ORGANOCATALYTIC ASYMMETRIC SYNTHESIS OF BIOACTIVE MOLECULES AND OXIDATION STUDIES IN IONIC LIQUIDS

A THESIS SUBMITTED TO THE

UNIVERSITY OF PUNE

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

BY

SHARAD P. PANCHGALLE

DIVISION OF ORGANIC CHEMISTRY

NATIONAL CHEMICAL LABORATORY

PUNE-411008, INDIA

November 2009

Dr. U. R. Kalkote
Scientist F
Division of Organic Chemistry

Telephone : + 91-20-25902578
Fax : + 91-20-25902629
E-mail : ur.kalkote@ncl.res.in
Website : www.ncl-india.org

CERTIFICATE

This is to certify that the work presented in the thesis entitled "**Organocatalytic asymmetric synthesis of bioactive molecules and oxidation studies in ionic liquids**" submitted by **Sharad P. Panchgalle** 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. Uttam R. Kalkote)
Research Guide
Scientist F
Division of Organic Chemistry
National Chemical Laboratory
Pune 411008, INDIA

5th November 2009

CANDIDATE'S DECLARATION

I hereby declare that the thesis entitled "**Organocatalytic asymmetric synthesis of bioactive molecules and oxidation studies in ionic liquids**" 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.

Sharad P. Panchgalle
Senior Research Fellow
Division of Organic Chemistry
National Chemical Laboratory
Pune-411008, INDIA

5th November 2009

Dedicated to

My parents

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. Uttam R. Kalkote** 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.

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Sharad P. Panchgalle

Contents

Abbreviations

Ac	-	Acetyl
AcOH	-	Acetic acid
Ac_2O	-	Acetic anhydride
Ar	-	Aryl
Aq	-	Aqueous
Bn	-	Benzyl
BnBr	-	Benzyl bromide
$BH_3 \cdot Me_2S$	-	Boron dimethyl sulfide complex
Boc	-	*tert*-Butoxy carbonyl
$(Boc)_2O$	-	Di-*tert*-butyl dicarbonate
*t*Bu	-	*tertiary* butyl
BuLi	-	Butyl lithium
Cat.	-	Catalytic
Cbz	-	Carbobenzyloxy
$CDCl_3$	-	Deuterated chloroform
DBAD	-	Dibenyl azodicarboxylate
DBU	-	1,8-Diazabicyclo[5.4.0]undec-7-ene
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
DIAD	-	Diisopropyl azodicarboxylate
DIBAL-H	-	Diisobutylaluminiumhydride
DMAC	-	*N, N*-Dimethylacetamide
DMP	-	2,2-Dimethoxypropane
DMF	-	*N, N*-Dimethylformamide
DMAP	-	*N,N*-Dimethylaminopyridine
DMSO	-	Dimethyl sulfoxide
Ee	-	Enantiomeric excess
equiv.	-	Equivalents
Et	-	Ethyl
EtOH	-	Ethanol
Et_2O	-	Diethyl ether
EtOAc	-	Ethyl acetate
Et_3N	-	Triethylamine

g	-	gram/s
h	-	hour/s
$HBSia_2$	-	di-siamylborane
Hz	-	Hertz
HPLC	-	High pressure liquid chromatography
IBX	-	Iodoxybenzoic Acid
Im	-	Imidazole
IR	-	Infrared
LDA	-	Lithium diisopropyl amide
LiHMDS	-	Lithium hexamethyl disilazide
m-CPBA	-	*m*-Chloroperbenzoic acid
Me	-	Methyl
MeOH	-	Methanol
mg	-	Milligram
min	-	Minutes
mL	-	Millilitre
mmnol	-	Millimole
M. p.	-	Melting point
Ms	-	Methanesulfonyl
MeI	-	Methyl iodide
Mes	-	2,4,6-trimethylbenzoate
$NaBH_4$	-	Sodiumborohydride
NaH	-	Sodium hydride
Ph	-	Phenyl
Py	-	Pyridine
PMB	-	*p*-Methoxy benzyl
p-TSA	-	*p*-Toluenesulfonic acid
RCM	-	Ring closing metathesis
rt	-	Room temperature
Et_3N	-	Triethylamine
TBAI	-	Tetra-*n*-butylammonium iodide
TBAF	-	Tetra-*n*-butylammonium fluoride
TBDMS	-	*tert*-Butyldimethyl silyl
TBDMSCl	-	*tert*-Butyldimethyl silyl chloride
TFA	-	Trifluoroacetic acid
Tf	-	Trifluoromethanesulfonate
THF	-	Tetrahydrofuran

TMS	-	Tetramethylsilane
TLC	-	Thin layer chromatography
Ts	-	*p*-Toluenesulphonyl (Tosyl)

General remarks

- ^{1}H NMR spectra were recorded on AV-200 MHz, MSL-300 MHz, AV-400 MHz and AV-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 AV-50 MHz, MSL-75 MHz, AV-100 MHz and AV-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.
- HPLC analysis were carried out on Shimatzu instrument
- 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 (230–400 mesh) used for flash column chromatography was purchased from Spectrochem Pvt. Ltd., 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 **"Organocatalytic asymmetric synthesis of bioactive molecules and oxidation studies in ionic liquids"** is divided into three chapters

Chapter 1: Introduction to asymmetric organocatalysis, proline catalyzed asymmetric synthesis of (*R*)-(+)-α-lipoic acid and β-adrenergic blockers based on α-aminoxylation of aldehydes.

Chapter 2: Organocatalytic asymmetric synthesis of (*R*)-coniceine and (*R*)-pipecolic acid based on α-amination of aldehydes.

Chapter 3: Inotoduction to ionic liquids and oxidation studies in ionic liquids.

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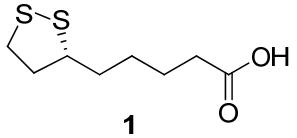
Chapter 1: Introduction to asymmetric organocatalysis, proline catalyzed asymmetric synthesis of (*R*)-(+)-α-lipoic acid and β-adrenergic blockers.

This chapter is further divided in three sections

Section A: Introduction to asymmetric organocatalysis

This section gives brief introduction of chirality, asymmetric synthesis particularly organocalytic asymmetric synthesis. 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[3,4] of carbonyl compounds.

Section B: Asymmetric synthesis of (*R*)-(+)-α-lipoic acid

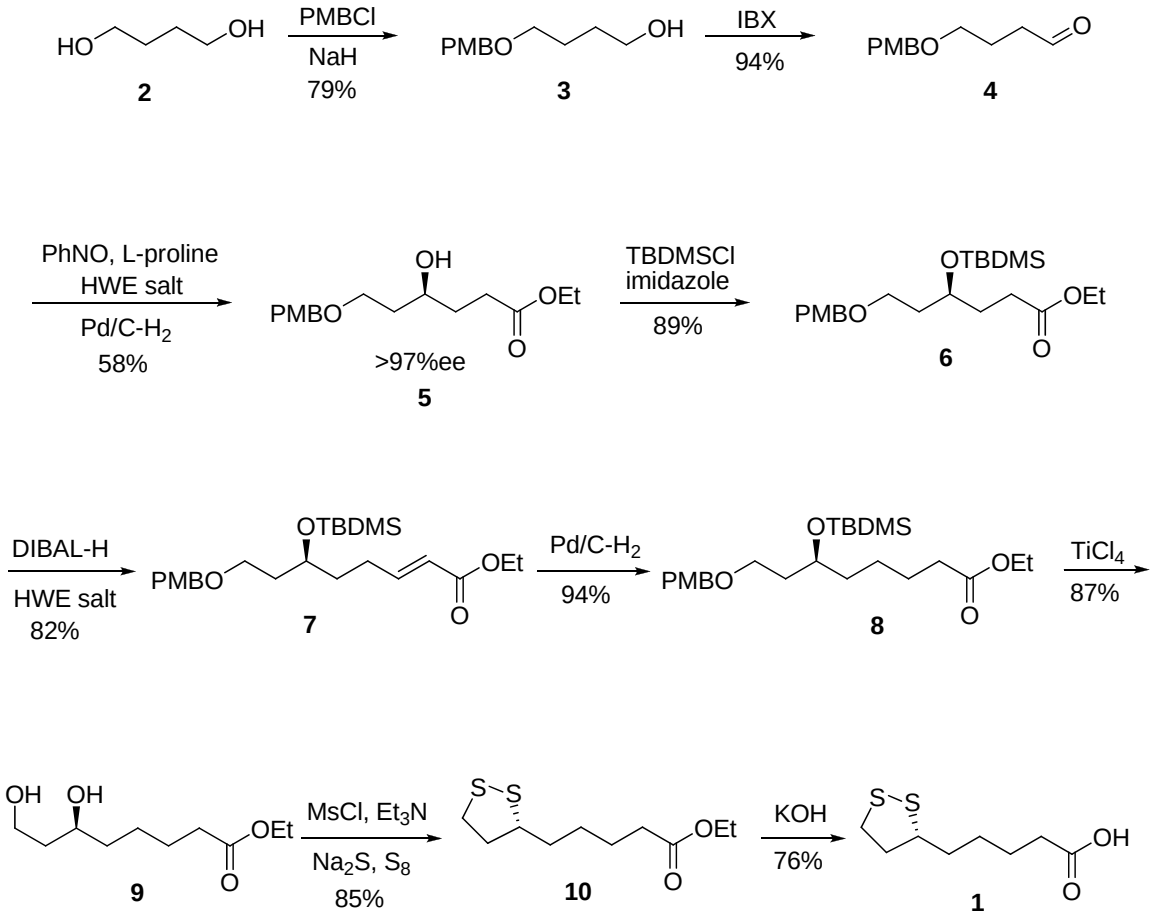


1

(*R*)-(+)-α-Lipoic acid

α-Lipoic acid is an important protein-bound coenzyme and growth factor found in plant and animal tissues as well as in microorganisms. α-Lipoic acid was first isolated by Reed and coworkers in 1950 and characterized as the cyclic disulphide 5-[3-(1,2-

dithiolanyl)]-pentanoic acid.[5] The absolute configuration of the natural a-(+)-lipoic acid was confirmed as *R* by the synthesis of its unnatural (-)-antipode from *S*-malic acid by Golding.[6] Lipoic acid is an important and powerful biological anti-oxidant that can directly scavenge free radicals and protect cells from oxidative damage. Lipoic acid and its derivatives are highly active as anti HIV and anti-tumor agents. The *R*-(+) enantiomer is much more effective than the *S*-(-)-enantiomer at enhancing insulin-stimulated glucose transport and non-oxidative and oxidative glucose metabolism. In view of this, a highly enantioselective synthesis of (*R*)-(+)-α-lipoic acid is highly desirable. We have successfully accomplished the synthesis of (*R*)-(+)-α-lipoic acid using sequential α-aminoxylation-HWE olefination[7] of aldehyde as key step.



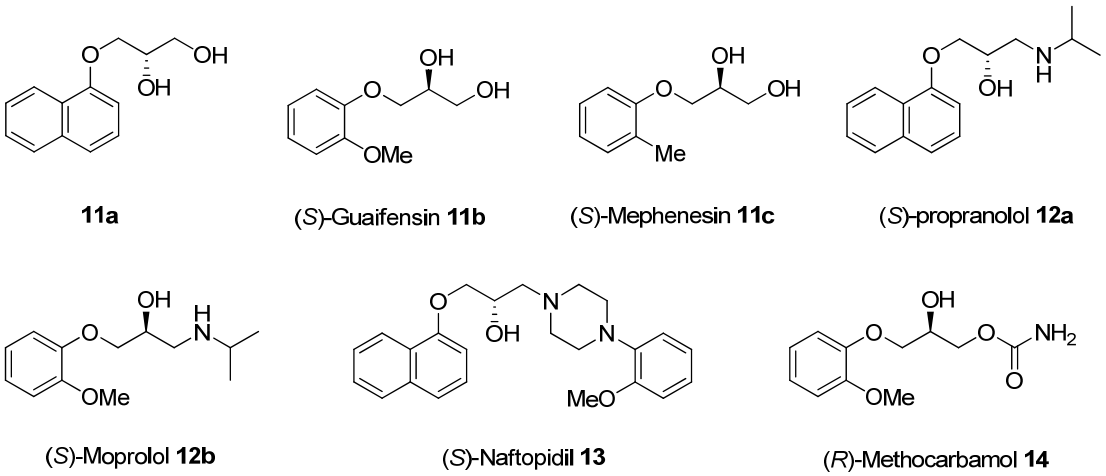
Scheme 1: Asymmetric synthesis of (*R*)-α-lipoic acid **1**

As illustrated in scheme 1, aldehyde **4** was obtained from diol **2** via monoprotection and IBX oxidation. Aldehyde **4** on L-proline catalyzed sequential α-aminoxylation-HWE olefination[7] followed by hydrogenolysis afforded chiral γ-hydroxy ester **5** which subsequently converted to γ-silyloxy ester **6**. Ester **6** was transformed into

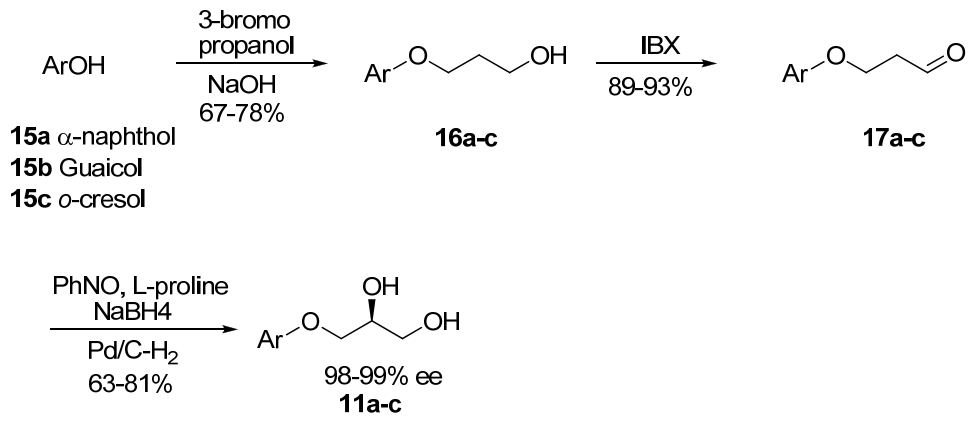
aldehyde by reduction and subjected to HWE olefination to obtain α,β-unsaturated ester **7**. α,β-Unsaturated ester **7** was transformed into dihydroxy ester **9** via hydrogenation and acid catalyzed silyl and benzyl deprotection. The dihydroxy ester **9** was converted to ethyl lipoate **10** via mesylation and treatment with Na_2S and sulfur. Finally saponification of ester **10** afforded (*R*)-α-lipoic acid **1**.

In summary *R*-(+)-α-lipoic acid **1** was synthesized efficiently from the readily available butane-1,4-diol as the achiral precursor.

Section B: Asymmetric synthesis of β-adrenergic blockers

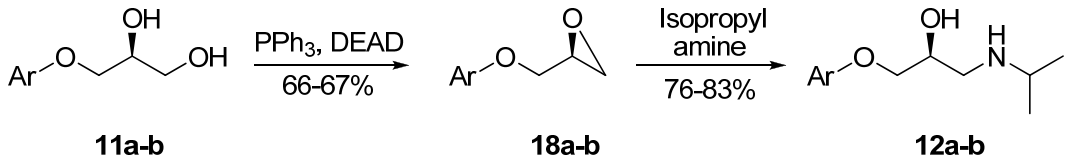


β-Adrenergic blocking agents (β-blockers) are important drugs, widely used for the treatment of hypertension and angina pectoris.[8] Generally, the (*S*)-isomers are known to be much more effective (50-500 fold) than the (*R*)-isomers, which often possess toxicity. Hence, the administration of optically pure (*S*)-isomers are highly desirable. This section describes the asymmetric synthesis of β-blockers (*S*)-guaifenesin **11b**, (S)-mephenesin **11c**, (*S*)-propranolol **12a**, (*S*)-moprolol **12b**, (*S*)-naftopidil **13** and (*R*)-methocarbamol **14**.



Scheme 2: Synthesis of diols **11a-c**

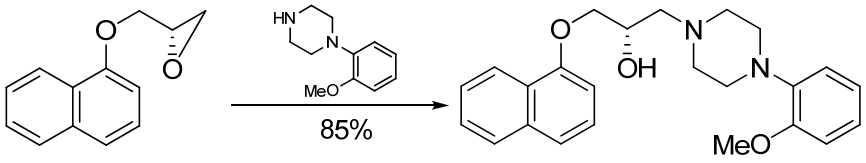
As illustrated in scheme 2, phenols **15a-c** on treatment with aqueous NaOH and 3-bromopropanol afforded alcohols **16a-c** which were oxidised to aldehydes **17a-c** with IBX. Aldehydes **17a-c** on α-aminoxylation,[3a] reduction with $NaBH_4$ and Pd/C catalyzed hydrogenolysis afforded chiral diols **11a-c** with excellent enantiopurities (98-99% ee).



11a-b **18a-b** **12a-b**

Scheme 3: Synthesis of (*S*)-propranolol and (*S*)-moprolol

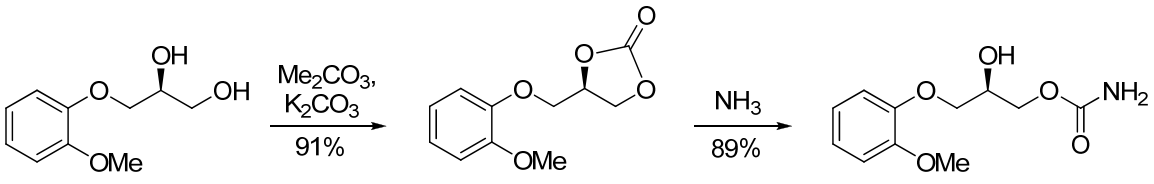
Chiral diols **11a-b** under Mitsunobu reaction conditions afforded epoxides **18a-b**, which on subsequent treatment with isopropylamine afforded β-Adrenergic blocking agents (*S*)-propranolol **12a** and (*S*)-moprolol **12b**.



18a **13**

Scheme 4: Synthesis of (*S*)-naftopidil

Similarly, epoxide **18a** on treatment with 1-(2-methoxyphenyl)piperazine afforded β-Adrenergic blocking agent (*S*)-naftopidil **13**.



11b **19** **14**

Scheme 5: Synthesis of (*R*)-methocarbamol

Diol **11b** on refluxing with dimethyl carbonate and K_2CO_3 afforded cyclic carbonate **19**. The carbonate **19** converted to desired (*R*)-methocarbamol **14** on treatment with liquid ammonia.

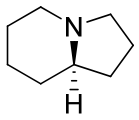
In summary various β-Adrenergic blockers were synthesized efficiently from the readily available phenols as the achiral precursor.

Chapter 2: Organocatalytic asymmetric synthesis of (*R*)-coniceine and (*R*)-pipecolic acid based on α-amination.

This chapter is divided in two sections.

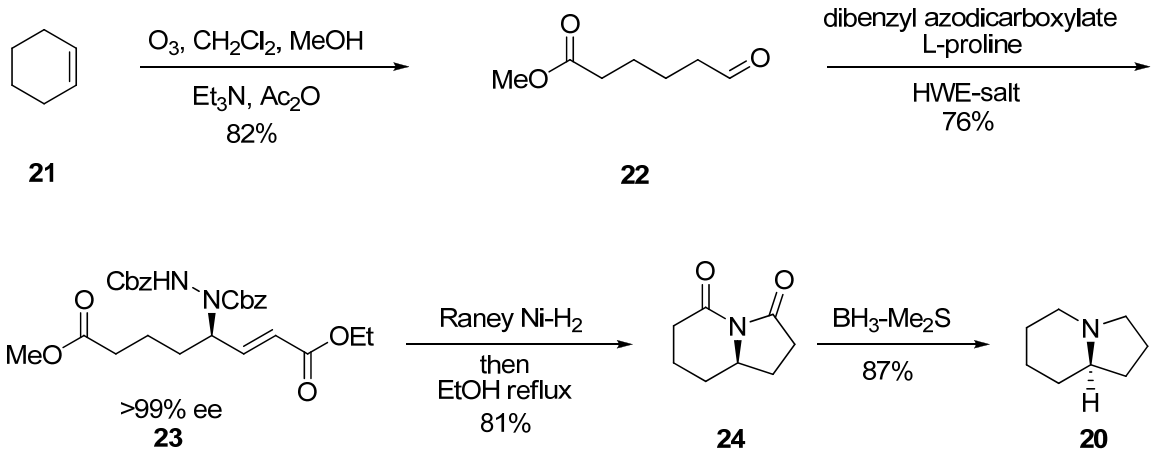
Section A: Asymmetric synthesis of (*R*)-coniceine

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.



(*R*)-Coniceine **20**

We have developed a route to the synthesis of (*R*)- coniceine **20** as a simple representative of the indozolidine alkaloids.



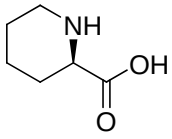
Scheme 6: Synthesis of (*R*)-coniceine

As illustrated in scheme 6, aldehyde **22** was obtained from ozonolysis of cyclohexene **21**. Aldehyde **21** on sequential one pot proline catalyzed α-amination-HWE olefination[9] afforded chiral γ-amino-α,β-unsaturated ester **23**. The chiral purity of **23**

was >98% determined by chiral HPLC analysis. Ester **23** on hydrogenolysis with Raney nickel followed by heating in ethanol afforded diamide **24**. The target (*R*)-coniceine **20** was obtained by reduction of diamide **24**.

Section B: Asymmetric synthesis of (*R*)-pipecolic acid

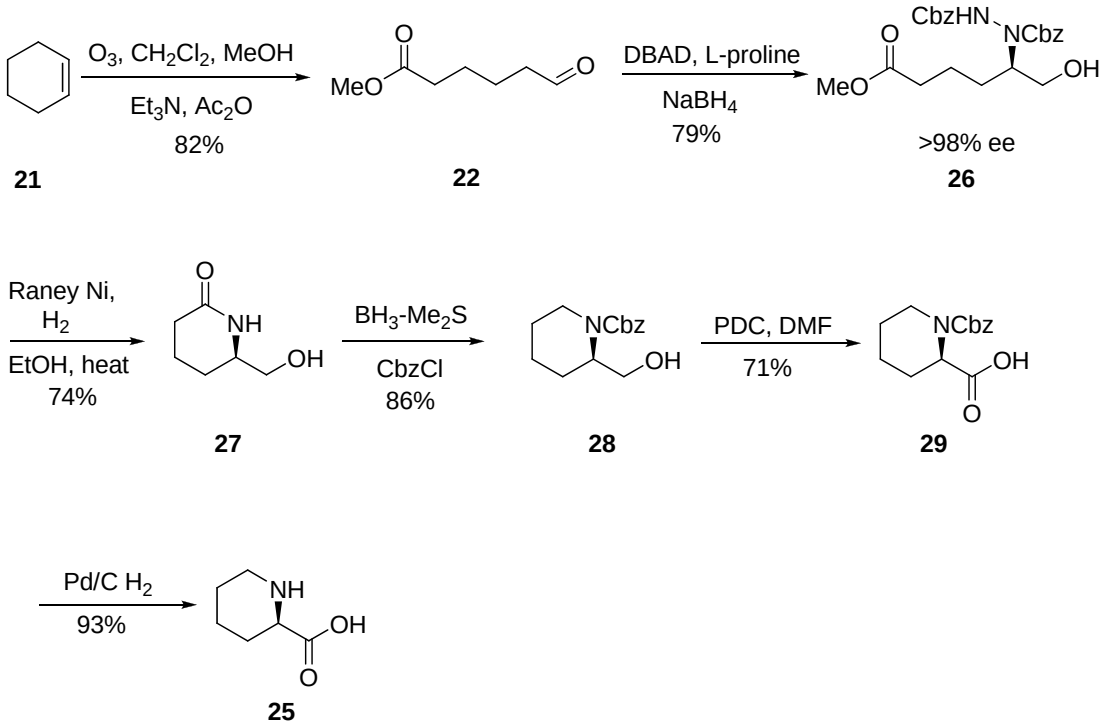
Cyclic amino acids are important building blocks in organic synthesis and occur in numerous natural products. For example, pipecolic acid moiety, also known as homoproline, is present in variety of bioactive molecules.[10-11] Incorporated into peptides, these cyclic amino acids confer rigidity to the proteins thus modifying biological activities.



25

(*R*)-Pipecolic acid

In this context, the asymmetric synthesis of (*R*)-pipecolic acid **25** is of importance.



Scheme 7: Synthesis of (*R*)-pipecolic acid

As illustrated in scheme 7, aldehyde **22** was subjected to proline catalyzed sequential α-amination[4a] reduction to obtain chiral 1,2-aminoalcohol **26**. The aminoalcohol **26** on Raney Ni catalyzed hydrogenolysis followed by heating in ethanol afforded lactam **27**. The lactam **27** was converted to corresponding amine and subsequently protected

as benzyl carbamte to afford N-protected amino alcohol **28**. The aminoalcohol **28** on oxidation with PDC in DMF afforded N-protected pipecolic acid **29**. The hydrogenolysis of **29** afforded target (*R*)-pipecolic acid **25**.

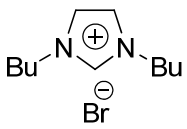
In summary (*R*)-coniceine and (*R*)-pipecolic acid **25** were synthesized efficiently from the readily available cyclohexene as the achiral precursor via asymmetric α-amination as key step.

Chapter 3: Introduction to ionic liquids and oxidation studies in ionic liquids

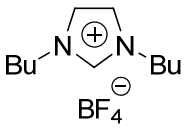
This chapter is further divided in three sections.

<u>Section A</u>: Introduction to ionic liquids

The past few years has witnessed the evolution of a new era in chemical research by the entry of ionic liquids as potential 'Green Designer Solvents' as novel replacements for volatile organic compounds traditionally used as industrial solvents.[12] Ionic liquids are systems consisting of salts that are liquid at ambient conditions. A brief history of ionic liquids and their emergence as environmentally benign solvents have been discussed in this section. Various types of ILs and their nomenclature are covered. The unique property of this ionic species, which gives liquid character to it, has been discussed in detail.



30
[bbim]Br



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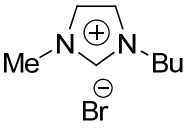

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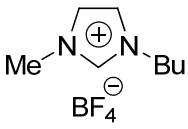
[bmim]Br



33
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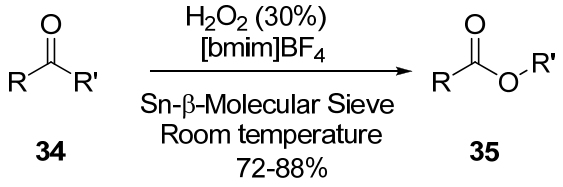
Among the various ionic liquids, imidazolium based ILs have attracted great deal of attention as a novel reaction media in organic synthesis due to their negligible vapor pressure, low melting point with high thermal and chemical stability. This section describes in details about the synthesis of a series of 1,3-di-*n*-butylimidazolium and 1-*n*-butyl-3-methylimidazolium based ILs.

<u>Section B</u>: Sn-β molecular sieve catalyzed Baeyer-Villiger oxidation in ionic liquid at room temperature

Baeyer-Villiger oxidation is attractive for practical applications into building blocks for complex bioactive molecules. This oxidation was made simpler by replacing

traditionally used peroxyacids with H_2O_2, a cheaper and less polluting reagent. Efficient activation of ketone oxidation by H_2O_2 was achieved by employing various catalysts.[13]

This section describes the efficient B-V oxidation of aromatic ketones with H_2O_2 catalyzed by Sn-β molecular sieve in ionic liquid. It also describes catalyst screening and catalyst recycling.

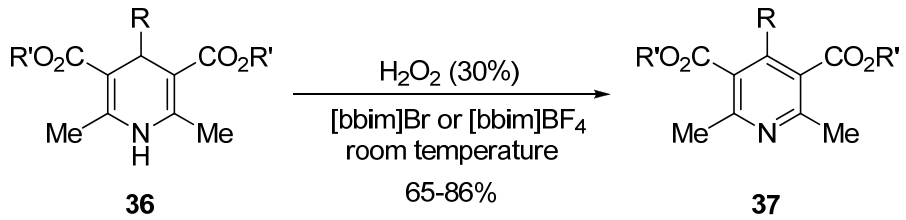


Scheme 8: Baeyer-Villiger oxidation of aromatic ketones

<u>Section C</u>: Oxidation of 4-substituted -1,4-dihydropyridines to pyridines with H_2O_2 in ionic liquids

In the human body, 1,4-dihydropyridine based drugs are oxidatively converted to the corresponding pyridine derivatives by the action of cytochrome P-450 or other related enzymes in the liver.[14] The oxidized compounds are largely devoid of the pharmacological activity of the parent compounds. These metabolites are important as reference standards and hence development of convenient method for their oxidation is important particularly for the synthesis of radiolabled compounds to study their biodegradation. Many methods were established for oxidation of 1,4-dihydropyridines but many suffer from drawbacks.

In this context this section describes the eco-friendly oxidation method of 4-substitued-1,4-dihydropyridines **36** to 4-substitutedpyridines **37** using aqueous 30% H_2O_2 in ionic liquids. It also describes recycling of the ionic liquid medium.



Scheme 9: Oxidation of 4-substituted-1,4-dihydropyridines

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Chapter 1

Introduction to asymmetric organocatalysis, proline catalyzed asymmetric synthesis of (*R*)-(+)-α-Lipoic acid and β-adrenergic blockers

1.1 SECTION A
INTRODUCTION TO ASYMMETRIC ORGANOCATALYSIS

1.1.1 Chirality

In 1815, French chemist Jean Baptiste Biot introduced the concept of chirality when he discovered optical activity in nature.[1] In 1848, one of his students Louis Pasteur achieved the first separation of enantiomers when he manually resolved a racemic mixture of tartaric acid salt based on differently shaped crystals.[2] Since then "Chirality" has become of tremendous importance in our daily life. A chiral object is one that possesses the property of "handedness". Thus chiral molecule can exist in at least two forms, which are mirror images of each others and can not be superimposed upon one another. A chiral object such as our hand is one that can not be placed on its mirror image so that all parts coincide (Figure 1).

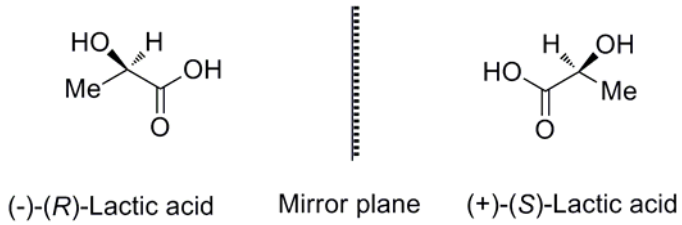


Figure 1. The two enantiomers of the lactic acid.

A chiral molecule and its mirror image are called enantiomers, and possess identical physical properties in an achiral environment. Two enantiomers can be differentiated through their ability to rotate the plane of polarized light by the same angle, but in opposite directions.

The majority of biological systems are composed of chiral molecules; all but one of the twenty amino acids that make up naturally occurring proteins are chiral. This implies that the two enantiomers of a molecule will interact differently with a living organism. Indeed, usually only one enantiomer of a drug provides the desired effect, while the other enantiomer is, at best, less or not active. However, in some cases the undesired enantiomer can have severe side effects. The most well-known and tragic example is the drug thalidomide, which was given as a racemic mixture during the 1960s to

alleviate the symptom of morning sickness in pregnant woman. It was later discovered that only one of the thalidomide enantiomers has the intended effect, while the other induces abnormalities in human embryos (Figure 2). Unfortunately, the situation is complicated by the racemisation of the desired enantiomer in the body.

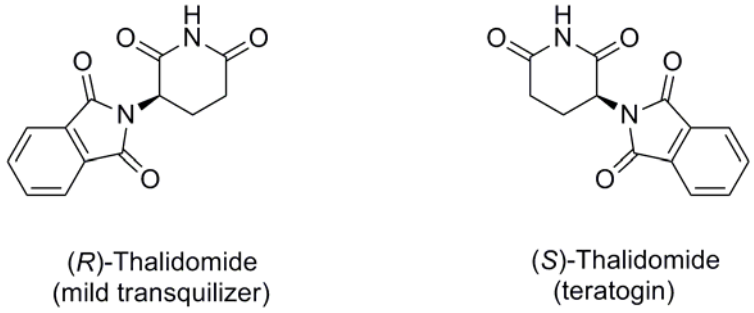


Figure 2. The two enantiomers of thalidomide.

Chiral molecules are not only primordial for the pharmaceutical industry but also for the perfumery and food industry; with our sense of taste and smell also depending on chirality. One enantiomeric form of a compound called limonene is primarily responsible for the odour of orange while the other enantiomer for the odour of lemon. Similarly the *S*-enantiomer of the amino acid, asparagine tastes sweet while the *R*-enantiomer tastes bitter (Figure 3).

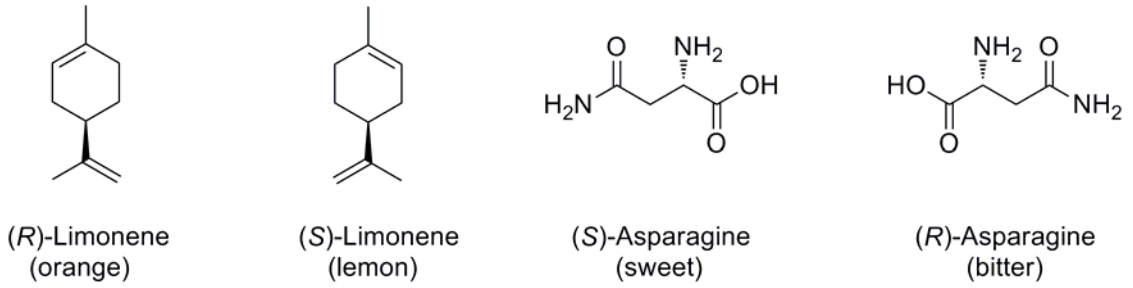


Figure 3. Enantiomers having different smell or taste.

These are just a few reasons why the field of asymmetric synthesis has developed enormously in recent decades. In 2001 this area of chemistry received the ultimate recognition with the Nobel Prize in chemistry being awarded to K. Barry Sharpless, William S. Knowles, and Ryoji Noyori for their work on catalytic asymmetric methods for oxidation and reduction.

1.1.2 The quest for the single enantiomer

There are three main ways to synthesis an enantiomerically pure or enriched compound

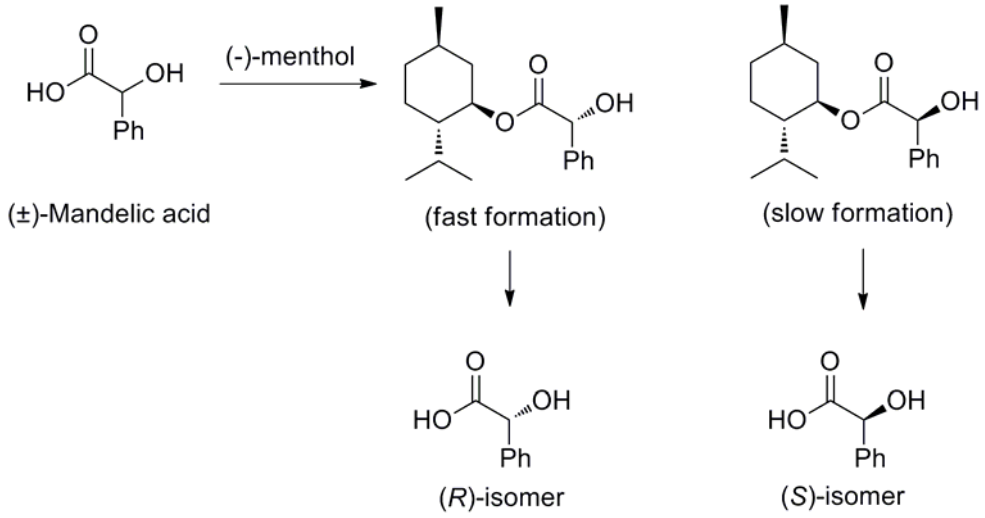
i) Resolution of racemic mixtures.

ii) The "Chiral pool" based on the use of a naturally occurring chiral starting material.

iii) Asymmetric synthesis (both through stoichiometric and catalytic processes).

1.1.2.1 Resolution of racemic mixtures

Resolution is the oldest, yet still widely used, method to obtain enantiopure compounds. Normally, the resolution is applied at the end of a racemic synthetic sequence, and is performed with the aid of an enantiomerically pure compound. However, because only one optical antipode is useful, half of the synthetic product is often discarded. Even if the wrong isomer can sometimes be converted to the active form, via racemisation and resolution, extensive work is required. A further drawback of this method is the need to use an equimolar amount of an enantiopure material; which can not always be recycled and reused. Even so, the resolution of racemates is a powerful method that is still widely used in industry. A typical example of resolution[3] is illustrated in Scheme 1.



Scheme 1. Classical resolution of (±)-mandelic acid using (-)-menthol

1.1.2.2 The chiral pool or "Chiron" approach

In this case, the synthetic method is based on the transformation of a naturally occurring enantiomerically pure starting material.[4] The most common chiral compounds offered by nature are amino acids, hydroxyl acids, carbohydrates, terpenes or alkaloids (Figure 4).

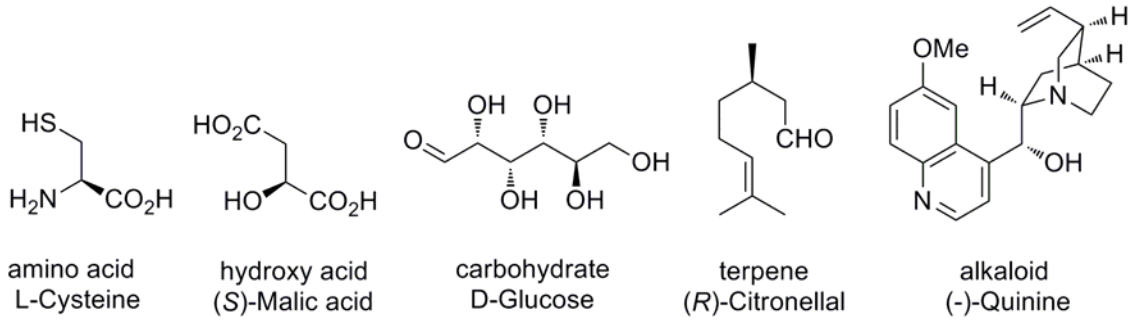
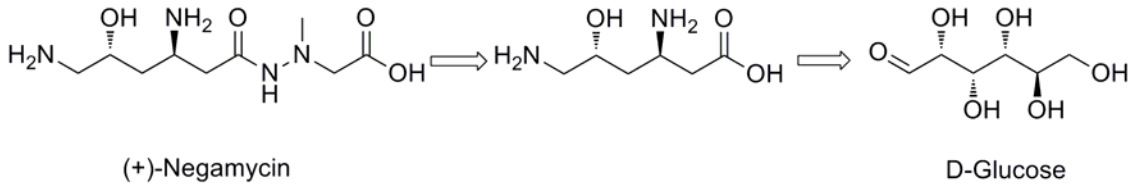


Figure 4. Example of naturally occurring chiral molecules.

A strong limitation of the chiral pool approach is the limited number of starting materials available, which can sometimes be very expensive or difficult to obtain, thus restricting the synthetic applications. Another disadvantage of this method is due to the chiral aspect of nature, which often produces only one of the two possible enantiomers of a compound.

The synthesis of (+)-negamycin, a broad-spectrum antibiotic, from glucose[5] is a typical example of the Chiron approach (Scheme 2).



Scheme 2. Retro synthesis of (+)-negamycin.

1.1.2.3 Asymmetric synthesis

The principle of asymmetric synthesis is the formation of a new stereogenic centre under the influence of a chiral group. This method is presently the most powerful and commonly used in the preparation of chiral molecules. Asymmetric synthesis can be further divided into four categories, depending of how the stereo-centre is formed:

a) Substrate-controlled methods.

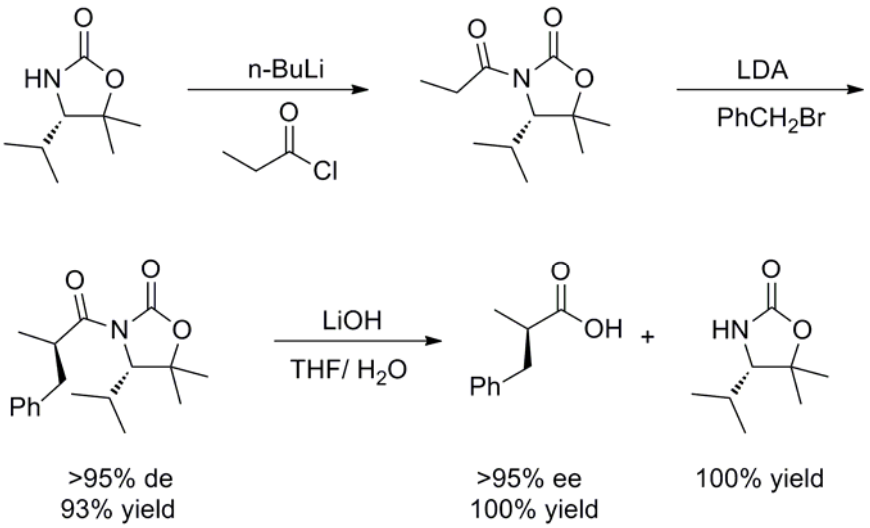
b) Auxiliary-controlled methods.

c) Reagent-controlled methods.

d) Catalyst-controlled methods.

In the case of the substrate-controlled method or "first generation of asymmetric synthesis", the formation of the new chiral centre is directed by the presence of a stereogenic unit that already exists within the chiral substrate. The auxiliary-controlled method or "second generation of asymmetric synthesis" is based on the same principle

as the first generation method in which the asymmetric control of the reaction is achieved by a chiral group in the substrate. The advantage of this method is that the enantiomerically pure chiral auxiliary is attached to an achiral substrate in order to direct the enantioselective reaction. The chiral auxiliary can be removed once the transformation is performed and often reused. This method usually offers high levels of selectivity and has proven itself to be very useful. However, this methodology suffers from the need of two extra steps to attach and remove the chiral auxiliary. Davies *et al.*[6] have developed a typical procedure where they use an "Evans type" chiral oxazolidinone to control the alkylation of an enolate (Scheme 3).



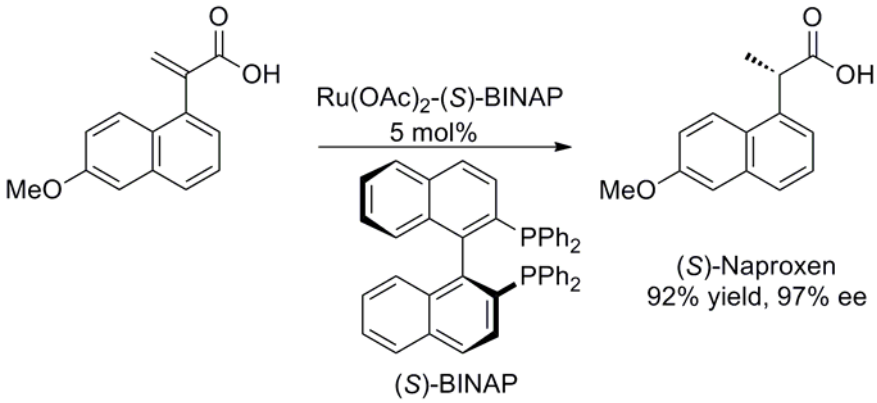
Scheme 3. Enantioselective alkylation directed by a chiral auxiliary.

In the third method, an achiral substrate is directly transformed to a chiral product using an enantiomerically pure chiral reagent. All three previously described chiral transformations have a common feature, which is the requirement of at least one equivalent of an enantiomerically pure compound. This requirement is not satisfactory from an economical and environmental perspective. Thus, the most significant advance in asymmetric synthesis during the past three decades has been the development and application of chiral catalysts to induce the transformation of an achiral molecule to an enantioenriched chiral product. Due to its importance, this process will be dealt within more details in the following section.

1.1.3 Asymmetric catalysis

Asymmetric catalysis is a combination of asymmetric synthesis, where a chiral molecule is used to govern an enantioselective transformation, and catalysis. In

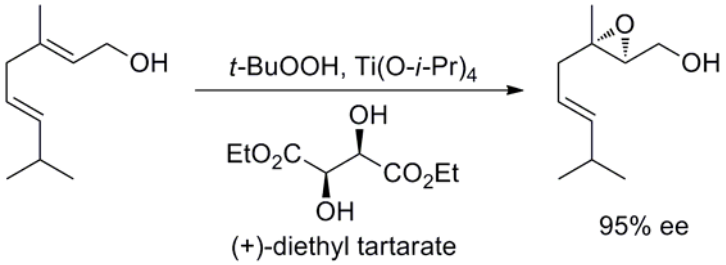
catalysis a small amount of a foreign material called "catalyst" speeds up a chemical process by decreasing the transition state energy, thus increasing the rate of the reaction without being consumed itself during the transformation. This process seems ideal for the preparation of chiral molecules since it only requires a limited amount of chiral catalyst to transform an achiral molecule into an enantioenriched chiral product. Noyori reported pioneering work in the field of catalytic asymmetric transformations in the mid 60s.[7] Although the enantioselectivity was poor, it opened up a new field in organic synthesis that became the focus of many brilliant research groups during the last decades. The most common asymmetric catalytic methods involve a transition metal, which once bonded to a chiral ligand, become the chiral catalyst. In 2001 the Nobel Prize in Chemistry was awarded to Dr. William S. Knowles, Prof. Ryoji Noyori, and Prof. K. Barry Sharpless for *"their development of catalytic asymmetric synthesis"*. Knowles and Noyori received half the Prize for their work on "*chirally catalysed hydrogenation reactions*" and Sharpless was rewarded with the other half of the Prize for his work on *"chirally catalysed oxidation reactions"*. This was the final recognition for a process which has had a remarkable impact on the chemical industry and especially the pharmaceutical industry where catalytic systems are used to prepare ton-scale of enantiopure drugs. An important example resulting from the work of Noyori,[8] and based on the work of Knowles, is the synthesis of the anti-inflammatory agent naproxen, involving a stereoselective catalytic hydrogenation reaction (Scheme 4).



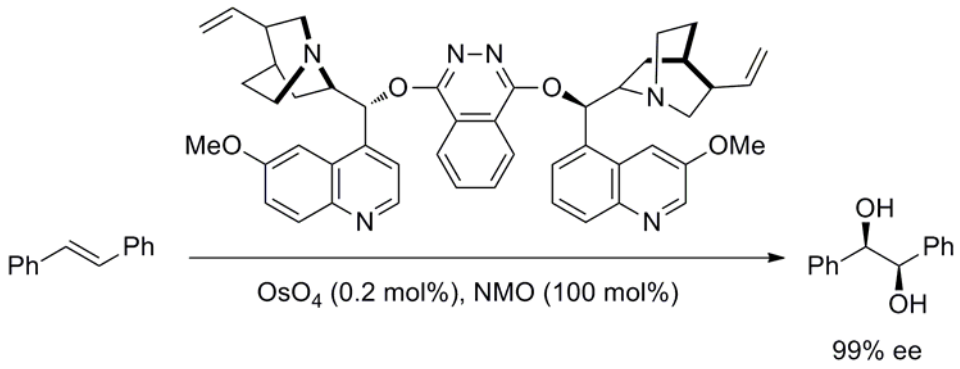
Scheme 4. Asymmetric synthesis of (*S*)-naproxen.

The hydrogenation catalyst in this reaction is an organometallic complex formed from ruthenium and a chiral organic ligand called (*S*)-BINAP. The reaction itself is truly remarkable because it proceeds with excellent enantiomeric excess (97%) and in high yield (92%). The development of highly enantioselective oxidation reactions by

Sharpless has proved to be crucial to organic synthesis. The asymmetric epoxidation of allylic alcohols,[9] and the asymmetric dihydroxylation of olefins,[10] became widely used tools in the synthesis of complex chiral molecules (Scheme 5 and 6).



Scheme 5. Sharpless epoxidation of allylic alcohol.



Scheme 6. Sharpless dihydroxylation of alkenes.

For decades, it was generally accepted that transition metal complexes and enzymes were the two main classes of very efficient asymmetric catalysts. Indeed, synthetic chemists have scarcely used small organic molecules as catalysts throughout the last century, even though some of the very first asymmetric catalysts were purely organic molecules. Already in 1912, Bredig reported a modestly enantioselective alkaloid-catalysed cyanohydrin synthesis. Only in recent years has the scientific community begun to appreciate the great potential of organocatalysis as a broadly useful methodology.

Today many methods using simple chiral molecules have been reported to catalyze asymmetric transformations with a very high degree of enantioselectivity. Currently, organocatalysis is one of the fastest growing areas in organic chemistry.[11]

1.1.4 Asymmetric organocatalysis

Organocatalysis is the catalysis of chemical transformations using purely organic molecule, which is composed of mainly carbon, hydrogen, nitrogen, sulfur, and phosphorus, and does not contain any metals. The concept of asymmetric catalysis has become synonymous with the use of metals in chiral environments.[12] Metal catalysts have some advantages: for example molecular and structural diversity and large reactivity patterns that can easily be tailored by variation of ligands. But there are also some disadvantages such as high price, toxicity, pollution, waste treatment and product contamination.[13]

A large number of asymmetric transformations are based on organic reagents. The chiral organic catalyst can be regenerated and reused for further reactions. The concept will certainly be helpful for development of a number of new catalytic reactions in the near future. On the other hand applications that are typically associated with metals, for example, as Lewis acids/ bases and as redox agents[14] can be emulated fairly well by organic compounds.

There is a dichotomy between organic and organometalic catalysis, particularly with respect to their reactivity and applications. On one hand organocatalytic reactions have evolved essentially from the ligand chemistry of organometalic reactions. Number of ligands were developed for metal mediated enantioselective catalytic reactions and are still among the most effective organocatalysts. It is thus not surprising that there are metal catalyzed reactions in which the metal free ligand is known to be active by itself, even in the same enantioselective transformation.[15] On the other hand, organocatalytic reactions can be more closely related to enzyme or antibody catalyzed reactions than organometalic processes. Indeed these small organic molecules, which are often known as artificial enzymes[16] show some characteristic features of bioorganic reactions.

Organic molecules catalyze chemical reactions through four different mechanisms:[11b]

a) Activation of a reaction based on the nucleophilic/electrophilic properties of the catalysts. The chiral catalyst is not consumed in the reaction and does not require parallel regeneration. This type of activation is reminiscent of conventional Lewis acid/ base activation.

b) Organic molecules that form reactive intermediates. The chiral catalyst is consumed in the reaction and requires a parallel catalytic cycle.

c) Phase transfer reactions. The chiral catalyst forms a host-guest complex with the substrate and shuttles between the standard organic solvent and second phase (i.e. the solid, aqueous or fluorous phase in which the reaction takes place).

d) Molecular cavity accelerated asymmetric transformations, in which the catalyst may choose between the competing substrates, depending on size and structure criteria. The rate acceleration of the given reaction is similar to the Lewis acid/ base activation and is a consequence of the simultaneous action of different polar functions.

In metal mediated enantioselective catalytic reactions, the metal plays an organisational role by translating chiral information and activating the reagents. In the absence of metal, the well organised transition state, which is required for the enantioselective transformation, can be formed either by passive or dynamic interactions, as is the case in biological systems. Passive binding refer to ordinary molecular recognition through hydrophobic, van der Waals and electrostatic interaction. Dynamic binding refers to interactions between catalyst and substrates at the reaction centres. Hydrogen bonding plays a crucial role in the determination of stereoselectivity of the reaction. Although this constitutes an energy contribution of only 1-6 Kcal mol^{-1} to the interactions, influence of hydrogen bonding on the conformational preferences by forming rigid three dimensional structures contributes to the affinity and selectivity of molecular recognition. Hydrogen bonding also plays an important role in stabilizing the reactive intermediates and in modulating the reactivity,[17] in a way very similar to enzyme catalysis. More and more evidence is being gathered on the complexity of the enantioselective transformation caused by the formation of aggregates (dimers) between substrates and catalyst with the highest enantioselectivity. These new findings challenge our traditional view, which is based essentially on the consideration of monomers.

The Lewis acid/base function of organometalic reagents can be emulated by organic systems and applied to enantioselective catalytic processes. A particularity of organocatalysts is the facile equilibrium between the electron rich and electron deficient states (i.e. the acidic and basic forms) of the same centre. It is easy to conceive this equilibrium simply by considering protonation-deprotonation, which on one hand can activate the reagent and on the other hand can contribute to the kinetic lability of the ligand. As a result of this equilibrium the same centre can act as Lewis acid or as a Lewis base, depending on the reaction conditions. Although in any given reaction one might have a clear idea of the role of the organic catalyst as either an acid or base, the

classification based on the electron donating or electron accepting ability of the molecules can be ambiguous. This acid-base dichotomy is well known in biological systems. In many enzymes one of the carboxy groups acts as an acid and the ionized form of another carboxy group acts as a base or as a nucleophile.[18] Moreover, the acid-base classification of the catalyst is hampered by the fact that a number of organocatalysts, for example, amino acids possess both acidic and basic functions and mediate the reaction by a push-pull mechanism.

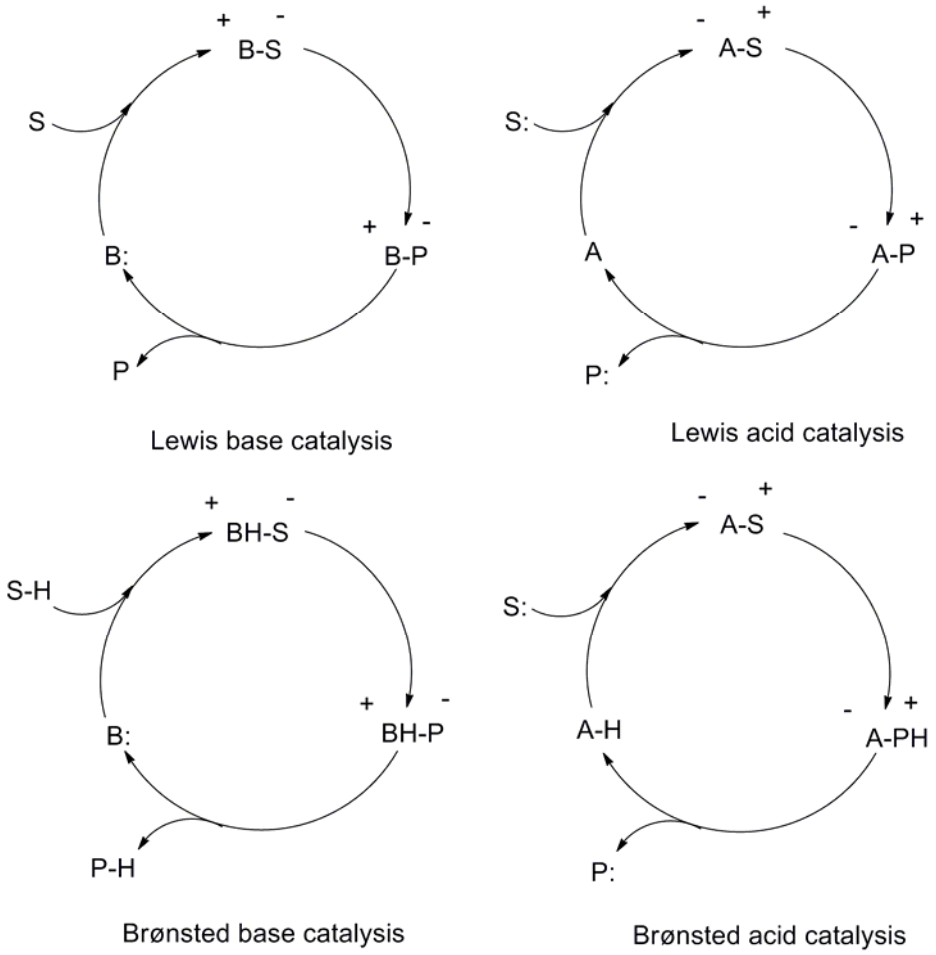


Figure 5. Organocatalysis cycles.

Recently, List[11e] introduced a system of classification based on the mechanism of catalysis (Figure 5). The four categories are Lewis base, Lewis acid, Brønsted base and Brønsted acid catalysis. Accordingly, Lewis base catalyst (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. Bronsted

base and acid catalytic cycles are initiated via a (partial) deprotonation or protonation, respectively.

Not all but some natural products like Cinchona alkaloids and its derivatives act as good catalysts.[19] Also some amino acids like proline and phenylalanine[15a] (Figure 6) and their derivatives have been used in enantioselective catalysts for a long time. The peptides derived from these amino acids are also showing good activity.

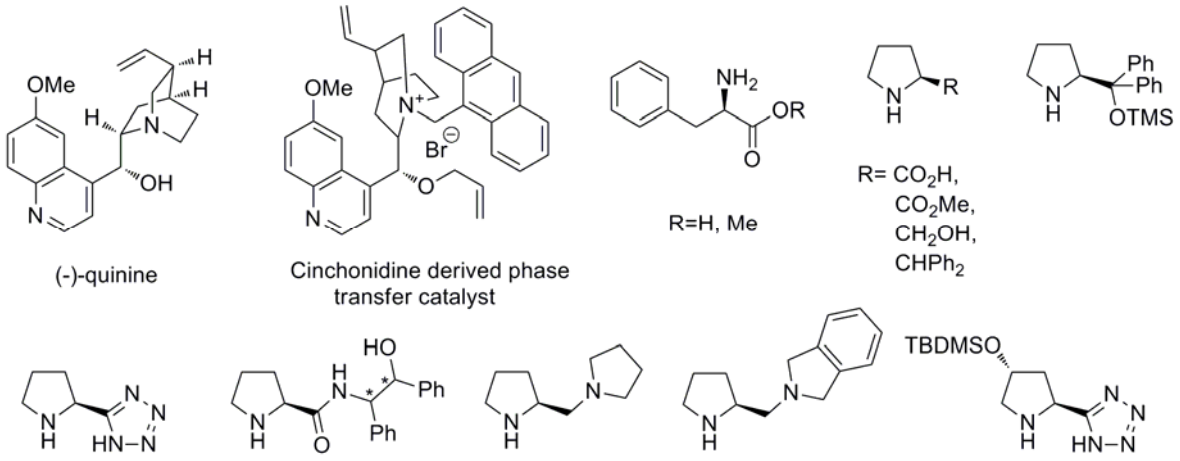
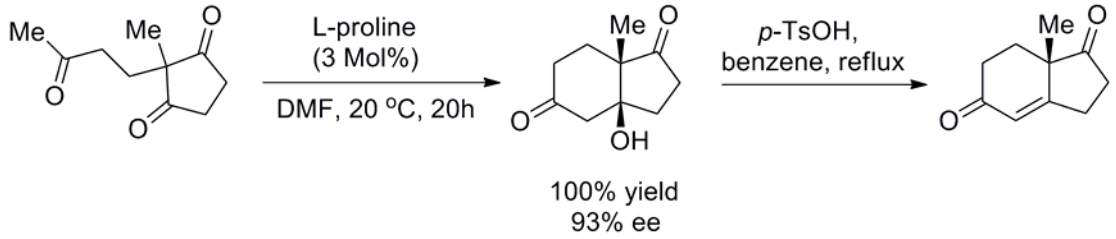


Figure 6. Some examples of organocatalysts derived from cinchona alkaloids and amino acids.

In early 1970 two groups independently reported Robinson annulation of meso triones in the presence of L-proline (3 mol %). Hajos and Parrish isolated ketol[20] while Wiechert and co-workers reported the synthesis of enone.[21]



Scheme 7. Proline catalyzed asymmetric Robinson annulation.

Till early 2000 very few groups were working on this topic and the field was very narrow. In 2000 List and Barbas has reported use of simple proline in asymmetric aldol reaction[22a] and after that, world has witnessed tremendous growth of this field. Simple amino acid like proline and it's derivatives has been used as organocatalysts for the asymmetric aldol reaction,[22] the Robinson annulation,[20,23] Diels-Alder reaction,[24] Michael reaction,[25] α-halogenation,[26] epoxidation[27] and Mannich reaction.[28]

1.1.5 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 be regarded as a bifunctional catalyst as the secondary amine acts as Lewis base and the acid group acts as Brønsted acid (Figure 7).

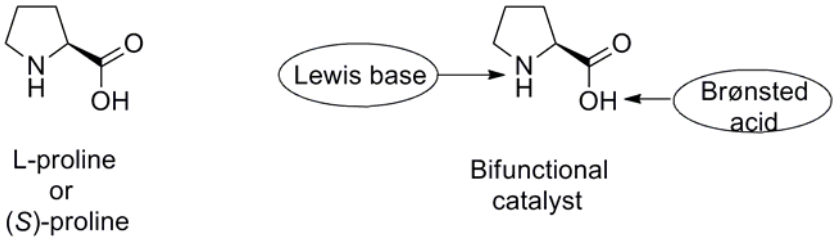


Figure 7. Proline and its bifunctional nature.

It can act as a nucleophile to carbonyl groups (iminium intermediate) or Michael acceptors (enamines) (Figure 8). 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.

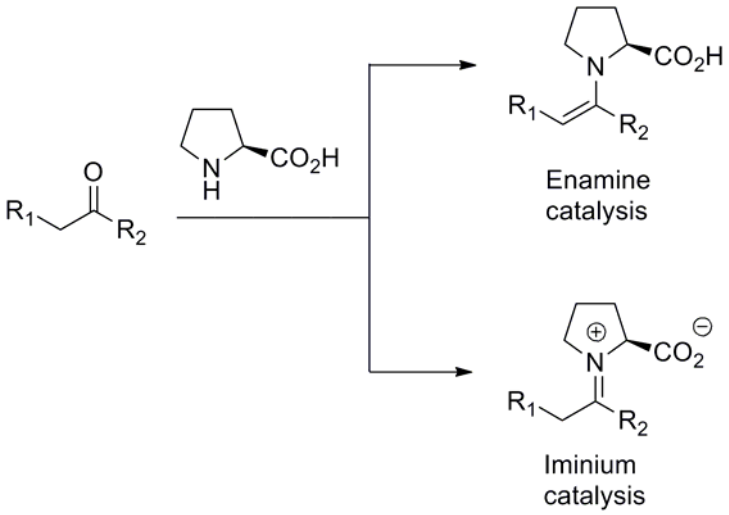
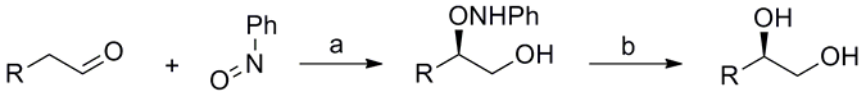


Figure 8. Modes of proline catalysis.

1.1.6 Proline catalyzed α-aminoxylation

1,2-diols are versatile starting materials for the synthesis of bioactive molecules.[4,29] Optically active α-hydroxyaldehydes and ketones are important intermediates in organic

synthesis as they are direct precursors to 1,2-diols and 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,[30a] Sharpless dihydroxylation of enol ethers,[30b] manganese–salen epoxidation of enol ethers,[30c] and Shi epoxidation of enol ethers.[30d] It is only rather recently that direct catalytic, asymmetric variants have been reported.[31] 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[32] of carbonyl compounds. When an aldehyde having α-hydrogen was reacted with nitrosobenzene 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 cleaved with $CuSO_4.5H_2O$ to give the corresponding diols in very high enantioselectivities (Scheme 8).



Scheme 8. *Reagents and conditions*: (a) (i) L-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 9. The observed enantioselectivitiy of the catalytic α-aminoxylation of aldehydes can be rationalized by 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*-aminophenyl group) with excellent enantioselectivities and in good yields.

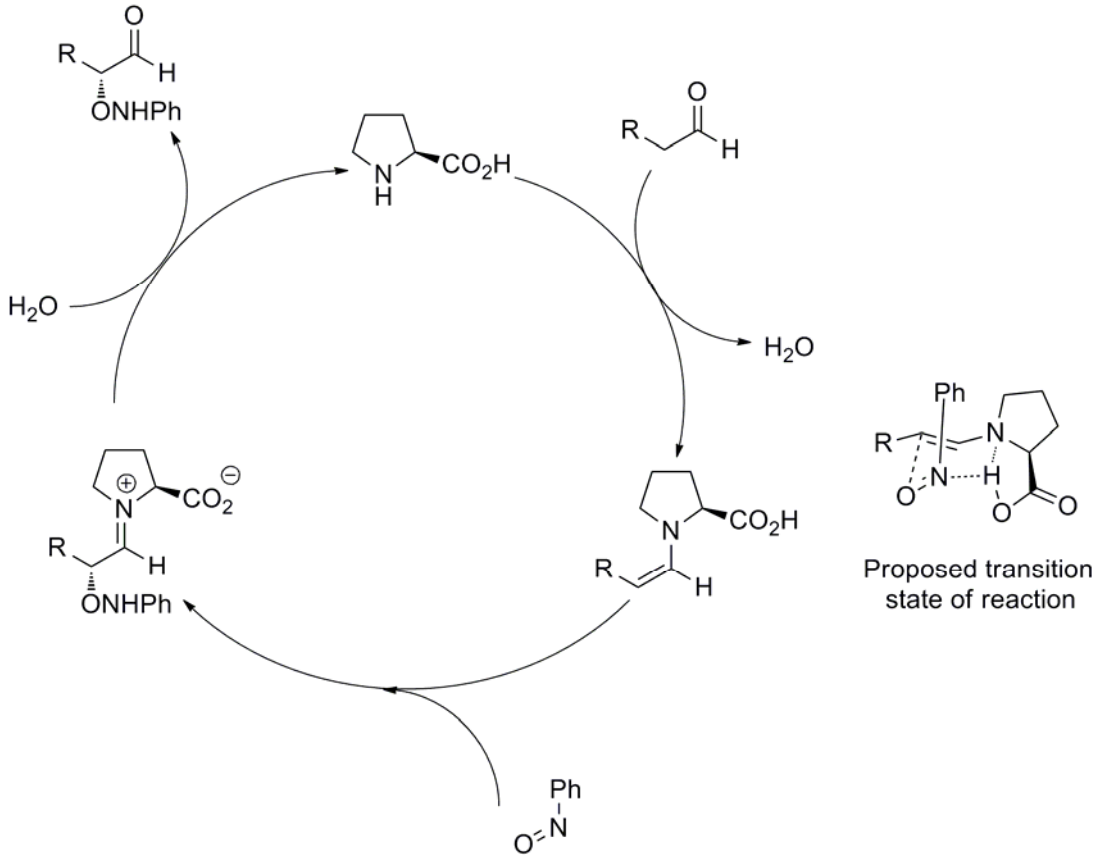


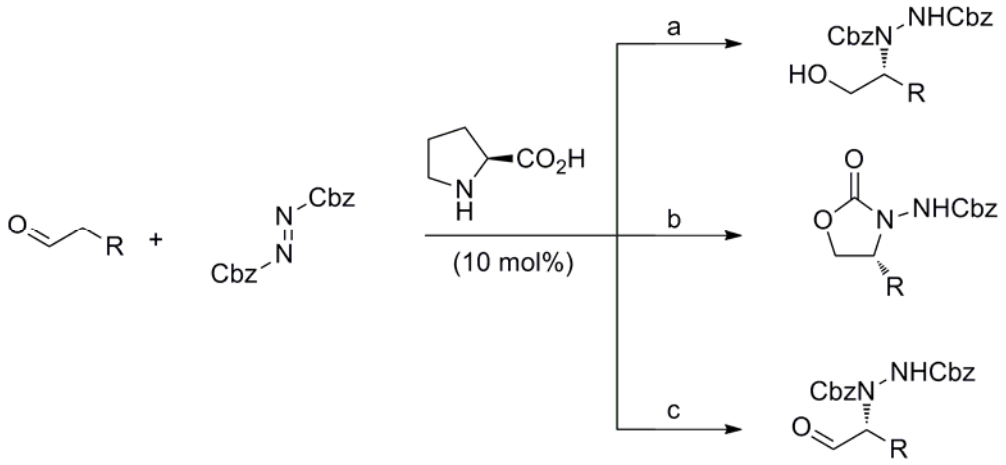
Figure 9. Proposed mechanism of the α-aminoxylation reaction

1.1.7 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[33] 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[33a] and Jørgensen[33b] disclosed the asymmetric α-amination of aldehydes (Scheme 9) using catalytic quantities of proline.

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



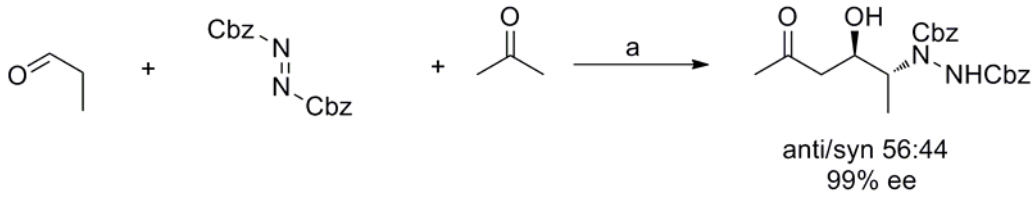
Scheme 9. *Reagents and conditions*: (a) CH_3CN, 0 °C, 3 h; $NaBH_4$, EtOH; (b) CH_2Cl_2, 25 °C; $NaBH_4$, MeOH; 0.5 N NaOH; (c) CH_2Cl_2, 25 °C; H_2O.

1.1.8 Sequential reactions involving α-aminoxylation/α-amination[34]

Proline derivatives catalyzed sequential transformations 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. Out of these sequential transformations involing α-aminoxylation/α-amination are described below.

1.1.8.1 Sequential α-amination-aldol[34a]

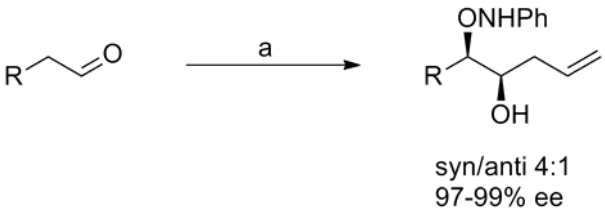
Barbas III *et al*. have developed a one-pot protocol for the synthesis of functionalized β-amino alcohols from aldehydes, ketones and azodicarboxylates (Scheme 10).



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

1.1.8.2 Sequential α-aminoxylation –allylation[34b]

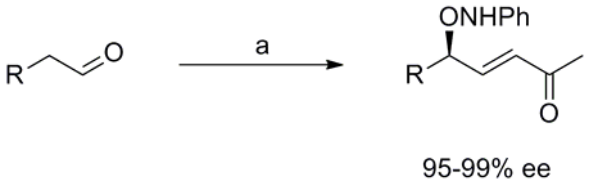
Zhong *et al.* have reported a facile, direct and rapid synthesis of enantiopure mono-substituted 1,2-diols using tandem α-aminoxylation-allylation reaction of aldehyde.



Scheme 11. *Reagents and conditions*: (a) PhNO, L-proline (20 mol%), DMSO, rt, 20 min then allyl bromide, In metal, NaI, 5 mim.

1.1.8.3 Sequential α-aminoxylation-olefination[34c]

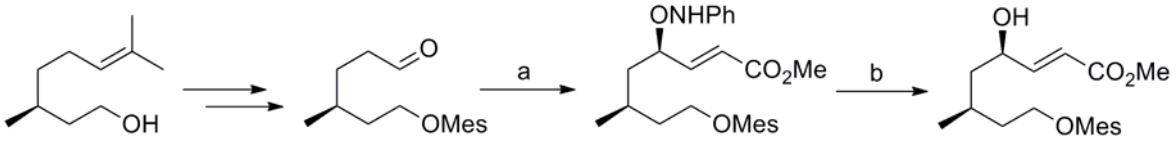
Zhong *et al*. have reported sequential asymmetric α-aminoxylation/Wadsworth-Emmons- Horner olefination of aldehydes for the synthesis of optically active *O*-amino-substituted allylic alcohols in good enantioselectivities using cesium carbonate as base (Scheme 12).



Scheme 12. *Reagents and conditions*: (a) PhNO, L-proline (20 mol %), DMSO, rt, 20 mim.; diethyl(2-oxopropyl)phosphonate, $CsCO_3$, 30 min.

1.1.8.4 Sequential α-aminoxylation-HWE olefination[34d]

MacMillan *et al.* reported sequential α-amination-Horner-Wadsworth-Emmons olefination of aldehyde obtained from (-)-citronellol to obtain chiral γ-hydroxy-α, β-unsaturated ester.



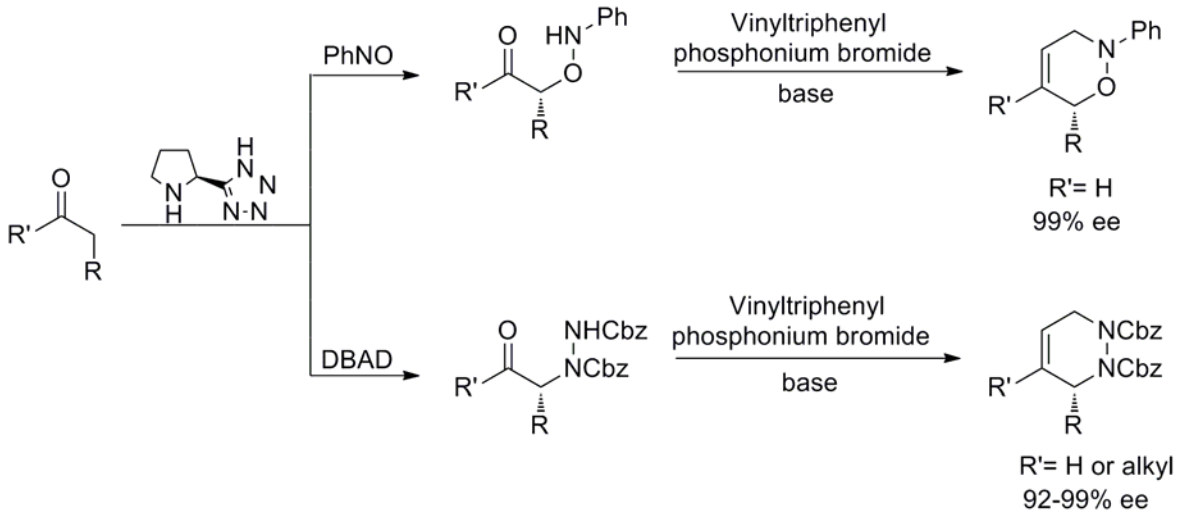
(-)-Citronellol

Scheme 13. *Reagents and conditions*: (a) PhNO, D-proline (40 mol %), DMSO; $(EtO)_2P(O)CH_2CO_2Me$, LiCl, DBU, -15 °C. (b) NH_4Cl, MeOH, 48 h.

1.1.8.5 Sequential α-functionalization-intramolecular Wittig cyclization[34e-g]

Ley et al. reported seqential α-aminoxylation/amination-intramolecular Wittig cyclization reaction to obtain chiral dihydro-1,2-oxazines and chiral 3,6-dihydropyridazines. After organocatalytic asymmetric α-functionlization of

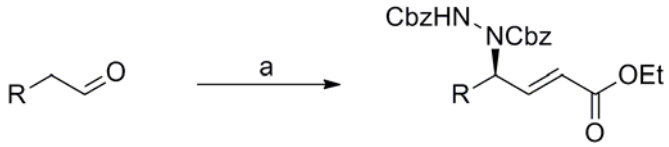
aldehydes/ketones, cyclized by Wittig reaction using vinyltriphenyl phosphonium bromide and base in one pot.



Scheme 14. α-functionalization and intramolecular Wittig cyclization.

1.1.8.6 Sequential α-amination-HWE olefination[34h]

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 (Scheme15).



Scheme 15. *Reactions and conditions*: (a) L-proline (10 mol%), DBAD (1 equi.), CH_3CN, 0 °C, 2h; 10 °C, 1h; $(EtO)_2P(O)CH_2CO_2Et$, LiCl, DBU, 0 °C, 45 min.

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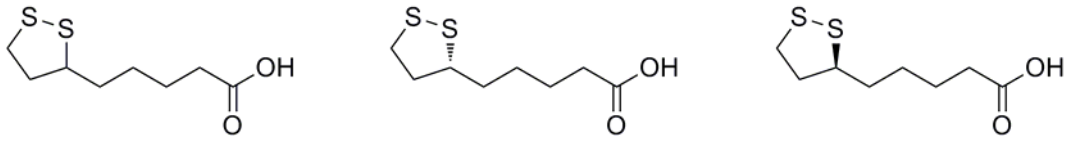
1.2 SECTION B
EANTIOSELECTIVE SYNTHESIS OF (*R*)-(+)-α-LIPOIC ACID

1.2.1 Introduction

Lipoic acid (**1**) was first isolated in 1951 by Reed and his co-workers[1] at the university of Texas in Austin. The first purified sample of lipoic acid was 30 mg of yellow crystals that were extracted from 100 kg of liver residue. Some believed that substance should be named thioctic acid because it contained two sulfur atoms (theion in Greek) and eight carbon atoms (octo in Greek). Finally, the substance was named as lipoic acid because of its ability to dissolve in lipids. α-Lipoic acid is not considered to be a vitamin because it is assumed that it can be synthesized by the body in small amounts from essential fatty acids.

Lipoic acid works at the cellular level to help essential substances for metabolism to enter the mitochondria. Lipoic acid is a powerful and well-known antioxidant. An increase in the amount of lipoic acid increases the amount of cellular fuel that is burned. This generates a greater energy reserve for the body that is available for growth, tissue repair and muscle development.

α-Lipoic acid does not accumulate in tissues and therefore does not have any toxicity in the amounts usually taken because it is distributed through the tissues. It is paticularly useful in protection of the eye and brain, the most sensitive of organs to free radical damage.



α-Lipoic acid **1** (*R*)-(+)-α-Lipoic acid **2** (*S*)-(-)-α-Lipoic acid **3**

Figure 1. Structure of α-lipoic acid

1.1.2 Role α-lipoic acid in Human Health

α-lipoic acid has been shown to have significant physiological as well as pharmacological properties.[2] There is no doubt that alpha lipoic acid have an important role in Human Health.[3]

- Alpha lipoic acid functions as a universal antioxidant and free radical scavenger.[4]
- Recycles both Fat and Water-soluble antioxidant vitamins.[5]
- Improves sugar metabolism and energy production. (i. e. controls diabetes).[6]
- Alpha lipoic acid is a co-enzyme associated with α-keto acid dehydrogenation.[7,8]
- α-lipoic acid acid has been used as a therapeutic agent in a number of conditions related to liver.[9]
- α-lipoic acid appears to have the potential to slow the process of aging.[10]
- α-lipoic acid significantly reduces inflammation and it also acts as an antitumour agent.[11]
- α-lipoic acid is an effective inhibitor of human immuno deficiency virus (HIV) replication.[12]
- α-lipoic acid has been found beneficial against radiation injury, smoking, heavy metal poisoning and chagas disease.[13]

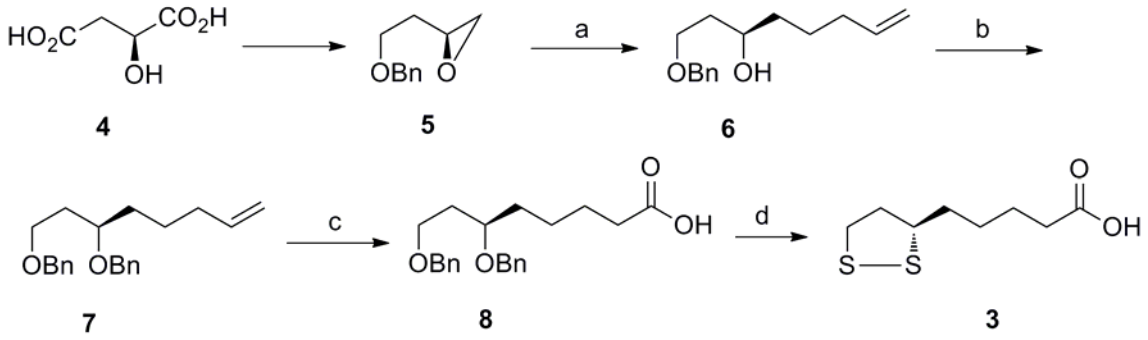
1.2.3 Review of literature

Reed and co-workers reported the isolation of α-lipoic acid in 1951 from liver residue. The chemical structure of α-lipoic acid was determined in the early 1950's and its absolute configuration was confirmed to be *R* in 1983, when Golding synthesized the complementary enantiomer from *S*-malic acid. It clearly indicates that scientists considered lipoic acid as small molecule and after knowing the biological activity and pharmaceutical importance the scientific community was attracted by its synthesis as a result a number of (±)-α-lipoic acid and optically active lipoic acids have been documented in the literature.

1.2.3.1 Golding *et al* (1983, Scheme 1)[14]

Golding and co-workers have utilized epoxide **5** as the chiral precursor, which was prepared by known procedure from *S*-malic acid **4**. Opening of epoxide with but-3-enyl magnesium chloride catalysed by lithium chloro cuprate delivered the compound **6**. Protection of the free hydroxyl group as benzyl ether **7** followed by hydroboration and oxidation gave the acid **8**. Esterification of acid **8** and removal of benzyl protection

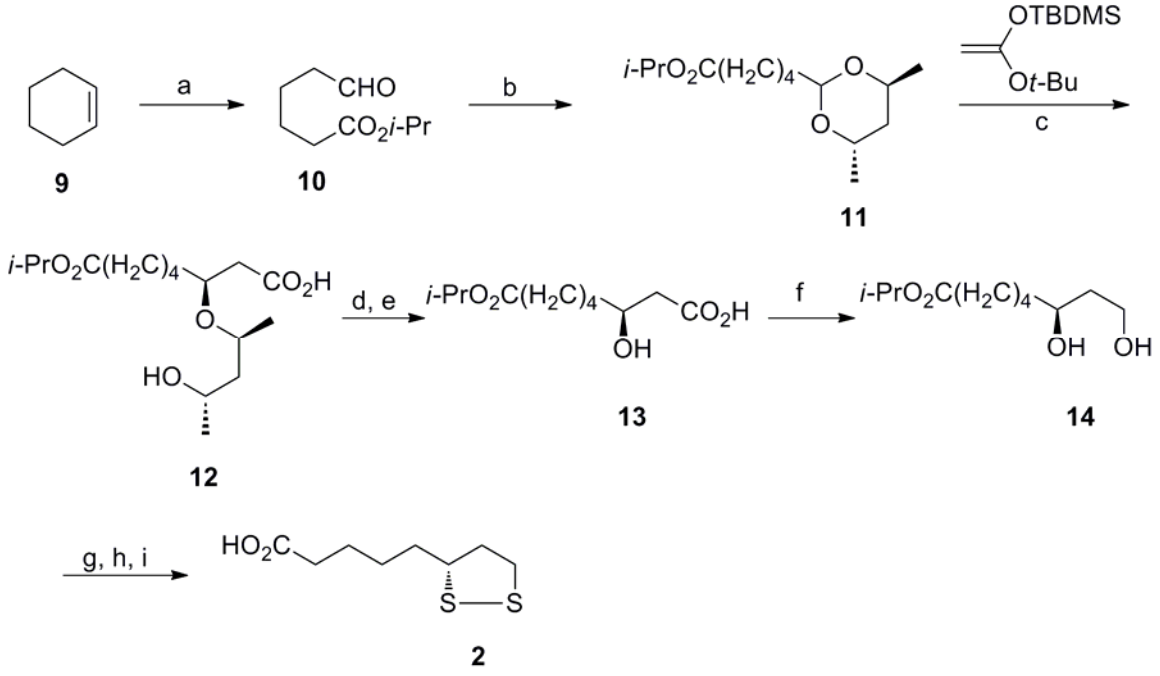
gave ester, which on mesylation followed by treatment of dimesylated compound with Na_2S, sulfur in DMF and final ester hydrolysis delivered *S*-lipoic acid **3**.



Scheme 1. *Reagents and conditions*: (a) CH_2=$CH_2CH_2CH_2MgCl$, Li_2CuCl_4 (cat), THF; (b) $PhCH_2Br$, NaH, THF; (c) (i) $HBSia_2$, THF, aq. H_2O_2-; (ii) PDC, DMF; (d) (i) MeOH-HCl; (ii) Pd/C, H_2; (iii) $MeSO_2Cl$, Et_3N; (iv) Na_2S, S, DMF; (v) aq. NaOH.

1.2.3.2 Elliott *et al* (1985, Scheme 2)[15]

Elliott and co-workers have reported the first synthesis of *R*-(+)-lipoic acid using highly diastereoselective $TiCl_4$ calalyzed aldol-type coupling of chiral acetal **11** with 1-*t*-butoxy-1-*t*-butyldimethylsilyloxyethene. The coupling product on hydrolysis followed by oxidation with Jones reagent gave acid **12**. Removal of the chiral auxiliary by β-elimination followed by reduction with borane delivered the diol ester **14**. The diol ester was converted in to *R*-(+)-lipoic acid by using Goldings Procedure.

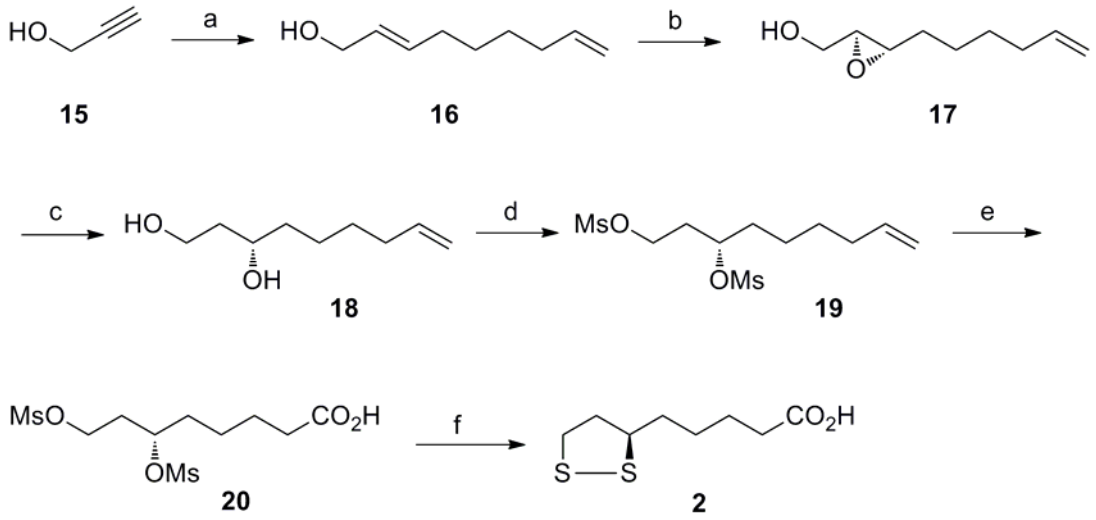


Scheme 2. *Reagents and conditions*: (a) O_3, ^{i}PrOH, -78 ^{o}C, Ac_2O, Et_3N; (b) (2*S*, 4*S*)-pentane-2, 4-diol, *p*-TsOH, Benzene; (c) (i) $TiCl_4$, CH_2Cl_2, -78 ^{o}C; (ii) TFA, H_2O; (d) Jones oxidation; (e)

Piperidinium acetate, benzene, reflux; (f) BH_3.THF, then 4 M aq. KOH; (g) $MeSO_2Cl$, Et_3N, 0^oC; (h) Na_2S, S, DMF; (i) aq. NaOH.

1.2.3.3 Sutherland *et al* (1986, 1990 Scheme 3)[16]

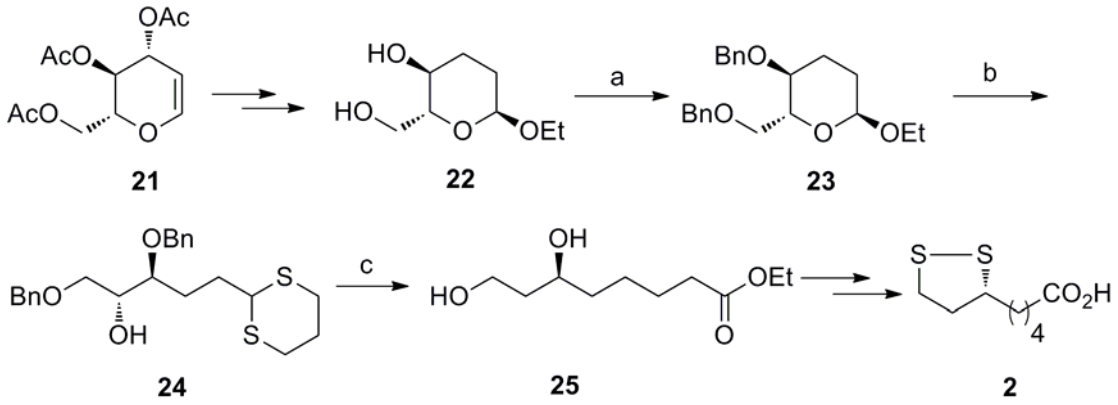
Sutherland and co-workers employed the alkylation of lithiodianion of propargyl alcohol **15** in liquid ammonia solution with 6-bromohex-1-ene followed by dissolving metal reduction to deliver the allyl alcohol **16**. Sharpless asymmetric epoxidation of allyl alcohol **16** gave the (2*S*, 3*S*)-epoxy alcohol **17**. Reduction of **17** with Red-Al and mesylation of the resulting diol to deliver the dimesylate **19**. Ruthenium tetroxide oxidation of the terminal double bond of **19** and final disulfide displacement of acid **20** delivered the *R*-(+)-Lipoic acid.



Scheme 3. *Reagents and conditions:* (a) Na, liq. NH_3, $Br(CH_2)_3CH{=}CH_2$; (b) L-(+)-diisopropyl tartarate, $Ti(OPr^i)_4$, TBHP, CH_2Cl_2, -20 ^oC; (c) Red-Al, THF; (d) $MeSO_2Cl$, Et_3N, CH_2Cl_2; (e) RuO_4 (f) Na_2S, S, DMF.

