ENANTIOSELECTIVE SYNTHESIS OF AMINOALCOHOLS AND CYCLOPROPANE CONTAINING BIOACTIVE MOLECULES AND ORGANIC TRANSFORMATIONS USING PIVALOYL CHLORIDE

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BY

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CERTIFICATE

The research work presented in thesis entitled **"Enantioselective Synthesis of Aminoalcohols and Cyclopropane Containing Bioactive Molecules and Organic Transformations using Pivaloyl Chloride"** was carried out by **Mr. Abhishek Dubey** at National Chemical Laboratory, Pune under my supervision. Such materials as obtained from other sources have been duly acknowledged in the thesis.

(Dr. Pradeep Kumar)
Research Guide

October 2010

CANDIDATE'S DECLARATION

I hereby declare that the thesis entitled **"Enantioselective Synthesis of Aminoalcohols and Cyclopropane Containing Bioactive Molecules and Organic Transformations using Pivaloyl Chloride"** submitted for the degree of Doctor of Philosophy in Chemistry to the University of Pune has not been submitted by me to any other university or Institution. This work was carried out at the National Chemical Laboratory, Pune, India.

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October 2010

"All the world is a laboratory for an enquiring mind"

Martin H. Fisher

Dedicated
To
My Beloved
Family

Acknowledgment

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Curriculum Vitae

ABBREVIATIONS

Ac	-	Acetyl
AcOH	-	Acetic acid
Ac_2O	-	Acetic anhydride
AIBN	-	2,2'-Azobisisobutyronitrile
Bn	-	Benzyl
BnBr	-	Benzyl bromide
$BH_3 \cdot Me_2S$	-	Boron dimethyl sulfide complex
Boc	-	*tert*-Butoxy carbonyl
$(Boc)_2O$	-	Di-*tert*-butyl dicarbonate
BuLi	-	Butyl lithium
DCM	-	Dichloromethane
DDQ	-	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
de	-	Diastereomeric excess
ds	-	Diastereoselectivity
DIBAL-H	-	Diisobutylaluminium hydride
DHP	-	Dihydropyran
$(DHQ)_2PHAL$	-	1,4-Bis(dihydroquinin-9-*O*-yl)phthalazine
DIPT	-	Diisopropyl tartrate
DMP	-	Dess–Martin periodinane
DMP	-	2,2-Dimethoxypropane
DMF	-	*N, N'*-Dimethylformamide
DMAP	-	*N,N'*-Dimethylaminopyridine
DMSO	-	Dimethyl sulfoxide
ee	-	Enantiomeric excess
eq. or equiv	-	Equivalents
EtOH	-	Ethanol
Et	-	Ethyl
Et_2O	-	Diethyl ether
EtOAc	-	Ethyl acetate
Et_3N	-	Triethylamine
h	-	Hours
Hz	-	Hertz

IBX	-	Iodoxybenzoic Acid
Im	-	Imidazole
i-Pr	-	Isopropyl
IR	-	Infrared
LDA	-	Lithium diisopropylamide
m-CPBA	-	*m*-Chloroperbenzoic acid
MeOH	-	Methanol
MsCl	-	Methanesulfonyl chloride
Ms	-	Methanesulfonyl
Me	-	Methyl
MeI	-	Methyl iodide
$NaBH_4$	-	Sodiumborohydride
NaH	-	Sodium hydride
Ph	-	Phenyl
Py	-	Pyridine
p-TSA	-	*para*-Toluenesulfonic acid
TEA	-	Triethylamine
TBAI	-	Tetra-*n*-butylammonium iodide
TBAF	-	Tetra-*n*-butylammonium fluoride
TBDMSCl	-	*tert*-Butyldimethyl chlorosilane
TBDMS	-	*tert*-Butyldimethylsilyl
TBDMS	-	*tert*-Butyldimethylsilyl
TBHP	-	*tert*-Butylhydroperoxide
THF	-	Tetrahydrofuran
TPP	-	Triphenylphosphine
*P*TSA	-	*p*-Toluenesulphonic acid
TsCl	-	*p*-Toluenesulphonyl chloride
$Ti(OPr^i)_4$	-	Titanium tetra isopropoxide
TEPA	-	Triethylphosphonoacetate

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 Finnigan MAT-1020 spectrometer at 70 *eV* using a direct inlet system.
- Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm^{-1}.
- Optical rotations were measured with a JASCO DIP 370 digital polarimeter.
- Melting points were recorded on Buchi 535 melting point apparatus and are uncorrected.
- All reactions are monitored by Thin Layer chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F-254) with UV light, I_2 and anisaldehyde in ethanol as development reagents.
- All solvents and reagents were purified and dried by according to procedures given in Vogel's Text Book of Practical Organic Chemistry. All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.
- All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 40 °C.
- Silica gel (60–120, 100-200 and 230-400) used for column chromatography was purchased from ACME Chemical Company, Mumbai, India.
- The compounds, scheme and reference numbers given in each section of chapter refers to that particular section of the chapter only.

ABSTRACT

The thesis entitled **"Enantioselective Synthesis of Aminoalcohols and Cyclopropane Containing Bioactive Molecules and Organic Transformations using Pivaloyl Chloride"** is divided into five chapters.

Chapter 1: Introduction to Sharpless Asymmetric Epoxidation, Aminohydroxylation, Tethered Aminohydroxylation and Jacobsen's Hydrolytic Kinetic resolution

Chapter 2: Tethered Aminohydroxylation Approach to the Syntheses of L-*threo*-Sphingosine, L-*threo*-Sphinganine (Safingol), L-*arabino*- and L-*xylo*-C_{18}-Phytosphingosine

Chapter 3: Studies Towards Enantioselective Synthesis of (-)-Galantinic Acid via Asymmetric and Chiral Pool Approach

Chapter 4: An Wadsworth-Emmons Approach Towards Synthesis of Cascarillic acid, Grenadamide and L-CCG-II

Chapter 5: Pivaloyl Chloride Mediated Transformation of Alcohols into Chlorides and Carbonyls

Chapter 1: Introduction to Sharpless Asymmetric Epoxidation, Aminohydroxylation, Tethered Aminohydroxylation and Jacobsen's Hydrolytic Kinetic resolution

This chapter gives a brief introduction to Sharpless asymmetric epoxidation (AE),[1] asymmetric aminohydroxylation (AA),[2] tethered aminohydroxylation[3] and Jacobsen's hydrolytic kinetic resolution (HKR).[4] Catalytic asymmetric reactions provide an especially practical entry into the chiral world due to their economical use of asymmetric inducing agents. Especially useful is the carbon-hetero atom bond forming reactions, since resulting functionality can be readily manipulated to produce many important classes of compounds.

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 aminohydroxylation (AA) in 1995, bagged him the 'Nobel Prize' (in part) in chemistry (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 gives 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 amino alcohols and epoxides either through chiral approach or asymmetric catalytic procedures and successfully employed these synthetic intermediate towards the synthesis of L-*threo*-sphingosine, L-*threo*-sphinganine (safingol), L-*arabino*-C_{18}-phytosphingosine, L-*xylo*-C_{18}-phytosphingosine, (-)-galantinic acid, casca- rillaic acid, grenadamide and CCG-II.

Chapter 2: Tethered Aminohydroxylation Approach to the Syntheses of L-*threo*-Sphingosine, L-*threo*-Sphinganine (Safingol), L-*arabino*-C_{18}-Phytosphingosine and L-*xylo*-C_{18}-Phytosphingosine

Sphingolipids are structurally diverse constituents of membranes in mammals, plants, fungi, yeast and in some prokaryotic organism and viruses.[6] Sphingolipids and some of their metabolites exhibit essentially all type of cell regulation such as cell proliferation,

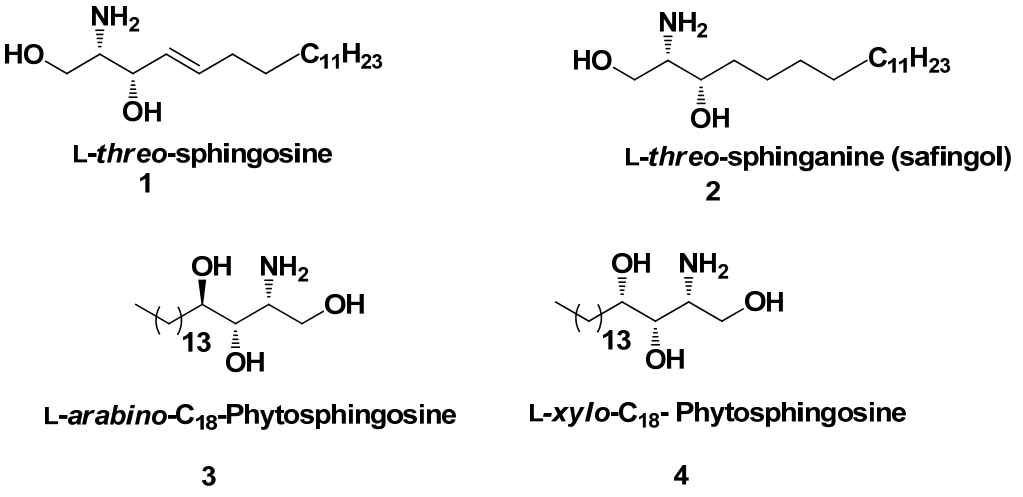


Fig. 1

differentiation, immune response, cell recognition, apoptosis, adhesion and signal transduction.[7] Studies have shown that defects in sphingolipid metabolism lead to several inherited and most common human diseases including diabetes,[8] cancers,[9] infection by microorganisms,[10] Alzheimer's disease,[11] heart disease and an array of neurological

syndromes.[12] Sphingosine[13] are known inhibitors of protein kinase C[14] and they are backbone of glycosphingolipids and phosphosphingolipids. This chapter summarizes our studies on the asymmetric syntheses of L-*threo*-sphingosine **1**, L-*threo*-sphinganine (safingol) **2**, L-*arabino*-C_{18}-phytosphingosine **3** and L-*xylo*-C_{18}-phytosphingosine **4** (**Fig. 1**).

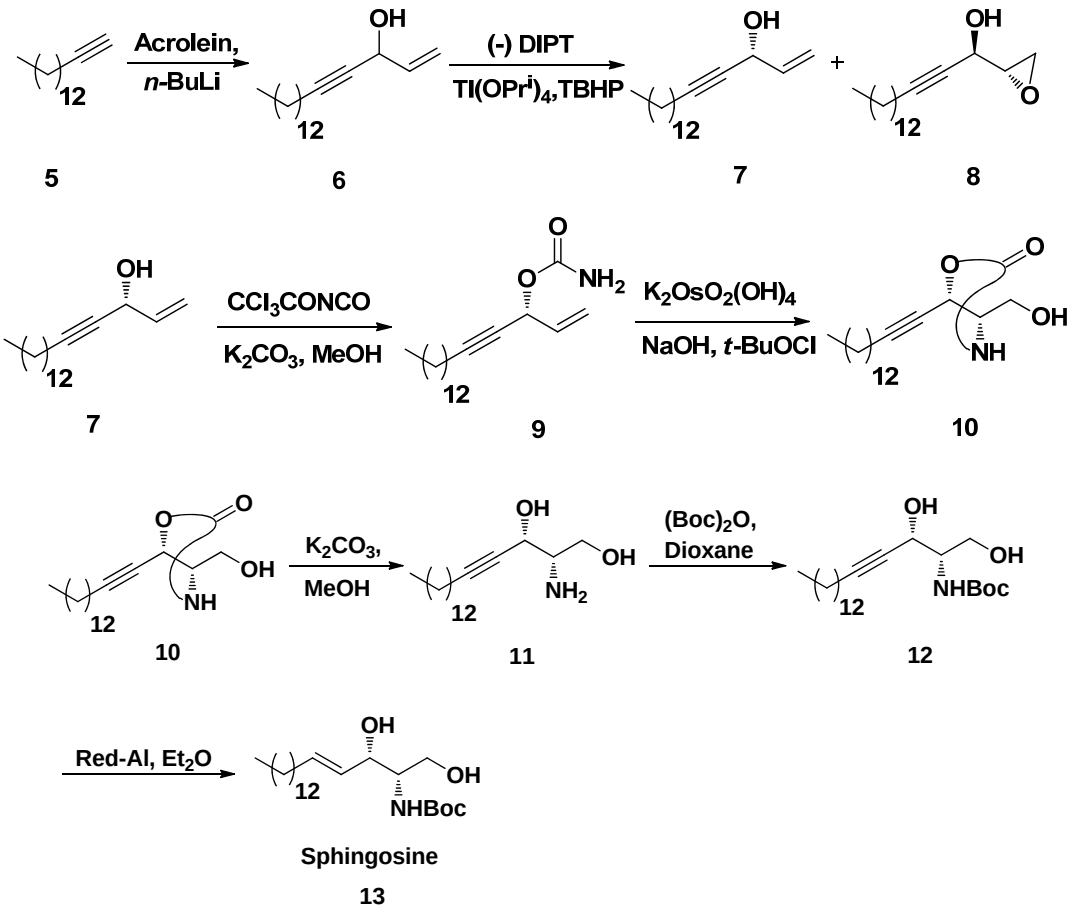
This chapter is further divided into four sections.

Section A: 1,2-Aminoalcohols

The vicinal amino alcohol[5] functionality is the key structural feature in a variety of bioactive molecules. In this section we have discussed different types of 1,2-aminoalcohols their sources and common methods used for their synthesis.

Section B: Enantioselective Synthesis of L-*threo*-Sphingosine

In the strategy employed towards the synthesis of L-*threo*-sphingosine **1**, the amino center was installed using tethered aminohydroxylation[3] in a highly regio-and stereoselective manner while the hydroxyl centre was derived from Sharpless kinetic resolution.[1] The Sharpless kinetic resolution of **6** using (-)-DIPT gave the required chiral hydroxy olefin **7**



Scheme 1: Synthesis of L-*threo*-sphingosine

in excellent enantioselectivity which was subsequently treated with trichloroacetyl isocyanate to produce the carbamate **9**. Tethered aminohydroxylation of **9** gave **10** in good yield and excellent diastereoselectivity (**Scheme 1**). Treatment with base furnished **11**.

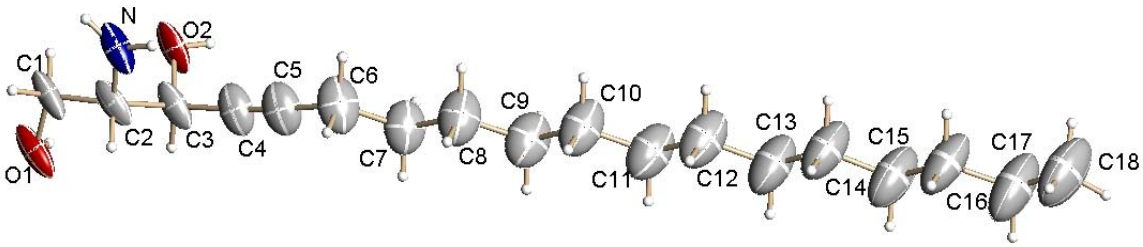
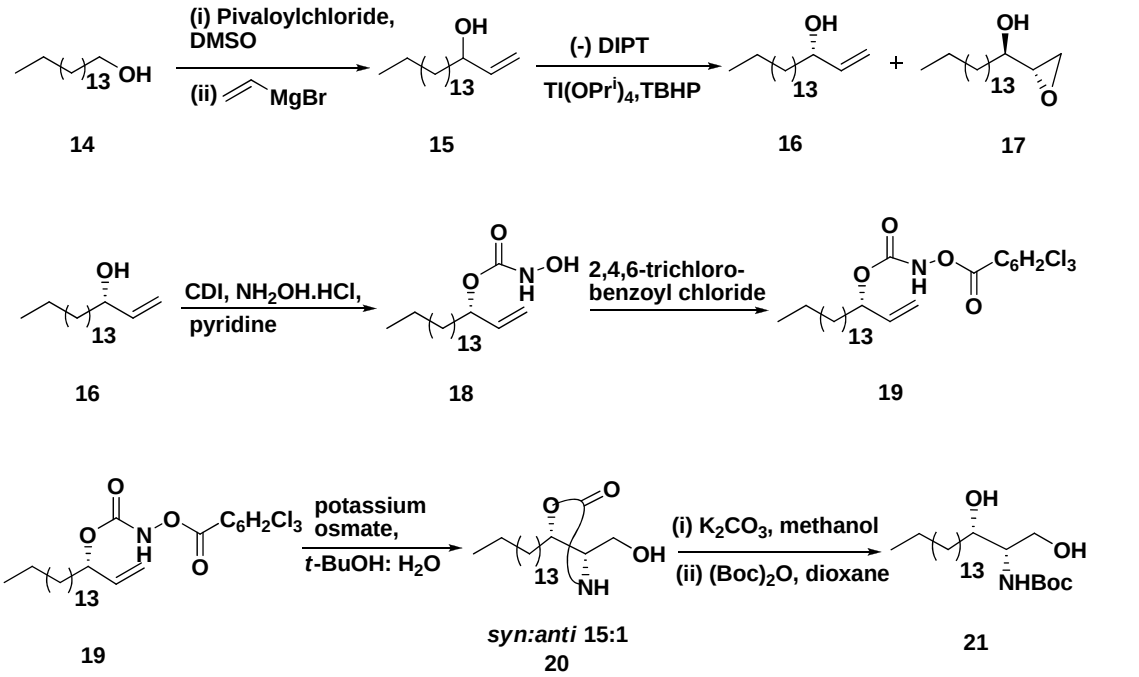


Fig. 2 ORTEP diagram of **11**

The syn relative stereochemistry of newely generated amino center and alcohol was confirmed by single crystal X-ray crystallography of **11** (**Fig. 2**). Compound **11** was converted to the target molecule sphingosine as its *N*-Boc-derivative **13** by Boc protection of amine **12** followed by reduction of alkyne into alkene.

Section C: Enantioselective Synthesis of L-*threo*-Sphinganine

L-*threo*-Dihydrosphingosine (safingol) **2** is of particular interest due to its medicinal importance. Safingol is an antineoplastic, antipsoriatic drug[15] and an inhibitor of protein kinase C (PKC)[16] and is known to act synergistically with anti-cancer drugs.[17] The



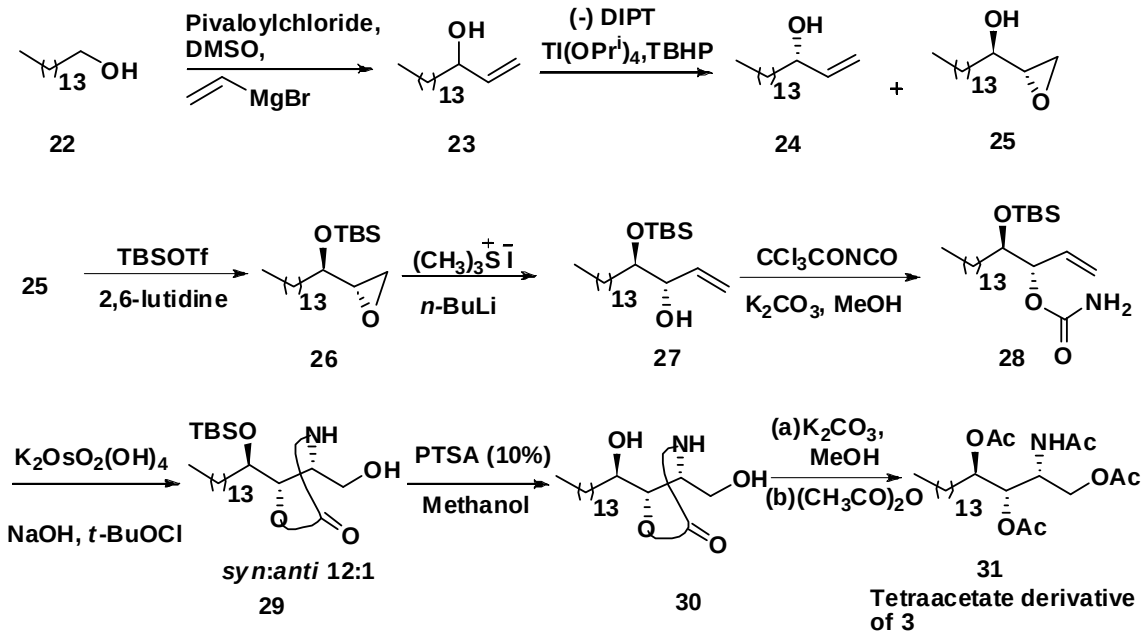
Scheme 2: Synthesis of L-*threo*-sphinganine

Sharpless kinetic resolution of **15** using (-)-DIPT gave the required chiral hydroxy olefin **16** in excellent enantioselectivity which was subsequently treated with CDI and hydroxyl amine hydrochloride to produce the hydroxylamine carbamate **18**. The carbamate **18** was then converted into trichlorobenzoyl *O*-derivatized hydroxycarbamate **19**. Tethered aminohydroxylation of **19** gave **20** in good diastereoselectivity which was converted to the target molecule sphinganine as its *N*-Boc protected derivative **21** (**Scheme 2**).

Section D: Enantioselective Synthesis of L-*arabino*-C_{18}-Phytosphingosine and L-*xylo*-C_{18}-Phytosphingosine

Phytosphingosine[6] exists in nature as one of the molecular species of sphingolipids in microorganisms, plants and many mammalian tissues such as brain, hair, intestine, uterus, liver, skin, kidney, and in blood plasma. Phytosphingosine is a potential heat stress signal in yeast cells and some of its derivatives exhibit important physiological activity. α- and β-Galactosyl and glucosylphytoceramides are highly potent against tumors.

Sharpless asymmetric kinetic resolution[1] of **23** using (-)-DIPT gave the required epoxy alcohol **25** and chiral allylic alcohol **24** in excellent enantioselectivity. The advantage of this method is that we have utilized both chiral allylic alcohol **24** and epoxy alcohol **25** for the synthesis of L-*xylo*-C_{18}-phytosphingosine **4** and L-*arabino*-C_{18}-phytosphingosine **3**, respectively.

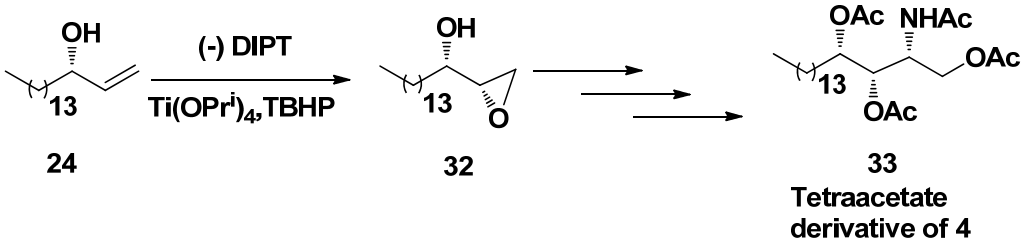


Scheme 3: Synthesis of L-*arabino*-C_{18}-phytosphingosine

TBS protection of epoxy alcohol **25** followed by epoxide opening with dimethylsulfonium methylide[18] furnished allylic alcohol **27** which was then further subjected to treatment with

trichloroacetylisocyanate to give the carbamate **28**. Tethered aminohydroxylation of **28** furnished **29** in good diastereoselectivity which was subsequently converted to the tetraacetate derivative **31** of L-*arabino*-C_{18}-phytosphingosine **3** by desilylation followed by basic hydrolysis of carbamate and acetylation (**Scheme 3**).

For the synthesis of L-*xylo*-C_{18}-phytosphingosine **4** (**Scheme 4**), the allylic alcohol **24** obtained by the chiral resolution of **23** was subjected to Sharpless asymmetric epoxidation to give the epoxide **32** as a single diastereomer, which was converted into the tetraacetate derivative **33** of L-*xylo*-C_{18}-phytosphingosine **4** following the same sequence of reactions as described for **3** (**Scheme 3**).



Scheme 4: Synthesis of L-*xylo*-C_{18}-phytosphingosine

Chapter 3: **Studies Towards Enantioselective Synthesis of (-)-Galantinic Acid via Asymmetric and Chiral Pool Approach**

(-)-Galantinic acid **34**, a nonproteinogenic amino acid, is a key component of the peptide antibiotic galantin I, isolated from a culture broth of *Bacillus pulvifaciens*.[19] Galantinic acid has attracted the attention of synthetic chemists due to its potent antibacterial biological activity and its impressive array of functionalities in C_7 frame work.

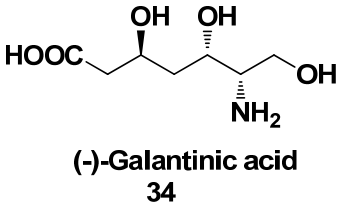
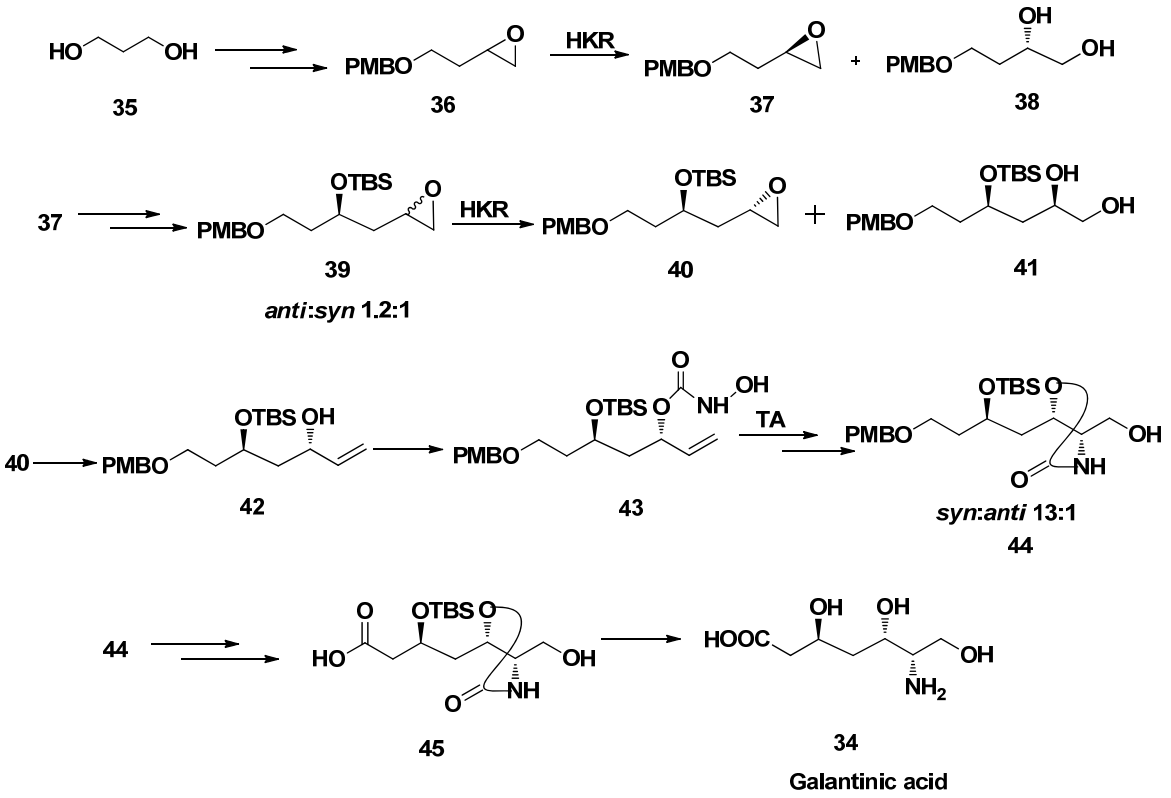


Fig. 3

We have developed an asymmetric and also a chiral pool approach for the enantioselective synthesis of (-)-Galantinic acid. This chapter is further divided into two sections.

Section A: Synthesis of (-)-Galantinic acid via Iterative Hydrolytic Kinetic Resolution and Tethered Aminohydroxylation

We have devised a new route to (-)-galantinic acid which is based on synthetic protocol developed by us for 1,3-diol[20] using hydrolytic kinetic resolution (HKR) and also by tethered aminohydroxylation (TA). The synthesis of (-)-galantinic acid **34** started from commercially available 1,3-propanediol **35** as illustrated in **Scheme 5**. Thus selective mono hydroxy protection followed by Swern oxidation of alcohol and subsequent conversion of aldehyde into epoxide by Corey–Chaykovsky reaction[21] gave the epoxide **36**. Epoxide **36** was subjected to Jacobsen HKR using (*R*,*R*)-Salen-Co^{III}-OAc complex as a



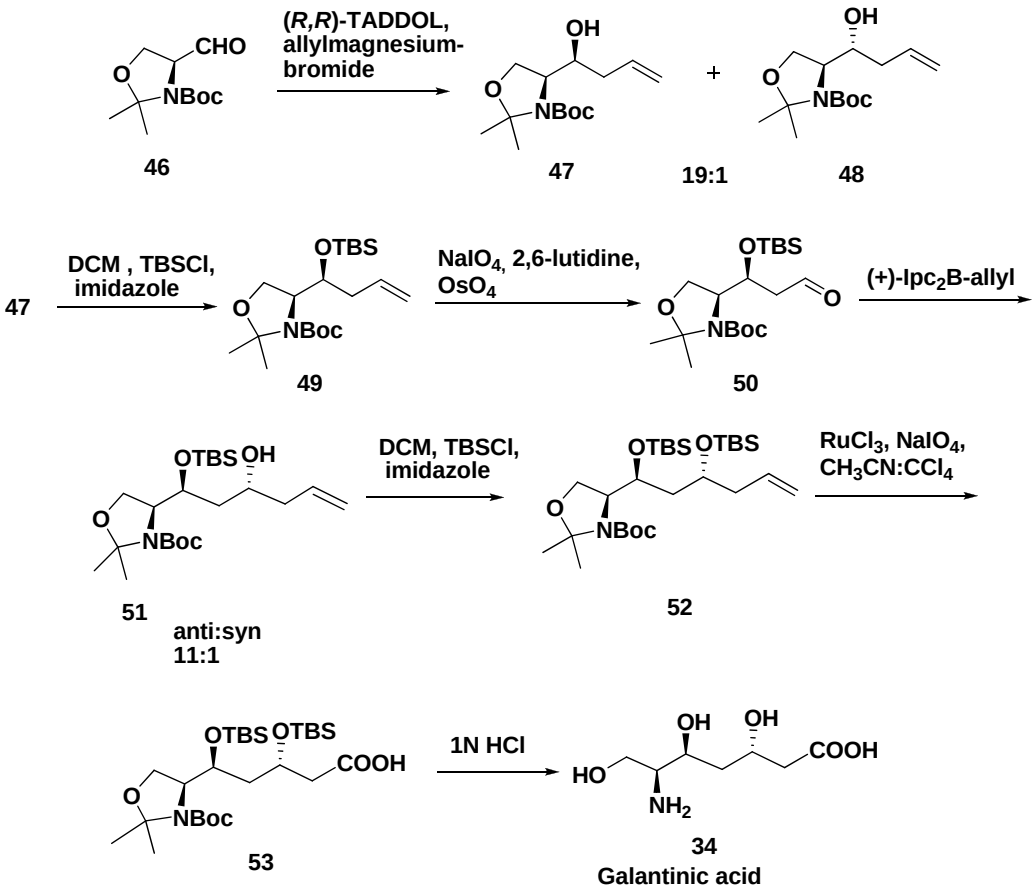
Scheme 5: Synthesis of (-)-galantinic acid

catalyst to give the enantiopure epoxide **37**. With enantiomerically pure epoxide in hand our next aim was to construct the 1,3-*anti*-diol. Thus epoxide **37** was treated with vinylmagnesium bromide in the presence of CuI to give the homoallylic alcohol. The hydroxyl group was protected as TBS ether followed by epoxidation with *m*-CPBA to give **39**. The epoxide **39** was found to be a mixture of two diastereomers (*anti*:*syn* 1.2:1). To construct the diastereomerically pure epoxide by means of Jacobsen HKR, the epoxide **39** was treated with (*S*,*S*)-Salen-Co^{III}-OAc complex to afford the epoxide **40** as a single diastereomer. Epoxide **40** was treated with dimethylsulfonium methylide to furnish the allylic

alcohol **42**. Alcohol **42** was converted into hydroxylamine **43** followed by reaction with 2,4,6-trichlorobenzoyl chloride and subjected to tethered aminohydroxylation under modified and optimized reaction conditions to furnish the amino alcohol **44** with complete regio- and good diastereoselectivity (*syn*:*anti* 13:1). With required framework in hand our next task was to protect the newly generated alcohol with TBS followed by PMB group removal by DDQ to afford the alcohol, which was oxidized to the aldehyde using Swern oxidation conditions followed by subsequent oxidation using $NaClO_2$ to give the desired acid **45**. This was further subjected to hydrolysis with K_2CO_3 in methanol to furnish the crude aminoalcohol. Subsequent acidification by 2N HCl produced (-)-galantinic acid **34**. The overall yield of the target compound **36** was found to be 1.5% from fifteen steps.

Section B: Synthesis of (-)-Galantinic acid via Chiral Pool Approach

In the chiral pool approach toward the synthesis of galantinic acid **34**, Garner's aldehyde

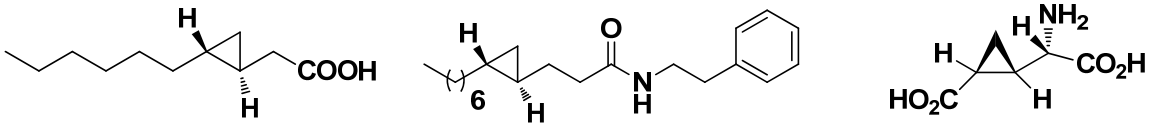


Scheme 6: Synthesis of (-)-galantinic acid

46 was used as the starting material which can be easily accessed from L-serine. Chiral allylation[22a] of **46** using TADDOL, allylmagnesium bromide, gave 19:1 ratio of *syn* **47** and *anti* **48** diastereomers which were separated by column chromatography. Protection of alcohol **47** by TBSCl to furnish **49** followed by chopping of the olefin **49** using $NaIO_4$ in dioxane and water (3:1) gave the aldehyde **50**. Compound **50** was subjected to asymmetric allylation[22b] to give the homoallylic alcohol **51** in *anti*:*syn* ratio (11:1). Subsequent TBS protection of newly generated alcohol followed by oxidation of olefin into acid produced **53**. The global deprotection under mild acidic conditions furnished (-)-galantinic acid **34** (**Scheme 6**).

Chapter 4: An Wadsworth-Emmons Approach Towards Synthesis of Cascarillic acid, Grenadamide and L-CCG-II

Cyclopropane ring systems are ubiquitous in nature and are contained in a large number of natural products, insecticides, and pharmaceutical drug candidates.[23] Wadsworth-Emmons cyclopropanation[24] has been known for over four decades but this reaction has rarely been exploited in synthesis. However, the utility of this reaction for the total synthesis is occasionally reported due to poor yield and stereospecificity of the reaction. We have developed a modified high yielding and high enantioselectivity reaction conditions for the construction of cyclopropane ring system, which was further employed in the synthesis of cascarillic acid **54**, grenadamide **55** and L-CCG-II **56** (**Fig. 4**). This chapter is further divided into two sections.



Cascarillic acid
54

Grenadamide
55

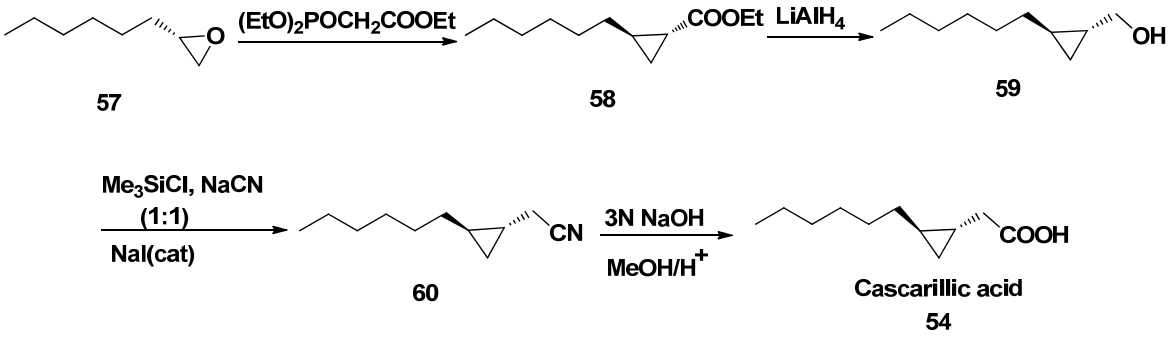
L-CCG-II
56

Fig. 4

Section A: Studies Towards the Total Synthesis of Cascarillic acid and Grenadamide

Cascarillic acid[27] was isolated from bark of the medicinal shrubs *Croton eluteria* L. The oil has been used for many years to treat the symptoms of colds and influenza as well as respiratory ailments including bronchitis. The synthesis of cascarillic acid **54** (**Scheme 7**) started from commercially available C_8-epoxide **57**. Epoxide was subjected under Wadsworth

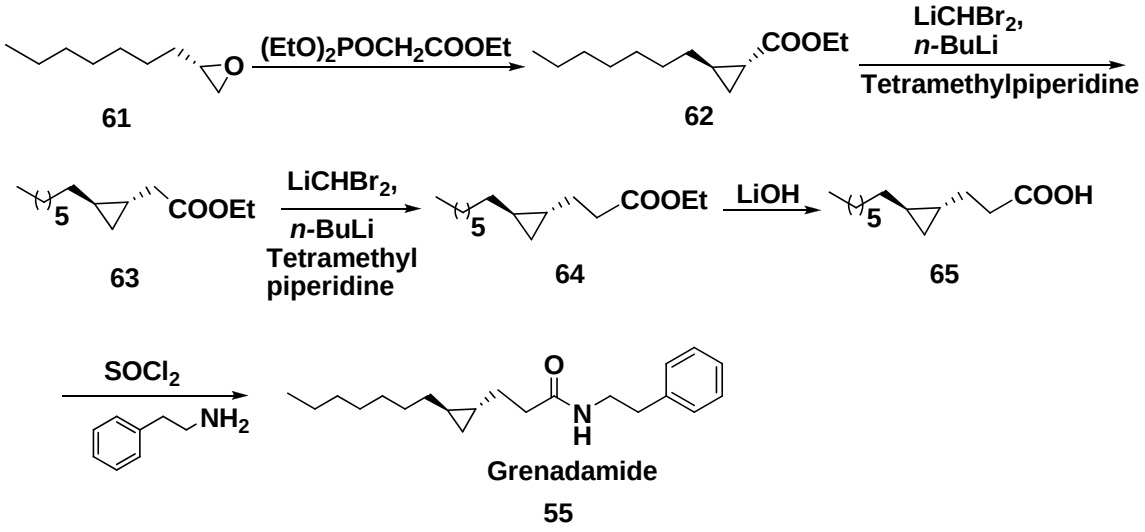
Emmons cycloproponation to provide **58** in excellent yield and in >95% ee. Compound **58** was then subjected to reduction to produce alcohol **59** followed by its conversion into the cyano compound **60**. Subsequent hydrolysis furnished Cascarillic acid **54**.



Scheme 7: Synthesis of cascarillic acid

Grenadamide[28] **55** is isolated from the marine cyanobacterium *Lyngbya majuscula*, by Sitachitta and Gerwick in 1998. This structurally unique cyclopropyl fatty acid derived metabolites were shown to demonstrate cannabinoid receptor binding activity, as well as cytotoxicity towards cancer cells. The hydrolytic kinetic resolution and Wadsworth Emmons cyclopropantion protocol is used as key steps in the synthesis.

The synthesis of grenadamide (**Scheme 8**) started from commercially available C_9-epoxide **61**. Epoxide **61** was subjected to Wadsworth Emmons cyclopropanation to provide cyclopropane derivative **62** in excellent yield and 98% ee. The double ester homologation



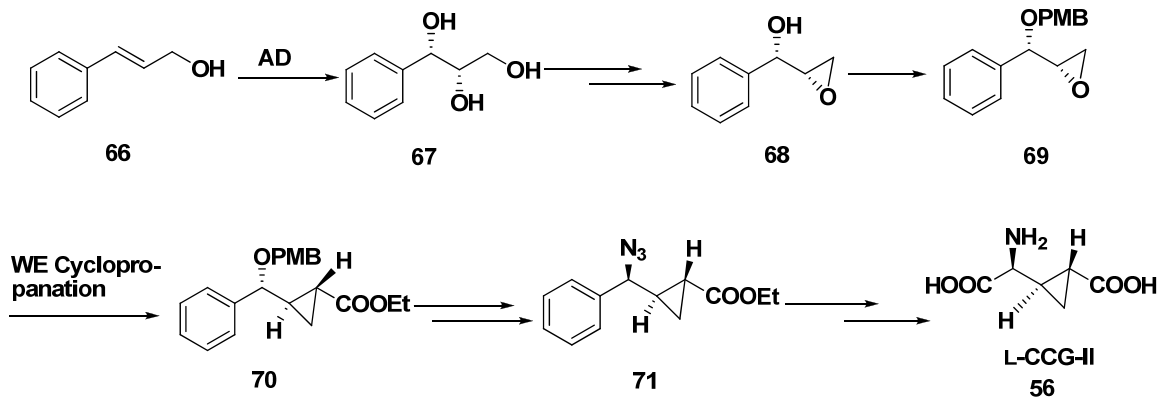
Scheme 8: Synthesis of grenadamide

furnished **64** in moderate yield. Subsequent ester hydrolysis followed by coupling with phenylethyl amine gave grenadamide **55**.

Section B: Studies Towards the Total Synthesis of L-CCG-II

L-Glutamic acid is known to function as an major excitatory neurotransmitter in the mammalian central nervous system. It plays a crucial role in the construction of memory and early learnings. L-CCG-II **56** is conformationally constrained form L-glutamic acid and found to agonist behavior more specific than L-glutamic acid. L-CCG-II was found to be agonist of metabotropic glutamate receptor (m-GluR). The Sharplesss asymmetric dihydroxylation[26] was used as source of chirality in the synthesis and Wadsworth-Emmons protocal is used for the construction of *trans*-cyclopropane ring.

The synthesis of L-CCG-II **56** (**Scheme 9**) started from commercially available cinnamyl alcohol **66** which was subjected to Sharpless asymmetric dihydroxylation to furnish the triol **67**. Compound **67** was converted into monotosyl derivative followed by base treatment to give the epoxide **68**, which was protected with PMBBr to provide the PMB protected epoxy alcohol **69**. Compound **69** was subjected to Wadsworth Emmons protocol to furnish **70** as a single diastereomer. The PMB–deprotection and conversion of alcohol into azide produced **71**. Compound **71** was then subjected to ester hydrolysis followed by oxidation of phenyl ring and reduction of azide to furnish the target molecule L-CCG-II **56**.



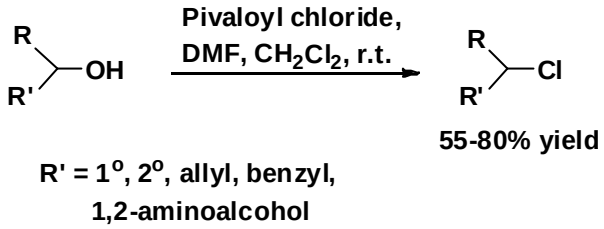
Scheme 9: Synthesis of L-CCG-II

Chapter 5: Pivaloyl chloride Mediated Transformation of Alcohols into Chlorides and Carbonyls

This chapter is further divided into two sections.

Section A: Pivaloyl chloride-DMF: A New Reagent for Conversion of Alcohols to Chlorides

Conversion of alcohols into the corresponding chlorides is one of the most important and commonly used transformation[29] in organic synthesis and development of such a procedure is still desirable in academia as well as in industrial research. A number of reagents have been employed to carry out this transformation. During our recent endeavor with HKR (hydrolytic kinetic resolution) mediated synthesis of biologically active compounds, we required to convert a diol into the required epoxide through pivalate via a three step-sequence reaction. Interestingly, we observed an efficient chlorination of alcohol instead of its protection as pivalate when reaction was performed in DMF. This could probably be attributed to the generation of a new reactive species responsible for chlorination and this observation prompted us to initiate a systematic investigation of pivaloyl chloride/DMF reagent system for chlorination of alcohol.



Scheme 10. Pivaloyl chloride-DMF mediated conversion of alcohols to chlorides

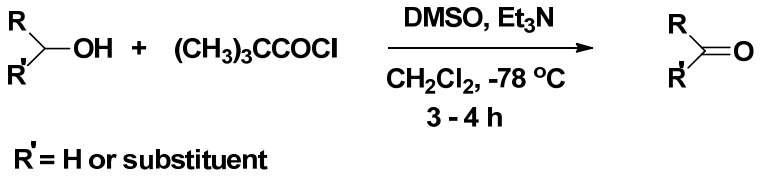
In a typical experimental procedure, when alcohols were treated with a pre-formed complex of DMF and pivaloyl chloride in dichloromethane, it gave the corresponding chloro compounds in good to excellent yields (**Scheme 10**). The present procedure is quite general as a wide range of structurally varied alcohols such as primary, secondary, allylic, homoallylic and benzylic ones underwent smooth conversion with pivaloyl chloride-DMF into their corresponding chlorides under mild reaction conditions in good to excellent yields of the corresponding chloride.

In order to examine the stereospecificity of the present method, we employed (*R*)-octane-2-ol and subjected this to reaction with pivaloyl chloride-DMF reagent to give (*S*)-2-chlorooctane, $[\alpha]_D^{20}$ +36.0° (*c* 0.8, ether). The measurement of optical rotation indicated that reaction occurs with inversion of configuration via S_N2 displacement. The involvement of Vilsmeier-Haack type complex as a possible reactive intermediate is invoked which adds on the hydroxyl group of the alcohol to form the cationic species followed by subsequent nucleophilic attack of chloride ion in S_N2 fashion to produce the corresponding chloride.

Section B: Dimethyl Sulfoxide-Pivaloyl Chloride: A New Reagent for Oxidation of Alcohols to Carbonyls

An efficient procedure for conversion of alcohols to the corresponding carbonyl compounds, an alternative to the classical Swern oxidation, is described. Pivaloyl chloride is employed as a mild and inexpensive electrophile. The chemistry of dimethyl sulfoxide has been the subject of monographs and reviews, since it is one of the most studied solvent and reagent in organic synthesis. Dimethyl sulfoxide coupled with various electrophiles such as trifluoroacetic anhydride, thionyl chloride, oxalyl chloride, *t*-butylhypochlorite, acetic anhydride, phosgene, bis-(trichloromethyl)carbonate, cyanuric chloride and $Ph_3P.X_2$ has been used in the classical Swern oxidation.[30] Oxalyl chloride which is routinely used electrophile has following disadvantages; it is moisture sensitive, expensive, toxic and its vapors are powerful irritant particularly to the respiratory system. Therefore use of a mild, efficient and inexpensive electrophile is highly desirable.

Although, pivaloyl chloride has been commonly employed as a protecting group for various functional groups, its synthetic potential still remains unexplored. With a view to extend its synthetic utility in organic transformations, we envisioned that the activation of pivaloyl chloride with DMSO could be advantageous in the classical Swern oxidation reaction. In a typical experimental procedure, when alcohol was treated with 2 equiv of pivaloyl chloride and 3 equiv of DMSO in CH_2Cl_2 at -78 ^oC followed by treatment with 5 equiv of Et_3N, the corresponding carbonyl compound was obtained in good to excellent yield (**Scheme 11**).



Scheme 11. DMSO-Pivaloyl chloride mediated oxidation of alcohols to carbonyls

The present procedure is quite general as a wide range of structurally varied alcohols such as primary, secondary, allylic, homoallylic, benzylic, acetylenic could be oxidized to carbonyl compounds in high yields.

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1.1 ASYMMETRIC EPOXIDATION (AE)

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.

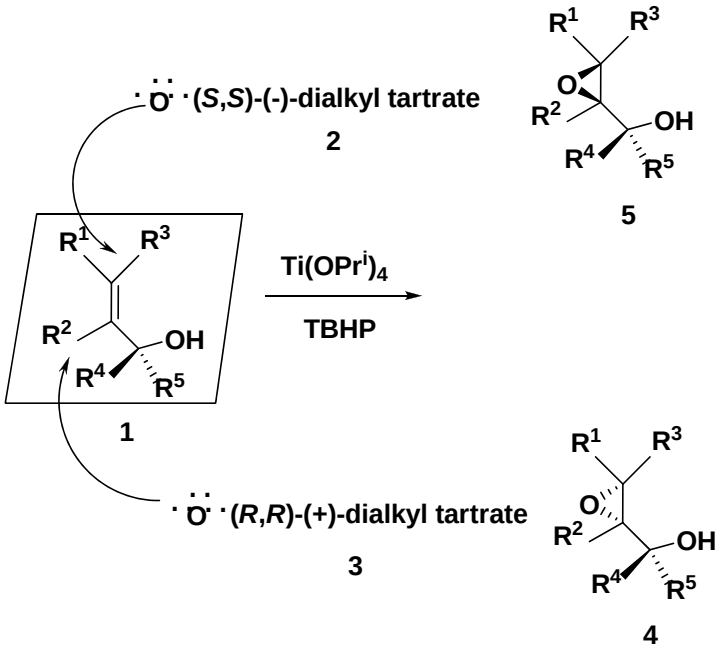
In the last two decades, many powerful asymmetric reactions have emerged as a result of the growing need to develop efficient and practical syntheses of biologically active compounds. Catalytic asymmetric reactions provide an especially practical entry into the chiral world due to their economical use 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 last three decades. 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.

Epoxides are versatile and important intermediates in organic chemistry. The strain of three membered heterocyclic ring makes them accessible to a large variety of reagents. Sharpless and Katsuki discovered a system for the asymmetric epoxidation of primary and secondary allylic alcohols that utilizes titanium tetraisopropoxide, a diakyl tartrate as a chiral ligand, and *tert*-butyl hydroperoxide as the oxidant.[8] Notably, this reaction exhibits high levels of enantioselectivity. Like other metal catalyzed epoxidations, this reaction also proceeds under mild conditions with good chemical yield and with high regio-and chemoselectivity.

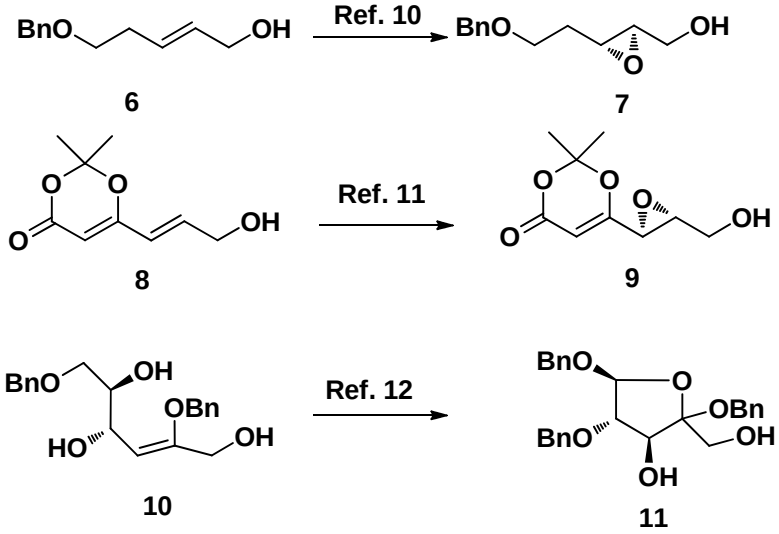
1.1.2. Asymmetric Epoxidation with the Titanium (IV) Tartrate Catalyst

The combination of $Ti(OPr^i)_4$, a dialkyl tartrate, and *tert*-butyl hydroperoxide epoxidizes most allyic alcohols in good chemical yield and with predictably high enantiofacial selectivity according to the empirical rule illustrated in **Scheme 1**. When an allylic alcohol (R^4, R^5 = H) **1** is drawn in a plane with the hydroxymethyl group positioned at the lower right, the delivery of oxygen occurs from the bottom side of the olefin to give the (2*S*)-

epoxide **5** if an (*R*,*R*)-dialkyl tartrate **3** is used as the chiral auxiliary. When an (*S*,*S*)-dialkyl **2** tartrate is employed, oxygen is delivered from the top side. The enantiofacial selectivity of the reaction is > 90% ee for substrate without a Z-olefinic substituent (R^3 = H). The degree of facial selectivity for a Z-allylic alcohol depends on the nature of the Z substituent R^3. The enantioselectivity for substrate with unbranched R^3 substituents ranges from 80 to 94% ee, but that for substrates with branched substituent is lower.[9]



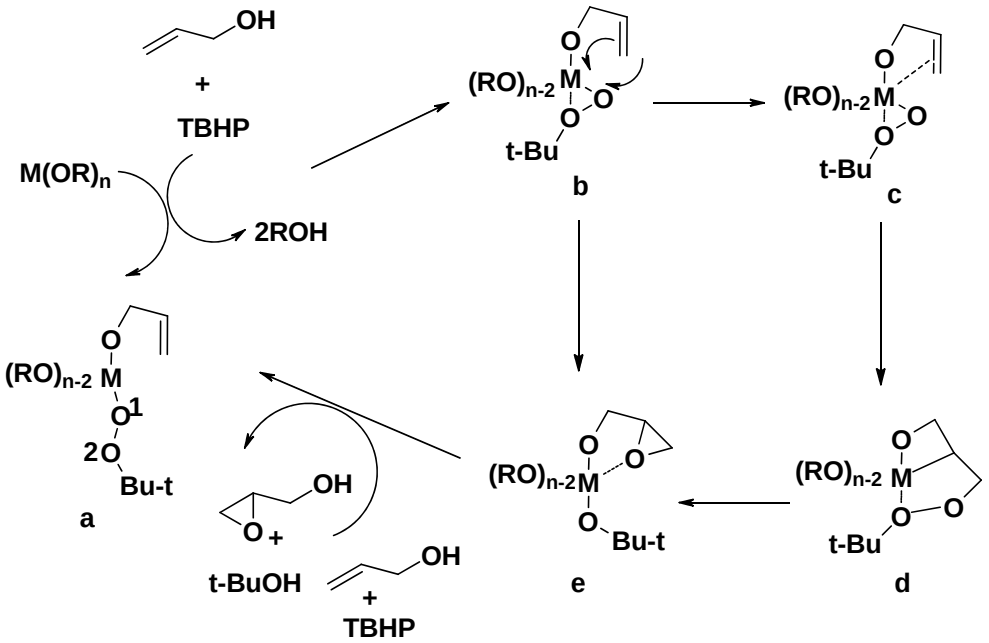
Scheme 1



Scheme 2 : Representative examples of epoxidations of allylic alcohols

1.1.3. Mechanism

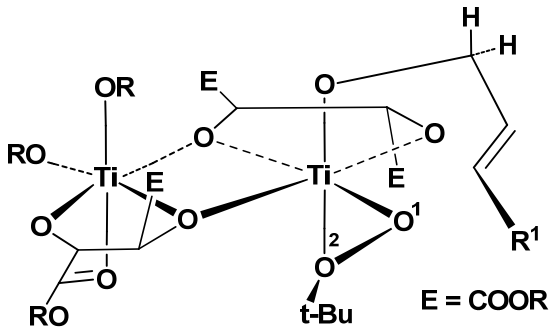
The reaction sequence proposed for the metal-catalyzed epoxidation of allylic alcohols is shown in **Scheme 3**.[13] Metal alkoxides generally undergo rapid ligand exchange with alcohols. When a metal alkoxide, an allylic alcohol, and an alkyl hydroperoxide are mixed, ligand exchange occurs to afford a mixture of complexes $M(OR)_{n-x-y}(OCH_2CH{=}CH_2)_x(OOR)_y$. Among them, only species such as '**a**', bearing both allylic alkoxide and alkyl hydroperoxide groups, are responsible for the epoxidation. The incorporated alkyl hydroperoxide is thought to be further activated by coordination of the second oxgen atom (O-2) to the metal center. The ensuing transfer of O-1 to the double bond of the allylic alcohol occurs in an intramolecular fashion is supported by comparison of the epoxidation rate of allylic alcohol with that of allyl methyl ether.[14] However controversy still surrounds the oxygen transfer process (**b-e**). One suggestion is that the double bond first coordinates to the metal center and then inserts into the μ2-alkyl hydroperoxide ligand to give an epoxide via the peroxometallocycle intermediate.[15] An alternative proposal is that the double bond attacks the distal oxygen along the axis of the O-O bond that is broken.[9,13d,15] Frontier molecular orbital treatment of peroxometal complexes also suggests that d-transition metal complexes of ROO^- exhibit electrophilic behaviour.[16]



Scheme 3

Finally, exchange of *tert*-butoxide and the epoxy alkoxide so formed with allylic alcohol and alkyl hydroperoxide completes the reaction cycle.

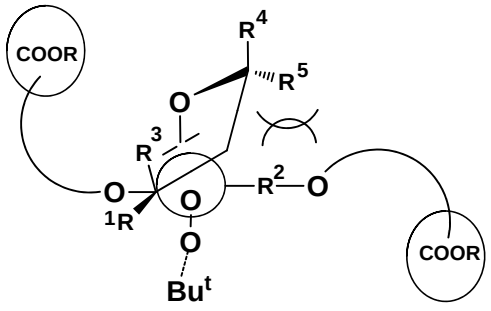
The titanium tartrate mediated asymmetric epoxidation of allylic alcohols also follows the same basic reaction pathway of **Scheme 3**. Therefore the remaining mechanistic question is how oxygen is transferred enantioselectively to substrates. To answer this question, structures of titanium-dialkyl tartrate complexes,[15,17] as well as those prepared from $Ti(OPr^i)_4$ and (*R*,*R*)-*N*,*N*'-dibenzyltartramide and from $Ti(OEt)_4$, (*R*,*R*)-diethyl tartrate, and Ph(CO)-N(OH)Ph were determined.[18] Based on the X-ray analysis of these complexes, the structure of the asymmetric epoxidation catalyst **12** (**Fig. 1**) has been proposed.



12

Fig. 1

When structure shown in **Fig. 1** is viewed down the distal peroxide oxygen-titanium bond axis (O^1-Ti), the symmetry of the tartrate "windmill arms" becomes apparent. Within this model, conformer **13** (**Fig 2**), in which the allylic alcohol and the TBHP-ligand align meridionally and the TiO-C-C=C dihedral angle is as small as 30°, has been suggested as a transition state.[9]

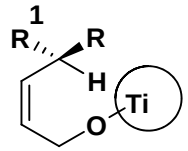


13

Fig 2.

This conformer experiences severe steric interactions only when $R^5 \neq H$. This explains the high efficiency of kinetic resolution of racemic secondary allylic alcohols where one enantiomer (R^4 = alkyl, R^5 = H) reacts much faster than the other isomer (R^4 = H, R^5 = alkyl).

The poor reactivity of *tertiary* allylic alcohols (R^4 and R^5 = alkyl) is rationalized analogously.[18] We also see that the Z olefinic substituent (R^3) is close to the hydroxymethyl group bound to titanium because of the small O-C-C=C dihedral angle. These interactions destabilize conformer **14** (**Fig. 3**) and lower the reactivity of this complex. The C-2 substituent (R^2) (**Fig. 2**) is also in the vicinity of the titanium complex, and only the E olefinic substituent (R^1) projects toward an open quadrant. This model explains following three observations.



14

Fig 3.

1. Bulky Z olefinic substituents retard epoxidation reactions, and substrate with branched Z substituents exhibit poor reactivity and decreased enantioselectivity. This may be rationalized by the conformational requirements for minimization of allylic strain due to the small C=C-C-OTi dihedral angle.[9] That is, the conformation in which H is in the plane of the olefin is energetically more accessible than the other two conformations (R and R' in-plane conformations). Thus the disposition of an alkyl group (R^1) to the bottom side raises the energy of the transition state depicted in **Fig. 3** [using (*R*,*R*) tartrate], causing retardation of the reaction and decreased enantioselectivity. When $R \neq R^1$, each enantiomer of a racemic substrate has different reactivity and treatment of such a racemic mixture with $Ti(OPr^i)_4$-tartrate affects kinetic resolution.
2. The C-2 substituent is near the Ti-tartrate moiety; its chirality also affects substrate reactivity. Thus enantiomers of a racemic substrate bearing a chiral C-2 substituent have different reactivities, and in some cases a good level of kinetic resolution is observed.
3. Except for a few examples, the E substituent, which is located in an open quadrant, has little effect on the stereoselectivity of the reaction. Therefore, the epoxidation of chiral *E*-allylic alcohols should proceed with same high level of enantioselectivity seen with achiral *E*-allylic alcohols.[19]

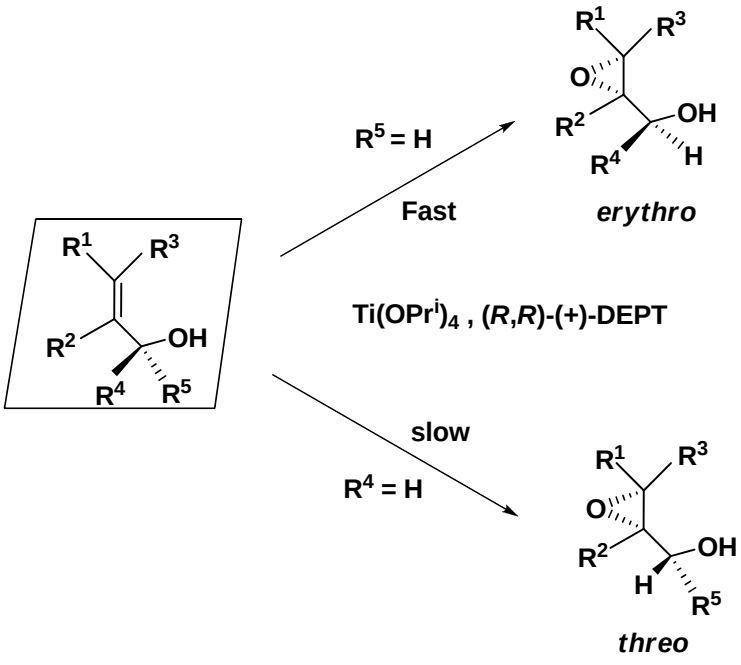
Since the principal difficulties (isolation of unstable and/or water soluble epoxy alcohols) with the stoichiometric reaction are mainly attributed to the mild Lewis acidity of titanium alkoxide and the aqueous workup required for hydrolysis of the stoichiometric catalyst, Sharpless discovered that addition of molecular sieves to the reaction mixture allows epoxidation to proceed to completion in the presence of only 5-10 mol% of the $Ti(OPr^i)_4$ and

6 mol% tartrate has been recommended as the most widely applicable system for asymmetric epoxidation.[20] Below the 5 mol% level, the enantioselectivity of the reaction decreases remarkably. The amount of tartrate ester must be carefully controlled, because a large excess of tartrate (>100 % excess) decreases the reaction rate while with too little tartrate (<10 % excess) the enantioselectivity may suffer.

1.1.4. Kinetic Resolution of Secondary Allylic Alcohols

The kinetic resolution of secondary allylic alcohols was first reported in 1981,[21] wherein some examples were performed with as little as 13-25% catalyst and there onwards complete catalytic manner developed,[22-25] key feature of this catalytic procedure is molecular sieves (zeolites).

With cyclohexyl (*E*)-1-propenyl carbinol as the model (R^1 = CH_3, R^2 = R^3 = R^4 = H, R^5 = C_6H_{11} and R^1 = CH_3, R^2 = R^3 = H, R^4 = C_6H_{11} in **Scheme 4**), it was found that the *S* enantiomer reacts 74 times faster than the *R* enantiomer at 0 ^oC when (*R*,*R*)-(+)-diisopropyl tartrate is used as the chiral auxiliary. As in the epoxidation of primary allylic alcohols,[1] the stereochemical course of the kinetic resolution processes has been highly predictable.

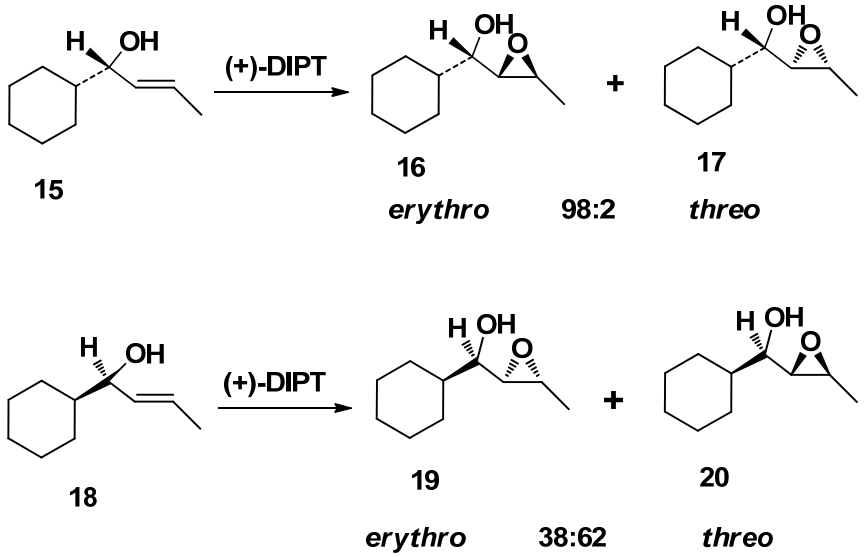


Scheme 4

When the secondary allylic alcohol is drawn so that the hydroxy group lies in the lower right corner of the plane (**Scheme 4**), the enantiomer that reacts rapidly with (*R*,*R*)-(+)-dialkyl

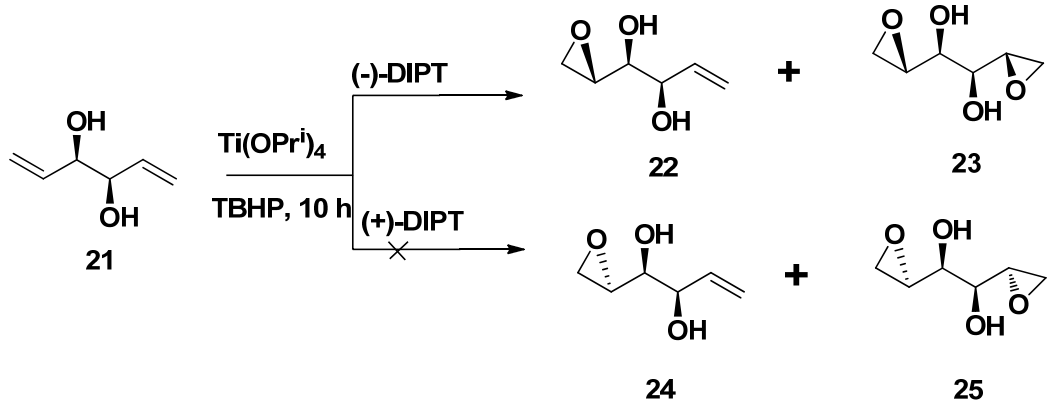
tartrate is the one in which the substituent (R^4) on C-1 is located above the plane. Epoxidation occurs from the underside to give the usual 2*S* epoxide (*erythro* selectivity, 98:2).

The slow-reacting enantiomer is the one in which the C-1 substituent (R^5) is located on the underside, interfering with the 'normal' delivery of the oxygen atom. This interference reduces the expected *threo* selectivity for the slow-reacting enantiomer (38 *erythro*:62 *threo*, **Scheme 5**).



Scheme 5

This enantioselection rule has consistently been observed for all secondary allylic alcohols except for those bulky Z substituents and 1,2-divinylethylene glycols. Kinetic resolution is very poor for allylic alcohols with bulky Z substituents, and reversed but high enantioselectivity is observed in the kinetic resolutions of 1,2-divinylethylene glycols **21**[26,27] (**Scheme 6**).



Scheme 6

The most important parameters in kinetic resolution are the relative rates of reaction of the two allylic alcohol enantiomers. The graph in **Fig. 4**, which represents solutions of **Eq. 1**, explains the relative rate difference to be related to the percent ee of unreacted allylic alcohol.[28]

$$K_{rel} = \frac{k_f}{k_s} = \frac{\ln(F/F^o)}{\ln(S/S^o)} = \frac{\ln(1-c)(1-ee)}{\ln(1-c)(1+ee)} \qquad \textbf{Eq. 1}$$

k_f = rate constant of fast reacting isomer

k_s = rate constant of fast reacting isomer

c = Fraction of consumption of racemate

ee = % ee/100

F = Concentration of the fast reacting isomer

S = Concentration of the slow reacting isomer

Three variables influence solutions to **Eq. 1**:

1. The percent conversion of the racemic materials.
2. The relative rate (k_{rel}) of reaction of the two enantiomers.
3. The percentage ee of the remaining substrates.

Knowledge of any two allows specification of the third. The maximum effectiveness of a kinetic resolution procedure is, of course, when $k_{rel} = \infty$, but a value of 50-100 is almost as effective. Actual value is in the range 15 to 700.

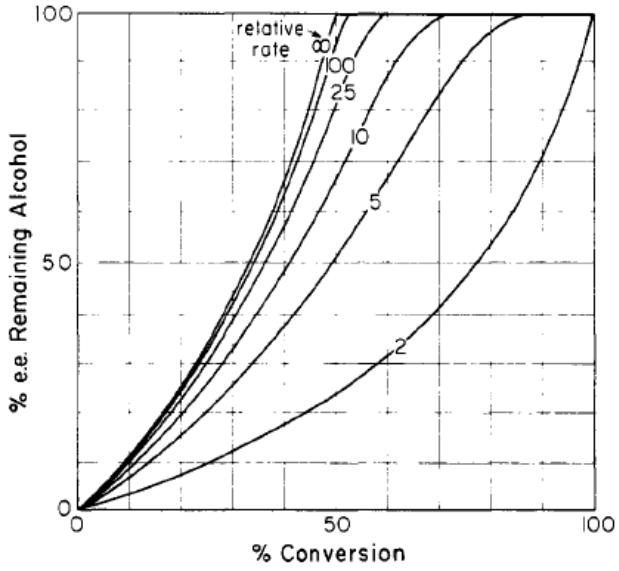
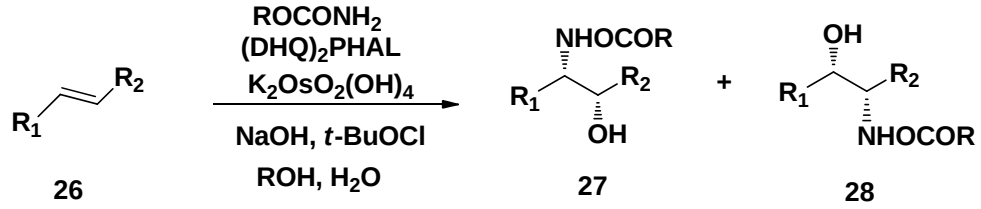


Fig. 4

1.2 TETHERED AMINOHYDROXYLATION (TA)

1.2.1. Introduction

The Sharpless aminohydroxylation reaction[29] has recently emerged as a powerful method of preparing vicinal amino alcohols from alkenes. The significance of this invention was immediately apparent to many researchers[30] as the AA reaction provides straightforward access to the amino alcohol array and in a wide variety of biologically active agents and natural products.[31] As a result, the reaction rapidly gained the prominence of its forerunners, the AE[1] and AD[32] 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 **26** to form amino alcohol products such as **27** or **28** (**Scheme 7**). Alternatively, the 1,4-bis-(9-*O*-dihydroquinidinyl)-phthalazine [$(DHQD)_2PHAL$] ligand directs addition to the β-face of **26**.



Scheme 7

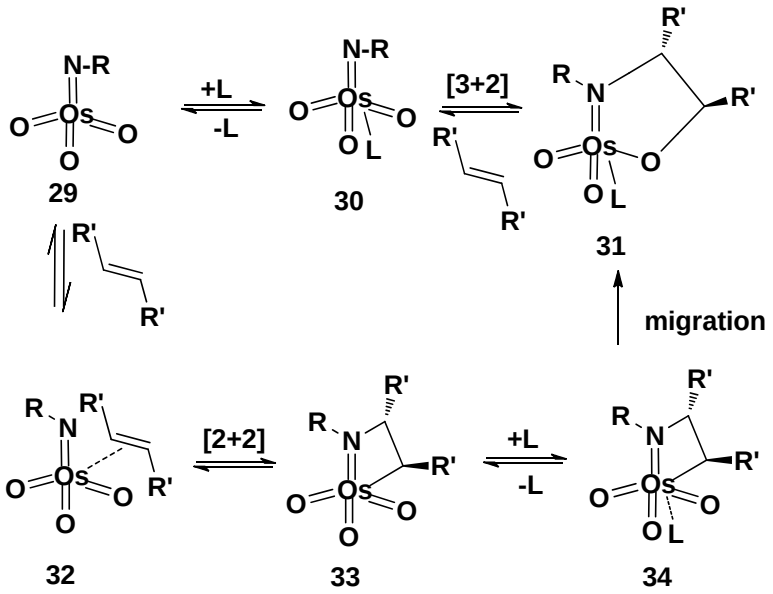
An additional complexity that is not manifested in the AD process involves the regioselectivity of the AA reaction. The oxidation of unsymmetrical alkene such as **26** ($R_1 \neq R_2$) can, in principle, give rise to two regioisomeric amino alcohol products **27** and **28**. In many cases, the conditions or the aromatic linker of the chiral ligand, for example phthalazine (PHAL) or anthraquinone (AQN), strongly influences the regioselectivity of the reaction.[33]

1.2.2. 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 **29**, which adds with '*syn*' stereospecificity to the alkene to give the azaglycolate complex **31**. Like in AD, two different

mechanisms have been proposed, both of which addresses the preferences of **29** to effect aminohydroxylation rather than dihydroxylation and other key aspects such as enantio-and regio selectivity.[33]

The first mechanism involves a formed [2+2] cycloaddition of the alkene to the imidotrioxoosmium species **29** to give the osmaazetidine **33**, followed by ligand co-ordination to form **34** and 1,2 migration of the carbon-osmium bond to give the osmium azaglycolate addition product **31**. This mechanism uses electronic arguments to account for the frequently observed preference for the nitrogen to add regioselectivly to the β-carbon of alkenes bearing an electron withdrawing group.[34] 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 **34** or by controlling the relative rate of final bond migration to give **33**.[35]

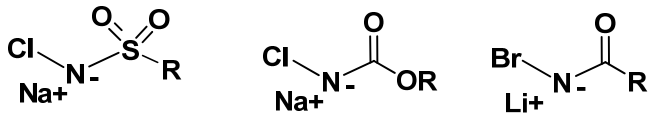


Scheme 8

The second mechanism is [3+2] cycloaddition of ligand-bound complex **30** 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 **31**. (**Scheme 8**)

1.2.3. 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. 5**)



Sulfonamide **Carbamate** **Amide**

35 **36** **37**

Fig. 5

(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.[36] 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.[37] 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[38] or with Red-Al.[39] In addition, 33% HBr/CH_3COOH has been used to cleave toluene sulfonamides.[40] 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.[41]

(ii) Carbamate variant: The discovery of carbamate based nitrogen sources[42] 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,[43] 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.[44] 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.[45] As with sulfonamides, carbamates with less sterically demanding *N*-substituents were found to give better results.

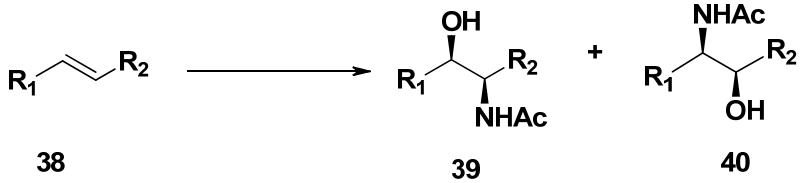
(iii) Amide variant: The most recent major variant of the AA reaction is based on *N*-halogenated amides.[46] This variant is comparable in scope to the carbamate based method and

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,[47] 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.[48]

1.2.4. 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:



38 39 40

Substrate	R_1	R_2	39 : 40
38a	$TBDPSOCH_2CH_2$	H	>20 : 1
38b	*p*-OMe-$C_6H_4OCH_2CH_2$	H	1.2 : 1
38c	$TBDPSOCH_2CH_2$	Et	2.0 : 1
38d	*p*-OMe-$C_6H_4OCH_2CH_2$	Et	1 : 3.5

Scheme 9

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.

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

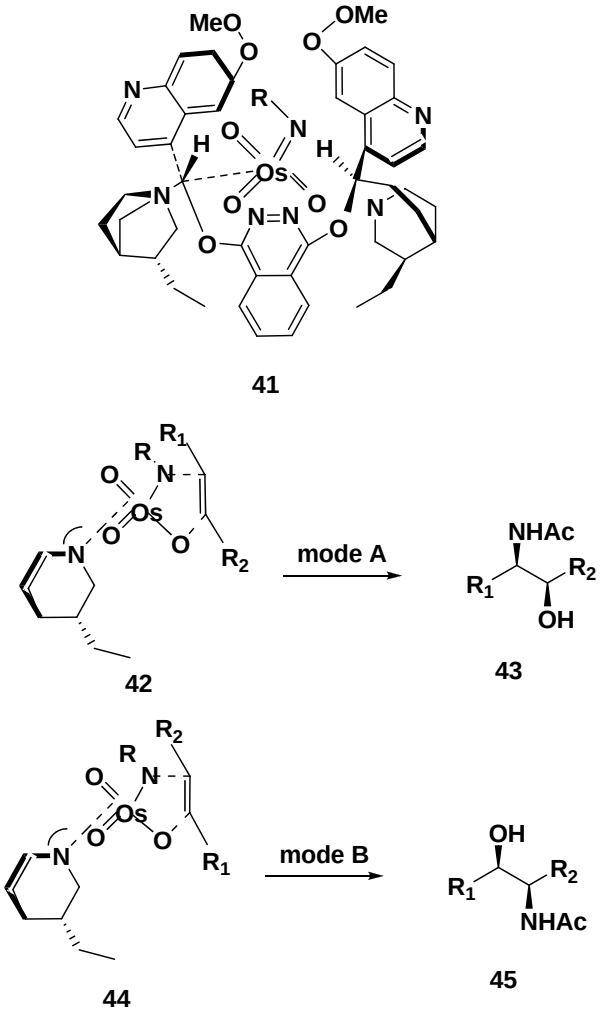


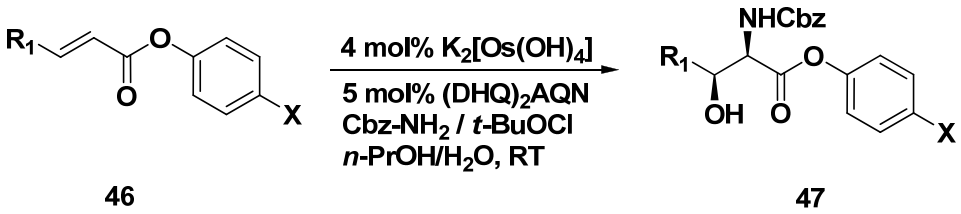
Fig. 6 : Proposed structure of the $AcN{=}OsO_3$— $(DHQD)_2PHAL$ catalyst **41**, and alternative alkene binding modes A and B.

The most comprehensive study of ligand-substrate interactions has been reported by Janda and co-workers.[37] They proposed a model for the AA reaction with phthalazine derived

ligands analogous to that proposed by Corey[47] for the AD reaction. As shown in **Fig. 6** 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.[37] 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.[48]

1.2.5. Panek Protocol

Asymmetric synthesis of β-hydroxy-α-amino acid can be performed, by making aryl ester substrates **46** successfully using Panek protocol. The reversal of regioselection may arise from a conformational change induced by the aryl ester functionality.[49]

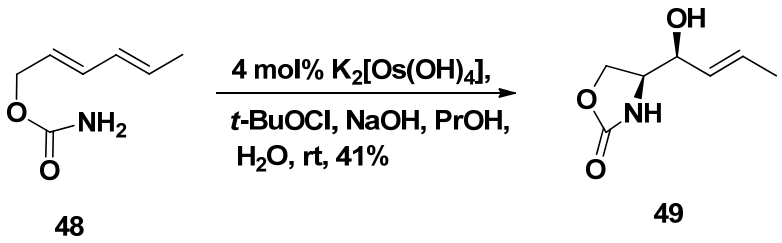


46 **47**

Scheme 10

1.2.6. Tethered Aminohydroxylation

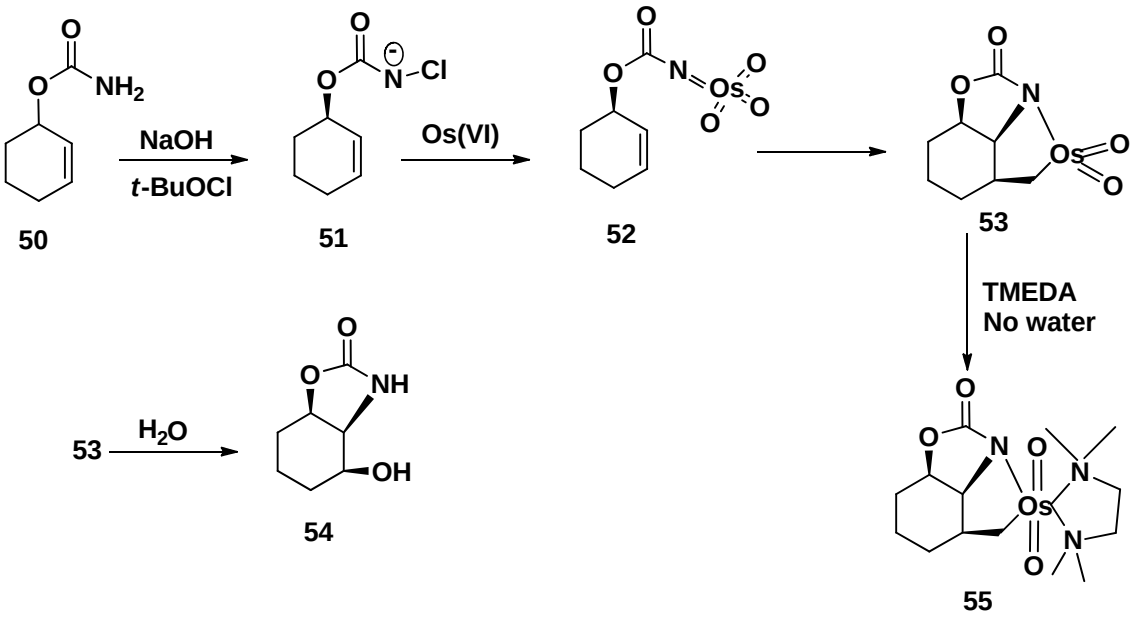
The discovery of asymmetric aminohydroxylation by Sharpless group has evolved and revolutionized the synthesis of protected amino alcohol functionality in single step. Though it has advantage of one-pot processes, several complicated problems has still to be solved. The major complication with this methodology is a lack of regiochemistry when unsymmetrical alkenes are oxidized. Recently, Donohoe and group[50] demonstrated the complete achievement of regioselectivity through tethering the source of nitrogen (carbamate) to both chiral and achiral allylic alcohols and discovered a method of controlling completely the regiochemistry of the product. Tethering the nitrogen source for an aminohydroxylation (such as a carbamate) to an allylic alcohol would allow an intramolecular aminohydroxylation to ensue with complete control of regioselectivity (and high levels of stereoselectivity when chiral allylic carbamates were subjected to the tethered aminohydroxylation, TA reaction (**Scheme 11**).



Scheme 11

During development of the reaction conditions, they examined the role of various amines as promoters for the TA of compound **48**. The presence of an amine is beneficial to the rate, with Sharpless' catalysts and *i*-Pr_2NEt giving the highest yields.[51] It has been observed that quinuclidine is not good at accelerating the reaction, and it is destroyed by one of the chlorinating agents present in solution. Importantly, there was no significant difference in rate (or yield) for oxidation using $(DHQ)_2PHAL$ and its pseudoenantiomer $(DHQD)_2PHAL$; this points to a role for the chiral ligand that does not include stereochemical induction.

The complete regioselectivity can be explained by the mechanism shown in **Scheme 12**. This mechanism suggests that *in situ* chlorination and deprotonation of the allylic carbamate gives a species **51** (a nitrene equivalent) that is capable of oxidizing potassium



Scheme 12

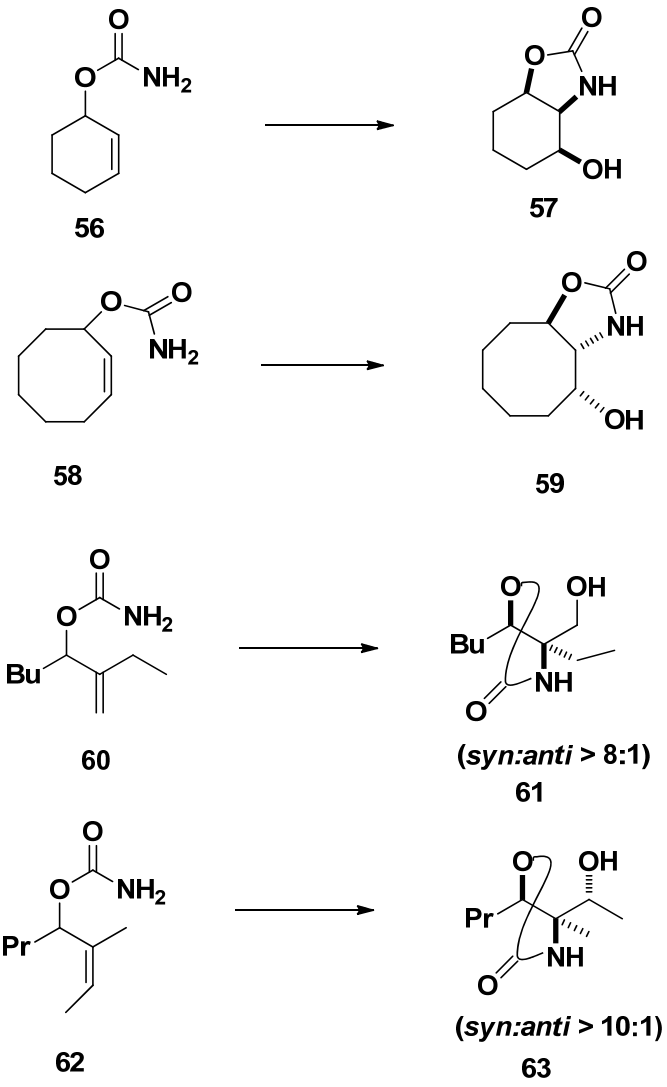
osmate [Os (VI)] to the osmium tetroxide analogue **52** [Os (VIII)]. Addition to the alkene gives azaglycolate osmate ester [Os (VI)] **53** which is oxidized and hydrolyzed *in situ*.

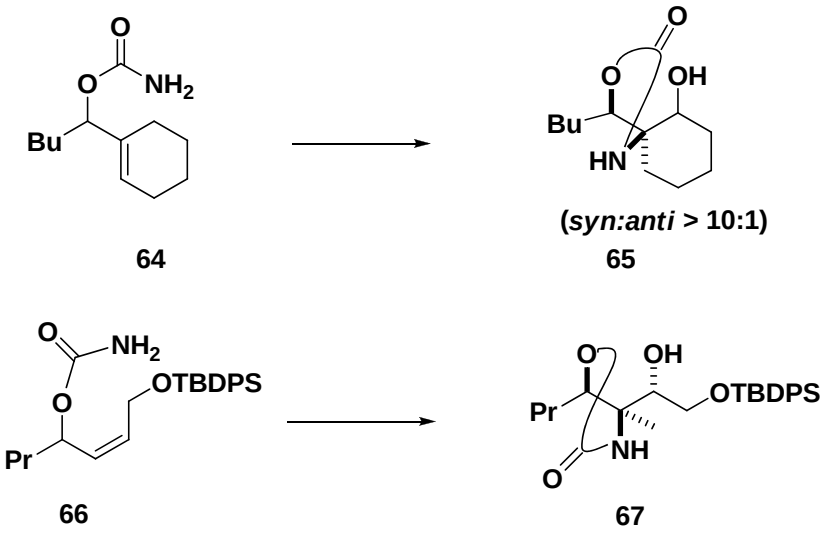
Two pieces of experimental evidence in support of this hypothesis:

(1) Repetition of the TA reaction using optimum conditions, but no potassium osmate, gave no cyclized products,

(2) The osmate ester **53** could be intercepted by the addition of TMEDA to the reaction mixture to give **55** (no water was present here to avoid hydrolysis of **53**).

In order to confirm the potential of this procedure, it was performed on a series of flexible, chiral, acyclic and cyclic allylic alcohol derivatives.





Scheme 13

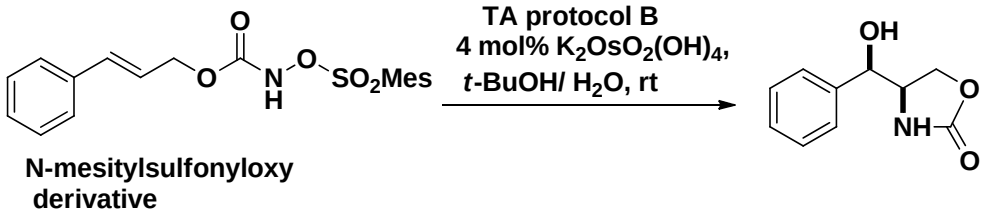
These results show that **(i)** the addition of nitrogen and oxygen is suprafacial (stereospecific) and **(ii)** the reaction is *syn* selective (stereoselective) in each case.

These results were encouraging, and the desired products were obtained in moderate yields with total control of regioselectivity. The reoxidant for an aminohydroxylation reaction is typically an *N*-halocarbamate salt prepared in situ (**TA protocol A**) by the action of NaOH and *t*-BuOCl on a primary carbamate (**Scheme 11**).[52] It has been observed that the *N*-chlorocarbamates thus produced have a limited lifetime in the reaction. In an AA reaction, one can compensate for this by using 3-3.5 equiv of carbamate (and NaOH and *t*BuOCl). Clearly, TA condition do not have this luxury in the TA reaction and thus sometimes have difficulty in driving the reaction to completion and occasionally chlorination of the alkene unit was a competing side reaction in the TA reaction and is partly responsible for lowering the yield. Therefore, a screen of alternative reoxidants for the TA reaction focusing on replacement of the chlorine of the *N*-halocarbamate salt that is generated in situ during oxidation with *t*-BuOCl and NaOH.

Protocol B:

In this case, the *N*-Cl unit has been replaced by a *N*-*O*-SO_2Mes group, which was introduced before the aminohydroxylation rather than being formed in situ. Allylic and homoallylic substrates were successfully oxidized using the novel and chlorine-free TA (named hereafter **TA protocol B**); the corresponding products were usually obtained in good yields.[50] Although this new protocol was significantly better than the original TA reaction based on *t*-BuOCl, the reaction sometimes proved capricious; that is, lower yields were obtained for no apparent reason on some substrates (**Scheme 14**). In addition, the formation of the TA

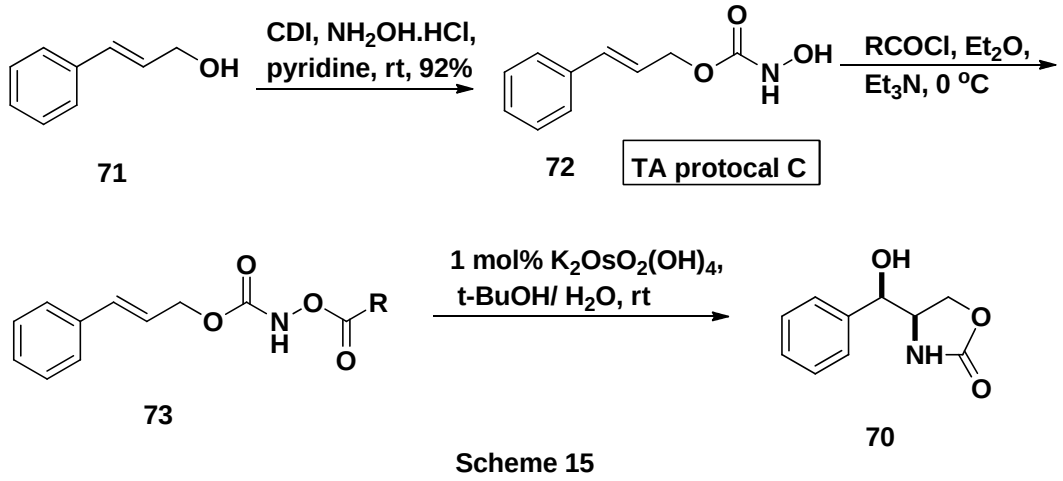
precursors from the corresponding alcohols could be problematic, leading to moderate yields and fairly unstable compounds.



Scheme 14

Protocol C:

Although encouraging results were obtained with the *O*-SO_2Mes reoxidant, no trend emerged as to which substrates would work well, or poorly, in the reaction. Donohoe



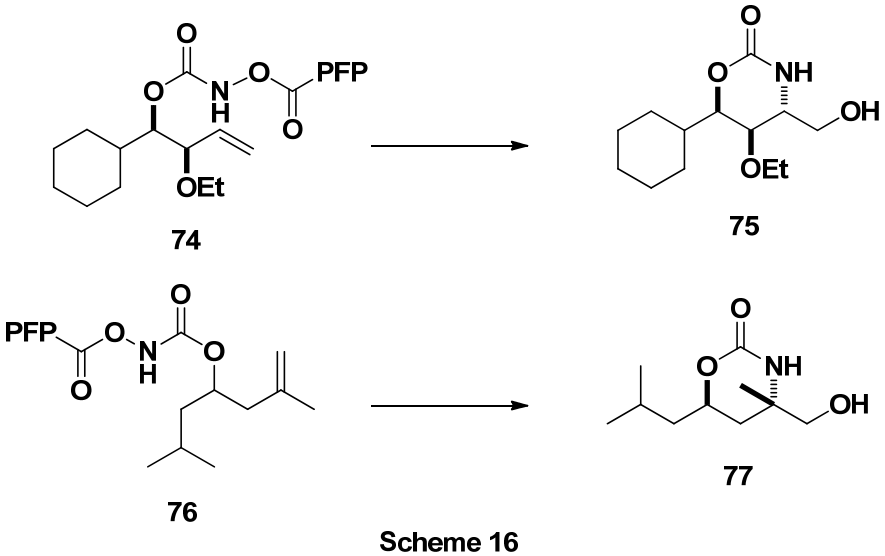
Scheme 15

decided to screen a wider range of leaving groups on the carbamate nitrogen. Cinnamyl alcohol **71** was chosen as a test substrate for this investigation as this alcohol is commercially available and a good example of a class of compounds (primary alcohol, *trans*-alkene) which were less than ideal under previous protocols.[50]

Interestingly, the *O*-pentafluorobenzoyl group (*O*-PFB) emerged as a superior reoxidant for the TA reaction, giving a dramatically improved yield (see entry **73d**).[53] It is noteworthy that the amount of potassium osmate could be significantly reduced to 1 mol % without lowering the yields; this change was not always possible before, especially with protocol A. These improvements render the novel TA protocol C very attractive as a synthetic route to vicinal amino alcohols.

Table 1 . Effect of Acyl-Based Leaving Group on the yield of the TA			
Entry	**R**	**yield of 73a-f**	**yield of 70**
73a	**Me**	**81%**	**52%**
73b	**2,4,6-$Cl_3C_6H_2$**	**85%**	**73%**
73c	**2,4,6-$Me_3C_6H_2$**	**81%**	**86%**
73d	**C_6F_5**	**95%**	**86%**
73e	***p*-ClC_6H_4**	**90%**	**86%**
73f	***t*-Bu**	**94%**	**0%**

Protocol C is also applicable to homoallylic alcohol derivatives that have previously been unsuitable for a TA reaction under both earlier sets of conditions. The high level of 1,3-acyclic stereocontrol in favour of the anti diastereoisomer is also noteworthy. Diastereoselectivity obtained above arises from an intermediate such as **A** or **B**, where the osmium atom has already undergone addition across an alkene unit and then been reoxidized.



Scheme 16

Molecular models shows that a boat like conformation **A** (with an equatorial R group) allows the best overlap between the oxidant and the δ-bonds of the alkene (this gives rise to 1,3-anti diastereoselectivity) **Fig. 7**. The corresponding chairlike transition state **B** (which would give

the *syn* isomer) suffers because this arrangement puts a larger distance between the orbitals of the alkene and the imido-osmium complex and is, therefore, disfavored.

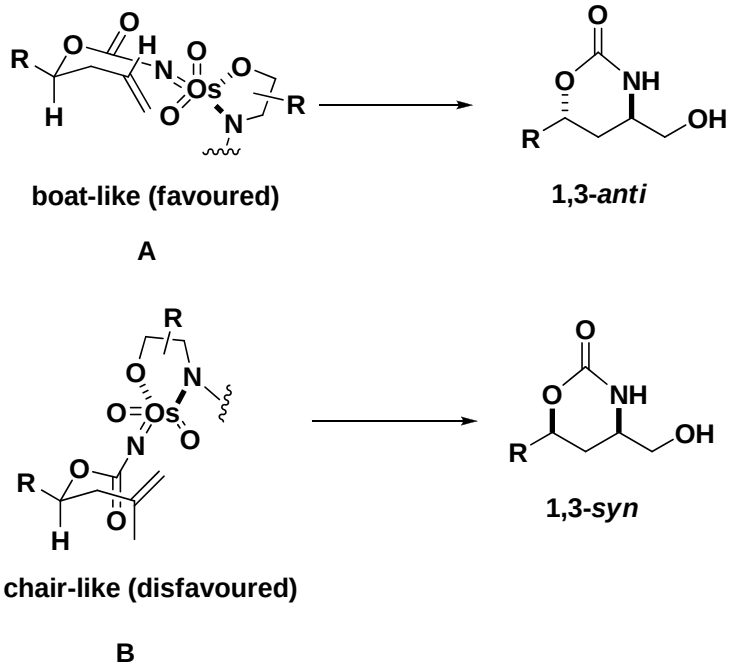


Fig. 7. Transition state model for 1,3-*anti*-diastereoselectivity

1.3 HYDROLYTIC KINETIC RESOLUTION (HKR)

1.3.1. Introduction

The search for new and efficient methods for the synthesis of optically pure compounds has been an active area of research in organic synthesis. Amongst various syntheses, the enantioselective syntheses of complex natural products containing multiple stereocentres are often the most challenging. Asymmetric catalysis provides a practical, cost-effective and efficient approach to the synthesis of such molecules. The use of catalytic methods not only provides an easy access to an enantiomerically pure product but also permits maximum variability in product structure with regard to stereochemical diversity, which is particularly important for making various synthetic analogues required for biological activity studies. While tremendous advances have been made in asymmetric synthesis, substrate-driven or catalytically induced resolution of racemates is still the most important industrial approach to the synthesis of enantiomerically pure compounds. In a kinetic resolution process, one of the enantiomers of the racemic mixture is transformed to the desired product while the other is recovered unchanged.

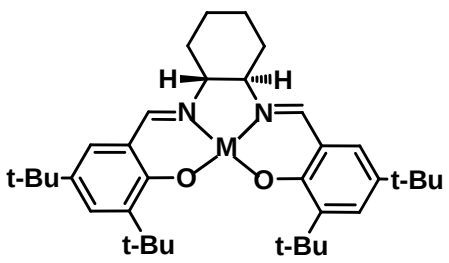
Epoxides are very important unit in a number of interesting natural products, moreover these are versatile building blocks that have been extensively used in the synthesis of complex organic compounds. Their utility as valuable intermediates has further expanded with the advent of asymmetric catalytic methods for their synthesis.[54]

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.

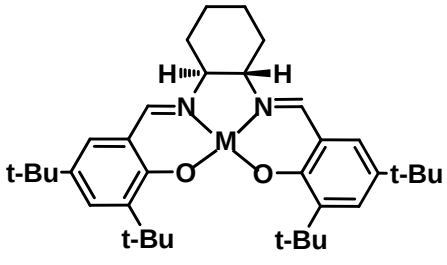
Among available methods for the preparation of enantio-enriched epoxides, the Sharpless epoxidation reaction has arguably had the most profound impact of any asymmetric catalytic reaction discovered thus far, providing general access to highly enantio-enriched epoxy alcohols.[55] More recently, the epoxidation of unfunctionalized conjugated olefins by chiral (salen)Mn(III) complexes has enabled the practical synthesis of certain classes of enantiomerically enriched epoxides.[56] 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.[57] Indirect routes to enantiopure epoxides involving asymmetric catalytic dihydroxylation or reduction reactions

have also proven highly valuable in specific contexts.[58] 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.[59] 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[60] or by enzymatic kinetic resolution methods,[61] and these compounds have become widely used starting materials for target-oriented synthesis.[62] 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 **78** (**Figure 8**) catalyzed efficient hydrolytic kinetic resolution (HKR) of a variety of terminal epoxides (**Scheme 17**).[63-65] 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 **78** had previously been commercialized and manufactured on a ton scale in the context of (salen)Mn epoxidation catalysts.[66] The cobalt analogues (*R*,*R*)-**78** and (*S*,*S*)-**78** proved equally accessible, and these are also now available in bulk.[67] Third, water is perhaps the ideal reagent for effecting the resolution reaction: it is inexpensive and



M = Co: (*R*,*R*)-**78**
M = Co-OAc: (*R*,*R*)-**78**-OAc

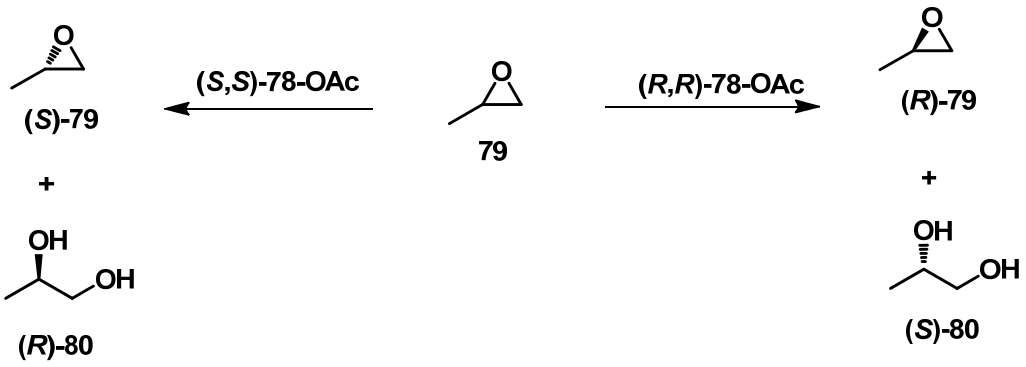


M = Co: (*S*,*S*)-**78**
M = Co-OAc: (*S*,*S*)-**78**-OAc

Fig. 8

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.[68] 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. [69-70] 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.[71] 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.[66] Jacobsen has discovered that the HKR is an extraordinarily general reaction, allowing efficient kinetic resolution of virtually any type of terminal epoxide.

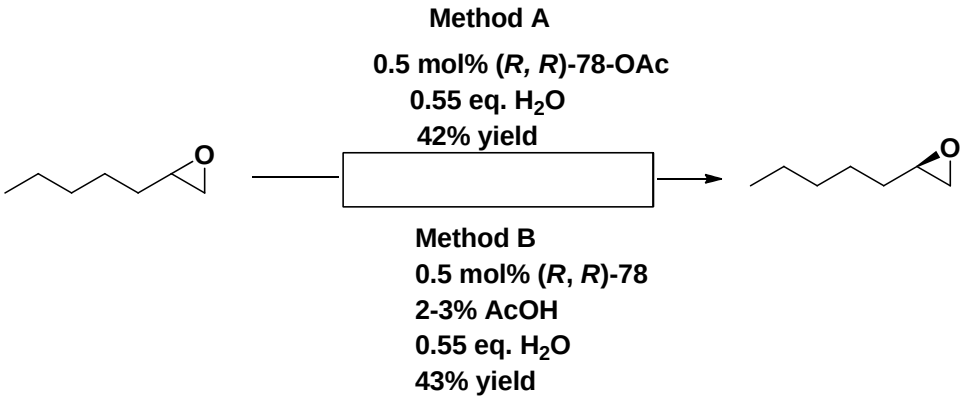


Scheme 17

1.3.2. Preparation of Catalyst and General Experimental Considerations

Both enantiomers of the (salen)CoII complex **78** are available commercially on research or commercial scale,[66] or they can be prepared from the commercially available ligands using $Co(OAc)_2$. The Co(II) complex **78** is catalytically inactive, however, and it must be subjected to one-electron oxidation to produce a (salen)CoIII X 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 **78**.OAc is convenient for use in HKR reactions both in terms of its preparation and reactivity. Two useful methods for the generation of complex **78**.OAc have been developed. Method A involves isolation of **78**.OAc as a crude solid prior to the HKR. The Co(II) complex **78** is dissolved in toluene to generate *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 **78**.OAc as a brown solid residue that can be used without further purification. Method B involves in situ generation of **78**.OAc under HKR conditions by suspension of the Co(II) complex **78** 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. Aside from the method of generation of **78**.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



Scheme 18 : General reaction

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 epoxidesbearing 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 atm osphere 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*)-**78**) (11.6 g, 19.2 mmol, 96%).

1.3.3. Attractive features of HKR

1. The reaction is applicable to a wide range of racemic terminal epoxide, most of them are quite inexpensive.
2. Access to highly enantio-enriched (99% ee) products in close to theoretical yields.
3. A practical and scaleable protocol.
4. The low loading (0.2 to 2 mol%) and recyclability of commercially available catalyst at low cost.
5. Use of water as nucleophile for epoxide ring opening.
6. The ease of product separation from the epoxide due to the large boiling point and polarity differences.
7. Both epoxide and diol are obtained in high yield and high optical purity.
8. Absence of useful alternative approaches to the preparation of enantio-pure terminal epoxides.

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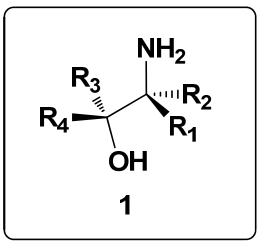
2.1 SECTION A

1,2-AMINOALCOHOLS

2.1.1. Introduction

1,2-Aminoalcohols are encountered in a large number of natural products and/or biologically active compounds.[1] Chiral β-amino alcohols are indispensable peptide isosteres for the development of HIV proteases,[2] renin[3] and ACE inhibitors.[4] They are also expected to serve as chiral building blocks for the construction of glycosidase inhibitors. Moreover, optically enriched 1,2-aminoalcohols are often used as building blocks for the preparation of chiral catalysts used in a variety of enantioselective processes.[5] The common name for this group varies from vicinal amino alcohol to β-amino alcohol, to 1,2-amino alcohol. The presence of moiety and the relative (as well as absolute) stereochemistry are generally important for the biological activity of molecules containing a vicinal amino alcohol. Due to wide variety of biological activities, applications and unique structure, 1,2-aminoalcohols have been targets of synthetic interest, and therefore a great deal of effort has been devoted towards their synthesis.



1

Mainly three general groups of vicinal amino alcohols have been reported in the literature.

(1) Naturally occurring molecules containing amino alcohols

(2) Synthetic pharmacologically active molecules containing amino alcohols

(3) Catalyst containing vicinal amino alcohols

(1) Naturally Occurring Molecules Containing Amino Alcohols

Hydroxy amino acids are one of the most common naturally occurring that contain a vicinal amino alcohol. The naturally occurring amino alcohols, serine and threonine are both biologically significant as well as being useful members of the chiral pool.[6] Some well known examples are shown in **Fig. 1**. Probably the most synthesized of this group is the dipeptide bestatin **2**.[7] Structurally bestatin is an aminopeptidase inhibitor that exhibits

immunomodulatory activity and is used clinically as an adjuvant in cancer chemotherapy. Cyclic depsipeptides are a large group of naturally occurring molecules that commonly contain nonproteogenic acids. Hapalosin **5** is an *anti*-β-hydroxy-γ-amino acids containing depsipeptide recently isolated from blue green algae.[8] Hapalosin has attracted considerable interest due to its ability to inhibit multidrug resistance (MDR) in drug resistant cancer cells. Another example of a vicinal amino alcohol containing amino acid is the lactone **AI-77-B 6**.[9] This compound was isolated from the culture broth of *Bacillus pumilus*. This compound is a structurally unique molecule with gastroprotective activity. **AI-77-B** is made up of two amino alcohol-containing components.

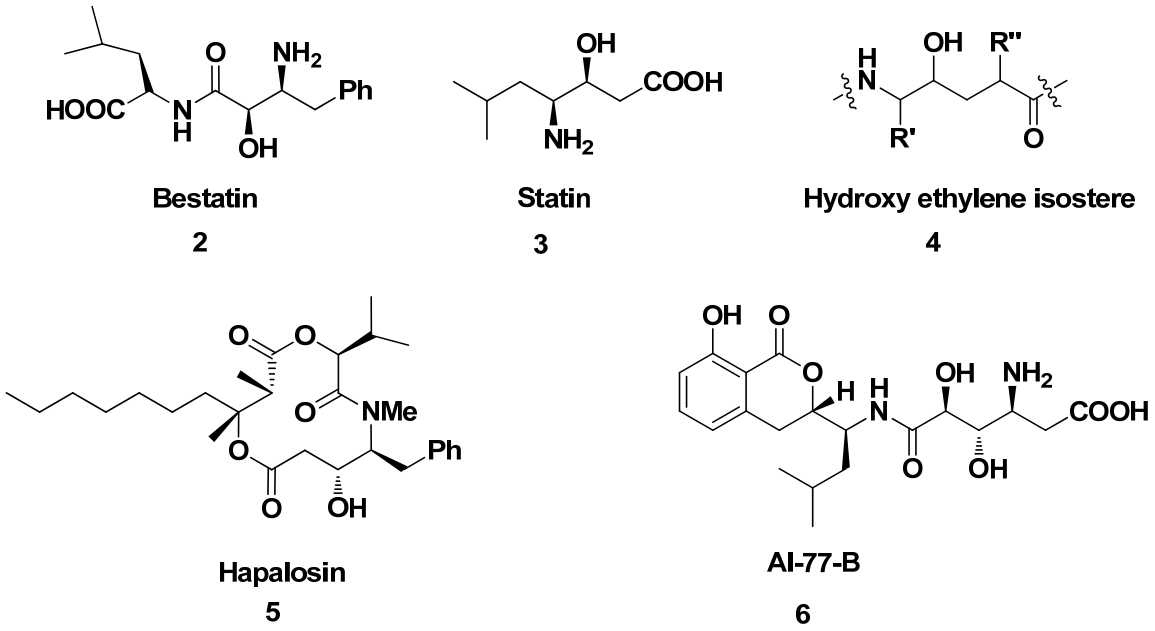


Fig. 1

Lipids and lipid-like molecules make up of a large class of naturally occurring molecules containing the vicinal amino alcohol moiety (**Fig. 2**). Possibly, the most synthesized molecule of all amino alcohols is sphingosine **7**.[10] Sphingosine **7** is a compound which was originally considered to be important in cell signaling.[11] Structurally sphingosine and analogues are 2-amino-1,3-diols. Sulfobacin B **8** is an interesting sphingosine analogue recently isolated.[12] This lipid is a von Willebrand factor receptor antagonist and as such should be a useful antithrombotic agent. Myriocin **9** is one member of a group of structurally similar lipids.[13] This densely functionalized amino alcohol contains additional

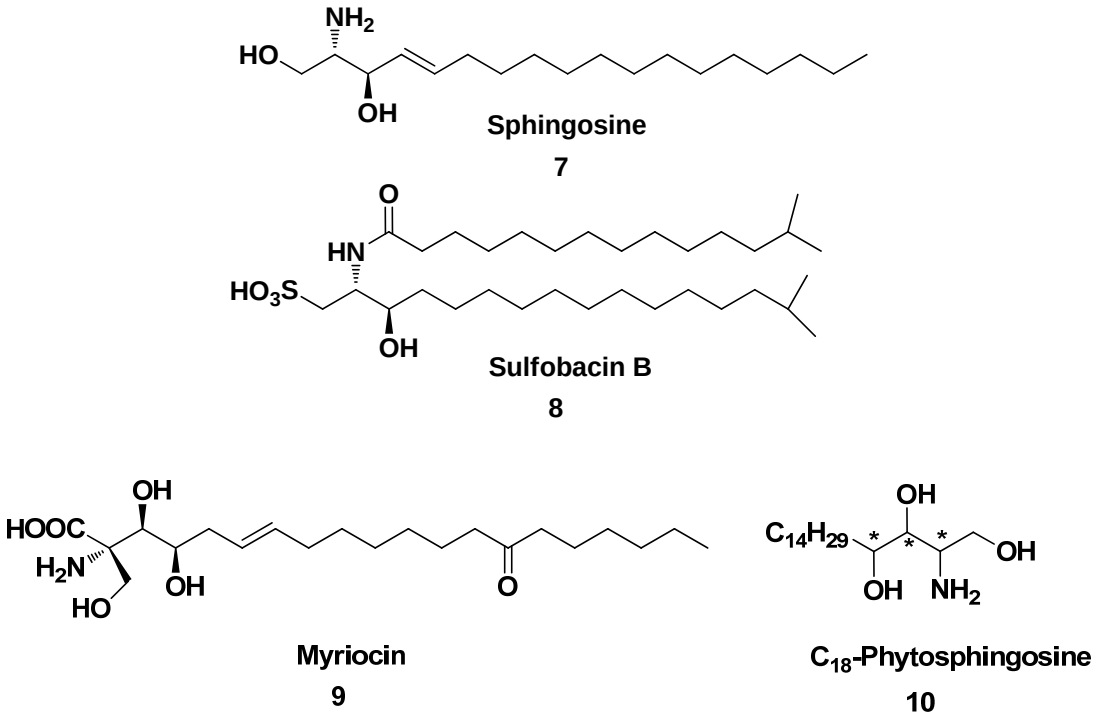


Fig. 2

hydroxyl groups as well as a carboxylic acid. These compounds, which are isolated from the thermophilic ascomycete *M. albomyces*, are potent immunostimulatory agents. Phytosphingosine **10** is a potential heat stress signal in yeast cells[14] and some of its derivatives exhibit important physiological activity. α- and β-Galactosyl and glucosylphytoceramides are highly potent against tumors.

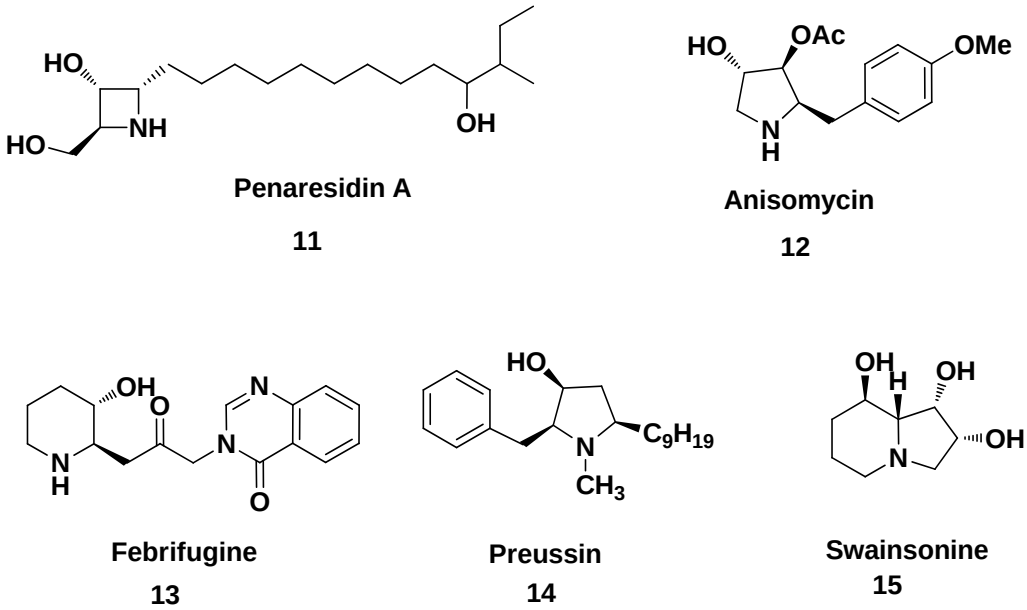
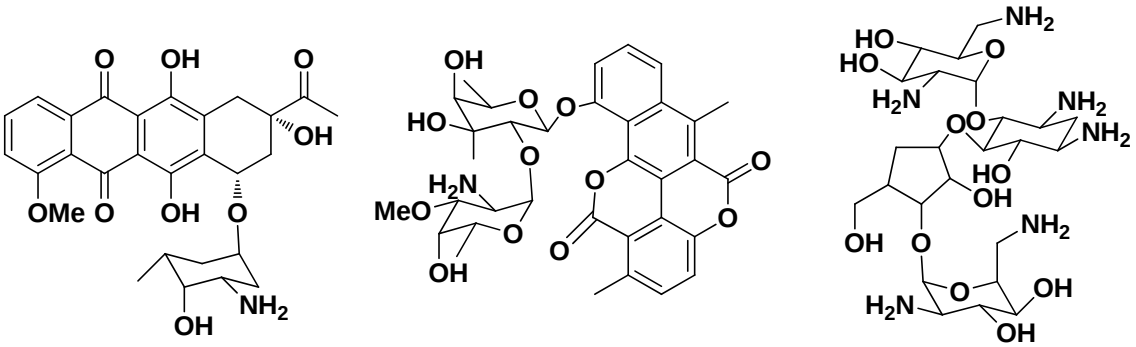


Fig. 3

A third large group of amino alcohols are the cyclic amino alcohols in which the amino group of the vicinal amino alcohol is contained within a ring. Some well-known examples[15] are shown in **Fig. 3**.

Sugars are yet another class, containing the amino alcohol moiety as components of larger molecules, either aglycones or other sugars. Daunomycin **16**,[16] elsamicin A **17**[17] and neomycin B **18**[18] are important examples (**Fig. 4**).



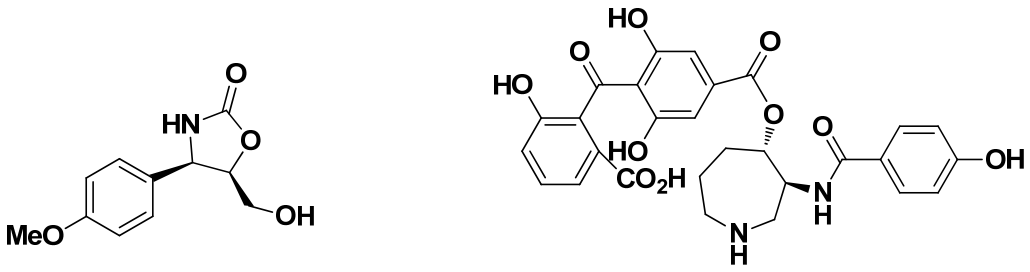
Daunomycin
16

Elsamicin A
17

Neomycin B
18

Fig. 4

Miscellaneous examples like cytoxazone **19**[19] contain the amino alcohol moiety as oxazolidinone ring. This compound is reported to be an immunoregulator. Balanol **20**,[20] isolated from the fungus *Verticillium balanoides*, is a structurally interesting amino alcohol in which both the hydroxyl and amino group are acylated. This azepino amino alcohol has attracted considerable synthetic interest due to its ability to inhibit protein kinase C (**Fig. 5**).



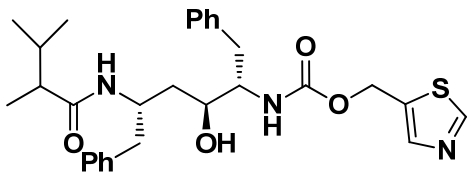
Cytoxazone
19

Balanol
20

Fig. 5

(2) Synthetic Pharmacologically Active Molecules

A host of synthetic molecules used as drugs or pharmacological agents also contain the vicinal amino alcohol moiety. Often these compounds are analogues of natural products which also contain a vicinal amino alcohol. Among the best known are the hydroxyethylene isostere peptidomimetics. This group of peptide analogues is typified by the HIV protease inhibitor squinavir **21**.[21] Recently, the amino alcohol **22** has been reported to selectivity interact with RNA.[22] This molecule was discovered in a random screening of commercially available amino alcohols. Molecules such as **22** which contain the vicinal amino alcohol are being investigated as anti-HIV agents. The amidine containing molecule **23** is reported to be an inhibitor of nitric oxide synthetase and has therapeutic implications for the treatment of a wide range of disease states[23] (**Fig. 6**).



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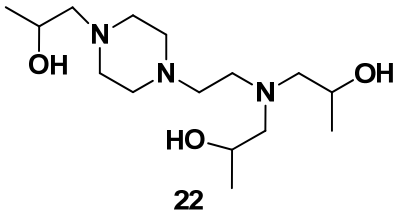

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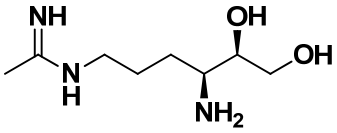


23

Fig. 6

The presence of the vicinal amino alcohol moiety in these pharmacologically active molecules is essential for their biological activity. The need to prepare these compounds as well as analogues has dramatically increased the importance of the development of methods for the synthesis of vicinal amino alcohol.

(3) Ligands and Chiral Auxiliaries

A number of chiral reagents utilize enantiomerically pure amino alcohols as ligands or chiral auxiliaries[24] (**Fig. 7**). The best known are the Evans auxiliaries **24**.[25] These amino alcohol derived oxazolidinones have been used for a host of reactions ranging from aldol condensations to Diels-Alder reactions. The oxazaborolidines **25** derived from proline have been extensively used for the asymmetric reductions of carbonyl compounds.[26] The ephedrine **26** derivative has been used as a chiral proton quench to deracemize an enolate.[27]

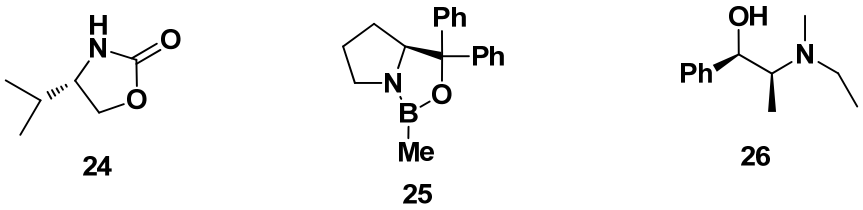


Fig. 7

2.1.2. Synthetic Routes to Vicinal Amino Alcohol

Just as there are many examples of molecules containing the vicinal amino alcohol moiety, there are an equally large number of synthetic routes to these molecules. The most common variant of functional group manipulation is the addition of a nucleophile to an α-amino carbonyl compound. Conceptually one can divide these syntheses into four different classes:

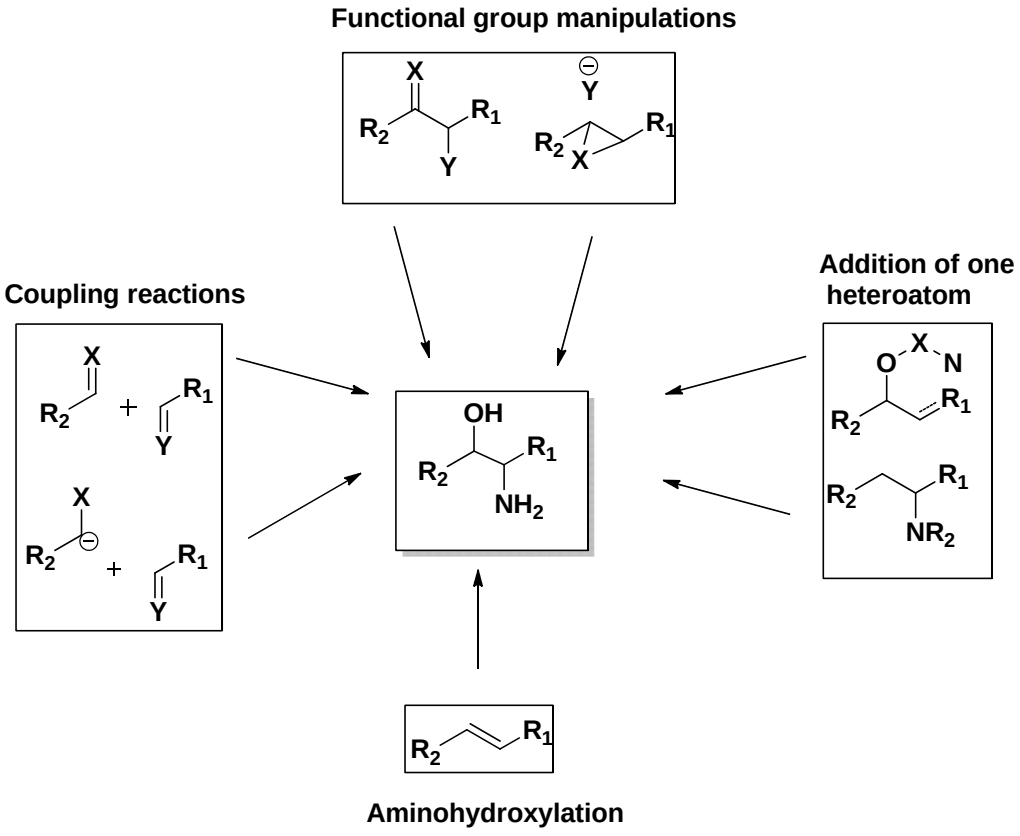


Fig. 8

(1) Functional group manipulation of a molecule containing both heteroatoms

(2) Addition of one heteroatom to a molecule which already contains one heteroatom

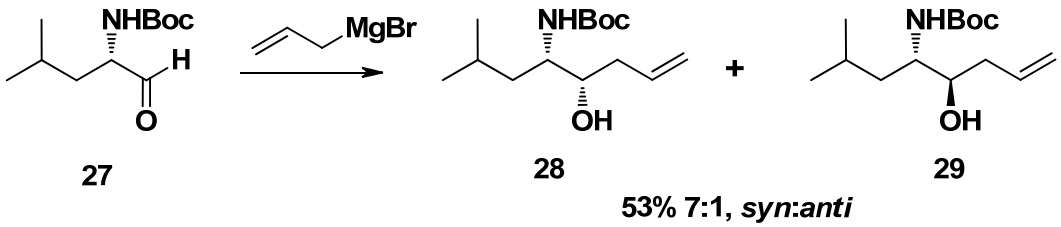
(3) Addition of both heteroatoms to a molecule which has neither

(4) Coupling of two molecules, each of which has one heteroatom.

(1) Functional Group Manipulation of a Molecule Containing Both Heteroatoms

There are two general versions of this disconnection. One involves reduction or nucleophilic addition to an imine or carbonyl group. The second involves opening of an epoxide, aziridine, cyclic thiocarbonate or cyclic sulfite/sulfate.

(i) Addition of a nucleophile to an α-amino carbonyl (**Scheme 1**)

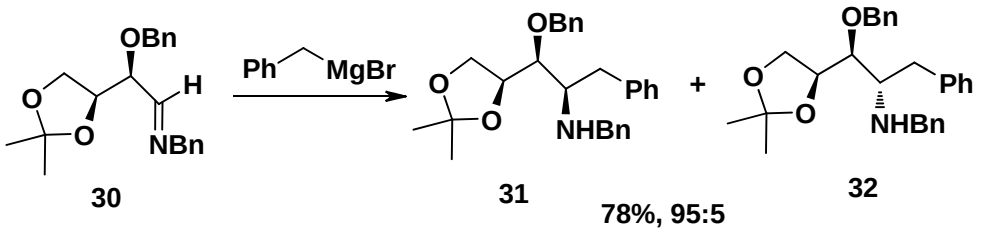


Scheme 1

The generation of high levels of diastereoselectivity and the stability of the α-amino carbonyl compound have sometimes been problems with this method. For example, the addition of allyl magnesium bromide to the α-amino aldehyde **27** produces only a moderate yield of a 7:1 mixture of *syn*- and *anti*-isomers **28** and **29** (**Scheme 1**).[28]

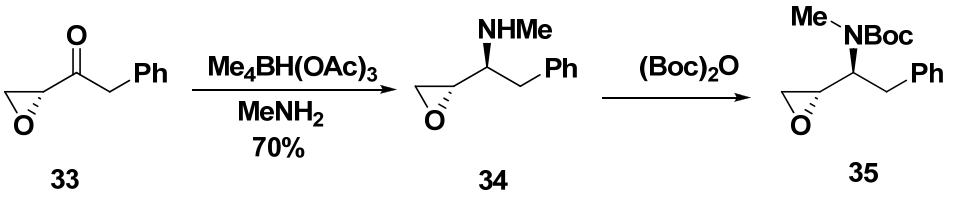
(ii) Addition of a nucleophile to an α-hydroxy imine (**Scheme 2**)

The corresponding reactions between a protected α-hydroxy imine and a nucleophile are not well represented due to the relative instability of the imines. One example in which a protected α-hydroxy imine used directly is shown in **Scheme 2**.[29] Imine **30** is treated with an organometallic reagent to provide the *syn*-isomer **31** as the major product. Yields for this reaction are generally good (37-78%).



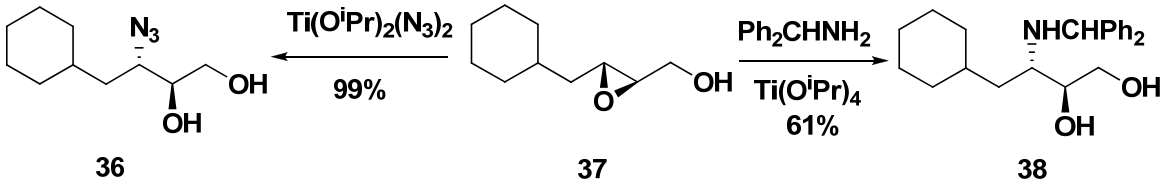
Scheme 2

(iii) Reductive amination (**Scheme 3**)[30]



Scheme 3

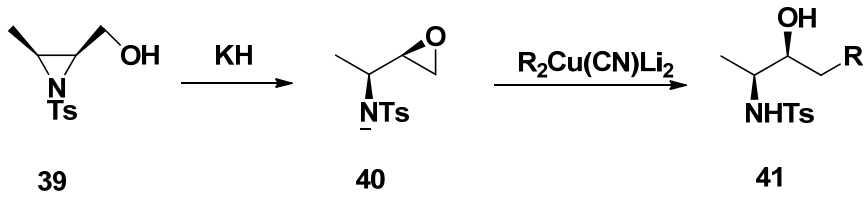
(iv) Ring opening reaction of epoxide (**Scheme 4**)[31-33]



Scheme 4

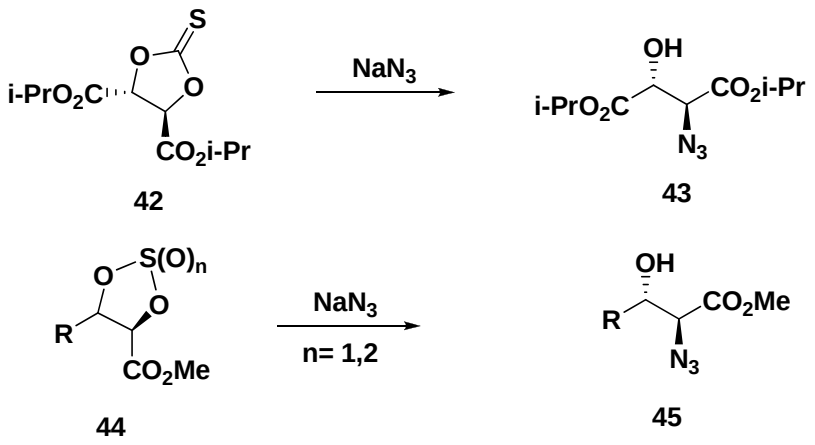
Amines and azide ion can readily open epoxides to form a vicinal amino alcohol or azido alcohol.[31] Azido alcohols are readily converted to the amino alcohols.[32] An example of this reaction is shown in **Scheme 4**.[33] Epoxide **37** is prepared from the corresponding allylic alcohol via a Katsuki-Sharpless asymmetric epoxidation. Treatment of **37** with benzyhydral amine provides vicinal amino alcohol **38** in good yield. Reaction of similarly substituted epoxides generally provides the regiochemistry shown. Similarly, reaction with azide provides the azido alcohol **36** in near quantitative yield.

(v) Ring opening reaction of aziridine (**Scheme 5**)[34,35]



Scheme 5

(vi) Ring opening reaction of cyclic thiocarbonates[36,37] and cyclic sulfites/sulfates[38] (**Scheme 6**)



42 **43**

44 **45**

Scheme 6

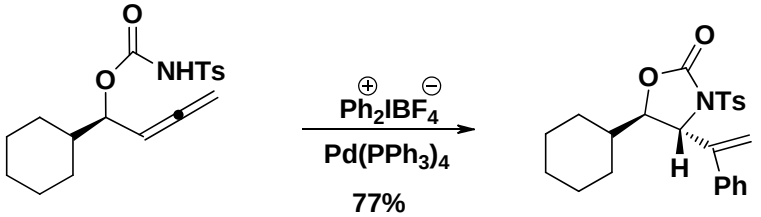
Thus, a number of routes using functional group manipulations are available to prepare vicinal amino alcohols. Most of these methods rely upon the stereochemical information already contained within the molecule to control the stereochemistry of the new stereocenter. Thus, these methods generally rely upon some other method to ultimately control the stereochemistry of the vicinal amino alcohol.

2. Addition of One Heteroatom

There are number of methods by which one hetero atom can be added to a molecule already containing a hetero atom.

(i) Addition of nitrogen (**Scheme 7**)

One method that has been utilized is the intramolecular addition of nitrogen to an electrophilic carbon, typically an olefin which has been activated by an electrophilic reagent.[39] A particularly interesting route is the intramolecular cyclization of the allenyl carbamate **46**. Reaction of **46** with an aryliodonium salt and a palladium catalyst provides oxazolidinone **47** (**Scheme 7**).

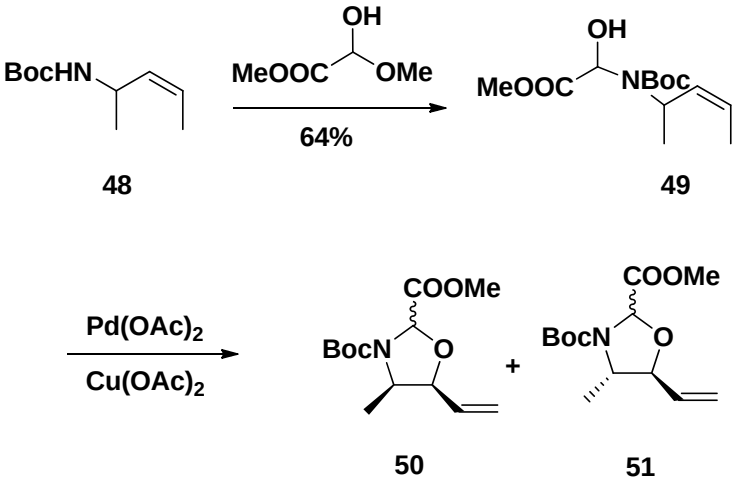


46 **47**

Scheme 7

(ii) Addition of oxygen (**Scheme 8**)

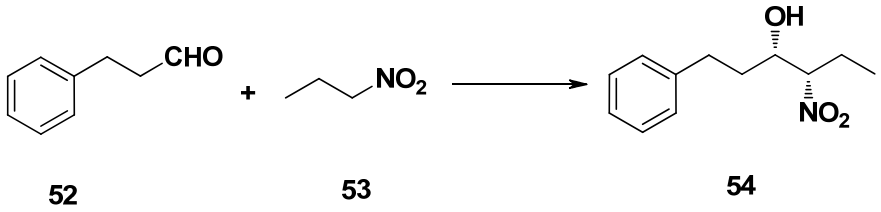
The addition of oxygen to a molecule already containing nitrogen is not a commonly used route to vicinal amino alcohols. A method analogous to the chemistry shown in **scheme 8** is the intramolecular reaction of a hemiaminal **49** with an olefin.[40] The nitrogen counterpart (nitrogen adds to olefin) has been reported.[41] In this interesting reaction, treatment of **49** with $Pd(OAc)_2$ provides a separable mixture of oxazolidines **50** and **51** in fair yield (**Scheme 8**). The diastereoselectivity in this reaction is unfortunately not particularly good. Conversion of **50** or **51** to the *N*-Boc amino alcohol is accomplished by ester hydrolysis, anodic oxidation and a final hydrolysis to the vicinal amino alcohol in > 90% yield.



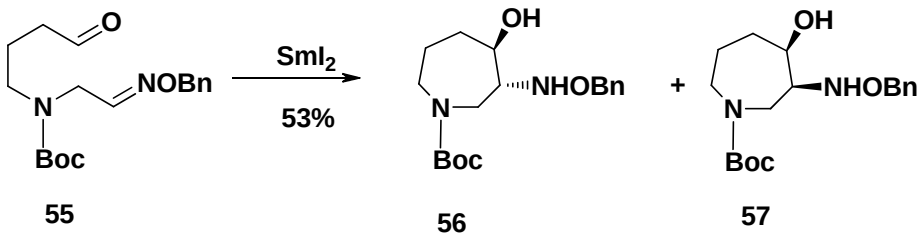
Scheme 8

3. Coupling Reaction

There are two general types of coupling reactions that have been used in the synthesis of vicinal amino alcohols, one is the Henry reaction[42] (**Scheme 9**) and other is Pinacol-type reaction[43] (**Scheme 10**).



Scheme 9

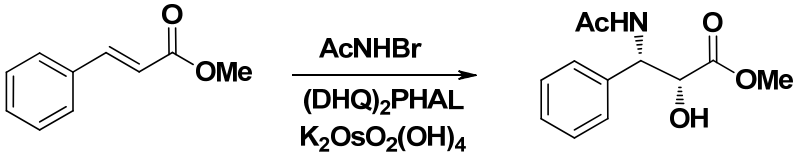


55 56 57

Scheme 10

4. Asymmetric aminohydroxylation

Asymmetric aminohydroxylation of olefin is possibly the most basic route to vicinal amino alcohols which can be prepared in single step using Sharpless[44] method in the presence of cinchona alkaloid ligands (**Scheme 11**).



58 59

Scheme 11

Thus, there are numerous routes to the vicinal amino alcohol moiety. The choice of synthetic route for a given application will vary depending upon substitution, as well as the relative and/or absolute stereochemistry desired. A key theme in many of these methods is the generation of enantiomerically pure compounds.

2.1.3. Synthetic Plan

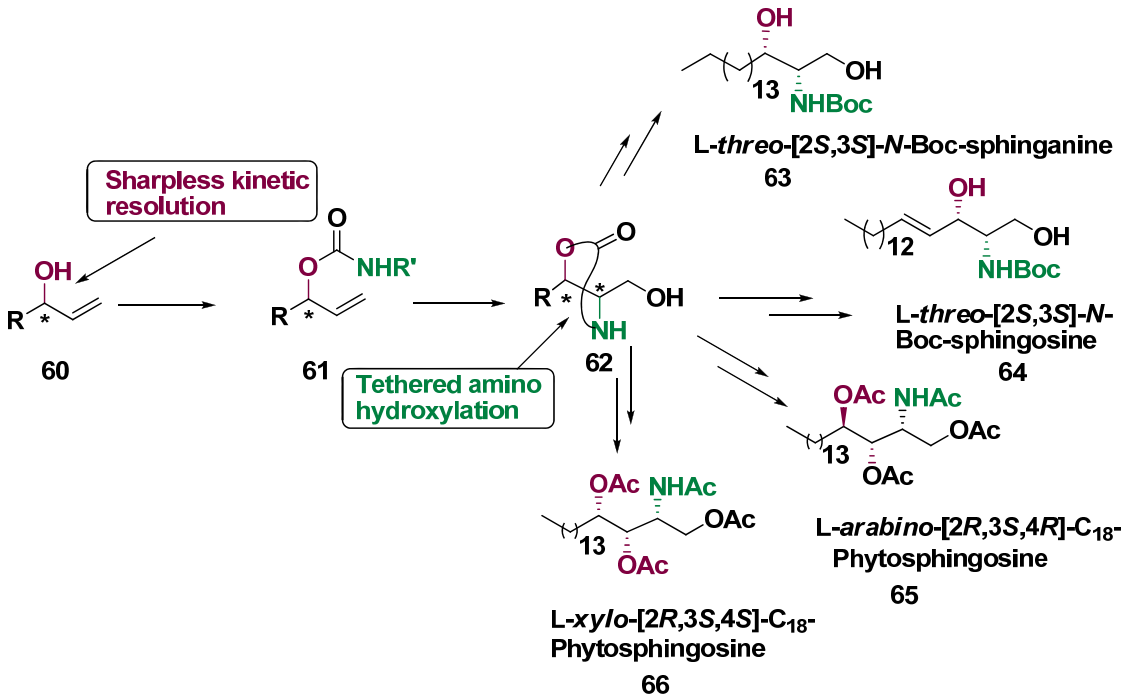
We have utilized Sharpless asymmetric kinetic resolution, tethered aminohydroxylation, a recent development in aminohydroxylation to synthesise the target molecules such as L-*threo*-sphingosine, L-*threo*-sphinganine and L-*arabino*- and L-*xylo*-C_{18}-phytosphingosine. Development of such a route would be useful for further studies on structure-activity relationships of these pharmacologically active derivatives. We recently developed a strategy leading to 2 stereoisomers of L-*threo*-sphingosine, 2 stereoisomers of L-*threo*-sphinganine and 4 stereoisomers of phytosphingosine 1,2-amino alcohol. In coming three sections we have discussed the synthesis of these sphingoid bases.

(i) **L-*threo*-sphingosine:** Sphingosines are known inhibitors of protein kinase C and they are backbone of glycosphingolipids and phosphosphingolipids. The synthetic strategy features the Sharpless kinetic resolution and tethered aminohydroxylation as the key steps.

(ii) **L-*threo*-sphinganine:** L-*threo*-dihydrosphingosine (safingol) is of particular interest due to its medicinal importance. Safingol is an antineoplastic, antipsoriatic drug and an inhibitor of protein kinase C (PKC) and is known to act synergistically with anti-cancer drugs. The amino alcohol moiety has been arrived via Sharpless asymmetric tethered aminohydroxylation.

(iii) **L-*arabino*- and L-*xylo*-C_{18}-phytosphingosine:** Phytosphingosine is a potential heat stress signal in yeast cells and some of its derivatives exhibit important physiological activity. α- and β-Galactosyl and glucosylphytoceramides are highly potent against tumors. The synthetic strategy features the Sharpless kinetic resolution and tethered aminohydroxylation as the key steps.

Retrosynthetic analysis: Our synthetic approach for the synthesis of sphingoid bases was envisioned through the retrosynthetic analysis as shown in **Scheme 12**. We visualized compound **62** as an important precursor from which all the target sphingoid bases (**63-66**) could be constructed. The amino stereocenter in **62** could be introduced by tethered aminohydroxylation, which in turn would be obtained from carbamate **61**. The carbamate **61** could be prepared from an allylic alcohol **60** which in turn would be derived from the Sharpless kinetic resolution. In this strategy, the amino center could be installed using tethered aminohydroxylation in a highly regio-and stereoselective manner while the hydroxyl centre would be derived from Sharpless kinetic resolution.



