SYNTHESIS OF BIOLOGICALLY ACTIVE COMPOUNDS EMPLOYING PROLINE CATALYSED REACTIONS, ASYMMETRIC DIHYDROXYLATION, AMINOHYDROXYLATION AND JACOBSEN'S HYDROLYTIC KINETIC RESOLUTION

A THESIS SUBMITTED TO THE

UNIVERSITY OF PUNE

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

BY

NAGENDRA B. KONDEKAR

DIVISION OF ORGANIC CHEMISTRY

NATIONAL CHEMICAL LABORATORY

PUNE-411008, INDIA

July 2009

NATIONAL CHEMICAL LABORATORY

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

Dr. Pradeep Kumar
Scientist F, FNASc
Division of Organic Chemistry

Telephone: + 91-20-25902050
Fax: + 91-20-25902629
E-mail: pk.tripathi@ncl.res.in
Website: http://www.ncl-india.org
http://www.ncl.org.in/pktripathi

CERTIFICATE

This is to certify that the work presented in the thesis entitled "**Synthesis of biologically active compounds employing proline catalysed reactions, asymmetric dihydroxylation, aminohydroxylation and Jacobsen's hydrolytic kinetic resolution**" submitted by **Nagendra B. Kondekar** was carried out by the candidate at National Chemical Laboratory, Pune under my supervision. Such materials as obtained from other sources have been duly acknowledged in the thesis.

(Dr. Pradeep Kumar)
Research Guide
Scientist F
Division of Organic Chemistry
National Chemical Laboratory
Pune 411008, INDIA **July 2009**

CANDIDATE'S DECLARATION

I hereby declare that the thesis entitled "**Synthesis of biologically active compounds employing proline catalysed reactions, asymmetric dihydroxylation, aminohydroxylation and Jacobsen's hydrolytic kinetic resolution**" submitted for the degree of Doctor of Philosophy in Chemistry to the University of Pune has not been submitted by me to any other university or Institution. This work was carried out at National Chemical Laboratory, Pune, India.

Nagendra B. Kondekar
Senior Research Fellow
Division of Organic Chemistry
National Chemical Laboratory
Pune-411008, INDIA

July 2009

Dedicated to

Aai, Bhau, Bapu,

Kaku and Mummy

There are those that look at things the way they are, and ask why? I dream of things that never were, and ask why not?

Anonymous

Acknowledgement

Any human accomplishment is the culmination of numerous contributions and endeavors. The present thesis is no exception. I take this opportunity to thank the special people whose kind support was the reason I could complete the task with confidence. It gives me immense pleasure to express my deep sense of gratitude to my research supervisor Dr. Pradeep Kumar for his advice, guidance, support and encouragement during every stage of this work. I do sincerely acknowledge freedom rendered to me by him for independent thinking, planning and executing the research. His endless enthusiasm and receptive attitude will always remain a source of inspiration for me.

My sincere thanks goes to Dr. Ganesh Pandey, Head, Division of Organic Chemistry, for his support and encouragement. I extend my gratitude to Dr. M. K. Gurjar (Former Head, OCT Division), Dr. S. P. Chavan, Dr. U R Kalkote, Dr. C. V. Ramana, Dr. H. V. Thulasiram, Dr. Ramligam and Dr. M. Muthukrishnan for their help during the course of this work.

I would like to thank my teachers Mulla *guruji*, Handrale *guruji*, B. B. Shindalkar *guruji*, Kukale *guruji* from my primary school days. Jadhav A. H and Prince sir from secondary school days and Gurav sir, Vibhute sir, Karde sir, and Kuberkar sir from post graduation days, they have played an important role in making me who I am, and will be guiding lights for all my future endeavors.

Thanks to all my senior colleagues Dr. Rodney Fernandes, Dr. Rajesh Pandey, Dr. Mandar Bodas, Dr. K. V. Subbarao, Dr. Vasu, I have learnt a great deal of chemistry from them and together with their achievements, they have been a source of inspiration to me. I would also like to thank my labmates, Dr. Priti, Dr. Satyendra, Puspesh, Shijo, Abhishek, Divya, Anand, Ankush, Rajesh, Anis, Shinde, Sachin, Partho, Rahul, Krishanu, Kiran, Menaka, Shruti for maintaining a warm and cheerful atmosphere in the lab.

I was always looking forward to lunch at *katta*, thanks to the cheerful company of the *katta* members over the period of time. Similarly no word can express the deep sense of gratitude for the members of the monthly group meeting, they were really interesting and educative.

My stay in NCL has been memorable because of the friends, Dilip, Vijay, Sharad, Tatya, Santosh, Ajay, Dr. Bhusare sir, Swarup, Ashish, Shafi, Aba, Suleman, Manmath, Ravi, Kishor, Mahesh, Kishan, Sudhir, Nilesh, Arun, Deepak, Gorakh, Bapu, Ankush, Bhaskar, Jogdand, Suresh, Kiran, Sachin, Ganesh, Nagesh, G. Sahoo, Smita, Abhijit, Keshriji, Bala, Nishant, Dharmendra, Sunil, Prasanna, ……. the list goes on.

My special thanks go to friends-cum-family Kulbhushan, Vinod, Awadut, Amol, Pandurang, Namdev, Shriram, Ram, Laxman, Nilkanth, Shital (I, II), Archana, Sharda,

Prerna, Pallavi, Manisha, Sonali, Kalpana, Sphurti and for being a strong support and extended family.

I have been fortunate to have friendship with people like Shankar, Hanmant, Dhondu, Santosh, Naresh, Prasad, Bharat, Ajit, and Kamlakar, which has stood the test of time and I am grateful to them for always encouraging me in whatever I choose to do.

I would like to express a deep sense of gratitude for my dear friend late Sachin Kore for always being there for me. His memories will always be with me.

I would specially like to thank Dr. Priti for endlessly correcting drafts of my thesis and Dr. Nilkanth for his valuable suggestions while writing thesis.

It is impossible to express my sense of gratitude for my family, grand mother (aai), uncle (Bhau), father (Bapu), mother (kaku), and aunty (Mummy) in mere words. Whatever I am and whatever I will be in future is because of their enormous blessings, hard work, commitments to my ambitions, and their selfless sacrifices. It was their single minded pursuit of the cause of my education that gave me the strength and will continue to guide my future. Although this eulogy is insufficient, I preserve an everlasting gratitude for them.

Words fall short to thank my brothers Jaiprakash, Mahendra, Surendra, Dhiraj and my sister Ashwani, and my brother-in-law Sachin Kale, sister-in-law Dhanshri and Sujit for their never ending encouragement and support. I wish to thank Priya, my wife, for her love, affection and support extended to me during last one year. She has brought a great deal of happiness to my life.

Help from the spectroscopy and mass groups is gratefully acknowledged. I sincerely thank Dr. Rajmohan, Mr. Sathe and Mrs. Shanta Kumari for their kind co-operation. Support from OCD office staff Catherine madam, Kulkarni madam, Tangaraji, Rannowde and Fernandes is also acknowledged.

I thank Director, National Chemical Laboratory, Pune for providing infrastructural facilities to complete my work successfully. I am also thankful to CSIR, New Delhi for the financial assistance in the form of fellowship. At last but not the least, I thank whole heartedly, the omnipotent God, the illimitable superior spirit, who revels himself in the slight details I am able to perceive with my frail and feeble mind.

Nagendra B Kondekar

Contents

Chapter 1

Introduction to Sharpless asymmetric dihydroxylation, aminohydroxylation, Jacobsen's hydrolytic kinetic resolution and proline catalysed reactions

Chapter 2

Asymmetric aminohydroxylation approach to the syntheses of HIV-protease inhibitor, hydroxyethylene dipeptide isostere and γ-amino acid derivative and synthesis of (*R*) - selegiline *via* hydrolytic kinetic resolution

Chapter 3

Studies towards asymmetric synthesis of (2*R*, 2'*R*)-(+)-Methylphenidate and (2*R*, 2'*R*)-*N*-[Phenyl(piperidin-2-Yl)methyl] benzamide

Chapter 4

An organocatalytic approach to *syn*- and *anti*-1,3-polyols and proline-mediated synthesis of piperidine and indozolidine natural products (*R*)-coiinine and (*S*)-coniceine

4.1 Section A: An organocatalytic approach to *syn*- and *anti*-1,3-polyols and its application to the synthesis of a hydroxy lactone pheromone component

4.2 Section B: Proline-catalysed synthesis of piperidine and indozolidine natural products (*R*)-coiinine and (*S*)-coniceine

Abbreviations

Ac	-	Acetyl
AcOH	-	Acetic acid
Ac_2O	-	Acetic anhydride
Bn	-	Benzyl
BnBr	-	Benzyl bromide
$BH_3 \cdot Me_2S$	-	Boron dimethyl sulfide complex
Boc	-	*tert*-Butoxy carbonyl
$(Boc)_2O$	-	Di-*tert*-butyl dicarbonate
BuLi	-	Butyl lithium
Cat.	-	Catalytic
$CDCl_3$	-	Deuterated chloroform
DBU	-	1,8-Diazabicyclo[5.4.0]undecene-7
DCM	-	Dichloromethane
$(DHQ)_2PHAL$	-	1,4-Bis(dihydroquinin-9-*O*-yl)phthalazine
$(DHQD)_2PHAL$	-	1,4-Bis(dihydroquinindin-9-*O*-l)phthalazine
DDQ	-	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	-	Diisobutylaluminiumhydride
DMP	-	2,2-Dimethoxypropane
DMF	-	*N, N′*-Dimethylformamide
DMAP	-	*N,N′*-Dimethylaminopyridine
DMSO	-	Dimethyl sulfoxide
ee	-	Enantiomeric excess
equiv.	-	Equivalents
EtOH	-	Ethanol
Et	-	Ethyl
Et_2O	-	Diethyl ether
EtOAc	-	Ethyl acetate
Et_3N	-	Triethylamine
Hz	-	Hertz
HPLC	-	High pressure liquid chromatography

IBX	-	Iodoxybenzoic Acid
Im	-	Imidazole
LiHMDS	-	Lithium hexamethyl disilazide
m-CPBA	-	*m*-Chloroperbenzoic acid
MeOH	-	Methanol
mg	-	Milligram
min	-	Minutes
mL	-	Millilitre
mmnol	-	Millimole
M. p.	-	Melting point
Ms	-	Methanesulfonyl
Me	-	Methyl
MeI	-	Methyl iodide
$NaBH_4$	-	Sodiumborohydride
NaH	-	Sodium hydride
Ph	-	Phenyl
Py	-	Pyridine
PMB	-	*para*-Methoxy benzyl
p-TSA	-	*par*a-Toluenesulfonic acid
RCM	-	Ring closing metathesis
TEA	-	Triethylamine
TBAI	-	Tetra-*n*-butylammonium iodide
TBAF	-	Tetra-*n*-butylammonium fluoride
TBDMS	-	*tert*-Butyldimethyl silyl
TBSCl	-	*tert*-Butyldimethyl silyl chloride
THF	-	Tetrahydrofuran
TPP	-	Triphenylphosphine
p-TSA	-	*p*-Toluenesulphonic acid
TsCl	-	*p*-Toluenesulphonyl chloride

- ^{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, ninhydrin and anisaldehyde in ethanol as development reagents.
- All solvents and reagents were purified and dried by according to procedures given in Vogel's Text Book of Practical Organic Chemistry. All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.
- All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 40 °C.
- Silica gel (60–120) used for column chromatography was purchased from ACME Chemical Company, Mumbai, India.
- All melting points and boiling points are uncorrected and the temperatures are in centigrade scale.
- 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 **"Synthesis of biologically active compounds, employing proline catalysed reactions, asymmetric dihydroxylation, aminohydroxylation and Jacobsen's hydrolytic kinetic resolution"** is divided into four chapters.

Chapter 1: Introduction to Sharpless asymmetric dihydroxylation, aminohydroxylation, Jacobsen's hydrolytic kinetic resolution and proline catalysed reactions.

Chapter 2: Asymmetric aminohydroxylation approach to the syntheses of HIV-protease inhibitor, hydroxyethylene dipeptide isostere and γ-amino acid derivative and synthesis of (*R*) - selegiline *via* hydrolytic kinetic resolution.

Chapter 3: Studies towards asymmetric synthesis of (2*R*, 2'*R*)-(+)-methylphenidate and (2*R*, 2'*R*)-*N*-[phenyl(piperidin-2-yl)methyl] benzamide.

Chapter 4: An organocatalytic approach to *syn*- and *anti*-1,3-polyols and proline-catalysed synthesis of piperidine and indozolidine natural products (*R*)-coiinine and (*S*)-coniceine.

Chapter 1: Introduction to Sharpless asymmetric dihydroxylation, aminohydroxylation, Jacobsen's hydrolytic kinetic resolution and proline catalysed reactions

This chapter gives a brief introduction to proline catalysed reactions[1,2] Sharpless asymmetric dihydroxylation (AD),[3] asymmetric aminohydroxylation (AA)[4] and Jacobsen's hydrolytic kinetic resolution (HKR).[5]

The field of asymmetric organocatalysis is rapidly developing and attracts an increasing number of research groups around the world. In particular, organocatalytic asymmetric synthesis have provided several new methods for obtaining chiral compounds.[1] In this connection, proline, an abundant, inexpensive amino acid available in both enantiomeric forms, has emerged as arguably the most practical and versatile organocatalyst.[1,2] Proline has also been found to be an excellent asymmetric catalyst for α-functionalization[6,7] of carbonyl 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 aminodihydroxylation (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.

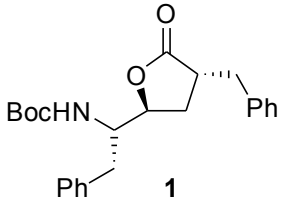
These methods have contributed to more advances in research not only in chemistry but also in material science, biology and medicine. This work gives access to new molecules needed to investigate hitherto undiscovered and unexplained phenomena in the molecular world.

In this chapter, we have described aforementioned catalytic reactions. During the course of our research work we have prepared chiral diols, amino alcohols and epoxides and successfully employed these synthetic intermediate towards the synthesis of (*R*)- selegiline, HIV-protease inhibitor, hydroxyethylene dipeptide isostere and *γ*-amino acid derivative, (2*R*, 2'*R*)-(+)-methylphenidate and *N*-[phenyl(piperidin-2-yl)methyl] benzamide, 1,3-polyols, (*S*)-5-((*S*)-2-hydroxyhexyl)-dihydrofuran-2(3*H*)-one, (*R*)– coiinine, (*S*)-coniceine.

<u>Chapter 2</u>: Asymmetric aminohydroxylation approach to the syntheses of HIV-protease inhibitor, hydroxyethylene dipeptide isostere and γ-amino acid derivative and synthesis of (*R*) - selegiline *via* hydrolytic kinetic resolution.

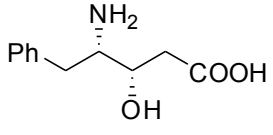
This chapter is further divided into two sections.

<u>Section A:</u> Asymmetric aminohydroxylation approach to the syntheses of HIV-protease inhibitor, hydroxyethylene dipeptide isostere and γ-amino acid derivative.



1

Hydroxyethylene dipeptide isostere

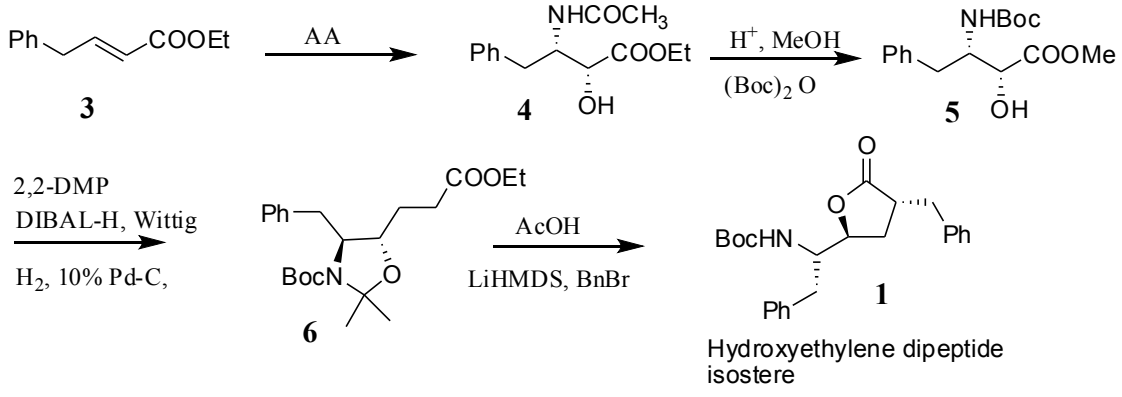


2

AHPPA

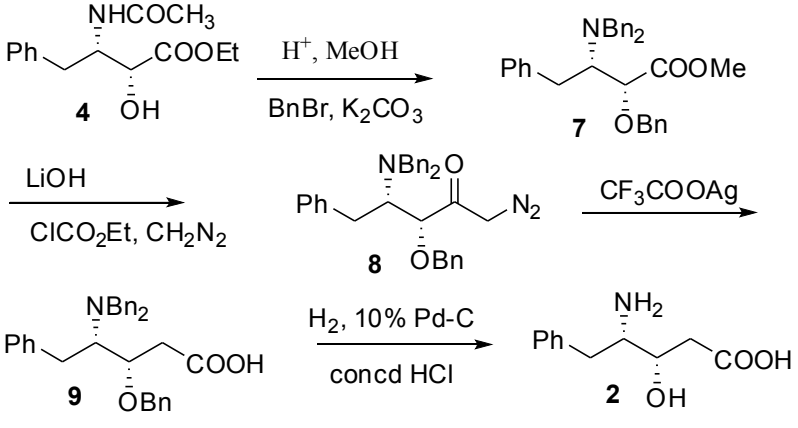
The advent of acquired immunodeficiency syndrome (AIDS) and the discovery of its causative agent, human immunodeficiency virus (HIV-1),[8] has given an impetus to the

development of efficient inhibitors of viral enzymes, in particular of the transcriptase and more recently of the proteinase (HIV-PR).[9] We have successfully accomplished the synthesis of hydroxyethylene dipeptide isostere using Sharpless asymmetric aminohydroxylation as the key step.



Scheme 1: Asymmetric synthesis of hydroxyethylene dipeptide isostere

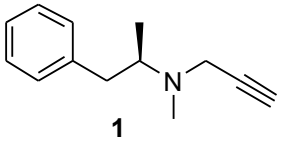
As illustrated in Scheme 1, the asymmetric aminohydroxylation of olefin **3** afforded the desired amino alcohol **4** which was subjected to hydrolysis to furnish the free amine with concomitant transesterification to the methyl ester. The successive conversion of amine into the Boc protected amino alcohol **5** followed by the acetonide protection, DIBAL-H reduction, Wittig reaction and hydrogenation gave compound **6**. Compound **6** on acetonide deprotection under acidic conditions underwent smooth cyclisation to give the lactone, which was alkylated with benzyl bromide using LiHMDS as a base to furnish the target compound **1**.



Scheme 2: Synthesis of (3*S*, 4*S*)-4-amino-3-hydroxy-5-phenylpentanoic acid (AHPPA)

Scheme 2 summarizes the synthesis of (3*S*, 4*S*)-4-amino-3-hydroxy-5-phenylpentanoic acid (AHPPA) from the common intermediate **4**. The cleavage of the *N*-acetyl group of **4** with concomitant transesterification and subsequent *N*- and *O*-benzylation afforded compound **7**. Base hydrolysis of the ester **7** furnished acid which was converted into mixed anhydride followed by reaction with diazomethane to give compound **8**. Wolff rearrangement furnished the acid **9** which on subsequent debenzylation and acid treatment furnished the target compound **2**.

<u>Section B:</u> Synthesis of (*R*)- selegiline *via* hydrolytic kinetic resolution

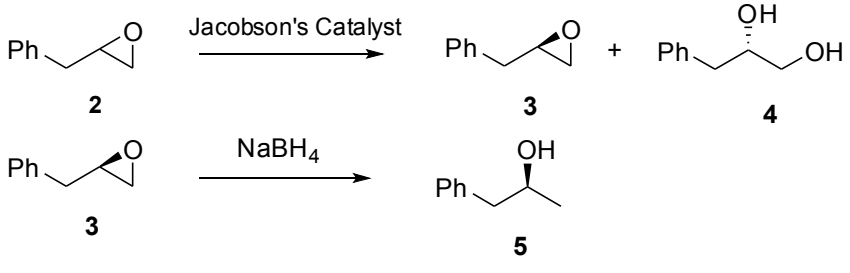


1

(*R*)-Selegiline

Selegiline also known as 1-deprenyl is an irreversible and selective monoamino oxidase- B (MAO-B) inhibitor and is administered alone or together with L-DOPA for the treatement of Parkinson's syndrome and Alzheimer's disease.[10] Subsequent studies have shown that (*R*)-selegiline **1** is more effective towards the treatment of Parkinson's disease as well as Alzheimer's disease when compared to racemic selegiline.[11]

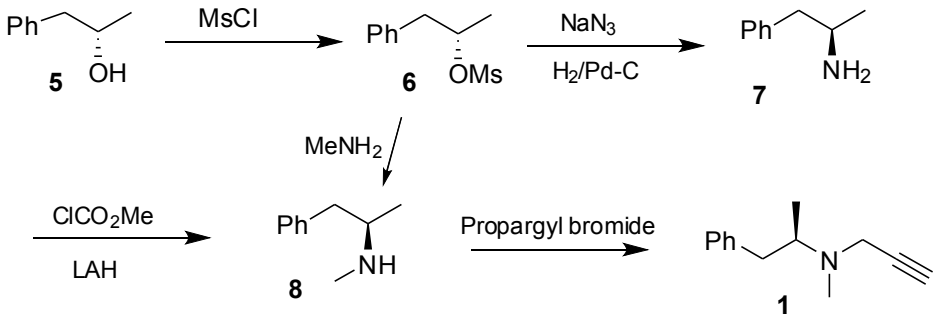
We have accomplished the asymmetric synthesis of (*R*)-selegiline using Jacobsen's HKR as a key step. Thus 2-benzyl oxirane **2** was subjected to Jacobsen's HKR using (*R, R*) - salen- Co^{III}-(OAc) complex (0.5 mol %) and distilled water (0.55 equiv) to afford (*R*)-2-benzyl oxirane **3** as a single enantiomer. Regioselective opening of **3** with sodium borohydride furnished alcohol **5** in quantitative yield (Scheme 1).



Scheme 1: Synthesis of alcohol **5**

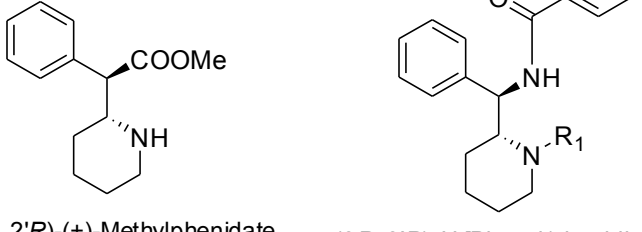
Alcohol **5** was subjected to mesylation followed by treatment with sodium azide and 10% Pd-C under hydrogenation atmosphere to give amine **7** which was monomethylated to

furnish compound **8**. Alternatively the compound **8** can be directly obtained from mesylate **6** by direct nucleophilic displacement of *O*-mesylate by methyl amine group. Finally amine **8** was converted to (*R*)-selegiline **1** using propargyl bromide and K_2CO_3.



Scheme 2: Synthesis of (*R*)-selegiline

<u>Chapter 3</u>: Studies towards asymmetric synthesis of (2*R*, 2'*R*)-(+)-methylphenidate and (2*R*, 2'*R*)-*N*-[phenyl(piperidin-2-yl)methyl] benzamide.

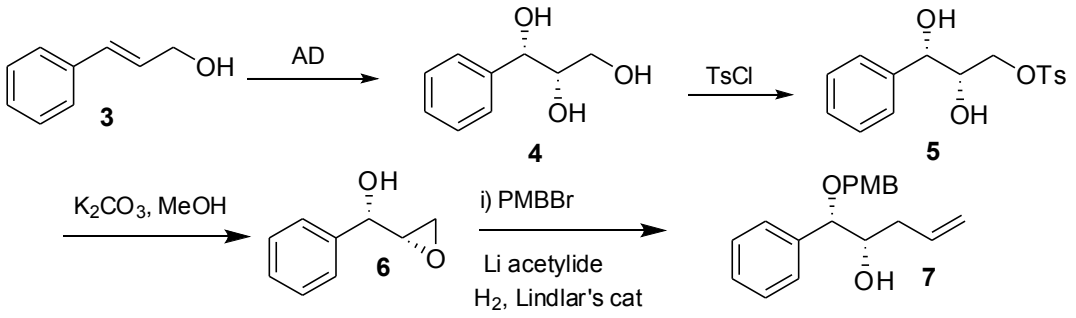


(2*R*, 2'*R*)-(+)-Methylphenidate **1**

(2*R*, 2'*R*)-*N*-[Phenyl(piperidin-2-yl) methyl] benzamide **2**

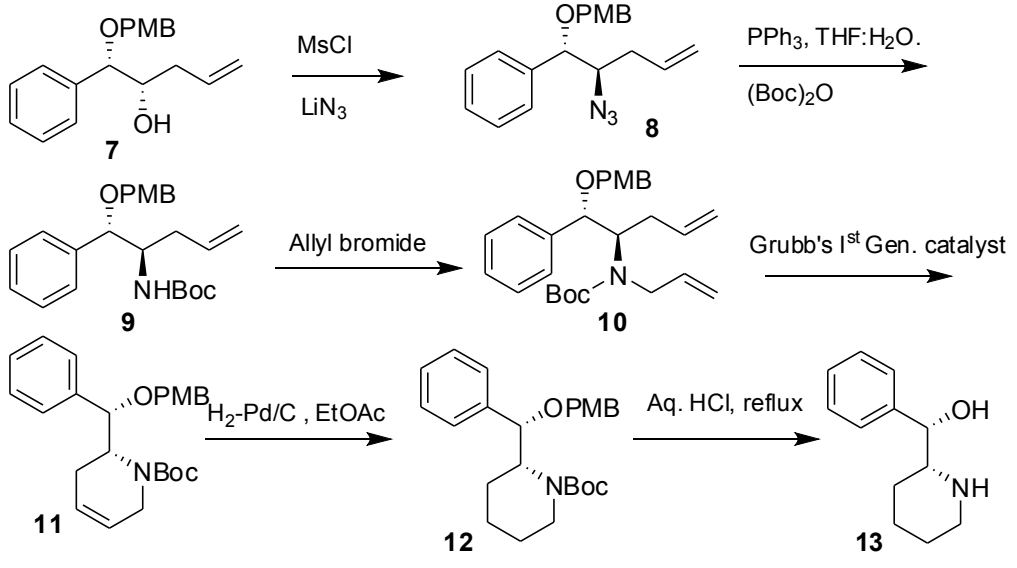
Methylphenidate (methyl 2-phenyl-2-(2'-piperidyl)-acetate)) **1** is commonly prescribed stimulant used in the treatment of attention deficit hyperactivity disorder (ADHD) in children and used for the treatment of narcolepsy and depression in adults.[12,13] In addition, *in vivo* and *in vitro* studies have determined that the pharmacological activity resides mainly in the D-*threo* enantiomer.[14]

Compounds having general structure as **2** are analgesics, diurectics, anticonvulsants, sedatives, cerebroprotective by mechanism of action on opiate receptors.[15]



Scheme 1: Synthesis of homoallyl alcohol

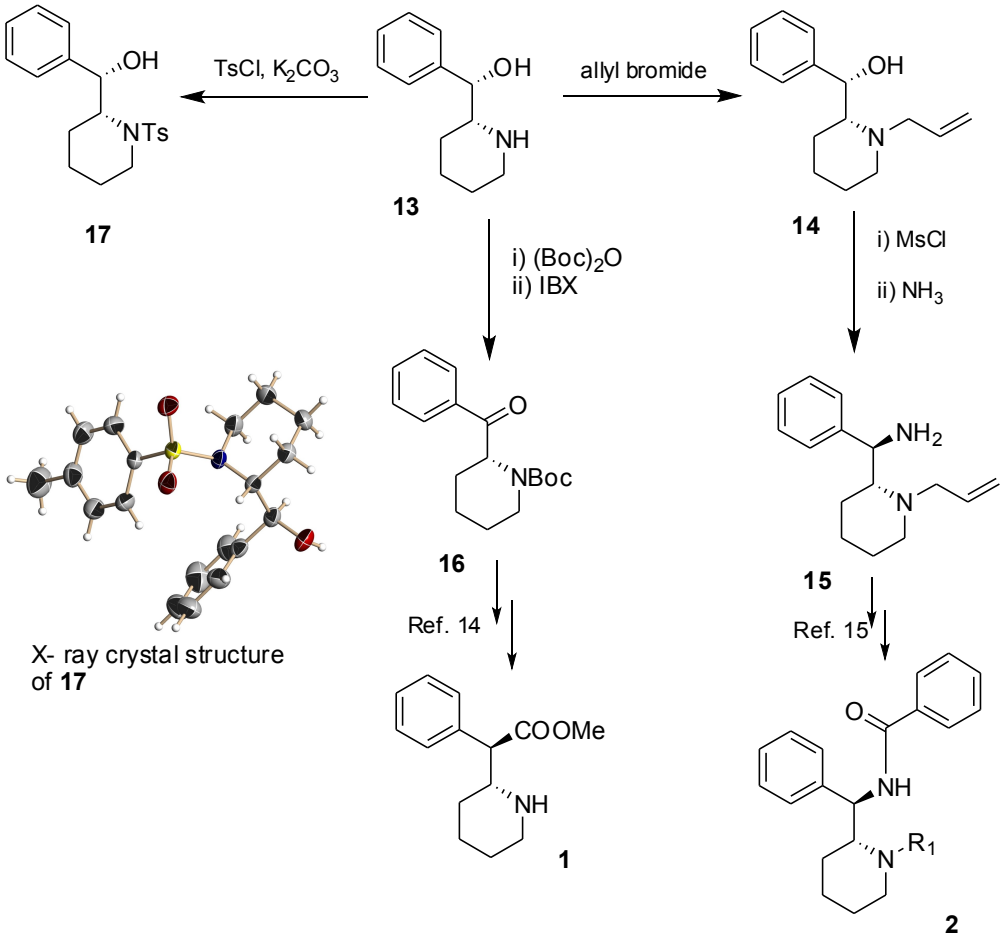
We have completed formal synthesis of these compounds using AD as the key step. As depicted in Scheme 1, the AD of cinnmoyl alcohol **3** furnished triol **4** which was mono tosylated and treated with base to give epoxide **6**. The free hydroxy group was then protected as PMB ether followed by epoxide opening with lithium acetylide, and partial reduction to furnish the homoallylic alcohol **7**. Alcohol **7** was treated with methane sulfonyl chloride, LiN_3 to furnish azide **8** (Scheme 2), which under Staudinger conditions was



Scheme 2: Synthesis of amino alcohol

converted to amine and *in situ* protected as carbamate using Boc anhydride to furnish compound **9.** Finally the *N*-allylation of the amide followed by ring closing metathesis afforded piperidine compound **11**, which on double bond reduction and global deprotection using aq. HCl furnished the free amino alcohol **13** (Scheme 2).

To confirm the stereochemistry, compound **13** was converted to monotosyl alcohol **17** which was obtained as crystalline solid and single X-ray crystal clearly established the structure of the compound. The relative stereochemistry of the amino alcohol was found to be *trans*. Boc protection of **13** followed by IBX oxidation afforded ketone **16** which can be converted to the target compound **1** by known procedure.[14] Similarly the *N*-alkylated amino alcohol **14** which was obtained by selective alkylation of **13**, can be converted to the compound **2** by the known procedure[15] (Scheme 3).



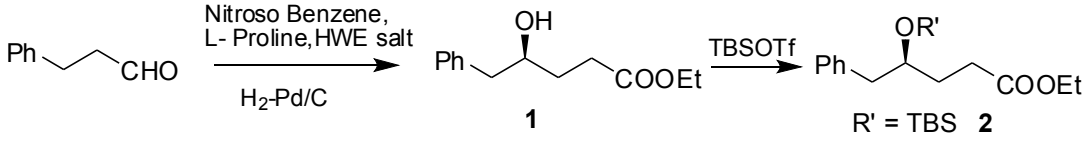
Scheme 3: Formal synthesis of (2*R*, 2'*R*)-(+)-methylphenidate and (2*R*, 2'*R*)-*N*-[phenyl(piperidin-2-yl)methyl] benzamide

Chapter 4: An organocatalytic approach to *syn*- and *anti* - 1,3-polyols and proline-catalysed synthesis of piperidine and indozolidine natural products (*R*)-coiinine and (*S*)-coniceine

This chapter is further divided into two sections**.**

Section A: Organocatalytic approach to *syn*- and *anti*-1, 3-polyols and its application to the synthesis of a hydroxy lactone pheromone component.

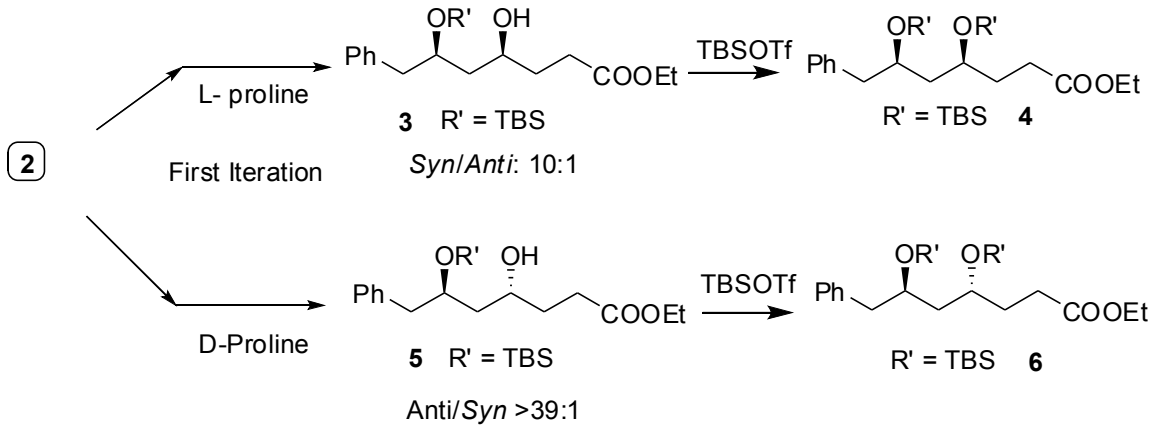
Proline has been found to be an excellent asymmetric catalyst for α-functionalization[6,7] of carbonyl compounds. Recently, Zhong *et. al.*[16] have reported the sequential aminoxylation-olefination reactions of aldehydes to generate protected allylic alcohols in high enantiomeric excess. We have devised a general iterative strategy for the synthesis of 1,3-*syn*/*anti*- polyols using Zhong's sequential aminoxylation, HWE olefination reaction. One cycle of iteration consists of four steps namely ester reduction to aldehyde, sequential aminoxylation, HWE olefination, reductive hydrogenation and protection of the resultant alcohol. This strategy is easily extendable for the synthesis of 1,3,5-polyols as shown by the representative synthesis of 1,3,5-*syn*/*syn* polyol.



Scheme 1: Synthesis of γ- hydroxy ester **1**

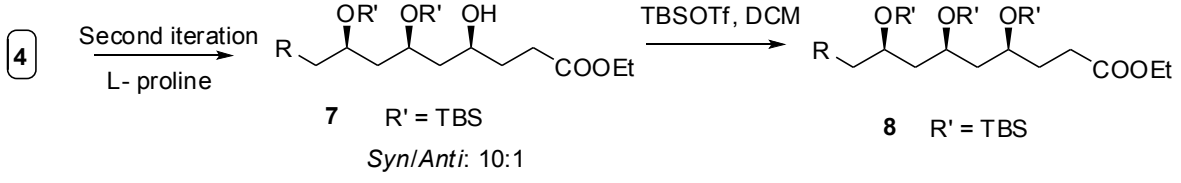
Thus, 3-phenylpropanal was subjected to α-aminoxylation with nitrosobenzene and L-proline followed by *in situ* Horner-Wadsworth-Emmons (HWE) olefination to furnish the aminoxy-olefinic ester which under hydrogenation conditions yielded γ-hydroxy ester **1** (Scheme 1).

The free hydroxy group of **1** was then protected as TBS ether followed by ester reduction to furnish aldehyde which was subjected again to the same three step iteration cycle to give the diol **3**. Depending upon the catalyst used (L/D)-proline in each iteration we have synthesized both (s*yn*/*anti*) diol **3** and **5** (Scheme 2).



Scheme 2: Iterative strategy for the synthesis of polyols

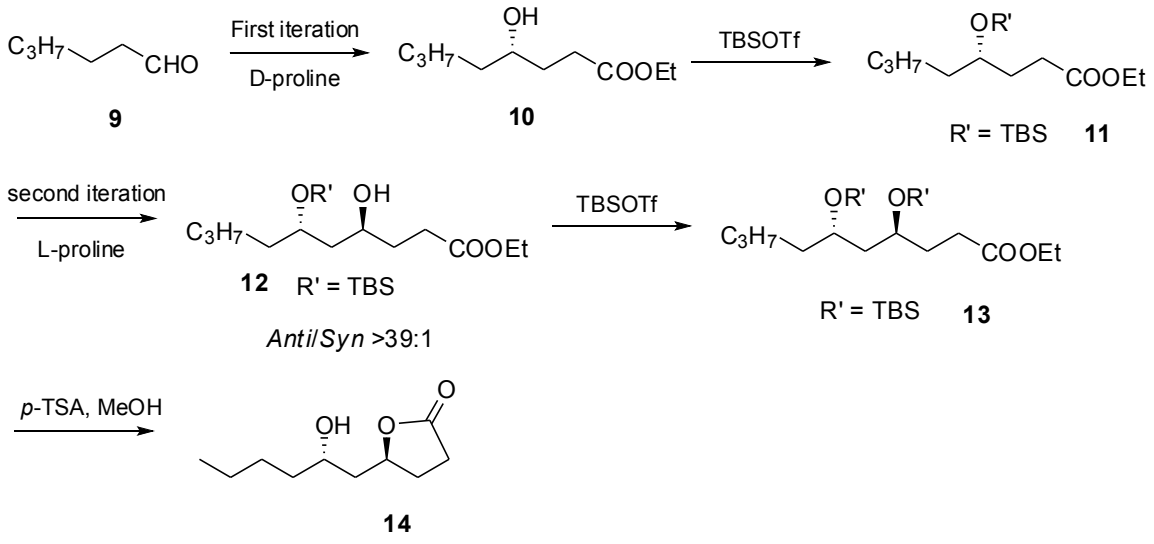
To illustrate the feasibility of synthesizing 1,3,5-polyol in this way *syn* diol **4** was subjected to second cycle of iteration to furnish 1,3,5-*syn*-/*syn*- triol as anticipated (Scheme 3).



Scheme 3: Stereoselective synthesis of triol derivative by second cycle of iteration

Prompted by the above findings, we embarked upon the total synthesis of (*S*)-3-((*S*)-2-hydroxyhexyl)dihydrofuran-2(3*H*)-one **14**, representative of 6-hydroxyalkan-4-olides, hydroxy lactones with chain lengths between 10 and 13 carbon atoms, which are part of the complex mixture of compounds that giant white butterfly *Idea leuconoe* hairpencils release as a pheromone.

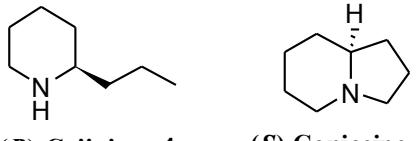
As depicted in Scheme 4, the commercially available hexanal **9** was subjected to aminoxylation, HWE olefination and reductive hydrogenation to furnish γ-hydroxy ester **10**, the free hydroxy group was then protected as TBS ether to give **11**. Compound **11** on reduction furnished aldehyde, which on first cycle of iteration using L-proline as a catalyst, afforded *anti*-diol **12**, which was further treated with TBSOTf to give TBS ether **13**. Finally silyl deprotection and lactonisation under acidic conditions gave the desired lactone **14**.



Scheme 4: Synthesis of (*S*)-3-((*S*)-2-hydroxyhexyl)dihydrofuran-2(3*H*)-one **14**

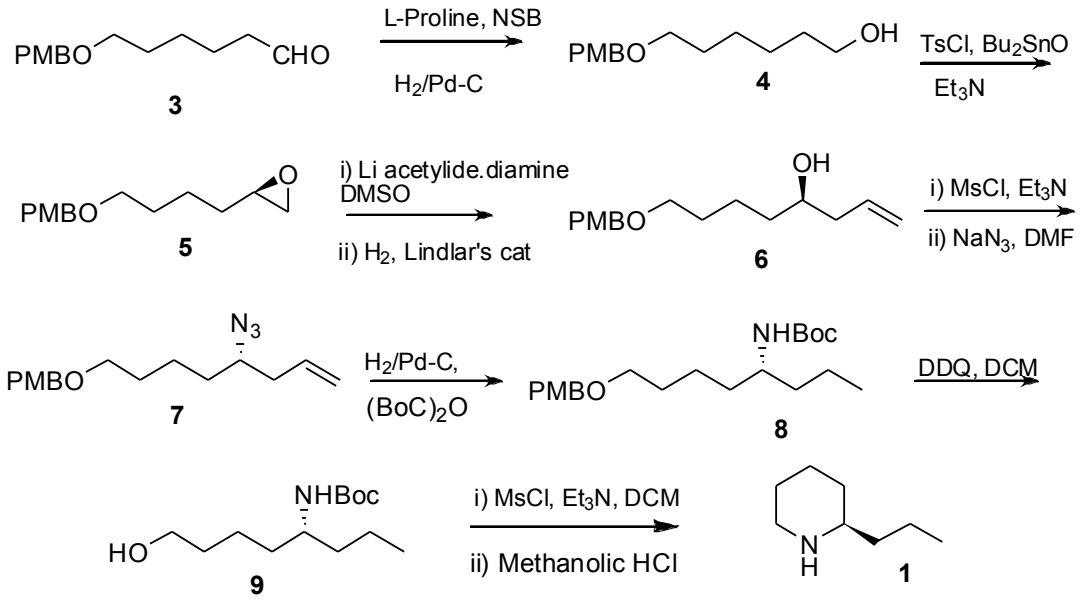
<u>Section B:</u> Proline-catalysed synthesis of piperidine and indozolidine natural products (*R*)-coiinine and (*S*)-coniceine.

The development of methods for the asymmetric synthesis of pyrrolidines, piperidines and ring-fused derivatives such as indolizidines remains an area of current interest due to the presence of such saturated heterocyclic rings in a large range of biologically important compounds. Almost invariably, these bioactive compounds, and in particular the naturally occurring derivatives, contain an asymmetric centre adjacent to the ring nitrogen atom.
We have developed a common route to the synthesis of both (*R*)-coiinine and (*S*)-coniceine as a simple representatives of the piperidine and indozolidine alkaloids respectively.



(*R*)-Coiinine 1 **(*S*)-Coniceine 2**

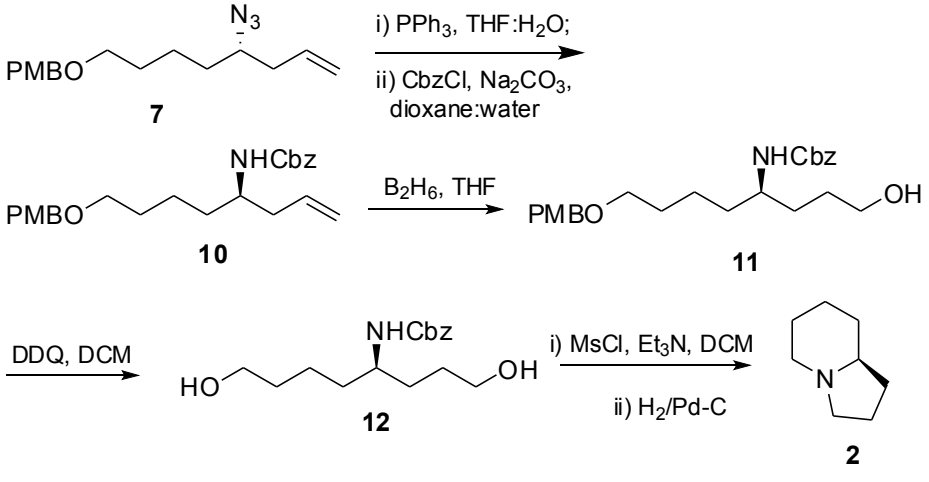
The synthesis of **1** started with aldehyde **3**, which on aminoxylation, $NaBH_4$ reduction and reductive hydrogenation gave the diol **4** which was monotosylated and treated with base to give the epoxide **5**. Epoxide **5** on opening with lithium acetylide and partial reduction gave the alcohol **6**. Alcohol was then treated sequentially with MsCl, sodium azide to give azide **7** which was converted into amine and *in situ* protected as ^{t}butyl carbamate **8**. Finally PMB deprotection, mesylation and base treatement afforded the target molecule **1** (Scheme 1).



Scheme 1: Synthesis of (*R*)-coiinine

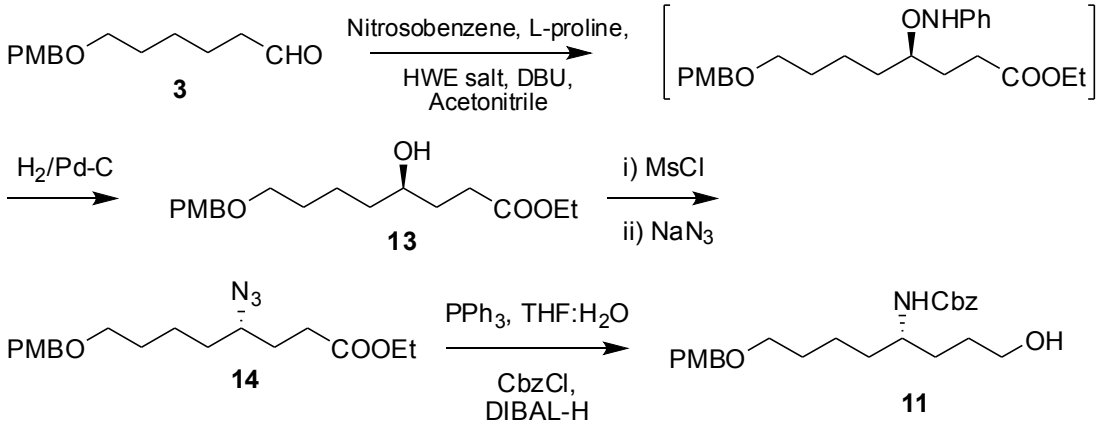
Similarly the synthesis of (*S*)-coniceine was achieved from azide **7**. The homoallylic azide **7** was subjected to Staudinger reaction and converted into amine which on Cbz protection, hydroboration–oxidation reaction, PMB deprotection furnished diol **12**. Mesylation of diol **12** with MsCl, concomitant deprotection of Cbz and nucleophilic displacement of OMs on hydrogenation with H_2/Pd-C led to the target compound **2** (Scheme 2).

Alternatively, in order to reduce the overall number of steps for the synthesis of (*S*)-coniceine **2**, compound **11** can be easily prepared form γ-hydroxy esters **13**. Thus sequential α-aminoxylation and HWE olefination of aldehyde **3** and subsequent reduction



Scheme 2: Synthesis of (*S*)-coniceine

of the obtained *O*-amine substituted ester furnished γ-hydroxy ester **13**. The free hydroxy group of **13** on mesyl protection and azide displacement gave azide ester **14**. Azide **14** was subjected to Staudinger reaction and converted into amine which on Cbz protection and subsequent DIBAL-H reduction gave compound **11** in good yield.



Scheme 12. Alternate synthesis of amino alcohol **11**.

1.4 References

1. Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed*. **2001**, *40*, 3726; (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed*. **2004***, 43*, 5138; (c) Houk, K. N.; List, B., Eds.; *Acc. Chem. Res*. **2004**, *37*, 8; (d) List, B.; Bolm, C., Eds.; *Adv. Synth. Catal*. **2004**, 346; (e) *Asymmetric Organocatalysis*; Berkessel, A., Gröger, H., Eds.; Wiley-VCH: Weinheim, **2005**; (f) List, B., Seayad, J. *Org. Biomol. Chem*. **2005**, *3*, 719.
2. For a review on proline-catalyzed asymmetric reactions see: List, B. *Tetrahedron* **2002**, *58*, 5573.
3. (a) Becker, H.; Sharpless, K. B. *Angew Chem*., *Int. Ed*. **1996**, *35*, 448; (b) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem*. *Rev*. **1994**, *94*, 2483.
4. (a) Becker, H.; Sharpless, K. B. *Angew Chem*., *Int. Ed*. **1996**, *35*, 448.
5. (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936; (b) Schaus, S. E.; Branalt, J.; Jacobson, E. N. *J. Org. Chem.* **1998**, *63*, 4876; (c) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal*. 2**001**, *343*, 5; (d) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307.
6. (a) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett*. **2003**, *44*, 8293; (b) Zhong, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4247; (c) Hayashi, Y.;

Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2003**, *43*, 1112; (d) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2003**, *125*, 10808; (e) Cordova, A.; Sunden, H.; Bøgevig, A.; Johansson, M.; Himo, F. *Chem. Eur. J*. **2004**, *10*, 3673.

7. (a) List, B. *J. Am. Chem. Soc*. **2002**, *125*, 5656; (b) Bogevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W., Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1790; (c) Kumaragurubaran, N.; Juhl, K.; Zhuang, W., Bogevig, A.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 6254; (d) Vogt, H.; Anderheiden, S.; Brase, S. *Chem. Commun.* **2003**, 2448; (e) Iwamura, H.; Mathew, S. P.; Blackmond, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 11770.
8. (a) Barre-Sinoussi, F.; Chermann, J. C.; Rey, F.; Nugeyre, M. T.; Chamaret, S.; Gruest, J.; Dauguet,C.; Axler-Blin, C.; Vezinet-Brun, F.; Rouzioux, C.; Rozenbaum, W.; Montagnier, L. *Science* **1983**, *220*, 868; (b) Gallo, R. C.; Salahuddin, S. Z.; Popovic, M.; Shearer, M.; Kaplan, M.; Haynes, B. F.; Palker, T. J.; Redfield, R.; Oleske, J.; Safai, B.;White, G.; Foster, P.; Markham, P. D. *Science* **1984**, *224*, 500.
9. (a) Gait, M. J.; Karn, *J. Tibtech*. **1995**, 13, 430; (b) Wiodawer, A.; Erickson, J. W. *Ann. Rev. Biochem*. **1993**, 62, 543; (c) Volker, E. J. *J. Chem. Educ*. **1993**, *70*, 3; (d) Kempf, D. J.; Sham, S. L. *Curr. Pharm. Des*. **1996**, *2*, 225.
10. (a) Mizutta, I.; Ohta, M.; Ohta, K.; Nishimura, M.; Mizutta, E.; Hayashi, K.; Kuna, S. *Biochem*. *Biophys. Res. Commun*. **2000**, *279*, 751; (b) Vaglini, F.; Pardini, C.; Cavalletti, M.; Maggio, R.; Corsini, G. U. *Brain Res*. **1996**, *741*, 68.
11. (a) Abu-Raya, S.; Blaugrund, E.; Trembovler, V.; Shilderman-Bloch, E.; Shohami, E.; Lazarovici, P. A. *J. Neurosci. Res*. **1999**, *58*, 456; (b) Paterson, I. A.; Tatton, W. G. *Adv. Pharmacol*. **1998**, *42*, 312.
12. Klein, R. G. *Arch. Gen. Psychiatry* **1995**, *52*, 429.
13. Barkley, R. A. *J. Child Psychol. Psychiatry* **1977**, *18*, 137.
14. Thai, D. L.; Sapko, M. T.; Reiter, C. T.; Bierer, D. E.; Parel, J. M. *J. Med. Chem*. **1998**, *41*, 591.
15. Dargazanil *et al*.US Patent 7205319 B2.
16. Zhong, G.;. Yu, Y.; *Org. Lett*. **2004**, *6*, 1637.

Chapter-1

Introduction to Sharpless asymmetric dihydroxylation, aminohydroxylation, Jacobsen's hydrolytic kinetic resolution and proline catalysed reactions

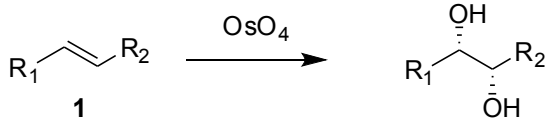
1.1. ASYMMETRIC DIHYDROXYLATION (AD)

1.1.1. Introduction

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

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

The osmium tetroxide-catalyzed asymmetric dihydroxylation (AD) of olefins, embedding two hydroxyl groups in a hydrocarbon framework is perhaps one of the most reliable and selective transformations in organic chemistry.



1 **2**

Scheme 1: Dihydroxylation of olefin

A series of discoveries[5] gave a best reaction condition for dihydroxylation to be a biphasic reaction carried out in 1:1 mixture of water: *t*-BuOH, using catalytic OsO_4, and

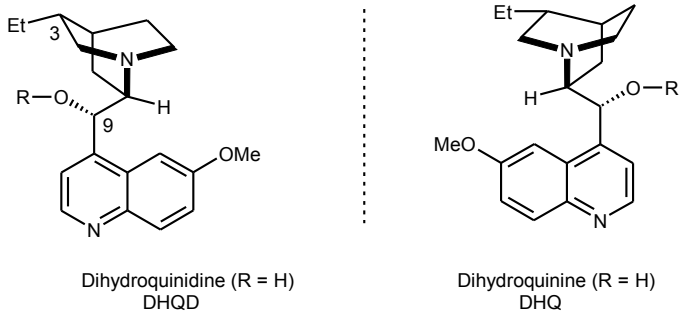


Figure 1. Cinchona Alkaloid Ligands for AD under Catalytic Conditions.[13,16]

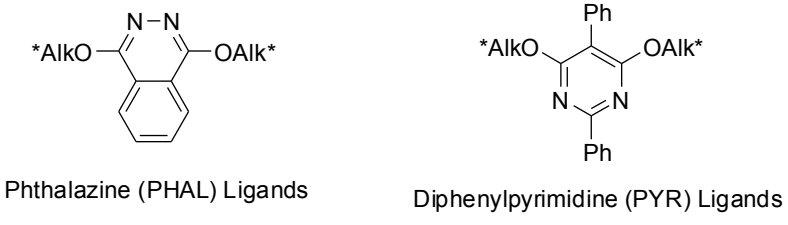


Figure 2. The latest generation of "dimeric" PHAL and PYR ligands

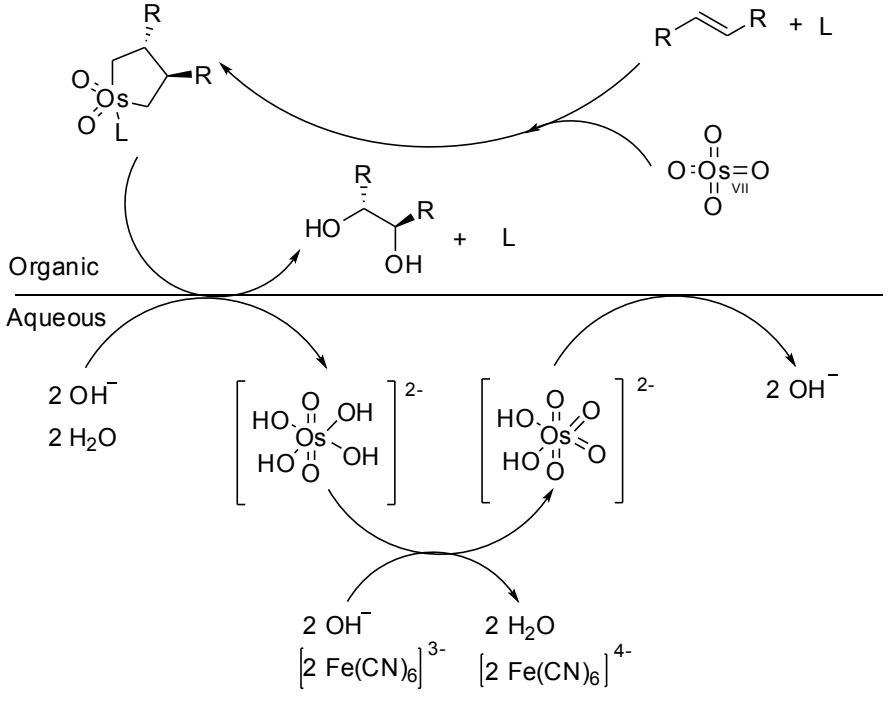
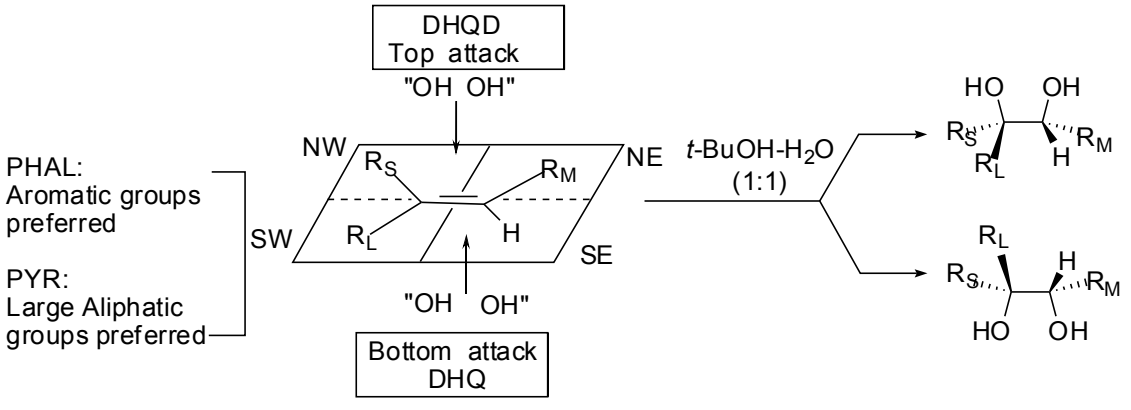


Figure 3. Catalytic cycle of the AD reaction with $K_3Fe(CN)_6$ as the Co-oxidant

$K_3Fe(CN)_6$ as the stoichiometric re-oxidant along with K_2CO_3, methane sulfonamide. In the presence of "dimeric" PHAL or PYR ligands.

1.1.2. Empirical rules for predicting the face selectivity

The face selectivity of the dihydroxylation can reliably be predicted using an empirical 'mnemonic device' (Scheme 2).[8] The plane of the olefin is divided into the four quadrants according to a simple set of rules. The SE quadrant is sterically inaccessible and, with few exceptions, no substituent other than hydrogen can be placed here. The NW quadrant, lying diagonally across from the SE quadrant, is slightly more open and the NE quadrant appears to be quite spacious. The SW quadrant is special in that its preferences are ligand dependent. Even though this SW quadrant normally accepts the largest group, especially in the case of PYR ligands, it is especially attractive for aromatic groups in the case of PHAL ligands.[8c] An olefin which is placed according to the above constraints receives the two OH groups from above, i.e. from the β-face, in the case of DHQD derived ligands and from the bottom, i.e. from the α-face, in the case of DHQ derivatives (Scheme 2).



Scheme 2. The mnemonic device for predicting the face selectivity

1.1.3. Reaction Conditions

The catalytic asymmetric dihydroxylation is performed in a 1:1 mixture of water and *t*-BuOH and the olefin concentration is usually 0.1 M.[9] The key reagents are 3 equivalents of $K_3Fe(CN)_6$ as the re-oxidant, 0.2-0.4 mol% osmium, 1 mol% of ligand, 3 equivalents of K_2CO_3 and 1 equivalent of $CH_3SO_2NH_2$. Additionally, the ligand can be recovered especially when large scale reactions are carried out. For PHAL ligand, the combined

organic layers are extracted with 3% aq. H_2SO_4 satuarated with K_2SO_4 (ca. 40 mL/1g of ligand). The ligand enters the aqueous phase as the hydrogen sulphate salt and the solution can be reused directly for the subsequent AD reaction without further purification. However, the amount of K_2CO_3 in the subsequent reaction should be increased in order to neutralize excess H_2SO_4 and also to release the ligand salt as its free base, and the volume of aqueous ligand solution added to the reaction mixture.

1.1.4. The cinchona alkaloid ligands and their substrate preferences

Phthalazine (PHAL) ligands

Due to the ready availability of second generation ligands i.e. PHAL[10] (Phthalazine) ligands are widely used and this ligand class reacts especially when aromatic groups are present, and remarkably high enantioselectivities were observed when the aromatic substituents appear in certain optimal locations[11] like in *trans*-stilbene for which the enantioselectivity is as high as 99.8%.[12] However, PHAL ligands give inferior results with aliphatic olefins, especially if they are branched near the double bond or if they have very small substituents.

Anthraquinone (AQN) ligands

The anthraquinone ligands are well suited for almost all olefins having aliphatic substituents[13] and diols derived from allyl halides or allyl alcohols can be obtained with satisfactory enantiomeric purity, thereby giving access to valuable chiral building blocks. The AQN derivatives are the ligands of choice for the AD reaction, except for olefins with aromatic or sterically demanding substituents.

Pyrimidine (PYR) ligands

The pyrimidine ligands are the ligands of choice for olefins with sterically demanding substituents.[14]

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

These ligands give improved enantioselectivities for almost all olefins except for terminal alkyl olefins which are better served by the AQN or PYR ligands.[15] The DPP ligand is normally slightly superior to the DP-PHAL ligand. The DPP derivatives are the optimal ligands for aromatic olefins and for certain *cis*-1,2-disubstituted olefins.

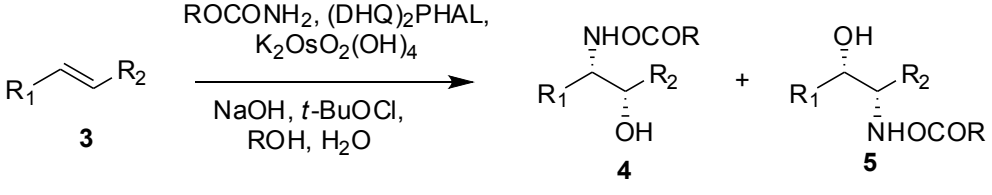
Indoline (IND) ligands

Cis-1,2-disubstituted olefins generally are poor substrates for the AD reaction and the IND derivatives are normally the ligands of choice.[16] However, in certain cases better results are obtained with the new second generation ligands.[17]

1.2. ASYMMETRIC AMINOHYDROXYLATION (AA)

1.2.1. Introduction

Asymmetric aminohydroxylation[6a] is very versatile as it facilitates a single step introduction of two functional groups viz amino (protected) and hydroxy group, from a wide range of simple alkene starting materials. The significance of this invention was immediately apparent to many researchers[18] as the AA reaction provides straightforward access to the amino alcohol array and in a wide variety of biologically active agents and natural products.[19] As a result, the reaction rapidly gained the prominence of its forerunners, the AE and AD processes. The reaction typified by the conversion shown in Scheme 3, 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 **3** to form amino alcohol products such as **4** or **5** (Scheme 3). Alternatively, the 1,4-bis-(9-*O*-dihydroquinidinyl)-phthalazine [$(DHQD)_2PHAL$] ligand directs addition to the β-face of **3**.



Scheme 3. Sharpless asymmetric aminohydroxylation

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 **3** (R1≠R2) can, in principle, give rise to two regioisomeric amino alcohol products **4** and **5**. In many cases, the conditions or the aromatic linker of the chiral ligand, for example phthalazine (PHAL) or anthraquinone (AQN), strongly influence the regioselectivity of the reaction.[20]

1.2.2 Mechanism

The proposed mechanism for the asymmetric aminohydroxylation is closely based on mechanistic studies of its forerunner, the AD reaction. The mechanism is [3+2] cycloaddition of ligand-bound complex **6** 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 **7**. Based on these results, a mechanistic scheme has been proposed in which two catalytic cycles, give different results for selectivity of the transformation (Figure 4). The primary cycle is mediated by the alkaloid derived ligand and in all but one of the AA methods reported to date,[21] the ligand is observed to improve catalytic turnover relative to the non-ligand-mediated reaction. Ligand mediated addition of imidotrioxoosmium(VIII) species **6** to the alkene gives azaglycolate species **7**. Reoxidation of **7** by the nitrogen source gives **8**, which can undergo hydrolysis to regenerate the initial osmium species and liberate product. The oxidized azaglycolate species **8** may also enter the secondary cycle and add to a second alkene to give the bis(azaglycolate)osmium species **9**. The addition step of this cycle is independent of the *Cinchona* alkaloid derived ligand and as a result, gives addition products with low enantio and regio-selectivity. Hydrolysis of **9** leads back to **7**, which can then re-enter either the primary or secondary cycle.

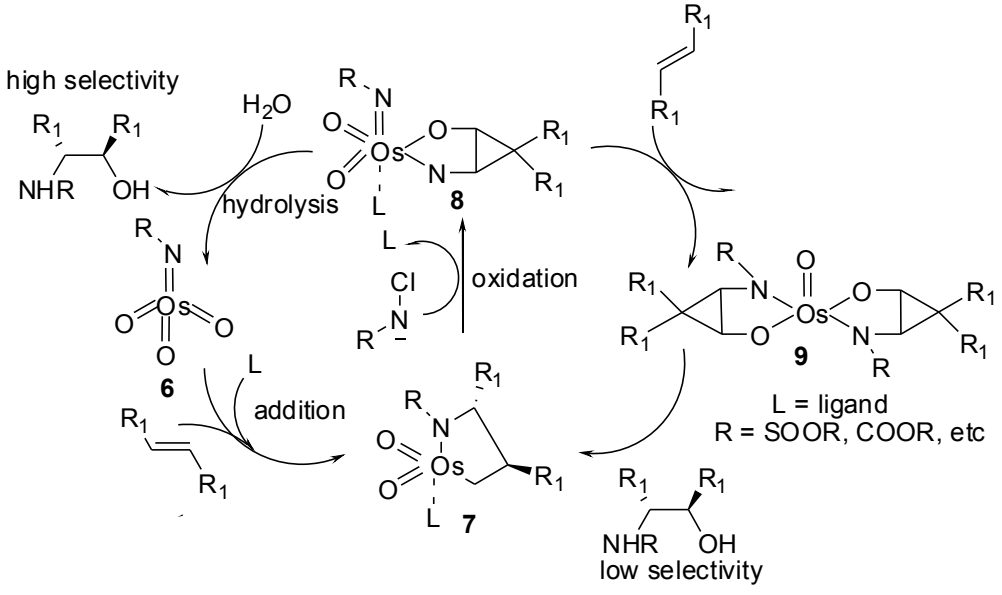


Figure 4. Proposed mechanism of asymmetric aminohydroxylation

The turnover-limiting step in both catalytic cycles is the hydrolysis of azaglycolate complexes **8** or **9**.[22] Control of the oxidation pathway is achieved by conducting the reaction in aqueous solvent mixtures, thereby favouring hydrolysis of **8**[22a] and dominance of the primary cycle. In comparison, all of the AA processes reported to date have been carried out under homogeneous conditions and suppression of the secondary cycle relies on effective hydrolysis.

1.2.3. 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 (Figure 5).

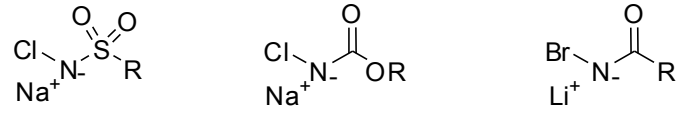


Figure 5. Various nitrogen sources.

(i) Sulfonamide variant 10: 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.[23] 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.[6c] 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[24] or with Red-Al.[25] In addition, 33% HBr/CH_3COOH has been used to cleave toluene sulfonamides.[6b] 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.[26]

(ii) Carbamate variant 11 : The discovery of carbamate based nitrogen sources[6d] 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,[27] 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.[28] 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.[29] As with sulfonamides, carbamates with less sterically demanding *N*-substituents were found to give better results.

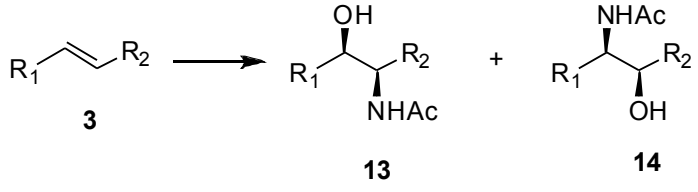
(iii) Amide variant 12 : The most recent major variant of the AA reaction is based on *N*-halogenated amides.[30] This variant is comparable in scope to the carbamate based method and works well with cinnamates, acrylates, styrenes, and terminal alkenes. It is advantageous in that only one equivalent 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,[31] 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.[32]

1.3.4. Regioselectivity

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

Alkene substitution

The AA of the homoallylic alcohol derivatives shown in Scheme 4 explains the general trend that the nitrogen prefers to add to the less substituted end of the alkene (Table 1). These 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.



Scheme 4. Aminohydroxylation of unsymmetrical olefins

Substrate	R_1	R_2	Ratio of products 13:14
3a	$TBDPSOCH_2CH_2$	H	>20:1
3b	*p*-OMe-$C_6H_4OCH_2CH_2$	H	1.2:1
3c	$TBDPSOCH_2CH_2$	Et	2.0:1
3d	*p*-OMe-$C_6H_4OCH_2CH_2$	Et	1:3.5

Table 1. Ratio of products in asymmetric aminohydroxylation of unsymmetrical olefins

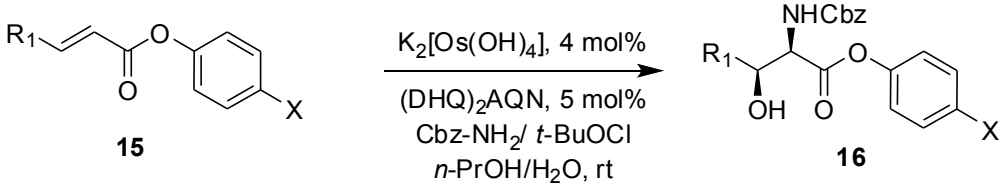
Alkene polarisation

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.

Panek protocol

Asymmetric synthesis of β-hydroxy-α-amino acid can be performed, by making aryl ester substrates **15** successfully using Panek protocol. The reversal of regioselection may arise from a conformational change induced by the aryl ester functionality.[32]



Scheme 5. Reversal of regioselection in asymmetric aminohydroxylation

1.3. HYDROLYTIC KINETIC RESOLUTION (HKR)

1.3.1. Introduction

The importance of epoxides in organic synthesis arises partly from the occurrence of the strained three-membered ring unit in a number of interesting natural products[33] but more so because the ring opening of epoxides allows straightforward elaboration to useful new functionality, often with generation of new carbon-carbon bonds. Indeed, reactions of epoxides with nucleophiles, Lewis acids, radicals, reducing agents, oxidizing agents, acids, and bases have all been well documented and utilized in synthesis.[34] Further, the stereospecific manner in which epoxides generally react renders these compounds attractive chiral building blocks for asymmetric synthesis.

Since those epoxides that are produced naturally are typically complex compounds available only in limited amounts, nature's chiral pool has not proven to be a useful direct source of optically active epoxides for use in organic synthesis. Instead, enantio-enriched epoxides have been accessed indirectly from the chiral pool via multistep procedures.[35] These, however, tend to be inherently inefficient, and the range of epoxides available by this approach is also quite limited. As a consequence, the preparation of enantio-enriched epoxides has long stood as a most significant target for asymmetric synthesis. In particular, the identification of catalytic asymmetric olefin oxidation methods has been an area of active research for several decades, and the advances made in this field have increased greatly the number of enantiomerically enriched epoxides available for use in organic synthesis.

Among available methods for the preparation of enantio-enriched epoxides, the Sharpless epoxidation reaction has arguably had the most profound impact of any asymmetric catalytic reaction discovered thus far, providing general access to highly enantio-enriched epoxyalcohols.[36] 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.[37] 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.[38] Indirect routes

to enantiopure epoxides involving asymmetric catalytic dihydroxylation or reduction reactions have also proven highly valuable in specific contexts.[39] 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.[40] 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[41] or by enzymatic kinetic resolution methods,[42] and these compounds have become widely used starting materials for target-oriented synthesis.[43] 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 **17** (Figure 6) catalyzed efficient hydrolytic kinetic resolution (HKR) of a variety of terminal epoxides (Scheme 6).[44-46] 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 **17** had previously been commercialized and manufactured on a ton scale in the context of (salen)Mn epoxidation catalysts.[47] The cobalt analogues (*R*,*R*)-**17** and (*S*,*S*)-**17** proved equally accessible, and these are also now available in bulk.[48] Third, water is perhaps the ideal reagent for effecting the resolution reaction: it is inexpensive and safe, and the rate of the ring-opening reaction can be controlled simply by modulating the rate of addition of water to the epoxide-catalyst mixture.[49] 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.[5,11]

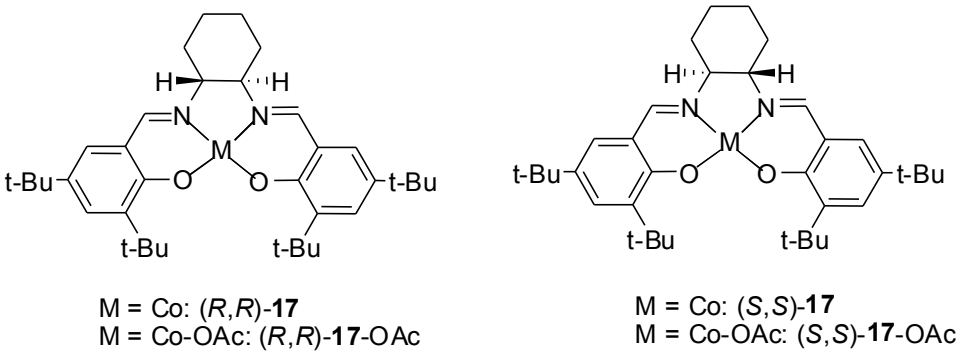
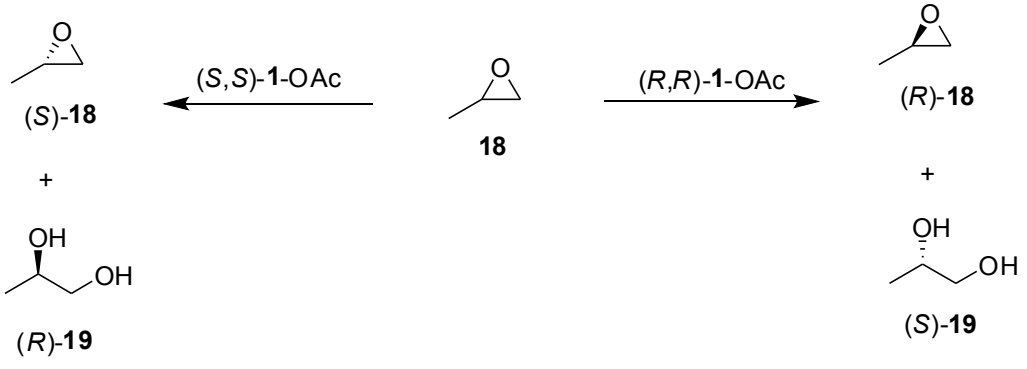


Figure 6. Jacobsen catalyst

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.[50] In addition, the commercial manufacture of enantio-enriched propylene oxide, epichlorohydrin, and styrene oxide using HKR



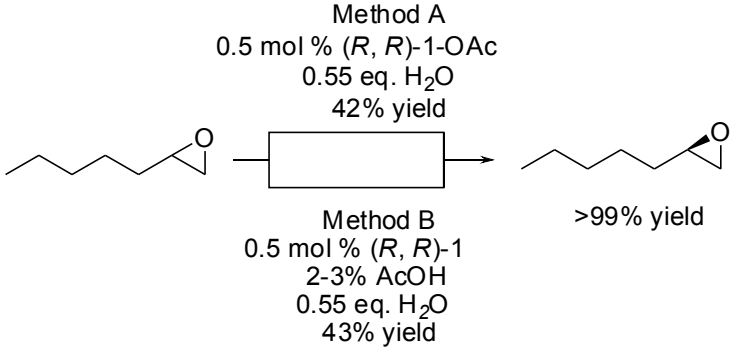
Scheme 6. Hydrolytic kinetic resolution of propylene oxide

methodology has been implemented, thereby reducing the cost of these useful chiral building blocks.[48] Jacobsen has discovered that the HKR is an extraordinarily general reaction, allowing efficient kinetic resolution of virtually any type of terminal epoxide.

1.3.2. Preparation of Catalyst and General Experimental Considerations

Both enantiomers of the (salen)CoII complex **17** are available commercially on research or commercial scale,[48] or they can be prepared from the commercially available ligands using $Co(OAc)_2$. The Co(II) complex **17** 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 **17**.OAc is convenient for use in HKR reactions both in terms of its preparation and reactivity. Two useful methods for the generation of complex **17**.OAc have been developed. Method A involves isolation of **17**.OAc as a crude solid prior to the HKR. The Co(II) complex **17** 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 **17**.OAc as a brown solid residue that can be used without further purification. Method B involves in situ generation of **17**.OAc under HKR conditions by suspension of the Co(II) complex **17** in epoxide or epoxide/solvent and addition of HOAc under an aerobic atmosphere. Catalyst obtained by both methods was examined for each of the epoxides described in this study. For certain substrates such as 1-hexene oxide, catalyst prepared by either method leads to essentially identical results. In these situations, *in situ* catalyst generation (method B) is preferable since the procedure avoids an extra solvent removal step. On the other hand, catalyst prepared by method A was found to be more effective with less reactive substrates (vide infra) and was applicable to all substrates examined. Therefore, if HKR did not afford epoxide in >99% ee with catalyst prepared by method B after optimization of solvent and catalyst loading, then catalyst prepared by method A was employed.



Scheme 7. General reaction

Aside from the method of generation of **17**.OAc, the only reaction parameters in the HKR that required optimization for individual substrates were catalyst loading and choice of solvent. With few exceptions, epoxide of >99% ee could be obtained using 0.55 equiv of

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

[(*R*,*R*)-*N*,*N*'-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminato(2-]cobalt(II) ((*R*,*R*)-1). A solution of cobalt(II) acetate tetrahydrate (5.98 g, 24.0 mmol) in MeOH (80 mL) was added to a solution of ligand [(*R,R*)-*N*,*N*'-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine] (10.9 g, 20.0 mmol) in CH_2Cl_2 (80 mL) via cannula under an atmosphere of N_2 with careful exclusion of air. A brick-red solid began to precipitate before addition was complete. The sides of the reaction flask were rinsed with MeOH (20 mL), and the mixture was allowed to stir for 15 min at room temperature and then 30 min at 0 °C. Precipitated solids were isolated by vacuum filtration and rinsed with cold (0 °C) MeOH (2 x 75 mL). The red solid was collected and dried in vacuo to yield [(*R*,*R*)-*N*,*N*'-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminato(2-)]cobalt(II) ((*R*,*R*)-**17**) (11.6 g, 19.2 mmol, 96%).

1.4 PROLINE CATALYZED ASYMMETRIC ORGANIC TRANSFORMATIONS

1.4.1. Introduction to organocatalysis

The broad utility of synthetic chiral molecules as single-enantiomer pharmaceuticals, in electronic and optical devices, as components in polymers with novel properties, and as probes of biological function, has made asymmetric catalysis a prominent area of investigation. Organocatalysis, or the use of small organic molecules to catalyse organic transformations, is a relatively new and popular field within the domain of chiral molecule (or enantioselective) synthesis. Although chemical transformations that use organic catalysts, or organocatalysts, have been documented sporadically over the past century, it was not until the late 1990s that the field of organocatalysis was 'born'.[51] It is now widely accepted that organocatalysis is one of the main branches of enantioselective synthesis (the other, previously accepted, branches being enzymatic catalysis and organometallic catalysis), and those who are involved in the synthesis of chiral molecules consider organocatalysis to be a fundamental tool in their catalysis toolbox.

This rediscovery has initiated an explosive growth of research activities in organocatalysis both in industry and in academia. The 1970s brought a milestone in the area of asymmetric organocatalysis, when two industrial groups led by Hajos and Wiechert published the first and highly enantioselective catalytic aldol reactions using simple amino acid proline as the catalyst. Organocatalysis is the catalysis of chemical transformations using a purely organic molecule, which is composed of mainly carbon, hydrogen, nitrogen, sulfur, and phosphorus, and does not contain any metals. The advent of organocatalysis brought the prospect of a complementary mode of catalysis, with the potential for savings in cost, time and energy, an easier experimental procedure, and reductions in chemical waste, which confers a huge direct benefit in the production of pharmaceutical intermediates when compared with transition metal catalysts. Organic molecules not only have ease of manipulation and a "green" advantage but also can be very efficient catalysts. Several aspects of organocatalysis will undoubtedly attract researchers' attention. Tremendous efforts will continue to be directed towards the discovery and design of catalysts with better efficiency, new reactivities and greater turnover numbers. And in near future asymmetric

organocatalysis may begin to catch up with the spectacular advancements of enantioselective transition metal catalysis.

Recently, List[52] introduced a system of classification based on the mechanism of catalysis (Figure 6). The four categories are Lewis base, Lewis acid, Bronsted base and Bronsted acid catalysis. Accordingly, Lewis base catalysts (B:) initiate the catalytic cycle via nucleophilic addition to the substrate (S). The resulting complex undergoes a reaction and then releases the product (P) and the catalyst for further turnover. Lewis acid catalysts (A) activate nucleophilic substrates (S:) in a similar manner. Brønsted base and acid catalytic cycles are initiated via a (partial) deprotonation or protonation, respectively.

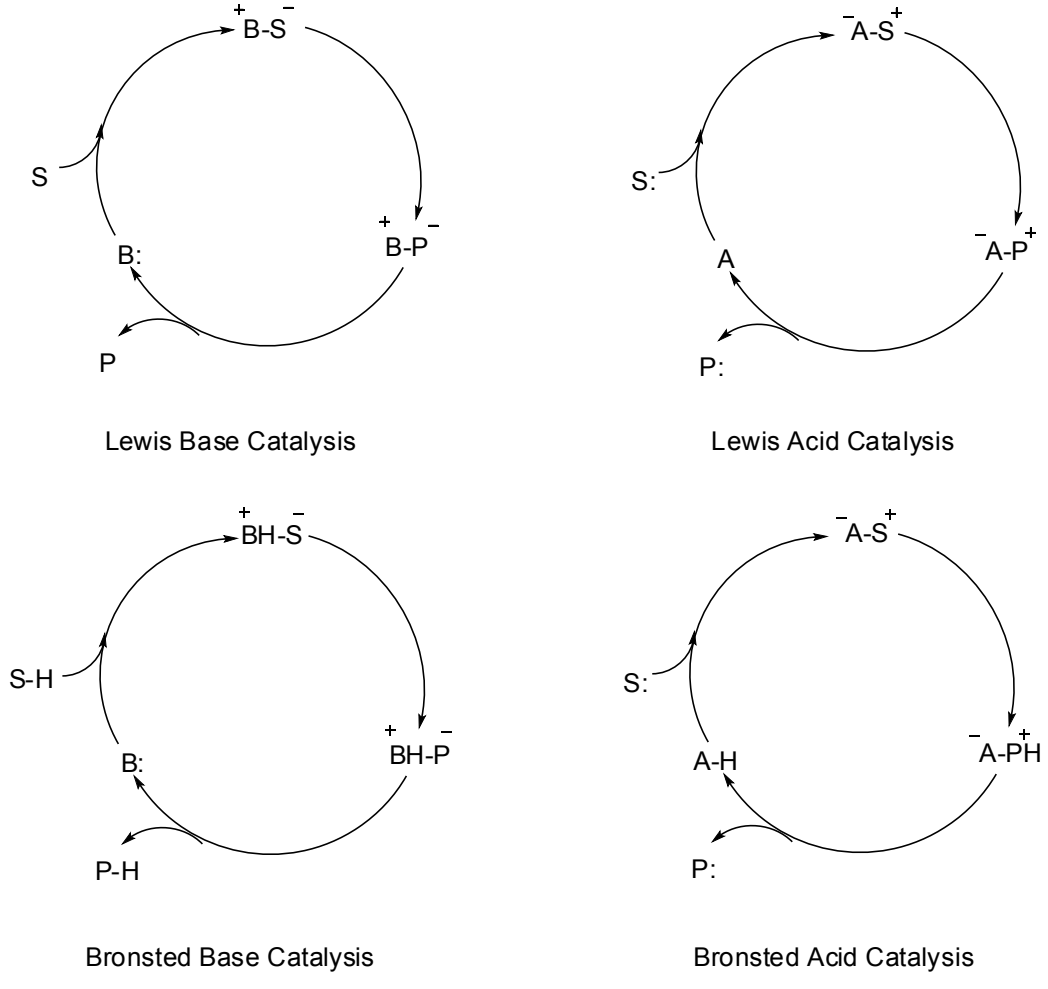


Figure 6. Organocatalytic cycles

1.4.2. Proline a "Universal catalyst"

Proline has been defined as a "universal catalyst" because of its high utility in variety of asymmetric organic transformations. Proline is the only natural amino acid with a secondary amine functionality, which raises the pKa value and better nucleophilicity as compared to other amino acids. It can act as a nucleophile to carbonyl groups (iminium intermediate) or Michael acceptors (enamines). It can be regarded as a bifunctional catalyst as the secondary amine acts as Lewis base and the acid group acts as Bronsted acid (Figure 7). The high stereoselectivity in the proline-catalyzed reactions is possibly due to its formation of organized transition states with many hydrogen bonding frameworks. Proline is not the only molecule to promote catalysis, but it still seems to be one of the best in the diversity of transformations.

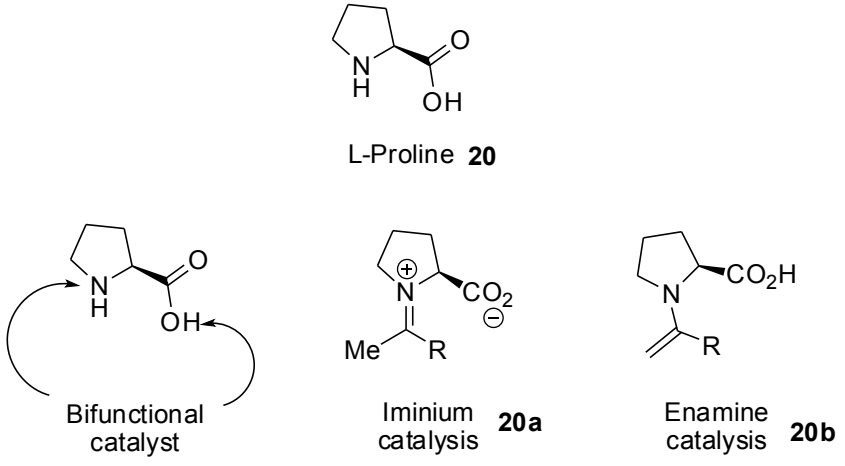


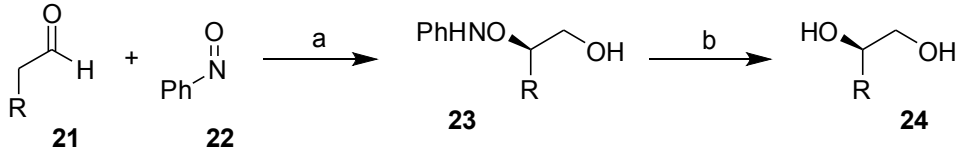
Figure 7. Modes of proline catalysis

It is known to catalyze aldol,[53] Diels-Alder,[54] Michael addition[55] and α-functionalization[56] among many other organic transformations.[57] Particularly proline-catalyzed α-aminoxylation[58] and α-amination[59] of carbonyl compounds have emerged as powerful methods because chiral building materials can be synthesized in effective manner starting from easily available materials.

1.4.3. Proline-catalyzed α-aminoxylation

Optically active α-hydroxyaldehydes and ketones are important intermediates in organic synthesis as they are direct precursors to 1,2-diols. Because of this utility many methods

have been developed for their preparation. The more prominent, well-established methods of enantioselective α-oxygenations include the use of Davis oxaziridine,[60a] Sharpless dihydroxylation of enol ethers,[60b] manganese–salen epoxidation of enol ethers,[60c] and Shi epoxidation of enol ethers.[60d] It is only rather recently that direct catalytic, asymmetric variants have been reported.[61] Most of these methods, however, require multiple manipulations and there is no direct method, nor catalytic asymmetric method for their synthesis from the corresponding aldehyde. Recently, proline has been found to be an excellent asymmetric catalyst for α-aminoxylation[58] of carbonyl compounds. When an aldehyde **21** without substitution at α-position was reacted with nitrosobenzene **22** in presence of L-proline in DMSO at ambient temperature, aminoxylation of the aldehyde takes place at the α-position. Aldehyde can be reduced *in situ* with sodium borohydride and the aminoxyl moiety undergoes hydrogenolysis with Pd/C, H_2 or $CuSO_4$ to give the corresponding diols **24** in very high enantioselectivities (Scheme 8).



Scheme 8. *Reaction and reagents*: (a) (i) S-proline (20 mol%), DMSO, 25 °C; (ii) $NaBH_4$, MeOH; (b) Pd/C, H_2 or 30 mol% $CuSO_4$. R = Ph, *i*-Pr, *n*-Bu, CH_2Ph etc. > 99% ee

The mechanism of the α-aminoxylation reaction is shown in figure 8. The observed enantioselectivitiy of the catalytic α-aminoxylation of aldehydes can be rationalized by

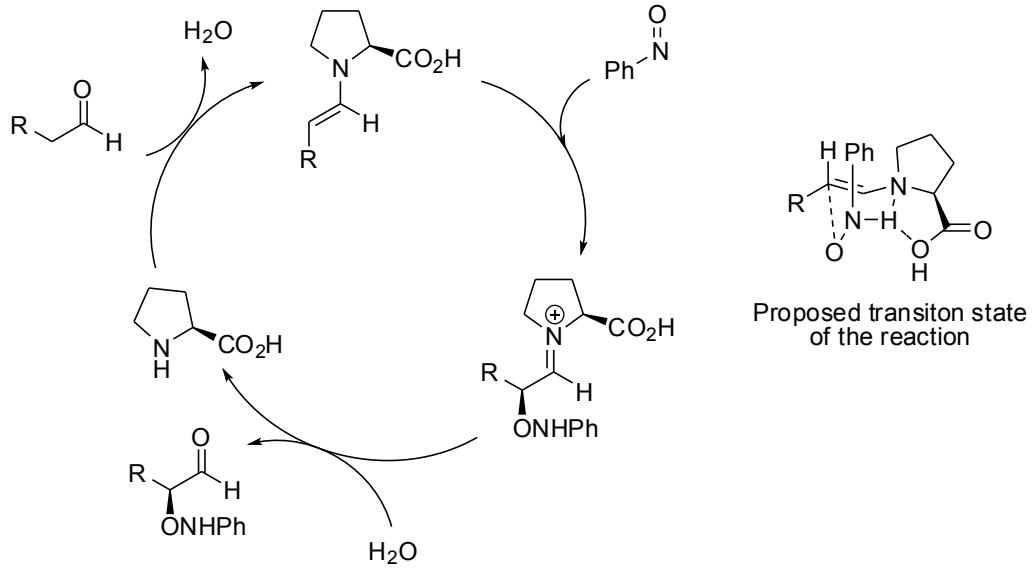


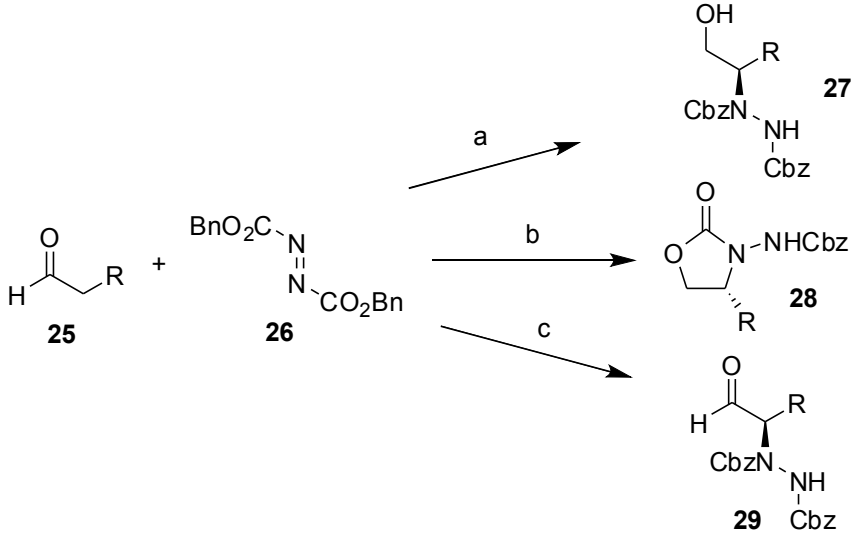
Figure 8. Proposed mechanism of the α-aminoxylation reaction

invoking an enamine mechanism operating through a chair transition state where the *Si* face of an α-enamine formed from the aldehyde and L-proline approaches the less hindered oxygen atom of nitrosobenzene to provide a chiral α-aminoxyaldehyde with *R* configuration. Since proline is commercially available in both enantiopure forms, a one pot sequential catalytic α-aminoxylation of aldehydes followed by *in situ* reduction with $NaBH_4$ affords *R*- or *S*- configured 1,2-diol units (the secondary alcohol "protected" by an *O*-amino group) with excellent enantioselectivities and in good yields.

1.4.4. Proline-catalyzed α-amination

The importance of optically active α-amino acids, α-amino aldehydes, and α-amino alcohols, formed by asymmetric catalysis, has stimulated an enormous development in synthetic strategies, and two different catalytic, enantioselective approaches are attractive: the *C-C* and the *C-N* bond-forming reactions.

Asymmetric α-amination[59] of aldehydes using proline-catalyzed reactions represent a direct approach synthesizing chiral building blocks such as α-amino acids, α-amino aldehydes, and α-amino alcohols. The use of organocatalysis, in particular proline represents a drastic change in approach to asymmetric α-amination. Recently, both List[59a] and Jørgensen[59b] disclosed the asymmetric α-amination of aldehydes (Scheme 9) using catalytic quantities of proline.



Scheme 9.*Reactions and conditions*: (a) L-proline (10 mol%), CH_3CN, 0 °C, 3 h; $NaBH_4$, EtOH; (b) L-proline (10 mol%), CH_2Cl_2, 25 °C; $NaBH_4$, MeOH; 0.5 N NaOH; (c) L-proline (10 mol%), CH_2Cl_2, 25 °C; H_2O.

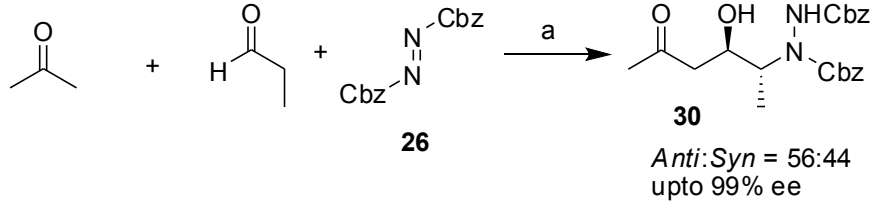
While both transition structures lead to identical products directed by the hydrogen bond from the carboxylic acid of proline, they presumably possess unique energies, so one transition state should be favored. However, the operative transition state has yet to be established.

1.4.5. Proline-catalyzed sequential transformations

Proline-catalyzed sequential transformations,[62] is a emerging research field in organic synthesis as synthesis of complex organic molecules could be accessible in one-pot procedure. Recently a variety of such transformations has been developed by different research groups, some of them are described below.

1.4.5.1. Sequential amination-aldol[62a]

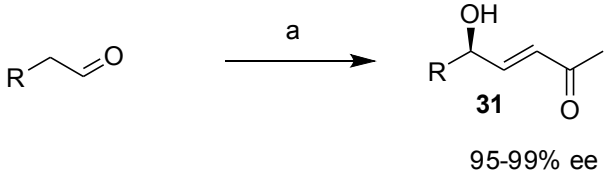
Barbas III *et al*. have developed a one-pot protocol for the synthesis of functionalized β-amino alcohols **30** from aldehydes, ketones and azodicarboxylates (Scheme 10).



Scheme 10. *Reactions and conditions*: (a) L-proline (20 mol%), CH_3CN, rt, 72 h, 80%.

1.4.5.2. Sequential aminoxylation-olefination[62b]

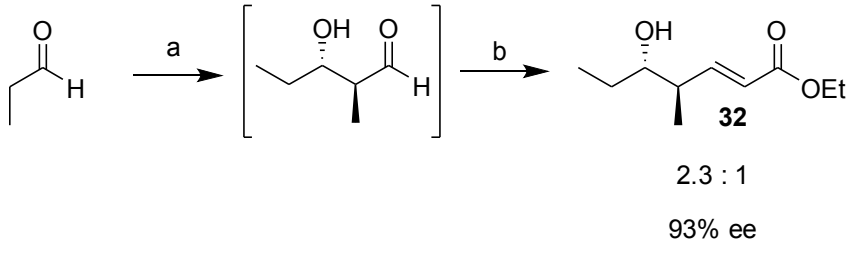
Zhong *et al*. have reported sequential asymmetric α-aminoxylation/Wadsworth-Emmons-Horner olefination of aldehydes for the synthesis of optically active *O*-amino-substituted allylic alcohols **31** in good enantioselectivities using cesium carbonate as base (Scheme 11).



Scheme 11. *Reactions and conditions*: (a) L-proline (20 mol%), nitrosobenzene (1.0 equiv.), DMSO, rt, 10-20 min then diethyl(2-oxopropyl)phosphonate, cesium carbonate (1.5 equiv.).

1.4.5.3. Sequential aldol-olefination[62c]

Cordova *et al*. have reported one-pot organocatalytic asymmetric tandem cross-aldol/Horner-Wittig-Emmons olefination for the synthesis of polyketide and carbohydrate derivatives (Scheme12).

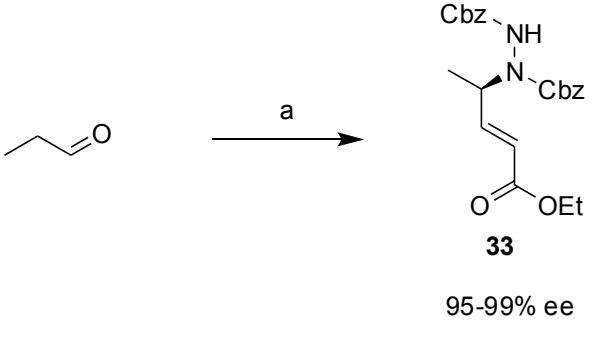


Scheme 12. *Reactions and conditions*: (a) L-proline (10 mol%), DMF; (b) Diethyl(2-oxopropyl)phosphonate, cesium carbonate (1.5 equiv.).

Apart from this transformation, Cordova *et al*. have also reported tandem Mannich olefination reaction.[62d]

1.4.5.4. Sequential α-amination-olefination[62e]

Kotkar *et al*. have reported sequential asymmetric α-amination/Wadsworth-Emmons-Horner olefination of aldehydes for the synthesis of optically active allylic amine in good enantioselectivities and yields (Scheme13).



Scheme 13. *Reactions and conditions*: (a) L-proline (20 mol%), DBAD (1.0 equiv.), CH_3CN, rt, 10-20 min then diethyl(2-oxopropyl)phosphonate, cesium carbonate (1.5 equiv.).

1.5 Reference

1. For recent reviews, see: *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: New York, **1993**.
2. (a) Katsuki, T.; Martin, V. S. *Org. React*. **1996**, *48*, 1; (b) Katsuki, T. *J. Mol. Catal. A: Chem*. **1996**, *113*, 87. For a recent review, see: Johnson, R. A.; Sharpless, K. B. *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: New York, **1993**, pp. 101.
3. (a) McDonald, F. E.; Towne, T. B. *J. Org. Chem.* **1995***, 60*, 5750; (b) Kennedy, R. M.; Tang. S. *Tetrahedron Lett.* **1992***, 33*, 3729; (c) Tang, S.; Kennedy, R. M. *Tetrahedron Lett.* **1992***, 33*, 5299; (d) Tang, S.; Kennedy, R. M. *Tetrahedron Lett.* **1992***, 33*, 5303; (e) Boyce, R. S.; Kennedy, R. M. *Tetrahedron Lett*. **1994**, *35*, 5133.
4. Sharpless, K. B.; Teranishi, A. Y.; Backvall, J.-E. *J. Am. Chem. Soc*. **1977**, *99*, 3120.
5. (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev*. **1994**, *94*, 2483; (b) Schroder, M. *Chem*. *Rev*. **1980**, *80*, 187.
6. (a) Li, G.; Chang, H.-T.; Sharpless, K. B. *Angew*. *Chem*., *Int. Ed*. **1996**, *35*, 451; (b) Li, G.; Sharpless, K. B. *Acta Chem. Scand*. **1996**, *50*, 649; (c) Rudolph, J.; Sennhenn, P. C.; Vlaar, C. P.; Sharpless, K. B. *Angew*. *Chem*., *Int. Ed.* **1996**, *35*, 2810; (d) Li, G.; Angert, H. H.; Sharpless, K. B. *Angew*. *Chem*., Int. *Ed*. **1996**, *35*, 2813; (e) Angelaud, R.; Landais, Y.; Schenk, K. *Tetrahedron Lett*. **1997**, *38*, 1407.
7. Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1995**, *34*, 1059.
8. (a) Kolb, H. C.; Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994***, 116*, 1278; (b) Sharpless, K. B.; Amberg, W; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992***, 57*, 2768; (c) Vanhessche, K. P. M.; Sharpless, K. B. *J. Org. Chem.* **1996***, 61*, 7978.
9. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992***, 57*, 2768.

10. Kolb, H. C.; Andersson, P. G.; Bennani, Y. L.; Crispino, G. A.; Jeong, K.-S.; Kwong, H.-L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 12226.

11. Becker, H.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **1996**, *35*, 448.

12. Crispino, G. A.; Jeong, K.-S.; Kolb, H. C.; Wang, Z.-M.; Xu, D.; Sharpless, K . B. *J. Org. Chem.* **1993**, *58*, 3785.

13. Becker, H.; King, S. B.; Taniguchi, M.; VanHessche, K. P. M.; Sharpless, K. B. *J. Org. Chem.* **1995**, *60*, 3940.

14. Wang, L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7568.

15. Wang, Z.-M.; Kakiuchi, K.; Sharpless, K. B. *J. Org. Chem*. **1994**, *59*, 6895.

16. (a) Baker, W.; Field, F.B. *J. Chem. Soc*. **1932**, 86 ; (b) Catlson, W. W.; Cretcher, L. H. *J. Am. Chem. Soc.* **1947**, *69*, 1952.

17. Gao. Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538.

18. Reiser, O. *Angew. Chem. Int. Ed.* **1996**, *35*, 1308.

19. Bergmier, S. C. *Tetrahedron* **2000**, *56*, 2561.

20. Tao, B.; Schlingloff, G.; Sharpless, K. B. *Tetrahedron Lett.* **1998**, *39*, 2507.

21. Han, K.; Cho, C.-W.; Janda, K. D. *Chem. Eur. J.* **1999**, *5*, 1565.

22. (a) Sharpless, K. B.; Fokin, V. V. USP 6, 350, 905/2002 (*Chem Abstr*., 134, 178, 819); (b) Rudolph, J.; Sennhenn, P. C.; Vlaar, C. P.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **1996**, *35*, 2810.