1.2.3.4 Rama Rao *et al* (1986, Scheme 4)[17]

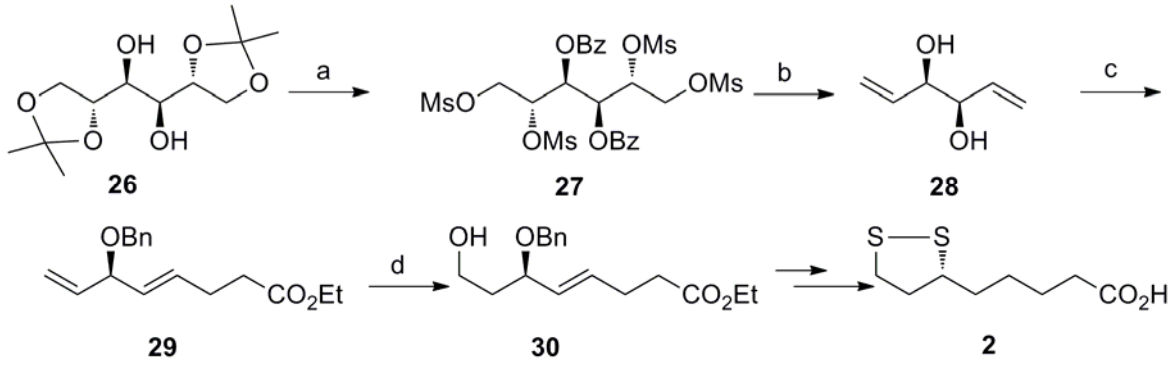
In Rama Rao's approach, sequence of reactions on 3,4,6-tri-*O*-acetyl-D-glucal **21** afforded compound **23**. Treatment of **23** with propane dithiol followed by xanthate formation and tri-n-butyl hydride mediated reductive removal afforded dithiane derivative **24**. Sequential dithiane deprotection, two carbon wittig olefination, hydrogenation using Raney nickel delivered the diol **25** which was converted into lipoic acid following the known procedure.



Scheme 4. *Reagents and conditions*: (a) BnBr, NaH; (b) (i) 1, 3-propane dithiol, $BF_3.Et_2O$, CH_2Cl_2; (c) (i) NaH, CS_2, MeI; (ii) n-Bu_3SnH, AIBN; (iii) HgO, $BF_3.OEt_2$; (iv) Ph_3P=CHCOOEt (v) H_2, Raney Ni.

1.2.3.5 Rama Rao *et al* (1987, Scheme 5)[18]

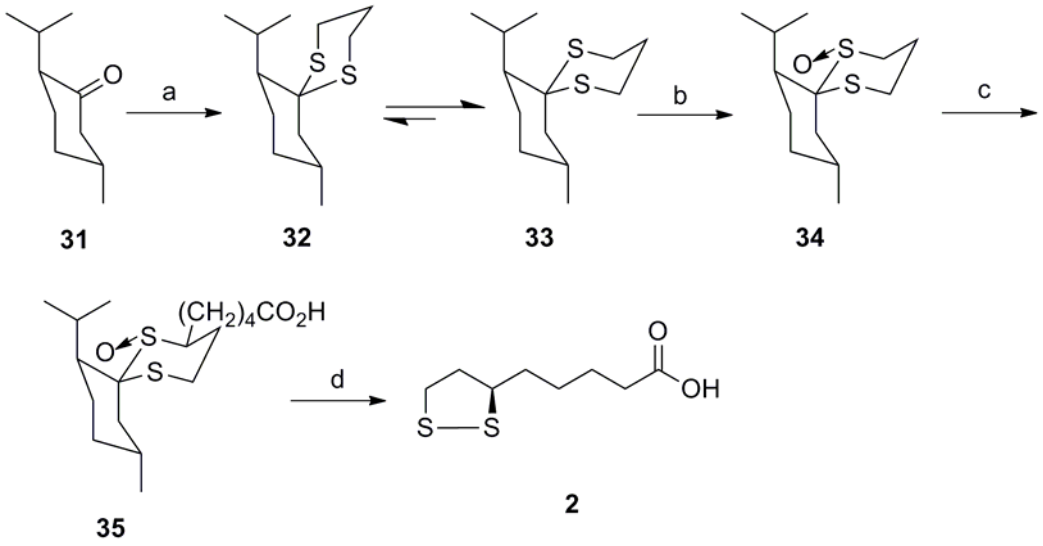
This approach involves the utilization of mannitol diacetonide **26** as a chiral precursor. Benzoyl protection of the hydroxyl groups followed by isopropylidene group deprotection and mesylation gave the tetra mesylate **27**. Treatment of **27** with sodium Iodide and Zinc dust followed by debenzoylation gave (3*R*, 4*R*)-1, 2-divinyl glycol **28**. Selective protection of hydroxyl group and claisen-ester rearrangement of the resultant monoprotected benzyl ether delivered the compound **29**. Sequential hydroboration, oxidation afforded alcohol **30** which was converted in to *R*-(+)-lipoic acid via known reaction sequence.



Scheme 5. *Reagents and conditions*: (a) (i) PhCOCl, Pyridine; (ii) 50 % aq. AcOH (iii) $MeSO_2Cl$, Et_3N, CH_2Cl_2; (b) (i) NaI, Zn, DMF, Reflux; (ii) NaOMe (c) (i) Bu_2SnO, Toluene, Reflux; (ii) 1.2 eq $PhCH_2Br$, DMF, 100 ^oC; (iii) $CH_3CH(OEt)_3$, Propionic acid (cat), 145 ^oC; (d) 9-BBN, $NaOH/H_2O_2$.

1.2.3.6 Ravindranathan *et al* (1987, Scheme 6)[19]

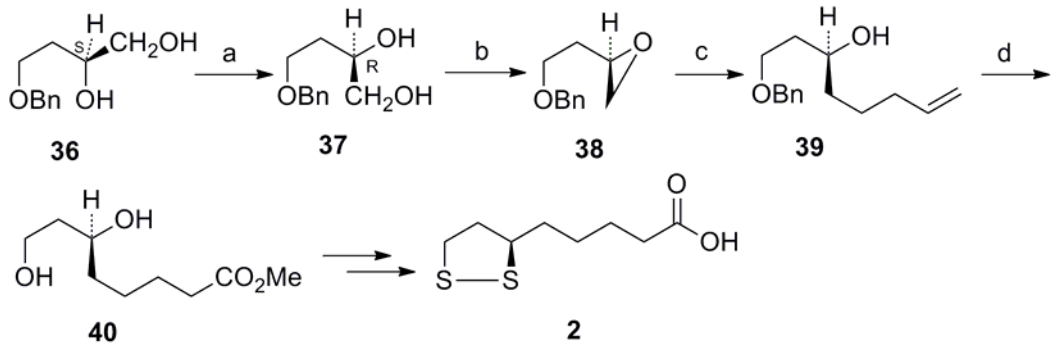
Ravindranathan's approach involves the formation of 1, 3-dithiane **33** from 1, 3-propane dithiol and L-menthone **31**. Regio selective oxidation of dithiane **33** afforded sulfoxide **34**. Stereo selective alkylation of **34** followed by hydrolytic cyclization afforded *R*-(+)-lipoic acid. In the similar manner *S*-lipoic acid prepared by using D-menthone. In their approach they recovered the starting menthones in almost quantitative yield. This is the shortest and probably the best synthesis for both the enantiomers of lipoic acid.



Scheme 6. *Reagents and conditions*: (a) 1,3-propanedithiol, $BF_3.Et_2O$; (b) $NaIO_4$, MeOH, 0 ^oC; (c) LDA, TMEDA, THF, $Br(CH_2)_4CO_2Li$, -78 ^oC; (d) aq. HCl, benzene.

1.2.3.7 Golding *et al* (1988, Scheme 7)[20]

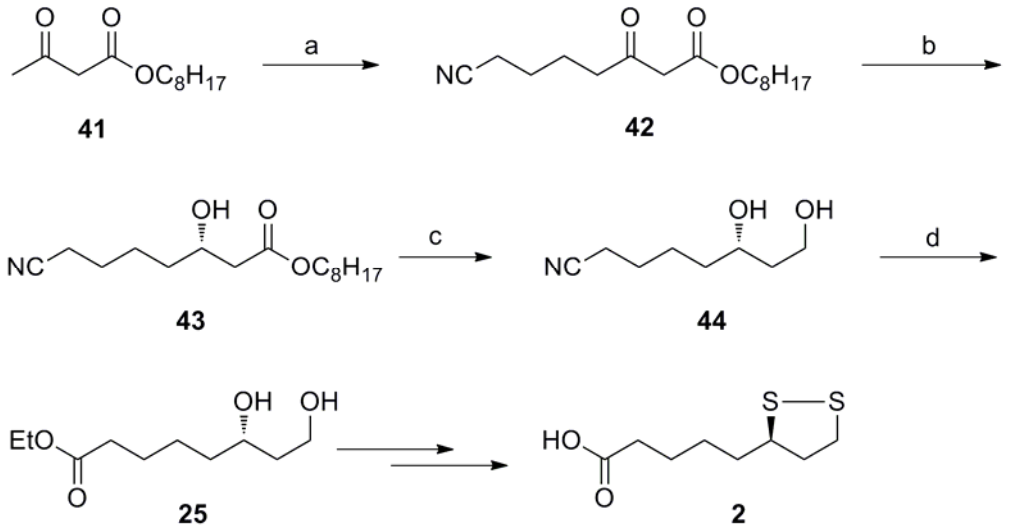
In this approach Golding and Brookes synthesized epoxide **38** (enantiomer of epoxide **5**) for the synthesis of *R*-Lipoic acid. They used the same starting material i.e *S*- malic acid but inverted the configuration of hydroxyl group to prepare the epoxide **38**. Epoxide **38** was converted in to *R*-Lipoic acid following the same sequence of reactions used in the earlier approach.



Scheme 7. *Reagents and conditions*: (a) (i) $MeSO_2Cl$, Et_3N; (ii) KOAc, Ac_2O; (iii) K_2CO_3, MeOH; (b) (i) PhCHO, H^+; (ii) NBS, ClF_2CCCl_2F; (iii) NaOH, glycol; (c) $CH_2{=}CH_2CH_2CH_2MgCl$, Li_2CuCl_4 (cat), THF; (d) (i) BnBr, NaH, THF; (ii) $HBSia_2$, THF, aq. H_2O_2; (iii) PDC, DMF; (iv) MeOH-HCl; (v) Pd/C, H_2.

1.2.3.8 Gopalan *et al* (1989, Scheme 8)[21]

Gopalan and Jacobs have utilized highly enantio selective yeast reduction of β-keto ester **42** as the key step to deliver the compound **43**. Reduction of ester **43** with $LiBH_4$ in THF at room temperature gave the cyano diol **44**. The diol was converted in to diol ester **25** by using ethanol in presence of acid. By a series of known reactions diol ester **25** was converted in to *R*-(+)-lipoic acid.

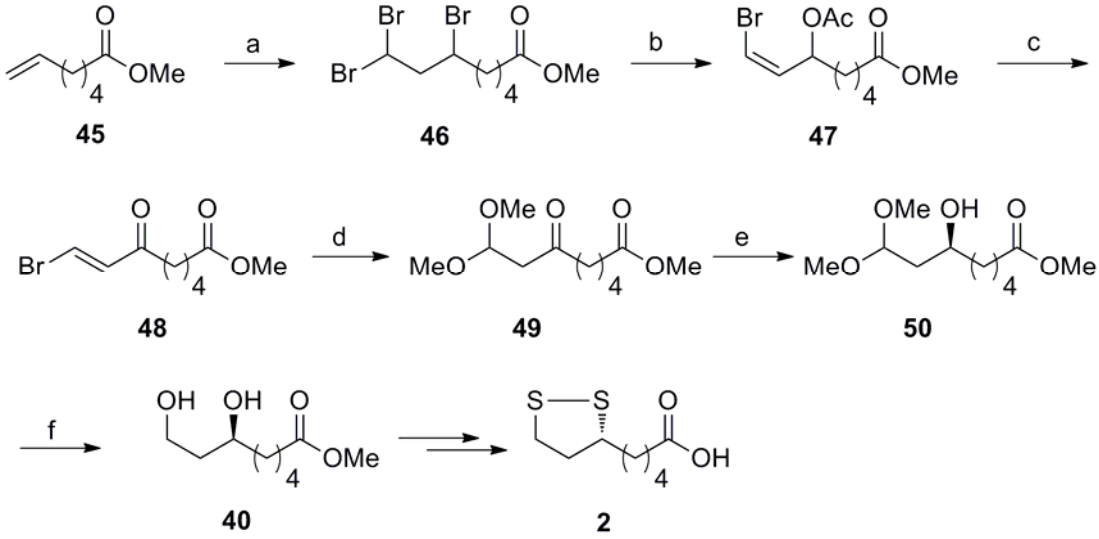


Scheme 8. *Reagents and conditions:* (a) (i) NaH, THF, HMPA, 0 ^oC; (ii) nBuLi, $I(CH_2)_3CN$; (b) Baker's Yeast (c) $LiBH_4$, THF, 0 ^oC; (d) EtOH, H^+, Reflux.

1.2.3.9 Bhalerao *et al* (1990, Scheme 9)[22]

Bhalerao and co-workers have used copper catalyzed bromoform addition to alkene **45** to give methyl-6, 8, 8-tribromooctonoate **46**, which on treatment with potassium acetate

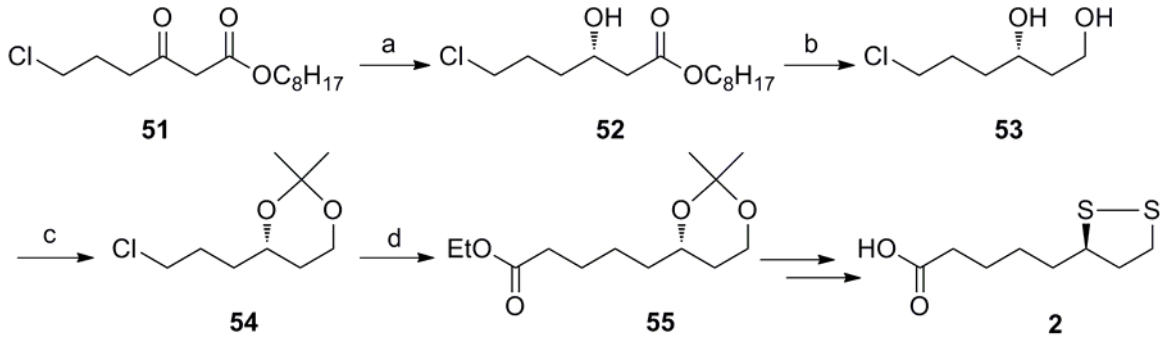
and 18-crown-6 in DMF gave compound **47**. Hydrolysis, Oxidation followed by treatment with triton-B gave the keto acetal **49**. The keto acetal **49** was reduced enantioselectively by baker's yeast to give compound **50**, which on treatment with H_3PO_4 in acetone followed by $NaBH_4$ reduction resulted in the formation of diol **40**. The diol was converted in to *R*-(+)-lipoic acid in a similar fashion reported earlier.



Scheme 9. *Reagents and conditions*: (a) Cu, $CHBr_3$, 80 %; (b) KOAc, 18-crown-6, DMF; (c) K_2CO_3, MeOH then PCC; (d) Triton B, MeOH; (e) Baker's Yeast, pH 4.5-5; (f) H_3PO_4, Acetone then $NaBH_4$.

1.2.3.10 Gopalan *et al* (1990, Scheme 10)[23]

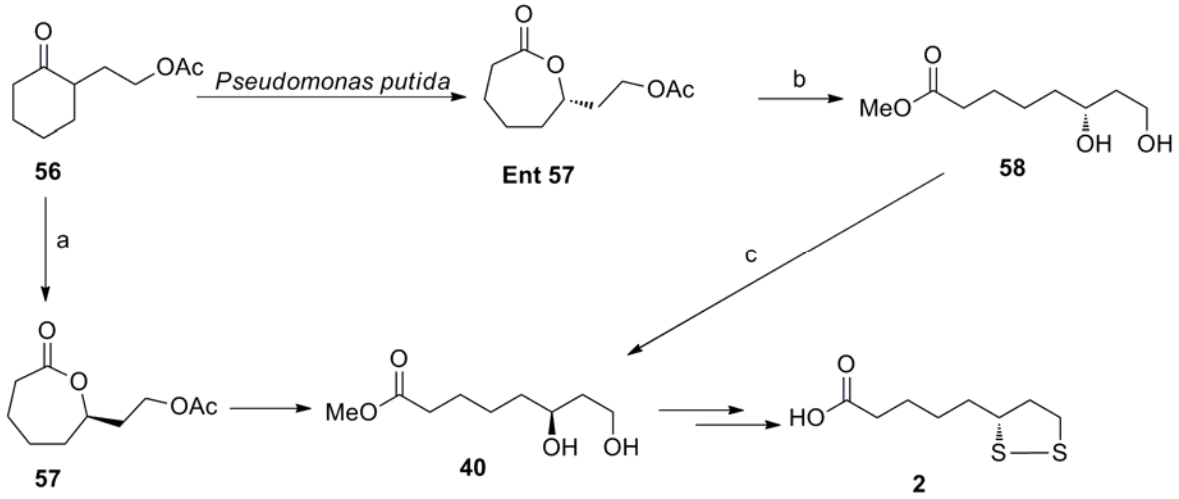
In this approach, Gopalan *et al.* reduced chloro β-ketoester **51** enantioselectively with baker's yeast to obtain chiral alcohol ester **52**. Ester **52** on reduction with $LiBH_4$, followed by protection of diol afforded **54**. Compound **54** on treatment with diethyl malonate and sodium hydride afforded ester **55** which converted to *R*-(+)-lipoic acid with reported method.



Scheme 10. *Reagents and conditions*: (a) Baker's yeast; (b) $LiBH_4$, THF; (c) $Me_2C(OMe)_2$, *p*-TsOH, CH_2Cl_2; (d) $CH_2(CO_2Et)_2$, NaH, DMF 75 ^oC then NaCN, DMSO, 165 ^oC.

1.2.3.11 Adger *et al* (1995)[24], Willetts *et al.* (1996)[25], Adger *et al.* (1997)[26] and Vogel *et al.* (2001)[27] (Scheme 11)

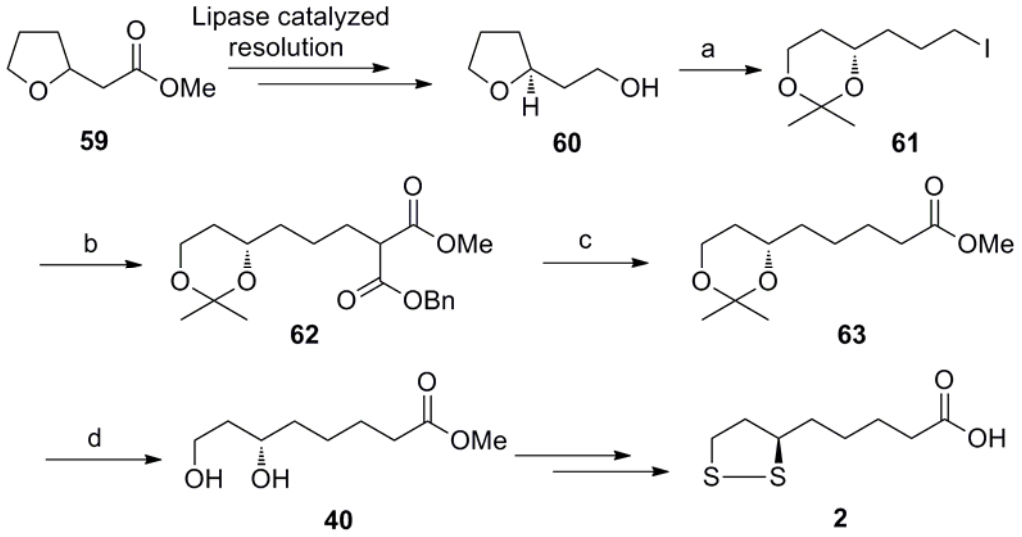
In these approaches except first, the common steps were enzymatic Baeyer-Villiger oxidation of 2-substituted cyclohexanone **56** to lactone **57**. The lactone on treatment with sodium methoxide in methanol afforded diol **58**. The diol then convered to *R*-(+)-lipoic acid with reported method. In first attempt Adger *et al*. obtained enantiomer of **57**, which later stage converted to desired one by Mitsunobu conditions.



Scheme 11. *Reagents and conditions*: (a) Enzymes; (b) MeONa, MeOH; (c) (i) *p*-NO_2-$C_6H_4CO_2H$, PPh_3, DEAD, THF; (ii) K_2CO_3, MeOH.

1.2.3.12 Iyengar et al. (1996, Scheme 12)[28]

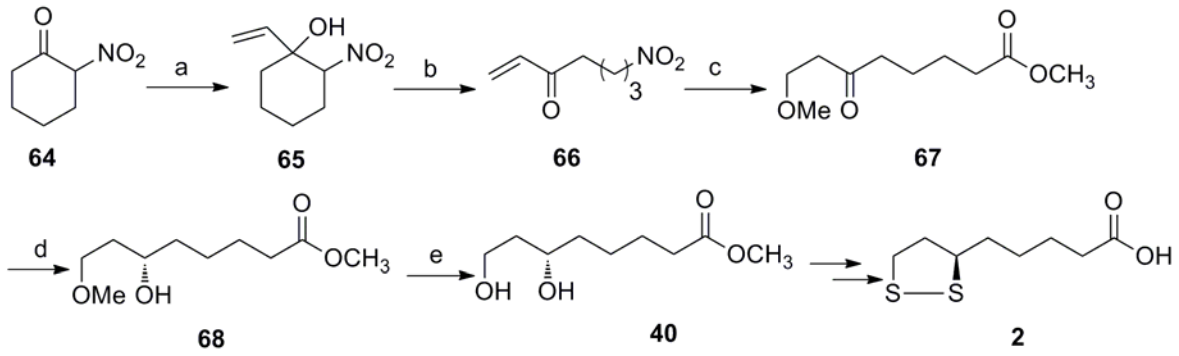
Iyenger and Laxmi have employed selective hydrolysis of methyl 2-(tetrahydro-2-furyl) acetate **59** using lipase as the key step. On lipase hydrolysis, *R*-isomer undergoes hydrolysis but *S*-isomer did not under go hydrolysis. So the *S*-ester was then reduced with $LiAlH_4$ to give the compound **60**. Regioselective opening of **60** with TMSCl, NaI in acetone gave iodo acetonide **61**. Alkylation of **61** with benzyl methyl malonate gave the compound **62**. Compound **62** on debenzylation, decarboxylation followed by hydrolysis in acidic condition furnished the diol ester **40**. Following the same procedure reported earlier the diol ester was converted to *R*-(+)-lipoic acid.



Scheme 12. *Reagents and conditions*: (a) TMSCl, NaI, acetone; (b) Benzyl methyl malonate, NaH, THF; (c) (i) Pd/C, H_2, 98 % (ii) 160 ^oC, 95%; (d) MeOH, H^+, 98 %.

1.2.3.13 Barua *et al.* (1996, Scheme 13)[29]

In this approach, Barua *et al.* exposed nitro alcohol **65**, obatined from reaction of ketone **64** and vinyl magnesium bromide, to copper sulphate adsorbed on silica gel to obtain ω-nitro-α,β-unsaturated ketone **66**. Compound **66** on treatment with sodium methoxide in methanol and sulfuric acid afforded oxo ester **67**. The oxo ester on reduction with baker's yeast gave alcohol **68**. The alcohol **68** on demethylation afforded diol **40** which converted to *R*-(+)-lipoic acid by known reaction sequence.

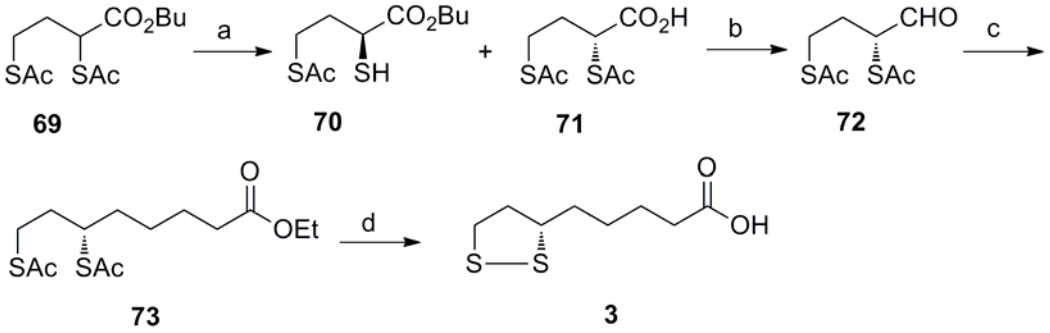


Scheme 13. *Reagents and conditions*: (a) CH_2=CHMgBr, THF; (b) $CuSO_4.SiO_2$, benzene; (c) MeONa/MeOH/H_2SO_4; (d) baker's yeast, glucose, H_2O; (e) Bu_4NI, $BF_3.Et_2O$, $CHCl_3$.

1.2.3.14 Fadnavis *et al* (1998, Scheme 14)[30]

In this approach Fadnavis and co-workers have synthesized both isomers of lipoic acid using lipase catalyzed regio and stereospecific hydrolysis of *n*-butyl ester of 2, 4-dithioacetyl butanoic acid **69**. Reduction of acid **71** with $BH_3.Me_2S$ followed by PCC

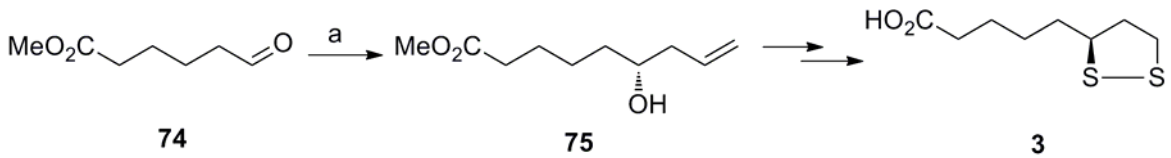
oxidation resulted in the formation of aldehyde **72**. Aldehyde on four carbon Wittig homologation and subsequent hydrogenation with Wilkinson's catalyst gave the ethyl ester **73**. Hydrolysis of **73** with wheatgerm lipase followed by treatment with oxidative enzyme mushroom tyrosinase in the same pot gave *S*-(-)-lipoic acid. Simultaneously *R*-(+)-lipoic acid was obtained in a similar fashion starting from **70**.



Scheme 14. *Reagents and conditions*: (a) *Candida rugosa* lipase, phosphate buffer; (b) (i) BH_3.DMS, 0 ^oC; (ii) PCC (c) (i) $Br^{-+}PPh_3(CH_2)_3COOEt$, NaHMDS, -78 ^oC; (ii) $(PPh_3)_3RhCl$, H_2; (d) (i) Wheatgerm Lipase, pH 7.0; (ii) Tyrosinase.

1.2.3.15 Zimmer *et al* (2000, Scheme 15)[31]

Zimmer and co-workers have employed calalytic asymmetric allyl stannation reaction as the key step to deliver the required stereochemistry. In the presence of 0.2 equivalents of (*S*)-BINOL, 0.2 eq. of $Ti(O^iPr)_4$ and 4 A^o molecular sieves the aldehyde **74** and allyl tributyl stannane provided *R*-alcohol **75** with 98 % enantiomeric excess. The homoallylic alcohol could be converted in to *S*-(-)-lipoic acid by known method. In the same fashion the synthesized *R*-antipode of lipoic acid by using (*R*)-BINOL.

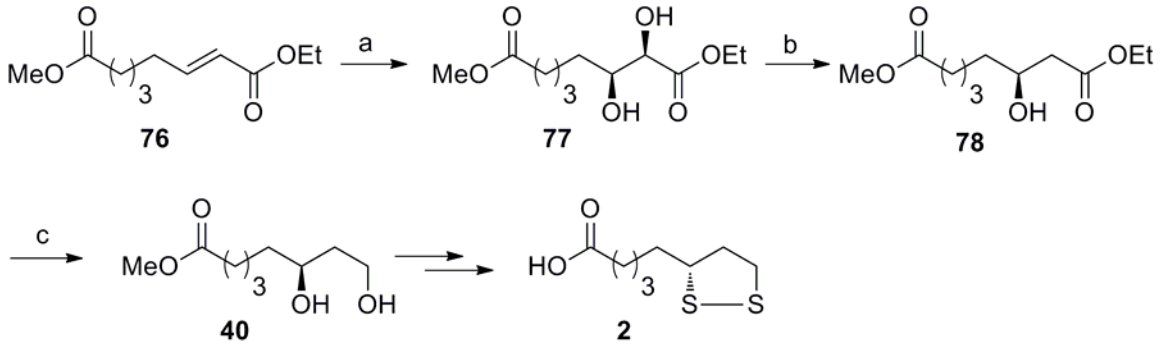


Scheme 15. *Reagents and conditions*: (i) (*S*)-BINOL (0.2 eq), $Ti(OPr^i)_4$ (0.2 eq), CH_2Cl_2, 2 days.

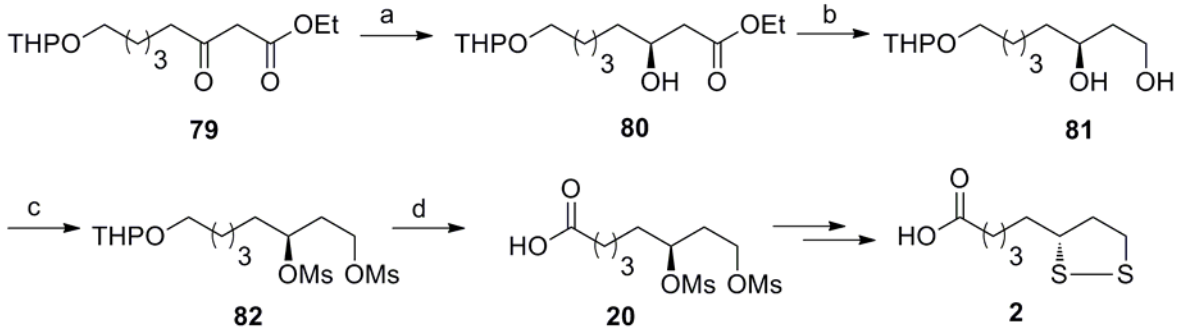
1.2.3.16 Sudalai *et al* (2001, Scheme 16 & Scheme 17)[32]

Sudalai and co-workers employed Sharpless asymmetric dihydroxylation of unsaturated ester **76** (Scheme 16) and Ru(II)-(*S*)-BINAP catalyzed asymmetric hydrogenation

reaction to get the β-hydroxy esters **79** (Scheme 17). These esters are the precursors for the synthesis of *R*-(+)-lipoic acid.



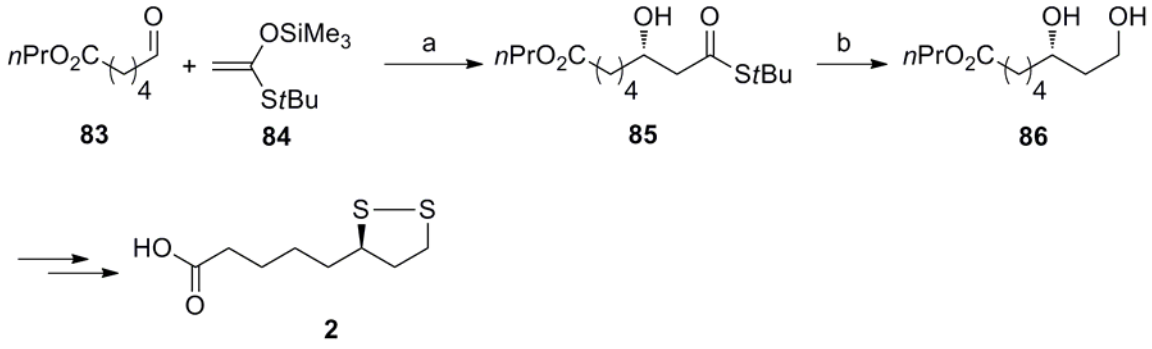
Scheme 16. *Reagents and conditions*: (a) OsO_4, $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, 0 ^oC; (b) (i) $SOCl_2$, Et_3N, CH_2Cl_2, 0 ^oC, 9 h; (ii) $RuCl_3$ (cat), $NaIO_4$; (iii) $NaBH_4$, DMAC, 20 % H_2SO_4; (c) $NaBH_4$, Et_3N, MeOH;DMF (2:1), AcOH, 0 ^oC, 5h.



Scheme 17. *Reagents and conditions*: (a) H_2 (400 Psi), MeOH, (S)-BINAP-Ru(II), 6h, 90 %; (b) $NaBH_4$, $CuSO_4$, EtOH, 7h: (c) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 ^oC, 6 h; (d) (i) *p*-TSA, MeOH, 10 h; (ii) PCC, CH_2Cl_2, 3 h and then Ag_2O, NaOH, 1 h.

1.2.3.17 Zimmer *et al.* (2002, Scheme 18)[33]

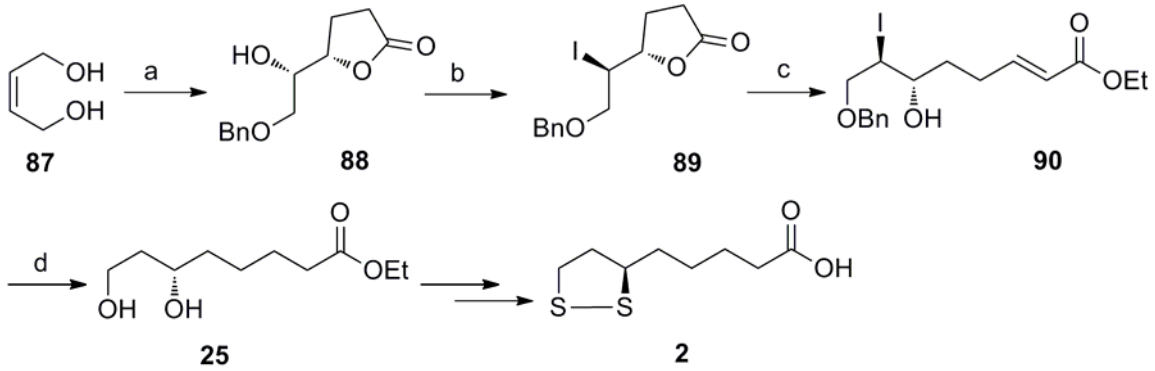
Zimmer and co workers utilized (*S*)-BINOL-Ti catalyzed Mukaiyama aldol reaction of functionalised aldehyde **83** with S-ketene silyl acetal **84** for the synthesis of intermediate of *R*-(+)-lipoic acid.



Scheme 18. *Reagents and conditions*: (a) $TiCl_4$, (*R*)-BINOL, Phenol, 0 ^oC, 5h; (b) NaBH4, *i*PrPH, 0 ^oC, 5h.

1.2.3.18 Chavan *et al.* (2004, Scheme 19)[34]

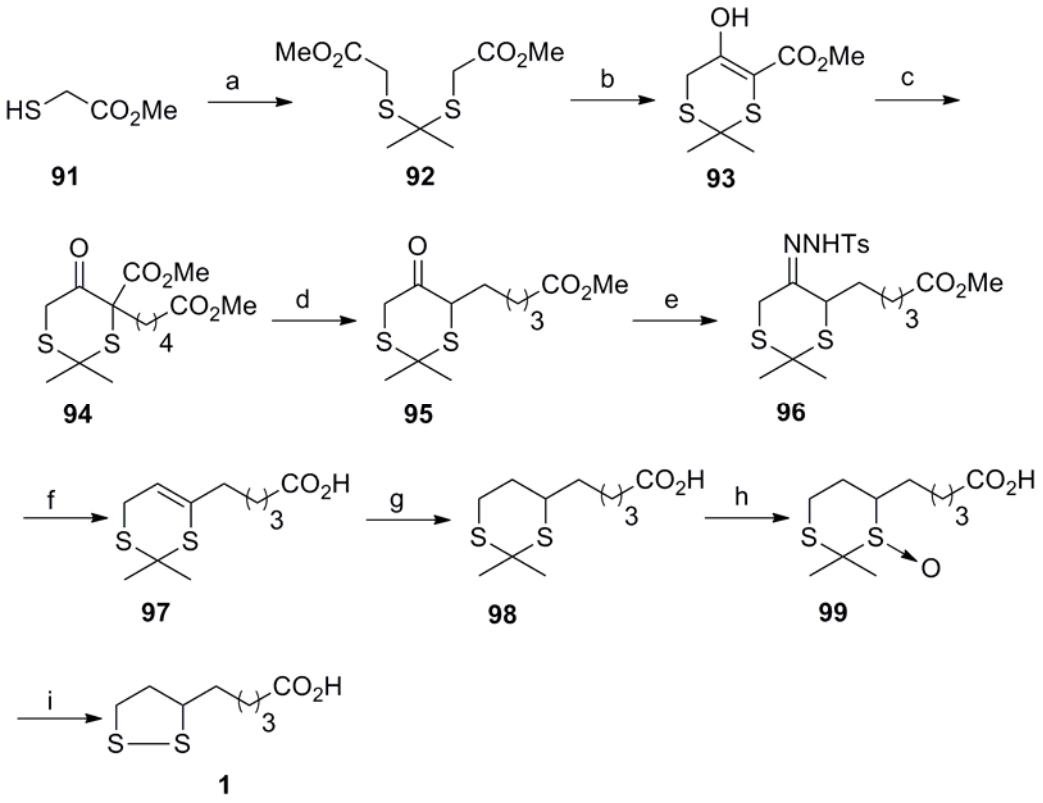
Chavan and co-workers started the synthesis of *R*-(+)-lipoic acid with cis-2-butene-1,4-diol **87**. The compound **87** on Claisen orthoester rearrangement and Shapless asymmetric dihydroxylation afforded hydroxy lactone **88**. Hydroxy lactone **88** on iodination followed by DIBAL-H reduction-Wittig olefination afforded unsaturated ester **90**. Intermediate **90** on Raney-Ni catalyzed hydrogenation afforded known intermediate **25** which converted to *R*-(+)-lipoic acid.



Scheme 19. *Reagents and conditions*: (a) Reference 35; (b) PPh_3, I_2, Im, 70 ^oC, 3h; (c) DIBAL-H, DCM, -78 ^oC, 1h; (ii) Ph_3PCHCO_2Et, 24h, rt; (d) W_2 Raney nickel, H_2, 24h.

1.2.3.19 Chavan *et al.* (2005, Scheme 20)[36]

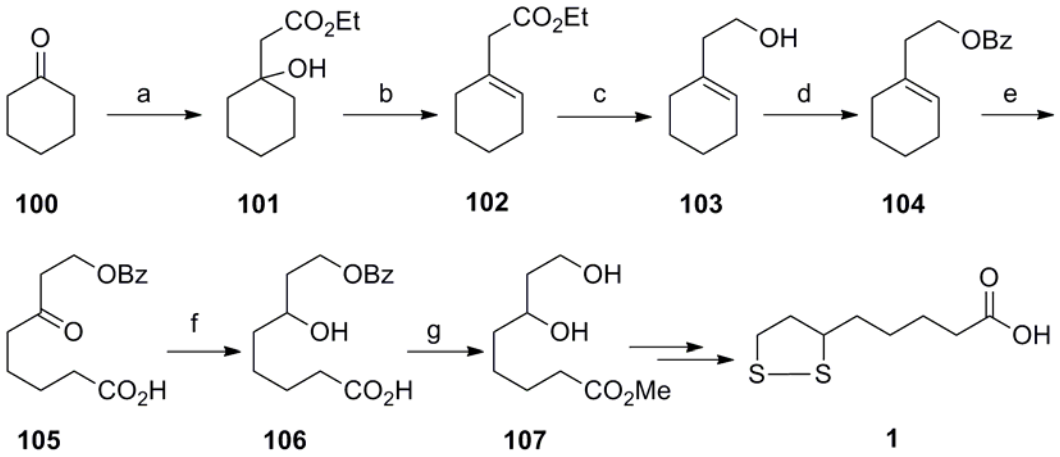
Chavan *et al* accomplished (±)-lipoic acid synthesis by using diester **92**, which was readily prepared in two steps from thioglycolic acid. Subjection of diester **95** to Dieckmann condensation delivered the β-keto ester **93** which exists in enolic form. Phase transfer catalysed alkylation of **93** followed by decarboxylation gave the ester **95**. The keto ester was converted into olefin acid **97** by treating with tosyl hydrazone followed by refluxing in presence of NaOH. Sequential reduction of double bond, oxidation to mono sulfoxide and final hydrolytic cyclization of **99** afforded (±)-lipoic acid.



Scheme 20. *Reagents and conditions*: (a) acetone, $BF_3.Et_2O$, 0 ^oC to rt 6h; (b) NaH, THF, 60 ^oC, 3 h; (c) K_2CO_3, $Br(CH_2)_4COOCH_3$, Bu_4NHSO_4, THF, rt; (d) DMSO, NaCl, H_2O, 140 ^oC; (e) $TsNHNH_2$, MeOH, rt, 3h; (f) NaOH (2 equiv), ^{i}PrOH, Reflux, 84 %; (g) Et_3SiH, TFA, 0 ^oC to rt, 2h; (h) $NaIO_4$, MeOH, 0 ^oC, 2 h; (i) aq. HCl:Benzene (1:1), 50 ^oC, 7 h.

1.2.3.20 Chavan *et al.* (2005, Scheme 21)[37]

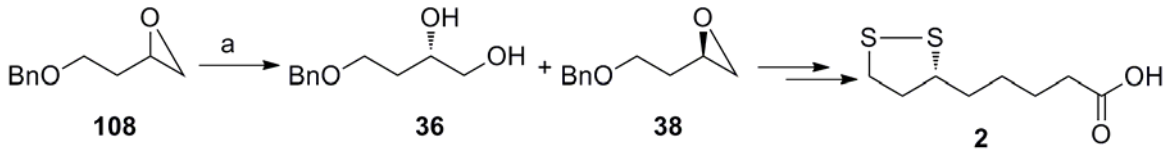
Chavan *et al* accomplished (±)-lipoic acid synthesis by using modified Reformatsky reaction. The elimination of the alcohol to furnish selectively the β, γ-unsaturated ester is another feature of this synthesis. Reformatsky reaction with chloroester was carried out on cyclohexanone to furnish alcohol ester **101**, which was then set for elimination using thionyl chloride and pyridine. The β,γ-unsaturated ester thus obtained was then reduced using DIBAL-H. The alcohol **103** formed, was then protected using benzoyl chloride to give benzoate ester **104**, which was then subjected to ozonolysis followed by Jones oxidation to furnish ketoacid **105**. The reduction of ketoacid **105**, followed by esterification, furnished diol ester **107.** The diol ester **107** was then converted into (±)-lipoic acid by known protocol.



Scheme 21. *Reagents and conditions*: (a) Zinc, $ClCH_2COOEt$, benzene-ether (1:1), reflux; (b) $SOCl_2$, pyridine, DCM; (c) DIBAL-H, DCM, -78 ^oC; (d) BzCl, Et_3N, DCM; (e) (i) O_3, DCM, -78 ^oC; (ii) Jones reagent; (f) $NaBH_4$, MeOH; (g) (i) CH_2N_2, ether, 0 ^oC; (ii) NaOMe, MeOH.

1.2.3.21 Bose *et al.* (2006, Scheme 22)[38]

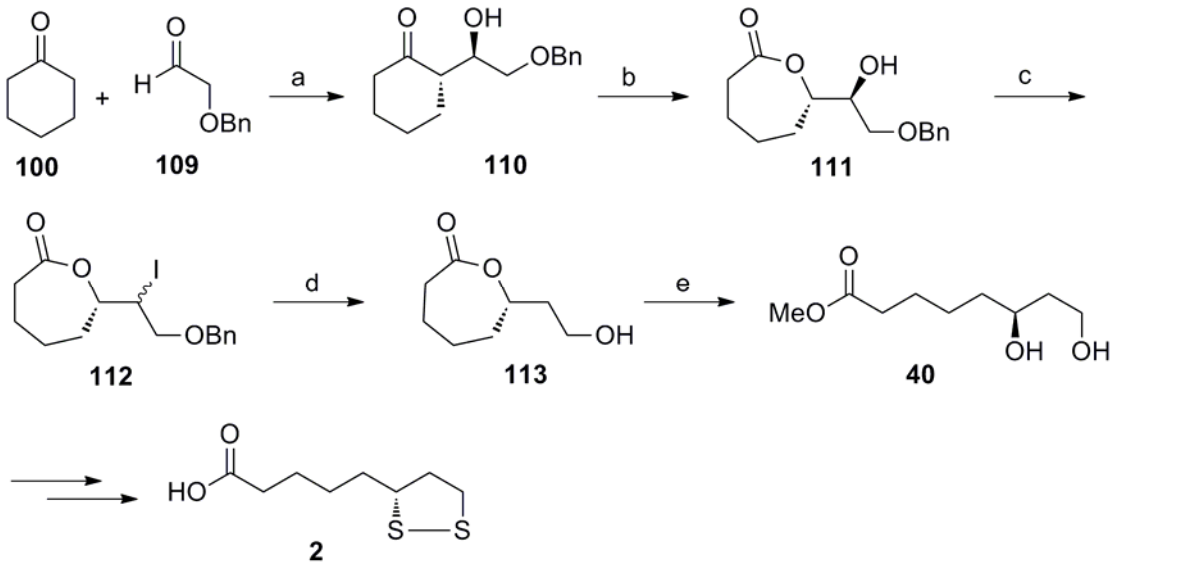
Bose and co-workers started synthesis of *R*-(+)-lipoic acid with racemic epoxide **108.** Epoxide **108** on (*R*,*R*)-salen-Co(III)-OAc complex catalyzed hydrolytic kinetic resolution to obtain known chiral epoxide **38**. The epoxide **38** then converted to *R*-(+)-lipoic acid by known reaction sequence.



Scheme 22. *Reagents and conditions*: (a) (*R*,*R*)-salen-Co(III)-OAc complex, H_2O.

1.2.3.22 Duan *et al.* (2008, Scheme 23)[39]

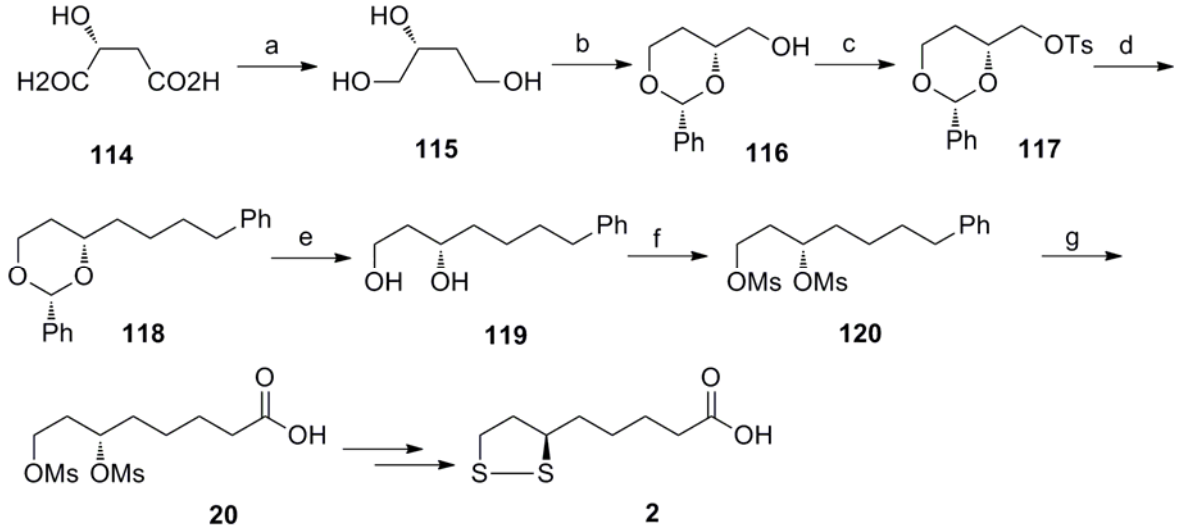
Duan and co-workers accomplished asymmetric synthesis of *R*-(+)-lipoic acid using L-proline catalyzed diastereoselective cross-aldol reaction as key step. Cyclohexanone **100** on L-proline catalyzed aldol reaction with aldehyde **109** afforded hydroxy ketone **110**. Ketone **110** on Baeyer-Villiger oxidation followed by iodination, hydrogenation afforded hydroxy lactone **113**. Lactone **113** on treatment with sodium methoxide afforded known diol **40** which converted to *R*-(+)-lipoic acid using known reaction sequence.



Scheme 23. *Reagents and conditions*: (a) L-proline, DMF, rt; (b) *m*-CPBA, CH_2Cl_2, rt; (c) PPh_3, I_2, Im, toluene, reflux; (d) W_2 Raney Ni, H_2, MeOH, et, (e) MeONa, MeOH, rt.

1.2.3.23 Huang *et al.* (2009, Scheme 24)[40]

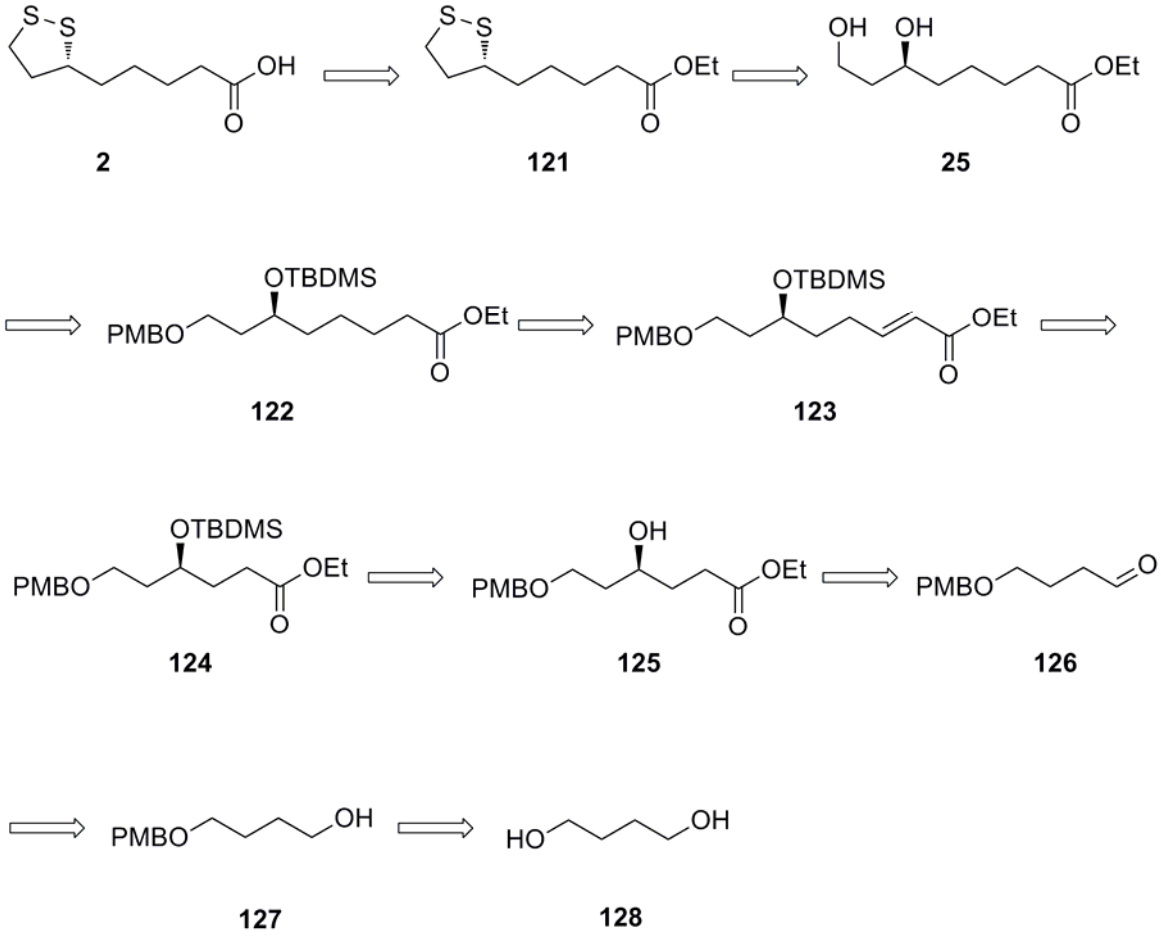
Huang and co-workers recently reported asymmeric synthesis of *R*-(+)-lipoic acid starting from (*R*)-malic acid **114**. (*R*)-malic acid convertd to triol **115** by literature method. Triol **115** on treatment with benzaldehyde under acidic conditions afforded acetal **116** which converted to its tosyl derivative **117**. Tosyl derivative **117** on treatment with Grignard reagent afforded **118**. Acetal **118** on iodine treatment gave diol **119** which converted to **120**. Compound **120** on tratment with Ruthenium chloride and sodium periodate afforded acid **20** which converted to *R*-(+)-lipoic acid by known reaction sequence.



Scheme 24. *Reagents and conditions*: (a) Ref. (b)PhCHO, TFA, CH_2Cl_2; (c)TsCl, Py, CH_2Cl_2 0 ^oC; (d) $Ph(CH_2)_3MgBr$, CuI, THF, -78 ^oC; (e) I_2, MeOH; (f) MsCl, Et3N, CH_2Cl_2; (g) $RuCl_3.xH_2O$, $NaIO_4$, CH_3CN: EtOAc: H_2O, (2:2:3), rt.

1.2.4 Present work

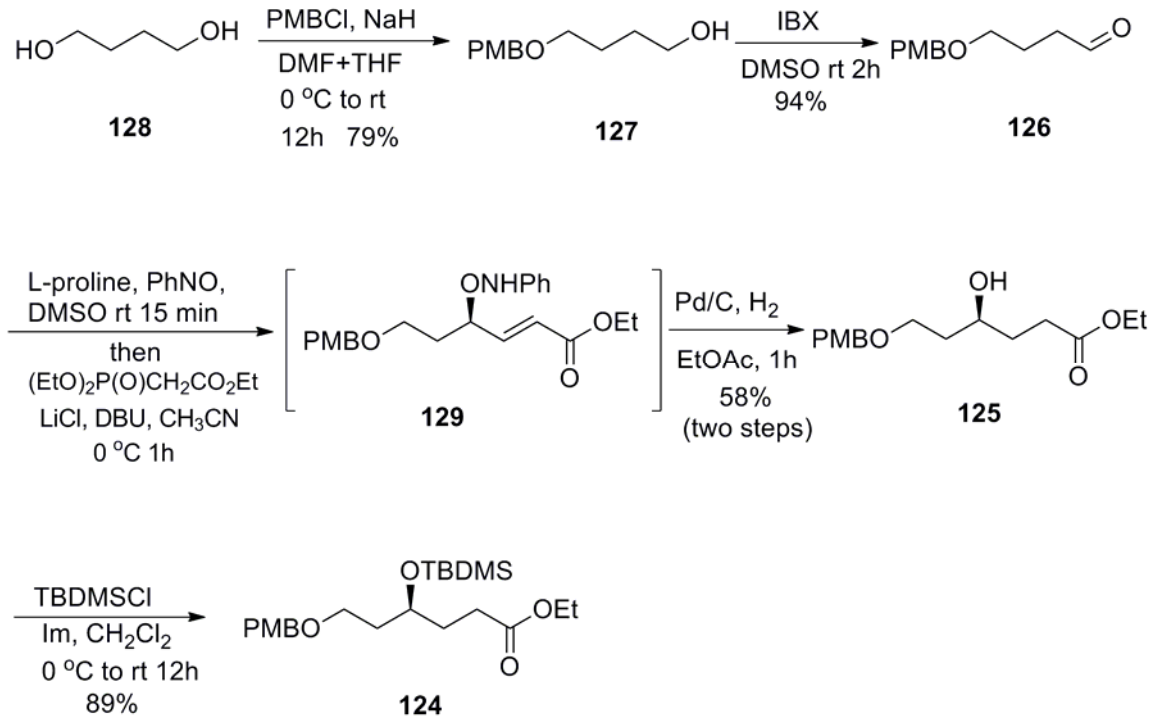
The efficient synthesis of complex molecules such as natural and pharmaceutical important products is still a challenge in synthetic organic chemistry. As can be seen from the above descriptions, the literature methods for the synthesis of (*R*)-(+)-α-lipoic acid (**2**), employ either chiral starting materials or expensive reagents. Hence, the synthesis of (*R*)-(+)-α-lipoic acid (**2**), starting from prochiral substrates using catalytic enantioselective reactions, is still desirable. The use of catalytic enantioselective reactions is advantageous as both the stereoisomers can be synthesized from the same prochiral substrate. Also, the use of oragnocatalysis provides methods for obtaining chiral compounds in environmentally benign manner and from easily available starting materials.



Scheme 25. Retrosynthetic analysis

The retrosynthetic analysis for the enantioselective synthesis of *R*-(+)-lipoic acid **2** is depicted in **Scheme 25**. It was envisaged that a simple basic hydrolysis could be used to obtain *R*-(+)-lipoic acid **2** from *R*-ethyl lipoate **121**, and this in turn should be prepared from available diol ester **25**. The diol ester **25** could be obtained from protected diol ester **122**, which could be easily obtained from α,β-unsaturated ester **123** via metal catalyzed hydroganation. The α,β-unsaturated ester **123** could be obtained from γ-silyloxy ester **124** via DIBAL-H reduction to aldehyde and two carbon HWE olefination. The γ-silyloxy ester **124** could be easily prepared from γ-hydroxy ester **125**. The γ-silyloxy ester **125** could be obtained from aldehyde **126** through seqential proline catalyzed α-aminoxylation-HWE olefination and Pd/C catalyzed hydrogenolysis. The aldehyde **126** could be obtained from oxidation of alcohol **127**, which could be obtained from mono-protection of 1,4-butanediol **128**.

Thus the synthesis starts from 1,4-butanediol, a relatively cheap starting material. As shown in **scheme 26**, the commercially available 1,4-butanediol **128** on treatment with one equivalent of sodium hydride and 4-methoxy benzyl chloride in 1:1 THF-DMF mixture undergoers mono-protection and afforded alcohol **127** in 79% yield. The alcohol **127** on oxidation with IBX in DMSO at room temperature afforded aldehyde **126** in 94% yield. The aldehyde **126** then subjected to L-proline (20 mol%) catalyzed α-aminoxylation with nitrosobenzene in DMSO at room temperature. Initial green colour of reaction mixture turned yellowish-orange in 15 minutes, indicated the complete consumption all nitrosobenzene. To this orange reaction mixture were added pre-cooled solution of pre-mixed triethyl phosphonoacetate, LiCl and DBU in acetonitrile at 0 ^{o}C. As these two reactions [α-aminoxylation and HWE olefination] were performed in one pot, termed as sequential α-aminoxylation-HWE olefination reaction. Thus formed γ-aminoxy α,β-unsaturated ester **129** was then subjected to Pd/C catalyzed hydrogenolysis without purification and characterization and obtained γ-hydroxy ester **125** in 58% over three steps. The starting material for hydrogenolysis reaction contains alcohol protected with *p*-methoxybenzyl group, which can be also deprotected under reaction conditions. To avoid breakage of 4-methoxybenzyl ether, reaction was monitored with TLC analysis and worked up after one hour. The optical purity of γ-hydroxy ester **125** was determined by chiral HPLC analysis. The γ-hydroxy ester **125** converted to its silyl ether **124** with TBDMSCl and imidazole in 89% yield.

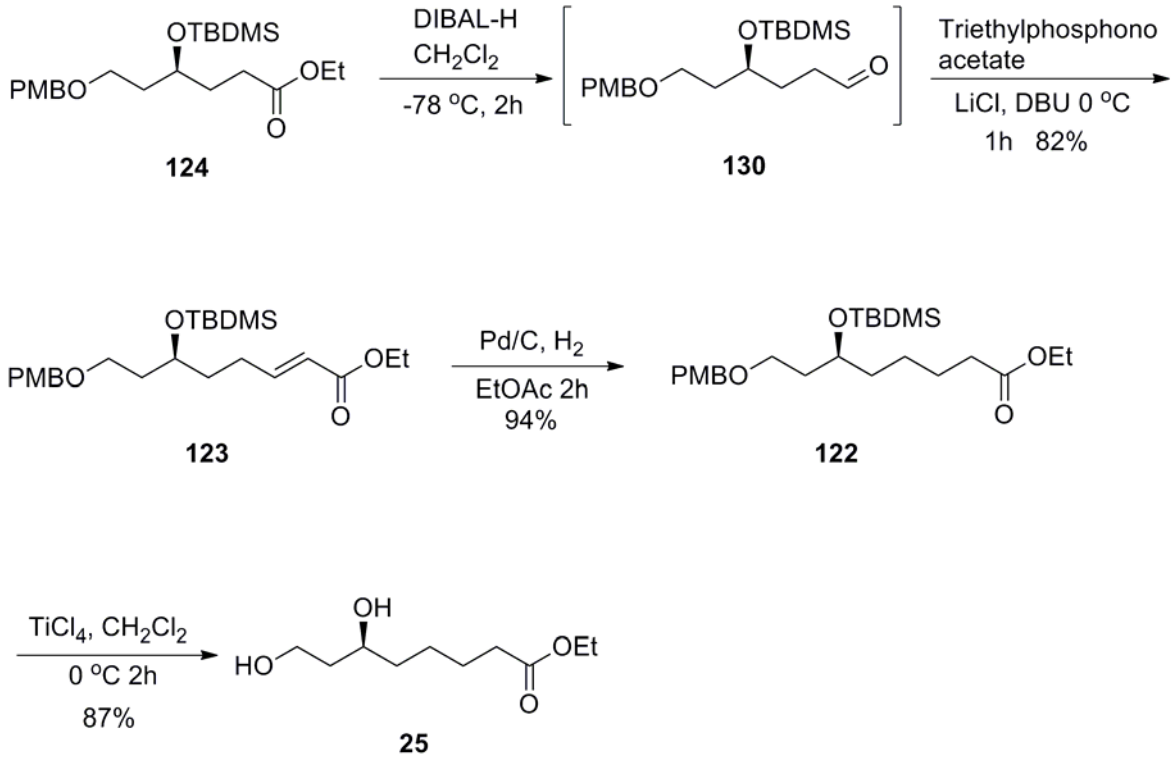


Scheme 26.

The next task was two carbon homologation. For this purpose, as shown in **scheme 27**, γ-silyloxy ester **124** was treated with 1 equivalent of DIBAL-H at -78 ^{o}C and obtained so called aldehyde **130** and used as it is for next step without purification and characterization. The so called aldehyde **130** on HWE olefination with triethyl phosphonoacetate, lithium chloride and DBU afforded α,β-unsaturated ester **123** in 82% yield over two steps. The α,β-unsaturated ester **123** on Pd/C catalyzed hydrogenation for 1h afforded saturated ester **122**. Ester **122** has two hydroxy groups masked as silyl ether and *p*-methoxybenzyl ether. The next task was the deprotection of silyl and *p*-methoxybenzyl groups to obtain dihydoxy ester **25**, a intermedite towards *R*-(+)-lipoic acid. For this purpose, ester **122** was treated with $TiCl_4$ in dicloromethane at 0 ^{o}C and obtained dihydoxy ester **25** in 87% yield.

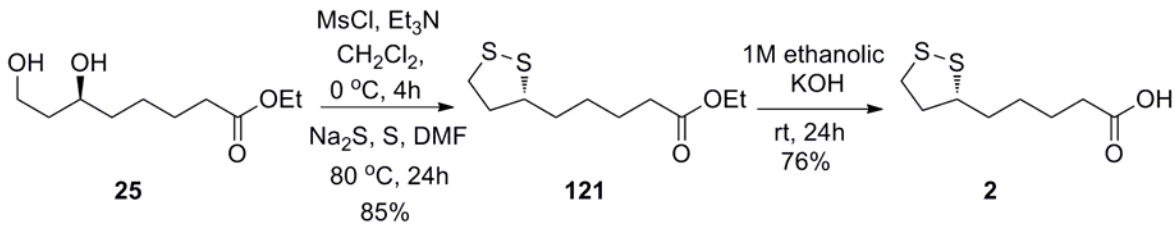
The diol **25** is the well known intermediate for the synthesis of *R*-(+)-Lipoic acid and was converted in to the final target molecule by a series of reactions. Accordingly as shown in **scheme 28**, diol **25** on tratment with MsCl in presence of Et_3N in anhydrous CH_2Cl_2 at 0 ^{o}C provided dimesylate. The dimesylate on treatment with Na_2S and sulfur in DMF at 80 ^{o}C for 24h afforded ethyl lipoate **121** in 85 % yield over two steps. The analytical data was in good agreement with literature data. Finally

hydrolysis of ethyl lipoate **121** with 0.1 M KOH aqueous solution in methanol at room temperature for 24h



Scheme 27.

afforded *R*-(+)-lipoic acid **2** in 76 % yield. In the ^{1}H-NMR spectrum disappearance of signals corresponding to ethyl group indicated the formation of hydrolyzed product. This was further confirmed by ^{13}C-NMR and elemental analysis.



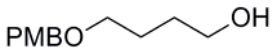
Scheme 28.

1.2.5 Conclusion

In summary *R*-(+)-α-lipoic acid was synthesized efficiently from the readily available starting material. L-proline catalyzed sequential α-aminoxylation-HWE olefination of aldehyde was used as key step.

1.2.6 Experimental

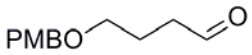
1) 4-(4'- methoxybenzyloxy)butanol (127)



To a solution of 1,4-butanediol **128** (6.0 g, 66.66 mmol) in dry DMF: THF (1:1)(100 mL) was added sodium hydride (60%, 2.933 g, 73.33 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 chloride (11.484 g, 9.94 mL, 73.33 mmol) with further stirring for 6 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 100 mL). The combined organic layers were washed with water (3 x 100 mL), brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residual oil was purified by silica gel column chromatography using petroleum ether/EtOAc (8:2) as eluent to furnish the mono-PMB protected alcohol **127**.

Yield: 11.060g (79%); yellow oil; IR ($CHCl_3$) ν_{max} 3457, 3061, 3009, 2891, 2589, 1652, 1643, 1581, 741 cm^{-1};^{1}H NMR (200 MHz, $CDCl_3$): δ=1.64-1.74 (m, 4H), 2.38 (brs, 1H), 3.50 (t, *J*= 5.81 Hz, 2H), 3.64 (t, *J*= 5.81 Hz, 2H), 3.81 (s, 3H), 4.46 (s, 2H), 6.86 (d, *J*= 8.72 Hz, 2H), 7.24 (d, *J*= 8.72 Hz, 2H) ; ^{13}C NMR (50 MHz, $CDCl_3$): δ= 26.0, 29.3, 54.8, 61.8, 69.6, 72.2, 113.4, 129.0, 129.9, 158.8 ppm.

2) 4-(4'- methoxybenzyloxy)butanal (126)

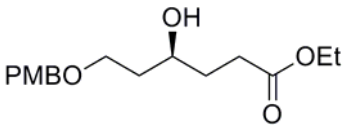


To solution of alcohol **127** (3.0 g, 14.28 mmol) in anhydrous dimethyl sulfoxide (18 mL) was added IBX (6.0 g, 21.42 mmol, 1.5 equi). After stirring at room temperature for 2h, the reaction mixture was diluted with water (10 mL), then with diethyl ether (2 x 75 mL). The diethyl ether layer was filtered through bed of celite. The filtrate was washed with water (50 mL), brine, dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under reduced pressure to afford aldehyde **126**.

Yield: 2.810 g (94%); yellow oil; IR ($CHCl_3$) ν_{max} 3069, 3007, 2949, 2839, 2356, 2045, 1719, 1577, 1513, 1251, 742 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ= 1.91-1.97 (m, 2H),

2.52-2.56 (m, 2H), 3.48 (t, *J*= 6.27 Hz, 2H), 3.81 (s, 3H), 4.42 (s, 2H), 6.87 (d, *J*= 8.53 Hz, 2H), 7.23 (d, *J*= 8.53 Hz, 2H), 9.78 (t, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 22.5, 40.9, 55.2, 68.8, 72.5, 113.7, 129.2, 130.3, 159.1, 202.2 ppm.

3) (4*S*)-Ethyl-4-hydroxy-6-(4'-methoxybenzyloxy)hexanoate (125)

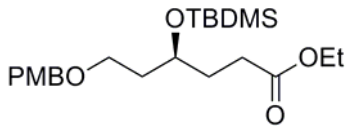


To a solution of aldehyde **126** (2.4 g, 11.53 mmol) and nitroso benzene (1.234 g, 11.53 mmol) in anhydrous DMSO (25 mL) was added L-proline (0.265 g, 2.30 mmol) at 20 °C. The mixture was vigorously stirred for 25 min under argon (the color of the reaction changed from green to yellow during this time), then cooled to 0 °C. Thereafter, a premixed and cooled (0 °C) solution of triethylphosphonoacetate (5.171 g, 4.57 mL, 23.07 mmol), DBU (3.512 g, 3.45 mL, 23.07 mmol) and LiCl (0.978 g, 23.07 mmol) in CH_3CN (25 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 (100 mL) and was extracted with Et_2O (5×50 mL). The combined organic layers were washed with water, brine, dried over anuhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product which was directly subjected to next step without purification. To the crude allylic alcohol in ethyl acetate (60 mL) was added Pd/C (10%, 0.2 g) under hydrogenation condition and the reaction mixture was allowed to stir for 4h. The mixture was filtered through a pad of celite and concentrated in vacuo to give γ-hydroxy ester. The crude product was then purified by using flash column chromatography using petroleum ether: EtOAc (75:25) as eluent to give **125** as a yellow oil.

Yield: 1.980 g (58%); yellow oil; $[\alpha]_D^{25}$ = -41.6 (*c* 1.12, $CHCl_3$); ee >97%, [Chiral HPLC analysis: Chiracel OD-H (250 x 4.6 mm) column; eluent: 2-prapanol: petroleum ether 50:50; flow rate: 0.5 mL/min., detector: 230 nm t_R=16.90 min., t_S= 18.59 min.]; IR ($CHCl_3$) ν_{max} 3453, 2997, 1733 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ= 1.24 (t, 3H), 1.69-1.81 (m, 4H), 2.36-2.50 (m, 2H), 3.12 (brs, 1H), 3.58-3.63 (m, 1H), 3.66-3.71 (m, 1H), 3.76-3.83 (m, 1H), 3.79 (s, merged, 3H), 4.11 (q, 2H), 4.43 (s, 2H), 6.85 (d, J= 8.54, 2H), 7.22 (d, J= 8.54, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ= 14.1, 30.5, 32.1, 36.3,

55.2, 60.3, 68.7, 70.5, 72.9, 113.7, 129.3, 129.8, 159.2, 174.0 ppm. Elemental Anal. Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 64.79; H, 8.14.

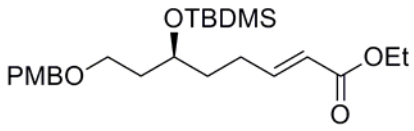
4) (4*S*)-Ethyl-4-(*tert*-butyldimethylsilyloxy)-6-(4-methoxybenzyloxy)-hexanoate (124)



To cold stirred solution of γ-hydroxy ester **125** (1.7 g, 5.74 mmol) in CH_2Cl_2 (18 mL) were added imidazole (0.429 g, 6.30 mmol) and 4-dimethylamino pyridine (0.070g, 0.57 mmol) at 0 °C and stirred for 30 min at that temperature. Thereafter, *tert*-butyldimethyl silyl chloride (0.950 g, 6.31 mmol) was added in portions maintaining the temearture 0 °C. After addition allow the reaction mixture to stirr at room temperature overnight. The reaction was quenched with saturated aqueous NH_4Cl solution, extracted with CH_2Cl_2 (2 x 20 mL). The combined organic phases were washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash column chromatography to afford silyl ether **124** as colourless oil.

Yield: 2.095 g (89%); yellow oil; $[\alpha]_D^{25}$ = -68.3 (*c* 1.21, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ= 0.07 (s, 3H), 0.08 (s, 3H), 0.90 (s, 9H), 1.27 (t, *J*= 7.15 Hz, 3H), 1.74-1.79 (m, 3H), 1.81-1.87 (m, 1H), 2.37 (t, *J*= 7.70 Hz, 2H), 3.52 (t, *J*= 6.33 Hz, 2H), 3.83 (s, 3H), 3.89-3.94 (m, 1H), 4.14 (q, 2H), 4.44 (q, 2H), 6.89 (d, J= 8.53, 2H), 7.27 (d, J= 8.53, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ= -4.6, -4.5, 14.1, 17.9, 25.8, 29.7, 32.0, 36.7, 55.2, 60.2, 66.5, 68.2, 72.6, 113.7, 129.2, 130.5, 159.0, 173.8 ppm.

5) (2*E*, 6*S*)-Ethyl-6-(*tert*-butyldimethylsilyloxy)-8-(4-methoxybenzyloxy)oct-2-enoate (123)

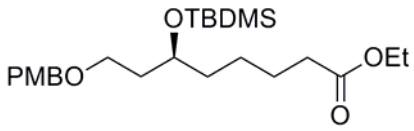


To a stirring solution of **124** (1.6 g, 3.90 mmol) in CH_2Cl_2 (20 mL) at -78 °C was added DIBAL-H (1 equi., 2M in toluene, 1.95 mL). After stirring for 1 h at –78 ^{o}C absolute MeOH (4.3 mL) was added to the reaction mixture and was allowed to attain the room temperature. Thereafter, a premixed and cooled (0 °C) solution of triethylphosphono acetate (1.830 g, 8.16 mmol), LiCl (0.692 g, 8.16 mmol) and DBU (0.940 g, 0.9 mL,

8.16 mmol) in CH_3CN (20 mL) was added quickly 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 and dichloromethane were evaporated under vacuum. This reaction mixture then poured into water (50 mL) and was extracted with Et_2O (5×25 mL). The combined organic layers were washed with water, brine, dried over anuhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product. The crude residue was purified by flash column chromatography to afford α,β-unsaturated ester **123**.

Yield: 1.395 g (82%); colourless oil; $[\alpha]_D^{25}$ = -29.71 (*c* 1.19, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ= 0.05 (s, 6H), 0.88 (s, 9H), 1.29 (t, *J*= 7.19 Hz, 3H), 1.57-1.64 (m, 1H), 1.70-1.83 (m, 3H), 2.20-2.26 (m, 1H), 2.34-2.40 (m, 1H), 3.52 (t, *J*= 7.78 Hz, 2H), 3.82 (s, 3H), 3.88-3.92 (m, 2H), 4.19 (q, 2H), 4.42 (dd, *J*= 9.79, 11.54 Hz, 2H), 5.81 (d, *J*= 15.56 Hz, 1H), 6.90 (d, *J*= 8.53 Hz, 2H), 6.99 (dt, *J*= 6.77, 15.56 Hz,1H), 7.26 (d, *J*= 8.53 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=-4.6, 14.2, 18.0, 25.8, 29.7, 32.0, 36.8, 55.2, 60.1, 66.5, 68.6, 72.6, 113.7, 121.1, 129.2, 130.4, 149.2, 159.0, 173.8 ppm.

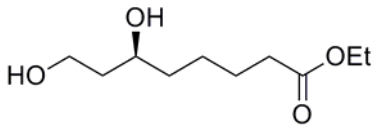
6) (6*S*)-Ethyl-6-(*tert*-butyldimethylsilyloxy)-8-(4-methoxybenzyloxy)octanoate (122)



To a solution of α,β-unsaturated ester **123** (0.700 g, 1.60 mmol) in EtOAc (50 mL) was added 10% Pd/C (100 mg) and stirred under H_2 balloon pressure for 2h. The reaction mixture was filtered through a bed of celite, concentrated under reduced pressure to obtain crude product. The crude residue was purified by flash column chromatography to afford saturated ester **122**.

Yield: 0.661 g 9(4%); yellow oil; $[\alpha]_D^{25}$ = -41.5 (*c* 0.95, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ= 0.04 (s, 6H), 0.87 (s, 9H), 1.26 (t, *J*= 7.32 Hz, 3H), 1.34-1.43 (m, 2H), 1.54-1.85 (m, 5H), 2.25-2.40 (m, 2H), 3.50 (t, *J*= 6.57 Hz, 2H), 3.81 (s, 3H), 3.85-3.89 (m, 1H), 4.10 (q, *J*= 7.32 Hz, 2H), 4.41 (dd, *J*= 2.53, 11.62 Hz, 2H), 6.86 (d, *J*=8.72 Hz, 2H), 7.24 (d, *J*=8.72 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=-4.6, 14.2, 18.0, 25.8, 29.7, 32.0, 34.3, 36.8, 37.1, 55.2, 60.1, 66.8, 69.1, 72.6, 113.7, 129.2, 130.6, 159.0, 173.7 ppm; LC-MS: *m/z* = 461.17 (M^+ + Na).

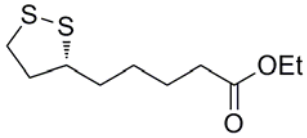
7) (6*S*)-Ethyl-4,6-dihydroxyoctanoate (25)



To a cold stirring solution of **122** (500 mg, 1.141 mmol) in anhydrous CH_2Cl_2 (10 mL) was added anhydrous $TiCl_4$ (0.5 mL) and stirred at that temperature for additional 2h. Reaction was quenched with ice pieces and extracted with CH_2Cl_2 (4 x 20 mL). The combined organic layer was washed with water and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification of crude material by flash column chromatography using EtOAc-Petroleum ether (40:60) afforded **25**.

Yield: 202 mg (87%); yellow oil; $[\alpha]_D^{25}$ = -1.19 (*c* 0.95, $CHCl_3$) { Lit. $[\alpha]_D^{23}$ = -1.23 (*c* 1.62, $CHCl_3$)}; IR ($CHCl_3$) ν_{max} 3020, 2400, 1731, 757 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ= 1.22 (t, *J*= 8.01 Hz, 3H), 1.35-1.40 (m, 3H), 1.57-1.74 (m, 5H), 2.21-2.36 (m, 2H), 3.46 (t, *J*= 6.10 Hz, 2H), 3.79 (brs, 2H), 3.81-3.90 (m, 1H), 4.07 (q, *J*= 8.01 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ= 14.2, 27.9, 28.2, 30.5, 35.4, 36.2, 60.1, 69.1, 73.3, 172.9 ppm.

8) (5*R*)-Ethyl-5-(1,2-dithiolan-3yl)pentanoate or (*R*)-Ethyl lipoate (121)

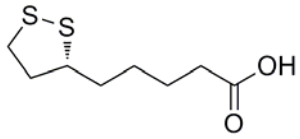


To a solution of ethyl 6,8-dihydroxyoctanoate **25** (100 mg, 0.49 mmol) in anhydous CH_2Cl_2 (5 mL) was added Et_3N (319 mg, 0.98 mmol) at 0 °C and $MeSO_2Cl$ (463 mg, 0.98 mmol) dropwise. The progress of the reaction was monitored by TLC. The reaction was quenched with water (5 mL) and the organic layer was washed with aq $NaHCO_3$ (2%, 10 mL). The organic layer was dried over anhyd Na_2SO_4, filtered, and concentrated under vacuum. The crude compound was used directly in the next reaction. The solution of crude mysilate, finely ground $Na_2S{\cdot}H_2O$ (410 mg, 0.6 mmol) and sulfur (54 mg, 0.6 mmol) in anhyd DMF (5 mL) was heated at 80 °C for 24 h and then stirred at room temperature for 1h. The reaction mixture was poured into ice-cold water (15 mL) and was extracted with EtOAc (3 × 20 mL) The combined organic

extracts were dried over anhyd Na_2SO_4, filtered, and evaporated under reduced pressure to furnish 98 mg (85%) of **121** as a yellow oil.

Yield: 98 mg (85%); yellow oil; $[\alpha]_D$= +59.81 (*c* 0.95, $CHCl_3$) {Lit.[17] $[\alpha]_D$= +61 (*c* 0.3, $CHCl_3$)}; IR ($CHCl_3$) ν_{max} 3020, 2400, 1731, 757 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.25 (t, *J* = 7.34 Hz, 3H), 1.46-1.53 (m, 2H), 1.66-1.71 (m, 4H), 1.89-1.93 (m, 1H), 2.37 (t, *J* = 7.86 Hz, 2H), 2.41-2.49 (m, 1H), 3.11-3.19 (m, 2H), 3.54-3.61 (m, 1H), 4.13 (q, *J* = 7.34 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ= 14.1, 24.3, 28.6, 33.7, 34.5, 38.4, 40.1, 56.2, 60.4, 171.2 ppm.

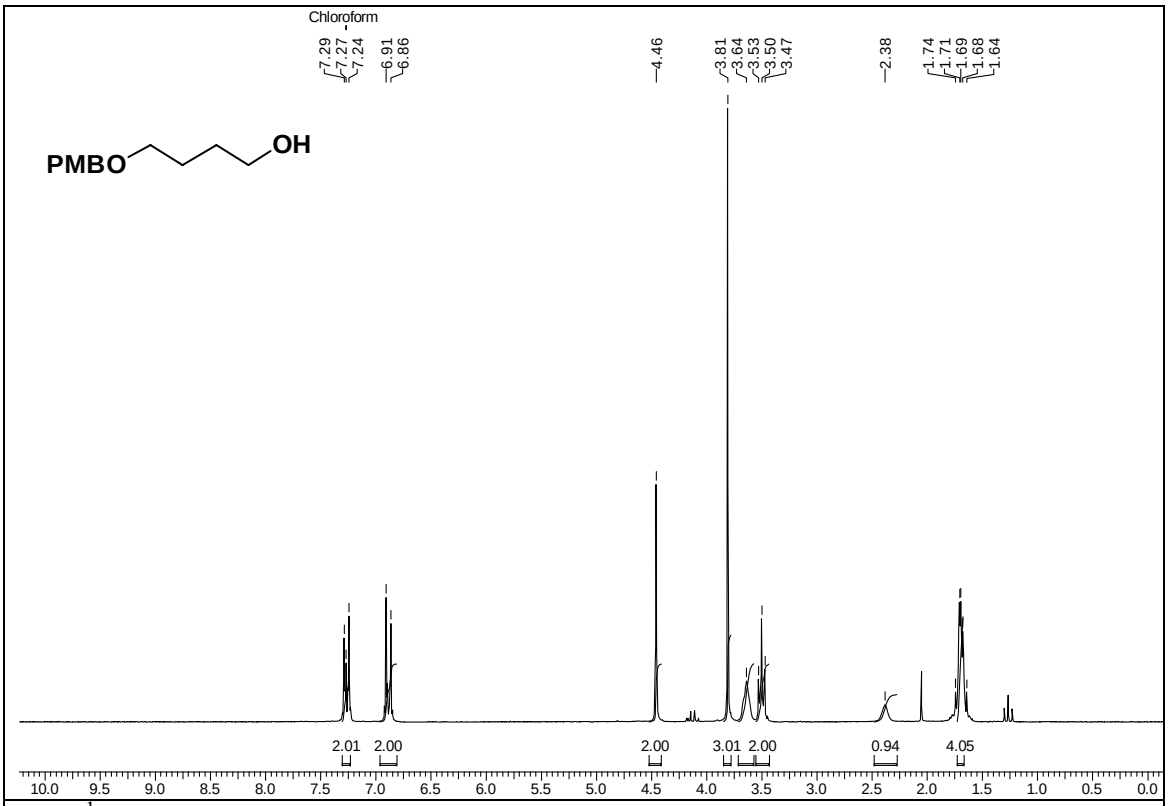
9) (*R*)-5-(1,2-dithiolan-3-yl)pentanoic acid or (*R*)-α-Lipoic acid (2)



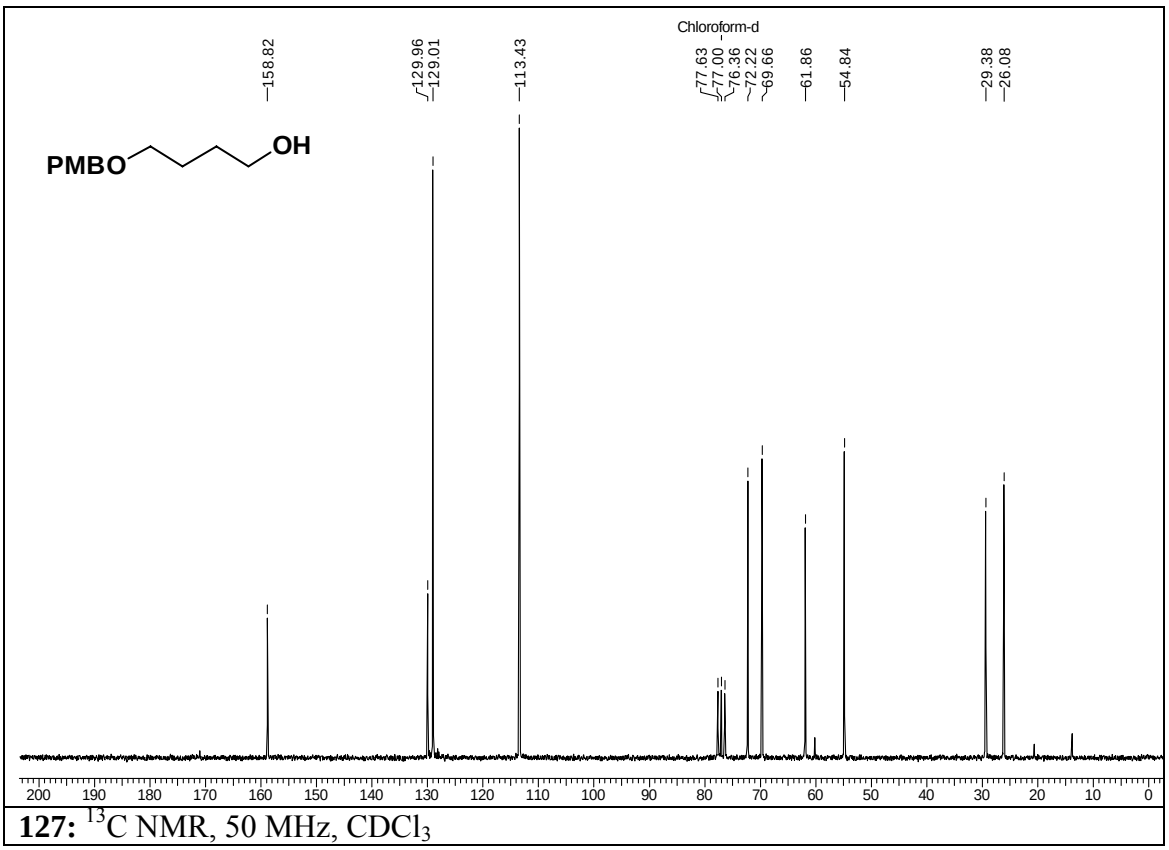
To a solution of **121** (80 mg, 0.341 mmol) in MeOH (5 mL) was added aqueous KOH (0.1 M, 4 mL) and stirred at r. t. for 24 h. MeOH was evaporated under reduced pressure and the reaction mixture was washed with Et_2O (2 x 10 mL) and the aqueous layer was acidified carefully with 6N HCl to pH 2. The product was extracted with Et_2O (2 x 10 mL) and the combined organic phases were dried over Na_2SO_4, filtered and concentrated on a rotary evaporator under reduced pressure to afford crude lipoic acid. The resulting residue was purified by flash column chromatography (silica gel) using EtOAc-petroleum ether (15:85) as an eluent, to afford **2** as yellow solid.

Yield: 54 mg (79%); yellow solid; mp 48 °C; $[\alpha]_D$= +103.18 (*c* 0.86, Benzene){Lit.[1] $[\alpha]_D$= +104 (*c* 0.88, Benzene)}; IR ($CHCl_3$) ν_{max} 3018, 2934, 1701 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.43-1.56 (m, 2H), 1.66-1.76 (m, 4H), 1.88-1.96 (m, 1H), 2.38 (t, *J* = 7.28 Hz, 2H), 2.43-2.51 (m, 1H), 3.09-3.22 (m, 2H), 3.35-3.61 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 24.3, 28.6, 33.7, 34.5, 38.4, 40.1, 56.2, 179.5 ppm. Elemental Anal. Calcd for $C_8H_{14}O_2S_2$: C, 46.57; H, 6.84; S, 31.8. Found: C, 46.49; H, 6.89; S, 31.79.

