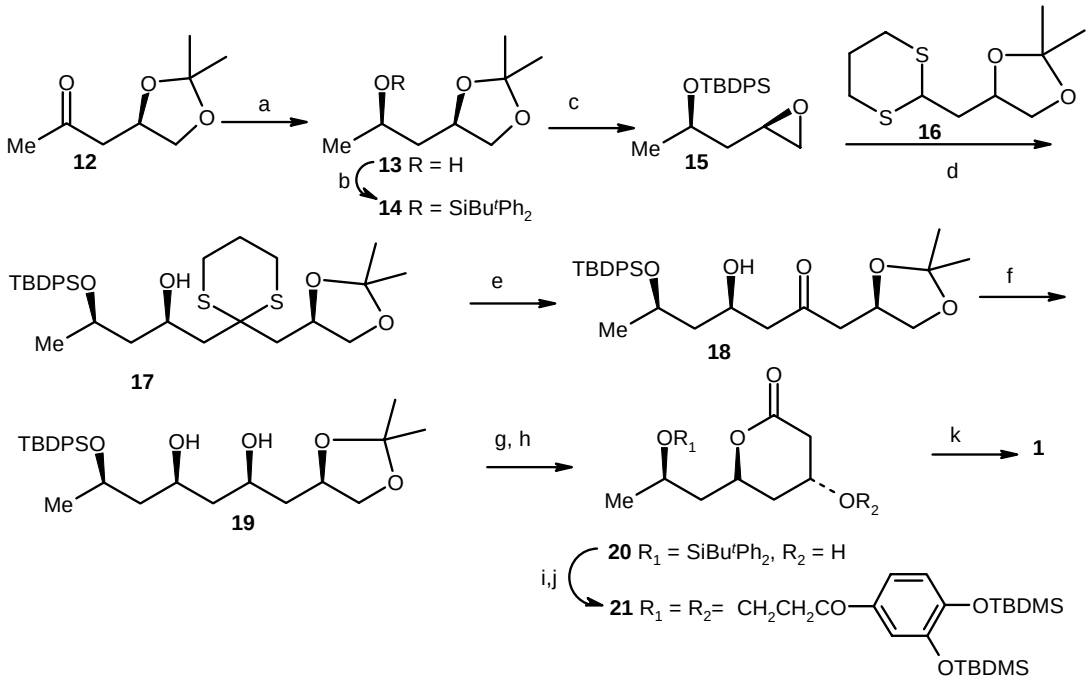
Scheme 1. *Reagents and conditions*: (a) K-Selectride, THF, -78 °C, 96%; (b) (i) 1N HCl, THF; (ii) $NaBH_4$, MeOH, 68% from both the steps; (c) (i) CSA, Benzene, 41%; (ii) **8**, $(EtO)_2POCl$, Et_3N, DMAP, MeCN; (d) *n*-Bu_4NF, THF, 54%.



Scheme 2. *Reagents and conditions*: (a) *n*-Bu_4NBH_4, aq. THF, 44%.

Mori *et al.* (1990).[9]

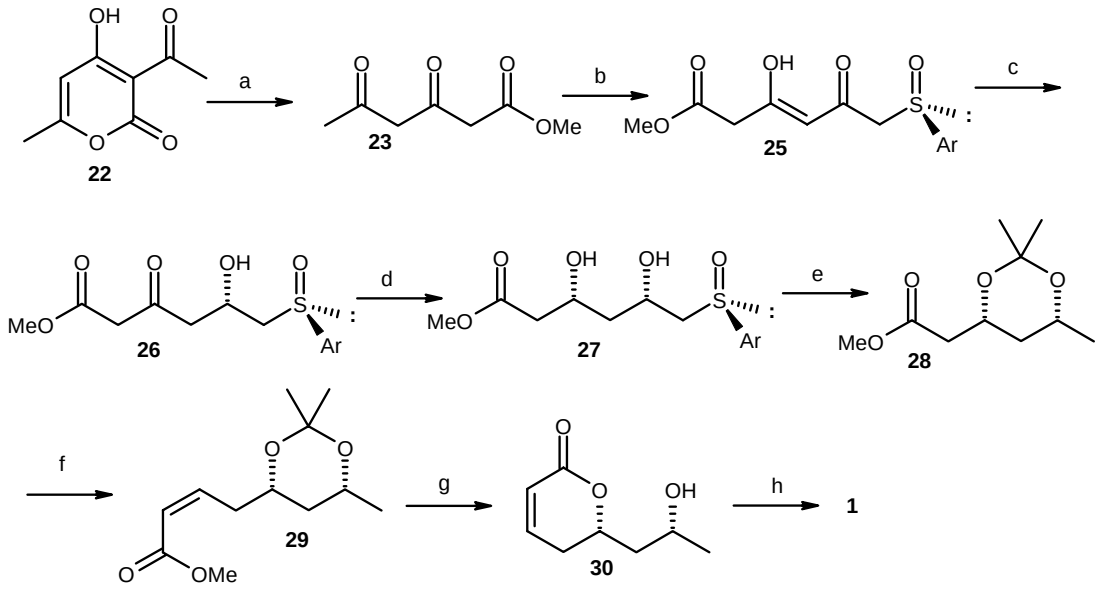
Mori and co-workers synthesized tarchonanthuslactone employing coupling reaction of a chiral dithiane with a chiral epoxide and highly *syn*-selective asymmetric reduction of the derived β-hydroxy ketone. The starting ketone 1**2** was prepared from 3(*S*)-3,4-isopropylidinedioxybutanal.[14] Reduction of ketone 1**2** with LAH in presence of LiI[15] afforded *syn*-triol derivative 1**3**, which was protected as silyl ether followed by transformation of acetonide group into an oxirane ring to afford the epoxide 1**5**. The coupling reaction of anion generated from dithiane 1**6** with epoxide 1**5** afforded dithiane 1**7**, which on deprotection of dithioacetal group with NBS[16] and subsequent reduction furnished the *syn*-diol derivative 1**9**. The acetonide was deprotected followed by oxidative cleavage of 1,2-diol moiety and subsequent oxidation of resulting lactol afforded the lactone **20**. Desilylation of lactone **20** followed by diesterification, base induced elimination and desilylation gave target molecule tarchonanthuslactone **1**.



Scheme 3. *Reagents and conditions*: (a) $LiAlH_4$/LiI, Et_2O, 0.5 h, 84%; (b) TBDPSCl, imidazole, DMF, 13 h, 92%; (c) (i) PPTS, Et_3N, MeOH, 4 h, 77%; (ii) TsCl, pyridine, 4.5 h, 89%; (iii) KH, Et_2O-CH_3OH (5:1), 1 h, 97%; (d) *n*-BuLi, THF, 40 h, 87%; (e) NBS, $AgNO_3$, aq. CH_3CN, 68%; (f) $LiAlH_4$/LiI, Et_2O, 0.5 h, 91%; (g) PPTS, Et_3N, MeOH, 4 h, 91%; (h) (i) $NaIO_4$, CH_3OH-H_2O, 20 min, 99%; (ii) MnO_2, EtOAc, 38 h, 87%; (i) TBAF, THF, benzoic acid, 12 h, 78%; (j) **8**, DCC, DMAP, CH_2Cl_2, 13 h, 77%; (k) (i) DBU, C_6H_6, 10 min, 98%; (ii) TBAF, THF, benzoic acid, 30 min, 96%.

Solladie *et al.* (1996).[10]

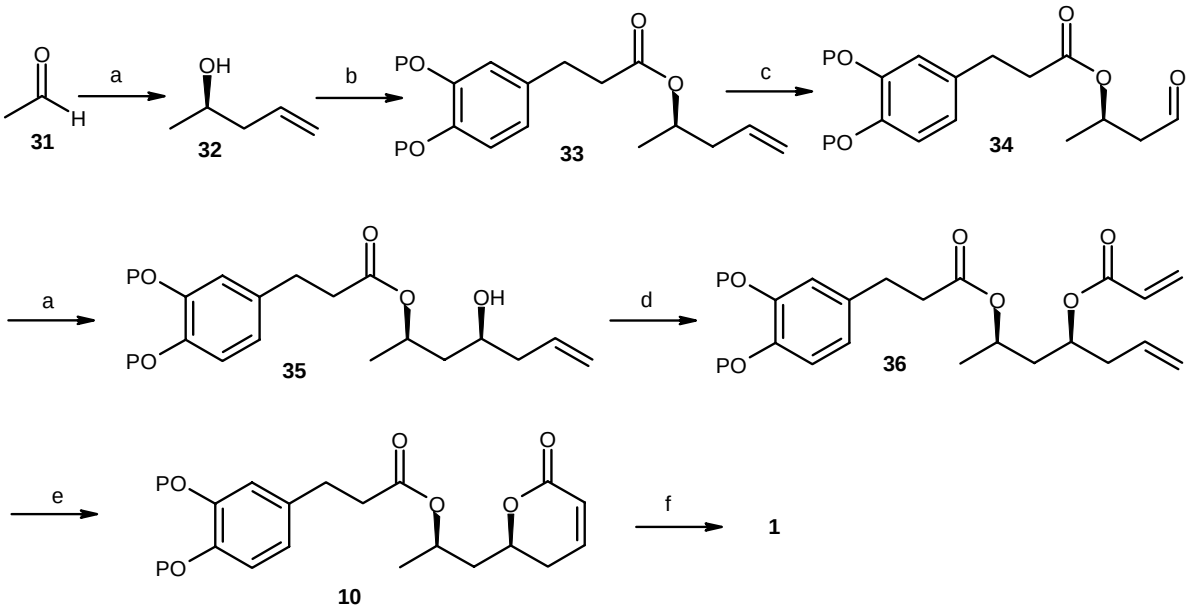
Solladie and co-workers synthesized tarchonanthuslactone employing stereoselective reduction of a β,δ-diketosulfoxide as a key step. As shown in Scheme 4 the diketoester **23** was obtained from dehydroacetic acid **22** by a known procedure.[17] Condensation of **23** with (-)-menthyl (*S*)-*p*-toluenesulfinate[18] **24** afforded (*R*)-diketosulfoxide **25** which on DIBAL reduction, followed by stereoselective reduction with $Et_2BOMe/NaBH_4$[19] gave *syn*-diol moiety **27**. Acetonide protection of **27** followed by ester reduction and subsequent Horner-Emmons type reaction with methyl bis-(trifluoroethyl)-phosphono acetate[20] afforded α,β-unsaturated ester **29**, which on hydrolysis, lactonization, coupling with TBS protected dihydrocaffeic acid, and desilylation gave the target compound **1**.



Scheme 4. *Reagents and conditions*: (a) $(MeO)_2Mg$, MeOH, 80%; (b) NaH, *t*-BuLi, **24**, THF, 70%; (c) DIBAL, THF, 44%; (d) Et_2BOMe, $NaBH_4$, THF, MeOH, −78 °C, 90%; (e) (i) $Me_2C(OMe)_2$, TsOH, acetone, rt, 94%; (ii) Raney Ni, MeOH, rt, 97%; (f) (i) DIBAL, hexane, −78 °C, 90%; (ii) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, KHMDS, 18-crown-6, THF, −65 °C, 84%; (g) (i) 0.1N HCl, MeOH, 86%; (ii) $ZnCl_2$, THF, 82%; (h) (i) **8**, DCC, DMAP, 83%; (ii) TBAF, THF, 82%.

Ramachandran *et al.* (2001).[11]

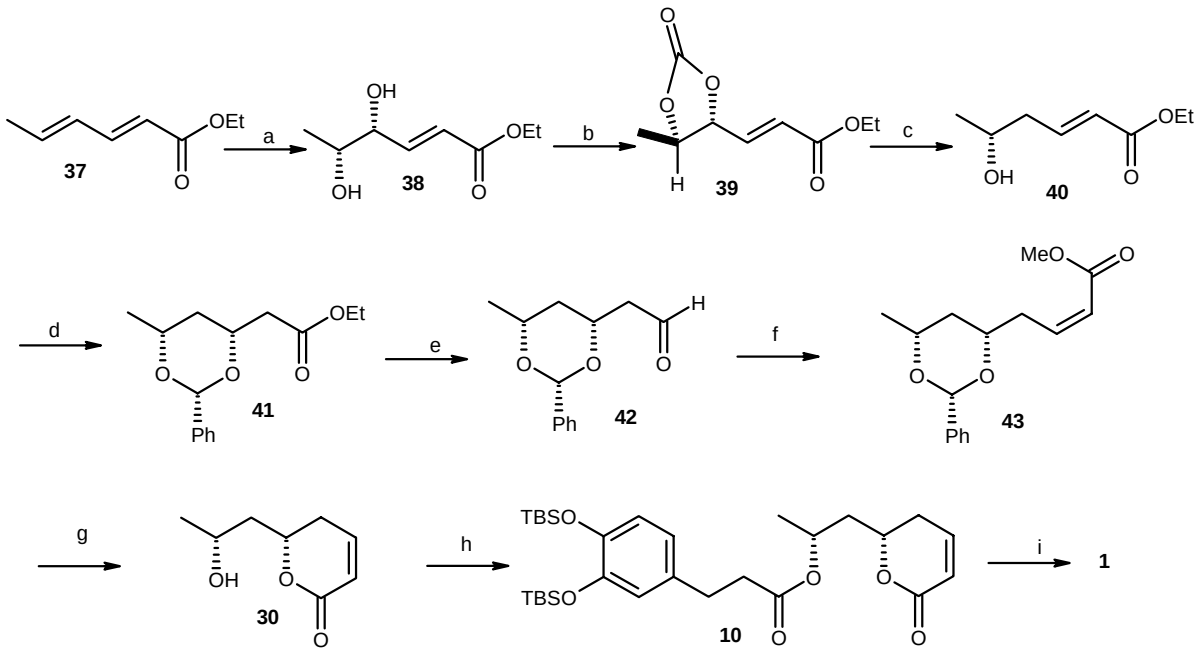
Ramachandran and co-workers reported the synthesis of tarchonanthuslactone by using asymmetric allylboration with *B*-allyldiisopinocampheylborane and ring-closing metathesis as the key steps. Asymmetric allylboration of **31** gave alcohol **32**, which on reaction with TBS protected dihydrocaffeic acid **8** followed by dihydroxylation and periodate cleavage furnished aldehyde **34**. The second allylboration of **34** followed by esterification and ring-closing metathesis[21] gave lactone **10**, which on TBS deprotection afforded the target molecule **1** (Scheme 5).



Scheme 5. *Reagents and conditions*: (a) $^{I}Ipc_2BAll$, ether-pentane, NaOH, H_2O_2, 71%; (b) **8**, DCC, CH_2Cl_2, 6 h, 81%, (c) OsO_4 (cat), Dioxane:H_2O (3:1), $NaIO_4$, rt, 77%; (d) Acryloyl chloride, Et_3N; (e) $(PCy_3)_2Ru(Cl)_2$=CH-Ph (20 mol%), CH_2Cl_2; (f) TBAF, THF, 80%.

Doherty *et al.* (2002).[12]

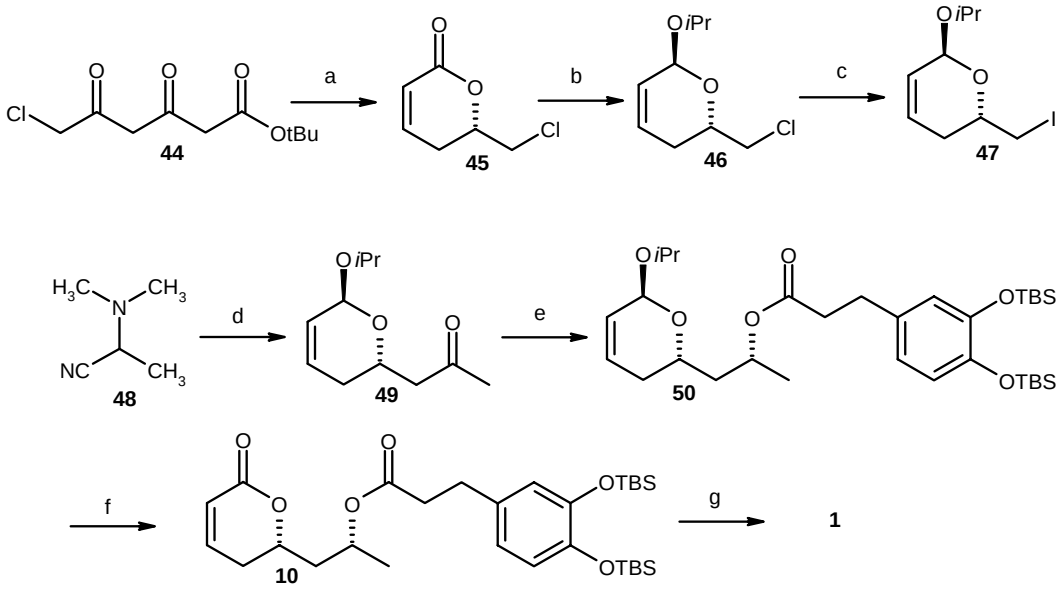
Doherty and co-workers accomplished the synthesis of tarchonanthuslactone by using the Sharpless asymmetric dihydroxylation,[22] palladium-catalyzed reduction[23] and a stereoselective base-catalysed acetal formation as the key step. Thus the asymmetric dihydroxylation of ethyl sorbate **37** followed by cyclic carbonate formation and palladium catalysed reduction gave the δ-hydroxy ester **40**, which on reaction with benzaldehyde furnished the 3,5-dihydroxy carboxylic ester **41**.[24] Ester **41** was converted into the *cis*-enoate **43** via reduction and Wittig reaction, which on benzylidene deprotection, cyclisation, coupling with TBS protected dihydrocaffeic acid **8** and TBS deprotection gave the target molecule **1** (Scheme 6).



Scheme 6. *Reagents and conditions*: (a) AD mix-β, 85%; (b) $(Cl_3CO)_2CO$, Py-CH_2Cl_2, 95%; (c) HCO_2H/Et_3N, 1% $Pd_2(dba)_3.CHCl_3$, PPh_3, THF, 66 ^oC, 92%; (d) PhCHO, *t*-BuOK, 64%; (e) DIBAL-H, 95%; (f) $(CF_3CH_2O)_2P(O)CH_2C(O)OCH_3$, KO*t*-Bu, 18-crown-6, -78 ^oC, 72%; (g) (i) $AcOH/H_20$; (ii) TsOH, PhH; (h) **8**, DCC, CH_2Cl_2, 3h, (i) TBAF, $PhCO_2H$, 85%.

Enders *et al.* (2003).[13]

Enders and co-workers accomplished the synthesis of tarchonanthuslactone employing the diastereoselective, chelation controlled reduction of methyl ketone. Chlorolactone **45**, prepared from *tert*-butyl 6-chloro-3,5-dioxohexanoate **44**, was converted into compound **47** via reduction, conversion of chloro into alcohol followed by conversion into iodo compound. **47** was reacted with α-amino nitrile **48** followed by hydrolysis to give methyl ketone **49**, which on chelation-control led *syn*-selective reduction with L-selectride[25] followed by coupling with TBS protected dihydrocaffeic acid **8** to afford the ester **50**. Oxidation of **50** followed by TBS deprotection gave the target molecule **1** (Scheme 7).

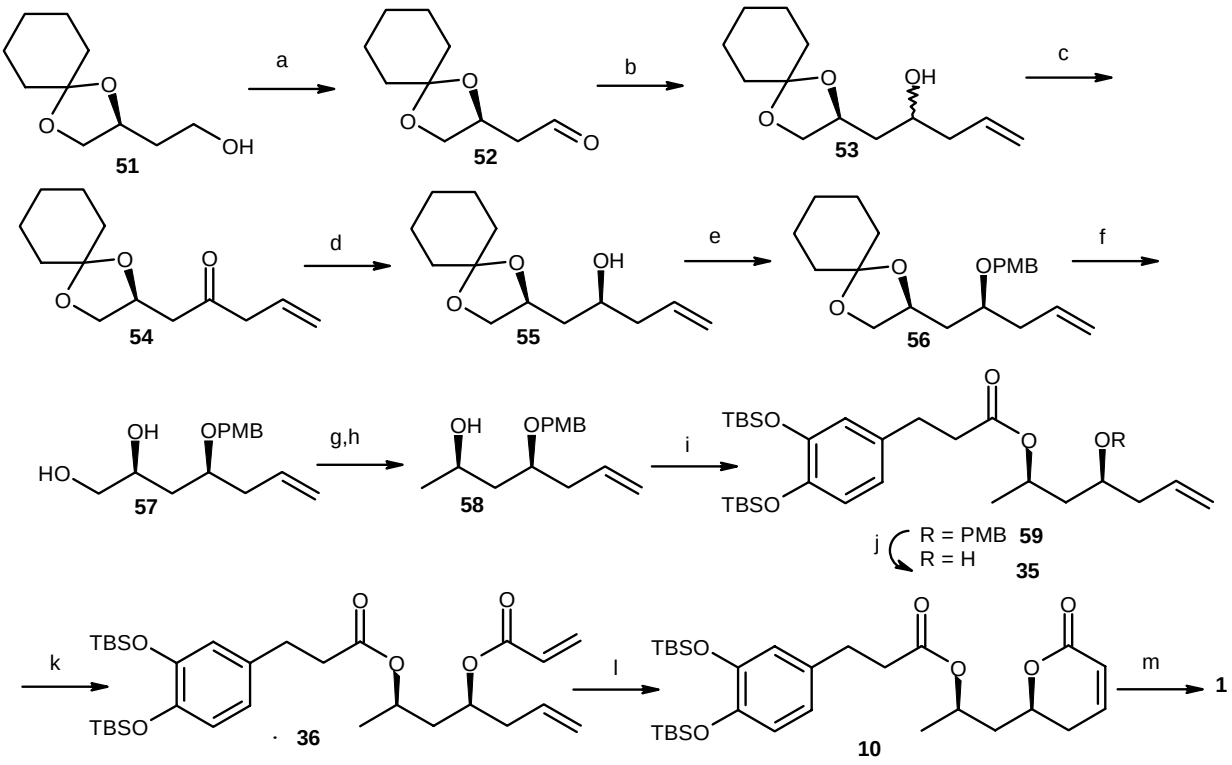


Scheme 7. *Reagents and conditions*: (a) (i) *rec* LBADH, cat. $NADP^+$, *i*PrOH, pH 5.5 buffer; (ii) $NaBH_4$, EtOH, 0 °C; (iii) cat. *p*TsOH, toluene, room temp., 14 h, 120 °C, 4 h; (b) (i) DIBAL-H, CH_2Cl_2, -78 °C; (ii) *i*PrOH, PPTS, C_6H_6, 80 °C; (c) (i) TBAA, NMP, 85 °C; (ii) K_2CO_3, MeOH, room temp.; (iii) PPh_3, imidazole, I_2, Et_2O/CH_3CN, 0 °C; (d) LDA, THF, 0 °C; **47**, -78 °C to room temp.; SiO_2; (e) (i) L-Selectride, CH_2Cl_2, -100 °C to room temp.; (ii) DCC, DMAP, **8**, CH_2Cl_2, room temp.; (f) PCC, CH_2Cl_2, room temp.; (g) TBAF, benzoic acid, THF, room temp.

Sabitha *et al.* (2005).[26]

Sabitha and co-workers accomplished the total synthesis of tarchonanthuslactone **1** employing two different routes.

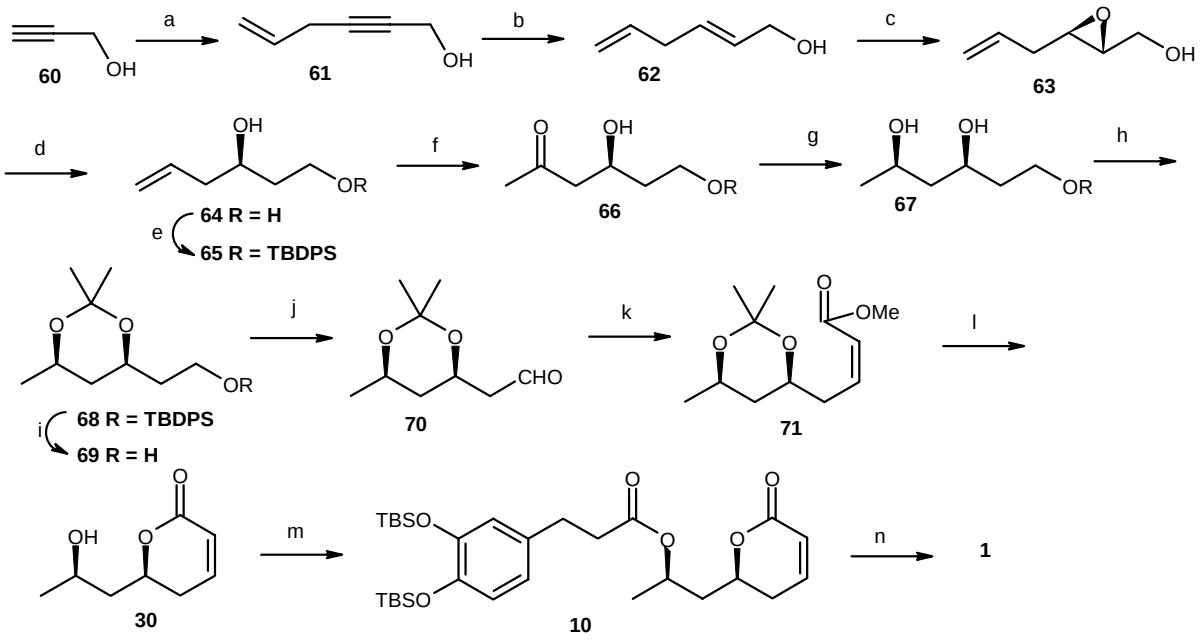
Route 1: In this approach they used $LiAlH_4$-LiI reduction and ring-closing metathesis as the key steps. They employed alcohol **51** as the starting material, which can be easily prepared from L-malic acid.[27] Thus, alcohol **51** was converted into keto compound **54** via oxidation, allylation and further oxidation. Compound **54** was converted into *syn*-diol derivative **55** *via* *syn*-stereoselective 1,3-asymmetric reduction using $LiAlH_4$-LiI. Protection of hydroxy group as PMB ether followed by acetonide deprotection furnished the diol **57**, which was converted into alcohol **58** by monotosylation and LAH reduction. Alcohol **58** was coupled with TBS protected dihydrocaffeic acid, followed by PMB deprotection, esterification and ring-closing metathesis to give compound **10**, which on desilylation afforded target molecule **1** (Scheme 8).



Scheme 8. Reagents and conditions: (a) IBX, DMSO, CH_2Cl_2, 3 h, 90%; (b) allyl bromide, Zn, THF, NH_4Cl, 4 h, 92%; (c) IBX, DMSO, CH_2Cl_2, 3 h, 85%; (d) $LiAlH_4$–LiI (3 equiv, 1:1), THF, -100 ^oC, ether, 94%; (e) NaH, PMBBr, THF, 87%; (f) PTSA, MeOH, 30 min, 0 ^oC, 90%; (g) TsCl, Et_3N, cat. DMAP, 3 h, CH_2Cl_2, 75%; (h) $LiAlH_4$, THF, rt, 3 h, 72%; (i) **8**, DCC, DMAP, DCM, 0 ^oC to rt, 2 h, 86%; (j) CH_2Cl_2:H_2O (9:1), DDQ, 2 equiv, rt, 2 h, 81%; (k) Acryloyl chloride, Et_3N, DMAP, 0 ^oC to rt, 2 h, 70%; (l) $(PCy_3)_2Ru(Cl)_2$=CH-Ph (10 mol %), CH_2Cl_2, rt, 3 h, 76%; (m) Oxone, aq MeOH, rt, 24 h, 80%.

Route 2: In another approach Sabitha and co-workers synthesized tarchonanthuslactone starting from propargyl alcohol by using Wacker oxidation and $LiAlH_4$-LiI reduction as key steps. Thus, alkylation of propargyl alcohol **60** and subsequent reduction followed by Sharpless asymmetric epoxidation[28] afforded **63**, which on reduction with RED-Al yielded diol **64**. Protection of hydroxy group as TBDPS ether followed by Wacker oxidation gave β-hydroxy ketone **66**, which was converted into *syn*-diol **67** using a LiI/$LiAlH_4$ protocol. Diol **67** was protected as acetonide, followed by desilylation and oxidation to afford the aldehyde **70**, which was subjected to Wadsworth-Emmons reaction to furnish *Z*-

unsaturated ester **71**. Deprotection of acetonide followed by lactonization afforded lactone **30**, which was coupled with TBS protected dihydrocaffeic acid followed by desilylation to afford target molecule **1** (Scheme 9).

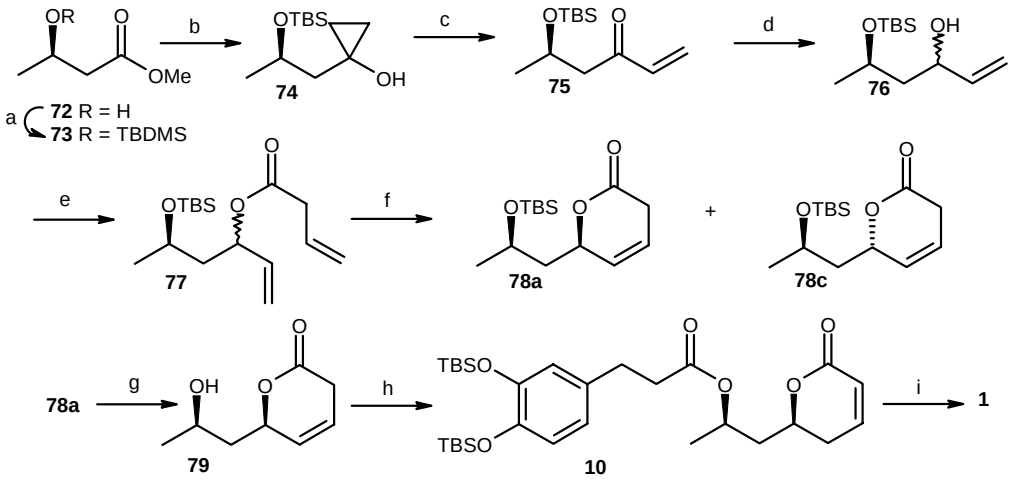


Scheme 9. *Reagents and conditions*: (a) (i) allyl bromide, Na_2CO_3/TBAI; (ii) CuI, DMF, rt, 82%; (b) $LiAlH_4$, THF, rt, 75%; (c) (i) (–)-DET, Ti(O-*i*-Pr)$_4$; (ii) TBHP, 4 A˚ MS; (iii) CH_2Cl_2, –20 ^oC, 82%; (d) Red-Al, THF, –15 ^oC to rt, 90%; (e) imidazole, TBDPSCl, CH_2Cl_2, 0 ^oC to rt, 1 h, 95%; (f) $PdCl_2$, CuCl, O_2, THF–H_2O (10:1) rt, 3–4 h, 65%; (g) $LiAlH_4$, LiI (1:1), Et_2O, –78 ^oC to rt, 1 h, 84%; (h) 2,2-DMP, PPTS, 12 h, 94%; (i) TBAF, THF, 1 h, 90%; (j) Dess–Martin periodinane, CH_2Cl_2, rt, 1 h, 88%; (k) $(CF_3CH_2O)_2P(O)CH_2COOCH_3$, NaH, THF, –80 ^oC, 0.5 h, 78%; (l) (i) 0.1 N HCl, MeOH, 86%; (ii) $ZnCl_2$, THF, 80%; (m) **8**, DCC, DMAP, 82%; (n) oxone, aq MeOH, rt, 24 h, 80%.

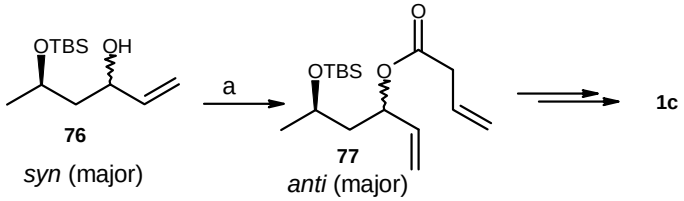
Singh *et al.* (2005).[29]

Singh and co-workers accomplished the synthesis of all the stereoisomers of tarchonanthuslactone from (*R*)-3-hydroxy butanoate employing the Kulinkovich reaction and ring-closing metathesis. Thus, (*R*)-3-hydroxy butanoate **72**[30] was protected as TBS ether and subjected to Kulinkovich reaction[31] with excess ethylmagnesium bromide followed by reaction with NBS in presence of Et_3N to afford α,β-unsaturated ketone **75**. Ketone **75** was subjected to Luche protocol[32] to obtain allylic alcohol **76**, in favor of *syn*-isomer, (*syn*:*anti* / 86:14), which was coupled with vinyl acetic acid followed by ring-

closing metathesis to furnish the lactone **78a**. The TBS group was removed followed by coupling of alcohol **79** with TBS protected dihydrocaffeic acid and subsequent elimination with DBU to give compound **10**, which on desilylation afforded target molecule **1** (Scheme 10). Alcohol **76** was subjected to Mitsunobu reaction,[33] followed by using the same reaction sequence to get the other diastereomer of tarchonanthuslactone (Scheme 11).

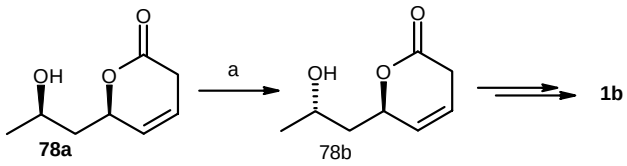


Scheme 10. *Reagents and conditions*: (a) TBDMSCl, imidazole, 0 ^{o}C; (b) Ti(O*i*-Pr)$_4$, EtMgBr, 20 ^{o}C, 87%; (c) NBS, Et_3N, 95%; (d) $NaBH_4$, $CeCl_3$, 91%; (e) vinyl acetic acid, DCC, DMAP, 83%; (f) $RuCl_2$(=CHPh)(PCy_3)(IEMS), CH_2Cl_2, 40 ^{o}C, 12 h, 90%; (g) 5% HF-H_2O/CH_3CN, 99%; (h) (i) **8**, DCC, DMAP; (ii) DBU, $CHCl_3$, 65%; (i) TBAF, C_6H_5COOH, 80%.



Scheme 11. *Reagents and conditions*: (a) vinyl acetic acid, PPh_3, DEAD, 88%.

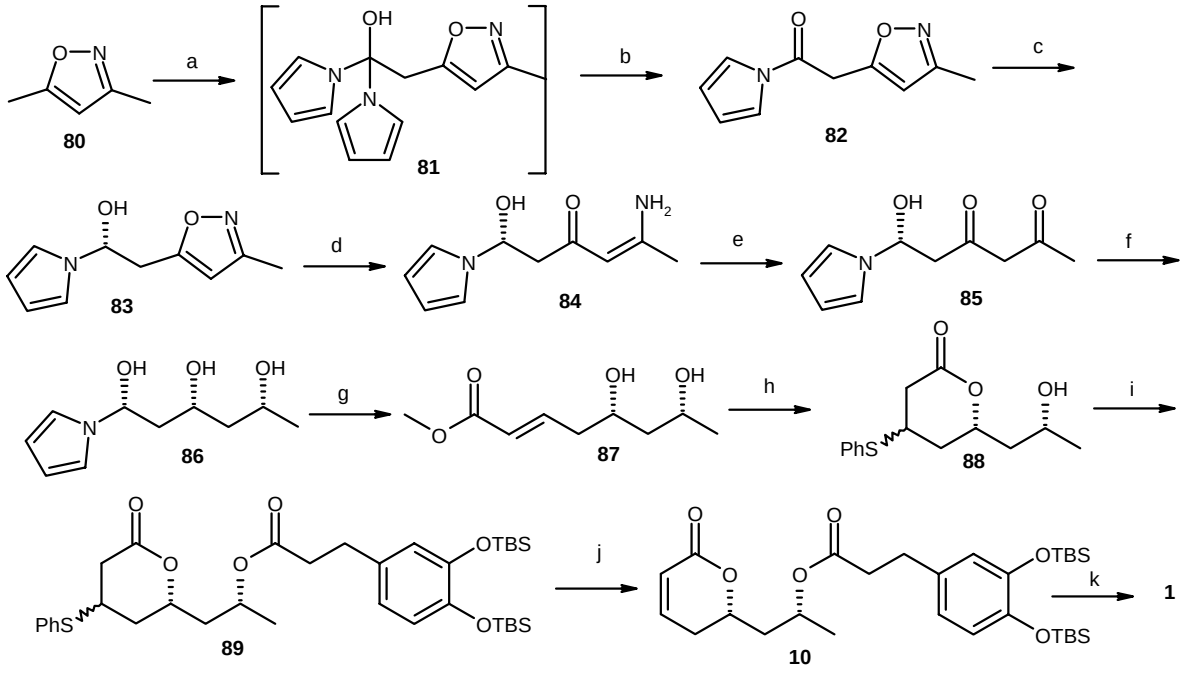
Similarly, the another stereoisomer **1b** was synthesized by inverting the stereochemistry in **78a**. Thus, Mitsunobu reaction of **78a** with formic acid followed by similar sequence of reaction afforded **1b** (Scheme 12).



Scheme 12. *Reagents and conditions*: (a) (i) HCOOH, PPh_3, DEAD; (ii) 3N HCl, dioxane, 78%.

Dixon *et al.* (2005).[34]

Dixon and co-workers accomplished the synthesis of tarchonanthuslactone employing the catalytic enantioselective reduction of an *N*-acyl pyrrole and diastereoselective *syn*-selective reductive cascade as the key steps. Thus, *N*-acyl pyrrole **82** was synthesized in two steps from 1,1′-carbonyldipyrrole (CDP).[35] Enantioselective reduction of **82** with Me-(*S*)-CBS reagent[36] furnished carbinol **83**, which on reductive cleavage followed by hydrolysis afforded diketone **85**. Treatment of **85** with dimethylmethoxy borane and sodium borohydride in THF/methanol[37] afforded the *syn*,*syn*-1,3,5-triol **86** in excellent diastereoselectivity. Triol **86** was subjected to HWE olefination and subsequent base catalyzed conjugate addition of benzenethiol followed by acid catalyzed lactonization to afford alcohol **88**. The esterification of alcohol **88** with TBS protected dihydrocaffeic acid **8** followed by elimination of benzene thiol afforded **10**, which on desilylation furnished target molecule **1** (Scheme 13).

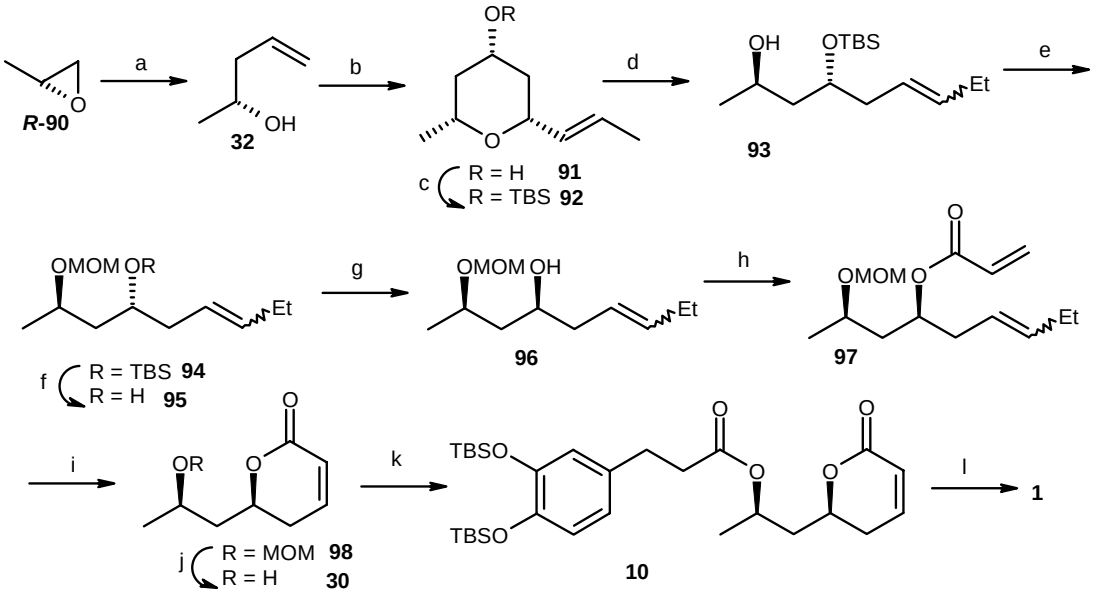


Scheme 13. *Reagents and conditions*: (a) *n*-BuLi, THF, –78 °C, then CDP in THF, then AcOH in THF; (b) DBU, THF, rt, 95% over two steps; (c) Me-(*S*)-CBS, $BH_3.SMe_2$ (1.7

equiv), CH_2Cl_2, –78 °C, 99%; (d) $Mo(CO)_6$, MeCN, reflux, then **83**, H_2O, rt, 69%; (e) MeCN:AcOH:H_2O/ 2:2:1, 99%; (f) Et_3BOMe, $NaBH_4$, THF:MeOH (3:1), 90%; (g) $(MeO)_2P(O)CH_2CO_2Me$, NaH, THF, 0 °C, 97%; (h) (i) PhSH, *i*Pr_2EtN, PhH, rt; (ii) Amberlyst A-15, MeCN, rt, 71% over two steps; (i) **8**, DCC, DMAP, CH_2Cl_2, rt, 77%; (j) DBU, CH_2Cl_2, 0 °C, 98%; (k) TBAF, $PhCO_2H$, THF, rt, 98%.

Yadav *et al.* (2007).[38]

Yadav and co-workers accomplished the synthesis of tarchonanthuslactone from propylene oxide employing the Prins cyclisation[39] and ring-closing metathesis as the key steps. Thus (*R*)-propylene oxide *R*-**90** (obtained via Jacobsen's hydrolytic kinetic resolution)[40,41] was converted into alcohol **32**, which on Prins cyclisation with crotonaldehyde followed by hydrolysis furnished tetrahydropyran **91**. Protection of hydroxy as TBS ether followed by treatment with Na in liquid ammonia gave 1,3-diol **93**, which was protected as MOM ether followed by TBS deprotection to afford alcohol **95**. Mitsunobu inversion of alcohol **95** furnished *syn*-diol compound **96**, which on esterification and ring-closing metathesis afforded lactone **98**. MOM was deprotected and alcohol **30** was esterified followed by desilylation to give the target molecule **1** (Scheme 14).

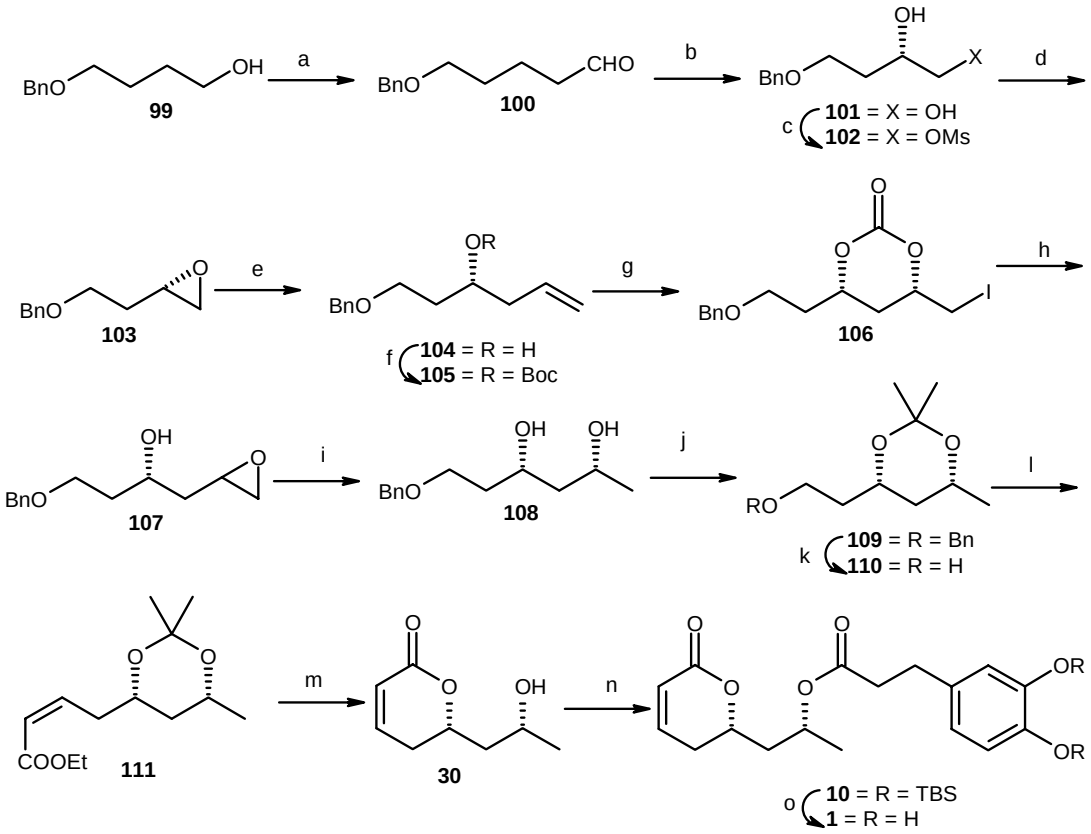


Scheme 14. *Reagents and conditions*: (a) CH_2=CHMgBr, CuBr, THF, -78 °C to -40 °C, 6 h, 80%; (b) crotonaldehyde, TFA, CH_2Cl_2, rt, 4 h, then K_2CO_3, MeOH, rt, 1 h, 70%; (c) TBSCl, imidazole, DMAP, CH_2Cl_2, 0 °C – rt, 4 h, 92%; (d) Na, liquid NH_3, THF, –33 °C,

45 min, 90%; (e) MOMCl, DIPEA, DMAP, CH_2Cl_2, 0 ^oC – rt, 4 h, 92%; (f) TBAF, THF, 0 ^oC – rt, 4 h, 94%; (g) *p*-$NO_2CH_2CO_2H$, DEAD, Ph_3P, THF, 0 ^oC – rt, 30 min, then K_2CO_3, MeOH, rt, 4 h, 75%; (h) acryloyl chloride, TEA, DMAP, CH_2Cl_2, 0 ^oC – rt, 1 h, 84%; (i) $RuCl_2$(=CHPh)(PCy_3)(IEMS), CH_2Cl_2, rt, 12 h, 60%; (j) TFA/CH_2Cl_2 (1:5), 0 ^oC – rt, 2 h, 85%; (k) **8**, DCC, DMAP, 5 h, 0 ^oC – rt, 83%; (l) TBAF, benzoic acid, THF, rt, 1 h, 82%.

Sudalai *et al.* (2007).[42]

Recently Sudalai and co-workers synthesized tarchonanthuslactone by using proline-catalyzed α-aminooxylation and iodine induced electrophilic cyclization as the key steps. Thus monoprotected 1,4-butane diol **99** was oxidized with IBX followed by proline catalyzed α-asymmetric aminooxylation[43] of resultant aldehyde **100** and subsequent reduction of the crude aminoxy product to yield the chiral diol **101**. Selective mesylation[44] of primary alcohol in **101** followed by base treatment afforded terminal epoxide **103**. Opening of epoxide **103** with vinylmagnesium bromide furnished homoallylic alcohol **104** which was converted into homoallylic *tert*-butyl carbonate **105** and further subjected to iodolactonization followed by base treatment to afford the *syn*-epoxy alcohol **107**. Reduction of epoxide **107** followed by protection of resultant diol **108** as acetonide and benzyl deprotection afforded alcohol **110** which on Swern oxidation followed by Horner-Wittig-Emmons olefination,[45] acetonide deprotection followed by cyclization furnished pyranone **30**. Esterification of **30** with **8**, followed by desilylation afforded target molecule **1** (Scheme 15).



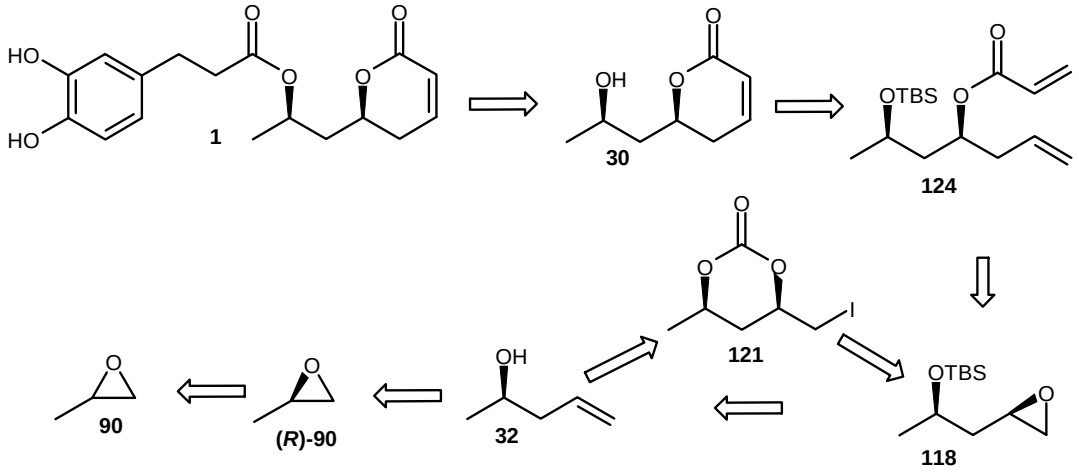
Scheme 15. *Reagents and conditions*: (a) IBX, DMSO, rt, 2 h, 95%; (b) (i) PhNO, D-proline (25 mol %), CH_3CN, -20 ^oC, 24 h then MeOH, $NaBH_4$; (ii) $CuSO_4$ (30 mol %), MeOH, 0 ^oC, 10 h, 87% (over two steps); (c) MsCl, Et_3N, CH_2Cl_2, 0 ^oC, 15 min, 92%; (d) K_2CO_3, MeOH, rt, 1 h, 95%; (e) vinylmagnesium bromide, THF, CuI, -40 ^oC, 1 h, 92%; (f) $(Boc)_2O$, DMAP, CH_3CN, rt, 5 h, 95%; (g) NIS, CH_3CN, -40 to 0 ^oC, 12 h, 85%; (h) K_2CO_3, MeOH, 0 ^oC to rt, 4 h, 90%; (i) $LiAlH_4$, THF, 50 ^oC, 6 h, 90%; (j) 2,2-dimethoxypropane, camphorsulfonic acid, rt, 4 h, 95%; (k) 10% Pd/C, H_2 (1 atm), MeOH, 12 h, 91%; (l) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^oC, 1 h; (ii) ethyl (di-*O*-tolylphosphono) acetate, NaH, THF, -78 to 0 ^oC, 1.5 h, 80% (over two steps); (m) pyridinium-*p*-toluene sulfonate, ethanol, 55 ^oC, 12 h, 75%; (n) TBS-protected dihydrocaffeic acid **8**, DCC, DMAP, CH_2Cl_2, 5 h, 81%; (o) TBAF, $PhCO_2H$, THF, rt, 88%

4.1.3. 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. Thus, numerous strategies for their synthesis have been developed with great success. With the development of an efficient approach to the synthesis of 1,3-polyols using iterative hydrolytic kinetic resolution, we became interested to apply this protocol for the synthesis of tarchonanthuslactone.

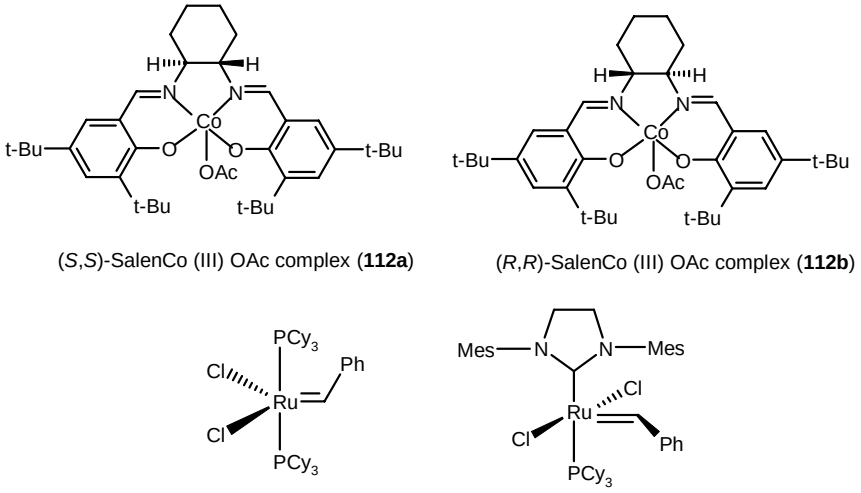
Our synthetic strategy for the synthesis of **1** is outlined in Scheme 16. We envisioned that the lactone moiety could be constructed by ring closing metathesis of the acrylate ester **124**, which in turn could be obtained from epoxide **118**. Epoxide **118** could either be prepared via hydrolytic kinetic resolution or diastereoselective iodine induced electrophilic cyclization of a homoallylic alcohol **32** which would be prepared from chiral propylene oxides **(*R*)-90** which in turn could be derived from racemic propylene oxide **90** via hydrolytic kinetic resolution.



Scheme 16. Retrosynthetic analysis of tarchonanthuslactone (1)

4.1.4. Results and discussion:

In designing a route to **1**, we chose propylene oxide as an appropriate starting material. Our synthesis of **1** requires two major reactions, Jacobsen's hydrolytic kinetic resolution[40,41] to install the stereogenic centres and ring- closing metathesis[19] to construct the δ-lactone moiety.



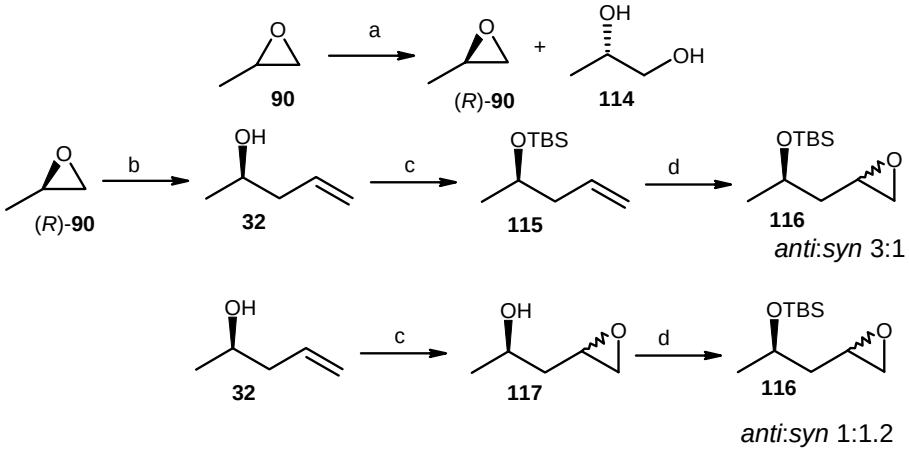
(*S*,*S*)-SalenCo (III) OAc complex (**112a**) (*R*,*R*)-SalenCo (III) OAc complex (**112b**)

Grubbs' 1st generation catalyst (**113a**) Grubbs' 2nd generation catalyst (**113b**)

Figure 2

As shown in Scheme 17, commercially available propylene oxide **90** was subjected to Jacobsen's HKR using (*R*,*R*)-salen-Co-OAc catalyst **112b** (Fig. 2) to give (*R*)-propylene oxide **(*R*)-90** as a single enantiomer;[44] $[\alpha]_D^{25}$ +11.4 (neat); lit.[40] $[\alpha]_D^{25}$ -11.6 (neat) (for (*S*)-propylene oxide), which was easily isolated from the more polar diol **114** by distillation. (*R*)-Propylene oxide **(*R*)-90** was treated with vinylmagnesium bromide in the presence of CuI to give the homoallylic alcohol **32** in excellent yield. The IR spectrum of **32** gave broad hydroxyl absorption at 3400 cm^{-1}. The ^1H NMR spectrum of **32** gave olefin peaks at 5.77-5.85 (multiplet, one proton), 5.12 (doublet, one proton), 5.09 (doublet, 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 alcohol **32** was first protected as the TBS ether, followed by epoxidation with *m*-CPBA. The epoxide thus obtained was found to be a mixture of two diastereomers (*anti*:*syn*/3:1). The desired *syn* isomer **118** was obtained only as a minor component.

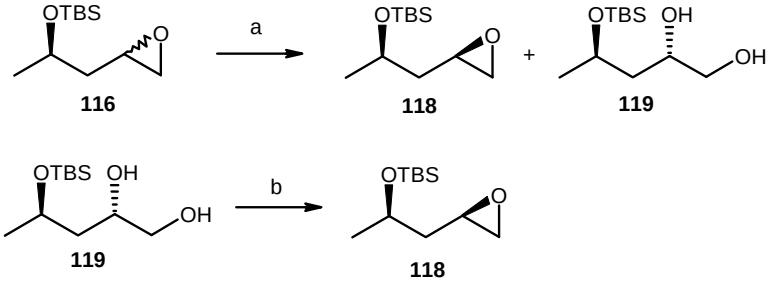
However, when epoxidation was carried out on alcohol **32** followed by hydroxy protection as the TBS-ether, the epoxide **116** was formed in favour of the desired *syn*-isomer (*syn*:*anti*/1.2:1). The ^{1}H NMR spectrum of **116** showed epoxide peaks at δ 3.02-3.05 (multiplet, one proton), 2.81-2.84 (multiplet, one proton), 2.52-2.54 (multiplet, one proton) in ^{1}H NMR spectrum. The ^{13}C NMR spectrum of **116** showed upfield carbons of epoxide at δ 66.5, 66.3, 49.6, 49.3, 47.2, 46.3, 42.9, 42.3, 25.7, 24.2 (both the diastereomers). The two diastereoisomers could not be differentiated on TLC.



Scheme 17. *Reagents and conditions*: (a) *R*,*R*-salen-Co-(OAc) (0.5 mol%), dist. H_2O (0.55eq), 0 ^{o}C, 14 h, (46% for *R*-**90**, 45% for **114**); (b) Vinylmagnesium bromide, THF, CuI, -20 ^{o}C, 12 h, 87% ; (c) *m*-CPBA, CH_2Cl_2, 0 ^{o}C to rt, 10 h, 96%; (d) TBDMSCl, imidazole, CH_2Cl_2, 0 ^{o}C to rt, 4 h, 95%.

In order to improve the diastereoselectivity, we attempted the hydrolytic kinetic resolution method (HKR) as depicted in Scheme 17. Thus, the HKR was performed on **116** with (*R*,*R*)-salen-Co-OAc complex **112b** (0.5 mol%) and water (0.55 eq) in THF (0.55 eq) to afford the epoxide **118** as a single stereoisomer (as determined from the ^{1}H and ^{13}C NMR spectral analysis) in 45% yield and the diol **119** in 47% yield. Epoxide **118** could easily be separated from the more polar diol **119** through silica gel column chromatography. As the HKR method provided the desired epoxide along with unwanted diol **119** in almost equal amounts, we thought it would be appropriate to convert diol **119** into the required epoxide **118** via internal nucleophilic substitution of a secondary mesylate.[46] Accordingly chemoselective pivalation of diol **119** with pivaloyl chloride followed by mesylation of the secondary hydroxyl and treatment of the crude mesylate with K_2CO_3 in methanol led to

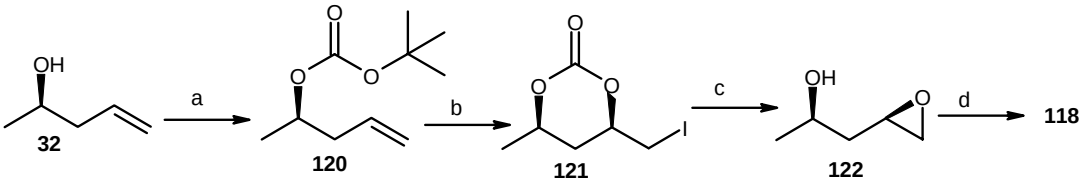
deprotection of the pivaloyl ester. Concomitant ring closure via intramolecular S_N2 displacement of the mesylate furnished the epoxide **118** in 61% overall yield (Scheme 18).



Scheme 18. *Reagents and conditions*: (a) *R*,*R*-salen-Co-(OAc) (0.5 mol%), dist. H_2O (0.55 eq), 0 ^oC, 24 h, (46% for **118**, 45% for **119**); (b) (i) PivCl, Et_3N, Cat. DMAP, rt; (ii) MsCl, Et_3N, DMAP, 0 ^oC to rt; (iii) K_2CO_3, MeOH, rt (61% for three steps).

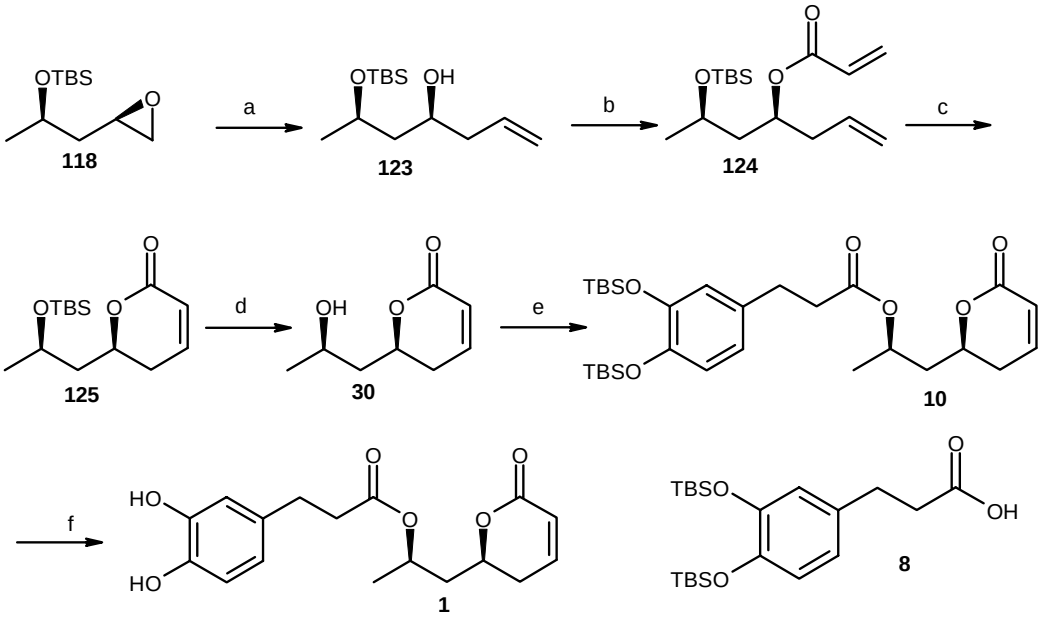
Synthesis of chiral epoxide 118 by diastereoselective iodine induced electrophilic cyclization (**Scheme 19**)

Alternatively, the epoxide **118** could also be prepared from homoallylic alcohol **32** based on modified Cardillo iodocyclization procedure in three steps sequence involving the protection of hydroxy group with Boc_2O, diastereoselective iodine induced electrophilic cyclization and saponification of corresponding iodo carbonate[47] (Scheme 19). Thus, alcohol **32** was treated with di-*tert*-butyl dicarbonate in the presence of DMAP in acetonitrile to give the corresponding homoallylic *tert*-butyl carbonate **120** in 90% yield. The IR spectrum of **120** showed absence of hydroxyl group, Boc carbonyl appeared at 1737 cm^{-1}. ^{13}C NMR spectra showed the ester carbonyl at 159.2. Subsequently, the diastereoselective electrophilic cyclization of **120** was carried out by treatment with IBr at –85 ^oC to afford the corresponding iodo carbonate **121** in 80% yield. In the ^1H NMR spectrum of **121** the resonances due to CH_2I were located at 3.43 as a doublet of doublet (J = 10.3, 4.2 Hz), and at 3.27 as a doublet of doublet (J = 10.6, 7.8 Hz). Finally, compound **121** was treated with K_2CO_3 in MeOH to furnish the *syn*-epoxy alcohol **122**[47] in excellent yield and 95:5 diastereoselectivity followed by protection of hydroxyl group as TBS ether to give the epoxide **118** in quantitative yield. In the ^1H NMR spectrum peaks owing to CH_2I group were absent. The epoxide peaks appeared at δ 2.81-2.83 (multiplet, two proton) and 2.51-2.53 (multiplet, one proton).



Scheme 19. *Reagents and conditions:* (a) Boc_2O, DMAP, CH_3CN, rt, 5 h, 90%; (b) IBr, PhMe, -85 ^oC, 1 h, 80%; (c) K_2CO_3, MeOH, rt, 2 h, 90%; (d) TBDMS-Cl, imidazole, CH_2Cl_2, 0 ^oC to rt, 4 h, 96%.

With substantial amounts of **118** in hand, we proceeded with the synthesis of **1** (Scheme 20). Thus opening of epoxide **118** with vinylmagnesium bromide in the presence of CuI in THF at –20 ^oC furnished the homoallylic alcohol **123** in 86% yield. The IR spectrum of **123** gave broad hydroxyl absorption at 3460 cm^{-1}. The ^1H NMR spectrum of **123** gave olefin peaks at δ 5.74-5.93 (multiplet, one proton), 5.15 (doublet, one proton), 5.06 (doublet, one proton). Alcohol **123** was then esterified with acryloyl chloride to afford the acryloyl ester **124** in 89% yield. The IR spectrum of **124** indicated absence of hydroxyl group, acryloyl carbonyl appeared at 1719 cm^{-1}. The carbonyl carbon appeared at δ 165.5 in the ^{13}C NMR spectrum. Subsequent ring closing metathesis of the ester with commercially available Grubbs' 1st generation catalyst[21] (10 mol%) in the presence of Ti(*i*-PrO)$_4$ (0.03 eq) in refluxing CH_2Cl_2 for 8 h afforded the α,β-unsaturated δ-lactone **125** in 87% yield having $[\alpha]_D^{25}$ –92.6 (*c* 0.84, $CHCl_3$). The IR spectrum of **125** showed characteristic carbonyl group absorption of α,β-unsaturated δ-lactone at 1718 cm^{-1}. The olefin protons appeared at 6.90 (doublet of doublet of doublet) with J = 10, 4.2, 3.9 Hz and 6.04 (doublet of doublet of doublet) with J = 10, 2.2, 2.2 Hz in the ^1H NMR spectrum. The olefinic carbons appeared at δ 144.9 and 121.1 in ^{13}C NMR spectrum. Desilylation of **125** with TBAF gave the hydroxy lactone **30** in 86% yield. The IR spectrum of **30** gave broad hydroxyl absorption at 3446 cm^{-1}. Treatment of **30** with TBS protected dihydrocaffeic acid **8** using DCC and a catalytic amount of DMAP furnished compound **10** in 85% yield, which was deprotected with TBAF to give tarchonanthuslactone **1** in 84% yield. The physical and spectroscopic data of **1** were in full agreement with literature data.[10]



Scheme 20. *Reagents and conditions:* (a) Vinylmagnesium bromide, THF, CuI, -20 ^{o}C, 1 h, 86%; (b) Acryloyl chloride, Et_3N, CH_2Cl_2, 0 ^{o}C to rt, 5 h, 89%; (c) $(PCy_3)_2Ru(Cl)_2$=CH-Ph (20 mol%), CH_2Cl_2, Ti(*i*-PrO)$_4$, reflux, 8 h , 87%; (d) TBAF, THF, rt, overnight, 86%; (e) **8**, DCC, DMAP, CH_2Cl_2, 5 h, 85%; (f) TBAF, THF, 1 h, 84%.