23. (a) Sharpless, K. B.; Chong, A. O.; Oshima, K. *J. Org. Chem*. **1976**, *41*, 177 ; (b) Herranz, E.; Sharpless, K. B. *J. Org. Chem*. **1978**, *43*, 177 ; (c) Herranz, E.; Biller, S. A.; Sharpless, K. B. *J. Am. Chem. Soc*. **1978**, *100*, 3596 ; (d) Herranz, E.; Sharpless, K. B. *J. Org. Chem*. **1980**, *45*, 2710.

24. (a) Sharpless, K. B.; Chong, A. O.; Oshima, K.; *J. Org. Chem.* **1976**, *41*, 177 ; (b) Back, J. E.; Oshima, K.; Palermo, R. E.; Sharpless, K. B. *J. Org. Chem.* **1979**, *44*, 1953 ; (c) Ji, S.; Gantler, L. B.; Waring, A.; Battisti, A.; Bank, S.; Closson, W. D. *J. Am. Chem. Soc.* **1967**, *89*, 5311.

25. Gold, E. H. Babad, *J. Org. Chem.* **1972**, *37*, 2208.

26. Andersson, M. A.; Epple, R. Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 472.

27. Green, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, Wiley & Sons Inc., New York, 2 nd edn., 1991.

28. (a) O'Brien, P. *Angew. Chem. Int. Ed.* **1999**, *38*, 326 ; (b) O'Brien, P.; Osborne, S. A.; Parker, D. D. *J. Chem. Soc. Perkin Trans*. **1998**, *1*, 2519 ; (c) O'Brien, P.; Osborne, S. A.; Parker, D. D. *Tetrahedron Lett*. **1998**, *39*, 4099.

29. Brucncko, M.; Schlingolff, G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **1997**, *36*, 1483.

30. Wallis, E. S.; Lane, J. F. in *Organic reactions*, Ed. R. Adams, Wiley & Sons, Inc, 561.

31. Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 11038.

32. Morgan, A. J.; Masse, C. E.; Panek, J. S. *Org. Lett*. **1999**, *1*, 1949.

33. Some, among many, notable examples: (i) Epothilones: Bollag, D. M.; McQueney, P. A.; Zhu, J.; Hensens, O.; Koupal, L.; Liesch, J.; Goetz, M.; Lazarides, E.; Woods, C. M. *Cancer Res.* **1995**, *55*, 2325; (j) FR901464: Nakajima, H.; Takase, S.; Terano, H.; Tanaka, H. *J. Antibiot.* **1997**, *50*, 96.

34. For reviews and lead references, see: (a) Winstein, S.; Henderson, R. B. In *Heterocyclic Compounds*, Vol. 1; Elderfield, R. C., Ed.; Wiley: New York, 1950; Chapter 1; (b) Parker, R. E.; Isaacs, N. S. *Chem. Rev.* **1959**, *59*, 737; (c) Barto´k, M.; La ´ng, K. L. Small Ring Heterocycles. In *The Chemistry of Heterocyclic Compounds*, Vol. 42, Part 3; Hassner, A., Ed.; Wiley: New York, 1985; Chapter 1; (d) Rao, A. S.; Paknikar, S. K.; Kirtane, J. G. *Tetrahedron* **1983**, *39*, 2323; (e) Smith, J. G. *Synthesis* **1984**, 629.

35. For examples, see: (a) Larchevêque, M.; Petit, Y. *Tetrahedron Lett.* **1987**, *28*, 1993; (b) Larchevêque, M.; Henrot, S. *Tetrahedron* **1990**, *46*, 4277; (c) de March, P.; Figueredo, M.; Font, J.; Monsalvatje, M. *Synth. Commun.* **1995**, *25*, 331; (d) Adiyaman, M.; Khanapure, S. P.; Hwang, S. W.; Rokach, J. *Tetrahedron Lett.* **1995**, *36*, 7367.

36. (a) Katsuki, T. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Chapter 18.1; (b) Rossiter, B. E. in *Asymmetric Synthesis*, Vol. 5; Morrison, J. D., Ed.; Academic Press: New York, 1985;

Chapter 7; (c) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; Chapter 4.1; (d) Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1.

37. Reviews: (a) Jacobsen, E. N.; Wu, M. H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Chapter 18.2; (b) Katsuki T. *Coord. Chem. Rev.* **1995**, *140*, 189; (c) Jacobsen, E. N. In *Comprehensive Organometallic Chemistry II*, Vol. 12; Wilkinson, G., Stone, F. G. A., Abel, E. W., Hegedus, L. S., Eds.; Pergamon: New York, 1995; pp 1097-1135.

38. For a recent review: Frohn, M.; Shi, Y. *Synthesis* **2000**, 1979.

39. For asymmetric dihydroxylation routes, see: (a) Kolb, H. C.; Sharpless, K. B. *Tetrahedron* **1992**, *48*, 10515. For asymmetric reduction methods, see: (b) Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1991**, *56*, 442; (c) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1993**, *34*, 5227; (d) Ramachandran, P. V.; Gong, B.; Brown, H. C. *J. Org. Chem.* **1995**, *60*, 41; (e) Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 2931.

40. For the most enantioselective methods developed to date involving synthetic catalysts: (a) Palucki, M.; Pospisil, P. J.; Zhang, W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 9333; (b) Collman, J. P.; Wang, Z.; Straumanis, A.; Quelquejeu, M.; Rose, E. *J. Am. Chem. Soc.* **1999**, *121*, 460. For methods involving biocatalysts, see: (c) Botes, A. L.; Weijers, C. A. G. M.; Botes, P. J.; van Dyk, M. S. *Tetrahedron: Asymmetry* **1999**, *10*, 3327, and references therein; (d) Goswami, A.; Totleben, M. J.; Singh, A. K.; Patel, R. N. *Tetrahedron: Asymmetry* **1999**, *10*, 3167, and references therein.

41. Gao, Y.; Klunder, J. M.; Hanson, R. M.; Masamune, H.; Ko, S. Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

42. Ladner, W. E.; Whitesides, G. M. *J. Am. Chem. Soc.* **1984**, *106*, 7250.

43. Hanson, R. M. *Chem. Rev.* **1991**, *91*, 437.

44. (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936; (b) Furrow, M. E.; Schaus, S. E.; Jacobsen, E. N. *J. Org.Chem*. **1998**, *63*, 6776.

45. For earlier studies involving (salen) metal-catalyzed reactions of epoxides that served as a foundation for the discovery of the HKR, see: (a) Tekeichi, T.; Arihara, M.;

Ishimori, M.; Tsuruta, T. *Tetrahedron* **1980**, *36*, 3391. (b) Maruyama, K.; Nakamura, T.; Nakamura, S.; Ogino, A.; Nishinaga, A. *React. Kinet. Catal. Lett.* **1991**, *45*, 165. (c) Larrow, J. F., Schaus, S. E., Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 7420.

46. The HKR is complementary to biocatalytic methods exploiting epoxide hydrolases. For a review, see: Archelas, A.; Furstoss, R. *Trends Biotechnol.* **1998**, *16*, 108.

47. (a) Larrow, J. F.; Jacobsen, E. N.; Gao, Y.; Hong, Y.; Nie, X.; Zepp, C. M. *J. Org. Chem.* **1994**, *59*, 1939; (b) Larrow, J. F.; Jacobsen, E. N. *Org. Synth*. **1997**, *75*, 1.

48. For information, see: http://www.rhodiachirex.com.

49. While it may be assumed that an "ideal" resolution would involve no added reagents i.e., an enantiomer undergoing selective isomerization or polymerizations the rate of such transformation may be difficult to control because of the exothermicity ($\not\in E$ > 30 kcal/mol) associated with epoxide ring opening. This is a special concern with reactions carried out on a large scale. The fact that the rate of nucleophile addition can be adjusted to control reaction rate therefore has significant practical advantages.

50. (a) Liu, Z. Y.; Ji, J. X.; Li, B. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3519; (b) O'Neil, I. A.; Cleator, E.; Southern, J. M.; Hone, N.; Tapolczay, D. J. *Synlett* **2000**, 695; (c) Fürstner, A.; Thiel, O. R.; Ackermann, L. *Org. Lett.* **2001**, *3*, 449; (d) Chow, S.; Kitching, W. *Chem. Commun.* **2001**, 1040; (e) Rodriguez, A.; Nomen, M.; Spur, B. W.; Godfroid, J. J.; Lee, T. H. *Tetrahedron* **2001**, *57*, 25.

51. MacMillian, D. W. C. *Nature* **2008**, *455*, 304.

52. Seayad, J.; List, B. *Org. Biomol. Chem*. **2005**, *3*, 719.

53. List, B.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc*. **2000**, *122*, 2395.

54. (a) Sabitha, G.; Fatima, N.; Reddy, E.V.; Yadav, J. S. *Adv. Synth. Catal*. **2005**, *347*, 1353; (b) Ramachary, D. B.; Chowdari, N. S.; Barbas, C. F. III *Synlett* **2003**, 1910.

55. Hechavarria Fonseca, M. T.; List, B.; *Angew. Chem., Int. Ed*. **2004**, *43*, 3958.

56. For α-functionalization reviews: (a) Franzen, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjarsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2005**, *127*, 18296; (b) Guillena, G.; Ramon, D. J. *Tetrahedron: Asymmetry* **2006**, *17*, 1465.

57. For a review of proline-catalyzed asymmetric reactions see: List, B. *Tetrahedron* **2002**, *58*, 5573.

58. (a) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett*. **2003**, *44*, 8293; (b) Zhong, G. *Angew. Chem., Int. Ed*. **2003**, *42*, 4247; (c) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed*. **2003**, *43*, 1112; (d) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2003**, *125*, 10808; (e) Cordova, A.; Sunden, H.; Bøgevig, A.; Johansson, M.; Himo, F. *Chem. A-Eur. J*. **2004**, *10*, 3673.

59. (a) List, B. *J. Am. Chem. Soc*. **2002**, *125*, 5656; (b) Bogevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W., Jorgensen, K. A. *Angew. Chem., Int. Ed*. **2002**, *41*, 1790; (c) Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bogevig, A.; Jorgensen, K. A. *J. Am. Chem. Soc*. **2002**, *124*, 6254; (d) Vogt, H.; Vanderheiden, S.; Brase, S. *Chem. Commun*. **2003**, 2448; (e) Iwamura, H.; Mathew, S. P.; Blackmond, D. G. *J. Am. Chem. Soc*. **2004**, *126*, 11770.

60. (a) Davis, F. A.; Bang-Chi C. *Chem. Rev*. **1992**, *92*, 919; (b) Morikawa, K.; Park, J.; Andersson, P.G.; Hashiyama, T.; Sharpless, K. B. *J. Am. Chem. Soc*. **1993**, *115*, 8463; (c) Adam, W.; Fell, R. T.; Stegmann, V. R.; Saha-Moller, C. R. *J. Am. Chem. Soc*. **1996**, *118*, 708; (d) Zhu, Y.; Tu, Y.; Yu, H.; Shi, Y. *Tetrahedron Lett*. **1998**, *39*, 7819.

61. Merino, P.; Tejero, T.; *Angew. Chem., Int. Ed*. **2004**, *43*, 2995.

62. (a) Chowdari, N. S.; Ramachary, D. B.; Barbas, C. F. III *Org. Lett*. **2003**, *5*, 1685; (b) Zhong, G.; Yu, Y. *Org. Lett*. **2004**, *6*, 1637; (c) Zhao, G. –L.; Liao, W, -W.; Cordova, A. *Tetrahedron Lett*. **2006**, *47*, 4929; (d) Liao, W. –W.; Ibrahem I.; Cordova A. *Chem. Commun*. **2006**, 674; (e) Kotkar, S. P.; Chavan V. B.; Sudalai A. *Org. Lett*. **2007**, *9*, 1001.

Chapter-2

Asymmetric aminohydroxylation approach to the syntheses of HIV-protease inhibitor, hydroxyethylene dipeptide isostere and γ-amino acid derivative and synthesis of (*R*) - selegiline *via* hydrolytic kinetic resolution

2.1. SECTION A

Asymmetric aminohydroxylation approach to the syntheses of HIV-protease inhibitor, hydroxyethylene dipeptide isostere and γ-amino acid derivative

2.1.1. Introduction

The last two decades have witnessed a considerable upsurge of interest in the use of enzyme inhibitors as therapeutic agents.[1] The advent of acquired immunodeficiency syndrome (AIDS) and the discovery of its causative agent, human immunodeficiency virus (HIV-1),[2] has given an impetus to the development of efficient inhibitors of viral enzymes, in particular of the transcriptase and more recently of the proteinase (HIV-PR).[3] Consequently numerous potent and selective HIV protease inhibitors have been designed based upon the transition state mimetic concept, incorporating hydroxyethylene and hydroxyethylamine dipeptide isosteres as the scissile site.[4]

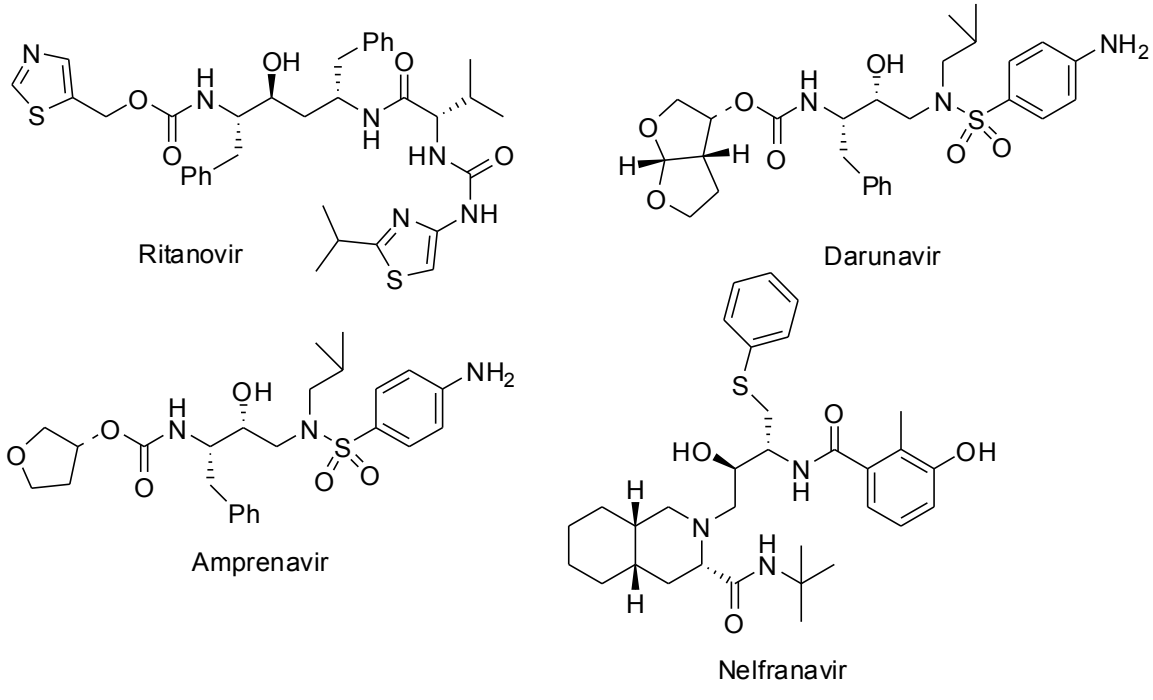
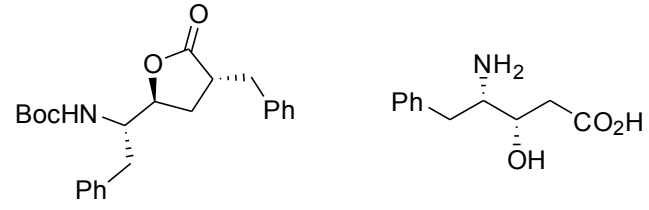


Figure 1. Structure of some protease inhibitors

In view of this, a highly enantioselective synthesis of the isostere unit **1** is still desirable. The development of new approaches to the stereo controlled synthesis of γ-amino β-

hydroxy acids has been a subject of immense interest within the context of biologically active peptide mimics.[5] The two well known examples are AHPPA (4-amino-3-hydroxy-5-phenylpentanoic acid) **2** and statin. They are the key constituents of microbially produced aspartic peptidase inhibitor, pepstatin.[6] AHPPA has also been employed for the design of HIV protease inhibitors.[7]



Phe-Phe hydroxyethylene dipeptide isostere

1

AHPPA

2

Figure 2. Protease inhibitors containing *syn*-amino alcohol unit.

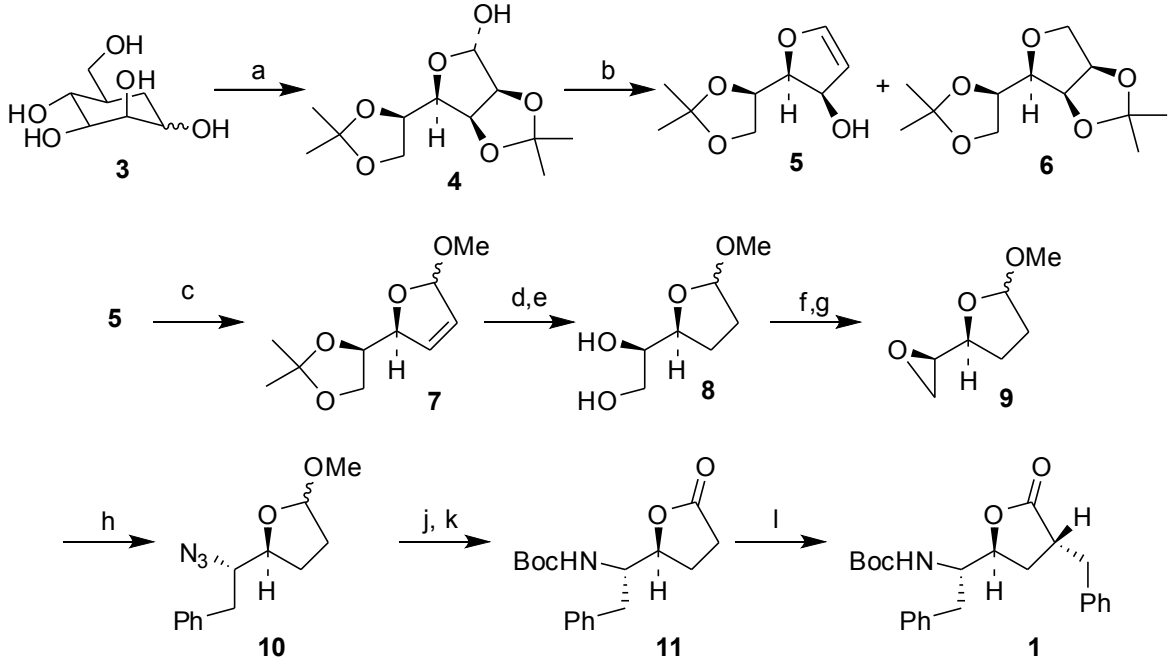
2.1.2. Review of Literature

While the majority of the earlier syntheses of isosteres and AHPPA use optically active amino acids as chiral pool material,[8,9,17] reports in which all the stereogenic centres are constructed by asymmetric synthesis are rather scarce.[10] A short review on some of the syntheses is described below.

Ghosh *et al.* (1991)[11]

Ghosh *et al*. reported an efficient and stereocontrolled synthesis of hydroxyethylene dipeptide isosteres **1** from commercially available, optically pure D-mannose. Thus, D-mannose **3** was converted to 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose **4**, deoxygenation of **4** at the C-2 position afforded the glycal **5**. Further dehydroxylation of glycal **5** at the C-3 position provided a mixture (52:48 by ^{1}H NMR) of methyl glycoside **7**. Catalytic hydrogenation of **7** with 10% palladium on charcoal afforded the corresponding saturated glycoside under hydrogenation condition. Removal of the isopropylidene group gave diol **8**. Glycosidic diol **8** was then converted to the desired epoxide **9** in the following two-step sequence, selective *O*-tosylation and treatment of the resulting crude tosylate with base. Regiospecific epoxide ring opening of **9** with phenylmagnesium bromide afforded glycosidic alcohol. Conversion of glycosidic alcohol to the corresponding azide **10** was

readily accomplished by a Mitsunobu reaction.[12] Grieco oxidation[13] of methyl furanoside **10** furnished corresponding azido γ-lactone. Catalytic hydrogenation of the resulting azido lactone with 10% palladium on charcoal in the presence of $(Boc)_2O$ furnished the Boc protected amino lactone **11**. Finally introduction of a benzyl group at C-2 was accomplished by stereoselective alkylation of **11** with benzyl iodide, to provide the desired alkylated lactone **1**.

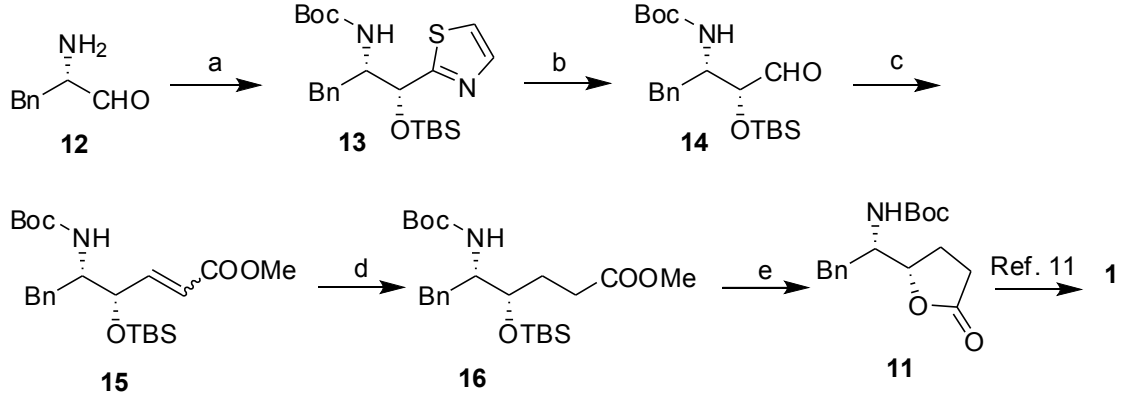


Scheme 1. *Reagents and conditions*: (a) Me_2CO, 3% H_2SO_4, 23 °C, 12 h; (b) $CC1_4$, $(Me_2N)P$, THF, -78 to 23 °C, 1 h; then Li, NH_3, -78 to 0 °C, 5 h; (c) MeOH, PPTS, CH_2C1_2, 0-23 °C, 12 h; (d) 10% Pd-C, H_2, EtOAC-MeOH (4:1), 5 h; (e) 40% aqueous AcOH, 90 °C, 3 h; (f) *p*-TsCl, pyridine, 0-23 °C, 12 h; (g) NaOMe, $CHCl_3$, 0 °C for 10 min; then 23 °C, 4 h; (h) (i) PhMgBr, CuI, THF, -40 to 0 °C, 3 h; (ii) Ph_3P, $EtO_2CN{=}NCO_2Et$, $Ph_2P(O)N_3$, PhMe, -10 to 23 °C, 12 h; (j) *m*-CPBA, BF_3.OEt, CH_2Cl_2, 0 °C, 3 h; (k) 10% Pd-C, H_2, EtOAc, $(Boc)_2O$, 6 h; (1) $(TMS)_2NLi$, THF, -78 °C, 30 min; $PhCH_2I$, -78 °C, 30 min; then $MeCH_2CO_2H$, -78 to 23 °C, 15 min.

Dondoni *et al.* (1995)[14]

Dondoni *et al*. synthesized hydroxyethylene dipeptide isostere **1** starting from L-phenylalanine. Thus *N*-monoprotected α-amino aldehyde **12** which was easily prepared from L-phenylalanine, was reacted with 2-(trimethylsily1)thiazole (2-TST) to furnish *syn*-amino alcohol **13** as major diastereomer.

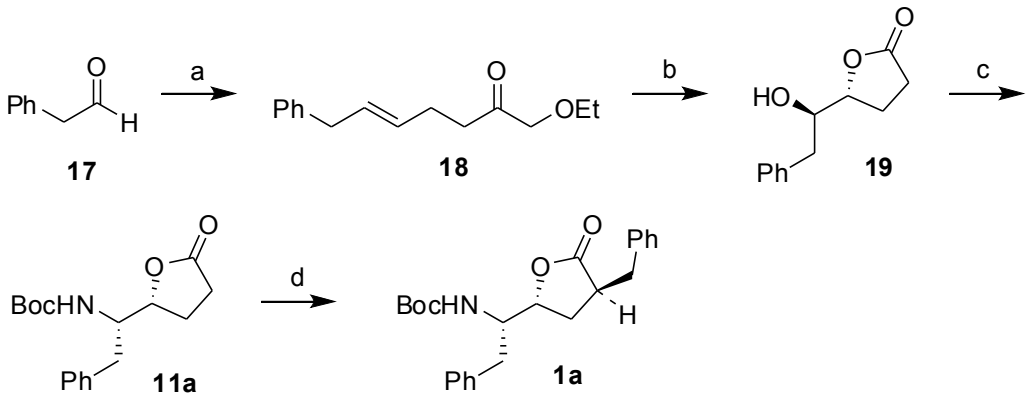
The resulting product **13** was then submitted to the one-pot thiazolyl-to-formyl unmasking sequence (*N*-methylation, reduction, hydrolysis)[15] to give the aldehyde **14** (Scheme 2). The Wittig olefination of aldehyde **14** with the stabilized ylide ((methoxycarbonyl)-methylene)triphenylphosphorane in toluene furnished **15** as a mixture of *E*- and *Z*-isomers in *ca*. 3:l ratio. Subsequent reduction by the use of nickel boride gave **16**. Finally the desilylation and concomitant lactonisation was achieved by treatment of compound **16** with tetrabutylammonium fluoride in THF at room temperature to furnish γ-lactone **11**. Stereoselective *anti*-alkylation at C-2 of lactone **11** gave the target compound **1**.[11]



Scheme 2. *Reagents and conditions*: (a) 2-(trimethylsilyl)thiazole; (b) (i) MeOTf; (ii) $NaBH_4$, THF; (iii) $CuO/CuCl_2/H_2O$; (c) $Ph_3P{=}CHCO_2Me$, Toluene; (d) $NiCl.6H_2O$-$NaBH_4$; (e) TBAF, THF-H_2O.

Ghosh *et al.* (1999)[16]

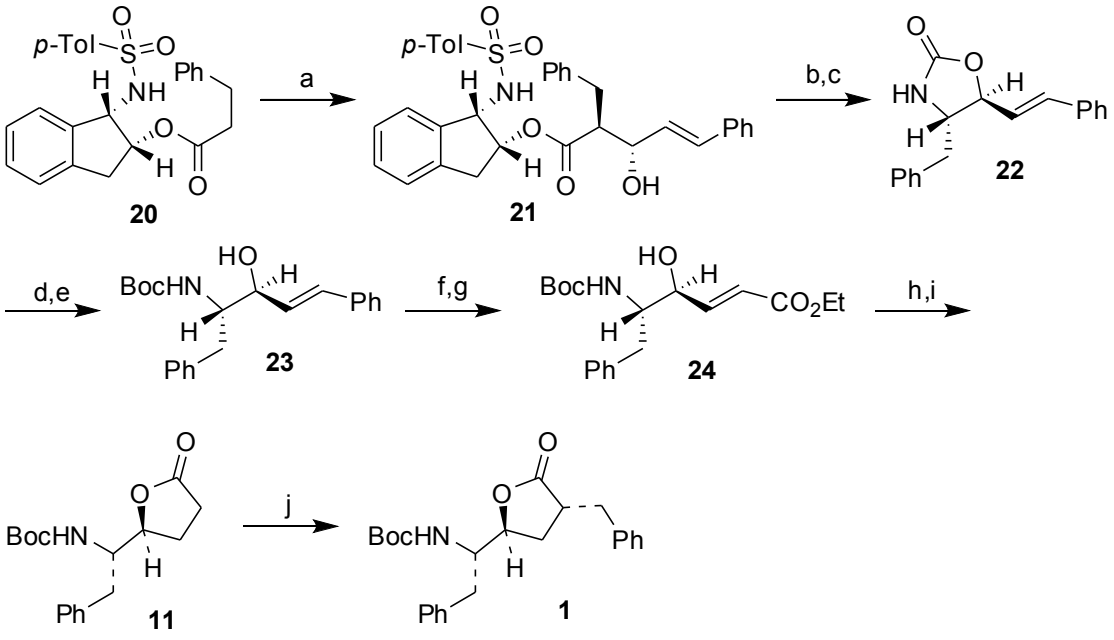
Ghosh *et al*. synthesized lactone **1a** as a part of core unit of ritanovir. Thus as illustrated in Scheme 3, γ,δ-unsaturated ester **18** was prepared by addition of vinyl magnesium bromide to phenylacetaldehyde **17**, followed by Claisen rearrangement of the resulting allylic alcohol with triethyl orthoacetate in the presence of propionic acid at 145 °C. Ethyl ester **18** was converted to lactone **19** utilizing Sharpless protocol using AD-mix-β. The hydroxy lactone **19** was transformed into protected amino lactone derivative **11a** in the following three steps sequence of mesylation with MsCl, displacement of the mesylate with NaN_3 and catalytic hydrogenation of the resulting azide over 10% Pd/C in EtOAc in the presence of $(Boc)_2O$ (overall 73% yield). The benzyl side chain at C-2 in isostere **1a** was installed by a stereoselective alkylation of lactone derivative **11a** as described previously.[11]



Scheme 3. *Reagents and conditions*: (a) (i) CH_2=CHMgBr, Et_2O, 0 °C, 57%; (ii) $MeC(OEt)_3$, $MeCH_2CO_2H$ (cat), 145 °C, 86%; (b) AD-Mix-β, $MeSO_2NH_2$, ^tBuOH, H_2O, 0 °C, then PhMe, 115 °C, 87%; (c) (i) MsCl, DMAP, Et_3N, CH_2Cl_2, 0 °C; (ii) NaN_3, DMF, 87%; (iii), H_2, 10% Pd-C, Et_3N, $(Boc)_2O$, EtOAc, 23 °C, 84%; (d) LiHMDS, THF, BnI, -78 °C, 70%.

Ghosh *et al.* (1999)[17]

Ghosh *et al.* reported another synthesis of phe-phe hydroxyethylene isostere as depicted in Scheme 4. Thus titanium enolate of **20** on reaction with cinnamaldehyde precomplexed with $TiCl_4$ afforded the *anti*-aldol product **21**. Removal of the chiral auxiliary, followed by Curtius rearrangement, provided the oxazolidinone **22**. Basic hydrolysis of **22** and subsequent protection of amine furnished the protected amino alcohol **23**. Thus, ozonolytic cleavage of the olefin **23** followed by reductive workup with triphenylphosphine gave the corresponding aldehyde. The crude aldehyde was then subjected to a Horner-Emmons olefination to provide α,β-unsaturated ester **24**. Catalytic hydrogenation of **24** over 10% Pd/ C provided the saturated ester quantitatively. The resulting ester was then lactonized with acetic acid in refluxing toluene to afford the γ-lactone **11** in 68% yield. For the preparation of hydroxyethylene Phe-Phe isostere, alkylation of **11** was carried out with lithium hexamethyldisilazide and benzyl iodide in THF, as has been accomplished previously.[11]

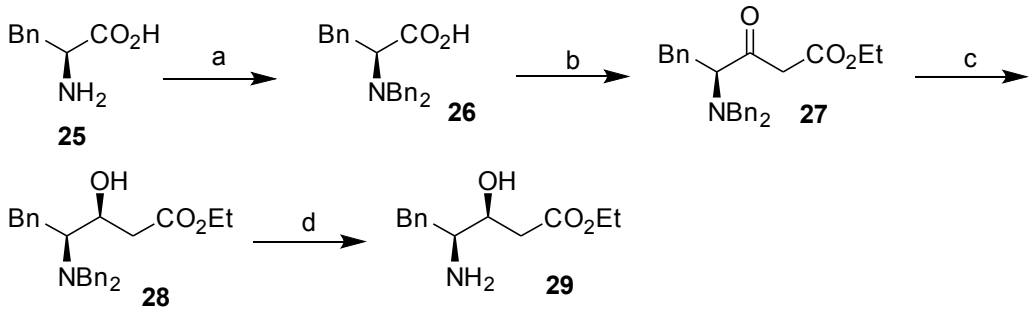


Scheme 4. *Reagents and conditions*: (a) $TiCl_4$, $^iPr_2NEt$, then (*E*)-PhCH=CHCHO, Bu_2BOTf, CH_2Cl_2, -78 °C, 68%; (b) 30% H_2O_2, LiOH, THF:H_2O (3:1), 23 °C, 85%; (c) DPPA, Et_3N, benzene, reflux, 92%; (d) aq KOH, EtOH, 70 °C; (e) $(Boc)_2O$, CH_2Cl_2, 23 °C, 85%; (f) O_3, CH_2Cl_2, PPh_3, -78 to 23 °C; (g) NaH, $(EtO)_2P(O)CH_2CO_2Et$, THF, 0 to 23 °C, 44% (from **22**); (h) H_2, 10% Pd/C, EtOAc:MeOH (1:1), 23 °C, 99%; (i) AcOH, toluene, 110 °C, 68%; (j) LiHMDS, BnI, THF, -78 °C, 77%.

Asymmetric synthesis of AHPPA

Reetz *et al*. (1989)[18]

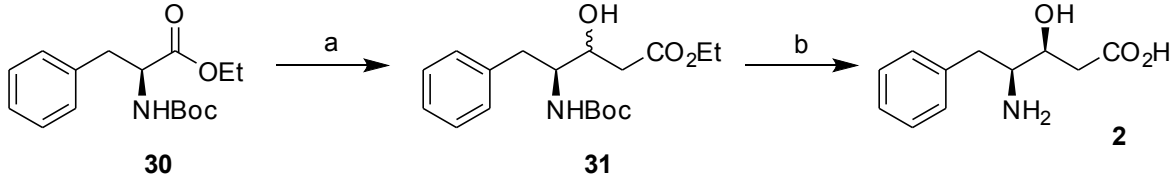
Reetz *et al*. synthesized ethyl ester of AHPPA **29** starting form naturally occurring L-phenyl alanine **25**. Thus protection of nitrogen with benzyl bromide provided the *N*,*N*-dibenzylated acid derivatives **26** which was converted into the imidazolides. Without isolation the latter was allowed to react with the magnesium enolate of malonic acid monoethyl ester at 0 to 40 °C, to afford keto esters **27** after acidic workup. Reduction of **27** using $NaBH_4$ in methanol at -20 °C occurred stereoselectively to form the desired (*S*,*S*)-products **28** preferentially (Scheme 5), which on deprotection of benzyl group using Pd-black/HCO_2H/MeOH afforded ethyl ester of AHPPA **29**.



Scheme 5. *Reagents and conditions:* (a) K_2CO_3/BnBr then KOH/H_2O/dioxane; (b) N,N-carbonyl diimidazole**,** then ^{i}PrMgCl/$CH_2(CO_2Et)CO_2H$; (c) $NaBH_4$/MeOH, -20 °C; (d) Pd-black/HCO_2H/MeOH.

Rich *et al.* (1980)[19]

Rich *et al*. synthesized AHPPA **2** starting form ethyl ester of naturally occurring L-phenyl alanine **30**. Thus L-phenyl alanine derivative **30** was easily converted into aldehyde which was treated with lithiated anion of ethyl acetate to furnish epimeric mixture of compound **31**. The desired *syn*-isomer was isolated by column chromatography, which on ester hydrolysis and Boc deprotection afforded the target compound AHPPA **2**.

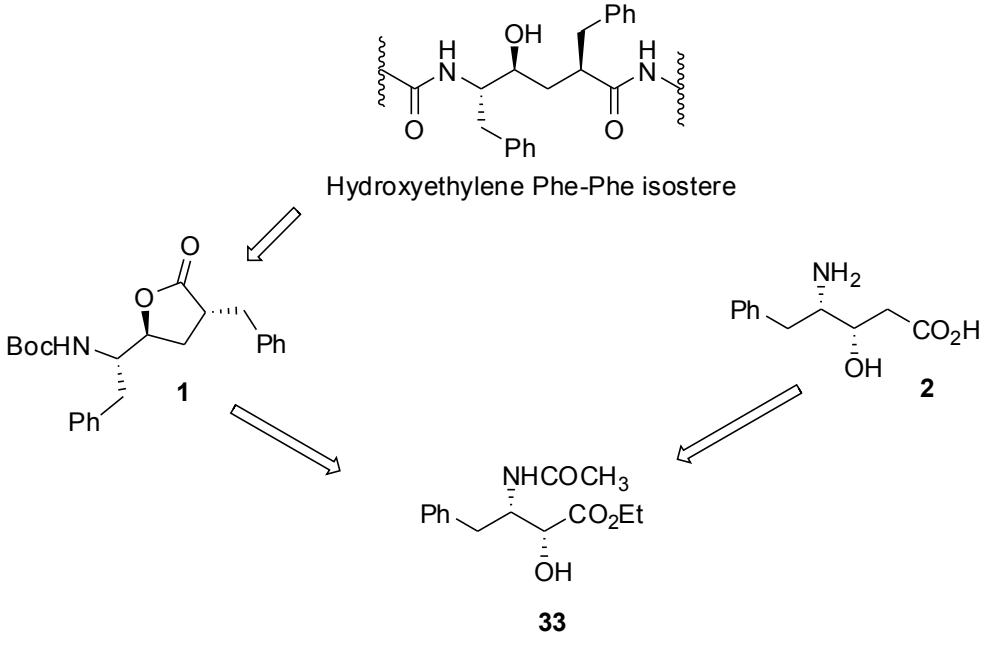


Scheme 6. *Reagents and conditions:* (a) DIBAL-H, -78 0 °C; (b) (i)$LiCH_2CO_2Et$, THF; (ii) NaOH; (iii) H^+.

2.1.3. Present work

Objective

As part of our research programme aimed at developing enantioselective syntheses of naturally occurring amino alcohols,[20] Sharpless asymmetric aminohydroxylation (AA)[21] was envisioned as a powerful tool, offering considerable opportunities for synthetic manipulations. We have now developed a new and enantioselective synthesis of lactone **1** and AHPPA **2** utilising Sharpless asymmetric aminohydroxylation as the key step.

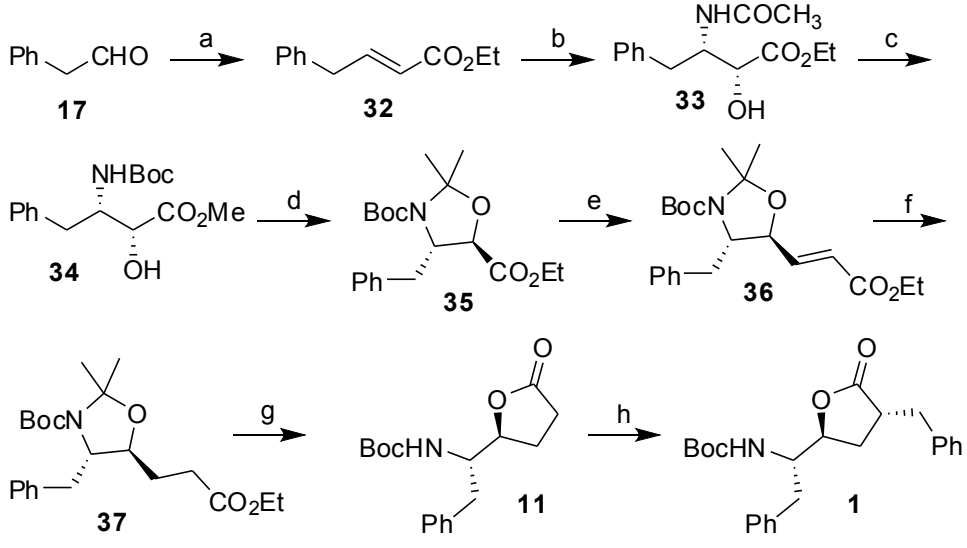


Scheme 7. Retrosynthetic analysis for synthesis of lactone **1** and AHPPA **2**

2.1.4. Results and Discussion

The synthesis of lactone **1** started from phenyl acetaldehyde **17**, a readily available starting material. Thus, treatment of **17** with (ethoxycarbonylmethylene) triphenylphosphorane in THF under reflux gave the Wittig product **32** in 85% yield. Appearance of peaks at δ 5.77 and in the range of δ 7.03-7.08 in ^{1}H NMR confirmed the formation of product. In the next, Sharpless aminohydroxylation step, it was envisioned that *N*-bromoacetamide would be the best nitrogen source of all those available at present[12b] for an easy chromatographic separation of the product and subsequent synthetic manipulation. Thus the asymmetric amino hydroxylation of the olefin **32** with potassium osmate (4 mol%) as oxidant in *tert*-

butanol–water (1:1) in the presence of $(DHQ)_2PHAL$ (5 mol%) as chiral ligand and freshly prepared *N*-bromoacetamide[22] as the nitrogen source, afforded the desired amino alcohol **33**[23] in 10:1 regioisomeric ratio and 64% yield with 89% ee, $[\alpha]_D^{20}$ -56.08 (*c* 0.8, CHCl3).[24] Appearance of singlet at δ 2.12 and multiplets in the range of δ 2.85-2.97, 4.35-4.39 in ^{1}H NMR and peaks at 3390, 3360, 1738 cm^{-1} in IR spectrum confirmed the formation of product (Scheme 8).

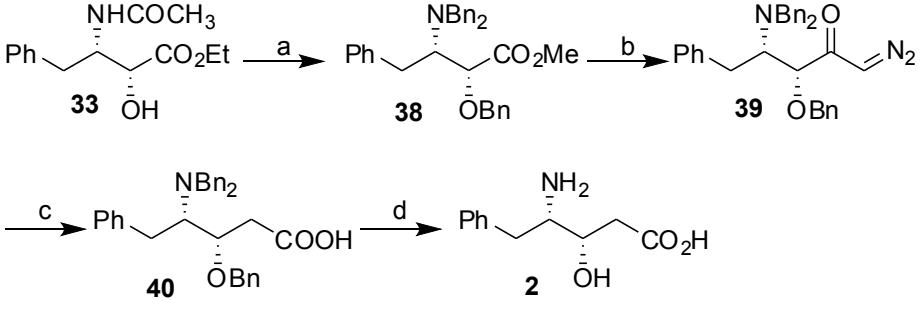


Scheme 8. *Reagents and conditions*: (a) $Ph_3P{=}CHCO_2Et$, THF, 0 °C to rt, 85%; (b) $(DHQ)_2PHAL$, $K_2[OsO_2(OH)_2]$, LiOH, *N*-bromoacetamide, *t*-butanol–H_2O (1:1), 0 °C to rt, 64%; (c) 0.5 M HCl in MeOH, reflux, then $(Boc)_2O$, Et_3N, DCM, 0 °C to rt, 87%; (d) 2,2-DMP, *p*-TSA, DCM, rt, 89%; (e) (i) DIBAL-H, DCM, -78 °C to rt; (ii) $Ph_3P{=}CHCO_2Et$, THF, 0 °C to rt, 46% (over two steps); (f) H_2, 10% Pd–C, EtOAc–MeOH, 90%; (g) AcOH, PhMe, reflux, 67%; (h) LiHMDS, BnBr, THF, -78 °C, 79%.

Further, in order to achieve the synthesis of target compound **1** from **33**, we required a suitable amino protecting group for further synthetic manipulation. To this end the amide **33** was subjected to hydrolysis using 0.5M HCl in methanol under reflux to furnish free amine with concomitant transesterification to the methyl ester. Appearance of singlet at δ 1.51, 3.77 in ^{1}H NMR confirmed the formation of product. The successive conversion of amine into the Boc protected amino alcohol **34** followed by further protection as acetonide using 2,2-dimethoxypropane in the presence of a catalytic amount of *p*-toluenesulfonic acid afforded **35** in 89% yield. Appearance of singlet at 1.38 and multiplet in the range of δ 1.58-1.60 in ^{1}H NMR and disappearance of peaks at 3434 cm^{-1} in IR spectrum confirmed

the formation of product. Reduction with DIBAL-H to the corresponding aldehyde and subsequent Wittig reaction with (ethoxycarbonylmethylene)triphenylphosphorane afforded the olefin **36**. Appearance of multiplet in the range of δ 5.76-5.85, 6.67-6.68 in ^{1}H NMR confirmed the formation of product. The olefin reduction by hydrogenation using 10% Pd–C gave **37** in 90% yield, which on acetonide deprotection using acetic acid followed by reflux in toluene underwent smooth lactonisation to furnish **11** in 67% yield. The appearance of peaks at 1768, 1710 cm^{-1} in IR spectrum and disappearance of peaks at δ 1.23, 4.08 in ^{1}H NMR confirmed formation of compound **11**. Lactone **11** was alkylated with benzyl bromide using LiHMDS as a base to furnish the desired compound **1** in good yield, $[\alpha]_D^{20}$ -41.7 (*c* 0.32, $CHCl_3$), lit.[17] $[\alpha]_D^{20}$ -40.0 (*c* 0.10, $CHCl_3$) along with a small amount (5%) of *cis*-alkylated product. This step completes the formal synthesis of the isostere since transformation of **1** to the isostere has been reported previously.[17]

Scheme 2 summarises the synthesis of (3*S*,4*S*)-4-amino-3-hydroxy-5-phenylpentanoic acid (AHPPA) from the common intermediate **33**.



Scheme 9. *Reagents and conditions*: (a) (i) 0.5M HCl in MeOH, reflux; (ii) BnBr, K_2CO_3, DCM, 79% (over two steps); (b) (i) LiOH, MeOH–H_2O (3:1); (ii) Et_3N, $ClCO_2Et$, THF, CH_2N_2, 38% (over two steps); (c) CF_3CO_2Ag, Et_3N, THF–H_2O, 60%; (d) (i) H_2, 10% Pd–C, EtOAc, rt; (ii) concd HCl, 80 °C, 62% (over two steps).

The cleavage of the *N*-acetyl group of **33** to the free amine was accomplished using 0.5M HCl in methanol under reflux with concomitant transesterification, *N*- and *O*-benzylation of resultant amino alcohol furnished compound **38**. The appearance of singlet at δ 4.51 and multiplet in the range of δ 7.25-7.32, 7.35-7.42 comfirmed the formation of compound **38**. Base hydrolysis of the ester furnished corresponding acid in good yield. For one carbon homologation of the acid, we attempted the following sequence. Acid was first converted into a mixed anhydride and subsequently treated with excess of diazomethane to furnish the

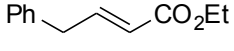
diazo compound **39** in moderate yield. Appearance of multiplet in the range of δ 4.22-4.31, 4.74-4.77 and disappearance of singlet at δ 4.51 in ^{1}H NMR confirmed the formation of compound **39**. Further treatment of **39** with silver oxide furnished desired acid **40** via Wolff rearrangement. Debenzylation of **40** led to the formation of the lactam, which on ring opening with concd. HCl furnished the target compound **2** in 73% yield {$[\alpha]_D^{20}$ -22.3 (*c* 0.36, H_2O), lit.17 $[\alpha]_D^{20}$ -24.0 (*c* 0.44, H_2O)}. The physical and spectroscopic data were in full agreement with the literature.[19]

2.1.5. Conclusion

In conclusion, enantioselective syntheses of lactone **1** and AHPPA **2** have been accomplished from a common intermediate **33** for the first time utilising Sharpless aminohydroxylation as the key step. A short reaction sequence and high overall yield of the target compounds render our strategy a good alternative to the known methods.

2.1.6. Experimental Section

(*E*)-Ethyl 4-phenylbut-2-enoate (32):



To a solution of (ethoxycarbonylmethylene)triphenylphosphorane (15.9 g, 45.8 mmol) in dry THF (150 mL) was added a solution of the aldehyde **17** (5.0 g, 41.6 mmol) in dry THF (50 mL). The reaction mixture was stirred for 24 h at room temperature. It was then concentrated and purified by silica gel column chromatography using petroleum ether/EtOAc (9.5/0.5) as eluent to afford the α,β-unsaturated olefin **32** as a colorless liquid.

Yield: 6.73 g, 85%

Mol. Formula: $C_{12}H_{14}O_2$

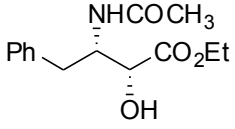
IR ($CHCl_3$, cm^{-1}): ν_{max} 3060, 2858, 1718, 1654, 1300, 1216, 1038.

^{1}H NMR (500 MHz, CDCl3): δ 1.23 (t, *J* = 7.2 Hz, 3H), 3.47 (dd, *J* = 1.2, 6.8 Hz, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 5.77 (td, *J* = 1.6, 15.9 Hz, 1H), 7.03-7.08 (m, 1H), 7.13(d, *J* = 8.4 Hz, 2H), 7.19-7.21 (m, 1H), 7.25-7.28 (m, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1, 38.3, 60.1, 122.3, 126.5, 128.6, 128.7, 137.6, 147.1, 166.3 ppm.

Analysis: Calcd.: C, 75.76; H, 7.42%; **Found:** C, 75.61; H, 7.28 %.

(2*R*,3*S*)-Ethyl 3-acetamido-2-hydroxy-4-phenylbutanoate (33):



$K_2[OsO_2(OH)_4]$ (0.27 g, 4.0 mol%) was dissolved with stirring in 90 mL of aqueous solution of $LiOH.H_2O$ (0.83 g, 19.7 mmol). After addition of *t*-BuOH (90 mL), $(DHQ)_2PHAL$ (0.72 mg, 5 mol%) was added and the mixture was immersed in a cooling bath set at 4 °C. After addition of olefin **32** (3.5 g, 18.4 mmol), *N*-bromo acetamide (2.8 g, 20.2 mmol) was added in one portion which resulted in an immediate color change to green and the mixture was vigorously stirred at the same temperature. The reaction was monitored by TLC, and pH (full conversion is indicated when the pH 7 of reaction mixture is attained). After 4 h, the reaction mixture was treated with Na_2SO_3 (2.5 g) and stirred at rt for 30 min. The organic layer was separated and the water layer extracted with ethyl acetate (3 x 60 mL), combined organic extracts were washed with brine and dried over Na_2SO_4. The residue was purified by silica gel column chromatography using EtOAc:pet.ether (6:4) to afford **33** as a syrupy liquid.

Yield: 3.12 g, 64%

Mol. Formula: $C_{14}H_{19}NO_4$

$[\alpha]_D^{25}$: -56.08 (*c* 0.8, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3390, 3360, 2983, 2361, 1738, 1657.

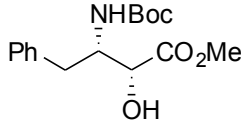
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.30 (t, J = 7.2 Hz, 3H), 2.15 (s, 3H), 2.77 (dd, J = 9.0, 13.9 Hz, 1H), 2.90 (dd, J = 9.0, 13.9 Hz, 1H), 4.24 (q, J = 7.2 Hz, 2H), 4.39–4.41 (m, 1H), 4.77 (dd, J = 2.0, 9.1 Hz, 1H), 6.52 (d, J = 8.9 Hz, 1H), 7.25–7.30 (m, 3H), 7.33-7.36 (m, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 22.9, 40.4, 52.8, 55.9, 61.6, 72.7, 126.7, 128.5, 129.3, 137.3, 170.9 ppm.

Analysis Calcd.: C, 63.38; H, 7.22; N, 5.28; **Found:** C, 63.21; H, 7.38; N, 5.43%

MS (GC–MS**):** m/z : 266 (M+1).

(2*R*,3*S*)-Methyl 3-(*tert*-butoxycarbonylamino)-2-hydroxy-4-phenylbutanoate (34):



Amino alcohol **33** (0.68 g, 2.56 mmol) was treated with 0.5 M HCl in methanol (68 mL), and heated under reflux for 15 h. After removal of solvent under reduced pressure, the residue was dissolved in fresh methanol (2x50 mL) and evaporated. Dry CH_2Cl_2 (20 mL) was added to the residue and solution cooled to 0 °C. To this suspension was added triethyl amine (0.86 mL, 6.15 mmol) in dry CH_2Cl_2 (5 mL) followed by $(Boc)_2O$ (0.92 mL, 3.84 mmol) in dry CH_2Cl_2 (5 mL). The reaction mixture was stirred for 30 min. at 0 °C and then for 24 h at room temperature. After TLC diagnosis, the reaction mixture was evaporated to near dryness and purified by silica gel column chromatography using EtOAc:pet.ether (3:7) to afford **34** as a syrupy liquid.

Yield: 0.69 g, 87%

Mol. Formula: $C_{16}H_{23}NO_5$

$[\alpha]_D^{25}$: -20.48 (*c* 0.7, $CHCl_3$)

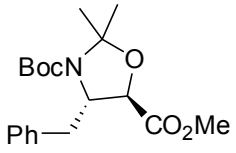
IR ($CHCl_3$, cm^{-1}): ν_{max} 3434, 3018, 2360, 1733, 1708, 1498, 1454, 1217, 1058.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.51 (s, 9H), 2.79-2.84 (m, 1H), 2.89-2.92 (m, 1H), 3.77 (s, 3H), 4.36-4.41 (m, 2H), 5.43 (bs, 1H), 7.25-7.29 (m, 3H), 7.33-7.36 (m, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 28.2, 40.2, 52.3, 57.1, 72.7, 79.9, 126.5, 128.5, 129.3, 137.3, 156.1, 171.9 ppm.

Analysis Calcd.: C, 62.12; H, 7.49; N, 4.53; **Found:** C, 62.28; H, 7.31; N, 4.37%

(4*S*,5*R*)-3-*tert*-Butyl 5-methyl 4-benzyl-2,2-dimethyloxazolidine-3,5-dicarboxylate (35):



To a solution of amino alcohol **34** (1.14 g, 3.5 mmol) in dry DCM (15 mL) was added 2,2-dimethoxy propane (0.1 mL, 8.75 mmol) and catalytic amount of *p*-TsOH (0.08 g). The reaction mixture was stirred at 0 °C to room temperature for 2 h. A pinch of $NaHCO_3$ was added and stirring was continued for additional 15 min and then the solution was extracted with EtOAc (3 x 10 mL). The combined extracts were washed with brine, dried (Na_2SO_4)

and concentrated. Silica gel column chromatography purification (EtOAc/petroleum ether:5/95) of the crude product gave **35** as a colourless liquid.

Yield: 1.06 g, 89%

Mol. Formula: $C_{19}H_{27}NO_5$

$[\alpha]_D^{25}$: -0.70 (*c* 1.8, $CHCl_3$)

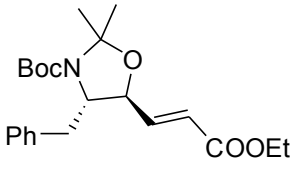
IR ($CHCl_3$, cm^{-1}): ν_{max} 3020, 2360, 1749, 1703, 1496, 1454, 1390, 1253, 1089.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.38 (s, 9H), 1.58-1.60 (m, 6H), 2.99-3.04 (m, 2H), 3.60 (s, 3H), 4.10-4.13 (m, 1H), 4.31-4.35 (m, 1H), 7.27-7.32 (m, 5H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 24.0, 26.5, 28.2, 39.4, 52.0, 64.0, 78.3, 80.3, 95.3, 126.7, 128.3, 129.5, 136.3, 150.9, 171.4 ppm.

Analysis Calcd.: C, 65.31; H, 7.79; N, 4.01; **Found:** C, 65.50; H, 7.61; N, 3.87%

(4*S*,5*S*)-*tert*-Butyl 4-benzyl-5-((*E*)-3-ethoxy-3-oxoprop-1-enyl)-2,2-dimethyloxazolidine-3-carboxylate (36):



To a solution of methyl ester **35** (1.0 g, 2.86 mmol) in CH_2Cl_2 (15 mL), was added DIBAL-H (1.36 mL 2.3 M solution in toluene, 3.14 mmol) at -78 °C under argon atmosphere. The reaction was stirred at this temperature for 40 min, then a solution of tartaric acid (5 mL) was added. The resulting mixture was stirred for 15 min and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL), the combined organic layers were dried (Na_2SO_4), and evaporated under reduced pressure to give aldehyde as a colourless liquid, which was directly used in the next step without further purification.

To a solution of (ethoxycarbonylmethylene)triphenylphosphorane (1.1 g, 3.14 mmol) in dry THF (150 mL) was added a solution of the above aldehyde in dry THF (50 mL). The reaction mixture was stirred for 24 h at room temperature. It was then concentrated and purified by silica gel column chromatography using petroleum ether/EtOAc (19/1) as eluent to afford the α,β-unsaturated olefin **36** as a colorless liquid.

Yield: 0.51 g, 46%

Mol. Formula: $C_{22}H_{31}NO_5$

$[\alpha]_D^{25}$: -0.64 (*c* 6.8, $CHCl_3$)

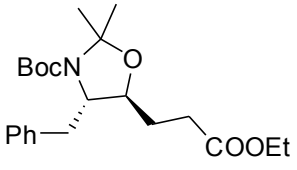
IR ($CHCl_3$, cm^{-1}): ν_{max} ν_{max} 3030, 2360, 1730, 1654, 1629, 1215.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (t, *J* = 7.1 Hz, 3H), 1.40-1.56 (m, 15H), 2.95 (d, *J* = 5.2 Hz, 2H), 4.01-4.09 (m, 2H), 4.17-4.22 (m, 2H), 5.76-5.85 (m, 1H), 6.67-6.68 (m, 1H), 7.26-7.27 (m, 3H), 7.31-7.34 (m, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.2, 28.3, 38.5, 60.4, 62.8, 79.2, 122.6, 126.7, 128.4, 129.5, 136.8, 165.9 ppm.

Analysis Calcd.: C, 67.84; H, 8.02; N, 3.60; **Found:** C, 67.69; H, 8.17; N, 3.75%

(4*S*,5*S*)-*tert*-Butyl 4-benzyl-5-(3-ethoxy-3-oxopropyl)-2,2-dimethyloxazolidine-3-carboxylate (37):



To a solution of olefin **36** (0.20 gm, 0.51 mmol) in ethyl acetate (8 mL) was added 10% Pd/C (0.02 g), and reaction mixture was stirred under hydrogen atmosphere for 12 h at room temperature. After completion of reaction as indicated by TLC, the reaction mixture was filtered through a celite pad and the filtrate was concentrated in vacuo. Silica gel column chromatography using petroleum ether/EtOAc (19/1) as eluent afforded the compound **37** as a colorless liquid.

Yield: 0.18 g, 90%

Mol. Formula: $C_{22}H_{33}NO_5$

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

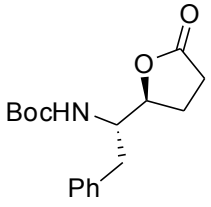
IR ($CHCl_3$, cm^{-1}): ν_{max} 3030, 2360, 1730, 1654, 1629, 1215.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.23 (t, *J* = 7.6 Hz, 3H), 1.48-1.54 (m, 15H), 1.58-1.72 (m, 2H), 2.08-2.10 (m, 2H), 2.84 (dd, *J* = 6.9, 13.7 Hz, 1H), 2.96 (dd, *J* = 6.9, 13.7 Hz, 1H), 3.68-3.77 (m, 1H), 4.02-4.04 (m, 1H), 4.08 (q, *J* = 7.6 Hz, 2H) 7.22-7.25 (m, 3H), 7.30-7.32 (m, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.2, 26.1, 28.4, 30.4, 41.5, 60.3, 60.9, 80.6, 126.6, 128.5, 129.4, 137.6, 172.9 ppm.

Analysis Calcd.: C, 67.49; H, 8.50; N, 3.58; **Found:** C, 67.35; H, 8.67; N, 3.74 %

***tert*-Butyl (*S*)-1-((*S*)-5-oxotetrahydrofuran-2-yl)-2-phenylethylcarbamate (11)**:



To a stirred solution of compound **37** (0.5 g, 1.3 mmol) in MeOH was added a catalytic amount of *p*-TSA at room temperature and the reaction mixture stirred overnight at the same temperature. Solid $NaHCO_3$ (0.1 g) was added and stirred for 30 min. The mixture was then filtered through a celite pad, washed with MeOH and concentrated. Silica gel column chromatography using petroleum ether:ethyl acetate (1:1) afforded **11** as a pale yellow liquid.

Yield: 0.26 g, 67%

Mol. Formula: $C_{17}H_{23}NO_4$

$[\alpha]_D^{25}$: -4.4 (*c* 0.84, $CHCl_3$) {Lit[17] -4.1 (*c* 0.73, $CHCl_3$)}

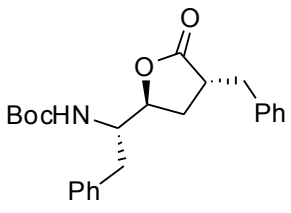
IR ($CHCl_3$, cm^{-1}): ν_{max} 3062, 1768,1710,1490, 1454, 1020.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.40 (s, 9H), 2.07-2.19 (m, 2H), 2.42-2.60 (m, 2H), 2.88 (dd, *J* = 7.5, 13.5 Hz, 1H), 2.96 (dd, *J* = 7.0, 13.5 Hz, 1H), 3.97-4.08 (m, 1H), 4.42-4.49 (m, 1H), 4.64 (d, *J* = 10.0 Hz, 1H), 7.20-7.35 (m, **5** H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 24.1, 28.2, 28.7, 39.4, 54.0, 79.9, 80.0, 126.4, 126.7, 128.6, 129.3, 137.1, 155.8, 177.2 ppm.

Analysis Calcd.: C, 66.86; H, 4.58; N, 7.60; **Found:** C, 66.71; H, 4.38; N, 7.51%

***tert*-Butyl-(*S*)-1-((2*S*,4*R*)-4-benzyl-5-oxotetrahydrofuran-2-yl)-2-phenylethylcarbamate (1)**:



Lithium hexamethyldisilazide (2 mmol) was prepared by the dropwise addition of 1.5 M *n*-BuLi in hexane (1.35 mL) to hexamethyldisilazane (0.46 mL, 2.2 mmol) in THF (2 mL) at

0 °C for 5 min and then warmed to 23 °C for 15 min. The resulting solution was cooled to -78 °C, and lactone **11** (0.305 g, 1 mmol) in THF (2 mL) was added dropwise for 5 min. The mixture was stirred at -78 °C for 30 min, and benzyl iodide (0.22 g, 1 mmol) in THF (1 mL) was added slowly for 2 min. The resulting reaction mixture was stirred at -78 °C for 30 min and then quenched with propionic acid (0.25 mL) in THF (1 mL), stirred for 5 min, and warmed to 23 °C for 15 min. Aqueous 10% citric acid (10 mL) and ethyl acetate *(*50 mL) were added, and the layers were separated. The aqueous layer was extracted with ethyl acetate (30 mL), and the combined extract was washed with aqueous $NaHCO_3$ and brine and dried (Na_2SO_4). Evaporation of solvents gave a residue which was flash chromatographed over silica gel **(**1:3 ethyl acetate:pet ether) to provide **1** .

Yield: 0.31 g, 79%

Mol. Formula: $C_{24}H_{29}NO_4$

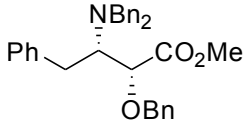
$[\alpha]_D^{25}$: -42.4 (*c* 0.2, $CHCl_3$) {Lit[17] -40 (*c* = 0.1, $CHCl_3$)}

IR ($CHCl_3$, cm^{-1}): ν_{max} 3060, 1768, 1710, 1490, 1454, 1302, 1249, 1032.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.35 (s, 9 H), 1.95 (m, 1H), 2.2 (m, 1H), 2.75 (dd, *J* = 8.0, 13.2 Hz, 1H), 2.85 (m, 2H), 2.98 (m, 1H), 3.12 (dd, *J* = 5.0, 14.1 Hz, 1H), 3.95 (q, *J* = 9.2 Hz, 1H), 4.2 (m, 1H), 4.5 (d, *J* = 10.1 Hz, 1H), 7.10-7.30 (m, 10 H) ppm.

Analysis Calcd.: C, 72.89; H, 7.39; N, 3.54; **Found:** C, 72.64; H, 7.50; N, 3.67%

(2*R*,3*S*)-Methyl 2-(benzyloxy)-3-(dibenzylamino)-4-phenylbutanoate (38):



Amino alcohol **33** (0.63 g, 2.38 mmol) was treated with 0.5 M HCl in methanol (63 mL), and heated under reflux for 15 h. After removal of solvent under reduced pressure, the residue was dissolved in fresh methanol (2x50 mL) and evaporated. Dry CH_2Cl_2 (20 mL) was added to the residue and solution cooled to 0 °C. To a 0 °C solution of crude amino alcohol (0.5 g, 2.38 mmol) in CH_2Cl_2 (5 mL) was added K_2CO_3 (1.98 g, 14.33 mmol) followed by benzyl bromide (1.4 mL, 11.94 mmol), in CH_2Cl_2 (2 mL). The reaction was allowed to warm to room temperature and was complete after stirring for 24 h, as indicated by TLC analysis. The reaction was quenched with H_2O at 0 °C and diluted with CH_2Cl_2.

The mixture was extracted with CH_2Cl_2, and the combined organic phases washed with brine, dried over Na_2SO_4, and concentrated in vacuo to afford crude benzylated product. Silica gel column chromatography using pet ether/ EtOAc (8/2) gave compound **38** as a colorless liquid.

Yield: 0.89 g, 79%

Mol. Formula: $C_{32}H_{33}NO_3$

$[\alpha]_D^{25}$: +22.97 (*c* 0.26, $CHCl_3$)

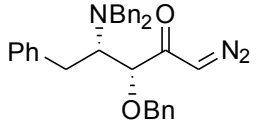
IR ($CHCl_3$, cm^{-1}): ν_{max} 3085, 1731, 1650, 1494, 1454, 1261, 1027.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.87-2.92 (m, 2H), 3.05-3.14 (m, 1H), 3.23-3.27 (m, 1H), 3.43-3.46 (m, 1H), 3.71(d, *J* = 3.7 Hz, 2H), 3.75-3.81 (m, 1H), 3.94-3.97 (m, 1H), 4.02-4.04 (m, 1H), 4.51 (s, 3H), 7.25-7.32 (m, 10H), 7.35-7.42 (m, 10H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 14.5, 33.4, 40.1, 54.8, 55.8, 60.4, 61.4, 64.9, 67.8, 126.1, 126.8, 127.4, 128.0, 128.4, 128.6, 128.9, 129.1, 129.3, 137.9, 138.1, 139.7, 170.5 ppm.

Analysis Calcd.: C, 80.14; H, 6.94; N, 2.92; **Found:** C, 80.31; H, 6.69; N, 3.04%

(3*R*,4*S*)-3-(Benzyloxy)-1-diazo-4-(dibenzylamino)-5-phenylpentan-2-one (39):



To a solution of (2*R*,3*S*)-methyl 2-(benzyloxy)-3-(dibenzylamino)-4-phenylbutanoate **38** (1.0 g, 2.10 mmol) in methanol: H_2O (3:1) (2 mL) at 0 °C was added LiOH (0.26 g, 6.26 mmol). The reaction mixture was stirred at 0 °C for 0.5 h, then 4 h at room temperature and concentrated in vacuo. The residue was acidified with 0.1M aqueous HCl and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, concentrated. To this crude acid in CH_2Cl_2 (10 mL) was added ethyl choloroformate (0.2 mL, 2.10 mmol), Et_3N (0.44 mL, 3.12 mmol), After stirring the reaction mixture for 1 h, freshly prepared CH_2N_2 (0.44 g, 10.4 mmol) was added, and reaction was allowed to stir at 0 °C for 1 h and at room temp. for 24 h, after completion of reaction the triethylamine hydrochloride precipitate was filtered and washed with ether (3x15 mL). The yellowish filtrate was then concentrated in vacuo, and the residue obtained was purified by column chromatography using pet ether: EtOAc (85:15) to afford α-diazo ketone **39** as a syrupy liquid.

Yield: 0.39 g, 38%

Mol. Formula: $C_{32}H_{31}N_3O_2$

$[\alpha]_D^{25}$: -2.87 (*c* 0.16, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 2964, 2361, 2106, 1813, 1749, 1680.

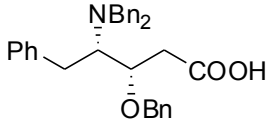
^{1}H NMR (500 MHz, $CDCl_3$): δ 2.96 (t, *J* = 12.4 Hz, 1H), 3.16–3.21 (m, 1H), 3.36 (d, *J* = 12.8 Hz, 2H), 3.53 (d, *J* = 12.9 Hz, 2H), 4.09 (d, *J* = 13.4 Hz, 2H), 4.24 (t, *J* = 6.9 Hz, 2H), 4.69–4.71 (m, 2H), 7.22–7.38 (m, 20H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 14.2, 29.9, 55.2, 64.7, 126.5, 127.1, 128.1, 128.6, 128.7, 128.8, 129.0, 129.3, 139.9 ppm.

Analysis Calcd.: C, 78.50; H, 6.38; N, 8.58; **Found:** C, 78.34; H, 6.51; N, 8.70%

MS (GC-Ms**):** m/z 490 (M+1).

(3*S*,4*S*)-3-(Benzyloxy)-4-(dibenzylamino)-5-phenylpentanoic acid (40):



To a flask carefully wrapped in aluminum foil (to exclude light during the reaction), containing diazo ketone **39** (0.5 g, 1.04 mmol) dissolved in tetrahydrofuran (8 mL), de-ionized water (1 mL) was added, and the flask is cooled to −25 °C. To this reaction mixture silver trifluoroacetate (0.03 g, 0.14 mmol) and triethylamine (0.44 mL, 3.12 mmol) were added in one portion (via syringe). The solution was allowed to warm to room temperature overnight. The solution was evaporated to dryness with a rotary evaporator and the residue was stirred for 1 h with saturated aqueous sodium bicarbonate ($NaHCO_3$) solution (10 mL). The reaction mixture was extracted with ethyl acetate (3 x 15 mL). The organic layer was washed with three additional portions of saturated aqueous $NaHCO_3$ solution (3 x 10 mL). The combined organic layers are dried over magnesium sulfate and evaporated on a rotary evaporator. Column chromatography of the crude product using MeOH: CH_2Cl_2 (1:19) gave the acid **40** as a white solid.

Yield: 0.29 g, 60%

Mol. Formula: $C_{32}H_{33}NO_3$

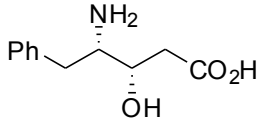
$[\alpha]_D^{25}$: -8.4 (*c* 1.0, $CHCl_3$)

IR (NaCl, 1% KBr, cm^{-1}): ν_{max} 3310, 3074, 3060, 1740, 1612, 1554, 1180, 1065.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.62-1.73 (m, 3H), 2.01-2.09 (m, 1H), 2.31-2.42 (m, 1H), 2.75-3.03 (m, 1H), 3.43-3.73 (m, 2H), 3.87-4.21 (m, 2H), 4.27-4.67 (m, 1H), 5.16-5.50 (m, 1H), 7.18-7.39 (m, 7H), 7.50 (t, *J* = 7.7 Hz, 5H), 7.63 (t, *J* = 7.3 Hz, 3H), 8.14 (d, *J* = 8.32 Hz, 5H) ppm.

Analysis Calcd.: C, 80.14; H, 6.94; N, 2.92; **Found:** C, 80.34; H, 6.63; N, 2.78%

(3*S*,4*S*)-4-Amino-3-hydroxy-5-phenylpentanoic acid (2):



A solution of acid **40** (0.29 g, 0.60 mmol) in EtOAc (5 mL) was added Pd/C (10% mol) and reaction mixture was stirred for 12 h under hydrogen atmosphere. After completion of reaction as indicated by TLC, the catalyst was removed by filtration and the solvent was evaporated to furnish lactam, which was directly used in the next step without purification. Lactam (0.11 g) was dissolved in conc. HCl (3 mL) and the reaction mixture was warmed to 80 °C for 3 h. Then the water was removed in vacuo to give the crude hydrochloride salt. The crude salt is applied to an ion exchange Dowex column [50X8-100(acidic form)] eluting first with water and then with a 2N NH_4OH solution to give acid **2** as a white solid.

Yield: 0.08 g, 62%

Mol. Formula: $C_{11}H_{15}NO_3$

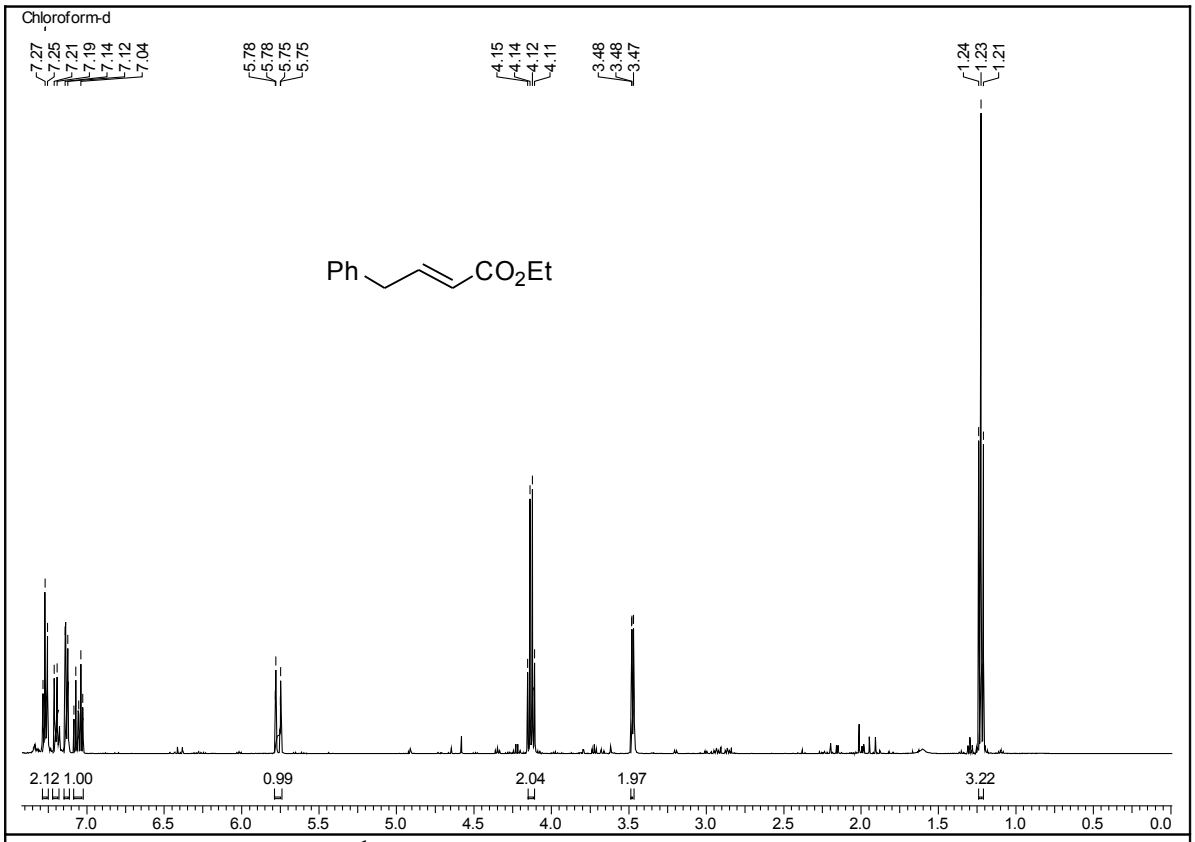
$[\alpha]_D^{25}$: -26.0 (*c* 0.40, H_2O) {Lit[19] -24 *(c* 0.44, H_2O)}

IR (NaCl, 1% KBr, cm^{-1}): ν_{max} 3304, 3074, 3060, 1756, 1612, 1554, 1508, 1431, 1358, 1180, 1065.

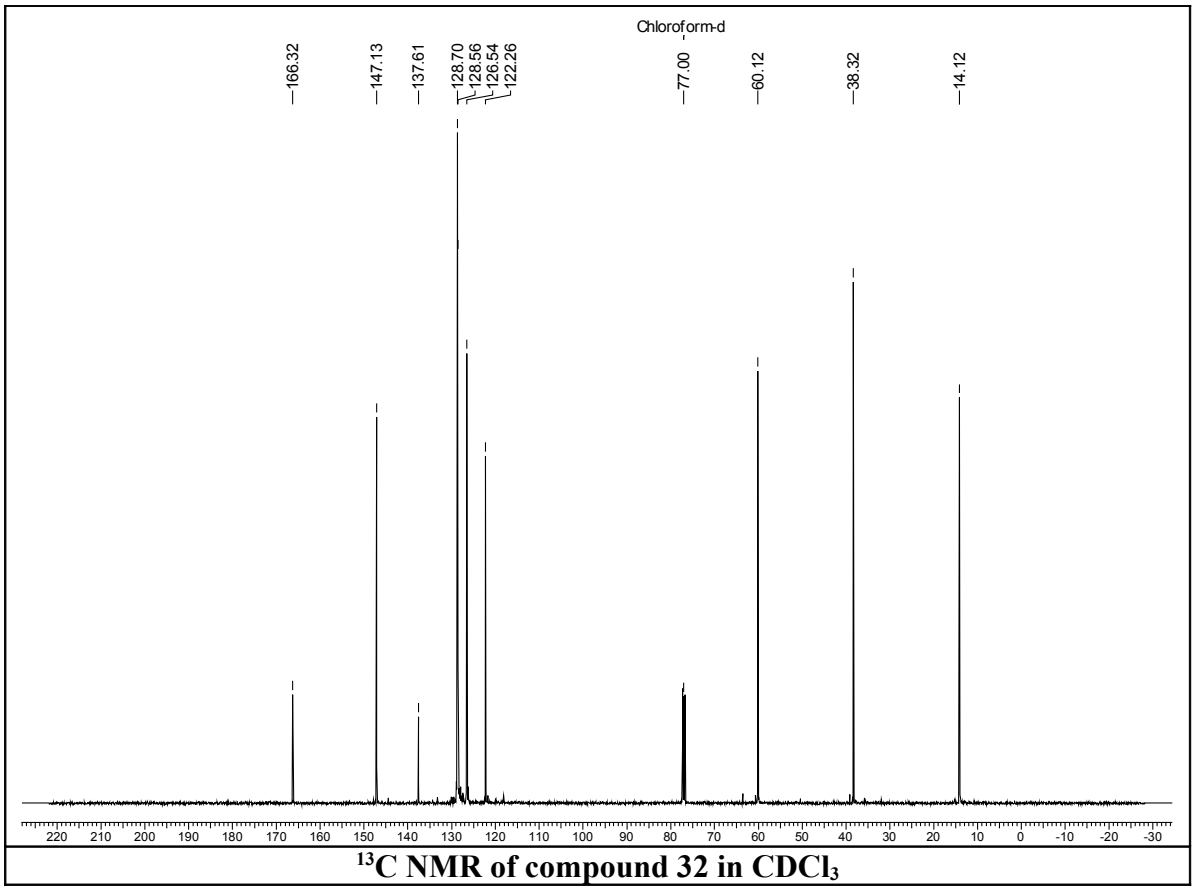
^{1}H NMR (200 MHz, D_2O): δ 2.49-2.61 (m, 2H), 2.73-3.29 (m, 2H), 3.45-3.68 (m, 1H), 3.99-4.19 (m, 1H), 7.40 (s, 5 H) ppm.

Analysis Calcd.: C, 63.14; H, 7.23; N, 6.69; **Found:** C, 63.29; H, 7.41; N, 6.51%