Scheme 12

2.1.4. References

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2.2 SECTION B

ENANTIOSELECTIVE SYNTHESIS OF L-*threo*-SPHINGOSINE

2.2.1. Introduction

Sphingolipids are structurally diverse constituents of membranes in mammals, plants, fungi, yeast and in some prokaryotic organism and viruses.[1] Sphingolipids and some of their metabolites exhibit essentially all type of cell regulation such as cell proliferation, differentiation, immune response, cell recognition, apoptosis, adhesion and signal transduction.[2]

Glycosphingolipids contain two basic structural motifs: carbohydrate and ceramide (**Fig. 1**). The ceramide portion consists of a sphingoid base and an amide-linked fatty acyl chain, e.g. stearoyl or palmitoyl. The structural variation in fatty acids (*N*-acyl portion, sphingosines and carbohydrates results in a great variety of chemically distinct glycosphingolipids.[3]

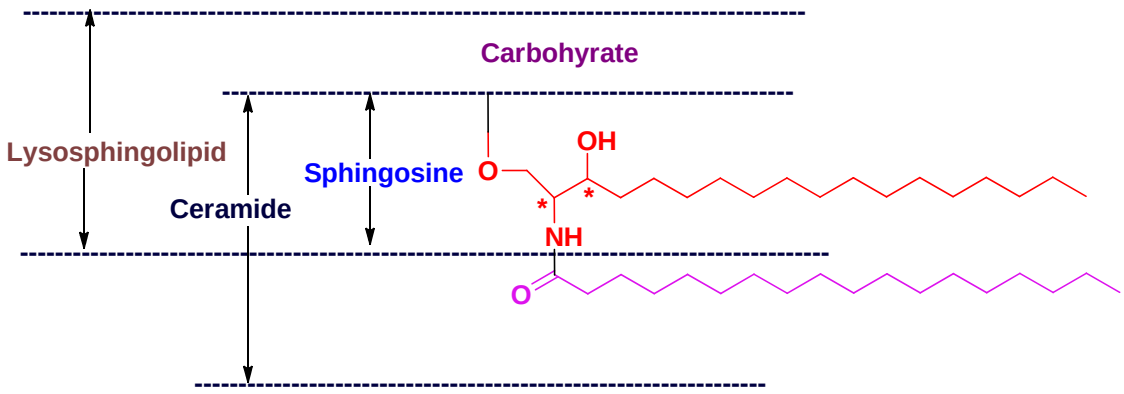
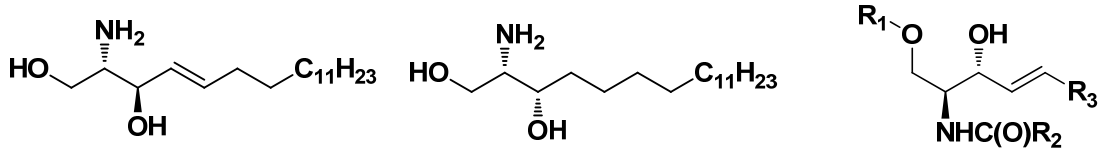


Fig. 1. Glycosphingolipid structure

Glycosphingolipids are found in the cell membrane of all animal and many plant cells, where they serve as identifying markers and regulate cellular recognition, growth and development.[4] They are thought to function by anchoring the hydrophobic ceramide portion (**Fig. 1**) in the plasma membrane exposing the hydrophilic carbohydrate portion to the surrounding exterior which specifies the intended biological function.[5] They are involved in several biological functions such as (i) HIV binding to galactosyl ceramide receptor sites in cells lacking the principal CD4 cellular receptor,[6] (ii) being unambiguous links between specific sphingolipids and malignant tumors which enables them to be used as 'biological markers' for possible early detection of cancer,[4] and (iii) potent and reversible inhibition of protein kinase C by

breakdown products of glycosphingolipids, e.g. sphingosine **1**, sphinganine **2** (dihydrosphingosine) and lysophingolipids (**Fig. 2**). Sphingosine **1** is the core structure of most sphingolipids **3**, which can vary in the nature of the headgroup R_1 and the structure of the *N*-acyl group R_2 (if one is present) (**Fig. 2**). Sphingosine analogues which differ in the nature of the sphingosine tail R_3 are also common, one being the saturated analogue sphinganine **2**. Sphingosines constitute a group of related long-chain aliphatic 2-amino-1,3-diols, of which 2-amino-D-*erythro*-4(*E*)-octadecene-1,3-diol (commonly called sphingosine **1**) occurs most frequently in animal glycosphingolipids. Studies have shown that defects in sphingolipid metabolism leads to several inherited and most common human diseases including diabetes,[7] cancers,[8] infection by microorganisms,[9] Alzheimer's disease,[10] heart disease and an array of neurological syndromes.[11]



D-*erythro*-sphingosine **1** L-*threo*-sphinganine **2** **3**

Fig. 2

In recent times, there has been tremendous upsurge of interest in the synthesis of structurally modified sphingosines as some of their analogues have been shown to bring morphological changes in neuronal cells[12] and behave as enzyme inhibitors.[13] Sphingosines[14] are known inhibitors of protein kinase C[15] and they are backbone of glycosphingolipids and phosphosphingolipids. This larger family of biomolecules is involved in a plethora of processes related to cell growth, differentiation, adhesion, and neuronal repair.

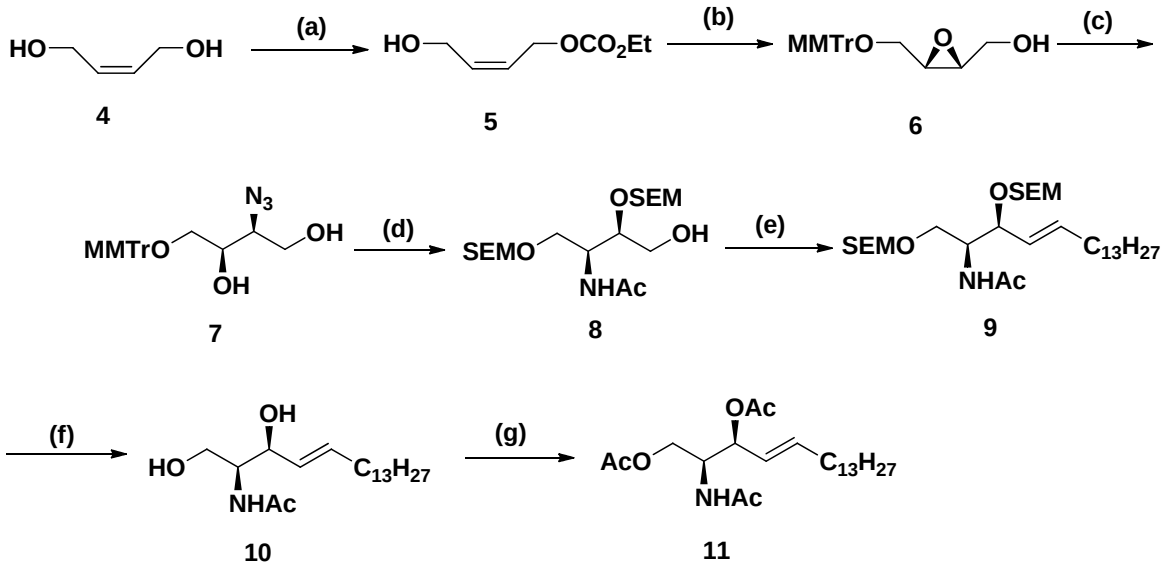
Any sphingosine synthesis must have two key issues. First, the D-*erythro* stereochemistry is most common, but all four possible diastereomers of the 2,3-amino alcohol unit are known and are all bioactive to different degrees.[16] Thus stereochemical control at C-2 and C-3 is crucial. Second, the attachment of functionally diverse tail groups (other than the $C_{13}H_{27}$ tail of sphingosine itself) by a *trans* double bond is required to access many different sphingosine derivatives that have been identified. The *trans* geometry is required for activity so control of the double-bond geometry is critical. High levels of stereocontrol are also desirable from a practical point of view. Because separation of the various sphingosine stereoisomers is difficult, only synthesis which have high levels of stereocontrol have practical value in making significant quantities of pure material.

2.2.2. Review of Literature

Due to the variety of their biological activity and their scarcity in nature, it is little wonder that L-*threo*-[2*S*,3*S*]-sphingosine **2** have become important synthetic targets. To provide homogeneous material for use in biophysical, biochemical and pharmacological studies, a variety of synthetic methods[17] has been developed. The vast majority of reported preparations of L-*threo*-[2*S*,3*S*]-sphingosine are chiral pool. Reported syntheses of L-*threo*-[2*S*,3*S*]-sphingosine have burgeoned in recent years because of increasing recognition of their biological relevance. A few interesting syntheses of L-*threo*-[2*S*,3*S*]-sphingosine are described below.

Kitagawa I. *et al.* (1989)[17l]

Kitagawa employed Sharpless asymmetric epoxidation and regiospecific ring-opening reaction of epoxide with azide. Sharpless asymmetric epoxidation of allylic alcohol **5** gave the epoxide **6** in 73% yield and 93% enantioselectivity. Epoxide was converted into 1,3-



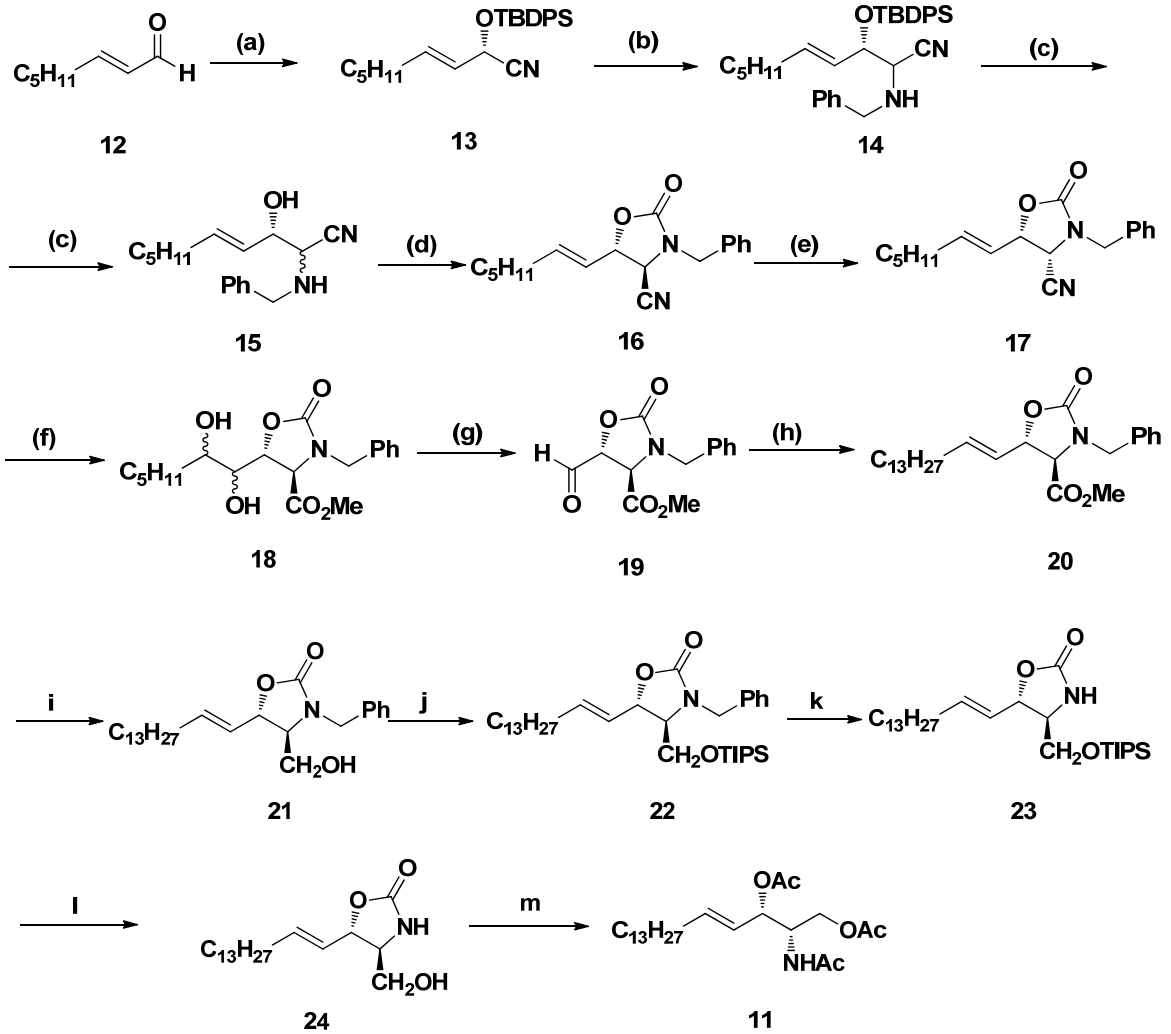
Scheme 1. *Reaction and condition*: (a) $(EtCO)_2O$, acetone, 55%; (b) [i] MMTrCl, Pyridine; [ii] 1% KOH-MeOH, 93%; [iii] (-)-DET, *t*-BuOOH, 78%; (c) $Ti(OPr^i)_2(N_3)$, Benzene, 83%; (d) (i) SEMCl, $^iPr_2NEt$; (ii) $LiAlH_4$; (iii) Ac_2O, Pyridine; (iv) 1% HCl-MeOH, 75% yield for four steps, (e) [i] Swern oxidation; [ii] $Ph_3PC_{14}H_{29}Br$, *n*-BuLi, 75 % yield for two steps; (f) [i] 9% HCl-MeOH; (ii) hν, PhSSPh, 95% for two steps; (g) Ac_2O, Pyridine, 75%.

diol **7** by regioselective opening with $Ti(OPr^i)_2(N_3)$ in 14:1 (1,2-diol : 1,3-diol). The diol **7** was converted into hydroxy-amide **8** by sequential benzoylation, methoxy-methylation reduction and acetylation. Compound **9** was prepared by Swern oxidation followed by Wittig

olefination and acidic hydrolysis. Photoisomerisation of **9** in the presence of PhSSPh followed by acetylation gave triacelyated **11** product in 11.94% overall yield.

Griengl *et al.* (2000)[17f]

Griengl described chemoenzymatic stereoselective mediated cyanohydrin preparation towards the synthesis of sphingosine. Treatment of (*E*)-2-octenal **12** with hydroxynitrile lyases gave cyanohydrin **13** in 99% ee and 90% yield. Compound **13** was converted into diastereomeric oxazolidinone **16** by sequential cyano protection, TBDPS deprotection, carbamate formation. The trans–oxazolidinone **16** was transformed into methyl ester **18** followed by conversion of heptanyl moiety into penta decyl **20** by oxidative clevage and modified Wittig reaction. Compound **20** was converted into **23** by $LiAlH_4$ followed by TBS protection and basic deprotection of nitrogen under $Na/NH_3(l)$ condition. Compound



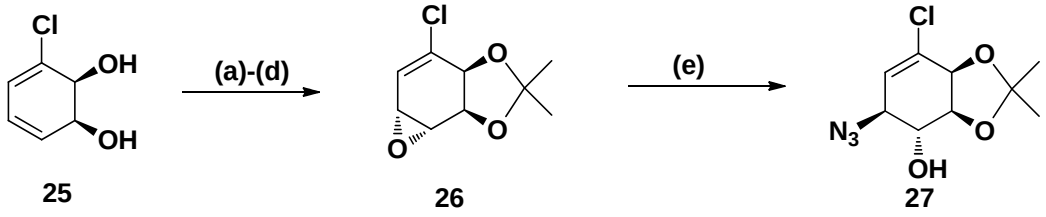
Scheme 2. *Reagents and conditions*: (a) (i) Hnl from *Hevea brasiliensis*, HCN, 100%; (ii) *tert*-butyldiphenylsilyl chloride, imidazole, DMF, rt, 90%; (b) (i) DIBAL-H, Et_2O, -70 ^oC then NH_4Br/MeOH; (ii) benzylamine, rt; (iii) $NaCN/NH_4Br$ in MeOH, -45 ^oC, 93%; (c)

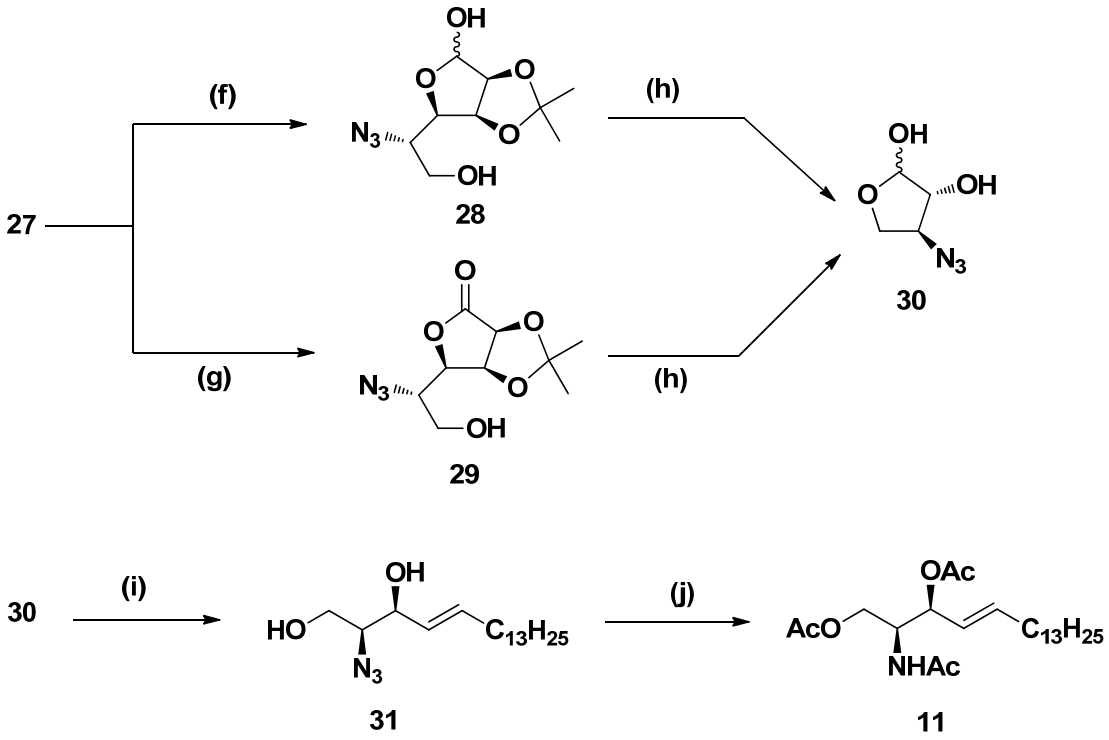
TBAF, THF, rt, 100%; (d) 1,1-carbonyldiimidazole, CH_2Cl_2, rt, 100%; (e) (i) HCl(g), Et_2O/MeOH then H_2O, 10 ^oC, 88%; (ii) MeOH, conc. HCl, reflux, 64%; (f) OsO_4, *N*-methylmorpholino-*N*-oxide, acetone/pH 6.8 phosphate buffer, rt, 93%; (g) $NaIO_4$, acetone/water, rt, 96%; (h) $C_{13}H_{27}CHI_2$, $CrCl_2$, DMF/THF, rt, 32%; (i) $LiBH_4$, THF, 30 min, 94%; (j) TIPSCl, DMF, 0 ^oC–rt, 96%; (k) Na/NH_3(l), -75 ^oC, 70%; (l) TBAF, THF, 0 ^oC, 94%; (m) (i) 2N KOH, EtOH, 85 ^oC, 90%; (ii) Ac_2O, triethylamine, DMAP, 0 ^oC, 95%.

23 was converted into triacelyated product **11** by desilylation, basic hydrolysis of carbamate and acetylation of amines and alcohols. This method gave triacetylated product in 14 steps and 12% overall yield.

Hudlicky *et al.* (1998)[17h]

Hudlicky reported chemoenzymatic synthesis of all four stereoisomers of sphingosine from chloro benzene. *Cis*-diene-diol **25** is obtained by enzymatic oxidation of chlorobenzene with toluene dioxygenase from the whole cells of *Pseudomonas putida* **39D**, *cis* diol was protected as acetonide and converted into desired epoxide **26**, *trans* azido alcohol **27** was accessed by exposure to NaN_3 in 91% yield. Subsequently C1-C6 olefin of azido alcohol **27** was oxidised followed by further oxidative clevage of the C2-C3 diol to liberate azido deoxy *threose* or *erythrose* which was subjected to direct olefination to give *trans*-azidosphingosine **31**. Azide **31** was acetylated under H_2S, pyridine, and H_2O and followed by peracetylation to give triacetyl-L-*threo*-sphingosine **11**. This method gave triacetylated product in 10 steps and 9% overall yield.

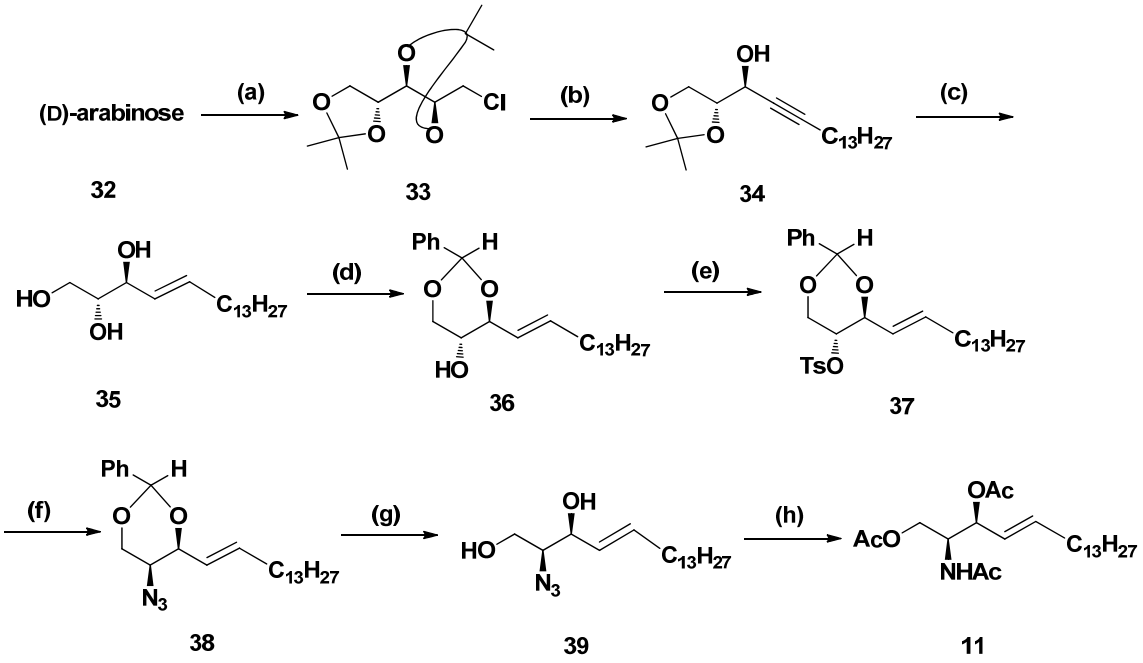




Scheme 3. *Reagents and conditions*: (a) 2,2-dimethoxypropane, cat. *p*-TsOH, CH_2Cl_2; (b) NBS, DME/H_2O (3:2), 0 °C; (c) NaOH, Bu_4HNSO_4, CH_2Cl_2 reflux; (d) *m*-CPBA, CH_2Cl_2, 64% for four steps; (e) NaN_3, NH_4Cl, DME/EtOH/H_2O (3:3:2), 65 °C, 75%; (f) (i) O_3 (excess), MeOH, -78 °C; (ii) $NaBH_4$, -30 °C to rt, 80% for two steps; (g) [i] O_3 (excess), MeOH, -78 °C; [ii] $NaBH_3CN$, pH ~3.0, 0 °C, 60% for two steps; (h) [i] Amberlyst 15 (wet) ion-exchange resin, strongly acidic, H_2O; [ii] $NaIO_4$, H_2O, 65% for two steps; (i) tetradecyltriphenylphosphonium bromide, *n*-BuLi, THF; (j) Ac_2O, pyridine, 24% for two steps.

Yadav *et al.* (1993)[17j]

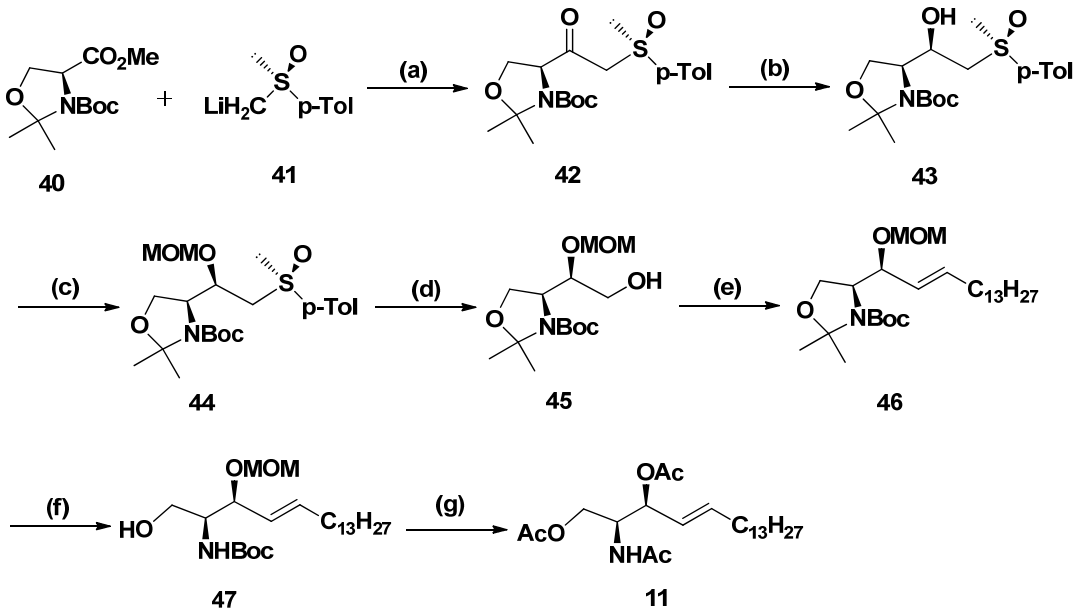
Yadav *et al.* utilized the D-arabinose **32** for the synthesis of L-*threo*-sphingosine. Compound **33** was converted into acetylenic alcohol under basic condition followed by alkylation to **34** by 1-bromotridecane. Compound **34** was reduced with $LiAlH_4$ followed by acetonide deprotection and 1,3-alcohol protection by benzaldehyde dimethyl acetal to afford **36** and subsequently free hydroxy of compound **36** was converted into azide, removal of benzylidene group reduction of azide into amine and acetylation furnished triacetyl-L-*threo*-sphingosine **11**.



Scheme 4. *Reagents and conditions*: (a) ref 17j; (b) (i) $LiNH_2/NH_3$, 98%; (II) $C_{13}H_{27}Br$, *n*-BuLi, 80%; (c) $LiAlH_4$, THF; (ii) pTSA, 75% for two steps; (d) benzaldehyde dimethyl acetal, 70%; (e) TsCl, CH_2Cl_2,78%; (f) NaN_3, DMF, 60 ^oC, 80%; (g) 3N HCl, THF, 65% (h) [i] $LiAlH_4$, THF; [ii] Ac_2O, pyridine, 70% for two steps.

Lomas *et al.* (1999)[17g]

Lomas *et al.* accomplished synthesis of sphingosine by chiral sulfoxide mediated reduction of β-keto sulfoxide **42**. Condensation of Garner's methyl ester **41** carbanion of (*R*)-(+)-

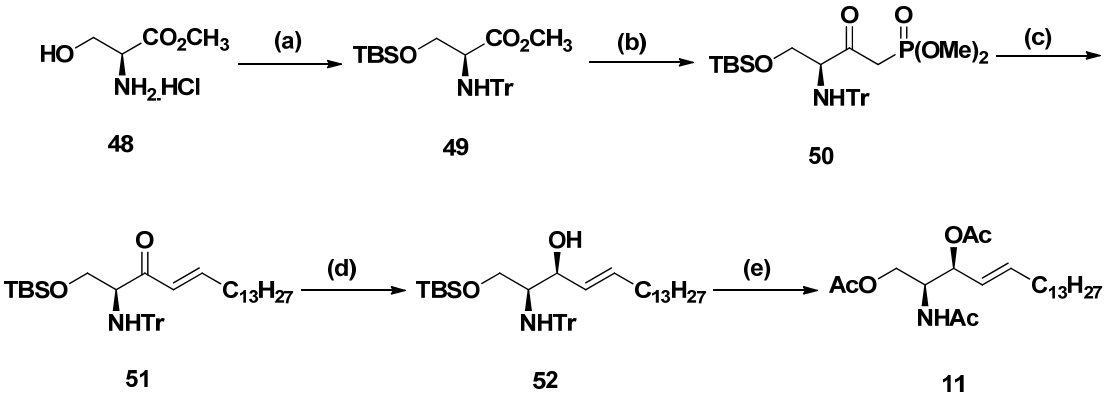


Scheme 5. *Reagents and conditions*: (a) condensation of **40** and **41,** 70%; (b) DIBAL-H/$ZnCI_2$, THF, -78 °C, 95%; (c) NaH, MOMCI, THF, 0 °C, 90%; (d) $(CF_3CO)_2O$, CH_3CN,

Collidine, 0 °C, 80%; (e) [i] $(COCl)_2$, DMSO, Et_3N, -78 °C; [ii] $CH_3(CH_2)_{12}CH_2PPhBr$, PhLi, LiBr, Et_2O/toluene, -30 °C to rt, 75%; (f) aq. AcOH (80%), 90%; (g) [i] CF_3CO_2H, H_2O; [ii] Ac_2O, Pyridine, DMAP (cat.), 85%.

methyl *p*-tolyl sulfoxide gave β-keto sulfoxide **41** in 70% yield, which was subjected to $LiAlH_4/ZnCl_2$ mediated reduction of β-keto sulfoxide in *syn* fashion **43,** then successive sulfoxide removal followed by alcohol oxidation and Julia olefination furnished **46** in very good yield. Compound **46** was converted into triacetylated sphingosine **11** by deprotection and acetylation.

Chung *et.al* (2002)[17e]

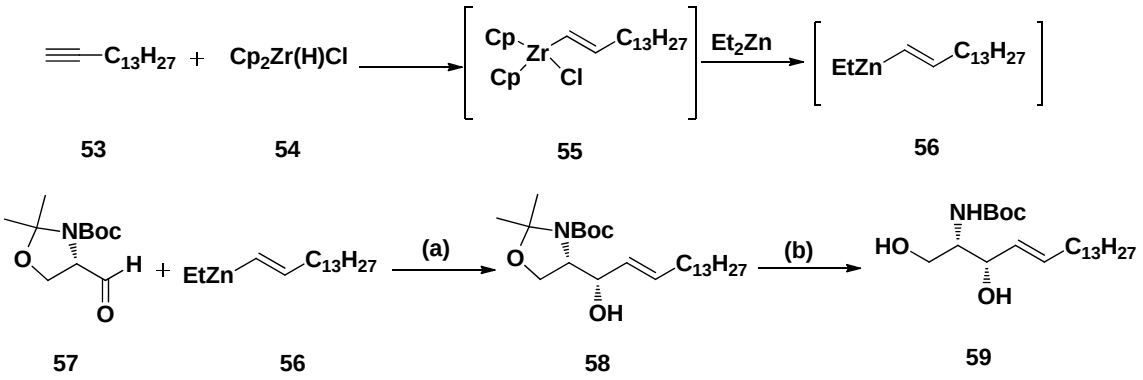


Scheme 6. *Reagents and conditions*: (a) (i) TBSCl, Et_3N, CH_2Cl_2, rt; (ii) TrCl, Et_3N, CH_2Cl_2, rt, 95% for two steps; (b) $LiCH_2PO(OMe)_2$, THF, -78 °C, 93%; (c) $C_{13}H_{27}CHO$, DBU, LiCl, THF, rt, 95%; (d) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C, 90%; (e) [i] 2N HCl, THF–MeOH, reflux, 85%; [ii] Ac_2O, pyridine, 0 °C, 70%.

Chung *et al.* utilized non-chelated controlled (open Felkin-Anh model) reduction of tritylated amino enone for the syn diastereomer. Serine ester **48** was converted into β-ketophosphonate **50** followed by Horner-Wadsworth-Emmons olefination with tridecane aldehyde to give tritylated amino enone **51**. Reduction of enone **51** with $NaBH_4$ in the presence of $CeCl_3 \cdot 7H_2O$ afforded the *N*,*O*-diprotected L-*threo*-sphingosine **52** in 92% de, via an open Felkin–Anh transition state (non-chelation control). Compound **52** was subjected to global deprotection under acidic condition followed by acetylation to furnish triacetylated L-*threo*-sphingosine **11**.

Murakami *et al.* (2000)[17b]

Murakami *et al.* utilized hydrozirconation of alkyne **53** followed by addition to Garner's aldehyde **57** in presence of $ZnCl_2$ to furnish **58** in very good *syn* selectivity (15:1). Compound **58** was then converted into **59** by acetonide deprotection under mild acidic condition.



Scheme 7. *Reagents and conditions*: (a) (i) **57** and **56** CH_2Cl_2, -30 °C to 0 °C, 92%; (b) AcOH-H_2O (9:1), 50 °C, 85%.

2.2.3. Present Work

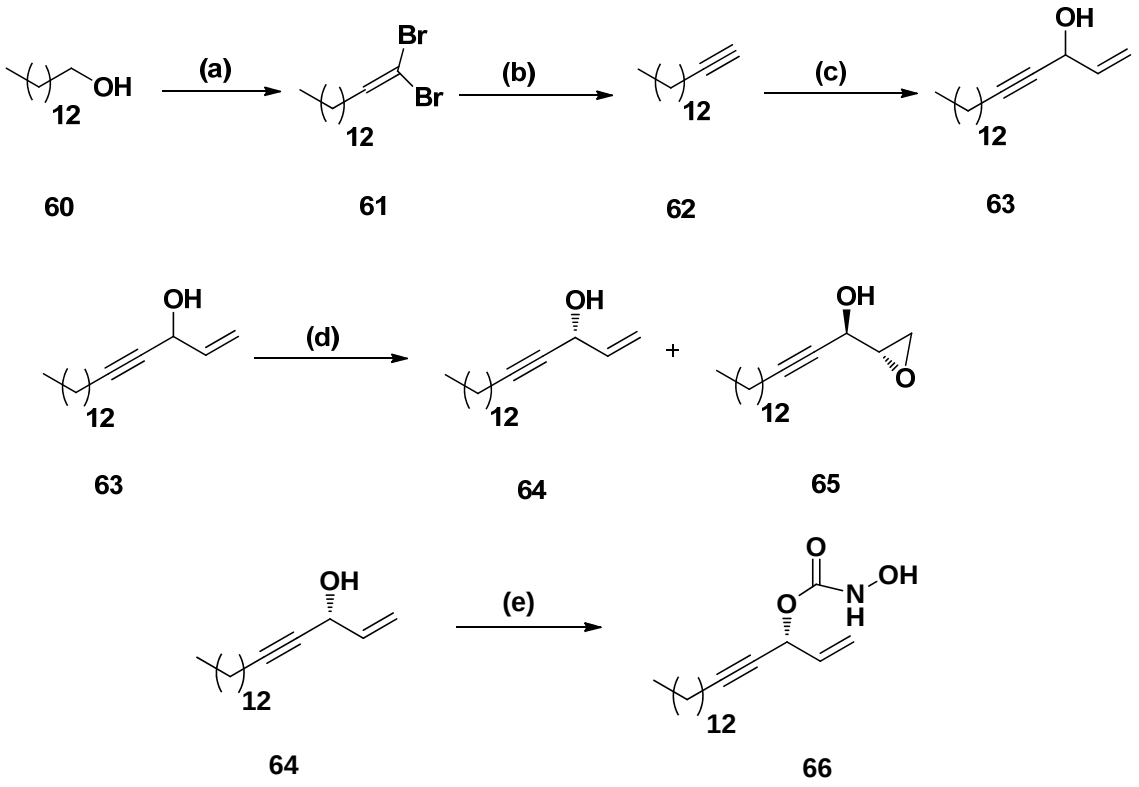
2.2.3.1. Objective

Given the vast chemistry, structural modifications and biological activities associated with sphingolipids, the synthesis of this class of vicinal amino alcohols has aroused considerable interest among several research groups around the world. Although a few syntheses are reviewed above, several more are documented in the literature. This explains the importance of research work in sphingolipid chemistry. As a part of our ongoing research program on the synthesis of sphingolipids bases and related aminoalcohols, we bacame interested in devising a common synthetic route by which a number of such compounds could be accessed. In the synthetic startegy employed Sharpless kinetic resolution is used to create chiral hydroxy centre and tethered amino hydroxylation to introduce the amino functionality. Using this strategy we have arrived at a common synthetic intermediate by which all the sphingoid bases such as sphingosine, sphinganine and phytosphingosine could be synthesised.

2.2.3.2. Results and Discussion:

The synthesis of L-*threo*-sphingosine started from commercially available tetradecanol **60** as depicted in **Scheme 8**. Homologation to the acetylene **62** was carried out by Corey-Fuchs protocol[18] in a three-step sequence involving pivaloyl chloride-DMSO mediated oxidation,[19]

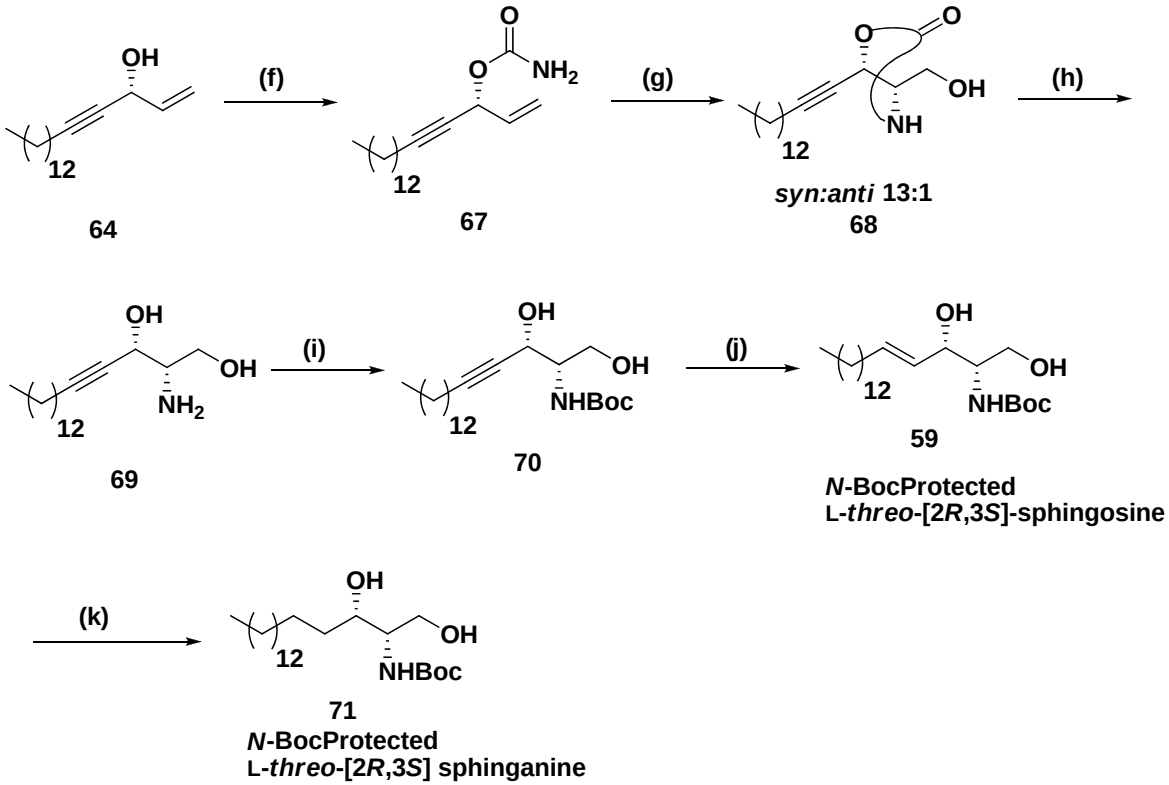
dibromomethylenation of the aldehyde and dehalogenation. Thus compound **60** was oxidized to the aldehyde using DMSO-pivaloyl chloride followed by dibromomethylenation with CBr_4 and PPh_3 in CH_2Cl_2 at -78 ^oC to furnish the dibromo olefin **61** in essentially quantitative yield. The ^1H NMR spectrum gave olefin protons at δ



Scheme 8. *Reagents and conditions*: (a) [i] Pivaloyl chloride, DMSO, Et_3N, CH_2Cl_2 -78 ^oC [ii] CBr_4, PPh_3, THF, -78 ^oC, 3 h, 73% yield of two step; (b) *n*-BuLi, THF, -78 ^oC, 3 h, 92%; (c) *n*-BuLi, freshly distilled acrolein, -78 ^oC, 2 h, 70%; (d) (-)-DIPT, $Ti(O^iPr)_4$, TBHP, dry DCM, molecular sieves, 3 Å, -20 ^oC, 3 days, 45% for **64** and 49% for **65**; (e) [i] CDI, pyridine, 40 ^oC, 4 h, then $NH_2OH.HCl$, 40 ^oC, 24 h, 30%; [ii] CDI, acetonitrile, 40 ^oC, 4 h, then $NH_2OH.HCl$, 40 ^oC, 24 h, 20%

6.39 protons at δ 6.39 (triplet) with coupling constant J = 8.7 Hz. Treatment of **61** with excess of *n*-BuLi in THF at -78 ^oC provided the pentadec-1-yne **62** in 92% yield. The ^1H NMR spectrum gave acetylenic protons at δ 2.51 (singlet). Treatment of **62** with *n*-BuLi in THF at -78 °C followed by addition of freshly distilled acrolein furnished the allylic alcohol **63** in 70% yield. The ^1H NMR spectrum gave olefin protons at δ 5.9-6.01 and 5.17-5.47. In the ^{13}C NMR spectrum of **63** olefin peaks appeared at δ 115.9, 137.6 and acetylenic carbons at 87.3 and 78.9. The secondary racemic alcohol **63** was subjected to Sharpless kinetic resolution[20] conditions using $Ti(O^iPr)_4$, (-)-DIPT as chiral auxiliary and TBHP as oxidant in

dry DCM at -20 ^{o}C for 3 days to give the chiral hydroxy olefin in 45% yield and 96% ee (determined from the corresponding Mosher's ester) **64** and chiral epoxy alcohol **65** in excellent yield. Both compounds **64** and **65** were throughly characterized



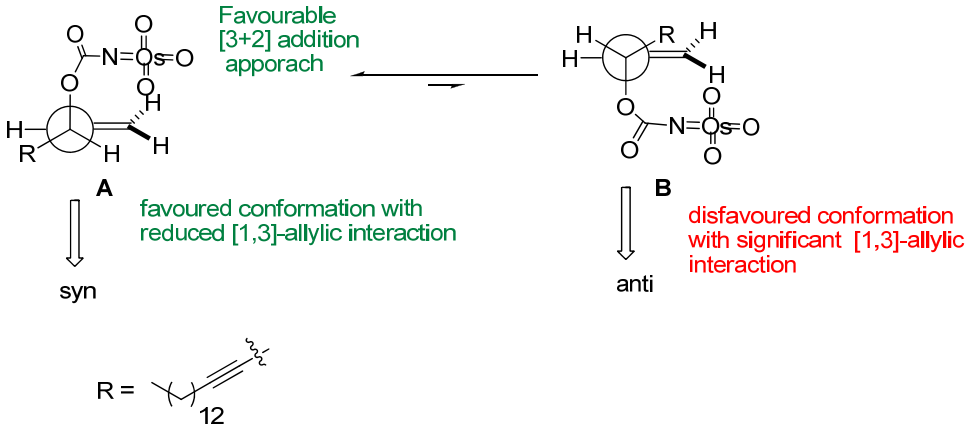
Scheme 9. *Reagents and conditions*: (f) $Cl_3CCONCO$, K_2CO_3, CH_2Cl_2:CH_3OH (1.5:1), 0 ^{o}C, 4 h, 85%; (g) NaOH, *t*-BuOCl, $^{i}Pr_2EtN$, potassium osmate, rt, 2.5 h, 65%; (h) K_2CO_3, methanol, rt, 6 h, 85%; (i) $(Boc)_2O$, dioxane, rt, 8 h, 82%; (j) Red-A1/Et_2O, 0 ^{o}C-rt, 24 h, 65%; (k) H_2/$Pd(OH)_2$, EtOAc, 2 h, 85%

using IR, ^{1}H NMR and ^{13}C NMR spectra. In the IR spectrum of **64,** olefin and hydroxyl stretching appeared at 1609 and 3511 cm^{-1} respectively. The ^{1}H and ^{13}C NMR spectra of **64** showed the presence of olefin peaks at δ 5.07-5.27 (m), 5.79-5.96 (m, 1H) and 114.2, 141.3 respectively. Having obtained the chiral allylic alcohol **64** in substantial amount and a suitable substrate for tethered aminohydroxylation[21] we then proceeded with the synthesis of target compound sphingosine. In order to prepare hydroxycarbamate **66** the alcohol **64** was reacted with CDI in pyridine, followed by the addition of hydroxylamine hydrochloride, to afford the hydroxy carbamate **66** albeit in poor yield. The use of acetonitrile instead of pyridine also failed to improve the yield substantially. Then we switched over to another tethered aminohydroxylation method[21a] (**Protocol A, chapter 1**). Accordingly the allylic alcohol **64** was treated with trichloroacetyl isocyanate using CH_2Cl_2:CH_3OH and K_2CO_3 as a

base to give the required carbamate **67** in excellent yield. The ^{1}H NMR spectrum of **67** clearly indicated broad singlet for $-NH_2$ at δ 4.68 and in the ^{13}C NMR spectrum amide carbonyl peak appeared at δ 156.6. The carbamate was converted into the oxazolidinone derivative **68** by a tethered aminohydroxylation protocol[21a] using *tert*-butyl hypochlorite as the oxidant, potassium osmate, NaOH, diisopropylethylamine and propanol as the solvent. The reaction proceeded smoothly to furnish the protected aminoalcohol **68** in 65% yield with complete regio- and very good diastereoselectivity (*syn:anti* 13:1, determined from ^{1}H NMR). The diastereomeric mixture could easily be separated by column chromatography. Compound **68** was fully characterized using IR, ^{1}H NMR and ^{13}C NMR spectra. In the IR spectrum hydroxyl and amine stretching appeared at 3506, 3362 cm^{-1}. The ^{1}H NMR and ^{13}C NMR spectra of **68** showed disappearance of olefin peaks and appearance of –*CH*(OH), -*CH*(NH) protons and carbon peaks at δ 3.88-4.03 (m), 4.99-5.14 (m) and δ 71.4, 80.3 respectively.

The key step in the TA as depicted in **Figure 3** is the intramolecular addition of the RN=Os=O fragment across the alkene leading to *syn* or *anti* relative stereochemistry. Generally the 1,3-allylic interaction plays a major role in determining the stereoselective outcome of the reaction. Between the two possible comformations **A** and **B** of tethered [3+2] cycloaddition, the 1,3-allylic interactions are minimised in conformation **A**, while such interactions are significant in conformation **B**. One would predict conformation **A** to be lower in energy and therefore the equilibrium is shifted towards the more stable conformation **A** thus leading to major *syn* product.

Fig. 3. Proposed transition states for the syn/anti selectivity observed during the TA reaction



The desired *syn*-diastereomer was subjected to hydrolysis with K_2CO_3 in methanol to furnish the crude aminoalcohol **69**. Delightfully the isolated compound **69** was found to be nice

crystal. In order to determine relative chemistry of tethered aminohydroxylation reaction product **69**, recrystallisation was done by slow evaporation of the solution mixture of DCM and hexane to give the clear crystalline solid, which was analysed for single X-ray crystallography. The ORTEP diagram (**Fig. 3**) clearly established the *syn* disposition of the H-atom in C-2, C-3 carbons thereby clarifying the *syn*-isomer.

Subsequent Boc protection using $(Boc)_2O$ in the presence of dioxane gave the Boc protected **70** in 82% yield, which was finally converted to the crystalline, enantiomerically pure *N*-Boc-L-*threo*-sphingosine[22] **59** in 65% yield by selective reduction of the C-C bond with Red-A1 in Et_2O. The physical and spectroscopic data of **36** were in full agreement with that reported.[22] Subsequently **59** was converted into *N*-Boc-L-*threo*-sphinganine **71** in 85% yield by reduction of double bond under $Pd(OH)_2/H_2$ condition.

X-ray Crystal Structure Analysis For Aminoalcohol

Crystal Data: Single crystals of the compound were grown by slow evaporation of the solution mixture of DCM and hexane. Colourless plate like crystal of approximate size 0.27 x 0.14 x 0.08 mm, was used for data collection on *Bruker SMART APEX* CCD diffractometer using Mo K_α radiation with fine focus tube with 50kV and 30mA. Crystal to detector distance 6.05 cm, 512 x 512 pixels / frame, multi run data acquisition. Total scans = 4, total frames = 2340, Oscillation / frame -0.3º, exposure / frame = 20.0 sec / frame, maximum detector swing angle = –30.0º, beam center = (260.2, 252.5), in plane spot width = 1.24, SAINT integration, range = 2.0 to 23.50º, completeness is upto 99.9%. SADABS correction applied, $C_{18}H_{35}NO_2$, M = 297.47. Crystals belong to Monoclinic, space group $P2_1$, a = 5.9598(5), b = 5.2424(4), c = 30.618(2)Å, Beta = 94.207(2) deg, V = 954.04(13)Å^3, Z = 2, D_c = 1.036 g/cc, μ (MoKα) = 0.066 mm^{-1}, T = 293(2) K, 7910 reflections measured, 2808 unique [I>2σ(I)], R value 0.0732, wR2 = 0.1667. All the data were corrected for Lorentzian, polarisation and absorption effects. SHELX-97 (ShelxTL) was used for structure solution and full matrix least squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model. Data collection and refinement parameters are listed in **Table 1**.

X-ray analysis revealed the conformation of the molecule and shows that C2, and C3 have *S* and *S* configurations respectively.

Fig 4: ORTEP diagram of the molecule. Ellipsoids are drawn at 40% probability.

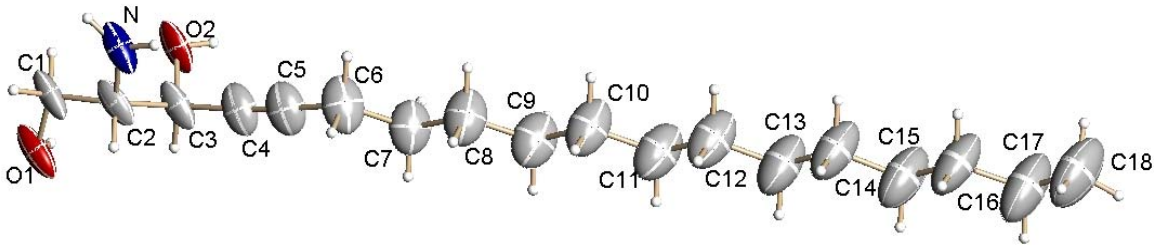
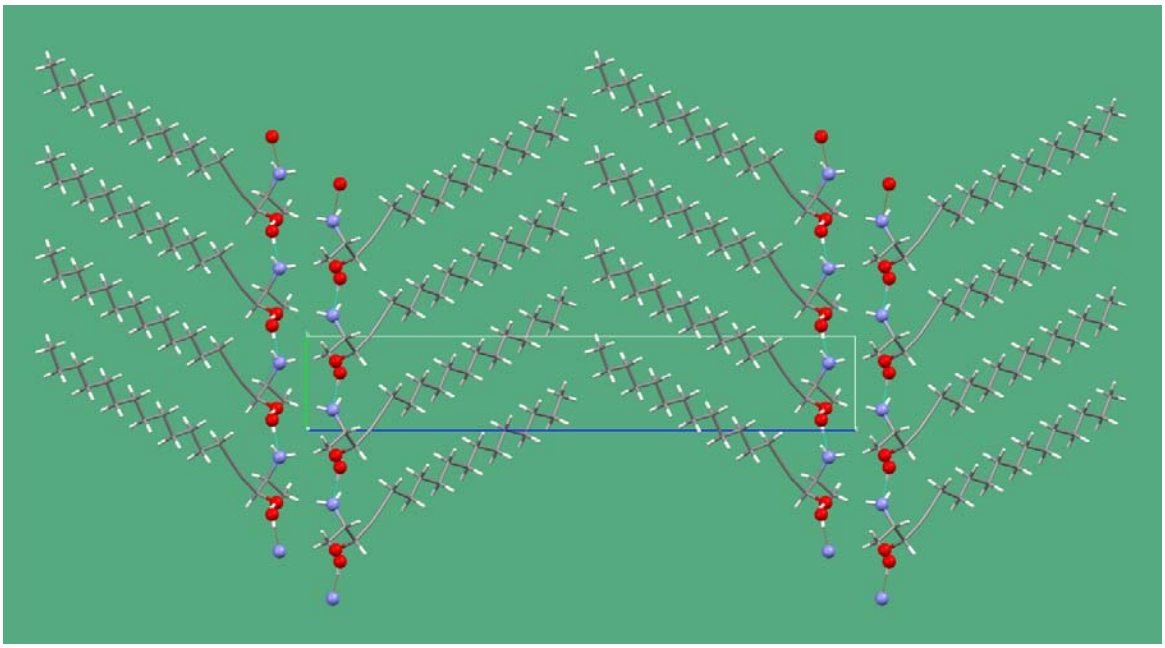


Fig 5: The molecules pack in a zigzag manner by the formation of N-H….O = 2.753 Å and O-H…O = 2.697 Å



2.2.3.3. Conclusion

We have accomplished the enantioselective synthesis of L-*threo*-sphingosine employing the Sharpless asymmetric aminohydroxylation as the key step in a highly concise manner. The problem of regioselectivity was overcome in the synthesis by tethered aminohydroxylation. A short reaction sequence and high-yielding steps renders our strategy a good alternative to the known methods.

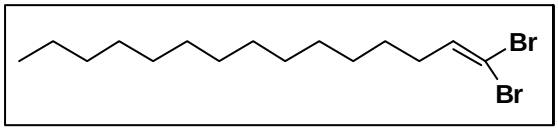
2.2.4. Experimental Section

General information

All reactions requiring anhydrous conditions were performed under a positive pressure of argon using oven-dried glassware (110 °C), which was cooled under argon. Solvents for

anhydrous reactions were dried according to Perrin *et al*.[23] Solvents used for chromatography were distilled at respective boiling points using known procedures. All commercial reagents were obtained from Sigma-Aldrich Chemical Co. and Lancaster Chemical Co. (UK). Progress of the reactions was monitored by TLC using precoated aluminium plates (Merck silica gel 60 F254). Column chromatographies were performed on silica gel 60-120/ 100-200/ 230-400 mesh obtained from S. D. Fine Chemical Co. India or Spectrochem India. Typical syringe and cannula techniques were used to transfer air- and moisture-sensitive reagents. IR spectra were recorded on a Perkin–Elmer infrared spectrometer model 599-B and model 1620 FTIR. ^{1}H NMR spectra were recorded on Bruker AC-200, Bruker AV-400 and Bruker DRX–500 instruments using deuterated solvent. Chemical shifts are reported in ppm. Proton coupling constants (*J*) are reported as absolute values in Hz and multiplicity (brs, broad; s, singlet; d, doublet; t, triplet; m, multiplet). ^{13}C NMR spectra were recorded on Bruker AC-200, Bruker AV-400 and Bruker DRX-500 instruments operating at 50 MHz, 100 MHz, and 125 MHz, respectively. ^{13}C NMR chemical shifts are reported in ppm relative to the central line of $CDCl_3$ (δ 77.0). Microanalytical data were obtained using a Carlo–Erba CHNS-0 EA 1108 elemental analyzer. All the melting points were recorded on a Büchi B-540 electrothermal melting point apparatus. Yields refer to chromatographically and spectroscopically pure compounds. Enantiomeric excess was determined using Mosher analysis.

1,1-dibromopentadec-1-ene (61):



To a stirred solution of pivaloyl chloride (4.96 mL, 69.97 mmol) in dry CH_2Cl_2 (50 mL) cooled to –78 ^{o}C was added dropwise dry DMSO (5.75 mL, 46.64 mmol) in dry CH_2Cl_2 (20 mL) over 20 min. The reaction mixture was stirred for 30 min. Alcohol **13** (5 g, 23.32 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise to the above reaction mixture over 20 min. After completion of the starting material (2 h), Et_3N (16.25 mL, 116 mmol) was added and stirred at –78 ^{o}C for further 30 min. The reaction mixture was brought to room temperature slowly and stirred for 30 min. The reaction mixture was poured into H_2O (150 mL) and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL) and combined organic layers were washed with H_2O (3 x 50 mL), brine (50 mL), dried (Na_2SO_4) and passed through short pad of silica gel. The filtrate was concentrated to give the aldehyde as pale yellow oil, which was used as such for the next step without purification.

To a cooled (0 ^{o}C) and stirred solution of carbon tetrabromide (15.6 g, 47.08 mmol) in CH_2Cl_2 (100 mL) was added triphenylphosphine (24.7 g, 94.17 mmol) in CH_2Cl_2 (30 mL) under argon. After 10 min, the reaction mixture was cooled to -78 ^{o}C and a solution of the above aldehyde (5.0 g, 23.54 mmol) in CH_2Cl_2 (20 mL) was introduced into the yellowish ylide solution. The mixture was stirred for 6 h at -78 ^{o}C, quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (99:1) as eluent gave dibromo compound **61** as a colourless liquid.

Yield: 6.23 g, 73% yield for two steps.

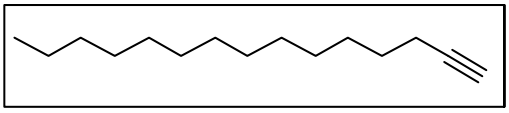
Mol. Formula: $C_{15}H_{28}Br_2$

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.2 Hz, 3H), 1.27-1.46 (brs, 22H), 2.04-2.15(q, *J* = 7.0, 14.27 Hz, 2H), 6.39 (t, *J* = 7.3 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.7, 27.8, 29.0, 29.4, 29.7, 31.9, 33.0, 88.4, 138.9.

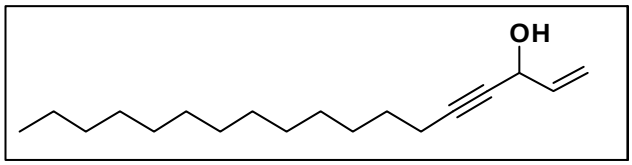
Anal. Calc.: C, 48.93; H, 7.67; **Found.** C, 48.75; H, 7.63%.

Pentadec-1-yne (62):



To a cooled (-78 ^{o}C) and stirred solution of **61** (5.8 g, 15.75 mmol) in THF (50 mL) was added *n*-BuLi (1.6 M solution in hexane, 49.23 mL, 78.76 mmol) drop wise over 20 min under argon. After 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether as eluent gave **62** (2.8 g, 85%) as a colourless oil.

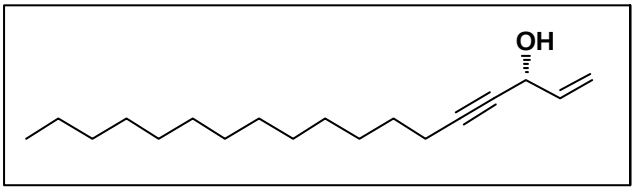
Octadec-1-en-4-yn-3-ol (63):



n-BuLi (1.6 M solution in hexane, 6.6 mL, 10.56 mmol) was added dropwise over 10 min to a solution of 1-pentadecyne **62** (2 g, 9.6 mmol) in dry THF (50 mL) at -78 ^{o}C. After stirring at -78 ^{o}C for 30 min, a solution of acrolein (2.15 g, 38.39 mol) in abs. THF (20 mL) was added, and the reaction mixture was stirred at -78 ^{o}C for 30 min, and allowed to

warm to -20 ^{o}C for 2 h and then quenched by the addition of sat. NH_4Cl (10 mL) and extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. Filtration through silica gel column using petroleum ether as the solvent to recover excess 1-pentadecyne followed by elution with petroleum ether/EtOAc (96:4) gave **63** (1.77 g, 70% Yield) as a low melting solid.

(*R*)-Octadec-1-en-4-yn-3-ol (64):



To a mixture of 3 Å molecular sieves (1.2 g) and Ti(^{i}PrO)$_4$ (6.19 mL, 20.79 mmol) in dry CH_2Cl_2 (40 mL), (-)-DIPT (5.23 mL, 24.96 mmol) was added dropwise over 10 min at –20 ^{o}C. The mixture was stirred for 20 min at –20 ^{o}C, and a solution of mixture of **63** (5.5 g, 20.79 mmol) in dry CH_2Cl_2 (20 mL) was added over 15 min. The reaction mixture was stirred for additional 30 min at –20 ^{o}C and TBHP (2.27 mL, 5.5 M solution in toluene, 12.48 mmol) was added dropwise over 15 min. The reaction mixture was kept at –20 °C by constant temperature bath and after 3 days the reaction was warmed to 0 ^{o}C, and quenched with H_2O (100 mL) and the mixture is stirred for 30 min, and then precooled (0 ^{o}C) freshly prepared ferrous sulfate heptahydrate (1.44 g, 5.19 mmol) in 10 mL of H_2O was added and reaction mixture is stirred for 30 min at rt. The two phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were treated with 30 mL of a precooled (0 ^{o}C) solution of 30% NaOH w/v in saturated brine. The two phase mixture was stirred vigorously for 1 h at 0 ^{o}C. Followed by dilution with 50 mL of water, the phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated to dryness. The crude product was then purified by flash chromatography on silica gel using petroleum ether/EtOAc (96:4) to give chiral hydroxy olefin **64** as a white solid compound.

Yield: 2.48 g, 45% (based on 50% conversion).

M.P.: 35-37 ^{o}C.

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

$[\alpha]_D^{25}$: -3.76 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 3440, 2210, 1611.

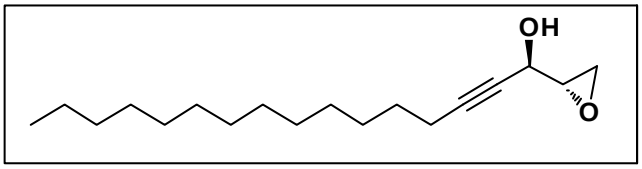
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.1 Hz, 3H), 1.26-1.56 (brs, 22H), 1.87-1.90 (d, *J* = 6.1 Hz, 1H), 2.20-2.27 (t, *J* = 6.9, 2H), 4.83- 4.90 (m, 1H), 5.17-5.49 (m, 2H), 5.9-6.06 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): 14.0, 18.7, 22.6, 28.5, 29.1, 29.3, 29.6, 31.9, 63.3, 78.8, 87.3, 115.9, 137.6.

MS(ESI): m/z 287.477 $(M+Na)^+$.

HRMS, (EI/DIP) for (M^+): calc. 264.24729, **Found:** 264.24697.

(*R*)-1-((*S*)-Oxirane-2-yl)hexadec-2-yn-1-ol (65):



Yield: 2.85 g, 49% (based on 50% conversion).

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

M.P.: 48-49 ^oC.

$[\alpha]_D^{25}$: -16.31 (*c* 1.0, $CHCl_3$).

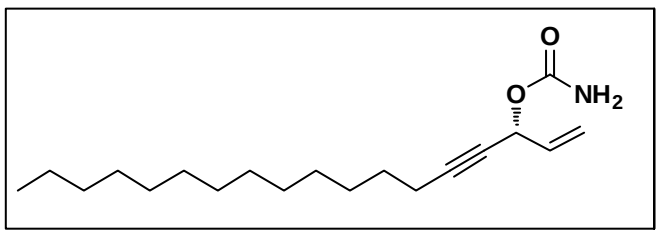
IR (neat, cm^{-1}): ν_{max} 3482, 3100, 2900, 2200.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.1 Hz, 3H), 1.26-1.58 (m, 22H), 2.11 (d, *J* = 5.0 Hz, 1H), 2.23 (dt, *J* = 6.9, 14.0 Hz, 2H), 2.82 (q, *J* = 3.9, 4.9 Hz, 1H), 2.92 (q, *J* = 2.6, 5.0 Hz, 1H), 3.25 (dt, *J* = 2.7, 3.9 Hz, 1H), 4.63 (sextet, *J* = 2.1, 4.9, 7.0 Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 18.6, 22.6, 28.4, 28.9, 29.0, 29.4, 29.6, 31.8, 44.3, 53.9, 61.1, 76.1, 87.6.

Analysis: Calcd.: C, 77.09 ; H, 11.50%; **Found:** C, 77.19; H, 11.44%.

(*R*)-Octadec-1-en-4-yn-3-yl carbamate (67):



Trichloroacetyl isocyanate (0.54 mL, 4.54 mmol) was added dropwise over 10 min to a solution of alcohol **64** (1.0 g, 3.78 mmol) in dry CH_2Cl_2 (5.67 mL, 1.5 mL/mmol) at 0 ^oC. After stirring for 2 h, or until TLC showed no starting material present, the mixture was concentrated under reduced pressure. The residue was dissolved in MeOH (7.56 mL, 2

mL/mmol), cooled to 0 ^{o}C and an aqueous K_2CO_3 solution (1.56 g, 11.34 mmol, 2 mL/mmol) was added. The cooling bath was removed and the mixture was allowed to stir for 4 h, by which time TLC showed complete conversion. The solvent was evaporated under reduced pressure and the aqueous residue was extracted with CH_2Cl_2 (3 x 25 mL). The combined organics were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to yield the crude carbamate, which was purified by flash column chromatography on silica gel using petroleum ether/EtOAc (8:2) as eluent to give carbamate **67** as white solid.

Yield: 0.98 g, 85%.

Mol. Formula: $C_{19}H_{33}O_2N$

M.P.: 50-51 ^{o}C.

$[\alpha]_D^{25}$: -3.67 (*c* 1.2, $CHCl_3$).

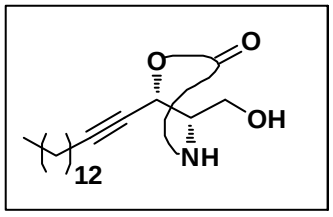
IR (neat, cm^{-1}): ν_{max} 3346, 1654.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6.0 Hz, 3H), 1.25-1.55 (m, 22H), 2.19-2.27 (m, 2H), 5.07 (brs, 2H), 5.24-5.56 (dd, *J* = 1.2, 18.0 Hz, 2H), 5.78-5.96 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 18.7, 22.6, 28.4, 28.8, 29.0, 29.4, 29.6, 31.9, 65.6, 75.4, 88.4, 118.1, 133.8, 155.9.

HRMS, (EI/DIP) for (M^+): calc. 307.25074, **Found:** 307.25068.

(4*R*,5*S*)-4-(Hydroxymethyl)-5-(pentadec-1-ynyl)oxazolidin-2-one (68):



A fresh aqueous solution of sodium hydroxide (18 mL, 0.08M, 58 mg, 1.46 mmol) was prepared. All but a few drops of this was added in one portion to a stirred solution of the allylic carbamate **67** (0.50 g, 1.62 mmol) in propan-1-ol (19.44 mL, 12 mL/mmol). The solution was allowed to stir for 5 min, before freshly prepared *tert*-butyl hypochlorite (0.176 g, 1.62 mmol) was added. The mixture was again allowed to stir for 5 min, to this was added $^{i}Pr_2EtN$ (14 mg, 5 mol%) in one portion. The mixture was allowed to stir for a further 5 min before the final addition of a solution of potassium osmate (23 mg, 4 mol%) in the remainder of the NaOH solution made earlier. The reaction was monitored by TLC and halted when no further change was detected. The reaction was quenched by the addition of sodium sulfite (100 mg/mmol), and allowed to stir for 30 min. The mixture was extracted with EtOAc (5 x

25 mL). The combined organics were washed with brine, dried over sodium sulfate and concentrated under reduced pressure to give the crude product which was found to be a mixture of *syn*:*anti* 13:1 (determined from ^{1}H NMR of crude compound). Purification by flash column chromatography on silica gel using petroleum ether/EtOAc (1:1) as eluent gave the carbamate **68** as a white solid.

Yield: 0.34 g, 65% yield.

Mol. Formula: $C_{19}H_{33}NO_2$

M.P.: 53-55 ^oC.

$[\alpha]_D^{25}$: -8.39 (*c* 0.9, $CHCl_3$).

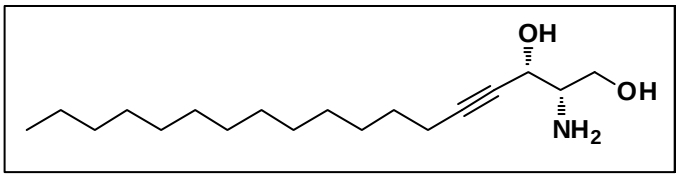
IR (neat, cm^{-1}): ν_{max} 3400, 2922, 2100, 1653.

^{1}H NMR (400 MHz, $CDCl_3$): 0.88 (t, *J* = 6.07 Hz, 3H), 1.24-1.52 (m, 22H), 1.84 (brs, 1H) 2.18-2.25 (m, 2H), 4.18- 4.27 (m, 1H), 4.47-4.68 (m, 2H), 5.45 (d, *J* = 7.96 Hz, 1H), 6.73 (brs, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4, 18.7, 22.8, 28.1, 28.9, 29.1, 29.3, 29.5, 31.9, 58.4, 65.0, 68.6, 74.6, 90.8, 157.9.

HRMS, (EI/DIP) for (M^+): calc. 323.24354, **Found:** 323.24346.

(2*S*,3*S*)-2-Aminooctadec-4-yne-1,3-diol (69):



To a stirred solution of TA product **86** (900 mg, 2.78 mmol) in MeOH (10 mL) was added K_2CO_3 (1.15 g, 8.35 mmol) and the reaction mixture was stirred for 6 h at room temperature until completion of the starting material and methanol was removed in vacuo. H_2O was added to the crude product and extracted with EtOAc (3 x 30 mL) and dried over sodium sulfate and concentrated to near dryness and crystallised from DCM:petroleum ether to give **69** as white shiny crystal.

Yield: 703 mg, 85% yield.

Mol. Formula: $C_{18}H_{35}NO_2$

M.P.: 81-83 ^oC; {lit.[17p] m.p. 82-83 ^oC}.

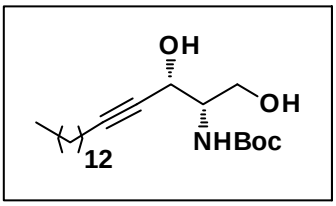
IR (neat, cm^{-1}): ν_{max} 3460, 3300, 2184.

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.1 Hz, 3H), 1.15-1.72 (m, 22H), 1.98-2.5 (m, 2H), 3.4-5.5 (m, 5H), 7.79 (brs, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 18.9, 22.7, 28.7, 29.3, 29.4, 29.7, 29.8, 31.9, 58.9, 60.2, 65.6, 76.5, 88.9.

HRMS, (EI/DIP) for (M^+): calc. 297.2649, **Found:** 297.2643.

***tert*-Butyl (2*S*,3*S*)-1,3-dihydroxyoctadec-4-yn-2-ylcarbamate (70):**



Compound **69** (500 mg, 1.68 mmol) was treated with Boc_2O (0.58 mL, 2.52 mmol) in dioxane and the reaction mixture stirred until completion of the starting material (8 h) and solvent was removed by vacuum evaporation. The crude material was purified by flash column chromatography on silica gel using petroleum ether/EtOAc (6:1) as eluent to give **70** as a colorless oil.

Yield: 547 mg, 82%.

Mol. Formula: $C_{19}H_{33}NO_2$

$[\alpha]_D^{25}$: -14.8 (*c* 0.5, $CHCl_3$).

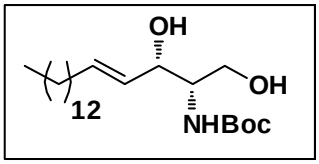
IR (neat, cm^{-1}): ν_{max} 3485, 2187, 1675.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 5.9 Hz, 3H), 1.25-1.63 (m, 31H), 2.21 (t, *J* = 6.8 Hz, 2H), 2.57 (brs, 2H), 3.79-3.94 (m, 3H), 4.58-4.61 (m, 1H), 5.17 (brs, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 18.7, 22.6, 28.3, 28.5, 28.9, 29.1, 29.3, 29.5, 29.6, 31.9, 55.9, 62.8, 63.4, 80.0, 87.3, 156.4.

MS(ESI): m/z 420.22 $(M+Na)^+$.

***tert*-Butyl (2*S*,3*S*,*E*)-1,3-dihydroxyoctadec-4-en-2-ylcarbamate (59):**



A solution of **70** (0.20 g, 0.5 mmol) in abs. Et_2O (5 mL) was added dropwise over 10 min to Red-A1 (3.5 M in toluene, 0.71 mL, 2.5 mmol) and abs. Et_2O (3 mL) at 0 ^oC. The clear soln. was stirred at room temperature for 24 h, then MeOH (1 mL) was added dropwise at 0 ^oC. After dilution with Et_2O (5 mL) and addition of sat. potassium sodium tartrate (3 mL), the mixture was vigorously stirred at room temperature for 3 h. The aq. layer was separated and

extracted with Et_2O (2 x 10 mL). The combined Et_2O extracts were washed with sat. potassium sodium tartrate and sat. NaCl, and dried over Na_2SO_4 and concentrated to near dryness. The crude material was purified by flash column chromatography on silica gel using petroleum ether/EtOAc (1:1) as eluent to give **59** (0.13 g, 65%) as a white solid.

Yield: 0.130 g, 65%.

Mol. Formula: $C_{19}H_{33}NO_2$

M.P.: 58-60 ^oC.

$[\alpha]_D^{25}$: -0.8 (*c* 1.0, $CHCl_3$) {lit.[22] -0.4 *(c* 1.0, $CHCl_3$)}.

IR (neat, cm^{-1}): ν_{max} 3460, 2900, 1670.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.8 Hz, 3H), 1.26-1.46 (m, 31H), 2.03-2.09 (m, 2H), 2.65 (brs, 1H) 3.58 (brs, 1H), 3.70 (dd, *J* = 3.5, 11.2 Hz, 1H), 3.94 (dd, *J* = 3.5, 11.2 Hz, 1H), 4.31 (t, *J* = 4.5, 9.5, 1H), 5.31 (d, *J* = 7.0, 1H), 5.53 (q, *J* = 6.2, 15.5 Hz, 1H), 5.79 (q, *J* = 6.5, 14.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.7, 28.4, 29.1, 29.2, 29.3, 29.7, 31.9, 32.3, 55.4, 62.6, 74.8, 79.8, 128.9, 134.2, 156.2.

2.2.5. X-ray Crystal Structure Analysis for compound 69

Table 1. Crystal data and structure refinement for compound **69**

Empirical formula	$C_{18}H_{35}NO_2$
Formula weight	297.47
Temperature	292(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, $P2_1$
Unit cell dimension	a = 5.9598(5) A^o alpha = 90^o b = 5.2424(4) A^o beta = 94.207(2) c = 30.618(2) A^o gamma = 90^o
Volume	954.04(13) A^3
Z, Calculated density	2, 1.036 Mg/m^3
Absorption coefficient	0.066 mm^{-1}
F(000)	332
Crystal size	0.27 x 0.14 x 0.08 mm
Theta range for data collection	2.00 to 23.50^o
Limiting indices	-6<=h<=6, -5<=k<=5, -34<=l<=34
Reflections collected / unique	7910 / 2808 [R(int) = 0.0324]
Completeness to theta	23.50 99.9%
Max. and min. transmission	0.9950 and 0.9825
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2808 / 1 / 193
Goodness-of-fit on F^2	1.182
Final R indices [I>2sigma(I)]	R1 = 0.0732, wR2 = 0.1667
R indices (all data)	R1 = 0.0975, wR2 = 0.1788
Absolute structure parameter	1(3)
Largest diff. peak and hole	0.141 and -0.124 $e.A^{-3}$

The crystallographic data have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 773906.

2.2.6. Spectra

1. ^1H & ^{13}C NMR spectra of **61**

2. ^1H & ^{13}C NMR spectra of **64**

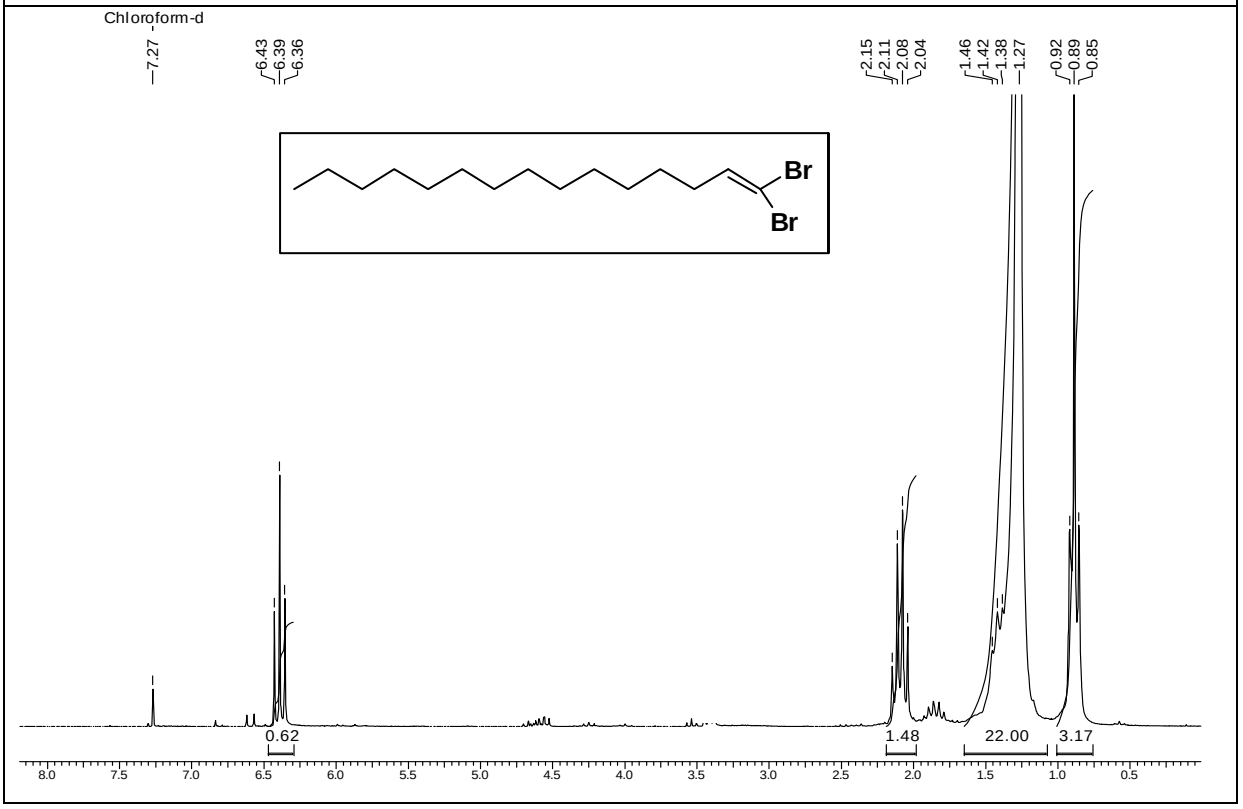
3. ^1H & ^{13}C NMR spectra of **67**

4. ^1H & ^{13}C NMR spectra of **68**

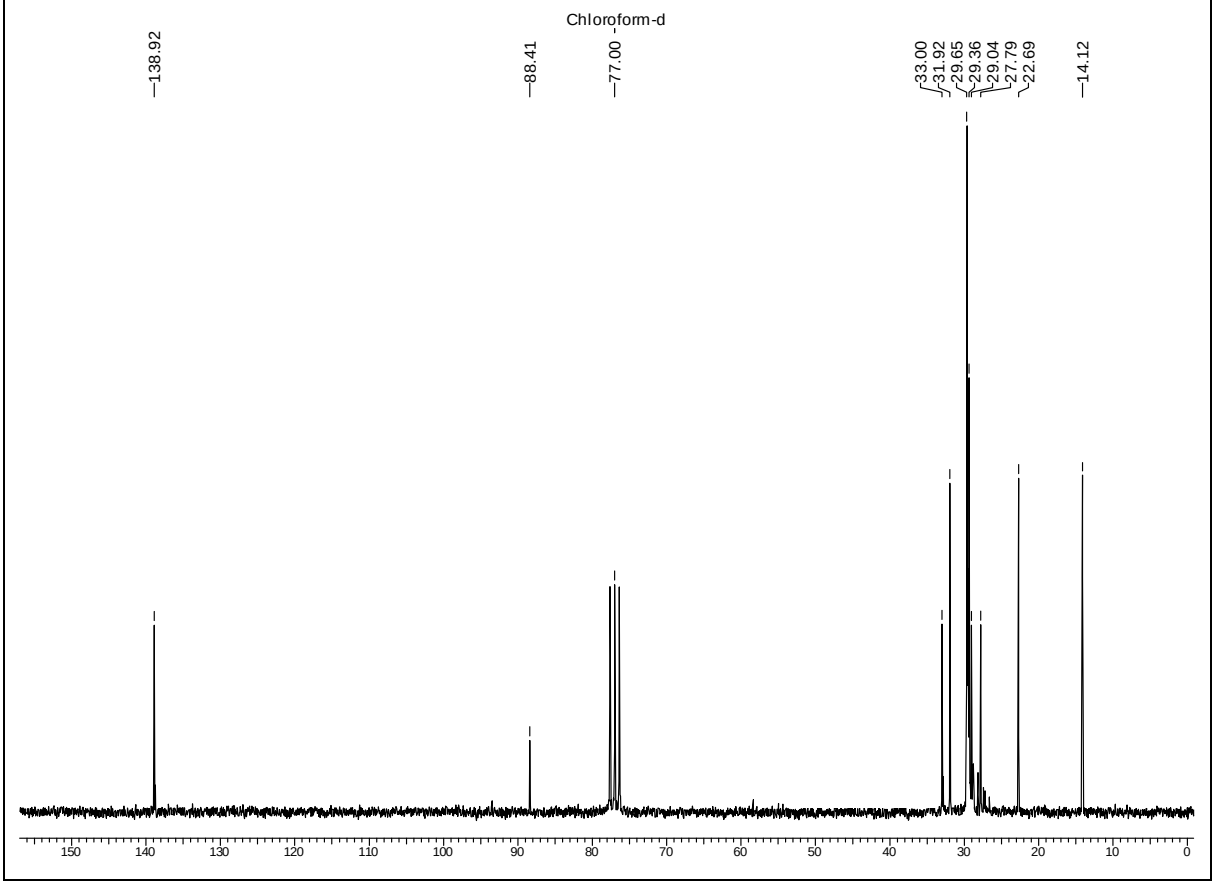
5. ^1H & ^{13}C NMR spectra of **70**

6. ^1H & ^{13}C NMR spectra of **59**

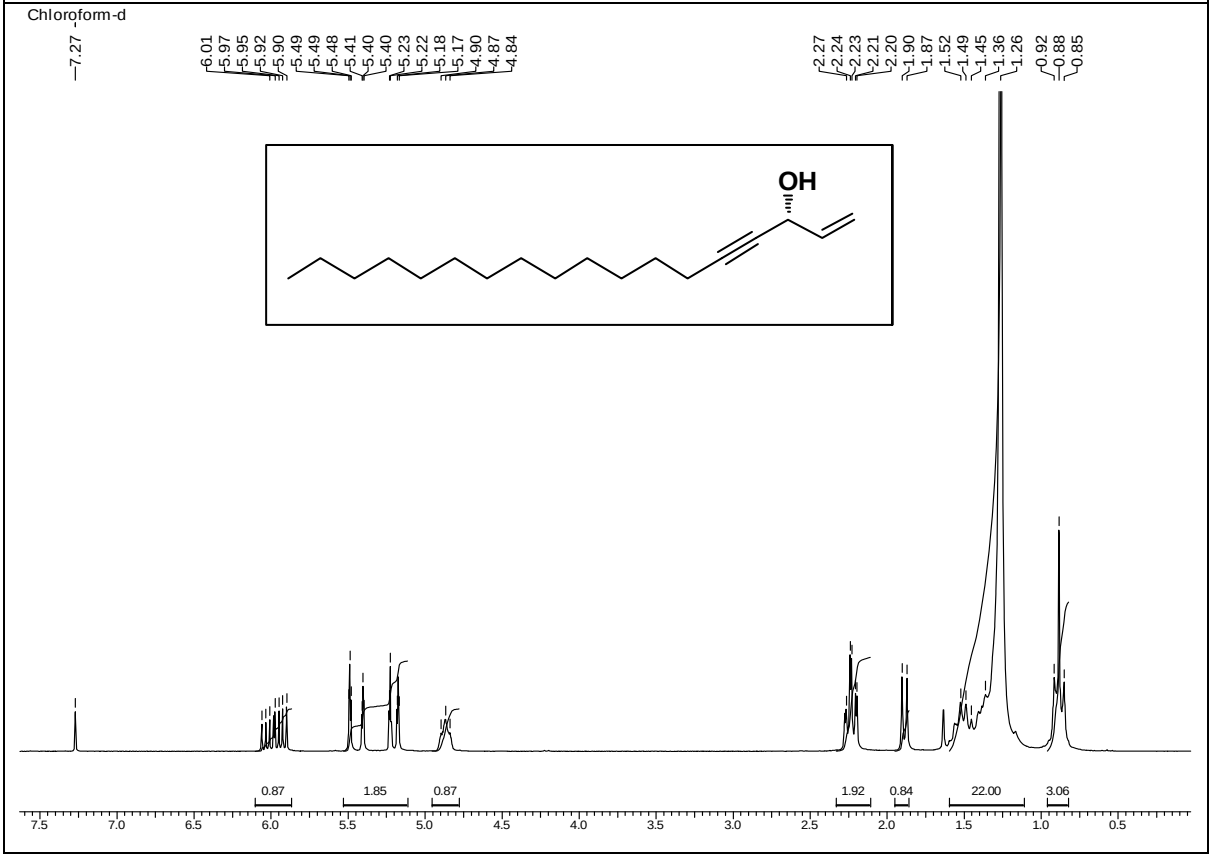
^{1}H NMR ($CDCl_3$, 400 MHz) spectra of 1,1-dibromopentadec-1-ene (61)



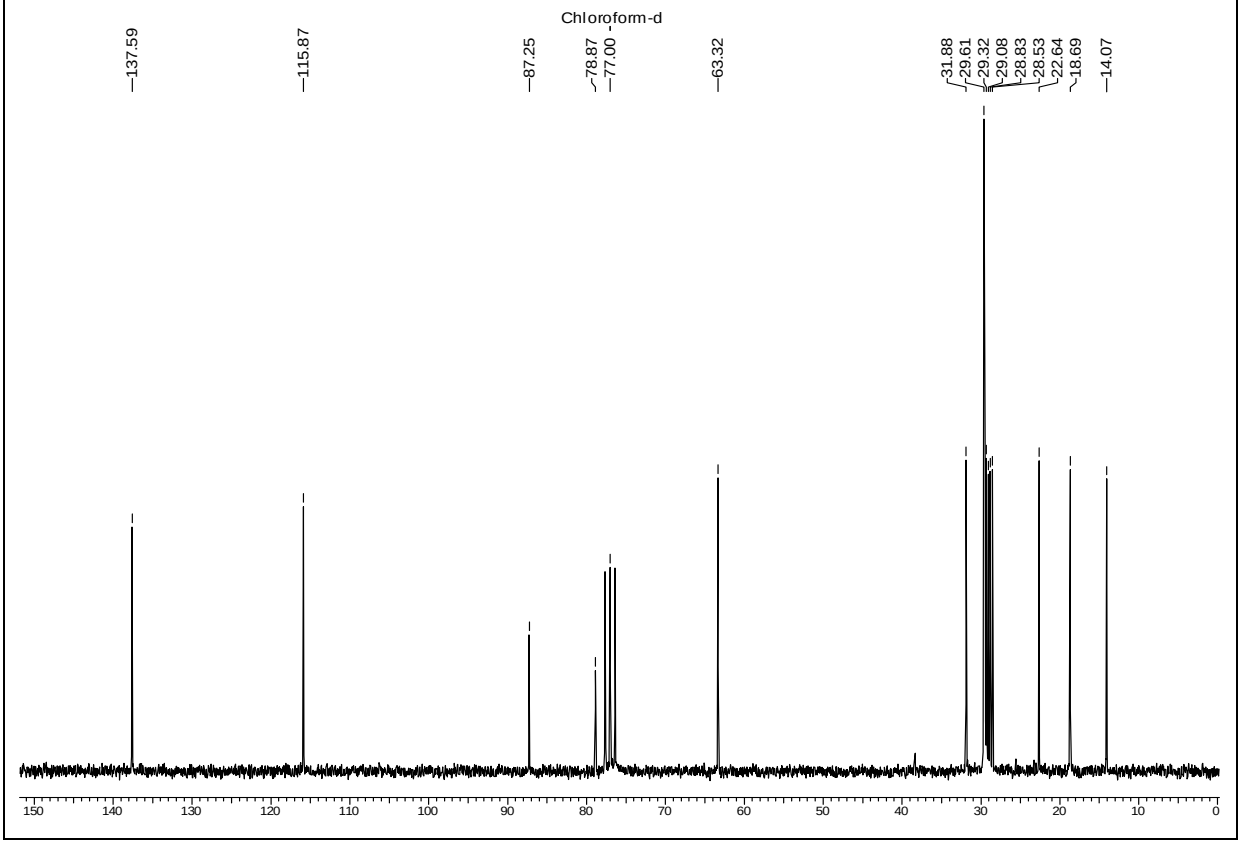
^{13}C NMR ($CDCl_3$, 100 MHz) spectra of 1,1-dibromopentadec-1-ene (61)



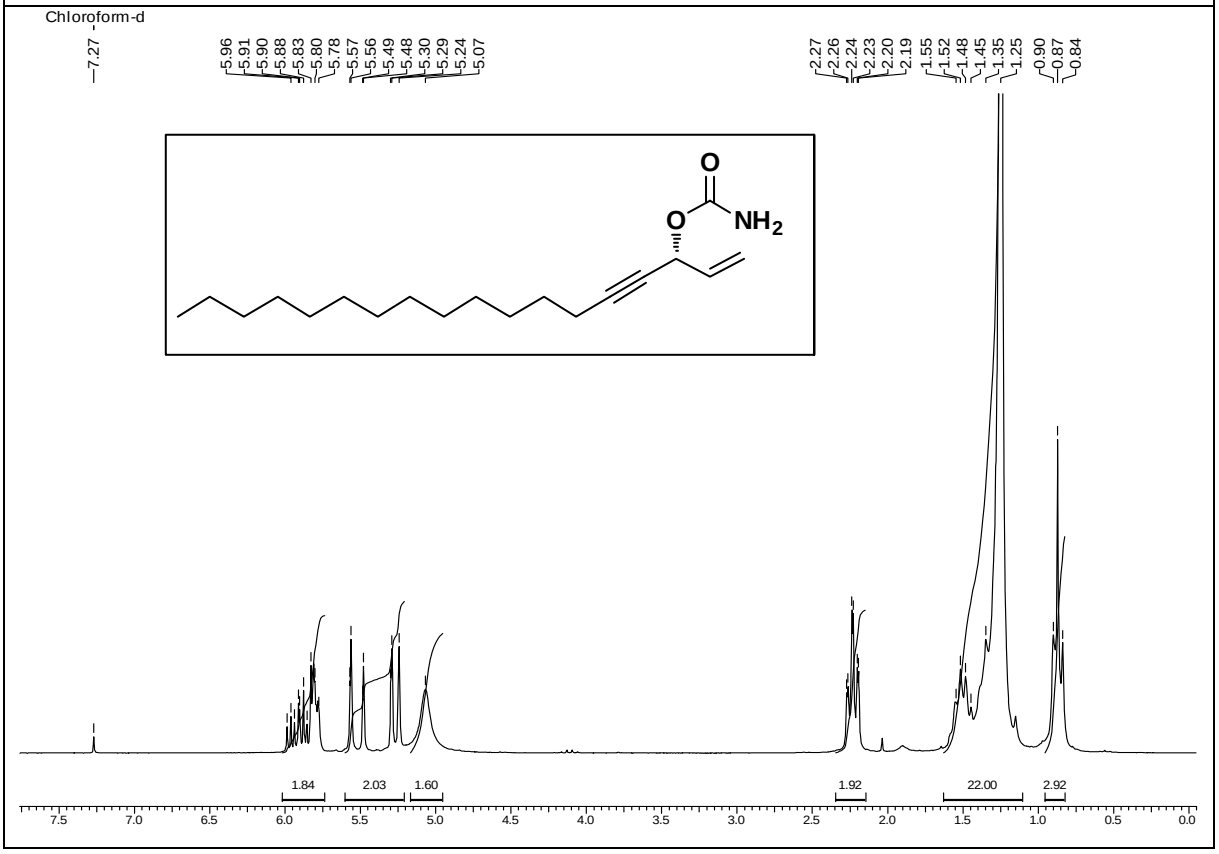
^{1}H NMR ($CDCl_3$, 200 MHz) spectra of (*R*)-Octadec-1-en-4-yn-3-ol (64)



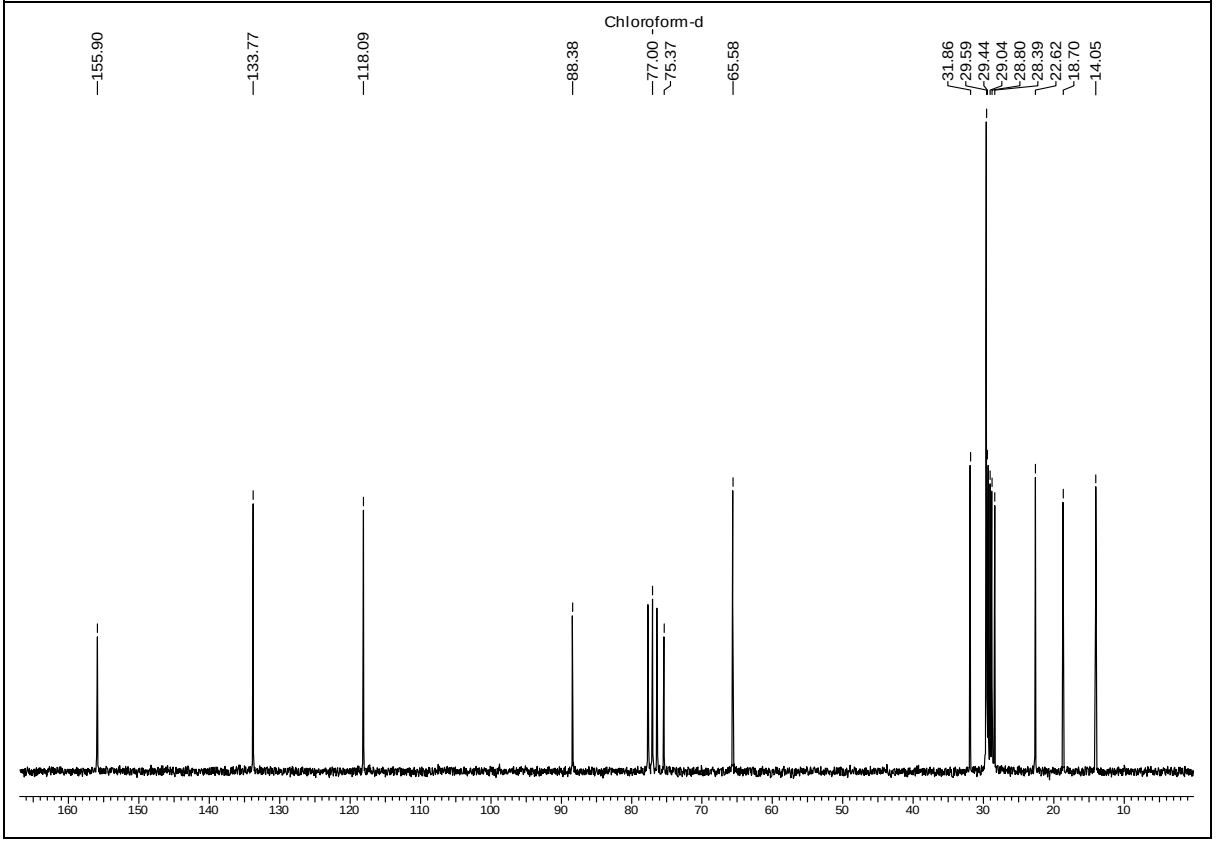
^{13}C NMR ($CDCl_3$, 50 MHz) spectra of (*R*)-Octadec-1-en-4-yn-3-ol (64)



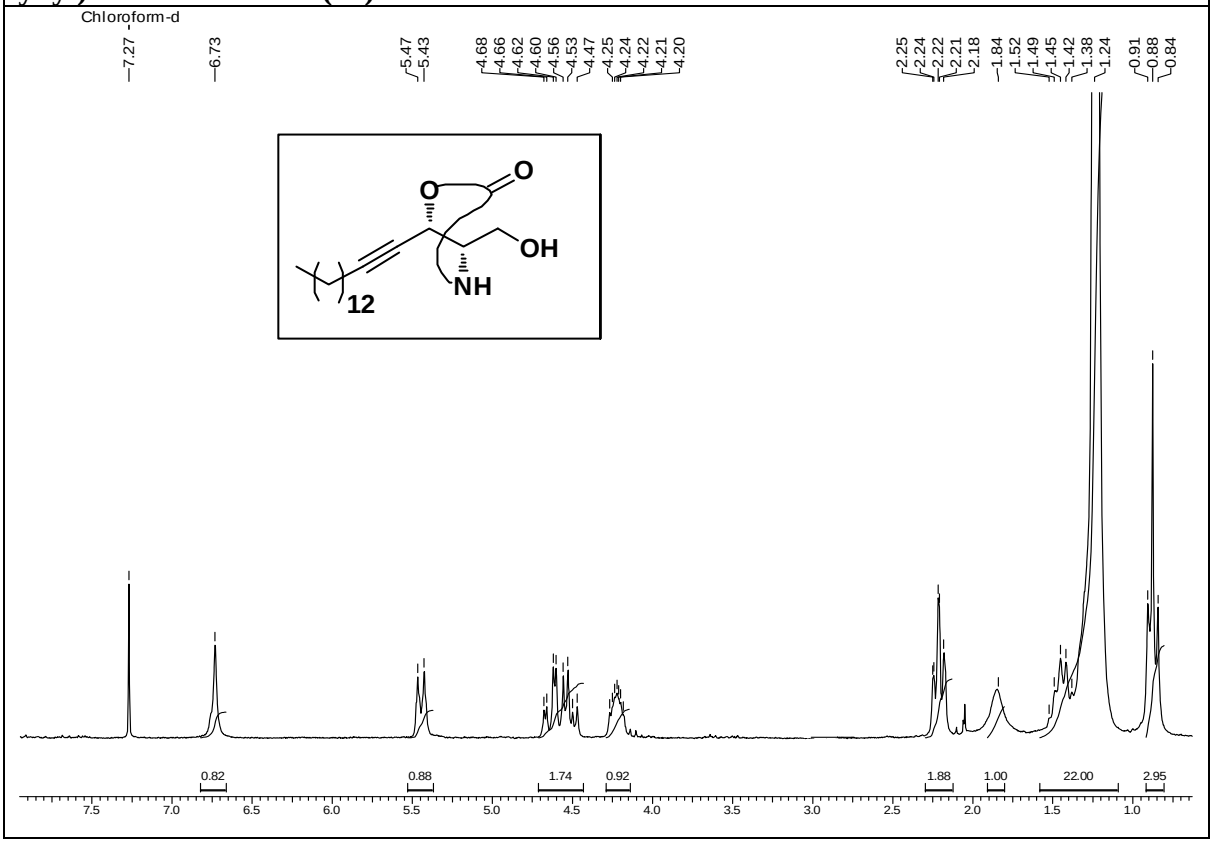
^{1}H NMR ($CDCl_3$, 200 MHz) spectra of (*R*)-Octadec-1-en-4-yn-3-yl carbamate (67)



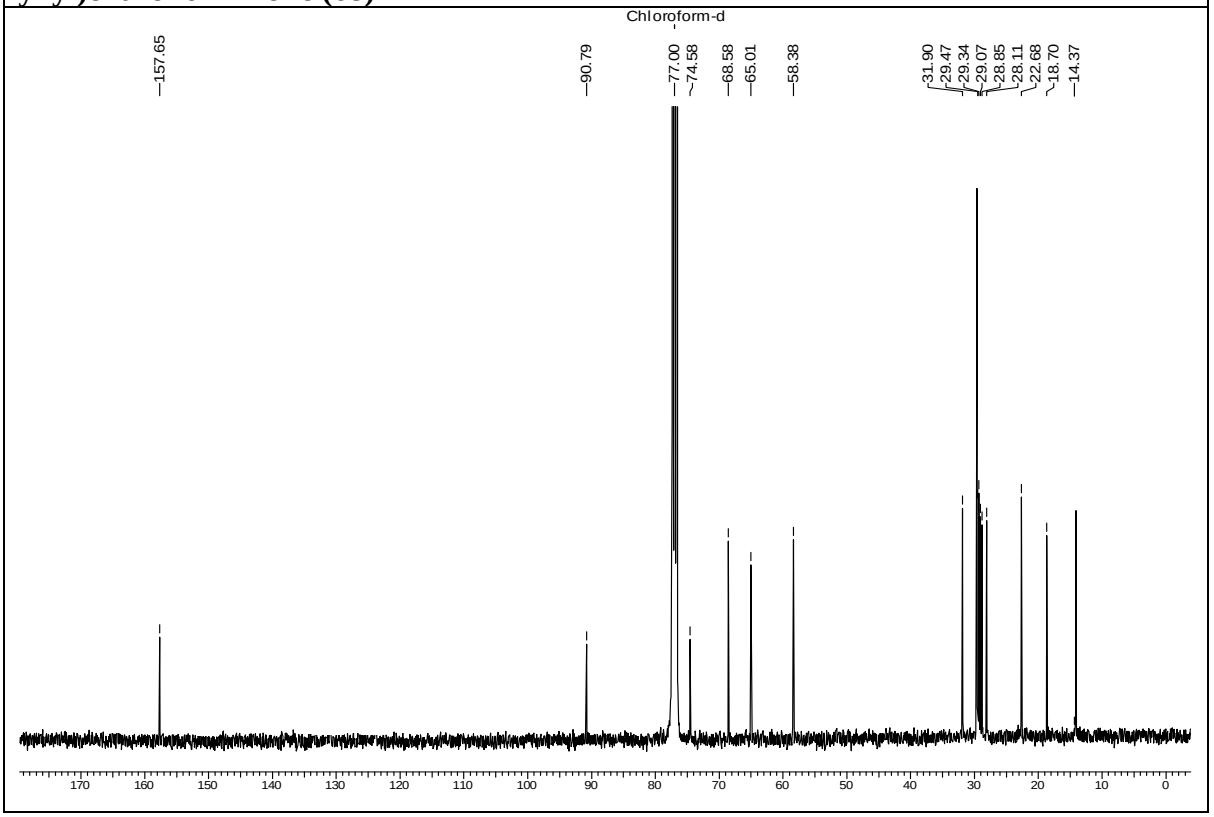
^{13}C NMR ($CDCl_3$, 50 MHz) spectra of (*R*)-Octadec-1-en-4-yn-3-yl carbamate (67)



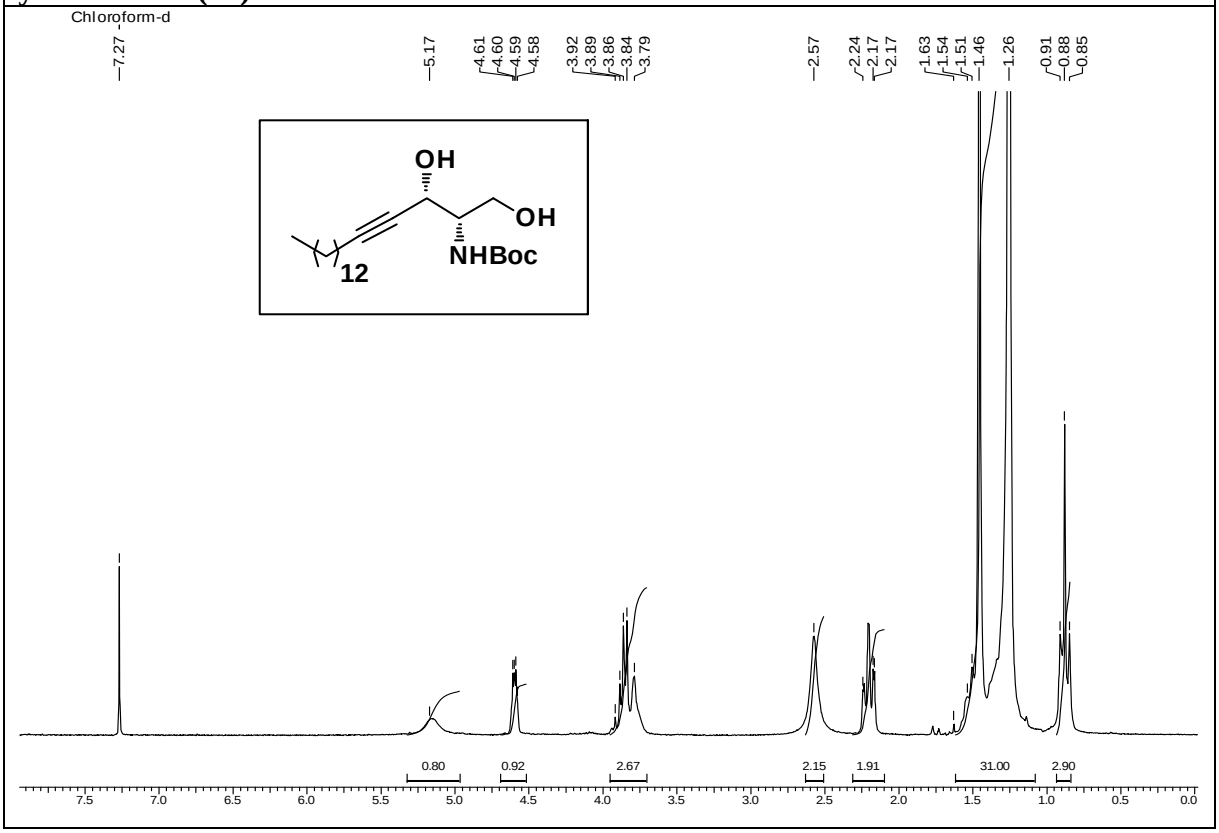
^{1}H NMR ($CDCl_3$, 400 MHz) spectra of (4*R*,5*S*)-4-(hydroxymethyl)-5-(pentadec-1-ynyl)oxazolidin-2-one (68)



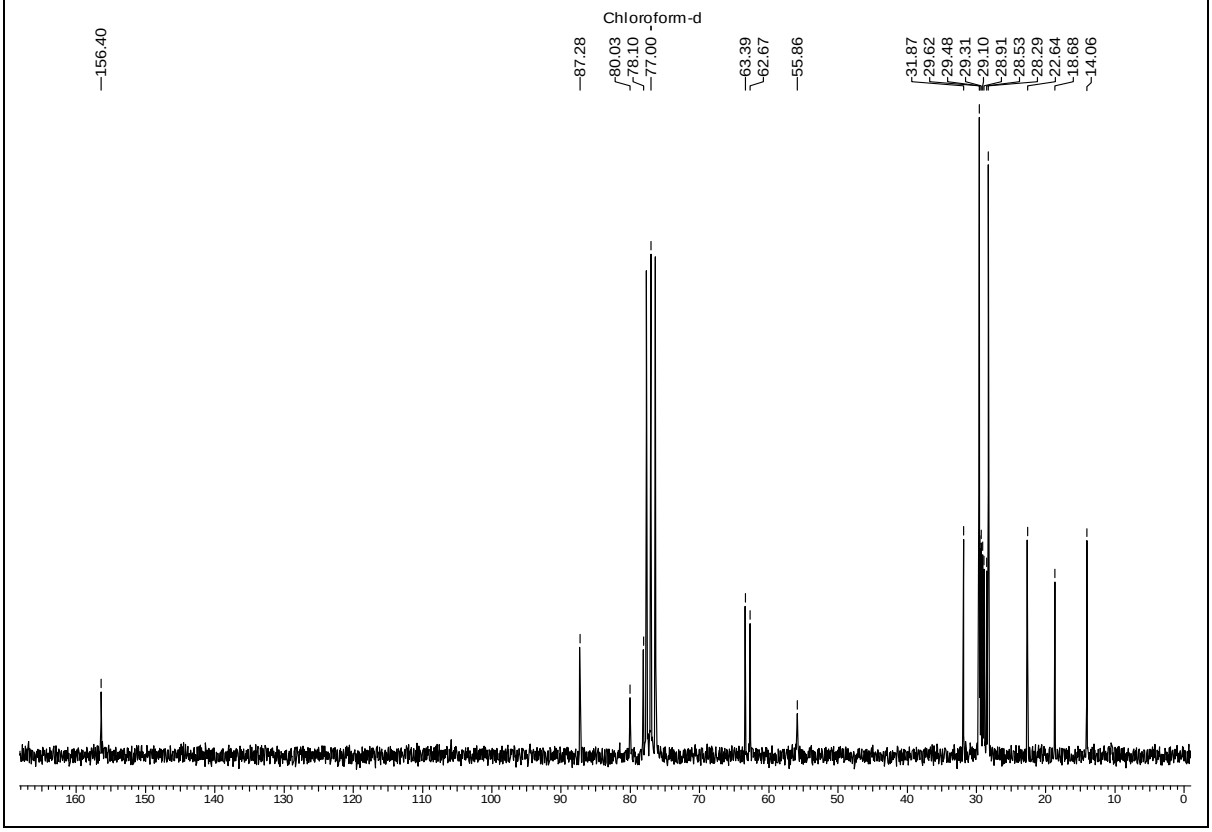
^{13}C NMR ($CDCl_3$, 100 MHz) spectra of (4*R*,5*S*)-4-(hydroxymethyl)-5-(pentadec-1-ynyl)oxazolidin-2-one (68)



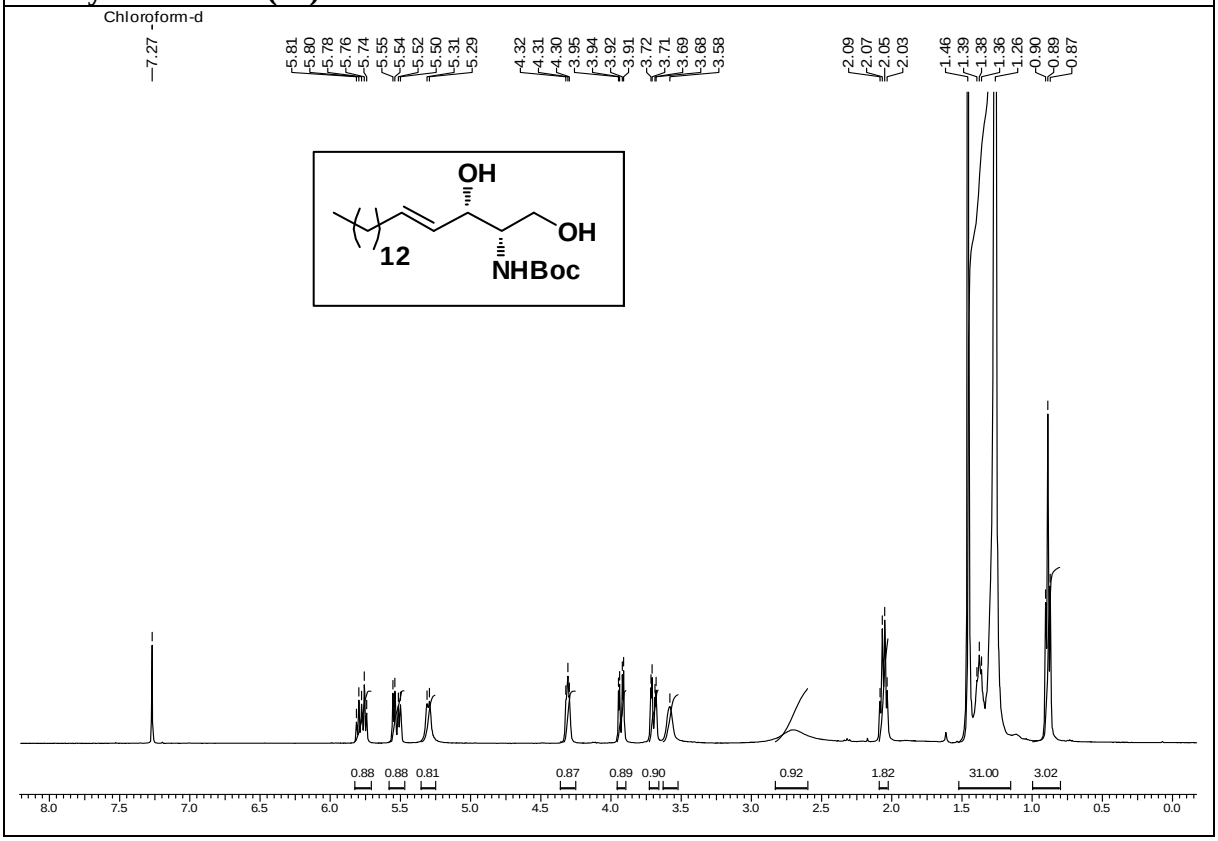
^{1}H NMR ($CDCl_3$, 200 MHz) spectra of *tert*-butyl (2*S*,3*S*)-1,3-dihydroxyoctadec-4-yn-2-ylcarbamate (70)



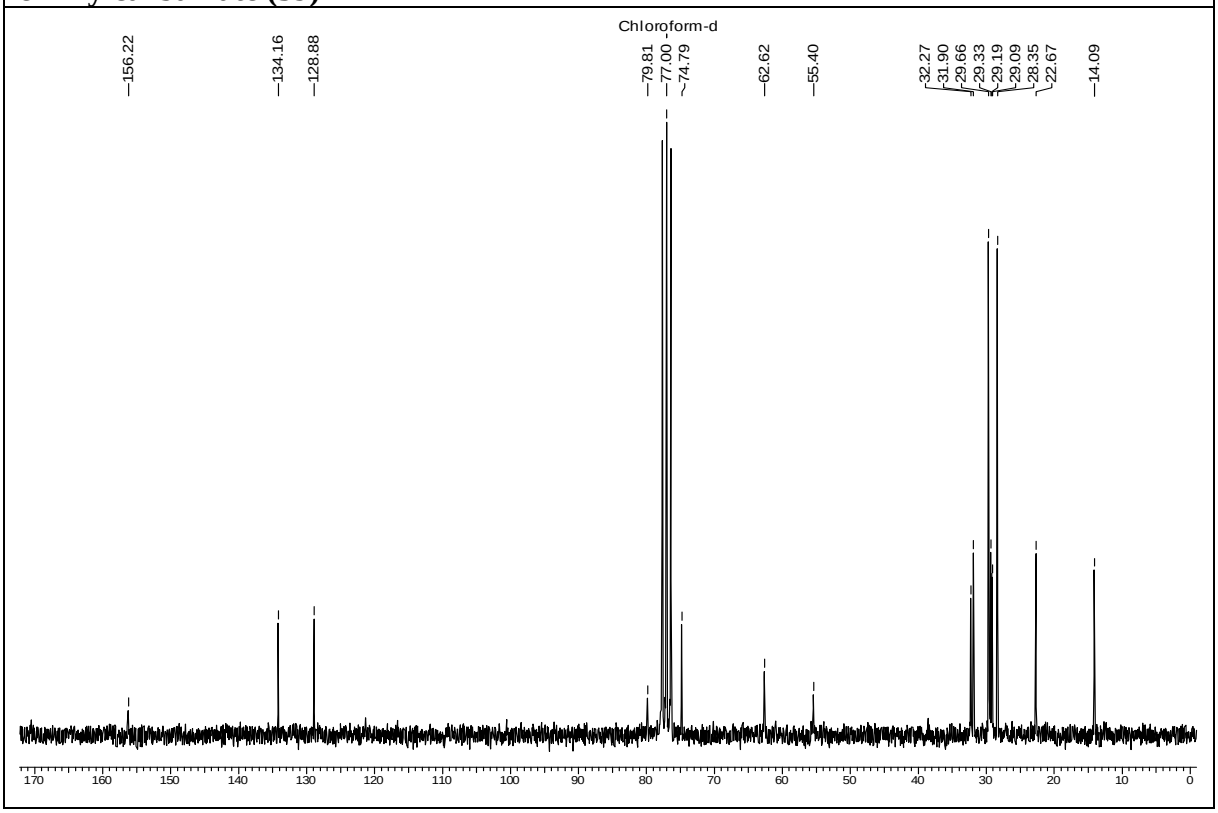
^{13}C NMR ($CDCl_3$, 50 MHz) spectra of *tert*-butyl (2*S*,3*S*)-1,3-dihydroxyoctadec-4-yn-2-ylcarbamate (70)



^{1}H NMR ($CDCl_3$, 400 MHz) spectra of *tert*-butyl (2*S*,3*S*,*E*)-1,3-dihydroxyoctadec-4-en-2-ylcarbamate (59)



^{13}C NMR ($CDCl_3$, 100 MHz) spectra of *tert*-butyl (2*S*,3*S*,*E*)-1,3-dihydroxyoctadec-4-en-2-ylcarbamate (59)



2.2.7. References

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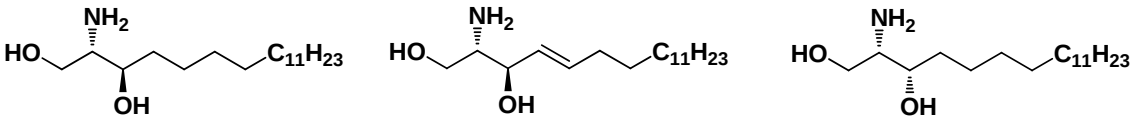
2.3 SECTION C

ENANTIOSELECTIVE SYNTHESIS OF L-*threo*-SPHINGANINE (SAFINGOL)

2.3.1 Introduction

The sphingolipids[1] comprise a complex range of lipids in which fatty acids are linked via amide bonds to a long-chain base or sphingoid. The root term "sphingo-" was first coined by J. L.W. Thudichum in 1884 because the enigmatic nature of the molecules reminded him of the riddle of the sphinx. The term "sphingolipid" was introduced by Herbert Carter and colleagues in 1947. While they are perhaps less enigmatic than they once were, sphingolipids are extremely versatile molecules and surprises are certainly expected as new knowledge is gained of their functions in healthy and diseased animal and plant tissues.[2] They are also found in a few bacterial genera (but especially *Sphingomonas* and *Sphingobacterium*). In recent years, it has become apparent that sphingolipids are involved in many of the more common human diseases including diabetes, many different cancers, microbial infections, Alzheimer's disease[3] and other neurological syndromes, and diseases of the cardiovascular and respiratory systems. Sphingolipids and their metabolism are therefore likely to prove of ever increasing interest to scientists. Sphinganine **1**, a dihydro derivative of sphingosine **2**, is intermediate in the biosynthesis of sphingolipids such as ceramides, sphingomyeline, cerebrosides and gangliosides which play important role in cell regulation and signal transduction,[1] with sphinganine itself found to be an inhibitor of



D-*erythro*-sphinganine **1**

D-*erythro*-sphingosine **2**

L-*threo*-sphinganine (safingol) **3**

Fig. 1

protein kinase C[4] and acts synergistically with anti cancer drugs (**Fig. 1**). Sphingosine **2** and sphiganine (dihydrosphingosines) **1** are naturally occurring (long-chain, aliphatic, 2-amino-1,3 diol) bioactive compounds. Sphingoid bases contain two chiral centres, viz. at carbon atoms 2 and 3. Natural sphingoid bases occur in the D-*erythro*-(2*S*,3*R*) configuration, but three additional unnatural isomers have also been reported.[5] Among the unnatural sphingoid bases L-*threo*-(2*S*,3*S*) dihydrosphingosine (safingol) **3** is of particular interest due to its

medicinal importance. Safingol **3** is an antineoplastic, antipsoriatic drug[6] and a competitive inhibitor of protein kinase C[7] and is known to act synergistically with anti-cancer drugs.[8] It is reported that safingol inhibits enzymatic activity and 3H-phorbal dibutarate binding of purified rat brain PKC (IC50 = 37.5 lM, 31 lM, respectively). It also inhibits human PKCa, the major overexpressed isoenzyme in MCF-7 DOXR cells (IC50 = 40 lM). Further, safingol enhances the cytotoxic effect of the chemotherapeutic agent mytomycin (MMC: Cat. No. 47589) in gastric cancer cells promoting drug induced apoptosis.[9-10]

Sphinganine is involved in several biological functions such as

(1) Sphinganine-1-phosphate aldolase catalyzes the reaction aldehyde-lyases, which cleaves C-C bonds. This participates in sphingolipids metabolism.

sphinganine 1-phosphate ⇌ phosphoethanolamine + palmitaldehyde

(2) ATP: sphinganine-1-phosphotransferase catalyses the chemical reaction transferring the phosphorus containing group with alcohol group as an acceptor.

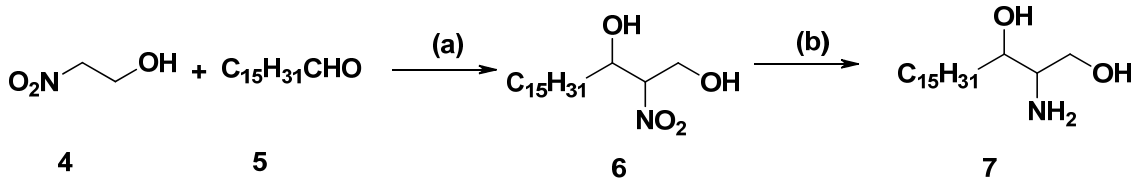
ATP + sphinganine ⇌ ADP + sphinganine 1-phosphate.

2.3.2 Review of Literature

Due to its promising biological activity, a number of syntheses of safingol **3** and its stereoisomers have been reported in the literature including methods based on an enantioselective Henry reaction[11] and ketone reduction,[12] multistep synthesis from (*Z*)-2-butene-1,4-diol,[13] a chiral oxazolidinyl ester[14] and resolution based methods.[15a–c] One of the most recent syntheses of safingol was reported by Lee *et al*.,[16] which was based on palladium-catalyzed oxazoline formation followed by cross metathesis. Another recent report by Chattopadhyay *et al.*[17] describes the synthesis by diasereoselective addition of allylmagnesium or lithium reagent to (*R*)-cyclohexylideneglyceraldehyde. Until now, however, dihydrosphingosines, has been independently synthesized by many research groups. Some of the interesting methods are described below.

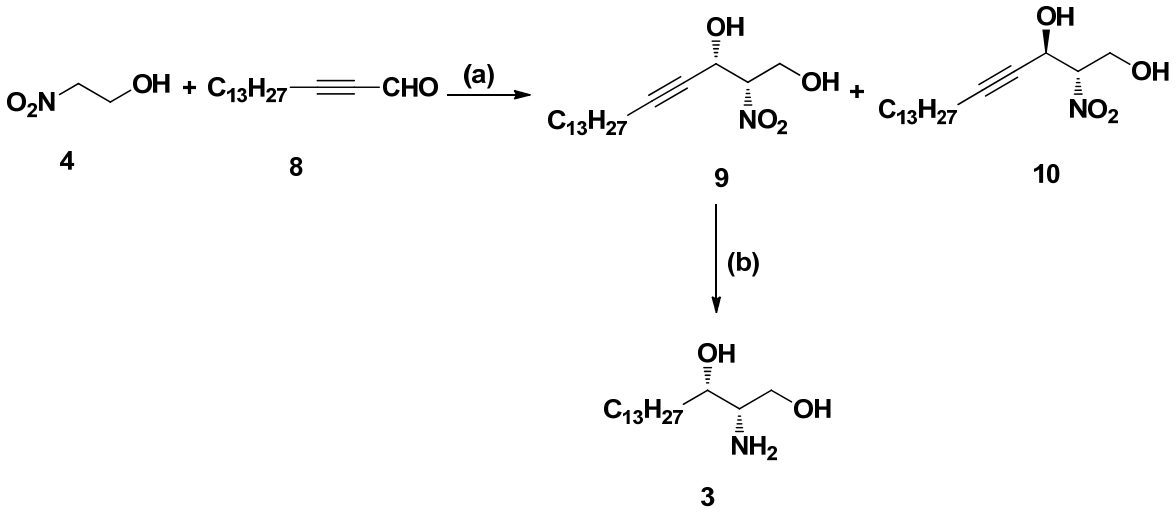
Grob *et al.* (1951)[15a]

An early synthesis of racemic sphinganine was reported by Grob and co-workers employing nitro-aldol reaction. Condensation of nitro ethanol **4** with palmityl aldehyde **5** gave the aldol product **6**. Reduction of the nitro group in **6** afforded racemic sphinganine **7**.



Scheme 1. *Reagents and conditions*: (a) OH^-, 28%; (b) H_2/Ni, MeOH, 50%.

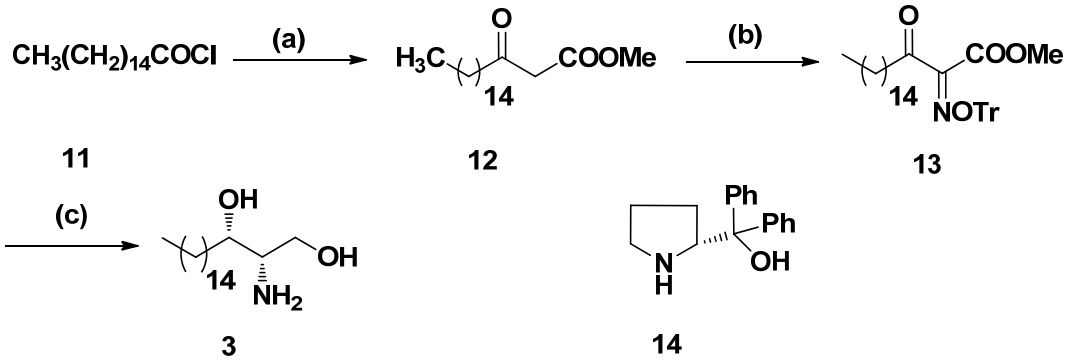
In another approach, Grob and Gradient carried out nitro aldol reaction on hexadecanyl aldehyde **8** to give 1:1 mixture of *threo*- and *erythro*-products **9** and **10** respectively. Diastereomers were separated by fractional crystallization. Sequential nitro group reduction followed by complete reduction of the triple bond furnished L-*threo*-sphinganine **3**. (**Scheme 2**)



Scheme 2. *Reagents and conditions*: (a) K_2CO_3, MeOH; (b) (i) Zn, HCl; (ii) H_2/Pd

Masui *et al*. (1998)[12]

In this method, stereoselective synthesis of sphinganine by the asymmetric borane reduction of α-oxoketoxime trityl is described. Condensation of palmityl chloride **11** with

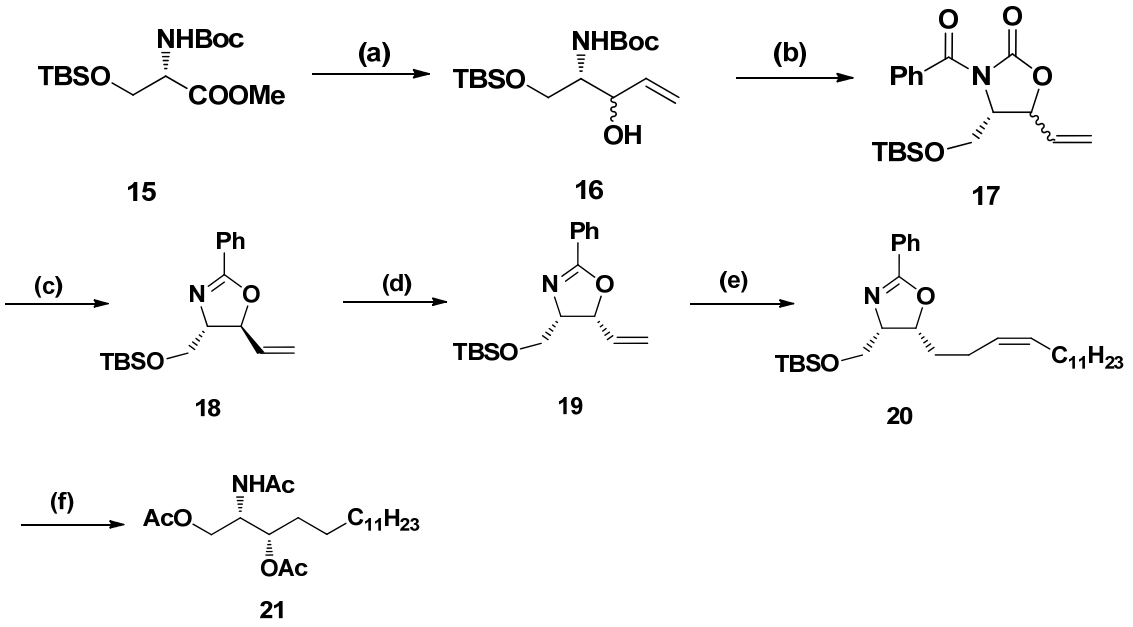


Scheme 3. *Reagents and conditions*: (a) $KOCOCH_2COOMe$, $MgCl_2$, Et_3N, CH_3CN, rt, 52%; (b) [i] BuONO, H_2SO_4, Et_2O, rt, 85%; [ii] TrCl, Et_2N, CH_2Cl_2, rt, 99%; (c) **14**, 89% ee.

malonic acid half ester potassium salt gave β-keto ester **12**. Nitrosation of **12** by butyl nitrite followed by *O*-tritylation afforded the ester **13**. The asymmetric borane reduction of **13** using catalyst **14** gave the amino alcohol **3**. (**Scheme 3**)

Cook *et al*. (2002)[18]

Cook and co-workers reported Pd-catalyzed isomerization of 5-vinyl oxazolines to vicinal amino alcohols. The synthesis of L-*threo*-sphinganine began with the protected L-serine derivative **15**. Diisobutyl aluminium hydride reduction of **15** followed by vinyl Grignard afforded the amino alcohol derivative **16** as a mixture of diastereomers. Cyclization of the alcohol **16** onto the Boc group and treatment with a Pd(0) catalyst provided the *trans*-oxazoline **17**. Partial hydrolysis of **17** followed by protection of hydroxyl group with TBSCl gave the *N*-benzoyl derivative **18**. Finally *cis*-oxazoline **19** was formed by activation of the secondary alcohol as mesylate and S_N2 displacement by the amide carbonyl. Hydroboration followed by Suzuki coupling gave **20**. Hydrogenation of the olefin **20** and hydrolysis under acidic conditions afforded L-*threo*-sphinganine, which was converted to the known triacetate **21**. (**Scheme 4**)

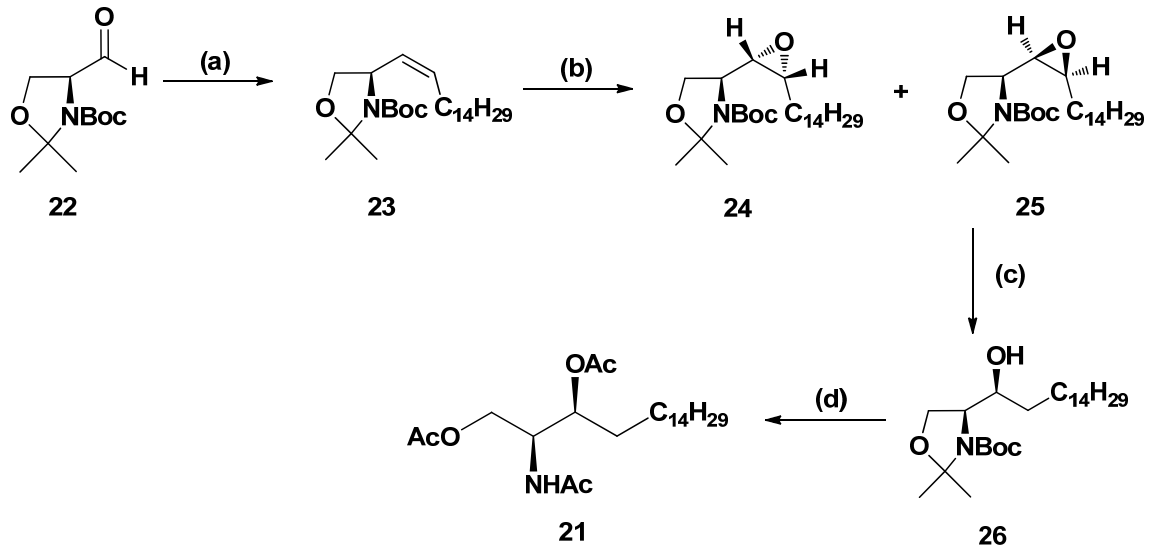


Scheme 4. *Reagents and conditions*: (a) [i] DIBAL-H, Toluene, -78 ^oC, 82%; [ii] vinyl magnesium bromide, THF, 59%; (b) NaH, THF, PhCOCl, 60%; (c) $Pd(PPh_3)_4$, CH_3CN, 90%; (d) [i] 2N HCl, THF, 77%; [ii] TBSCl, imidazole, 70%; [iii] CH_3SO_2Cl, Et_3N, 99%; (e) 9-

BBN, THF, $Pd(PPh_3)_4$, *Z*-1-bromotridecane, NaOH, THF, 52%; (f) [i] H_2, Pd/C, EtOAc, 86%; [ii] 2N HCl, THF, NaOH, 66%; [iii] Ac_2O, pyridine, 71%.

Ogino *et al*. (2000)[19]

Ogino *et al*. reported stereoselective synthesis for L-*threo*-sphinganine starting from L-serine. Garner's protected serine aldehyde **22** gave olefin **23** under Wittig conditions. The epoxidation of olefin **23** gave mixture of **24** and **25**. Reduction of epoxide **25** gave L-*threo*-sphinganine which was converted to known triacetate **21**. (**Scheme 5**)



Scheme 5. *Reagents and conditions*: (a) $C_{15}H_{31}PPh_3Br$, LiHMDS, -78 ^oC, 66%; (b) *m*CPBA, rt, 84% for **24** and 4% for **25**; (c) $LiAlH_4$, 0 ^oC, 80%; (d) CF_3COOH, Ac_2O, DMAP, rt, 83%.

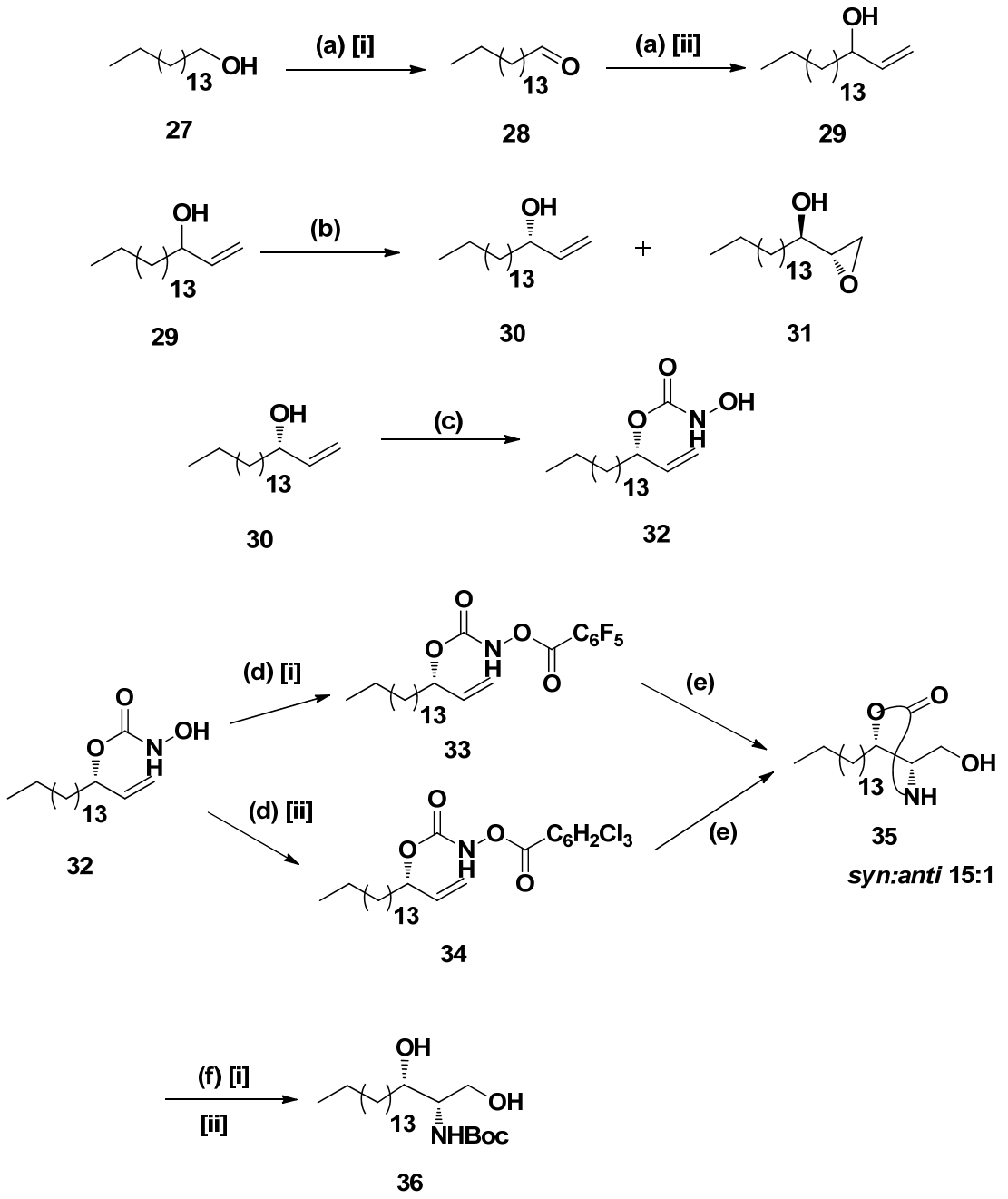
2.3.3. Present work

2.3.3.1. Objective

Although several syntheses[11-20] of target compound have already been reported, each method suffers either from multisteps, low yielding steps or from poor stereo or regioselectivity. Therefore we considered developing a practical, concise, expeditious and high-yielding synthesis of the target molecule. The Sharpless asymmetric aminohydroxylation provides versatile and expeditious procedure for the synthesis of amino alcohol functionality in single step. We have utilized tethered aminohydroxylation[21] modifications for the asymmetric aminohydroxylation to synthesize the target molecule.

2.3.3.2. Results and Discussion

An alternative synthetic sequence for the synthesis of L-*threo*-sphinganine employing tethered aminohydroxylation is shown in **Scheme 6**. Pentadecyl alcohol **27** was oxidized under DMSO-pivaloyl chloride conditions to afford the corresponding aldehyde **28** which was treated with vinylmagnesium bromide in dry THF at -78 ^{o}C to furnish the racemic alcohol **29** in 82% yield. The IR spectrum of **29** showed the presence of olefin and hydroxyl stretching at 1611, 3499 cm^{-1} respectively. In the ^{1}H NMR spectrum olefin peaks appeared at δ 5.07-5.27 (m) for terminal protons and δ 5.79-5.96 (m) for internal proton. In the ^{13}C NMR spectrum of **29** olefin peaks appeared at δ 114.4, 141.3. The secondary racemic alcohol **29** was subjected to Sharpless kinetic resolution conditions[22] using Ti(O^{i}Pr)$_4$, (-)-DIPT as chiral auxiliary and TBHP as oxidant in dry DCM at -20 ^{o}C for 4 days to give the chiral hydroxy olefin **30** and chiral epoxy alcohol **31** in excellent yield. Both compounds **30** and **31** were throughly characterized using IR, ^{1}H NMR and ^{13}C NMR spectra. Having obtained the chiral allylic alcohol **30** in substantial amount and a suitable substrate for tethered aminohydroxylation, we then proceeded with the synthesis of target compound sphinganine. In order to prepare hydroxycarbamate **32**, the alcohol **30** was reacted with CDI in pyridine, followed by the addition of hydroxylamine hydrochloride, to afford the hydroxy carbamate **32** in 85% yield. The ^{1}H NMR spectrum of **32** clearly indicated broad singlet for –NH at δ 7.20 and in the ^{13}C NMR spectrum amide carbonyl peak appeared at δ 159.1. In the IR spectrum of **32**, olefin, amine, hydroxyl and carbonyl stretching appeared at 1609, 3482, 1716 cm^{-1} respectively. According to modified tethered aminohydroxylation condition[21e] *O*-pentafluorobenzoyl derivative (**TA protocol C Chapter 1**) is reported to give excellent yield under tethered aminohydroxylation. With this view in mind we converted hydroxy carbamate **32** into *O*-pentafluorobenzoyl derivative **33** but it was found to be unstable under reaction conditions and also during column purification. We then turned our attention towards another modification of this reaction using *O*-2,4,6-trichlorobenzoyl derivative. To our delight, reaction went smoothly and we isolated *O*-2,4,6-trichlorobenzoyl **34** derivative in excellent yield. In the IR spectrum amine, carbonyl and benzene ring stretching appeared at 3420, 1745, 1710 and 1660 cm^{-1}. The ^{1}H NMR and ^{13}C NMR spectra of **34** showed two phenylic proton at δ 7.41 (singlet, two protons), and δ 128.3, 128.6, 133.6, 135.5 (for phenyl ring proton), 155.4 and



Scheme 6. *Reagents and conditions*: (a) [i] Pivaloyl chloride, DMSO, Et_3N, -78 ^oC; [ii] Vinyl bromide, Mg, -78 ^oC, 2 h, 82% yield of two step; (b) (-)-DIPT, $Ti(O\text{-}^iPr)_4$, TBHP, dry DCM, molecular sieves, 3 A^o, -20 ^oC, 4 days, 47% for **30** and 48% for **31**; (c) CDI, pyridine, 40 ^oC, 4 h, then $NH_2OH.HCl$, 40 ^oC, 24 h, 85%; (d) [i] Pentafluorobenzoyl chloride, Et_3N, ether, 0 ^oC, 1 h, 35%; [ii] 2,4,6-trichlorobenzoyl chloride, Et_3N, EtO, 0 ^oC, 1 h, 85%; (e) Potassium osmate dihydrate, *t*-BuOH:H_2O (3:1), 20 min, 75%; (f) [i] K_2CO_3, methanol, rt, 6 h; [ii] $(Boc)_2O$, dioxane, 8 h, 72% yield for two steps.

163.1 (for two carbonyl peaks). Compound **34** was subjected to the modified tethered aminohydroxylation[21e] using potassium osmate dihydrate as oxidant in *t*-butanol:H_2O solvent

system (1:1) to furnish the oxazolidinone **35** in 75% yield. Compound **35** was fully characterized using IR, ^{1}H NMR and ^{13}C NMR spectra. In the IR spectrum hydroxyl, amine and carbonyl stretching appeared at 3438, 2949, 1710 cm^{-1}. The ^{1}H NMR and ^{13}C NMR spectra of **35** showed disappearance of olefin peaks and appearance of -*CH*(NH), –*CH*(OH) protons and carbon peaks at δ 3.53-3.83 (m), 4.31-4.40 (m) and δ 59.5, 79.2 respectively. Our next objective was conversion of **35** into the known L-*threo*-sphinganine which was easily achieved by treatment of **35** with potassium carbonate in methanol to give the amino diol which on subsequent Boc protection of amine furnished the target molecule **36** in 72% yield. The physical and spectroscopic data of **36** were in full agreement with those reported.[16b]

2.3.3.3. Conclusion

We have accomplished the enantioselective synthesis of L-*threo*-sphinganine employing the Sharpless asymmetric aminohydroxylation as the key step in a highly concise manner. The problem of regioselectivity was overcome in the synthesis by tethered aminohydroxylation. A short reaction sequence and high-yielding steps renders our strategy a good alternative to the known methods.

2.3.4. Experimental Section

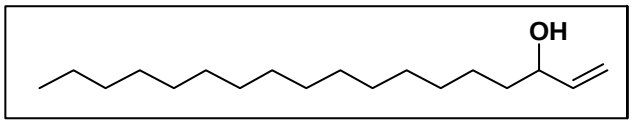
General information

General information as described in section B.

1-Hexadecanal (28):

To a stirred solution of pivaloyl chloride (10.14 mL, 82.4 mmol) in dry CH_2Cl_2 (100 mL) cooled to –78 ^{o}C was added dropwise dry DMSO (8.77 mL, 123.6 mmol) in dry CH_2Cl_2 (20 mL) over 20 min. The reaction mixture was stirred for 30 min. Alcohol **27** (10 g, 41 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise to the above reaction mixture over 20 min. After completion of the starting material (2 h), Et_3N (28.7 mL, 206 mmol) was added and stirred at –78 ^{o}C for further 30 min. The reaction mixture was brought to room temperature slowly and stirred for 30 min. The reaction mixture was poured into H_2O (150 mL) and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL) and combined organic layers were washed with H_2O (3 x 50 mL), brine (50 mL), dried (Na_2SO_4) and passed through short pad of silica gel. The filtrate was concentrated to give the aldehyde **28** (9.7 g) as pale yellow oil, which was used as such for the next step without purification.

Octadec-1-en-3-ol (29):



To a stirred solution of Mg (2.94 g, 120.9 mmol) in dry THF (30 mL), vinyl bromide solution (40.32 mL, 2.0 M solution in dry THF, 80.6 mmol) was added dropwise over 30 min and the Grignard reagent thus formed was cooled to 0 ^{o}C. Aldehyde **28** (9.7 g, 40.3 mmol) in dry THF (10 mL) was added dropwise to the above reaction mixture over 20 min. After 2 h stirring at 0 ^{o}C, the reaction mixture was quenched with saturated NH_4Cl solution (10 mL), and the aqueous layer was extracted with EtOAc (4 x 20 mL) and the combined organic layers were washed with brine and dried over Na_2SO_4. The extracts were concentrated to near dryness and purified by silica gel column chromatography using petroleum ether/EtOAc (96:4) as eluent to give **29** as a pale yellow solid.

Yield: 9.08 g, 82%.

M.P.: 46-48 ^{o}C.