4.1.5. Conclusion

In conclusion, a practical and enantioselective synthesis of tarchonanthuslactone has been achieved using iterative hydrolytic kinetic resolution (HKR) to generate both the stereocentres and ruthenium catalyzed ring-closing metathesis (RCM) to construct the δ-lactone moiety. The synthetic strategy described here has significant potential to the synthesis of a variety of other biologically important substituted 1,3-polyol-5,6-dihydropyran-2-one-containing natural products.

4.1.6 Experimental Section

(*R*)-Propylene oxide (*R*-90).

***R*-90**

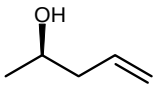
The racemic propylene oxide **90** was resolved to chiral epoxide ***R*-90** in high enantiomeric excess (> 99% ee) by the HKR method following a literature procedure.[40]

Yield: 14.71 g, 90%

Mol. Formula: C_3H_6O

$[\alpha]_D^{25}$: +11.4 (neat); lit.[40] $[\alpha]_D^{25}$ -11.6 (neat) for (*S*)-propylene oxide.

(*R*)-Pent-4-en-2-ol (32).



32

A round bottomed flask was charged with copper (I) iodide (1.64 g, 8.6 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, 172 mL, 172.4 mmol) was injected to it. A solution of propylene oxide ***R*-90** (5 g, 86.1 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 to afford the crude product which on distillation provided homoallylic alcohol **32** as a colorless liquid.

Yield: 6.5g, 87%

Mol. Formula: $C_5H_{10}O$

$[\alpha]_D^{25}$: - 9.92 (*c* 3.0, Et_2O); lit.[11] $[\alpha]_D^{24}$- 9.84 (*c* 3.2, Et_2O).

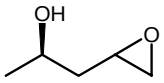
b.p. 115 ^oC, lit.[11] 115 ^oC.

IR ($CHCl_3$, cm^{-1}): ν_{max} 3400, 3078, 2931, 2975, 1562, 1457, 1432, 1243, 1071, 914.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.77-5.85 (m, 1H), 5.12 (d, *J* = 6.6 Hz, 1H), 5.09 (d, *J* = 2.4 Hz, 1H), 3.80-3.86 (m, 1H), 2.22-2.38 (m, 2H), 1.82 (s, 1H), 1.18 (d, *J* = 6.1, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 134.6, 116.6, 66.5, 43.2, 22.1.

1-Oxiranyl-propan-2-ol (117).



117

To a stirred solution of olefin **32** (6 g, 69.7 mmol) in CH_2Cl_2 (50 mL) at 0 ^oC was added *m*-CPBA (50%) (28.85 g, 83.6 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 **117** as a colorless liquid in diastereomeric mixture (1.1:1).

Yield: 6.83 g, 96%.

Mol. Formula: $C_5H_{10}O_2$

$[\alpha]_D^{25}$: -10.5 (*c*, 0.86, $CHCl_3$).

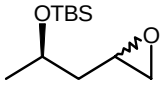
IR ($CHCl_3$, cm^{-1}): ν_{max} 3436, 3192, 2968, 2932, 2852, 1471, 1379, 1265, 1206, 1101, 944, 878.

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.06-4.10 (m, 1H), 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), 1.18 (d, J = 6.3 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 66.5, 66.3, 49.6, 49.3, 47.2, 46.3, 42.9, 42.3, 25.7, 24.2 (both the diastereomers).

Analysis Calcd.: C, 58.80; H, 9.87; **Found:** C, 58.69; H, 9.82.

***tert*-Butyldimethyl-(1-methyl-but-3-enyloxy)-silane (116).**



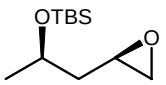
116

To a stirred solution of alcohol **117** (6 g, 58.8 mmol) in CH_2Cl_2 (25 mL) was added imidazole (8.0 g, 117.5 mmol). To this solution *t*-butyl dimethylchlorosilane (10.63 g, 70.5 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 **116** as a colorless liquid.

Yield: 12.08 g, 95%

Mol. Formula: $C_{11}H_{24}O_2Si$

Compound 118.



118

A solution of epoxide **116** (5 g, 23.1 mmol) and (*R,R*)-Salen-Co(III)-OAc (0.076 g, 0.12 mmol) in THF (0.3 mL) was stirred at 0 ^{o}C for 5 min, and then distilled water (229 μL, 12.7 mmol) was added. After stirring for 24 h, it was concentrated and purified by silica gel column chromatography using pet ether/EtOAc (19:1) to afford **118 (**2.3g, 46%) as a yellow color liquid. Continued chromatography with pet ether/EtOAc (3:2) provided the diol **119** as a brown color liquid as a single diastereomer.

Yield: 2.3g, 46%

Mol. Formula: $C_{11}H_{24}O_2Si$

$[\alpha]_D^{25}$: - 11.4 (*c* 0.67, $CHCl_3$).

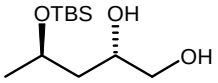
IR ($CHCl_3$, cm^{-1}): ν_{max} 3018, 2958, 2930, 1858, 1472, 1463, 1377, 1256, 1216, 1101, 1005, 938, 878, 760.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.01-4.08 (m, 1H), 3.02-3.04 (m, 1H), 2.76-2.80 (m, 1H), 2.46-2.50 (m, 1H), 1.67-1.71 (m, 1H), 1.50-1.52 (m, 1H), 1.19 (d, *J* = 6.3 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 66.3, 48.8, 45.8, 42.1, 25.4, 23.3, 17.6, -5.0, -5.3.

Analysis Calcd.: C, 61.05; H, 11.18%; **Found:** C, 61.12; H, 11.08%.

Compound 119.



119

Yield: 2.25g, 45%

Mol. Formula: $C_{11}H_{26}O_3Si$

$[\alpha]_D^{25}$: + 32.6 (*c* 1.04, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 3430, 3018, 2957, 2931, 2859, 1652, 1471, 1379, 1256, 1212, 1101, 1036, 971, 869, 758.

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.22-4.31 (m, 1H), 4.04-4.14 (m, 1H), 3.46-3.70 (m, 2H), 1.67-1.81 (m, 2H), 1.32-1.50 (m, 2H), 1.27 (d, *J* = 6.1 Hz, 3H), 0.90 (s, 9H), 0.10 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 68.9, 66.7, 66.3, 41.1, 25.6, 23.4, 17.7, -4.7, -5.1.

Analysis Calcd.: C, 56.36; H, 11.18%; **Found:** C, 56.72; H, 11.07%.

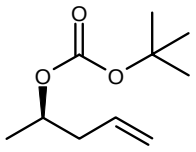
Conversion of 119 into 118.

Diol **119** (2 g, 8.5 mmol) was dissolved under argon in dry CH_2Cl_2 (25 mL) and treated with pivaloyl chloride (1.13 g, 9.4 mmol), Et_3N (1.03 g, 10.2 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 (0.978 g, 8.5 mmol), Et_3N (1.033 g, 10.2 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 (1.17 g, 8.5 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 **118** as a yellow color liquid.

Yield: 1.13 g, overall yield 61%

$[\alpha]_D^{25}$: +9.8 (*c* 0.50, $CHCl_3$).

Carbonic acid *tert*-butyl ester 1-methyl-but-3-enyl ester (120).



120

To a solution of alcohol **32** (5 g, 58.05 mmol) in CH_3CN (80 mL) were added $(Boc)_2O$ (19 g, 87.06 mmol) and DMAP (2.84, 23.25 mmol). After 5 h of stirring, the solvent was evaporated under reduced pressure. The residue was taken up in EtOH (60 mL) and imidazole (19.76 g, 290.25 mmol) was added. The resulting mixture was stirred at room temperature for 15 min and then CH_2Cl_2 was added. The organic layer was washed with water, dried (Na_2SO_4) and concentrated. Purification of the crude product by silica gel column chromatography using pet ether/EtOAc (19:1) as eluent afforded **120** as a colorless liquid.

Yield: 9.73 g, 90%

Mol. Formula: $C_{10}H_{18}O_3$

$[\alpha]_D^{25}$: –32.4 (*c* 0.98, $CHCl_3$).

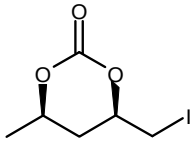
IR (neat, cm^{-1}): ν_{max} 3019, 2962, 2923, 2844, 1737, 1642, 1520, 1474, 1463, 1392, 1374, 1266, 1222, 1116, 1092, 994, 836.

^{1}H NMR (200 MHz, $CDCl_3$): δ 5.79 (dt, *J* = 7.0, 7.1, 17.2 Hz, 1H); 5.05-5.14 (m, 2H), 4.70-4.87 (m, 1H), 2.24-2.45 (m, 2H), 1.47 (s, 9H), 1.25 (d, *J* = 6.6 Hz, 3H).

^{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%.

4-Iodomethyl-6-methyl-[1,3]dioxan-2-one (121).



121

To a solution of carbonate **120** (2g, 10.74 mmol) in toluene at –85 ^oC was slowly added a solution of IBr (1 M in CH_2Cl_2, 3.55g, 17.18 mmol). After being stirred at –85 ^oC for 1 h, the resulting mixture was quenched with 20% aqueous $Na_2S_2O_3$ and 5% aqueous $NaHCO_3$ solution (1/1) and diluted with ether (50 mL). The aqueous phase was extracted with ether (2 x 100 mL). The organic extracts were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography using pet ether/EtOAc (3:2) as eluent yielded **121** as a light yellow colour liquid.

Yield: 2.2 g, 80%

Mol. Formula: $C_6H_9IO_3$

$[\alpha]_D^{25}$: –25.8 (*c* 0.94, $CHCl_3$).

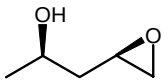
IR (neat, cm^{-1}): ν_{max} 3081, 3019, 2986, 2932, 1744, 1390, 1368, 1324, 1239, 1191, 1106, 1084, 987.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.57-4.63 (m, 1H), 4.42-4.48 (m, 1H), 3.43 (dd, *J* = 10.3, 4.2 Hz, 1H), 3.27 (dd, *J* = 10.6, 7.8 Hz, 1H), 2.38-2.43 (m, 1H), 1.64-1.72 (m, 1H), 1.45 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 148.3, 77.3, 74.5, 35.7, 21.0, 5.3.

Analysis Calcd.: C, 28.15; H, 3.54%. **Found:** C, 28.04; H, 3.57%.

1-Oxiranyl-propan-2-ol (122).



122

To a solution of cyclic carbonate **121** (4 g, 15.62 mmol) in anhydrous MeOH (50 mL) at room temperature was added K_2CO_3 (6.47 g, 46.88 mmol) and the reaction was stirred for 2 h. The mixture was diluted with ether (50 mL) and quenched with saturated aqueous $Na_2S_2O_3$ and saturated aq. $NaHCO_3$ solution (1/1). The aqueous phase was extracted with ether (3 x 50 mL). The organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. Purification of the crude product by silica gel column chromatography using pet ether/EtOAc (9:1) as eluent afforded the epoxide **122** (1.44 g, 90%) as a colorless liquid.

Yield: 1.44 g, 90%

Mol. Formula: $C_5H_{10}O_2$

$[\alpha]_D^{25}$: -18.7 (*c* 1.1, $CHCl_3$).

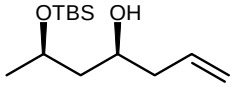
IR (neat, cm^{-1}): ν_{max} 3442, 3190, 2957, 2932, 2858, 1468, 1379, 1260, 1218, 1115, 952, 911, 874.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.93-4.10 (m, 1H), 3.02-3.05 (m, 1H), 2.81-2.83 (m, 2H), 2.51-2.53 (m, 1H), 1.82-1.86 (m, 1H), 1.71-1.74 (m, 1H), 1.18 (d, J = 6.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 66.4, 49.8, 46.5, 39.9, 23.

Analysis Calcd.: C, 58.80; H, 9.87 %; **Found:** C, 58.65; H, 9.66%.

6-(*tert*-Butyldimethylsilanyloxy)-hept-1-en-4-ol (123).



123

A round bottomed flask was charged with copper(I)iodide (0.88 g, 4.6 mmol), gently heated under vaccum and slowly cooled with a flow of argon and THF (20 mL) was added.

This suspension was cooled to –20 ^{o}C, stirred and vinylmagnesium bromide (1M in THF, 18.5 mL, 18.5 mmol) was added to it. A solution of epoxide ***ent*-118** (1.0 g, 4.6 mmol) in THF (15 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 × 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 (9:1) as eluent afforded **123** as a colorless liquid.

Yield: 0.96g, 86%

Mol. Formula: $C_{13}H_{28}O_2Si$

$[\alpha]_D^{25}$: –36.5 (*c* 0.82, $CHCl_3$)

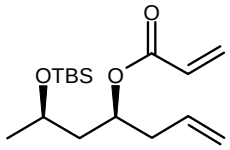
IR ($CHCl_3$, cm^{-1}): ν_{max} 3460, 2959, 2857, 1640, 1448, 1376, 1255, 1078.

^{1}H NMR (200 MHz, $CDCl_3$): δ 5.74-5.93 (m, 1H), 5.15 (d, *J* = 6.9 Hz, 1H), 5.06 (d, *J* = 2.9 Hz, 1H), 4.03-4.23 (m, 1H), 3.80-3.86 (m, 1H), 2.19-2.26 (m, 2H), 1.53-1.60 (m, 2H), 1.21 (d, *J* =7 Hz, 3H), 0.90 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 134.9, 117.1, 70.3, 69.5, 45.3, 42.0, 25.8, 24.4, 17.8, -4.0, -4.9.

Analysis Calcd.: C, 63.87; H, 11.55%; **Found:** C, 63.82; H, 11.38.

Acrylic acid 1-[2-(*tert*-butyldimethylsilanyloxy)-propyl]-but-3-enyl ester (124).



124

Acryloyl chloride (0.370 g, 0.33 mL, 4.09 mmol) was added drop wise under argon to a solution of **123** (1g, 4.09 mmol) and triethylamine (1.65 g, 2.3 mL, 16.31 mmol) in dry CH_2Cl_2 (10 mL) at 0 ^{o}C. The mixture was stirred for 5 h 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 30mL) and combined organic layer was washed with brine, dried (Na_2S0_4) and concentrated. Purification of crude

product by silica gel column chromatography using pet ether/EtOAc (9:1) as eluent afforded **124** as a colorless liquid.

Yield: 1.09g, 89%

Mol. Formula: $C_{16}H_{30}O_3Si$

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

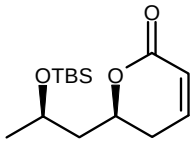
IR ($CHCl_3$, cm^{-1}): ν_{max} 3081, 3022, 2958, 2930, 2897, 2858, 1719, 1638, 1619, 1472, 1463, 1437, 1407, 1377, 1297, 1258, 1116, 1065, 967, 919.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.35 (dd, *J* = 17.1, 1.6 Hz, 1H), 6.08 (dd, *J* = 17.1, 10.2, 1H), 5.79 (dd, *J* = 10.2, 1.7 Hz, 1H), 5.66-5.77 (m, 1H), 5.09-5.16 (m, 2H), 5.03-5.07 (m, 1H), 3.78-3.93 (m, 1H), 2.33-2.42 (m, 2H), 1.59-1.72 (m, 2H), 1.18 (d, *J* = 6.1, 3H), 0.89 (s, 9H), 0.05 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.5, 133.3, 130.3, 128.7, 117.8, 71.0, 65.5, 43.5, 38.9, 25.8, 23.4, 18.0, -4.4, -4.8.

Analysis Calcd.: C, 64.38; H, 10.13%. **Found:** C, 64.22; H, 10.14%.

6-[2-(*tert*-butyldimethylsilanyloxy)-propyl]-5,6-dihydro-pyran-2-one (125).



125

Grubb's catalyst (0.139 g, 0.17 mmol) dissolved in CH_2Cl_2 (10 mL) was added drop wise to a refluxing solution of acrylate **124** (0.50 g, 1.68 mmol), Ti(*i*-PrO)$_4$ (14 mg, 0.05 mmol) in dry CH_2Cl_2 (60 mL). Refluxing was continued for 8 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 (8:2) as eluent to afford **125** as colorless oil.

Yield: 0.394 g, 87% from both the steps

Mol. Formula: $C_{14}H_{26}O_3Si$

$[\alpha]_D^{25}$: –92.6 (*c* 0.84, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 3019-2857, 1718, 1472, 1445, 1424, 1380, 1255, 1216.

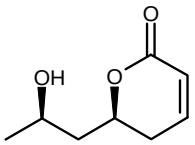
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.90 (ddd, *J* = 10, 4.2, 3.9 Hz, 1H), 6.04 (ddd, *J* = 10, 2.2, 2.2, 1H), 4.61 (dddd, *J* = 8, 8, 8, 5.1 Hz, 1H), 4.16-4.21 (m, 1H), 2.31-2.35 (m, 2H), 1.86 (

ddd, J = 14.3, 8.1, 8.1 Hz, 1H), 1.62 (ddd, J = 14.8, 5.4, 4.2 Hz, 1H), 1.18 (d, J = 6 Hz, 3H), 0.88 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 164.2, 144.9, 121.1, 75.2, 64.6, 43.9, 29.4, 25.5, 23.1, 17.7, -4.5,-5.1.

Analysis Calcd.: C, 62.18; H, 9.69%. **Found:** C, 62.09; H, 9.74%.

6-(2-Hydroxypropyl)-5,6-dihydro-pyran-2-one (30).



30

Lactone (0.30 g, 1.11 mmol) **125** and benzoic acid (0.20 g, 1.64 mmol) were dissolved in THF (5 mL), followed by the drop wise addition of TBAF (1.66 mL, 1M solution in THF). The reaction mixture was stirred at room temperature for overnight, concentrated, and extracted with EtOAc (3 x 30 mL). Evaporation of the solvent and purification by silica gel column chromatography using pet ether/EtOAc (3:7) as eluent afforded **30** as a pale yellow liquid.

Yield: 0.149 g, 86%

Mol. Formula: $C_8H_{12}O_3$

$[\alpha]_D^{25}$: –115.4 (c 0.9, $CHCl_3$), lit.[10] $[\alpha]_D$ –111 (c 1.0, $CHCl_3$).

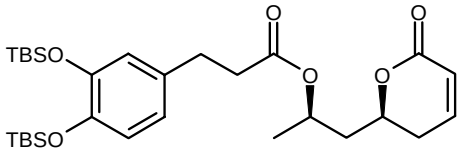
IR ($CHCl_3$, cm^{-1}): ν_{max} 3446, 3019, 2973, 2400, 1719, 1516, 1422.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.87-6.93 (m, 1H), 6.02 (d, J = 10 Hz, 1H), 4.59-4.69 (m, 1H), 4.05-4.11 (m, 1H), 2.37-2.43 (m, 2H), 2.02 (ddd, J = 14, 8, 8 Hz, 1H), 1.76 (ddd, J = 14.0, 5.2, 4.4 Hz, 1H), 1.26 (d, J = 6 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 164.1, 145.3, 121.1, 76.7, 65.0, 43.4, 29.4, 23.6.

Analysis Calcd.: C, 61.52; H, 7.74; %; **Found:** C, 61.61; H, 7.86%.

3-[3,4-Bis-(*tert*-butyldimethylsilanyloxy)-phenyl]-propionic acid 1-methyl-2-(6-oxo-3,6-dihydro-2*H*-pyran-2-yl)-ethyl ester (10).



10

To a solution of hydroxylactone **30** (100 mg, 0.64 mmol) in CH_2Cl_2 (10 mL) were added TBS-protected dihydrocaffeic acid **8** (0.289 g, 0.70 mmol), DCC (0.145 g, 0.70 mmol) and catalytic amount of DMAP. The reaction mixture was stirred for 5 h. The mixture was filtered through a pad of celite and concentrated. Purification of the crude material with silica gel chromatography using pet ether/EtOAc (3:1) as eluent yielded the TBS-protected tarchonanthuslactone **10** as a colorless oil.

Yield: 0.299 g, 85%

Mol. Formula: $C_{29}H_{48}O_6Si_2$

$[\alpha]_D^{25}$: –44.8 (*c* 0.85, $CHCl_3$), lit.[10] $[\alpha]_D$ –44.0 (*c* 1.0, $CHCl_3$).

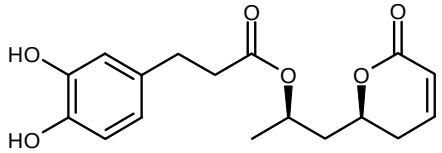
IR ($CHCl_3$, cm^{-1}): ν_{max} 2956, 2931, 2858, 1730, 1605, 1576, 1511, 1472, 1421.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.61-6.85 (m, 4H), 6.04 (d, *J* = 9.4 Hz, 1H), 5.06-5.15 (m, 1H), 4.36-4.50 (m, 1H), 2.82 (t, *J* = 7.5 Hz, 2H), 2.56 (t, *J* = 7.6 Hz, 2H), 2.29-2.35 (m, 2H), 2.13-2.26 (m, 1H), 1.78-1.85 (m, 1H), 1.28 (d, *J* = 6.5 Hz, 3H), 0.99 (s, 9H), 0.98 (s, 9H), 0.19 (s, 6H), 0.18 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 172.3, 163.9, 146.5, 145.1, 144.7, 133.3, 121.1, 121.0, 120.7, 74.8, 67.0, 40.6, 36.1, 30.1, 28.9, 25.8, 20.1, 18.3, -4.2.

Analysis Calcd.: C, 63.46; H, 8.81%, **Found:** C, 63.38; H, 8.64%.

Tarchonanthuslactone (1).



1

A solution of TBAF (0.82 mL, 1M in THF) was added to a stirred solution of TBS protected tarchonanthuslactone **10** (0.150 g, 0.27 mmol) and benzoic acid (0.1 g, 0.82 mmol) in THF. The mixture was stirred at room temperature for 1 h. The solvent was evaporated and extracted with EtOAc (3 x 20 mL). Evaporation of the solvent and

purification of crude product by silica gel column chromatography using pet ether/EtOAc (1:1) as eluent yielded tarchonanthuslactone **1** as a gummy liquid.

Yield: 0.074 g, 84%

Mol. Formula: $C_{17}H_{20}O_6$

$[\alpha]_D^{25}$: –76.2 (*c* 0.6, $CHCl_3$**)**; lit.[9a] $[\alpha]_D^{25}$ –76.5 (*c* 0.4, $CHCl_3$).

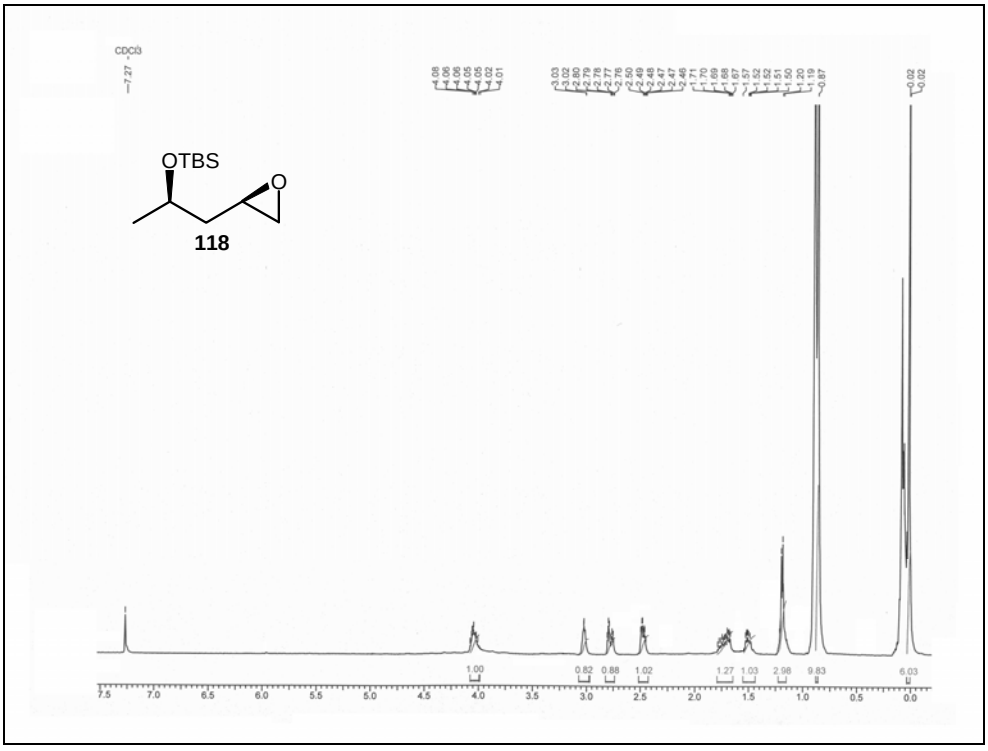
IR ($CHCl_3$, cm^{-1}): ν_{max} 3600, 3521,3510, 3467, 3200, 1722, 1602, 1520, 1446, 1385, 1260, 1041.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.80-6.85 (m, 1H), 6.69-6.77 (m, 2H), 6.56 (d, *J* = 8.04, 1H), 6.02 (d, *J* =9.9 Hz, 1H), 5.06-5.14 (m, 1H), 4.15-4.20 (m, 1H), 2.82 (t, *J* =7 Hz, 2H), 2.60 (t, *J* =7 Hz, 2H), 2.26-2.32 (m, 1H), 2.17-2.25 (m,1H), 2.07 (ddd, *J* = 14, 8.5, 6 Hz, 1H), 1.72-1.77 (m, 1H), 1.25 (d, *J* =6 Hz, 3H).

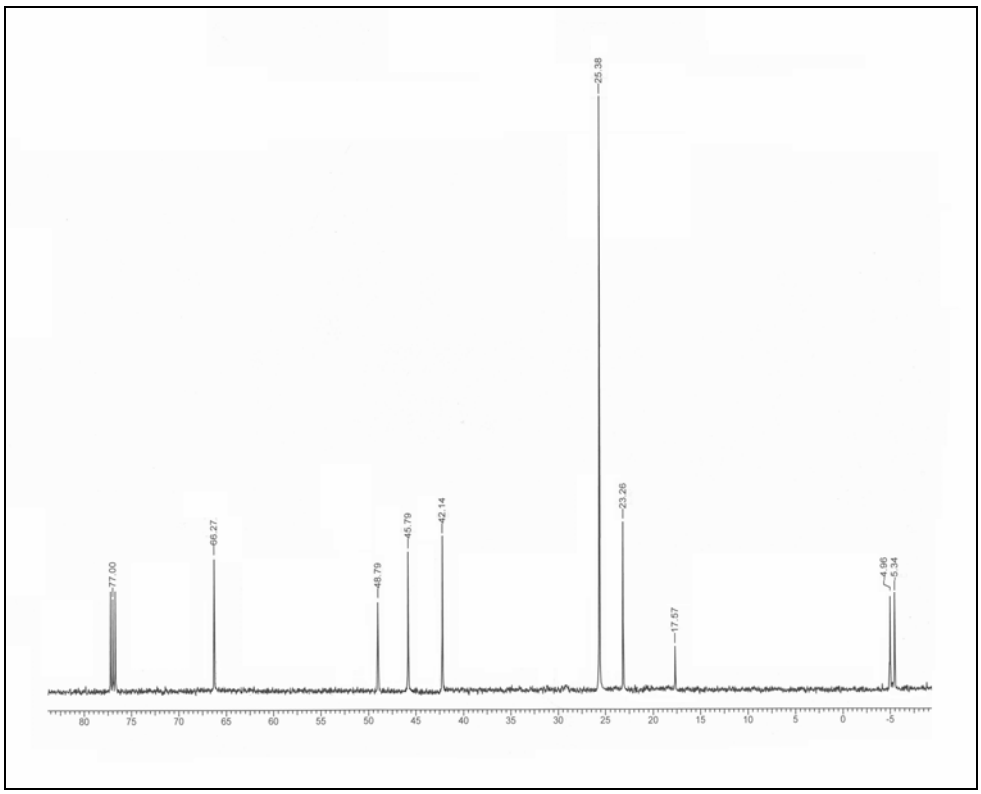
^{13}C NMR (125 MHz, $CDCl_3$): δ 172.9, 165.2, 145.7, 143.9, 142.4, 132.6, 120.7, 120.2, 115.3, 75.2, 67.2, 40.7, 35.9, 30.1, 28.9, 20.4.

4.1.7 Spectra

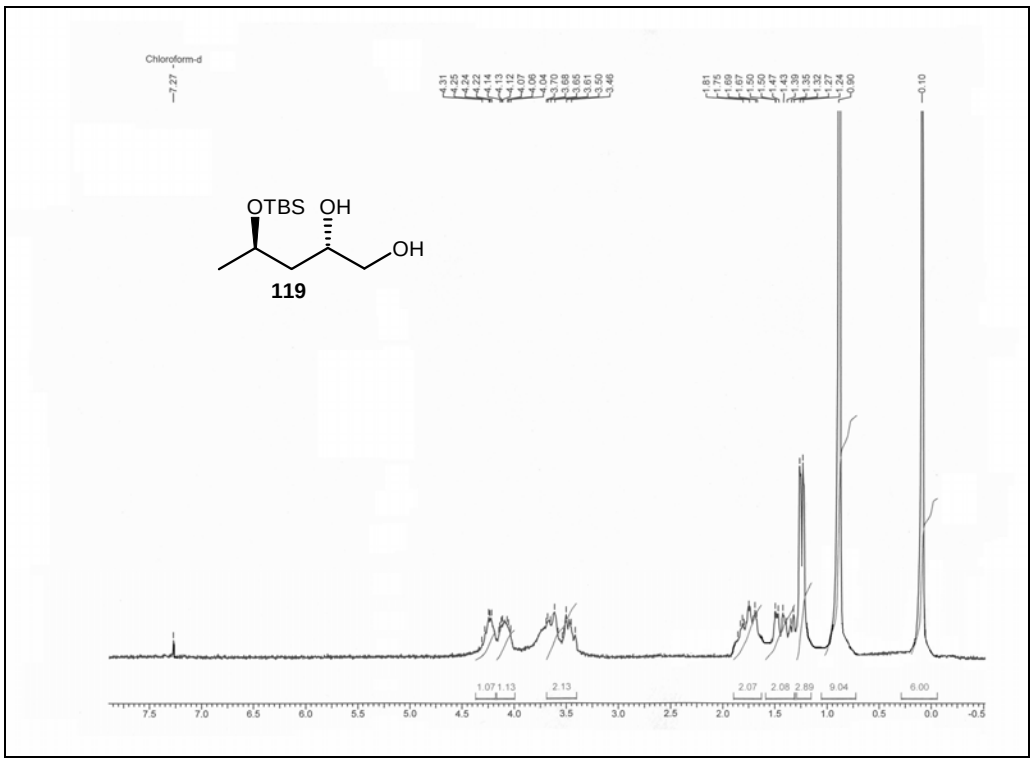
1. ^{1}H and ^{13}C NMR spectra of 118
2. ^{1}H and ^{13}C NMR spectra of 119
3. ^{1}H and ^{13}C NMR spectra of 120
4. ^{1}H and ^{13}C NMR spectra of 122
5. ^{1}H and ^{13}C NMR spectra of 123
6. ^{1}H and ^{13}C NMR spectra of 124
7. ^{1}H and ^{13}C NMR spectra of 125
8. ^{1}H and ^{13}C NMR spectra of 30
9. ^{1}H and ^{13}C NMR spectra of 10
10. ^{1}H and ^{13}C NMR spectra of 1



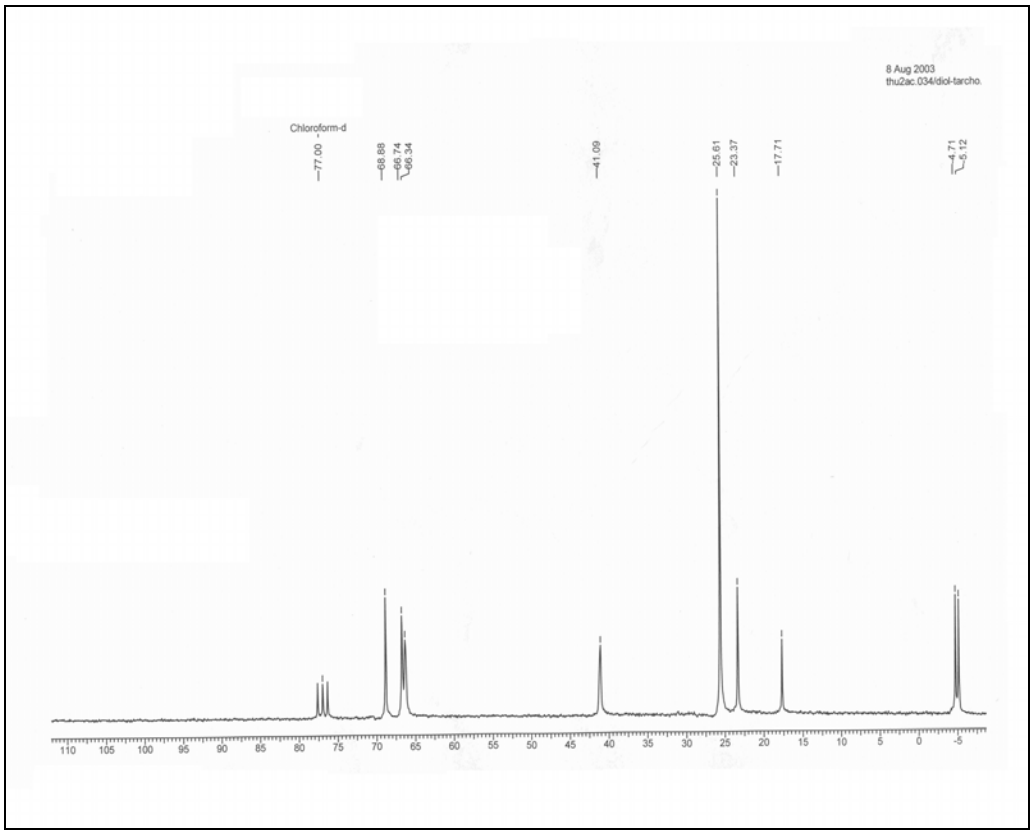
^{1}H NMR Spectrum of compound 118 in $CDCl_3$



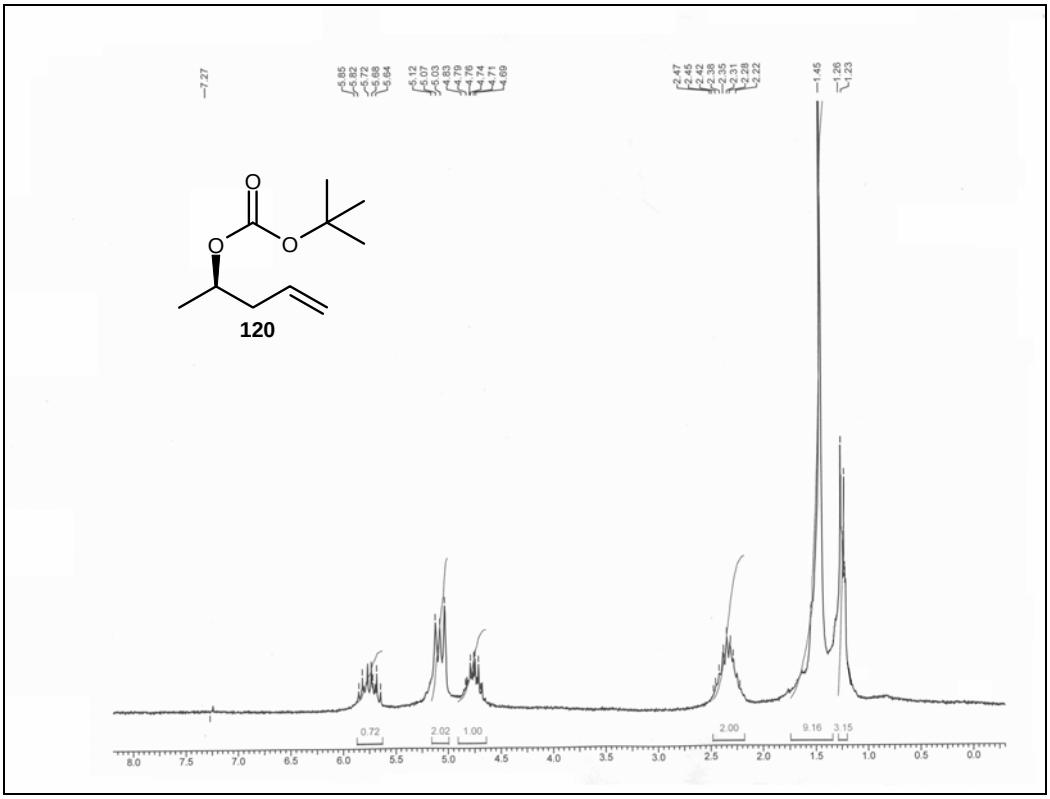
^{13}C NMR Spectrum of compound 118 in $CDCl_3$



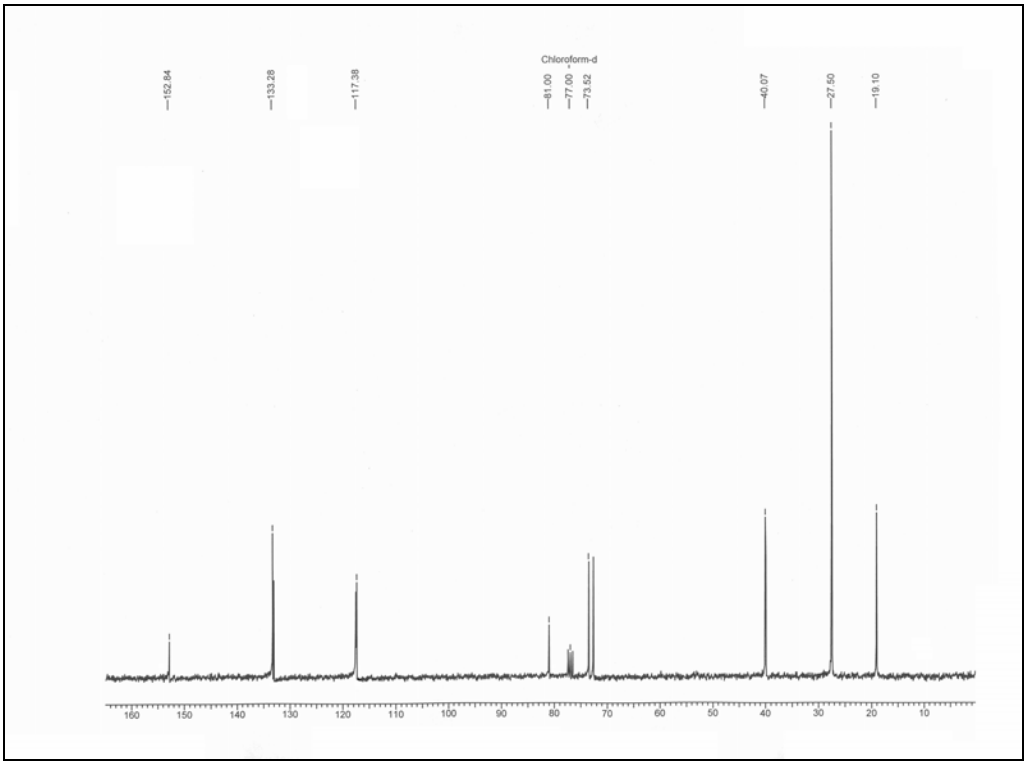
^{1}H NMR Spectrum of compound 119 in $CDCl_3$



^{13}C NMR Spectrum of compound 119 in $CDCl_3$

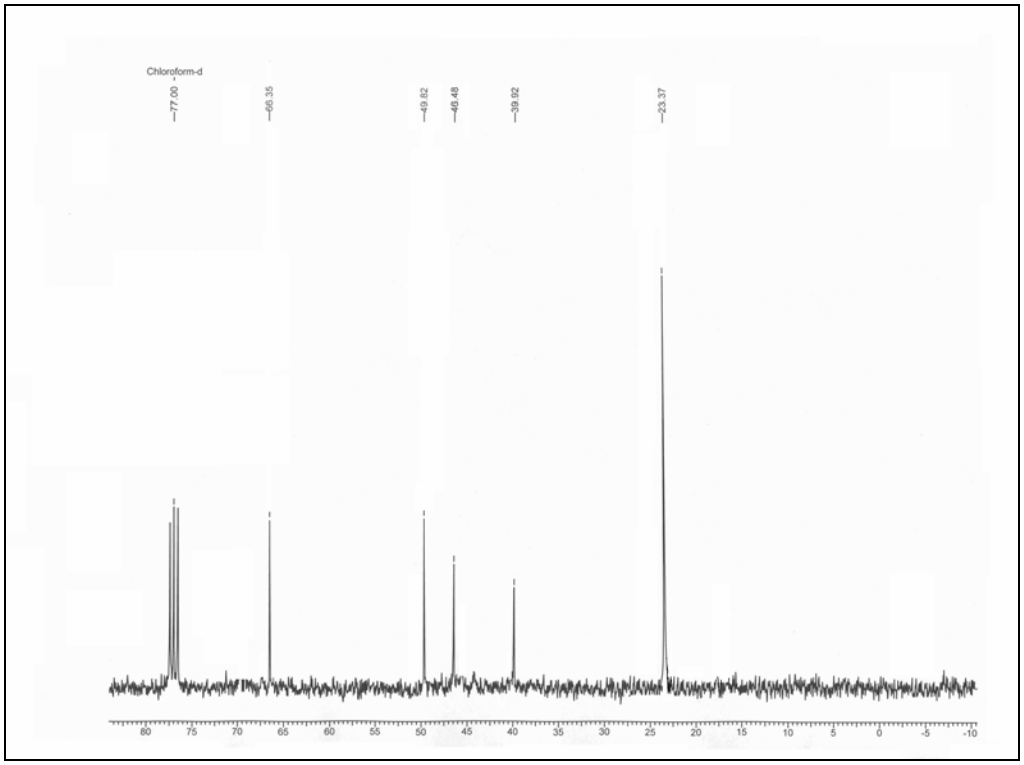


^{1}H NMR Spectrum of compound 120 in $CDCl_3$

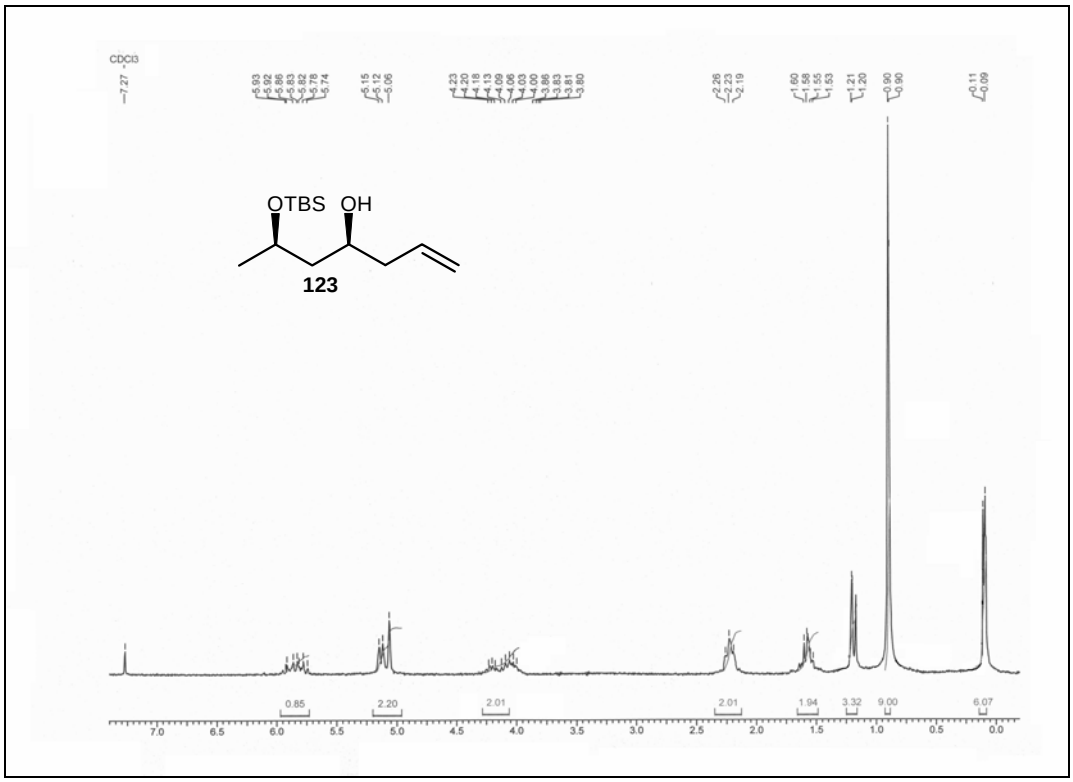


^{13}C NMR Spectrum of compound 120 in $CDCl_3$

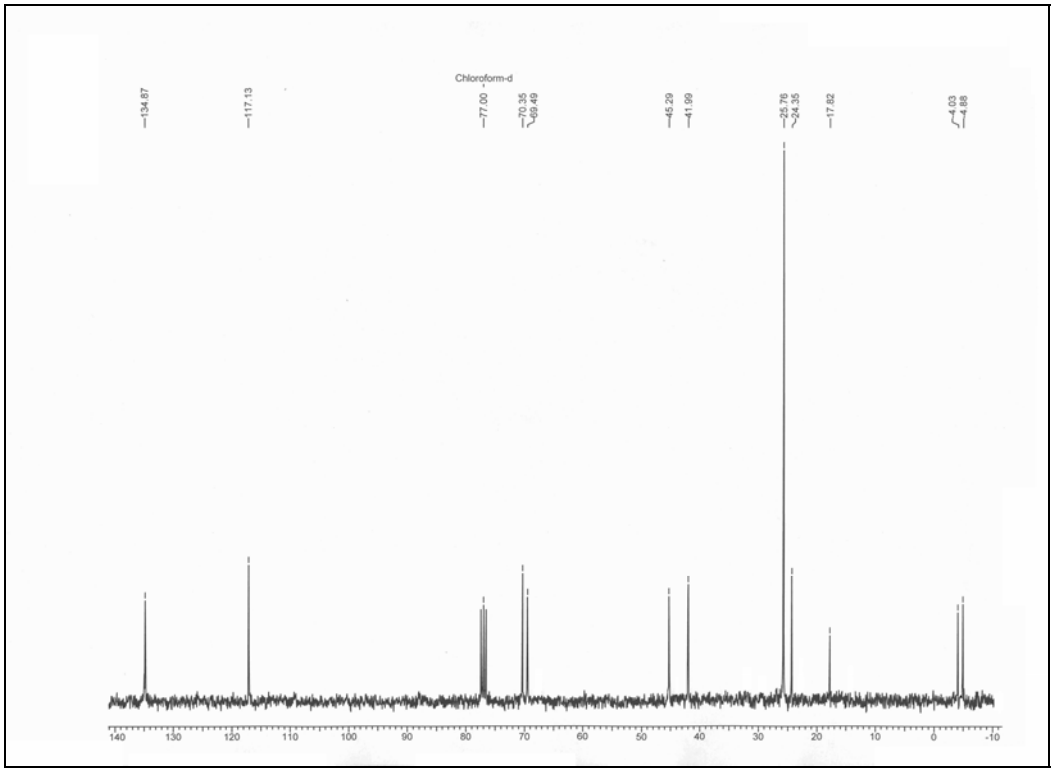
^{1}H NMR Spectrum of compound 122 in $CDCl_3$



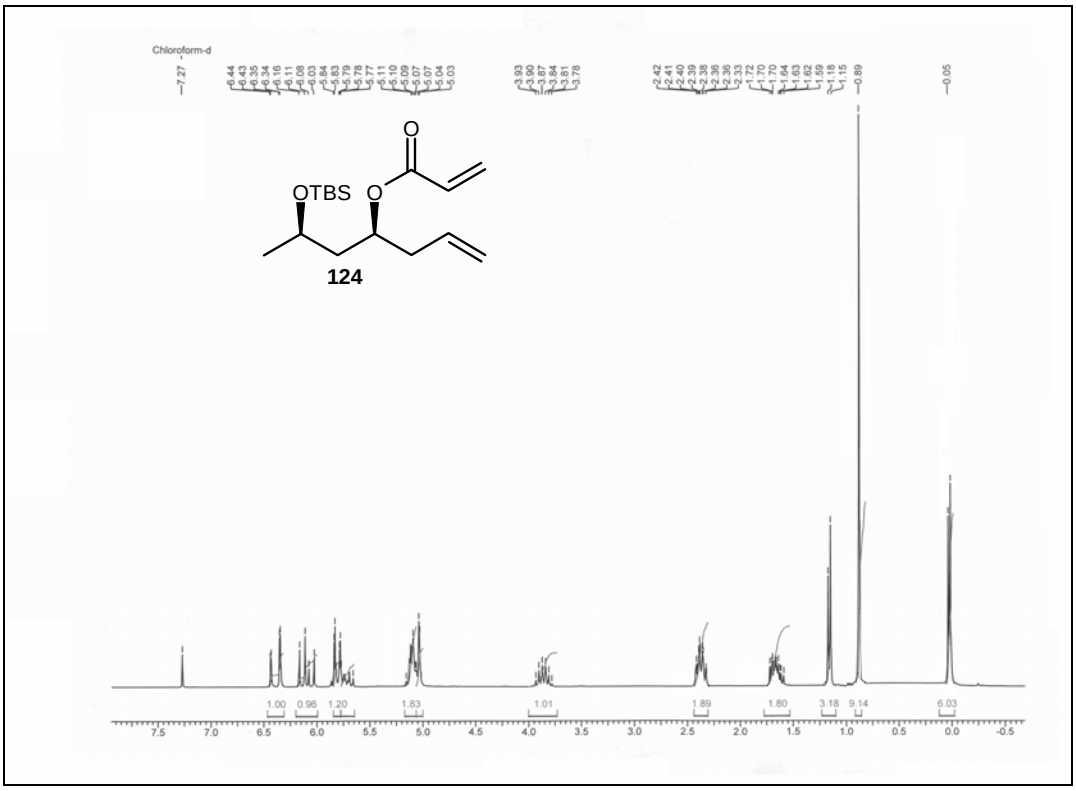
^{13}C NMR Spectrum of compound 122 in $CDCl_3$



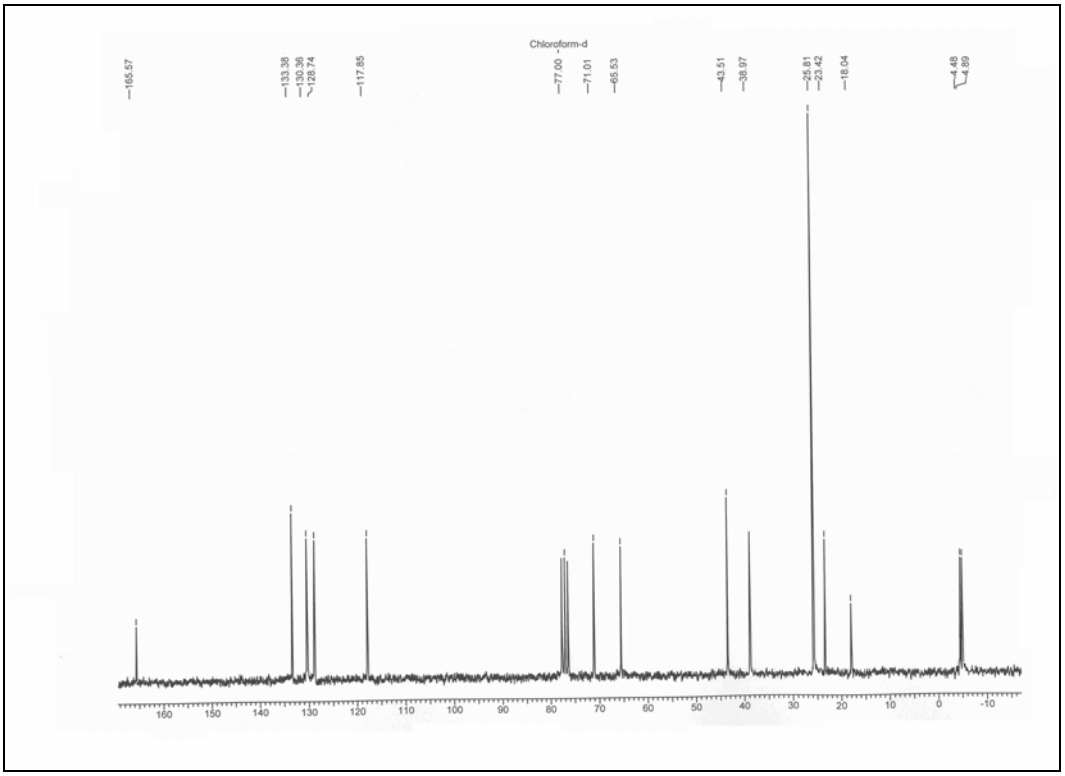
^{1}H NMR Spectrum of compound 123 in $CDCl_3$



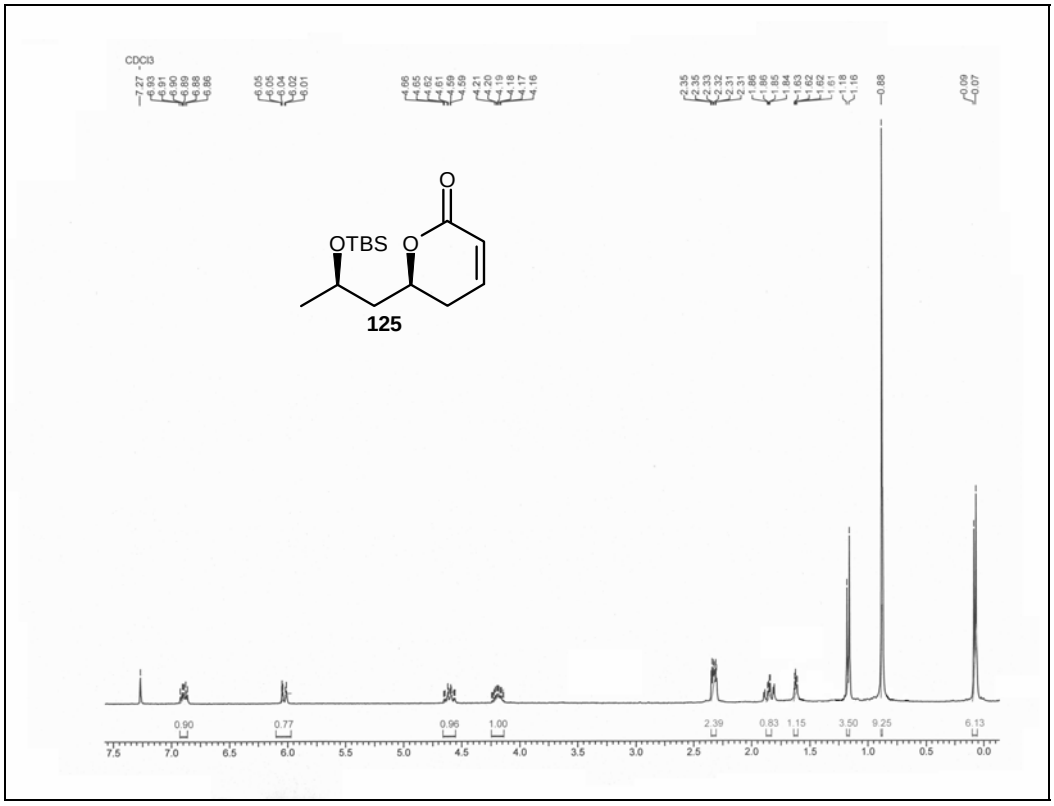
^{13}C NMR Spectrum of compound 123 in $CDCl_3$



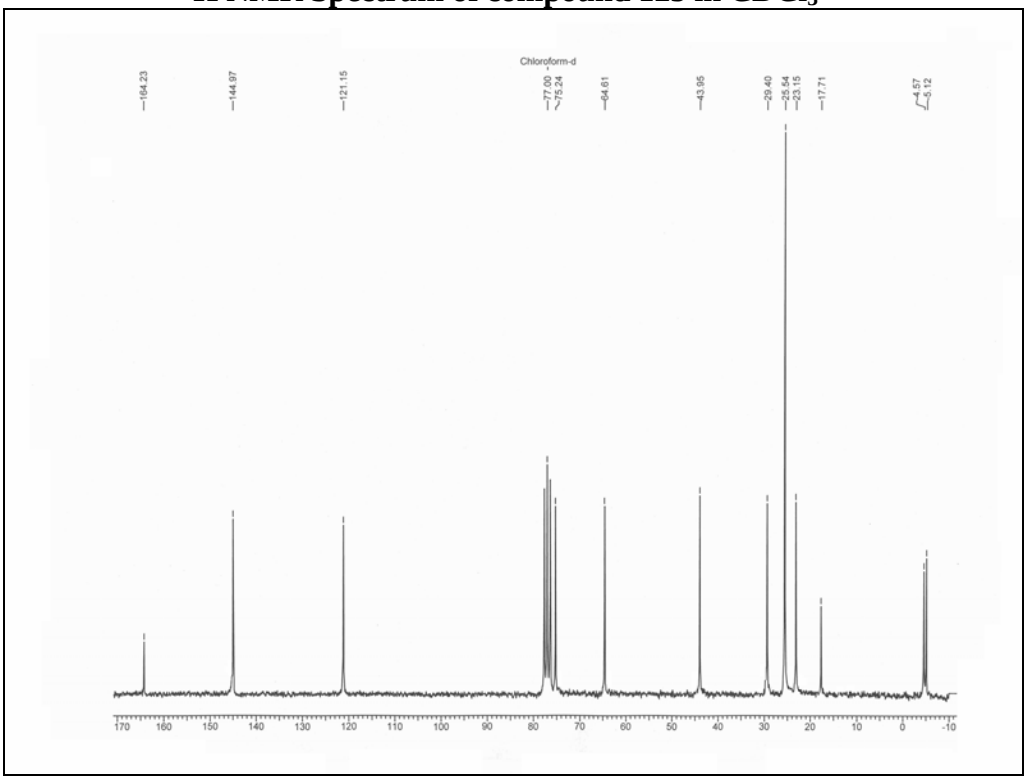
^{1}H NMR Spectrum of compound 124 in $CDCl_3$



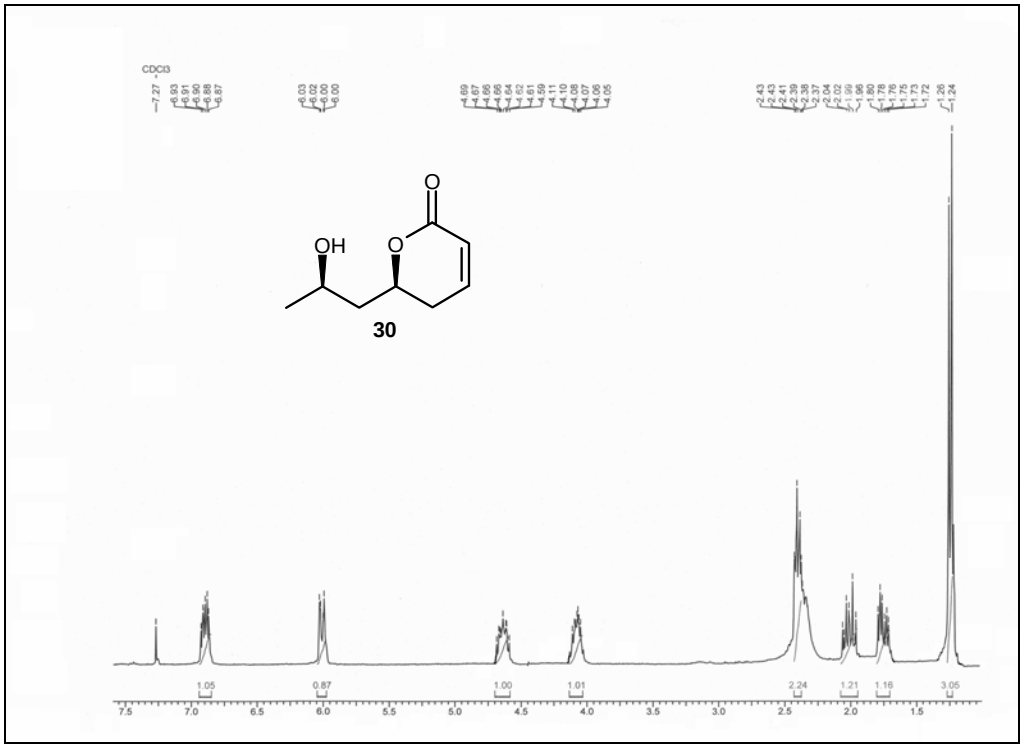
^{1}H NMR Spectrum of compound 124 in $CDCl_3$



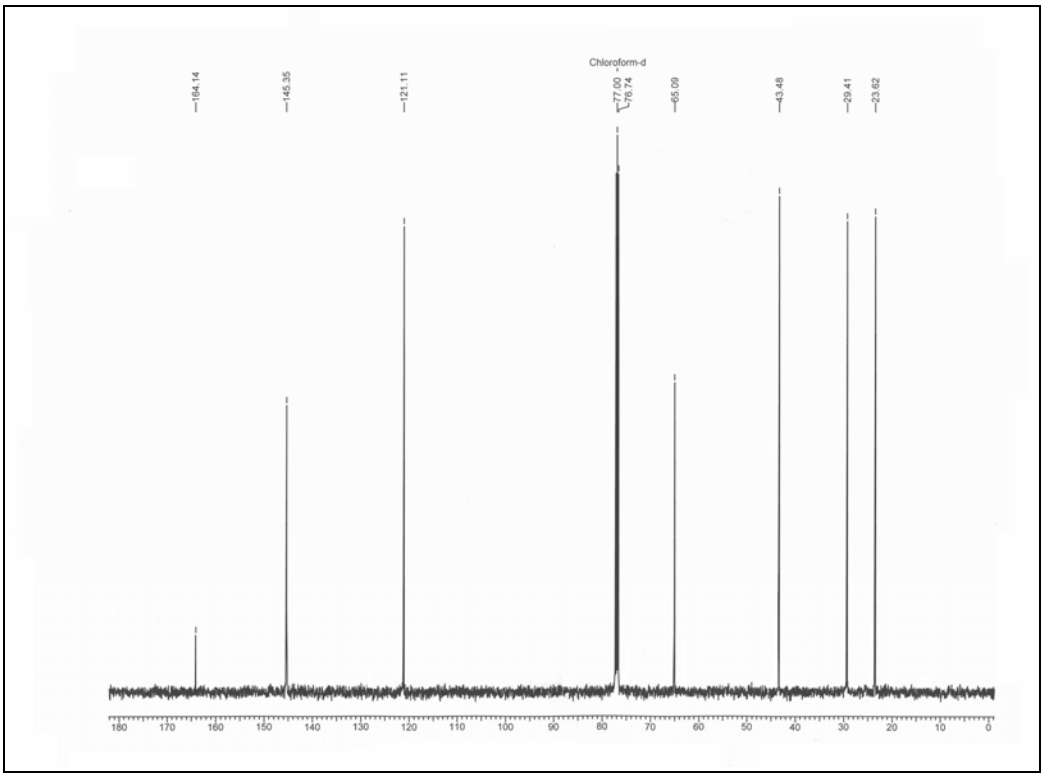
^{1}H NMR Spectrum of compound 125 in $CDCl_3$



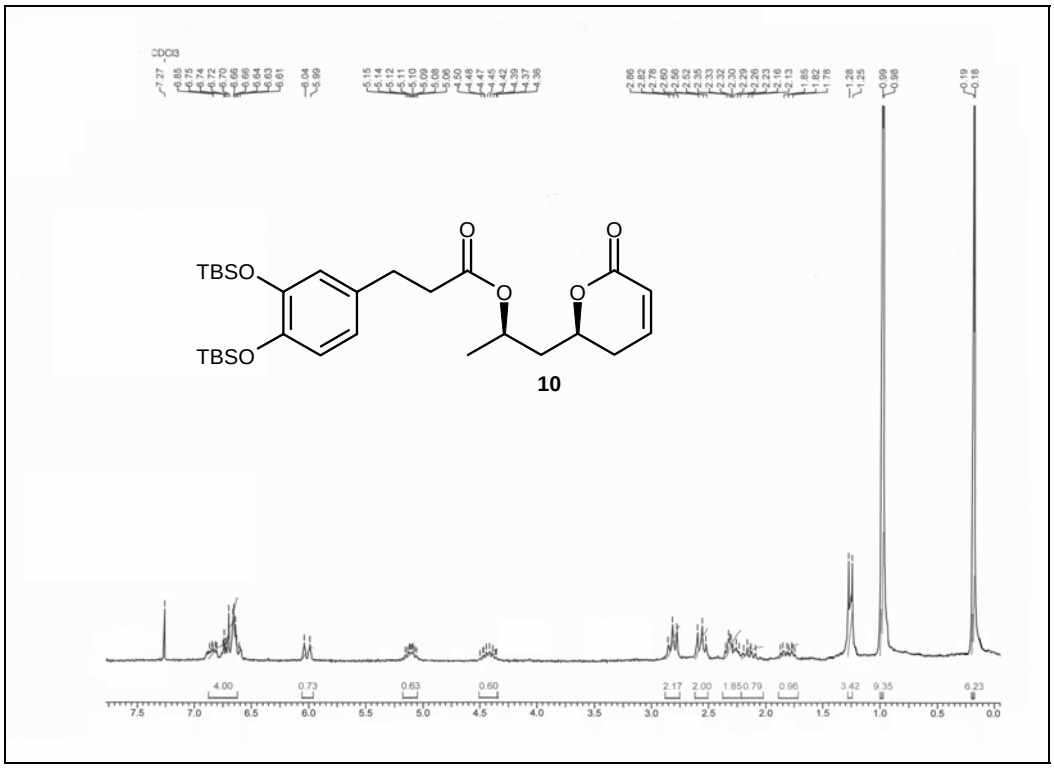
^{13}C NMR Spectrum of compound 125 in $CDCl_3$