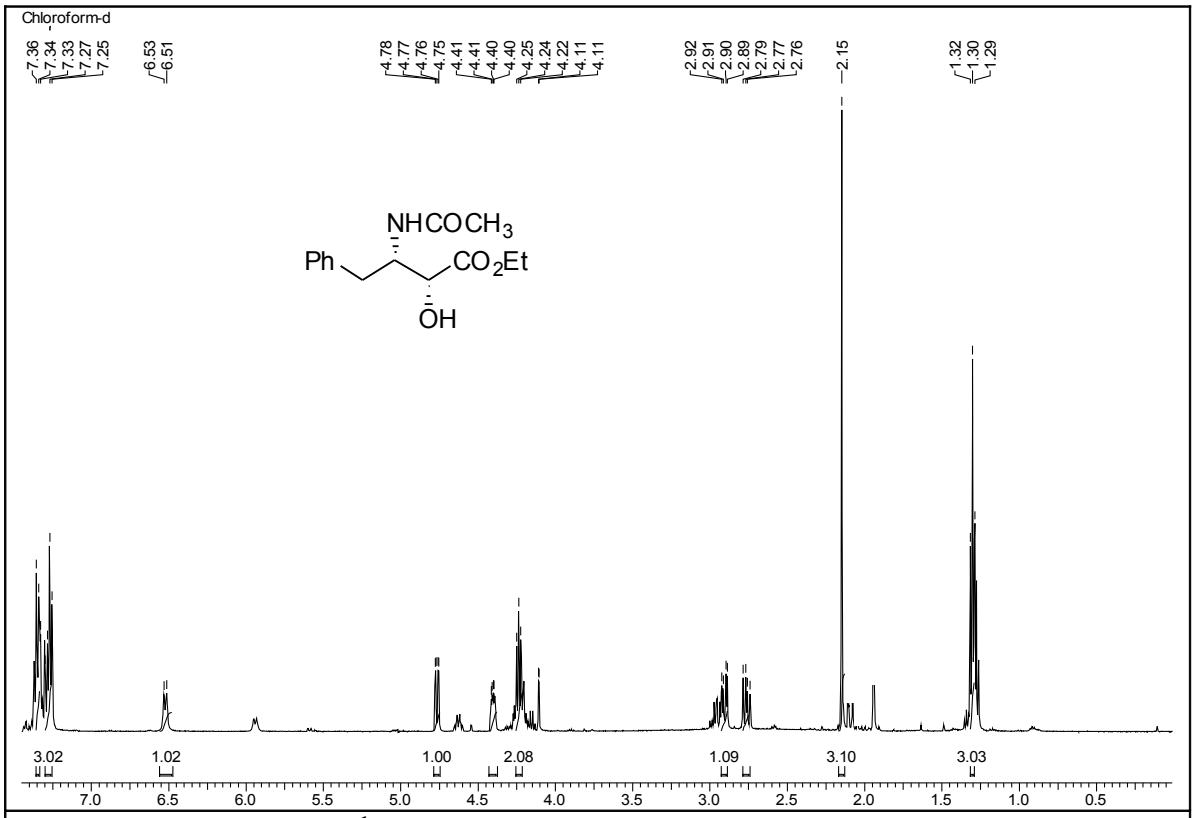
2.1.7. Spectras



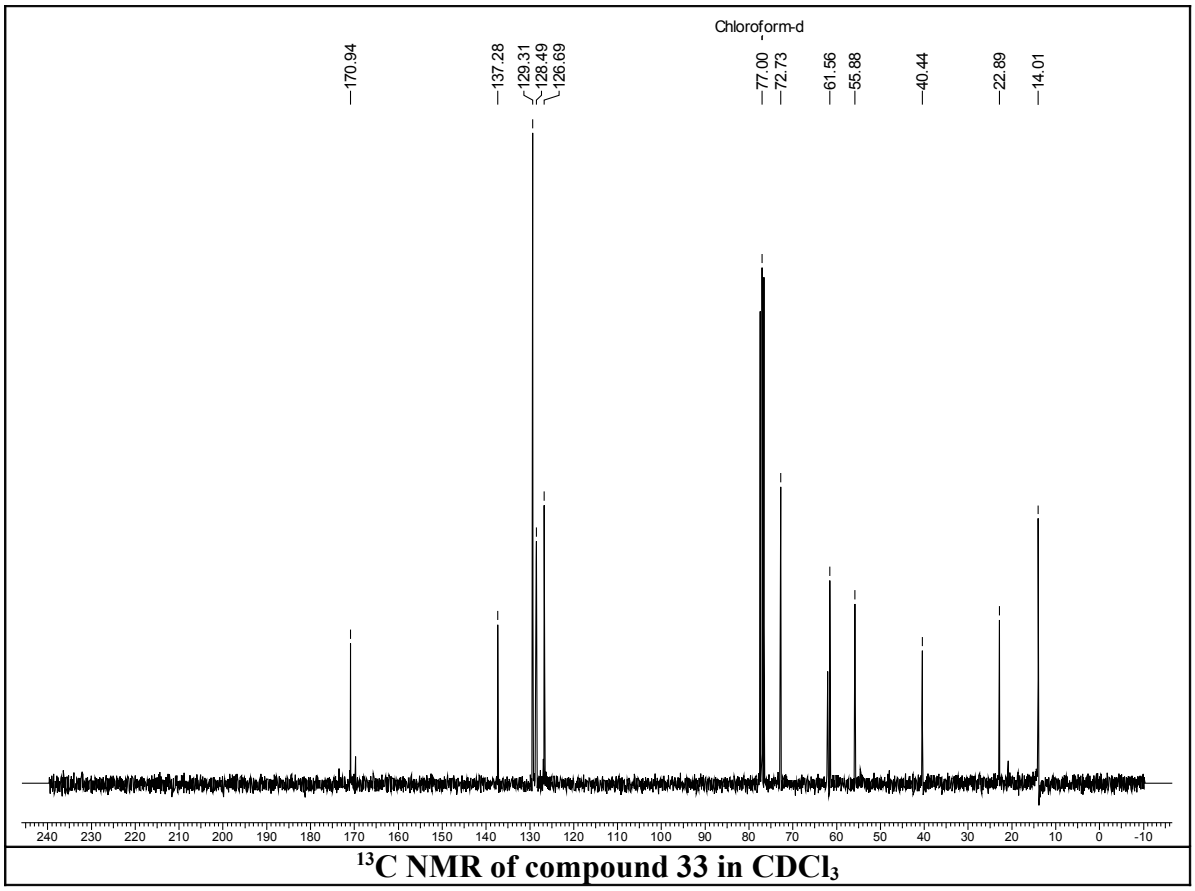
^{1}H NMR of compound 32 in $CDCl_3$



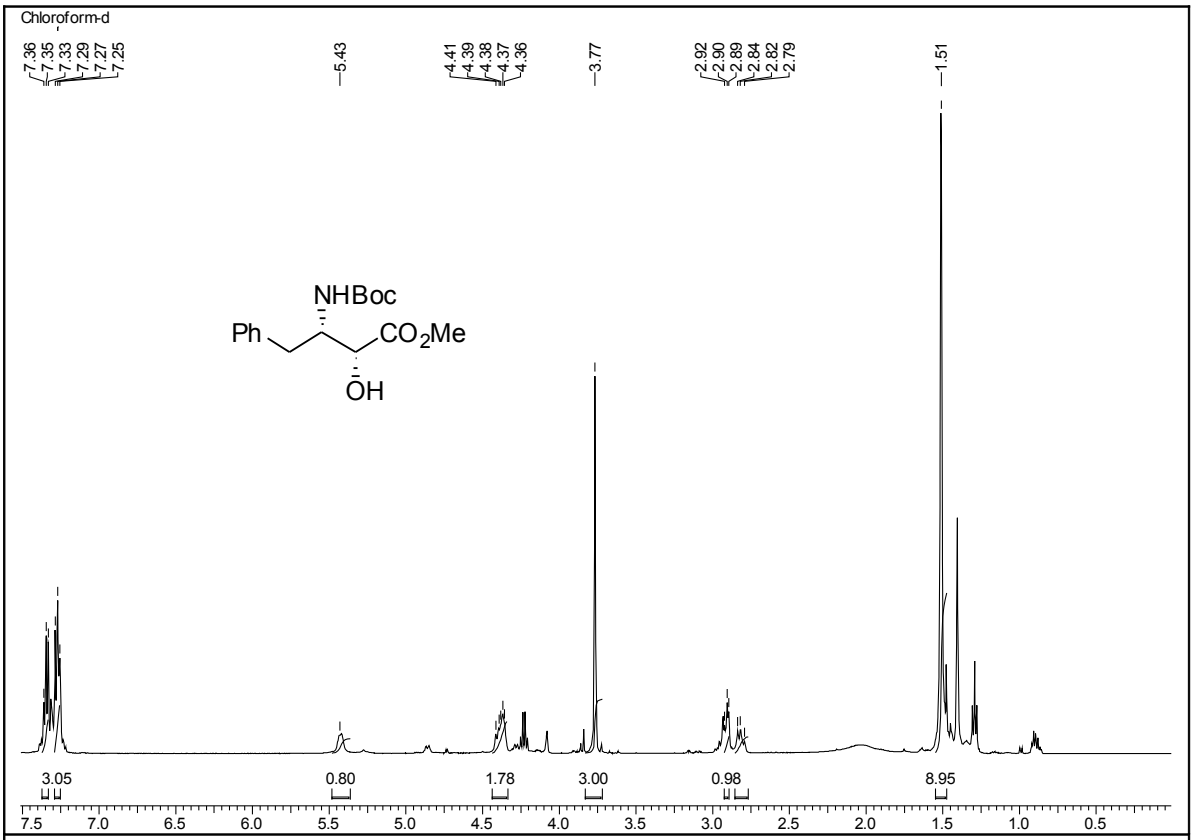
^{13}C NMR of compound 32 in $CDCl_3$



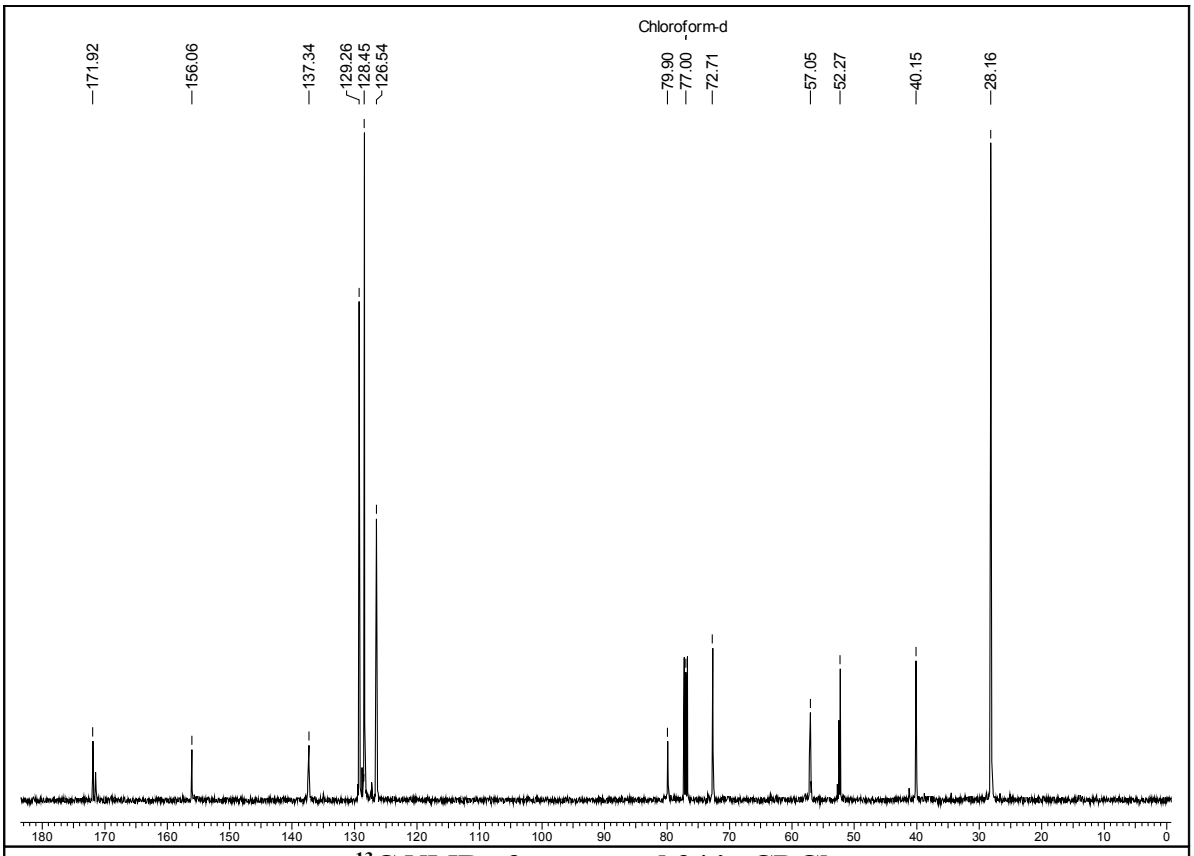
^{1}H NMR of compound 33 in $CDCl_3$



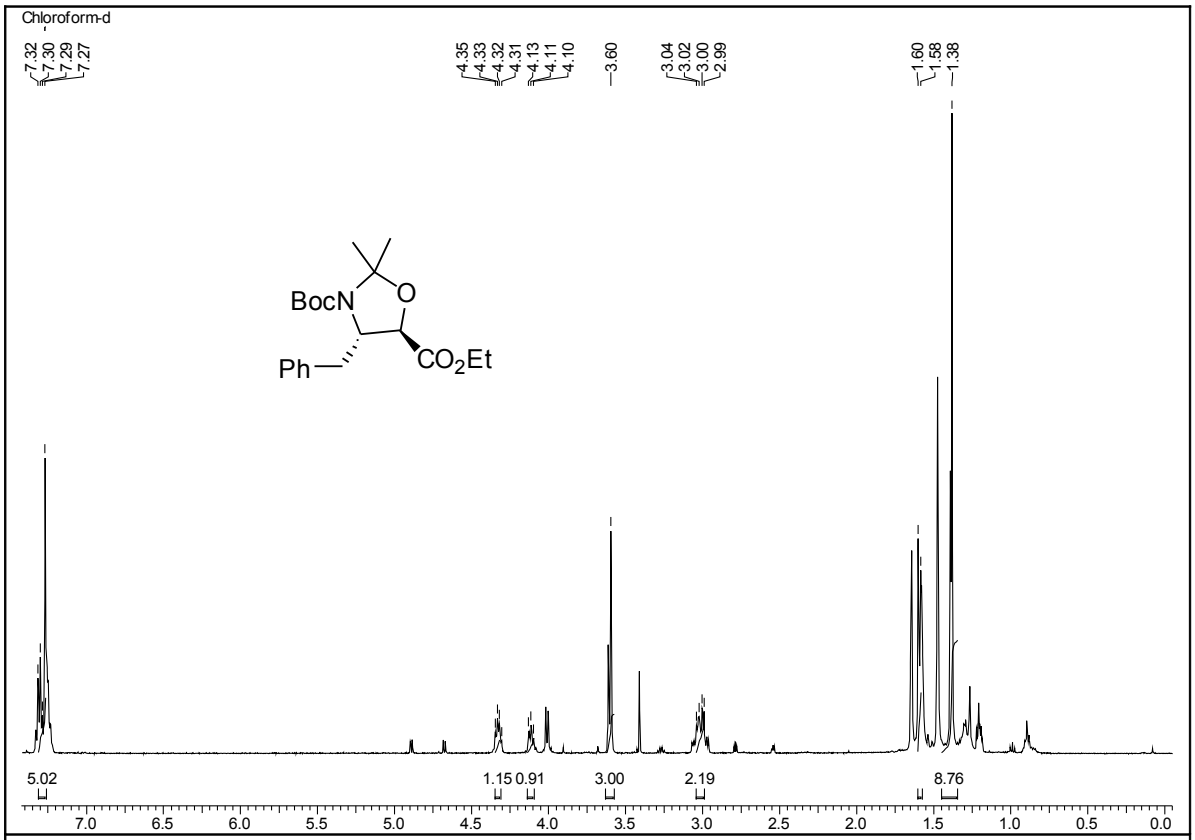
^{13}C NMR of compound 33 in $CDCl_3$



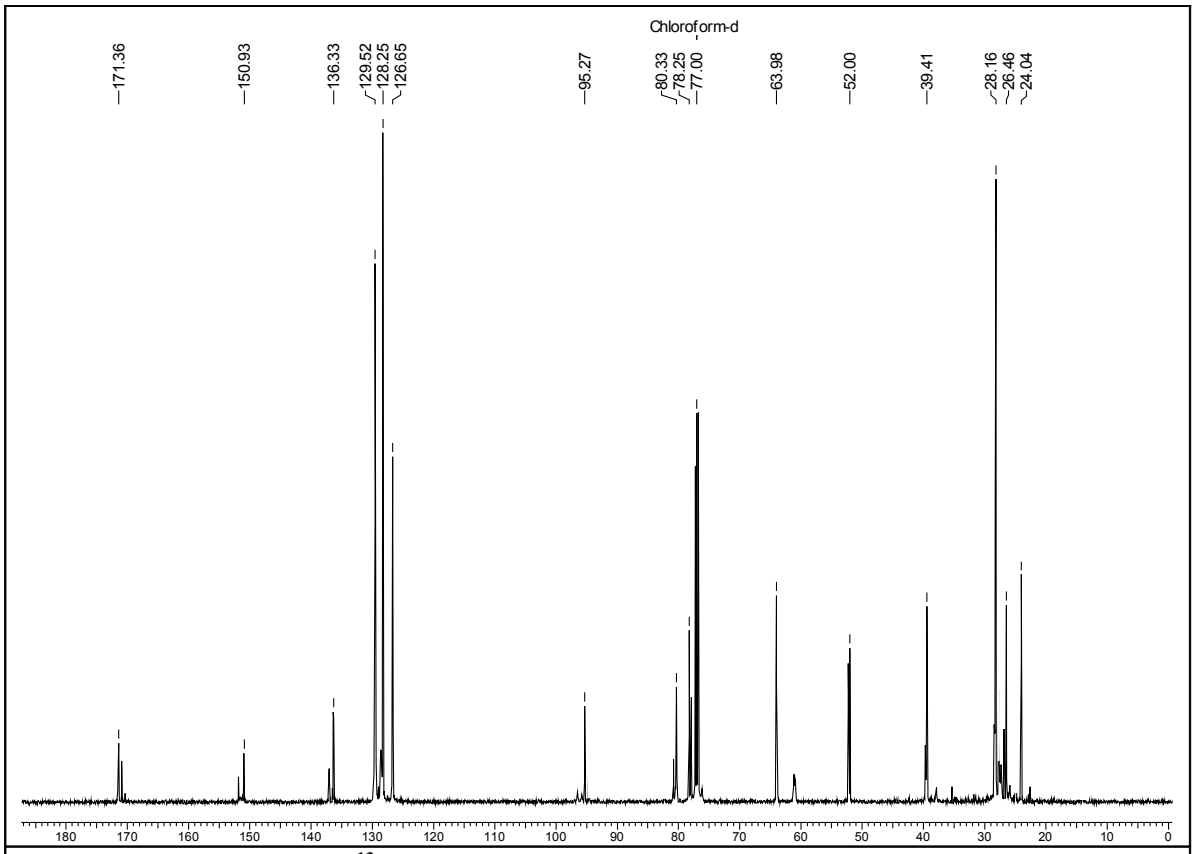
^{1}H NMR of compound 34 in $CDCl_3$



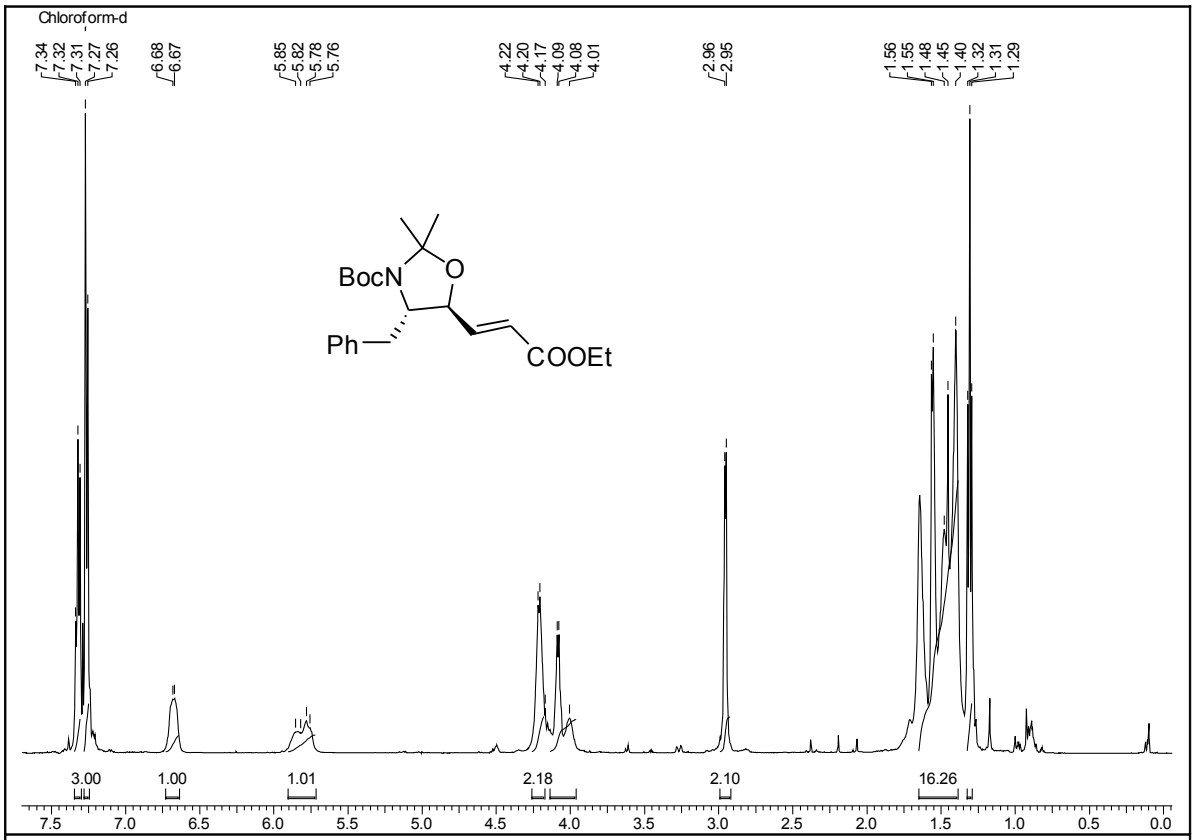
^{13}C NMR of compound 34 in $CDCl_3$



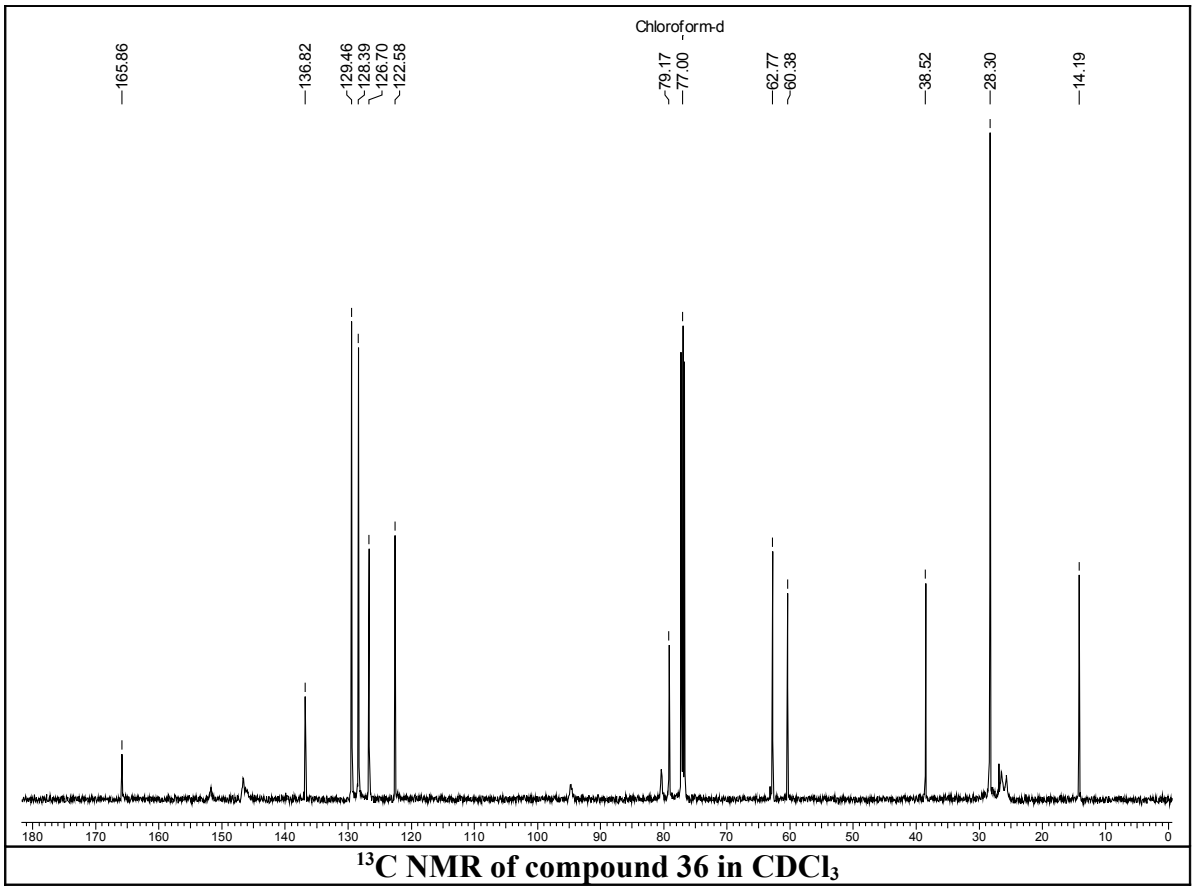
^{1}H NMR of compound 35 in $CDCl_3$



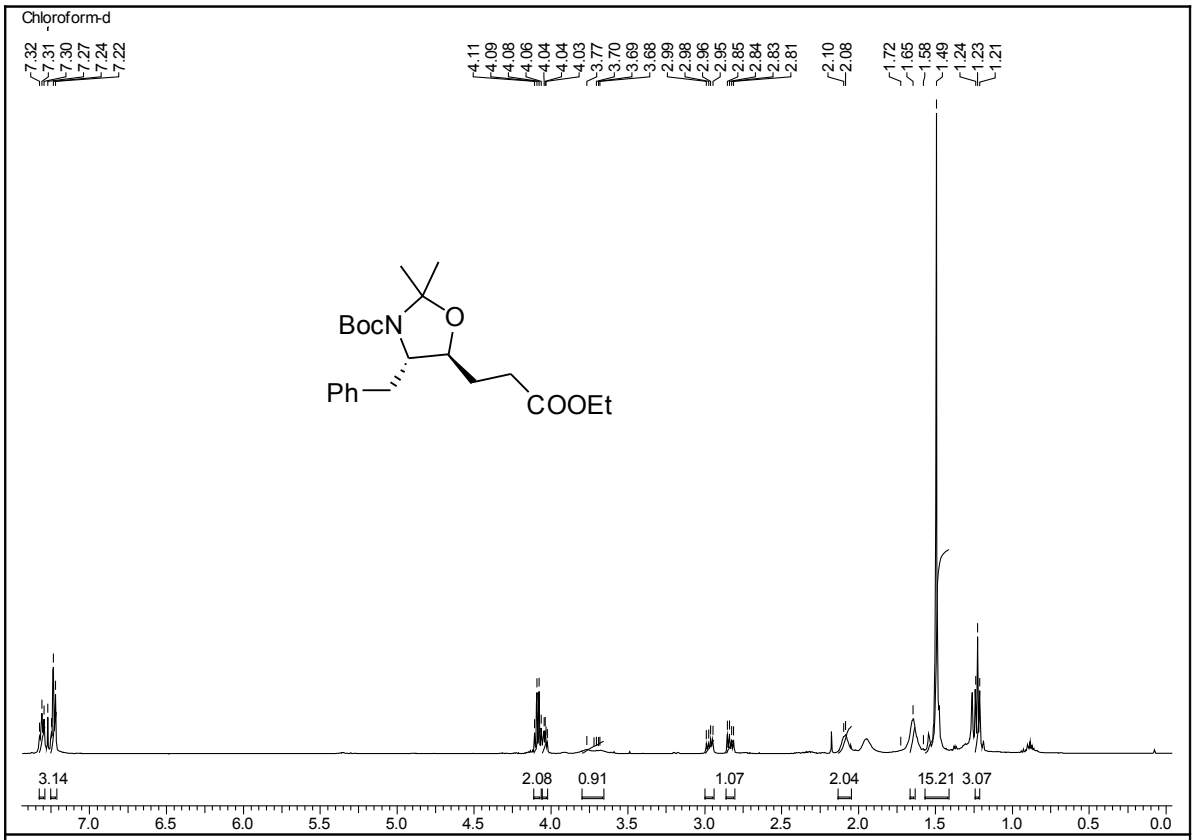
^{13}C NMR of compound 35 in $CDCl_3$



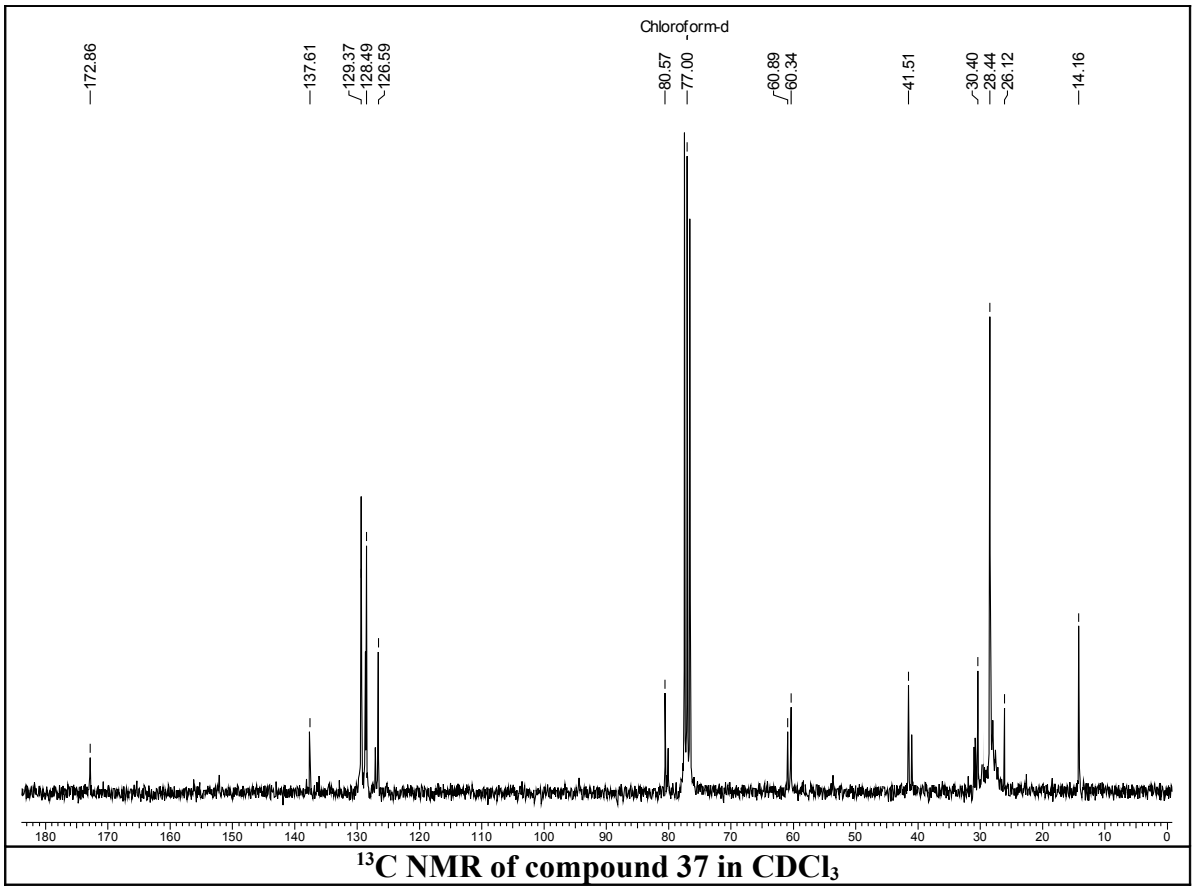
^{1}H NMR of compound 36 in $CDCl_3$



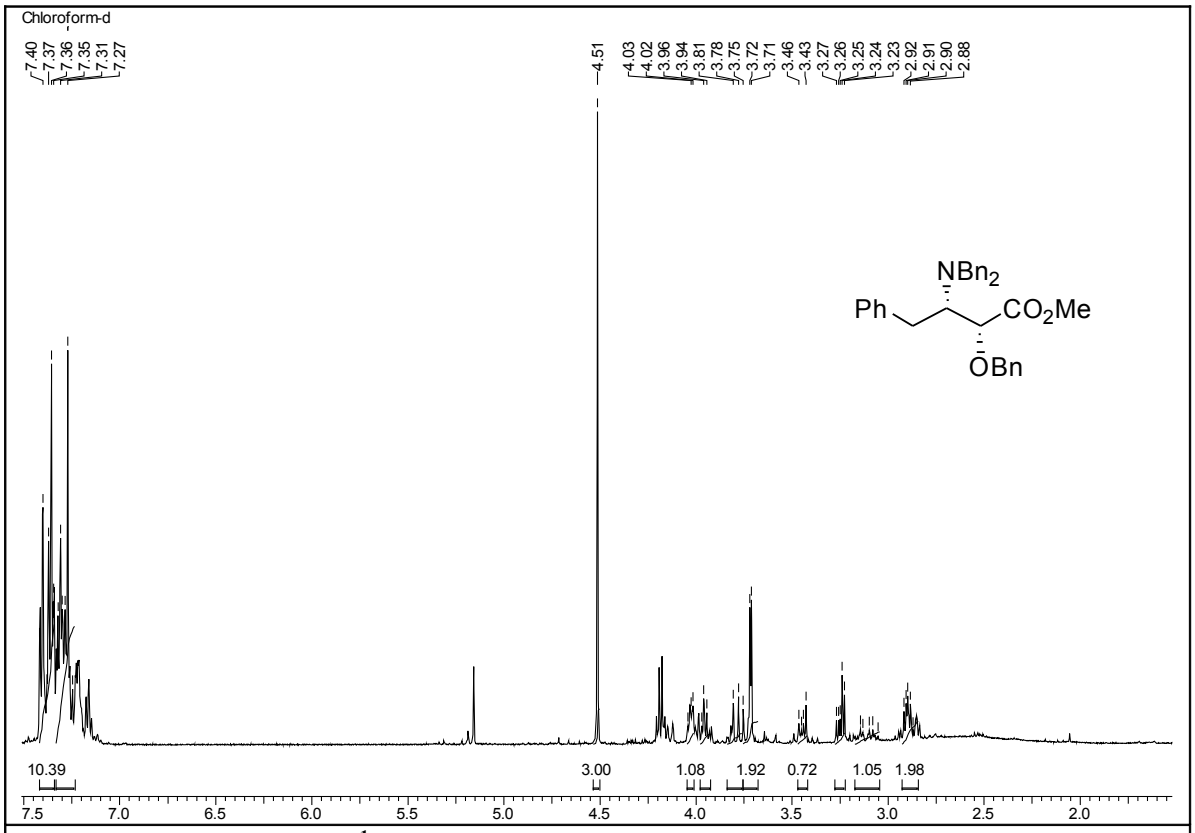
^{13}C NMR of compound 36 in $CDCl_3$



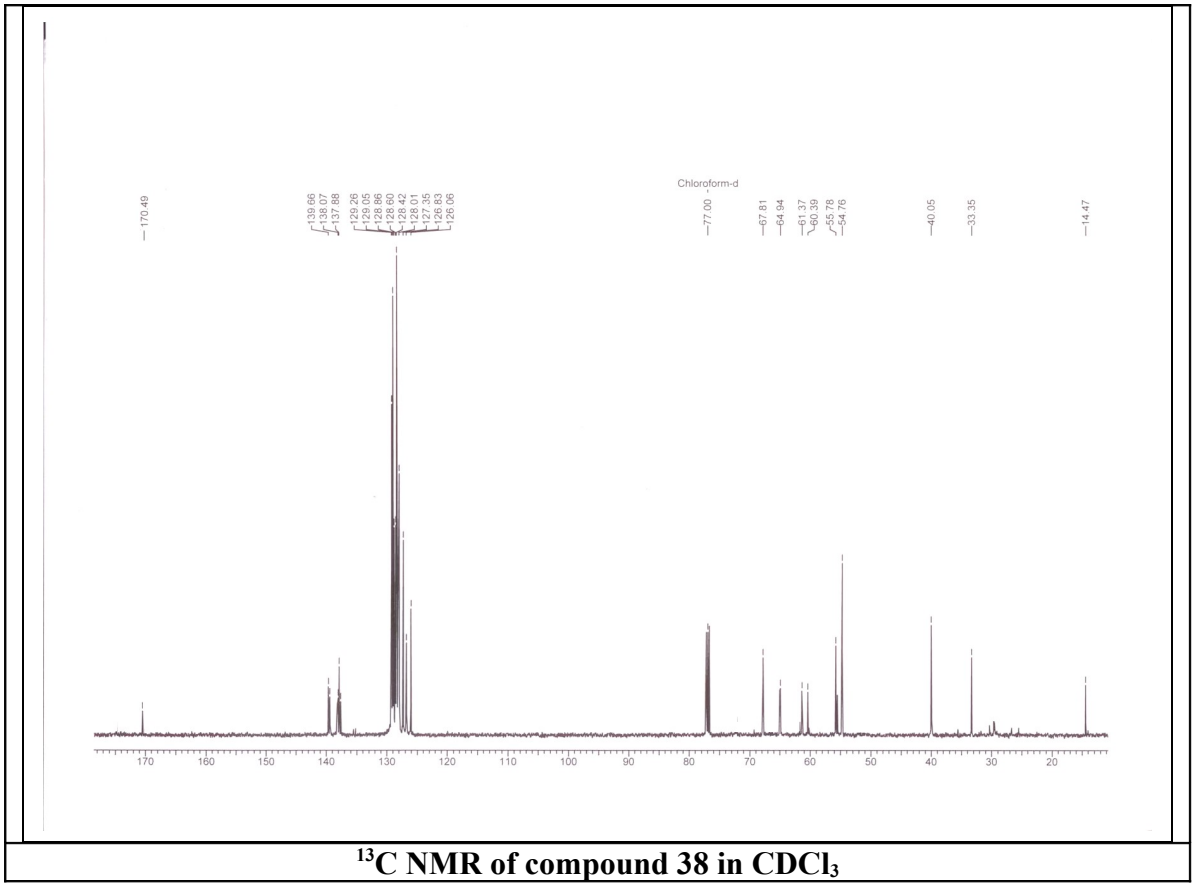
^{1}H NMR of compound 37 in $CDCl_3$



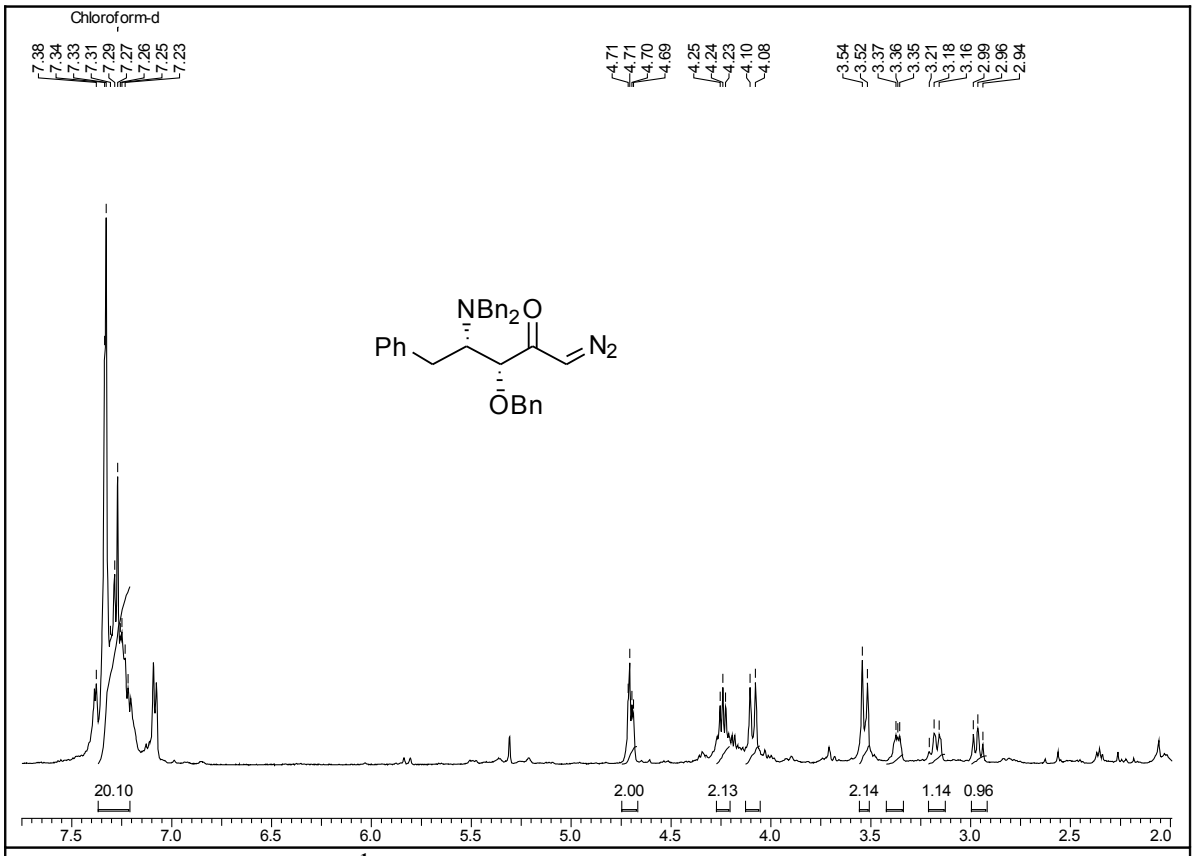
^{13}C NMR of compound 37 in $CDCl_3$



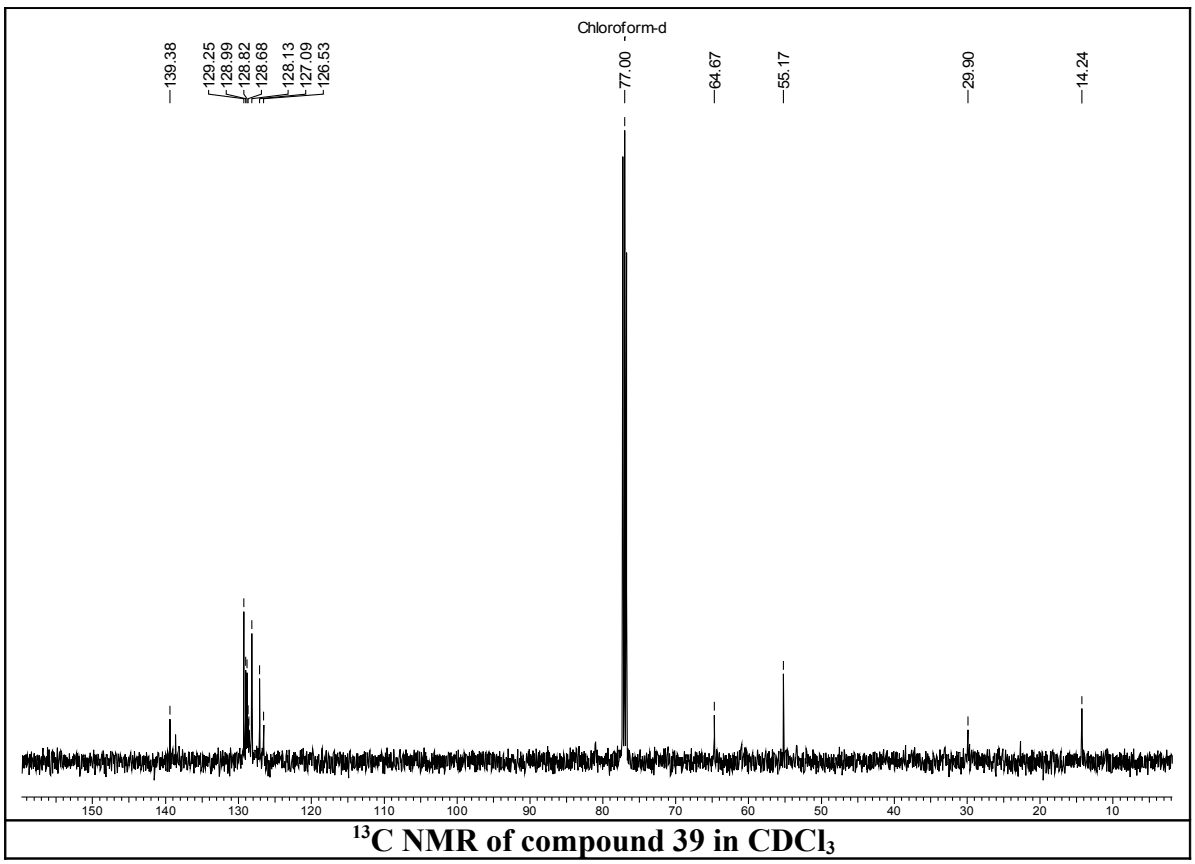
^{1}H NMR of compound 38 in $CDCl_3$



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



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



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

2.1.8. References

1. Sandler, M.; Smith, H. J. Design of Enzyme Inhibitors as Drugs;Oxford: Oxford, UK, 1989.
2. (a) Barre-Sinoussi, F.; Chermann, J. C.; Rey, F.; Nugeyre, M. T.; Chamaret, S.; Gruest, J.; Dauguet, C.; Axler-Blin, C.; Vezinet-Brun, F.; Rouzioux, C.; Rozenbaum, W.; Montagnier, L. *Science* **1983**, *220*, 868; (b) Gallo, R. C.; Salahuddin, S. Z.; Popovic, M.; Shearer, M.; Kaplan, M.; Haynes, B. F.; Palker, T. J.; Redfield, R.; Oleske, J.; Safai, B.; White, G.; Foster, P.; Markham, P. D. *Science* **1984**, *224*, 500.
3. (a) Gait, M. J.; Karn, J. *Tibtech*. **1995**, *13*, 430; (b) Wiodawer, A.; Erickson, J. W. *Ann. Rev. Biochem*. **1993**, *62*, 543; (c) Volker, E. J. *J. Chem. Educ*. **1993**, *70*, 3; (d) Kempf, D. J.; Sham, S. L. *Curr. Pharm. Des*. **1996**, *2*, 225.
4. (a) Katz, R. A.; Skalka, A. M. *Ann. Rev. Biochem*. **1994**, *63*, 133; (b) Huff, R. J. *J. Med. Chem*. **1991**, *34*, 2305 and references cited therein.
5. Williams, R. M. In *Biologically Active Peptides: Design, Synthesis and Utilisation*; Williams, W. V.; Weiner, D. B. Eds.; Technomic; Lancaster, **1993**; Vol. 1, p 187.
6. (a) Umezawa, H.; Aoyagi, T.; Morishima, H.; Matsuzaki, M.; Hamada, M.; Takeuchi, T. *J. Antibiot*. **1970**, *23*, 259; (b) Omura, S.; Imamura, N.; Kawakita, N.; Mori, Y.; Yamazaki, Y.; Masuma, R.; Takahashi, Y.; Tanaka, H.; Huang, L.; Woodruff, H. *J. Antibiot*. **1986**, *39*, 1079.
7. Moore, M. L.; Bryan, W. M.; Fakhury, S. A.; Magaard, V. W.; Huffan, W. F.; Dayton, B. D.; Meek, T. K.; Hyland, L. J.; Dreyer, G. B.; Metcalf, B. W.; Gorniak, J. G.; Debouck, C. *Biochem. Biophys. Res. Commun*. **1989**, *159*, 420.
8. (a) Tao, J.; Hoffman, R. V. *J. Org. Chem*. **1997**, *67*, 6240 and references cited therein.
9. (a) Reetz, M. T.; Drewes, M. W.; Matthews, B. R.; Lennick, K. J. *J. Chem. Soc., Chem. Commun*. **1989**, 1474; (b) Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem., Int. Ed.* **1987**, *26*, 1141; (c) Gennari, C.; Pain, G.; Moresca, D. J. *J. Org. Chem.* **1995**, *60*, 6248.
10. Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc*. **1981**, *103*, 2127.
11. Ghosh, A. K.; McKee, S. P.; Thompson, W. J. *J. Org. Chem*. **1991**, *56*, 6500.
12. Lal, B.; Pramanik, B. N.; Manhas, M. S.; Bose, A. K.; *Tetrahedron Lett.* **1977**, *23*, 1977.

13. Grieco, P. A.; Oguri, T.; Yokoyama, Y. *Tetrahedron Lett.* **1978**, *19*, 419.
14. Dondoni, A.; Perrone, D.; Semola, M. T. *J. Org. Chem*. **1995**, *60*, 7927.
15. Dondoni, A**.;** Marra, A**.;** Perrone, D. *J. Org. Chem*. **1993**, *58*, 275.
16. Ghosh, A. K.; Shin, D.; Mathivanan, P. *Chem. Commun*. **1999**, 1025.
17. Ghosh, A. K.; Fidanze, S. *J. Org. Chem*. **1998**, *63*, 6146.
18. Reetz, M. T.; Drewes, M. W.; Matthews, B. R.; Lennick K. *Chem. Commun*. **1989**, 1474.
19. Rich, D. H.; Sun, E. T. O. *J. Med. Chem*. **1980**, *23*, 27.
20. (a) Fernandes, R. A.; Kumar, P. *Tetrahedron:Asymmetry* **1999**, *10*, 4797; (b) Fernandes, R. A.; Kumar, P. *Eur. J. Org. Chem*. **2000**, 3447; (c) Fernandes, R. A.; Kumar, P. *Tetrahedron Lett*. **2000**, *41*, 10309; (d) Pandey, R. K.; Fernandes, R. A.; Kumar, P. *Tetrahedron Lett*. **2002**, *43*, 4425; (e) Naidu, S. V.; Kumar, P. *Tetrahedron Lett*. **2003**, *44*, 1035; (f) Kandula, S. V.; Kumar, P. *Tetrahedron Lett*. **2003**, *44*, 1957; (g) Gupta, P.; Fernandes, R. A.; Kumar, P. *Tetrahedron Lett*. **2003**, *44*, 4231; (h) Pandey, R. K.; Upadhyay, P. K.; Kumar, P. *Tetrahedron Lett*. **2003**, *44*, 6245.
21. (a) Li, G.; Chang, H. T.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1996**, *35*, 451; For a review on the Sharpless asymmetric aminohydroxylation, see: (b) Bodkin, J. A.; McLeod, M. D. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2733.
22. Oliveto, E. P.; Gerold, C. *Org. Synth. Coll. Vol. IV*, **1963**, 104.
23. During the column purification of **33**, the corresponding dihydroxy compound (12%) was also isolated as side product.
24. The regioisomeric ratio of **33** was determined based on ^{1}H NMR spectra and the enantiomeric excess (ee) was calculated using Mosher analysis by converting ester **35** into the the corresponding alcohol and then derivatising it as the Mosher ester. The ee was found to be 89%.

2.2. SECTION B

Synthesis of (*R*)-selegiline *via* hydrolytic kinetic resolution

2.2.1. Introduction

Selegiline also known as 1-deprenyl is an irreversible and selective monoamine oxidase- B (MAO-B) inhibitor and is administered alone or together with L-DOPA for the treatment of Parkinson's syndrome and Alzheimer's disease.[1] It is used in the treatment of Parkinson's disease as it prevents the brains dopamine cells from oxidative stress.[1,2] It has immune-system boosting and *anti*-neurodegenerative effect.[2] Subsequent studies have shown that (*R*)-selegiline **1** is more effective towards the treatment of Parkinson's disease as well as Alzheimer's disease when compared to racemic selegiline.[3] In addition, selegiline stimulates the release of superoxide dismutase (SOD). SOD is key enzyme which helps to quench the products of damaging free radicles.[2] Some of the MAO inhibitors are shown in Fig.1. Structurally similar chiral amine such as (*R*)-tamsulosin hydrochloride (Fig.1) is employed in the symptomatic treatment of benign prostatic hyperplasia.[4]

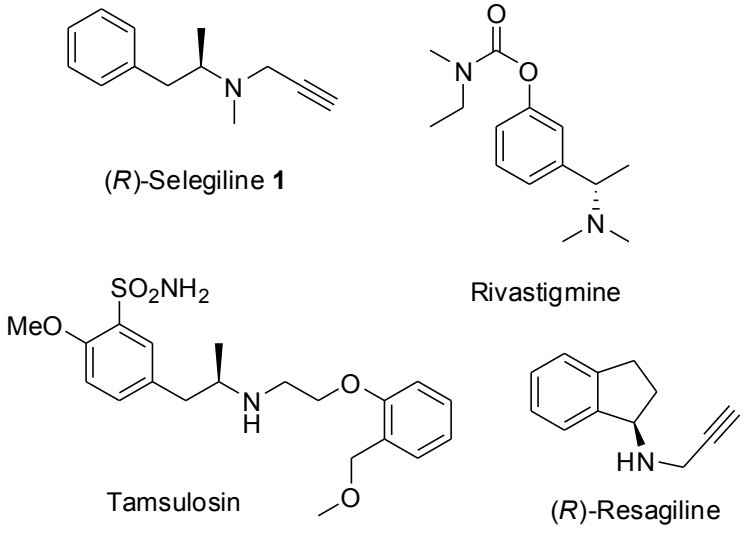


Figure 1. Some MAO inhibitors

Various methods for the synthesis of selegiline are documented in the literature.[1,5-7] Majority of the asymmetric synthesis reported uses chiral pool as the starting material.[5] Recently there has been reports of its synthesis using proline catalysed reactions, Sharpless

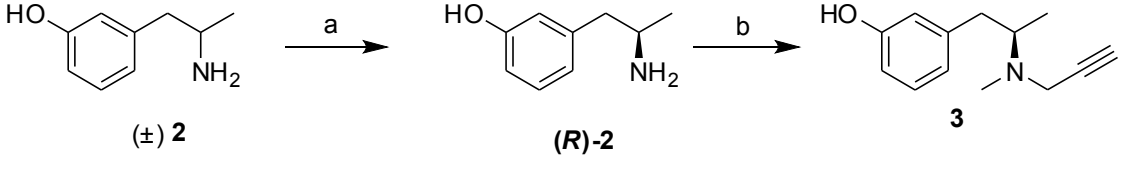
asymmetric dihydroxylation and regioselective aziridine opening as the key steps.[7] Surprisingly there is no report of use of HKR for the synthesis of this molecule. In continuation of our interest on hydrolytic kinetic resolution and its application towards the asymmetric synthesis of various natural products,[8] we became interested in devising a simple and straightforward route to (*R*)-selegiline using Jacobsen's HKR of terminal epoxide. The Jacobsen's HKR method uses readily accessible cobalt-based chiral salen complexes as catalyst and water as the only reagent to resolve a racemic epoxide into the enantiomerically enriched epoxide and diol in high enantiomeric excess. These advantages have made it a very attractive asymmetric synthetic tool.[9]

2.2.2. Review of Literature

Several approaches have been reported in the literature for the synthesis of racemic as well as optically active (*R*)-selegiline. A few interesting and recent syntheses of (*R*)-selegiline are described below.

Sterling *et al*. (2002)[1a]

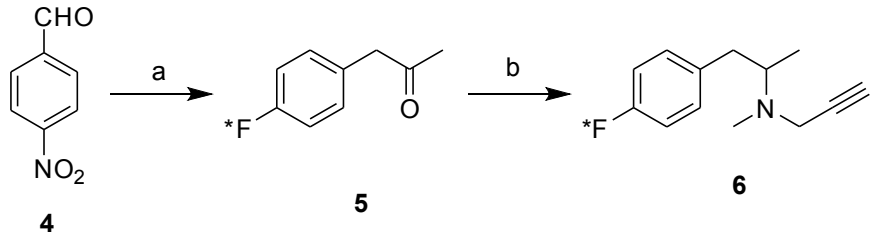
Sterling *et al*. have reported the synthesis of (*R*)-3-hydroxy selegiline **3**, involving classical resolution of amine (±)-**2** with D-tartaric acid to give optically pure amine (*R*)-**2**. Subsequent propargylation and reaction with ethyl formate gave formate derivative, which on reduction yielded (*R*)-3-hydroxy selegiline **3** (Scheme 1).



Scheme 1: (a) D-Tartaric acid, MeOH, reflux; then 25% NH_4OH, 25 °C; (b) (i) Propargyl bromide, K_2CO_3, 25 °C; (ii) HCO_2Et, reflux, then $LiAlH_4$, THF, 5 - 25 °C.

Plenevaux *et al*. (2002)[5c]

Plenevaux *et al*. synthesized racemic 4-[^{18}F]fluoroselegiline **6** starting from 4-nitrobenzaldehyde **4** via the three step procedure. Thus, substitution of **4** by [^{18}F] fluoride followed by reaction with (1-chloro-1-(trimethylsilyl)ethyl)lithium and hydrolysis furnished 4-[^{18}F]fluorophenylacetone **5**, which on reductive alkylation with *N*-methylpropynylamine afforded **6** (Scheme 2).

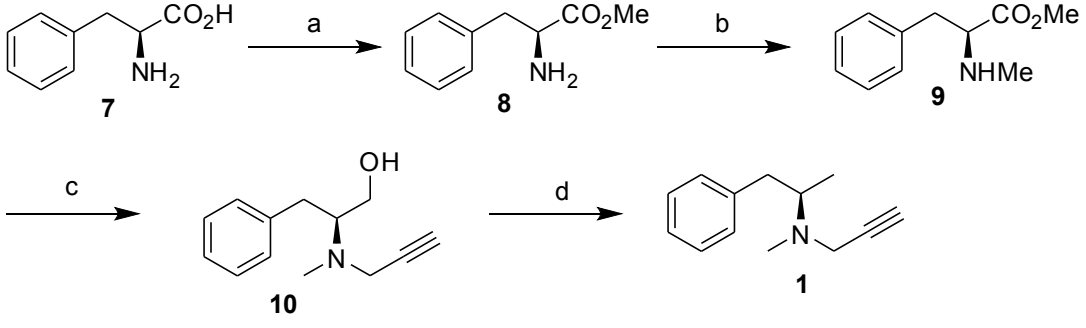


4 5 6

Scheme 2: (a) (i) KF, 65%; (ii) 1-Chloro-1-(trimethylsilyl)ethyl lithium, hydrolysis, 50%; (b) *N*-Methylpropynylamine, $NaBH_3CN$, 35%.

www.selegiline.com[2]

In this method, L-phenyl alanine **7** was used as the starting material for the preparation of (*R*)-selegiline **1**. Thus methyl ester of phenyl alanine **8** on condensation with formic acid gave *N*-formyl derivative, which on subsequent reduction furnished *N*-methyl derivative **9**. Propargylation and reduction of ester **9** with $LiAlH_4$ yielded alcohol **10**, which on subsequent reaction with thionyl chloride followed by reduction, afforded (*R*)-selegiline **1** (Scheme 3).



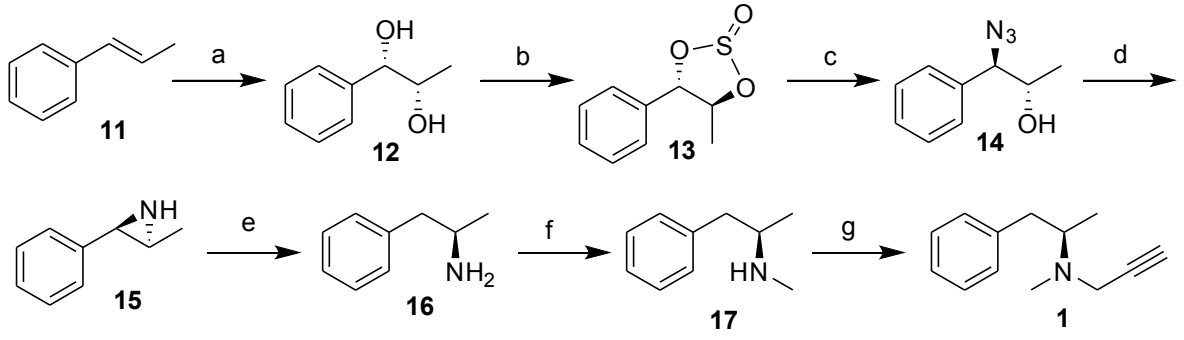
7 8 9 10 1

Scheme 3: (a) MeOH, 95%; (b) HCO_2H then $NaBH_4$, 85%; (c) Propargyl bromide, then $LiAlH_4$; (d) $SOCl_2$, reduction.

Sudalai *et al.* (2004)[7a]

Sudalai *et al*. synthesized (*R*)-selegiline **1** using asymmetric dihydroxylation as key step. Thus β-methyl styrene **11** was subjected to Sharpless AD reaction to give chiral diol **12** which on treatment with $SOCl_2$ gave the corresponding cyclic sulfite **13**. Treatment of cyclic sulfite **13** with sodium azide afforded the corresponding azido alcohol **14** which on treatment with triphenylphosphine gave chiral aziridine **15**. Aziridine **15** underwent stereospecific and regioselective ring opening at the benzylic position using Pd-catalyzed reductive ring opening with ammonium formate under transfer hydrogenation conditions to

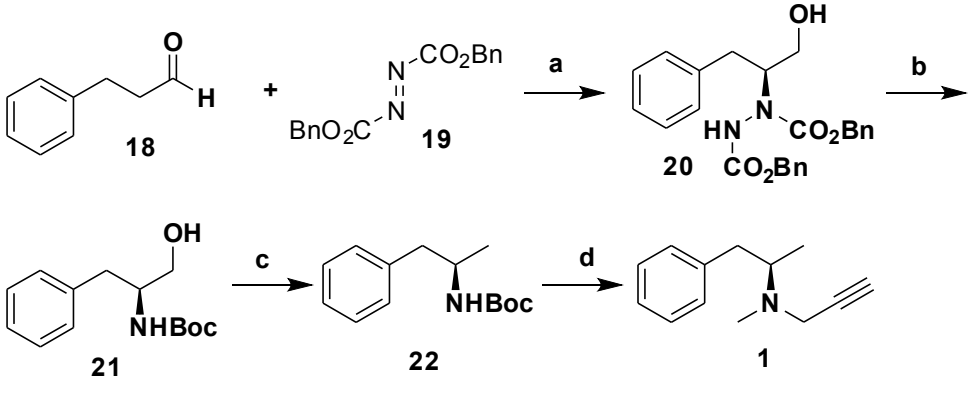
produce amine **16** which was converted to (*R*)-selegiline **1** using known sequence of reactions (Scheme 4).



Scheme 4: (a) OsO_4, $(DHQ)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH–H2O, 0 °C, 82%; (b) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 85%; (c) NaN_3, acetone–H2O, 80 °C, 82%; (d) PPh_3, CH_3CN, 90%; (e) Pd/C (10%), HCO_2NH_4, MeOH, reflux, 88%; (f) (i) $ClCO_2CH_3$, CH_2Cl_2, aq K_2CO_3, 45min, 90% (ii) $LiAlH_4$, dry THF, 65 °C, 65%; (g) propargyl bromide, K_2CO_3, CH_3CN, 25 °C, 72%.

Sudalai *et al.* (2004)[7b]

Sudalai *et al.* have recently developed another approach for the synthesis of (*R*)-selegiline **1** using α-amination and α-aminoxylation of aldehyde catalysed by proline. Thus amination of phenyl propanal **18** using D-proline as catalyst and subsequent reduction using $NaBH_4$ funished amino alcohol **20**. Raney nickel treatment gave free amine which was protected as Boc derivative using $(Boc)_2O$ to furnish **21**. Deoxygenation of OH group of **21** by tosylation and LAH treatment furnished amine **22**, which was subsequently transformed into (*R*)-selegiline **1** by *N*-alkynation (Scheme 5).



Scheme 5. *Reagents and conditions*: (a) Dibenzyl azodicarboxylate, D-proline (10 mol %), 0–20 °C, 3 h then $NaBH_4$, EtOH, 95%; (b) (i) H_2 (60 psi), Raney-Nickel, MeOH, AcOH, 16

h, (ii) $(Boc)_2O$, Et_3N, CH_2Cl_2, 0 °C, 1 h, 66% for two steps; (c) (i) *p*-TsCl, Et_3N, CH_2Cl_2, 2 h, (ii) $LiAlH_4$, THF, reflux, 4 h, 81% for two steps; (d) propargyl bromide, K_2CO_3, CH_3CN, 12 h, 72%.

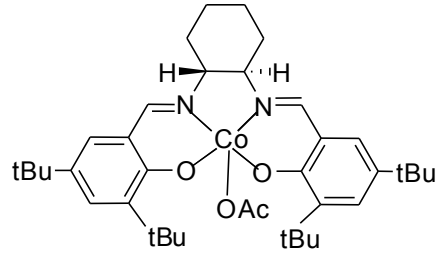
2.2.3. Present work

Objective:

Given the biological activities associated with (*R*)-selegiline, interest in the synthesis of this class of compounds continues unabated. Although a few syntheses are reviewed in foregoing section, several more are documented in the literature. There has been surprisingly no report on the synthesis of this molecule using Jacobsen's HKR method. We thought it would be worthwhile to design a synthetic route for this molecule using Jacobsen's HKR method as a key step. The Jacobsen's HKR method uses readily accessible cobalt-based chiral salen complex (Fig. 2) as catalyst and water as the only reagent to resolve a racemic epoxide into the enantiomerically enriched epoxide and diol in high enantiomeric excess. These advantages have made it a very attractive asymmetric synthetic tool.[9]

2.2.4. Results and discussion

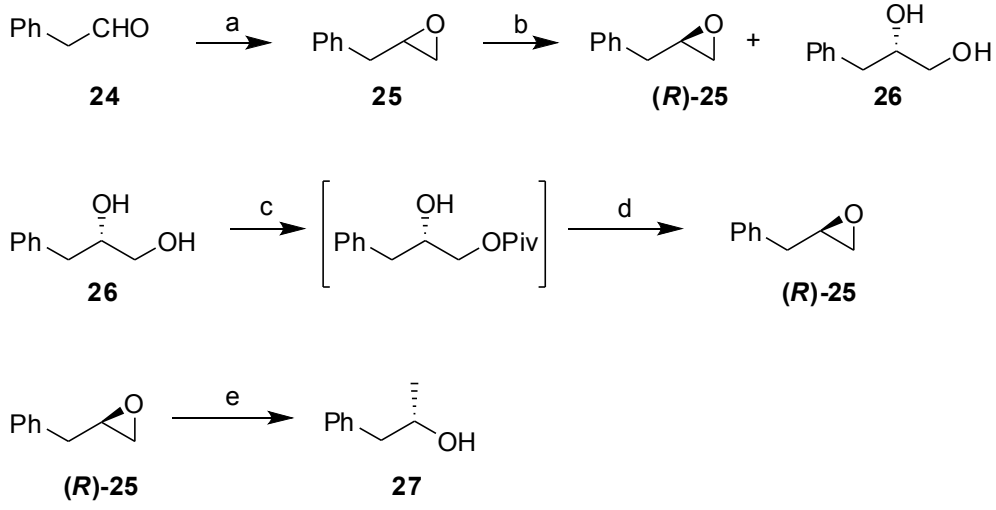
The synthesis commences from commercially available phenyl acetaldehyde **24**, which on treatment with dimethylsulfoxonium methylide gave 2-benzyl oxirane **25** in 82% yield (Scheme 6). Appearance of peaks at δ 2.56 and in the range of δ 2.76-2.79 in ^{1}H NMR confirmed the formation of epoxide **25**. The racemic epoxide **25** was then subjected to Jacobsen's HKR using (*R,R*)–salen-Co^{III} (OAc) complex **23** (0.5 mol%) and distilled water (0.55 equiv) to afford (*R*)-2-benzyl oxirane (***R***)-**25** as single enantiomer in 42% yield and 95% ee,[10] along with diol **26**



(*R*,*R*)-SalenCo (III) OAc complex **23**

Figure 2. Jacobsen's catalyst

in 45% yield and 96% ee. The epoxide (***R***)-**25** was easily separated from polar diol **26** by vacuum distillation {105 °C/14 mm}. As the Jacobsen's HKR method provides the desired epoxide (***R***)-**25** along with undesired diol **26** in almost equal amount, we thought it would be appropriate to convert the

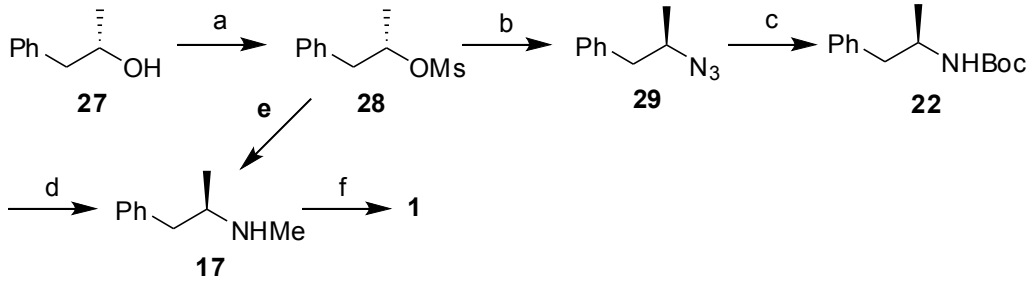


Scheme 6. *Reagents and conditions:* (a) $(CH_3)_3SO$, NaH, DMSO, 82%; (b) *R,R*-salen-Co^{III}-(OAc) (0.5 mol%), dist. H_2O (0.55%), 0 °C, 8 h, (42% for **(*R*)-25**, 45% for **26**); (c) PivCl, Et_3N, Cat. DMAP, rt; (d) (i) MsCl, Et_3N, DMAP, 0 °C to rt; (ii) K_2CO_3, MeOH, rt (63% for three steps c-d); (e) $NaBH_4$, EtOH, reflux, 2 h, 81%.

residual diol **26** into epoxide (***R***)-**25** via a three step process of internal nucleophilic substitution of the secondary mesylate of diol **26**.[11] Thus regioselective pivalation of the primary hydroxy group of diol **26** followed by mesylation of the secondary hydroxy and the treatment of crude mesylate with K_2CO_3 in methanol led to deprotection of the pivaloyl ester. Concomitant ring closure via intramolecular S_N2 displacement of the mesylate furnished the (*R*)-2-benzyl oxirane (***R***)-**25** in 63% yield. Epoxide **(*R*)-25** was then subjected to regioselective opening with sodium borohydride to furnish the desired alcohol **27** in 81% yield (Scheme 6). Appearance of peaks at δ 1.27, 2.78 in ^1H NMR and a broad peak at 3365 cm^{-1} in IR spectrum confirmed the formation of alcohol **27**.

With substantial amount of enantiomerically pure alcohol **27** in hand, we then proceeded towards the synthesis of target compound **1** (Scheme 7). The protection of the alcohol **27** with MsCl and Et_3N afforded compound **28** in excellent yield. Appearance of singlet at δ

2.50 in ^{1}H NMR and disappearance of broad peak at 3365 cm^{-1} in IR spectrum confirmed the formation of compound **28**, which on treatment with sodium azide in DMF furnished azide **29** with



Scheme 7. *Reagents and conditions*: (a) MsCl, Et_3N, DMAP, DCM, 0 °C to rt, 85%; (b) NaN_3, DMF, 50 °C, 8 h, 61%; (c) H_2-Pd/C, $(Boc)_2O$, EtOAc, 90%; (d) $LiAlH_4$, THF, 0 °C to rt, 69%; (e) Aq. $MeNH_2$, DMF, 50 °C, 18 h, 60%; (f) Propargyl bromide, K_2CO_3, acetonitrile, 72%.

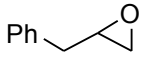
inversion of the configuration. Disappearance of singlet at δ 2.50 in ^{1}H NMR and appearance of a broad peak at 2110 cm^{-1} in IR spectrum confirmed the formation of azide **29**. The azide was then easily converted to Boc protected amine **22** on treatment with 10% H_2/Pd-C and $(Boc)_2O$. Appearance of singlet at δ 1.42 in ^{1}H NMR and disappearance of a broad peak at 2110 cm^{-1} in IR spectrum confirmed the formation of compound **22**. Subsequent carbamate reduction by $LiAlH_4$ gave the monomethylated compound **17** in 69% yield. Appearance of singlet at δ 2.44 in ^{1}H NMR confirmed the formation of compound **17**. Alternatively the compound **17** can be directly obtained from mesylate **28** in moderate yield by direct nucleophilic displacement of *O*-mesylate group by methyl amine. Thus compound **28** on treatment with excess of aqueous CH_3NH_2 in DMF directly gave compound **17** in 60% yield. Finally amine **17** was converted to (*R*)-selegiline **1** using propargyl bromide and K_2CO_3. $[\alpha]_D^{25}$ – 10.7 (*c* 6.5, EtOH){Lit.[13] $[\alpha]_D^{25}$ – 10.8 (*c* 6.48, EtOH)} The physical and spectroscopic data were in full agreement with the literature.[7b]

2.2.5. Conclusion

In conclusion a short, simple and highly enantioselective synthesis of (*R*)-selegiline was achieved employing HKR as the key step. This strategy is easily amenable to prepare other members of MAO inhibitors. Currently studies are in progress in this direction.

2.2.6. Experimental Section:

2-Benzyloxirane (25):



To a solution of trimethylsulfoxonium iodide (1.37 gm, 6.24 mmol) in dry DMSO (5 mL) was added NaH (0.15 gm, 6.24 mmol). After 1 h, phenyl acetaldehyde **24** (0.5 gm, 4.16 mmol) dissolved in THF (5 mL) was added at 25 °C. After stirring for 5 h ice was added to the reaction mixture and the reaction mixture was extracted with ethyl acetate (2 x 20 mL). The organic layer was washed with water (2 x 10 mL), brine, dried (Na_2SO_4). Solvent was removed under reduced pressure and the crude product was purified by column chromatography to get pure compound **25** as colourless liquid.

Yield: 0.42 g, 42%

Mol. Formula: $C_9H_{10}O$

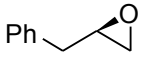
IR ($CHCl_3$, cm^{-1}): ν_{max} 3019, 1635, 1496, 1215, 1083.

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.56 (dd, J = 2.7, 5.1 Hz, 1H), 2.76-2.79 (m, 1H), 2.82-2.86 (m, 1H), 2.88-2.98 (m, 1H), 3.11-3.20 (m, 1H), 7.24-7.36 (m, 5H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 38.5, 46.4, 52.0, 126.3, 128.2, 128.7, 137.0 ppm.

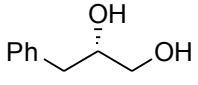
Analysis Calcd.: C, 80.56; H, 7.51; **Found:** C, 80.75; H, 7.34.

(*R*)-2-Benzyloxirane ((*R*)-25):



A solution of epoxide **(±)-25** (1.0 g, 7.45 mmol) and (*R,R*)-Salen-Co(III)-OAc (0.025 g, 0.037 mmol) was stirred at 0 °C for 5 min, and then distilled water (73 μL, 4.09 mmol) was added. After stirring for 8 h, the enantiomerically pure epoxide (***R***)-**25** was isolated by vacuum distillation (105 °C/14mm) and the residue containing diol was purified by silica gel column chromatography using pet ether/EtOAc (3:2) to afford diol **26** as a brown color liquid.

(*S*)-3-Phenylpropane-1,2-diol (26):



Yield: 0.51 gm, 45%

Mol. Formula: $C_9H_{12}O_2$

$[\alpha]_D^{25}$: - 35.0 (*c* 1.04, EtOH); [Lit[14] $[\alpha]^{18}_D$ -35.4° (*c* 1.00, EtOH)].

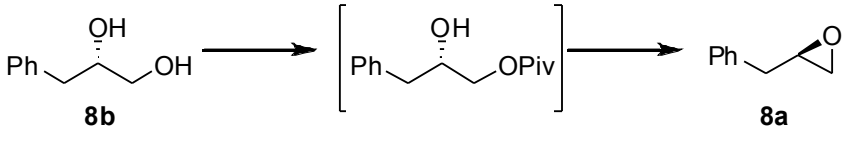
IR ($CHCl_3$, cm^{-1}): ν_{max} 3365, 2968, 1600, 1452, 1080.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.76-2.87 (m, 4H), 3.46-3.55 (m, 1H), 3.89-4.00 (m, 1H), 7.23-7.40 (m, 5H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 39.5, 65.7, 73.0, 126.4, 128.4, 129.3, 137.9 ppm.

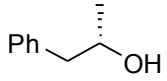
Analysis Calcd.: C, 71.03; H, 7.95; **Found:** C, 71.23; H, 7.75.

Conversion of Diol into epoxide:



Conversion of **26** into (***R***)-**25**: Diol **26** (0.2 g, 1.31 mmol) was dissolved in dry CH_2Cl_2 (2 mL) under argon and treated with pivaloyl chloride (0.178 mL, 1.44 mmol), Et_3N (0.22 mL, 1.57 mmol), and catalytic amount of DMAP. The resulting mixture was stirred at room temperature for 2 h quenched with water and then extracted with CH_2Cl_2. Removal of volatiles under reduced pressure gave an oily crude monopivalate. This compound was then dissolved in dry CH_2Cl_2 (10 mL) under argon and treated with MsCl (0.11mL, 1.44 mmol), Et_3N (0.219 mL, 1.57 mmol), and catalytic amount of DMAP. The reaction mixture was stirred at room temperature for 1 h and then quenched with water. The water layer was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated to give a crude product, which was dissolved in MeOH (10 mL) and treated with K_2CO_3 (0.199 g, 1.31 mmol). This mixture was stirred overnight at room temperature and then filtered through celite. Removal of the volatiles under reduced pressure, followed by column chromatography on silica gel (petroleum ether/EtOAc 19:1) produced the epoxide (***R***)-**25** (0.11 g, overall yield 63%) as a yellow liquid.

(*S*)-1-Phenylpropan-2-ol (27):



$NaBH_4$ (0.99 g, 26.08 mmol) was added to (*R*)-epoxide (***R***)-**25** (1g, 7.45 mmol) in EtOH (10 mL), and the mixture was refluxed for 2 h. After diluting with ether and quenching with saturated NH_4Cl, the mixture was filtered. The precipitate was washed thoroughly with ether. The ether layer was washed with H_2O, and the aqueous layer was re-extracted with DCM. The combined organic phases were dried (Na_2SO_4), concentrated under reduced pressure and purified by flash chromatography to yield alcohol **27**.

Yield: 0.82 g, 81%

Mol. Formula: $C_9H_{12}O$

$[\alpha]_D^{25}$: - 38.21 (*c* 2.04, $CHCl_3$)

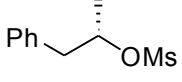
IR ($CHCl_3$, cm^{-1}): ν_{max} 3365, 2968, 1600, 1452, 1080.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27 (d, *J* = 6.3 Hz, 3H), 2.66-2.69 (bs, 1H), 2.78 (d, *J* = 6.6 Hz, 2H), 3.95-4.10 (m, 1H), 7.24-7.41 (m, 5H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0, 45.2, 68.0, 125.6, 127.7, 128.9, 138.3 ppm.

Analysis Calcd.: C, 79.37; H, 8.88; **Found:** C, 79.55; H, 9.02.

(*S*)-1-Phenylpropan-2-yl methanesulfonate (28):



To an ice-cold stirred solution of **27** (1.0 g, 7.34 mmol) and triethylamine (1.84 mL, 13.21 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise methanesulfonyl chloride (0.68 ml, 8.8 mmol) over 15 min. The resulting mixture was allowed to warm upto room temperature and stirred for 5 h. After diluting with 25 mL CH_2Cl_2, the solution was washed with water (3 x 15 mL), brine, dried over Na_2SO_4 and concentrated to give the crude mesylated product. Silica gel column chromatography of the crude product gave mesylate **28** as a colourless liquid.

Yield: 1.33 g, 85%

Mol. Formula: $C_{10}H_{14}O_3S$

$[\alpha]_D^{25}$: - 32.81 (*c* 1.44, $CHCl_3$)

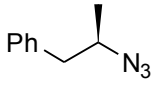
IR ($CHCl_3$, cm^{-1}): ν_{max} 3029, 2360, 2341, 1604, 1496, 1350, 1174.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.49 (d, J = 6.3 Hz, 3H), 2.50 (s, 3H), 2.93-2.98 (m, 2H), 4.81-4.97 (m, 1H), 7.23-7.38 (m, 5H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9, 37.2, 42.5, 80.8, 126.6, 128.2, 129.2, 136.5 ppm.

Analysis Calcd.: C, 56.05; H, 6.59; S, 14.96; **Found:** C, 56.19; H, 6.73; S, 14.83;

(*R*)-(2-Azidopropyl)benzene (29):



To a solution of above mesylated product **28** (1 gm, 4.66 mmol) in dry DMF (10 mL) was added portion wise NaN_3 (1.82 g, 28.00 mmol) and the resulting suspension was stirred for 8 h at 50 °C. After cooling the reaction mixture to room temperature, Et_2O (15 mL) and H_2O (15 mL) were added and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. Silica gel column chromatography of the crude product gave azide **29** as a yellowish liquid.

Yield: 0.458 g, 61%

Mol. Formula: $C_9H_{11}N_3$

$[\alpha]_D^{25}$: - 66.49 (*c* 0.92, $CHCl_3$)

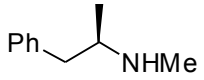
IR ($CHCl_3$, cm^{-1}): ν_{max} 3029, 2110, 1604, 1496, 1453, 1255, 1085.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.24 (d, J = 6.7 Hz, 3H), 2.65-2.88 (m, 2H), 3.62-3.72 (m, 1H), 7.17-7.34 (m, 5H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 18.7, 42.3, 58.3, 126.4, 128.2, 129.1, 137.6 ppm.

Analysis Calcd.: C, 67.06; H, 6.88; N, 26.07; **Found:** C, 67.25; H, 7.03; N, 26.21;

(*R*)-*N*-Methyl-1-phenylpropan-2-amine (17):



Procedure 1:

To a solution of mesylate **28** (0.48 g, 2.63 mmol) in DMF (15 mL) at room temperature was added methylamine (40% in water, 8.2 mL, 105.3 mmol). After the mixture was stirred at 50 °C for 12 h, another portion of methylamine (4.1 mL, 52.68 mmol) was added, and the resulting mixture was stirred for 8 h at 50 °C. Then, the mixture was diluted with ether (100 mL) and water (30 mL). The aqueous phase was extracted with ether (4 x 10 mL). The combined extracts were washed with water (1x 20 mL) and brine (2 x 20 mL), dried over anhydrous Na_2SO_4, and filtered. Removal of solvent left an oil which was purified by flash chromatography (5% EtOH/0.5% Et_3N/CH_2Cl_2), to afford **17** (0.2 g, 60%) as a colorless oil.

Procedure 2:

To a solution of azide **29** (1.0 g, 6.2 mmol) in ethyl acetate was added 10% Pd/C (50 mg) and Boc_2O (1.63 mL, 6.82 mmol). The resulting solution was stirred under hydrogen atmosphere for 12 h at room temperature until disappearance of the azido alcohol as monitored by TLC. The reaction mixture was filtered through a celite pad to remove the catalyst and the filtrate was concentrated in vacuo. Silica gel column chromatography of the crude product using EtOAc/pet ether (1:19) as eluent gave **22** (1.31 g, 90%) as a colorless liquid.

Yield : 1.31 gm, 90%

Mol. Formula: $C_{14}H_{21}NO_2$

$[\alpha]_D^{25}$: +7.62 (c 0.8, CHCl3)

IR ($CHCl_3$, cm^{-1}): 3360,2978, 2935, 1703, 1456, 1366, 1250, 1173, 1061.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.08 (d, *J* = 6.7 Hz, 3H), 1.42 (s, 9H), 2.64 (dd, *J* =13.3, 7.3 Hz, 1H), 2.84 (dd, *J* = 13.4, 5.6 Hz, 1H), 3.82–3.92 (m, 1H), 4.37 (br s, 1H), 7.14–7.32 (m, 5H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 20.1, 28.4, 43.0, 47.41, 78.9, 126.2, 128.2, 129.4, 138.2, 155.0 ppm.

Analysis calcd. C, 71.46; H, 8.99; N, 5.95%; **found** C, 71.5; H, 8.84; N, 6.09%.

To a stirred suspension of $LiAlH_4$ (76 mg, 2 mmol) in THF (5 mL) was added dropwise a solution of *tert*-butyl (*R*)-1-phenylpropan-2-ylcarbamate **22** (235 mg, 1 mmol) in THF (2 mL) at 0 °C. The reaction mixture was refluxed for 4 h and then cooled to 0 °C and the excess $LiAlH_4$ was quenched by addition of EtOAc. The reaction mixture was treated with 20% NaOH (0.5 mL), the white precipitate formed was filtered off and the residue was washed with EtOAc (3x10 mL). The combined EtOAc layer was dried over anhyd Na_2SO_4, solvent was distilled off under reduced pressure, and the crude product was purified by column chromatography over silica gel using $CHCl_3$ as eluent to yield the corresponding pure *N*-methyl amine **17**.

Yield: 0.2 g, 60%

Mol. Formula: $C_{10}H_{15}N$

$[\alpha]_D^{25}$: - 21.35 (*c* 0.4, $CHCl_3$)

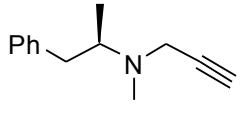
IR ($CHCl_3$, cm^{-1}): ν_{max} 3329, 2926, 1654, 1621, 1495, 1453, 1084.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12 (d, J = 6.2 Hz, 3H), 2.21 (bs, 1H), 2.44 (s, 3H), 2.65-2.94 (m, 3H), 7.23-7.37 (m, 5H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 19.1, 33.3, 42.7, 55.9, 125.7, 127.9, 128.8, 139.0 ppm.

Analysis Calcd.: C, 80.48;; H, 10.13; **Found:** C, 80.61; H, 10.27

***N*-Methyl-*N*-((*R*)-1-phenylpropan-2-yl)prop- 2-yn-1-amine: (*R*)-selegiline (1):**



To a stirred solution of (*R*)-2-(methylamino)-1- phenylpropane **17** (0.2 g, 1.34 mmol) in CH_3CN (10 mL) were added anhyd K_2CO_3 (0.28 g, 2.01 mmol) and propargyl bromide (0.48 g, 4.02 mmol). The reaction mixture was then stirred for 12 h at 25 °C, the solid residue formed was then filtered off, and the solvent was distilled off under reduced pressure to give the crude product, which was purified by column chromatography over silica gel using $CHCl_3$ as eluent to give pure (*R*)-selegiline **1**.

Yield: 0.18 g, 72%

Mol. Formula: $C_{13}H_{17}N$

$[\alpha]_D^{25}$: -10.7 (c 6.5, EtOH)

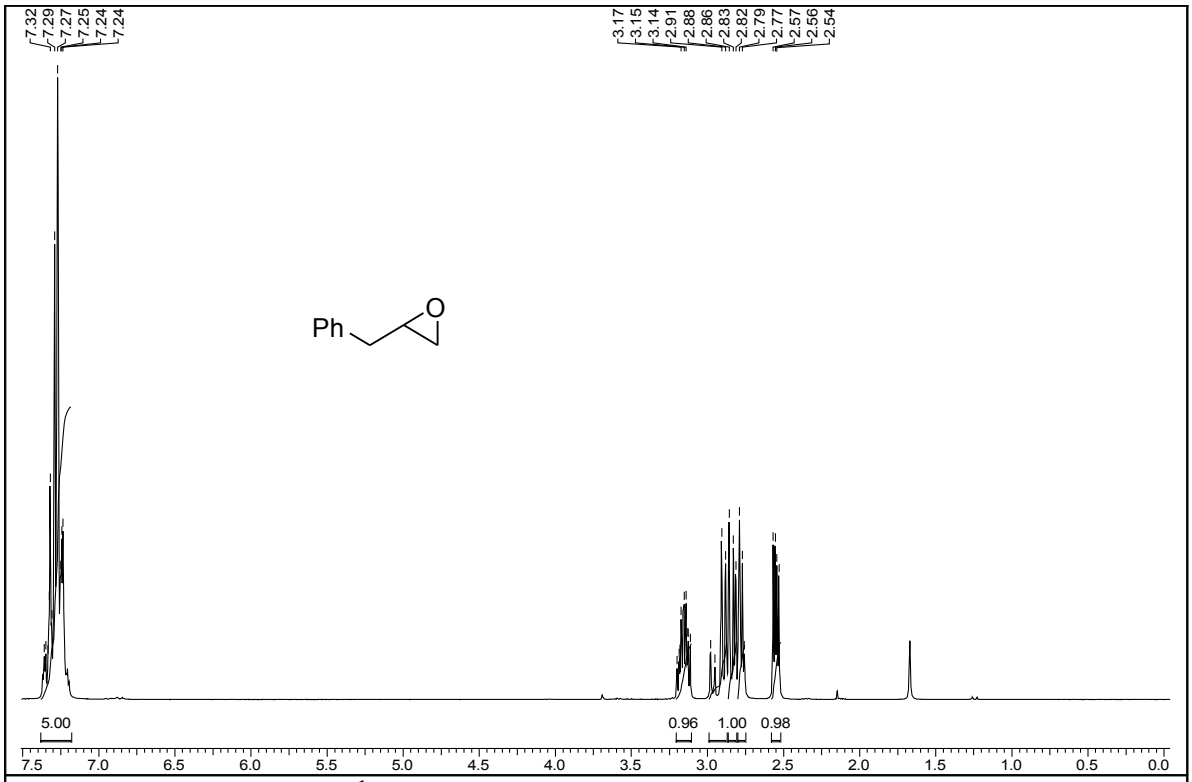
IR ($CHCl_3$, cm^{-1}): ν_{max} 3029, 2110, 1604, 1496, 1453, 1255, 1085.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.95 (d, J = 6.0 Hz, 3H), 2.25 (t, J = 2.0 Hz, 1H), 2.35 (s, 3H), 2.40–2.55 (m, 1H), 2.80–3.10 (m, 2H), 3.40 (d, J = 2.0 Hz, 2H), 7.00–7.50 (m, 5H)

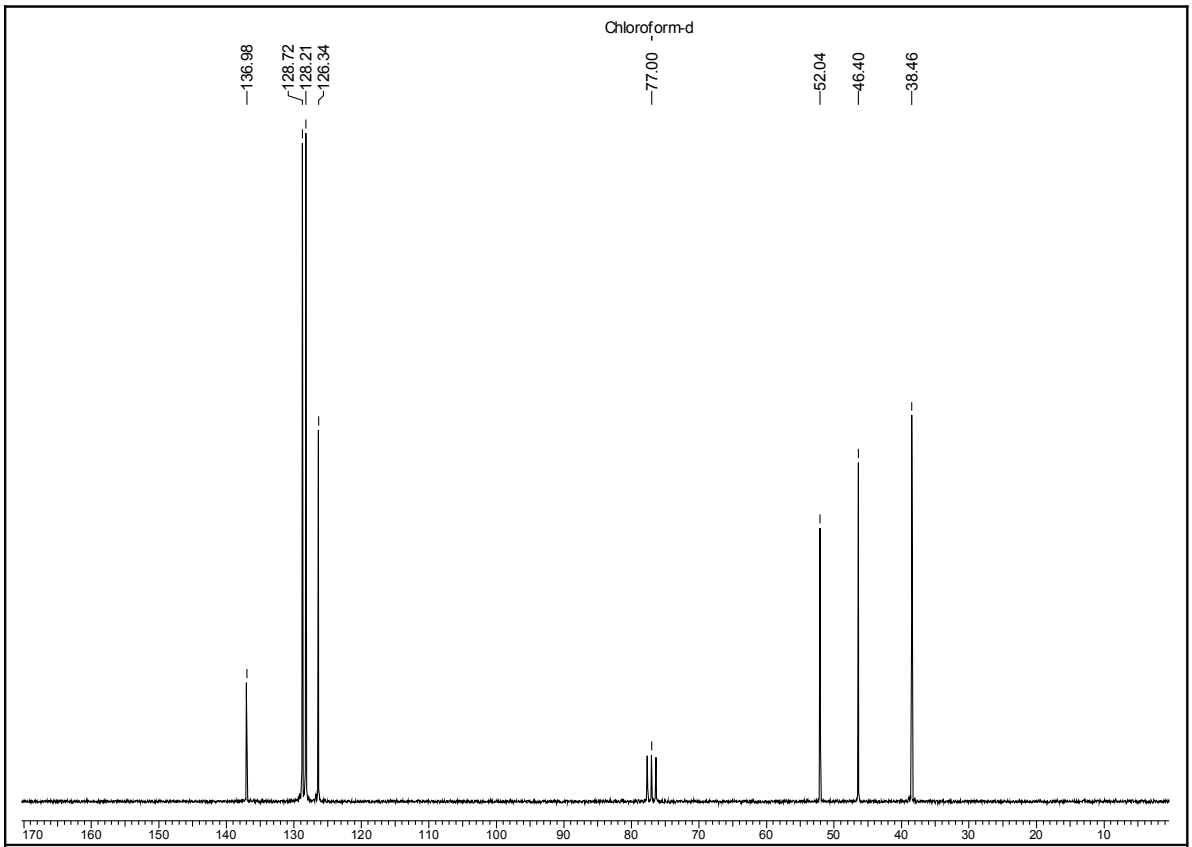
^{13}C NMR (75 MHz, $CDCl_3$): δ 21.1, 31.4, 46.8, 51.9, 60.8, 68.1, 82.2, 125.6, 128.3, 128.6, 140.2 ppm.

Analysis Calcd.: C, 83.37; H, 9.14; N, 7.47%; **Found:** C, 83.34; H, 9.11; N, 7.53%.

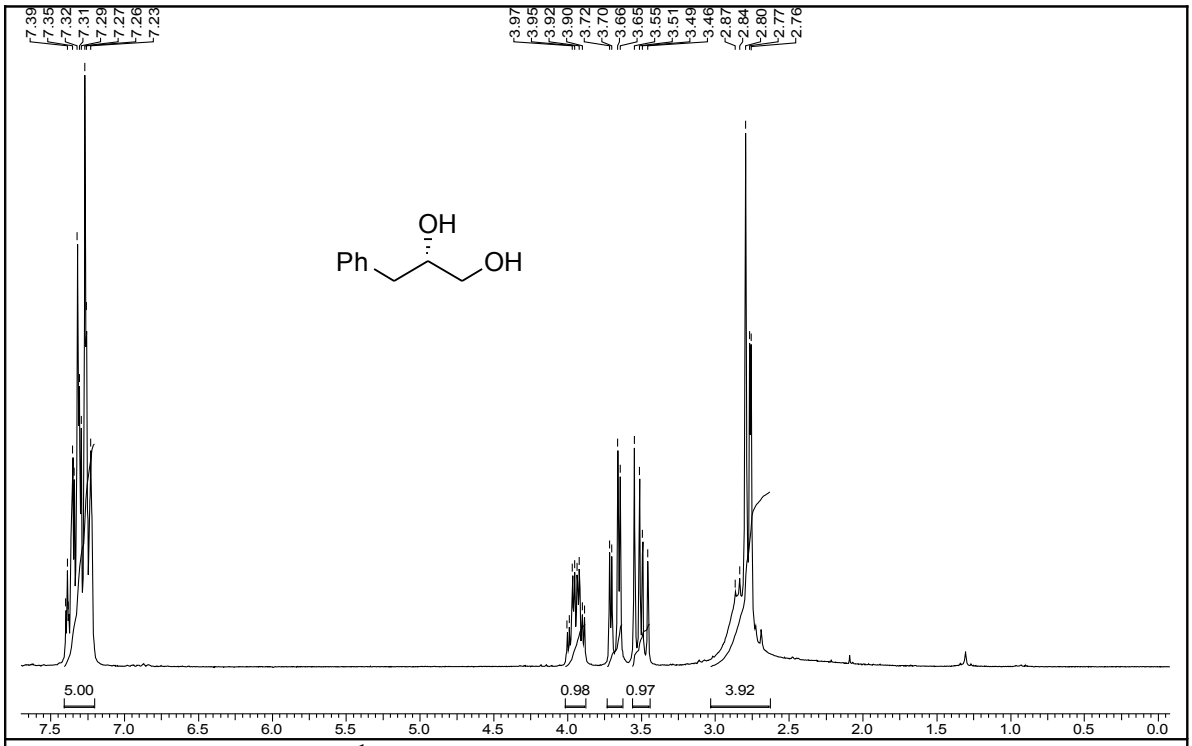
2.2.7. Spectra



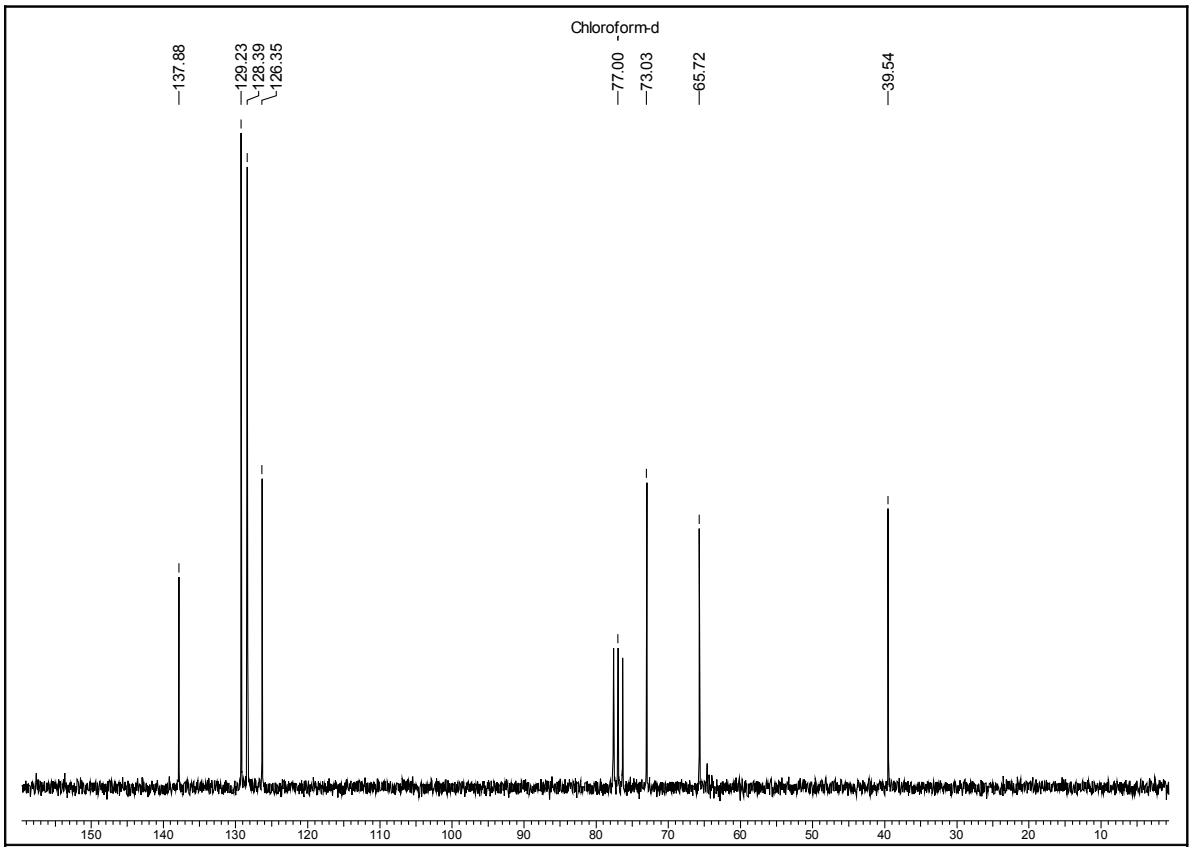
^{1}H-NMR of compound 25 in $CDCl_3$



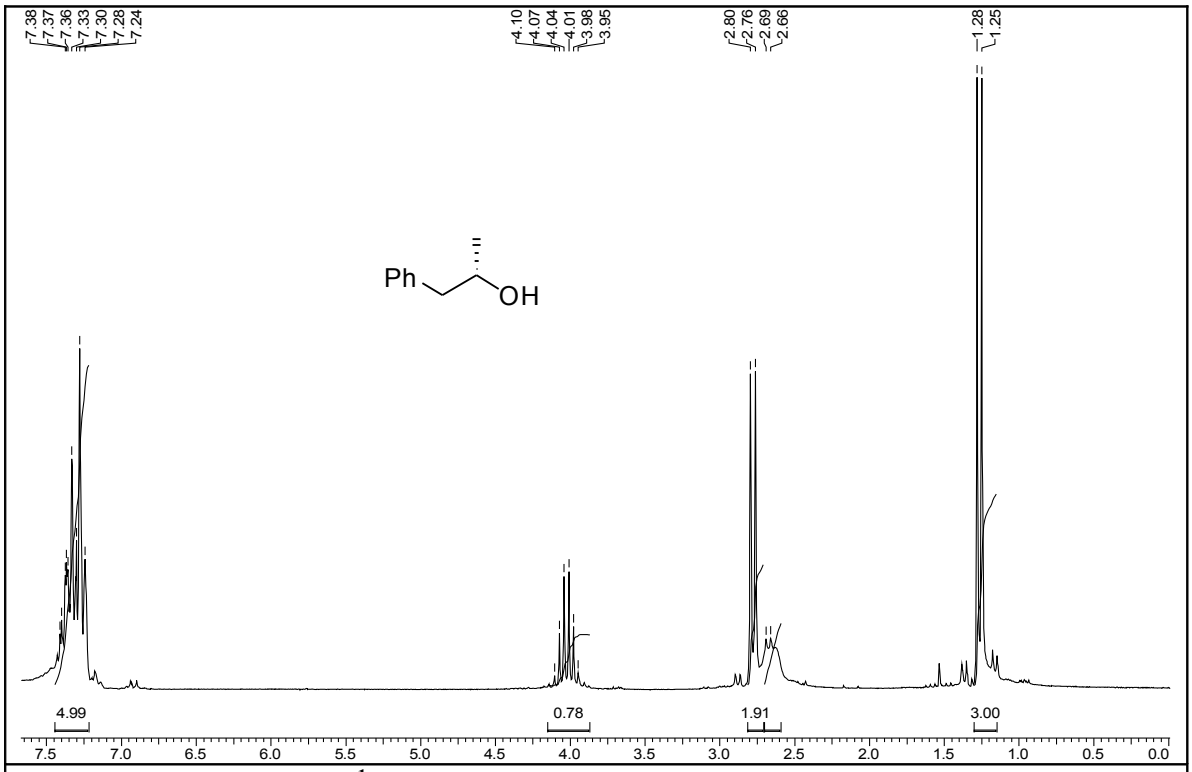
^{13}C-NMR of compound 25 in $CDCl_3$



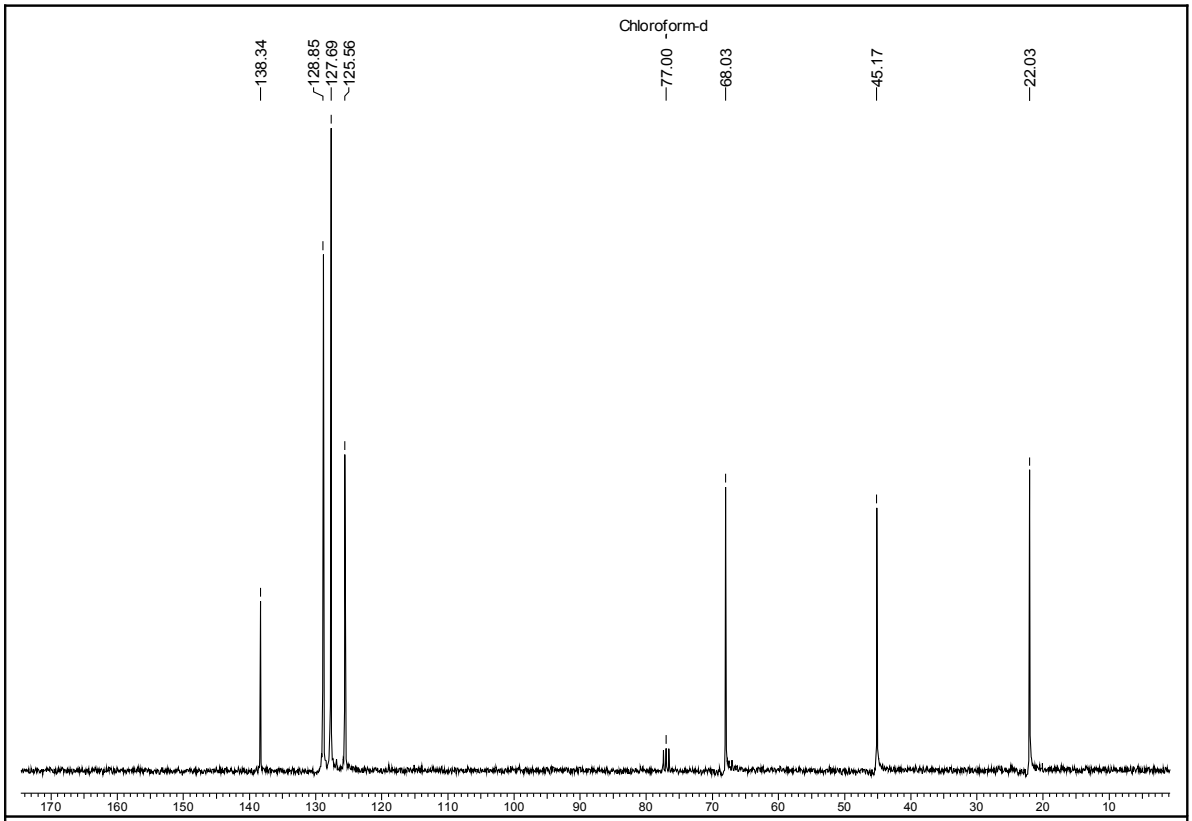
^{1}H-NMR of compound 26 in $CDCl_3$



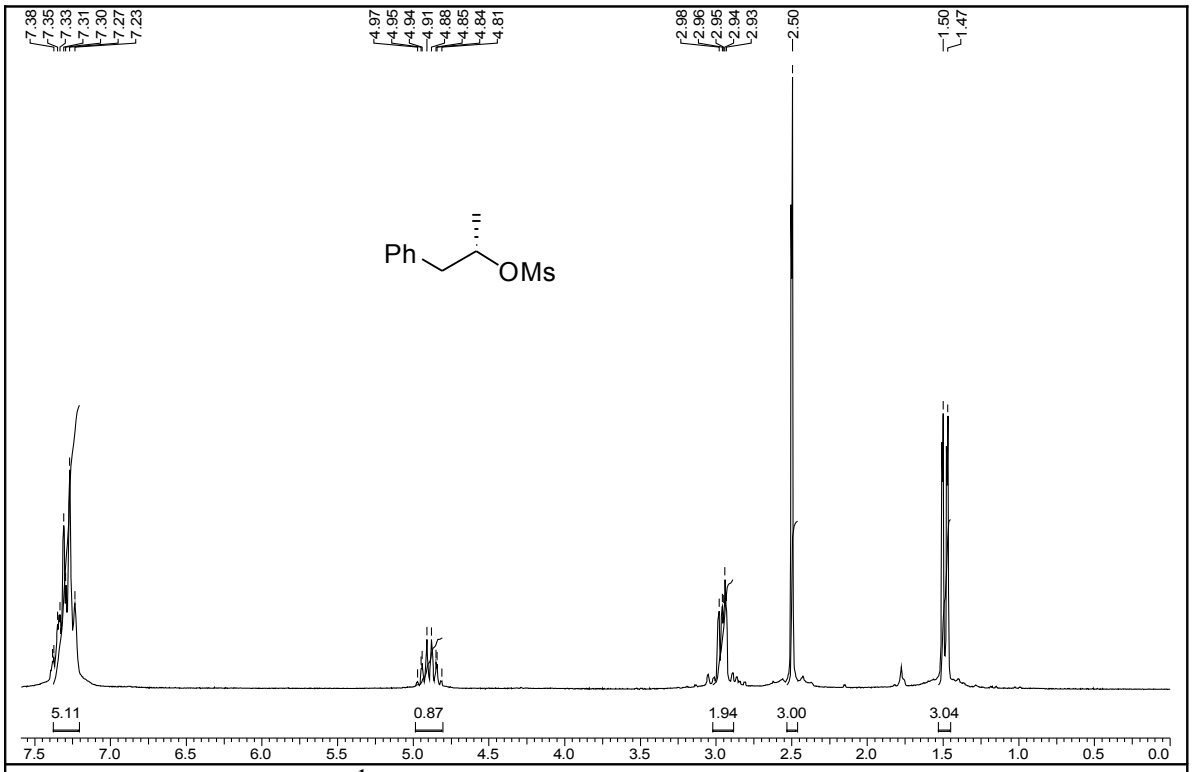
^{13}C-NMR of compound 26 in $CDCl_3$



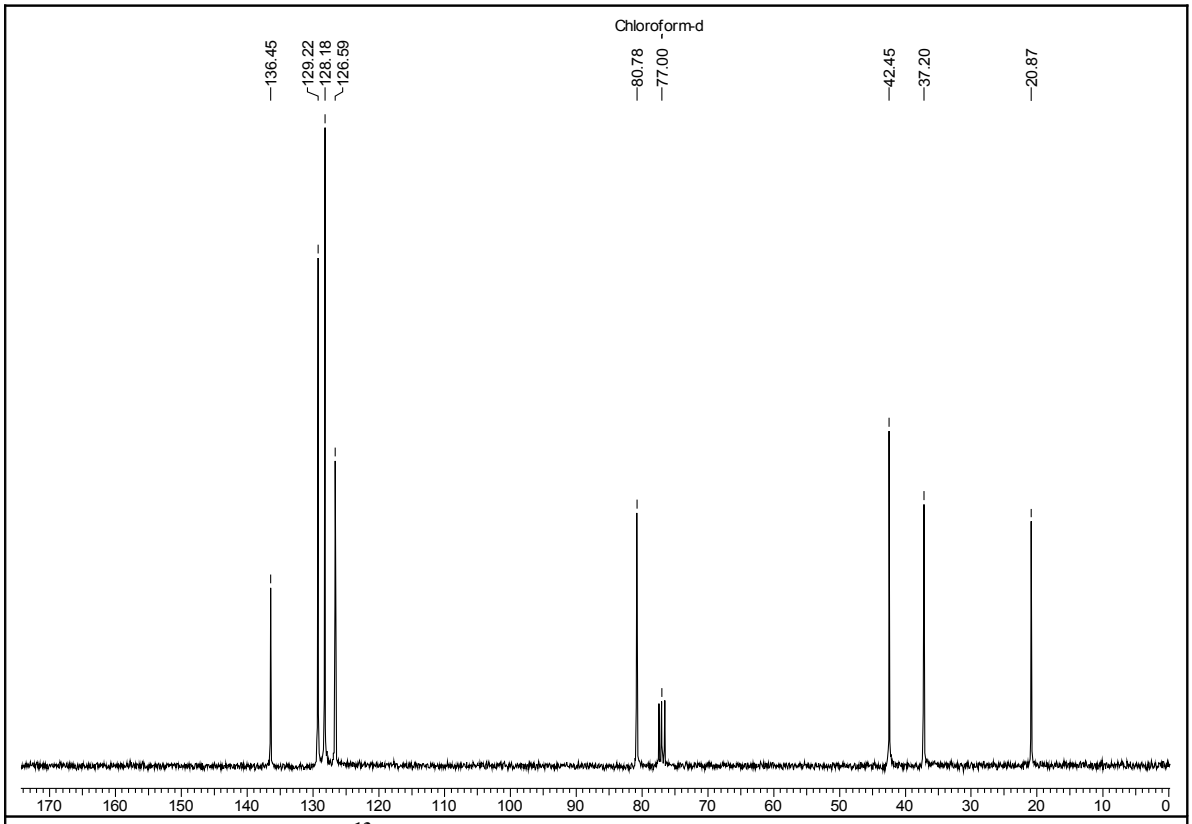
^{1}H-NMR of compound 27 in $CDCl_3$



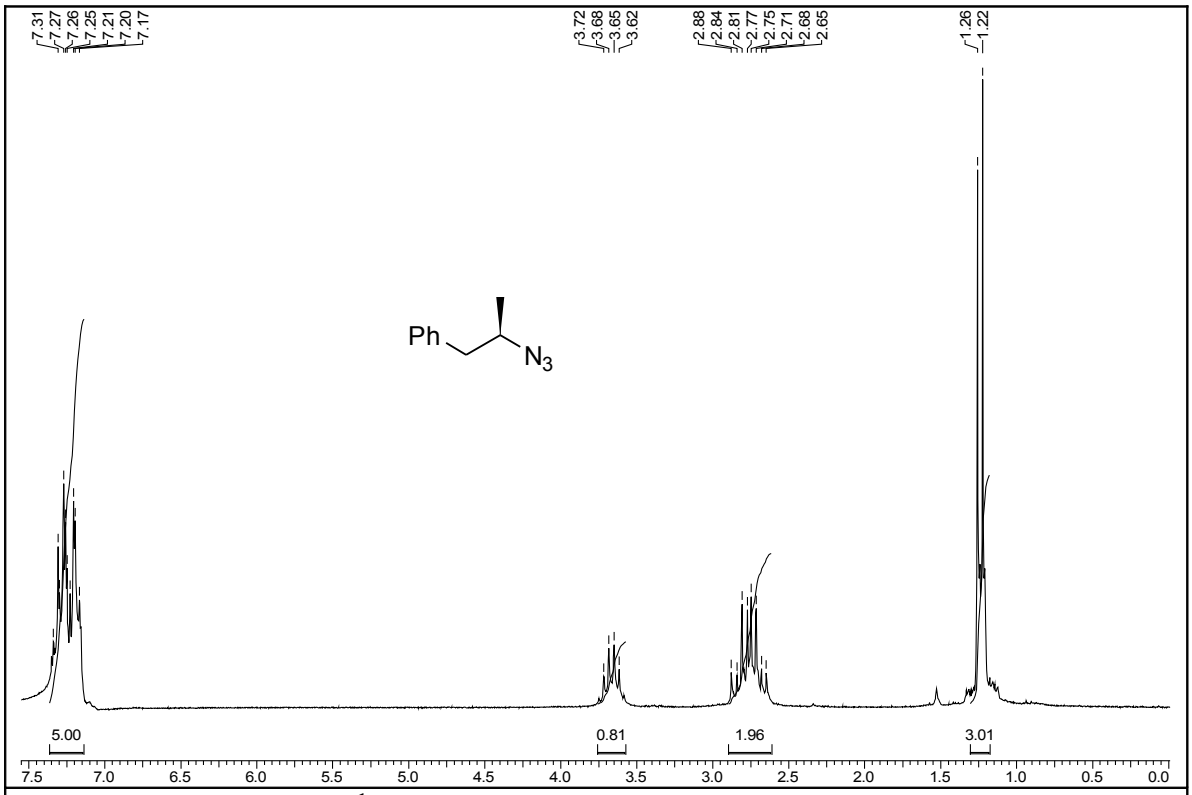
^{13}C-NMR of compound 27 in $CDCl_3$



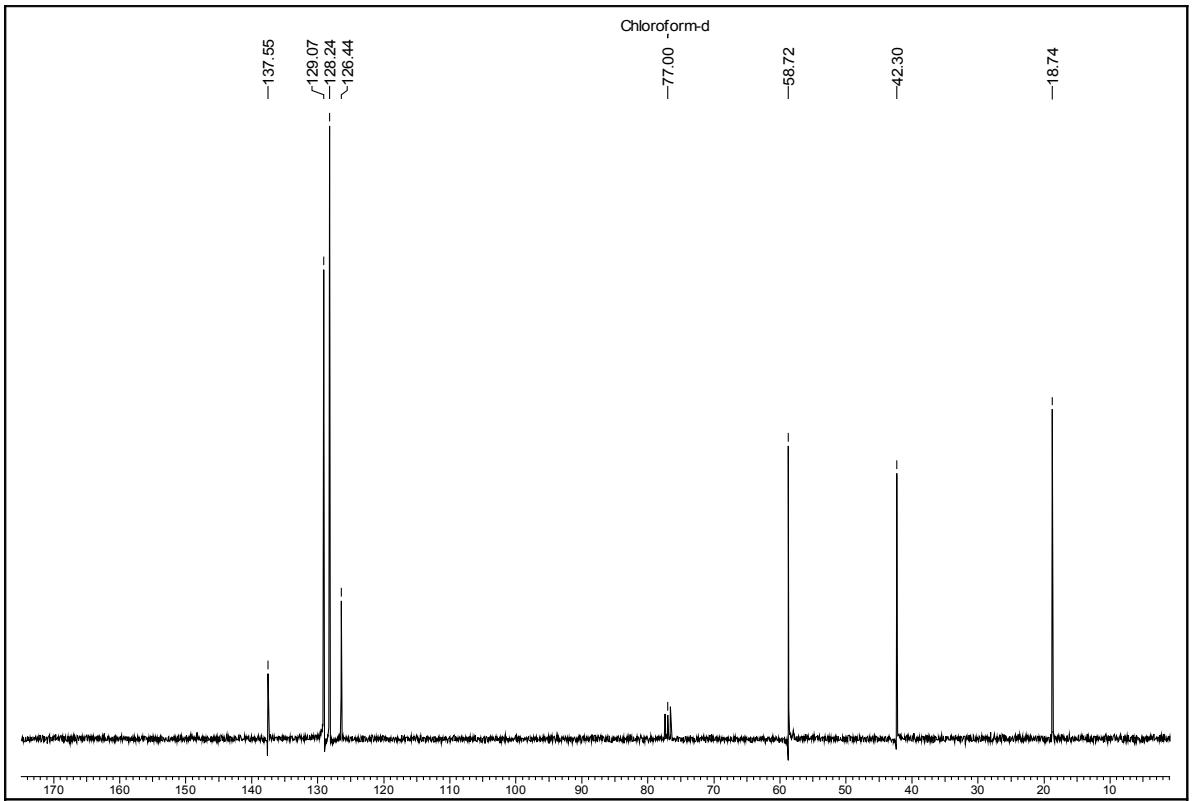
^{1}H-NMR of compound 28 in $CDCl_3$



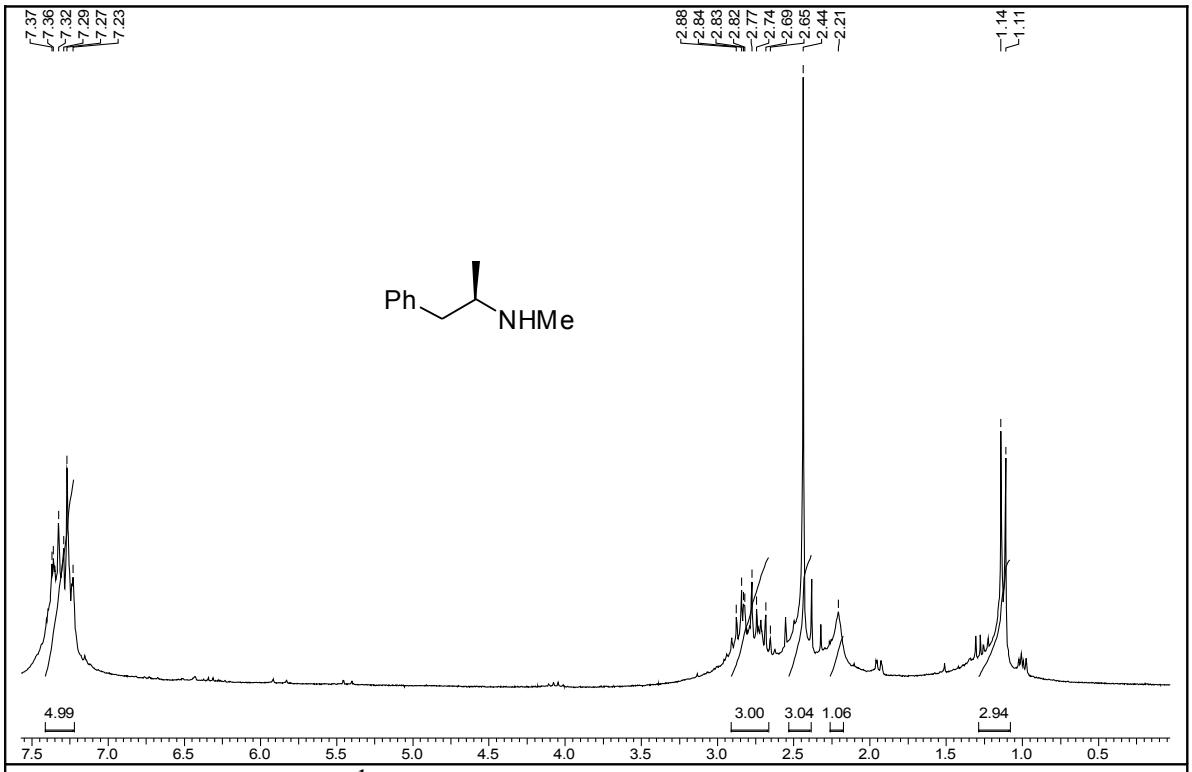
^{13}C-NMR of compound 28 in $CDCl_3$



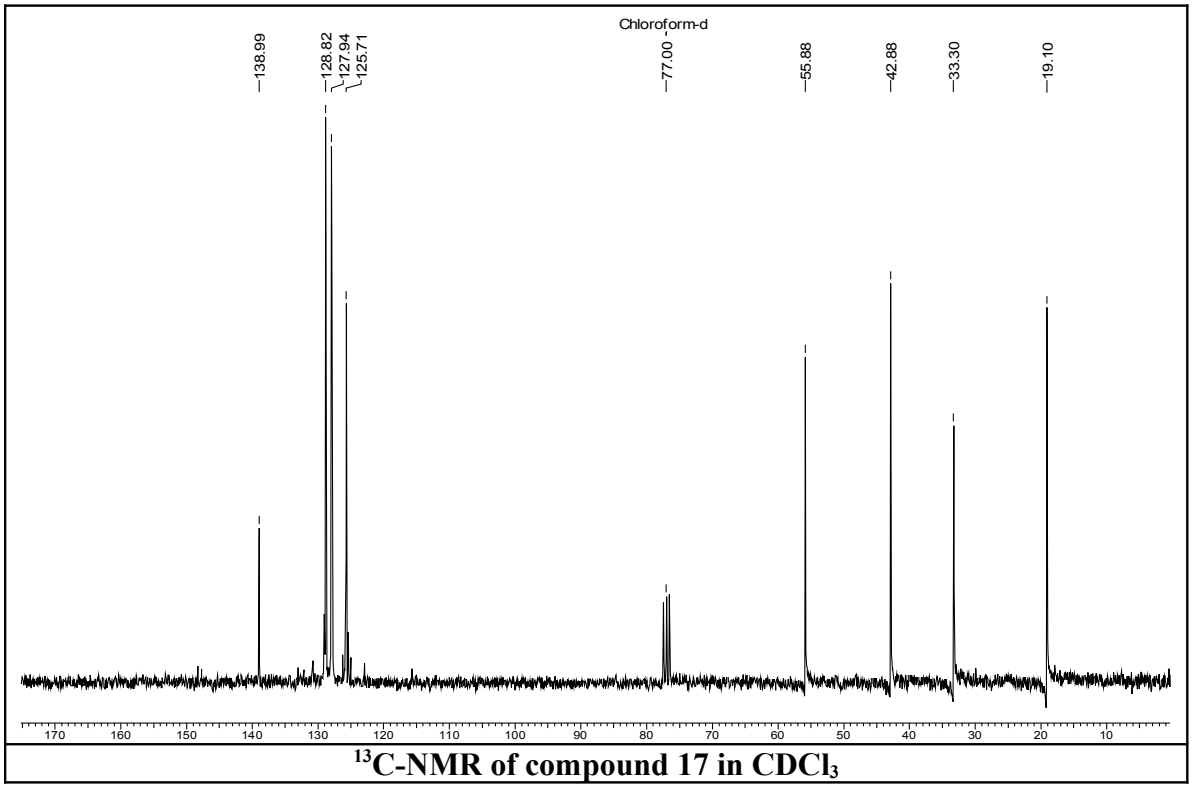
^{1}H-NMR of compound 29 in $CDCl_3$



^{13}C-NMR of compound 29 in $CDCl_3$



^{1}H-NMR of compound 17 in $CDCl_3$



^{13}C-NMR of compound 17 in $CDCl_3$

2.2.8. References

1. (a) Sterling, J.; Herzing, Y.; Goren, T.; Finkelstein, N.; Lerner, D.; Glodenburg, W.; Miskolczi, I.; Molner, S.; Rental, F.; Tamas, T.; Toth, G.; Zagyva, A.; Zekany, A.; Lavina, G.; Gross, A.; Friedman, R.; Razin, M.; Huang, W.; Krais, B.; Chorev, M.; Youdim, M. B.; Weinstock, M. *J. Med. Chem*. **2002**, *45*, 5260; (b) Mizutta, I.; Ohta, M.; Ohta, K.; Nishimura, M.; Mizutta, E.; Hayashi, K.; Kuna, S. *Biochem. Biophys. Res. Commun*. **2000**, *279*, 751; (c) Vaglini, F.; Pardini, C.; Cavalletti, M.; Maggio, R.; Corsini, G. U. *Brain Res*. **1996**, *741*, 68; (d) Goering, B. K. Ph.D. Dissertation, Cornell University, 1995.
2. www.selegiline.com
3. (a) Abu-Raya, S.; Blaugrund, E.; Trembovler, V.; Shilderman-Bloch, E.; Shohami, E.; Lazarovici, P. A Monoamine Oxidase-B Inhibitor, Protects NGF-Di.erentiated PC12 Cells Against Oxygen Glucose Deprivation. *J. Neurosci. Res*. **1999**, *58*, 456; (b) Paterson, I. A.; Tatton, W. G. Antiapoptotic Actions of Monoamine Oxidase B Inhibitors. *Adv. Pharmacol*. **1998**, *42*, 312; (c) Lyle, F. R. U.S. Patent 5 973 257, 1985; *Chem. Abstr*. **1985**, *65*, 2870.
4. (a) Niigata, K.; Fujikura, T.; Hashimoto, S.; Takenaka, T. Yamanouchi Pharmaceutical Co., EP0034432, **1981**; (b) Niigata, K.; Fujikura, T. Yamanouchi Pharmaceutical Co., U.S. Patent 4,731,478, **1988**; (c) Niigata, K.; Fujikura, T. Yamanouchi Pharmaceutical Co., U.S. Patent 4,761,500, **1988**.
5. (a) Fowler, J. S. *J. Org. Chem*. **1977**, *42*, 2637; (b) Gyogy, B.; Jozsef, K. CA 110: 44960g; (c) Plenevaux, A.; Flower, S. F.; Dewey, S.L.; Wolf, A. P.; Guillaume, M. *Int. J. Radiat. Appl. Instrum. Part A, Appl. Radiat. Isot.* **1991**, *42*, 121.
6. (a) Josef, H. CA 113:590e; (b) Josef, H. CA 117:150680; (c) Ott-Dombrowski, S.; Richard, C.; Jeorge, S.; Hans, W. CA 124: 288969x.
7. (a) Sayyed, I. A.; Sudlai, A. *Tetrahedron: Asymmetry* **2004**, *15*, 3111; (b) Talluri, S. K.; Sudlai, A. *Tetrahedron* **2007**, 63, 9758.
8. For the applications of HKR see review: (a) Kumar, P.; Naidu, S. V.; Gupta, P. *Tetrahedron* **2007**, *63*, 2745; (b) Kumar, P; Gupta, P. *Synlett* **2009**, 1367; (c) Kumar, P.; Naidu, S. V.; Gupta, P. *J. Org. Chem.* **2005**, *70*, 2843; (d) Kumar, P ; Gupta, P.;

Naidu, S. V. *Chem. Eur. J.* **2006**, *12*, 1397 ; (e) Kumar, P.; Naidu, S. V. *J. Org. Chem.* **2006**, *71*, 3935; (f) Pandey, S. K.; Kumar, P. *Eur. J. Org. Chem.* **2007**, 369; (g) Pandey, S. K.; Pandey, M.; Kumar, P. *Tetrahedron Lett*. **2008**, *49*, 3297; (h) Gupta, P.; Kumar, P. *Eur. J. Org. Chem.* **2008**, 1195; (i) Tripathi, D.; Kumar, P. *Tetrahedron Lett*. 2008, *49*, 7012.