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

IR (neat, cm^{-1}): ν_{max} 3499, 1611.

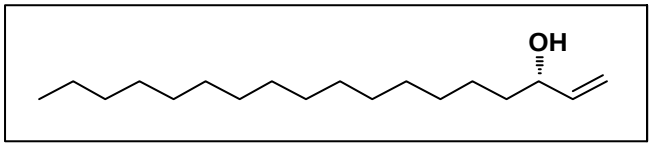
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.1 Hz, 3H), 1.26 (brs, 26H), 1.41-1.55 (m, 2H), 1.59 (brs, 1H), 4.05-4.15 (m, 1H), 5.07-5.27 (m, 2H), 5.79-5.96 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 22.7, 25.3, 25.7, 29.3, 29.7, 31.9, 37.0, 62.6, 73.2, 114.4, 141.3.

MS(ESI): m/z 269.44 $(M+H)^+$, 291.48 $(M+Na)^+$.

Anal. Calcd.: C, 80.53; H, 13.52%; **Found**: C, 80.43; H, 13.49%.

3-(*S*)-Octadec-1-en-3-ol (30):

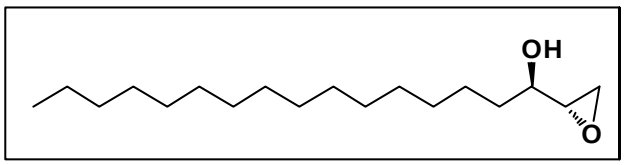


To a mixture of 3 Å molecular sieves (225 mg) and $Ti(^{i}PrO)_4$ (1.34 mL, 4.50 mmol) in dry CH_2Cl_2 (40 mL) (-)-DIPT (1.2 mL, 5.73 mmol) was added dropwise over 10 min at –20 ^{o}C. The mixture was stirred for 20 min at –20 ^{o}C, and a solution of mixture of **29** (1.1 g, 4.09 mmol) in dry CH_2Cl_2 (5 mL) was added over 10 min. The reaction mixture was stirred for additional 30 min at –20 ^{o}C and TBHP (3.4 mL, 3 M solution in toluene, 10.24

mmol) was added dropwise over 15 min. The reaction mixture was kept at –20 °C by constant temperature bath and after 4 days, the reaction was warmed to 0 ^{o}C, and quenched with H_2O (30 mL) and the mixture was stirred for 30 min, and then precooled (0 ^{o}C) freshly prepared ferrous sulfate heptahydrate (278 mg, 1 mmol) in 10 mL of H_2O was added and reaction mixture was stirred for 30 min at rt. The two phases were separated and the aqueous phase is extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were treated with 6 mL of a precooled (0 ^{o}C) solution of 30% NaOH w/v in saturated brine. The two phase mixture is stirred vigorously for 1 h at 0 ^{o}C. Followed by dilution with 50 mL of water, the phases are separated and the aqueous layer is extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated to dryness. The crude product was then purified by flash chromatography on silica gel using petroleum ether/EtOAc (96:4) as eluent to give chiral hydroxy olefin **30** (0.52 g, 47% yield, based on 50% conversion) as a white solid.: $[\alpha]_D^{25}$: + 8.3 (*c* 0.32, $CHCl_3$).

Further elution with petroleum ether/EtOAc (92:8) gave the epoxide **31** as a white solid.

1-Oxiranyl-hexadecan-1-ol (31):



Yield: 0.56 g, 48% (based on 50% conversion).

Mol. Formula: $C_{18}H_{36}O_2$

M.P.: 56-57 ^{o}C.

$[\alpha]_D^{25}$: -6.3 (*c* 1.3, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 3482, 2854, 1211.

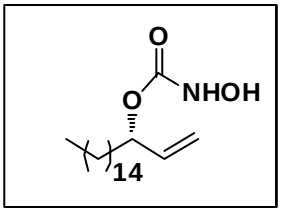
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.1 Hz, 3H), 1.26 (brs, 26H), 1.49-1.59 (m, 2H), 2.71-2.84 (m, 2H), 3.04-3.21 (m, 1H), 3.86-3.94 (m, 1H), 4.48 (brs, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 21.6, 22.5, 25.2, 29.2, 31.8, 33.4, 43.4, 54.6, 68.4, 70.1, 72.1.

MS(ESI): m/z 307.48 $(M+Na)^+$.

Analysis: Calcd.: C, 76.0; H, 12.76%; **Found**: C, 75.89; H, 12.64%.

(*S*)-Octadec-1-en-3-ylhydroxycarbamate (32):



N,*N*-Carbonyldiimidazole (1.81 g, 11.16 mmol) was added to alcohol **30** (2 g, 7.44 mmol) in pyridine (30 mL) at 40 °C. After complete adduct formation between the alcohol and *N*,*N*-carbonyldiimidazole (~4 h), hydroxylamine hydrochloride (1.29 g, 18.61 mmol) was added and the reaction mixture stirred for 24 h at 40 °C. The reaction was quenched with 1M hydrochloric acid (10 mL), partitioned, and the aqueous layer extracted with Et_2O (35 mL) and EtOAc (3 x 30 mL). The combined organic layers were then washed sequentially with H_2O (30 mL) and brine (2 x 30 mL), dried (Na_2SO_4), filtered and the solvent was azeotropically removed with toluene. The crude product was then purified by flash chromatography on silica gel using petroleum ether/EtOAc (85:15) as eluent to give hydroxyl carbamate **32** as a white crystalline solid.

Yield: 2.07 g, 85%.

Mol. Formula: $C_{19}H_{37}NO_3$

M.P: 72-74 ^oC.

$[\alpha]_D^{25}$: 4.3 (*c* 1.0, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 3482, 2854, 1716.

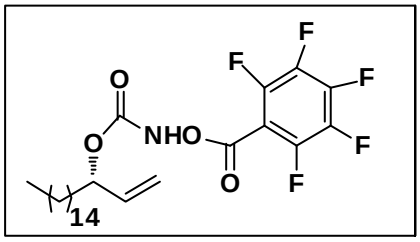
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.1 Hz, 3H), 1.26 (brs, 26H), 1.53-1.68 (m, 2H), 5.16-5.31 (m, 3H), 5.69-5.86 (m, 1H), 7.20 (brs, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1, 22.7, 24.9, 29.3, 29.6, 31.9, 34.2, 77.1, 117.1, 136.1, 159.1.

MS(ESI): m/z 350.43 $(M+Na)^+$, 366.3549 $(M+K)^+$.

Analysis: Calcd.: C, 69.68; H, 11.39; N, 4.28%; **Found:** C, 69.87; H, 11.31; N, 4.38%.

(*S*)-Octadec-1-en-3-ylperfluorobenzoyloxycarbamate (33):



To an ice-cold solution of hydroxycarbamate **32** (2.2 g, 6.71 mmol) in Et_2O (4:1; 5 mL/mmol) was added Et_3N (1.02 mL, 7.38 mmol), before the addition of the pentafluorobenzoyl chloride (0.869 mL, 6.03 mmol) in small portions. The reaction was quenched with HCl (1M aq. sol., 50 mL) and the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed sequentially with H_2O (30 ml), $NaHCO_3$ (aq. sat. sol., 30 mL) and brine (30 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel using petroleum ether/EtOAc (98:2) as eluent to give *O*-pentafluoro hydroxycarbamate **33**, which was found to decompose during purification on column chromatography.

Mol. Formula: $C_{26}H_{36}F_5NO_4$

M.P.: 47-49 ^oC.

$[\alpha]_D^{25}$: -16.3 (*c* 1.0, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 3444, 2977, 1764, 1651.

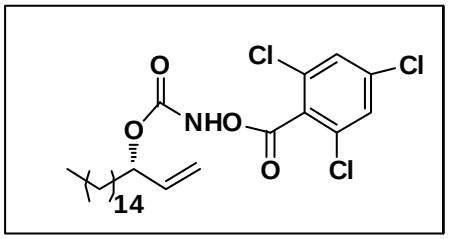
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 5.9 Hz, 3H), 1.25 (brs, 26H), 1.50-1.77 (m, 2H), 5.20-5.35 (m, 3H), 5.71-5.88 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.7, 24.8, 29.3, 29.8, 31.9, 34.1, 78.6, 117.1, 118.7, 134.5, 135.4, 146.8, 148.2, 155.6, 158.5.

^{19}F NMR : -162.4, -148.5, -138.5 ppm.

MS(ESI): m/z 544.46 $(M+Na)^+$, 560.52 $(M+K)^+$.

(*S*)-Octadec-1-en-3-yl 2,4,6-trichlorobenzoyloxycarbamate (34):



To an ice-cold solution of hydroxycarbamate **32** (2.2 g, 6.71 mmol) in Et_2O (4:1; 5 mL/mmol) was added Et_3N (1.02 mL, 7.38 mmol), before the addition of the 2,4,6-trichlorobenzoyl chloride (1.03 mL, 6.71 mmol) in small portions. The reaction was quenched with HCl (1M aq. sol., 20 mL) and the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed sequentially with H_2O (30 mL), $NaHCO_3$ (aq. sat. sol., 30 mL) and brine (30 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel using

petroleum ether/EtOAc (96:4) as eluent to give *O*-trichloro substituted hydroxycarbamate **34** as a white solid compound.

Yield: 3.05 g, 85%

Mol. Formula: $C_{26}H_{38}Cl_3NO_4$

M.P.: 46-47 ^oC.

$[\alpha]_D^{25}$: -8.8 (*c* 1.0, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 3420, 2982, 1745, 1710, 1660.

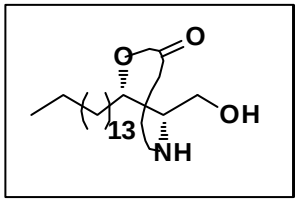
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 5.9 Hz, 3H), 1.25 (brs, 26H), 1.55-1.78 (m, 2H), 5.20-5.36 (m, 3H), 5.72-5.89 (m, 1H), 7.41 (s, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 22.7, 24.9, 29.3, 29.7, 31.9, 34.2, 78.4, 117.7, 128.3, 128.6, 133.6, 135.5, 137.7, 155.4, 163.1.

MS(ESI): m/z 556.317$(M+Na)^+$, 558.33 $(M+Na+2)^+$.

Analysis: Calcd.: C, 58.38; H, 7.16; N, 2.62%; **Found:** C, 58.30; H, 7.02; N, 2.55%.

(4*R*,5*R*)-4-(Hydroxymethyl)-5-pentadecyloxazolidine-2-one (35):



To a solution of *O*-trichlorobenzoyl substituted hydroxycarbamate **34** (0.50 g, 0.93 mmol) in *t*-butanol and H_2O (18 mL, 3:1, 20 mL/mmol) was added dropwise a solution of potassium osmate dihydrate (13.7 mg, 4 mol %) in H_2O (0.5 mL) over 10 min. The reaction was quenched by addition of sodium sulfite (200 mg/mmol) and the solvent azeotropically removed with toluene. The crude product was found to be a mixture of *syn*:*anti* 15:1 (determined from ^{1}H NMR of crude compound), which was purified by flash column chromatography on silica gel using petroleum ether/EtOAc (6:4) as eluent to give the aminoalcohol **35** as white solid.

Yield: 230 mg, 75%.

M.P.: 87-89 ^oC.

Mol. Formula: $C_{19}H_{37}NO_3$

$[\alpha]_D^{25}$: -9.8 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 2949, 1710.

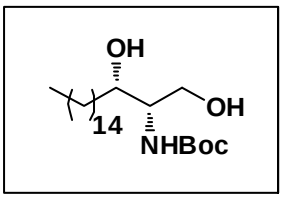
^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.88 (t, *J* = 5.9 Hz, 3H), 1.26-1.91 (m, 28 H), 3.53-3.83 (m, 3H), 4.31-4.40 (m, 1H), 6.41 (s, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 14.1, 22.7, 24.6, 29.3, 29.6, 31.9, 34.8, 59.5, 63.5, 79.2, 160.4.

MS(ESI): m/z 350.3427 $(M+Na)^+$.

Analysis: Calcd.: C, 69.68; H, 11.39; N, 4.28%; **Found:** C, 69.56; H, 11.33; N, 4.38%.

***tert*-Butyl(2*S*,3*S*)-1,3-dihydroxyoctadecane-2-ylcarbamate (36):**



To a stirred solution of TA product **35** (300 mg, 0.92 mmol) in MeOH (5 mL) was added K_2CO_3 (379 mg, 2.74 mmol) and the reaction mixture was stirred until completion of the starting material (6 h) and methanol was removed in vacuo. Water was added to the crude product and extracted with EtOAc (3 x 10 mL) and dried over sodium sulfate and concentrated to near dryness. The residue was subsequently treated with Boc_2O (0.32 mL, 1.38 mmol) in dioxane and the reaction mixture stirred until completion of the starting material (8 h) and solvent was removed by vacuum evaporation. Purification by silica gel flash chromatography ($MeOH/CH_2Cl_2$, 5/95) gave **36** as a white solid.

Yield: 265 mg, 72% yield for two steps.

Mol. Formula: $C_{23}H_{47}NO_4$

$[\alpha]_D^{25}$: +18.8 (*c* 1.0, $CHCl_3$); {Lit[16b] **$[\alpha]_D^{25}$:** +19.8 (*c* 1.0, $CHCl_3$}.

IR (neat, cm^{-1}): 3400, 2970, 1690.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.5 Hz, 3H), 1.26 (brs, 26H), 1.46 (s, 9H), 1.50-1.56 (m, 2H), 2.10 (brs, 2H), 3.53 (brs, 1H), 3.75-3.80 (m, 2H), 4.01 (dd, *J* = 3.5, 11.5 Hz, 1H), 5.32-5.48 (brs, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.7, 25.9, 28.4, 29.4, 29.7, 31.9, 34.5, 54.6, 62.6, 74.5, 79.7, 156.0.

MS(ESI): m/z 424.33 $(M+Na)^+$.

2.2.5 Spectra

1. ^{1}H & ^{13}C NMR spectra of **29**

2. ^{1}H & ^{13}C NMR spectra of **32**

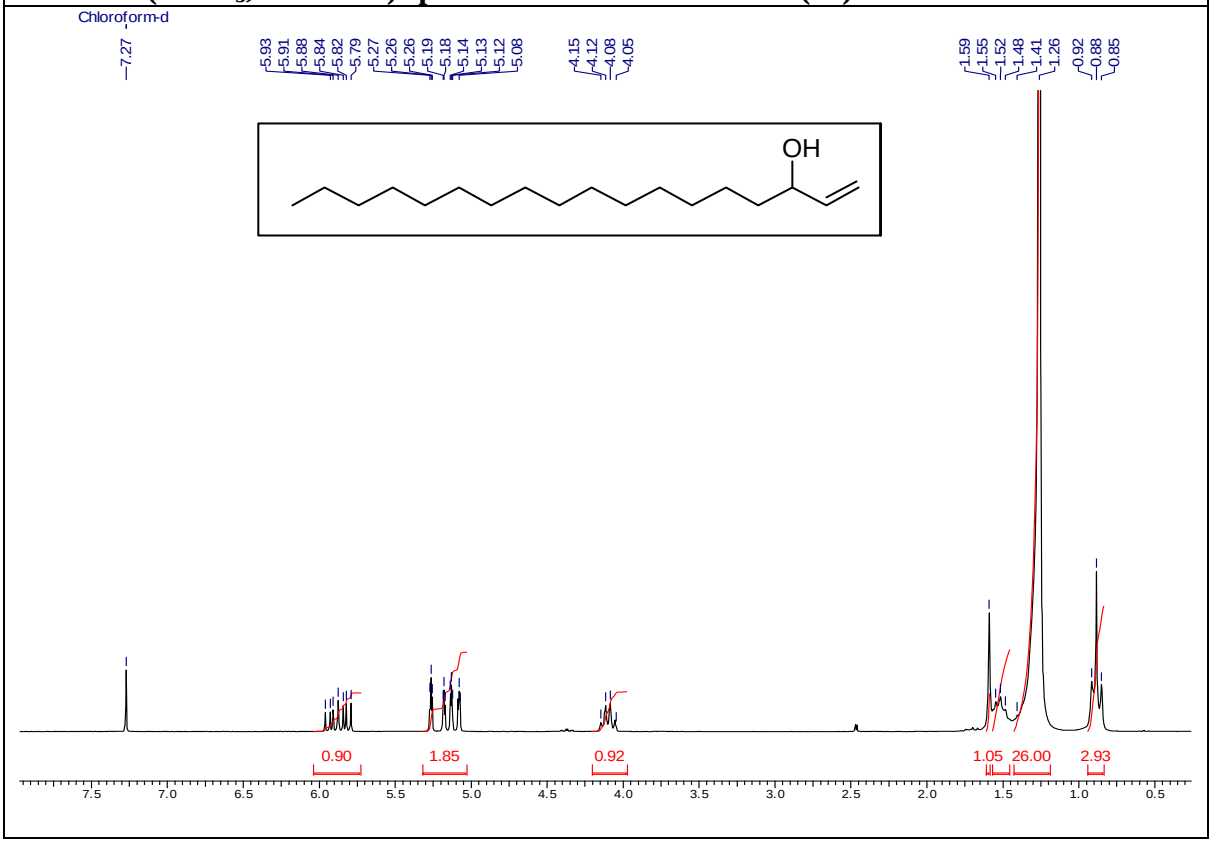
3. ^{1}H, ^{13}C & ^{19}FNMR spectra of **33**

4. ^{1}H & ^{13}C NMR spectra of **34**

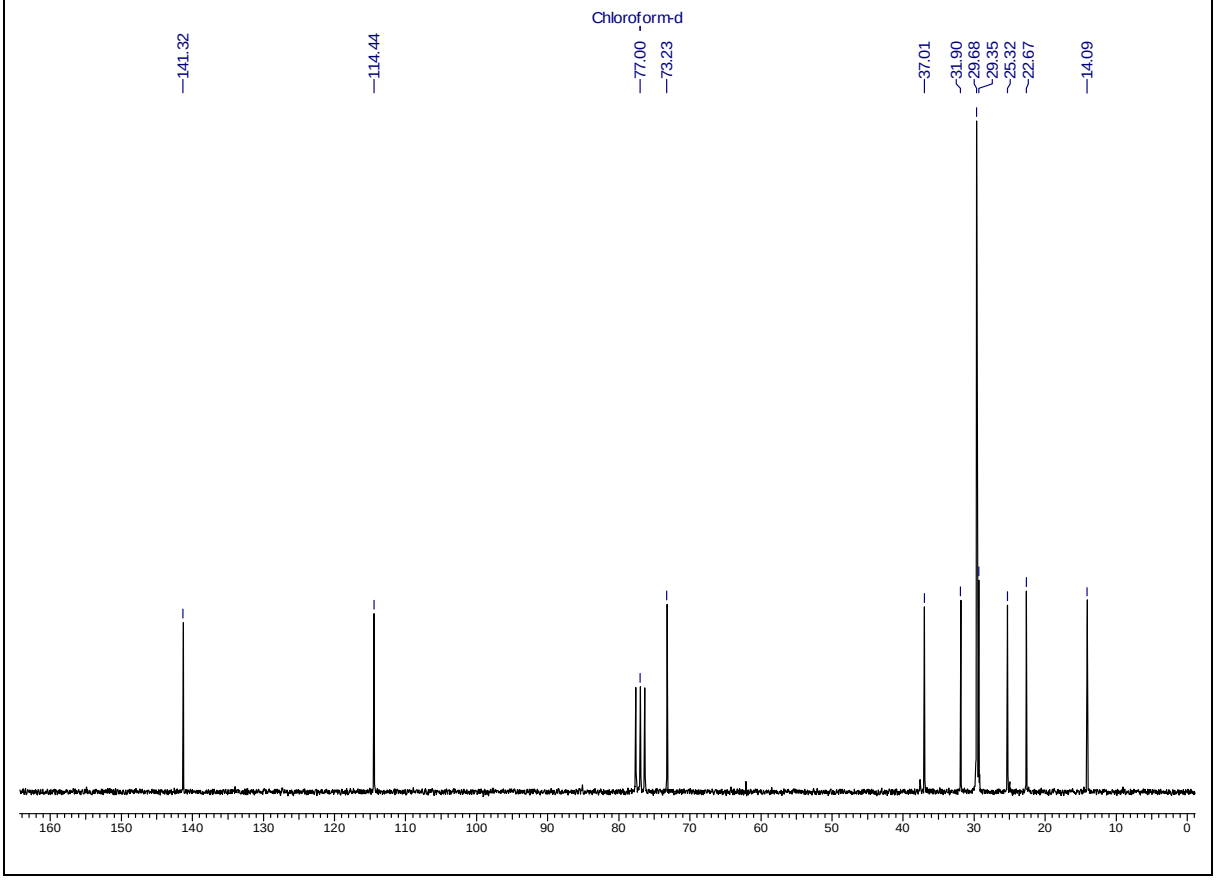
5. ^{1}H & ^{13}C NMR spectra of **35**

6. ^{1}H & ^{13}C NMR spectra of **36**

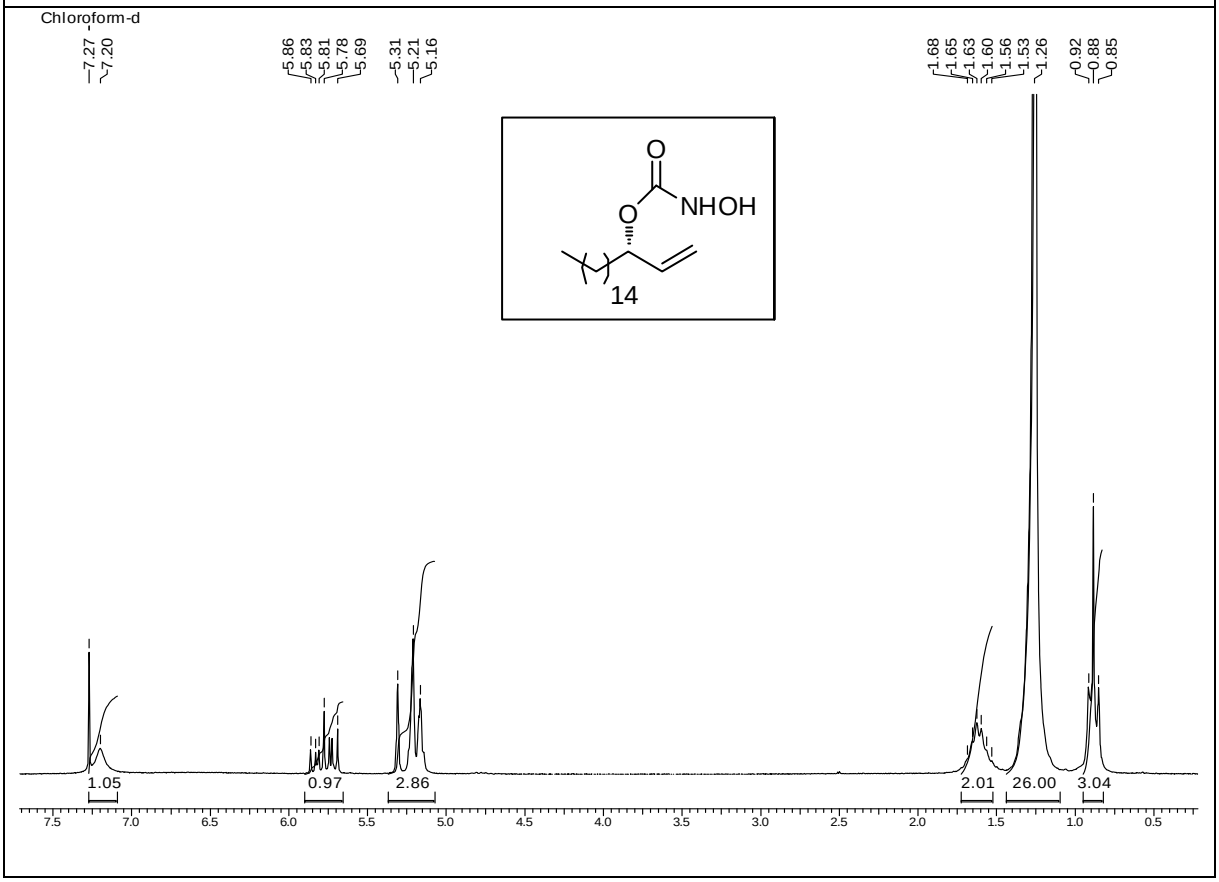
^{1}H NMR ($CDCl_3$, 200 MHz) spectra of Octadec-1-en-3-ol (29)



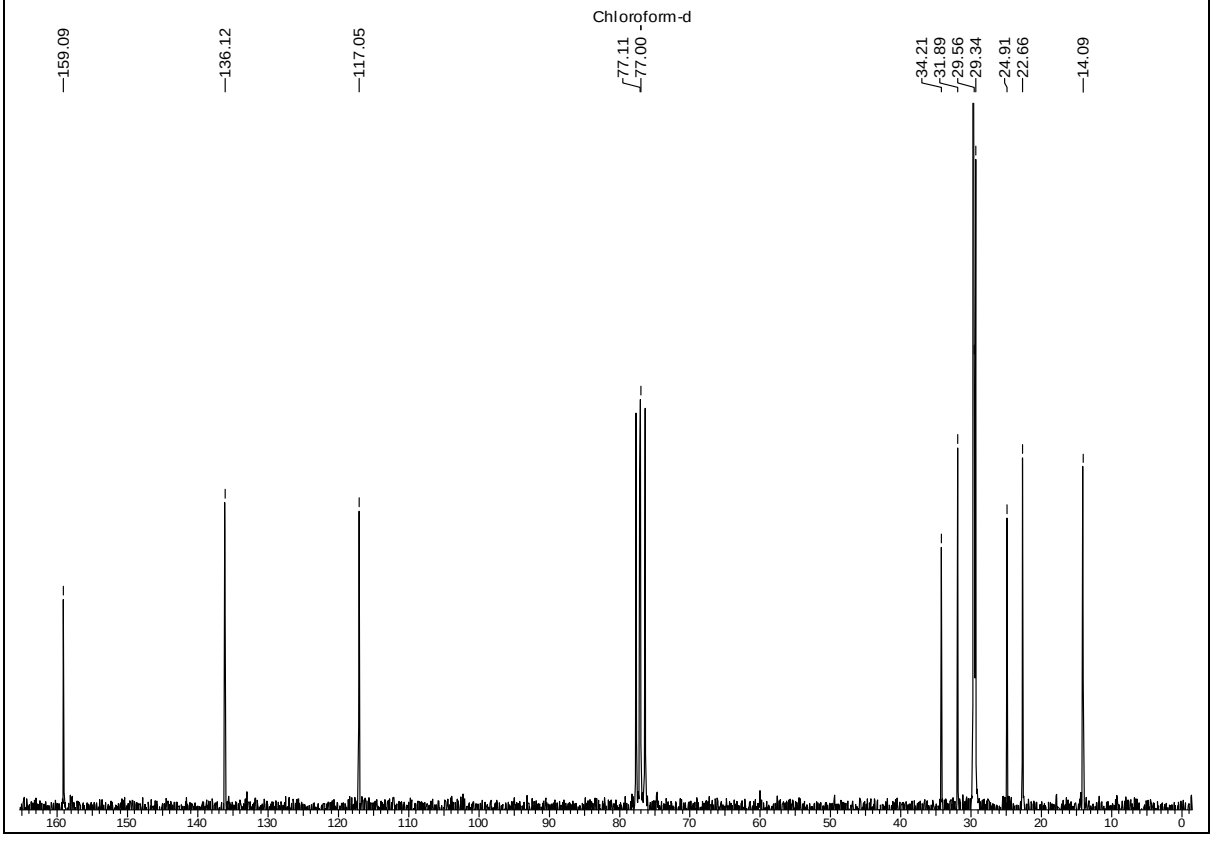
^{13}C NMR ($CDCl_3$, 50 MHz) spectra of Octadec-1-en-3-ol (29)



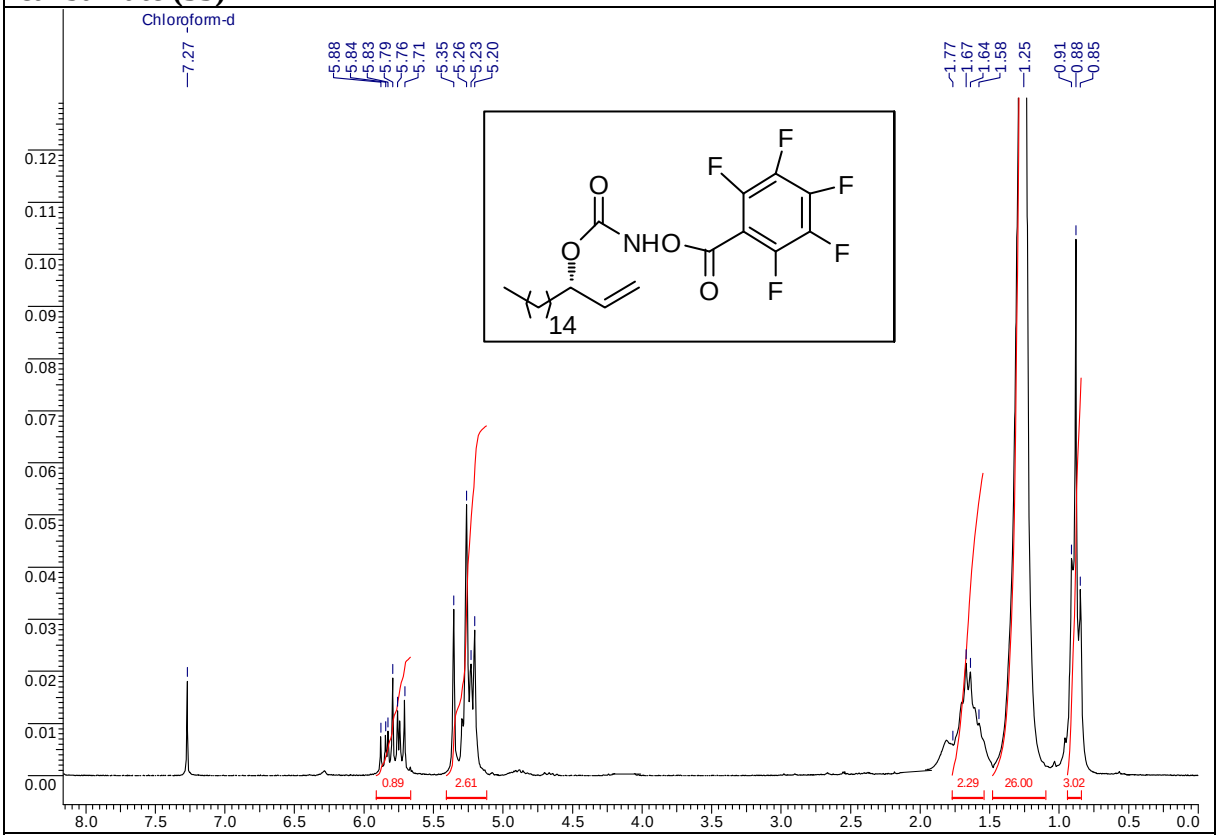
^{1}H ($CDCl_3$, 200 MHz) spectra of (*S*)-Octadec-1-en-3-ylhydroxycarbamate (32)



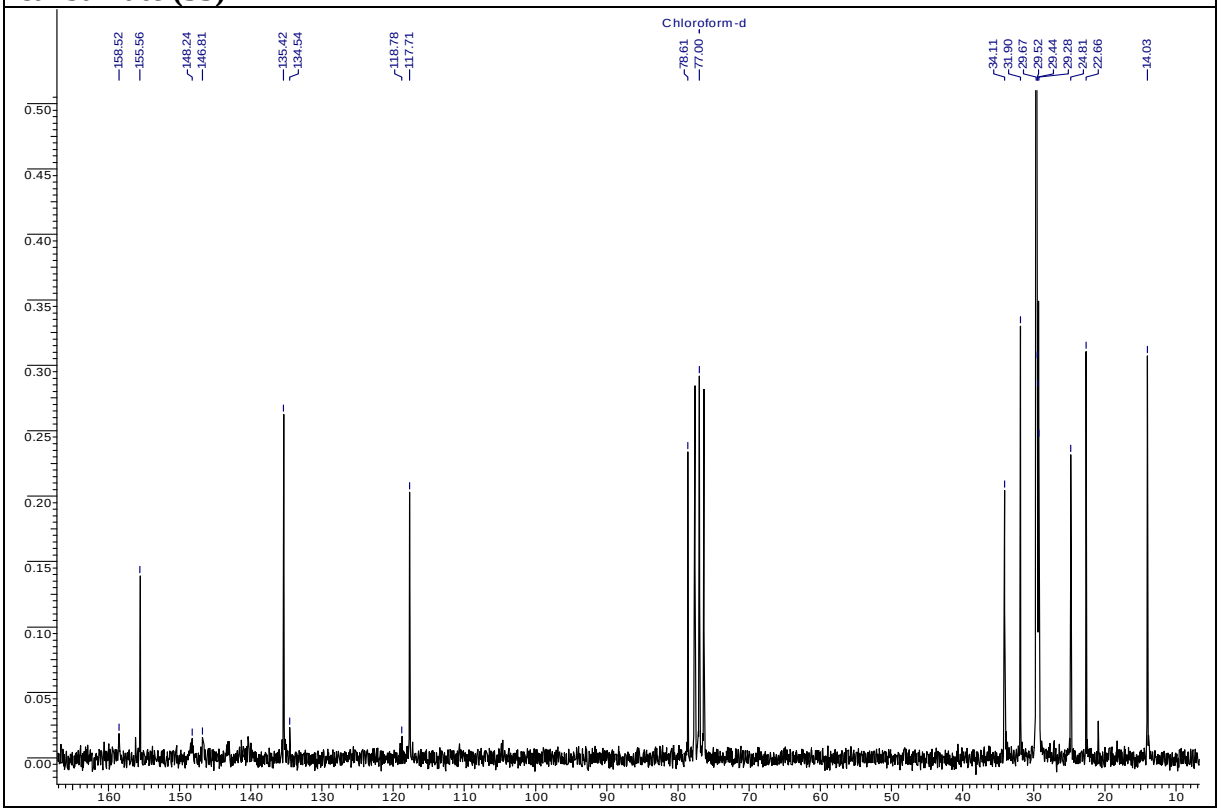
^{13}C NMR ($CDCl_3$, 50 MHz) spectra of (*S*)-Octadec-1-en-3-ylhydroxycarbamate (32)



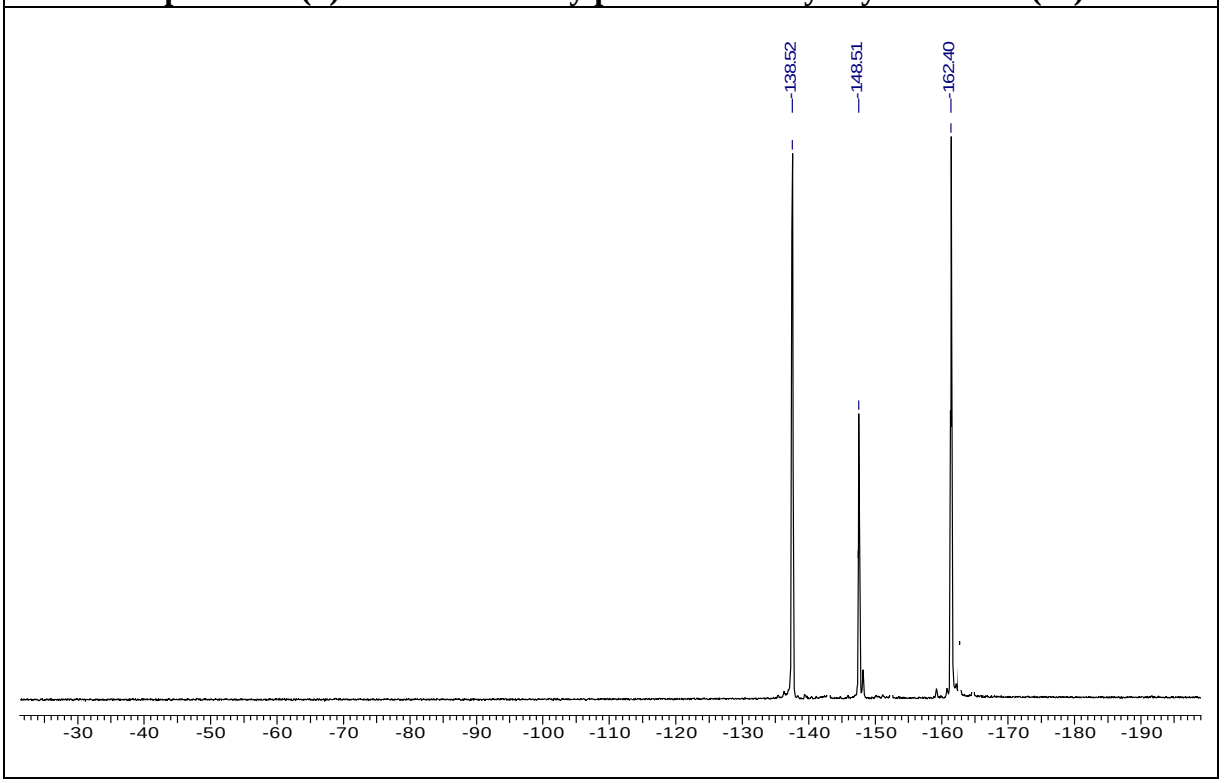
^{1}H NMR ($CDCl_3$, 200 MHz) spectra of (*S*)-Octadec-1-en-3-ylperfluorobenzoyloxy-carbamate (33)



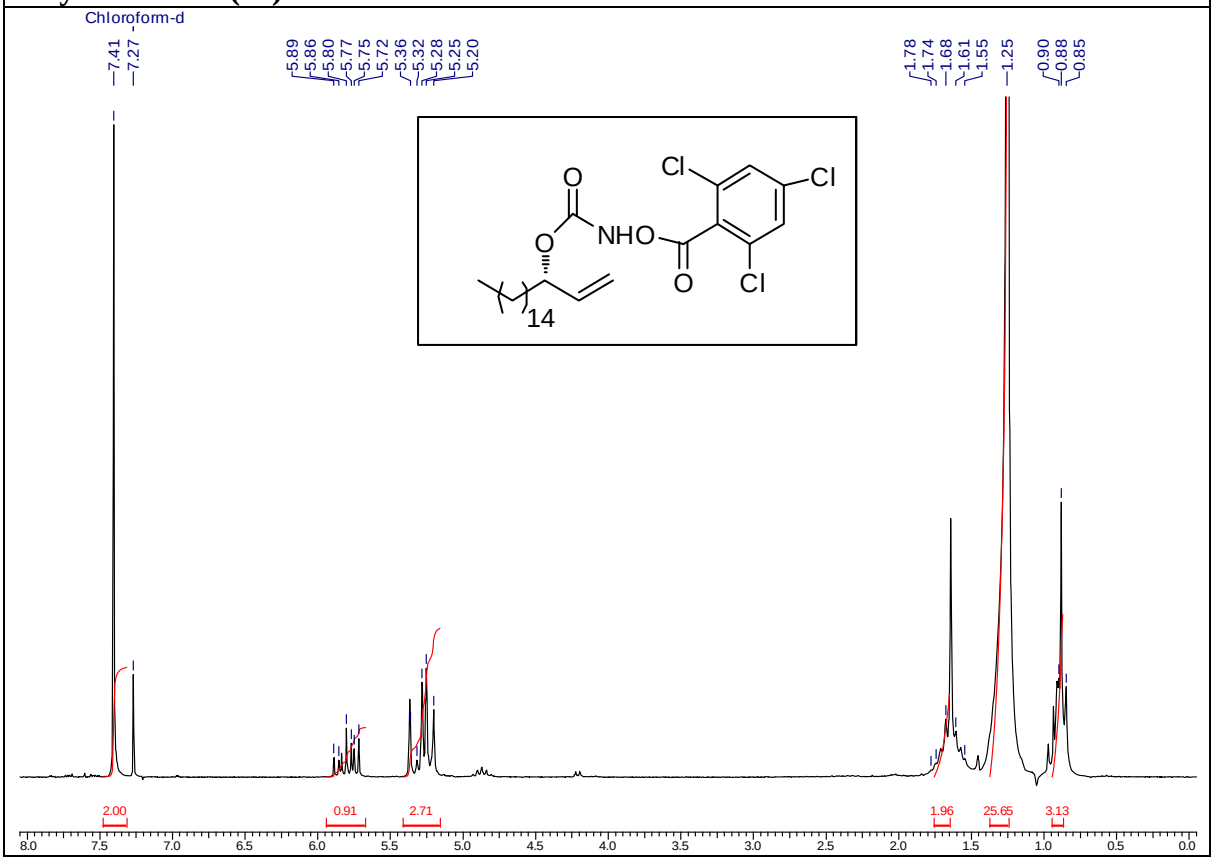
^{13}C NMR ($CDCl_3$, 50 MHz) spectra of (*S*)-Octadec-1-en-3-ylperfluorobenzoyloxy-carbamate (33)



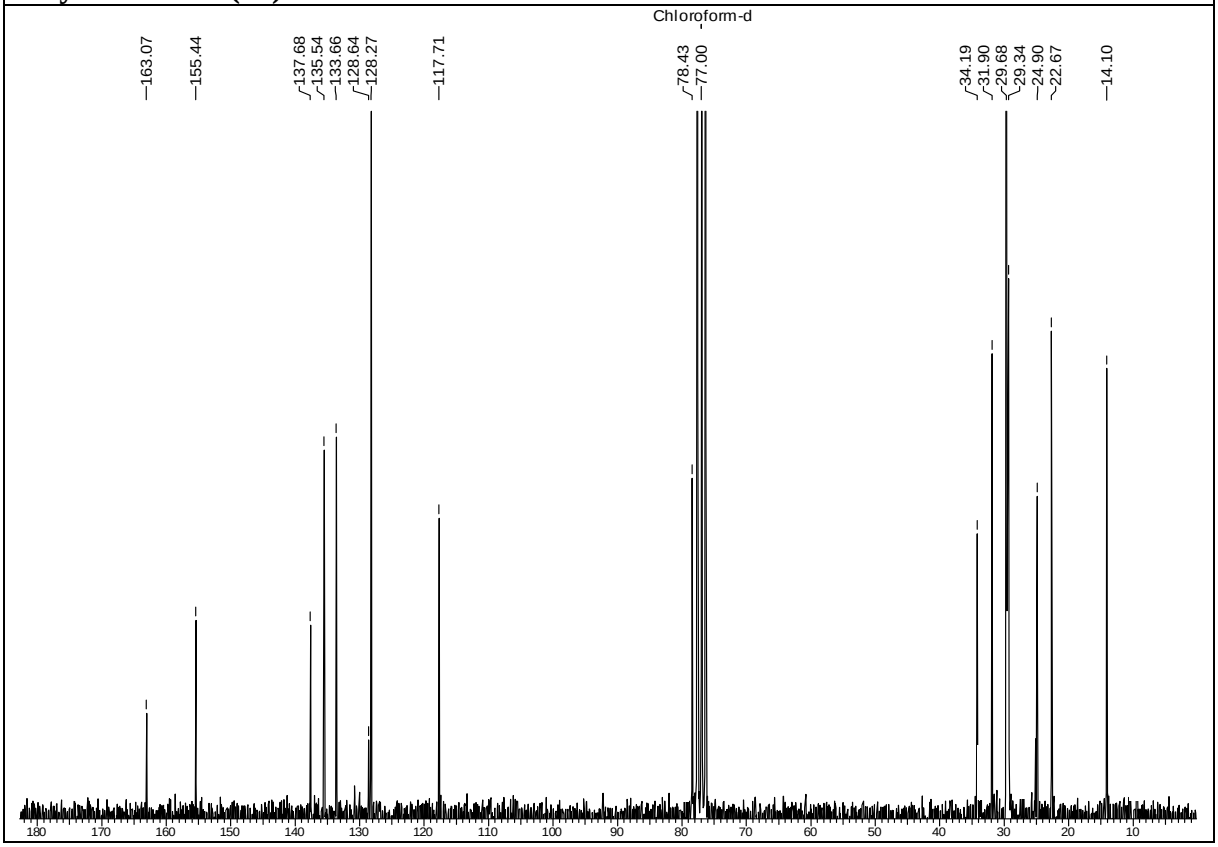
^{19}F NMR spectra of (*S*)-Octadec-1-en-3-ylperfluorobenzoyloxycarbamate (33)



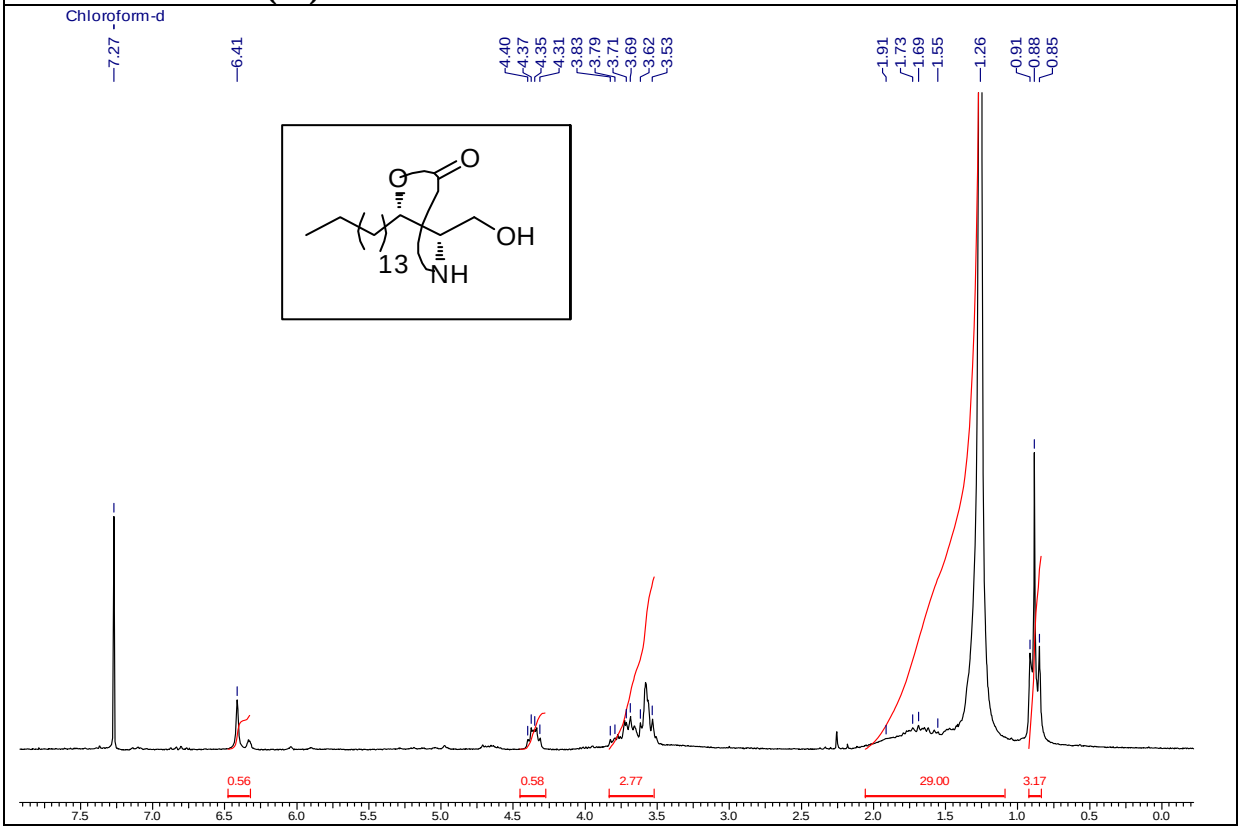
^{1}H NMR ($CDCl_3$, 200 MHz) spectra of (*S*)-Octadec-1-en-3-yl-2,4,6-trichlorobenzoyloxycarbamate (34)



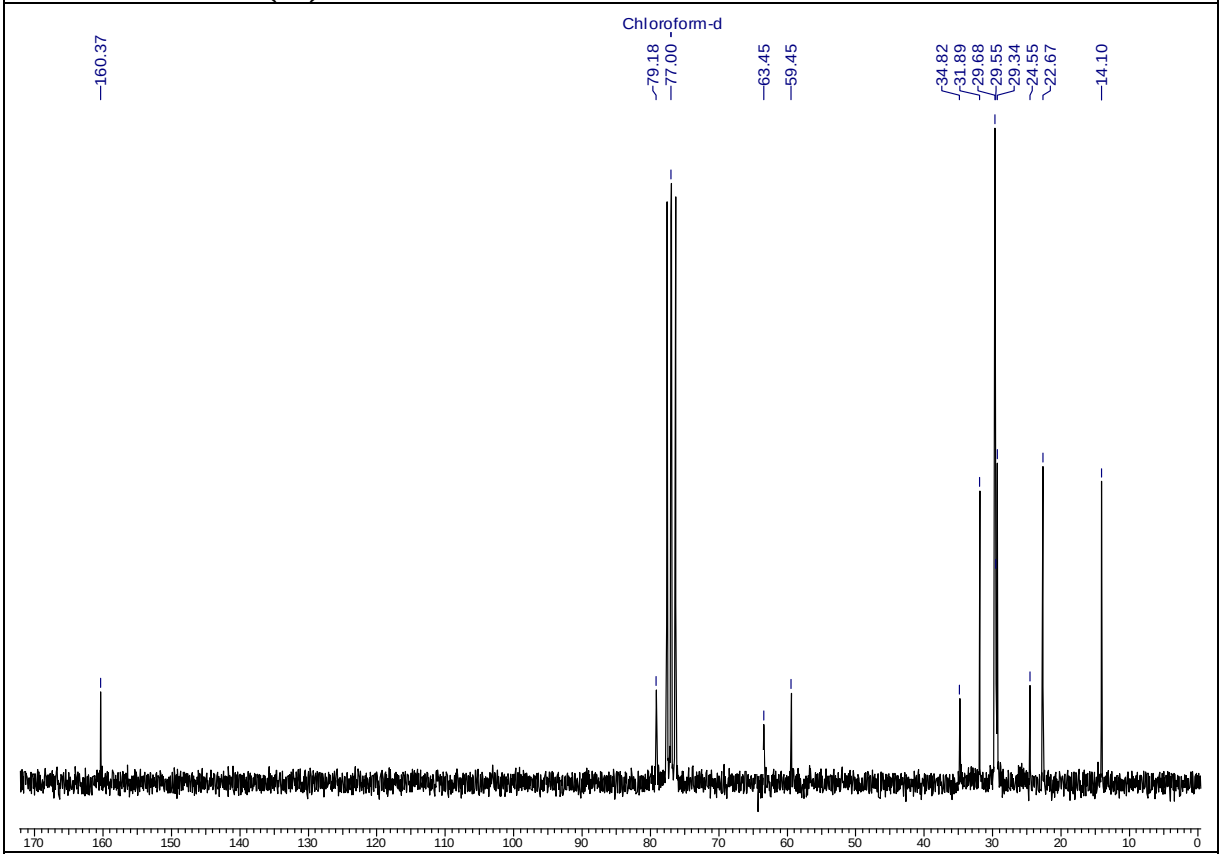
^{13}C NMR ($CDCl_3$, 50 MHz) spectra of (*S*)-Octadec-1-en-3-yl-2,4,6-trichlorobenzoyloxycarbamate (34)



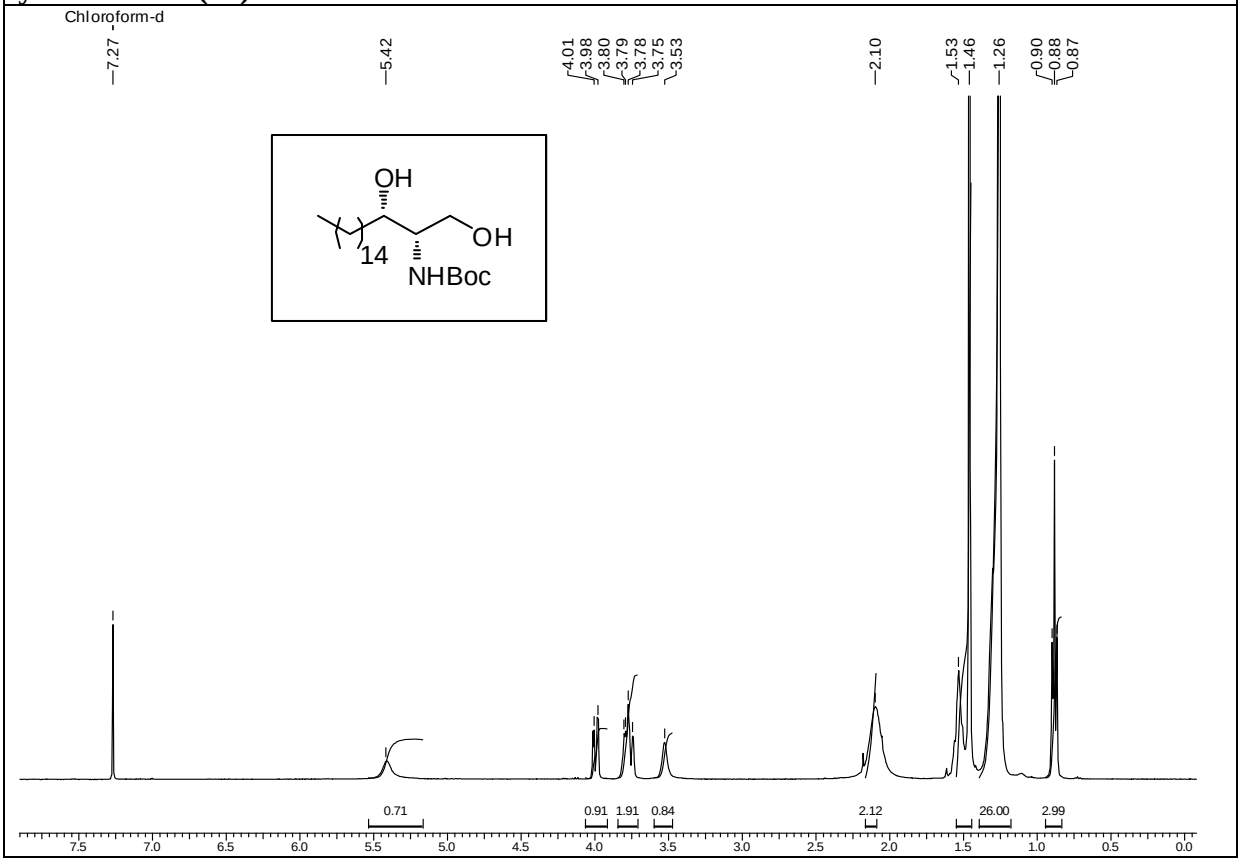
^{1}H NMR ($CDCl_3$, 500 MHz) spectra of (4*R*,5*R*)-4-(hydroxymethyl)-5-pentadecyl-oxazolidine-2-one (35)



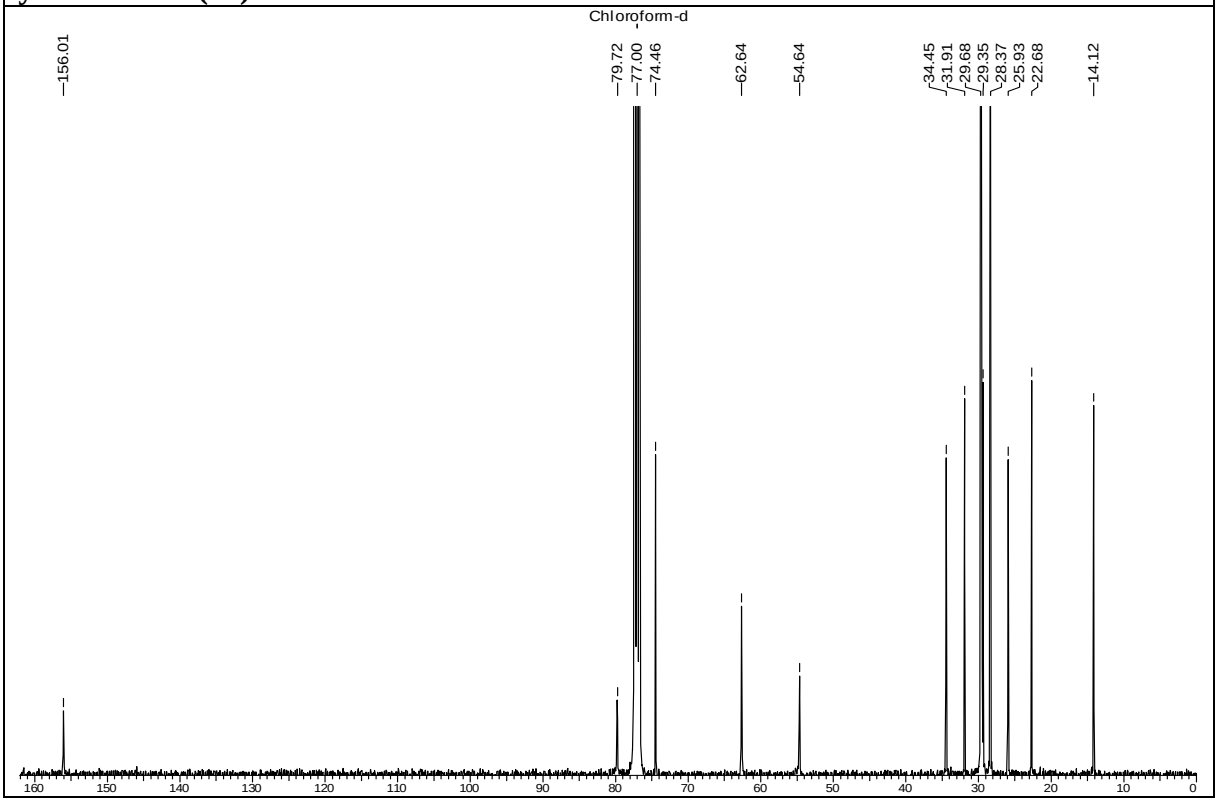
^{13}C NMR ($CDCl_3$, 125 MHz) spectra of (4*R*,5*R*)-4-(hydroxymethyl)-5-pentadecyl-oxazolidine-2-one (35)



^{1}H NMR ($CDCl_3$, 400 MHz) spectra of *tert*-butyl(2*S*,3*S*)-1,3-Dihydroxyoctadecane-2-ylcarbamate (36)



^{13}C NMR ($CDCl_3$, 100 MHz) spectra of *tert*-butyl(2*S*,3*S*)-1,3-Dihydroxyoctadecane-2-ylcarbamate (36)



2.2.6. References

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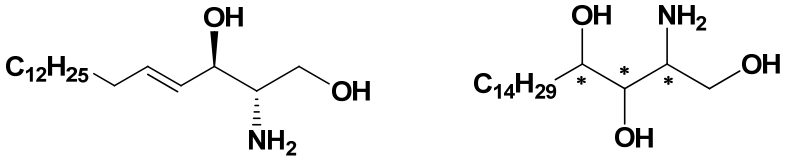
2.4 SECTION D

ENANTIOSELECTIVE SYNTHESIS OF L-*arabino*- AND L-*xylo*-C_{18} - PHYTOSPHINGOSINE

2.4.1. Introduction

Besides fatty acids, triglycerides, glycophospholipids and cholesterol, sphingolipids are the most important constituents of the membranes in eukaryotic cells, and in some prokaryotic organisms and viruses.[1] More than 300 different types of complex sphingolipids have been isolated, and new examples from a variety of sources continue to be isolated and characterized.[2] Because of their amphiphilic character, these compounds are able to form double layers. As a result, they form cell walls that are about 6 nm in diameter. Moreover, sphingolipids are essential for cell-to-cell communication, cell growth and cell differentiation, though the role of particular compounds is difficult to determine because of the very complex nature of these processes. In recent years, information has been collected that relates to the role of sphingolipids as second messenger molecules. Furthermore, sphingolipids seem to be involved in apoptosis, though its exact role remains to be elucidated. In human skin, sphingolipids crucially contribute to the essential water permeability barrier. Sphingolipids mediate, among other things, cell-cell interactions and immune responses.



Sphingosine
1

Phytosphingosine
2

Fig. 1

The most important sphingolipids are sphingosine **1** and phytosphingosine **2**. Phytosphingosines **3-10** constitute a group of related long chain aliphatic 2-amino-1,3,4-triols of which D-*ribo*-C_{18}-phytosphingosine ((2*S*,3*S*,4*R*)-2-aminooctadecane-1,3,4-triol) **8** is the most predominant. D-*ribo*-Phytosphingosine was first isolated from the mushroom *Amanita muscaria* in 1911 by Zellner as a nitrogen-containing substance "fungus cerebrin"[3] and it is very important for, keratinocytes and constitutes 40% of the membrane content. Due to its plant origin and its structural similarity to sphingosine, the name "phytosphingosine" was coined for this base.[4] However, it is now evident that plants are not the only preserve for

phytosphingosines; they are widely distributed as a structural component of sphingolipids in yeast, fungi, mammalian tissues and marine organisms.[5] Because of the additional free hydroxy group in phytosphingosine, additional hydrogen bonds can be formed, which may enhance the rigidity of the multicellular lipid layer. This in turn leads to a decrease in transepidermal water loss. Furthermore, galactosyl- and glucosyl phytosphingolipids exhibit significant anticancer activity.

The long-chain base of the majority of the phytosphingolipids has 18-carbons; minor amounts of other chain lengths, especially C_{20}, are also found, depending on the origin.

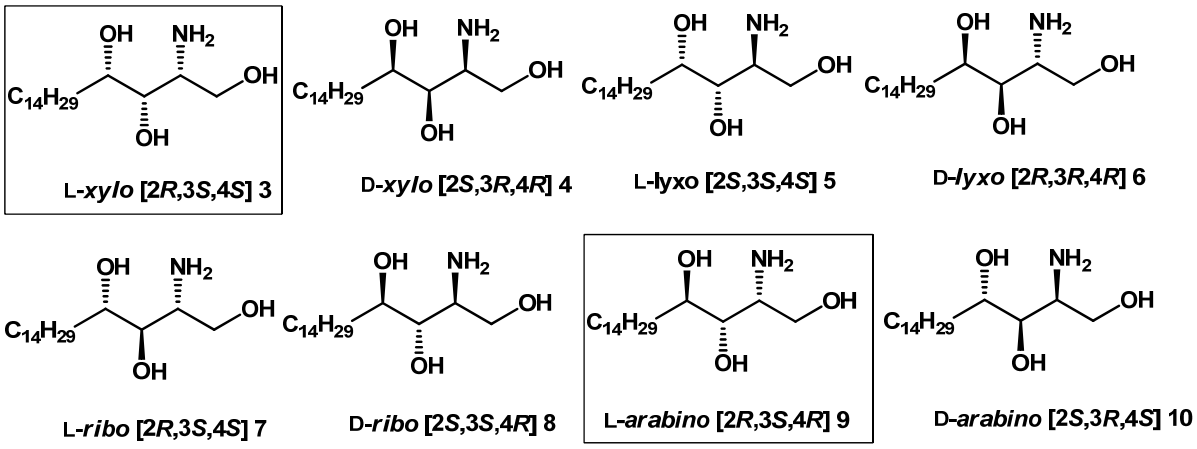


Fig. 2. C_{18}-phytosphingosine stereoisomers

Phytosphingosines derivatives, exhibit a wide range of biological activities, which are particularly fascinating. Natural products isolated from a variety of species have proven to be particularly fertile sources of phytosphingosine containing glycosphingolipids (GSL's). A number of α-galactosyl ceramides isolated from the *Agelus* genus of sponge have been shown to have immunostimulatory properties. Agelasphin-9b **11** (**Fig. 3**), a potent, immunostimulatory compound, has been utilized as a lead in structure activity studies by Kirin Brewery Company (Japan) to determine a novel, potent, cytotoxic agent.[6] Their investigations identified KRN7000 **12**, currently in clinical trials as a chemotherapeutic agent for treating liver tumors. Although the identification of a potential new cancer chemotherapeutic agent was significant, the discovery of the novel mode of action of this compound has even greater implications.[7-10]

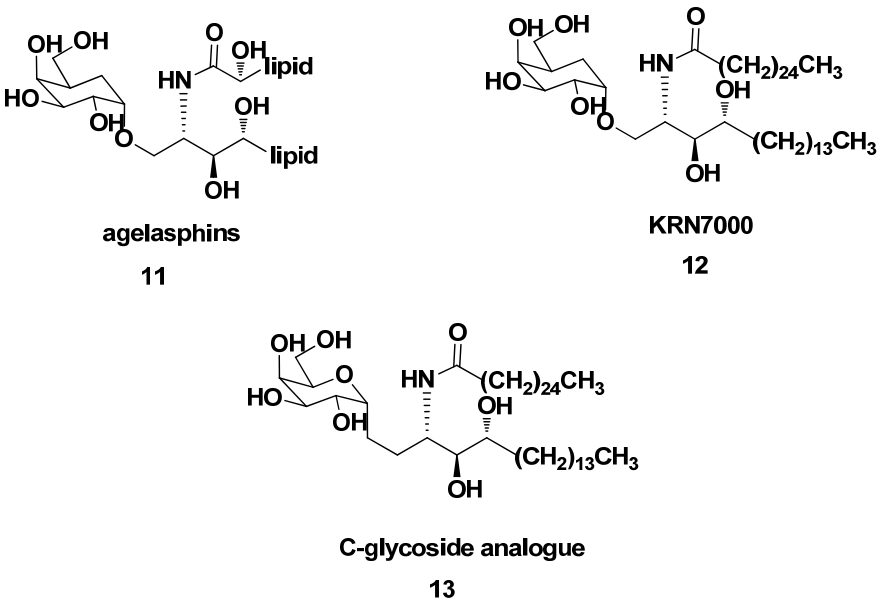


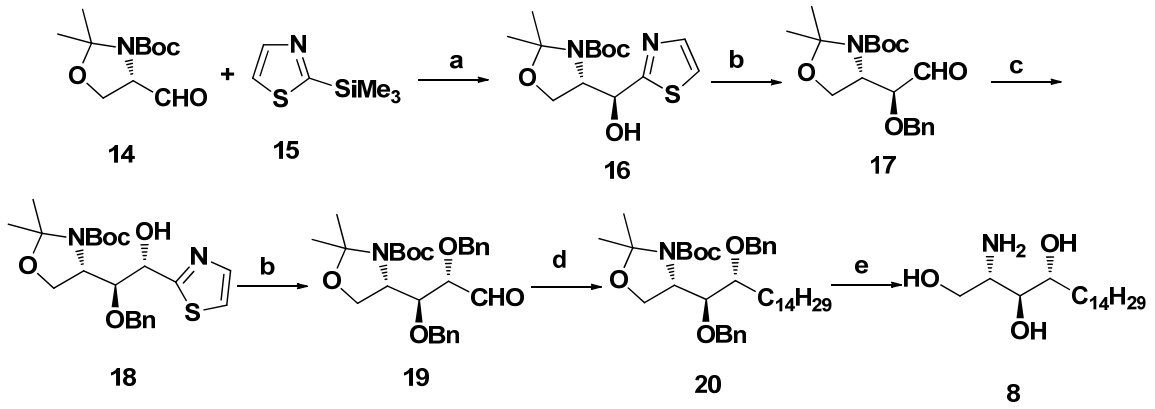
Fig. 3. C_{18}-phytosphingosine analogues

2.4.2. Review of Literature

Due to the variety of biological properties of phytosphingosine itself and phytosphingosine-containing sphingolipids, and their scarcity in nature, a great deal of effort has been devoted toward the synthesis of phytosphingosine. In general these approaches can be placed into three main categories. The first two rely on the chiral pool of amino acids (L-serine)[11] and carbohydrates[12] as the source of chirality. The third category of syntheses is based on asymmetric reactions.[13-20] Most syntheses have focused on the preparation of D-*ribo*-(2*S*,3*S*,4*R*)-phytosphingosine **8**. It is therefore of great interest to synthesize other phytosphingosine diastereomers to learn about the precise function of individual sphingolipids in vivo. The design of an efficient and improved route to phytosphingosines therefore continues to be important. A few interesting syntheses of phytosphingosine are described below.

Dondoni *et al*. (1990)[15]

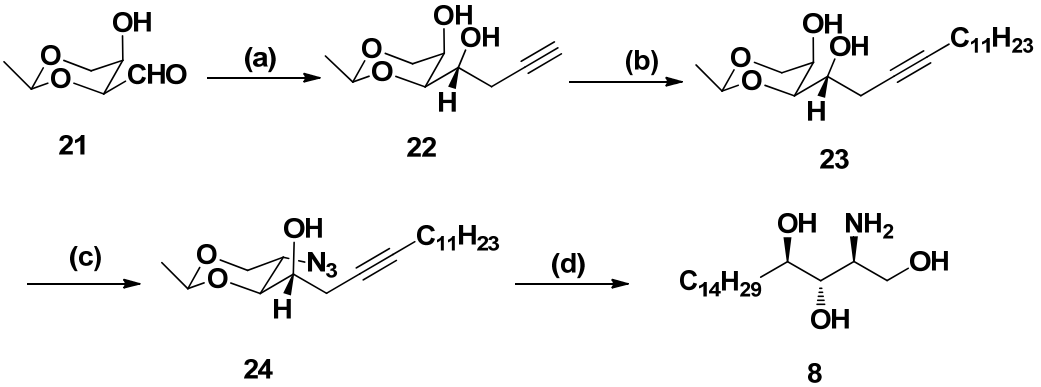
Dondoni *et al*. were the first to report the exploitation of **14** for the preparation of phytosphingosines. Homologation with 2-TMS-thiazole (2-TST) **15** proceeded with high *anti*-selectivity (92:8) to give **16**. Compound **16** was converted in a 3 stage-one pot process into **17** in 73% yield. A second homologation again proceeded in a stereoselective manner (~6:1 ratio of *anti*:*syn*), and after hydroxyl protection, the aldehyde was unmasked as before to give **19**. Aldehyde **19** was subjected to Wittig reaction; subsequent Raney nickel reduction, followed by treatment with TFA, afforded *ribo*-phytosphingosine (**Scheme 1**).

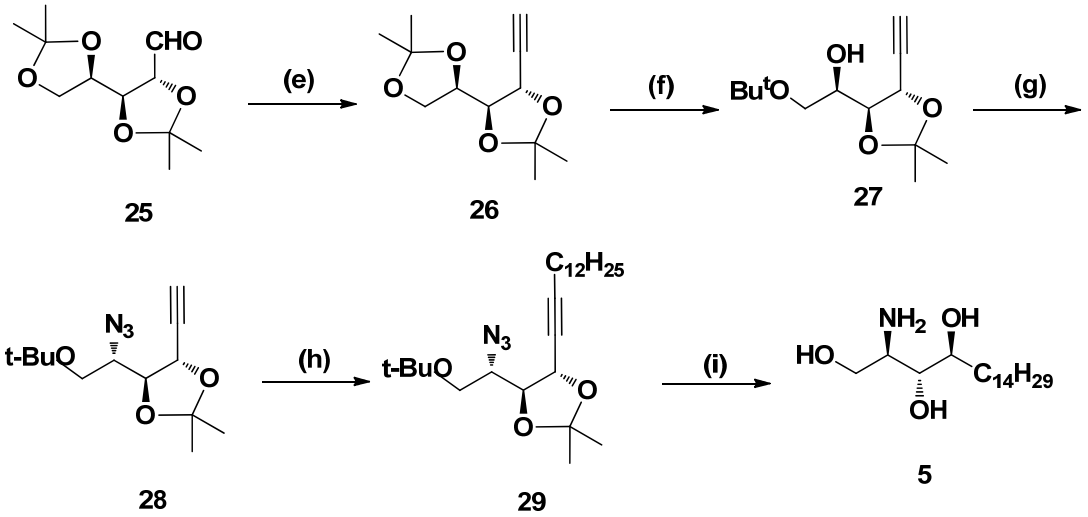


Scheme 1. *Reagents and conditions*: (a) CH_2Cl_2, rt, 20 h, then *n*-Bu_4NF, 85%; (b) [i] NaH, reflux, BnBr, THF, *n*-Bu_4NI, 73%, [ii] MeI, CH_3CN, reflux, 12 h then $NaBH_4$, MeOH, -10 ^oC, 30 min then $HgCl_2$, CH_3CN, H_2O, 15 min, 73%;(c) 2-TST, THF, 0 ^oC, 63%; (d) [i] $C_{13}H_{27}P^+Ph_3Br^-$,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

Wu *et al.* (1995)[16]

In Wu's approach, the reaction of 2,4-*O*-ethylidene-D-threose **21** with prop-2-ynyl bromide/Zn gave **22** (*erythro*:*threo*, 11.7:1). Alkyne substitution, triflation of 2-OH and azide displacement furnished **23**. Deprotection of acetal and hydrogenation of azide and alkyne gave D-*ribo*-phytosphingosine **8**. In order to synthesize L-*lyxo*-phytosphingosine, **25** was first converted into the alkyne **26**. Conversion of terminal acetonide into *t*-butyl ether gave **27**. Mesylation of hydroxyl and azide displacement followed by alkyne substitution furnished **29**. Deprotection of acetonide and hydrogenation afforded L-*lyxo*-phytosphingosine **5** (**Scheme 2**).

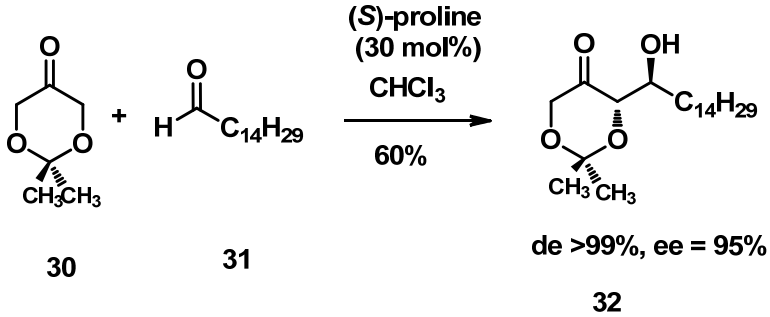


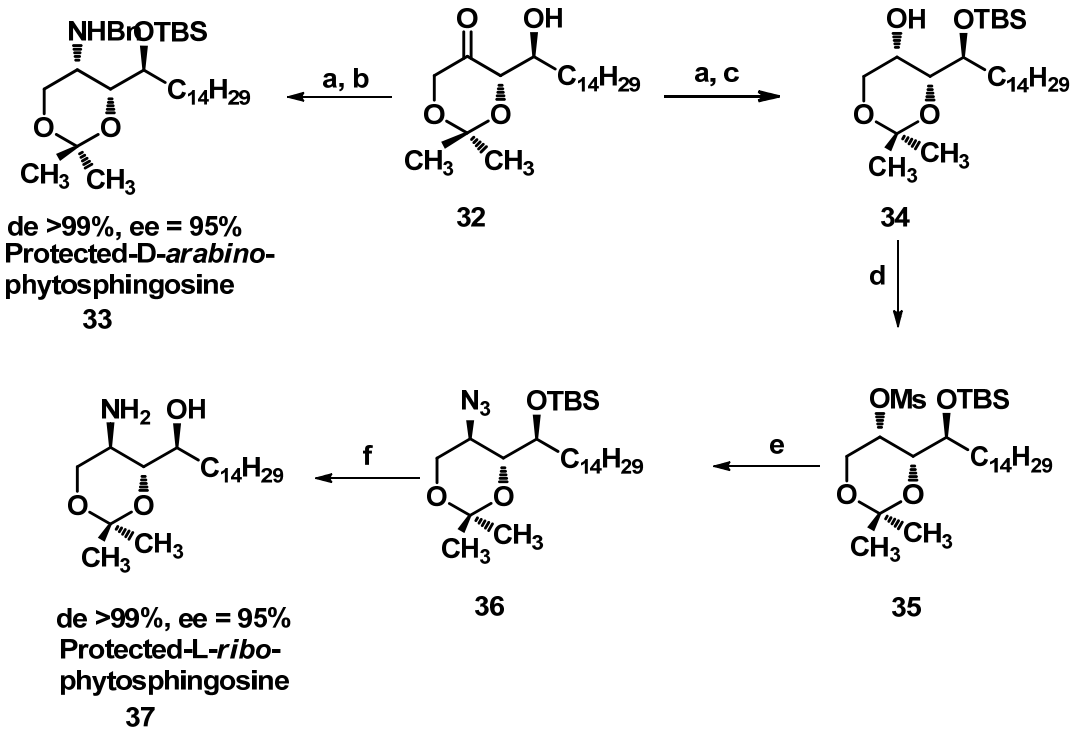


Scheme 2. *Reagents and conditions*: (a) prop-2-ynyl bromide, Zn, DMF-Et_2O, 85%; (b) *n*-BuLi, $C_{11}H_{23}Br$, THF-HMPA, 74%; (c) [i] Tf_2O, Py, CH_2Cl_2, -78 ^oC to rt; [ii] NaN_3, DMF, rt, 82%; (d) [i] 90% CF_3CO_2H; [ii] 10% Pd-C, MeOH; (e) [i] CBr_4, Ph_3P, Zn, CH_2Cl_2, 62%; [ii] *n*-BuLi, THF,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

Enders *et al*. (2006)[17]

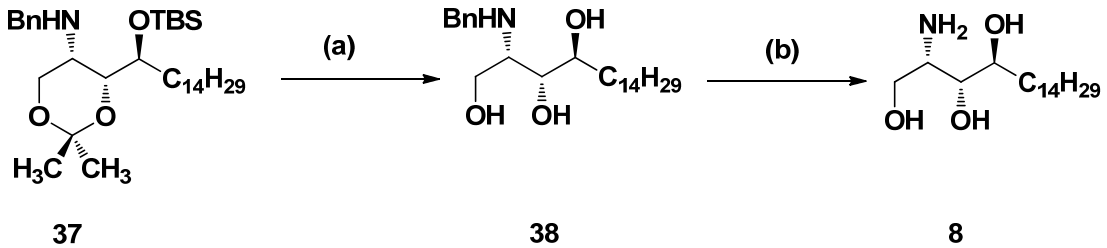
Organocatalytic asymmetric synthesis was employed by Enders *et al*. to the syntheses of D-*arabino*- and L-*ribo*-phytosphingosine. Thus, the simple (*S*)-proline catalyzed aldol reaction of the dioxanone **30** with pentadecanal **31** directly delivered gram amounts of the selectively acetonide protected ketotriol **32**, precursor of the core unit of phytosphingosines in excellent stereoisomeric purity. Protection of hydroxy as TBS ether followed by reductive amination of **32** gave 1,3-aminoalcohol **33** in good yield. For the synthesis of *syn*-1,3-aminoalcohol, **33** was first transformed to the corresponding *anti*-1,3-diol **34** by a highly diastereoselective reduction with L-Selectride followed by mesylation





Scheme 3. *Reagents and conditions*: Diastereoselective reductive amination and ketone–amine conversion. (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, –20 ^oC, 95%, de > 99%; (b) $BnNH_2$, $NaBH(OAc)_3$, AcOH, CH_2Cl_2, -20 ^oC, 94%, de >99%; (c) L-Selectride, THF, –78 ^oC, 93%, de >99%; (d) MsCl, DMAP, CH_2Cl_2, –10 to 0 ^oC, 91%, de >99%; (e) NaN_3, 18-crown-6, DMF, 100 ^oC, 80%, de >99%; (f) LAH, THF, 0 ^oC, 98%, de >99%.

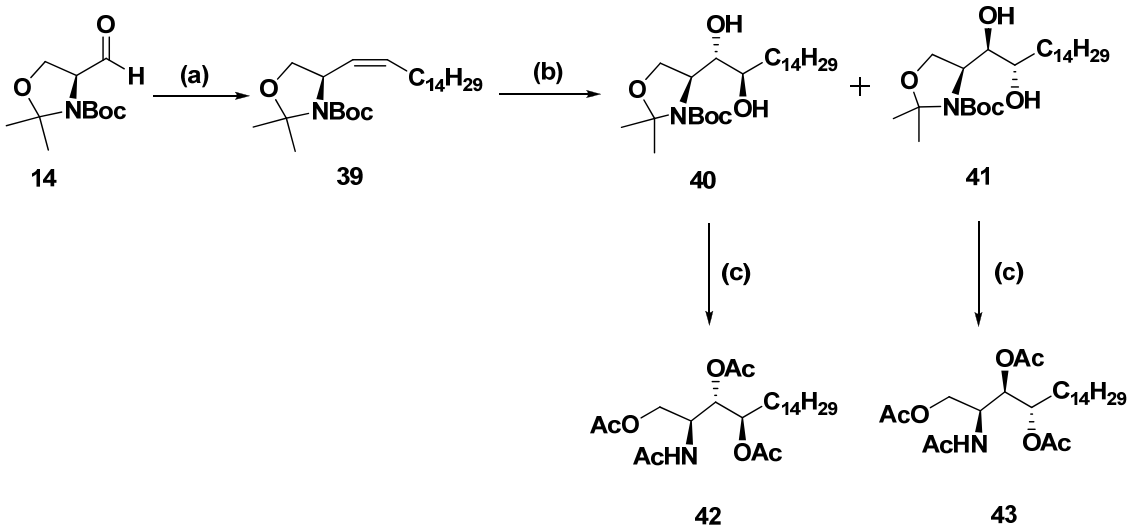
and subsequent azidation to furnish **36** with complete inversion of the stereogenic centre. Subsequent reduction of the azide **36** and deprotection the silyl- and acetonide group followed by hydrogenation afford D-*arabino*-phytosphingosine **10** in 99% yield (**Scheme 3 and 4**).



Scheme 4. *Reagents and conditions*: (a) [i] TBAF, THF, $MgSO_4$, 50 ^oC; [ii] TFA, THF, 50 ^oC, 92%; (b) H_2, Pd/C, MeOH, 99%

Ogino *et al.* (2000)[18]

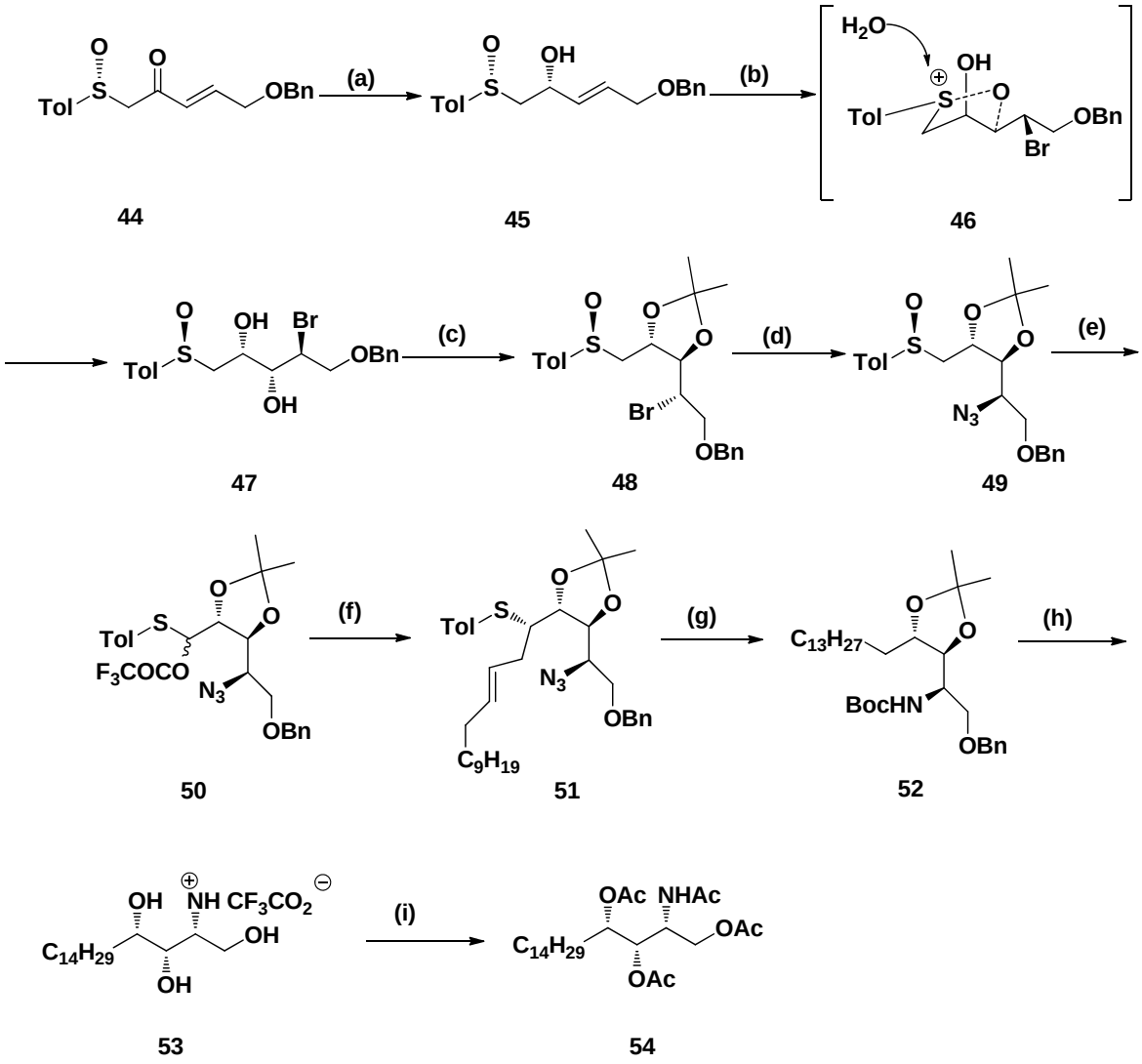
Ogino *et al.* accomplished the synthesis of L-*arabino*-phytosphingosine by Wittig reaction of Garner's aldehyde with pentadecyltriphenylphosphonium bromide using LHMDS in very good yield and selectivity (Z/E = 91:9). Compound **39** was then subjected to osmylation conditions followed by deprotection and acetylation to furnish tetraacetylated L-*arabino*-phytosphingosine **43**.



Scheme 5. *Reagents and conditions*: (a) $C_{15}H_{31}PPh_3Br$, LHMDS, -78 °C, 74%; (b) *N*-methylmorpholine *N*-oxide hydrate, OsO_4, rt, 68% (c) [i] CF_3CO_2H, rt, 78%; [ii] Ac_2O, DMAP, rt, 67%

Raghvan et al. (2003)[19]

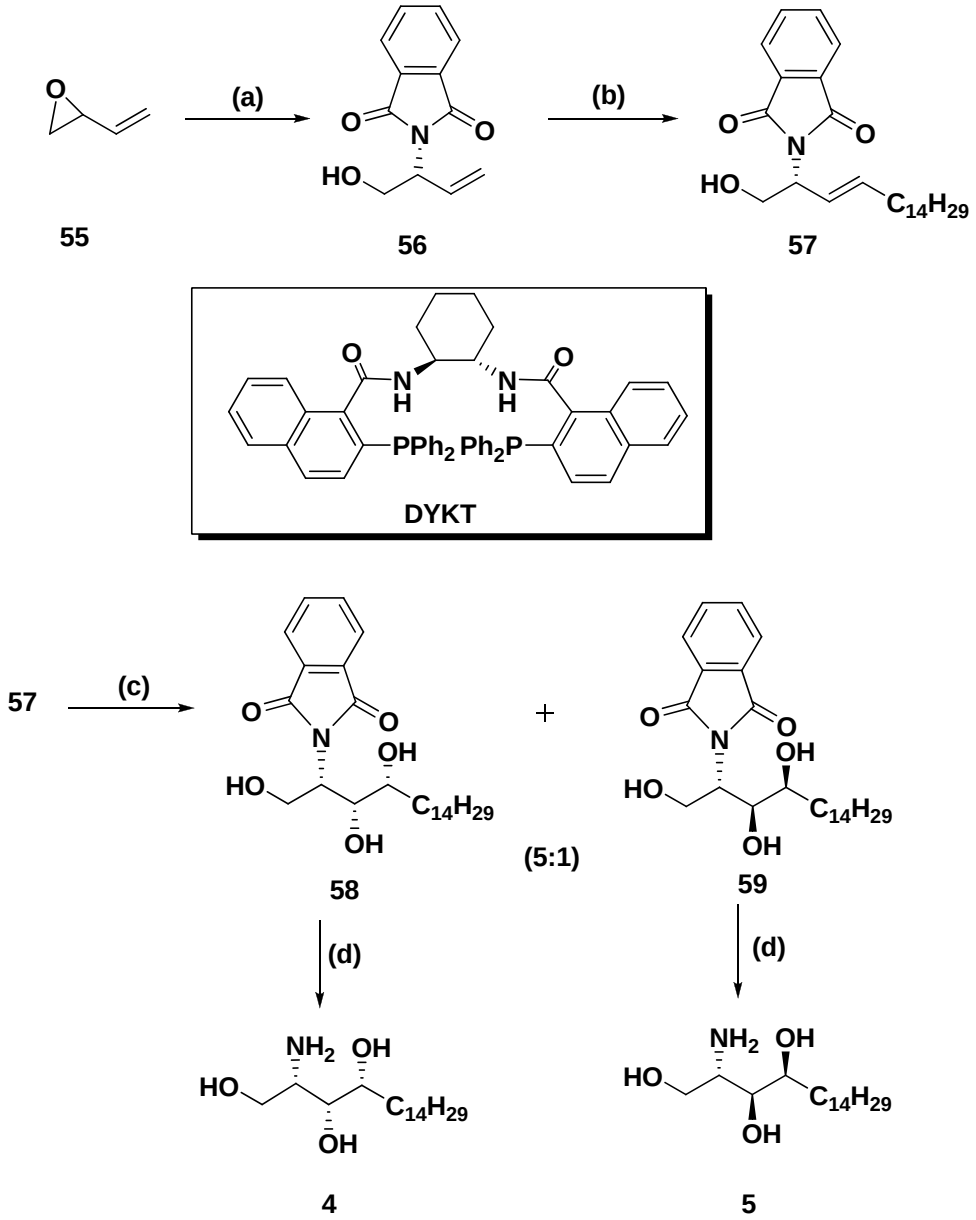
Raghvan *et al.* utilized stereoselective bromohydration of β-hydroxy-γ,δ-unsaturated sulfoxides **45** π-complexed to a bromonium ion via intramolecular nucleophilic attack by the sulfinyl moiety. Compound **48** was converted into azido compound **49** followed by C_{13} hydrocarbon insertion by Pummerer ene reaction to afford compound **51**. Five transformations were effected in a one pot operation, by treatment of the sulfide **51**, with Ra-Ni in methanol in the presence of di-*tert*-butyl dicarbonate under an atmosphere of hydrogen to yield the acetonide **52**. The double bond and the azide were reduced with the resulting amine to transform into a urethane and the toluene thio group and benzyl ether were hydrogenolysed under the reaction conditions. The acetonide **52** was then deprotected to give the triol **53**, which when acetylated afforded the tetraacetate derivative **54** of L-*xylo*-[2*R*,3*S*,4*S*]-C_{18}-phytosphingosine **3**.



Scheme 6. *Reagents and conditions*: (a) DIBAL, THF, −78 °C, 91%; (b) NBS, H_2O, toluene, rt, 88%; (c) 2,2-DMP, acetone, CSA (cat.), rt, 86%. (d) NaN_3, DMSO, 85 °C, 75%; (e) TFAA, CH_2Cl_2, 0 °C; (f) $C_{13}H_{26}$, $SnCl_4$, 0 °C, 65% for the two steps; (g) Ra-Ni, H_2, $(Boc)_2O$, MeOH, rt, reflux, 68%; (h) TFA:H_2O, 0 °C; (i) Ac_2O, DMAP (cat.), pyridine, rt, 78%.

Castillo´n *et al* (2009)[20]

Castillo´n *et al* utilised dynamic kinetic asymmetric transformation for the synthesis of chiral synthon **56**. Compound **56** was treated with 1-hexadecene under Grubb's second generation catalyst to furnish compound **57**. Olefin was subjected to asymmetric dihydroxylation conditions afford **58** and **59** by using different ligands. The synthesis of compound **4** and **5** was achieved by treatment of **58** and **59** with hydrazine, respectively.



Scheme 7. *Reagents and conditions*: (a) Phthalimide, Na_2CO_3, $(\eta^3C_3H_5PdCl)_2$, 99%; (b) 1-hexadecene, Grubbs second generation catalyst, CH_2Cl_2, reflux, 12 h, 99% (c) OsO_4, K_2CO_3, $K_3Fe(CN)_6$, $(DHQ)_2PYR$, 99% (d) NH_2NH_2, MeOH, reflux, 82%.

2.4.3. Present Work

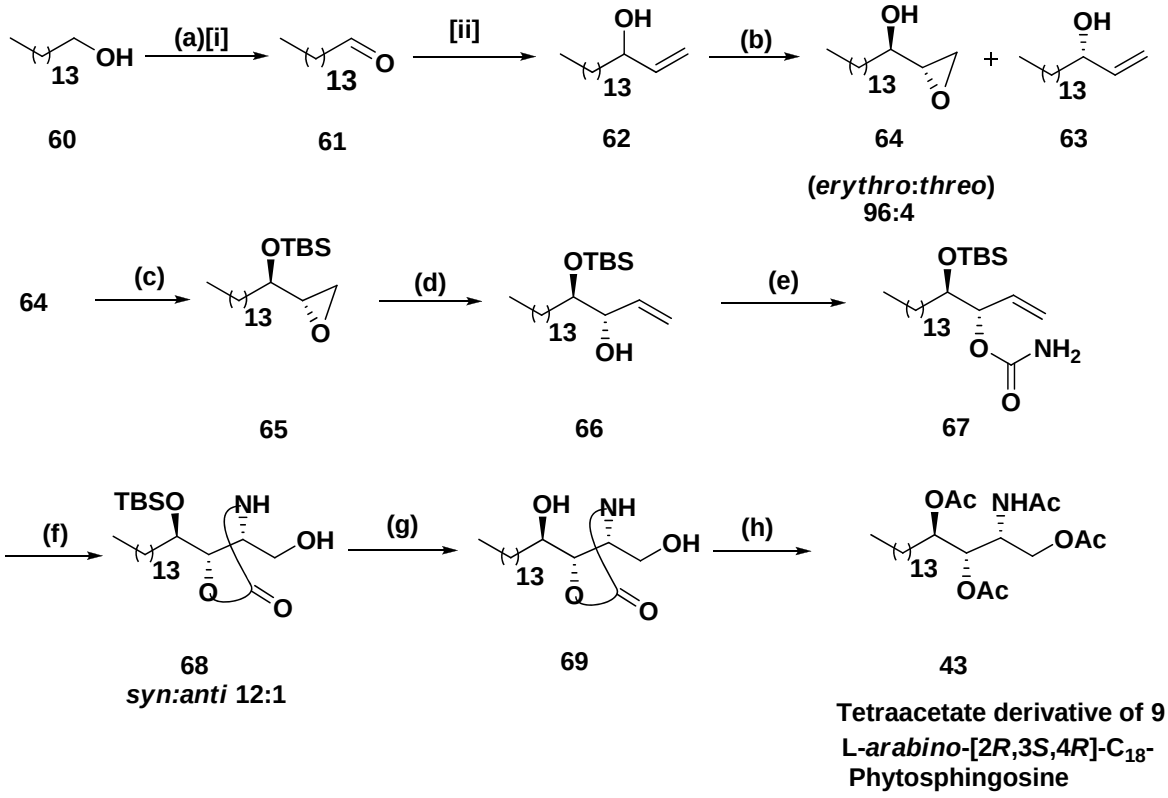
2.4.3.1. Objective

Given the vast chemistry, structural modifications and biological activities associated with sphingolipids, the synthesis of this class of vicinal amino alcohols has aroused considerable interest among several research groups around the world.[11-20] This speaks the significance of ongoing research work in the area of sphingolipid chemistry. Most syntheses have focused on the preparation of D-*ribo*-(2*S*,3*S*,4*R*)-phytosphingosine. It is therefore of great interest to synthesize other phytosphingosine diastereomers to learn about the precise function of individual sphingolipids in vivo. The design of an efficient and improved route to phytosphingosines therefore continues to be important. We have developed a general synthetic strategy for the synthesis of L-*arabino*-[2*R*,3*S*,4*R*]-C_{18}-phytosphingosine and L-*xylo*-[2*R*,3*S*,4*S*]-C_{18}-phytosphingosine by using Sharpless kinetic resolution[21] for preparation of chiral allylic alcohol and tethered aminohydroxylation[22] for the installation of amino stereocenter.

2.4.3.2. Results and Discussion

The synthesis of L-*arabino*-[2*R*,3*S*,4*R*]-C_{18}-phytosphingosine **9** started from commercially available pentadecanol-1 **60** as illustrated in **Scheme 8**. Pentadecanol-1 **60** was oxidized under DMSO-pivaloyl chloride conditions to afford the corresponding aldehyde **61** which was treated with vinylmagnesium bromide in dry THF at -78 ^{o}C to furnish the racemic alcohol **62** in 88% yield. The ^{1}H NMR spectrum gave olefin protons at δ 5.08-5.27 and 5.79-5.96. In the ^{13}C NMR spectrum of **62** olefin peaks appeared at δ 114.4, 141.3. In the IR spectrum of **62,** olefin and hydroxyl peaks appeared at 1611 and 3499 cm^{-1} respectively. The racemic alcohol **62** was subjected to Sharpless kinetic resolution conditions[21] using Ti(O^{i}Pr)$_4$, (-)-DIPT as chiral auxiliary and TBHP as oxidant in dry DCM at -20 ^{o}C for 4 days to give the chiral hydroxy olefin **63** and chiral epoxy alcohol **64** in excellent yield. Both compounds **63** and **64** were thoroughly characterized using IR, ^{1}H NMR and ^{13}C NMR spectra. Chiral allylic alcohol **63** was found in 46% yield and 97% ee (determined from ^{1}HNMR of the corresponding Mosher's ester). The ^{1}H NMR spectrum of **64** showed epoxide protons at δ 2.67-2.76 (multiplet, two protons) and 3.27 (multiplet, one proton). The epoxide **64** was found to be a mixture of *erythro* and *threo* (96:4), the ^{13}C NMR spectrum of **64** showed

upfield carbons of epoxide at δ 44.5, 43.5 and 52.3, 51.8 as a diastereomeric mixture. The diastereomeric mixture *erythro* and *threo* (96:4) of epoxide **64** was subsequently treated with TBSOTf in the presence 2,6-lutidine to furnish the silylated derivative **65** in 90% yield.



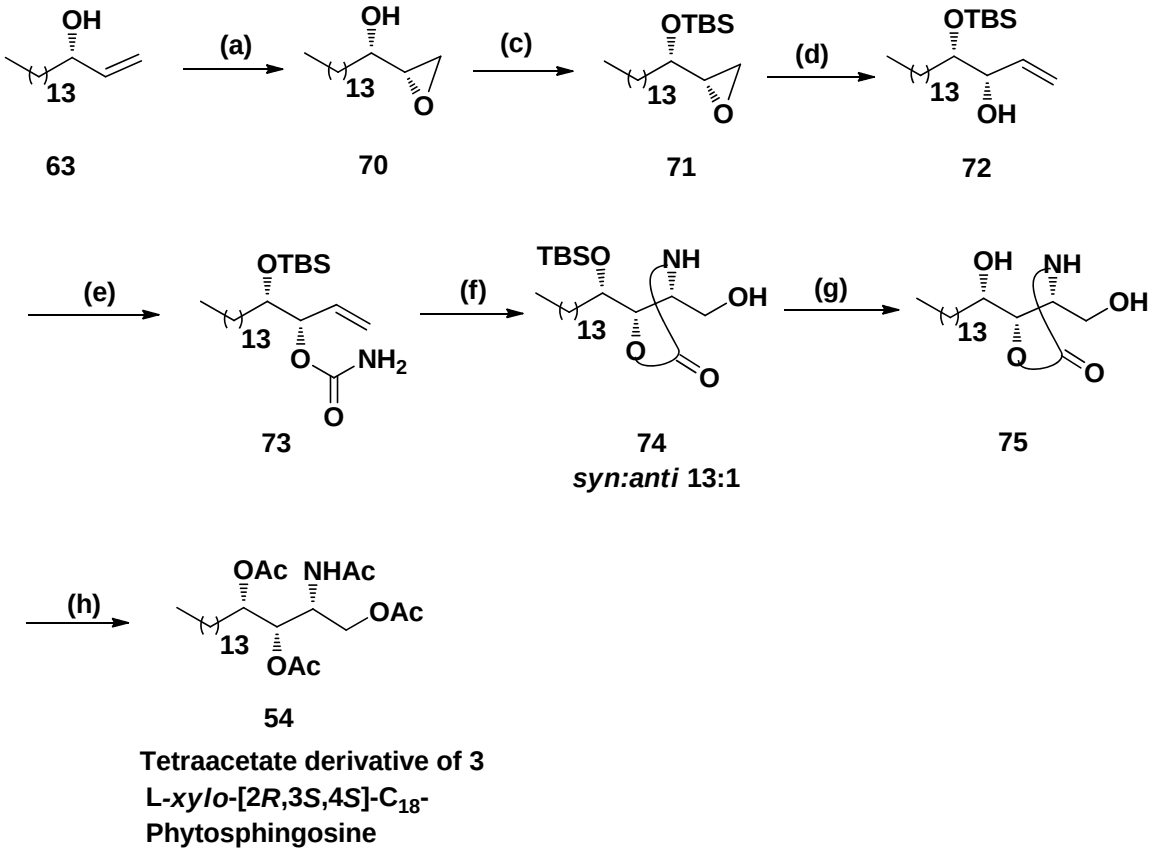
Scheme 8. *Reagents and conditions*: (a) [i] Pivaloyl chloride, DMSO, Et_3N, -78 ^oC; [ii] vinyl bromide, Mg, -78 ^oC, 2 h, 88%; (b) (-)-DIPT, $Ti(O^iPr)_4$, TBHP, CH_2Cl_2, molecular sieves, 3 Å, -20 ^oC, 4 days, 49% for **64** and 46% for **63**; (c) TBS-OTf, 2,6-lutidine, dry CH_2Cl_2, 15 min, -10 ^oC, 90%; (d) $(CH_3)_3S^+I^-$, *n*-BuLi, -20 ^oC, 75% (e) $Cl_3CCONCO$, K_2CO_3, CH_2Cl_2:CH_3OH (1.5:1), 4 h, 90%; (f) NaOH, *t*-BuOCl, $^iPr_2EtN$, potassium osmate, 2.5 h, 66%; (g) TsOH (Cat.), MeOH, 78%; (h) (i) K_2CO_3, methanol, rt, 6 h ; (ii) Ac_2O, pyridine, DMAP (cat), overnight, 82% for two steps.

The required *erythro*-isomer **65** could easily be separated by column chromatography in 90% yield. The IR spectrum of **65** indicated absence of hydroxyl groups. In order to get the allylic alcohol, epoxide **65** was treated with excess of dimethylsulfonium methylide[23] (generated from trimethylsulphonium iodide and *n*-BuLi) to furnish the allylic alcohol **66** in 75% yield. The ^1H NMR spectrum gave olefin protons at δ 5.16-5.34 and 5.77-5.94. In the ^{13}C NMR spectrum of **66** olefin peaks appeared at δ116.4, 136.5. In the IR spectrum of **66**, olefin and

hydroxyl stretching appeared at 1614 and 3466 cm^{-1} respectively. Having obtained the chiral allylic alcohol **66**, in substantial amount and a suitable substrate for tethered aminohydroxylation we then proceeded with the synthesis of target compound phytosphingosine. Alcohol **66** was then reacted with trichloroacetyl isocyanate in CH_2Cl_2 to give the corresponding isocyanate which on treatment with aq. K_2CO_3 and methanol furnished the carbamate **67** in 90% yield. The ^1H NMR spectrum of **67** clearly indicated broad singlet for $–NH_2$ at δ 4.79 and in the ^{13}C NMR spectrum carbamate carbonyl peak appeared at δ 156.3. The carbamate was converted into the oxazolidinone derivative **68** by a tethered aminohydroxylation protocol **A** using *tert*-butyl hypochlorite as the oxidant, potassium osmate, NaOH, diisopropylethylamine and propanol as the solvent. The reaction proceeded smoothly to furnish the protected aminoalcohol **68** in 66% yield with complete regio- and excellent diastereoselectivity (*syn*:*anti* 12:1, determined from ^1H NMR). The diastereomeric mixture could easily be separated by column chromatography. Compound **68** was fully characterized using IR, ^1H NMR and ^{13}C NMR spectra. In the IR spectrum hydroxyl and amine stretching appeared at 3506, 3362 cm^{-1}. The ^1H NMR and ^{13}C NMR spectra of **68** showed disappearance of olefin peaks and appearance of –*CH*(OH), -*CH*(NH) protons and carbon peaks at δ 3.85-4 (m), 3.65-3.8 (m) and δ 71.9, 80.3 respectively.

The desired *syn*-diastereomer was subjected to desilylation using *p*-TSA and methanol to give the alcohol **69** in 78% yield, which on hydrolysis with K_2CO_3 in methanol furnished the crude aminoalcohol. Subsequent acylation using Ac_2O in the presence of pyridine and catalytic amount of DMAP produced the tetraacetate derivative of phytosphingosine[18] **9** in 82% overall yield having m.p. 48-49 ^oC, [lit.[18] m.p. 47-49 ^oC] and $[\alpha]_D^{20}$ -25.95 (*c* 1.5, $CHCl_3$); {lit.[18] $[\alpha]_D^{20}$ -25.1 (*c* 1.5, $CHCl_3$)}. The IR spectrum of **43** showed presence of acetyl carbonyls at 1744 cm^{-1}. The ^1H NMR spectrum of **43** gave acetyl methyl protons at δ 2.03 (singlet, one methyl), 2.04 (singlet, two methyl), 2.07 (singlet, one methyl), the chiral protons at δ 3.95-4.05 (multiplet, two protons), 4.5-4.67 (multiplet, one proton), 5.02-5.18 (multiplet, two proton), amine proton 5.92 (doublet, one proton). The ^{13}C NMR spectrum gave chiral carbons at δ 72.4, 71.4, 63.5 and 47.5 and four carbonyl carbons at δ 171.1, 170.7, 170.6 and 170.3. The physical and spectroscopic data were identical with those reported.[18]

The overall yield of the target compound **43** was found to be 11% from eight steps.



54

Tetraacetate derivative of 3
L-*xylo*-[2*R*,3*S*,4*S*]-C_{18}-Phytosphingosine

Scheme 9. *Reagents and conditions*: (a) (-)-DIPT, $Ti(O^iPr)_4$, TBHP, CH_2Cl_2, molecular sieves, 3 Å, -20 ^oC, 4 days, 75%. Further (c) to (h) as described for **43**

For the synthesis of L-*xylo*-[2*R*,3*S*,4*S*]-C_{18}-phytosphingosine, the allylic alcohol **63** obtained by the chiral resolution of **62** was subjected to Sharpless asymmetric epoxidation to give the epoxide **70** in 75% yield as a single diastereomer, The ^1H NMR spectrum of **70** showed absence of olefin protons and appearance of epoxide protons at δ 2.72-2.78 (multiplet, 1H), 2.81-2.82 (m, 1H) and 3.01-3.06 (multiplet, 1H). The ^{13}C NMR spectrum of **70** showed upfield carbons of epoxide at δ 43.4 and 54.5. Compound **70** was converted into the tetraacetate derivative of L-*xylo*-[2*R*,3*S*,4*S*]-C_{18}-phytosphingosine **3** following the same sequence of reactions as described for **43** (**Scheme 9**). The physical and spectroscopic data of **54** were in accord with those described in literature.[19]

2.4.3.3. Conclusions

In summary, we have developed a facile and practical enantioselective synthesis of sphingoid bases in high overall yields. The main advantage of this strategy is its versatility, leading to the synthesis of two stereoisomers, L-*arabino*-[2*R*,3*S*,4*R*]-C_{18}-phytosphingosine and L-*xylo*-[2*R*,3*S*,4S]-C_{18}-phytosphingosine. The synthetic strategy is flexible and would permit the synthesis of not only the stereoisomers of sphingoid bases but also the other lipids bearing

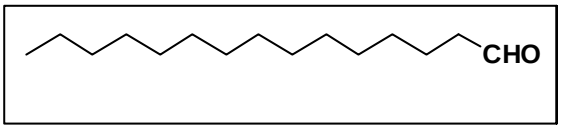
skeleton-modified sphingoid bases backbone with different chain length and substitution patterns.

2.4.4. Experimental Section

General information

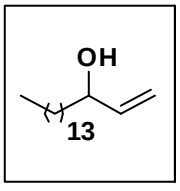
General information as described in section B.

Pentadecanal-1 (61):



To a stirred solution of pivaloyl chloride (12.9 mL, 105 mmol) in dry CH_2Cl_2 (50 mL) cooled to –78 ^oC was added dropwise dry DMSO (4.97 mL, 70 mmol) in dry CH_2Cl_2 (20 mL) over 20 min. The reaction mixture was stirred for 30 min. Alcohol **60** (8 g, 35 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise to the above reaction mixture over 20 min. After completion of the starting material (2 h), Et_3N (24.34 mL, 175 mmol) was added and stirred at –78 ^oC for further 30 min. The reaction mixture was brought to room temperature slowly and stirred for 30 min. The reaction mixture was poured into H_2O (150 mL) and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL) and combined organic layers were washed with H_2O (3 x 50 mL), brine (50 mL), dried (Na_2SO_4) and passed through short pad of silica gel. The filtrate was concentrated to give the aldehyde **61** as pale yellow oil, which was used as such for the next step without purification.

Heptadec-1-en-3-ol (62):



To a stirred solution of Mg (2.57 g, 106 mmol) in dry THF (30 mL), vinyl bromide solution (29.4 mL, 3.0 M solution in dry THF, 88.33 mmol) was added dropwise over 30 min and the Grignard reagent thus formed was cooled to 0 ^oC. Aldehyde **61** (8 g, 35.3 mmol) in dry THF (30 mL) was added dropwise over 20 min to the above reaction mixture. After 2 h stirring at 0 ^oC the reaction mixture was quenched with saturated NH_4Cl solution (20 mL), and the aqueous layer was extracted with EtOAc (4 x 50 mL) and the combined organic layers were washed with brine and dried over Na_2SO_4. The extracts were concentrated to near dryness and purified by silica gel column

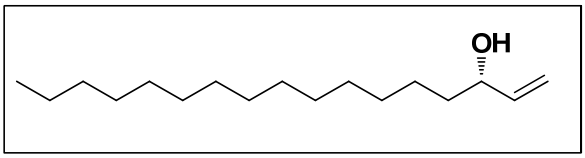
chromatography using petroleum ether/EtOAc (95:5) as eluent to give **62** as a pale yellow solid.

Yield: 7.84 g, 88%.

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

M.P.: 46-47 ^{o}C.

(*S*)-Heptadec-1-en-3-ol (63):



To a mixture of 3 Å molecular sieves (1.5 g) and Ti(^{i}PrO)$_4$ (9.0 mL, 30.26 mmol) in dry CH_2Cl_2 (100 mL), (-)-DIPT (8.07 mL, 38.51 mmol) was added dropwise over 10 min at –20 ^{o}C. The mixture was stirred for 20 min at –20 ^{o}C, and a solution of **62** (7.0 g, 27.5 mmol) in dry CH_2Cl_2 (25 mL) was added dropwise over 10 min. The reaction mixture was stirred for additional 30 min at –20 ^{o}C and TBHP (12.5 mL, 5.5 M solution in toluene, 68.75 mmol) was added dropwise over 10 min. The reaction mixture was kept at –20 °C by constant temperature bath and after 4 days reaction was warmed to 0 ^{o}C, and quenched with H_2O (100 mL) and the mixture is stirred for 60 min, and then precooled (0 ^{o}C) freshly prepared ferrous sulfate heptahydrate (1.52 g, 5.5 mmol) in 10 mL of water was added and reaction mixture is stirred for 30 min at room temperature. The two phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were treated with 30 mL of a precooled (0 ^{o}C) solution of 30% NaOH w/v in saturated brine. The two phase mixture was stirred vigorously for 1 h at 0 ^{o}C. Followed by dilution with 50 mL of water, the phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated to dryness. The crude product was then purified by flash chromatography on silica gel using petroleum ether/EtOAc (95:5) as eluent to give chiral hydroxy olefin **63** as a white solid. Further elution with petroleum ether/EtOAc (9:1) gave the epoxide **64** as a white solid.

Yield: 3.22 g, 46% (based on 50% conversion).

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

M.P.: 46-47 ^{o}C.

$[\alpha]_D^{25}$: +2.38 (*c* 1.0, $CHCl_3$).

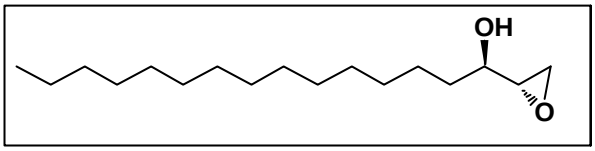
IR (neat, cm^{-1}): ν_{max} 3499, 2899, 1611.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.1 Hz, 3H), 1.26-1.55 (m, 26H), 4.05-4.15 (m, 1H), 5.08-5.27 (m, 2H), 5.79-5.96 (m, 1H).

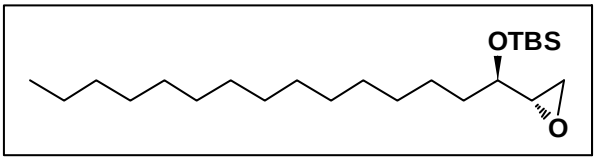
^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 22.7, 25.3, 29.3, 29.7, 31.9, 37.0, 73.2, 114.4, 141.3.

Analysis: Calcd.: C, 80.24; H, 13.47%. **Found:** C, 79.95; H, 13.73%.

(2*S*,3*S*)-1-Oxiranyl-pentadecan-1-ol (64):



***tert*-Butyldimethyl((*R*)-1-((*S*)-oxiran-2-yl)pentadecyl)oxy)silane (65):**



To a solution of **64** (3.0 g, 11.09 mmol) in dry CH_2Cl_2 (10 mL) was added 2,6-lutidine (2.08 mL, 17.88 mmol) at 0 ^oC and stirred for 15 min. To this TBSOTf (2.18 mL, 13.31 mmol) was added dropwise over 10 min and stirred for 10 min. After consumption of starting material, the ice-cooled solution was added to the reaction mixture and then aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL), dried over anhydrous Na_2SO_4 and concentrated to near dryness. The crude product was purified by silica gel column chromatography using petroleum ether/EtOAc (99:1) as eluent to give **65** as a colorless liquid.

Yield: 3.84 g, 90%.

Mol. Formula: $C_{23}H_{48}O_2Si$

$[\alpha]_D^{25}$: –4.1 (*c* 1.0, $CHCl_3$).

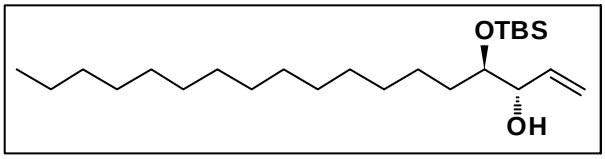
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.07 (s, 3H), 0.12 (s, 3H), 0.85-0.93 (m, 12H), 1.26 (brs, 24H), 1.48-1.56 (m, 2H), 2.55 (q, *J* = 2.7, 5.1, 1H), 2.76-2.81 (m, 1H), 2.89-2.96 (m, 1H), 3.21-3.30 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.9, -4.4, 14.1, 18.2, 22.7, 24.9, 25.7, 25.8, 29.4, 29.7, 31.9, 35.3, 44.7, 54.8, 71.3.

MS(ESI): m/z 385.7 $(M+H)^+$, 407.61 $(M+Na)^+$.

Analysis: Calcd.: C, 71.81; H, 12.58%. **Found:** C, 71.65; H, 12.73%.

(3*S*,4*R*)-4-((*tert*-Butyl-dimethylsilyl)oxy)octadec-1-en-3-ol (66):



To a suspension of trimethylsulfonium iodide (6.47 g, 31.71 mmol) in dry THF (20 mL) at –20 ^{o}C was added n-BuLi (21.07 mL, 1.6 M solution in hexane, 31.71 mmol) dropwise over 20 min and stirred for 30 min. Then the epoxide **65** (2.0 g, 5.19 mmol) in dry THF (10 mL) was added to the above reaction mixture and slowly allowed to warm to 0 ^{o}C over 1 h. The reaction mixture was then stirred at ambient temperature for 2 h. After completion of the starting material the reaction mixture was quenched with H_2O (20 mL) and extracted with EtOAc (4 x 30 mL). The combined extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated to near dryness. The residue was purified by flash silica gel column chromatography using petroleum ether/EtOAc (94:6) as eluent to give **66** as a colorless liquid.

Yield: 1.55 g, 75%.

Mol. Formula: $C_{24}H_{50}O_2Si$

$[\alpha]_D^{25}$: –2.5 (*c* 1.0, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 3446, 1614.

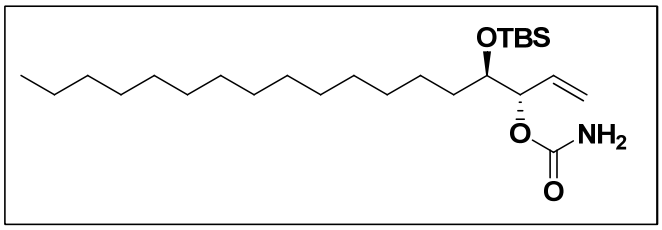
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.09 (s, 3H), 0.10 (s, 3H), 0.85-0.91 (m, 12H), 1.26-1.43 (m, 26H), 2.27 (brs, 1H), 3.66-3.71 (m, 1H), 4.08-4.12 (m, 1H), 5.17-5.34 (m, 2H), 5.77-5.94 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.5, -4.4, 14.1, 18.1, 22.7, 25.6, 25.7, 25.8, 29.4, 29.6, 29.7, 31.6, 31.9, 75.4, 75.9, 116.4, 136.5.

MS(ESI): m/z; 421.72 $(M+Na)^+$.

Analysis: Calcd.: C, 72.29; H, 12.64%. **Found:** C, 72.27; H, 12.63%.

(3*S*,4*R*)-4-((*tert*-Butyldimethylsilyl)oxy)octadec-1-en-3-yl carbamate (67):



Trichloroacetyl isocyanate (0.536 mL, 4.51 mmol) was added dropwise over 10 min to a solution of alcohol **66** (1.5 g, 3.76 mmol) in dry CH_2Cl_2 (1.7 mL) at 0 ^{o}C. After stirring for 2 h, or until TLC showed no starting material present, the mixture was concentrated under reduced pressure. The residue was dissolved in MeOH (2.2 mL), cooled to 0 ^{o}C and aqueous K_2CO_3 solution (1.55 g, 3.4 mL, 11.28 mmol) was added. The cooling bath was removed and

the mixture was allowed to stir for 4 h, by which time TLC showed complete conversion. The solvent was evaporated under reduced pressure and the residue was extracted with CH_2Cl_2 (4 x 25 mL). The extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to yield the crude carbamate, which was purified by flash silica gel column chromatography using petroleum ether/EtOAc (8:2) as eluent to give **67** as a colorless syrupy liquid.

Yield: 1.49 g, 90%.

Mol. Formula: $C_{25}H_{51}NO_3Si$

$[\alpha]_D^{25}$: –27.5 (*c* 1.0, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 3446, 1644.

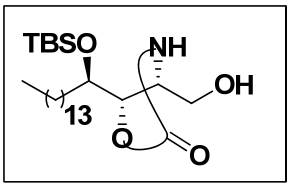
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.06 (s, 3H), 0.08 (s, 3H), 0.88-0.91 (m, 12H), 1.26-1.41 (m, 26 H), 3.77-3.84 (m, 1H), 4.79 (brs, 2H), 5.01-5.06 (m, 1H), 5.24-5.34 (m, 2H); 5.81-5.98 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): -4.6, -4.4, 14.1, 18.2, 22.7, 25.4, 25.9, 29.3, 29.5, 29.7, 31.9, 33.6, 73.7, 78.8, 118.7, 132.9, 156.3.

MS(ESI): m/z 442.39 $(M+H)^+$.

Analysis: Calcd.: C, 67.97; H, 11.64; N, 3.17%. **Found:** C, 67.81; H, 11.69; N, 3.25%.

(4*S*,5*R*)-5-((*R*)-1-(*tert*-Butyldimethylsilyl)pentadecyl)-4-(hydroxymethyl)oxazolidin-2-one (68):



A solution of sodium hydroxide (12.5 mL, 0.08M, 43 mg, 1.08 mmol) was prepared. A small amount of this solution was used to dissolve potassium osmate dihydrate (17 mg, 4 mol%) in a separate vial and the remaining sodium hydroxide solution was added in one portion to a stirred solution of the allylic carbamate **67** (0.53 g, 1.2 mmol) in propan-1-ol (14.5 mL, 12 mL/mmol). To this reaction mixture was added freshly prepared *t*-butyl hypochlorite (0.12 mL, 1.13 mmol) and the mixture was allowed to stir for 5 min. To this was added $^iPr_2EtN$ (10 mg, 5 mol%) in one portion. The mixture was allowed to stir for a further 5 min before the final addition of a solution of potassium osmate in the remainder of the NaOH solution made earlier. The reaction mixture was stirred until consumption of the starting material and reaction mixture was quenched with sodium sulfite (100 mg/mmol), subsequently diluted

with EtOAc. The reaction mixture was extracted with EtOAc (3 x 10 mL), dried over Na_2SO_4 and concentrated to near dryness. The crude product was found to be a mixture of *syn*:*anti* 12:1 (determined from ^{1}H NMR of crude compound) and was purified by flash silica gel column chromatography using petroleum ether/EtOAc (7:3) as eluent to give **68**, as a thick syrupy liquid.

Yield: 0.362 g, 66%,

Mol. Formula: $C_{25}H_{51}NO_4Si$

$[\alpha]_D^{25}$: +28.47 (*c* 1.3 , $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 3419, 1644.

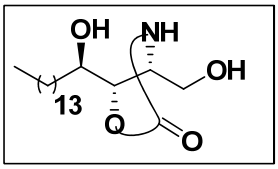
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.09 (s, 3H), 0.10 (s, 3H), 0.88-0.91 (m, 12H), 1.26 (m, 24 H), 1.39-1.53 (m, 2H), 3.42-3.6 (m, 1H), 3.65-3.8 (m, 1H), 3.85-4.0 (m, 2H), 4.32 (m, 1H), 6.55 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): -4.6, -4.4, 14.0, 17.9, 22.6, 24.9, 25.7, 29.3, 29.6, 31.8, 32.8, 54.3, 63.8, 71.9, 80.3, 160.3.

MS(ESI): m/z 480.70 $(M+Na)^+$.

Analysis: Calcd.: C, 65.59; H, 11.23; N, 3.06%. **Found:** C, 65.35; H, 11.48; N, 3.36%.

(4*S*,5*R*)-4-(Hydroxymethyl)-5-((*R*)-1-hydroxypentadecyl)oxazolidin-2-one (69):



To a solution of TA product **68** (0.2 g, 0.43 mmol) in MeOH (5 mL) was added catalytic amount of *p*-TSA. The reaction mixture was stirred for 1 h and it was filtered and concentrated to near dryness. The crude product was purified by silica gel column chromatography using petroleum ether/EtOAc (3:7) as eluent to afford **69** as a white solid.

Yield: 0.117 g, 78%.

M.P.: 60-62 ^oC.

Mol. Formula: $C_{19}H_{37}NO_4$

$[\alpha]_D^{25}$: +8.70 (*c* 1, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 3340, 2800, 1650.

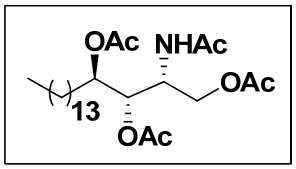
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.1 Hz, 3H), 1.26-1.73 (m, 26H), 2.30-2.37 (m, 1H), 3.37-3.95 (m, 4H), 4.10 (t, *J* = 3.7 Hz, 1H), 4.24-4.28 (m, 1H), 6.99 (brs, 1H).

^{13}C NMR (50 MHz, DMSO-d_6): δ 14.5, 22.6, 25.5, 29.2, 29.5 31.8, 32.3, 54.9, 63.6, 70.9, 80.6, 159.1.

MS(ESI): m/z 344.48 $(M+H)^+$.

Analysis: Calcd.: C, 66.43; H, 10.86; N, 4.08%. Found: C, 66.38; H, 10.85; N, 4.03%.

(2*R*,3*S*,4*R*)-2-Acetamidooctadecane-1,3,4-triyltriacetate (43):



To a stirred solution of **69** (90 mg, 0.26 mmol) in MeOH (3 mL) was added K_2CO_3 (72 mg, 0.39 mmol) and the reaction mixture was stirred for 6 h until consumption of the starting material and methanol was removed in vacuo. H_2O was added to the crude product and extracted with EtOAc (3 x 10 mL) and dried over Na_2SO_4 and concentrated to near dryness. The crude material was subsequently acetylated with acetic anhydride (0.053 g, 0.52 mmol), pyridine (0.043 g, 0.54 mmol) and DMAP (cat). After overnight stirring, the solvent was evaporated and the residue was purified on silica gel column using petroleum ether/EtOAc (5:1) as eluent to give tetraacetate **43** as a white solid.

Yield: 104 mg, 82%

M.P.: 48-49 ^oC; [lit.[18] mp 47-49 ^oC].

Mol. Formula: $C_{26}H_{47}NO_7$

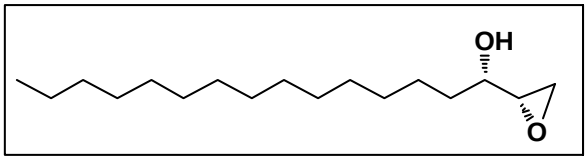
$[\alpha]_D^{20}$: –25.95 (*c* 1.5, $CHCl_3$); {lit.[18] $[\alpha]_D^{20}$ –25.1 (*c* 1.5, $CHCl_3$)}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.86 (t, *J* = 6 Hz, 3H), 1.2-1.3 (m, 24 H), 1.55 (m, 2H), 2.03 (s, 3H), 2.04 (s, 6H), 2.07 (s, 3H), 3.95-4.05 (m, 2H), 4.5 (m, 1H), 5.02-5.18 (m, 2H), 5.92 (d, *J* = 10.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.6, 21.2, 21.4, 23.6, 25.5, 30.1, 32.4, 33.9, 47.5, 63.5, 71.4, 72.4, 170.3, 170.6, 170.7, 171.1.

MS(ESI): m/z 486.645 $(M+H)^+$, 508.641 $(M+Na)^+$.

(*S*)-1-((*S*)-Oxiran-2-yl)pentadecan-1-ol (70):



To a mixture of 3 Å molecular sieves (600 mg) and $Ti(O^iPr)_4$ (3.57 mL, 11.79 mmol) in dry CH_2Cl_2 (50 mL) (-)-DIPT (2.46 mL, 11.79 mmol) was added dropwise over 10 min at –20 °C. The mixture was stirred for 20 min at –20 °C, and a solution of **63** (3 g, 11.79 mmol) in dry CH_2Cl_2 (25 mL) was added slowly over 15 min. The reaction mixture was stirred for additional 30 min at –20 °C and TBHP (4.2 mL, 5.5M solution in toluene, 23.58 mmol) was added over 15 min. The reaction mixture was kept at –20 °C by constant temperature bath and after 4 days reaction was warmed to 0 °C, and quenched with H_2O (100 mL) and the mixture is stirred for 40 min, and then precooled (0 °C) freshly prepared ferrous sulfate heptahydrate (819 mg, 2.94 mmol) in 10 mL of water was added and reaction mixture is stirred for 30 min at rt. The two phases were separated and the aqueous phase is extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were treated with 20 mL of a precooled (0 °C) solution of 30% NaOH w/v in saturated brine. The two phase mixture was stirred vigorously for 1 h at 0 °C. Followed by dilution with 50 mL of water, the phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated to dryness. The crude product was then purified by flash chromatography on silica gel using petroleum ether/EtOAc (9:1) as eluent to give epoxide **70** as a white solid.

Yield: 2.39 g, 75%.

M.P.: 46-48 °C.

Mol. Formula: $C_{17}H_{34}O_2$

$[\alpha]_D^{25}$: –3.83 (*c* 1.0, $CHCl_3$).

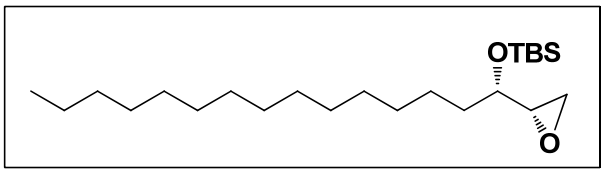
^{1}H NMR (200 MHz, $CDCl_3$): 0.88 (t, *J* = 6.0, 3H), 1.26-1.61 (m, 26H), 1.78 (s, 1H), 2.72-2.78 (m, 1H), 2.81-2.82 (m, 1H), 3.01-3.06 (m, 1H), 3.82-3.89 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 22.7, 25.3, 29.3, 29.5, 29.6, 31.9, 33.4, 43.4, 54.5, 68.4.

MS(ESI): m/z 293.41 $(M+Na)^+$.

Analysis: Calcd.: C, 75.50; H, 12.67%. **Found:** C, 75.65; H, 12.58%.

***tert*-Butyldimethyl((*S*)-1-((*S*)-oxiran-2-yl)pentadecyl)oxy)silane (71):**



Compound **71** was prepared following the procedure as described for **65**.

Yield: 85%.

$[\alpha]_D^{25}$: –4.16 (*c* 1.0, $CHCl_3$).

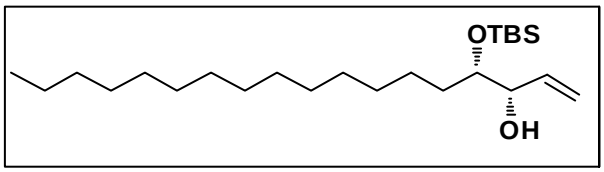
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.07 (s, 3H), 0.12 (s, 3H), 0.84-0.93 (m, 12H), 1.26 (s, 24 H), 1.49-1.53 (m, 2H), 2.55 (q, *J* = 2.7, 5.1 Hz, 1H), 2.75-2.83 (m, 1H), 2.87-2.97 (m, 1H), 3.19-3.33 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.8, -4.4, 14.1, 18.1, 22.6, 24.8, 25.2, 25.6, 25.7, 25.9, 29.3, 29.5, 29.6, 29.7, 31.9, 35.2, 44.8, 54.7, 72.3.

MS(ESI): m/z 385.73 $(M+H)^+$, 407.54 $(M+Na)^+$.

Anal. Calcd.: C, 71.81; H, 12.58%. **Found:** C, 71.73; H, 12.66%.

(3*S*,4*S*)-4-(*tert*-Butyldimethylsilyl)oxy)octadec-1-en-3-ol (72):



Compound **72** was prepared following the procedure as described for compound **66**.

Yield: 70%.

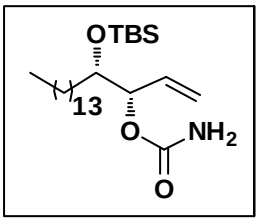
$[\alpha]_D^{25}$: –1.78 (*c* 1.0, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.09 (s, 3H), 0.10 (s, 3H), 0.89-0.91 (m, 12H), 1.26-1.52 (m, 26 H), 3.66-3.74 (m, 1H), 4.08-4.12 (m, 1H), 5.16-5.35 (m, 2H), 5.77-5.94 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.5, -4.4, 14.1, 18.1, 22.9, 25.6, 25.7, 25.8, 29.4, 29.5, 29.6, 29.7, 31.6, 31.9, 75.4, 75.8, 116.4, 136.6.

Anal. Calcd.: C, 72.29; H, 12.64%. **Found:** C, 72.36; H, 12.56%.

(3*S*,4*S*)-4-(*tert*-Butyldimethylsilyl)oxy)octadec-1-en-3-yl carbamate (73):



Compound **73** was prepared following the procedure as described for compound **67**.

Yield: 90%.

$[\alpha]_D^{25}$: –27.5 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 3446, 1644.

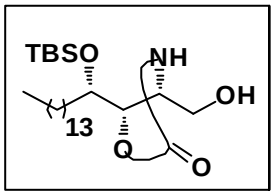
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.07 (s, 3H), 0.10 (s, 3H), 0.85-0.90 (m, 12H), 1.26-1.43 (m, 26 H), 3.69-3.77 (m, 1H), 4.60-4.77 (bs, 2H), 5.07-5.35 (m, 3H), 5.78-5.95 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.8, -4.4, 14.1, 18.2, 22.7, 25.4, 25.8, 29.5, 29.6, 29.7, 31.9, 33.6, 73.9, 79.8, 118.7, 132.9, 159.

MS(ESI): m/z 442.39 $(M+H)^+$.

Anal.Calcd. : C, 67.97; H, 11.64; N, 3.17%. **Found:** C, 68.11; H, 11.67; N, 3.22%.

(4*S*,5*R*)-5-((*S*)-1-(*tert*-Butyldimethylsilyloxy)pentadecyl)-4-(hydroxymethyl)oxa-zolidin-2-one (74):



Comopund **74** was prepared following the procedure as described for compound **68**.

Yield: 55%.

$[\alpha]_D^{25}$: +8.70 (*c* 1.0 , $CHCl_3$).

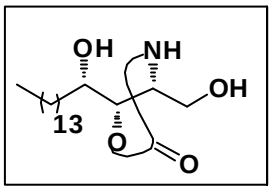
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.09 (s, 3H), 0.10 (s, 3H), 0.87-0.92 (m, 12H), 1.26-1.55 (m, 26 H), 2.51 (brs, 1H), 3.50-3.56 (m, 1H), 3.70-3.74 (m, 1H), 3.91-3.98 (m, 1H), 4.27-4.32 (m, 1H), 6.14 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.6, -4.4, 14.1, 18.0, 22.7, 25.0, 25.7, 25.8, 29.4, 29.6, 29.7, 31.9, 33.0, 54.0, 63.3, 72.0, 80.3, 159.8.

MS(ESI): m/z Anal. 480.70 $(M+Na)^+$.

Anal. Calcd. : C, 65.59; H, 11.23; N, 3.06%. **Found:** C, 65.64; H, 11.28; N, 3.18%.

(4*S*,5*R*)-4-(Hydroxymethyl)-5-((*S*)-1-hydroxypentadecyl)oxazolidin-2-one (75):



Compound **75** was preapred following the procedure as described for compound **69**.

Yield: 75%.

M.P.: 58-59 ^oC.

$[\alpha]_D^{25}$: +43.48 (*c* 1.0, $CHCl_3$).

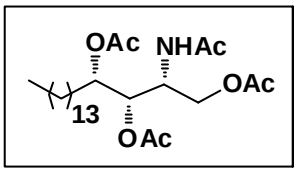
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.1 Hz, 3H), 1.26-1.75 (m, 26H) 2.34 (brs, 1H), 3.54-3.94 (m, 4H), 4.10 (t, *J* = 3.7 Hz, 1H), 4.24-4.28 (m, 1H), 6.97 (s, 1H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 14.1, 22.7, 25, 29.3, 29.5, 29.6, 29.7, 31.9, 32.9, 53.4, 63.7, 73.4, 79.8, 158.4.

MS(ESI): m/z 344.47 $(M+H)^+$.

Anal. Calcd.: C, 66.43; H, 10.86; N, 4.08%. **Found:** C, 66.35; H, 10.85; N, 4.02%.

(2*R*,3*S*,4*S*)-2-Acetamidooctadecane-1,3,4-triyl triacetate (54):



Compound **54** was preapred following the procedure as described for compound **43**.

Yield: 72%.

M.P.: 51-52 °C, [lit.[19] mp 51-53 °C].

$[\alpha]_D^{20}$: –7.0 (*c* 1.2, $CHCl_3$); {lit.[19] $[\alpha]_D^{20}$ – 7.2 (*c* 1.2, $CHCl_3$)}.

^{1}H NMR (400 MHz, $CDCl_3$): 0.88 (t, *J* = 6.2 Hz, 3H), 1.26 (brs, 24 H), 1.51-1.72 (m, 2H), 2.05-2.09 (m, 12H), 4.19-4.22 (m, 1H), 4.40-4.47 (m, 2H), 4.55-4.57 (m, 1H), 5.06-5.09 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 20.6, 20.9, 22.6, 23.0, 24.9, 25.8, 29.2, 30.1, 31.8, 33.3, 46.9, 62.9, 70.4, 71.9, 169.7, 170, 170.1, 170.5.

MS(ESI): m/z 486.645 $(M+H)^+$, 508.641 $(M+Na)^+$.