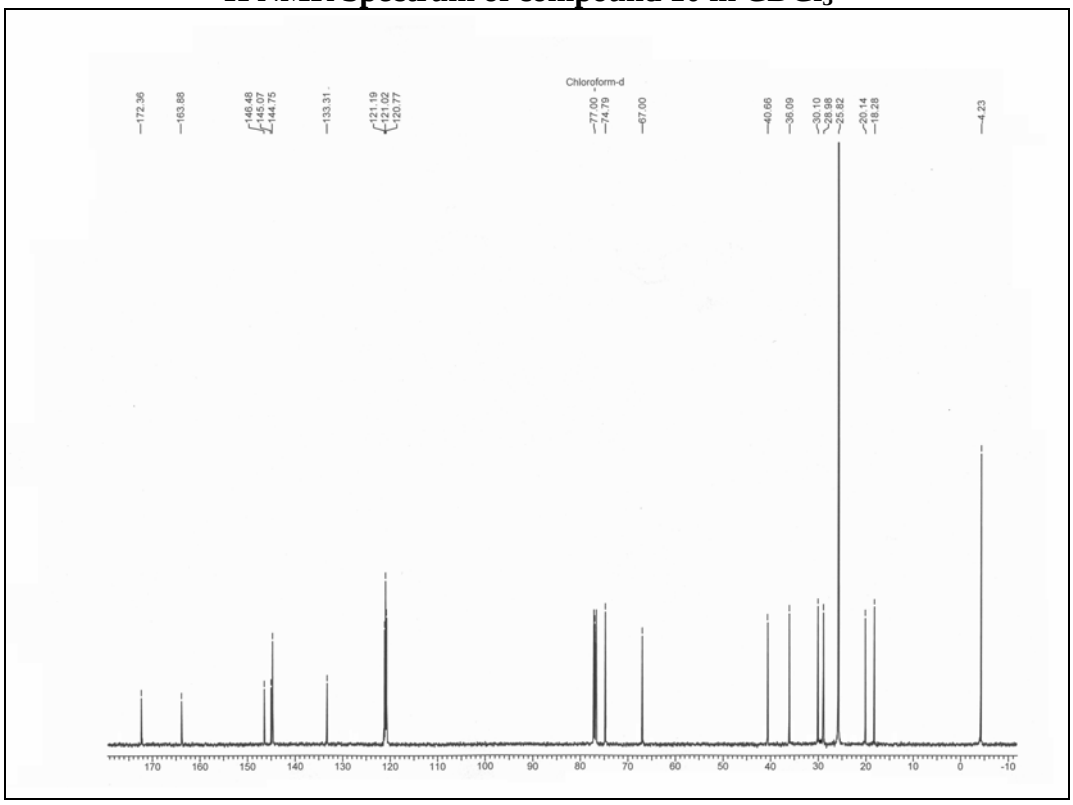
^{1}H NMR Spectrum of compound 30 in $CDCl_3$



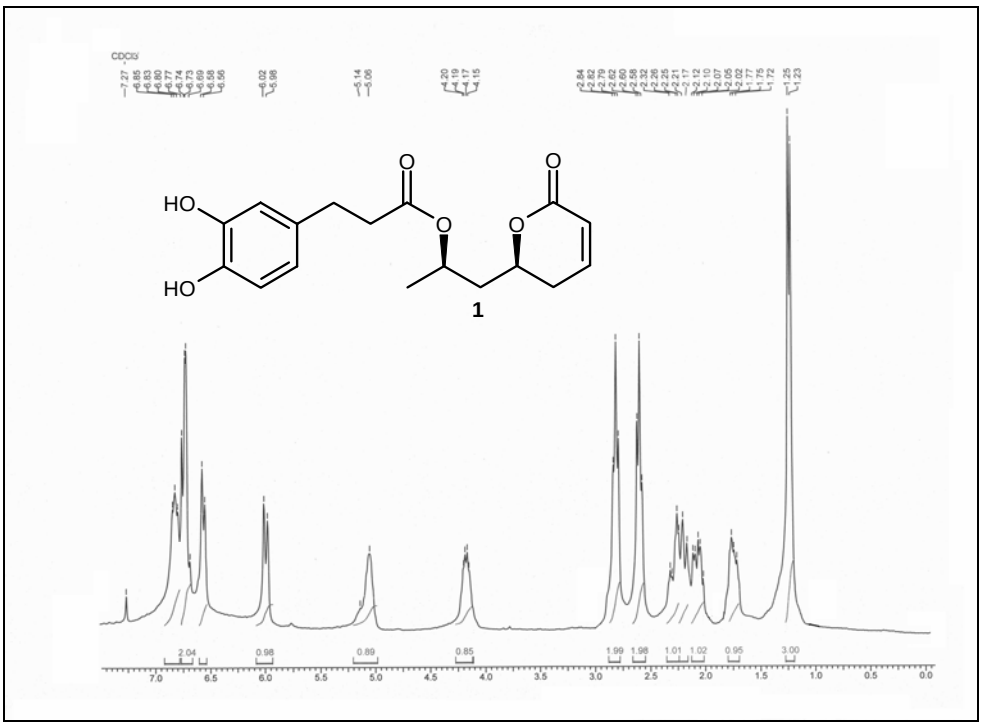
^{1}H NMR Spectrum of compound 30 in $CDCl_3$



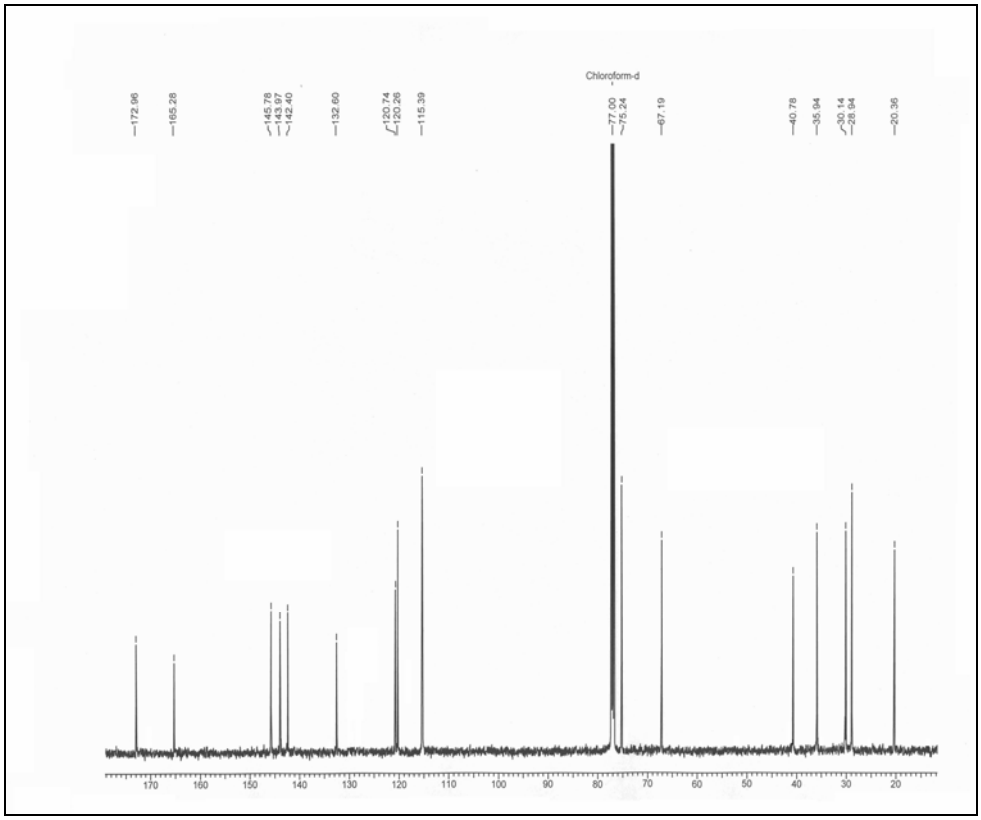
^{1}H NMR Spectrum of compound 10 in $CDCl_3$



^{1}H NMR Spectrum of compound 10 in $CDCl_3$



^{1}H NMR Spectrum of compound 1 in $CDCl_3$



^{13}C NMR Spectrum of compound 1 in $CDCl_3$

4.2 SECTION B

ENANTIOSELECTIVE TOTAL SYNTHESIS OF CRYPTOCARYA DIACETATE

4.2.1. Introduction

The leaves and bark of the South African plant, *Cryptocarya latifolia*, have been long sought after for their legendary magical and medicinal properties.[48] These alleged properties range from the treatment of headaches and morning sickness to the treatment of cancer, pulmonary diseases, and various bacterial and fungal infections.[48] Motivated by these claims, van Staden has tested crude extracts of *C. latifolia* and found significant activity as cyclooxygenase inhibitors (COX-2/COX-1).[49] In a search to find the molecular origins of these effects, Horn found a series of related 6-substituted 5,6-dihydropyran-2-ones in the biologically active hexane and acetone extracts, including cryptocarya diacetate **2** and cryptocarya triacetate **3**,[50] along with two bicyclic pyranone/polyol structures cryptocaryolone **126** and cryptocaryolone diacetate **127** (Figure 1).[50b] The use of activity-guided fractionation led to the discovery of more complex 1,3-polyol/5,6- dihydropyran-2-one natural products from related trees [51, 52] such as passifloricin A and 5,7-bis-*epi*-passifloricin A.[52-54]

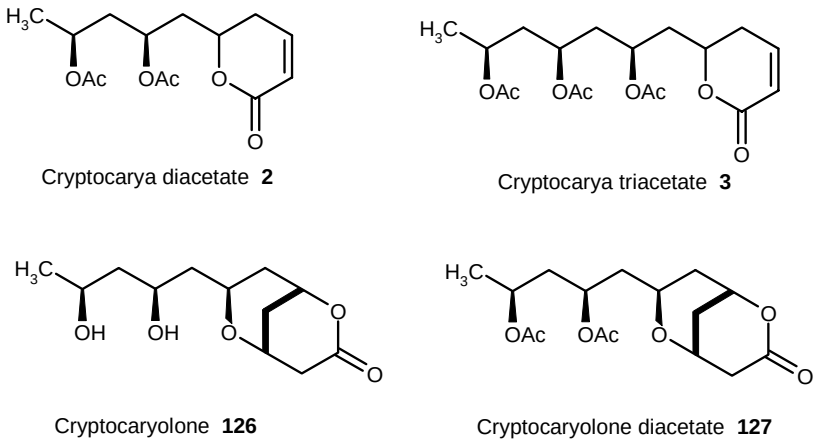


Figure 3

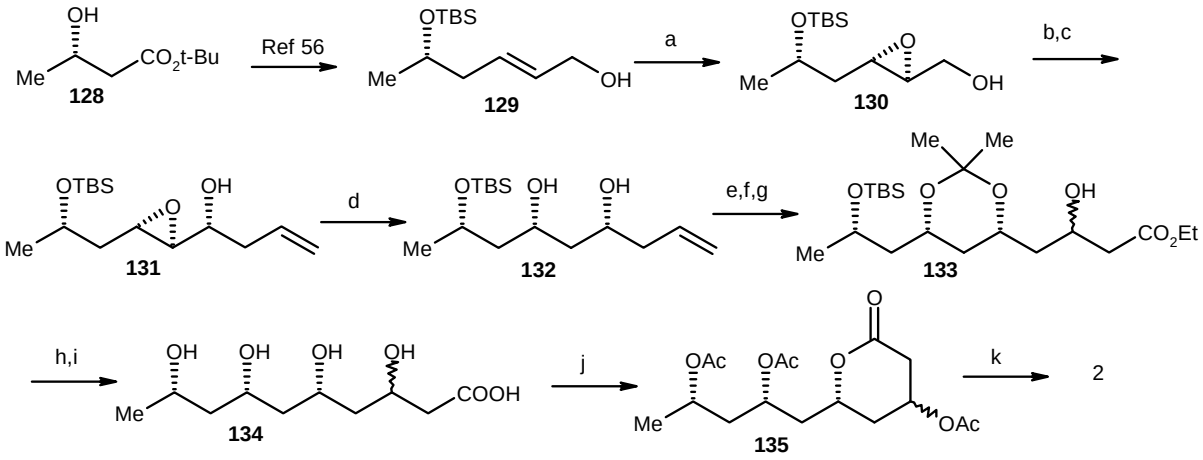
Horn has determined the absolute and relative stereochemistry of the cryptocarya acetates **2** and **3** by a combination of Mosher ester analysis and Rychnovsky ^{13}C NMR/ acetonide analysis.[50b] Finally Nakata confirmed their result by an enantioselective total synthesis of both cryptocarya diacetate and cryptocarya triacetate.[55]

4.2.2. Review of Literature

Various methods for the synthesis of Cryptocarya diacetate **2** have been described in the literature. Nakata et al.[55] confirmed the stereochemistry of **2** via a multistep synthesis, starting with optically active (*S*)-*tert*-butyl 3-hydroxybutyrate. Most of the approaches to the 1,3-diol system are based on asymmetric methods such as Sharpless asymmetric dihydroxylation,[56] Jacobsen's hydrolytic kinetic resolution,[57] asymmetric allylation of aldehydes on solid phase[58] and Prins cyclisation.[59] A detailed report of these syntheses is described below.

Nakata *et al*. (1999).[55]

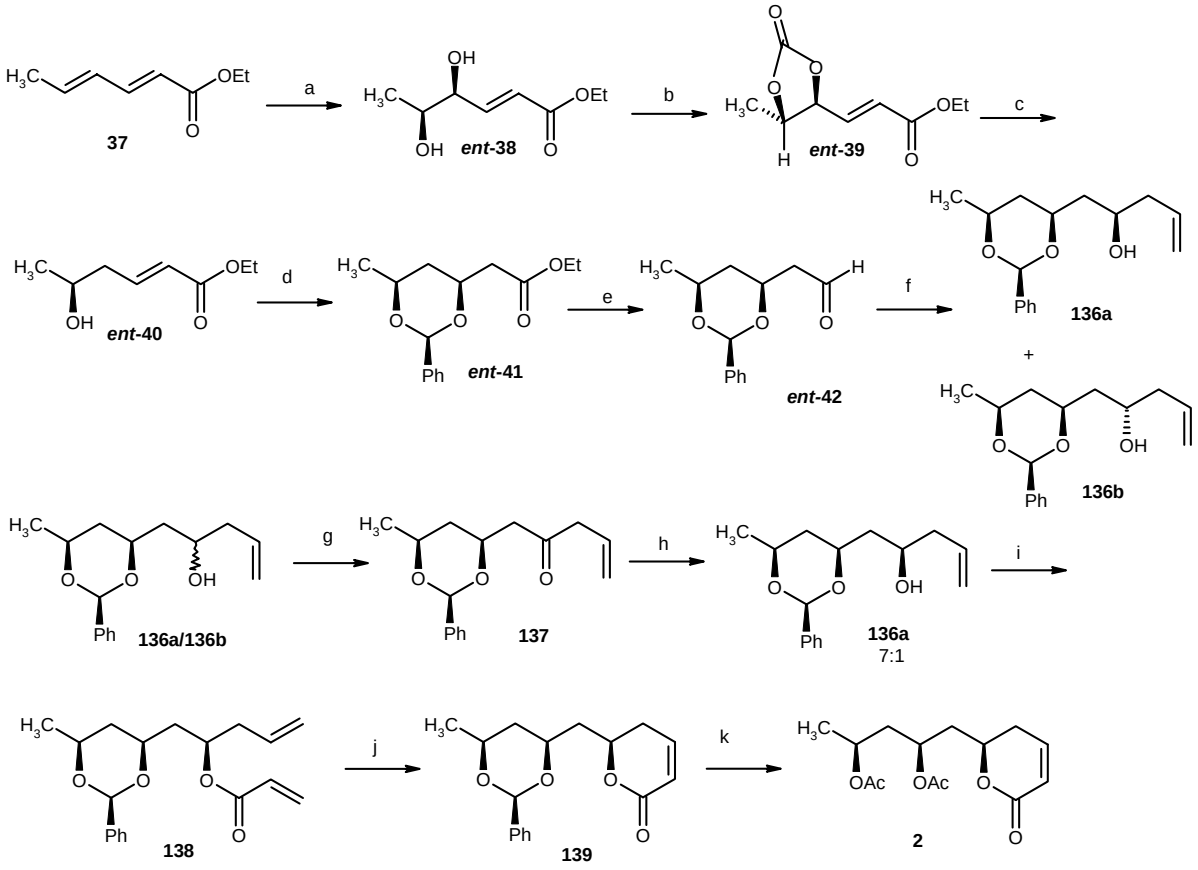
Nakata and co-workers synthesized cryptocarya diacetate by using the Sharpless asymmetric epoxidation and stereoselective addition of an allyl group to the epoxy aldehyde as the key steps. Thus allylic alcohol **129**[60] (prepared from (*S*)-*t*-butyl 3-hydroxybutyrate **128**) was subjected to Sharpless asymmetric epoxidation[28] to give epoxide **130**,[61] which on Swern oxidation followed by treatment of resulting aldehyde with allyltributyltin[62] in the presence of $LiClO_4$ afforded alcohol **131**. The reductive ring opening of epoxide with Cp_2TiCl and *t*-BuSH in THF[63] afforded 1,3-*syn*-diol **132** which on acetonide protection, oxidative cleavage and aldol condensation furnished hydroxy ester **133**. Deprotection of TBS and acetonide group followed by base hydrolysis and acetylation afforded the triacetoxy-δ-lactone **135**, which on reaction with DBU gave the target molecule **2** (Scheme 21).



Scheme 21. *Reagents and conditions*: (a) *t*-BuOOH, (+)-DET, Ti(O*i*-Pr)$_4$, 4A^o MS, CH_2C1_2, -21°C, 80%; (b) $(COC1)_2$, DMSO, CH_2Cl_2, -78°C; Et_3N, -78 °C- rt; (c) allyl$SnBu_3$, 5 M $LiC1O_4$, ether, rt, 60% from **130**; (d) Cp_2TiC1, *t*-BuSH, THF, rt, 78%; (e) $Me_2C(OMe)_2$, CSA, acetone, rt, 97%; (f) OsO_4–*t*-BuOH, NMO, acetone-H_2O, rt; $NaIO_4$, THF-H_2O, rt, 92%; (g) LDA, EtOAc, THF, –78 °C, 90%; (h) Dowex® 50W-X2, MeOH-H_2O, rt; (i) LiOH, THF–H_2O, rt; Dowex® 50W-X_2; (j) Ac_2O, DMAP pyridine, rt; (k) DBU, toluene, rt, 59% from **133**.

Doherty *et al.* (2001).[56]

Doherty and co-workers synthesized cryptocarya diacetate employing the Sharpless asymmetric dihydroxylation[22] and palladium-catalyzed reduction[23] as the key steps. Thus the asymmetric dihydroxylation of ethyl sorbate **37** followed by cyclic carbonate formation and palladium catalyzed reduction gave the δ-hydroxy ester ***ent*-40**, which on reaction with benzaldehyde furnished the 3,5-dihydroxy carboxylic ester ***ent*-41**.[64] To generate the third stereocentre, ester ***ent*-41** was converted into aldehyde followed by allylation to get the 1.2:1 ratio of the desired and undesired homoallylic alcohol *syn*-**136a** and *anti*-**136b**. All the attempts to improve selectivity were unsuccessful. Thus to improve the selectivity, the alcohol **136a** and **136b** was converted into *β*,*γ*-unsaturated ketone followed by reduction using L-selectride at -90 ^{o}C to afford alcohol **136a** in 7: 1 ratio. Alcohol **136a** was esterified followed by ring-closing metathesis, benzylidene deprotection and acetylation to afford the target molecule **2** (Scheme 22).

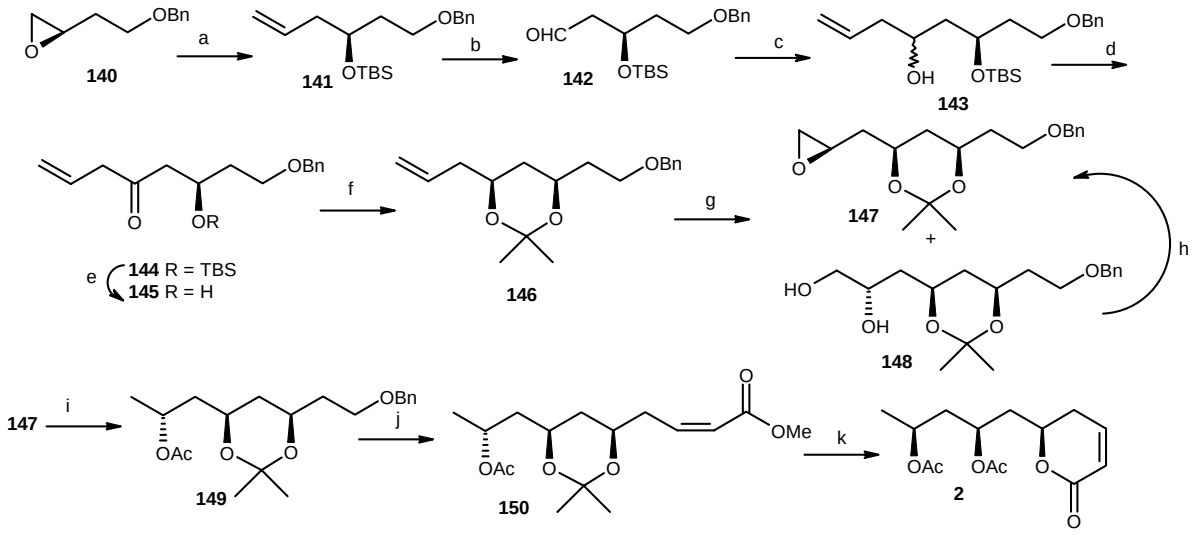


Scheme 22. *Reagents and conditions*: (a) 1% OsO_4, 1.1% $(DHQ)_2PHAL$, $K_3Fe(CN)_6$, $MeSO_2NH_2$, *t*-BuOH/H_2O, 0 ^oC, 71%; (b) $(Cl_3CO)_2CO$, Pyridine, CH_2Cl_2, 87%; (c) HCO_2H, Et_3N, 1% $Pd_2(dba)_3.CHCl_3$, PPh_3, THF, 66 ^oC, 89%; (d) PhCHO, *t*-BuOK, 64%; (e) DIBAL-H, 95%; (f) allylmagnesium chloride, 90%; (g) Dess-Martin, 90%; (h) Li(*s*-Bu)$_3$BH, THF, −90 ^oC, 87%; (i) acrylic acid, DCC, DMAP, CH_2Cl_2, rt, 83%; (j) $(Cy_3P)_2Cl_2Ru$=CHPh, 88%; (k) 4:1 AcOH/H_2O then Ac_2O/DMAP, 77%.

Radha Krishna *et al.* (2005).[57]

Radha Krishna and co-workers reported the synthesis of cryptocarya diacetate by using iterative Jacobsen's hydrolytic kinetic resolution[40,41] and reduction of a ketone as the key steps. As shown in Scheme 23, epoxide **140** (obtained by Jacobsen's HKR of a homoallylic alcohol derivative) was opened with vinylmagnesium bromide followed by TBS protection to afford olefin **141**, ozonolysis of olefin **141** followed by allylation,

oxidation and TBS deprotection afforded ketone **145**, which on selective reduction with $NaBH_4$ in the presence of $B(Et)_2OMe$[65] resulted in exclusive formation of *syn*-1,3-diol, which was characterized as acetonide **146**. Epoxidation of **146** followed by Jacobsen's HKR afforded enantiopure epoxide **147** and diol **148**. Diol **148** was also converted into epoxide **147** with routine functional group transformation. Reductive ring opening of epoxide, followed by acetylation, benzyl deprotection, oxidation and subsequent Wittig olefination with $(F_3CCH_2O)_2POCH_2COOMe$ furnished α,β-unsaturated ester **150**. Finally, acid catalyzed deprotection of the acetonide group with concomitant cyclisation and acetylation afforded target molecule **2**.

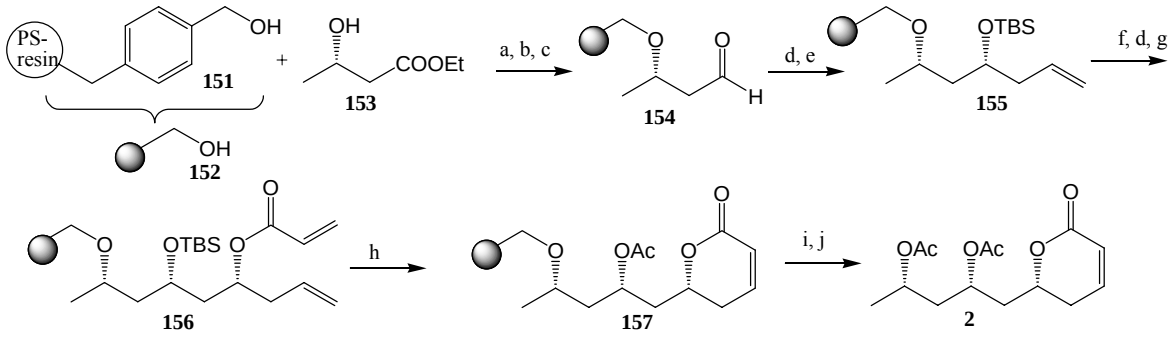


Scheme 23. *Reagents and conditions*: (a) (i) vinylmagnesium bromide, THF, CuI, rt, 74%, (ii) TBSCl, imidazole, rt, 82%; (b) O_3, CH_2Cl_2, –78 °C, 0.5 h, then Me_2S, rt, 0.5 h; (c) allyl bromide, Zn NH_4Cl, THF, rt, 82%; (d) PCC, NaOAc, CH_2Cl_2, rt, 72%; (e) HF–pyridine, THF, rt, 63%, (f) (i) $B(Et)_2OMe$, $NaBH_4$, THF, 75%, (ii) 2,2-dimethoxypropane, PTSA, DMSO, 94%; (g) (i) oxone, acetone, $NaHCO_3$, EDTA (cat.) 73%, (ii) (*R*,*R*)-(salen)CoIII(OAc **112b**, 0.55 equiv H_2O, 43%; (h) (i) LAH, THF, rt, 89%, (ii) Ac_2O, pyridine, DMAP (cat.), CH_2Cl_2, rt, 94%; (i) (i) PhCOCl, Et_3N, CH_2Cl_2, rt, (ii) TsCl, Et_3N, CH_2Cl_2, rt, (iii) K_2CO_3, MeOH, rt; (j) (i) Pd/C, H_2, EtOAc, rt, 95%, (ii) IBX, DMSO, rt, (iii) $(F_3CCH_2O)_2POCH_2COOMe$, KHMDS, 18-crown-6, THF, –78 °C, 79% over two steps; (k) (i) 80% aq AcOH, (ii) PTSA, C_6H_6, (iii) Ac_2O, pyridine, CH_2Cl_2, DMAP (cat.), rt, 86% over three steps.

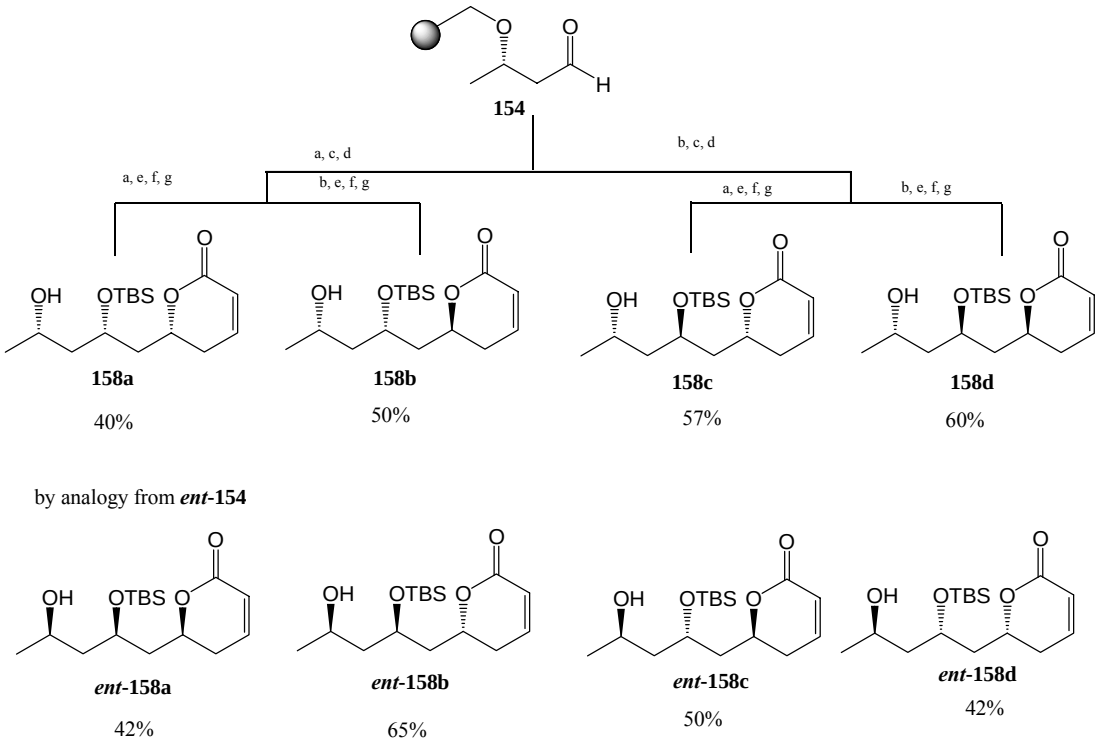
Waldmann *et al.* (2006).[58]

Waldmann and co-workers synthesized all isomers of cryptocarya diacetate by enantiocomplementary allylation of solid phase-bound aldehyde employing chiral allylboranes. (*S*)-3-Hydroxybutyric acid ester was immobilized on Wang resin, activated as the trichloroacetimidate and converted into polymer-bound aldehyde in two steps. Allylation of **154** with *l*-Ipc$_2$BAll and protection of the secondary alcohol as silyl ether furnished resin **155**, which was formed in a *syn* : *anti* ratio of 85 : 15. Ozonolysis of **155** followed by second allylation and esterification furnished acrylic ester **156**, which on ring-closing metathesis with Grubbs II generation catalyst afforded lactone **157**. Release from the solid support, with consecutive cleavage of the silyl group and subsequent acetylation, yielded a mixture of four stereoisomers (Scheme 24).

Based on above reaction sequence, all eight stereoisomers were synthesized for cryptocarya diacetate (Scheme 25).



Scheme 24. *Reagents and conditions*: (a) **152** (1.2 mmol g^{-1}), trichloroacetonitrile, DBU, CH_2Cl_2, then **138**, $BF_3.OEt_2$, cyclohexane/CH_2Cl_2; (b) DIBAL–H, THF, –78 ^oC to rt, 16 h, (c) IBX, DMSO/THF, rt, 16 h; (d) (i) 3 equiv. Ipc$_2$BAll, THF, –78 ^oC, (ii) pH 7 buffer, H_2O_2 30%, DMF/MeOH 1 : 1, 0 ^oC, 2 h; (e) TBS–Cl, imidazole, cat. DMAP, CH_2Cl_2, rt, 16 h; (f) O_3, CH_2Cl_2, –78 ^oC, then PPh_3, –78 ^oC to rt; (g) acryloyl chloride, Et_3N, cat. DMAP,CH_2Cl_2, 0 ^oC to rt, 16 h; (h) 2 X 20 mol% Grubbs II catalyst, CH_2Cl_2, reflux, 24 h; (i) trifluoroacetic acid/CH_2Cl_2 1 : 2, 20 min, rt; (j) Ac_2O, Et_3N, cat. DMAP, CH_2Cl_2, 0 ^oC to rt, 3 h.

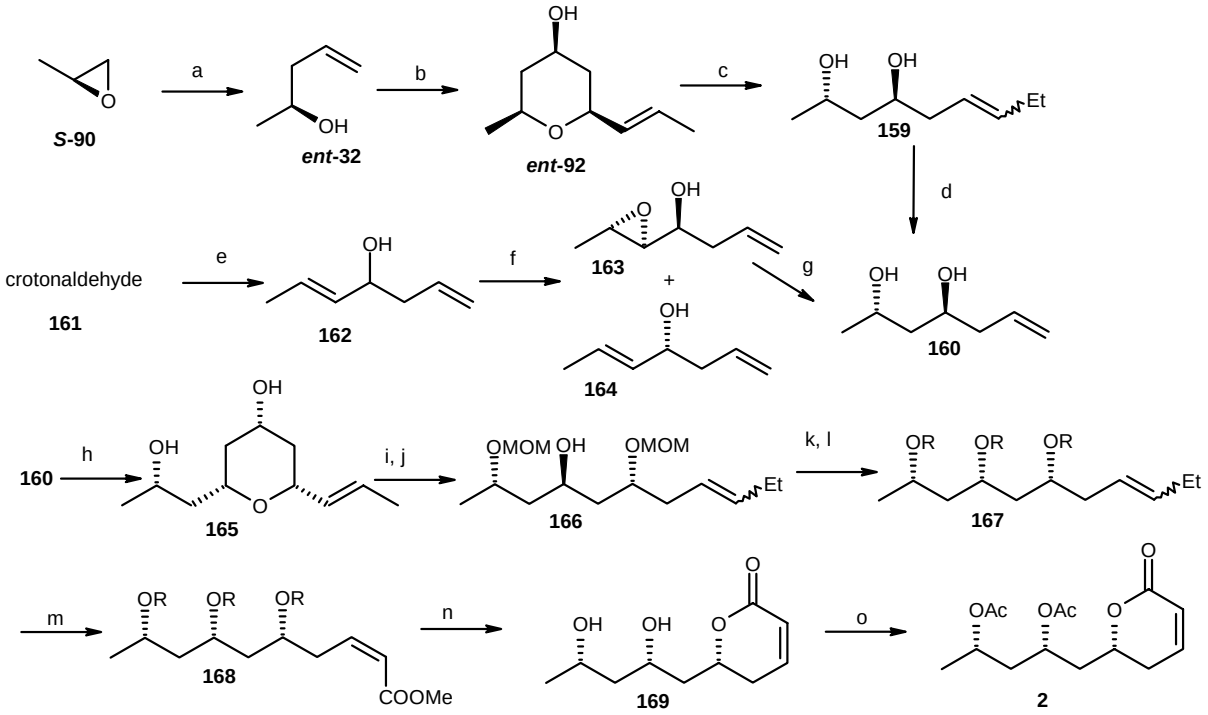


Scheme 25. *Reagents and conditions*: (a) (i) 3 equiv. Ipc_2BAll, THF, -78 ^oC; (ii) pH 7 buffer, H_2O_2 30%, DMF/MeOH 1 : 1, 0 ^oC, 2 h; (b) (i) 3 equiv. 2, THF, –78 ^oC; (ii) pH 7 buffer, H_2O_2 30%, DMF/MeOH 1 : 1, 0 ^oC, 2 h; (c) TBSCl, imidazole, cat. DMAP, CH_2Cl_2, rt, 16 h; (d) O_3, CH_2Cl_2, –78 ^oC, then PPh_3, –78 ^oC to rt; (e) acryloyl chloride, Et_3N, cat. DMAP, CH_2Cl_2, 0 ^oC to rt, 16 h; (f) 20 mol% Grubbs II catalyst, CH_2Cl_2, reflux, 24 h; (g) 10 equiv. DDQ, CH_2Cl_2, pH 7 buffer, 0 ^oC to rt, 16 h.

Yadav *et al.* (2007).[59]

Yadav and co-workers accomplished the synthesis of tarchonanthuslactone from propylene oxide employing the Prins cyclisation as the key step. Thus (*R*)-propylene oxide (***S*)-90** (obtained via Jacobsen's hydrolytic kinetic resolution)[40,41] was converted into alcohol ***ent*-32**, which on Prins cyclisation[39] with crotonaldehyde followed by hydrolysis furnished tetrahydropyran ***ent*-92**. Treatment of ***ent*-92** with Na in liquid ammonia gave 1,3-diol **159**, as a 1: 1 diastereomeric mixture, which on ozonolysis and Wittig olefination afforded diol **160**. Alternatively, diol **160** was obtained from crotonaldehyde via allylation, Sharpless asymmetric epoxidation and reduction. Prins cyclisation of **160** with crotonaldehyde followed by hydrolysis resulted tetrahydropyran **165**. Protection of hydroxy as MOM ether followed by treatment with Na in liquid ammonia gave alcohol **166**, as a 1: 1

diastereomeric mixture. Mitsunobu reaction of alcohol **166**, followed by MOM protection, ozonolysis and Wadsworth-Emmons reaction using methyl(bistrifluoroethyl)phosphonoacetate furnished *Z*-unsaturated ester **168**, which on MOM deprotection, lactonization and acetylation afforded target molecule cryptocarya diacetate **2** (Scheme 26).



Scheme 26. *Reagents and conditions*: (a) vinylmagnesium bromide, CuCN, THF, –78 to –40 ^{o}C, 4 h, 92%; (b) crotonaldehyde, TFA, CH_2Cl_2 then K_2CO_3, MeOH, rt, 4 h, 70%; (c) Na, liq. NH_3, THF, –33 ^{o}C, 45 min, 90%; (d) O_3, TPP, CH_2Cl_2, –78 ^{o}C, then CH_3PPh_3I, KO^{t}Bu, THF, 0 ^{o}C, 2 h, 60%; (e) allyl bromide, Zn, DMF, rt, 30 min, 85%; (f) (+)-DIPT, Ti(O*i*Pr)$_4$, CH_2Cl_2, TBHP (49 mol %), 4 A˚ MS, –20 ^{o}C, 20 h, 40% of **163**; (g) Red-Al, THF, rt, 12 h, 82%; (h) crotonaldehyde, TFA, CH_2Cl_2 then K_2CO_3, MeOH, rt, 4 h, 55%; (i) MOMCl, DIPEA, DMAP, CH_2Cl_2, 0 ^{o}C–rt, 4 h, 92%; (j) Na, liq NH_3, THF, –33 ^{o}C, 45 min, 86%; (k) DEAD, TPP, *p*-$C_6H_4(NO_2)COOH$, THF, 30 min, 0 ^{o}C–rt then K_2CO_3, MeOH, rt, 1 h, 78%; (l) MOMCl, DIPEA, DMAP, CH_2Cl_2, 0 ^{o}C–rt, 4 h, 90%; (m) O_3, TPP, CH_2Cl_2, –78 ^{o}C then $(F_3CCH_2O)_2POCH_2COOMe$, NaH, 0 ^{o}C, 2 h, 70%; (n) conc. HCl, MeOH, rt, 6 h then *p*TSA, benzene, rt, 4 h; (o) Ac_2O, py, DMAP, CH_2Cl_2, rt, 3 h, 70% (three steps).

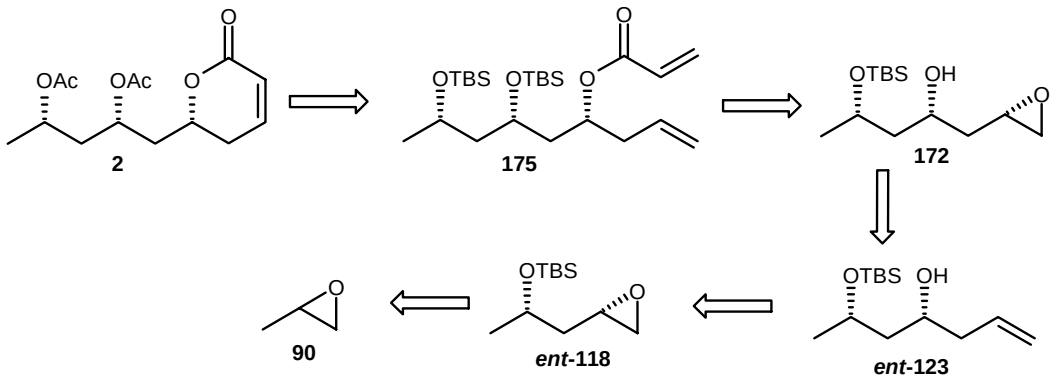
4.2.3. Present work:

Objective:

As discussed in foregoing section, with the development of an efficient approach to the synthesis of 1,3-polyols and its subsequent application towards the synthesis of tarchonanthuslactone through HKR, our attention was further focused to extrapolate this protocol for the synthesis of cryptocarya diacetate. Although quite a few synthesis of cryptocarya diacetate are documented in the literature, a general strategy with limited steps and higher optical purity is still desirable.

In this section we describe our successful endeavors to the stereoselective total synthesis of cryptocarya diacetate **2**, employing hydrolytic kinetic resolution (HKR),[40,41] diastereoselective iodine induced electrophilic cyclization[43] and ring-closing metathesis[19] as the key steps. The HKR method involves the readily accessible cobalt based chiral salen complex as catalyst (Figure 2) and water to resolve a racemic epoxide into an enantiomerically enriched epoxide and diol in high enantiomeric excess. Similarly the iodolactonization of an enantiomerically pure homoallylic alcohol directs the epoxidation of a double bond in diastereoselective manner to afford the *syn*-epoxy alcohol.

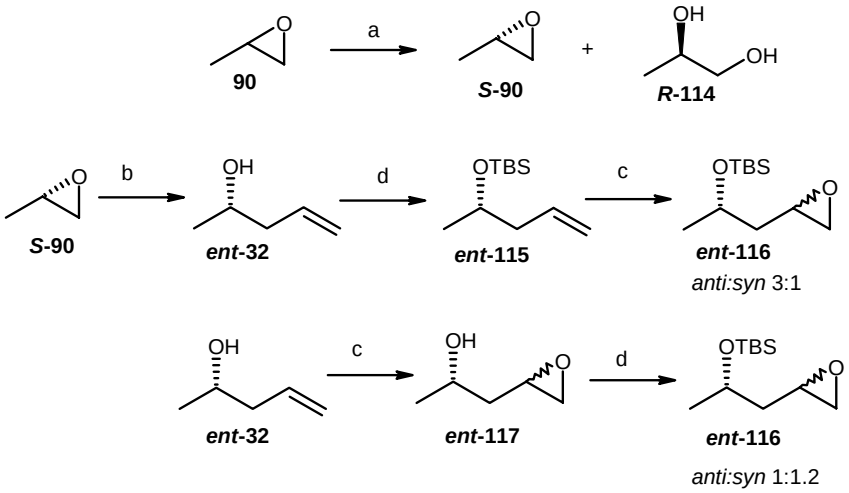
Our retrosynthetic strategy for the synthesis of **2** is outlined in Scheme 27. We envisioned that the lactone moiety could be constructed by ring closing metathesis of an acrylate ester **175**, which in turn could be obtained from epoxide **172**. The epoxide **172** could be prepared from homoallylic alcohol ***ent*-123** via diastereoselective iodine induced electrophilic cyclization, which in turn could be prepared from epoxide ***ent*-118**. The epoxide ***ent*-118** could be prepared via iterative HKR from racemic propylene oxide **90**.



Scheme 27. Retrosynthetic analysis for Cryptocarya diacetate

4.2.4. Results and Discussion:

In designing a route to **2**, we chose propylene oxide as an appropriate starting material. Our synthesis of **2** requires three major reactions, Jacobsen's hydrolytic kinetic resolution, diastereoselective iodine induced electrophilic cyclization to install the stereogenic centers, and ring-closing metathesis to construct the δ-lactone moiety. As shown in Scheme 28, commercially available propylene oxide **90** was subjected to Jacobsen's HKR by using (*S*,*S*)-salen-Co-OAc catalyst **112a** (Figure 2) to give (*S*)-propylene oxide[40] **(*S*)-90** as a single isomer, $[\alpha]_D^{25}$ -11.4 (neat); lit.[40] $[\alpha]_D^{25}$ -11.6 (neat), which was easily isolated from the more polar diol **(*R*)-114** by distillation.



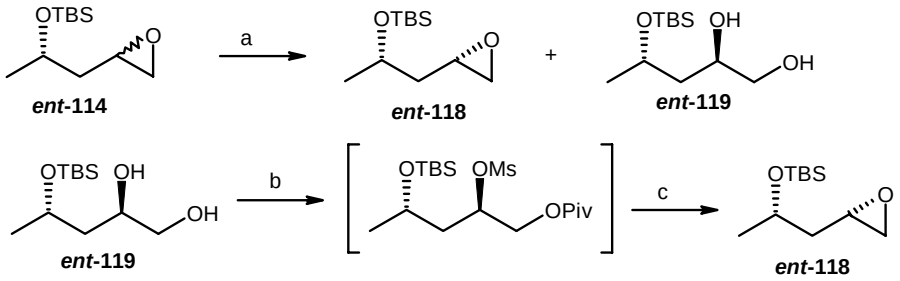
Scheme 28. (a) *S*,*S*-Salen-Co-(OAc) (0.5 mol%), dist. H_2O (0.55eq), 0 ^oC, 14 h, (45% for **(*S*)-90**, 43% for **(*R*)-114**); (b) Vinylmagnesium bromide, CuI, THF, -20 ^oC, 12 h, 87%; (c) *m*-CPBA, CH_2Cl_2, 0 ^oC to rt, 10 h, 96%; (d) TBDMS-Cl, imidazole, CH_2Cl_2, 0 ^oC to rt, 4 h, 95%.

With enantiomerically pure epoxide **(*S*)-90** in hand, our next aim was to construct the *syn*-1,3-diol. To establish the second stereogenic center with required stereochemistry, we then examined the stereoselective epoxidation of a homoallylic alcohol. Thus (*S*)-propylene oxide **(*S*)-90** was treated with vinylmagnesium bromide in the presence of CuI to give the homoallylic alcohol ***ent*-32** in excellent yield. The IR spectrum of ***ent*-32** gave broad hydroxyl absorption at 3400 cm^{-1}. The ^1H NMR spectrum of ***ent*-32** gave olefin peaks at 5.77-5.85 (multiplet, one proton), 5.12 (doublet, one proton), 5.09 (doublet, one proton). We then further proceeded to explore the stereoselective outcome of epoxidation reaction

with and without hydroxyl group protection. Towards this end, the hydroxyl group of homoallylic alcohol ***ent*-32** was first protected as the TBS ether, followed by epoxidation with *m*-CPBA. The epoxide thus obtained was found to be a mixture of two diastereomers (*anti:syn* / 3:1). The desired *syn* isomer of ***ent*-116** was obtained only as a minor component. On the contrary, the epoxidation on homoallylic alcohol ***ent*-32** followed by hydroxy group protection as the TBS-ether gave the epoxide ***ent*-116** in favour 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).

Synthesis of diastereomerically pure epoxide *ent*-118 and conversion of diol *ent*-119 into epoxide *ent*-118 (Scheme 29).

With epoxides ***ent*-114** (*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, which could further be elaborated to *syn*/*anti*-1,3-polyol moiety. Towards this end, the epoxide ***ent*-114** was treated with (*S*,*S*)-salen-Co-OAc complex **112a** (0.5 mol%) and water (0.55 eq) in THF (0.55 eq) to afford the epoxide ***ent*-118** as a single stereoisomer (as determined from the ^{1}H and ^{13}C NMR spectral analysis) in 46% yield and the diol ***ent*-119** in 45% yield. Epoxide ***ent*-118** could easily be separated from the more polar diol ***ent*-119** through silica gel column chromatography.



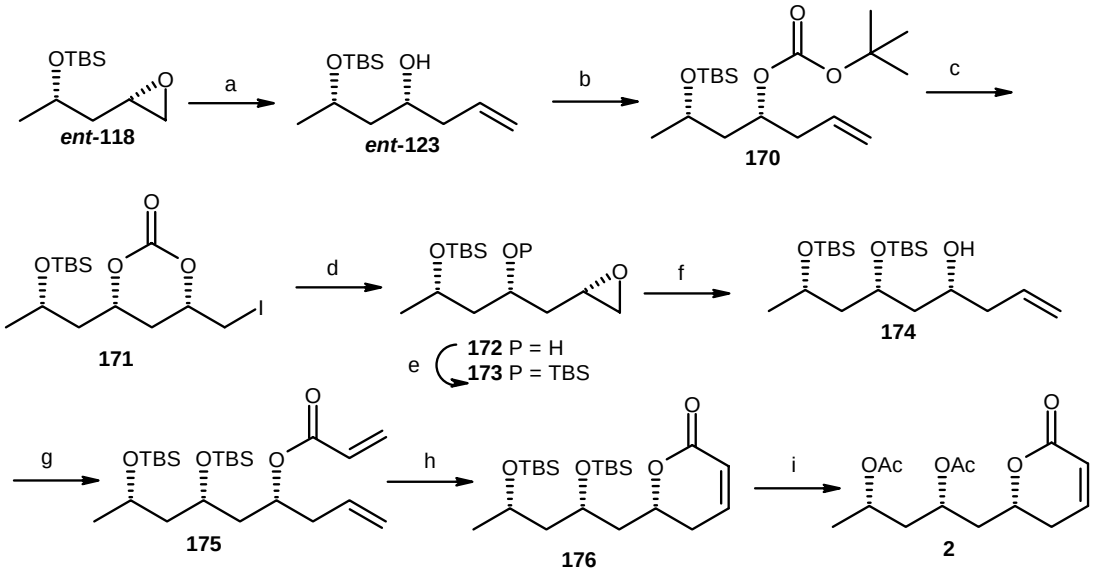
Scheme 29. (a) *S*,*S*-Salen-Co-(OAc) (0.5 mol%), dist. H_2O (0.55 eq), THF, 0 ^{o}C, 24 h, (46% for ***ent*-118**, 45% for ***ent*-119**); (b) (i) PivCl, Et_3N, Cat. DMAP, rt, 2 h; (ii) MsCl, Et_3N, DMAP, 0 ^{o}C to rt, 1h; (c) K_2CO_3, MeOH, rt, overnight, (61% for three steps).

In order to achieve the synthesis of target molecule **2**, we required epoxide ***ent*-118** in substantial amount. As the HKR method provided the desired epoxide ***ent*-118** along with unwanted diol ***ent*-119** 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.[46] Accordingly, chemoselective pivalation of diol ***ent*-119** with pivaloyl chloride followed by mesylation of the secondary hydroxyl and treatment of the crude mesylate product with K_2CO_3 in methanol led to deprotection of the pivaloyl ester. Concomitant ring closure via intramolecular S_N2 displacement of the mesylate furnished the epoxides ***ent*-118** in 61% overall yield (Scheme 29).

Synthesis of cryptocarya diacetate 2

The synthesis of cryptocarya diacetate **2** was accomplished starting from epoxide ***ent*-118** as depicted in Scheme 30. Thus, ***ent*-118** was first treated with vinylmagnesium bromide in the presence of CuI in THF at –20 ^oC to give the homoallylic alcohol ***ent*-123** in 82% yield. The IR spectrum of ***ent*-123** gave broad hydroxyl absorption at 3460 cm^{-1}. The ^1H NMR spectrum of ***ent*-123** gave olefin peaks at δ 5.74-5.93 (multiplet, one proton), 5.15 (doublet, one proton), 5.06 (doublet, one proton). With substantial amount of homoallylic alcohol in hand we then investigated the stereoselective epoxidation of the C-C double bond. As a more direct approach the diastereoselective epoxidation of the homoallylic alcohol ***ent*-123** was examined without success using Sharpless protocol[66] with *tert*-butyl hydroperoxide in the presence of vanadium acetylacetonate. The desired *syn*-epoxy alcohol **172** was isolated in moderate yield with low selectivity. To achieve this transformation with an excellent level of diastereoselectivity, we applied a three-step sequence based on a modified Cardillo iodo cyclization procedure.[47] Following this methodology, the homoallylic *tert*-butyl carbonate **170** was prepared from the corresponding alcohol ***ent*-123** in 90% yield by treatment with di-*tert*-butyl dicarbonate in the presence of DMAP in acetonitrile. The IR spectrum of **170** showed absence of hydroxyl group, Boc carbonyl appeared at 1737 cm^{-1}. ^{13}C NMR spectra showed the ester carbonyl at 153.2. The diastereoselective iodine induced electrophilic cyclization of the homoallylic *tert*-butyl carbonate **170** with IBr at low temperature (-85 ^oC) furnished the iodo carbonate **171** which was directly treated with K_2CO_3 in methanol to give the desired *syn*-epoxy alcohol **172** as a single diastereomer in 81% yield. The IR spectrum of **172** gave broad hydroxyl

absorption at 3471 cm^{-1}. The epoxide peaks appeared at δ 3.08-3.14 (multiplet, one proton), 2.79 (doublet of doublet, J = 4.8, 4.0 Hz, one proton), 2.52 (doublet of doublet, J = 5.1, 2.8 Hz, one proton). The epoxy alcohol **172** was treated with TBS chloride to furnish the TBS protected epoxide **173** in 89% yield. The IR spectrum of **173** showed absence of hydroxyl group. The opening of the epoxide **173** with vinylmagnesium bromide in the presence of CuI in THF at –20 ^{o}C furnished the homoallylic alcohol **174** in 80% yield. The IR spectrum of **174** gave broad hydroxyl absorption at 3469 cm^{-1}. The ^{1}H NMR spectrum of **174** gave olefin peaks at δ 5.74-5.96 (multiplet, one proton), 5.15 (doublet, J = 6.1 Hz, one proton), 5.07 (doublet, J = 2.9 Hz, one proton). Alcohol **174** was esterified with acryloyl chloride in the presence of Et_3N and catalytic amount of DMAP to afford the acryloyl ester **175** in 82% yield. The IR spectrum of **175** indicated absence of hydroxyl group, acryloyl carbonyl appeared at 1719 cm^{-1}. The carbonyl carbon appeared at δ 165.8 in the ^{13}C NMR spectrum. Subsequent ring closing metathesis[21] of ester **175** with commercially available Grubbs' 1st generation catalyst **113a** 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 **176** in 84% yield having +42.69 (*c* 0.82, $CHCl_3$). The IR spectrum of **176** showed characteristic carbonyl group absorption of α,β-unsaturated δ-lactone at 1721 cm^{-1}. The olefin protons appeared at 6.88 (doublet of doublet of doublet) with J = 9.6, 5.8, 2.1 Hz, 6.05 (doublet of doublet of doublet) with J = 9.6, 1.9, 1.6 Hz, in the ^{1}H NMR spectrum. The olefinic carbons appeared at δ 144.8 and 121.5 in ^{13}C NMR spectrum.



Scheme 30. (a) Vinylmagnesium bromide, THF, CuI, -20 ^{o}C, 1 h, 82%; (b) Boc_2O, DMAP, CH_3CN, rt, 5 h, 90%; (c) IBr, PhMe, -85 ^{o}C, 1 h; (d) K_2CO_3, MeOH, rt, 2 h, 81% from both the steps; (e) TBDMS-Cl, Imidazole, DMF, 0 ^{o}C to rt, 22 h, 89%; (f) Vinylmagnesium bromide, THF, CuI, -20 ^{o}C, 1 h, 80%; (g) Acryloyl chloride, Et_3N, CH_2Cl_2, 0 ^{o}C to rt, 5 h, 82%; (h) $(PCy_3)_2Ru(Cl)_2$=CH-Ph (20 mol%), CH_2Cl_2, Ti(*i*PrO)$_4$ (0.03 eq.), reflux, 6 h , 84%; (i) i) TBAF, THF, rt, overnight; ii) Ac_2O, pyridine, 2 h, 75% from both the steps.

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 **113b** without addition of any Ti(*i*-PrO)$_4$. Now all that remained to complete the synthesis was to remove the TBS group and acylate the resulting diol. Thus desilylation of **176** with TBAF gave the diol, which was directly acylated by addition of acetic anhydride and pyridine to give the cryptocarya diacetate **2** in 75% yield. The physical and spectroscopic data of **2** were in full agreement with the literature data.[55,56]

4.2.5. Conclusion

In conclusion, a practical and efficient strategy has been developed for the syntheses of 1,3-polyols/5,6-dihydropyran-2-ones. The synthetic protocol has been well utilized for the synthesis of cryptocarya diacetate, in which all the stereocenters were established by hydrolytic kinetic resolution and diastereoselective iodine induced electrophilic cyclization and lactone moiety has been achieved by ring closing metathesis. The synthetic strategy which is amenable to both *syn*-and *anti*-1,3-polyols, has significant potential for further extension to the synthesis of a variety of other biologically important 1,3-polyol-substituted 5,6-dihydropyran-2-one containing natural products. Currently studies are in progress in this direction.

4.2.6. Experimental Section

(*S*)-Propylene oxide (*S*-90).

S-90

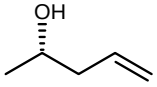
The racemic propylene oxide **90** was resolved to chiral epoxide ***S*-90** in high enantiomeric excess by the HKR method following a literature procedure.[40]

Yield: 14.71 g, 90%

Mol. Formula: C_3H_6O

$[\alpha]_D^{25}$: –11.4 (neat); lit.[40] $[\alpha]_D^{25}$ -11.6 (neat)

(*S*)-Pent-4-en-2-ol (*ent*-32).



***ent*-32**

A round bottomed flask was charged with copper (I) iodide (1.64 g, 8.6 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, 172 mL, 172.4 mmol) was injected to it. A solution of propylene oxide ***S*-90** (5 g, 86.1 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 to afford the crude homoallylic alcohol ***ent*-32** which on distillation provided ***ent*-32** as a colorless liquid.

Yield: 6.5g, 87%

Mol. Formula: $C_5H_{10}O$

$[\alpha]_D^{25}$: +10.86 (*c* = 3.2 in Et_2O).

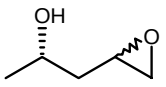
B. P. 115 ^oC, lit.[11] 115 ^oC

IR ($CHCl_3$, cm^{-1}): ν_{max}3400, 3078, 2931, 2975, 1562, 1457, 1432, 1243, 1071, 914.

^{1}H NMR (500 MHz, $CDCl_3$): δ5.77-5.85 (m, 1H), 5.12 (d, *J* = 6.6 Hz, 1H), 5.09 (d, *J* = 2.4 Hz, 1H), 3.80-3.86 (m, 1H), 2.22-2.38 (m, 2H), 1.82 (s, 1H), 1.18 (d, *J* = 6.1, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 134.6, 116.6, 66.5, 43.2, 22.1.

1-Oxiranyl-propan-2-ol (*ent*-117).



***ent*-117**

To a stirred solution of olefin ***ent*-32** (6 g, 69.7 mmol) in CH_2Cl_2 (50 mL) at 0 ^oC was added *m*-CPBA (50%) (28.85 g, 83.6 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 ***ent*-117** as a colorless liquid in diastereomeric mixture (1.1:1).

Yield: 6.83 g, 96%.

Mol. Formula: $C_5H_{10}O_2$

$[\alpha]_D^{25}$: +12.2 (c = 0.79 in $CHCl_3$).

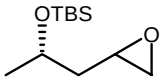
IR ($CHCl_3$, cm^{-1}): ν_{max} 3436, 3192, 2968, 2932, 2852, 1471, 1379, 1265, 1206, 1101, 944, 878.

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.06-4.10 (m, 1H), 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), 1.18 (d, J = 6.3 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 66.5, 66.3, 49.6, 49.3, 47.2, 46.3, 42.9, 42.3, 25.7, 24.2 (both the diastereomers).

Analysis Calcd.: C, 58.80; H, 9.87; **Found:** C, 58.69; H, 9.82.

***tert*-Butyldimethyl-(1-methyl-but-3-enyloxy)-silane (*ent*-116).**



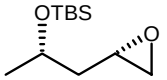
***ent*-116**

To a stirred solution of alcohol ***ent*-117** (6 g, 58.8 mmol) in CH_2Cl_2 (25 mL) was added imidazole (8.0 g, 117.5 mmol). To this solution *t*-butyldimethylchlorosilane (10.63 g, 70.5 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 ***ent*-116** as a colorless liquid.

Yield: 12.08 g, 95%

Mol. Formula: $C_{11}H_{24}O_2Si$

Compound *ent*-118.



***ent*-118**

A solution of epoxide ***ent*-116** (5 g, 23.1 mmol) and (*S,S*)-Salen-Co(III)-OAc (0.076 g, 0.12 mmol) in THF (0.3 mL) was stirred at 0 ^{o}C for 5 min, and then distilled water (229 μL, 12.7 mmol) was added. After stirring for 24 h, it was concentrated and purified by silica gel column chromatography using pet ether/EtOAc (19:1) to afford ***ent*-118 (**2.3g, 46%) as a yellow color liquid. Continued chromatography with pet ether/EtOAc (3:2) provided the diol ***ent*-119** as a brown color liquid as a single diastereomer.

Yield: 2.3g, 46%

Mol. Formula: $C_{11}H_{24}O_2Si$

$[\alpha]_D^{25}$: +9.6 (*c* 0.53, $CHCl_3$).

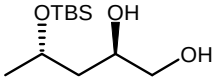
IR ($CHCl_3$, cm^{-1}): ν_{max} 3018, 2958, 2930, 1858, 1472, 1463, 1377, 1256, 1216, 1101, 1005, 938, 878, 760.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.01-4.08 (m, 1H), 3.02-3.04 (m, 1H), 2.76-2.80 (m, 1H), 2.46-2.50 (m, 1H), 1.67-1.71 (m, 1H), 1.50-1.52 (m, 1H), 1.19 (d, *J* = 6.3 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 66.3, 48.8, 45.8, 42.1, 25.4, 23.3, 17.6, -5.0, -5.3.

Analysis Calcd.: C, 61.05; H, 11.18%; **Found:** C, 61.12; H, 11.08%.

Compound *ent*-119.



***ent*-119**

Yield: 2.25g, 45%

Mol. Formula: $C_{11}H_{26}O_3Si$

$[\alpha]_D^{25}$: -33.8 (*c* 0.92, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 3430, 3018, 2957, 2931, 2859, 1652, 1471, 1379, 1256, 1212, 1101, 1036, 971, 869, 758.

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.22-4.31 (m, 1H), 4.04-4.14 (m, 1H), 3.46-3.70 (m, 2H), 1.67-1.81 (m, 2H), 1.32-1.50 (m, 2H), 1.27 (d, *J* = 6.1 Hz, 3H), 0.90 (s, 9H), 0.10 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 68.9, 66.7, 66.3, 41.1, 25.6, 23.4, 17.7, -4.7, -5.1.
Analysis Calcd.: C, 56.36; H, 11.18%; **Found:** C, 56.72; H, 11.07%.

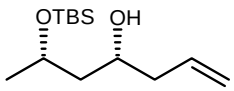
Conversion of *ent*-119 into *ent*-118.

Diol ***ent*-119** (2 g, 8.5 mmol) was dissolved under argon in dry CH_2Cl_2 (25 mL) and treated with pivaloyl chloride (1.13 g, 9.4 mmol), Et_3N (1.03 g, 10.2 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 (0.978 g, 8.5 mmol), Et_3N (1.033 g, 10.2 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 (1.17 g, 8.5 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 ***ent*-118** as a yellow color liquid.

Yield: 1.13 g, overall yield 61%

$[\alpha]_D^{25}$: +9.8 (*c* 0.50, $CHCl_3$).

6-(*tert*-Butyldimethylsilanyloxy)-hept-1-en-4-ol (*ent*-123).



***ent*-123**

A round bottomed flask was charged with copper(I)iodide (0.88 g, 4.6 mmol), gently heated under vaccum 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, 18.5 mL, 18.5 mmol) was added to it. A solution of epoxide ***ent*-118** (1.0 g, 4.6 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 pet ether/EtOAc (9:1) as eluent afforded ***ent*-123** as a colorless liquid.

Yield: 0.92g, 82%

Mol. Formula: $C_{13}H_{28}O_2Si$

$[\alpha]_D^{25}$: +32.8 (*c* 0.76, $CHCl_3$)

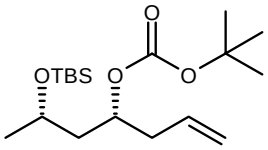
IR ($CHCl_3$, cm^{-1}): ν_{max} 3460, 2959, 2857, 1640, 1448, 1376, 1255, 1078.

^{1}H NMR (200 MHz, $CDCl_3$): δ δ = 5.74-5.93 (m, 1H), 5.15 (d, *J* = 6.9 Hz, 1H), 5.06 (d, *J* = 2.9 Hz, 1H), 4.03-4.23 (m, 1H), 3.80-3.86 (m, 1H), 2.19-2.26 (m, 2H), 1.53-1.60 (m, 2H), 1.21 (d, *J* =7 Hz, 3H), 0.90 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 134.9, 117.1, 70.3, 69.5, 45.3, 42.0, 25.8, 24.4, 17.8, -4.0, -4.9.

Analysis Calcd.: C, 63.87; H, 11.55%; **Found:** C, 63.82; H, 11.38%.

Carbonic acid *tert*-butyl ester 1-[2-(*tert*-butyldimethylsilanyloxy)-propyl]-but-3-enyl ester (170).



170

To a solution of alcohol ***ent*-123** (2 g, 8.2 mmol) in CH_3CN (40 mL) were added $(Boc)_2O$ (2.68 g, 12.3 mmol) and DMAP (0.400 g, 3.3 mmol). After 5 h of stirring, the solvent was evaporated under reduced pressure. The residue was taken up in EtOH (30 mL) and imidazole (2.79 g, 41.0 mmol) was added. The resulting mixture was stirred at room temperature for 15 min and then CH_2Cl_2 was added. The organic layer was washed with water, dried (Na_2SO_4) and concentrated. Purification of the crude product by silica gel column chromatography using pet ether/EtOAc (19:1) as eluent gave **170** as a colorless liquid.

Yield: 1.94 g, 90%

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

$[\alpha]_D^{25}$: (*c* 1.2, $CHCl_3$)

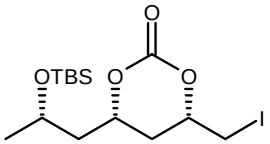
IR ($CHCl_3$, cm^{-1}): ν_{max} 3020, 2958, 2931, 2858, 1737, 1643, 1521, 1473, 1463, 1394, 1370, 1280, 1216, 1115, 1092, 994.

^{1}H NMR (200 MHz, $CDCl_3$): δ 5.72-5.87 (m, 1H), 5.15 (d, *J* = 7.5 Hz, 1H), 5.06 (d, *J* = 2.9 Hz, 1H), 4.79-4.90 (m, 1H), 3.85-4.0 (m, 1H), 2.32-2.45 (m, 2H), 1.79-1.90 (m, 1H), 1.58-1.69 (m, 1H), 1.48 (s, 9H), 1.19 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 153.2, 133.5, 117.9, 81.6, 73.9, 65.6, 43.5, 38.9, 27.8, 25.8, 23.5, 18.1, -4.4, -4.8.

Analysis Calcd.: C, 62.74; H, 10.53%; Found: C, 62.72; H, 10.37%.

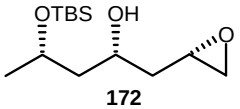
4-[2-(*tert*-Butyldimethylsilanyloxy)-propyl]-6-iodomethyl-[1,3]dioxan-2-one (171).



171

To a solution of carbonate **170** (2 g, 5.8 mmol) in toluene at –85 ^oC was slowly added a solution of IBr (1 M in CH_2Cl_2, 0.80 g, 9.3 mmol). After being stirred at –85 ^oC for 1 h, the resulting mixture was quenched with 20% aqueous $Na_2S_2O_3$ /5% aqueous $NaHCO_3$ solution (1/1) and diluted with ether (20 mL). The aqueous phase was extracted with ether (2 × 50 mL). The organic extracts were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was used as such for the next step due to extensive decomposition.

4-(*tert*-Butyldimethylsilanyloxy)-1-oxiranyl-pentan-2-ol (172).



172

To a solution of cyclic carbonate **171** (2.09 g, 5.0 mmol) in anhydrous MeOH (20 mL) at room temperature was added K_2CO_3 (2.09 g, 15.1 mmol) and the reaction was stirred for 2 h. The mixture was diluted with ether (20 mL) and quenched with saturated aqueous $Na_2S_2O_3$ and saturated aq. $NaHCO_3$ solution (1/1). The aqueous phase was extracted with ether (3 × 50 mL). The organic extracts were washed with brine, dried (Na_2SO_4) and

concentrated. Purification of the crude product by silica gel column chromatography using pet ether/EtOAc (7:3) as eluent afforded the epoxide **172** as a colorless oil.