9. (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936; (b) Schaus, S. E.; Brnalt,J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 4876.
10. The enantiomeric purity of the epoxide **(*R*)-25** was estimated to be 95% by chiral HPLC analysis using Chiracel OJ-H 250 cm x 4.6 mm, HPLC Cartridge (Chiracel OJ-H), IPA–PE(1:99), wavelength 254 nm, 1.0 mL/min, Retention time (min): 12.47 (major) and 13.29 (minor).
11. (a) Takao, K.; Ochiai, H.; Yoshida, K.; Hashizuka, T.; Koshimura, H.; Tadano, K.; Ogawa, S. *J. Org. Chem*. **1995**, *60*, 8179; (b) Nicolaou, K. C.; Webber, S. E. *Synthesis* **1986**, 453.
12. Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307.
13. Merck index vol. The Merck Index. An Encyclopedia of Chemicals, Drugs and Biologicals, 13th ed.; Merck: Whitehouse Station, NJ, **2001**.
14. Sone, H.; Shibata, T.; Fujita, T.; Ojika, M.; Yamada, K. *J. Am. Chem. Soc*. **1996**, *118*, 1874.

Chapter-3

Studies towards asymmetric synthesis of (2*R*, 2'*R*)-(+)-methylphenidate and (2*R*, 2'*R*)-*N*-[phenyl(piperidin-2-yl)methyl] benzamide

Asymmetric synthesis of (2*R*, 2'*R*)-(+)-methylphenidate and (2*R*, 2'*R*)-*N*-[phenyl(piperidin-2-yl)methyl] benzamide

3.1. Introduction

Attention deficit hyperactivity disorder (ADHD) is the most commonly diagnosed behavioral disorder in children. ADHD persists across the full span of development, from preschool to school age and adolescence, and frequently continues into adult life.[1] The diagnosis of ADHD is a clinical rather than a specific medical diagnosis. Racemic (±)-*threo*-methylphenidate hydrochloride (methyl phenyl-(2-piperidyl)acetate) is a mild nervous system stimulant and is currently the most widely used drug for the treatment of children with ADHD.[2,3] The psychostimulant properties of (±)-*threo*-methylphenidate have been linked to its binding to a site on the dopamine receptor, resulting in inhibition of dopamine re-uptake and enhanced levels of synaptic dopamine. This stimulation is believed to regulate attention and impulsivity of ADHD in children. Racemic (±)-*threo* methylphenidate, however, possesses side effects, e.g., anorexia, insomnia, weight loss, dizziness, dysphoria, and has potential for substance abuse in patients, especially when administered intravenously or through inhalation as it produces an euphoric effect. It has been postulated that the euphoric effect of (±)-*threo*-methylphenidate is primarily due to the action of l- or (2*S*,2'*S*)-(±)-*threo*-enantiomer. Enhanced relief for patients with ADHD was recently documented[4] with newly formulated D- or (2*R*,2'*R*)-(+)-*threo* methylphenidate (Figure 1), while reducing side effects and euphoric effects. Additionally, it has been shown that (2*R*,2'*R*)-(+)-*threo*-methylphenidate **1** is more potent in the induction of locomotor activity and has a higher affinity for the dopamine transporter than the (2*S*,2'*S*)-(±)-*threo*-enantiomer ***ent*-1**.[5] A recent report has demonstrated that pharmacological specificity resides entirely in the (2*R*,2'*R*)-(+)-*threo* methylphenidate **1** and that the binding of the (2*S*,2'*S*)-(-)-*threo*-enantiomer ***ent*-1** in human brain is mostly non-specific.[6] Thus, to segregate the desired pharmacological activities from side effects, there is a great interest for preparing enantiomerically pure (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride **1** on a large scale.

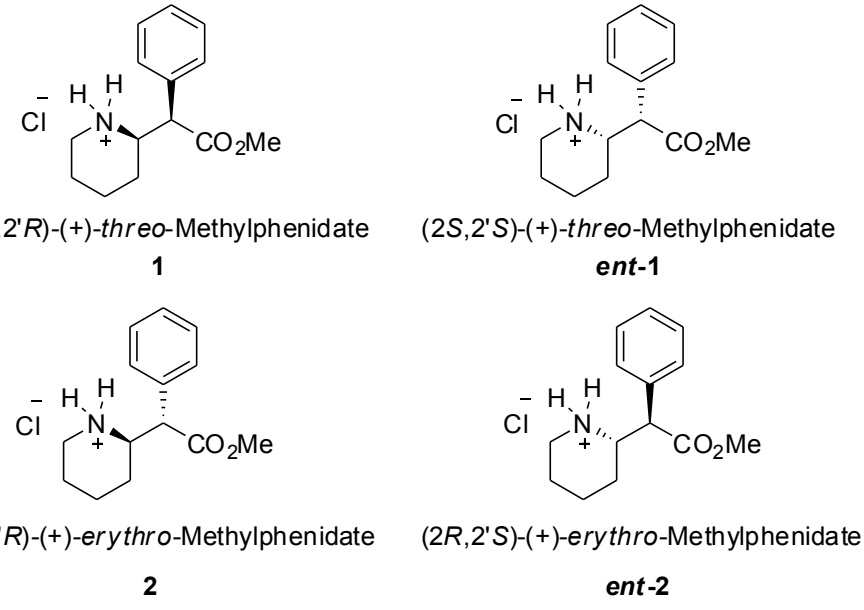


Figure 1. Four isomers of methylphenidate

Subsequent studies led to the discovery that the (2*R*,2'*R*)-(+)-*threo*-enantiomer was 5[7] to 38[8] times more active than the (2*S*,2'*S*)-(-)- *threo*-enantiomer. The metabolic pathway for methylphenidate in dogs and rats has also been delineated.[9] While the development of efficient routes for the synthesis of racemic (±)-*threo*-methylphenidate and its analogues for structure-activity relationship studies remains a topic of interest.[10-13]

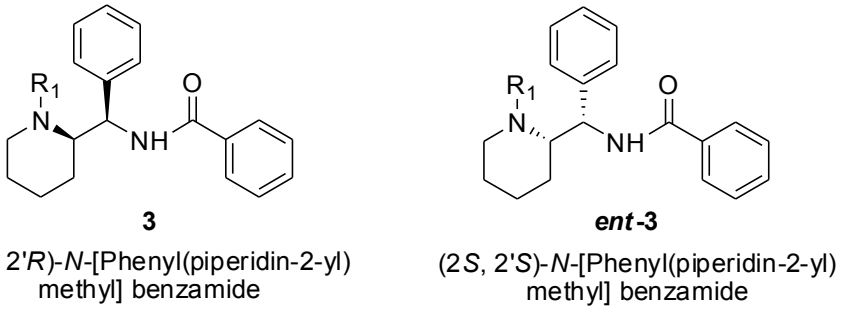


Figure 2. Two isomers of Benzamide

Compounds having structures which is analogous to that of the compounds shown above (Figure 2) are described as analgesics, diuretics, anticonvulsants, anesthetics, sedatives, cerebroprotective agents, by a mechanism of action on the opiate receptors.[14] Other compounds having analogous structures are described as 5-HT-3 antagonist which are useful in the treatment of psychotic disorder, neurological diseases, gastric syndromes,

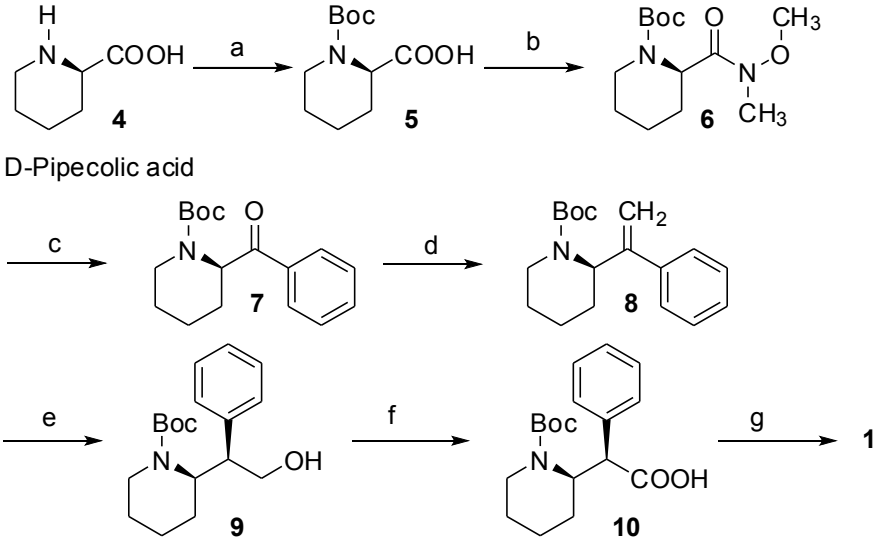
nausea and vomiting. These compounds are devoid of activity on the opiate or 5-HT-3 receptors and exhibit a particular activity as specific inhibitors of the glycine, transporter glyt1 and or glyt2. The compounds preferred as inhibitor of the glyt1 transporter are of the configuration (1*S*,2*S*), while the compounds preferred as inhibitors of the glyt2 transporter are of the configuration (1*R*,2*R*).

3.2. Review of Literature

Various approaches to the preparation of enantiomerically pure (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride **1** are reviewed. These approaches include synthesis using enantiomerically pure precursors obtained by resolution, classical and enzyme-based resolution approaches, enantioselective synthesis approaches, and approaches based on enantioselective synthesis of (2*S*,2'*R*)-*erythro*-methylphenidate followed by epimerization at the 2-position.

Perel *et al*. (1998)[15]

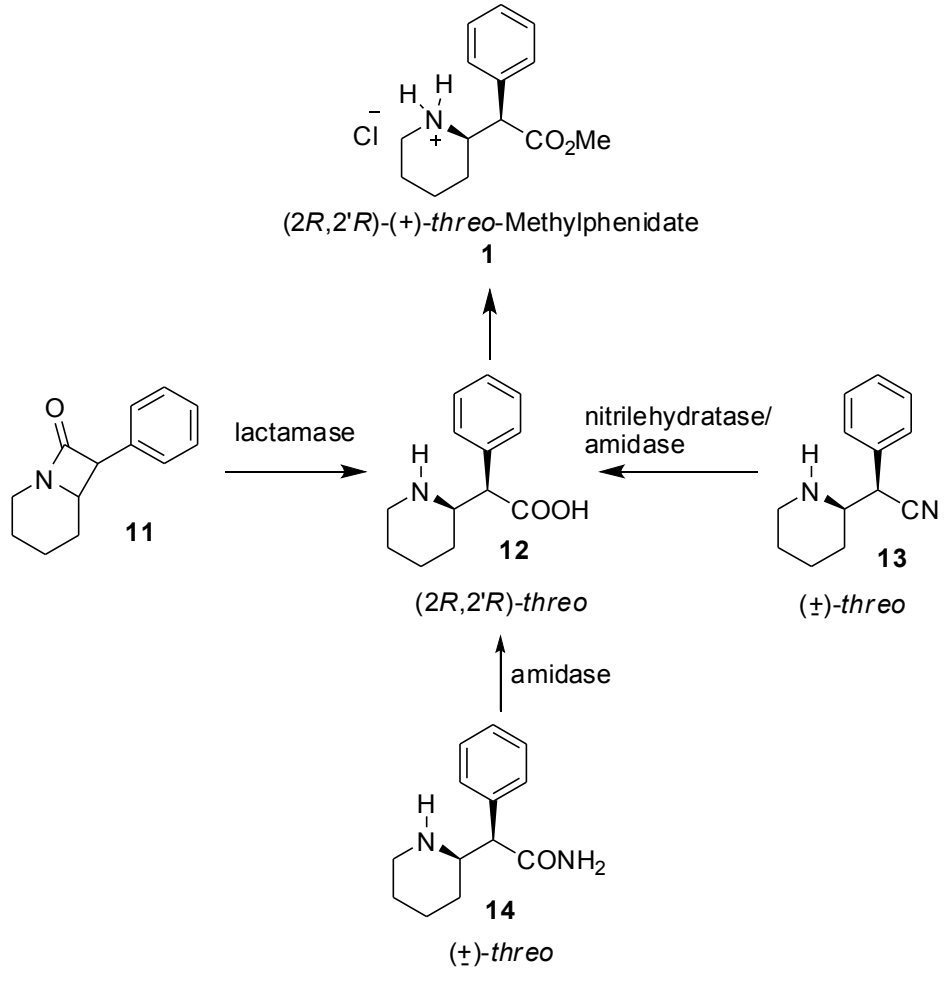
Perel *et al*. synthesised (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride **1** using an enantiomerically pure starting material, D-pipecolic acid **4**. Enantiomerically pure D-pipecolic acid **4** was protected with a Boc group to afford *N*-Boc-D-pipecolic acid **5** in 97% yield (Scheme 1).[15] **5** was converted into key amino ketone **7** in two steps involving its conversion to the *N*-methoxy-*N*-methyl amide **6**, followed by the reaction of amide **6** with phenyllithium. The amino ketone **7** underwent a Wittig olefination with methyltriphenylphosphonium bromide in the presence of potassium *tert*-butoxide to give the alkene **8** in high yield. The transformation of alkene **8** to the desired *threo* diastereomer of alcohol **9**, was achieved *via* hydroboration/oxidation. Hydroboration with BH_3.THF gave a 72:28 mixture of *threo* and *erythro* isomers respectively, from which the *threo* alcohol **9** was isolated after chromatography. Oxidation of *threo* alcohol **9** with PDC in DMF followed by esterification of the resulting acid **10** with diazomethane, and *N*-Boc group deprotection with 3N methanolic HCl furnished (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride **1** in 67% yield after recrystallization from ethanol/ether.



Scheme 1. *Reagents and conditions*: (a) $(Boc)_2O$, TEA, 97%; (b) BOP, TEA, *N*,*O*-Dimethylhydroxylamine hydrochloride, 93%; (c) PhLi, then H^+/H_2O, 73%; (d) Methyltriphenylphosphonium bromide, $K^+O^-{}^t$Bu, 93%; (e) (i) BH_3.THF, (ii) NaOH, H_2O_2, 64%; (f) PDC/DMF; (g) (i) CH_2N_2; (ii) methanolic HCl, 63% (over two steps).

Zeitlin *et al.* (1998)[16]

Enzymatic hydrolysis of (±)-*threo*-methylphenidate **1** free base with an esterase/lipase enzyme, obtained from various microorganisms, was reported by Zeitlin *et al.* to furnish (2*R*,2'*R*)-(+)-*threo*-methylphenidate in 96% ee. (±)-*trans*-7-Phenyl-1-azabicyclo[4.2.0]octan-8-one **11** was also hydrolyzed using a lactamase enzyme in pH 7 phosphate buffer (Scheme **2**) to afford (2*R*,2'*R*)-threoritalinic acid **12** with >96% ee. (2*R*,2'*R*)-*threo*-Ritalinic acid **12** was also obtained by hydrolysis of (±)-*threo*-2-phenyl-2-(2-piperidyl)acetamide **14** with amidase or (±)-*threo*-2-phenyl-2-(2-piperidyl)acetonitrile **13** using a nitrile hydratase and amidase enzymes in 98% ee.[16] (2*R*,2'*R*)-*threo*-Ritalinic acid **12** furnished (2*R*,2'*R*)-*threo*-methylphenidate hydrochloride **1** after esterification and HCl salt formation.

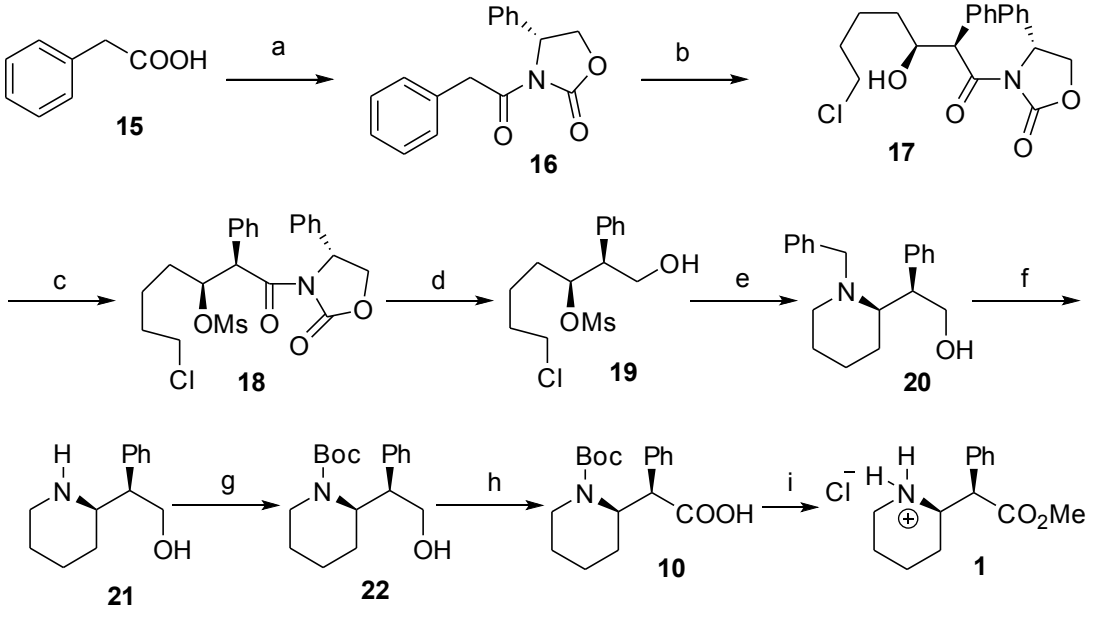


Scheme 2.

M Prashad *et al.* (1999)[17]

Mahavir Prashad *et al.* reported the first enantioselective synthesis of (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride **1**, which involved an asymmetric aldol condensation of 5-chlorovaleraldehyde with the (*Z*)-boron enolate derived from *N*-phenylacetyl-(*R*)-4-phenyl-2-oxazolidinone **16** as the key step to generate both stereogenic centers of **1** with desired absolute configuration (Scheme 3).[17] Mesylation of **17** with either methanesulfonic anhydride and pyridine in dichloromethane or methanesulfonyl chloride and triethylamine in toluene yielded the mesylate **18** in 92% yield. Reductive removal of the chiral auxiliary in **18** with sodium borohydride in THF and water furnished the desired alcohol **19** in 91% yield. Treatment of alcohol **19** with benzylamine at 85 °C afforded the desired piperidine intermediate **20** in 60% yield. Hydrogenation of **20** with 10% Pd-C in ethanol furnished the

amino alcohol **21** in 92% yield, which was acylated with di-*tert*-butyl dicarbonate to afford the *N*-Boc-protected alcohol **22** in 82% yield. Oxidation of alcohol **22** with $NaIO_4$ and $RuCl_3$ furnished the acid **10** in 80% yield which on treatment with methanol in the presence of HCl gas at 50 °C gave the desired (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride **1** in 70% yield. The enantiomeric purity of **1** was >99% ee and the overall yield from phenylacetic acid was 13% after 9 steps.

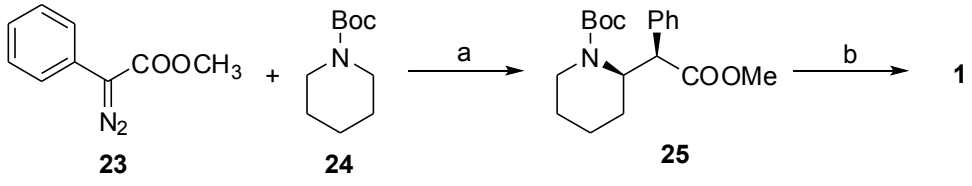


Scheme 3. *Reagents and conditions*: (a) (*R*)-4-Phenyl-2-oxazolidine, pivaloyl chloride, Et_3N, toluene, 78%; (b) (i) *n*-Bu_2BOTf, DIEA, CH_2Cl_2 or toluene, -20 °C to rt; (ii) 30% H_2O_2, MeOH, 78%; (c) Ms_2O, C_5H_5N, 0 °C or MsCl, Et_3N, 92%; (d) $NaBH_4$, THF-H_2O, 0 °C to rt, 91%; (e) $PhCH_2NH_2$, 85 °C, 3 h, 60%; (f) H_2, 10% Pd-C, EtOH, 92%; (g) $(Boc)_2O$, THF, 82%; (h) $NaIO_4$, $RuCl_3.H_2O$, CCl_4, 80%; (i) MeOH, HCl, 50 °C, overnight, 70%.

Winkler *et al.* (2000)[18-19]

Winkler *et al.* reported[18-19] an enantioselective synthesis of (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride **1** based on the rhodium-mediated C-H insertion of methyl phenyldiazoacetate **23** with *N*-Boc-piperidine **24**. Thus, reaction of methyl phenyldiazoacetate **23** with *N*-Boc-piperidine **24** in cyclohexane at 50 °C in the presence of 1 mol% of Rh_2(5R-MEPY)$_4$ led to the selective formation of *N*-Boc-D-*threo*-

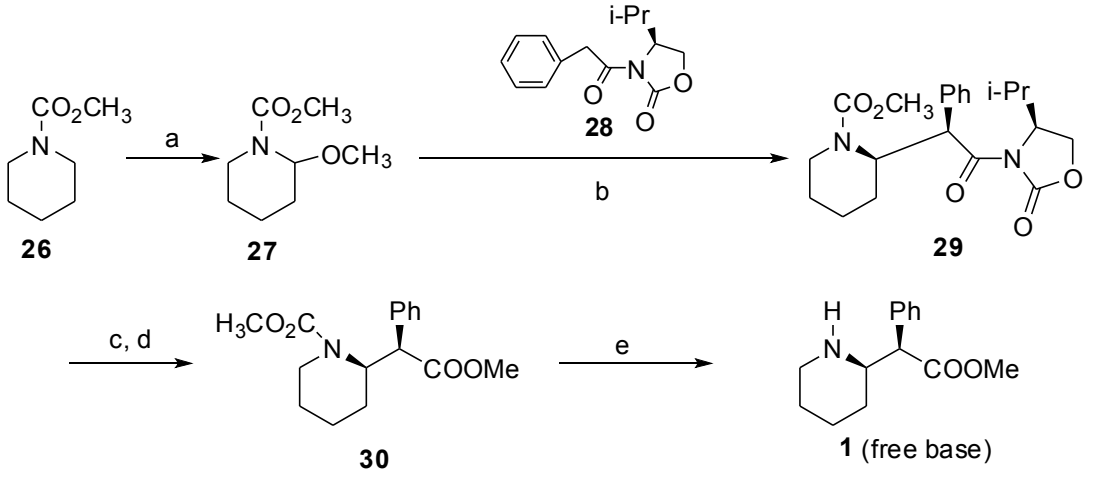
methylphenidate **25** in 64.5% yield (Scheme **4**). Deprotection of **25** with HCl gas in methanol furnished crude (2*R*,2'*R*)-(+)-*threo*-methylphenidate hydrochloride **1** in 68.5% yield with 94% de and 69% ee. Two recrystallizations of this crude product from a mixture of ethanol and diethyl ether (1:1 v/v) gave **1** in 26% yield with 95% de and >95% ee.



Scheme 4. *Reagents and conditions*: (a) Rh_2(5R-MEPY)$_4$, cyclohexane; (b) HCl, MeOH, or (a) Rh_2(S-biDOSP)$_2$, 2,3-dimethoxybutane, rt; (b) TFA.

Matsumura *et al*. (2000)[20,21]

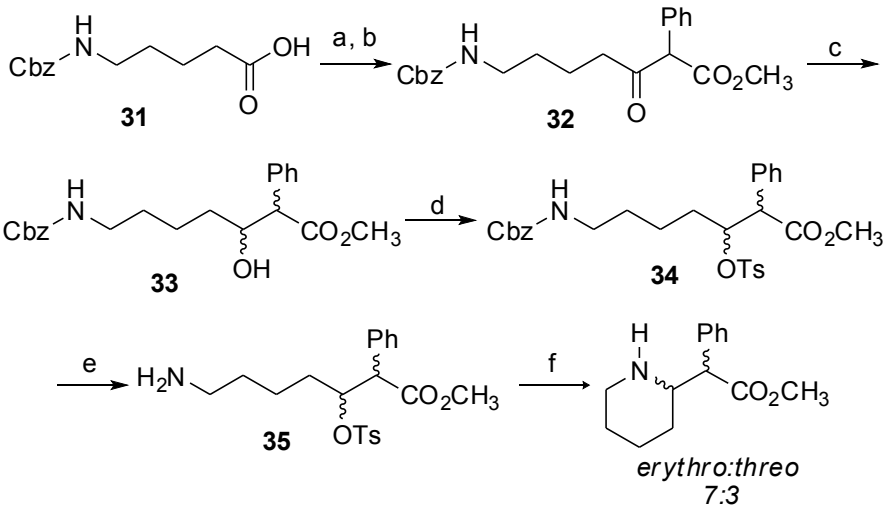
Matsumura *et al.*[20,21] described a convenient method for the preparation of (2*R*,2'*R*)-(+)-*threo*-methylphenidate **1** free base starting from the easily available *N*-methoxycarbonylpiperidine **26** involving a highly stereoselective coupling reaction of the α-methoxylated carbamate **27** with the Evans imide **28** as the key step (Scheme **5**). An electrochemical α-methoxylation of **26** in methanol afforded the *N*-protected α-methoxypiperidine **27** in 85% yield. The C-C bond forming reaction between **27** and **28** was successfully achieved by using a combination of $TiCl_4$ and diisopropylethylamine (DIPEA) to give the coupled product **29** with high diastereo- and enantioselectivity. Deprotection of the chiral auxiliary furnished acid, which on subsequent esterification afforded **30**. The deprotection at the *N*-methoxycarbonyl group with $(CH_3)_3SiI$ afforded (2*R*,2'*R*)-(+)-*threo*-methylphenidate **1** free base in 75% yield.



Scheme 5. *Reagents and conditions*: (a) 2.3 F/mol of electricity in MeOH containing Et_4NBF_4; (b) $TiCl_4$, DIPEA, CH_2Cl_2, -78 °C to rt; (c) LiOOH, H_2O/THF, rt; (d) CH_2N_2, ether, 2 h; (e) Me_3SiI, CH_2Cl_2, rt; 75%.

Seido *et al.* (1998)[22]

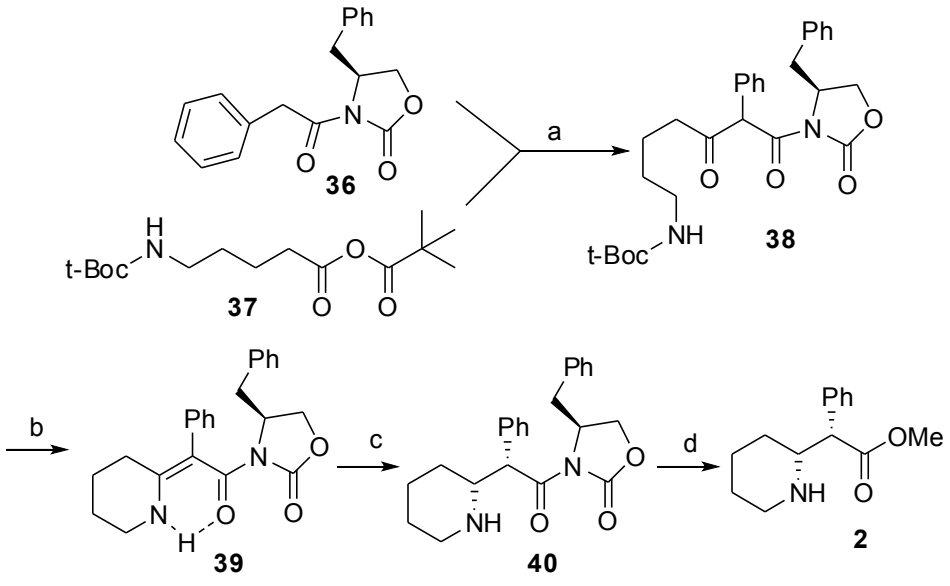
Another potential approach towards **1** was reported by Seido *et al.*[22] utilizing an asymmetric reduction of the ketone **32** as the key step. Acylation of the lithium enolate of methyl phenylacetate with imidazolide, obtained by treatment of the acid **31** with *N*,*N*'-carbonyldiimidazole gave the ketoester **32** in 66.4% yield (Scheme 6). Asymmetric reduction of **32** with [RuI(*p*-cymene)(*S*)-binap]I, $SnCl_2$, and CSA in methanol at 80 °C afforded the alcohol **33** as a mixture of *syn* and *anti* forms in 87.4% yield. The ratio of *syn* to *anti* isomers was 76.3:23.7 and the enantiomeric purity of each form was 95.6% ee and 97.8% ee respectively. Tosylation of **33** with *p*-toluenesulfonyl chloride and pyridine in the presence of catalytic amounts of DMAP yielded a diastereomeric mixture of tosylate **34** in 61.8% yield. Deprotection of the *N*-Cbz group in **34** by hydrogenation over 5% Pd-C followed by cyclization of the resulting amino tosylate **35** with potassium carbonate in methanol furnished methylphenidate as a mixture of *erythro* and *threo* isomers in a 7:3 ratio and 77.5% yield.



Scheme 6. *Reagents and conditions*: (a) *N*,*N*'-carbonyldimidazole, THF; (b) $PhCH_2CO_2CH_3$, LDA; (c) [RuI(*p*-cymene)(*S*)-binap]I, cat. $SnCl_2$, CSA, H_2, MeOH; (d) TsCl, DMAP, Pyridine; (e) H_2, Pd-C; (f) K_2CO_3, MeOH.

M Prashad *et al.* (1999)[23]

Mahavir Prashad *et al*. reported[23] an enantioselective synthesis of (2*S*,2'*R*)-*erythro*-methylphenidate **2** utilizing Evans (*S*)-4-benzyl-2-oxazolidinone chiral auxiliary to control the diastereofacial selectivity in the hydrogenation of enamine intermediate **39**. Acylation of (*S*)-4-benzyl-*N*-phenylacetyl-2-oxazolidinone **36** with the mixed anhydride **37**, followed by deprotection of the *N*-Boc group with TFA, and neutralization of the reaction mixture with $NaHCO_3$ afforded the enamine intermediate **39** (Scheme 7). Hydrogenation of enamine **39** with 10% Pd-C in ethyl acetate furnished **40** in 95% yield with an excellent diastereoselectivity (97:3). Treatment of **40** with methanol in the presence of LnI_3 afforded the desired (2*S*,2'*R*)-*erythro*-methylphenidate **2** in 85% yield and 94% ee.



Scheme 7. *Reagents and conditions*: (a) LiHMDS, THF, 0 °C, 1 h; (b) (i) CF_3CO_2H, CH_2Cl_2, 0 °C to rt, 4 h, (ii) $NaHCO_3$, 30% in two steps; (c) 10% Pd–C, EtOAc, rt, 24 h, 95%; (d) MeOH, LnI_3, THF, rt, 16 h, 85%.

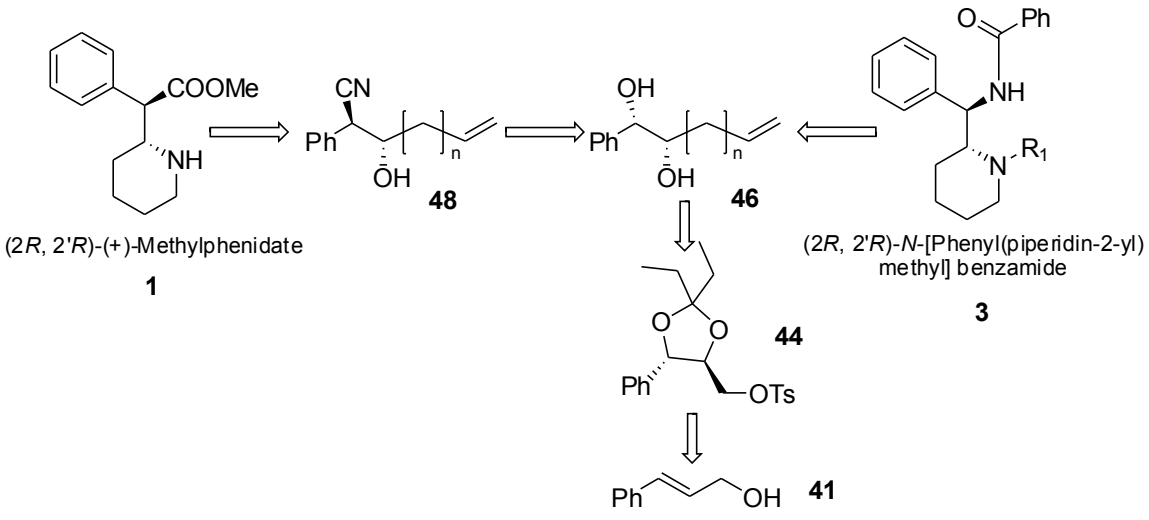
3.3. Present work

Objective

(2*R*, 2'*R*)-(+)-Methylphenidate **1,** (2*R*, 2'*R*)-*N*-[Phenyl(piperidin-2-Yl)methyl] benzamide **3** and their derivatives have attracted a great deal of interest among synthetic organic chemists and medicinal chemists worldwide as attractive synthetic targets due to their interesting biological properties. As part of our research programme aimed at developing enantioselective syntheses of bioactive molecules[24] we became interested in devising an efficient route to **1** and **3** and present study describes our endeavors towards the formal synthesis of compound **1** and compound **3** from commercially available cinnamyl alcohol employing Sharpless asymmetric dihydroxylation (AD) and ring closing metathesis (RCM) as the key steps.

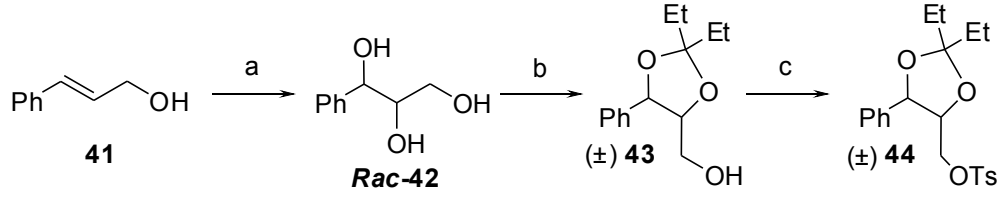
3.4. Results and discussion

Our initial approach for the synthesis of compound **1** and **3** was envisioned *via* the retrosynthetic route as shown in Scheme 8. The diol **46** was thought to be the common intermediate which can easily be obtained from cinnamyl triol **44**. The triol **44** was obtained from the cinnamyl alcohol **41** by OsO_4 catalysed *cis* dihydroxylation.



Scheme 8: Retrosynthetic route for the synthesis of compound **1** and compound **3**.

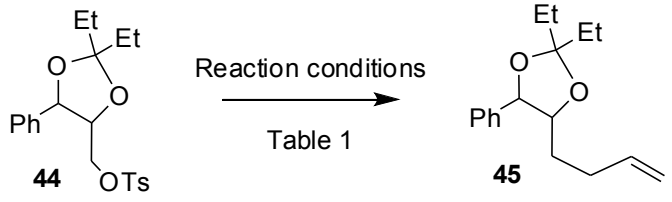
Thus commercially available cinnamyl alcohol **41** was subjected to OsO_4 catalysed dihydroxylation to give triol **42**, appearance of multiplet in the range of δ 3.31-3.36 and broad singlet at δ 3.93, and appearance of broad peak at 3300 cm^{-1} in IR spectrum confirmed the formation of triol. Selective protection of the secondary hydroxy groups was achieved by using 3-pentanone to give ketal **43**. Appearance of multiplet in the arrange of δ 1.00-1.10 and 1.73-1.92 confirmed the formation of ketal. The free primary hydroxy group of **43** was then converted into a leaving group by protecting as *p*-toluene sulphate derivative using tosyl chloride to furnish **44** in 90% yield.



Scheme 9: *Reagents and conditions*: (a) OsO_4, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH, H_2O, 84%; (b) 3-pentanone, CSA, DCM, 85%; (c) TsCl, Et_3N, DCM, 90%.

With the tosylate **44** in hand our next aim was to displace tosyl group with suitable alkyl group, towards this end we tried various conditions to displace the tosyl group with allyl group using allyl magnesium bromide. The results are summarized in Table 1. The reaction gave best result with simultaneous addition of tosylate **44** to Grignard reagent (allyl

magnesium bromide) in Et_2O. The appearance of olefinic protons in the range of δ 4.93-5.00 as multiplet and δ 5.75-5.83 as multiplet confirmed the formation of the product.

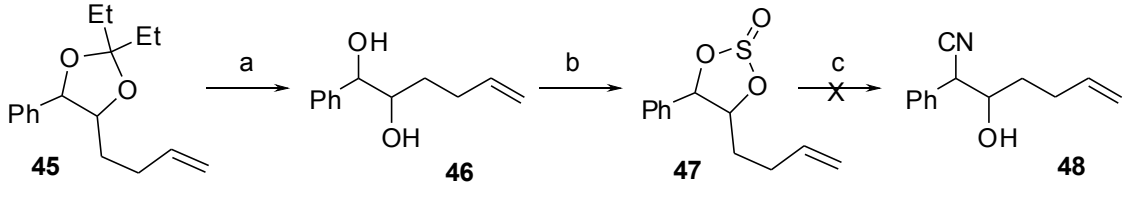


Scheme 10: *Reagents and conditions*: Allyl Bromide, Mg, various additives, solvent.(see Table 1)

Sr. No	Reaction conditions	Time (h)	Temperature (°C)	Yield (%)	Additive	Solvent
1	Allyl bromide	12	-30	0	CuI	THF
2	Allyl bromide	12	-78	0	CuI	THF
3	Allyl bromide	12	-78	0	CuI	Et_2O
4	Allyl bromide	24	25	<5	-	Et_2O
5	Allyl bromide	24	25	40	-	Et_2O
6	Allyl bromide	96	25	70	-	Et_2O
7	Allyl bromide	96	25	40	-	THF

Table 1: Various conditions for the tosyl displacement

With the olefin **45** in hand, we then deprotected the ketal using *p*-TSA in methanol to give diol olefin **46** in excellent yield. The IR spectrum of **46** clearly shows a broad peak at 3401 cm^{-1} corresponding to hydroxy absorption.

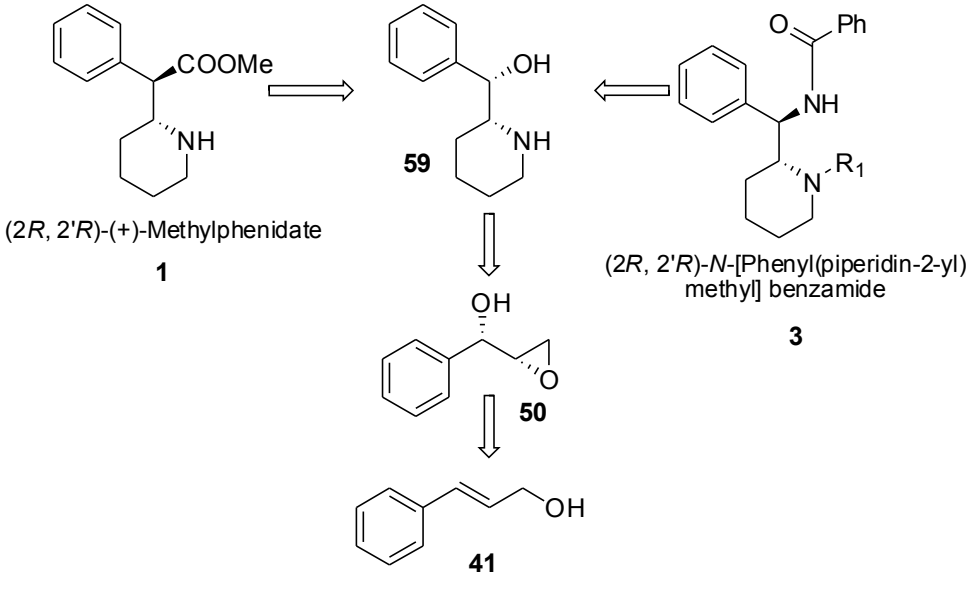


Scheme 11: *Reagents and conditions*: (a) *p*-TSA, MeOH, 92%; (b) $SOCl_2$, Et_3N, DCM, 65%; (c) NaCN, DMF, 80 °C.

The essential feature of our synthetic strategy was based on the presumption that the nucleophilic opening of the cyclic sulphite **47** would occur in a regioselective manner at the α-carbon atom.[25] The diol **46** was then subjected to freshly distilled thionyl chloride in presence of triethyl amine to give cyclic sulphite **47** in 65% yield. The absence of peak at

3304 cm^{-1} in IR spectrum and deshielding of benzylic proton from δ 4.30 to 5.52 clearly showed the formation of cyclic sulphite. Cylic sulphite **47** was then subjected to regioselective and stereoselective displacement by sodium cyanide but to our disappointment we did not get the expected product but ended up with complex reaction mixture, which was difficult to characterize. Then we attempted at conversion of diol **46** into cyclic sulphate using sulphuryl chloride at -78 °C but the desired product could not be obtained. We then switched over to different strategy to functionalize the diol **42** by regioselective differentiation of the two hydroxy group and then displacement of each group.

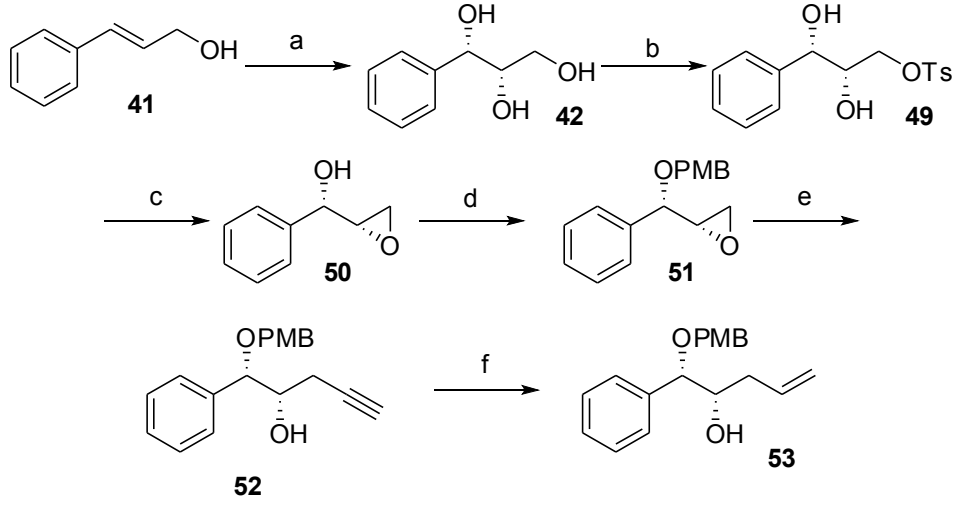
Our new approach for the synthesis of compound **1** & **3** was envisioned *via* the retrosynthetic route as shown in Scheme 12. The amino-alcohol **59** was thought to be the common intermediate from which both compounds **1** and **3** can be easily synthesized. The amino alcohol **59** could be obtained from the epoxide **50** by series of reactions involving regioselective epoxide opening and RCM. The epoxide **50** in turn could be easily synthesized by the Sharpless asymmetric dihydroxylation (AD) of cinnamyl alcohol **41**.



Scheme 12. Retrosynthetic analysis of compound **1** & **3**.

Thus the commercially available cinnamyl alcohol **41** 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 **42** in 84% yield with ee > 95%, $\{[\alpha]_D^{25}$: +20.8 (*c* 3.5,

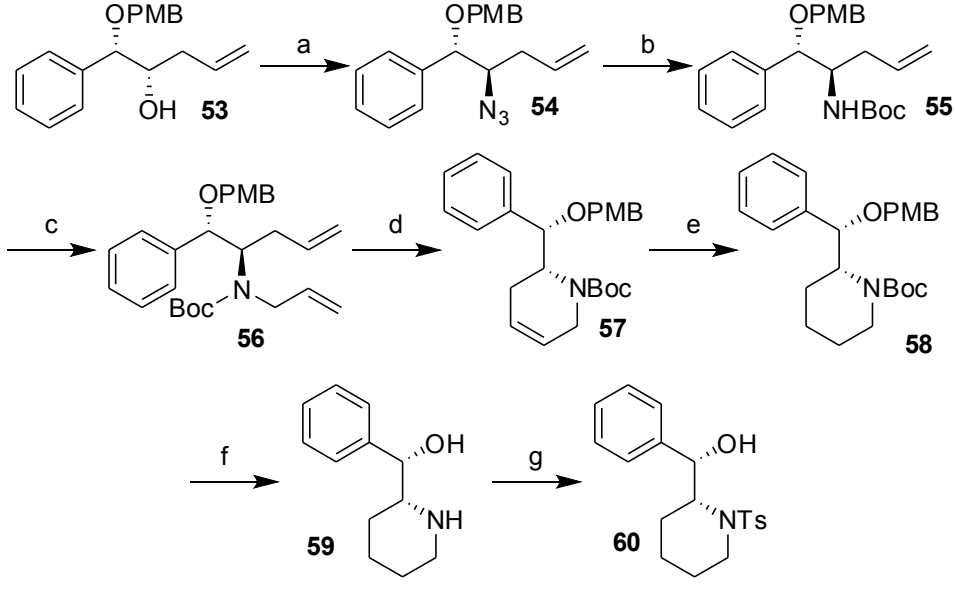
$CHCl_3$); Lit[26] {$[\alpha]_D$ [25]: +20.92 (*c* 3.68, $CHCl_3$)}. The regioselective primary monotosylation of this triol **42** with tosyl chloride and catalytic Bu_2SnO, furnished the tosyl diol **49** in excellent yield. The appearance of peak at δ 2.37 in ^{1}H- NMR shows the presence of tosyl group (Scheme 13). Base treatment of this compound **49** in presence of K_2CO_3 in methanol furnished hydroxyl epoxide **50**. 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 **50** was then protected as PMB ether using PMB-bromide to give **51**. 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. The regioselective opening of epoxide **51** using lithium acetylide ethylene diamine complex gave the homopropargyl alcohol **52** which on partial reduction using Lindlar's catalyst gave the homoallylic alcohol **53**. The appearance of olefinic protons in the range of δ 4.86-4.96 as multiplet and δ 5.62-5.83 as multiplet confirmed the formation of the product (Scheme 13).



Scheme 13: *Reagents and conditions*: (a) $(DHQ)_2PHAL$ (1mol%), 0.1M OsO_4 (0.4mol%), K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, *t*-BuOH/H_2O (1:1), 0 °C, 24 h, 84%; (b) TsCl, Et_3N, Bu_2SnO, DCM, 89%; (c) K_2CO_3, MeOH, 76%; (d) PMB-Br, NaH, DMF, 85%; (e) LiC≡CH–ethylene diamine, DMSO, rt, 10 h, 65%; (f) H_2, $Pd/BaSO_4$, quinoline, benzene, 1 bar, rt, 2 h, 95%.

The free hydroxy group of **53** was converted into *O*-mesylate, The attempted displacement of *O*-mesylate with sodium azide resulted in sluggish reaction and the starting material coluld not be fully converted into the product even with excess of sodium azide, but

nucleophilic displacement with lithium azide in dry DMF afforded compound **54** in 60% yield. The IR spectrum of **54** showed strong azide absorption at 2110 cm^{-1}. The azide **54** was then subjected to Staudinger reaction[27] and converted into amine which on Boc protection with $(Boc)_2O$ led to **55** in 80% yield (two steps, one pot). The IR spectrum of **55** showed absence of azide absorption at 2110 cm^{-1} and ^{1}H-NMR showed the appearance of singlet at δ 1.28. Compound **55** was then alkylated with allyl bromide in the presence of NaH to produce **56** in 85% yield. Treatment of **56** with the Grubbs' first generation catalyst[28] (Scheme 14) in toluene furnished the 3,4-dehydropiperidine **57** in 94% yield. The appearance of olefinic protons in the range of δ 5.55-5.71 as multiplet confirmed the formation of the product. After catalytic hydrogenation of the double bond of **58** in EtOAc over Pd-C, the deprotection of *p*-methoxybenzyl and Boc groups was achieved with aq. HCl to furnish amino alcohol **59** in 74% yield. In order to concludingly prove the structure of the amino alcohol, **59** was monotosylated using 1 equiv. of TsCl in Et_3N, to furnish **60** in good yield as a crystalline white solid. The single X-ray structure analysis of **60** clearly showed the relative stereochemistry of the OH and NH groups to be *anti*.



Scheme 14: *Reagents and conditions*: (a) (i) MsCl, Et_3N, DCM; (ii) LiN_3, DMF, (60% over two steps); (b) (i) TPP, THF:H_2O; (ii) $(Boc)_2O$, dioxane: H_2O, 80%; (c) Allyl bromide, NaH, DMF, 85%; (d) Grubb's catalyst, Toluene, 94%; (e) H_2-Pd/C, EtOAc, 92%; (f) HCl (1N) 74%; (g) TsCl, Et_3N, 80%.

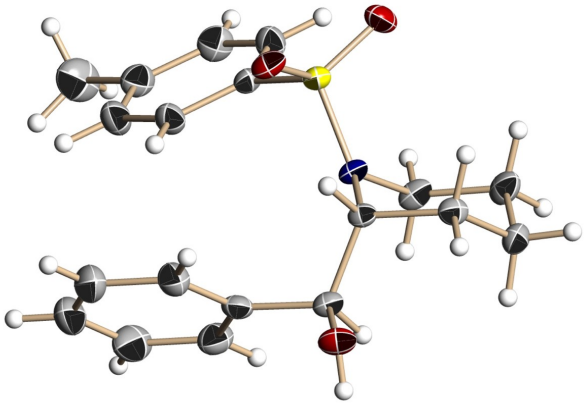
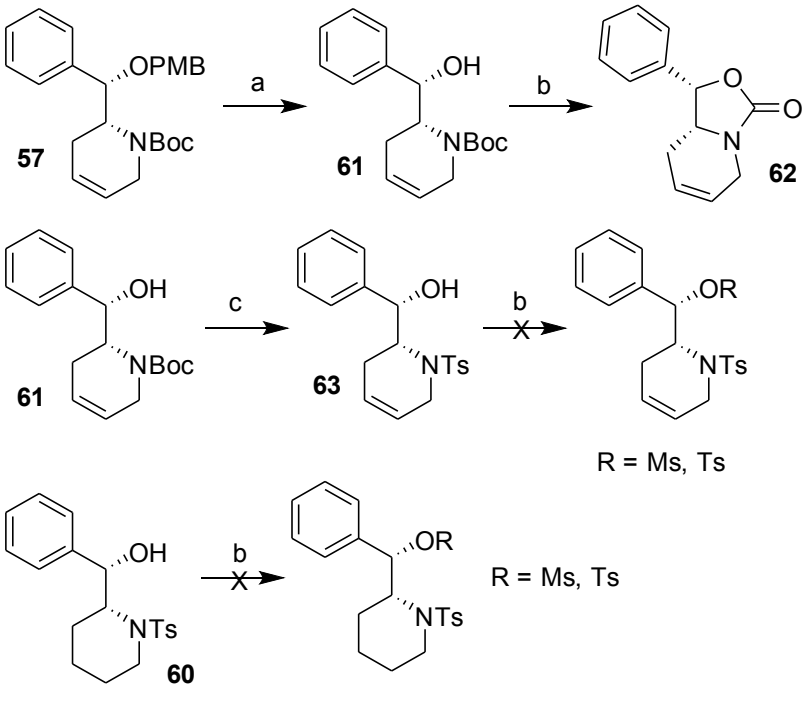


Figure 3. The ORTEP diagram of the (*S*)-phenyl((*R*)-1-tosylpiperidin-2-yl)methanol **60**

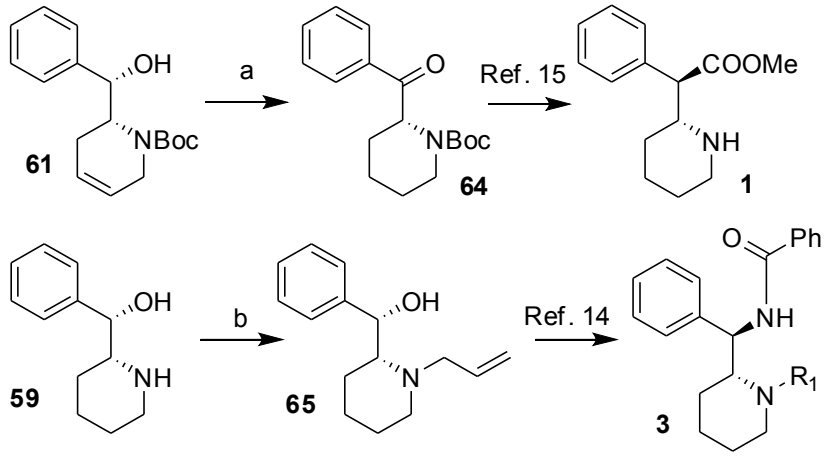
After completing the synthesis of compound **57** and confirming the relative stereochemistry, our next aim was to convert the PMB protected hydroxy group into its mesyl or tosyl derivative. Thus deprotection of PMB ether in presence of DDQ furnished alcohol **61**.



Scheme 15: *Reagents and conditions*: (a) DDQ, DCM: H_2O, 79%; (b) TsCl, Et_3N, DMAP, or MsCl, Et_3N, DCM; (c) (i) HCl (1M), 74%; (ii) TsCl, Et_3N, DMAP.

The attempted conversion of free hydroxy into mesyl derivative furnished oxazolidine **62** in quantitative yield. Further various attempts to carryout the reaction, changing the protecting groups at nitrogen from Boc to Ts and introducing unsaturation in the piperidine ring failed to give the desired products (Scheme 15).

To overcome this problem, free hydroxy group of **61** was converted into ketone which on reduction with Pd-C under hydrogenation conditions gave compound **64**. The conversion of ketone **64** into target molecule **1** is documented in the literature.[15] Similarly with amino alcohol **59** in hand we tried to convert it into target compound **3** (Scheme 16). Thus selective *N*-alkylation of **59** using allyl bromide and K_2CO_3 furnished the *N*-allyl compound **65**. Appearance of multiplet in the range of δ 5.13-5.17 and 5.21-5.27 confirmed the formation of the product. The conversion of *N*-allylic alcohol **65** to the various substituted diamines of the general formula **3** is documented in literature.[14]



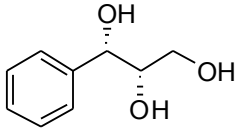
Scheme 16: *Reagents and conditions*: (a) (i) IBX, EtOAc; (ii) H_2-Pd/C, EtOAc, 83%; (b) Allyl bromide, K_2CO_3; CH_3CN, 65%.

3.5. Conclusion

In conclusion, practical and stereocontrolled formal synthesis of (2*R*, 2'*R*)-(+)-Methylphenidate **1** & (2*R*, 2'*R*)-*N*-[Phenyl(piperidin-2-Yl)methyl] benzamide **3** is achieved and the synthetic strategy described here has significant potential for the development of structural variants on the piperidine ring.

3.6. Experimental Section

(1*S*,2*S*)-1-Phenylpropane-1,2,3-triol (42):



To a mixture of $K_3Fe(CN)_6$ (36.80 g, 111.8 mmol), K_2CO_3 (15.44 g, 111.8 mmol), $(DHQ)_2PHAL$ (0.290 g, 1 mol%) in *t*-BuOH/H_2O (1:1, 380 mL) at 0 °C was added osmium tetroxide (1.47 mL, 0.1 M solution in toluene, 0.4 mol%), followed by methanesulfonamide (3.57 g, 37.26 mmol). After stirring for 5 min at 0 °C, cinnamyl alcohol **41** (5.0 g, 37.26 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 24 h and then quenched with solid sodium sulfite (55.0 g). The stirring was continued for additional 15 min and then the solution was extracted with EtOAc (3 x 200 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated. Silica gel column chromatography of the crude product using EtOAc/petroleum ether (6:4) gave **42** as a syrupy liquid.

Yield: 5.26 g, 84%

Mol. Formula: $C_9H_{12}O_3$

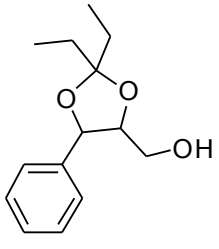
$[\alpha]_D^{25}$: +38.83 (*c* 1.00, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3424, 2931, 1447, 1215, 1008.

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.31-3.36 (m, 2H), 3.64-3.66 (m, 1H), 3.93 (bs, 3H), 4.51 (d, *J* = 7.1 Hz, 1H), 7.23-7.27 (m, 5H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 62.6, 74.2, 75.7, 126.5, 127.6, 128.1, 140.5 ppm.

((±)-2,2-Diethyl-5-phenyl-1,3-dioxolan-4-yl)methanol (43):



To a solution of the triol **42** (2.0 g, 11.9 mmol), in dry DCM (20 mL) was added 3-pentanone (5.0 mL), *p*-TsOH (0.2 g) and stirred overnight. Solid $NaHCO_3$ (0.50 g) was added and stirred for 30 min. The reaction mixture was filtered through a pad of neutral alumina and concentrated. Silica gel column chromatography using petroleum ether:ethyl acetate (9:1) gave **43** as a colorless liquid.

Yield: 2.38 g, 85%

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

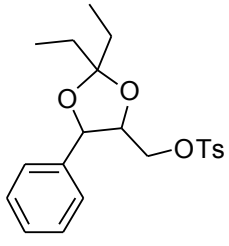
IR ($CHCl_3$, cm^{-1}): ν_{max} 3359, 2935, 1596, 1447, 1215, 1050.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.00-1.10 (m, 6H), 1.73-1.92 (m, 4H), 2.49 (bs, 1H), 3.59-3.68 (m, 1H), 3.82-3.92 (m, 2H), 4.86 (d, J = 8.6 Hz, 1H), 7.31-7.44 (m, 5H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 8.1, 30.4, 60.5, 78.9, 83.8, 112.8, 126.5, 128.2, 128.5, 137.8 ppm.

Analysis Calcd.: C, 71.16; H, 8.53; **Found:** C, 71.29; H, 8.35%

((±)-2,2-Diethyl-5-phenyl-1,3-dioxolan-4-yl)methyl 4-methylbenzenesulfonate (44):



To a mixture of alcohol **43** (2.0 g, 8.5 mmol), in dry dichloromethane (20 mL) was added *p*-toluenesulfonyl chloride (1.77 g, 9.3 mmol) and triethylamine (2.35 mL, 16.9 mmol) at 0 °C and reaction was stirred at room temperature under nitrogen. The reaction was monitored by TLC, after completion of reaction (45 min) the mixture was quenched by adding water. The solution was extracted with dichloromethane (3 x 10 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 **44** as a viscous liquid.

Yield: 3.00 g, 90%

Mol. Formula: $C_{21}H_{26}O_5S$

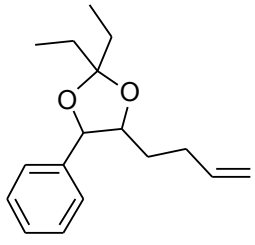
IR ($CHCl_3$, cm^{-1}): ν_{max} 3002, 2985, 1496, 1453, 1399, 1173, 1009.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89-1.05 (m, 6H), 1.66-1.81 (m, 4H), 2.46 (s, 3H), 3.84-3.92 (m, 1H), 4.13 (dd, *J* = 4.0, 11.0 Hz, 1H), 4.23 (dd, *J* = 4.0, 11.0 Hz, 1H), 4.80 (d, *J* = 8.7 Hz, 1H), 7.32-7.37 (m, 7H), 7.75-7.80 (m, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 7.9, 21.5, 30.1, 30.2, 67.2, 79.0, 80.7, 113.5, 122.4, 126.4, 126.8, 127.9, 128.6, 129.7, 129.9, 131.4, 132.7, 137.0, 144.8 ppm.

Analysis Calcd.: C, 64.59; H, 6.71; S, 8.21; **Found:** C, 64.71; H, 6.54; S, 8.11%

(±)-4-(But-3-enyl)-2,2-diethyl-5-phenyl-1,3-dioxolane (45):



To a stirred suspension of allylmagnesium bromide (7.8 mL, 89.6 mmol,) in diethyl ether (4 mL) was added tosyl compound **44** (5.0 g, 12.8 mmol) and the reaction mixture was allowed to stir at room temperature. After stirring the resultant mixture for 4 days, the reaction mixture was quenched by addition of sat. ammonium chloride. Reaction mixture was extracted with diethyl ether (3 x 20 mL). Organic layer was separated, washed with brine, dried ($MgSO_4$) and evaporated. Column chromatography (EtOAc/pet. ether: 1/19) of the residue gave alkene **45** as a colorless liquid.

Yield: 2.33 g, 70%

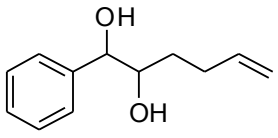
Mol. Formula: $C_{17}H_{24}O_2$

IR ($CHCl_3$, cm^{-1}): ν_{max} 3066, 2928, 2253, 1610, 1494, 1454, 1197, 1050.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.01 (t, *J* = 7.5 Hz, 3H), 1.07 (t, *J* = 7.5 Hz, 3H), 1.68-1.74 (m, 2H), 1.76-1.80 (m, 2H), 1.83-1.88 (m, 2H), 2.06-2.15 (m, 1H), 2.21-2.30 (m, 1H), 3.77-3.83 (m, 1H), 4.54 (d, *J* = 8.8 Hz, 1H), 4.93-5.00 (m, 2H), 5.75-5.83 (m, 1H), 7.33-7.43 (m, 5H) ppm.

Analysis Calcd.: C, 78.42; H, 9.29; **Found:** C, 78.58; H, 9.05%

(±)-1-Phenylhex-5-ene-1,2-diol (46):



To a stirred solution of compound **45** (1.0 g, 5.2 mmol) in MeOH was added a catalytic amount of *p*-TSA (0.1 g) at room temperature and the reaction mixture stirred overnight at the same temperature. Solid $NaHCO_3$ (0.1 g) was added and stirred for 30 min. The mixture was then filtered through a celite pad, washed with MeOH, concentrated and column purified using petroleum ether:ethyl acetate (7:3) to give **46** as a pale yellow liquid

Yield: 0.68 g, 92%

Mol. Formula: $C_{12}H_{16}O_2$

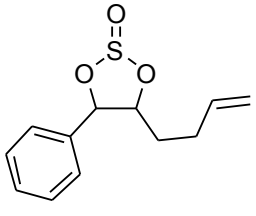
IR ($CHCl_3$, cm^{-1}): ν_{max} 3401, 2920, 2250, 1640, 1494, 1453, 1197, 1047, 909.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.28-1.39 (m, 2H), 1.93-2.14 (m, 2H), 2.94 (bs, 2H), 3.54-3.63 (m, 1H), 4.30 (d, J = 6.5 Hz, 1H), 4.81-4.92 (m, 2H), 5.57-5.74 (m, 1H), 7.20-7.30 (m, 5H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 29.8, 31.7, 75.3, 77.9, 114.9, 126.8, 128.1, 128.5, 128.7, 138.1 ppm.

Analysis Calcd.: C, 74.97; H, 8.39; **Found:** C, 74.84; H, 8.52%

Compound 47:



To a solution of diol **46** (1.0 g, 5.2 mmol) in dry CH_2Cl_2 (10 mL) was added Et_3N (2.9 mL, 20.8 mmol). The mixture was cooled in an ice bath and thionyl chloride (0.76 mL, 10.4 mmol) added dropwise. The reaction mixture was stirred for 30 min and then quenched by adding water (10 mL). The phases were separated and aqueous phase extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phase was dried over Na_2SO_4 and concentrated.

Silica gel column chromatography (EtOAc/petroleum ether, 1:4) of the crude product gave cyclic sulphite **47** as a colorless liquid.

Yield: 0.81 g, 65%

Mol. Formula: $C_{12}H_{14}O_3S$

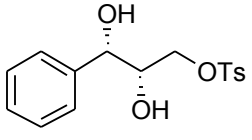
IR ($CHCl_3$, cm^{-1}): ν_{max} 3066, 2928, 2253, 1610, 1494, 1454, 1197, 1050.

^{1}H NMR (200 MHz, $CDCl_3$): (major diastereomer): δ 1.86-1.94 (m, 1H), 2.00-2.09 (m, 1H), 2.13-2.23 (m, 1H), 2.26-2.34 (m, 1H), 4.75-4.80 (m, 1H), 4.94-5.03 (m, 2H), 5.52 (d, J = 9.0 Hz, 1H), 5.69-5.78 (m, 1H), 7.39-7.50 (m, 5H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): (major diastereomer): δ 29.8, 31.5, 84.4, 88.8, 115.9, 127.3, 127.8, 129.1, 129.7, 134.0, 136.5 ppm.

Analysis Calcd.: C, 60.48; H, 5.92; S, 13.46; **Found:** C, 60.32; H, 6.08; S, 13.21%

(2*S*,3*S*)-2,3-Dihydroxy-3-phenylpropyl 4-methylbenzenesulfonate (49):



To a mixture of triol **42** (4.00 g, 23.66 mmol), in dry dichloromethane (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 triethylamine (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 (45 min) 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 **49** as a viscous liquid.

Yield: 6.8 g, 89%

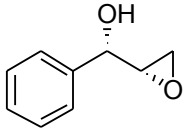
Mol. Formula: $C_{16}H_{18}O_5S$

$[\alpha]_D^{25}$: +13.82 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3403, 1496, 1453, 1399, 1173, 1009.

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.37 (s, 3H), 2.83 (bs, 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), 7.65-7.69 (d, *J* = 8.3 Hz, 2H) ppm.
^{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, 145.0 ppm.
Analysis Calcd.: C, 59.61; H, 5.63; S, 9.95; **Found:** C, 59.75; H, 5.49; S, 9.74%

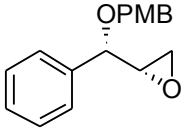
(*S*)-((*S*)-Oxiran-2-yl)(phenyl)methanol (50):



To a solution of compound **49** (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 one hour. After completion of the reaction (progress of reaction was monitored by TLC), 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 $MgSO_4$, solvent was evaporated under reduced pressure to give crude epoxide **50**, which was further purified by column chromatography using EtOAc /pet ether (7:3) as eluent.

Yield: 0.354 g, 76%
Mol. Formula: $C_9H_{10}O_2$
$[\alpha]_D^{25}$: +18.54 (*c* 1.0, $CHCl_3$)
IR ($CHCl_3$, cm^{-1}): ν_{max} 3438, 2934, 1612, 1513, 1454, 1247, 1097.
^{1}H NMR (200 MHz, $CDCl_3$): δ 2.71-2.79 (m, 2H), 3.10-3.17 (m, 1H), 4.35 (d, *J* = 5.7 Hz, 1H), 7.26-7.36 (m, 5H) ppm.
^{13}C NMR (125 MHz, $CDCl_3$): δ 45.3, 56.0, 74.4, 126.2, 128.0, 128.4, 140.0 ppm.
Analysis Calcd.: C, 71.98; H, 6.71; **Found:** C, 72.07; H, 6.56%

(*S*)-2-((*S*)-(4-Methoxybenzyloxy)(phenyl)methyl)oxirane (51):



To a solution of hydroxyl alcohol **50** (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 2 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 (8:2) as eluent furnished the mono-PMB protected epoxide **51** as a colorless oil.

Yield: 3.06 g, 85%

Mol. Formula: $C_{17}H_{18}O_3$

$[\alpha]_D^{25}$: +41.3 (*c* 1.8, $CHCl_3$)

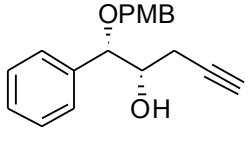
IR ($CHCl_3$, cm^{-1}): ν_{max} 3012, 1612, 1514, 1465, 1249, 1035.

^{1}H NMR (200 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), 4.09-4.12 (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) ppm.

^{13}C NMR (125 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 ppm.

Analysis Calcd.: C, 75.53; H, 6.71; **Found:** C, 75.68; H, 6.84%

(1*S*,2*S*)-1-(4-Methoxybenzyloxy)-1-phenylpent-4-yn-2-ol (52):



To a stirred solution of epoxide **51** (1.5 g, 5.9 mmol) in DMSO (5 mL) at 0 °C was added lithium acetylide-EDA complex (0.814 g, 8.84 mmol). The mixture was stirred at r.t. for 10 h. To the mixture were added 50 mL of 20% aq. H_2SO_4 and 50 mL of ether. After the biphasic mixture was stirred overnight, the product was extracted with ether. The organic

layer was washed with water, brine, dried (Na_2SO_4), concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) as eluent gave acetylide **52** as a colorless syrupy liquid.

Yield: 1.06 g, 65%

Mol. Formula: $C_{19}H_{20}O_3$

$[\alpha]_D^{25}$: +54.1 (*c* 2.9, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3468, 3292, 3062, 2909, 1612, 1513, 1454, 1302, 1249, 1032.

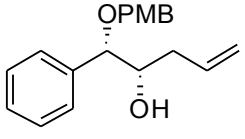
^{1}H NMR (200 MHz, $CDCl_3$): δ 2.07-2.09 (m, 1H), 2.15-2.19 (m, 1H), 2.36-2.40 (m, 1H), 3.84 (m, 3H), 3.87-3.91 (m, 1H), 4.25 (d, *J* = 10.9 Hz, 1H), 4.42-4.49 (m, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 7.25 (d, *J* = 8.7 Hz, 2H), 7.40-7.45 (m, 5H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 22.4, 55.1, 70.4, 73.1, 80.4, 83.1, 113.7, 127.5, 128.3, 128.5, 129.5, 129.6, 138.0, 159.2 ppm.

Analysis Calcd.: C, 77.00; H, 6.80; **Found:** C, 77.15; H, 6.63%

MS (ESI): m/z 297.0679 (M^++H), 319.1123 (M^++Na), 335.0899 (M^++K).

(1*S*,2*S*)-1-(4-Methoxybenzyloxy)-1-phenylpent-4-en-2-ol (53):



To a solution of **52** (1.0 g, 3.37 mmol) in ethyl acetate (10 mL) was added Lindlar's catalyst (0.050 g) and few drops of quinoline. The reaction mixture was stirred for 2 h under a balloon of H_2 at room temperature and filtered through a celite pad. The filtrate was concentrated and the residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1) as eluent to give **53** as a pale yellow oil.

Yield: 0.96 g, 95%

Mol. Formula: $C_{19}H_{22}O_3$

$[\alpha]_D^{25}$: +23.6 (*c* 1, $CHCl_3$)

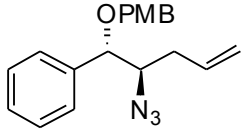
IR ($CHCl_3$, cm^{-1}): ν_{max} 3399, 3019, 1613, 1514, 1249, 1215, 1036.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.88-2.01 (m, 2H), 2.87 (bs, 1H), 3.64-3.66 (m, 1H), 3.71 (s, 3H), 4.07-4.13 (m, 2H), 4.28 (d, *J* = 11.0 Hz, 1H), 4.86-4.96 (m, 2H), 5.62-5.83 (m, 1H), 6.78 (d, *J* = 8.8 Hz, 2H), 7.11 (d, *J* = 8.8 Hz, 2H), 7.24-7.30 (m, 5H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 36.6, 55.1, 70.2, 74.4, 84.3, 113.8, 117.0, 127.8, 128.2, 128.5, 129.5, 129.8, 134.5, 138.4, 159.2 ppm.

Analysis Calcd.: C, 76.48; H, 7.43; **Found:** C, 76.62; H, 7.58%

1-(((1*S*,2*R*)-2-Azido-1-phenylpent-4-enyloxy)methyl)-4-methoxybenzene (54):



To an ice-cold stirred solution of **53** (1.0 g, 3.35 mmol) and triethylamine (0.93 mL, 6.7 mmol) in anhydrous CH_2Cl_2 (15 mL) was added dropwise methanesulfonyl chloride (0.31 mL, 4.02 mmol) over 15 min. The resulting mixture was allowed to warm up to room temperature and stirred for 2 h. After diluting with 25 mL CH_2Cl_2, the solution was washed with water (3 x 20 mL), brine, dried over Na_2SO_4 and concentrated to give the crude mesylated product. This was used for the next step without further purification.

To a solution of above mesylated product (1.3 g, 3.45 mmol) in dry DMF (15 mL) was added portion wise LiN_3 (1.52 g, 31.1 mmol) and the resulting suspension was stirred for 24 h at 45 °C. After cooling the orange solution to room temperature, Et_2O (50 mL) and H_2O (50 mL) were added and the aqueous layer was extracted with Et_2O (3 x 40 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. Silica gel column chromatography of the crude product using pet ether/EtOAc: (98/2) gave azide **54** as a yellowish liquid.

Yield: 0.65 g, 60%

Mol. Formula: $C_{19}H_{21}N_3O_2$

$[\alpha]_D^{25}$: -14.54 (*c* 1, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3017, 2936, 2110, 1642, 1612, 1514, 1455, 1249,1216.

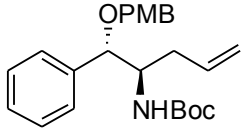
^{1}H NMR (200 MHz, $CDCl_3$): δ 2.17-2.42 (m, 2H), 3.39-3.49 (m, 1H), 3.73 (s, 3H), 4.12 (d, *J* = 11.2 Hz, 1H), 4.29-4.40 (m, 2H), 5.00-5.10 (m, 2H), 5.60-5.82 (m, 1H), 6.80 (d, *J* = 8.7 Hz, 2H), 7.15 (d, *J* = 8.7 Hz, 2H), 7.29-7.33 (m, 5H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 34.1, 55.2, 66.1, 70.4, 82.3, 113.8, 118.0, 127.7, 128.3, 128.5, 129.4, 129.8, 134.1, 138.1, 159.2 ppm.

Analysis Calcd.: C, 70.57; H, 6.55; N, 12.99; **Found:** C, 70.72; H, 6.38; N, 12.78%

MS (ESI): m/z 346.0216 (M^++Na).

***tert*-Butyl (1*S*,2*R*)-1-(4-methoxybenzyloxy)-1-phenylpent-4-en-2-ylcarbamate (55):**



To a solution of azide **54** (1.0 g, 3.10 mmol) in THF (20 mL)/ water (1.0 mL) was added PPh_3 (1.21 g, 4.6 mmol) and mixture was stirred at room temperature for 12 h. The mixture was concentrated and then 1,4-dioxane (15 mL)/ water (15 mL) and Na_2CO_3 (0.78 g, 7.3 mmol) were added and stirred for another 10 min at 0 °C. To this ice cold solution, $(Boc)_2O$ (1.00 mL, 4.13 mmol) was added and mixture stirred overnight at 0 °C to room temperature. The solvent was evaporated at reduced pressure and extracted with EtOAc (3 x 25 mL). The combined organic layer was washed with brine, water, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using EtOAc/petroleum ether (1:9) gave compound **55** as a white solid.

Yield: 0.98 g, 80%

Mol. Formula: $C_{24}H_{31}NO_4$

$[\alpha]_D^{25}$: -21.36 (*c* 1.4, $CHCl_3$)

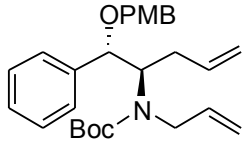
IR ($CHCl_3$, cm^{-1}): ν_{max} 2964, 1693, 1611, 1514, 1439, 1249.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.28 (s, 9H), 2.12 (t, *J* = 6.6 Hz, 2H), 3.71 (s, 3H), 3.72-3.79 (m, 1H), 4.10 (d, *J* = 11.4 Hz, 1H), 4.37-4.45 (m, 2H), 4.57 (d, *J* = 9.5 Hz, 1H), 4.86-4.94 (m, 2H), 5.49-5.70 (m, 1H), 6.79 (d, *J* = 8.7 Hz, 2H), 7.15 (d, *J* = 8.7 Hz, 2H), 7.19-7.29 (m, 5H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 28.2, 33.1, 55.0, 70.7, 82.3, 113.7, 117.0, 127.0, 127.5, 128.2, 129.2, 135.0, 138.9, 155.3, 159.1 ppm.

Analysis Calcd.: C, 72.52; H, 7.86; N, 3.52; **Found:** C, 72.69; H, 7.81; N, 3.62%

***tert*-Butyl allyl((1*S*,2*R*)-1-(4-methoxybenzyloxy)-1-phenylpent-4-en-2-yl)carbamate (56):**



To a solution of **55** (2.0 g, 5.03 mmol) in DMF (20 mL), NaH (0.805 g of 60% dispersion in oil, 20.12 mmol) was added through solid addition funnel at 0 °C. The mixture was stirred for 30 min at 0 °C and freshly distilled allyl bromide (1.74 mL, 20.12 mmol) was added dropwise. After 4 h at room temperature, the reaction was quenched by addition of ice pieces. The reaction mixture was diluted with EtOAc (25 mL), and the aqueous phase was extracted with EtOAc (3 X 40 mL). The combined organic phase was washed with water (40 mL) and brine (40 mL), dried over $MgSO_4$, and concentrated in vacuo. Silica gel column chromatography (EtOAc/petroleum ether, 1:9) of the crude product gave compound **56** as a pale yellow oil.

Yield: 1.87 g, 85%

Mol. Formula: $C_{27}H_{35}NO_4$

$[\alpha]_D^{25}$: +26.21 (*c* 2.4, $CHCl_3$)

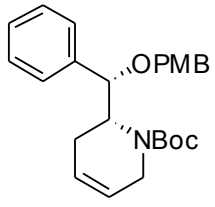
IR ($CHCl_3$, cm^{-1}): ν_{max} 3066, 2976, 1691, 1612, 1514, 1455, 1366, 1248, 1172, 1036.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.29 (s, 9H), 2.63-2.70 (m, 2H), 2.98-3.13 (m, 1H), 3.30-3.40 (m, 1H), 3.49-3.57 (m, 1H), 3.73 (s, 3H), 4.03-4.16 (m, 1H), 4.24-4.53 (m, 2H), 4.76-5.00 (m, 4H), 5.11-5.32 (m, 1H), 5.54-5.75 (m, 1H), 6.77-6.82 (m, 2H), 7.13 (d, *J* = 6.7 Hz, 2H), 7.23-7.30 (m, 5H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.8, 28.3, 55.1, 70.6, 79.1, 82.6, 113.7, 116.4, 116.5, 127.5, 125.6, 127.9, 128.0, 128.2, 129.3, 129.6, 130.1, 130.4, 135.6, 136.2, 140.0, 155.0, 159.1 ppm.

Analysis Calcd.: C, 74.11; H, 8.06; N, 3.20; **Found:** C, 74.24; H, 8.16; N, 3.03%

(*R*)-*tert*-Butyl 6-((*S*)-(4-methoxybenzyloxy)(phenyl)methyl)-5,6-dihydropyridine-1(2*H*)-carboxylate (57):



To a solution of **56** (1.00 g, 2.28 mmol) in anhydrous toluene (10 mL) was added a solution of Grubb's first generation catalyst (0.094 g, 0.11 mmol) in toluene (2 mL) over 4 h at room temperature. The mixture was stirred for 12 h at room temperature and was then concentrated in vacuo. Silica gel column chromatography (EtOAc/petroleum ether, 1:9) of the crude product gave compound **57** as a white solid.

Yield: 0.88 g, 94%

Mol. Formula: $C_{25}H_{31}NO_4$

$[\alpha]_D^{25}$: +29.5 (*c* 1.4, $CHCl_3$)

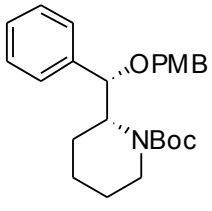
IR ($CHCl_3$, cm^{-1}): ν_{max} 3014, 1693, 1605, 1510, 1368, 1216.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.06 (s, 9H), 1.18-1.31 (m, 1H), 1.35-1.45 (m, 1H), 2.18-2.30 (m, 1H), 2.51-2.66 (m, 1H), 3.33-3.45 (m, 1H), 3.73 (s, 3H), 4.19-4.29 (m, 2H), 4.36-4.44 (m, 1H), 5.55-5.71 (m, 2H), 6.78 (d, *J* = 8.6 Hz, 2H), 7.09 (d, *J* = 8.6 Hz, 2H), 7.23-7.29 (m, 5H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 25.6, 27.9, 28.1, 40.3, 53.4, 55.2, 70.5, 79.0, 79.2, 113.7, 122.8, 123.4, 127.7, 127.9, 128.0, 128.2, 129.4, 130.2, 139.9, 154.1, 159.1 ppm.

Analysis Calcd.: C, 73.32; H, 7.63; N, 3.42; **Found:** C, 73.51; H, 7.78; N, 3.25%

(*R*)-*tert*-Butyl 2-((*S*)-(4-methoxybenzyloxy)(phenyl)methyl)piperidine-1-carboxylate (58):



To the olefin **57** (0.5 g, 1.22 mmol) in ethyl acetate was added Pd-C (10%) (0.050 g), a drop of Et_3N and the reaction mixture was allowed to stir overnight under hydrogenation

conditions. On completion of reaction (until ^{1}H NMR analysis of the crude mixture indicated complete conversion), the mixture was filtered through a pad of celite and concentrated in vacuo to give saturated piperidine. The crude product was then purified by using flash column chromatography using pet ether: EtOAc (85:15) as eluent to give **58** as a colorless white crystalline solid.

Yield: 0.464 g, 92%

Mol. Formula: $C_{25}H_{33}NO_4$

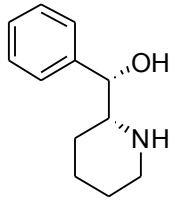
$[\alpha]_D^{25}$: +25.3 (*c* 0.8, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3014, 1693, 1605, 1510, 1368, 1216..

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.15 (s, 9H), 1.49-1.62 (m, 6H), 2.18-2.29 (m, 1H), 2.84 (t, *J* = 13.5 Hz, 1H), 3.82 (s, 3H), 4.11 (d, *J* = 11.4 Hz, 1H), 4.32 (m, 1H), 4.41 (d, *J* = 11.4 Hz, 1H), 4.56 (d, *J* = 9.2 Hz, 1H), 6.9 (d, *J* = 8.7 Hz, 2H), 7.22 (d, *J* = 8.7 Hz, 2H), 7.30-7.34 (m, 5H) ppm.

Analysis Calcd.: C, 72.96; H, 8.08; N, 3.40; **Found:** C, 73.09; H, 8.18; N, 3.27%

(*S*)-Phenyl((*R*)-piperidin-2-yl)methanol (59):



To a solution of **58** (0.5 mg, 1.21 mmol) in EtOH (5 mL) was added 1 M HCl (5 mL). The solution was refluxed for 3 h, and then the solvents were removed by evaporation *in vacuo*. The residue was taken up in EtOAc (20 mL) and washed with saturated $NaHCO_3$ solution and brine (20 mL of each). The combined aqueous layers were extracted with EtOAc (40 mL), and the combined organic layer was then dried ($MgSO_4$) and concentrated to give a yellow oil. Purification by column chromatography using pet. ether/EtOAc (3/7) gave the amino alcohol **59** as a waxy solid.

Yield: 0.171 g, 74%

Mol. Formula: $C_{12}H_{17}NO$

$[\alpha]_D^{25}$: +56.0 (*c* = 0.95, MeOH) {Lit.[29] **$[\alpha]_D^{25}$** +55.0 (*c* = 0.90, MeOH)}.

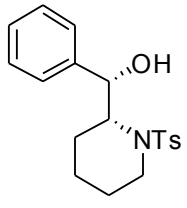
IR ($CHCl_3$, cm^{-1}): ν_{max} 3379, 3018, 1648, 1453, 1215, 1050.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.34-1.41 (m, 2H), 1.45-1.76 (m, 4H), 2.75 (dt, *J* = 3.9, 8.0 Hz, 1H), 2.99 (td, *J* = 2.7, 11.7 Hz, 1H), 3.29-3.35 (m, 1H), 4.25 (bs, 2H), 5.10 (d, *J* = 2.6 Hz, 1H), 7.17-7.33 (m, 5H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 23.7, 24.9, 25.1, 46.0, 61.9, 74.8, 126.2, 127.2, 128.1, 141.6 ppm.

Analysis Calcd.: C, 75.35; H, 8.96; N, 7.32; **Found:** C, 75.51; H, 8.79; N, 7.21%

(*S*)-Phenyl((*R*)-1-tosylpiperidin-2-yl)methanol (60):



To a solution of **59** (0.2 g, 1.04 mmol) in dry CH_2Cl_2 (4 mL) at 0 °C was added tosyl chloride (0.22 g, 1.1 mmol), Et_3N (0.27 mL, 1.9 mmol). The reaction mixture was stirred at room temperature for 5 h and then poured into Et_2O-H_2O mixture. The organic phase was separated and the aqueous phase extracted with Et_2O. The combined organic phases were washed with water, brine, dried (Na_2SO_4) and concentrated. The crude residue was purified by silica gel column chromatography(pet ether/ ethyl acetate: 85/15) to afford **60** as a white crystalline solid.

Yield: 0.29 g, 80%

Mol. Formula: $C_{19}H_{23}NO_3S$

$[\alpha]_D^{25}$: +45.2 (*c* 1.3, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3504, 3020, 160, 1454, 1328, 1216, 1092.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.28-1.44 (m, 4H), 1.69 (bs, 2H), 1.88-1.97 (m, 1H), 2.31 (s, 3H), 3.00-3.15 (m, 1H), 3.46-3.55 (m, 1H), 4.07-4.13 (m, 1H), 4.97 (d, *J* = 6.9 Hz, 1H), 7.07 (d, *J* = 8.2 Hz, 2H), 7.23-7.33 (m, 7H) ppm.

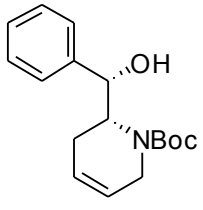
^{13}C NMR (50 MHz, $CDCl_3$): δ 19.1, 21.4, 23.4, 23.6, 42.5, 57.6, 74.2, 126.6, 127.1, 127.8, 128.4, 129.4, 137.6, 141.9, 142.8 ppm.

Analysis Calcd.: C, 66.06; H, 6.71; N, 4.05; S, 9.28; **Found:** C, 66.21; H, 6.59; N, 4.17; S, 9.12%

MS (ESI): m/z 368.0766 (M^++Na), 384.0653 (M^++K).

Crystallographic data of 60. ($C_{19}H_{23}NO_3S$): M = 345.44, Crystal dimensions 0.22x 0.16 x 0.15 mm^3, monoclinic, space group $P2_1/c$, a = 6.506(4), b = 7.427(5), c = 36.28(2) Å, β = 91.910(10)°, V = 1752.0(19) Å^3, Z = 4, ρ_{calcd} = 1.310 gcm^{-3}, μ (Mo-K$_\alpha$) = 0.201 mm^{-1}, $F(000)$ = 736, $2\theta_{max}$ = 52.00°, T = 297(2) K, 9084 reflections collected, 3427unique, 2828 observed ($I > 2\sigma(I)$) reflections, 222 refined parameters, R value 0.0498, $wR2$ = 0.1191 (all data R = 0.0610, $wR2$ = 0.1249), S = 1.098, minimum and maximum transmission 0.9567 and 0.9710; maximum and minimum residual electron densities +0.316 and –0.250 e Å^{-3}.

(*R*)-*tert*-Butyl 6-((*S*)-hydroxy(phenyl)methyl)-5,6-dihydropyridine-1(2*H*)-carboxylate (61):



To a solution of **57** (0.5 g, 1.22 mmol) in a mixture of CH_2Cl_2 and H_2O (18/1) (10 mL) was added DDQ (0.304 g, 1.34 mmol, 1.1 equiv). After 15 min, the reaction mixture was quenched with an aqueous saturated $NaHCO_3$ solution (5.0 mL). The mixture was diluted with water (10 mL) and CH_2Cl_2 (15 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 X 20 mL). The combined organic layer was washed with water (40 mL) and brine (40 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified on silica gel to afford **61** as a white solid.

Yield: 0.28 g, 79%

Mol. Formula: $C_{17}H_{23}NO_3$

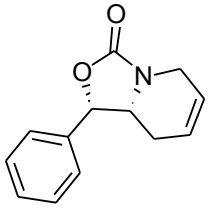
$[\alpha]_D^{25}$: +38.2 (*c* 1.3, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3434, 3014, 1693, 1605, 1453, 1413, 1368, 1253, 1027.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.14 (s, 9H), 1.38-1.59 (m, 1H), 1.99-2.12 (m, 1H), 2.26-2.35 (m, 1H), 2.51-2.62 (m, 1H), 3.40-3.53 (m, 1H), 4.05-4.11 (m, 1H), 4.60 (d, *J* = 8.9 Hz, 1H), 5.65-2.82 (m, 2H), 7.21-7.31 (m, 5H) ppm.

Analysis Calcd.: C, 70.56; H, 8.01; N, 4.84; **Found:** C, 70.73; H, 8.12; N, 4.61%

(1*S*,8a*R*)-1-Phenyl-8,8a-dihydro-1*H*-oxazolo[3,4-a]pyridin-3(5*H*)-one (62):



To an ice-cold stirred solution of **61** (1.0 g, 3.09 mmol) and triethylamine (0.861 mL, 6.2 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise methanesulfonyl chloride (0.29 mL, 3.71 mmol) over 15 min. The resulting mixture was allowed to warm up to room temperature and stirred for 2 h. After diluting with 25 mL CH_2Cl_2, the solution was washed with water (3 x 25 mL), brine, dried over Na_2SO_4 and concentrated to give the bicyclic product which was purified by the column chromatography.

Yield: 0.65 g, 87%

Mol. Formula: $C_{13}H_{13}NO_2$

$[\alpha]_D^{25}$: +45.5 (*c* 1.2, $CHCl_3$)

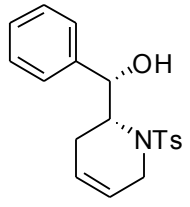
IR ($CHCl_3$, cm^{-1}): ν_{max} 3014, 1756, 1652, 1598, 1497, 1419, 1267, 1016.

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.33-2.45 (m, 2H), 3.60-3.80 (m, 2H), 4.11-4.22 (m, 1H), 5.13 (d, *J* = 6.7 Hz, 1H), 5.74-5.89 (m, 2H), 7.36-7.43 (m, 5H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 29.7, 41.1, 58.1, 82.6, 122.9, 123.7, 125.5, 128.9, 138.0, 158.6 ppm.

Analysis Calcd.: C, 72.54; H, 6.09; N, 6.51; **Found:** C, 72.71; H, 6.19; N, 6.39%

(*S*)-Phenyl((*R*)-1-tosyl-1,2,3,6-tetrahydropyridin-2-yl)methanol (63):



To a solution of **61** (0.2 g, 0.69 mmol) in EtOH (5 mL) was added 1M HCl (5 mL). The solution was stirred for 3 h, and then the solvents were removed by evaporation *in vacuo*. The residue was taken up in EtOAc (10 mL) and washed with saturated $NaHCO_3$ solution and brine (15 mL of each). The combined aqueous layers were extracted with EtOAc (15 mL), and the combined organic layers were then dried ($MgSO_4$) and concentrated to give a yellow oil. To a solution of above compound (0.13 g, 0.69 mmol) in dry CH_2Cl_2 (2 mL) at 0 °C was added tosyl chloride (0.16 g, 0.82 mmol), Et_3N (0.10 mL, 1.4 mmol). The reaction mixture was stirred at room temperature for 5 h and then poured into Et_2O-H_2O mixture. The organic phase was separated and the aqueous phase extracted with Et_2O. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The crude residue was purified on silica gel to afford **63** as a white solid.

Yield: 0.19 g, 80%

Mol. Formula: $C_{19}H_{21}NO_3S$

$[\alpha]_D^{25}$: +52.2 (*c* 1.4, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3502, 3022, 2862, 2360, 1596, 1463, 1215, 1159 1095.

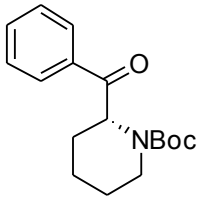
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.12-2.19 (m, 1H), 2.38 (m, 3H), 2.42-2.48 (m, 1H), 3.61-3.66 (m, 1H), 3.97-4.02 (m, 1H), 4.39 (t, *J* = 7.3 Hz, 1H), 4.78 (d, *J* = 7.5 Hz, 1H), 5.63-5.6 (m, 1H), 5.74-5.78 (m, 1H), 7.16 (d, *J* = 7.7 Hz, 2H), 7.33-7.41 (m, 7H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 23.5, 41.5, 55.0, 74.8, 122.6, 124.2, 126.7, 127.0, 128.2, 128.6, 129.5, 137.3, 141.8, 143.0 ppm.

Analysis Calcd.: C, 66.45; H, 6.16; N, 4.08; S, 9.34; **Found:** C, 66.25; H, 6.29; N, 4.14; S, 9.15%

MS (ESI): m/z 366.4592 (M^++Na), 382.4328 (M^++K).

(*R*)-*tert*-Butyl 2-benzoylpiperidine-1-carboxylate (64):



To a solution of alcohol **61** (0.5 g, 1.71 mmol) in DMSO (5 mL) was added IBX (0.96 g, 3.43 mmol) in one portion and the reaction mixture was stirred for 1 h. The reaction mixture was quenched by addition of ice pieces and the crude reaction mixture was filtered through a pad of celite and filtrate was extracted with EtOAc (3 x 15mL) and the combined organic layer was washed with water (15 mL), brine, dried (Na_2SO_4) and concentrated to give the crude ketone, which was used in the next step without purification.

To the crude ketone in ethyl acetate (5 mL) was added Pd-C (10%) (0.050 g), a drop of Et_3N and the reaction mixture was allowed to stir overnight under hydrogenation condition. On completion of reaction (until ^{1}H NMR analysis of the crude mixture indicated complete conversion), the mixture was filtered through a pad of celite and concentrated in vacuo to give the saturated piperidine. The crude product was then purified by flash column chromatography using pet ether: EtOAc (8:2) as eluent to give **64** as a colorless white crystalline solid.

Yield: 0.412 g, 83%

Mol. Formula: $C_{17}H_{23}NO_3$

$[\alpha]_D^{25}$: +25.6 (*c* 1, $CHCl_3$) {Lit[15] +25.8 (*c* 1.06, $CHCl_3$)}

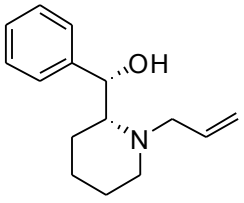
IR ($CHCl_3$, cm^{-1}): ν_{max} 2977, 2856, 1687, 1596, 1448, 1409, 1249, 1170, 1056.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.36 (brs, 2H), 1.43 (s, 9H), 1.56 (m, 2H), 1.78 (m, 1H), 2.06 (m, 1H), 3.12 (m, 1H), 3.89 (m, 1H), 5.55 (d, J = 11.7, 1H),) 7.41 (m, 2H), 7.50 (m, 1H), 7.87 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 19.92, 24.95, 26.18, 28.29, 42.57, 56.09, 79.94, 128.1, 128.5, 132.8, 135.8, 155.8, 200.9 ppm.

Analysis Calcd.: C, 70.56; H, 8.01; N, 4.84; **Found:** C, 70.71; H, 7.85; N, 4.62%

(*S*)-((*R*)-1-Allylpiperidin-2-yl)(phenyl)methanol (65):



A solution of **59** (0.2 g, 1.04 mmol) in acetonitrile (2.0 mL) was cooled at 0 °C and K_2CO_3 (0.14 g, 1.04mmol) was added. The mixture was stirred for 30 min at 0 °C and freshly distilled allyl bromide (0.09 mL, 1.04 mmol) was added dropwise. After 2 h at room temperature, the reaction was quenched by addition of ice pieces. The reaction mixture was then diluted with EtOAc (5 mL), and the aqueous phase was extracted with EtOAc (3 X 10 mL). The combined organic layer was washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified on silica gel column chromatography (EtOAc/MeOH, 97/3) to afford compound **65** as a pale yellow oil.

Yield: 0.157 g, 65%

Mol. Formula: $C_{15}H_{21}NO$

$[\alpha]_D^{25}$: +46.2 (*c* 0.9, $CHCl_3$)

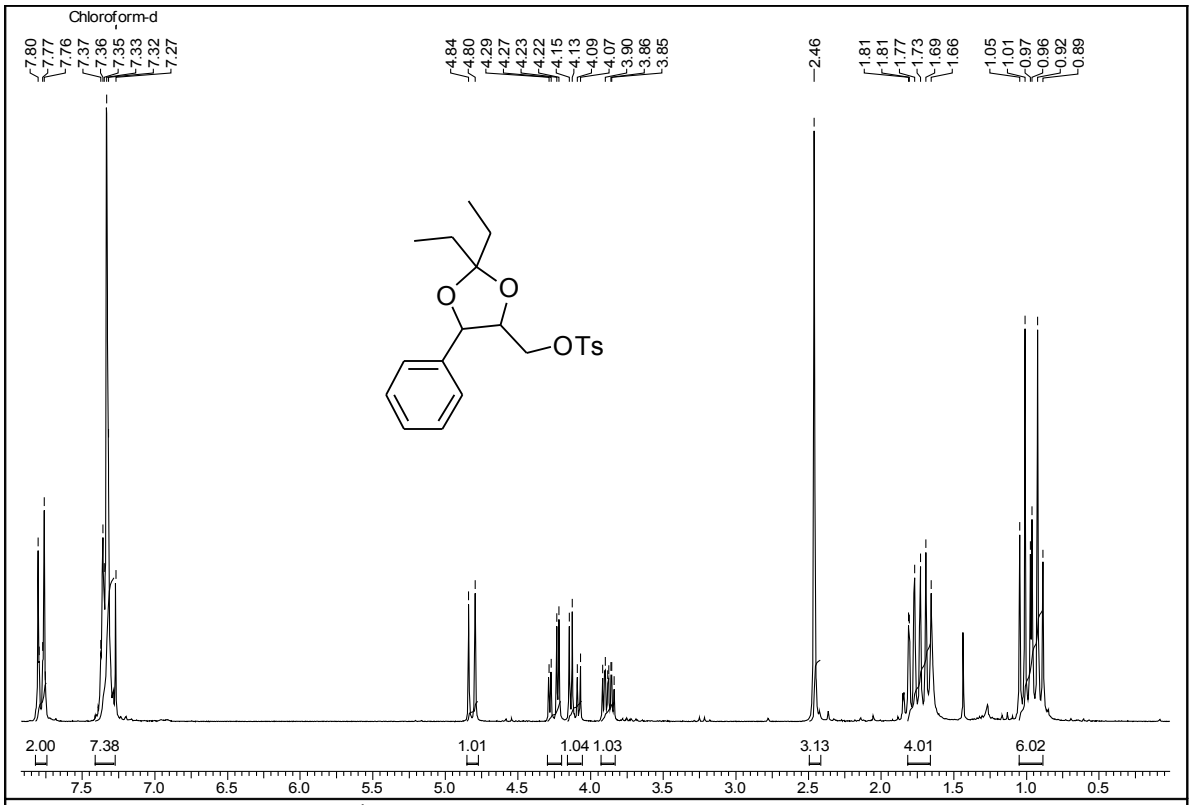
IR ($CHCl_3$, cm^{-1}): ν_{max} 3379, 3018, 1648, 1453, 1215, 1050.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.84-0.97 (m, 2H), 1.25-1.39 (m, 2H), 1.47-1.56 (m, 2H), 2.23 (dt, *J* = 2.9, 8.9 Hz, 1H), 2.39 (td, *J* = 3.2, 11.1 Hz, 1H), 2.92-3.02 (m, 1H), 3.17 (dd, *J* = 8.1, 14.6 Hz 1H), 3.52-3.56 (m, 1H), 5.13-5.17 (m, 1H), 5.21-5.27 (m, 2H), 5.85-6.05 (m, 1H), 7.16-7.30 (m, 5H) ppm.

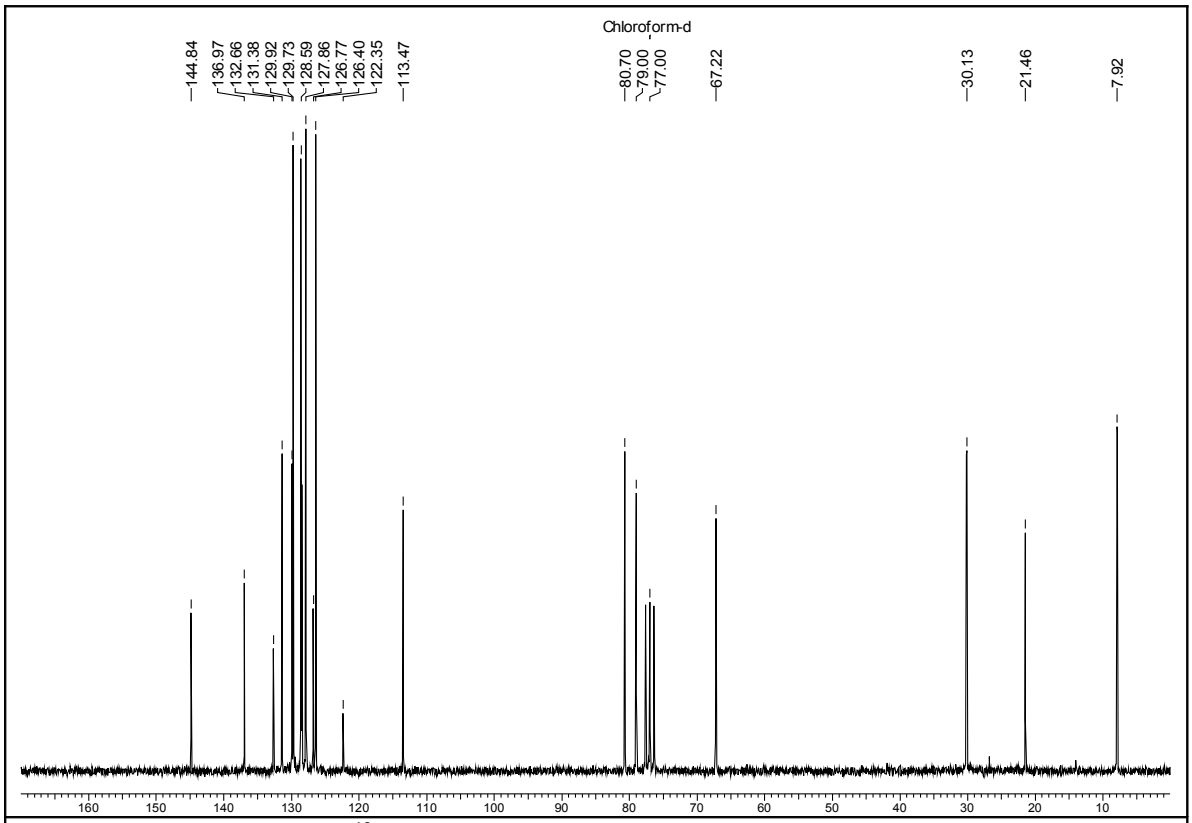
^{13}C NMR (50 MHz, $CDCl_3$): δ 23.2, 23.6, 25.4, 53.0, 56.2, 64.4, 69.7, 118.2, 125.5, 126.5, 127.8, 133.7, 141.3 ppm.