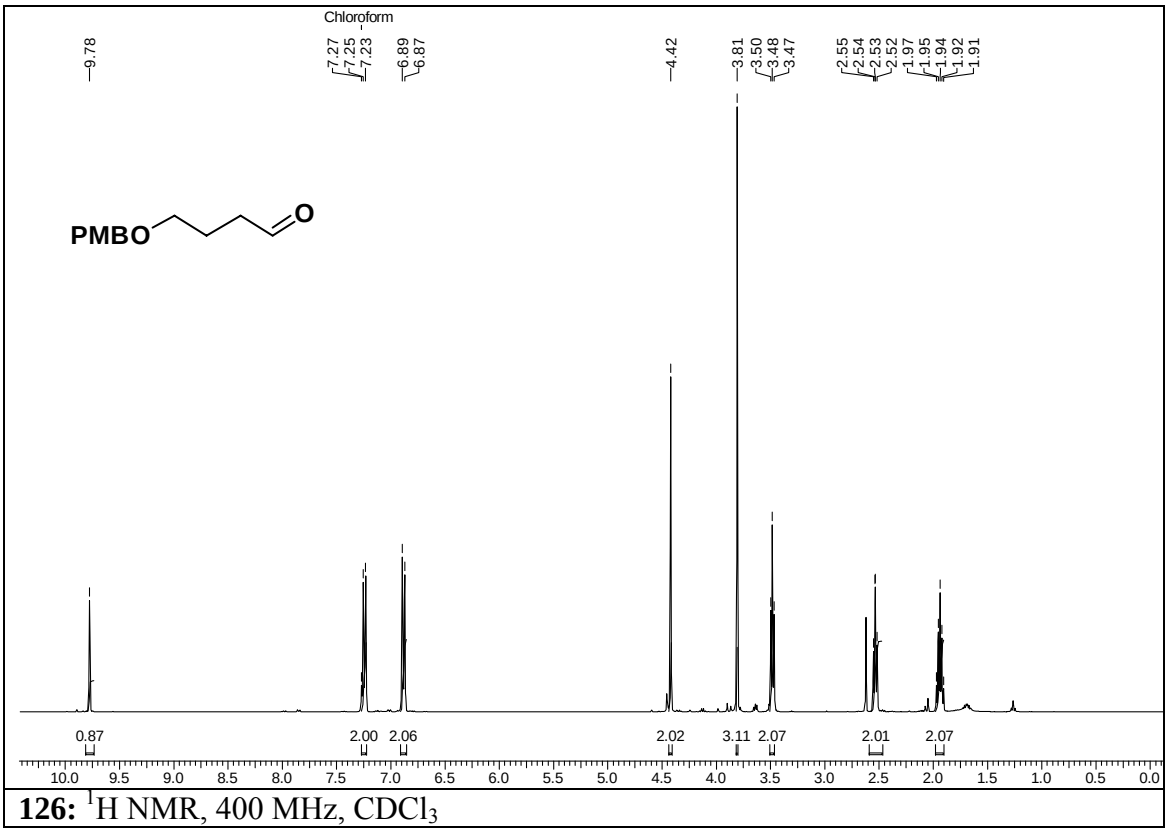
1.2.7 Analytical Data



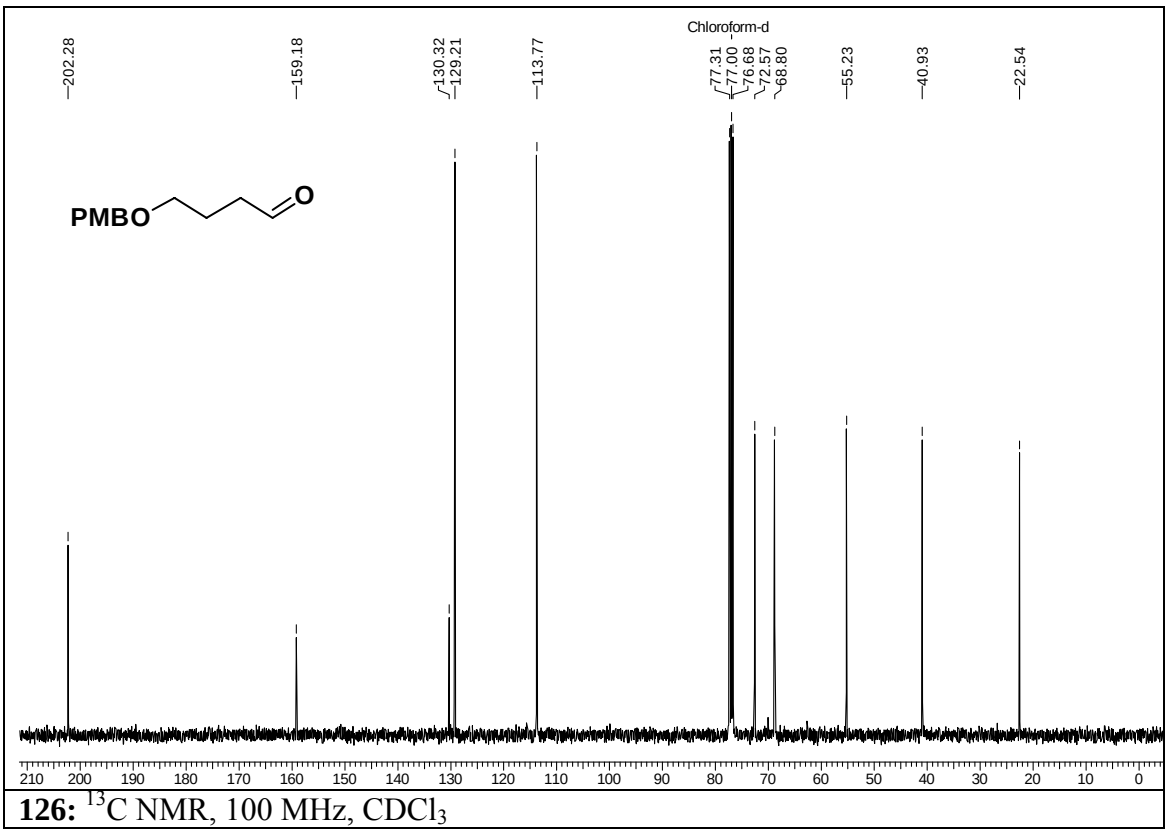
127: ^{1}H NMR, 400 MHz, $CDCl_3$



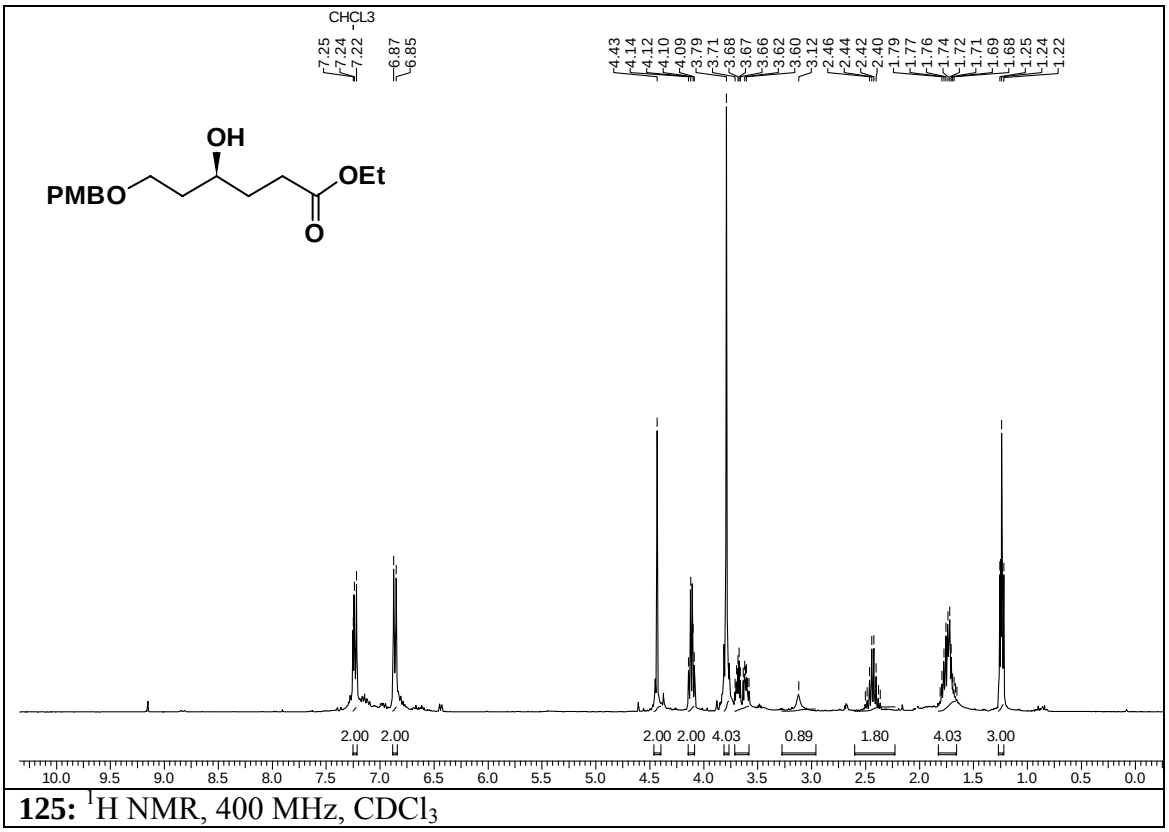
127: ^{13}C NMR, 50 MHz, $CDCl_3$



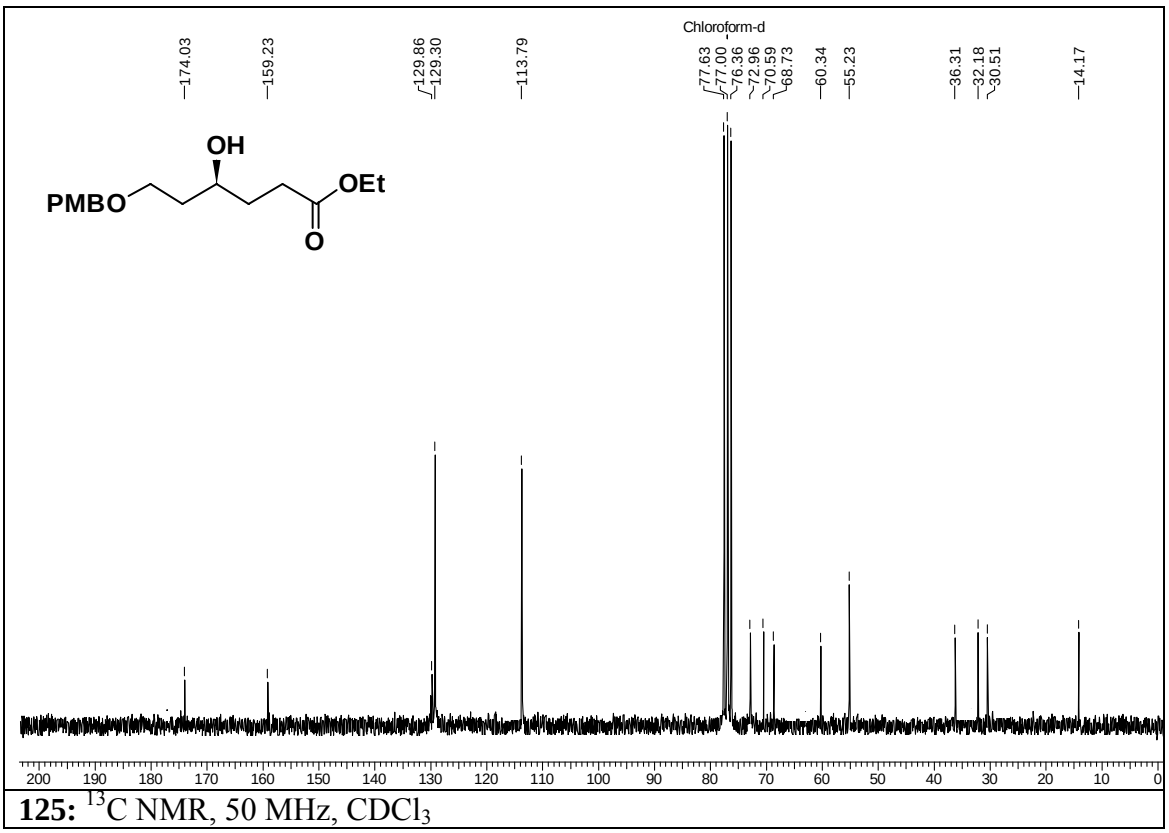
126: ^{1}H NMR, 400 MHz, $CDCl_3$



126: ^{13}C NMR, 100 MHz, $CDCl_3$

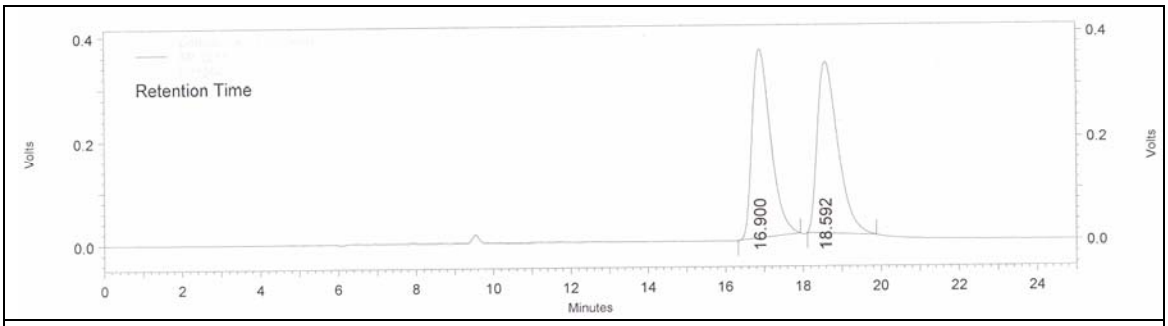


125: ^{1}H NMR, 400 MHz, $CDCl_3$



125: ^{13}C NMR, 50 MHz, $CDCl_3$

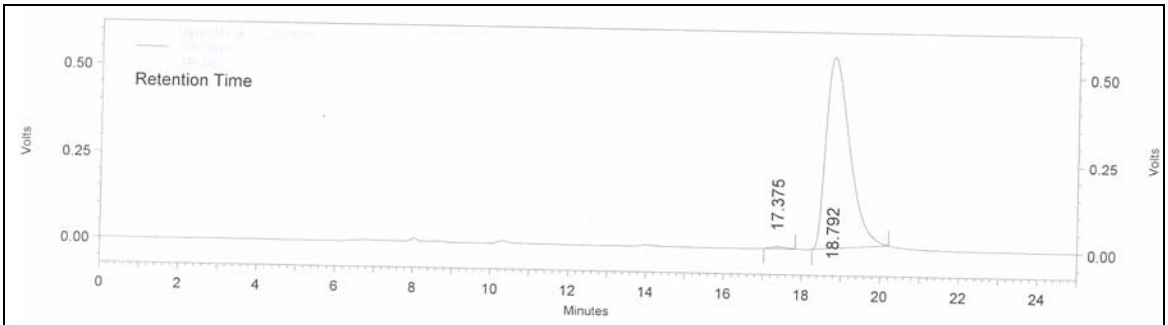
Chiral HPLC Analysis of compound 125



Racemic sample chromatograph

Pk #	Retention Time	Area	Area %	Height	Height Percent
1	16.900	12133286	49.950	362962	52.45
2	18.592	12157576	50.050	329056	47.55
Totals		24290862	100.000	692018	100.00

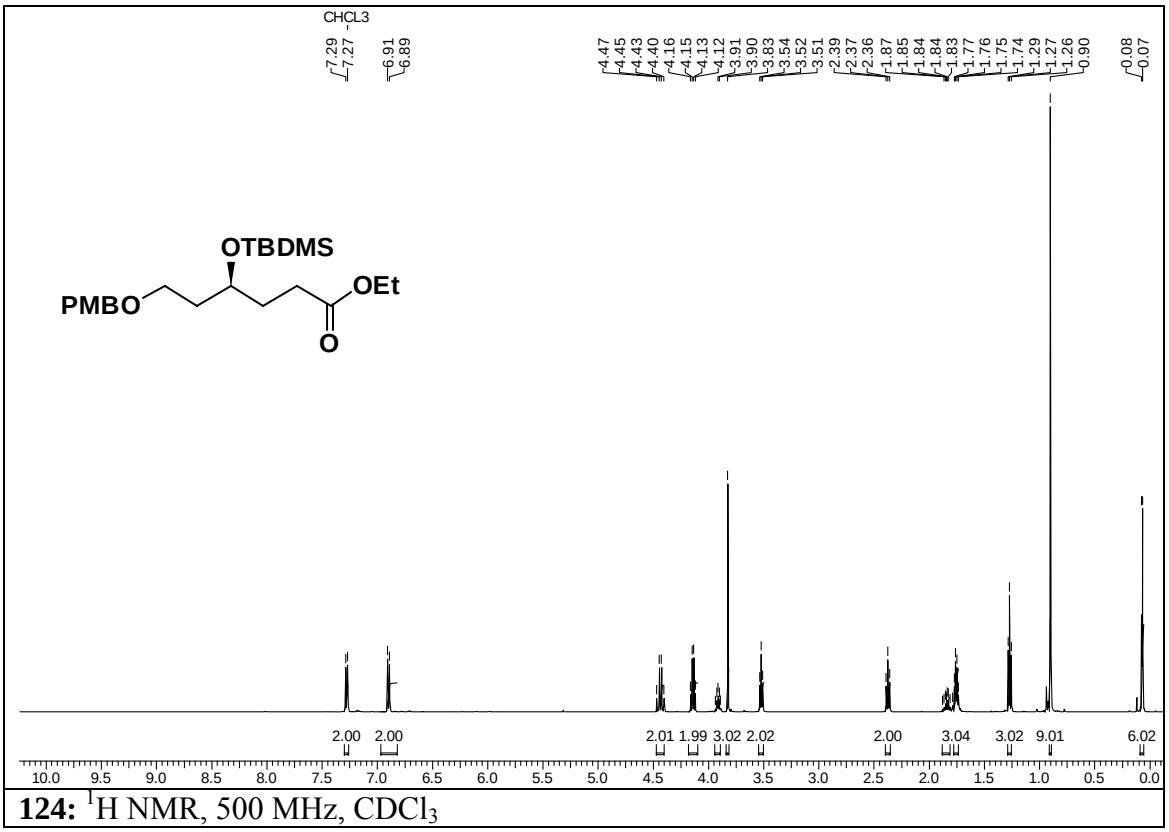
Column : Chiracel OD-H (250 x 4.6mm)
Mobile phase : 2-Propanol + Pet. ether (5:95)
Wavelenth : 230 nm
Flow : 0.5 mL/min
Concentration : 1.00 mg/1.0 mL mobile phase
Injection vol. : 20 µL



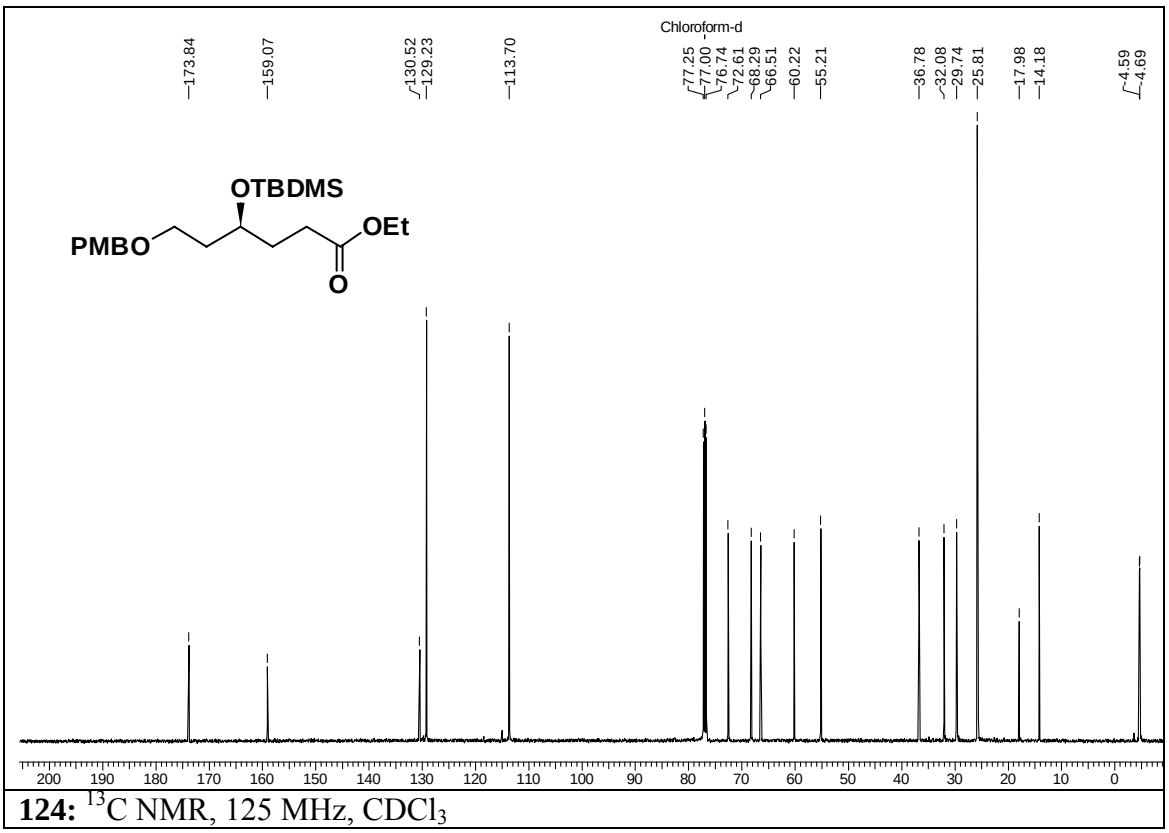
Chiral sample chromatograph

Pk #	Retention Time	Area	Area %	Height	Height Percent
1	14.925	5376	0.403	359	0.64
2	16.517	1329750	99.597	55816	99.36
Totals		1335126	100.000	56175	100.00

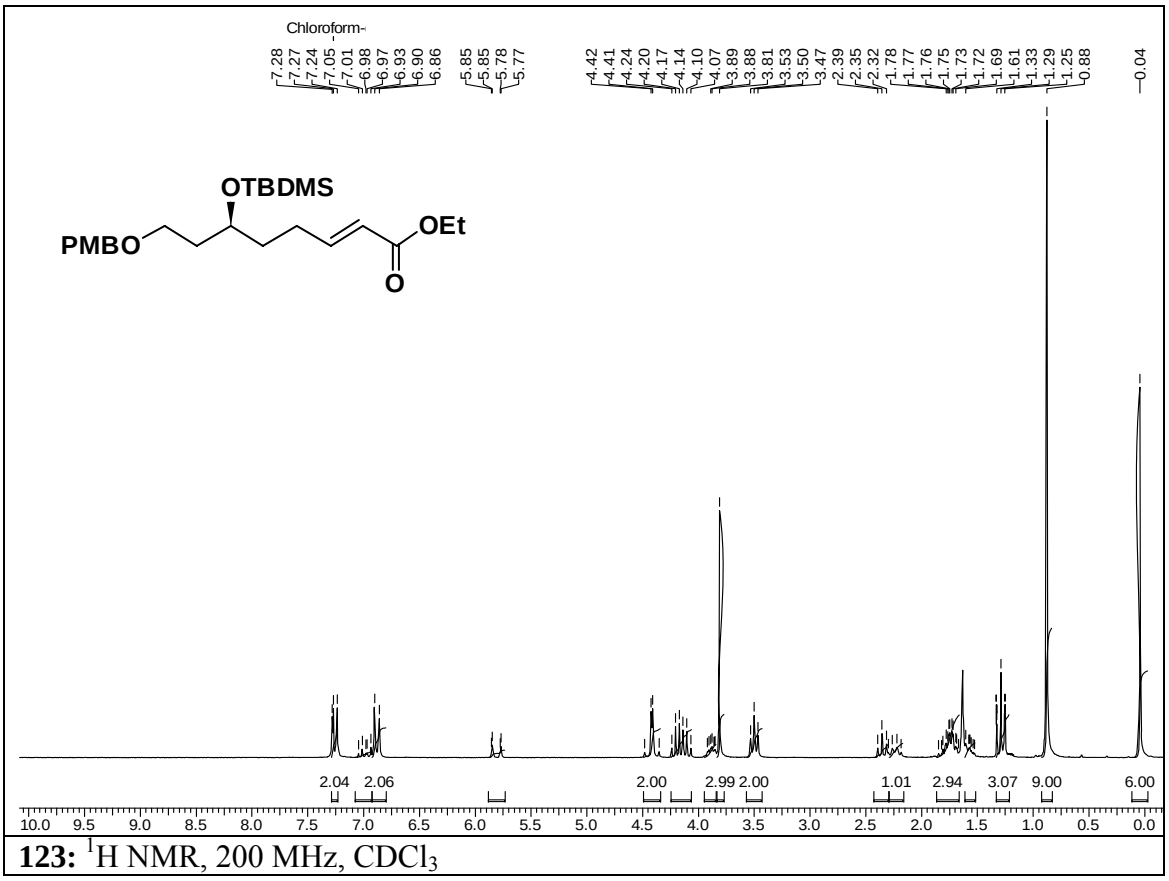
Column : Chiracel OD-H (250 x 4.6mm)
Mobile phase : 2-Propanol + Pet. ether (5:95)
Wavelenth : 230 nm
Flow : 0.5 mL/min
Concentration : 1.00 mg/1.0 mL mobile phase
Injection vol. : 20 µL



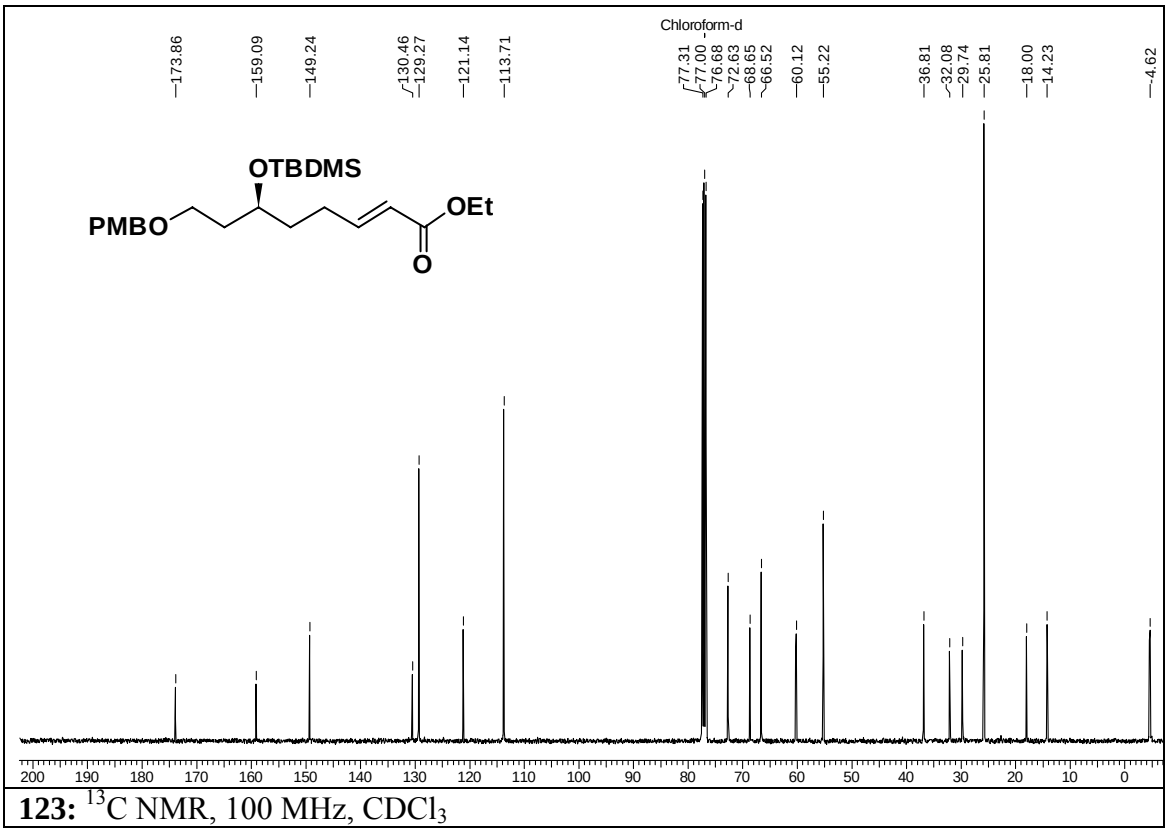
124: ^{1}H NMR, 500 MHz, $CDCl_3$



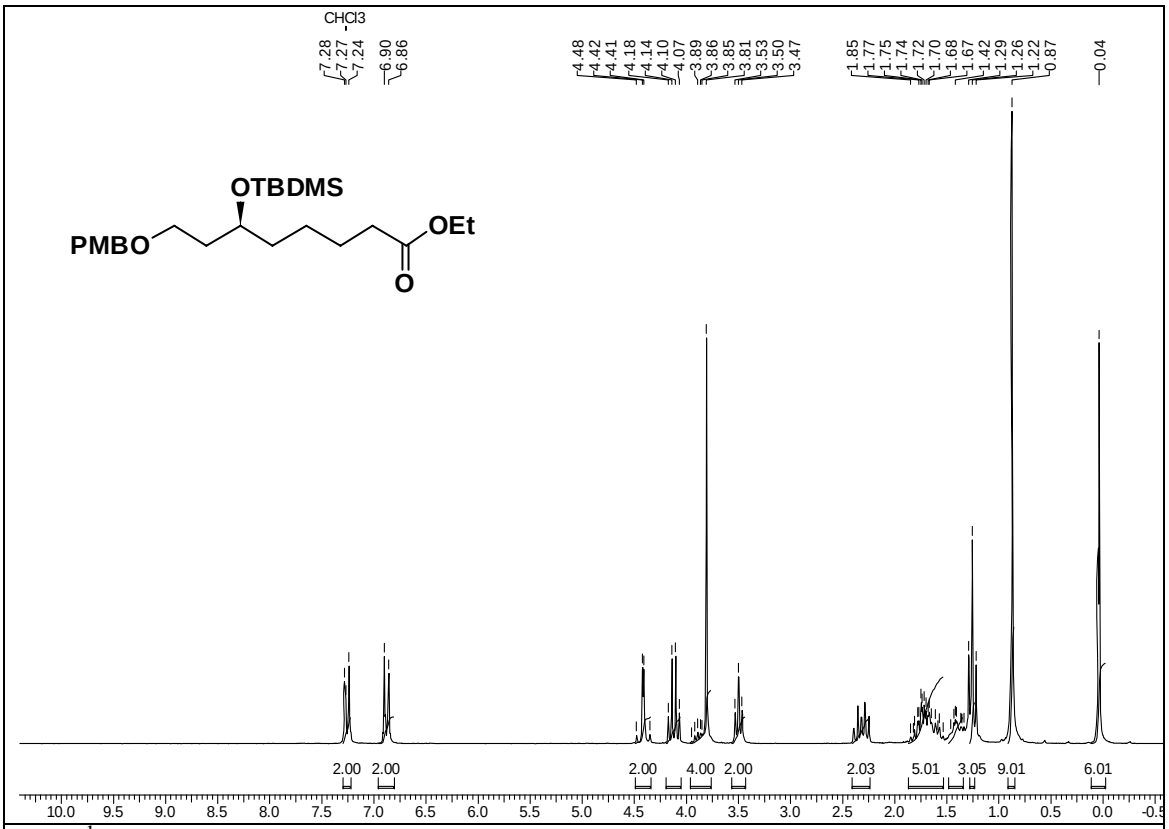
124: ^{13}C NMR, 125 MHz, $CDCl_3$



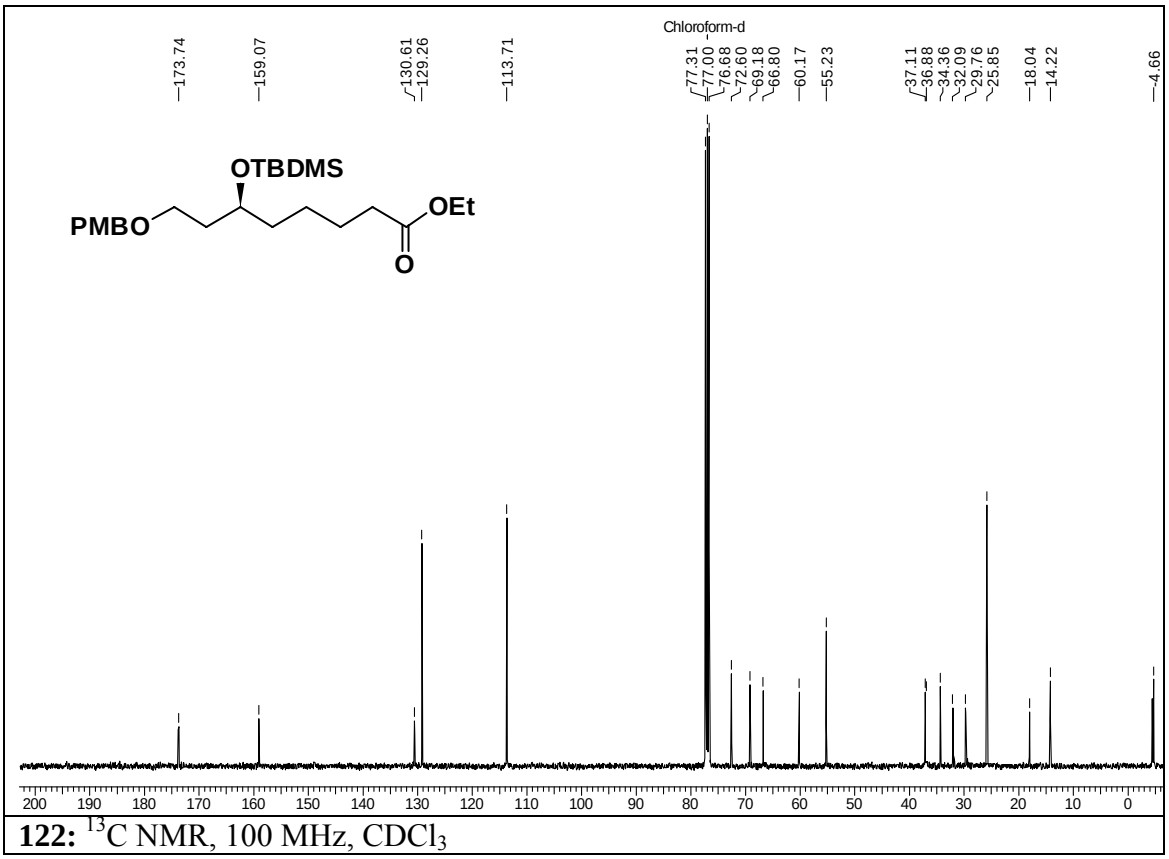
123: ^{1}H NMR, 200 MHz, $CDCl_3$



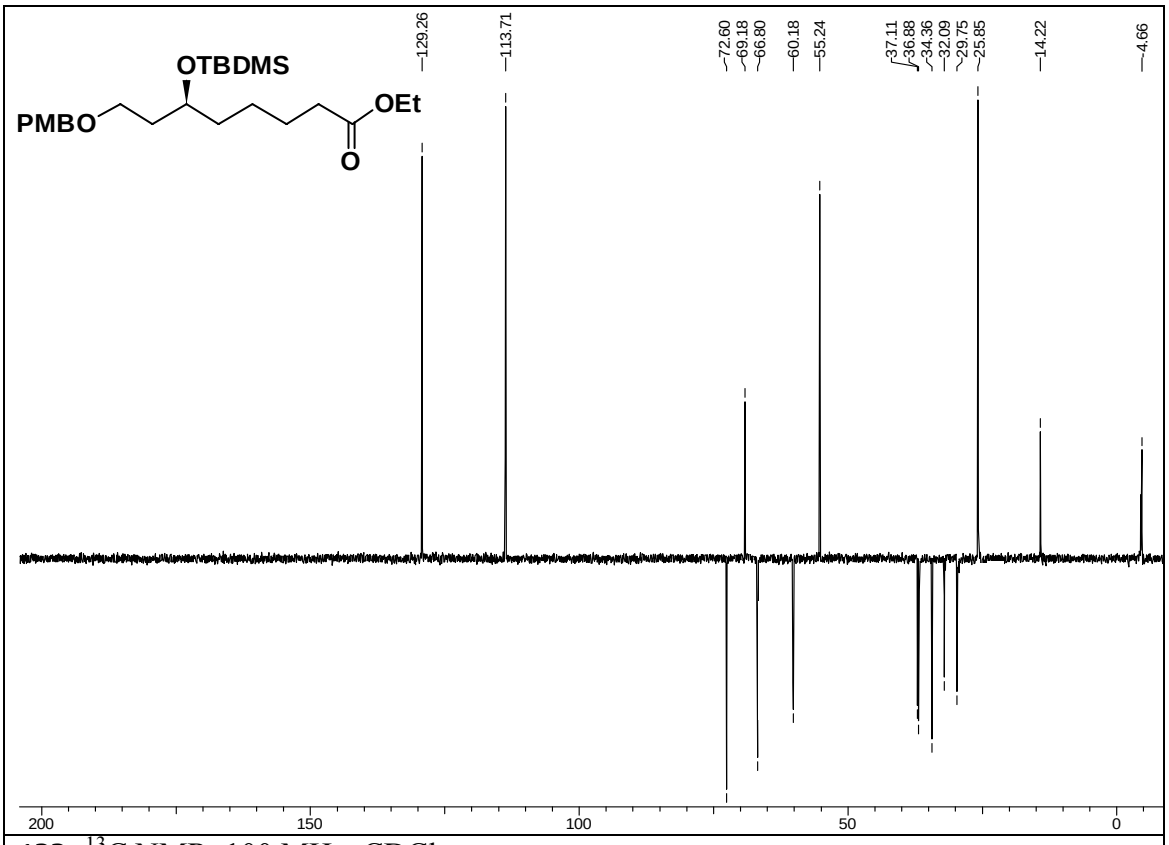
123: ^{13}C NMR, 100 MHz, $CDCl_3$



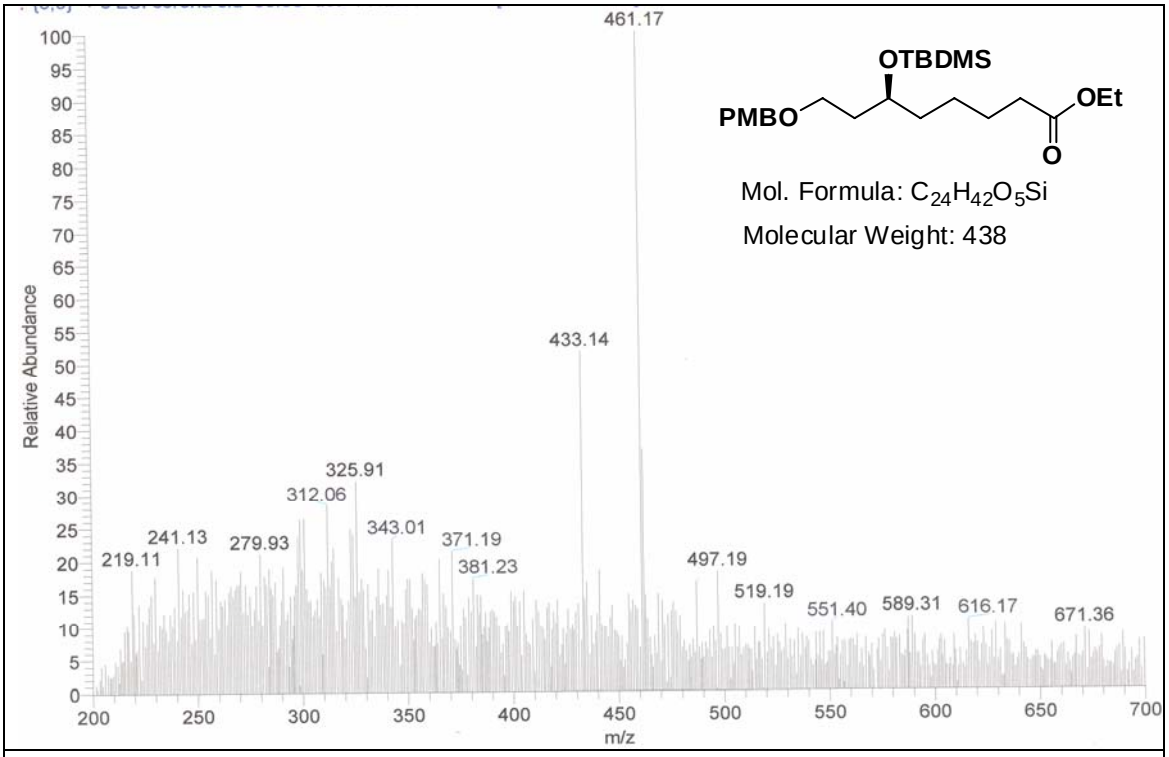
122: ^{1}H NMR, 200 MHz, $CDCl_3$



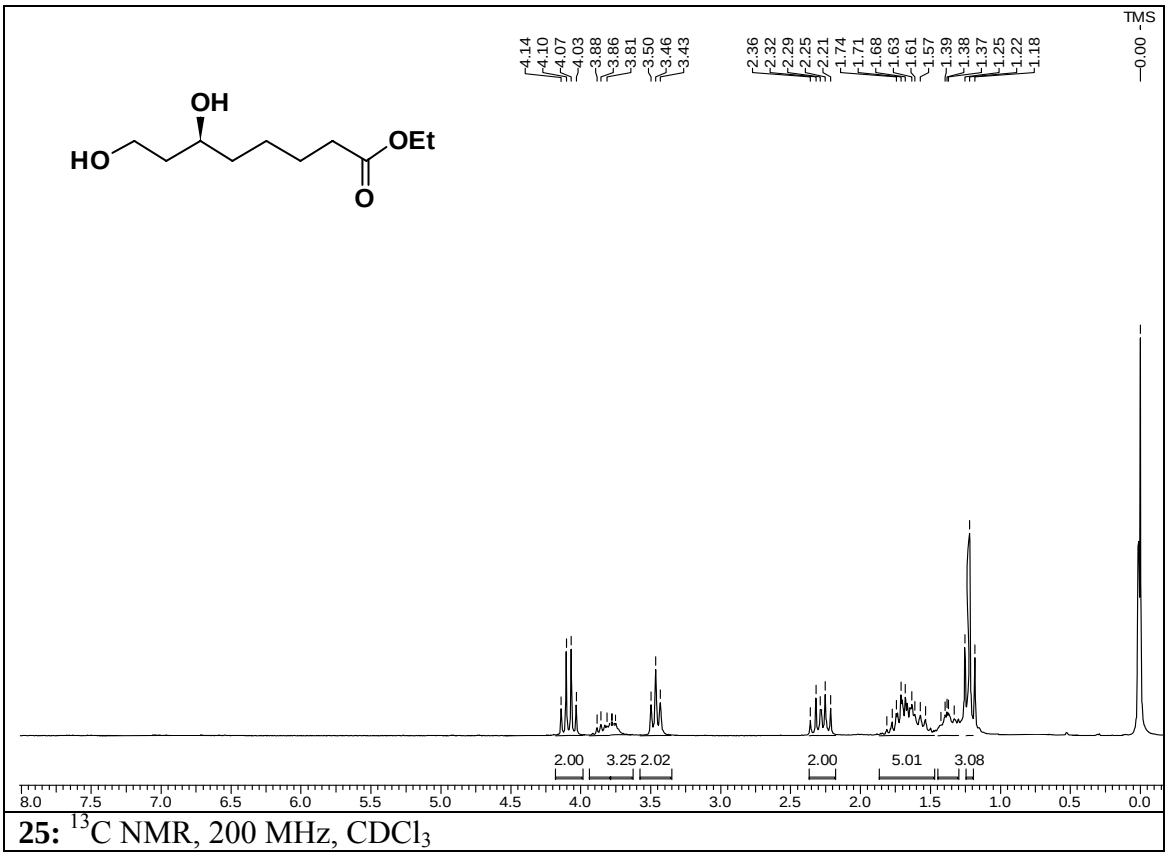
122: ^{13}C NMR, 100 MHz, $CDCl_3$



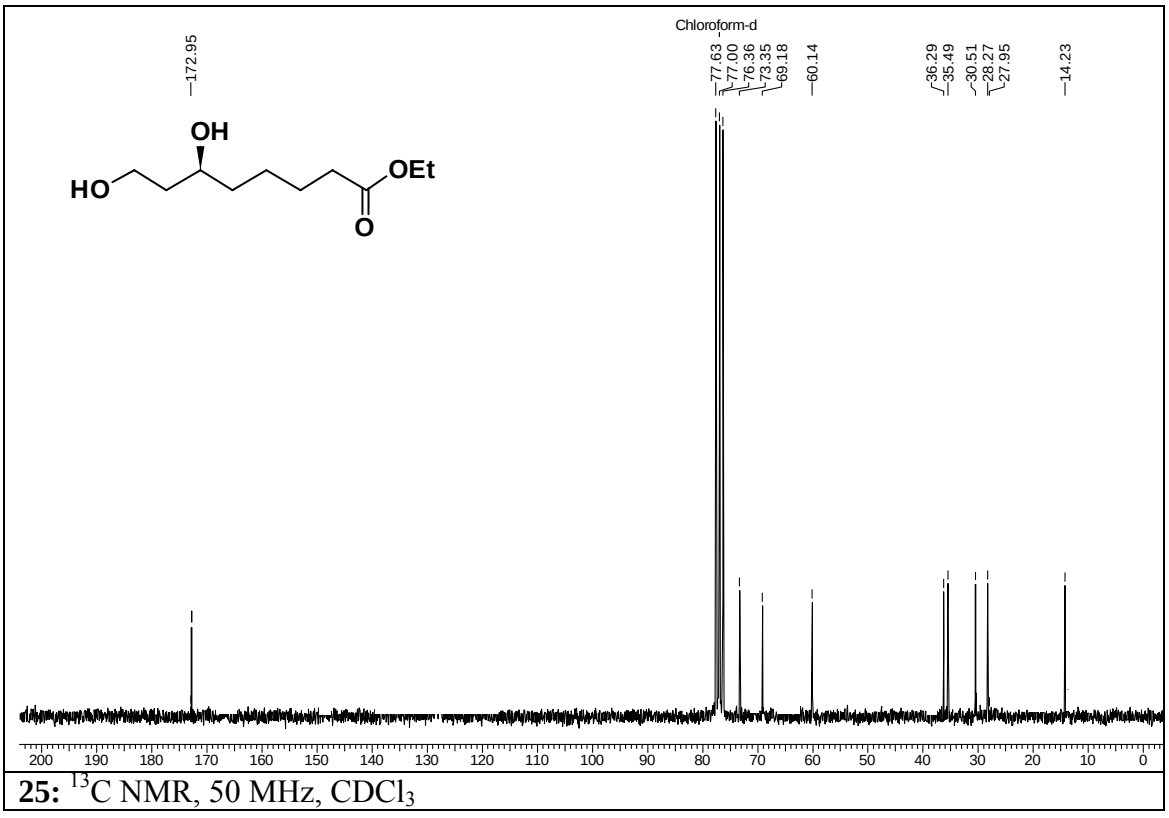
122: ^{13}C NMR, 100 MHz, $CDCl_3$



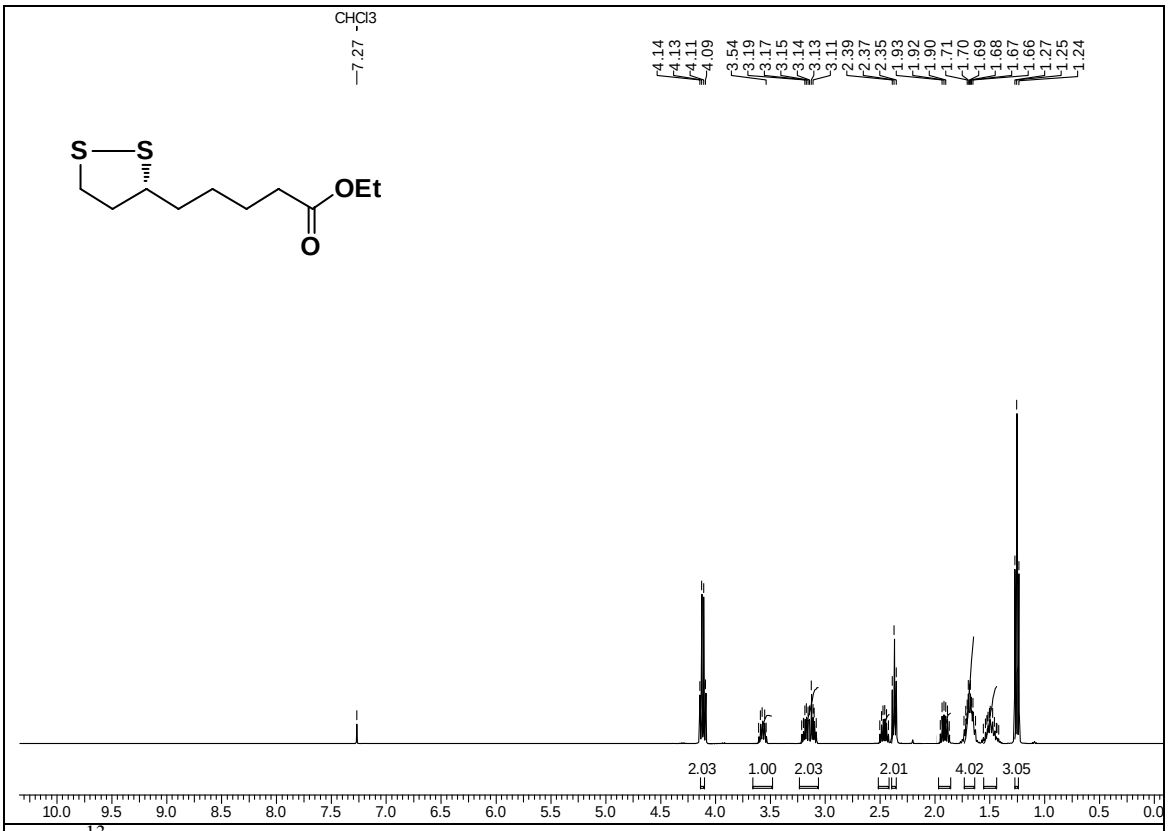
122: LC-MS



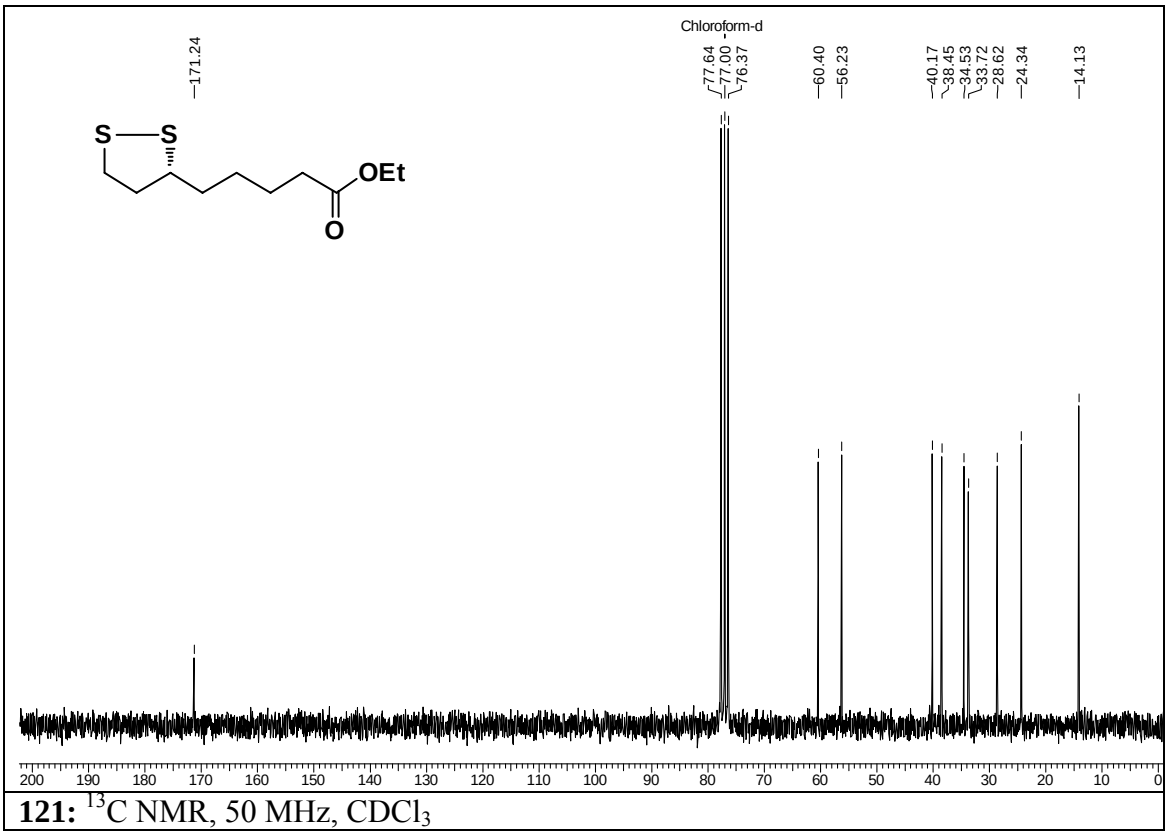
25: ^{13}C NMR, 200 MHz, $CDCl_3$



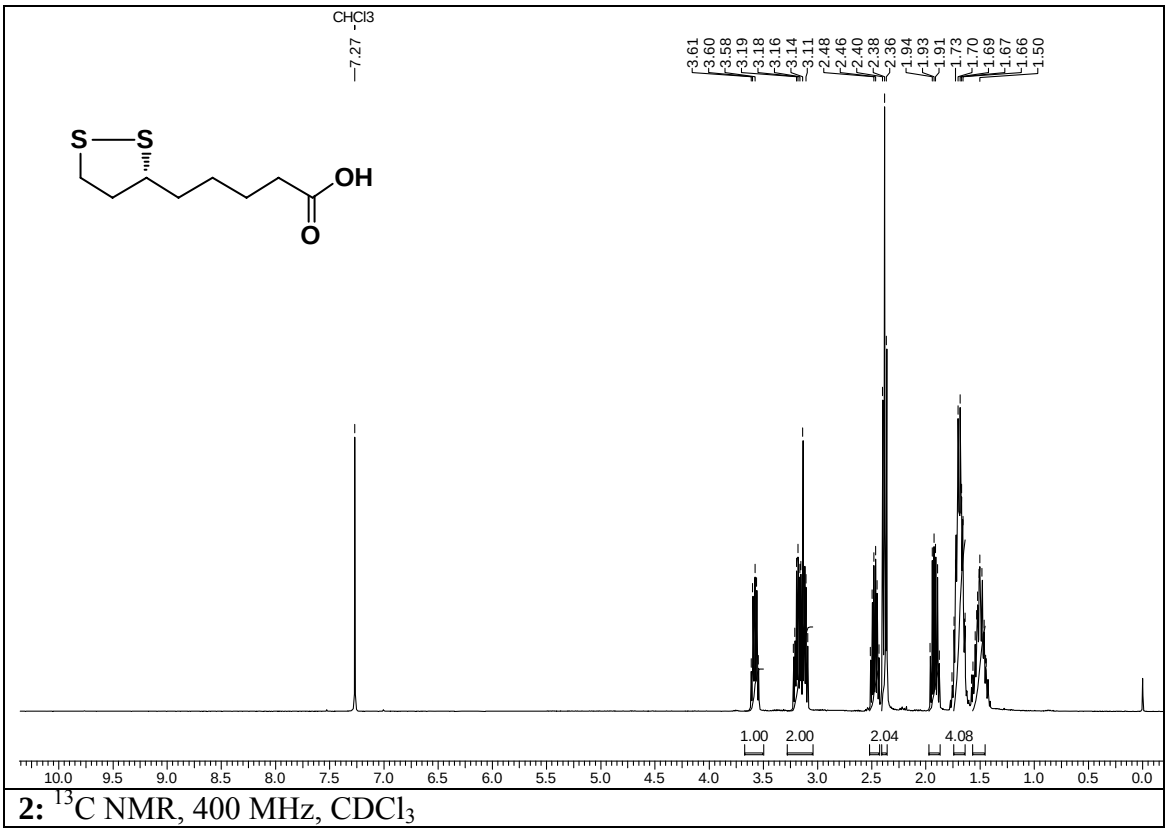
25: ^{13}C NMR, 50 MHz, $CDCl_3$



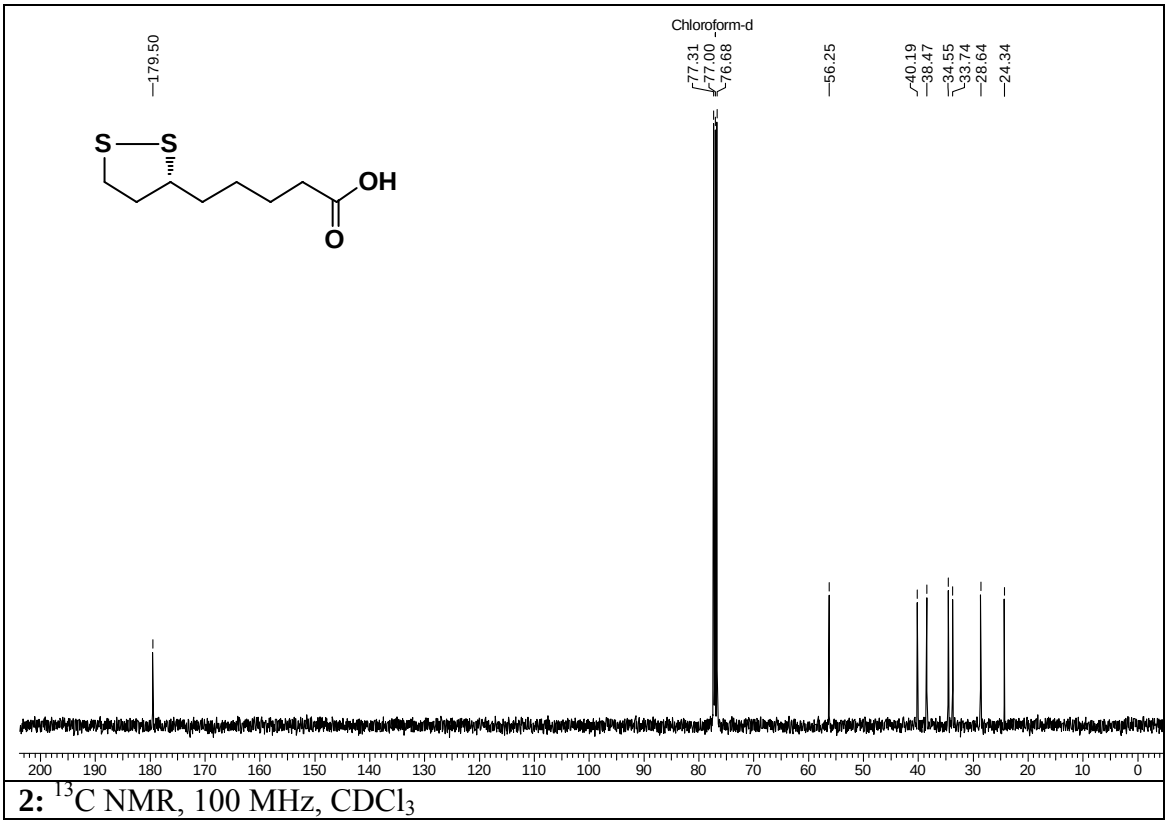
121: ^{13}C NMR, 400 MHz, $CDCl_3$



121: ^{13}C NMR, 50 MHz, $CDCl_3$



2: ^{13}C NMR, 400 MHz, $CDCl_3$



2: ^{13}C NMR, 100 MHz, $CDCl_3$

1.2.8 References

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1.3 SECTION C

ASYMMETRIC SYNTHESIS OF β-ADRENERGIC BLOCKERS AND RELATED DRUG MOLECULES

1.3.1 Introduction

β-blockers, also known as β-adrenergic blocking agents, are drugs that block adrenaline **1** and noradrenaline **2** from binding to beta receptors on nerves. Propranolol **3** was the first clinically useful β-blocker (**Figure 1**). It was invented by Scotish pharmacologist Sir James W. Black in early 1950s. This invention revolutionalized the medical management of angina pectoris and is considered to be one of the most important contributions to clinical medicine and pharamacology of 20th century.[1] For this invention, in 1988 Sir James W. Black was awarded Nobel Prize in Medicine.

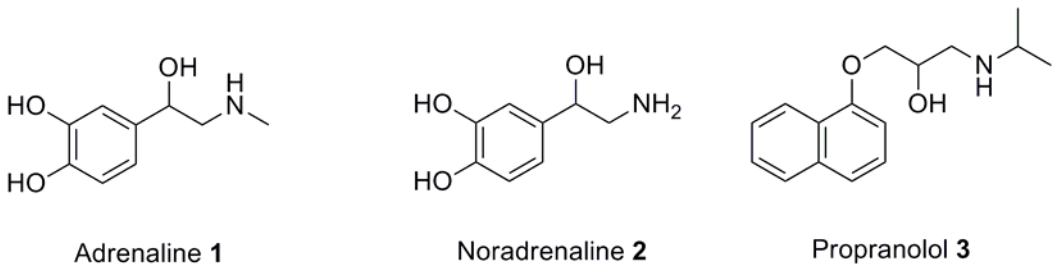


Figure 1.

There are three types of beta receptors and they control several functions based on their location in the body.

a) β_1 receptors are located in the heart, eyes and kidneys.

b) β_2 receptors are found in the lungs, gastrointestinal tract, liver, uterus, blood vessels and skeletal muscle.

c) β_3 receptors are located in fat cells.

Stimulation of β_1 receptors by adrenaline induces a positive chronotropic and inotropic effect on the heart and increases cardiac conduction velocity and automaticity. Stimulation of β_1 receptors on the kidney causes renin release. Stimulation of β_2 receptors induces smooth muscle relaxation, induces tremor in skeletal muscle, and increases glycogenolysis in the liver and skeletal muscle. Stimulation of β_3 receptors induces lipolysis.

The heart contains β_1 and β_2-adrenergic receptors in the proportion 70:30. In heart failure, cardiac β_1 receptors are reduced in number and population. Blockade of

cardiac β_1 receptors causes a decrease in heart rate, myocardial contractility, and velocity of cardiac contraction. β-blockers cause the heart muscle to work less, thus requiring less oxygen; in time of oxygen lack, such as during a heart attack or severe angina, this action can be life-saving. Because of the reduction in the oxygen requirement of the heart muscle, the beta-blocking drugs are effective in preventing the chest pain of angina pectoris.Because patients with angina have a high risk of developing a heart attack over ensuing years, β-blockers are important for both pain and prevention. Some of the β-blockers are listed below (**Figure 2**).

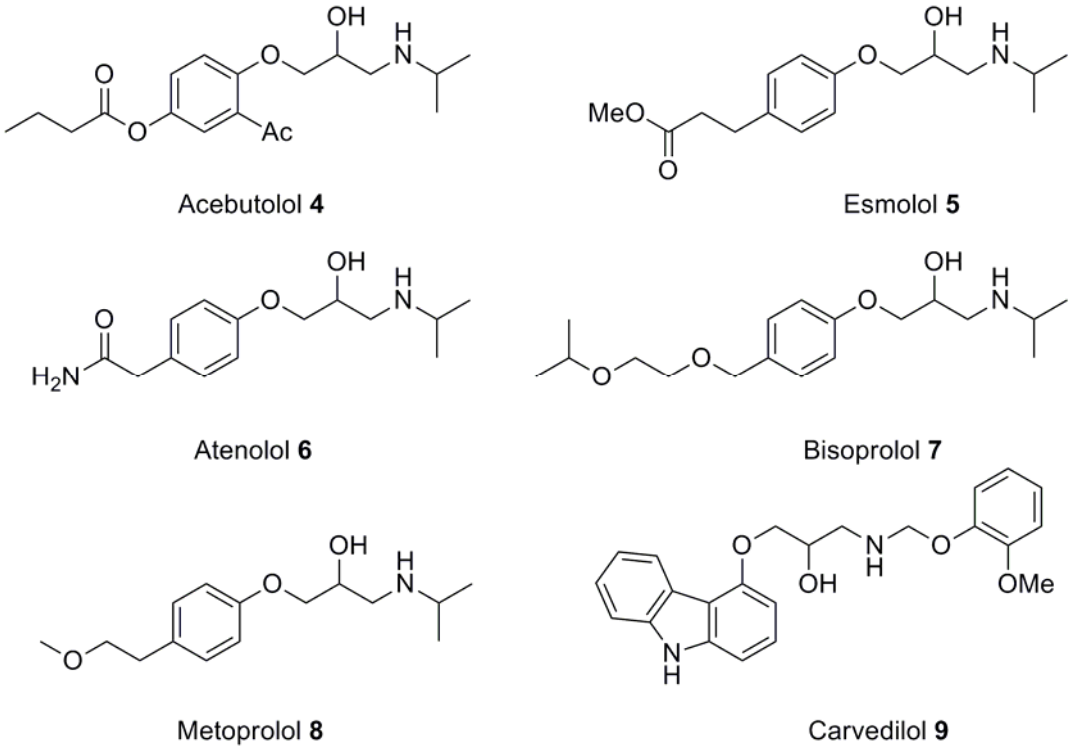


Figure 2.

β-blockers differ in the type of β-receptors they block. It is therefore expected that non-selective β-blockers have an antihypertensive effect. Antianginal effects result from negative chronotropic and inotropic effects, which decrease cardiac workload and oxygen demand. The antiarrhythmic effects of β-blockers arise from sympathetic nervous system blockade-resulting in depression of sinus node function and atrioventricular node conduction, and prolonged atrial refractory periods.

The quest for optically pure molecules has intensified during recent years. β-Adrenergic blocking agents of the 3-(aryloxy)-2-hydroxy-(*N*-isopropyl)-propylamine type, are such a group of drugs whose biological activity is associated with only *S* enantiomer. For instance, (*S*)-propranolol **10** (**Figure 3**) is 100-fold more potent than

the *R* isomer.[2] Due to this we planned enantioselective synthesis of b-blockers and related drug molecules shown in **figure 3**. Among these (*S*)-propranolol **10**, (*S*)-naftopidil **11** and (*S*)-moprolol **12** are antihypertensive drugs[3a] where as (*R*)-methocarbamol **13** is skeletal muscle relaxant.[3b] (*S*)-guaifenesin **14** has been used in treatment of cough,[4] gout,[5] fibromyalgia,[6] primary dysmenorrheal[7] and (*S*)-mephenesin **15** has been used as centrally acting muscle relaxant.

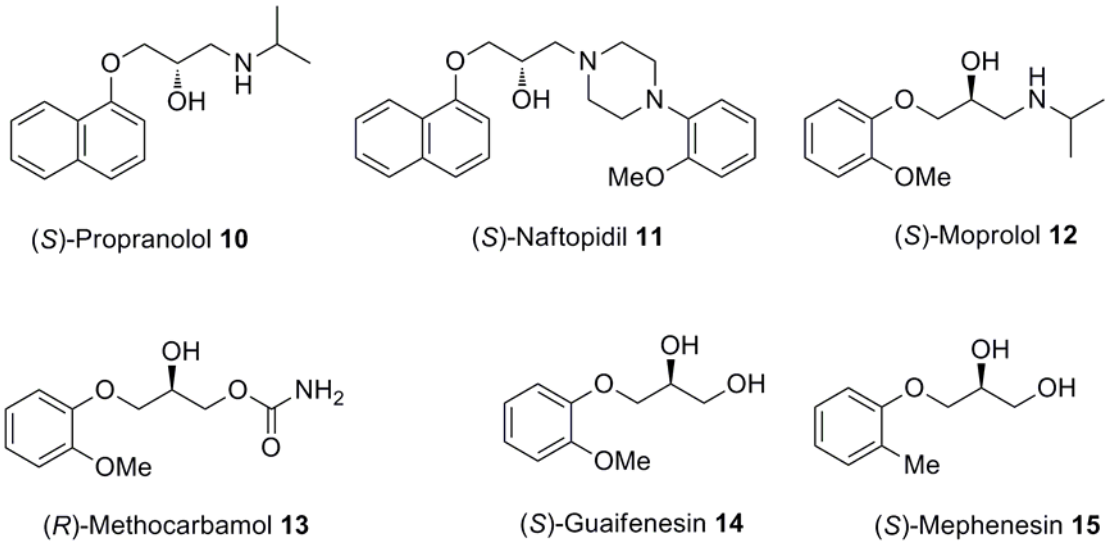


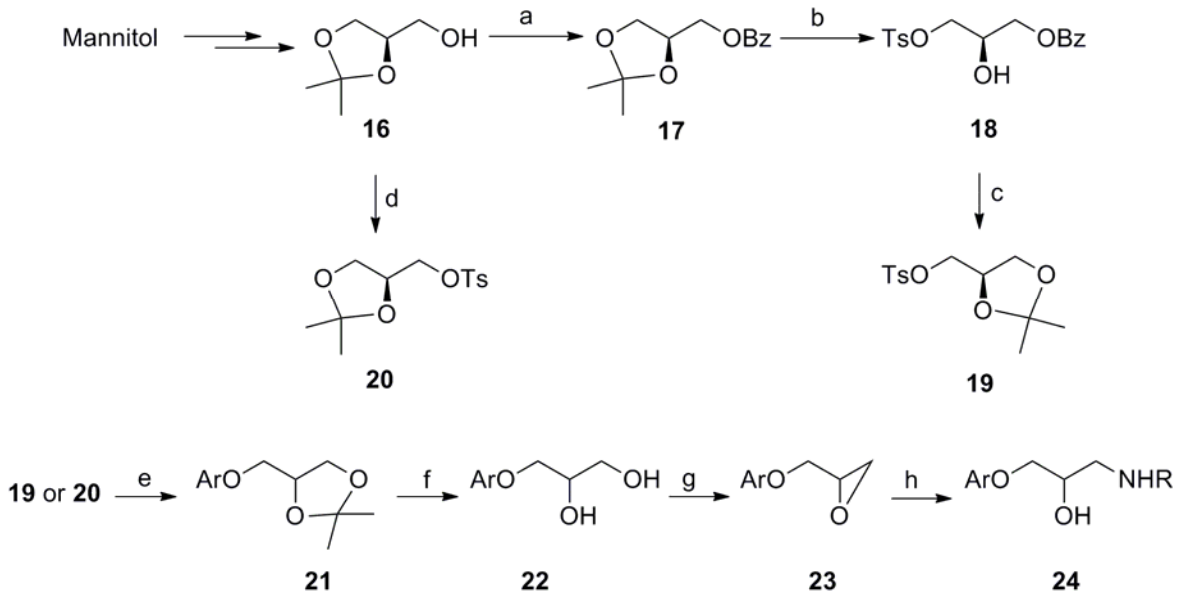
Figure 3.

1.3.2 Review of literature

Many routes[8-28] for asymmetric synthesis of β-blockers are reported in literature. Among them some are discussed below.

1.3.2.1 Nelson *et al.* (1977, Scheme 1)[9]

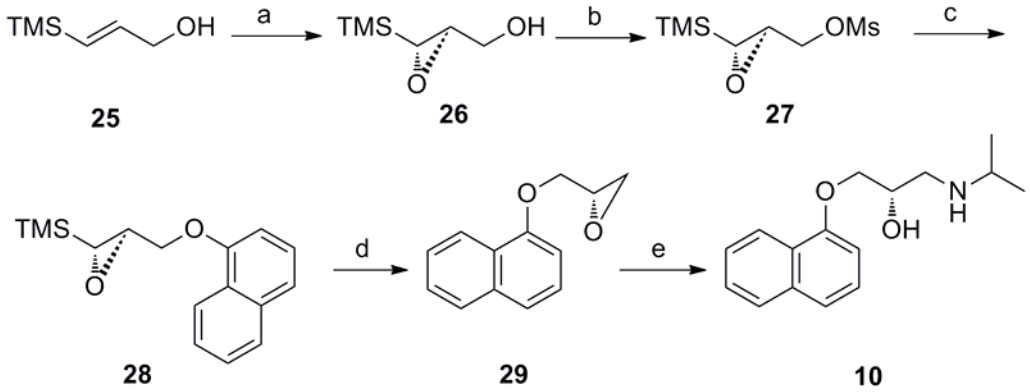
Nelson and co-workers obtained the chiral alcohol **16** from D-mannitol. The chiral alcohol **16** then transformed into two tosylate enantiomers **19** and 2**0** by synthetic manipulations. Tosylate (**19** or **20**) treated with various phenols to obtain diols **22**. Diol **22** then converted to epoxide **23** via tosylation. Epoxide **23** on tratement with amine afforded β-blockers **24**. In this approach authors got both the enantiomers of various β-blockers depending upon tosylate (**19** or **20**), phenol and amine used. In this synthesis the also synthesized (*S*)-guaifenesin **14** and (*S*)-mephenesin **15** with guaiacol and *o*-cresol as phenols.



Scheme 1. *Reagents and conditions*: (a) BzCl, KOH, DMF; (b) (i) H_3O^+; (ii) TsCl, Py; (c) (i) H_2, Pd/C; (ii) Acetone, $ZnCl_2$; (d) TsCl, Py; (e) ArOH, NaOH; (f) H_3O^+; (g) (i) TsCl, Py; (ii) NaOH; (h) RNH_2.

1.3.2.2 Katsuki (1984, Scheme 2)[12]

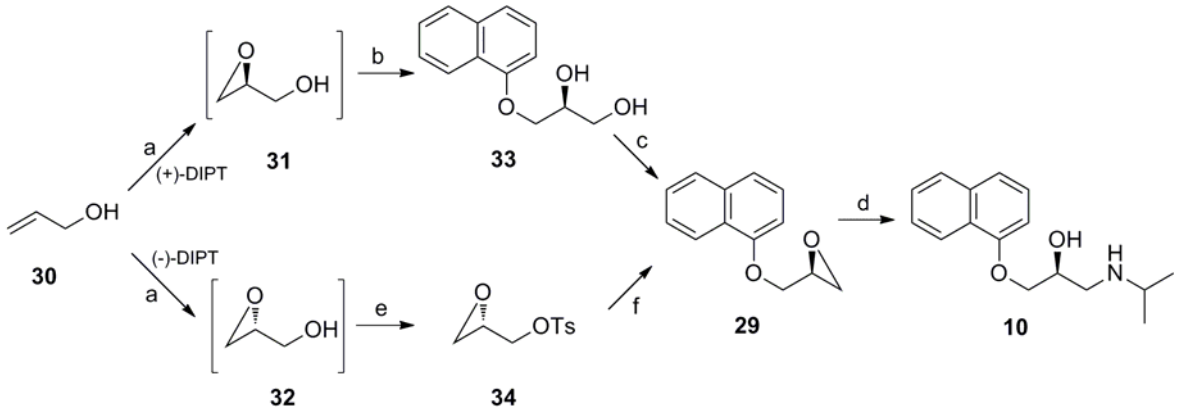
Katsuki started the synthesis of (*S*)-propranolol **10** from allyl alcohol via Sharpless asymmetric epoxidation to obtain epoxy alcohol **26**. The epoxy alcohol **26** then converted to its naphthoxy derivative **28**. Compound **28** on treatment with TBAF afforded epoxide **29** which converted to (*S*)-propranolol **10** by iso-propyl amine treatment.



Scheme 2. *Reagents and conditions*: (a) Ti(O*i*Pr)$_4$, *t*-BuOOH, (-)-diisopropyl tartarate; (b) MsCl, Et_3N, CH_2Cl_2, -20 °C; (c) 1-naphthol, NaOH; (d) TBAF, THF; (e) isopropyl amine.

1.3.2.3 Sharpless *et al.* (1986, Scheme 3)[15]

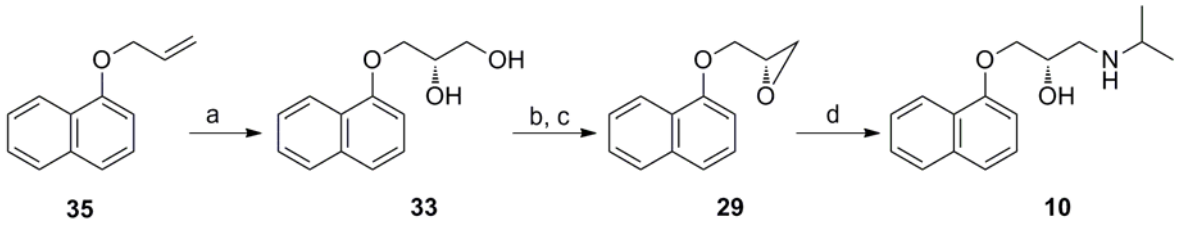
Sharpless and co-workers started the synthesis with asymmetric epoxidation of allyl alcohol **30** to obtain enantiomeric epoxy alcohols **31** and **32** using (+)-diisopropyl tartarate and its enatiomer respectively. Epoxy alcohol **31** then opened with sodium salt of 1-naphthol to obtain diol **33**. Diol **33** converted to known epoxide **29** which then converted to (*S*)-propranolol **10** by isopropyl amine treatment. In another approach epoxy alcohol **32** converted to tosyl derivative **34** which then coupled with 1-naphthol to obtain known epoxide **29**.



Scheme 3. *Reagents and conditions*: (a) $Ti(OiPr)_4$, Cumene hydroperoxide; (b) Sodium-1-naphthoxide, $Ti(OiPr)_4$; *t*-BuOH; (c) (i) HBr, AcOH; (ii) NaOH; (d) isopropyl amine; (e) TsCl, Et_3N; (f) 1-naphthol, NaH, DMF.

1.3.2.4 Rama Rao *et al.* (1990, Scheme 4)[18]

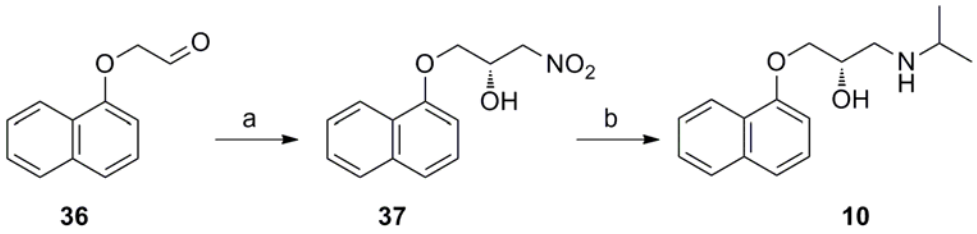
Rama Rao and co-workers started synthesis of (*S*)-propranolol with chichona alkaloid catalyzed asymmetric dihydroxylation of allyl ether of 1-naphthol **35**. The resultant diol **33** converted to epoxide **29** by treatment firstly with TsCl and Et_3N and then sodium methoxide in methanol. The epoxide **29** opened with excess isopropyl amine to obtain (*S*)-propranolol **10**.



Scheme 4. *Reagents and conditions*: (a) OsO_4, $K_3Fe(CN)_6$, DHQDPCB, *t*-BuOH, H_2O; (b) TsCl, Et_3N; (c) NaOMe, MeOH; (d) Isopropyl amine.

1.3.2.5 Shibasaki et al. (1993, Scheme 5)[20]

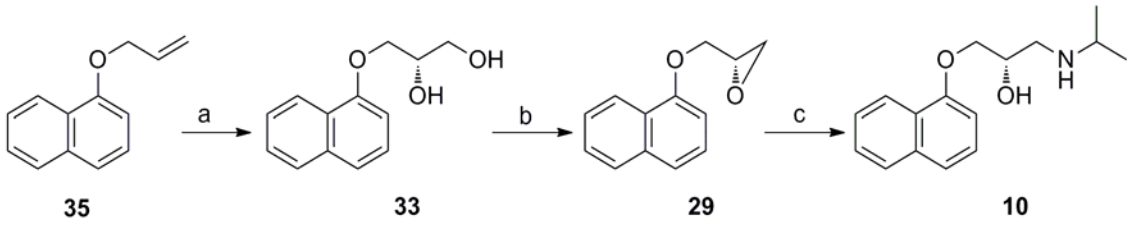
Shibasaki and co-workers used La-(*R*)-BINOL complex catalyzed asymmetric nitro-aldol reaction as key step towards the synthesis of (*S*)-propranolol. Aldehyde **36** on treatment with nitromethane in presence of La-(*R*)-BINOL complex to afford the chiral nitro alcohol **37**. The nitroalcohol **37** on 10% PtO_2 catalyzed hydrogenation in presence of acetone afforded (*S*)-propranolol **10**.



Scheme 5. *Reagents and conditions*: (a) La-(*R*)-BINOL complex (10 mol%), THF, -50 °C; (b) 10% PtO_2, H_2, MeoH, rt, 2h then acetone, 50 °C, 16h.

1.3.2.6 Sharpless *et al.* (1993, Scheme 6)[21]

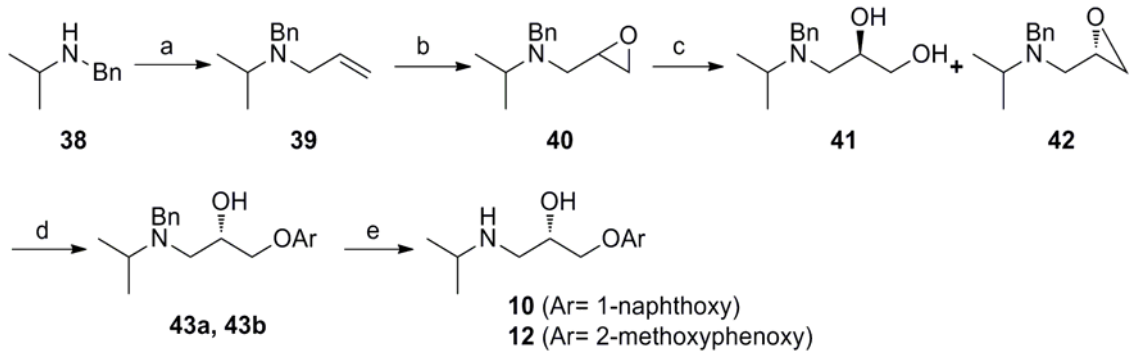
In this approach Sharpless and co-workers employed AD-mix-β catalyzed Sharpless asymmetric dihydroxylation of allyl ether of 1-naphthol **35** to obtain diol **33**. Diol **33** then transformed into epoxide **29** with trimethyl orthoacetate, acetyl bromide and potassium carbonate. The epoxide **29** on treatment with isopropyl amine afforded (*S*)-propranolol **10**. This approach is some what similar to Rama Rao's approach.



Scheme 6. *Reagents and conditions*: (a) AD-mix-β, *t*-BuOH, H_2O, 0 °C, $MeC(OMe)_3$, AcBr then K_2CO_3, MeOH; (c) isopropyl amine, H_2O.

1.3.2.7 Hou *et al.* (1999, Scheme 7)[24]

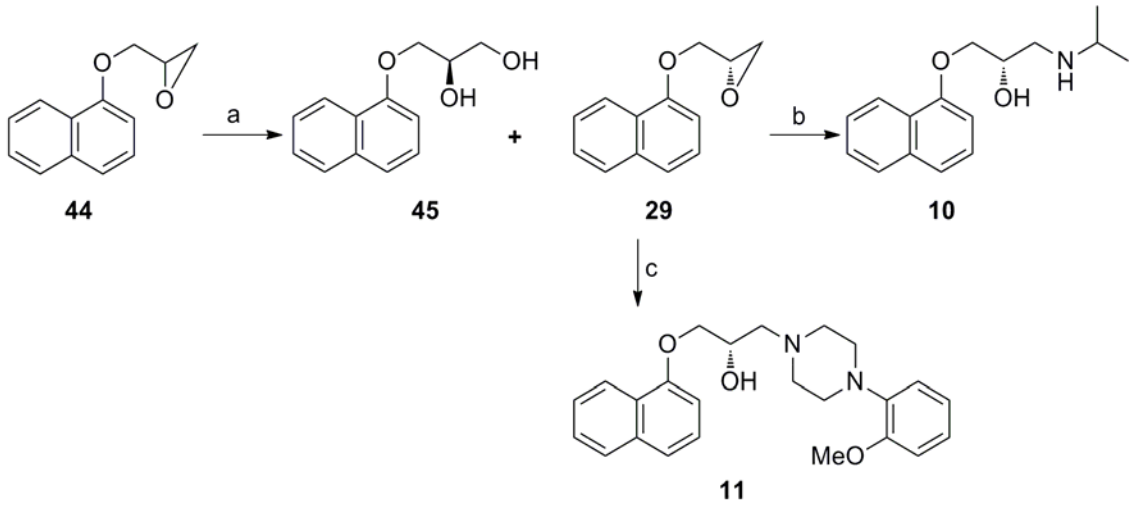
Hou and co-workers synthesized various β-blockers including (*S*)-propranolol **10** and (*S*)-moprolol **12**. In this approach the synthesized racemic epoxide **40** from substituted allyl amine **39** with Li_2PdCl_4, cupric chloride followed by sodium sulfide. The epoxide **40** then on (*S,S*)-salen Co(III)OAc catalyzed Jacobsen hydrolytic kinetic resolution afforded chiral diol **41** and chiral epoxide **42**. The epoxide **42** on opening with various phenols followed by hydrogenation afforded β-blockers.



Scheme 7. *Reagents and conditions*: (a) Allyl bromide, NaOH, DMF; (b) Li_2PdCl_4, $CuCl_2$, DMF, -10 °C, then $Na_2S.9H_2O$; (c) (*S*,*S*)-salen Co(III)OAc, H_2O; (d) ArOH, Et_3N, reflux; (e) 10% Pd/C, H_2, EtOH.

1.3.2.8 Bose *et al*. (2005, Scheme 8)[26]

In this approach Bose and co-workers utilized (*R*,*R*)-salen Co(III)OAc catalyzed Jacobsen hydrolytic kinetic resolution of epoxide **44**. Hydrolytic kinetic resolution of epoxide **44** afforded chiral diol **45** and chiral epoxide **29**. The epoxide **29** then opened with isopropyl amine to afford (*S*)-propranolol **10** and with 1-(2-methoxyphenyl)piperizine to afford (*S*)-naftopidil **11**.

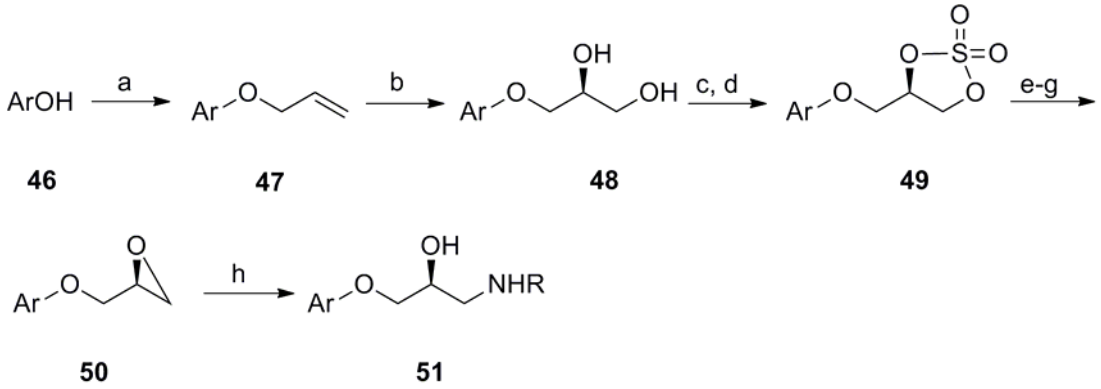


Scheme 8. *Reagents and conditions*: (a) (*R*,*R*)-salen Co(III)OAc, H_2O; (b) isopropyl amine, H_2O, rt; (c) 1-(2-methoxyphenyl)piperizine, 2-propanol, reflux.

1.3.2.9 Sudalai *et al.* (2005, Scheme 9)[27]

In this approach Sudalai and co-workers synthesized various β-blockers including (*S*)-propranolol **10** and (*S*)-moprolol **12**. The synthesis started with $(DHQD)_2$-PHAL catalyzed Sharpless asymmetric dihydroxylation of allyl ethers of phenols. The

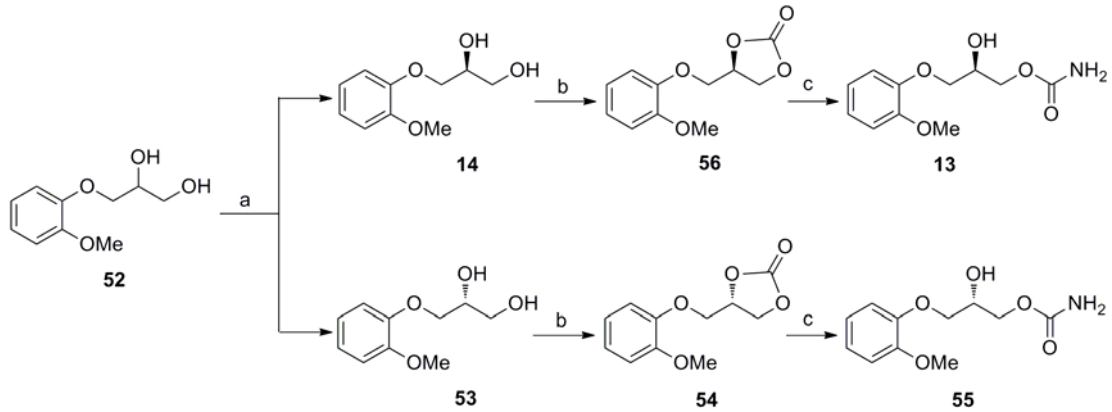
resultant diols **48** then converted to epoxides **50** via cyclic sulfate. The epoxides on treatment with amines afforded β-blockers.



Scheme 9. *Reagents and conditions*: (a) Allyl bromide, K_2CO_3, acetone, reflux, 12h; (b) cat. OsO_4, $(DHQD)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH/H_2O, 0 °C, 12h; (c) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 40 min.; (d) cat. $RuCl_3.3H_2O$, $NaIO_4$, CH_3CN:H_2O, 0 °C, 30 min.; (e) LiBr, THF, 25 °C, 2-3h; (f) 20% H_2SO_4, Et_2O, 25 °C, 10h; (g) K_2CO_3, MeOH, 0 °C, 2h; (h) R-NH_2, H_2O (cat.), reflux, 2h.

1.3.2.10 Bredikhin *et al.* (2007, Scheme 10)[28]

Bredikhin and co-workers resolved guaifenesin **52** by entrainment method. The chiral guaifenesin **14** and **53** then converted cyclic carbonates which then opened with ammonia to obtain both enantiomers of methocarbamol.



Scheme 10. *Reagents and conditions*: (a) resolution by entrainment; (b) $(EtO)_2CO$, NaOMe, 130 °C; (c) NH_3, 2-propanol, rt.

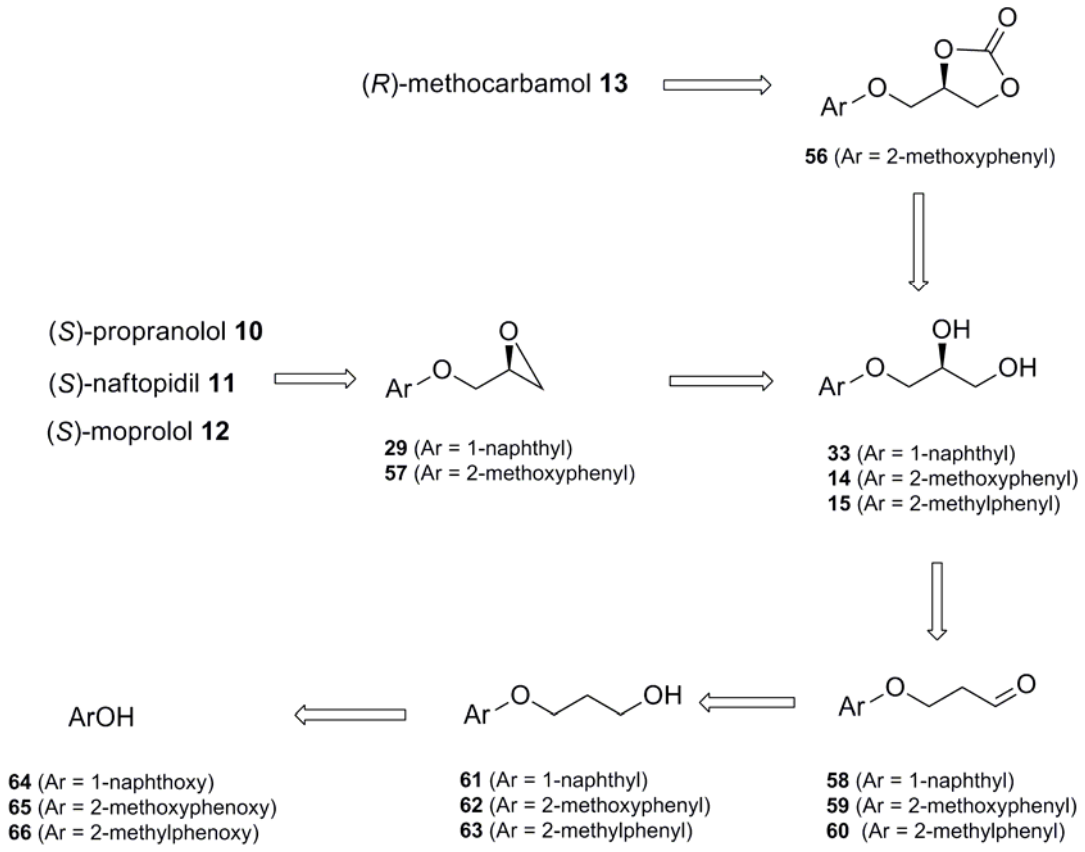
1.3.3 Present work

Synthesis of enantiomerically pure bioactive molecules explored in recent years because

(i) biological activity is often associated with only one enantiomer;

(ii) enantiomers may exhibit very different types of activity, both of which may be beneficial or one may be beneficial and the other undesirable.

