ENANTIOSELECTIVE SYNTHESIS OF BIOACTIVE MOLECULES USING ASYMMETRIC DIHYDROXYLATION, REDUCTION, BROMINATION AND OXIDATIONS INVOLVING *C-H* AND *C-N* BONDS

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By

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Dedicated to
My
Parents
&Teachers

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CERTIFICATE

Certified that the work incorporated in the thesis entitled "**Enantioselective Synthesis of Bioactive Molecules using Asymmetric Dihydroxylation, Reduction, Bromination and Oxidations involving C-H and C-N Bonds**" was carried out by the candidate under my supervision. Such material as had been obtained from other sources has been duly acknowledged in the thesis.

(Dr. A. Sudalai)

Research Supervisor

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Milind

ABBREVATIONS

AD	Asymmetric Dihydroxylation
AIBN	2,2'-Azobisisobutyronitrile
Ac	Acetyl
Ar	Aryl
bp	Boiling Point
Bz	Benzoyl
Bn	Benzyl
DHPA	Dihydroxypropyl adenine
BOC	N-*tert*-Butoxycarbonyl
DHQ	Dihydoquinine
DHQD	Dihydroquinidine
DMF	Dimethyl formamide
DMSO	Dimethyl sulphoxide
ee	Enantiomeric excess
Et	Ethyl
EtOAc	Ethyl acetate
EtOH	Ethyl alcohol
g	Grams
h	Hours
IR	Infra red
M^+	Molecular ion
Me	Methyl
mg	Milligram
min	Minutes
ml	Milliliter
mp	Melting point
MS	Mass spectrum
NMR	Nuclear Magnetic Resonance
NBS	N-Bromosuccinimide
Pet. ether	Petroleum ether
Ph	Phenyl
PTSA	p-Toluene sulfonic acid
Py	Pyridine
RT	Room Temperature
TEA	Triethyl amine
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TBHP	*Tert*. Butyl hydrogen peroxide

GENERAL REMARKS

1. All solvents were distilled and dried before use.
2. Petroleum ether refers to the fraction collected in the boiling range 60-80^{o}C.
3. Organic layers after every extraction were dried over anhydrous sodium sulfate.
4. Column Chromatography was perfo rmed over silica gel (60-120 mesh).
5. TLC analyses were performed over glass plates coated with silica gel (5-25 μ) containing UV active G-254 additive.
6. IR spectra were recorded on a Perkin-Elmer model 683 B or 1605 FT-IR and absorptions were expressed in cm^{-1}.
7. ^{1}H and ^{13}C-NMR spectra were recorded on Brucker FT AC-200 and MSL-300 MHz instruments using TMS as an internal standard. The following abbreviations were used. s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet, and dd = doublet of doublet.
8. Mass spectra (MS) were recorded on an automated finnigan MAT 1020C mass spectrometer using ionization energy of 70eV.
9. Optical rotations were carried out on JASCO-181 digital polarimeter at 25^{o}C using sodium D light.
10. All melting points and boiling points are uncorrected and the temperatures are in centigrade scale.
11. Elemental analyses were done on Carlo ERBA EA 110B instrument.
12. The compounds, scheme and reference numbers given in each chapter refers to that particular chapter only.
13. The ligand used in asymmetric dihydroxylation reaction are $(DHQD)_2$-PHAL, $(DHQ)_2$-PHAL, DHQD-CLB, DHQ-CLB were purchased from Aldrich.

ABSTRACT

The thesis entitled **"Enantioselective Synthesis of Bioactive Molecules using Asymmetric Dihydroxylation, Reduction, Bromination and Oxidations involving C-H and C-N Bonds"** is divided into four chapters.

The title of the thesis clearly highlights two aspects of the synthetic organic chemistry: (i) the achievement of efficient stereospecific synthesis of bioactive molecules (ii) development of transition metal-based catalytic methods for useful organic transformations. **Chapter 1** describes the enantioselective synthesis of (R)-Lipoic acid, an anti-HIV and anti-tumor agent and (R)-1-butyryl glycerol, a novel angiogenesis factor, using OsO_4-catalyzed asymmetric dihydroxylation. **Chapter 2** also deals with the application of OsO_4-catalyzed asymmetric dihydroxylation as a key reaction for the enantioselective synthesis of (S)-Xibenolol, a β-adrenergic blocker for the treatment of hypertension and (R)-Fepradinol, an anti-inflammatory drug. **Chapter 3** presents the asymmetric synthesis of (R)-Baclofen, a $GABA_B$ receptor agonist using Ru(II)-(S)-BINAP-catalyzed asymmetric hydrogenation and acyclic nucleotides, (S)-2,3-dihydroxypropyl-(9)-adenine *via* asymmetric dihydroxylation approaches. **Chapter 4** comprises the development of catalytic methods for asymmetric dibromination of olefins, peroxidation of alkyl arenes and oxidation of nitroaldols, thus producing chiral dibromides, unsymmetrical peroxides and α-keto acids respectively.