Analysis Calcd.: C, 77.88; H, 9.15; N, 6.05; **Found:** C, 77.71; H, 9.28; N, 6.17%

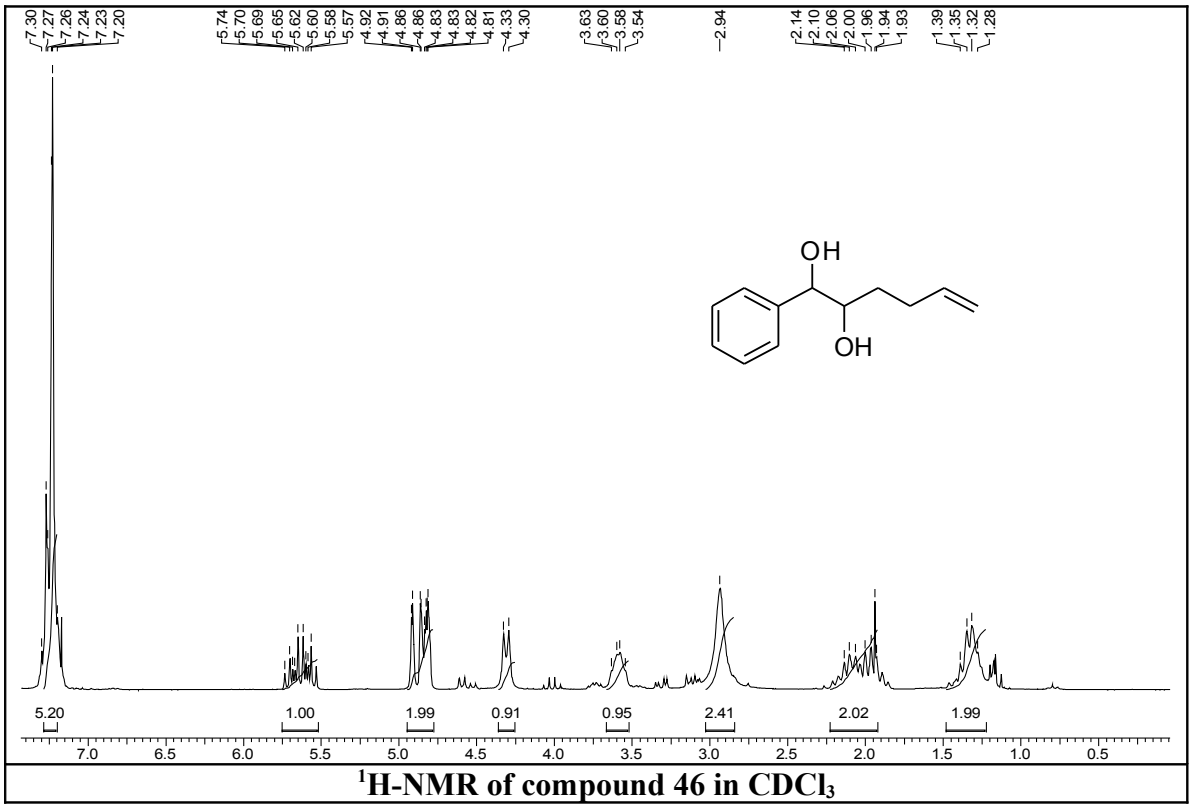
3.7. Spectras



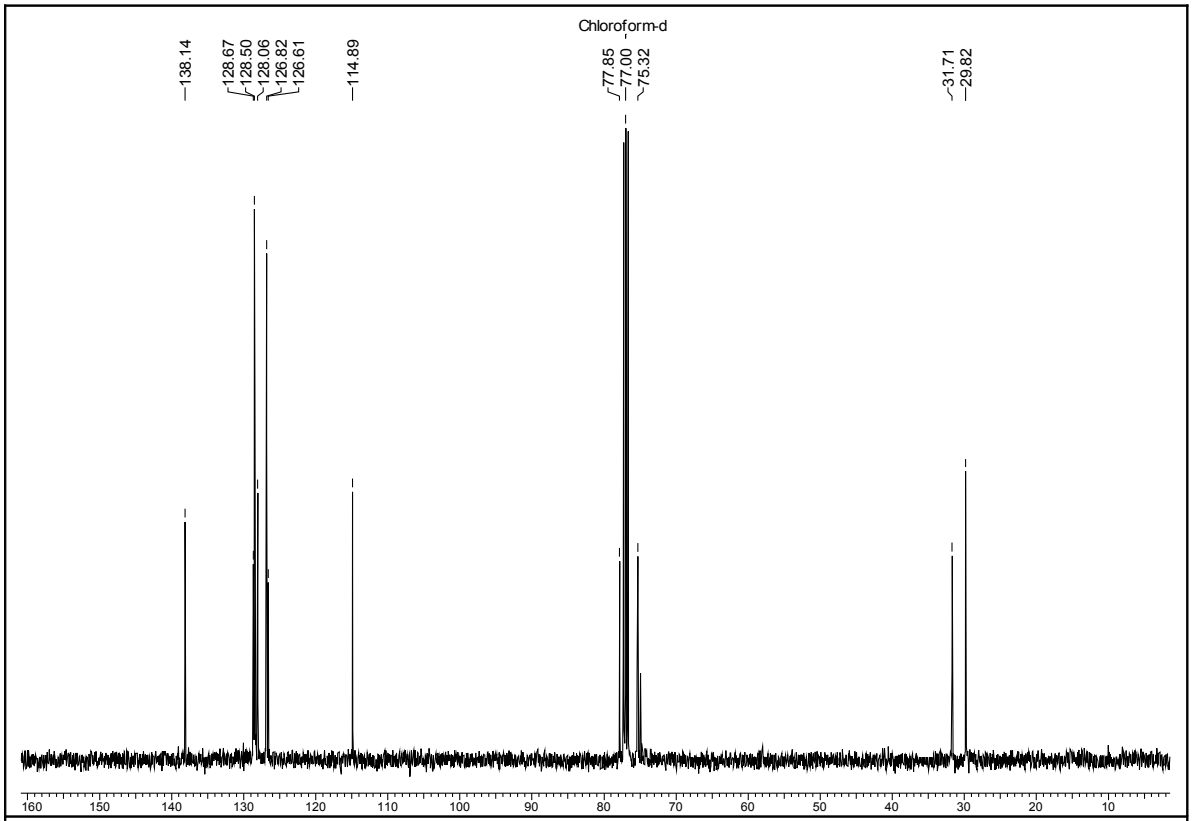
^{1}H-NMR of compound 44 in $CDCl_3$



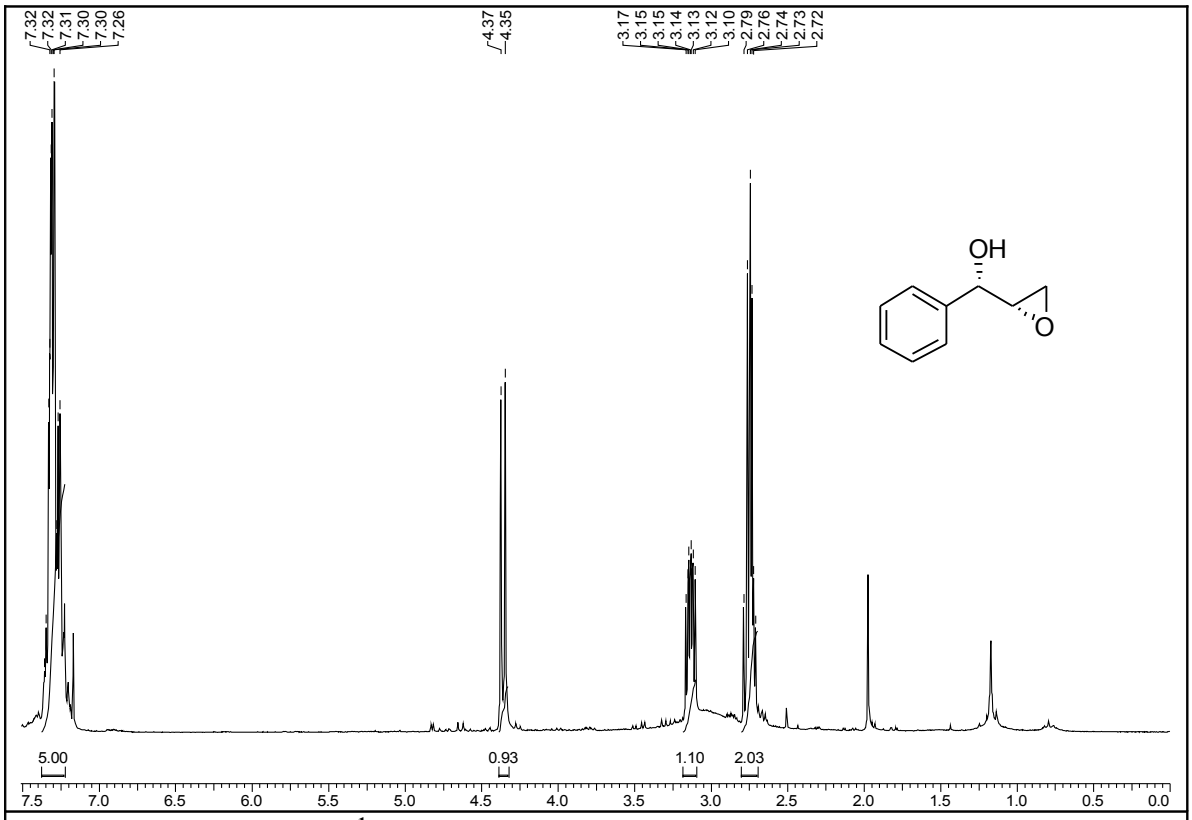
^{13}C-NMR of compound 44 in $CDCl_3$



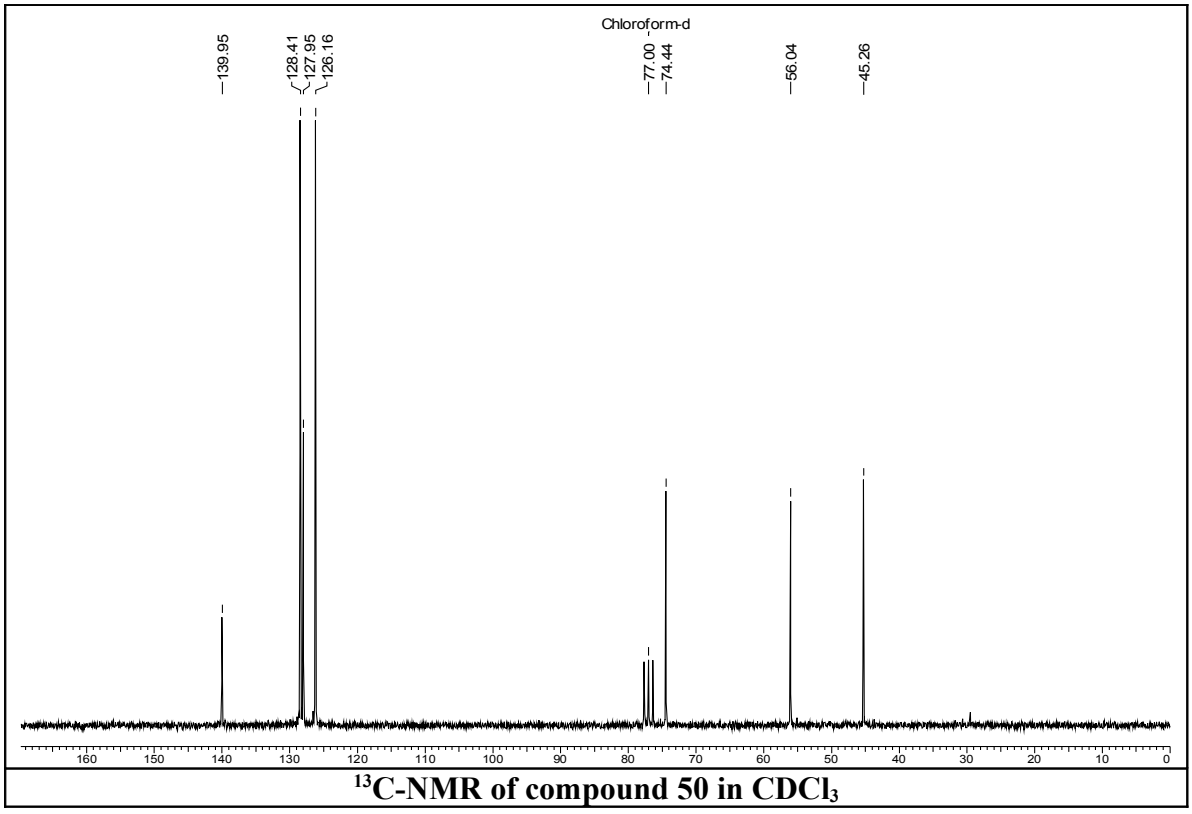
^{1}H-NMR of compound 46 in $CDCl_3$



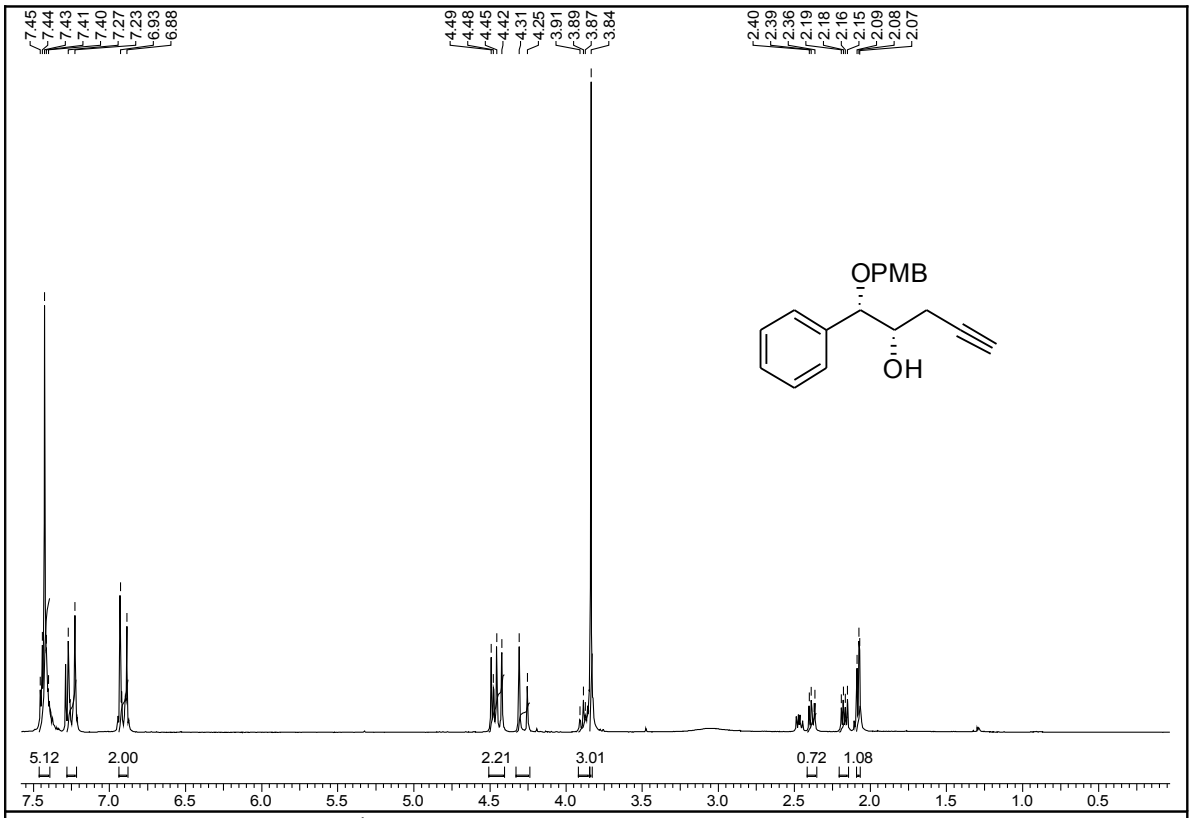
^{13}C-NMR of compound 46 in $CDCl_3$



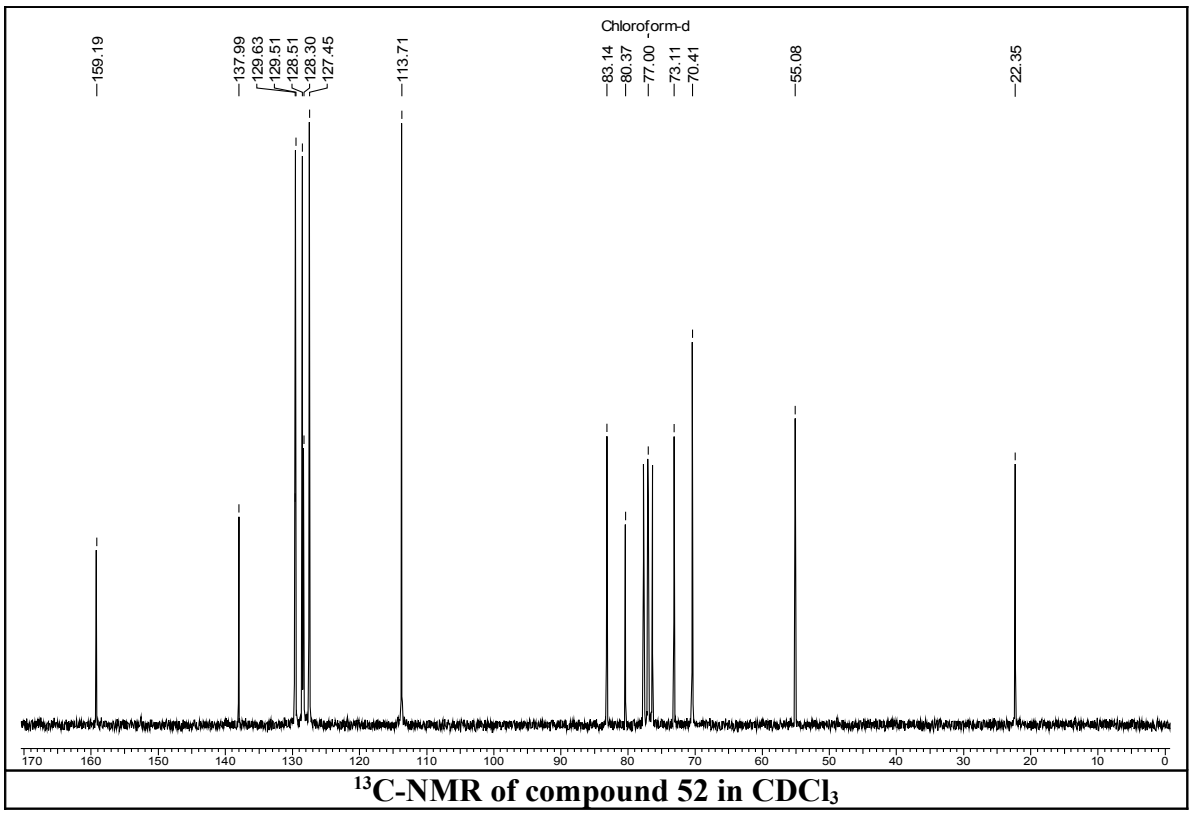
^{1}H-NMR of compound 50 in $CDCl_3$



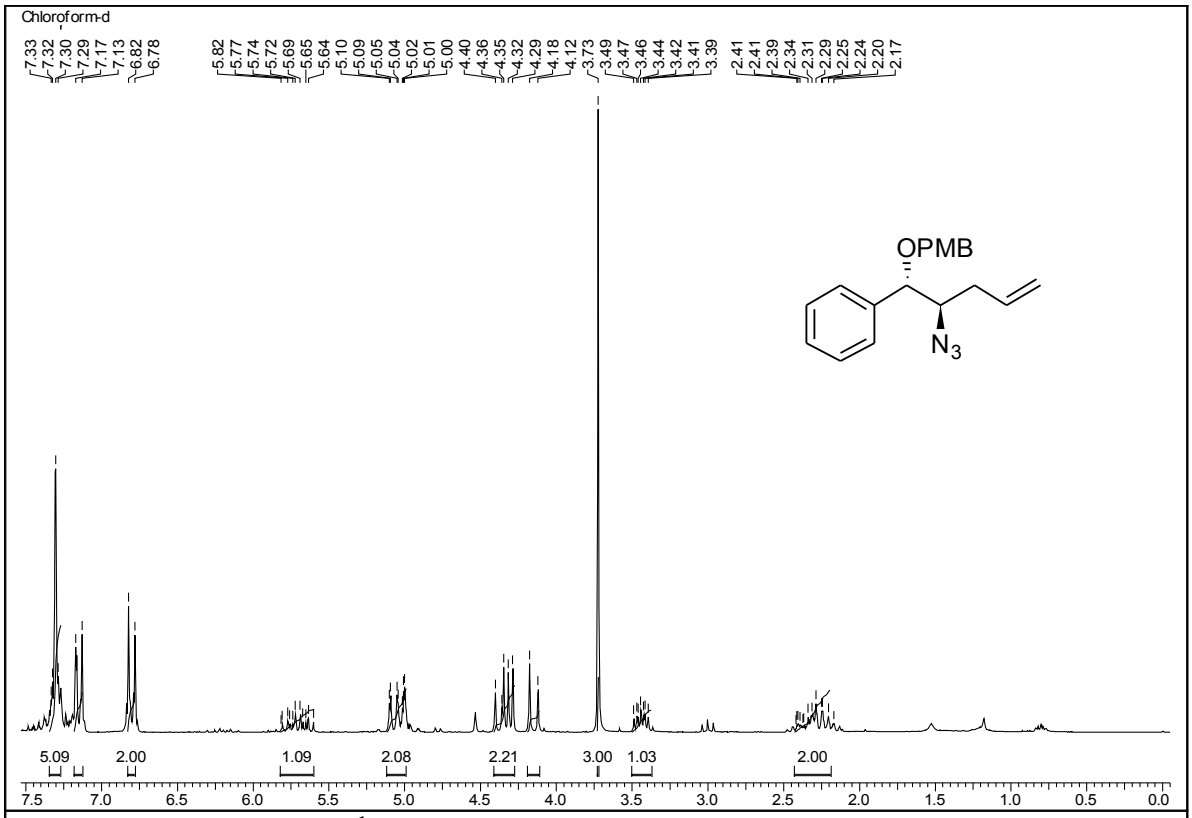
^{13}C-NMR of compound 50 in $CDCl_3$



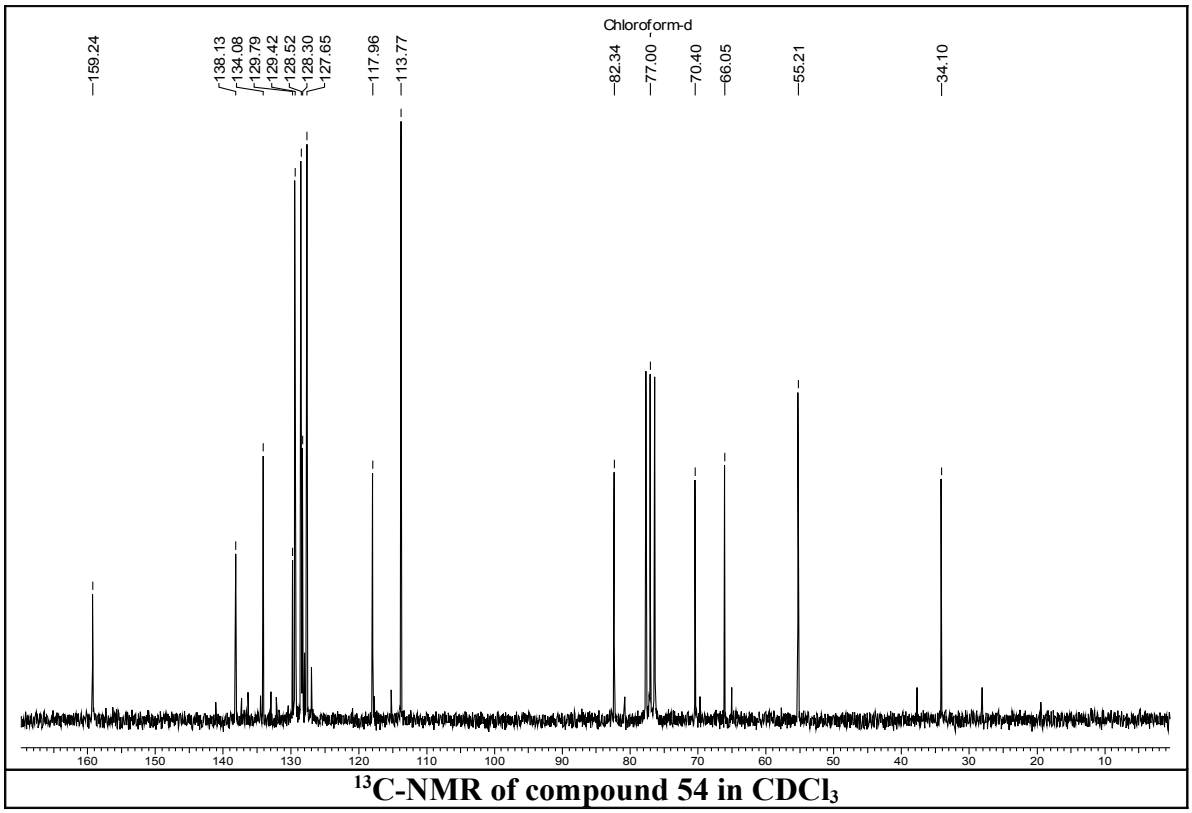
^{1}H-NMR of compound 52 in $CDCl_3$



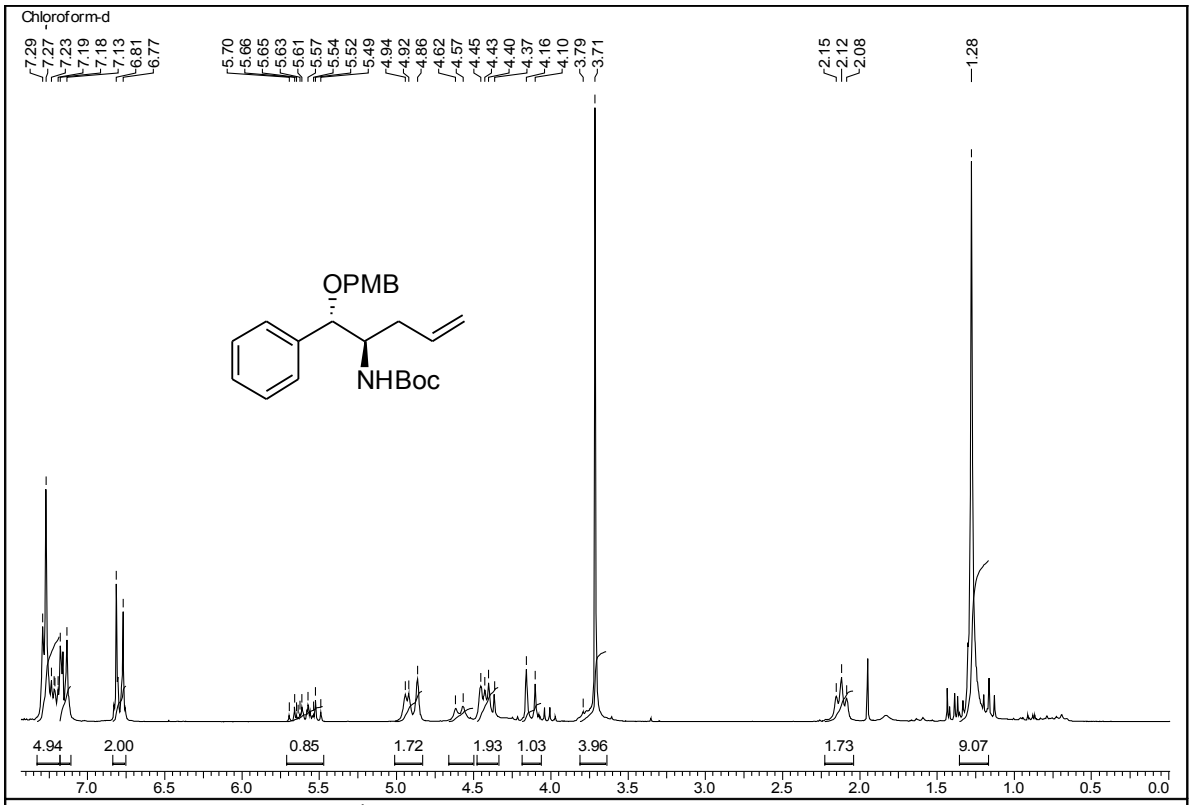
^{13}C-NMR of compound 52 in $CDCl_3$



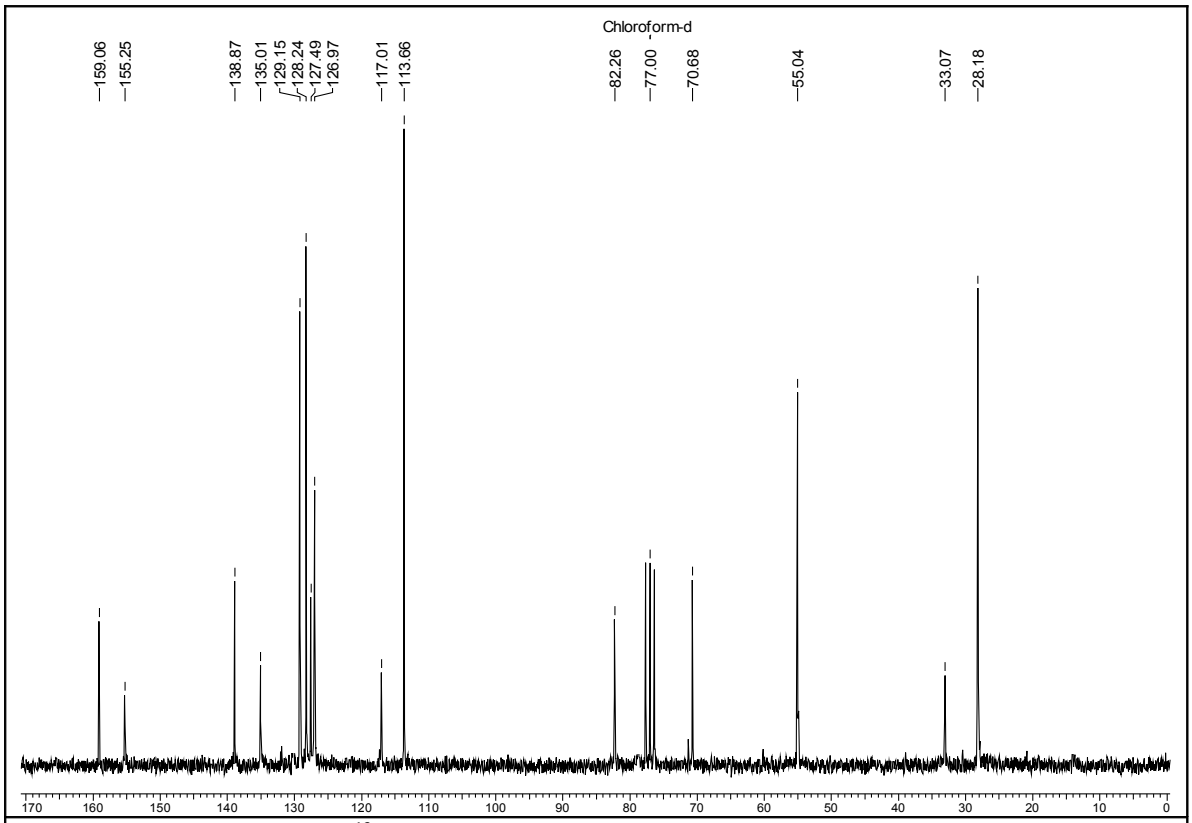
^{1}H-NMR of compound 54 in $CDCl_3$



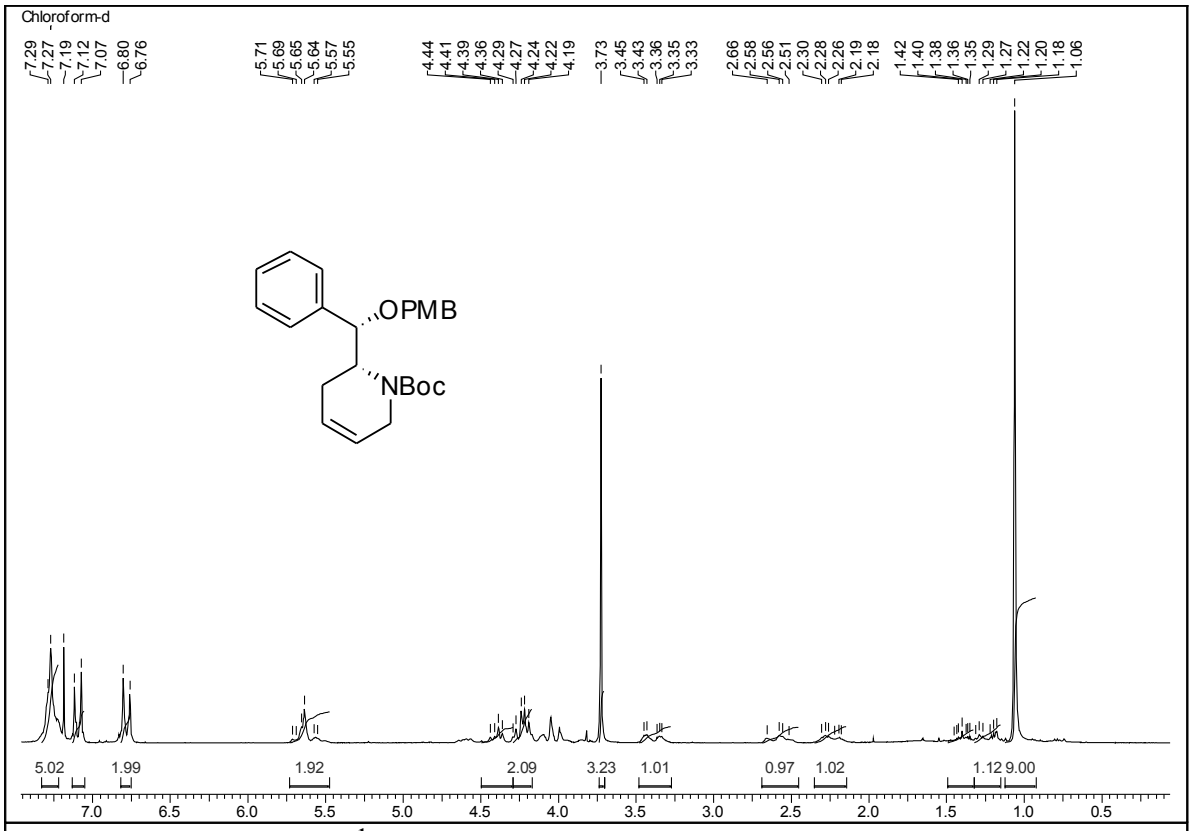
^{13}C-NMR of compound 54 in $CDCl_3$



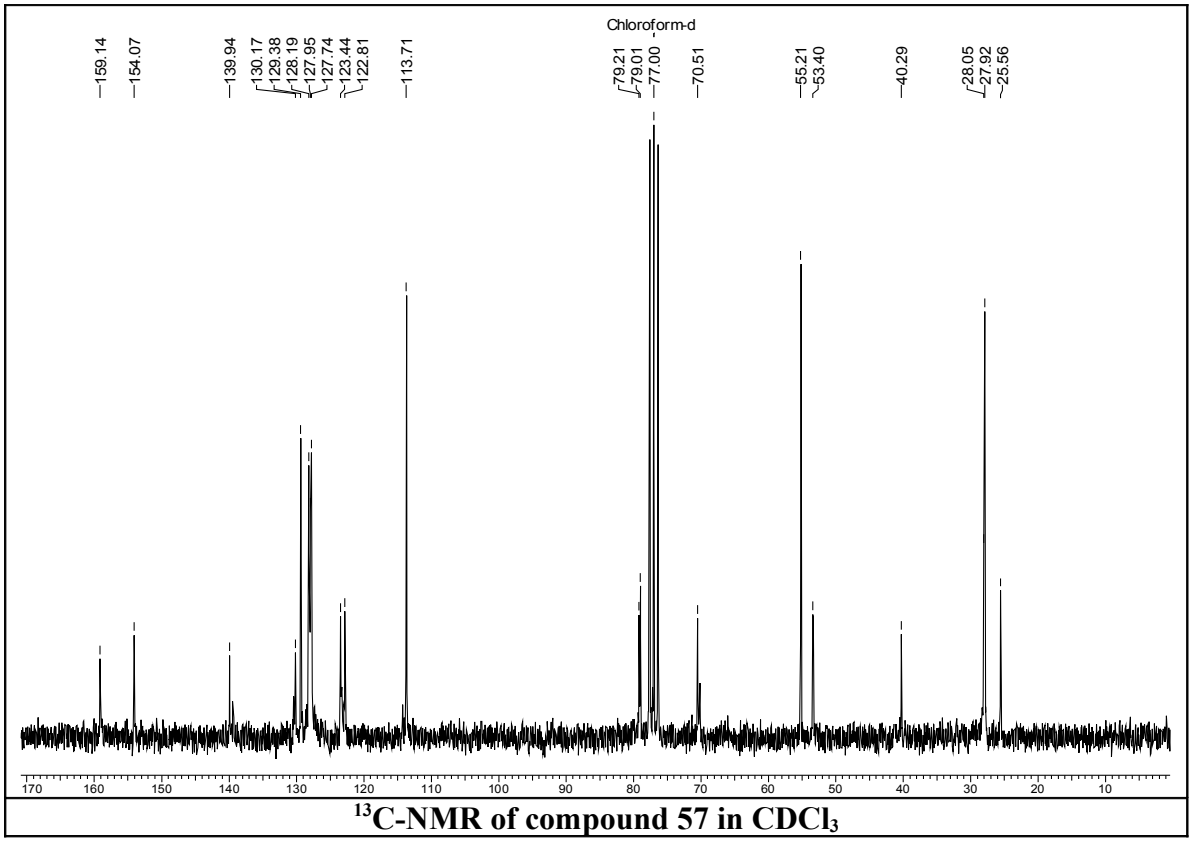
^{1}H-NMR of compound 55 in $CDCl_3$



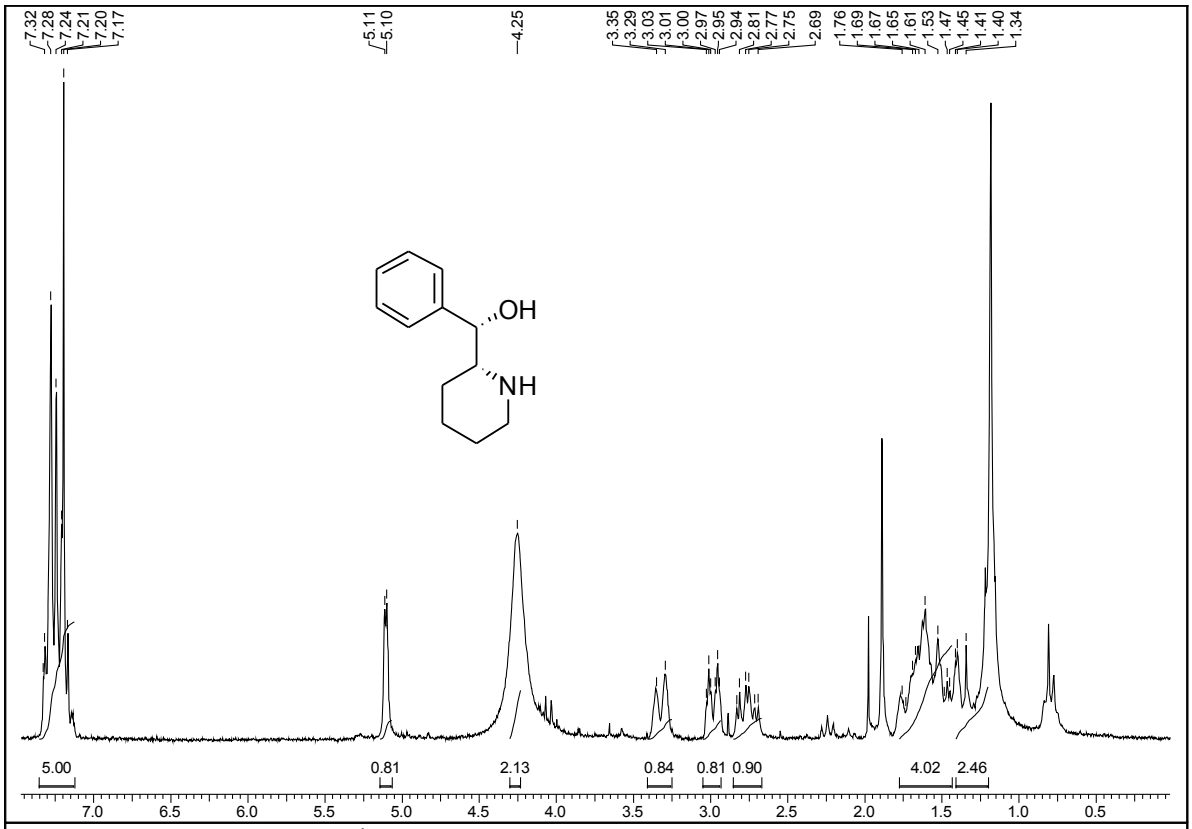
^{13}C-NMR of compound 55 in $CDCl_3$



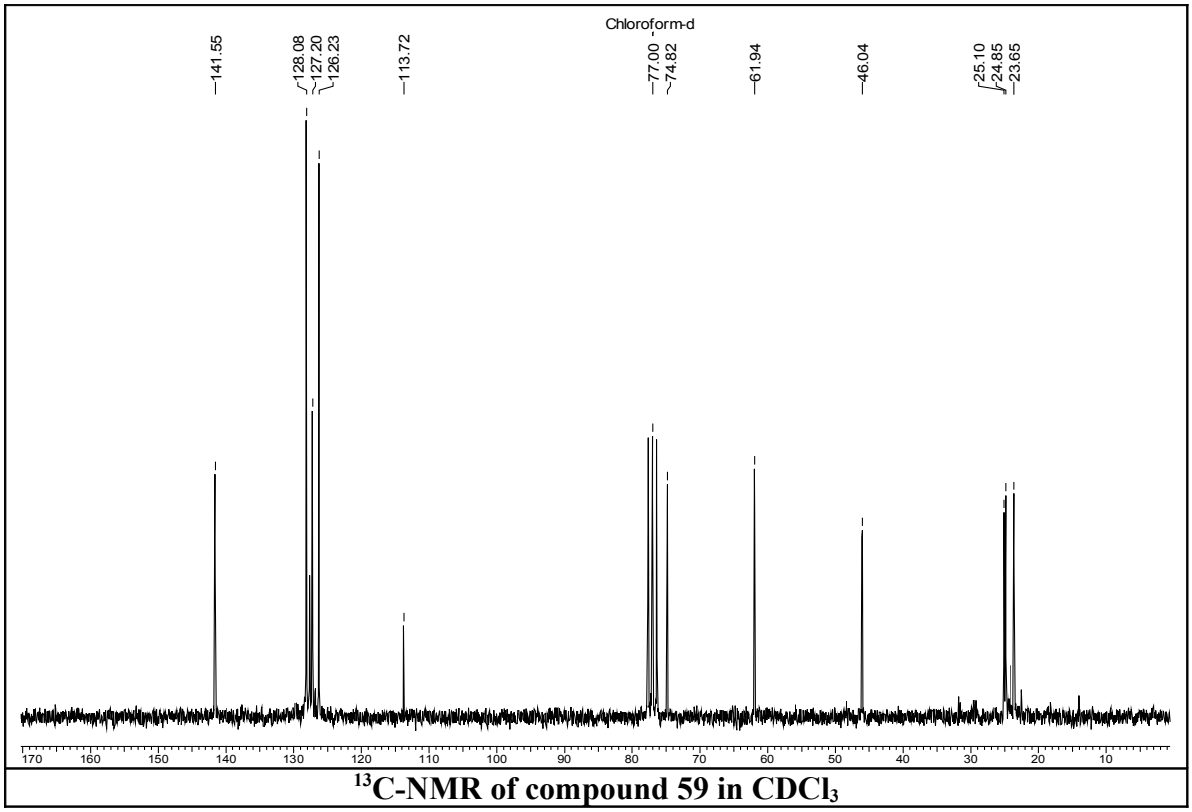
^{1}H-NMR of compound 57 in $CDCl_3$



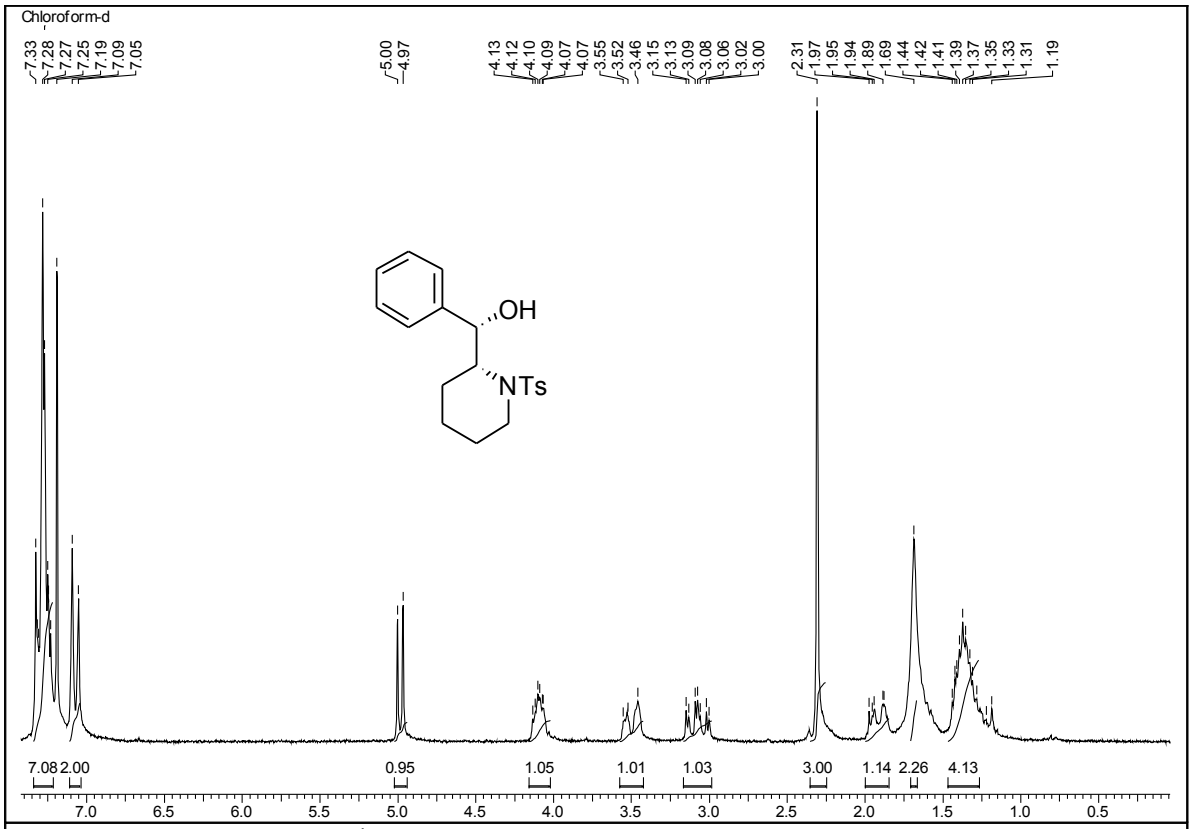
^{13}C-NMR of compound 57 in $CDCl_3$



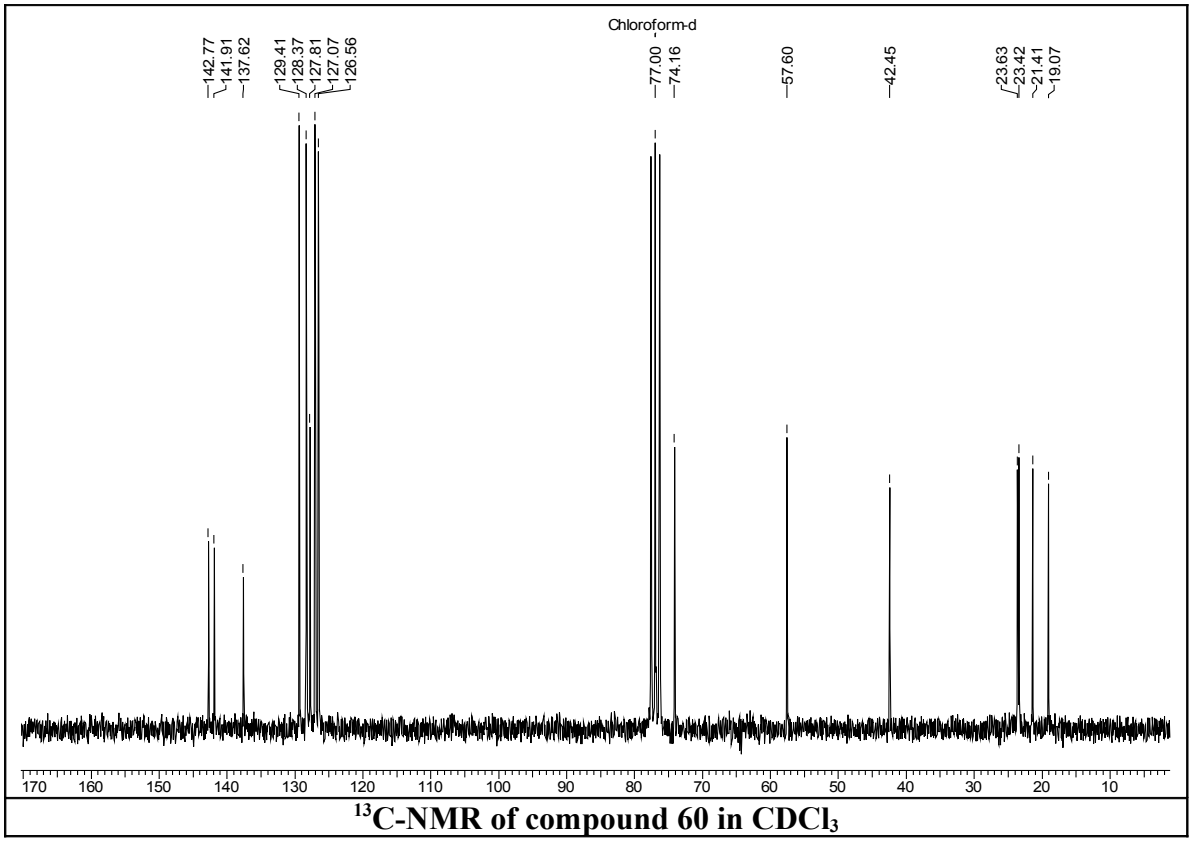
^{1}H-NMR of compound 59 in $CDCl_3$



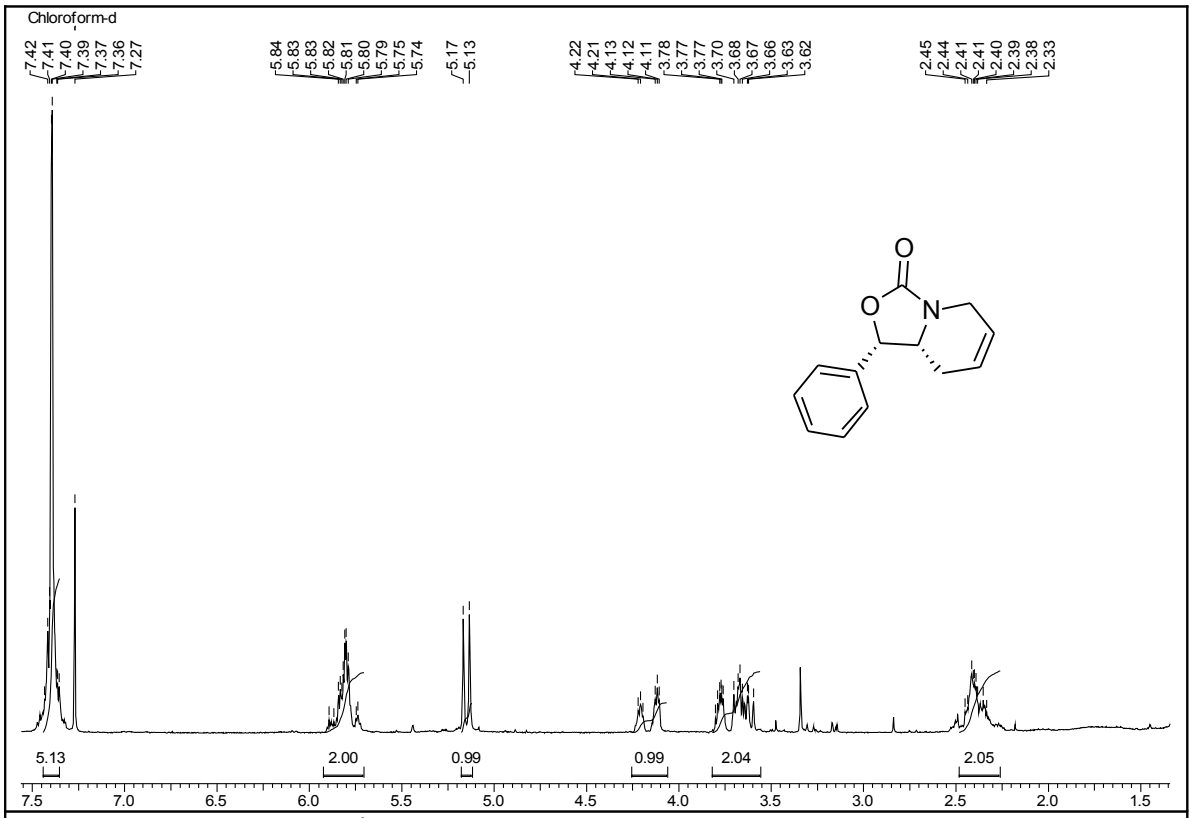
^{13}C-NMR of compound 59 in $CDCl_3$



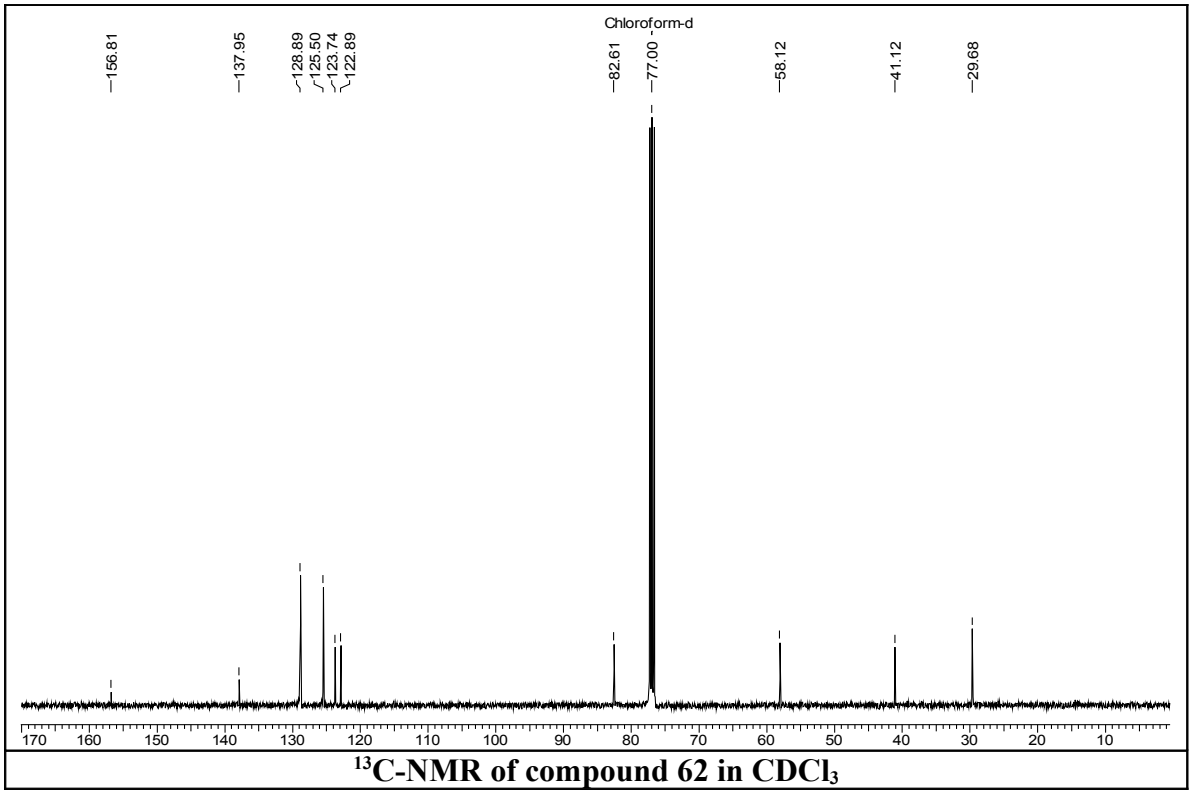
^{1}H-NMR of compound 60 in $CDCl_3$



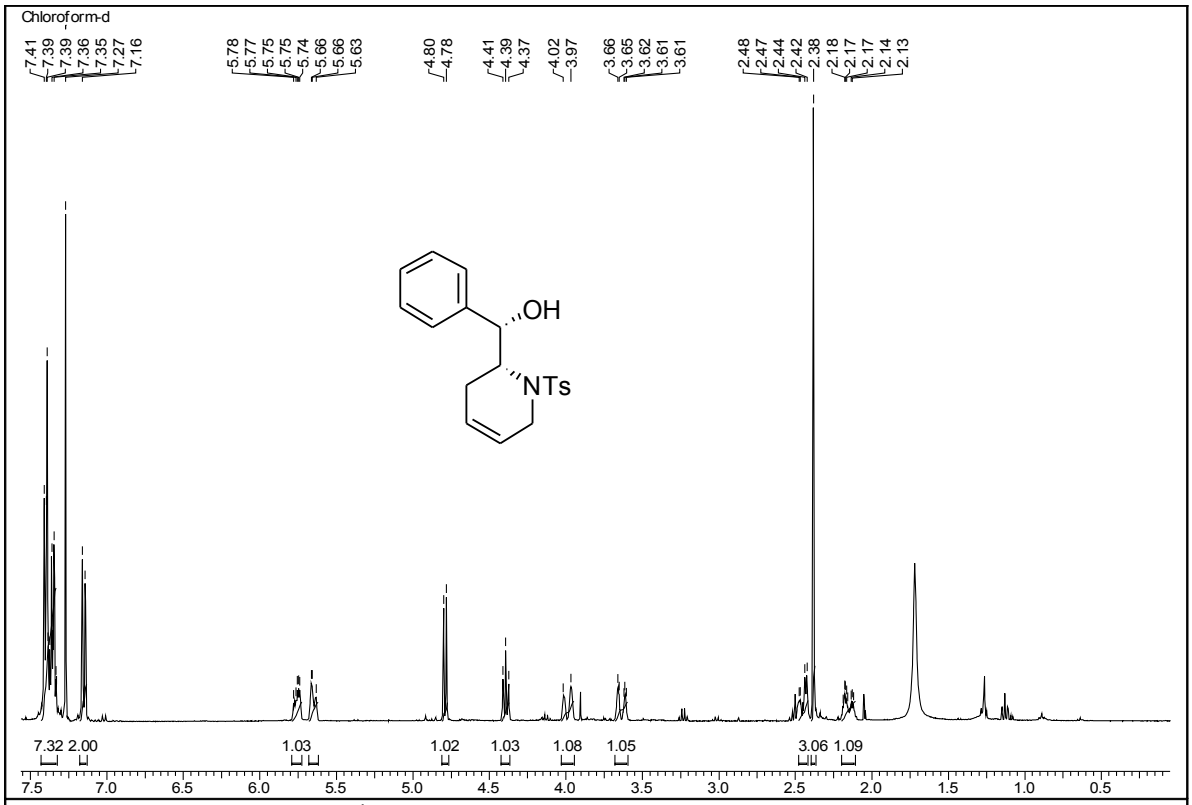
^{13}C-NMR of compound 60 in $CDCl_3$



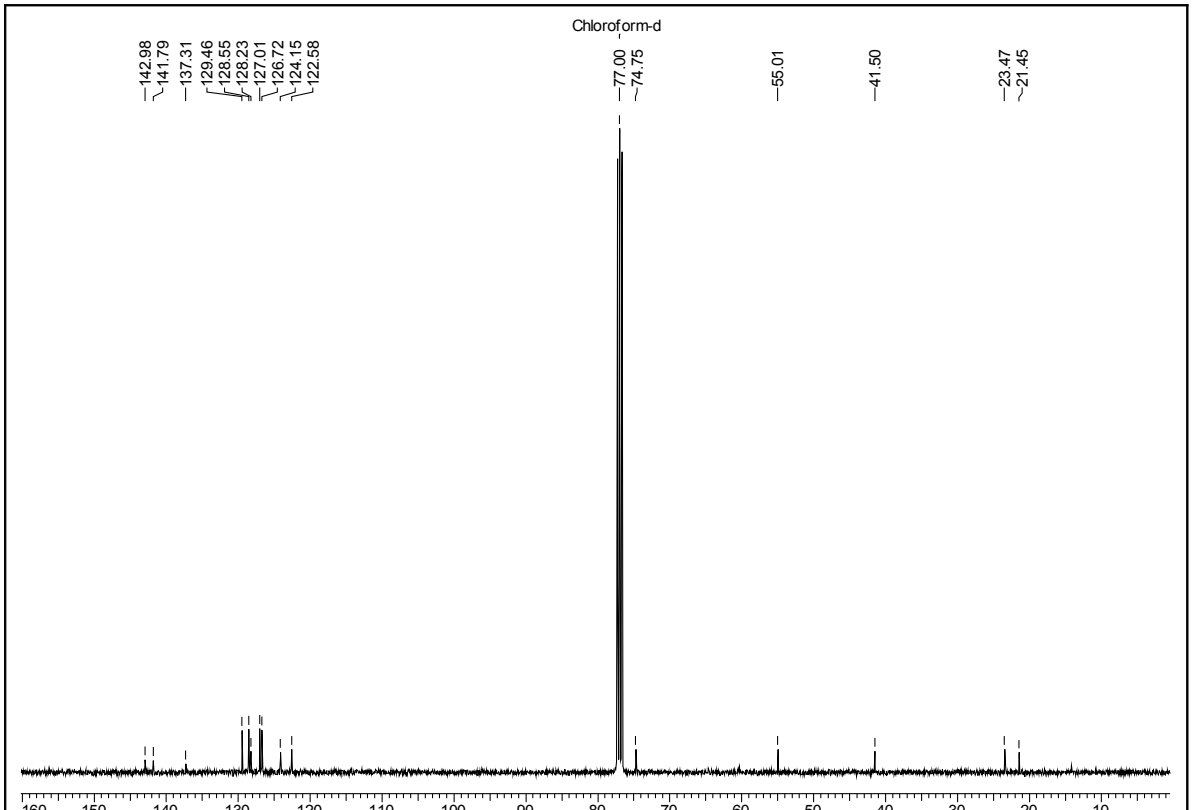
^{1}H-NMR of compound 62 in $CDCl_3$



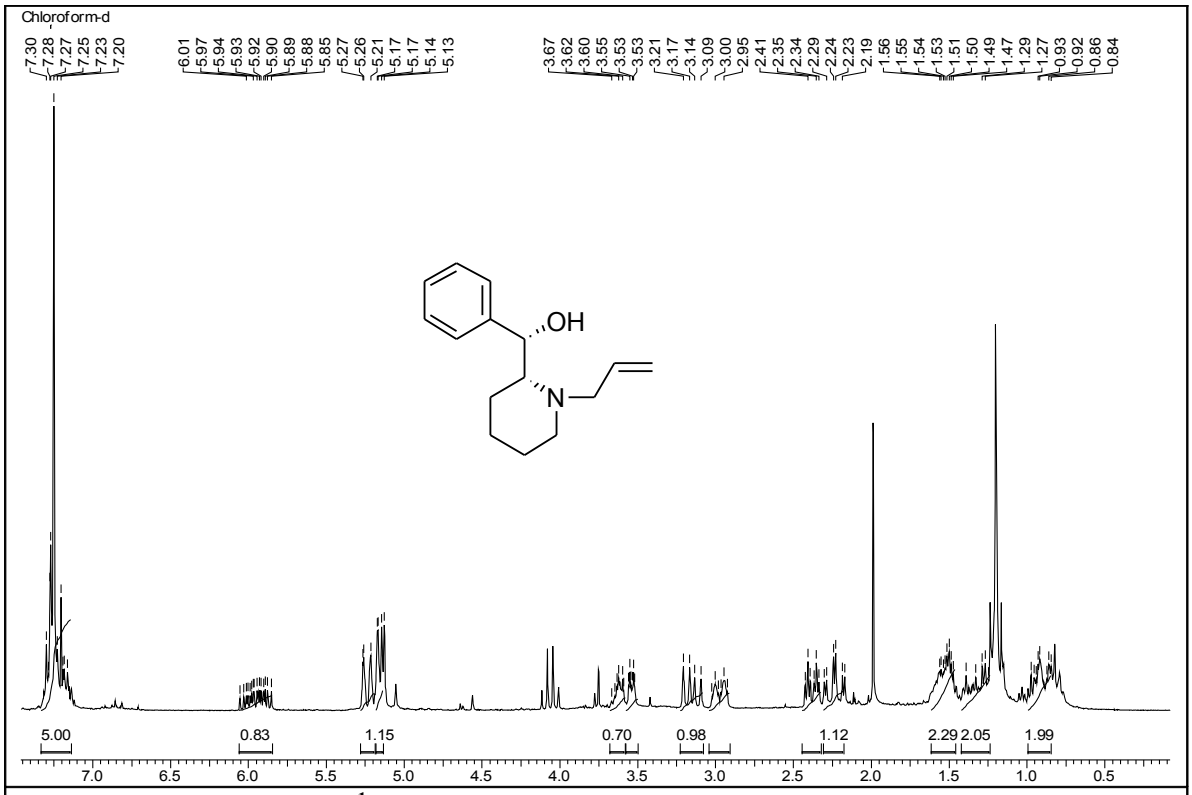
^{13}C-NMR of compound 62 in $CDCl_3$



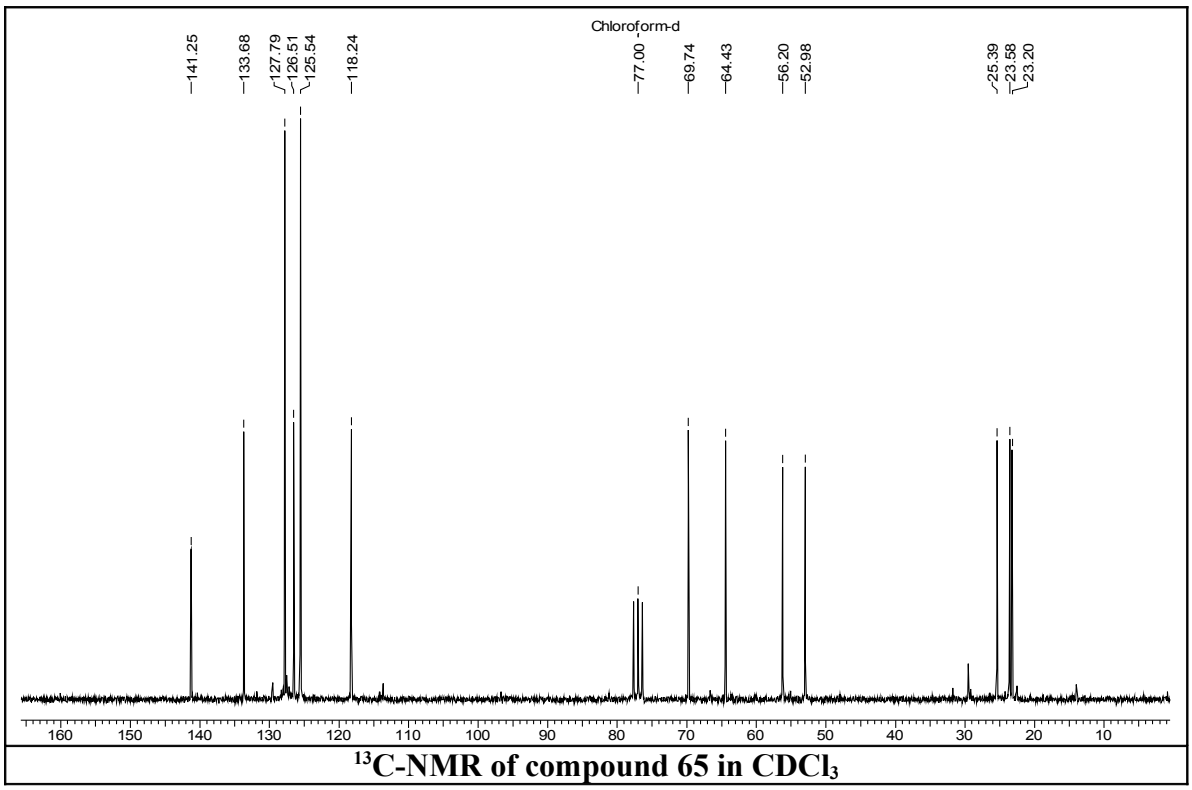
^{1}H-NMR of compound 63 in $CDCl_3$



^{13}C-NMR of compound 63 in $CDCl_3$



^{1}H-NMR of compound 65 in $CDCl_3$



^{13}C-NMR of compound 65 in $CDCl_3$

3.8. References

1. Hechtman, L. *Psychiatr. Clin. North Am*. **1992**, *1*, 553.
2. Millichap, J. G. *Ann. N. Y. Acad. Sci*. **1973**, *205*, 321.
3. Swanson, J. M.; Kingsbourne M., Attention and Cognitive Development, Eds. G. H. Hale, M. Lewis, Plenum Press: New York, 1979, pp. 249.
4. Zeitlin, A. L.; Dariani, M. M.; Stirling, D. I. *US Patent* 5,908,850, **1999**.
5. Patrick, K. S.; Caldwell, R. W.; Ferris, R. M.; Breese, G. R. *J. Pharm. Exp. Ther*. **1987**, *241*, 152.
6. Ding, Y. S.; Fowler, J. S.; Volkow, N. D.; Dewey, S. L.; Wang, G. J.; Logan, J.; Gatley, S. J.; Pappas, N. *Psychopharmacology* **1997**, *131*, 71.
7. Rometsch, R. *US Patent* 2,957,880, 1960.
8. Maxwell, R. A.; Chaplin, E.; Eckhardt, S. B.; Soares, J. R.; Hite, G. *J. Pharmacol. Exp. Ther*. **1970**, *173*, 158.
9. Egger, H.; Bartlett, F.; Dreyfuss, R.; Karliner, J. *Drug Metabolism and Disposition* **1981**, *9*, 415.
10. Deutsch, H. M.; Shi, Q.; Gruszeck-Kowalik, E.; Schweri, M. M.; *J. Med. Chem*. **1996**, *39*, 1201.
11. Axten, J. M.; Krim, L.; Kung, H. F.; Winkler, J. D. *J. Org. Chem*. **1998**, *63*, 9628.
12. Winkler, J. D.; Axten, J. A.; Krim, L. *World Patent Application No*. WO 99/36403, **1999**.
13. Dias, L. C.; dePiloto Fernandes, M. A. *Synth. Commun*. **2000**, *30*, 1311.
14. Dargazanil *et al*.*US Patent* 7205319 B2, **2007**.
15. Thai, D. L.; Sapko, M. T.; Reiter, C. T.; Bierer, D. E.; Perel, J. M. *J. Med. Chem*. **1998**, *41*, 591.
16. Zeitlin, A. L.; Stirling, D. I. *US Patent* 5,733,756, **1998**.
17. Prashad, M.; Kim, H. Y.; Lu, Y.; Liu, Y.; Har, D.; Repič, O.; Blacklock, T. J.; Giannousis, P. *J. Org. Chem*. **1999**, *64*, 1750.
18. Axten, J. M.; Ivy, R.; Krim, L.; Winkler, J. D. *J. Am. Chem. Soc*. **1999**, *121*, 6511.
19. Winkler, J. D.; Axten, J. M.; Krim, L. *US Patent* 6,025,502, **2000**.
20. Matsumura, Y.; Kanda, Y.; Shirai, K.; Onomura, O.; Maki, T. *Org. Lett*. **1999**, *1*, 175.

21. Matsumura, Y.; Kanda, Y.; Shirai, K.; Onomura, O.; Maki, T. *Tetrahedron* **2000**, *56*, 7411.
22. Seido, N.; Nishikawa, T.; Sotoguchi, T.; Yuasa, Y.; Miura, T.; Kumobayashi, H. *US Patent* 5,801,271, **1998**.
23. Prashad, M.; Liu, Y.; Kim, H. Y.; Repič, O.; Blacklock, T. J. *Tetrahedron: Asymmetry* **1999**, *10*, 3479.
24. (a) Pandey, S. K.; Pandey, M.; Kumar, P. *Tetrahedron Lett*. **2008**, *49*, 2397; (b) Gupta, P.; Kumar, P. *Eur. J. Org. Chem*. **2008**, 1195; (c) Tripathi, D.; Kumar, P. *Tetrahedron Lett.* **2008**, *49*, 7012. (d) Kandula, S. V.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 6149; (e) Gupta, P.; Naidu, S. V.; Kumar, P. *Tetrahedron Lett*. **2004**, *45*, 849; (f) Naidu, S. V.; Gupta, P.; Kumar, P. *Tetrahedron Lett.* **2005**, *46*, 2129; (g) Kumar, P.; Naidu, S.V.; Gupta, P. *J. Org. Chem.* **2005**, *70*, 2843; (h) Kumar, P.; Naidu, S.V. *J. Org. Chem.* **2005**, *70*, 4207; (i) Kumar, P.; Gupta, P.; Naidu, S. V. *Chem. Eur. J.* **2006**, *12*, 1397; (j) Kumar, P.; Naidu, S. V. *J. Org. Chem.* **2006**, *71*, 3935. (k) Gupta, P.; Fernandes, R. A.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 4231; (l) Kandula, S. V.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 1957; (m) Kondekar, N. B.; Kandula, S. V.; Kumar, P. *Tetrahedron Lett.* **2004**, *45*, 5477; (n) Gupta, P.; Naidu, S. V.; Kumar, P. *Tetrahedron Lett.* **2004**, *45*, 9641.
25. For reviews on cyclic sulfites/sulfates, see: (a) Lohray, B. B. *Synthesis* **1992**, 1035; (b) Byun, H.-S.; He, L.; Bittman, R. *Tetrahedron* **2000**, *56*, 7051.
26. Lallana, E.; Freire, F.; Seco, J. M.; Quiñoá, E.; Riguera, R. *Org. Lett*. **2006**, *8*, 4449.
27. Staudinger, H.; Meyer, J. *Helv. Chim. Acta.* **1919**, *2*, 635.
28. Miller, S. J.; Blackwell, M. E.; Grubbs, R. H. *J. Am. Chem. Soc.***1996**, *118*, 9606.
29. Luis, J.; Ruano, G.; Alemán, J.; Cid, M. B. *Synthesis* **2006**, 687.

Chapter-4

An organocatalytic approach to *syn*- and *anti*-1,3-polyols and proline-catalysed synthesis of piperidine and indozolidine natural products (*R*)-coiinine and (*S*)-coniceine

4.1. SECTION A

An organocatalytic approach to *syn*- and *anti*-1,3-polyols and its application to the synthesis of a hydroxy lactone pheromone component

4.1.1. Introduction

The 1,3-skipped polyol systems with *anti*- or *syn*-configuration are structural units of several natural products including clinically valuable polyene macrolide antibiotics. This has aroused great interest among synthetic organic chemists, resulting in an onslaught of activity directed at the development of efficient, stereoselective approaches to the assembly of 1,3-diols.[1] Despite the numerous strategies to synthesize polyols through substrate-controlled asymmetric induction, the interest in the new methods of its synthesis continues unabated.[2] We have recently developed a diastereoselective and iterative approach for the synthesis of 1,3-polyols using Jacobsen's hydrolytic kinetic resolution of racemic epoxide by which in principle one can prepare all the stereoisomers from easily available epoxides.[2b] However, the sequence of reaction suffers from a disadvantage due to the loss of 50% of starting compound as diol in each resolution step. Within the context of this work, the most widely used method to prepare 1,3-polyols in an iterative fashion are by allyl addition sequence utilizing stoichiometric amounts of chiral borons[3] and titanium.[4] Recently, Kirsch and coworkers have developed an efficient catalytic, iterative synthetic route to 1,3-polyols using Overmann esterification, [5a] while chromium-mediated asymmetric allylation has been reported by Kishi *et al*.[5b] However, the method involves a greater number of steps for each iteration[5a] (Kirsch *et al*.) or requires stringent reaction conditions[5b] (Kishi *et al*.) and uses an expensive catalyst. In view of the above considerations, there is still need for a versatile synthetic method that addresses the following issues: mild reaction conditions, minimum steps for each iteration, cheap and readily available catalysts, and flexible construction of possible isomers. In recent years, there has been growing interest in the use of small organic molecules to catalyze reactions in organic synthesis.[6] As a result, the area of organocatalysis has now emerged as a promising strategy and as an alternative to expensive protein catalysis and toxic metal

catalysis,[7] thus becoming a fundamental tool in the catalysis toolbox available for asymmetric synthesis.[8] Proline is among the most successful secondary amine based organocatalysts which have been widely employed in the asymmetric aldol,[9] Mannich,[10] Michael addition,[11] and α-functionalization,[12] viz. α-aminoxylation-,[12c] α-amination-,[13] and α-aminoxylation directed tandem reactions,[14] among many others,[15] providing rapid, catalytic, and atom-economical access to enantiomerically pure products. Similarly, organocatalytic tandem processes are emerging as powerful methods for the rapid synthesis and construction of complex target molecules from simple and readily available precursors while minimizing yield, time, and energy losses.[16]

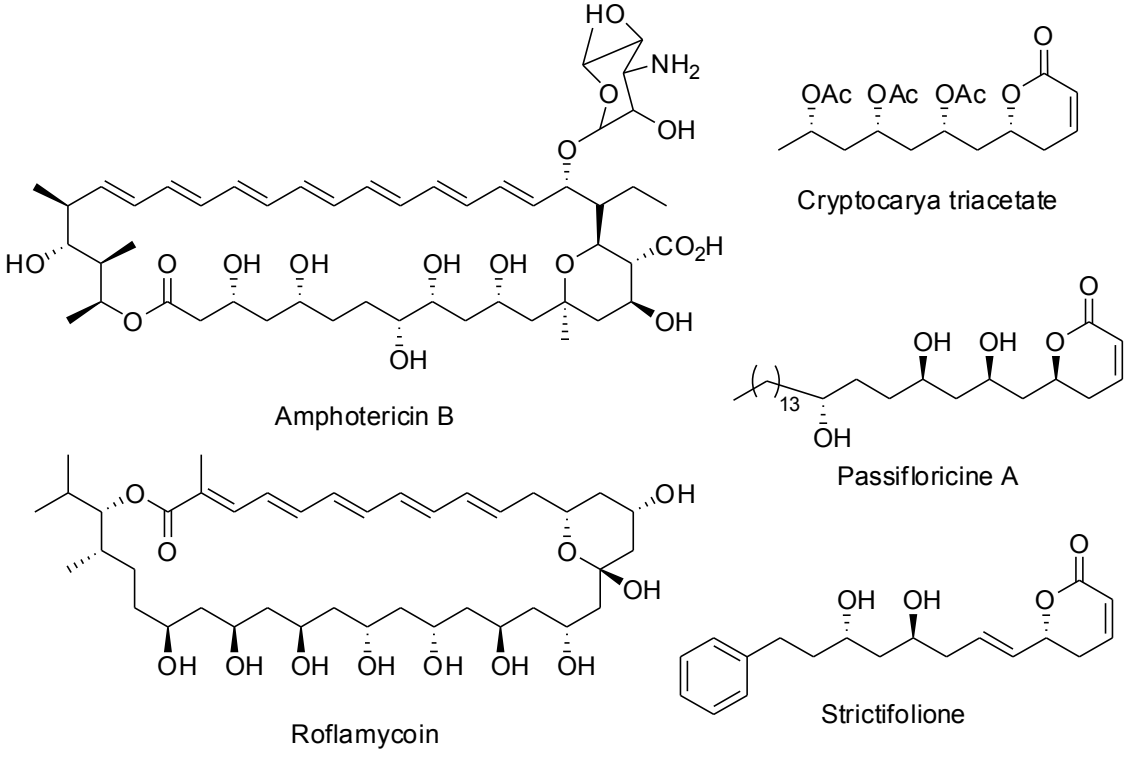
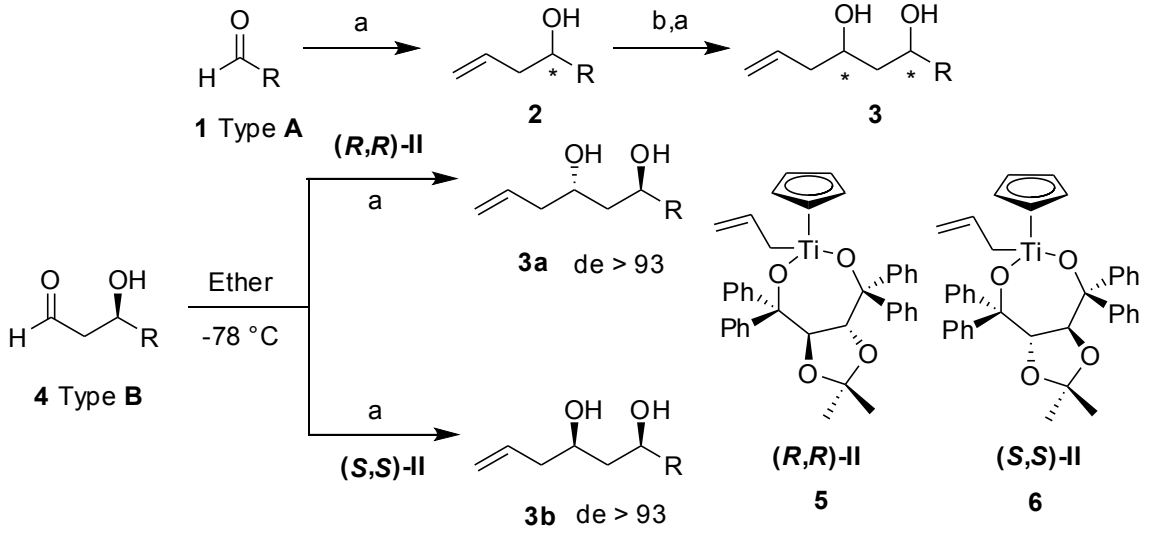


Figure 1. Representative examples of bioactive molecules containing 1,3-polyol moiety.

4.1.2. Review of Literature

Cossy *et al.* (2000)[4a]

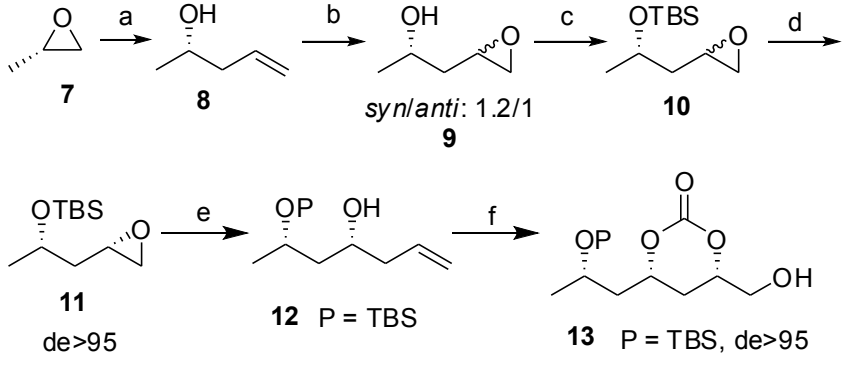
Cossy *et al.* developed an enantioselective synthesis of *syn*- and *anti*-1,3-diols *via* allyltitanation of unprotected *β*-hydroxyaldehyde. Thus *syn*- or *anti*-1,3-diols were obtained with good to excellent enantiomeric excess by allyltitanation of nonprotected *β*-hydroxyaldehydes of **4** (type **B)** with cyclopentadienyldialkoxyallyltitanium complexes (*R,R*)-**II** or (*S,S*)-**II**[17] (Scheme 1). *β*-Hydroxyaldehydes **4** (type **B**) were prepared in two steps by allyltitanation of aldehydes of **1** (type **A)**. Treatment of aldehydes **1** with either complex (*R,R*)-**II** or (*S,S*)-**II** in ether at -78 °C afforded homoallylic alcohols **2** with good enantiomeric excess (ee) 93-96%[18,19] and in high yield (85-92%). The transformation of these homoallylic alcohols to the corresponding *β*-hydroxyaldehydes **4** (type **B**) was achieved by using sodium periodate in the presence of a catalytic amount of osmium tetraoxide.[20] These *β*-hydroxyaldehydes were unstable and were treated directly with the allytitanium complexes. When *β*-hydroxyaldehydes **4** (type **B**) were treated with the allyltitanium complex (*R,R*)-**II 5**, the *anti*-1,3-diols **3a** were isolated in high yield (75-83%) and with diastereomeric excess up to 93%. When the *β*-hydroxyaldehydes **4** (type **B**) were treated with the (*S,S*)-**II 6**, complex, the *syn*-1,3-diols **3b** were obtained in high yields (78-85%) and with diastereoisomeric excess up to 93%.



Scheme 1. *Reactions and conditions*: (a) cyclopentadienyldialkoxyallyltitanium complex **(*R*,*R*)-II** or **(*S*,*S*)-II** , Ether, -78 °C; (b) $NaIO_4$, OsO_4.

Kumar *et al.* (2006)[2b]

Pradeep Kumar *et al.* developed an efficient method for the synthesis of *syn*-/*anti*-1,3-polyols using Jacobsen's hydrolytic kinetic resolution and regioselective opening of epoxide by vinyl magnesium bromide. Thus optically pure propylene oxide **7** easily obtained by Jacobsen's hydrolytic kinetic resolution (HKR) of racemate, was regiosectively opened using vinyl magnesium bromide to furnish homo allyl alcohol **8**, which was subjected to *m*-CPBA epoxidation to furnish hydroxy epoxide **9**. Epoxide **9** on TBS protection furnished the TBS ether **10** which served as a precursor for the next Jacobsen's hydrolytic kinetic resolution. Compound **10** was then subjected to Jacobsen's HKR to give chirally pure epoxide **11**. The *syn*- and *anti*-configuration of 1,3-polyol moiety can be manipulated simply by changing the Jacobsen's catalyst in the hydrolytic kinetic resolution step. The synthesis of *syn*-/*syn*- 1,3,5 polyols was achieved by iodolactonisation of the diol **12**.

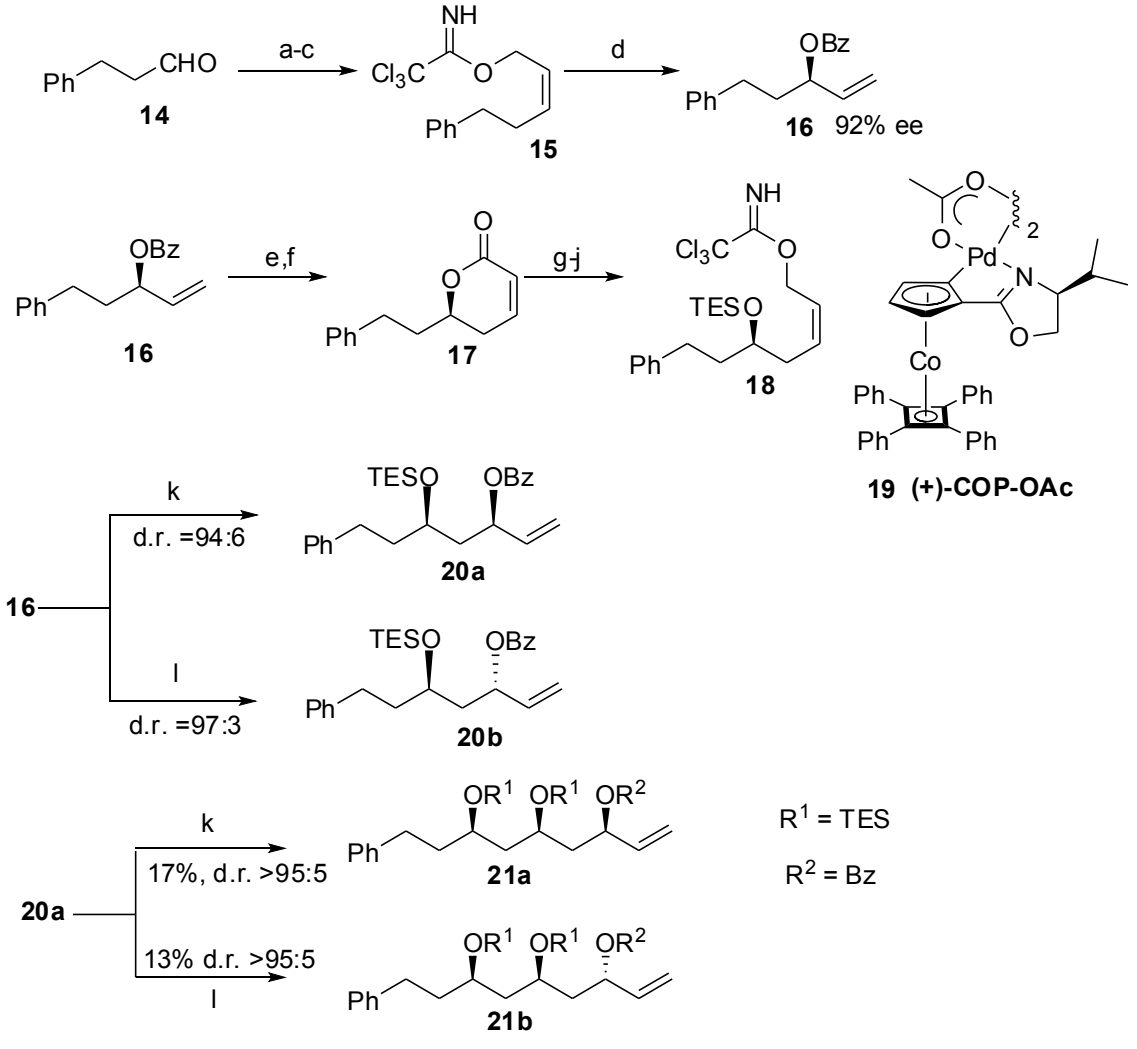


Scheme 2. *Reactions and conditions*: a) Vinylmagnesium bromide, CuI, THF, -20 °C, 12 h, 87%; b) *m*-CPBA, CH_2Cl_2, 0 °C to rt, 10 h, 96%; (c) TBSCl, imidazole, CH_2Cl_2, 0 °C to rt, 4 h, 95%; (d) (*S*,*S*)-Salen- Co-(OAc) (0.5 mol%), dist. H_2O (0.55 equiv), THF, 0 °C, 24 h; (e) Vinylmagnesium bromide, THF, CuI, -20 °C, 1 h, 82%; (f) (i) Boc_2O, DMAP, CH_3CN, rt, 5 h, 90%; (ii) IBr, PhMe, -85 °C, 1 h.

Kirsch *et al.* (2007)[21]

Kirsch *et al.* developed an iterative systematic approach to the 1,3-polyol motif to provide access to all possible stereoisomers by utilizing the catalytic asymmetric Overman esterification for the construction of all stereogenic centers. The first stereogenic center was

introduced by reaction of trichloroacetimidate **15**[22] with benzoic acid in the presence of palladacyclic (+)-COP-OAc **19** (1 mol%).[23] The conversion in CH_2Cl_2 at 23 °C provided (*R*)-allylic ester **16** in 93% yield and 92% ee after 16 h (Scheme 3).

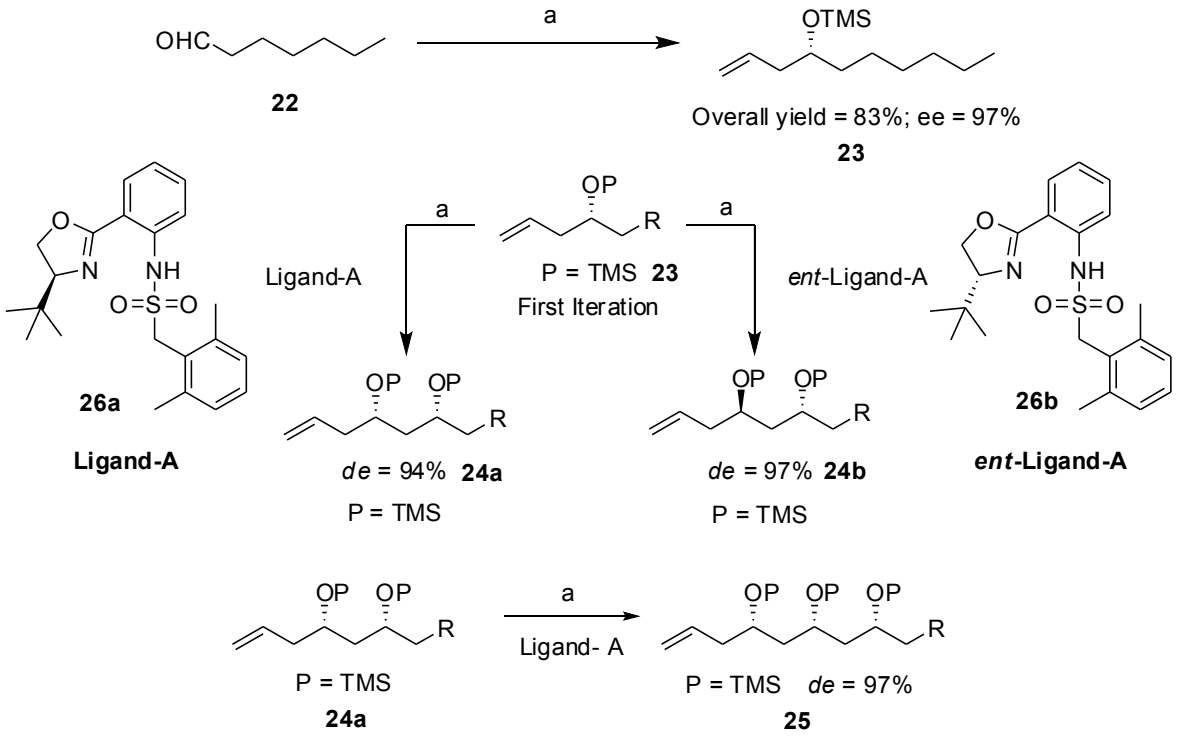


Scheme 3. *Reagents and conditions*: (a) (i) $(PhO)_2P(O)CH_2CO_2Et$, NaH, 0 °C, THF; (ii) 3-phenylpropionaldehyde, -78 °C, 85%; (b) DIBAL-H, -78 °C, CH_2Cl_2; (c) Cl_3CCN, DBU (10 mol%), 23 °C, CH_2Cl_2; (d) PhCOOH, (+)-COP-OAc (1 mol%), 23 °C, CH_2Cl_2, 93%; (e) (i) DIBAL-H, -78 °C, CH_2Cl_2; (ii) $CH_2{=}CHCH_2CO_2H$, DCC, DMAP (15 mol%), 23 °C, CH_2Cl_2, 88%; (f) (i) Grubbs II (1 mol%), 38 °C, CH_2Cl_2; (ii) DBU (10 mol%), 23 °C, CH_2Cl_2, 82%; (g) $NaBH_4$, $CeCl_3.7H_2O$, 0 °C, MeOH, 91%; (h) (i) TESOTf, 2,6-lutidine, 0 °C, CH_2Cl_2; (ii) K_2CO_3, 0 °C, MeOH, 90%; (j) Cl_3CCN, DBU (10 mol%), 23 °C, CH_2Cl_2, 94%; (k) PhCOOH, (+)-COP-OAc (1 mol%), 23 °C, CH_2Cl_2, 95%; (l) PhCOOH, (-)- COP-OAc (1 mol%), 23 °C, CH_2Cl_2, 94%.

A series of transformations consisting of transesterification,[24] ring-closing metathesis,[25] and base-catalyzed double bond isomerization[26] led to the formation of α,β-unsaturated δ-lactone **17**.[27] The lactone ring was opened with $NaBH_4$/ $CeCl_3.7H_2O$ followed by the formation of the corresponding bis silyl ether. The protecting group on the primary alcohol was removed selectively, and then the *Z*-configured allylic alcohol was converted into trichloroacetimidate **18**. The imidate was subsequently reacted with benzoic acid in the presence of (+)-COP-OAc **19** (1 mol%) to create the next stereogenic center. Under catalyst control, *syn*-1,3-diol **20a** was produced in high diastereoselectivity (dr = 94 : 6). The sequence with (-)-COP-OAc ***ent*-19** (1^{OH}-$3S^{OH}$), a modification that resulted in the formation of *anti*-1,3-diol **20b** in excellent yield and diastereoselectivity (dr = 97 : 3). The feasibility of this apporch was further illustrated by synthesizing 1,3-polyols in this way.

Kishi *et al.* (2008)[28]

Kishi *et al.* recently developed Cr-mediated catalytic asymmetric allylation approach for the synthesis of homoallyl alcohol. Thus **22** was subjected to the Cr-mediated catalytic asymmetric allylation in the presence of sulfonamide ligand-A **26a**, followed by TMS protection, to furnish the anticipated, protected allylic alcohol **23** in 83% yield and 97% ee. Further this reaction sequence was used in iterative fashion for the synthesis of *syn*-/*anti*-1,3,-polyols. One cycle of iteration is composed of a three-step operation, i.e., oxidative cleavage of the olefin to form an aldehyde, catalytic asymmetric allylation, and protection of the resultant alcohol. Thus, TMS-protected allylic alcohol **23** was subjected to first cycle of iteration in the presence of sulfonamide ligand **A** or its enantiomer ***ent*-A**, followed by TMS protection to furnish *syn*-/ *anti*-diol **24a** and **24b** respectively. The ^{1}H NMR analysis revealed that the diastereomeric purity of resultant **24a** and **24b** was de > 92% and de > 95%, respectively. Similarly the second iteration of the alcohol **24a** furnished the *syn*/*syn*-triol **25** in good yield and de>95%.



Scheme 4: *Reagents and conditions*: (a) **(**i) CrBr, Mn, Et_3N, 2,6-Lutidine, allyl bromide, Ligand-A, $Zr(Cp)_2Cl_2$ (ii) TMS-Cl, Et_3N.

4.1.3. Present work

Objective

Recently, Zhong *et al*. have reported an α-aminoxylation directed tandem reaction catalyzed by proline which involves a sequential α-aminoxylation, HWE-olefination reaction at ambient temperature furnishing *O*-amino-substituted allylic alcohol from readily available achiral aldehydes.[14a] We envisioned that this reaction could give us stereocontrolled synthetic access to 1,3-polyol motifs. However, it may be pertinent to mention here that the chirality of the already established 1,3-polyol chain makes the stereoselective chain elongation a challenging process.[29] Our iterative strategy for the synthesis of polyols is outlined in Figure 2.

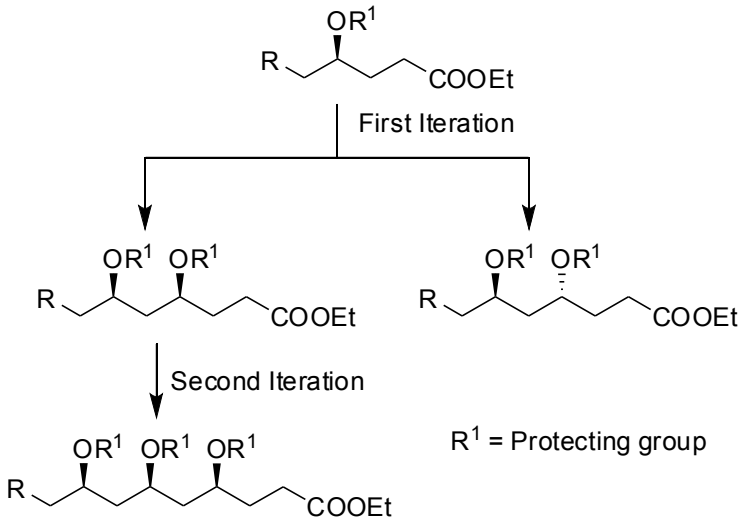
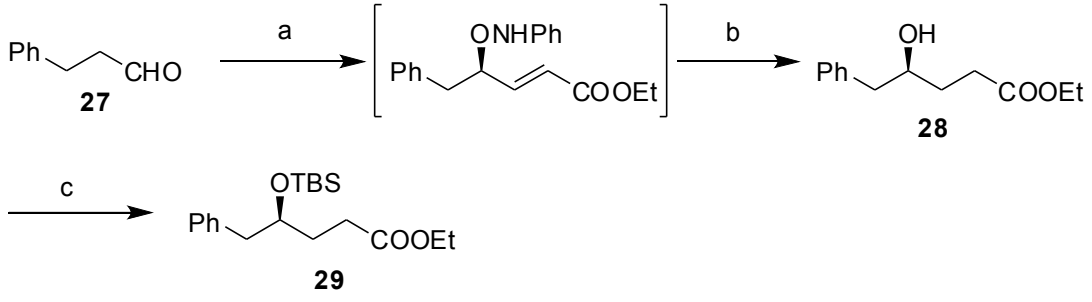


Figure 2. General synthetic strategy to the synthesis of 1,3-polyols

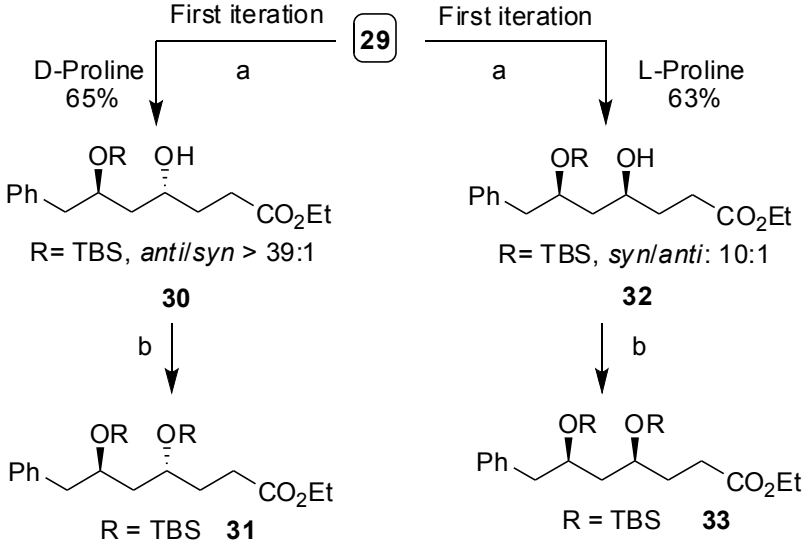
4.1.4. Results and discussion

Toward the synthesis of 1,3-polyols, our first goal was to synthesize *γ*-hydroxy ester **28** in a tandem fashion (Scheme 5). Thus, the commercially available phenyl propanal **27** was subjected to sequential α-aminoxylation (L-proline as a catalyst) followed by HWE-olefination reaction, to furnish *O*-amino-substituted allylic alcohol. In an effort to minimize handling of intermediates and its time-consuming purification, the crude product obtained after workup was directly subjected to hydrogenation conditions using catalytic amounts of Pd/C to furnish the *γ*-hydroxy ester **28** in good yield. The appearance of singlets at δ -0.12, 0.03, 0.91 in ^{1}H NMR and disappearance of peak at 3488 cm^{-1}in IR spectrum confirmed the formation of compound **29**. Thus, in two steps and one column purification, *γ*-hydroxy ester **28** was obtained in 71% yield and 98% ee.[30]



Scheme 5. *Reagents and Conditions*: (a) Nitrosobenzene, L-proline, DMSO, HWE salt, DBU, LiCl, CH_3CN; (b) H_2/Pd-C, EtOAc; (c) TBSOTf, 2,6- Lutidine, DCM.