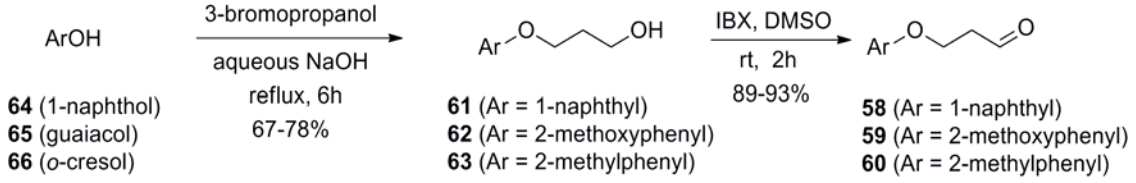
Due to this the quest for chiral drug is intensified. As can be seen from the above descriptions, the literature methods for the synthesis of β-blockers employ either chiral expensive reagents or wastage of half of material (in case of hydrolytic kinetic resolution). Hence the asymmetric synthesis of β-blockers starting from prochiral substrates using catalytic enantioselective reactions, is still desirable. When the catalyst is available in both enantiomeric forms, the asymmetric synthesis is advantageous as both the stereoisomers can be synthesized from the same prochiral substrate. Also, the use of oragnocatalysis provides methods for obtaining chiral compounds in environmentally benign manner and from easily available starting materials.

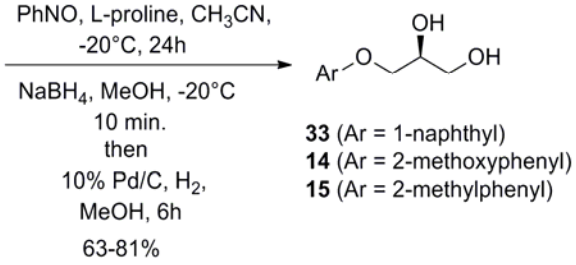


Scheme 11. Retrosynthetic analysis

According to proposed retrosynthetic analysis (**Scheme 11**), we envisaged that all above mentioned β-blockers and related drug molecules can be easily synthesized from corresponding phenols by synthetic manipulations with L-proline catalyzed asymmetric α-aminoxylation of aldehyde as key step.

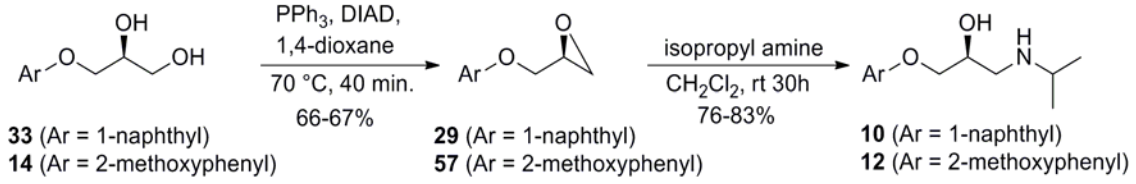
As per retrosynthetic analysis, as shown in **scheme 12**, we initiated synthesis from commercially available phenols (1-naphthol **64**, guaiacol **65** and *o*-cresol **66**). Phenols **64-66** on reflux with aqueous NaOH solution and 3-bromopropanol for 6 h furnished alcohols **61-63** in 67-78% yield. Oxidation of alcohols **61-63** was carried out with IBX in DMSO affording aldehydes **58-60** in 89-93% yield. Aldehydes **58-60** was then subjected to L-proline (20 mol%) catalyzed asymmetric α-aminoxylation with nitosobenzene at -20 °C for 24h and subsequently reduction was carried out with $NaBH_4$ in methanol. The crude aminoxy intermediates without purification was subjected to Pd/C catalyzed hydrogenolysis to obtain diols **33**, (*S*)-guaifenesin **14** and (*S*)-mephenesin **15** in 63-81% yields over two steps and >98% optical purity. The optical purity was determined with chiral HPLC analysis.





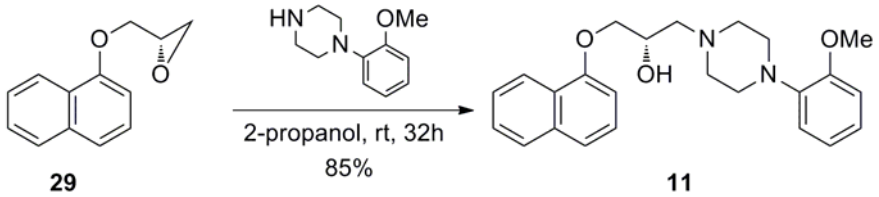
Scheme 12.

The diols **33** and **14** were then converted to epoxides **29** and **57** respectively under Mitsunobu reaction conditions using PPh_3 and DIAD in one step with 66-67% yield. The epoxides **29** and **57** then on stirring with isopropyl amine in CH_2Cl_2 at room temperature for 30 hours afforded (*S*)-propranolol (**10**) and (S)-moprolol (**12**) in 76-83% yield as shown in **scheme 13**.



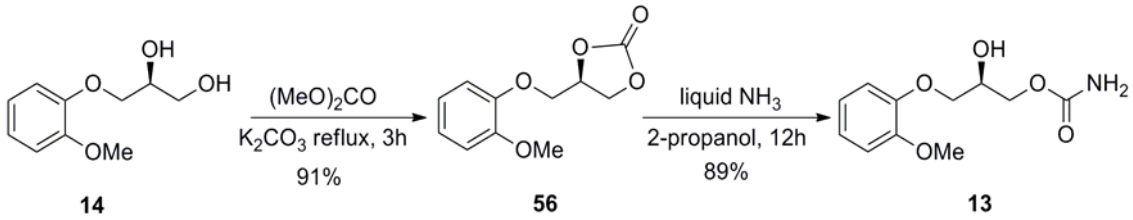
Scheme 13.

Synthesis of (*S*)-naftopidil **11** was accomplished from epoxide **29**. Epoxide **29** and 1-(2-methoxyphenyl)-piperazine was refluxed in 2-propanol for 32h, afforded (*S*)-naftopidil **11** in 85% yield and >98% ee (**Scheme 14**).



Scheme 14.

Finally synthesis of (*R*)-methocarbamol **13** was accomplished from (*S*)-guaifenesin **14** via cyclic carbonate **56**. Accordingly (*S*)-guaifenesin **14** on treatment with dimethyl carbonate and anhydrous K_2CO_3 under reflux conditions afforded cyclic carbonate **56** in 91% yield. The cyclic carbonate **56** on exposure to liquid ammonia in stoppered flask for 12h afforded (*R*)-methocarbamol **13** in 89% yield (**Scheme 15**). All compounds were well characterized and matching with literature one.



Scheme 15.

1.3.4 Conclusion

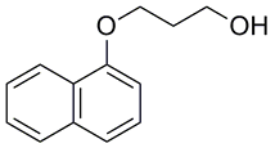
In conclusion, we have achieved highly enantioselective, efficient synthesis of the β-adrenergic blockers and related drug molecules: (*S*)-guaifenesin, (*S*)-mephenesin, (*S*)-(-)-propranolol, (*S*)-(+)-moprolol, (*S*)-(+)-naftopidil and (*R*)-(+)-methocarbamol employing proline catalyzed asymmetric α-aminoxylation of aldehyde as key step and source of chirality. Excellent yields, simple and environmental friendly procedures and the easy availability of starting materails are some of the salient features of this approach. Excellent yields, simple and environmental friendly procedures and the easy availability of starting materails are some of the merits of this approach.

1.3.5 Experimental

1) 3-(Arylxy)propanol

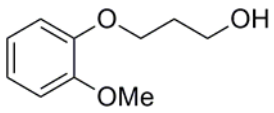
To a stirring solution of substituted phenol **64/65/66** (20 mmol) in 10% aqueous NaOH solution (20 mL) were added 3-bromopropanol (3.056 g, 22 mmol). After refluxing for 6h, the reaction mixture extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layer was washed with water (1 x 50 mL), brine, dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under reduced pressure. Resulting residue was purified by flash column chromatography (silica gel) using EtOAc-petroleum ether (15:85) as an eluent, affording the alcohol **61/62/63.**

(a) 3-(1'-Naphthoxy)propanol (61)



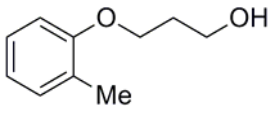
Yield: 2.706 g (67%); yellow oil; IR ($CHCl_3$) ν_{max} 3461, 3059, 3011, 2889, 2580, 1657, 1641, 1589, 735 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ= 1.64 (brs, 1H), 2.13-2.25 (m, 2H), 3.97 (t, *J*= 5.94Hz, 2H), 4.30 (t, *J*= 5.94Hz, 2H), 6.83 (d, *J*= 8.46 Hz, 1H), 7.32-7.52 (m, 4H), 7.76-7.84 (m, 1H), 8.18-8.26 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ= 31.8, 59.7, 64.9, 104.5, 120.1, 121.6, 125.0, 125.3, 125.7, 126.2, 127.3, 134.3, 154.3 ppm.

(b) 3-(2-Methoxyphenoxy)propanol (62)



Yield: 2.839 g (78%); yellow oil; ^1H NMR (200 MHz, $CDCl_3$): δ= 2.05-2.17 (m, 2H), 2.36 (brs, 1H), 3.84 (s, 3H), 3.87 (t, 2H), 4.23 (t, *J*=5.81 Hz, 2H), 6.88-7.01 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ= 31.47, 55.41, 60.25, 67.18, 111.27, 112.86, 120.54, 120.94, 147.85, 148.96 ppm.

(c) 3-(2-Methylphenoxy)propanol (63)

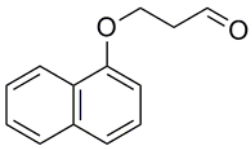


Yield: 2.357 g (71%); yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ= 2.01-2.13 (m, 2H), 2.22 (s, 3H), 3.88 (t, *J*= 6 Hz, 2H), 4.12 (t, *J*= 6 Hz, 2H), 6.82-6.91 (m, 2H), 7.12-7.20 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=15.85, 31.81, 59.29, 64.59, 110.52, 120.02, 126.11, 126.48, 130.25, 156.58 ppm.

2) 3-(Aryloxy)propanal

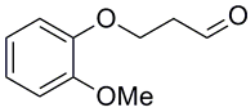
To solution of alcohol **61/62/63** in anhydrous dimethyl sulfoxide was added IBX (1.5 equi). After stirring at room temperature for 2h, the reaction mixture was diluted with water (10 mL), then with diethyl ether (100 mL). The diethyl ether layer was filtered through a bed of celite. The filtrate was washed with water (50 mL), brine, dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under reduced pressure to afford aldehyde **58/59/60**.

(a) 3-(1'-Naphthoxy)propanal (58)



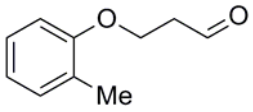
Yield: 2.202 g (89%); yellow oil; IR ($CHCl_3$) ν_{max} 3061, 3011, 2957, 2837, 2356, 2045, 1721, 1587, 1511, 1257, 749 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ= 2.99-3.06 (m, 2H), 4.48 (t, *J*= 6.07 Hz, 2H), 6.84 (d, *J*= 8.47 Hz, 1H), 7.33-7.53 (m, 4H), 7.76-7.84 (m, 1H), 8.14-8.22 (m, 1H), 9.94 (t, *J*=1.64 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ= 43.0, 61.7, 104.6, 120.6, 121.7, 125.2, 125.3, 125.6, 126.4, 127.3, 134.3, 153.9, 200.1 ppm.

(b) 3-(2-Methoxyphenoxy)propanal (59)



Yield: 2.483 g (93%); yellow oil; IR ($CHCl_3$): 3067, 3009, 2951, 2835, 2358, 2042, 1723, 1593, 1504, 1260, 751 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ= 2.92-2.99 (m, 2H), 3.83 (s, 3H), 4.35 (t, *J*=6.32 Hz, 2H), 6.88-6.97 (m, 4H), 9.88 (t, *J*= 1.39 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ= 43.19, 55.75, 62.91, 111.94, 114.15, 120.81, 121.86, 147.71, 149.58, 200.37 ppm.

(c) 3-(2-Methylphenoxy)propanal (60)

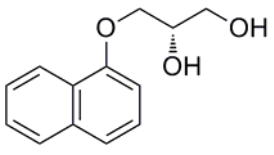


Yield: 1.866 g (90%); yellow oil; IR ($CHCl_3$): 3064, 3004, 2958, 2837, 2358, 2046, 1725, 1593, 1504, 1253, 744 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ= 2.17 (s, 3H), 2.87-2.94 (m, 2H), 4.32 (t, *J*= 6 Hz, 2H), 6.82-6.91 (m, 2H), 7.11-7.20 (m, 2H), 9.88 (t, *J*= 1.77 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=15.85, 43.00, 61.44, 110.76, 110.95, 120.59, 126.59, 130.50, 156.30, 200.36 ppm.

3) (S)-3-(Aryloxy)propane-1,2-diol

To a solution of aldehyde **58/59/60** (10 mmol) and nitrosobenzene (1.070 g, 10 mmol) in CH_3CN (50 mL) was added L-proline (0.230 g, 2 mmol, 20 mol %) at -20°C. The reaction mixture was allowed to stir at the same temperature for 24 h followed by addition of MeOH (25 mL) and $NaBH_4$ (0.570 g, 15 mmol) to the reaction mixture, which was stirred for 10 min. After addition of phosphate buffer, the resulting mixture was extracted with EtOAc (3 x 50 mL) and the combined organic phases were dried over Na_2SO_4, filtered and concentrated on rotary evaporator under reduced pressure to afford crude aminoxy alcohol. To a solution of crude aminoxy alcohol in MeOH was added 10% Pd/C (100 mg) carefully. The reaction mixture was then stirred in a hydrogen atmosphere (1 atm of H_2) for 6 h. After completion of the reaction (monitored by TLC), the reaction mixture was filtered through a celite pad and then concentrated to near dryness. Purification by flash column chromatography (silica gel) using EtOAc-petroleum ether (40:60) as an eluent afforded diol **33/14/15**.

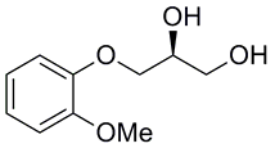
(a) (*S*)-3-(1'-Naphthoxy)propane-1,2-diol (33)



Yield: 1.722 g (79%); white solid; mp 113-115°C; $[\alpha]_{25}^{D}$ +6.69 (*c* 1.05 MeOH); ee >98% [Chiral HPLC analysis: Kromasil 5-Cellucoat (250 x 4.6 mm) column; eluent: ethanol: hexane 20:80; flow rate: 0.5 mL/min., detector: 254 nm t_R=15.13 min., t_S= 16.85 min.]; IR ($CHCl_3$) ν_{max} 3443, 3024, 2887, 2589, 1647, 1635, 1597, 735 cm^{-1}; ^1H

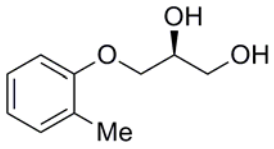
NMR (400 MHz, $CDCl_3$): δ= 2.34 (brs, 2H), 3.84-3.97 (m, 2H), 4.22-4.24 (m, 2H), 4.26-4.31 (m, 1H), 6.83 (d, *J*= 7.53 Hz, 1H), 7.36-7.40 (m, 1H), 7.46-7.53 (m, 4H), 7.81-7.83 (m, 1H), 8.21-8.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 63.8, 69.2, 70.5, 105.0, 120.9, 121.5, 125.3, 125.4, 125.7, 126.5, 127.6, 134.5, 154.0 ppm. Elemental Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.47; H, 6.39.

(b) (*S*)-3-(2'-methoyphenoxy)propane-1,2-diol or (*S*)-Guaifenesin (14)



Yield: 1.871 g (81%); white crystals; mp 101-103°C; $[\alpha]_{25}^{D}$ +8.41 (*c* 1.10, MeOH); ee >99% [Chiral HPLC analysis: Kromasil 5-Cellucoat (250 x 4.6 mm) column; eluent: ethanol: hexane 20:80; flow rate: 0.5 mL/min., detector: 254 nm t_R=17.60 min., t_S= 18.67 min.]; IR ($CHCl_3$): 3390, 3018, 2957, 2859, 2400, 1711, 1460, 1362, 1216, 1093, 927, 837, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ= 3.73-3.82 (m, 2H), 3.84 (s, 3H), 4.01-4.08 (m, 2H), 4.10-4.13 (m, 1H), 6.86-6.91 (m, 3H), 6.93-6.97 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 55.75, 63.80, 70.00, 72.02, 111.74, 114.60, 121.06, 122.11, 147.90, 149.53 ppm; LC-MS: *m/z* = 199.14 (M^+ + 1), 221.14 (M^+ + Na); Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.54; H, 7.14.

(c) (*S*)-3-(2'-methylphenoxy)propane-1,2-diol or (*S*)-Mephenesin (15)

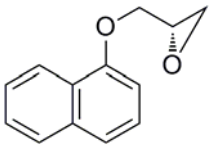


Yield: 0.880 g (88%); white crystals; mp 70-71°C; $[\alpha]_{25}^{D}$= -19.16 (*c* 0.910, Hexane: 2-propanol 4:1); ee >98% [Chiral HPLC analysis: Chiralcel OD (250 x 4.6 mm) column; eluent: 2-propanol: petroleum ether 7.5:92.5; flow rate: 1 mL/min., detector: 220 nm t_R=15.85 min., t_S= 18.18 min.]; IR ($CHCl_3$): 3448, 3064, 3004, 2881, 2580, 1652, 1647, 1593, 742 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ= 1.63 (brs, 2H), 2.22 (s, 3H), 3.73-3.91 (m, 2H), 4.03-4.13 (m, 3H), 6.80-6.92 (m, 2H), 7.12-7.19 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=16.17, 63.79, 68.97, 70.54, 111.06, 120.93, 126.58, 126.87, 130.74, 156.37 ppm; LC-MS: *m/z* = 205.16 (M^+ + Na); Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.87; H, 7.76.

(4) (*S*)-2-((Aryloxy)-methyl)oxirane

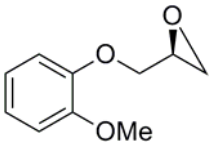
To solution of diol **33**/**14** (6.88 mmol) in anhydrous 1,4-dioxane (25 mL) was added PPh_3 (2.703 g, 10.32 mmol, 1.5 equi) at stirred at 70°C for 10 minutes. Diisopropyl azodicarboxylate (2.084 g, 10.32 mmol, 1.5 equi) diluted in 20 mL anhydrous 1,4-dioxane was added dropwise and the reaction mixture was stirred at same temperature for further 40 minutes. The reaction mixture was cooled to room temperature, washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under reduced pressure. Purification by flash column chromatography (silica gel) using EtOAc-petroleum ether (15:85) as an eluent afforded epoxide **29/57**.

(a) (*S*)-2-((1'-Naphthoxy)-methyl)oxirane (29)



Yield: 0.921 g (67%); yellow oil; $[\alpha]_{25}^{D}$ -33.97 (*c* 1.52, MeOH) {Lit.[7i] $[\alpha]_{25}^{D}$ -33.9 (*c* 1.55, MeOH)}; IR ($CHCl_3$) ν_{max} 3443, 3420, 3031, 1265 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ= 2.84-2.88 (dd, *J*= 2.6, 4.9 Hz, 1H), 2.95-2.99 (m, 1H), 3.46-3.54 (m, 1H), 4.10-4.18 (dd, *J*= 5.5, 11.1 Hz, 1H), 4.37-4.44 (dd, *J*= 3.1, 10.9 Hz, 1H), 6.80 (d, *J*= 7.3 Hz, 1H), 7.32-7.53 (m, 4H), 7.76-7.84 (m, 1H), 8.26-8.34 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ= 44.4, 50.0, 68.7, 104.8, 120.6, 121.9, 125.1, 125.4, 125.6, 126.3, 127.3, 134.3, 154.0 ppm.

(b) (*S*)-2-((2'-methoyphenoxy)-methyl)oxirane (57)

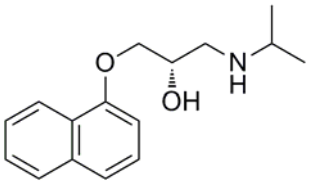


Yield: 0.509 g (66%); colourless oil; $[\alpha]_{25}^{D}$ +9.98 (*c* 1.2, EtOH) {Lit.[2f] $[\alpha]_{25}^{D}$ +9.83 (*c*, 1.2, EtOH)}; IR ($CHCl_3$): 3011, 2952, 1613, 1513, 1435, 1243, 1159, 827, 753 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ= 2.72 (dd, *J*= 2.6, 4.9 Hz, 1H), 2.89 (t, *J*= 4.9 Hz, 1H), 3.35–3.43 (m, 1H), 3.86 (s, 3H), 3.99 (dd, *J*= 5.5, 11.3 Hz, 1H), 4.20 (dd, *J*= 3.6, 11.3 Hz, 1H), 6.84–7.00 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ= 44.8, 50.1, 55.7, 70.0, 111.8, 114.1, 120.7, 121.8, 147.8, 149.5 ppm.

(5) (*S*)-1-(isopropylamino)-3-(1'-aryloxy)propan-2-ol

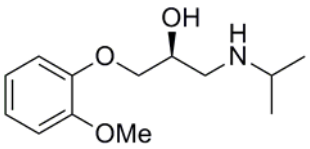
To a stirring solution of epoxide **29/57** (2.5 mmol) in 10 mL dichloromethane was added slowly isopropyl amine (1.475 g, 25 mmol). The reaction mixture was stirred for 30 hours at room temperature, then excess isopropyl amine was removed under reduced pressure. The residue was diluted with water and extracted with EtOAc (2 x 25 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator under reduced pressure. Purification by flash column chromatography (silica gel) using EtOAc-petroleum ether (75:25) as an eluent afforded **10/12**.

(a) (*S*)-1-(isopropylamino)-3-(1'-naphthoxy)propan-2-ol or (*S*)-Propranolol (10)



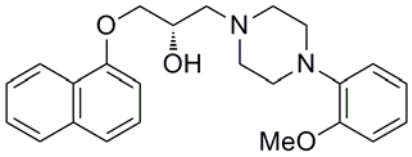
Yield: 0.537 g (83%), white solid; mp 71-72°C; $[\alpha]_{25}^{D}$ -9.78 (*c* 0.55, EtOH) { Lit.[27] $[\alpha]_{20}^{D}$ -9.9 (*c* 0.5, EtOH)}; IR ($CHCl_3$) ν_{max} 3410, 3281, 3011, 2989, 1271 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ= 1.23 (d, *J* = 6.2 Hz, 6 H), 2.90–3.13 (m, 3H), 4.05-4.21 (m, 2H), 4.35-4.46 (m, 1H), 5.14 (brs, 2H), 6.73 (d, *J* = 7.2 Hz, 1H), 7.25-7.50 (m, 4H), 7.74-7.81 (m, 1H), 8.20-8.26 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ= 21.4, 49.0, 49.5, 67.4, 70.3, 104.8, 120.4, 121.7, 125.1, 125.3, 125.6, 126.2, 127.3, 134.2, 154.0 ppm; LC-MS: *m/z* = 260.17 (M^+ + 1), 282.20 (M^+ + Na).

(b) (*S*)-1-(isopropylamino)-3-(2'-methoyphenoxy)propan-2-ol or ((*S*)-Moprolol (12)



Yield: 0.252 g (76%), white solid, mp 82-83 °C; $[\alpha]_{25}^{D}$ -5.69 (*c*, 4.54, EtOH) {Lit.[24] $[\alpha]_{20}^{D}$ -5.6 (*c*, 4.5, EtOH)}; ^1H NMR (200 MHz, $CDCl_3$): δ= 1.09 (d, *J*= 6.3 Hz, 6H), 2.74–2.95 (m, 3H), 3.80 (s, 3H), 3.97-4.00 (m, 2H), 4.12-4.18 (m, 1H), 4.26 (brs, 2H), 6.76–6.95 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ= 22.0, 48.9, 49.1, 55.5, 67.5, 72.3, 111.6, 114.1, 120.7, 121.4, 147.9, 149.3 ppm; LC-MS: *m/z* = 240.26 (M^+ + 1).

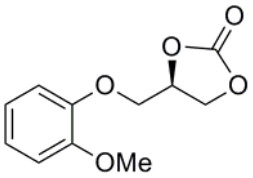
6) (*S*)-1-[4-(2'-methoxyphenyl)-piperazin-1-yl]-3-(1'-naphthoxy)-2-propanol or (*S*)-(+)-Naftopidil (11)



To a solution of epoxide **29** (0.400 g, 2 mmol) in anhydrous 2-propanol (10 mL) was added 1-(2-methoxyphenyl) piperazine (0.384 g, 2 mmol, 1 equi) and the reaction mixture was refluxed for 32 hours. After completion of reaction, the solvent was removed under reduced pressure and purification by flash column chromatography (silica gel) using EtOAc-petroleum ether (60:40) as an eluent afforded (*S*)-(+)-naftopidil **11**.

Yield: 0.666 g (85%); yellow solid; mp 126-127°C; $[\alpha]_{25}^{D}$ +4.66 (*c* 1.55, MeOH) {Lit.[26] $[\alpha]^{D}$ +4.5 (*c* 1.5, MeOH)}; IR ($CHCl_3$) ν_{max} 3403, 3031, 2977, 2907, 1261, 1225 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ= 2.70-2.79 (m, 4H), 2.94 (t, *J*= 5.2 Hz, 2H), 3.10-3.18 (m, 4H), 3.87 (s, 3H), 4.15-4.19 (dd, *J*= 5.0, 9.5 Hz, 1H), 4.21-4.25 (dd, *J*= 5.0, 9.5 Hz, 1H), 4.28-4.34 (m, 1H), 6.84-6.89 (m, 2H), 6.92-6.97 (m, 2H), 7.01-7.04 (m, 1H), 7.36-7.40 (m, 1H), 7.44-7.50 (m, 3H), 7.80-7.82 (m, 1H), 8.29 (d, *J*= 4.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 50.6, 53.5, 55.3, 60.8, 65.5, 70.4, 104.8, 111.1, 118.1, 120.5, 120.9, 121.8, 122.9, 125.1, 125.5, 125.7, 126.3, 127.4, 134.4, 141.0, 152.1, 154.3 ppm. LC-MS: *m/z* = 393.36 (M^+ + 1), 415.36 (M^+ + Na). Elemental Anal. Calcd for $C_{24}H_{28}N_2O_3$: C, 73.44; H, 7.19; N, 7.14. Found: C, 73.41; H, 7.14; N, 7.18.

7) (*R*)-4-((2-methoxyphenoxy)methyl)-1,3-dioxolan-2-one (56)

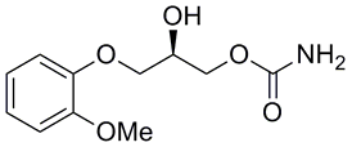


To a stirred mixture of diol **33** (0.500 g, 2.52 mmol) and dimethyl carbonate (0.681 g, 7.56 mmol) was added K_2CO_3 (0.010 g, 0.075 mmol) and then refulxed (73-75°C) for 3 h. Then methanol formed and excess dimethyl carbonate were distilled off under reduced pressure. The residue was extracted with dichloromethane (2 x 25 mL). The combined organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography

(silica gel) using EtOAc-petroleum ether (10:90) as an eluent afforded cyclic carbonate **56**.

Yield: 0.514 g (91%), white solid, mp 89-90 °C; $[\alpha]_{25}^{D}$ +17.3 (*c*, 1, EtOH) {Lit.[28] $[\alpha]_{22}^{D}$ +17.7 (*c*, 1, EtOH)}; IR ($CHCl_3$): 3021, 2968, 2400, 1797, 1465, 1362, 1213, 1097, 917, 831, 664 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ= 3.82 (s, 3H), 4.17-4.22 (m, 2H), 4.58 (d, *J* = 6.7 Hz, 2H), 4.96-5.02 (m, 1H), 6.86-7.02 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 55.7, 66.2, 69.1, 74.4, 112.3, 116.4, 120.9, 123.3, 147.3, 150.2, 154.7 ppm; LC-MS: *m/z* = 247.07 (M^+ + Na).

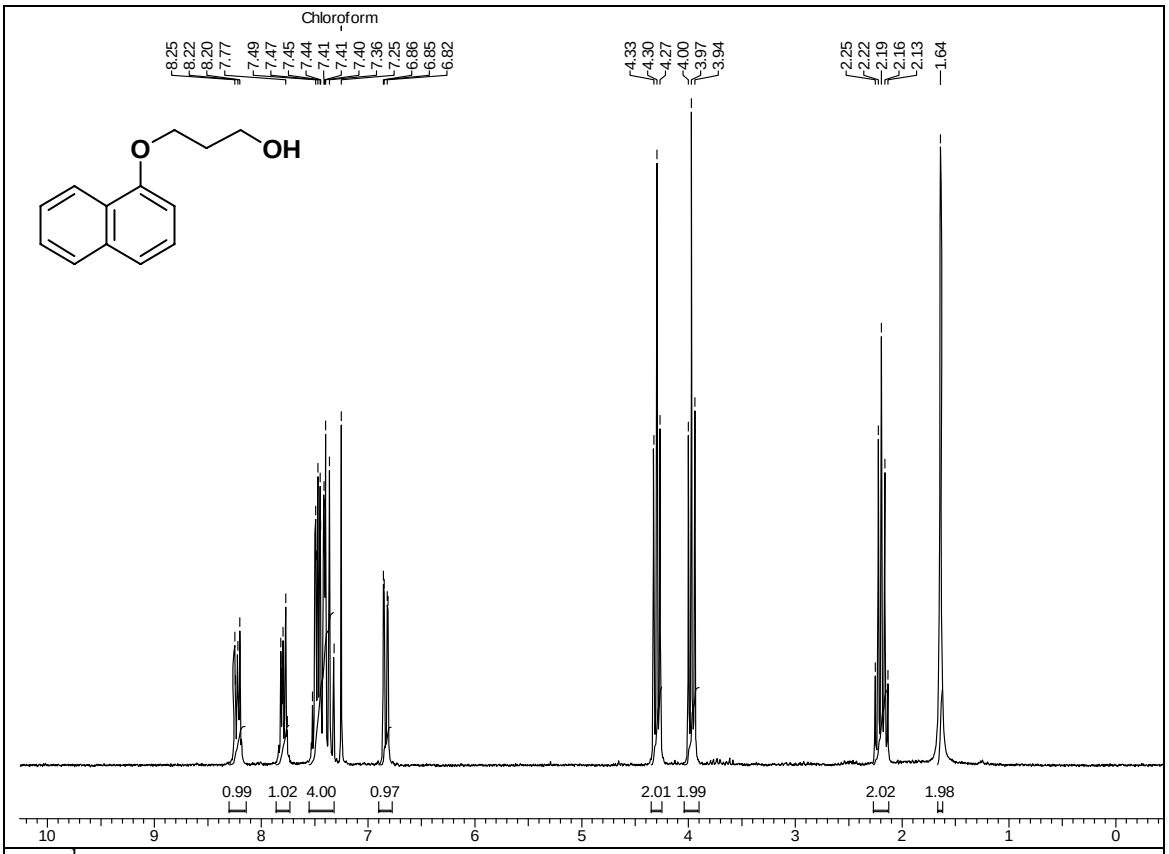
8) (*R*)-1-Carbamoyloxy-2-hydroxy-3-(2-methoxyphenoxy)propane or (*R*)-Methocarbamol (13)



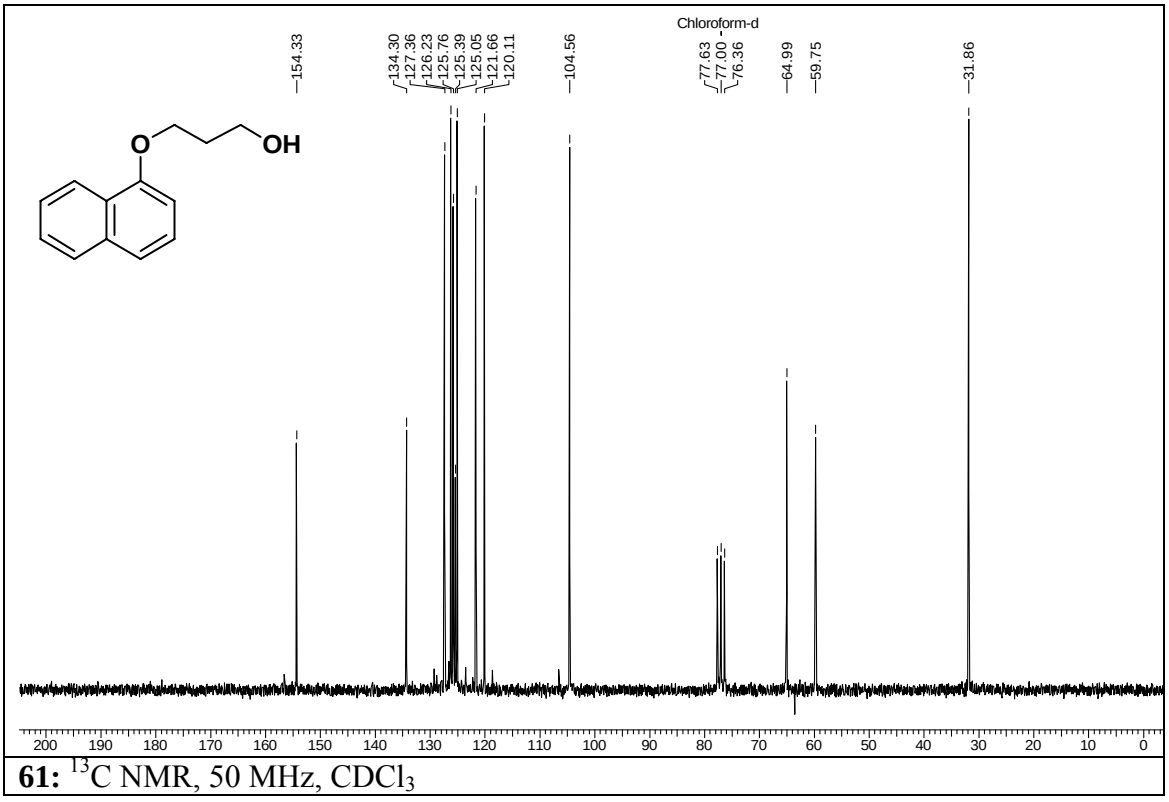
To a room temperature stirring solution of carbonate **56** (0.527 g, 2.35 mmol) in 2-propanol (5 mL) was added liquid ammonia (0.25 mL). The resultant mixture was stirred for 12h in tightly stoppered manner. Evaporation of 2-propanol and excess ammonia under reduced pressure, followed by recrystallization of residue from ethyl acetate afforded **13**.

Yield: 0.505 g (89%), white solid, mp 113-114 °C; $[\alpha]_{25}^{D}$ +0.78 (*c*, 1, MeOH) {Lit.[28] $[\alpha]_{22}^{D}$ +0.5 (*c*, 1, MeOH)}; ^1H NMR (200 MHz, $CDCl_3$): δ= 3.78 (s, 3H), 3.93-4.10 (m, 5H), 5.25 (brs, 1H), 6.56 (brs, 2H), 6.84-7.00 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 55.6, 65.1, 67.4, 70.2, 112.4, 113.8, 120.9, 121.3, 148.2, 149.3, 156.9 ppm; Anal. Calcd for $C_{11}H_{15}NO_5$: C, 54.77; H, 6.27; N, 5.81. Found: C, 55.69; H, 6.31; N, 5.79; LC-MS: *m/z* = 264.05 (M^+ + Na).

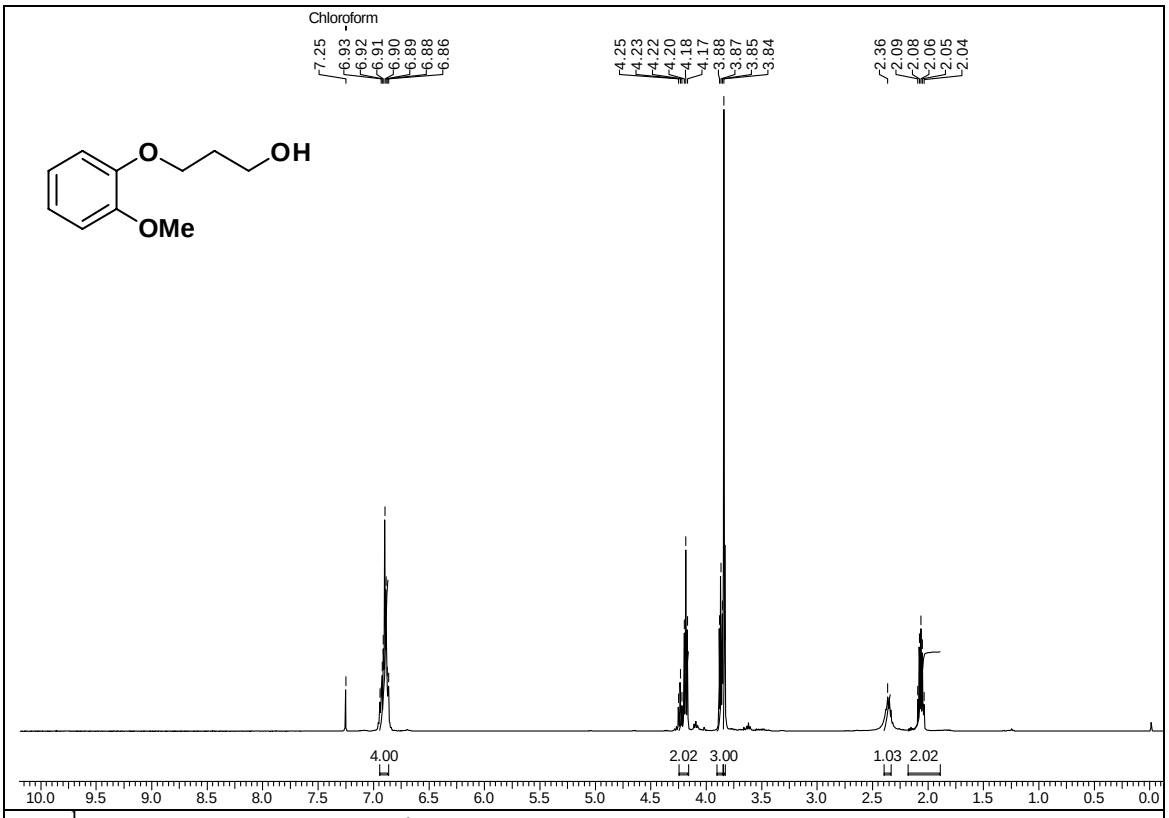
1.3.6 Analytical Data



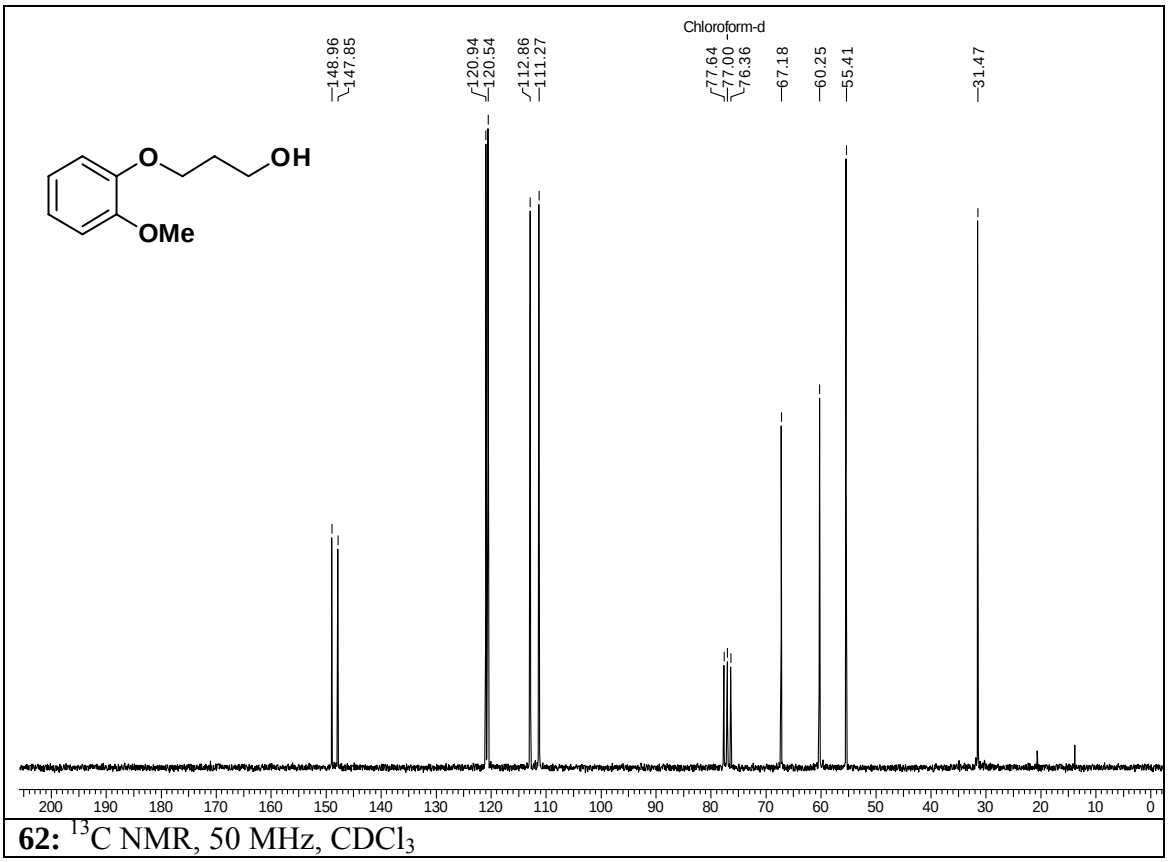
61: ^{1}H NMR, 200 MHz, $CDCl_3$



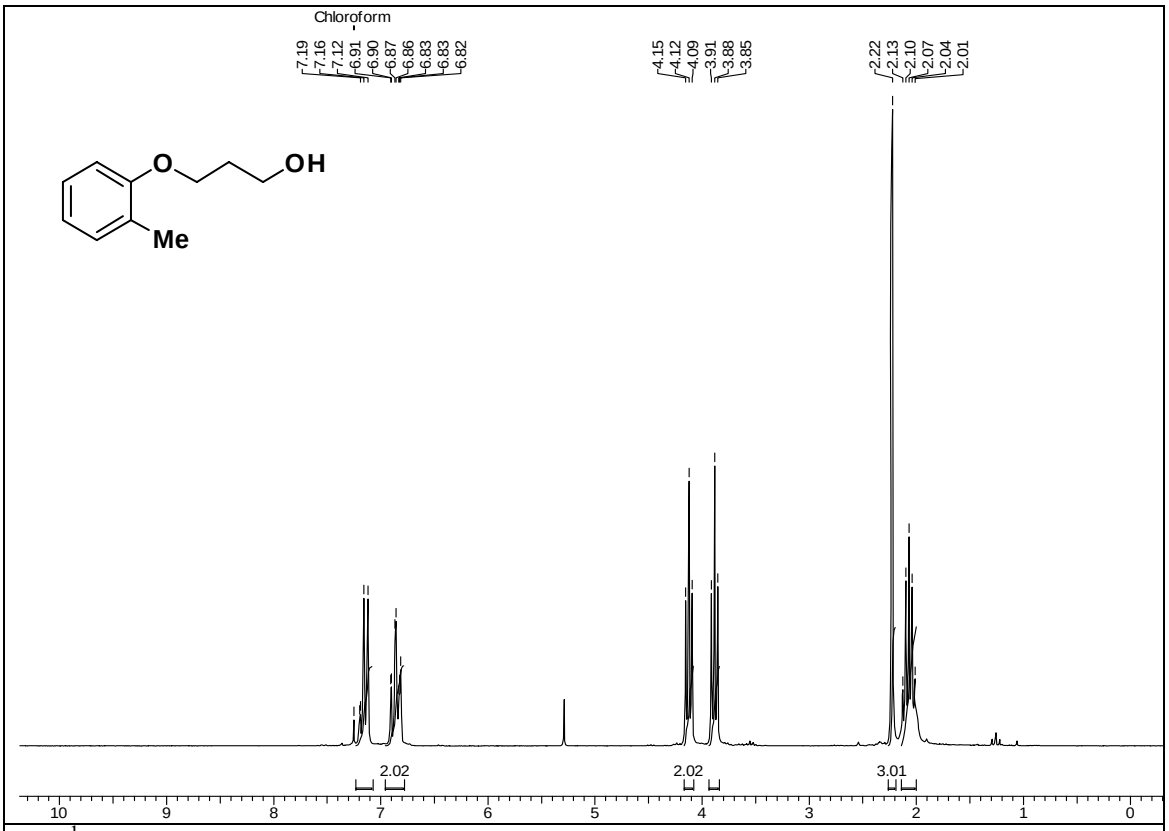
61: ^{13}C NMR, 50 MHz, $CDCl_3$



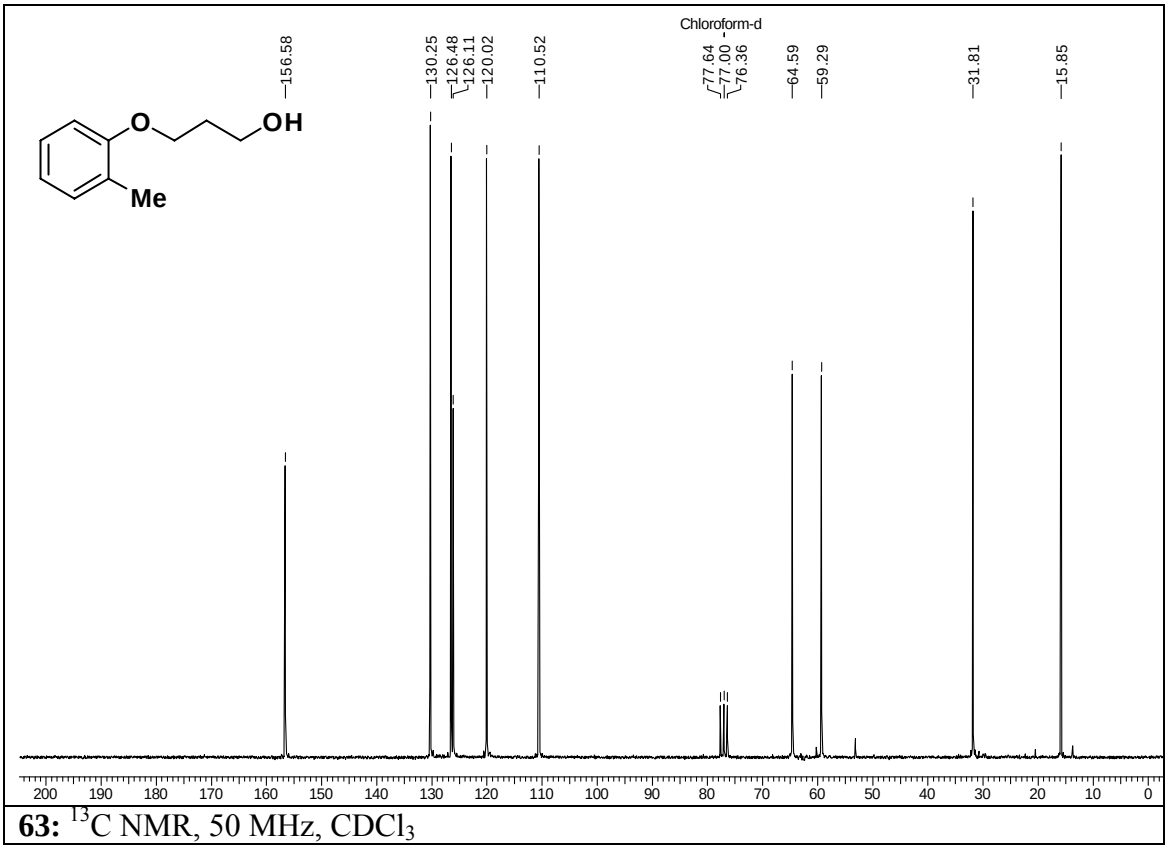
62: ^{1}H NMR, 200 MHz, $CDCl_3$



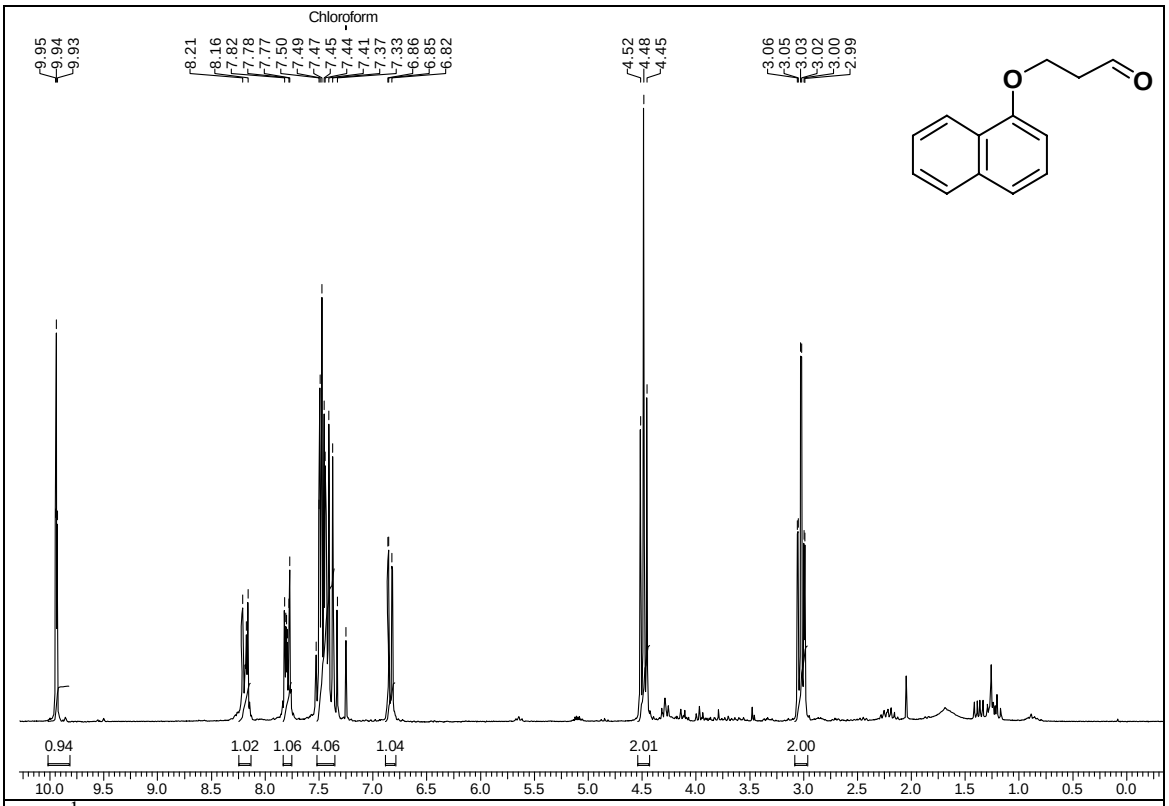
62: ^{13}C NMR, 50 MHz, $CDCl_3$



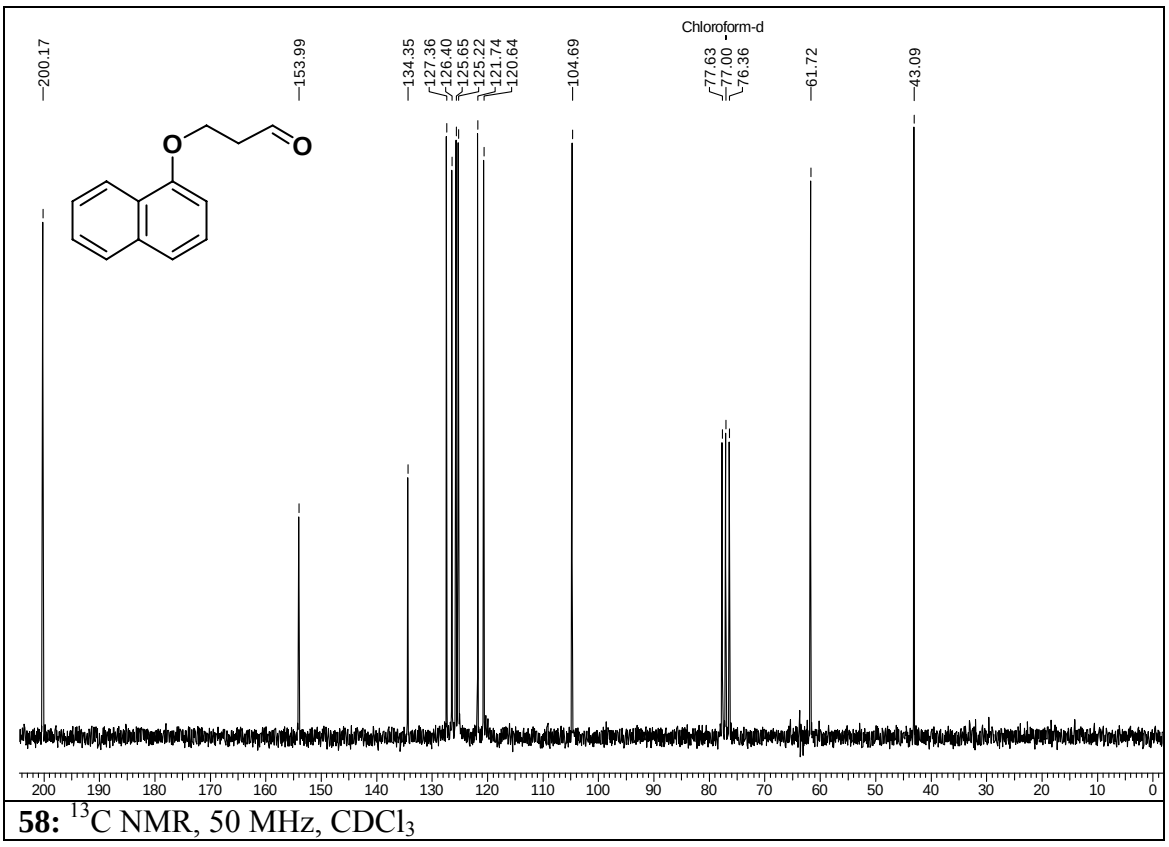
63: ^{1}H NMR, 200 MHz, $CDCl_3$



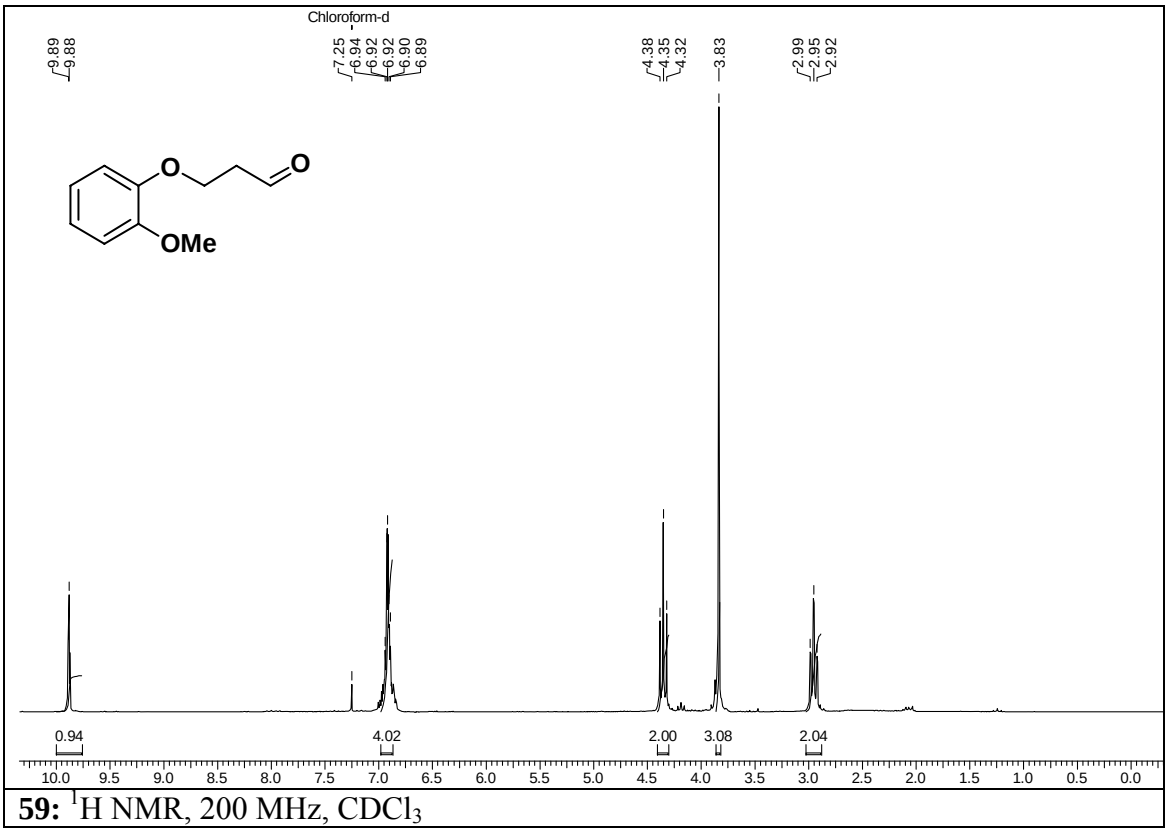
63: ^{13}C NMR, 50 MHz, $CDCl_3$



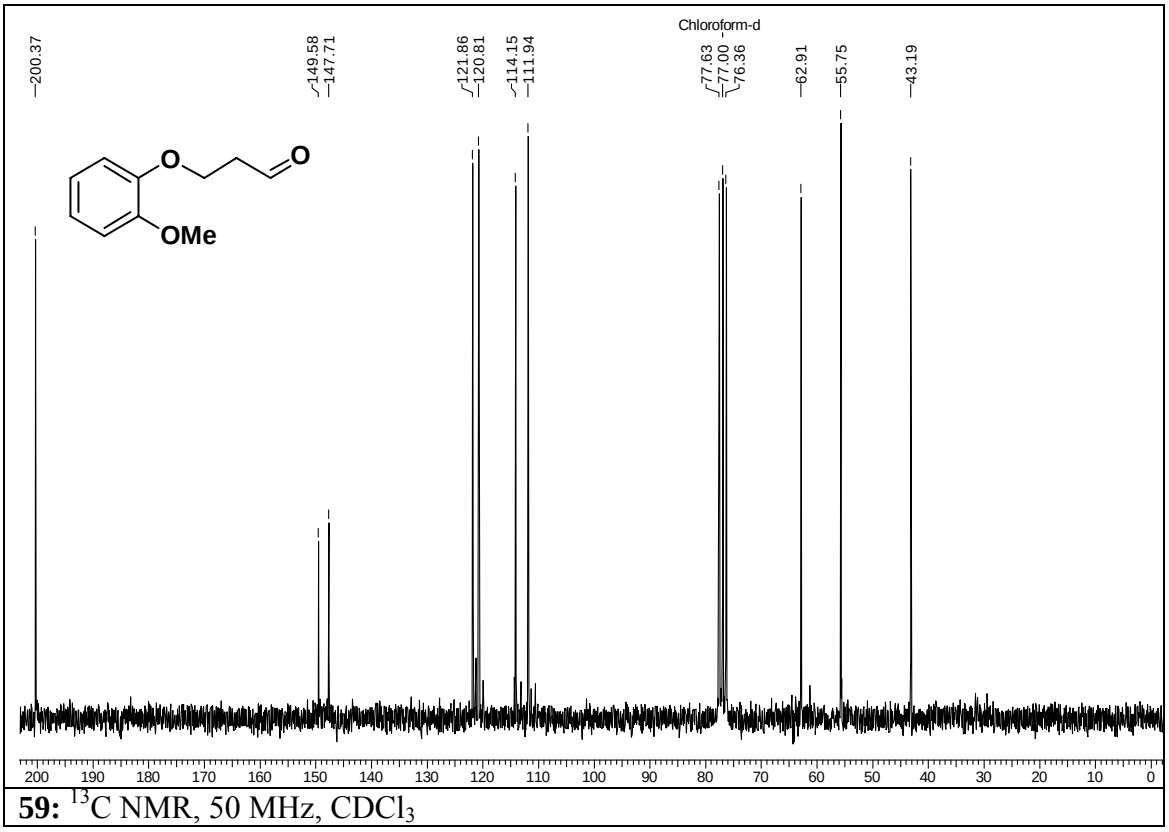
58: ^{1}H NMR, 200 MHz, $CDCl_3$



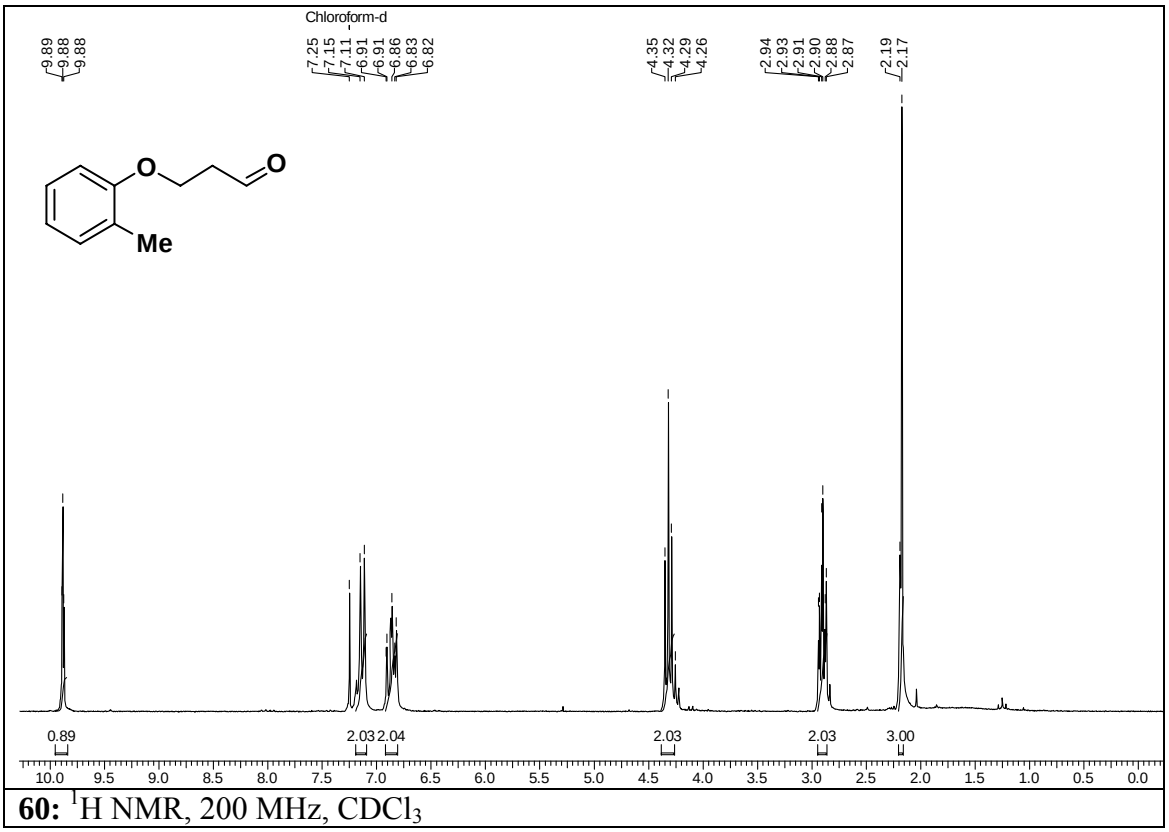
58: ^{13}C NMR, 50 MHz, $CDCl_3$



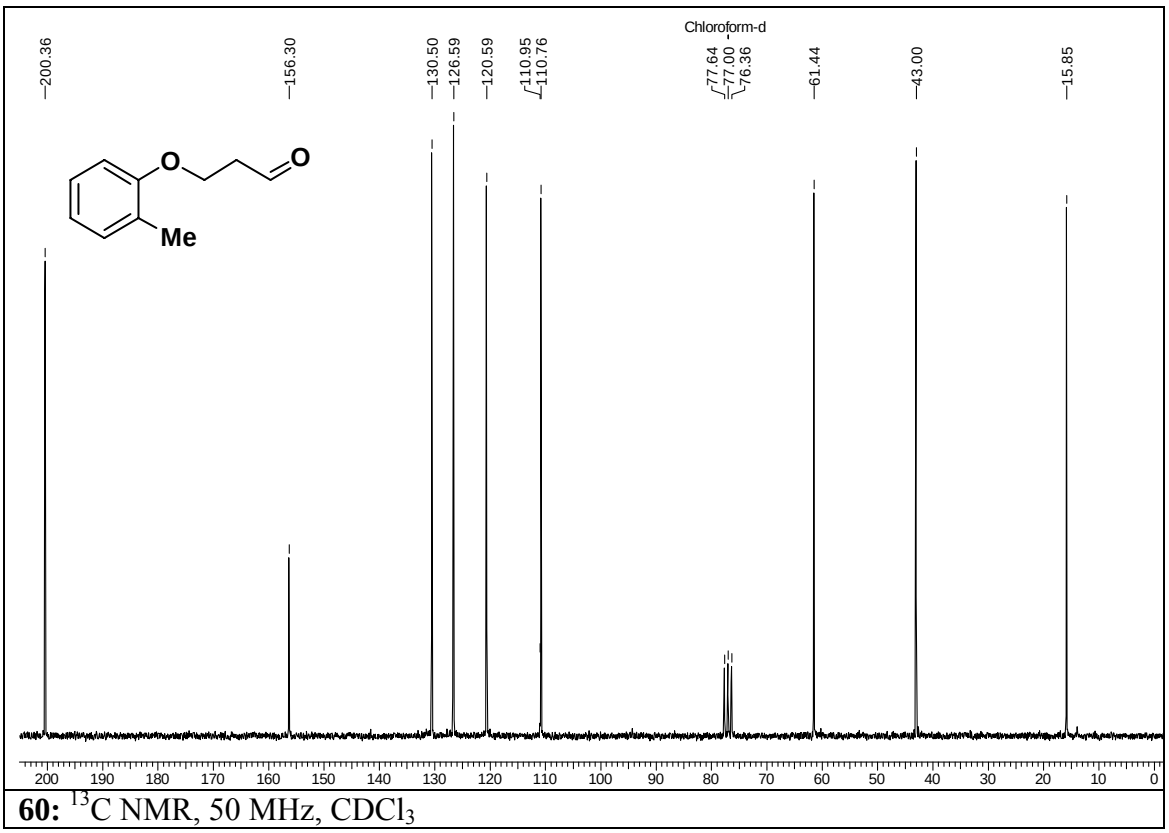
59: ^{1}H NMR, 200 MHz, $CDCl_3$



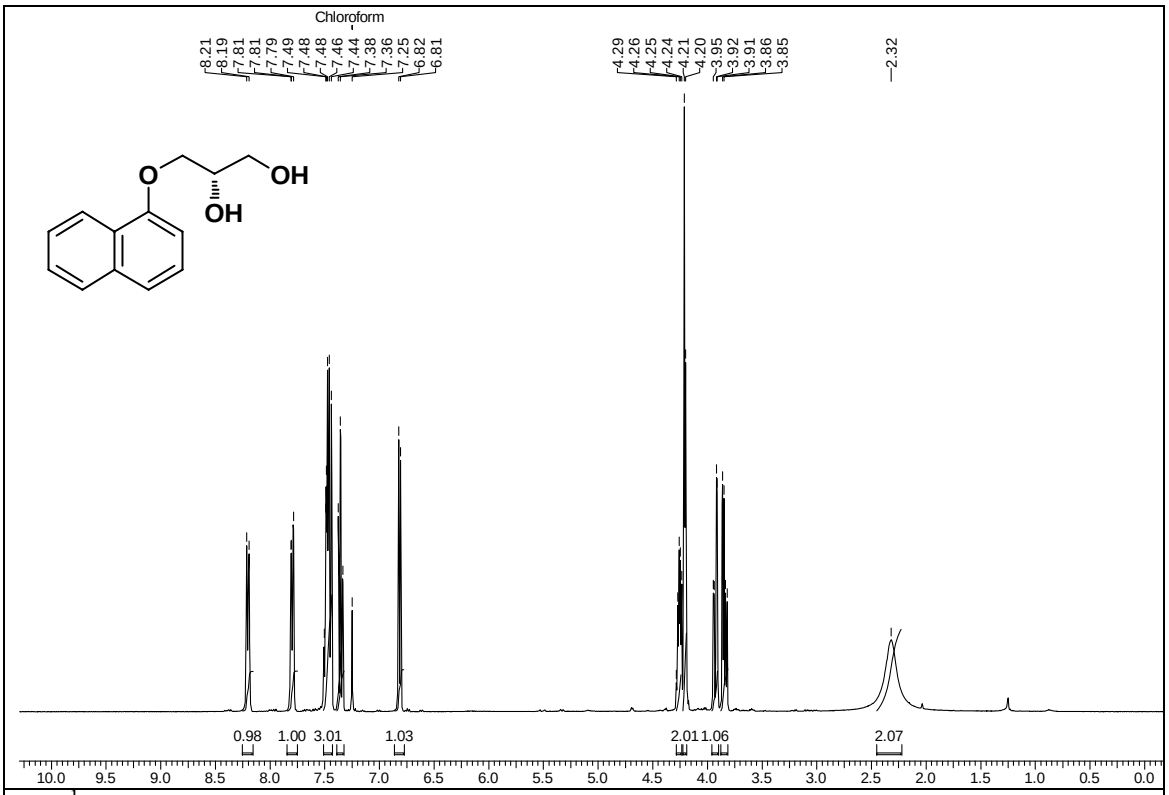
59: ^{13}C NMR, 50 MHz, $CDCl_3$



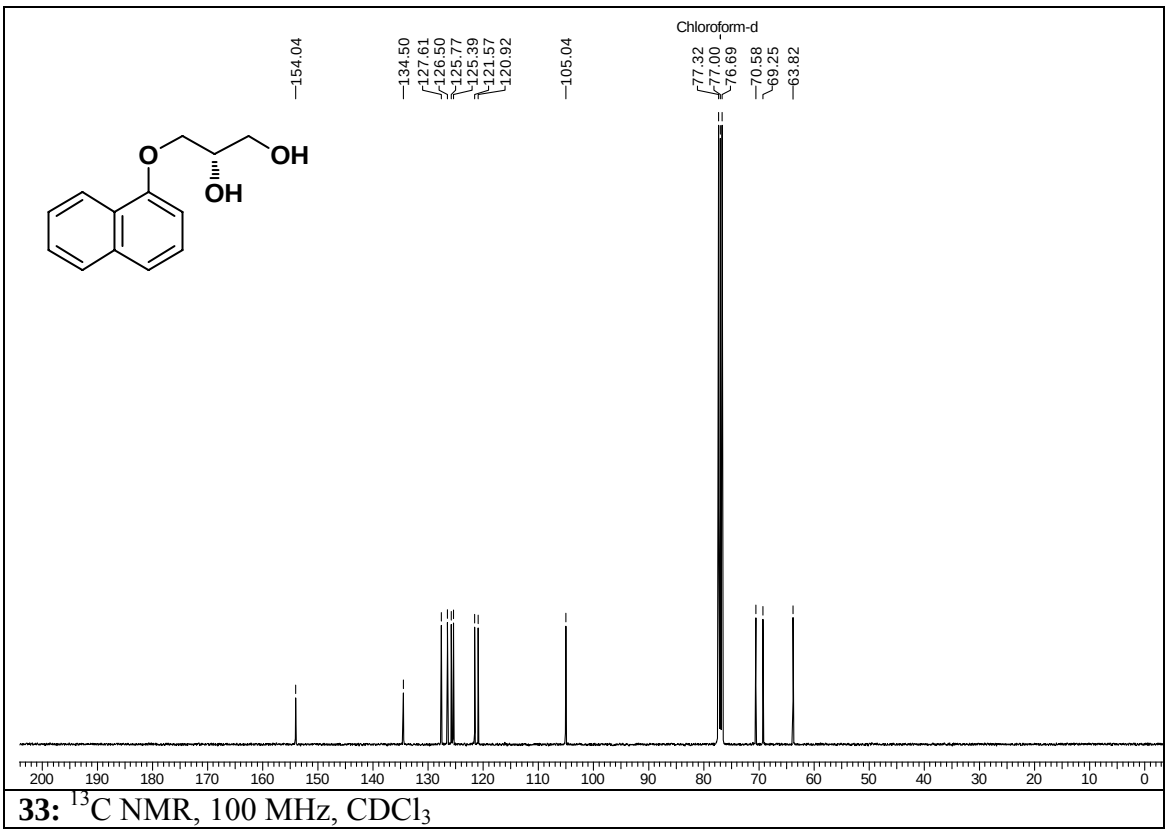
60: ^{1}H NMR, 200 MHz, $CDCl_3$



60: ^{13}C NMR, 50 MHz, $CDCl_3$

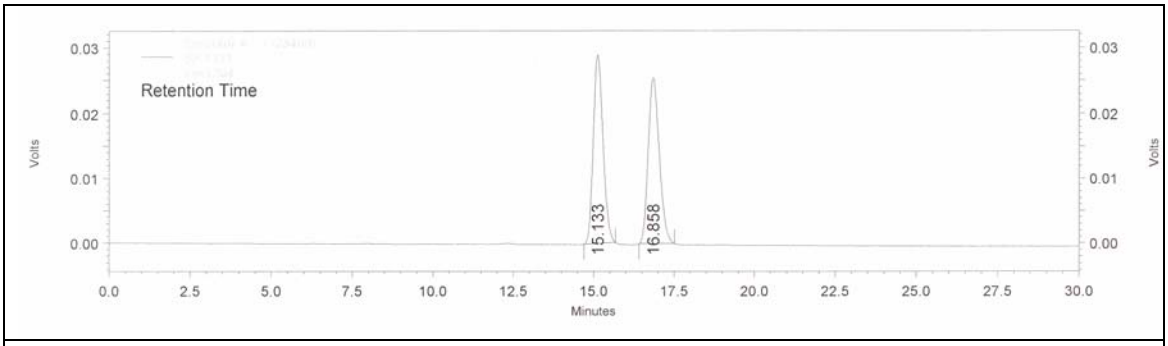


33: ^{1}H NMR, 400 MHz, $CDCl_3$



33: ^{13}C NMR, 100 MHz, $CDCl_3$

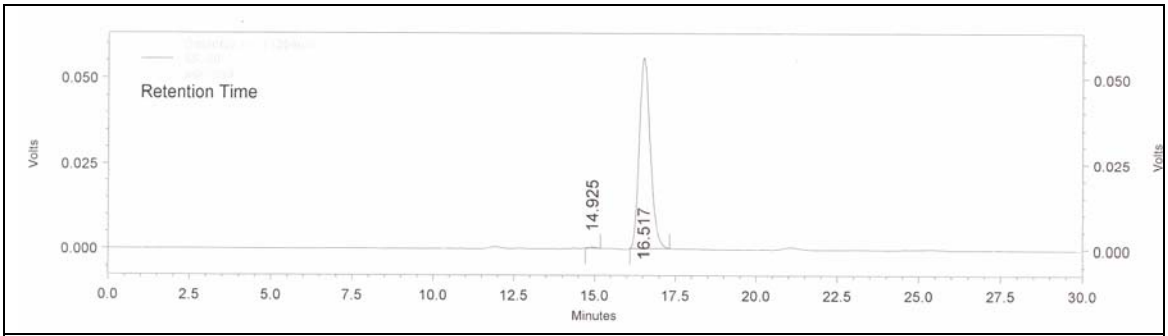
Chiral HPLC Analysis of compound 33



Racemic sample chromatograph

Pk #	Retention Time	Area	Area %	Height	Height Percent
1	15.133	615876	49.979	29004	53.21
2	16.858	616391	50.021	25506	46.79
Totals		1232267	100.000	54510	100.00

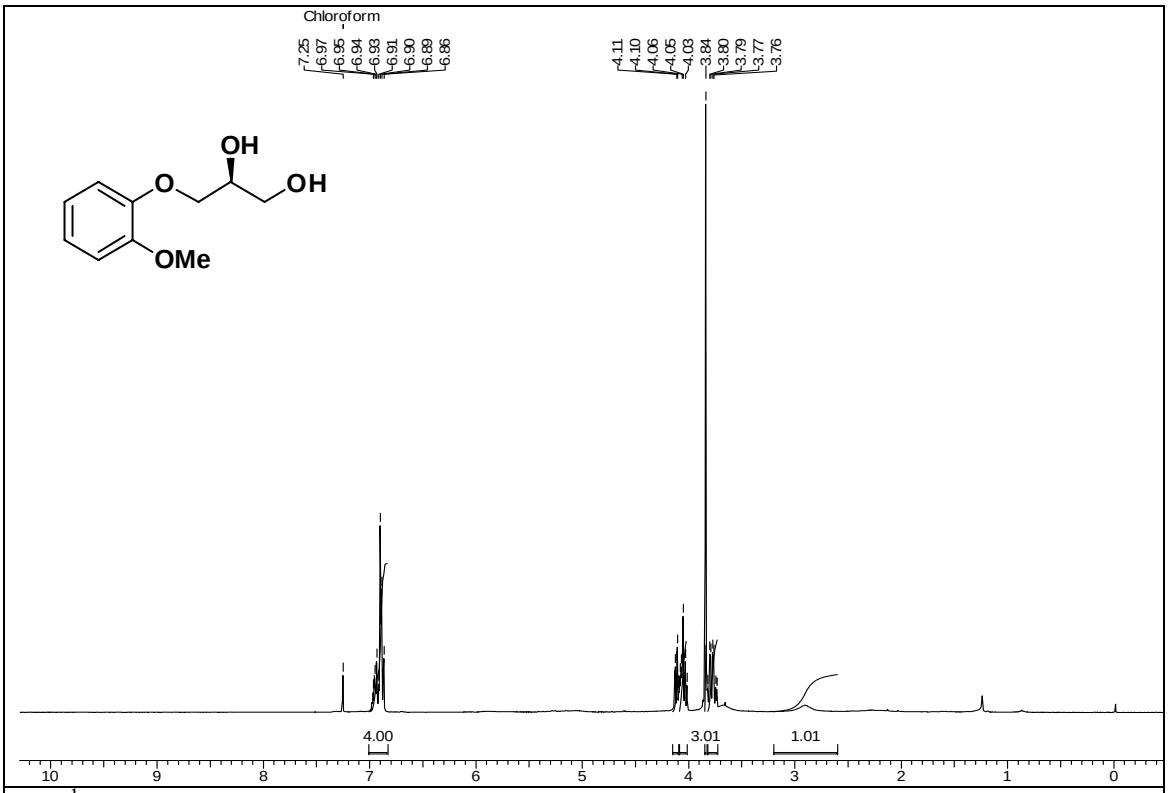
Column : Kromasil-5-Cellucoat (250 x 4.6mm)
Mobile phase : Ethanol + Hexane (20:80)
Wavelenth : 254 nm
Flow : 0.5 mL/min
Concentration : 1.03 mg/1.0 mL mobile phase
Injection vol. : 10 µL



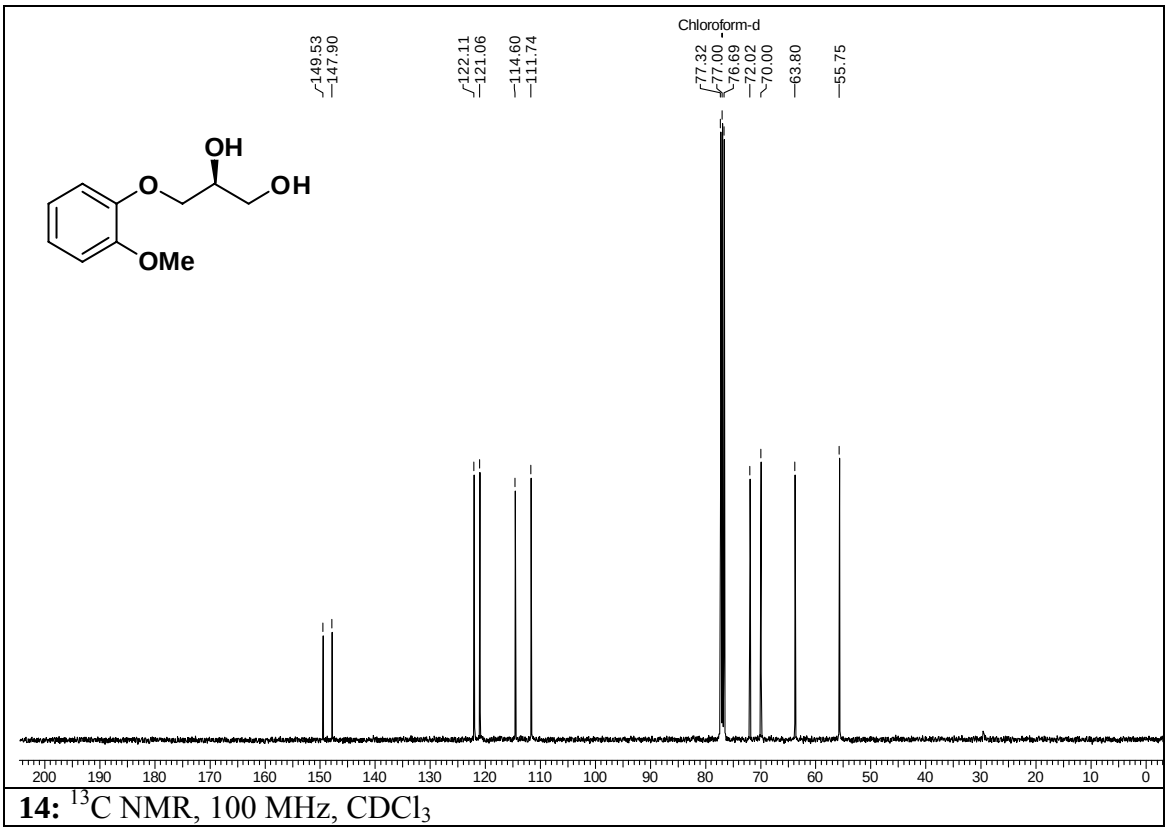
Chiral sample chromatograph

Pk #	Retention Time	Area	Area %	Height	Height Percent
1	14.925	5376	0.403	359	0.64
2	16.517	1329750	99.597	55816	99.36
Totals		1335126	100.000	56175	100.00

Column : Kromasil-5-Cellucoat (250 x 4.6mm)
Mobile phase : Ethanol + Hexane (20:80)
Wavelenth : 254 nm
Flow : 0.5 mL/min
Concentration : 0.97 mg/1.0 mL mobile phase
Injection vol. : 5 µL

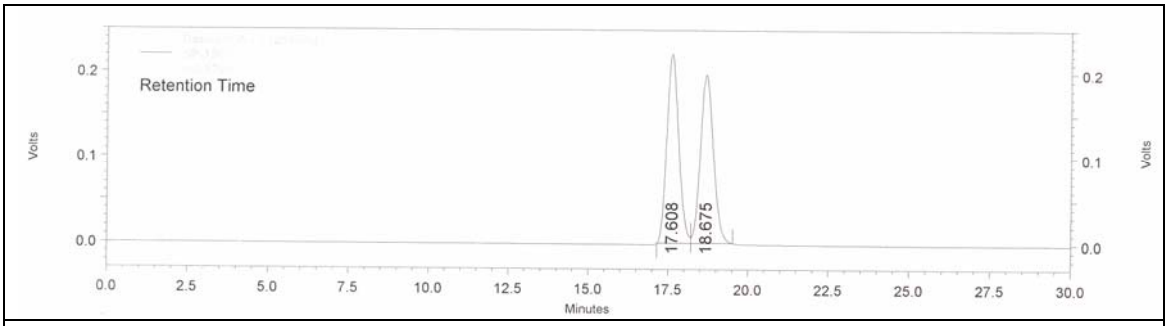


14: ^{1}H NMR, 400 MHz, $CDCl_3$



14: ^{13}C NMR, 100 MHz, $CDCl_3$

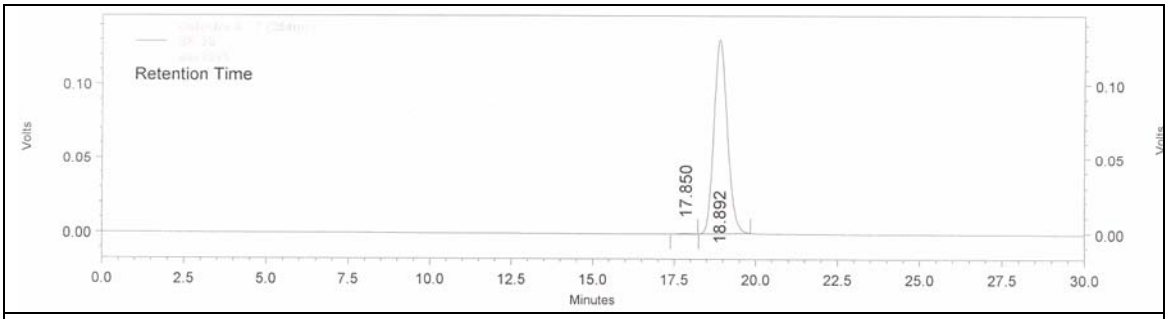
Chiral HPLC Analysis of compound 14



Racemic sample chromatograph

Pk #	Retention Time	Area	Area %	Height	Height Percent
1	17.608	5738996	50.611	221315	52.47
2	18.675	5600522	49.389	197287	47.13
Totals		11339518	100.000	418602	100.00

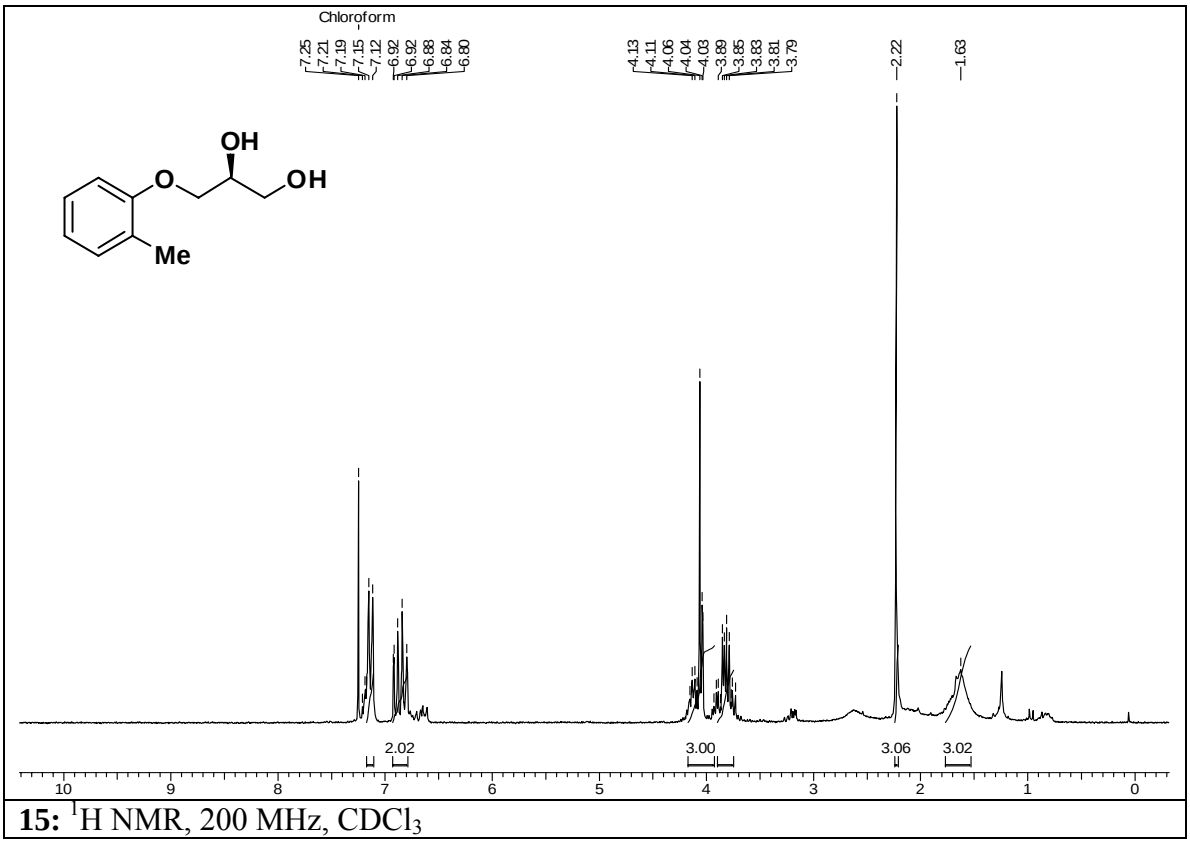
Column : Kromasil-5-Cellucoat (250 x 4.6mm)
Mobile phase : Ethanol + Hexane (20:80)
Wavelenth : 254 nm
Flow : 0.5 mL/min
Concentration : 2.0 mg/2.0 mL mobile phase
Injection vol. : 10 µL



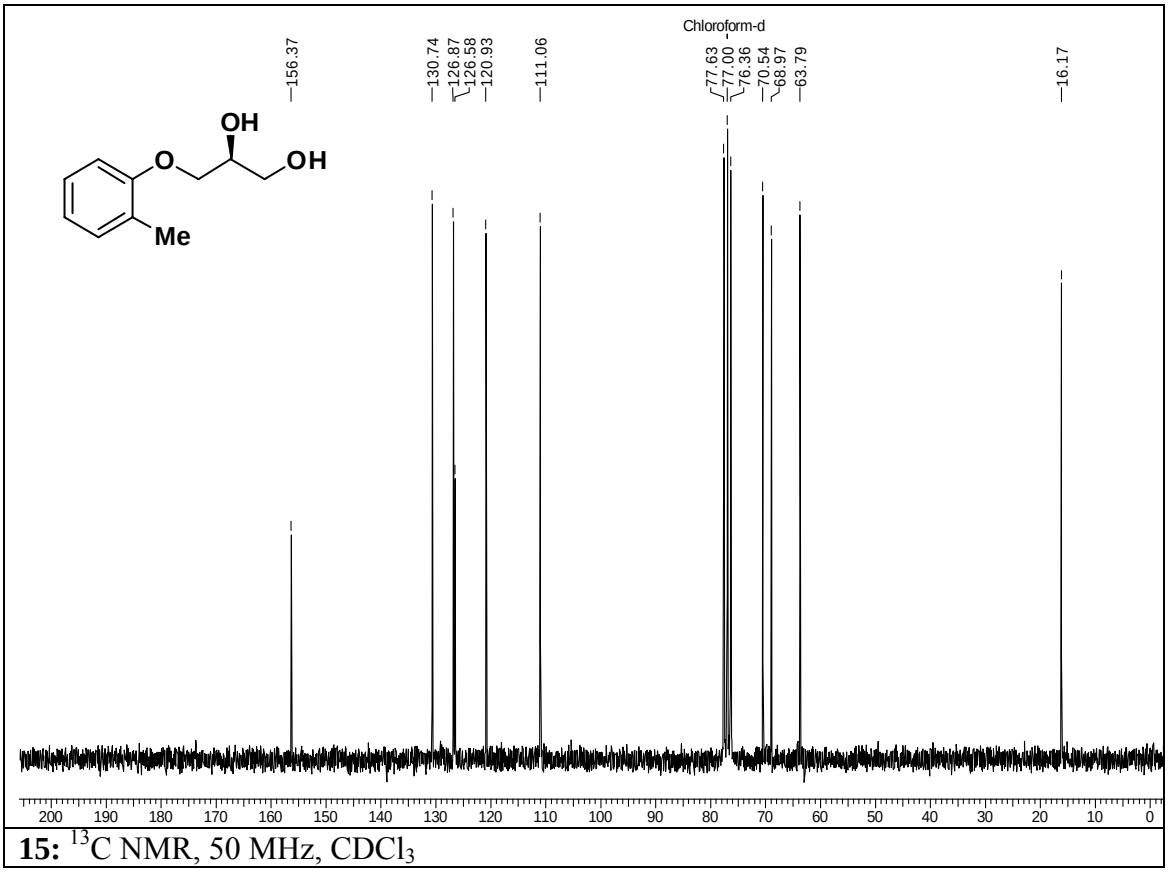
Chiral sample chromatograph

Pk #	Retention Time	Area	Area %	Height	Height Percent
1	17.850	6390	0.171	288	0.22
2	18.892	3738228	99.829	130342	9978
Totals		3744618	100.000	130630	100.00