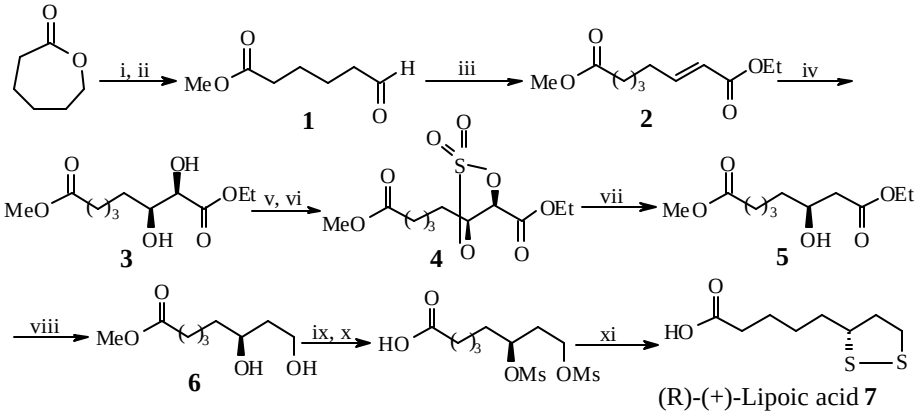
CHAPTER-I

OsO_4-catalyzed asymmetric dihydroxylation of olefins (AD) is the most practical and potential reaction to yield diols with high degree of stereoselectivity and optical purity.[1] It is insensitive to oxygen, easy to handle and performed in water at room temperature in the presence of derivatives of dihydroquinidine and dihydroquinine ligands. This chapter is divided into two sections and each section represents the application of asymmetric dihydroxylation methodology for the synthesis of bioactive molecules.

SECTION-I

Asymmetric Synthesis of (R)–Lipoic acid, an Anti-HIV and Anti-tumor Agent, *via* OsO_4-Catalyzed Asymmetric Dihydroxylation Approach[2]

(R)-Lipoic acid (6, 8-dithiooctanoic acid, **7**) is the naturally occurring cyclic disulfide compound and found to display an extremely high level of biological activity. Its catalytic oxidative decarboxylation of pyruvate to acetate, plays an important role as a protein bound transacylating cofactor of several multienzymatic dehydrogenases complexes.[3] Their salts have cytoprotective activity and are analgesic and anti-inflammatory drugs as well as agents for the treatment of retroviral infections.[4] This section presents the enantioselective synthesis of (R)-Lipoic acid (**7**) *via* asymmetric dihydroxylation approach (**Scheme 1**). Precursor, octenedioic ester (**2**) was synthesized in 2 steps from easily available ∈-caprolactone. It was subjected to OsO_4-catalyzed asymmetric dihydroxylation in the presence of $(DHQD)_2$-PHAL as a chiral ligand to afford chiral diol **3** in 92% yield and 96%ee. The diol **3** was converted to cyclic sulfate **4** under the standard reaction conditions in 81% overall yield.[5] Reductive ring opening of **4** by $NaBH_4$ gave the intermediate **5** in 76% yield. Further, the selective reduction of the β-hydroxyester **5** was achieved using $NaBH_4$ in the presence of Et_3N in combination with solvents (MeOH and DMF) to afford diol **6** in 65% yield. Subsequently, diol **6** was mesylated and transformed to (R)-(+)-Lipoic acid **7** by following the literature procedures.