Yield: 1.22 g, 81% from both the steps.

Mol. Formula: $C_{13}H_{28}O_3Si$

$[\alpha]_D^{25}$: +21.58 (*c* 0.88, $CHCl_3$)

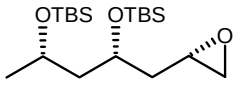
IR ($CHCl_3$, cm^{-1}): ν_{max} 3471, 3019, 2957, 2931, 2859, 2400, 1662, 1377, 1258, 1216, 1082, 836, 758.

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.09-4.16 (m, 1H), 3.96-4.03 (m, 1H), 3.08-3.14 (m, 1H), 2.79 (dd, *J* = 4.8, 4.0 Hz, 1H) 2.52 (dd, *J* = 5.1, 2.8 Hz, 1H), 1.69-1.74 (m, 2H), 1.63-1.67 (m, 2H), 1.22 (d, *J* = 6.1 Hz, 3H), 0.91 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 69.6, 69.2, 49.5, 46.5, 45.6, 39.9, 25.7, 24.4, 17.8, -3.9, -4.9.

Analysis Calcd.: C, 59.95; H, 10.84%; **Found:** C, 59.82; H, 10.79%.

2-[2,4-Bis-(*tert*-butyldimethylsilanyloxy)-pentyl]-oxirane (173).



173

To a stirred solution of alcohol **172** (1 g, 3.8 mmol) in DMF (5 mL), imidazole (0.52 g, 7.6 mmol) was added. To this solution *t*-butyldimethylchlorosilane (0.69 g, 4.6 mmol) was added at 0 ^oC and reaction stirred at room temperature for 22 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc (3 × 100 mL). The extract 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 gave **173** as a colorless oil.

Yield: 1.28 g, 89%

Mol. Formula: $C_{19}H_{42}O_3Si_2$

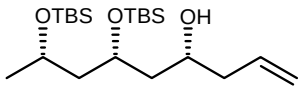
IR ($CHCl_3$, cm^{-1}): ν_{max} 2957, 2931, 2888, 2858, 1619, 1473, 1464,1384, 1362, 1257, 761

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.21-4.28 (m, 1H), 3.99-4.04 (m, 1H), 3.11-3.21 (m, 1H), 2.80 (dd, *J* = 4.9, 4.0, 1H), 2.54 (dd, *J* = 5, 2.9 Hz, 1H), 1.72-1.76 (m, 2H), 1.65-1.71 (m, 2H), 1.21 (d, *J* = 6.1, 3H), 0.89 (s, 18H), 0.12 (s, 6H), 0.11 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 69.6, 66.8, 65.7, 49.2, 47.8, 43.1, 25.8, 24.0, 18.1, -4.3, -4.4.

Analysis Calcd.: C, 60.90; H, 11.30%; **Found:** C, 60.81; H, 11.49%.

6,8-Bis-(*tert*-butyldimethylsilanyloxy)-non-1-en-4-ol (174).



174

A round bottomed flask was charged with copper (I) iodide (51 mg, 0.27 mmol), gently heated under vaccum and slowly cooled with a flow of argon followed by addition of THF. This suspension was cooled to –20 ^{o}C, stirred and vinylmagnesium bromide (1M in THF, 5.34 mL, 5.4 mmol) was added to it. A solution of epoxide **173** (1 g, 2.7 mmol) in THF (10 mL) was added to the above reagent and the mixture was stirred at –20 ^{o}C for 1 h. After completion of the reaction, the mixture was quenched with a saturated aqueous solution of NH_4Cl. The water layer was extracted with EtOAc (3 × 50 mL). The total 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 **174** as a colorless liquid.

Yield: 0.86 g, 80%

Mol. Formula: $C_{21}H_{46}O_3Si_2$

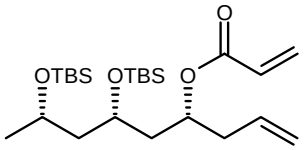
IR ($CHCl_3$, cm^{-1}): ν_{max} 3469, 3079, 3006, 2956, 2931, 2887, 1642, 1472, 1463, 1376, 1257, 1216, 1064, 918, 837, 759, 667.

^{1}H NMR (200 MHz, $CDCl_3$): δ 5.74-5.96 (m, 1H), 5.15 (d, *J* = 6.1 Hz, 1H), 5.07 (d, *J* = 2.9 Hz, 1H), 4.13-4.22 (m, 1H), 3.94-4.07 (m, 1H), 3.77-3.84 (m, 1H), 2.26 (ddd, *J* = 18.0, 12.3, 7.0 Hz, 2H), 1.70-1.74 (m, 2H), 1.62-1.68 (m, 2H), 1.16 (d, *J* = 6.1 Hz, 3H), 0.90 (s, 9H), 0.88 (s, 9H), 0.12 (s, 6H), 0.07 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 134.9, 117.2, 69.1, 67.7, 65.7, 45.7, 42.4, 40.0, 25.8, 24.4, 17.9, -4.1, -4.9.

Analysis Calcd.: C, 62.62; H, 11.51%; Found: C, 62.81; H, 11.74%.

Acrylic acid 1-[2,4-bis-(*tert*-butyldimethylsilanyloxy)-pentyl]-but-3-enyl ester (175).



175

Acryloyl chloride (0.27 g, 0.24 mL, 3.0 mmol) was added dropwise under argon to a solution of **174** (1.2 g, 3.0 mmol) and triethylamine (1.2 g, 1.7 mL, 11.9 mmol) in dry CH_2Cl_2 (15 mL) at 0 ^oC. The mixture was stirred for 5 h 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 × 40 mL) and combined organic layer was washed with brine and dried (Na_2SO_4) and concentrated. Purification of the crude product by silica gel column chromatography using pet ether/EtOAc (19:1) as eluent afforded the acrylate **175** as a colorless oil.

Yield: 1.12 g, 82%

Mol. Formula: $C_{24}H_{48}O_4Si_2$

$[\alpha]_D^{25}$: +25.84 (c = 0.98 in $CHCl_3$)

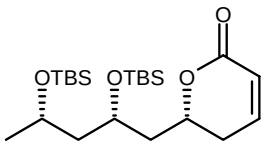
IR ($CHCl_3$, cm^{-1}): ν_{max} 3081, 2952, 2932, 2896, 2850, 2710, 2401, 1719, 1639, 1619, 1472, 1463, 1438, 1407, 1377, 1362, 1297, 1275, 1215, 1199, 1067, 1048, 967, 919, 759.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.43 (dd, J = 17.3, 1.8 Hz, 1H), 6.11 (dd, J = 17.1, 10.2 Hz, 1H), 5.82 (dd, J = 10.3, 2.1 Hz, 1H), 5.70-5.75 (m, 1H), 5.09-5.12 (m, 2H), 5.04-5.06 (m,1H), 3.79-3.96 (m, 2H), 2.29-2.43 (m, 2H), 1.69-1.83 (m, 2H), 1.41-1.58 (m, 2H), 1.15 (d, J = 6.1 Hz, 3H), 0.89 (s, 18 H), 0.06 (s, 6H), 0.04 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.8, 133.4, 130.3, 128.9, 117.9, 70.9, 66.1, 65.5, 48.5, 40.8, 39.0, 25.9, 24.4, 17.9, -4.0, -4.1.

Analysis Calcd.: C, 63.10; H, 10.59%; **Found:** C, 63.18; H, 10.64%.

6-[2,4-Bis-(*tert*-butyldimethylsilanyloxy)-pentyl]-5,6-dihydro-pyran-2-one (176)



176

Ist generation Grubbs' catalyst **113a** (0.073 g, 0.09 mmol) dissolved in CH_2Cl_2 (10 mL) was added dropwise to a refluxing solution of **175** (0.40 g, 0.9 mmol), Ti(*i*PrO)$_4$ (7 mg, 0.03 mmol) in dry CH_2Cl_2 (100 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 pet ether/EtOAc (8:2) as eluent to afford **176** as a colorless oil.

Yield: 0.315g, 84%

Mol. Formula: $C_{22}H_{44}O_4Si_2$

$[\alpha]_D^{25}$: +42.69 (*c* 0.82, $CHCl_3$).

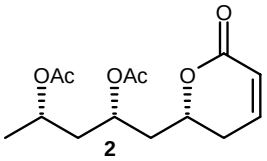
IR (neat, cm^{-1}): ν_{max} 3020, 2955, 2930, 2887, 2857, 1721, 1472, 1463, 1423, 1387, 1361, 1255, 1216, 1180, 1061, 975, 836.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.88 (ddd, *J* = 9.6, 5.8, 2.1 Hz, 1H), 6.05 (ddd, *J* = 9.6, 1.9, 1.6 Hz, 1H), 4.54-4.65 (m, 1H), 4.09-4.22 (m, 1H), 3.87-4.02 (m, 1H), 2.29-2.39 (m, 2H), 1.95-2.07 (m, 1H), 1.74-1.78 (m, 1H), 1.60-1.66 (m, 2H), 1.17 (d, *J* = 6.1 Hz, 3H), 0.88 (s, 18 H), 0.09 (s, 6H), 0.07 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 163.9, 144.8, 121.5, 74.4, 66.2, 65.3, 48.2, 42.7, 30.1, 25.8, 24.3, 17.9, -4.2, -4.3.

Analysis Calcd.: C, 61.63; H, 10.34%; Found: C, 61.58; H, 10.46%.

Cryptocarya diacetate (2).



2

Lactone **176** (0.30 g, 0.7 mmol) and benzoic acid (0.26 g, 2.1 mmol) were dissolved in THF (5 mL), followed by the dropwise addition of TBAF (2.1 mL, 1M solution in THF). The reaction mixture was stirred at room temperature for overnight, concentrated, and extracted with EtOAc (3 x 30 mL). Evaporation of the solvent gave the crude product which was directly used for the next step.

To a solution of crude diol in CH_2Cl_2 was added Ac_2O (1.15 g, 1.06 ml, 11.3 mmol), pyridine (5 ml) and a catalytic amount of DMAP. The reaction was stirred for 2 h, after which 1 mL of a saturated solution of sodium bicarbonate was added. The layers were

separated and the aqueous layer was extracted with diethyl ether (3 × 25 mL). The organic layer were combined and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification by silica gel column chromatography using pet ether/EtOAc (4:1) as eluent yielded cryptocarya diacetate **2** as a colorless oil.

Yield: 0.149 g, 75% from both the steps

Mol. Formula: $C_{14}H_{20}O_6$

$[\alpha]_D^{25}$: +53.6 (*c* 1, $CHCl_3$), lit.[46a] $[\alpha]_D^{22}$: +55.8 (*c* 1.06, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 3010, 2962, 1732, 1438, 1365, 1233, 1167, 1118, 1032, 984.

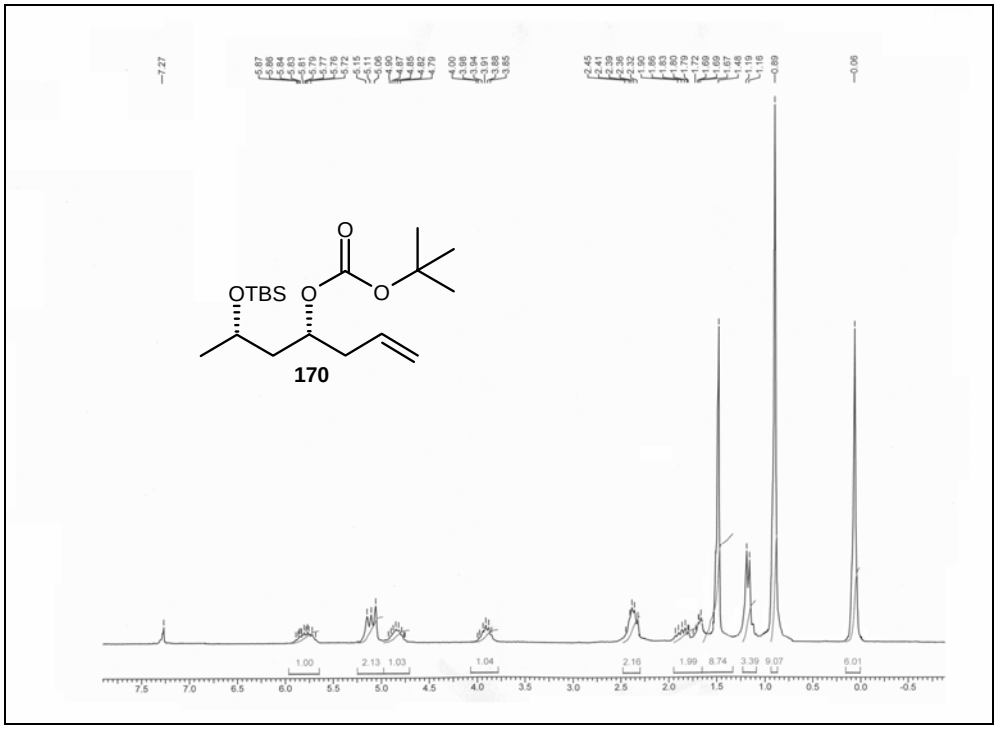
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.89 (ddd, *J* = 9.7, 6.1, 2.3 Hz, 1H), 6.03 (ddd, *J* = 9.7, 2.1, 1.3 Hz, 1H), 5.08-5.24 (m, 1H), 4.90-5.04 (m, 1H), 4.43-4.55 (m, 1H), 2.49 (ddd, *J* = 18, 6.5, 5 Hz, 1H), 2.30-2.38 (m, 1H), 2.19 (ddd, *J* = 14.7, 8.6, 6.5 Hz, 1H), 2.05 (s, 3H), 2.02 (s, 3H), 2.0-1.95 (m, 1H), 1.93-1.83 (m, 2H), 1.27 (d, *J* = 6.1 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 170.5, 170.3, 163.6, 144.5, 121.3, 74.9, 67.8, 67.6, 40.4, 39.5, 29.2, 21.2, 21.1, 20.0.

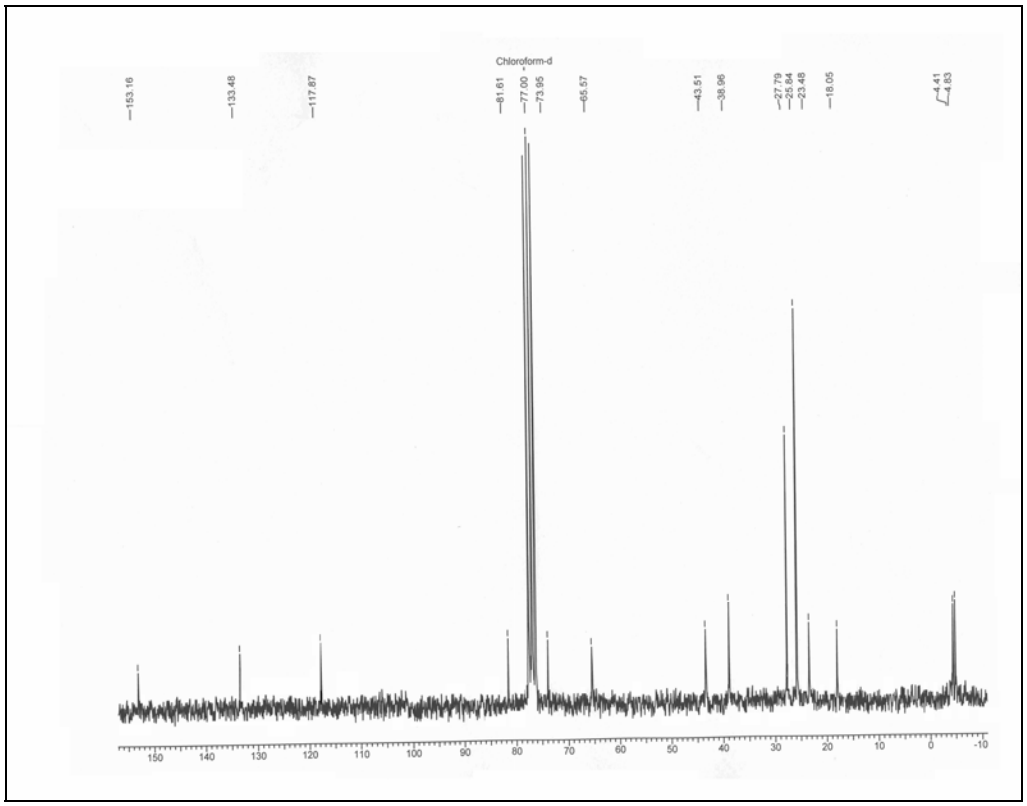
Analysis Calcd.: C, 59.14; H, 7.09%, **Found:** C, 59.29; H, 7. 21%.

4.2.7 Spectra

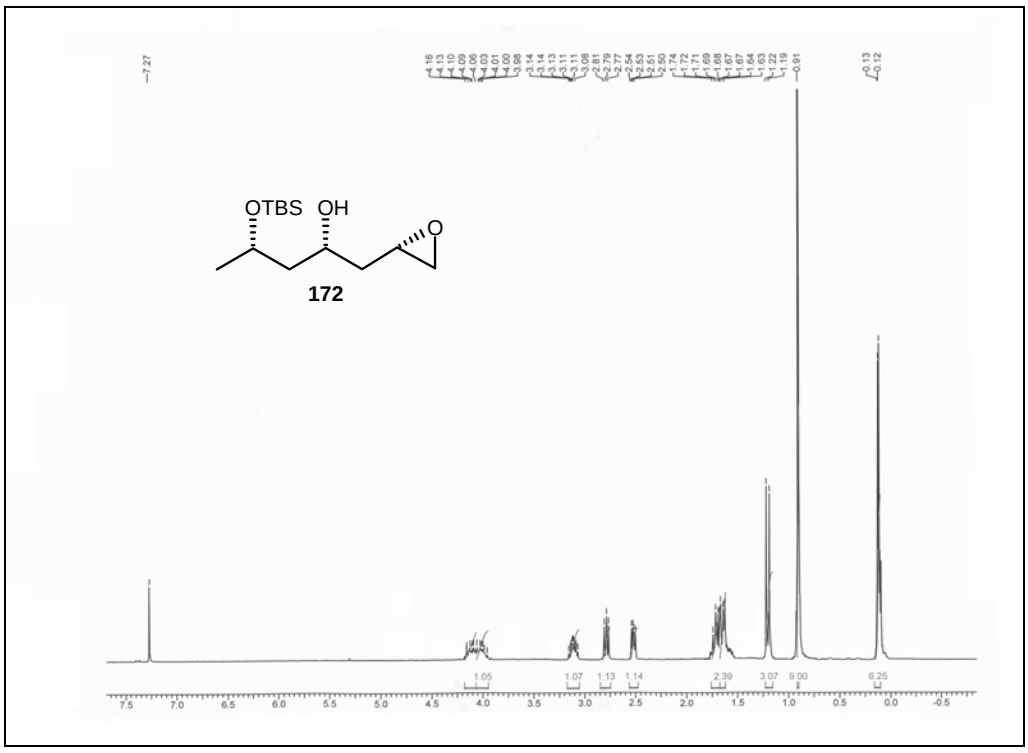
1. ^{1}H and ^{13}C NMR spectra of 170
2. ^{1}H and ^{13}C NMR spectra of 172
3. ^{1}H and ^{13}C NMR spectra of 174
4. ^{1}H and ^{13}C NMR spectra of 175
5. ^{1}H and ^{13}C NMR spectra of 176
6. ^{1}H and ^{13}C NMR spectra of 2



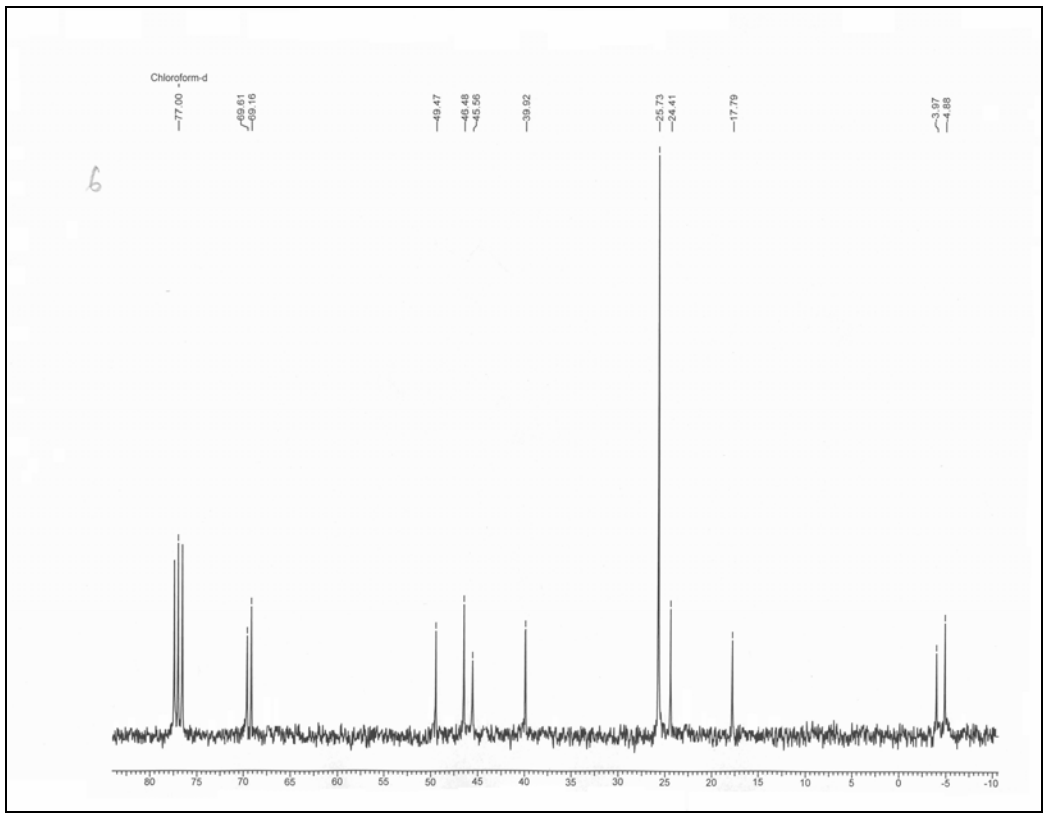
^{1}H NMR Spectrum of compound 170 in $CDCl_3$



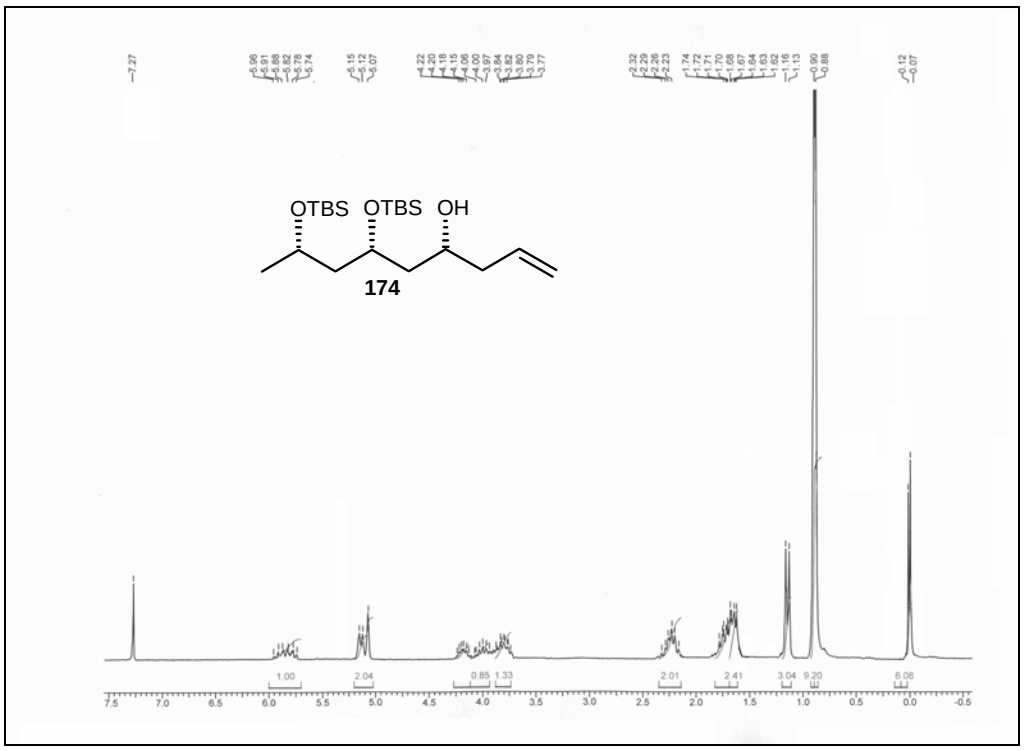
^{13}C NMR Spectrum of compound 170 in $CDCl_3$



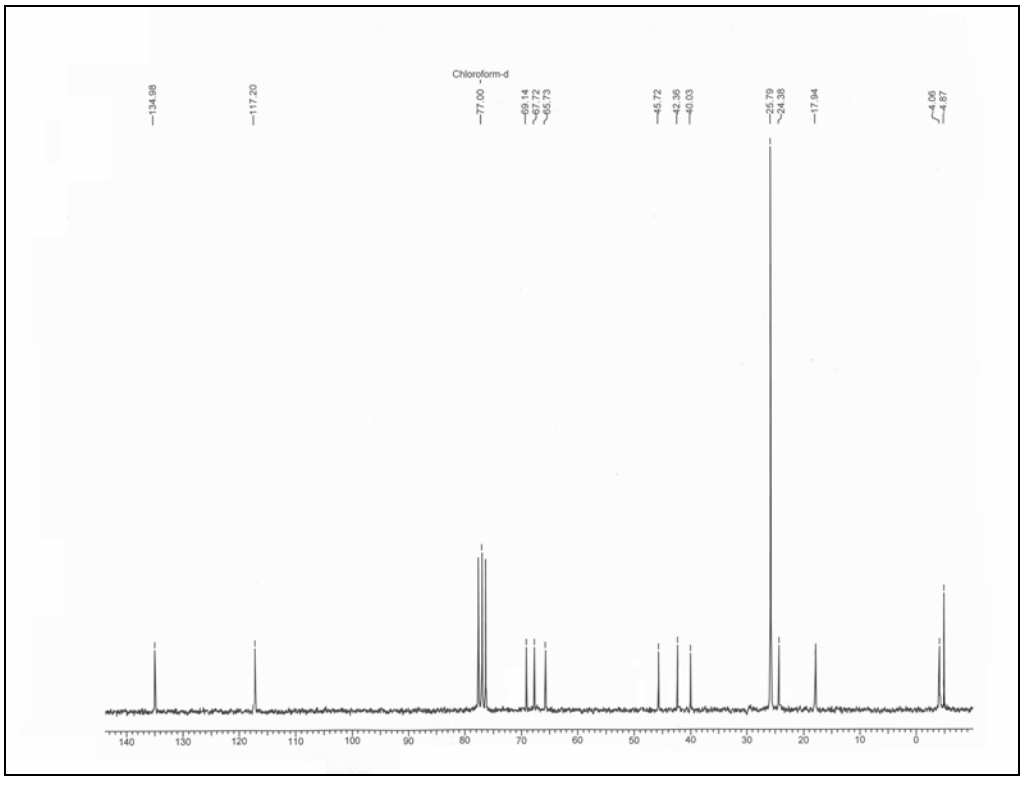
^{1}H NMR Spectrum of compound 172 in $CDCl_3$



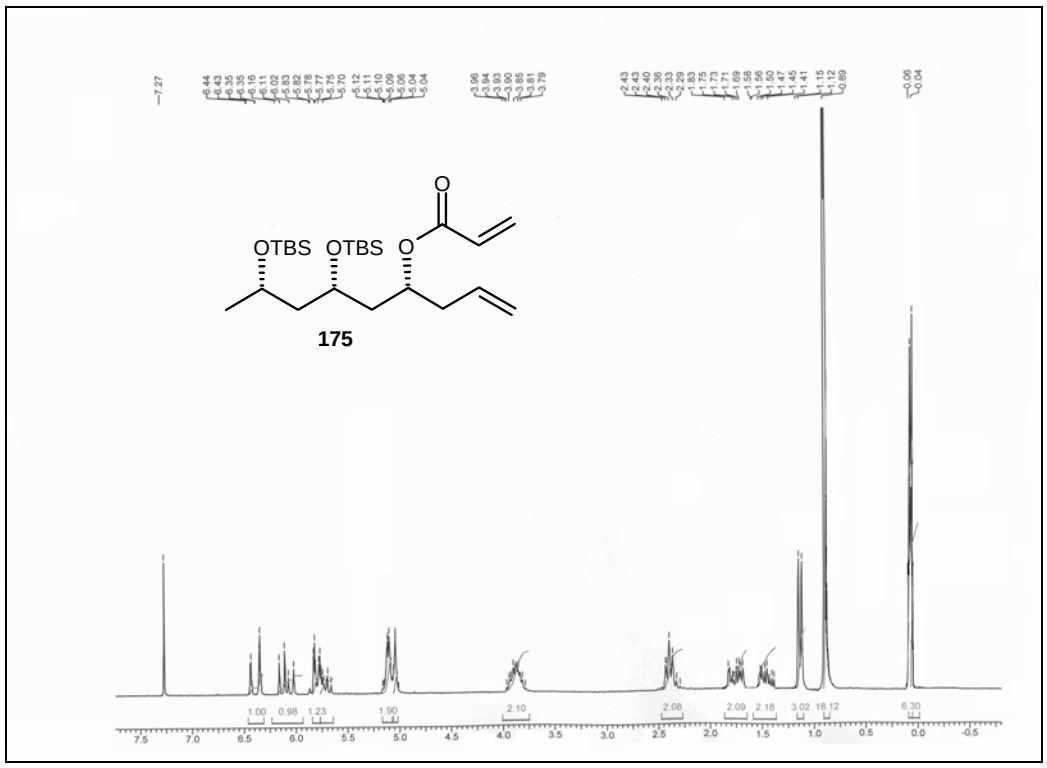
^{13}C NMR Spectrum of compound 172 in $CDCl_3$



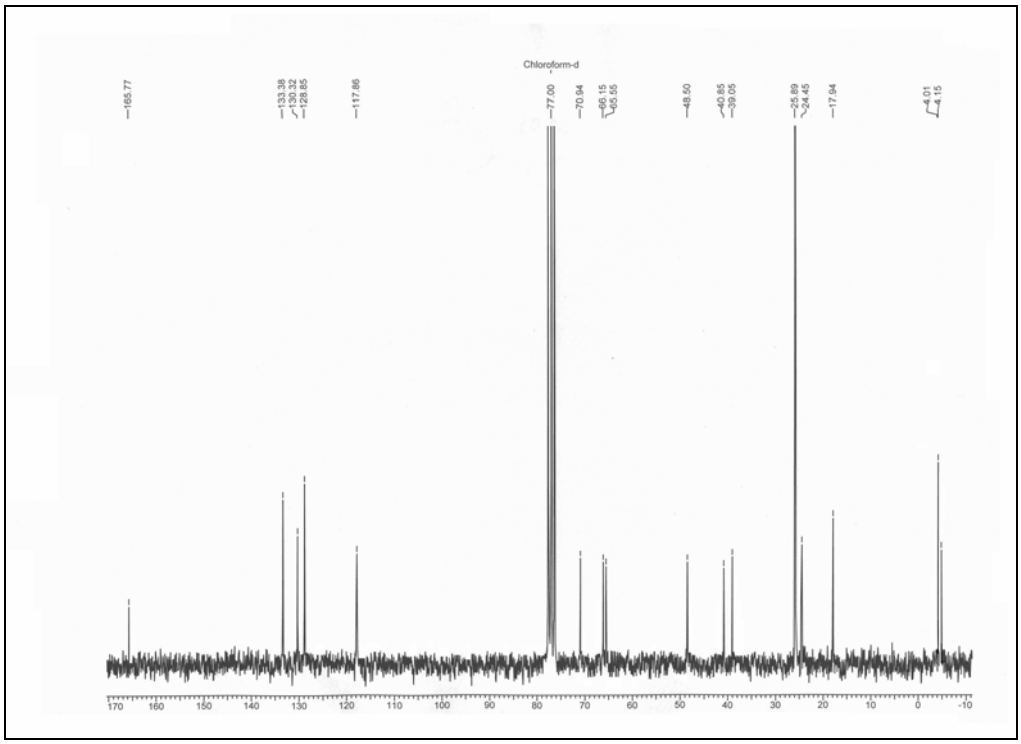
^{1}H NMR Spectrum of compound 174 in $CDCl_3$



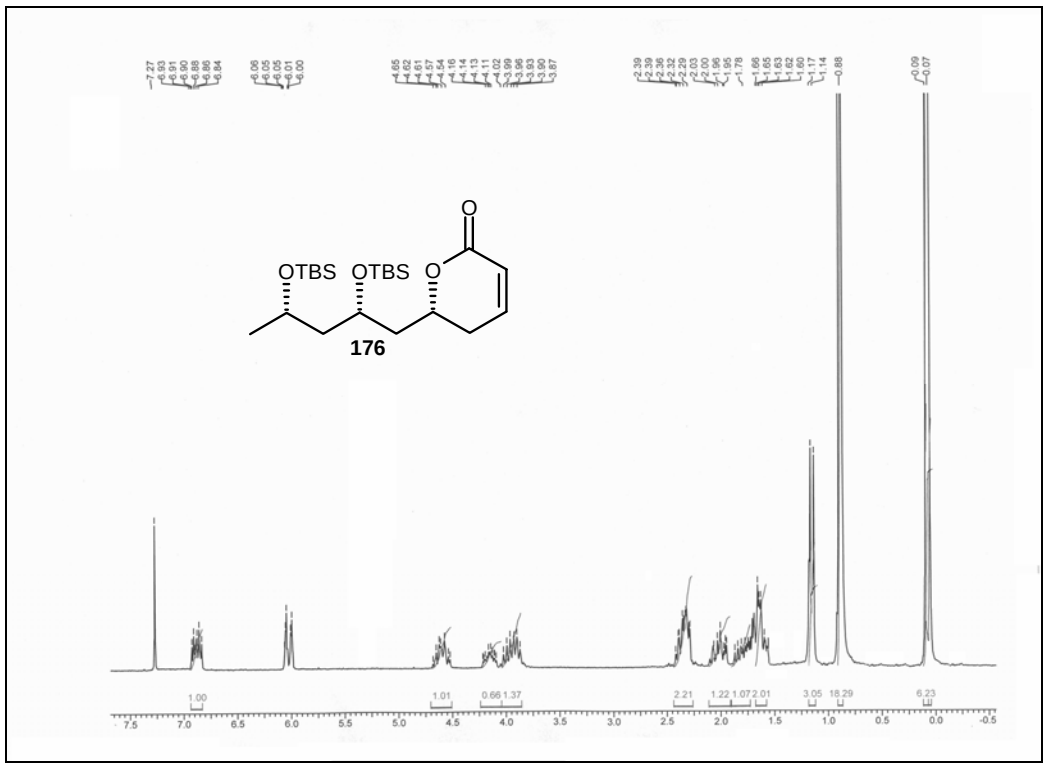
^{13}C NMR Spectrum of compound 174 in $CDCl_3$



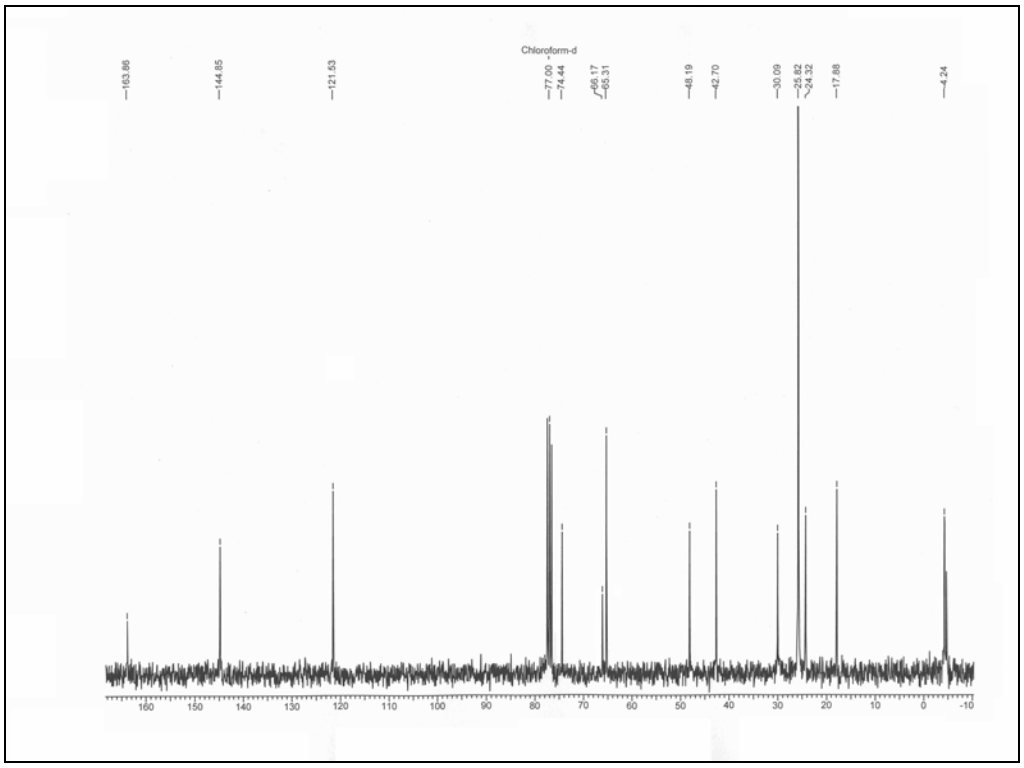
^{1}H NMR Spectrum of compound 175 in $CDCl_3$



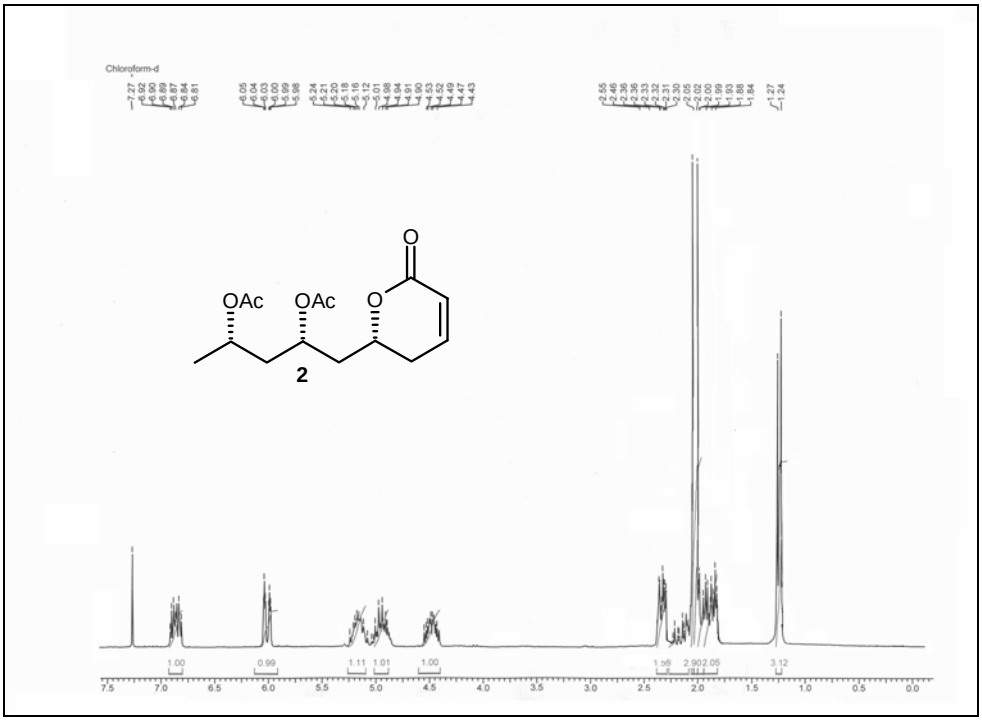
^{13}C NMR Spectrum of compound 175 in $CDCl_3$



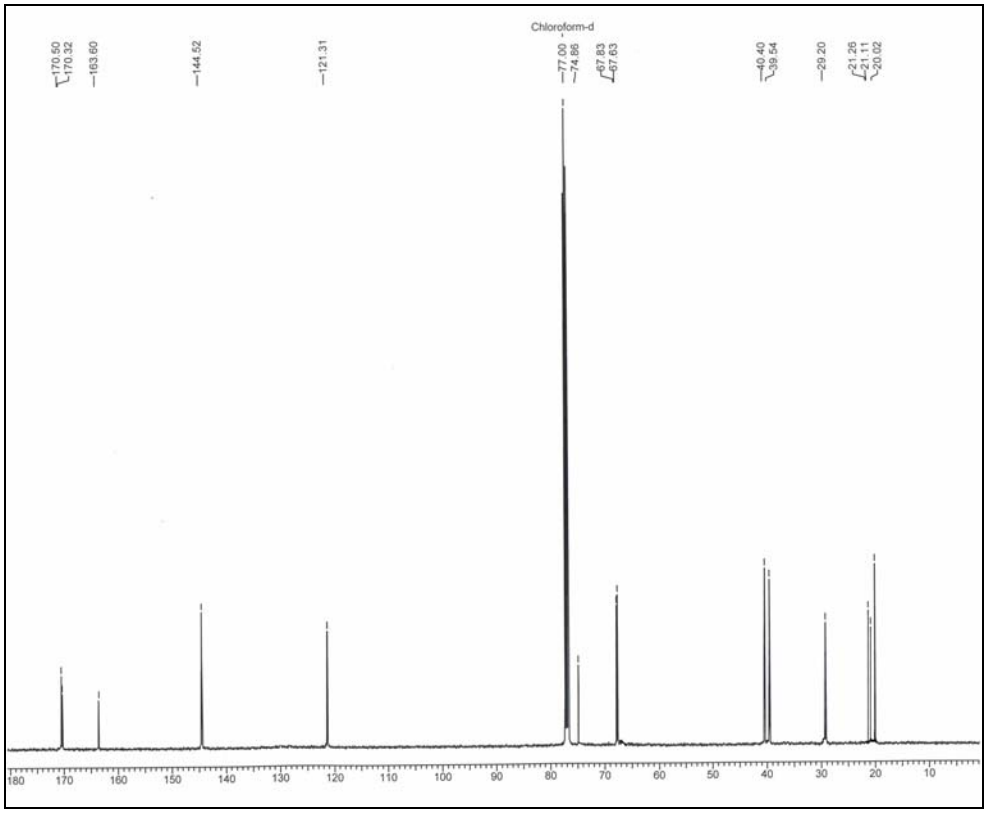
^{1}H NMR Spectrum of compound 176 in $CDCl_3$



^{13}C NMR Spectrum of compound 176 in $CDCl_3$



^{1}H NMR Spectrum of compound 2 in $CDCl_3$



^{13}C NMR Spectrum of compound 2 in $CDCl_3$

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CHAPTER-5

ENANTIOSELECTIVE TOTAL SYNTHESIS OF MACROLACTONES: DECARESTRICTNE D, HERBARUMIN III

5.1 SECTION A

TOTAL SYNTHESIS OF DECARESTRICTINE D

5.1.1. Introduction

The control of cholesterol blood level is of considerable interest for the control of coronary diseases which are responsible for about 40% of morbidity in developed countries. Efficient drugs are now on the market and most of these compounds, known as statins or mevinic acids, are more or less related to a family of lactonic compounds derived from the lead compounds compactin and mevinolin.[1,2]

Decarestrictine D **1**, a 10 membered lactone was isolated independently from *Penicillium corylophilum*, *P. simplicissimum*[3] and from the Canadian Tuchahoe fungi *Polyporus tuberaster*.[79] It shows inhibitory activity against cholesterol biosynthesis at 10^{-7} M, in HEP-G2 liver cell.[78a] The structural difference between **1** and the well known HMG-CoA inhibitors such as mevinolin, compactin and other synthetic cholesterol-lowering agent suggests a different mode of action operative with **1**. In addition **1** is highly selective in that it exhibits no significant antibacterial, antifungal, antiprotozoal or antiviral activity.[3,4] Considering its strong and selective biological profile, decarestrictine D has attracted a great deal of interest among synthetic organic chemists worldwide as an attractive synthetic target towards developing a new cholesterol lowering drug.

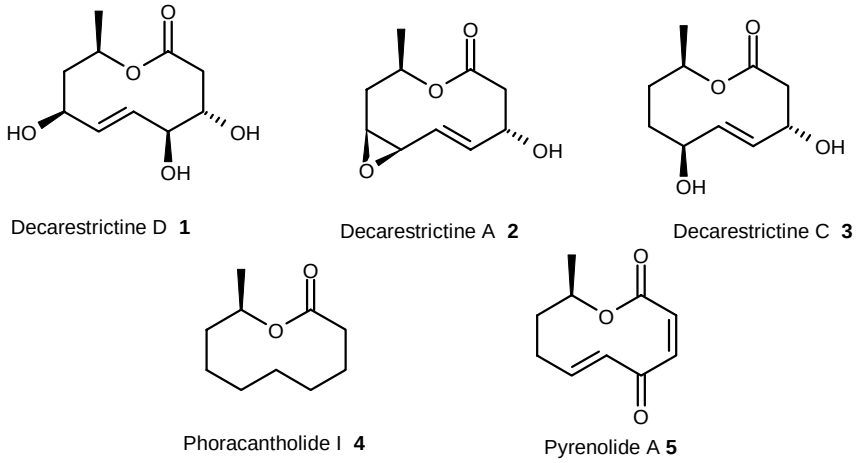


Figure1

However recent studies revealed DNA-binding activity[5] for decarestrictine D and the corresponding bisglycosylated derivatives, disclosing new avenues of opportunities in structure-activity relationship. Such significant biological properties exhibited by decarestrictine D contributed much to the interest in devising synthetic approaches to this family of natural products.

While the relative stereochemistry was provided by X-ray analysis[3b], its absolute configuration has been established by its total synthesis[6] and X-ray analysis of a chiral derivative.[5] Some other members of the 10-membered lactone family are decarestrictine A and C (**2** and **3**), phoracantholide I **4** and pyrenolide A **5**.

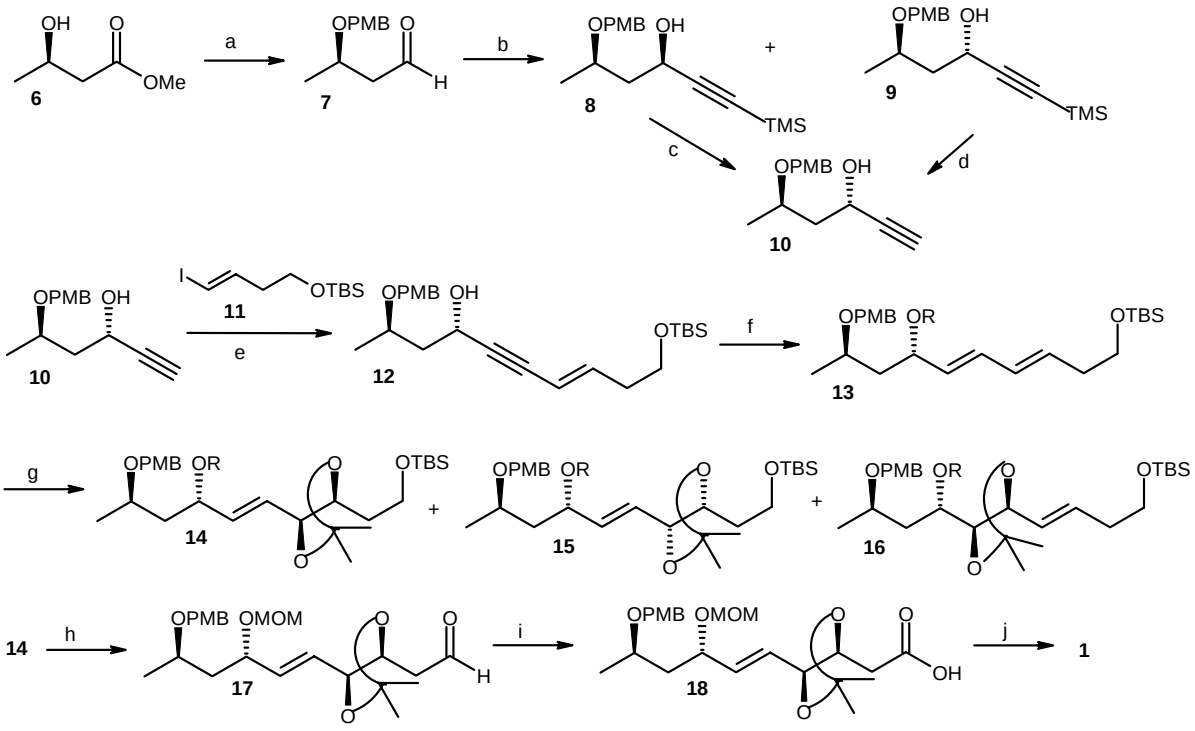
5.1.2. Review of Literature

So far five total syntheses of decarestrictine D have been reported in the literature.[6-10] Most of the approaches described are based on macrolactonization as the key step to construct the macrolactones. Moreover, the stereogenic centers were mainly derived from chiral pool starting materials, asymmetric catalysis or a chiral induction. A detailed report of these syntheses is described below.

Andrus *et al*. (1996).[6]

Andrus and co-workers accomplished the synthesis of Decarestrictine D by using the Sharpless asymmetric dihydroxylation[11] and Corey-Nicolaou lactonization[12] as the key steps. Thus, protection of (*R*)-(-)-methyl 3-hydroxybutnoate **6** as the PMB ether, followed by reduction and subsequent reaction with lithio(trimethylsilyl)acetylene afforded *syn*- and *anti*- alcohol **8** and **9** in (1.2 : 1 ratio) respectively. *syn*-Alcohol **8** was separated through flash chromatography followed by Mitsunobu reaction[13] and desilylation to give propargyl alcohol **10**, which can also be obtained by desilylation of *anti*-alcohol **9**. Sonogashira coupling[14] of **10** with vinyl iodide **11**[15] gave the (*E*)-enyne alcohol **12** which on reduction followed by MOM protection afforded (*E*, *E*)-diene **13**. Asymmetric dihydroxylation[11] of **13** followed by acetonide protection furnished compound **14** along with minor quantity of isomer **15** and **16**. To complete the synthesis, the TBS ether was removed followed by oxidation to acid, and PMB deprotection to afford acid **18**, which was subjected to

cyclization using Corey -Nicolaou lactonization[12] to get the target molecule decarestrictine D **1** (Scheme 1).

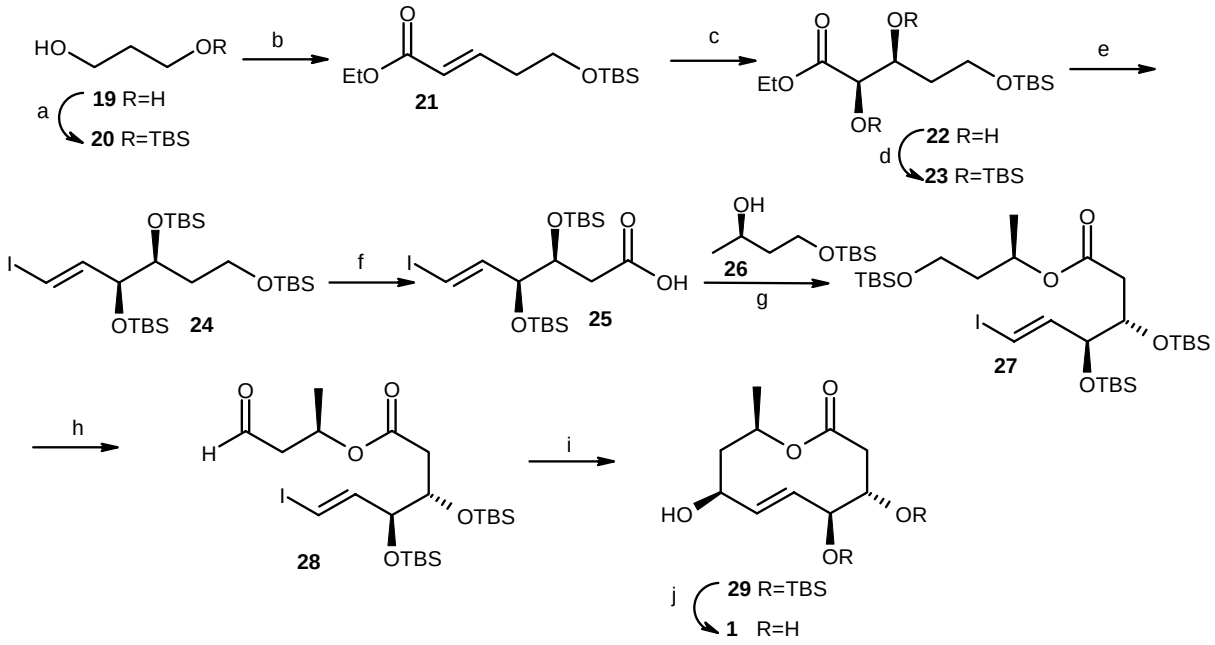


Scheme 1. *Reagents and conditions*: a) (i) *p*-methoxybenzyl trichloroacetimidate, PPTS, CH_2Cl_2/ C_6H_{12}, 24 h, 74%; (ii) DIBAL, CH_2Cl_2, -78 ^oC, 90%; (b) Li-C≡C-TMS, *n*-butyllithium, THF, 60% for **9**, 26.4% for **10**; (c) (i) PNBA, DEAD, Ph_3P, 94%; (ii) K_2CO_3, MeOH, 93%; (d) TBAF, THF, 99%; (e) **12**, *n*-propylamine, $Pd(PPh_3)_4$, CuI, 84%; (f) (i) LAH, THF, 92%; (ii) MOMCl, DIPEA, CH_2Cl_2, 98%; (g) (i) AD-mix-α, *t*-BuOH/H_2O; (ii) DMP, PPTS, CH_2Cl_2, 77.4% from two steps; (h) (i) TBAF, THF; (ii) IBX, DMSO, 92% from both the steps; (i) (i) $NaClO_2$, *t*-BuOH; (ii) DDQ, CH_2Cl_2, 89% from both the steps; (j) (i) (2-pyr-S)$_2$, Ph_3P, $AgClO_4$, C_6H_6, 33%; (ii) Dowex, MeOH, 58%.

Pilli *et al.* (1998).[7]

Pilli and co-workers accomplished the synthesis of decarestrictine D from 1,3-propane diol and polyhydroxybutyrate by using stereoselective intramolecular Nozaki-Hiyama-Kishi[16] coupling as the key step. As shown in scheme 2 the preparation of iodo compound required monosilylation of 1,3-propane diol **19**, followed by Swern oxidation[17] and Wittig

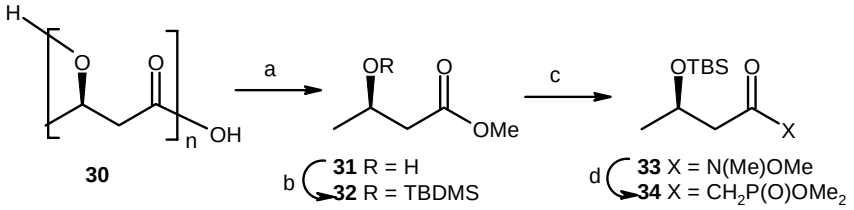
olefination to give the α,β-unsaturated ester **21** which was subjected to Sharpless asymmetric dihydroxylation to get the diol **22**. Diol was protected as TBS ether followed by reduction of ester to afford aldehyde which was immediately subjected to Takai's conditions[18] to afford the *E*-**24**. Selective desilylation, followed by Jones oxidation afforded carboxylic acid **25**, which was coupled with **26** under Yamaguchi condition to afford **27**. Selective deprotection of primary TBS group followed by oxidation and Nozaki-Hiyama-Kishi[16] reaction gave **29**, which on desilylation afforded target molecule **1** (Scheme 2).



Scheme 2. *Reagents and conditions*: (a) (i) NaH, THF, TBSCl, 0 °C, 91%; (b) (i) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C; (ii) $(EtO)_2P(O)CHNaCOOEt$, THF, 0 °C, 70% from both the steps; (c) AD-mix α, $CH_3SO_2NH_2$, H_2O/*t*-BuOH, 94%; (d) TBSCl, DMF, imidazole, 100%; (e) (i) DIBAL-H (2.0 equiv.), toluene, -95 °C; (ii) $CrCl_2$, CHI_3, THF, 55 °C; (f) Jones reagent, acetone, 0 °C (53%, 3 steps); (g) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF, **26**, DMAP, C_6H_6, 83%; (h) (i) HF.pyr, C_5H_5N, THF; (ii) Dess-Martin periodinane, CH_2Cl_2, H_2O; (i) $CrCl_2$-0.5% $NiCl_2$, DMF, 30%; (j) TBAF, HF, CH_3CN, 80%.

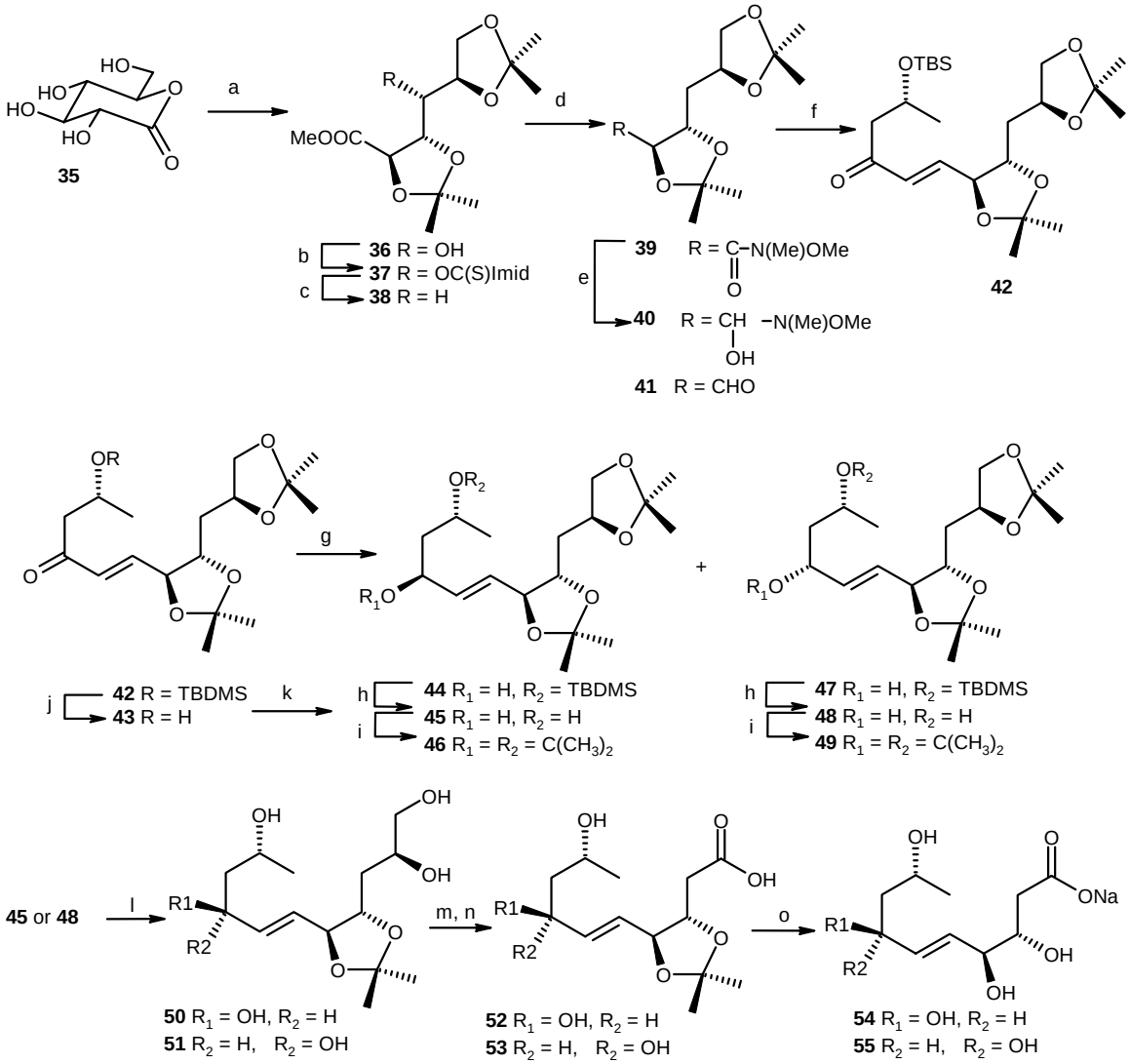
Chapleur *et al.* (1999).[8]

Chapleur and co-workers synthesized seco-acid of decarestrictine D and its C7 epimer from D-gluconolactone and poly(3-hydroxybutyric acid), by using Horner-Emmons olefination[19] and stereoselective reduction as the key steps. Thus, poly(3-hydroxybutyric acid) **30** was depolymerized according to literature procedure[20] to provide hydroxy ester **31**, which was protected as silyl ether and homologated to ketophosphonate **34** via Weinreb amide (Scheme 3).[21]



Scheme 3. *Reagents and conditions*: (a) H_2SO_4, 1,2-dichloroethane:MeOH, reflux, 72 h; (b) TBDMSCl, CH_2Cl_2, NEt_3, DMAP; (c) *N*-methoxy-*N*-methylamine hydrochloride, $(CH_3)_2CHMgBr$, THF, -10 ^oC, 86%; (d) $LiCH_2P(O)OMe_2$, THF, -100 ^oC

As shown in Scheme 4 synthesis of aldehyde fragment started from known ester **36** which was prepared from D-gluconolactone **35**.[22] Thus the removal of alcohol group of **36** followed by Weinreb amide formation and reduction afforded hemi-aminal **40**, which was subjected to Horner-Emmons olefination to furnish *trans*-olefin **42**. Reduction of the carbonyl group at C-8 of enone **42** under Luche conditions afforded 1:1 mixture of C7 epimer which were separable on column chromatography. Each of them was separately desilylated and the resulting diols were protected as acetonide to afford **46** or **49**. To explore the stereoselective reduction, the TBS group was deprotected to afford hydroxy ketone, which was reacted with tetramethylammonium triacetoxy borohydride[23] in acetonitrile to provide a (*anti* : *syn*) 9:1 mixture of the diols **45** and **48**. Selective deprotection of primary isopropylidene group followed by diol cleavage with subsequent oxidation of resulting aldehyde afforded acids **52** and **53** which on acetonide deprotection afforded target seco-acids **54** and **55**.

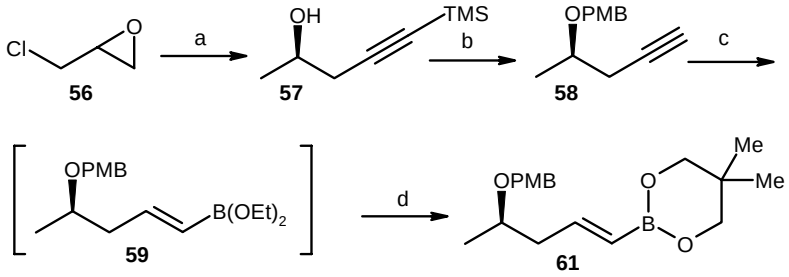


Scheme 4. *Reagents and conditions*: (a) DMP, Acetone, *p*-TSA; (b) $(Imid)_2CS$, pyridine/CH_2Cl_2, rt, 18 h; (c) Bu_3SnH, 1.2 equiv, AIBN, degassed toluene, 6 h, 60-65%; (d) MeNH(OMe).HCl, THF then *i*-PrMgCl, -20 ^oC; (e) $LiAlH_4$, THF, 0 ^oC, 89%; (f) **34**, 1.5 equiv, Et_2O, $LiOH.H_2O$, then **39**, Et_2O, 82%; (g) $NaBH_4$, $CeCl_3$, MeOH, 90%; (h) TBAF, THF; (i) DMP, Acetone, *p*-TSA cat., 95% 2 steps; (j) AcOH:H_2O:THF, 3:7:20, 4 days, rt; (k) $Me_4NBH(OAc)_3$, CH_3CN:AcOH, 1:1; (l) AcOH:H_2O:THF, 9:1:5, 55 ^oC, 80%; (m) $NaIO_4$, 1.5 equiv, MeOH:H_2O; (n) 2-methyl-2-butene, *t*-BuOH then $NaClO_2$, NaH_2PO_4, H_2O; (o) AcOH:H_2O:THF, 1:1:2, 60 ^oC, 20 h then NaOH.

Kobayashi *et al.* (2005).[9]

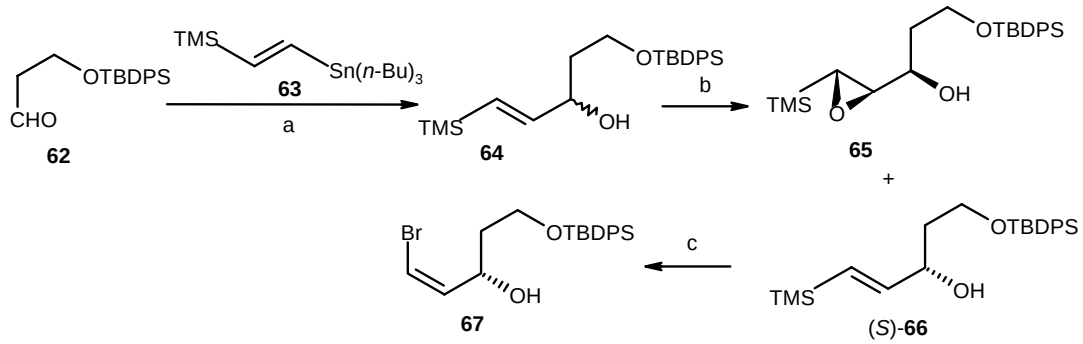
Kobayashi and co-workers synthesized decarestrictine D by a nickel-catalyzed coupling[24] reaction between the corresponding *cis*-bromide and *trans*-borate. The boronate

ester **61** required for the coupling reaction was synthesized from epichlorohydrin. Thus, opening of epichlorohydrin **56** with the lithium anion[25] derived from TMS acetylene followed by reduction of resulting chloro alcohol gave **57**. Protection of **57** as PMB ether followed by TMS deprotection afforded acetylene **58**, which was converted into the boronate ester **61** by hydroboration, ligand exchange with MeCHO,[26] and transesterification of the resulting diethyl boronate **59** with diol **60** (Scheme 5).