Column : Kromasil-5-Cellucoat (250 x 4.6mm)
Mobile phase : Ethanol + Hexane (20:80)
Wavelenth : 254 nm
Flow : 0.5 mL/min
Concentration : 0.86 mg/1.0 mL mobile phase
Injection vol. : 5 µL

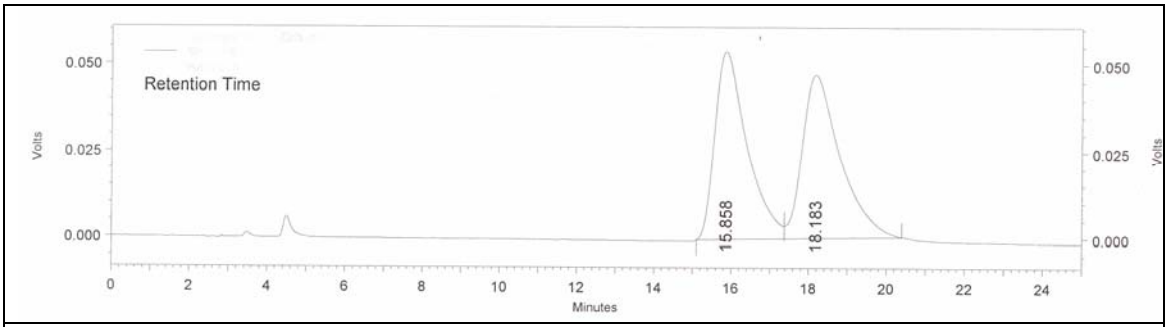


15: ^{1}H NMR, 200 MHz, $CDCl_3$



15: ^{13}C NMR, 50 MHz, $CDCl_3$

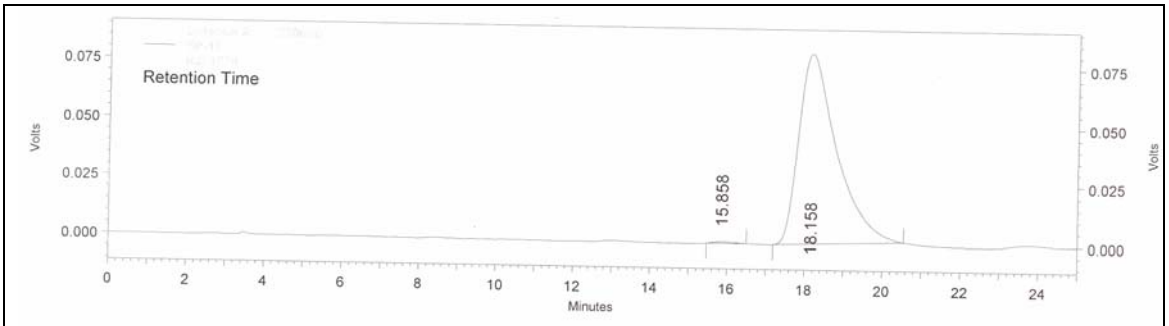
Chiral HPLC Analysis of compound 15



Racemic sample chromatograph

Pk #	Retention Time	Area	Area %	Height	Height Percent
1	15.858	3159781	49.552	54201	53.47
2	18.183	3216951	50.448	47163	46.53
Totals		6376752	100.000	101364	100.00

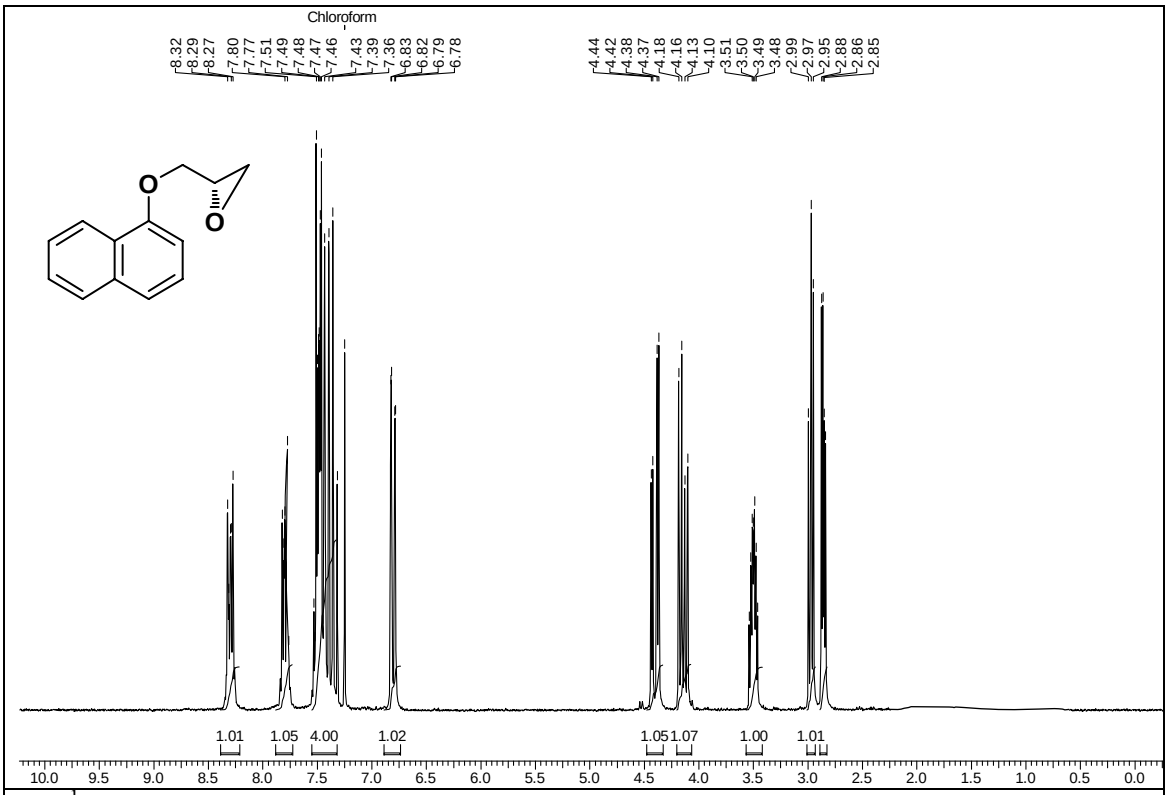
Column : Chiralcel OD (250 x 4.6mm)
Mobile phase : 2-propanol + Pet. Ether (7.5: 92.5)
Wavelenth : 220 nm
Flow : 1.0 mL/min
Concentration : 1.15 mg/2.0 mL mobile phase
Injection vol. : 5 µL



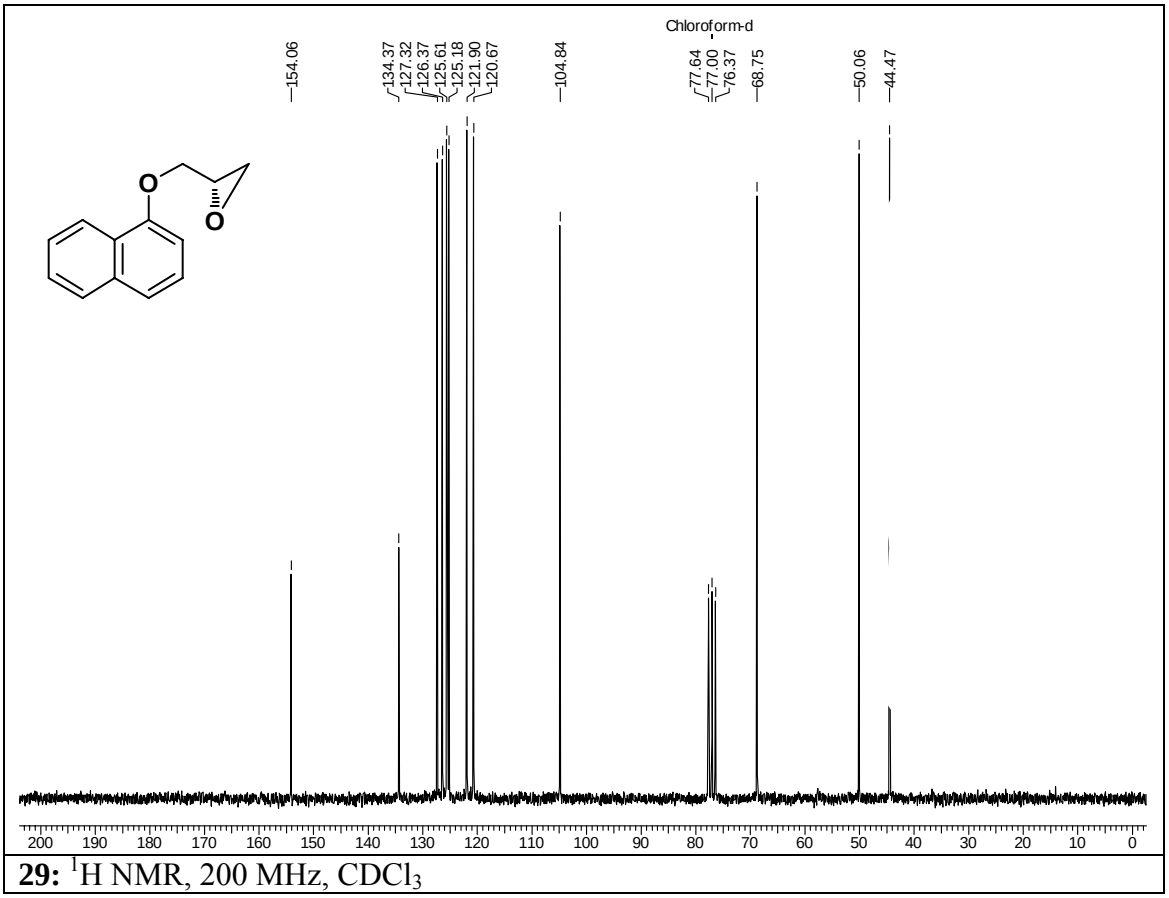
Chiral sample chromatograph

Pk #	Retention Time	Area	Area %	Height	Height Percent
1	15.858	20521	0.370	644	0.79
2	18.158	5526666	99.630	81164	99.21
Totals		5547187	100.000	81808	100.00

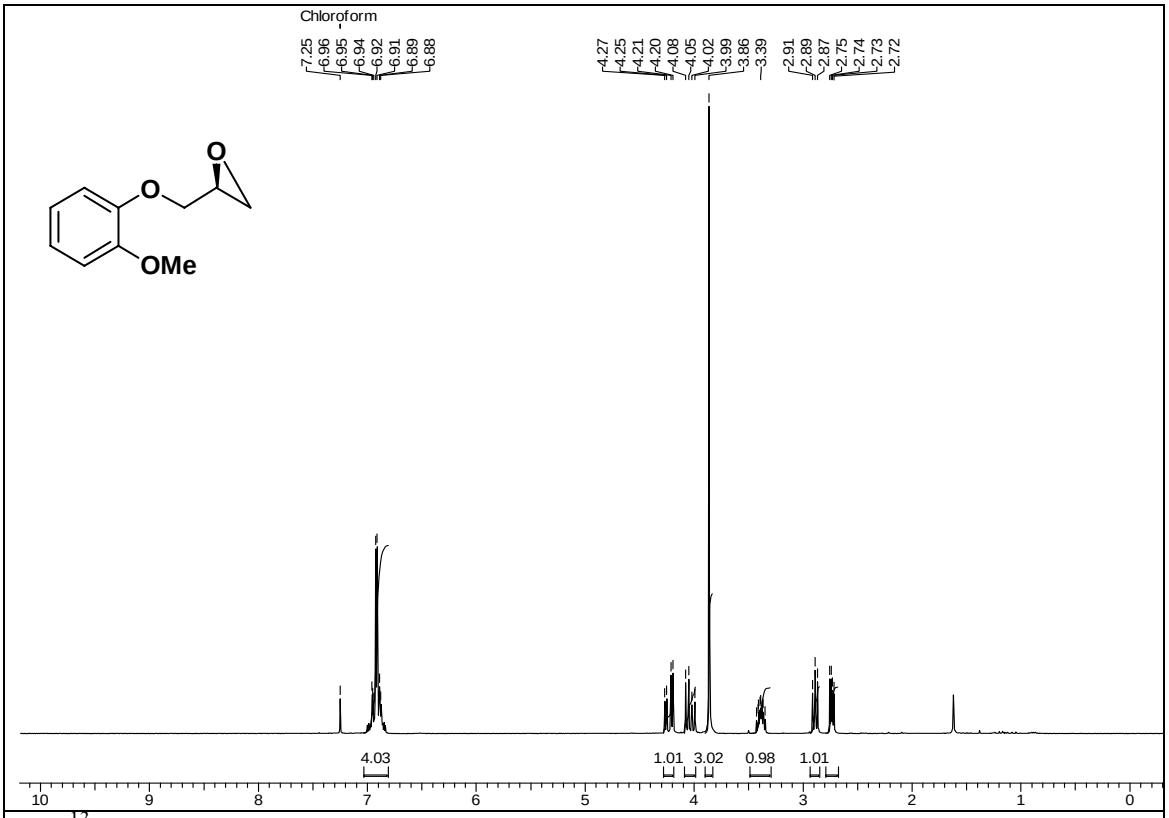
Column : Chiralcel OD (250 x 4.6mm)
Mobile phase : 2-propanol + Pet. Ether (7.5: 92.5)
Wavelenth : 220 nm
Flow : 1.0 mL/min
Concentration : 0.50 mg/1.5 mL mobile phase
Injection vol. : 5 µL



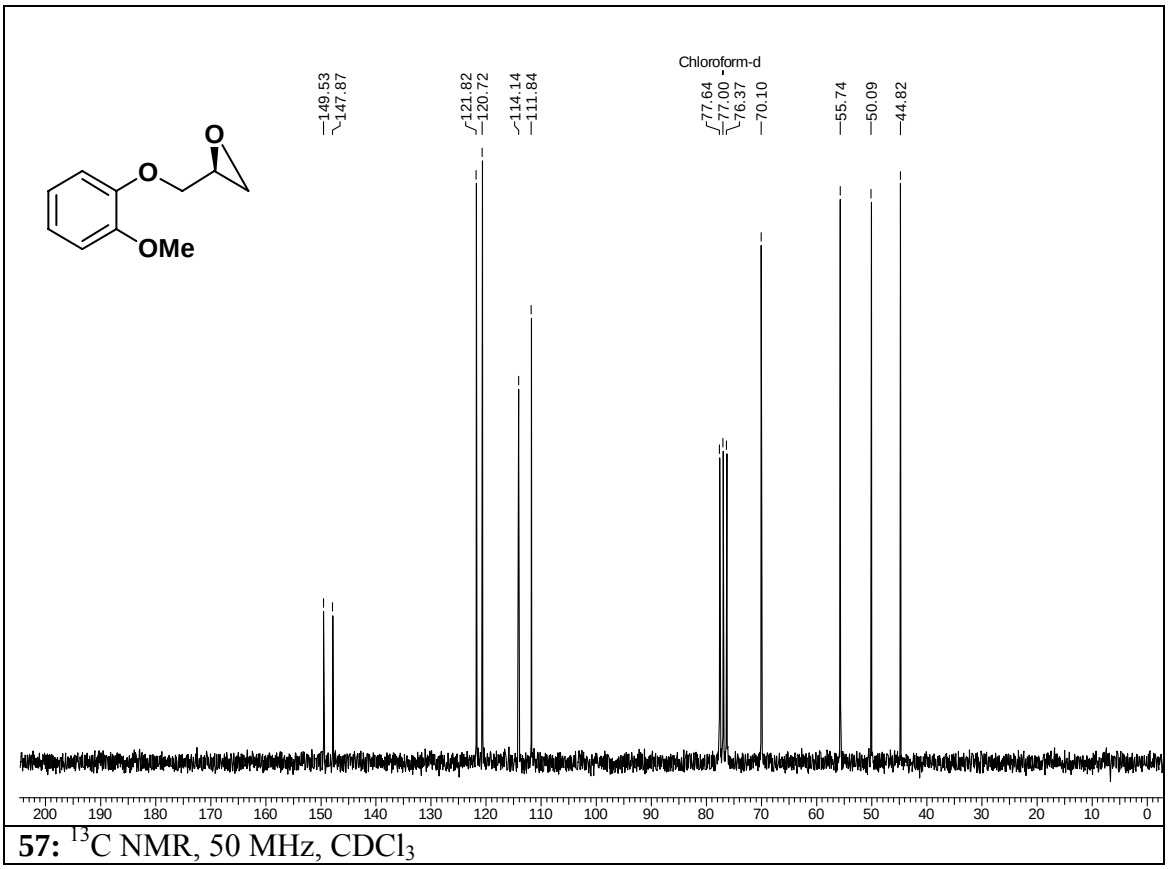
29: ^{1}H NMR, 200 MHz, $CDCl_3$



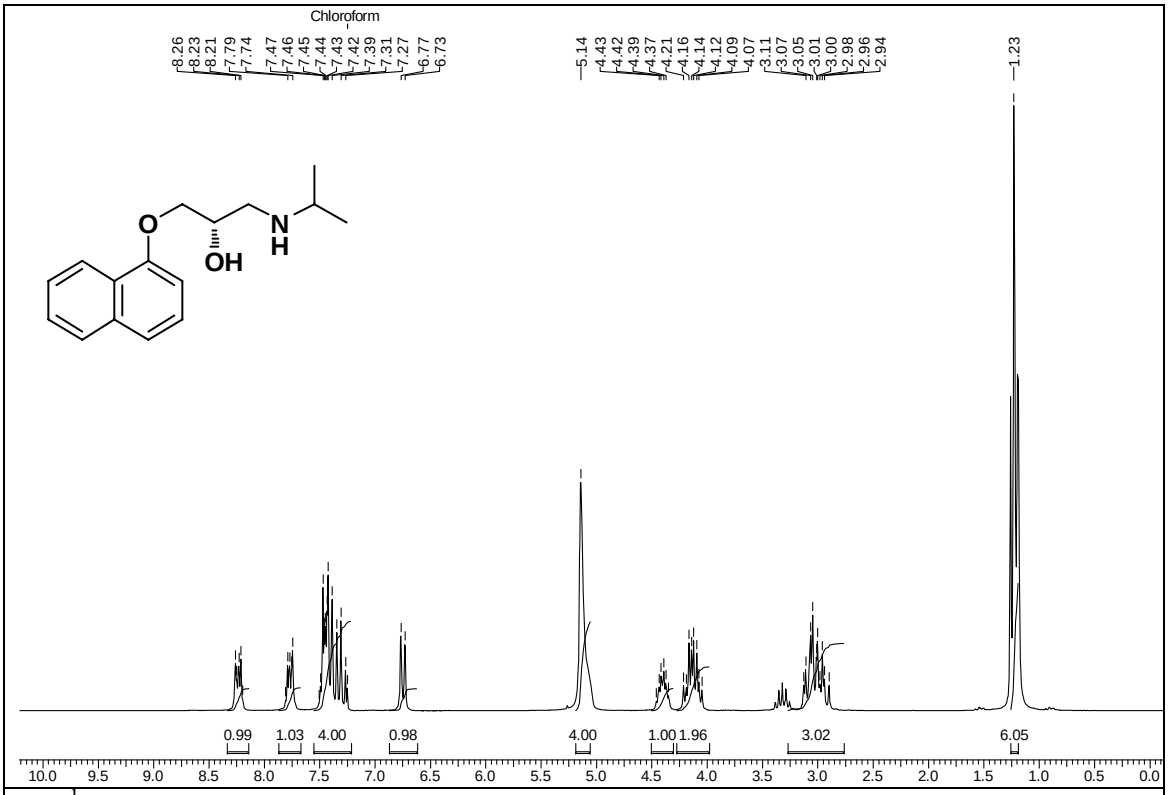
29: ^{1}H NMR, 200 MHz, $CDCl_3$



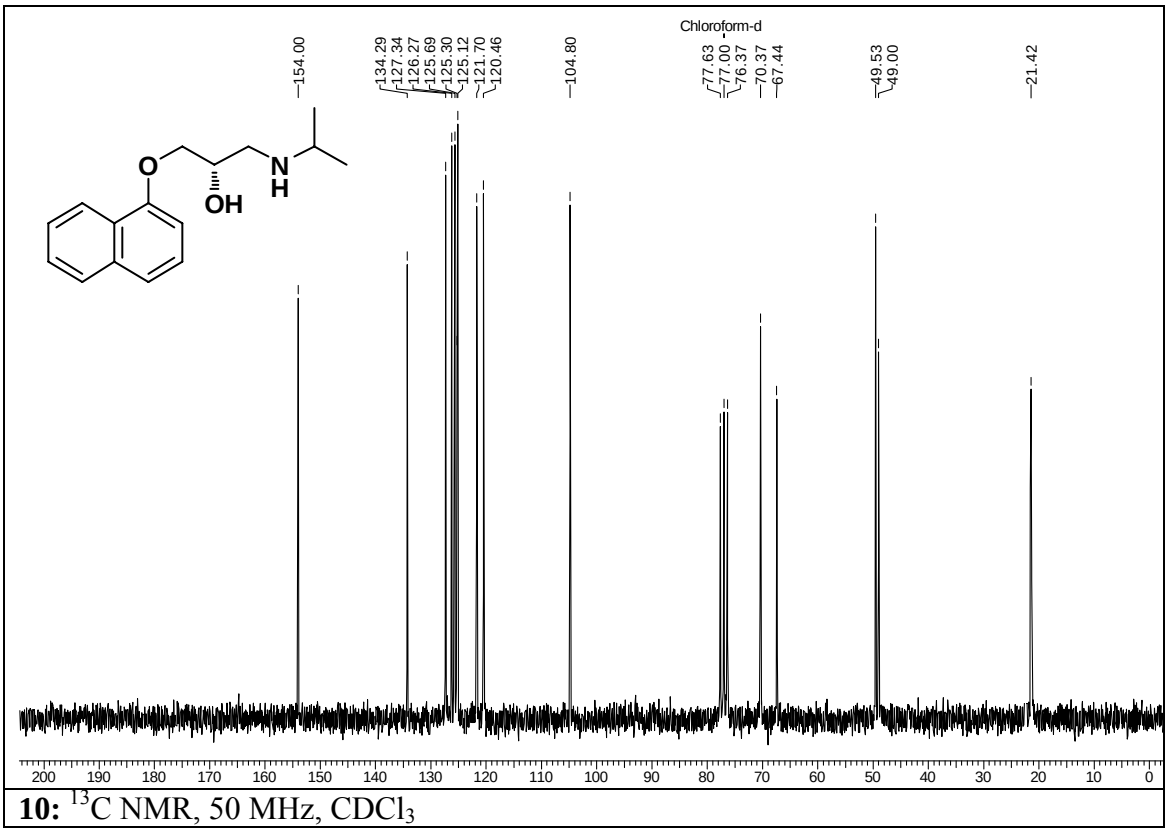
57: ^{13}C NMR, 50 MHz, $CDCl_3$



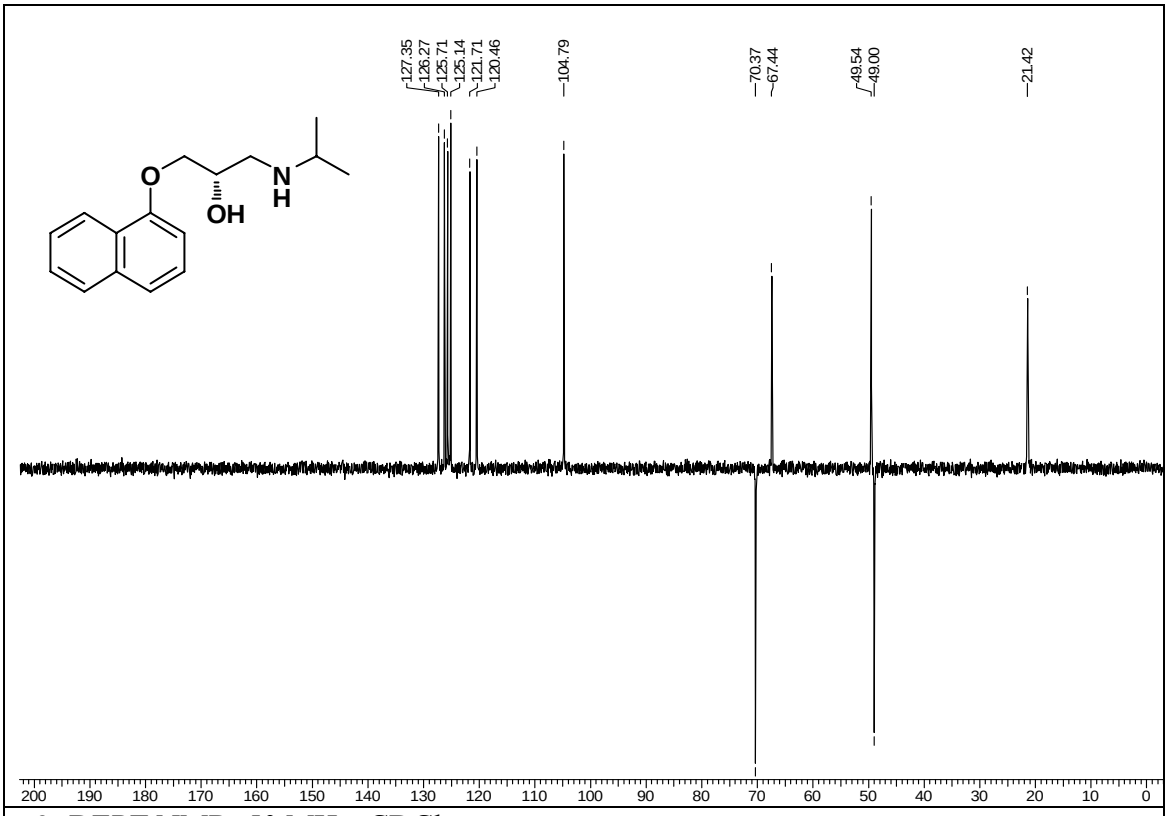
57: ^{13}C NMR, 50 MHz, $CDCl_3$



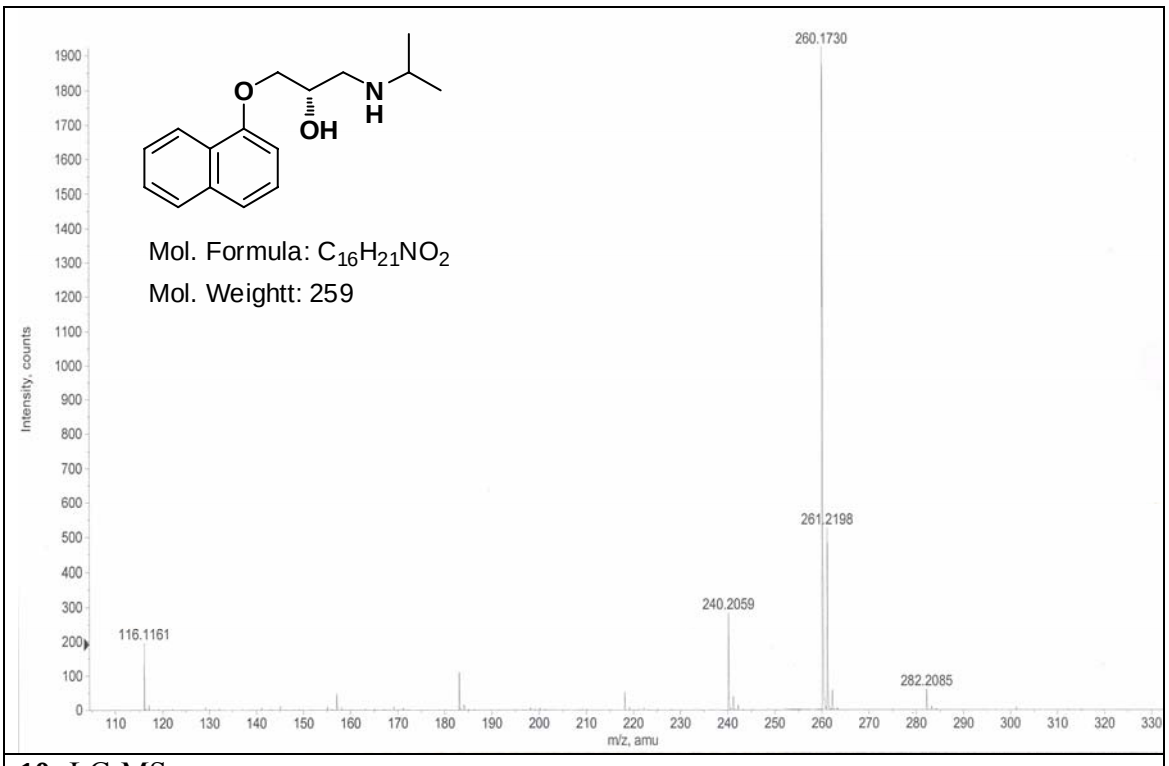
10: ^{1}H NMR, 200 MHz, $CDCl_3$



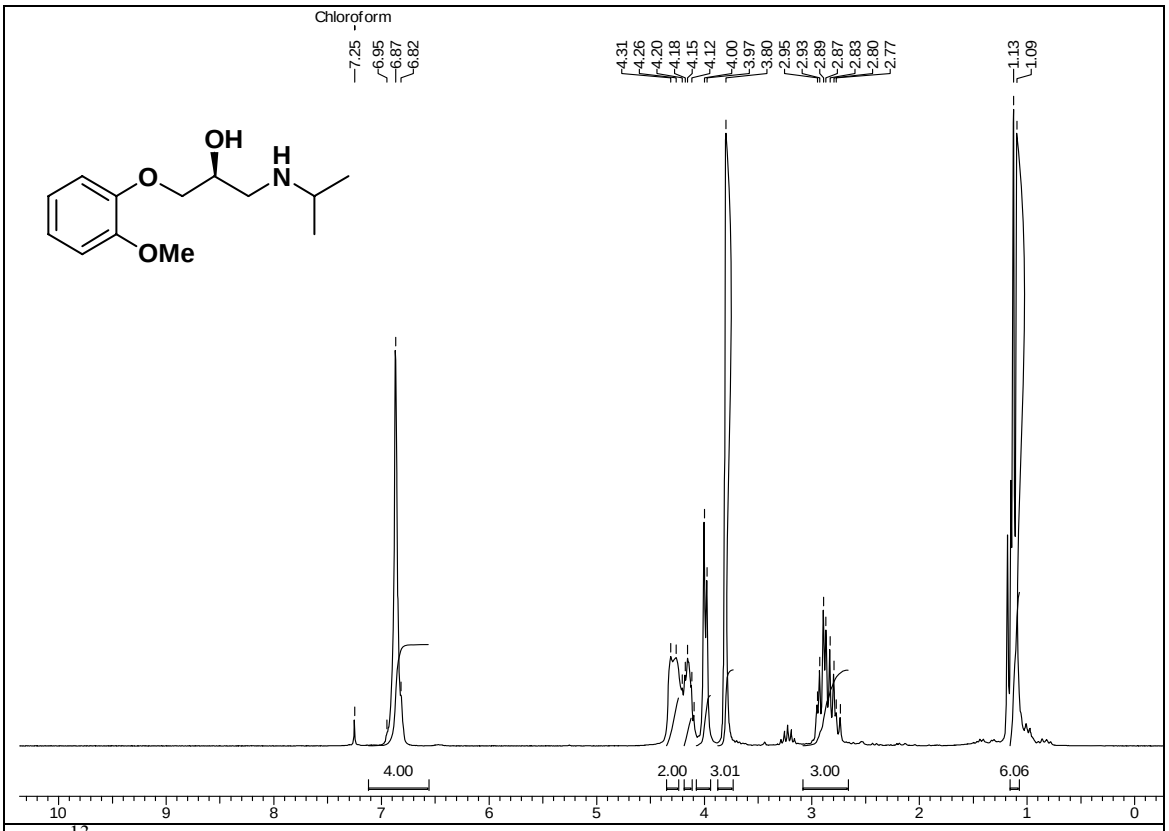
10: ^{13}C NMR, 50 MHz, $CDCl_3$



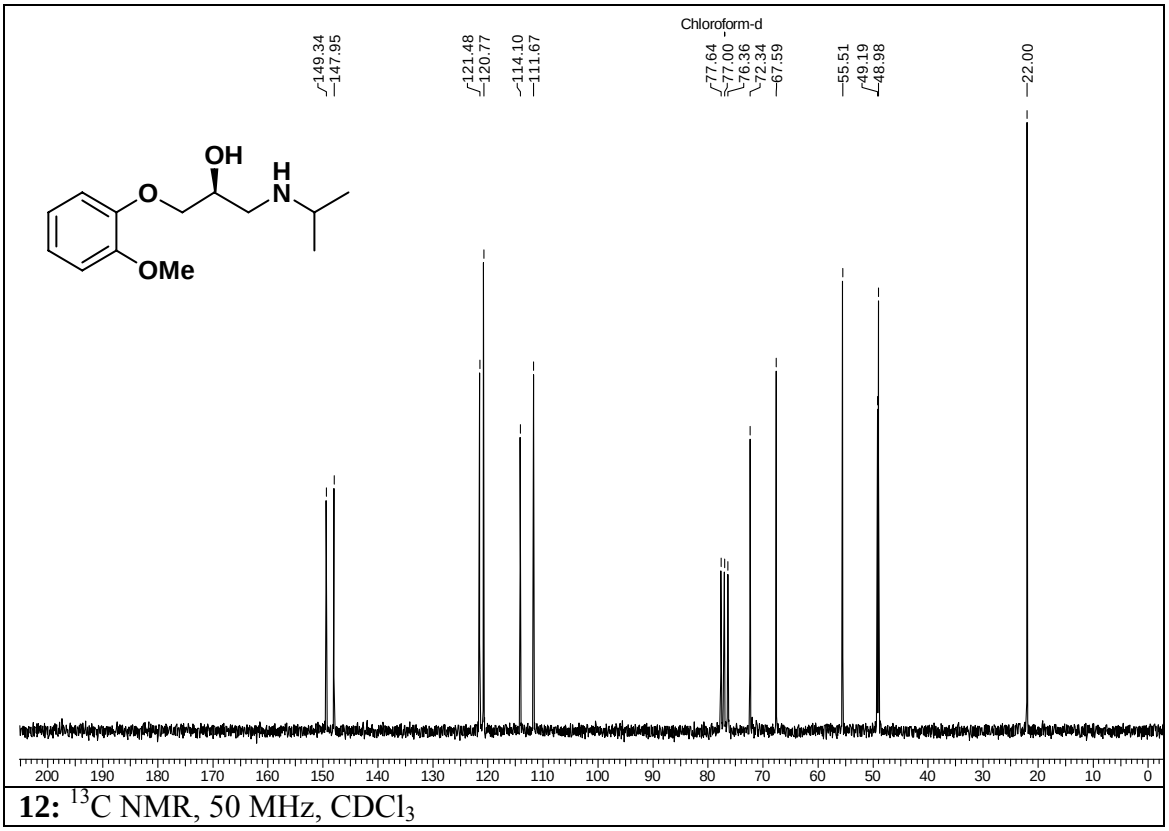
10: DEPT NMR, 50 MHz, $CDCl_3$



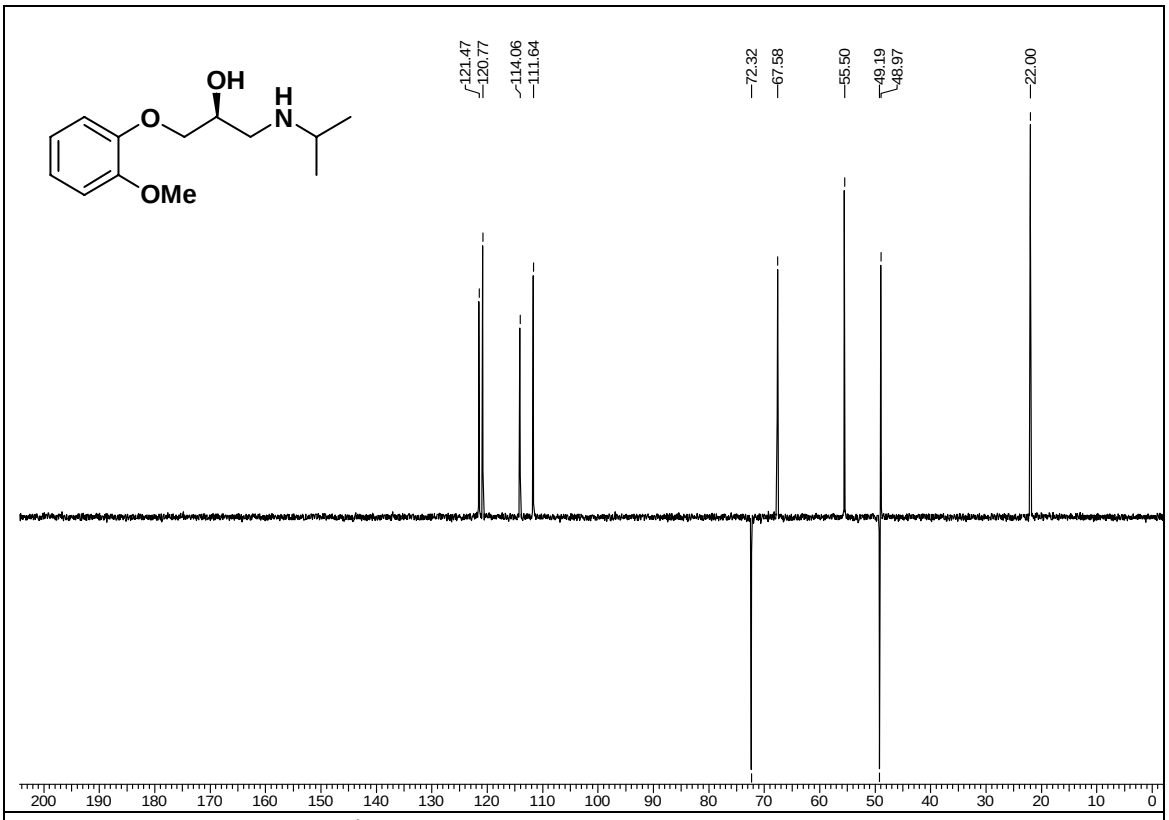
10: LC-MS



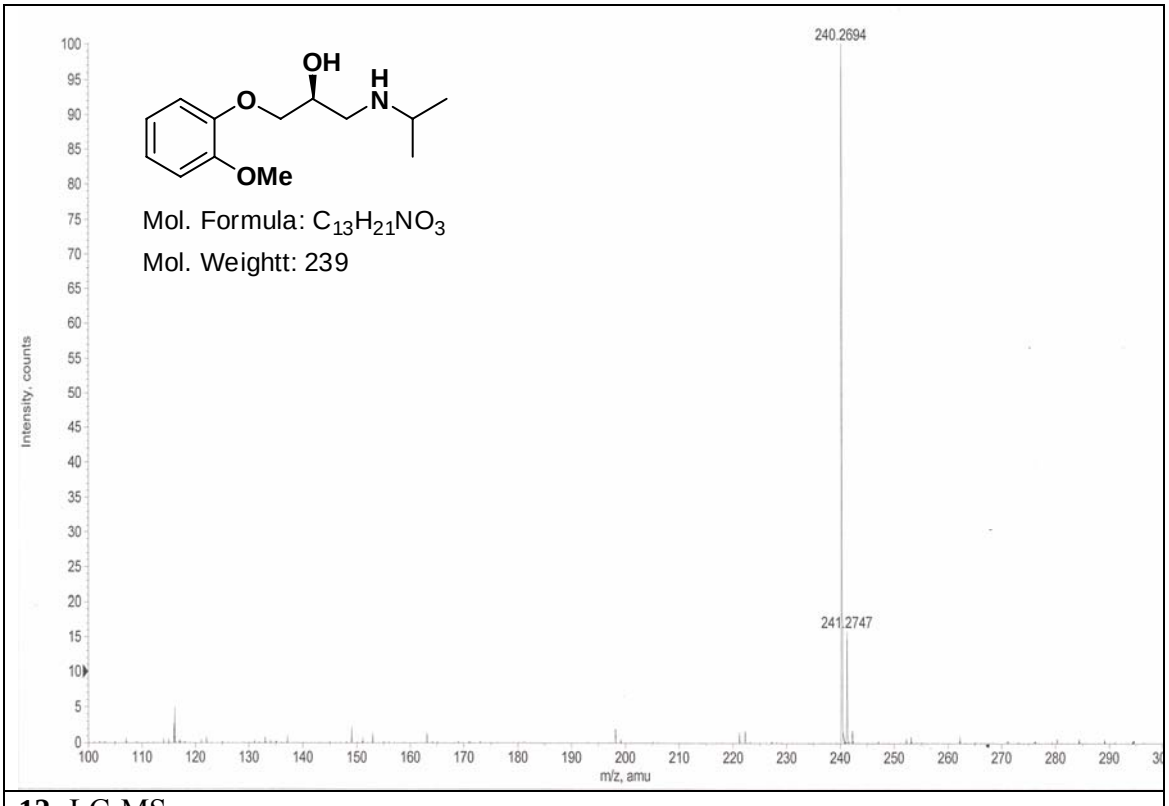
12: ^{13}C NMR, 50 MHz, $CDCl_3$



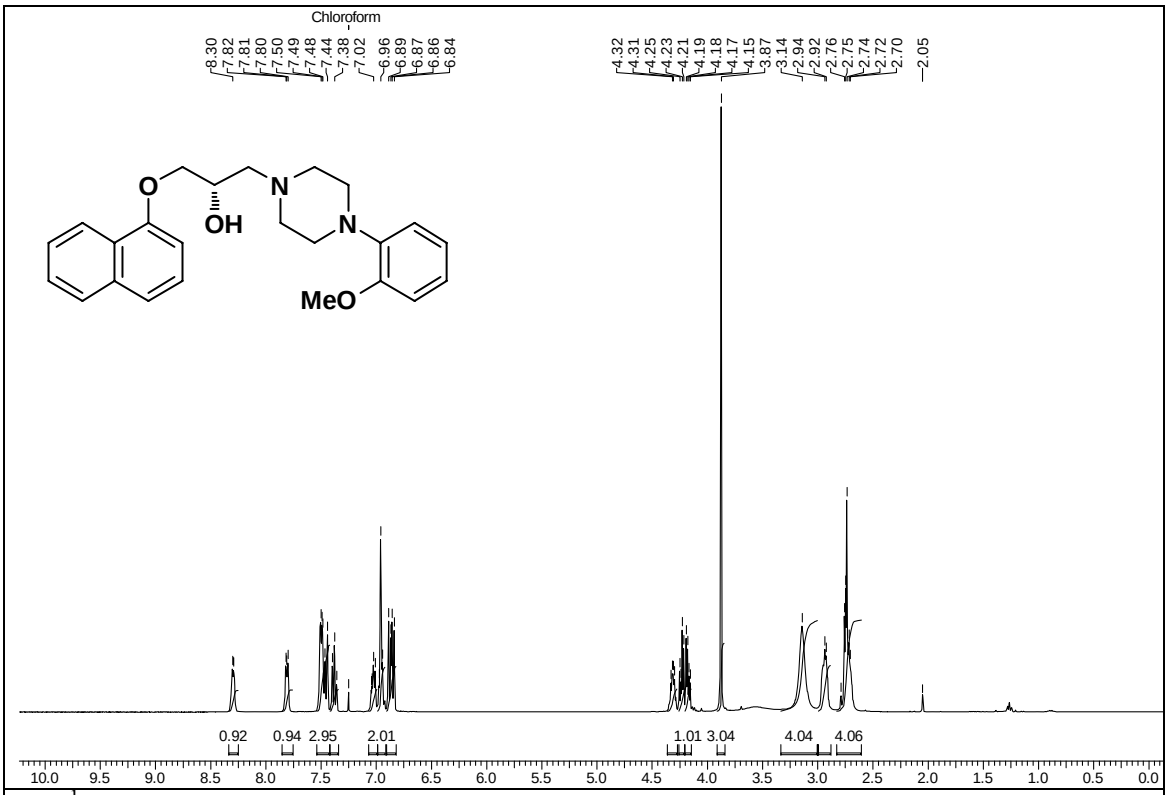
12: ^{13}C NMR, 50 MHz, $CDCl_3$



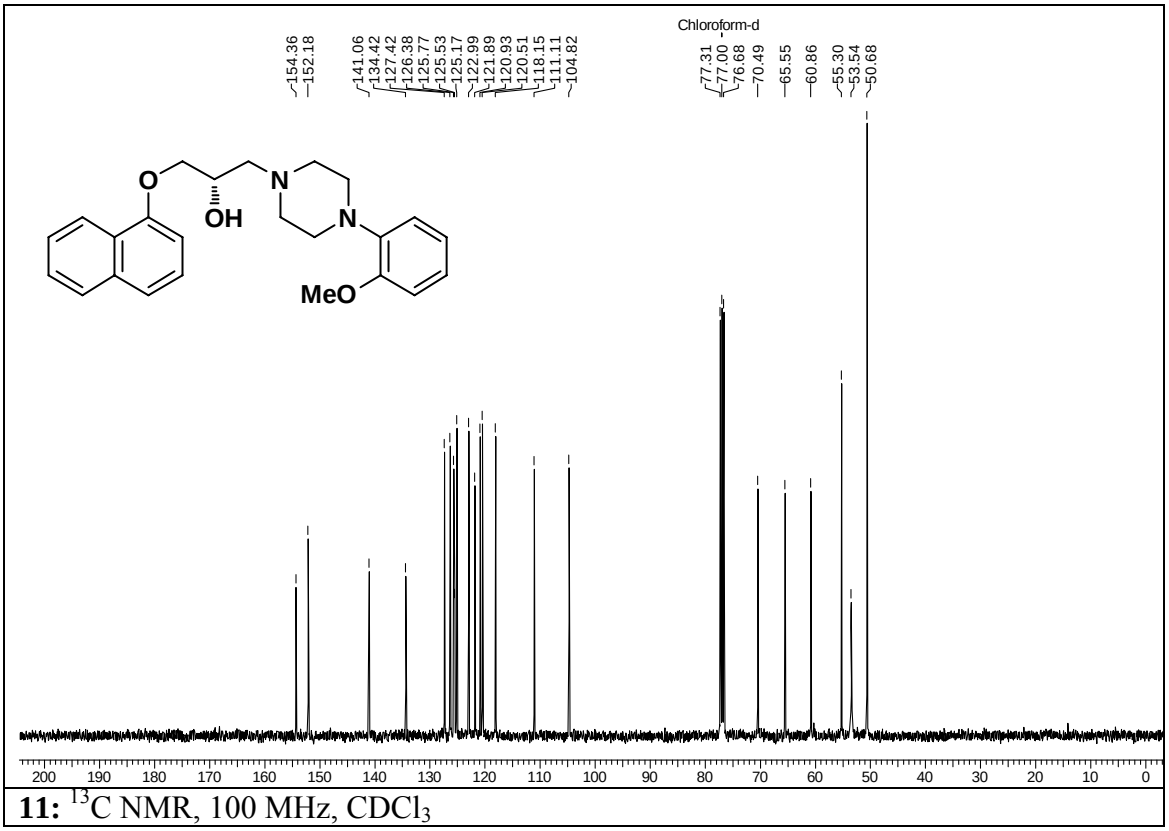
12: DEPT, 50 MHz, $CDCl_3$



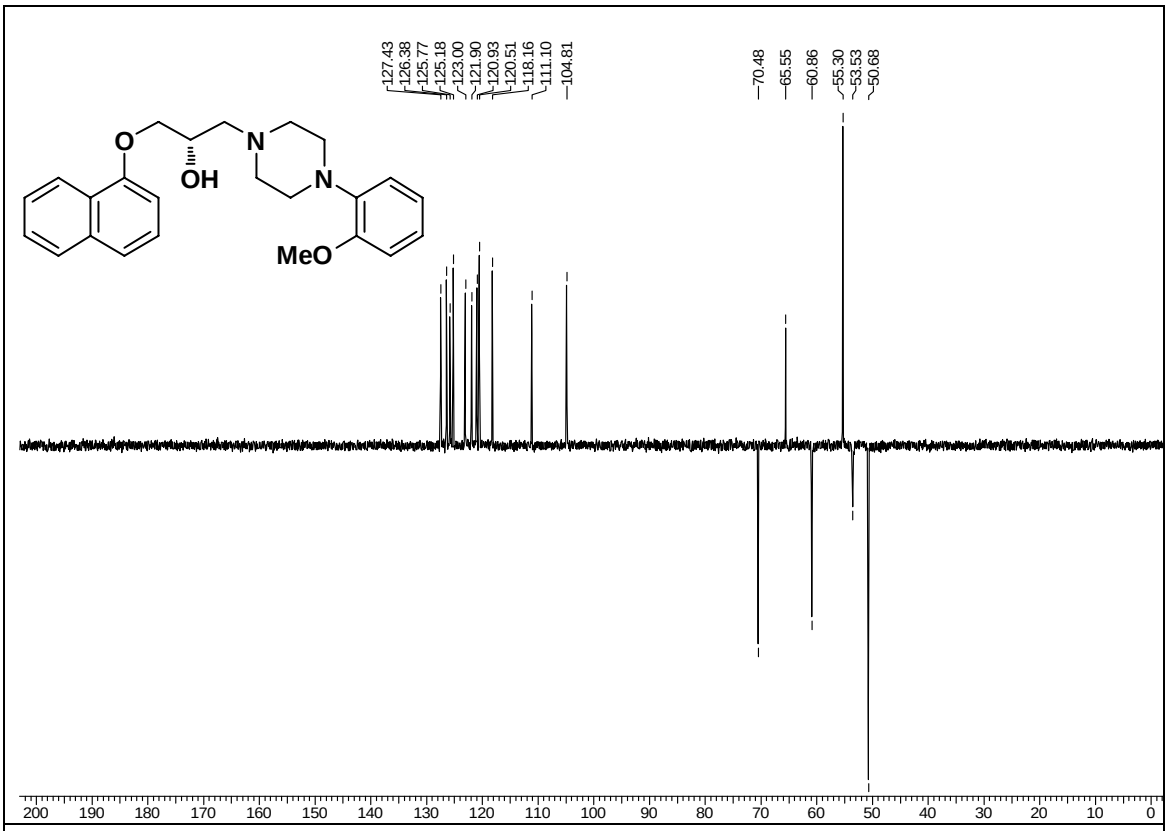
12: LC-MS



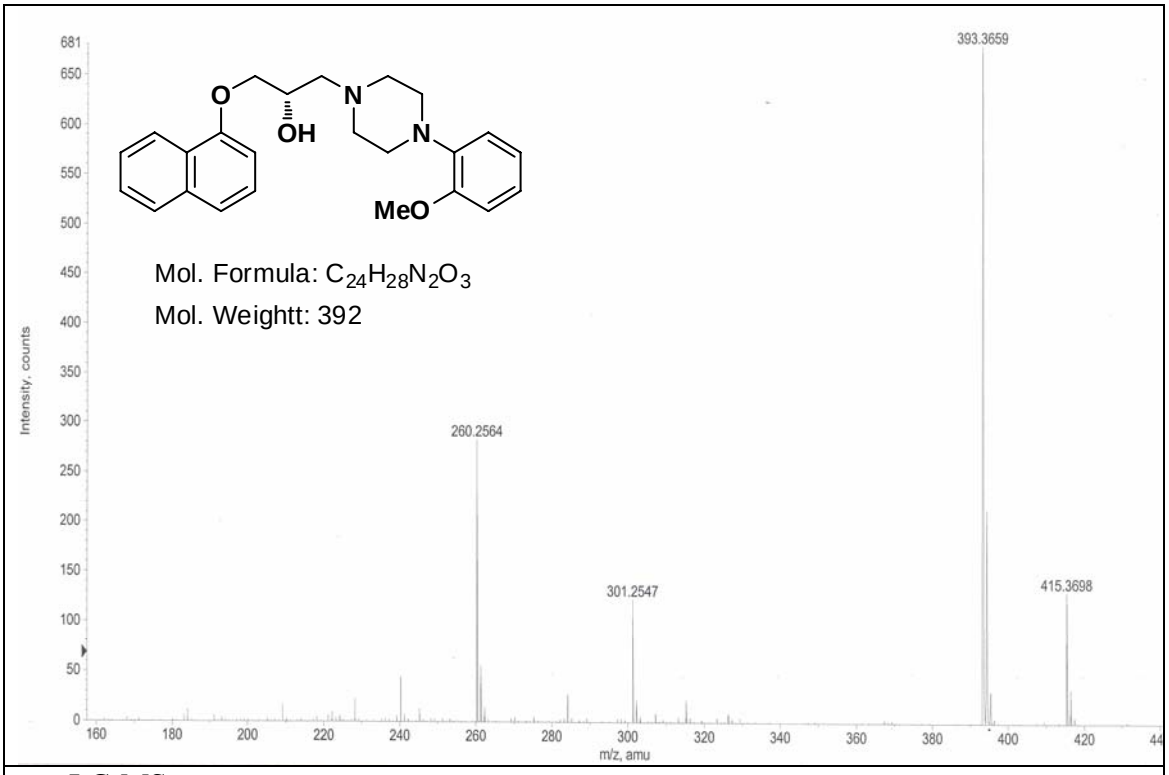
11: ^{1}H NMR, 400 MHz, $CDCl_3$



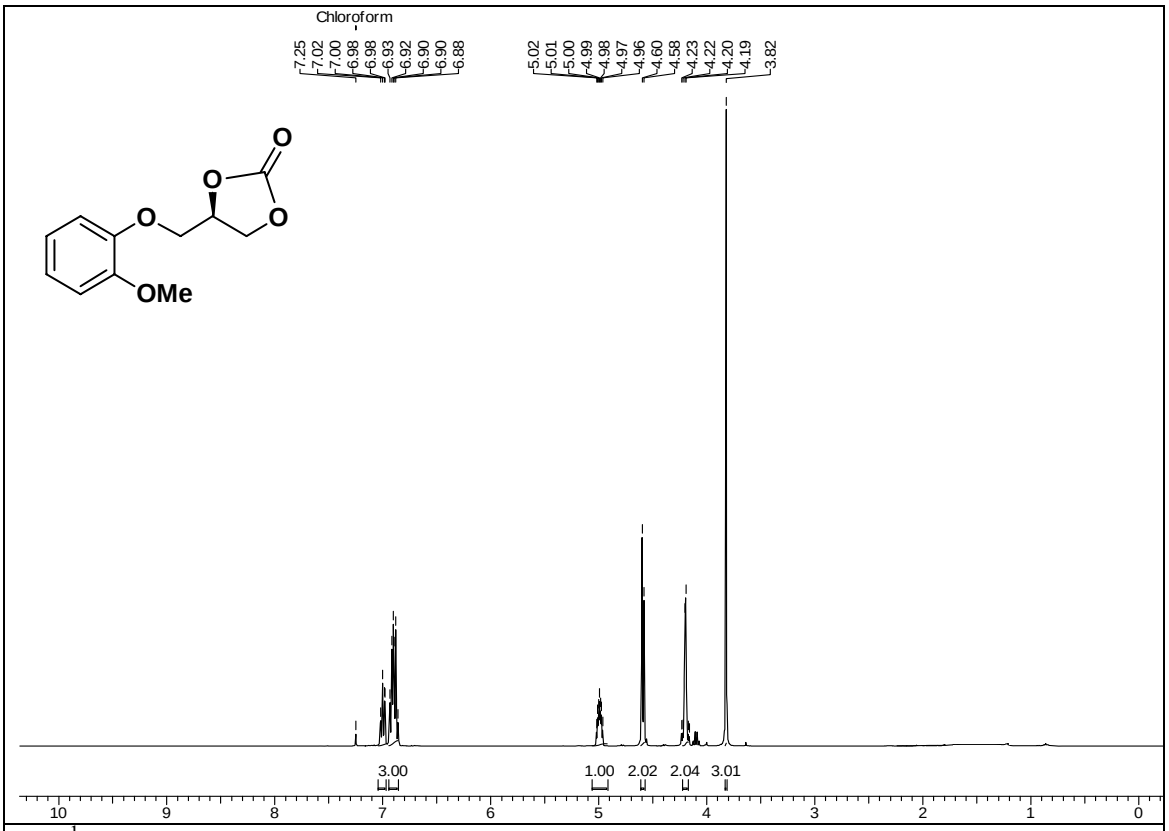
11: ^{13}C NMR, 100 MHz, $CDCl_3$



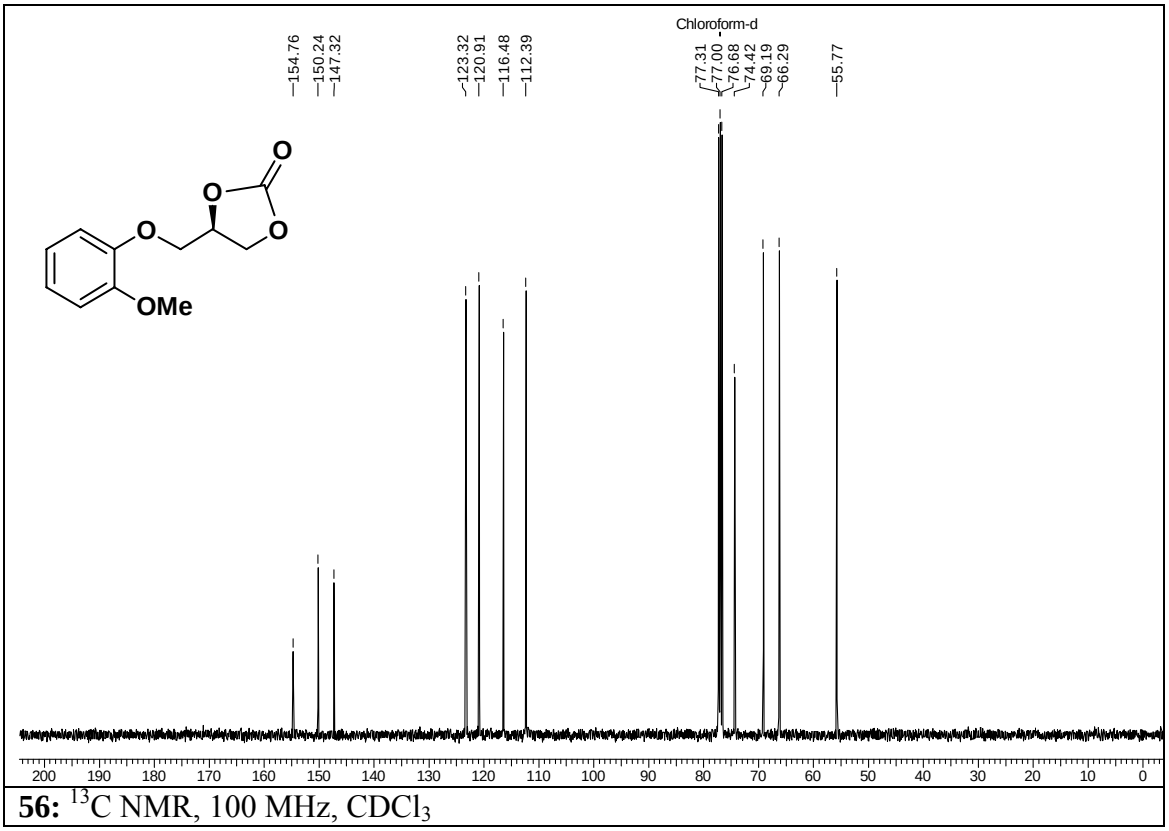
11: DEPT NMR, 100 MHz, $CDCl_3$



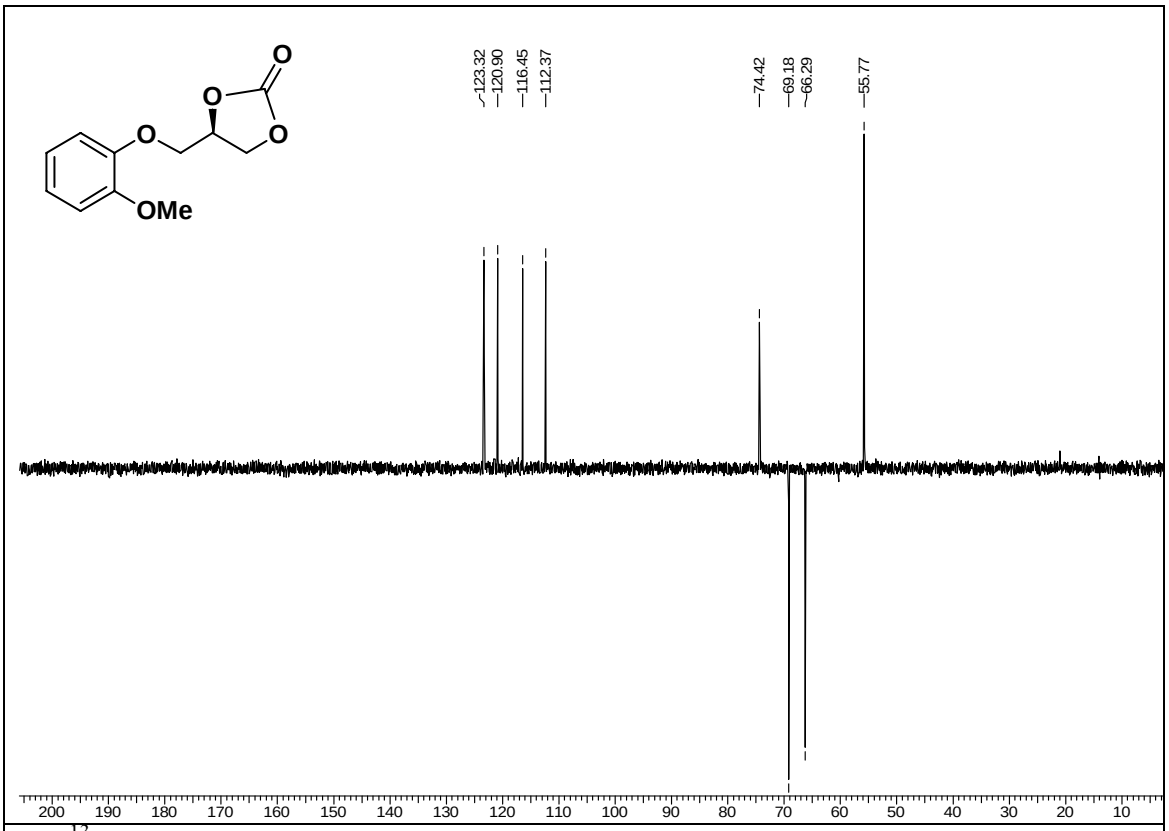
11: LC-MS



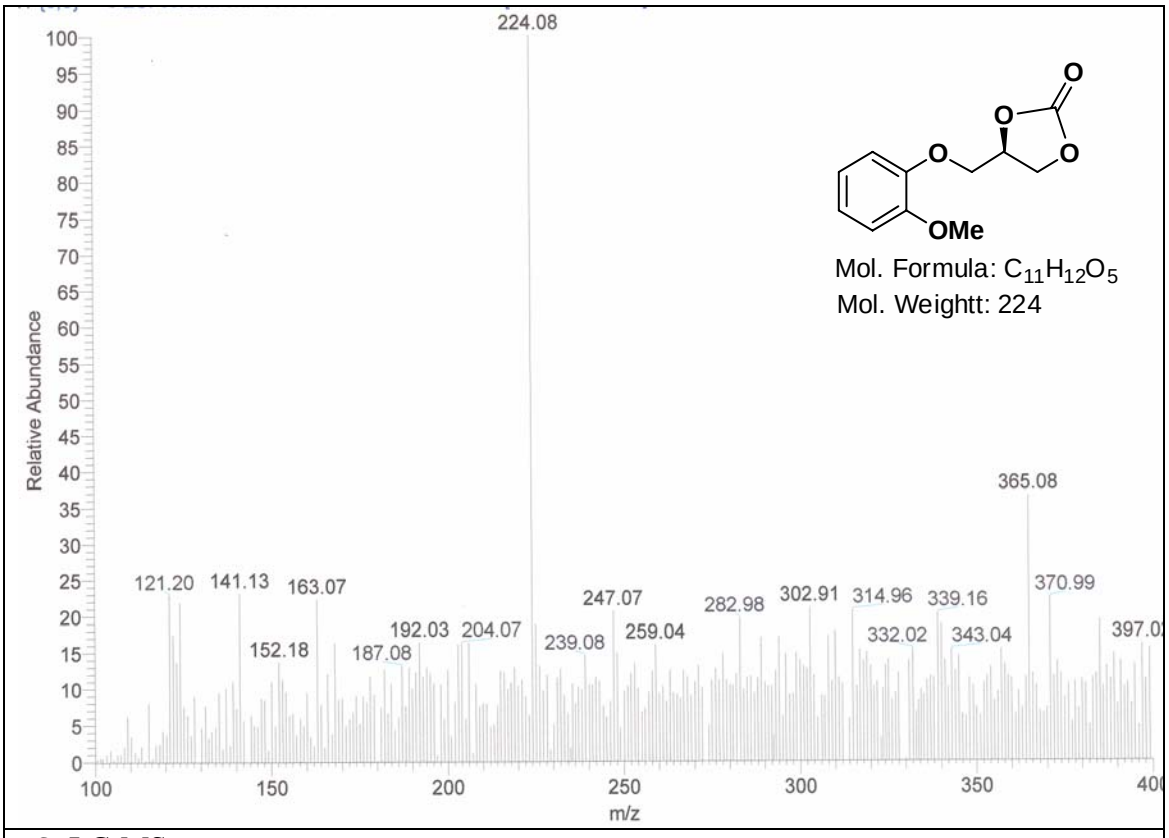
56: ^{1}H NMR, 400 MHz, $CDCl_3$



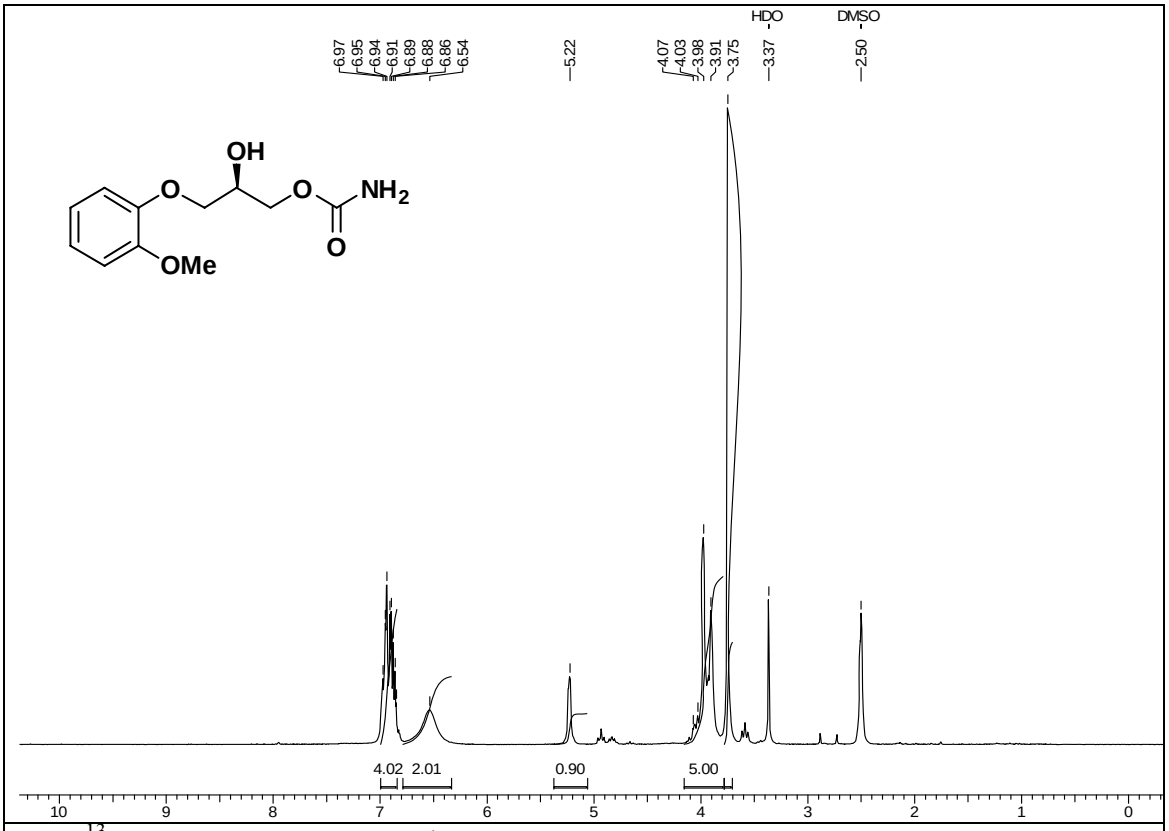
56: ^{13}C NMR, 100 MHz, $CDCl_3$



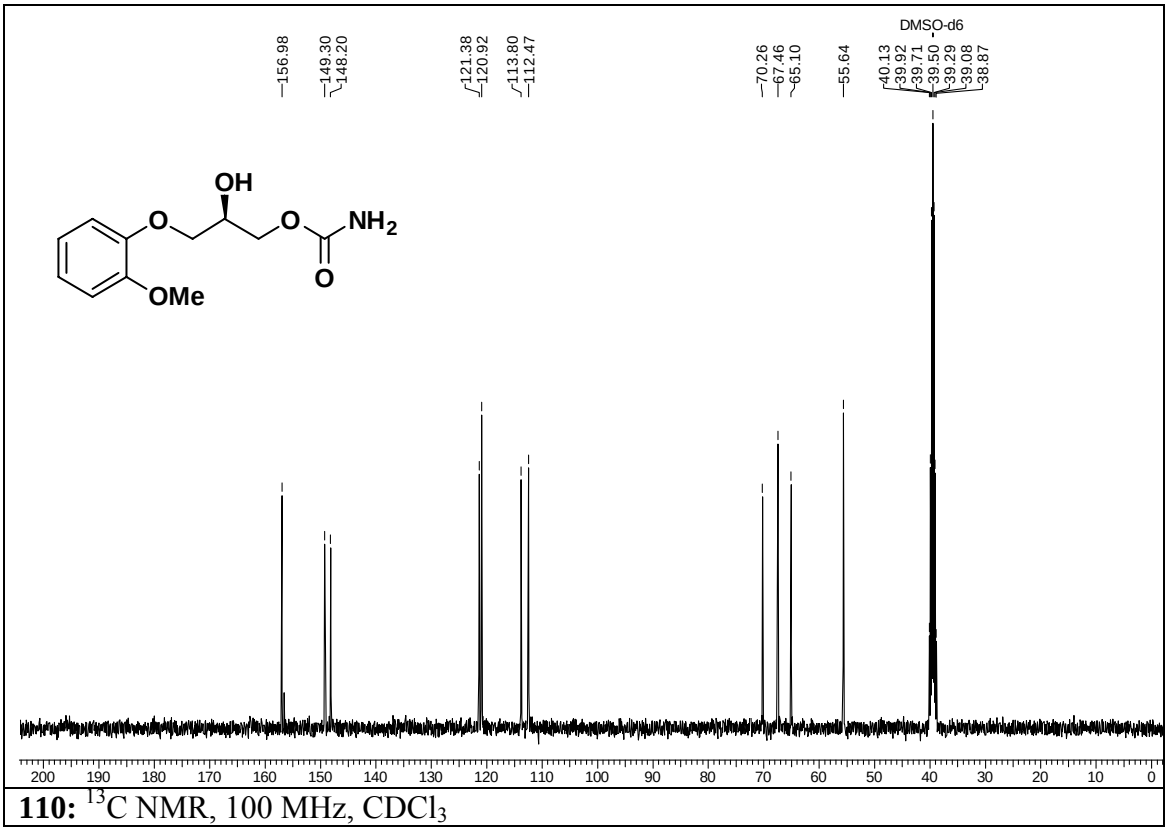
56: ^{13}C NMR, 100 MHz, $CDCl_3$



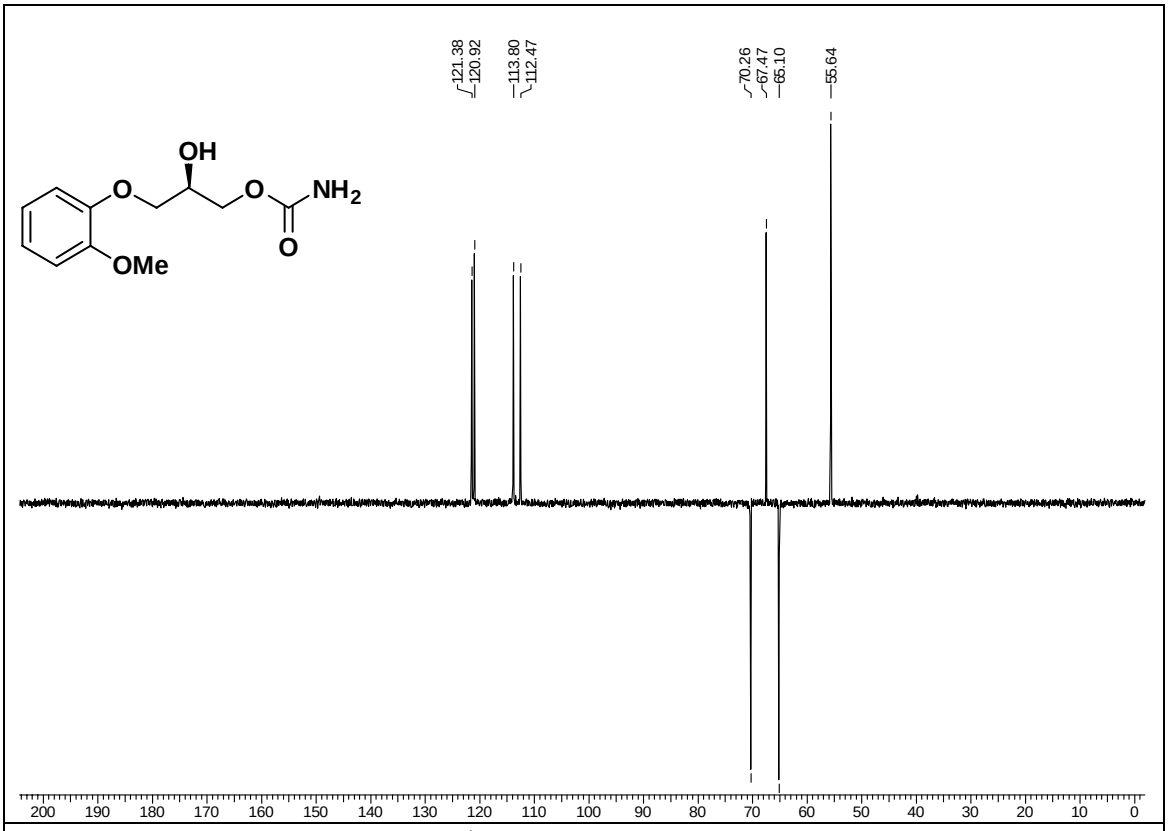
56: LC-MS



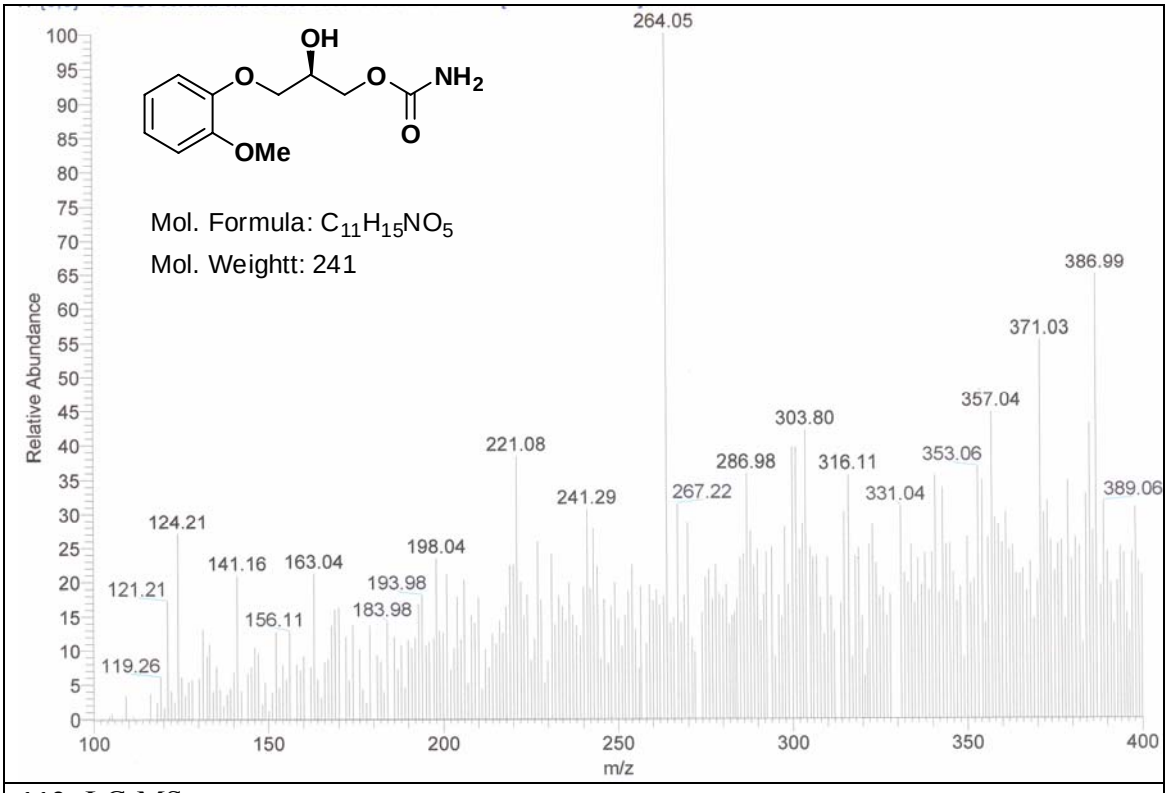
110: ^{13}C NMR, 100 MHz, $CDCl_3$



110: ^{13}C NMR, 100 MHz, $CDCl_3$



110: DEPT NMR, 100 MHz, $CDCl_3$



110: LC-MS

1.3.7 References

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Chapter 2

Organocatalytic asymmetric synthesis of (*R*)-coniceine and (*R*)-pipecolic acid based on α-amination of aldehyde

2.1 SECTION A

ASYMMETRIC SYNTHESIS OF (*R*)-CONICEINE

2.1.1 Introduction

Coniceine or indolizidine (**1** or **2**) represent an important class of biologically active compounds including alkaloids such as slaframine **3**, castanospermine **4** (a potent glycosidase inhibitor) and many more. 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. 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]

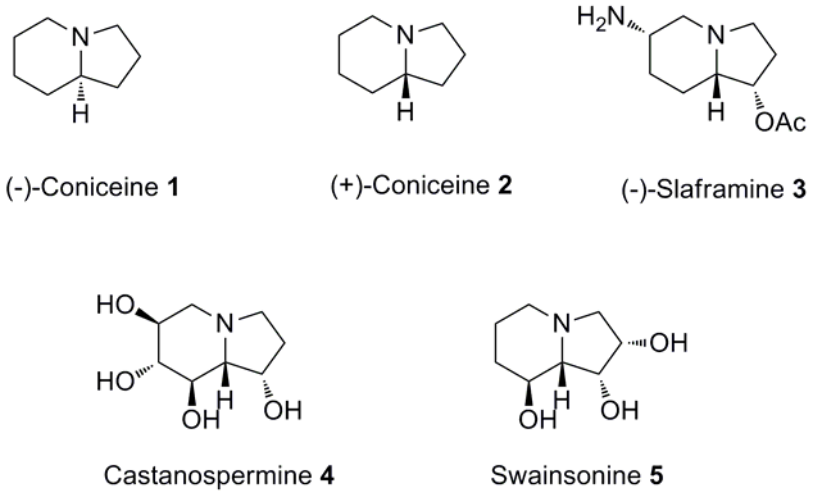


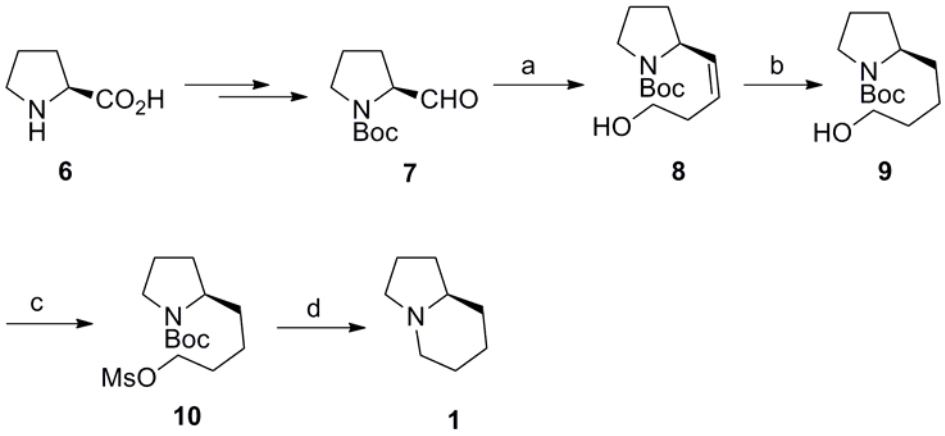
Figure 1.

2.1.2 Review of Literature

(*R*)-Coniceine is popular target for the demonstration of chiral methodology in the indolizidine field. Several approaches[1-31] have been reported in the literature for the synthesis of racemic as well as optically active (*S*)-coniceine **1** or (*R*)-coniceine **2**. A few interesting and recent syntheses of (*R*)-coniceine **1** are described below.

2.1.2.1 Sibi *et al.* (1999, Scheme 1)[21]

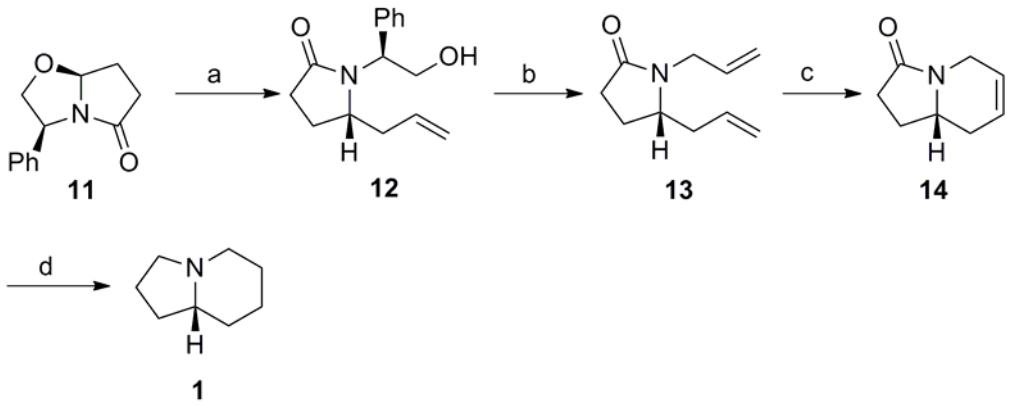
Sibi and co-workers used L-proline for chiral pool approach synthesis of (*R*)-coniceine **1**. For this L-proline **6** converted to aldehyde **7** by a sequence of reactions which on Wittig olefination afforded alcohol **8**. Alcohol **8** converted to (*R*)-coniceine **1** via treatment with methane trifluorosulfonyl chloride.



Scheme 1. Reagents and conditions: (a) $HO(CH_2)_2CH_2PPh_3Br$, LiHMDS; (b) H_2, Pd/C; (c) MsCl, Et_3N; (d) 3M HCl then $NaHCO_3$.

2.1.2.3 Meyers *et al.* (2000, Scheme 2)[22]

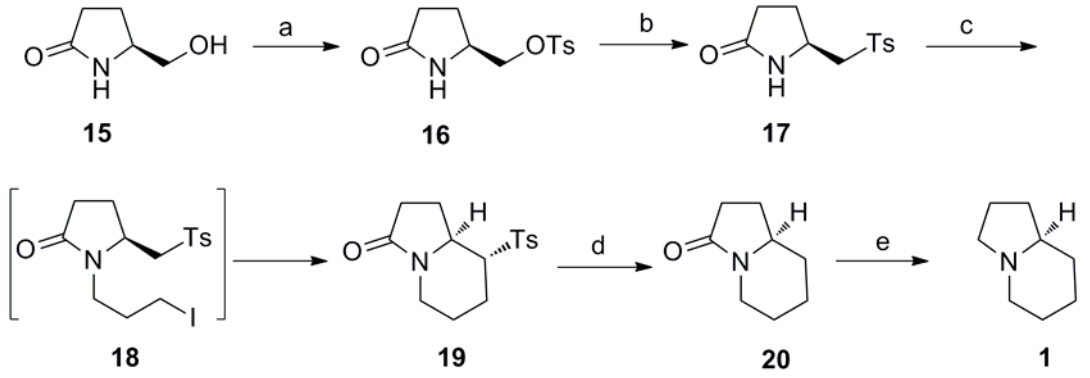
Meyers and co-worker utilized Ti-mediated allylsilane addition to bicyclic lactum **11** derived from chiral phenyl glycinol. The resultant allylation product **12** on deprotection of chiral auxiliary subjected to allylation followed by ring closing metathesis to obtain bicyclic lactum. Bicyclic lactum on hydrogenation and reduction with lithium aluminium hydride afforded (*R*)-coniceine **1**.



Scheme 2. Reagents and conditions: (a) allyltrimethylsilane, $TiCl_4$; (b) (i) Ca/NH_3; (ii) NaH, allyl bromide; (c) Grubb's 2nd generation catalyst; (d) (i) H_2, $Pd(OH)_2$; (ii) $LiAlH_4$.

2.1.2.3 Nájera *et al.* (2001, Scheme 3)[25]

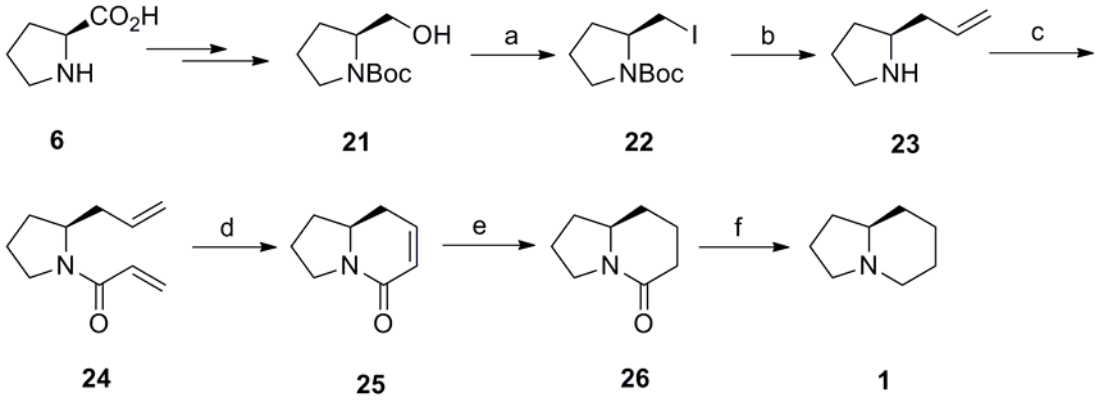
Nájera and co-workers started the synthesis from (S)-pyroglutaminol **15**. Compound **15** converted to sulfone **17** via tosyl derivative. Sulfone **17** dialkylated at nitrogen atom and α-sufonyl position using 1,3-diiodopropane as elctrophile and sodium hydride as base. The indolizidine derivative **19** thus obtained converted to (*R*)-coniceine **1** via treatment with sodium-amalgum and reduction with lithium aluminium hydride.



Scheme 3. Reagents and conditions: (a) TsCl, DMAP, Et_3N, CH_2Cl_2; (b) (i) 4-methylthiphenol, NaOH, CH_3CN, reflux; (ii) Oxone, H_2O, MeOH, rt; (c) 1,3-diiodopropane, NaH, DMF, 0 ^oC; (d) Na-Hg, MeOH, Na_2HPO_4; (e) $LiAlH_4$, Et_2O.

2.1.2.4 Chang *et al.* (2001, Scheme 4)[26]

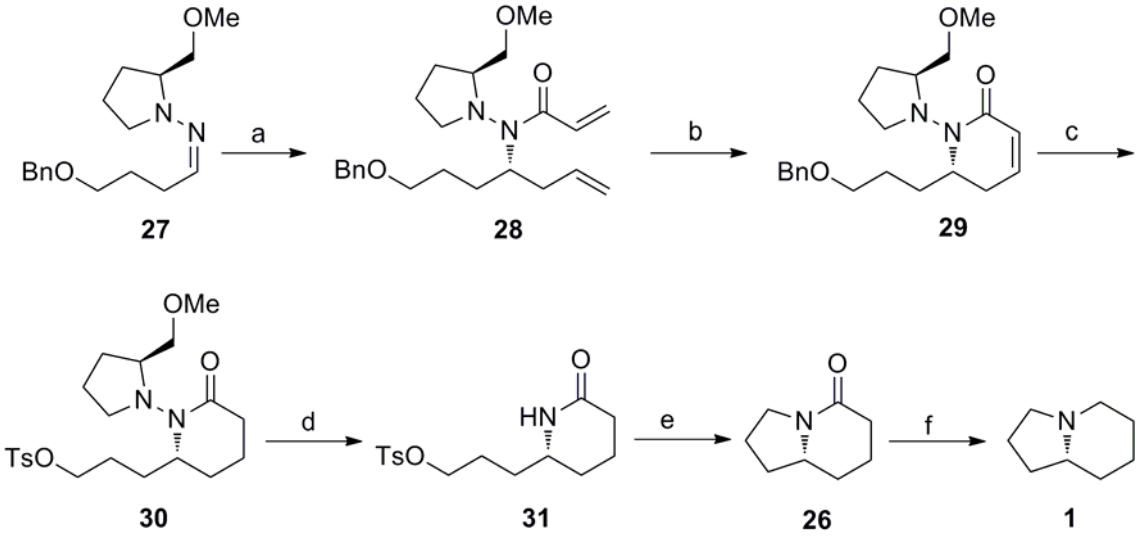
Chang and co-workers converted L-proline **6** to 2-allylpyrrolidine **23** via iodination. Allylpyrrolidine **23** on treatment with acryloyl chloride followed by ring closing metathesis afforded lactum **25**. Lactum **25** on hydrogenation and reduction with lithium aluminium hydride furnished (*R*)-coniceine **1**.