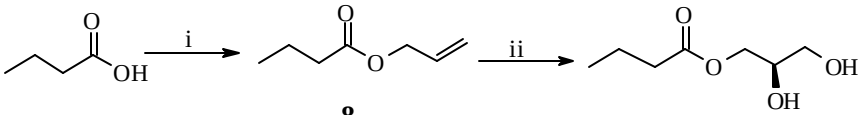


Scheme 1: (i) MeOH, conc. H_2SO_4, 60°C, 30 min.; 94% (ii) Swern oxidation / PCC, DCM, 0°C, 1h, 68% (iii) $(EtO)_2POCH_2COOEt$, NaH, THF, -78°C, 1.5h; 70%; (iv) cat. OsO_4, $(DHQD)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, *t*BuOH:H_2O, RT, 18h; 92%, $[\alpha]^{25}_D$ = +9.39° (c = 1.02, EtOH); (v) $SOCl_2$, Et_3N, DCM, 0°C 45 min.; 94%; (vi) cat. $RuCl_3$, $NaIO_4$, CH_3CN : H_2O, 0°C 30 min., 86%, $[\alpha]^{25}_D$ = +54.25 (c = 1.2 EtOH); (vii) $NaBH_4$, DMAC, 20% H_2SO_4, 2h; 76%, $[\alpha]^{25}_D$ = -13.59° (c = 1.2, EtOH); (viii) $NaBH_4$, Et_3N, MeOH: DMF (2:1), AcOH, 5 h; 65%, $[\alpha]^{25}_D$ = - 3.4° (c = 0.14, $CHCl_3$); (ix) $MeSO_2Cl$, TEA, DCM, 0°C, 2h; 90%, -19.0° (c = 1.0, $CHCl_3$); (x) 0.1 M KOH, RT, 20h, 55%; (xi) KOH, H_2O, $Na_2S.9H_2O$, S_8, DMF, HCl, 45%, $[\alpha]^{25}_D$ = + 96.4° (c = 1.86, C_6H_6).

SECTION-II

Asymmetric Synthesis of (R)-(+)-Monobutyrin, a Novel Angiogenesis Factor *via* OsO_4-Catalyzed Asymmetric Dihydroxylation

(R)-Monobutyrin (1-butyrylglycerol, **9**) is a naturally occurring lipid that stimulates angiogenesis. It is secreted by differentiating adipocites. It also stimulates one or more of the following endothelial cell function *in vitro*: protease production, motility, and proliferation.[6] The (R)-isomer is always bioactive. This section describes single step asymmetric synthesis of Monobutyrin *via* asymmetric dihydroxylation of allylbutyrate as shown in the **Scheme 2**. The allylbutyrate **8** was prepared from the esterification of butyric acid with allyl alcohol. Then it was subjected to OsO_4-catalyzed asymmetric dihydroxylation in presence $(DHQD)_2$-PHAL as chiral ligand using $K_3Fe(CN)_6$ or NMO as a co-oxidant to give in optically active (R)-Monobutyrin **9** in 96% yield and 50% ee.



8 (R)-Monobutyrin **9**

Scheme 2: (i) $SOCl_2$, $CH_2=CHCH_2OH$; 82%; (ii) OsO_4, $(DHQD)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3 or NMO, *t*BuOH:H_2O 20h., 96%, $[\alpha]^{25}_D = +0.67^o$ (c = 1.2, C_6H_6)

CHAPTER 2

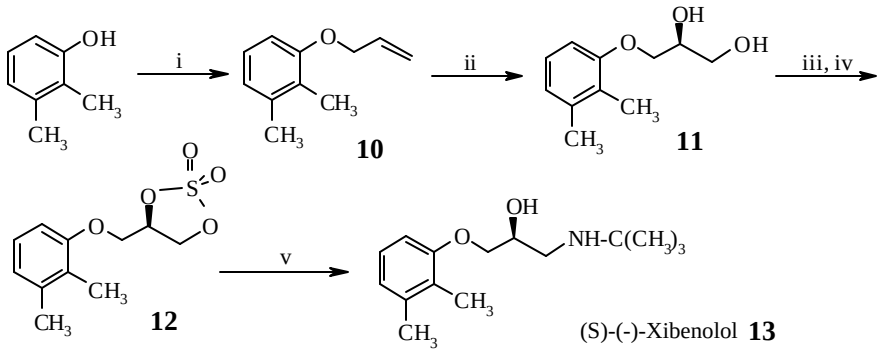
This chapter deals with the formation of chiral cyclic sulfates of 1,2-diols and their application to asymmetric synthesis of (S)-Xibenolol, an anti-inflammatory agent and (R)-Fepradinol, a β-adrenergic blocking agent. Cyclic sulfates[5] have properties similar to epoxides but are more reactive than epoxides. However, in contrast to epoxides, reactions of cyclic sulfates with variety of nucleophiles are regiospecific leading to the formation of a single regioisomer. This chapter is divided into two sections.

SECTION-I

Chiral Cyclic Sulfate Mediated Asymmetric Synthesis of (S)-Xibenolol : A Versatile b-Adrenergic Blocker