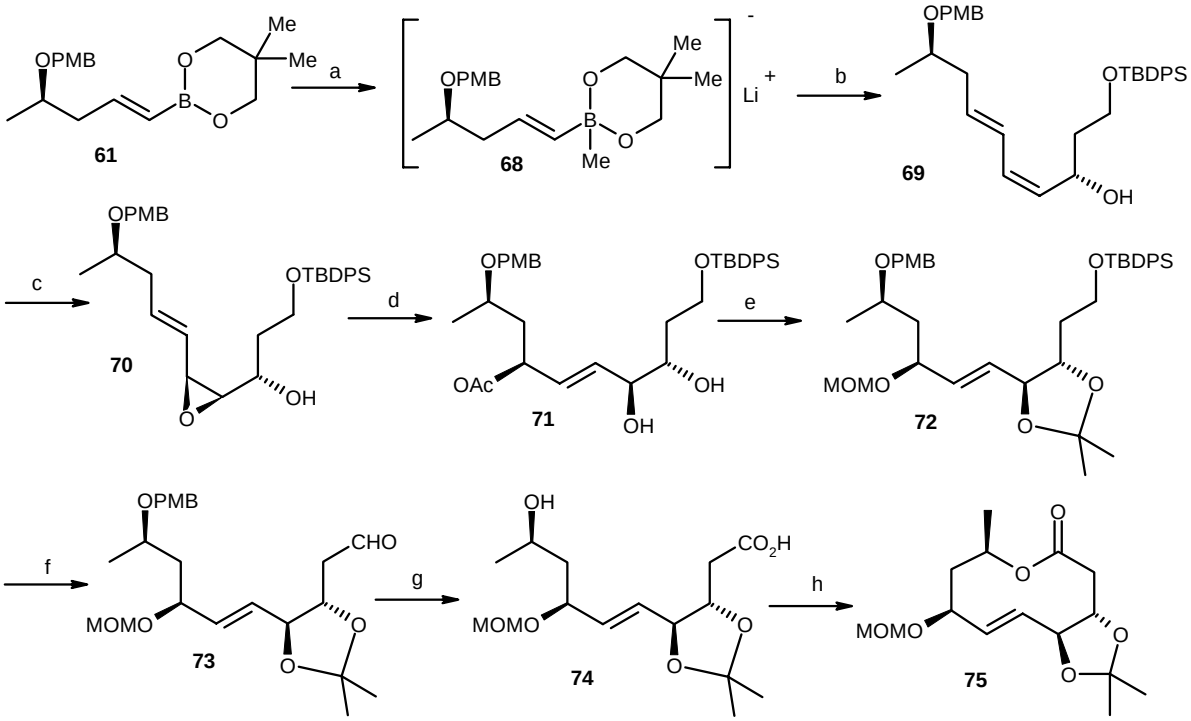
Scheme 5. *Reagents and conditions*: a) (i) Li-C≡C-TMS, $BF_3.OEt_2$, ; (ii) LAH, THF, 4 h, 82% from both the steps; (b) (i) PMBCl, NaH, NaI; (ii) K_2CO_3, MeOH, 81% from both the steps; (c) (i) $HB(Ipc)_2$, THF, 3 h; (ii) MeCHO, reflux, overnight; (d) 2,2-dimethyl 1,3-propanediol **60**, 2 days, 57% from **58**.

Synthesis of other key intermediate **66** was commenced with addition of the lithium anion derived from **63** and *n*-BuLi to aldehyde **62**. Racemic alcohol rac-**64** produced was then subjected to the kinetic resolution[27] by using Sharpless asymmetric epoxidation[28] to furnish a mixture of epoxy alcohol **65** and the remaining allylic alcohol (*S*)-**66**, which on bromination and TMS deprotection afforded cis bromide **67** (Scheme 6).

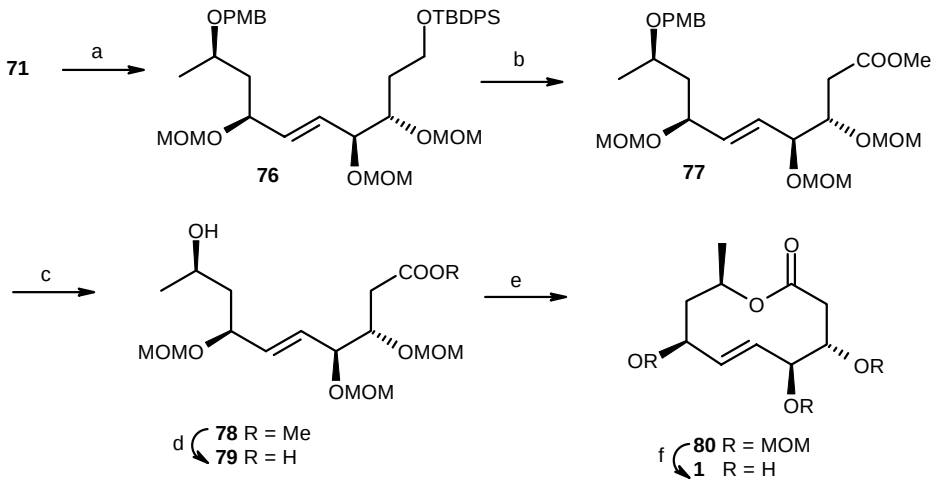


Scheme 6. *Reagents and conditions*: (a) **63**, *n*-BuLi, THF, 91%; (b) *t*-BuOOH, D-(-)-DIPT, $Ti(O\text{-}i\text{-}Pr)_4$, -20 ^oC, 13 h, 43%; (c) (i) Br_2, CH_2Cl_2, -78 ^oC; (ii) TBAF, THF, -78 ^oC, 77% from both the steps.

Nickel-catalyzed coupling of **61** and **67** furnished dienyl alcohol **69**, which on epoxidation and subsequent palladium-catalyzed reduction furnished diol acetate **71**. First **71**, was converted into its acetonide derivative followed by TBS deprotection, oxidation, PMB deprotection to afford seco-acid **74** which, on macrolactonization afforded lactone **75** in less yield (Scheme 7). To improve the yield, the acetyl group of **71** was deprotected followed by MOM protection to afford tri-MOM derivative which was converted into seco-acid **79** via TBDPS deprotection, esterification, PMB deprotection and hydrolysis. Yamaguchi macrolactonization[29] of acid **79** followed by MOM deprotection afforded target molecule1 (Scheme 8).



Scheme 7. *Reagents and conditions*: (a) MeLi, Et_2O/THF, 0 ^oC; (b) **67**, Ni cat., overnight, 76%; (c) *m*-CPBA, CH_2Cl_2, 70%; (d) AcOH, $Pd(PPh_3)_4$, THF, 30 min., 68% ; (e) (i) DMP, CH_2Cl_2; (ii) LiOH; (iii) MOMCl, 79% (3 steps); (f) (i) TBAF, THF, 86%; (ii) Swern oxidation, 84% (g) (i) $NaClO_2$; (ii) DDQ; (h) $Cl_3C_6H_2COCl$, DMAP, 17%.

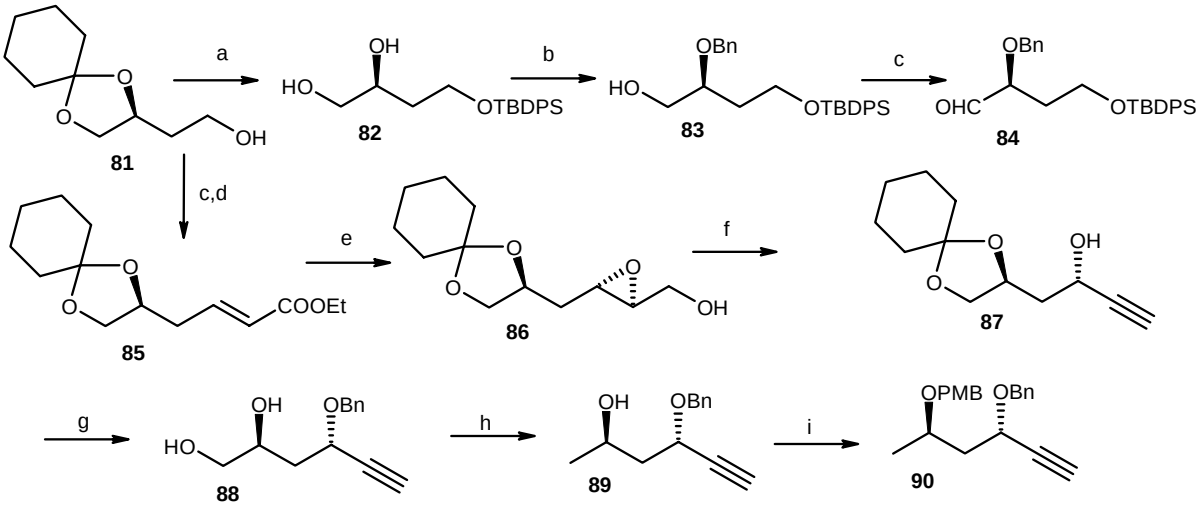


Scheme 8. *Reagents and conditions*: (a) (i) MeLi, THF, 2 h, 82%; (ii) MOMCl, DIPEA, CH_2Cl_2, overnight, 99%; (b) (i) TBAF, THF, 2 h, 100%; (ii) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2; (iii) $NaClO_2$, 2-methyl-2-butene, H_2O/*t*-BuOH, 2h; (iv) CH_2N_2, Et_2O, 75% from three steps; (c) DDQ, CH_2Cl_2/H_2O, 2 h, 100%; (d) NaOH, THF/H_2O, 100%; (e) $Cl_3C_6H_2COCl$, DMAP, toluene, 40%; (f) PPTS, *n*-BuOH, 81%.

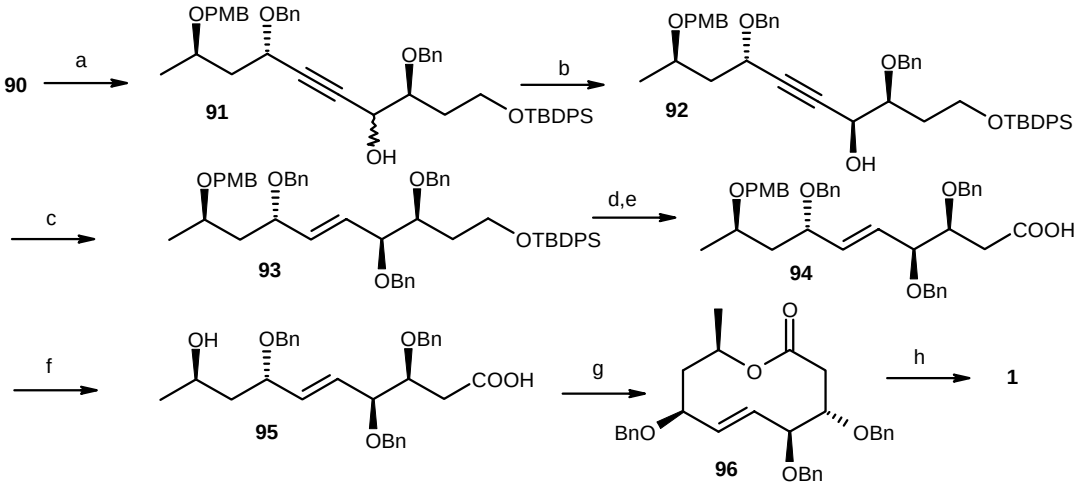
Radha Krishna *et al.* (2006).[10]

Radha Krishna and co-workers accomplished the synthesis of decarestrictine D from malic acid using Sharpless asymmetric epoxidation and Yamaguchi macrolactonization as the key steps. Accordingly, the synthesis of **1** starts with compound **81**, which is readily obtained from L-malic acid.[30] Thus, silylation of **81** and then deprotection of cyclohexylidene group furnished diol **82** which was converted into a benzylidene derivative followed by subsequent regioselective reductive ring-opening to afford the primary alcohol **83**, which was oxidized under Swern conditions to afford aldehyde **84**. To prepare alkyne **90**, alcohol **81** was subjected to Swern oxidation followed by Wittig olefination to furnish α,β-unsaturated ester **85**, which on reduction followed by Sharpless asymmetric epoxidation afforded epoxy alcohol **86**. Chlorination of epoxide **86** followed by base induced elimination gave propargylic alcohol, which was protected as benzyl ether, and cyclohexylidene group was cleaved to afford the diol **88**. Monotosylation of the primary hydroxyl group of **88** followed by reduction and PMB protection furnished fragment **90** (Scheme 9). Coupling of aldehyde **224** with acetylenic anion generated from **90** yielded **91** as diastereomeric mixture, which on oxidation and further reduction with K-selectride[31] afforded **92**. Reduction of **92** followed by benzyl protection and TBDPS

deprotection afforded primary alcohol which was oxidized to acid. Finally benzyl deprotection followed by Yamaguchi lactonization and global debenzylation afforded target molecule **1** (Scheme 10).



Scheme 9. *Reagents and conditions*: (a) (i) TBDPSCl, imidazole, CH_2Cl_2, 0 ^oC –rt, 4 h, 90%; (ii) CSA, MeOH, rt, 0.5 h, 85%; (b) (i) α,α- Dimethoxytoluene, PPTS, CH_2Cl_2, 0 ^oC – rt, 3 h, 78%; (ii) DIBAL–H, CH_2Cl_2, 0 ^oC –rt, 3 h, 75%; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^oC, 95%; (d) $Ph_3PCHCOOEt$, benzene, reflux, 2 h, 70%; (e) $LiAlH_4/AlCl_3$, ether, 0 ^oC, 6 h, 65%; (ii) (+)-DIPT, $Ti(O\textit{i}Pr)_4$, cumene hydroperoxide, CH_2Cl_2, -20 ^oC, 12 h, 85%; (f) CCl_4, Ph_3P, $NaHCO_3$, reflux, 1 h, 90%; (ii) LDA, THF, -78 ^oC to -40 ^oC, 3 h, 65%; (g) (i) BnBr, NaH, THF, 0 ^oC – rt, 6 h, 80%; (ii) CSA, MeOH, rt, 0.5 h, 85%; (h) (i) TsCl, Et_3N, CH_2Cl_2, 0 ^oC –rt, 12 h, 75%; (ii) $LiAlH_4$, THF, 0 ^oC –rt, 2 h, 90%; (i) PMBBr, NaH, THF, 0 ^oC –rt, 12 h, 75%.



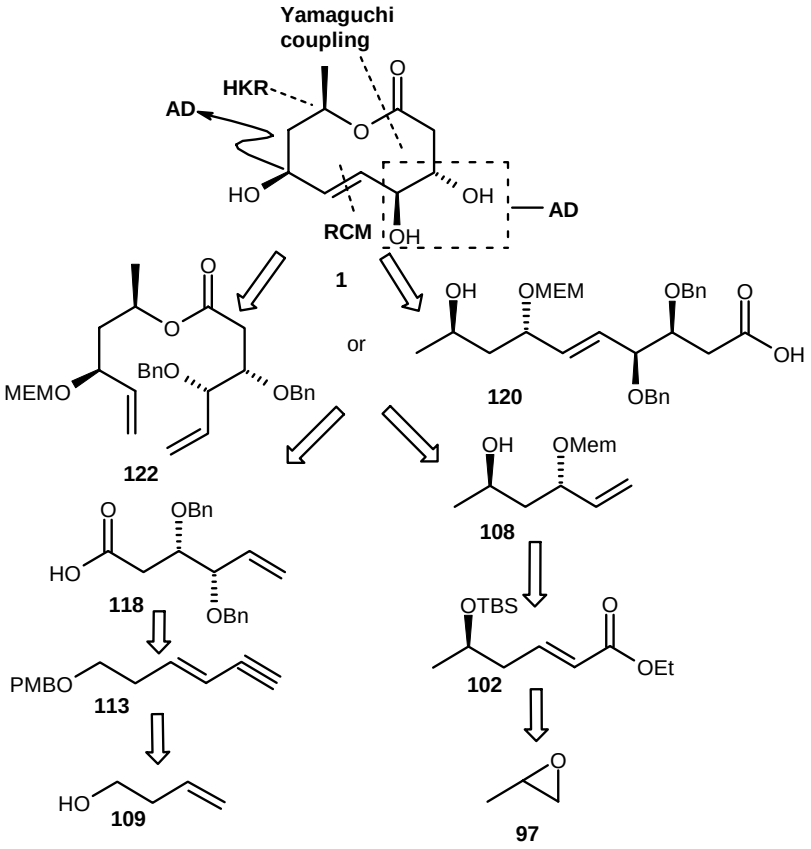
Scheme 10. *Reagents and conditions*: (a) *n*-BuLi, **84**, THF, -78 ^{o}C, 3 h, 70%; (b) (i) Dess–Martin periodinane, CH_2Cl_2, 0 ^{o}C – rt, 2 h, 90%; (ii) K-Selectride, THF, -78 ^{o}C, 3 h, 80%; (c) (i) Red-Al, ether, 0 ^{o}C – rt, 2 h, 95%; (ii) BnBr, NaH, THF–DMF (9:1), 0 ^{o}C – rt, 4 h, 75%; (d) TBAF, THF, 0 ^{o}C – rt, 12 h, 95%; (e) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^{o}C 1 h; (ii) $NaClO_2$, $NaH_2PO_4.2H_2O$, *t*-BuOH–2-methyl-2-butene (3:1), 0 ^{o}C – rt, 12 h, 80% for two steps; (f) DDQ, CH_2Cl_2–H_2O (19:1), rt, 1 h, 80%; (g) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 0 ^{o}C – rt, 4 h, then DMAP, toluene, reflux, 12 h, 45%; (h) $TiCl_4$, CH_2Cl_2, 0 ^{o}C –rt, 1 h (65%).

5.1.3. Present work:

Objective:

Considering its strong and selective biological profile, decarestrictine D has attracted a great deal of interest among synthetic organic chemists worldwide as an attractive synthetic target towards developing a new cholesterol lowering drug. Though, the syntheses of **1** and its seco-acid as discussed earlier have been reported by various research groups,[6-10] a simple and flexible synthesis to overcome the problems of reported synthesis is highly desirable. Amongst the literature reports, synthetic strategies that are based on 1,3-chiral induction to establish the C7 stereocentre suffer from low diastereoselectivity.[6,8] Similarly the Sharpless AD reaction of a diene[6] to generate the C3 and C4 stereocentres and stereoselective reduction of a keto group by L-selectride[10] to establish the C4 stereocentre were found to give a mixture of two regioisomers and stereoisomers respectively. Pilli's synthesis also suffers from use of excess of the toxic Chromium reagent coupled with a mixture of two diastereomers at C7 centre. In addition, majority of the approaches known for decarestrictine D are based on the macrolactonization for the key macrocyclization and suffer from the low yield (17-45%) of the target molecule.[6,9-10] Thus a synthetic strategy with high enantioselectivity and high yielding steps is highly important. Owing to a peculiar biological activity and attracted by the structural potential of decarestrictine D for structure-activity relationship studies, we became interested in developing a practical route to the target molecule **1**.

Herein we describe our successful endeavors towards the total synthesis of **1** employing hydrolytic kinetic resolution (HKR), Sharpless asymmetric dihydroxylation (AD), Yamaguchi coupling, cross metathesis and ring-closing metathesis (RCM) as the key steps. Our retrosynthetic analysis is based on convergent approach as outlined in Scheme 11. We envisioned that the ring-closing could be effected by Yamaguchi macrolactonization of seco acid **120** or by ring-closing metathesis of diene **122**. Seco acid **120** in turn could be derived from cross-metathesis of alcohol **108** and acid **118**. Diene **122** could be prepared by Yamaguchi coupling of the same fragments **108** and **118**. Both the fragments **108** and **118** could be obtained from olefins **102** and **113** respectively via AD. Olefins **102** and **113** in turn could be derived from the commercially available propylene oxide **97** and 3-butene-1-ol **109** respectively.

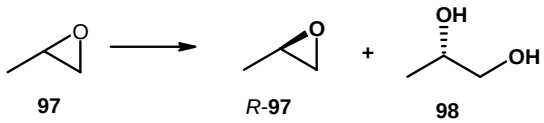


Scheme 11. Retrosynthetic route to decarestrictine D

5.1.4. Results and Discussion:

Synthesis of alcohol 108 (**Scheme 12, 13**)

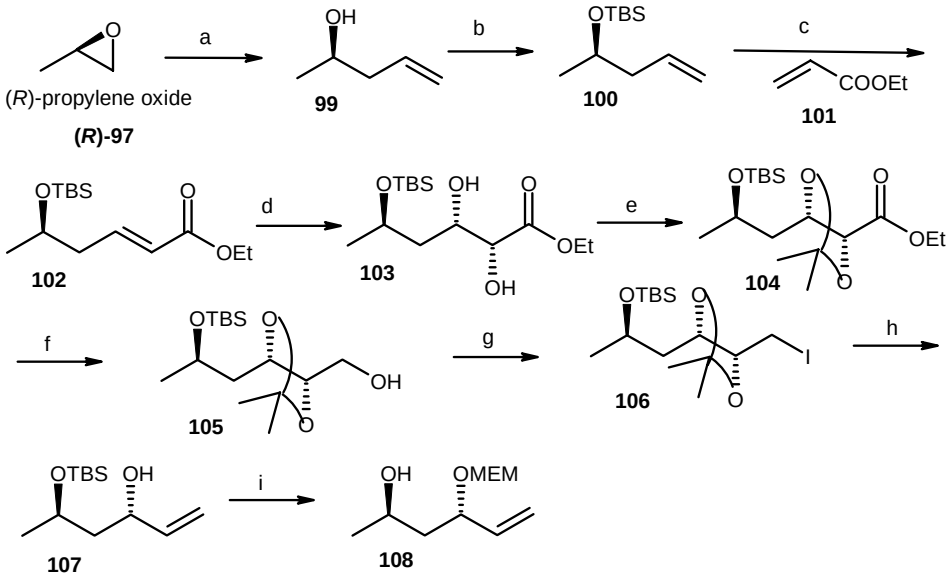
The synthesis of alcohol **108** started from commercially available propylene oxide. Thus, racemic propylene oxide **97** was resolved by using *R*,*R*-salen-Co(III)OAc to give (*R*)-propylene oxide (*R*)-**97**.[32] $[\alpha]_D^{25}$ +11.4 (neat); lit.[32] $[\alpha]_D^{25}$ -11.6 (neat) (for (*S*)-propylene oxide), which was easily isolated from the more polar diol **98** by distillation (Scheme 12).



Scheme 12. *Reagents and conditions:* (a) *R*,*R*-salen-Co-(OAc) (0.5 mol%), dist. H_2O (0.55eq), 0 ^oC, 14 h, (46% for *R*-**97**, 45% for **98**)

The ring opening of (*R*)-propylene oxide (*R*)-**97** with vinylmagnesium bromide afforded alcohol **99**. The IR spectrum of **99** gave broad hydroxyl absorption at 3400 cm^{-1}. The ^1H NMR spectrum of **99** gave olefin peaks at 5.77-5.85 (multiplet, one proton), 5.12 (doublet, one proton), 5.09 (doublet, one proton). The protection of hydroxy group of **99** as TBS ether furnished the olefin **100** in 94% yield. The IR spectra of **100** showed absence of hydroxyl absorption. The olefin **100** on cross metathesis[33] with ethyl acrylate **101** using Grubb's second generation catalyst afforded the *trans*-olefin **102** in 80% yield. The IR spectrum of **102** showed the ester carbonyl absorption at 1714 cm^{-1} and olefin C=C stretching at 1655 cm^{-1}. The ^1H NMR spectrum gave olefin protons at δ 6.99 (doublet of triplet) with the coupling constant J = 19.7, 2.8 Hz and δ 5.87 (doublet of triplet) with the coupling constant J = 15.5, 2.9 Hz indicating *trans*-olefin. The olefin **102** was treated with osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of $(DHQ)_2PHAL$ under AD conditions[11] to give the diol **103** in 96% yield with >95% de. The IR spectrum of **103** showed hydroxyl absorption at 3439 cm^{-1} and ester carbonyl at 1734 cm^{-1}. The ^1H NMR indicated absence of olefin protons. The chiral protons appeared at δ 4.20-4.05 (multiplet) and 3.98 (doublet). The chiral carbons appeared at δ 74.1 and 69.3 in the ^{13}C NMR spectrum. The diastereomeric excess of diol **103** was determined from its ^1H and ^{13}C NMR spectral data. Treatment of diol with 2,2-dimethoxy propane in the presence of catalytic amount of *p*-TSA gave compound **104** in good yield. The IR spectrum of **104** indicated absence of hydroxyl groups. The acetonide methyl protons appeared at δ 1.43

(singlet) and 1.45 (singlet) in the ^{1}H NMR spectrum and typical quaternary carbon of acetonide appeared at 110.6 in the ^{13}C NMR spectrum. Reduction of **104** using DIBAL-H provided the alcohol **105** in 94% yield. The IR spectrum of **105** gave hydroxyl absorption at 3461 cm^{-1} and the ester carbonyl group was absent. Alcohol **106** was converted into iodo **106** in 87% yield. In the ^{1}H NMR spectrum of **106** the resonances due to CH_2I were located at 3.31 and 3.25 as a doublet (J = 4.9 Hz). Reductive elimination of **106** using Zn/EtOH gave the allylic alcohol **107** in 94% yield. In the ^{1}H NMR spectrum of **107** peaks owing to CH_2I and isopropylidene group were absent. The terminal olefinic proton showed peaks at δ 6.03-5.79 (multiplet, 1H) and at δ 5.36-5.06 (multiplet, 2H). All other protons resonated at the expected chemical shift. The ^{13}C spectrum displayed peaks at 113.7, 141.1 corresponding to olefinic carbons. Alcohol **107** was protected as MEM ether using MEM-Cl, DIPEA in anhydrous CH_2Cl_2 at ambient temperature followed by subsequent TBS deprotection to give the required alcohol fragment **108** in 75% yield from both the steps. The IR spectra of **108** showed hydroxyl absorption at 3469 cm^{-1}. The ^{1}H NMR spectra of **108** showed singlet resonated at δ 4.83 (OCH_2O), δ 3.39 (OCH_3), and a multiplet at 3.60−3.41 (OCH_2CH_2O) corresponding with MEM group. The ^{13}C NMR spectrum showed resonances at 58.8, 66.6, 71.6 and 92.1 (Scheme 13).

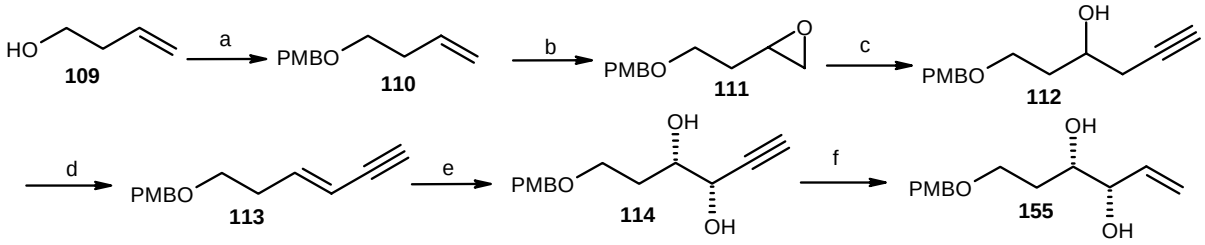


Scheme 13. *Reagents and conditions:* (a) vinylmagnesium bromide, THF, , CuI, -20 ^{o}C, 12 h, 89%; (b) TBDMS-Cl, imidazole, CH_2Cl_2, 0 ^{o}C to rt, 4 h, 94%; (c) $RuCl_2$(=CHPh)(PCy_3)(IEMS), benzene, rt, 20 h, 80%; (d) $(DHQ)_2PHAL$, K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, OsO_4 (0.1M in toluene), *t*-BuOH–H_2O (1:1), 0 ^{o}C, 24 h, 96%; (e)

p-TSA, 2,2-DMP, CH_2Cl_2, 2 h, 89%; (f) DIBAL-H, CH_2Cl_2, 0 ^oC to rt, 2 h, 94%; (g) (i) TsCl, Et_3N, CH_2Cl_2, 2h; (ii) NaI, *t*-butanone, reflux, 6 h, 87% from both the steps; (h) Zn, EtOH, reflux, 8 h, 94%; (i) (i) MEMCl, DIPEA, CH_2Cl_2, 8 h; (ii) TBAF, THF, 6 h, 75% from both the steps.

Synthesis of acid 118 (Scheme 14, 15)

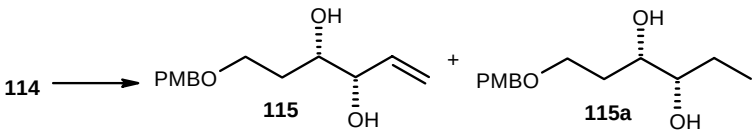
The synthesis of acid fragment **118** commenced from commercially available 3-butene-1-ol **109**. In order to generate the *trans*-olefin to execute AD, 3-butene-1- ol was converted into the enyne moiety. Thus, protection of alcohol **109** with PMB bromide in the presence of NaH afforded **110**. The ^1H NMR spectrum of **110** showed benzylic protons at δ 4.53 (singlet, 2 H) and aromatic protons at δ 7.24 (doublet) and 6.85 (doublet) with coupling constant J = 8.8 Hz. Epoxidation of **110** with *m*-CPBA afforded epoxide **111** in 96% yield. The ^1H NMR spectrum of **111** showed epoxide protons at δ 3.01-2.10 (multiplet, 1 H), 2.77 (doublet of doublet, 1 H, with coupling constant J = 4.9, 1.2 Hz) and 2.51 (doublet of doublet, with coupling constant J = 4.9, 2.4 Hz). The ^{13}C NMR spectrum of **111** showed upfield carbons characteristic of epoxide at δ 54.9 and 45.7. Ring opening of **111** with lithium acetylide.EDA complex in DMSO at room temperature furnished acetylide **112**. IR spectrum of **112** showed hydroxyl absorption at 3454 cm^{-1}. In the ^1H NMR spectrum of **112** a singlet at δ 2.51 was attributed to acetylenic proton. Protection of hydroxy group of **112** as mesyl and subsequent elimination using DBU afforded the enyne **113** in 82% yield. The IR spectrum of **113** showed the olefin C=C stretching at 1612 cm^{-1}. The ^1H NMR spectrum gave olefin protons at δ 6.27 (doublet of triplet) with the coupling constant J = 15.6, 7.3, 1.5 Hz indicating *trans*-olefin. The ^{13}C NMR spectrum showed olefinic carbon at 113.7 and 110.3. The enyne **113** was further treated with osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of $(DHQ)_2PHAL$ under AD conditions to give the diol **114** in 94% yield with 94% ee (Scheme 53). The enantiomeric excess of diol was determined by converting it into Mosher ester and by ^{19}F spectroscopy. The IR spectrum of **114** showed hydroxyl absorption at 3307 cm^{-1}. The ^1H NMR indicated absence of olefin protons. The chiral protons appeared at δ 4.23 (doublet of doublet, J = 3.7, 2.1 Hz, 1H) and 3.89-3.84 (multiplet).



Scheme 14. *Reagents and conditions:* (a) PMBBr, NaH, THF, 0 ^{o}C to rt, 2 h, 93%; (b) *m*-CPBA, CH_2Cl_2, 0 ^{o}C to rt, 8 h, 96%; (c) LiC≡CH-ethylene diamine, DMSO, 0 ^{o}C to rt, overnight, 89%; (d) (i) MsCl, Et_3N, CH_2Cl_2, 0 ^{o}C to rt, 2 h; (ii) DBU, toluene, reflux, 4 h, 82% from two steps; (e) $(DHQ)_2PHAL$, K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, OsO_4 (0.1M in toluene), *t*-BuOH–H_2O (1:1), 0 ^{o}C, 24 h, 94%; (f) Lindlar's catalyst, pyridine : octene : EtOAc (1 : 1 : 10), 2 h, 94%.

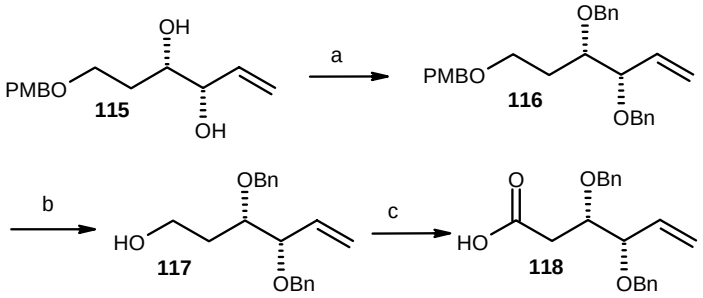
The partial hydrogenation of **114** proved to be challenging. Irrespective of whether catalytic quantity or several molar equivalent of quinoline were present, the mixture of **115** and over hydrogenated product **115a** was formed (Table 1). However the use of 1-octene as a co- solvent along with EtOAc in the presence of pyridine (EtOAc/ pyridine/ 1-octene = 10:1:1) furnished the olefinic diol **115** as a single product in 94% yield.[34] In the ^{1}H NMR spectrum of **115** peak owing to acetylide was absent. The terminal olefinic group showed peaks at δ 5.94-5.77 (multiplet, 1H) and 5.38-5.19 (m, 2H). All other protons resonated at the expected chemical shift. The ^{13}C spectrum displayed peaks at 113.7 and 137.4 corresponding to olefinic carbons.

Table 1. Partial hydrogenation of **114**



S. No	Base	Solvents	**115** : **115a**
1.	Quinoline (catalytic)	EtOAc	0 : 100
2.	Quinoline (10 equiv.)	EtOAc	10 : 90
3.	Quinoline (10 equiv.)	Benzene	30 : 70
4.	Pyridine	Octene/EtOAc (1:10)	100 : 0

The treatment of diol **115** with benzyl bromide in the presence of NaH gave dibenzyl olefin **116**. IR spectrum of **116** showed absence of hydroxyl absorption, in the ^{1}H NMR spectrum, the benzylic protons appeared at δ 4.63 (doublet of doublet, J = 11.4, 8.2 Hz, 2H), 4.44-4.35 (m, 2H). Compound **116** on PMB deprotection[35] by using DDQ furnished the alcohol **117** in 93% yield. The IR spectra of **117** showed hydroxyl absorption at 3377 cm^{-1}. In the ^{1}H NMR spectra, the peaks owing to PMB group disappeared. The alcohol **117** was oxidized to aldehyde by using IBX[36] followed by subsequent oxidation using $NaClO_2$ to give the required acid fragment **118** in 80% yield (Scheme 15). The IR spectra of **118** showed hydroxyl absorption at 3305 cm^{-1} and acid carbonyl at 1714 cm^{-1}. The ^{1}H NMR and ^{13}C spectra of **118** were compatible with the assigned structure.



Scheme 15. *Reagents and conditions:* (a) BnBr, NaH, THF, 0 ^{o}C to rt, 4 h, 85%; (b) DDQ, CH_2Cl_2/H_2O, rt, 30 min, 93%; (c) (i) IBX, EtOAc, reflux, 3 h; (ii) $NaClO_2$, NaH_2PO_4, DMSO, overnight, 80%.

Synthesis of decarestrictine D through cross metathesis and Yamaguchi macrolactonization (**Scheme 16**)

With substantial amount of both the fragments in hand, we required to generate the *trans*-olefin and carry out the subsequent reactions to complete the synthesis of target molecule. We then proceeded with the synthesis initially by cross-olefin metathesis (Scheme 16).

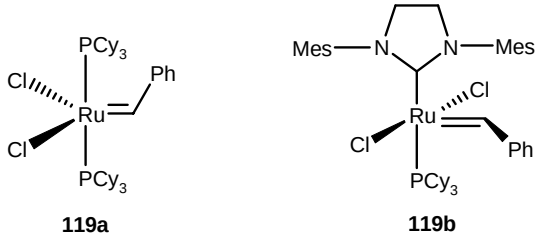
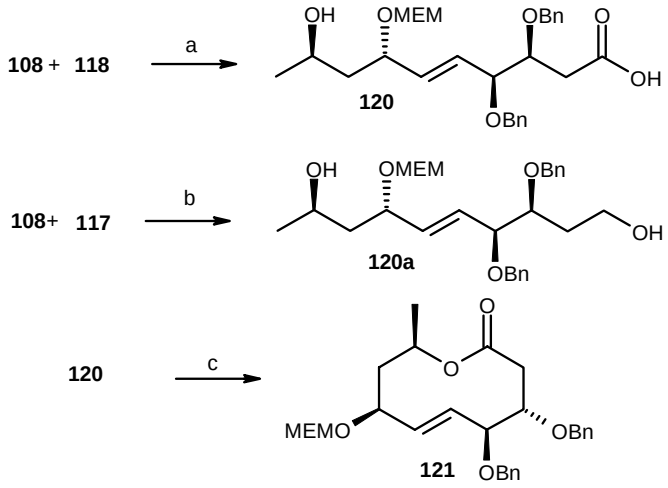


Figure 2. Grubbs' catalyst

Thus cross- metathesis of olefin **108** (2 equiv.) and acid **118** (1 equiv.) with Grubb's second generation catalyst (20 mol%) **119b** (Fig. 2) furnished the seco-acid **120** in 54% yield with olefin ratio (5:1) in favour of *E*-isomer. The required *trans*-isomer could easily be separated through flash column chromatography. To improve the yield and *E*-selectivity, we further investigated the cross-metathesis reaction with different functionalities in both the fragments. Thus olefin **108** was coupled with olefin **117** (precursor of olefin **118**) in presence of Grubb's 2nd generation catalyst **119b** to furnish the coupled product **120a** albeit in low yield and poor selectivity. Even the use of TBS, acetate as protecting groups, could not improve the results in terms of yield and selectivity.



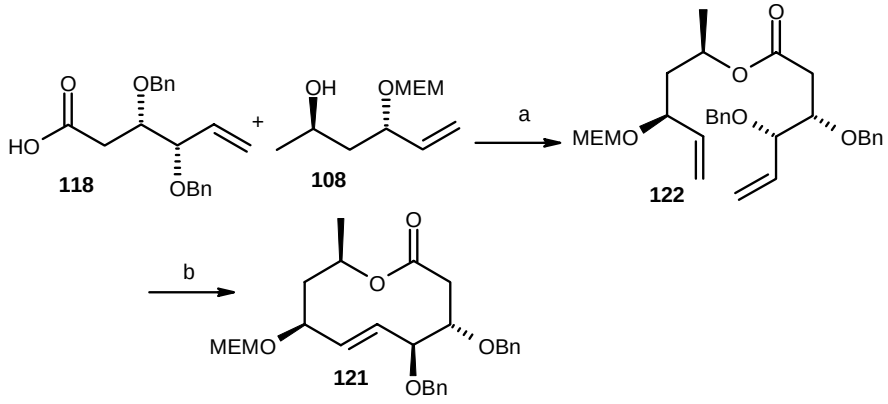
Scheme 16. *Reagents and conditions:* (a) $RuCl_2(=CHPh)(PCy_3)(IEMS)$, CH_2Cl_2, rt, 2 days, 54%; (b) $RuCl_2(=CHPh)(PCy_3)(IEMS)$, CH_2Cl_2, rt, 2 days, 38%; (c) 2,4,6-trichlorobenzoyl chloride, DMAP, THF, reflux, 1 h, 32%.

With desired seco-acid **120** in hand, we turned our attention to get the macrolactone *via* Yamaguchi macrocyclization. However, macrolactonization of **120** under Yamaguchi conditions[29] provided the macrocyclic lactone **121** in 32% yield only. The low yield obtained could probably be attributed to destabilizing nonbonded, trans-annular interactions and unfavourable entropic factors.[37] (Scheme 16).

Synthesis of decarestrictine D through ring-closing metathesis (Scheme 56)

In order to circumvent the problem of low yield in the cross-metathesis step as well as macrolactonization, we thought it appropriate to use Yamaguchi coupling reaction initially

for the diene ester formation and then ring-closing metathesis[38] for macrocyclization as the last step in the synthesis (Scheme17).

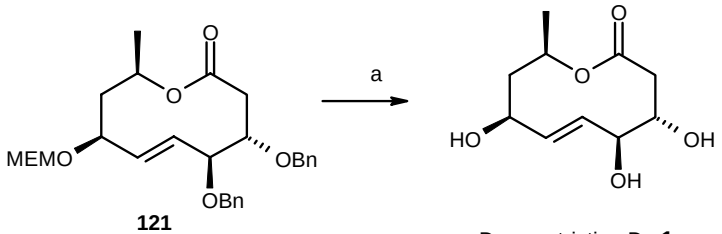


Scheme 17. *Reagents and conditions*: (a) 2,4,6-trichlorobenzoyl chloride, DMAP, Et_3N, THF, 0 ^oC - rt, 20 h, 89%; (b) $(PCy_3)_2$ $Ru(Cl)_2$=CH–Ph (20 mol %), CH_2Cl_2, reflux, 14 h, 82%.

To this end the alcohol **108** was coupled with acid **118** under Yamaguchi conditions to give the diene **122** in 89% yield. The IR spectra of **122** showed ester carbonyl at 1720 cm^{-1}. In ^{13}C NMR, peak owing to carbonyl carbon was present at δ 171.2 The diene **122** was treated with Grubbs first generation catalyst **119a** to give the α,β-unsaturated lactone **121** in 82% yield with olefin ratio (8:1) in favour of *E*-isomer, which were separable on column chromatography. The IR spectrum of **121** showed carbonyl group of lactone at 1718 cm^{-1}. The olefin protons appeared at 5.72 (dd, J = 15.8, 6.3 Hz, 1H), 5.67 (dd, J = 15.8, 2.1 Hz, 1H) 5.72 (doublet of doublet) with J = 15.8, 6.3 Hz and 5.67 (doublet of doublet) with J = 15.8, 2.1 Hz in the ^1H NMR spectrum indicating *trans*-olefin. The olefinic carbons appeared at δ 139.5 and 127.5 in ^{13}C NMR spectrum.

Removal of protecting groups

Treatment of **121** with titanium tetrachloride[39] at 0 °C (Scheme 18) for the deprotection of MEM-group, resulted in the simultaneous removal of both the protective groups, affording decarestrictine D in 78% yield. $[\alpha]_D^{25}$ –63.7 (*c* 0.46, EtOH); [lit.[3b] $[\alpha]_D$ – 62.0 (*c* 0.4, EtOH)]. The physical and spectroscopic data of **1** were in full agreement with the literature data.[3]



121 Decarestrictine D **1**

Scheme 18. *Reagents and conditions:* (a) $TiCl_4$, CH_2Cl_2, 0 ^oC - rt, 30 min, 78%.

5.1.5. Conclusion

In conclusion, a convergent and efficient total synthesis of decarestrictine, with high enantioselectivities has been accomplished in which stereocentres were generated by means of Jacobsen's HKR and asymmetric dihydroxylation, and lactone moiety was achieved by ring closing metathesis. This approach could be used for synthesis of other isomers of decarestrictine D for structure activity relationship. Currently work is in progress in this direction.

5.1.6. Experimental Section

(*R*)-Propylene oxide ((*R*)-97).

(*R*)-**97**

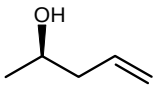
The racemic propylene oxide **97** was resolved to (*R*)-propylene oxide (***R*)-97** in high enantiomeric excess by the HKR method following a literature procedure.[32]

Yield: 14.71 g, 90%

Mol. Formula: C_3H_6O

$[\alpha]_D^{25}$: +11.4 (neat), lit.[32] $[\alpha]_D^{25}$ –11.6 (neat) (for (*S*)-propylene oxide).

(*R*)-Pent-4-en-2-ol (99).



99

A round bottomed flask was charged with copper (I) iodide (1.64 g, 8.6 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 ^{o}C and vigorously stirred, and vinylmagnesium bromide (1M in THF, 172 mL, 172.4 mmol) was injected to it. A solution of propylene oxide (*R*)-**97** (5 g, 86.09 mmol) in THF (10 mL) was added slowly to the above reagent, and the mixture was stirred at –20 ^{o}C 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 to afford the crude homoallylic alcohol which on distillation provided alcohol **99** (6.6g, 89%) as a colorless liquid (bp 115 ^{o}C, lit.[40] 115 ^{o}C).

Yield: 6.6 g, 89%

B.P.: 115 ^{o}C, lit.[40] 115 ^{o}C

Mol. Formula: $C_5H_{10}O$

$[\alpha]_D^{25}$ **:-** 9.92 (*c* 3.0, Et_2O); lit.[115] $[\alpha]_D^{24}$- 9.84 (*c* 3.2, Et_2O)

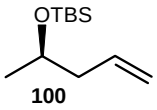
IR ($CHCl_3$, cm^{-1}): ν_{max} 3400, 3078, 2931, 2975, 1562, 1457, 1432, 1243, 1071, 914.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.77-5.85 (m, 1H), 5.12 (d, *J* = 6.6 Hz, 1H), 5.09 (d, *J* = 2.4 Hz, 1H), 3.80-3.86 (m, 1H), 2.22-2.38 (m, 2H), 1.82 (s, 1H), 1.18 (d, *J* = 6.1, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 134.6, 116.6, 66.5, 43.2, 22.1.

Analysis Calcd.: C, 69.72; H, 11.70%; **Found:** C, 69.61; H,11.75%.

(*R*)- *tert*-Butyldimethyl-(pent-4-en-2-yloxy)-silane (100).



100

To a stirred soluion of alcohol **99** (3.0 g, 34.83 mmol) in CH_2Cl_2 (25 mL), imidazole (3.57, 52.24 mmol) was added. To this solution *t*-butylchlorodimethyl silane (5.77 g, 38.31 mmol) was added at 0 ^{o}C 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 X 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 (49:1) as eluent provided **100**.

Yield: 6.56 g, 94%.

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

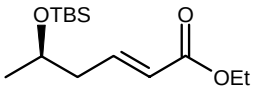
IR ($CHCl_3$, cm^{-1}): ν_{max} 3079, 2956, 2930, 2896, 2858, 1642, 1472, 1463, 1361, 1255, 1129, 1087, 1004, 914, 836.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.77-5.83 (m, 1H), 5.07 (d, *J* = 7.5 Hz, 1H), 5.01 (d, *J* = 8.1 Hz, 1H), 3.80-3.86 (m, 1H), 2.21 (dd, *J* = 15.4, 6.5, 2H), 1.15 (d, *J* = 6.6 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 135.6, 116.5, 68.5, 44.4, 25.9, 23.4, 18.4, -4.5, -4.7.

Analysis Calcd.: C, 65.93; H, 12.07%; Found C, 65.86; H, 12.12%.

(*R*,*E*)-Ethyl 5-(*tert*-butyldimethylsilyloxy)hex-2-enoate (102).



102

The olefin **100** (2g, 9.98 mmol) was diluted with benzene (20 ml) and degassed for 15 minutes. Ethyl acrylate **101** (2.5g, 24.95 mmol freshly distilled) was then added to the reaction flask followed by Grubb's 2nd generation catalyst (0.169g, 0.20 mmol). The reaction was allowed to stir for 20 h under argon at room temperature, at which time, it was allowed to oxidize by opening the reaction to air and stirring overnight. The dark brown solution was then concentrated. Silica gel column chromatography of the crude product using pet ether/EtOAc (19:1) as eluent provided the α,β-unsaturated ester **102** as a light yellow colour liquid.

Yield: 2.18 g, 80%.

Mol. Formula: $C_{14}H_{28}O_3Si$

$[\alpha]_D^{25}$: -6.38 (*c* 1.02, $CHCl_3$).

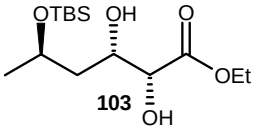
IR (neat, cm^{-1}): ν_{max} 3021, 2958, 2931, 2898, 1714, 1655, 1472, 1463, 1446, 1369, 1258, 1178, 1086, 1047, 998, 838.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.99 (dt, *J* = 19.7, 2.8 Hz, 1H), 5.87 (dt, *J* = 15.5, 2.9 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.88-4.0 (m, 1H), 2.31 (dd, *J* = 13.25, 5.9, 2H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.18 (d, *J* = 5.9 Hz, 3H), 0.88 (s, 9H), 0.05 (S, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.3, 145.9, 123.1, 67.5, 59.9, 42.3, 25.7, 23.7, 17.9, 14.1, -4.7, -5.0.

Analysis Calcd.: C, 61.72; H, 10.36%; **Found** C, 61.80; H, 10.38%.

(2*R*,3*S*,5*R*)-Ethyl 5-(*tert*-butyldimethylsilyloxy)-2,3-dihydroxyhexanoate (103).



103

To a mixture of $K_3Fe(CN)_6$ (7.25 g, 22.02 mmol), K_2CO_3 (3.04 g, 22.02 mmol) and $(DHQ)_2PHAL$ (57 mg, 1 mol%), in *t*-BuOH-H_2O (1:1, 40 mL) cooled at 0 ^oC was added OsO_4 (0.29 mL, 0.1 M sol in toluene, 0.4 mol%) followed by methanesulfonamide (0.70 g, 7.34 mmol). After stirring for 5 min at 0 ^oC, the olefin **102** (2.0 g, 7.34 mmol) was added in one portion. The reaction mixture was stirred at 0 ^oC for 24 h and then quenched with solid sodium sulfite (11 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 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 diol **103** as a colorless syrupy liquid.

Yield: 2.16 g, 96%

Mol. Formula: $C_{14}H_{30}O_5Si$

$[\alpha]_D^{25}$: –10.37 (*c* 1.26, $CHCl_3$).

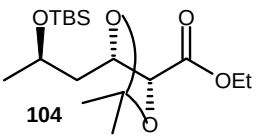
IR (neat, cm^{-1}): ν_{max} 3439, 3020, 2958, 2931, 2401, 1734, 1656, 1472, 1446, 1257, 1215, 1085, 978.

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.27 (q, *J* = 7.2 Hz, 2H), 4.20-4.05 (m, 2H), 3.98 (d, *J* = 6.6 Hz, 1H), 3.28 (brs, 1H), 3.11 (brs, 1H), 1.93 (dd, *J* = 10.8, 1.3 Hz, 1H), 1.54 (dd, *J* = 8.2, 6.2 Hz, 1H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.20 (d, *J* = 6.0 Hz, 3H), 0.89 (s, 9H), 0.09 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$): δ -5.3, -4.7, 14.0, 17.8, 23.2, 25.6, 42.2, 61.5, 66.4, 69.3, 74.1, 173.2.

Analysis Calcd.: C, 54.87; H, 9.87; Found C, 54.74; H, 9.82.

(4*R*,5*S*)-Ethyl-5-((*R*)-2-(*tert*-butyldimethylsilyloxy)propyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (104).



104

To a solution of the diol **103** (2.0 g, 6.53 mmol), *p*-TSA (50 mg) in CH_2Cl_2 (75 mL) was added 2,2-dimethoxypropane (1.02 g, 1.2 mL, 9.79 mmol) and mixture stirred for 2 h. Solid $NaHCO_3$ was added and stirred for 1.5 h. 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) as eluent gave acetonide ester **104** as a colorless liquid.

Yield: 2.01 g, 89%

Mol. Formula: $C_{17}H_{34}O_5Si$

$[\alpha]_D^{25}$: –23.05 (*c* 1.40, $CHCl_3$)

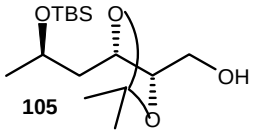
IR (neat, cm^{-1}): ν_{max} 3021, 2957, 2931, 1751, 1655, 1473, 1375, 1216, 1144, 1084, 952, 839, 758.

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.26 (q, *J* = 8.0 Hz, 2H), 4.16-4.09 (m, 1H), 4.07-4.03 (m, 2H), 1.70-1.61 (m, 2H), 1.45 (s, 3H), 1.43 (S, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.19 (d, *J* = 6.4 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 170.5, 110.6, 78.9, 75.8, 65.1, 61.0, 43.3, 27.1, 25.6, 24.4, 17.8, 14.0, -4.5, -5.2.

Analysis Calcd.: C, 58.92; H, 9.89%; **Found** C, 59.01; H, 9.86%.

((4*S*,5*S*)-5-((*R*)-2-(*tert*-Butyldimethylsilyloxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (105).



105

To a solution of ester **104** (2 g, 5.77 mmol) in dry CH_2Cl_2 (20 mL) at 0 ^oC was added dropwise DIBAL-H (6.35mL, 6.35 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 sod./pot. 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 (17:3) as eluent gave alcohol **105** as a colorless liquid.

Yield: 1.65 g, 94%

Mol. Formula: $C_{15}H_{32}O_4Si$

$[\alpha]_D^{25}$: –42.51 (*c* 1.20, $CHCl_3$).

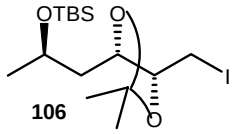
IR ($CHCl_3$, cm^{-1}): ν_{max} 3461, 3019, 2957, 2931, 2858, 1719, 1472, 1380, 1256, 1215, 1167, 1047, 952.

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.05-4.00 (m, 2H), 3.80-3.70 (m, 1H), 3.63 (d, *J* = 4.9 Hz, 2H), 2.18 (s, 1H), 1.58 (t, *J* = 5.7 Hz, 2H), 1.40 (s, 3H), 1.38 (s, 3H), 1.19 (d, *J* = 6.1 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 108.6, 81.5, 73.7, 65.5, 61.9, 42.7, 27.4, 26.8, 25.8, 24.6, 17.9, -4.5, -5.0.

Analysis Calcd.: C, 59.17; H, 10.59%; **Found** C, 59.23; H, 10.57%.

***tert*-Butyl((*R*)-1-((4*S*,5*R*)-5-(iodomethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propan-2-yloxy)- dimethyl-silane (106).**



106

To a stirred solution of alcohol **105** (1.2 g, 3.94 mmol) in CH_2Cl_2 (40 mL) at 0 ^oC under nitrogen was added triethyl amine (1.65 mL, 11.82 mmol) followed by tosyl chloride (0.90 g, 4.73 mmol). After being stirred for 2 h at room temperature, the reaction mixture was diluted with H_2O, and extracted with CH_2Cl_2 (50 mL). The combined organic layers were washed with water, brine and dried (Na_2SO_4). The solvent was removed under reduced pressure to give tosyl as pale yellow oil, which was used as such for the next step, without further purification.

Tosyl (1.8 g, 3.92 mmol) was dissolved under argon in dry *t*-butanone (20 mL) and was treated with NaI (1.76 g, 11.77 mmol). The reaction mixture was refluxed for 6 h. After cooling to room temperature the volatiles were removed under reduced pressure. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (19:1) as eluent gave iodo compound **106** as a colorless liquid.

Yield: 1.42 g, 87%

Mol. Formula: $C_{15}H_{31}IO_3Si$

$[\alpha]_D^{25}$: –38.04 (*c* 1.0, $CHCl_3$).

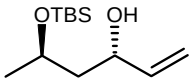
IR ($CHCl_3$, cm^{-1}): ν_{max} 3020, 2957, 2930, 2857, 2400, 1522, 1472, 1382, 1299, 1215, 1035, 837.

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.07-3.88 (m, 2H), 3.55-3.51 (m, 1H), 3.31 (d, J = 4.9 Hz, 1H), 3.25 (d, J = 4.9 Hz, 1H), 1.57 (t, J = 6.7 Hz, 2H), 1.43 (s, 3H), 1.41 (s, 3H), 1.19 (d, J = 6.2 Hz, 3H), 0.91 (s, 9H), 0.08 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 109.5, 81.9, 78.3, 68.7, 37.8, 27.3, 25.6, 25.5, 18.1, 3.8, -3.8, -4.2.

Analysis Calcd.: C, 43.48; H, 7.54%; **Found** C, 43.36; H, 7.48%.

(3*S*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)hex-1-en-3-ol (107).



107

A mixture of compound **106** (1.4 g, 3.38 mmol) and zinc (0.44 g, 6.76 mmol) in refluxing ethanol (15 mL) under nitrogen was stirred for 8 h. The zinc was filtered and filtrate concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) as eluent gave **107** as a light yellow liquid.

Yield: 0.73 g, 94%

Mol. Formula: $C_{12}H_{26}O_2Si$

$[\alpha]_D^{25}$: –29.18 (*c* 1.0, $CHCl_3$)

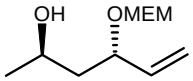
IR ($CHCl_3$, cm^{-1}): ν_{max} 3451, 3081, 2955, 2936, 2856, 1642, 1472, 1456, 1384, 1226, 1075, 940.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.03-5.79 (m, 1H), 5.36-5.06 (m, 2H), 4.52-4.41 (m, 1H), 4.24-4.06 (m, 1H), 2.18 (brs, 1H), 1.75-1.62 (m, 2H), 1.23 (d, J = 6.2, 3H), 0.92 (s, 9H), 0.10 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 141.1, 113.7, 69.6, 66.9, 44.5, 25.7, 23.0, 17.9, -4.5, -5.0.

Analysis Calcd.: C, 62.55; H, 11.37%; **Found** C, 62.48; H, 11.41%.

(2*R*,4*S*)-4-((2-Methoxyethoxy)methoxy)hex-5-en-2-ol (108).



108

A mixture of compound **107** (0.5 g, 2.17 mmol), diisopropylethylamine (0.84 g, 1.13 mL, 6.5 mmol), MEM-Cl (0.32 g, 0.30 mL, 2.60 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature for 8 h. The reaction mixture was quenched with water and extracted with

CH_2Cl_2, washed with water, brine, dried (Na_2SO_4) and evaporated to afford crude product, which was used as such for the next step without purification.

To a solution of olefin (0.69 g, 2.17 mmol) in THF (10 mL) was added TBAF (3.25 mL, 3.25 mmol, 1.0 M solution in THF) at room temperature. The reaction mixture was stirred for 6 h and then diluted with water and extracted with EtOAc. 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 (7:3) as eluent gave alcohol **108** as a colorless liquid.

Yield: 0.33 g, 75%

Mol. Formula: $C_{10}H_{20}O_4$

$[\alpha]_D^{25}$: –95.88 (*c* 1.22, $CHCl_3$).

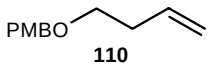
IR ($CHCl_3$, cm^{-1}): ν_{max} 3462, 3016, 2968, 2893, 2448, 1645, 1456, 1422, 1367, 1241, 1216, 1133, 1098, 993.

^{1}H NMR (200 MHz, $CDCl_3$): δ 5.80-5.63 (m, 1H), 5.29-5.15 (m, 2H), 4.83 (s, 2H), 4.05-3.90 (m, 1H), 3.74-3.69 (m, 1H), 3.60-3.41 (m, 4H), 3.39 (s, 3H). 2.39 (brs, 1H), 1.71-1.57 (m, 2H), 1.21 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 137.7, 116.7, 92.11, 73.9, 71.6, 66.6, 63.1, 58.8, 44.5, 23.3.

Analysis Calcd.: C, 58.80; H, 9.87%; **Found** C, 58.64; H, 9.81%.

1-((But-3-enyloxy)methyl)-4-methoxybenzene (110).



110

To a solution of 3-butene-1-ol **109** (5.0 g, 69.34 mmol) in dry THF (50 mL) was added sodium hydride (50%, 5.0 g, 104.00 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 (16.73 g, 83.21 mmol) and *tetra n*-butylammonium iodide (2.56 g, 6.93 mmol) with further stirring for 2 h at room 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. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (8:2) as eluent furnished the mono-PMB protected olefin **110** as a colorless oil.

Yield: 12.40 g, 93%

Mol. Formula: $C_{12}H_{16}O_2$

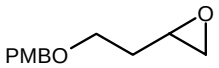
IR ($CHCl_3$, cm^{-1}): ν_{max} 3024, 2953, 2891, 1562, 1479, 1246, 1127, 1069, 1032, 887.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.24 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.80-5.63 (m, 1H), 5.29-5.15 (m, 2H), 4.53 (s, 2H), 3.83 (s, 3H), 3.42 (t, *J* = 6.6 Hz, 2H), 1.71-1.57 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 155.6, 137.9, 132.8, 129.6, 116.8, 113.8, 73.0, 69.1, 55.4, 32.9.

Analysis Calcd.: C, 74.97; H, 8.39%; **Found** C, 74.86; H, 8.43%.

2-(2-(4-Methoxybenzyloxy)ethyl)oxirane (**111).**



111

To a stirred solution of olefin **110** (7 g, 36.41 mmol) in CH_2Cl_2 (50 mL) at 0 ^oC was added *m*-CPBA (50%) (15.08 g, 43.69 mmol). The reaction mixture was stirred at room temperature for 8 h and quenched by saturated $NaHCO_3$ solution, extracted with CH_2Cl_2, washed with sat. $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using pet ether/EtOAc (17:3) as eluent afforded the epoxide **111** as a colorless liquid.

Yield: 7.28 g, 96%

Mol. Formula: $C_{12}H_{16}O_3$

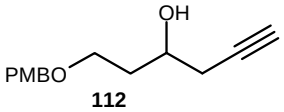
IR ($CHCl_3$, cm^{-1}): ν_{max} 3016, 2962, 2948, 2869, 1478, 1403, 1382, 1219, 1136, 918, 828.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.24 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 4.52 (s, 2H), 3.84 (s, 3H), 3.58 (t, *J* = 6.3 Hz, 2H), 3.01-3.10 (m, 1H), 2.77 (dd, *J* = 4.9, 1.2 Hz, 1H), 2.51 (dd, *J* = 4.9, 2.4 Hz, 1H), 1.69-1.88 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 158.1, 130.3, 128.9, 113.6, 72.4, 66.5, 54.9, 49.8, 45.7, 32.8.

Analysis Calcd.: C, 69.21; H, 7.74%; **Found** C, 69.26; H, 7.72%.

1-(4-Methoxybenzyloxy)hex-5-yn-3-ol (112).



112

A dark brown slurry of lithium acetylide EDA complex (7.74g, 84.03 mmol) in dry DMSO (10 mL) was stirred with epoxide **111** (7g, 33.61 mmol) overnight at room temperature. After the reaction mixture was quenched with ice, 0.3N H_2SO_4 was used to neutralize the resultant basic solution to pH 7, after which the product was extracted with ether, washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using pet ether/EtOAc (17:3) as eluent yielded the acetylide alcohol **112** as a light yellow color liquid.

Yield: 7.0 g, 89%

Mol. Formula: $C_{14}H_{18}O_3$

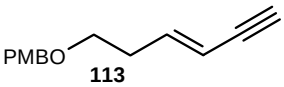
IR ($CHCl_3$, cm^{-1}): ν_{max} 3454, 2957, 2898, 2861, 2214, 1466, 1390, 1360, 1257, 1100, 1005, 980, 835, 777.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.24 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 4.54 (s, 2H), 3.81 (s, 3H), 3.59 (t, *J* = 6.3 Hz, 2H), 3.10-3.15 (m, 1H), 2.77-2.50 (m, 2H), 2.51 (s, 1H), 1.88-2.01 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 156.7, 130.5, 129.0, 113.6, 80.4, 75.9, 72.2, 68.8, 66.3, 55.6, 33.4, 33.1.

Analysis Calcd.: C, 71.77; H, 7.74%; **Found** C, 71.58; H, 7.70%.

(*E*)-1-((Hex-3-en-5-ynyloxy)methyl)-4-methoxybenzene (113).



113

To a stirred solution of acetylide alcohol **112** (6.5 g, 27.74 mmol) in CH_2Cl_2 (40 mL) at 0 ^oC under nitrogen was added triethyl amine (5.61 g, 7.7 mL, 55.49 mmol) followed by mesyl chloride (3.81 g, 33.29 mmol). After being stirred for 2 h at room temperature, the reaction mixture was diluted with H_2O, and extracted with CH_2Cl_2 (50 mL). The combined organic layers were washed with water, brine and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude product was used as such for the next step without further purification.

To a solution of mesyl (7 g, 22.41 mmol) in toluene (50 mL) were added DBU (3.75 g, 3.68 mL, 24.65 mmol). The reaction mixture was heated to reflux for 4 h. The reaction was cooled to room temperature and diluted with water and EtOAc. The two phases were separated and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic phases 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 acetylide olefin **113** as a colorless syrupy liquid.

Yield: 3.97 g, 82%.

Mol. Formula: $C_{14}H_{16}O_2$

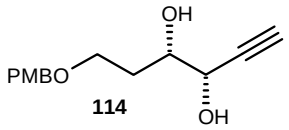
IR ($CHCl_3$, cm^{-1}): ν_{max} 3011, 2935, 2862, 2100, 1719, 1612, 1586, 1514, 1465, 1422, 1363, 1249, 1173, 1095, 1035, 822, 757.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 6.27 (dt, *J* = 7.3, 1.5 Hz, 1H), 5.60-5.51 (m, 1H), 4.45 (s, 2H), 3.82 (s, 3H), 3.50 (t, *J* = 6.6 Hz, 2H), 2.81 (s, 1H), 2.41 (q, *J* = 6.7 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 156.2, 142.9, 130.2, 129.2, 113.7, 110.3, 82.2, 76.1, 72.6, 68.5, 55.2, 33.4.

Analysis Calcd.: C, 77.75; H, 7.46%; **Found** C, 77.82; H, 7.42%.

(3*S*,4*S*)-6-(4-Methoxybenzyloxy)hex-1-yne-3,4-diol (114).



114

To a mixture of $K_3Fe(CN)_6$ (11.42 g, 34.68 mmol), K_2CO_3 (4.79 g, 34.68 mmol) and $(DHQ)_2PHAL$ (90 mg, 1 mol%), in *t*-BuOH-H_2O (1:1, 60 mL) cooled at 0 ^oC was added OsO_4 (0.46 mL, 0.1 M sol in toluene, 0.4 mol%) followed by methanesulfonamide (1.10 g, 11.56 mmol). After stirring for 5 min at 0 ^oC, the olefin **113** (2.5 g, 11.56 mmol) was added. The reaction mixture was stirred at 0 ^oC for 24 h and then quenched with solid sodium sulfite (17 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 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 diol **114** as a colorless syrupy liquid.

Yield: 2.72 g, 94%

Mol. Formula: $C_{14}H_{18}O_4$

$[\alpha]_D^{25}$: +12.77 (*c* 0.9, $CHCl_3$).

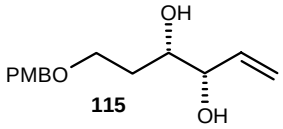
IR (neat, cm^{-1}): ν_{max} 3307, 3019, 2935, 2400, 1656, 1514, 1367, 1216, 1076, 992, 858.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.23 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 4.46 (s, 2H), 4.23 (dd, *J* = 3.7, 2.1 Hz, 1H), 3.89-3.84 (m, 1H), 3.80 (s, 3H), 3.73-3.65 (m, 2H), 3.09 (brs, 1H), 2.88 (brs, 1H), 2.47 (s, 1H), 1.99-1.79 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.3, 129.7, 129.4, 113.9, 82.2, 74.1, 73.8, 72.9, 67.7, 65.8, 55.2, 32.0.

Analysis Calcd.: C, 67.18; H, 7.25%; **Found** C, 67.21; H, 7.24%.

(3*S*,4*S*)-6-(4-Methoxybenzyloxy)hex-1-ene-3,4-diol (115).



115

To a solution of **114** (2.5 g, 9.99 mmol) in 5 mL of ethyl acetate/pyridine/1-octene (10:1:1) was added Lindlar's catalyst (10 mg). The reaction mixture was stirred for 2 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 (3:2) as eluent to give olefin **115** as a colorless liquid.

Yield: 2.37 g, 94%.

Mol. Formula: $C_{14}H_{20}O_4$

$[\alpha]_D^{25}$: +10.45 (*c* 1.0, $CHCl_3$).