2.4.5. Spectra

1. ^{1}H & ^{13}C NMR spectra of **63**

2. ^{1}H & ^{13}C NMR spectra of **70**

3. ^{1}H & ^{13}C NMR spectra of **65**

4. ^{1}H & ^{13}C NMR spectra of **66**

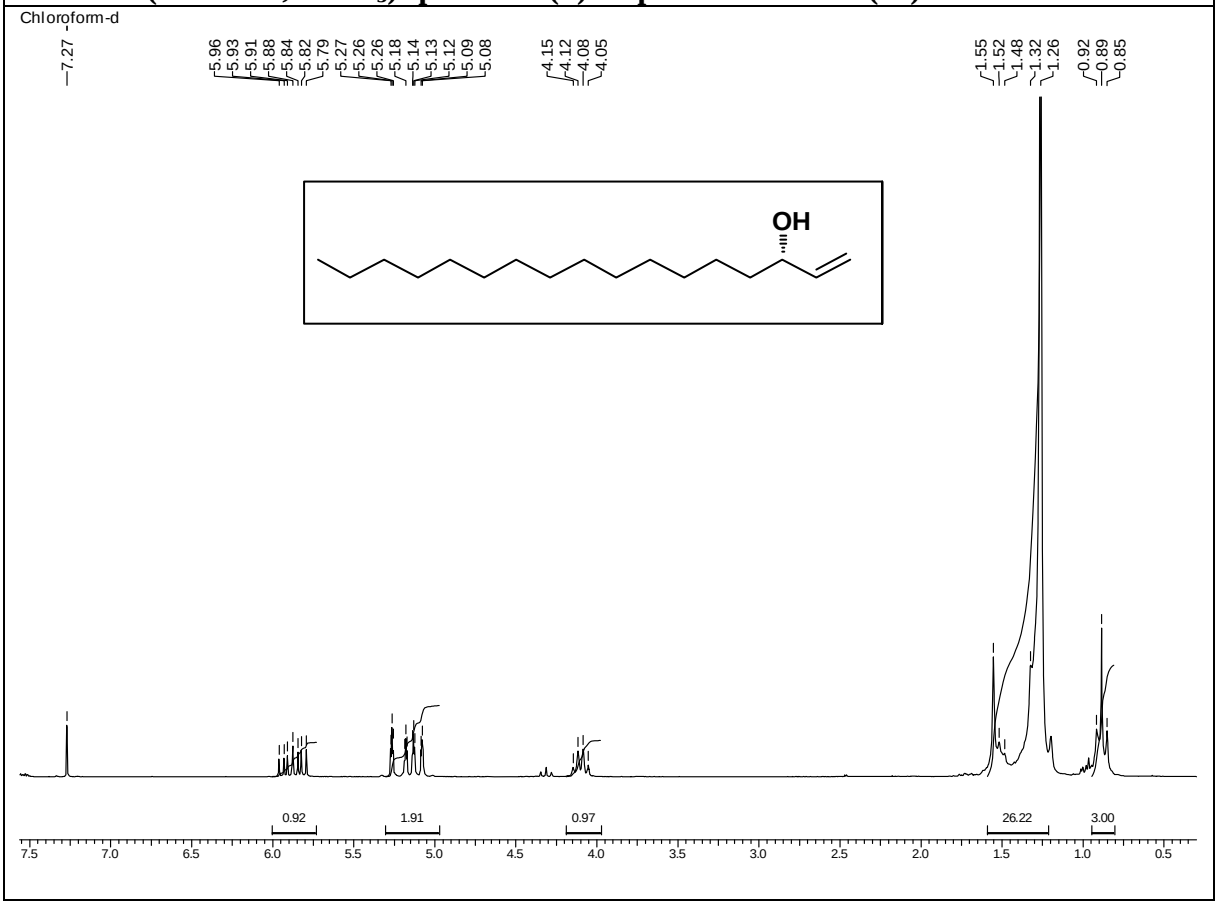
5. ^{1}H & ^{13}C NMR spectra of **67**

6. ^{1}H & ^{13}C NMR spectra of **68**

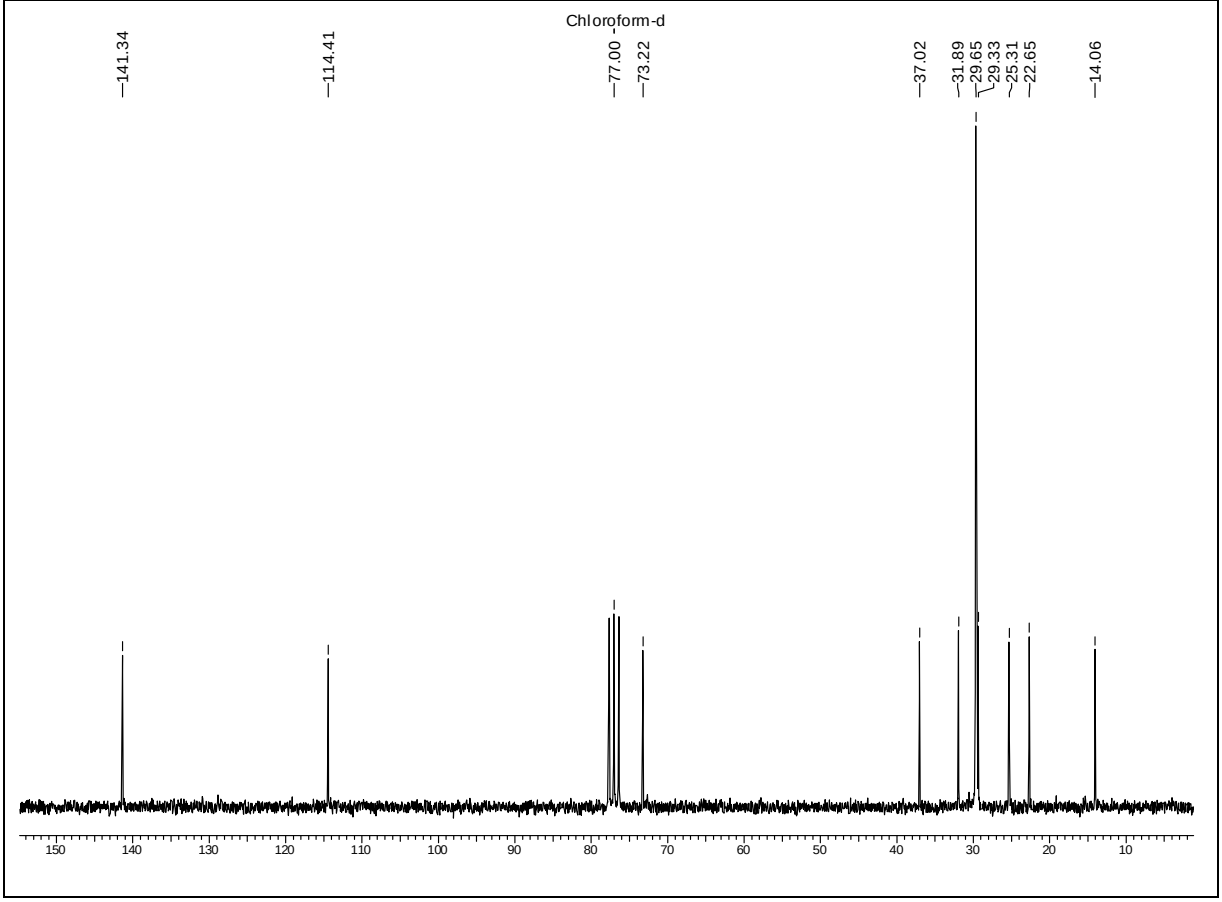
7. ^{1}H & ^{13}C NMR spectra of **69**

8. ^{1}H & ^{13}C NMR spectra of **54**

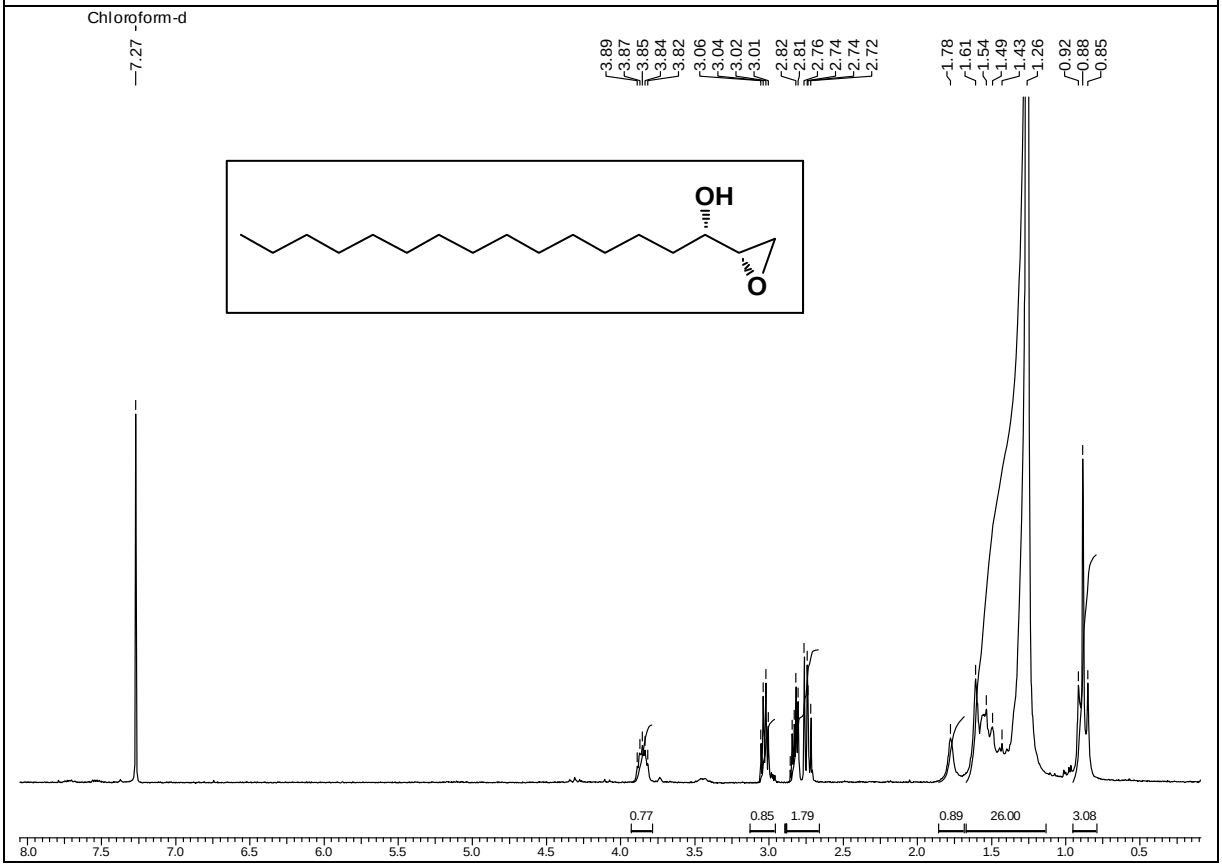
^{1}H NMR (200 MHz, $CDCl_3$) spectra of (*S*)-Heptadec-1-en-3-ol (63)



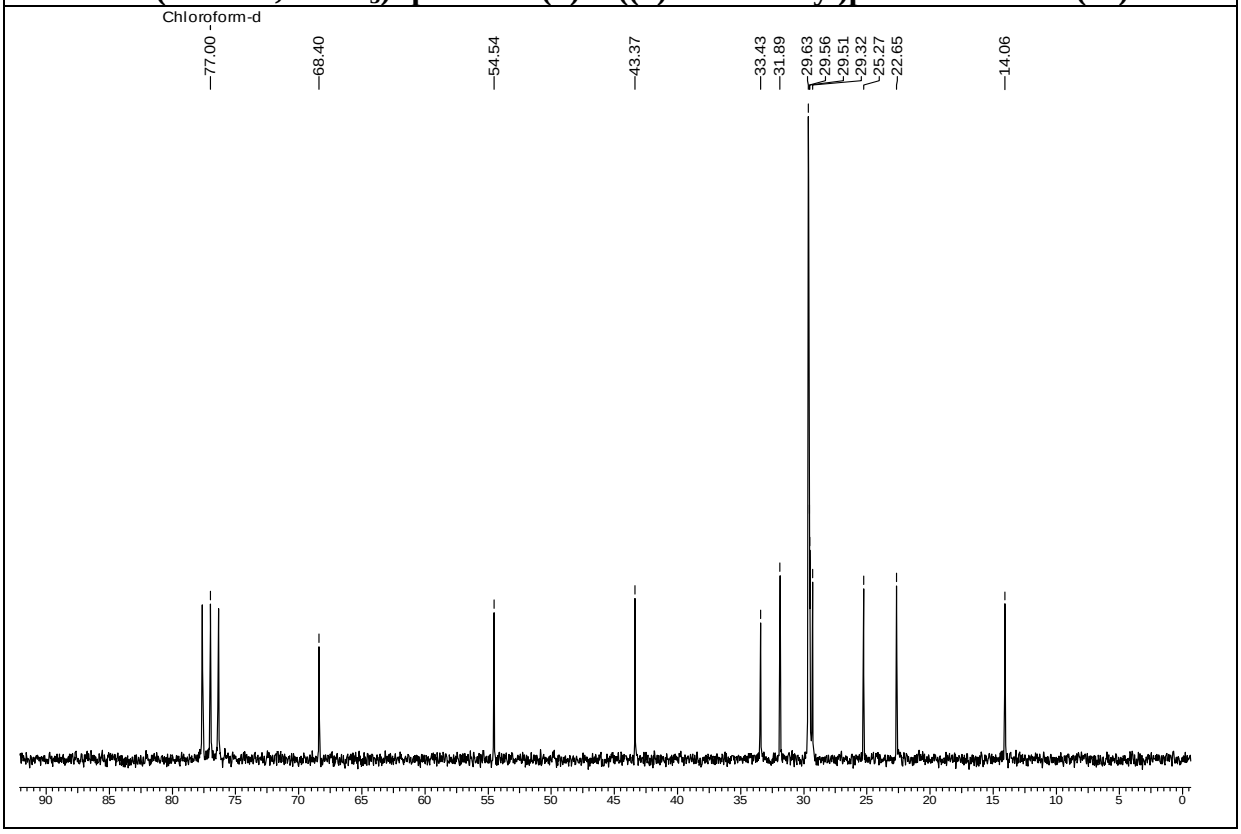
^{13}C NMR (50 MHz, $CDCl_3$) spectra of (*S*)-Heptadec-1-en-3-ol (63)



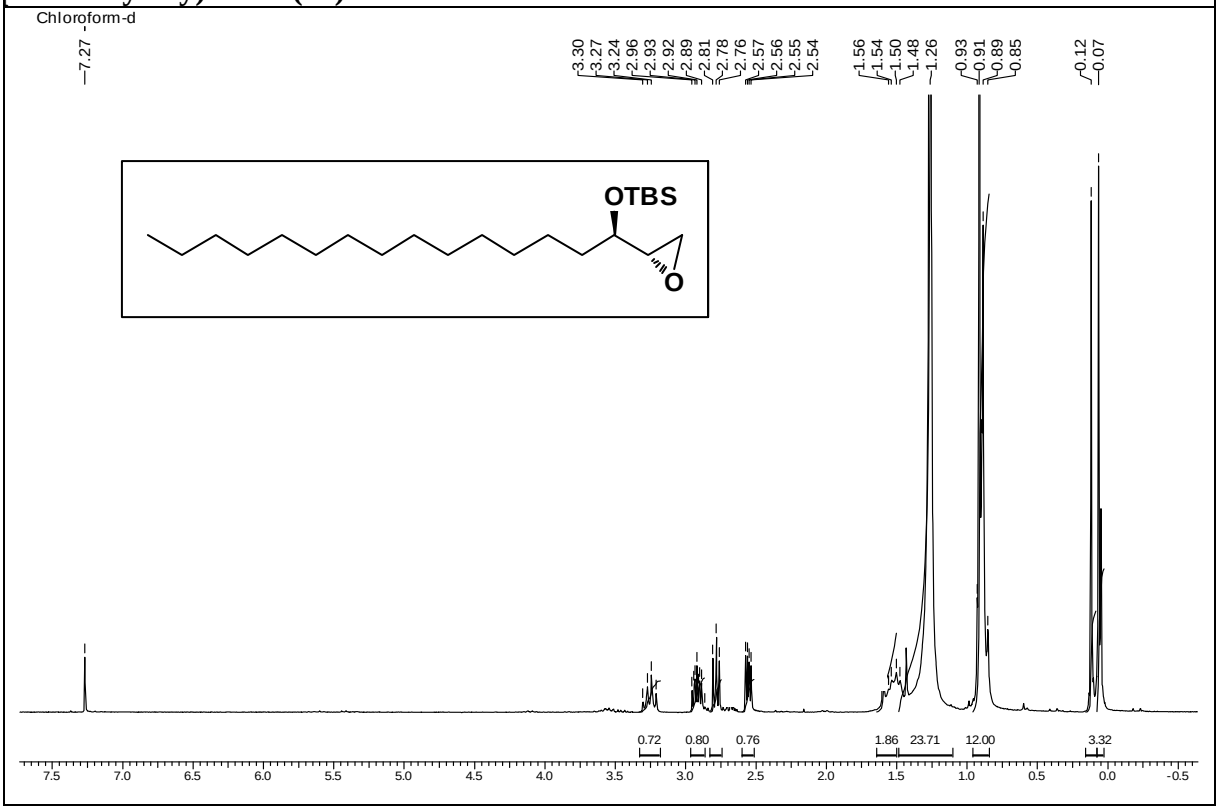
^{1}H NMR (200 MHz, $CDCl_3$) spectra of (*S*)-1-((*S*)-Oxiran-2-yl)pentadecan-1-ol (70)



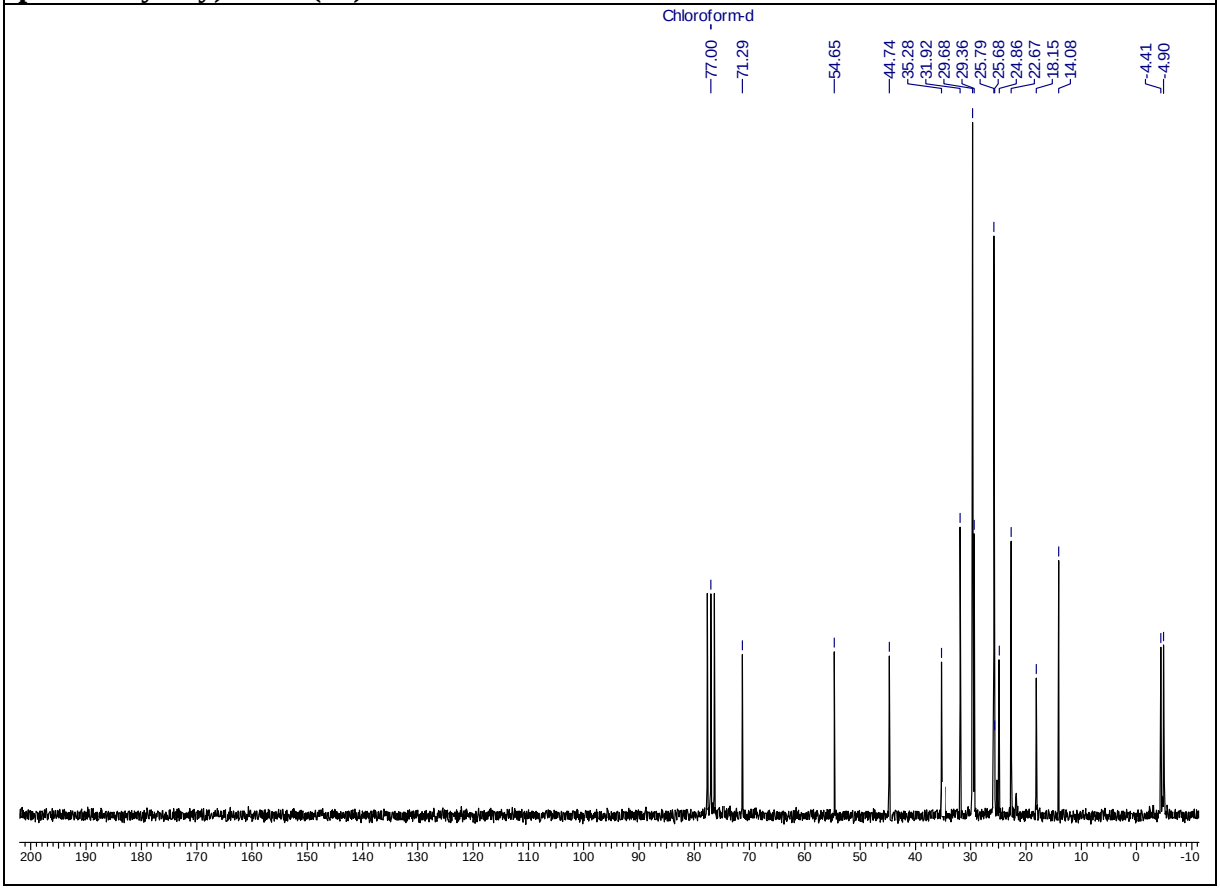
^{13}C NMR (50 MHz, $CDCl_3$) spectra of (*S*)-1-((*S*)-Oxiran-2-yl)pentadecan-1-ol (70)



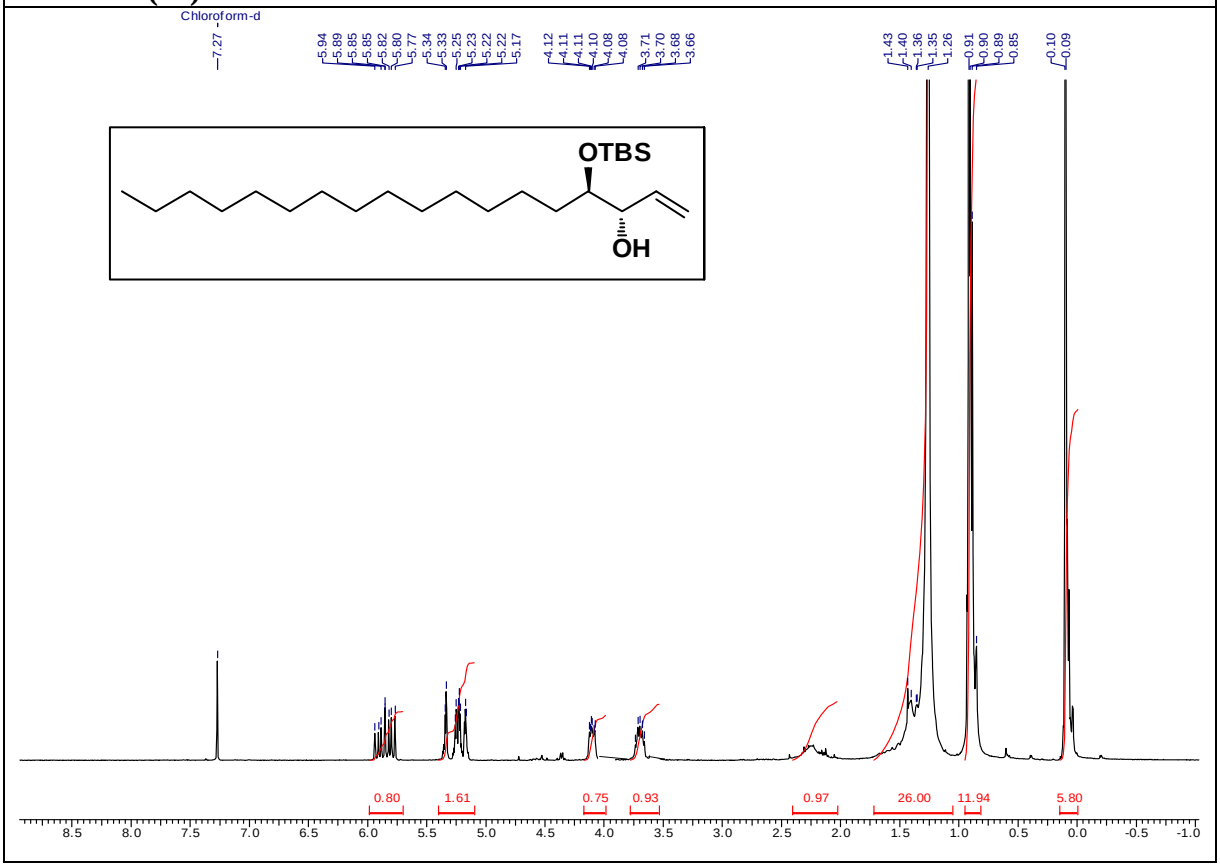
^{1}H NMR (200 MHz, $CDCl_3$) spectra of *tert*-Butyldimethyl((*R*)-1-((*S*)-oxiran-2-yl) pentadecyloxy)silane (65)



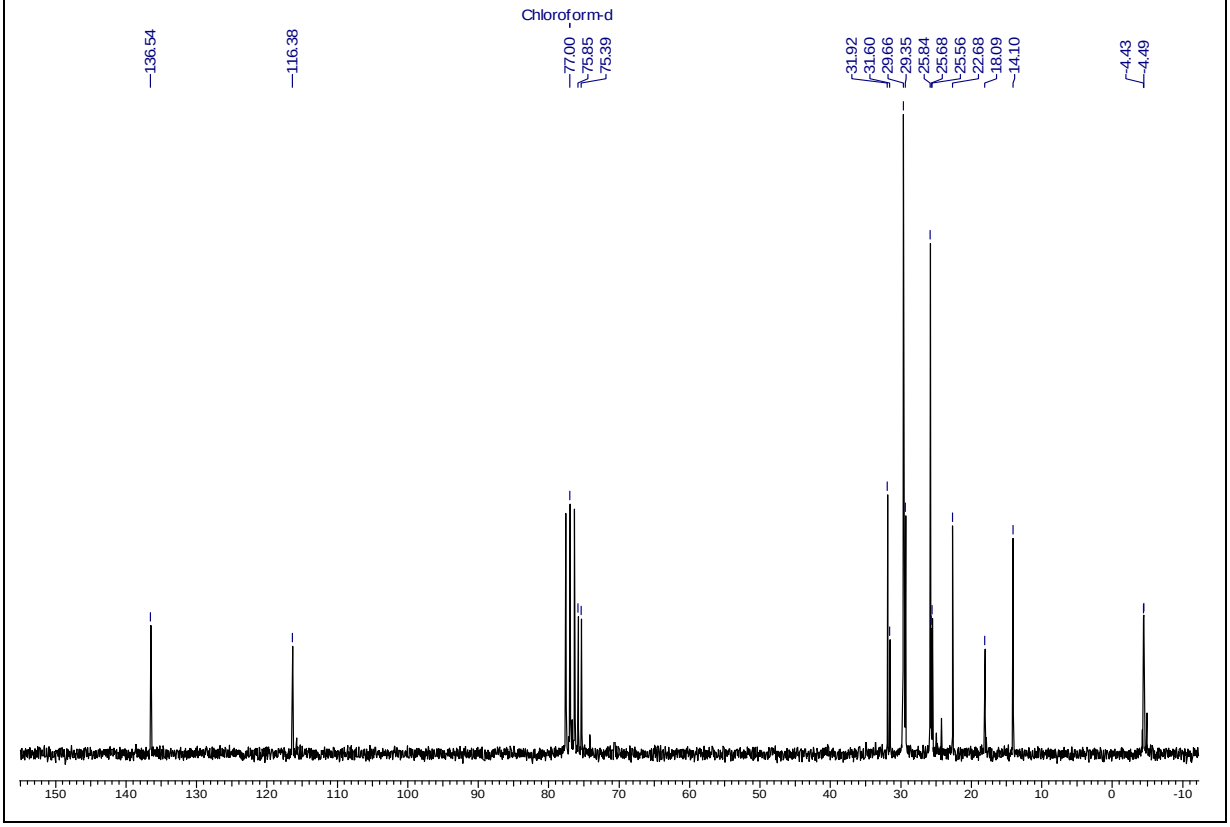
^{1}H NMR (200 MHz, $CDCl_3$) spectra of *tert*-Butyldimethyl((*R*)-1-((*S*)-oxiran-2-yl) pentadecyloxy)silane (65)



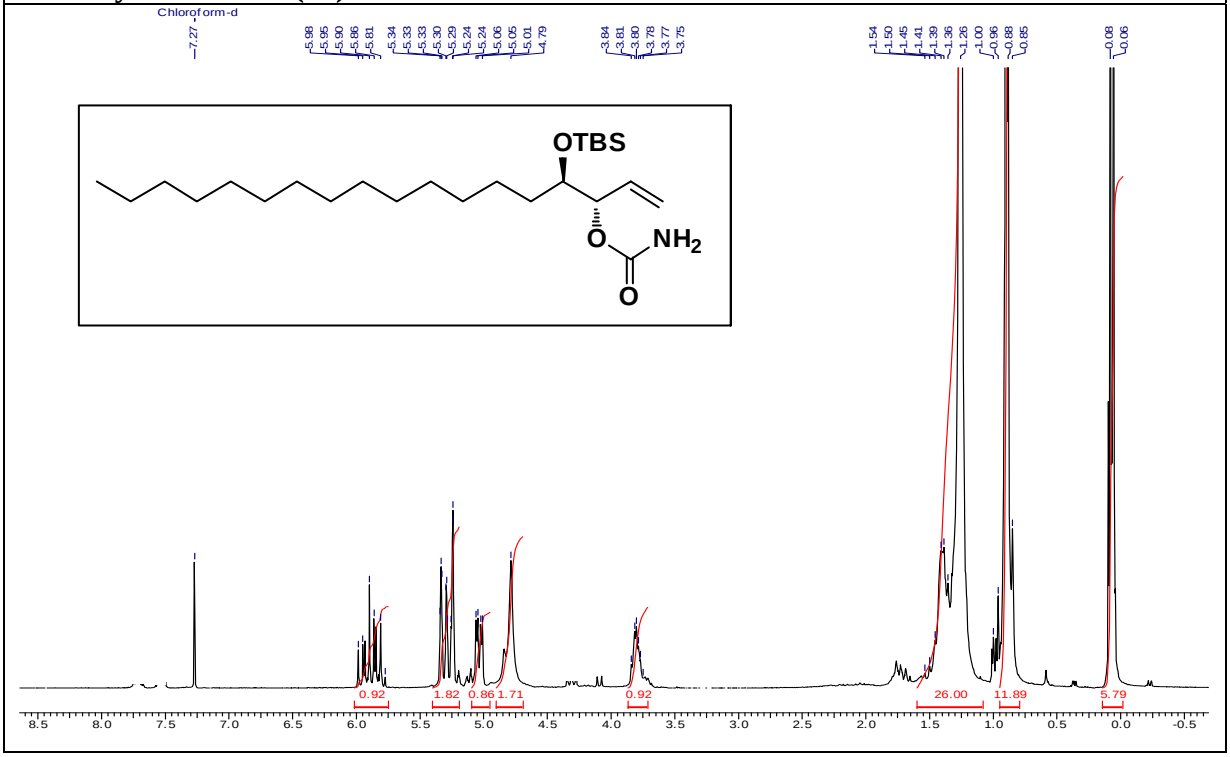
^{1}H NMR (200 MHz, $CDCl_3$) spectra of (3*S*,4*R*)-4-*tert*-Butyl-dimethylsilyl)oxy)octa-dec-1-en-3-ol (66)



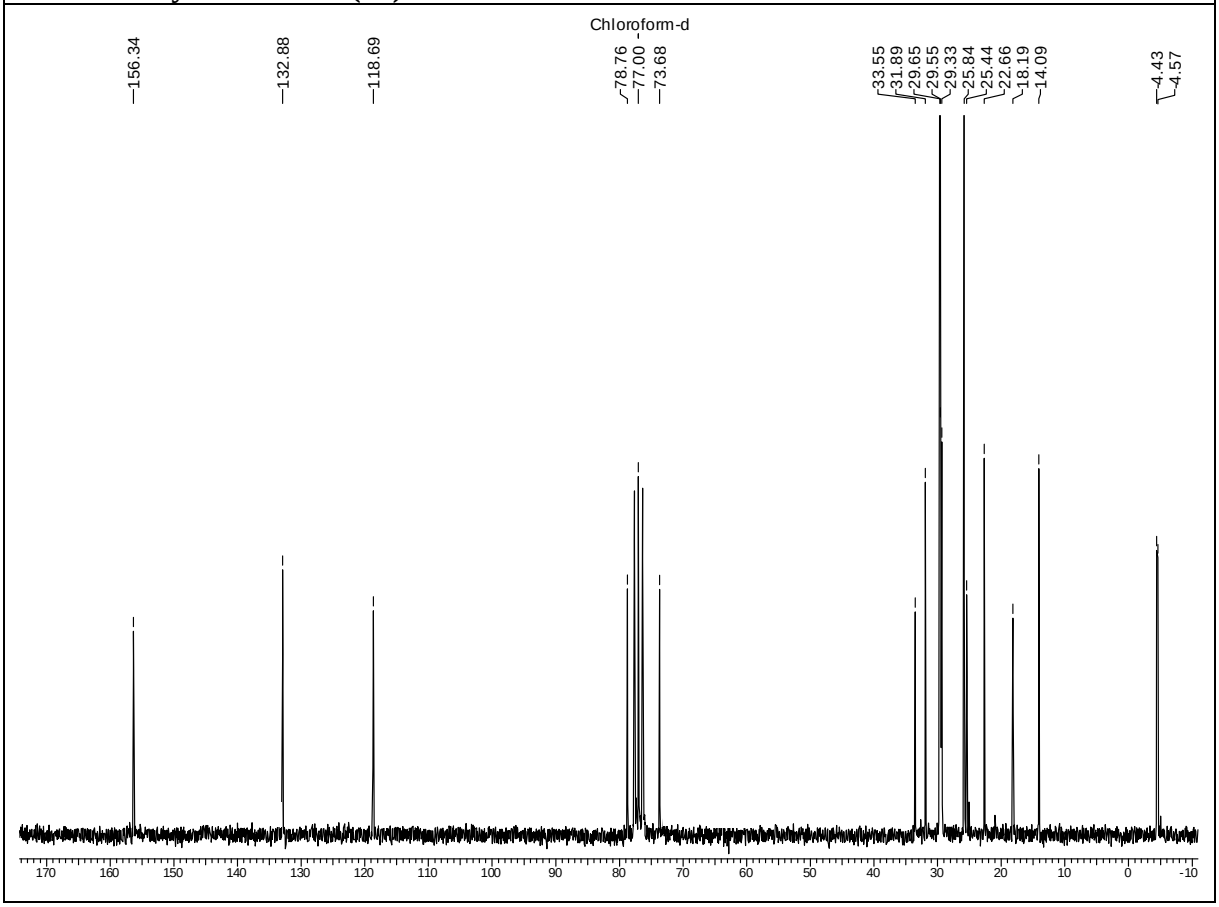
^{13}C NMR (50 MHz, $CDCl_3$) spectra of (3*S*,4*R*)-4-*tert*-Butyl-dimethylsilyl)oxy)octa-dec-1-en-3-ol (66)



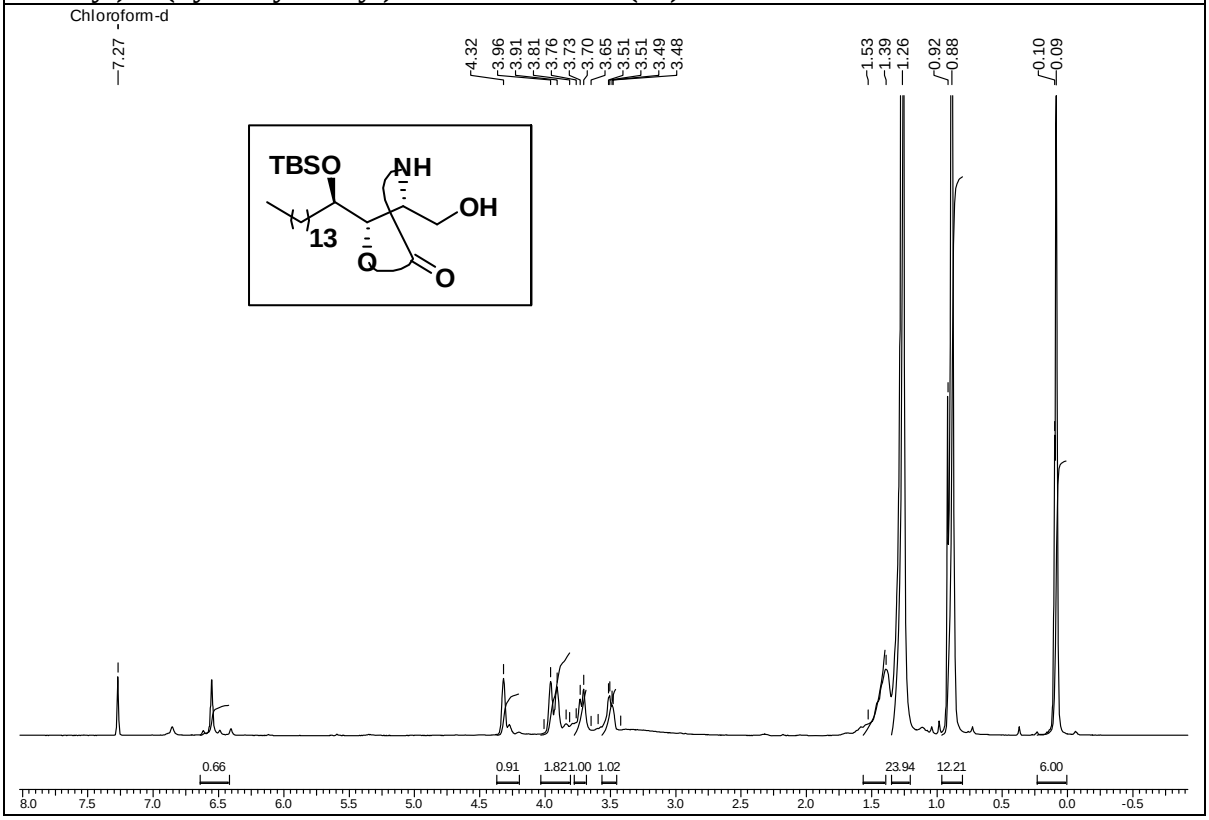
^{1}H NMR ($CDCl_3$, 400 MHz) spectra of (3*S*,4*R*)-4-((*tert*-Butyldimethylsilyl)oxy)octa-dec-1-en-3-ylcarbamate (67)



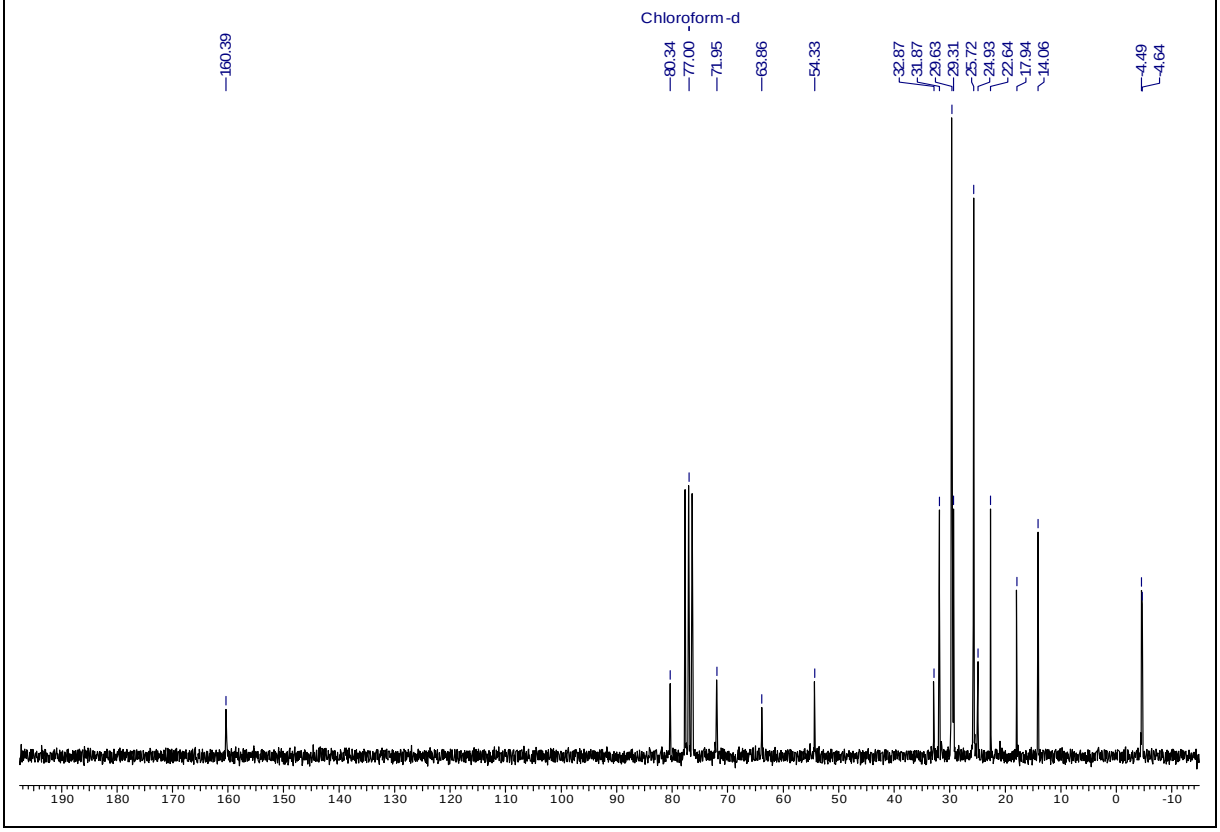
^{13}C NMR ($CDCl_3$, 400 MHz) spectra of (3*S*,4*R*)-4-((*tert*-Butyldimethylsilyl)oxy)octa-dec-1-en-3-ylcarbamate (67)



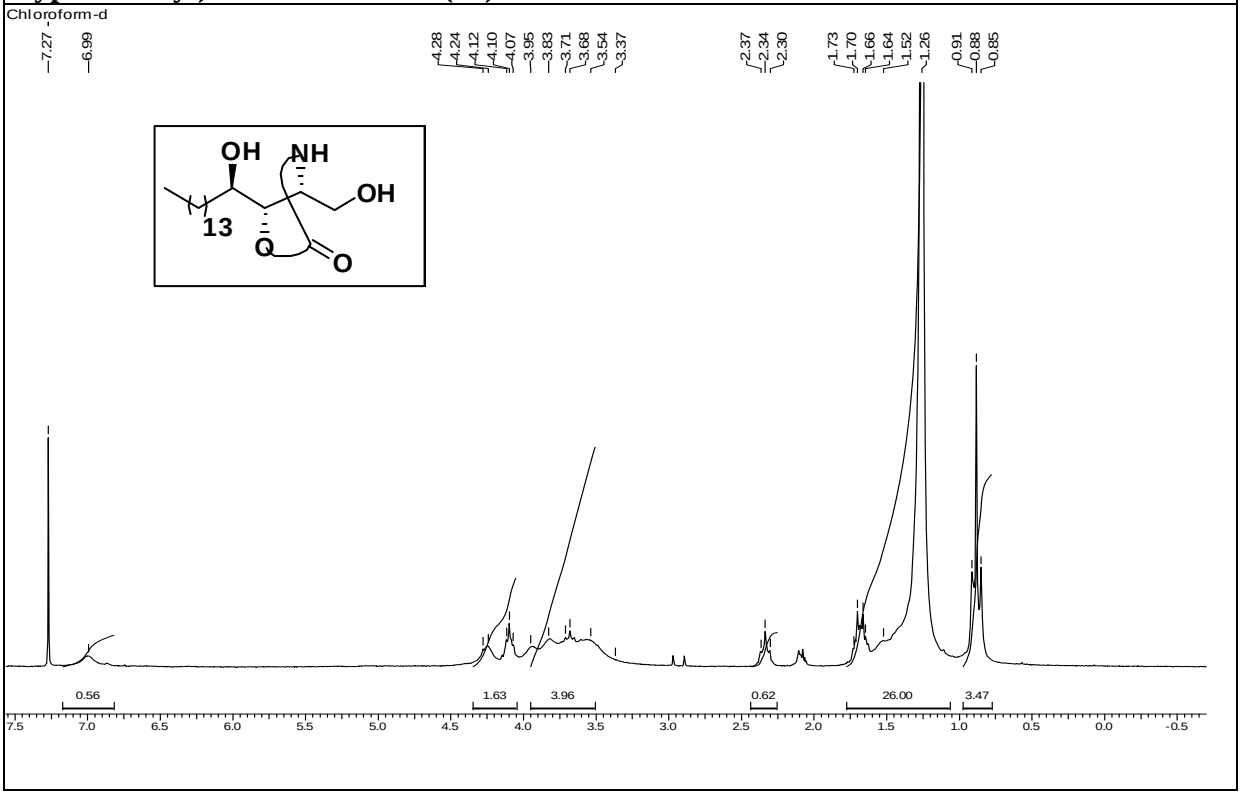
^{1}H NMR ($CDCl_3$, 400 MHz) spectra of (4*S*,5*R*)-5-((*R*)-1-(*tert*-Butyldimethylsilyl)pentadecyl)-4-(hydroxymethyl)oxazolidin-2-one (68)



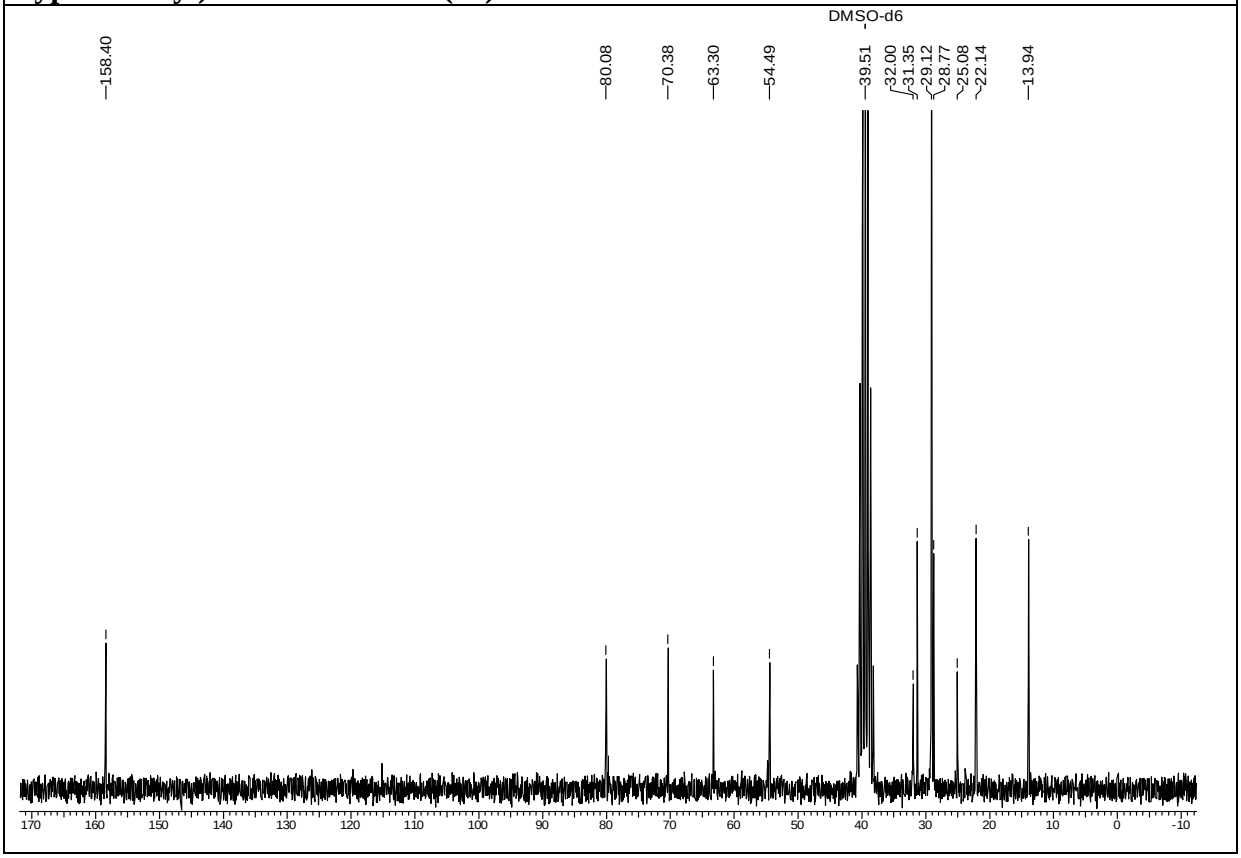
^{13}C NMR ($CDCl_3$, 100 MHz) spectra of (4*S*,5*R*)-5-((*R*)-1-(*tert*-Butyldimethylsilyl)pentadecyl)-4-(hydroxymethyl)oxazolidin-2-one (68)



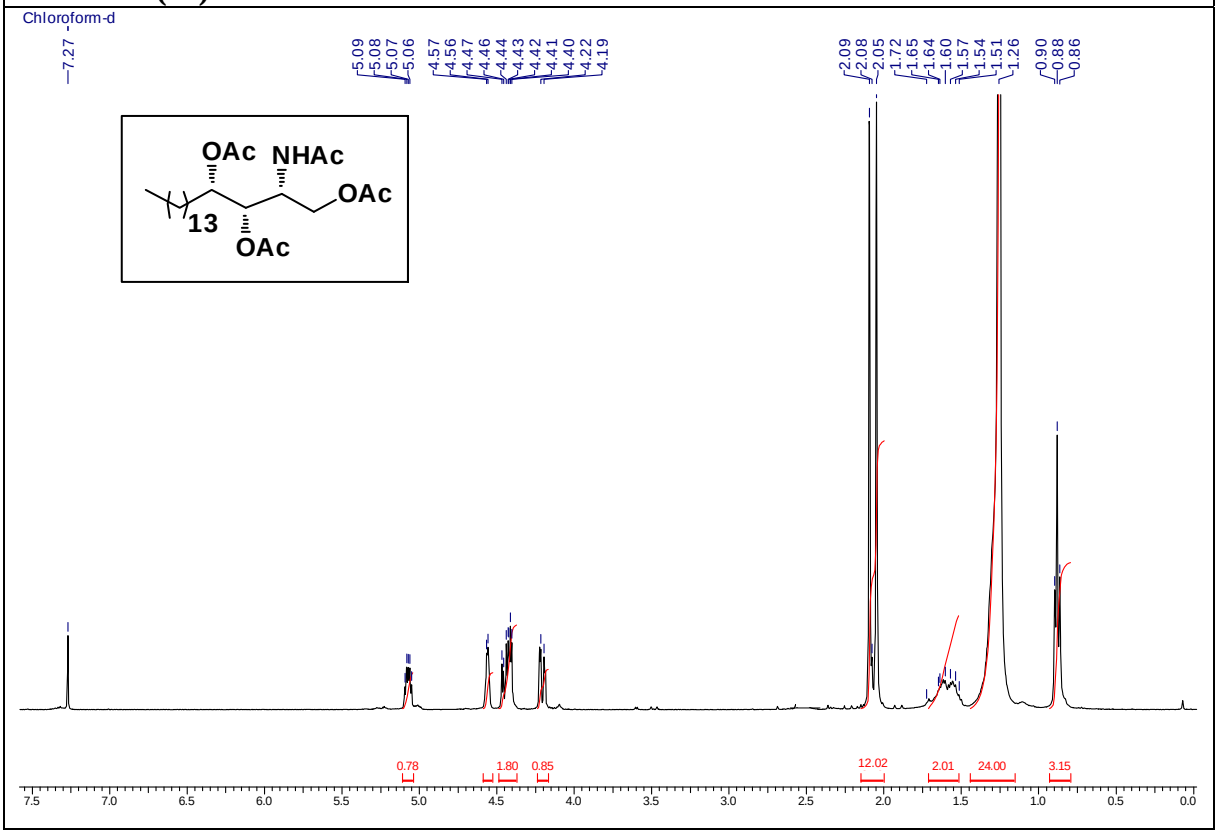
^{1}H NMR ($CDCl_3$, 200 MHz) spectra of (4*S*,5*R*)-4-(Hydroxymethyl)-5-((*R*)-1-hydroxypentadecyl)oxazolidin-2-one (69)



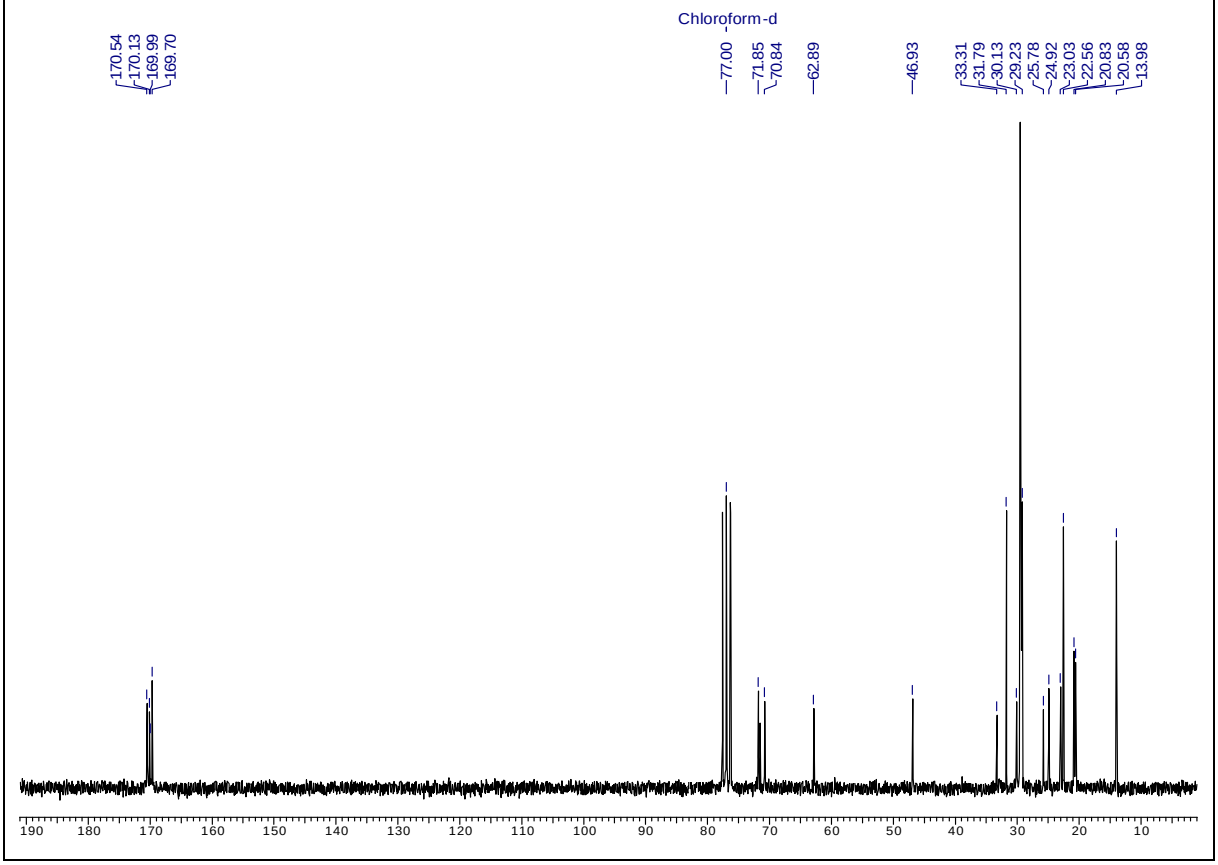
^{13}C NMR (DMSO-d_6, 50 MHz) spectra of (4*S*,5*R*)-4-(Hydroxymethyl)-5-((*R*)-1-hydroxypentadecyl)oxazolidin-2-one (69)



^{1}H NMR ($CDCl_3$, 400 MHz) spectra of (2*R*,3*S*,4*S*)-2-Acetamidooctadecane-1,3,4-triyl triacetate (54)



^{13}C NMR ($CDCl_3$, 100 MHz) spectra of (2*R*,3*S*,4*S*)-2-acetamidooctadecane-1,3,4-triyl triacetate (54)



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3.1 SECTION A

ENANTIOSELECTIVE SYNTHESIS OF (-)-GALANTINIC ACID

3.1.1. Introduction

(-)-Galantinic acid **1**, a nonproteinogenic amino acid, is a constituent of the peptide antibiotic galantin I **2b**, which was isolated from the culture broth of *Bacillus pulvifaciens*.[1] Galantin I structure is constituent of unusual amino acids, galantinamic acid **3** and galantinic acid **1**. Galantinic acid **1** was isolated from galantin I by chemical degradation and was originally assigned the structure **4**. The originally proposed structure **4** was later shown to be incorrect by total synthesis and was revised by Ohfune and co-workers, who also reported the first synthesis of galantinic acid.[2a,b] It is interesting to note that although many β-hydroxy-γ-amino acids are constituents of natural products with potent biological activity such as didemnin[3a] or dolastatin 10,[3b] the corresponding ε-amino

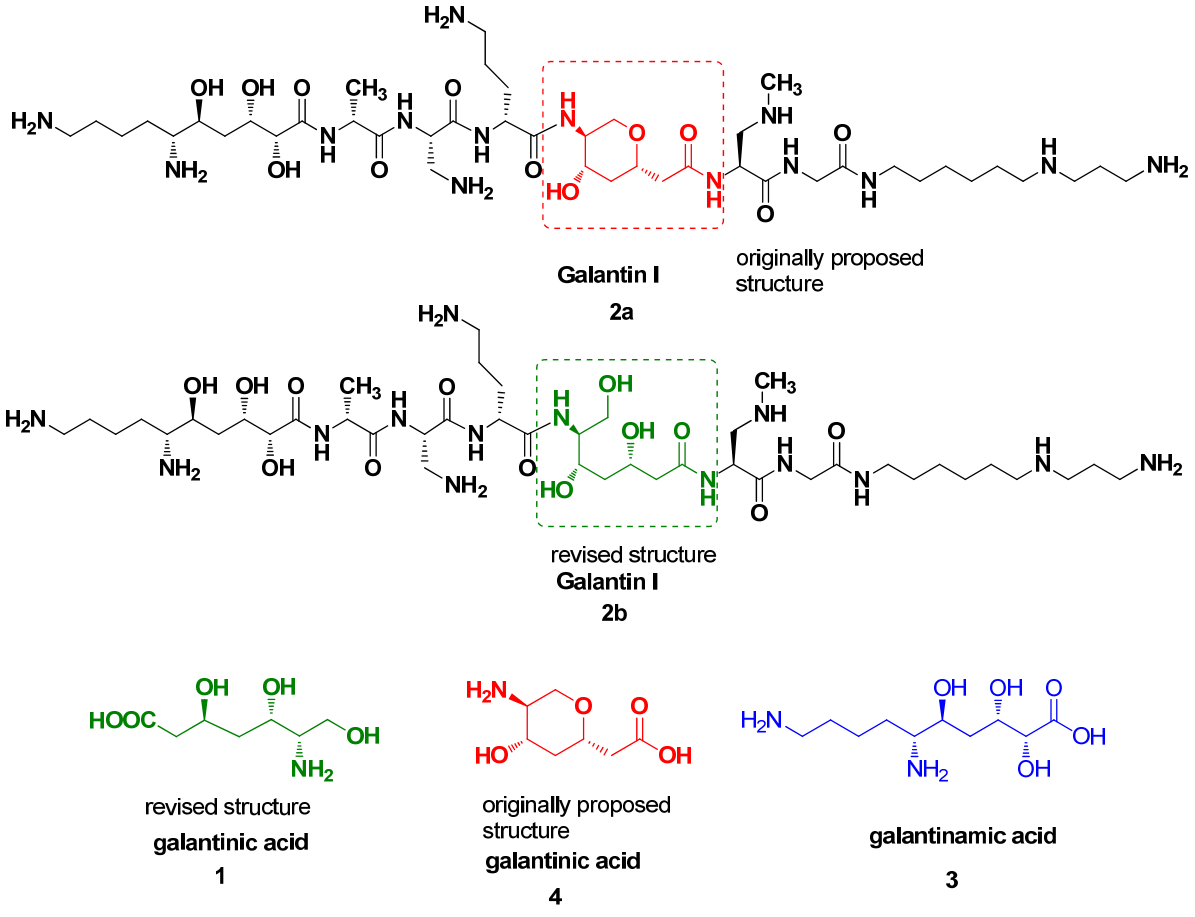


Figure 1: Structures of **galantinic acid 1, galantin I 2, galantinamic acid 3** and originally proposed structure of **galantinic acid 4**

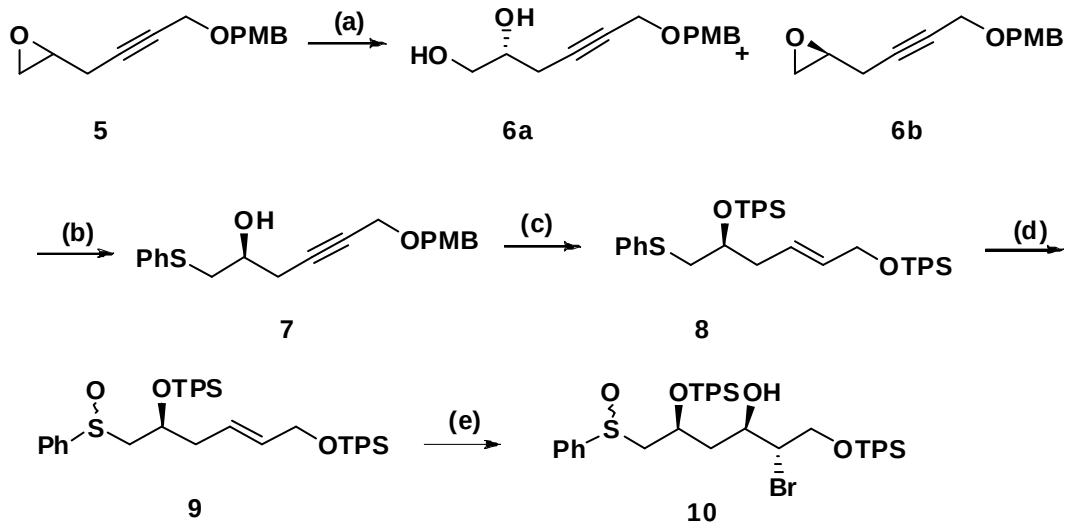
acids resulting from an additional insertion of an acetate unit are much less frequently observed.[4] Galantinic acid has attracted the attention of synthetic chemists due to its potent antibacterial activity and impressive array of functionalities with C_7 frame work.

3.1.2. Review of Literature

Various methods for its synthesis have been reported in the literature.[5] Most of the enantioselective syntheses known for galantinic acid derive the asymmetry from chiral pool starting materials, such as serine aldehyde and mannitol etc.[5a–f] However, synthetic approaches involving achiral substrate as starting materials are rather scarce. Only two asymmetric methods for the synthesis of (-)-galantinic acid have been documented in the literature[5g,h] which are described below.

Raghavan, S. *et al.* (2003)[5g]

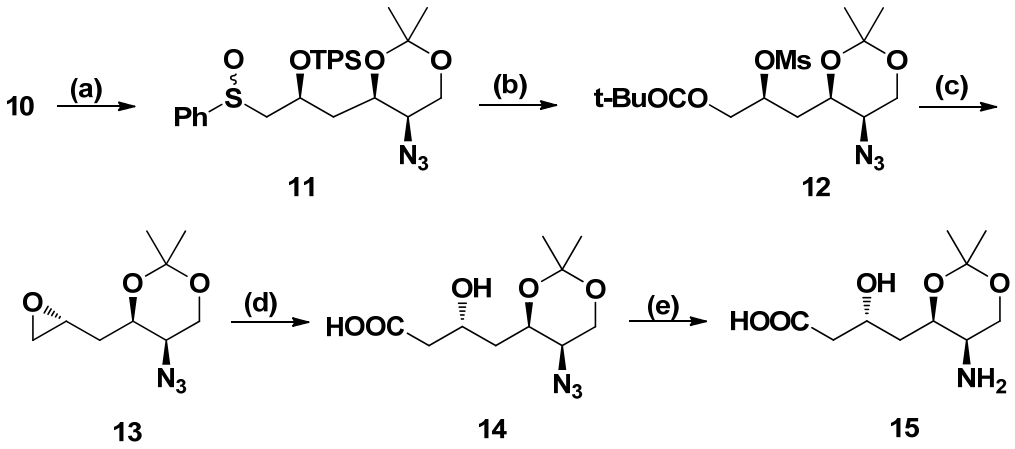
Sadagopan Raghavan and co-workers reported the stereoselective synthesis of protected (-)-galantinic **15** acid using a sulfinyl moiety as an internal nucleophile through 1,3-asymmetric induction (**Scheme 1**). Triethylamine-promoted opening of epoxide **6b** by thiophenol afforded the homopropargyl alcohol **7** which on *p*-methoxybenzyl group deprotection and subsequent reduction of the resulting propargyl alcohol with $LiAlH_4$ and silyl ether protection afforded **8**. Oxidation of sulfide **8** with $NaIO_4$ yielded an equimolar, inseparable mixture of sulfoxides **9** which on treatment with *N*-bromosuccinimide (NBS) furnished bromohydrin **10**.



Scheme 1. *Reagents and conditions*: (a) (*S*,*S*)-Salen.Co(III)OAc catalyst, H_2O, THF, rt, 42.5% of **6a** and 49% of **6b**; (b) [i] PhSH, Et_3N, CH_3CN, rt, 85%; (c) [i] DDQ, CH_2Cl_2/H_2O

(19:1), rt, 80%; [ii] $LiAlH_4$, THF, 60 °C, 78%; [iii] TBDPSCl, Imd., CH_2Cl_2, rt, 96%; (d) $NaIO_4$, THF, MeOH, H_2O, rt, 85%; (e) NBS, toluene, H_2O, rt, 75%.

Selective deprotection of the primary silyl ether in **10,** acetonide protection and displacement of the bromide by an azide afforded acetonide **11**. The compound **11** was subjected to Pummerer rearrangement and reduction of the resulting aldehyde to alcohol and TPS deprotection afforded diol, which on selective pivalation and mesylation furnished **12**. Hydrolysis of the pivalate ester led to concomitant displacement of the mesyl group to afford epoxide **13** with an inversion of configuration. The epoxide was opened with sodium cyanide, using Sharpless protocol to yield the β-hydroxy cyano compound which on hydrolysis with aq. alkaline hydrogen peroxide yielded the β-hydroxy acid **14** which on reduction with 5% Pd/C under an atmosphere of hydrogen afforded the protected galantinic acid derivative **15** in 1% overall yield from seventeen steps.

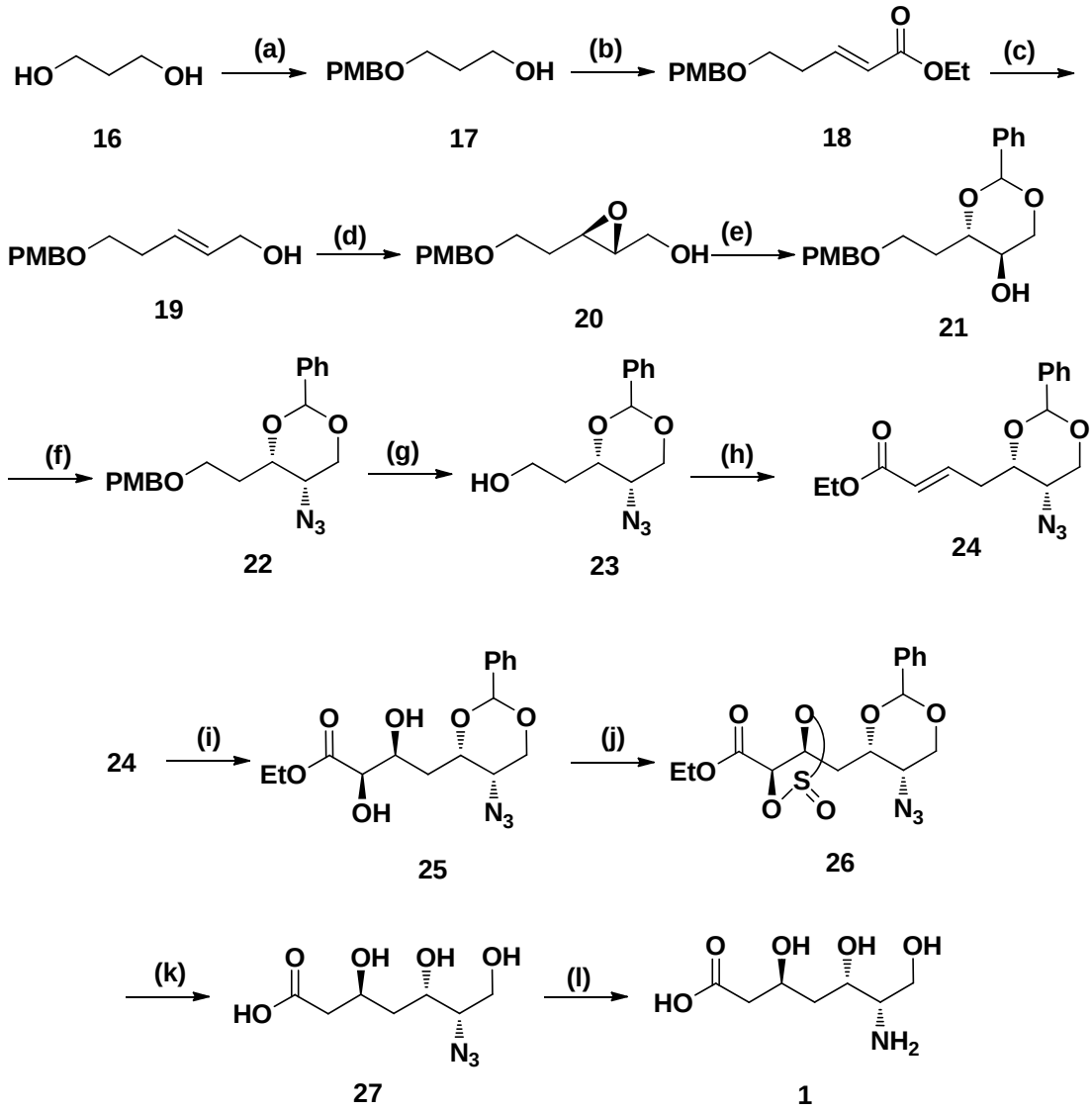


Scheme 2. *Reagents and conditions*: (a) [i] CSA, CH_2Cl_2/MeOH (1:1), rt, 78%; [ii] 2.2-DMP, acetone, CSA, rt, 90%; [iii] NaN_3, DMSO, 80 °C, 75%; (b) [i] $(CF_3CO)_2O$, Et_3N, CH_2Cl_2, rt, [ii] aq. $NaHCO_3$, $NaBH_4$, 0 °C, 70%; [iii] *n*-Bu_4NF, AcOH, THF, rt, 70%; [iv] pivaloyl-Cl, Et_3N, DMAP, CH_2Cl_2, 0 °C; [v] MsCl, Et_3N, CH_2Cl_2, 0 °C; (c) 0.2 N NaOH, MeOH, 0 °C to rt, 65% overall yield for 3 steps; (d) [i] NaCN, Ti(O*i*Pr)$_4$, *n*-Bu_4NI, DMSO, 70 °C, 80%; [ii] 3 N NaOH, 30% H_2O_2, 70 °C, 1 h, 90 °C, 1 h, 70%; (e) H_2, Pd/C, MeOH, 80%.

Kumar, P. *et al* . (2004)[5h]

Pradeep Kumar and co-workers reported the enantioselective synthesis of (-)-galantinic acid **1**, using Sharpless asymmetric epoxidation, dihydroxylation and the regioselective nucleophilic opening of a cyclic sulfite as the key steps. The synthesis started from commercially available 1,3-propanediol **16** which on PMB protection, Swern oxidation and

Wittig olefination followed by DIBAL-H reduction and asymmetric epoxidation provided the epoxide **20**, which was further converted into triol and protected as 1,3-benzylidene compound **21**. The free alcohol was converted into azide **22** and PMB protecting group was cleaved with DDQ to furnish the alcohol **23**. Compound **23** on PCC



Scheme 3. *Reagents and conditions*: (a) *p*-$CH_3OC_6H_5CH_2Cl$, NaH, dry DMF, rt, 86%; (b) [i] PCC, anhyd. CH_3COONa, dry CH_2Cl_2, 0 ^oC– rt; [ii] Ph_3P=CHCOOEt, dry THF, rt, 81%; (c) DIBAL–H, dry CH_2Cl_2, 0 ^oC–rt, 92%; (d) $Ti(OPr^i)_4$, (-)-DIPT, *t*-BuOOH, dry CH_2Cl_2, -25 ^oC, 72%; (e) [i] 60% DMSO, $HClO_4$, 0 ^oC, 89%; [ii] $C_6H_5CH(OMe)_2$, *p*-TSA (cat.), DMAP (cat.), dry CH_2Cl_2, rt, 65%; (f) [i] MsCl, Et_3N, dry CH_2Cl_2, 83%; [ii] NaN_3, dry DMF, 78%; (g) DDQ, dry CH_2Cl_2, rt, 91%; (h) [i] PCC, anhyd. CH_3COONa, dry CH_2Cl_2, rt; [ii] Ph_3P=CHCOOEt, dry THF, rt, 83%; (i) $(DHQ)_2PHAL$, OsO_4, $CH_3SO_2NH_2$, K_3FeCN_6, K_2CO_3, *t*-BuOH/H_2O (1:1), 0 ^oC, 87%; (j) $SOCl_2$, Et_3N, 89%; (k) [i] $NaBH_4$, THF, MeOH; [ii] 4N H_2SO_4, rt, 77%; (l) 10% Pd/C, H_2, MeOH, rt, 88%.

oxidation and Wittig olefination followed by Sharpless asymmetric dihydroxylation provided the diol **25**, which was further converted into cyclic sulfite **26**. For the synthesis of β-hydroxy compound **27**, the cyclic sulfite **26** was opened with hydride followed by acid treatment to give the azido alcohol **27** which on hydrogenation led to the target compound (-)-galantinic acid **1** in 6% overall yield from twelve steps.

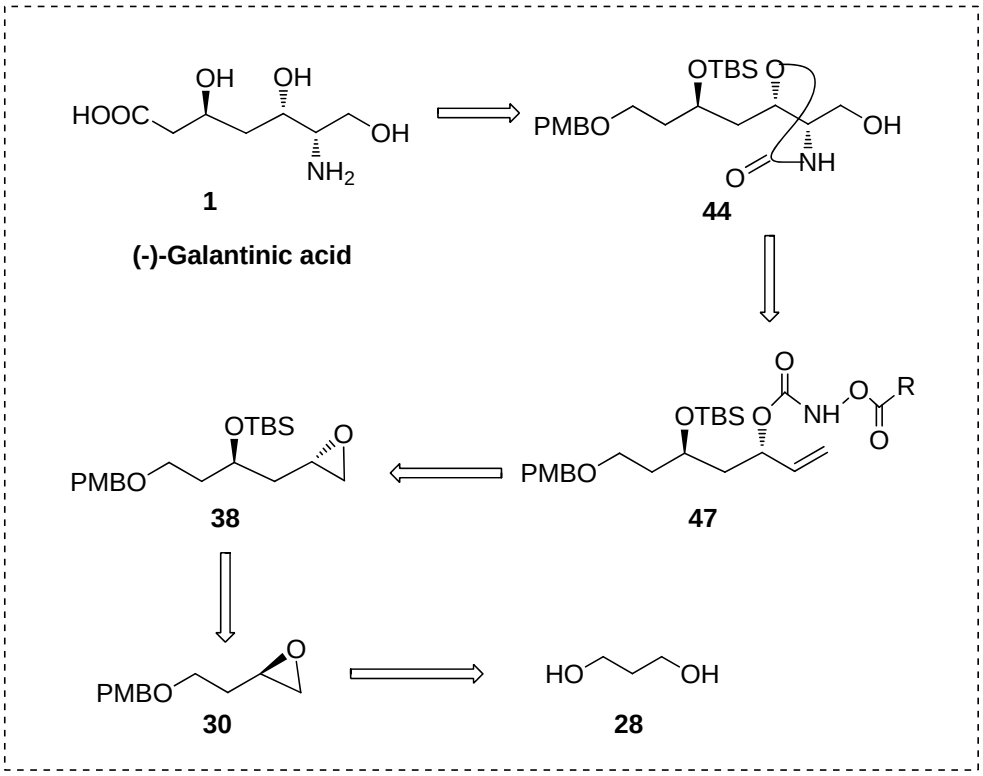
3.1.3. Present Work

3.1.3.1. Objective

The synthesis of (-)-galantinic acid **1** reported to date employ chiral pool starting materials (L-serine and D-ribonolactone); 1,2-asymmetric induction in the vicinal amino alcohol formation and 1,3-asymmetric induction in the diol formation. As a part of our research programme aimed at developing enantioselective synthesis of biologically active aminoalcohols,[6] we thought it would be worthwhile devising a new route to (-)-galantinic acid based on synthetic protocol developed by us for 1,3-diol[7] using hydrolytic kinetic resolution[8] (HKR) and also by tethered aminohydroxylation (TA).[9] The tethered aminohydroxylation has emerged as a powerful method of preparing vicinal amino alcohols in a regio- and stereoselective manner. This method overcomes the problem of low regioselectivity mainly encountered during the asymmetric aminohydroxylation,[10] a recent discovery of Sharpless to introduce amine and alcohol functionality in a single step in enantio- and stereoselective way.

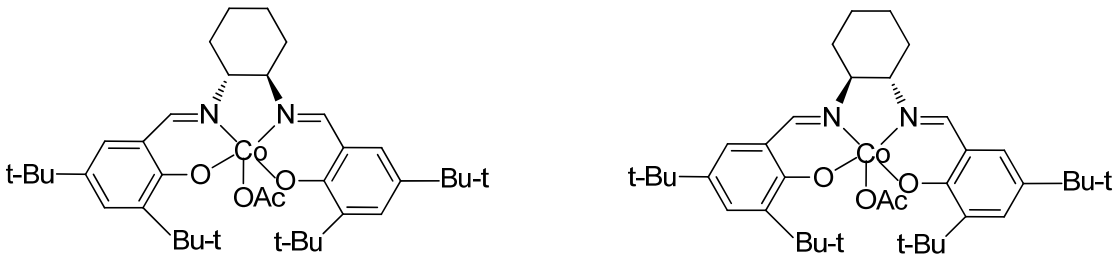
3.1.3.2. Results and Discussion

Our retrosynthetic analysis for the synthesis of (-)-galantinic acid **1** is outlined in **Scheme 4**. We envisioned that the amino stereocenter in **44** could be introduced by tethered aminohydroxylation, which in turn would be obtained from *O*-derivatized hydroxyamine **47**. The *O*-derivatized hydroxyamine **47** could be prepared from an allylic alcohol which in turn would be derived by the epoxide opening of **38**. Initial two stereogenic centers can easily be established by iterative hydrolytic kinetic resolution and vinylation form **30**, which could be easily derived from commercially available starting material 1,3-propane-diol **28**.



Scheme 4. Retrosynthetic analysis of (-)-galantinic acid (1).

The synthesis of (-)-galantinic acid started from commercially available 1,3-propanediol **28** as illustrated in **Scheme 5**. Thus selective mono hydroxy protection of **28** with *p*-methoxybenzyl chloride in the presence of NaH gave the mono protected diol **29** in 86% yield. The ^{1}H NMR spectrum gave benzylic protons at δ 4.85 (singlet, two protons) and aromatic protons at δ 7.28 (doublet) and 7.65 (doublet) with coupling constant J = 10.0 Hz and J = 9.8 Hz. The IR spectrum gave hydroxyl absorption at 3410 cm^{-1}. The compound



(*R*,*R*)-Salen-Co(III)OAc complex

31

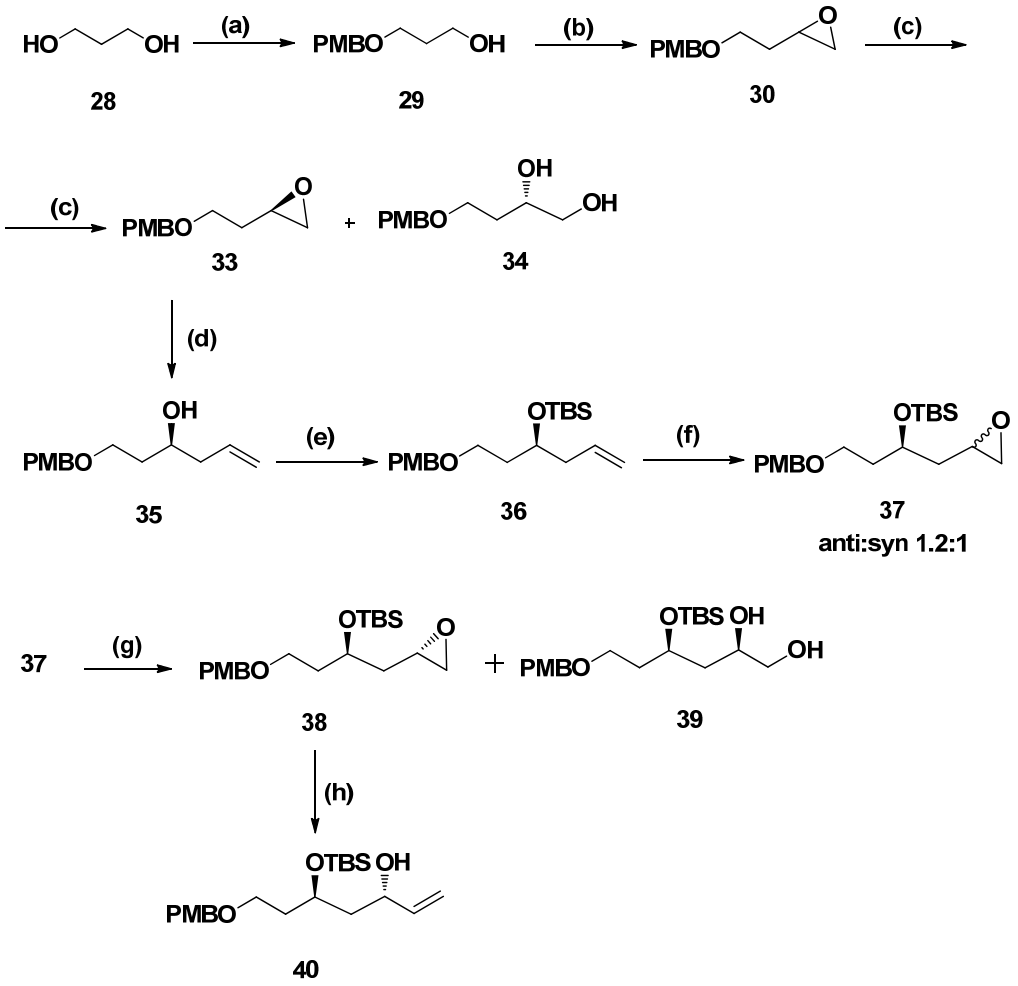
(*S*,*S*)-Salen-Co(III)OAc complex

32

Fig. 2.

29 was oxidized to the corresponding aldehyde under Swern oxidation conditions[11] followed by Corey–Chaykovsky reaction[12] with dimethylsulfoxonium methylide to afford the racemic

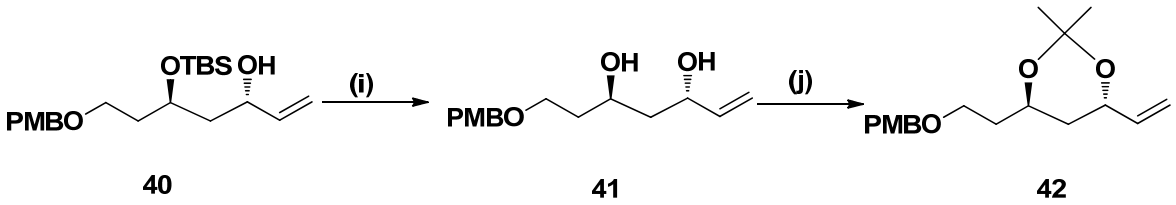
epoxide **30** in 71% yield. The epoxide peaks appeared at δ 2.53-2.57 (m, one proton), 2.78-2.83 (m, one proton), 3.07-3.11(m, one proton), in ^{1}H NMR spectrum. The ^{13}C NMR spectrum of **30** showed carbons of epoxide at δ 50, 47. Jacobsen's hydrolytic kinetic resolution of rac-epoxide (±)-**30** with (*R*,*R*)-Salen-Co-OAc catalyst **31** gave (*R*)-epoxide **33** in ee>98% [HPLC: Chiracel OD-H column (2-propanol/petroleum ether = 4:96, flow rate 0.5 mL/min, λ=220 nm). Retention time (min): 18.59 (major) and 19.4 (minor). The racemic standard was prepared in the same way with racemic epoxide, ee >98% in 48% yield, which was easily isolated from the more polar diol (*S*)-**33** by silica gel



Scheme 5. *Reagents and conditions*: (a) PMBCl, NaH, TBAI, 0 ^{o}C, DMF, 6 h, 86%; (b) [i] Oxalyl chloride, DMSO, Et_3N, -78 ^{o}C, 4 h; [ii] Trimethylsufoxonium iodide, DMSO, NaH, 0 ^{o}C, 5 h, 71%; (c) (*R*,*R*)-Salen-Co^{III}-(OAc) (0.5 mol %), distd. H_2O (0.60 equiv), 0 ^{o}C, 24 h, (47% for **33**, 48% for **34**); (d) Vinylmagnesium bromide, CuI, THF, -40 ^{o}C, 4 h, 90%; (e) TBSCl, imidazole, DCM, 6 h, 95%; (f) *m*CPBA, DCM, 0 ^{o}C, 10 h, 88%; (g) (*S*,*S*)-Salen-Co^{III}-(OAc) (0.5 mol %), distd H_2O (0.55 equiv), THF (0.55 equiv), 0 ^{o}C, 22 h, (46% for **38**); (h) $(CH_3)_3S^+I^-$, *n*-BuLi, -20 ^{o}C, 4 h, 85%.

column chromatography**.** With enantiomerically pure epoxide (*R*)-**33** in hand, our next aim was to construct the *anti*-1,3-diol. To establish the second stereogenic center with required stereochemistry,we then examined the stereoselective epoxidation of homoallylic alcohols.

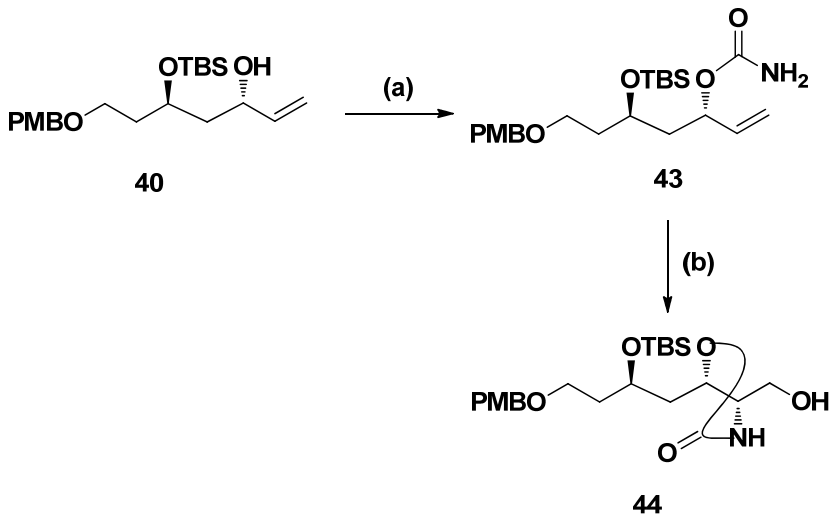
Thus, epoxide (*R*)-**33** was treated with vinylmagnesium bromide in the presence of CuI to give the homoallylic alcohol (*S*)-**35** in 90% yield. The IR spectrum of (*S*)-**35** gave broad hydroxyl absorption at 3386 cm^{-1}. The ^1H NMR spectrum of (*S*)-**35** gave olefin peaks at δ 5.06-5.17 (multiplet, two protons) and 5.74-5.94 (multiplet, one proton). In order to get more anti-selectivity in epoxidation reaction, we initially protected the hydroxyl group of homoallylic alcohols (*S*)-**35** as TBS ether **36**, followed by epoxidation with *m*-CPBA to give **37**. The ^1H NMR spectrum of epoxide **37** showed absence of olefin protons at δ 5.06-5.17 and 5.74-5.94. The epoxide **37** obtained was found to be a mixture of two diastereomers (*anti:syn*; 1.2:1) as determined by ^1H and ^{13}C NMR spectral analysis. The diastereomeric epoxide peaks appeared at δ 2.35-2.43 (multiplet, 0.83 proton), 2.43-2.51 (multiplet, 1 proton); 2.72 (triplet, 0.83 proton), 2.74-2.82 (triplet, one proton) and 2.98-3.11 (multiplet, one proton), 3.11-3.15 (multiplet, 0.83 proton) in ^1H NMR spectrum. The ^{13}C NMR spectrum of **37** showed upfield carbons of epoxide at δ 47.6, 47.7; 49.6, 49.7 and other stereocentre at δ 72.6, 72.5 as a diastereomeric mixture. The two diastereomers could not be differentiated on TLC. We next attempted the Jacobsen's hydrolytic kinetic



Scheme 6. *Reagents and conditions*: (a) *p*-TSA, MeOH; (b) 2,2-DMP, *p*-TSA, DCM.

resolution (HKR). In the structure of galantinic acid, the 1,3-diol is arranged in an *anti*-fashion, therefore the epoxide **37**, rich in *anti*-isomer was chosen as substrate for further resolution by HKR method. Epoxide **37** was treated with (*S,S*)-salen-Co-OAc complex (0.55 mol%) and water (0.61 eq) in THF (0.4 eq) to afford the epoxide **38** as a single stereoisomer (determined from the ^1H and ^{13}C NMR spectral analysis) in 46% yield and the diol **39** in 40% yield. Epoxide **38** could easily be separated from the more polar diol **39** through silica gel column chromatography. In order to generate tethered aminohydroxylation precursor, epoxide **38** was treated with excess of dimethylsulfonium methylide[13] (generated from trimethylsulphonium iodide and *n*-BuLi) to furnish the allylic alcohol **40** in excellent yield.

The IR spectrum of (*S*)-**40** gave broad hydroxyl absorption at 3430 cm^{-1}. The ^1H NMR spectrum of (*S*)-**40** gave olefin peaks at δ 5.04-5.29 (multiplet, two protons) and 5.76-5.92 (multiplet, one proton). The relative stereochemistry of 1,3-diol **40** was determined by using Rychnovsky's acetonide method[14] (**Scheme 6**). TBS deprotection furnished the diol **41**, which on treatment with 2,2-DMP gave the acetonide **42**. *Anti*-acetonide **42** was confirmed by the appearance of the methyl carbons resonance at δ 22.7 ppm and the acetal carbon at δ 100.7 ppm. Alcohol **40** was then reacted with trichloroacetyl isocyanate in CH_2Cl_2 to give the corresponding isocyanate which on treatment with aq. K_2CO_3 and methanol furnished the carbamate **43** in 95% yield. The IR spectrum of (*S*)-**42** gave broad hydroxyl absorption at 1692 cm^{-1}. The carbamate **43** was subjected to TA[9] using *tert*-butyl hypochlorite as the oxidant, potassium osmate, NaOH, diisopropylethylamine and propanol as the solvent. However, we could isolate only 15% of the protected aminoalcohol **44** along with starting material and unidentified side products as major compounds (**Scheme 7**).

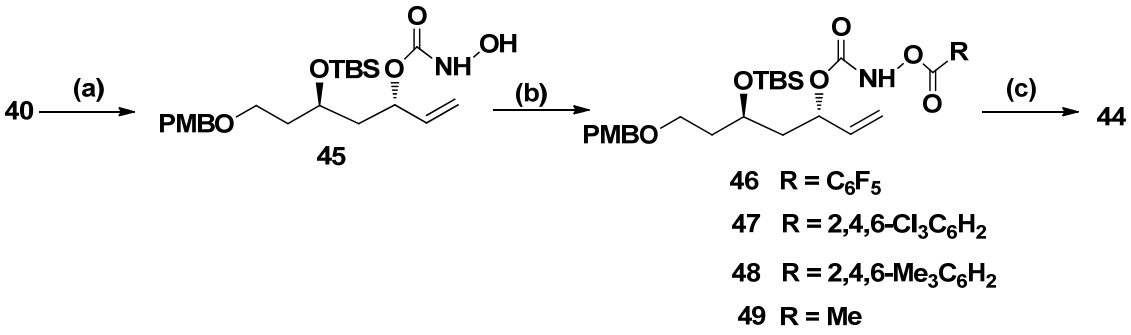


40 43 44

Scheme 7. *Reagents and conditions*: (a) $Cl_3CCONCO$, K_2CO_3, CH_2Cl_2:CH_3OH (1.5:1), 4 h, 95%; (b) NaOH, *t*-BuOCl, $^iPr_2EtN$, potassium osmate, 2.5 h, 15%.

The limited life time of *N*-chlorocarbamates, produced in situ by the action of NaOH and *t*-BuOCl on a primary carbamate and chlorination of the alkene unit as a competing side reaction in the TA reaction may be responsible for lowering the yield.[9e] In an asymmetric aminohydroxylation reaction, one can compensate for this by using 3-3.5 equiv of carbamate (and NaOH and *t*BuOCl). Clearly, we do not have this luxury in the TA reaction and thus we have difficulty in driving the reaction to completion and chlorination of the alkene unit was a competing side reaction. Therefore, we turned our attention on replacement of the chlorine of the *N*-halocarbamate salt that is generated in situ during oxidation with *t*-BuOCl and NaOH.

The N-Cl unit was replaced by a N-O-CO-R group, hydroxycarbamate which was introduced before the aminohydroxylation rather than being formed in situ. Alcohol **40** was reacted with CDI in pyridine, followed by the addition of hydroxylamine hydrochloride, to afford the hydroxy carbamate **45** in excellent yield 85%. The resulting hydroxyl carbamate **45** was then treated with pentafluorobenzoyl chloride, in ether, to yield 80% the pentafluorobenzoyl *O*-derivatized hydroxycarbamates **46**, which was then subjected to TA protocol to furnish protected amino alcohol, but we found very poor yield (10-20%) along with major side product.



Scheme 8. *Reagents and conditions*: (a) CDI, pyridine, $NH_2OH.HCl$, 40 ^oC, 26 h, 85%; (b) 2,4,6-trichlorobenzoyl chloride, Et_3N, 0 ^oC, 1 h, 90%; (c) $K_2OsO_4.2H_2O$, *t*-BuOH: H_2O (3:1), 1 h, 10-20%.

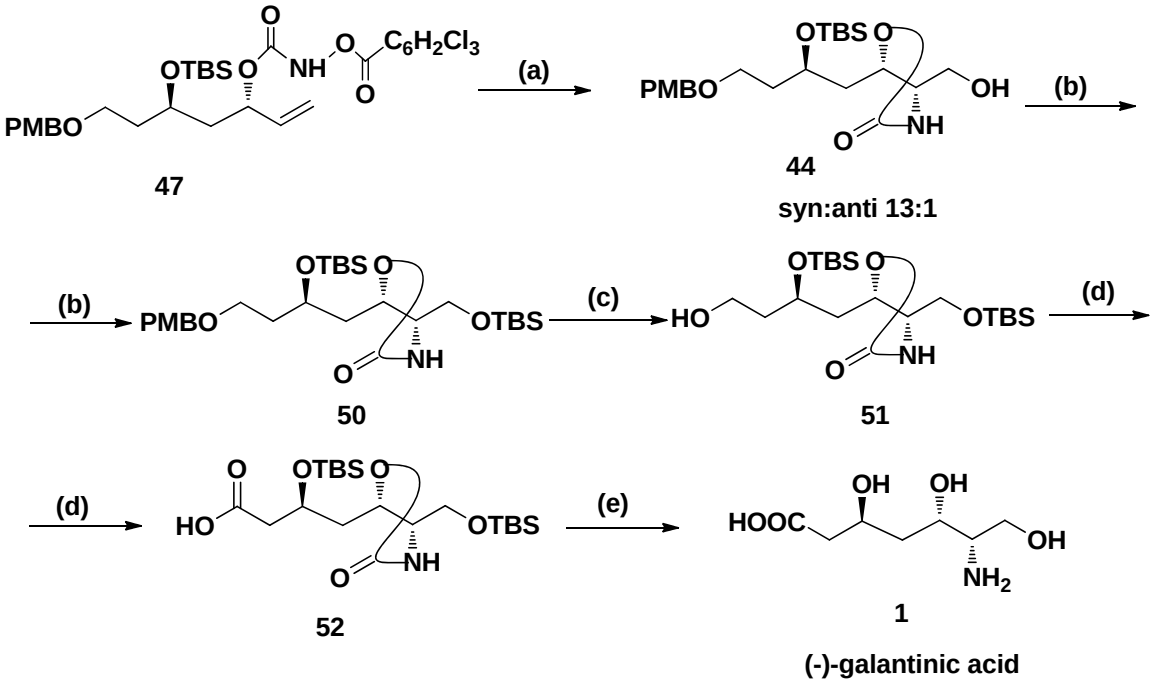
Table 1: Reaction of *O*-2,4,6-trichlorobenzoyl hydroxycarbamate with Potassium osmate dihydrate at different concentration

Potassium osmate (Conc. in mol%)	Yield (%) of **44**
1	20
2	10
4	10
6	5

We reasoned that lower yield obtained may be due to the labile nature of pentafluorobenzoyl *O*-derivatized hydroxycarbamates. To improve the yield of reaction we next attempted at other *O*-derivatised hydroxycarbamate (**47** to **49**) derived from 2,4,6- trichlorobenzoyl

chloride, 2,4,6-trimethylbenzoyl chloride and acyl chloride also (**Scheme 8**), but we could not improve the yield even by increasing potassium osmate concentration, surprisingly we got lower yield pattern (**Table 1**), this may be due to the unstable nature of reacting intermediate azaglycolate osmate ester.

By this observation, we then decided to increase the volume of reaction from 20 mL/mmol to 40 mL/mmol and slow addition of potassium osmate solution to overcome the possibility of fast reaction by one pot addition of potassium osmate. To our delight we



Scheme 9. *Reagents and conditions*: (a) $K_2OsO_4.2H_2O$, *t*-BuOH:H_2O (3:1), 40 mL/mmol; 3 h, 75%; (b) TBSCl, imidazole, DCM, 2 h, 85%; (c) DDQ, THF: H_2O (18:1), 0 ^oC, 3 h, 93%; (d) [i] Oxalyl chloride, DMSO, Et_3N, -78^oC, 4 h; [ii] $NaClO_2$, DMSO, NaH_2PO_4, 12 h, 73% for two step; (e) [i] K_2CO_3, methanol, 0 ^oC, 6 h; [ii] acidified with 2N HCl, 55% for two steps

could obtain the desired protected aminoalcohol **44** in 75% yield with complete regio- and excellent diastereoselectivity (*syn:anti* 13:1, determined from ^1H NMR). The diastereomeric mixture could easily be separated by column chromatography.

The key step in the TA as depicted in **Figure 3** is the intramolecular addition of the RN=Os=O fragment across the alkene leading to *syn* or *anti* relative stereochemistry. Generally the 1,3-allylic interaction plays a major role in determining the stereoselective outcome of the reaction. Between the two possible comformations **A** and **B** of tethered [3+2] cycloaddition, the 1,3-allylic interactions are minimised in conformation **A**, while such

interactions are significant in conformation **B**. One would predict conformation **A** to be lower in energy and therefore the equilibrium is shifted towards the more stable conformation **A** thus leading to major *syn* product.

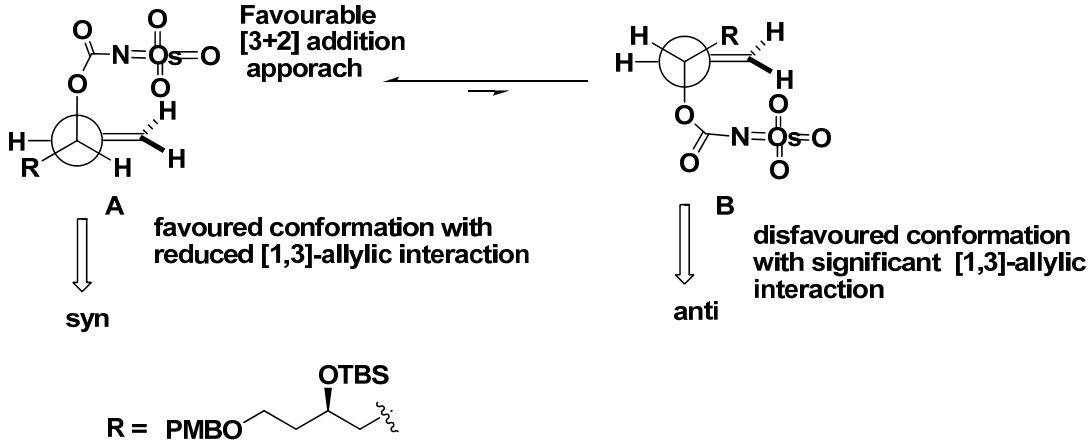


Figure 3. Proposed transition states for the syn/anti selectivity observed during the TA reaction

With required framework in hand our next task was to protect the newly generated alcohol with TBS chloride to give the TBS ether **50** in 85% yield. The PMB group was removed by DDQ to afford the alcohol **51** in 93% yield. The alcohol was oxidized to the aldehyde using Swern oxidation conditions followed by subsequent oxidation using $NaClO_2$ in DMSO under buffer conditions to give the acid **52** in 73% yield. Compound **52** was further subjected to hydrolysis with K_2CO_3 in methanol to furnish the crude aminoalcohol. Subsequent acidification by 2N HCl produced (-)-galantinic acid **1** in 55% yield from two steps (Scheme 8). The physical and spectroscopic data of **1** were in complete agreement with those described in literature $[\alpha]_D^{25}$: -29.7 (*c*, 0.5, H_2O); {lit.[2] $[\alpha]_D^{25}$ -29.4 (*c*, 0.5, H_2O)}. The overall yield of the target compound **1** was found to be 1.5% from fifteen steps.

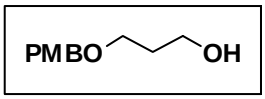
3.1.3.3. Conclusion

We have developed a new synthetic approach to (-)-galantinic acid using iterative hydrolytic kinetic resolution and tethered aminohydroxylation as key steps.

3.1.4. Experimental

All reactions were carried out under argon or nitrogen in oven-dried glassware using standard gas-light syringes, cannulas and septa. Melting points are uncorrected. Solvents and reagents were purified and dried by standard methods prior to use. Optical rotations were measured at room temperature sodium D line on JASCO-181 digital polarimeter. IR spectra were recorded on an FT-IR instrument. ^{1}H NMR spectra were recorded at 200 MHz, 400 MHz and 500 MHz and are reported in parts per million (delta) downfield relative to $CDCl_3$ as internal standard and ^{13}C NMR spectra were recorded at 50 MHz, 100 MHz and 125 MHz and are assigned in parts per million (delta) relative to $CDCl_3$. Column chromatography was performed on silica gel (100–200 and 230–400 mesh) using a mixture of petroleum ether and ethyl acetate as the eluent. Microanalytical data were obtained using a Carlo–Erba CHNS-0 EA 1108 elemental analyzer. Enantiomeric excess was determined using chiral HPLC.

3-(4-Methoxybenzyloxy)propan-1-ol (29):



To a solution of 1,3-propanediol **28** (5.0 g, 65.71 mmol) in dry DMF (200 mL) was added sodium hydride (60%, 2.90 g, 72.28 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 chloride (11.32 g, 10.75 mL, 72.28 mmol) and *tetra n*-butylammonium iodide (2.6 g, 6.57 mmol) with further stirring for 6 h at the same temperature. The reaction mixture was quenched with addition of cold water at 0 ^{o}C. The two phases were separated and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with water (3 x 100 mL), brine, dried over Na_2SO_4 and concentrated. The residual oil was purified by silica gel column chromatography using petroleum ether/EtOAc (6:4) as eluent to furnish the mono-PMB protected alcohol **29** as colorless oil.

Yield: 11.09 g, 86%.

Mol. Formula: $C_{11}H_{16}O_3$

IR (neat, cm^{-1}): ν_{max} 3410, 2940, 2863, 1612, 1513, 1249, 1175, 1098.

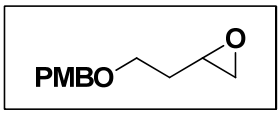
^{1}H NMR (500 MHz, $CDCl_3$): δ 2.22-2.27 (m, 2H), 2.82 (brs. 1H), 4.02 (t, *J* = 5.2 Hz, 2H), 4.15 (t, *J* = 5.6 Hz, 2H), 4.20 (s, 3H), 4.85 (s, 2H), 7.28 (d, *J* = 10 Hz, 2H), 7.65 (d, *J* = 9.8 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 32.2, 55.2, 61.5, 68.7, 72.8, 113.8, 129.2.

MS(ESI): 219 $(M+Na)^+$.

Analysis: Calcd.: C, 67.32; H, 8.22%; **Found**: C, 67.44; H, 8.33%.

2-(2-(4-Methoxybenzyloxy)ethyl)oxirane (30):



(i) Swern oxidation. To a solution of oxalyl chloride (3.33 mL, 38.21 mmol) in dry CH_2Cl_2 (50 mL) at -78 ^oC was added dropwise dry DMSO (5.42 mL, 76.43 mmol) in CH_2Cl_2 (20 mL). After 30 min, alcohol **29** (5.0 g, 25.47 mmol) in CH_2Cl_2 (20 mL) was added over 10 min giving copious white precipitate. After stirring for 1 h at -78 ^oC, the reaction mixture was brought to -60 ^oC and Et_3N (15.62 mL, 112.24 mmol) was added slowly and stirred for 30 min allowing the reaction mixture to warm to room temperature. The reaction mixture was then diluted with water (100 mL) and CH_2Cl_2. The organic layer was separated and washed with water and brine, dried over Na_2SO_4 and passed through short pad of celite. The filtrate was concentrated to give the aldehyde (4.70 g, 95%) as pale yellow oil, which was used as such for the next step without purification.

(ii) To a solution of trimethylsulfoxonium iodide (7.98 g, 36.29 mmol) in dry DMSO was added NaH (0.87 g, 36.29 mmol). After 1 h, aldehyde (4.7 g, 24.19 mmol) dissolved in THF was added at 25 ^oC. After stirring for 5 h ice was added to the reaction mixture and the reaction mixture was extracted with water, brine, dried over Na_2SO_4. Solvent was removed under pressure and the crude product was purified by silica gel column chromatography using pet ether/EtOAc (95:5) to get pure epoxide **30** as colorless liquid.

Yield: 3.77 g, 71%.

Mol. Formula: $C_{12}H_{16}O_3$

IR (neat, cm^{-1}): ν_{max} 3490, 2940, 2863, 1612, 1513, 1249, 1175, 1098.

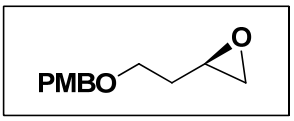
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.70-1.91 (m, 2H), 2.53-2.57 (m, 1H), 2.78-2.83 (m, 1H), 3.07-3.11 (m, 1H), 3.62 (t, *J* = 6.9 Hz, 2H), 3.83 (s, 3H), 4.48 (s, 2H), 6.90 (d, *J* = 8.7 Hz, 2H,), 7.30 (d, *J* = 8.7 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 32.8, 47.0, 50.0, 55.1, 66.6, 72.6, 113.7, 129.2, 130.2 159.1.

MS(ESI): 231 $(M+Na)^+$.

Analysis: Calcd.: C, 69.21; H, 7.74%; **Found**: C, 69.38; H, 7.68%.

(*R*)-2-(2-(4-Methoxybenzyloxy)ethyl)oxirane (33):



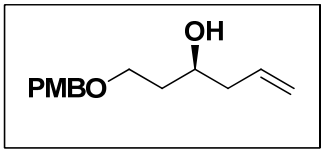
Racemic epoxide (±)-**30** (8.0 g, 38.41 mmol), THF (583 μL) were added to (*R*,*R*)-Salen-Co^{III}-OAc catalyst **31** (127 mg, 0.192 mmol, 0.5 mol%) and the solution was cooled to 0 ^{o}C. Every 5 min, H_2O (50 μL) was added until 414 μL (0.60 equiv., 23.04 mmol) had been added; after another 5 min the ice bath was removed and the reaction was stirred at room temperature for 24 h. The reaction mixture was concentrated and purified through silica gel column chromatography using petroleum ether/EtOAc (95:5) as eluent to furnish the epoxide (*R*)-**33** as a single stereoisomer as a yellow colored liquid. Continued chromatography with petroleum ether/EtOAc (6:4) provided the diol (*S*)-**34** as a brown colored liquid as a single enantiomer.

Yield: 3.84 g, 48%.

$[\alpha]_D^{25}$: –12.98 (*c* 1, $CHCl_3$).

HPLC: Chiracel OD-H column (2-propanol/petroleum ether= 4:96, flow rate 0.5 mL/min, λ=220 nm). Retention time (min): 18.59 (major) and 19.4 (minor). The racemic standard was prepared in the same way with racemic epoxide, ee >98%.

(*S*)-1-(4-Methoxybenzyloxy)hex-5-en-3-ol (35):



A round bottomed flask was charged with copper(I)iodide (0.274 mg, 1.44 mmol), gently heated under vacuum and slowly cooled with a flow of argon and THF (20 mL) was added. This suspension was cooled to –40 ^{o}C, stirred and vinylmagnesium bromide (1M in THF, 28.8 mL, 28.8 mmol) was added to it. A solution of epoxide (*R*)-**33** (3.0 g, 14.4 mmol) in THF (15 mL) was added to the above reagent and the mixture was stirred at –40 ^{o}C for 4 h. After consumption of starting material, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl. The water layer was extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. Purification of crude product by silica gel column chromatography using petroleum ether/EtOAc (9:1) as eluent afforded (*S*)-**35** as a colorless liquid.

Yield: 3.06 g, 90%.

Mol. Formula: $C_{14}H_{20}O_3$

$[\alpha]_D^{25}$: –5.98 (*c* 1.35, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 3386, 1640, 1603, 1493, 1453, 1243.

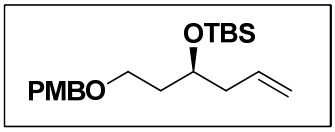
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.70-1.91 (m, 2H), 2.53-2.57 (m, 1H), 2.78-2.83 (m, 1H), 3.07-3.11 (m, 1H), 3.62 (t, *J* = 6.9 Hz, 2H), 3.83 (s, 3H), 4.48 (s, 2H), 6.91 (d, *J* = 8.72 Hz, 2H), 7.30 (d, *J* = 8.7 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 35.8, 41.9, 55.2, 68.7, 70.5, 72.9, 113.8, 117.5, 129.3, 130.0 134.9, 159.2.

MS(ESI): 259 $(M+Na)^+$.

Analysis: Calcd.: C, 71.16; H, 8.53%; **Found:** C, 71.21; H, 8.47%.

(*S*)-*tert*-Butyl(1-(4-methoxybenzyloxy)hex-5-en-3-yloxy)dimethylsilane (36):



To a stirred solution of alcohol **35** (5 g, 21.86 mmol) in CH_2Cl_2 was added imidazole (2.88 g, 42.37 mmol). To this solution *t*-butyl dimethylchlorosilane (4.78 g, 31.77 mmol) was added at 0 ^oC and the reaction was stirred at rt for 6 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and concentrated. Purification of crude product by silica gel column chromatography using petroleum ether/EtOAc (95:5) as eluent afforded (*S*)-**36** as a colorless liquid.

Yield: 7.04 g, 95%.

Mol. Formula: $C_{20}H_{34}O_3Si$

$[\alpha]_D^{25}$: +16.12 (*c* 1.65, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 1641, 1606, 1491, 1462.

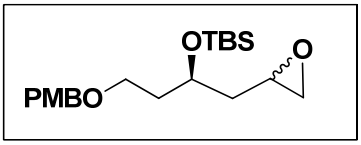
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.05 (s, 3H), 0.06 (s, 3H), 0.89 (s, 9H), 1.63-1.80 (m, 2H), 2.19-2.26 (m, 2H), 3.51 (t, *J* = 6.3 Hz, 2H), 3.81 (s, 3H), 3.84-3.95 (m,1H), 4.43 (Abq, *J* = 11.5 Hz, 2H), 4.48-5.09 (m, 2H), 5.71-5.92 (m, 1H), 6.89 (d, *J* = 8.7 Hz, 2H), 7.27 (d, *J* = 8.7 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.7, -4.4, 18.1, 25.9, 36.7, 42.3, 55.2, 66.7, 68.9, 72.6, 113.7, 116.9, 129.3, 130.7, 134.9, 159.1.

MS(ESI) m/z: 373 $(M+Na)^+$.

Analysis: Calcd.: 68.52; H, 9.78%; **Found:** C, 68.49; H, 9.73%.

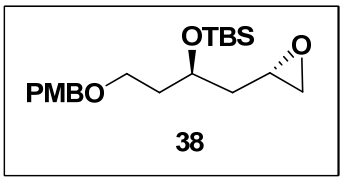
***tert*-Butyl((*R*)-4-(4-methoxybenzyloxy)-1-((*S*)-oxiran-2-yl)butan-2-yloxy)dimethylsil-ane (37):**



To a stirred solution of olefin **36** (5 g, 14.26 mmol) in CH_2Cl_2 (100 mL) at 0 ^oC was added *m*-CPBA (50%) (5.41 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 over Na_2SO_4, concentrated and purified by silica gel column chromatography using pet ether/EtOAc (9:1) as eluent to yield the epoxide **37** as a colorless liquid in diastereomeric mixture (*anti:syn* = 1.2:1).

Yield: 4.6 g, 88%.

***tert*-Butyl((*R*)-4-(4-methoxybenzyloxy)-1-((*S*)-oxiran-2-yl)butan-2-yloxy)dimethyl-silane (38):**



A solution of epoxide **37** (4 g, 10.92 mmol) and (*S*,*S*)-Salen-Co^{III}-OAc **32** (0.036 g, 0.055 mmol) in THF (0.4 mL) was stirred at 0 ^oC for 5 min, and then distilled water (108 µL, 6.01 mmol) was added. After stirring for 24 h, it was concentrated and purified by silica gel column chromatography using pet ether/EtOAc (9:1) as eluent to afford **38** (1.84 g, 46%) as a yellow colored liquid, Continued chromatography with pet ether/EtOAc (3:2) provided the diol **39** as a brown colored liquid as a single diastereomer.

Yield: 1.84 g, 46%.

Mol. Formula: $C_{20}H_{34}O_3Si$

$[\alpha]_D^{25}$: -14.0 (*c* 1, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 2960, 2860, 1470, 1410, 1340, 1250, 1095, 1035, 840, 780.

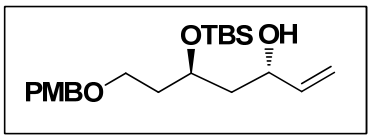
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.06 (s, 3H), 0.08 (s, 3H), 0.89 (s, 9H), 1.62-1.72 (m, 2H), 1.77-1.90 (m, 2H), 2.43-2.51 (m, 1H), 2.74-2.82 (m, 1H), 2.98-3.11 (m, 1H), 3.51 (t, *J* = 6.4 Hz, 2H), 3.81 (s, 3H), 4.04-4.11 (m, 1H), 4.42 (Abq, *J* = 11.5 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 7.26 (d, *J* = 8.7 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.9, -4.7, 18.0, 25.8, 37.7, 40.6, 47.7, 49.7, 55.2, 66.3, 67.5, 72.6, 113.8, 129.3, 130.5, 159.1.

MS(ESI) m/z: 389 $(M+Na)^+$, 405 $(M+K)^+$.

Analysis: Calcd.: C, 52.67; H, 9.2%; **Found:** C, 52.74; H, 9.11%.

(3*S*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-7-(4-methoxybenzyloxy)hept-1-en-3-ol (40):



To a stirred solution of dry THF was added trimethylsulfonium iodide (13.91 g, 68.19 mmol) at -20 ^oC. The reaction was stirred for 20 min followed by addition of *n*-BuLi (42.6 mL, 1.6 M, 68.19 mmol). After 40 min, epoxide **38** (5.0 g, 13.63 mmol) in THF was added dropwise. The reaction mixture was stirred at -20 ^oC for 3 h and quenched by saturated solution of ammonium chloride. The two phases were separated and the aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with water (3 x 50 mL), brine, dried over 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 allylic alcohol **40** as colorless oil.

Yield: 4.41 g, 85%.

Mol. Formula: $C_{21}H_{36}O_4Si$

$[\alpha]_D^{25}$: -5.25 (*c* 1.3, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 3430, 3018, 2957, 2931, 2859, 1652, 1471, 1379, 1256, 1212, 1101, 1036, 971, 869, 758.

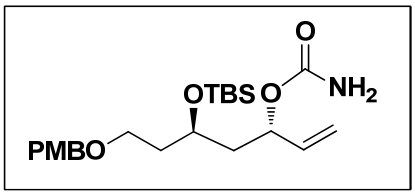
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.09 (s, 3H), 0.11 (s, 3H), 0.9 (s, 9H), 1.63-1.73 (m, 2H), 1.85-1.97 (m, 2H), 2.44-2.94 (brs, 1H), 3.5 (t, *J* = 6.4 Hz, 2H), 3.81 (s, 3H), 4.06-4.31 (m, 2H), 4.43 (Abq, *J* = 11.4 Hz, 2H), 5.04-5.29 (m, 2H), 5.76-5.92 (m, 1H), 6.88 (d, *J* = 8.7 Hz, 2H), 7.25 (d, *J* = 8.7 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.7, -4.3, 17.9, 25.8, 36.4, 42.4, 55.2, 68.4, 68.6, 69.6, 72.3, 113.8, 113.9, 129.3, 130.4, 140.0, 141.1, 159.2.

MS(ESI) m/z: 403 $(M+Na)^+$.

Analysis: Calcd.: C, 66.27; H, 9.53%; **Found:** C, 66.32; H, 9.47%.

(3*S*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-7-(4-methoxybenzyloxy)hept-1-en-3-ylcarb-amate (43):



Trichloroacetyl isocyanate (0.594 g, 0.37 mL, 3.15 mmol) was added dropwise to a solution of the alcohol **40** (1.0 g, 2.62 mmol) in dry dichloromethane 3.93 mL (1.5 mL/mmol) at 0 ^{o}C. After consumption of starting material (2 h), the mixture was concentrated under reduced pressure. The residue was dissolved in methanol 5.24 mL (2 mL/mmol), cooled to 0 ^{o}C and an aqueous potassium carbonate solution (1.09 g, 7.86 mmol, 2 mL/mmol) was added. The cooling bath was removed and the mixture was allowed to stir for 4 h, by which time TLC showed complete conversion. Methanol was evaporated under reduced pressure and the aqueous residue was extracted with dichloromethane (25 mL x 3). The combined organics were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to yield the crude carbamate, which was purified by flash column chromatography on silica gel using petroleum ether/EtOAc (7:3) as eluent to give carbamate **43** as colorless oil.

Yield: 1.05 g, 95%.

Mol. Formula: $C_{22}H_{37}NO_5Si$

$[\alpha]_D^{25}$: -5.0 (*c* 1, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 3370, 1692, 1308, 1276, 1140, 974, 771, 699.

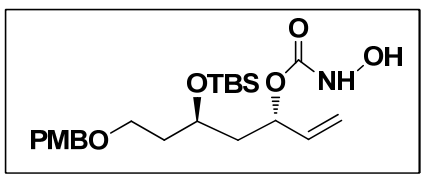
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.04 (s, 3H), 0.06 (s, 3H), 0.88 (s, 9H), 1.67-1.86 (m, 4H), 3.52 (t, *J* = 6.6 Hz, 2H), 3.81 (s, 3H), 3.87-3.98 (m, 1H), 4.42 (s, 2H), 4.80 (brs, 1H), 5.12-5.30 (m, 3H), 5.71-5.90 (m, 1H), 6.88 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 8.7 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.9, -4.6, 18.0, 25.8, 37.6, 42.1, 55.2, 66.2, 66.4, 72.5, 72.6, 113.7, 115.7, 129.2, 130.5, 136.9, 156.3, 159.

MS(ESI) m/z: 446.63 $(M+Na)^+$.

Analysis: Calcd.: C, 62.38; H, 8.80; N, 3.31%; **Found:** C, 62.32; H, 8.75, N, 3.3%.

(3*S*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-7-(4-methoxybenzyloxy)hept-1-en-3-ylhydroxycarbamate (45):



N,*N*- Carbonyldiimidazole (1.70 g, 10.50 mmol) was added to the alcohol **40** (2.0 g, 5.25 mmol) in pyridine at 40 ^{o}C. Hydroxyl amine hydrochloride (0.803 g, 11.56 mmol) was added

after complete adduct formation between alcohol and CDI (~ 4 h). The reaction was stirred for 24 h at 40 ^{o}C, quenched with 1M HCl, partitioned and aqueous layer extracted with diethyl ether and ethyl acetate. The combined organic layer was washed with water and brine, dried. The solvent was azeotropically removed with toluene. The crude product was purified by flash column chromatography on silica gel using petroleum ether/EtOAc (8:2) as eluent to give hydroxylamine **45** as colorless oil.

Yield: 1.96 g, 85%.

Mol. Formula: $C_{22}H_{37}NO_6Si$

$[\alpha]_D^{25}$: -11.40 (*c* 1, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 3253, 1700, 1516, 1306, 1256, 1138, 971, 771, 694.

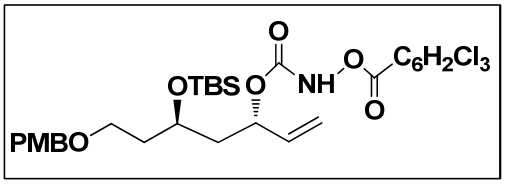
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.03 (s, 3H), 0.05 (s, 3H), 0.88 (s, 9H), 1.71-1.88 (m, 4H), 3.52 (t, *J* = 6.3 Hz, 2H), 3.81 (s, 3H), 3.85-3.97 (m, 1H), 4.41 (ABq, *J* = 11.4 Hz, 2H), 5.14-5.33 (m, 3H), 5.75-5.86 (m, 1H), 6.88 (d, *J* = 8.6 Hz, 2H), 7.25 (d, *J* = 8.6 Hz, 2H), 7.35 (brs, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.6, -4.5, 18.0, 25.8, 36.6, 41.9, 55.2, 66.3, 66.4, 72.6, 73.8, 113.7, 117.0, 129.5, 130.2, 136.2, 158.4, 159.1.

MS(ESI) m/z: 462 $(M+Na)^+$, 478 $(M+K)^+$.

Analysis: Calcd.: C, 60.11; H, 8.48; N, 3.19%; **Found:** C, 60.17; H, 8.56, N, 3.2%.

(3*S*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-7-(4-methoxybenzyloxy)hept-1-en-3-yl-2,4,6-trichlorobenzoyloxycarbamate (47) :



To an ice-cold solution of hydroxycarbamate **45** (1.0 g, 2.27 mmol) in Et_2O (4:1; 5 ml/mmol) was added Et_3N (0.348 mL, 2.50 mmol), before the addition of the 2,4,6-trichlorobenzoyl chloride (0.355 mL, 2.27 mmol) in small portions. The reaction was quenched with HCl (1M aq. sol., 25 mL) and the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed sequentially with water (30 ml), $NaHCO_3$ (aq. sat. sol., 30 ml) and brine (30 ml), dried ($NaSO_4$), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography using petroleum ether/ethyl acetate (97:3) as eluent to give *O*-trichlorobenzoyl substituted hydroxylamine **47** as pale yellow oil.

Yield: 1.32 g, 90%.

Mol. Formula: $C_{29}H_{38}Cl_3NO_7Si$

$[\alpha]_D^{25}$: -3.19 (*c* 1.2, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 3425, 2965, 1760, 1740, 1652, 1471, 1101, 1036, 971, 869, 758.

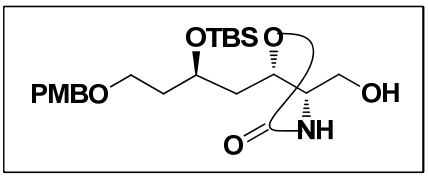
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.04 (s, 3H), 0.05 (s, 3H), 0.88 (s, 9H), 1.66-1.87 (m,4H), 3.52 (t, *J* = 6.5 Hz, 2H), 3.80 (s, 3H), 3.87-4.02 (m, 1H), 4.41 (ABq, *J* = 11.8 Hz, 2H), 5.14-5.45 (m, 3H), 5.72-5.88 (m, 1H), 6.87 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.38-7.40 (m, 2H), 8.4 (brs, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.9, -4.4, 17.9, 25.8, 37.5, 42.0, 55.2, 66.0, 66.2, 72.5, 75.3, 113.7, 117.3, 128.2, 129.1, 130.4, 133.6, 135.5, 135.8, 137.6, 155.1, 159.0, 163.

MS(ESI) m/z: 670 $(M+Na)^+$.

Analysis: Calcd.: C, 53.83; H, 5.92; N, 2.16%; **Found:** C, 53.56; H, 6.21, N, 2.26%.

(4*R*,5*R*)-5-((*R*)-2-(*tert*-Butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)butyl)-4-(hydroxymethyl)oxazolid-in-2-one (44):



To a solution of *O*-trichlorobenzoyl substituted hydroxycarbamate **47** (0.50 g, 0.772 mmol) in *t*-butanol and water 30 mL (3:1, 40 mL/mmol) was added dropwise a solution of potassium osmate dihydrate (5 mg, 0.015 mmol, 2 mol %) in water (5 mL). The reaction was quenched by addition of sodium sulfite (200 mg/mmol) and the solvent azeotropically removed with toluene. The crude product was purified by flash column chromatography on silica gel using petroleum ether/EtOAc (6:4) as eluent to afford the aminohydroxylated product **44** as colorless syrupy oil.

Yield: 0.25 g, 75%.

Mol. Formula: $C_{22}H_{37}NO_6Si$

$[\alpha]_D^{25}$: -27.33 (*c* 1.3, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 3386, 2930, 1698, 1490, 1435, 1285, 1072, 818, 768.

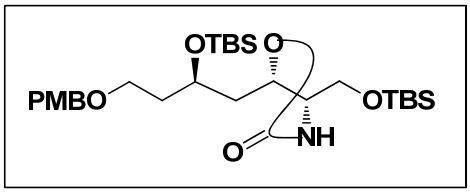
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.07 (s,3H), 0.08 (s, 3H), 0.87 (s, 9H), 1.64-1.90 (m, 4H), 3.13-3.34 (brs, 1H), 3.46-3.64 (m, 5H), 3.80 (s, 3H), 4.04-4.09 (m, 1H), 4.36-4.56 (m, 3H), 6.59-6.66 (brs, 1H), 6.88 (d, *J* = 8.7 Hz, 2H), 7.25 (d, *J* = 8.7 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ -4.8, -4.5, 18.0, 25.8, 37.8, 43.0, 55.2, 59.6, 63.5, 65.9, 66.1, 72.6, 75.9, 113.8, 129.3, 130.3, 159.1, 159.5.

MS(ESI) m/z: 462 $(M+Na)^+$.

Analysis: Calcd.: C, 60.11; H, 8.48; N, 3.19%; **Found:** C, 60.18; H, 8.41, N, 3.11%.

(4*R*,5*R*)-5-((*R*)-2-(*tert*-Butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)butyl)-4-((*tert*-butyldimethylsilyloxy)methyl)oxazolidin-2-one (50):



To a stirred solution of alcohol **44** (0.20 g, 0.454 mmol) in CH_2Cl_2 was added imidazole (46 mg, 0.682 mmol). To this solution *t*-butyl dimethylchlorosilane (102 mg, 0.682 mmol) was added at 0 ^oC and the reaction was stirred at rt for 6 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4), concentrated and purified using silica gel chromatography of crude product using EtOAc/petroleum ether (2:8) as eluent to give the protected aminohydroxylated product **50** as a thick colorless liquid.

Yield: 0.214 g, 85%.

Mol. Formula: $C_{28}H_{51}NO_6Si_2$

$[\alpha]_D^{25}$: -33.33 (*c* 1, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 3289, 2900, 1690, 1101, 1044, 971, 869, 769.

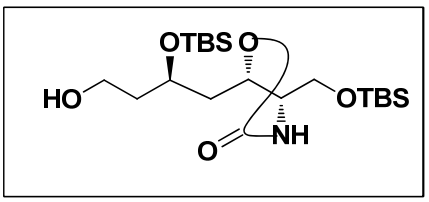
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.06-0.07 (m, 12H), 0.87-0.88 (m, 18H), 1.59-1.95 (m, 4H), 3.42-3.59 (m, 5H), 3.81 (s, 3H), 4.02-4.14 (m, 1H), 4.4 (ABq, *J* = 11.5 Hz, 2H), 4.46-4.45 (m, 1H), 5.85 (brs, 1H) 6.88 (d, *J* = 8.6 Hz, 2H), 7.25 (d, *J* = 8.6 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 5.6, -4.8, -4.5, 18.0, 18.1, 25.7, 25.8, 37.9, 43.2, 55.2, 59.2, 64.4, 65.9, 66.0, 72.6, 76.2, 113.7, 129.2, 130.4, 159.1, 159.3.

MS(ESI) m/z: 576 $(M+Na)^+$.

Analysis: Calcd.: C, 60.72; H, 9.28; N, 2.53%; **Found:** C, 60.67; H, 9.35, N, 2.47%.

(4*R*,5*R*)-5-((*R*)-2-(*tert*-Butyldimethylsilyloxy)-4-hydroxybutyl)-4-((*tert*-butyldimethyl silyloxy)methyl)oxazolidin-2-one (51):



To a stirring solution of PMB ether **50** (200 mg, 0.374 mmol) in CH_2Cl_2/H_2O (20:1) was added DDQ (170 mg, 0.749 mmol). The resulting mixture was stirred for 3 h at 0 ^oC. The

mixture was poured into saturated aqueous $NaHCO_3$ and further diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The solvents were removed under reduced pressure to give the crude product mixture as yellow oil. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (1:1) as eluent gave **51** as a colorless solid.

Yield: 0.145 g, 93%.

Mol. Formula: $C_{20}H_{43}NO_5Si_2$

$[\alpha]_D^{25}$: -30.18 (*c* 1, $CHCl_3$).

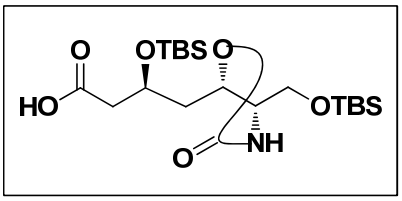
IR (neat, cm^{-1}): ν_{max} 3251, 2929, 1688, 1451, 1101.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.11 (s, 3H), 0.12 (s, 3H), 0.88-0.89 (m, 18H), 1.66-1.72 (m, 1H), 1.77-1.83 (m, 1H), 1.85-1.92 (m, 2H), 2.27 (brs, 1H), 3.47-3.50 (m, 1H), 3.59-3.60 (m, 2H), 3.70-3.74 (m, 1H), 3.79-3.84 (m, 1H), 4.15-4.20 (m, 1H), 4.50-4.54 (m, 1H), 6.14 (brs, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ -4.9, -4.5, 17.9, 18.1, 25.7, 25.8, 39.2, 42.6, 59.2, 59.3, 64.3, 67.1, 76.2, 159.3.

MS(ESI) m/z: 456 $(M+Na)^+$.

(*S*)-3-(*tert*-Butyldimethylsilyloxy)-4-((4*R*,5*R*)-4-((*tert*-butyldimethylsilyloxy)methyl)-2-oxooxazolidin-5-yl)butanoic acid (52):



A solution of oxalyl chloride (0.087 g, 0.060 mL, 0.691 mmol) in dry CH_2Cl_2 (10 mL) at -78 ^oC was added dropwise dry DMSO (0.108 g, 0.098 mL, 1.38 mmol) in CH_2Cl_2 (2 mL). After 30 min, alcohol **51** (200 mg, 0.461 mmol) in CH_2Cl_2 (3 mL) was added over 10 min giving a copious white precipitate. After stirring for 1 h at -78 ^oC the reaction mixture was brought to -60 ^oC and Et_3N (0.205 g, 0.282 mL, 2.02 mmol) was added slowly and stirred for 30 min allowing the reaction mixture to warm to room temperature. The reaction mixture was poured into water (10 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL) and combined organic layers were washed with water (3 x 10 mL), brine (20 mL), dried (Na_2SO_4) and passed through short pad of silica gel. The filtrate was

concentrated to give the aldehyde (180 mg) as pale yellow syrup, which was used as such for the next step without further purification.

A solution of 79% $NaClO_2$ (56 mg, 0.625 mmol) in 1.0 mL of water was added dropwise a stirred solution of above crude aldehyde (180 mg, 0.416 mmol) in 0.5 mL of DMSO and NaH_2PO_4 (37 mg, 0.312 mmol) in 1.0 mL of water over a period of 5 min at room temperature. The mixture was left overnight at room temperature, then 5% aqueous solution of $NaHCO_3$ was added. The aqueous phase was extracted three times with CH_2Cl_2 and washed with brine, dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (2:8) as eluent gave the acid **52** as a yellowish solid.

Yield: 0.150 g, 73%.

Mol. Formula: $C_{20}H_{41}NO_6Si_2$

M.P.: 68 ^oC.

$[\alpha]_D^{25}$: -13.45 (*c* 0.5, $CHCl_3$).

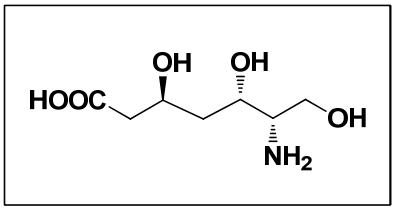
IR (neat, cm^{-1}): ν_{max} 3400, 2957, 1730, 1652.

^1H NMR (200 MHz, $CDCl_3$): δ 0.06-0.13 (m, 12H), 0.88 (s, 18H), 1.79-1.96 (m, 2H), 2.55-2.65 (m, 2H), 3.47-3.55 (m, 1H), 3.60-3.62 (m, 2H), 4.36-4.52 (m, 1H), 4.54-4.61 (m, 1H), 6.09 (brs, 1H), 9.82 (brs, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ -5.3, -4.6, -4.3, 18.1, 18.3, 26.0, 39.5, 45.8, 59.4, 64.6, 67.3, 76.5, 159.6, 178.5.

Analysis: Calcd.: C, 53.65; H, 9.23; N, 3.13%; **Found:** C, 53.56; H, 9.2, N, 3.18%.

(3*S*,5*S*,6*S*)-6-Amino-3,5,7-trihydroxyheptanoic acid (-)-galantinic acid (1):



To a stirred solution of TA product **52** (100 mg, 0.223 mmol) in methanol (3 mL) was added potassium carbonate (92 mg, 0.67 mmol) and the reaction mixture was stirred until completion of the starting material (6 h) and methanol was removed in vacuo. Water was added to the crude product and extracted with ethyl acetate (3 x 3 mL) and dried over sodium sulphate and concentrated to near dryness which was subsequently treated with 2N HCl to afford crude crystals of **1**. These were recrystallized from H_2O/MeOH to give pure (-)-galantinic acid **1**.

Yield: 23 mg, 55%.

M.P. : 128 ^{o}C (lit.[3] 125 -130 ^{o}C).

$[\alpha]_D^{25}$: -29.7 (*c*, 0.5, H_2O); {(lit.[2] $[\alpha]_D^{25}$ -29.4)}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.51-1.83 (m, 2H), 2.37 (dd, *J* = 5.8, 13.6 Hz, 1H), 2.49 (dd, *J* = 6.5, 13.8 Hz, 1H), 3.13 (dt, *J* = 7.0, 12.2 Hz, 1H), 3.61 (q, *J* = 8.3, 14.9 Hz, 1H), 3.91-4.21 (m, 3H).