β-Adrenergic blocking agents (β-blockers) are cardiovascular drugs which exhibit three fundamental functions such as lowering the blood pressure (anti-hypertensive), return of the heart to rhythmic beating (anti-arrhythmics) and the general improvement of the heart muscle tone (cardiotonics). Xibenolol ((S)-[1-(dimethylethyl)amino]-3-(2,3-dimethylphenoxy)-2-

propanol, **13**) is a new β-adrenergic blocking agent clinically tested in its racemic form. It exhibits much more potent β-blocking activity than Propranolol.[7] Generally, it is accepted that most of the therapeutic actions of β-blocking agents, including anti-hypertensive and cardiovascular actions, are mediated mainly by the (S) and (-) isomer only.[8] In the view of this aspect we undertook the asymmetric synthesis of (S)-Xibenolol as shown in the **Scheme 3**. Our approach for synthesis of (S)-Xebenolol involves O-allylation of 2,3-dimethylphenol using allyl bromide to give allyl ether **10** in 97% yield, which was subjected to AD in presence $(DHQD)_2$-PHAL to afford chiral diol **11** in 94% yield. The diol **11** was activated by transforming it into cyclic sulfate **12** in two steps in 81% overall yield, under the standard reaction conditions.[5] Regiospecific opening of cyclic sulfate **12** with *tert*-butyl amine afforded (S)-(-)-Xibenolol (**13**) in 90% yield and 67% ee.



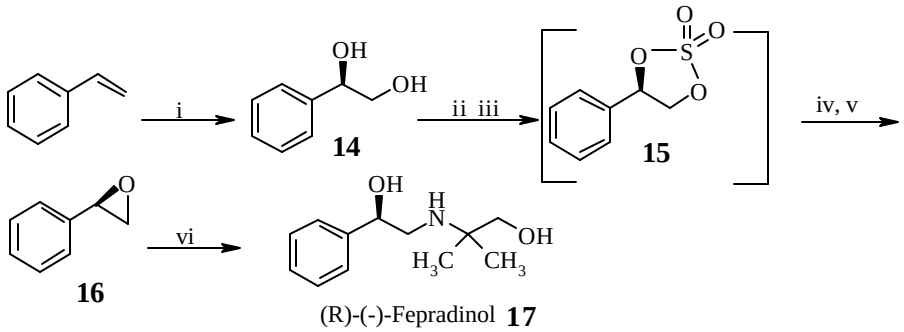
Scheme 3: (i) K_2CO_3, CH_2=$CHCH_2Br$, CH_3COCH_3, 56°C, 12h; 97%; (ii) cat. OsO_4, $(DHQD)_2$-PHAL, K_3FeCN_6, K_2CO_3, *t*BuOH:H_2O, RT, 12h., 94%; $[\alpha]^{25}_D$ = +4.25° (c = 1.0, $CHCl_3$); (iii) $SOCl_2$, Et_3N, DCM, 0°C, 40 min.; 94%, $[\alpha]^{25}_D$ = +24.25° (c = 16, $CHCl_3$); (iv) cat. $RuCl_3$, $NaIO_4$, CH_3CN:H_2O, 0°C, 30 min., 86%, $[\alpha]^{25}_D$ = -8.8° (c = 1.0, $CHCl_3$); (v) *t*Bu-NH_2, reflux, 1h, 20% H_2SO_4, Et_2O, 20 h, 90%, $[\alpha]^{25}_D$ = -17.58° (c = 1.0, $CHCl_3$).

SECTION-II

Asymmetric Synthesis of Novel Non-steroidal Anti-inflammatory Agent, (R)-Fepradinol

(R)-Fepradinol (1-phenyl-2-(α,α'-dimethylethanolamino)ethanol, **17**) is a non-steroidal antiinflammetry drug. It possesses a potent inhibitory activity on the acute inflammation in rodents and that its anti-inflammatory activity does not seem to be related to an inhibitory effect on prostaglandin biosynthesis.[9] Fepradinol also possesses structural similarities to that of other β-adrenergic blockers[10] which account for the cardiovascular drugs. Our stratergy for asymmetric synthesis of (R)-Fepradinol involves styrene as precursor as shown in **Scheme 4.** It was subjected to AD in the presence of $(DHQD)_2$-PHAL ligand to give chiral styrene diol **14** in 92% yield and 80%ee. The diol **14** was activated, by converting to cyclic sulfate **15** in two

steps. However, cyclic sulfate **15** was found to be less stable and hence it was directly transformed to its epoxide **16** in two steps in 40% overall yield. The regiospecific opening of epoxide **16** with 2-amino-2-methylpropanol was achieved to give (R)-(-)-Fepradinol (**17**) in 55% yield.