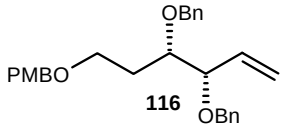
IR ($CHCl_3$, cm^{-1}): ν_{max} 3428, 3017, 2957, 2935, 2868, 2401, 1612, 1586, 1513, 1464, 1422, 1249, 1216, 1083, 933, 849.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.3 Hz, 2H), 6.89 (d, *J* = 8.3 Hz, 2H), 5.94-5.77 (m, 1H), 5.38-5.19 (m, 2H), 4.44 (s, 2H), 3.95 (t, *J* = 5.7 Hz, 2H), 3.79 (s, 3H), 3.69-3.62 (m, 2H), 2.75 (brs, 2H), 1.84-1.76 (m, 2H)

^{13}C NMR (50 MHz, $CDCl_3$): δ 159.2, 137.40, 129.8, 129.2, 116.9, 113.7, 75.8, 73.0, 72.7, 67.7, 55.1, 32.4.

Analysis Calcd.: C, 66.65; H, 7.99%; **Found** C, 66.58; H, 8.04%.

1-(((3S,4S)-3,4-Bis(benzyloxy)hex-5-enyloxy)methyl)-4-methoxybenzene (116).



To the above diol **115** (2 g, 7.93 mmol) in DMF (10 mL) at 0 ^{o}C was added NaH (60% dispersion in mineral oil, 0.95 g, 23.78 mmol). After 15 min, benzyl bromide (3.25 g, 2.3 mL, 19.02 mmol) was introduced and the reaction further stirred for 4 h at room temperature. Water was carefully added to the reaction mixture, extracted with ether, washed with water and dried (Na_2SO_4). Silica gel column chromatography of the crude product using petroleum/ EtOAc (9:1) as eluent afforded dibenzyl **116** as a light yellow colour oil.

Yield: 2.91 g, 85%.

Mol. Formula: $C_{28}H_{32}O_4$

$[\alpha]_D^{25}$: –29.62 (*c* 0.7, $CHCl_3$).

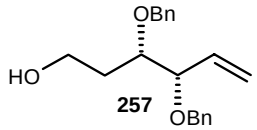
IR ($CHCl_3$, cm^{-1}): ν_{max} 3019, 2933, 2401, 1612, 1513, 1454, 1216, 1153, 1076, 992, 857, 758.

^{1}H NMR (200 MHz, $CDCl_3$): δ δ 7.30-7.21 (m, 10H), 7.13 (d, *J* = 8.7 Hz, 2H), 6.79 (d, *J* = 8.7 Hz, 2H), 5.84-5.67 (m, 1H), 5.26-5.17 (m, 2H), 4.63 (dd, *J* = 11.4, 8.2 Hz, 2H), 4.44-4.35 (m, 2H), 4.29 (s, 2H), 3.83-3.77 (m, 1H), 3.71 (s, 3H), 3.67-3.47 (m, 1H), 3.45-3.40 (m, 2H), 1.70-1.56 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 159.0, 138.8, 138.5, 135.3, 130.5, 129.2, 128.2, 128.1, 127.9, 127.8, 127.6, 127.4, 127.3, 118.6, 113.6, 82.6, 78.1, 73.4, 72.4, 70.4, 66.3, 55.1, 31.2.

Analysis Calcd.: C, 77.75; H, 7.46%; **Found** C, 77.82; H, 7.45%.

(3*S*,4*S*)-3,4-Bis(benzyloxy)hex-5-en-1-ol (117).



To a solution of dibenzyl **116** (2.5g, 5.78 mmol) in CH_2Cl_2 (18 mL) and H_2O (1 mL) at 0 ^{o}C was added DDQ (1.57 g, 6.94 mmol) in portions. The resultant mixture was stirred at

room temperature for 0.5 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 (7:3) as eluent afforded alcohol **117** as pale yellow oil.

Yield: 1.68 g, 93%

Mol. Formula: $C_{20}H_{24}O_3$

$[\alpha]_D^{25}$: –19.90 (*c* 1.38, $CHCl_3$).

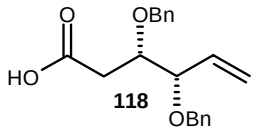
IR (neat, cm^{-1}): ν_{max} 3377, 3019, 2400, 1654, 1496, 1454, 1215, 1070, 993, 857, 759.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26-7.20 (m, 10H), 5.86-5.68 (m, 1H), 5.32-5.23 (m, 2H), 4.70 (t, *J* = 11.4 Hz ,1H), 4.57-4.51 (m, 2H), 4.38 (d, *J* = 11.9 Hz, 1H), 3.93 (t, *J* = 7.1 Hz, 1H), 3.61-3.71 (m, 2H), 1.62-1.41 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 71138.2, 134.8, 128.4, 128.0, 127.9, 127.7, 119.1, 82.2, 78.6. 73.2, 70.6, 60.2, 33.2.

Analysis Calcd.: C, 76.89; H, 7.74%; **Found** C, 76.84; H, 7.78%.

(3*S*,4*S*)-3,4-Bis(benzyloxy)hex-5-enoic acid (118).



118

To a solution of alcohol **117** (1.5 g, 4.80 mmol) in EtOAc (20 mL) was added IBX (4.03g, 14.41 mmol) in one portion and the reaction mixture was refluxed for 3 h. The reaction mixture was filtered through a pad of celite and filtrate was concentrated to give the crude aldehyde, which was used for the next step without purification.

A solution of 79% $NaClO_2$ (0.651 g, 7.20 mmol) in 1.0 mL of water was added dropwise to a stirred solution of above crude aldehyde (1.49 g, 4.80 mmol) in 0.5 mL of DMSO and NaH_2PO_4 (0.432 g, 3.6 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. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (4:1) as eluent gave the acid **118** (1.25 g, 80%) as a syrupy liquid.

Yield: 1.25 g, 80%.

Mol. Formula: $C_{20}H_{22}O_4$

$[\alpha]_D^{25}$: –33.3 (*c* 0.7, $CHCl_3$).

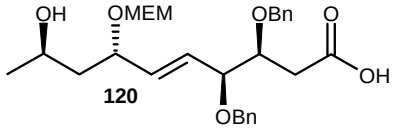
IR (neat, cm^{-1}): ν_{max} 3305, 3019, 2976, 2401, 1714, 1520, 1497, 1454, 1423, 1215, 1152, 1072, 993, 933, 854, 757.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33-7.28 (m, 10H), 5.94-5.76 (m, 1H), 5.40-5.32 (m, 2H), 4.76 (d, *J* = 11.4 Hz, 2H), 4.67 (d, *J* = 10.9 Hz, 1H), 4.44 (d, *J* = 11.9 Hz, 1H), 4.11-3.97 (m, 2H), 2.70 (dd, *J* = 4.2 Hz, 1H), 2.52 (dd, *J* = 8.2 Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 176.9, 138.1, 134.4, 128.3, 127.9, 127.7, 119.4, 81.01, 77.4, 75.9, 73.5, 36.2.

Analysis Calcd.: C, 73.60; H, 6.79%; **Found** C, 73.48; H, 6.74%.

(3*S*,4*S*,7*S*,9*R*,*E*)-3,4-Bis(benzyloxy)-9-hydroxy-7-((2-methoxyethoxy)methoxy)dec-5-enoic acid (120).



120

The acid **118** (0.100 g, 0.31 mmol) was diluted with CH_2Cl_2 (20 ml) and degassed for fifteen minutes. Alcohol **108** (0.125 g, 0.61 mmol freshly distilled) was then added to the reaction flask followed by 2nd generation Grubb's catalyst (26 mg, 0.03 mmol). The reaction was allowed to reflux for 2 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. Silica gel column chromatography of the crude product using pet ether/EtOAc (3:2) as eluent provided the olefin **120** as a light yellow color syrupy liquid.

Yield: 0.83 g, 54%.

Mol. Formula: $C_{28}H_{38}O_8$

$[\alpha]_D^{25}$: –23.05 (*c* 1.40, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 3442, 3038, 2983, 2931, 1720, 1655, 1478, 1362, 1216, 1149, 1084, 956.

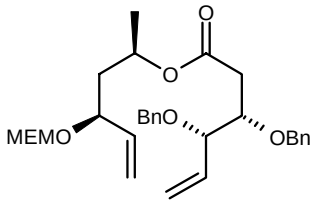
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.26-7.32 (m, 10H), 5.72 (dd, *J* = 16.2, 7.1 Hz, 1H), 5.63 (dd, *J* = 16.2, 7.1 Hz, 1H), 4.86 (s, 2H), 4.67-4.74 (m, 2H), 4.57-4.63 (m, 2H), 3.73-3.95

(m, 1H), 3.60-3.70 (m, 1H), 3.47-3.55 (m, 2H), 3.30-3.39 (m, 4H), 3.25 (s, 3H), 2.46-2.68 (m, 2H), 1.65-1.80 (m, 2H), 1.18 (d, J = 6.6 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 177.4, 138.5, 132.2, 129.5, 128.3, 127.9, 127.5, 92.8, 82.1, 74.0, 73.3, 72.5, 71.7, 70.7, 66.2, 62.3, 59.5, 47.0, 36.7, 23.8.

Analysis Calcd.: C, 66.91; H, 7.62%; **Found** C, 66.97; H, 7.64%.

4-((2-Methoxyethoxy)methoxy)hex-5-en-2-yl 3,4-bis(benzyloxy)hex-5-enoate (122).



122

To a solution of acid **118** (500 mg, 1.53 mmol) in THF, was added triethyl amine (0.32 mL, 2.30 mmol) and 2, 4, 6-trichlorobenzoyl chloride (0.36 mL, 2.30 mmol) under nitrogen atmosphere at 0 ^{o}C and the reaction mixture was allowed to stir under this condition for 1 h. To this, alcohol **108** (0.31 g, 1.53 mmol) in THF (5 mL) and catalytic amount of 4-dimethyl aminopyridine (DMAP) were added successively at 0 ^{o}C. Stirring was continued for additional 20 h at rt. The reaction mixture was quenched with water and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were thoroughly washed with saturated sodium bicarbonate solution, brine, dried (Na_2SO_4), and concentrated to afford the crude product which was purified by silica gel column chromatography using ethyl acetate: light petroleum (1:9) to afford the ester **122** as a colorless syrupy liquid.

Yield: 0.70 g, 89%

Mol. Formula: $C_{30}H_{40}O_7$

$[\alpha]_D^{25}$: –41.42 (c 0.8, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3052, 2961, 2921, 1751, 1655, 1478, 1373, 1216, 1144, 1097, 952, 874, 758.

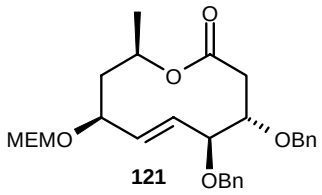
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.24-7.29 (m, 10H), 5.76 (ddd, J = 17.3, 10.0, 7.1 Hz, 1H), 5.63 (dddd, J = 17.7, 10.0, 7.6, 5.5 Hz, 1H), 5.35-5.12 (m, 4H), 4.90 (s, 2H), 4.74-4.69 (m, 1H), 4.68-4.63 (m, 1H), 4.60-4.54 (m, 2H), 4.09-4.0 (m, 2H), 3.95-3.89 (m, 2H), 3.71-3.64

(m, 2H), 3.51-3.44 (m, 2H), 3.3 (s, 3H), 2.67-2.47 (m, 2H), 1.95-1.70 (m, 2H), 1.19 (d, J = 6.3 Hz, 3H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 171.2, 138.5, 138.2, 137.8, 134.6, 129.5, 128.2, 127.5, 119.2, 117.5, 92.8, 81.2, 74.0, 73.3, 72.5, 71.7, 68.1, 67.1, 58.9, 41.9, 36.7, 20.5.

Analysis Calcd.: C, 70.29; H, 7.86%; **Found** C, 70.21; H, 7.88%.

(*E*)-4,5-Bis(benzyloxy)-8-((2-methoxyethoxy)methoxy)-10-methyl-4,5,9,10-tetrahydro-3H-oxecin-2(8H)-one (121).



121

(i) Through Yamaguchi macrolactonization: To a solution of seco acid **120** (0.150 g, 0.30 mmol) in THF (4 mL) were added Et_3N (0.10 mL, 0.75 mmol) and 2,4,6-trichlorobenzoyl chloride (0.182 g, 0.75 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 dropwise to a solution of DMAP (0.273 g, 2.24 mmol) in benzene (20 mL) at 80 ^oC over 1 h and the mixture was stirred for additional 1 h under reflux. The reaction mixture was washed with aq. citric acid solution and brine. The organic layer was dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using pet ether/EtOAc (3:2) as eluent provided the lactone **121** as a light yellow color syrupy liquid.

Yield: 0.046 g, 32 %.

(ii) Through RCM: A mixture of diene **122** (0.2 g, 0.39 mmol) and Grubbs'2nd generation catalyst (0.065 g, 0.0078 mmol) in degassed CH_2Cl_2 (50 mL) was stirred under reflux for 14 h. The reaction mixture was evaporated and then purified on silica gel by eluting with light petroleum: EtOAc (4:1) to afford **121** as a thick syrupy liquid.

Yield: 0.16 g, 82 %.

Mol. Formula: $C_{28}H_{36}O_7$

$[\alpha]_D^{25}$: –7.8 (c 0.43, $CHCl_3$)

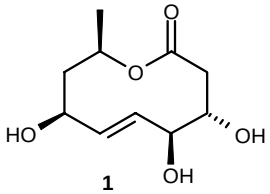
IR ($CHCl_3$, cm^{-1}): ν_{max} 3416, 2952, 2931, 1728, 1362, 1236, 1046, 948, 869.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29-7.36 (m, 10H), 5.72 (dd, *J* = 15.8, 6.3 Hz, 1H), 5.67 (dd, *J* = 15.8, 2.1 Hz, 1H), 5.19-5.14 (m, 1H), 4.81 (s, 2H), 4.65 (d, *J* = 12.5 Hz, 1H), 4.54 (d, *J* = 11.9 Hz, 1H), 4.48 (d, *J* = 12.5 Hz, 1H), 4.47 (d, *J* = 11.9 Hz, 1H), 3.92-3.86 (m, 2H), 3.76-3.73 (m, 2 H), 3.72-3.69 (m, 2 H), 3.57-3.55 (m, 1H), 3.40 (s, 3H), 2.64 (dd, *J* = 15.2, 9.2 Hz, 2H), 1.81-1.55 (m, 2H), 1.19 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 178.5, 139.5, 132.8, 129.5, 128.3, 127.9, 127.5, 92.8, 81.1, 76.4, 74.1, 73.3, 70.7, 68.1, 60.1, 53.5, 47.4, 42.2, 29.6, 23.7.

Analysis Calcd.: C, 69.38; H, 7.49%; **Found** C, 69.27; H, 7.53%.

Decarestrictine D (1).



1

To a solution of **121** (0.150 g, 0.31 mmol) in anhydrous CH_2Cl_2 (5 mL) under nitrogen at 0 ^oC was added $TiCl_4$ (0.587 g, 0.34 mL, 3.1 mmol). After 30 min, excess of reagent was quenched with water, extracted with CH_2Cl_2, washed with water, dried (Na_2SO_4), evaporated. The reaction mixture was purified on silica gel by eluting with EtOAc to afford decarestrictine D **1** as a light yellow color solid.

Yield: 52 mg, 78%

Mol. Formula: $C_{10}H_{16}O_5$

$[\alpha]_D^{25}$: –63.7 (*c* 0.46, $CHCl_3$)

m.p. 116-118 ^oC; (lit.[81] mp 114-115 ^oC)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3422, 2952, 2926, 2845, 1712, 1146, 1042, 969.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.92 (dd, *J* = 15.9, 7.6 Hz, 1H), 5.85 (dd, *J* = 15.9, 2.7 Hz, 1H), 5.18-5.14 (m, 1H), 4.77 (brs, 1H), 4.43 (dd, *J* = 3.7, 1.6 Hz, 1H), 4.21 (m, 1H), 3.91 (brs, 1H), 2.63 (dd, *J* = 14.4, 1.9 Hz, 1H) 2.42 (dd, *J* = 14.4, 6.4 Hz, 1H), 1.94-1.84 (m, 2H), 1.55 (brs, 2H), 1.23 (d, J = 6.6 Hz, 3H).

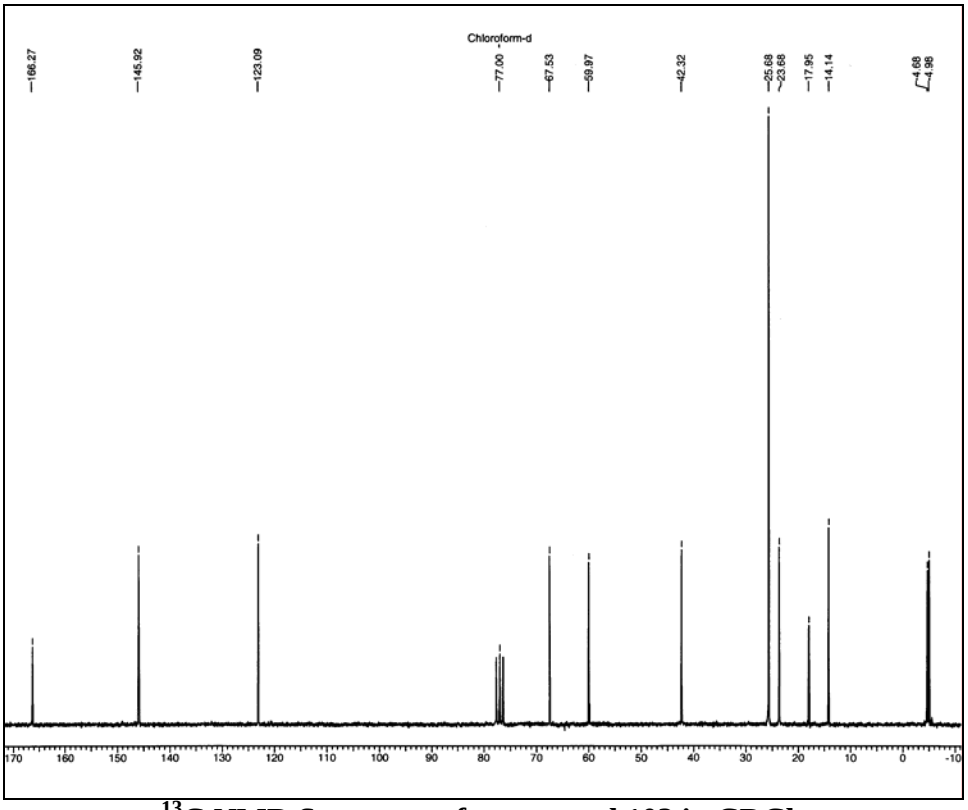
^{13}C NMR (75 MHz, $CDCl_3$): δ 174.9, 133.7, 129.7, 73.9, 72.5, 72.2, 66.3, 43.1, 33.2, 21.3.

Analysis Calcd.: C, 55.55; H, 7.46%; **Found:** C, 55.41; H, 7.50%.

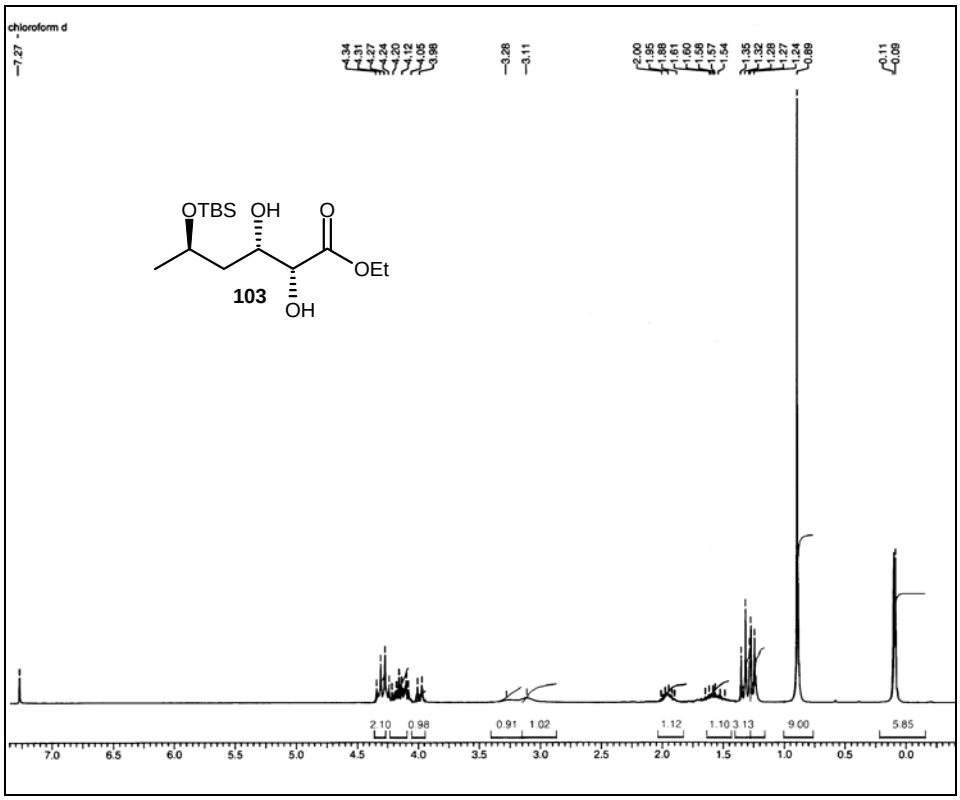
5.1.7 Spectra

1. ^{1}H and ^{13}C NMR spectra of 102
2. ^{1}H and ^{13}C NMR spectra of 103
3. ^{1}H and ^{13}C NMR spectra of 105
4. ^{1}H and ^{13}C NMR spectra of 106
5. ^{1}H and ^{13}C NMR spectra of 107
6. ^{1}H and ^{13}C NMR spectra of 108
7. ^{1}H and ^{13}C NMR spectra of 113
8. ^{1}H and ^{13}C NMR spectra of 114
9. ^{1}H and ^{13}C NMR spectra of 115
10. ^{1}H and ^{13}C NMR spectra of 118
11. ^{1}H and ^{13}C NMR spectra of 120
12. ^{1}H and ^{13}C NMR spectra of 121
13. ^{1}H and ^{13}C NMR spectra of 122
14. ^{1}H and ^{13}C NMR spectra of 1

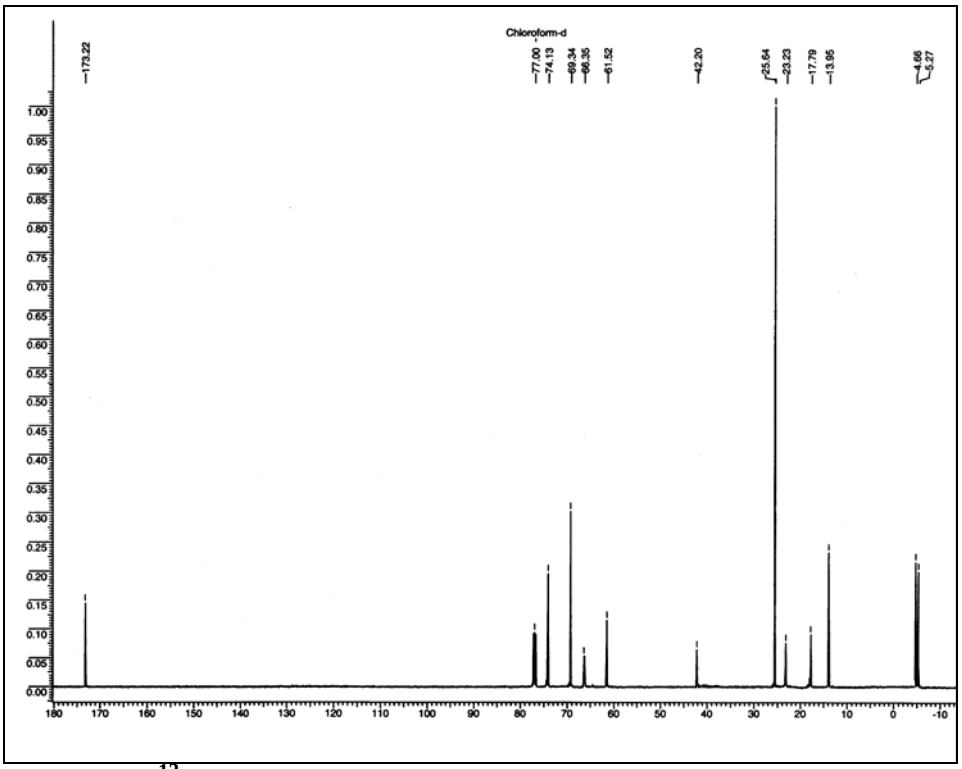
^{1}H NMR Spectrum of compound 102 in $CDCl_3$



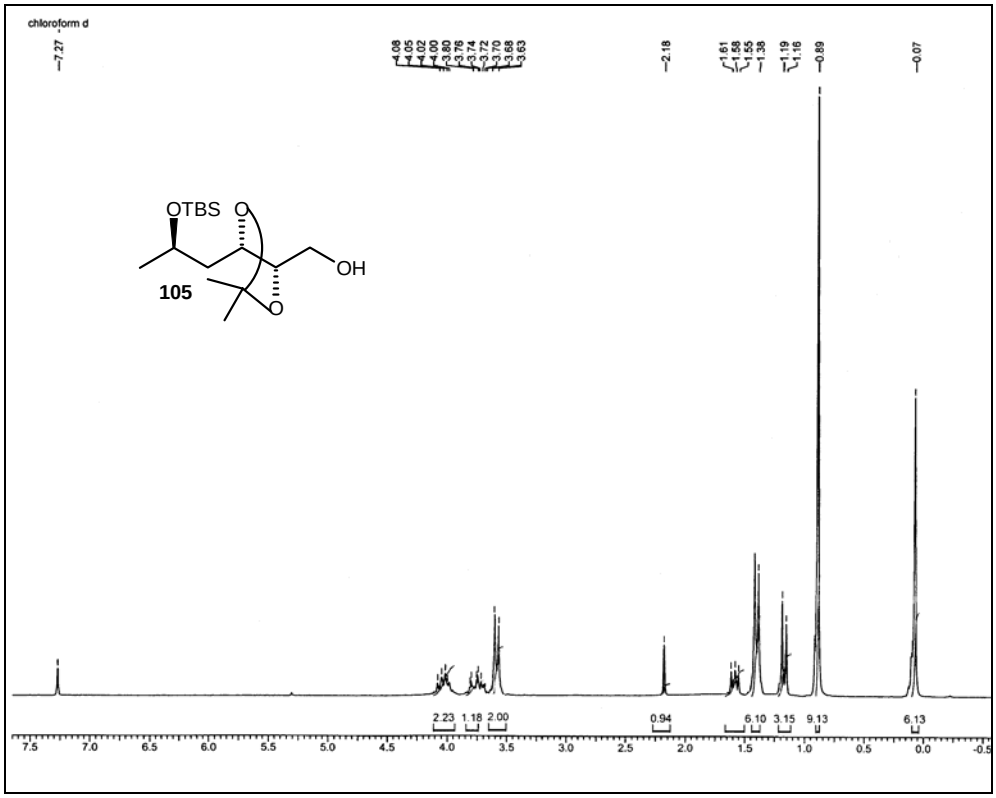
^{13}C NMR Spectrum of compound 102 in $CDCl_3$



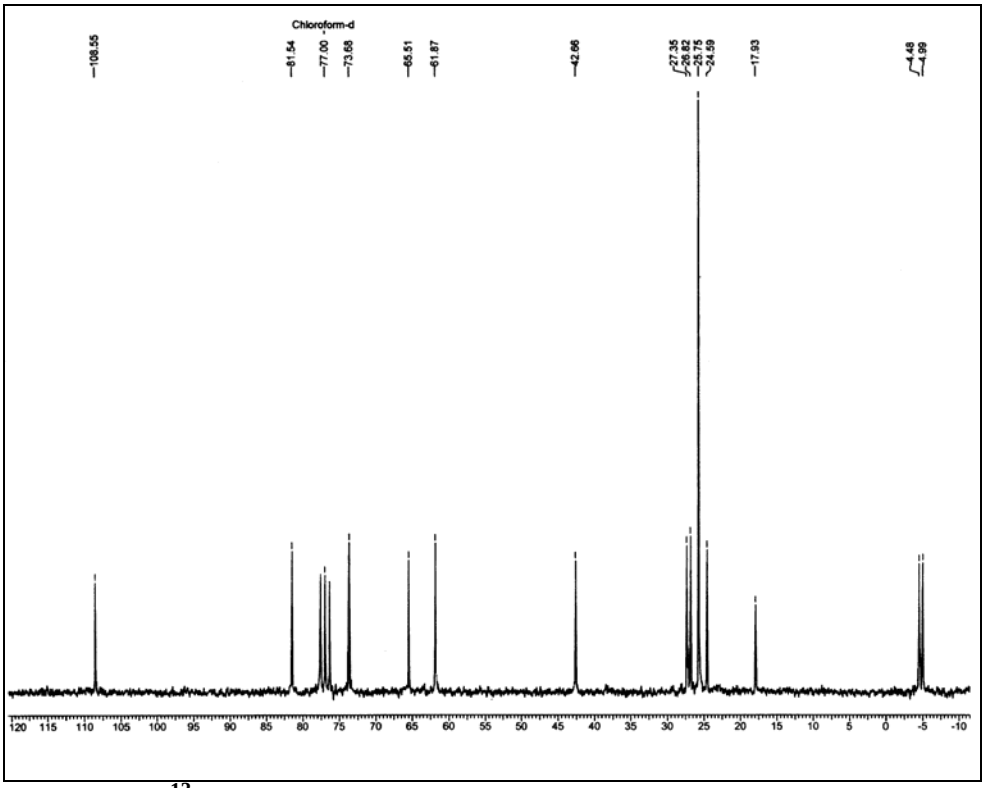
^{1}H NMR Spectrum of compound 103 in $CDCl_3$



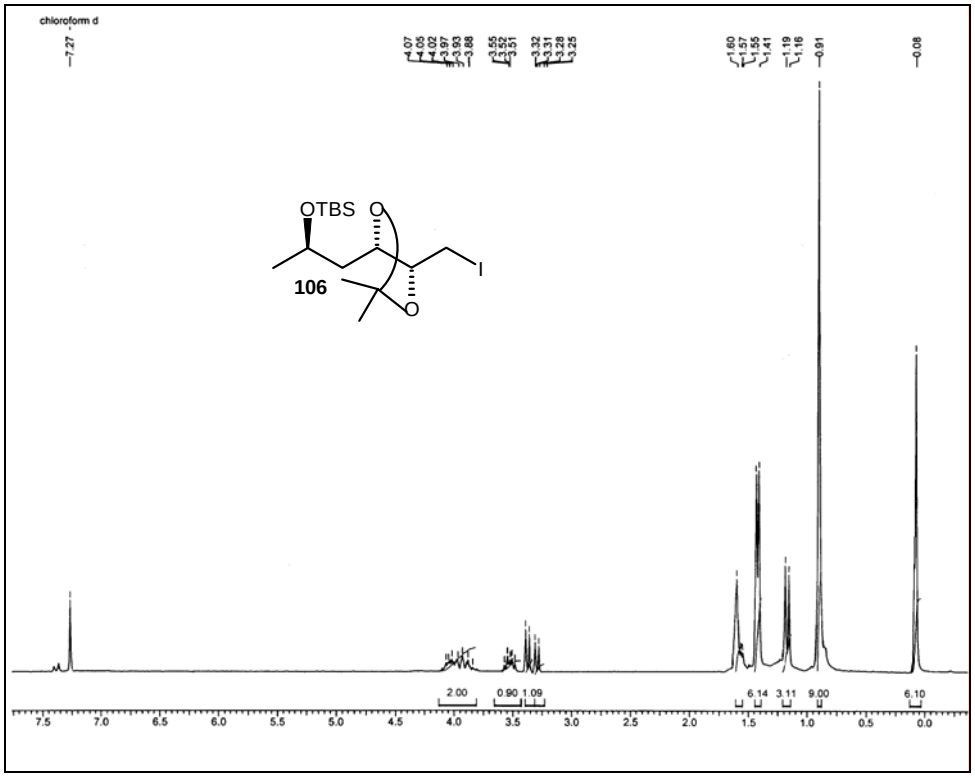
^{13}C NMR Spectrum of compound 103 in $CDCl_3$



^{1}H NMR Spectrum of compound 105 in $CDCl_3$



^{13}C NMR Spectrum of compound 105 in $CDCl_3$



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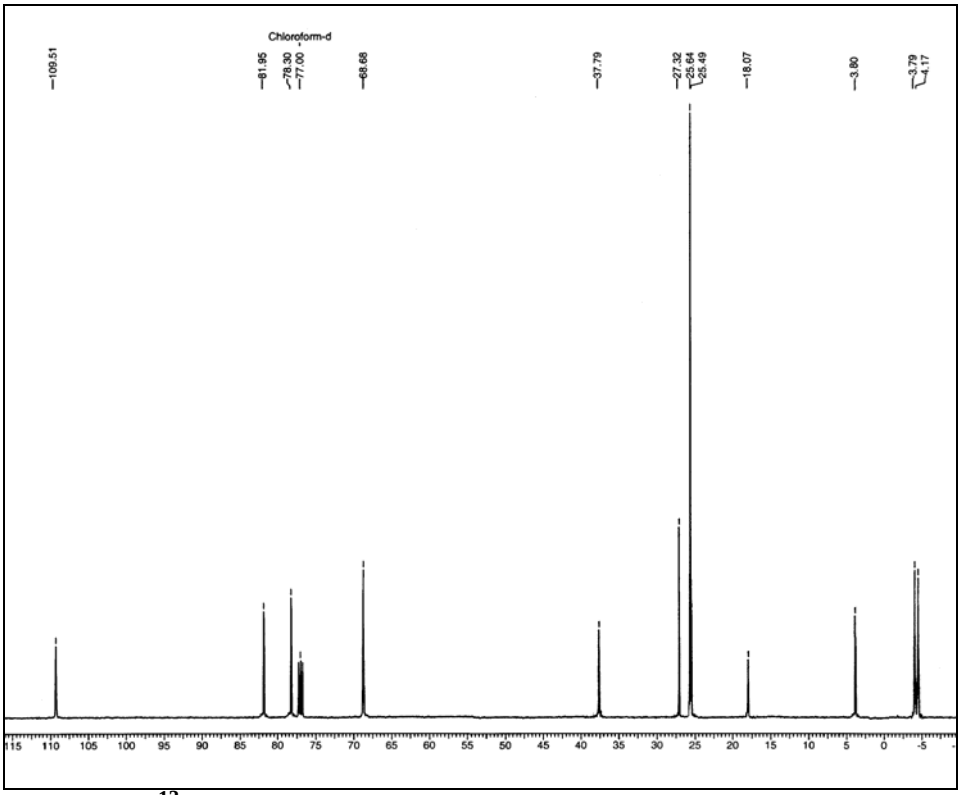
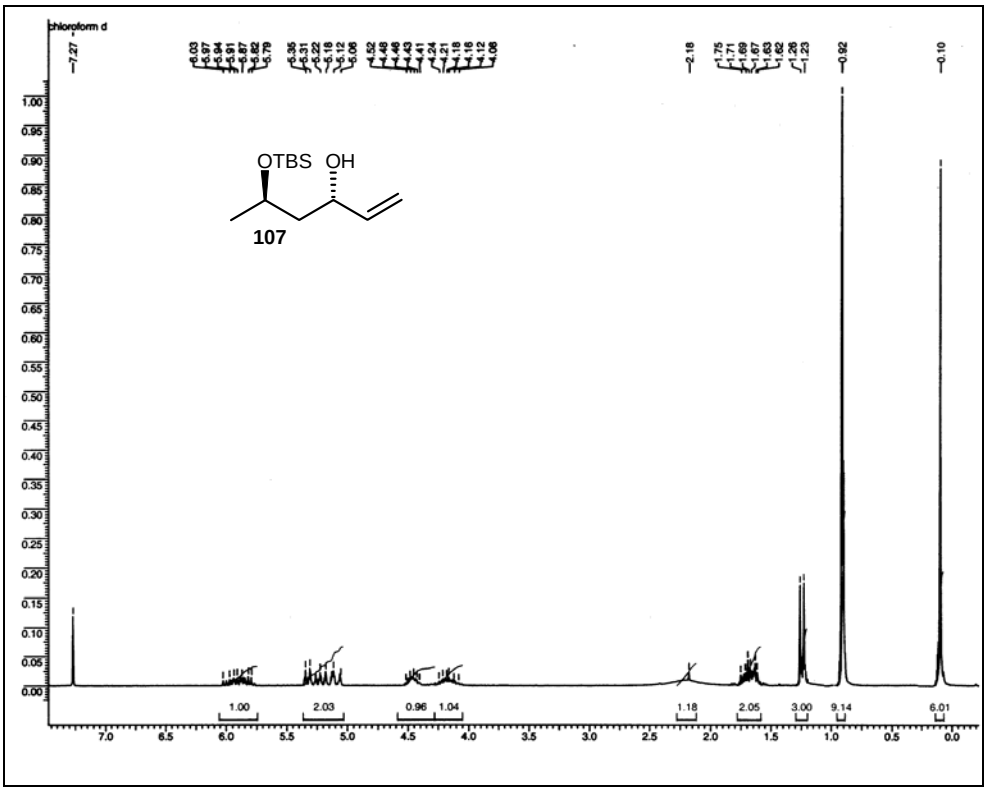


^{13}C NMR Spectrum of compound 106 in $CDCl_3$



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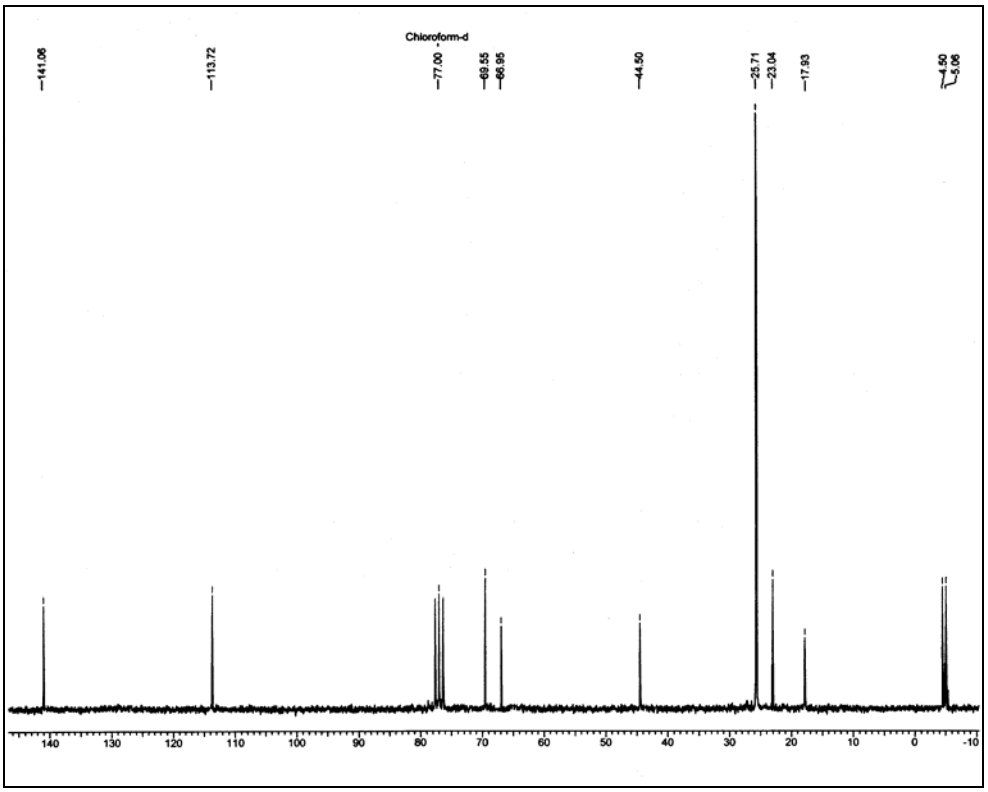

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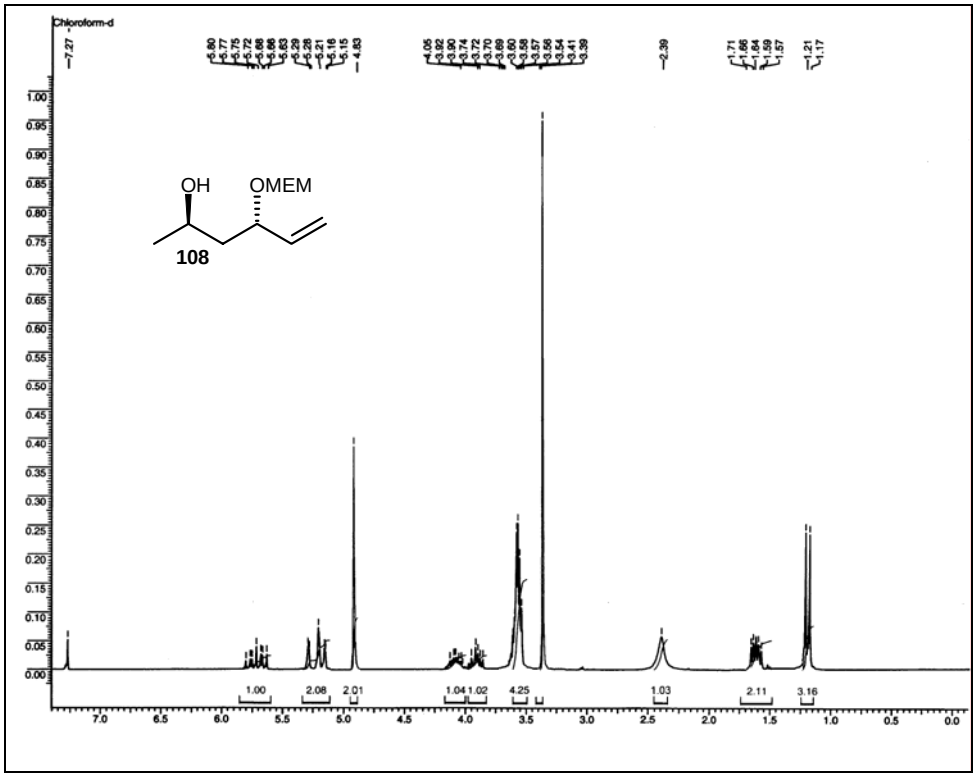

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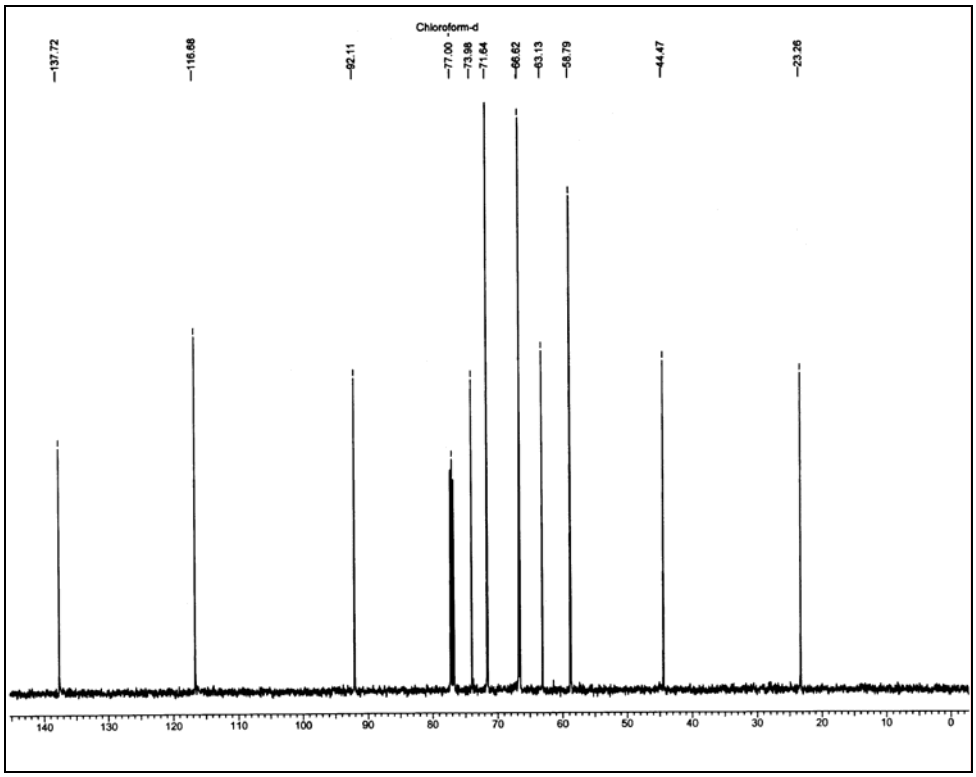
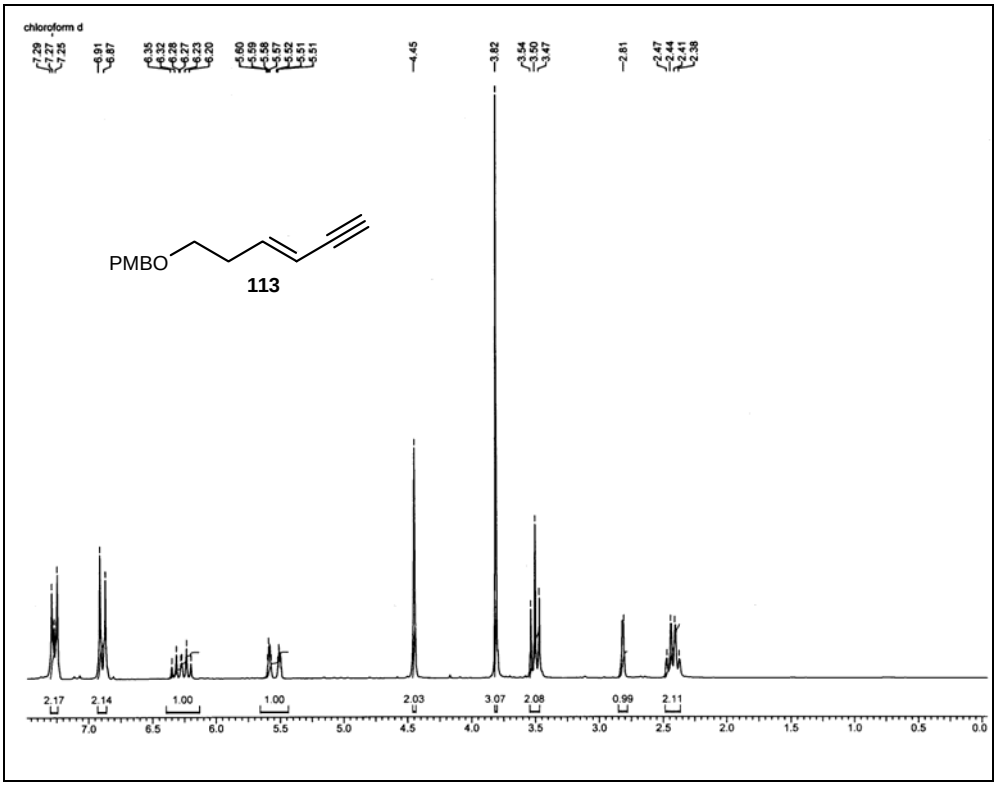


^{13}C NMR Spectrum of compound 108 in $CDCl_3$



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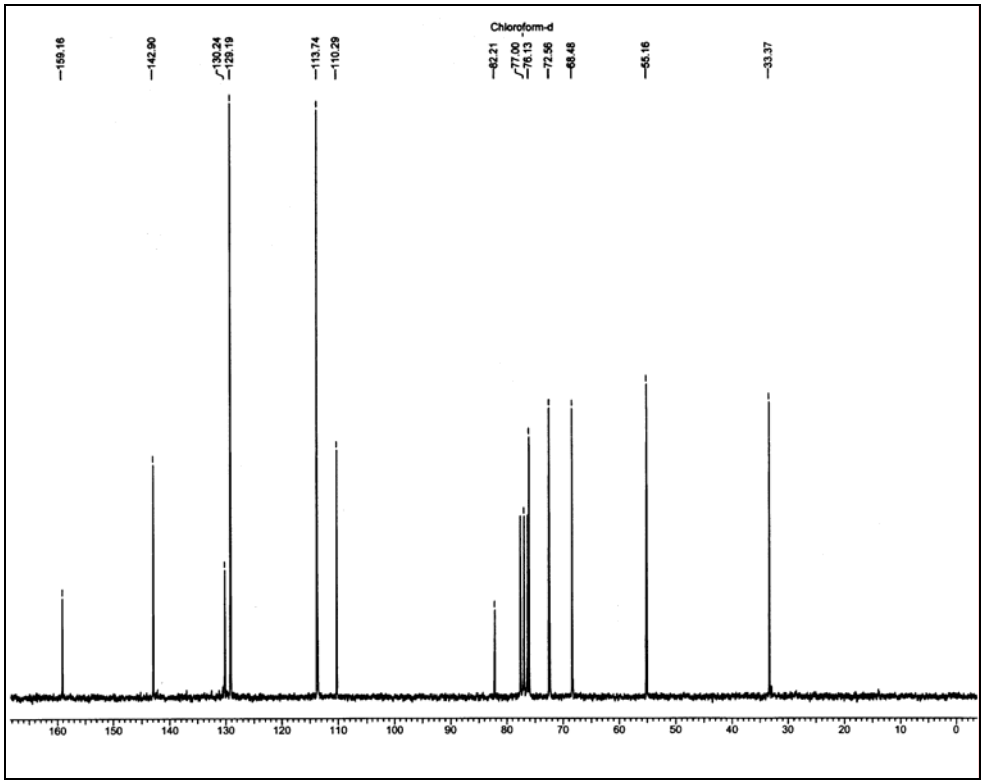

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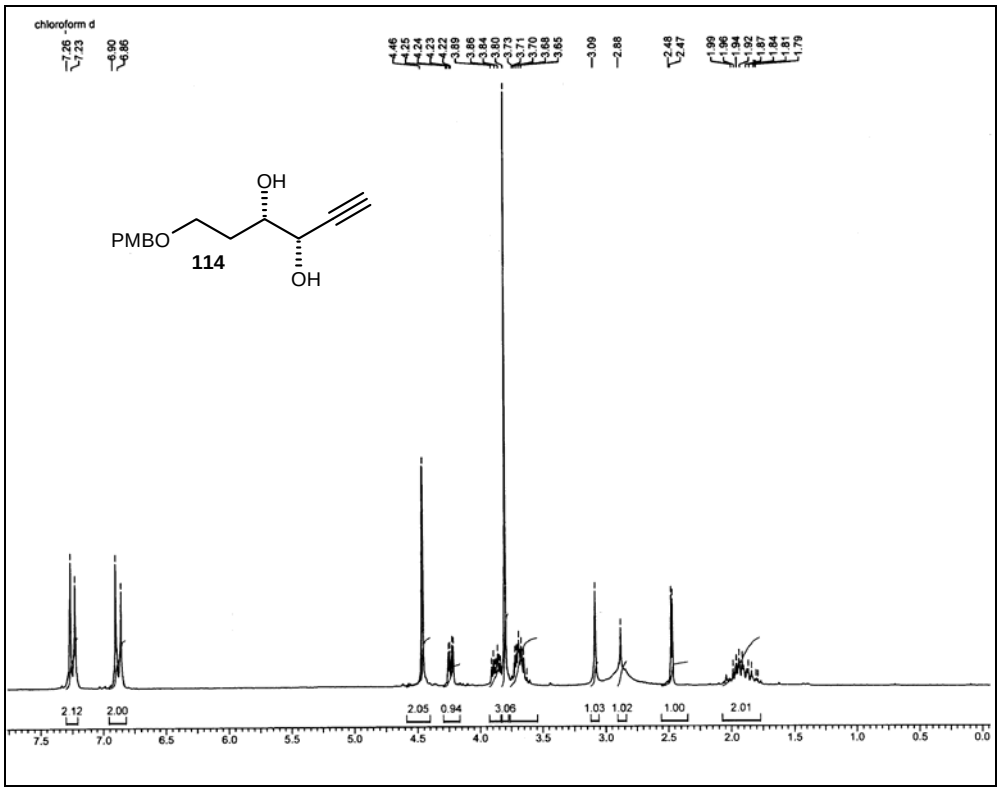

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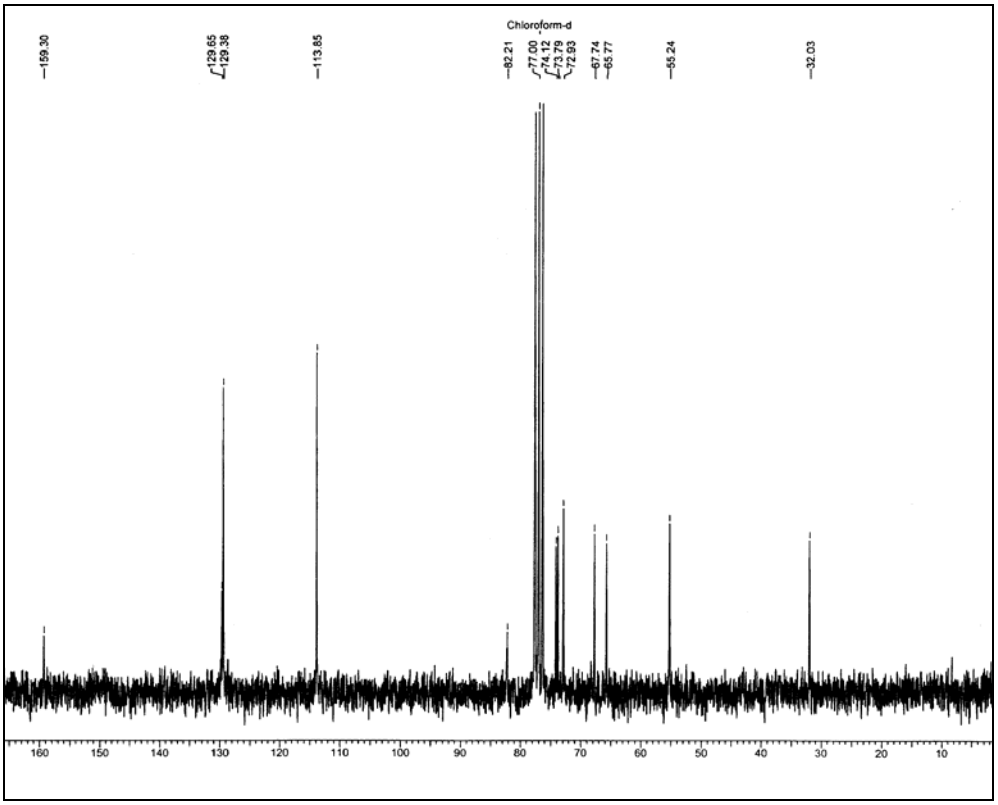
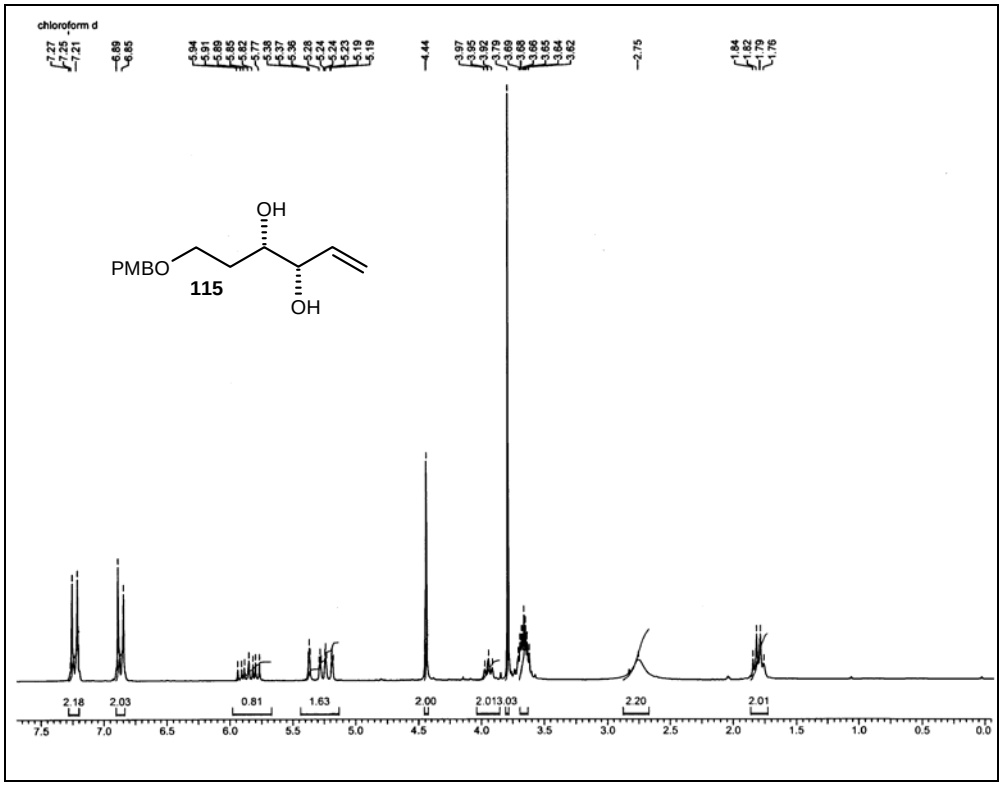
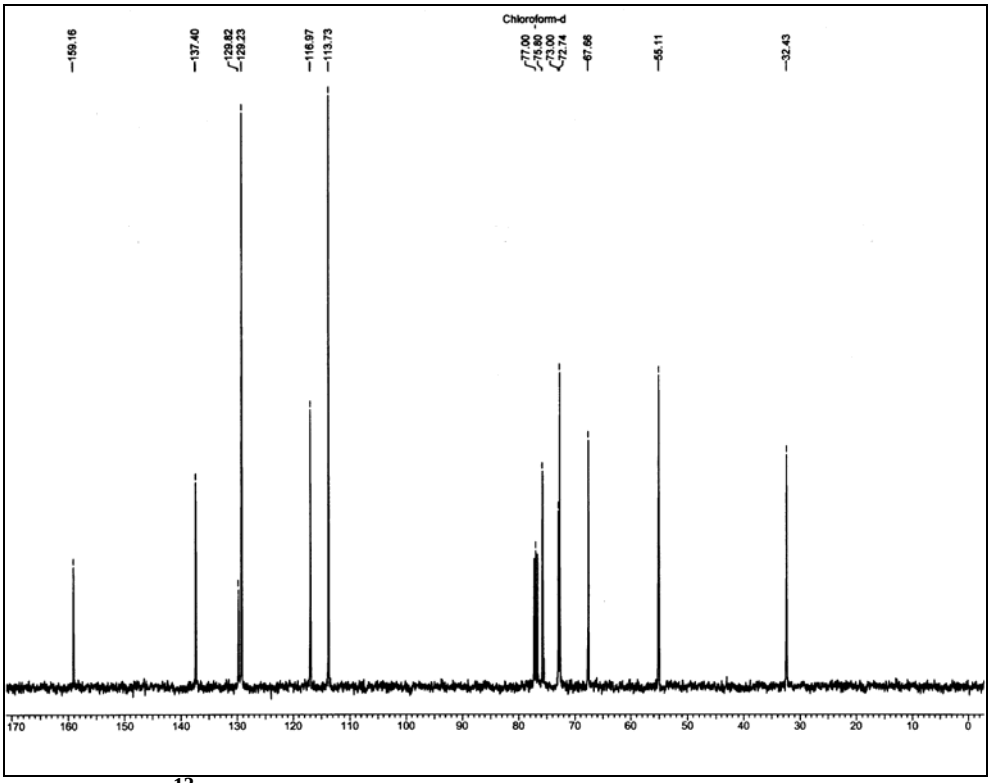


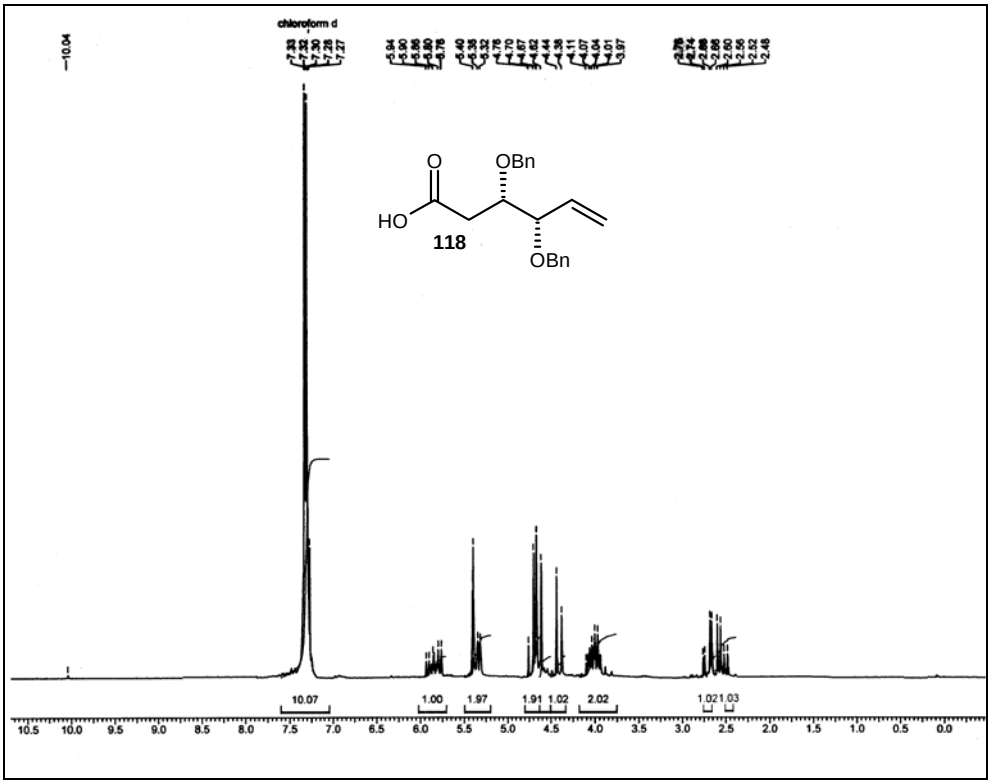
^{13}C NMR Spectrum of compound 114 in $CDCl_3$



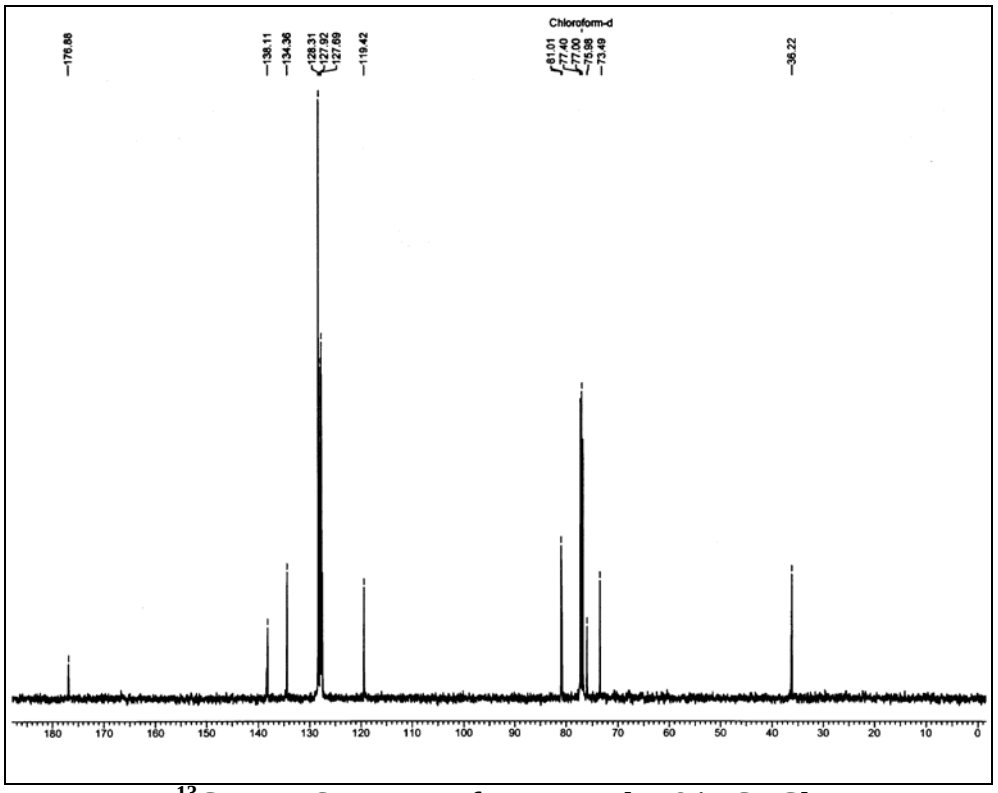
^{1}H NMR Spectrum of compound 115 in $CDCl_3$



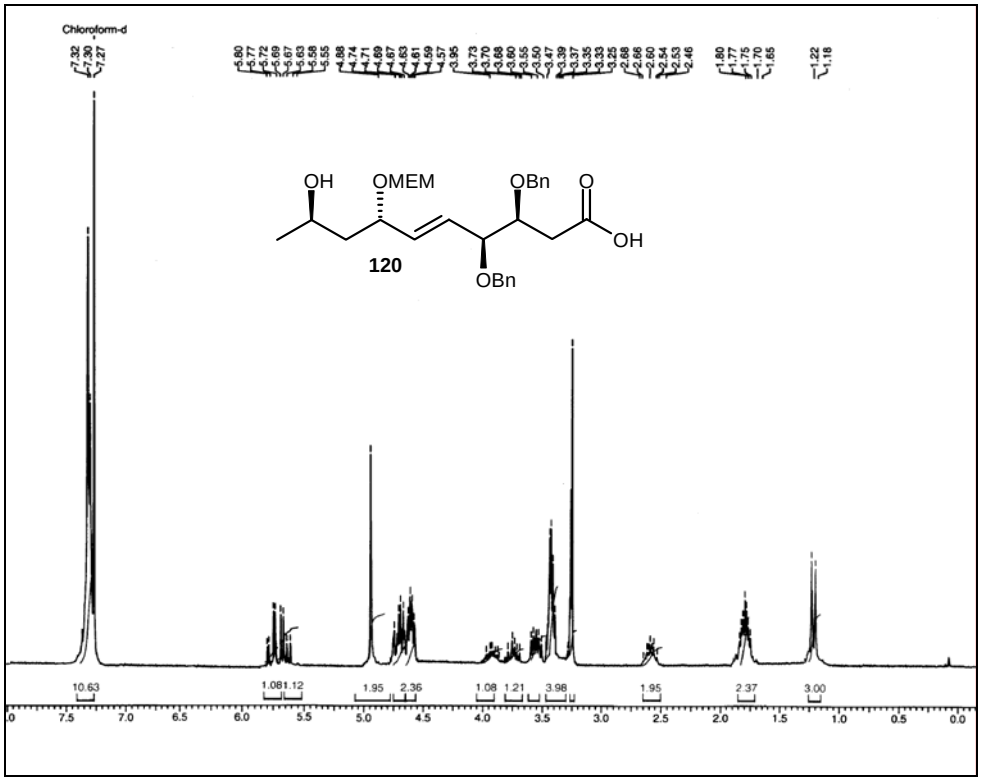
^{13}C NMR Spectrum of compound 115 in $CDCl_3$