Scheme 4. Reagents and conditions: (a) Imidazole, I_2, PPh_3, Et_2O, rt; (b) (i) CuI, vinylmagnesium bromide, THF, -40 ^oC; (ii) TFA, CH_2Cl_2, 0 ^oC; (c) acryloyl chloride, Et_3N, CH_2Cl_2, 0 ^oC; (d) $(Im)Cl_2PCy_3RuCHPh$, CH_2Cl_2, rt; (e) H_2, PtO_2, EtOAc, rt; (f) $LiAlH_4$, Et_2O.

2.1.2.5 Couture *et al.* (2008, Scheme 5)[30]

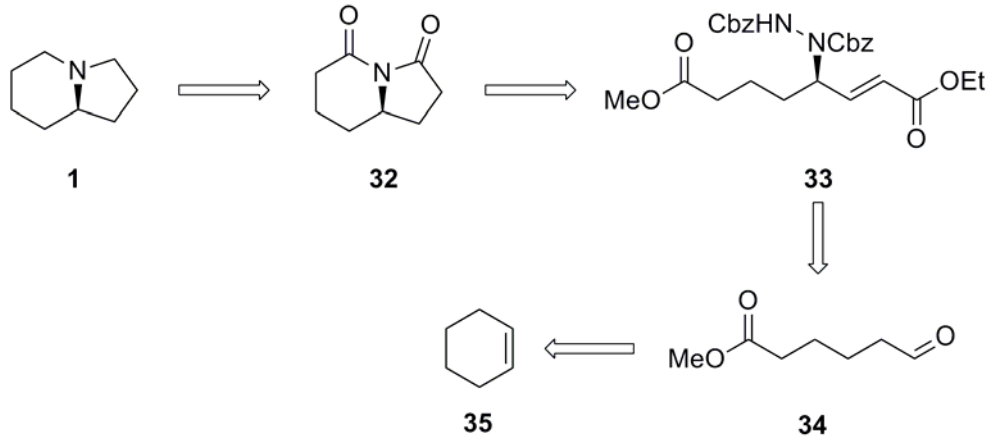
Couture and co-workers used stereoslective 1,2-addition on SAMP hydrazone followed by ring closure metathesis to obtain lactum **26**. Lactum **26** then converted to (*R*)-coniceine **1** by reduction with lithium aluminium hydride.



Scheme 5. Reagents and conditions: (a) (i) allyl lithium reagent, -78 ^{o}C (ii) acryloyl chloride, -78 ^{o}C; (b) (Im)$Cl_2PCy_3RuCHPh$, CH_2Cl_2, reflux; (c) (i) H_2, Pd/c, EtOH, rt; (ii) TsCl, Et_3N, rt; (d) magnesium monoperoxyphthalate, MeOH, rt; (e) NaH, THF, 20 ^{o}C then reflux; (f) $LiAlH_4$, THF, reflux.

2.1.3 Present work

Novel route to complex molecules such as natural and pharmaceutical important products is still a challenge in synthetic organic chemistry. As can be seen from the above descriptions, the literature methods for the synthesis of (*R*)-(-)-coniceine (**1**), employ either chiral starting materials or expensive chiral auxilaries. Hence, the synthesis of (*R*)-(-)-coniceine (**1**), starting from prochiral substrates using catalytic enantioselective reactions, is still desirable. As chiral catalysts are available in both enantiomeric forms, its advantageous as both the stereoisomers of product can be synthesized from the same prochiral substrate. Also, the use of oragnocatalysis provides methods for obtaining chiral compounds in environmentally benign manner and from easily available starting materials.

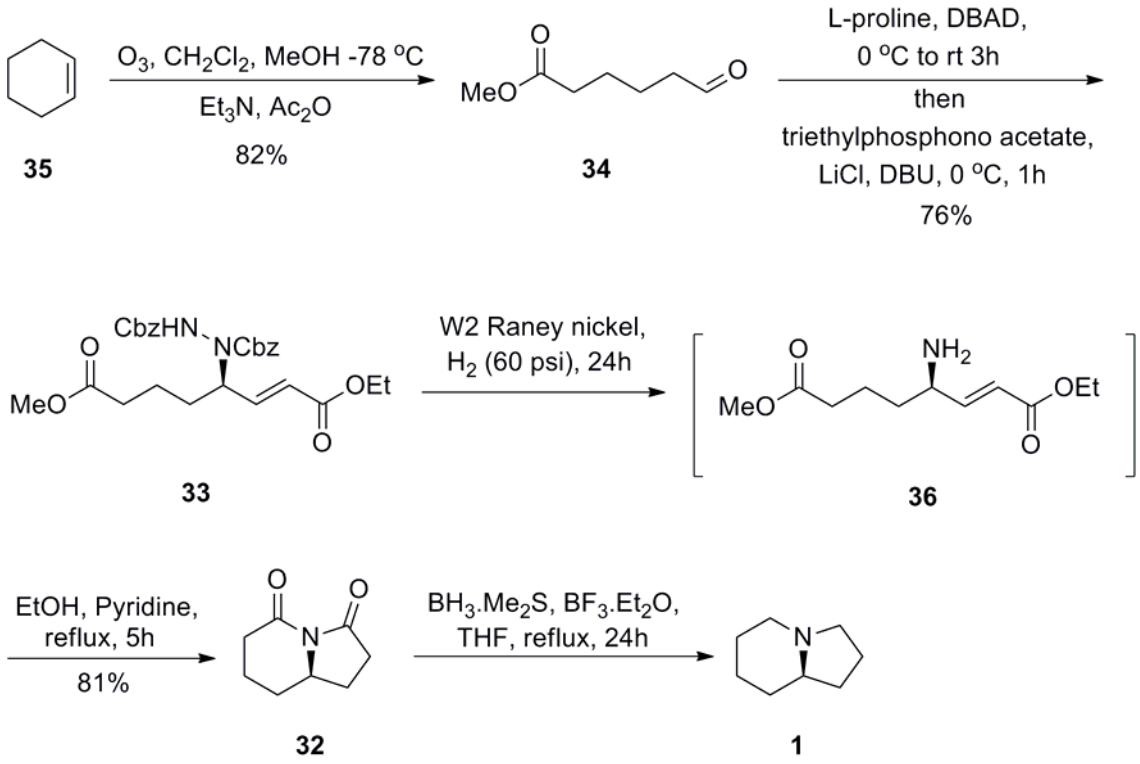


Scheme 6. Retrosynthetic analysis

The retrosynthetic analysis for the enantioselective synthesis of *R*-(-)-coniceine **1** is depicted in **Scheme 6**. It was envisaged that a simple reduction of bicyclic lactum **32** could afford *R*-(-)-coniceine **1**. Bicyclic lactum **32** could be prepared from the γ-amino-α,β-unsaturated ester **33**. The γ-amino-α,β-unsaturated ester **33** could be obtained from aldehyde **34** through seqential proline catalyzed α-amination-HWE olefination. The aldehyde **34** could obtained from cyclohexene **35** through ozonolysis.

Accordingly, as shown in **scheme 7**, synthesis starts from cyclohexene **35**, a relatively cheap starting material. Cyclohexene **35** on ozonolysis in presence of $NaHCO_3$ at -78 ^oC in CH_2Cl_2/MeOH mixture followed by treatment with acetic anhydride and triethyl amine afforded aldehyde **34** in 82% yield. The aldehyde **34** then subjected to L-proline (10 mol%) catalyzed α-amination with dibenzylazodicarboxylate in CH_3CN at 0 ^oC for 2h and 1h at room temperature. The initial dark yellow colour turns to faint yellow. To this reaction mixture were added pre-cooled solution of pre-mixed triethyl phosphonoacetate, LiCl and DBU in acetonitrile at 0 ^oC. As these two reactions [α-amination and HWE olefination] were performed in one pot, termed as sequential α-amination-HWE olefination reaction. The optical purity of γ-amino-α,β-unsaturated ester **33** is >99%, determined by chiral HPLC analysis. The γ-amino-α,β-unsaturated ester **33** then subjected to W2 Raney Nickel catalyzed hydrogenolysis in methanol in presence of catalytic glacial acetic acid. After 24h, TLC analysis shown completion, the catalyst was filtered through a bed of celite and concentrated under reduced pressure. The crude γ-amino ester **36** in ethanol then heated to reflux for 5h in presence of catalytic pyridine afforded bicyclic lactum **32** in 81% yield. The bicyclic lactum **32** on treatment with borane-dimethyl sulfide in presence of boron trifluoride

etherate afforded target *R*-coniceine **1** in 87% yield. The analytical data of *R*-coniceine **1** is in agreement with literature data.



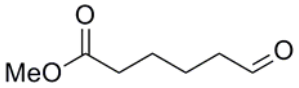
Scheme 7.

2.1.4 Conclusion

In conclusion the short and efficient enantioselective synthesis of (R)-(-)-coniceine was achieved using sequential α-amination-HWE olefination of aldehyde as key step and source of chirality. Cheap starting material, fewer steps are additional salient features of this synthesis.

2.1.5 Experimenal

1) Methyl-6-oxohexanoate (34)

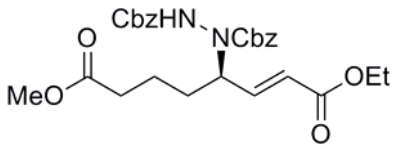


To a cooled solution of cyclohexene **35** (6.161 g, 75 mmol) and sodium hydrogen carbonate (2.000 g) in dicloromethane (250 mL) and methanol (50 mL) at -78 °C, ozone was bubbled. Ozone addition was stopped when solution turns blue and nitrogen was bubbled at the same temperature till blue colour disappears.The solution was filtered

and concentrated to 50 mL, diluted with benzene (80 mL) and again concentrated to 50 mL. The solution diluted with dichloromethane (225 mL) and cooled to 0 ^{o}C, and added Et_3N (16 mL, 113 mmol) and acetic anhydride (21.24 mL, 225 mmol) and stirred for additional 15 minutes at that temperature. The solution allowed to stir at room temperature for 4h. The solution washed with 150 mL portions of 0.1N hydrochloric acid, 10% sodium hydroxide solution and water. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain crude aldehyde **34**. The crude aldehyde **34** was purified by high vacuum distillation.

Yield: 8.871 g (82%); colourless liquid; IR ($CHCl_3$) ν_{max} 2987, 2952, 1735, 1714, 1252, 678 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ= 1.60-1.67 (m, 4H), 2.28-2.35 (m, 2H), 2.41-2.47 (m, 2H), 3.64 (s, 3H), 9.74 (t, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ= 21.2, 24.0, 33.4, 43.1, 51.3, 173.5, 202.0 ppm.

2) (4*R*,2*E*)-1-ethyl-8-methyl-4-(*N*,*N*'-(dibenzyloxycarbonyl)hydrazinyl)oct-2-enedioate (33)

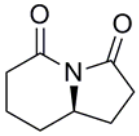


To a cooled solution of dibenzyl azodicarboxylate (DBAD) (3.280 g, 10 mmol) and L-proline (0.115 mg, 10 mol %) in dry CH_3CN (100 mL) at 0 °C was added aldehyde **34** (1.44 g, 10 mmol), and the mixture was stirred for 2 h at 0 °C and further at 10 °C for 1 h. This was followed by addition of lithium bromide (1.300 g, 15 mmol), triethyl phosphonoacetate (3.360 g, 15 mmol), and DBU (1.520 g, 10 mmol) in that sequence, and the whole mixture was stirred at 5 °C for 45 min. It was then quenched by the addition of aqueous ammonium chloride solution and extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the crude product **33**, which was then purified by flash column chromatography (packed with silica gel 60-120 mesh) using petroleum ether and ethyl acetate as eluents to afford the pure product **33**.

Yield: 3.891 g (76%); viscous liquid; $[\alpha]_D^{25}$ = +17.4 (*c* 1.0, $CHCl_3$); ee >99%, [Chiral HPLC analysis: Chiracel OJ-H (250 x 4.6 mm) column; eluent: 2-prapanol: petroleum ether 2.5:97.5; flow rate: 0.7 mL/min., detector: 260 nm t_R=87.44 min., t_S= 89.49 min.]; IR ($CHCl_3$) ν_{max} 3389, 3020, 2926, 2852, 1758, 1715, 1289, 1215, 1041, 757 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ= 1.26 (t, 3H), 1.60-1.73 (m, 5H), 2.31 (t, 2H), 3.64 (s, 3H), 4.14-4.19 (q, 2H), 4.69-4.83 (m, 1H), 5.16 (m, 4H), 5.91 (brs, 1H), 6.60 (d, *J* = 15.5 Hz,

1H), 6.81-6.86 (m, 1H), 7.31 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): δ= 14.0, 21.0, 30.0, 33.2, 51.4, 58.1, 60.4, 67.5, 122.9, 127.7, 128.0, 128.1, 128.3, 135.4, 144.4, 155.5, 156.4, 166.0, 173.7 ppm; Elemental Anal. Calcd for $C_{27}H_{32}N_2O_8$: C, 63.27; H, 6.29; N, 5.47. Found: C, 63.31; H, 6.19; N, 5.41. LC-MS: *m/z* = 535.43 (M^+ + Na).

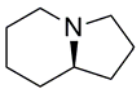
3) *R*-hexahydroindolizine-3,5-dione (32)



The solution of **33** (2.0 g, 3.90 mmol) in MeOH (50 mL) and acetic acid (10 drops) was treated with Raney nickel (5 g, excess) under H_2 (80 psig) atmosphere for 24 h. The reaction mixture was filtered over celite and concentrated to give crude γ-amino ester which on strirring in EtOH in presence of catalytic pyridine at 50 °C for 5h cyclized to product **32** (purified by flash chromatography using ethyl acetate as eluent).

Yield: 0.484 g (81%); viscous liquid; $[\alpha]_D^{25}$ = +26.1 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) ν_{max} 2918, 2854, 1668, 1461, 1377, 1112, 721 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ= 1.37-1.47 (m, 4H), 1.86-1.95 (m, 2H), 2.32 (t, *J* = 8.6 Hz, 2H), 2.40-2.61 (m, 2H), 3.55-3.61 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ= 19.5, 22.5, 27.8, 30.4, 33.2, 55.2, 172.7, 174.5 ppm.

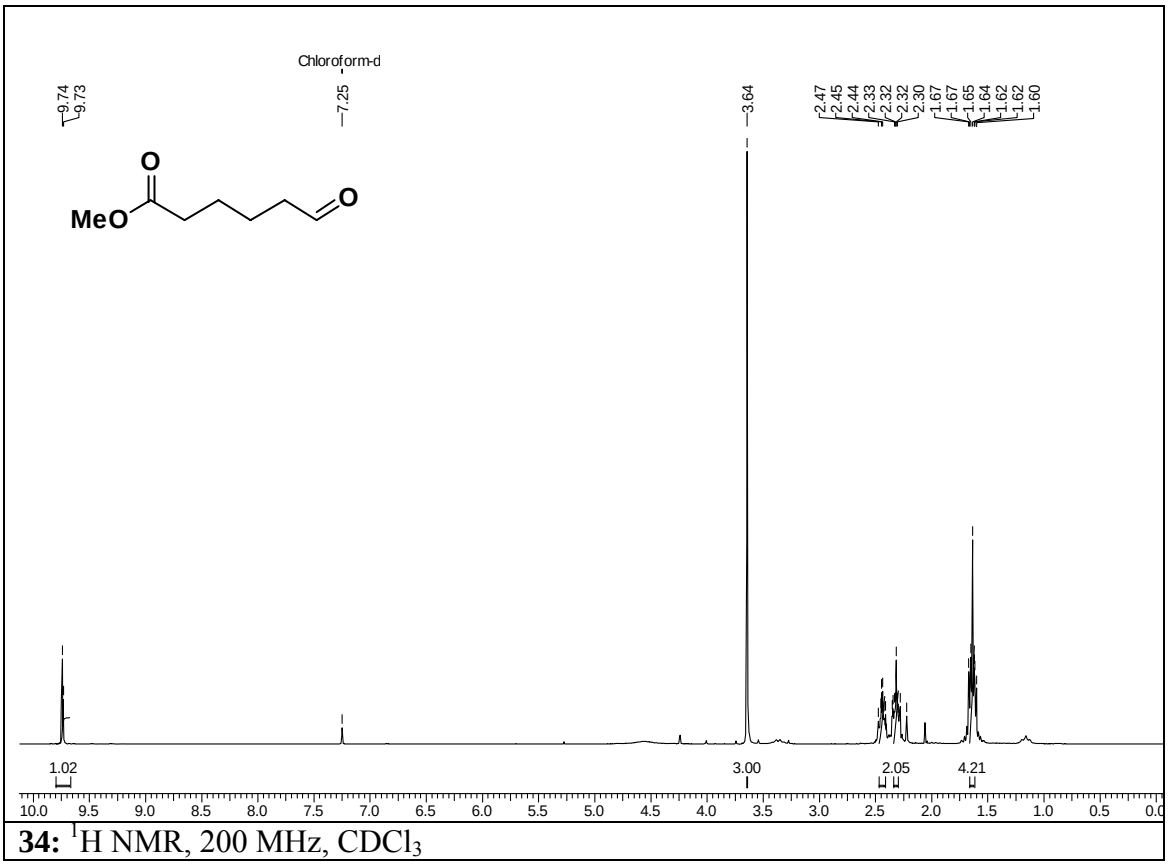
4) (*R*)-(-)-coniceine (1)



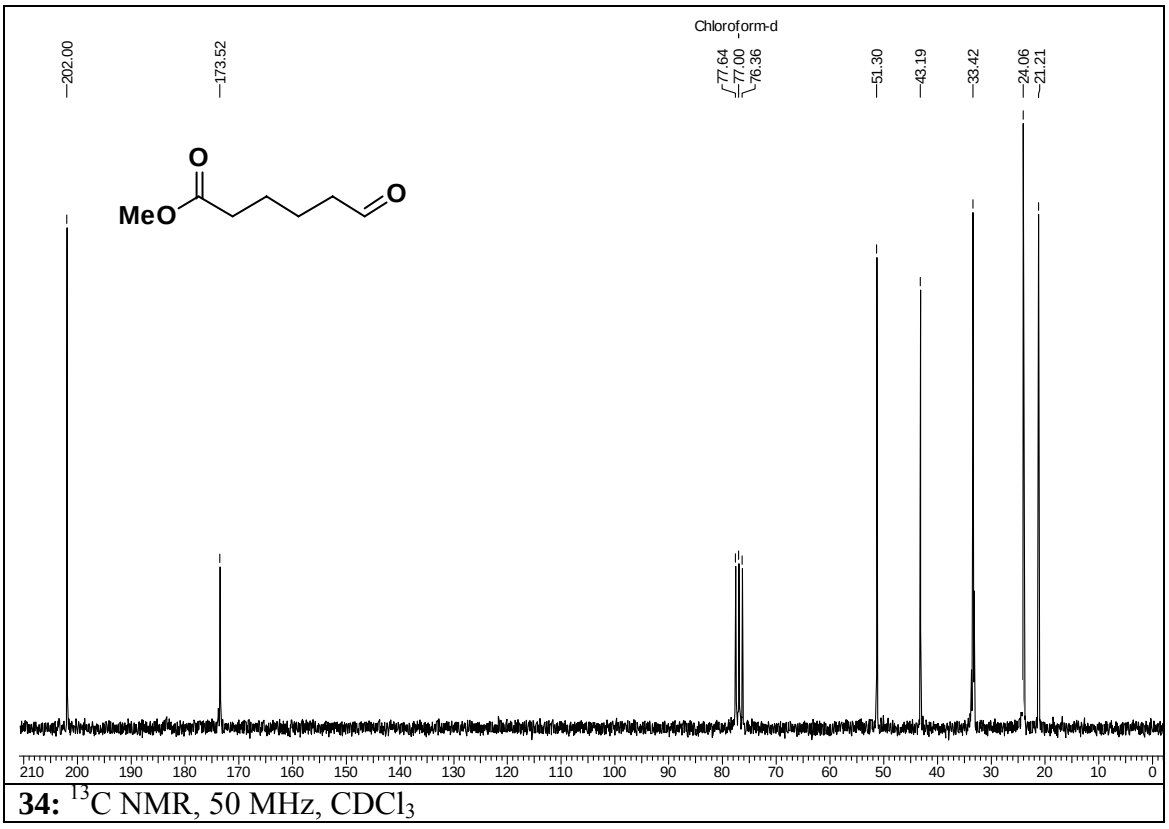
To the solution of bicyclic lactum **32** (0.306 g, 2 mmol) in THF (15 mL) under argon atmosphere added $BF_3.Et_2O$ (0.282 g, 2 mmol, 1equi) and boron-dimethyl sulfide (0.304 g, 4 mmol, 2 equi) dropwise. Once H_2 ceasing stopped, the solution refluxed for 24h. The solution concentrated under reduced pressure, the residue was purified by flash column chromatography to obtain (*R*)-(-)-coniceine **1**.

Yield: 0.217 g (87%); viscous liquid; $[\alpha]_D^{25}$ = -9.97 (*c* 1.24, EtOH) {Lit.[30] $[\alpha]_D^{25}$ = -9.8 (*c* 1.10, EtOH)}; IR ($CHCl_3$) ν_{max} 2952, 2920, 1461, 1454, 1320,1255, 1096 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ= 1.20-1.42 (m, 11H), 1.95 (dt, *J* = 3.6,11.2 Hz, 1H), 2.07 (q, *J* = 9.0 Hz, 1H); 3.02-3.13 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ= 20.5, 24.5, 25.4, 30.5, 31.0, 53.0, 54.2, 64.3 ppm. Elemental Anal. Calcd for $C_8H_{15}N$: C, 76.74; H, 12.07; N, 11.19. Found: C, 76.77; H, 12.01; N, 11.07.

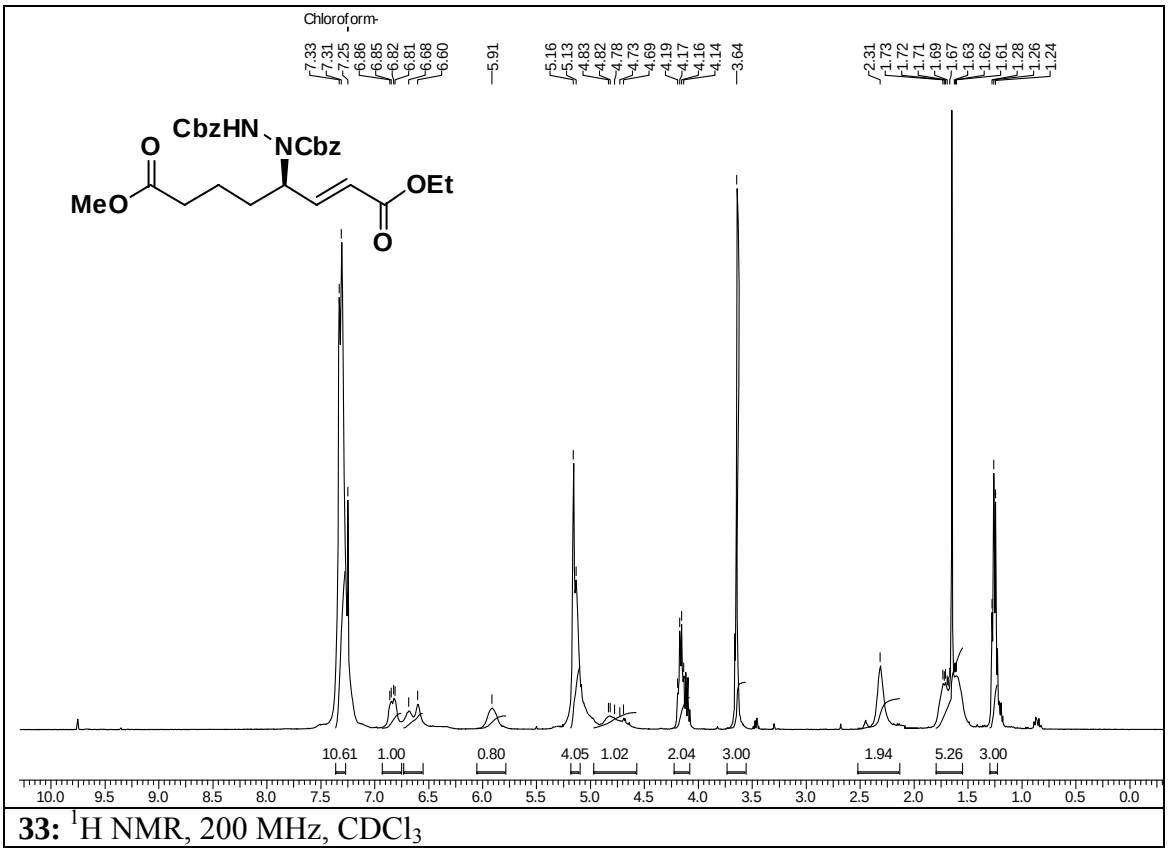
2.1.6 Analytical Data



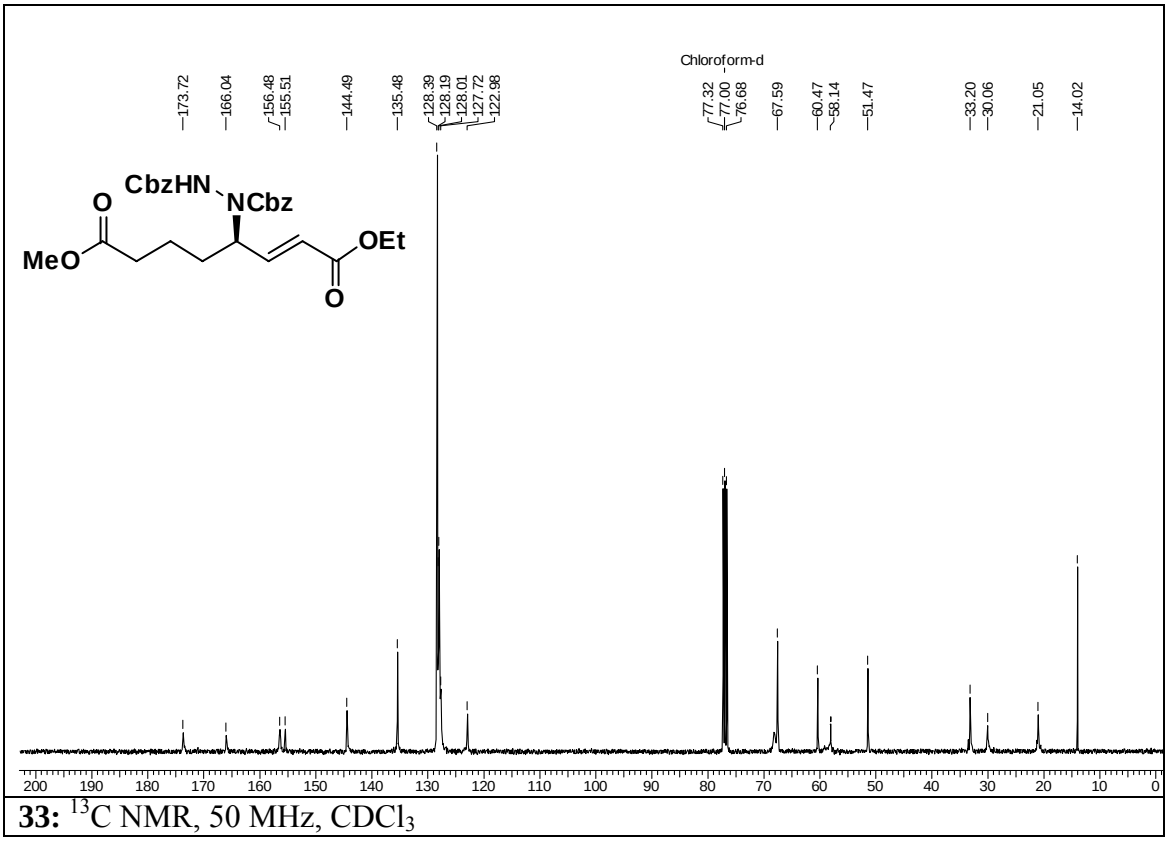
34: ^{1}H NMR, 200 MHz, $CDCl_3$



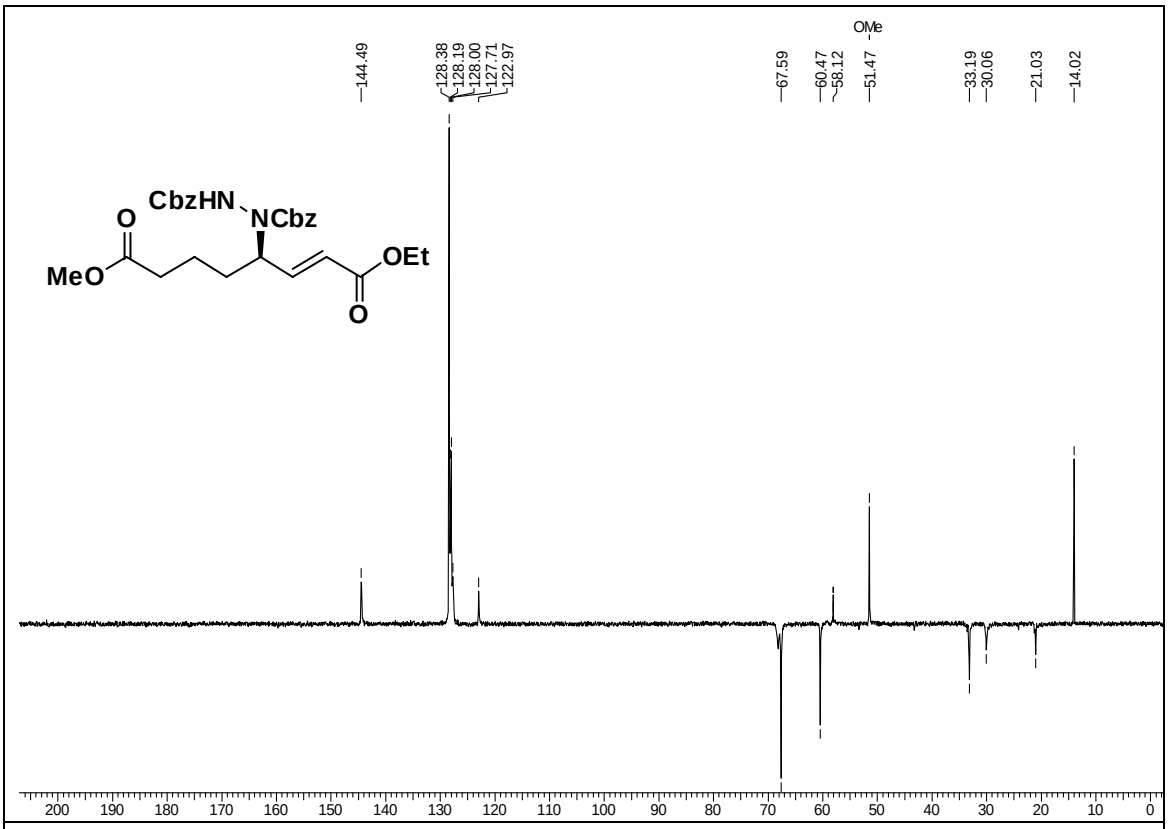
34: ^{13}C NMR, 50 MHz, $CDCl_3$



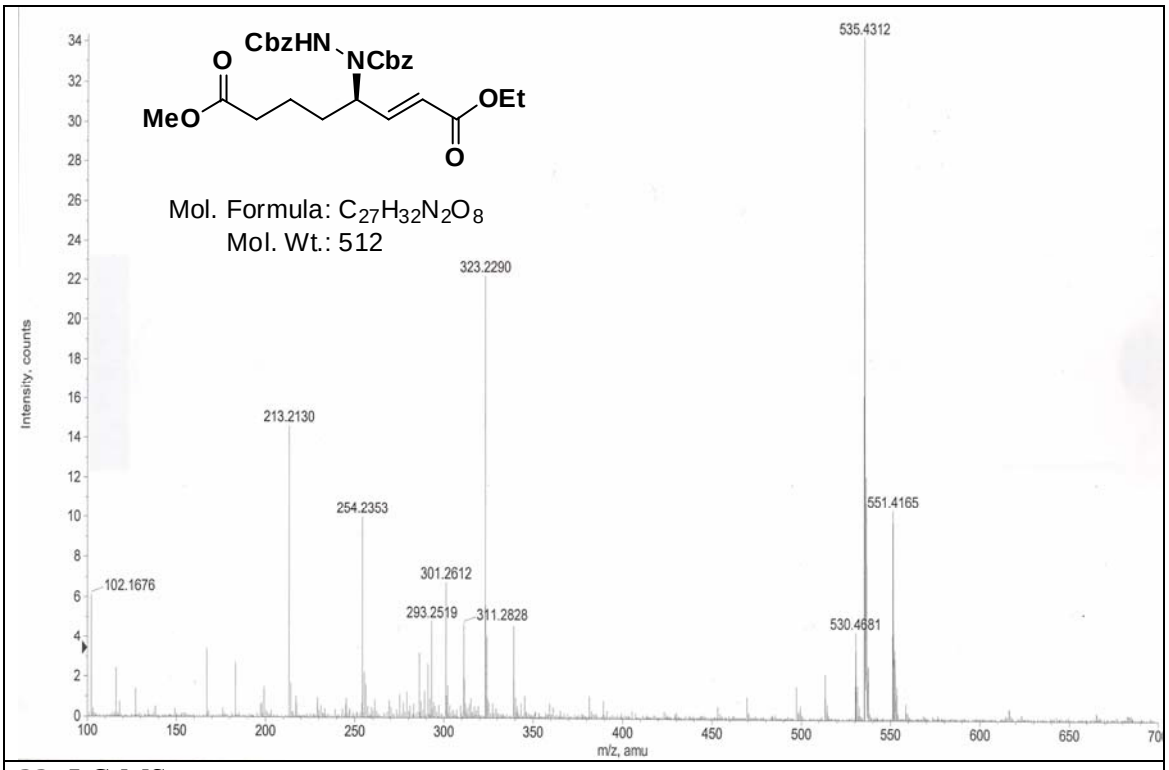
33: ^{1}H NMR, 200 MHz, $CDCl_3$



33: ^{13}C NMR, 50 MHz, $CDCl_3$

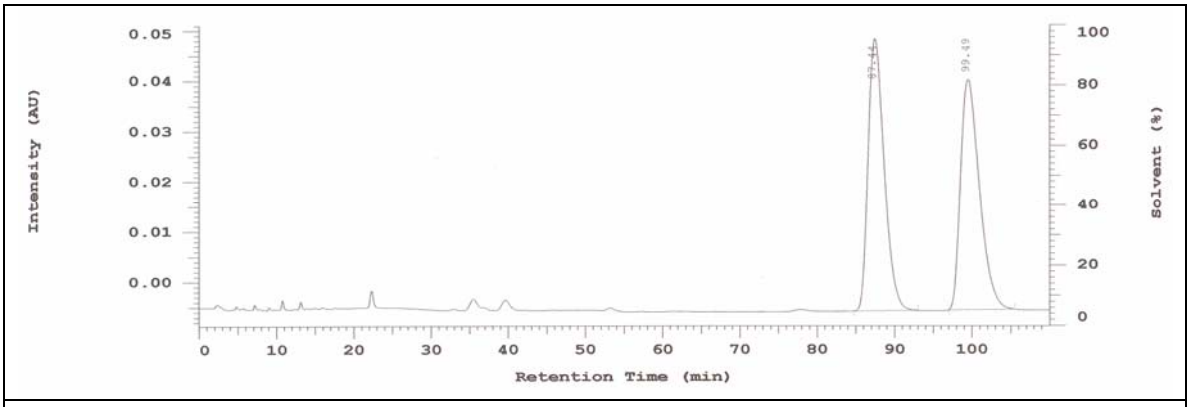


33: DEPT NMR, 200 MHz, $CDCl_3$



33: LC-MS

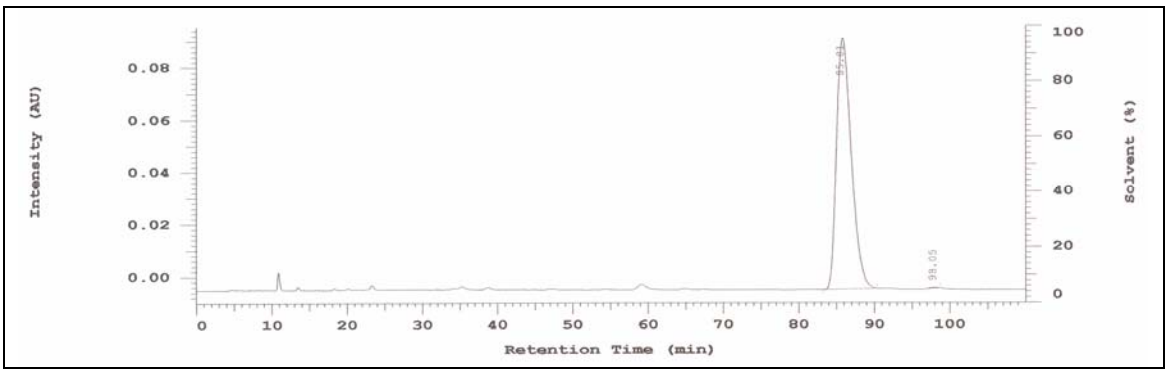
Chiral HPLC Analysis of compound 33



Racemic sample chromatograph

No.	Retention Time	Height	Area	Area %
1	87.44	27007	3879914	50.173
2	9949	22833	3853116	49.827
		49840	7733030	100.000

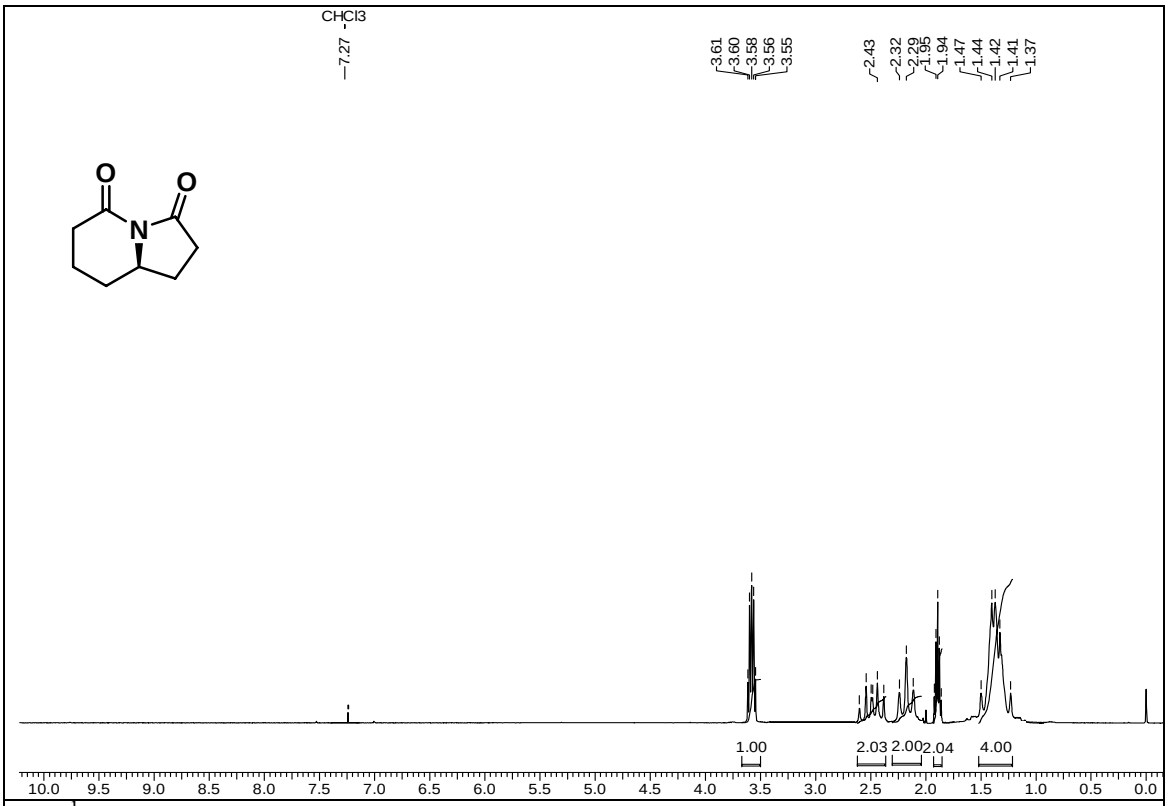
Column : Chiracel OJ-H (250 x 4.6mm)
Mobile phase : 2-Propanol + Pet. ether (2.5:97.5)
Wavelenth : 260 nm
Flow : 0.7 mL/min
Concentration : 1.00 mg/1.0 mL mobile phase
Injection vol. : 10 µL



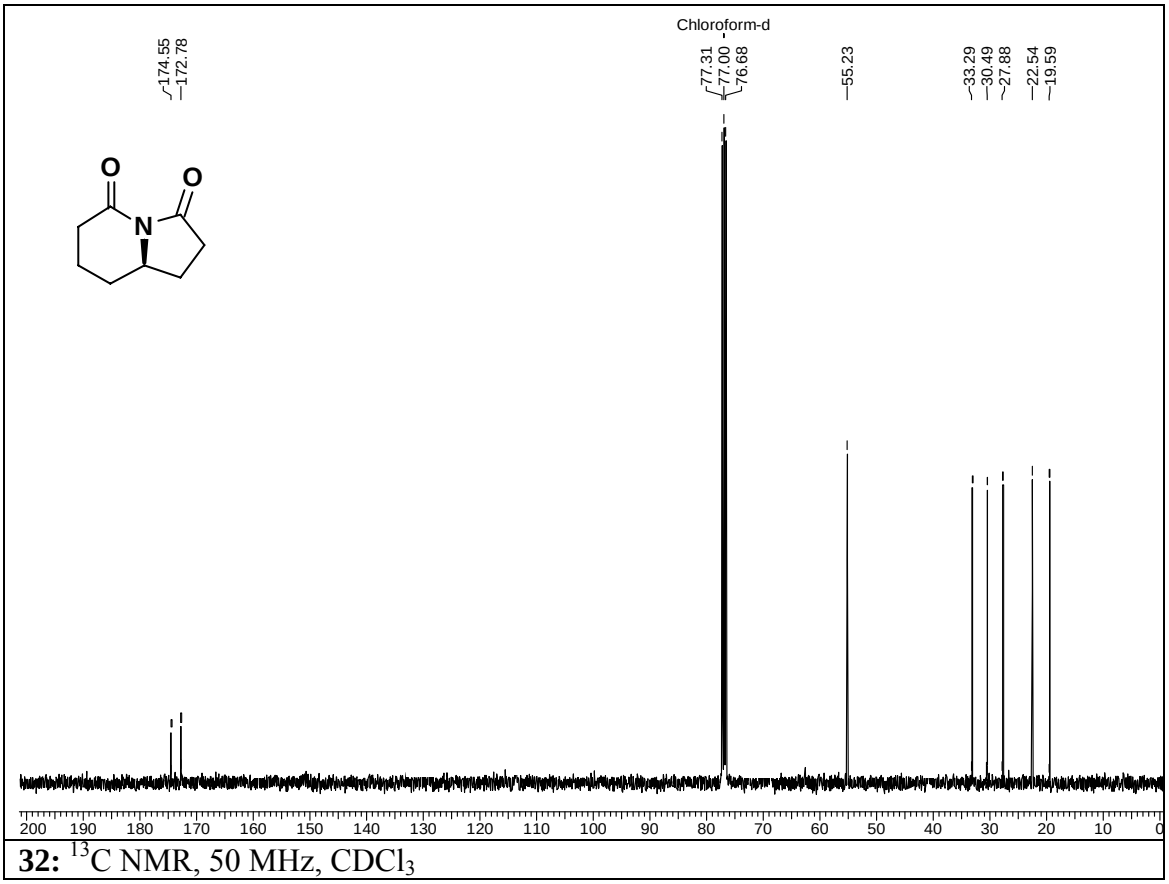
Chiral sample chromatograph

No.	Retention Time	Height	Area	Area %
1	85.81	47796	6491675	99.858
2	98.05	139	9247	0.142
		47935	6500922	100.000

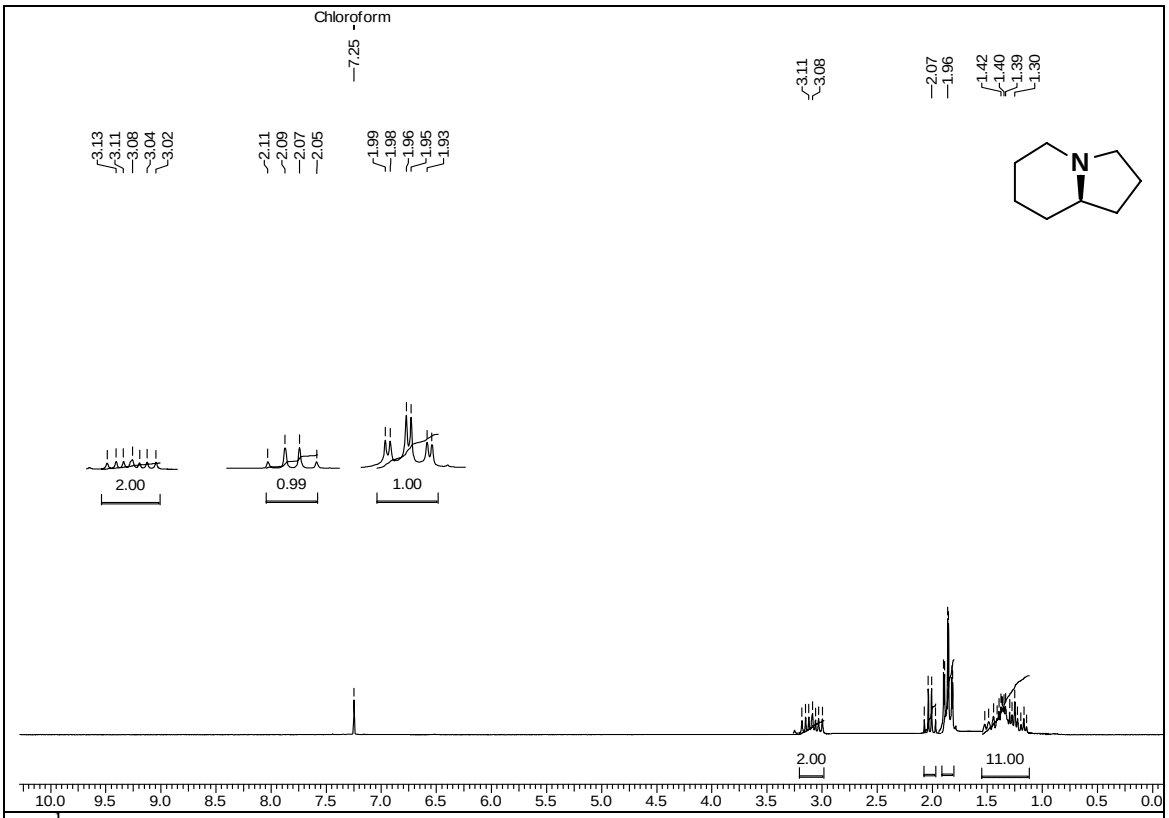
Column : Chiracel OJ-H (250 x 4.6mm)
Mobile phase : 2-Propanol + Pet. ether (2.5:97.5)
Wavelenth : 260 nm
Flow : 0.7 mL/min
Concentration : 1.00 mg/1.0 mL mobile phase
Injection vol. : 10 µL



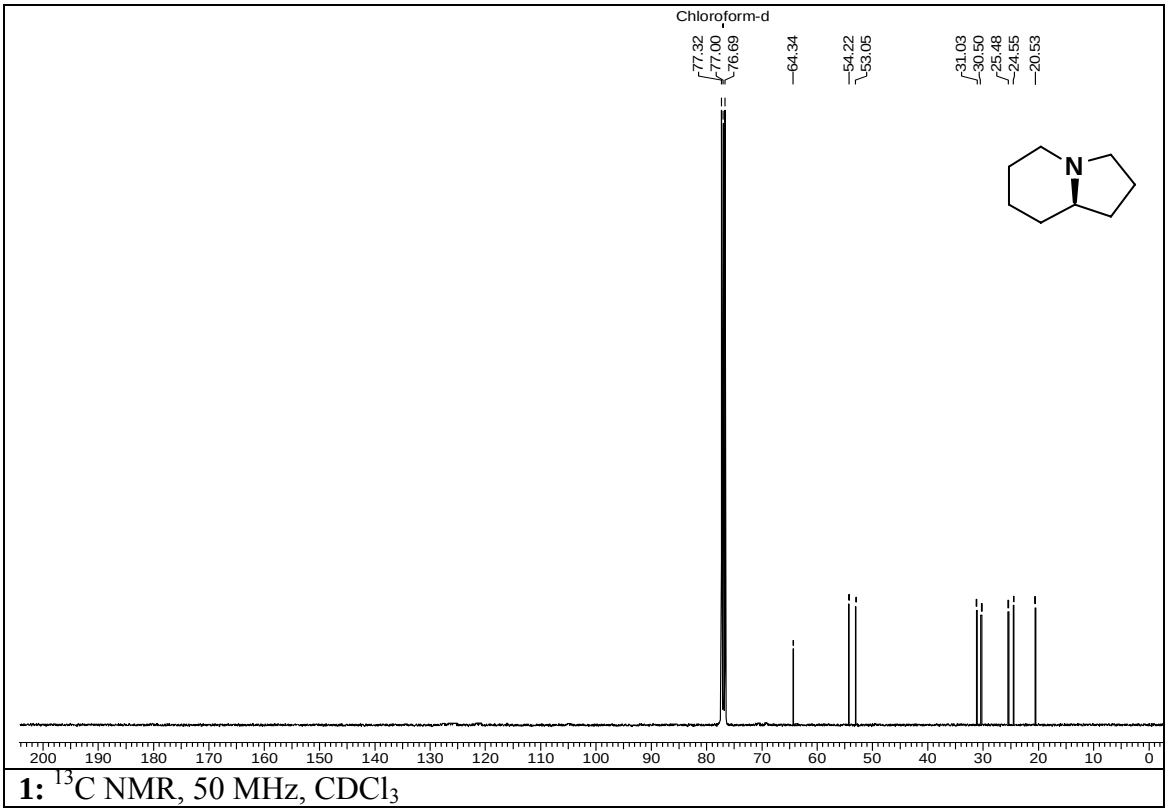
32: ^{1}H NMR, 200 MHz, $CDCl_3$



32: ^{13}C NMR, 50 MHz, $CDCl_3$



1: ^{1}H NMR, 200 MHz, $CDCl_3$



1: ^{13}C NMR, 50 MHz, $CDCl_3$

2.1.7 References

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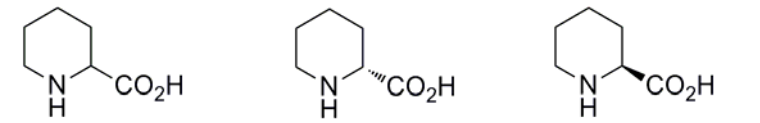
2.2 SECTION B

ASYMMETRIC SYNTHESIS OF (*R*)-PIPECOLIC ACID

2.2.1 Introduction

Pipecolic acid **1** (so named pipecolinic acid, homoproline, or 2-piperidinecarboxylic acid) is a non proteinogenic amino acid (**Fig. 1**).



Pipecolic acid **1** (*R*)-Pipecolic acid **1** (*S*)-Pipecolic acid **1**

Figure 1.

Pipecolic acid is a component of several secondary metabolites in plants and fungi.[1] Pipecolic acid, that is a metabolite of lysine, is also found in human physiological fluids and is thought to play an important role in the central inhibitory γ-aminobutyric acid system.[2] Pipecolic acid serves as a substrate of some peptides and polyketide synthetases, resulting in the formation of secondary metabolites with interesting pharmacological activities such as the immunosuppressors rapamycin,[3] FK506[4] and immunomycin, or the antitumor antibiotic sandramycin.[5] It is also a precursor to numerous compounds such as synthetic peptides,[6] local anaesthetics or potential enzyme inhibitors.[7]

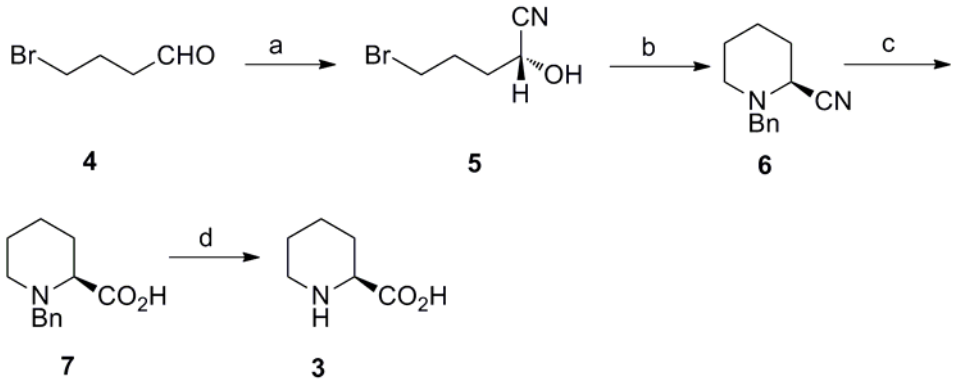
2.2.2 Review of Literature

Many chemists have been inspired by the important bioactivities of pipecolic acid and derivatives and have therefore developed new enantioselective methods to synthesize these compounds. A few, interesting synthesis of pipecolic acid are describes below.

2.2.2.1 Nazabadioko *et al.* (1998, Scheme 1)[8]

Chemoenzymatic synthesis of (*S*)-2-cyanopiperidine **6** provided an access to (*S*)-pipecolic acid. This synthesis is based on a (*R*)-oxynitrilase-catalysed reaction for the enantioselective preparation of the bromo cyanohydrine derivative **5**. This compound

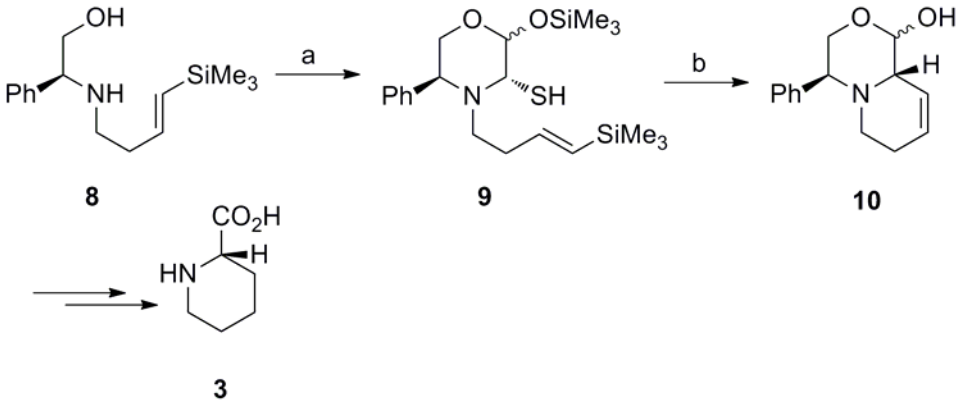
was transformed to piperidine **6** in two steps (**Scheme 1**): first, the transformation of hydroxyl group in trifluoromethanesulfonyloxy and its substitution by benzylamine, and second, the subsequent cyclization by a slower substitution of the bromine yielded compound **6**. A careful hydrolysis to prevent racemization followed by hydrogenolysis gave enantiopure (*S*)-pipecolic acid **3**.



Scheme 1. *Reagents and conditions*: (a) (*R*)-oxynitrilase; (b) (i) Tf_2O, Pyridine, H_2O; (ii) $BnNH_2$, Et_3N; (c) (i) EtOH, HCl gas; (ii) Na_2CO_3; (iii) 6N HCl reflux; (d) H_2, $Pd(OH)_2$, 3N HCl.

2.2.2.2 Agami *et al.* (2000, Scheme 2)[9]

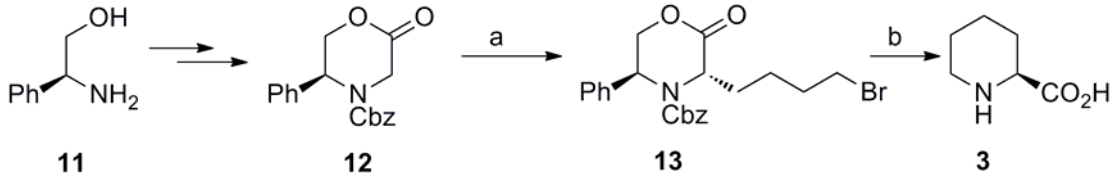
Agami and co-workers used (*S*)-phenyl glycinol as chiral inductor for an enantioselective synthesis of (*S*)-pipecolic acid **3**. Morpholine **9** was obtained from the condensation between phenylglycinol derived amino alcohol **8** and glyoxal in the presence of thiophenol. The key-step was a highly diastereoselective ene-iminium cyclisation between iminium ion (generated by action of Lewis acid) and the vinylsilane moieties. The intermediate **10** was converted in three steps into (*S*)-pipecolic acid **3**.



Scheme 2. *Reagents and conditions*: (a) glyoxal, PhSH, TMSCl, Et_3N; (b) $ZnCl_2$.

2.2.2.3 Roos *et al.* (2000, Scheme 3)[10]

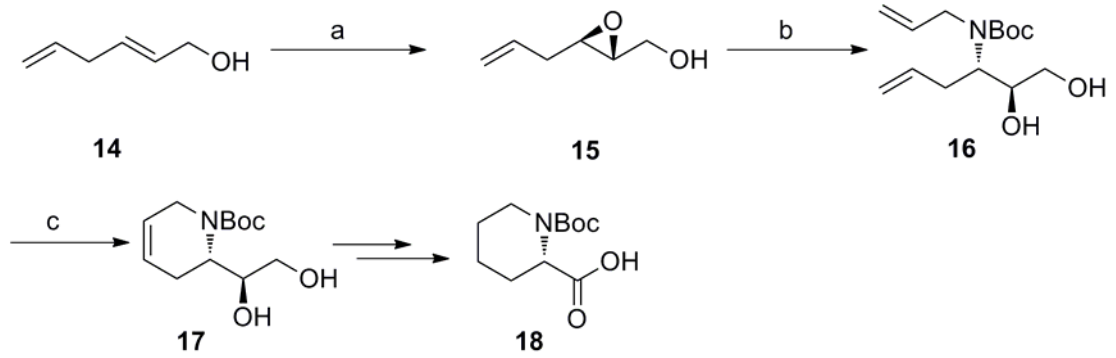
Roos and co-workers also used (*S*)-phenylglycinol as starting material. Lactone **12**, prepared in three steps from (*S*)-phenylglycinol **11**, was alkylated with a bromotriflate to afford diastereoisomerically pure compound **13**. Treatment of **13** with hydrogen induced cleavage of the benzyloxycarbonyl group with concomitant cyclization and debenzylation of the cyclic lactone to give enantiopure **3**.



Scheme 3. *Reagents and conditions*: (a) NaHMDS, $Br(CH_2)_4OTf$; (b) H_2, Pd/C.

2.2.2.4 Ginesta *et al.* (2002, Scheme 4)[11]

Ring-closing metathesis (RCM) has been exploited in a recent synthesis of pipecolic acid from the known enantiomerically enriched epoxyalcohol **15**, synthesized from the allylic alcohol **14** via a Sharpless epoxidation (**Scheme 4**). Nucleophilic epoxide ring-opening using allylamine was followed by protection of the amino group by Boc_2O. The key intermediate **17** was obtained by a RCM, catalyzed by the Grubbs' reagent, of the doubly unsaturated amine **16** with 72% yield. Hydrogenation and oxidation led to *N*-Boc-pipecolic acid **18**.

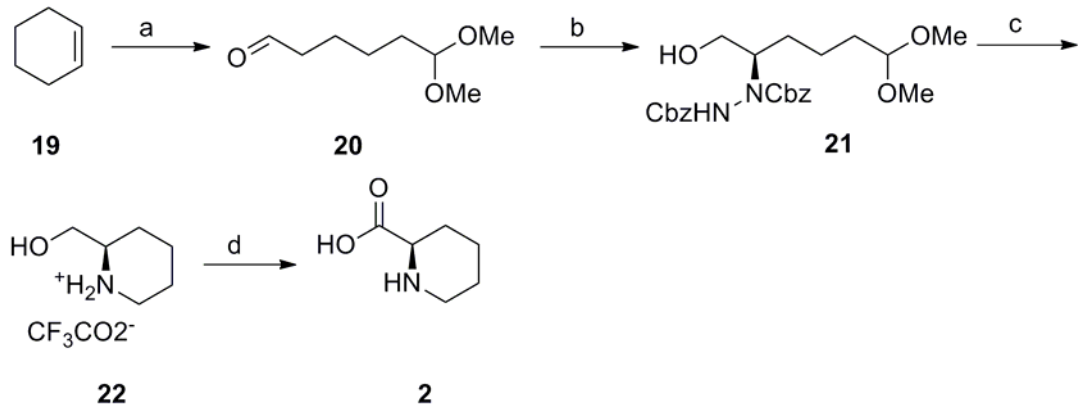


Scheme 4. *Reagents and conditions*: (a) Sharpless epoxidation; (b) allyl amine, LiClO4, Boc_2O, ultrasonics; (c) Grubb's catalyst.

2.2.2.5 Greck *et al.* (2009, Scheme 5)[12]

Greck and co-workers used L-proline catalyzed asymmetric amination of aldehyde protocol for synthesis of (*R*)-pipecolic acid. Aldehyde **20** obtained from cyclohexene

via ozonolysis. Aldehyde **20** on L-proline catalyzed amination followed by reduction with sodium borohydride afforded aminoalcohol **21**. Under hydrogenation conditions aminoalcohol **21** undergoes cyclization to afford cyclic aminoalcohol **22**. Alcohol **22** on oxidation with potassium permagnate afforded (R)-pipecolic acid.**2**.

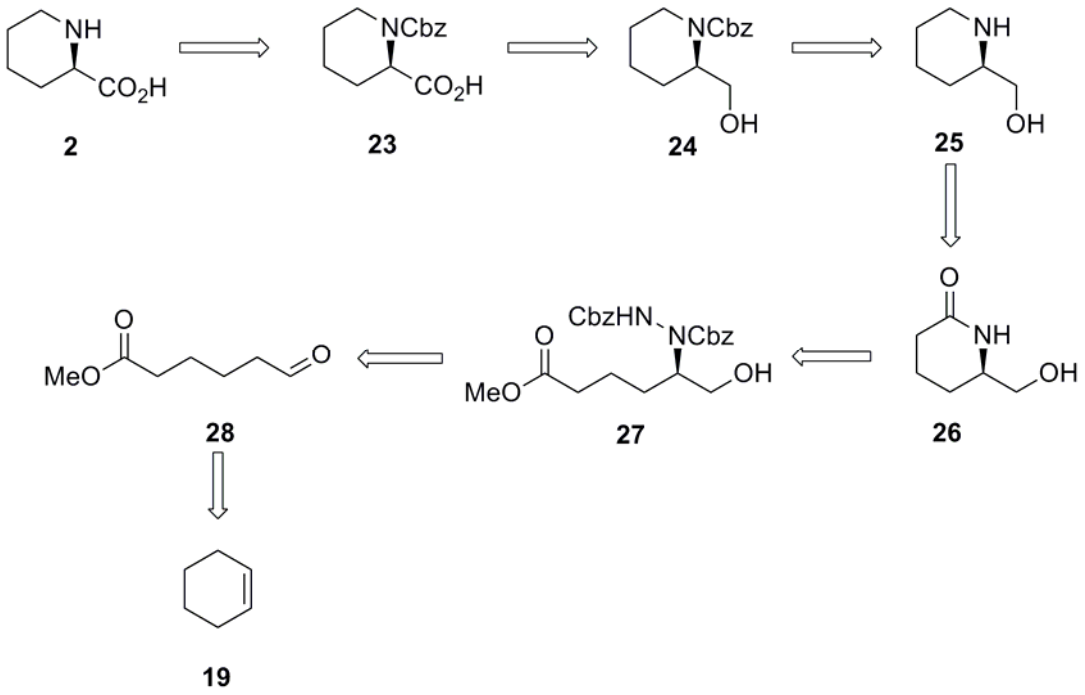


Scheme 5. *Reagents and conditions*: (a) O_3, CH_2Cl_2, MeOH -78 ^oC; (b) L-proline, DBAD, CH_3CN then $NaBH_4$, MeOH; (c) (i) H_2, Pd/C; (ii) Raney Ni, MeOH, H_2, rt; (iii) H_2, PtO_2, H_2O, TFA,; (d) $KMnO_4$, H_2SO_4, rt.

2.2.3 Present work

Even though few methods are reported for the synthesis of pipecolic acid, most of these methods suffer from the fact that they make use of chiral starting materials, expensive reagents. Hence, the synthesis of (*R*)-pipecolic acid **2**, starting from prochiral substrates using catalytic enantioselective reactions, is highly desirable.

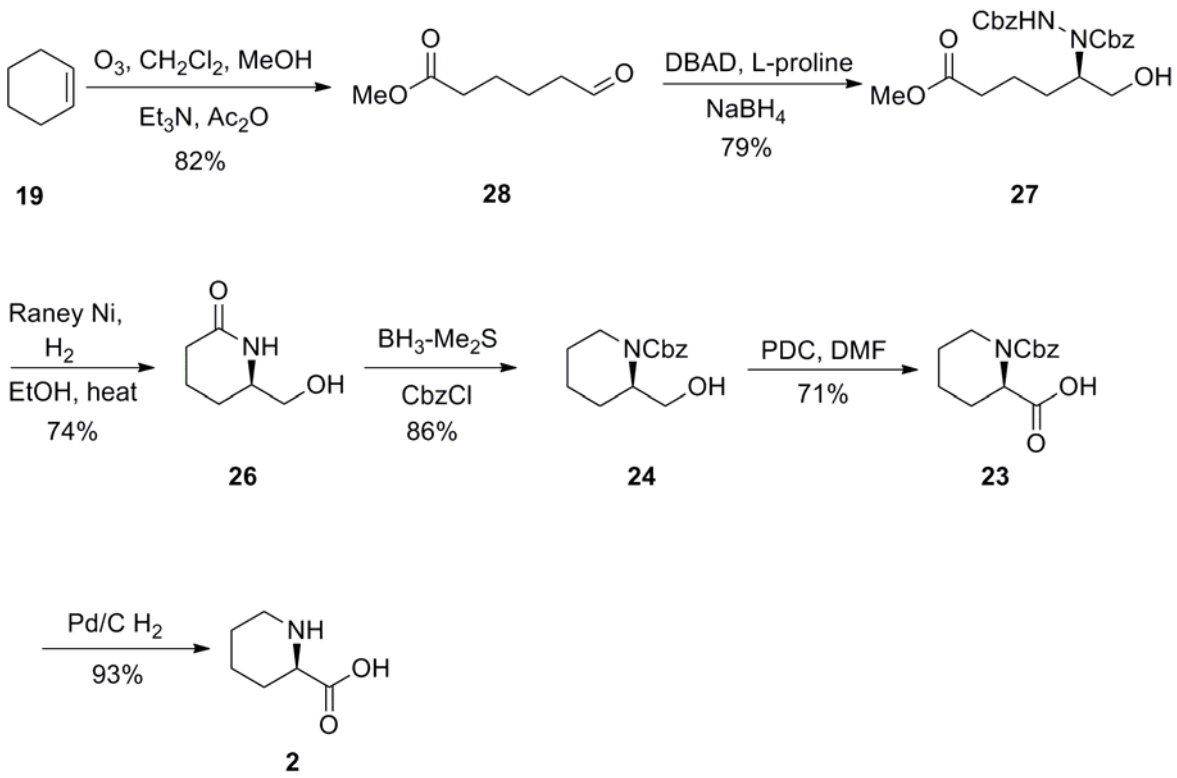
The retrosynthetic analysis for the enantioselective synthesis of (*R*)-pipecolic acid **2** is depicted in **Scheme 6**. It was envisaged that (*R*)-pipecolic acid **2** could be obtained from protected (*R*)-pipecolic acid **23**. The protected pipecolic acid could be synthesized from *N*-protected aminoalcohol **24**. The protected alcohol **24** could be accessible from lactum **26** via aminoalcohol **25**. The lactum **26** could be obtained from aminohydroxyl ester **27**. The Aminoalcohol **27** could be obtained from aldehyde **28**, which could be accessible from cyclohexene **19** via ozonolysis.



Scheme 6. Retrosynthetic analysis

Accordingly, as shown in **scheme 7**, synthesis starts from cyclohexene **19**, a relatively cheap starting material. Conversion of cyclohexene **19** to aldehyde **28** was discussed in earlier section (Chapter 2, Section A, compound **34**). The aldehyde **28** subjected to L-proline catalyzed α-amination followed by reduction with $NaBH_4$ and obtained chiral 1,2-aminoalcohol **27** in 79% yield. The 1,2-aminoalcohol **27** on Raney nickel catalyzed hydrogenolysis for 24h followed by reflux in ethanol afforded lactum **26** in 74% yield. The lactum **26** then reduced to amino alcohol **25** with borane-dimethyl sulfide complex. The amino alcohol **25** immediately protected as benzyl carbamate **24** to avoid decomposition of aminoalcohol.

Compound **24** on oxidation with PDC in DMF at room temperature afforded protected pipecolic acid **23** in 71% yield. Last task was the unmasking the amino group to obtain (*R*)-pipecolic acid **2**. Pd/C catalyzed hydrogenation of acid **23** afforded (*R*)-pipecolic acid in 93% yield.



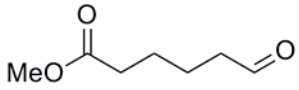
Scheme 7.

2.2.4 Conclusion

In conclusion, it's a demonstration of green, straightforward access to unnatural (*R*)-pipecolic acid using natural L-proline as source of chirality and as organocatalyst for the stereoslective formation of C-N bond.

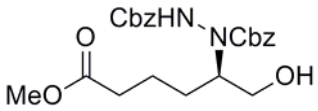
2.2.5 Experimental

1) Methyl-6-oxohexanoate (28)



Refer Chapter 2, Section A compound **34**.

2) (5*R*)-Methyl-5-(*N,N'*-(dibenzyloxycarbonyl)hydrazinyl)-6-hydroxyhexanoate (27)

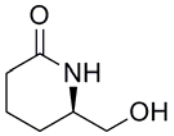


A mixture of dibenzyl azodicarboxylate (90%, 8.25 g, 25 mmol, 1 equiv) and L-proline (287 mg, 2.49 mmol, 10 mol %) in CH_3CN (200 mL) was taken and cooled to 0 ^oC, aldehyde **28** (3.600 g, 25 mmol) was added to it and the reaction mixture was allowed

to stir at the same temperature for 2 h and then warmed to 20 ^{o}C within 1 h. After the reaction mixture became colorless it was cooled to 0 ^{o}C, treated with EtOH (150 mL) and $NaBH_4$ (1.2 g), and was stirred for 5 min at 0 ^{o}C. The reaction mixture was worked up by adding half-concentrated aq ammonium chloride solution and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (pet. ether–ethyl acetate = 85:15).

Yield: 8.769 g (79%); viscous liquid; $[\alpha]_D^{25}$ = +27.6 (*c* 1.16, $CHCl_3$); ee >99%, [Chiral HPLC analysis: Chiracel OD-H (250 x 4.6 mm) column; eluent: 2-prapanol: petroleum ether 05:95; flow rate: 0.5 mL/min., detector: 260 nm t_R=61.56 min., t_S= 69.41 min.]; IR ($CHCl_3$) ν_{max} 3453, 2997, 1733 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ= 1.52-1.72 (m, 4H), 2.31 (t, *J* = 8 Hz, 2H), 3.50 (s, 3H), 4.13-4.24 (m, 2H), 4.67-4.83 (m, 1H), 5.15 (s, 4H), 7.33 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): δ= 22.3, 28.0, 34.5, 51.5, 58.6, 60.5, 67.8, 68.2, 127.7, 127.9, 128.1, 128.4, 135.5, 155.4, 156.6, 166.1 ppm. Elemental Anal. Calcd for $C_{23}H_{28}N_2O_7$: C, 62.15; H, 6.35; N, 6.30. Found: C, 62.18; H, 6.29; N, 6.27.

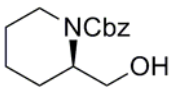
3) (*R*)-6-(Hydroxymethyl)piperidin-2-one (26)



The solution of **27** (6.0 g, 13.51 mmol) in MeOH (100 mL) and acetic acid (10 drops) was treated with Raney nickel (6 g, excess) under H_2 (80 psig) atmosphere for 24 h. The reaction mixture was filtered over celite and concentrated to give crude γ-amino ester which on strirring in EtOH in presence of catalytic pyridine at 50 °C for 5h cyclized to form product **26** (purified by flash chromatography using ethyl acetate as eluent).

Yield: 1.289 g (74%); yellow liquid; $[\alpha]_D^{25}$ = +47.1 (*c* 1.05, $CHCl_3$); IR ($CHCl_3$) ν_{max} 2854, 1668, 1461, 1377, 1112, 721 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.64-1.76 (m, 4H), 2.38 (t, *J* = 8Hz, 2H), 3.55-3.61 (m, 1H), 3.82-3.96 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ= 24.9, 29.6, 37.0, 55.7, 66.2, 171.1 ppm.

4) (*R*)-1-(Benzyloxycarbonyl)-2-(hydroxymethyl)piperidine (24)



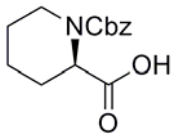
To the solution of lactum **26** (0.516 g, 4 mmol) in THF (20 mL) under argon atmosphere added $BF_3.Et_2O$ (0.564 g, 4 mmol, 1equi) and boron-dimethyl sulfide (0.304 g, 4 mmol, 1 equi) dropwise. Once H_2 ceasing stopped, the solution refluxed for

24h. The solution concentrated under reduced pressure, the residue was purified by flash column chromatography to obtain amino alcohol **25**.

To the solution of amino alcohol **25** and $NaHCO_3$ (1.2 equi.) in water (25 mL) was added benzylchloroformate at 0 °C and stirred at that temperature for 2h. The reaction mixture was extracted with diethyl ether (2 x 50 mL), washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude product. The crude product was purified to obtain **24**.

Yield: 0.856 g (86%); viscous liquid; $[\alpha]_D^{25}$ = +10.3 (*c* 1.15, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ= 1.39-1.82 (m, 6H), 2.85-3.06 (m, 1H), 3.59-3.68 (m, 1H), 3.80-3.85 (m, 1H), 3.90 (d, *J* = 8 Hz, 1H), 4.32-4.46 (m, 1H), 5.14 (s, 2H), 7.36 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ= 22.5, 30.4, 40.0, 52.8, 54.4, 61.2, 68.1, 127.7, 128.4, 136.6, 156.6 ppm.

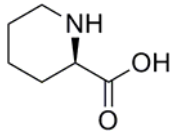
5) (*R*)-*N*-(benzyloxycarbonyl)-pipecolic acid (23)



To a solution of alcohol **24** (0.400 g, 1.60 mmol) in DMF (10 mL) was added PDC (2.416 g, 6.4 mmol, 4 equi.) at room temperature and stirred at that temperature till reaction completion. After completion reaction mixture was diluted with water (100 mL) and extracted with EtOAc (2 x 30 mL), washed with water, brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure to obtain crude product. The crude product was purified by flash column chromatography to obtain pure acid **23**.

Yield: 0.299 g (71%); $[\alpha]_D^{25}$ = +59.1 (*c* 1.15, AcOH) {Lit.[13] $[\alpha]_D^{25}$ = +59.7 (*c* 1.15, AcOH)}; ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.33-1.47 (m, 2H), 1.65-1.72 (m, 3H), 2.24-2.33 (m, 1H), 2.98-3.13 (m, 1H), 4.08 (dd, *J*= 8 Hz, 11 Hz, 1H), 4.89-5.02 (m, 1H), 5.16 (s, 2H), 7.32 (m, 5H), 10.63 (brs, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ= 20.6, 20.7, 24.5, 26.5, 41.7, 54.3, 67.5, 127.8, 128., 136.4, 155.8, 156.6, 177.3 ppm.

6) (*R*)-Pipecolic acid (2)

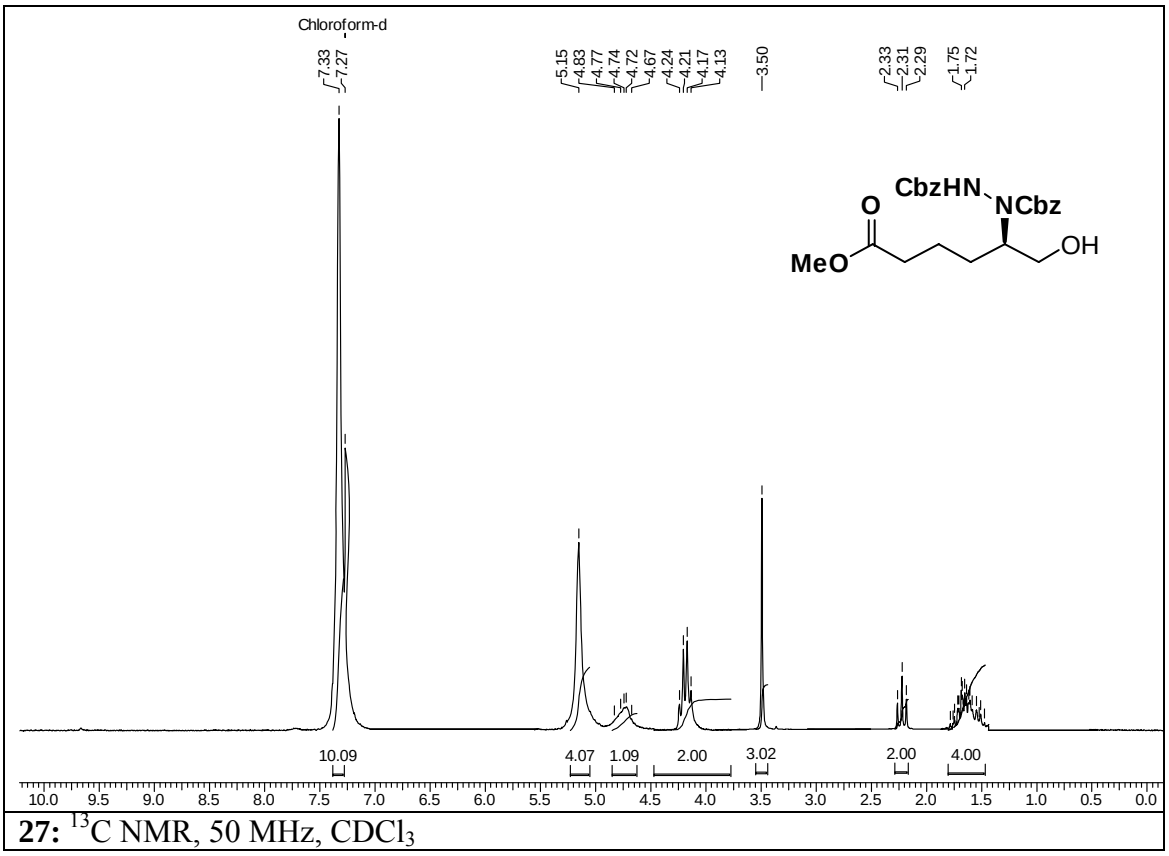


A solution of acid **23** (0.200 g, 0.76 mmol) in methanol (20 mL) and water (10 mL) was stirred under H_2 balloon pressure in presence of catalytic Pd/C (50 mg) for 4h. The

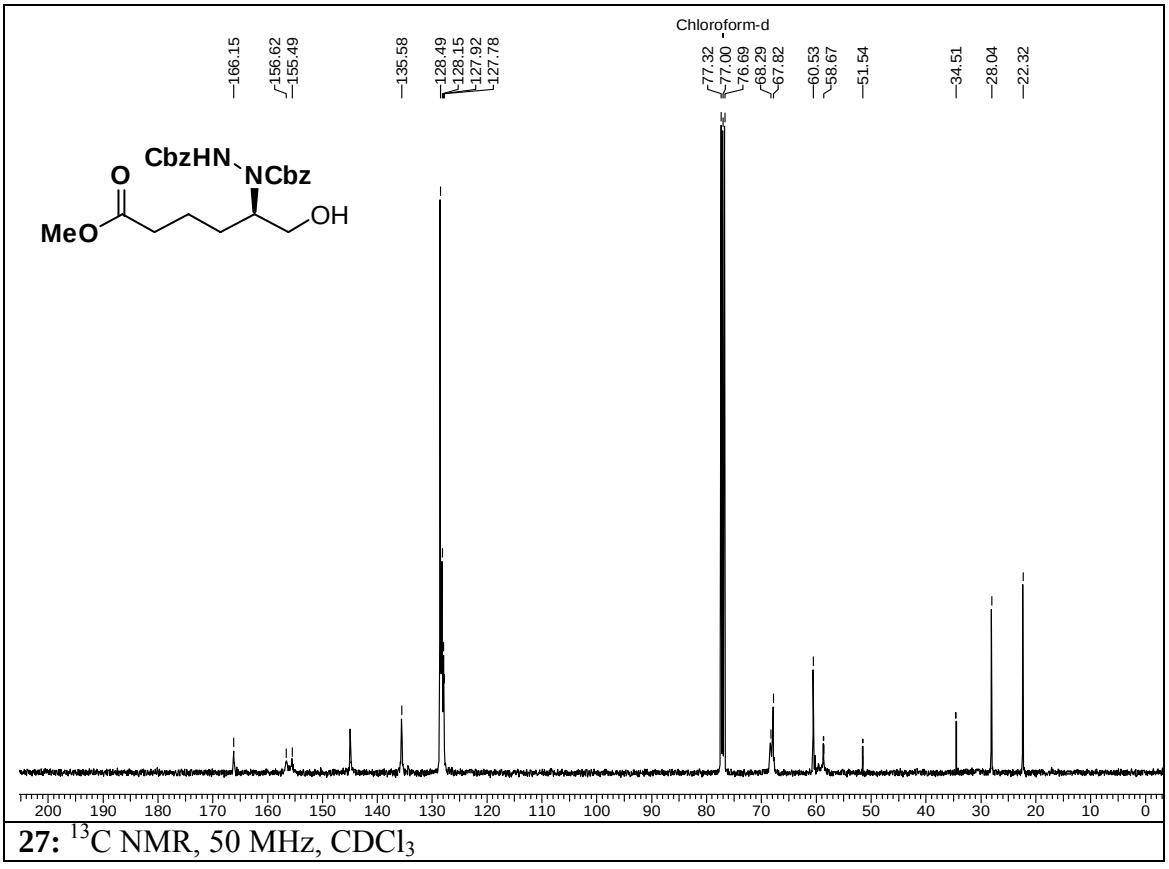
catalyst was filtered through a bed of celite and washed with water. The flitrate was concentrated under vacuum to obtain (*R*)-pipecolic acid **2**.

Yield: 0.091 g (93%); mp 272 °C; $[\alpha]_D^{25}$ = +26.9 (*c* 1.15, water) { Lit.[13] $[\alpha]_D^{25}$ = +25.8 (*c* 1, water)}; ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.61-1.73 (m, 3H), 1.85-1.92 (m, 2H), 2.26-2.30 (m, 1H), 2.99-3.06 (m, 1H), 3.43-3.46 (m, 1H), 3.89 (dd, *J* = 8 Hz, 10 HZ, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 21.30, 21.32, 25.7, 43.7, 57.0, 172.0 ppm.