Scheme 4: (i) cat. OsO_4, DHQD-CLB, $K_3Fe(CN)_6$, K_2CO_3, *t*BuOH:H_2O, RT, 12h, 92%, $[\alpha]^{25}_D$ = -32.3° (c = 1.04, EtOH); (ii) $SOCl_2$, Et_3N, DCM, 0°C, 40 min, 78%; (iii) cat. $RuCl_3$, $NaIO_4$, CH_3CN:H_2O, 0°C, 30 min; (iv) anhyd. LiBr, THF, 60°C, 45 min. 20% H_2SO_4, Et_2O, 4h; 58%; (v) K_2CO_3, MeOH, -10C 2h, 90%, $[\alpha]^{25}_D$ = -17.4° (c = 0.14, $CHCl_3$); (vi) HO-CH_2-C$(CH_3)_2$-NH_2, 90°C, 3h, 55%, $[\alpha]^{25}_D$ = -19.25° (c = 0.5, EtOH);

CHAPTER 3

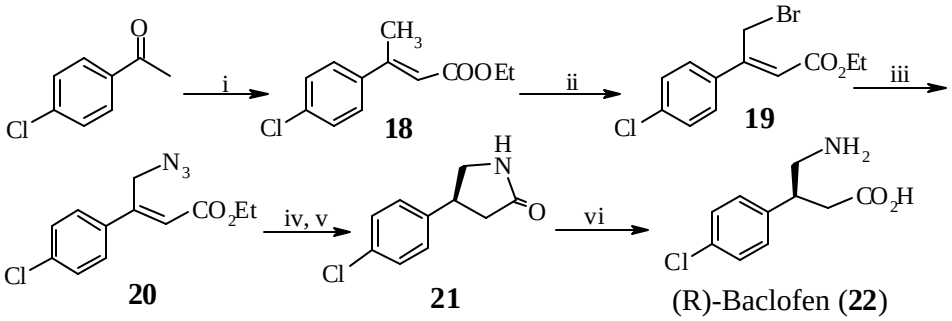
This chapter deals with the asymmetric synthesis of (R)-Baclofen (22), a $GABA_B$ receptor agonist and acyclic nucleotide (24), anti-cholestermic agents, using Ru(II)-(S)-BINAP-catalyzed asymmetric hydrogenation and OsO_4-catalyzed asymmetric dihydroxylation respectively.

SECTION-I

Synthesis of (R)-(-)-Baclofen, a Novel $GABA_B$ Receptor Agonist, *via* Ru(II)-BINAP Catalyzed Asymmetric Hydrogenation

γ-Aminobutryric acids (GABA) are important neurotransmitters and used in the treatment of epilepsy. Their deficiency is associated with diseases that exhibit neuromuscular dysfuntions such as epilepsy, Huntigton and Parkinsons' disease.[11] (R)-Baclofen [*g*-amino-*b*-(*p*-chlorophenyl)butyric acid, **22**] is one of the neurotransmitter,[12] its asymmetric synthesis is presented in **Scheme 5**. Reformatsky reaction of 4-chloroacetophenone with ethylbromoacetate followed by dehydration gave α,β-unsaturated ester **18** in 78% overall yield. It was then subjected to allylic bromination with NBS to give bromo-derivative **19** in 92% yield. Subsequent displacement of bromide moiety in **19** by azido group afforded the key

intermediate, azido-derivative **20** in 78%. It was subjected to Ru(II)-(S)-BINAP catalyzed asymmetric hydrogenation followed by Co-catalyzed reduction of azido-moiety with $NaBH_4$ led to the formation of chiral 3-arylpyrrolidine moiety **21**. Hydrolysis of pyrrolidine moiety in **21** with dil. HCl gave optically active (R)-baclofen (**22**).

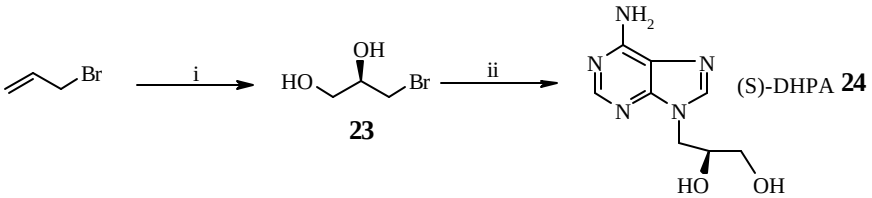


Scheme 5: i) Br-CH_2CO_2Et, Zn, benzene, reflux, *p*-TSA, toluene; 120°C, 78%; ii) NBS, AIBN, CCl_4, reflux, 10h; 92%; ii) NaN_3, EtOH:H_2O (80:20), 80°C, 8h, 78%; iv) Ru (II)-(S)-BINAP, H_2, MeOH, 200 *psi*, 50°C, 20 h; 68%; $\alpha]_D^{25}$ = - 18.66° (c = 0.3, MeOH); v) $CoCl_2$, $NaBH_4$, H_2O, 25°C, 30 min, 80%; vi) 20% HCl, 100°C, 3h, 76%, $[\alpha]_D^{25}$ = - 1.34° (c = 0.6, H_2O).