MS (ESI) m/z: 194 $(M+H)^+$

3.1.5. Spectra

1. ^{1}H & ^{13}C NMR spectra of **33**

2. HPLC spectra of **33**

3. ^{1}H & ^{13}C spectra of **35**

4. ^{1}H & ^{13}C NMR spectra of **36**

5. ^{1}H & ^{13}C NMR spectra of **38**

6. ^{1}H & ^{13}C NMR spectra of **40**

7. ^{13}C NMR spectra of **42**

8. ^{1}H & ^{13}C NMR spectra of **43**

9. ^{1}H & ^{13}C NMR spectra of **44**

10. ^{1}H & ^{13}C NMR spectra of **47**

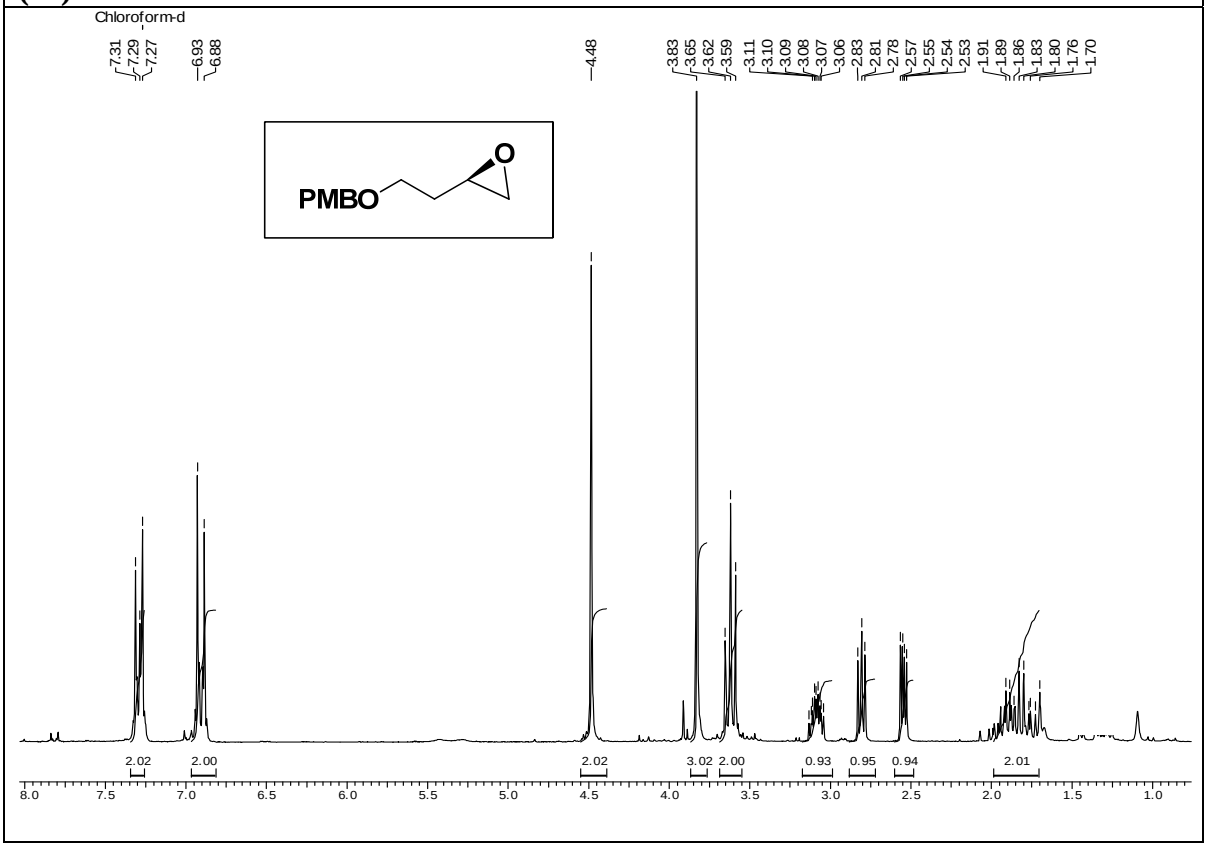
11. ^{1}H & ^{13}C NMR spectra of **50**

12. ^{1}H & ^{13}C NMR spectra of **51**

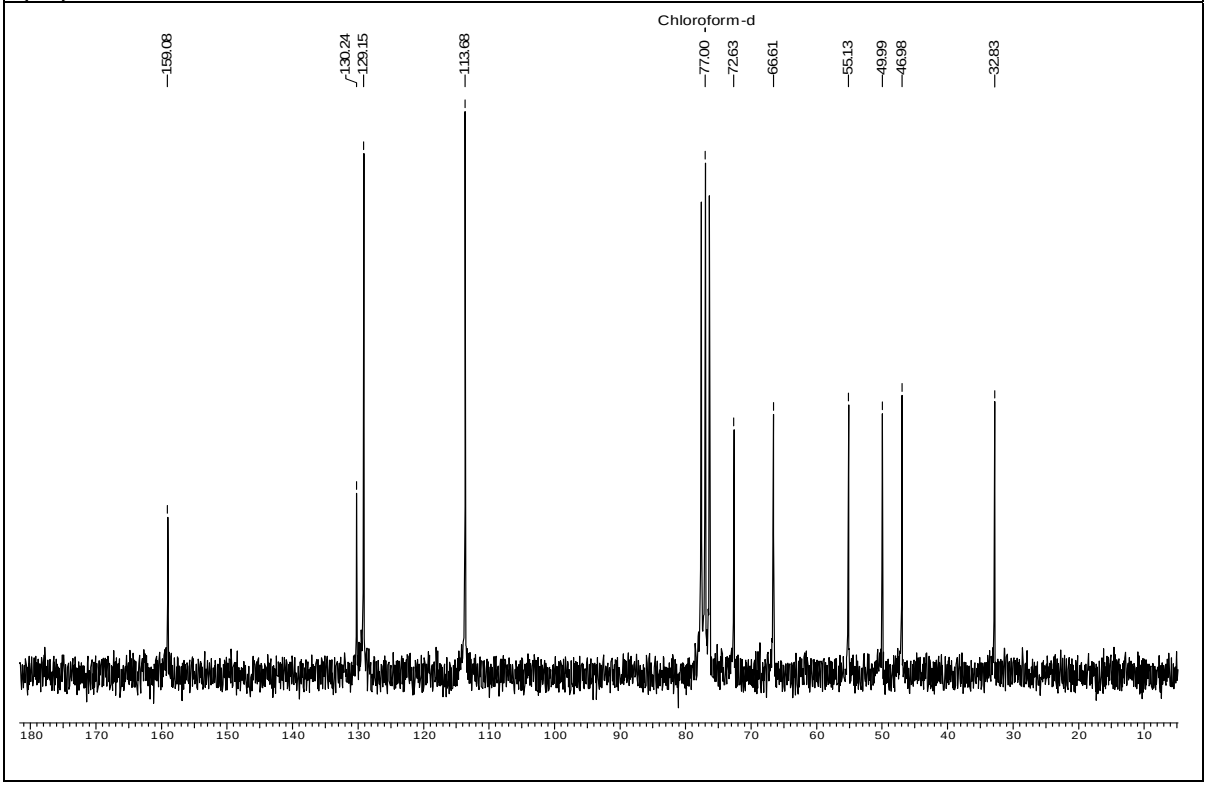
13. ^{1}H & ^{13}C NMR spectra of **52**

14. ^{1}H spectra and mass spectra of **1**

^{1}H NMR ($CDCl_3$, 200 MHz) spectra of (*R*)-2-(2-(4-Methoxybenzyloxy)ethyl)oxirane (33)

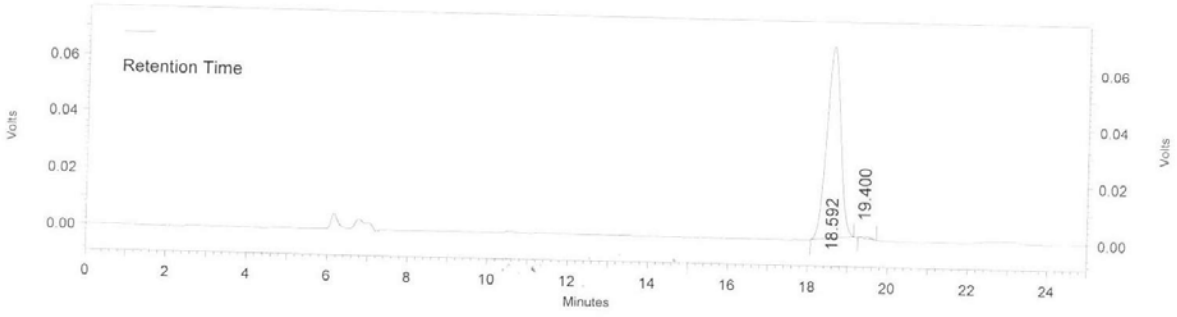


^{13}C NMR ($CDCl_3$, 50 MHz) spectra of (*R*)-2-(2-(4-Methoxybenzyloxy)ethyl)oxirane (33)



Shimadzu CLASS-VP V6.12 SP5

Method Name: C:\CLASS-VP\Method ch 2.met
Data Name: C:\CLASS-VP\Data\Dr Tripathi\Tri-1141
User: System
Acquired: 11/17/09 5:04:46 PM
Printed: 11/17/09 5:31:43 PM
Sample Name PMB- PRo (C)



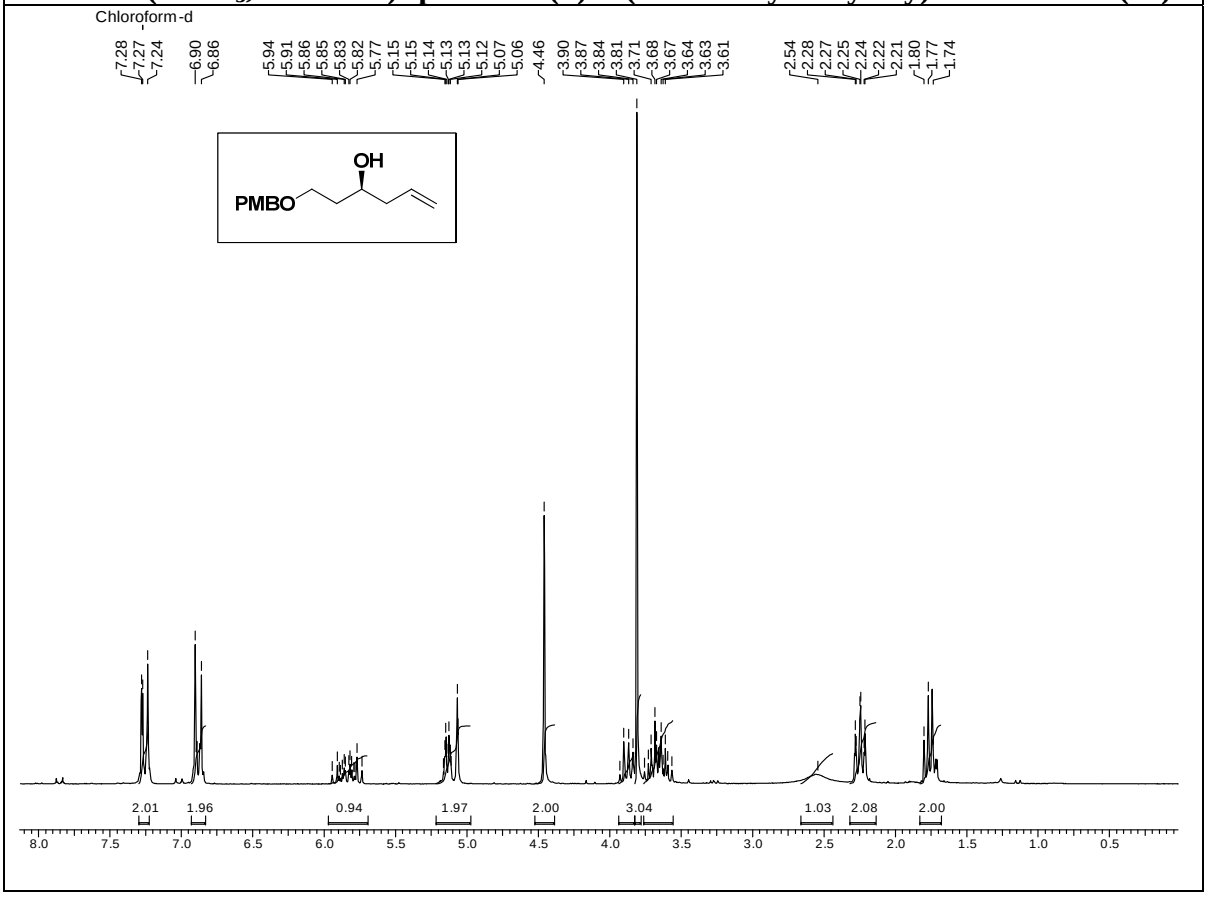
Detector A - 1
(220nm)

Pk #	Retention Time	Area	Area %	Height	Height Percent
1	18.592	1627887	99.322	67714	99.06
2	19.400	11116	0.678	641	0.94
Totals		1639003	100.000	68355	100.00

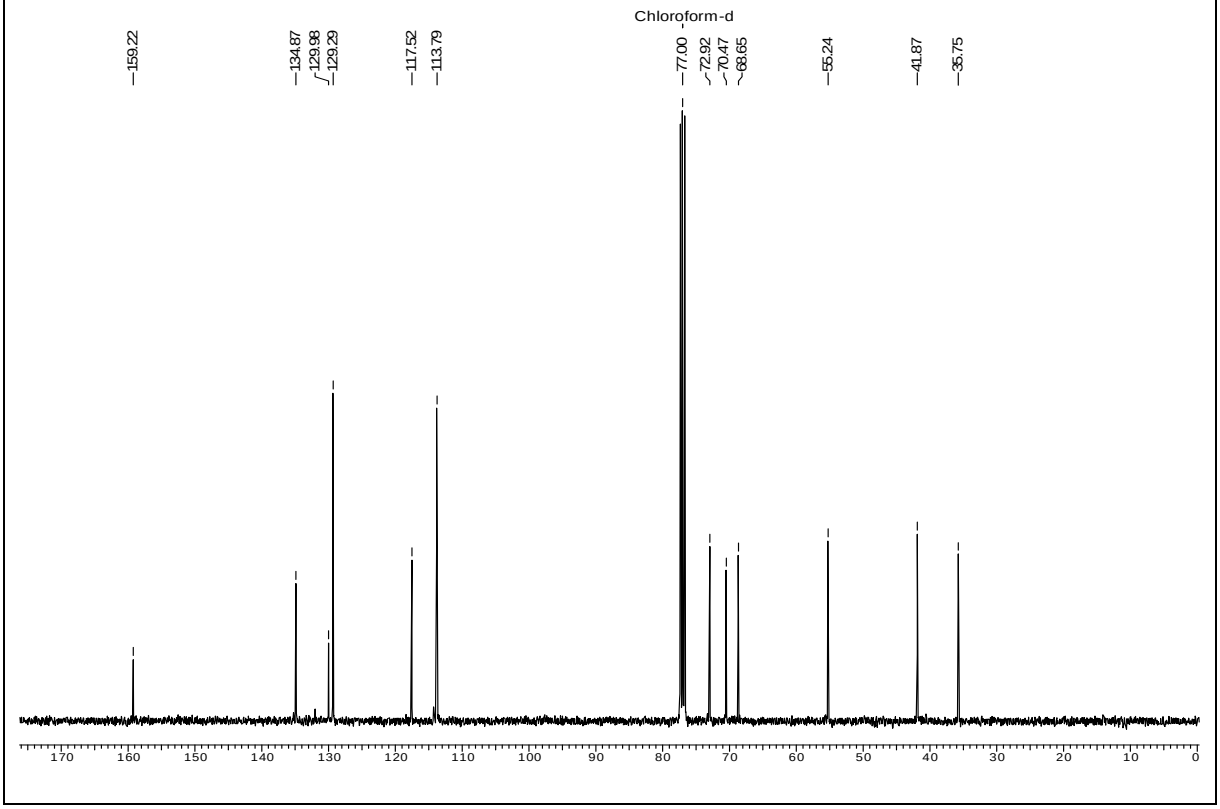
Grp Leader :Dr Tripathi P. K.
Column :Chiralcel OD-H (250x4.6mm)
Mobile Phase : IPA: PE: (04 : 96)
Wavelength : 220 nm
Flow Rate : 0.5mL/min(21Kgf)
Sample Con :1mg/ 2mL Inj vol- 2ul

Kunte

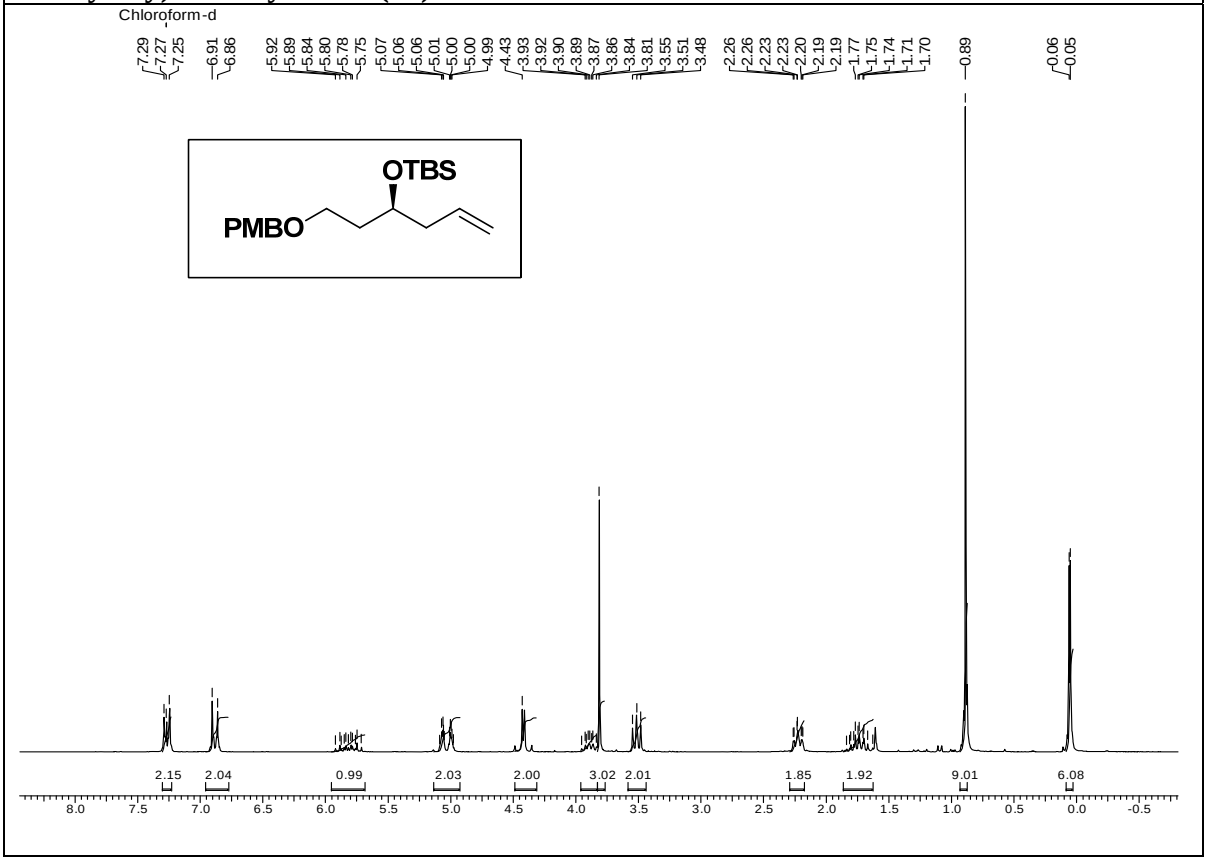
^{1}H NMR ($CDCl_3$, 200 MHz) spectra of (*S*)-1-(4-Methoxybenzyloxy)hex-5-en-3-ol (35)



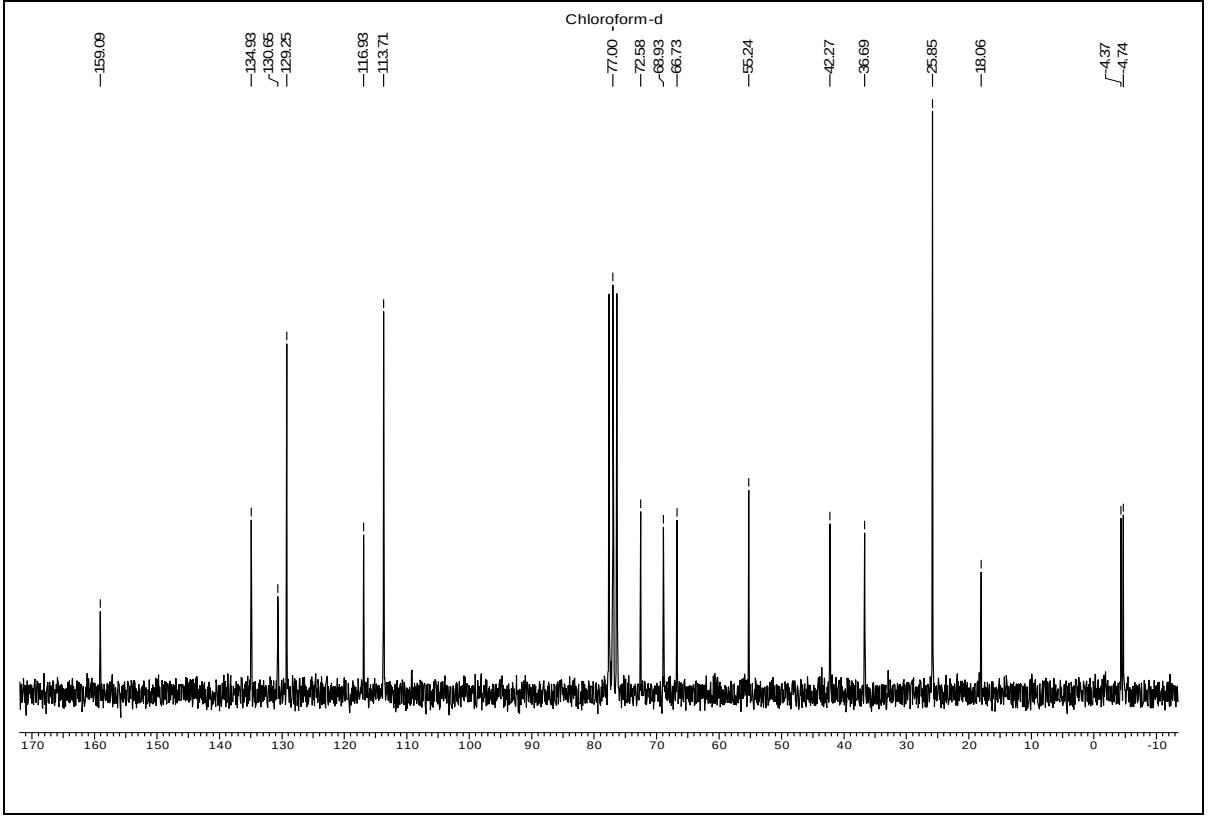
^{13}C NMR ($CDCl_3$, 125 MHz) spectra of (*S*)-1-(4-Methoxybenzyloxy)hex-5-en-3-ol (35)



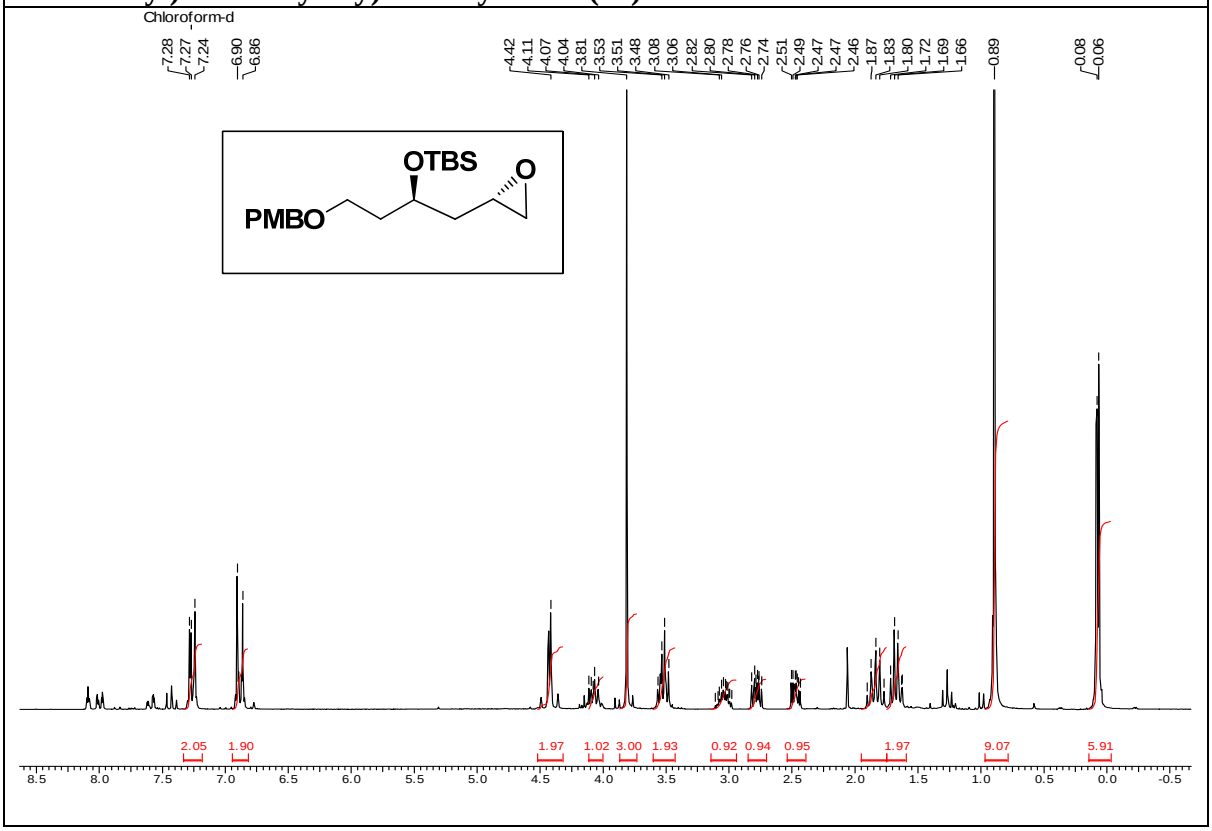
^{1}H NMR ($CDCl_3$, 200 MHz) spectra of (*S*)-*tert*-Butyl(1-(4-methoxybenzyloxy)hex-5-en-3-yloxy)dimethylsilane (36)



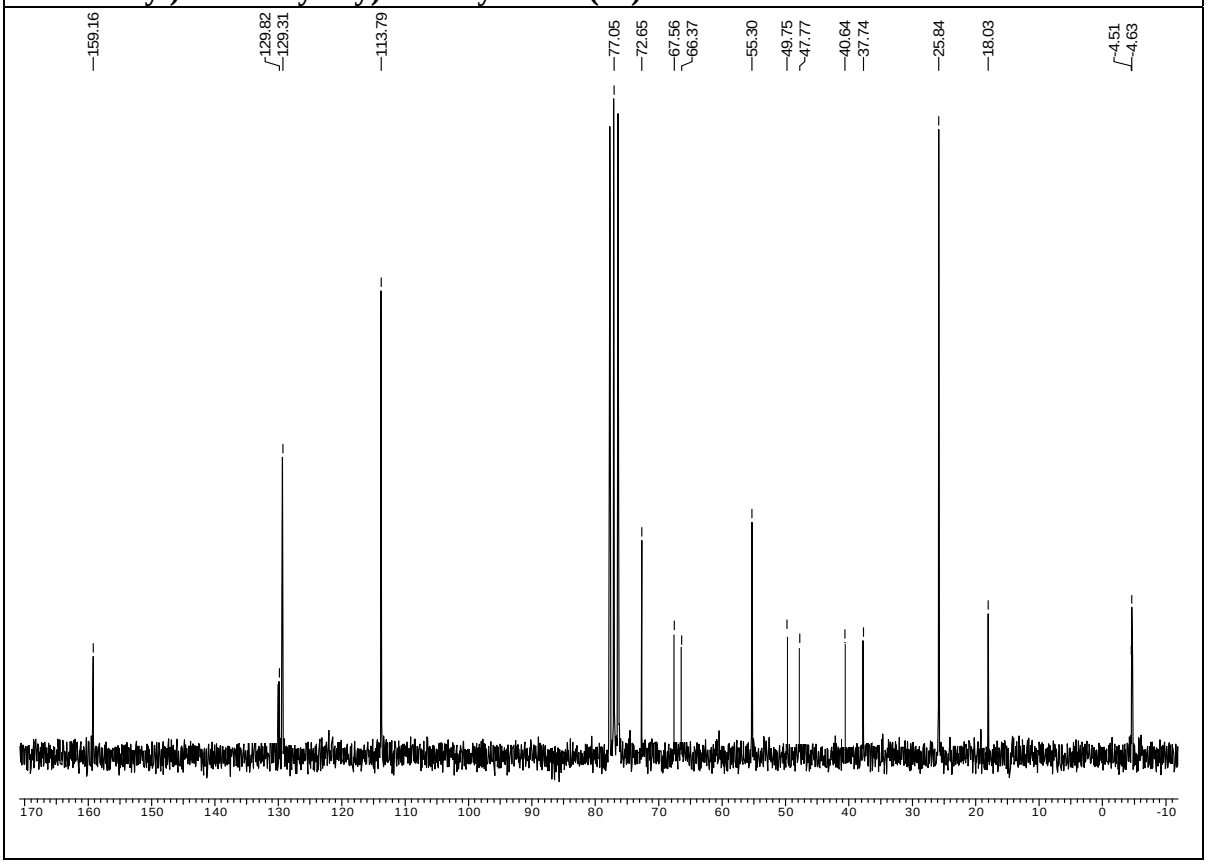
^{13}C NMR ($CDCl_3$, 50 MHz) spectra of (*S*)-*tert*-Butyl(1-(4-methoxybenzyloxy)hex-5-en-3-yloxy)dimethylsilane (36)



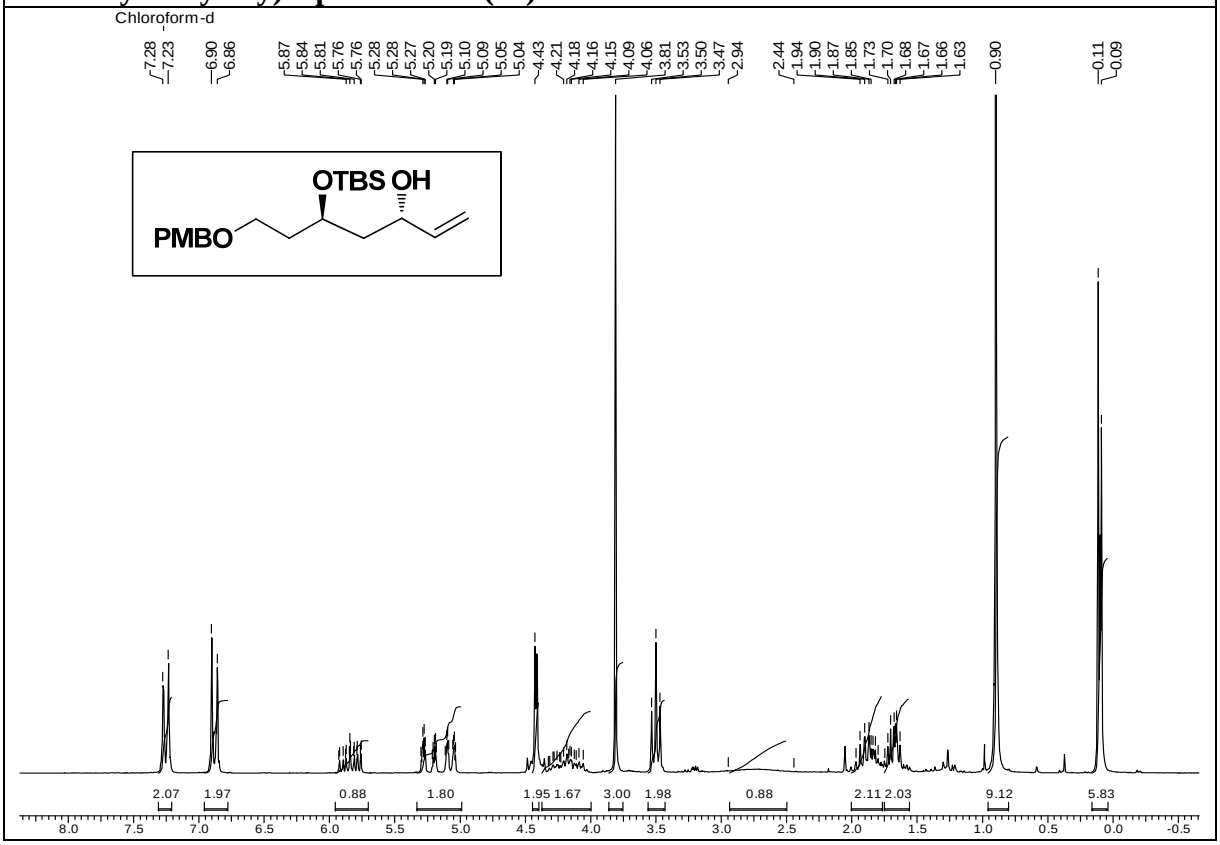
^{1}H NMR (CDCl$_3$, 200 MHz) spectra of *tert*-Butyl((*R*)-4-(4-methoxybenzyloxy)-1-((*S*)-oxiran-2-yl)butan-2-yloxy)dimethylsilane (38)



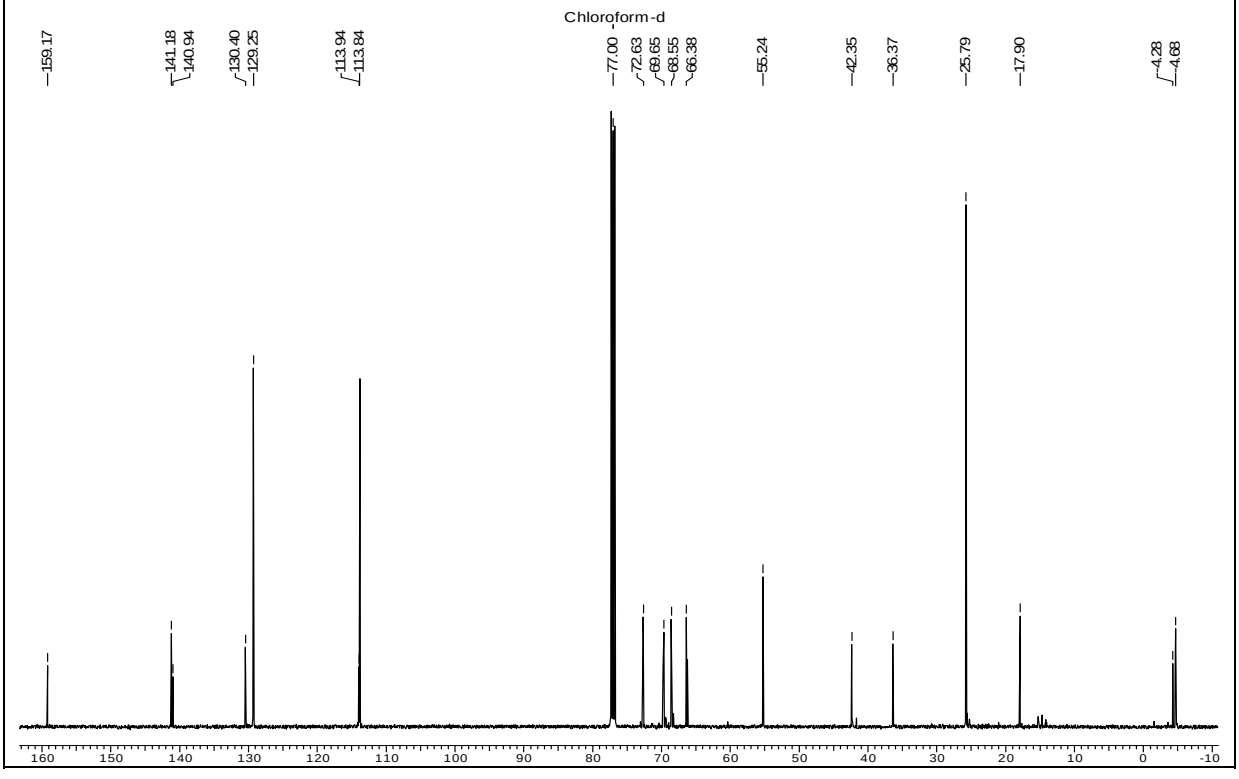
^{13}C NMR (CDCl$_3$, 50 MHz) spectra of *tert*-Butyl((*R*)-4-(4-methoxybenzyloxy)-1-((*S*)-oxiran-2-yl)butan-2-yloxy)dimethylsilane (38)



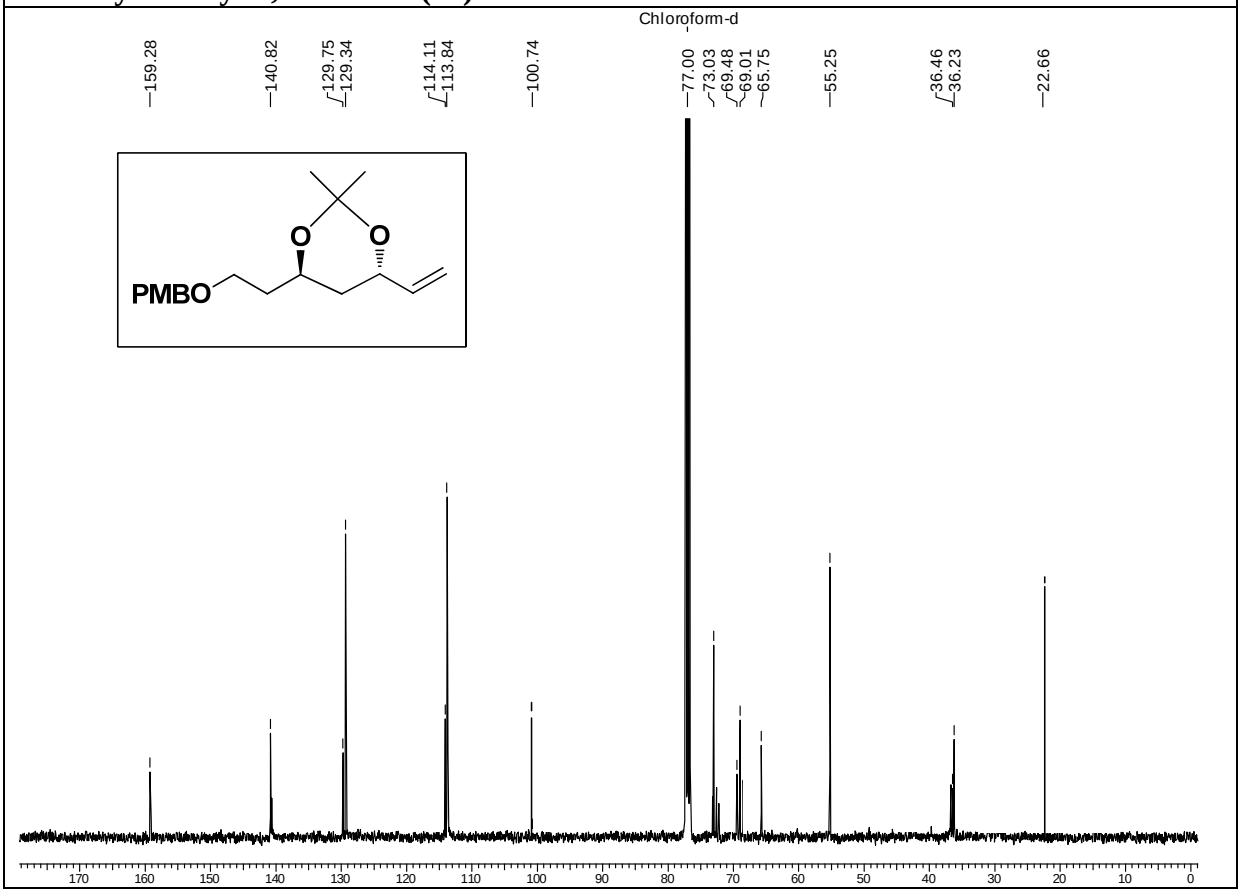
^{1}H NMR ($CDCl_3$, 200 MHz) spectra of (3*S*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-7-(4-methoxybenzyloxy)hept-1-en-3-ol (40)



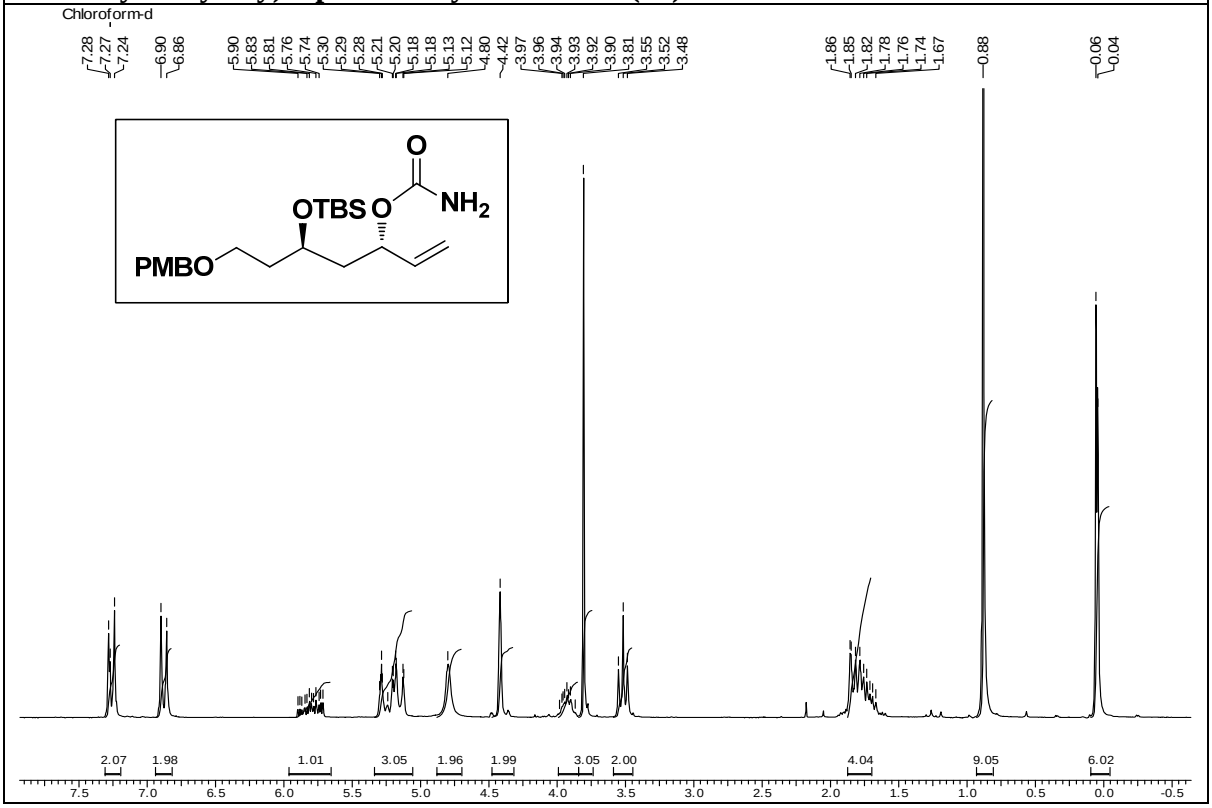
^{13}C NMR ($CDCl_3$, 50 MHz) spectra of (3*S*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-7-(4-methoxybenzyloxy)hept-1-en-3-ol (40)



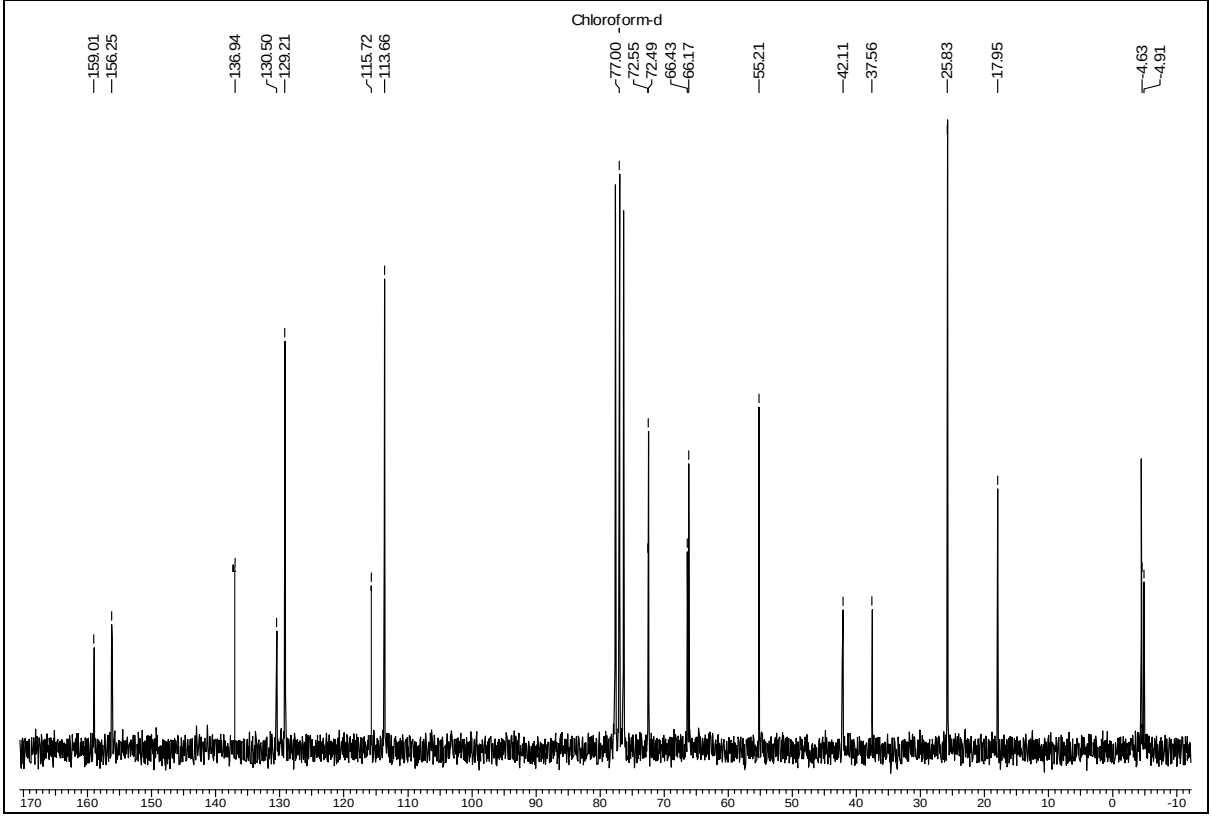
^{13}C NMR ($CDCl_3$, 100 MHz) spectra of (4*R*,6*S*)-4-(2-((4-methoxybenzyl)oxy)ethyl)-2,2-dimethyl-6-vinyl-1,3-dioxane (42)



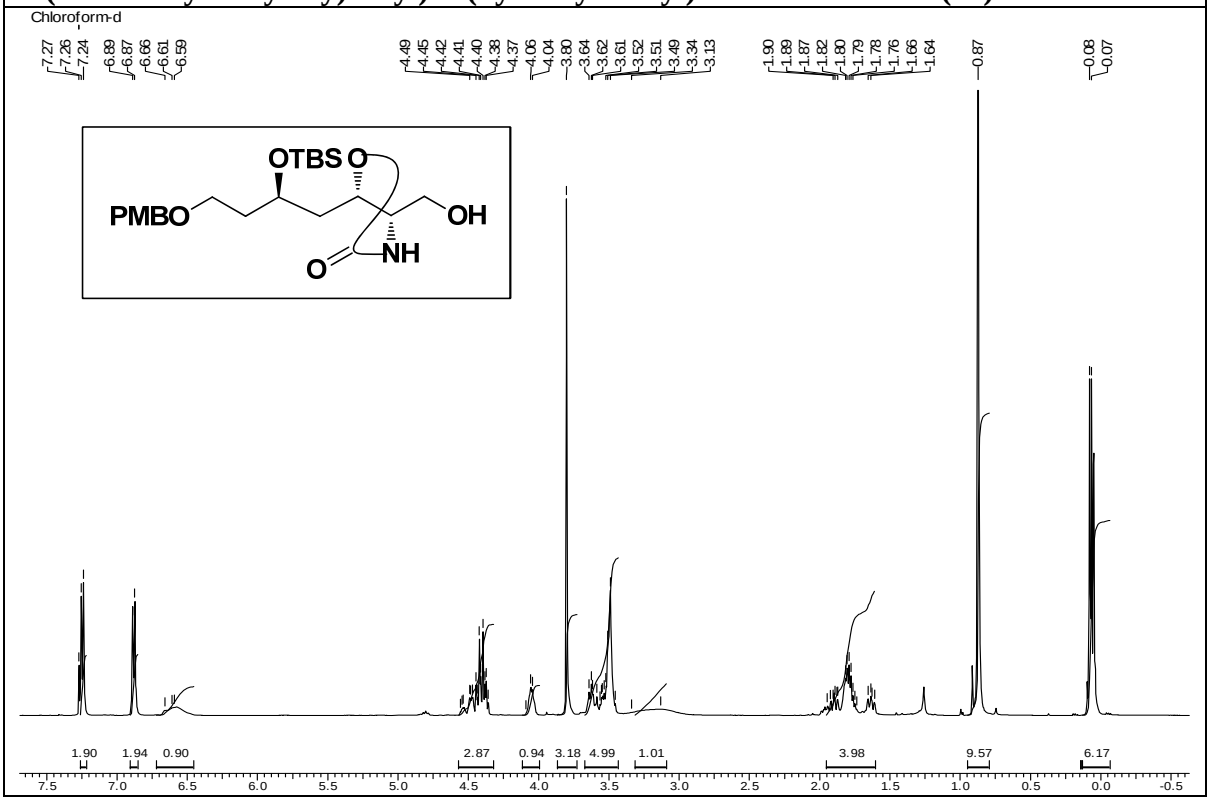
^{1}H NMR ($CDCl_3$, 200 MHz) spectra of (3*S*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-7-(4-methoxybenzyloxy)hept-1-en-3-ylcarbamate (43)



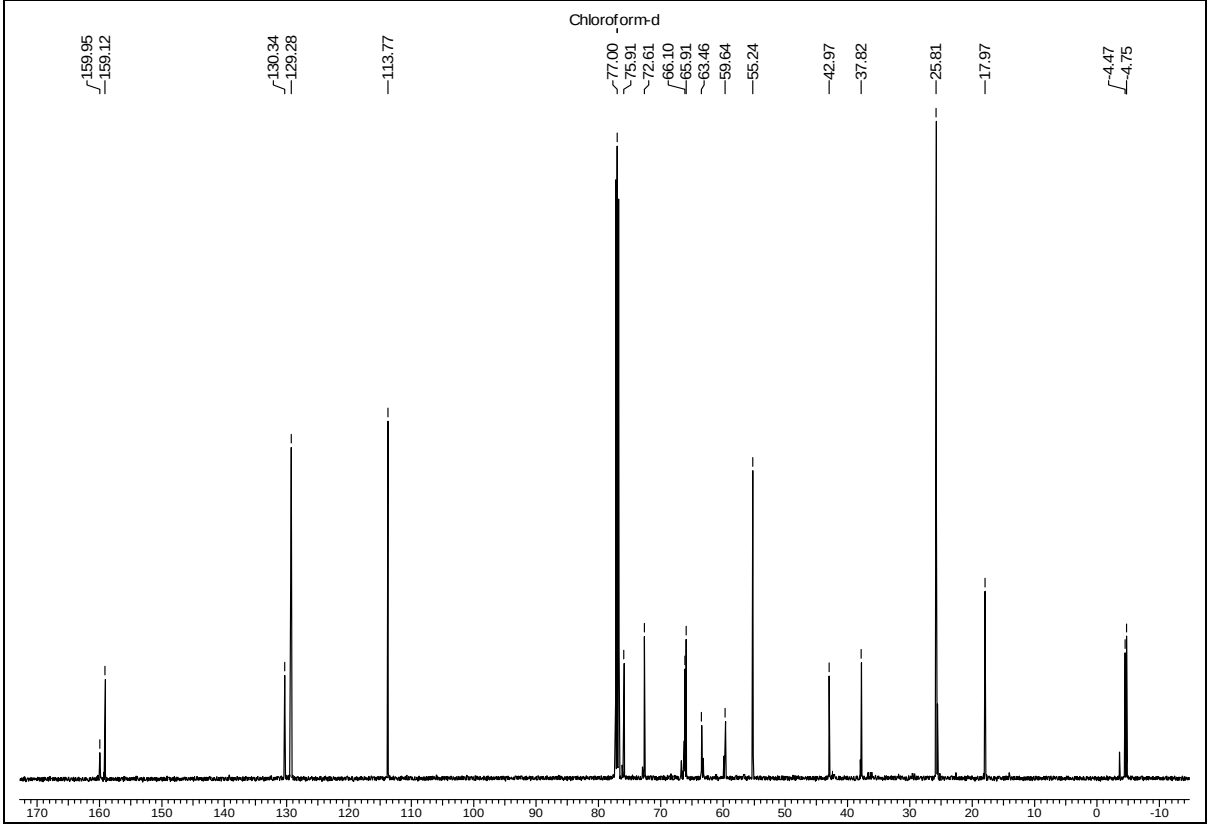
^{13}C NMR ($CDCl_3$, 50 MHz) spectra of (3*S*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-7-(4-methoxybenzyloxy)hept-1-en-3-ylcarbamate (43)



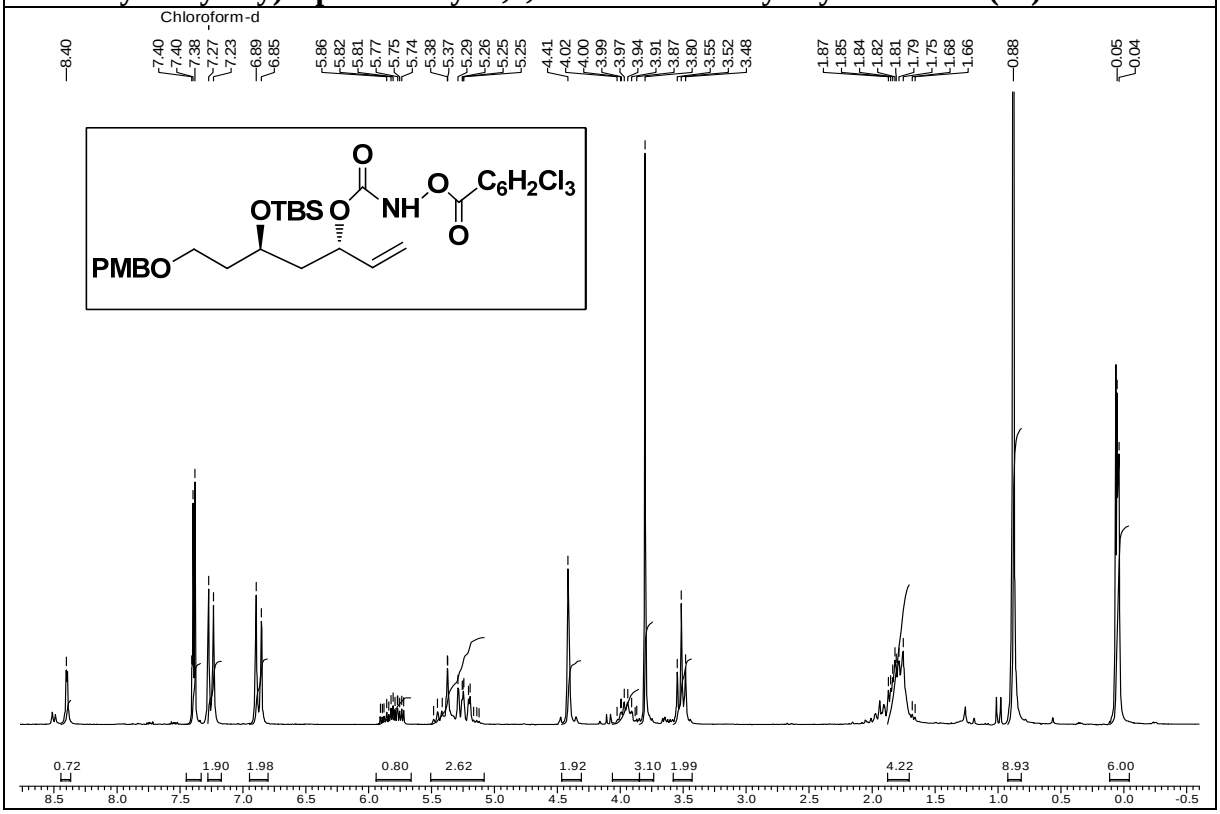
^{1}H NMR ($CDCl_3$, 500 MHz) spectra of (4*R*,5*R*)-5-((*R*)-2-(*tert*-Butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)butyl)-4-(hydroxymethyl)oxazolid-in-2-one (44)



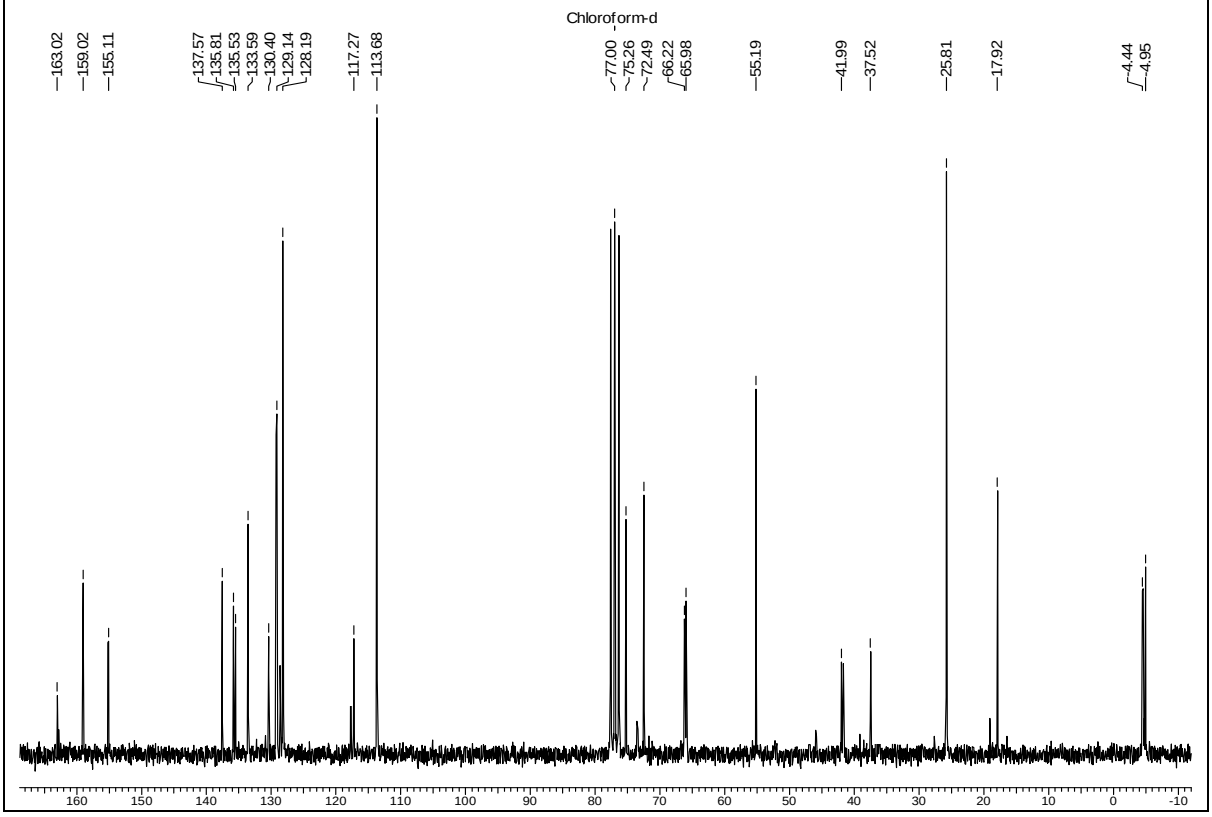
^{13}C NMR ($CDCl_3$, 125 MHz) spectra of (4*R*,5*R*)-5-((*R*)-2-(*tert*-Butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)butyl)-4-(hydroxymethyl)oxazolid-in-2-one (44)



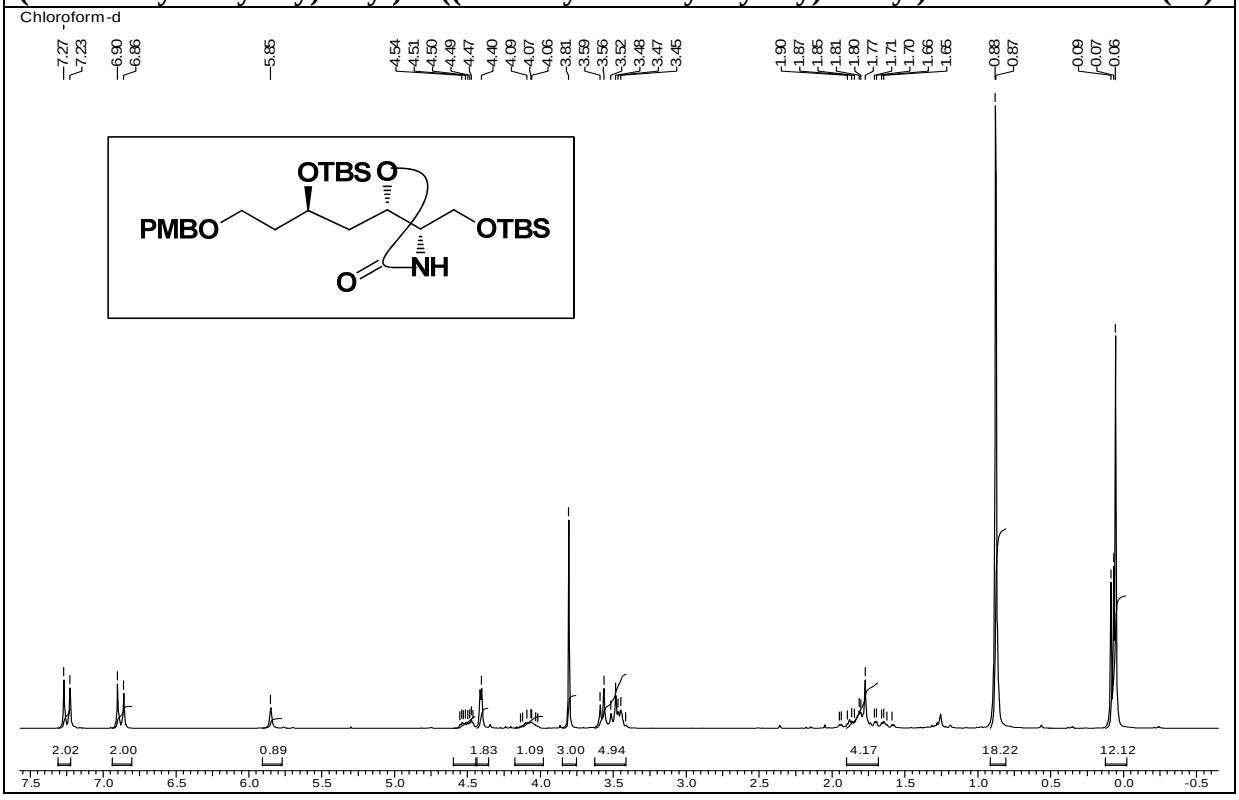
^{1}H NMR ($CDCl_3$, 200 MHz) spectra of (3*S*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-7-(4-methoxybenzyloxy)hept-1-en-3-yl-2,4,6-trichlorobenzoyloxycarbamate (47)



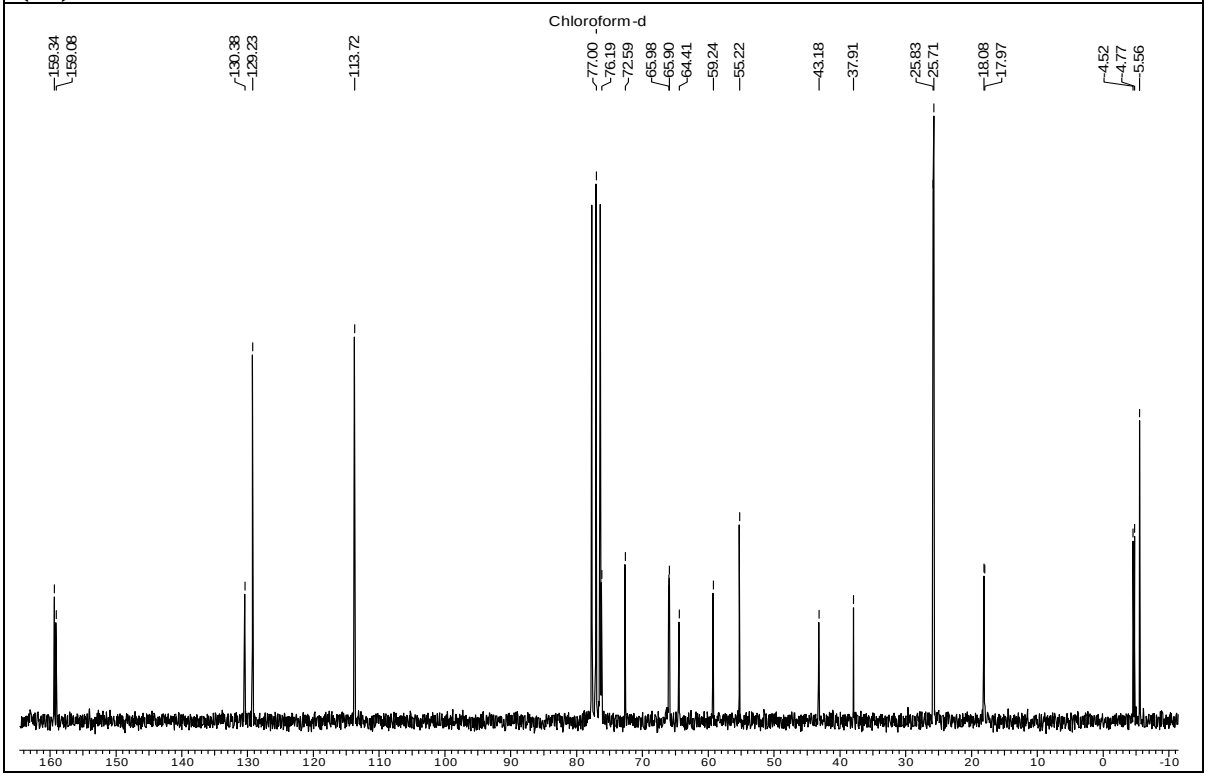
^{13}C NMR ($CDCl_3$, 50 MHz) spectra of (3*S*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-7-(4-methoxybenzyloxy)hept-1-en-3-yl-2,4,6-trichlorobenzoyloxycarbamate (47)



^{1}H NMR ($CDCl_3$, 500 MHz) spectra of (4*R*,5*R*)-5-((*R*)-2-(*tert*-Butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)butyl)-4-((*tert*-butyldimethylsilyloxy)methyl)oxazolidin-2-one (50)

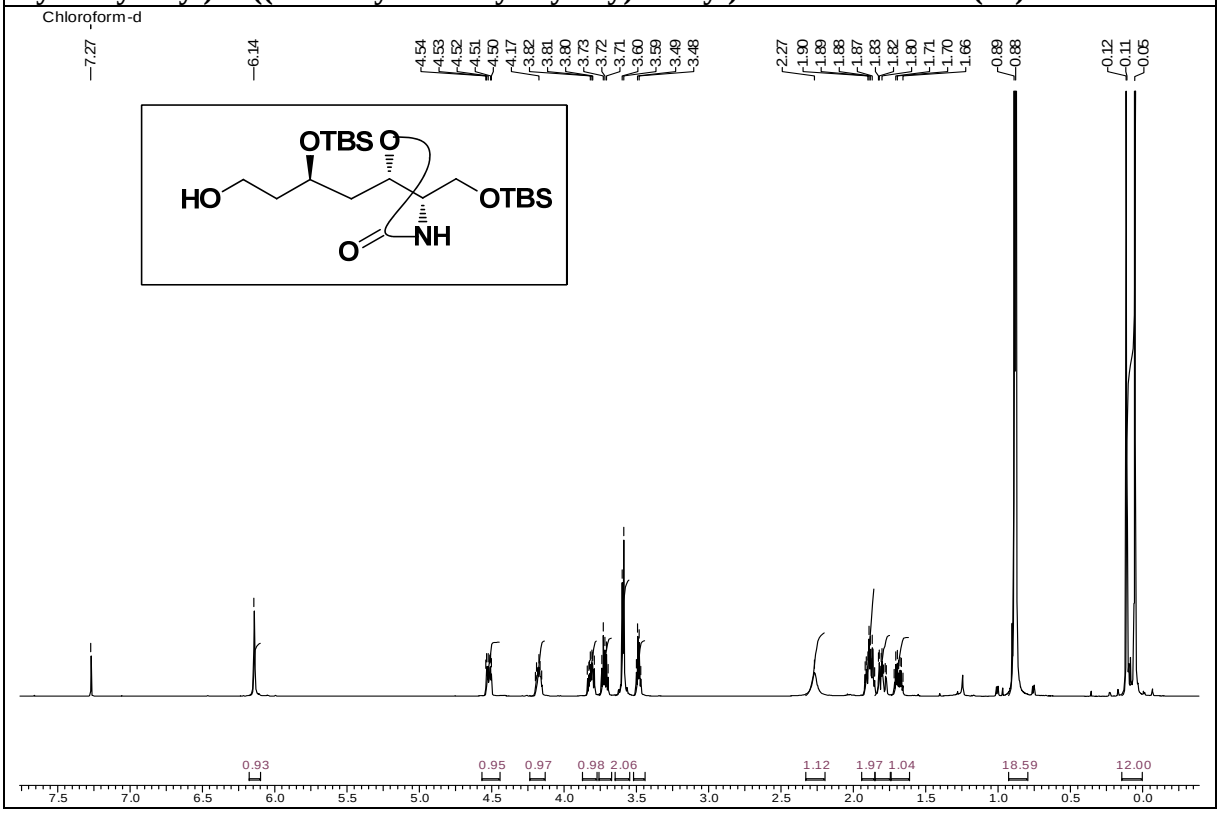


^{13}C NMR ($CDCl_3$, 125 MHz) spectra of (4*R*,5*R*)-5-((*R*)-2-(*tert*-Butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)butyl)-4-((*tert*-butyldimethylsilyloxy)methyl)oxazolidin-2-one (50)

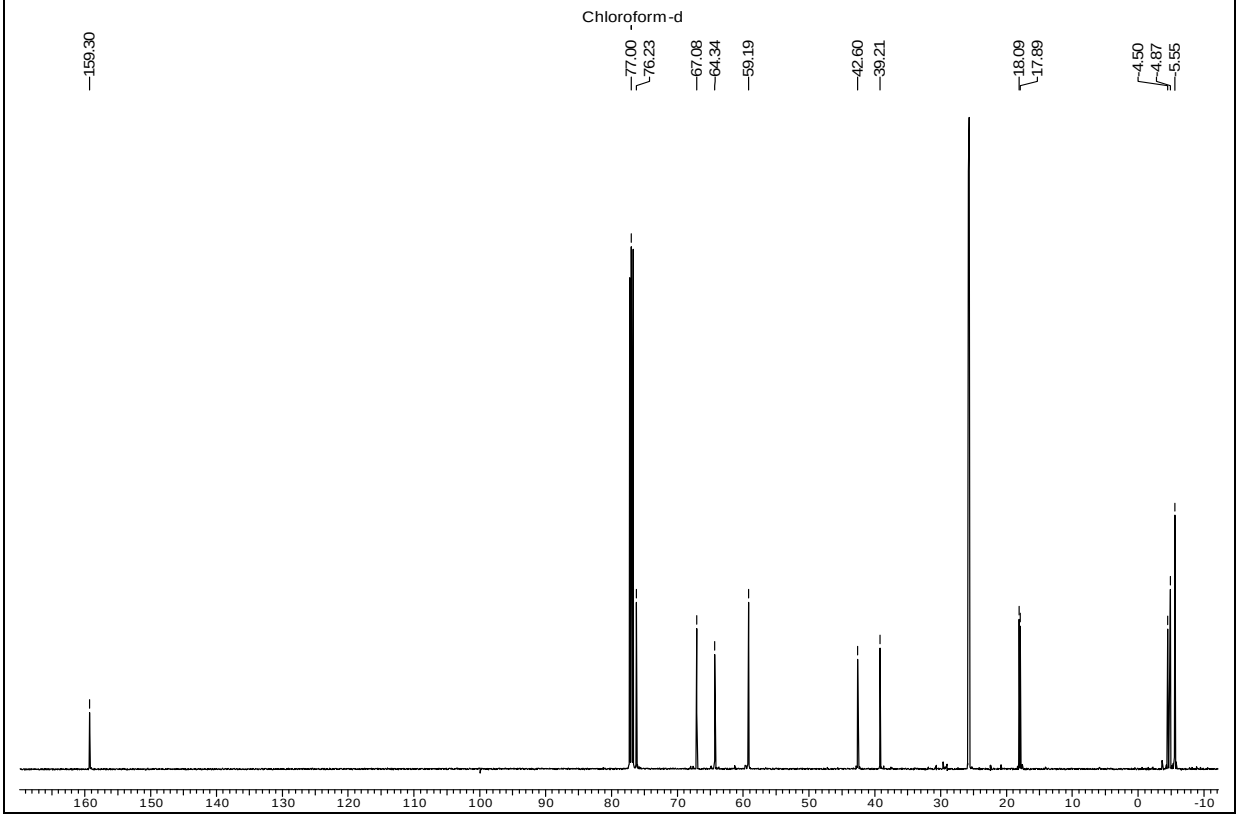


^{1}H NMR ($CDCl_3$, 400 MHz) spectra of (4*R*,5*R*)-5-((*R*)-2-(*tert*-Butyldimethylsilyloxy)-4-

hydroxybutyl)-4-((*tert*-butyldimethylsilyloxy)methyl)oxazolidin-2-one (51)

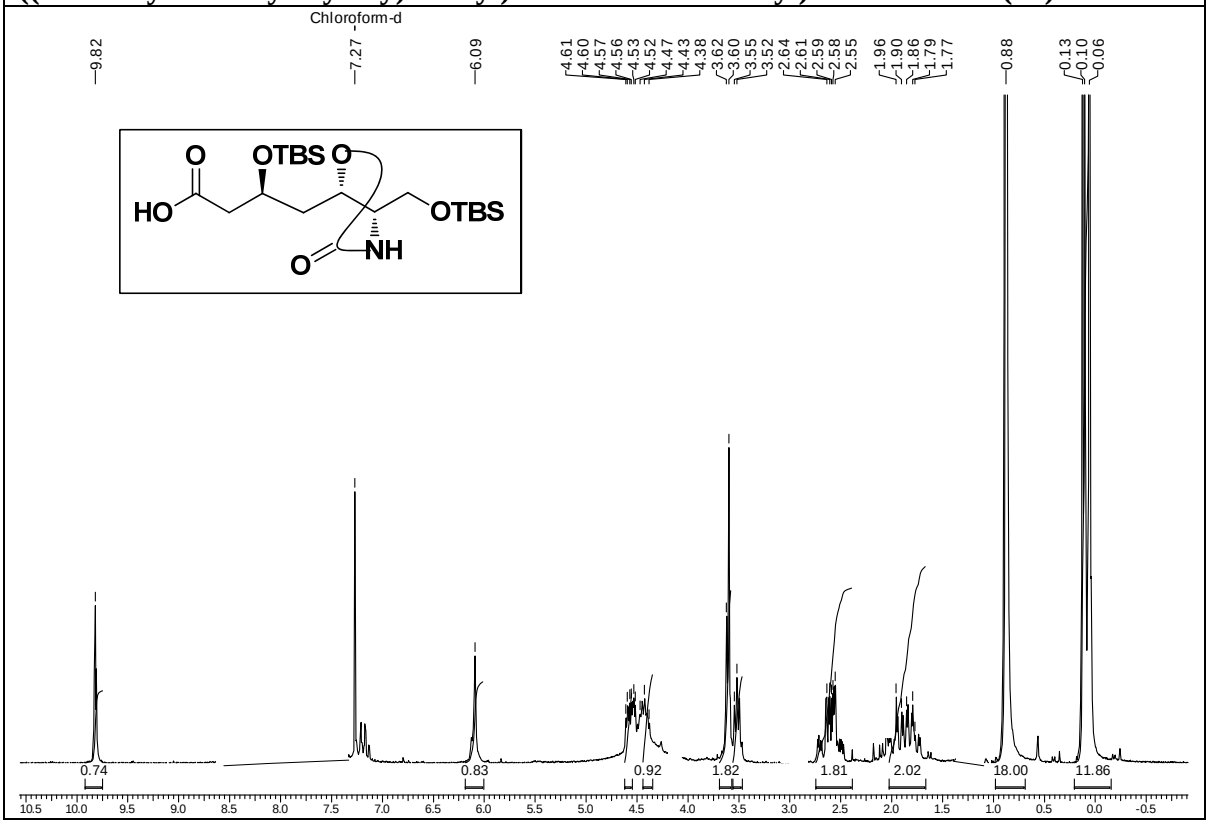


^{13}C NMR ($CDCl_3$, 100 MHz) spectra of (4*R*,5*R*)-5-((*R*)-2-(*tert*-Butyldimethylsilyloxy)-4-hydroxybutyl)-4-((*tert*-butyldimethylsilyloxy)methyl)oxazolidin-2-one (51)

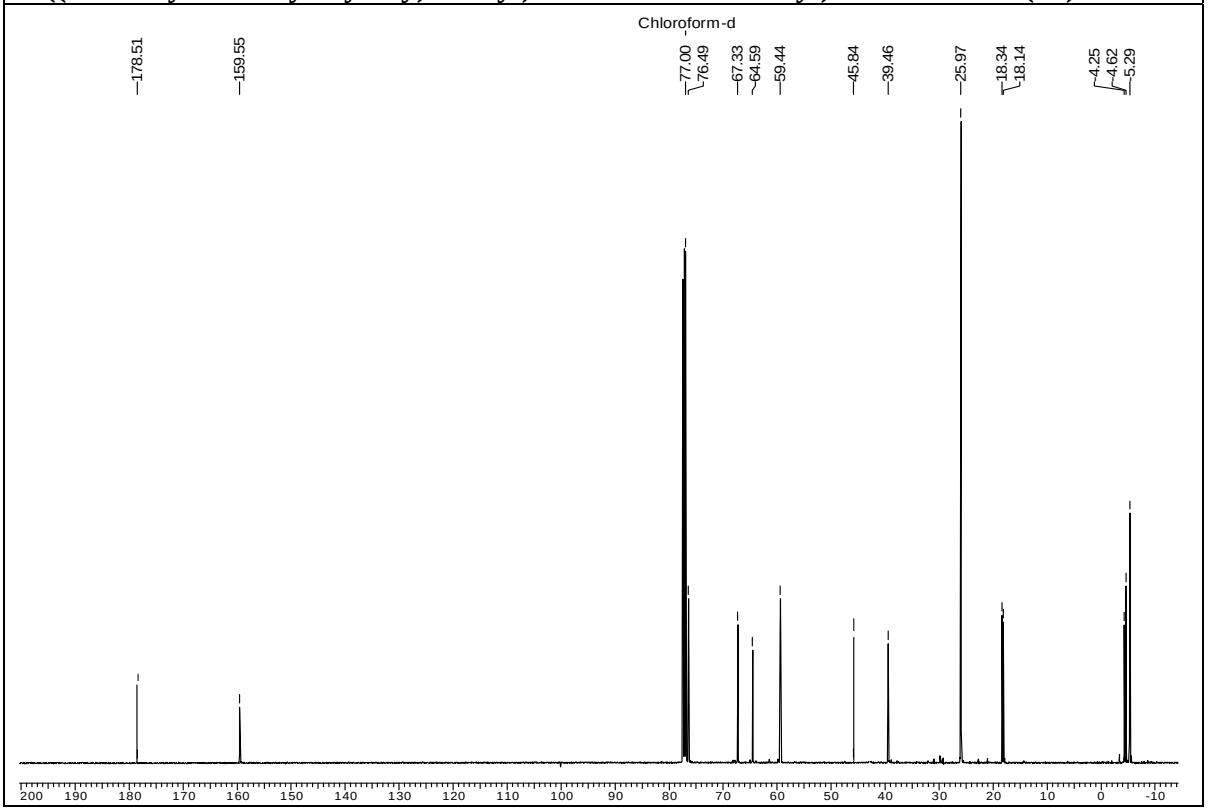


^{1}H NMR ($CDCl_3$, 200 MHz) spectra of (*S*)-3-(*tert*-Butyldimethylsilyloxy)-4-((4*R*,5*R*)-4-

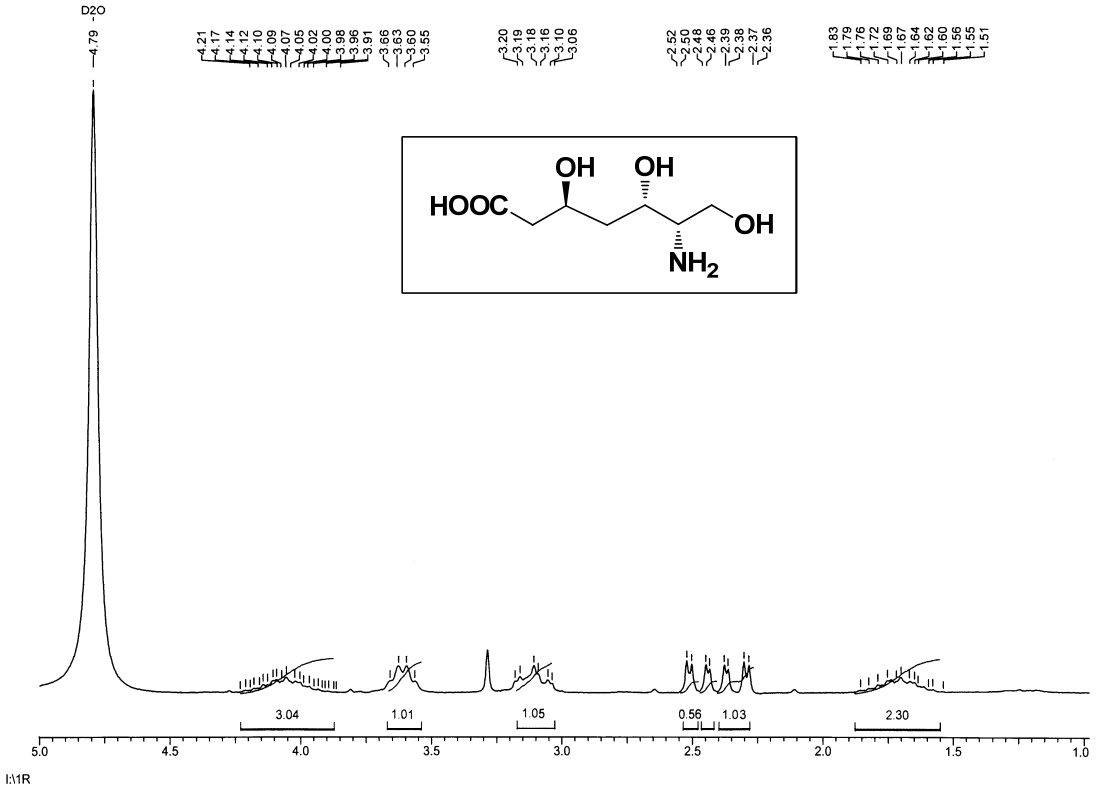
((tert-butyldimethylsilyloxy)methyl)-2-oxooxazolidin-5-yl)butanoic acid (52)

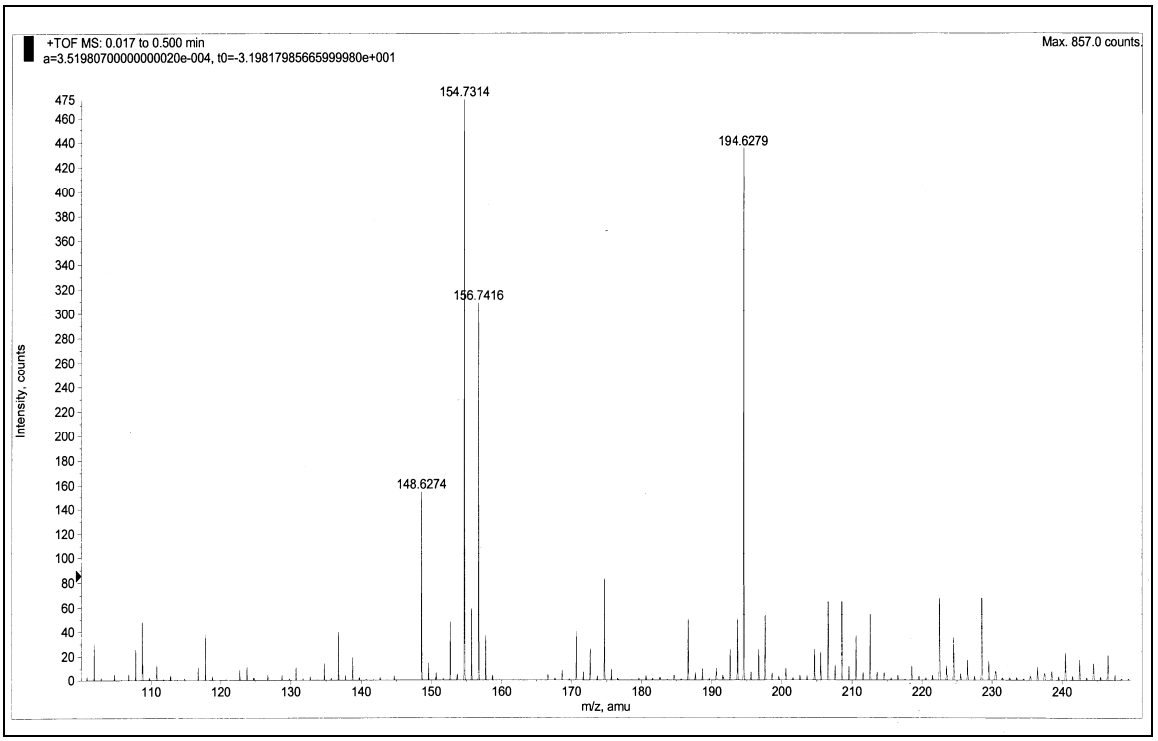


^{13}C NMR ($CDCl_3$, 100 MHz) spectra of (*S*)-3-(*tert*-Butyldimethylsilyloxy)-4-((4*R*,5*R*)-4-((*tert*-butyldimethylsilyloxy)methyl)-2-oxooxazolidin-5-yl)butanoic acid (52)



^{1}H NMR(D_2O, 500 MHz) & mass spectra of (3*S*,5*S*,6*S*)-6-amino-3,5,7-trihydroxy-heptanoic acid or (-)-galantinic acid (1)





3.1.6. References:

1. Shoji, J.; Sakajaki, R.; Koizumi, K.; Matsurra, S. J. *J. Antibiot.* **1975**, *28*, 122.
2. (a) Sakai, N.; Ohfune, Y. *Tetrahedron Lett.* **1990**, *31*, 4151; (b) Sakai, N.; Ohfune, Y. *J. Am. Chem. Soc.* **1992**, *114*, 998.
3. For didemnins, see for example: (a) Rinehart, K. L.; Gloer, J. B.; Hughes, R. G.; Renis, H. E.; McGovern, J. P.; Swynenberg, E. B.; Stringfellow, D. A.; Kuentzel, S. L.; Li, L. H. *Science* **1981**, *211*, 933. (b) Dolastatin 10: Pettit, G. R.; Kamano, Y.; Herald, C. L.; Tuinman, A. A.; Boettner, F. E.; Kizu, H.; Schmidt, J. M.; Baczynskyj, L.; Tomer, K. B.; Bontems, R. J. *J. Am. Chem. Soc.* **1987**, *109*, 6883.
4. See, for example: Kondo, S. I.; Akita, E.; Sezaki, M. *J. Antibiot.* **1966**, *19*, 137.
5. (a) Ikota, N. *Heterocycles* **1991**, *32*, 521; (b) Kumar, J. S. R.; Datta, A. *Tetrahedron Lett.* **1999**, *40*, 1381; (c) Kiyooka, S.; Goh, K.; Nakamura, Y.; Takesue, H.; Hena, M. A. *Tetrahedron Lett.* **2000**, *41*, 6599; (d) Moreau, X.; Campagne, J. *Tetrahedron Lett.* **2001**, *42*, 4467; (e) Bethuel, Y.; Gademann, K. *Synlett* **2006**, 1580; (f) Nagaiah, K.; Sreenu, D.; Purnima, K. V.; Rao, R. S.; Yadav, J. S. *Synlett* **2009**, 1386; (g) Raghavan, S.; Ramakrishna Reddy, S. *J. Org. Chem.* **2003**, *68*, 5754; (h) Pandey, S. K.; Kandula, S. R.; Kumar, P. *Tetrahedron Lett.* **2004**, *45*, 5877.
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3.2 SECTION B

SYNTHESIS OF (-)-GALANTINIC ACID VIA CHIRAL POOL APPROACH

3.2.1. Introduction

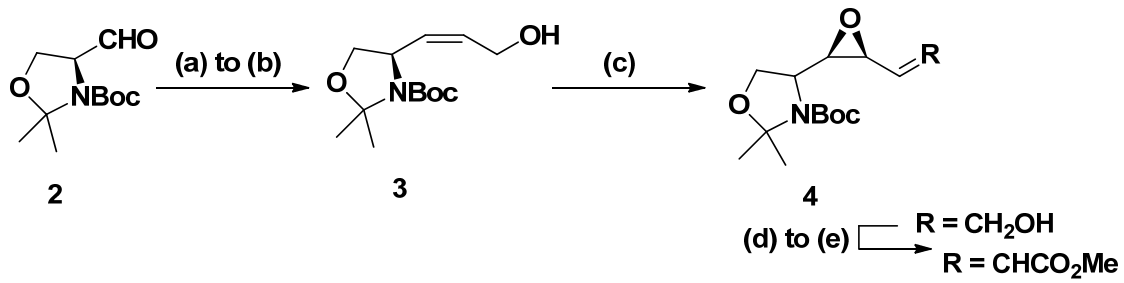
In the preceding section we have discussed the synthesis by (-)-galantinic acid **1** by asymmetric approach. Though the synthetic strategy employed looks attractive, however due to the large number of steps involved in the synthesis, the target compound could be assembled in 1.5% overall yield. To overcome the problem of low yield, we yet attempted at another alternative synthetic strategy using chiral pool starting material to install the stereocenters and assemble the target molecule by further synthetic manipulation. Here we describe our successful endeavors towards high-yielding, efficient synthesis of (-)-galantinic acid.

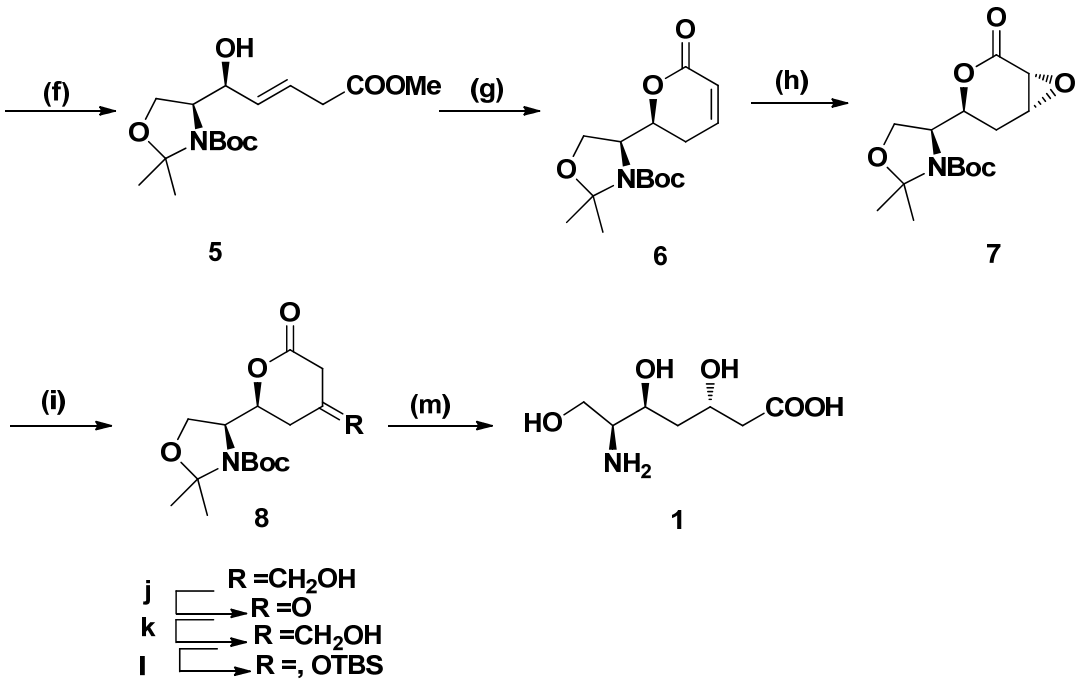
3.2.2. Review of Literature

Several approaches for the synthesis of (-)-galantinic acid have been documented in the literature.[1,2] Most of these approaches employ chiral pool starting materials.[2a-f] Some of the recent syntheses of (-)-galantinic acid **1** are described below.

Ohfune, Y. *et al.* (1990)[1a]

Ohfune and co-workers revised the structure of (-)-galantinic acid and reported its first synthesis. The synthesis began with Garner's aldehyde **2**, which was converted to Z-allylic alcohol **3** followed by epoxidation with mCPBA to furnish the epoxy alcohol **4** with the desired stereochemistry. Elongation of the C2 unit **6** was carried out by Swern oxidation and Wittig olefination. The epoxide was cleaved reductively by the use of Miyashita's reagent to give β,γ-unsaturated ester **5**. The key step of the synthesis is characterized by the stereocontrolled introduction of the 3,5-dihydroxyl groups of **1** using an epoxidation strategy to both the acyclic and cyclic intermediates, **3** and **6**, respectively. Compound **6**





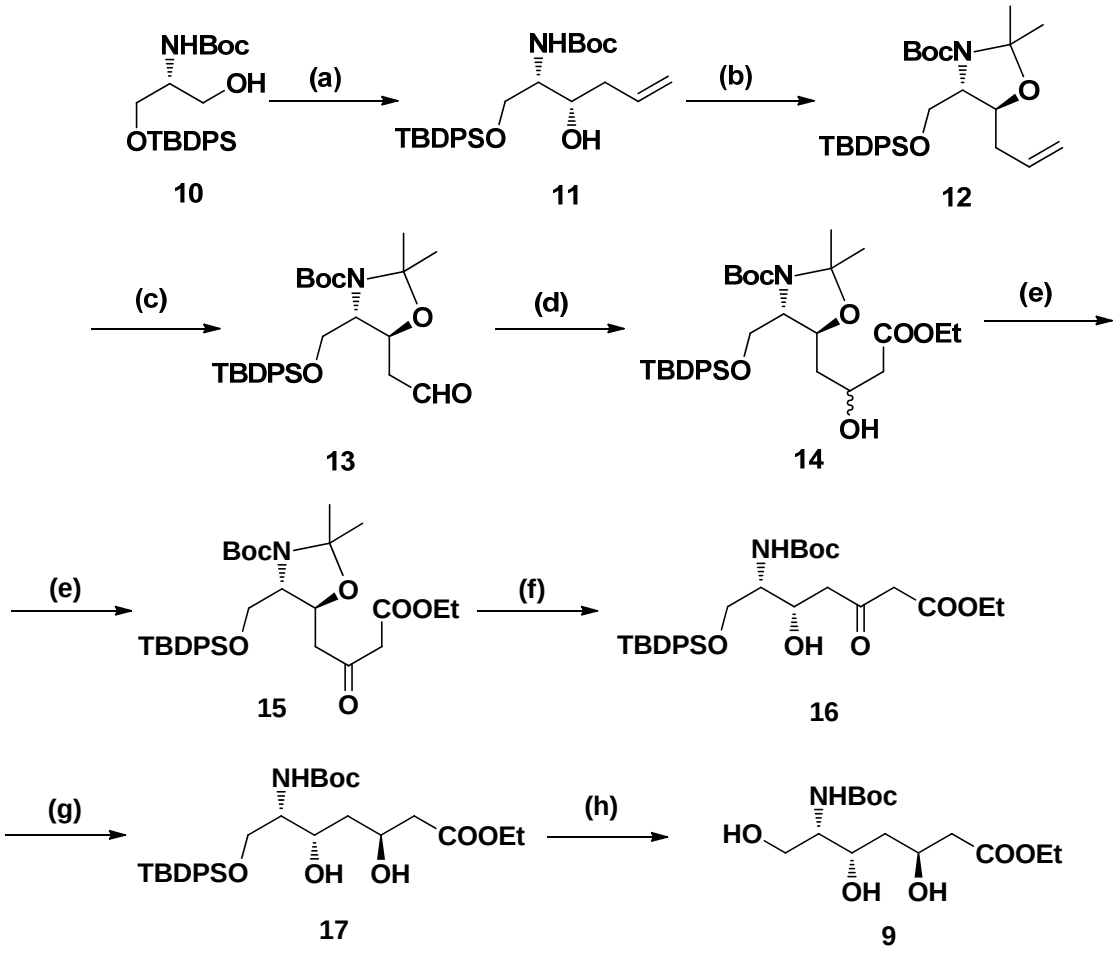
Scheme 1. *Reagents and conditions*: (a) $(CF_3CH_2O)_2P(O)CH_2Me$, NaH, l8-crown-8, THF, -78 °C, 82%; (b) *i*-Bu_2AlH, Et_2OBF_3, CH_2Cl_2, -78 °C, 78%; (c) *m*CPBA, CH_2Cl_2, 0 °C, 87%; (d) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, -90 °C, 87%; (e) Ph_3PCHCO_2Me, benzene, rt, 92%; (f) $Na^+[PhSeB(OEt)_3]^-$, EtOH, rt, 94%; (g) 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), benzene, reflux, 42%; (h) *t*-BuOOH, Triton B, THF, 0 °C, 54%; (i) PhBeH. *i*-PrOH, rt, 94%; (i) TFAA, DMSO, CH_2Cl_2, Et_3N, -78 °C; (k) $NH_3.BH_3$, citric acid, THF-H_2O (10/1), rt, (78% from 12; 14/12 =3/1); (l) TBDMSCl, TBSOTf, 2,6-lutidine, CH_2Cl_2, -78 °C, 64%; (m) Trifluoro acetic acid (TFA), CH_2C1_2, rt.

was reduced under modified Miyashita's reagent followed by oxidation and immediate reduction with $NH_3.BH_3$ and then global deprotection under acidic conditions to furnish (-)-galantinic acid **1** (**Scheme 1**).

Datta, A. *et al.* (1999)[2b]

Datta and co-workers reported the synthesis of (-)-galantinic derivative **9**. The strategy demonstrated the utility of chelation-controlled Grignard reaction on chiral α-amino aldehydes towards stereoselective formation of syn-1,2-amino alcohol unit. Swem oxidation of **10** and *in-situ* reaction of the resulting aldehyde with allylmagnesium bromide, following a chelation-controlled protocol,[7] provided the expected *syn-l,2-amino* alcohol **11** (*syn*:*anti* > 95:5). Acetonide protection of newely generated alcohol and amino functional group followed by conversion of olefin into aldehyde **13** by oxidative clevage and subsequently

Reformatsky reaction led to β-hydroxy ester **14**. Newely generated alcohol was oxidised to ketone **15** followed by acetonide deprotection and subsequent reduction of **16** with sodium triacetoxyborohydride following Evans' protocol afforded the *anti*-1,3-diol **17** (92:8) in good yield, by an efficient application of the β-hydroxy group directed reduction of a ketone, the *anti*-1,3-diol unit. Finally, deprotection of the silylether linkage under standard conditions culminated in the target galantinic acid derivative **9**.

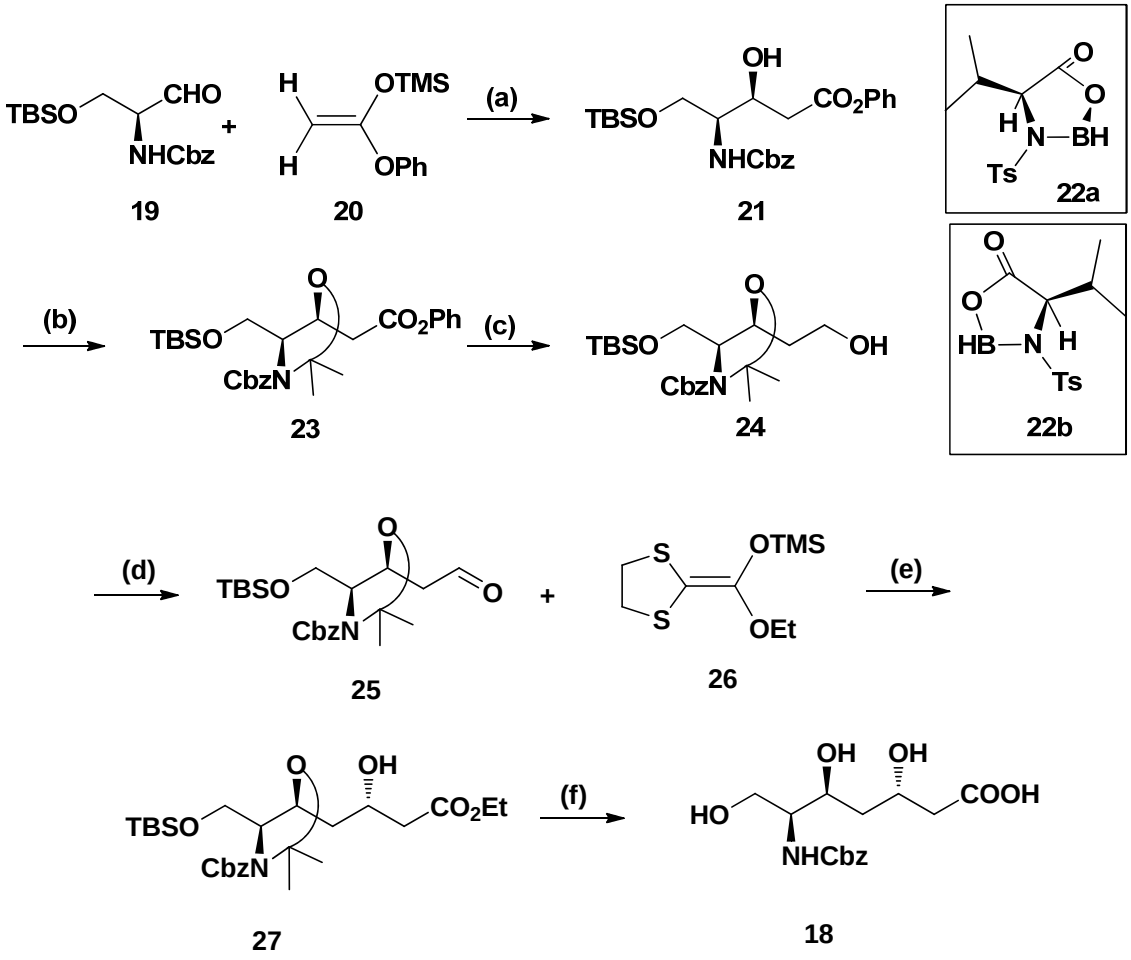


Scheme 2. *Reagents and conditions*: (a) Swern oxidation, then H_2C=CH-CH_2MgBr, 61%; (b) $Me_2C(OMe)_2$, PPTS, 85%; (c) OsO_4, NMO then $NaIO_4$ (impregnated on silica gel), 92%; (d) $BrZnCH_2CO_2Et$, Et_2O, 77%; (e) PDC, CH_2CI_2, 85%, (f) aqueous 80% AcOH, 84%; (g) $NaB(OAc)_3H$, CH_3CN, AcOH, -20°C, 72%; (h) Bu_4NF, THF, 97%.

Kiyooka, S. *et al* . (2000)[2c]

Kiyooka and co-workers accomplished the synthesis of *N*-Cbz-galantinic acid **18** under promoter control on enantioselective acyclic stereoselection based on chiral oxazaborolidinone-promoted aldol reactions. The aldol reaction of **19** with silyl nucleophile **20** in the presence of (*S*)-**22a** furnished the desired *syn*-aldol product (*syn*-**21**) in a ratio of

10:1, which was converted into acetonide **23** followed by reduction with DIBAL-H to give the corresponding alcohol **24** in 94% yield. The second aldol reaction of aldehyde **25**, with silyl nucleophile **26**, in the presence of (*R*)-**22b** afforded the desired 1,3-*anti*-diol as a single isomer in 76% yield. Desulfurization with *n*-Bu_3SnH and AIBN quantitatively gave *anti*-aldol product **27**. The protecting groups of *anti*-**27** were cleaved upon treatment with 80% AcOH at room temperature for 2 days to give *N*-Cbz-galantinic acid **18** in 75% yield.

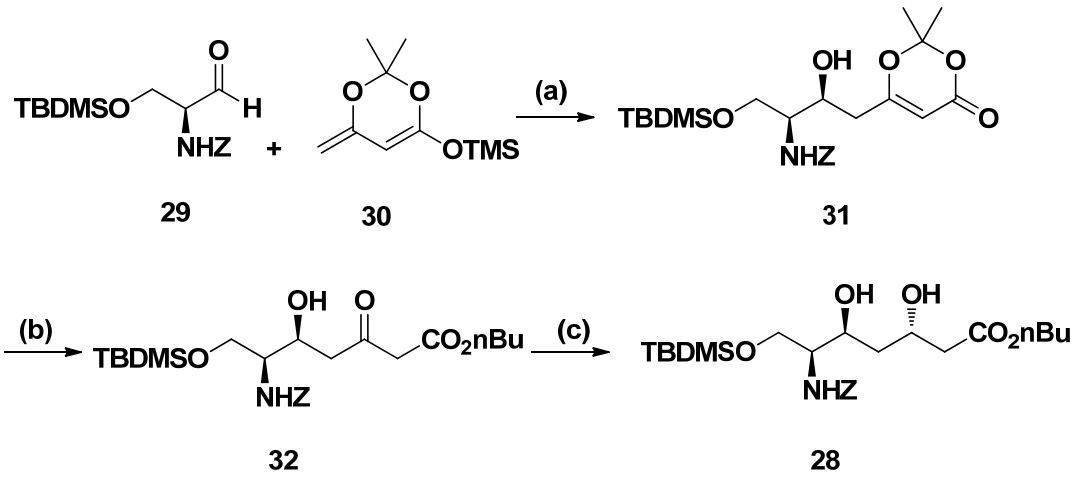


Scheme 3. *Reagents and conditions*: (a) **22a**, CH_2Cl_2, -78 ^oC, 74%; (b) 2,2-DMP, acetone, CSA, 68%; (c) DIBAL-H, CH_2Cl_2, -78 ^oC, 94%; (d) Swern oxidation, 88%; (e) [i] **22b**, $C_2H_5N_2$, -78 ^oC, 76%; [ii] *n*-BuSnH, AIBN, 95%; (f) 80% AcOH, rt, 75%.

Campagne, J.-M. *et al* . (2001)[2d]

Campagne and co-workers reported the synthesis of *N-(Z)*-galantinic butyl ester **28** using two highly diastereoselective reactions, namely a vinylogous Mukaiyama reaction and a 1,3-hydroxy directed Evans reduction. The reaction of known serinal aldehyde **29** with dienolate **30**, in the presence of 10% of $Eu(fod)_3$ led to the formation of the vinylogous aldol product **31** with a good (9:1) diastereoselectivity. The dioxinone ring was opened-up by refluxing **31**

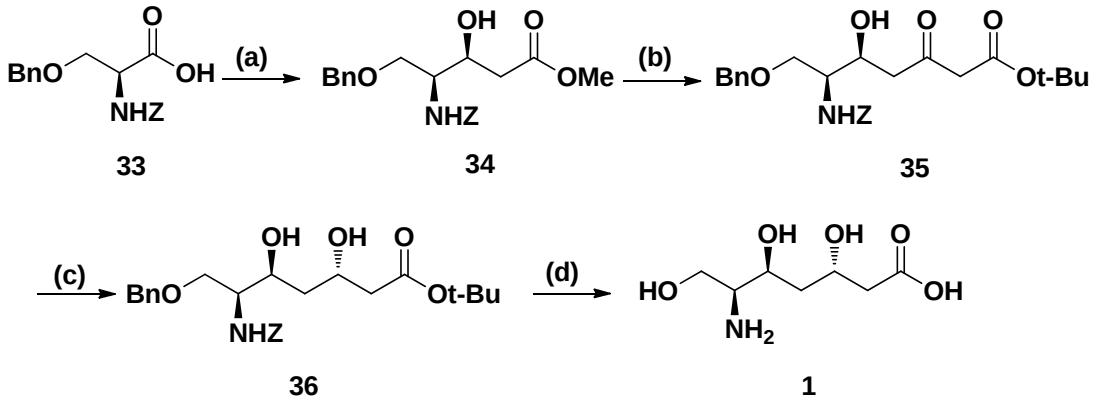
in butanol at 120 °C, to give the keto-alcohol **32** which on reduction under Evans conditions led to the galantinic butyl ester **28** in 56% yield (over two steps) and 98:2 diastereoselectivity (**Scheme 4**).



Scheme 4. *Reagents and conditions*: (a) 10% $Eu(fod)_3$, DCM, 0 ^oC to room temperature, 60%; (b) *n*-butanol, reflux; (c) $NaHB(OAc)_3$, CH_3CN/AcOH, 56% for two steps.

Gademann, K. *et al* . (2006).[2e]

Gademann and co-workers accomplished the synthesis of (–)-galantinic acid **1** *via* Heathcock–Claisen condensation, Evans reduction and deprotection in 10% overall yield from protected serine. The synthesis started from the β-hydroxy-γ-amino acid **34**, which was prepared from protected serine **33** (**Scheme 5**). A Claisen condensation using the procedure of Heathcock gave the hydroxyketoester **35** in 75% yield. The keto ester **35** was reduced by directed hydride delivery following the method of Evans to give the *anti*- 3,5-



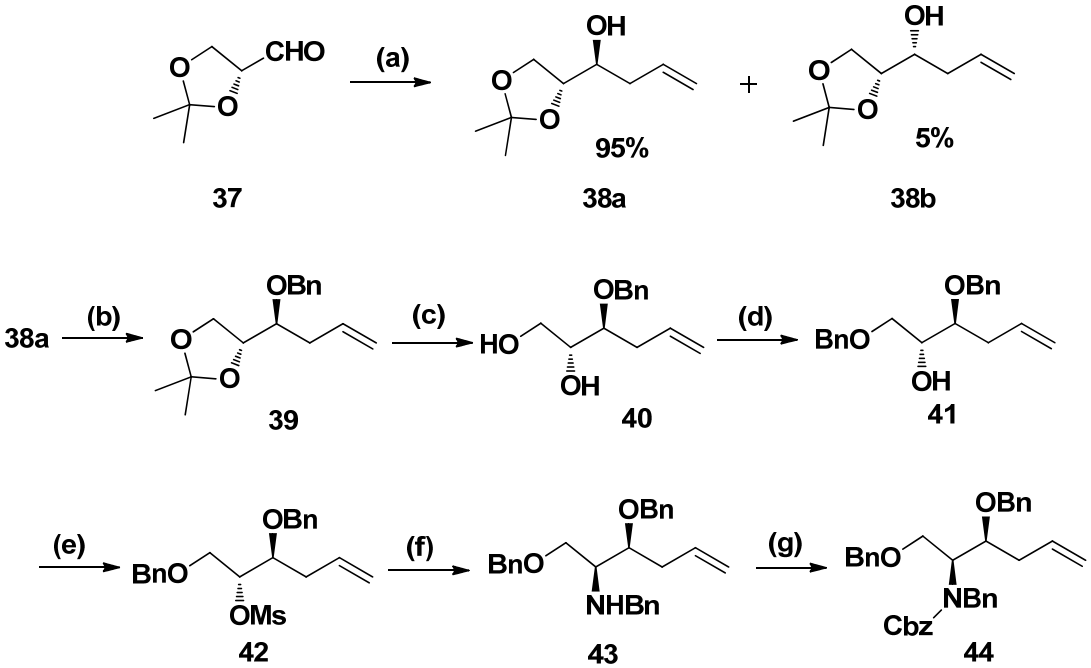
Scheme 5. *Reagents and conditions*: (a) [i] carbonyldiimidazole, KO_2CCH_2COOMe, $MgCl_2$, 74%; [ii] $NaBH_4$, Et_2O, (90%, dr, 1.2:1), 42% after recryst.; (b) $C_6H_{11}O_2Li$, THF, 75%; (c)

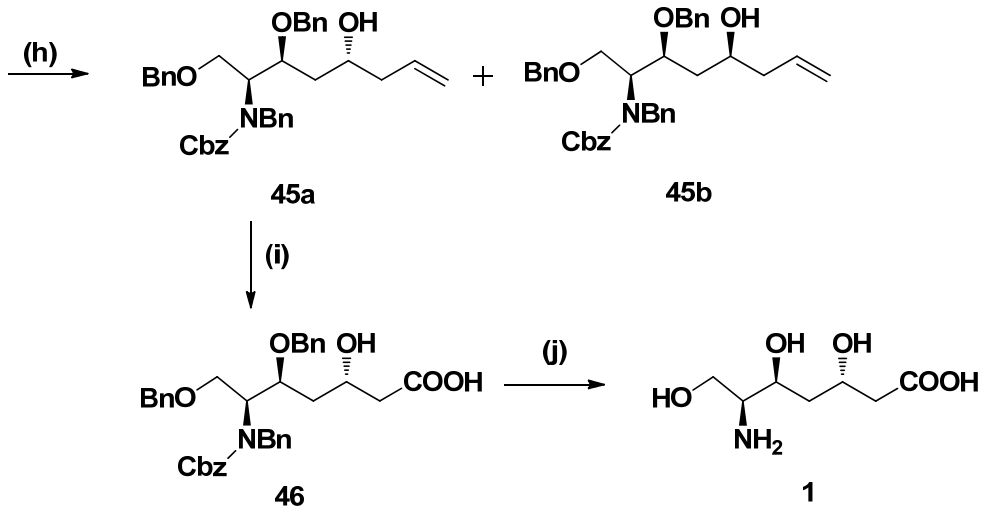
$Me_4NB(OAc)_3H$, MeCN, AcOH, 81%; (d) [i] H_2, Pd/C, MeOH, AcOH; [ii] CH_2Cl_2, CF_3CO_2H, 50% for two steps.

diol **36** in excellent stereoselectivity (>95:5). The diol **36** was then deprotected first by hydrogenolysis and short treatment with trifluoroacetic acid to afford a sample of (–)-galantinic acid **1**.

Nagaiah, K. *et al.* (2009).[2f]

Nagaiah and co-workers accomplished the synthesis of (–)-galantinic acid **1** *via* Zn-mediated stereoselective allylation of (*R*)-2,3-O-*iso*-propylidineglyceraldehyde **37** to give the corresponding homo allylic alcohol as a mixture of diastereomers **38a** and **38b** (*anti*/*syn* = 95:5) in 92% overall yield. The required stereoisomer was protected as its benzyl derivatives **39**; subsequent hydrolysis of the 2,3-O-*iso*-propylidene afforded the diol **40**, which on selective protection of primary hydroxyl group followed by conversion of secondary alcohol into protected amine afforded compound **44**. The olefin was converted to aldehyde and subjected to chelation-controlled diastereoselective allylation by addition of allyl(tributyl)stannane in the presence of magnesium bromide at 0 °C to give the corresponding homoallylic alcohol as a mixture of isomers **45a** and **45b** in 72% overall





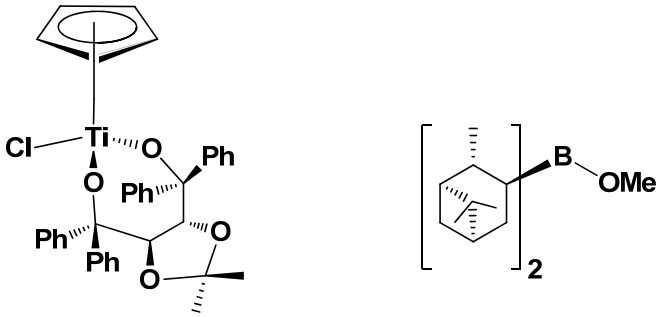
Scheme 6. *Reagents and conditions*: (a) Zn, allyl bromide, THF, sat. aq NH_4Cl, 0 °C to rt, 92%; (b) BnBr, NaH, THF, 0 °C to rt, 90%; (c) 2M HCl, THF, 0 °C to rt, 90%; (d) Bu_2SnO, BnBr, benzene, reflux, 88%; (e) MsCl, DIPEA, CH_2Cl_2, 0 °C to rt, 82%; (f) $BnNH_2$, 120 °C, 85%; (g) CbzCl, sat. $NaHCO_3$, EtOH, 0 °C, 90%; (h) [i] OsO_4 (cat.), NMO, acetone–H_2O (4:1); [ii] $NaIO_4$, THF–H_2O, (4:1); [iii] Allyl (tributyl)stannane, $MgBr_2 \cdot Et_2O$, CH_2Cl_2, 0 °C, 72% for three steps; (i) [i] OsO_4 (cat.), NMO, *t*-BuOH; [ii] $NaIO_4$, THF–H_2O (4:1); [iii] $NaClO_2$, 20% $NaH_2PO_4.2H_2O$, *t*-BuOH, 0 °C to rt, 85% for three steps; (j) 10% Pd/C, H_2 gas, MeOH, 86%.

yield. To generate terminal carboxylic acid, the olefin was oxidised. Global deprotection by catalytic hydrogenolysis furnished the target compound, (–)-galantinic acid (**1**) in 86% yield.

3.2.3. Present Work

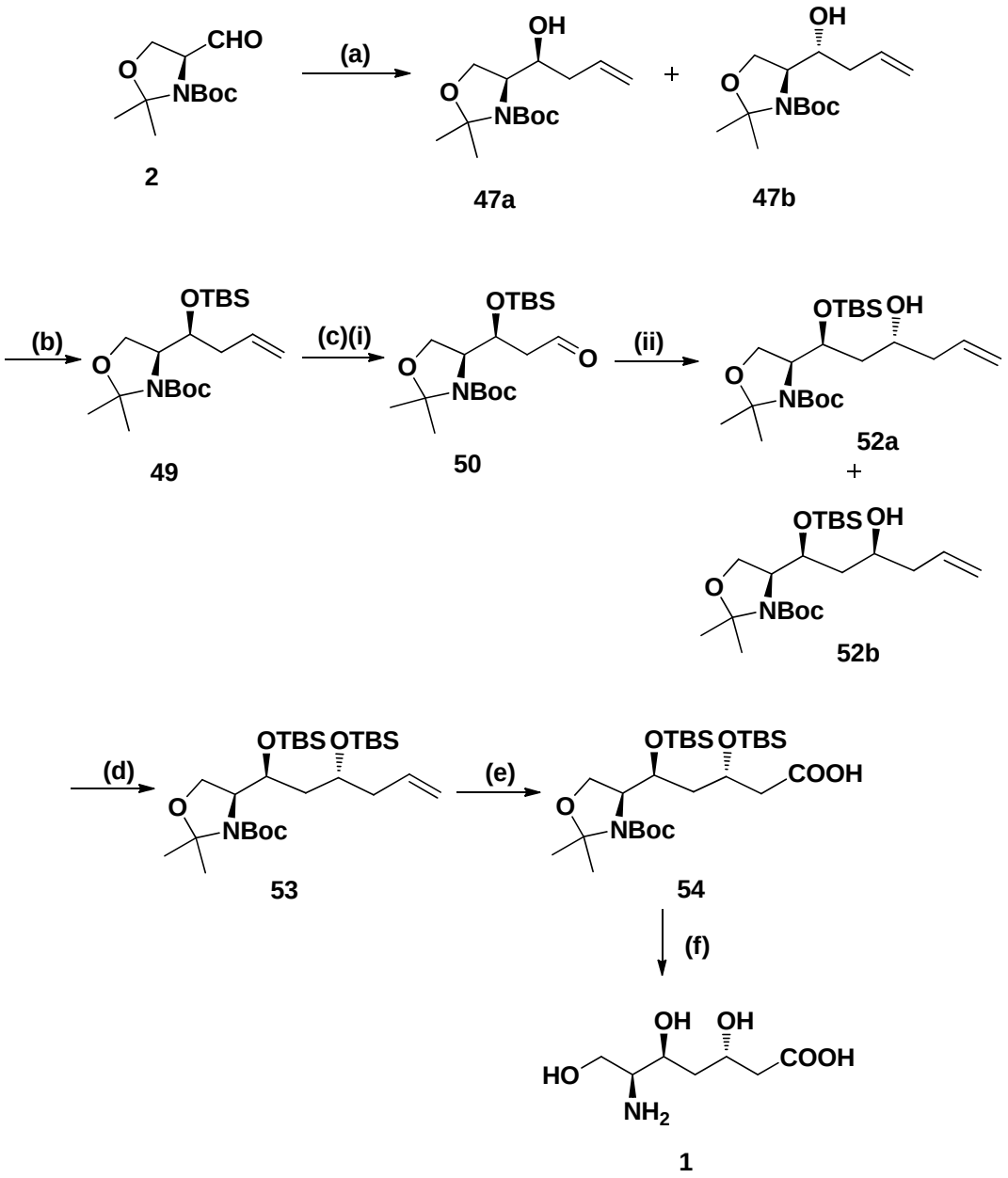
3.2.3.1. Results and Discussion

In our chiral approach towards synthesis of galantinic acid **1**, Garners aldehyde **2** was used as the starting material whose synthesis has been reported from L-serine.[3] In order to generate *syn* aminoalcohol **47a,** Garner's aldehyde **2** was subjected to asymmetric allylation[4] using an allylating reagent prepared from (*R*,*R*)-TADDOL **48**, allylmagnesium chloride at -78 ^oC to give homoallylic alcohol in excellent yield with diastereomeric ratio (19:1) of *syn* **47a** and *anti* **47b,** respectively which were easily separated by column chromatography. The IR spectrum of compound **47a** gave broad hydroxyl absorption at 3400 cm^{-1}. The ^1H NMR spectrum of **47a** gave olefin peaks at δ 5.05-5.21 (multiplet, two



48 51

Fig. 1



Scheme 7. *Reagents and conditions*: (a) (*R*,*R*)-TADDOL **48**, allylmagnesium chloride, -78 ^{o}C, 93%; (b) TBSCl, imidazole, CH_2Cl_2, 0 ^{o}C to rt, 95%; (c) (i) $NaIO_4$, 2,6-lutidine, OsO_4,

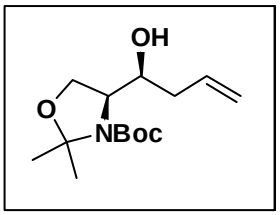
dioxane:H_2O(3:1), 90%; (ii) (+Ipc_2B-allyl) **51**, 86%; (d) TBSCl, imidazole, CH_2Cl_2, 0 ^oC to rt, 90%; (e) $RuCl_3.3H_2O$, $NaIO_4$, CCl_4−CH_3CN−H_2O (2:2:3), 80%; (f) 1N HCl in dioxane: THF(1:1), 45%.

protons) and 5.69-5.92 (multiplet, one proton). The newely generated alcohol was protected by TBS using TBSCl and imidazole to furnish **49** in excellent yield. With substantial amount of **49** in hand our next aim was to synthesize the 1,3-*anti* alcohol. Towards this the olefin **49** was subjected to oxidative cleavage[5] by using $NaIO_4$, 2,6- lutidine and OsO_4 to furnish the aldehyde **50,** which was subjected to asymmetric allylation[6] using an allylating reagent prepared from (+)-Ipc_2BOMe **51**, and allylmagnesium bromide at -78 ^oC to give the homoallylic alcohol in 86% yield with diastereomeric ratio (11:1) of *anti* **52a** and *syn* **52b** respectively which were separated by column chromatography.

The newely generated alcohol was protected by TBS using TBSCl, imidazole to furnish **53** in excellent yield. Having prepared the required fremework, our next aim was to oxidise the olefin into acid using $RuCl_3$ and $NaIO_4$ to give the acid **54**. The ^1H NMR spectrum of **54** showed absence of olefinic protons at δ 5.0-5.08 and 5.70-5.91. The ^{13}C NMR spectrum of **54** showed acidic carbon at δ 177.2. Finally, global deprotection of all acid labile protecting group with 1N HCl in dioxane: THF (1:1) furnished (-)-galantinic acid **1** in 45% yield. The physical and spectroscopic data of **1** were in complete agreement with those described in literature ($[\alpha]_D^{25}$: -29.7 (*c*, 0.5, H_2O); (lit.[1b] $[\alpha]_D^{25}$ -29.4 (*c*, 0.5, H_2O). The overall yield of the target compound **1** was found to be 19.8% from seven steps.

3.2.4. Experimental Section

(*S*)-*tert*-Butyl 4-((*S*)-1-hydroxybut-3-enyl)-2,2-dimethyloxazolidine-3-carboxylate (47a):



Allylmagnesium chloride in THF (5.6 mL of a 0.8 M solution, 4.5 mmol) was added dropwise over 10 min at 0 ^oC under argon to a solution of (*R,R*)-cyclopentadienyl (4*R*,*trans*)-2,2-dimethyl-*α,α,α′,α′*-tetraphenyl-1,3-dioxolane-4,5-dimethanolato-O,O-titani-um chloride (3.06 g, 5.0 mmol) in 60 mL of ether. After stirring for 1 h at 0 ^oC, the reaction mixture was cooled to -78 ^oC, and a solution of *tert*-butyl(4*S*)-2,2-dimethyl-4-formyloxazolidine-3-carboxylate **2** (917 mg**,** 4 .0 mmol) in ether (5 mL) was added over 5 min. Stirring was

continued at -78 ^{o}C for 3 h. The reaction mixture was then treated with 20 mL of aqueous 45% NH_4F solution, sitrred for 12 h at room temperature, filtered through Celite, and extracted twice with ether (50 mL). The combined organic phases were washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure. The diastereomeric ratio was determined to be greater than 19:1 in favour of syn as determined by integration of the carbon signals of the newely formed chiral center. These two diastereomers can be separated by silica gel chromatography with gradient solvent system (20% to 25% EtOAc in petroleum ether) to give homoallylic alcohol **47a** as colorless syrupy liquid.

Yield: 1.0 g, 93%.

Mol. Formula: $C_{14}H_{25}NO_4$

$[\alpha]_D^{25}$: -17.27 (*c* 0.95, $CHCl_3$), {lit[4] **$[\alpha]_D^{25}$** -17.0 (*c* 0.95, $CHCl_3$)}.

IR (neat, cm^{-1}): ν_{max} 3400, 2980, 2800, 1705, 1653, 1380, 1360

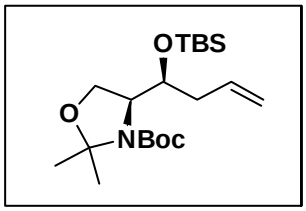
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (s, 6H), 1.49 (s, 9H), 2.21-2.49 (m, 2H), 2.85 (brs, 1H), 3.50- 4.09 (m, 4H), 5.05-5.21 (m, 2H), 5.69-5.92 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 26.2, 28.3, 36.2, 65.3, 71.3, 72.0, 79.4, 99.1, 117.6, 133.4, 155.6.

MS(ESI): m/z 272.20 $(M+H)^+$.

Analysis: Calcd.: C, 61.97; H, 9.29; N, 5.16%; **Found:** C, 66.68; H, 9.35; N, 5.11%.

(*S*)-*tert*-Butyl-4-((*S*)-1-(*tert*-butyldimethylsilyloxy)but-3-enyl)-2,2-dimethyloxazolidine -3-carboxylate (49):



To a stirred solution of alcohol **47a** (1.0 g, 3.68 mmol) in CH_2Cl_2 was added imidazole (0.5 g, 7.37 mmol). To this solution *t*-butyl dimethylchlorosilane (0.832 g, 5.52 mmol) was added at 0 ^{o}C and the reaction was stirred at rt for 6 h. The reaction was monitored by TLC and halted when no further change was detected. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl, and allowed to stir for 10 min. The aqueous layer was extracted with CH_2Cl_2 (25 mL x 3). The combined organics were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel using petroleum ether/EtOAc (98:2) as eluent to give TBS protected **49** as oily liquid.

Yield: 1.35 g, 95%.

Mol. Formula: $C_{20}H_{39}NO_4Si$

$[\alpha]_D^{25}$: -22.21 (*c* 1, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 2999, 1670, 1653, 1380, 1360

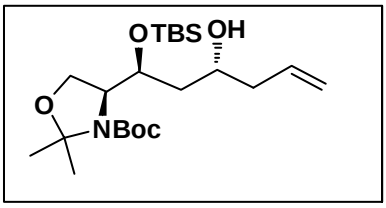
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.87 (s, 9H), 1.49-1.63 (m, 15H), 2.03-2.31 (m, 2H), 3.81-3.97 (m, 2H), 4.08-4.22 (m, 2H), 5.01-5.09 (m, 2H), 5.69-5.9 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.5, 22.6, 25.8, 26.7, 28.6, 35.8, 60.3, 63.2, 71.2, 79.9, 94.9, 116.7, 136.4, 152.2.

MS(ESI): m/z 408.55 $(M+Na)^+$.

Analysis: Calcd.: C, 62.29; H, 10.19; N, 3.63%; **Found:** C, 62.20; H, 10.11; N, 3.79%.

(*S*)-*tert*-Butyl-4-((1*S*,3*R*)-1-(*tert*-butyldimethylsilyloxy)-3-hydroxyhex-5-enyl)-2,2-dimethyloxazolidine-3-carboxylate (52a):



To a solution of compound **49** (1 g, 2.70 mmol) in dioxane-water (3:1, 27 ml) were added 2,6-lutidine (0.63 ml, 5.4 mmol), OsO_4 (2.5% in 2-methyl-2-propanol, 1.65 mg, 0.016 mmol), and $NaIO_4$ (2.31 g, 10.8 mmol). The reaction was stirred at 25 ^oC and monitored by TLC. After the reaction was complete, water (50 ml) and CH_2Cl_2 (50 ml) were added. The organic layer was separated, and the water layer was extracted by CH_2Cl_2 (50 ml) three times. The combined organic layer was washed with brine and dried over Na_2SO_4. The organic layer was concentrated to give the aldehyde **50** as pale yellow oil, which was used as such for the next step without purification.

Yield: 0.89 g, 90%

(+)-B-Methoxydiisopinocampheylborane (1.45 g, 4.59 mmol) was dissolved in 20 ml of ether under argon and cooled to -78 ^oC. To this solution was added a 1.0 M solution of allylmagnesium bromide in ether (4.5 ml, 4.4 mmol) via syringe. The resulting mixture was stirred at -78 ^oC for 15 min and warmed to room temperature over 1 h, upon which time a white precipitate appeared. The solvent was removed via rotary evaporator and pumped under high vacuum for 1 h. The white residue was then dissolved in 30 ml toluene and cooled to -78 ^oC. The aldehyde **50** (0.89, 2.29 mmol) in 10 ml of toluene was cooled to -78 ^oC and transferred to the chiral allylborane solution via cannula over a 20 min period. The reaction

was stirred for 6 h and quenched with 10 ml of 1.0 M NaOH solution at -78 ^{o}C. Aqueous H_2O_2 solution (30%, 10 ml) was added, and the mixture stirred at room temperature overnight. The mixture was extracted with ether (3 x 25 ml). The organic extraction were combined, washed with saturated $NaHCO_3$ and NaCl solution, dried over Na_2SO_4, and concentrated. The diastereomeric ratio was determined to be greater than 12:1 in favour of *anti* as determined by integration of the carbon signals of the newely formed chiral center. These two diastereomers can be separated by silica gel chromatography with gradient solvent system (5% to 10% EtOAc in petroleum ether) to give anti-homoallylic alcohol **52a** as a oily liquid.

Yield: 0.98 g, 86%.

Mol. Formula: $C_{22}H_{43}NO_5Si$

$[\alpha]_D^{25}$: -30.45 (*c* 0.5, $CHCl_3$).

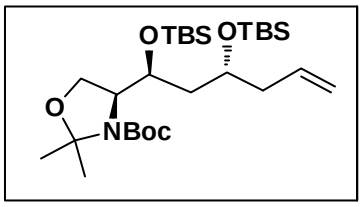
IR (neat, cm^{-1}): ν_{max} 3503, 2930, 1702, 1653, 1388, 1256, 1093.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.88 (s, 9H), 1.25 (s, 6H), 1.45-1.61 (m, 11H), 2.17- 2.27 (m, 2H), 3.79-4.46 (m, 5H), 5.06-5.16 (m, 2H), 5.71-5.93 (m, 1H).

MS(ESI): m/z 452.32 $(M+Na)^+$.

Analysis: Calcd.: C, 61.50; H, 10.09; N, 3.26%; **Found:** C, 62.39; H, 10.11; N, 3.29%.

(*S*)-*tert*-Butyl-4-((5*S*,7*R*)-7-allyl-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-5-yl)-2,2-dimethyloxazolidine-3-carboxylate (53):



To a stirred solution of alcohol **52a** (500 mg, 1.16 mmol) in CH_2Cl_2 was added imidazole (157 mg, 2.32 mmol). To this solution *t*-butyl dimethylchlorosilane (262 mg, 1.74 mmol) was added at 0 ^{o}C and the reaction was stirred at rt for 4 h. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl, and allowed to stir for 10 min. The aqueous layer was extracted with CH_2Cl_2 (25 mL x 3). The combined organics were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel using petroleum ether/EtOAc (98:2) as eluent to give TBS protected **53** as oily liquid.

Yield: 633 mg, 90%.

Mol. Formula: $C_{28}H_{57}NO_5Si_2$

$[\alpha]_D^{25}$: -33.37(*c* 1.1, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 2956, 2930, 2858, 1696, 1653, 1383, 1255, 1095.

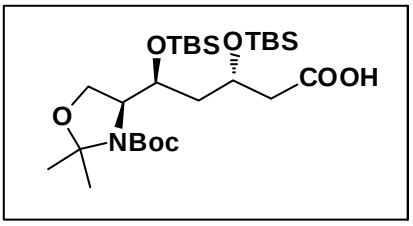
^{1}H NMR (200 MHz, $CDCl_3$): 0.03 (s, 6H), 0.06 (s, 6H), 0.88 (s, 9H), 0.92 (s, 9H), 1.12-1.63 (m, 17H), 2.20- 2.30 (m, 2H), 3.67-3.96 (m, 3H), 4.06-4.30 (m, 2H), 5.0-5.08 (m, 2H), 5.70-5.91 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.6, -4.4, -3,7, -3.6, 25.8, 26, 26.6, 26.7, 28.4, 28.7, 40.2, 43.3, 60.9, 62.7, 63.1, 68.9, 79.9, 94.9, 116.9, 135.3, 152.6.

MS(ESI): m/z 544.80 $(M+H)^+$, 566.78 $(M+Na)^+$.

Analysis: Calcd.: C, 61.83; H, 10.56; N, 2.58%; **Found:** C, 62.1; H, 10.41; N, 2.49%.

(3*S*,5*S*)-5-((*S*)-3-(*tert*-Butoxycarbonyl)-2,2-dimethyloxazolidin-4-yl)-3,5-bis((*tert*-butyldimethylsilyl)oxy)pentanoic acid (54):



Compound **53** (300 mg, 0.551 mmol) was dissolved in 14 ml of 2:2:3 CCl_4−CH_3CN−H_2O, $NaIO_4$ (235 mg, 1.10 mmol) and $RuCl_3.3H_2O$ (10 mg, 0.027 mmol) was then added. The resulting mixture was stirred vigorously at room temperature for 3 h. The mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using pet ether/EtOAc (8:2) as eluent provided **54** as a brown color syrupy liquid.

Yield: 248 mg, 80%.

Mol. Formula: $C_{27}H_{55}NO_7Si_2$

$[\alpha]_D^{25}$: -29.23(*c* 1.2, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 3373, 2930, 2858, 1708, 1384, 1256, 1098.

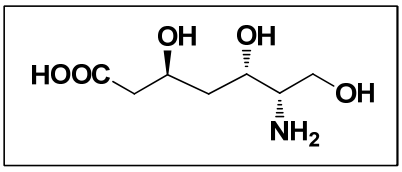
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.02 (s, 6H), 0.04 (s, 6H), 0.78 (s, 9H), 0.81 (s, 9H), 1.18-1.63 (m, 17H), 2.34-2.70 (m, 2H), 3.78-3.98 (m, 2H), 4.02-4.27 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ –5.1, –4.6, -3.7, 17.8, 25.6, 26.6, 28.4, 28.7, 29.7, 38.5, 44.2, 60.7, 63.1, 67.1, 68.7, 80.3, 95, 152.6, 177.2.

MS(ESI): m/z 562.80 $(M+H)^+$, 584.78 $(M+Na)^+$.

Analysis: Calcd.: C, 57.71; H, 9.87; N, 2.49%; **Found:** C, 57.61; H, 9.81; N, 2.48%.

(3*S*,5*S*,6*S*)-6-Amino-3,5,7-trihydroxyheptanoic acid (-)-galantinic acid (1):



Yield: 30 mg, 45%.

M.P.: 128-129 ^{o}C (lit.[1b] 125 -130 ^{o}C).

$[\alpha]_D^{25}$: -29.7 (*c*, 0.5, H_2O); {lit.[1b] **$[\alpha]_D^{25}$** -29.4 (*c*, 0.5, H_2O)}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.51-1.83 (m, 2H), 2.37 (dd, *J* = 5.8, 13.6 Hz, 1H), 2.49 (dd, *J* = 6.5, 13.8 Hz, 1H), 3.13 (dt, *J* = 7.0, 12.2 Hz, 1H), 3.61 (q, *J* = 8.32, 14.91 Hz, 1H), 3.91-4.21 (m, 3H).

MS (ESI) m/z: 194 $(M+H)^+$.

3.2.5 Spectra

1. ^{1}H & ^{13}C NMR spectra of **47a**

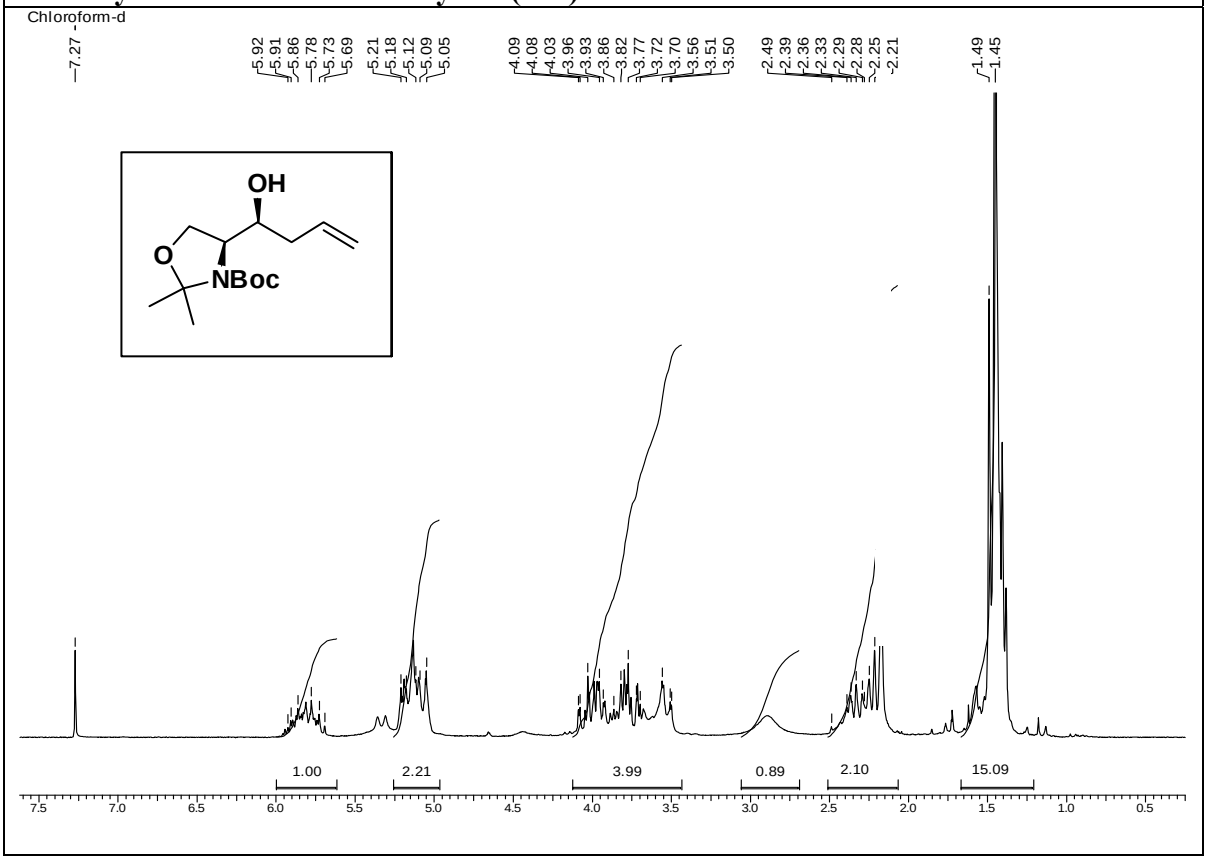
2. ^{1}H & ^{13}C NMR spectra of **49**

3. ^{1}H NMR spectra of **52a**

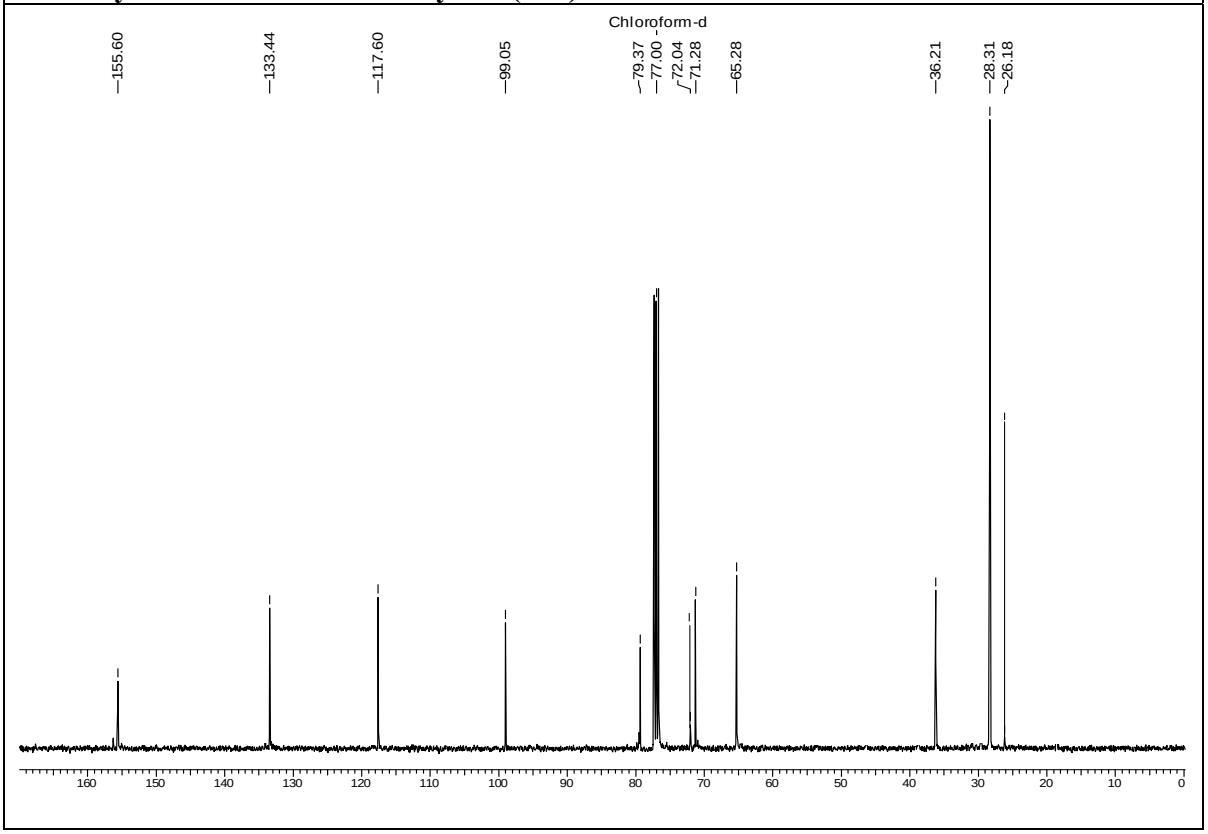
4. ^{1}H & ^{13}C NMR spectra of **53**

5. ^{1}H & ^{13}C NMR spectra of **54**

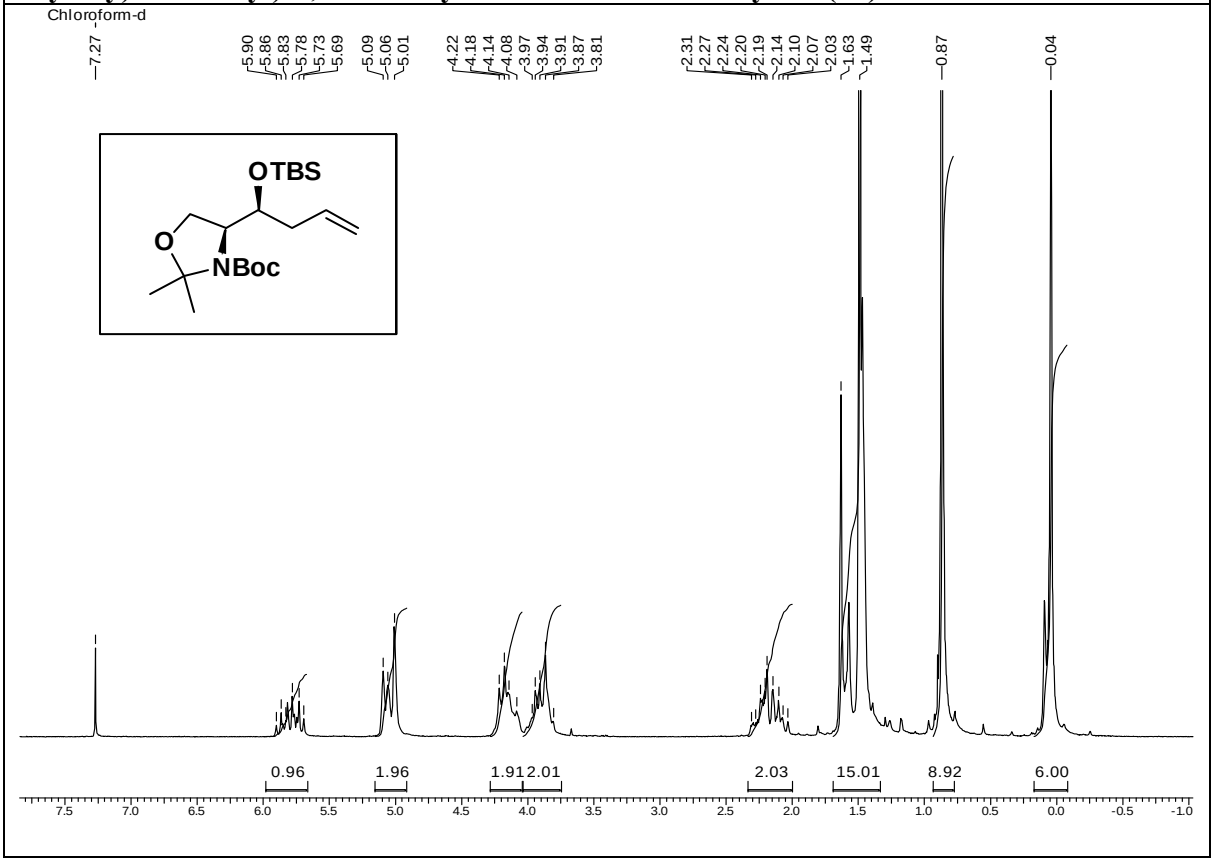
^{1}H NMR (400 MHz, $CDCl_3$) spectra of (*S*)-*tert*-butyl-4-((*S*)-1-hydroxybut-3-enyl)-2,2-dimethyl-oxazolidine-3-carboxylate (47a)



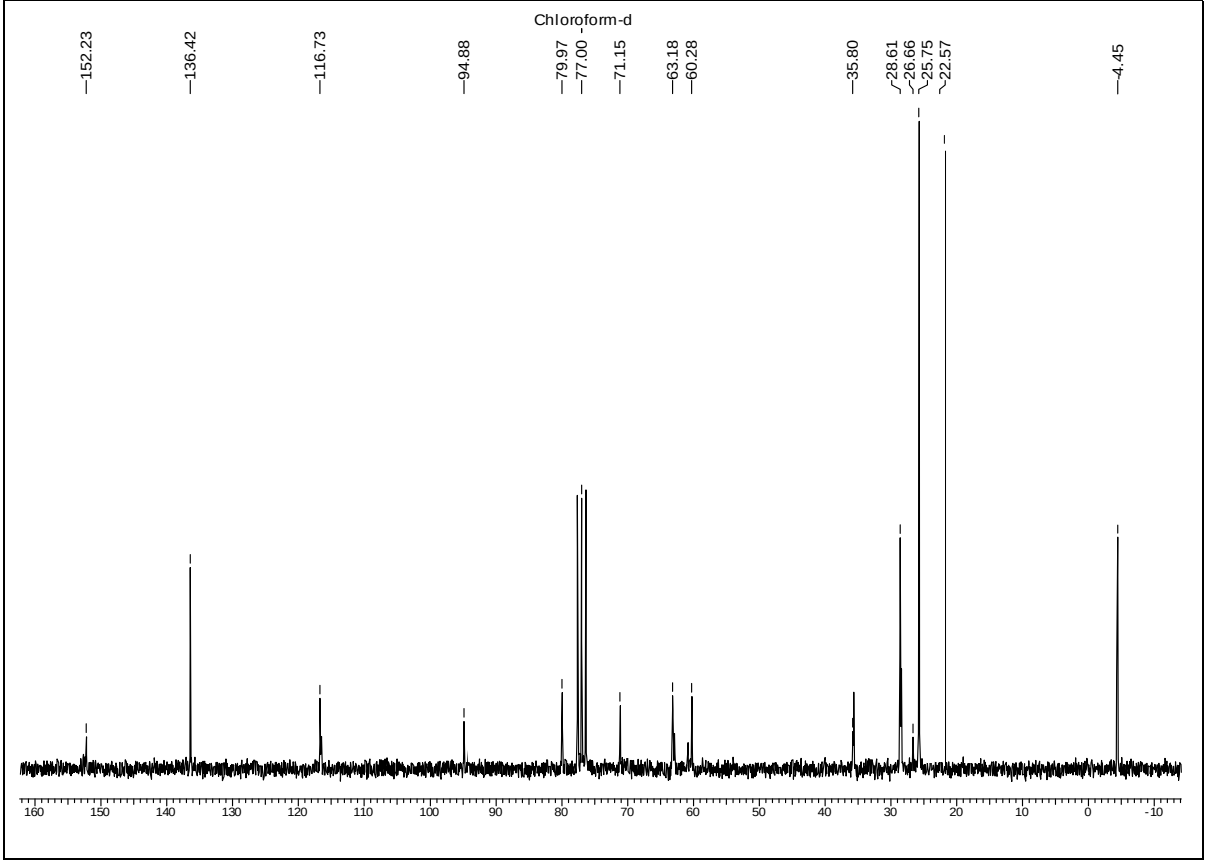
^{13}C NMR (100 MHz, $CDCl_3$) spectra of (*S*)-*tert*-butyl-4-((*S*)-1-hydroxybut-3-enyl)-2,2-dimethyl-oxazolidine-3-carboxylate (47a)



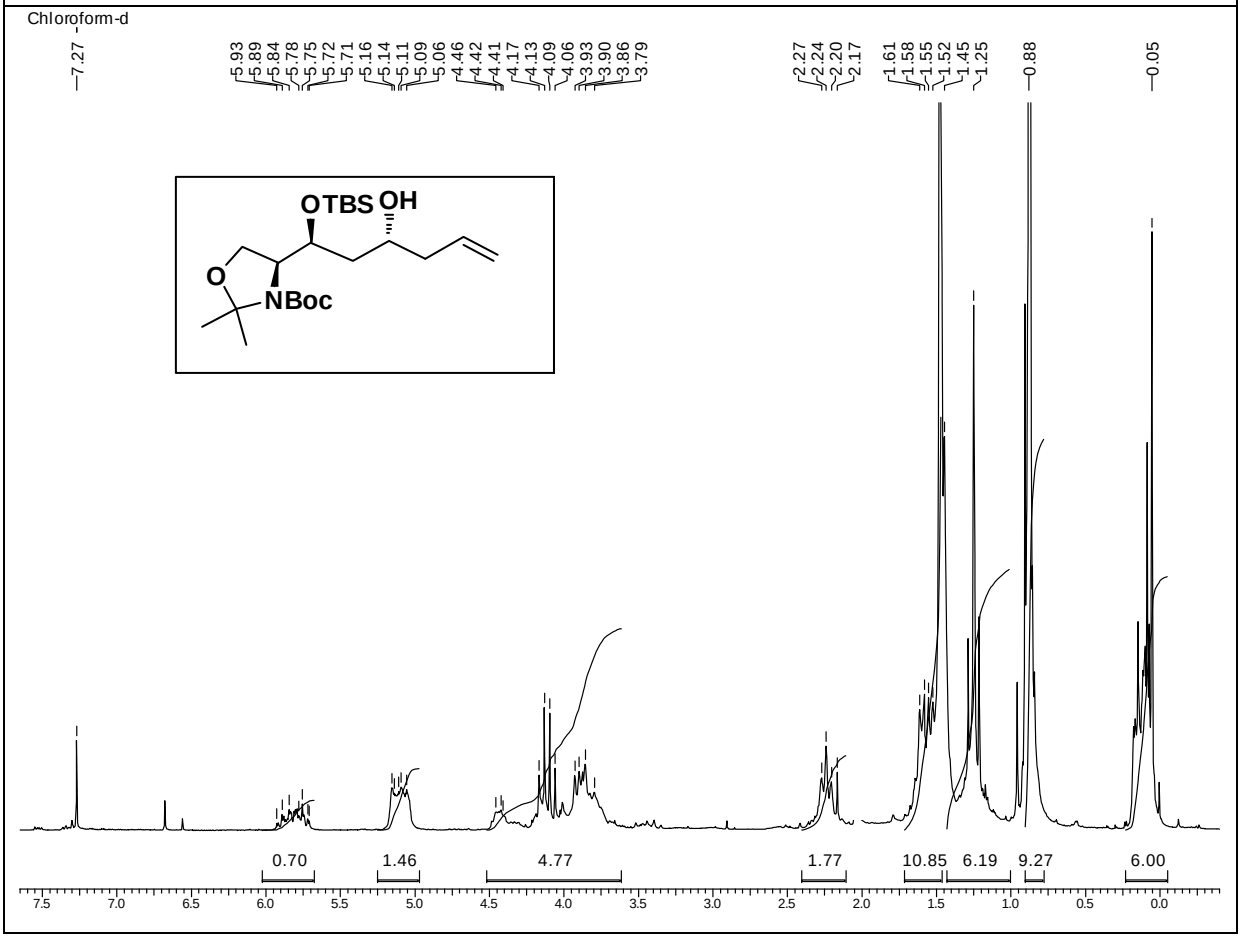
^{1}H NMR (200 MHz, $CDCl_3$) spectra of (*S*)-*tert*-butyl-4-((*S*)-1-(*tert*-butyldimethylsilyloxy)but-3-enyl)-2,2-dimethyloxazolidine-3-carboxylate (49)



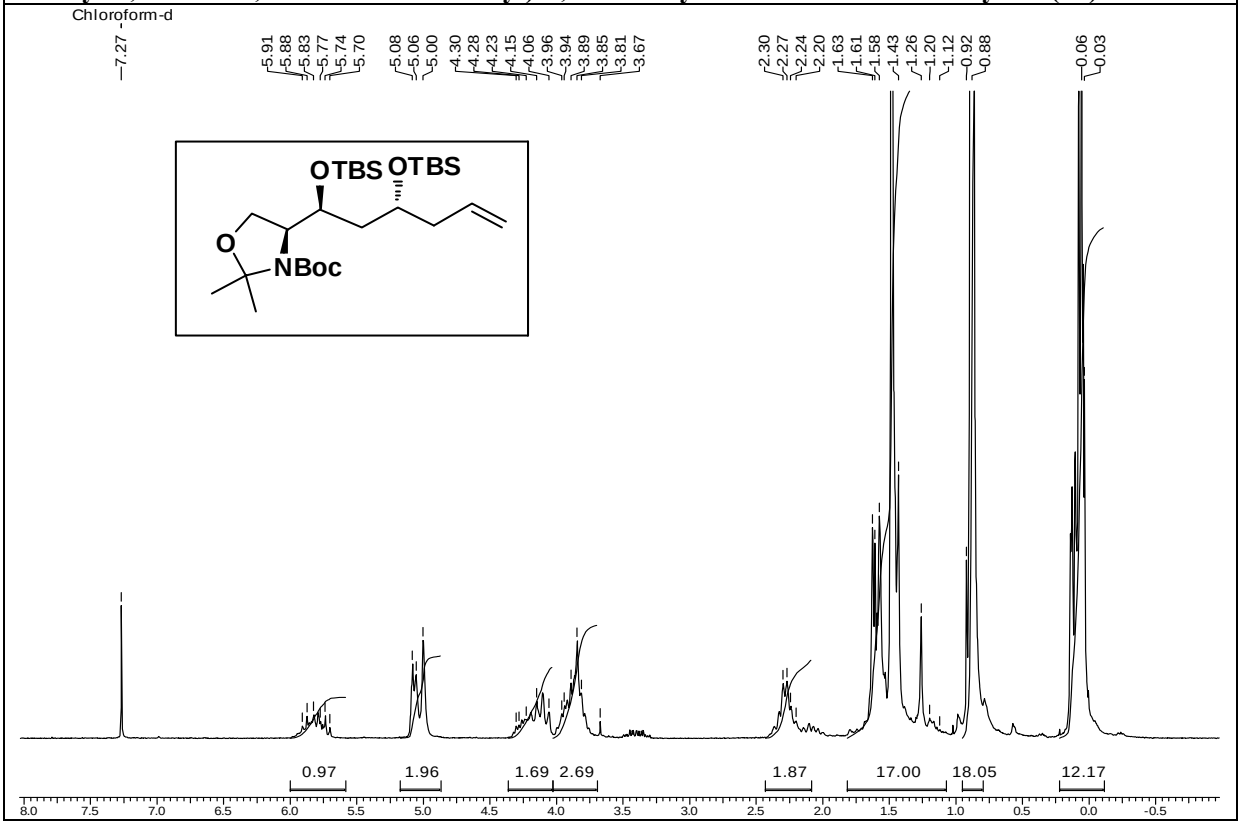
^{13}C NMR (50 MHz, $CDCl_3$) spectra of (*S*)-*tert*-butyl-4-((*S*)-1-(*tert*-butyldimethylsilyloxy)but-3-enyl)-2,2-dimethyloxazolidine-3-carboxylate (49)



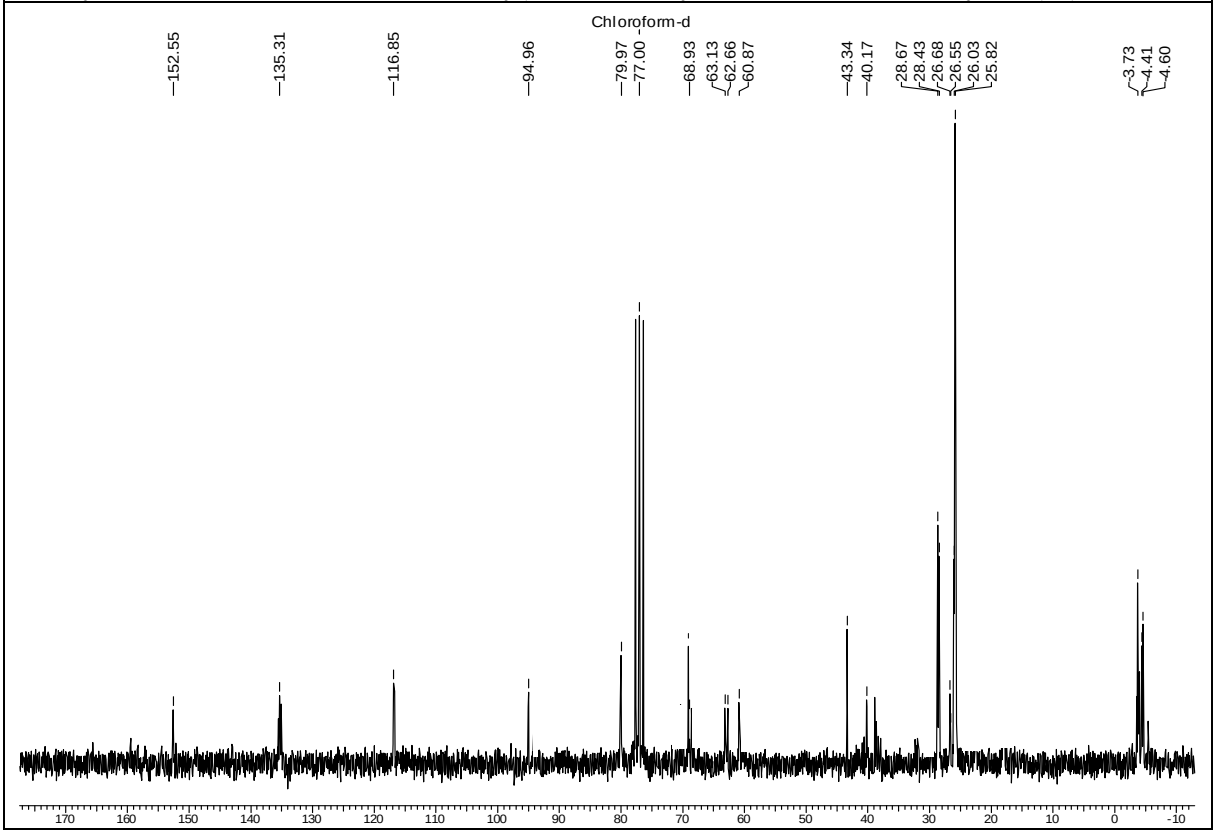
^{1}H NMR (400 MHz, $CDCl_3$) spectra of (*S*)-*tert*-butyl-4-((1*S*,3*R*)-1-(*tert*-butyldimethyl-silyloxy)-3-hydroxyhex-5-enyl)-2,2-dimethyloxazolidine-3-carboxylate (52a)



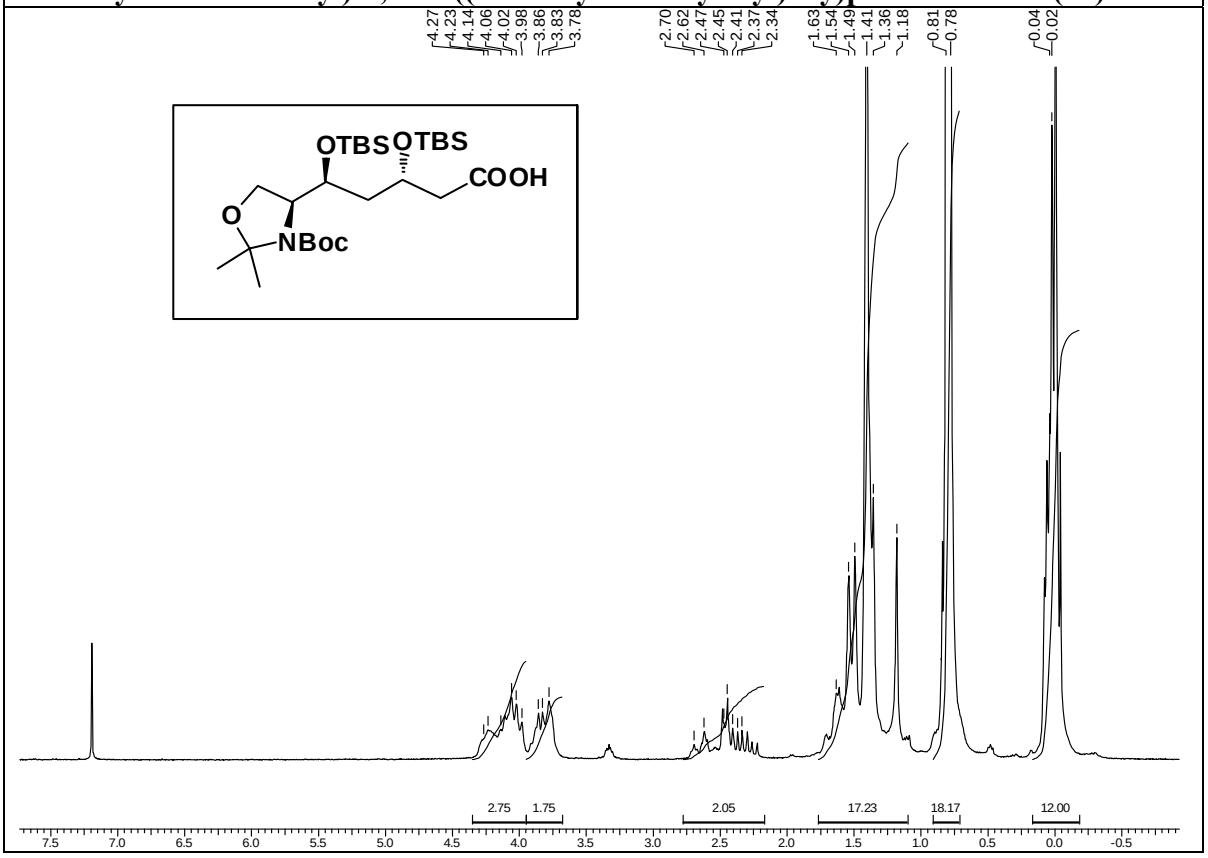
^{1}H NMR (200 MHz, $CDCl_3$) spectra of (*S*)-*tert*-butyl-4-((5*S*,7*R*)-7-allyl-2,2,3,3,9,9,10, 10-octa-methyl-4,8-dioxa-3,9-disilaundeca-n-5-yl)-2,2-dimethyloxazolidine-3-carbo- xylate (53)



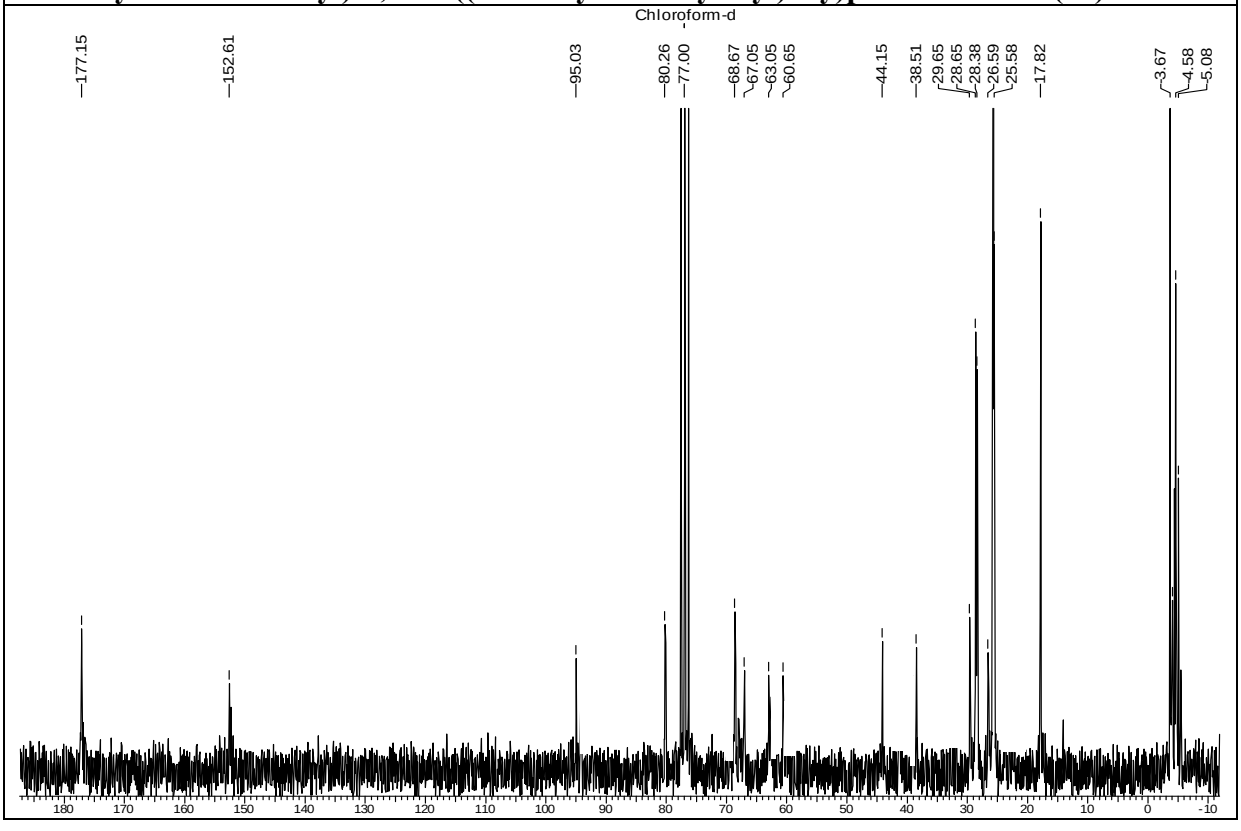
^{13}C NMR (50 MHz, $CDCl_3$) spectra of (*S*)-*tert*-butyl-4-((5*S*,7*R*)-7-allyl-2,2,3,3,9,9,10, 10-octa-methyl-4,8-dioxa-3,9-disilaundeca-n-5-yl)-2,2-dimethyloxazolidine-3-carboxylate (53)



^{1}H NMR (200 MHz, $CDCl_3$) spectra of (3*S*,5*S*)-5-((*S*)-3-(*tert*-butoxycarbonyl)-2,2-dimethyloxazolidin-4-yl)-3,5-bis((*tert*-butyldimethylsilyl)oxy)pentanoic acid (54)



^{13}C NMR (50 MHz, $CDCl_3$) spectra of (3*S*,5*S*)-5-((*S*)-3-(*tert*-butoxycarbonyl)-2,2-dimethyloxazolidin-4-yl)-3,5-bis((*tert*-butyldimethylsilyl)oxy)pentanoic acid (54)



3.2.6. References:

1. (a) Sakai, N.; Ohfune, Y. *Tetrahedron Lett.* **1990**, *31*, 4151; (b) Sakai, N.; Ohfune, Y. *J. Am. Chem. Soc.* **1992**, *114*, 998.
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4.1 SECTION A

STUDIES TOWARDS THE TOTAL SYNTHESIS OF CASCARILLIC ACID AND GRENADAMIDE

4.1.1. Introduction

Cyclopropane ring systems are ubiquitous in nature and are contained in a large number of natural products, insecticides, and pharmaceutical drug candidates.[1-3] In addition, the chemistry of cyclopropyl group-containing amino acids, whether natural products or analogues of naturally occurring amino acids, has advanced tremendously in the past 20 years. Many of these amino acids and their various derivatives have interesting and important biological activities, and no pharmaceutical research laboratory today will forget to attach a cyclopropyl group instead of an isopropyl or a *gem*-dimethyl carbon moiety to a physiologically active molecule, especially when adjacent to a nitrogen atom. In fact, the patent literature lists over 200 pharmaceutically relevant compounds containing a cyclopropylamine moiety. The broad-spectrum antibiotics Ciprofloxacin, Trovafloxacin, and Moxifloxacin are probably the best-known examples.