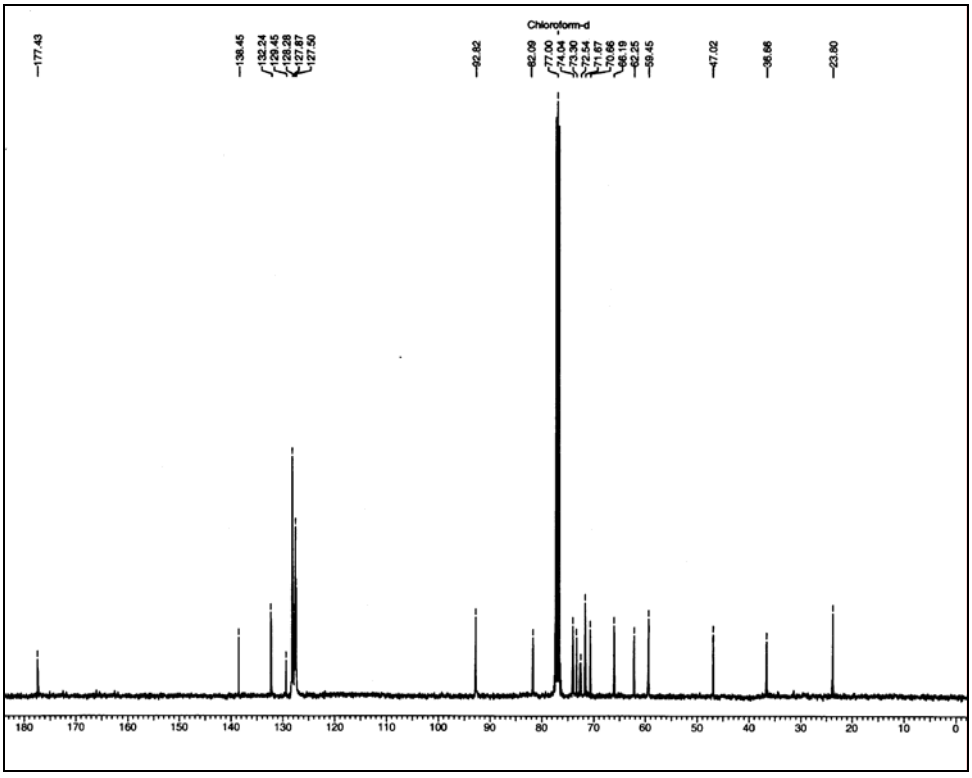
^{1}H NMR Spectrum of compound 118 in $CDCl_3$



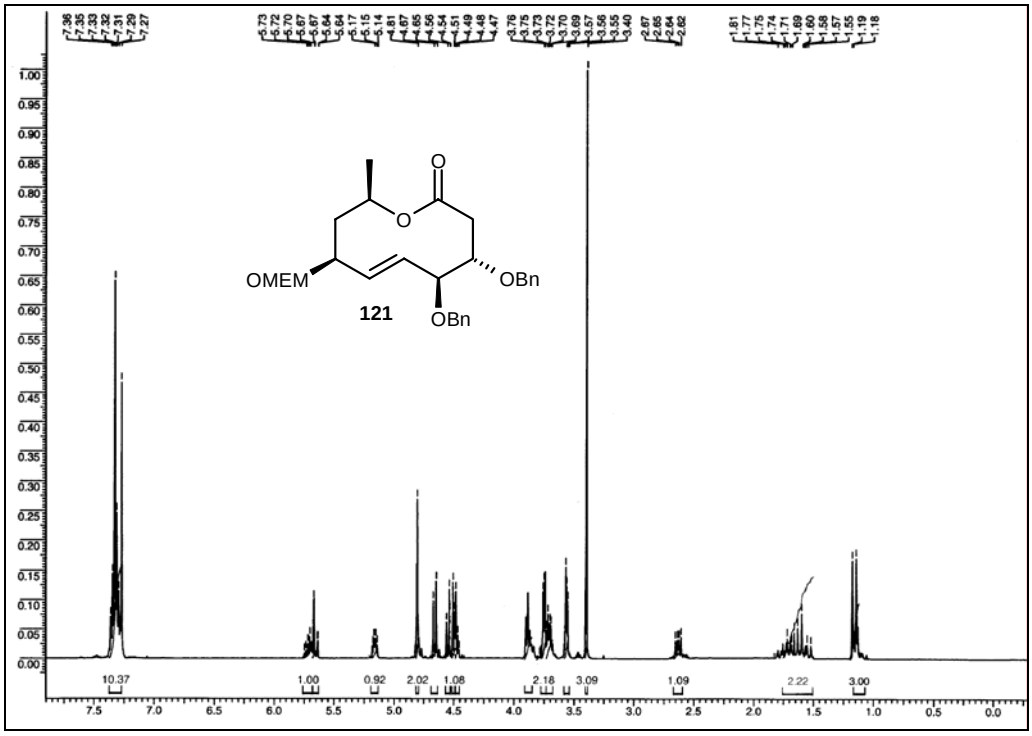
^{13}C NMR Spectrum of compound 118 in $CDCl_3$



^{1}H NMR Spectrum of compound 120 in $CDCl_3$



^{13}C NMR Spectrum of compound 120 in $CDCl_3$



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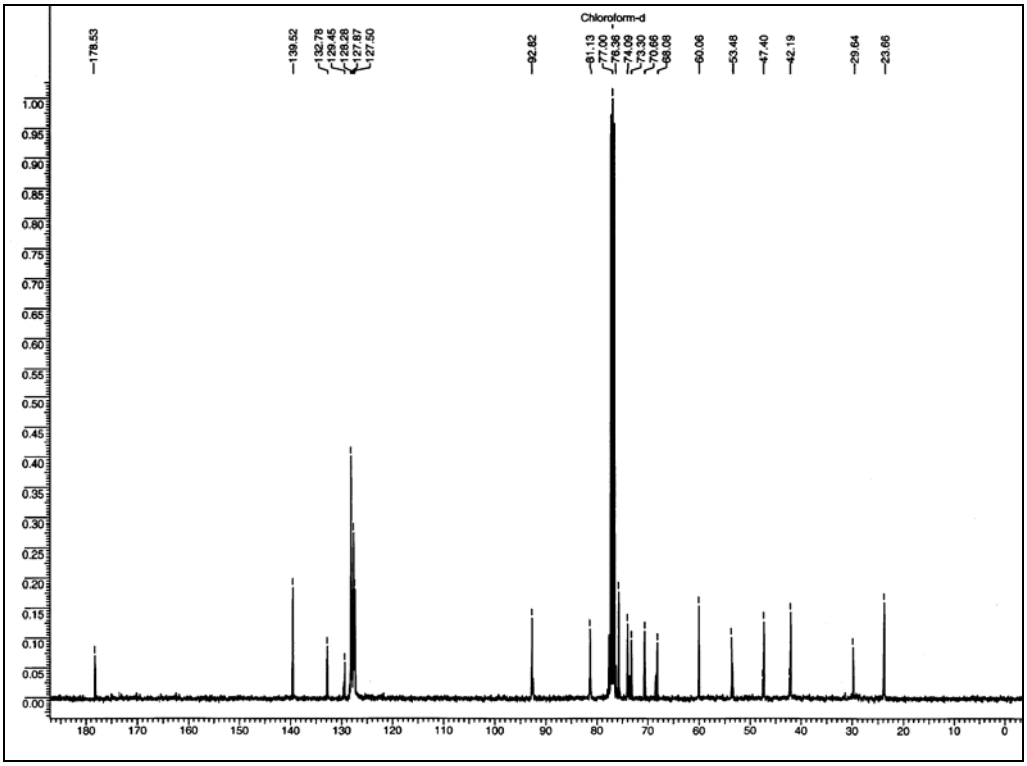

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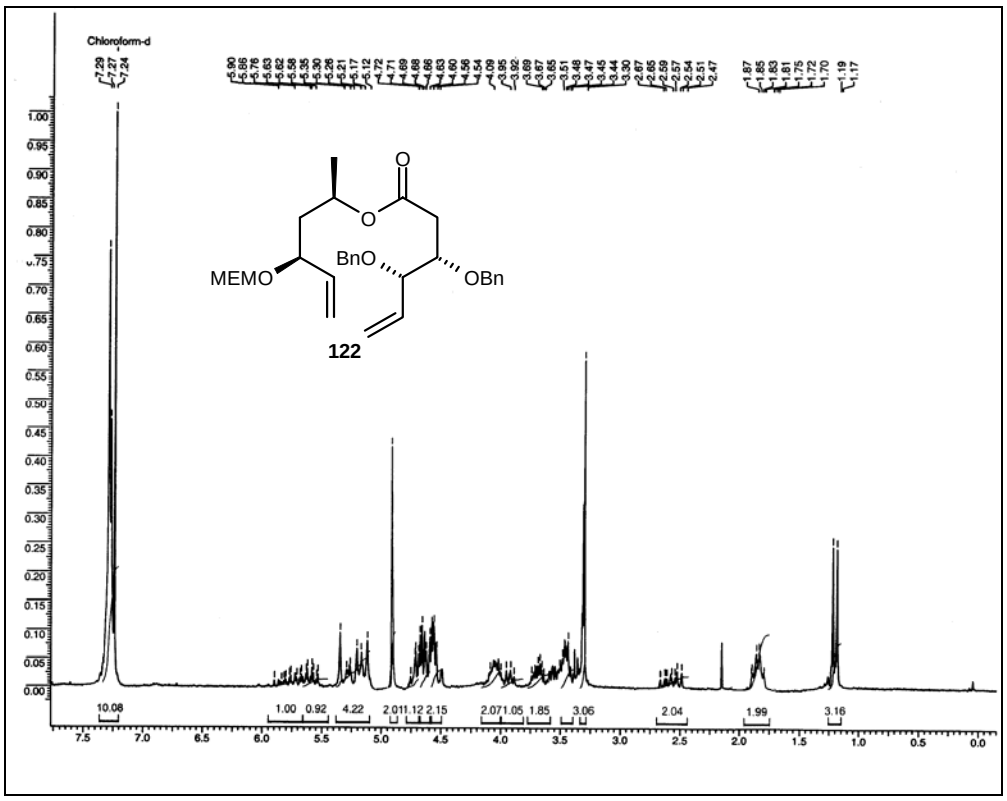
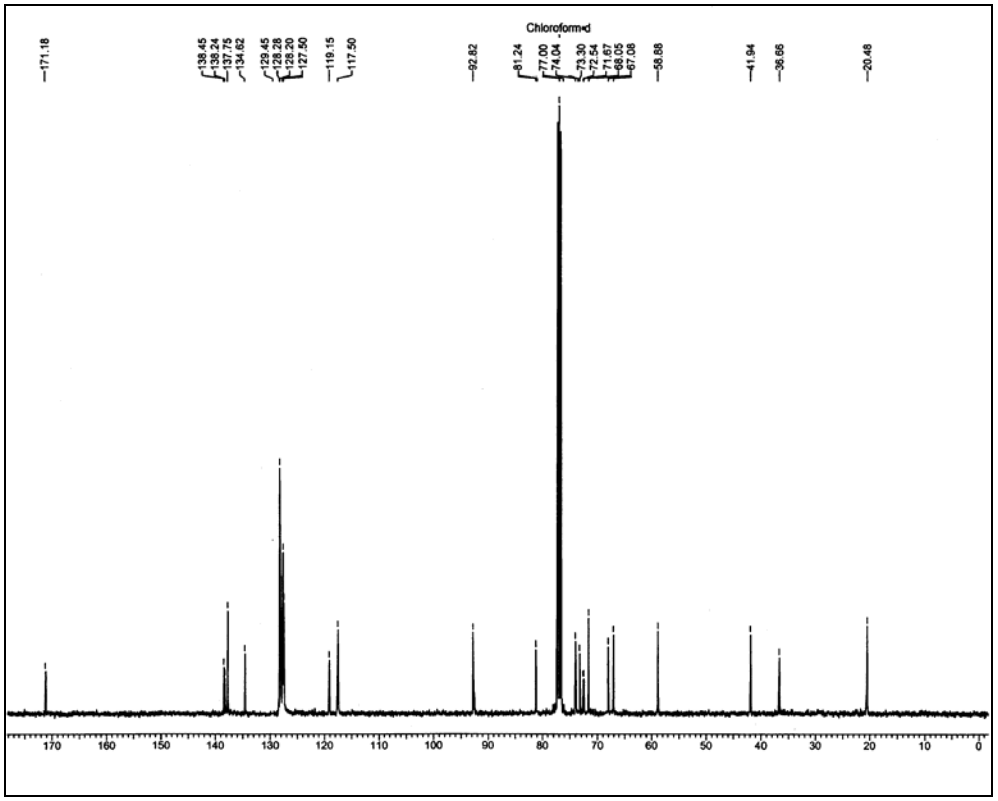
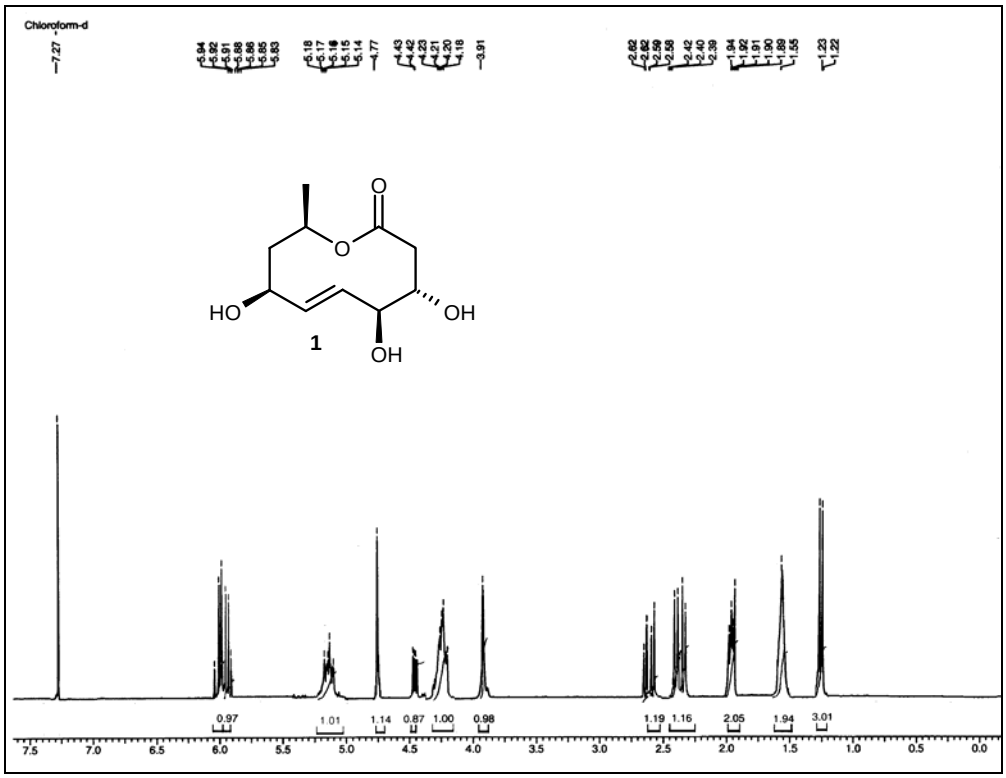


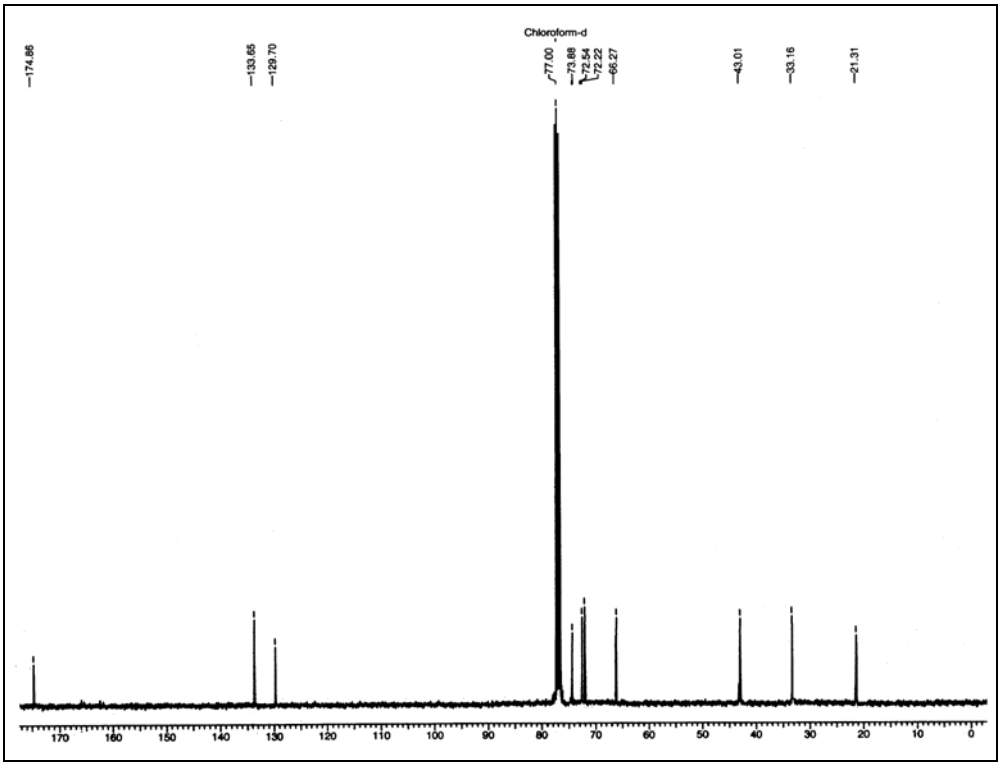
^{1}H NMR Spectrum of compound 122 in $CDCl_3$



^{13}C NMR Spectrum of compound 122 in $CDCl_3$



^{1}H NMR Spectrum of compound 1 in $CDCl_3$



^{13}C NMR Spectrum of compound 1 in $CDCl_3$

5.2 SECTION B

AN ASYMMETRIC TOTAL SYNTHESIS OF HERBARUMIN III

5.2.1. Introduction

Weeds, diseases, and infestations by insects have always been major threats in the agricultural production of food, feed, and fiber, often giving rise to life-threatening periods of famine or causing serious food poisoning in vast parts of the world population. Protecting crops against these weeds by chemical means dates back probably more than 4000 years and parallels the general development of agricultural practice. Extracts of plants containing chemicals of potential herbicidal activity have been used to different degrees over the years and often not in a systematic way. The first modern organic herbicides were introduced in the early 1943. The use of DDT[41] as an insecticide, the plant hormone-based phenoxy-acetic acid derivatives as herbicides,[42] organophosphates,[43] and some time later the carbamates as insecticides[44] and thiram as a fungicide[45] appeared in the market in the quantum progress.

Weeds are plants that are competitive, persistent, pernicious, and interfere negatively with the production and quality of crops and in certain situation with human activity. These are troublesome in many ways primarily; they reduce the crop yield by competing for water, light, soil nutrients, space and carbon dioxide. Besides the agriculture field and roadside blockage, weeds are widespread through wetland habitats causing displacement of native plants, which are important for source of food and shelter for wildlife. Ecological process, such as oxygen production, may also change because invasive plants affect water chemistry and flow. Unrestricted invasion can block drainage pipe, impede navigation and hinder commercial and recreational fishing.

Since weeds are so prevalent in wide area of agricultural field, forest and wetland, and causing the damage of human resources, appropriate management techniques are required. The common methods to stop weeds include prevention, culture mechanical, biological and chemical means. Of these, chemically weed control is well-established technology to support sustainable production of crop and play a valuable role in agribusiness. The

chemicals used effectively to kill weedy plant or interrupt the plant normal growth are commonly known as herbicides. They provide a convenient, economical and efficient way to manage the crop production by selective destruction of noxious harmful plants.

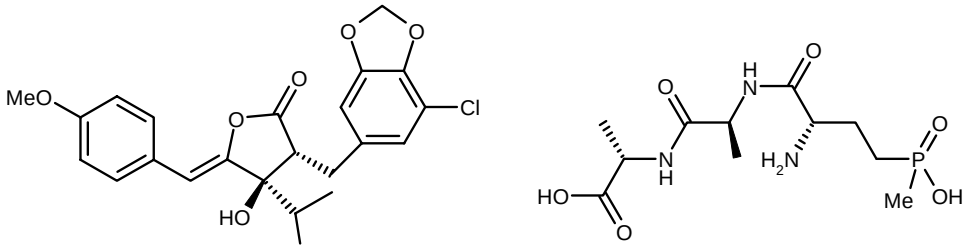
Although a plethora of synthetic organic herbicides[46] are well established in the marketplace for long time to control different species of weeds, a number of serious disadvantages are associated with these. Conventional herbicides contain chemicals that contribute to a variety of adverse effects. These toxic chemicals are carcinogens that have been linked to health problems such as lymphoma, genetic damage, reproductive effects and heart-related issues. Chemical compounds are breathed in during or after spraying and can also be absorbed through the skin as a result of direct contact. Access must be restricted to areas treated with chemical herbicides. Furthermore, toxic chemicals from herbicides may seep into groundwater as a result of rain, runoff, watering the area or soil absorption. These herbicides also kill beneficial soil microbes; thus disrupting the normal condition of the soil.

So, considering the aforesaid limitations of synthetic organic chemicals as herbicides, alternative approaches are gaining increased platform to control weed in environmentally safe way. Plants produce hundreds of thousands of compounds that are not involved in the primary metabolism of the plants; the compounds involved in interspecific chemical interaction called allelopathy[47] with higher plants are often phytotoxic or herbicidal to other species or even to the species producing them. The importance of allelopathy in nature and in agroecosystem has attracted researcher's attention with the main goal of using the phenomenon in biological control of weeds. Currently, active involvement of scientist from different disciplines made allelopathy a multidisciplinary subject and transformed the research from basic to applied, enabling use of allelopathy in agriculture and forestry.

There are various examples of alleochemicals; these phytotoxic compounds released from plant are used as natural source of herbicides. Phytotoxic compounds from plants and microorganisms represent a wide range of chemistries and mechanism of action that have potential in the design and development of new herbicides. Some of light-activated compounds (photosensitizers)-naphtho and anthraquinones produced by fungi and higher

plants, quinine and isoquinoline alkaloids are potentially useful for herbicides. Terpenoids, monoterpenes, sesquiterpenes lactones and triterpenes and fatty acids also show promising herbicidal activity.

Cyanobacterin **123**[48] produced by the filamentous, freshwater cyanobacterium Scytonema hofmanni inhibits photosynthesis and causes extensive damage to the thylakoid membranes of the chloroplasts. With a spectrum of activity encompassing species of cyanobacteria and eukaryotic algae as well as higher plants, cyanobacterin might be utilized as a commercial algicide. Bilanafos **124**[49], a tripeptide from Streptomyces hygroscopicus (Figure 3), which degrades to phosphinothricin in target plants, is the only commercial herbicide produced by biosynthesis.



Cyanobacterin **123** Bilanafos **124**

Figure 3

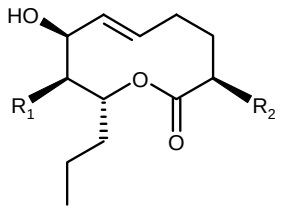
Similarly, rhizobitoxine,[50] a compound produced by the bacterium *Rhizobium japonicum* is an effective herbicide in amounts as low as 3 ounces/acre. Cinmethylin,[51] a potential herbicide is a product based on 1,8-cineole produced by *Salvia* species (sage).

Like insects, weeds can develop resistance when continually selected by a single herbicide or group of herbicides having the same mechanism of toxic action. Weeds develop resistance in one of the two ways. Firstly, a few individuals in a population may possess a gene that enhances metabolic detoxification reactions, thereby breaking down the herbicides fast enough to avoid its phytotoxicity. The second and more prevalent method is the occurrence of some individuals with a gene that alters the biochemical target site of herbicides, making the plant resistant to injury. In either case, if these infrequent individuals escape control and successfully go to seed, comparatively more of these

resistant individuals will occur in the population during the next growing cycle. Eventually, most of the population will be resistant to the herbicide.

So continuous searching and synthesis of natural products and their analogues with potent herbicidal activity, finding new mode of activity and structure activity relationship establishment are genuinely new era of research for weed management.

Recently, searching for herbicidal agent from *Phoma herbarum*, Westend led to isolation of new medium sized lactone (7*S*,9*R*)-7-hydroxy-9-propyl-5-nonen-9-olide (**127**) along with already characterized two compounds (7*S*,8*S*,9*R*)-7,8-dihydroxy-9-propyl-5-nonen-9-olide **125** and (2*R*,7*S*,8*S*,9*R*)-2,7,8-trihydroxy-9-propyl-5-nonen-9-olide **126** (Fig.4). The trivial name of newly found nonenolide was given herbarumin III (**127**) following earlier nomenclature.



R_1 = OH; R_2 = H; Herbarumin I **125**
R_1 = R_2 = OH; Herbarumin II **126**
R_1 = R_2 = H; Herbarumin III **127**

Figure 4

This ten membered lactone (**127**) exist in a chair-chair-chair conformation[52] as in the case of herbarumin I. All these nonenolides (**51**, **264**, **265**) caused relevant inhibition of radicle growth of seedlings of *Amaranthus hypochondriacus* L. when tested by the Petri dish bioassay.[53,54] Herbarumin III inhibited radicle growth with higher potency than 2,2-dichlorophenoxy acetic acid (IC_{50} = 2 X 10^{-5} M). It also interacted with bovine-brain calmodulin-dependant enzyme camp phosphodiesterase.

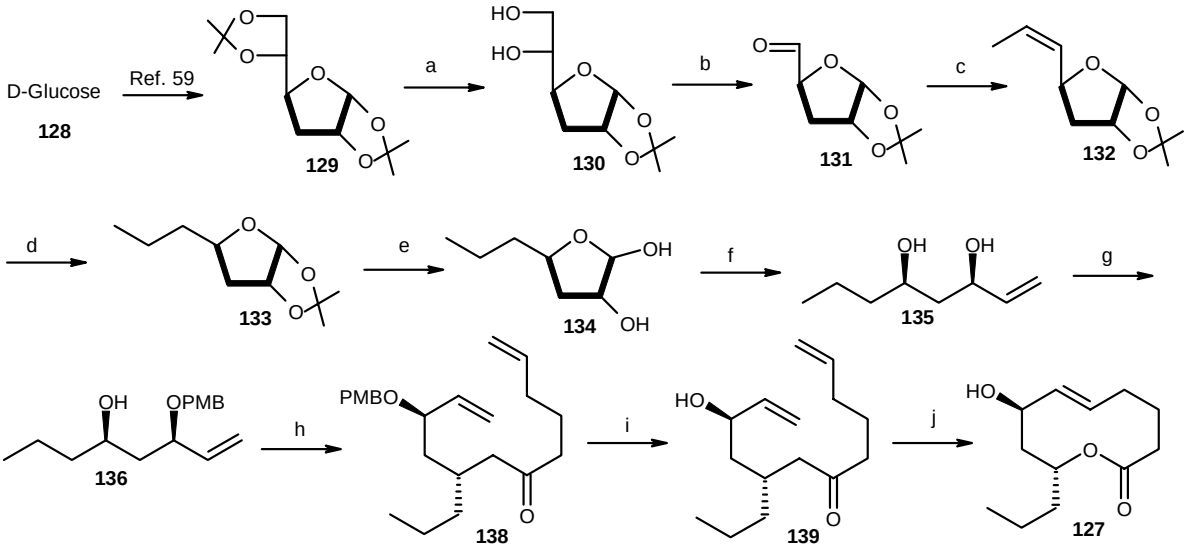
5.2.2. Review of Literature

In the literatute so far four syntheses are known for herbarumin III. The enantioselective syntheses known for herbarumin III derive the asymmetry either from chiral pool material

such as glucose[55] and glyceraldehydes,[56] by chemoenzymatic method[57] or by Sharpless asymmetric epoxidation.[58] A detailed report of these synthesis is described below.

Gurjar *et al* . (2004).[55]

Gurjar and co-workers accomplished the synthesis of herbarumin starting from D-glucose using ring-closing metathesis as the key step. As shown in scheme 19, D-glucose **128** was converted into its 3-deoxyglucose derivative **129** via known literature procedure.[59] Regioselective monohydrolysis of the 5,6-*O*-isopropylidene moiety of **129** afforded diol **130**, which on oxidative cleavage followed by two carbon homologation and hydrogenation afforded *n*-propyl derivative **133**. Deprotection of the 1,2-*O*-isopropylidene group of compound **133** afforded the lactol **134** which was subjected to Wittig methylenation[60] using methylenetriphenylphosphorane to afford the olefinic intermediate **135**. Selective protection of the allylic hydroxyl group as its PMB-ether and esterification of the other hydroxyl group with 5-hexenoic acid **137**[61] gave the diene **138**, which on PMB deprotection followed by ring-closing metathesis[38] afforded target molecule herbarumin **127**.

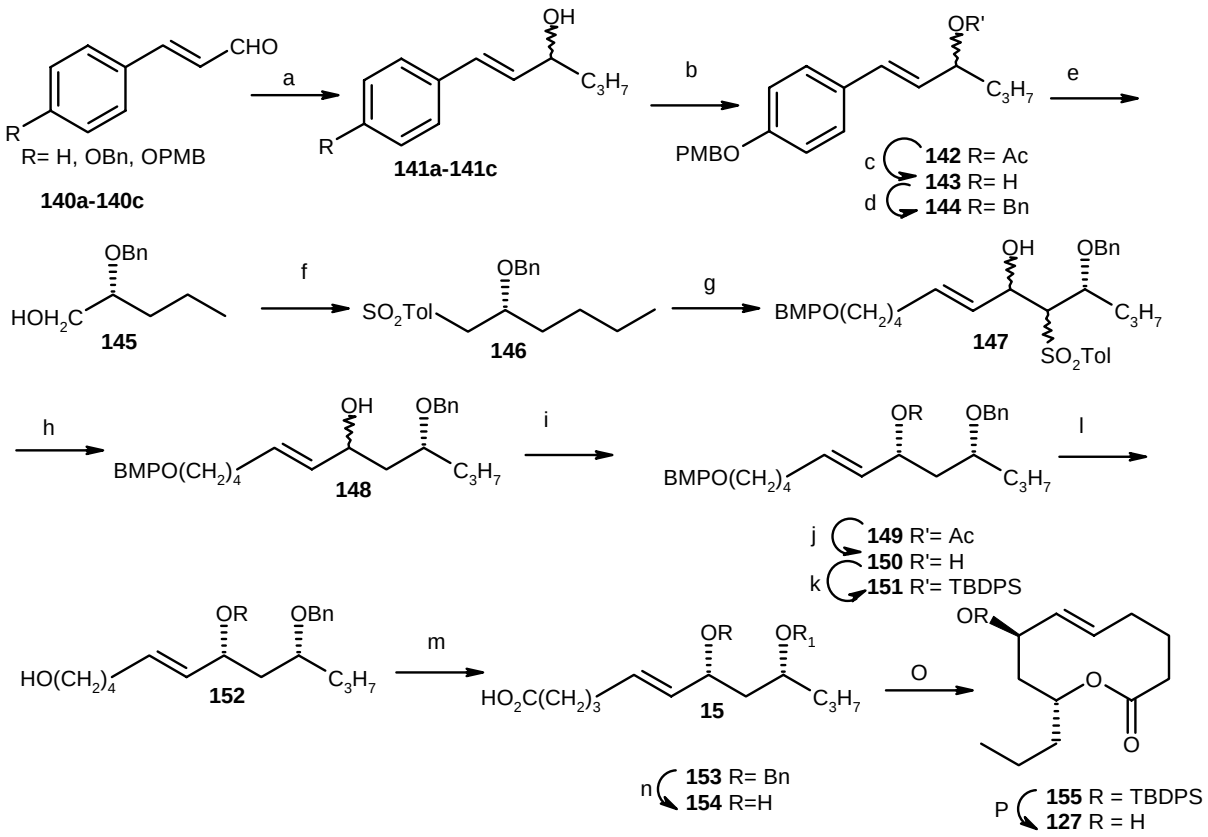


Scheme 19. *Reagents and conditions*: (a) 0.8% H_2SO_4, MeOH, rt, 12 h, (84%); (b) silica gel supported $NaIO_4$, CH_2Cl_2, rt, 30 min (95%); (c) $Br^-P^+Ph_3CH_2CH_3$, *n*-BuLi, THF, -78 to 0 ^oC, 3 h (82%); (d) H_2, Pd/C, 1 bar, rt, 3 h (92%); (e) 20% AcOH in H_2O, conc. H_2SO_4 (catalytic), reflux, 6 h (93%); (f) $I^-P^+Ph_3CH_3$, *n*-BuLi, THF, 0 ^oC to rt, 12 h (76%); (g)

PMBCl, NaH, DMF, 0 ^{o}C, 1 h, (94%); (h) 5-hexenoic acid **137**, 2,4,6-trichlorobenzoyl chloride, DMAP, THF, 11 in THF, 0 ^{o}C to rt, 4 h (82%); (i) DDQ, CH_2Cl_2/H_2O (18:1), rt, 30 min (94%); (j) (i) $RuCl_2(=CHPh)(PCy_3)_2$, CH_2Cl_2, reflux, 4 days, (36%) (52% starting material recovered), (ii) $RuCl_2(=CHPh)(PCy_3)(IEMS)$, CH_2Cl_2, reflux, 16 h, (78%).

Nanda *et al.* (2005).[57]

Nanda and co-workers accomplished the synthesis of herbarumin III by a chemoenzymatic approach using lipase catalyzed irreversible transesterification. Thus, *trans*-cinnamaldehyde **140a-c** on Grignard reaction yielded allylic alcohol **141a-c**, which was subjected to lipase catalyzed irreversible transesterification with vinyl acetate and CAL-B to afford (*R*)-acetate and (*S*)-alcohol. The mixture of (*R*)-acetate and (*S*)-alcohol was converted into (*R*)-acetate by employing strategy reported by Kanerva and Vanttinen.[62] It was observed that the substrate **140b** and **140c** provided better ee than **140a**. Deprotection of the acetate group in **142** followed by benzyl protection afforded compound **144**,[63] which on ozonolysis followed by reduction afforded alcohol **145**. Alcohol **145** was converted into sulfone derivative **146** which was then condensed with *(E)*-7-(4-methoxybenzyloxy)hept-2-enal to yield compound **147**. Removal of *p*-toluene sulfone group[64] followed by second enzymatic transesterification afforded acetate **149**. The acetate group was deprotected and alcohol was protected as TBDPS ether, followed by PMB deprotection to furnish alcohol **152**, which was converted into acid **153**. Finally benzyl deprotection followed by Yamaguchi macrocyclization and TBS deprotection afforded target molecule **127** (Scheme 20).

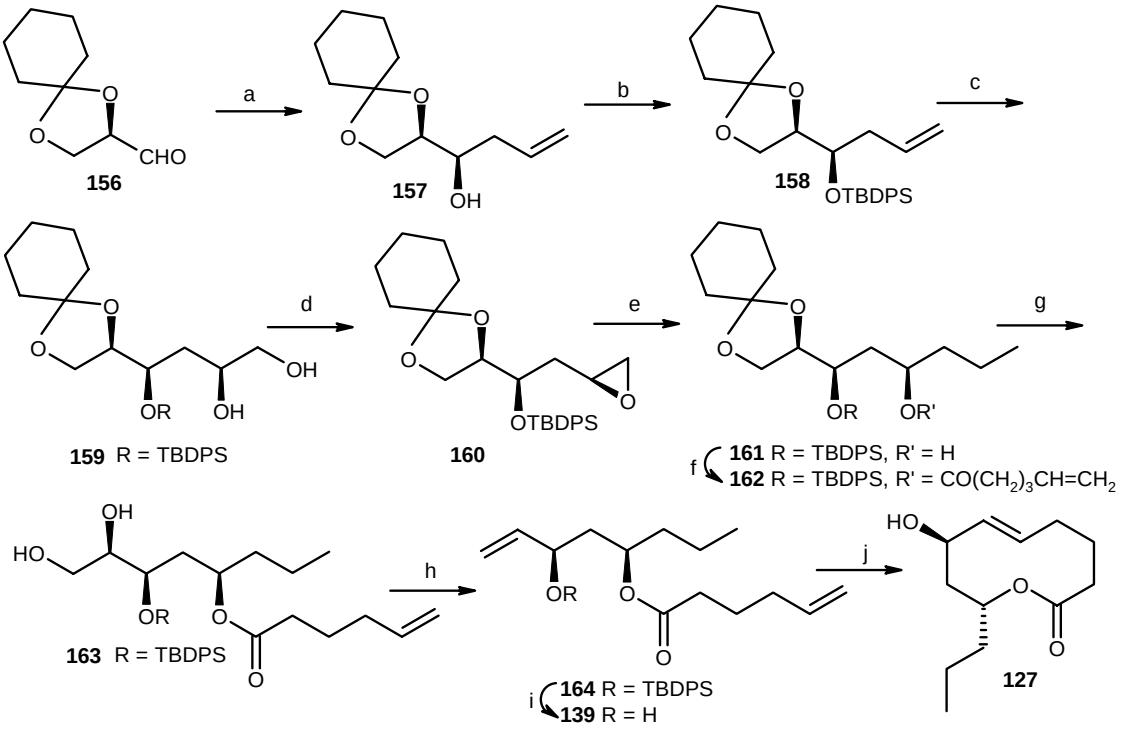


Scheme 20. *Reagents and conditions*: (a) *n*PrMgBr, ether, rt; (b) (i) VAC, CAL-B, DIPE; (ii) TPP, DIAD, AcOH, THF; (c) K_2CO_3, MeOH; (d) $BnO(C{=}NH)CCl_3$, CSA; (e) O_3, DCM, Me_2S, $NaBH_4$/MeOH, 82%; (f) (i) I_2, TPP, Im, 88%; (ii) $TolSO_2Na$, DMF, 65%; (g) LDA, -78 ^oC, *E*-7-(4-methoxybenzyloxy)hept-2-enal, 78%; (h) Al/Hg, THF, 60%; (i) (i) CAL-B, VAC, DIPE; (ii) TPP, DIAD, AcOH, 90% de; (j) K_2CO_3/MeOH; (k) TBDPSCl, imidazole, DMF, 86%; (l) DDQ, 82%; (m) (i) DMSO, $(COCl)_2$, Et_3N, -78 ^oC, 88%; (ii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, 80%; (n) Li–NH_3 (1), 3-hexyne; (o) (i) vinyl acetate, $Pd(OAc)_2$, lipase, TBME, 31%; (ii) Et_3N, DMAP, pH, 80 ^oC, 83%; (p) TBAF, THF.

Chattopadhyay *et al.* (2006).[56]

Chattopadhyay and co-workers reported the synthesis of Herbarumin III using (*R*)-cyclohexylidene glyceraldehydes **156** as the chiral template. Thus, *syn*-homoallylic alcohol **157** was prepared following a literature procedure.[65] Alcohol **157** was silylated with TBDPSCl followed by Sharpless asymmetric dihydroxylation[11] with AD mix-β to furnish

diol **159**. Regioselective monotosylation of the primary hydroxyl group of **159** followed by base treatment furnished epoxide **160**, which was opened with EtMgBr to give alcohol **161**. Esterification of alcohol **161** with hexenoic acid **137** followed by deacetalization furnished diol **163**, which on mesylation followed by elimination afforded olefin **164**. Desilylation of olefin followed by ring-closing metathesis afforded target molecule **127** (Scheme 21).

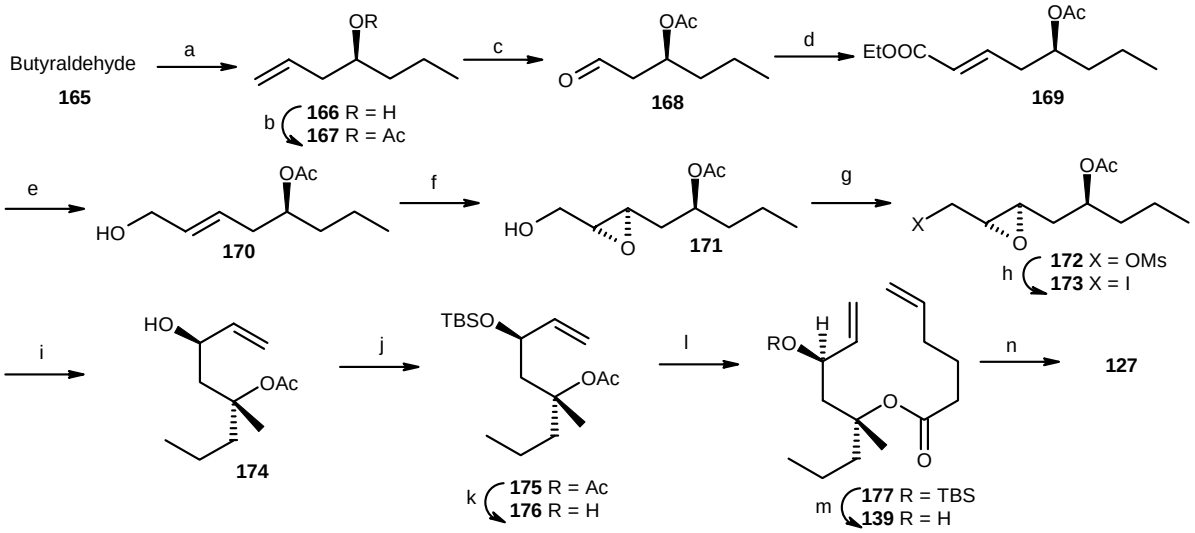


Scheme 21. *Reagents and conditions*: (a) Ref. 65; (b) TBDPSCl/imidazole/CH_2Cl_2 (88%); (c) AD mix-β/*t*-BuOH–H_2O (1:1) (78%); (d) *p*-TsCl/pyridine (94%); K_2CO_3/MeOH (86%); (e) EtMgBr/Cu_2Br_2/THF/-78 ^oC (72%); (f) CH_2=CH$(CH_2)_3$COOH **137**, DCC/DMAP (cat.)/CH_2Cl_2 (69%); (g) aqueous TFA (81%); (h) MsCl/pyridine; Zn/NaI/DMF (63%); (i) TBAF/THF/-78 ^oC (88%), (j) Grubb's second generation catalyst/CH_2Cl_2 (63%).

Barua *et al.* (2006).[58]

Barua and co-workers accomplished the synthesis of herbarumin III by using the Keck's asymmetric allylation and Sharpless epoxidation as the key steps. Thus, as shown in Scheme 22, butyraldehyde **165** was subjected to Keck's asymmetric allylation[66] followed by acetylation and oxidative cleavage to afford aldehyde **168** which on Wittig reaction

afforded the α,β-unsaturated ester **169**. Reduction of ester followed by Sharpless asymmetric epoxidation[28] afforded epoxide **171** as a single isomer. Alcohol group in epoxide **171** was activated as mesyl, which was converted into iodo with subsequent reductive fragmentation to give allylic alcohol **174**. Protection of the free OH group of **174** as a TBS ether and subsequent deacetylation furnished compound **176**, which on esterification with hexenoic acid **137** followed by desilylation and ring-closing metathesis afforded target molecule **127**.



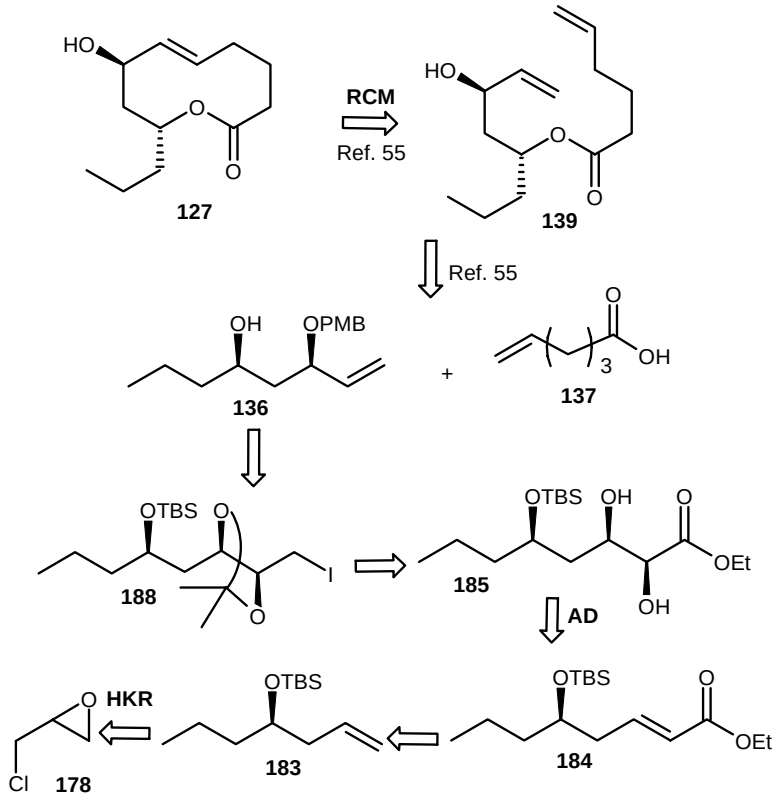
Scheme 22. *Reagents and conditions*: (a) (*R*)–BINOL, 4 A˚ ms, Ti(*i*–OPr)$_4$, allyltributyl tin, CH_2Cl_2, −78 to −20 ˚C, 80%; (b) acetic anhydride, I_2, 94%; (c) OsO_4, $NaIO_4$, 2,6-lutidine, dioxane–water, 87%; (d) triphenyl carbethoxymethyl phosphonium chloride (1.2 eqv.), basic alumina, microwaves, 74%; (e) DIBAL, THF, −78 ^{o}C, 90%; (f) Ti(*i*–OPr)$_4$, (−)-DET (diethyl tartrate), TBHP (*tert*-butylhydroperoxide), CH_2Cl_2, −20 ^{o}C, 70%; (g) MsCl, Et_3N, CH_2Cl_2, 90%; (h) NaI, acetone, 80%; (i) Zn, I_2 (cat.), MeOH, reflux, 76%; (j) TBSCl, imidazole, DMF, 93%; (k) K_2CO_3, MeOH, 89%; (l) 5-hexenoic acid **137**, DCC, DMAP (cat.), CH_2Cl_2, 86%; (m) TBAF, THF, 0 ^{o}C, 75%; (n) Grubbs catalyst, CH_2Cl_2, reflux, 55%.

5.2.3. Present work:

Objective:

As part of our research program aimed at developing enantioselective synthesis of naturally occurring lactones and macrolactones, we became interested in developing a simple and feasible route to Herbarumin III employing the Jacobsen's hydrolytic kinetic resolution and Sharpless asymmetric dihydroxylation as the source of chirality from the commercially available starting material epichlorohydrin.

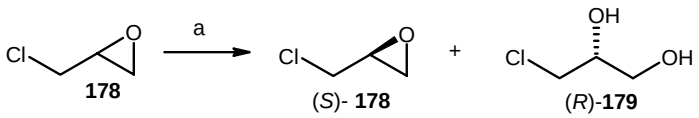
Our synthetic strategy for the synthesis of herbarumin III **127** is outlined in Scheme 23. **127** could be prepared from alcohol **136** and acid **137** by Yamaguchi coupling followed by ring-closing metathesis following literature procedure.[55] The alcohol **136** could be derived from the base induced reductive elimination of **188**, which in turn would be prepared from the diol **185**. The diol **185** would be obtained by the Sharpless asymmetric dihydroxylation of olefin **184** which in turn could be prepared from epichlorohydrin **178**.



Scheme 23. Retrosynthetic analysis for Herbarumin III (127).

5.2.4. Results and Discussion:

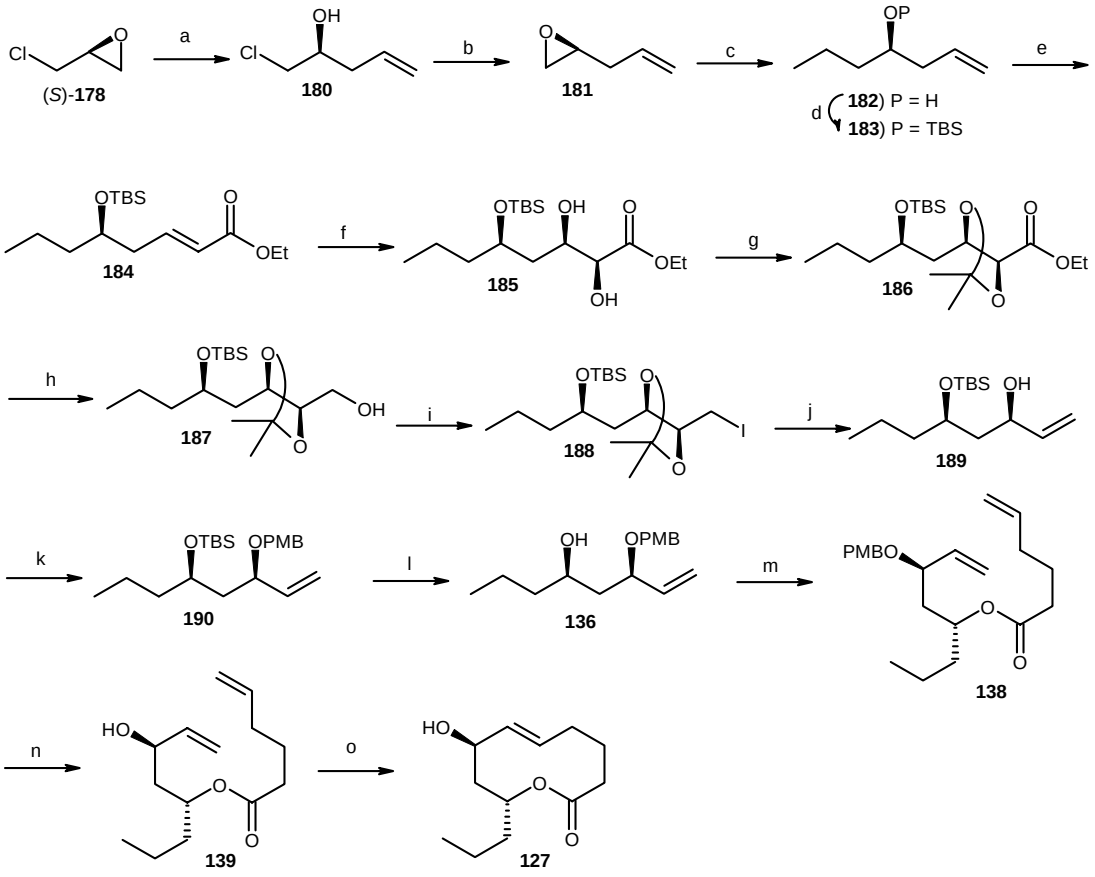
In designing a route to **127** we chose racemic epichlorohydrin as an appropriate starting material. Thus, as shown in Scheme 24 racemic epichlorohydrin **178** was subjected to Jacobsen's HKR by using (*R*,*R*)-salen-Co-OAc catalyst to give (*S*)-epichlorohydrin (*S*)-**178** as a single isomer, which was easily isolated from the more polar diol (*R*)-**179** by distillation.[32]



Scheme 24. *Reagents and conditions:* (a) *R*,*R*-salen-Co-(OAc) (0.5 mol%), dist. H_2O (0.55 eq), 0 ^oC, 19 h, (46% for (*S*)-**178**, 45% for (*R*)-**179**.

Thus epichlorohydrin (*S*)-**178** was opened with vinylmagnesium bromide to afford chlorohydrin **180**. The IR spectrum of **180** gave broad hydroxyl absorption at 3400 cm^{-1}. The ^1H NMR spectrum of **180** showed olefin peaks at 5.74-5.87 (multiplet, one proton), 5.08-5.19 multiplet, one proton). Base treatment of chlorohydrin **180** furnished epoxide **181** in 90% yield. The IR spectrum of **181** indicated absence of hydroxyl group. In the ^1H NMR spectrum peaks owing to epoxide were present at 2.91-3.03 (multiplet, 1H), 2.73 (doublet of doublet, 1H) with J = 5.0, 4.0 Hz and 2.48 (doublet of doublet, 1H) with J = 5.0, 2.6 Hz. The epoxide **181** was opened with propylmagnesium bromide[67] to afford homoallylic alcohol **182** in 78% yield. The IR spectrum of **182** gave broad hydroxyl absorption at 3425 cm^{-1}. The protection of hydroxy group of **182** as TBS ether gave the olefin **183** in 94% yield. The IR spectra of **183** showed absence of hydroxyl absorption. The olefin **183** was oxidized to aldehyde in the presence of OsO_4 and $NaIO_4$[68] followed by reaction with (ethoxycarbonylmethylene)-triphenylphosphorane in benzene under reflux conditions to furnish the *trans*-olefin **184** in 89% yield. The IR spectrum of **184** showed the ester carbonyl absorption at 1712 cm^{-1} and olefin C=C stretching at 1661 cm^{-1}. The ^1H NMR spectrum gave olefin protons at δ 6.89-7.05 (multiplet), and 5.80 (doublet of triplet) with the coupling constant J = 15.7, 1.4 Hz indicating *trans*-olefin. The dihydroxylation of **184** with osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of $(DHQD)_2PHAL$ ligand under the AD conditions[11] gave the diol **185** in 95% yield and

>96% ee. The IR spectrum of **185** showed hydroxyl absorption at 3446 cm^{-1} and ester carbonyl at 1733 cm^{-1}. The ^1H NMR indicated absence of olefin protons. Treatment of diol **185** with 2,2-dimethoxypropane in the presence of *p*-TSA gave compound **186** in 91% yield. The IR spectrum of **186** indicated absence of hydroxyl groups. The acetonide methyl protons appeared at δ 1.44 (singlet) and 1.46 (singlet) in the ^1H NMR spectrum and typical quaternary carbon of acetonide appeared at 110.7 in the ^{13}C NMR spectrum. Compound **186** on reduction with DIBAL-H furnished the alcohol **187** in 88% yield. The IR spectrum of **187** gave hydroxyl absorption at 3459 cm^{-1} and the ester carbonyl group was absent. The alcohol **187** was converted into an *O*-tosyl derivative which on treatment with sodium iodide furnished the iodide **188** in 85% yield. In the ^1H NMR spectrum of **188** the resonances due to CH_2I were located at 3.35-3.19 as a multiplet. Iodide **188** on reductive fragmentation using Zn powder in refluxing ethanol furnished the allylic alcohol **189** in 92% yield. In the ^1H NMR spectrum of **189** peaks owing to CH_2I and isopropylidene group were absent. The terminal olefinic proton showed peaks at δ 5.87 (doublet of quartet) with J = 17.1, 11.9, 6.7, 1.0 Hz, 5.23 (doublet of doublet) with J = 17.1, 15.5, 1.6 Hz, and at 5.07 (doublet of doublet) with J = 11.9, 10.36, 1.51 Hz. The ^{13}C spectrum displayed peaks at 113.9, 140.9 corresponding to olefinic carbons. Alcohol **189** was protected as PMB ether and TBS was deprotected to give alcohol **136** in 87% yield. Further transformation to achieve the total synthesis of target molecule **127** was carried out using the literature procedure as reported by Gurjar *et al.*[55] Thus Yamaguchi coupling with hexenoic acid **137**[61] gave the diene **138** in 80% yield. The PMB group of diene was deprotected to give compound **139** in 95% yield as a precursor for RCM. Finally ring closing metathesis[38] of **139** using Grubb's second generation catalyst proceeded smoothly to give herbarumin III **127** in 76% yield, $[\alpha]_D^{25}$ +21.8 (*c* 0.1, EtOH); [lit.[53a] +22.0 (*c* 0.1, EtOH)]. The physical and spectral data of **127** were in full agreement with the literature data[53a] (Scheme 25).



Scheme 25. *Reagents and conditions:* (a) Vinylmagnesium bromide, Ether, CuI, –78 to –40 ^{o}C, 19 h, 72%; (b) KOH, 90%; (c) C_3H_7MgBr, THF, CuI, –20 ^{o}C, 4 h, 78%; (d) TBSCl, CH_2Cl_2, 0 ^{o}C to rt, 2.5 h, 94%; (e) (i) OsO_4, $NaIO_4$, 2,6-Lutidine, 1,4-Dioxane: H_2O (3:1), 0 ^{O}C; (ii) $Ph_3P{=}CHCO_2Et$, benzene, reflux, overnight, 84% from two steps; (f) $(DHQD)_2PHAL$, K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, OsO_4 (0.1M in toluene), *t*-BuOH–H_2O (1:1), 0 ^{o}C, 24 h, 95%; (g) *p*-TSA, 2,2-DMP, CH_2Cl_2, 1.5 h, 91%; (h) DIBAL-H, CH_2Cl_2, 0 ^{o}C to rt, 2 h, 88%; (i) (i) TsCl, Et_3N, CH_2Cl_2, 2h; (ii) NaI, *t*-butanone, reflux, 6 h, 85% from both the steps; (j) Zn, EtOH, reflux, 3 h, 92%; (k) PMBBr, NaH, THF, 1 h, 90%; (l) TBAF, THF, 8 h, 87%; (m) **137**, 2,4,6-trichlorobenzoyl chloride, DMAP, THF, **136** in THF, 0 ^{o}C-rt, 4 h, 80%; (n) DDQ, CH_2Cl_2/H_2O, rt, 30 min, 95%; (o) $RuCl_2(=CHPh)(PCy_3)(IEMS)$, CH_2Cl_2, reflux, 16 h, 76%.

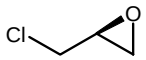
5.2.5. Conclusion

In conclusion, an efficient total synthesis of herbarumin III with high enantioselectivity has been developed in which stereocentres were established by Jacobsen's hydrolytic kinetic

resolution and Sharpless asymmetric dihydroxylation, and lactone moiety was achieved by ring closing metathesis. Further application of this methodology to the syntheses of all the isomers of Herbarumin and other biologically active compounds for the structure-activity relationship studies is currently underway in our laboratory.

5.2.6. Experimental Section

(*S*)- Epichlorohydrin ((*S*)-178).

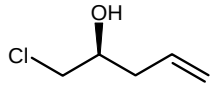


(*S*)-**178**

The racemic epichlorohydrin **178** was resolved to (*S*)-epichlorohydrin **(*S*)-178** in high enantiomeric excess by the HKR method following a literature procedure.[32]

$[\alpha]_D^{25}$: = +30.6 (*c* 1.2, MeOH); lit.[32] for (*R*)-epichlorohydrin $[\alpha]_D^{25}$ = –32.8 (*c* 1.27, MeOH).

(*S*)-1-Chloropent-4-en-2-ol (180).



180

A round bottomed flask was charged with copper (I) iodide (0.103 g, 0.54 mmol), gently heated under vacuum, and slowly cooled with a flow of argon, and dry diethyl ether (30 mL) was added. This suspension was cooled to –20 ^oC and vigorously stirred, and vinylmagnesium bromide (1M in THF, 108 mL, 108.08 mmol) was injected to it. A solution of epichlorohydrin (*S*)-**178** (5 g, 54.04 mmol) in diethyl ether (10 mL) was added slowly to the above reagent, and the mixture was stirred at –73 ^oC to –40 ^oC 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 which on vacuum distillation provided homoallylic alcohol (*S*)-1-chloropent-4-en-2-ol **180** as a colorless liquid (4.7 g, 72%).

Yield: 4.7 g, 72%.

B. P. 66-69 ^oC/21 mm of Hg

$[\alpha]_D^{27}$ = +5.2 (*c* 1.4, $CHCl_3$)

Mol. Formula: C_5H_9ClO

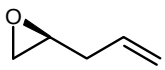
IR ($CHCl_3$, cm^{-1}): ν_{max} 3400, 3078, 2931, 2975, 1562, 1457, 1432, 1243, 1071, 914.

^{1}H NMR (500 MHz, $CDCl_3$): δ 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 (125 MHz, $CDCl_3$): δ 38.4, 48.9, 70.4, 118.1, 133.2.

Analysis Calcd.: C, 49.80; H, 7.52%; **Found:** C, 49.69; H, 7.55%.

(*S*)-2-Allyloxirane (181).



181

KOH (2.8 g, 49.76 mmol) is added to the homoallylic alcohol **180** (5 g, 41.47 mmol) in a flask fitted with distillation head. The mixture is heated and the epoxide **181** distilled over as a colourless liquid.

Yield: 3.14 g, 90%.

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

B. P. 80-82 ^oC

$[\alpha]_D^{25}$: -16.2 (neat)

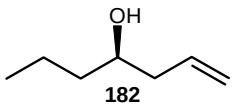
IR (neat, cm^{-1}): ν_{max} 2995, 1647, 1410, 920.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.23-2.37 (m, 2H), 2.48 (dd, *J* = 5.0, 2.6 Hz), 2.73 (dd, *J* = 5.0, 4.0 Hz, 1H), 2.91-3.03 (m, 1H), 5.03-5.22 (m, 2H), 5.68-5.92 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 36.4, 46.4, 51.1, 117.5, 133.0.

Analysis Calcd.: C, 71.39; H, 9.59%; **Found:** C, 71.58; H, 9.53%.

(*R*)-Hept-1-en-4-ol (182).



182

A round bottomed flask was charged with copper(I)iodide (0.91 g, 0.48 mmol), gently heated under vaccum and slowly cooled with a flow of argon and THF (20 mL) was added. This suspension was cooled to –30 ^oC, stirred and ethylmagnesium bromide [prepared from Mg (2.31 g, 95.10 mmol and ethyl bromide (10.36 g, 95.10 mmol) in THF] was

added to it. A solution of epoxide **181** (4.0 g, 47.55 mmol) in THF (10 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 100 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using Pet ether/EtOAc (9:1) as eluent provided alcohol **182** as a colorless liquid.

Yield: 4.24 g, 78%.

Mol. Formula: $C_7H_{14}O$

$[\alpha]_D^{25}$: -17.4 (*c* 1.1, $CHCl_3$)

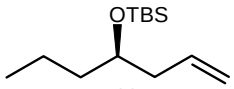
IR (neat, cm^{-1}): ν_{max} 3425, 3019, 2927, 2106, 1601, 1493, 1455, 1251, 1123, 863, 758.

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.91 (t, *J* = 6.6 Hz, 3H), 1.30-1.54 (m, 4H), 2.02-2.11 (m, 2H), 2.34 (brs, 1H), 3.54-3.59 (m, 1H), 5.02-5.11 (m, 2H), 5.74-5.79 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 19.2, 38.9, 42.2, 71.1, 117.2, 135.5.

Analysis Calcd.: C, 73.63; H, 12.36%; **Found:** C, 73.51; H, 12.42%.

(*R*)-*tert*-Butyl(hept-1-en-4-yloxy)dimethylsilane (183).



183

To a stirred soluion of alcohol **182** (4.0 g, 35.03 mmol) in CH_2Cl_2 (25 mL), imidazole (3.58, 52.54 mmol) was added. To this solution *t*-butylchlorodimethylsilane (5.81g, 38.53 mmol) was added at 0 ^{o}C 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 X 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 (49:1) as eluent provided **183**.

Yield: 7.52 g, 94%

Mol. Formula: $C_{13}H_{28}OSi$

$[\alpha]_D^{25}$: -21.2 (*c* 1.0, $CHCl_3$).

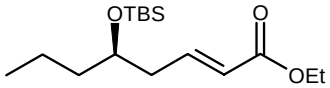
IR ($CHCl_3$, cm^{-1}): ν_{max} 3086, 2972, 2921, 2892, 1640, 1493, 1453, 1359, 1248, 1075, 1002, 916, 872.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.06 (s, 6H), 0.89 (s, 9H), 0.92 (t, *J* = 6.6 Hz, 3H), 1.32-1.59 (m, 2H), 1.62-1.71 (m, 1H), 2.05-2.18 (m, 1H), 2.22-2.36 (m, 2H), 3.74-3.82 (m, 1H), 5.02-5.12 (m, 2H), 5.75-5.86 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ -4.5, 14.3, 17.8, 18.2, 25.6, 40.8, 41.1, 70.9, 116.8, 135.2

Analysis Calcd.: C, 68.35; H, 12.35%; **Found:** C, 68.24; H, 12.38%.

(*R*,*E*)-Ethyl 5-(*tert*-butyldimethylsilyloxy) oct-2-enoate (184).



184

To a solution of compound **183** (4 g, 17.51 mmol) in dioxane-water (3:1, 40 mL) were added 2,6-lutidine (4.1 mL, 35.02 mmol), OsO_4 (0.1M solution in toluene, 3.5 mL, 0.35 mmol) and $NaIO_4$ (14.98 g, 70.04 mmol). The reaction was stirred at 25 ^oC for 3 hours. After the reaction was complete, water (10 mL) and CH_2Cl_2 (20 mL) were added. The organic layer was separated, and the water layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layer was washed with brine and dried (Na_2SO_4) to give crude aldehyde which was used as such for the next step without further purification.

To a solution of (ethoxycarbonylmethylene)triphenylphosphorane (7.85 g, 22.57 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 **184** as a pale yellow liquid.

Yield: 4.42 g, 84%

Mol. Formula: $C_{16}H_{32}O_3Si$

$[\alpha]_D^{25}$: –23.1 (*c* 1.1, $CHCl_3$).

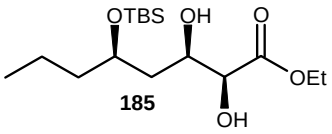
IR ($CHCl_3$, cm^{-1}): ν_{max} 3056, 3019, 2962, 2916, 1712, 1661, 1472, 1463, 1372, 1269, 1182, 1094.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.89-7.05 (m, 1H), 5.80 (dt, *J* = 15.7, 14.3, 1.4 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.72-3.83 (m, 1H), 2.30-2.40 (m, 2H), 1.39-1.50 (m, 4H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.92 (t, *J* = 6.6 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 166.3, 145.9, 123.1, 71.0, 59.9, 40.1, 39.4, 25.7, 18.4, 17.9, 14.1, -4.7.

Analysis Calcd.: C, 63.95; H, 10.73%; **Found:** C, 63.88; H, 10.81%.

(2*S*,3*R*,5*R*)-Ethyl 5-(*tert*-butyldimethylsilyloxy)-2,3-dihydroxyoctanoate (185).



185

To a mixture of $K_3Fe(CN)_6$ (6.57 g, 19.97 mmol), K_2CO_3 (2.76 g, 19.97 mmol) and $(DHQD)_2PHAL$ (52 mg, 1 mol%), in *t*-BuOH-H_2O (1:1, 35 mL) cooled at 0 ^oC was added OsO_4 (0.27 mL, 0.1 M sol in toluene, 0.4 mol%) followed by methane sulfonamide (0.63 g, 6.66 mmol). After stirring for 5 min at 0 ^oC, the olefin **184** (2.0 g, 6.66 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 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 diol **185** as a colorless syrupy liquid.

Yield: 2.12 g, 95%

Mol. Formula: $C_{16}H_{34}O_5Si$

$[\alpha]_D^{25}$: –11.2 (*c* 1.0, $CHCl_3$)

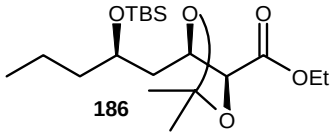
IR ($CHCl_3$, cm^{-1}): ν_{max} 3446, 3018, 2958, 2898, 2412, 1733, 1665, 1465, 1261, 1092.