2.2.6 Analytical Data

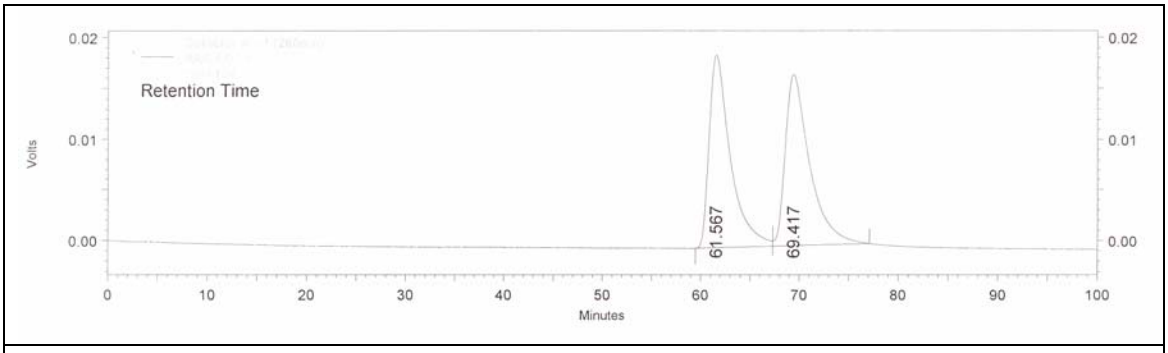


27: ^{13}C NMR, 50 MHz, $CDCl_3$



27: ^{13}C NMR, 50 MHz, $CDCl_3$

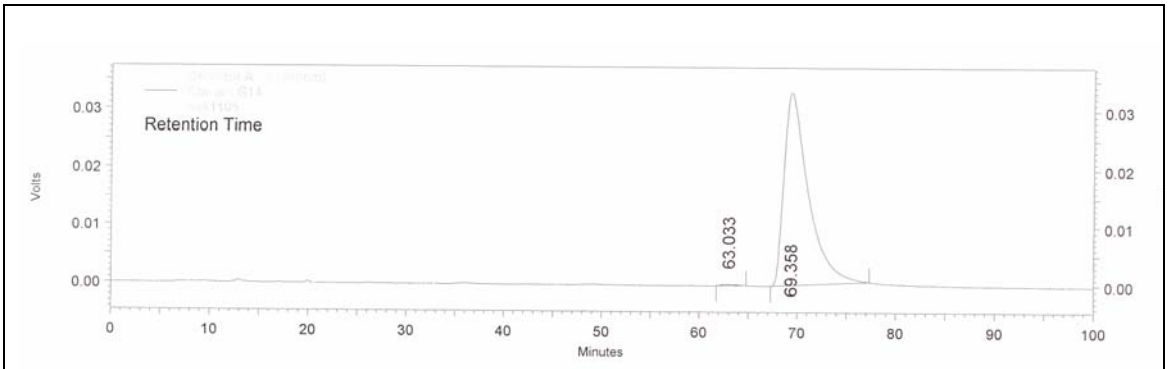
Chiral HPLC Analysis of compound 27



Racemic sample chromatograph

Pk #	Retention Time	Area	Area %	Height	Height Percent
1	61.567	2864968	49.591	19002	52.94
2	69.417	2912212	50.409	16891	47.06
Totals		5777180	100.000	35893	100.00

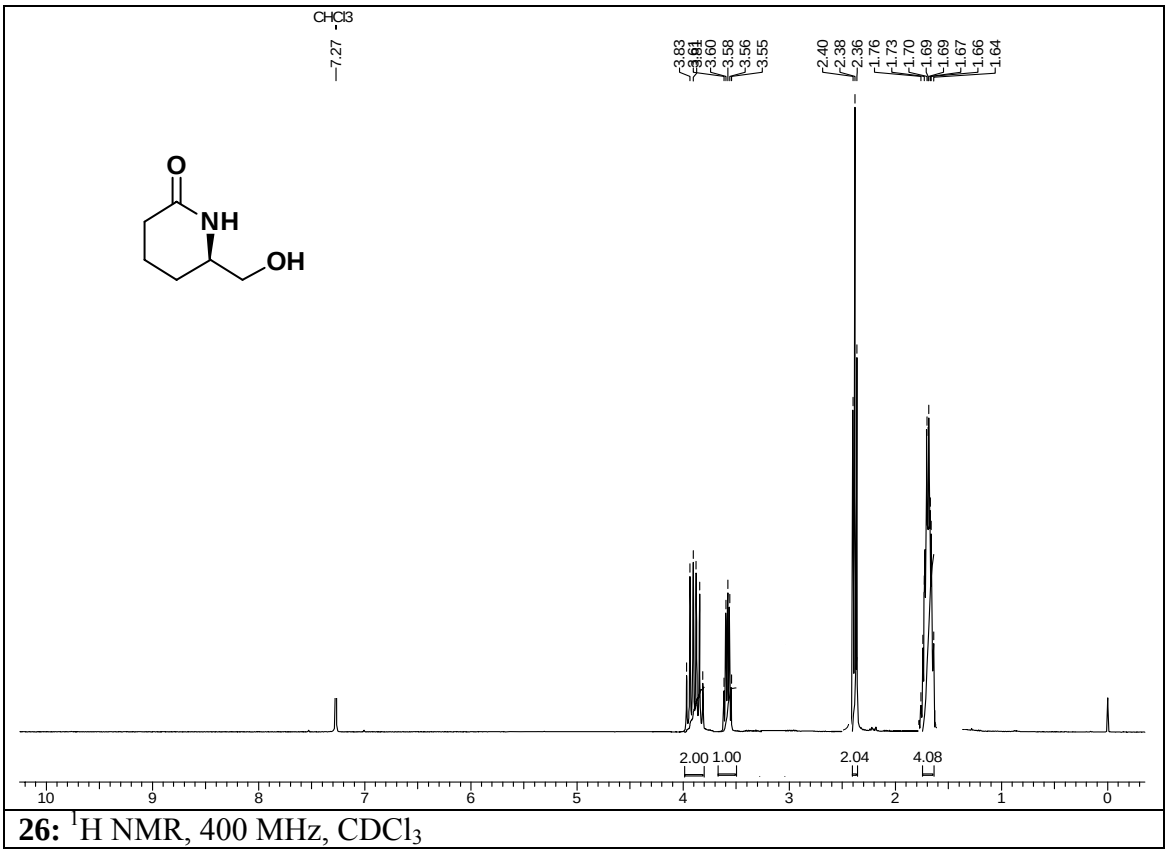
Column : Chiracel OD-H (250 x 4.6mm)
Mobile phase : 2-Propanol + Pet. ether (05:95)
Wavelenth : 260 nm
Flow : 0.5 mL/min
Concentration : 1.00 mg/1.0 mL mobile phase
Injection vol. : 10 µL



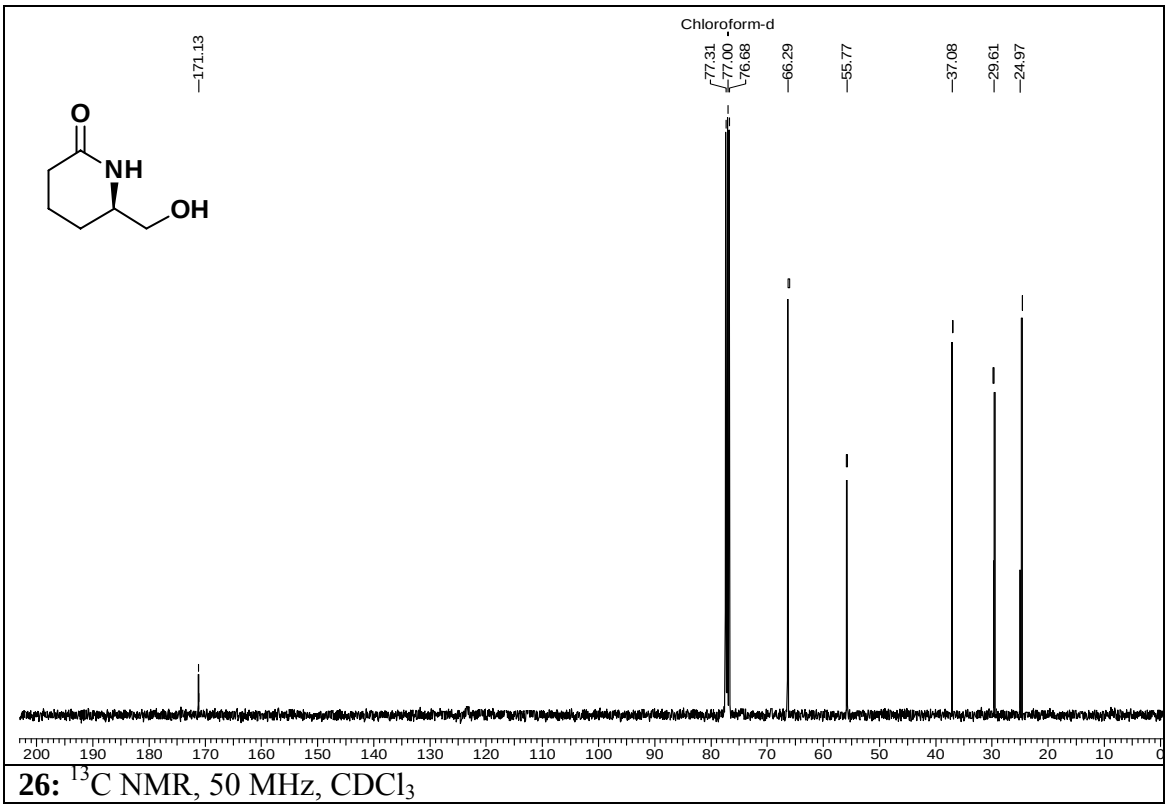
Chiral sample chromatograph

Pk #	Retention Time	Area	Area %	Height	Height Percent
1	16.900	12133286	49.950	362962	52.45
2	18.592	12157576	50.050	329056	47.55
Totals		24290862	100.000	692018	100.00

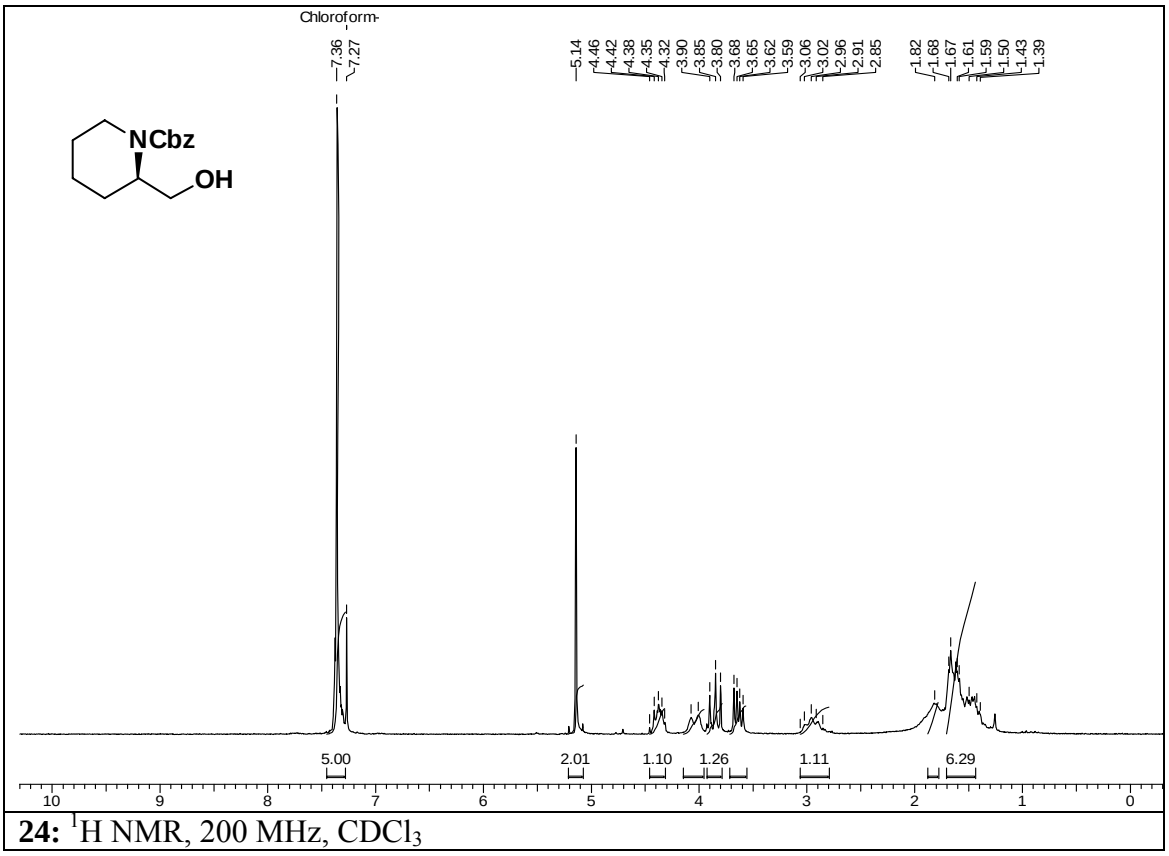
Column : Chiracel OD-H (250 x 4.6mm)
Mobile phase : 2-Propanol + Pet. ether (05:95)
Wavelenth : 260 nm
Flow : 0.5 mL/min
Concentration : 1.00 mg/1.0 mL mobile phase
Injection vol. : 10 µL



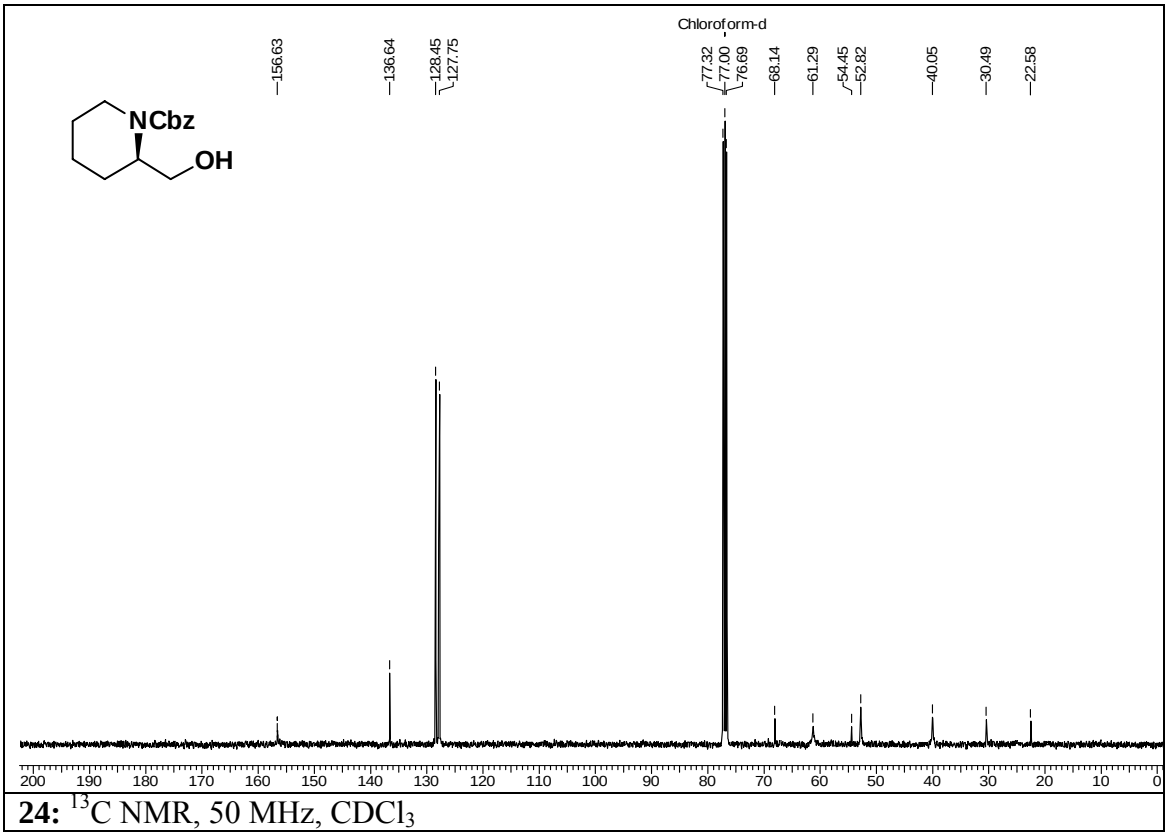
26: ^{1}H NMR, 400 MHz, $CDCl_3$



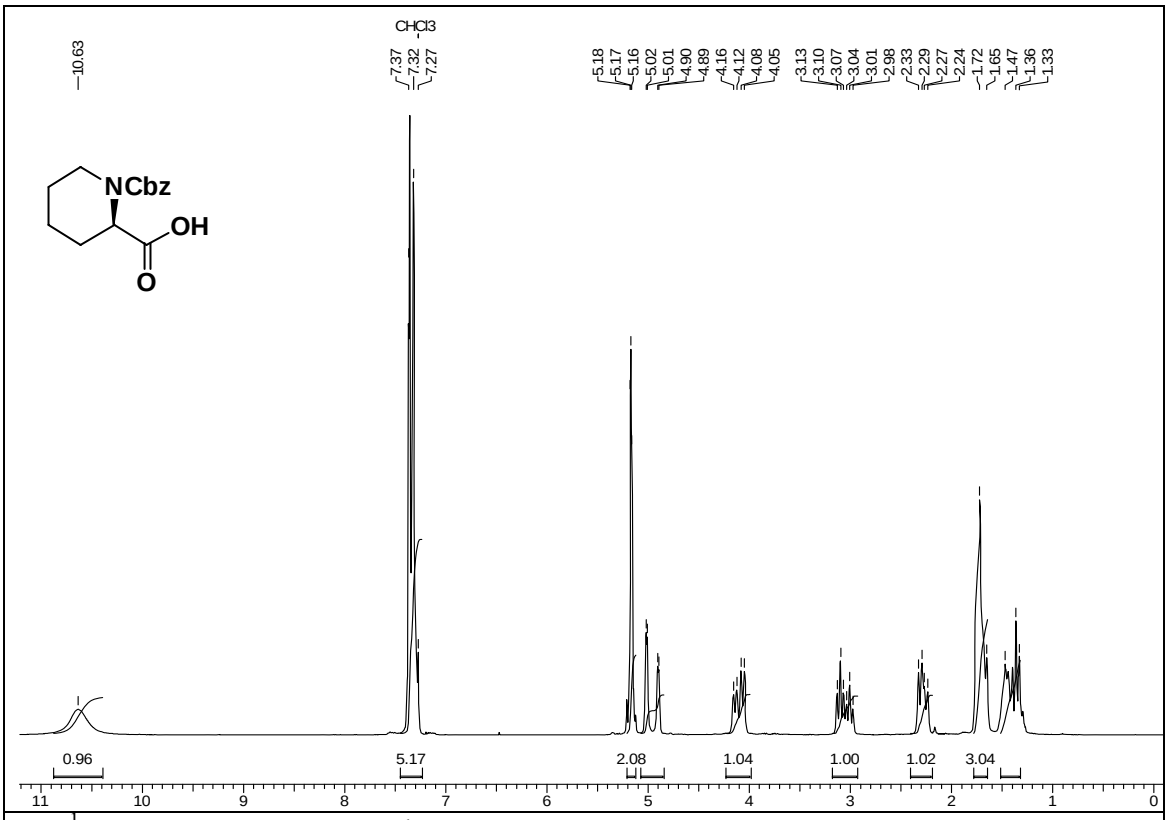
26: ^{13}C NMR, 50 MHz, $CDCl_3$



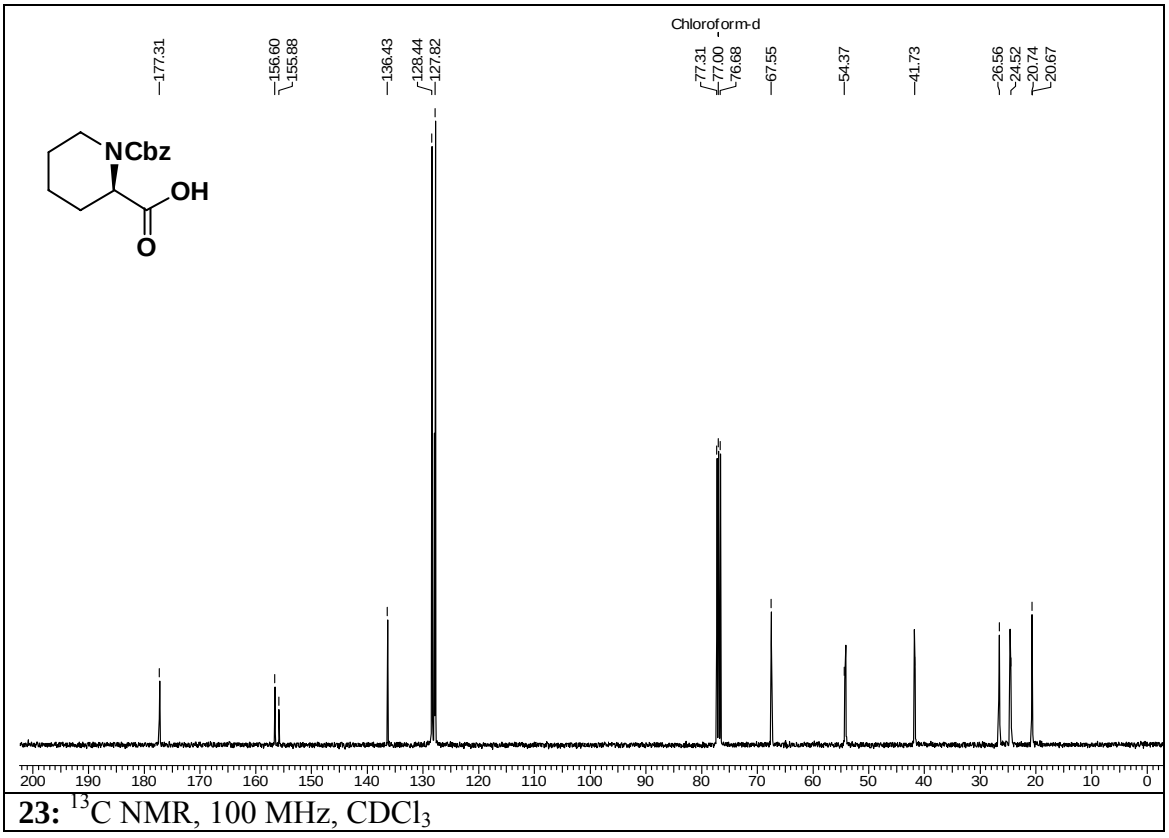
24: ^{1}H NMR, 200 MHz, $CDCl_3$



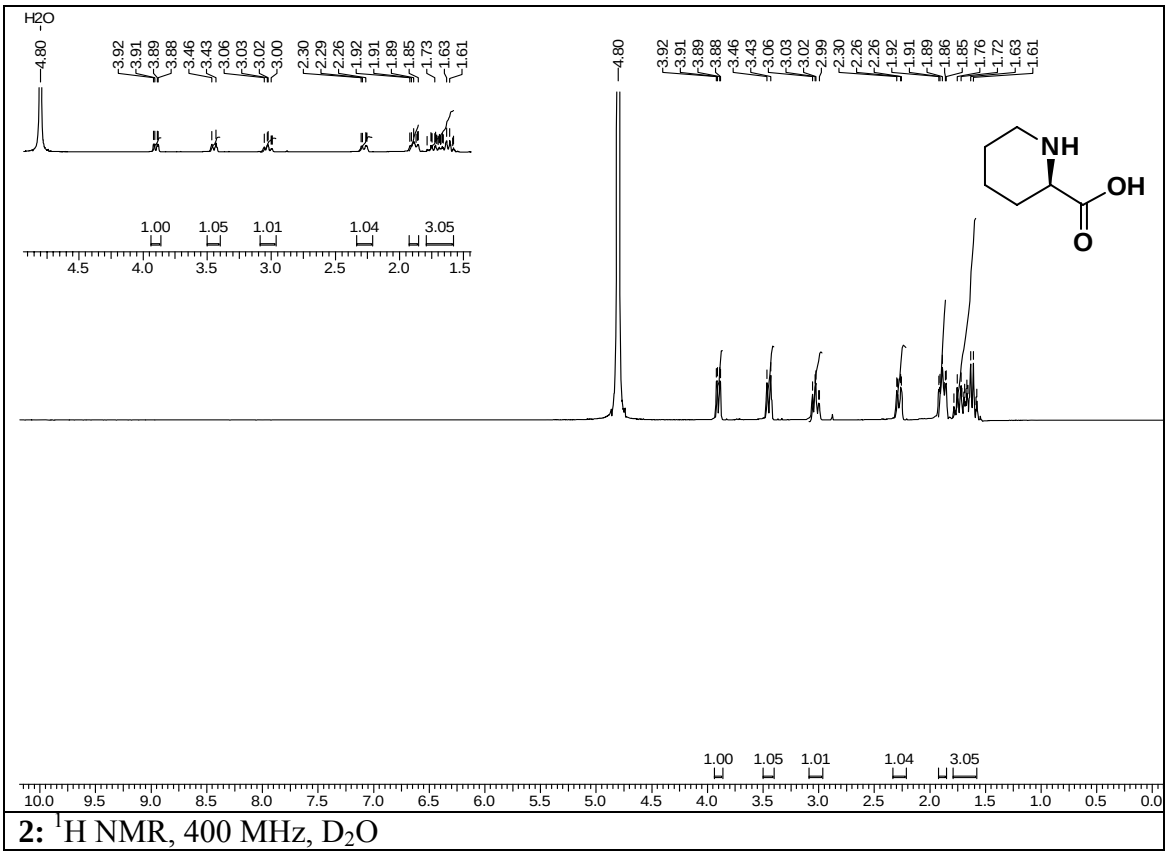
24: ^{13}C NMR, 50 MHz, $CDCl_3$



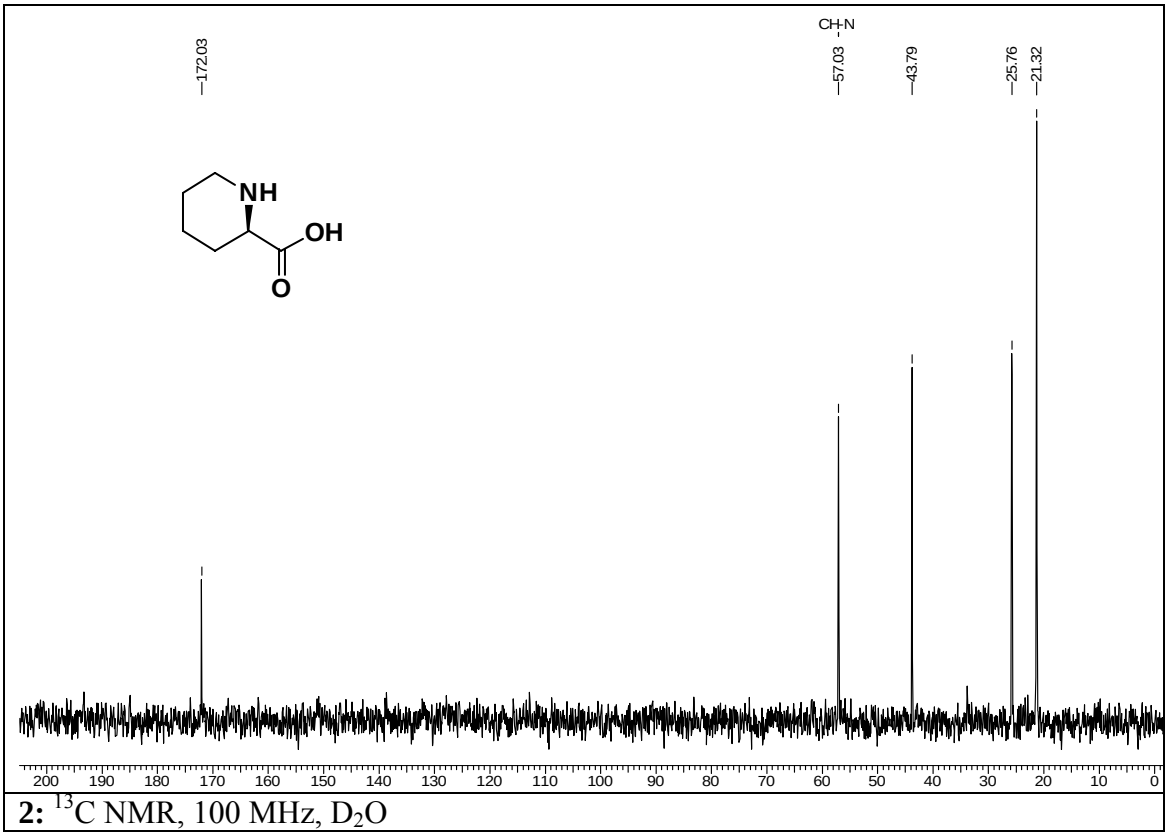
23: ^{1}H NMR, 400 MHz, $CDCl_3$



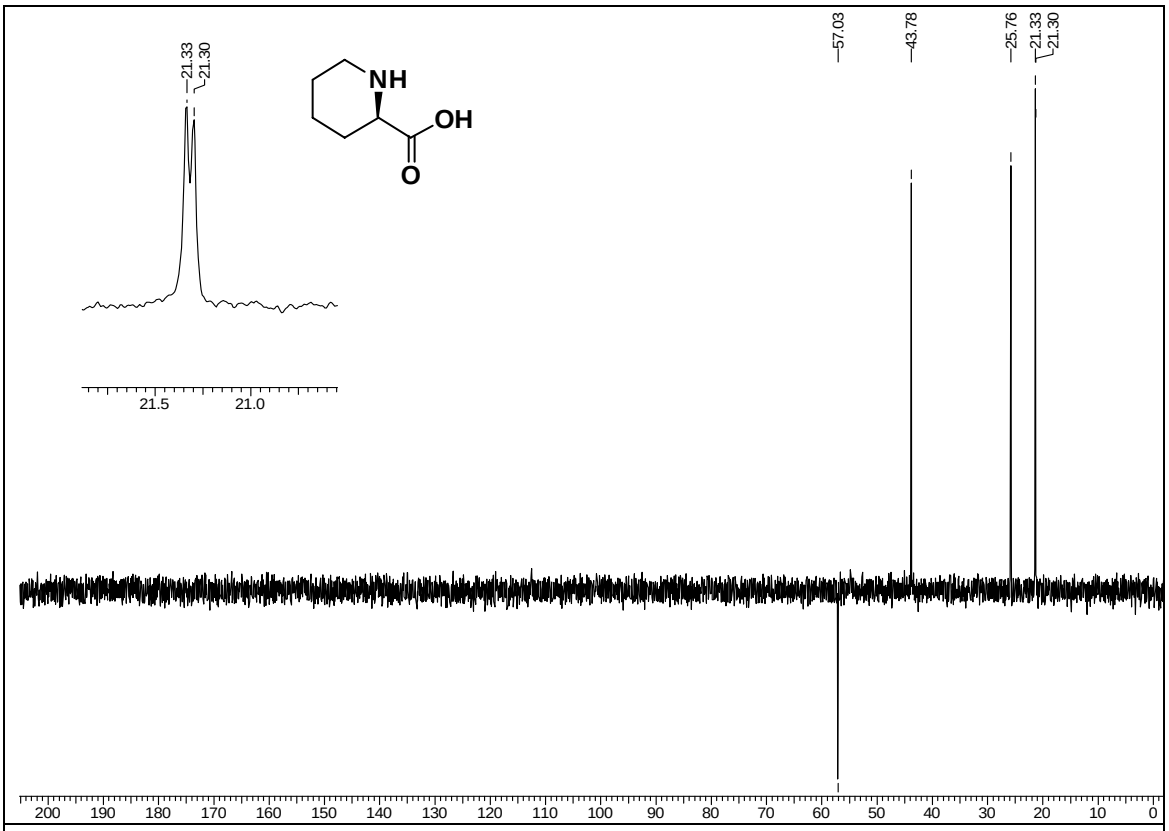
23: ^{13}C NMR, 100 MHz, $CDCl_3$



2: ^{1}H NMR, 400 MHz, D_2O



2: ^{13}C NMR, 100 MHz, D_2O



2: DEPT NMR, 100 MHz, D_2O

2.2.7 References

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Chapter 3

Introduction to ionic liquids and oxidation studies in ionic liquids

3.1 SECTION A

INTRODUCTION TO IONIC LIQUIDS

3.1.1 Green Chemistry

Green chemistry is the universally accepted term to describe the movement towards more environmentally acceptable chemical processes and products. Green chemistry encompasses education, research and commercial application across the entire supply chain for chemicals. Green chemistry can be achieved by applying environmentally friendly technologies-some old and some new.[1] Hundreds of tones of hazardous waste are released to the air, water, and land by industry every hour of every day. The chemical industry is the biggest source of such waste. The present day challenge for chemists is to develop new products, processes and services that achieve the social, economic and environmental benefits. This requires a new approach which sets out to reduce the materials and energy intensity of chemical processes and products, minimize or eliminate the dispersion of harmful chemicals in the environment, maximize the use of renewable resources and extend the durability and recyclability of products. The drive towards clean technology in the chemical industry with an increasing emphasis on the reduction of waste at source will require a high level of innovation and new technology. Solvents constitute a major factor in deciding the efficacy of an environmental friendly technology. The ideal solvent should have a very low volatility, it should be chemically and physically stable, recyclable and reusable, and eventually easy to handle. In addition, solvents that allow more selective and rapid transformations will have a significant impact.

3.1.2 Solvent innovations

3.1.2.1 Water

Water has been successfully used as a solvent in some biphasic industrial metal catalyzed reactions since last 30 years.[2-4] However, its application is still limited due to (i) low miscibility of organic substrates in water, giving rise to low reaction rates; (ii) water is protic coordinating solvent and so it can react with halo organics and more vigorously with organometallic complexes by halide-carbon or metal-carbon bond hydrolysis; (iii) from an environmental perspective, trace amount of organic compounds in water are very difficult to remove.

3.1.2.2 Perflourinated solvents

More recently, perfluorinated solvents have proven their utility for many organic and catalytic reactions.[5-6] Nevertheless, specific ligands must be designed to solubilize catalyst in the perfluorinated phase. Moreover, the decomposition of fluorous solvents at high temperature leads to formation of toxic compounds. Moreover, fluorous compounds are often detected in the organic phase.

3.1.2.3 Supercritical fluids

Supercritical fluids have also been used described as new solvents for organic and catalytic reactions.[7-8] Their physical properties and chemical stability make them eligible to be called as green solvents. Unfortunately, critical conditions needed for their handling is still a limitation.

3.1.2.4 Ionic liquids

Since last two decades, Ionic liquids (ILs) have seen come up as a novel class of solvents.[9-10] The history of IL started from the first ionic compound which is a liquid at room temperature viz. ethyl ammonium nitrate ($[EtNH_3]^+[NO_3]^-$) was synthesized by Walden, in 1914 from the reaction of ethylamine with concentrated nitric acid.[11] This IL had a melting point of 12-14 ^oC. These early studies on liquid salts did not lead to an explosion of interest in ionic liquids and it was not before the late 1940's that the next ionic liquids were discovered by Hurley and Wier. While looking for an inexpensive and facile method for aluminum electroplating they noted that by mixing powdered alkylpyridinium chlorides with $AlCl_3$ a reaction took place resulting in the formation of a liquid.[12] These ionic liquids incorporate organic cations, i.e. the type of cations used in the ionic liquids that now form the basis of modern synthetic applications, and chloroaluminate anions. While such anions are still being used in synthesis and catalysis, they have become less popular than other more inert anions. This is mainly due to their sensitivity towards air and moisture and the fact that extraction of certain organic products may result in the destruction of these particular ionic liquids. Osteryoung, Wilkes, Hussey and Zaworotko working on electrochemical aspects of the chloroaluminates were largely responsible for bringing ionic liquids to the attention of a wider scientific community.[13] They were studying chloroaluminates as solvents for transition metal complexes[14] and as reaction media for stoichiometric organic synthesis.[15] Chauvin and Osteryoung independently combined these two features, i.e. that ionic liquids could dissolve transition metal complexes and support organic chemistry. Chauvin showed that nickel complexes dissolved in acidic chloroaluminate

ionic liquids represent an excellent system for the dimerisation of alkenes[16] while Osteryoung used Ziegler-Natta catalysts in acidic chloroaluminates to polymerise ethylene.[17] It was Zaworotko who made the next leap forward, this being the synthesis of water-stable ionic liquids that contain tetrafluoroborate, hexafluorophosphate, nitrate, sulfate and acetate anions.[18]

However, one person who stands out as having made a considerable contribution to the field, looking at both the fundamental properties and applications of ionic liquids is K. Seddon at the University of Belfast. He is perhaps the person who has done most to popularize ionic liquids resulting in such intensive research activity around the world. Ionic liquids have since been utilized as in separation processes[19] as extractants for heavy metals with potential applications in the nuclear processing industry[20] as lubricants[21] as matrices in MALDI mass spectrometry[22] and even as propellants for small satellites.[23] The first industrial process using ionic liquid technology in chemical synthesis has also been reported[24] and numerous others are expected to follow. They also find additional use in enzyme catalysis or in multiphase bio-process operations. In the present work, emphasis will be given to second generation ionic liquids i.e. dialkylimidazolium salts rather than the air and moisture sensitive first generation ones (chloroaluminates). Processes based on these stable ionic liquids have been stressed and a brief account of the various features of ionic liquids as designer solvents are presented.

Generally IL refers to molten salts, which contain ions. Only those liquids, which are non-corrosive, and have low viscosity, are chosen to be called as Ionic Liquids. So classes belonging to molten inorganic salts viz. molten sodium chloride will not be considered under the heading IL. Room temperature Ionic Liquids (RTILs) are emerging as novel replacements for volatile organic compounds (VOCs) traditionally used as industrial solvents. These solvents are often liquids at room temperature and consist entirely of ionic species. They have many fascinating properties since both the thermodynamics and kinetics of reactions in IL are different to those in conventional molecular solvents. These “Designer Solvents” aptly named-consists of an anionic and a cationic part, which can be varied for a particular end use or to possess a particular set of properties.

3.1.3 Classification of ionic liquids

ILs are classified into two categories.

i. Binary ionic liquids – salts where equilibrium is involved.

ii. Simple salts – made of single anion and cation.

The first category, the first generation ILs, contains a mixture of metal halide and dialkylimidazolium chloride. These contain several ionic species and their melting point and other properties depend on the mole fractions of the individual components. The second class, generally termed as second generation ILs, consists of simple cation and anion e.g. ethyl ammonium nitrate ($[EtNH_3]^+[NO_3]^-$), dialkylimidazolium ILs [bmim]Br. The third generation ILs consist of chiral ILs made from either chiral cations or anions, mono-alkyl imidazoluim ILs and task specific ILs. ILs generally are composed of relatively large organic cations and inorganic or organic anions and have a melting range of –96 ^oC to 100 ^oC. Cations are mainly alkyl quaternary ammonium or phosphonium moiety which may be a part of a heterocyclic ring.

3.1.4 Recent developments in cations and anions

3.1.4.1 Cations

The cations are generally organic components with low symmetry and bulk in size. Those described until now are based on ammonium **1**,[25-27] sulfonium **2**,[28] phosphonium **3**,[29] imidazolium **4**,[30-33] pyridinium **5**,[34-36] pyrrolidinium **6**,[37] thiazolium **7**,[38] triazolium **8**,[39] oxazolium **9**,[40] and pyrazolium **10**[41] (**Figure 1**). Of particular interest are the salts based on the N,N-dialkylimidazolium cation **4** because of the wide spectrum of physico-chemical

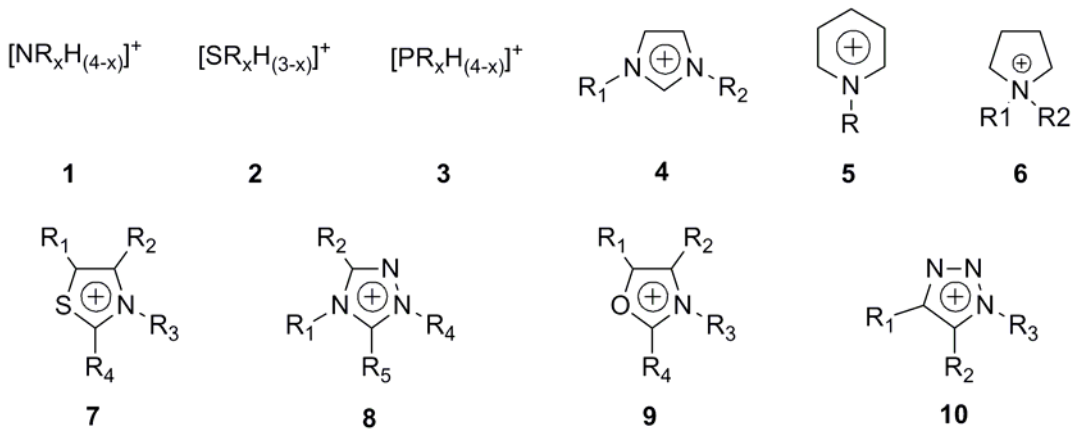


Figure 1. Examples of cations described in ionic liquids.

properties available in that class. Liquid imidazolium salts are generally obtained by anion exchange from imidazolium halide precursors.

3.1.4.2 Anions

Concerning the anions, they can be classified in two parts; those which give polynuclear anions, e.g. Al_2Cl_7, Al_3Cl_{10}, Au_2C_{l7}, Fe_2C_{l7}, Sb_2F_{11}. These anions are formed by the reaction of the corresponding Lewis acid, e.g. $AlCl_3$ with the mononuclear anion, e.g. $AlCl_4$. They are particularly air and moisture sensitive. The second class of anions corresponds to mononuclear anions which lead to neutral, stoichiometric ionic liquids, e.g. Cl^-, Br^-, ClO_4^-, BF_4^-, PF_6^-, SbF_6^-, $ZnCl_3^-$, $CuCl_2^-$, $SnCl_3^-$, $N(CF_3SO_2)_2^-$, $N(C_2F_5SO_2)_2$, $N(FSO_2)_2^-$, $C(CF_3SO_2)_3^-$, $CF_3CO_2^-$, $CF_3SO_3^-$, $CH_3SO_3^-$, $CH_3CO_2^-$, NO_3^-, TsO^- etc. Of particular interest is the trifluoromethylsufonylamide anion [NTf_2^-],[42-43] which gives particularly thermally stable salts (up to 400 ^oC).

3.1.5 Features of ILs which make them as attractive potential solvents

ILs possesses a variety of special physical and chemical properties which make them as attractive potential solvents in many organic reactions.

(1) Negligible vapour pressure and non-flammable, therefore product can be easily isolated by vacuum distillation.

(2) High thermal stability and operate over large temperature range.

(3) Its a very good solvent to dissolve a wide range of organic, inorganic, organometallic compounds and polymeric material.

(4) ILs are often composed of poorly co-ordinating ions, so they have the potential to be highly polar yet non-coordinating solvents.

(5) ILs are immiscible with a number of organic solvents and thus provide a nonaqueous, polar alternative for two-phase systems.

(6) It serves as a good medium to solubilize gases such as H_2, CO, O_2 and CO_2 and many reactions are now being performed using ionic liquids and supercritical CO_2.

(7) Ionic liquids have polarities comparable to alcohols, but in contrast to alcohols, however, many ionic liquids are non-nucleophilic, which can have a pronounced effect on a catalyzed reaction.

(8) ILs possesses excellent and variable Lewis/Brønsted acidity.

(9) Most of the ionic liquids can be stored without decomposition for a long period of time.

3.1.6 Applications of ionic liquids

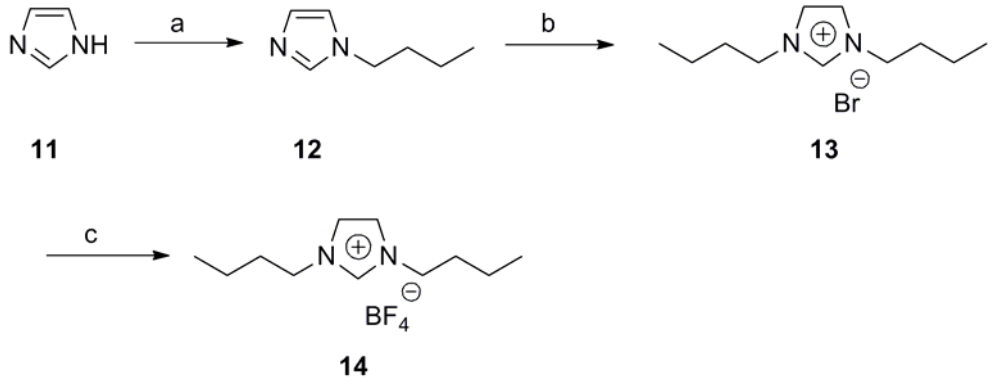
Numerous literature material is available which shows the importance[9-10] of ILs as well as those covering specific topics such as catalysis (including biocatalysis) in ionic

liquids,[44] synthesis of organometallic complexes in ionic liquids,[45] biphasic systems and supported ionic liquids,[46] solvent properties,[47] ionic liquids with fluorine containing anions,[48] analytical applications of ionic liquids,[49] chiral ionic liquids,[50] electrochemistry in ionic liquids.[51]

3.1.7 Synthesis of ionic liquids

The number of ionic liquids continues to grow at an ever increasing rate, however only few are used by the wider community. The majority of the ionic liquids in use are prepared via salt metathesis reactions and one of the greatest challenges in the field of ionic liquids concerns their synthesis in high purity. Until ionic liquids of well-defined purity are commercially available at acceptable prices, the reliability of the data reported will remain somewhat ambiguous and catalyst performance in these new media must be compared with some caution. At present, many research groups working in the field prepare their solvents themselves, inevitably leading to variations in quality and purity data are seldom provided.

There are several methods available for the synthesis of ionic liquids but they suffer from several drawbacks such as multi step synthesis, lower yield, harsh reaction conditions and long reaction time.



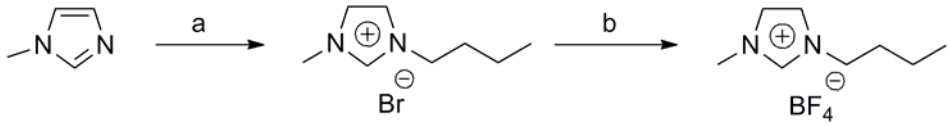
11 **12** **13**

14

Scheme 1. *Reagents and conditions*: (a) *n*-butyl bromide, KOH, acetonitrile, 0 °C, 92%; (b) 1-butyl bromide, 70 °C, 4h, 96%; (c) $NaBF_4$, H_2O, rt, 5h, 86%.

Imidazole **11** on treatment with butyl bromide in KOH at 0 °C in acetonitrile afforded 1-*n*-butyl imidazole **12**. Then 1-*n*-butyl imidazole **12** on quarternization with *n*-butyl bromide at 70 °C afforded 1,3-di-*n*-butylimidazolium bromide ([bbim]Br) **13**. 1,3-di-n-butylimidazolium bromide ([bbim]Br) **13** on metathesis with sodium tetrafluoroborate afforded 1,3-di-*n*-butylimidazolium tetrafluoroborate ([bbim]BF_4) **14** (as shown in **scheme 1)**.

Similarly commercially available 1-methyl imidazole **15** on quarternization with *n*-butyl bromide at 70 °C afforded 1-*n*-butyl-3-methylimidazolium bromide ([bmim]Br) **16**. Then 1-*n*-butyl-3-methylimidazolium bromide ([bmim]Br) **16** on metathesis with sodium tetrafluoroborate afforded 1-*n*-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) **17 (**as shown in **scheme 2**). All prepared ionic liquids were characterized by ^{1}H NMR and ^{13}C NMR spectroscopy. ^{1}H NMR was recorded neat using $CDCl_3$ as external lock.



15 **16** **17**

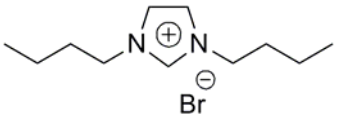
Scheme 2. *Reagents and conditions*: (a) *n*-butyl bromide, 70 °C, 4h, 97%; (b) $NaBF_4$, Acetone, rt, 5h, 86%.

3.1.8 Conclusion

This section described the introduction of ionic liquids and synthesis of ionic liquids [bbim]Br, [bbim]BF_4, [bmim]Br and [bmim]BF_4,

3.1.9 Experimental

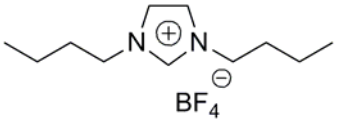
1) 1,3-Di-*n*-butylimidazolium bromide ([bbim]Br) (13)



A mixture of 1-*n*-butylimidazole **12** (12.4 g, 0.1 mol) and *n*-butyl bromide (15 g, 0.11mol) was heated with stirring at 70 °C for 4 h. The excess 1-butyl bromide was distilled off at 80 °C under reduced pressure (10 mm Hg) over 2 h leaving behind the product [bbim]Br **13** as colourless viscous liquid.

Yield: 24.9 g (96%); colourless viscous liquid; IR ($CHCl_3$) ν_{max} 3413, 3051, 2869, 1634, 1569, 1462, 1161, 757 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ= 0.97 (t, 6H), 1.33-1.47 (m, 4H), 1.85-2.00 (m, 4H), 4.39 (t, 4H), 7.62 (s, 2H), 10.49 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ= 12.8, 18.8, 31.6, 49.1, 121.9, 135.9 ppm.

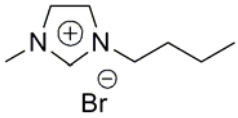
2) 1,3-Di-*n*-butylimidazolium tetrafluoroborate ([bbim]BF_4) (14)



To a solution of 1,3-di-*n*-butylimidazolium bromide ([bbim]Br) **13** (13.0 g, 0.05 mol) in water (20 mL) was added a solution of sodium tetrafluoroborate (6.58 g, 0.06 mol) in water (20 mL). The reaction mixture was stirred at room temperature for 5 h. The IL, [bbim]BF_4 separated out as an immiscible layer. The mixture was extracted with dichloromethane (3x 30 mL). The combined organic layer was washed with water and brine and dried over anhydrous $MgSO_4$. The solvent was distilled off under reduced pressure leaving behind the pure IL, [bbim]BF_4 **14** as colourless viscous oil.

Yield: 11.47 g (86%); colourless viscous liquid; IR ($CHCl_3$) ν_{max} 3401, 3067, 2874, 1635, 1563, 1465, 1167, 753 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ= 0.95 (t, 6H), 1.27-1.46 (m, 4H), 1081-1.96 (m, 4H), 4.25 (t, 4H), 7.52 (s, 2H), 8.99 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ= 13.1, 19.1, 31.8, 49.5, 122.3, 135.4 ppm.

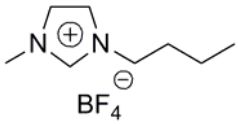
3) 1-***n*-Butyl-3-methylimidazolium bromide ([bmim]Br) (16)**



A mixture of 1-methylimidazole (7.2 g, 0.1 mol) and *n*-butyl bromide (15 g, 0.11mol) was heated with stirring at 70 °C for 4 h. The excess 1-*n*-butyl bromide was distilled off at 80 °C under reduced pressure (10 mm Hg) over 2 h leaving behind the product [bmim]Br as colourless viscous liquid.

Yield: 21.233 g (97%); colourless viscous liquid; IR ($CHCl_3$) ν_{max} 3410, 3045, 2869, 1563, 1475, 1149, 759 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ= 0.92 (t, J = 7.3, 3H), 1.28-1.41 (m, 2H), 1.82-1.92 (m, 2H), 4.09 (s, 3H), 4.29 (t, J =7.3, 2H), 7.39 (s, 1H), 7.50 (s, 1H), 10.43 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ= 13.2, 19.3, 31.9, 36.3, 49.7, 122.1, 123.6, 136.5 ppm.

4) 1-*n*-Butyl-3-methylimidazolium tetrafluoroborate (bmimBF_4) (17)

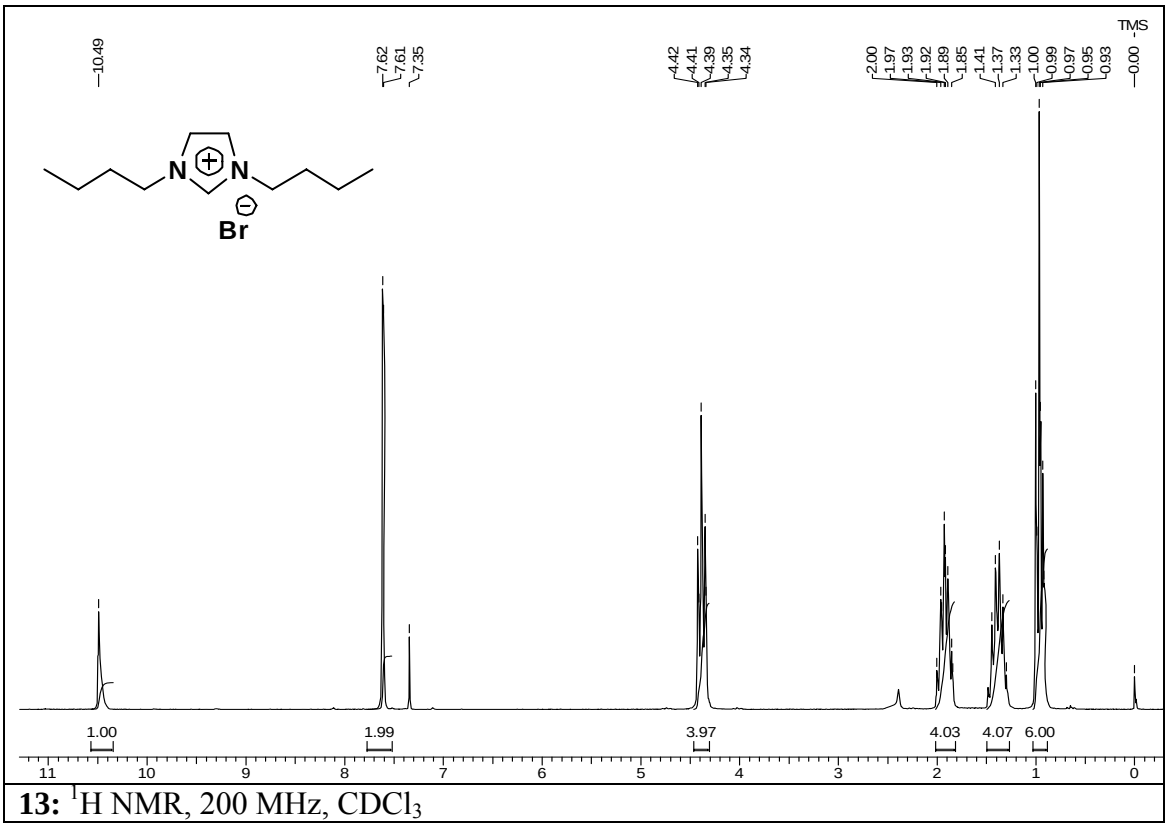


To a solution of 1-*n*-butyl-3-methylimidazolium bromide ([bmim]Br) **16** (10.945 g, 0.05 mol) in water (20 mL) was added a solution of sodium tetrafluoroborate (6.58 g, 0.06 mol) in water (20 mL). The reaction mixture was stirred at room temperature for 5 h. The IL, [bmim]BF_4 separated out as an immiscible layer. The mixture was extracted

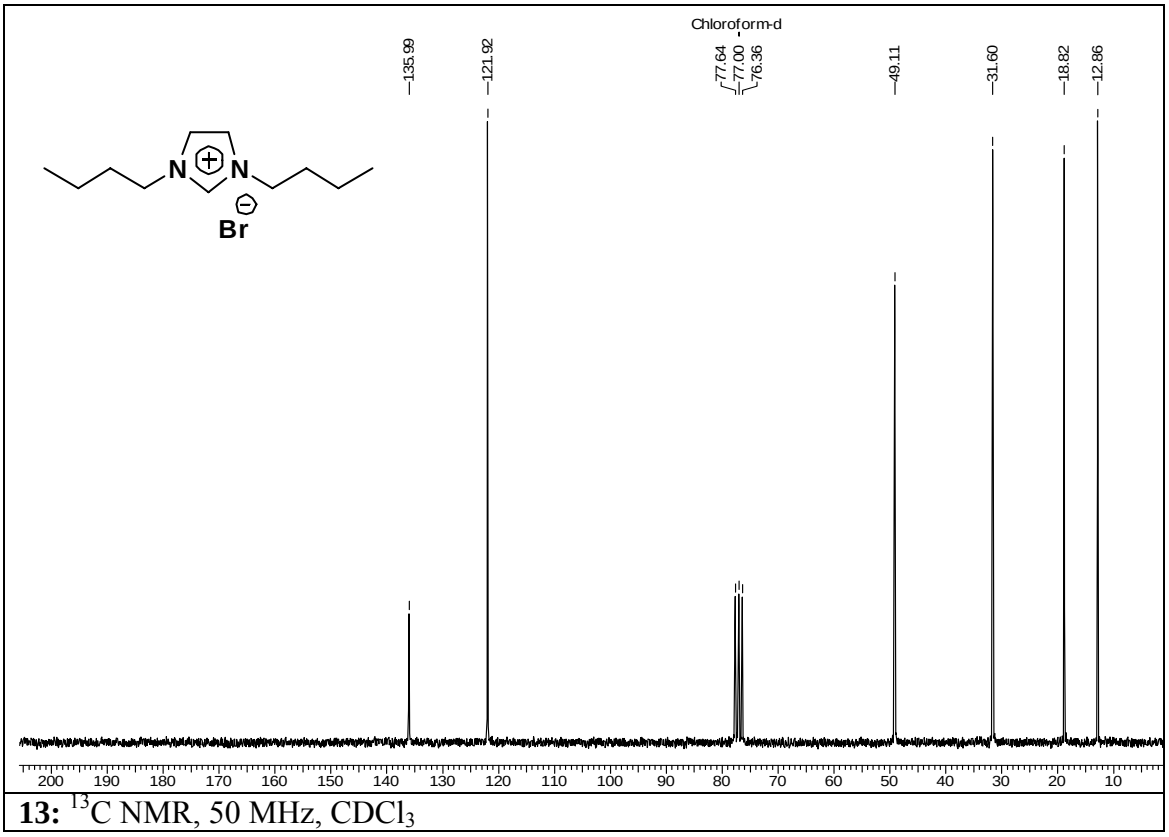
with dichloromethane (3x 30 mL). The combined organic layer was washed with water and brine and dried over anhydrous $MgSO_4$. The solvent was distilled off under reduced pressure leaving behind the pure IL, [bmim]BF_4 **17** as colourless viscous oil.

Yield:10.048 g (89%); colourless viscous oil; IR ($CHCl_3$) ν_{max} 3407, 3055, 2871, 1635, 1559, 1167, 757 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ= 0.93 (t, *J* =7.3, 3H), 1.29-1.42 (m, 2H), 1.80-1.90 (m, 2H), 3.99 (s, 3H), 4.22 (t, *J* = 7.3, 2H), 7.25 (s, 1H), 7.33 (s, 1H), 9.35 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ= 12.9, 18.8, 31.6, 36.1, 49.2, 121.8, 123.3, 136.4 ppm.

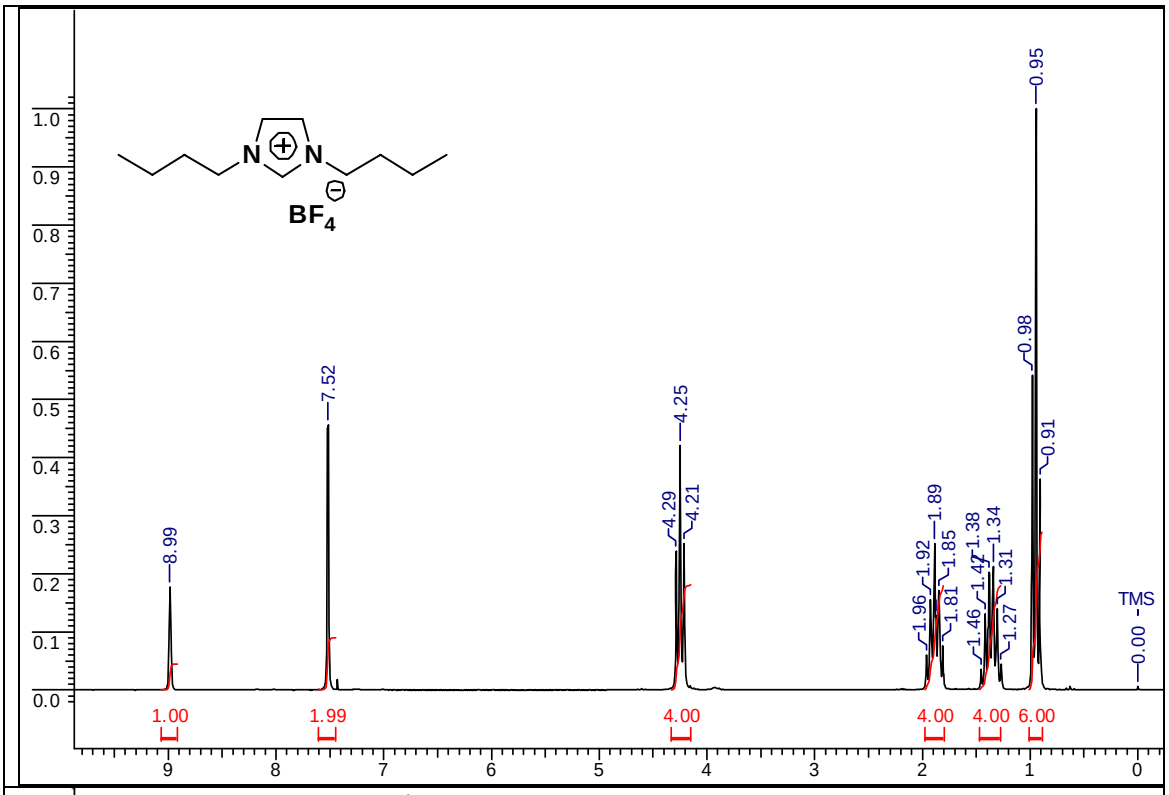
3.1.10 Analytical Data



13: ^{1}H NMR, 200 MHz, $CDCl_3$



13: ^{13}C NMR, 50 MHz, $CDCl_3$



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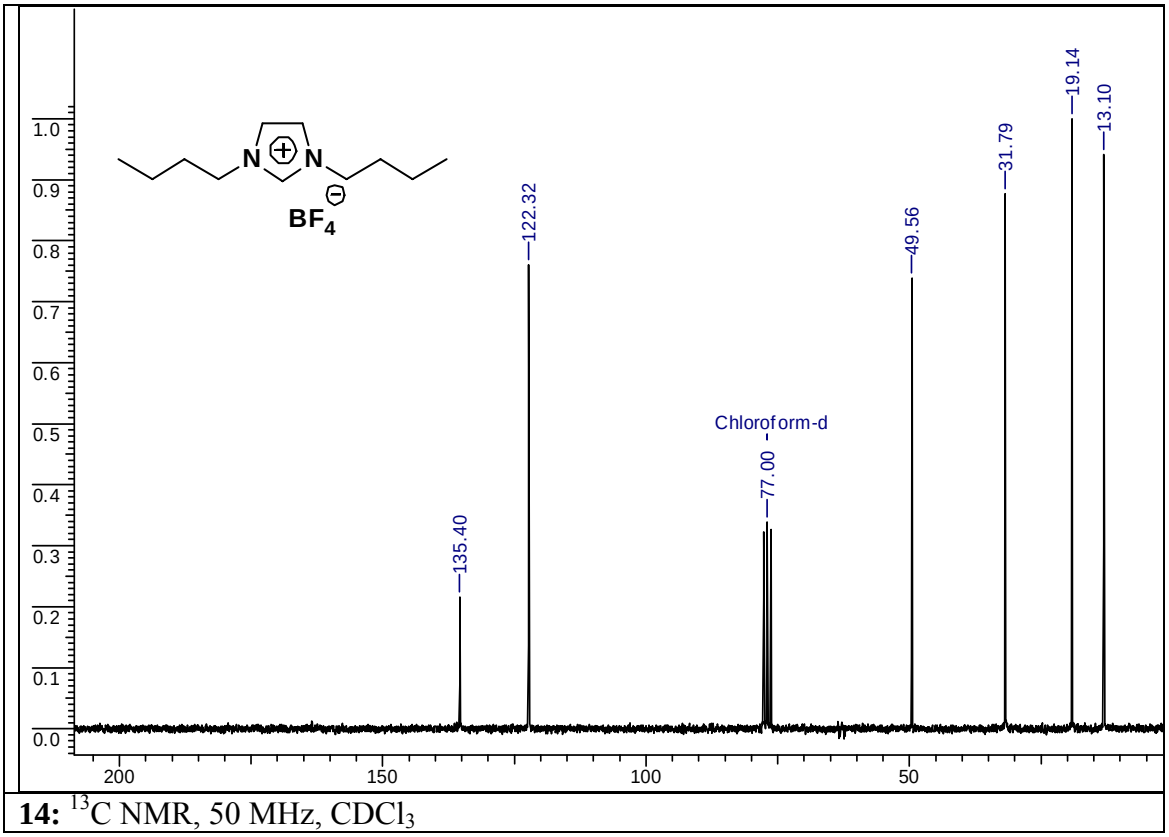

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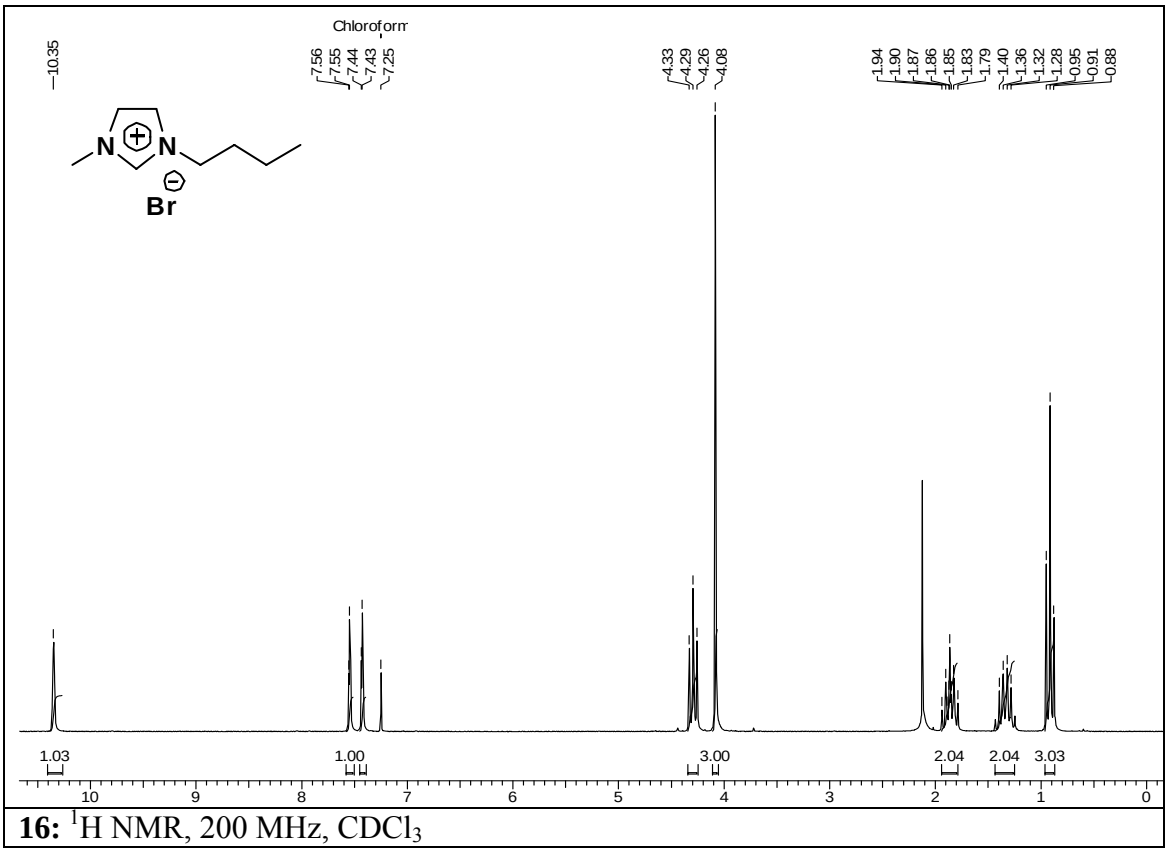

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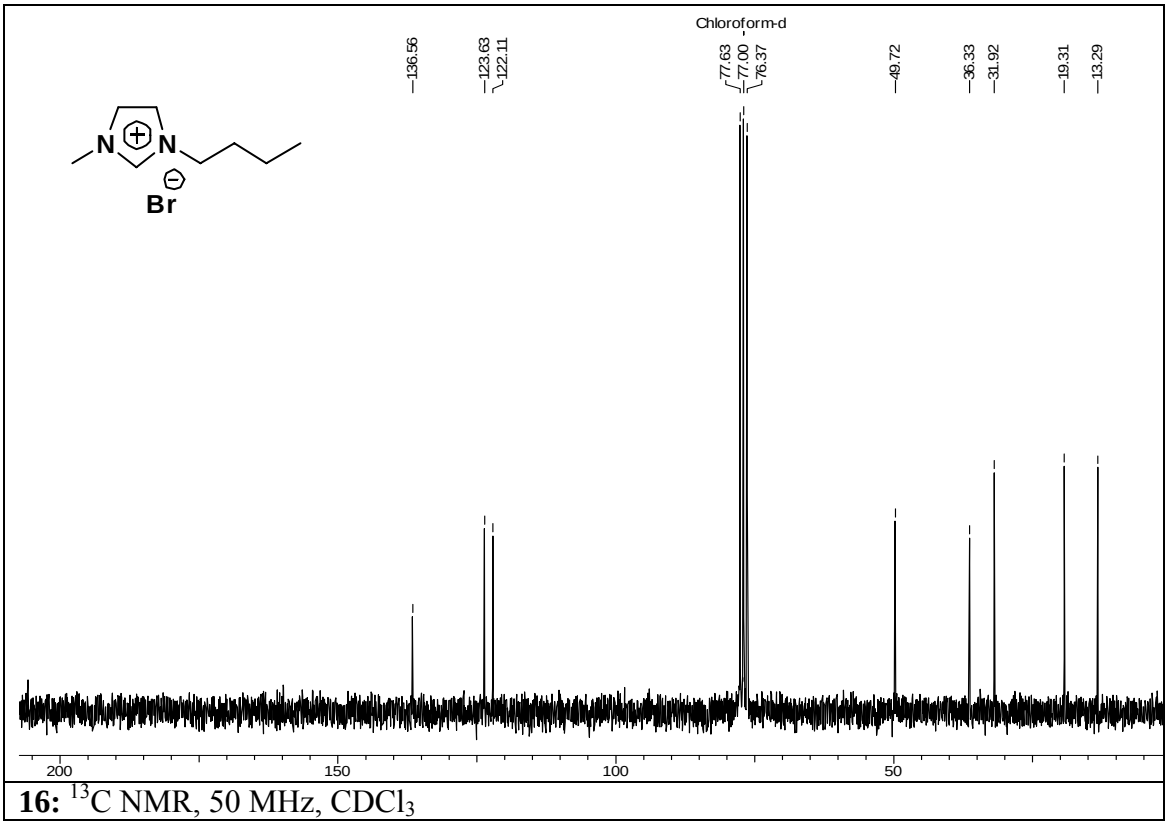
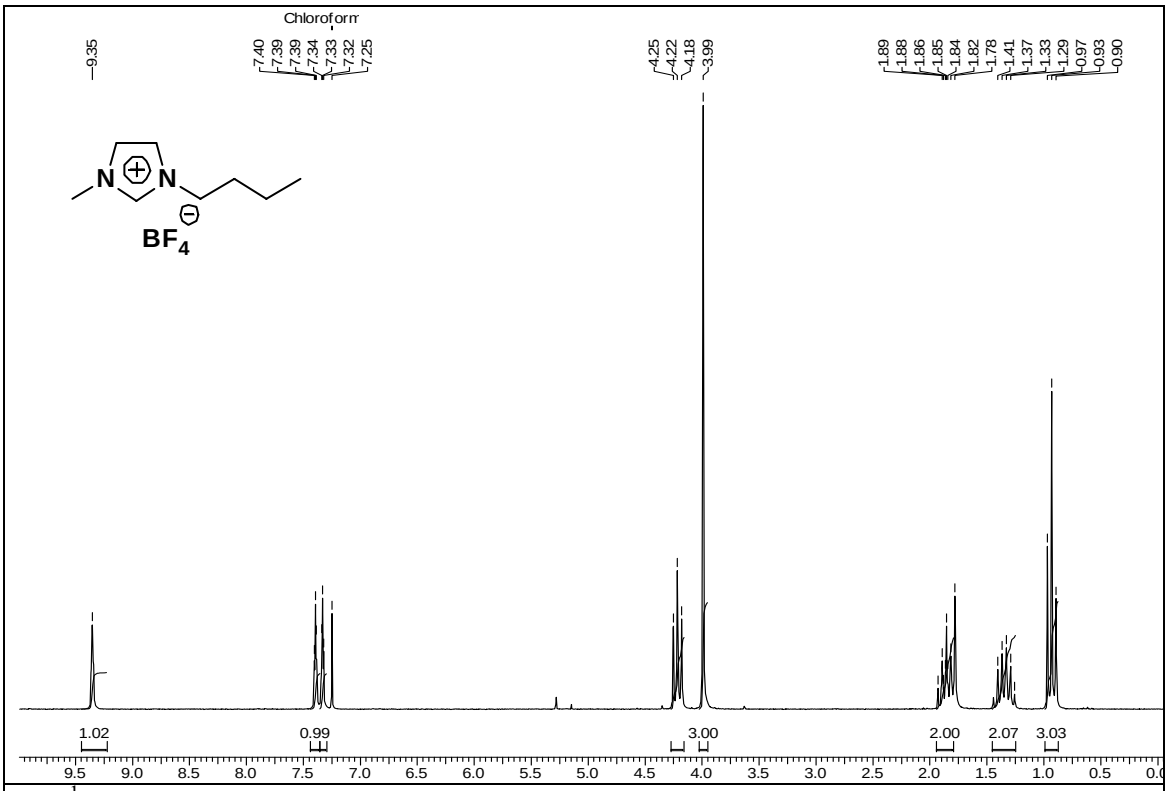
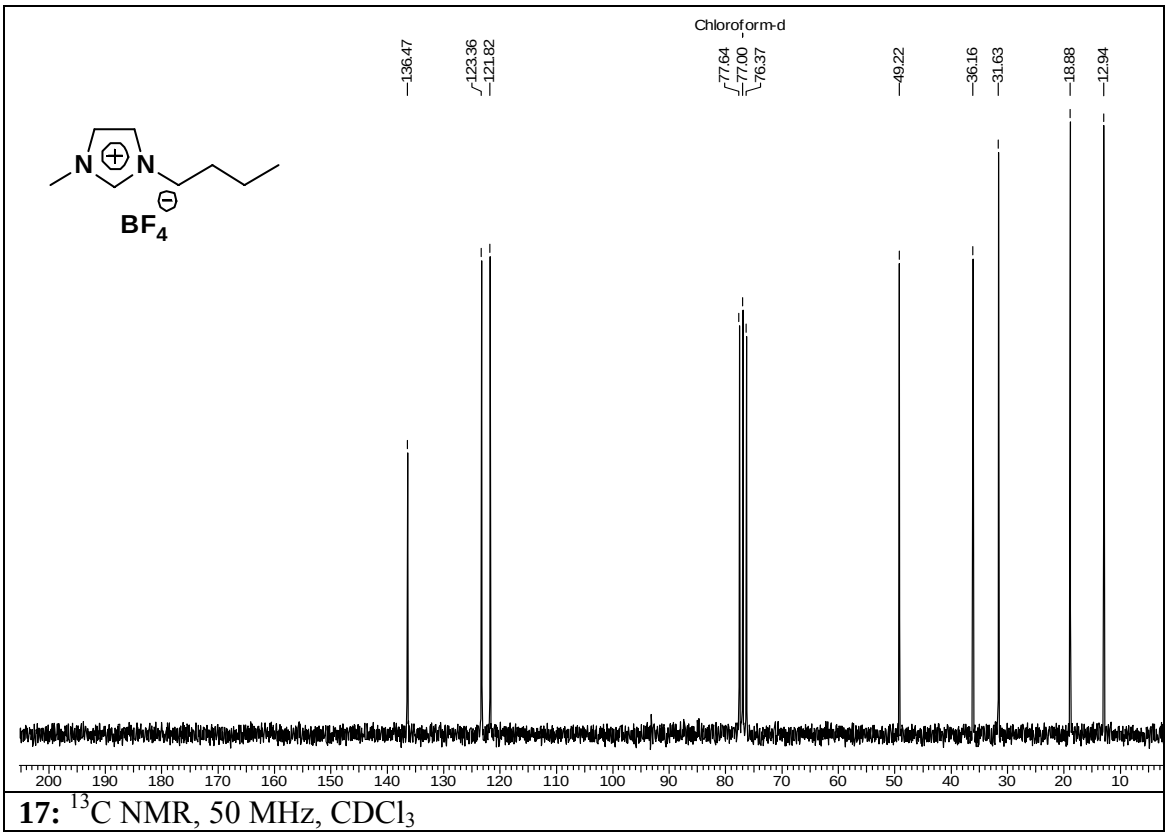


16: ^{13}C NMR, 50 MHz, $CDCl_3$



17: ^{1}H NMR, 200 MHz, $CDCl_3$



17: ^{13}C NMR, 50 MHz, $CDCl_3$

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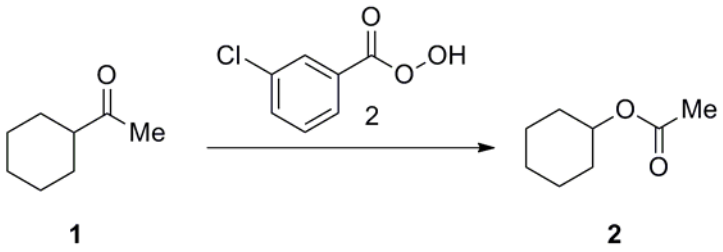
3.2 SECTION B

BAEYER-VILLIGER OXIDATION OF AROMATIC KETONES IN IONIC LIQUIDS

3.2.1 Introduction

More than 100 years ago **Adolf von Baeyer** (1835-1917) and **Victor Villiger** (1868-1934) opened a new area to organic chemists by reporting the oxidation of ketone to ester (**Scheme 1**), commonly known as Baeyer-Villiger oxidation or Baeyer-Villiger rearrangement.[1]

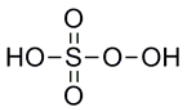


1 **2**

Scheme 1. Typical Baeyer-Villiger oxidation

Baeyer–Villiger oxidation is attractive for practical applications into building blocks for complex bioactive molecules. Key features of the Baeyer-Villiger oxidation are its stereospecificity and predictable regiochemistry. Due to vast applications of this oxidation reaction, Baeyer and Villiger awarded Nobel Prize in chemistry in 1905.

In the very first communication, Baeyer-Villiger used Caro's acid **3** (**Figure 1**) as reagent. Tradionally reagents typically used to carry out this rearrangement are *m*-chloroperoxybenzoic acid (*m*-CPBA), peroxyacetic acid, or peroxytrifluoroacetic acid. Reactive or strained ketones (cyclobutanones, norbornanones) react with hydrogen peroxide or hydroperoxides to form lactones. Disodium phosphate or sodium bicarbonate is often added as a buffering agent to prevent transesterification or hydrolysis.



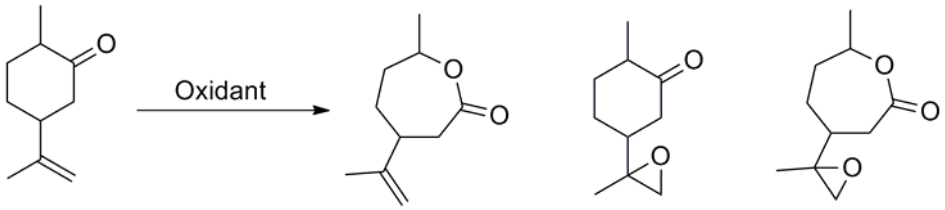
3

Figure 1. Caro's acid

This oxidation was made simpler by replacing traditionally used peroxyacids with hydrogen peroxide,[2] a cheaper and less polluting reagent. More benefits were expected

from the catalytic version of this oxidation by minimizing reactant use and waste production. Efficient activation of ketone oxidation by hydrogen peroxide was achieved by employing dissolved platinum complexes,[3] zeolites[4,5] and sulfonated resins.[6]

Recently Sn-β molecular sieve was reported as a potential heterogeneous catalyst for this oxidation in 1,4-dioxane at elevated temperature[7] (**Scheme 2**). Excellent selectivity and yields of ester or lactones were described from saturated as well as unsaturated ketones. Corma and co-workers employed a concept that involves selective activation of a carbonyl group with a catalyst[8,9] which has been activated earlier by Lewis acids followed by reaction with hydrogen peroxide.

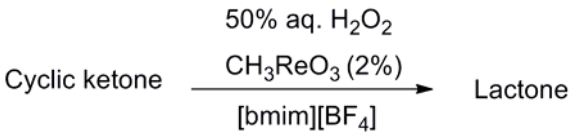


Oxidants			
1. Sn-zeolite beta H_2O_2	100%	0%	0%
2. *m*CPBA	11%	71%	18%
3. Ti zeolite beta H_2O_2	0%	79% + epoxide opening product	0%

Scheme 2.

In recent years the use of room temperature ionic liquids (ILs) as 'green' solvents in organic synthetic processes has gained considerable importance due to their solvating ability, negligible vapour pressure, easy recyclability and reusability. Many reactions have been reported recently using ionic liquids as reaction media and as rate enhancers.

Recently Bernini[10] reported methyltrioxorenium catalysed Baeyer–Villiger oxidation in ionic liquid (**Scheme 3**).



Scheme 3.

3.2.2 Present work

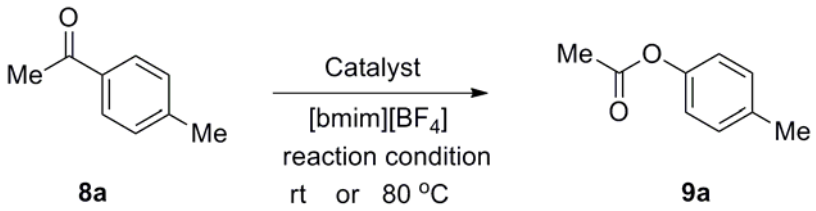
In order to avoid the use of costlier methyltrioxorenium, we decided to develop an efficient

and practical method for Baeyer–Villiger oxidation using Sn-β molecular sieve[7] and hydrogen peroxide in ionic liquid.

For this purpose as model ketone we choose 4-methylacetophenone **8a**. 4-Methyl acetophenone (**8a**) on reaction with H_2O_2 (30%) in presence of a Sn-β molecular sieve catalyst (20%) in ionic liquid [bmim][BF_4] at room temperature gave Baeyer-Villiger oxidation product (**9a**) in 88% yield in 10 hours. The workup procedure involved simple filtration of the catalyst and extraction of the product with ethyl acetate.

4-Methyl acetophenone (**8a**) on reaction with H_2O_2 (30%) in presence of Sn-β molecular sieve catalyst (20%) in dioxane at room temperature remains unchanged. This "confirms" that the ionic liquid is essential for the transformation at room temperature. However, Corma reported the Baeyer–Villiger oxidation using Sn-β molecular sieve in dioxane at 80 °C. Similarly it was also observed that 4-methyl acetophenone (**8a**) remains unchanged when treated with H_2O_2 (30%) at room temperature and 80 °C in presence of Ti-silicalite-1,[11] Sn-silicalite-1[12] and all-silica-β[13] in ionic liquid. This study "confirms" that the presence of the ionic liquid and Sn are critical for the Baeyer-Villiger oxidation (Table 1, entry 2–4).

In order to examine whether the reaction occurs over the tetrahedral Sn-β framework or on the extra framework Sn in the form of SnO_2, Sn was impregnated on all-Si-β[14] and was used as a catalyst for the Baeyer–Villiger oxidation of 4-methyl acetophenone (**8a**) in ionic liquid at room temperature and 80 °C. It was observed that **8a** was unchanged. This observation confirms the presence of Sn in the β-framework of the molecular sieve and not occluded as SnO_2.



Scheme 4.

Table 1. Feasibility of Baeyer–Villiger oxidation towards various catalysts, at room temperaure (rt) and 80 °C in ionic liquid

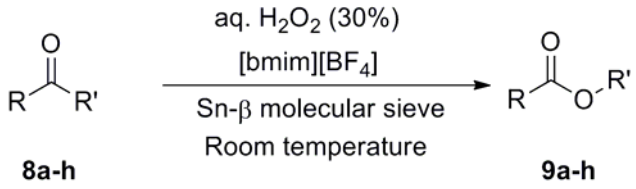
Entry	Ketone	Catalyst	Reaction time/h	Yield (%) at room tempearture	Yield (%) at 80 °C
1	8a	Sn-β molecular sieve	10	88	86
2	8a	Sn silicate-1	10	--	--
3	8a	Ti-silicate-1	10	--	--
4	8a	All silica β	10	--	--
5	8a	All silica β Sn impregnated	10	--	--

The catalyst as well as the ionic liquid which is responsible for bringing about the reaction, were recovered and reused for the reaction with identical results. Thus the recyclability of both was confirmed (**Table 2**).

Table 2. B-V oxidation of ketone (8a-b) to esters (9a-b) with recovered Sn-β molecular sieve and recorved ionic liquid [bmim][BF_4] at room temperature

Entry	Ketone	Product	Time/h	Yield (%)		
				Cycle I	Recycle I	Recycle II
1	**8a**	**9a**	10	88	86	86
2	**8b**	**9b**	10	83	81	80

In order to prove the generality of the above protocol, a variety of aryl ketones (**8a–h**) were oxidized under identical conditions to esters (**9a–h**; Table 3) over 9–10 h. The results are in accordance with the reported migration trends of the R & R' groups. The IR spectrum all products shows peak corresponding to ester.



Scheme 5.

Table 3 B-V oxidation of ketones (**8a–i**) with H_2O_2 (30%) and catalytic Sn-β molecular sieve to esters (**9a–i**) at room temperature in [bmim][BF_4]

Sr. No.	Compound **8**		Compound **9**		Yield (%)	Melting point/°C
	R	R'	R	R'		
a	CH_3	4-CH_3-C_6H_4	CH_3	4-CH_3-C_6H_4	88	Oil[15]
b	CH_3	4-OH-C_6H_4	CH_3	4-OH-C_6H_4	87	62[15,16]
c	CH_3	C_6H_5	CH_3	C_6H_5	72	Oil[15]
d	4-Cl-C_6H_4	CH_3	4-Cl-C_6H_4	CH_3	80	Oil[15]
e	2-Cl-C_6H_4	CH_3	2-Cl-C_6H_4	CH_3	77	Oil[15]
f	4-Cl-C_6H_4	C_6H_5	4-Cl-C_6H_4	C_6H_5	72	105[17]
g	4-Cl-C_6H_4	4-OH-C_6H_4	4-Cl-C_6H_4	4-OH-C_6H_4	76	117[18]
h	C_6H_5	4-OH-C_6H_4	C_6H_5	4-OH-C_6H_4	83	161[19]

3.2.3 Conclusion

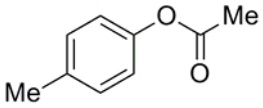
In conclusion it is demonstration of an efficient and mild protocol for the oxidation of aryl ketones to esters at room temperature with 30% aqueous H_2O_2 and catalytic Sn-β molecular sieve in ionic liquid. Our protocol is in accordance with the "atom economy" and does not generate any by-products except water. The ionic liquid and catalyst are recyclable.

3.2.4 Experimental

Typical procedure for Baeyer–Villiger oxidation

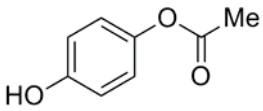
Aqueous H_2O_2 (30%, 2.5 mL) was added to a mixture of 4-methyl acetophenone (**8a**, 0.500 g, 3.731 mmol), Sn-b molecular sieve (0.100 g, 20 wt %) and [bmim][BF_4] (1.0 g, 4.428 mmol) and stirred at room temperature for 10 hours. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, water (10 mL) was added. The catalyst Sn-b molecular sieve was recovered by a simple filtration on Whatman filter paper and dried at 120 °C for 2 h (0.087 g, 87%) and reused as such. The filtrate was extracted with ethyl acetate (3 x 10 mL). The organic layer was separated and washed with brine (2 x 4 mL), dried over anhydrous sodium sulfate, filtered and concentrated in a vacuum to obtain 4-methylphenyl acetate (**9a**, 0.492 g, 88%) as an oil. The aqueous layer was concentrated under reduced pressure to recover the ionic liquid (0.94 g, 94%) and reused as such.

1) 4-Methylphenyl acetate (9a)



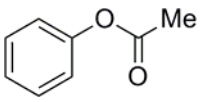
Colourless liquid; IR ($CHCl_3$) ν_{max} 2952, 2920, 1732, 1605, 1461, 1454, 1320,1255, 1096 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ= 2.28 (s, 3H), 2.34 (s, 3H), 6.94 (d, *J* = 8 Hz, 2H), 7.15 (d, *J* = 8 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ= 20.4, 20.6, 120.9, 129.5, 135.0, 148.2, 169.3 ppm.

2) 4-Hydroxyphenyl acetate (9b)



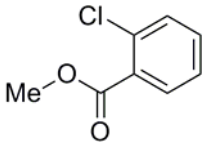
White solid, mp. 62 °C; IR ($CHCl_3$) ν_{max} 2967, 2927, 1733, 1461, 1451, 1313,1234, 1089 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ= 2.28 (s, 3H), 7.00 (d, *J* = 8 Hz, 2H), 7.31 (d, *J* = 8 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ= 20.4, 122.6, 129.0, 130.6, 148.8, 168.6 ppm.

3) Phenyl acetate (9c)



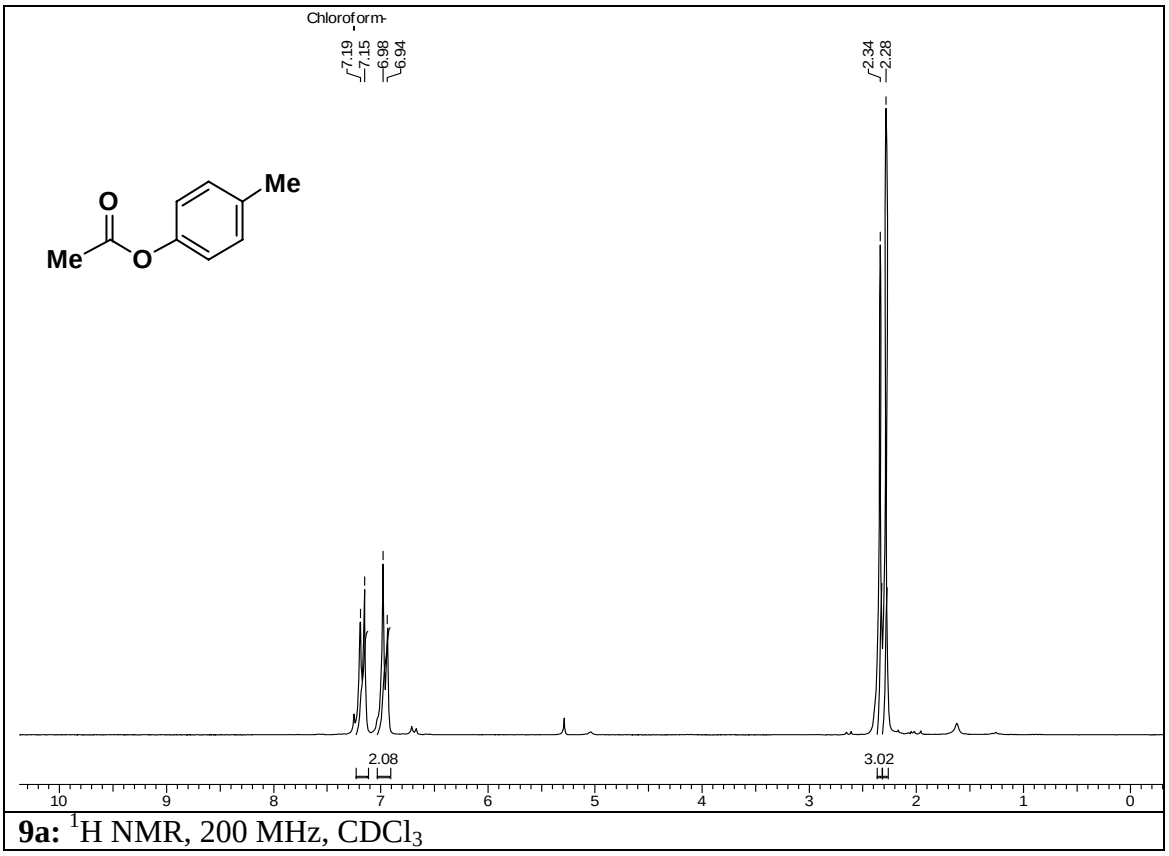
Colourless liquid; IR ($CHCl_3$) ν_{max} 2952, 2920, 1735, 1452, 1439, 1331,1255, 907 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ= 2.36 (s, 3H), 71.2-7.17 (m, 2H), 7.29-7.32 (m, 1H), 7.41-7.48 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ= 20.9, 121.4, 125.6, 129.2, 150.5, 169.3 ppm.

4) Methyl-2-chlorobenzoate (9e)

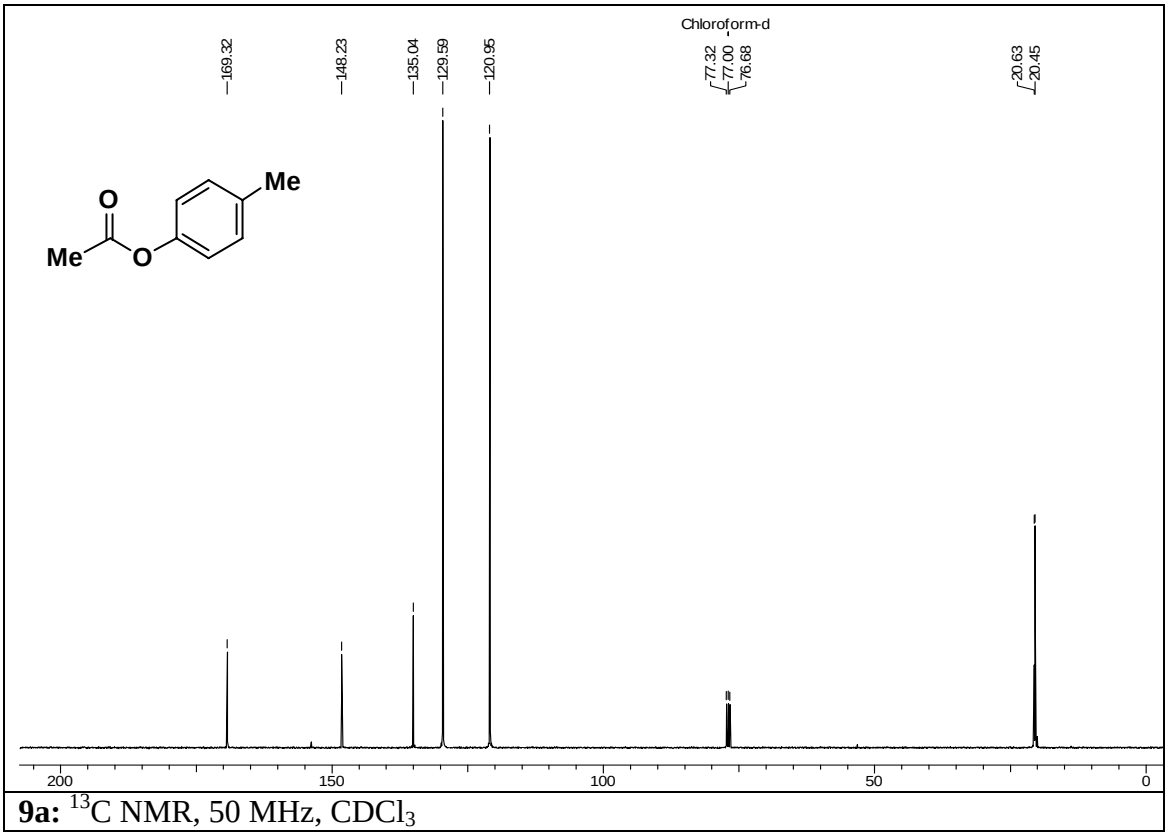


Yelloq liquid; IR ($CHCl_3$) ν_{max} 2954, 2926, 1735, 1461, 1439, 1311,1250, 1091 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ= 3.95 (s, 3H), 6.85-7.00 (m, 2H), 7.41-7.50 (m, 1H), 7.81-7.86 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ= 52.0, 112.2, 117.3, 118.9, 129.7, 135.4, 161.4, 170.3 ppm.