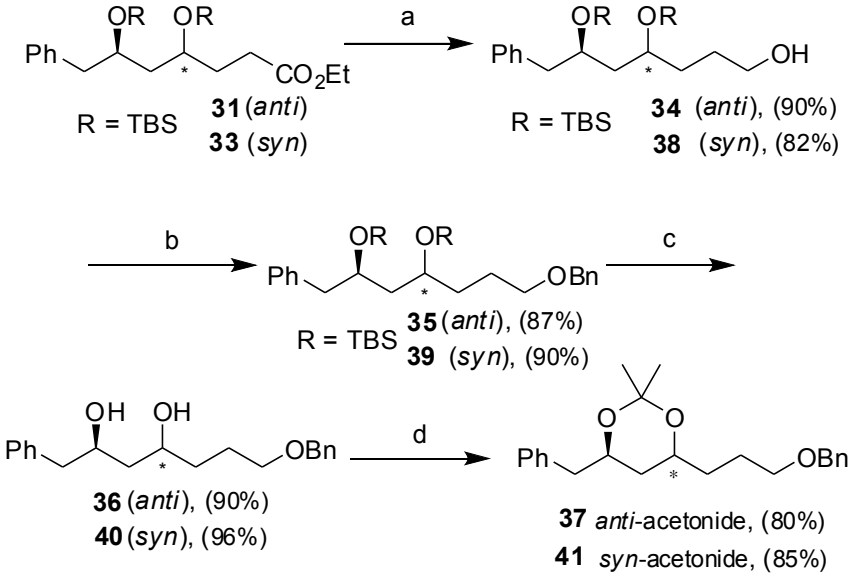
The free hydroxy group of γ-hydroxy ester **28** was protected as TBS ether using TBSOTf to furnish compound **29**. The appearance of singlets at δ -0.12, 0.03, 0.91 in ^{1}H NMR and disappearance of peak at 3488 cm^{-1}in IR spectrum confirmed the formation of compound **29**. With a substantial amount of the TBS ether **29** in hand, we then proceeded toward the first cycle of iteration (Scheme 6). Each cycle of iteration consists of four steps, viz. DIBAL-H reduction of ester to aldehyde, sequential α-aminoxylation, HWE olefination, and H_2-Pd/C reduction, followed by TBS protection of the hydroxy group to eventually furnish the TBS protected γ-hydroxy ester.



Scheme 6. *Reagents and Conditions*: (a) (i) DIBAL-H, -78 °C; (ii) Nitroso benzene, D/L-Proline, DMSO, HWE salt, DBU, LiCl, CH_3CN; (iii) H_2/Pd-C, EtOAc; (b) TBSOTf, 2,6-lutidine, DCM.

As illustrated in Scheme 6, the DIBAL-H reduction of ester **29** furnished the corresponding aldehyde which on α-aminoxylation using D-proline as a catalyst followed by HWE olefination and subsequent Pd/C reduction gave the *anti*-diol **30** in 65% yield. The ^{1}H NMR analysis revealed the diastereomeric purity (de) of the reaction to be >95%, and appearance of the peaks in the range of δ 3.55-3.63 and 3.81-3.90 in ^{1}H NMR and a broad peak at 3493 cm^{-1} in IR spectrum confirmed the formation of *anti*-diol **30**. Further TBS protection of free hydroxy group afforded TBS ether **31** in 95% yield. Disappearance of peak at 3493 cm^{-1} in IR spectrum confirmed the formation of **31**. Following similar

iteration with L-proline-catalyzed sequence of reactions provided the *syn*-diol **32** as a 10:1 unseparable mixture of diastereomers in 63% yield. Nevertheless, after protection of the hydroxy group of **32** with TBS, we were able to separate the major diastereomer **33** in 89% yield in diastereomerically pure form as determined from ^{1}H NMR. Appearance of the peaks in the range of δ 3.83-4.01 in ^{1}H NMR and disappearance of broad peak at 3493 cm^{-1} in IR spectrum confirmed the formation of compound **33**. These findings could probably be attributed to match/mismatch effect of the TBS group, without any appreciable change in yield of the reaction[31] (Scheme 6).

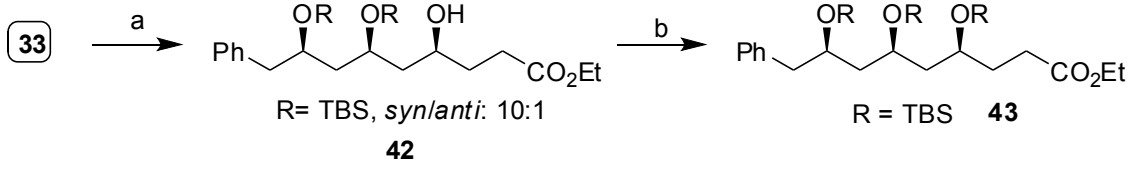


Scheme 7. *Reagents and Condition*s: (a) DIBAL-H, -78 °C; (b) BnBr, NaH, DMF; (c) *p*-TSA, MeOH; (d) 2,2-DMP, *p*-TSA, DCM.

The relative stereochemistry of 1,3-diols **30** and **32** was determined by using Rychnovsky's acetonide method[32] (Scheme 7). Thus, DIBAL-H reduction of esters **31** and **33** afforded alcohols **34** and **38**, respectively, which on benzyl protection gave compounds **35** and **39**. Subsequent TBS deprotection furnished the diols **36** and **40**, which on treatment with 2,2-DMP gave the *anti*-acetonide **37** and *syn*-acetonide **41**, respectively. The appearance of methyl resonance peaks at δ 19.8 and 30.2 ppm and acetal carbon resonating at δ 98.5 ppm confirmed the presence of *syn*-acetonide **41**. Similarly, *anti*-acetonide **37** was confirmed by the appearance of the methyl carbons resonance at δ 24.8 ppm and the acetal carbon at *δ* 100.3 ppm (Scheme 7). This iterative sequence is particularly attractive because of mild

reaction conditions, use of proline as a cheap and commercially available catalyst,[33] and the overall short reaction sequence involving four steps and two column purifications per iteration. Since the stereochemical outcome of the reaction can be predicted on the basis of the catalyst used, this method gives an easy access to 1,3 *syn*-/*anti*-diols with predictable and useful stereocontrol in good yield.

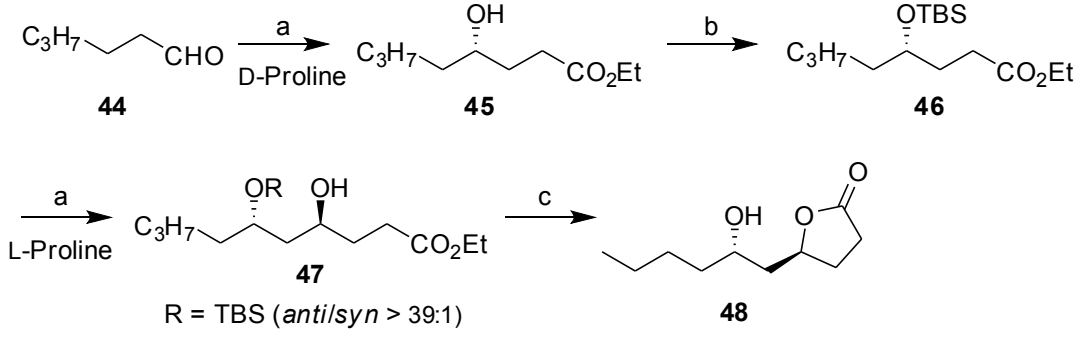
To illustrate the feasibility of this approach for preparing 1,3,5-polyols, we further attempted the synthesis of a *syn*/*syn*-1,3,5-triol as a representative example (Scheme 8). Thus, by subjecting *syn*-diol **33** to a second cycle of iteration using the L-proline-catalyzed sequence of reactions, triol **42** was obtained as a 10:1 unseparable mixture of diastereomers in 61% yield as determined from ^{1}H NMR. Appearance of a broad peak at 3436 cm^{-1} in IR spectrum and peaks at m/z 539.4416 (M^++H), 561.4312 (M^++Na), 579.3909 (M^++K) in the mass spectrum confirmed the formation of compound **42**. However, the diastereomerically pure triol was obtained as the TBS ether **43** in 88% yield, after TBS protection of the hydroxy group of **42** and separation by flash chromatography. Disppearance of a broad peak at 3436 cm^{-1} in IR and appearance of clear multiplets in the range of δ 3.55-3.61, 3.81-3.97, 4.00-4.18 confirmed the formation of compound **43**.



Scheme 8. *Reagents and Condition*s: (a) (i) DIBAL-H, -78 °C; (ii) Nitroso benzene, L-Proline, DMSO, HWE salt, DBU, LiCl, CH_3CN, 61%; (iii) H_2/Pd-C, EtOAc; (b) TBSOTf, 2,6 Lutidine, DCM, 88%.

As an outgrowth from these efforts, we became interested in the application of this approach for the expedient total synthesis of (2*S*,3*S*)-2-hydroxyhexylcyclopentanone **48**, representative of 6-hydroxyalkan-4-olides, hydroxy lactones with chain lengths between 10 and 13 carbon atoms, which are part of the complex mixture of compounds that giant white butterfly *Idea leuconoe* hairpencils release as a pheromone (Scheme 9). They seem to act synergistically with the other pheromone components and are probably involved in male-male interactions.[34] To this end, commercially available hexanal **44** was subjected to sequential α-aminoxylation (D-proline as a catalyst), HWE olefination, and reductive

hydrogenation to furnish the *γ*-hydroxy ester **45** in 65% yield and 94% ee.[35] This on TBS protection (**45** → **46**) followed by a first cycle of iteration using L-proline catalyzed reaction conditions afforded the *anti*-diol **47**, with de >95% as determined from ^{1}H NMR. Appearance of broad singlet at δ 3.64 and multiplet at δ 3.95-4.01 in ^{1}H NMR and broad peak at 3434 cm^{-1} in IR spectrum confirmed the formation of *anti*-diol **47**. Subsequent acid treatment with *p*-TSA in methanol resulted in deprotection of TBS group and concomitant lactonization to furnish the required lactone **48**. Appearance of multiplet at δ 3.81-3.92, 4.73-4.83 in ^{1}H NMR and broad peak at 3468 cm^{-1} corresponding to OH group and 1764 cm^{-1} corresponding to carbonyl absorption in IR spectrum confirmed the formation of **48**.



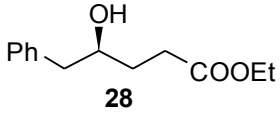
Scheme 9. *Reagents and Condition*s: (a) (i) DIBAL-H, reduction of ester (ii) Nitroso benzene, D/L-Proline, DMSO, HWE salt, DBU, LiCl, CH_3CN; (iii) H_2/Pd-C, EtOAc; (b) TBSOTf, 2,6-lutidine, DCM; (c) *p*-TSA, MeOH.

4.1.5. Conclusion

In conclusion, a practical and efficient iterative approach to the stereocontrolled synthesis of 1,3-polyols from commercially available and inexpensive starting materials has been developed. The advantages of using this process are as follows: (a) the reaction uses mild reaction conditions (at room temperature, air and moisture are tolerated), (b) the *O*-amino-substituted allylic alcohol that is formed after sequential α-aminoxylation and HWE olefination can be isolated in good yield and is converted to *γ*-hydroxy ester without requiring a separate column purification step, and (c) both enantiopure forms of proline are commercially available, and thus, in principle, all possible combinations of 1,3,5-polyols can be accessed. The synthetic utility of this protocol was further demonstrated by the asymmetric synthesis of a pheromone component, (2*S*,3*S*)-2-hydroxyhexylcyclopentanone.

4.1.6. Experimental Section

(*S*)-Ethyl 4-hydroxy-5-phenylpentanoate (28):



28

General procedure A:

To a solution of phenyl propanal (2.0 g, 14.4 mmol) and nitroso benzene (1.55 g, 14.4 mmol) in anhydrous DMSO (29 mL) was added L-proline (0.67 g, 5.8 mmol) at 20 °C. The mixture was vigorously stirred for 25 min under argon (the color of the reaction changed from green to yellow during this time), then cooled to 0 °C. Thereafter, A premixed and cooled (0 °C) solution of triethylphosphonoacetate (8.68 mL, 43.4 mmol), DBU (6.48 mL, 43.4 mmol) and LiCl (1.83 g, 43.4 mmol) in CH_3CN (29 mL) was added quickly (1-2 min) at 0 °C. The resulting mixture was allowed to warm to room temperature over 1 h, and quenched by addition of ice pieces. The acetonitrile was evaporated under vacuum. This reaction mixture was then poured into water (100 mL) and extracted with Et_2O (5×100 mL). The combined organic layers were washed with water, brine, dried (Na_2SO_4) and concentrated in vacuo to give crude product which was directly subjected to next step without purification. To the crude allylic alcohol in ethyl acetate was added Pd-C (10%) under hydrogenation conditions and the reaction mixture was allowed to stir overnight. On completion of reaction (until ^{1}H NMR analysis of the crude mixture indicated complete conversion), the mixture was filtered through a pad of celite and concentrated in vacuo to give γ-alcohol. The crude product was then purified by using flash column chromatography using pet ether: EtOAc (85:15) as eluent to give (*S*)-ethyl 4-hydroxy-5-phenylpentanoate **28** as a colorless liquid.

Yield: 2.73 g, 71%

Mol. Formula:

$[\alpha]_D^{25}$: +14.54 (*c* 1, $CHCl_3$).

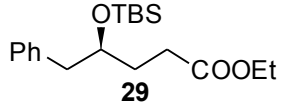
IR ($CHCl_3$, cm^{-1}): ν_{max} 3488, 1731, 1602, 1494, 1022.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.26 (t, J = 7.1 Hz, 3H), 1.71-2.01 (m, 3H), 2.49 (t, J = 7.0 Hz, 2H), 2.66-2.88 (m, 2H), 3.80-3.93 (m, 1H), 4.12 (q, J = 7.1 Hz, 2H), 7.20-7.34 (m, 5H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9, 30.5, 31.3, 43.8, 60.1, 71.5, 126.1, 128.2, 129.1, 138.2, 173.8 ppm.

The analytical data are identical to those reported elsewhere.[36]

(*S*)-Ethyl 4-(*tert*-butyldimethylsilyloxy)-5-phenylpentanoate (29):



29

To an ice-cold stirred solution of **28** (1.0 g, 4.49 mmol) in CH_2Cl_2 (10 mL) were added 2,6-lutidine (2.6 mL, 11.24 mmol) and TBSOTf (3.10 mL, 6.74 mmol) at 0 °C. The resulting mixture was stirred for 1 h at 0 °C before H_2O (20 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Silica gel column chromatography (petroleum ether: ethyl acetate: 99:1) of the crude product gave TBS ether **29** as a colourless liquid.

Yield:1.37 g, 91%

Mol. Formula: $C_{19}H_{32}O_3Si$

$[\alpha]_D^{25}$: - 2.08 (*c* 1.1, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 2955, 1736, 1684, 1454, 1088.

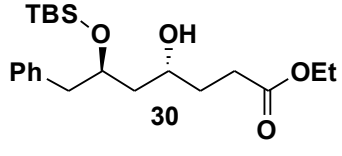
^{1}H NMR (400 MHz, $CDCl_3$): δ -0.12 (s, 3H), 0.03(s, 3H), 0.91 (s, 9H), 1.26 (t, *J* = 7.0 Hz, 3H), 1.69-1.78 (m, 1H), 1.80-1.89 (m, 1H), 2.37-2.47 (m, 2H), 2.73 (dd, *J* = 6.3, 13.2 Hz, 1H), 2.79 (dd, *J* = 6.3, 13.2 Hz, 1H), 3.92-3.98 (m, 1H), 4.13 (q, *J* = 7.0 Hz, 2H), 7.18-7.23 (m, 3H), 7.27-7.31 (m, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -5.0, -4.9, 14.1, 17.9, 25.8, 29.8, 31.5, 43.8, 60.1, 72.4, 126.1, 128.1, 129.6, 138.6, 173.6 ppm.

Analysis Calcd. C, 67.81; H, 9.58; Found: C, 67.99; H, 9.41.

Anti isomer:

(4*R*, 6*R*)-Ethyl 6-(*tert*-butyldimethylsilyloxy)-4-hydroxy-7-phenylheptanoate (30)



30

To a solution of ethyl ester **29** (1.0 g, 2.97 mmol) in CH_2Cl_2 (15 mL), was added DIBAL-H (1.43 mL 2.3 M solution in toluene, 3.26 mmol) at -78 °C under argon atmosphere. The reaction was stirred at this temperature for 40 min. Then a solution of tartaric acid (5 mL) was added. The resulting mixture was stirred for 15 min and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL), the combined organic layers were dried (Na_2SO_4), filtered and evaporated under reduced pressure to give aldehyde as a colourless liquid, which was directly used in the next step without further purification. Following the general procedure A (D-proline as a catalyst) **30** was obtained as a crude product (>95% diastereomeric excess) and was purified by flash column chromatography using petroleum ether:ethyl acetate (90:10) to furnish pure diol **30** as a colorless liquid.

Yield: 0.65 g, 65%

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

$[\alpha]_D^{25}$: -5.51 (*c* 1.30, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 3493, 2930, 1727, 1603, 1454, 1216.

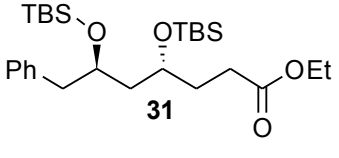
^{1}H NMR (200 MHz, $CDCl_3$): δ -0.39 (s, 3H), -0.08 (s, 3H), 0.83 (s, 9H), 0.89-0.92 (m, 2H), 1.27 (t, *J* = 7.2 Hz, 3H) 1.77-1.90 (m, 2H), 2.40-2.57 (m, 2H), 2.76 (d, *J* = 6.6 Hz, 2H), 3.55-3.63 (m, 1H), 3.81-3.90 (m, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 7.17-7.20 (m, 2H), 7.22-7.27 (m, 3H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -5.4, -4.9, 14.2, 17.9, 25.8, 26.8, 31.1, 37.8, 60.4, 73.8, 76.8, 126.1, 128.2, 129.7, 129.8, 138.7, 173.8 ppm.

MS (ESI): m/z 381.3861 (M^++H), 403.4595 (M^++Na), 419.4212 (M^++K).

Analysis Calcd. C, 66.27; H, 9.53; Found C, 66.42; H, 9.63.

(4*R*, 6*R*)-Ethyl 4,6-bis(*tert*-butyldimethylsilyloxy)-7-phenylheptanoate (31):



31

To an ice-cold stirred solution of **30** (0.5 g, 1.31 mmol) in CH_2Cl_2 (5 mL) were added 2,6-lutidine (0.38 mL, 3.28 mmol) and TBSOTf (0.45 mL, 1.97 mmol) at 0 °C. The resulting

mixture was stirred for 1 h at 0 °C before H_2O (10 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Silica gel column chromatography purification (petroleum ether) of the crude product gave TBS ether **31** as a colorless liquid.

Yield: 0.68 g, 95%

Mol. Formula: $C_{27}H_{50}O_4Si_2$

$[\alpha]_D^{25}$: + 8.79 (*c* 1.70, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 3020, 2857, 1729, 1603, 1559, 1538, 1404, 1216.

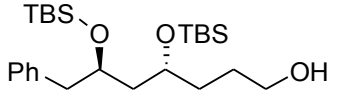
^{1}H NMR (400 MHz, $CDCl_3$): δ -0.07 (s, 3H), 0.07 (s, 3H), 0.08 (s, 6H), 0.92 (s, 9H), 0.93 (s, 9H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.60-1.83 (m, 3H), 1.92-2.01 (m, 1H), 2.43 (t, *J* = 7.5 Hz, 2H), 2.82 (d, *J* = 6.3 Hz, 2H), 3.87 (quientet, *J* = 6.0 Hz, 1H), 4.01 (quientet, *J* = 6.0 Hz, 1H), 4.21 (q, *J* = 7.0 Hz, 2H), 7.25-7.29 (m, 3H), 7.33-7.37 (m, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ -4.6, -4.3, 14.2, 18.0, 25.8, 25.9, 29.8, 32.4, 44.4, 45.1, 60.2, 69.1, 71.5, 126.1, 128.1, 129.7, 138.8, 173.7 ppm.

MS (ESI): m/z 495.4796 (M^++H), 517.6717 (M^++Na), 533.4339, (M^++K).

Analysis Calcd. C, 65.53; H, 10.18; Found C, 65.28; H, 10.36.

(4*R*, 6*R*)-4,6-Bis(*tert*-butyldimethylsilyloxy)-7-phenylheptan-1-ol (34)



34

To a solution of **31** (2.0 g, 4.04 mmol) in dry DCM (70 mL) at 0 °C was added dropwise DIBAL-H (10.1 mL, 10.1 mmol, 1 M in toluene) through a syringe. The reaction mixture was allowed to warm to room temperature over 1 h, then recooled to 0 °C and treated with sat. aqueous solution of sodium potassium tartrate (50 mL). The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with water, brine, dried (Na_2SO_4), filtered and concentrated in vacuo. Silica gel column chromatography of the crude product using petroleum ether:ethyl acetate (8:2) as eluent gave **34** as colorless oil.

Yield:1.64 g, 90%

Mol. Formula: $C_{25}H_{48}O_3Si_2$

$[\alpha]_D^{25}$: + 3.53 (*c* 1.12, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 3300, 3087, 2858, 1603, 1495, 1454, 1256, 1216, 1030.

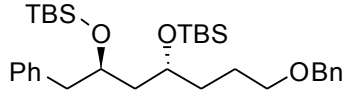
^{1}H NMR (200 MHz, $CDCl_3$): δ -0.05 (s, 3H), 0.09 (s, 9H), 0.93 (s, 9H), 0.94 (s, 9H), 1.64-1.75 (m, 6H), 1.82 (bs, 1H), 2.81 (dd, *J* = 1.7, 8.8 Hz, 1H), 2.84 (dd, *J* = 1.7, 8.8 Hz, 1H), 3.68-3.74 (m, 2H), 3.84-3.92 (m, 1H), 3.95-4.08 (m, 1H), 7.23-7.35 (m, 5H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ -4.5, -4.3, -4.2, 18.0, 25.8, 25.9, 28.2, 33.9, 44.5, 44.6, 63.0, 70.0, 71.6, 126.1, 128.1, 129.7, 138.8 ppm.

MS (ESI): m/z 453.4679 (M^++H), 475.6094 (M^++Na).

Analysis Calcd. C, 66.31; H, 10.68; Found C, 66.56; H, 10.57.

(5*R*,7*R*)-5-Benzyl-7-(3-(benzyloxy)propyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecane (35):



35

To a solution of **34** (0.14 g, 0.31 mmol) in dry DMF (2 mL) was added sodium hydride (60%, 0.024 g, 0.62 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 benzyl bromide (0.55 mL, 0.46 mmol) and *tetra n*-butylammonium iodide (catalytic) with further stirring for 1 h at the same 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 5 mL). The combined organic layers were washed with water (3 x 5 mL), brine, dried (Na_2SO_4) and concentrated. The residual oil was purified by silica gel column chromatography (ethyl acetate:petroleum ether, 1:49) to furnish the protected alcohol **35** as a colorless oil.

Yield: 0.14 g, 87%

Mol. Formula: $C_{32}H_{54}O_3Si_2$

$[\alpha]_D^{25}$: + 0.28 (*c* 1.22, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 3029, 2952, 2856, 1604, 1461, 1454, 1255, 1096.

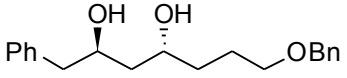
^{1}H NMR (500 MHz, $CDCl_3$): δ -0.21 (s, 3H), -0.08- -0.06 (m, 9H), 0.77 (s, 9H), 0.78 (s, 9H), 1.43-1.61 (m, 6H), 2.63-2.71 (m, 2H), 3.40 (t, J = 6.6 Hz, 2H), 3.69 -3.74 (m, 1H), 3.85-3.90 (m, 1H), 4.44 (s, 2H), 7.08 -7.12 (m, 3H), 7.17- 7.23 (m, 3H), 7.27-7.28 (m, 4H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ -4.5, -4.2, -4.1, 18.0, 25.4, 25.9, 34.2, 44.6, 45.2, 70.0, 70.4, 71.5, 72.8, 126.0, 127.4, 127.5, 128.1, 128.3, 129.7, 138.6, 138.9 ppm.

MS (ESI): m/z 543.2448 (M^++H), 565.247 (M^++Na), 581.2300, (M^++K).

Analysis Calcd. C, 70.79; H, 10.02; Found C, 70.62; H, 10.11.

(2*R*, 4*R*)-7-(Benzyloxy)-1-phenylheptane-2,4-diol (36):



36

To a stirred solution of compound **35** (0.5 g) in MeOH was added a catalytic amount of *p*-TSA at room temperature and the reaction mixture stirred for 30 min at the same temperature. Solid $NaHCO_3$ (0.1 g) was added and stirred for 30 min. The mixture was then filtered through a celite pad, washed with MeOH and concentrated to give crude compound which was purified by silica gel column chromatography (ethyl acetate:petroleum ether, 4:6) to furnish the alcohol **36** as a colorless oil.

Yield: 0.26 g, 90%

Mol. Formula: $C_{20}H_{26}O_3$

$[\alpha]_D^{25}$: + 5.20 (*c* 1.1, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 3373, 2957, 2857, 1602, 1495, 1454, 1217, 1093.

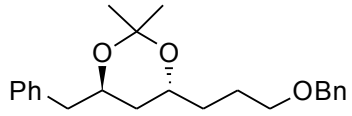
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.48-1.53 (m, 2H), 1.56-1.58 (m, 2H), 1.63-1.69 (m, 2H), 2.70-2.73 (m, 2H), 2.82 (bs, 1H), 3.41-3.48 (m, 3H), 3.81-3.92 (m, 1H), 4.06-4.11 (m, 1H), 4.44 (s, 2H), 7.14-7.17 (m, 3H), 7.21-7.30 (m, 7H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 26.1, 34.4, 41.8, 43.8, 68.6, 69.8, 70.3, 72.8, 126.1, 127.5, 127.6, 128.2, 128.3, 129.2, 137.9, 138.5 ppm.

MS (ESI): m/z 337.291 (M^++Na), 353.266 (M^++K).

Analysis Calcd. C, 76.40; H, 8.33; Found C, 76.12; H, 8.45.

(4*R*, 6*R*)-4-Benzyl-6-(3-(benzyloxy)propyl)-2,2-dimethyl-1,3-dioxane (37):



37

To a solution of the diol **36** (0.06 g, 0.19 mmol), in dry DCM (2 mL) was added 2,2-dimethoxypropane (2 mL), *p*-TsOH (0.02 g) and stirred overnight. Solid $NaHCO_3$ (0.05 g) was added and stirred for 30 min. The reaction mixture was filtered through a pad of neutral alumina and concentrated. Silica gel column chromatography using petroleum ether:ethyl acetate (24:1) gave **37** as a colorless liquid.

Yield: 0.053 g, 80%

Mol. Formula: $C_{23}H_{30}O_3$

$[\alpha]_D^{25}$: - 41.68 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 3028, 2926, 2856, 1604, 1454, 1262, 1118.

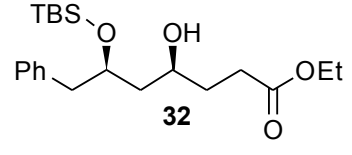
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.34 (s, 3H), 1.38 (s, 3H), 1.45-1.53 (m, 2H), 1.56-1.64 (m, 2H), 1.67-1.78 (m, 2H), 2.65-2.75 (m, 1H), 2.91-3.01 (m, 1H), 3.45-3.55 (m, 2H), 3.77-3.91 (m, 1H), 4.02-4.17 (m, 1H), 4.53 (s, 2H), 7.24-7.39 (m, 10H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 24.8, 25.8, 32.4, 38.1, 42.1, 66.5, 67.4, 70.1, 72.9, 100.3, 126.1, 127.5, 127.6, 128.2, 128.3, 129.2, 138.4, 138.6 ppm.

MS (ESI): m/z 355.478 (M^++H), 377.475 (M^++Na), 393.461 (M^++K).

Analysis Calcd. C, 77.93; H, 8.53; Found C, 77.67; H, 8.65.

(4*S*,6*R*)-Ethyl 6-(*tert*-butyldimethylsilyloxy)-4-hydroxy-7-phenylheptanoate (32):



32

To a solution of ethyl ester **29** (1.0 g, 2.97 mmol) in CH_2Cl_2 (15 mL), DIBAL-H (1.43 mL 2.3 M solution in toluene, 3.26 mmol) was added at -78 °C under argon atmosphere. The reaction was stirred at this temperature for 40 min. Then a solution of tartaric acid (5 mL) was added. The resulting mixture was stirred for 15 min and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL), the combined organic layers were dried (Na_2SO_4), filtered and evaporated under reduced pressure to give

aldehyde as a colorless liquid, which was directly used in the next step without further purification. Following the general procedure A (L-proline as a catalyst) **6** was obtained as a crude product, which was found to be inseparable mixture of *syn*: *anti* (10: 1) diols with *syn* diol **32** as a major component.

Yield: 0.629g, 63%

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

IR ($CHCl_3$, cm^{-1}): ν_{max} 3493, 2930, 1727, 1603, 1454, 1216.

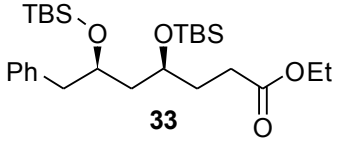
^{1}H NMR (200 MHz, $CDCl_3$): (Major isomer of diastereomeric mixture): δ 0.03 (s, 3H), 0.11 (s, 3H), 0.91 (m, 9H), 1.21-1.26 (m, 4H), 1.50-1.53 (m, 1H), 1.66-1.70 (m, 2H), 2.32-2.39 (m, 2H), 2.68-2.90 (m, 2H), 3.36-3.42 (m, 1H), 3.70-3.80 (m, 1H), 4.09-4.10 (m, 2H), 7.17-7.27 (m, 5H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): (Major isomer of diastereomeric mixture): δ -4.8, -4.4, 14.1, 17.8, 25.8, 30.2, 32.4, 42.8, 44.8, 60.2, 69.7, 74.0, 126.3, 128.3, 129.5, 132.0, 138.1, 173.9 ppm.

MS (ESI): m/z 381.3861 (M^++H), 403.4595 (M^++Na), 419.4212 (M^++K).

Analysis Calcd. C, 66.27; H, 9.53; Found C, 66.48; H, 9.39.

(4*S*, 6*R*)-Ethyl 4,6-bis(*tert*-butyldimethylsilyloxy)-7-phenylheptanoate (33):



33

To an ice-cold stirred solution of **32** (0.5 g, 1.31 mmol) in CH_2Cl_2 (5 mL) were added 2,6-lutidine (0.38 mL, 3.28 mmol) and TBSOTf (0.45 mL, 1.97 mmol) at 0 °C. The resulting mixture was stirred for 1 h at 0 °C before H_2O (10 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Silica gel column chromatography (petroleum ether) of the crude product gave TBS ether **33** as a colourless liquid.

Yield: 0.64 g, 89%

Mol. Formula: $C_{27}H_{50}O_4Si_2$

$[\alpha]_D^{25}$: - 3.54 (*c* 1.22, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 3020, 2857, 1729, 1603, 1559, 1538, 1404, 1216.

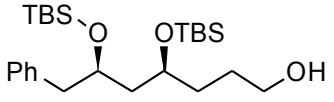
^{1}H NMR (200 MHz, $CDCl_3$): δ -0.15 (s, 3H), -0.02 (s, 3H), 0.06 (s, 6H), 0.86 (s, 9H), 0.89 (s, 9H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.44-1.55 (m, 1H), 1.62-1.74 (m, 2H), 1.76-1.90 (m, 1H), 2.29 (t, *J* = 7.7 Hz, 2H), 2.73 (dd, *J* = 1.6, 8.7 Hz, 1H), 2.76 (dd, *J* = 1.6, 8.7 Hz, 1H), 3.83-4.01 (m, 2H), 4.10 (q, *J* = 7.2 Hz, 2H), 7.14-7.31 (m, 5H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ -4.8, -4.5, -4.4, 14.2, 17.9, 18.0, 25.8, 29.6, 31.8, 44.2, 60.2, 68.3, 70.7, 126.1, 128.1, 129.7, 138.7, 173.7 ppm.

MS (ESI): m/z 495.4796 (M^++H), 517.6717 (M^++Na), 533.4339 (M^++K).

Analysis Calcd. C, 65.53; H, 10.18; Found C, 65.27; H, 10.04.

(4*S*, 6*R*)-4,6-Bis(*tert*-butyldimethylsilyloxy)-7-phenylheptan-1-ol (38):



38

To a solution of **33** (0.63 g, 1.27 mmol) in dry DCM (7 mL) at 0 °C was added dropwise DIBAL-H (1.59 mL, 19.5 mmol, 1.99 M in toluene) through a syringe. The reaction mixture was allowed to warm to room temperature over 1 h, then recooled to 0 °C and treated with sat. aqueous solution of sodium potassium tartrate (5 mL). The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were washed with water, brine, dried (Na_2SO_4), filtered and concentrated in vacuo. Silica gel column chromatography of the crude product using petroleum ether:ethyl acetate (8:2) as eluent gave **38** as colorless oil.

Yield: 0.47 g, 82%

Mol. Formula: $C_{25}H_{48}O_3Si_2$

$[\alpha]_D^{25}$: - 6.5 (*c* 1.8, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 3300, 3087, 2858, 1603, 1495, 1454, 1256, 1216, 1030.

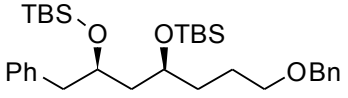
^{1}H NMR (400 MHz, $CDCl_3$): δ -0.12 (s, 3H), 0.00 (s, 3H), 0.09 (s, 3H), 0.10 (s, 3H), 0.89 (s, 9H), 0.91 (s, 9H), 1.47-1.58 (m, 4H), 1.63- 1.71 (m, 2H), 1.84 (bs, 1H), 2.72-2.81 (m, 2H), 3.56-3.64 (m, 2H), 3.90-3.96 (m, 2H), 7.18-7.23 (m, 3H), 7.27-7.31 (m, 2H) ppm. **^{13}C**

NMR (100 MHz, $CDCl_3$): δ -4.8, -4.4, 18.0, 25.9, 27.8, 33.2, 44.0, 44.3, 63.0, 69.2, 70.9, 126.1, 128.1, 129.7, 138.8 ppm.

MS (ESI): m/z 453.4679 (M^++H), 475.6094 (M^++Na).

Analysis Calcd. C, 66.31; H, 10.68; Found C, 66.54; H, 10.51.

(5*R*, 7*S*)-5-Benzyl-7-(3-(benzyloxy)propyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecane (39):



39

To a solution of **38** (0.14 g, 0.31 mmol) in dry DMF (2 mL) was added sodium hydride (60%, 0.024 g, 0.62 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 benzyl bromide (0.55 mL, 0.46 mmol) and *tetra n*-butylammonium iodide (catalytic) with further stirring for 1 h at the same 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 5 mL). The combined organic layers were washed with water (3 x 5 mL), brine, dried (Na_2SO_4) and concentrated. The residual oil was purified by silica gel column chromatography (EtOAc/petroleum ether, 1:50) to furnish the protected alcohol **39** as a colorless oil.

Yield: 0.15 g, 90%

Mol. Formula: $C_{32}H_{54}O_3Si_2$

$[\alpha]_D^{25}$: + 4.69 (*c* 1.2, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 2952, 2856, 1461, 1454, 1255, 1096.

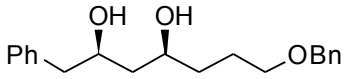
^{1}H NMR (200 MHz, $CDCl_3$): δ -0.24 (s, 3H), -0.11 (s, 3H), 0.0 (s, 3H), 0.01 (s, 3H) 0.80 (s, 9H), 0.84 (s, 9H), 1.46-1.58 (m, 6H), 2.57-2.78 (m, 2H), 3.39 (t, *J* = 6.3 Hz, 2H), 3.73 -3.95 (m, 2H), 4.44 (s, 2H), 7.13-7.28 (m, 10H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ -4.8, -4.3, 18.0, 25.1, 25.9, 33.6, 44.2, 44.7, 69.3, 70.6, 70.9, 72.7, 126.0, 127.4, 127.5, 128.1, 128.3, 129.8, 138.6, 139.0 ppm.

MS (ESI): m/z 543.2448 (M^++H), 565.247 (M^++Na), 581.2300, (M^++K).

Analysis Calcd. C, 70.79; H, 10.02; Found C, 70.91; H, 10.15.

(2*R*, 4*S*)-7-(Benzyloxy)-1-phenylheptane-2,4-diol (40):



40

To a stirred solution of compound **39** (0.5 gm) in MeOH was added a catalytic amount of *p*-TSA at room temperature and the reaction mixture stirred for 30 min at the same temperature. Solid $NaHCO_3$ (0.1 g) was added and stirred for 30 min. The mixture was then filtered through a celite pad, washed with MeOH and concentrated to give crude compound which was purified by silica gel column chromatography (ethyl acetate:petroleum ether, 4:6) to furnish the alcohol **40** as a colorless oil.

Yield:0.28 g, 96%

Mol. Formula: $C_{20}H_{26}O_3$

$[\alpha]_D^{25}$: - 2.49 (*c* 0.8, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 3373, 2957, 2857, 1602, 1495, 1454, 1217, 1093.

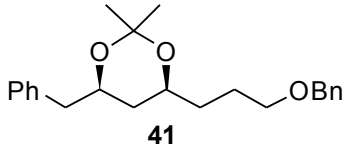
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (bs, 2H), 1.54-1.60 (m, 2H), 1.61-1.68 (m, 2H), 1.76 (quintet, *J* = 6.0 Hz, 2H), 2.77 (dd, *J* = 7.0, 13.3 Hz, 1H), 2.85 (dd, *J* = 7.0, 13.3 Hz, 1H), 3.55 (t, *J* = 6.0 Hz, 2H), 3.85-3.90 (m, 1H), 4.10-4.18 (m, 1H), 4.55 (s, 2H), 7.25-7.31 (m, 3H), 7.33-7.41 (m, 7H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 25.9, 35.5, 42.1, 44.4, 70.4, 72.5, 73.1, 73.7, 126.4, 127.7, 128.4, 129.4, 137.9, 138.2 ppm.

MS (ESI): m/z 337.291 (M^++Na), 353.266 (M^++K).

Analysis Calcd. C, 76.40; H, 8.33; Found C, 76.61; H, 8.48.

(4*R*, 6*S*)-4-Benzyl-6-(3-(benzyloxy)propyl)-2,2-dimethyl-1,3-dioxane (41):



41

To a solution of the diol **40** (0.06 g, 0.19 mmol), in dry DCM (2 mL) was added 2,2-dimethoxypropane (2 mL), *p*-TsOH (0.020 g) and stirred overnight. Solid $NaHCO_3$ (0.05 g) was added and stirred for 30 min. The reaction mixture was filtered through a pad of

neutral alumina and concentrated. Silica gel column chromatography using petroleum ether:ethyl acetate (24:1) gave **41** as a colorless liquid.

Yield: 0.057g, 85%

Mol. Formula: $C_{23}H_{30}O_3$

$[\alpha]_D^{25}$: - 10.71 (*c* 0.6, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 2926, 2856, 1604, 1454, 1262, 1118.

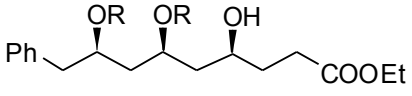
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (s, 6H), 1.46-1.56 (m, 2H), 1.59-1.71 (m, 4H), 2.62 (dd, *J* = 5.5, 13.3 Hz, 1H), 2.93 (dd, *J* = 5.5, 13.3 Hz, 1H), 3.46 (dt, *J* = 1.8, 6.3 Hz, 2H), 3.71-3.78 (m, 1H), 3.99-4.05 (m, 1H), 4.48 (s, 2H), 7.22-7.24 (m, 3H), 7.27-7.33 (m, 7H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 19.8, 25.3, 30.2, 32.9, 36.3, 43.0, 68.7, 70.1, 72.8, 98.5, 126.2, 127.5, 127.6, 128.2, 128.3, 129.4, 137.9, 139.5 ppm.

MS (ESI): m/z 355.478 (M^++H), 377.475 (M^++Na), 393.461 (M^++K).

Analysis Calcd. C, 77.93; H, 8.53; Found C, 77.67; H, 8.69.

(4*S*, 6*S*, 8*R*)-Ethyl 6,8-bis(*tert*-butyldimethylsilyloxy)-4-hydroxy-9-phenylnonanoate (42):



R = TBS **42**

To a solution of ethyl ester **33** (1.00 g, 2.02 mmol) in CH_2Cl_2 (15 mL), was added DIBAL-H (1.11 mL 1.99 M solution in toluene, 2.22 mmol) at -78 °C under argon atmosphere. The reaction was stirred at this temperature for 40 min. Then a solution of tartaric acid (5 mL) was added. The resulting mixture was stirred for 15 min and the organic layer separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL), the combined organic layers were dried (Na_2SO_4), filtered and evaporated under reduced pressure to give aldehyde as a colorless liquid, which was directly used in the next step without any further purification. Following the general procedure A (L-proline as a catalyst) **16** was obtained as a crude product, which was found to be inseparable mixture of *syn*:*anti* (10:1) diols with *syn* diol **42** as a major component.

Yield: 0.66 g, 61%

Mol. Formula: $C_{29}H_{54}O_5Si_2$

IR ($CHCl_3$, cm^{-1}): ν_{max} 3436, 2929, 1726, 1604, 1514, 1463, 1215, 1093.

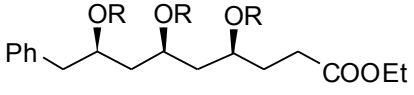
^{1}H NMR (200 MHz, $CDCl_3$): (Major isomer of diastereomeric mixture): δ -0.14 (s, 3H), 0.02 (s, 3H), 0.08 (s, 3H), 0.09 (s, 3H), 0.87 (m, 9H), 0.90 (m, 9H), 1.25-1.26 (m, 4H), 1.50-1.55 (m, 2H), 1.66-1.75 (m, 4H), 2.25-2.32 (m, 1H), 2.44-2.54 (m, 1H), 2.71-2.81 (m, 2H), 3.55-3.60 (m, 2H), 3.89-3.92 (m, 2H), 4.09-4.16 (m, 1H), 7.16-7.20 (m, 3H) 7.25-7.29 (m, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): (Major isomer of diastereomeric mixture): δ -4.7, -4.4, 18.0, 25.9, 27.8, 29.7, 33.2, 43.9, 44.4, 63.1, 69.1, 70.9, 126.1, 128.1, 129.8, 138.8, 177.1 ppm.

MS (ESI): m/z 539.4416 (M^++H), 561.4312 (M^++Na), 579.3909 (M^++K).

Analysis Calcd. C, 64.63; H, 10.10; Found C, 64.88; H, 10.23.

(4*S*, 6*S*, 8*R*)-Ethyl 4,6,8-tris(*tert*-butyldimethylsilyloxy)-9-phenylnonanoate (43):



R = TBS **43**

To an ice-cold stirred solution of **42** (0.2 g, 0.9 mmol) in CH_2Cl_2 (2 mL) were added 2,6-lutidine (0.26 mL, 2.25 mmol) and TBSOTf (0.310 mL, 1.35 mmol) at 0 °C. The resulting mixture was stirred for 1 h at 0 °C before H_2O (20 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Silica gel column chromatography using petroleum ether:ethyl acetate (99:1) of the crude product gave TBS ether **43** as a colourless liquid.

Yield: 0.21 g, 88%

Mol. Formula: $C_{35}H_{68}O_5Si_3$

$[\alpha]_D^{25}$: + 5.67 (*c* 0.8, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 2929, 1730, 1471, 1216.

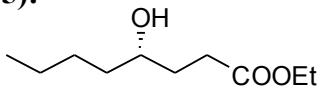
^{1}H NMR (200 MHz, $CDCl_3$): δ -0.19 (s, 3H), -0.05 (s, 3H), 0.04 (s, 6H), 0.06 (s, 3H), 0.08 (s, 3H), 0.85 (s, 9H), 0.89 (s, 9H), 0.90 (s, 9H), 1.26-1.30 (m, 3H), 1.42-1.49 (m, 2H), 1.55-1.61 (m, 4H), 2.02-2.10 (m, 2H), 2.70 (dd, *J* = 6.5, 13.3 Hz, 1H), 2.78 (dd, *J* = 6.5, 13.3 Hz, 1H), 3.55-3.61(m, 2H), 3.81-3.97 (m, 2H), 4.00-4.18 (m, 1H), 7.15-7.27 (m, 5H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ -5.3, -4.8, -4.7, -4.3, 18.0, 18.1, 18.4, 25.9, 26.0, 28.3, 29.7, 33.5, 44.2, 44.7, 63.4, 69.4, 70.9, 126.0, 128.1, 129.8, 139.1, 173.8 ppm.

Analysis Calcd. C, 64.36; H, 10.49; Found C, 64.54; H, 10.61.

Synthesis of (2*S*, 5*S*)-2-hydroxyhexyl cyclopentanone

(*S*)-Ethyl 4-hydroxyoctanoate (45):



45

Commercially available hexanal **44** (2.0 g, 20 mmol) was subjected to the general prodecure A (D-proline as a catalyst) to furnish crude product, which was purified by column chromatography using petroleum ether: EtOAc (95:5) to give (*S*)-ethyl 4-hydroxyoctanoate **45** as colorless liquid.

Yield: 2.44 g, 65 %

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

$[\alpha]_D^{25}$: - 0.93 (*c* 2.24, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3430, 2934, 1718, 1465, 1177.

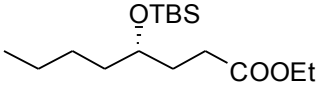
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.86-0.93 (m, 3H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.32-1.36 (m, 3H), 1.41-1.45 (m, 2H), 1.62-1.93 (m, 4H), 2.44 (t, *J* = 7.2 Hz, 2H), 3.55-3.67 (m, 1H), 4.11 (q, *J* = 7.2 Hz, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 13.8, 22.4, 27.5, 30.4, 31.9, 36.9, 60.1, 70.5, 174.0 ppm.

MS (ESI): m/z 211.2468 (M^++Na).

Analysis Calcd. C, 63.80; H, 10.71; Found C, 63.59; H, 10.91.

(*S*)-Ethyl 4-(*tert*-butyldimethylsilyloxy)octanoate (46):



46

Following the procedure as described for the synthesis of compound **29** , (*S*)-ethyl 4-(*tert*-butyldimethylsilyloxy)octanoate was obtained from compound **45** (1g, 5.3 mmol) as a

crude product which was purified by column chromatography using petroleum ether: EtOAc (99:1) to give (*S*)-ethyl 4-(*tert*-butyldimethylsilyloxy)octanoate **46** as colorless liquid.

Yield:1.48 g, 92%

Mol. Formula: $C_{16}H_{34}O_3Si$

$[\alpha]_D^{25}$: + 9.96 (*c* 1.78, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 2858, 1726, 1463, 1256.

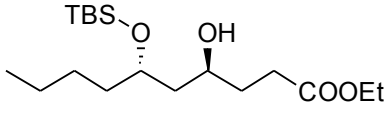
^{1}H NMR (400 MHz, $CDCl_3$): δ -0.04 (s, 6H), 0.89 (s, 12H), 1.24-1.30 (m, 7H), 1.41-1.46 (m, 2H), 1.65-1.72 (m, 1H), 1.77-1.85 (m, 1H), 2.33-2.38 (m, 2H), 3.66-3.72 (m, 1H), 4.12 (q, *J* = 7.2 Hz, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ -4.9, -4.7, 13.9, 14.0, 17.8, 22.6, 25.7, 27.2, 29.8, 31.5, 36.6, 59.9, 70.9, 173.5 ppm.

MS (ESI): m/z 325.4028 (M^++Na).

Analysis Calcd. C, 63.52; H, 11.33; Found C, 63.31; H, 11.17.

(4*S*, 6*S*)-Ethyl 6-(*tert*-butyldimethylsilyloxy)-4-hydroxydecanoate (47):



47

Following the prodecure as described for the synthesis of **30**, crude (4*S*, 6*S*)-ethyl 6-(*tert*-butyldimethylsilyloxy)-4-hydroxydecanoate **47** was obtained (>95% diastereomeric excess) from compound **46** (1 g, 3.3 mmol) using L-proline as a catalyst. This compound was then purified by column chromatography using petroleum ether: EtOAc (95:5) to furnish (4*S*, 6*S*)-ethyl 6-(*tert*-butyldimethylsilyloxy)-4-hydroxydecanoate **47** as a colorless liquid.

Yield:0.69 g, 60%

Mol. Formula: $C_{18}H_{38}O_4Si$

$[\alpha]_D^{25}$: + 2.85 (*c* 1.40, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 3434, 2957, 1722, 1463, 1216.

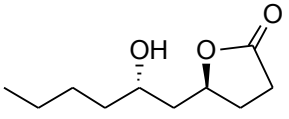
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.08 (s, 3H), 0.10 (s, 3H), 0.89 (s, 12H), 1.23-1.34 (m, 7H), 1.55-1.64 (m, 4H), 1.70-1.77 (m, 2H), 2.37-2.53 (m, 2H), 3.64 (bs, 1H), 3.95-4.01 (m, 2H), 4.10-4.16 (q, J = 7.3 Hz, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ -4.9, -4.7, 13.9, 14.1, 17.8, 22.7, 25.7, 27.9, 30.4, 32.8, 35.7, 41.2, 60.2, 67.3, 71.6, 173.9 ppm.

MS (ESI): m/z 347.5696 (M^++H), 369.5734 (M^++ Na), 385.5597 (M^++K).

Analysis Calcd. C, 62.38; H, 11.05; Found C, 62.61; H, 11.21.

(5*S*, 2*S*)-Hydroxyhexyl dihydrofuran-2(3*H*)-one (48):



48

To a stirred solution of compound **47** (0.5 g) in MeOH was added a catalytic amount of *p*-TSA at room temperature and the reaction mixture stirred overnight at the same temperature. Solid $NaHCO_3$ (0.1 g) was added and stirred for 30 min. The mixture was then filtered through a celite pad, washed with MeOH and concentrated and column purified using petroleum ether:ethyl acetate (80:20) to give (5*S*, 2*S*)-hydroxyhexyl dihydrofuran-2(3*H*)-one **48** as a pale yellow liquid.

Yield: 0.25 g, 94%

Mol. Formula: $C_{10}H_{18}O_3$

$[\alpha]_D^{25}$: + 58.92 (*c* 1.15, Et_2O).

IR ($CHCl_3$, cm^{-1}): ν_{max} 3468, 2931, 1764, 1459, 1185.

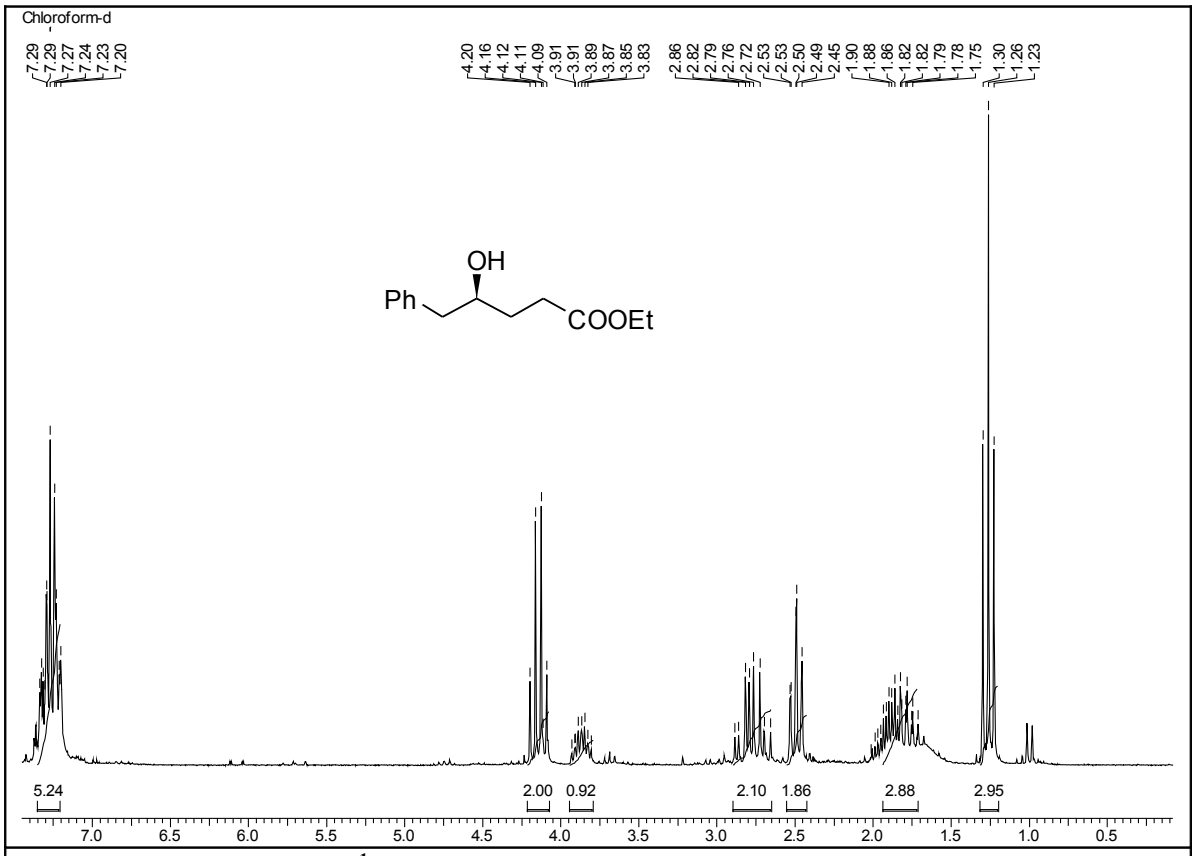
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.91 (t, J = 7.1 Hz, 3H), 1.28-1.39 (m, 3H), 1.41-1.48 (m, 2H), 1.60-1.89 (m, 3H), 1.92-1.99 (m, 2H), 2.29-2.41 (m, 1H), 2.50-2.59 (m, 2H), 3.81-3.92 (m, 1H) 4.73-4.87 (m, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 22.5, 27.5, 28.4, 28.8, 37.6, 43.1, 68.2, 78.2, 177.3 ppm.

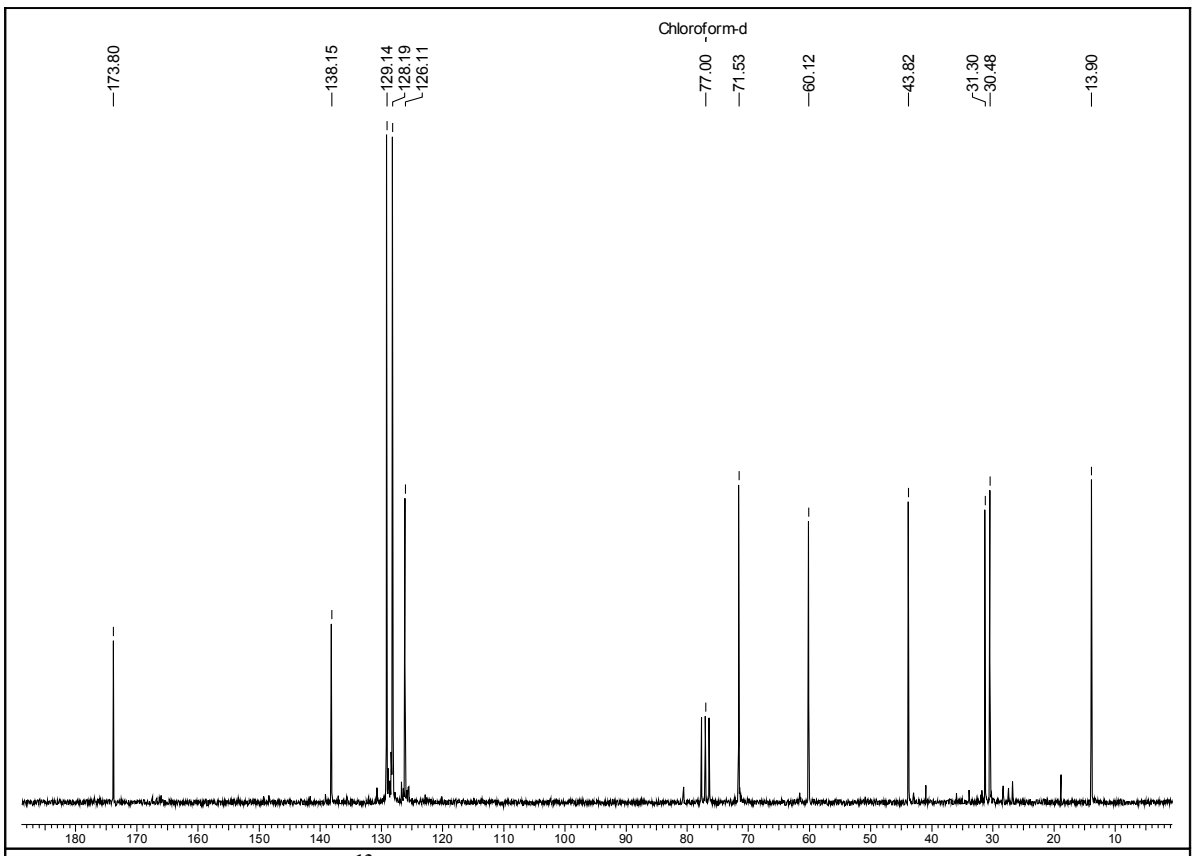
MS (ESI): m/z 209.3111 (M^++Na), 225.3125 (M^++K).

Analysis Calcd. C, 64.49; H, 9.74; Found C, 64.70; H, 9.56.