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.28 (q, *J* = 7.1 Hz, 2H), 4.02-4.12 (m, 2H), 3.96 (d, *J* = 4.2 Hz, 1H), 3.09 (brs, 2H), 1.63-1.82 (m, 2H), 1.49-1.56 (m, 2H), 1.32 (t, *J* = 7.1 Hz, 3H), 0.95 (t, *J* = 6.6 Hz, 3H), 0.90 (s, 9H), 0.10 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 173.2, 74.1, 71.2, 69.4, 61.7, 39.9, 38.7, 25.8, 17.9, 17.9, 14.2, 14.1, -4.6.

Analysis Calcd.: C, 57.45; H, 10.24; **Found** C, 57.36; H, 10.21.

(4*S*,5*R*)-Ethyl 5-((*R*)-2-(*tert*-butyldimethylsilyloxy)pentyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (186).



186

To a solution of the diol **185** (2.0 g, 5.98 mmol), *p*-TSA (50 mg) in CH_2Cl_2 (50 mL) was added 2,2-dimethoxypropane (0.93 g, 1.1 mL, 8.97 mmol) and mixture stirred for two hours. Solid $NaHCO_3$ 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 **186** as a colorless liquid.

Yield: 2.04 g, 91%.

Mol. Formula: $C_{19}H_{38}O_5Si$

$[\alpha]_D^{25}$: –24.1 (*c* 0.8, $CHCl_3$).

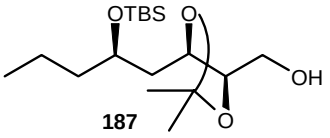
IR ($CHCl_3$, cm^{-1}): ν_{max} 3021, 2952, 2946, 1742, 1664, 1471, 1375, 1216, 1135, 1078, 964, 856.

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.22 (q, *J* = 7.1 Hz, 2H), 4.03-4.14 (m, 2H), 3.85-3.94 (m, 1H), 1.80-1.94 (m, 2H), 1.61-1.74 (m, 2H), 1.46 (s, 3H), 1.44 (s, 3H), 1.36-1.39 (m, 2H), 1.30 (t, *J* = 7.1 Hz, 3H), 0.92 (t, *J* = 6.6 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 6H)

^{13}C NMR (75 MHz, $CDCl_3$): δ 170.7, 110.7, 79.2, 76.1, 69.3, 61.2, 41.1, 40.4, 38.7, 27.2, 25.8, 18.4, 17.9, 14.3, 14.1, -4.53.

Analysis Calcd.: C, 60.92; H, 10.23; **Found:** C, 61.04; H, 10.18%.

((4*R*,5*R*)-5-((*R*)-2-(*tert*-Butyldimethylsilyloxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-methanol (187).



187

To a solution of ester **186** (1.9 g, 5.07 mmol) in dry CH_2Cl_2 (20 mL) at 0 ^oC was added dropwise DIBAL-H (5.58 mL, 5.58 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 sod./pot. 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 (17:3) as eluent gave alcohol **187** as a colorless liquid.

Yield: 1.48 g, 88%

Mol. Formula: $C_{17}H_{36}O_4Si$

$[\alpha]_D^{25}$: -16.2 (*c* 1.1, $CHCl_3$).

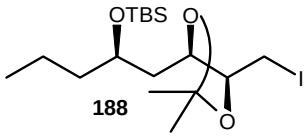
IR ($CHCl_3$, cm^{-1}): ν_{max} 3459, 3021, 2958, 2946, 1720, 1469, 1374, 1265, 1221, 1164, 1047, 963, 942.

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.14-3.97 (m, 2H), 3.81 (d, *J* = 6.2 Hz, 2H), 3.78-3.63 (m, 1H),1.73-1.62 (m, 2H), 1.60-1.44 (m, 2H), 1.43 (s, 3H), 1.41 (s, 3H), 1.40-1.38 (m, 2H), 0.94 (t, *J* = 6.6 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 108.6, 81.7, 73.6, 69.6, 61.9, 40.9, 38.6, 26.9, 25.8, 18.6, 17.7, 14.3, -4.36.

Analysis Calcd.: C, 61.40; H, 10.91; **Found** C, 61.52; H, 10.89.

((*R*)-1-((4*R*,5*S*)-5-(Iodomethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pentan-2-yloxy)(*tert*-butyl)dimethylsilane (188).



188

To a stirred solution of alcohol **187** (1.4 g, 4.21 mmol) in CH_2Cl_2 (40 mL) at 0 ^oC under nitrogen was added triethyl amine (1.65 mL, 11.82 mmol) followed by tosyl chloride (0.90 g, 4.73 mmol). After being stirred for 2 h at room temperature, the reaction mixture was diluted with H_2O, and extracted with CH_2Cl_2 (50 mL). The combined organic layers were washed with water, brine and dried (Na_2SO_4). The solvent was removed under reduced pressure to give tosyl as a pale yellow oil, which was used as such for the next step, without further purification.

Tosyl (2.05 g, 4.21 mmol) was dissolved under argon in dry *t*-butanone (20 mL) and was treated with NaI (1.89 g, 12.65 mmol). The reaction mixture was refluxed for 6 h. After cooling to room temperature the volatiles were removed under reduced pressure. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (19:1) as eluent gave iodo compound **188** as a colorless liquid.

Yield: 1.58 g, 85%

Mol. Formula: $C_{17}H_{35}IO_3Si$

$[\alpha]_D^{25}$: –64.7 (*c* 1.0, $CHCl_3$).

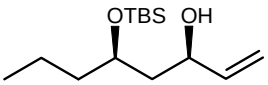
IR ($CHCl_3$, cm^{-1}): ν_{max} 3020, 2965, 2932, 2856, 1522, 1468, 1384, 1298, 1211, 1028, 968.

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.95-3.83 (m, 2H), 3.65-3.53 (m, 1H), 3.35-3.19 (m, 2H), 1.84-1.64 (m, 2H), 1.62-1.41 (m, 4H), 1.44 (s, 3H), 1.41 (s, 3H), 0.95 (t, *J* = 6.6 Hz, 3H), 0.91 (s, 9H), 0.07 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 108.9, 80.1, 78.2, 69.5, 40.6, 38.5, 27.3, 27.2, 25.9, 18.6, 18.0, 14.4, 5.41, -4.29, -4.60.

Analysis Calcd.: C, 46.15; H, 7.97%; Found C, 46.22; H, 7.90%.

(3*R*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)oct-1-en-3-ol (189).



189

A mixture of **188** (1.5 g, 3.39 mmol), Zinc (0.44 g, 6.78 mmol) in refluxing ethanol (15 mL) under nitrogen was stirred for 3h. The zinc was filtered and filtrate concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) as eluent gave **189** as a light yellow liquid.

Yield: 0.81 g, 92%.

Mol. Formula: $C_{14}H_{30}O_2Si$

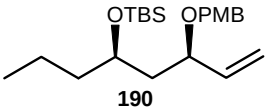
IR (neat, cm^{-1}): ν_{max} 3445, 3082, 3958, 2932, 2858, 1645, 1472, 1464, 1379, 1256, 1216, 1127, 1066, 922, 836.

^{1}H NMR (200 MHz, $CDCl_3$): δ5.87 (dq, *J* = 17.1, 11.9, 6.7, 1.0 Hz, 1H), 5.23 (dd, *J* = 17.1, 15.5, 1.6 Hz, 1H), 5.07 (dd, *J* = 11.9, 10.36, 1.51 Hz, 1H), 4.32-4.23 (m, 1H), 4.15-3.92 (m, 1H), 1.68-1.63 (m, 2H), 1.55-1.48 (m, 2H), 1.37-1.23 (m, 2H), 0.94 (t, *J* = 6.6 Hz, 3H), 0.91 (s, 9H), 0.11 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 140.9, 113.9, 71.8, 69.6, 43.0, 40.1, 25.8, 18.7, 17.8, 14.2, -4.10, -4.73.

Analysis Calcd.: C, 65.06; H, 11.70%; **Found:** C, 65.11; H, 11.81%.

***tert*-Butyl((4*R*,6*R*)-6-(4-methoxybenzyloxy)oct-7-en-4-yloxy)dimethylsilane (190).**



190

To a solution of **189** (0.50 g, 1.93 mmol) in dry THF (20 mL) was added sodium hydride (50%, 0.11 g, 2.32 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 (0.36 g, 2.13 mmol) and tetra *n*-butylammonium iodide (0.71 g, 0.19 mmol) with further stirring for 1 h at the same temperature. The reaction mixture was quenched with addition of cold water and EtOAc 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 **190** as colorless oil.

Yield: 0.66 g, 90%

Mol. Formula: $C_{22}H_{38}O_3Si$

$[\alpha]_D^{25}$ **:** –38.3 (*c* 1.1, $CHCl_3$)

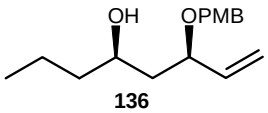
IR ($CHCl_3$, cm^{-1}): ν_{max} 3085, 2951, 2936, 2847, 1641, 1487, 1464, 1378, 1247, 1121, 1055, 913, 839.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.22 (d, *J* = 8.2 Hz, 2H), 6.88 (d, *J* = 8.3 Hz, 2H), 5.82-5.65 (m, 1H), 5.26-5.19 (m, 2H), 4.32 (s, 2H), 4.04-3.99 (m, 1H), 3.98-3.94 (m, 1H), 3.79 (s, 3H), 1.68-1.61 (m, 2H), 1.48-132 (m, 4H), 0.92 (t, *J* = 6.9 Hz, 3H), 0.90 (s, 9H), 0.09 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.1, 139.6, 129.7, 129.5, 116.9, 114.1, 81.7, 72.3, 71.6, 55.3, 43.9, 40.4, 25.9, 18.7, 17.6, 14.3, -4.3, -4.6.

Analysis Calcd.: C, 69.79; H, 10.12%; **Found:** C, 69.65; H, 10.16%.

(4*R*,6*R*)-6-(4-Methoxybenzyloxy)oct-7-en-4-ol (136).



136

To a solution of **190** (0.65 g, 1.72 mmol) in THF (10 mL) was added TBAF (2.58 ml, 2.58 mmol, 1.0 M solution in THF) at room temperature. The reaction mixture was stirred for 1

h and then diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, concentrated. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 3:1) to give **136** as a colorless oil.

Yield: 0.395 g, 87%.

Mol. Formula: $C_{16}H_{24}O_3$

$[\alpha]_D^{25}$: - 9.6 (*c* 0.80, $CHCl_3$).

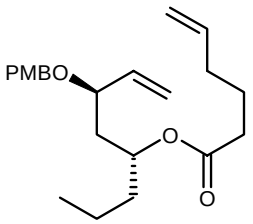
IR ($CHCl_3$, cm^{-1}): ν_{max} 3448, 3073, 2985, 2931, 2852, 1634, 1469, 1445, 1257, 1221, 1127, 918, 834.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.21 (d, *J* = 8.2 Hz, 2H), 6.84 (d, *J* = 8.3 Hz, 2H), 5.84-5.66 (m, 1H), 5.29-5.21 (m, 2H), 4.54 (d, *J* = 11.1 Hz, 1H), 4.26 (d, *J* = 11.2 Hz, 2H), 4.06-4.01 (m, 1H), 4.0-3.96 (m, 1H), 3.80 (s, 3H), 3.59 (brs, 1H), 1.69-1.60 (m, 2H), 1.44-1.26 (m, 2H), 0.94 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.3, 138.3, 129.9, 124.5, 117.5, 113.9, 81.2, 71.1, 69.8, 55.2, 42.5, 39.8, 18.6, 14.1.

Analysis Calcd.: C, 72.62; H, 9.19%; Found C, 72.54; H, 9.28%.

(4*R*,6*R*)-6-(4-Methoxybenzyloxy)oct-7-en-4-yl hex-5-enoate (138).



138

To a solution of 5-hexenoic acid **137** (0.86 g, 0.75 mmol) in THF, was added triethyl amine (0.16 mL, 1.13 mmol) and 2, 4, 6-trichlorobenzoyl chloride (0.18 mL, 1.13 mmol) under nitrogen atmosphere at 0 ^oC and the reaction mixture was allowed to stir under this condition for 1 h. To this, alcohol **136** (0.20 g, 0.76 mmol) in THF (5 mL) and catalytic amount of 4-dimethyl aminopyridine (DMAP) were added successively at 0 ^oC. Stirring was continued for additional 3 h at rt. The reaction mixture was quenched with water and extracted with ethyl acetate (3x50 mL). The combined organic layers were thoroughly washed with saturated sodium bicarbonate solution, brine, dried (Na_2SO_4), and concentrated to afford the crude product. Silica gel column chromatography of the crude

product using petroleum ether/EtOAc (49:1) as eluent afforded the ester **138** as a colorless liquid.

Yield: (0.22 g, 80%).

Mol. Formula: $C_{22}H_{32}O_4$.

$[\alpha]_D^{25}$: + 34.2 (*c* 0.80, CHCl3).

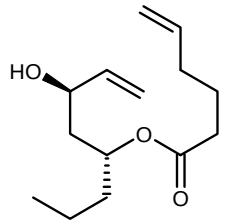
IR (neat, cm^{-1}): ν_{max} 3078, 3012, 2934, 2816, 1740, 1472, 1265, 1211, 1127, 964, 836.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.2 Hz, 2 H), 6.88 (d, *J* = 8.3 Hz, 2 H), 5.83-5.62 (m, 2 H), 5.29-4.96 (m, 5 H), 4.54 (d, *J* = 11.2 Hz, 1 H), 4.26 (d, *J* = 11.2 Hz, 1 H), 3.79 (s, 3 H), 3.74-3.70 (m, 1 H), 2.21 (t, *J* = 7.1 Hz, 2 H), 2.07-2.0 (m, 3 H), 1.70-1.63 (m, 3 H), 1.51-1.44 (m, 2 H), 1.42-1.27 (m, 2 H), 0.86 (t, 3 H, *J* = 6.6 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 172.5, 158.7, 138.0, 137.4, 130.2, 129.1, 117.7, 115.0, 113.3, 77.3, 70.7, 69.2, 54.8, 39.7, 36.3, 33.4, 32.8, 23.8, 18.1, 13.6.

Analysis Calcd.: C, 73.30; H, 8.95%; **Found:** C,73.12; H, 9.02%

(4*R*,6*R*)-6-Hydroxyoct-7-en-4-yl hex-5-enoate (139).



139

To a solution of above ester **138** (0.20 g, 0.55 mmol) in CH_2Cl_2 (9.5 mL) and water (0.5 mL) was added 2,3-dichloro-5,6-dicyano benzoquinone (DDQ) (0.15 g, 0.67 mmol). Reaction mixture was stirred at rt for 30 min. After completion (monitored by TLC), the reaction mixture was extracted with ethyl acetate (3x40 mL). The combined organic fractions were washed with saturated sodium bicarbonate solution followed by brine, dried (Na_2SO_4) and concentrated to afford the crude product. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (19:1) as eluent gave compound **139** as a oily liquid.

Yield: 0.13 g, 95%

Mol. Formula: $C_{14}H_{24}O_3$

$[\alpha]_D^{25}$: + 7.6 (*c* 1.0, $CHCl_3$)

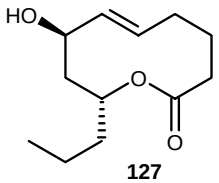
IR (neat, cm^{-1}): ν_{max} 3412, 3086, 3012, 2916, 2809, 1742, 1239, 1214, 1096, 986, 904.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.89-5.67 (m, 2 H), 5.21-4.93 (m, 5 H), 4.11 (q, 1 H, *J* = 12.5, 6.4 Hz), 2.48 (br s, 1 H), 2.25 (t, 2 H, *J* = 7.2 Hz), 2.04 (q, 2 H, *J* = 14.1, 6.9 Hz), 1.83-1.51 (m, 6 H), 1.48-1.22 (m, 2 H), 0.87 (t, 3 H, *J* = 7.1 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 173.3, 140.5, 137.5, 115.4, 114.7, 71.4, 70.3, 41.5, 36.6, 33.7, 32.9, 23.9, 18.3, 13.8.

Analysis Calcd.: C, 69.96; H, 10.07%, **Found:** C, 69.78; H, 10.02%.

Herbarumin III (127)



127

A mixture of **139** (100 mg, 0.42 mmol) in anhydrous CH_2Cl_2 (100 mL) and Grubbs' second generation catalyst (35 mg, 0.04 mmol) was degassed with argon for 15 min, and refluxed for 16 h. Solvent was removed under reduced pressure to leave highly dark brown colored residue. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) as eluent afforded herbarumin III (**127**) as a colorless liquid.

Yield: 128 mg, 51%

Mol. Formula: $C_{12}H_{20}O_3$

$[\alpha]_D^{25}$: +21.8 (*c* 0.1, EtOH).

IR (neat, cm^{-1}): ν_{max} 3443, 3019, 2962, 1723, 1640.

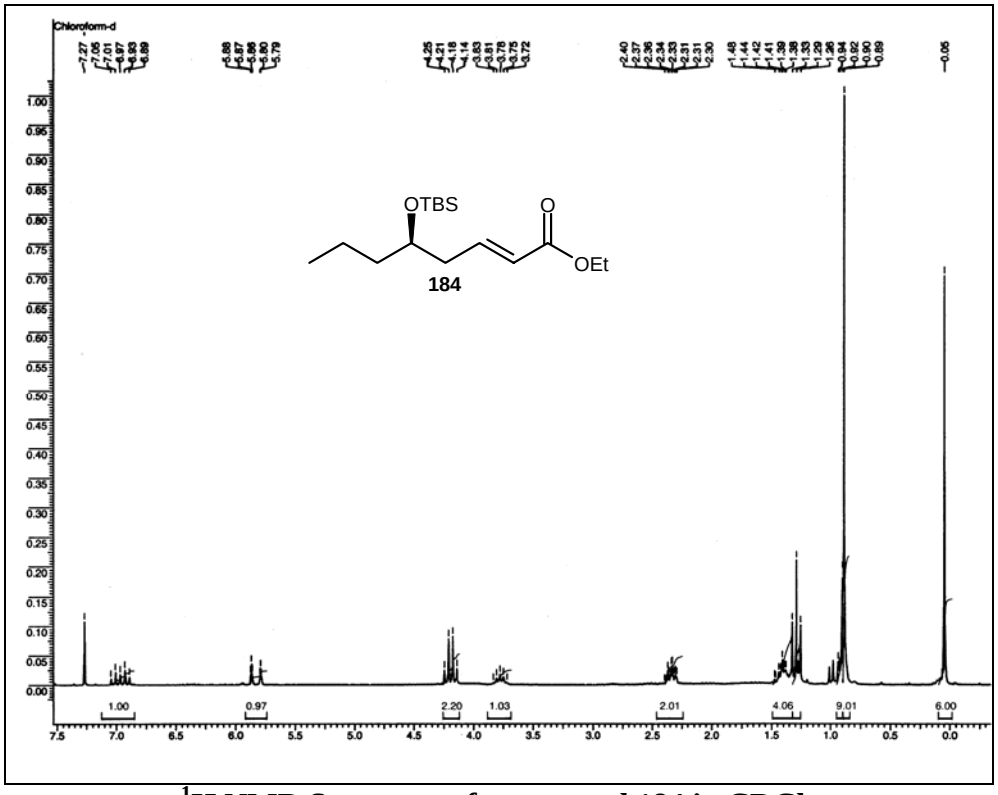
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.91 (t, 3 H, *J* = 7.4 Hz), 1.33 (m, 2 H), 1.42 (m, 1 H), 1.54 (dddd, 1 H, *J* = 13.8, 9.3, 8.6, 4.9 Hz), 1.77 (m, 1 H), 1.82 (m, 1 H), 1.84 (m, 1 H), 1.98 (m, 1 H), 1.99 (m, 1 H), 2.00 (m, 1 H), 2.28 (dd, 1 H, *J* = 6.1, 13.0 Hz), 2.37 (m, 1 H), 4.42 (t, 1 H, *J* = 2.4 Hz), 5.30 (m, 1 H) 5.46 (m, 1 H), 5.62 (d, 1 H, *J* = 16.1 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 176.7, 134.6, 124.9, 68.0, 67.8, 40.6, 37.5, 34.6, 33.7, 26.0, 18.4, 13.9.

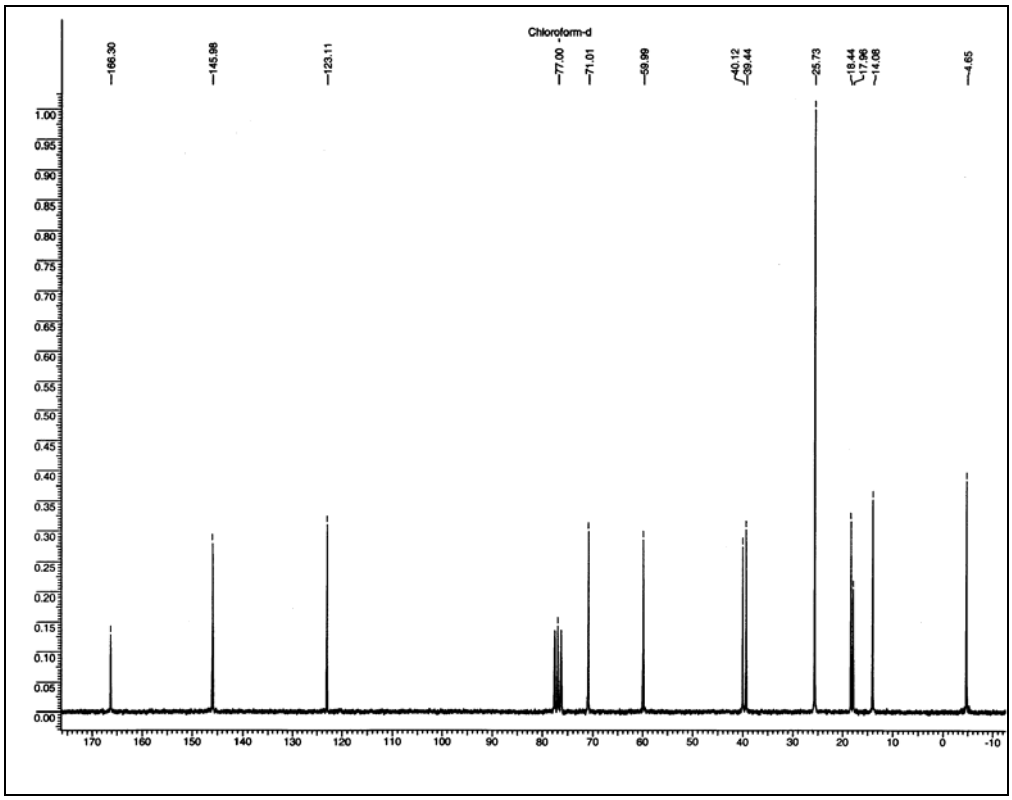
Analysis Calcd.: C, 67.89; H, 9.50%; **Found:** C, 67.75; H, 9.46%.

5.2.7 Spectra

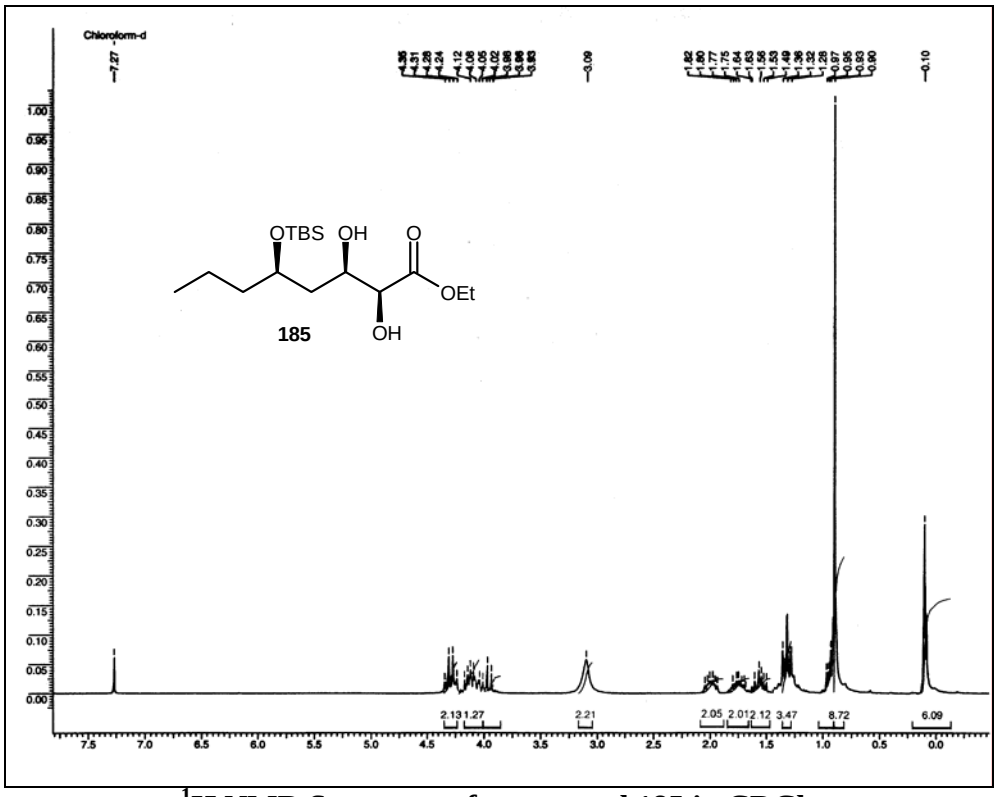
1. ^{1}H and ^{13}C NMR spectra of 184
2. ^{1}H and ^{13}C NMR spectra of 185
3. ^{1}H and ^{13}C NMR spectra of 186
4. ^{1}H and ^{13}C NMR spectra of 187
5. ^{1}H and ^{13}C NMR spectra of 188
6. ^{1}H and ^{13}C NMR spectra of 189
7. ^{1}H and ^{13}C NMR spectra of 136
8. ^{1}H and ^{13}C NMR spectra of 138
9. ^{1}H and ^{13}C NMR spectra of 127



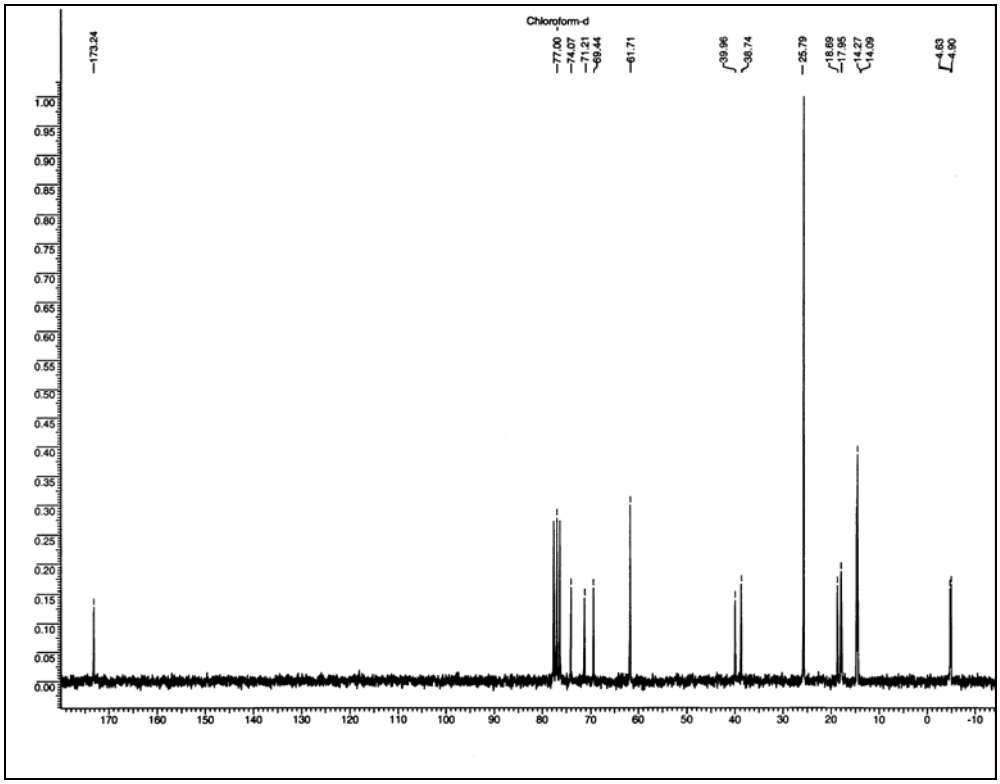
^{1}H NMR Spectrum of compound 184 in $CDCl_3$



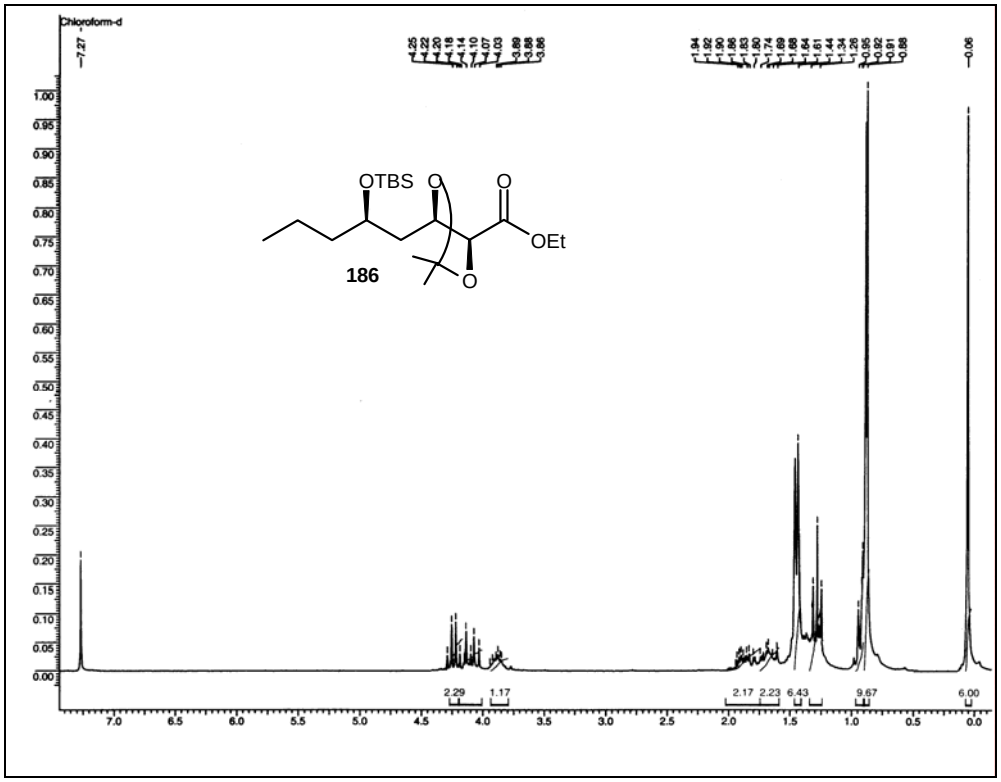
^{13}C NMR Spectrum of compound 184 in $CDCl_3$



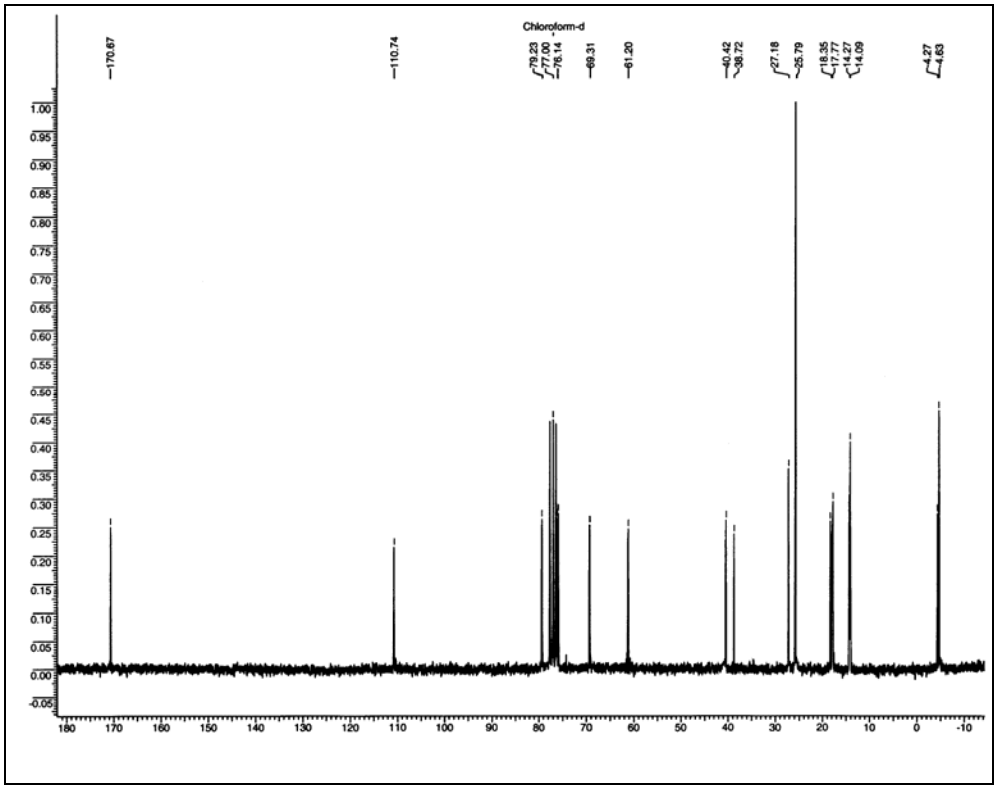
^{1}H NMR Spectrum of compound 185 in $CDCl_3$



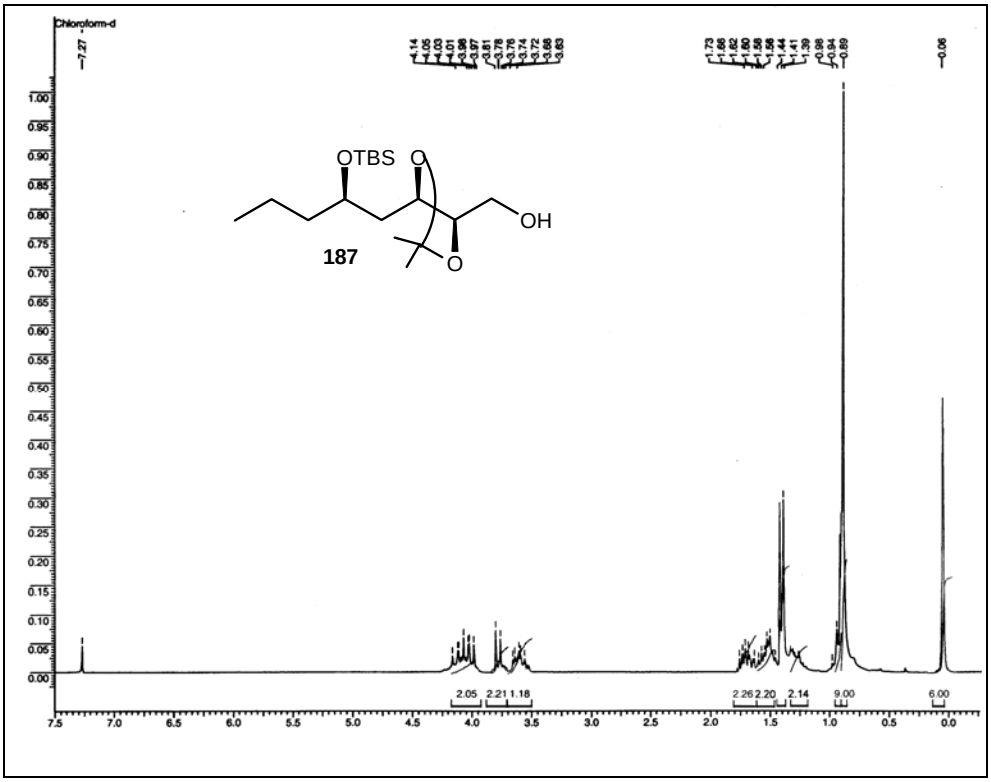
^{13}C NMR Spectrum of compound 185 in $CDCl_3$



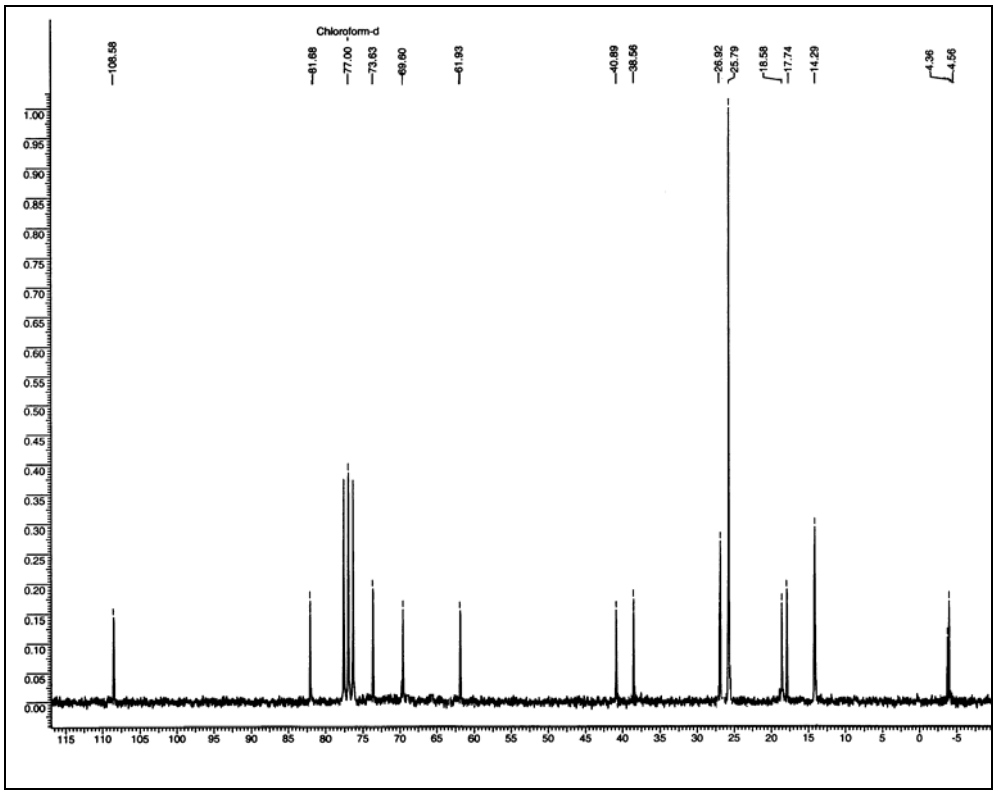
^{1}H NMR Spectrum of compound 186 in $CDCl_3$



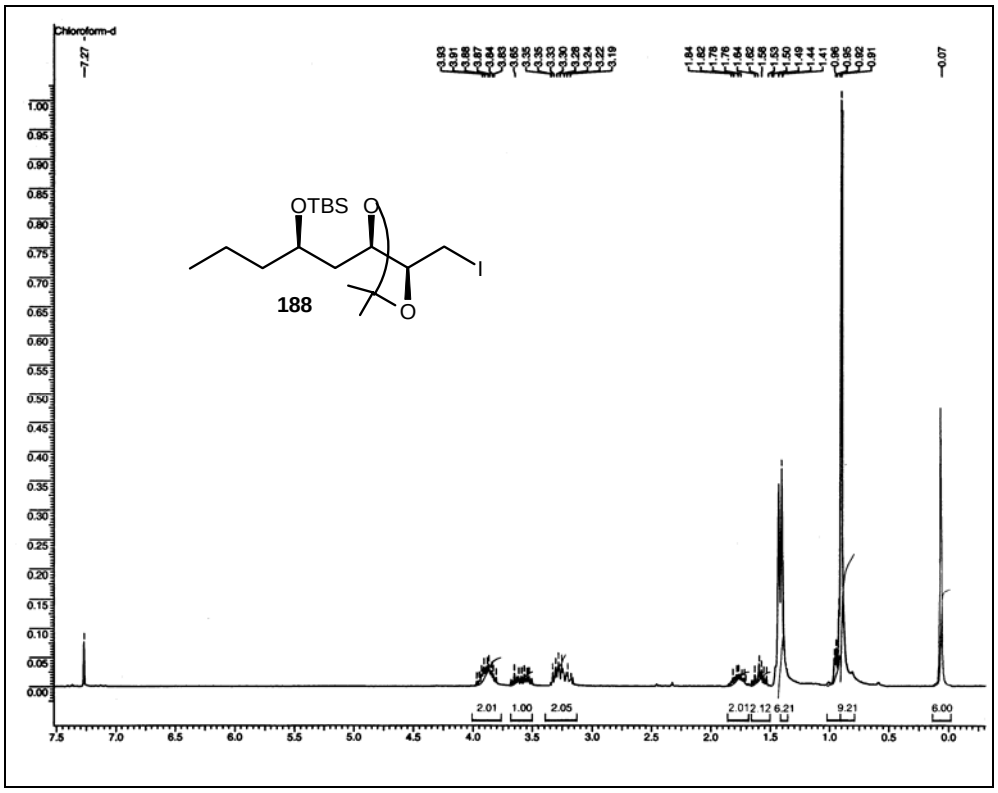
^{13}C NMR Spectrum of compound 186 in $CDCl_3$



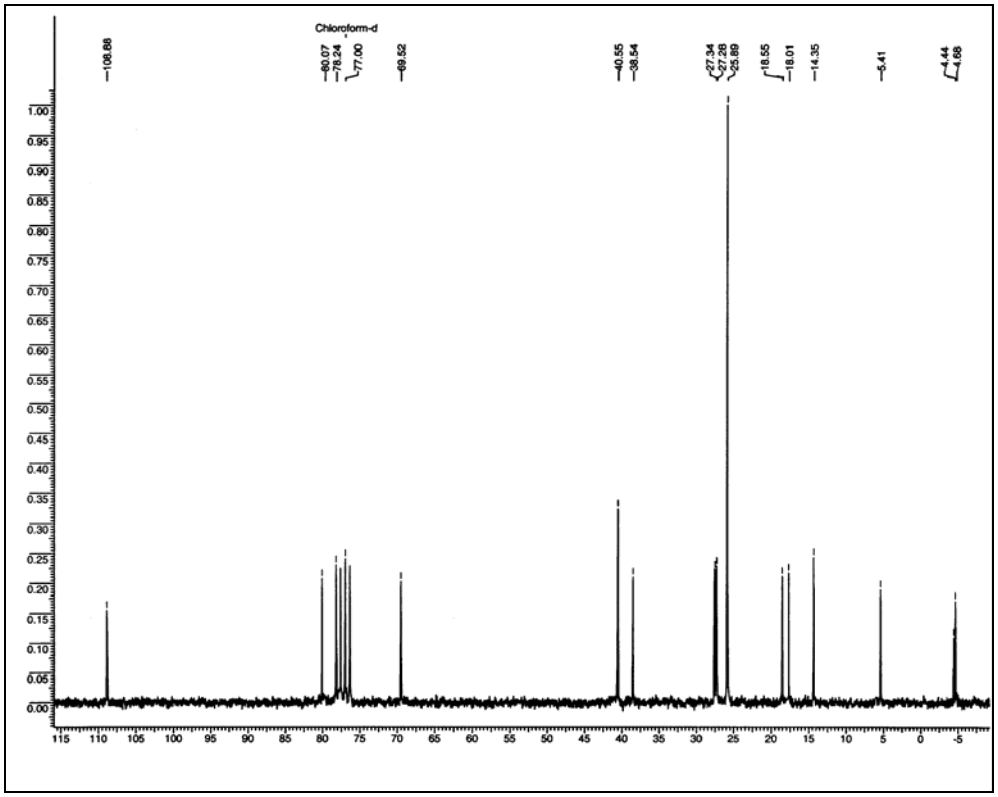
^{1}H NMR Spectrum of compound 187 in $CDCl_3$



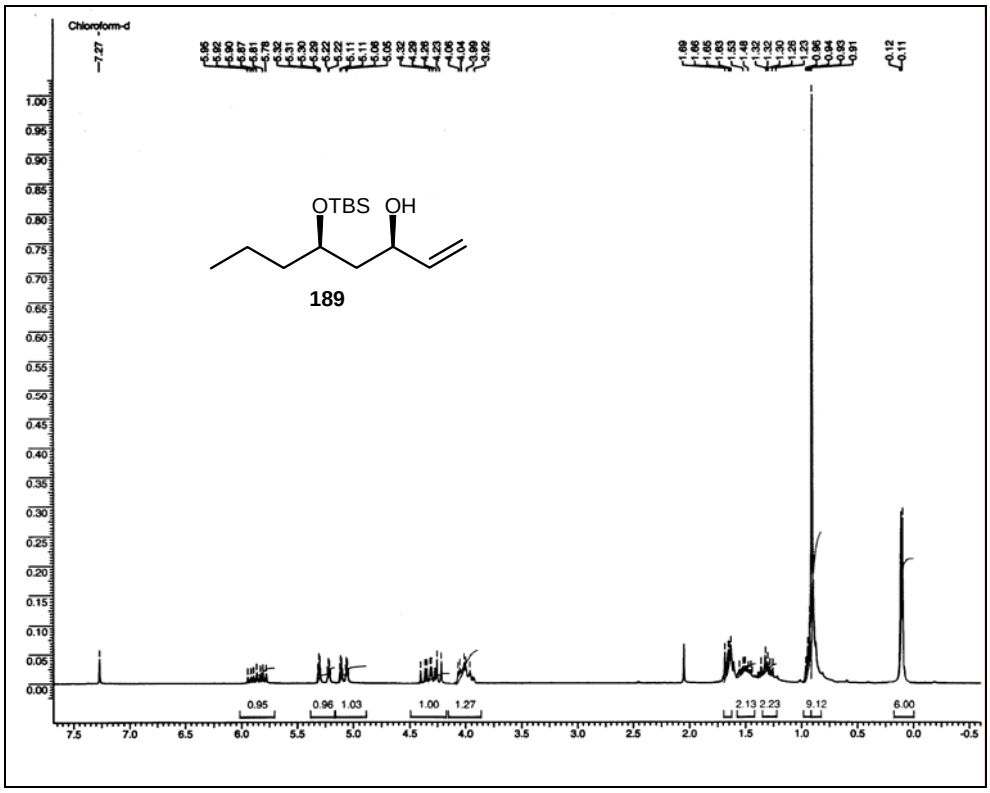
^{13}C NMR Spectrum of compound 187 in $CDCl_3$



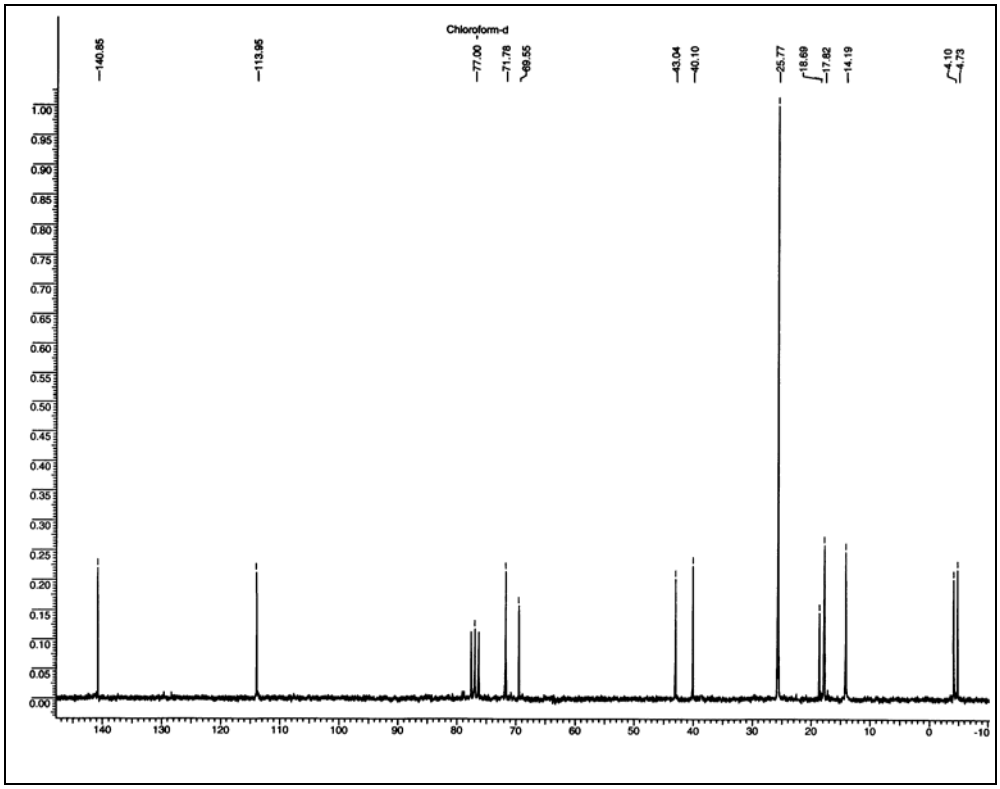
^{1}H NMR Spectrum of compound 188 in $CDCl_3$



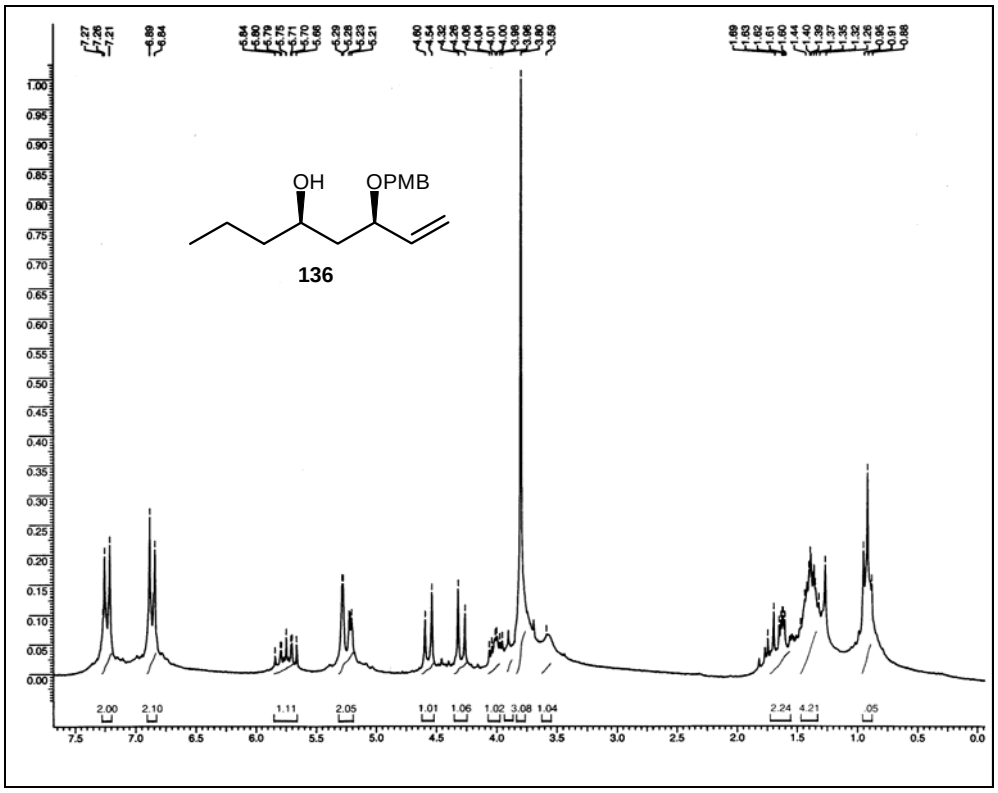
^{13}C NMR Spectrum of compound 188 in $CDCl_3$



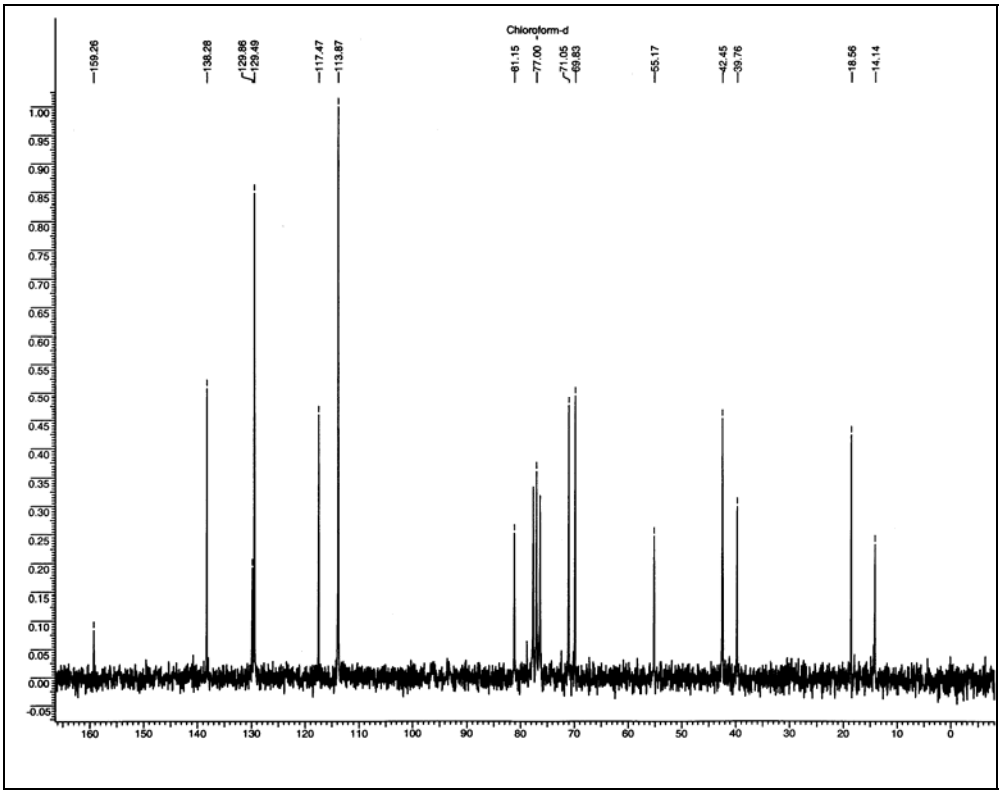
^{1}H NMR Spectrum of compound 189 in $CDCl_3$



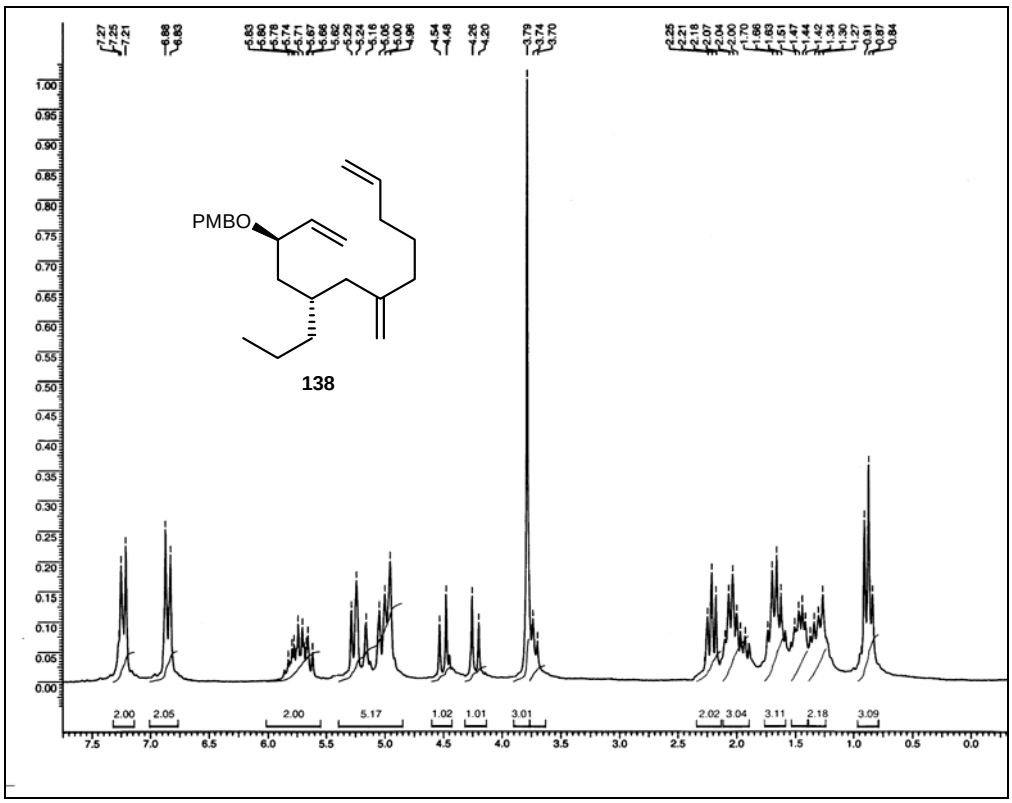
^{13}C NMR Spectrum of compound 189 in $CDCl_3$



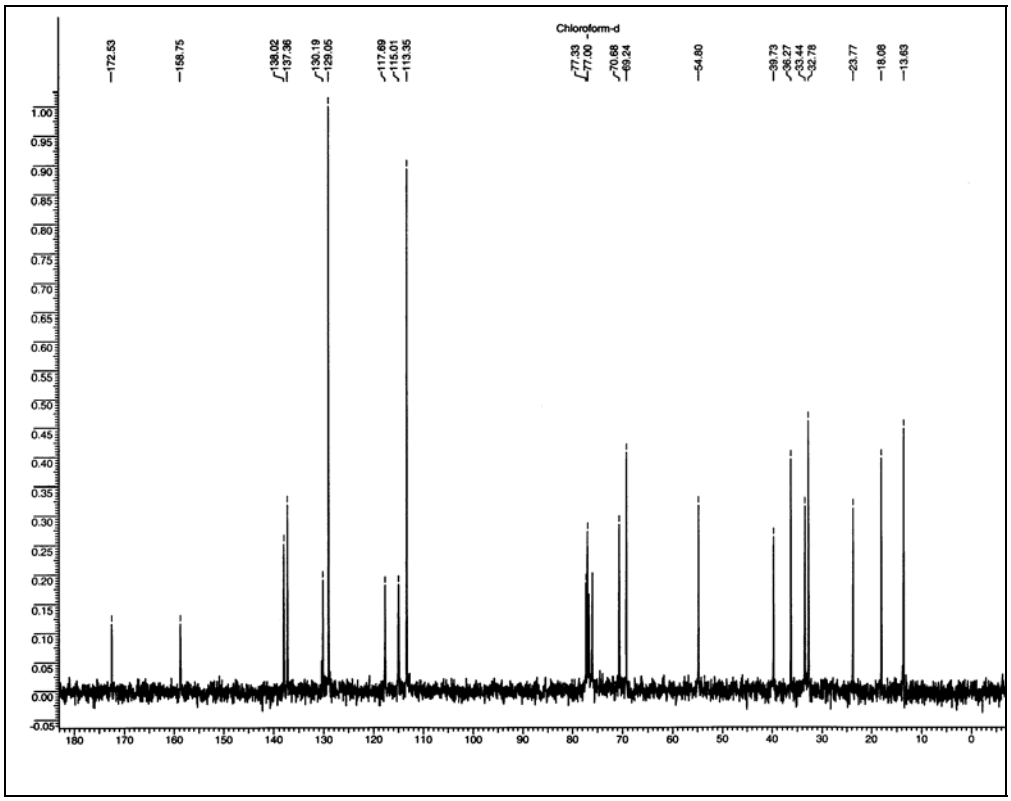
^{1}H NMR Spectrum of compound 136 in $CDCl_3$



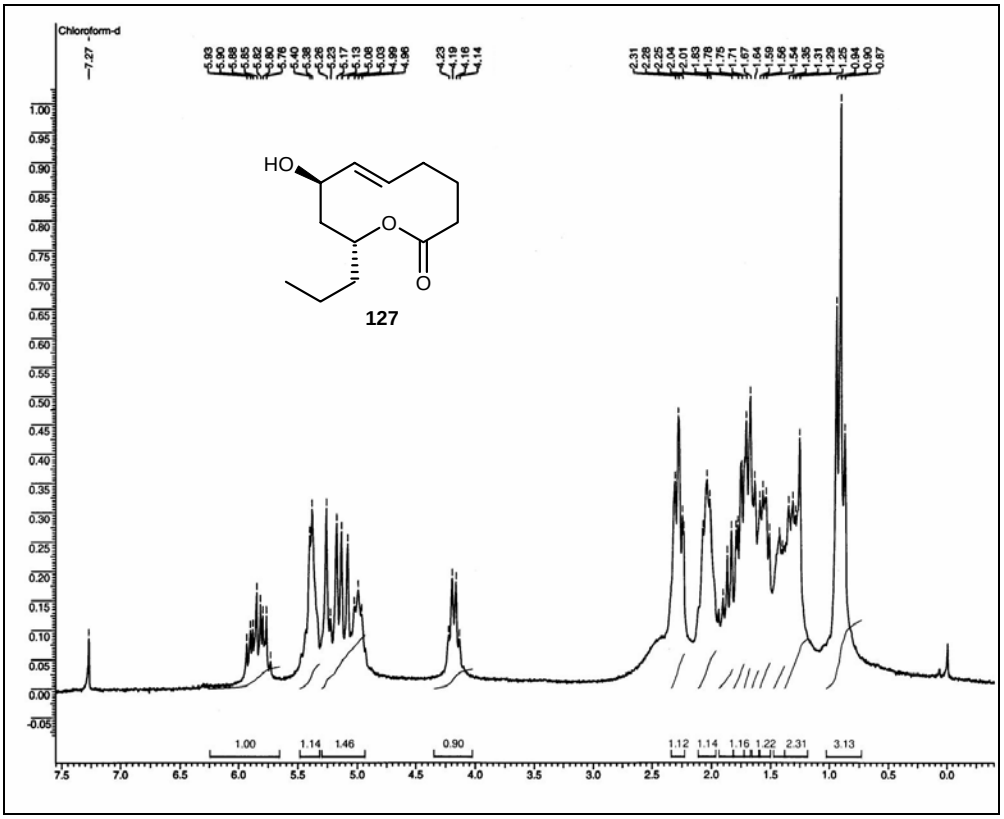
^{13}C NMR Spectrum of compound 136 in $CDCl_3$



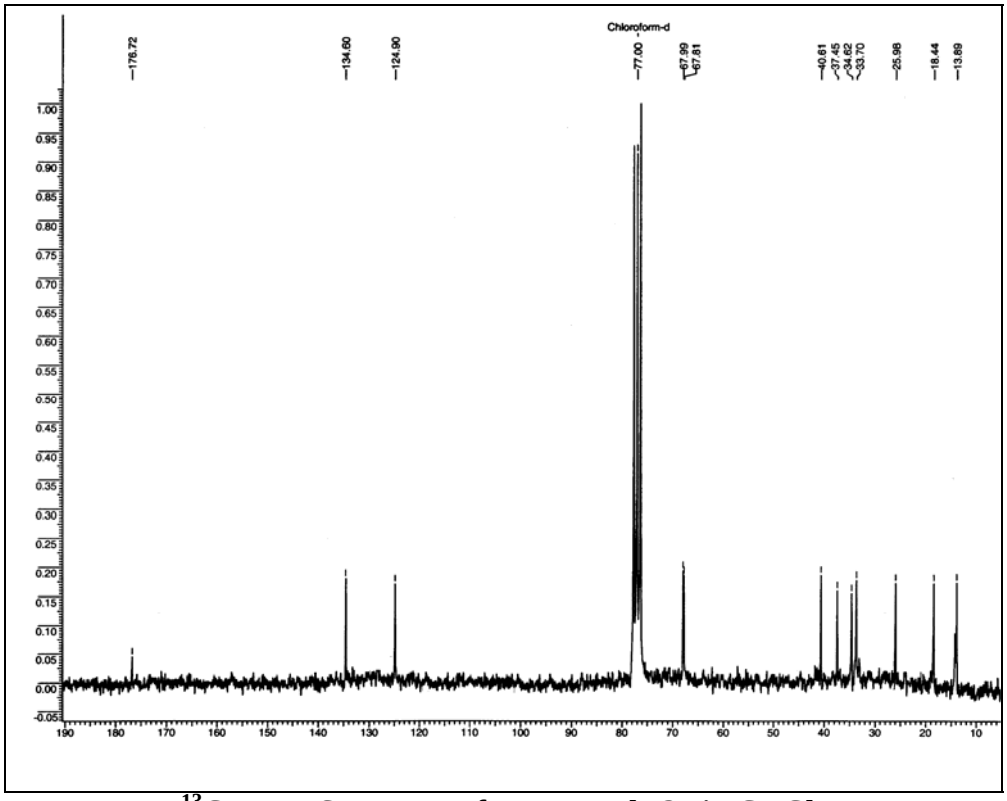
^{1}H NMR Spectrum of compound 138 in $CDCl_3$



^{13}C NMR Spectrum of compound 138 in $CDCl_3$



^{1}H NMR Spectrum of compound 127 in $CDCl_3$



^{13}C NMR Spectrum of compound 127 in $CDCl_3$

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1. An asymmetric dihydroxylation route to (*S*)-oxybutynin

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2. A practical enantioselective synthesis of massoialactone via hydrolytic kinetic resolution

   Priti Gupta, S. Vasudeva Naidu and Pradeep Kumar*

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3. An efficient total synthesis of sulfobacin A

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6. A simple and efficient approach to 1,3-polyols: Application to the synthesis of cryptocarya diacetate

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7. Enantioselective synthesis of tarchonanthuslactone via iterative hydrolytic kinetic resolution

   Priti Gupta, S. Vasudeva Naidu and Pradeep Kumar*

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8. Enantioselective syntheses of (−)-pinellic acid, α- and β-dimorphecolic acid

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9. Formal synthesis of herbarumin III

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10. An efficient total synthesis of decarestrictine D

    Priti gupta and Pradeep Kumar*

    (*Communicated*)

11. An improved process for the preparation of enantiomerically pure cyclohexylphenyl glycolic acid.

    Pradeep Kumar, Rodney, A. Fernandes and **Priti Gupta**

    US Patent 6, 825, 378. Dt of grant: 30-11-04

REVIEW:

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

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

   (*Tetrahedron* Report No. 791, *Tetrahedron* **2007**, *63*, 2745–2785.

Symposia/ Conferences Attended

1. An asymmetric synthesis of Tarchonanthuslactone and Kurzilactone by Jacobsen's hydrolytic kinetic resolution.

   Presented at NSC-5 in CLRI Chennai, India in Feb 2003.

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 enantioselective total synthesis of sulfobacin A.

   Presented at NSC-6 in IIT Kanpur, India in Feb 2004.

4. Total synthesis of biologically active molecules via Sharpless asymmetric dihydroxylation and Jacobsens hydrolytic kinetic resolution.

Participated as speaker in the Junior National Organic Symposium Trust (J-nost) , 2006, Jaipur, India.

5. Total synthesis of biologically active molecules via Sharpless asymmetric dihydroxylation and Jacobsens hydrolytic kinetic resolution.

   Invited as a speaker to participate in 11th Nost conference held at Goa (2007).