SECTION-II

Synthesis of Acyclic Nucleoside Analog, (S)-2,3-Dihydroxypropyl-(9)-adenine, a Novel Anti-Viral Agent

(S)-2,3-Dihydroxypropyl-(9)-adenine (DHPA, **25**) is a acyclic nucleoside possessing wide range of antiviral activities. The (S)-DHPA inhibits the replication *in vitro* of several DNA and RNA viruses including vaccinia, herpes simplex, measles, and vesicular stomatitis. (S)-enantiomer has broad-spectrum activity and low acute toxicity.[13] The asymmetric synthesis of (S)-DHPA from readily available allyl bromide is presented in **Schemes 6**. In order to synthesize **24**, the strategy adopted was : (i) asymmetric dihydroxylation of allyl bromide in the presence of $(DHQ)_2$-PHAL ligand to yield chiral bromodiol **23**; (ii) N-alkylation of chiral bromodiol **23** with adenine.



Scheme 6: (i) cat. OsO_4, $(DHQ)_2$-PHAL, $K_3Fe(CN)_6$, tBuOH:H_2O (1:1), K_2CO_3, 0-4°C, 20h, 58%, $[\alpha]^{25}_D$ = -5.1° (c = 2.0, $CHCl_3$); (ii) Na-Adenine, 90°C, DMF, 4h. 45%, $[\alpha]^{25}_D$ = -23.2° (c = 0.8, MeOH);

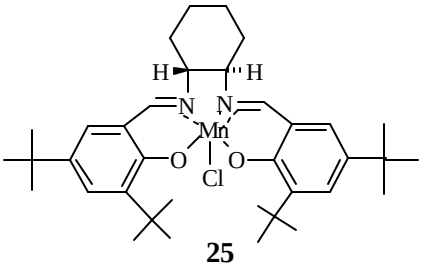
CHAPTER 4

This chapter highlights the importance of transition metals such as Mn, Ru, Cu, *etc*. and their complexes as catalysts for some useful organic transformations. It is divided into three sections.

SECTION-I:

Chiral Manganese(III)-Salen as Catalyst in Asymmetric Bromination of Olefins with N-Bromosuccinimide

Chiral Mn (III)-salen complex **25** (Jacobson's catalyst) is a well-known catalyst for asymmetric epoxidation, aziridination, hydroxylation, resolution of epoxide *etc*..[14] Herein, we discovered yet another new application of this novel catalyst in asymmetric dibromination of olefins (**26**) using NBS as bromine source[15] (**Scheme 7**). The resulting chiral dibromides (**27**) can be transformed to chiral *vic*-diazides, diamines, diols, dithiols and aziridines, which are otherwise difficult to prepare, by direct addition to olefins. Thus asymmetric dibromination of olefins can provide a potential route to prepare variety of chiral dibromo-compounds which are useful intermediates in organic synthesis.



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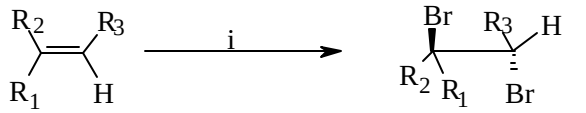


26 Yields 45-90% **27**

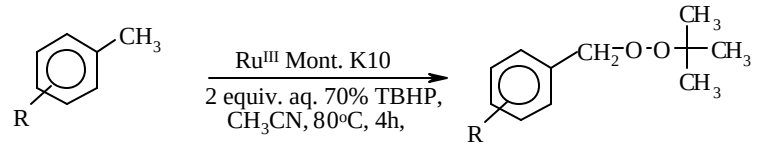
Scheme 7: i) cat. **25**, NBS, C_6H_6, 30°C, 4h

SECTION-II

Catalytic C-H Oxidation of Alkyl Arenes to Aryl *tert.* Butyl Peroxide with TBHP over Ru(III)-Exchanged Montmorillonite K10[16]

The selective oxidation at the benzylic C-H bond of alkyl arenes constitutes a potential route for the functionalisation of alkyl arenes into oxygenated derivatives such as peroxides, alcohols, aldehydes, ketones and acids. The reaction selectivity to produce specific oxygenated derivatives such as peroxides is of crucial importance. We developed a mild and efficient catalytic method for the benzylic oxidation of alkyl arenes (**28**) to the corresponding *tert.* butyl aryl peroxides (**29**) using Ru^{III}-exchanged Montmorillonite K10 as a reusable catalyst and aq. 70% *tert.* butyl hydroperoxide (TBHP) as oxidant. General method of peroxidation is given in

Scheme 8.