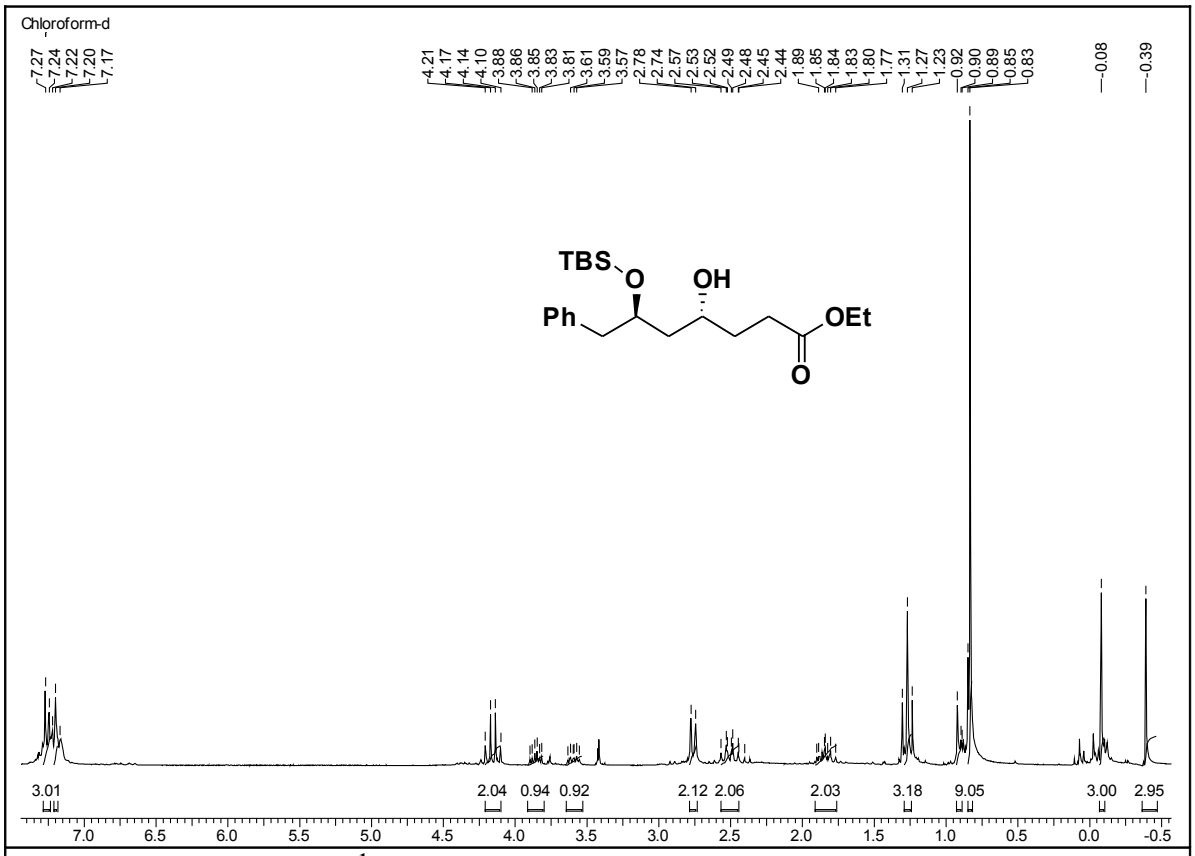
4.1.7. Spectra



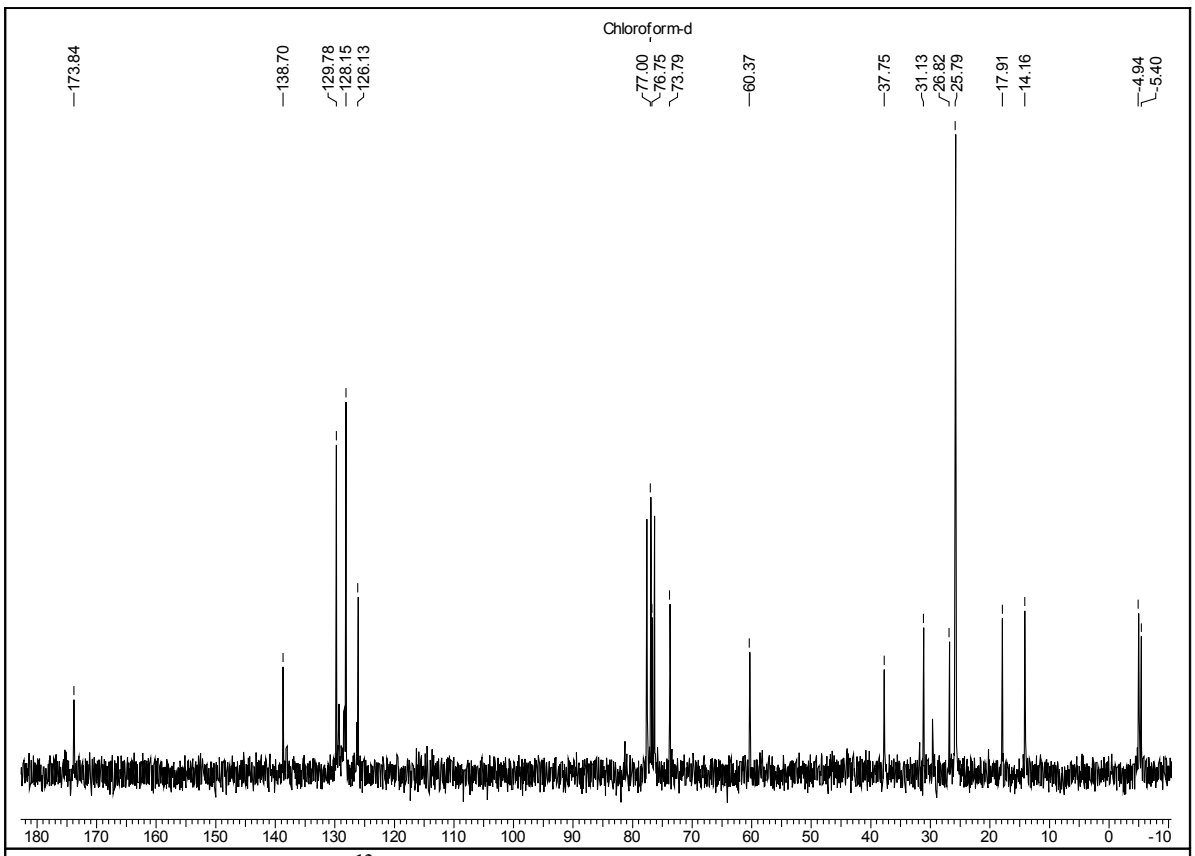
^{1}H-NMR of compound 28 in $CDCl_3$



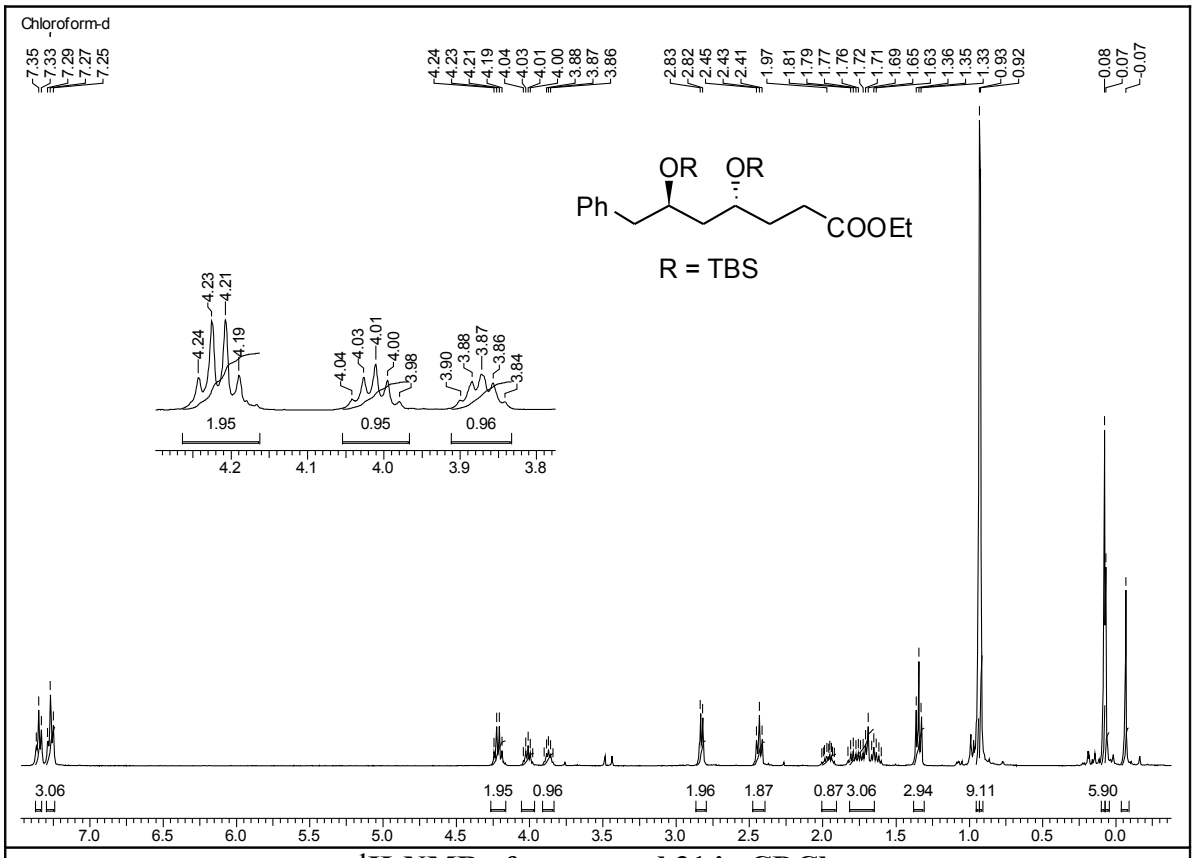
^{13}C-NMR of compound 28 in $CDCl_3$



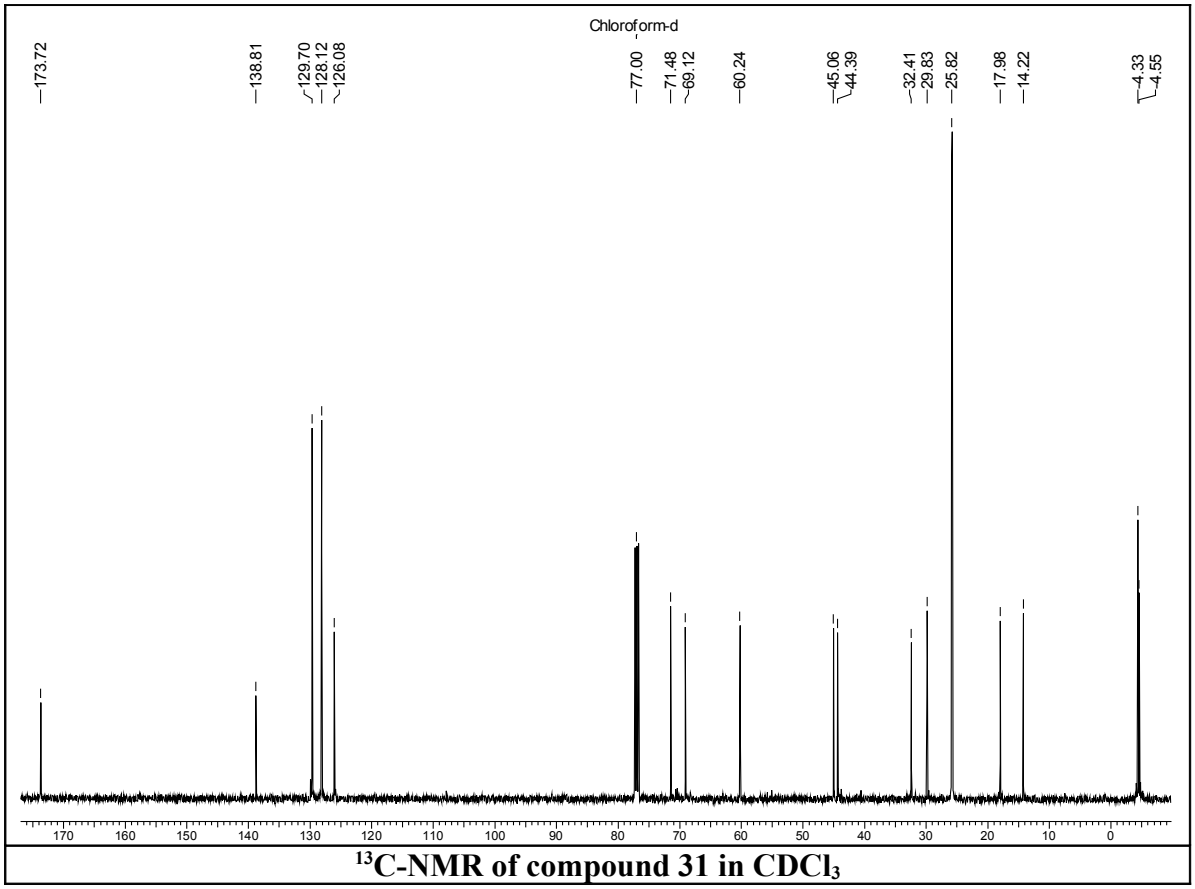
^{1}H-NMR of compound 30 in $CDCl_3$



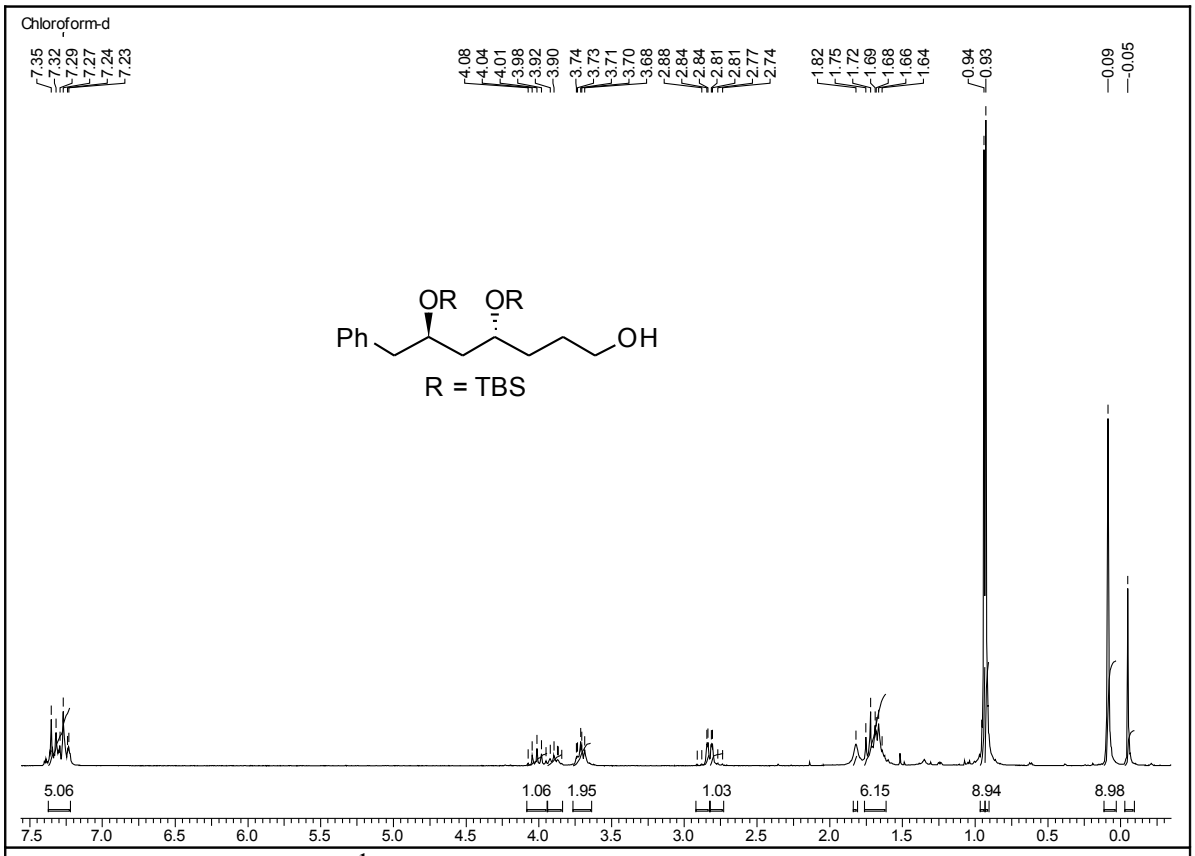
^{13}C-NMR of compound 30 in $CDCl_3$



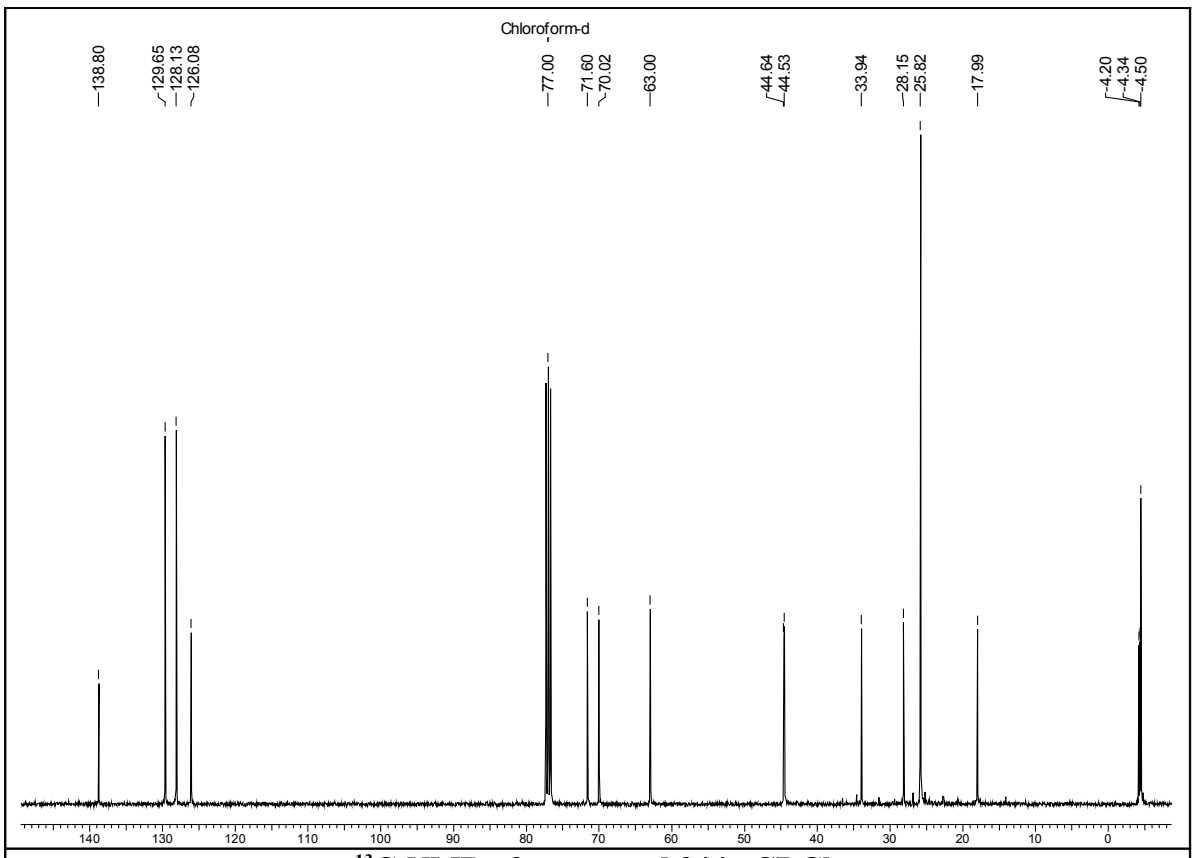
^{1}H-NMR of compound 31 in $CDCl_3$



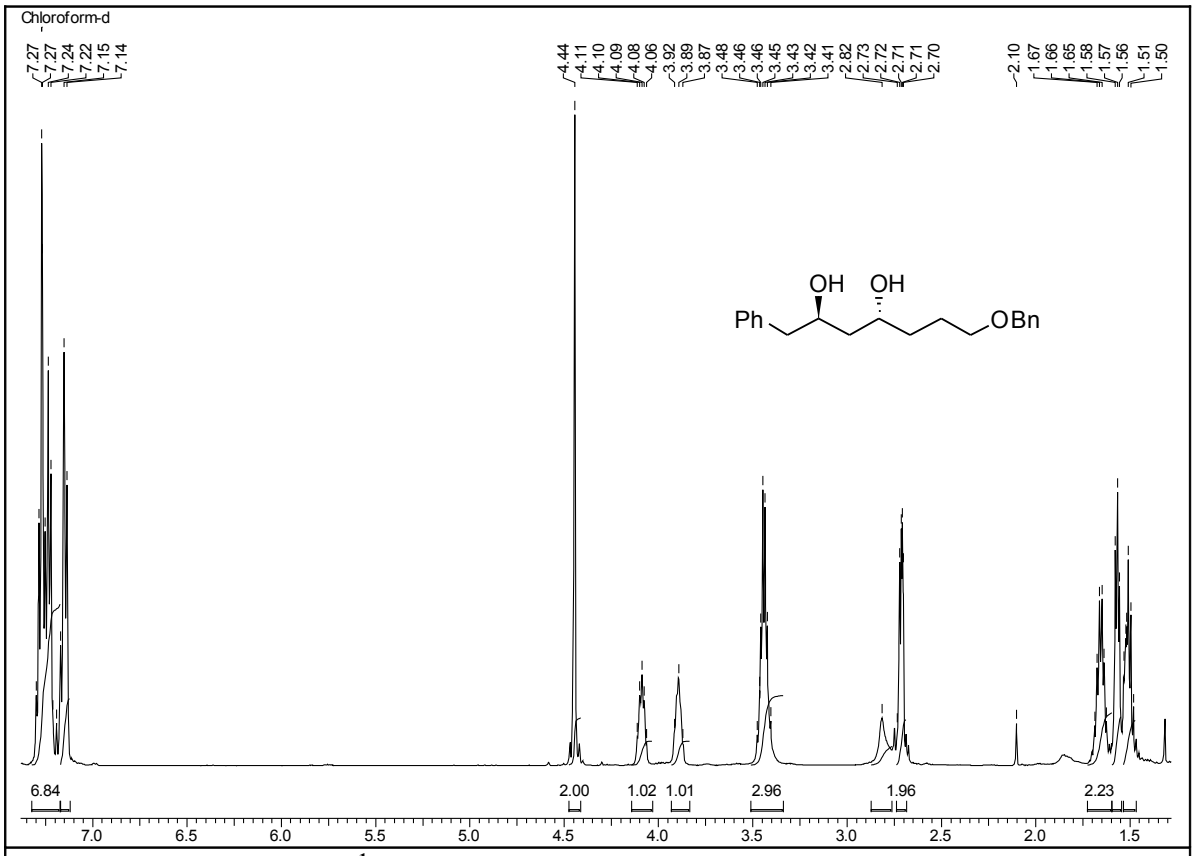
^{13}C-NMR of compound 31 in $CDCl_3$



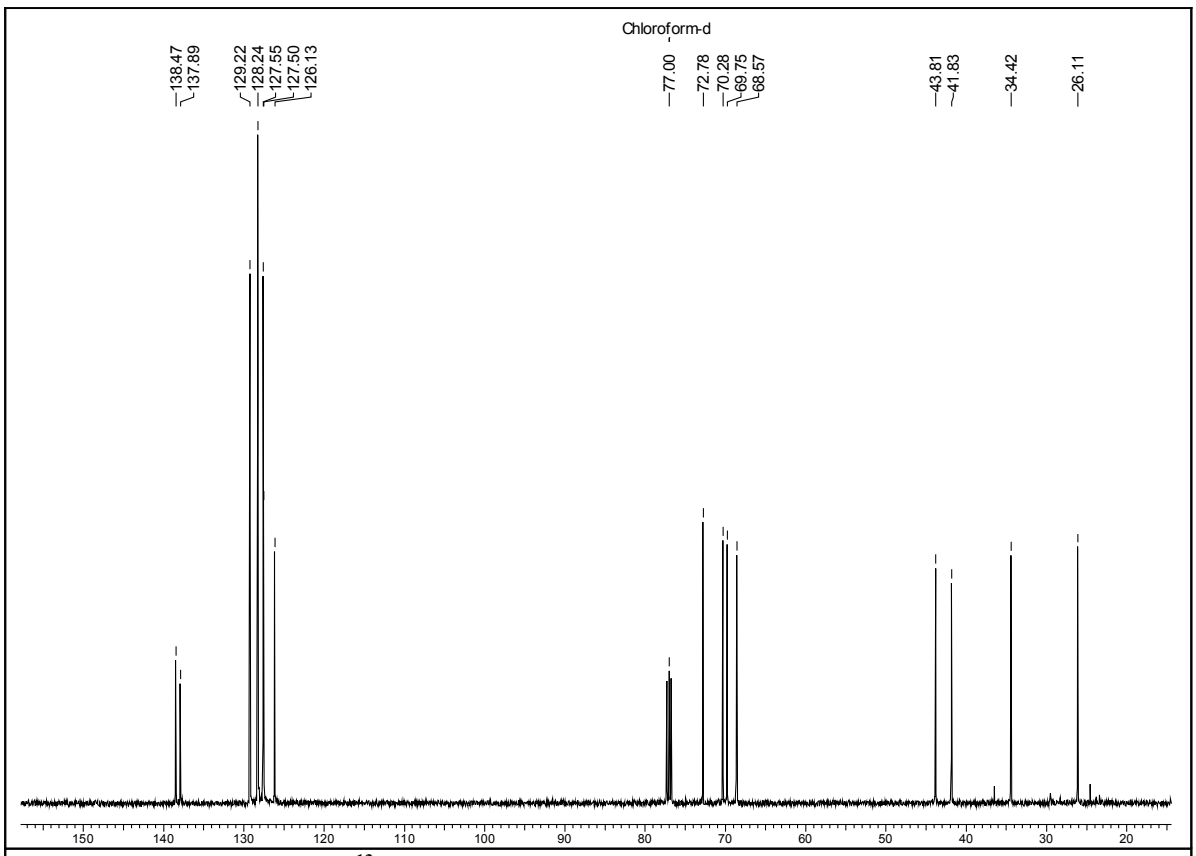
^{1}H-NMR of compound 34 in $CDCl_3$



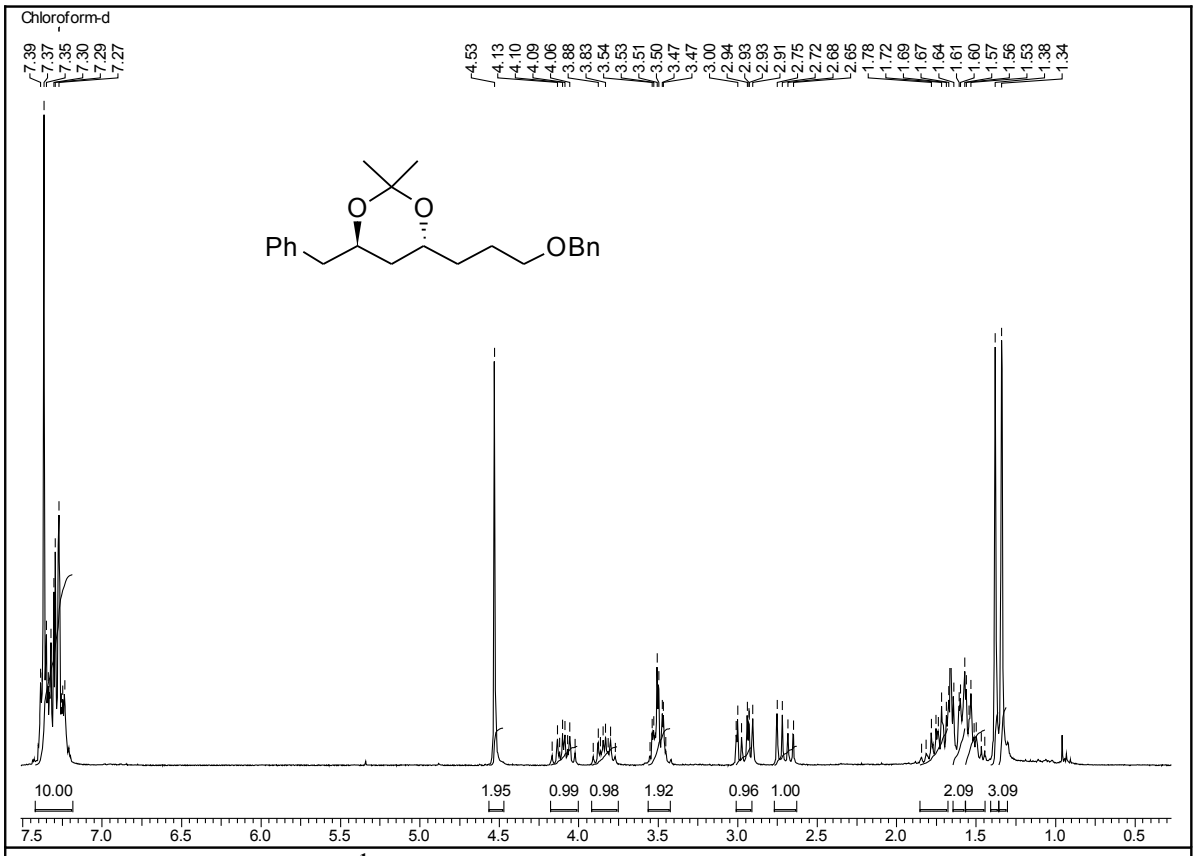
^{13}C-NMR of compound 34 in $CDCl_3$



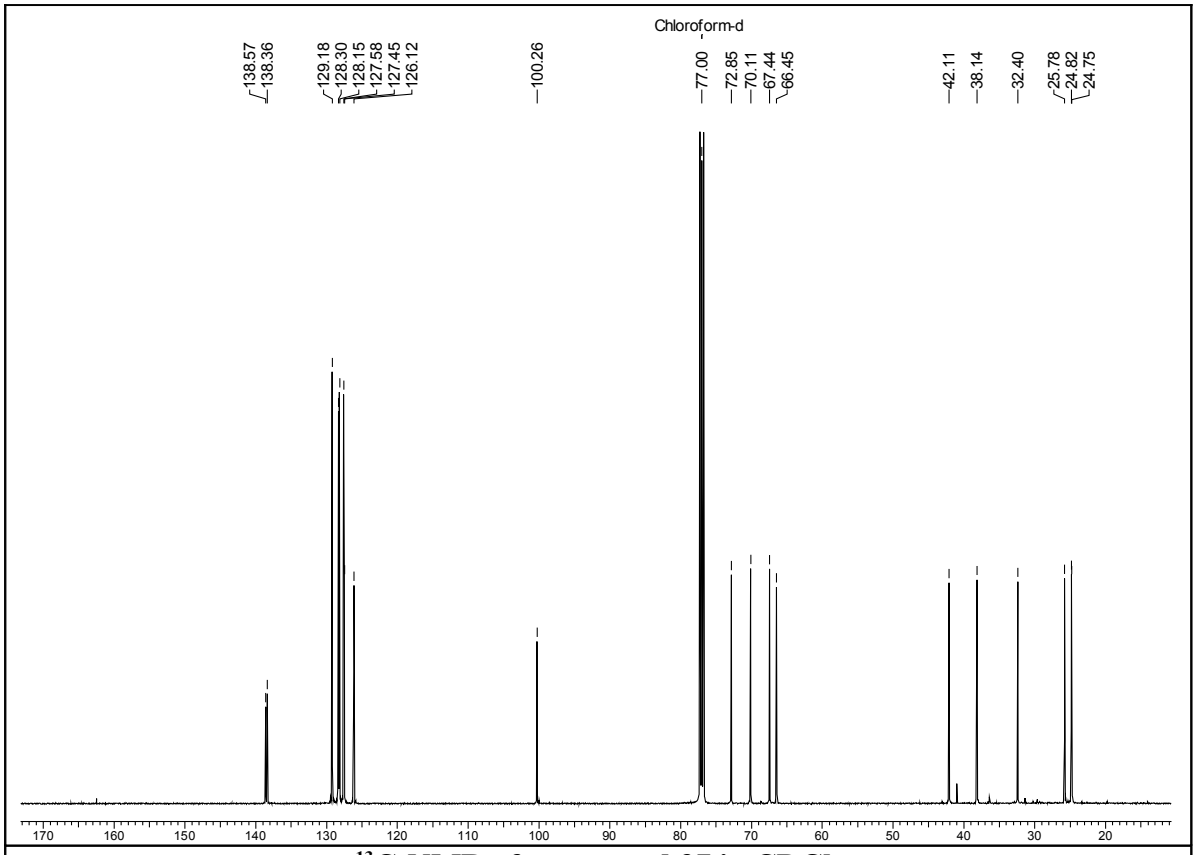
^{1}H-NMR of compound 36 in $CDCl_3$



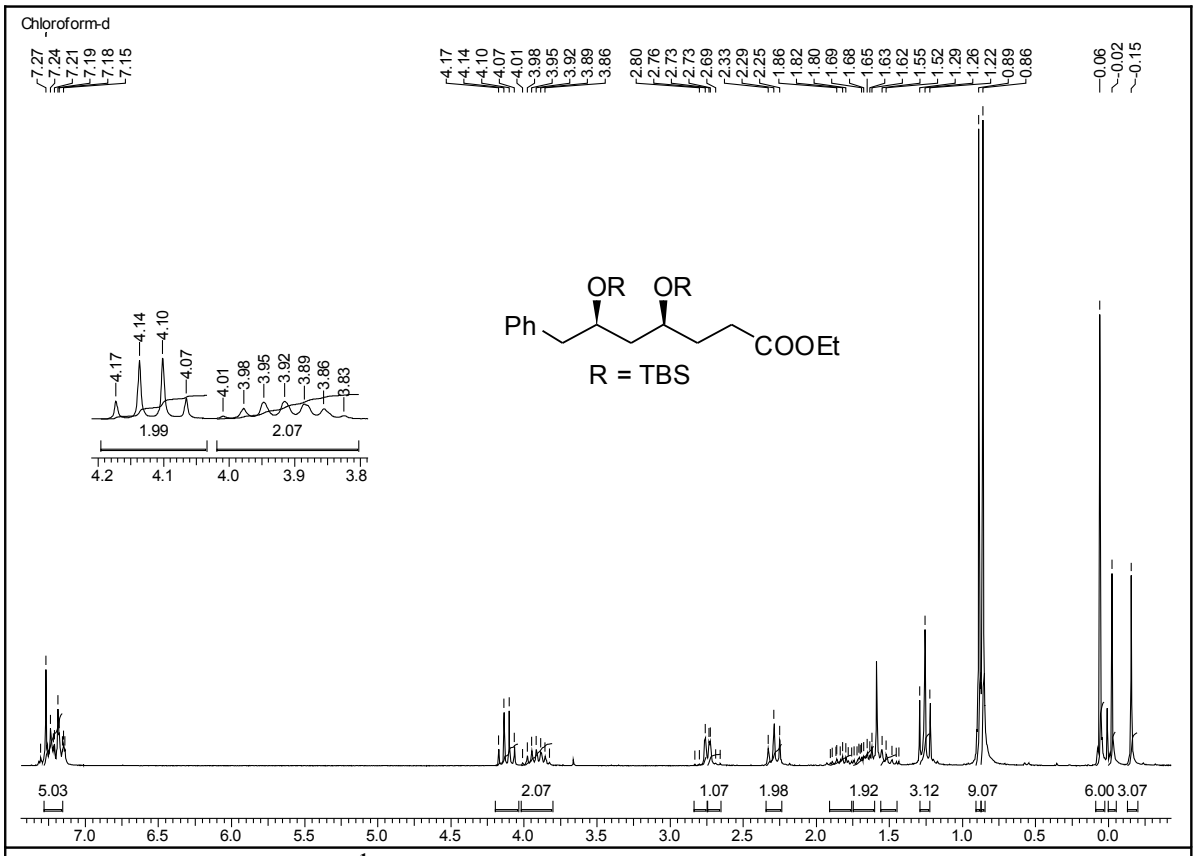
^{13}C-NMR of compound 36 in $CDCl_3$



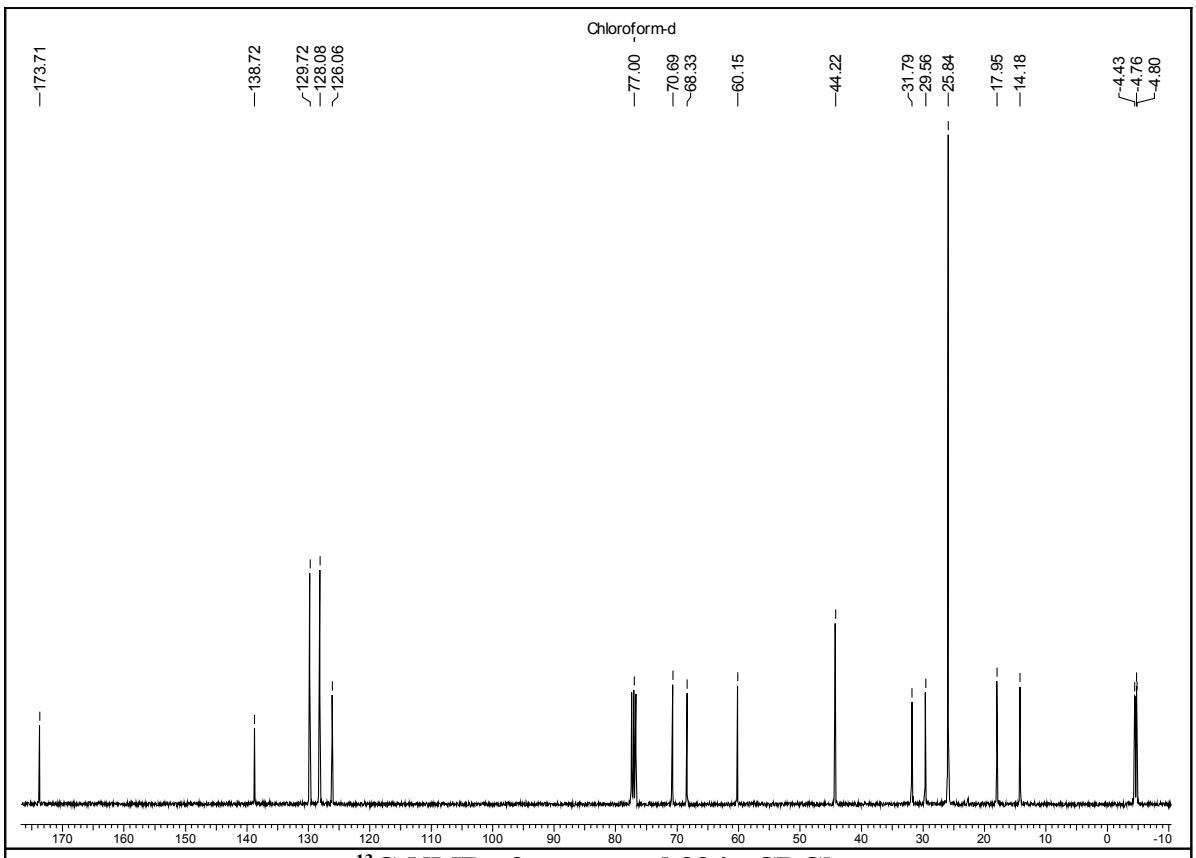
^{1}H-NMR of compound 37 in $CDCl_3$



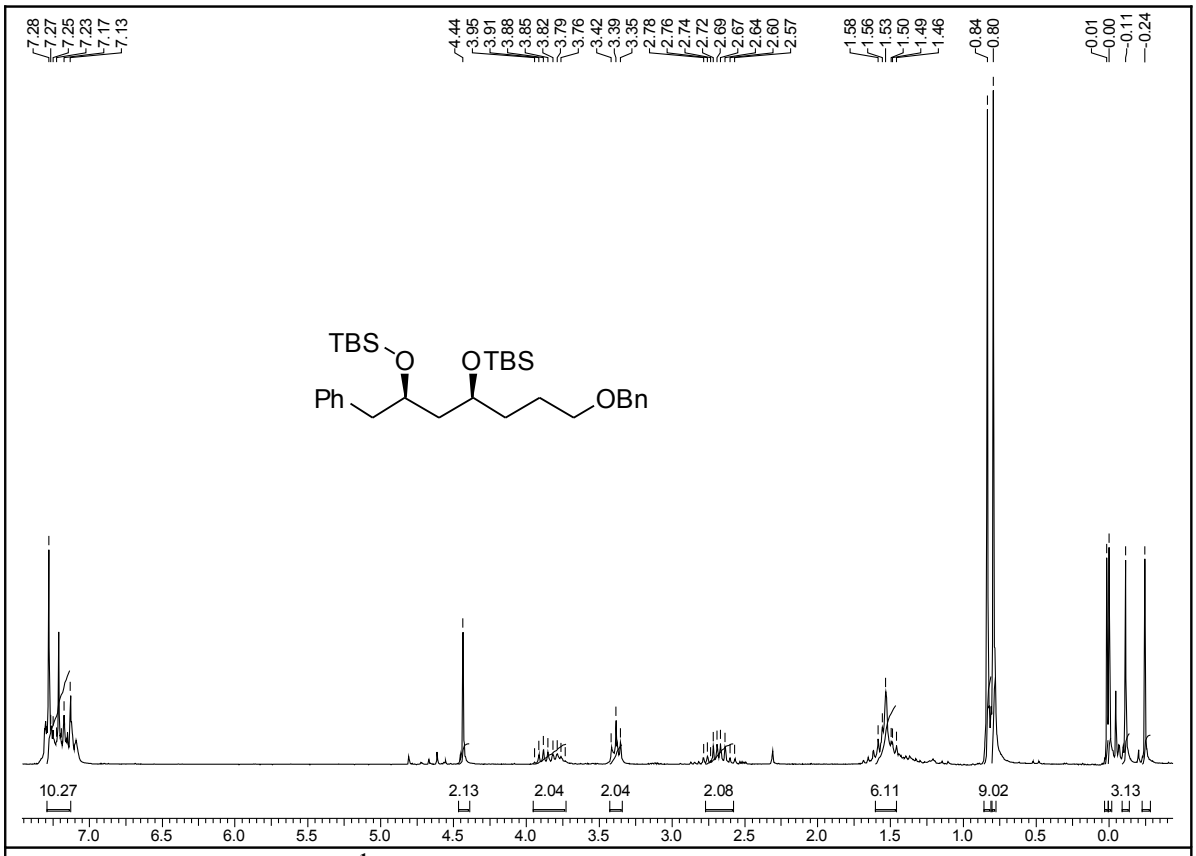
^{13}C-NMR of compound 37 in $CDCl_3$



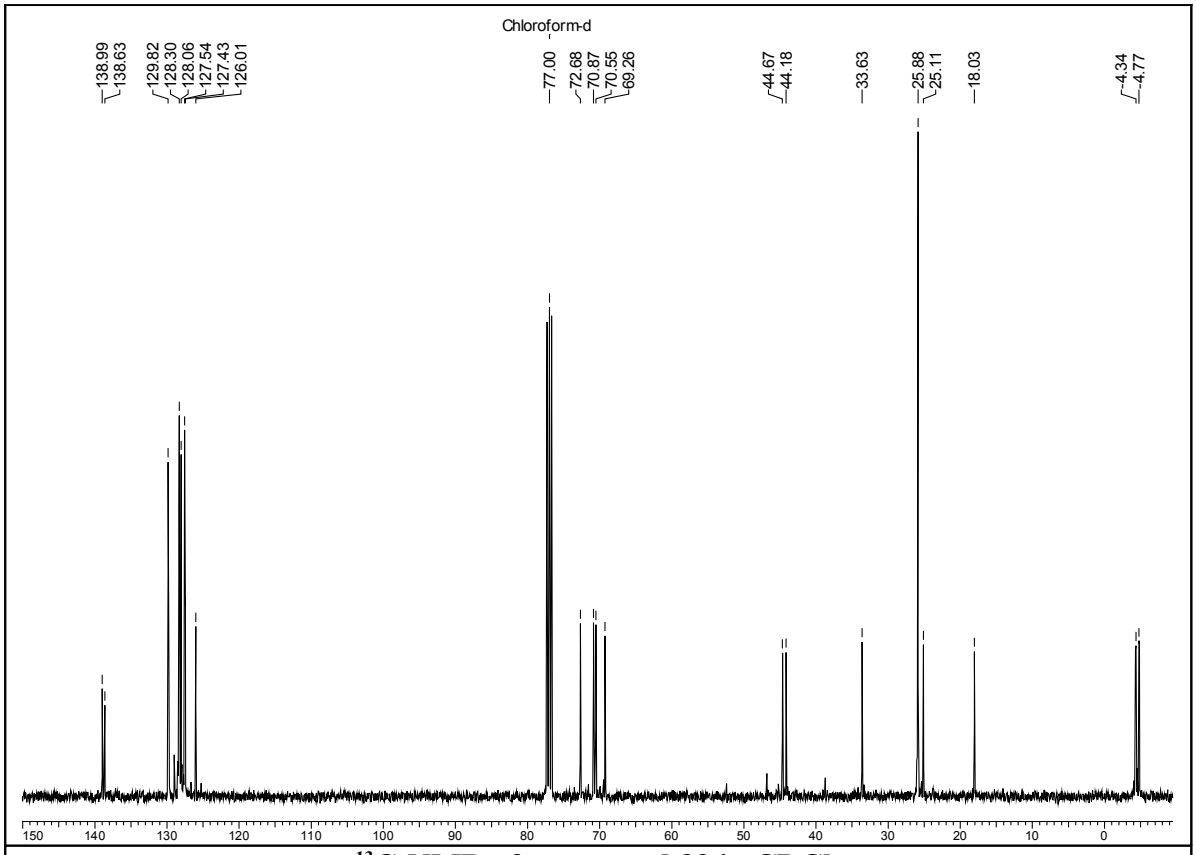
^{1}H-NMR of compound 33 in $CDCl_3$



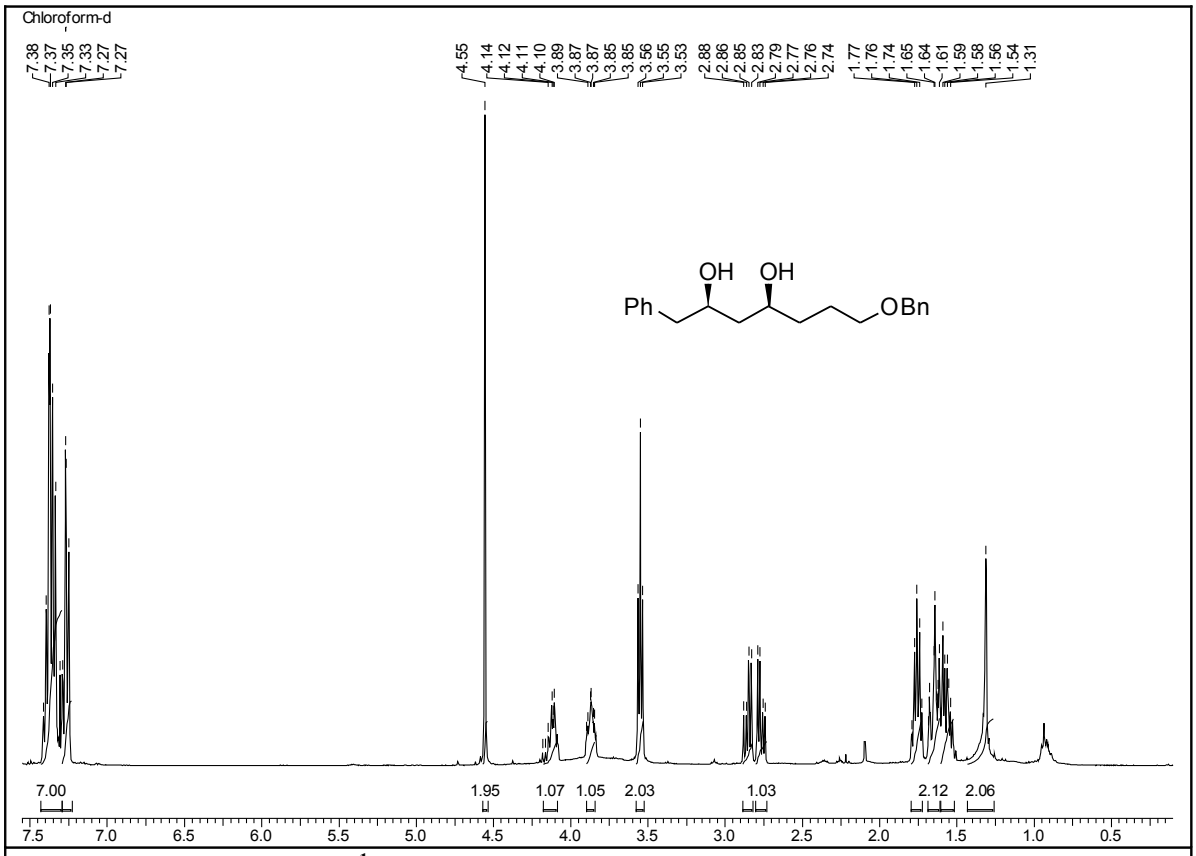
^{13}C-NMR of compound 33 in $CDCl_3$



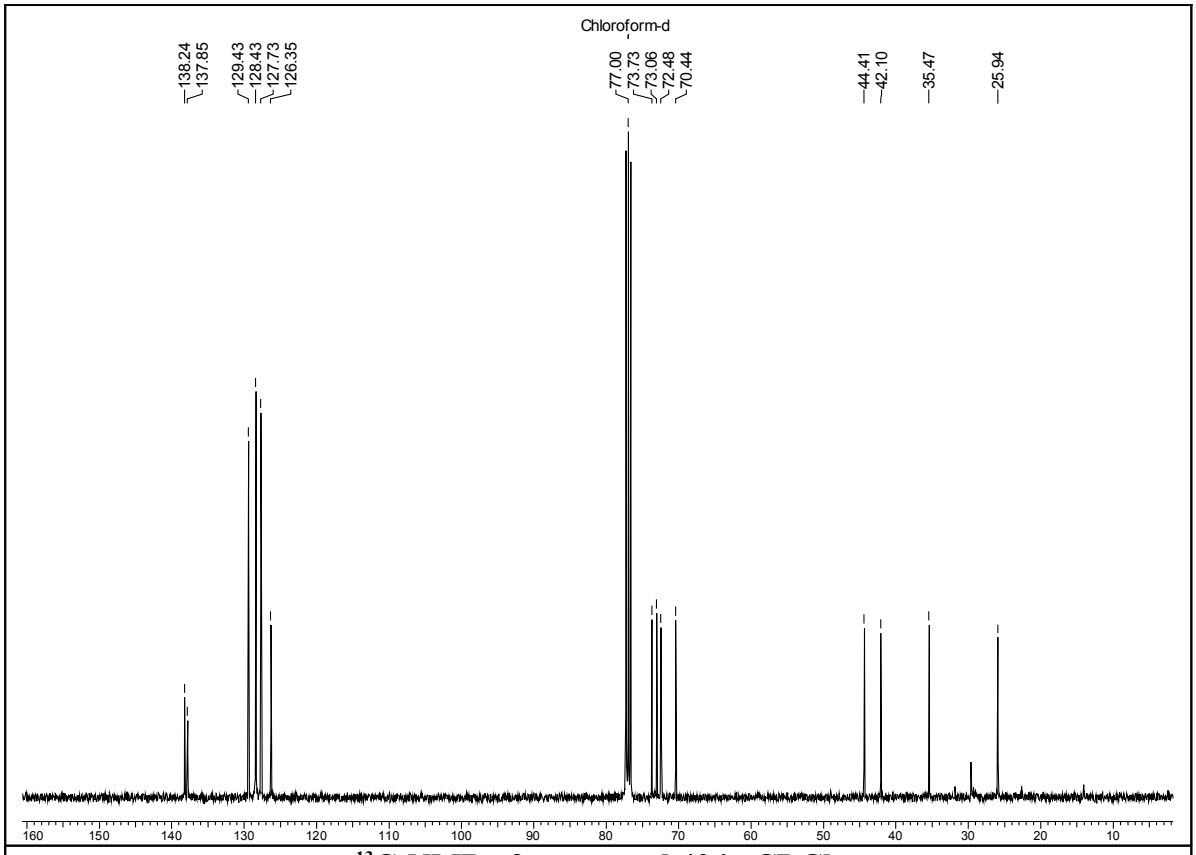
^{1}H-NMR of compound 39 in $CDCl_3$



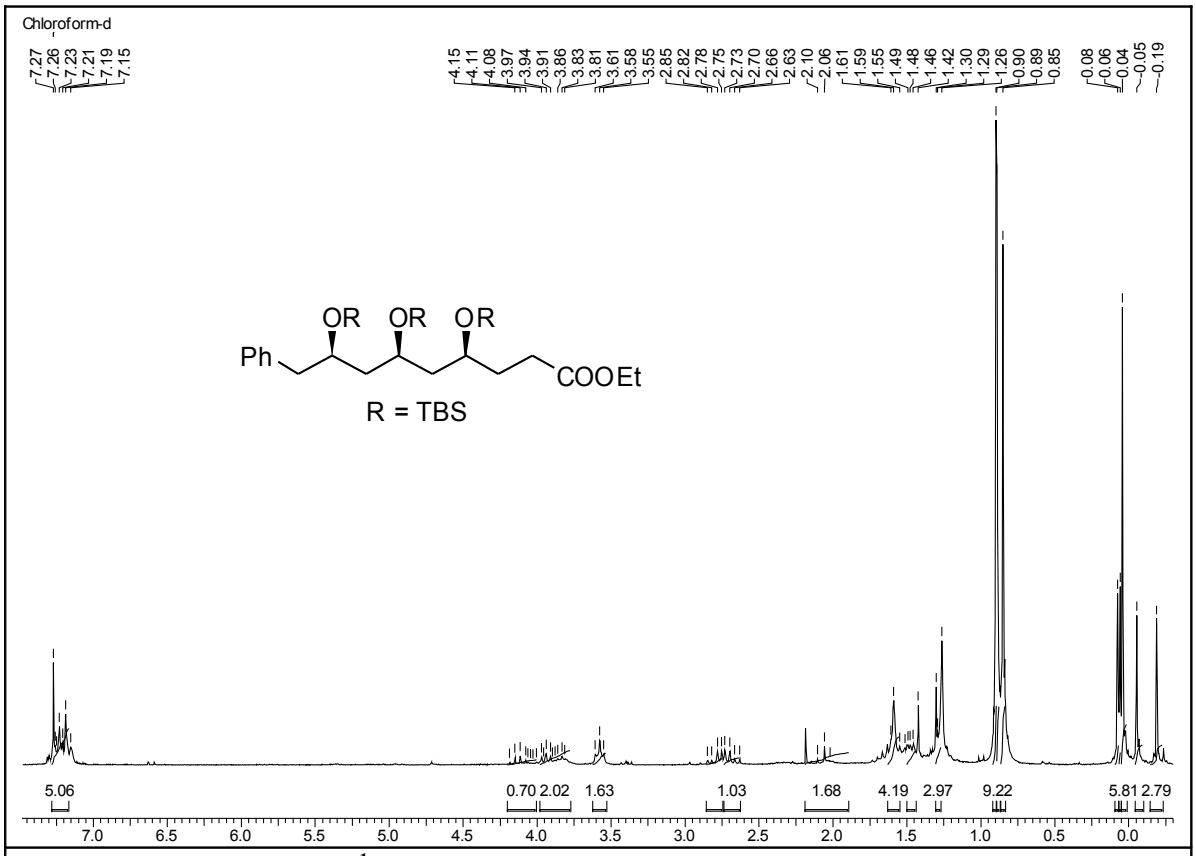
^{13}C-NMR of compound 39 in $CDCl_3$



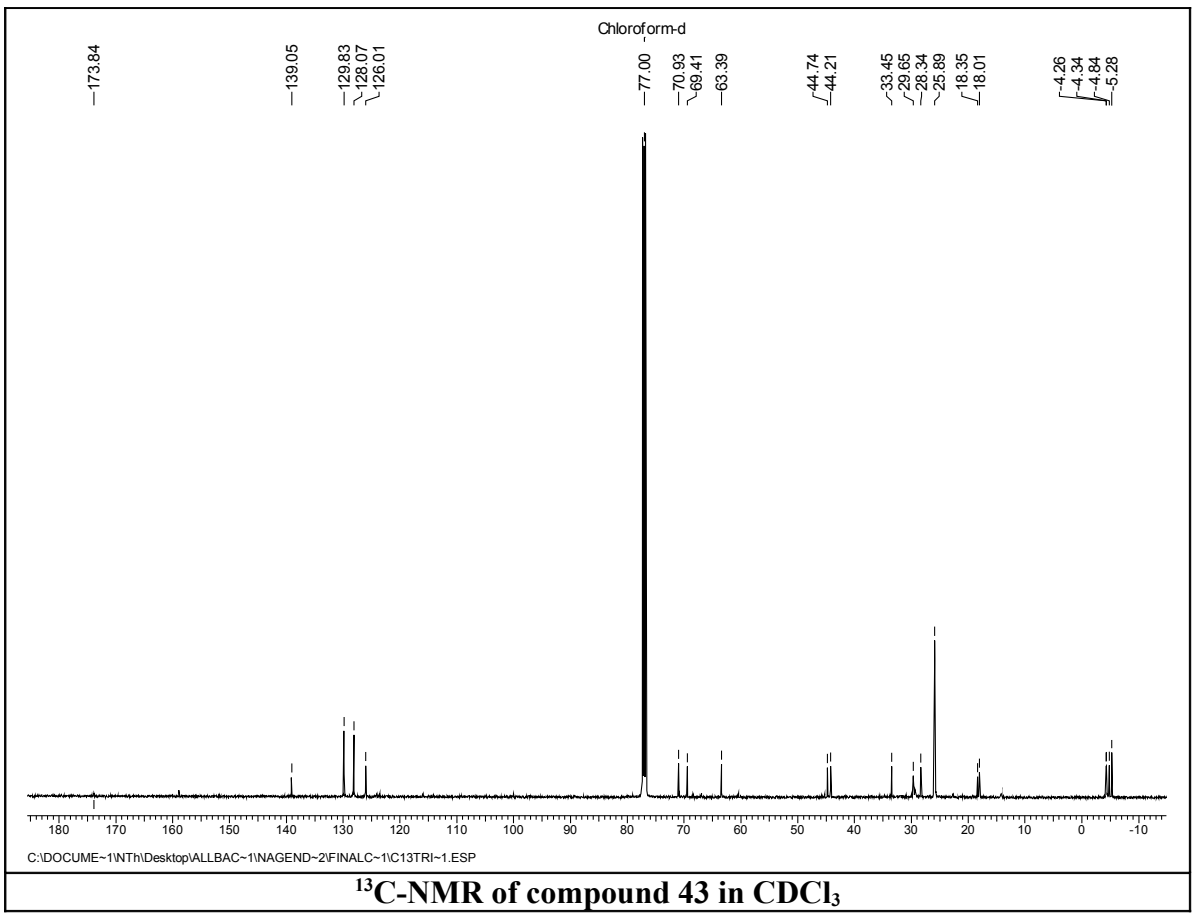
^{1}H-NMR of compound 40 in $CDCl_3$



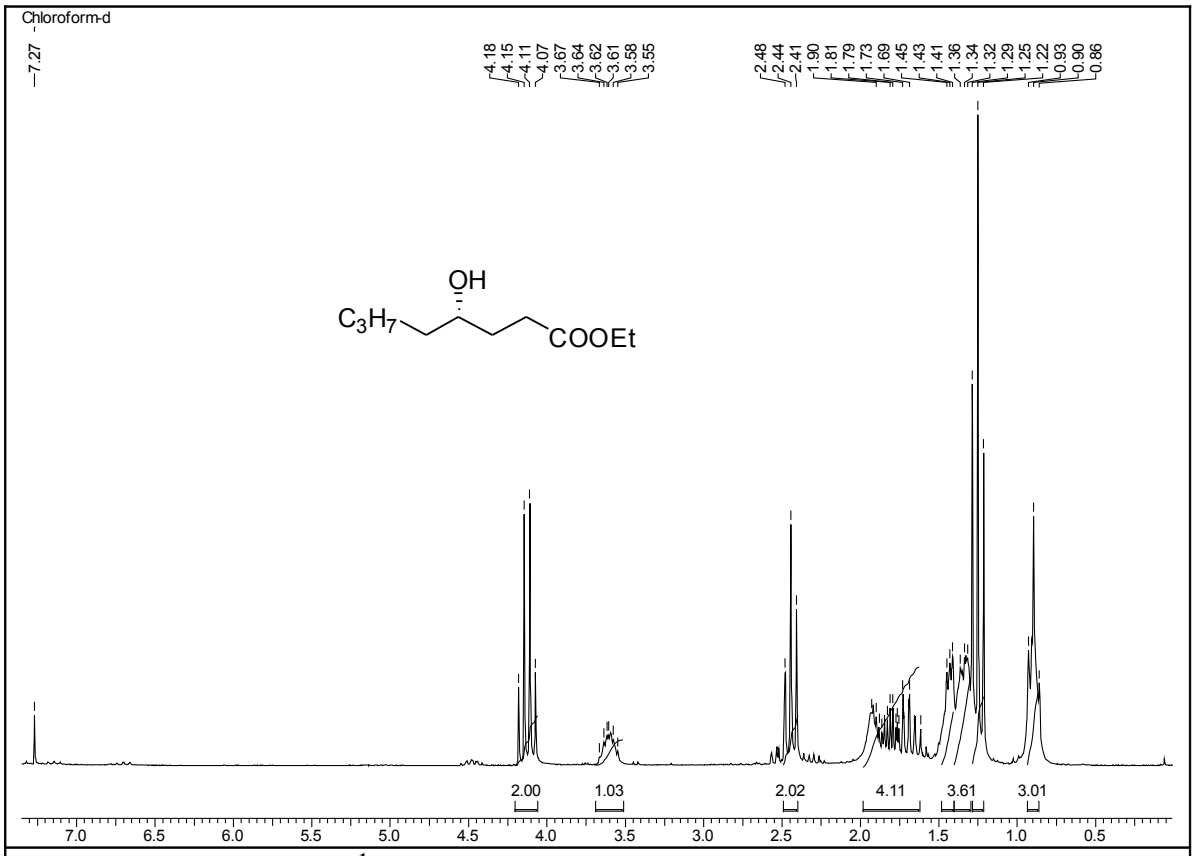
^{13}C-NMR of compound 40 in $CDCl_3$



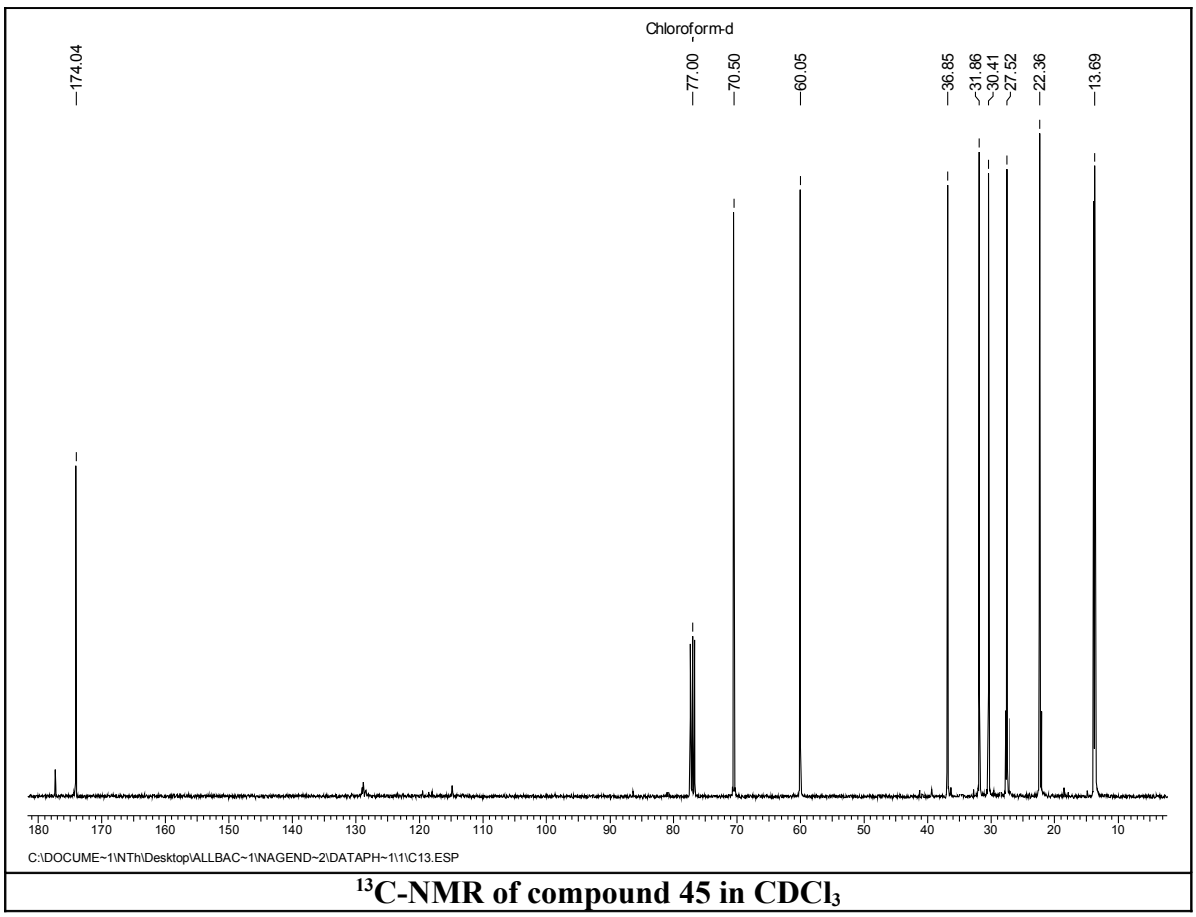
^{1}H-NMR of compound 43 in $CDCl_3$



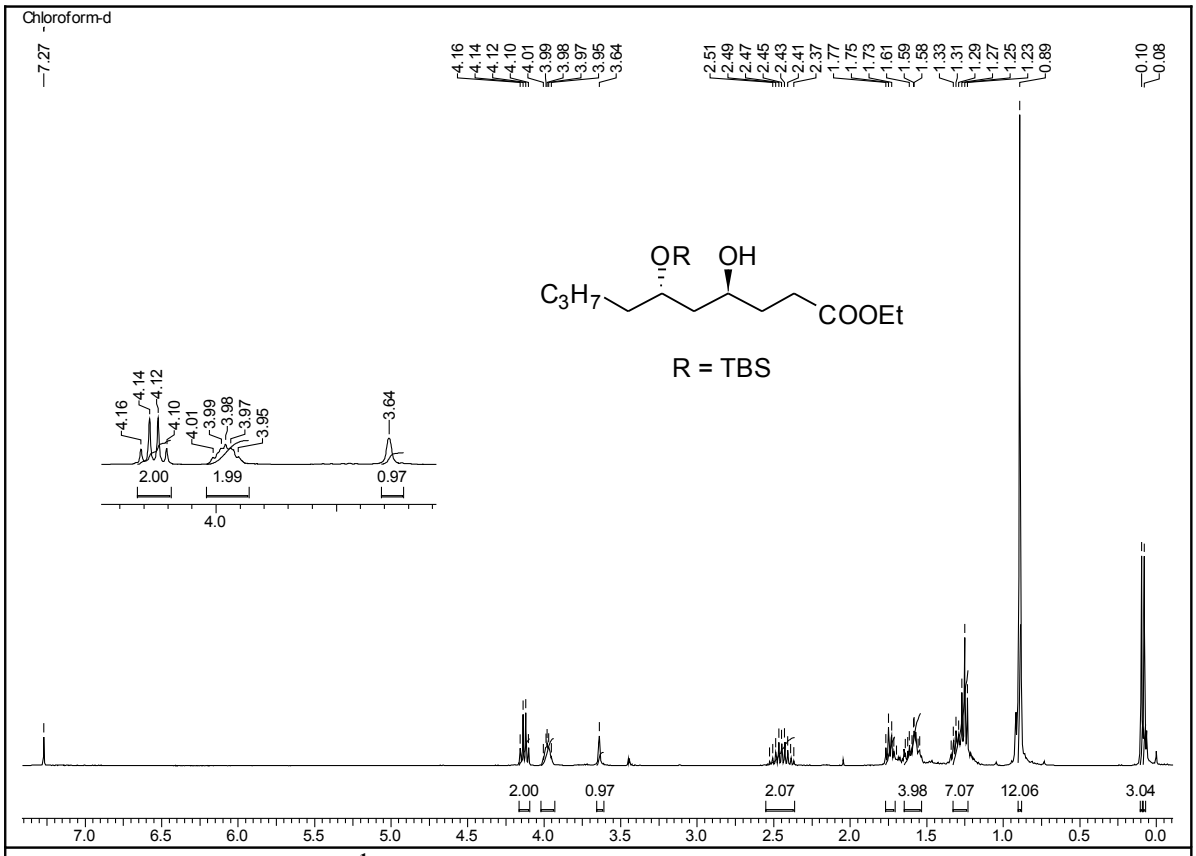
^{13}C-NMR of compound 43 in $CDCl_3$



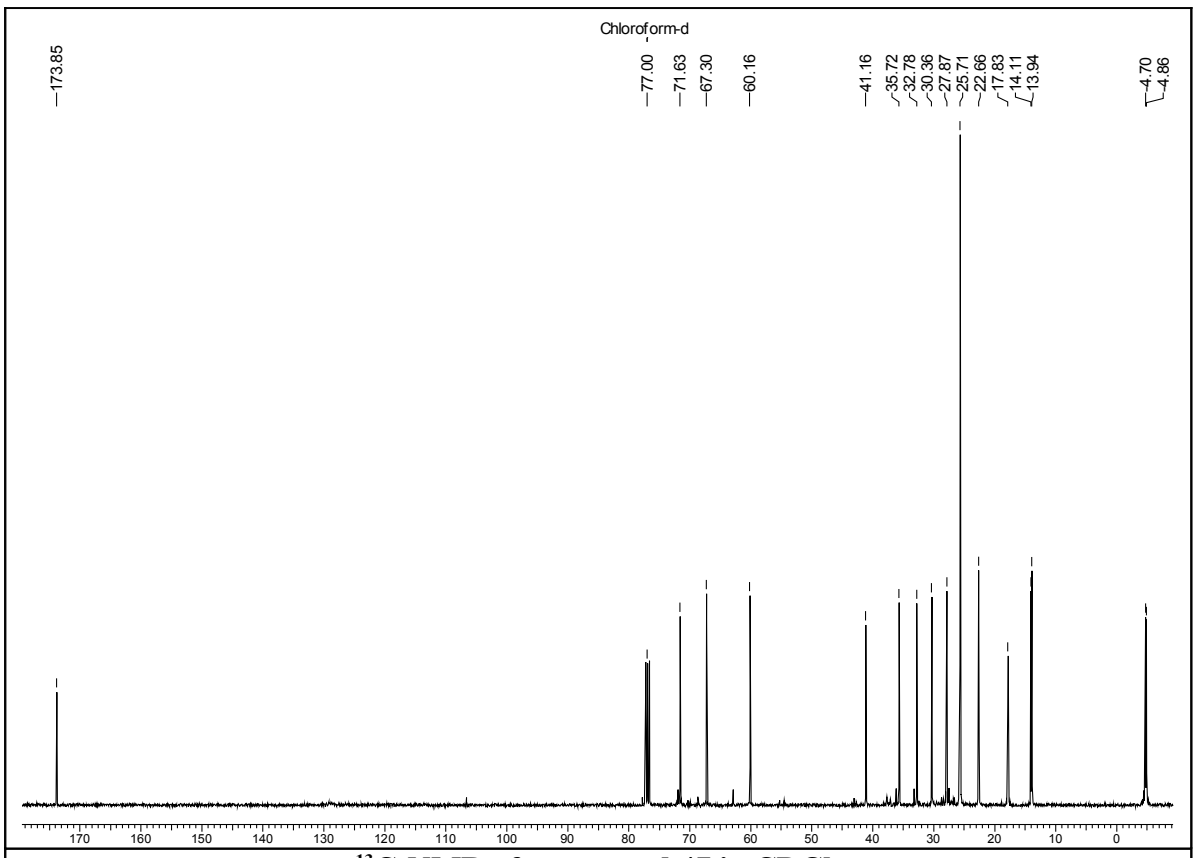
^{1}H-NMR of compound 45 in $CDCl_3$



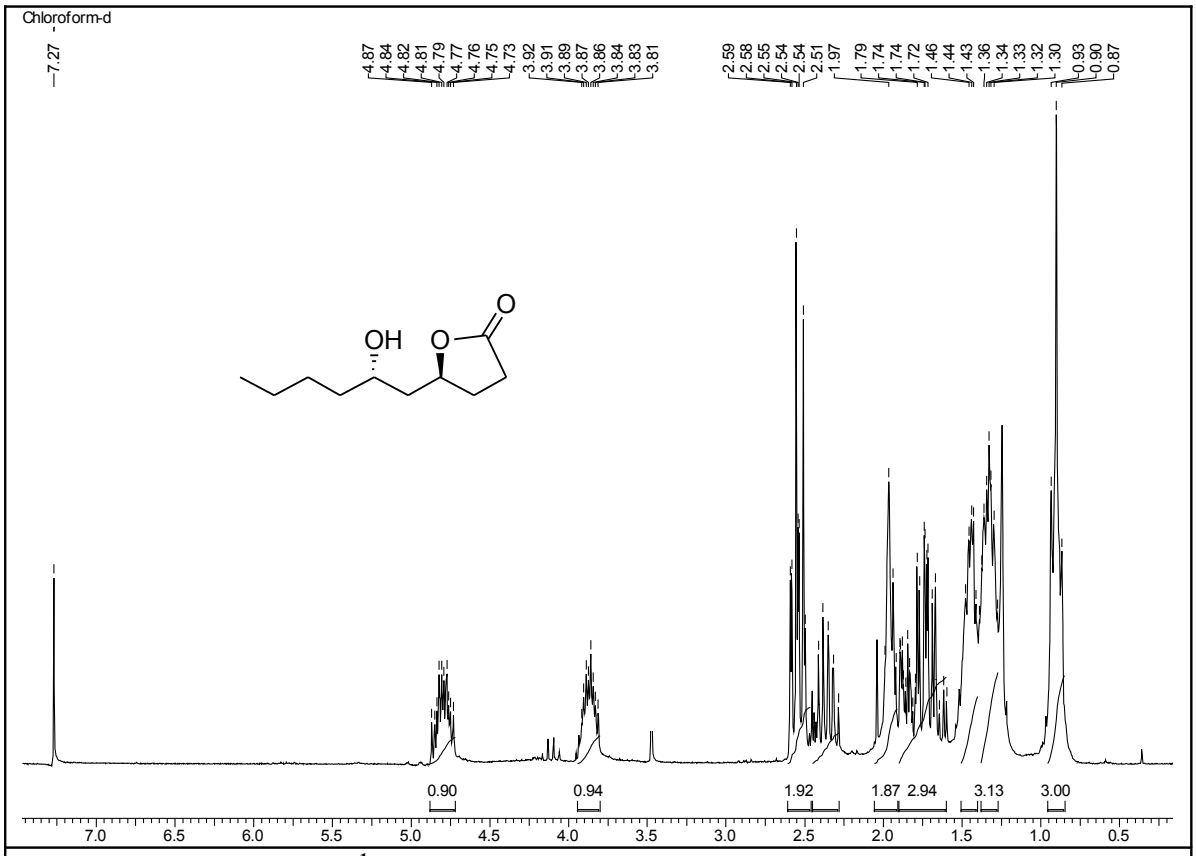
^{13}C-NMR of compound 45 in $CDCl_3$



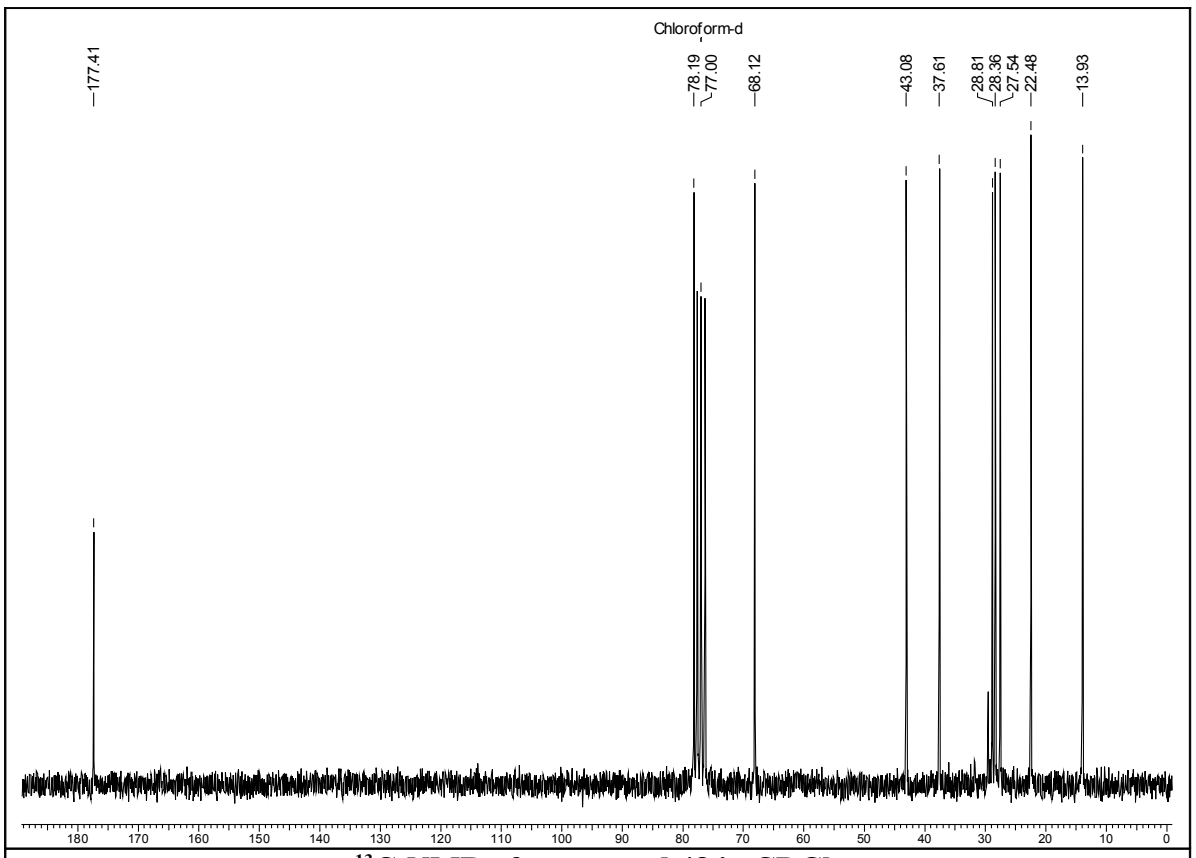
^{1}H-NMR of compound 47 in $CDCl_3$



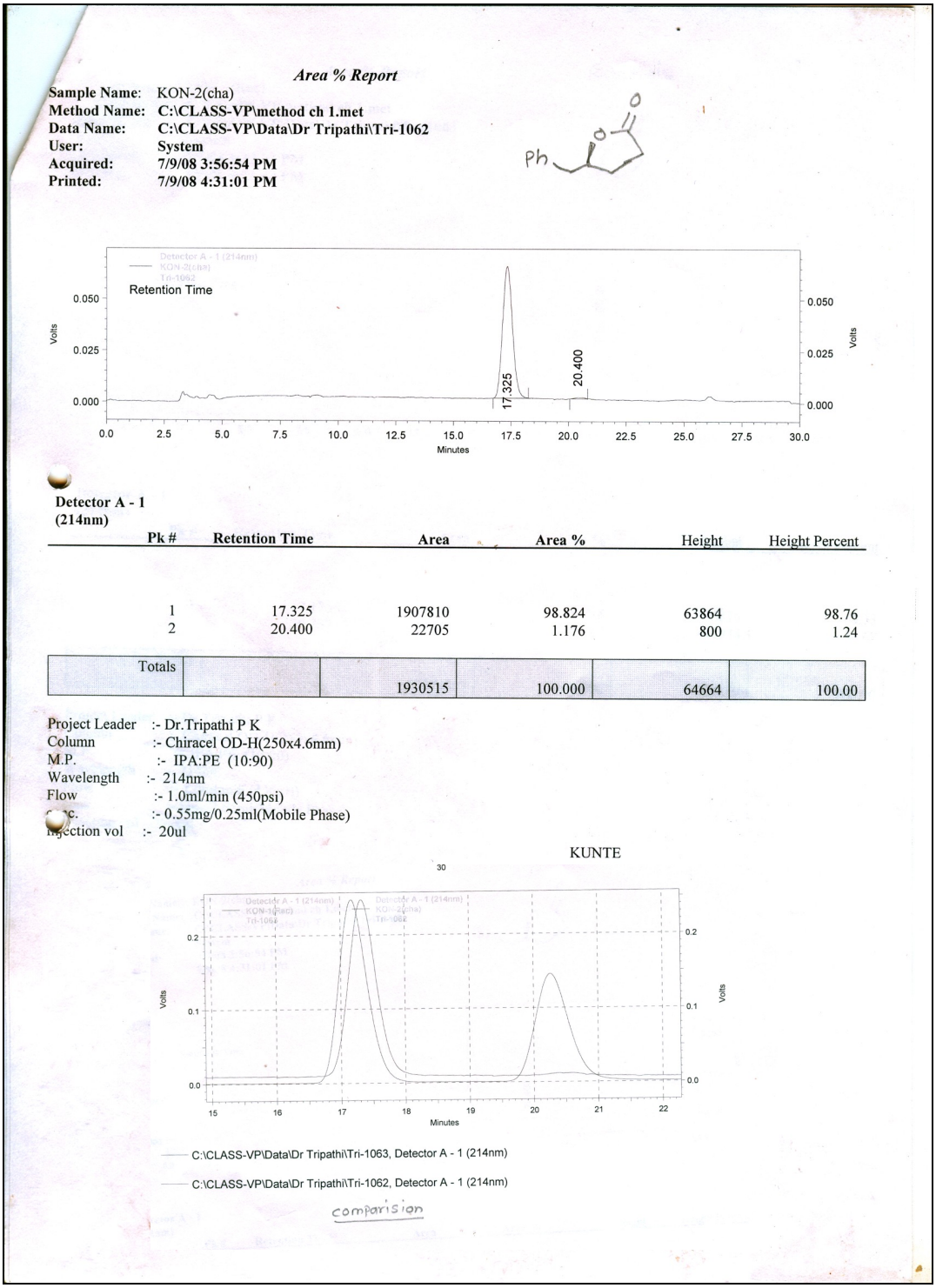
^{13}C-NMR of compound 47 in $CDCl_3$



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



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



Area % Report

Sample Name: KON-2(cha)
Method Name: C:\CLASS-VP\method ch 1.met
Data Name: C:\CLASS-VP\Data\Dr Tripathi\Tri-1062
User: System
Acquired: 7/9/08 3:56:54 PM
Printed: 7/9/08 4:31:01 PM

Detector A - 1 (214nm)

Pk #	Retention Time	Area	Area %	Height	Height Percent
1	17.325	1907810	98.824	63864	98.76
2	20.400	22705	1.176	800	1.24
Totals		1930515	100.000	64664	100.00

Project Leader :- Dr.Tripathi P K
Column :- Chiracel OD-H(250x4.6mm)
M.P. :- IPA:PE (10:90)
Wavelength :- 214nm
Flow :- 1.0ml/min (450psi)
Conc. :- 0.55mg/0.25ml(Mobile Phase)
Injection vol :- 20ul

KUNTE

Figure 3. HPLC chart of lactone for ee determination of (*S*)-Ethyl 4-hydroxy-5-phenylpentanoate **28**

4.1.8. Reference

1. For reviews on this subject, see: (a) Bode, S. E.; Wolberg, M.; Müller, M. *Synthesis* **2006**, 557; (b) Schneider, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 1375; (c) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021; (d) Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041; (e) Hoveyda, A. M.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307; (f) Oishi, T.; Nakata, T. *Synthesis* **1990**, 635; (g) Reetz, M. T. *Angew. Chem., Int. Ed.* **1984**, *23*, 556.
2. (a) Chen, K.; Richter, J. M.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 7247; (b) Kumar, P.; Gupta, P.; Naidu, S. V. *Chem. A Eur. J.* **2006**, *12*, 1397; (c) Chen, C.; Luo, S.; Jordan, R. F. *J. Am. Chem. Soc.* **2008**, *130*, 12892.
3. (a) Garcia, A. B.; Leßmann, T.; Umarye, J. D.; Mamane, V.; Sommer, S.; Waldmann, H. *Chem. Commun.* **2006**, 3868; (b) Dreher, S. D.; Leighton, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 341; (c) Barrett, A. G. M.; Braddock, D. C.; de Koning, P. D.; White, A. J. P.; Williams, D. J. *J. Org.Chem.* **2000**, *65*, 375; (d) Schneider, C.; Rehfeuter, M. *Chem. A Eur. J.* **1999**, *5*, 2850; (e) Paterson, I.; Wallace, D. J.; Gibson, K. R. *Tetrahedron Lett.* **1997**, *38*, 8911; (f) Hoffmann, R. W.; Stürmer, R. *Synlett* **1990**, 759; (g) Schreiber, S. L.; Goulet, M. T. *J. Am. Chem. Soc.* **1987**, *109*, 8120.
4. (a) BouzBouz, S.; Cossy, J. *Org. Lett.* **2000**, *2*, 501; (b) Knochel, P.; Brieden, W.; Rozema, M. J.; Eisenberg, C. *Tetrahedron Lett.* **1993**, *34*, 5881.
5. (a) Binder, J. T.; Kirsch, S. F. *Chem. Commun.* **2007**, 4164; (b) Zhang, Z.; Aubry, S.; Kishi, Y. *Org. Lett.* **2008**, *10*, 3044.
6. (a) Dalko, P. L.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138; (b) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley VCH: Weinheim, 2005; (c) Seayed, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719.
7. Dalko, P. I. *Enantioselective Organocatalysis: Reactions and Experimental Procedures*; Wiley-VCH: Weinheim, 2007.
8. MacMillian, D. W. C. *Nature* **2008**, *455*, 304.
9. (a) Casas, J.; Engqvist, M.; Ibrahem, I.; Kaynak, B.; Cordova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1343; (b) List, B.; Lerner, R. A.; Barbas, C. F. III. *J. Am. Chem. Soc.* **2000**, *122*, 2395.

10. (a) Sabitha, G.; Fatima, N.; Reddy, E. V.; Yadav, J. S. *Adv. Synth. Catal.* **2005**, *347*, 1353; (b) Ramachary, D. B.; Chowdari, N. S.; Barbas, C. F. III. *Synlett* **2003**, 1910.
11. Hechavarria Fonseca, M. T.; List, B. *Angew. Chem., Int. Ed.* **2004**, *43*, 3958.
12. For α-functionalization reviews, see: (a) Franzen, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjærsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296; (b) Guillena, G.; Ramon, D. J. *Tetrahedron:Asymmetry* **2006**, *17*, 1465; (c) For a comprehensive review on α-aminoxylation, see: Merino, P.; Tejero, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 2995, and references cited therein.
13. (a) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656; (b) Bogevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1790; (c) Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bogevig, A.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 6254; (d) Vogt, H.; Vanderheiden, S.; Brase, S. *Chem. Commun.* **2003**, 2448.
14. (a) Zhong, G.; Yu, Y. *Org. Lett.* **2004**, *6*, 1637; (b) Lu, M.; Zhu, D.; Lu, Y.; Hou, Y.; Tan, B.; Zhong, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 10187.
15. (a) Pidathala, C.; Hoang, L.; Vignola, N.; List, B. *Angew. Chem.,Int. Ed.* **2003**, *42*, 2785; (b) Fonseca, M. T. H.; List, B. *Angew. Chem., Int. Ed.* **2004**, *43*, 3958; (c) For a review of proline-catalyzed asymmetric reactions, see: List, B. *Tetrahedron* **2002**, *58*, 5573; (d) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138.
16. For reviews on organocatalytic tandem reactions, see: (a) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570; (b) Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037; (c) Walji, A. M.; MacMillan, D. W. C. *Synlett* **2007**, 1477.
17. Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321.
18. The enantiomeric excess of homoallylic alcohols was determined by HPLC analysis, Chiralcel-AD2 column (hexane/2-propanol).
19. All new homoallylic alcohols exhibited satisfactory spectroscopic data (^{1}H and ^{13}C NMR, IR, MS).
20. Demuth, M.; Ritterskamp, P.; Weight, E.; Schaffner, K. *J. Am. Chem.Soc.* **1986**, *108*, 4149.

21. Binder, J. T.; Kirsch, S. F. *Chem. Commun.* **2007**, 4164.
22. Overman, L. E.; Owen C. E.; Pavan, M.M. *Org. Lett*. **2003**, *5*, 1809.
23. (a) Anderson, C. E.; Kirsch, S. F.; Overman, L. E.; Richards C. J.; Watson, M. P. *Org. Synth.* **2007**, *84*, 148; (b) Stevens A. M.; Richards, C. J. *Organometallics*, **1999**, *18*, 1346.
24. The transesterification step consisting of reductive cleavage and subsequent esterification was required, since vinylacetic acid does not react in the allylic esterification reactions catalyzed by COP-OAc.
25. For a review, see: Deiters A.; Martin, S. F. *Chem. Rev*. **2004**, *104*, 2199; for a related example, see: Andreana, P. R.; McLellan, J. S.; Chen Y.; Wang, P. G. *Org. Lett*. **2002**, *4*, 3875.
26. (a) Virolleaud M. A.; Piva, O. *Synlett* **2004**, 2087.
27. For a review, see: Boucard, V.; Broustal G.; Campagne, J.M. *Eur. J. Org. Chem*. **2007**, 225; for selected examples, see: Trost B. M.; Yeh, V. S. C. *Org. Lett*. **2002**, *4*, 3513.
28. Zhang, Z.; Aubry, S.; Kishi, Y. *Org. Lett.* **2008**, *10*, 3044.
29. Masamune, S.; Choy, W.; Peterson, J. S.; Sita, L. S. *Angew. Chem.,Int. Ed.* **1985**, *24*, 1.
30. In order to determine the chiral purity of (*S*)-ethyl 4-hydroxy-5-phenylpentanoate **28** formed, it was converted into known lactone by treatment with *p*-TSA in methanol. HPLC: Chiracel OD-H column (2-propanol/petroleum ether) 10:90, flow rate 1.0 mL/min, λ) 214 nm). Retention time (min): 17.17 (major) and 20.67 (minor). The racemic standard was prepared in the same way with racemic γ-hydroxy ester, ee 98%.
31. Overall yield per iteration cycle can be slightly improved by following the two-step process for aldehyde formation that is reduction of ester to alcohol followed by IBX oxidation.
32. Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett*. **1990**, *31*, 945.
33. Cost of L-proline in Aldrich catalogue 2009-2010 for 100 g is INR 4404 (USD $60.40).

34. Nishida, R.; Schulz, S.; Kim, C. H.; Fukami, H.; Kuwahara, Y.; Honda, K.; Hayashi, N. *J. Chem. Ecol.* **1996**, *22*, 949.
35. In order to determine the chiral purity of (*S*)-ethyl 4-hydroxyoctanoate **45** formed it was converted into known lactone on treatment with *p*-TSA in methnol. Chiral GC using cyclodextrin TA column (70 kPa pressure, 140 °C isotherm for 30 min, minor enantiomer 17 min, major enantiomer 15 min). The racemic standard was prepared in the same way with racemic *γ*-hydroxy ester, ee 94%.
36. Kotkar, S. P.; Suryawanshi, G. S.; Sudalai, A. *Tetrahedron:Asymmetry* **2007**, *18*, 1795.

4.2. SECTION B

Proline-catalysed synthesis of piperidine and indozolidine natural products (*R*)-coiinine and (*S*)-coniceine

4.2.1. Introduction

The substituted piperidines and ring fused piperidines such as indolizidines are among the most ubiquitous heterocyclic building blocks in both natural products and synthetic compounds with important biological activities.[1] The interest in the piperidine and indolizidine alkaloids is well displayed by the wealth of published material detailing there sources and biological activities and there structure diversity makes them interesting providing grounds for organic chemists.

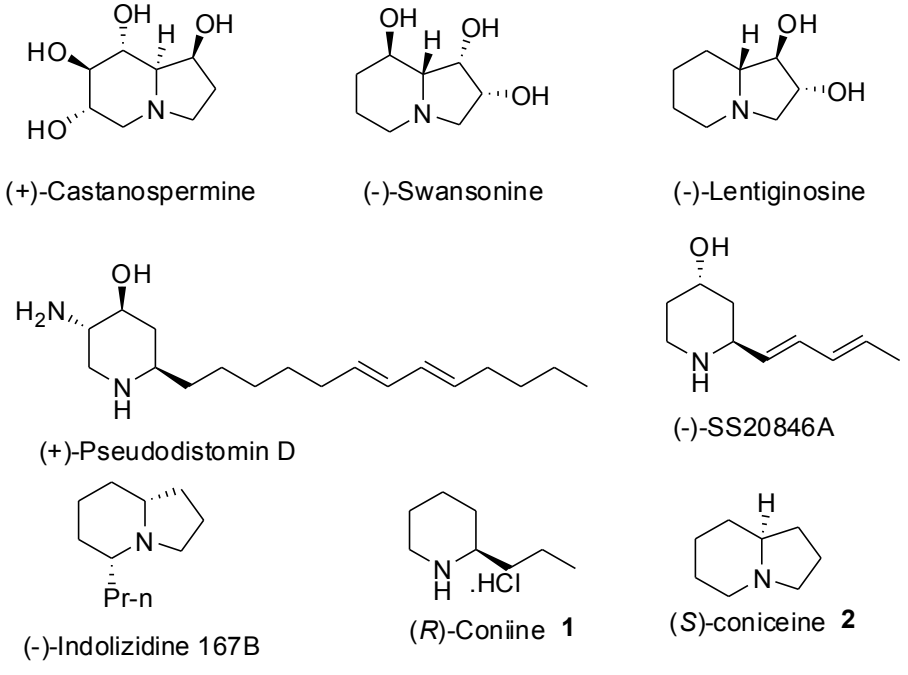


Fig. 1. Some of the important piperidine and indolizidine containing natural products and bioactive molecules.

Therefore considerable efforts have been directed towards synthesizing them[2] in stereo and enantioselective manner[3] and the interest in their chemistry remains unabated. (*R*)- coniine and (*S*)- coniceine the simplest members of piperidine and indolizidine alkaloids respectively have attracted great interest from chemists as an representative targets

demonstrating the viability of the synthetic routs to piperidine and indolizidine derivaties and there are numerous successful asymmetric synthesis of these molecules.[4]

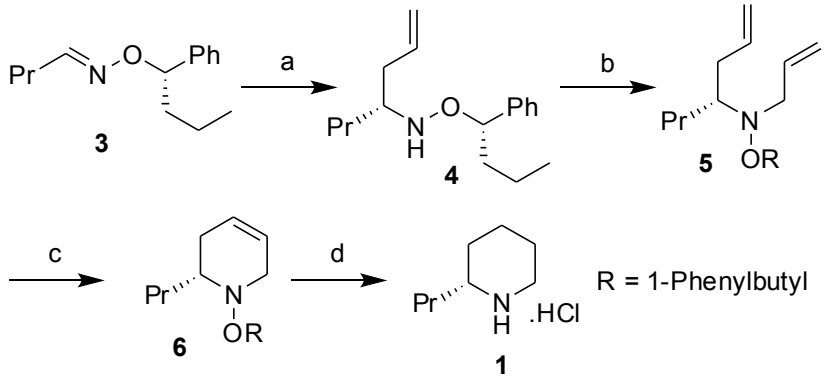
4.2.2. Review of Literature

(*S*)-2-Propylpiperidine alkaloid (*R*)-(-)-coniine, and (*S*)-coniceine are popular target for the demonstration of chiral methodology in the piperidine and indolizidine field. (*S*)-Coniine is a poisonous hemlock alkaloid extracted from the plant *Conium maculatum* and from many tropical subspecies. Several approaches have been reported in the literature for the synthesis of racemic as well as optically active coniine, and (*S*)-coniceine. A few interesting and recent syntheses of coniine ((*R*)-(-)-**1**, (*S*)-(+)-***ent*-1**), and coniceine ((*S*)-(+)-**2**, (*R*)-(-)-***ent*-2**) are described below.

Approches towards synthesis of (*R*)-/(*S*)-coniine

Moody *et al.* (2000)[5]

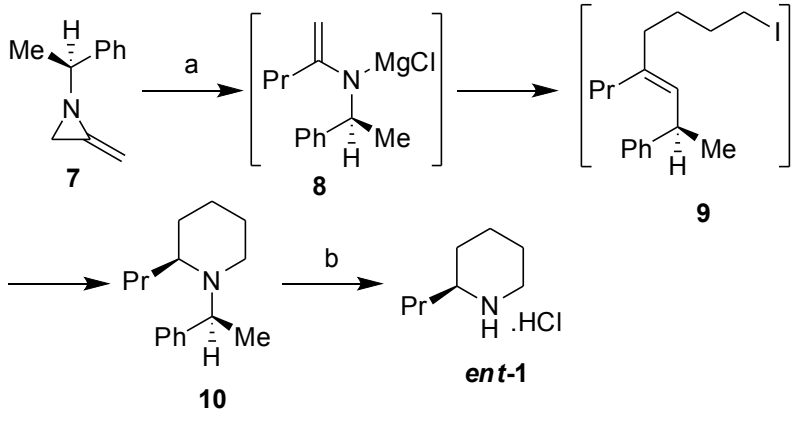
Moody *et al*. accomplished the synthesis of (*R*)-(-)-coiinine **1** by ring closing metathesis reactions of the diene **5**. The diene **5**, is easily accessible by the addition of an alkene containing organometallic reagent to the aldoxime ether **3**, followed by *N*-allylation of the resulting hydroxylamine **4**. The RCM reaction was carried out by heating the diene **5** in dichloromethane in the presence of Grubbs' catalyst furnishing the compound **6** in modest yield, which was hydrogenated over Pd/C to give (*R*)-(-)-coniine.



Scheme 1. *Reagents and conditions*: (a) AllylMgBr, $BF_3.Et_2O$; (b) K_2CO_3, allyl bromide, acetonitrile; (c) Grubb's catalyst, DCM; (d) H_2-Pd/C, MeOH, HCl in Et_2O.

Shipman *et al.* (2001)[6]

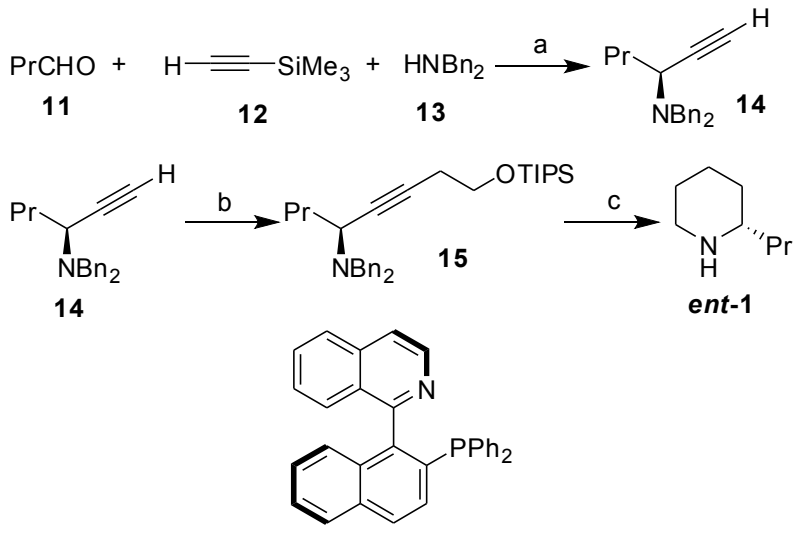
Shipman *et al*. synthesized (*S*)-coniine by making use of multi-component coupling reaction of 2-methyleneaziridine **7**.[7] Thus, ring opening of **7** with EtMgCl in presence of copper(I) iodide furnished metalloenamine **8** in a regiocontrolled fashion, which was treated with 1,3-diiodopropane, and sodium triacetoxyborohydride to afford piperidine **10** as a single diastereomer (97% de). Finally hydrogenolysis of **10** furnished (*S*)-(+)-coniine hydrochloride ***ent*-1** in 93% yield (Scheme 2).



Scheme 2. *Reagents and conditions*: (a) (i) EtMgCl, CuI, THF, -30 °C → rt; (ii) $ICH_2CH_2CH_2I$, 40 °C; (iii) $NaBH(OAc)_3$; (b) $Pd(OH)_2$, H_2, HCl, EtOH.

Knochel *et al*. (2004)[8]

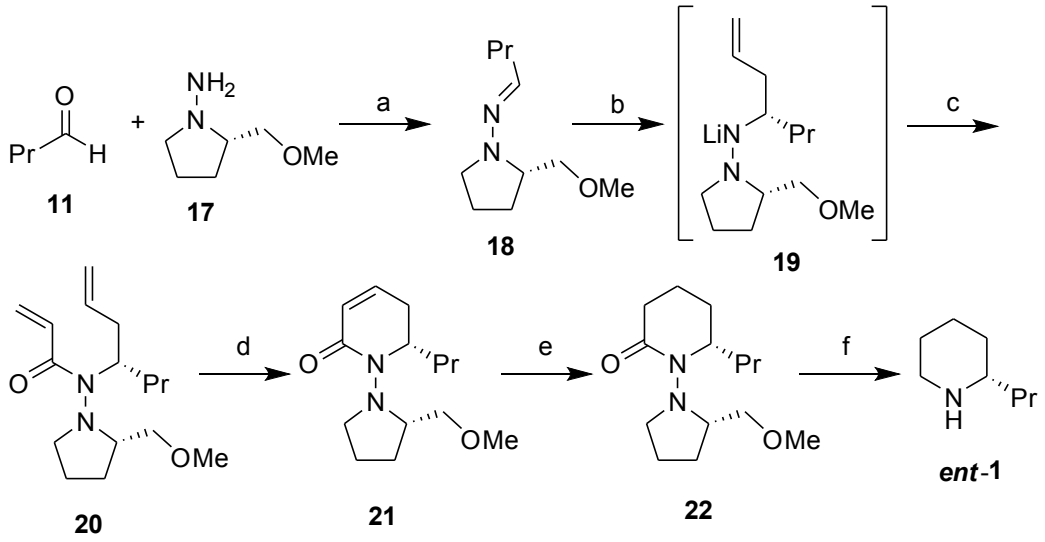
Knochel *et al*. developed one-pot three-component addition reaction of trimethylsilylacetylene **11**, aldehydes **12** and dibenzylamine **13** in presence of CuBr/Quinap **16** as catalyst, to furnish enantiomerically enriched propargylamine **14** in good yield and excellent enantiomeric excess. Thus chiral propargylamine **14** was alkylated with ethylene oxide followed by protection with TIPSCl to afford **15** in 70% overall yield.[9] The hydrogenolysis of benzyl groups and the reduction of the triple bond was achieved by hydrogenation of **15** in methanol leading to an intermediate primary amine which was desilylated with Bu_4NF and subjected to an intramolecular Mitsunobu reaction[10] to afford (*S*)-(+)-coniine ***ent*-1** in 5 steps with 41% overall yield (Scheme 3).



Scheme 3. *Reagents and conditions*: (a) (i) CuBr (cat), (*R*)-quinap (cat), toluene, rt, 6d; (ii) Bu_4NF; (b) (i) *n*-BuLi, -78 °C; (ii) ethylene oxide, $BF_3.OEt_2$; (iii) TIPSCl, DMF; (c) (i) H_2, Pd/C, MeOH; (ii) Bu_4NF; (iii) PPh_3, DEAD.

Couture *et al*. (2007)[11]

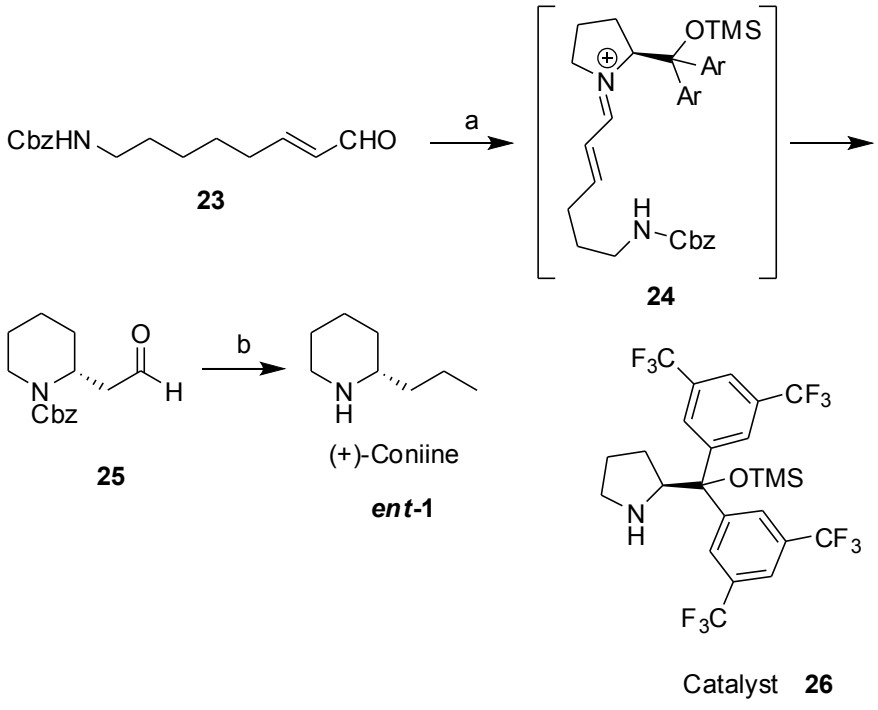
Couture *et al*. synthesized (*S*)-coniine ***ent*-1** by making use of a highly diastereoselective nucleophilic 1,2-addition of aldehyde **11** on chiral aliphatic SAMP hydrazone **17**. Thus hydrazone **17** on treatment with aldehyde **11** furnished compound **18**. Treatment of **18** with allyllithium gave the transient lithium hydrazide salt **19**, which was intercepted with acryloyl chloride to afford dienehydrazides **20**. On subjecting dienehydrazides **20** to ring-closing metathesis condition gave chiral α,*β*-unsaturated piperidones **21**, which on catalytic hydrogenation provided corresponding hydrazides **22**. Treatment of hydrazides **22** with the BH_3.THF complex, followed by aqueous alkaline workup effected reductive N-N bond cleavage with the concomitant reduction of the lactam carbonyl group. Finally treatment with HCl in Et_2O afforded the target natural product ***ent*-1** as its hydrochloride salt (Scheme 4).



Scheme 4. *Reagents and conditions*: (a) $MgSO_4$, rt, 12 h; (b) Allyl-Li, Et_2O, -78 °C to rt; (c) acryloyl chloride, -78 °C to rt; (d) Grubb's catalyst II, CH_2Cl_2, rt, 24 h; (e) H_2, Pd/C, EtOH, rt, 12 h; (f) BH_3.THF, then HCl, EtO_2.

Fustero *et al*. (2007)[12]

Fustero *et al*. reported an intramolecular aza-Michael reaction approach for the synthesis of (*S*)-coniine ***ent*-1**. Thus intramolecular aza-Michael reaction (IMAMR) of carbamates **23** bearing remote α,*β*-unsaturated aldehydes as Michael acceptors (Scheme 5), in presence of catalyst **26** and phenyl acetic acid as additive furnished aldehyde **25** which was subsequently transformed into (+)-coiinine ***ent* -1** by Wittig homologation and hydrogenation of the double bond.



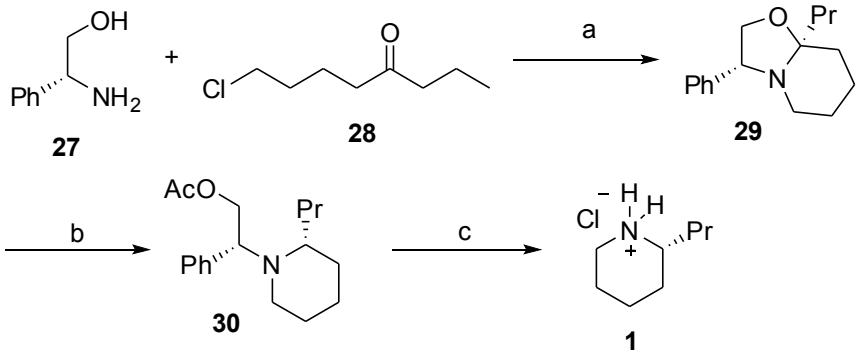
Scheme 5. *Reagents and conditions*: (a) Catalyst **26**, $PhCO_2H$, $CHCl_3$, -50 °C to -30 °C, 80%; (b) (i) PPh_3MeBr, ^tBuOK, THF; (ii) H_2, Pd/C, EtOH, rt, 12 h.

Approches towards synthesis of (*R*)-/(*S*)-coniceine

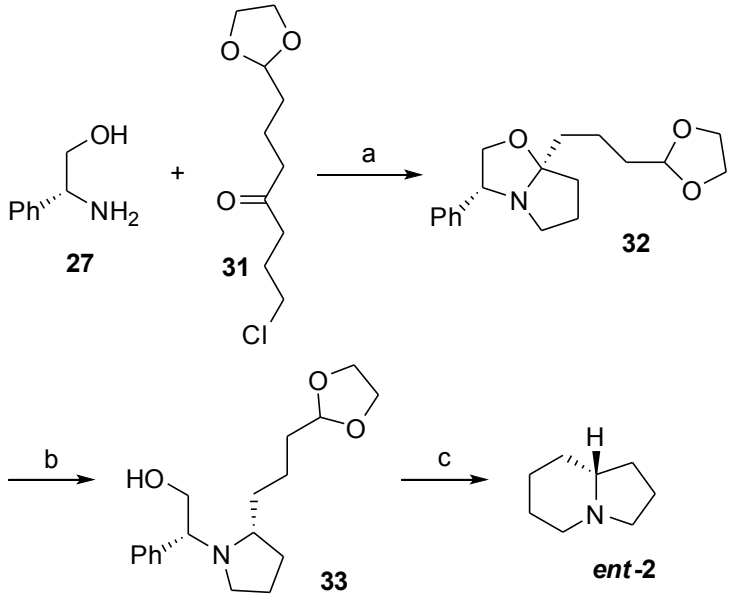
Pedrosa *et al*. (2000)[13]

Pedrosa *et al*. synthesised (-)-coniine and (*S*)-coniceine from (*R*)-phenylglycinol and γ- or δ-chloroketones. Condensation of (*R*)-(2)-phenylglycinol **27** and with δ - or γ -chloroketones **28** and **31** respectively furnished chiral bicyclic oxazolidines **29** and **32** (Scheme 6, 7). (-)-Coniine **1** was obtained from **29** by hydrogenolysis over $Pd(OH)_2$ on carbon followed by treatment with hydrogen chloride in anhydrous diethyl ether (Scheme 6).

Similarly, reductive ring opening of oxazolidines **32** by treatment with lithium aluminium hydride yielded a mixture of diastereomeric 2-substituted pyrrolidines **33** in 74% yield with total retention of configuration. The major diastereoisomer **33** was transformed into enantiopure (*R*)-(-)-coniceine ***ent*-2**. Thus hydrolysis of **33** and hydrogenation over 10% Pd/C in methanol containing a 2 M solution of HCl furnished (*R*)-(-)-coniceine ***ent*-2** (Scheme 7).



Scheme 6. *Reagents and conditions*: (a) Et_3N, $CHCl_3$; (b) (i) $LiAlH_4$, THF, 0 °C, 12 h; (ii) Ac_2O, DMPA, rt; 1.5 h; (c) H_2, $Pd(OH)_2$, HCl, Et_2O.

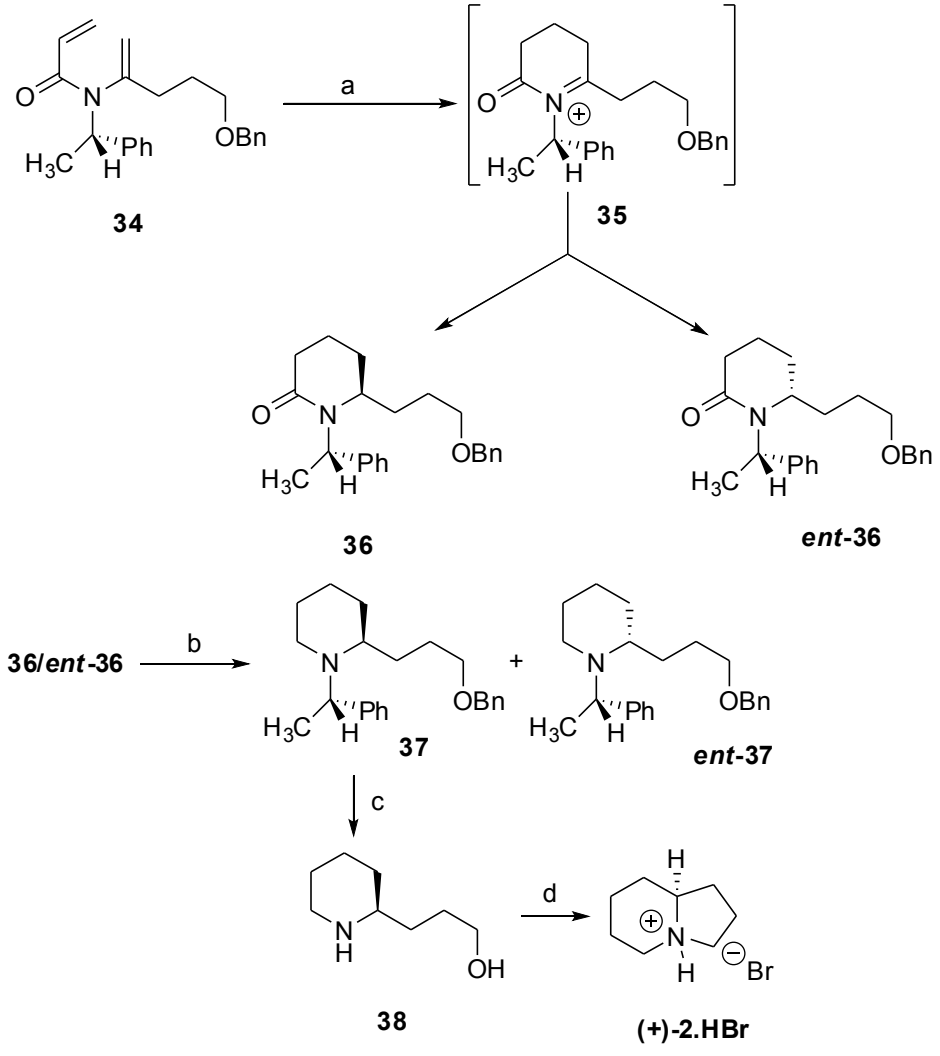


Scheme 7. *Reagents and conditions*: (a) Et_3N, $CHCl_3$; (b) $LiAlH_4$, Et_2O, 0 °C; (c) H_2, 10% Pd/C, EtOH, 2M HCl.

Gardette *et al*. (2007)[14]

Gardette *et al*. described a new synthetic route to the hydrobromide salt of (+)-coniceine **2**. Thus reductive photocyclisation of dienamide **34** furnished, two diastereomeric piperidinones as an inseparable mixture, the desired (10*S*,6*S*)-isomer **36** and the undesired (10*S*,6*R*)-isomer ***ent*-36** (Scheme 8). Reduction of the amide function in the **36**/***ent*-36** mixture using $LiAlH_4$ in refluxing THF gave a mixture of amines **37** and ***ent*-37**. This mixture was easily separated by column chromatography, thus affording pure **37** in around 61% yield and pure ***ent*-37** in around 16% yield. Debenzylation of **37** using 10% Pd/C with

HCO_2NH_4 as the hydrogen source[15] afforded amino alcohol **38**. Finally cyclization of aminoalcohol **38** was achieved using CBr_4 and PPh_3 in MeCN, aqueous workup gave (+)-coniceine hydrobromide **2**.**HBr** in 58% yield for the last two steps.



Scheme 8. *Reagents and conditions*: (a) hυ, $NaBH_4$, quartz reactor; (b) $LiAlH_4$, THF, Δ. **37**: 61%, ***ent*-37**: 16%; (c) HCO_2NH_4, 10% Pd/C, MeOH, Δ; (e) CBr_4, PPh_3, MeCN, rt, 58% (for two steps).

4.2.3. Present work

Objective

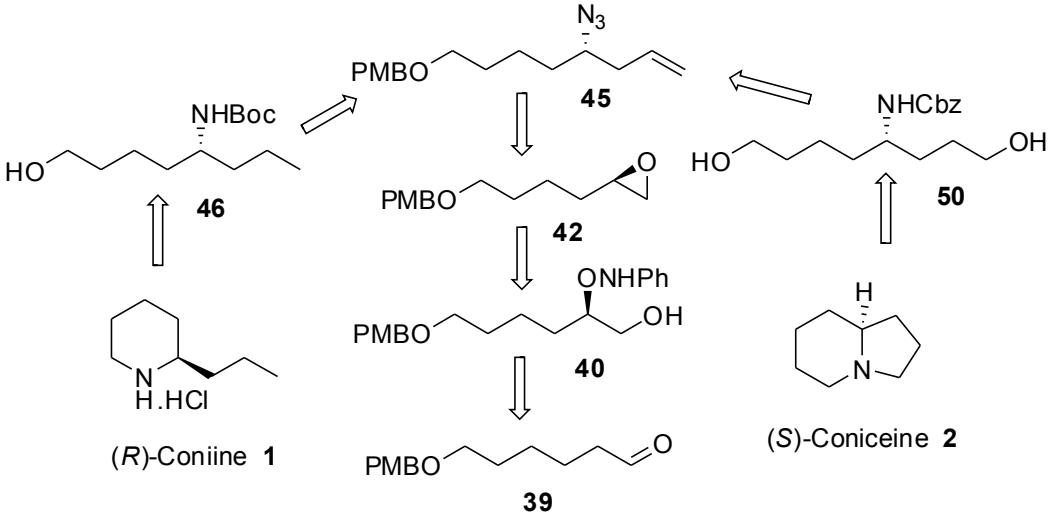
Given the vast chemistry, structural modifications and biological activities associated with the piperidine and indolizidine molecules, interest in the synthesis of these class of compounds remains unabated. Although a few syntheses are reviewed above, several more are documented in the literature. This explains the importance of research work in this area.

With the development of an efficient approach to the synthesis of 1,3-polyols using α-aminoxylation and sequential α-aminoxylation HWE olefination reaction catalysed by proline and its subsequent application towards the synthesis of hydroxy lactones, our attention was further focused to extrapolate the above knowledge to the synthesis of indolizidine and piperidine alkaloids.

4.2.4. Results and discussion

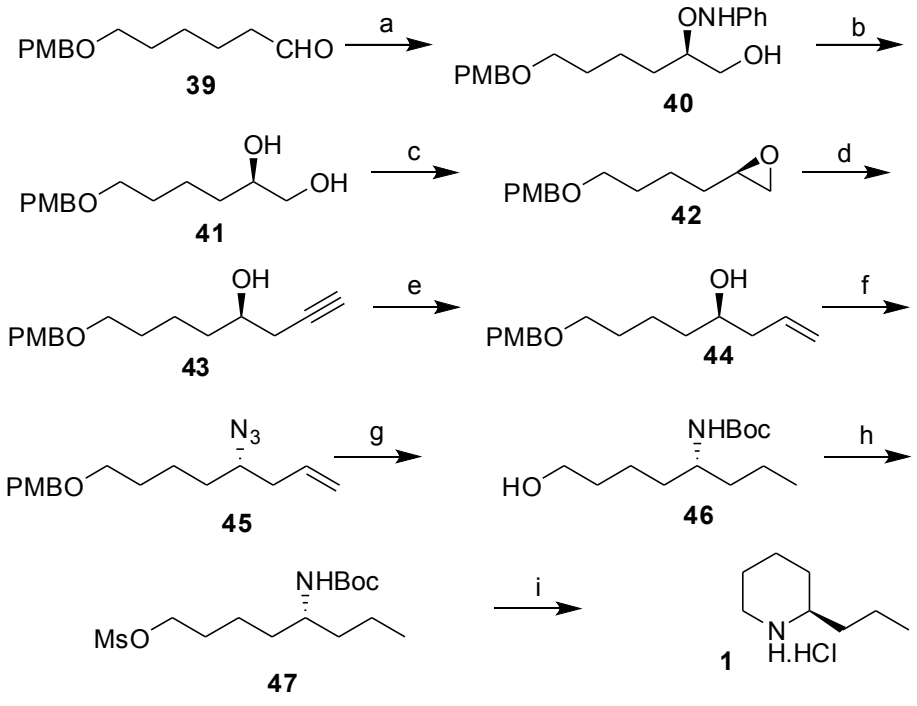
In recent years, there has been growing interest in the use of small organic molecules to catalyze reactions in organic synthesis.[16] As a result, the area of organocatalysis has now emerged as a promising strategy and as an alternative to expensive protein catalysis and toxic metal catalysis,[17] thus becoming a fundamental tool in the catalysis toolbox available for asymmetric synthesis.[18] Proline is among the most successful secondary amine based organocatalysts which have been widely employed in the asymmetric aldol, Mannich, Michael addition, and α-functionalization, viz. α-aminoxylation-, α-amination-, and α-aminoxylation directed tandem reactions, among many others, providing rapid, catalytic, and atom-economical access to enantiomerically pure products.[19]

In continuation of our interest in organocatalysis[19] and asymmetric synthesis of piperidine and indolizidine alkaloids[20] we have recently accomplished the syntheses of (*R*)-coniine and (*S*)- coniceine, employing α-aminoxylation and sequential α-aminoxylation HWE olefination reaction catalysed by proline.



Scheme 9. Retrosynthetic route for the syntheses of (*R*)-coniine **1** and (*S*)- coniceine **2**.

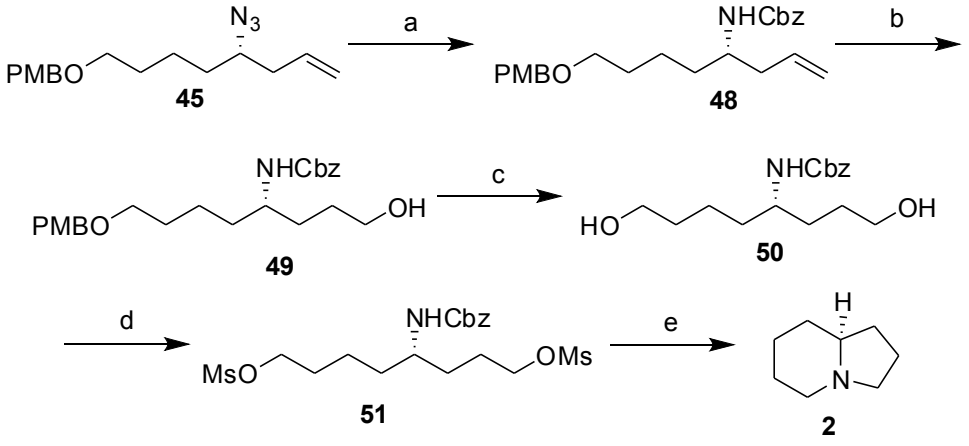
Our synthetic approach for the synthesis of (*R*)-coniine **1** and (*S*)-coniceine **2** was envisioned via the retrosynthetic route shown in the Scheme 9. Azide **45** was thought to be common intermediate for synthesis of both the molecules, which could be easily obtained from the epoxide **42** which in turn could be prepared from aminoxyalcohol **40**. Alcohol **40** could be easily obtained by the α-aminoxylation of the corresponding aldehyde **39**. Thus as shown in Scheme 10, synthesis of azide **45** began with the OPMB protected aldehyde **39**, which was subjected to α-aminoxylation catalysed by L-proline, followed by in situ reduction using $NaBH_4$ to furnish the *O*-amino-substituted diol **40** in 71% yield and >95% ee.[21] Appearance of multiplet in the range of δ 3.44-3.52, 3.63-3.69 and 3.93-4.00 in ^{1}H NMR and a peak at 3304 cm^{-1} in IR spectrum confirmed the formation of the compound **40**. Diol **40** was subjected to reductive hydrogenation condition to afford diol **41**, which on selective monotosylation and base treatment furnished epoxide **42** in 79% yield. Appearance of multiplet in the range of δ 2.45-2.49, 2.73-2.77, 2.87-2.94 in ^{1}H NMR and disappearance of OH peak at 3412 cm^{-1} in IR spectrum confirmed the formation of the epoxide **42**. Regioselective opening of epoxide **42** with lithium acetylide.EDA complex afforded homopropargyl alcohol **43**, which on partial reduction using H_2-Pd/C gave homoallyl alcohol **44**. Appearance of olefin protons as multiplets in the range of δ 5.00-5.02, 5.06-5.10, 5.64-5.85 in ^{1}H NMR confirmed the formation of the compound **44**. The free hydroxy group of **44** was then converted into azide **45** following a two step process of mesylation and sodium azide treatment. Appearance of peak at 2104 cm^{-1} and disappearance of peak at 3464 cm^{-1} in IR spectrum confirmed the formation of azide **45**. This azide **45** was used as a common precursor for the synthesis of (*R*)-coniine **1** and (*S*)-coniceine **2**. For the synthesis of (*R*)-coniine **1**, the double bond reduction and in situ conversion of azide to Boc protected amine was achieved in one step using H_2/Pd-C and $(Boc)_2O$. Subsequent PMB deprotection using DDQ, afforded the hydroxy compound **46**. Appearance of peak at 3464, 1740 cm^{-1} and disappearance of peak at 2104 cm^{-1} in IR spectrum confirmed the formation of compound **46**. The free hydroxy group of **46** was protected as mesyl ester followed by base treatment to furnish Boc protected (*R*)-coniine. The HCl salt of (*R*)-coniine **1** was easily achieved by Boc deprotection using methanolic HCl. {$[\alpha]_D^{25}$: -8.64 (*c* 0.25, EtOH)}; Lit[13] {$[\alpha]_D^{25}$: -7.3 (*c* 0.33, EtOH)}. The physical and spectroscopic data of **1** were in full agreement with the literature data.



Scheme 10. *Reagents and conditions*: (a) (i) L-Proline, nitrosobenzene, DMSO; (ii) $NaBH_4$, MeOH, 71% (over two steps); (b) H_2/Pd-C, EtOAc, 85%; (c) (i) TsCl, Bu_2SnO, Et_3N; (ii) K_2CO_3, MeOH, 79%; (d) Li. Acetylide, DMSO, 82%; (e) H_2-Lindlar's catalyst, EtOAc, 90%; (f) (i)MsCl, Et_3N; (ii) NaN_3, DMF, 68%; (g) (i) H_2/Pd-C, $(Boc)_2O$, EtOAc; (ii) DDQ, $NaHCO_3$, DCM: H_2O, 80%; (h) MsCl, Et_3N, 85%; (i) NaH, -78 °C, HCl in methanol, 90%.

Similarly for the synthesis of (*S*)-coniceine **2**, the azide **45** was subjected to Staudinger reaction and converted into amine which on Cbz protection with benzyl chloroformate led to compound **48**. Appearance of peak at 1716 cm^{-1} and disappearance of peak at 2104 cm^{-1} in IR spectrum confirmed the formation of compound **48**. The compound **48** was subjected to hydroboration-oxidation reaction to afford alcohol **49** as confirmed by the appearance of peak at 3318 cm^{-1} in IR and disappearance of olefin protons in the range of δ 4.53-4.65, 5.69-5.89 in ^1H NMR spectrum. Further in order to achieve the synthesis of **2** the PMB group was deprotected and the free hydroxy groups were protected as mesyl ester to furnish **51**. Appearance of singlet at δ 2.99 and disappearance of doublet at δ 6.89, 7.27 in ^1H NMR confirmed the formation of mesylate **51**. Finally the concomitant Cbz deprotection and cyclisation under hydrogenation condition furnished (*S*)-coniceine **2** in excellent yield (Scheme 11). $[\alpha]_D^{25}$: + 9.5 (*c* 1.1, EtOH), {Lit[13] {$[\alpha]_D^{25}$: +10.2 (*c* 1.76,

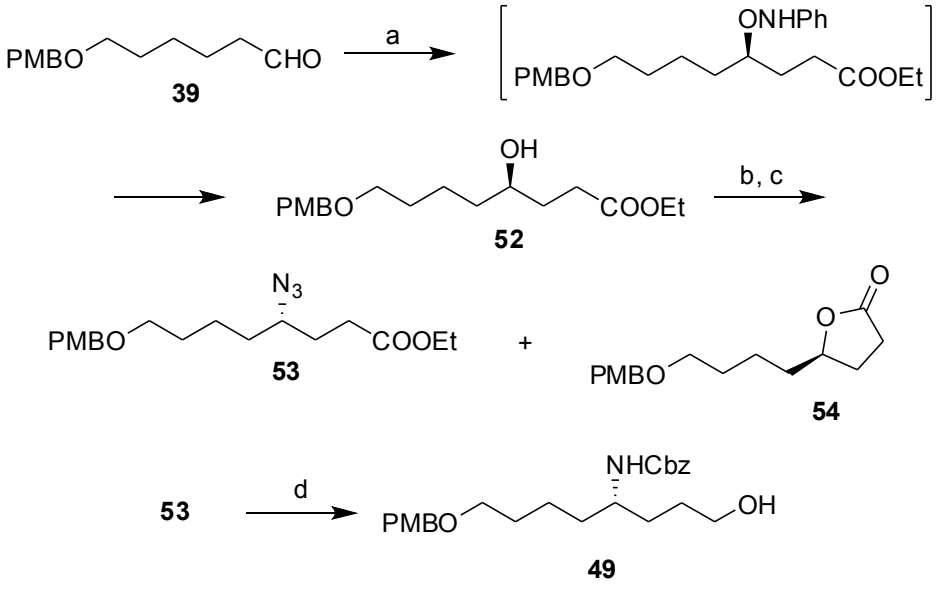
EtOH)}. The physical and spectroscopic data of **2** were in full agreement with the literature data.[13]



Scheme 11. *Reagents and conditions*: (a) (i) TPP, THF:H_2O then CbzCl, Na_2CO_3, 1,4-dioxane:H_2O, 90%; (b) BH_3.THF, THF, then H_2O_2, 86%; (c) DDQ, $NaHCO_3$, DCM: H_2O, 86%; (d) MsCl, Et_3N, 84%; (e) H_2-$Pd(OH)_2$, EtOAc, 80%.

Alternatively, in order to reduce the overall number of steps for the synthesis of (*S*)-coniceine **2**, compound **49** can be easily prepared form γ-hydroxy esters **52**. We have recently reported a two step one column modification to sequential α-aminoxylation and HWE olefination reaction of aldehyde reported by Zhong *et al*. where in one can prepare γ-hydroxy esters in moderate to good yields and excellent ee.[19] Thus sequential α-aminoxylation and HWE olefination of aldehyde **39** and subsequent reduction of the obtained *O*-amine substituted ester furnished γ-hydroxy ester **52** in 65% yield and 95% ee.[22] Appearance of quartet at δ 4.18 and doublets at δ 6.91, 7.29 in ^{1}H NMR along with appearance of broad peak at 3452 cm^{-1} in IR spectrum confirmed the formation of γ-hydroxy ester **52**. The free hydroxy group of **52** on mesyl protection using mesyl chloride and azide displacement gave azide ester **53** along with a small amount of lactone **54**. Disappearance of peak at 3452 cm^{-1} and appearance of peat at 2099 cm^{-1} in IR spectrum confirmed the formation of azide. Similarly, disappearance of peak at 3452 cm^{-1} and appearance of peak at 1768 cm^{-1} in IR spectrum confirmed the formation of lactone **54**. Lactone is probably formed during mesylation step. Azide **53** was subjected to Staudinger reaction and converted into amine which on Cbz protection with benzyl chloroformate led

to NHCbz ester, which on subsequent DIBAL-H reduction gave compound **49** in good yield.



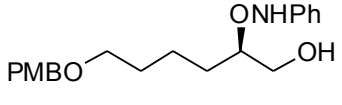
Scheme 12. *Reagents and conditions*:. (a) Nitrosobenzene, L-proline, DMSO, HWE salt, DBU, LiCl, CH_3CN; (b) H_2/Pd-C, EtOAc, 65% (over two steps); (c) (i) MsCl, Et_3N; (ii) NaN_3, DMF, 71% (over two steps); (d) (i) TPP, THF: H_2O then CbzCl, Na_2CO_3, 1,4 dioxane:H_2O; (ii) DIBAL–H, DCM, 0 °C, 60% (over two steps).

4.2.5. Conclusion

In conclusion, α-aminoxylation and sequential α-aminoxylation, HWE olefination approaches have been successfully applied towards the synthesis of (*S*)-coniceine and (*R*)-coniine. The present methods are easily amenable for the synthesis of variety of piperidine and indolizidine alkaloids and currently studies are in progress towards this direction.

4.2.6. Experimental Section

(*R*)-6-(4-Methoxybenzyloxy)-2-(phenylaminooxy)hexan-1-ol (40):



To a stirred solution of 6-(4-methoxybenzyloxy)hexanal **39** (1.00 g, 4.24 mmol) and nitrosobenzene (0.379 g, 3.53 mmol) in DMSO (9 mL) was added L-proline (0.097 g, 0.84 mmol, 20 mol %) in one portion at 25 °C. After 1 h, the temperature was lowered to 0 °C, followed by dilution with anhyd. MeOH (10 mL) and careful addition of excess $NaBH_4$ (0.643 g, 17.0 mmol). The reaction was quenched after 10 min by pouring the reaction mixture into a vigorously stirred biphasic solution of Et_2O and aqueous HCl (1 M). The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phases were dried over anhyd Na_2SO_4, concentrated, and purified by column chromatography over silica gel using EtOAc/Pet. Ether (40:60) as eluent to give pure aminoxy alcohol **40**.

Yield: 1.03 g, 71%

Mol. Formula: $C_{20}H_{27}NO_4$

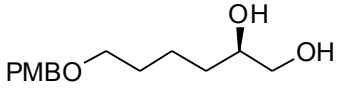
IR ($CHCl_3$, cm^{-1}): ν_{max} 3304, 3028, 2979, 2358, 1714, 1600, 1494, 1454, 1029.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.44-1.68 (m, 8H), 3.44-3.52 (m, 3H), 3.63-3.69 (m, 1H), 3.83 (s, 3H), 3.93-4.00 (m, 1H), 4.46 (s, 2H), 6.88-6.93 (m, 2H), 6.98-7.04 (m, 2H), 7.22-7.38 (m, 5H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 22.4, 29.6, 29.7, 55.2, 65.0, 69.7, 72.5, 83.8, 113.7, 114.7, 122.3, 122.8, 128.9, 129.2, 130.5, 148.4, 159.1 ppm.

Analysis Calcd.: C, 69.54; H, 7.88; N, 4.05; **Found:** C, 69.67; H, 7.71; N, 4.17%

(*R*)-6-(4-Methoxybenzyloxy)hexane-1,2-diol (41):



The aminoxy alcohol **40** (1.00 g, 2.89 mmol) was dissolved in methanol (10 mL) and to the solution was added 10% Pd/C (0.050 g) and the reaction mixture was stirred in a hydrogen atmosphere (1 atm, balloon pressure) for 12 h. After completion of the reaction (monitored by TLC) the reaction mixture was filtered through a celite pad, concentrated, and the crude product was then purified by silica gel chromatography using EtOAc/Pet. ether (40:60) as eluent to give pure diol **41**.

Yield: 0.625 g, 85%

Mol. Formula: $C_{14}H_{22}O_4$

$[\alpha]_D^{25}$: + 0.84 (*c* 0.5, $CHCl_3$)

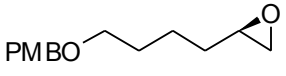
IR ($CHCl_3$, cm^{-1}): ν_{max} 3412, 3018, 2938, 1612, 1513, 1248, 1215.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.33-1.56 (m, 6H), 2.81 (bs, 2H), 3.27-3.40 (m, 3H), 3.49-3.56 (m, 1H), 3.59-3.63 (m, 1H), 3.72 (s, 3H), 4.35 (s, 2H), 6.80 (d, *J* = 8.70, 2H), 7.18 (d, *J* = 8.70, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 22.1, 29.5, 32.7, 55.2, 66.5, 69.8, 72.0, 72.4, 113.7, 129.2, 130.4, 159.1 ppm.

Analysis Calcd.: C, 66.12; H, 8.72%, **Found:** C, 66.02; H, 8.84%

(*R*)-2-(4-(4-Methoxybenzyloxy)butyl)oxirane (42):



To a mixture of diol **41** (0.21 g, 0.83 mmol), in dry dichloromethane (5 mL) was added dibutyltin oxide (0.004 g, 0.016 mmol) followed by the addition of *p*-toluenesulfonyl chloride (0.16 g, 0.83 mmol) and triethylamine (0.12 mL, 3.3 mmol) and reaction was stirred at room temperature under nitrogen. The reaction was monitored by TLC, after completion of reaction (15 min) the mixture was quenched by adding water. The solution was extracted with dichloromethane (3 x 10 ml) and then combined organic phase was washed with water, dried (Na_2SO_4) and concentrated. To this crude mixture in MeOH at 0 °C was added K_2CO_3 (0.22 g, 1.56 mmol) and the resultant mixture was allowed to stir for 1 h at same temp. After completion of reaction as indicated by TLC the reaction was quenched by addition of ice pieces and methanol was evaporated. The concentrated reaction mixture was then extracted with ethyl acetate (3 x 20 mL), the combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The column chromatography of crude product using pet ether:ethyl acetate (9:1) gave the epoxide **42** as a colorless liquid.

Yield: 0.15 gm, 79%

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

$[\alpha]_D^{25}$: + 4.18 (*c* 1.00, $CHCl_3$)

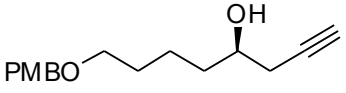
IR ($CHCl_3$, cm^{-1}): ν_{max} 2934, 2858, 1612, 1586, 1513, 1463, 1248.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.52-1.67 (m, 6H), 2.45-2.49 (m, 1H), 2.73-2.77 (m, 1H), 2.87-2.94 (m, 1H), 3.46 (t, J = 6.3 Hz, 2H), 3.81 (s, 3H), 4.44 (s, 2H), 6.88 (d, J = 8.7, 2H), 7.27 (d, J = 8.7, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 22.6, 29.4, 32.2, 46.9, 52.1, 55.1, 69.7, 72.5, 113.7, 129.1, 130.6, 159.1 ppm.

Analysis Calcd.: C, 71.16; H, 8.53%; **Found:** C, 71.04; H, 8.65%.

(*R*)-8-(4-Methoxybenzyloxy)oct-1-yn-4-ol (43):



To a solution of epoxide **42** (0.5 g, 2.11 mmol) in DMSO (2 mL) at 0 °C was added lithium acetylide-EDA complex (0.29 g, 3.16 mmol) in one portion. The reaction mixture was stirred at 0 °C for 30 min and 12 h at room temperature. The excess of reagent was quenched with 0.3 N H_2SO_4 and extracted with diethylether, washed with water, brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel chromatography by eluting with light petroleum: EtOAc (9:1) to afford the alkyne product **43** as a colorless liquid.

Yield: 0.46 g, 82%

Mol. Formula: $C_{16}H_{22}O_3$

$[\alpha]_D^{25}$: +1.07 (*c* 1.02, $CHCl_3$)

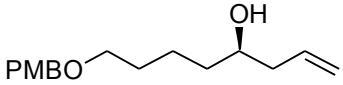
IR ($CHCl_3$, cm^{-1}): ν_{max} 3438, 3305, 3016, 2937, 2250, 1608, 1463, 1249.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.43-1.68 (m, 6H), 1.79 (bs, 1H), 2.06 (t, J = 2.6 Hz, 1H), 2.33-2.42 (m, 2H), 3.46 (t, J = 6.3 Hz, 2H), 3.71-3.74 (m, 1H), 3.81 (s, 3H), 4.44 (s, 2H), 6.88 (d, J = 8.7, 2H), 7.27 (d, J = 8.7, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 22.3, 27.3, 29.5, 35.9, 55.3, 69.8, 70.8, 72.6, 80.9, 113.8, 129.2, 130.6, 131.5, 159.1 ppm.

Analysis Calcd.: C, 73.25; H, 8.45%; **Found:** C, 73.38 H, 8.31%.

(*R*)-8-(4-Methoxybenzyloxy)oct-1-en-4-ol (44):



To a solution of homopropargyl alcohol **43** (1.00 g, 3.81 mmol) in ethyl acetate (10 mL) was added Lindlar's catalyst (0.08 g). The reaction mixture was stirred for 0.5 h under a balloon of H_2 at room temperature and filtered through a celite pad. The filtrate was concentrated and the residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1) as eluent to give **44** (0.90 g, 90%) as a pale yellow oil.

Yield: 0.90 g, 90%

Mol. Formula: $C_{16}H_{24}O_3$

$[\alpha]_D^{25}$: + 3.60 (*c* 1.35, $CHCl_3$)

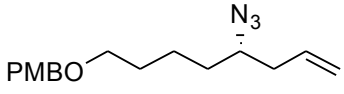
IR ($CHCl_3$, cm^{-1}): ν_{max} 3464, 2983, 1614, 1587, 1514, 1447, 1373, 1098.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.32-1.43 (m, 5H), 1.52-1.59 (m, 2H), 2.01-2.24 (m, 2H), 3.37 (t, *J* = 2.6 Hz, 2H), 3.48-3.61 (m, 1H), 3.72 (s, 3H), 4.35 (s, 2H), 5.00-5.02 (m, 1H), 5.06-5.10 (m, 1H), 5.64-6.85 (m, 1H), 6.78 (d, *J* = 8.7, 2H), 7.18 (d, *J* = 8.7, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 22.1, 29.4, 36.2, 41.7, 54.8, 69.7, 70.3, 70.9, 72.2, 113.5, 117.3, 129.0, 134.8, 158.8 ppm.

Analysis Calcd.: C, 72.69; H, 9.15%; **Found:** C, 72.80; H, 9.29%.

(*S*)-1-((5-Azidooct-7-enyloxy)methyl)-4-methoxybenzene (45)



To an ice-cold stirred solution of homoallyl alcohol **44** (1.0 g, 3.78 mmol) and triethylamine (0.95 mL, 6.8 mmol) in anhydrous CH_2Cl_2 (75 mL) was added dropwise methanesulfonyl chloride (0.32 mL, 4.16 mmol) over 15 min. The resulting mixture was allowed to warm up to room temperature and stirred for 2 h. After diluting with 100 mL CH_2Cl_2, the solution was washed with water (3 x 50 mL), brine, dried over Na_2SO_4 and concentrated to give the crude mesylated product. This was used for the next step without further purification. To a solution of above mesylated product in dry DMF (15 mL) was added portionwise NaN_3 (1.47 g, 22.69 mmol) and the resulting suspension was stirred for 24 h at 45 °C. After cooling the orange solution to room temperature, Et_2O (50 mL) and

H_2O (50 mL) were added and the aqueous layer was extracted with Et_2O (3 x 40 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. Silica gel column chromatography of the crude product using petroleum ether gave azide **45** as a yellowish liquid.

Yield: 0.74 g, 68%

Mol. Formula: $C_{16}H_{23}N_3O_2$

$[\alpha]_D^{25}$: - 21.41 (*c* 1.25, $CHCl_3$)

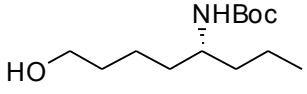
IR ($CHCl_3$, cm^{-1}): ν_{max} 2931, 2253, 2104, 1607, 1512, 1465, 1258.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.48-1.66 (m, 6H), 2.27-2.34 (m, 2H), 3.31-3.36 (m, 1H), 3.46 (t, *J* = 6.2 Hz, 2H), 3.81 (s, 3H), 4.44 (s, 2H), 5.10-5.12 (m, 1H), 5.15-5.21 (m, 1H), 5.72-5.92 (m, 1H), 6.89 (d, *J* = 8.70, 2H), 7.27 (d, *J* = 8.70, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 22.8, 29.4, 33.7, 38.7, 55.2, 62.2, 69.7, 72.5, 113.7, 118.0, 129.2, 130.6, 133.9, 159.1 ppm.

Analysis Calcd: C, 66.41; H, 8.01; N, 14.52%; **Found:** C, 66.56; H, 8.17; N, 14.65%.

(*R*)-*tert*-Butyl 8-hydroxyoctan-4-ylcarbamate (46):



To a solution of azide **45** (0.80 gm, 2.76 mmol) in ethyl acetate (8 mL) was added 10% Pd/ C (0.05 gm) and Boc_2O (0.7 mL, 3.04 mmol). The resulting solution was stirred under hydrogen atmosphere for 12 h at room temperature until disappearance of the azido alcohol as monitored by TLC. The reaction mixture was filtered through a celite pad to remove the catalyst and the filtrate was concentrated in vacuo. To a crude solution of above ester (0.96 g, 2.61 mmol) in CH_2Cl_2 (9.5 mL) and water (0.5 mL) was added 2,3-dichloro-5,6-dicyano benzoquinone (DDQ) (0.66 g, 2.88 mmol). Reaction mixture was stirred at rt for 30 min. After completion (monitored by TLC), the reaction mixture quenched by addition of ice cooled aq. solution of $NaHCO_3$ and reaction mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layer was washed with saturated sodium bicarbonate solution followed by brine, dried (Na_2SO_4) and concentrated to afford the crude product. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (8:2) as eluent gave compound **46** as a oily liquid.

Yield: 0.542 g, 80%

Mol. Formula: $C_{13}H_{27}NO_3$

$[\alpha]_D^{25}$: + 4.32 (*c* 1.72, $CHCl_3$)

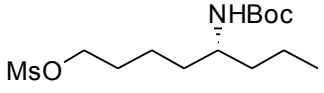
IR ($CHCl_3$, cm^{-1}): ν_{max} 3464, 2984, 2256, 1740, 1518, 1478, 1465, 1243.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88-0.99 (m, 3H), 1.25-1.35 (m, 4H), 1.43 (s, 9H), 1.52-1.79 (m, 4H), 1.94-2.04 (m, 2H), 2.26-2.44 (m, 1H), 3.63 (t, *J* = 6.4 Hz, 2H), 4.30 (t, *J* = 6.7 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 14.0, 19.1, 22.0, 27.4, 28.4, 30.5, 32.5, 35.4, 38.0, 62.7, 65.5, 167.7 ppm.

Analysis Calcd.: C, 63.64; H, 11.09; N, 5.71%; **Found:** C, 63.80; H, 11.21; N, 5.58%.

(*R*)-5-(*tert*-Butoxycarbonylamino)octyl methanesulfonate(47):



To an ice-cold stirred solution of **46** (0.3 g, 1.22 mmol) and triethylamine (0.31 mL, 2.2 mmol) in anhydrous CH_2Cl_2 (7 mL) was added dropwise methanesulfonyl chloride (0.10 mL, 1.34 mmol) over 15 min. The resulting mixture was allowed to warm up to room temperature and stirred for 2 h. After diluting with 15 mL CH_2Cl_2, the solution was washed with water (3 x 25 mL), brine, dried over Na_2SO_4 and concentrated to give the crude mesylated product. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (8:2) as eluent gave compound **47** as a oily liquid.