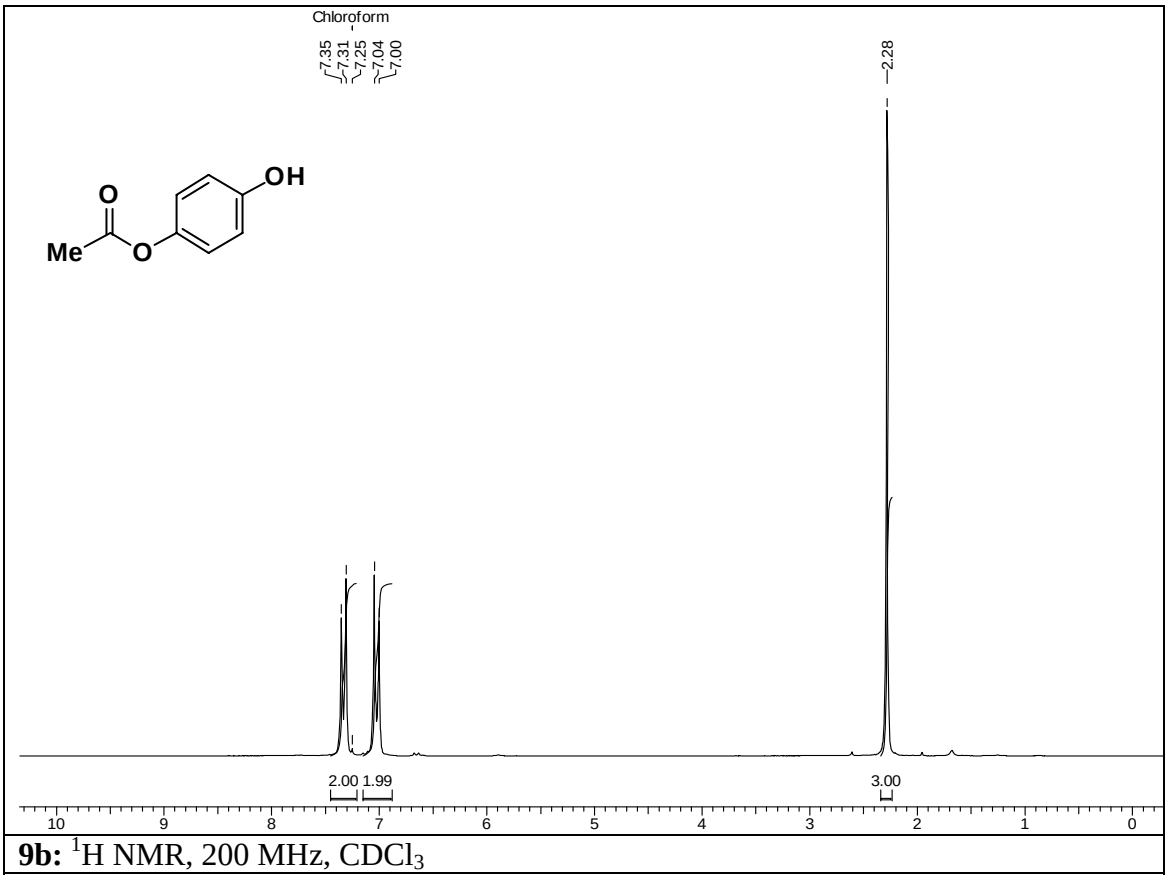
3.2.5 Analytical Data



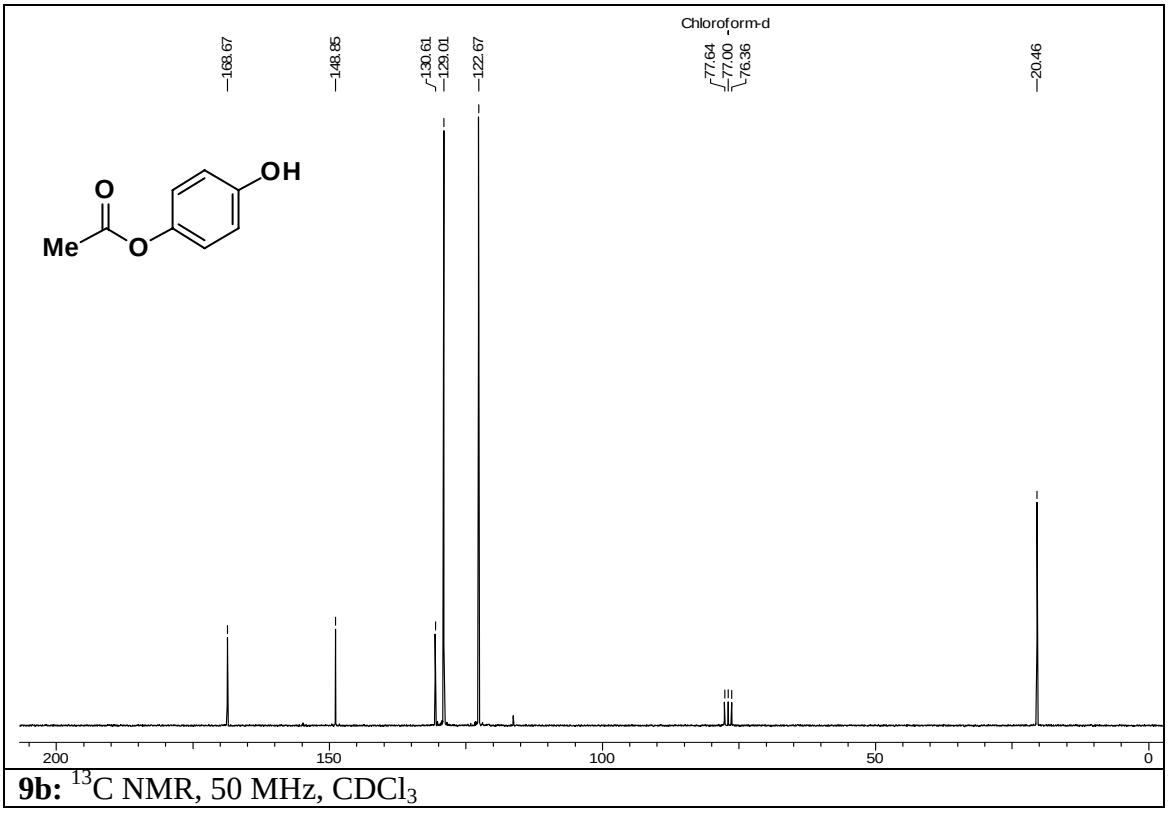
9a: ^{1}H NMR, 200 MHz, $CDCl_3$



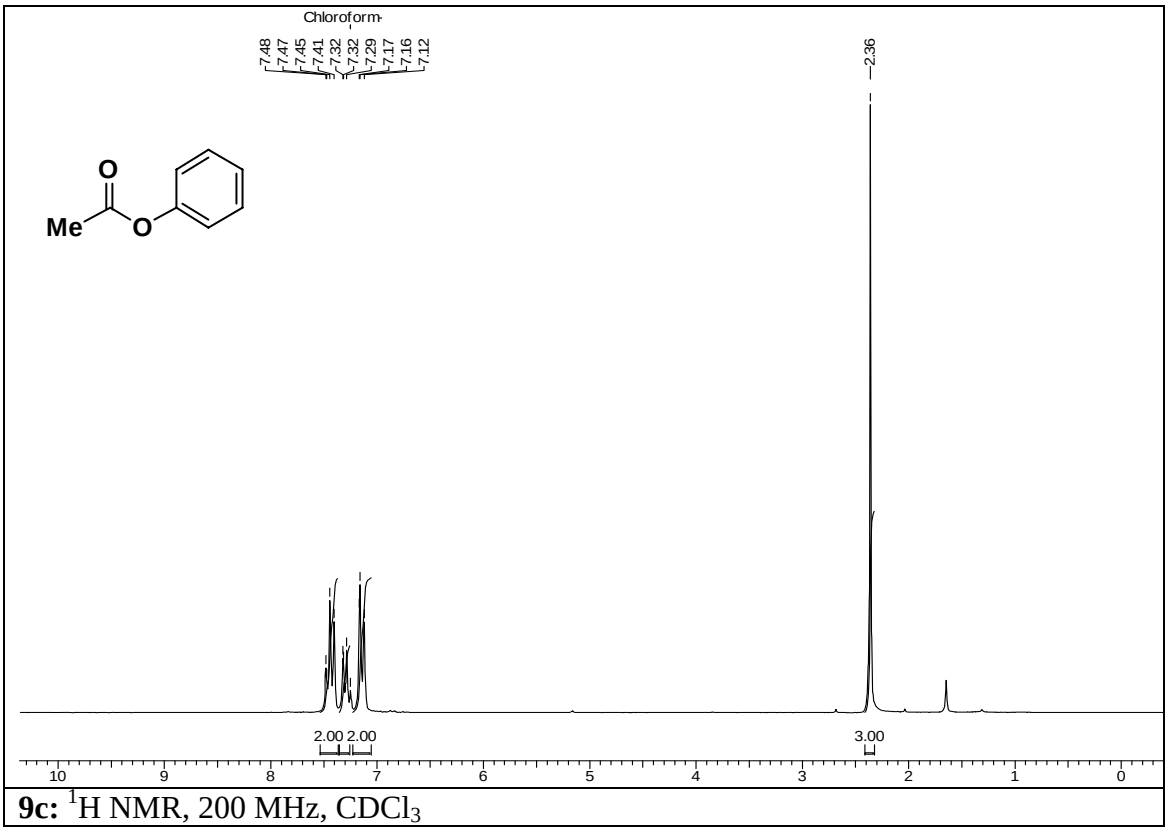
9a: ^{13}C NMR, 50 MHz, $CDCl_3$



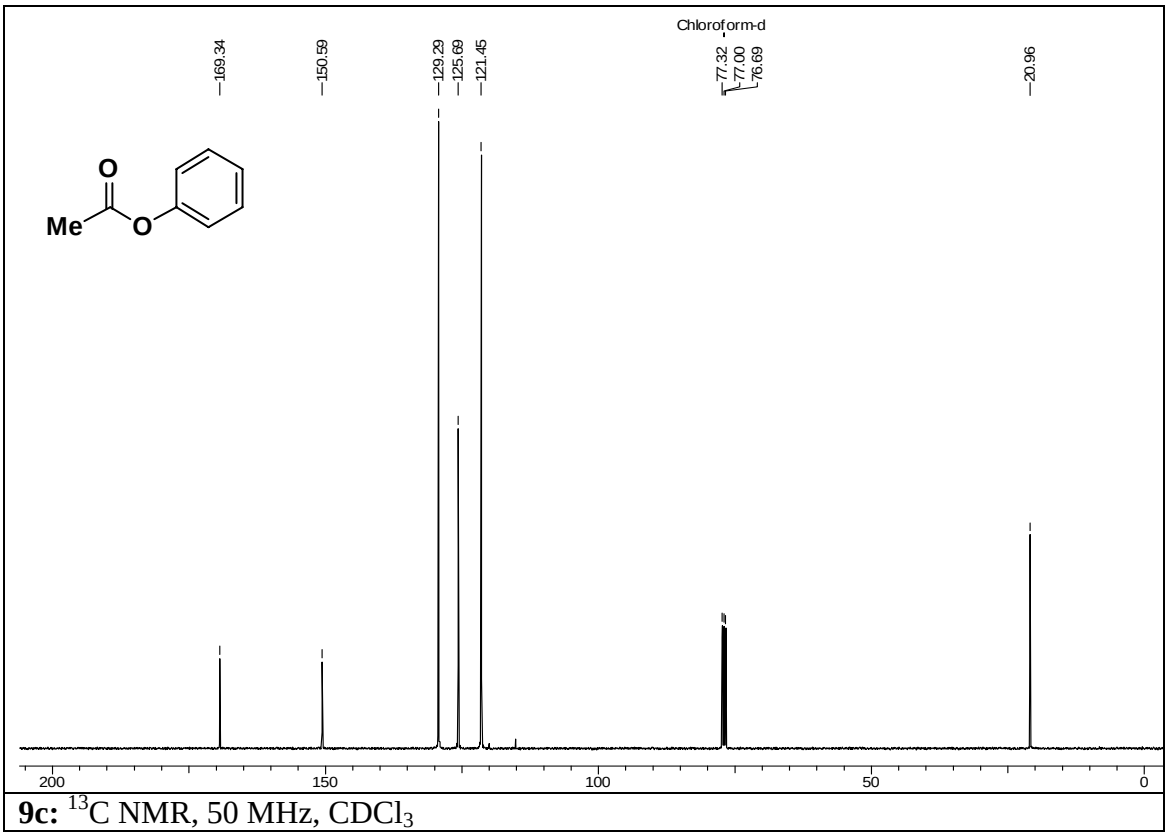
9b: ^{1}H NMR, 200 MHz, $CDCl_3$



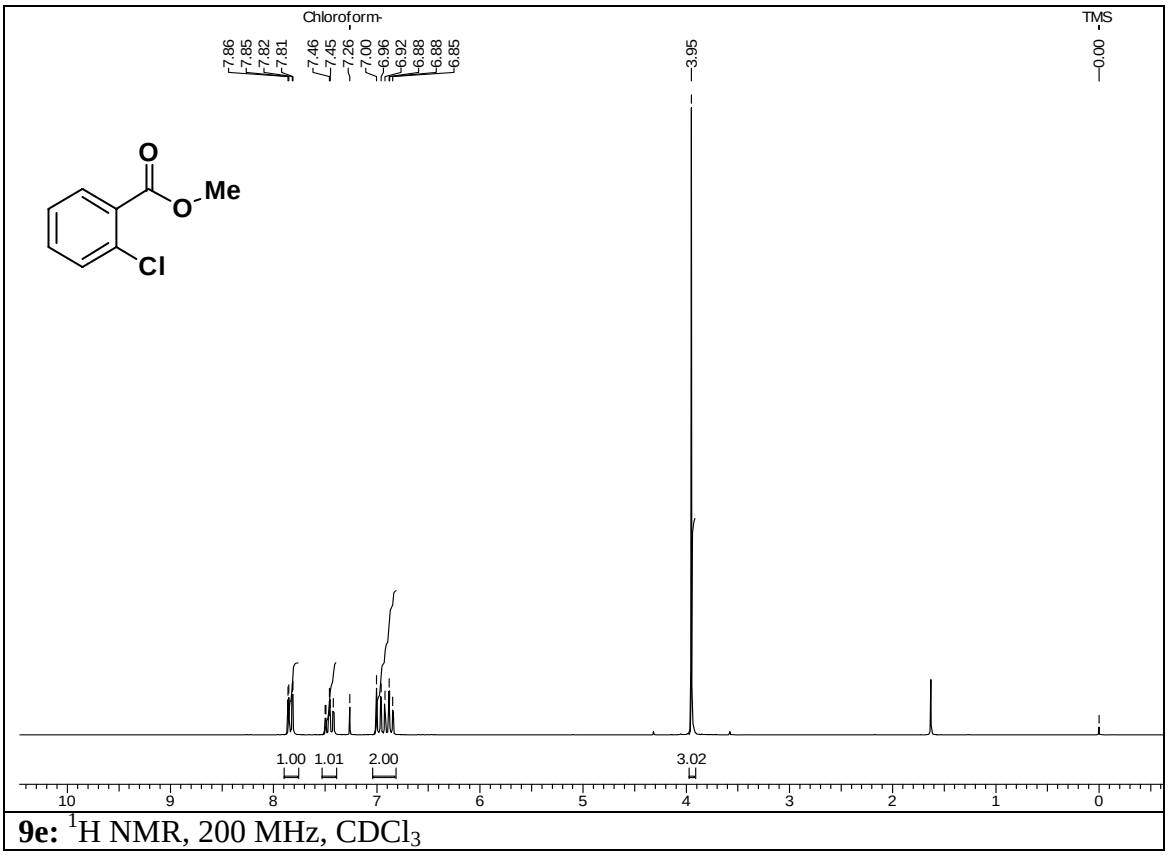
9b: ^{13}C NMR, 50 MHz, $CDCl_3$



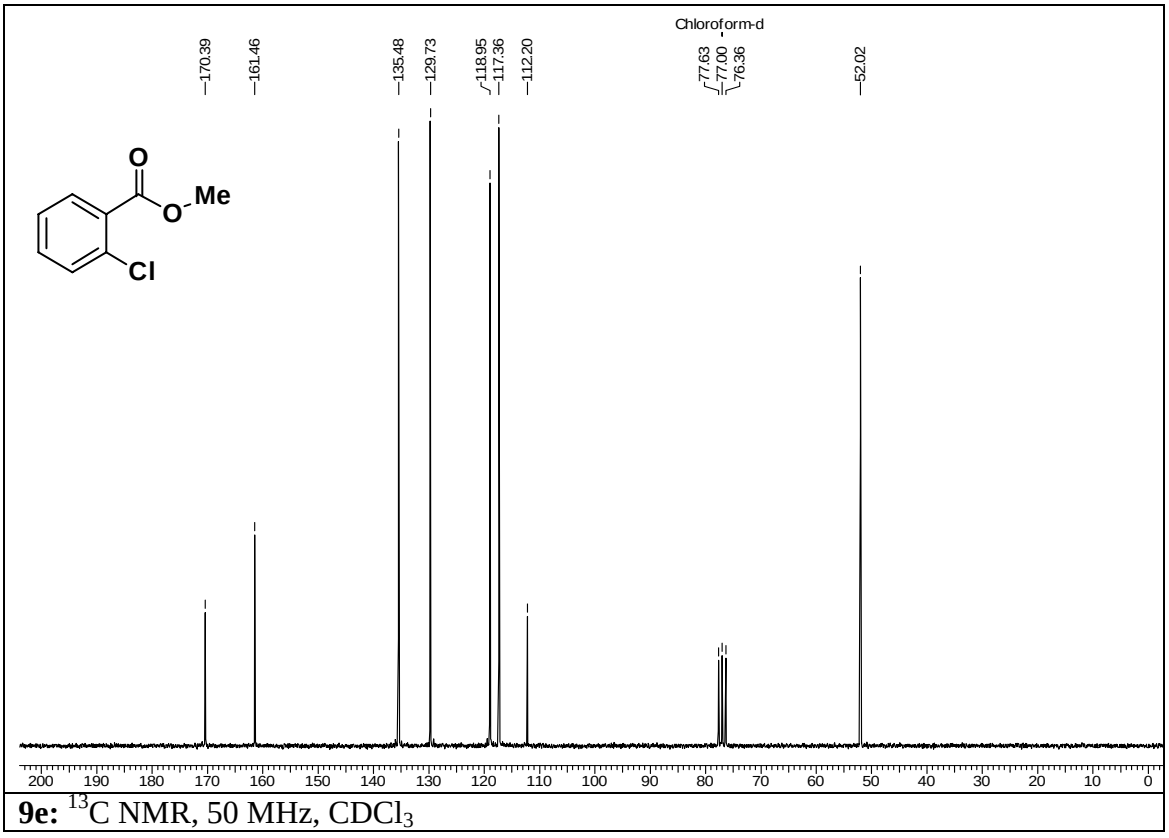
9c: ^{1}H NMR, 200 MHz, $CDCl_3$



9c: ^{13}C NMR, 50 MHz, $CDCl_3$



9e: ^{1}H NMR, 200 MHz, $CDCl_3$



9e: ^{13}C NMR, 50 MHz, $CDCl_3$

3.2.6 References

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12. Mal, N. K.; Ramaswamy, V.; Ganapathy, S.; Ramaswamy, A. V. *Chem. Commun.* **1994**, 1993.
13. Serrano, D. P.; Van Grieken, R.; Sanchez, P.; Sanz, R.; Rodriguez, L. *Microporous Mesoporous Mater.* **2001**, *46*, 35.
14. The Sn-impregnated all-silica b sample was prepared using all-silica β and tin chloride pentahydrate solution. 10 g of all-silica b was added to a solution containing 0.48 g of $SnCl_4 \cdot 5H_2O$ and 8 ml of water with constant stirring. The homogeneous mixture thus obtained was then dried at 80 °C for 5 h. Dried powder was further subjected to calcinations in air at 560 °C for 12 h. The resultant material showed no structural damage and 1.6% Sn content.
15. ^{1}H NMR agrees with the structures.
16. Melting point matches with reported; Dictionary of Organic Compounds, 6th edn., Chapman & Hall, London, p. 571.
17. Melting point matches with reported; Dictionary of Organic Compounds, 6th edn., Chapman & Hall, London, p. 1290.
18. Melting point matches with the authentic prepared from p-chlorobenzoic acid and hydroquinone.

19. Melting point matches with reported; Dictionary of Organic Compounds, 6th edn., Chapman & Hall, London, p. 571.

3.3 SECTION C

OXIDATION OF 1,4-DIHYDROPYRIDINE WITH AQUEOUS H_2O_2 IN IONIC LIQUIDS

3.3.1 Introduction

Almost more than 100 years ago, Hantzsch[1] prepared 1,4-dihydropyridines (DHPs) by a method widely known as Hantzsch dihydropyridine synthesis. Substantial research activities have been devoted to the chemistry & biology of the Hantzsch dihydropyridine derivatives (*e. g*. Hantzsch esters) because of their wide applications in hot areas such as synthesis of substituted pyridines, serving as effective redox catalysts under mild conditions, modeling the NAD(P)H coenzyme to study its oxidation mechanism in living system[2] and emerging as highly effective calcium channel antagonist with suitable pharmacological profiles. Hantzsch 1,4-dihydropyridine nucleus is common to numerous bioactive compounds, which include various vasodilator,[3a] antihypertensive,[3b] bronchodilator,[3c] antiatherosclerotic, hepatoprotective, antitumor, antimutagenic, geroprotective and antidiabetic agents. DHPs have found commercial utility as calcium channel blockers, as exemplified by therapeutic agents such as nifedipine **1**,[3d] nitrendipine **2**,[3e] nimodipine **3**,[3f] amlodipine **4,** felodipine **5** & nicardipine **6** (**Figure1**).

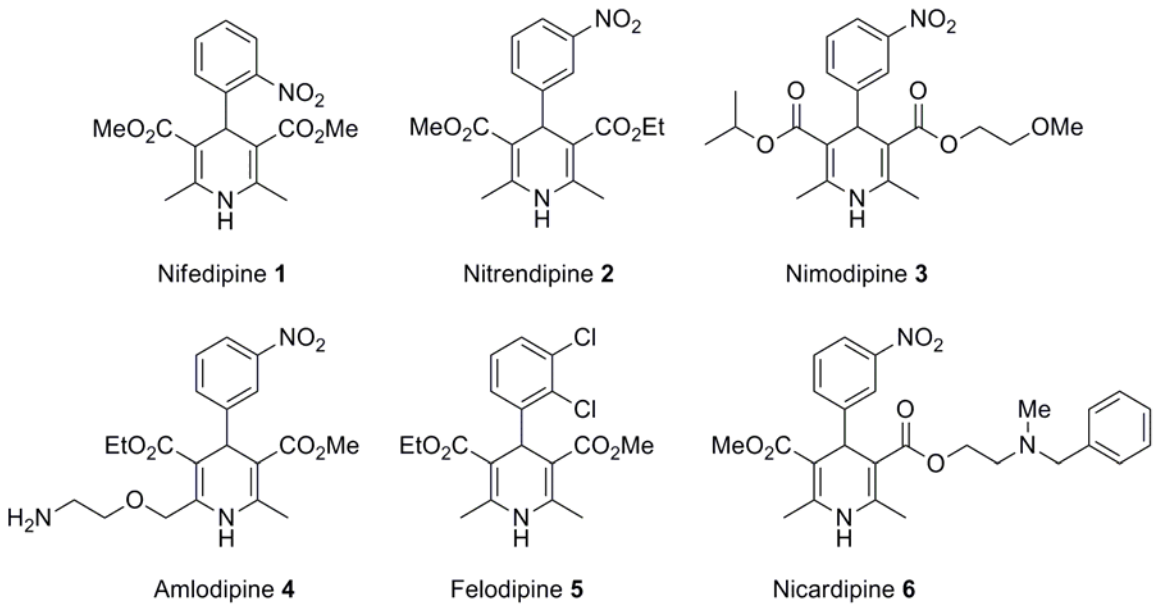
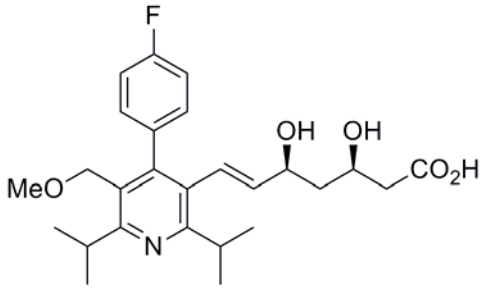


Figure 1.

In the human body, 1,4-dihydropyridine based drugs are oxidatively converted to the corresponding pyridine derivatives by the action of cytochrome P-450 or other related enzymes in the liver.[2a] These oxidized compounds are largely devoid of the pharmacological activity of the parent compounds. These metabolites are important as reference standards and hence development of convenient method for their oxidation is important particularly for the synthesis of radiolabled compounds to study their biodegradation. Additionally, dihydropyridines are often produced in synthetic sequence, which have to be oxidized to pyridines; and provide the easiest method to obtain pyridine derivatives.

In recent years Böcker and co-workers have studied the metabolism of Hantzsch 1,4-DHPs and shown that first metabolic step includes aromatization to corresponding pyridine derivatives,[4] which have found its application for the treatment of atherosclerosis and other coronary deseases. The main representative of such type of compounds is cerivastatin **7**[5] (**Figure 2**).



Cerivastatin **7**

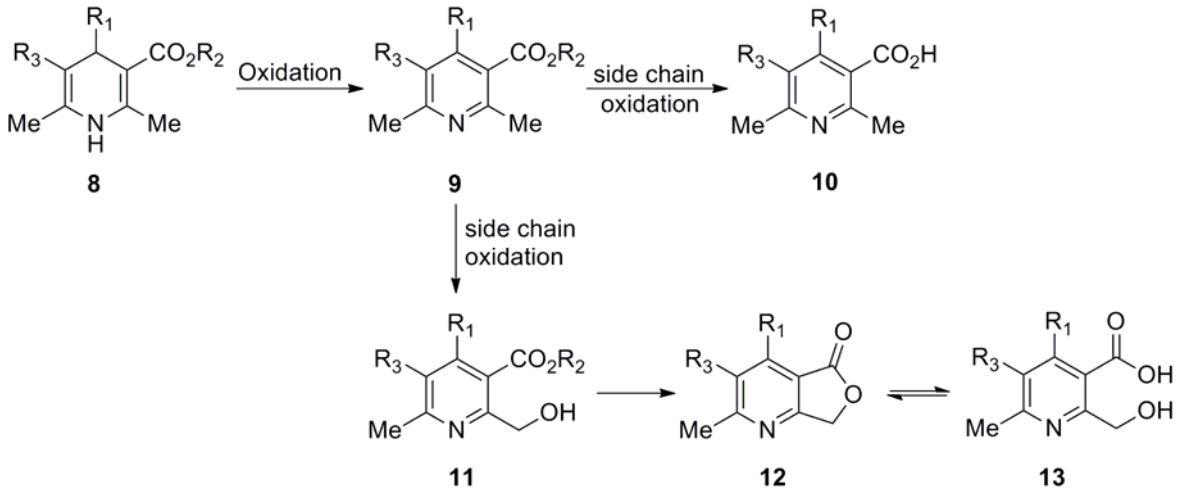
Figure 2.

3.3.2 Calcium Antagonist

"Calcium antagonist" are inhibitors of electromechanical coupling which cause a dose –dependent reduction of transmembranal Ca^{2+} influx into the cells of contractile system such that the Ca^{2+}-dependent myofibril-ATPase converts less phosphate bound energy into mechanical work. Accordingly, the oxygen demand of the beating heart and contractile tonus of the coronary and the peripheral resistance vessels are reduced. This mechanism of action results in three different fundamental effects,

1. the direct damping of myocardial workload metabolism,
2. an increase in blood supply to the coronary vessels,
3. a reduction in arterial flow resistance.

The vasodilating effect of calcium antagonist find clinical application especially in the treatment of oxygen deficiency of the heart such as angina pectoris.[6]



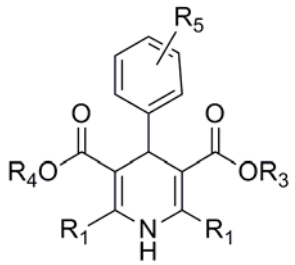
Scheme 1. Generalized scheme for metabolism of 1,4- DHP drugs

Scheme 1 represents generalized scheme for metabolism of 1,4-dihydropyridine drugs. According to this scheme, P-450 enzymes have been shown to catalyze pyridine formation, methyl hydroxylation (often accompanied by lactone formation involving anchimeric assistance) and various modes of side chain oxidation, including the oxidative cleavage of R_2.

3.3.3 Structure Activity Relationship

An optimum in biological activity, (vasodilation, reduction in blood pressure) of 1,4-DHPs is to be expected when the following structural parameters are met-

1. 1,4-DHP unsubstituted at nitrogen.
2. Lower alkyl groups are optimal substituent (R_1 & R_2) in 2, 6 position. Replacement of one alkyl group by amino is tolerated.
3. Carboxylate groups are superior to the other acceptor substituents such as CN, COR, SO_2R, $CONR_2$, NO_2 etc. both in the position 3 & 5. The alcohol component of the ester group can be saturated, unsaturated, straight or branched chain. 1,4-DHPs with non-identical ester groups ($R_3 \neq R_4$) are in many cases superior to the corresponding derivative with identical substitution.



14

4. A phenyl substituent is superlative in the 4-position, eventhough its replacement by other monocyclic or polycyclic arenes or heteroarenes is possible within limits. Monosubstitution of phenyl ring (R_5) by acceptor substituents such as NO_2, CN, CF_3 etc. in ortho or meta position has positive influence, para-substitution on the other hand causes a marked reduction or even loss of activity.

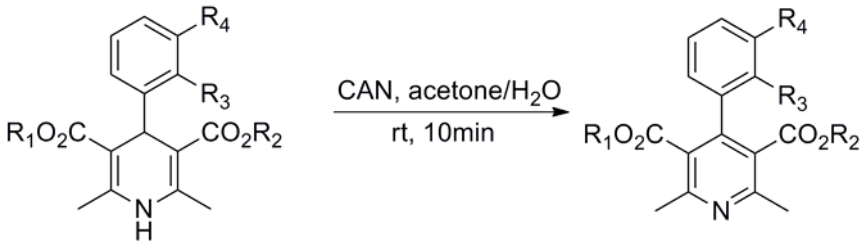
Since 1,4-DHPs constitute an important class of bioactive molecules and also provide the easiest way to pyridine derivatives, newer and improved methods to effect the oxidation of 1,4-DHP systems continued to be investigated.

3.3.4 Literature survey for aromatization of 1,4-DHPs

A vast amount of literature[7] is known on conversion of 1,4-dihydropyridines to the corresponding pyridines. This section is restricted to only few of the recent methods described in the literature.

3.3.4.1 Pfister *et al.* (1990, Scheme 2)[7a]

Pfister and co-workers reported the aromatization of 1,4-DHPs using aqueous solution of ceric ammonium nitrate (2 equiv) and acetone as the solvent at room temperature. This reaction is general and fast but used expensive reagent like CAN. Secondly, CAN slowly attacks solvents.

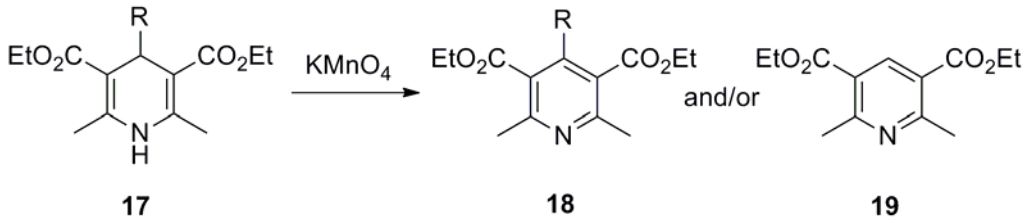


15 **16**

Scheme 2.

3.3.4.2 Eynede *et al.* (1994, Scheme 3)[7b]

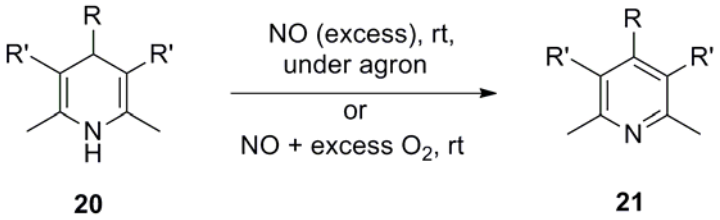
Eynede and co-workers reported oxidation of 1,4-DHPs using potassium permanganate either supported on montmorillonite KSF or by using 15-crown-5 as the catalyst to yield **18** and/or **19**.



Scheme 3.

3.3.4.3 Ohasawa *et al.* (1995, Scheme 4)[7c]

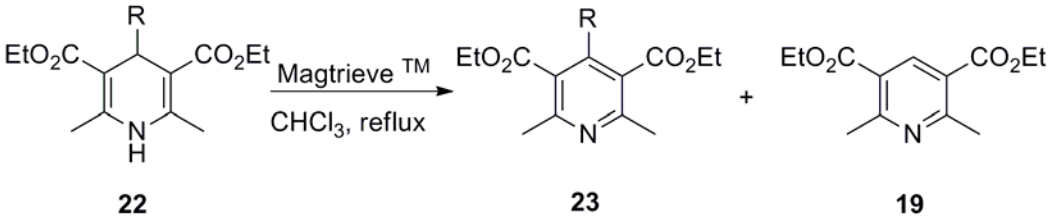
Ohasawa and co-workers described oxidation of 1,4-DHPs either in absence or presence of oxygen. Under anaerobic conditions, excess of nitric oxide is required and under aerobic conditions, excess of molecular oxygen is required which oxidizes nitric oxide to NO_2, which eventually oxidizes 1,4-DHPs (**Scheme 4**). The reaction system is although quite simple and easy to perform since the oxidant used is supplied as gas, the ease of availability of gaseous NO makes it less attractive. This reaction lacks generality since NO was used in excess.



Scheme 4.

3.3.4.5 Ko *et al.* (1998, Scheme 5)[7d]

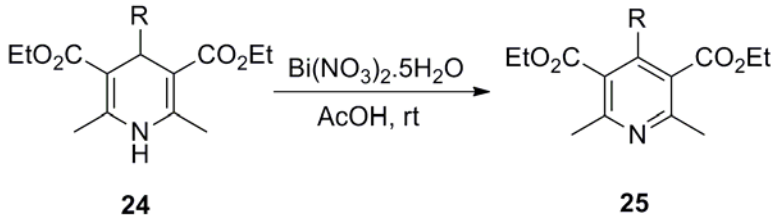
Recently, Ko and co-workers described oxidation of 1,4-DHPs using magnetically retrievable and safe oxidant Magtrieve in chloroform under reflux **(Scheme 5)**.



Scheme 5.

3.3.4.6 Mashraqui *et al.* (1998, Scheme 6)[7e]

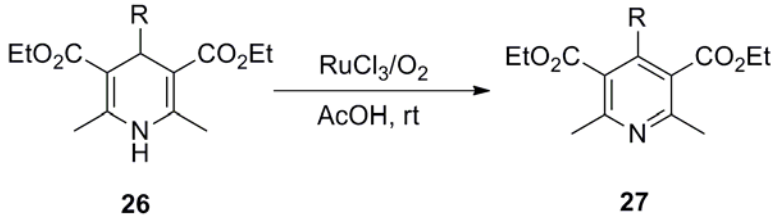
Mashraqui and co-workers reported the oxidation using easily available $Bi(NO_3)_3.5H_2O$ using acetic acid as the solvent. The reaction is very simple and the reagent used is easily available and economically cheap but the major drawback of the reaction is the ring nitration (**Scheme 6**).



Scheme 6.

3.3.4.7 Mashraqui *et al.* (1998, Scheme 7)[7f]

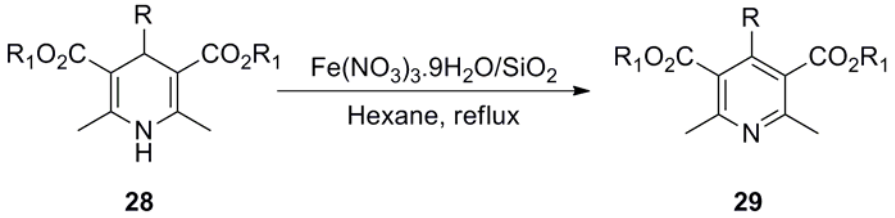
In another approach Mashraqui and co-workers reported recently the oxidation of 1,4-DHPs using $RuCl_3$ and molecular oxygen at room temperature using acetic acid as the solvent of choice. But the reaction involved use of costly reagent $RuCl_3$ (**Scheme 7**). Yields are poor to quantitative depending on the substrate.



Scheme 7.

3.3.4.8 Khadilkar *et al.* (1998, Scheme 8)[7g]

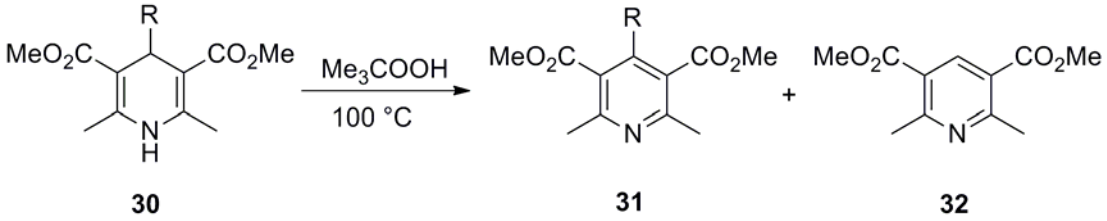
Khadilkar *et al.* utilized ferric nitrate supported on silica gel for the aromatization of 1,4-DHPs in refluxing hexane (**scheme 8**).



Scheme 8.

3.3.4.9 Chavan *et al.* (1998, Scheme 9)[7h]

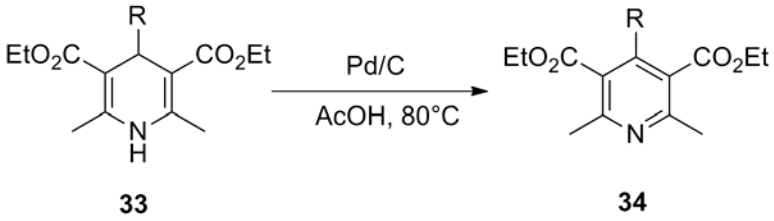
Chavan and co-workers achieved aromatization of 1,4-DHPs using aqueous *tert*-butylhydroperoxide.



Scheme 9

3.3.4.10 Hayashi *et al.* (2002, Scheme 10)[7i]

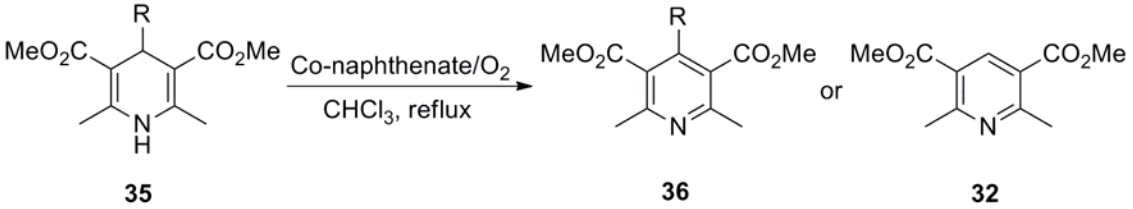
Hayashi and co-workers reported a method for oxidation of Hantzsch 1,4-dihydropyridines by Palladium on carbon in acetic acid.



Scheme 10.

3.3.4.11 Chavan *et al.* (2003, Scheme 11)[7j]

Chavan and co-workers reported a method for auto oxidation of Hantzsch 1,4-dihydropyridinesto pyridines using Co(II)-naphthenate catalyst.

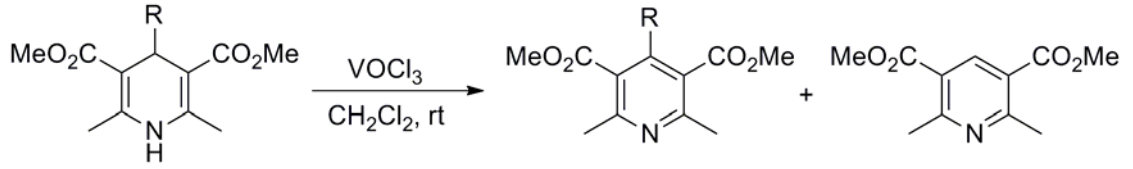


35 36 32

Scheme 11.

3.3.4.12 Litvić et al (2008, Scheme 12)[7k]

Recently Litvić and co-workers reported for aromatization of 1,4-dihydropyridines employing urea-hydrogen peroxide adduct as oxidnt catalyzed by 20 mol% of molecular iodine.



37 38 32

Scheme 12.

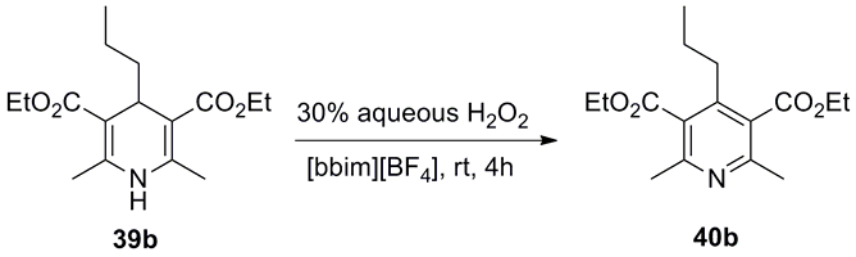
3.3.5 Present work

The oxidation of 1,4-dihydropyridines to the corresponding pyridine derivatives is well documented. However, many of the reported oxidation procedures either require strong oxidants, severe conditions, excess of the oxidants or a costly catalyst or cumbersome workup procedures. An additional drawback in almost all the reported procedures is the loss of isopropyl group from 4-isopropyldihydropyridine. In view of the above limitations, practical and efficient approach for this oxidative transformation is desirable.

In recent years, the use of room temperature ionic liquids (I.Ls.) as 'green' solvents in organic synthetic processes has gained importance due to their solvating ability, negligible vapour pressure, easy recyclability and reusability. Thus we decided

to develop a method for oxidative transformation using ionic liquid. In due course, reagent search for oxidation zeroed on aqueous hydrogen peroxide. H_2O_2 is the obvious choice due to its ready availability, very high active oxygen content per mole, the by-product being water and its wide industrial acceptability.

Initial oxidation reaction was performed on 2,6-dimethyl-1, 4-dihydro-4-(1-propyl)-3,5-pyridinedicarboxylic acid, diethyl ester (**39b**) with H_2O_2 (30%) in ionic liquid 1,3-di-*n*-butylimidazolium tetra fluoroborate [bbim][BF_4] at room temperature for 4 h. The workup involved simple extraction with ether to furnish corresponding pyridine (**40b**) in high yield (**Scheme 13**). The ionic liquid separated after the ether extraction was reused for oxidation of dihydropyridine with fresh H_2O_2 at room temperature and identical results were obtained, which proved the recyclability of ionic liquid.

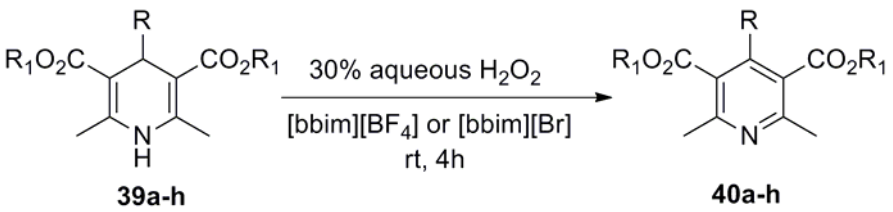


39b **40b**

Scheme 13.

In order to prove the generality of the above protocol, a variety of 1,4-DHPs **(39a–h)** were oxidised under the identical reaction conditions to pyridines (**40a–h, Table 1**, **Scheme 14**). The purity of all the products was checked by HPLC and were characterised by the analysis of their ^{1}H NMR spectra. The HPLC of the product was identical with authentic material prepared by reported procedure. A noteworthy feature is efficient aromatization of 1,4-DHPs to pyridines at room temperature. More importantly the 4-alkyl substituted DHPs (**1a–c**, Table 1) smoothly undergo oxidation to the corresponding 4-alkyl pyridines. This is in marked contrast to most of the earlier reported methods, which invariably furnish dealkylated pyridines.

Identical results were obtained when 1,3-di-*n*-butylimidazolium bromide ([bbim][Br]) was used as an ionic liquid.



39a-h **40a-h**

Scheme 14.

Table 1 Oxidation of 1,4-dihydropyridines (**39a-h**) with H_2O_2 in [bbim][BF_4] or [bbim][Br] to pyridines (**40a-h**) at room temperature

1,4-DHP	R	R_1	Pyridine	Yield %	
				[bbim][BF_4]	[bbim][Br]
39a	CH_3	CH_3CH_2	**40a**	69	71
39b	$CH_3CH_2CH_2$	CH_3CH_2	**40b**	83	82
39c	$(CH_3)_2CH$	CH_3CH_2	**40c**	76	73
39d	C_6H_5	CH_3	**40d**	82	86
39e	2-Cl-C_6H_4	CH_3	**40e**	79	73
39f	2-NO_2-C_6H_4	CH_3	**40f**	79	81
39g	4-NO_2-C_6H_4	CH_3	**40g**	69	89
39h	4-OMe-C_6H_4	CH_3	**40h**	68	78

3.3.6 Conclusion

In conclusion, an efficient oxidation of 1,4-dihydropyridines to pyridines at room temperature with H_2O_2 in ionic liquids, is demonstrated. The protocol is in accordance with the 'atom economy' and does not generate any byproducts since hydrogen peroxide is the only oxidant used and the Ionic liquid is recyclable.

3.3.7 Experimental

a) Typical procedure for oxidation of 1,4-DHP using aqueous H_2O_2 and [bbim][BF_4]

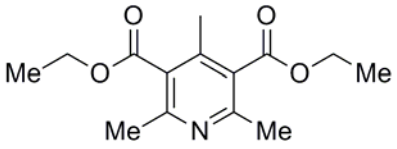
A mixture of dialkyl 2,6-dimethyl-1, 4-dihydro-4-substituted-3,5-pyridine dicarboxylate (**39a-h**, 1.0 mmol), H_2O_2 (30%, 2 ml) and [bbim][BF_4] (1.340g, 5.0 mmol) was stirred at room temperature for 4 h. The reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was extracted with diethyl ether (3 x 15 ml). The organic layer was separated and washed with brine (2 x 4 ml), dried over anhydrous sodium sulfate. It was filtered and concentrated in vacuum to obtain dialkyl-4-substituted-2, 6-dimethyl-3,5-pyridinedicaboxylate (**40a-h**).

b) Typical procedure for oxidation of 1,4-DHP using aqueous H_2O_2 and [bbim][Br]

A mixture of dialkyl-2,6-dimethyl-1,4-dihydro-4-substituted-3,5-pyridinedicarboxylate ester (**39a-h**, 1.0 mmol), H_2O_2 (30%, 1 ml) and [bbim][Br] (1.305g, 5.0 mmol) was stirred at room temperature for 4 h. The reaction was monitored by TLC. After the

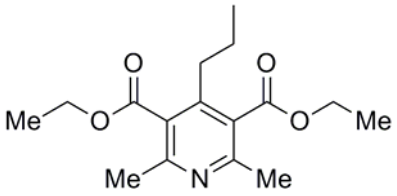
completion of the reaction, the reaction mixture was extracted with diethyl ether (3 × 15 ml). The organic layer was separated and washed with brine (2 × 4 ml), dried over anhydrous sodium sulfate. It was filtered and concentrated in vacuum to obtain dialkyl-4-substituted-2, 6-dimethyl-3,5-pyridinedicaboxylate (**40a-h**).

1) diethyl 2,4,6-trimethyl-3,5-pyridinedicarboxylate (40a)



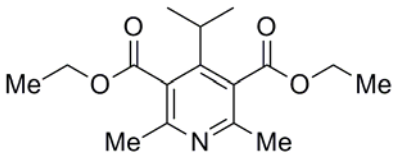
Yellow oil, IR ($CHCl_3$) ν_{max} 2982, 2936, 2907, 2875, 1723, 1571, 1447, 1411, 1378, 1285, 1241, 1221, 1173, 1107, 1042, 938, 858, 837, 778, 569 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.36 (t, *J*= 7.2 Hz, 6H), 2.25 (s, 3H), 2.50 (s, 6H), 4.36 (q, *J* = 7.2 Hz, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.8, 16.6, 22.5, 61.2, 127.3, 141.7, 154.5, 168.0 ppm. Elemental Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.32; H, 7.26; N, 5.21.

2) diethyl-4-(1-propyl)-2, 6-dimethyl-3,5-pyridinedicaboxylate (40b)



Yellow oil, IR ($CHCl_3$) ν_{max} [2981], 2912, 2867, 1731, 1241, 835, 767 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.91 (t, *J*= 7.2 Hz, 3H), 1.37 (t, *J* = 7.2 Hz, 6H), 1.46-1.61 (m, 2H), 2.49 (s, 6H), 2.54 (t, *J*= 5.6 Hz, 2H), 4.37 (q, *J*= 7.2 Hz, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 14.2, 22.8, 24.0, 33.3, 61.4, 127.1, 146.2, 154.9, 168.4 ppm. Elemental Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.49; H, 7.94; N, 4.69.

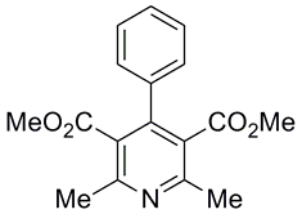
3) diethyl-4-(2-propyl)-2, 6-dimethyl-3,5-pyridinedicaboxylate (40c)



Yellow oil, IR ($CHCl_3$) ν_{max} 2983, 2901, 2865, 1729, 1241, 938, 858, 847, 773, 561 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): 1.20 (t, *J*= 8.1 Hz, 6H), 1.29 (d, *J*= 8.3 Hz, 6H), 2.6

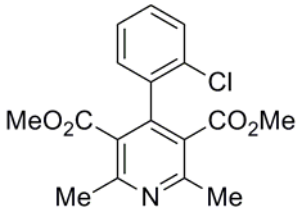
(s, 6H), 2.69-2.75 (m, 1H), 4.3 (q, *J*= 8.1 Hz, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): 14.1, 22.2, 25.6, 28.3, 61.9, 127.1, 143.5, 154.7, 168.2 ppm.

4) dimethyl-4-phenyl-2, 6-dimethyl-3,5-pyridinedicaboxylate (40d)



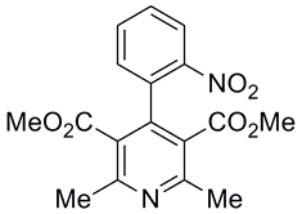
Yellow solid, mp. 136-138 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.82 (s, 6H), 3.54 (s, 6H), 7.18-7.25 (m, 2H), 7.41-7.46 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.3, 52.8, 126.9, 128.5, 129.9, 130.4, 133.6, 152.7, 153.0, 164.1 ppm.

5) dimethyl-4-(2-chlorophenyl)-2, 6-dimethyl-3,5-pyridinedicaboxylate (40e)



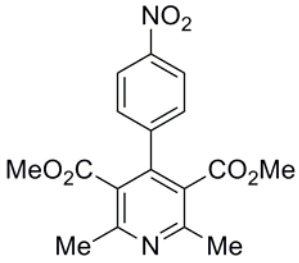
Yellow solid, mp. 69-70 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.62 (s, 6H), 3.50 (s, 6H), 7.10-7.15 (m, 1H), 7.24-7.30 (m, 2H), 7.38-7.42 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.6, 52.2, 126.4, 126.7, 129.3, 130.1, 130.3, 133.0, 135.9, 145.0, 156.8, 167.7 ppm.

6) dimethyl-4-(2-nitrophenyl)-2, 6-dimethyl-3,5-pyridinedicaboxylate (40f)



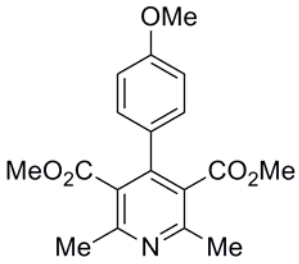
Yellow solid, mp. 105-106 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.62 (s, 6H), 3.48 (s, 6H), 7.15-7.20 (m, 1H), 7.54-7.62 (m, 2H), 8.15-8.20 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.0, 51.6, 125.8, 126.1, 128.7, 129.3, 129.8, 132.3, 135.2, 144.3, 156.2, 167.0 ppm.

7) dimethyl-4-(4-nitrophenyl)-2, 6-dimethyl-3,5-pyridinedicaboxylate (40g)



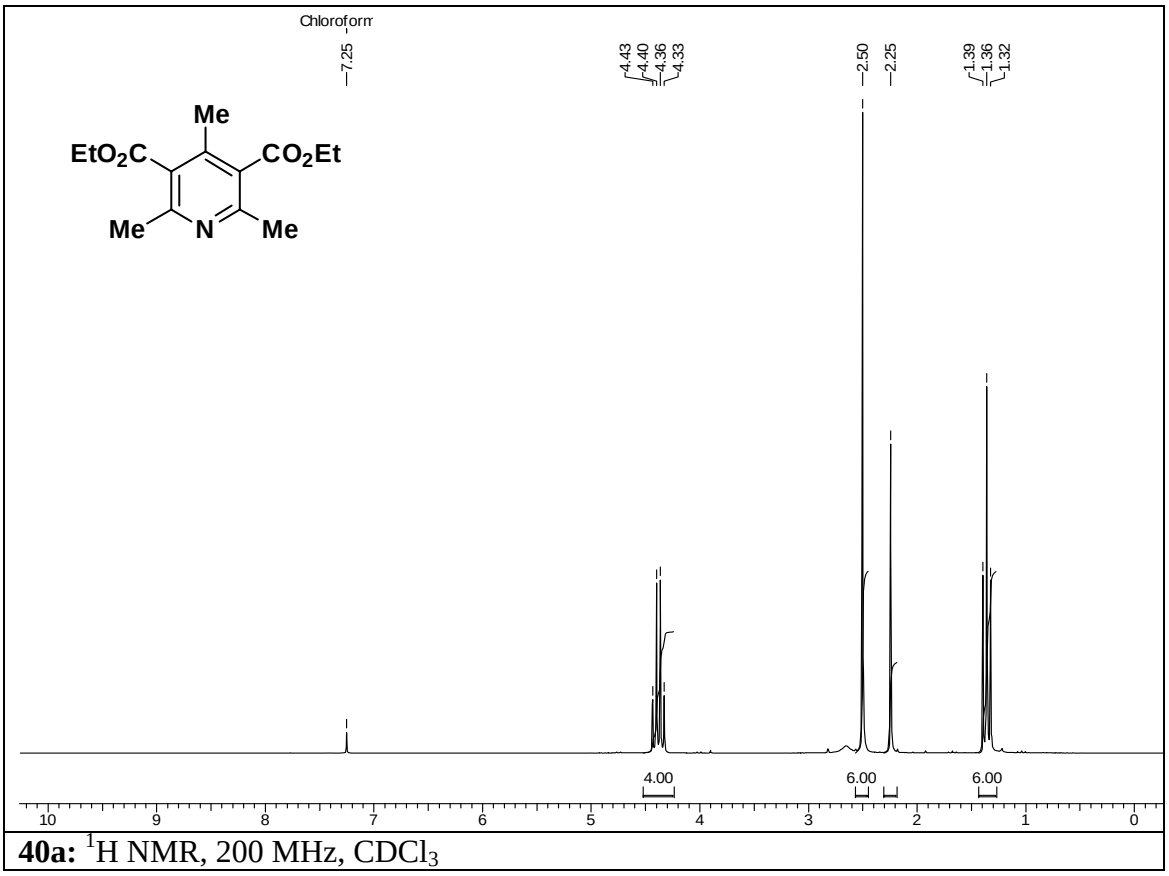
Yellow solid, mp. 146-148 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.57 (s, 6H), 3.51 (s, 6H), 7.36 (d, *J*= 8 Hz, 2H), 8.19 (d, *J*= 8 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.7, 52.1, 123.0, 125.8, 128.7, 143.0, 144.0, 148.0, 155.6, 168.2 ppm.

8) dimethyl-4-(4-methoxyphenyl)-2, 6-dimethyl-3,5-pyridinedicaboxylate (40h)

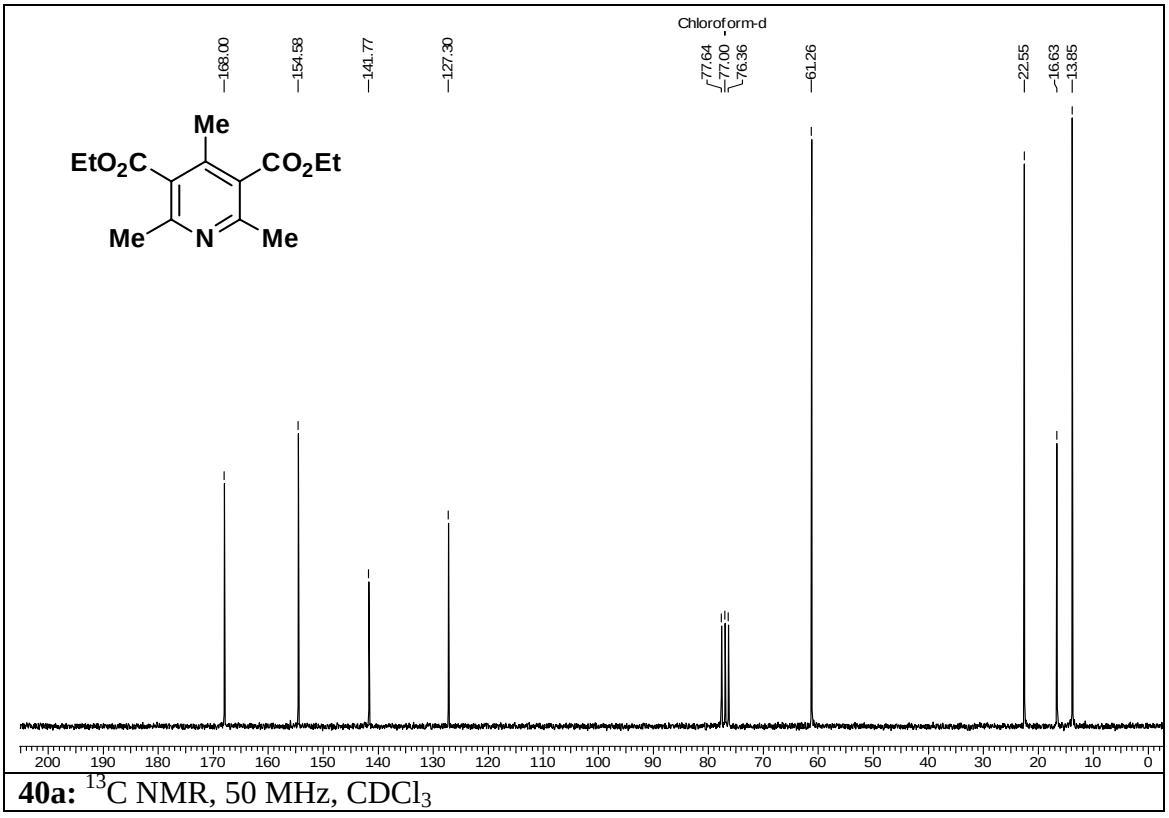


Yellow solid, mp. 114-115 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.55 (s, 6H), 3.55 (s, 6H), 3.80 (s, 3H), 6.85 (d, *J*= 8.8 Hz, 2H), 7.13 (d, *J*= 8.8 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.8, 52.1, 55.0, 113.6, 126.8, 128.4, 129.0, 145.6, 155.2, 159.6, 168.5 ppm.

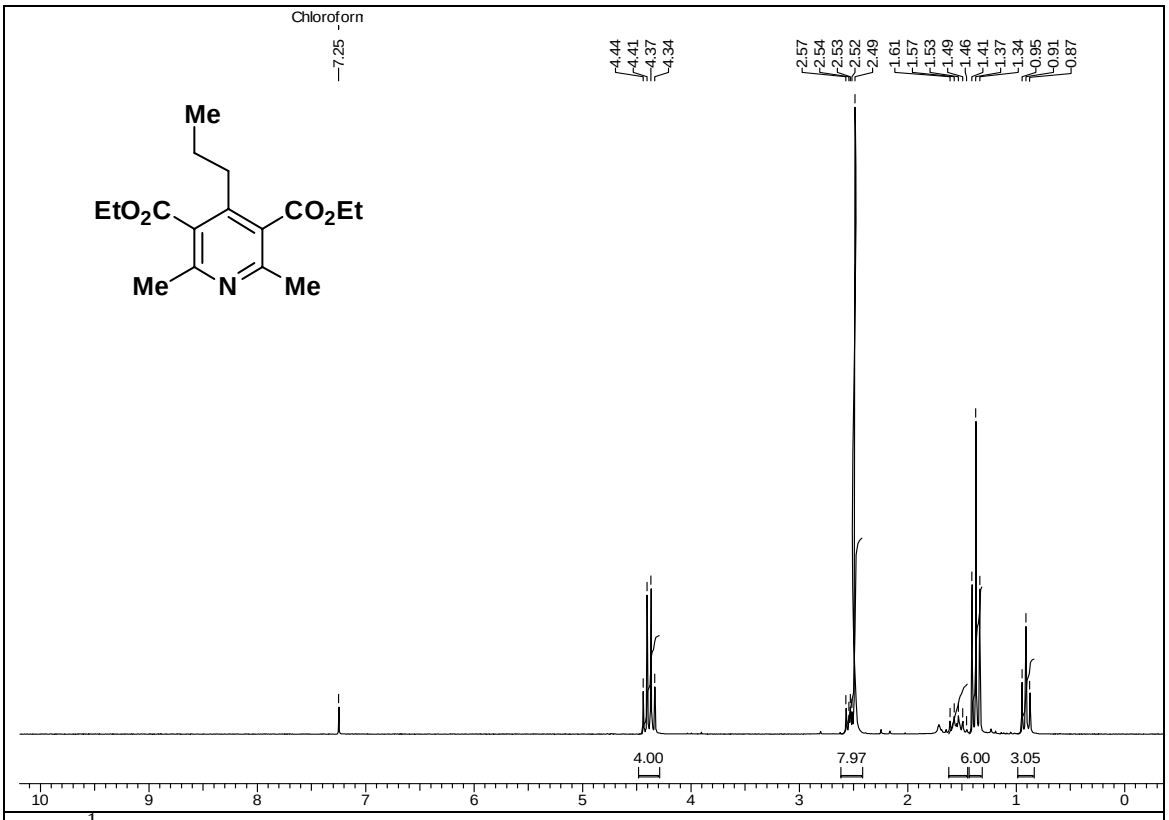
3.3.8 Analytical Data



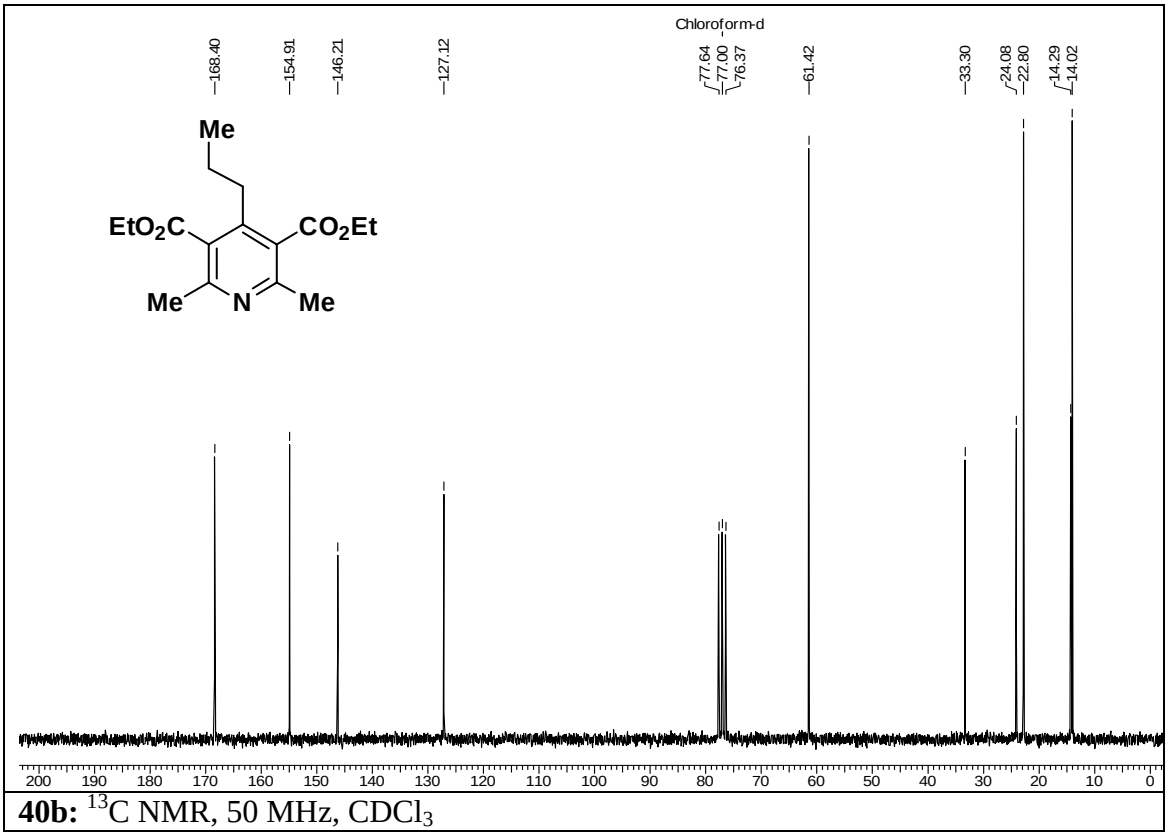
40a: ^{1}H NMR, 200 MHz, $CDCl_3$



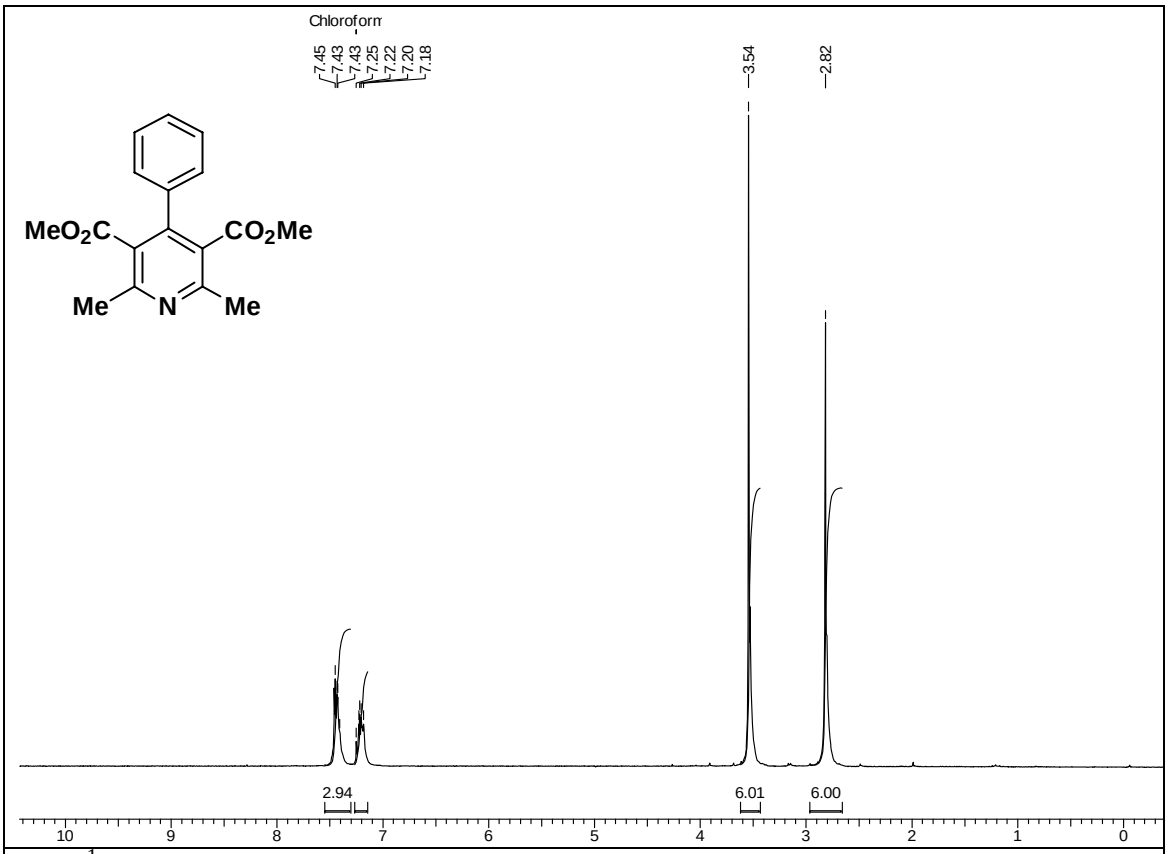
40a: ^{13}C NMR, 50 MHz, $CDCl_3$



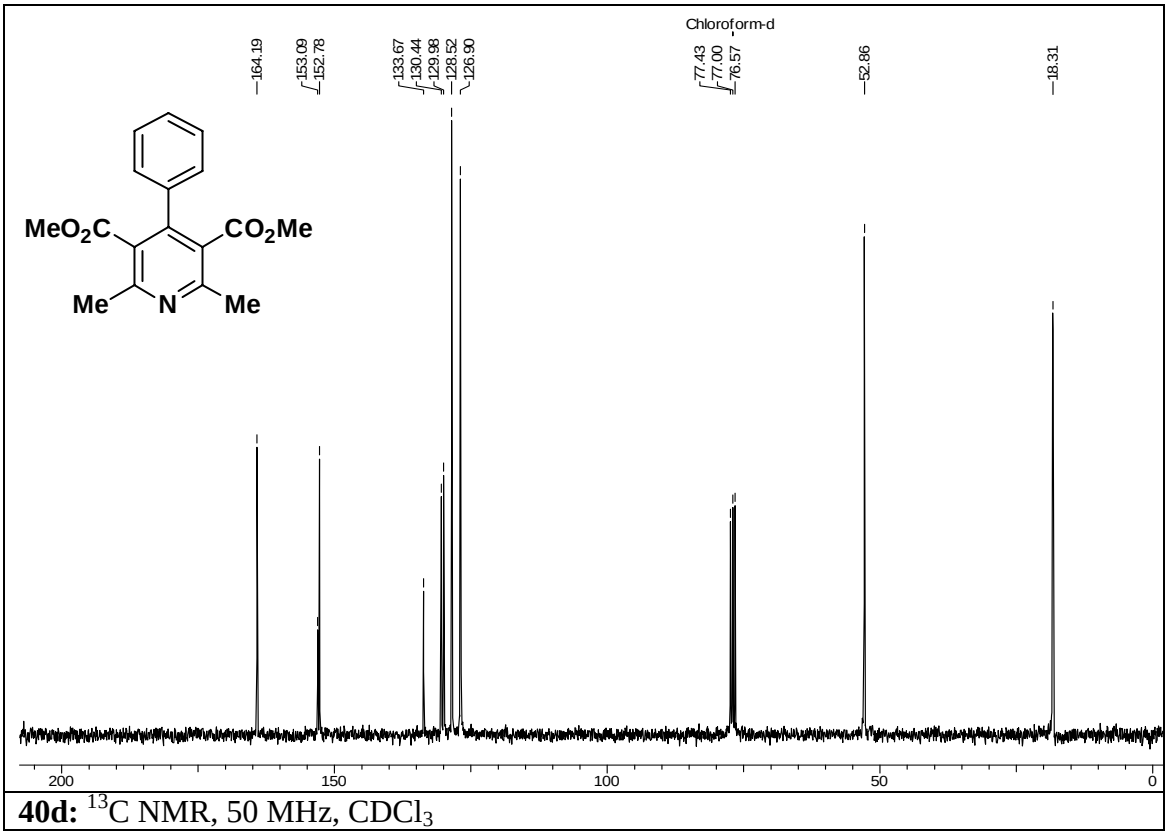
40b: ^{1}H NMR, 200 MHz, $CDCl_3$



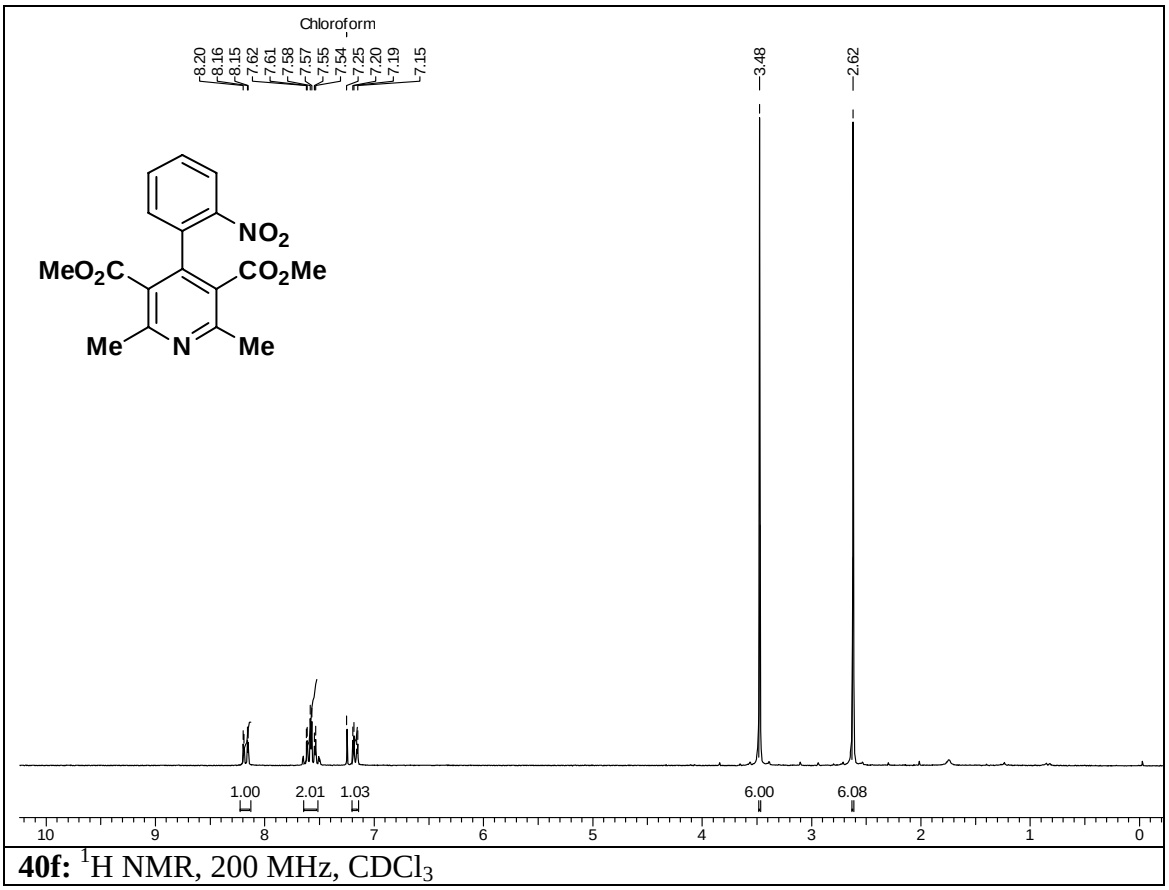
40b: ^{13}C NMR, 50 MHz, $CDCl_3$



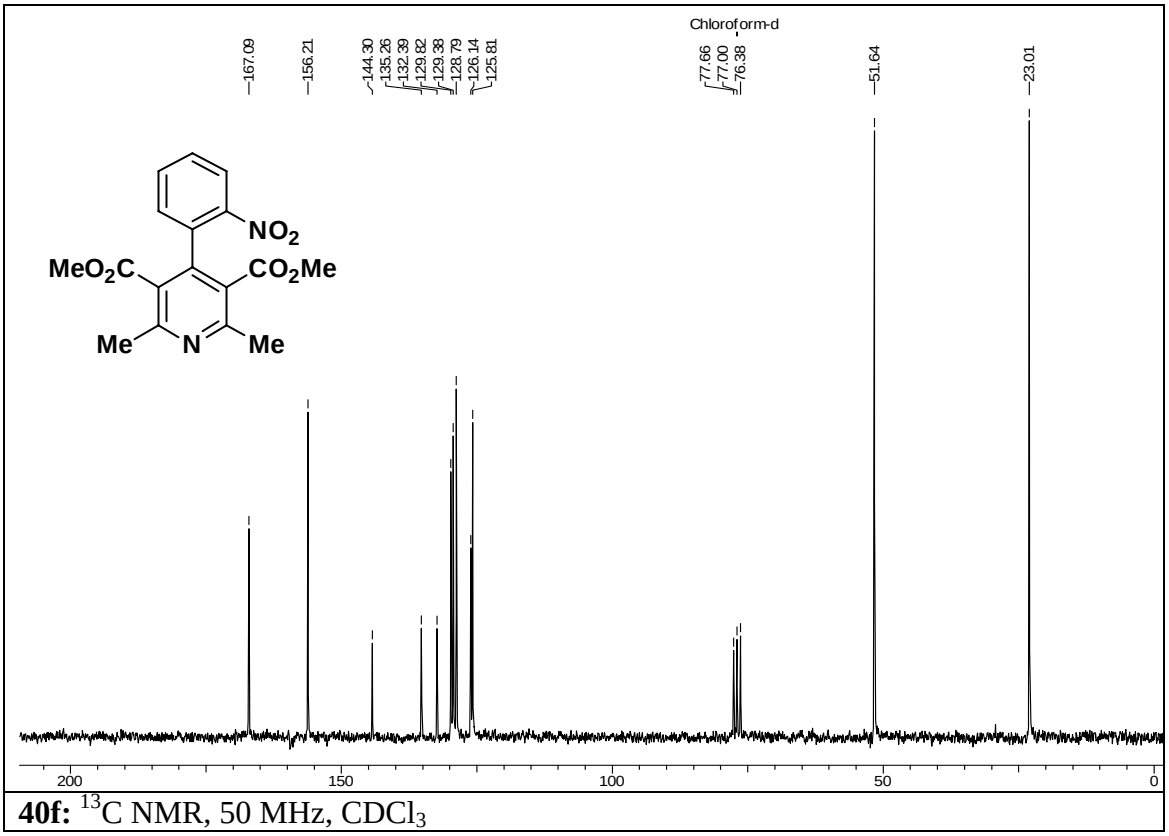
40d: ^{1}H NMR, 200 MHz, $CDCl_3$



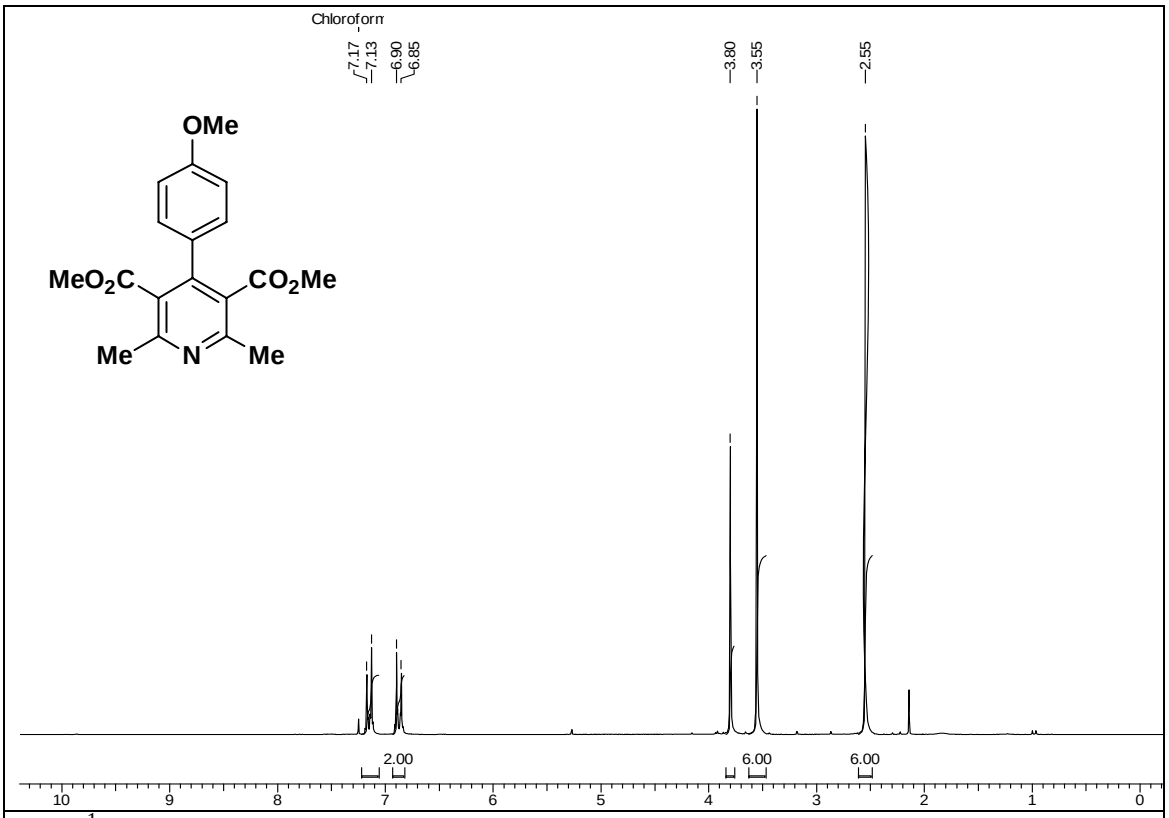
40d: ^{13}C NMR, 50 MHz, $CDCl_3$



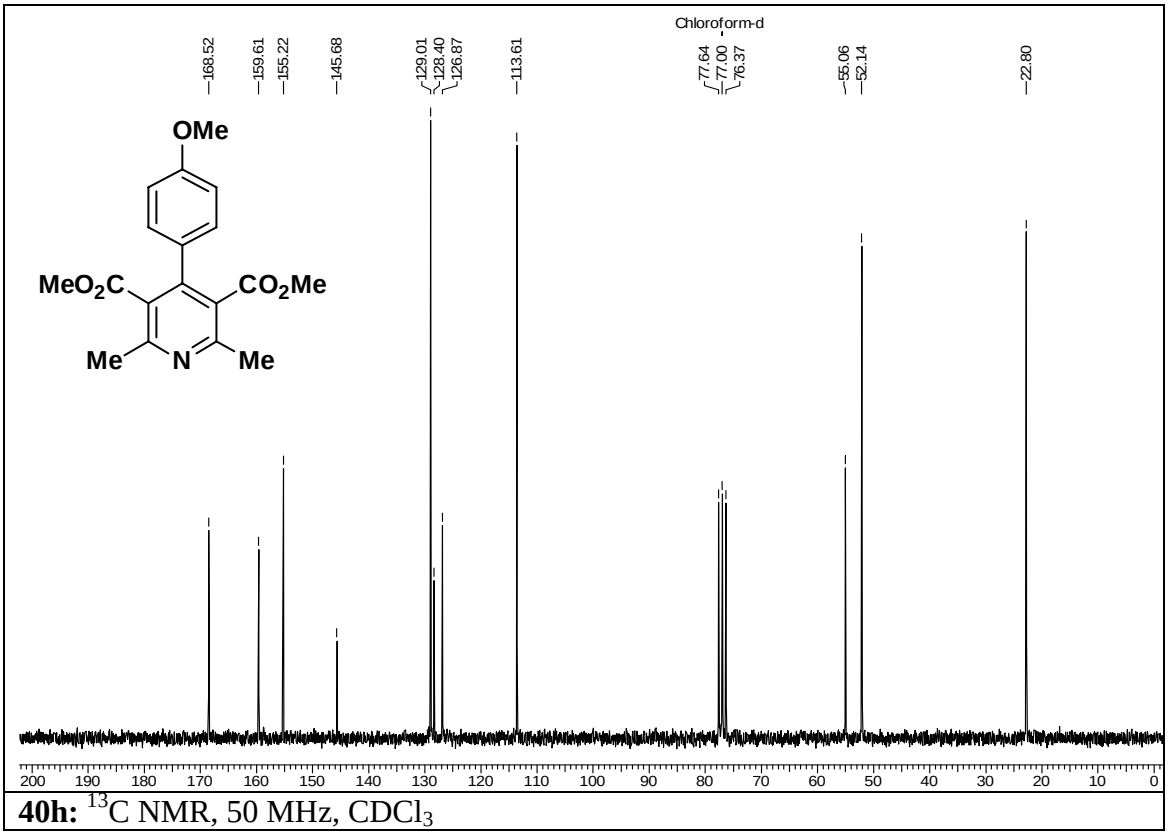
40f: ^{1}H NMR, 200 MHz, $CDCl_3$



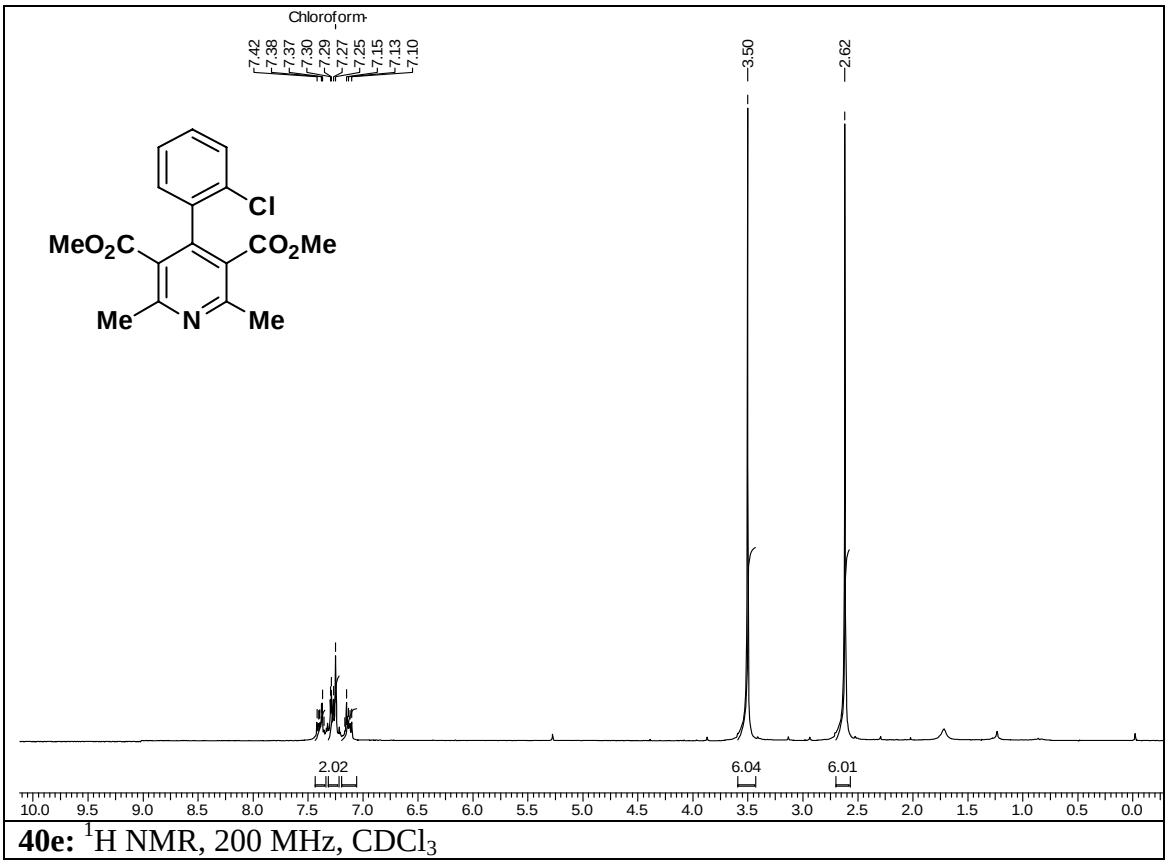
40f: ^{13}C NMR, 50 MHz, $CDCl_3$



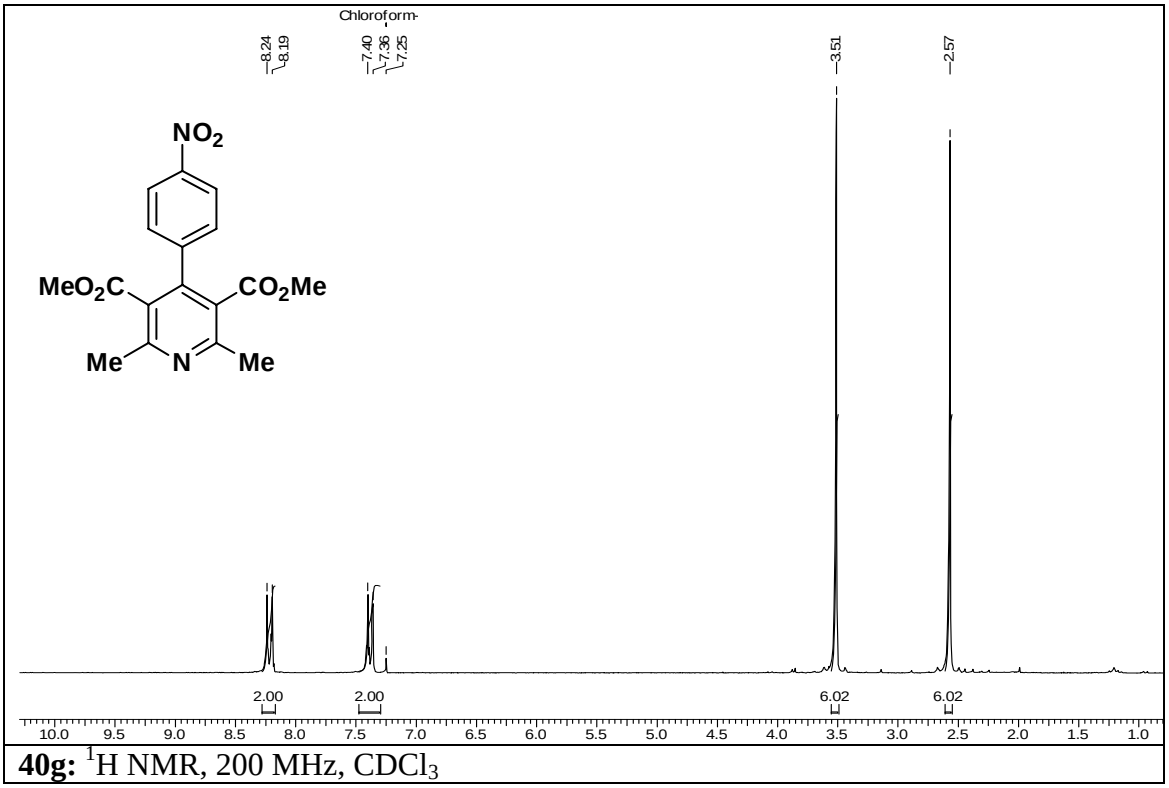
40h: ^{1}H NMR, 200 MHz, $CDCl_3$



40h: ^{13}C NMR, 50 MHz, $CDCl_3$



40e: ^{1}H NMR, 200 MHz, $CDCl_3$



40g: ^{1}H NMR, 200 MHz, $CDCl_3$

3.3.9 References

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2. (a) Bocker, R. H.; Guengerich, F. P.; *J. Med. Chem*. **1986**, *29*, 1596. (b) Meijer, H. P.; Pandit, U. K.; *Tetrahedron* **1985**, *41*, 467. (c) Zhu, X. Q.; Liu, Y. C.; Cheng, J-P. *J. Org*. *Chem*. **1999**, *64*, 8980.
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