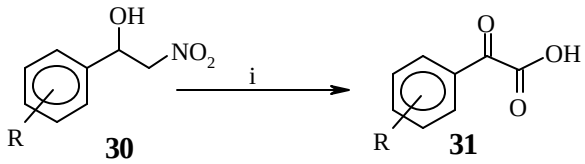
28 R = H, CH_3, Cl, etc **29**

Scheme 8 :

SECTION III

Cu-Catalyzed C-N Oxidation of Aryl Nitroaldols: A High Yield Synthesis of *a* -Aryl Keto Acids[17]

This section provides a new method of synthesis of α-aryl keto acid (**31**) from the corresponding aryl nitroaldols (**30**) in a single step using Cu-salts as catalysts. The starting materials (**30**) are easily prepared by Henry reaction. General method for synthesis of aryl α-keto acids is presented in the **Scheme 9**.



30 **31**

R = H,CH_3, OCH_3, Cl, etc. Yields 41-88%

Scheme 9: (i) cat. Cu-Satls, air, 30% aq. AcOH:MeOH (1:1), 90 °C, 4h.

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List of Publications

1. "Catalytic Selective Oxidation of Alkyl Arenes to Aryl *tert*-Butyl Peroxides with TBHP over Ru-Exchanged Montmorillonite K 10, **Milind D. Nikalje** and A. Sudalai,

Tetrahedron, **1999,** *55,* 5903-5908

2. "Synthesis of α-Aryl Keto Acids *via* Cu-Catalyzed Oxidative Conversion of Aryl Nitroaldols", **Milind D. Nikalje**, Sayyed Iliyas Ali, Gajanan K. Dewkar and A. Sudalai, *Tetrahedron Letters*, **2000,** *41* (6), 959**.**
3. "Asymmetric dihydroxylation and hydrogenation approaches to the enantioselective synthesis of (R)-(+)-lipoic acid", T. T. Upadhya, **M. D. Nikalje** and A. Sudalai, *Tetrahedron Lett.* **2001**, *42*, 4891-4893.
4. Review on "Recent Advances in Clay-Catalyzed Organic Transformations", **Milind D. Nikalje**, Prodeep Phukan and Arumugam Sudalai, *Organic Preparation and Procedures International*, **2000,** *32*, 1-40.
5. "Pyridinium Hydrobromide Perbromide : A Versatile Catalyst for Azidridination of Olefins using Chloramine-T", Sayyed Iliyas Ali, **Milind D. Nikalje**, and A. Sudalai, Organic Letters, **1999**, 5, 5893
6. "An Exceptionally Stable Ti-Superoxide Radical Ion: A Novel Heterogeneous Catalyst for the Direct Conversion of Aromatic Primary Amines to Nitrocompounds", Gajanan K. Dewkar, **Milind D. Nikalje**, Iliyas Sayyed Ali, Abhimany,u S. Paraskar, H. S. Jagtap and A. Sudalai , *Angw. Chem. Int. Ed. Eng.* **2001**, *40*, 405-409
7. Formamide Assisted One-Pot Conversion of Aromatic Aldehydes into the Corresponding Nitriles, **Milind D. Nikalje**, Sayyed Iliyas Ali, Gajanan K. Dewkar, Abhimanyu S. Paraskar, H. S. Jagtap and A. Sudalai, *J. Chem. Res. Syn.*, **2000**, 30.
8. "Aluminum (III) Chloride – catalyzed reaction of 1,1,1-trichoroethane with aromatic compounds : A facile synthesis of symmetrical 1,1-diphenylethylenes", B. Jayachandran, Prodeep Phukan, Milind D. Nikalje, T. Daniel and A. Sudalai, *Ind. J. Chem. B*, 2001**,** ***39B***, 954-957.

CHAPTER-1

SECTION-I

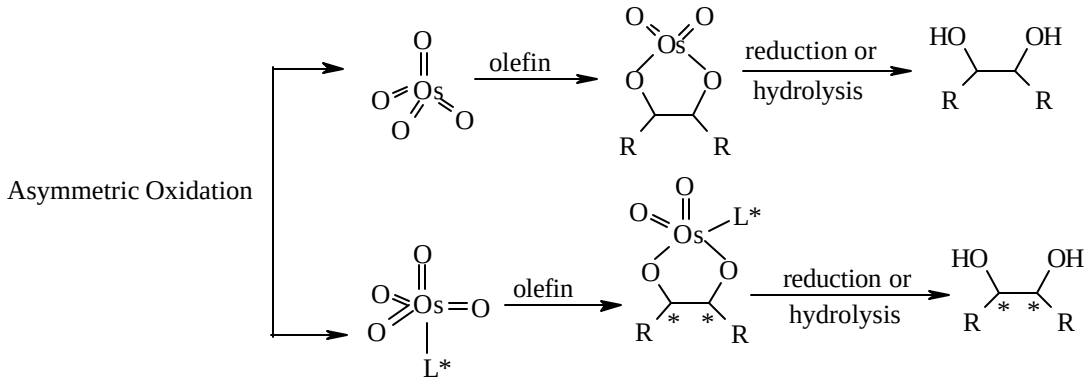
Asymmetric Synthesis of (R)-(+)-Lipoic acid, an anti-HIV and anti-tumor agent, *via* OsO_4-Catalyzed Asymmetric Dihydroxylation Approach

Since ADH has figured the prominent reactions for introducing chirality into the molecules in this as well as subsequent chapter, it is apt to give a brief account of it.