Yield: 0.34 g, 85%

Mol. Formula: $C_{14}H_{29}NO_5S$

$[\alpha]_D^{25}$: + 2.80 (*c* 1.16, $CHCl_3$)

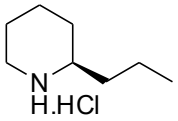
IR ($CHCl_3$, cm^{-1}): ν_{max} 2985, 1742, 1464, 1447, 1373, 1242, 1047.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.90 (t, *J* = 6.7 Hz, 3H), 1.32-1.43 (m, 18H), 1.68-1.85 (m, 2H), 3.00 (s, 3H), 3.53 (bs, 1H), 4.22 (t, *J* = 6.5 Hz, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.8, 18.9, 21.7, 28.2, 28.8, 34.8, 37.1, 37.6, 49.9, 69.9, 78.7, 155.7 ppm.

Analysis Calcd.: C, 51.99; H, 9.04; N, 4.33; S, 9.91%; **Found:** C, 52.11; H, 9.11; N, 4.21; S, 9.79%

(*R*)-(-)-Coniine (1):



To a solution of mesyl ester **47** (0.10 g, 0.31 mmol) in DMF cooled to 0 °C was added NaH (0.01 g, 60% dispersion in oil). On completion of reaction as indicated by TLC (3h) the reaction mixture was cooled to 0 °C, quenched by addition of ice pieces, and the reaction mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic layer was washed with water, brine, and dried (Na_2SO_4). Silica gel column chromatography (EtOAc: Pet.ether/ 9:1) furnished the compound as a colorless liquid.

To the above product (0.05 gm, 0.22 mmol) in dry CH_2Cl_2 (2 mL) was added methanolic HCl (2 mL) in catalytic amount. The reaction mixture was stirred at room temperature for 2 h and then saturated aq. $NaHCO_3$ added and extracted with dichloromethane (3 x 5 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel column chromatography using CH_3OH/CH_2Cl_2 (1:10) as eluent to give **1** as solid compound. The physical and spectroscopic data of **1** were in full agreement with the literature data.[13]

Yield: 0.032 g, 90%

Mol. Formula: $C_8H_{17}N$

$[\alpha]_D^{25}$: - 8.64 (*c* 0.25, EtOH), {Lit[13] {$[\alpha]_D^{25}$: -7.3 (*c* 0.33, EtOH)}

IR ($CHCl_3$, cm^{-1}): ν_{max} 3020, 2962, 1215.

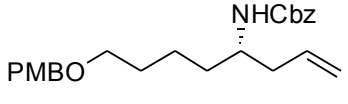
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.96 (t, *J* = 7.0 Hz, 3H), 1.46 (bs, 4H), 1.93 (bs, 5H), 2.85-2.92 (m, 2H), 3.45-3.50 (m, 1H), 9.14-9.39 (m, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 13.8, 18.7, 22.3, 22.4, 28.2, 35.4, 45.0, 57.3 ppm.

MS (ESI): m/z 128.2709 (M^++H)

Analysis Calcd.: C, 75.52; H, 13.47; N, 11.01%; **Found:** C, 75.65; H, 13.34; N, 11.15%.

(*S*)-Benzyl 8-(4-methoxybenzyloxy)oct-1-en-4-ylcarbamate (48):



To a solution of azide **45** (2.0 g, 6.91 mmol) in THF (30 ml)/ water (4.5 ml) was added PPh_3 (2.71 g, 10.36 mmol) and mixture was stirred at room temperature for 12 h. The mixture was concentrated and then 1,4-dioxane (25 mL)/ water (25 mL) and Na_2CO_3 (1.60 g, 15.20 mmol) were added and stirred for another 10 min at 0 °C. To this ice cold solution, benzyl chloroformate (1.28 mL, 8.98 mmol) was added and mixture stirred overnight at 0 °C to room temperature. The solvent was evaporated at reduced pressure and extracted with EtOAc (3 x 25 mL). The combined organic layer was washed with brine, water, dried (Na_2SO_4) and concentrated. Silica gel column chromatography (EtOAc/petroleum ether, 1:19) of the crude product gave compound **48** as a white solid.

Yield: 2.47 g, 90%

Mol. Formula: $C_{24}H_{31}NO_4$

$[\alpha]_D^{25}$: - 5.22 (*c* 1.8, $CHCl_3$)

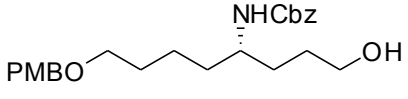
IR ($CHCl_3$, cm^{-1}): ν_{max} 3438, 3019, 2928, 1716, 1510, 1215.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.43-1.53 (m, 4H), 1.54-1.64 (m, 2H), 1.94 (bs, 1H), 2.21-2.30 (m, 1H), 3.46 (t, *J* = 6.3 Hz, 2H), 3.65-3.74 (m, 1H), 3.83 (s, 3H), 4.45 (s, 2H), 4.53-4.65 (m, 1H), 5.06-5.12 (m, 4H), 5.69-5.89 (m, 1H), 6.91 (d, *J* = 8.70, 2H), 7.30 (d, *J* = 8.70, 2H), 7.35-7.41 (m, 5H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 22.5, 29.4, 34.2, 39.3, 50.5, 55.1, 69.6, 72.3, 113.6, 117.6, 127.8, 128.3, 129.1, 130.5, 134.1, 136.6, 155.9, 159.0 ppm.

Analysis Calcd.: C, 72.52; H, 7.86; N, 3.52%; **Found:** C, 72.39; H, 7.98; N, 3.61%.

(*S*)-Benzyl 1-hydroxy-8-(4-methoxybenzyloxy)octan-4-ylcarbamate (49):



To a solution of olefin **48** (0.54 g, 1.36 mmol) in dry THF (10 mL) at 0 °C under argon atmosphere was added BH_3.DMS (0.207 g, 2.04 mmol, 2 M solution in THF) and the reaction mixture was allowed to warm to room temperature and stirred for 3 h. The reaction flask was cooled to 0 °C and then a solution of NaOH (0.108 g, 2.72 mmol) in EtOH/H_2O (2:1, 10 mL), followed by H_2O_2 (0.5 mL, 4.08 mmol, 30% w/v solution in water) were added drop wise over 15 min. It was then allowed to stir at room temperature for 6 h. The product was taken up in EtOAc and the aqueous layer extracted with EtOAc (3 x 15 mL). The combined organic layer was washed with brine, water, dried (Na_2SO_4) and

concentrated. Silica gel column chromatography (EtOAc/petroleum ether, 4:6) of the crude product gave alcohol **49** as a colourless liquid.

Yield: 0.49 g, 86%

Mol. Formula: $C_{24}H_{33}NO_5$

IR ($CHCl_3$, cm^{-1}): ν_{max} 3318, 3019, 2922, 1685, 1540, 1463, 1377, 1216, 1030.

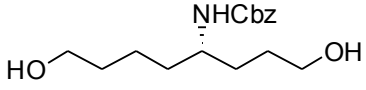
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.42-1.46 (m, 4H), 1.54-1.60 (m, 6H), 1.90 (bs, 2H), 3.42 (t, *J* = 6.3 Hz, 2H), 3.64 (t, *J* = 5.5 Hz, 3H), 3.80 (s, 3H), 4.42 (s, 2H), 5.09 (s, 2H), 6.89 (d, *J* = 8.70, 2H), 7.27 (d, *J* = 8.70, 2H), 7.33-7.36 (m, 5H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): *δ* 22.4, 28.6, 29.4, 31.6, 35.0, 50.9, 55.1, 62.2, 66.4, 69.7, 72.3, 113.6, 127.8, 128.3, 129.2, 130.4, 136.5, 156.3, 159.0 ppm.

Analysis Calcd.: C, 69.37; H, 8.00; N, 3.37; **Found:** C, 69.51; H, 8.15; N, 3.19%.

MS (ESI): m/z 438.2811 (M^++Na)

(*S*)-Benzyl 1,8-dihydroxyoctan-4-ylcarbamate (50):



To a solution of above hydroxy amine **49** (0.23 g, 0.603 mmol) in CH_2Cl_2 (9.5 mL) and water (0.5 mL) was added 2,3-dichloro-5,6-dicyano benzoquinone (DDQ) (0.15 g, 0.66 mmol). Reaction mixture was stirred at rt for 30 min. After completion (monitored by TLC), the reaction mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic fraction was washed with saturated sodium bicarbonate solution followed by brine, dried (Na_2SO_4) and concentrated to afford the crude product. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (6:4) as eluent gave compound **50** as an oily liquid.

Yield: 0.14 g, 86%

Mol. Formula: $C_{16}H_{25}NO_4$

$[\alpha]_D^{25}$: +2.53 (*c* 0.32, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3300, 3087, 2858, 1740, 1603, 1495, 1454, 1256, 1216, 1030.

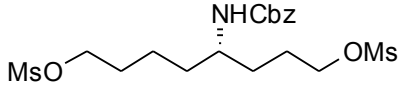
^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.39-1.59 (m, 10H), 2.58 (bs, 2H), 3.57-3.63 (m, 4H), 3.81-3.85 (m, 1H), 4.77-4.85 (bs, 1H), 5.08 (s, 2H), 7.34 (m, 5H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0, 28.7, 31.8, 32.3, 35.2, 51.0, 62.3, 62.4, 66.3, 128.0, 128.1, 128.5, 136.6, 156.6 ppm.

Analysis Calcd.: C , 65.06; H, 8.53; N, 4.74; **Found:** C, 65.19; H, 8.41; N, 4.88%.

MS (ESI): m/z 296.2657 (M^++H), 318.2326 (M^++Na).

(*S*)-4-(Benzyloxycarbonylamino)octane-1,8-diyl dimethanesulfonate (51):



To an ice-cold stirred solution of diol **50** (0.5 g, 1.69 mmol) and triethylamine (0.94 mL, 6.8 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise methanesulfonyl chloride (0.31 mL, 4.06 mmol) over 15 min. The resulting mixture was allowed to warm up to room temperature and stirred for 2 h. After diluting with 25 mL CH_2Cl_2, the solution was washed with water (3 x 15 mL), brine, dried over Na_2SO_4 and concentrated to give the crude mesylated product. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (7:3) as eluent gave compound **51** as an oily liquid.

Yield: 0.64 g, 84%

Mol. Formula: $C_{18}H_{29}NO_8S_2$

$[\alpha]_D^{25}$: + 0.82 (*c* 1.0, $CHCl_3$)

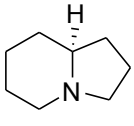
IR ($CHCl_3$, cm^{-1}): ν_{max} 3022, 2933, 2360, 1710, 1512, 1355, 1217.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.39-1.54 (m, 5H), 1.67-1.86 (m, 5H), 2.77-2.89 (m, 1H), 2.99 (s, 6H), 4.10-4.27 (m, 4H), 4.60-4.70 (m, 1H), 5.09 (s, 2H), 7.35 (m, 5H), ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 21.8, 25.7, 28.7, 31.5, 34.9, 37.3, 50.4, 66.7, 69.6, 128.0, 128.2, 128.5, 136.4 ppm.

Analysis Calcd.: C, 47.88; H, 6.47; N, 3.10; S, 14.20%; **Found:** C, 47.98; H, 6.31; N, 3.23; S, 14.31%.

(*S*)-(+)-Coniceine (2):



To the above mesylated product **51** (0.05 g, 0.11 mmol) in EtOAc (5 mL) was added $Pd(OH)_2$ (0.015 g) and reaction mixture was stirred under hydrogenation condition for 12 h, until disappearance of the mesyl compound as monitored by TLC. The reaction mixture was filtered through a celite pad to remove the catalyst and the filtrate was concentrated in vacuo. Silica gel column chromatography using CH_3OH/CH_2Cl_2 (1:10) as eluent gave **2** as solid compound. The physical and spectroscopic data of **2** were in full agreement with the literature data.

Yield: 0.011 g, 80%

Mol. Formula: $C_8H_{15}N$

$[\alpha]_D^{25}$: + 9.5 (*c* 1.1, EtOH), {Lit[13] $[\alpha]_D^{25}$: +10.2 (*c* 1.76, EtOH)}

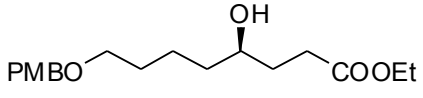
IR ($CHCl_3$, cm^{-1}): ν_{max} 2952, 2920, 1461, 1454, 1320,1255, 1096.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.12-1.87 (m, 11 H), 1.95 (dt, *J* = 3.6,11.2 Hz, 1H), 2.07 (q, *J* = 9.0 Hz, 1H), 3.02-3.12 (m, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 20.5, 24.5, 25.4, 30.4, 31.0, 53.0, 54.2, 64.3 ppm.

Analysis Calcd.: C, 76.74; H, 12.07; N, 11.19%; **Found:** C, 76.91; H, 12.25; N, 11.01%.

(*R*)-Ethyl 4-hydroxy-8-(4-methoxybenzyloxy)octanoate (52) :



To a solution of 6-(4-methoxybenzyloxy)hexanal **39** (2.0 g, 8.57 mmol) and nitroso benzene (0.92 g, 8.57 mmol) in anhydrous DMSO (18 mL) was added L-proline (0.40g, 3.42 mmol) at 20 °C. The mixture was vigorously stirred for 25 min under argon (the color of the reaction changed from green to yellow during this time), then cooled to 0 °C. Thereafter, A premixed and cooled (0 °C) solution of triethylphosphonoacetate (5.12 mL, 25.7 mmol), DBU (3.83 mL, 25.7 mmol) and LiCl (1.09 g, 25.7 mmol) in CH_3CN (18 mL) was added quickly (1-2 min) at 0 °C. The resulting mixture was allowed to warm to room temperature over 1 h, and quenched by addition of ice pieces. The acetonitrile was evaporated under vacuum. This reaction mixture then poured into water (50 mL) and was extracted with Et_2O (5×100 mL). The combined organic layers were washed with water, brine, dried (Na_2SO_4) and concentrated in vacuo to give crude product which was directly

subjected to next step without purification. To the crude allylic alcohol in ethyl acetate was added Pd-C (10%) under hydrogenation condition and the reaction mixture was allowed to stir overnight. On completion of reaction (until ^{1}H NMR analysis of the crude mixture indicated complete conversion), the mixture was filtered through a pad of celite and concentrated in vacuo to give γ-alcohol. The crude product was then purified by flash column chromatography using pet ether: EtOAc (85:15) as eluent to give (*R*)-ethyl 4-hydroxy-8-(4-methoxybenzyloxy)octanoate **52** as a colorless liquid.

Yield: 1.78 g, 65%

Mol. Formula: $C_{18}H_{28}O_5$

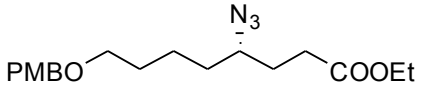
IR ($CHCl_3$, cm^{-1}): ν_{max} 3452, 2928, 1731, 1613, 1586, 1462, 1248, 1097.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.29 (t, *J* = 7.0 Hz, 3H), 1.37-1.51 (m, 4H), 1.54-1.78 (m, 4H), 2.33-2.56 (m, 2H), 3.48 (t, *J* = 6.3 Hz, 2H), 3.62-3.69 (m, 1H), 3.84 (s, 3H), 4.18 (q, *J* = 7.0 Hz, 2H), 4.46 (s, 2H), 6.91 (d, *J* = 8.70, 2H), 7.29 (d, *J* = 8.70, 2H) ppm.

Analysis Calcd.: C, 66.64; H, 8.70%; **Found:** C, 66.52; H, 8.86%.

MS (ESI): m/z 325.3509 (M^++H), 347.3415 (M^++Na), 363.3388, (M^++K).

(*S*)-Ethyl 4-azido-8-(4-methoxybenzyloxy)octanoate (53) :



To an ice-cold stirred solution of **52** (1.0 g, 3.08 mmol) and triethylamine (0.86 mL, 6.16 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise methanesulfonyl chloride (0.27 mL, 3.4 mmol) over 15 min. The resulting mixture was allowed to warm up to room temperature and stirred for 2 h. After diluting with 15 mL CH_2Cl_2, the solution was washed with water (3 x 50 mL), brine, dried over Na_2SO_4 and concentrated to give the crude mesylated product. This was used for the next step without further purification.

To a solution of above mesylated product in dry DMF (10 mL) was added portion wise NaN_3 (1.20 g, 18.5 mmol) and the resulting suspension was stirred for 24 h at 45 °C. After cooling the orange solution to room temperature, Et_2O (25 mL) and H_2O (25 mL) were added and the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure.

Silica gel column chromatography (petroleum ether: EtOAc/ 95:5) of the crude product gave azide **53** as a yellowish liquid.

Yield: 0.76 g, 71%

Mol. Formula: $C_{18}H_{27}N_3O_4$

$[\alpha]_D^{25}$: + 10.37 (*c* 1.54, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 2937, 2860, 2099, 1732, 1613, 1586, 1462, 1247, 1098.

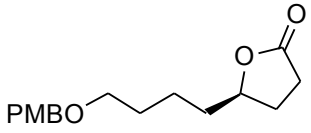
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.29 (t, *J* = 7.2 Hz, 3H), 1.55-1.81 (m, 8H), 2.39-2.49 (m, 2H), 3.29-3.38 (m, 1H), 3.48 (t, *J* = 6.0 Hz, 2H), 3.83 (s, 3H), 4.19 (q, *J* = 7.2 Hz, 2H), 4.46 (s, 2H), 6.91 (d, *J* = 8.7, 2H), 7.29 (d, *J* = 8.7, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 22.7, 29.3, 30.7, 34.0, 55.1, 60.4, 62.0, 69.5, 72.4, 113.6, 129.1, 130.4, 159.0, 172.8 ppm.

Analysis Calcd.: C, 61.87; H, 7.79; N, 12.03%; **Found:** C, 61.65; H, 7.63; N, 12.17%.

MS (ESI): m/z 372.3995 (M^++Na), 387.3571 (M^++K)

(*R*)-5-(4-(4-Methoxybenzyloxy)butyl)dihydrofuran-2(3*H*)-one (54) :



Yield: 0.21 g, 25%

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

$[\alpha]_D^{25}$: + 9.58 (*c* 1.24, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 2938, 2863, 2253, 1768, 1612, 1513, 1460, 1356, 1248, 1035.

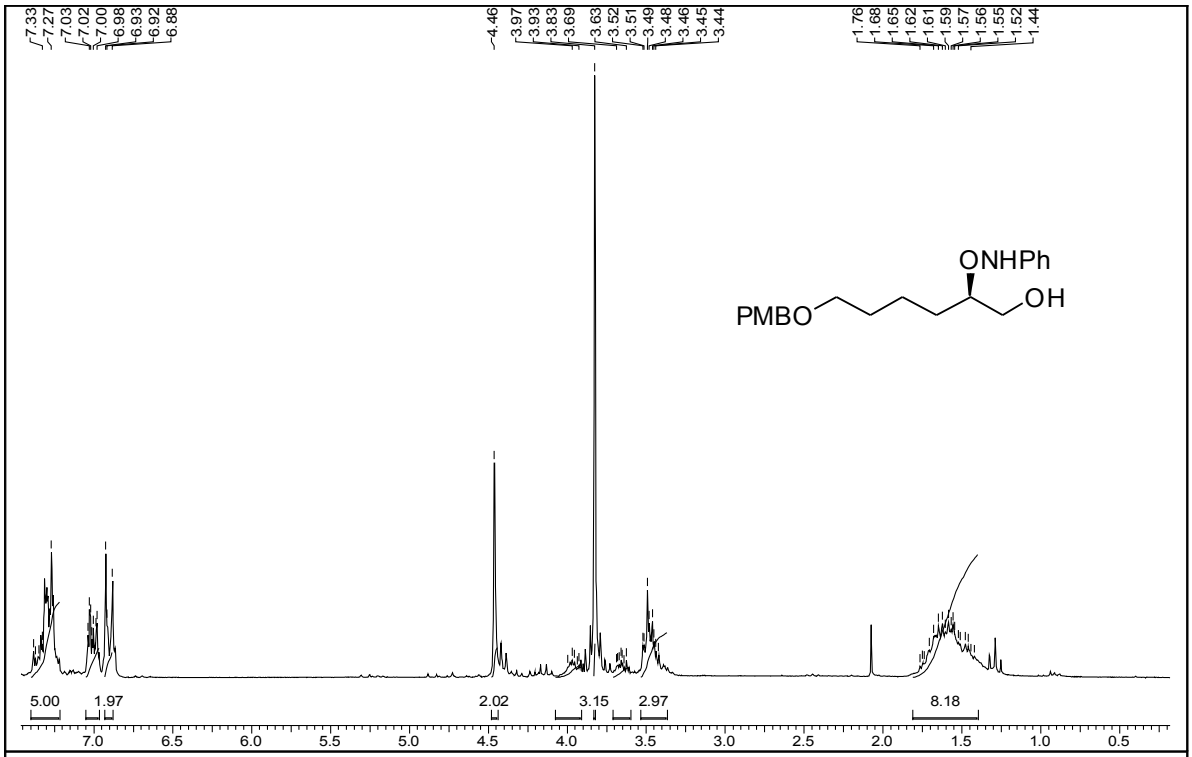
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.26-1.38 (m, 2H), 1.56-1.83 (m, 6H), 2.39-2.60 (m, 2H), 3.48 (t, *J* = 6.1 Hz, 2H), 3.84 (s, 3H), 4.11-4.23 (m, 1H), 4.46 (s, 2H), 6.91 (d, *J* = 8.70, 2H), 7.29 (d, *J* = 8.70, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 27.7, 28.6, 29.2, 35.1, 55.0, 66.4, 72.3, 80.7, 113.5, 129.0, 130.3, 158.9, 177.1 ppm.

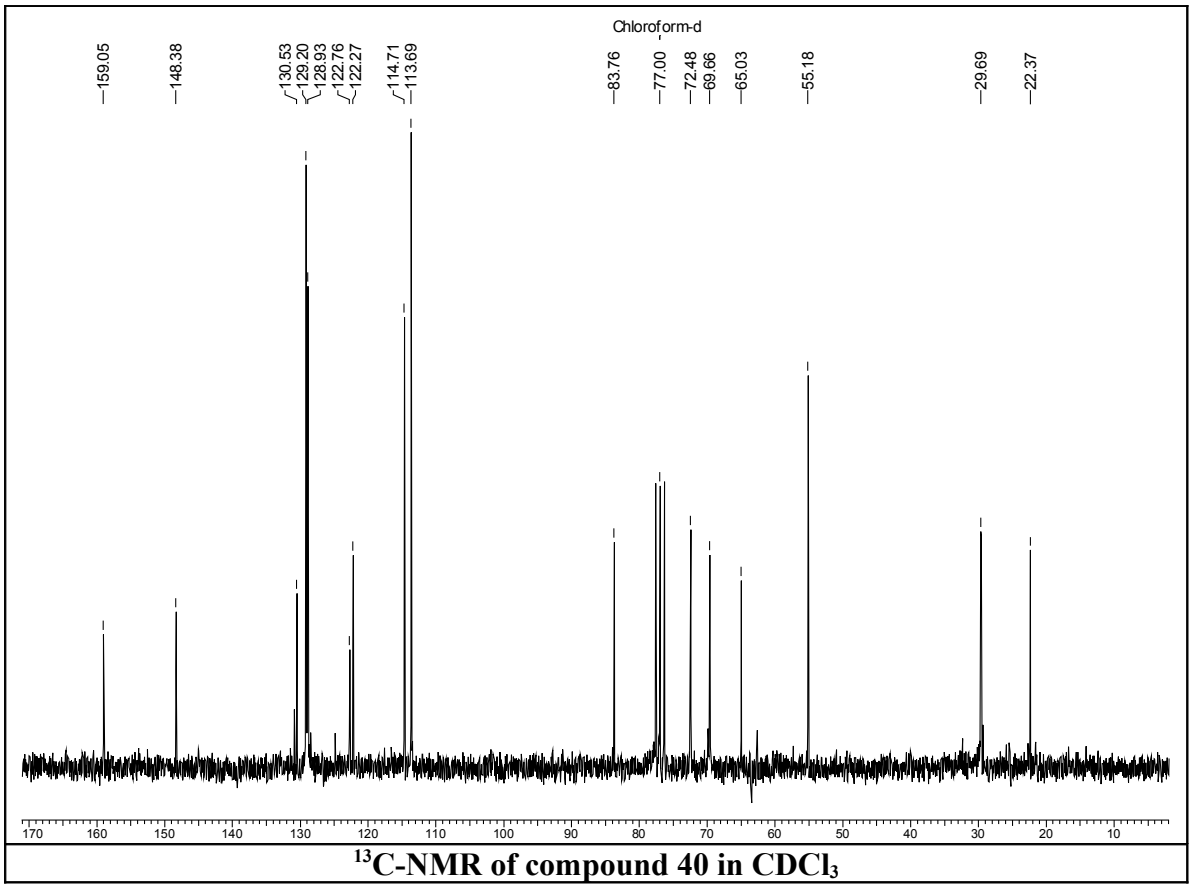
Analysis Calcd.: C, 69.04; H, 7.97%; **Found:** C, 69.21; H, 8.07%.

MS (ESI): m/z 301.3093 (M^++Na), 317.3053 (M^++K)

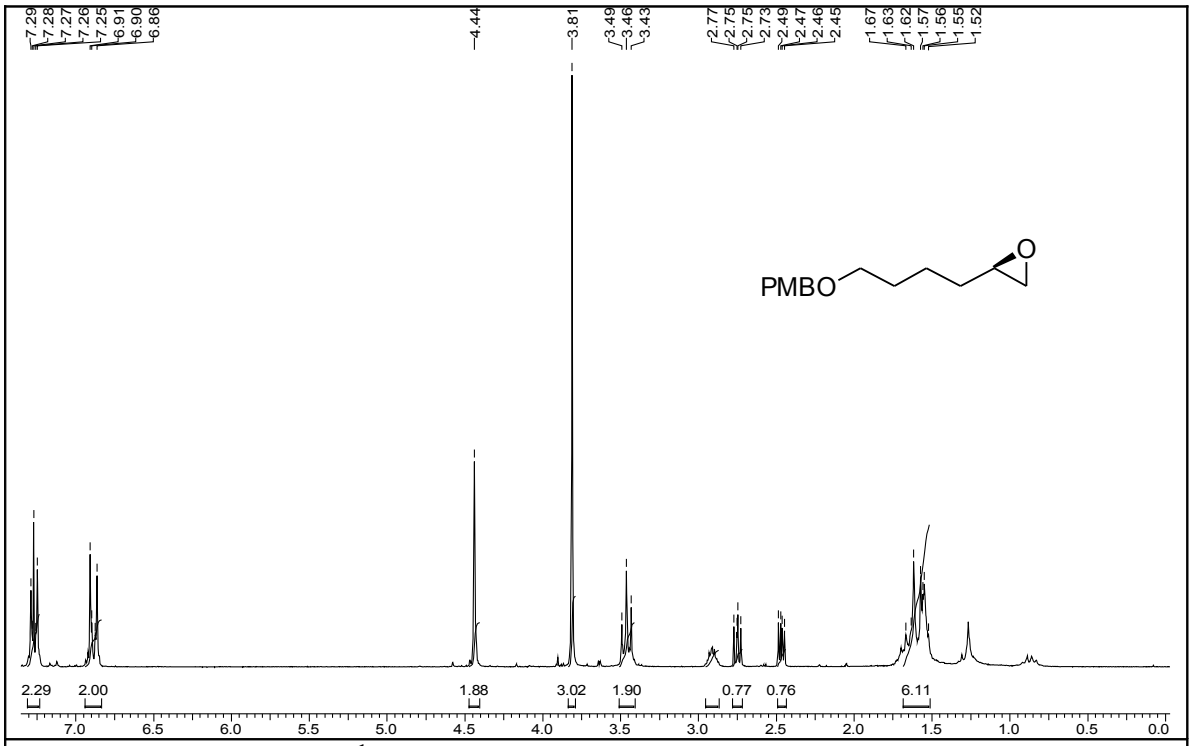
4.2.7. Spectras



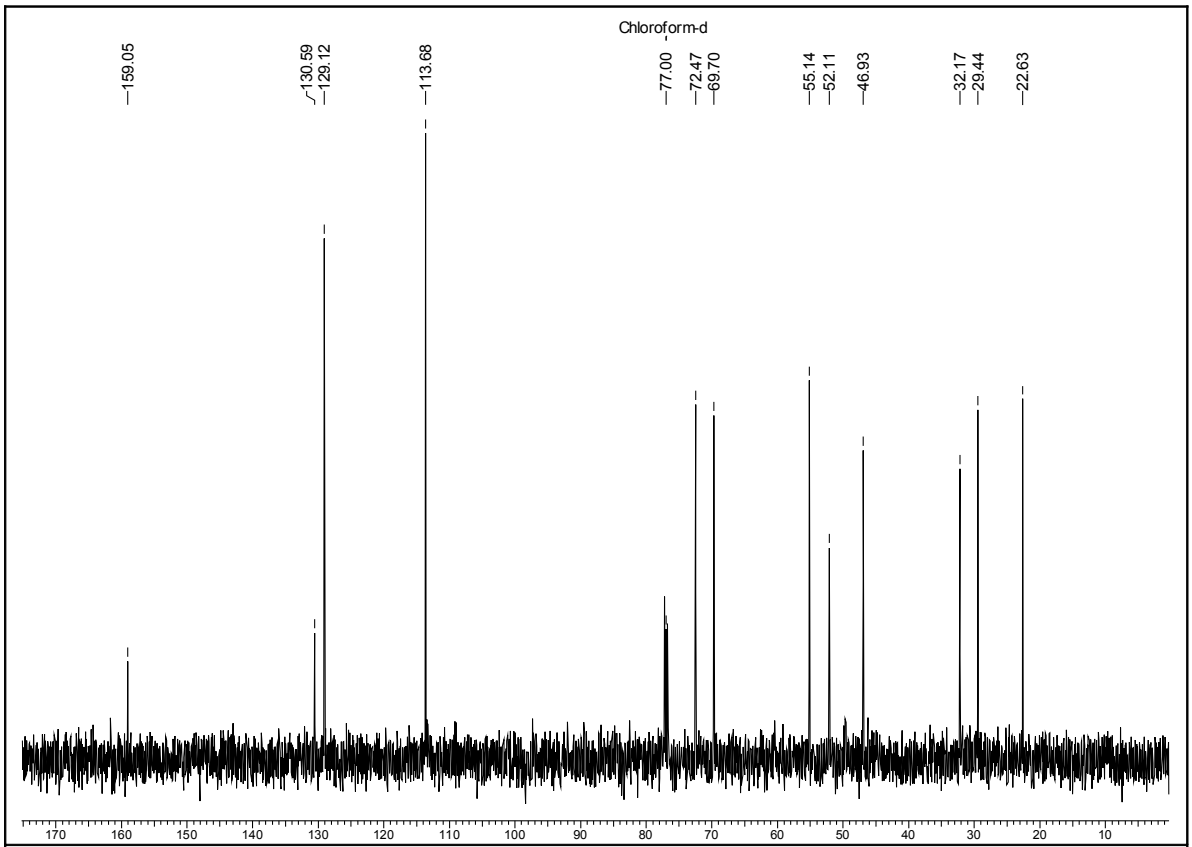
^{1}H-NMR of compound 40 in $CDCl_3$



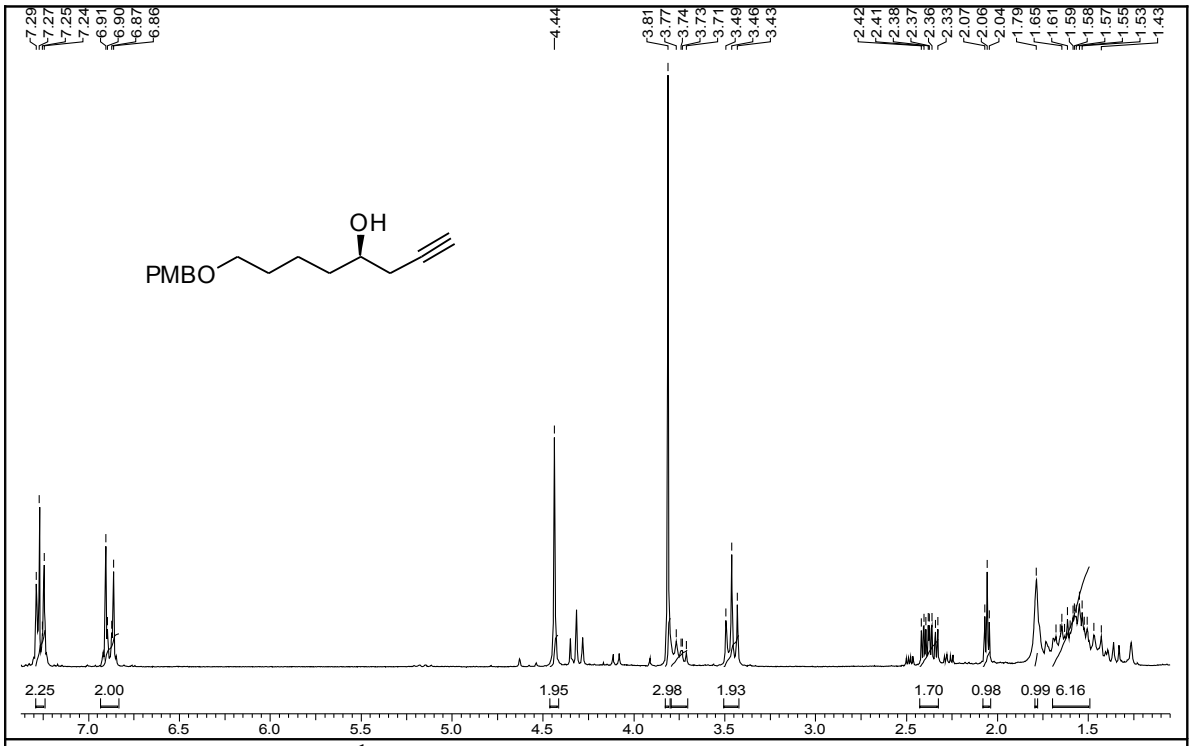
^{13}C-NMR of compound 40 in $CDCl_3$



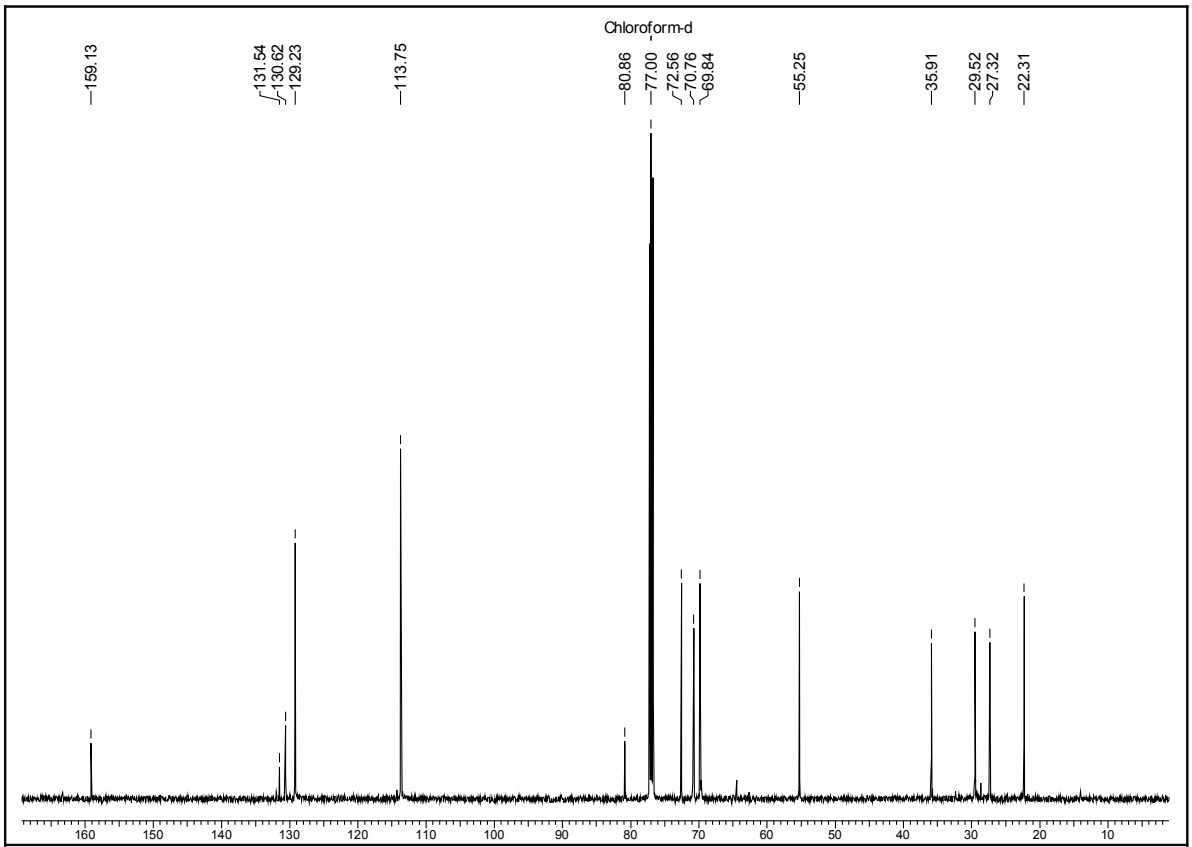
^{1}H-NMR of compound 42 in $CDCl_3$



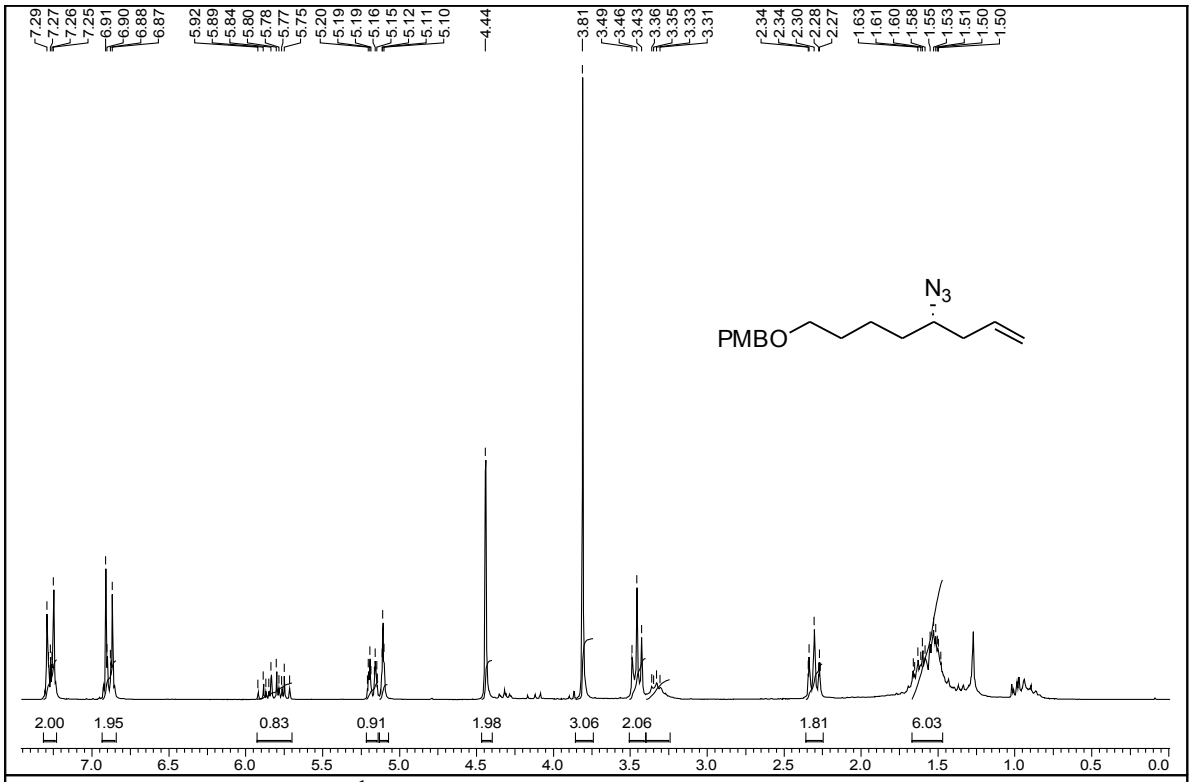
^{13}C-NMR of compound 42 in $CDCl_3$



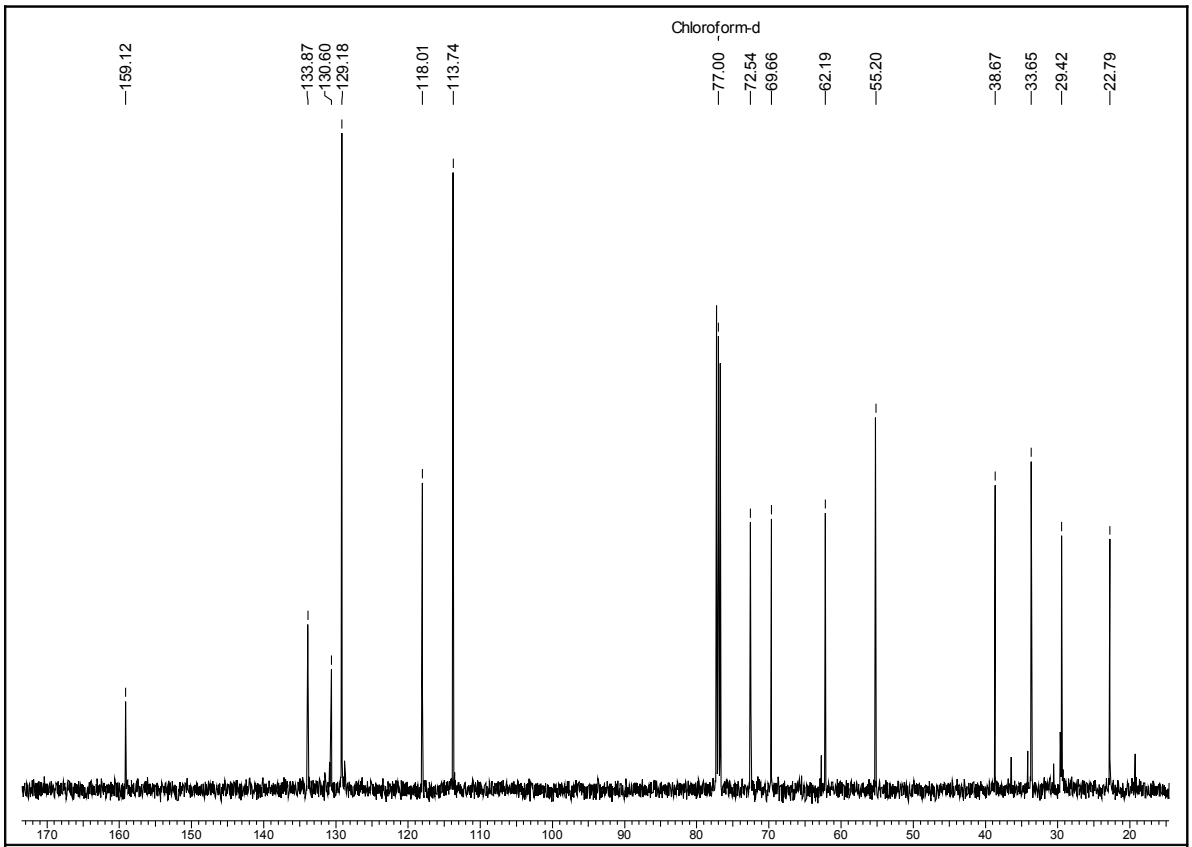
^{1}H-NMR of compound 43 in $CDCl_3$



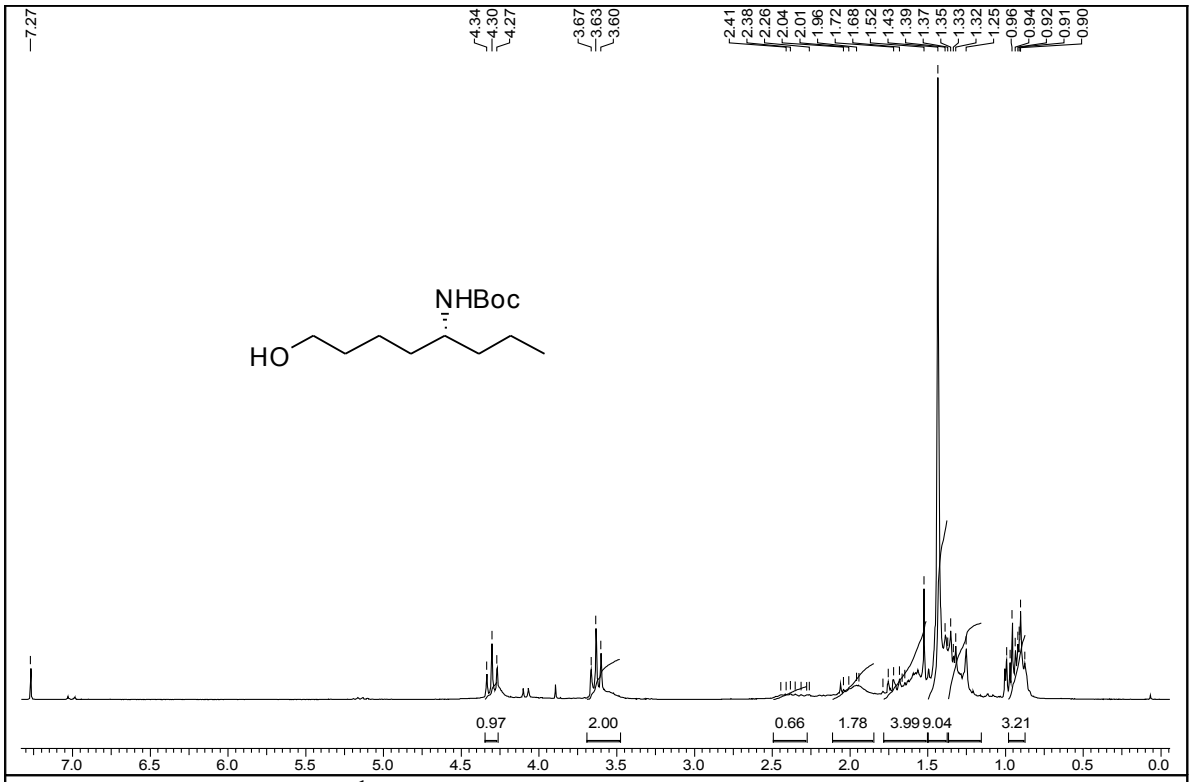
^{13}C-NMR of compound 43 in $CDCl_3$



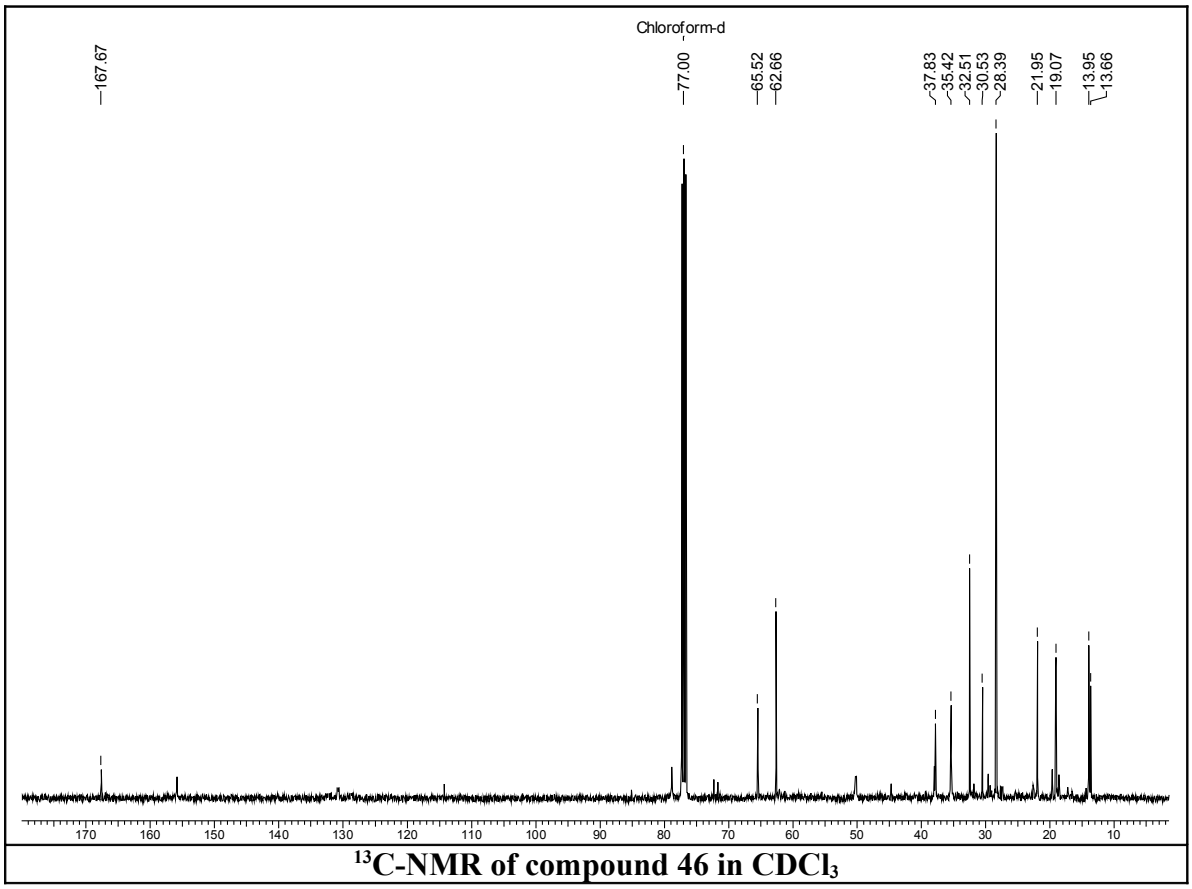
^{1}H-NMR of compound 45 in $CDCl_3$



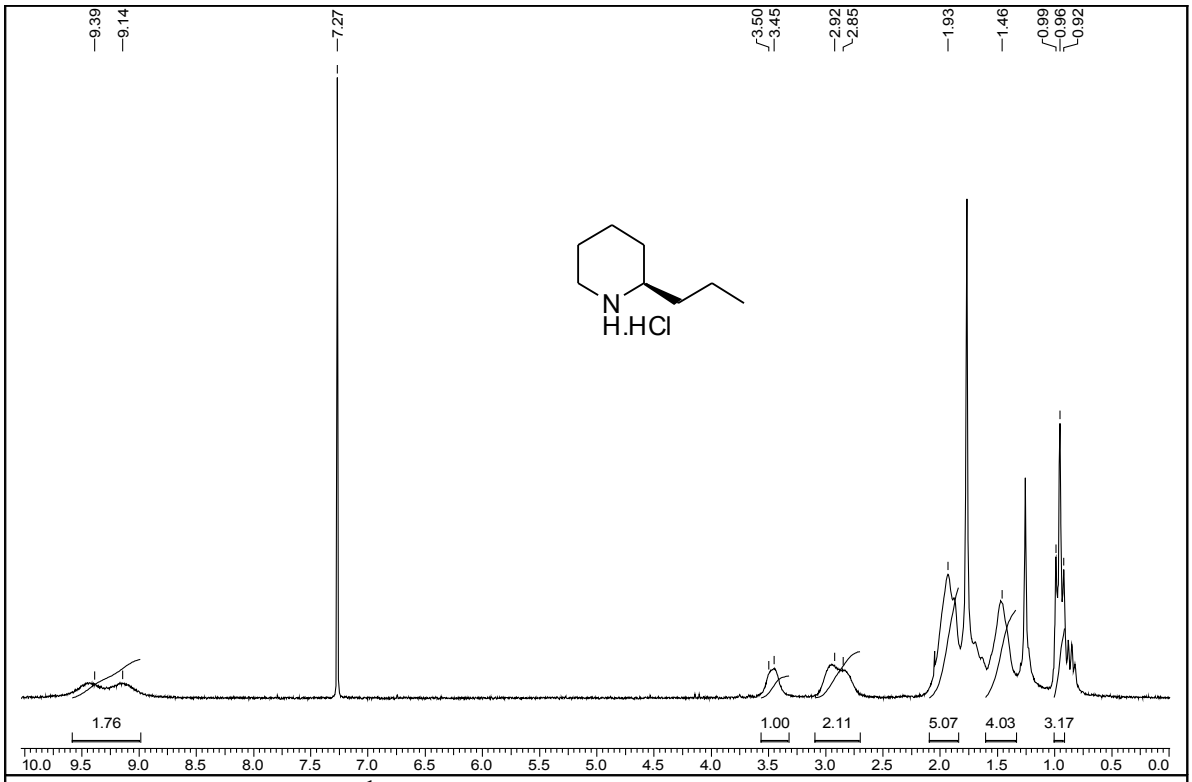
^{13}C-NMR of compound 45 in $CDCl_3$



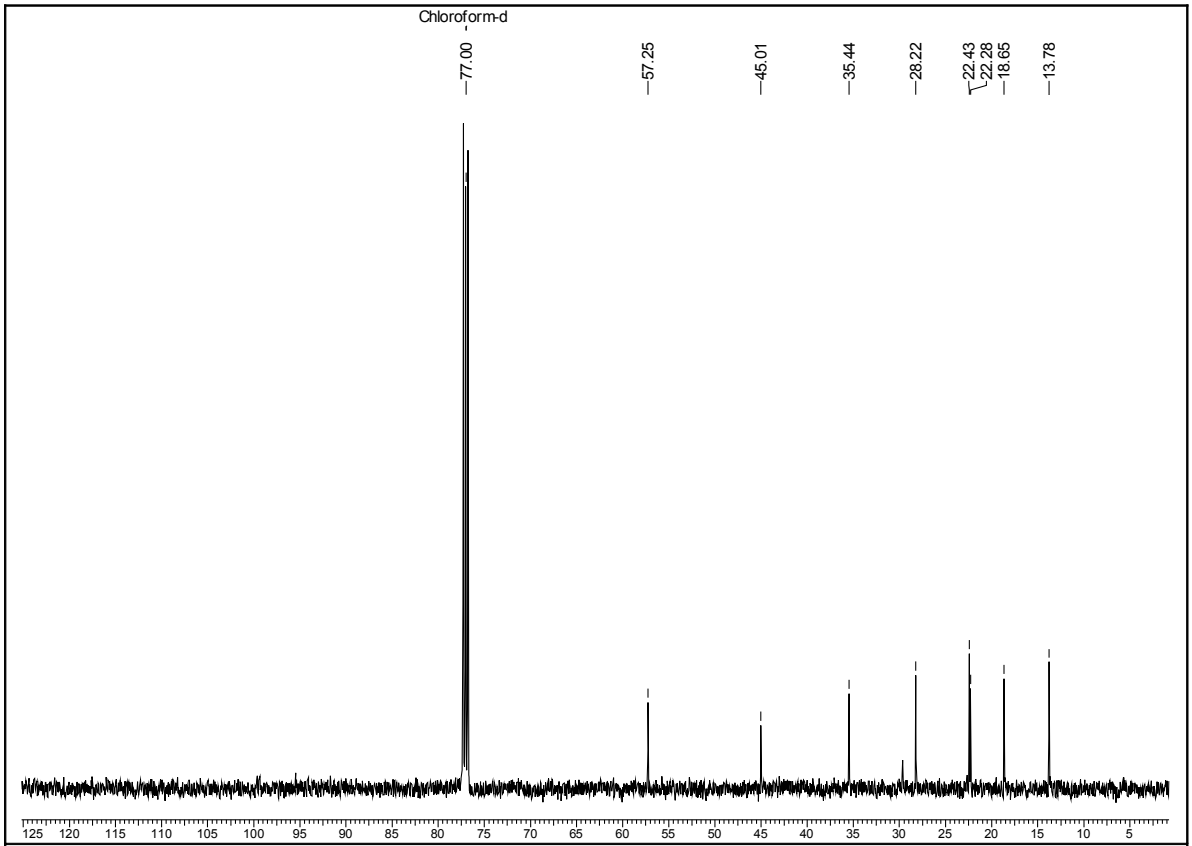
^{1}H-NMR of compound 46 in $CDCl_3$



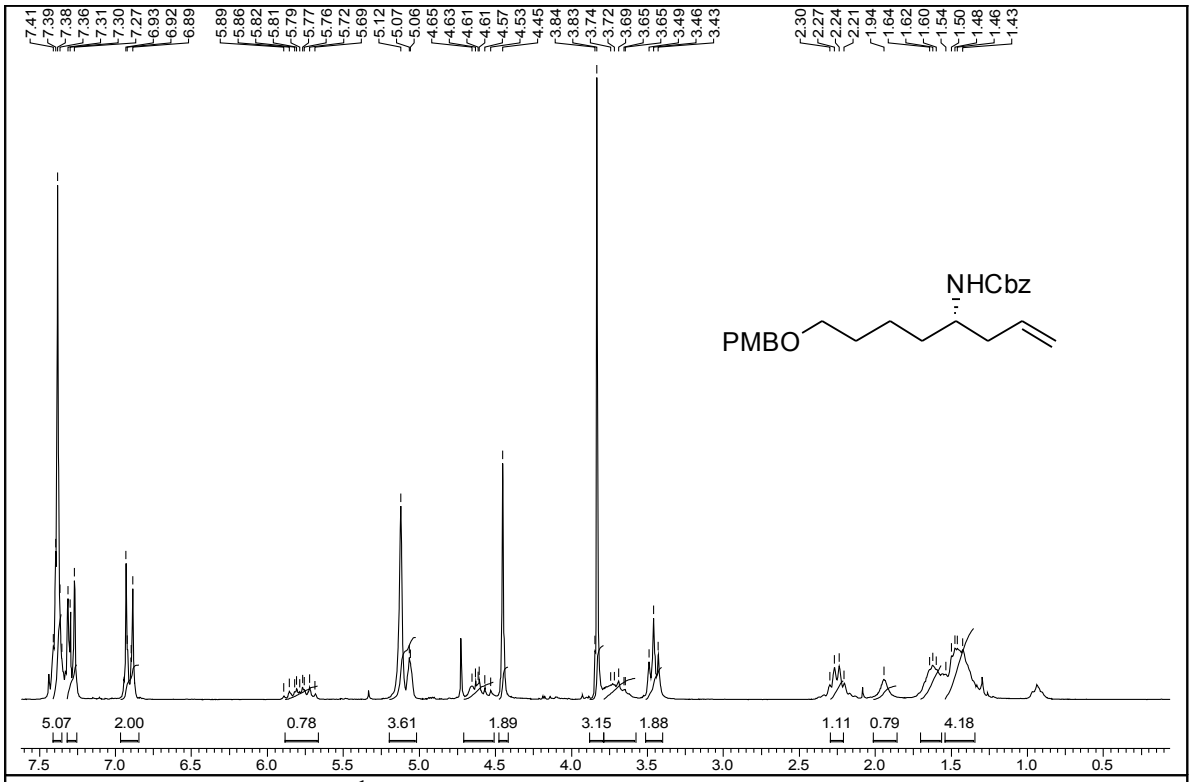
^{13}C-NMR of compound 46 in $CDCl_3$



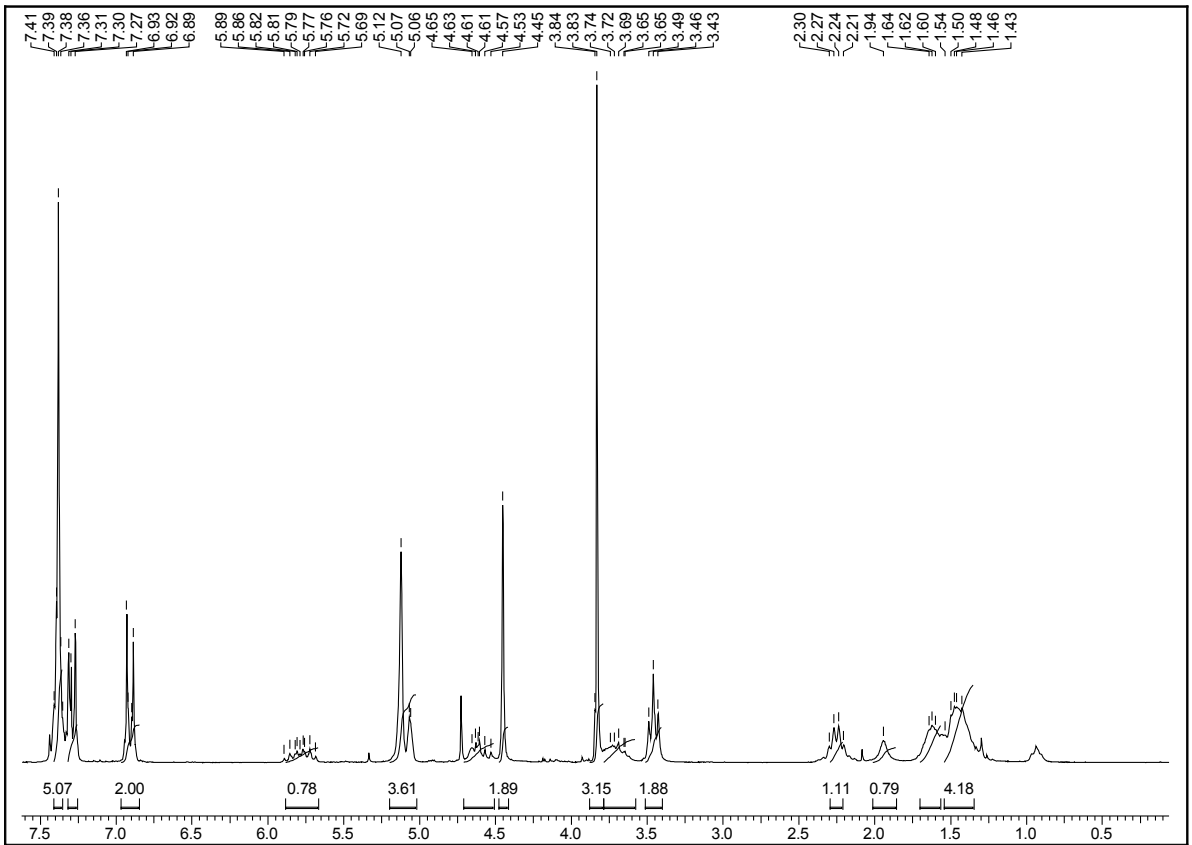
^{1}H-NMR of compound 1 in $CDCl_3$



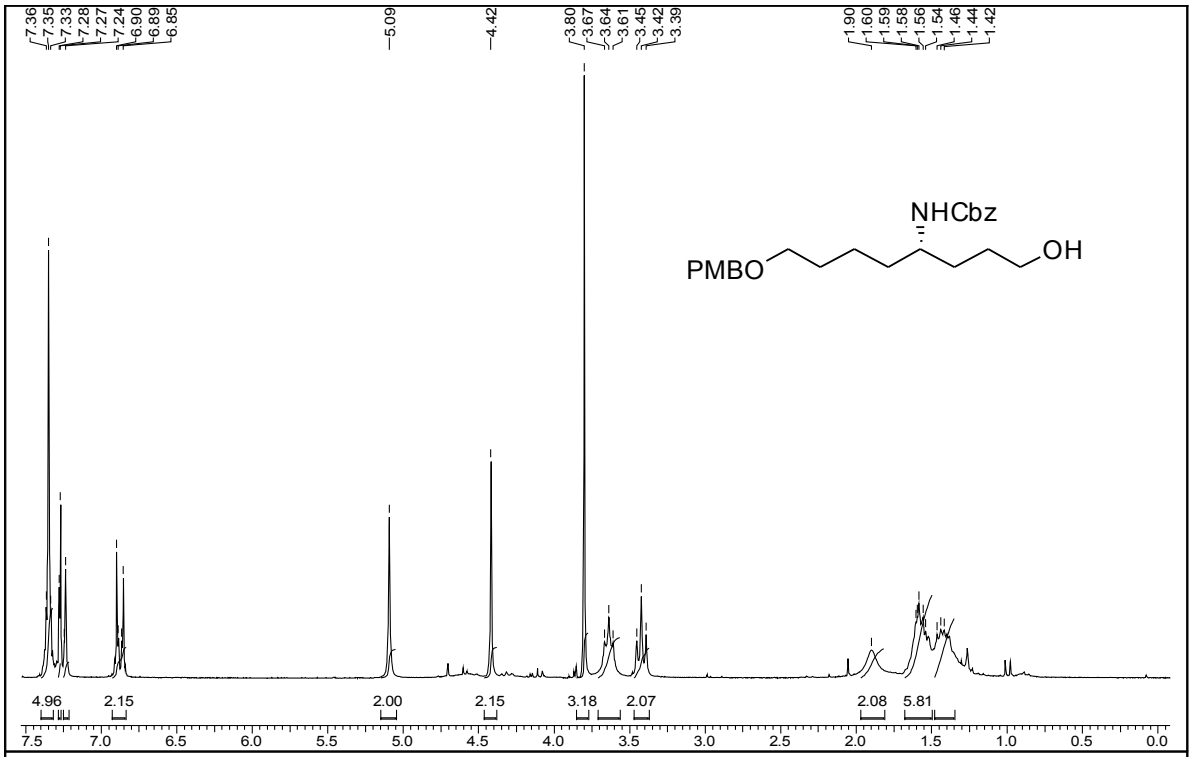
^{13}C-NMR of compound 1 in $CDCl_3$



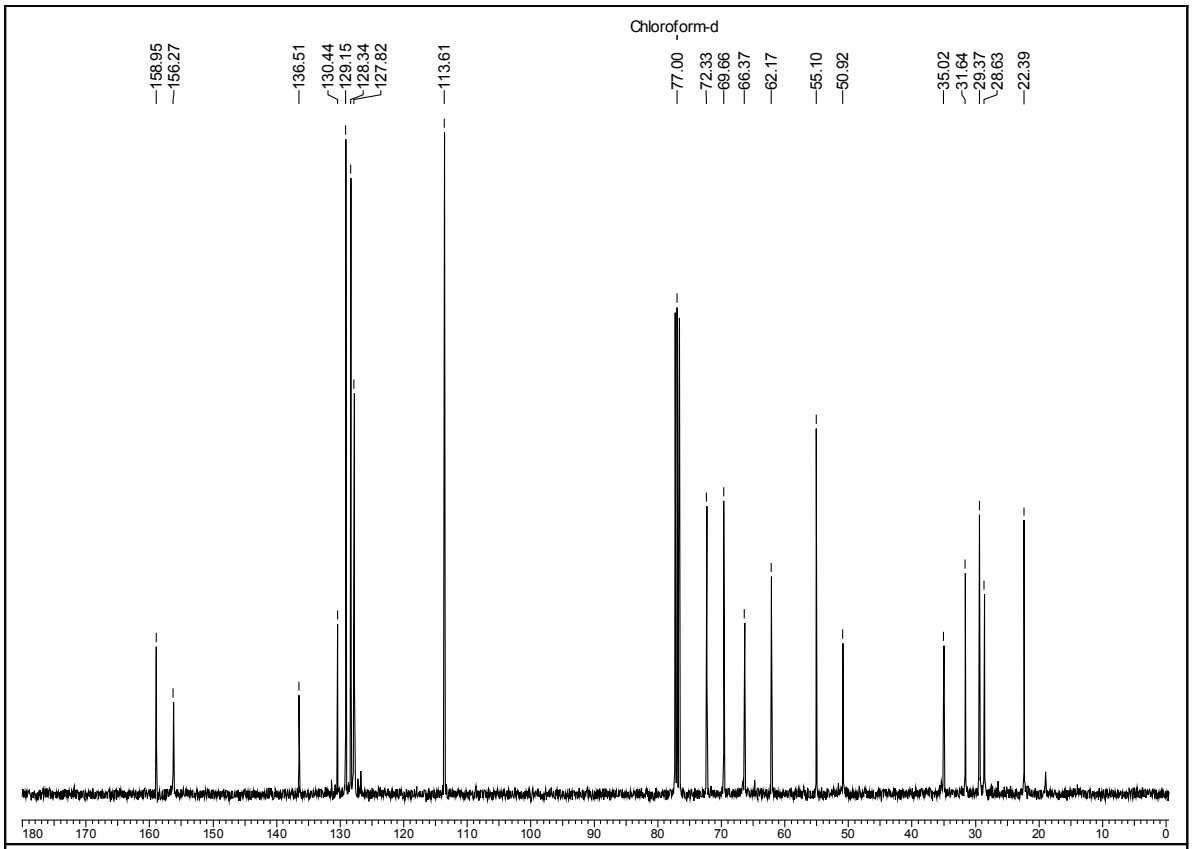
^{1}H-NMR of compound 48 in $CDCl_3$



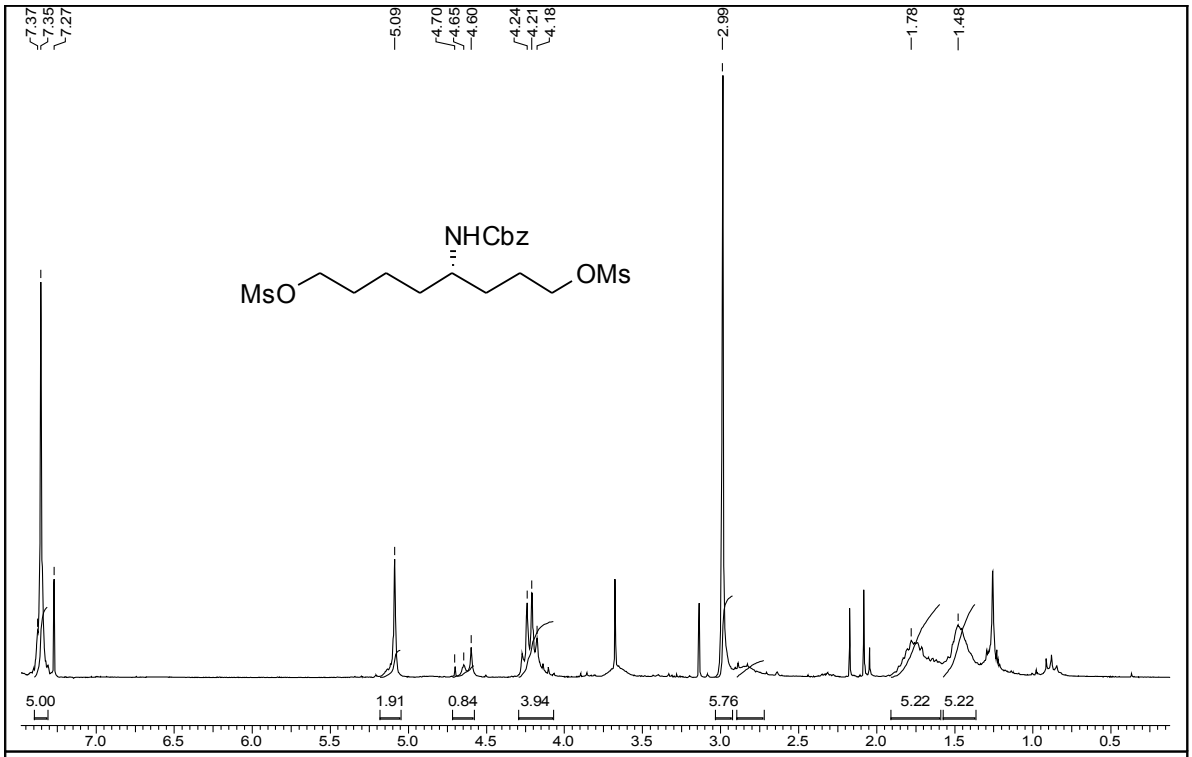
^{13}C-NMR of compound 48 in $CDCl_3$



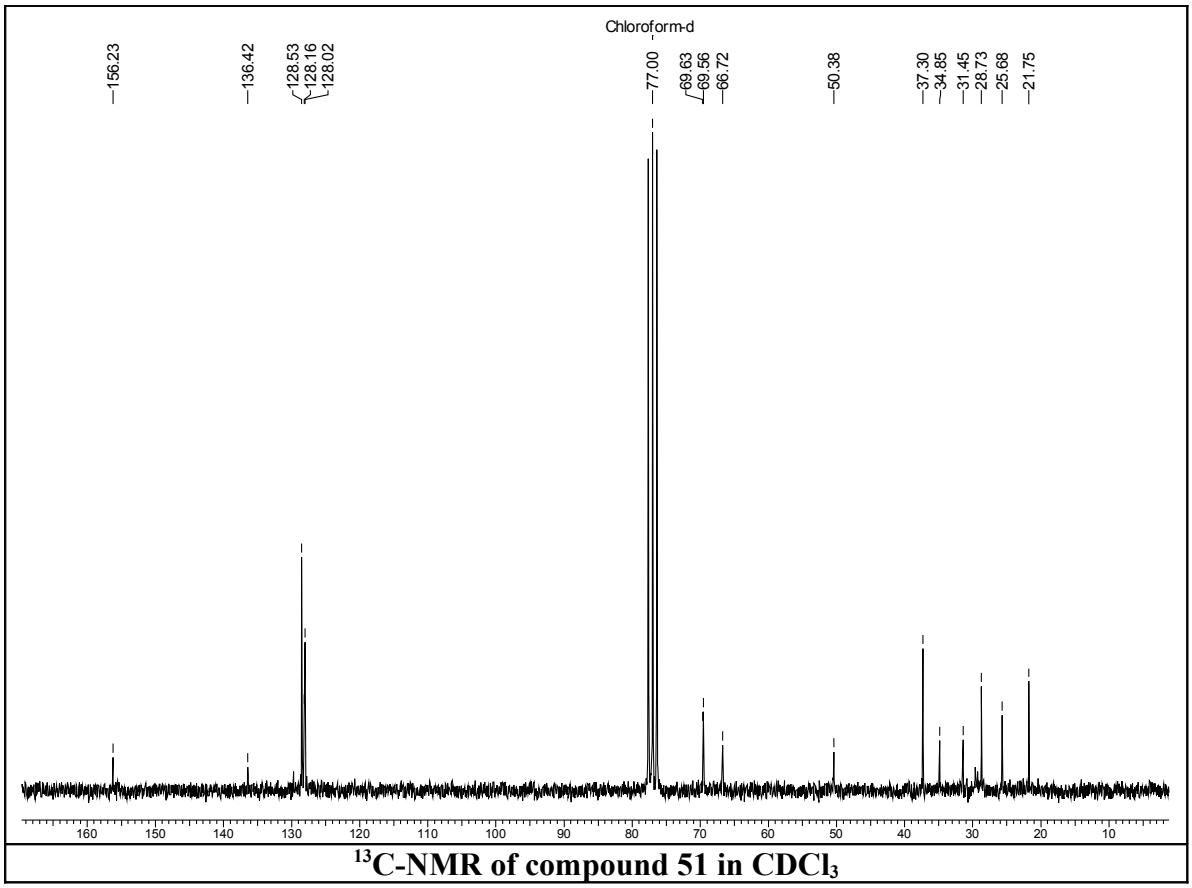
^{1}H-NMR of compound 49 in $CDCl_3$



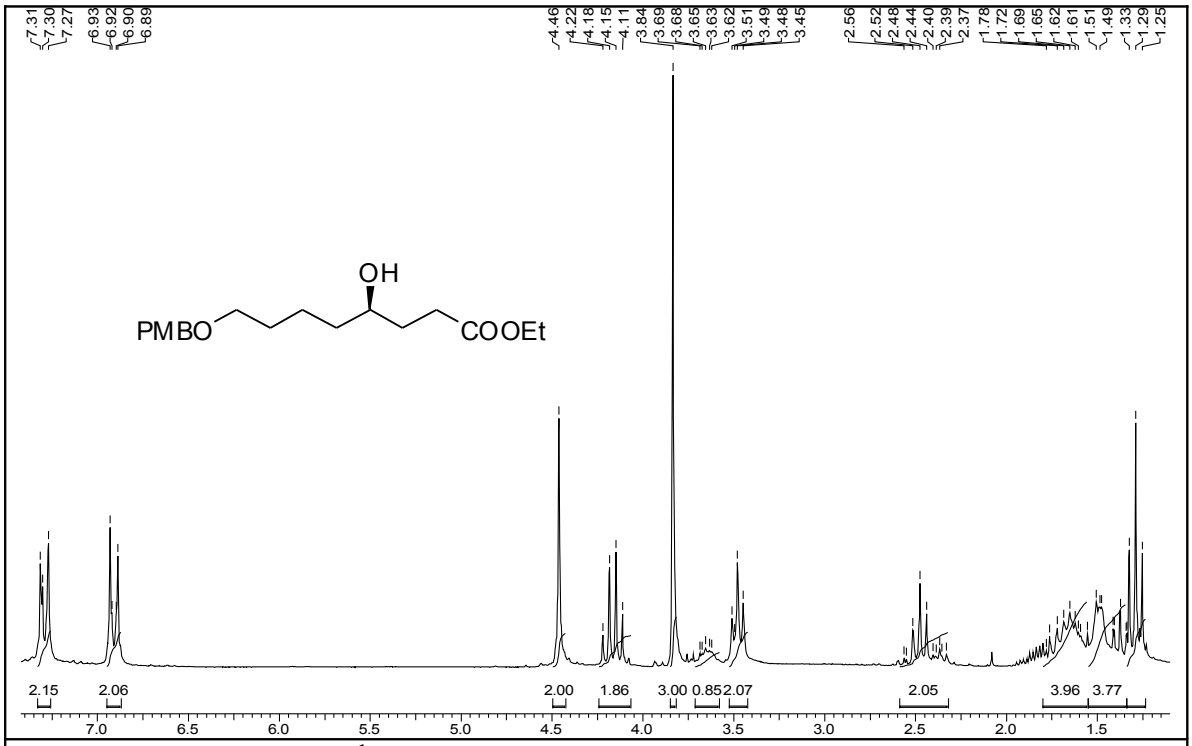
^{13}C-NMR of compound 49 in $CDCl_3$



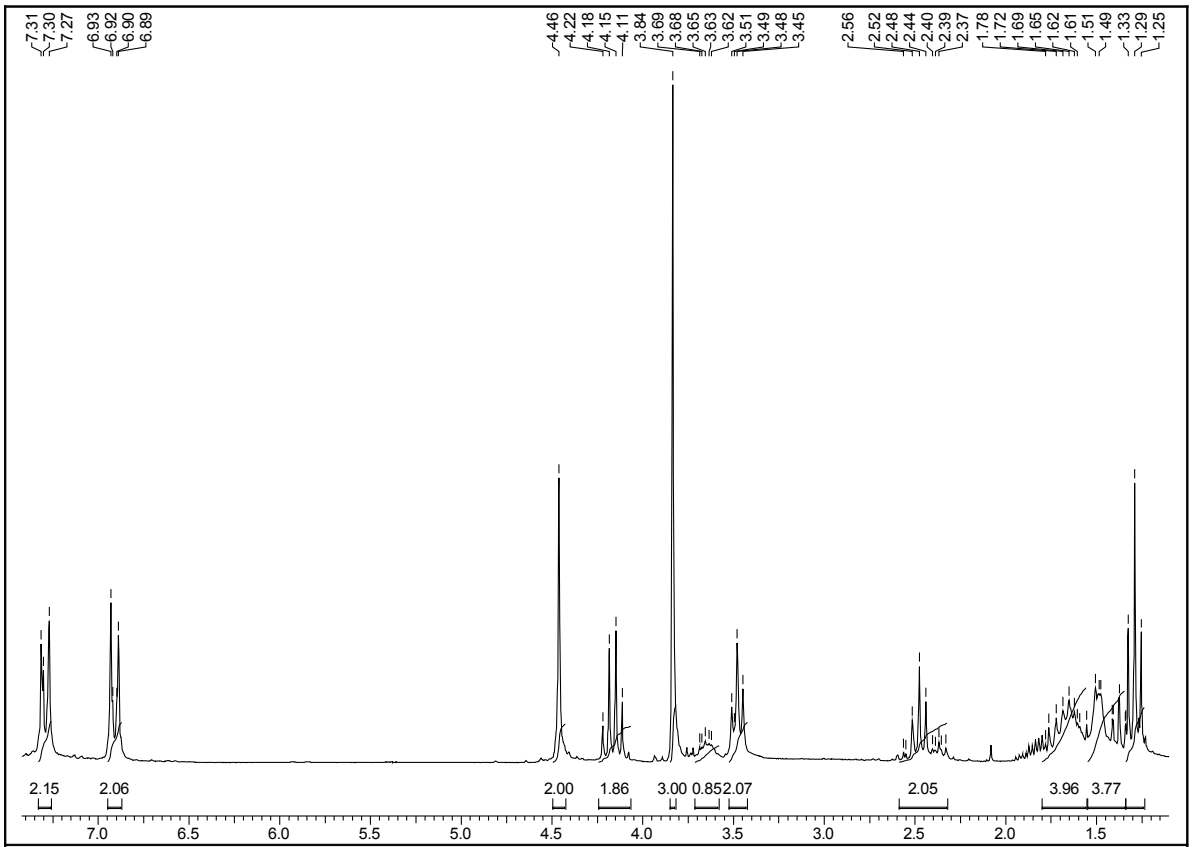
^{1}H-NMR of compound 51 in $CDCl_3$



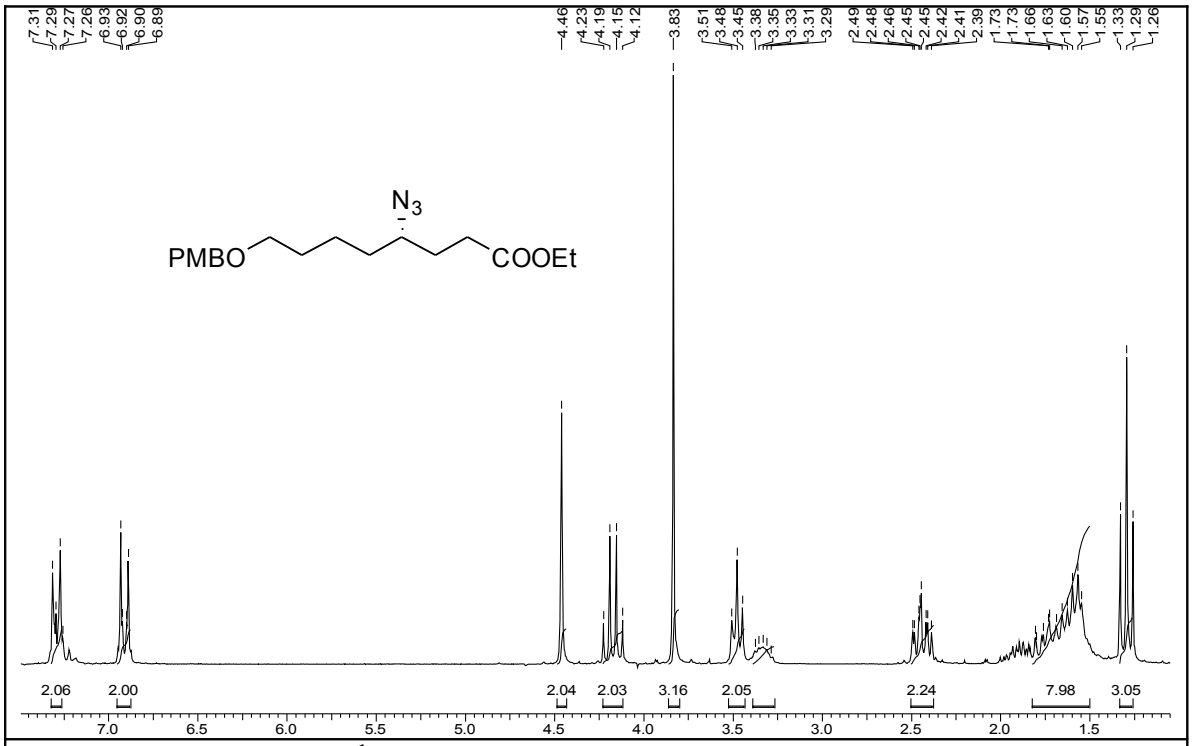
^{13}C-NMR of compound 51 in $CDCl_3$



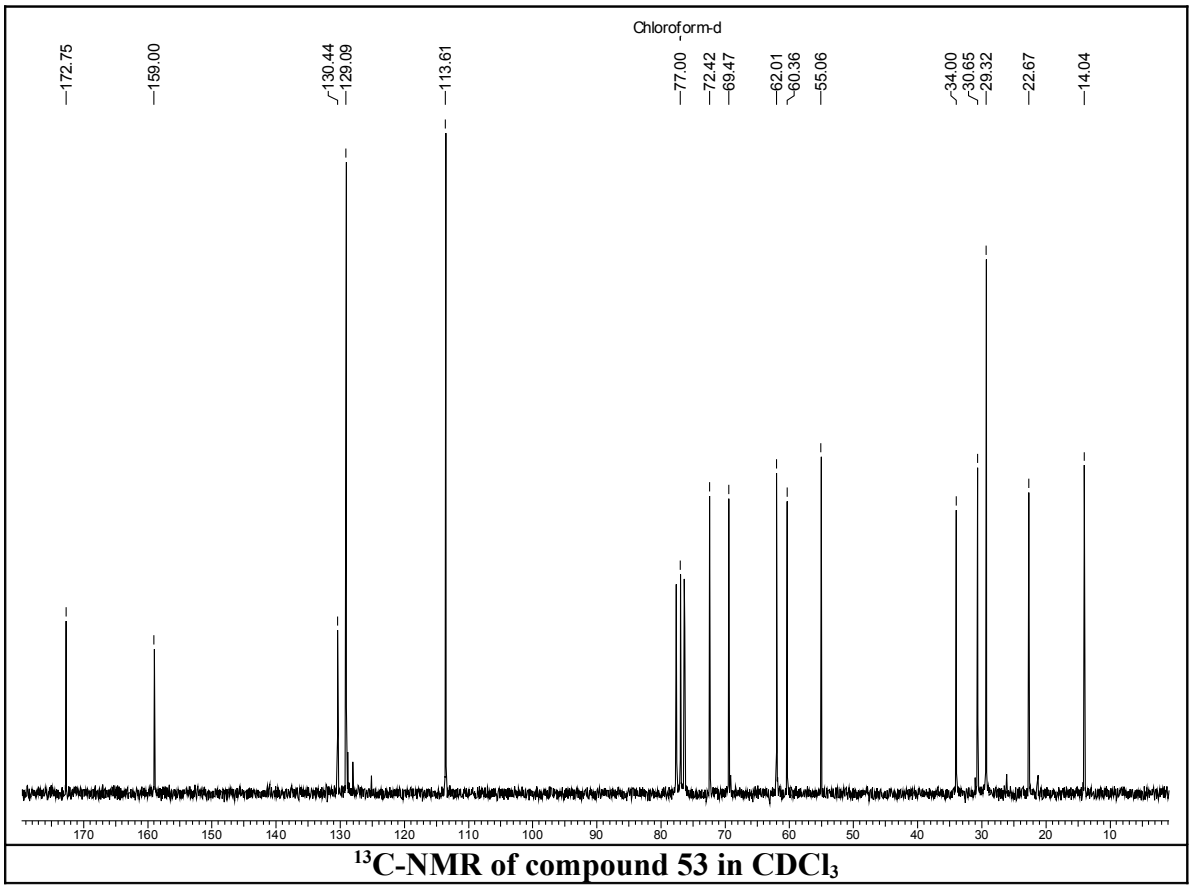
^{1}H-NMR of compound 52 in $CDCl_3$



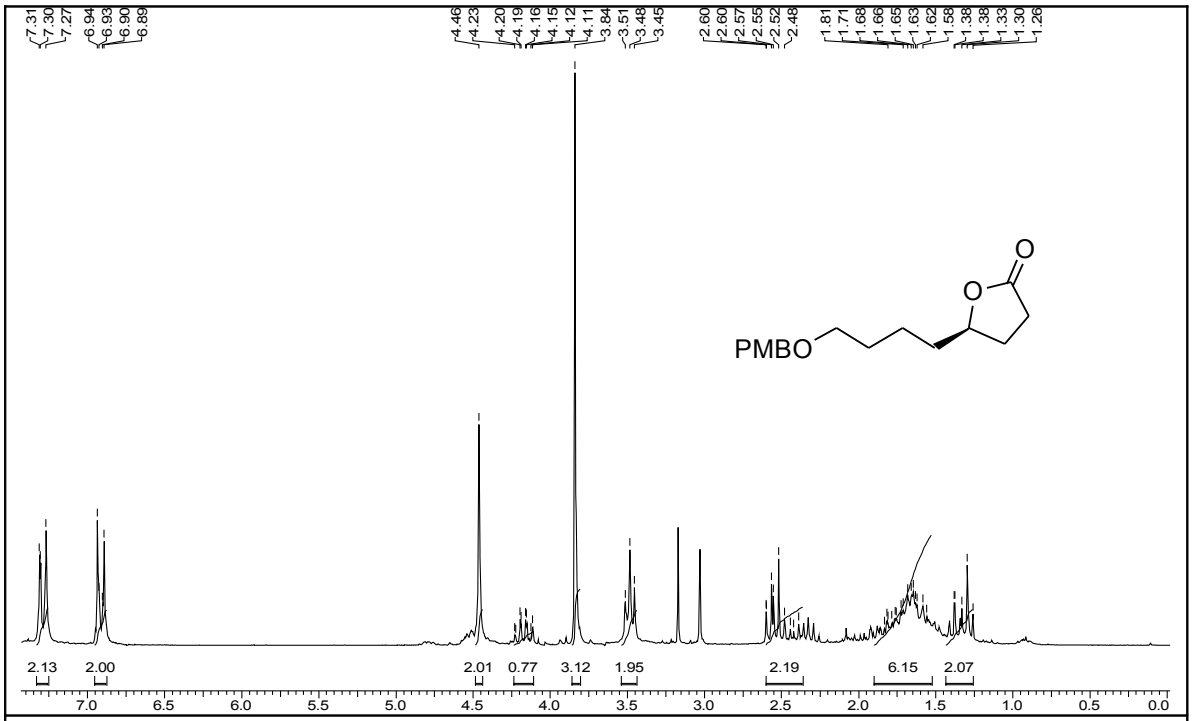
^{13}C-NMR of compound 52 in $CDCl_3$



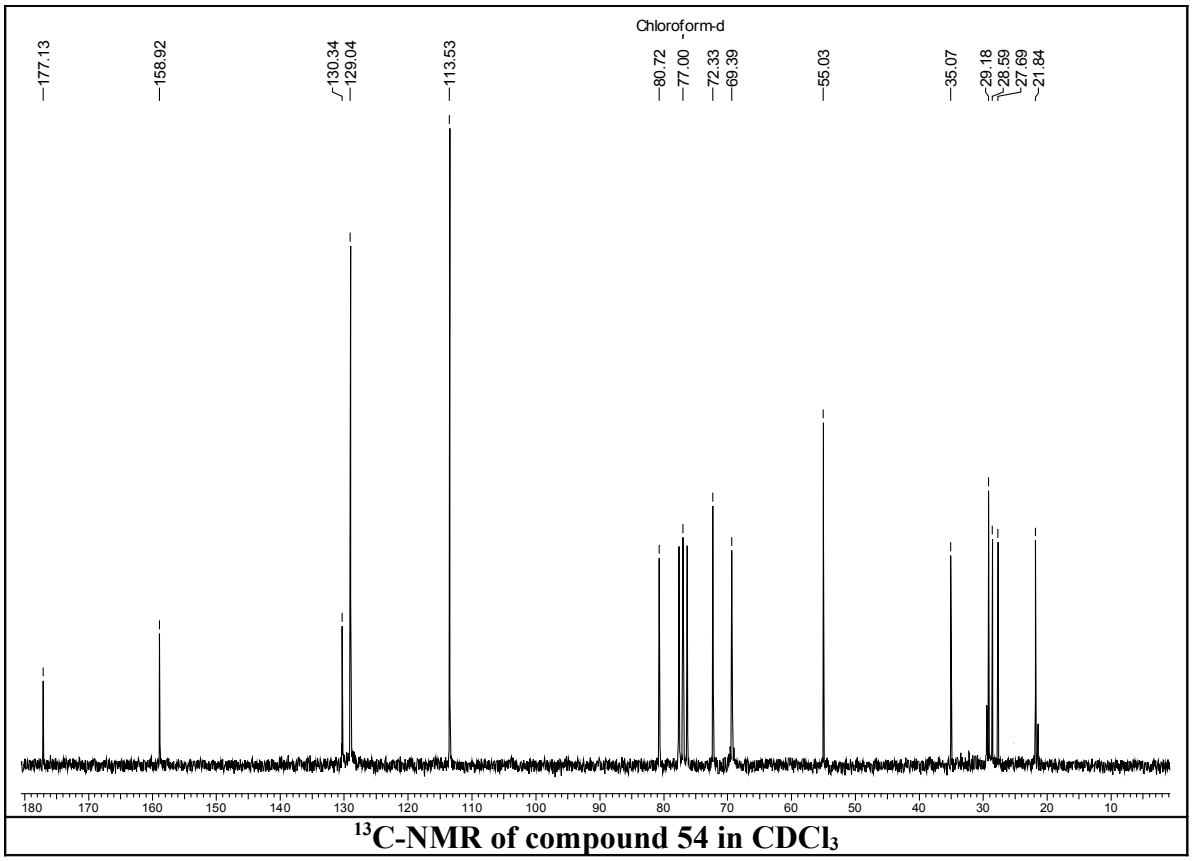
^{1}H-NMR of compound 53 in $CDCl_3$



^{13}C-NMR of compound 53 in $CDCl_3$



^{1}H-NMR of compound 54 in $CDCl_3$

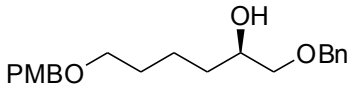


^{13}C-NMR of compound 54 in $CDCl_3$

4.2.8. References:

1. (a) Lebrun, S.; Couture, A.; Deniau, E.; Grandclaudon P. *Org. Lett.* **2007**, *9*, 2473; (b) Takahata, H.; Ouchi, H.; Ichinose, M.; Nemoto H. *Org. Lett*. **2002**, *4*, 3459.
2. (a) Rubiralta, M.; Giralt, E.; Diez, A. *Piperidine. Structure, Preparation,Reactivity and Synthetic Applications of Piperidine and Its Derivatives*; Elsevier: Amsterdam, 1991; (b) For a recent review, see: Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781.
3. (a) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *J. Chem. Soc.*, *Chem. Commun.* **1998**, 633; (b) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59,* 2953; (c) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem*. **2003**, 3693; (d) Couty, F. *Amino Acids* **1999**, *16*, 297.
4. For recent syntheses of enantiopure coniceine see: (a) Munchhof, M. J.; Meyers, A. I. *J. Org. Chem*. **1995**, *60*, 7084; (b) Takahata, H.; Kubota, M.; Takahashi, S.; Momose, T. *Tetrahedron: Asymmetry* **1996**, *7*, 3047; (c) Arisawa, M.; Takezawa, E.; Nishida, A.; Mori, M.; Nakagawa, M. *Synlett* **1997**, 1179; (d) Sánchez-Sancho, F.; Herradó N, B. *Tetrahedron: Asymmetry* **1998**, *9*, 1951; (e) Sibi, M. P.; Christensen, J. W. *J. Org. Chem*. **1999**, *64*, 6434; (f) Davies, S. B.; McKervey, M. A. *Tetrahedron Lett*. **1999**, *40*, 1229; (g) Groaning, M. D.; Meyers, A. I. *Chem. Commun*. **2000**, 1027; (h) Arisawa, M.; Takahashi, M.; Takezawa, E.; Yamaguchi, T.; Torizawa, Y.; Nishida, A.; Nakagawa, M. *Chem. Pharm. Bull*. **2000**, *48*, 1593; (i) Andrés, J. M.; Herráiz-Sierra, I.; Pedrosa, R.; Pérez-Encabo, A. *Eur. J. Org. Chem*. **2000**, 1719; (j) Lim, S. H.; Ma, S.; Beak, P. *J. Org. Chem*. **2001**, *66*, 9056; (k) Costa, A.; Nájera, C.; Sansano, J. M. *Tetrahedron: Asymmetry* **2001**, *12*, 2205; (l) Park, S. H.; Kang, H. J.; Ko, S.; Park, S.; Chang, S. *Tetrahedron: Asymmetry* **2001**, *12*, 2621; (m) Yoda, H.; Katoh, H.; Ujihara, Y.; Takabe, K. *Tetrahedron Lett*. **2001**, *42*, 2509; (n) Dieter, R. K.; Chen, N.; Watson, R. T. *Tetrahedron* **2005**, *61*, 3221.
5. Hunt, J. C. A.; Laurent, P.; Moody, C. J. *Chem Comm*. **2000**, 1771.
6. Hayes, J. F.; Shipman, M.; Twin, H. *Chem Comm*. **2001**, 1784.
7. Hayes, J. F.; Shipman M.; Twin, H. *Chem. Commun*. **2000**, 1791.
8. Gommermann N.; Knochel, P. *Chem Comm*. **2004**, 2324.
9. Yamaguchi, M.; Hirao, I. *Tetrahedron Lett*. **1983**, *24*, 391.
10. Hughes, D. L. *Org. React*. **1992**, *42*, 335.

11. Lebrun, S.; Couture, A.; Deniau, E.; Grandclaudon, P. *Org Lett*. **2007**, *9*, 2473.
12. Fustero, S.; Jiménez, D.; Moscardó, J.; Catalán, S.; del Pozo, C. *Org Lett*. **2007**, *9*, 5283.
13. Andrés, J. M.; Herráiz-Sierra, I.; Pedrosa, R.; Pérez-Encabo, A. *Eur. J. Org Chem*. **2000**, 1719.
14. Hjelmgaard, T.; Gardette, D.; Tannerb, D.; Aitkena, D. J. *Tetrahedron: Asymmetry* **2007**, *18*, 671.
15. Ram, S.; Ehrenkaufer, R. E. *Tetrahedron Lett*. **1984**, *25*, 3415.
16. (a) Dalko, P. L.; Moisan, L. *Angew. Chem., Int. Ed*. **2004**, *43*, 5138; (b) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley VCH: Weinheim, 2005; (c) Seayed, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719.
17. Dalko, P. I. *Enantioselective Organocatalysis: Reactions and Experimental Procedures*; Wiley-VCH: Weinheim, 2007.
18. MacMillian, D. W. C. *Nature* **2008**, *455*, 304.
19. Kondekar, N. B.; Kumar, P. *Org. Lett*. **2009**, *11*, 2611 and references cited therein.
20. (a) Bodas M. S.; Kumar, P. *Tetrahedron Lett*. **2004**, *45*, 8461; (b) Bodas M. S.; Kumar, P *J. Org. Chem*. **2005**, *70*, 360; (c) Kandula, S. V.; Kumar, P. *Tetrahedron Lett*. **2003**, *44*, 1957; (d) Kandula, S. V.; Kumar, P. *Tetrahedron:Asymmetry* **2005**, *16*, 3268; (e) Cherian, S. K.; Kumar, P. *Tetrahedron:Asymmetry* **2007**, *18*, 982; (f) Pandey, S. K.; Kumar, P. *Tetrahedron Lett*. **2005**, *46*, 4091; (g) Kandula, S. V.; Kumar, P. *Tetrahedron:Asymmetry* **2005**, *16*, 3579.
21. The enantiomeric excess (ee) was calculated using Mosher analysis by converting alcohol **41** into the monobenzyl alcohol and then converting to its Mosher ester. The enantiomeric excess (ee) was found to be >95%.



55

22. The enantiomeric excess (ee) of **52** was calculated using Mosher analysis by converting it as the Mosher ester. The ee was found to be 95%.

Publications

1. Application of the asymmetric aminohydroxylation reaction for the syntheses of HIV-protease inhibitor, hydroxyethylene dipeptide isostere and γ-amino acid derivative
   Nagendra B Kondekar, Subba Rao V. Kandula and Pradeep Kumar
   Tetrahedron Lett. **2004**, *45*, 5477–5479.
2. Iterative approach to enantiopure *syn*/*anti*-1,3-polyols via proline-catalyzed sequential α-aminoxylation and Horner-Wadsworth-Emmons olefination of aldehydes
   Nagendra B Kondekar and Pradeep Kumar
   Organic Lett. **2009**, *11*, 2611-2614.
3. Synthesis of (*R*)-selegiline via hydrolytic kinetic resolution
   Nagendra B Kondekar and Pradeep Kumar (Submitted for publication).
4. α-Aminoxylation and sequential α-aminoxylation HWE olefination approaches for the synthesis of core of piperidine and indozolidine alkaloids
   Nagendra B Kondekar and Pradeep Kumar (Submitted for publication).
5. An asymmetric synthesis of (2*R*, 2'*R*)-(+)-methylphenidate via Sharpless asymmetric dihydroxylation
   Nagendra B Kondekar and Pradeep Kumar (To be communicated).

Oral Presentation

Total Synthesis of Biologically Active Natural Products, in *J-NOST* (Junior-National Organic Symposium Trust) held at Amritsar, Punjab, India in **Nov 2007** organized by National organic symposium trust (*NOST*) India.

Posters presented at symposia / conferences attended

1. An asymmetric synthesis of (*S*)-pipecolic acid. Presented at fifth national symposium in chemistry (NSC-5) at CLRI Chennai, India in **Feb 2003**.

2. Asymmetric synthesis of 4-amino-5-hexenoic acid and hydroxyl ethylamine isostere. Presented at sixth national symposium in chemistry (NSC-6) at IIT Kanpur, India in **Feb 2004**.

3. Participated in the second International conference on organic synthesis and process chemistry (OSPC)- 2005 held in Hyderabad in **Feb 2005**.

4. Enantioselective synthesis of D-(+)-*threo* methylphenidate. Presented at ACS International conference "Building bridges and forging bonds between biology and chemistry" held in NCL Pune, India in **Jan 2006**.

Educational Qualification

M.Sc. (Master of Science) **Organic Chemistry (*Distinction*)**
Swami Ramanand Teerth Marathwada University Nanded, Maharashtra, India.
1998-2000.

B.Sc. (Bachelor of Science) Chemistry, Physics, Mathematics
Swami Ramanand Teerth Marathwada University Nanded, Maharashtra, India.
1995-1998.

Fellowships and Awards

- Secured *Third Place* in S.R.T.M. University Nanded (India) in Master of Science (Chemistry) **1998-2000**
- **2002-2004**: Junior Research Fellowship awarded by Council of Scientific and Industrial Research (CSIR), India (www.csir.res.in)
- **2004-2007**: Senior Research Fellowship awarded by Council of Scientific and Industrial Research (CSIR), India.

Examinations Qualified

- **Feb 2001**, Qualified *Graduate Aptitude Test* in Engineering (GATE) conducted by Indian Institute of Technology (IIT) Kanpur India with 96.99% score.
- **June 2000**, Qualified *State Eligibility Test,* Eligibility (SET) test for the lectureship at the University
- **June 2000,** Qualified *National Eligibility Test,* Eligibility (NET) test for the lectureship at the University
- Qualified entrance exam for Bhabha Atomic Research Center BARC (www.barc.ernet.in) and Tata institute of fundamental research (TIFR, Mumbai).

Research Interests

- Development of new asymmetric synthetic methodologies and its applications to the synthesis of bioactive molecules with special emphasis on organocatalysis.
- Total synthesis of bioactive molecules and their application to the medicinal chemistry and material chemistry.