Moreover, many cyclopropane-containing unnatural products have been prepared to test the bonding features of this class of highly strained cycloalkanes[4] and to study enzyme mechanism or inhibition.[5] Cyclopropanes have also been used as versatile synthetic intermediates in the synthesis of more functionalized cycloalkanes[6,7] and acyclic compounds.[8] In recent years, most of the synthetic efforts have focused on the enantioselective synthesis of cyclopropanes.[9] This has remained a challenge ever since it was found that the members of the pyrethroid class of compounds were effective insecticides.[10] New and more efficient methods for the preparation of these entities in enantiomerically pure form are still evolving, the rigidity of the three membered ring renders this group an appealing structural unit for the preparation of molecules with defined orientation of pendant functional groups.

4.1.2. Cyclopropanation Reaction

Mainly three general types of stereoselective cyclopropanation reactions from olefins have been reported in the literature (**Fig. 1**)

(1) Halomethylmetal mediated cyclopropanation reactions (**eq 1**),

(2) Transition metal-catalyzed decomposition of diazo compounds (**eq 2**)

(3) Nucleophilic addition-ring closure sequence (**eqs 3** and **4**).

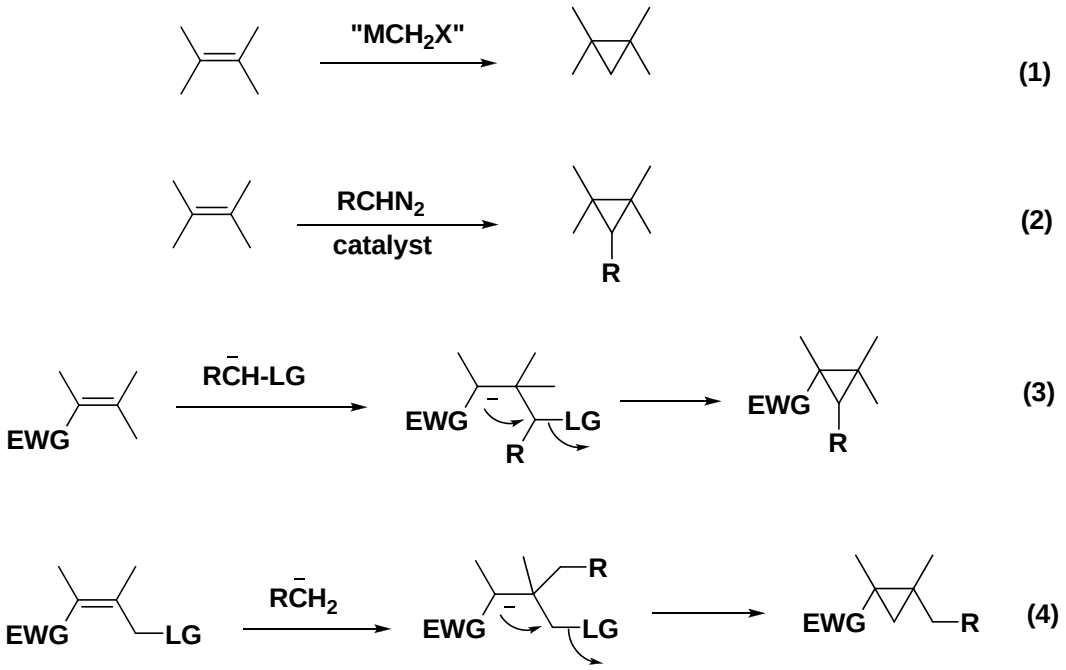
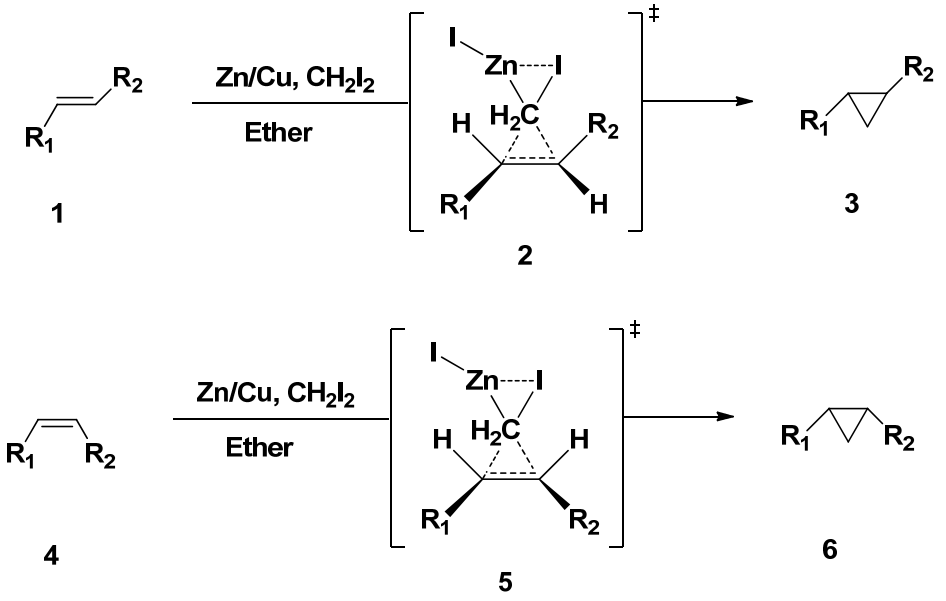


Fig. 1

(1) Halomethylmetal (Zn, Sm, Al)-Mediated Cyclopropanation Reactions

The observation that diiodomethane reacts with zinc to give an iodomethylzinc species was first reported in 1929 by Emschwiller.[11] However, about 30 years later, Simmons and Smith[12] were the first to appreciate that this reagent ($IZnCH_2I$) could be used for the stereospecific conversion of alkenes to cyclopropanes (**Scheme 1**).[13] The cyclopropanation reactions using these reagents are characteristically stereospecific, proceeding through a



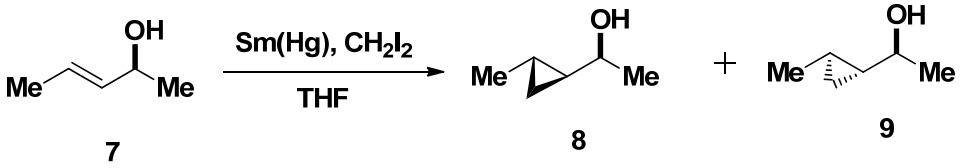
Scheme-1

"butterfly-type" transition structure.[14] One major advantage of the reaction is its excellent chemoselectivity, since it is applicable to a variety of olefins and compatible with several functional groups such as enamines, enol ethers, esters, ketones, etc. (vide infra). Simmons and Smith's seminal studies were quickly followed by the development of several alternative methods to prepare related $ZnCH_2X$ species or to activate the zinc metal.[15]

Table 1. Important Methods for the preparation of Cyclopropanating Reagents

Reactants	Reagents
Oxidative Addition	
Zn/activator, XCH_2I	$IZnCH_2X$ (X = Cl, I)
Sm/activactor, CH_2I_2	$ISmCH_2I$
Alkyl Exchange	
Et_2Zn, CH_2I_2	$EtZnCH_2I$ or $Zn(CH_2I)_2$
$EtZnI$, CH_2I_2	$IZnCH_2I$
CF_3COOH, Et_2Zn, CH_2I_2	$CF_3COOZnCH_2I$
2,4,6-$Cl_3C_6H_2OH$, Et_2Zn, CH_2I_2	2,4,6-$Cl_3C_6H_2OZnCH_2I$
$C_4F_9C(O)OCH_2I$, Et_2Zn, *hv*	$C_4F_9C(O)OCH_2ZnEt$
R_3Al, CH_2I_2	R_2AlCH_2I
Nucleophilic Displacement	
ZnX_2, CH_2N_2	$XZnCH_2X$
ZnX_2, CH_2N_2	$Zn(CH_2I)_2$

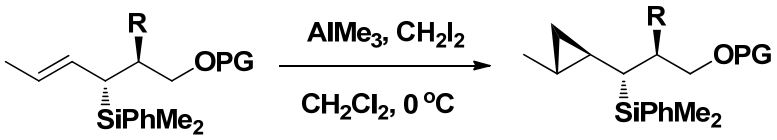
(i) Cyclopropanation of (*E*)-3-penten-2-ol[16]



7 8 9

Scheme 2

(ii) Cyclopropanation of Chiral Allylsilanes[17]



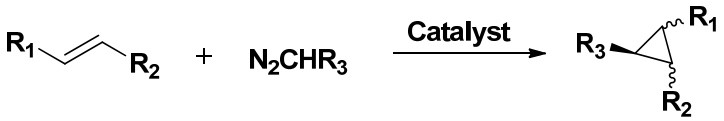
10 11

Scheme 3

These reports were followed by the discovery of several new halomethylmetal reagents that are also very effective cyclopropanating reagents with unique properties and reactivities. **Table 1** gives an overview of some preparative methods to generate these reagents.

(2) Transition Metal Catalysed Decomposition of Diazoalkanes

The cyclopropanation of olefins using the transition metal-catalysed decomposition of diazoalkanes is one of the most extensively studied reactions of the organic chemist's arsenal.[18]



12 13 14

Scheme 4

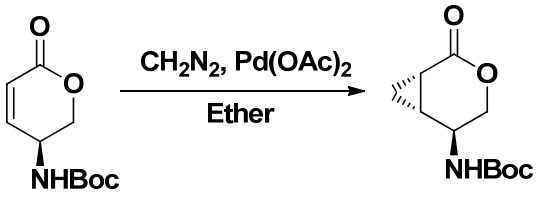
The diazo precursors **15-18** are divided according to their electronic properties, as shown in **Fig. 2**.

15 16 17 18

Fig. 2. Common diazoalkane precursor

Both inter- and intramolecular versions of this reaction have been developed and exploited in synthesis. The nature of the starting diazo reagent, as well as the type of the reaction to be carried out (inter- vs intramolecular), plays a key role in the appropriate selection of the most efficient catalyst for a given transformation.

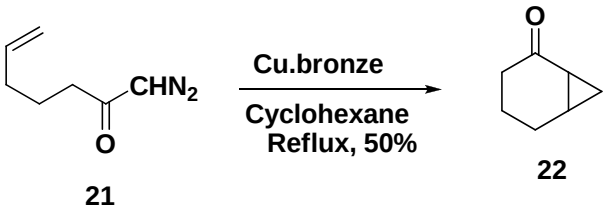
(i) Intermolecular Cyclopropanation[19]



19 20

Scheme 5

(ii) Intramolecular Cyclopropanation[20]



21 22

Scheme 6

(3) Nucleophilic Addition-ring Closure Sequence (Michael Initiated Ring Closure)

Cyclopropanation reactions which involves a conjugate addition to an electrophilic alkene to produce an enolate, which then subsequently undergoes an intramolecular ring closure, are defined as Michael initiated ring closure (MIRC) reactions.[21-24] Although there are exceptions, cyclopropanations via the MIRC reaction of acyclic olefins are usually nonstereospecific, and both (*E*)- and (*Z*)-olefins give the *trans*-cyclopropanes.

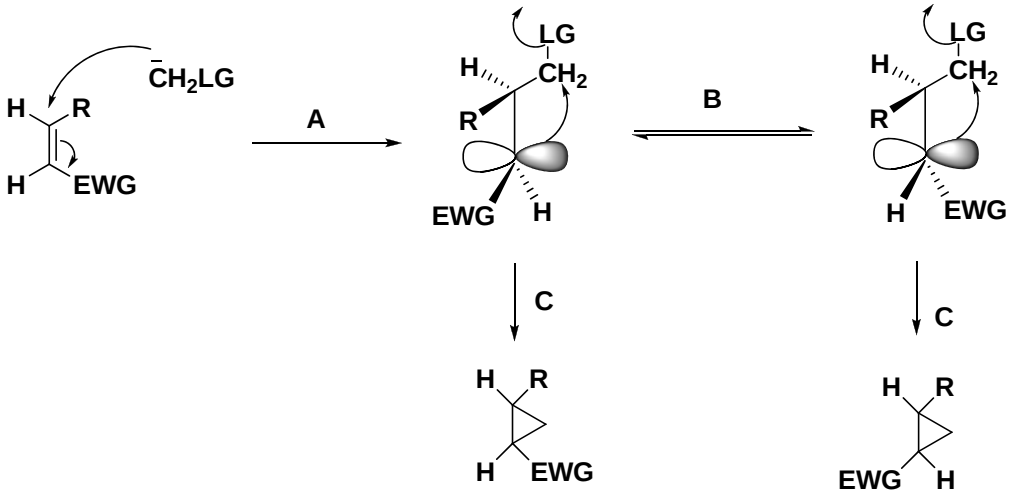
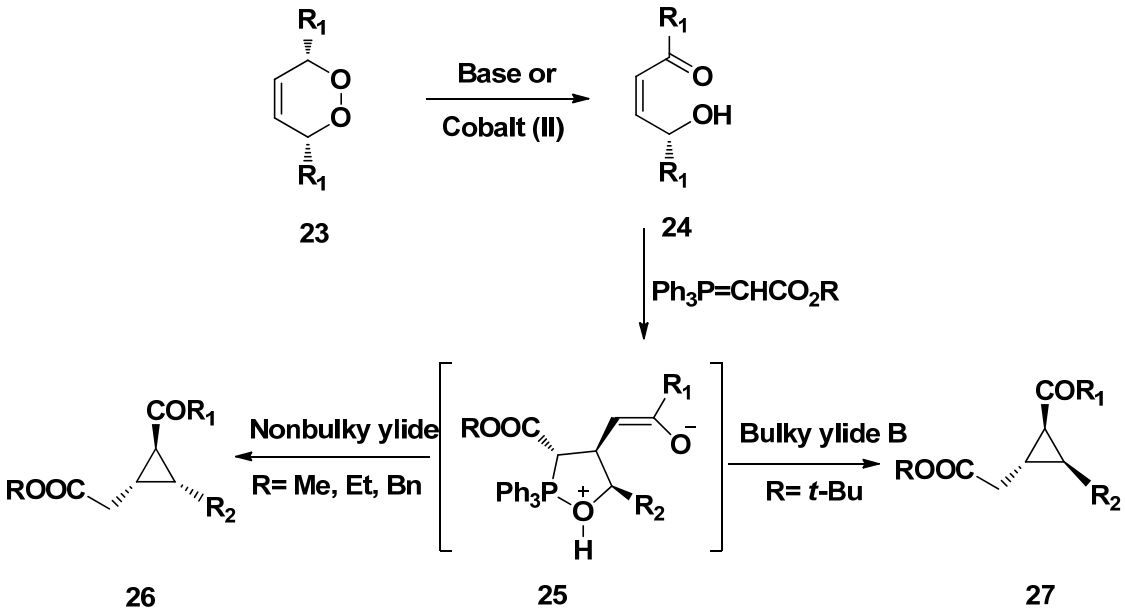


Fig. 3 Michael initiated ring closure cycloproponation reaction

Stereospecific cyclopropanation reactions using the MIRC reaction are observed only when the ring closure process (**Fig. 3**, step C) is faster than the rotation around the single bond in

the first intermediate formed (Step B). Conversely, the formation of a configurationally stable tetrahedral intermediate after the first addition may also lead to a stereospecific process.



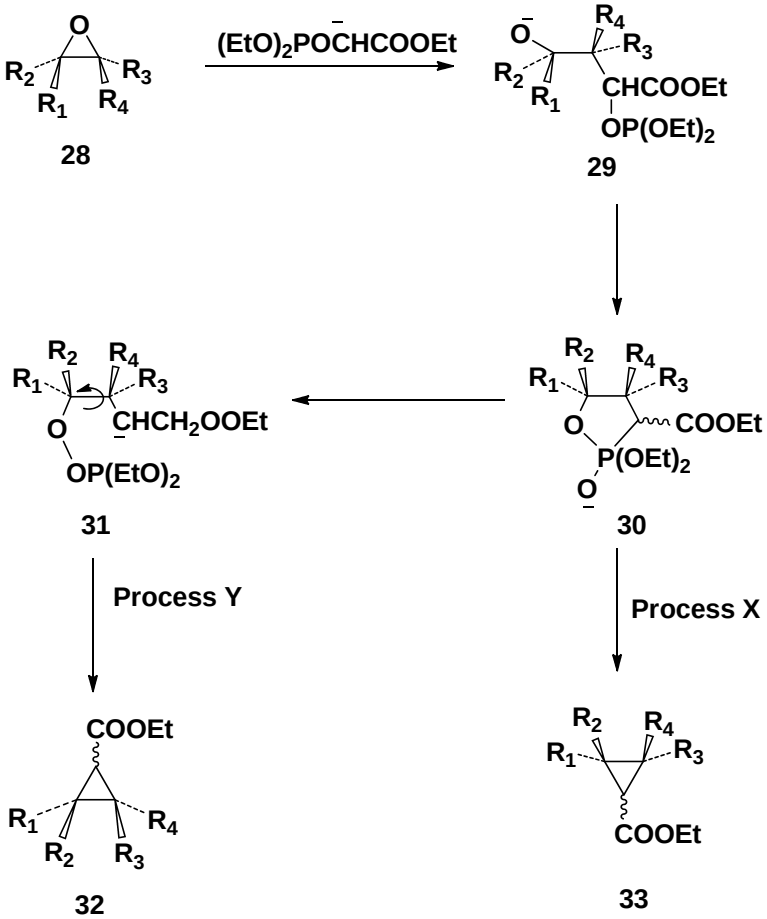
Scheme-7

4.1.3. Wadsworth-Emmons Cyclopropanation

Wadsworth-Emmons cyclopropanation[25] (reaction between epoxides and phosphonates to form cyclopropanecarboxylic acid derivatives) has been known for over four decades but this reaction has rarely been exploited in synthesis due to poor yield and uncertainty in stereospecificity of the reaction. Although certain aspects of the reaction pathway are well understood, there remains some disagreement concerning the overall mechanistic scheme. Different explanations have come to clarify the overall mechanistic scheme.

Denney view[26]

Denney postulated a stepwise decomposition of the intermediate **30** (process **Y** in **Scheme 8**) to give **32** *via* an intramolecular S_N2 displacement. This proposal was based on the observation that carboethoxymethylenetriphenylphosphorane reacted at 200 ^oC with cyclohexene oxide to form ethyl 7-norcaranecarboxylate and with optically active styrene oxide to form optically active *trans*-2-phenylcyclopropanecarboxylate. Denney's inversion mechanism has been supported by Tomoskozi[27] and Walborsky,[28] who established the absolute configuration of optically active *trans*-2-phenylcyclopropanecarboxylic acid.



Scheme-8

In addition to the inversion mechanism the possibility of a competitive direct collapse of **30** (process **X**) either through a concerted process or through a zwitterion intermediate to yield **33** has been suggested.[28-30] Walborsky argued for the occurrence of the competitive direct collapse based on the low optical yields of *trans*-2-phenylcyclopropanecarboxylic acid that had been reported by other workers.[28]

Ghirardelli view[31]

In order to clarify the overall mechanistic scheme, Ghirardelli *et al.* investigated this reaction with optically active *trans*-2,3-dimethyloxiranes **34** and *cis*-2,3-dimethyloxiranes **38**. The use of these two epoxides is advantageous in that the product ratios of *trans*- to *cis*-2,3-dimethylcyclopropanecarboxylic acids that were formed could be directly related to the extent of occurrence of each of the two competing processes.

Table 2

Percent composition of product mixture from reaction of oxides with triethyl phosphonoacetate anion

2,3-Dimethyloxirane	2,3-Dimethylcyclopropanecarboxylic acid			
	trans		cis,cis	cis,trans
	(+)-**35a**	(±) **35**	**36**	**37**
2*R*,3*R*(**34**)	93		6	1
cis-**38**		4	6	90

The above **table 2** results are consistent with Denney's inversion mechanism, since the major product formed in each case requires that its epoxide precursor undergoes an even number of inversions. From the table it is clear that complete reversal of the relative proportions of **36** to **37** produced in each of the two reactions would appear to rule out the existence of an intermediate common to the production of *cis* acids in each as well as

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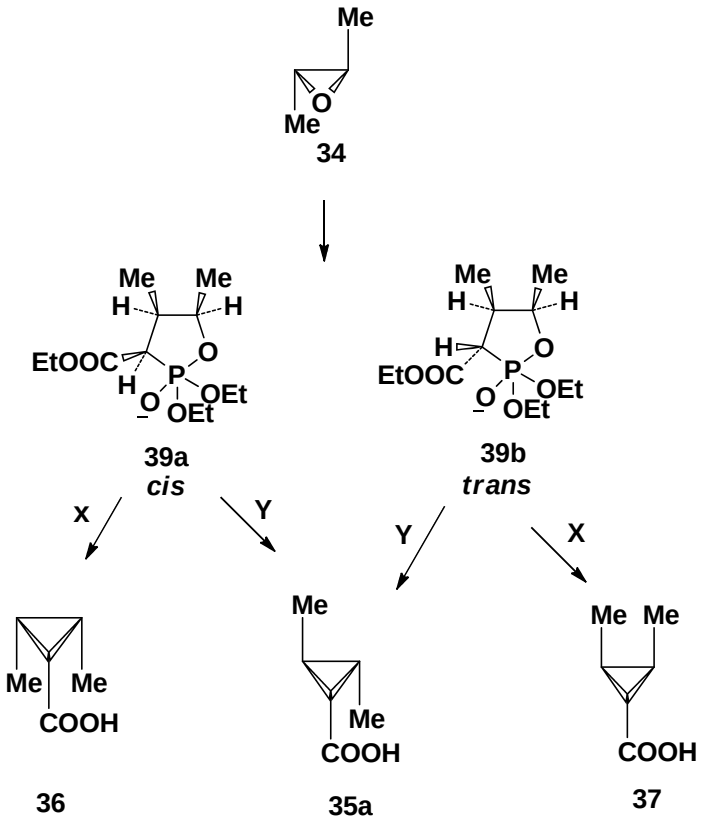


Scheme 9

ruling out their origin in contamination of the active oxide by the *cis* isomer. It is thus probable that the **36** and **37** produced from active oxide **34** and the (±)-**35** from the *cis* oxide **38** arose through a concerted collapse of the corresponding phosphonate esters **30**. (**Scheme 9**)

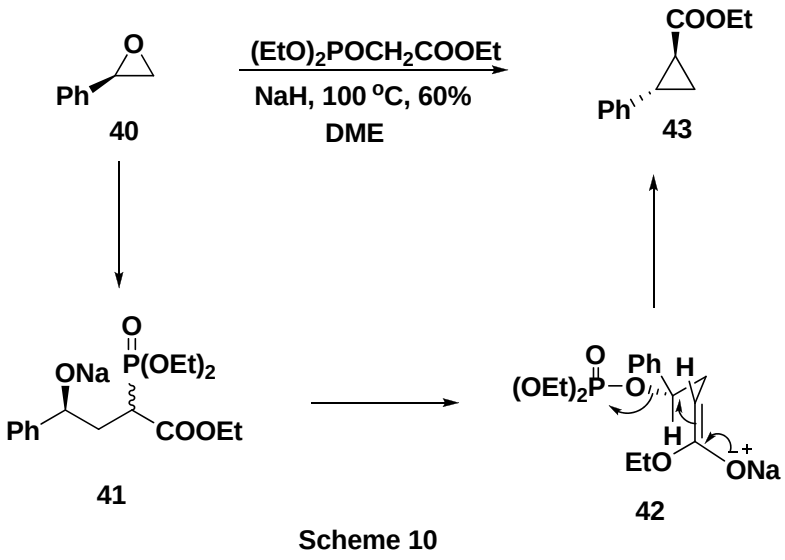
Two important factors in this reaction

(a) The relative amount of **39a** and **39b** produced

(b) The relative probabilities of processes X (collapse) and Y (phosphonate opening, then rear side attack) for each

Armstrong view[32]

Armstrong addressed this issue by converting enantiomerically pure (*R*)-styrene oxide **40** to the (*S*,*S*)-*trans*-2-phenylcyclopropanecarboxylate **43** of >95% ee, thus demonstrating essentially complete inversion of the epoxide configuration.



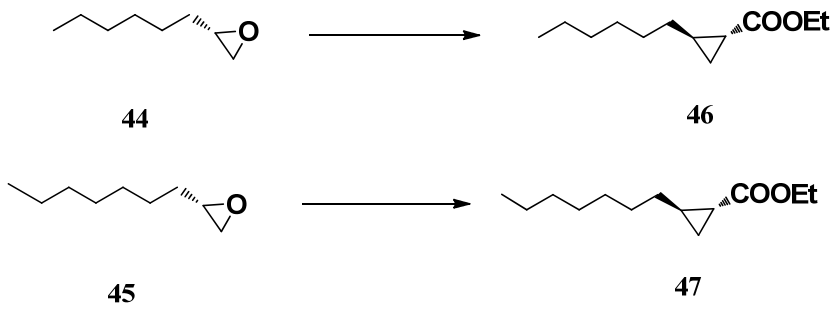
Scheme 10

This is in accordance with the proposed mechanism (**Scheme 10**), which involves epoxide opening followed by migration of the phosphonate group from carbon to oxygen and subsequent S_N2 ring closure.

4.1.4. Optimisation of Reaction Condition

Applicability of the Wadsworth-Emmons cyclopropanation reaction to complex total synthesis has not been explored to larger extent. Therefore, at the outset of our studies, we considered developing an optimised and general synthetic reaction conditions in order to get excellent enanatioselectivity and good yield of this reaction.

We have chosen commercially available (*S*)-2-hexyloxirane **44** and (*S*)-2-heptyloxirane **45** for our study. Screening of a range of solvents, bases, and temperatures (**Table 3**) revealed that the highest yields were obtained using 4 equiv of phosphonate and NaH in toluene at 110 °C, providing the desired **46** and **47** in 85% yield and >95% and 98% ee, respectively.



Scheme 11

Base and Solvent: Since the anion of TEPA can be formed by almost any base (hydrides, hydroxides, alkoxides, amines, and alkyllithiums), we used KO^{t}Bu and NaH in different solvents at different temperatures to find a suitable reaction condition. DME, THF, toluene andd hexane were selected as the reaction solvent. For telescoping of the epoxidation to cyclopropanation better solubility of the TEPA anion is very important during reaction; we found that DME and toluene both works well for this purpose.

Temperature: The rate of reaction was considerably slow at temperature below 50 °C. Therefore, all the reactions were conducted at 80 °C or higher. A careful in-process monitoring (**Fig. 1**) of the reaction revealed that at 80 °C most of the epoxide **44** was consumed in ca. 12 h, and the reaction mixture contained about 5-10% of intermediate. Once the epoxide was consumed, the temperature of the reaction could be raised to 110 °C to "burn-off" the remaining intermediate. This gives improved yield of the reaction in comparison to direct raise of the temperature upto 110 ^{o}C.

Phosphonate Concentration: We found that increasing phosphonate upto 4 equiv dramatically improved the yield upto 85%.

Having optimised the reaction conditions for **44** and **45**, we then turned our attention towards successful implementation of this strategy, leading to enantioselective synthesis cascarillic acid **48**, grenadamide **49**. Here we describe our successful endeavours towards the enantioselective synthesis of cascarillic acid and grenadamide.

Table. 3. Effects of various parameters on the reaction

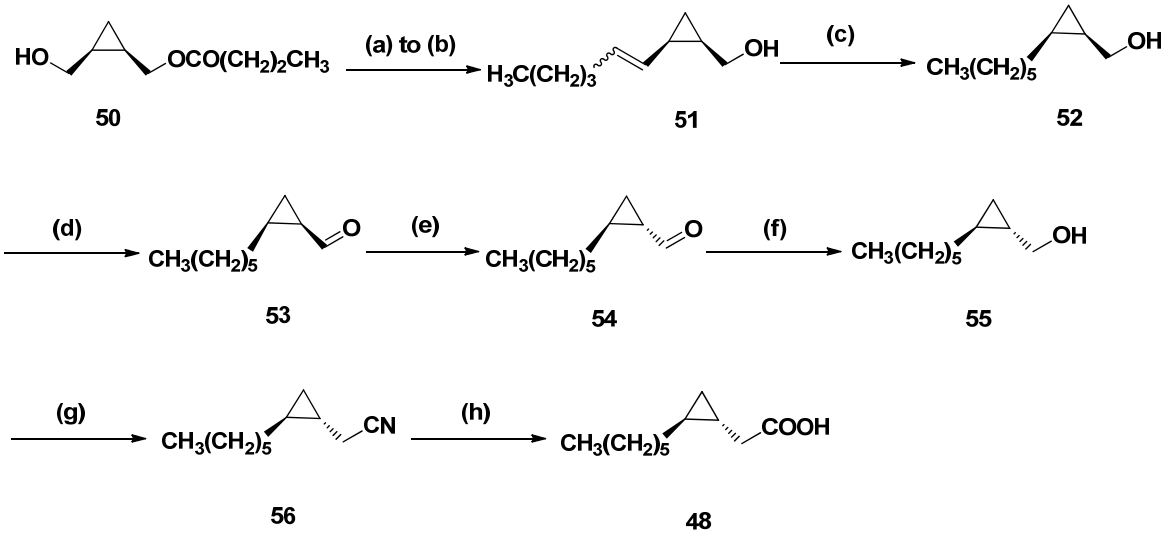
Entry	Base	Eq. TEPA	Solvents	Temp.(^{o}C)	Time (h)	Yield (%)	ee (%)
1.	KO^{t}Bu	2	DME	80	18	55	88
2.		2	Toluene	80	24	65	91
3.		2	THF	80	32	40	75
4.	NaH	2	DME	90	18	75	91
5.		2	Toluene	100	24	55	87
6.		3	THF	80	24	45	79
7.		2	Toluene	110	18	60	90
8.		2	Hexane	70	32	50	85
9.		4	Toluene	110	16	85	>95
10.	KO^{t}Bu	3	DME	90	18	70	87
11.		3	Toluene	110	20	65	93
12.		3	Hexane	70	24	55	90

4.1.5. Review of Literature for Cascarillic Acid

Only two asymmetric methods for the synthesis of (-)-cascarillic acid have been documented in the literature[33,34] as described below.

Baird *et al.* (2004)[33]

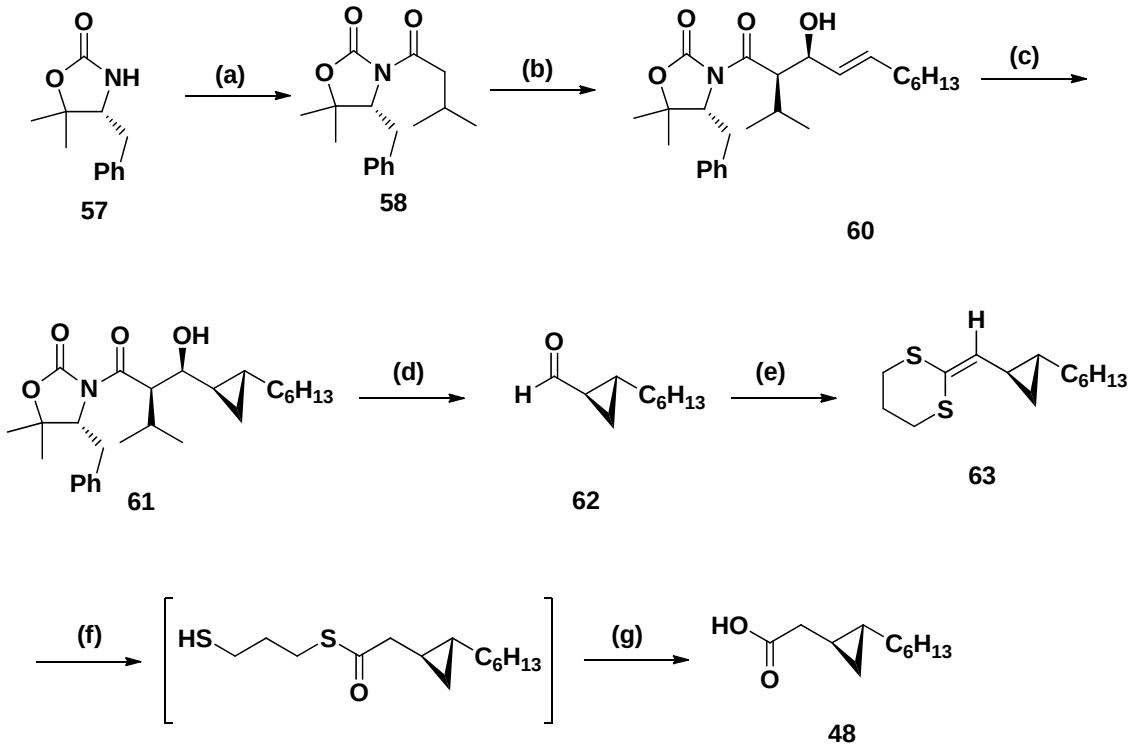
Baird *et al.* have accomplished the synthesis of cascarillic acid **48** by oxidation of monobutyrate ester **50** followed by Wittig reaction to furnish **51**. Reduction to the alcohols, then di-imide reduction of the alkene led to the *cis*-cyclopropane **52**. To form the *trans*-cyclopropane **54**, the alcohol **52** was oxidised to the aldehyde **53** and this was epimerised under basic conditions to **54**. Reduction of **54** to the *trans*-alcohol **55**, then bromination, formation of the nitrile **56** and hydrolysis gave [(1*S*,2*R*)-2-hexylcycloprop-1-yl]-acetic acid **48**.



Scheme 12. *Reagents and conditions*: (a) PCC, CH_2Cl_2; (b) $Br^-P^+Ph_3(CH_2)_4Me$, *n*-BuLi, THF, -40 ^oC; (c) $LiAlH_4$, THF; (d) N_2H_4, H_2O, $NaIO_4$, CH_3COOH, $CuSO_4$, *i*-PrOH; (e) NaOMe, MeOH; (f) 1,2-bis-diphenylphosphinoethane, Br_2, CH_2Cl_2; (g) NaCN, DMSO; (h) NaOH, H_2O, EtOH.

Bull *et al.* (2006)[34]

Bull *et al.* have reported chiral auxiliary mediated diastereoselective cyclopropanation reaction. Compound 5,5-dimethyloxazolidin-2-one **(*R*)-57** on treatment with isovaleroyl chloride gave *N*-isovaleroyl-oxazolidin- 2-one **(*R*)-58** in 87% yield. Treatment of *N*-acyloxazolidin-2-one (*R*)-**58** with (*E*)-non-2-enal **59** resulted in *syn*-aldol **60** in 93% de, Reaction of *syn*-aldol **60** with Et_2Zn/CH_2I_2 resulted in a highly stereoselective cyclopropanation reaction to afford *syn*-cyclopropyl aldol **61** in >95% de and 94% yield. Cyclopropane **61** under basic condition underwent a *retro*-aldol reaction to give the parent chiral auxiliary **(*R*)-57** and the desired 2-hexylcyclopropanecarboxaldehyde **(*R,R*)-62** in 85% yield. Aldehyde **62** was converted into 1,4-dithiane which underwent Peterson elimination followed by sequential acid and base treatment to give cascarillic acid **48**.



Scheme 13. *Reagents and conditions*: (a) *n*-BuLi, isovaleroyl chloride, THF, –78 to 0 °C; (b) 9-BBN-OTf, *i*-Pr_2NEt, CH_2Cl_2, 0 °C; (*E*)-non-2-enal (**59**), –78 °C to rt; (c) Et_2Zn, CH_2I_2, CH_2Cl_2, –10 °C to 0 °C, ; (d) KHMDS, THF, –40 °C; (e) *n*-BuLi, (1,3-dithian-2-yl)trimethylsilane, THF, 0 °C, then (*R*,*R*)-**62**, –30 °C; (f) *p*-TSA, THF–H_2O, reflux; (g) KOH, acetone–H_2O, reflux.

4.1.6. Present Work

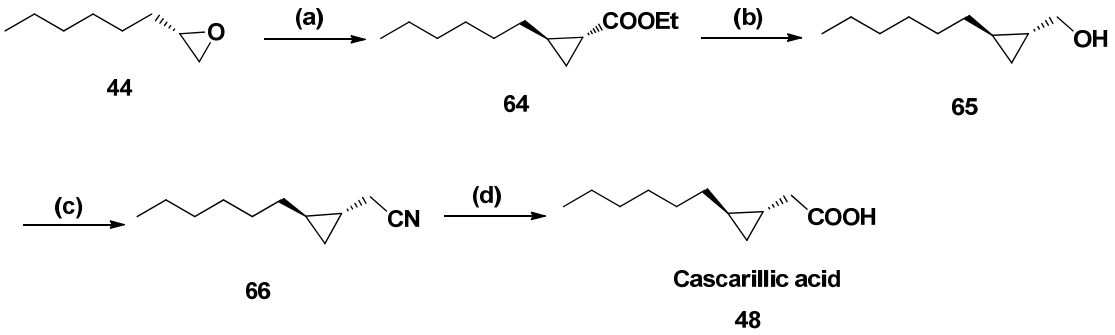
4.1.6.1. Objective

As discussed in foregoing section, only two syntheses[33,34] of cascarillic acid have been reported. Baird and co-workers have confirmed the absolute stereochemistry of this natural product to be (3*S*,4*R*) through its total synthesis in 11 steps from *meso-cis*-1,2-dihydroxymethylcyclopropane. This synthesis included an enzymatic desymmetrisation step to introduce the stereogenic centres of the cyclopropane ring, and an epimerisation step to invert a *cis*-cyclopropane ring into its corresponding *trans*-isomer. Consequently, Bull and co-workers now reported an alternative synthetic strategy that affords cascarillic acid in six steps from the chiral auxiliary (*R*)-*N*-isovaleroyl-4-benzyl-5,5-dimethyl-oxazolidin-2-one **58**. Both these methods suffer either from multisteps, epimerization steps and unwanted

protection and deprotection step of chiral auxiliary. Taking into account the drawback of reported methods, we considered developing a practical, concise, expeditious and high-yielding synthesis of the target molecule.

4.1.6.2. Results and Discussion

An alternative synthetic sequence for the synthesis of cascarillic acid employing optimized Wadsworth-Emmons cyclopropanation is shown in **Scheme 14**. Commercially available (*S*)-2-hexyloxirane **44** was subjected to Wadsworth-Emmons cyclopropanation to furnish the ester **64**. The IR spectrum of **64** showed the presence of ester peak at 1727 cm^{-1}. In the ^{1}H NMR spectrum cyclopropane methylene peaks appeared at δ 0.63-0.72 (m) and ethyl ester peak appeared at 1.04-1.34 for methyl and for $–CH_2$ at δ 4.01 (q). In the ^{13}C NMR spectrum of **64** cyclopropane methylene peaks appeared at δ 14.0. The ester group is subjected to reduction with $LiAlH_4$ to furnish alcohol **65**. The IR spectrum of **65** showed the disappearance of ester peak and presence of broad hydroxyl peak at 3350 cm^{-1}. Alcohol was converted into nitrile compound by using combination of Me_3SiCl:NaCN (1:1) and NaI. The IR spectrum of compound **66** showed the presence of nitrile peak at 2251 cm^{-1}. In the ^{1}H NMR spectrum $-CH_2CN$ peak appeared at δ 2.36 (m) and in the ^{13}C NMR spectrum of **66** nitrile carbon peak appeared at δ 118. Finally nitrile **66** was converted into acid **48** by basic hydrolysis, which was fully characterized by ^{1}H & ^{13}C NMR spectroscopy.



Scheme 14 : *Reagents and conditions*: (a) $(EtO)_2POCH_2COOEt$, NaH, 80 ^{o}C (8 h) then 110 ^{o}C (6 h), 85%; (b) $LiAlH_4$, THF, -10 ^{o}C, 80%; (c) Me_3SiCl, NaCN (1:1), NaI (cat), DMF:Acetonitrile, 65 ^{o}C, 80%; (d) 3N NaOH, reflux, $MeOH/H^{+}$, 75%.

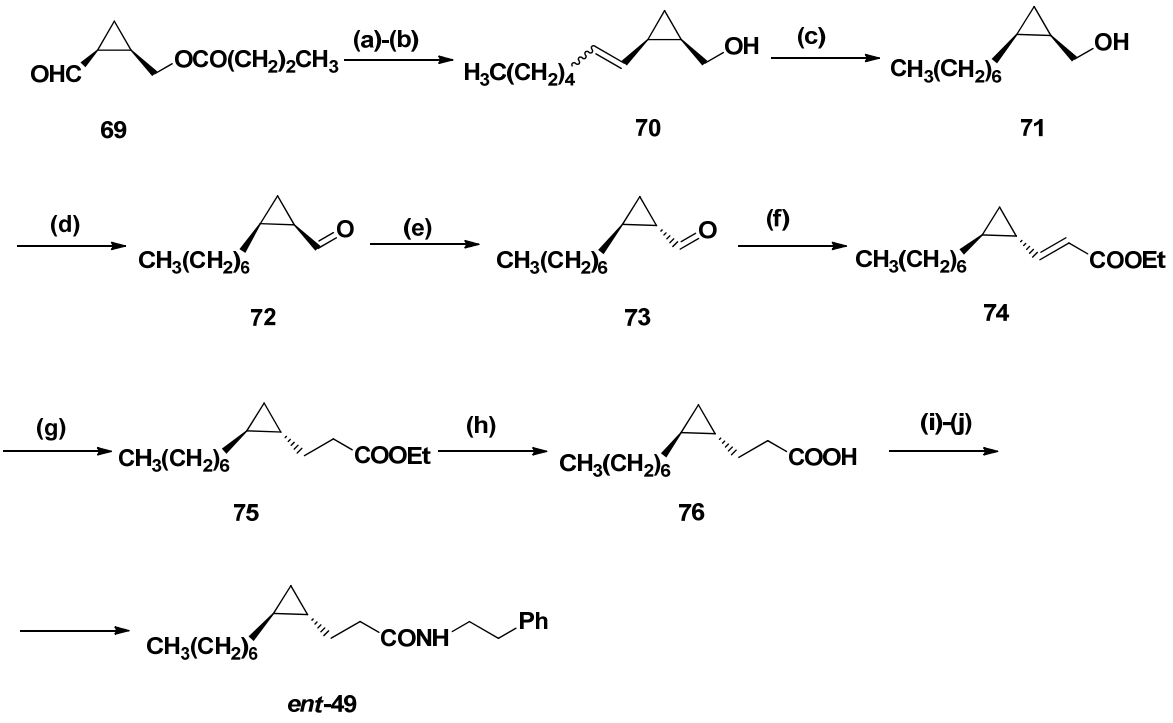
The cyclopropane protons (4H) appeared as multiplet at δ 0.30-0.37($-CH_2$), 0.48-0.64 (-CH) and another proton at δ 0.70-0.91 (-CH). The acid proton resonated at δ 9.61 as (brs, 1H). ^{13}C NMR spectrum along with DEPT spectrum showed the presence of single methylene carbon

resonating at δ 12.0, was ascribed to the cyclopropane –$\underline{C}H_2$ while other carbon peaks appeared at δ 13.9, 14.1, 18.9, 22.6, 29.1, 29.3, 32.0, 33.8, 38.9. The carbonyl carbon peaks of free acid resonated at δ 179.9. Thus, we have accomplished the synthesis of cascarillic acid in four steps and in 41% overall yield. The physical and spectroscopic data of **48** were in full agreement with that reported in literature.[34]

4.1.7. Review of Literature for Grenadamide

Baird *et al.* (2004)[35]

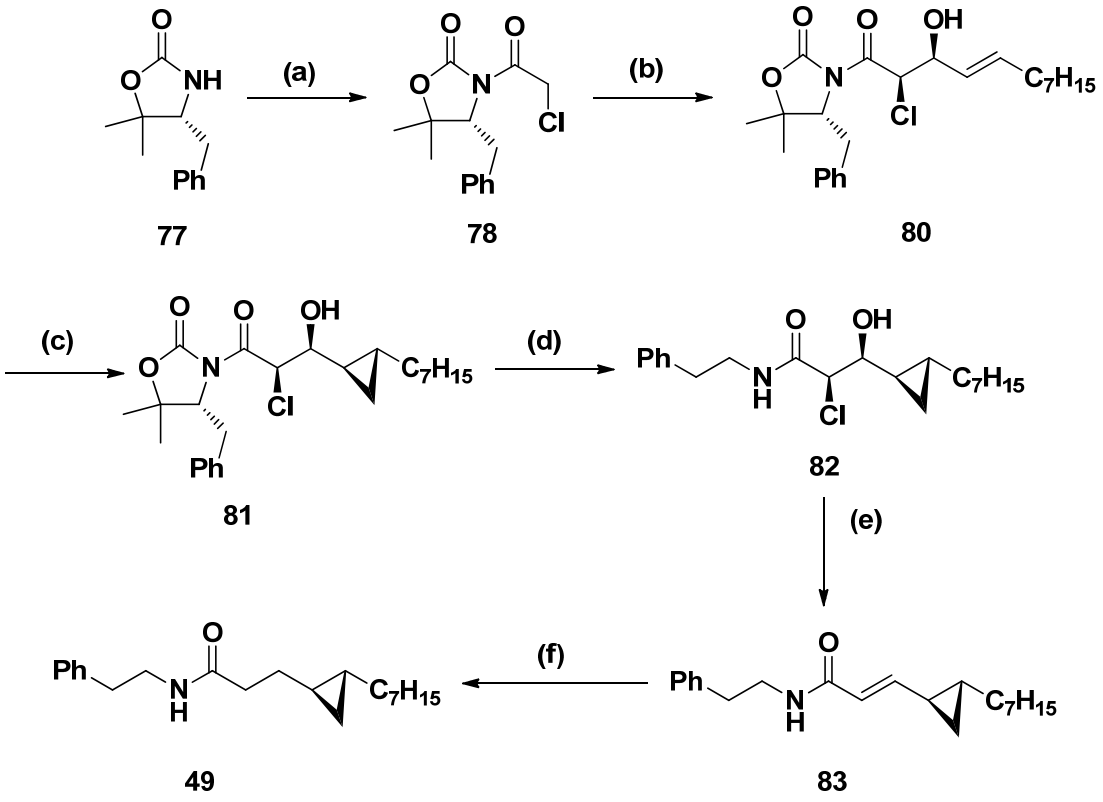
Baird *et al.* have accomplished the synthesis of grenadamide by using enzymatic hydrolysis and epimerisation steps. The selective enzymatic hydrolysis of *cis*-cyclopropane-1,2-dimethanol di-*n*-butyrate **67** to (2*R*-*n*-butyryloxymethyl-cycloprop-1*S*-yl)methanol **68**, followed by oxidation furnished **69.** Compound **69** on Wittig reaction and hydrolysis of ester followed by subsequent di-imide reduction of the alkene led to the *cis*-cyclopropane **71**. Oxidation to **71** and epimerisation using sodium methoxide in methanol gave a 19:1 mixture of **73** and **72**; reaction of the mixture with ethoxycarbonyl triphenylphosphorane gave the *trans* ester **74**. The double bond reduction followed by basic hydrolysis furnished **76**, which was converted into the corresponding acid chloride and coupled with 2-phenylethylamine to give the grenadamide ***ent*-49**.



Scheme 15. *Reagents and conditions*: (a) $BrPh_3P(CH_2)_5CH_3$, *n*-BuLi, THF, -78 ^oC (55%; *Z*:*E* 4.6:1); (b) K_2CO_3, MeOH, 86%; (c) aq. $CuSO_4$, hydrazine hydrate, $NaIO_4$, *i*PrOH, AcOH, 86%; (d) PCC, CH_2Cl_2, 91%; (e) NaOMe, MeOH, reflux, (84%; 19:1 *trans*:*cis*); (f) $Ph_3PCHCOOEt$, toluene, 71%; (g) $KO_2CN{=}NCO_2K$, AcOH, MeOH, rt, 83%; (h) KOH, EtOH, H_2O, rt, 86%; (i) $SOCl_2$; (j) $PhCH_2CH_2NH_2$, 52% for two steps.

Bull, S. D. *et al.* (2005)[36]

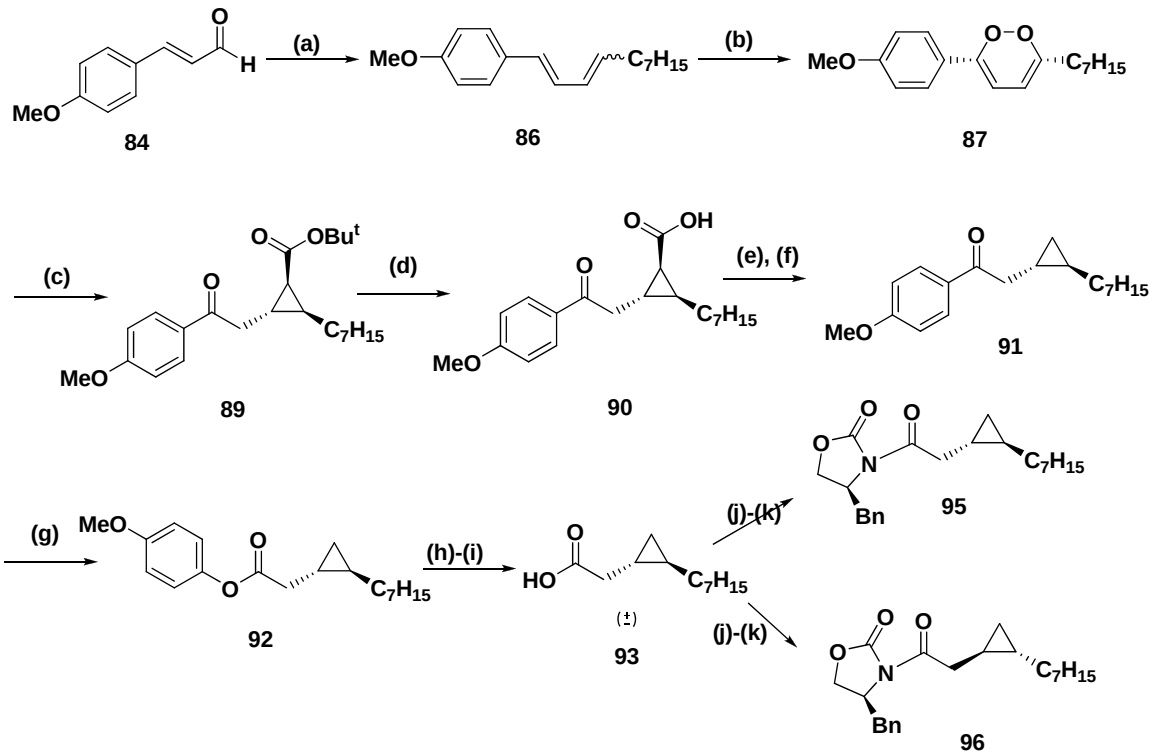
Bull, S. D. *et al.* have accomplished the synthesis of grenadamide by chiral auxiliary mediated cyclopropanation. The chiral auxiliary **(*R*)-77** was treated with chloroacetyl chloride to furnish chloroacetyl-oxazolidin-2-one **78** in 78% yield. Treatment of **78** with (*E*)-dec-2-enal **79** resulted in *syn*-aldol **80** in 92% de. Reaction of *syn*-aldol **80** with Et_2Zn/CH_2I_2 resulted in a highly stereoselective cyclopropanation reaction, to afford *syn*-cyclopropyl aldol **81** in >95% de. Compound **81** was transformed into grenadamide **82** by replacing the oxazolidin-2-one fragment with phenylethylamine, to furnish the amide **82** in 89% yield, which on treatment with SmI_2 resulted in β-elimination to afford (*E*)-α,β-unsaturated amide **83** in 85% yield. Conjugate reduction of the alkene functionality of vinyl-cyclopropane **83** with $NaBH_4$ and $CoCl_2$ in MeOH/THF furnished grenadamide **49** in 88% yield.

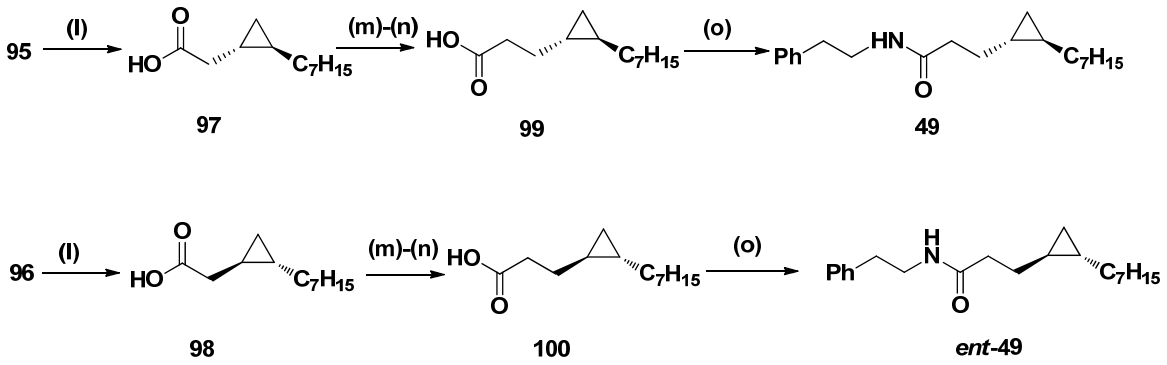


Scheme 16. *Reagents and conditions*: (a) *n*-BuLi, THF, -78 ^{o}C; chloroacetyl chloride, 78%; (b) 9-BBN-OTF, iPr_2NEt, CH_2Cl_2, 0 ^{o}C; (*E*)-dec-2-enal **79**, -78 ^{o}C, 74%; (c) Et_2Zn, CH_2I_2, CH_2Cl_2, -10 to 0 ^{o}C, 98%; (d) phenethylamine, 25 ^{o}C, 89%; (e) SmI_2, THF, 25 ^{o}C, 85%; (f) $CoCl_2$, MeOH/THF (2:1), 25 ^{o}C; $NaBH_4$, DMF, 88%.

Taylor, D. K. *et al.* (2006)[37]

Taylor *et al.* reported the synthesis of Grenamide by Wittig coupling of 4-methoxycinnamaldehyde **84** and octyltriphenylphosphonium iodide **85** to produce diene **86**. Photolysis of 1,3-diene **86** in the presence of oxygen and rosebengal bis(triethylammonium) salt gave the desired 1,2-dioxine **87** in 37% yield. Reaction of the *tert*-butyl ester ylide **88** with 1,2-dioxine **87** gave cyclopropane **89** in 55% yield. The *tert*-butyl ester of compound **89** was hydrolyzed in the presence of 99% formic acid to give acid **90** in 89% yield, which was subsequently decarboxylated using the Barton protocol to produce **91** in 86% yield. Baeyer–Villiger oxidation of the resultant ketone **91** using MCPBA proceeded with excellent selectivity to give phenol ester **92** in 91% yield. The ester **92** was hydrolysed to acid **93** and resolved by Evans' auxiliary **94** and converted into pure diastereomeric product **95** and **96**. The auxiliary was then cleaved and the





Scheme 17. *Reagents and conditions*: (a) Octyltriphenylphosphonium iodide, KO*t*Bu, THF, 0 ^{o}C to rt, 77%; (b) O_2, rose bengal bis(triethylammonium)salt (cat.), CH_2Cl_2, *hv*, 5 ^{o}C, 37%; (c) $Ph_3P{=}CHCO_2tBu$ **88**, LiBr, 55%; (d) 99% Formic acid (excess), rt, 89%; (e) DCC, 2-mercaptopyridine *N*-oxide, CH_2Cl_2, 0 ^{o}C; (f) *t*BuSH, benzene, *hv*, rt, 86% for two steps; (g) *m*CPBA, CH_2Cl_2, rt, 91%; (h) MeOH, conc. H_2SO_4 (cat.) reflux, 93%; (i) 2N KOH, MeOH–H_2O (4:1), rt, 93%; (j) Oxalyl chloride, DMF (cat.), DCM, 0 ^{o}C (2 h) to rt (2 h); (k) (*S*)-(-)-4-Benzyl-2-oxazolidinone, *n*BuLi, THF, −78 ^{o}C, 69% for two steps; (l) LiOH, H_2O_2 30%, H_2O, THF, 0 ^{o}C, ; (m) Oxalyl chloride, DMF (cat.), DCM, 0 ^{o}C (2 h) → rt (2 h); (n) CH_2N_2, triethylamine, Et_2O, 0 ^{o}C, ; (o) $PhCO_2Ag$, phenethylamine, THF, Et_3N, −15 ^{o}C→rt, .

enantiomerically pure fatty acids **97** and **98** were subjected to the Arndt–Eistert protocol to give (−)-**99** and (+)-**100**. Compound **99** and **100** were converted into the corresponding acid chlorides and coupled with 2-phenylethylamine to give grenadamide **49** and ***ent*-49**.

4.1.8. Present Work

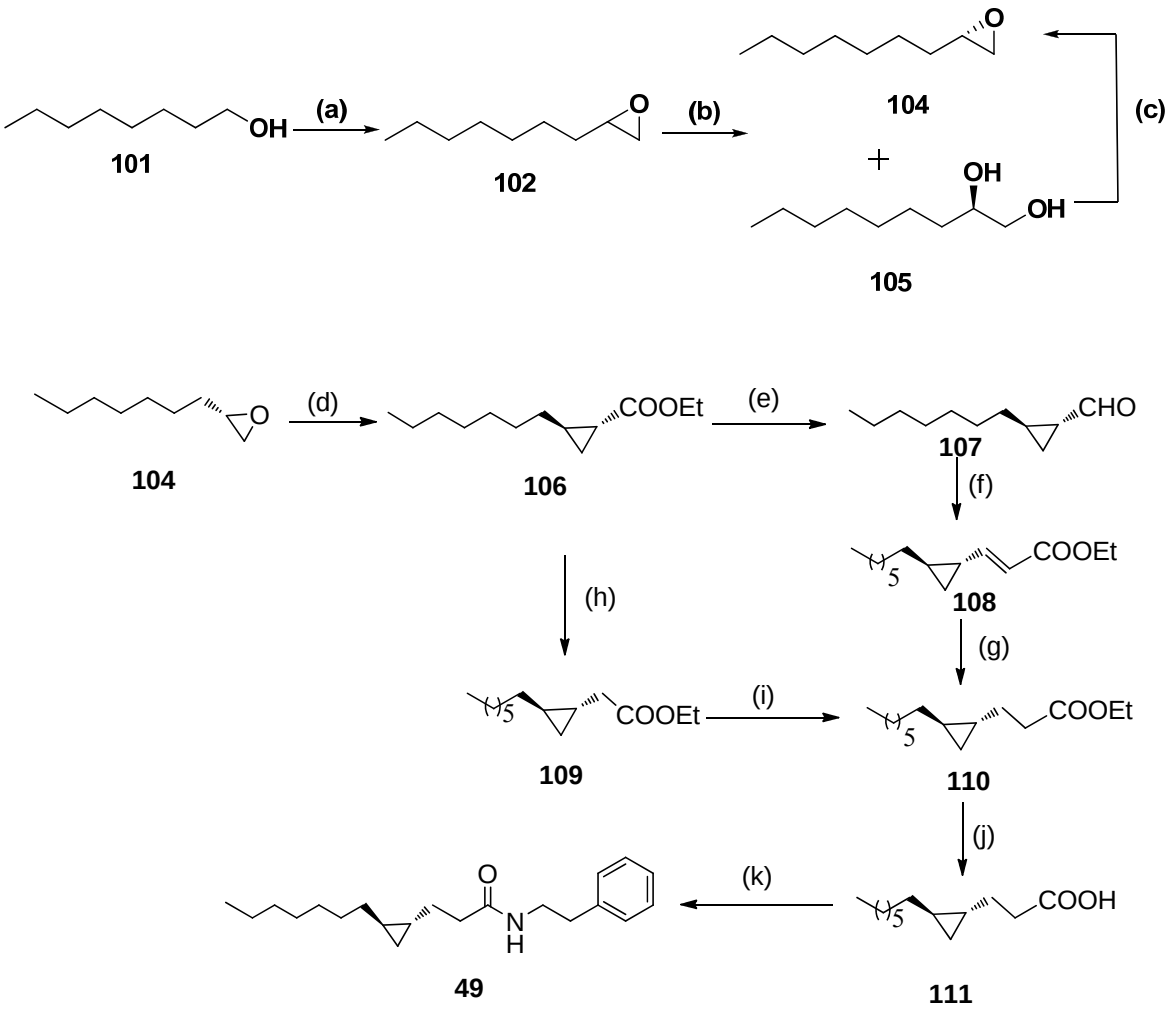
4.1.8.1. Objective

Although few synthesis[35-38] of target molecule as described above has been reported but drawback associated with these methods are that they suffer either from multisteps, epimerization steps and unwanted protection and deprotection step of chiral auxiliary. Therefore a practical, concise, expeditious and high-yielding synthesis of the target molecule is highly desirable.

4.1.8.2. Results and Discussion

The synthesis of (-)-grenadamide started from commercially available octan-1-ol **101** as illustrated in **Scheme 18**. The compound **101** was oxidized to the corresponding aldehyde

under Swern oxidation conditions[39] followed by Corey–Chaykovsky reaction[40] with dimethylsulfoxonium methylide to afford the racemic epoxide **102** in 85% yield. The epoxide peaks appeared at δ 2.53-2.57 (m, one proton), 2.78-2.83 (m, one protons), 3.07-3.11(m, one proton), in ^{1}H NMR spectrum. The ^{13}C NMR spectrum of **30** showed carbons of epoxide at δ 50.0, 47.0. Jacobsen's hydrolytic kinetic resolution[41] of rac-epoxide (±)-**102** with (*S*,*S*)-Salen-Co-OAc catalyst **103** gave (*S*)-epoxide **104** in >98% ee [HPLC: Chiracel OD-H column (2-propanol/petroleum ether=4:96, flow rate 0.5 mL/min, λ=220



Scheme 18 : *Reagents and conditions*: (a) (i) Oxalyl chloride, DMSO, Et_3N, -78^{o}C, 4 h; (ii) Trimethylsufoxonium iodide, DMSO, NaH, 0 ^{o}C, 5 h, 85%; (b) (*S*,*S*)-Salen-Co^{III}-(OAc) **103** (0.5 mol %), distd H_2O (0.60 equiv), 0 ^{o}C, 24 h, (48% for **104**, 48% for **105**); (c) [i] Pivaloyl chloride, Et_3N, CH_2Cl_2, 6 h; [ii] CH_3SO_2Cl, Et_3N, CH_2Cl_2, 2 h; [iii] K_2CO_3, MeOH, 1 h, 72% for three steps; (d) $(EtO)_2POCH_2COOEt$, NaH, 80 ^{o}C (8 h) then 110 ^{o}C (6 h), 85%; (e) DIBAL, THF, -78 ^{o}C, 10 h, 72%; (f) $Ph_3PCHCOOEt$, toluene, 12 h, 71%; (g) $KO_2CN{=}NCO_2K$, AcOH, MeOH, rt, 48 h, 73%; (h) $LiCHBr_2$, -90 ^{o}C, tetramethyl piperidine,

55%; (i) $LiCHBr_2$, -90 ^oC, tetramethyl piperidine, 60%; (j) LiOH, MeOH:H_2O (3:2), 82%; (k) $SOCl_2$, $PhCH_2CH_2NH_2$, 4 h, 65%.

nm). Retention time (min): 18.59 (major) and 19.4 (minor). The racemic standard was prepared in the same way with racemic epoxide, ee >98% in 48% yield, which was easily isolated from the more polar diol (*R*)-**105** by silica gel column chromatography**.** With enantiomerically pure epoxide (*S*)-**104** in hand, our next aim was to construct the cyclopronane unit. (*S*)-Epoxide **104** was subjected to Wadsworth-Emmons cyclopropanation to furnish cyclopropane ester **106** in 85% yield. The IR spectrum of **106** showed the presence of ester peak at 1727 cm^{-1}. In the ^1H NMR spectrum cyclopropane methylene peaks appeared at δ 0.63-0.72 (m) and ethyl ester peak appeared at δ 1.04-1.34 (for $–CH_3$) and at δ 4.01 (q, for $–CH_2$). In the ^{13}C NMR spectrum of **106** cyclopropane methylene peaks appeared at δ 14.0.

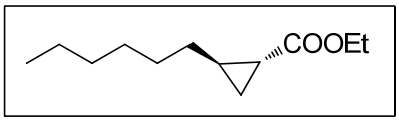
In order to prepare compound **110**, we thought to convert ester **106** into aldehyde **107** followed by 2-C Wittig reaction, but we observed an epimerisation of chiral center in aldehyde **107**, then we turned our attention towards sequential homologation of ester. The ester group of compound **106** was double homologated[42] to furnish compound **110** in moderate yield for two steps by using combination of $LiCHBr_2$:*n*-BuLi: tetramethylpiperidine reagent. The ester group of compound **110** was hydrolysed under basic conditions using LiOH to furnish acid **111** in 82% yield. The IR spectrum of **111** showed the presence of acid peak at 3420 cm^{-1}. ^1H NMR spectrum showed the disappearance of ethyl ester peaks. Acid **111** was converted into acid chloride by using $SOCl_2$ and acid chloride was finally coupled with phenylethylamine to furnish greanadamide **49** in 65% yield. In the ^1H NMR of compound **49**, the cyclopropane protons (4H) appeared as multiplet at δ 0.28-0.32 ($-CH_2$), 0.51-0.54 (-CH) and at δ 0.51-0.54 (-CH). The -NH proton resonated at δ 5.43 (brs, 1H) and phenyl proton resonate at 7.19-7.43 (m, 5H). ^{13}C NMR spectrum along with DEPT spectrum showed the presence of single methylene carbon resonating at δ 11.4, was ascribed to the cyclopropane $–\underline{C}H_2$ while other carbon peaks appeared at δ 14.1, 18.2, 19.5, 22.6, 27.0, 29.3, 29.6, 29.9, 31.9, 32.6, 35.7, 36.9, 40.5, 126.5, 128.7, 138.9. The carbonyl carbon peaks of amide group resonated at δ 173.1. The physical and spectroscopic data of **49** were in full agreement with those reported.[37]

4.1.9. Experimental Section

General information

All reactions requiring anhydrous conditions were performed under a positive pressure of argon using oven-dried glassware (110 °C), which was cooled under argon. Solvents for anhydrous reactions were dried according to Perrin *et al*.[43] Solvents used for chromatography were distilled at respective boiling points using known procedures. Progress of the reactions was monitored by TLC using precoated aluminium plates (Merck silica gel 60 F254). Column chromatographies were performed on silica gel 60-120/ 100-200/ 230-400 mesh obtained from S. D. Fine Chemical Co. India or Spectrochem India. IR spectra were recorded on a Perkin–Elmer infrared spectrometer model 599-B and model 1620 FTIR. ^{1}H NMR spectra were recorded on Bruker AC-200, Bruker AV-400 and Bruker DRX–500 instruments using deuterated solvent. Chemical shifts are reported in ppm. Proton coupling constants (*J*) are reported as absolute values in Hz and multiplicity (brs, broad; s, singlet; d, doublet; t, triplet; m, multiplet). ^{13}C NMR spectra were recorded on Bruker AC-200, Bruker AV- 400 and Bruker DRX-500 instruments operating at 50 MHz, 100 MHz, and 125 MHz, respectively. ^{13}C NMR chemical shifts are reported in ppm relative to the central line of $CDCl_3$ (δ 77.0). Microanalytical data were obtained using a Carlo–Erba CHNS-0 EA 1108 elemental analyzer. All the melting points were recorded on a Büchi B-540 electrothermal melting point apparatus. Yields refer to chromatographically and spectroscopically pure compounds. Enantiomeric excess was determined using Mosher analysis.

(1*R*,2*R*)-Ethyl 2-hexylcyclopropanecarboxylate (64):



To a suspension of sodium hydride (4.67 g, 116.97 mmol, 60% in mineral oil) in toluene (100 ml) at 0 ^{o}C was added triethylphosphonoacetate (31 ml, 155.99 mmol) dropwise over 30 min. After stirring for 10 min, epoxide **44** (5 g, 38.99 mmol) in 20 mL of toluene was added dropwise over 20 min, followed by heating at 80 ^{o}C for 8 h, then raising temperature upto 110 ^{o}C. After completion of reaction (6 h), the solution was cooled to room temperature, diluted with EtOAc (100 ml), then washed with saturated aqueous NH_4Cl (100 ml). After drying over Na_2SO_4 and concentration in vacuo, the crude material was purified by flash

chromatography using petroleum ether/EtOAc (98:2) as eluent, to give the desired cyclopropane derivative **64** as syrupy colorless oil.

Yield: 6.57 g, 85%.

Mol. Formula: $C_{12}H_{22}O_2$

$[\alpha]_D^{25}$: -25.4 (*c* 1.2, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 2927, 2958, 2856, 1727, 1613, 1583, 1452, 1410, 1177, 1097, 757.

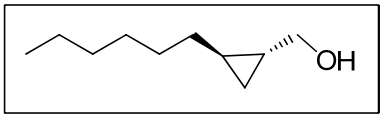
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.63-0.72 (m, 1H), 0.88 (t, *J* = 5.2 Hz, 3H), 1.04-1.34 (m, 16H), 4.1 (q, *J* = 7.0, 14.2 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 14.2, 15.4, 20.1, 22.5, 22.8, 28.9, 29.0, 31.7, 33.0, 60.2, 174.5.

MS(ESI): m/z 221.30 $(M+Na)^+$.

Anal. Calcd.: C, 72.68; H, 11.18%; **Found:** C, 72.35; H, 11.02%.

(1*R*,2*R*)-2-Hexylcyclopropyl)methanol (65):



To a stirred suspension of $LiAlH_4$ (765 mg, 20.17 mmol) in dry THF (100 mL) at -10 °C was added ester **64** (5 g, 25.21 mmol) over 20 min under argon atmosphere. After stirring for 20 min, the reaction was quenched by adding 10% aqueous NaOH at 0 °C. The mixture was filtered with pad of celite, and washed with EtOAc. The organic layer was dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) as eluent gave **65** as a colorless syrupy liquid.

Yield: 3.15 g, 80%.

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

$[\alpha]_D^{25}$: -22.24 (*c* 1.0, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 3350, 2854, 1466, 1216, 1033.

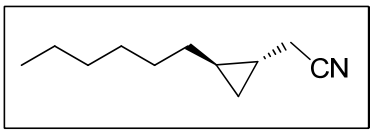
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.26-0.41 (m, 2H), 0.55-0.67 (m, 1H), 0.76-0.91 (m, 4H), 1.15-1.47 (m, 10H), 1.70 (brs, 1H), 3.44 (dd, *J* = 1.9, 7.0 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 9.84, 14.0, 17.1, 21.0, 23.0, 29.0, 29.5, 31.8, 33.5, 67.0.

MS (ESI): m/z 178.96 $(M+Na)^+$.

Anal. Calcd. **:** C, 76.86; H, 12.90 %; **Found:** C, 76.65; H, 12.72%.

2-((1*S*,2*R*)-2-Hexylcyclopropyl)acetonitrile (66):



A solution of alcohol **65** (2.0 g, 12.10 mmol), NaCN (1.25 g, 25.59 mmol), NaI (5-10 mg) in CH_3CN (20 mL) and DMF (10 mL) was deaerated, under an argon atmosphere, and Me_3SiC1 (3.24 mL, 25.29 mmol) was added at room temperature. The mixture was then placed in a preheated (60-65 ^oC) oil bath and heated with stirring for 6 h. After consumption of starting material, the mixture is poured into H_2O (100 mL) and the mixture extracted with Et_2O (100 mL). The organic phase was washed with H_2O (5 x 50 mL) and with brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (95:5) as eluent gave **66** as a pale yellow color syrupy liquid.

Yield: 1.69 g, 80%.

Mol. Formula: $C_{11}H_{19}N$

$[\alpha]_D^{25}$: -17.97 (*c* 1.0, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 2927, 2251, 1460, 1215, 668.

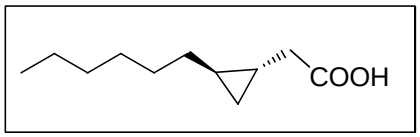
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.37-0.51 (m, 2H), 0.60-0.81 (m, 2H), 0.89 (t, *J* = 6.6 Hz, 3H), 1.15-1.5 (m, 10H), 2.36 (dd, *J* = 2.3, 6.6 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 11.9, 13.9, 14.0, 18.9, 21.5, 22.5, 29.0, 29.2, 31.7, 33.3, 118.8.

MS (ESI): m/z 188.16 $(M+Na)^+$.

Anal. Calcd.: C, 79.94; H, 11.59; N, 8.47 %; **Found:** C, 79.75; H, 11.70; N, 8.23%.

2-((1*S*,2*R*)-2-Hexylcyclopropyl)acetic acid (48):



A solution of nitrile **66** (1.0 g, 6.05 mmol) and 20 mL of 3N NaOH in 58 mL of methanol was refluxed for 6 h. Then reaction mixture was cooled to 0 ^oC, acidified to pH 5 with 1M aqueous hydrochloric acid, and partitioned between EtOAc and brine. The organic phase was washed with H_2O (1 x 50 mL) and with brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (8:2) as eluent gave **48** as a pale yellow color syrupy liquid.

Yield: 0.84 g, 75%.

Mol. Formula: $C_{11}H_{20}O_2$

$[\alpha]_D^{25}$: –9.80 (*c* 0.50, $CHCl_3$); {lit.[34]: **$[\alpha]_D^{25}$** –10.5 (*c* 0.553, $CHCl_3$)}.

IR (neat, cm^{-1}): ν_{max} 3420, 2855, 1711, 1458, 1216, 759, 668.

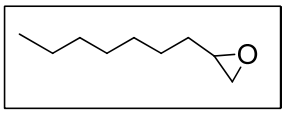
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.30-0.37 (m, 2H), 0.48-0.64 (m, 1H), 0.70-0.91 (m, 4H), 1.11-1.47 (m, 10H), 2.26 (d, *J* = 7.2 Hz, 2H), 9.61 (brs, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 12.0, 13.9, 14.1, 18.9, 22.6, 29.1, 29.3, 32.0, 33.8, 38.9, 179.9.

MS (ESI): m/z 207.31 $(M+Na)^+$.

Anal. Calcd. : C, 71.70; H, 10.94 %; **Found:** C, 71.90; H, 10.70%.

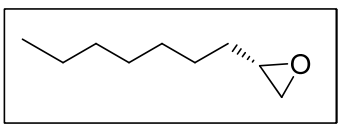
2-Heptyloxirane (102):



(i) Swern oxidation. To a solution of oxalyl chloride (9.88 mL, 115.18 mmol) in dry CH_2Cl_2 (100 mL) at -78 ^oC was added dropwise over 20 min dry DMSO (16.35 mL, 230.36 mmol) in CH_2Cl_2 (30 mL). After 30 min, alcohol **101** (10.0 g, 76.78 mmol) in CH_2Cl_2 (30 mL) was added dropwise over 20 min giving copious white precipitate. After stirring for 2 h at -78 ^oC, the reaction mixture was brought to -60 ^oC and Et_3N (47.08 mL, 337.83 mmol) was added dropwise over 20 min and stirred for 30 min allowing the reaction mixture to warm to room temperature. The reaction mixture was then diluted with H_2O (100 mL) and CH_2Cl_2. The organic layer was separated and washed with H_2O and brine, dried over Na_2SO_4 and passed through short pad of celite. The filtrate was concentrated to give the aldehyde (9.37 g, 95%) as pale yellow oil, which was used as such for the next step without purification.

(ii) To a solution of trimethylsulfoxonium iodide (16.05 g, 72.94 mmol) in dry DMSO was added NaH (2.91 g, 72.94 mmol, 60% in mineral oil). After 1 h, aldehyde (9.35 g, 72.94 mmol) dissolved in THF was added at 25 ^oC. After stirring for 2 h ice was added to the reaction mixture and the reaction mixture was extracted with H_2O, brine, dried over Na_2SO_4. Solvent was removed under pressure and the crude product was purified by silica gel column chromatography using pet ether/EtOAc (97:3) to give pure epoxide **102** (7.86 g, 72%) as colorless liquid.

(*S*)-2-Heptyloxirane (104):



Racemic epoxide (±)-**102** (8.0 g, 56.24 mmol) in THF (583 μL) was added to (*S*,*S*)-Salen-Co^{III}-OAc catalyst (223 mg, 0.337 mmol, 0.6 mol%) and the solution was cooled to 0 ^oC.

Every 5 min, H_2O (50 µL) was added until 556 µL (0.55 equiv., 30.93 mmol) had been added; after another 5 min the ice bath was removed and the reaction was stirred at room temperature for 24 h. The reaction mixture was concentrated and purified by silica gel column chromatography using petroleum ether/EtOAc (97:3) as eluent to furnish the epoxide (*S*)-**104** as a single stereoisomer as a yellow liquid. Yield: 3.84 g, 48%; $[\alpha]_D^{25}$: -9.4 (*c* 1.15, $CHCl_3$);. Continued chromatography with petroleum ether/EtOAc (6:4) provided the diol (*R*)-**105** as a brown liquid as a single enantiomer.

Yield: 3.84 g, 48%.

Mol. Formula: $C_9H_{18}O$

$[\alpha]_D^{25}$: -9.4 (*c* 1.15, $CHCl_3$).

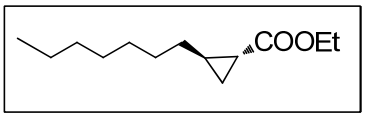
IR (neat, cm^{-1}): ν_{max} 2970, 2923, 923, 842.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.7 Hz, 3H), 1.28-1.52 (m, 12H), 2.47 (dd, *J* = 4.9, 3.2 Hz, 1H), 2.72 (dd, *J* = 4.9, 4.1 Hz, 1H), 2.88-2.92 (m, 1H).

MS(ESI): m/z 165.33 $(M+Na)^+$.

Anal. Calcd.: C, 76.00; H, 12.76%; **Found:** C, 76.35; H, 12.54%.

(1*R*,2*R*)-Ethyl 2-heptylcyclopropanecarboxylate (106):



To a suspension of sodium hydride (4.25 g, 106.35 mmol, 60% in mineral oil) in toluene (100 ml) at 0 °C was added triethylphosphonoacetate (27.78 ml, 140.06 mmol) dropwise over 15 min. After stirring for 10 min, epoxide **104** (5 g, 35.15 mmol) was added dropwise over 15 min, followed by heating at 80 °C for 8 h, then temperature increased to 110 °C and stirred for 6 h. The reaction mixture was cooled to room temperature, diluted with EtOAc (100 ml), and then washed with saturated aqueous ammonium chloride (100 ml). The organic phase was separated and the aqueous phase extracted with Et_2O (3 x 50 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by flash chromatography using petroleum ether/EtOAc (99:1) to give cyclopropane **106** as a thick colorless oil.

Yield: 6.34 g, 85%.

Mol. Formula: $C_{13}H_{24}O_2$

$[\alpha]_D^{25}$: -16.2 (*c* 1.0, $CHCl_3$).

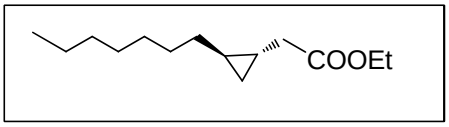
IR (neat, cm^{-1}): ν_{max} 2933, 2855, 1730.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.31-0.36 (m, 2H), 0.53-0.66 (m, 1H), 0.76-0.8 (m, 1H), 0.89 (t, *J* = 6.1 Hz, 3H), 1.21-1.39 (m, 15H), 4.10 (q, *J* = 7.2, 14.3, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 11.6, 13.9, 14.1, 18.7, 22.8, 29.3, 29.4, 29.5, 29.6, 31.9, 33.8, 60.6, 179.9.

Analysis: Calcd.: C, 76.00; H, 12.76%; **Found:** C, 75.73; H, 12.99%.

Ethyl 2-((1*S*,2*R*)-2-heptylcyclopropyl)acetate (109):



To a ice cooled solution of 2,2,6,6-tetramethylpiperidine (5.76 g, 33.9 mmol) in 40 mL of THF, *n*-butyllithium (19.4 mL, 1.6 M in hexane, 31.08 mmol) was added dropwise. This mixture was added dropwise to a stirred solution of dibromomethane (2.17 mL, 31.06 mmol) in 40 mL of THF, cooled with a -90 ^oC bath (dry ice/diethyl ether). After 5 min, a solution of of ethyl ester **106** (3 g, 14.12 mmol) in 30 mL of THF was added dropwise over 15 min, and 10 min later a solution of *n*-butyllithium (44.15 mL, 1.6 M in hexane, 70.64 mmol) was added dropwise. The -90 ^oC cooling bath was replaced with a 30 ^oC water bath, and then stirred for 15 min. The reaction mixture was added via cannula to a rapidly stirred, ice-cooled solution of acidic ethanol (prepared from 5 mL of acetyl chloride in 25 mL of absolute ethanol). The mixture was diluted with 200 mL of ether, washed with 10% sulfuric acid, 5% aqueous sodium bicarbonate, and saturated brine, dried over Na_2SO_4 and concentrated under reduced presssure to give a crude product which was purified by chromatography on silica eluting with petroleum ether/EtOAc (98:2) to give homologated ester **109** as a pale yellow liquid.

Yield: 1.75 g, 55%.

Mol. Formula: $C_{14}H_{26}O_2$

$[\alpha]_D^{25}$: -13.99 (*c* 1.0, $CHCl_3$).

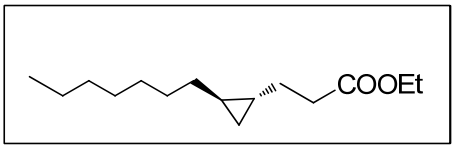
IR (neat, cm^{-1}): ν_{max} 2933, 2874, 1736.

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.29-0.31 (m, 2H), 0.47-0.54 (m, 1H), 0.75-0.82 (m, 1H), 0.88 (t, *J* = 6.1 Hz, 3H), 1.19-1.35 (m, 15H), 2.15-2.25 (m, 2H), 4.13 (q, *J* = 7.1, 14.1 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 11.6, 14.1, 14.2, 14.3, 18.6, 22.7, 29.4, 29.6, 31.9, 33.9, 39.2, 60.2, 173.3.

Analysis: Calcd.: C, 74.29; H, 11.58%; **Found:** C, 74.33; H, 11.49%.

Ethyl 3-((1*R*,2*R*)-2-heptylcyclopropyl)propanoate (110):



To a ice cooled solution of 2,2,6,6-tetramethylpiperidine (2.7 g, 15.88 mmol) in 40 mL of THF, *n*-butyllithium (9.1 mL, 1.6 M in hexane, 14.56 mmol) was added dropwise. This mixture was added dropwise to a stirred solution of dibromomethane (1 mL, 14.56 mmol) in 40 mL of THF, cooled with a -90 ^{o}C bath (dry ice/diethyl ether). After 5 min, a solution of ethyl ester **109** (1.5 g, 6.62 mmol) in 30 mL of THF was added dropwise over 15 min, and 10 min later a solution of *n*-butyllithium (20.7 mL, 1.6 M in hexane, 33.1 mmol) was added dropwise. The -90 ^{o}C cooling bath was replaced with a 30 ^{o}C water bath, and then stirred for 15 min. The reaction mixture was added via cannula to a rapidly stirred, ice-cooled solution of acidic ethanol (prepared from 5 mL of acetyl chloride in 25 mL of absolute ethanol). The mixture was diluted with 200 mL of ether, washed with 10% sulfuric acid, 5% aqueous sodium bicarbonate, and saturated brine, dried over Na_2SO_4 and concentrated under reduced pressure to give a crude product which was purified by silica gel column chromatography with petroleum ether/EtOAc (96:4) to give homologated ester **110** as a colorless syrupy liquid.

Yield: 955 mg, 60%.

Mol. Formula: $C_{15}H_{28}O_2$

$[\alpha]_D^{25}$: -13.00 (*c* 1.0, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 2938, 2871, 1734.

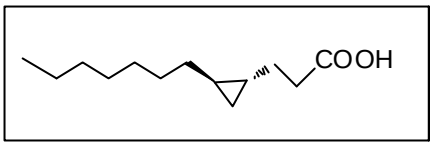
^{1}H NMR (400 MHz, $CDCl_3$): δ : 0.26-0.28 (m, 2H), 0.49-0.53 (m, 1H), 0.71-0.85 (m, 1H), 0.85 (t, *J* = 6.3 Hz, 3H), 1.22-1.49 (m, 15H), 1.56-1.66 (m, 2H), 2.28 (t, *J* = 7.3 Hz, 2H), 4.13 (q, *J* = 7.0, 14.2 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 11.7, 14.1, 14.2, 18.1, 18.8, 22.7, 26.9, 29.3, 29.6, 29.9, 31.9, 32.5, 34.7, 60.1, 173.9.

MS (ESI): m/z 241.33 $(M+H)^+$.

Anal. Calcd for $C_{13}H_{24}O_2$ (240.38): C, 74.95; H, 11.74 %; **Found:** C, 74.70; H, 11.64%.

3-((1*R*,2*R*)-2-Heptylcyclopropyl)propanoic acid (111):



To the ester **110** (400 mg, 1.66 mmol) dissolved in MeOH (10 mL) and H_2O (6.67 mL) was added $LiOH.H_2O$ (208 mg, 4.98 mmol) and stirred at 0 ^oC to room temperature for 5 h. The reaction mixture was further diluted with H_2O (5 mL) and stirred for 30 min then concentrated by rotary evaporator to quarter of its volume. The mixture was acidified (upto pH 5) with 1 M HCl and the reaction mixture was extracted with EtOAc (3 x 10 mL). The combined organic layer was washed with brine (2 x 10 mL) and dried over anhydrous Na_2SO_4, concentrated and the crude product was purified by column chromatography eluting with petroleum ether/EtOAc (9:1) to give **111** as a pale yellow color syrupy liquid.

Yield: 371 mg, 82%.

Mol. Formula: $C_{13}H_{24}O_2$

$[\alpha]_D^{25}$: -13.99 (*c* 1.0, $CHCl_3$).

IR (neat, cm^{-1}): ν_{max} 3420, 2855, 1711, 1458, 1216, 759, 668.

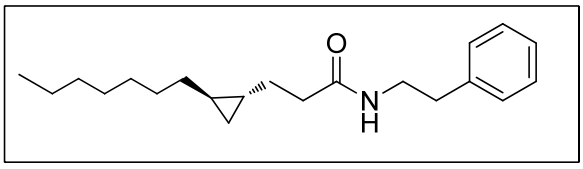
^{1}H NMR (400 MHz, $CDCl_3$): δ : 0.32-0.35 (m, 2H), 0.54-0.59 (m, 1H), 0.78-0.82 (m, 1H), 0.89 (t, *J* = 6.1 Hz, 3H), 1.27-1.39 (m, 12H), 1.53-1.68 (m, 2H), 2.26-2.28 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 11.9, 13.9, 14.1, 18.7, 22.8, 29.3, 29.6, 31.9, 33.8, 38.9, 179.9.

MS (ESI): m/z 235.33 $(M+Na)^+$.

Anal. Calcd for $C_{13}H_{24}O_2$ (212.33): C, 73.54; H, 11.39 %; **Found:** C, 73.70; H, 11.44%.

3-((1*R*,2*R*)-2-Heptylcyclopropyl)-*N*-phenethylpropanamide (49):



3-((1*R*,2*R*)-2-Heptylcycloprop-1-yl)propionic acid **111** (100 mg, 0.47 mmol) was treated with thionyl chloride (3 mL) and refluxed for 2 h. The excess of thionyl chloride was distilled off to give a residue of 3-((1*R*,2*R*)-(2-heptylcyclopropyl)-propionyl chloride. The residue was cooled to 5 ^oC and treated with phenylethyl amine (0.285 g, 2.35 mmol) under nitrogen atmosphere. A white precipitate was formed and the reaction was stirred for 2 h. The mixture was diluted with H_2O and the product was extracted with ether (2 x 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to give a crude product which was purified by chromatography on silica eluting with petroleum ether/EtOAc (1:1) to give 3-((1*R*,2*R*)-(2-heptyl-cyclopropyl)-*N*-phenethylpropionamide **49** as a pale yellow solid.

Yield: 96 mg, 65%.

M.P.: 48-49 °C lit.[36]: 46-47 °C.

Mol. Formula: $C_{21}H_{33}NO$

$[\alpha]_D^{25}$: –11.80 (*c* 1.0, $CHCl_3$); {lit.[36]: **$[\alpha]_D^{25}$:** –11.0 (*c* 1.0, $CHCl_3$)}

IR (neat, cm^{-1}): ν_{max} 3320, 2935, 1678, 1560, 1216, 759.

^{1}H NMR (400 MHz, $CDCl_3$): δ : 0.28-0.32 (m, 2H), 0.51-0.54 (m, 1H), 0.75-0.79 (m, 1H), 0.86 (t, *J* = 6.7 Hz, 3H), 1.09-1.12 (m, 2H), 1.13-1.48 (m, 10H), 1.54-1.62 (m, 2H), 2.12 (t, *J* = 7.3 Hz, 2H), 2.83 (t, *J* = 7.0 Hz, 2H), 3.53 (q, *J* = 6.7, 13.0 Hz, 2H), 5.43 (brs, 1H), 7.19-7.43 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 11.4, 14.1, 18.2, 19.5, 22.6, 27.0, 29.3, 29.6, 29.9, 31.9, 32.6, 35.7, 36.9, 40.5, 126.5, 128.7, 138.9, 173.1.

MS (ESI): m/z 338.49 $(M+Na)^+$.

4.1.10 Spectra

1. ^{1}H & ^{13}C NMR spectra of **64**

2. ^{1}H & ^{13}C NMR spectra of **65**

3. ^{1}H & ^{13}C NMR spectra of **66**

4. ^{1}H & ^{13}C NMR spectra of **48**

5. ^{1}H & ^{13}C NMR spectra of **106**

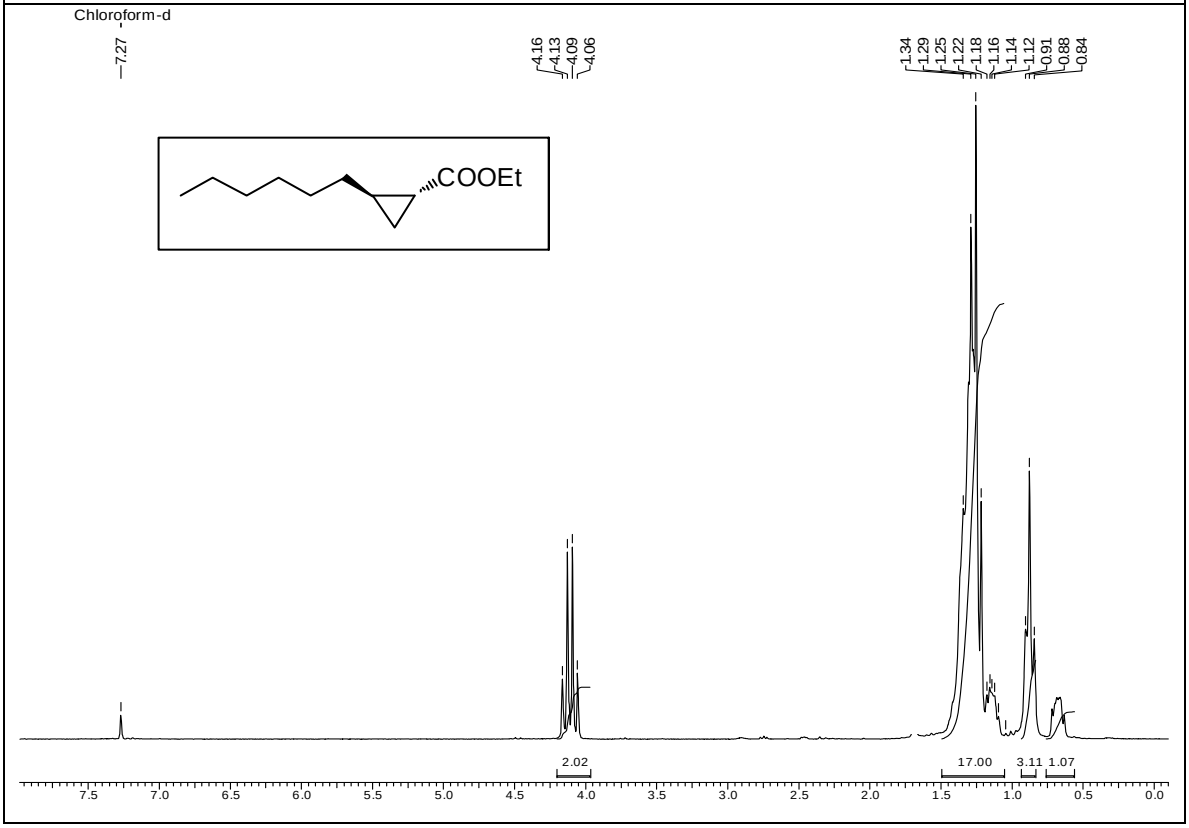
6. ^{1}H & ^{13}C NMR spectra of **109**

7. ^{1}H & ^{13}C NMR spectra of **110**

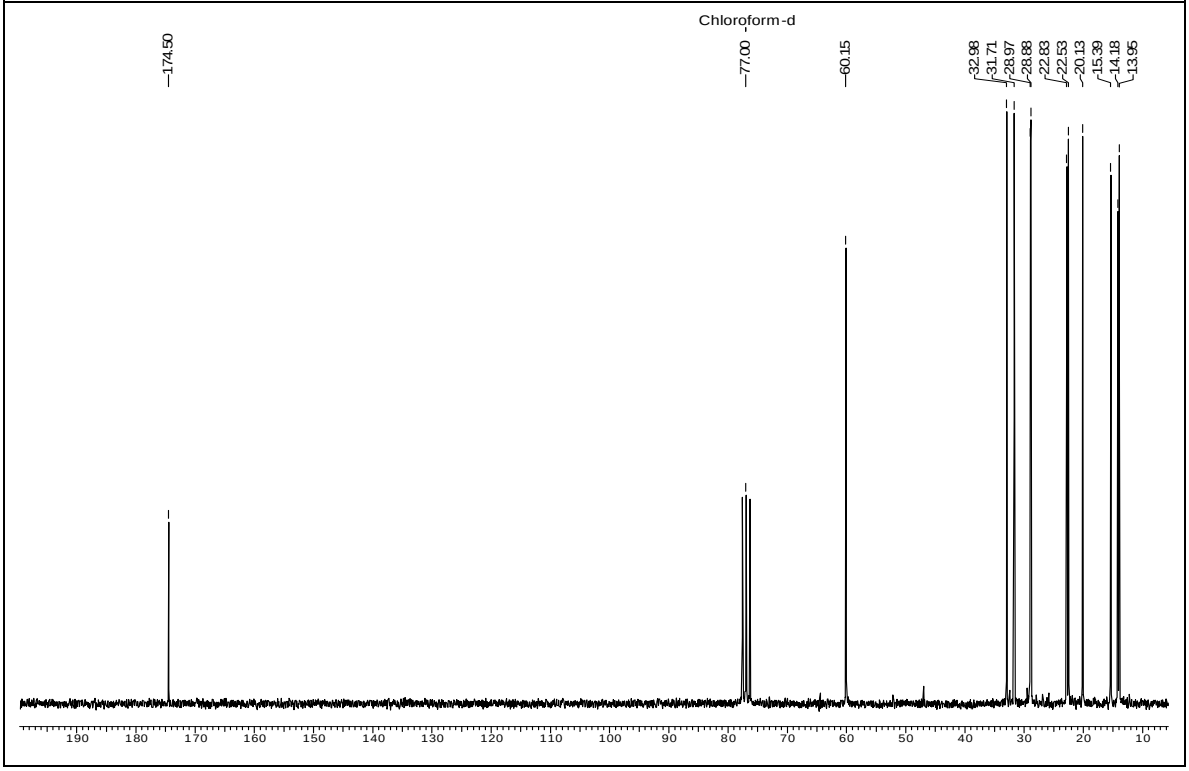
8. ^{1}H & ^{13}C NMR spectra of **111**

9. ^{1}H & ^{13}C NMR spectra of **49**

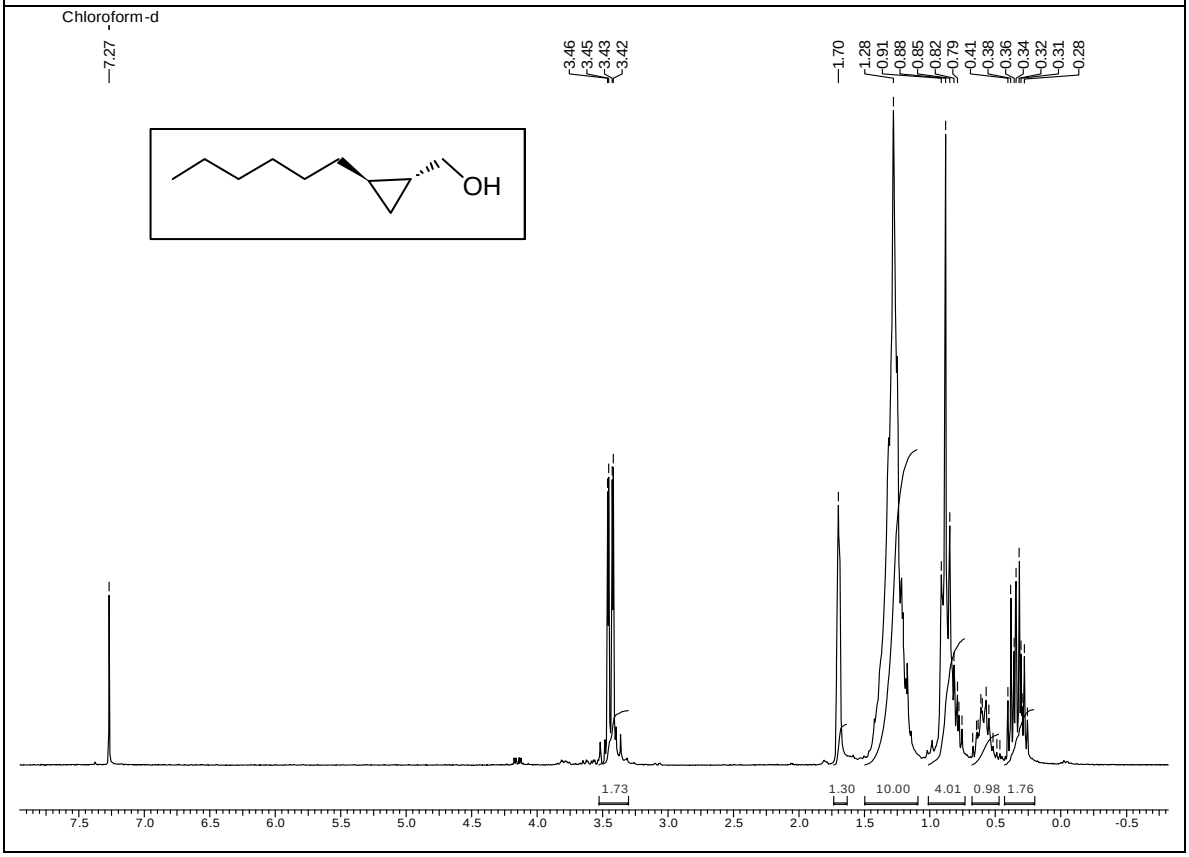
^{1}H NMR ($CDCl_3$, 400MHz) of compound (1*R*,2*R*)-Ethyl 2-hexylcyclopropanecarbo- xylate (64)



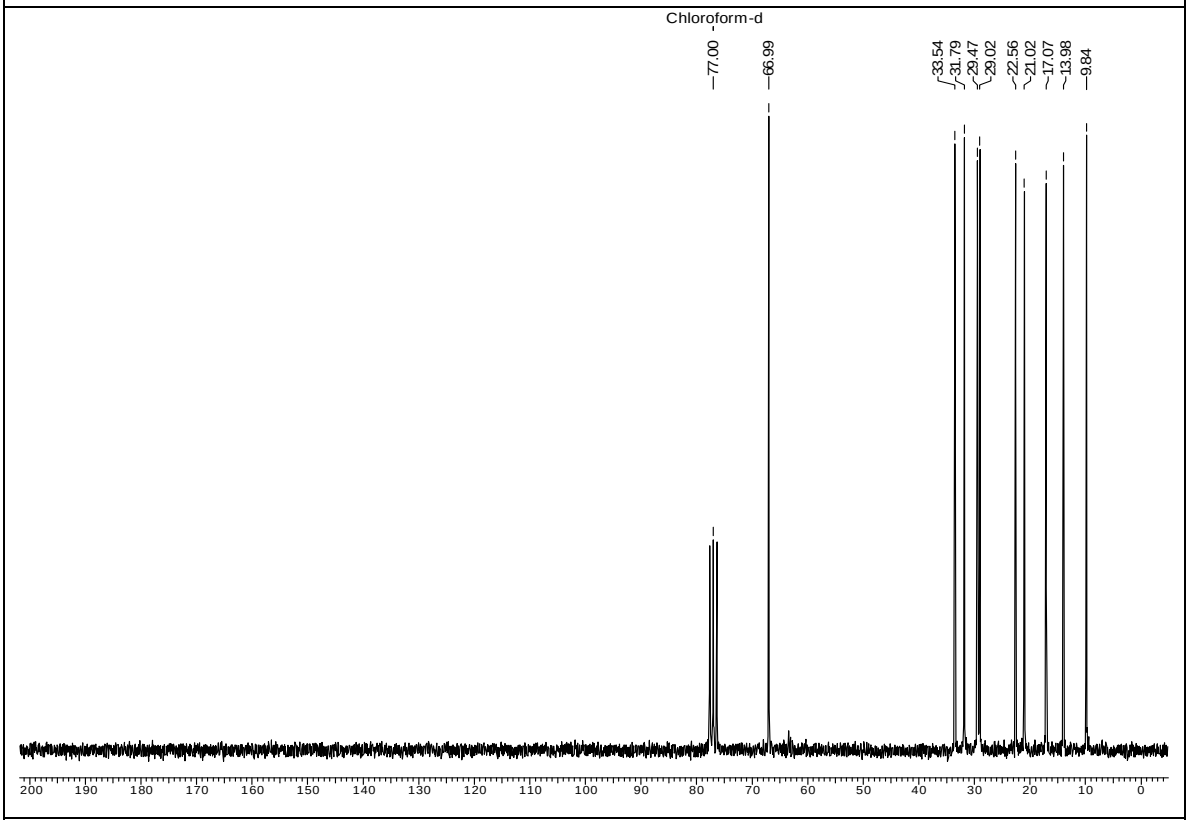
^{13}C NMR ($CDCl_3$, 100MHz) of compound (1*R*,2*R*)-Ethyl 2-hexylcyclopropanecarbo- xylate (64)



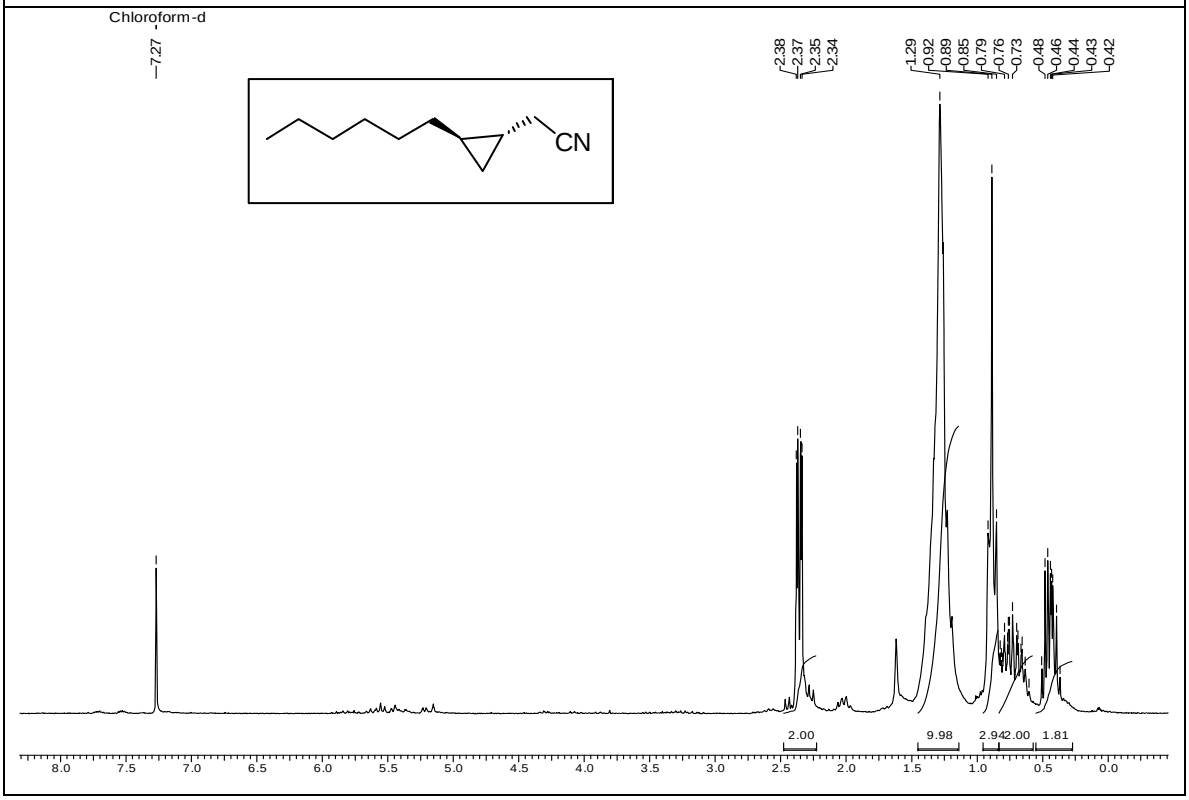
^{1}H NMR ($CDCl_3$, 400MHz) of compound (1*R*,2*R*)-2-Hexylcyclopropyl)methanol (65)



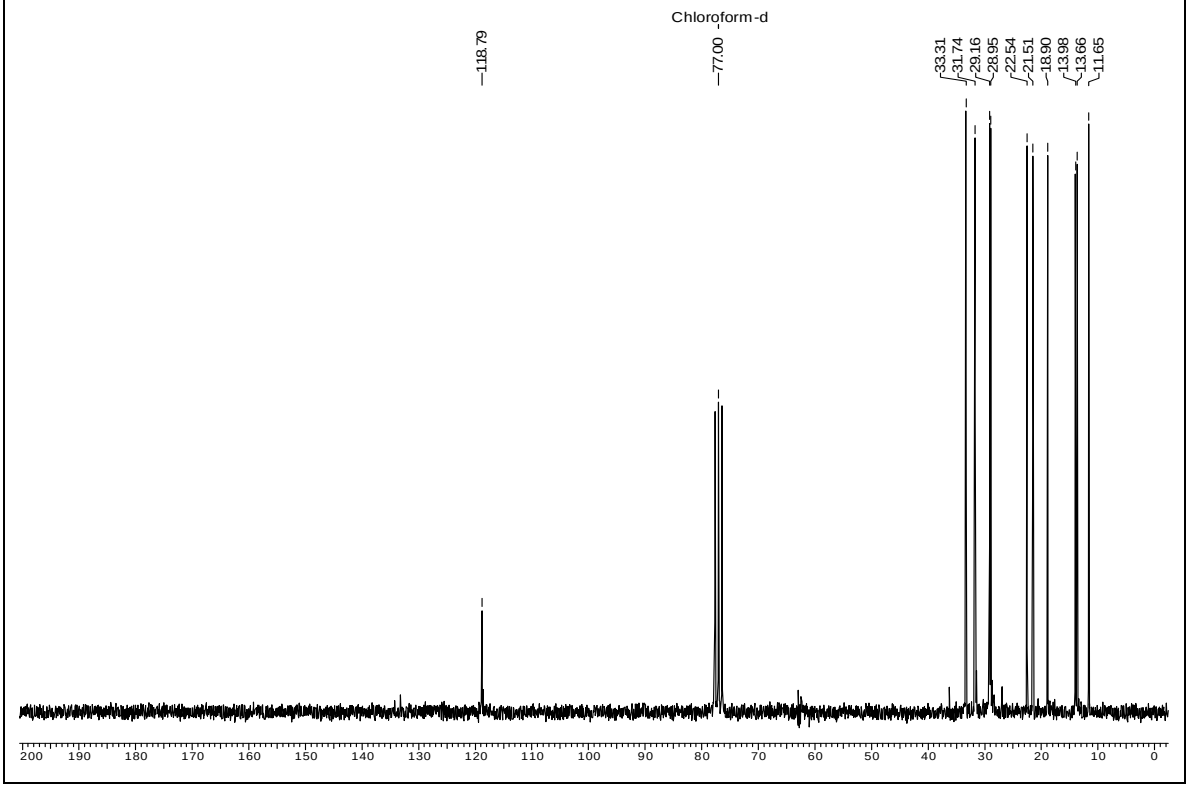
^{13}C NMR ($CDCl_3$, 100MHz) of compound (1*R*,2*R*)-2-Hexylcyclopropyl)methanol (65)



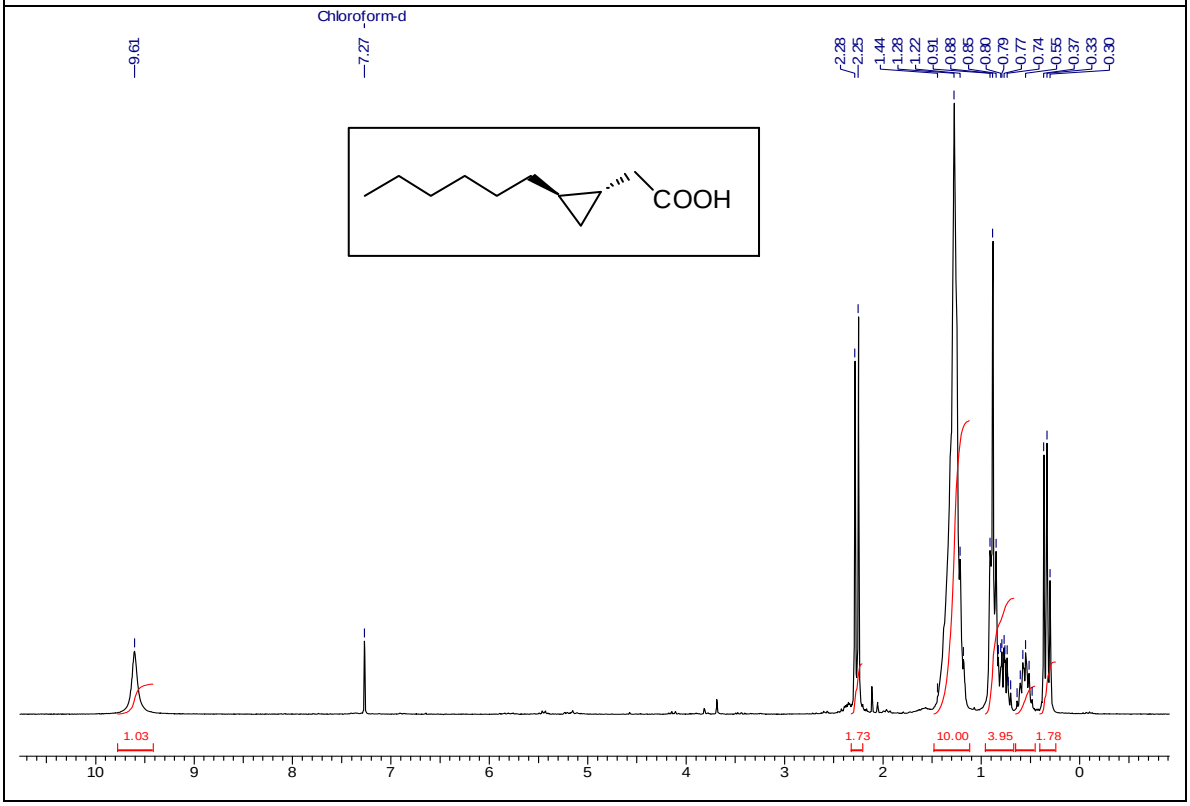
^{1}H NMR ($CDCl_3$, 200MHz) of compound 2-((1*S*,2*R*)-2-Hexylcyclopropyl)acetonitrile (66)



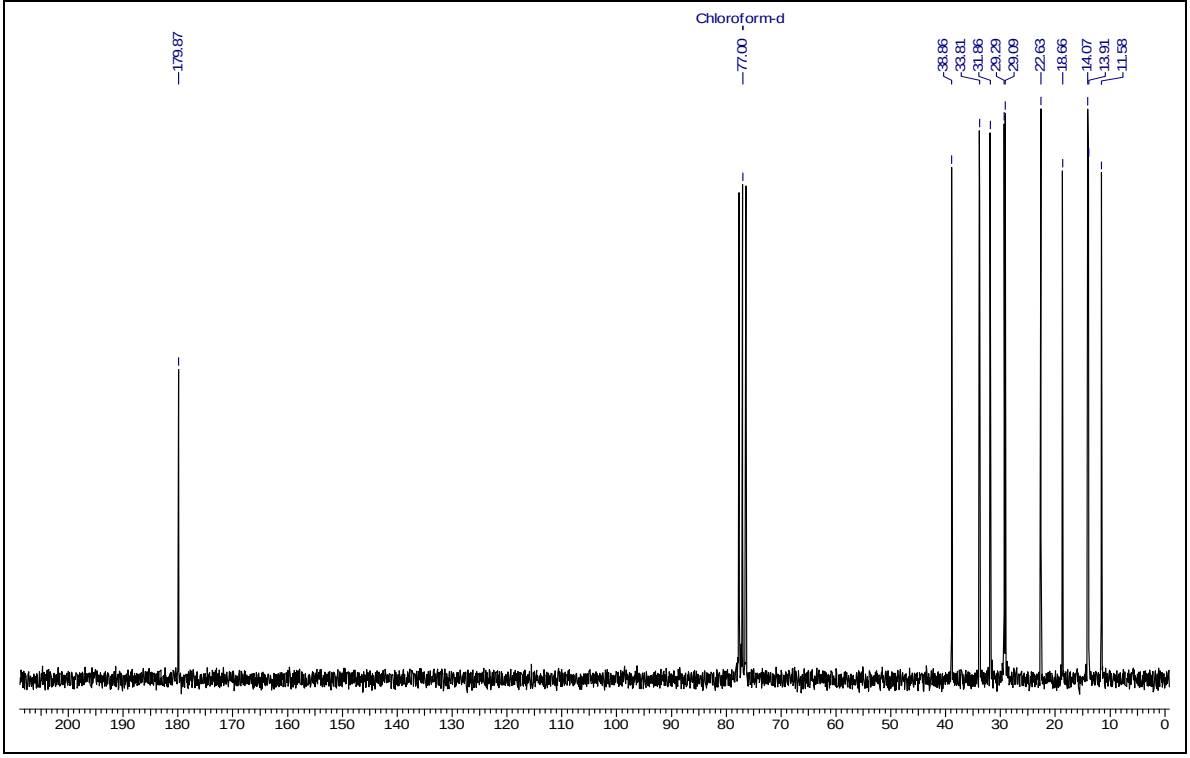
^{13}C NMR ($CDCl_3$, 50MHz) of compound 2-((1*S*,2*R*)-2-Hexylcyclopropyl)acetonit-rile (66)



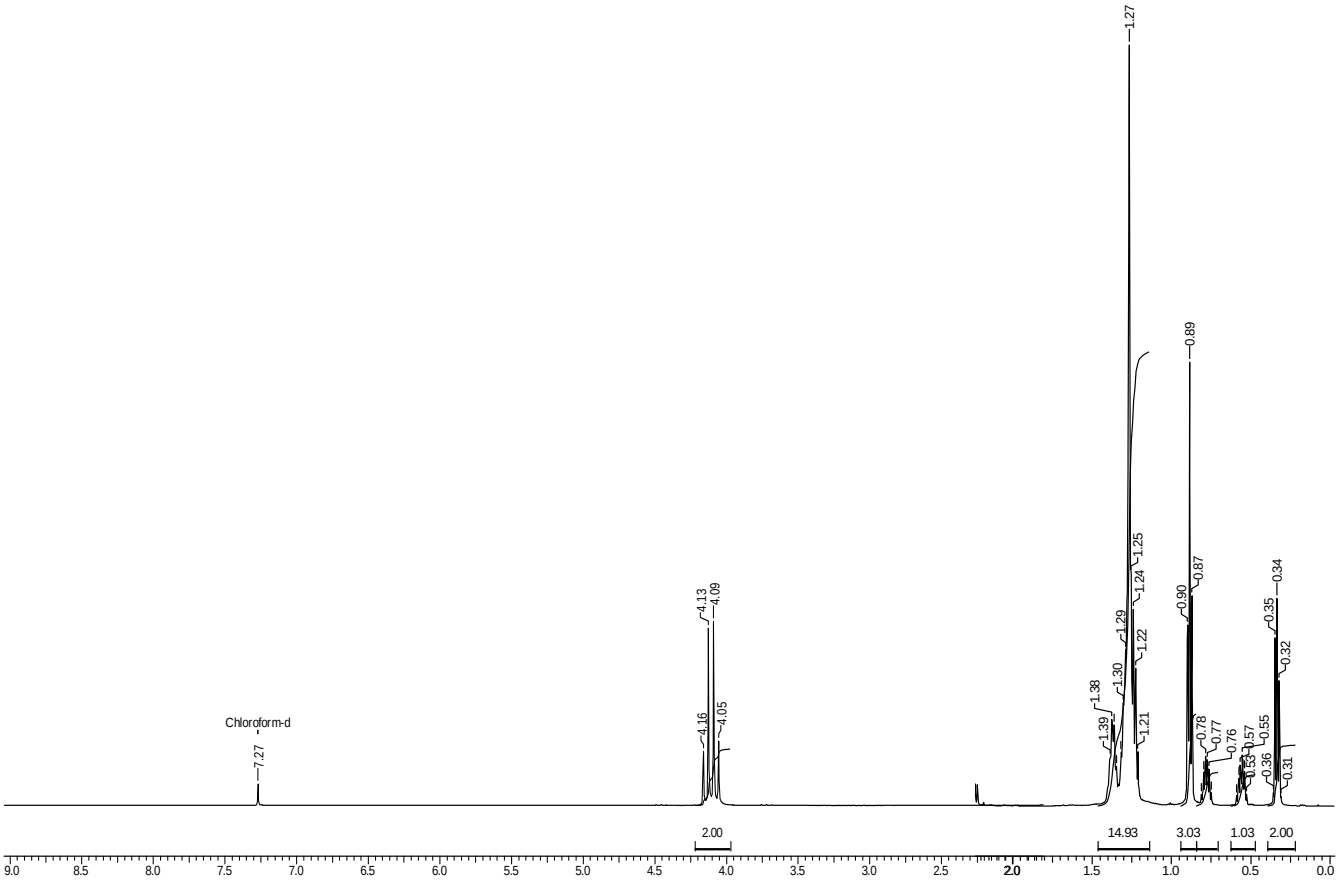
^{1}H NMR ($CDCl_3$, 400MHz) of compound 2-((1*S*,2*R*)-2-Hexylcyclopropyl)acetic acid (48)



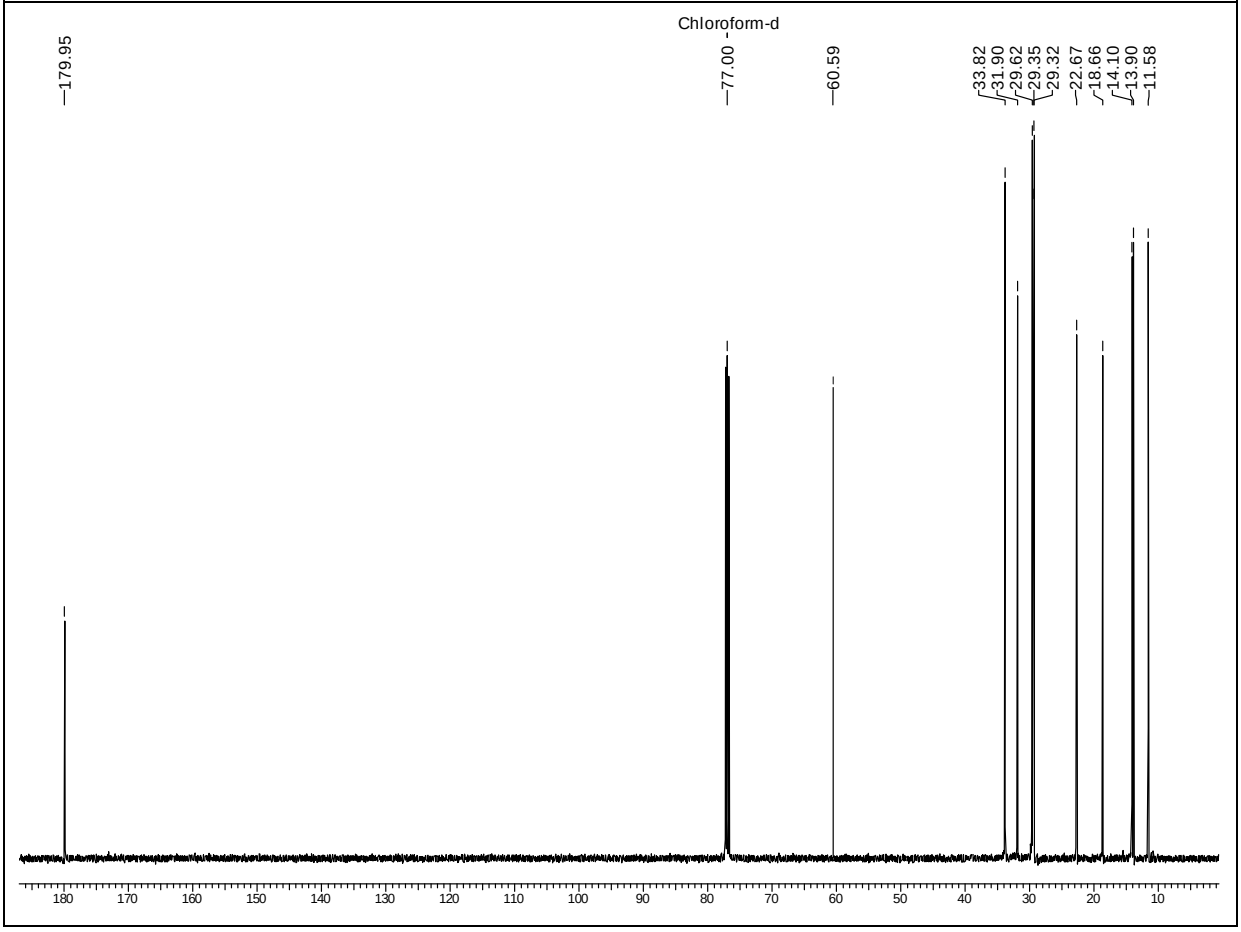
^{13}C NMR ($CDCl_3$, 100MHz) of compound 2-((1*S*,2*R*)-2-Hexylcyclopropyl)acetic acid (48)



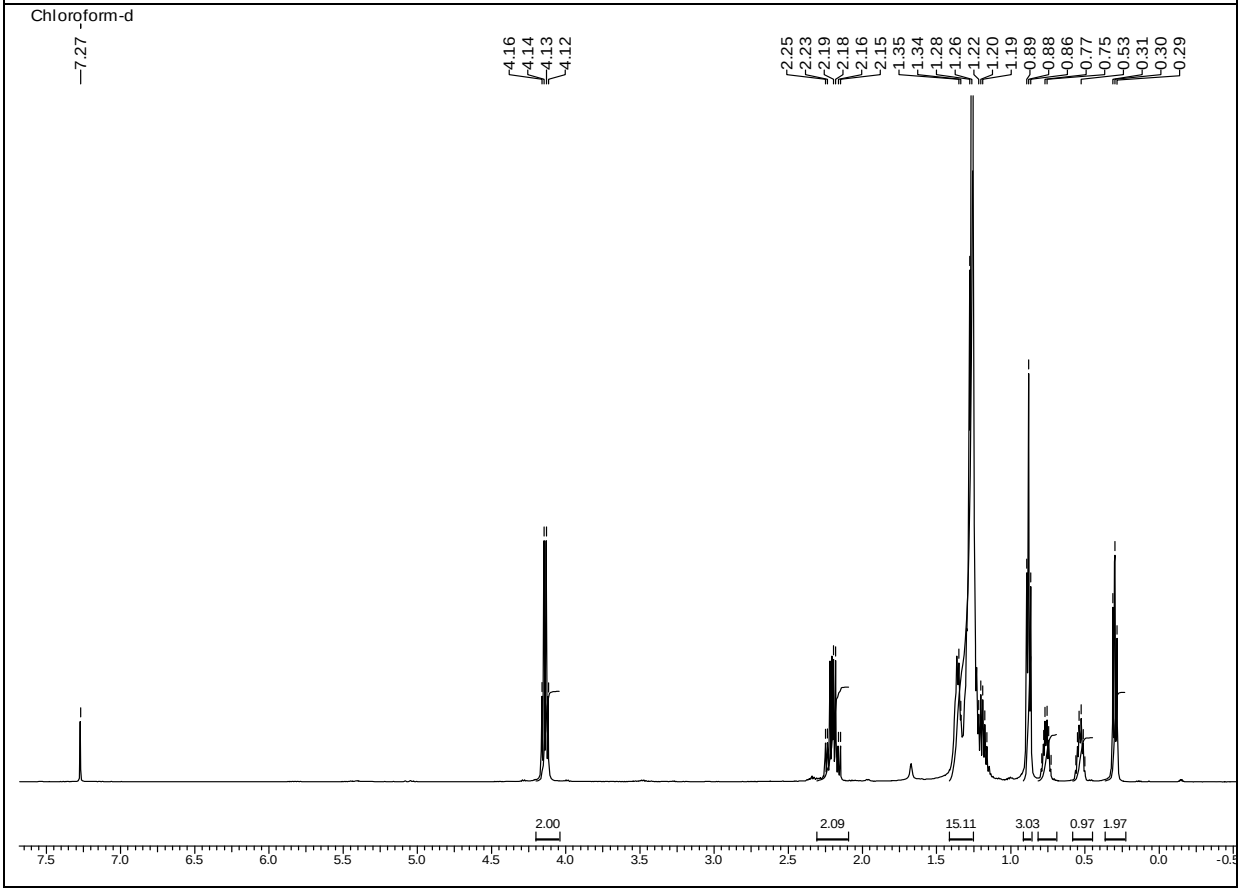
^{1}H spectra ($CDCl_3$, 500 MHz) of compound (1*R*,2*R*)-ethyl 2-heptylcyclopropanecarboxylate (106)



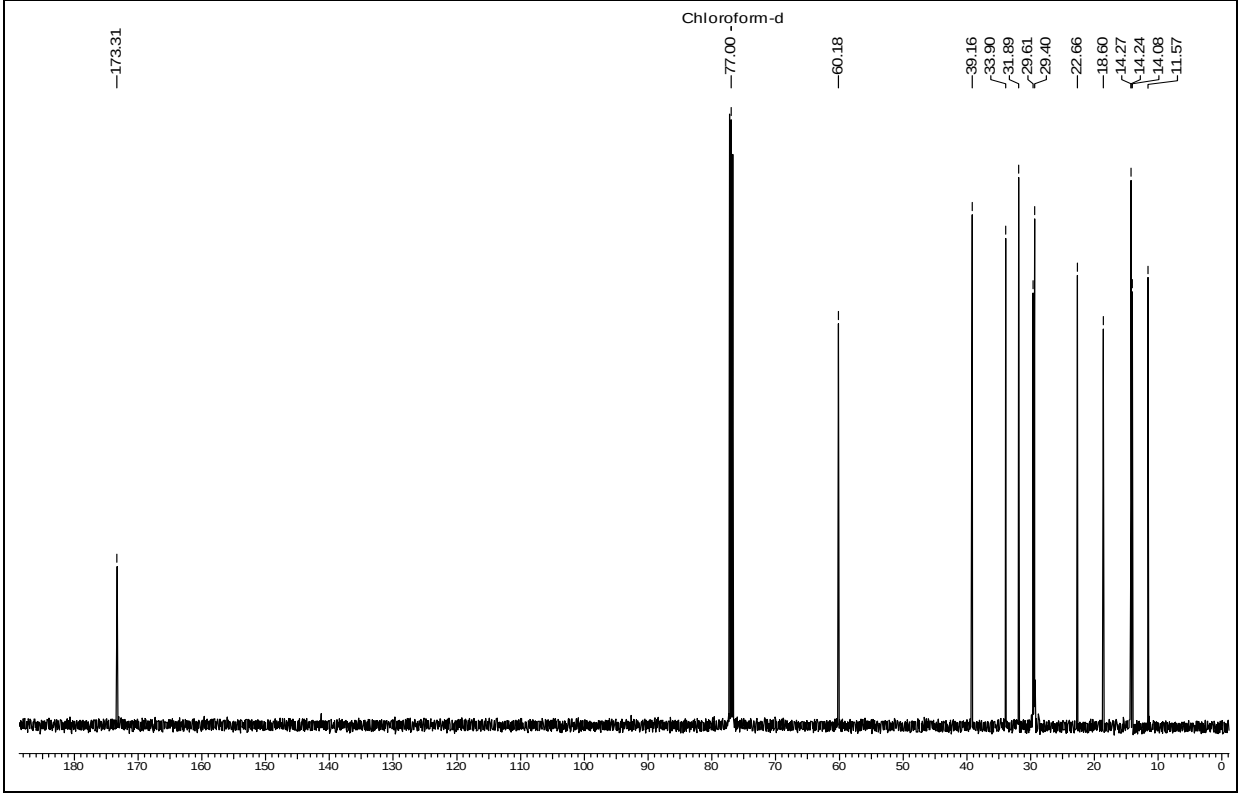
^{13}C spectra ($CDCl_3$, 100 MHz) of compound (1*R*,2*R*)-ethyl 2-heptylcyclopropanecarboxylate (106)



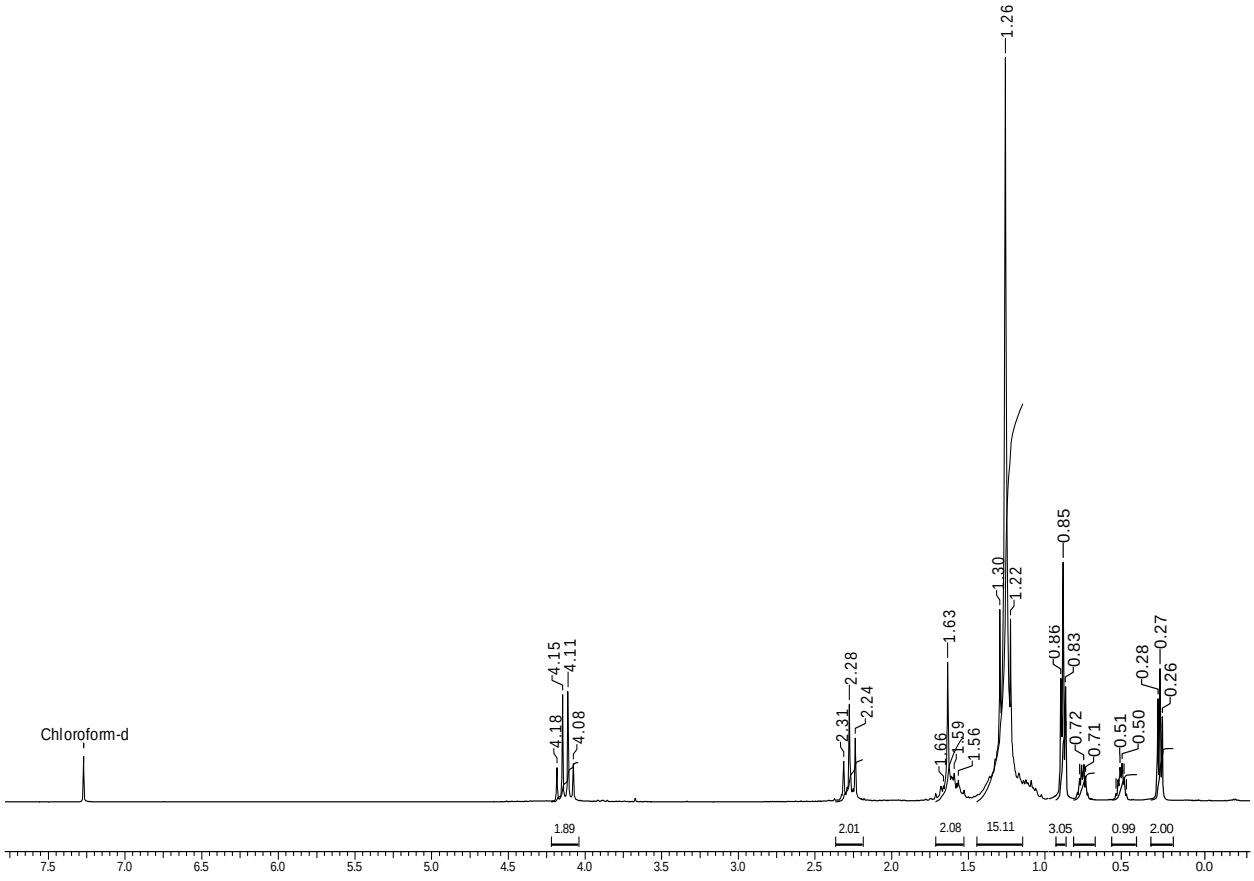
^{1}H spectra ($CDCl_3$, 500 MHz) of compound ethyl 2-((1*S*,2*R*)-2-heptylcyclopropyl)acetate (109)



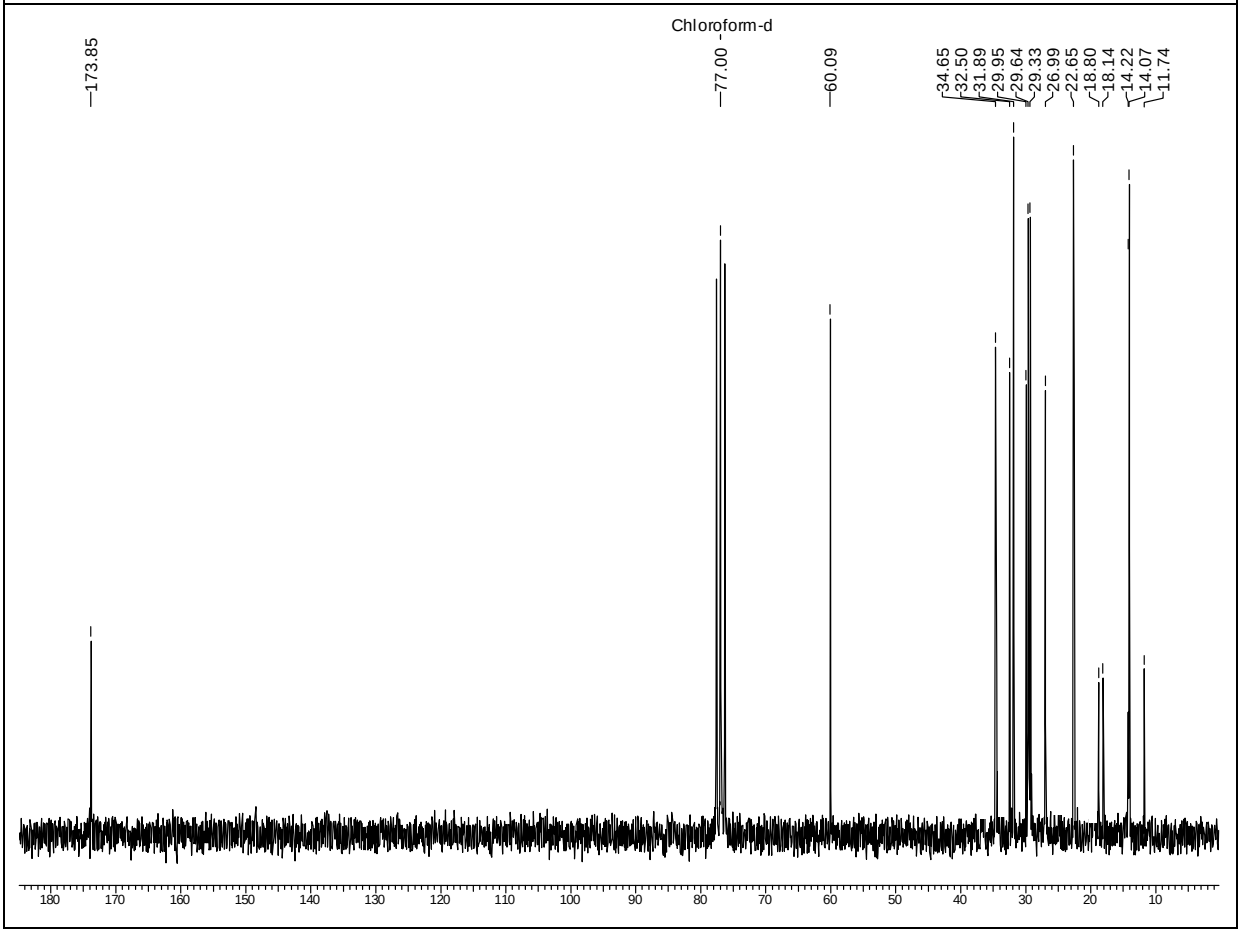
^{13}C spectra ($CDCl_3$, 125 MHz) of compound ethyl 2-((1*S*,2*R*)-2-heptylcyclopropyl)acetate (109)



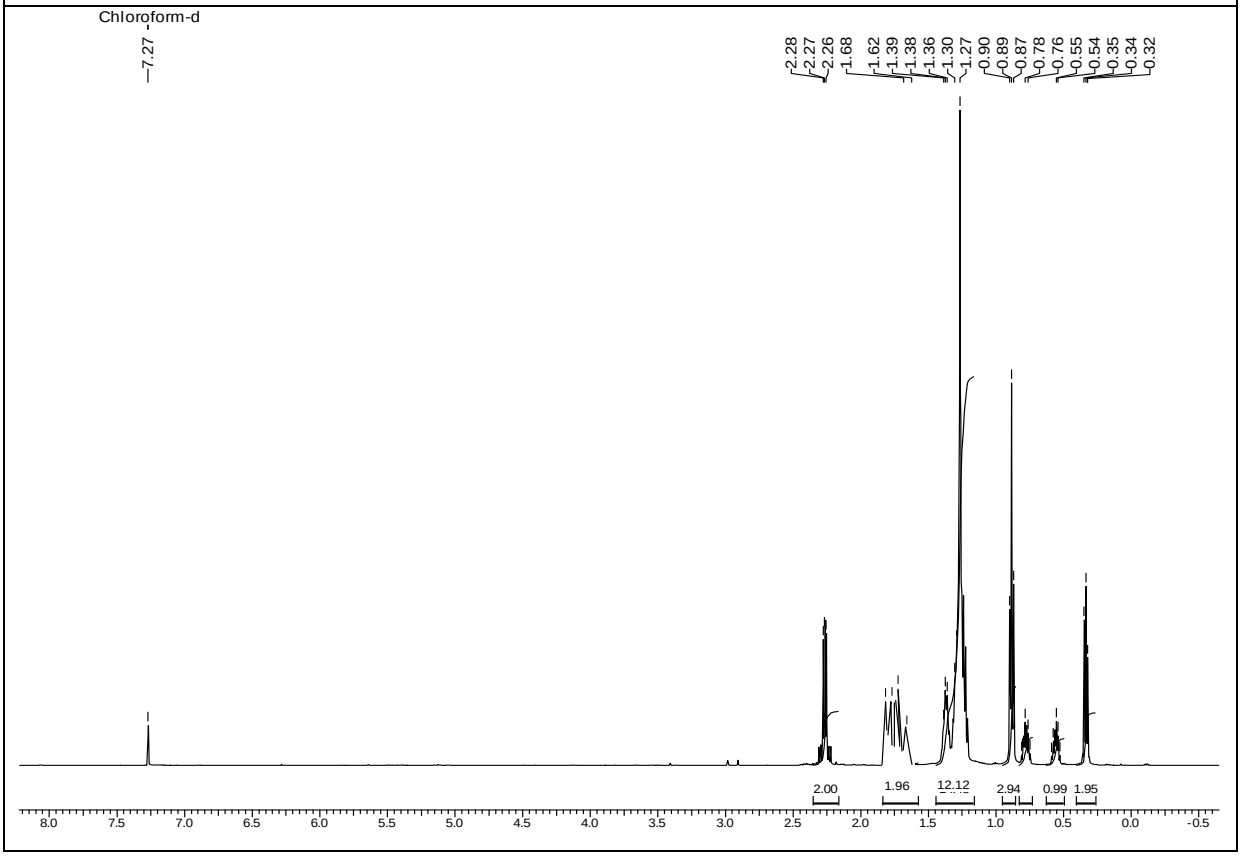
^{1}H spectra ($CDCl_3$, 400 MHz) of compound ethyl 3-((1*R*,2*R*)-2-heptylcyclopropyl)propanoate (110)



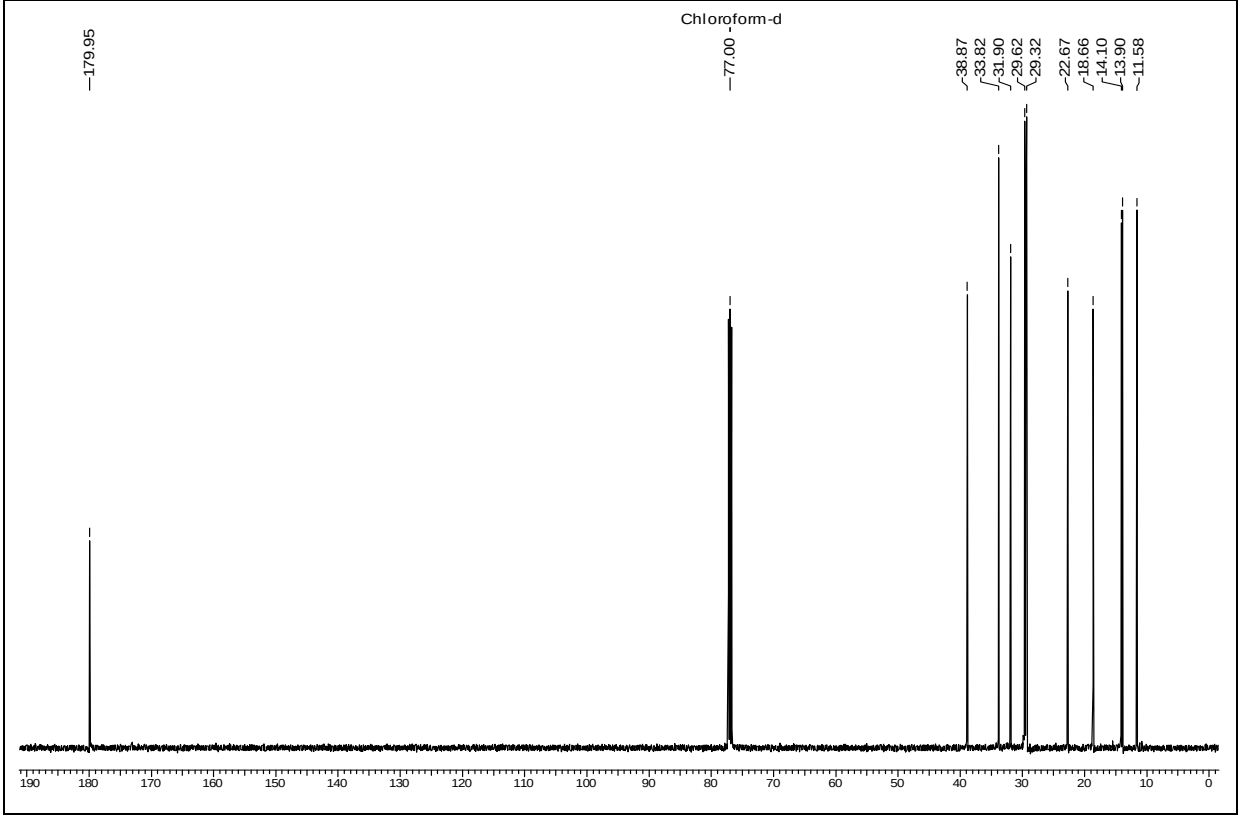
^{13}C spectra ($CDCl_3$, 100 MHz) of compound ethyl 3-((1*R*,2*R*)-2-heptylcyclopropyl)propanoate (110)



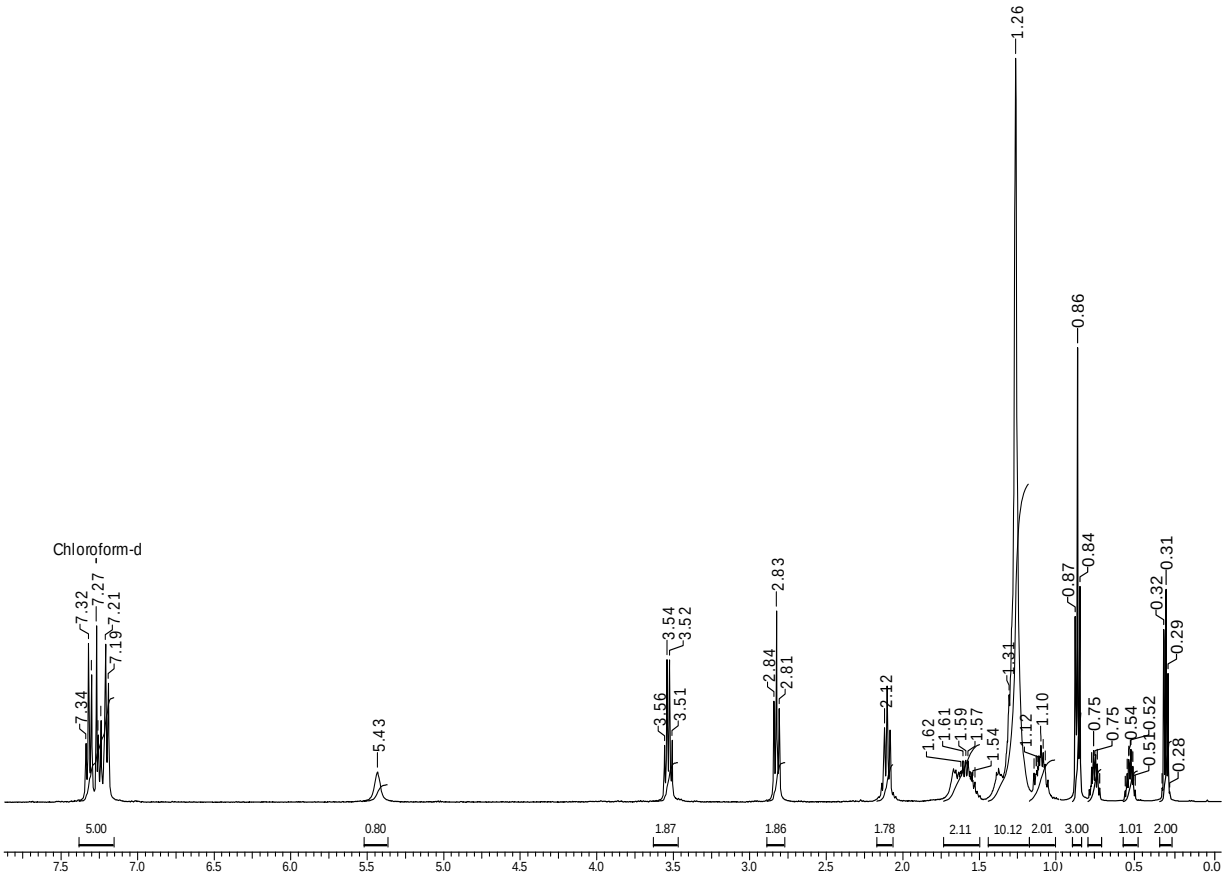
^{1}H spectra ($CDCl_3$, 400 MHz) of compound 3-((1*R*,2*R*)-2-heptylcyclopropyl)propanoic acid (111)



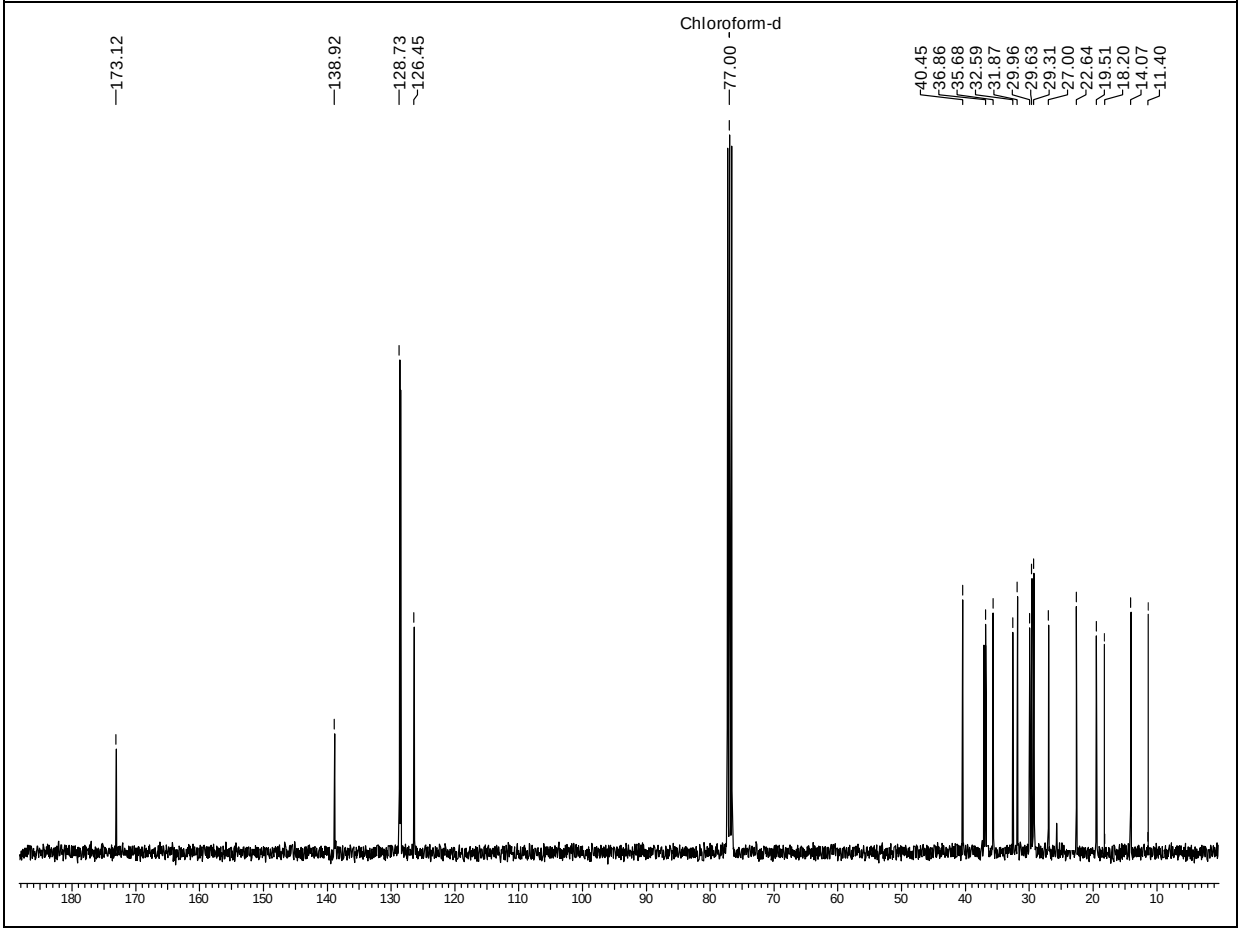
^{13}C spectra ($CDCl_3$, 100 MHz) of compound 3-((1*R*,2*R*)-2-heptylcyclopropyl)propanoic acid (111)



^{1}H spectra ($CDCl_3$, 400 MHz) of compound 3-((1*R*,2*R*)-2-heptylcyclopropyl)-*N*-phenethylpropa namide (49)



^{13}C spectra ($CDCl_3$, 100 MHz) of compound 3-((1*R*,2*R*)-2-heptylcyclopropyl)-*N*-phenethylpropanamide (49)



4.1.11. References:

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4.2 SECTION B

ENANTIOSELECTIVE SYNTHESIS OF L-CCG-II

4.2.1. Introduction

L-Glutamic acid is known to function at many synapses in the mammalian central nervous system as an excitatory neurotransmitter and is implicated in the construction of memory and early learning's as well as pathogenesis of neuron damage to cause various neuronal diseases.[1] The glutamate receptors are classified as ionotropic type (iGluR's) and metabotropic type (mGluR's). mGlu's are further subdivided into *N*-methyl D-aspartic acid (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) and kainic acid (KA) receptors according to their selective action as agonist. A structure activity study has revealed that the alternation of any of the functional groups of L-Glu results in significant decrease or even loss of its excitatory capability.

Carboxycyclopropyl glycines (CCG's) are conformationally constrained analogues of glutamate receptors, which are useful pharmacological tools for analysis of glutamate neurotransmitter system. The *cis* **1** and the *trans* **2** CCG's were isolated along with *Exo*-3,4-methanoproline **3** from immature fruits of *Aesculus parviflora* and *Blighia sapida*.[2] Both the plants are assigned to the family Sapindaceae, and both amino acid cause hypoglycemic symptoms in animals. The *cis* isomer is known as potent growth inhibitor in mung bean seedlings (**Fig. 1**).

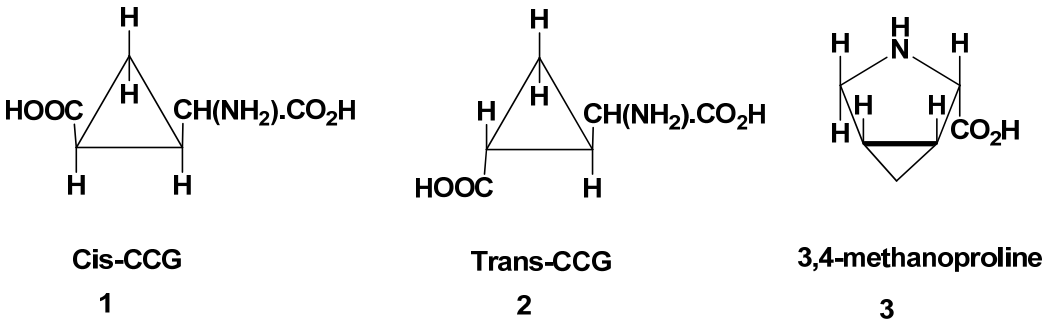


Fig. 1

CCG has three stereogenic centers and thus can exist in eight isomeric forms. As mentioned, it is regarded as conformationally constrained analogue of glutamic acid. A closer look reveals that presence of a cyclopropane ring in 3,4 position of glutamic acid restricts its conformation either in the extended or folded form there by giving rise to *cis* or *trans* form.

Thus L-Glutamic would give a set of four L-CCG's and another four D-CCG's could be realised from D-Glutamic acid (**Fig. 2**).

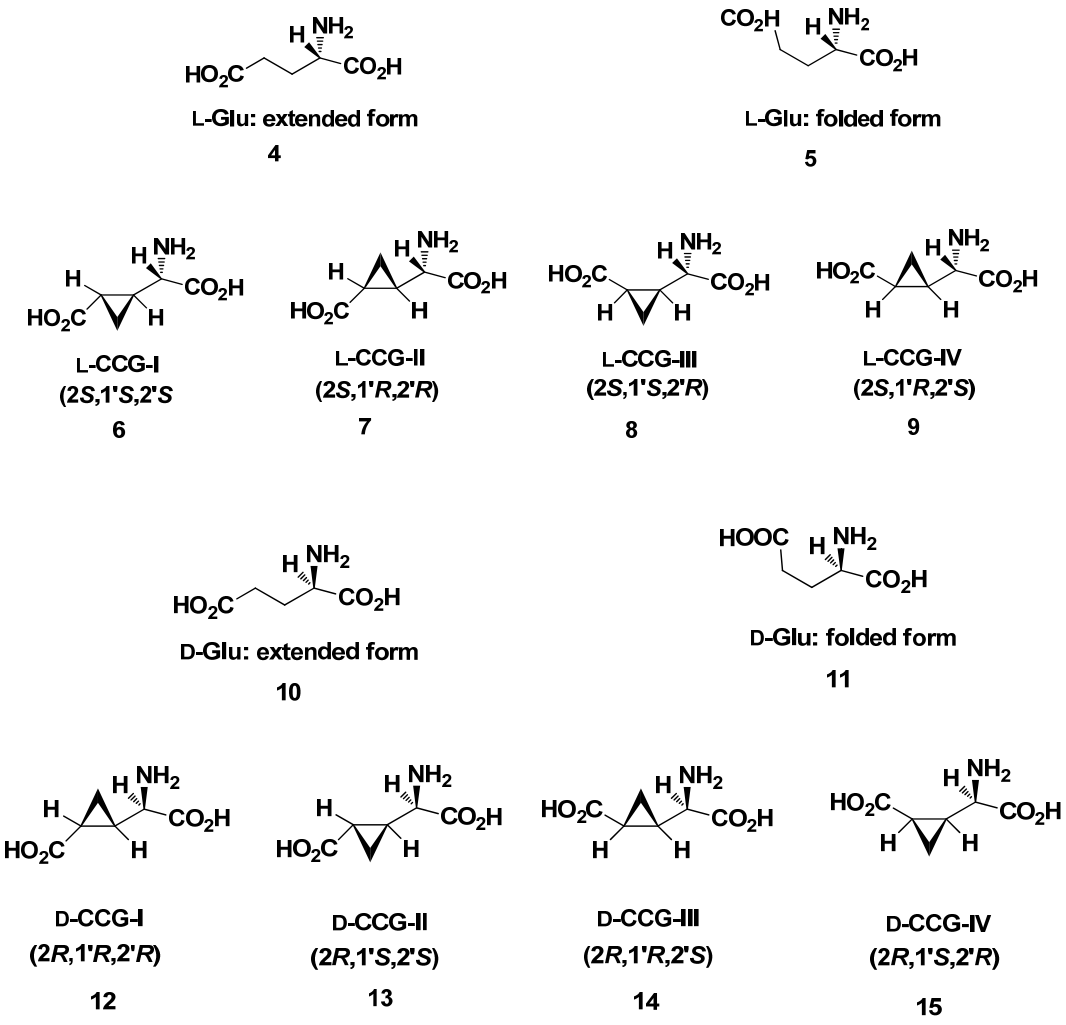


Fig. 2

Thus it was hypothesised that each glutamate subtype requires a particular conformation of glutamate for its selective activation *i.e.* conformational requirement for activity of receptors. In this regard CCG plays a crucial role. Presence of a cyclopropane ring restricts the conformation of glutamic acid either in the extended form or folded form and thus effects induced by each CCG's will provide information about the steric requirements of the receptors.

Among the four diastereomers of CCG, the extended type was identified as potent and selective agonist of mGluRs. On the other hand, CCG-IV, one of the folded forms exhibited affinity to NMDA receptors. CCG-II and CCG-III are not potent agonist but were inhibitor of glutamate transport system at the excitatory synapses.

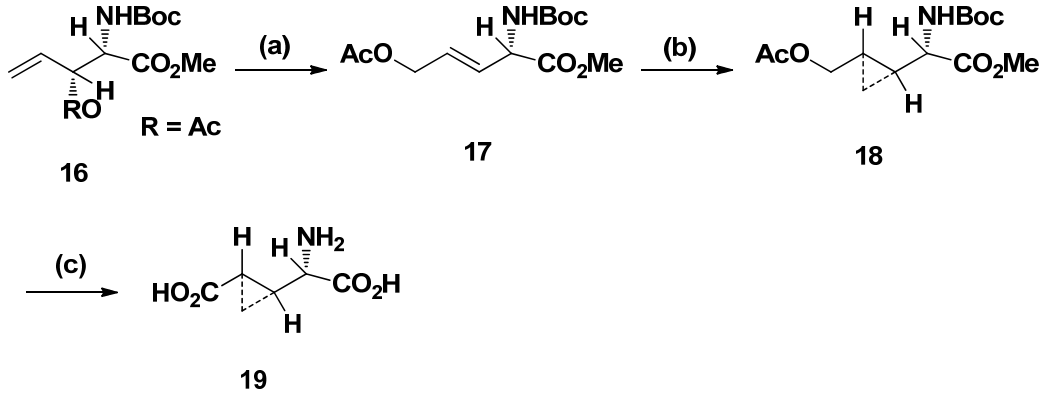
4.2.2. Review Literature

Several approaches have been reported in the literature for the synthesis of racemic as well as optically active L-CCG-II. Here the reported methods have been broadly categorised into different approaches based on cyclopropanation techniques towards the total synthesis of CCG both in racemic as well as chiral form.

4.2.2.1. Metal Catalysed Cyclopropanation

Ohfune *et al.* approach-1 (1985)[3]

Ohfune *et al.* reported one of the first syntheses of CCG in 1985 where they efficiently utilised Pd catalysed cyclopropanation of allylic double bond with diazomethane to render the racemic *trans* CCG **19**.

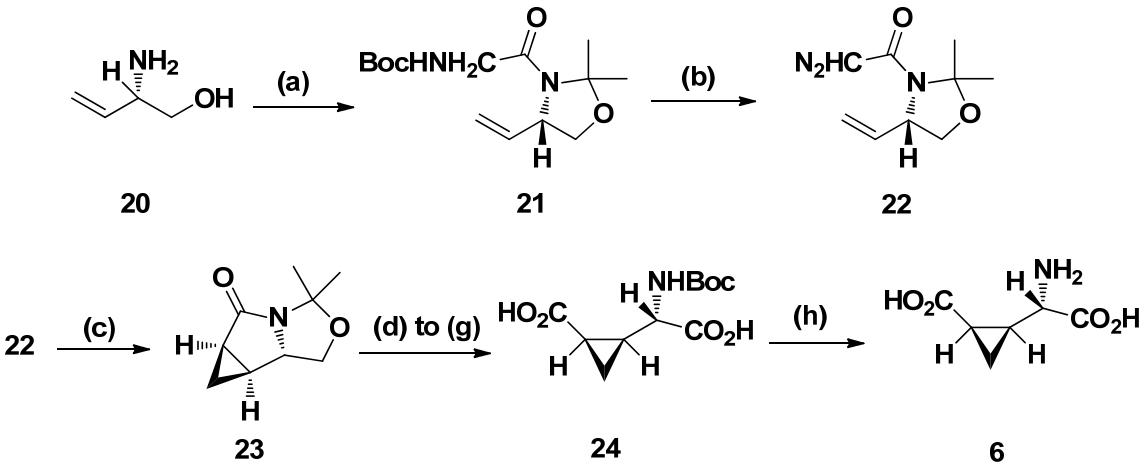


Scheme 1. *Reagents and conditions*: (a) $Pd(CH_3CN)_2Cl_2$, benzene, 60 ^oC, 60%; (b) $Pd(CH_3CN)_2Cl_2$, CH_2N_2, Et_2O, rt, 68%; (c) [i] K_2CO_3, MeOH, 97%; [ii] PhSeCN, *n*-Bu_3P, 100%; [iii] 0.5 N KOH, THF; [iv] CF_3COOH, 76% for two steps.

Thus, Pd (II) catalysed [3,3]-sigmatropic rearrangement of allylic acetate **16** followed by cyclopropanation by using excess of diazomethane in the presence of same catalyst gave **18**, which on, saponification, oxidation and deprotection furnished *trans* (±) CCG **19** (**Scheme 1**).

Ohfune's *et al.* approach-2 (1988)[4a]

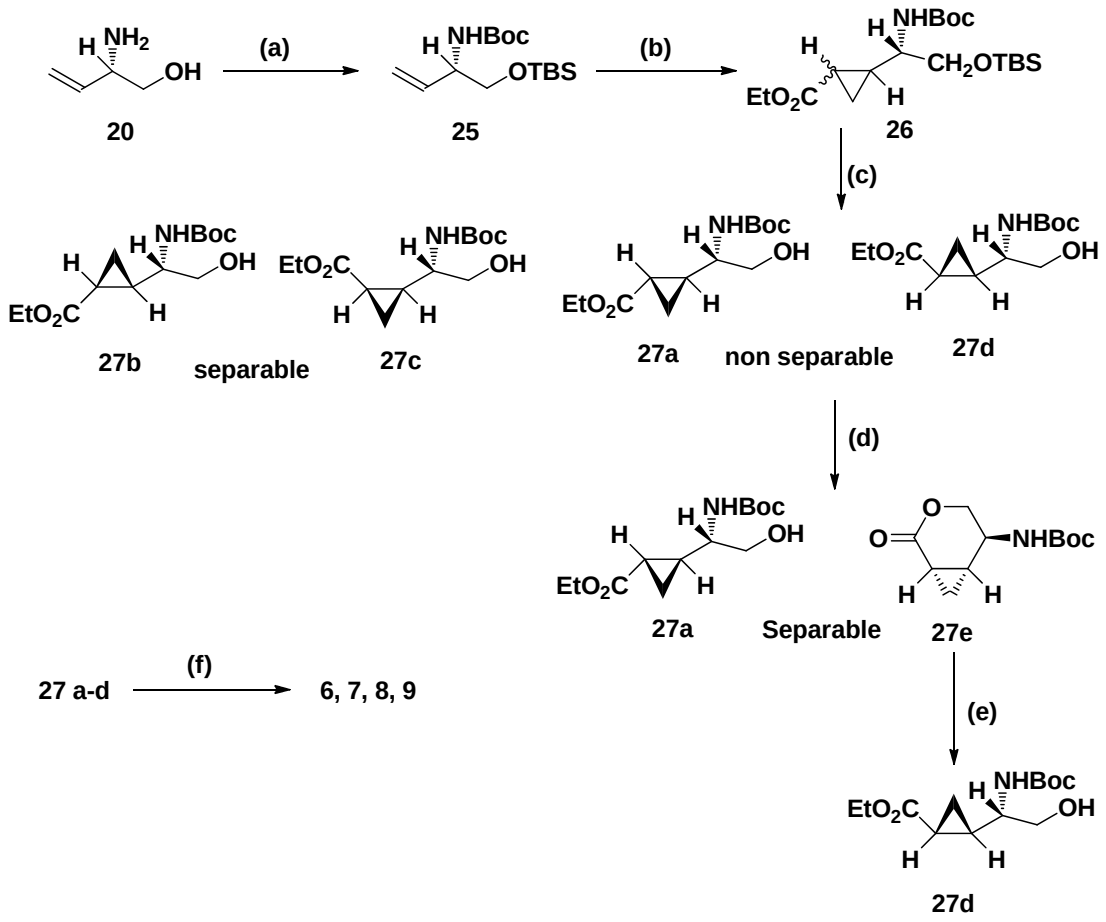
In continuation of their effort to construct the cyclopropane ring catalysed by Pd, all the four diastereomers of α-(carboxycyclopropyl) glycine were realised starting from (2*S*)-2-amino-3-butenol *via* inter and intra molecular cyclopropanation with diazocarbonyl compounds.



Scheme 2. *Reagent and Conditions*: (a) [i] *N*-*t*-Boc-glycyl-*O*-succinate, Et_3N, THF, -20 ^oC; [ii] 2,2-dimethoxypropane, acetone, CSA, 80 ^oC, 62% for two steps; (b) [i] TMSOTf, 2,6-lutidine, rt; [ii] $NaNO_2$, citric acid, pH 3, 0 ^oC, 43% for two steps; (c) $Pd(OAc)_2$ toluene, 80 ^oC,; (d) 60% acetic acid, rt; (e) 0.5 N NaOH, 70 ^oC; (f) Di-*tert*-butyl dicarbonate, Et_3N, dioxane-H_2O (l:l), rt; (g) Jone's reagent, acetone, 0 ^oC, 59% for four steps. (h) [i] TFA, 0 ^oC; [ii] Dowex 50Wx4 (elution with 3% NH_3; [iii] 1 N HCl, pH 3.0, 65% for three steps .

Accordingly, synthesis of *cis* CCG was accomplished through intramolecular cyclopropanation of the diazoamide. (2*S*)-2-Amino-3-butenol **20** was subjected to react with *N*-*t*-Boc-glycl-*O*-succinate followed by protection with DMP in the presence of CSA to furnish the *t*-Boc protected compound **21**. Removal of Boc with TMSOTf/2,6-lutidine gave the desired amine **22**. Sequential treatment of amine with $NaNO_2$/pH 3 buffer and catalytic palladium (II) acetate yielded the mixture of cycloadduct **23** in 6:1 ratio. The required major isomer was isolated and subjected to acetonide removal followed by hydrolysis of amide and its protection as *t*-Boc. Jone's oxidation of hydroxy group and final removal of amine protection furnished the L-CCG-III **6** (**Scheme 2**).

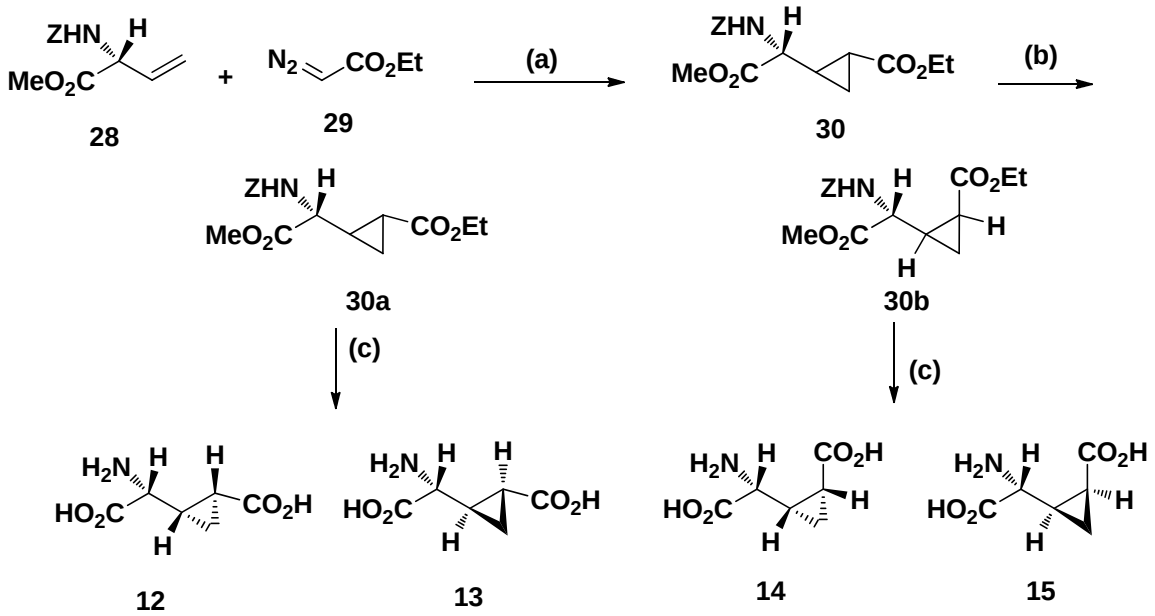
Intermolecular cycloaddition[4b] of ethyl diazoacetate catalysed by $Pd(OAc)_2$ was performed over protected compound of **20** to furnish a mixture of protected cyclopropane products in 41% yield. Two of them, **27b** & **27c**, could easily be separated by medium pressure column chromatography after the removal of silyl protection with CSA. While the other two, **27a** & **27d** having almost same R_f were treated with CSA/DCM to give a separable mixture of **27a** and δ-lactone (**27e**), which were separated by column. Hydrolysis and esterification of **27e** provided **27d**. Jone's oxidation of **27a-d** followed by saponification and acid treatment rendered all the four diastereomers of CCG's (**6, 7, 8, 9**) (**Scheme 3**).



Scheme 3. *Reagents and conditions*: (a) [i] Boc_2O, Dioxane, rt, [ii] TBSCl, imidazole, CH_2Cl_2, rt, 75% for two steps; (b) Ethyl diazoacetate, $Pd(OAc)_2$, rt, 88%; (c) CSA, EtOH, rt; (d) CSA, EtOH, rt; (e) Hydrolysis and saponification, 87%; (f) [i] Jone's oxidation, [ii] 0.5 N NaOH, and [iii] TFA (80%), 65% for three steps.

Pellicciari's *et al.* (1990)[5]

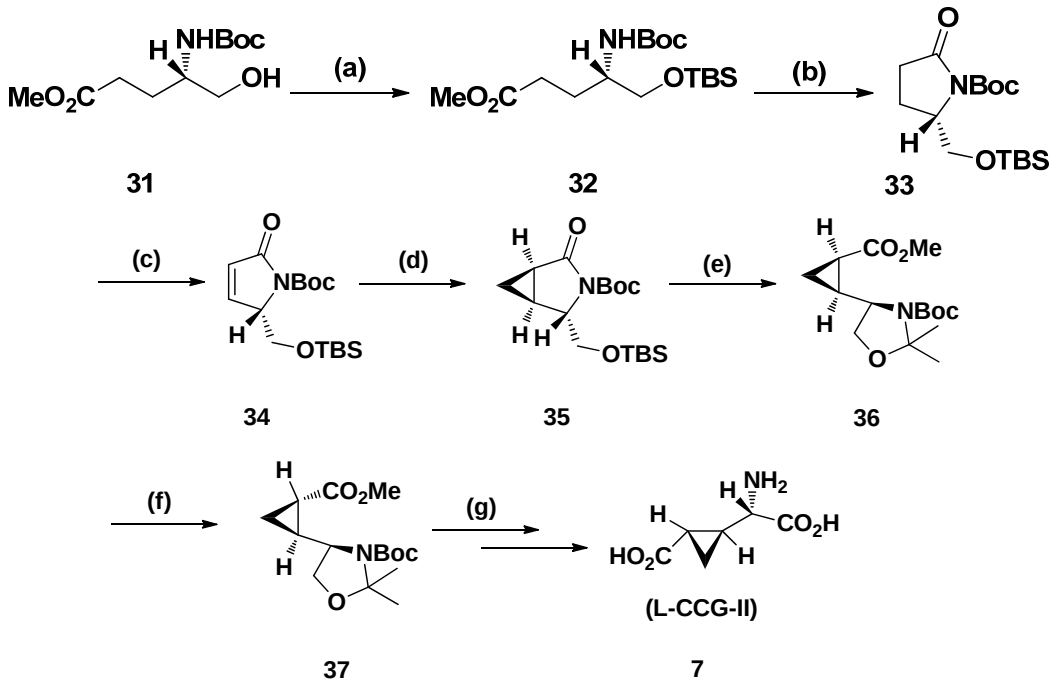
Pellicciari introduced a dirhodium (II) tetraacetate catalysed cyclopropanation of *N*-protected-D-vinyl glycine ester **28** with ethyl diazoacetate **29** to give mixture of all four diastereomers of cyclopropane **30**, with the *trans* isomer predominating.[46] MPLC and/derivatisation technique led to the separation of all these isomers of D-CCG's (**Scheme 4**).



Scheme 4. *Reagents and conditions*: (a) $Rh_2(OAc)_4$, CH_2Cl_2, 85%; (b) m.p.1.c.; (c) [i] 6N HCI. reflux, 3h; [ii] Dowex l x 8, AcO- form, 61% .

Ohfune *et al.* Approach-3 (1993)[6]

The study of action of [KN(TMS)$_2$] on cyclopropyl ester anion generated from *cis* ester to deliver the *trans* isomer quantitatively paved the path to yet another synthesis of L-CCG-II. Thus the bicyclic lactam **35** obtained from glutamic acid was subjected to methanolysis followed by acetonide protection to furnish the *cis* ester **36**. Deprotonation with bis(trimethylsilyl)amide (-78 ^{o}C to -15 ^{o}C) followed by treatment with acetic acid gave the *trans* isomer exclusively. This *trans* ester was transformed into **7** through routine organic transformations[6] (**Scheme 5**).

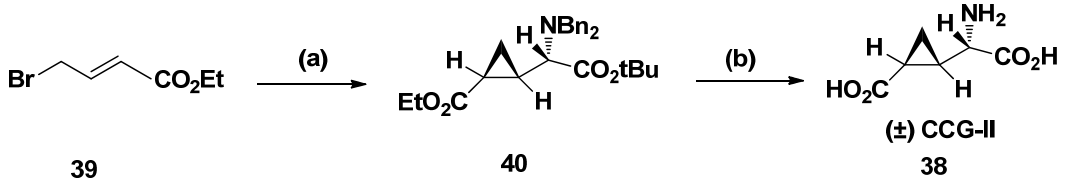


Scheme 5. *Reagents and conditions*: (a) TBSCl, imidazole, CH_2Cl_2, 85%; (b) NaH, Boc_2O, 75%; (c) LHMDS, TMSCl, $Pd(OAc)_2$, 65%; (d) CH_2N_2, $Pd(OAc)_2$; (e) [i] MeOH, CSA; [ii] CSA, DMP, 72%; (f) $KN(TMS)_2$, THF, -78 ^oC; (g) [i] AcOH, -78 ^oC; [ii] $(Boc)_2O$, Et_3N, EtOH; [iii] Jone's oxidation; [iv] 0.5 N NaOH; [v] TFA (80%), 44% for five steps.

4.2.2.2. Cyclopropanation *via* MIRC

Yamaguchi *et al.* (1990)[8]

A concise and stereoselective synthesis of (±)-CCG-II **38** was accomplished by Yamaguchi *et al.* wherein they have employed a Michael type addition of lithium enolate of *N*,*N*-dibenzylglycinate to β-substituted α,β-unsaturated ester previously described by Joucla *et al.*[7] to construct the cyclopropyl derivative. Thus the anion generated from glycine equivalent at –78 ^oC employing LDA as the base was subjected to react with 4-bromoethylcrotonate **39** to render the *threo* selective formation of cyclopropane **40**. Further functional group transformation led to (±)-CCG-II[8] (**Scheme 6**).



39 40 38

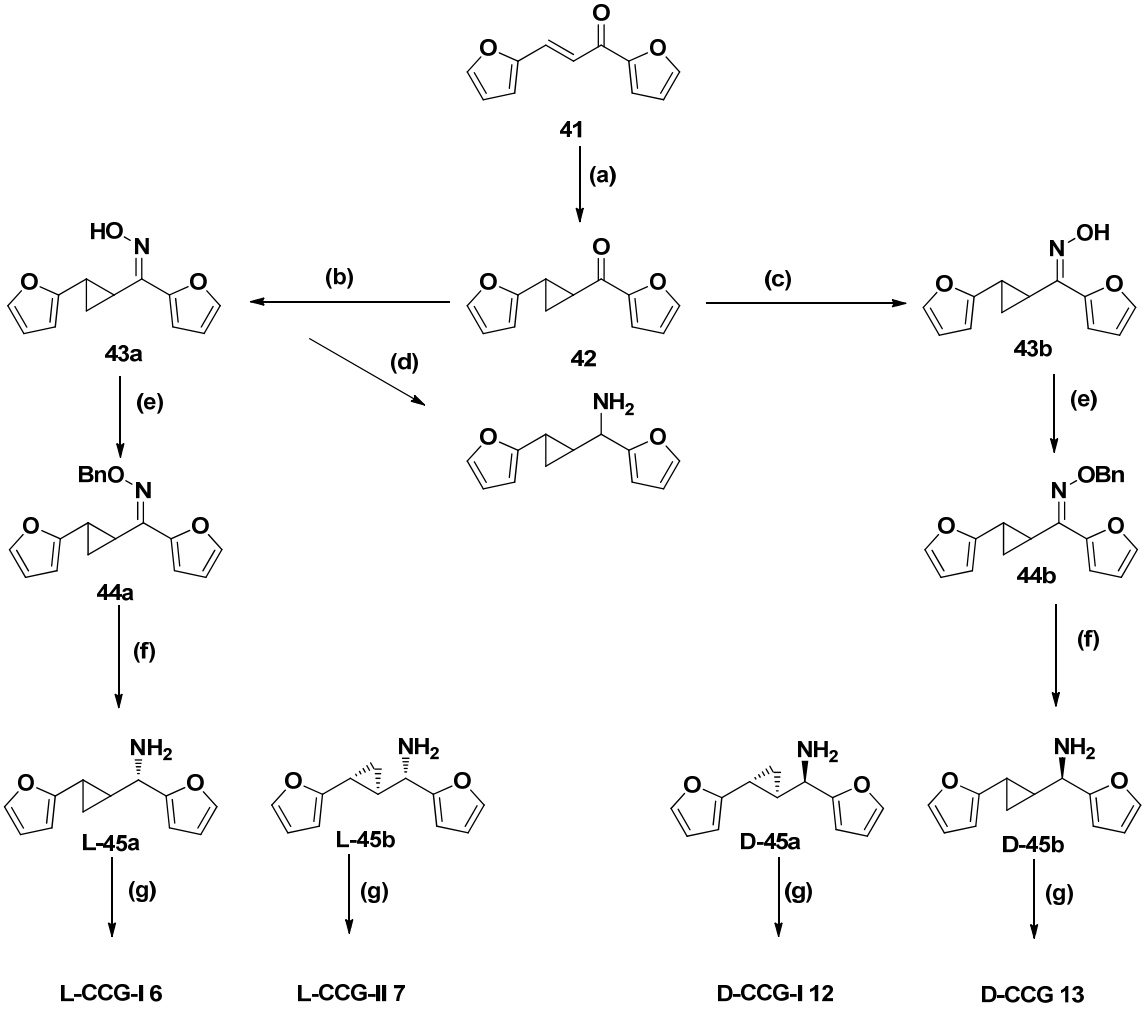
Scheme 6. *Reagents and conditions*: (a) LDA, $Bn_2NCH_2CO_2tBu$, THF, -78 ^oC, 55%; (b) [i] TFA, 83%; [ii] H_2, Pd/C, 78%.

4.2.2.3. Sulfoxonium Ylide Cyclopropanation

Demir *et al.* (1998)[9]

Demir *et al.* described a sulfoxonium ylide mediated cyclopropanation and enantioselective oxime reduction towards the synthesis of CCG. Treatment of *trans*-1,3-di-(2-furyl) propenone **41** with trimethylsulfoxonium iodide gave the cyclopropylketone **42** in good yield. It was converted predominantly into *E* (**43a**) or *Z* (**43b**) oxime selectively by reacting either with $NH_2OH.HCl$/NaOH or $NH_2OH.HCl$/NaOAc-EtOH respectively. The oxime reduction with $BH_3.SMe_2$ in THF afforded the *rac*-amine. For the synthesis of optically active amino acids the oximes were converted to *O*-benzyloxime ethers using NaH and benzyl bromide in high yields. Enantioselective reduction of *E*-oxime was achieved by $BH_3.SMe_2$ in the

presence of oxaborolidine catalyst prepared from chiral amino alcohols. The reduced products were separated by flash column chromatography and the oxidations of furan rings were carried out with ozone at –78 °C to furnish amino acids L-CCG-I and L-CCG-II[9] (**Scheme 7**).



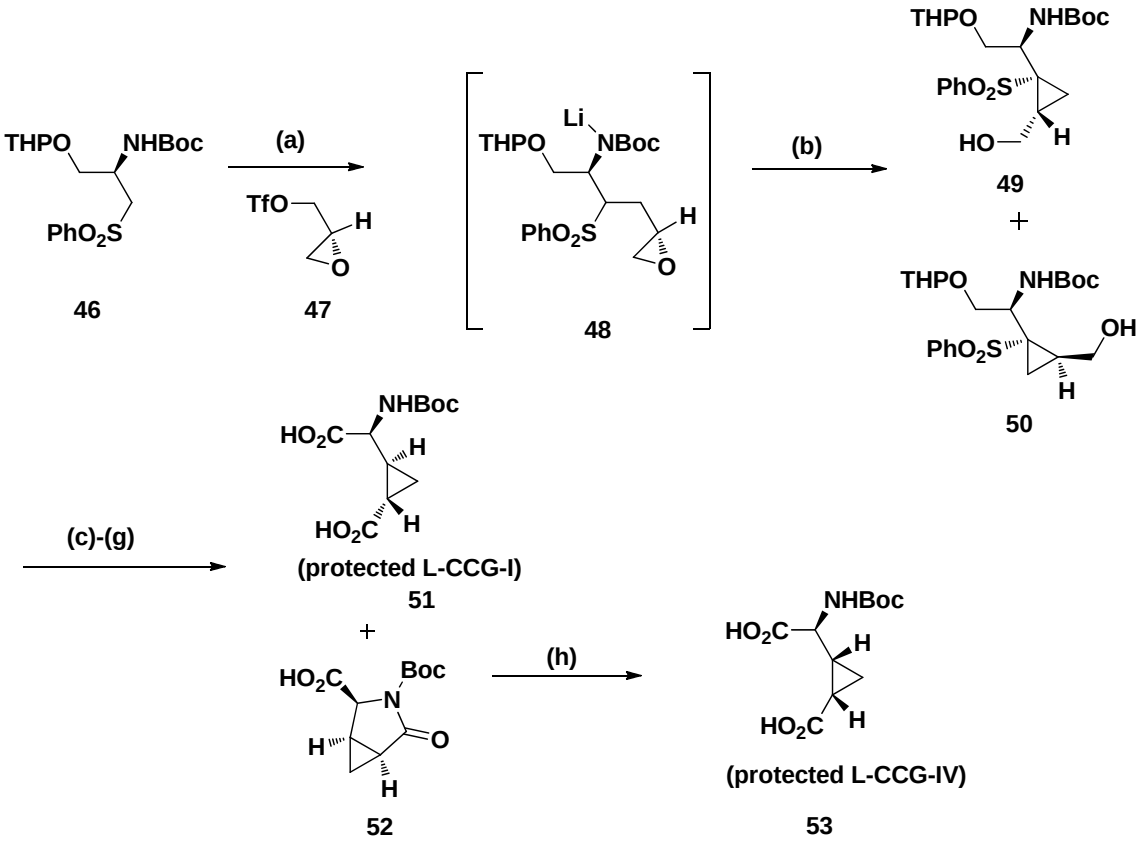
Scheme 7. *Reagents and conditions*: (a) Me_3SOI, NaH, DMSO, 94%; (b) $H_2NOH.HCl$, NaOH; (c) $H_2NOH.HCl$, NaOAc, EtOH; (d) $BH_3.SMe_2$, THF, 88%; (e) NaH, BnBr, DMF, 92%; (f) BH_3.THF (cat.), 89%; (g) O_3, MeOH, 90%.

4.2.2.4. Miscellaneous Approaches

Sasaki *et al.* (1995)[10]

Central to their synthesis was the generation of cyclopropyl moiety by addition of excess of *n*-BuLi to already generated β-epoxy sulfone, which undergoes an intramolecular epoxide ring opening. Thus the compound **48** was obtained from the reaction of dilithiated species of

sulfone **46** with (2*R*)-glycidyl triflate **47**. Subsequent treatment with one more equivalent of *n*-BuLi generated a new sulfonyl carbanion which led to cyclopropyl



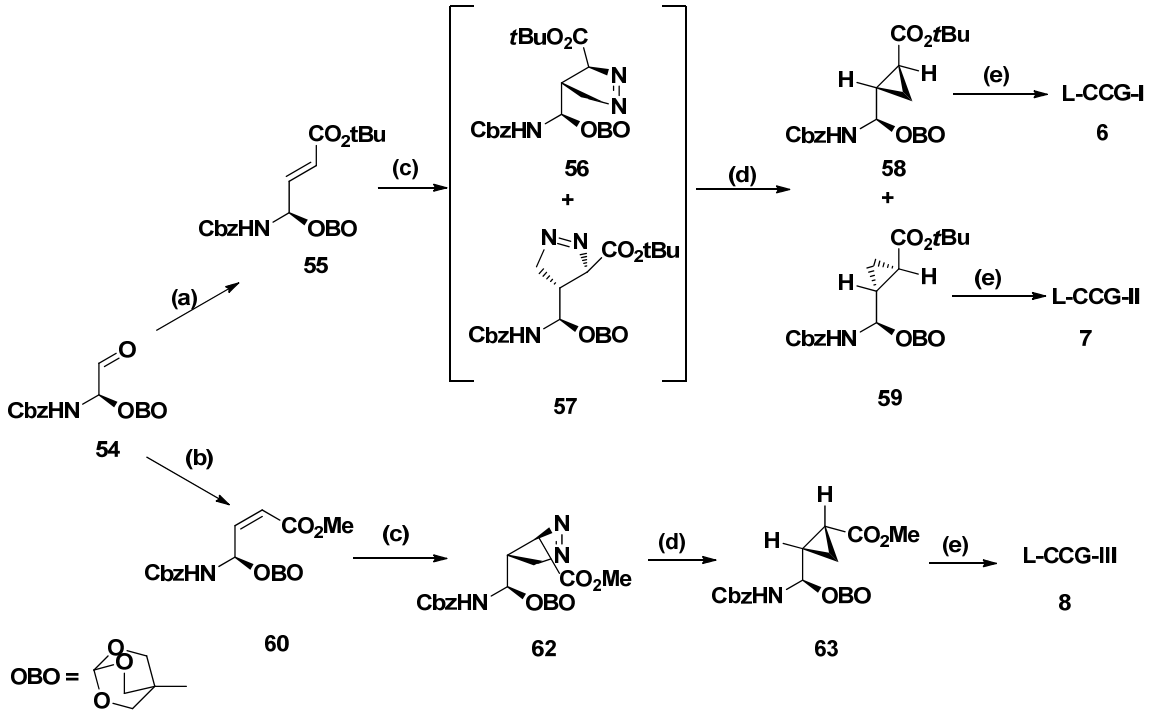
Scheme 8. *Reagents and conditions*: (a) *n*-BuLi, THF, (2*R*)-glycidyl triflate **47**, -78 °C; (b) *n*-BuLi, THF, -78 °C to rt, 73% for two steps; (c) MsCI, Et_3N, CH_2CI_2; (d) NaH, DMF, 0 °C; (e) EtOH, pyridinium *p*-toluenesulfonate, 50 °C; (f) 6% Na-Hg, Na_2HPO_4, MeOH, 0 ^oC; (g) Jones oxidation, acetone, 0 ^oC; (h) LiOH, MeOH, rt, 34% for six steps.

carbinols **49** and **50**. Hydrolysis of THP ether, reductive desulfonylation and Jones oxidation gave a mixture of Boc protected (2*S*,1'*R*,2'*S*) **51** and lactam **52**. Base hydrolysis of lactam gave the Boc protected *cis* isomer **53**[10] (**Scheme 8**).

Ortuño and Lajoie *et al.* (1999)[11]

Lajoie *et al.* described a non catalysed stereocontrolled 1,3-dipolar cycloaddition of diazomethane on the chiral *E* or *Z*-3,4-L-didehydroglutamate. The stereochemical control was provided by the presence of the bulky OBO function. The *E*-3,4-L-didehydroglutamte was obtained by the olefination of the Cbz-L-Ser-aldehyde-OBO **54** with Wittig Horner reagent. Addition of ethereal diazomethane gave a mixture of highly unstable pyrazone **56** and **57**, which was subjected to photolysis condition to give 6:1 mixture of *syn*-and *anti-trans* cyclopropane derivatives, **58** and **59**, which were separated by chromatography and

recrystallisation. Removal of all the protecting groups with HCl rendered the cyclopropane CCG-I **6** and CCG-II **7**. Similarly the *Z*-3,4-didehydroglutamate was obtained by treatment



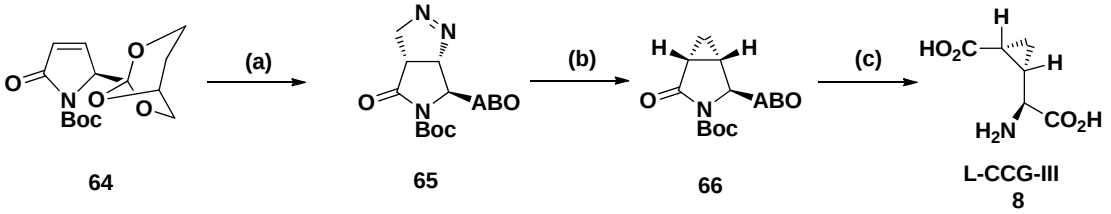
Scheme 9. *Reagents and conditions*: (a) $(Ph)_3PdCH_2CO_2tBu$, CH_2Cl_2, 78%; (b) $(CF_3CH_2O)_2P(O)CHCO_2Me$, NaH, THF, -78 °C, 74%; (c) CH_2N_2, Et_2O; (d) hν, CH_2Cl_2, benzophenone, -45 °C, 75%: **58**, 12%: **59**, 60%: **63**; (e) 6 N HCl, 90 °C, 96%: **6**, 91%: **7**, 93%: **8**.

of serine aldehyde with $Na(CF_3\text{-}CH_2O)_2P{=}CHCO_2Et$ as 9:1 *Z*:*E* mixture. Here treatment with ethereal diazomethane rendered the pyrazoline **61** exclusively, which was further, converted to CCG-III **119** through same sequence of reactions (**Scheme 9**).

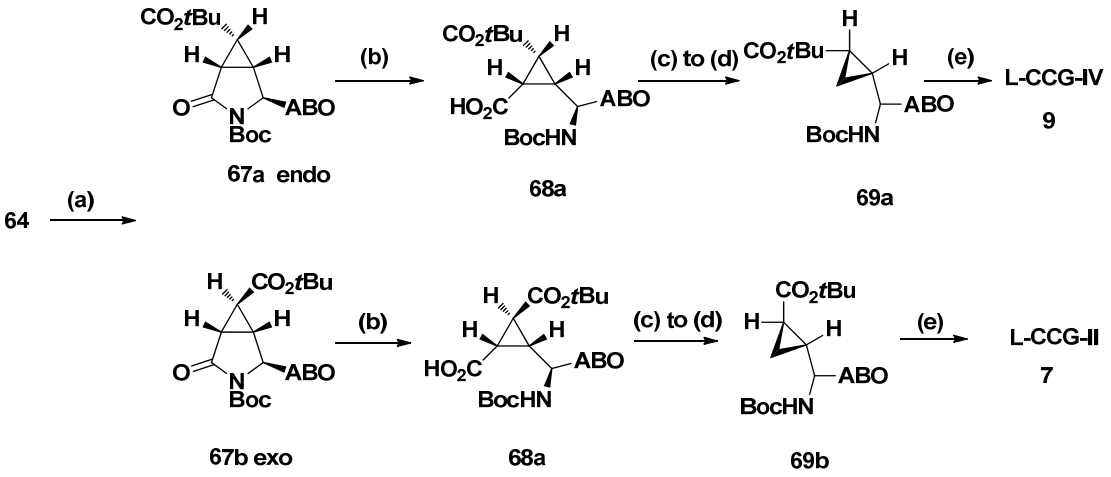
Oba *et al.* (2005)[12]

A stereocontrolled approach to L-CCG was described using 3,4-didehydro-L-pyroglutamate as the chiral template and bulky 2,7,8-trioxabicyclo[3.2.1]octyl group (ABO ester) as the stereodirecting carboxyl-protecting group during cyclopropanation with diazomethane. Stereospecific cyclopropanation was carried out by 1,3-dipolar cycloaddition of diazomethane to the unsaturated orthoglutamate **64** followed by photolysis of pyrazoline **65** resulting in exclusive formation of cycloadduct **66**. Exclusive formation of one product indicates the addition of diazomethane to the olefin opposite to bulky ABO ester. Acidic hydrolysis of the cyclopropane and ion exchange treatment rendered L-CCG-III **8**[12] (**Scheme 10**).

An alternation in the 3,4 methanoglutamic acid framework by change in cyclopropanation of the olefin in **64** with sulfur ylide to render the γ-carboxyl group in the cyclopropane ring followed by decarboxylation of the original carboxyl group included in the pyroglutamate framework delivered L-CCG-IV and L-CCG-II.



Scheme 10. *Reagent and conditions*: (a) CH_2N_2, ether; (b) Hg-lamp (400 W), benzophen-one, MeCN, 0 ^oC, 64% (two steps); (c) 1 M HCl reflux; then Dowex 50W-X8, 61%.



Scheme 11. *Reagent and conditions*: (a) $Me_2S{=}CHCO_2{}^tBu$, DMSO, **67a**: 40%, **67b**:29%; (b) 1 M LiOH, THF; (c) 4-methylmorpholine, $ClCO_2{}^iBu$, THF; then 2-mercaptopyridine N-oxide, Et_3N, THF; (d) *tert*-BuSH, W-lamp (100 W), **69a**: 85% (three steps), **69b**: 51% (three steps); (e) 1 M HCl reflux; then Dowex 50W-X8, **9**: 86%, **7**: 84%. ABO = 5-methyl-2,7,8-trioxabicyclo[3.2.1]oct-1-yl.

Thereby, treatment of **64** with *tert*-butyl dimethylsulfuranylidene acetate gave slightly excess of *endo* product, giving 67:33 mixtures of **67a** and **67b**. The compounds were separated by column chromatography and chemoselective ring opening of lactam **68a** with LiOH gave crude **68b**. Barton decarboxylation of **68a** using mercaptopyridine *N*-oxide rendered the fully protected cyclopropane **69a**. Final deprotection on treatment with HCl gave the L-CCG-IV (**9**). On the other hand the extended form of CCG (**7**) was realised by treatment of the *exo* product **67b** under similar conditions (**Scheme 11**).

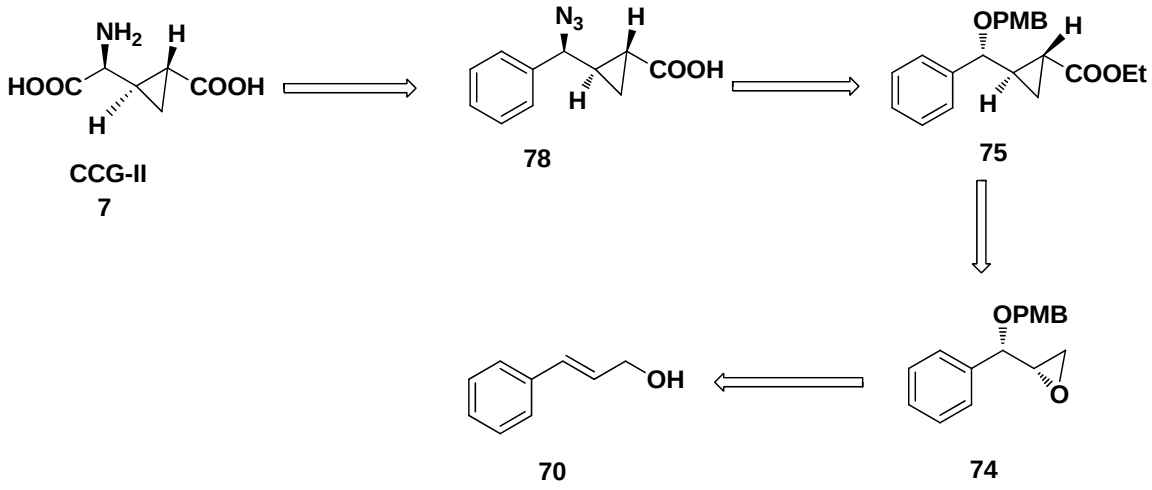
4.2.3. Present Work

4.2.3.1. Objective

As a pharmacological tool, L-CCG-II have played an important role for the investigation of the mechanism underlying the glutamate function as well as the design of useful therapeutic drugs of various neuronal diseases. Much attention has been paid to the modification of these compounds, which has led to the discovery of several other potent and selective agonists or antagonists for mGluRsa. A variety of synthetic protocols have been developed to meet the increasing demand. As part of our research programme aimed at developing enantioselective syntheses of bioactive molecules we became interested in devising an efficient route to L-CCG-II **7** and present study describes our endeavors towards the total synthesis of compound L-CCG-II from commercially available cinnamyl alcohol **70** employing Sharpless asymmetric dihydroxylation (AD)[13] and Wadsworth-Emmons cyclopropanation[14] as the key steps.

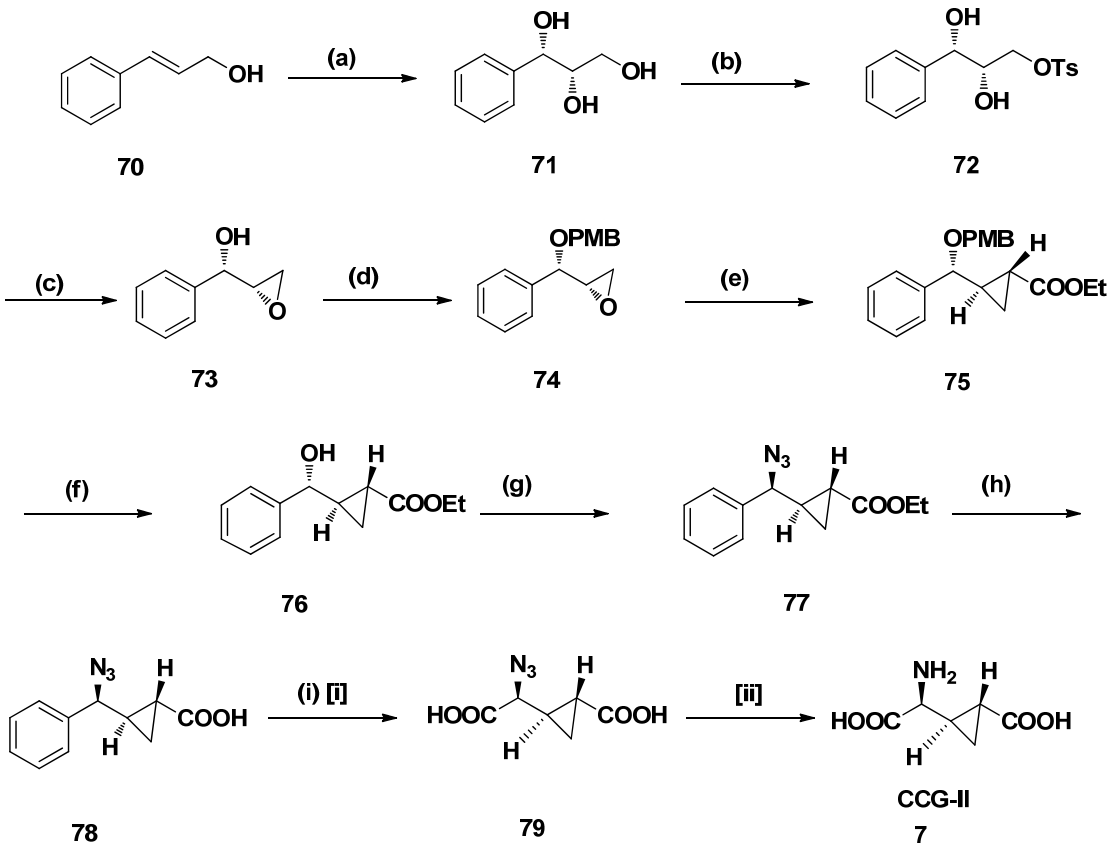
4.2.3.2. Results and discussion

Our synthetic approach for the synthesis of compound **7** was envisioned *via* the retrosynthetic route as shown in **Scheme 12**. The compound **7** could be obtained from compound **75** by series of reaction involving oxidation of phenyl ring, ester hydrolysis and conversion of alcohol into azide. The compound **75** could be obtained from epoxide **74** by Wadsworth-Emmons cyclopropanation reaction. The epoxide **74** in turn could be easily synthesized by the Sharpless asymmetric dihydroxylation (AD) of cinnamyl alcohol **70**.



Scheme 12

The synthesis of L-CCG-II **7** started from commercially available cinnamyl alcohol **70** as illustrated in **Scheme 13**. Cinnamyl alcohol **70** was subjected to Sharpless asymmetric dihydroxylation using OsO_4 and $K_3Fe(CN)_6$ as co-oxidant in the presence of $(DHQ)_2PHAL$ as ligand to give triol **71** in 84% yield with ee > 95%,{$[\alpha]_D^{25}$: +20.8 (*c* 3.5, $CHCl_3$); Lit[15] $[\alpha]_D^{25}$: +20.92 (*c* 3.68, $CHCl_3$)}. The appearance of multiplet in the range of δ 3.31-3.36 and broad singlet at δ 3.93, and appearance of broad peak at 3300 cm^{-1} in IR spectrum confirmed the formation of triol. The regioselective primary monotosylation[16] of triol **71** with tosyl chloride and catalytic Bu_2SnO, furnished the tosyl diol **72** in 89% yield. The appearance of peak at δ 2.37 in ^1H NMR shows the presence of tosyl group (**Scheme 13**).



Scheme 13. *Reagents and conditions*: (a) $(DHQ)_2PHAL$ (1 mol%), 0.1M OsO_4 (0.4 mol%), $CH_3SO_2NH_2$, K_2CO_3, $K_3Fe(CN)_6$, *t*-BuOH:H_2O (1:1), 30 h, 84%, (b) TsCl, Et_3N, CH_2Cl_2, Bu_2SnO, 0 ^oC, 6 h, 89%; (c) K_2CO_3, MeOH, 15 min, 79%; (d) PMBBr, NaH, THF, 0 ^oC, 6 h, 86%; (e) $(EtO)_2POCH_2COOEt$, NaH, 80 ^oC to 110 ^oC, 14 h, 75%; (f) DDQ, CH_2Cl_2:H_2O, (18:1), 3 h, 85%; (g) (i) MsCl, Et_3N, DMAP, CH_2Cl_2, 1 h; (ii) NaN_3, DMF, 60 ^oC, 8 h, 85%; (h) LiOH, MeOH:H_2O (3:2), 5 h, 82%; (i) [i] $RuCl_3$, $NaIO_4$, 70 ^oC, 15 min; [ii] $Pd(OH)_2$, H_2, MeOH, 2 h, for two steps 72%.

Base treatment of compound **72** in the presence of K_2CO_3 in methanol furnished epoxy alcohol **73** in 79% yield. The appearance of multiplet in the range of δ 2.71-2.79 and 3.10-3.17 confirmed the presence of epoxide. The free hydroxy group of epoxide **73** was then protected as PMB ether using PMB-bromide to give **74** in 86% yield. The appearance of singlet at δ 3.82 in ^{1}H NMR and disappearance of broad peak at 3300 cm^{-1} in IR confirmed the formation of product. With the epoxide **74** in hand, our next aim was to construct the cyclopropane ring. Towards this end, we used the Wadsworth-Emmons cyclopropanation reaction optimised by us which furnished **75** in 75% yield as a single diastereomer. The appearance of cyclopropane $–CH_2$ in the range of δ 1.05-1.29 and ethyl ester peaks as triplet and quartet at δ 1.05-1.29, 4.08 and appearance of peak at 1729 cm^{-1} in IR spectrum confirmed the formation of ethyl ester derivative of cyclopropane. In order to introduce amino group, PMB-protected hydroxyl was deprotected by DDQ to furnish the free alcohol **76** in 85% yield. The appearance of broad peak at 3343 cm^{-1} in IR spectrum confirmed the presence of alcohol. The hydroxyl group of **76** was converted into *O*-mesylate, followed by the nucleophilic displacement with NaN_3 in dry DMF to afford compound **77** in 85% yield. The IR spectrum of **77** showed strong azide absorption at 2097 cm^{-1}. Compound **77** was then subjected to ester hydrolysis by using LiOH to furnish the acid **78** in 82% yield, the appearance of broad peak at 3400 cm^{-1} in IR spectrum and disappearance of ethyl ester peaks in ^{1}H and ^{13}C confirmed the formation of acid **78**.

Compound **78** was subjected to phenyl group oxidation[17] by using combination of $RuCl_3.3H_2O$, $NaIO_4$, to furnish the diacid **79**, which unfortunately underwent decomposition during work-up and purification. We then decided to directly proceed for next step for reduction of azide into amine by using $Pd(OH)_2$ without column purification of diacid which furnished L-CCG-II **7** in 72% yield as (over two steps), m.p. 255-256 ^oC; lit.[4b] mp 255-258 ^oC and $[\alpha]_D^{25}$ -19.68 (*c* 0.51, H_2O) lit.[4b] $[\alpha]_D^{25}$ -20.2 (*c* 0.51, H_2O). In the ^{1}H NMR of compound **7**, the doublet appearing at δ 3.55 integrating for one proton was attributed to the cyclopropane glycine –C*H*. The four cyclopropane protons appeared as ddd at δ 2.01, dddd at δ 1.84, ddd at δ 1.36 and ddd at δ 1.22. ^{13}C NMR spectrum along with DEPT spectrum showed the presence of single methylene carbon resonating at δ 13.5 was ascribed to the cyclopropane $–\underline{C}H_2$ while other carbon peaks appeared at δ 56.8 (CH), δ 21.9 (CH), δ 19.5 (CH). The carbonyl carbon peaks of free acid resonated at δ 177.3 and δ 172.4. The physical and spectroscopic data were identical with those reported.[4b] The overall yield of the target compound **7** was found to be 16% from nine steps.

4.2.3.3. Conclusions

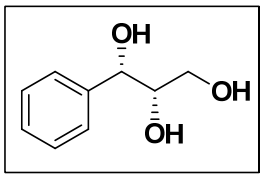
In summary, we have developed a facile and practical enantioselective synthesis of L-CCG-II **118**. The key step involves the conversion of epoxide to cyclopropane compound using Wadsworth-Emmons cyclopropane protocol and Sharpless asymmetric dihydroxylation as the key step. The synthetic strategy is flexible and would permit the synthesis of other analogues of CCG structural stereochemical variation.

4.2.4. Experimental Section

General Information

General information as described in section A.

(1*S*,2*S*)-1-Phenylpropane-1,2,3-triol (71):



To a mixture of $K_3Fe(CN)_6$ (73.61g, 223 mmol), K_2CO_3 (30.9 g, 223 mmol) and $(DHQ)_2PHAL$ (580.55 mg, 1 mol%), in *t*-BuOH-H_2O (1:1, 745.36 mL, 5 mL/mmol) cooled at 0 ^oC was added OsO_4 (2.98 mL, 0.1 M sol in toluene, 0.4 mol%) followed by methane sulfonamide (7.08 g, 74 mmol). After stirring for 5 min at 0 ^oC, the olefin **70** (10 g, 74 mmol) was added in one portion. The reaction mixture was stirred at 0 ^oC for 30 h and then quenched with solid sodium sulfite (10 g). The stirring was continued for 45 min and the solution was extracted with EtOAc (5 x 200 mL). The combined organic phases were washed (10% KOH, then brine), dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether:EtOAc (3:7) as eluent gave the triol **71** as thick syrupy liquid.

Yield: 10.52 g, 85%.

Mol. Formula: $C_9H_{12}O_3$

$[\alpha]_D^{25}$: +20.8 (*c* 3.5, $CHCl_3$); {lit.[16] **$[\alpha]_D^{25}$:** +20.92 (*c* 3.68, $CHCl_3$)}.

IR (neat, cm^{-1}): 3369, 2932, 1447, 1215, 1008, 770, 702, 668.

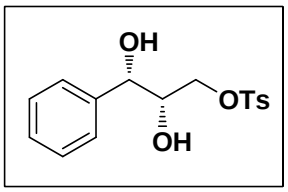
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.26-3.36 (m, 2H), 3.64-3.69 (m, 1H), 4.3 (brs, 3H), 4.54 (d, *J* =7.1 Hz, 1H), 7.23-7.27(m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 63.0, 74.6, 76.0, 126.7, 127.9, 128.4, 140.5.

MS (EI) *m/z* (%): 191 $(M+Na)^+$.

Analysis: Calcd.: C, 64.27; H, 7.19%; **Found:** C, 63.99; H, 7.42%.

(2*S*,3*S*)-Dihydroxy-3-phenylpropyl 4-methylbenzenesulfonate (72):



To a mixture of triol **71** (4.00 g, 23.66 mmol), in dry CH_2Cl_2 (40.0 mL) was added dibutyltin oxide (0.292 mg, 0.2 mol %) followed by the addition of *p*-toluenesulfonyl chloride (4.94 g, 26.0 mmol) and Et_3N (3.62 mL, 26.0 mmol) and reaction was stirred at room temperature under nitrogen. The reaction was monitored by TLC, after completion of reaction (6 h) the mixture was quenched by adding water. The solution was extracted with dichloromethane (3 x 100 mL) and then combined organic phase was washed with water, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of crude product using petroleum ether:EtOAc (7:3) as eluent afforded monotosyl compound **72** as a viscous liquid.

Yield: 6.8 g, 89%.

Mol. Formula: $C_{16}H_{18}O_5S$

$[\alpha]_D^{25}$: +15.4 (*c* 1.2, $CHCl_3$).

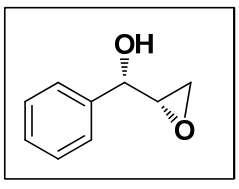
IR ($CHCl_3$, cm^{-1}): ν_{max} 3503, 1729, 1493, 1359, 1189, 1175, 1096, 973, 758, 665.

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.37 (s, 3H), 2.83 (brs, 2H), 3.77-3.82 (m, 2H), 3.91-3.98 (m, 1H), 4.55 (d, *J* = 6.1 Hz, 1H), 7.19-7.27 (m, 7H), 7.67 (d, *J* = 8.3 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 21.5, 70.4, 73.4, 73.5, 126.5, 127.8, 128.1, 128.5, 129.8, 132.2, 139.7, 145.

Analysis Calcd.: C, 59.61; H, 5.63; S, 9.95%; **Found:** C, 59.75; H, 5.49; S, 9.74%.

(*S*)-((*S*)-Oxiran-2-yl)(phenyl)methanol (73):



To a solution of compound **72** (1.0 g, 3.1 mmol) in methanol (10 mL) at 0 °C was added solid K_2CO_3 (0.857g, 6.2 mmol) in one portion and continued the stirring at 0 °C for 15 min. After consumption of starting material (15 min), solvent was evaporated under reduced pressure. Residue was diluted with water (5 mL), extracted with ethyl acetate (2 x 15 mL). Organic layer was washed with water, brine, dried over Na_2SO_4. Solvent was evaporated under

reduced pressure to give crude epoxide **73**, which was further purified by column chromatography using petroleum ether:EtOAc (8:2) as eluent to afford epoxide **73** as a viscous liquid.

Yield: 0.367 g, 79%.

Mol. Formula: $C_9H_{10}O_2$

$[\alpha]_D^{25}$: +7.89 (*c* 2.74, $CHCl_3$).

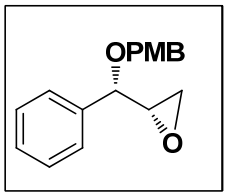
IR ($CHCl_3$, cm^{-1}): ν_{max} 3460, 3019, 2896, 1612, 1513, 1454, 1215, 1043, 755, 700, 668.

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.71-2.79 (m, 2H), 3.10-3.17 (m, 1H), 4.36 (d, *J* = 5.7 Hz, 1H), 7.26-7.36 (m, 5H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 45.3, 56.0, 74.4, 126.2, 128.0, 128.4, 140.

HRMS, (EI/DIP) for (M^+): calc. 150.06018, **Found:** 150.05492.

(*S*)-2-((*S*)-(4-Methoxybenzyloxy)(phenyl)methyl)oxirane (74):



To a solution of epoxy alcohol **73** (2.03 g, 13.51 mmol) in dry THF (20 mL) was added sodium hydride (60%, 0.810 g, 20.57 mmol) at 0 °C. The reaction mixture was then stirred at room temperature for 30 min after which it was again cooled to 0 °C. To this was added slowly *p*-methoxybenzyl bromide (1.84 mL, 14.86 mmol) and *tetra n*-butylammonium iodide (0.50 g, 1.35 mmol) with further stirring for 6 h at room temperature. The reaction mixture was quenched with addition of cold water at 0 °C. The two phases were separated and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic layer was 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 (93:7) as eluent furnished the PMB protected epoxide **74** as a colorless oil.

Yield: 3.14 g, 86%.

Mol. Formula: $C_{17}H_{18}O_3$

$[\alpha]_D^{25}$: +41.3 (*c* 1.8, $CHCl_3$).

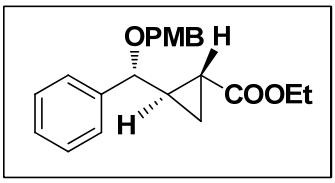
IR ($CHCl_3$, cm^{-1}): ν_{max} 3031, 2836, 1612, 1513, 1454, 1248, 1173, 1086, 1035, 821, 754.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.60 (dd, *J* = 2.6, 4.8 Hz, 1H), 2.72-2.77 (m, 1H), 3.23-3.29 (m, 1H), 3.82 (m, 3H), 4.10 (d, *J* = 6.5 Hz, 1H), 4.43-4.59 (m, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 7.29 (d, *J* = 8.7 Hz, 2H), 7.38-7.41 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 44.1, 55.1, 55.2, 70.3, 82.1, 113.7, 127.1, 128.2, 128.5, 129.3, 130.0, 138.1, 159.1.

Analysis Calcd.: C, 75.53; H, 6.71%; **Found:** C, 75.68; H, 6.84%.

(1*R*,2*R*)-Ethyl 2-((*R*)-(4-methoxybenzyloxy)(phenyl)methyl)cyclopropanecarboxylate (75):



To a suspension of sodium hydride (1.33 g, 33.29 mmol, 60% in mineral oil) in toluene (30 mL) was added triethylphosphonoacetate (8.8 mL, 44.36 mmol) dropwise over 15 min. After stirring at room temperature epoxide **74** (3 g, 11.09 mmol) in 20 mL of toluene was added dropwise over 10 min, followed by heating at 80 ^oC for 8 h and then temperature raised upto 110 ^oC for 6 h. The solution was cooled to room temperature, diluted with ethyl acetate (50 mL), then washed with saturated aqueous ammonium chloride (50 mL). After drying over Na_2SO_4 and concentration in vacuo, the crude material was purified by flash chromatography using petroleum ether:EtOAc (96:4), to yield the desired cyclopropane carboxylate **75** as a thick colorless oil.

Yield: 2.83 g, 75%.

Mol. Formula: $C_{21}H_{24}O_4$

$[\alpha]_D^{25}$: +9.3 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 2927, 2957, 2855, 1729, 1624, 1456, 1375, 1215, 1027, 759, 669.

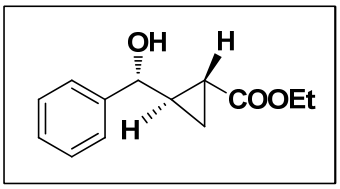
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10-1.27 (m, 5H), 1.69-1.85 (m, 2H), 3.82 (s, 3H), 4.08 (q, *J* = 2.1, 7.2 Hz, 2H), 4.2 (ABq, *J* = 11.2 Hz, 2H), 4.46 (d, *J* = 4.2 Hz, 1H), 6.7 (d, *J* = 8.2 Hz, 2H), 7.22-7.40 (m, 7H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 12.6, 14.2, 17.5, 27.9, 55.2, 60.4, 69.8, 71.4, 76.4, 77.6, 79.7, 113.7, 127.0, 128.5, 129.2, 129.4, 130.2, 140.8, 159.1, 173.9.

MS(ESI): m/z 363.30 $(M+Na)^+$.

HRMS, (EI/DIP) for (M^+): calc. 340.14909, **Found:** 340.1437.

(1*R*,2*R*)-Ethyl 2-((*R*)-hydroxy(phenyl)methyl)cyclopropanecarboxylate (76):



To a stirring solution of PMB ether **75** (2 g, 5.87 mmol) in CH_2Cl_2/H_2O (20:1) was added DDQ (2.66 g, 11.75 mmol). The resulting mixture was stirred for 3 h at 0 ^oC. The mixture was poured into saturated aqueous $NaHCO_3$ and further diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The solvents were removed under reduced pressure to give the crude product mixture as yellow oil. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (8:2) as eluent gave **76** as a colorless solid.

Yield: 1.09 g, 85%.

Mol. Formula: $C_{13}H_{16}O_3$

$[\alpha]_D^{25}$: +11.9 (*c* 1.0, $CHCl_3$).

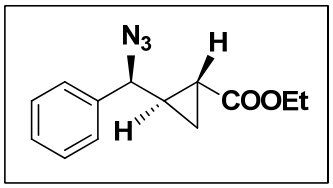
IR ($CHCl_3$, cm^{-1}): ν_{max} 3343, 3012, 1612, 1514, 1465, 1249, 1035.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.13-1.20 (m, 1H), 1.22-1.29 (m, 4H), 1.68-2.05 (m, 3H), 4.09 (q, *J* = 2.3, 6.5 Hz, 2H), 4.51 (d, *J* = 6.5 Hz, 1H), 7.33-7.40 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 12.2, 14.1, 17.7, 28.4, 60.5, 73.9, 126, 127.8, 142.8, 173.8.

HRMS, (EI/DIP) for (M^+): calc. 220.10705, **Found:** 220.10574.

(1*R*,2*R*)-Ethyl 2-((*S*)-azido(phenyl)methyl)cyclopropanecarboxylate (77):



To a solution of **76** (700 mg, 3.17 mmol) in dry CH_2Cl_2 (20 mL) at 0°C was added methanesulfonyl chloride (0.37 mL, 4.76 mmol), Et_3N (0.66 mL, 4.76) and DMAP (cat). After consumption of starting material (8 h), the reaction mixture was poured into Et_2O-H_2O mixture. The organic phase was separated and the aqueous phase extracted with Et_2O (3 x 20 mL). The combined organic phases were washed with water, brine, dried (Na_2SO_4) and concentrated to a yellow syrupy liquid, which was used as such in the next step.

To the solution of above mesylate in dry DMF (20 mL) was added NaN_3 (824 mg, 12.88 mmol) and the reaction mixture stirred at 70 °C for 8 h. It was cooled and poured into water

and extracted with Et_2O (4 x 20 mL). The organic extracts were washed with water, brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography using petroleum ether:EtOAc (9:1) as eluent gave **77** as a pale yellow color liquid.

Yield: 662 mg, 85%.

Mol. Formula: $C_{13}H_{15}N_3O_2$

$[\alpha]_D^{25}$: –27.9 (*c* 1.0, $CHCl_3$).

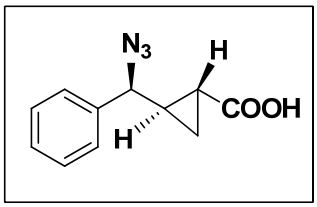
IR (neat, cm^{-1}): ν_{max} 2924, 2892, 2097, 1726, 1615, 1463, 1372, 1181, 1074, 1029, 761.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.81-0.93 (m, 1H), 0.96-1.25(m, 4H), 1.52-1.84 (m, 2H), 4.08 (m, 2H), 4.17 (d, *J* = 6.5 Hz, 1H), 7.14-7.32 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 12.2, 12.9, 14, 25.8, 55.1, 66.2, 126.9, 128.7, 129.6, 138.2, 173.

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

(1*R*,2*R*)-2-((*S*)-Azido(phenyl)methyl)cyclopropanecarboxylic acid (78):



To the ester **77** (400 mg, 1.63 mmol) dissolved in MeOH (10 mL) and H_2O (6.67 mL) was added $LiOH.H_2O$ (205 mg, 4.89 mmol) and stirred at 0 ^oC to room temperature for 5 h. The reaction mixture was further diluted with H_2O (5 mL) and stirred for 30 min then concentrated by rotary evaporator to quarter of its volume. The mixture was acidified with 1 M HCl (pH 3) and the reaction mixture was extracted with EtOAc (3 x 10 mL). The combined organic layer was washed with brine (2 x 10 mL) and dried over anhydrous Na_2SO_4, filtered, evaporated and the crude product was purified by column chromatography using petroleum ether:EtOAc (7:3) as eluent to give **78** as a pale yellow color syrupy liquid.

Yield: 255 mg, 82%.

Mol. Formula: $C_{11}H_{11}N_3O_2$

$[\alpha]_D^{25}$: –13.2 (*c* 0.36, $CHCl_3$).

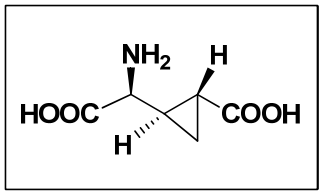
IR (neat, cm^{-1}): ν_{max} 3032, 2862, 2100, 1700, 1601, 1455, 1431, 1290, 1229, 1161, 1074, 738, 700.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.06-1.41 (m, 2H), 1.68-2.03 (m, 2H), 4.31 (d, *J* = 6.5 Hz, 1H), 7.13-7.47 (m, 5H), 10.05 (brs, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.1, 13.8, 26.9, 66.1, 126.9, 128.7, 128.9, 138.1, 179.6.

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

(1*R*,2*R*)-2-((*S*)-Amino(carboxy)methyl)cyclopropanecarboxylic acid (7):



Compound **78** (100 mg, 0.460 mmol) was dissolved in a mixture of CCl_4 (4 mL), CH_3CN (4 mL) and distilled H_2O (8 mL). The vigorously stirred mixture was heated to reflux temperature. Subsequently $NaIO_4$ (2.95 g, 13.8 mmol) and fresh $RuCl_3$ hydrate (14 mg, 0.069 mmol) were added. The colour changed from black via orange to yellow within 2 min, after which heterogeneous mixture was poured into a mixture of DCM and ice water (1:1). After stirring for 30 min, the pH of the mixture was adjusted to 10 with aq. NaOH (3M) and the mixture was extracted with DCM. The aq. layer was acidified with conc. HCl (pH<3) and extracted with EtOAc (10 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to diacid **79** as a brown color syrupy liquid. This was directly used for next step. To a solution of **79** (60 mg, 0.324 mmol) in methanol (4 mL) was added in portions 10% $Pd(OH)_2$ (10 mg, 0.0810 mmol), and the mixture was hydrogenated under H_2 and at room temperature for 2-2.5 h. The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure. The residue was concentrated and then dissolved in water and purified on Amberlite CG-50 resin (NH_4^+ form), eluting with 1.5% aq NH_4OH. The eluents were concentrated under reduced pressure to furnish **7** as colorless crystalline solid.

Yield: 52 mg, 72% yield.

Mol. Formula: $C_6H_9O_4N$

M.P.: 255-256 ^oC; [lit.[4b] mp 255-258 ^oC].

$[\alpha]_D^{25}$: -19.68 (*c* 0.51, H_2O), {lit.[4b] **$[\alpha]_D^{25}$:** -20.2 (*c* 0.51, H_2O)}.

^{1}H NMR (500 MHz, D_2O): δ 1.22 (ddd, *J* = 5.0, 6.3, 8.9 Hz, 1H), 1.36 (ddd, *J* = 5.0, 4.9, 8.9 Hz, 1H), 1.84 (dddd, *J* = 4.1, 6.3, 8.9, 8.9 Hz, 1H), 2.01 (ddd, *J* = 5.0, 4.9, 8.9 Hz, 1H), 3.55 (d, *J* = 9.8 Hz,1 H).

^{13}C NMR (125 MHz, D_2O): δ 13.5, 19.5, 21.9, 56.8, 172.4, 177.3.

4.2.5. Spectra

1. ^{1}H & ^{13}C NMR spectra of **71**

2. ^{1}H & ^{13}C NMR spectra of **72**

3. ^{1}H & ^{13}C NMR spectra of **73**

4. ^{1}H & ^{13}C NMR spectra of **74**

5. ^{1}H & ^{13}C NMR spectra of **75**

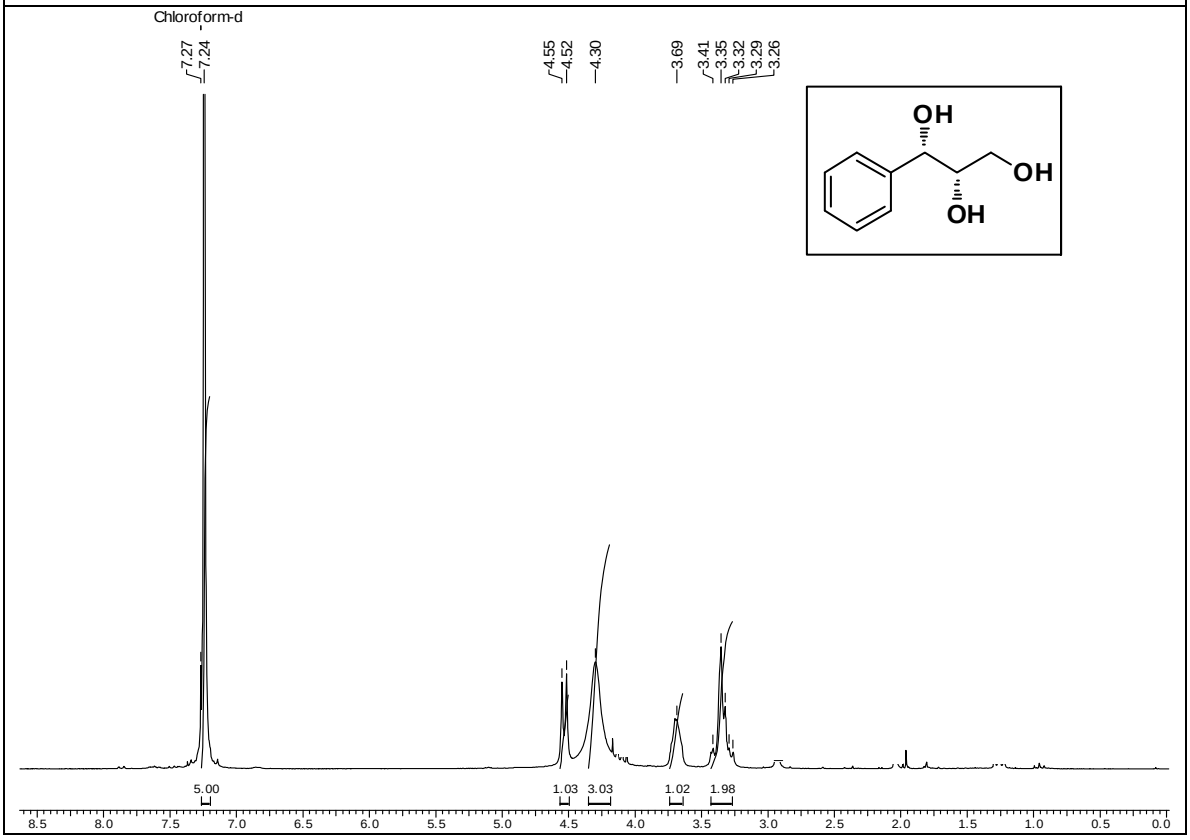
6. ^{1}H & ^{13}C NMR spectra of **76**

7. ^{1}H & ^{13}C NMR spectra of **77**

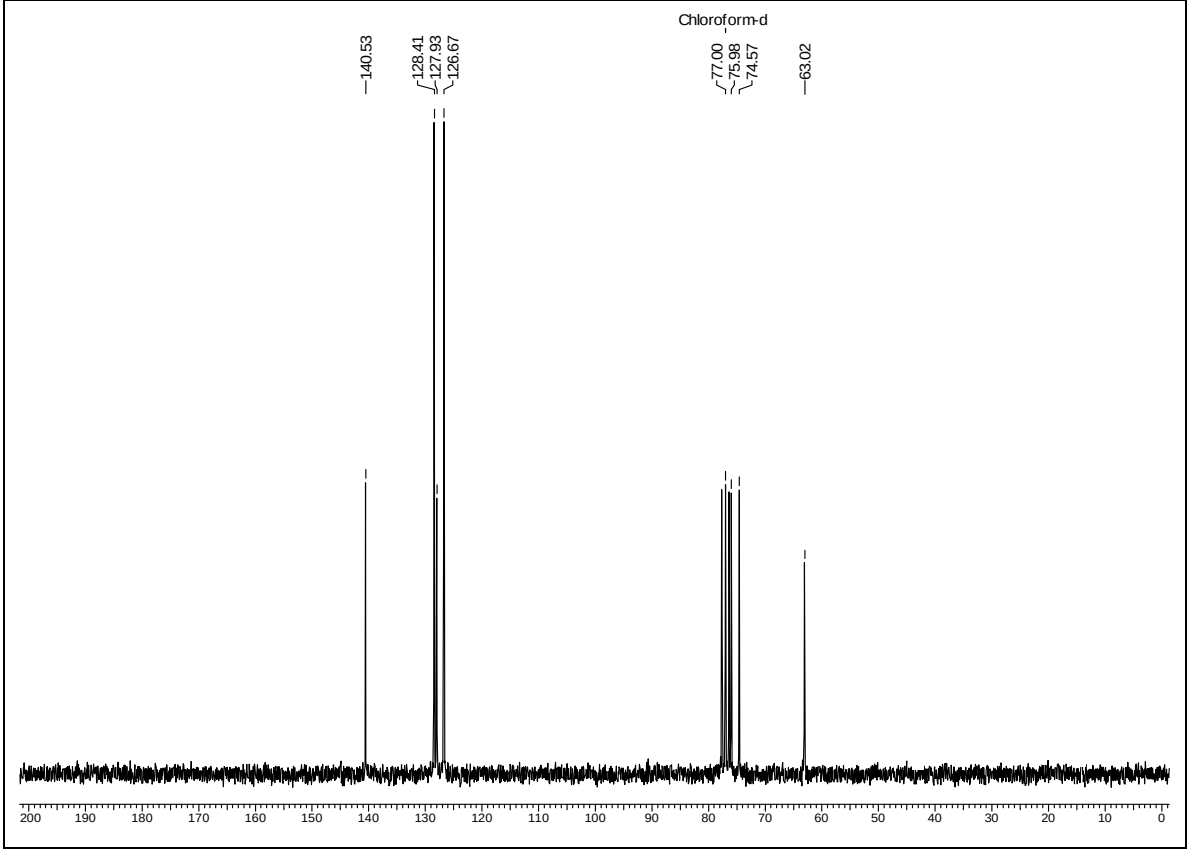
8. ^{1}H & ^{13}C NMR spectra of **78**

9. ^{1}H & ^{13}C NMR spectra of **7**

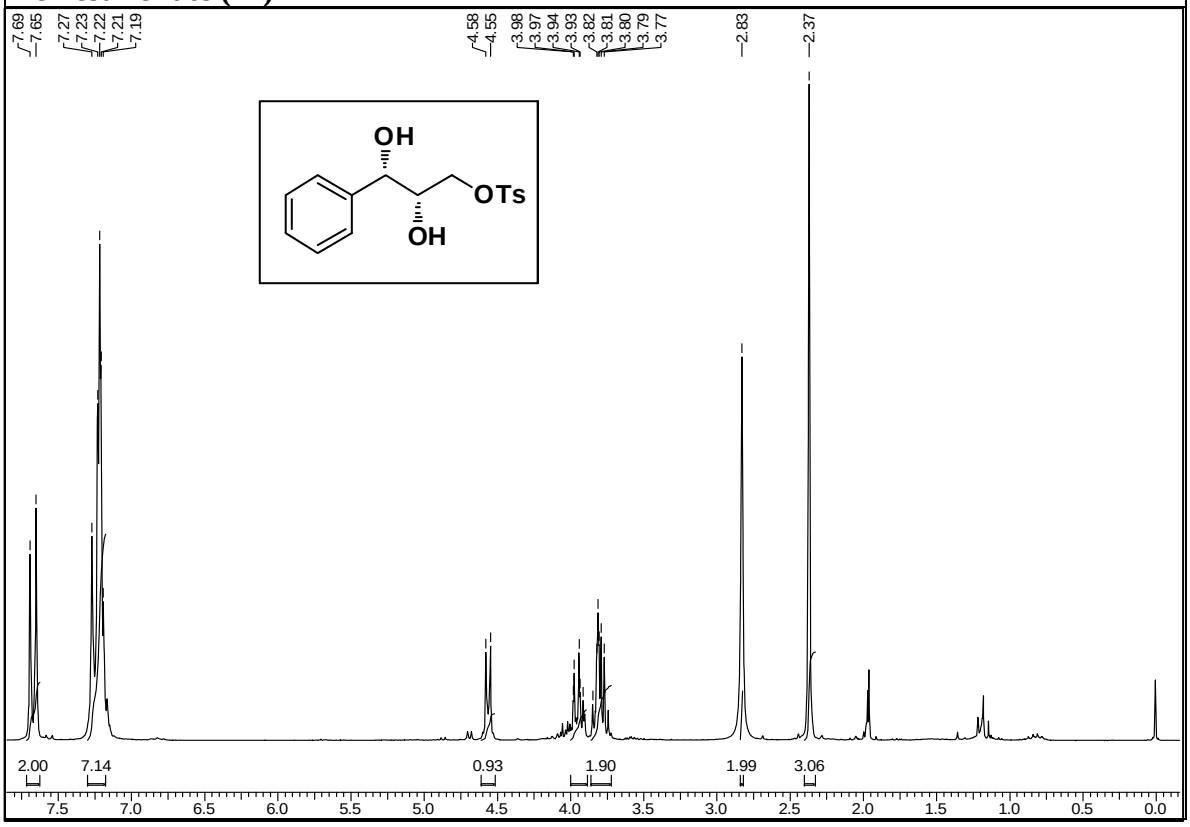
^{1}H NMR ($CDCl_3$, 400MHz) of (1*S*,2*S*)-1-Phenylpropane-1,2,3-triol (71)



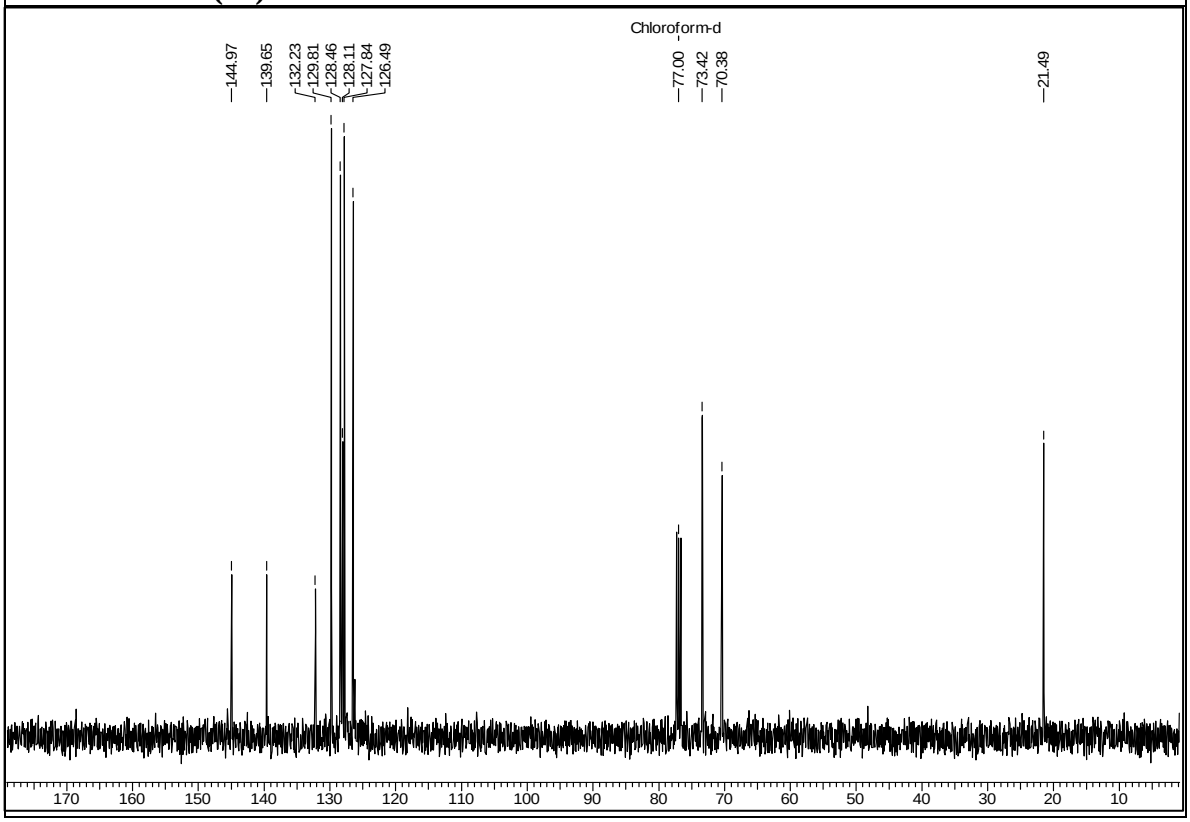
^{13}C NMR ($CDCl_3$, 100MHz) of (1*S*,2*S*)-1-Phenylpropane-1,2,3-triol (71)



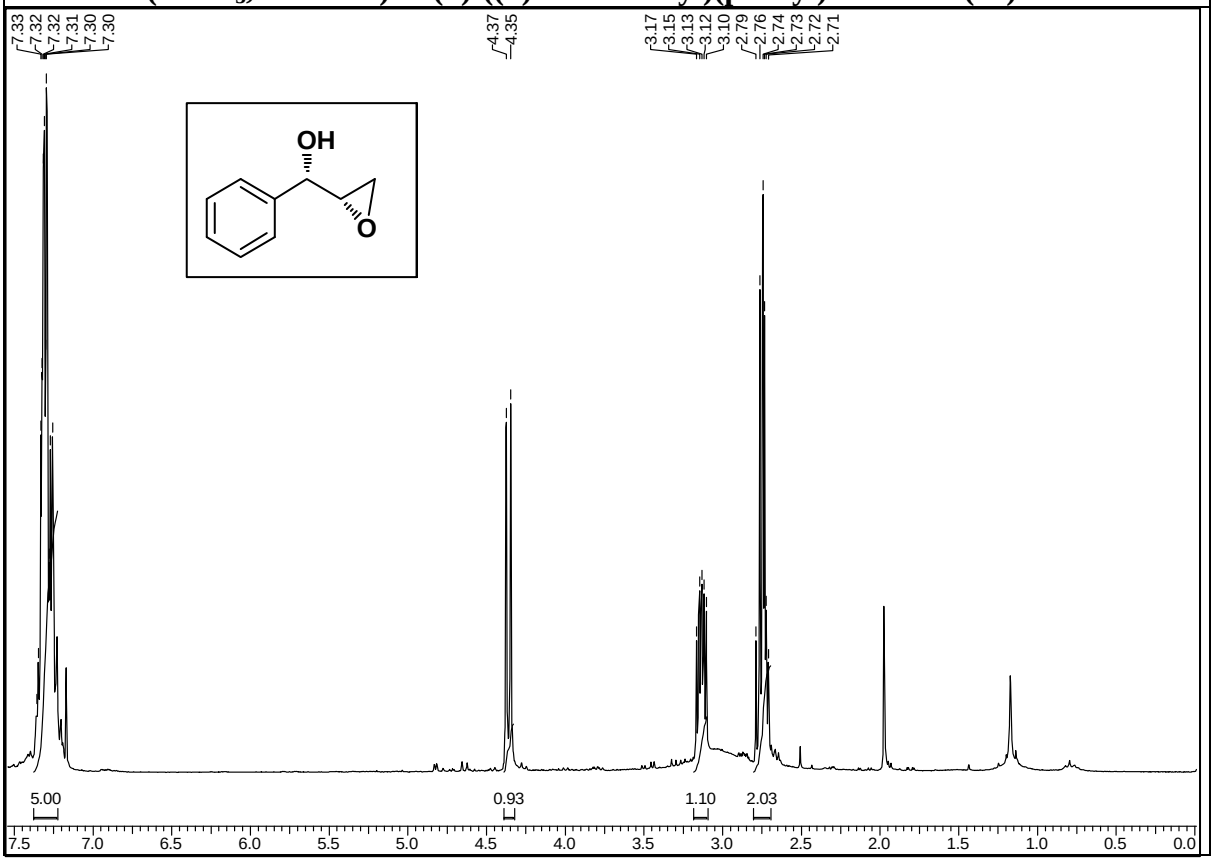
^{1}H NMR ($CDCl_3$, 200MHz) of (2*S*,3*S*)-2,3-Dihydroxy-3-phenylpropyl-4-methylbenzen esulfonate (72)



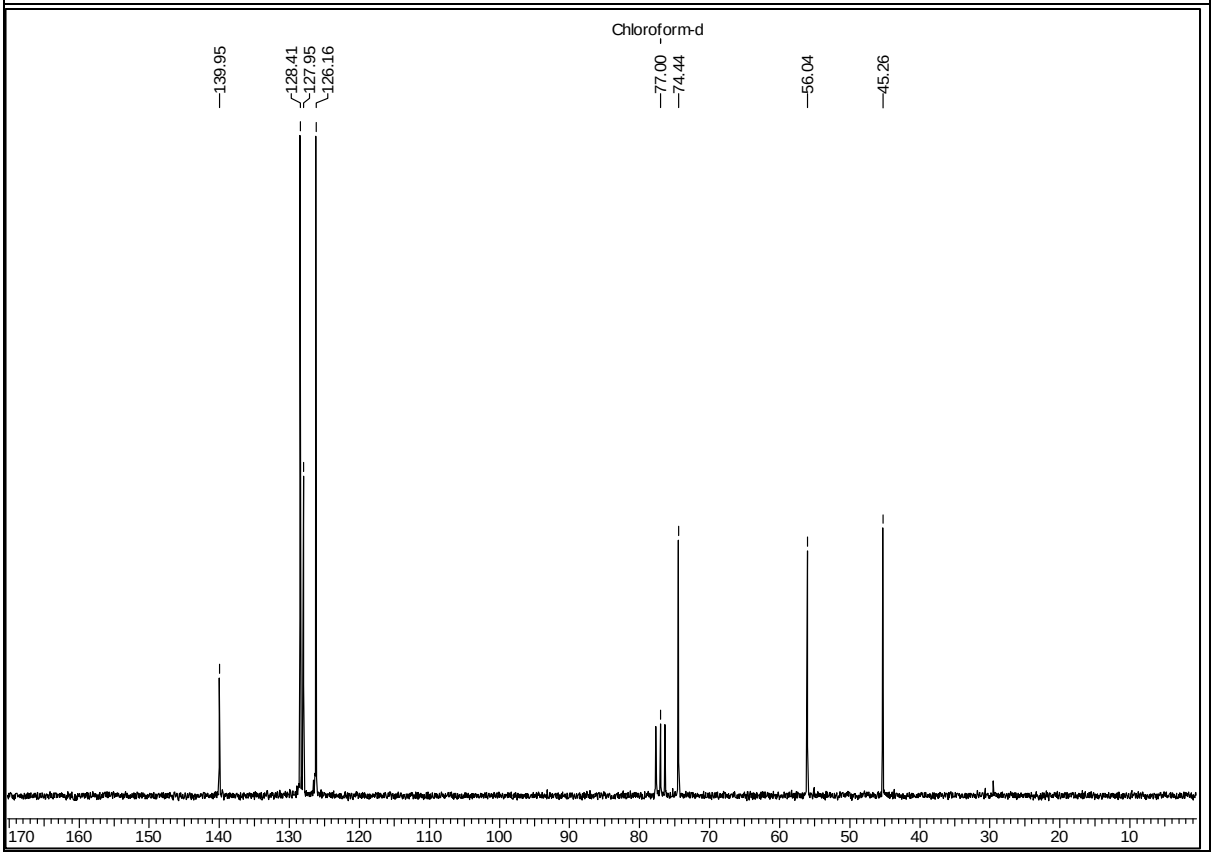
^{13}C NMR ($CDCl_3$, 50MHz) of (2*S*,3*S*)-2,3-Dihydroxy-3-phenylpropyl 4-methylbenzenesulfonate (72)



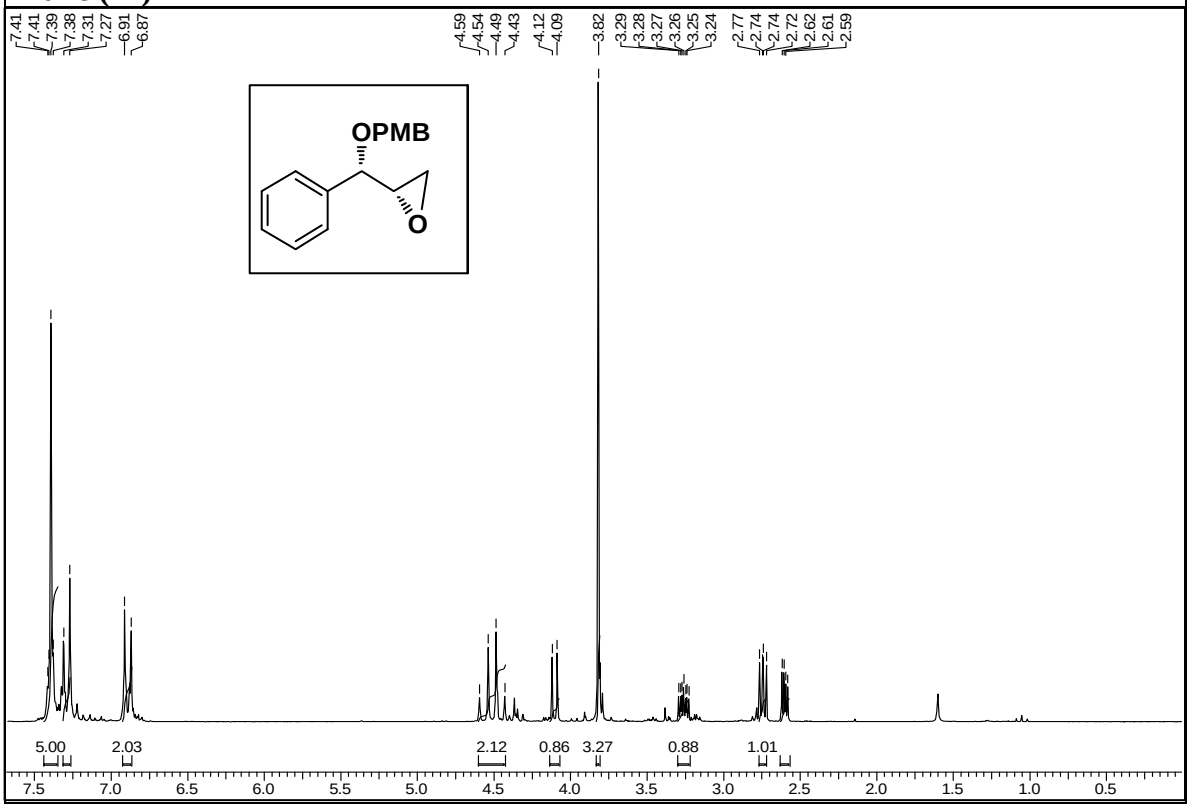
^{1}H NMR ($CDCl_3$, 200MHz) of (*S*)-((*S*)-Oxiran-2-yl)(phenyl)methanol (73)



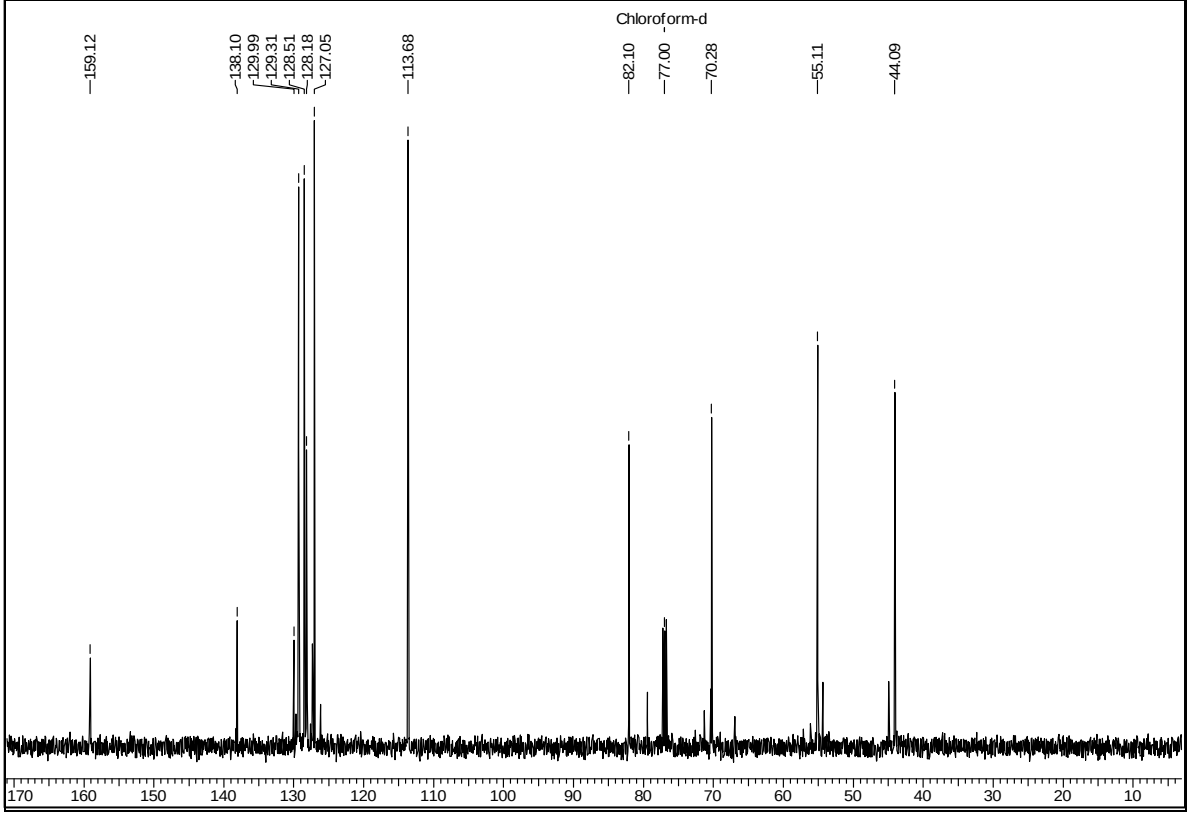
^{13}C NMR ($CDCl_3$, 50MHz) of (*S*)-((*S*)-Oxiran-2-yl)(phenyl)methanol (73)



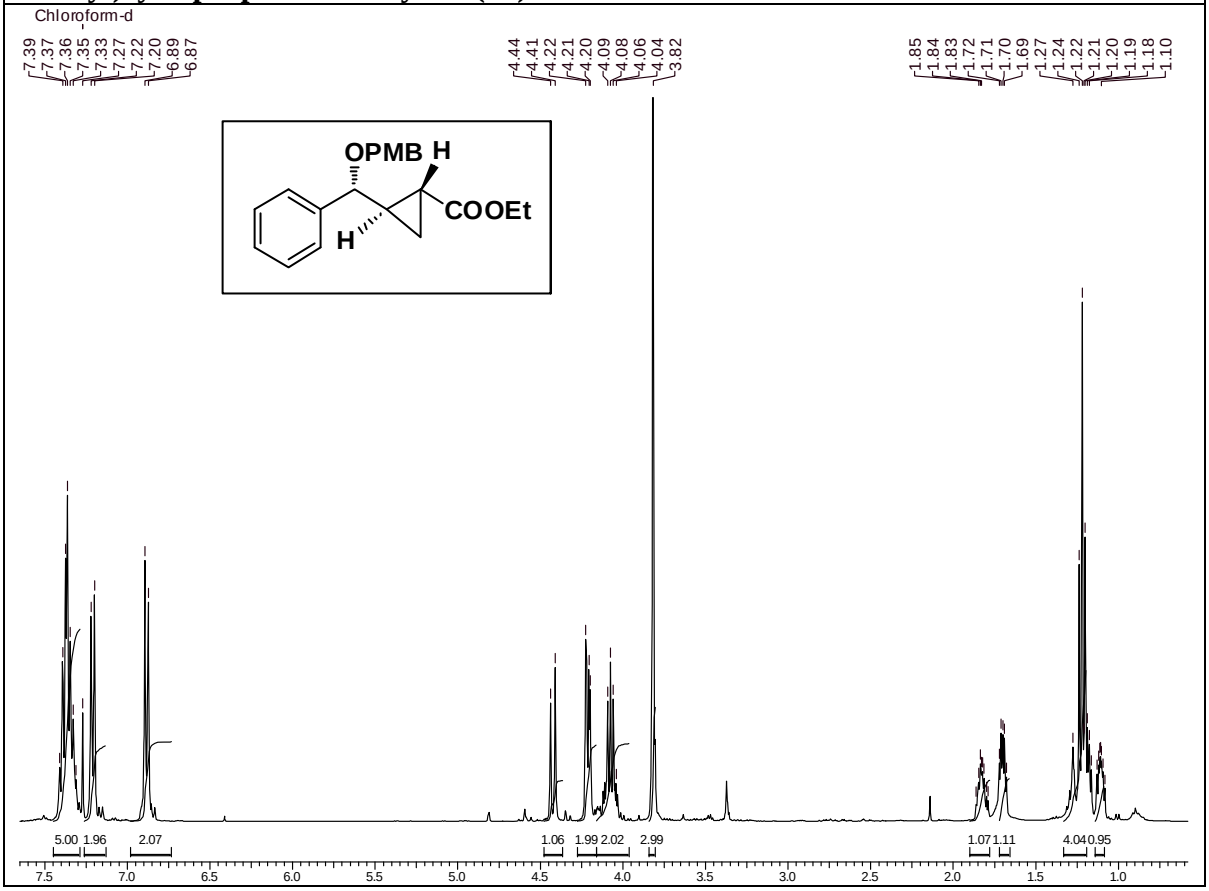
^{1}H NMR ($CDCl_3$, 400MHz) of (*S*)-2-((*S*)-(4-Methoxybenzyloxy)(phenyl)methyl)oxirane (74)



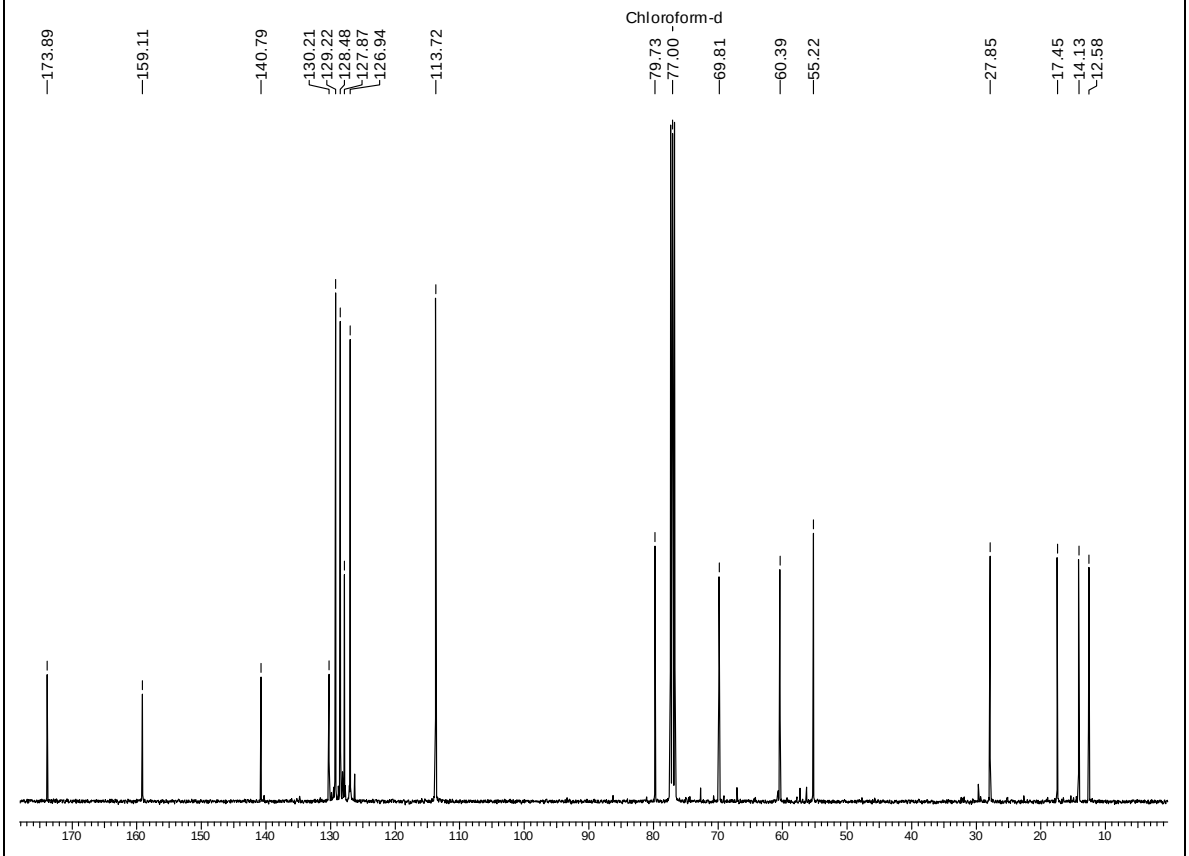
^{13}C NMR ($CDCl_3$, 100MHz) of (*S*)-2-((*S*)-(4-Methoxybenzyloxy)(phenyl)methyl)oxirane (74)



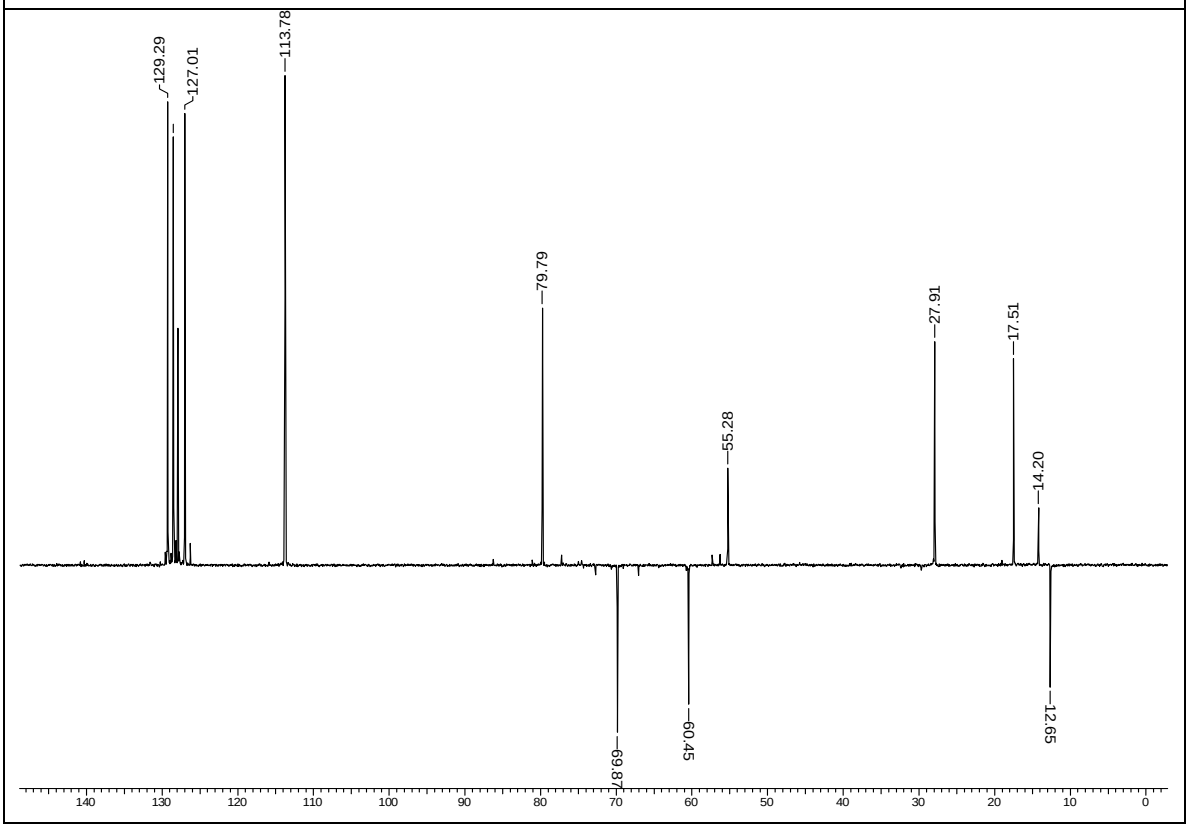
^{1}H NMR ($CDCl_3$, 400MHz) of (1*R*,2*R*)-Ethyl 2-((*R*)-(4-methoxybenzyloxy)(phenyl) methyl)cyclopropanecarboxylate (75)



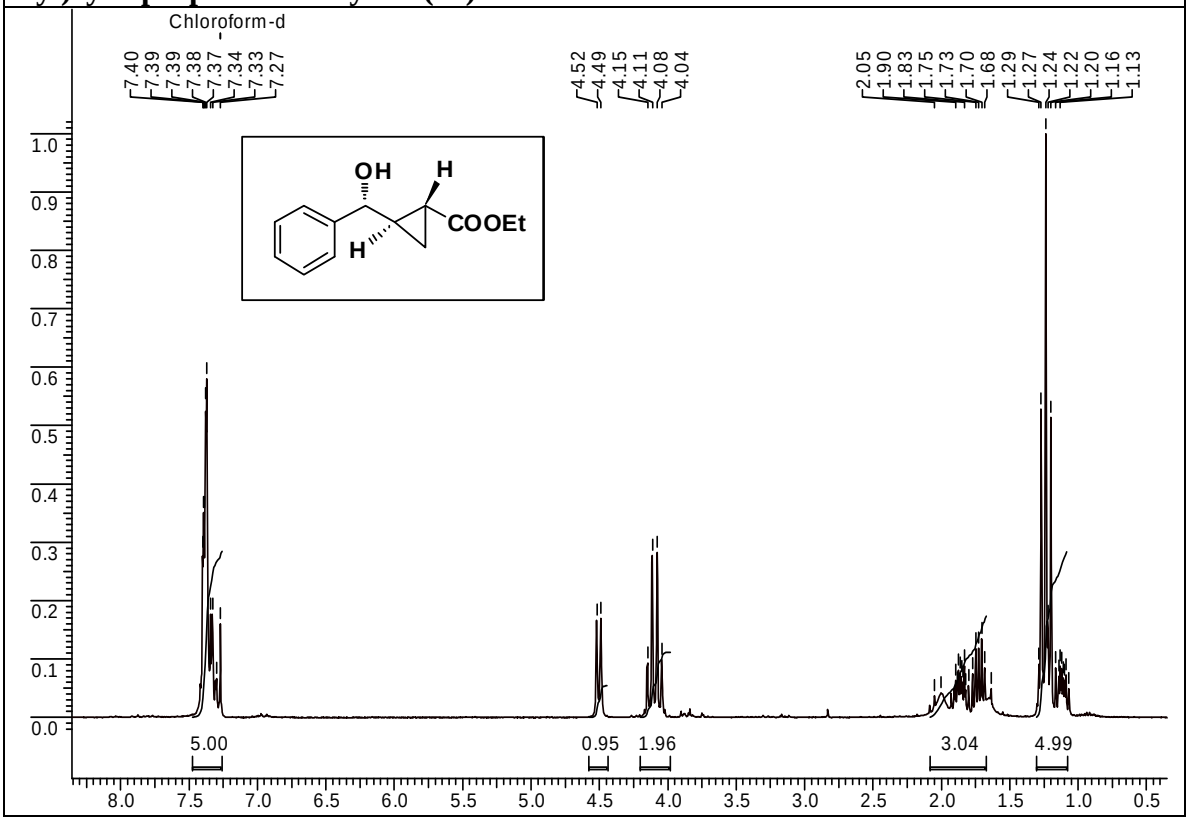
^{13}C NMR ($CDCl_3$, 100MHz) of (1*R*,2*R*)-Ethyl 2-((*R*)-(4-methoxybenzyloxy) (phenyl) methyl)cyclopropanecarboxylate (75)



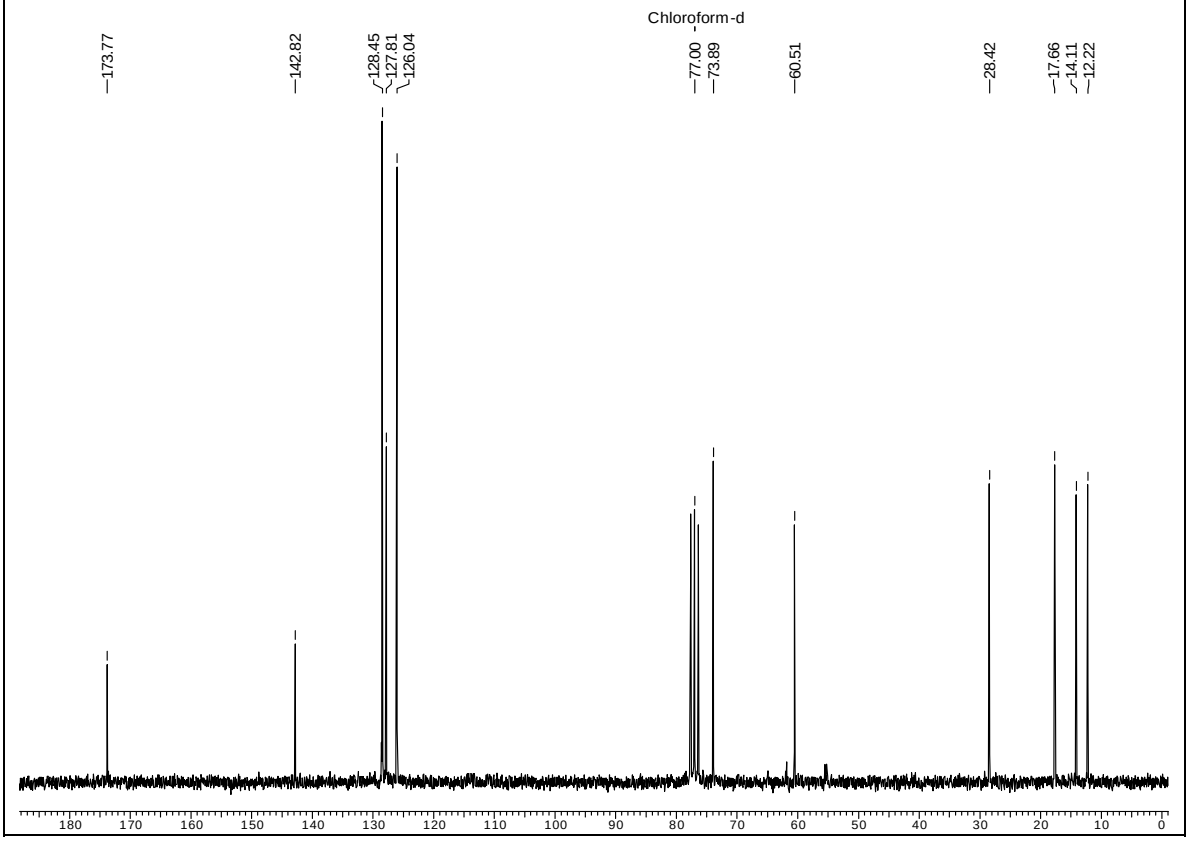
DEPT ($CDCl_3$, 100 MHz) spectrum of compound 75



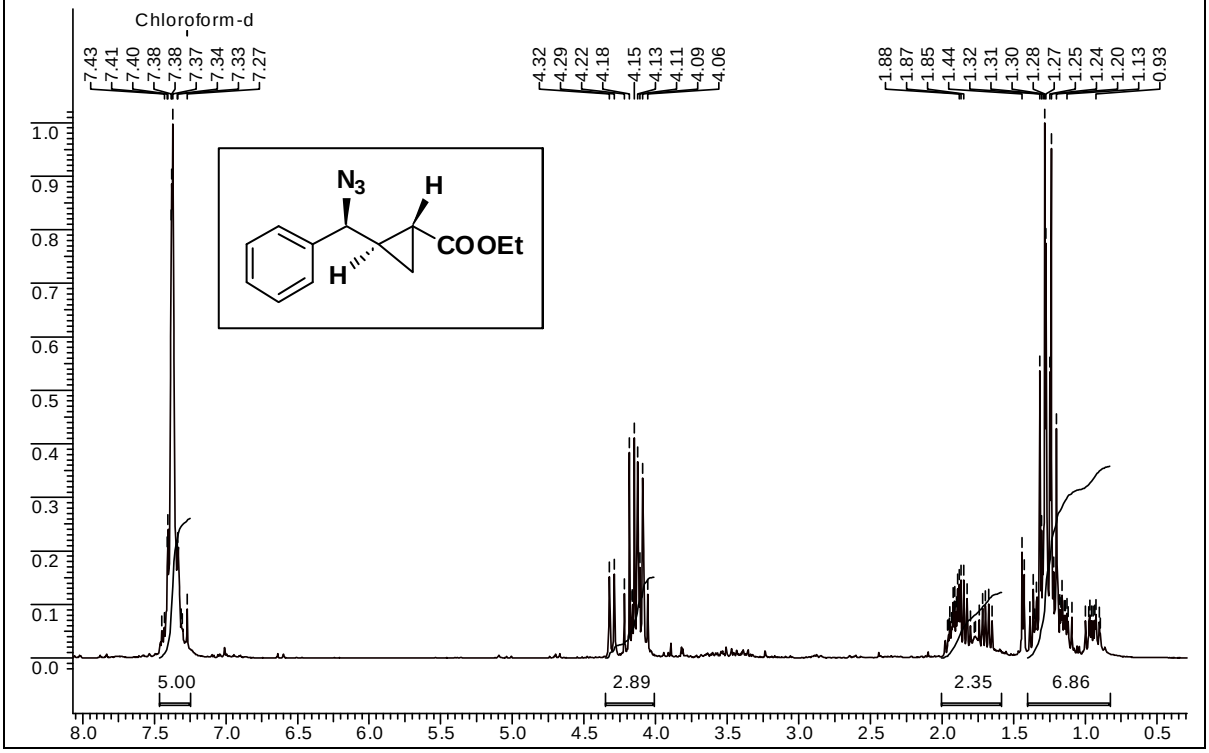
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (1*R*,2*R*)-Ethyl 2-((*R*)-hydroxy(phenyl)methyl)cyclopropanecarboxylate (76)



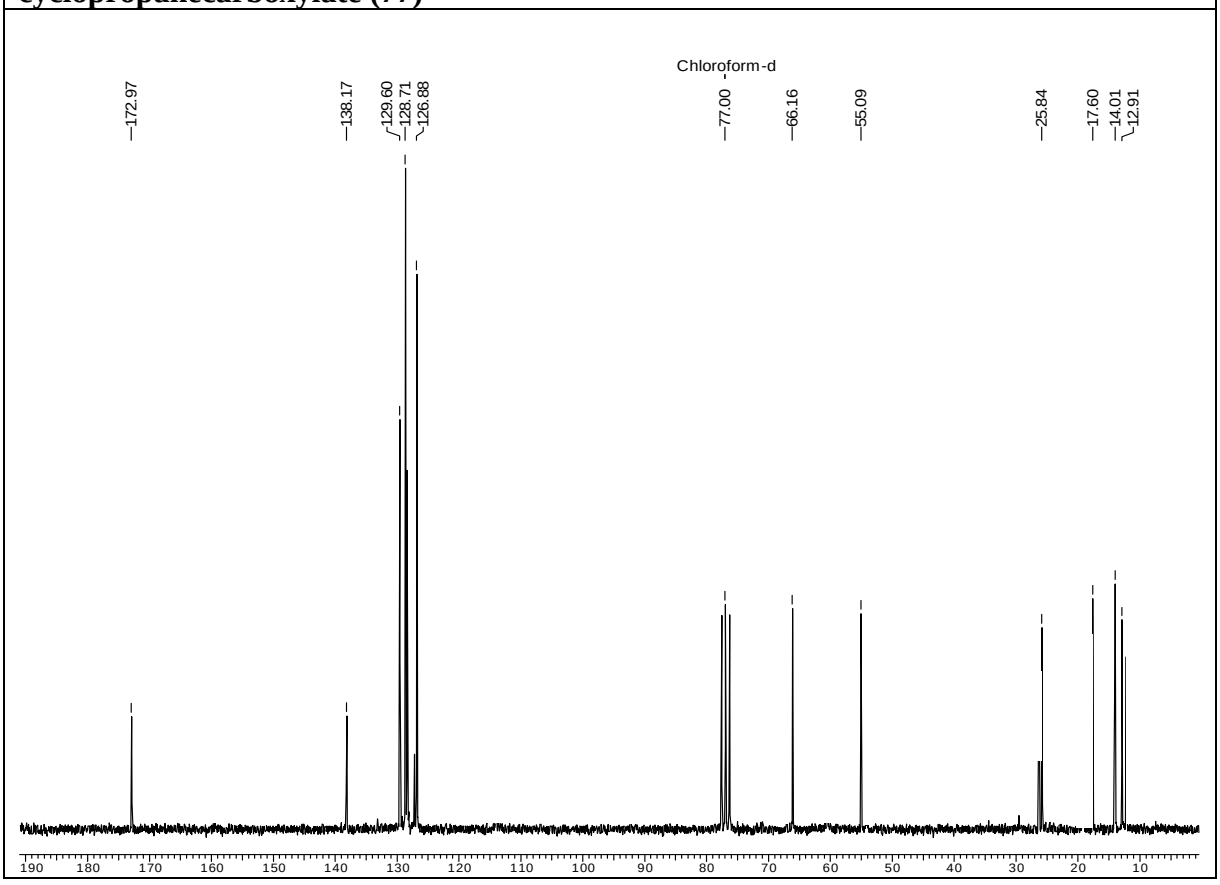
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of (1*R*,2*R*)-Ethyl 2-((*R*)-hydroxy(phenyl)methyl)cyclopropanecarboxylate (76)



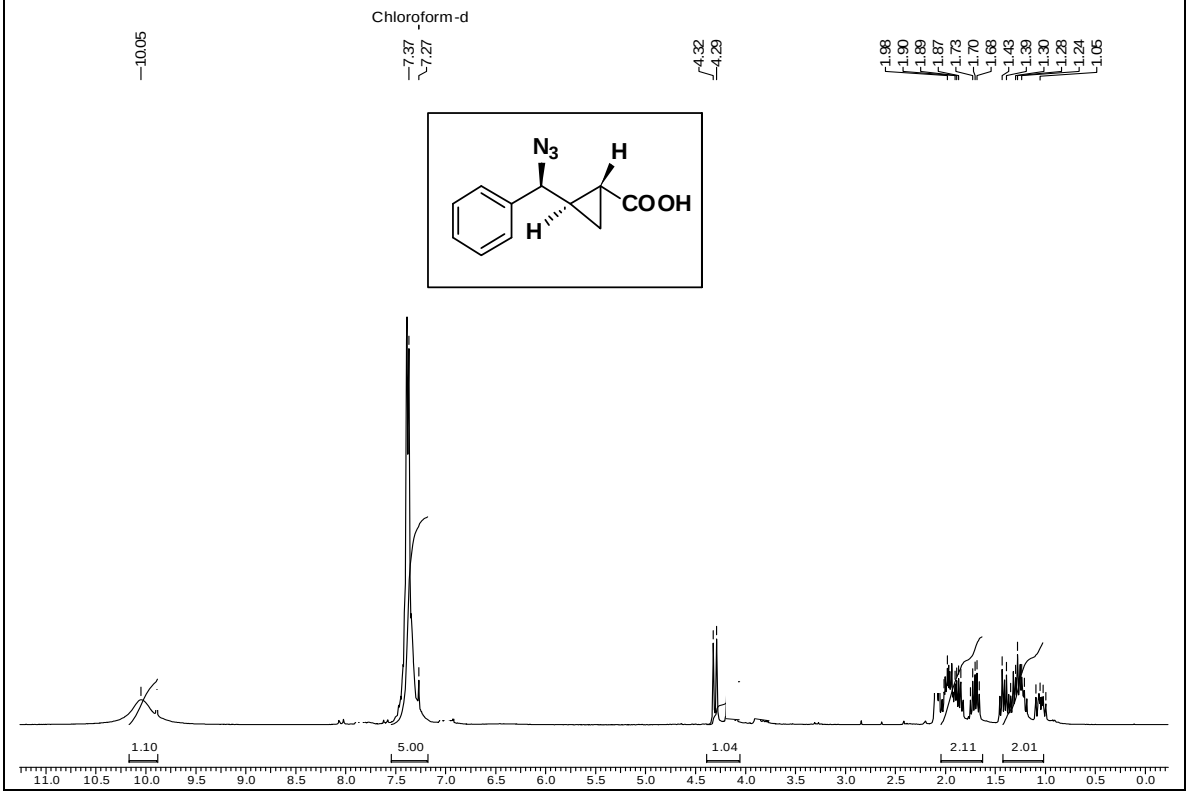
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (1*R*,2*R*)-Ethyl 2-((*S*)-azido(phenyl)methyl) cyclopropanecarboxylate (77)



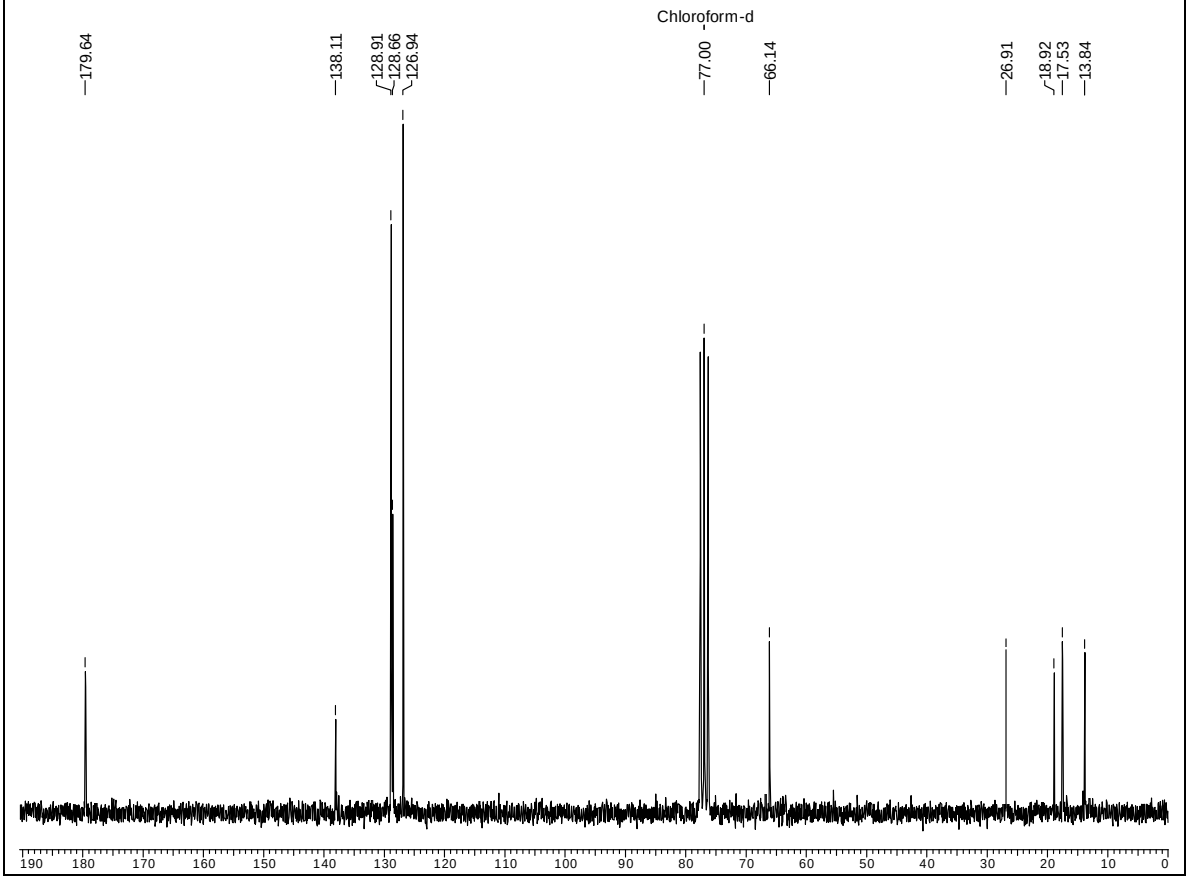
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of (1*R*,2*R*)-Ethyl 2-((*S*)-azido(phenyl)methyl) cyclopropanecarboxylate (77)



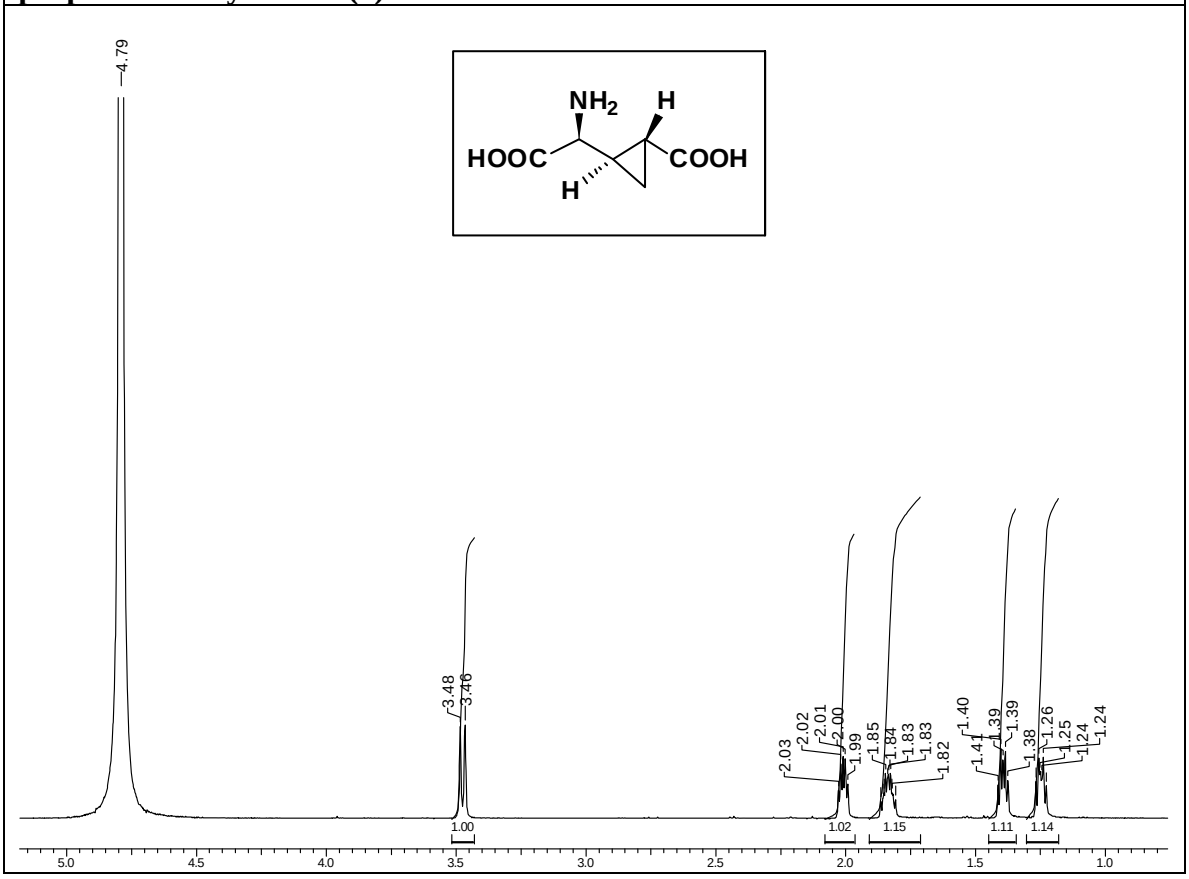
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of (1*R*,2*R*)-2-((*S*)-Azido(phenyl)methyl)cyclopropanecarboxylic acid (78)



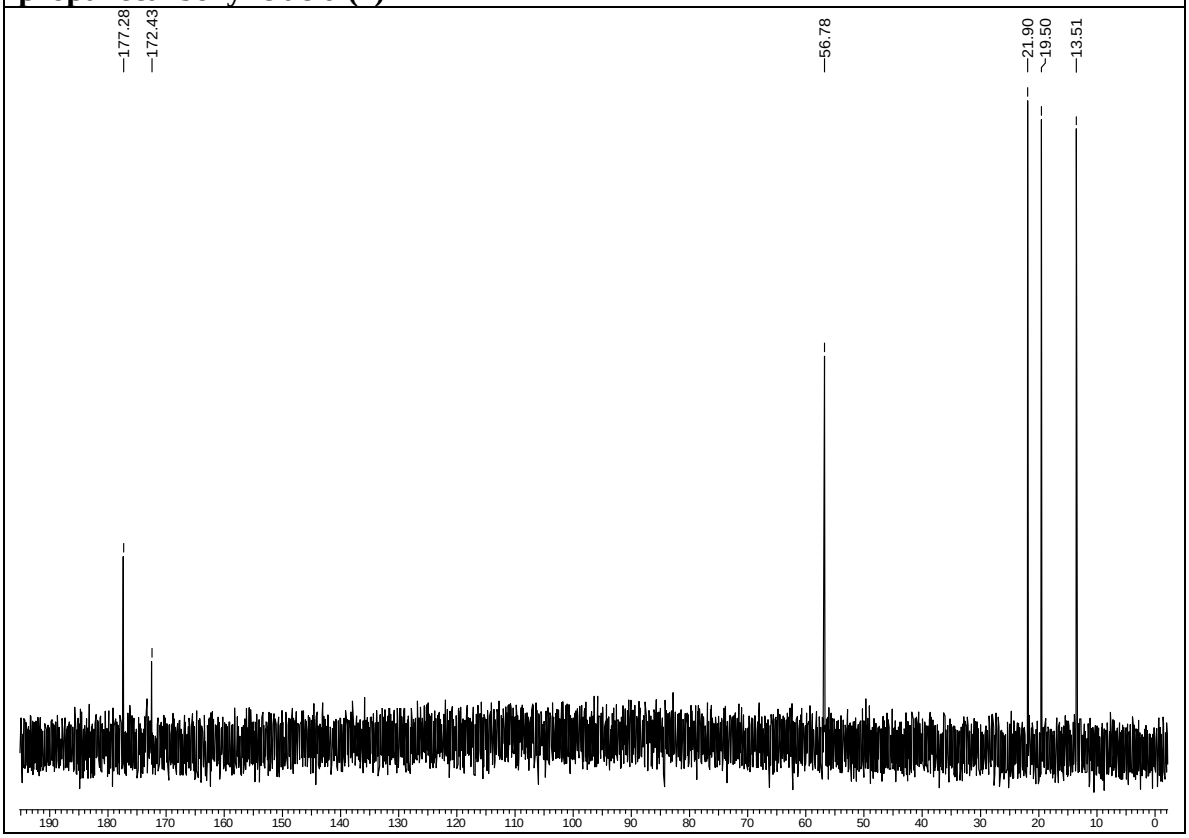
^{13}C NMR ($CDCl_3$, 100 MHz) spectrum of (1*R*,2*R*)-2-((*S*)-Azido(phenyl)methyl)cyclopropanecarboxylic acid (78)

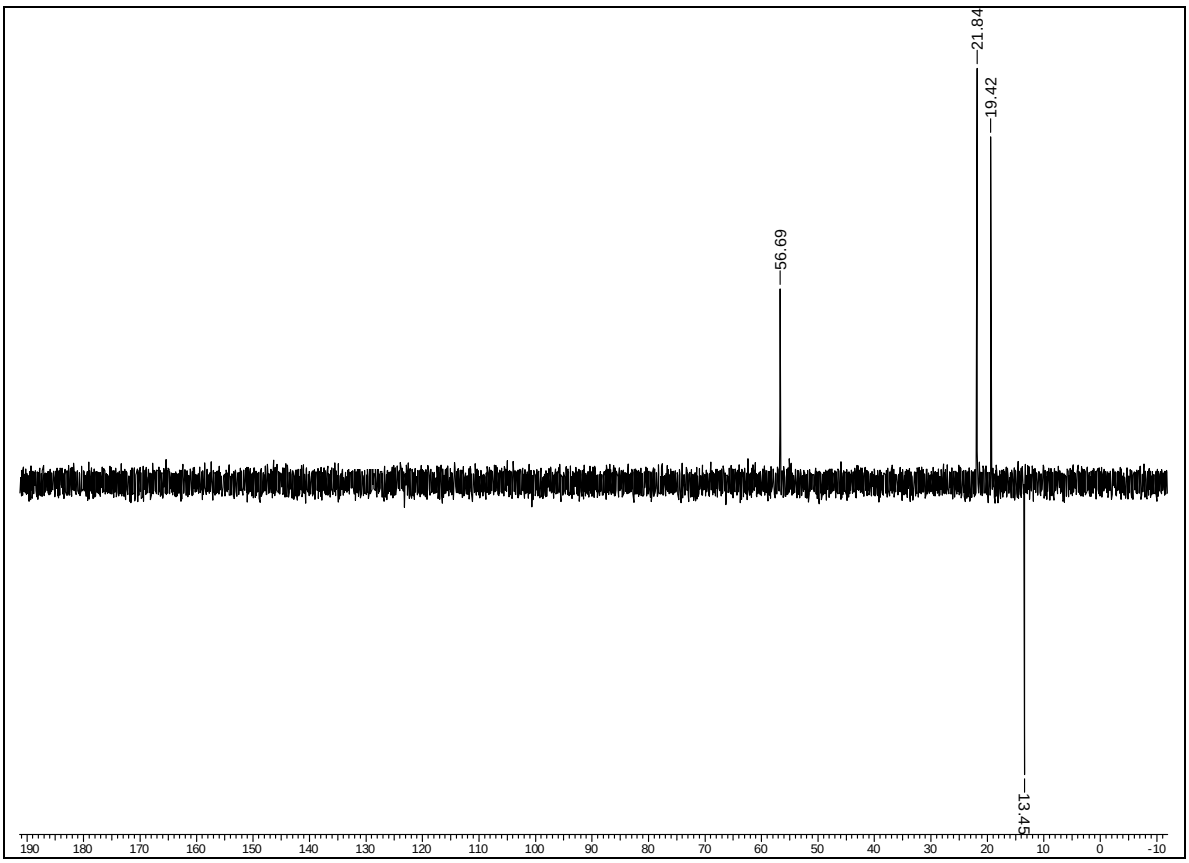


^{1}H NMR (D_2O, 500 MHz) spectrum of (1*R*,2*R*)-2-((*S*)-amino(carboxy)methyl)cyclopropanecarboxylic acid (7)



^{13}C NMR (D_2O, 125 MHz) spectrum of (1*R*,2*R*)-2-((*S*)-amino(carboxy)methyl)cyclopropanecarboxylic acid (7)





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5.1 SECTION A

PIVALOYL CHLORIDE-DMF COMPLEX MEDIATED CHLORINATION OF ALCOHOLS

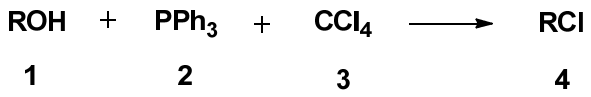
5.1.1. Introduction

The transformation of alcohols into the corresponding alkyl halides is one of the most studied reactions in organic synthesis, and many reagents can be usually used. Often the conversion requires elaborate reagents and quite drastic reaction conditions. For instance, reflux of alcohols in aqueous hydrochloric acid yields the corresponding alkyl chlorides.[1] This method, though very simple, is limited to robust substrates. To perform chlorination or bromination of hydroxyl groups on polyfunctionalized fragile substrates, more elaborated reagents have been developed and widely used for instance, thionyl chloride,[2] phosphorus halides,[3] phenylmethyleniminium,[4] benzoxazolium,[5] benzothiazolium salts,[6] Vilsmeier-Haack,[7] and Viehe salts.[8] In this context, the development of efficient reagents to use in mild conditions has interested organic chemists. The procedure based on the use of triphenylphosphine-carbon tetrahalides seems to meet these requirements but suffers the inconvenience of generating stoichiometric triphenylphosphine oxide as byproduct. To resolve these drawbacks, (chloro-phenylthiomethylene)dimethylammonium chloride was reported as a mild reagent for selective chlorination and bromination of primary alcohols.[9] However, the reagent has to be prepared through a two-step procedure that requires flash-chromatography workup. Other solutions may be the use of polymer-supported triphenyl phosphine or a filterable phosphine source such as 1,2-bis(diphenylphosphino) ethane.[10] More recently, a mild conversion of alcohols to alkyl halides using halide-based ionic liquids such as 1-*n*-butyl-3-methylimidazolium was reported.[11]

5.1.2. Review of Literature

Synder *et al.* (1968)[3]

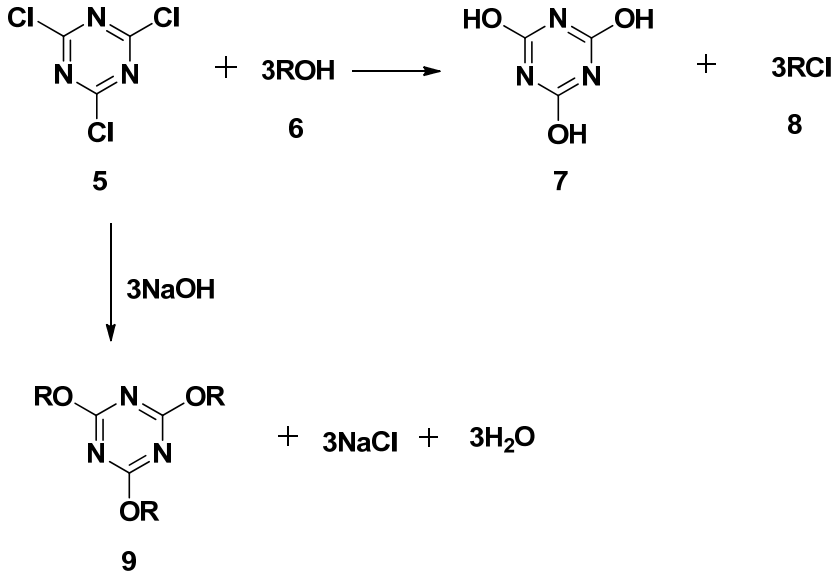
Synder *et al*. have developed an efficient method for the chlorination of primary and secondary alcohol **1** by using combination of triphenylphosphine **2** and carbon tetra chloride **3**. This method is also applicable for thiol. This reaction proceeds with inversion of configuration at chiral center.



Scheme 1

Sandler *et al.* (1970)[12]

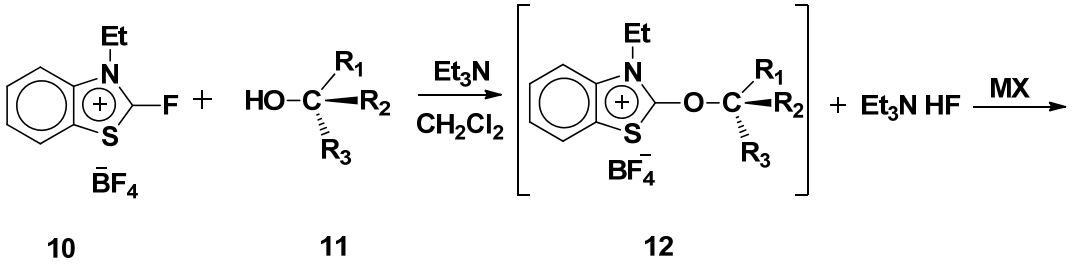
Sandler *et al*. have utilised cyanuric chloride **5** for the chlorination of alcohols. Cyanuric chloride can be conveniently used to hydrochlorinate primary, secondary and tertiary alcohols. Cyanuric chloride has the advantage that it can be conveniently handled, requires no added base and gives no isomerised product.

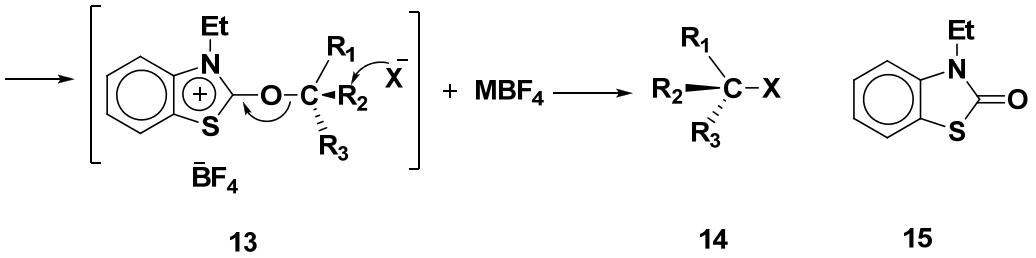


Scheme 2

Mukaiyama *et al.* (1976)[6]

Mukaiyama *et al*. have demonstrated chlorination of alcohol by using benzothiazolium salt **10**. In this reaction the intermediate salt **12** is generated from the alcohol **11** and



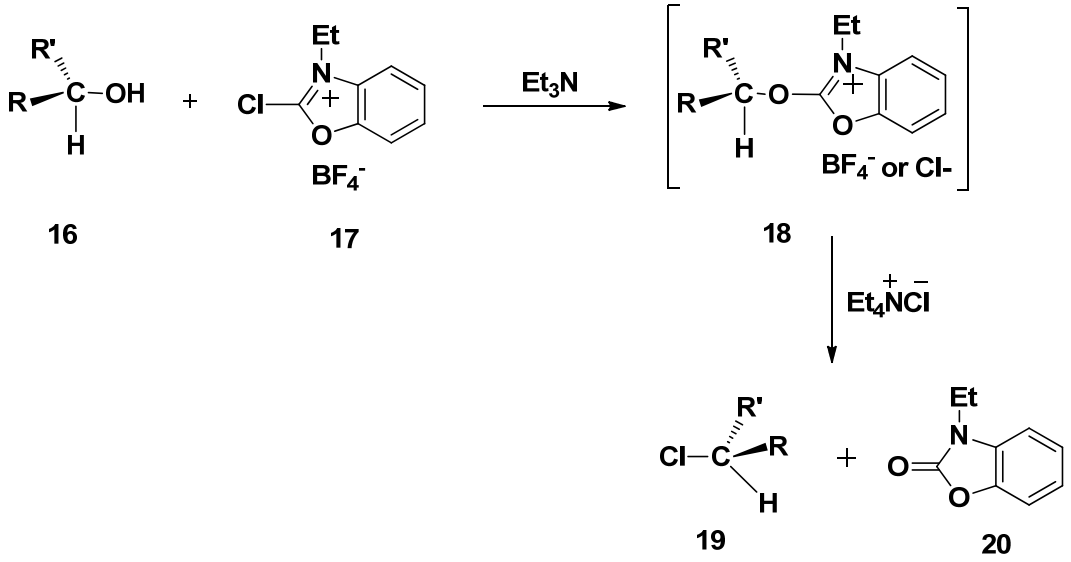


Scheme 3

benzothiazolium salt **10** through an addition-elimination process. The anion exchange of the salt **12** took place rapidly on addition of an alkali metal halide to yield the second intermediate **13**. In a final step, the counter ion (X^-) entered the reaction center from the site opposite to the benzothiazolium moiety through an S_N2 type transition state to give the alkyl chloride **14** and 1-ethyl-2-benzothiazolinone **15**. This method is not applicable for alicyclic compounds.

Mukaiyama *et al.* (1977)[5]

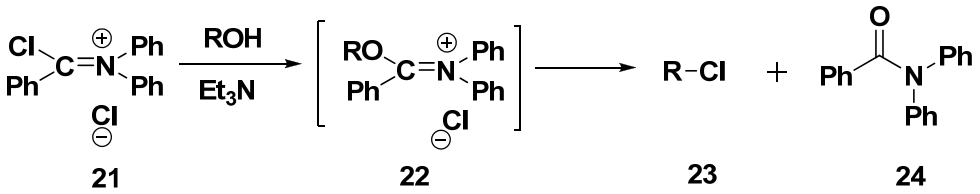
Mukaiyama *et al*. have reported another reagent 2-chloro-3-ethylbenzoxazolium **17** for efficient chlorination of alcohol present in carbohydrates and steroids. In reaction alkoxybenzoxazolium salts **18** forms, which in turn reacts with chloride ion to afford alkyl chloride **19** and 3-ethyl-2-benzoxazolinone **20**. This reaction is stereospecific in nature and goes through inversion of configuration at chiral center.



Scheme 4

Fujisawa *et al*. (1984)[4]

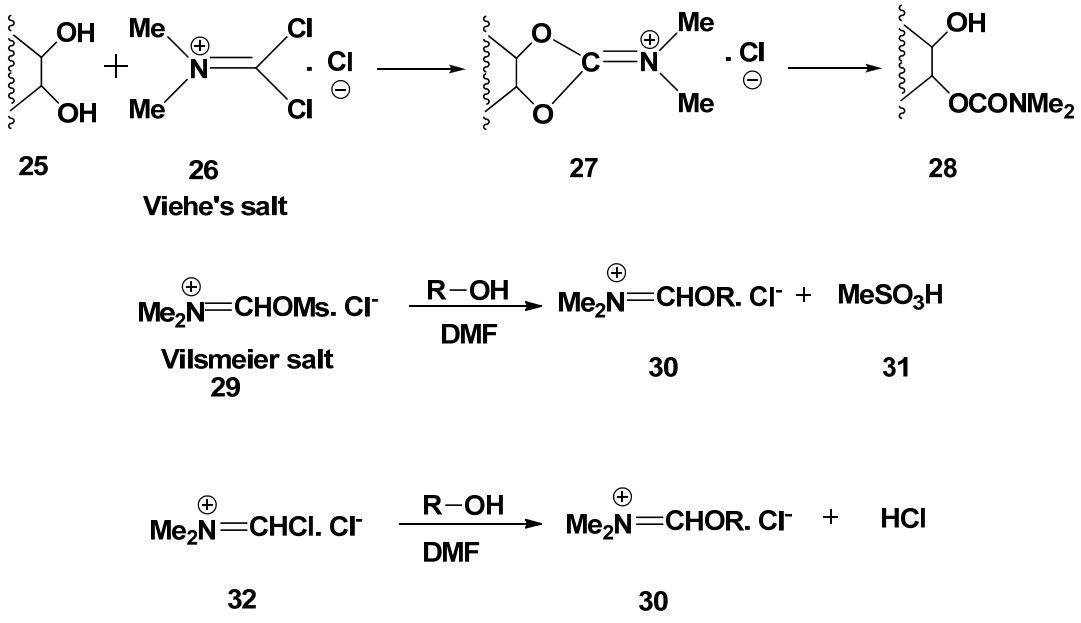
Fujisawa *et al*. have utilised *N*,*N*-diphenychlorophenylmethyleniminium chloride **21** for the chlorination of primary, secondary and alicyclic alcohols. *N*,*N*-diphenychlorophenylmethyleniminium reacts with alcohol in presence of triethylamine to furnish *N*,*N*-diphenylalkoxyphenylmethyleniminium salt **22**, which in turn reacts with chloride ion through S_N2 type process to afford alkyl chloride **23** and *N*,*N*-diphenylbenzamide **24**.



Scheme 5

Benazza *et al*. (1992)[7,8]

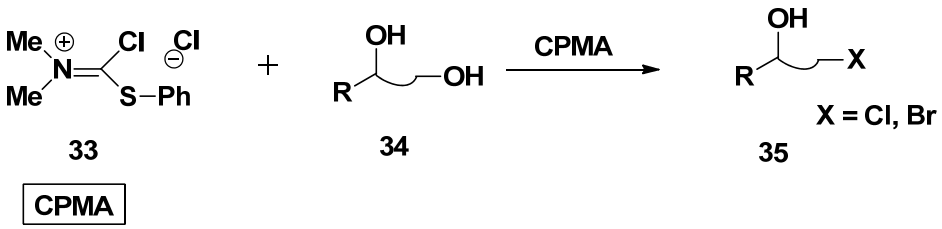
Benazza *et al*. have utilised Viehe's salt (*N*-dichloromethylene-*N*,*N*-dimethylammonium-chloride) **26**, Vilsmeier and Haack's salt **29** (iminium chloride) for chlorination of unprotected itols at primary carbon under very mild conditions.



Scheme 6

Mioskowski *et al.* (2000)[9]

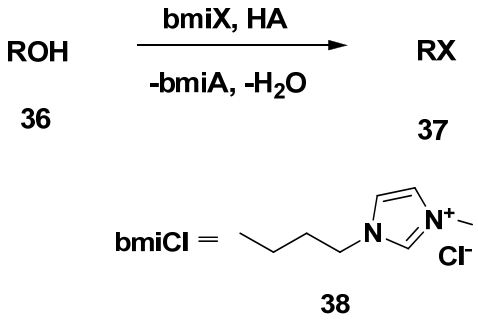
Mioskowski *et al*. have developed an efficient method for chlorination of alcohol by using (chloro-phenylthiomethylene)dimethylammonium chloride **33**. This method is known for selective chlorination of primary hydroxyl group in presence of unprotected secondary alcohol. The mild reaction conditions involved are compatible with the major alcohol protecting groups as well as with acid sensitive functional group like epoxides.



Scheme 7

Ren *et al.* (2001)[11]

Ren *et al*. have recently investigated a new method for chlorination of alcohol by ionic liquids. In this method alcohols were efficiently converted to alkyl chlorides using 1-n-butyl-3-methylimidazolium chloride **38** in the presence of Brönsted acid at room temperature in very mild condition. The method is applicable for primary, secondary and tertiary alcohols.



Scheme 8

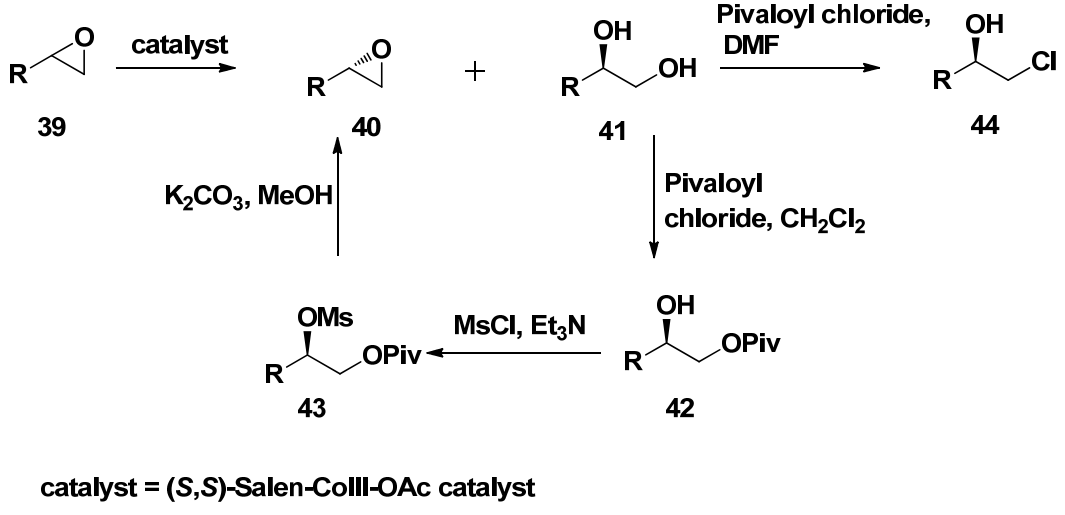
5.1.3. Present Work

5.1.3.1. Objective

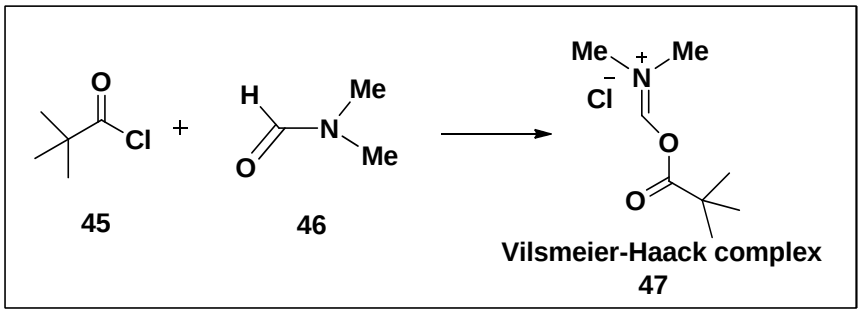
Conversion of alcohols into the corresponding chlorides is one of the most important and commonly used transformation in organic synthesis and development of such a procedure is still desirable in academia as well as in industrial research. A number of reagents have been employed to carry out this transformation.[1-11] All these reagent, though very useful and efficient, often suffer acid sensitive groups, two steps preparation of reagent and substrate specific in nature. During our recent endeavors with HKR (hydrolytic kinetic resolution) mediated synthesis of biologically active compounds, we required to convert a diol into the required epoxide through pivalate via a three step-sequence reaction (**Scheme 9**). Interestingly, we observed an efficient chlorination of alcohol instead of its protection as pivalate when reaction was performed in DMF. This could probably be attributed to the generation of a new reactive species responsible for chlorination. This prompted us to investigate this reaction systematically which eventually led to the development of a general and mild method for efficient chlorination of alcohols by using pivaloyl chloride-DMF complex.

5.1.3.2. Results and Discussion

A search of literature revealed that when pivaloyl chloride reacts with DMF, it forms Vilsmeier-Haack type complex (**Scheme 10**).

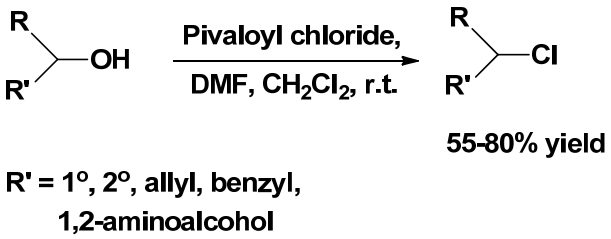


Scheme 9



Scheme 10

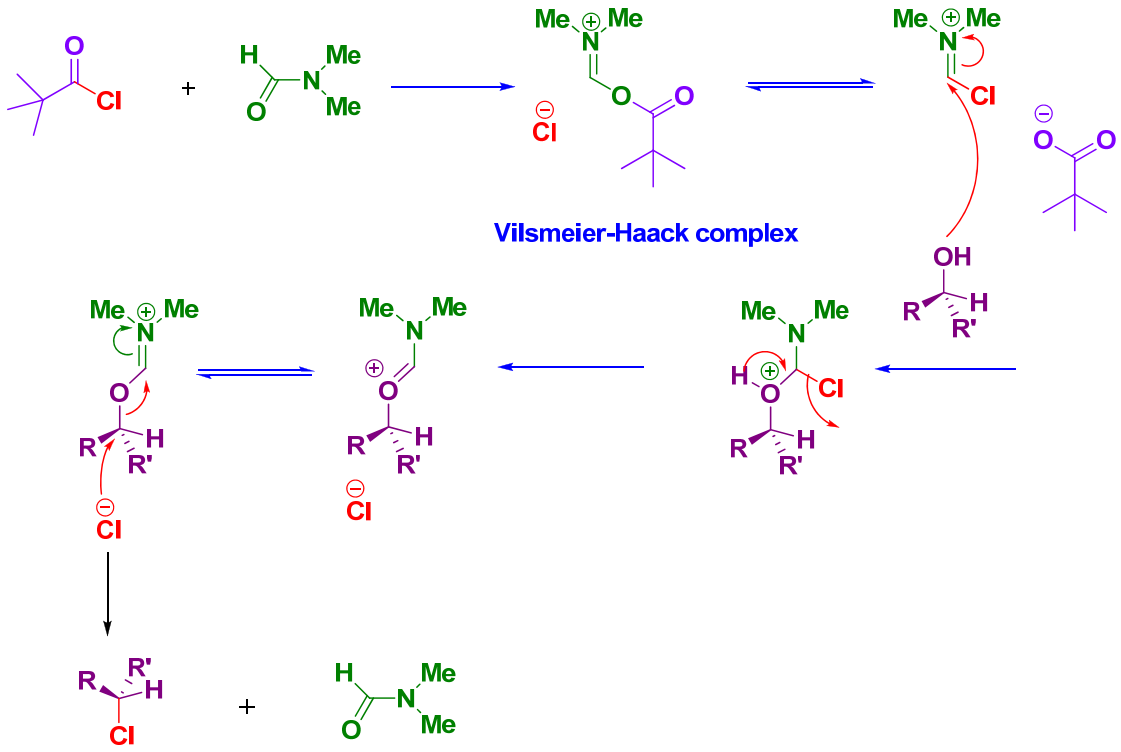
In order to understand the reaction pathway, the chlorination of *p*-methoxybenzyl alcohol was carried out at different temperatures. At 0 ^{o}C and -10 ^{o}C, the reaction was slow and did not proceed to completion and chlorinated product was obtained in <50% yield along with the recovered alcohol. At room temperature, this system effects rapidly the quantitative conversion of alcohol to the chloride, which can be recovered chemically pure after a simple aqueous workup. In a typical experimental procedure, when alcohols were treated with a pre-formed complex of DMF and pivaloyl chloride in dichloromethane, it gave the corresponding chloro compounds in moderate to good yields.



Scheme 11. Pivaloyl chloride-DMF mediated conversion of alcohols to chlorides

The present procedure is quite general as a wide range of structurally varied alcohols such as primary, secondary, allylic, homoallylic and benzylic ones underwent smooth conversion with pivaloyl chloride-DMF into their corresponding chlorides under mild reaction conditions in moderate to good yields of the corresponding chloride (**Table 1**). The reaction is generally fast, requiring 20 min to 5 h for completion in most of the cases. Reduced rates were observed with secondary alcohols and sterically constrained alcohol. It should be mentioned here that in some cases small amount (5-15% yield) of the pivaloyl ester of the corresponding alcohol was also obtained as a side product. The superiority of this procedure can be clearly visualized in chlorination of β-amino alcohol leading to the corresponding chloro compound in good yield without formation of any side product (**Table 1**, entry 10). The cleavage of acetonide group under the reaction conditions

employed was not observed. It should be mentioned here that the amino acid based azide thus prepared could serve as a useful building block to synthesise a new class of unnatural *C*-glycosyl amino acid featuring a triazole moiety between the sugar and amino acid entities.[13] PMBCl , an important protecting group in organic synthesis was also synthesised from the corresponding alcohol (**Table 1**, entry 1). Our method yielded the product in excellent yield free from any acidic impurities while the conventional method of its synthesis using hydrochloric acid generally affords the product contaminated with acidic impurities.

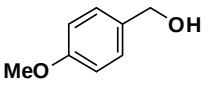
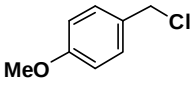
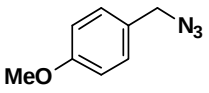
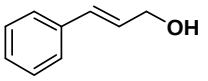
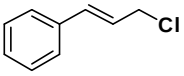
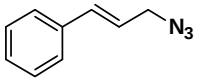
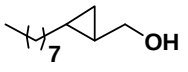
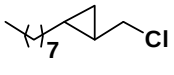
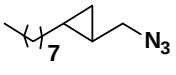
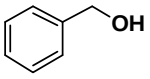
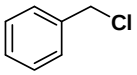
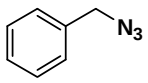
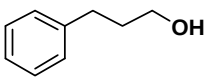
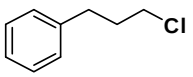
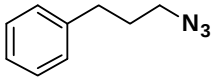
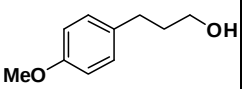
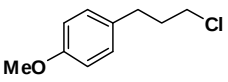
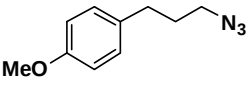
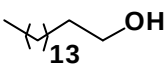
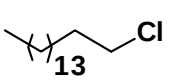
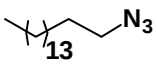


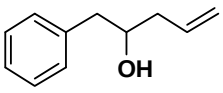
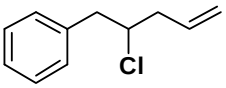
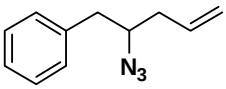
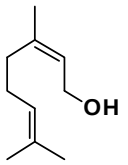
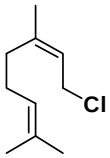
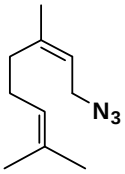
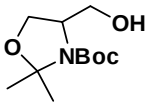
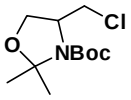
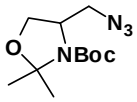
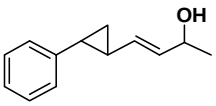
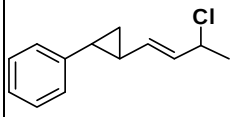
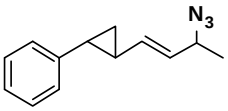
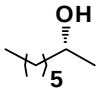
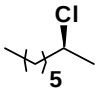
Scheme 12. Proposed mechanism for chlorination of alcohols

In order to examine the stereospecificity of the present method, we employed (*R*)-octane-2-ol (Table 1, entry 12) and subjected this to reaction with pivaloyl chloride-DMF reagent to give (*S*)-2-chlorooctane, $[\alpha]_D^{20}$ +36.0° (*c*, 0.8, ether); {lit.[5] $[\alpha]_D^{20}$ +33.0° (*c*, 0.8, ether)}. The measurement of optical rotation and its comparison with literature values indicated that reaction occurs with inversion of configuration via S_N2 displacement leading to the corresponding chloro product in enantiomerically pure form. A possible explanation for reaction mechanism is depicted in **Scheme 12.** The involvement of Vilsmeier-Haack type complex as a possible reactive intermediate is invoked which adds on the hydroxyl group

of the alcohol to form the cationic species followed by subsequent nucleophilic attack of chloride ion in S_N2 fashion to produce the corresponding chloride.

Table 1. Dimethylformamide-pivaloyl chloride mediated conversion of alcohols to azides via chlorides

Entry	Alcohol	Product	Rect-ion time	Yield[a] (%)	Azide	Yield (%)
1.			20 min	80		70
2.			30 min	70		60
3.			30 min	80		60
4.			20 min	80		75
5.			2 h	70		60
6.			2 h	70		60
7.			1 h	75		65

8.			5 h	60		50
9.			1h	65		60
10.			4 h	55		50
11.			4 h	60		50
12.			1 h	60	-	-

a. Crude yield of the chloro products

Some of the crude chloro compounds which were found to be volatile and unstable were subsequently treated with sodium azide in DMF at 60 °C to afford the corresponding azide in good yield.

5.1.3.3. Conclusion

In conclusion, a mild, general and efficient synthesis of conversion of alcohols into chlorides has been developed. The noteworthy feature of the present method is the use of pivaloyl chloride-DMF as a mild, non-toxic and inexpensive reagent coupled with simple operation and ease of work-up. We believe this will present a better and more practical alternative to the existing methodologies.

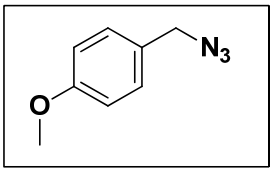
5.1.4. Experimental

All reactions requiring anhydrous conditions were performed under positive pressure of argon using oven-dried glassware (110 ^{o}C), which was cooled under argon. DCM and DMF were distilled from CaH_2 and stored over molecular sieves and KOH respectively.

Solvents used for chromatography were distilled at respective boiling points using known procedures. Infrared spectra were recorded with an ATI MATSION RS-1 FT-IR spectrometer. ^{1}H & ^{13}C NMR spectra were recorded on Brucker AC-200, Brucker MSL-300 and Brucker DRX-500 instruments using deuterated solvent. Chemical shifts are reported in ppm. Elemental analyses were carried out with a Carlo Erba CHNS-O analyser.

Representative Procedure: Chlorination of *p*-methoxybenzyl alcohol. A mixture of pivaloyl chloride (1.30 g, 10.86 mmol) and DMF (5 mL) was stirred at room temperature for 1 h. To the mixture was first added CH_2Cl_2 (25 mL) followed by alcohol (1 g, 7.24 mmol). The reaction was monitored (TLC) until the complete disappearance of starting material. Water (20 mL) was added, and then the organic phase was washed with 15 mL of a saturated solution of Na_2CO_3, followed by 1N HCl and brine. The organic layers were dried over Na_2SO_4, and the solvent evaporated to yield *p*-methoxybenzyl chloride (0.91 g, 80%). Crude chloro compound was subsequently treated with sodium azide in DMF at 60 °C to afford the azide in good yield.

1-(Azidomethyl)-4-methoxybenzene:



Yield: 70%.

Physical State: Pale yellow color liquid.

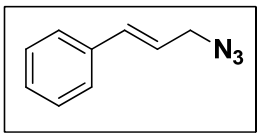
Mol. Formula: $C_8H_9N_3O$

IR (neat, cm^{-1}): ν_{max} 1620, 2152 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.86 (s, 3H), 4.31 (s, 2H), 6.96 (d, *J* = 8.7 Hz, 2H), 7.28 (d, *J* = 8.7 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 54.2, 55, 113.9, 127.2, 129.6, 159.5.

(*E*)-(3-Azidoprop-1-en-1-yl)benzene:



Yield: 60%.

Physical State: Pale yellow color syrupy liquid.

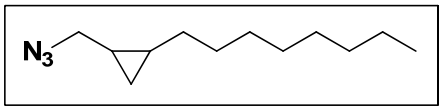
Mol. Formula: $C_9H_9N_3$

IR ($CHCl_3$, cm^{-1}): ν_{max} 1620, 1640, 2138.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.96 (d, *J* = 6.3 Hz, 2H), 6.19-6.34 (m, 1H), 6.68 (d, *J* = 16.7 Hz, 1H), 7.29-7.47 (m, 5H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 52.9, 122.3, 126.5, 128.1, 128.6, 134.4, 135.9.

1-(Azidomethyl)-2-octylcyclopropane:



Yield: 60%.

Physical State: Colorless syrupy liquid.

Mol. Formula: $C_{12}H_{23}N_3$

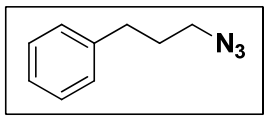
IR ($CHCl_3$, cm^{-1}): ν_{max} 2122.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.34-0.48 (m, 2H), 0.62-0.74 (m, 1H), 0.77-0.98 (m, 4H), 1.21-1.44 (m, 14 H), 2.99-3.18 (m, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 10.6, 14.1, 17.3, 17.8, 22.7, 29.3, 29.4, 29.6, 31.9, 33.5, 55.5.

Anal. Calcd.: C, 68.85; H, 11.07; N, 20.07. **Found.** C, 68.55; H, 11.38; N, 20.0.

(3-Azidopropyl)benzene:



Yield: 60%.

Physical State: Colorless syrupy liquid.

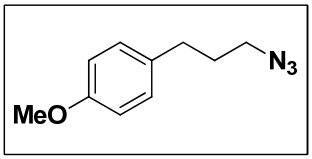
Mol. Formula: $C_9H_{11}N_3$

IR ($CHCl_3$, cm^{-1}): ν_{max} 1640, 2100.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.90-2.06 (m, 2H), 2.73 (t, *J* = 7.3 Hz, 2H), 3.31 (t, *J* = 6.82 Hz, 2H), 7.23-7.41 (m, 5H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 30.3, 32.6, 50.5, 126, 128.3, 140.7.

1-(3-azidopropyl)-4-methoxybenzene:



Yield: 60%.

Physical State: Colorless liquid.

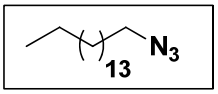
Mol. Formula: $C_{10}H_{13}N_3O$

IR ($CHCl_3$, cm^{-1}): ν_{max} 1654, 2110.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.90 (q, *J* = 6.4, 14.7 Hz, 2H), 2.67 (t, *J* = 6.4 Hz, 2H), 3.29 (t, *J* = 6.8, 2H), 3.81 (s, 3H), 6.87 (d, *J* = 8.6 Hz, 2H), 7.13 (d, *J* = 8.6 Hz, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 30.5, 31.7, 50.5, 55.1, 113.8, 129.3, 132.8, 157.9.

1-Azidohexadecane :



Yield: 65%.

Physical State: Colorless liquid.

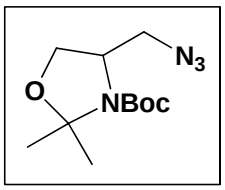
Mol. Formula: $C_{16}H_{33}N_3$

IR ($CHCl_3$, cm^{-1}): ν_{max} 2134, 2900.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.89 (t, *J* = 6.2 Hz, 3H), 1.27 (s, 26H), 1.54-1.64 (m, 2H), 3.26 (t, *J* =7.5 Hz, 3H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.1, 22.7, 26.7, 28.8, 29.2, 29.3, 29.5, 29.6, 29.7, 31.9, 51.4.

***tert*-Butyl 4-(azidomethyl)-2,2-dimethyloxazolidine-3-carboxylate:**



Yield: 50%.

Physical State: Colorless liquid.

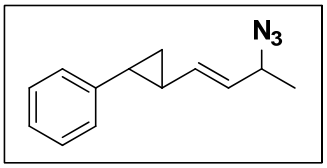
Mol. Formula: $C_{11}H_{20}N_4O_3$

IR ($CHCl_3$, cm^{-1}): ν_{max} 1690, 2134.

^{1}H NMR ($CDCl_3$, 200 MHz): 1.18-1.19 (m, 6H), 1.47 (s, 9H), 1.54-1.59 (m, 2H), 3.82-4.02 (m, 2H), 4.16-4.30 (m, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz): 27.1, 28.3, 55.5, 62.9, 65.0, 80.5, 93.9, 151.5.

(*E*)-(2-(3-Azidobut-1-enyl)cyclopropyl)benzene:



Yield: 50%.

Physical State: Colorless liquid.

Mol. Formula: $C_{13}H_{15}N_3$

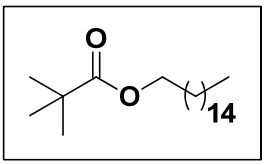
IR ($CHCl_3$, cm^{-1}): ν_{max} 1632, 2100, 2800.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.85-0.94 (m, 2H), 1.19-1.33 (m, 5H), 2.51-2.60 (m, 1H), 5.38-5.72 (m, 1H), 5.94-6.05 (m, 1H), 7.17-7.43 (m, 5H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 11.1, 11.4, 21.0, 21.4, 64.6, 122.0, 122.6, 125.3, 128.4, 128.7, 131.2.

Anal. Calcd.: C, 73.21; H, 7.09; N, 19.70. **Found.** C, 73.01; H, 7.16; N, 19.65.

Heptadecyl pivalate:



Physical State: Colorless syrupy liquid.

Mol. Formula: $C_{21}H_{42}O_2$

IR ($CHCl_3$, cm^{-1}): ν_{max} 1742 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.88 (t, *J* = 6.0 Hz, 3H), 1.2 (s, 9H), 1.26 (brs, 26H),1.51-1.65 (m, 2H), 4.04 (t, *J* = 6.8 Hz, 2H).

5.1.5. Spectra

1. ^{1}H & ^{13}C NMR spectra of **1-(Azidomethyl)-4-methoxybenzene**

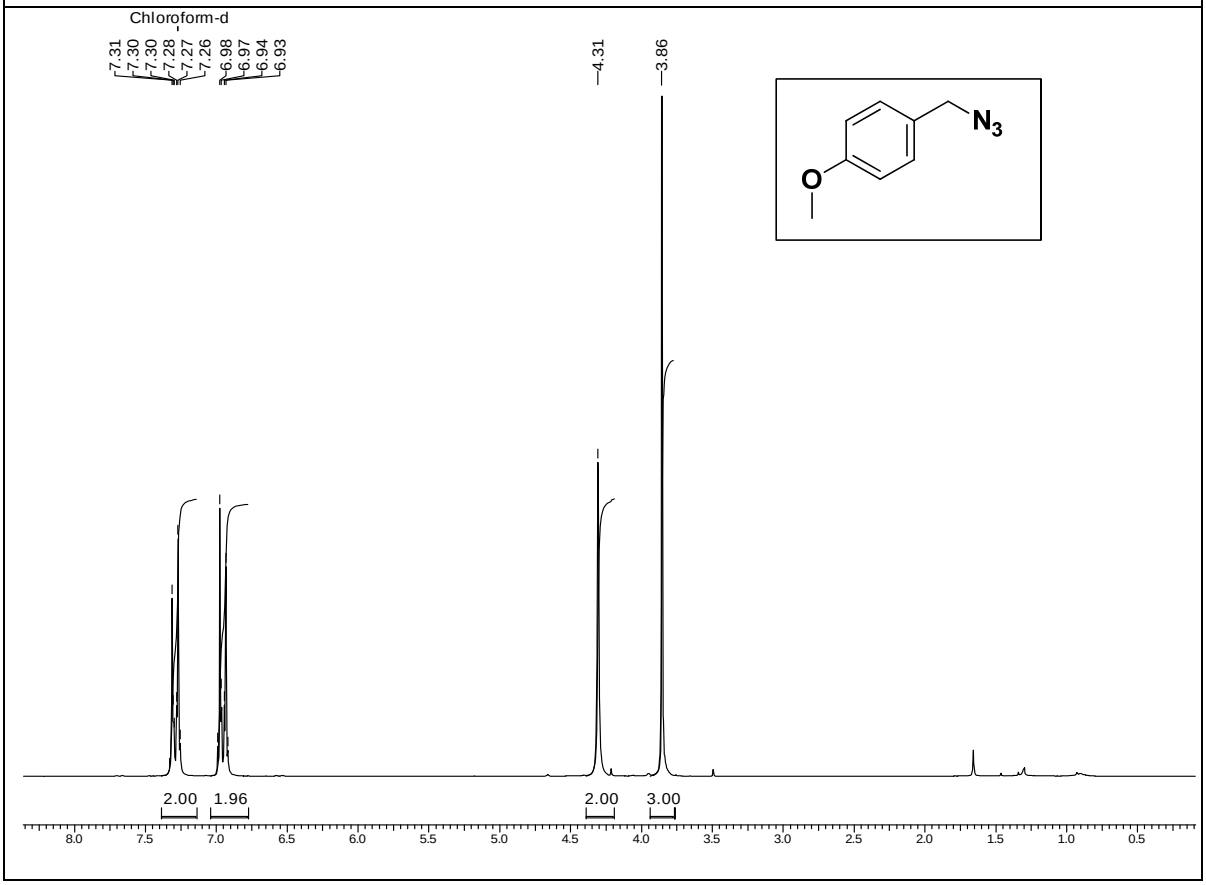
2. ^{1}H & ^{13}C NMR spectra of **1-(Azidomethyl)-2-octylcyclopropane**

3. ^{1}H & ^{13}C NMR spectra of **1-(3-azidopropyl)-4-methoxybenzene**

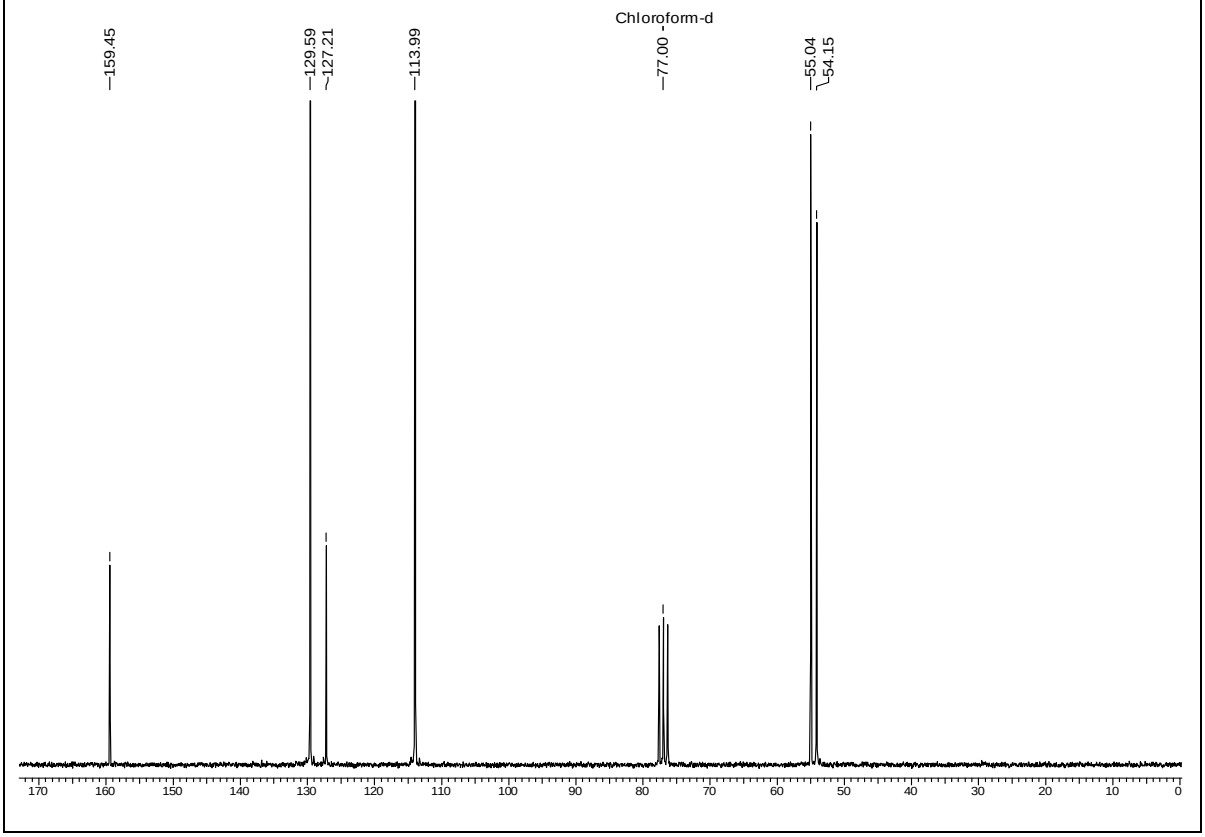
4. ^{1}H & ^{13}C NMR spectra of **(*E*)-(3-Azidoprop-1-en-1-yl)benzene**

5. ^{1}H & ^{13}C NMR spectra of ***tert*-Butyl 4-(azidomethyl)-2,2-dimethyloxazolidine-3-carboxylate**

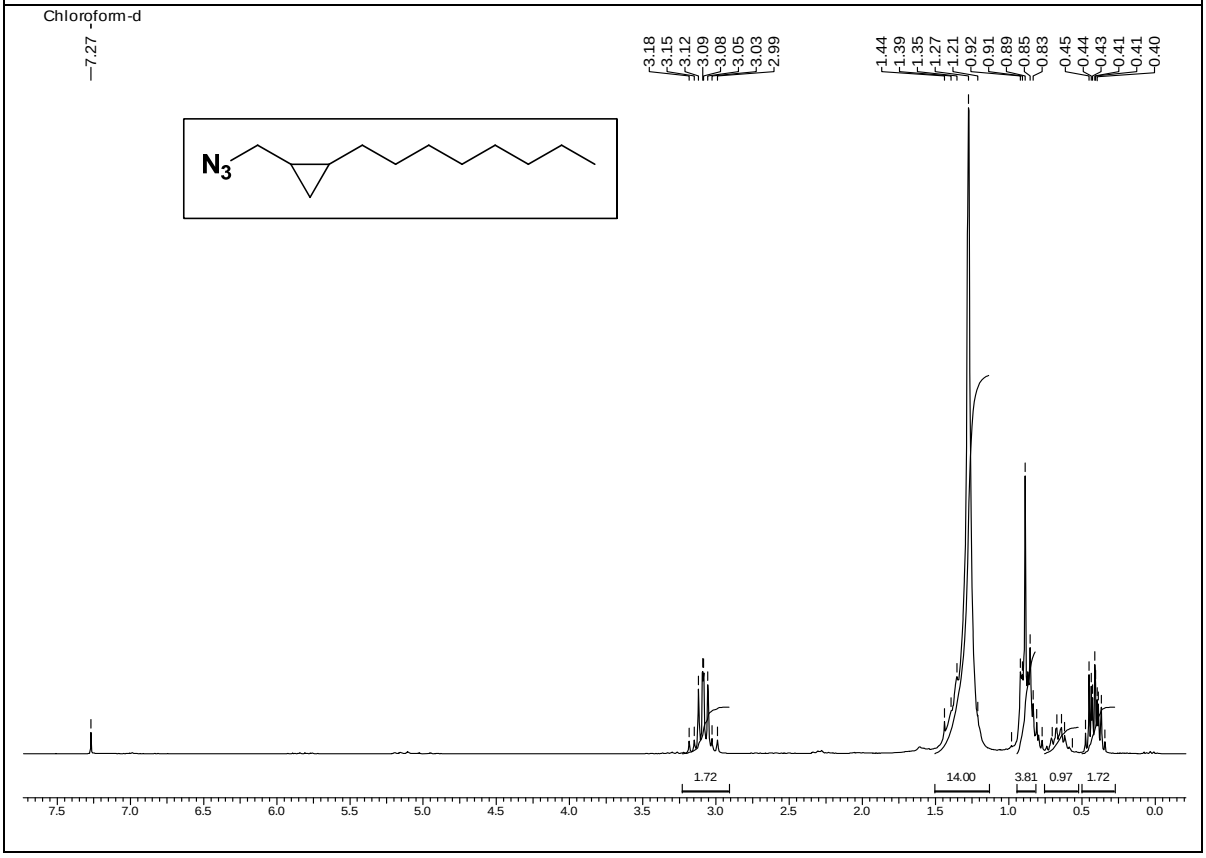
^{1}H NMR ($CDCl_3$, 200 MHz) spectra of 1-(Azidomethyl)-4-methoxybenzene



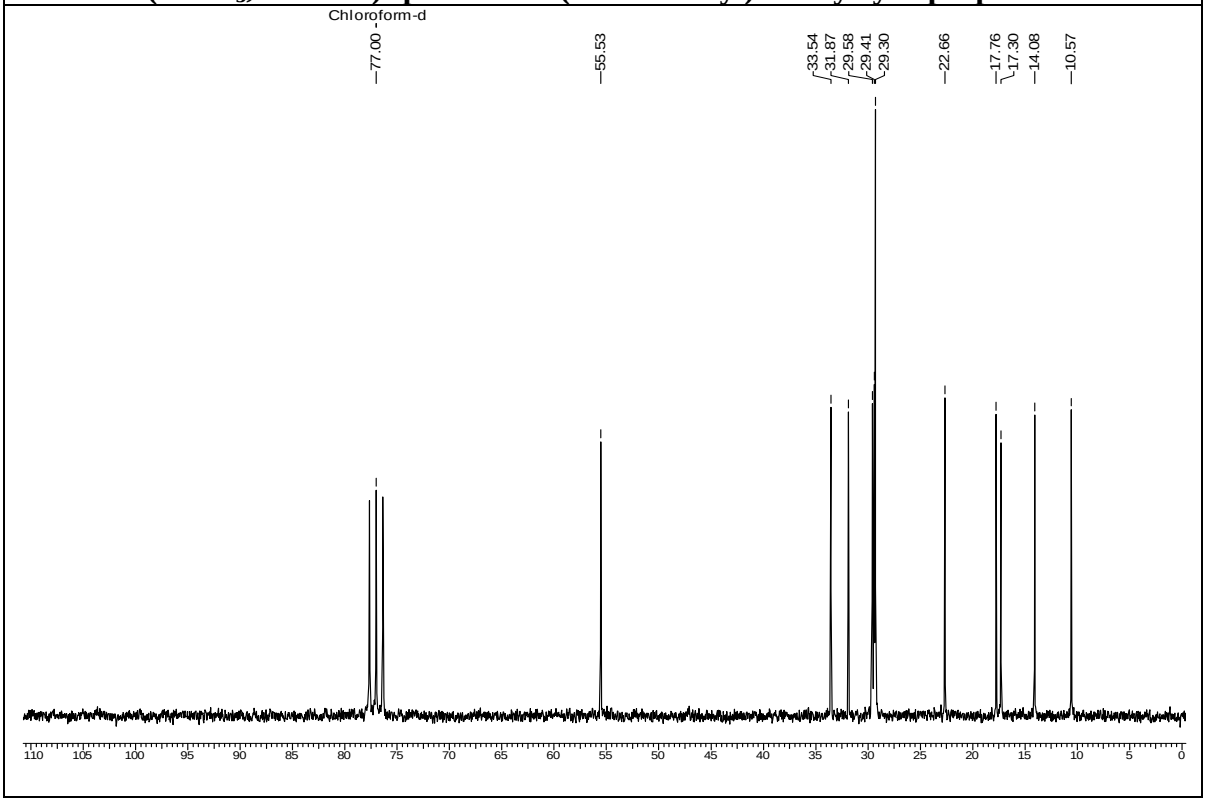
^{13}CNMR ($CDCl_3$, 50 MHz) spectra of 1-(Azidomethyl)-4-methoxybenzene



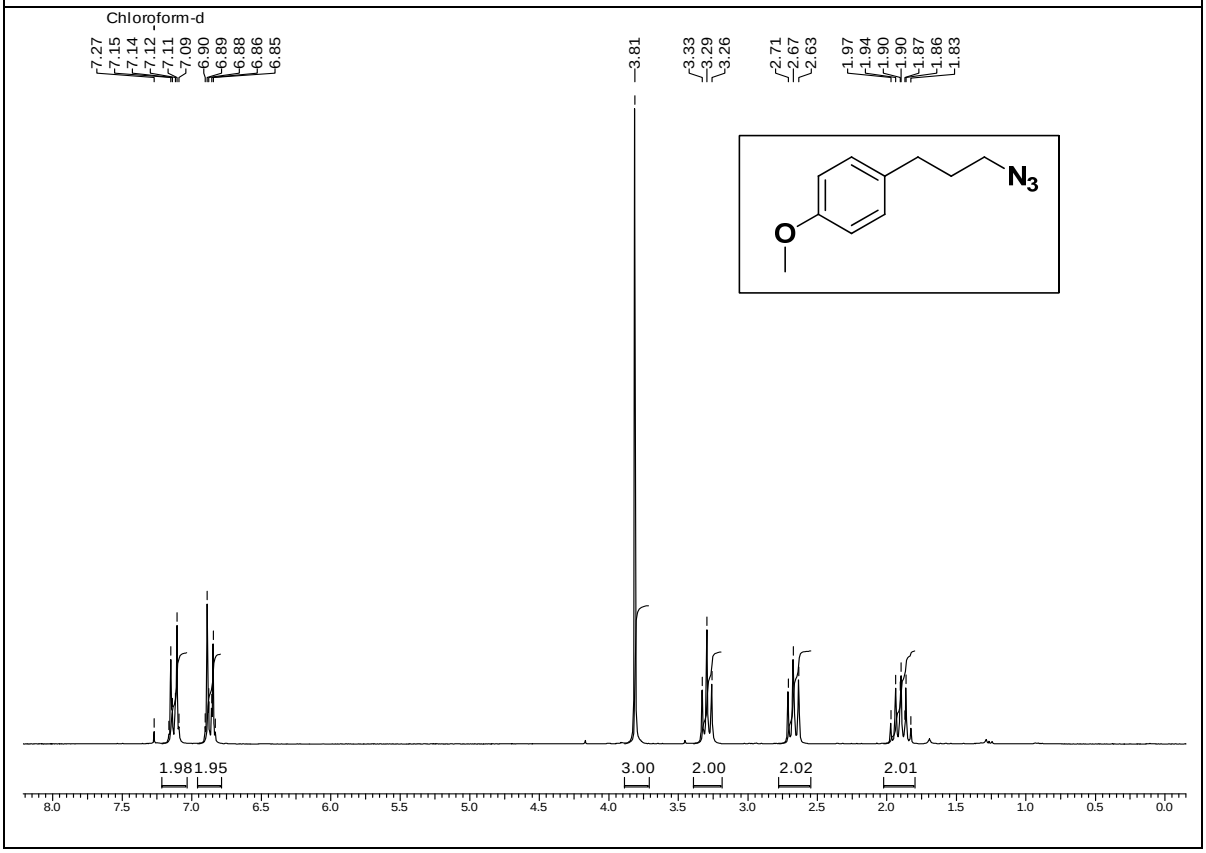
^{1}H NMR ($CDCl_3$, 200 MHz) spectra of 1-(Azidomethyl)-2-octylcyclopropane



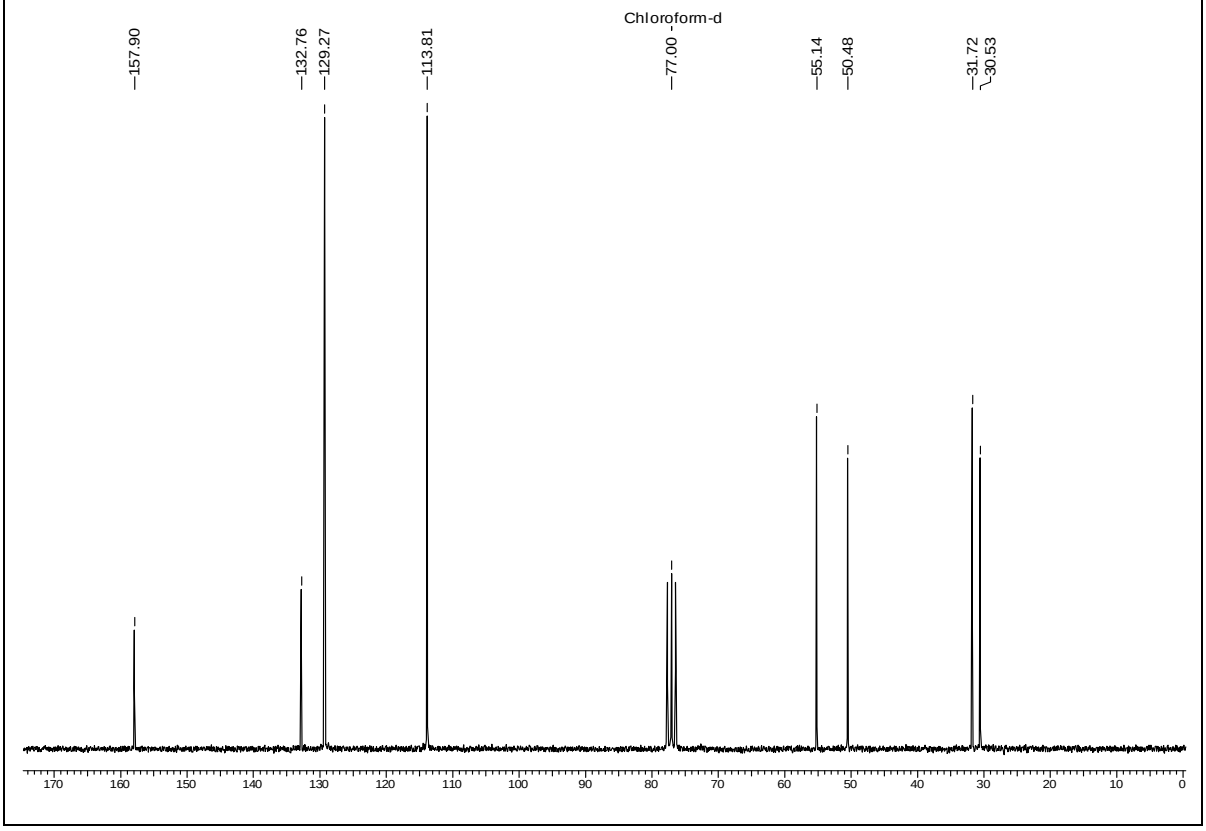
^{13}CNMR ($CDCl_3$, 50 MHz) spectra of 1-(Azidomethyl)-2-octylcyclopropane



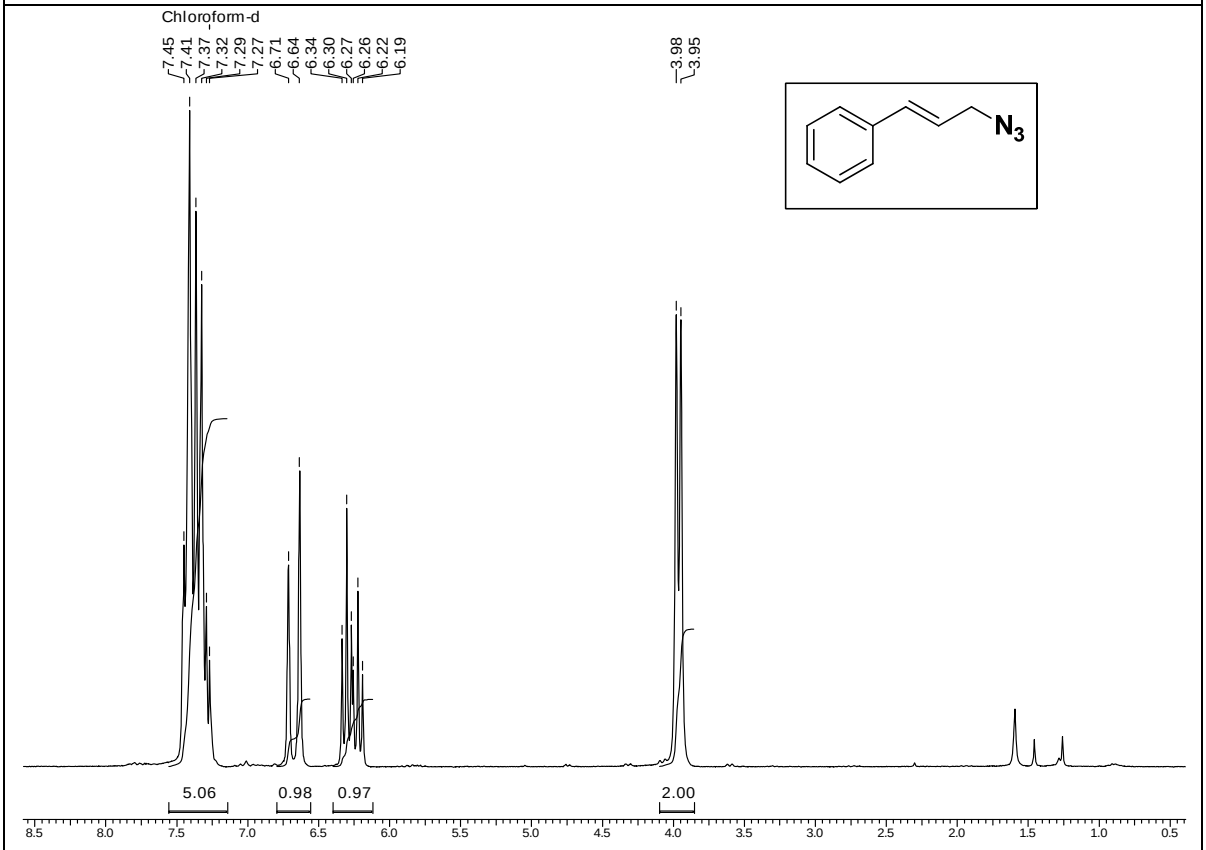
^{1}H NMR ($CDCl_3$, 200 MHz) spectra of 1-(3-azidopropyl)-4-methoxybenzene



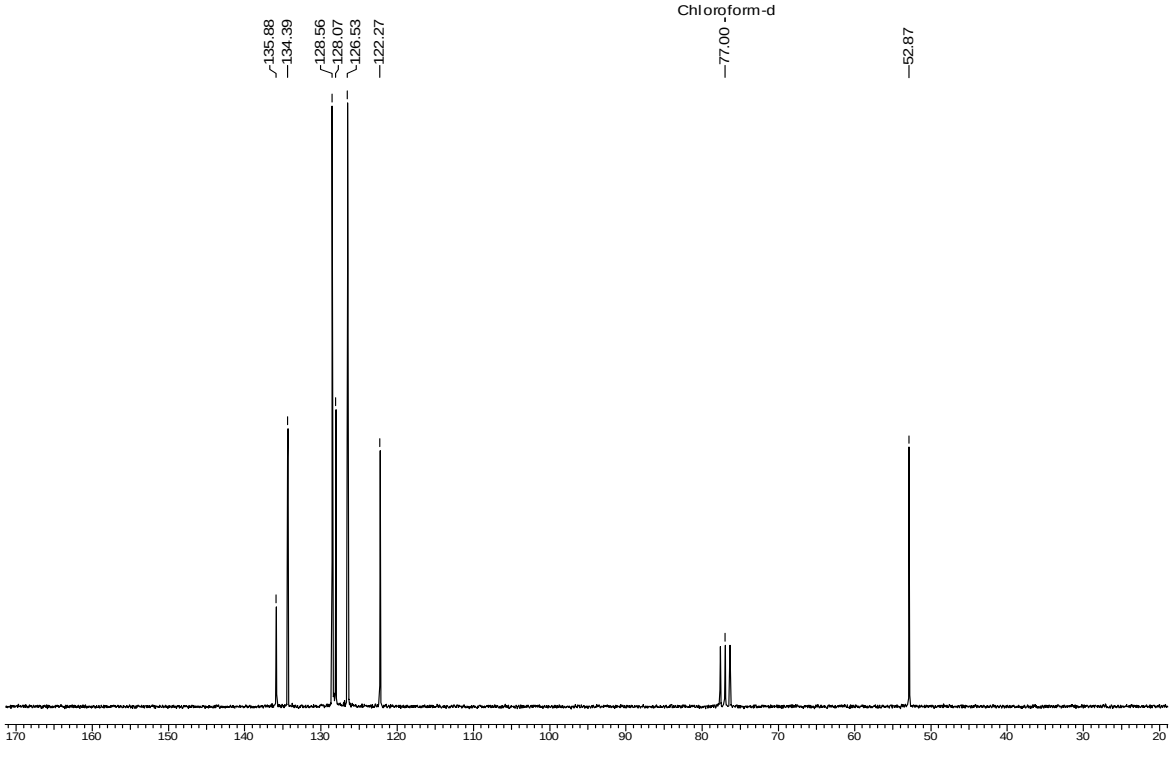
^{13}CNMR ($CDCl_3$, 50 MHz) spectra of 1-(3-azidopropyl)-4-methoxybenzene



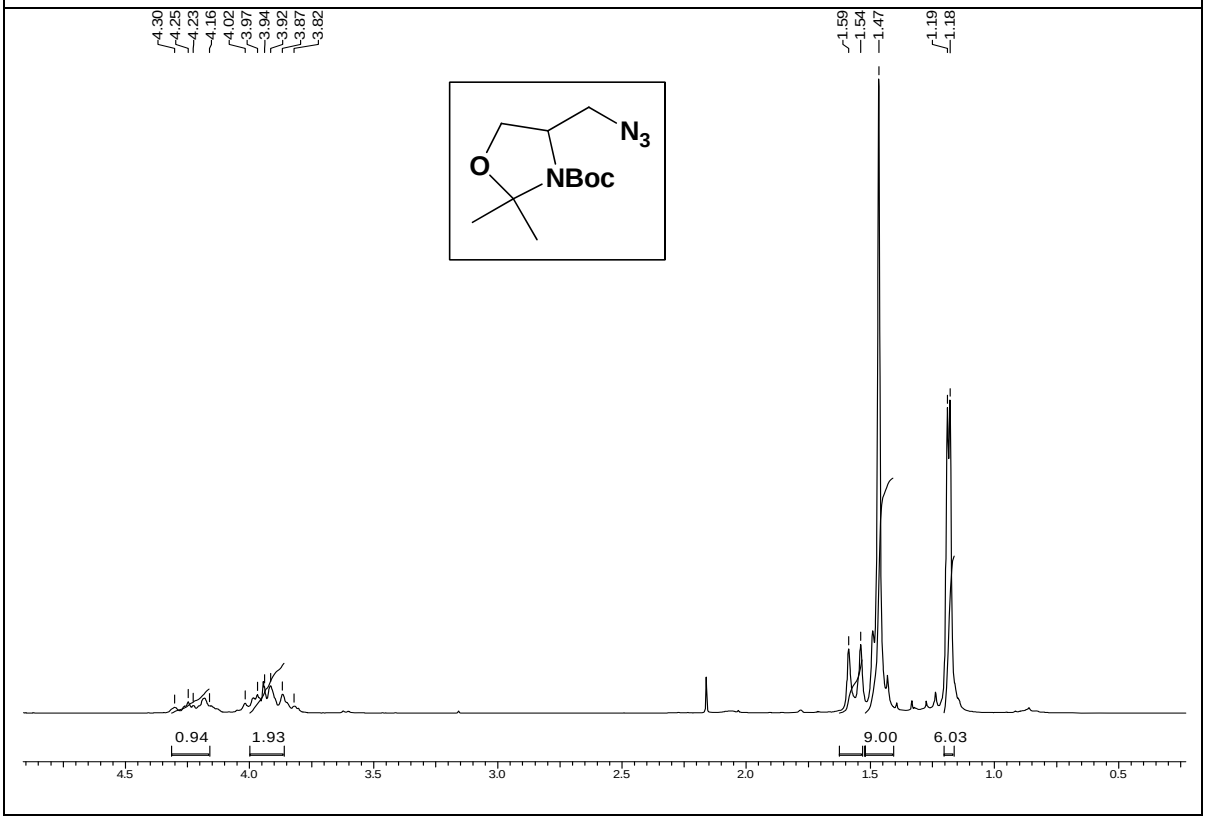
^{1}H NMR ($CDCl_3$, 200 MHz) spectra of (*E*)-(3-Azidoprop-1-en-1-yl)benzene



^{13}CNMR ($CDCl_3$, 50 MHz) spectra of (*E*)-(3-Azidoprop-1-en-1-yl)benzene



^{1}H NMR ($CDCl_3$, 200 MHz) spectra of *tert*-Butyl 4-(azidomethyl)-2,2-dimethyloxazolidine-3-carboxylate



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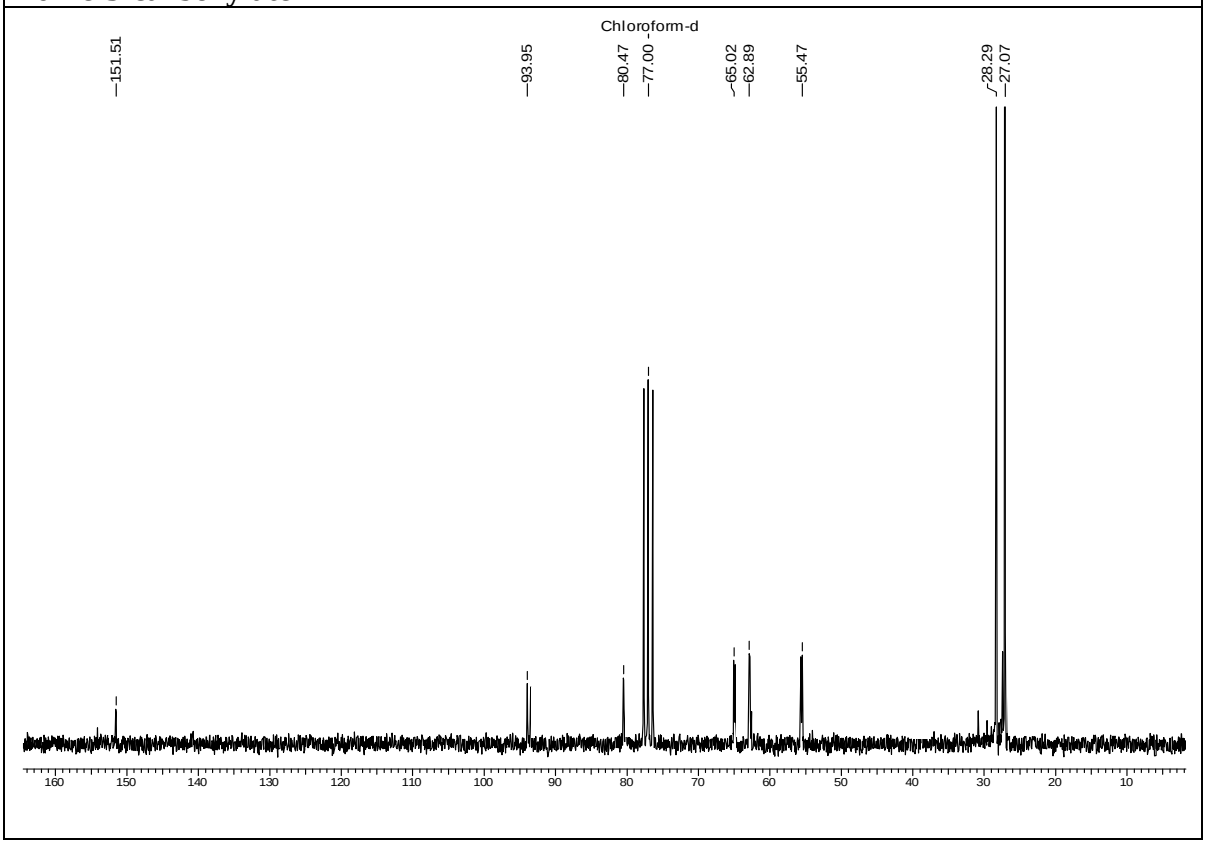

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5.2 SECTION B

DIMETHYL SULFOXIDE-PIVALOYL CHLORIDE: A NEW REAGENT FOR OXIDATION OF ALCOHOLS TO CARBONYLS

5.2.1. Introduction

Carbonyl compounds are of great importance as intermediates to prepare other functional groups in organic synthesis. In particular, aldehydes and *N*-protected (*R*)-amino aldehydes are important and versatile compounds.

Oxidation of alcohols to the corresponding carbonyl compounds is one of the most important synthetic procedures,[1] and the development of selective and efficient reagents for that conversion, especially when other oxidizable functional groups are also present, has interested organic chemists for a long time. In this context, notwithstanding the availability of many preparative methods, the restrictions that accompany some of them make new, mild, and selective procedures highly desirable. One of the most common methods for this oxidation is via activated DMSO,[2] which involves a variety of electrophilic reagents as activators.

The chemistry of dimethyl sulfoxide has been the subject of monographs[3] and reviews,[4] since it is one of the most studied solvent and reagent in organic synthesis. Dimethyl sulfoxide prepared in 1866,[5] has until recently held eminence in chemistry as a solvent of some importance but has not been considered a reactant. Since the time that dimethyl sulfoxide was first employed as an oxidising agent,[6] the knowledge edge concerning the variety of compounds that can be oxidized by dimethyl sulfoxide has grown considerably. Mild conditions, uncomplicated work-ups, and high yields with which most oxidations can be effected have elevated this technique into prominence.

The structure of DMSO is usually represented by the following resonance hybrid. Resonance structure I owes its existence to the ability of the 3d orbitals of sulfur to accommodate an additional electron pair, in this case the p electrons of the oxygen.[7] Although there is still debate over which hybrid best represents the structure of DMSO,

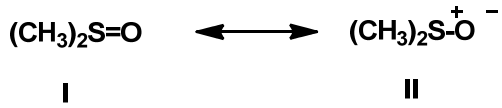


Fig. 1: Resonance hybrid structure of DMSO

or sulfoxides in general, it seems certain that the sulphur oxygen bond can be justly characterized as being semipolar.[8] The oxidizing capacity of DMSO is somewhat dependent on its ability to act as a nucleophile.

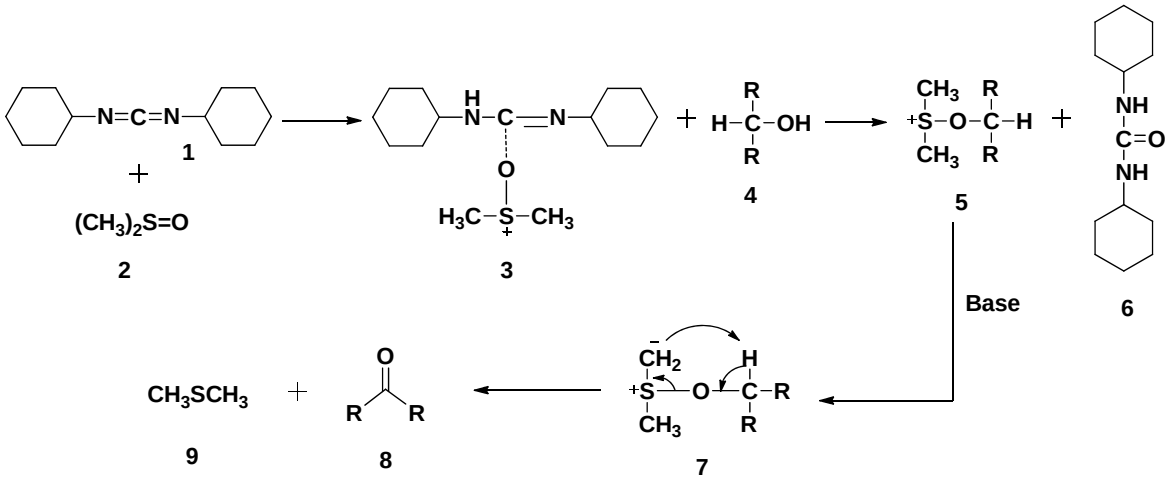
Most of the methods for the oxidation of alcohols utilize dimethyl sulfoxide as a reagent via dimethyl alkoxysulfonium salts that react with a base to give the carbonyl compound and dimethyl sulfide. The electrophilic reagents that have been used to activate dimethyl sulfoxide include acetic anhydride,[15j] methanesulfonic anhydride,[15a,b] sulfur trioxide/pyridine,[15d] phosphorus pentoxide,[9] thionyl chloride,[15c] and oxalyl chloride[15e] among others. Generally, the activation of DMSO can be violent and exothermic, and successful activation requires low temperatures, usually -60 °C. Of all the activators, the highest yields of carbonyl compounds, with minimal byproduct formation, were obtained with thionyl chloride and oxalyl chloride, especially the latter. The reaction proceeds via alkoxysulfonium salts that react with a base to give the carbonyl compound and dimethyl sulfide. The major disadvantage of the reaction is the formation of methylthioalkyl ethers as a by-product due to the Pummerer rearrangement of the alkoxysulfonium ylide. Amongst all activators, oxalyl chloride was found to be the best as high yields of carbonyl compounds were obtained with minimal Pummerer product. Although DMSO–oxalyl chloride is routinely used, the method is still associated with some disadvantages such as a violent reaction during the formation of the ylide and toxicity associated with vapors of the latter. Unfortunately, oxalyl chloride is moisture sensitive and dangerously toxic, and its vapor is a powerful irritant, particularly to the respiratory system and to the eyes.

5.2.2. Review of Literature

Currently there are a number of methods available via activated DMSO for the oxidation of alcohols to the corresponding carbonyl compounds. Among all activators, oxalyl chloride was found to be the best as high yields of carbonyls were obtained with minimal Pummerer product. A few intresting methods are described below.

Pfitzner-Moffatt *et al.* (1965)[10]

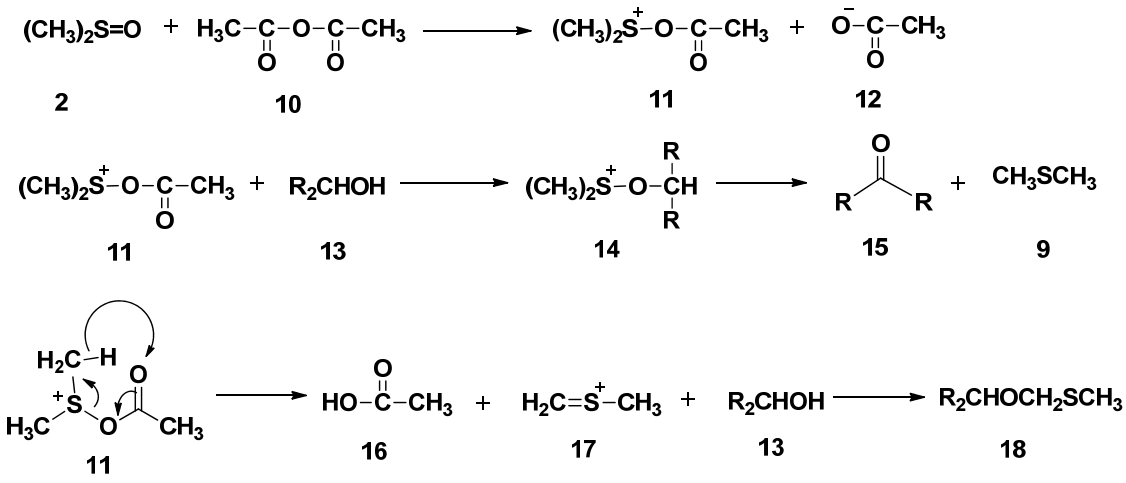
Pfitzner and Moffatt have utilised the combination of DCC **1** and DMSO **2** mediated oxidation of alcohols to the corresponding carbonyls compound. This reaction condition is applicable for nucleotides, nucleosides and carbohydrates and wide variety of primary, secondary alcohols. The main disadvantage of this method is that some substrates undergo epimerisation to a more stable conformation.



Scheme 1

Goldman *et al.* (1965)[2j]

This method, which is similar to the Pfitzner-Moffatt technique, utilizes DMSO and acetic anhydride **10** mixtures to oxidize primary and secondary alcohols to the corresponding carbonyl compound. This method appears to be superior to the DMSO-DCC method in hindered systems. Formation of acetates as well as increased amounts of methylthiomethyl ether **18** as side products are disadvantages of this method.

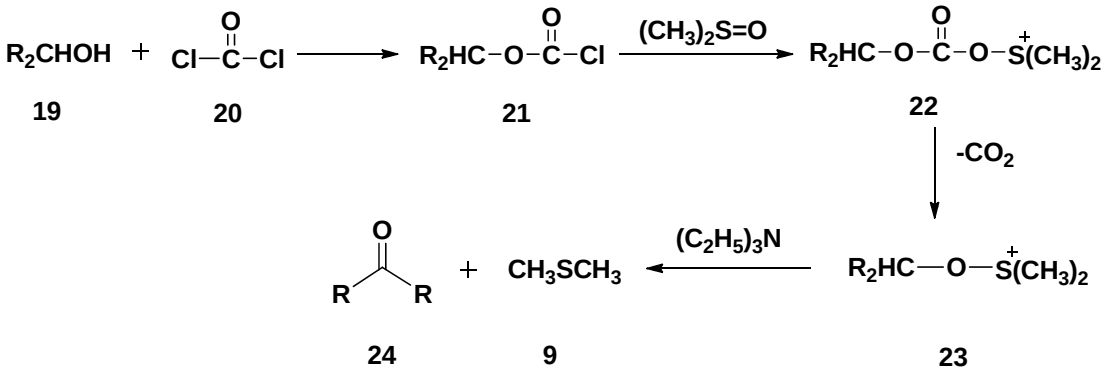


Scheme 2

Barton *et al.* (1964)[11]

Another approach to the oxidation of alcohols involves conversion of the alcohol **19** to the chloroformate **21** which will react with DMSO at room temperature or below in the presence of a base like triethylamine, to give the corresponding aldehyde or ketone. The chloroformate **21** has two purposes in the reaction. It first acts as the electrophilic group to activate the

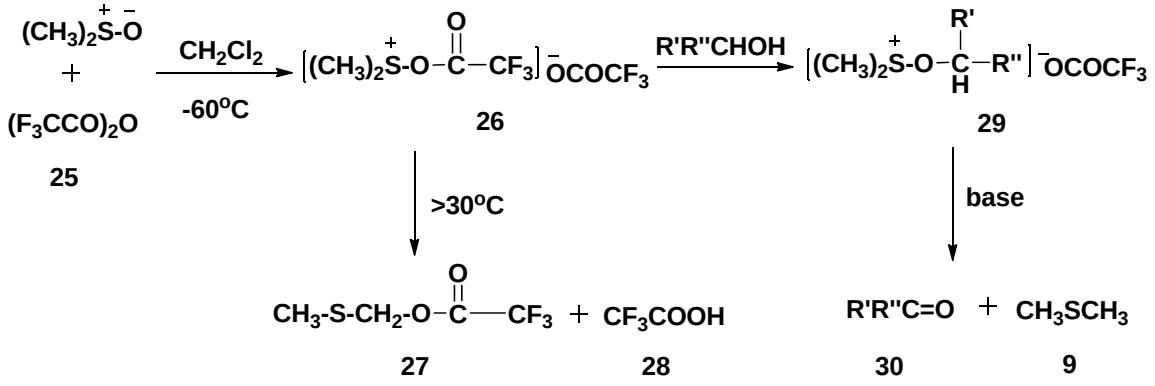
DMSO giving salt **22**, and second as the source of the alcohol subactivated DMSO. Intermediate **22** collapses giving carbon dioxide and the dimethylalkoxysulfonium salt intermediate **23** which, in the presence of the base triethylamine gives the corresponding carbonyl compound.



Scheme 3

Swern *et al.* (1976)[2d,g]

Swern has developed a raction condition in which acetic anhydride **25** and certain other anhydrides in combination with DMSO can oxidise alcohols to carbonyls under mild conditions. The problem associated with this reaction is unstability of reacting intermediate and formation of trifluoroacetoxymethyl methyl sulfide **27**.

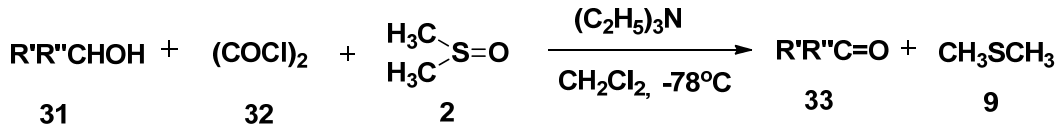


Scheme 4

Swern *et al.* (1978)[2e]

The Swern oxidation, named after Daniel Swern, is a chemical reaction whereby a primary or secondary alcohol is oxidised to an aldehyde or ketone using oxalyl chloride as an

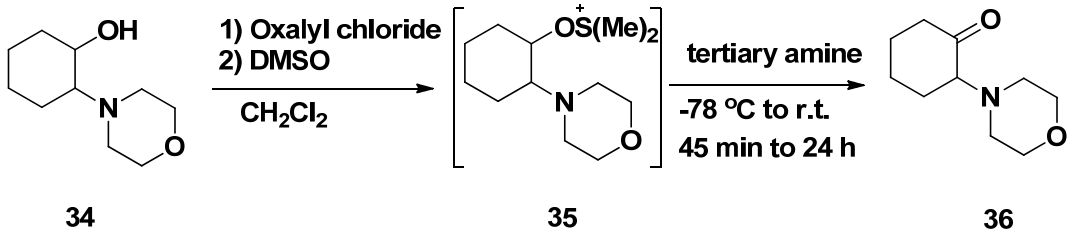
electrophile for activation of DMSO, and an organic base mainly triethylamine. This reaction is known for its mild character and wild tolerance of functional groups.



Scheme 5

Singaram *et al.* (1997)[2f]

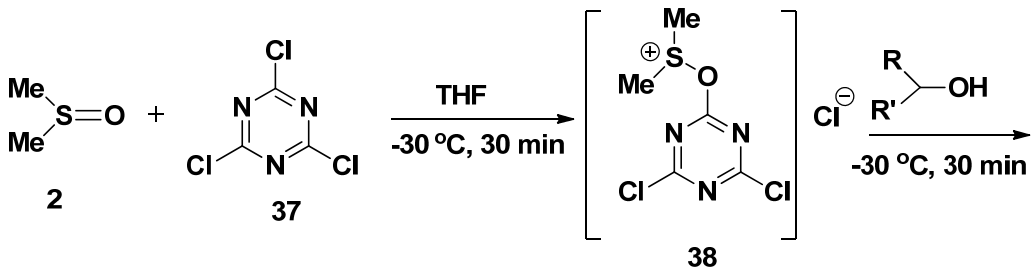
Singaram has optimised Swern oxidation reaction condition for *β*-amino alcohols **34** by using hindered base. This reaction condition is favourable when sensitive optically active amino alcohol substrates are to be oxidised. Moreover this condition is good for minimal epimerization of sensitive *β*-amino alcohols.

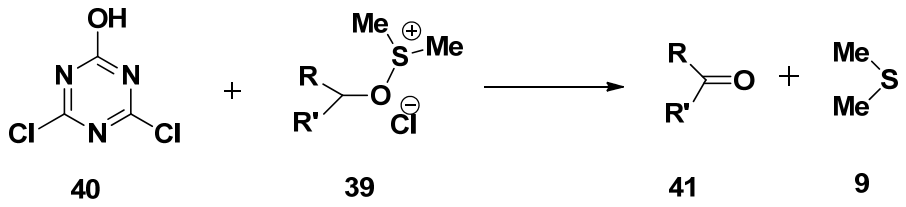


Scheme 6

Giacomelli *et al.* (2001)[2n]

Giacomelli reported oxidation of alcohols into the corresponding carbonyl compounds using DMSO, activated by 2,4,6-trichloro[1,3.5]-triazine (cyanuric chloride, TCT) **37**, under Swern oxidation conditions. This method is also applicable to *N*-protected *β*-aminoalcohols.



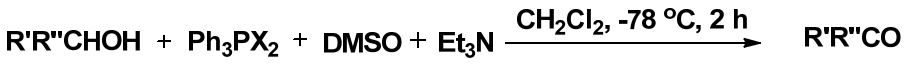


40 39 41 9

Scheme 7

Singh *et al.* (2002)[2o]

Singh *et al.* have developed a very convenient method for oxidation of alcohols to corresponding carbonyl compounds by using combination of triphenylphosphine dibromide ($Ph_3P.Br_2$) or triphenylphosphine dichloride ($Ph_3P.Cl_2$) and DMSO as good alternative to classical Swern oxidation. This method is applicable for primary, secondary, allylic, and benzylic alcohols.



42 43 44

Scheme 8

5.2.3. Present Work

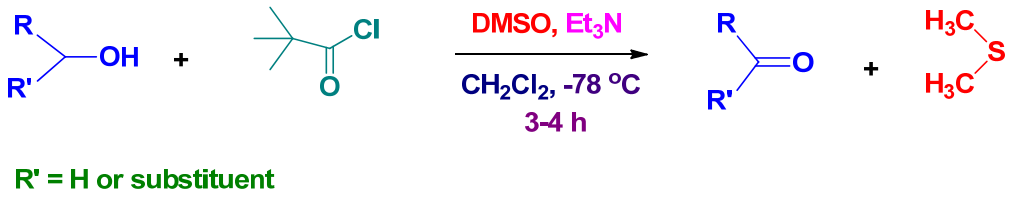
5.2.3.1. Objective

The oxidation of alcohols to the corresponding carbonyl compounds is one of the most important and frequently used synthetic procedures and the development of such procedure is still desirable in academic as well as in industrial research. Dimethyl sulfoxide coupled with various electrophiles such as trifluoroacetic anhydride,[2a,b] thionyl chloride,[2c,d] oxalyl chloride,[2e,f] *t*-butylhypochlorite,[2g] *N*,*N*-dicyclohexylcarbodiimide,[2h,10] acetic anhydride,[2i,j] phosgene,[2k,l] bis-(trichloromethyl)carbonate,[2m] cyanuric chloride[2n] and $Ph_3P.X_2$[2o] has been used in the classical Swern oxidation. Oxalyl chloride which is routinely used electrophile has following disadvantages; it is moisture sensitive, expensive, toxic and its vapors are powerful irritant particularly to the respiratory system. Therefore use of a mild, efficient and

inexpensive electrophile is highly desirable. With this view in mind, we considered developing a new route to the oxidation of alcohols to carbonyl compounds employing pivaloyl chloride as an electrophile.

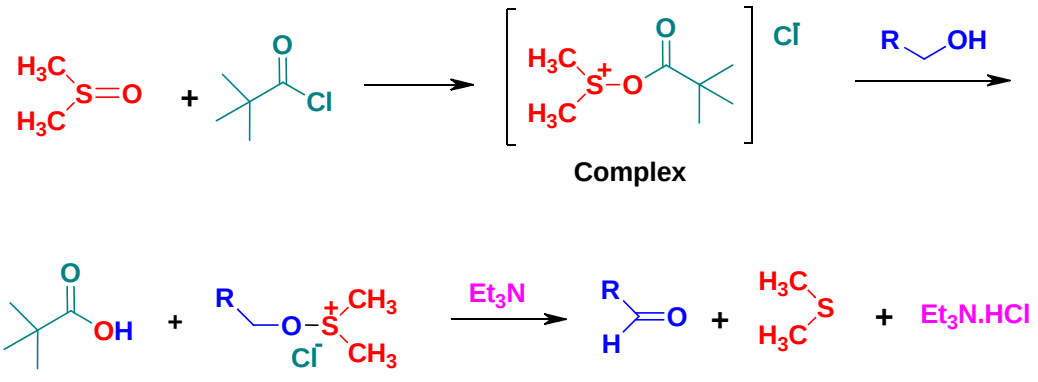
5.2.3.2. Results and Discussion

Although, pivaloyl chloride has been commonly employed as a protecting group for various functional groups, its synthetic potential still remains unexplored. With a view to extend its synthetic utility in organic transformations, we envisioned that the activation of pivaloyl chloride with DMSO could be advantageous in the classical Swern oxidation reaction. In a typical experimental procedure, when alcohol was treated with 2 equiv of pivaloyl chloride and 3 equiv of DMSO in CH_2Cl_2 at -78 ^oC followed by treatment with 5 equiv of Et_3N, the corresponding carbonyl compound was obtained in good to excellent yield (**Scheme 9**).



Scheme 9. DMSO-Pivaloyl chloride mediated oxidation of alcohols to carbonyls

In order to understand the reaction pathway, the oxidation of 1-octanol was carried out at different temperatures. At -78 ^oC and -60 ^oC, the reaction was complete and desired product was obtained in high yield (95%), however, at -40 ^oC and -30 ^oC, the reaction was

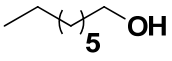
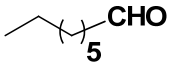
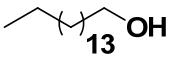
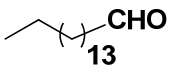
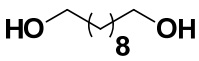
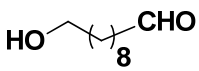
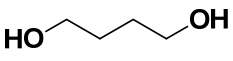
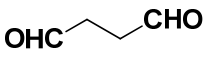


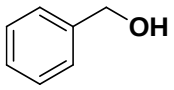
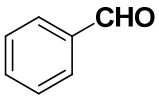
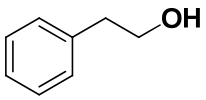
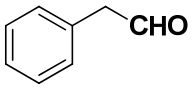
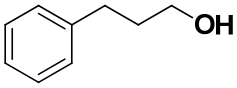
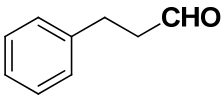
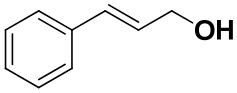
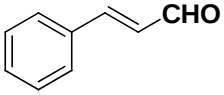
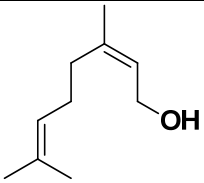
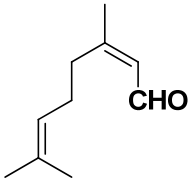
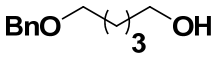
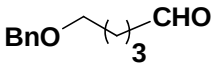
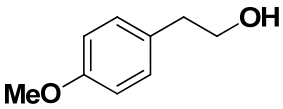
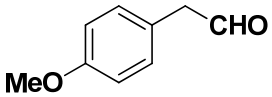
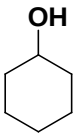
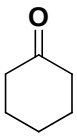
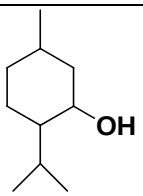
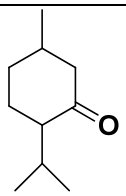
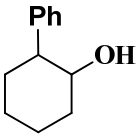
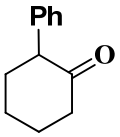
Scheme 10. Proposed mechanism for oxidation of alcohols to carbonyls

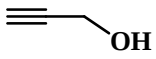
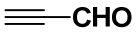
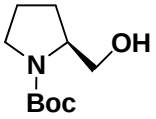
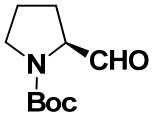
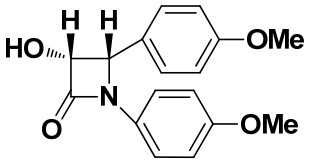
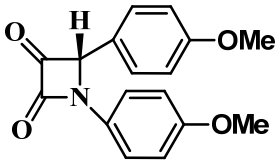
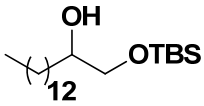
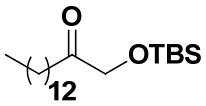
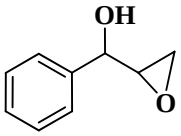
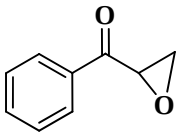
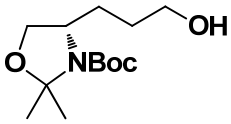
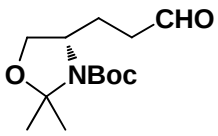
incomplete and oxidized product was obtained in <50% yield along with the recovered alcohol. At 0 ^{o}C, the reaction did not proceed at all and the starting material was completely recovered. This could probably be attributed to the nature of complex formed during the reaction that may not be stable at high temperature (**Scheme 10**).

The present procedure is quite general as a wide range of structurally varied alcohols such as primary, secondary, allylic, homoallylic, benzylic, acetylenic could be oxidized to carbonyl compounds in high yields. The superiority of this procedure can be clearly visualized in oxidation of β-amino alcohols leading to the corresponding carbonyls in good yields (**Table 1,** entry 16, 17). In this connection it should be mentioned that the oxidation of *N*-protected β-amino alcohol using DMSO/cyanuric reagent required a prolonged reaction time leading to *N*-deprotected compound along with the desired product.[10] A noteworthy feature of this reaction is that the epimerization of a chiral centre could not be observed under the reaction conditions employed (**Table 1**, entry 16 & 17). It may be pointed out that the oxidation of an alcohol having silyl ethers could also be carried out successfully in high yields (**Table 1**, entry 18). Similarly epoxy alcohol could be smoothly converted into epoxy ketone in reasonably good yield (**Table 1**, entry 19).

Table 1. Dimethyl sulfoxide-pivaloyl chloride mediated oxidation of alcohols to carbonyls

S.No.	**Substrate**	**Product**[a]	**Yield** (%)[b]
1			95
2			92
3			89
4			86

5			96
6			92
7			94
8			88
9			94
10			86
11			84
12			96
13			89
14			88

15			72
16			85
17			60
18			85
19			85
20			70

(a) Products were characterized by spectral data (IR, ^{1}H NMR, ^{13}C NMR etc.) and also by comparison with authentic samples.

(b) Isolated pure yields. (c) The optical purity was checked by measuring the optical rotation of the products.

5.2.3.3. Conclusion

In conclusion, we have demonstrated that DMSO-pivaloyl chloride combination serves as an efficient reagent to effect the oxidation of a variety of alcohols to carbonyl compounds. This could be used as an alternative to the classical Swern oxidation reaction.

5.2.4. Experimental

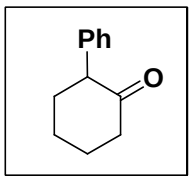
General information as described in section A.

General procedure for the oxidation of alcohols to carbonyls:

To a stirred a solution of DMSO (3 equiv) in DCM was added pivaloyl chloride (2 equiv) in dry DCM and solution was cooled to –78 ^{o}C. The reaction mixture was stirred for 15 min and the alcohol (1 equiv) in dry DCM was added dropwise. After consumption of the starting material (nearly 1 h), Et_3N (5 equiv) was added and reaction mixture stirred at –78 ^{o}C for further 30 min and then brought to rt and stirred again for 30 min. The reaction mixture was quenched with saturated NH_4Cl and water and organic layer were separated. The aqueous layer was extracted with dichloromethane and combined organic layers was washed with brine solution, and concentrated to near dryness. The crude product was purified using silica gel column chromatography and characterized by comparison with authentic samples and by spectral data.

Physical and spectroscopic data of compounds (Table 1, entries **1** to **13**, **15** & **20**) were in agreement with known values**.**

2-Phenylcyclohexanone:



Physical State: Yellow crystalline solid.

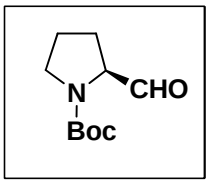
M. P.: 37 ^{o}C.

IR ($CHCl_3$, cm^{-1}): ν_{max} 1700, 1450.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.43-1.52 (m, 4H), 1.58-1.70 (m, 2H), 2.24-2.34 (m, 1H), 2.68-2.81 (m, 1H), 5.14-5.17 (m, 1H), 7.24-7.33 (m, 5H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 24.5, 27.1, 34.4, 41.4, 56.4, 126.0, 127.5, 127.9, 138.3, 209.1.

(*S*)-*tert*-Butyl-2-formylpyrrolidine-1-carboxylate:



Physical State: Colourless liquid.

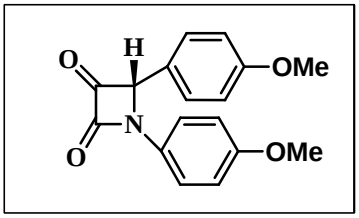
$[\alpha]_D^{25}$: –99.49 (*c* 0.66, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 1724.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.44 (d, *J* = 9.8 Hz, 9H), 1.73-2.21 (m, 4H), 3.41-3.61 (m, 2H), 4.0- 4.22 (m, 1H), 9.45(s, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 23.5, 24.2, 26.3, 27.5, 46.3, 64.9, 80.2, 200.2.

(*S*)-3,4-Bis-(4-methoxyphenyl)-azetidine-2,3-dione:



Physical State: Yellow solid.

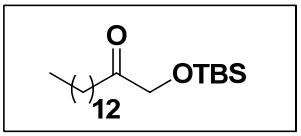
M. P.: 143 °C.

IR ($CHCl_3$, cm^{-1}): ν_{max} 1832, 1809, 1753.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.79 (s, 3H), 3.89 (s, 3H), 5.52 (s, 1H), 6.86-6.95 (m, 4H), 7.25 (d, *J* = 8.8 Hz, 2H), 7.46 (d, *J* = 8.8 Hz, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 55.2, 55.4, 74.4, 114.6, 114.8, 119.6, 123.5, 127.7, 129.8, 157.8, 160.1, 160.4, 191.1.

1-*tert*-Butyldimethylsilyloxy)-pentadecan-2-one:



Physical State: Colourless syrupy liquid

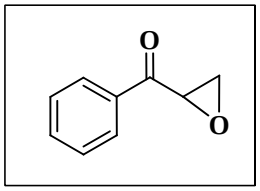
IR ($CHCl_3$, cm^{-1}): ν_{max} 1704.

^{1}H NMR ($CDCl_3$, 200 MHz): δ .04-.09 (m, 6H), 0.84-0.92 (m, 12H), 1.18-1.26 (m, 26H), 4.16 (s, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ -5.7, 14, 18.2, 22.6, 23.3, 25.6, 25.8, 26.4, 26.9, 29.2, 29.3, 29.6, 31.9, 38.2, 211.02.

Anal. Calcd : C, 71.28; H, 12.51. **Found:** C, 71.11; H, 12.32.

Oxirane-2-yl-(phenyl)-methanone:



Physical State: White solid.

M. P.: 44 ^{o}C.

IR ($CHCl_3$, cm^{-1}): ν_{max} 1692.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.97 (dd, *J* = 2.5, 6.6 Hz, 1H), 3.13 (dd, *J* = 4.6, 6.6 Hz, 1H), 4.25 (dd, *J* = 2.5, 4.4 Hz, 1H), 7.47-7.68 (m, 3H), 8.02-8.08 (m, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 47.4, 50.9, 128.1, 128.7, 133.8, 135.2, 194.5.

5.2.5. Spectra

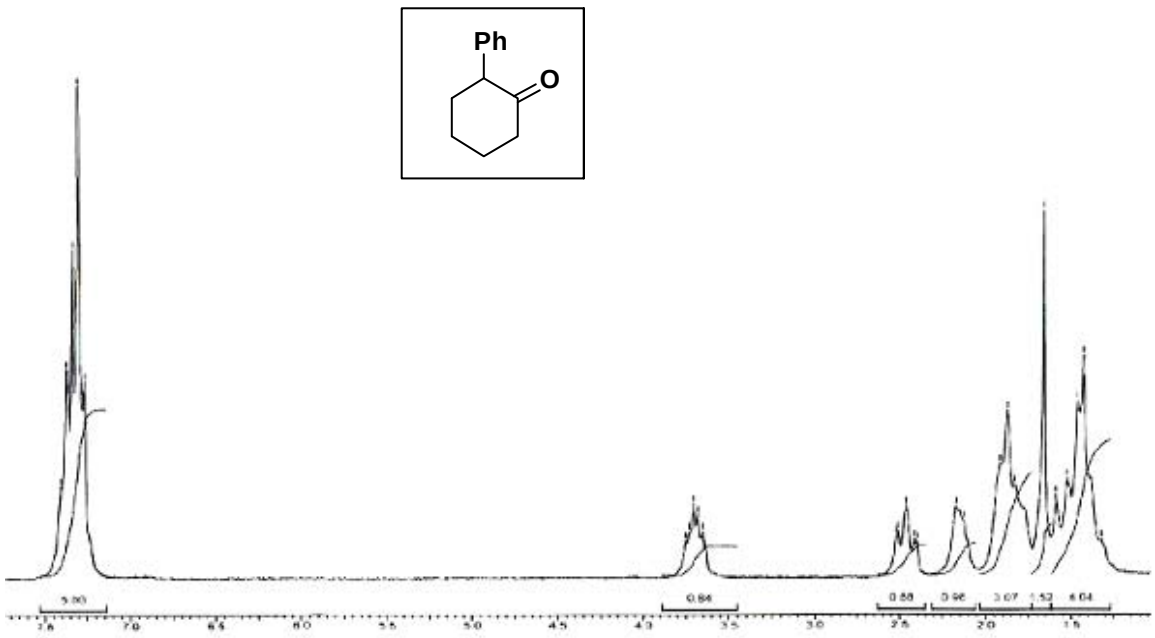
1. ^{1}H & ^{13}C NMR spectra of **2-Phenylcyclohexanone**

2. ^{1}H & ^{13}C NMR spectra of **(*S*)-*tert*-Butyl-2-formylpyrrolidine-1-carboxylate**

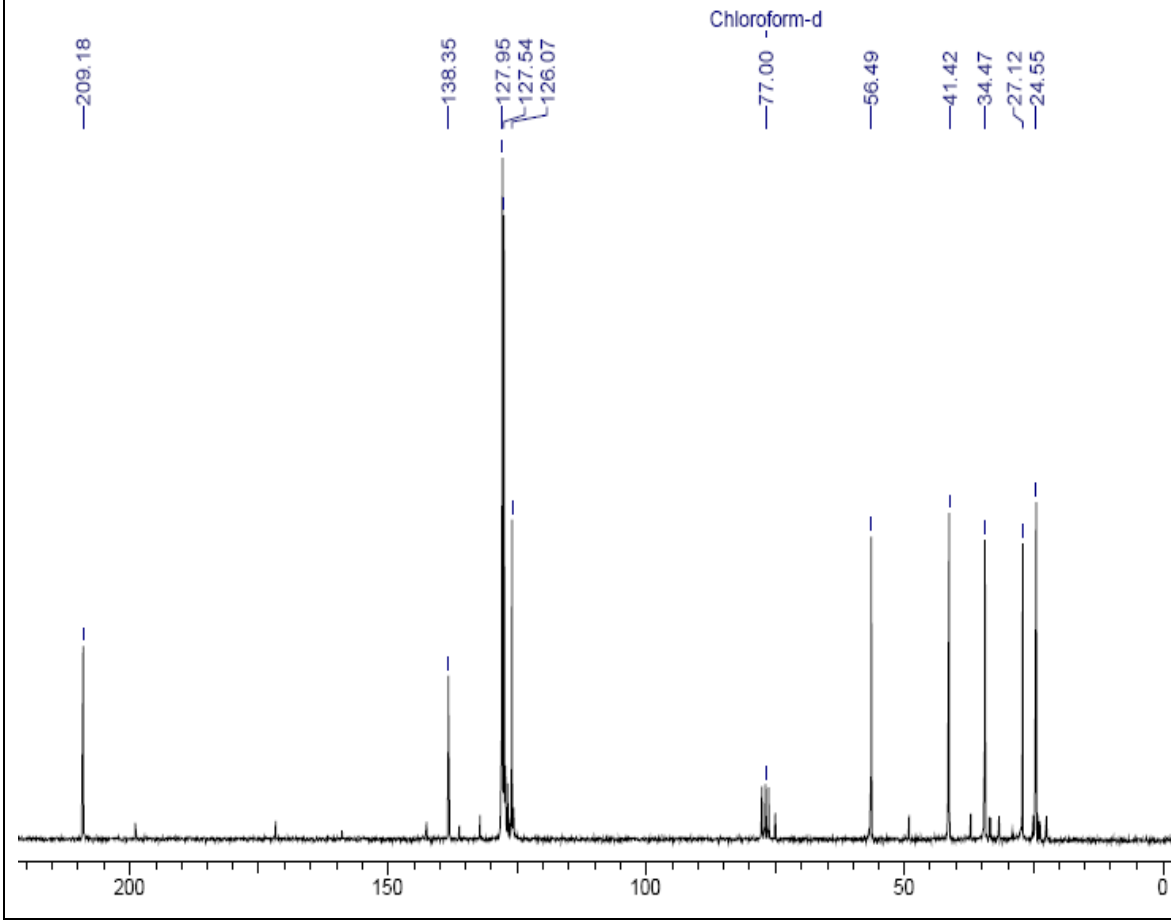
3. ^{1}H & ^{13}C NMR spectra of **(*S*)-3,4-Bis-(4-methoxyphenyl)-azetidine-2,3-dione**

4. ^{1}H & ^{13}C NMR spectra of **Oxirane-2-yl-(phenyl)-methanone**

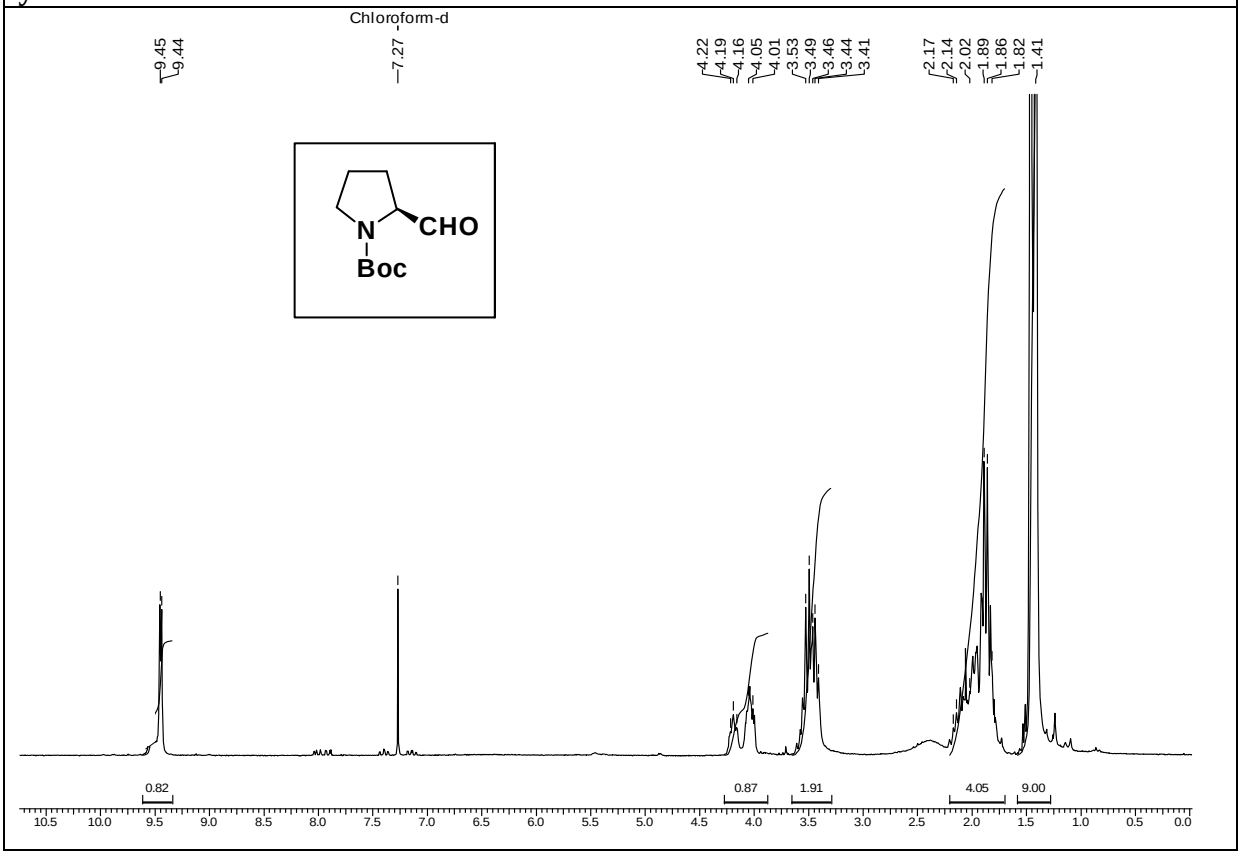
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of 2-Phenylcyclohexanone



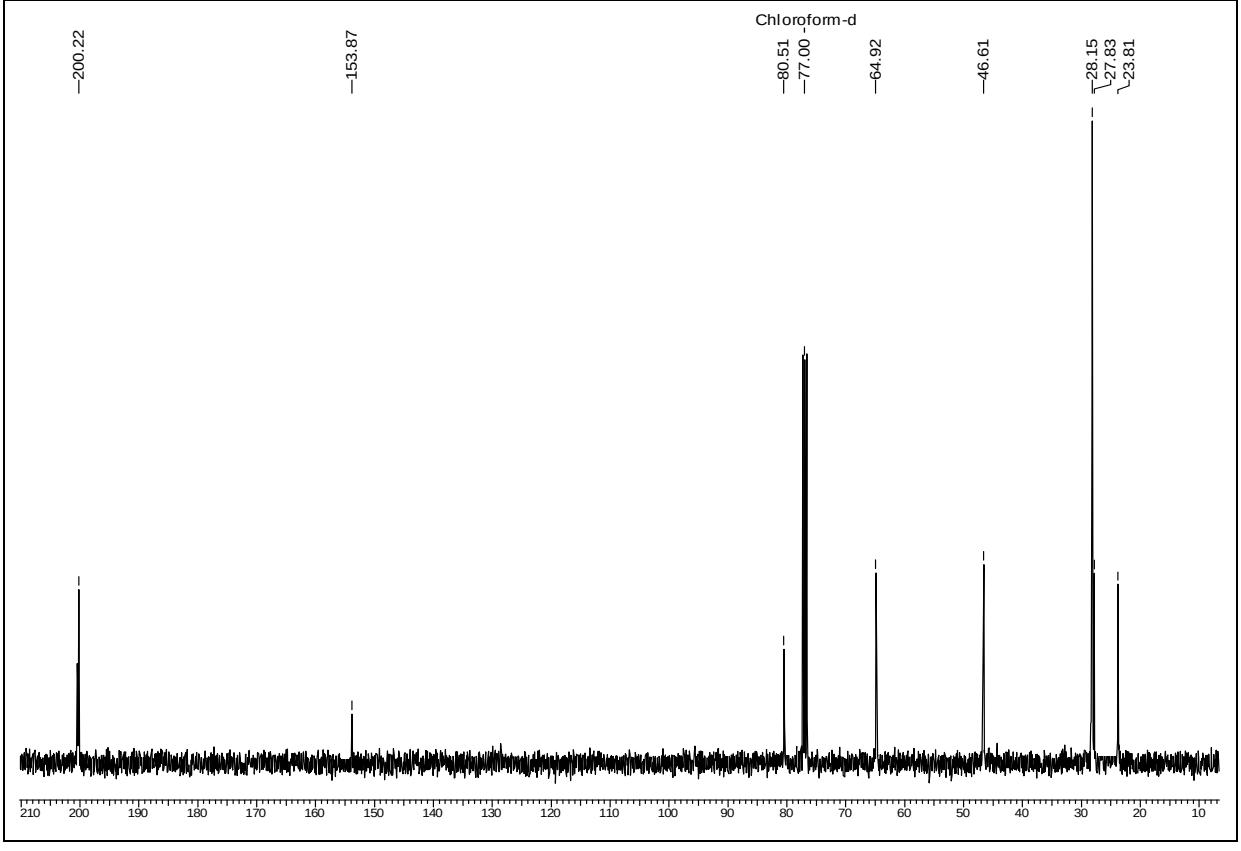
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of 2-Phenylcyclohexanone



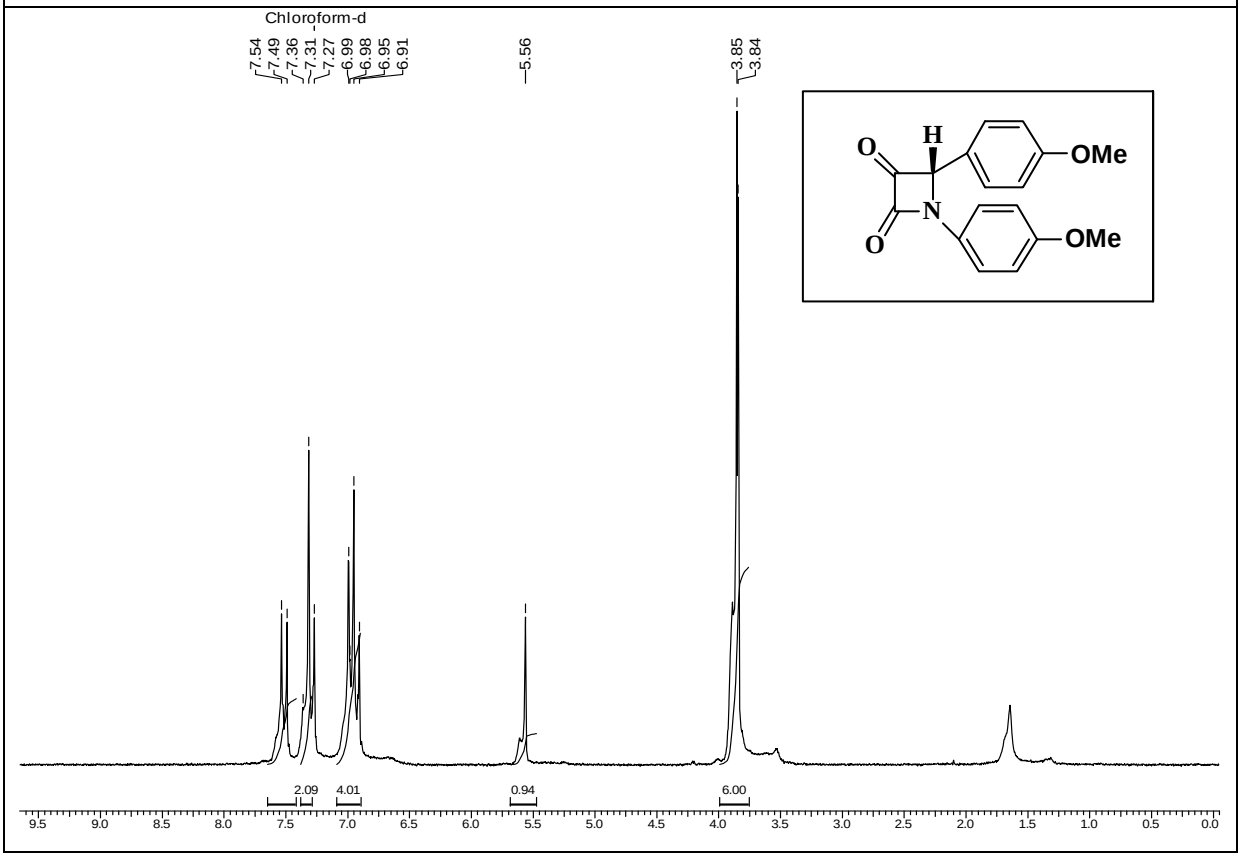
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (*S*)-*tert*-Butyl-2-formylpyrrolidine-1-carboxylate



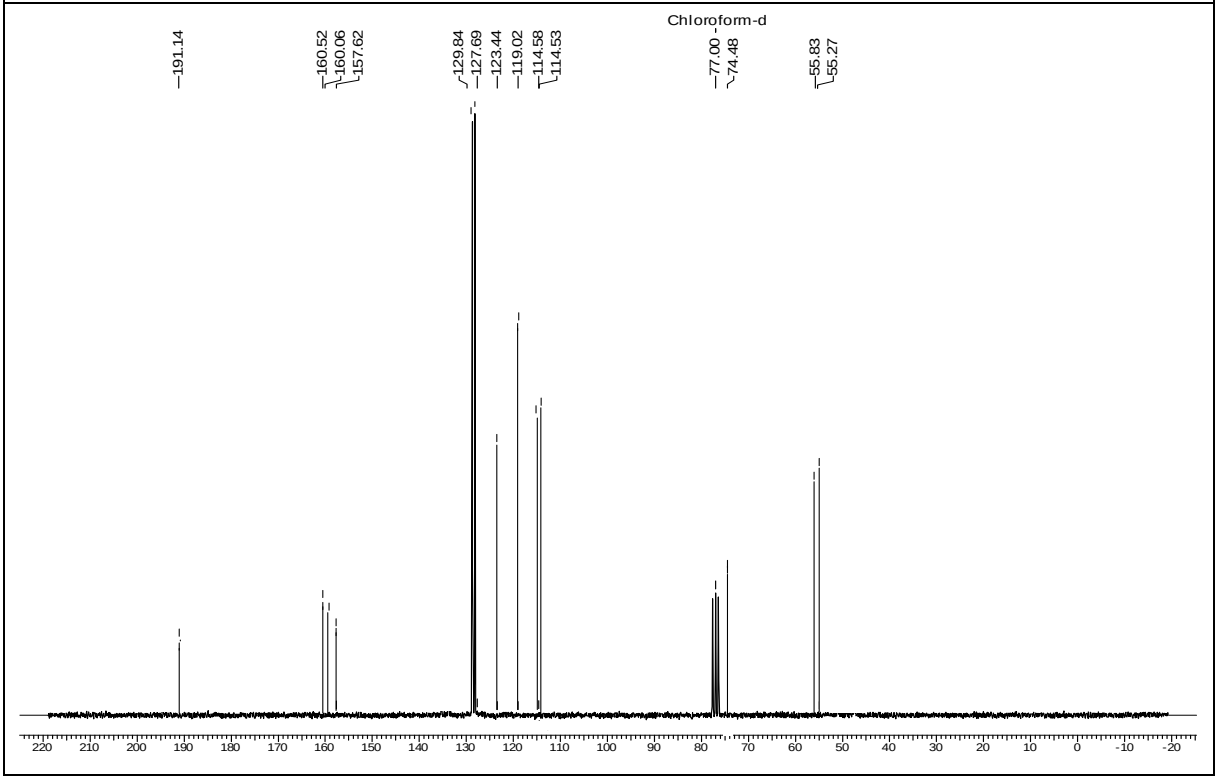
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of (*S*)-*tert*-Butyl-2-formylpyrrolidine-1-carboxylate



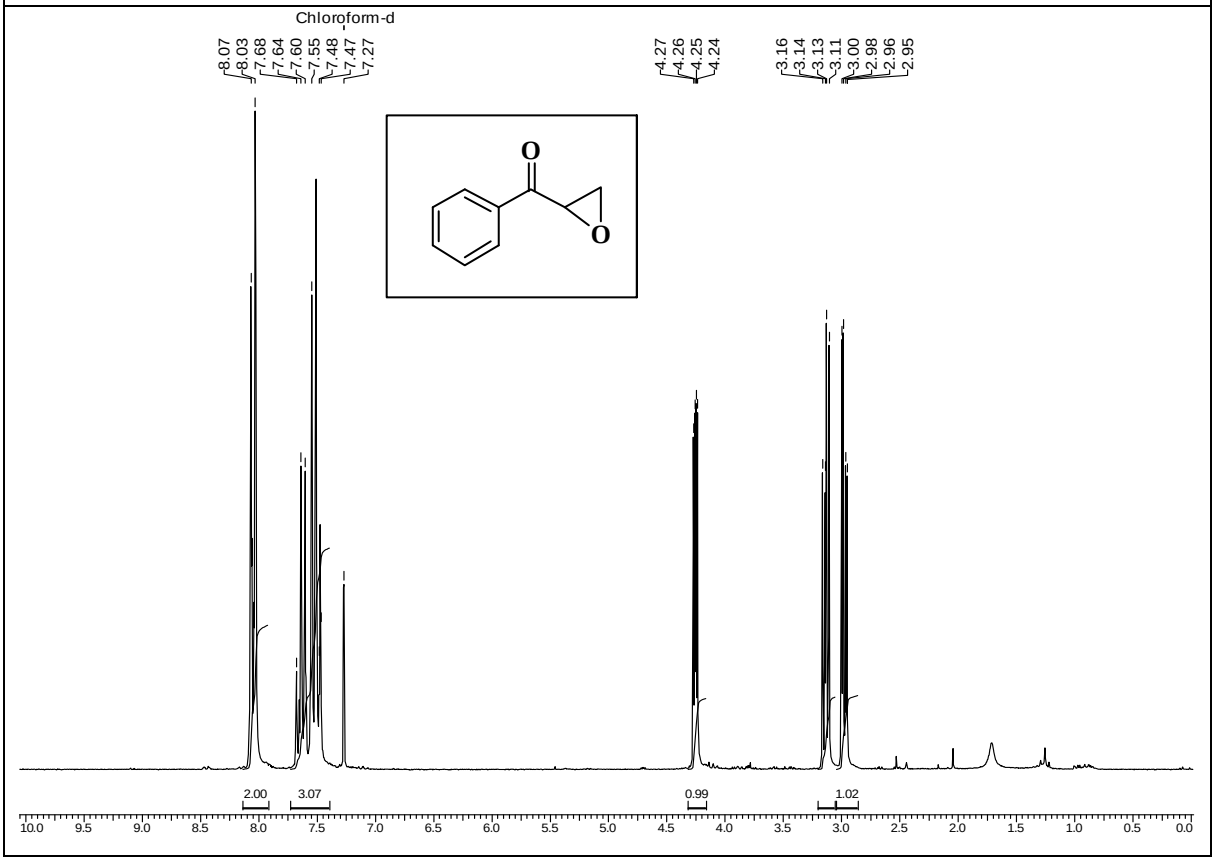
^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of (*S*)-3,4-Bis-(4-methoxyphenyl)-azetidine-2,3-dione



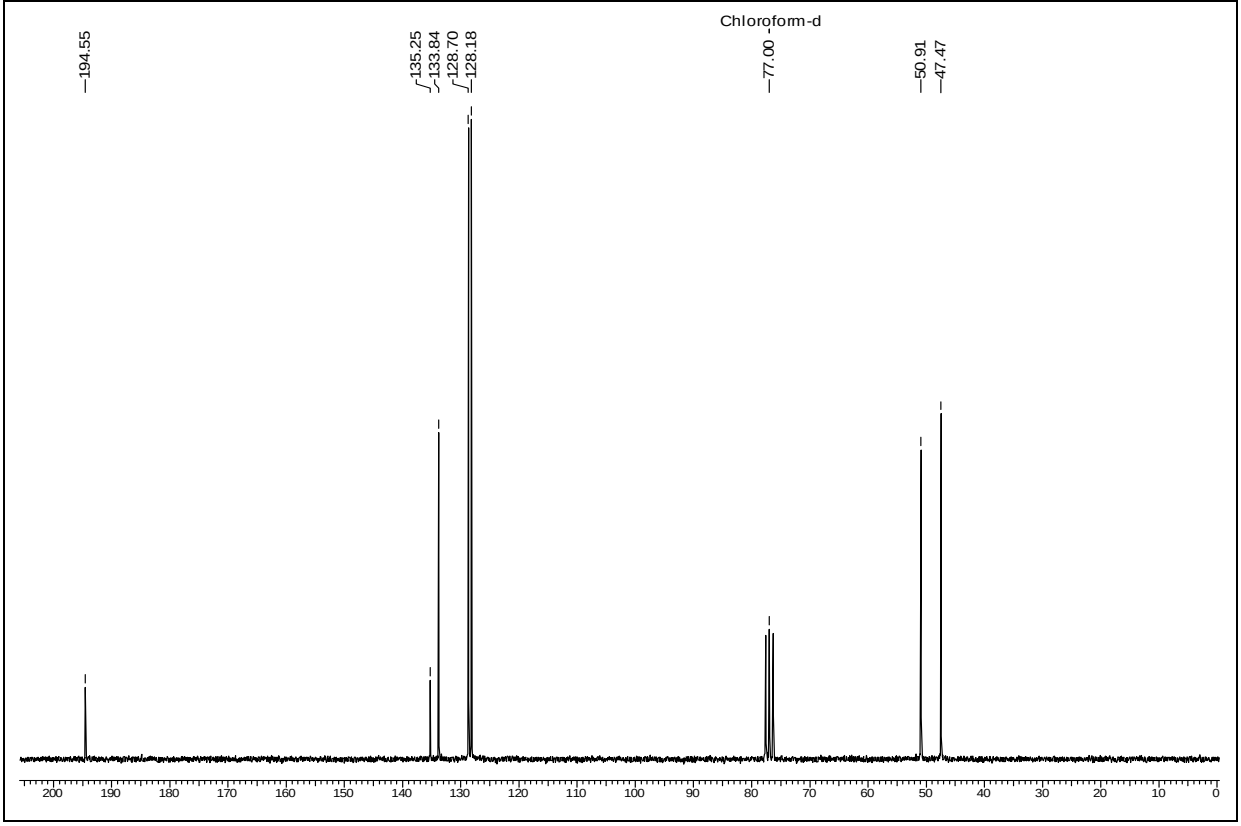
^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of (*S*)-3,4-Bis-(4-methoxyphenyl)-azetidine-2,3-dione



^{1}H NMR ($CDCl_3$, 200 MHz) spectrum of Oxirane-2-yl-(phenyl)methanone



^{13}C NMR ($CDCl_3$, 50 MHz) spectrum of Oxirane-2-yl-(phenyl)methanone



5.2.6. References

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Curriculum Vitae

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B.Sc. (Bachelor of Science) in Chemistry, Zoology, Botany. (First class). (1997-2000)

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Fellowships and Awards

- **2005-2007**: Junior Research Fellowship, Awarded by Council of Scientific and Industrial Research (CSIR), India (www.csir.res.in)
- **2007-2010**: Senior Research Fellowship, Awarded by Council of Scientific and Industrial Research (CSIR), India.

Examinations Qualified

- Qualified examination for Scientist 'B' National level examination Defence Research Development Organisation 2004.

Teaching experience

One and half year experience of teaching to Post graduate students at National Degree college, Barhalgang, Gorakhpur, Uttar Pradesh, India, **(From Sep 2003-Feb 2005)**

Publications

1. DimethylSulfoxide-Pivaloyl Chloride: A new reagent for oxidation of alcohol to carbonyls **Abhishek Dubey**, Subbarao V. Kandula and Pradeep Kumar* *Syn .Comm.* **2008**, *38*, 746-753.

2. A tethered aminohydroxylation route to L-*arabino*-[2*R*,3*S*,4*R*] and L-*xylo*-[2*R*,3*S*,4*S*]-C_{18}-phytosphingosines
Abhishek Dubey and Pradeep Kumar*
Tetrahedron Lett. **2009**, *50*, 3425-3427.

3. Pivaloyl Chloride-Dimethylformamide: A new reagent for conversion of alcohols to chlorides
Abhishek Dubey, Arun K. Upadhyay and Pradeep Kumar*
Tetrahedron Lett. **2010**, *51*, 744-746.

4. Synthesis of (-)-galantinic acid via iterative hydrolytic kinetic resolution and tethered aminohydroxylation
Abhishek Dubey, Shruti V. Kauloorkar and Pradeep Kumar*
Tetrahedron **2010**, *66*, 3159-3164.

5. A general and concise asymmetric synthesis of sphingosine, safingol and phytosphingosines via tethered aminohydroxylation
Abhishek Dubey, Vedavati G. Puranik and Pradeep Kumar*

(*Org. Bio. Chem*. DOI: 10.1039/C0OB00117A**)**

6. An enantioselective synthesis of L-CCG-II, cascarillic acid and grenadamide by using modified Wadsworth-Emmons cyclopropanation
Abhishek Dubey and Pradeep Kumar*
(To be communicated)

7. Iterative asymmetric allylation approach towards the synthesis of (-)-galantinic acid
Abhishek Dubey and Pradeep Kumar*
(To be communicated)

Symposia/Conferences/Workshop attended

1. Participated in CSIR-NSFC Joint Workshop on Organic Chemistry and Chemical Biology: Bridging Bonds for 21st Century, NCL, held at Pune, in **April 2007**.

2. Participated in 4th INSA-KOSEF Symposium in Organic Chemistry, NCL, held at Pune in **Feb 2009**.

Oral Presentation

"**Total Synthesis of Biologically Active Natural Products"** at the *J-NOST* (Junior National Organic Symposium Trust) held at Madurai Kamraj University, Tamilnadu, India in **Dec 2008** organized by National organic symposium trust (NOST) India.