1.0.1 Asymmetric Dihydroxylation of Olefins

During the last decade a number of powerful asymmetric reactions have emerged as a result of the growing need to develop efficient and practical synthesis of enantiomerically pure and biologically active compounds. Biological systems, in most cases, recognize the member of a pair of enantiomers as different compounds. Thus one enantiomer may act as a very effective therapeutic drug whereas other is either highly toxic or totally inactive. There are several methods to obtain enantiomerically pure compounds which include classical optical resolution, chromatographic separation of enantiomer, enzymatic resolution and asymmetric synthesis.[1] In recent years much attention has been focused on the catalytic asymmetric synthesis. It often has significant economic advantages over stoichiometric asymmetric synthesis for industrial-scale production of enantiomerically pure compounds. All these asymmetric reactions crucially depend on ligand acceleration effect (LAE).[2] Among the reported asymmetric reactions, Sharpless's ligand accelerated catalysis is critical for success of a catalytic asymmetric dihydroxylation (AD). It has become the most general single method for the oxygenation of unactivated olefins.[3]

In 1936, Criegee *et al* have found that addition of pyridine to osmylation, accelerates the rate of reaction considerably and this property is shared by other tertiary amines as well.[4] Sharpless later showed that excellent enantioselectivities could be realized when chiral amines were added to OsO_4-mediated asymmetric oxidation of olefins. The ligands used by the Sharpless group were representatives of the cinchona alkaloid family, dihydroquinidine (DHQD) and dihydroquinine (DHQ).[5] The simplified mechanism of achiral and chiral dihydroxylation is given in the **Scheme 1**.

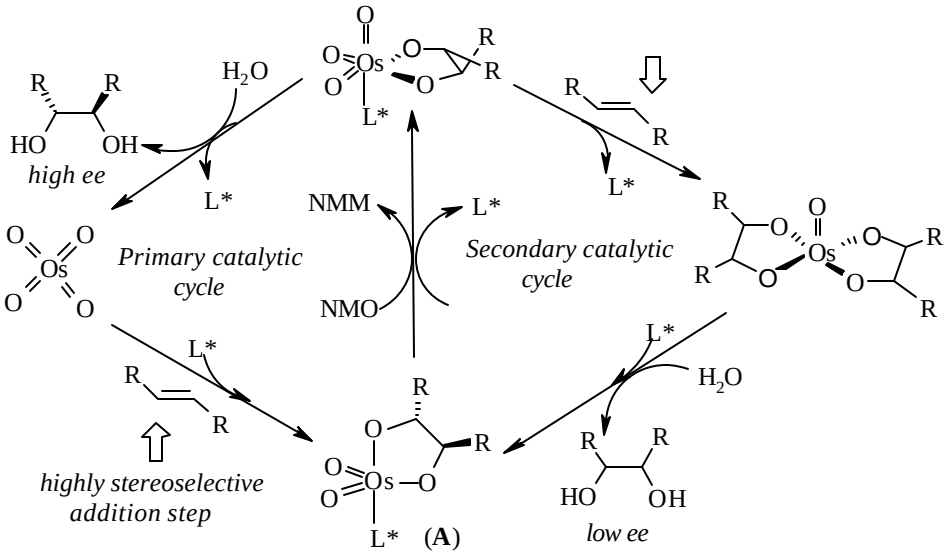


<u>Scheme 1</u> : Mechanism of OsO_4-Catalyzed Dihydroxylation of Olefin

In order to establish a catalytic method, several co-oxidants such as sodium or potassium chlorate,[6] hydrogen peroxide,[7] *tert*-butyl hydroperoxide[8] and N-methylmorpholine N-oxide[9] (NMO) were introduced to minimize the amount of toxic and costly osmium. Marko and Sharpless[10] have established the most practical and suitable catalytic method with NMO as co-oxidant. Although much better results were obtained with NMO the ee's of the diol was less than those produced by the stoichiometric reactions (primary catalytic cycle, **Scheme 2**). The origin of the discrepancy in the presence of catalytic osmium was due to involvement of second catalytic cycle (secondary catalytic cycle, **Scheme 2**), which exhibited low or no ee.

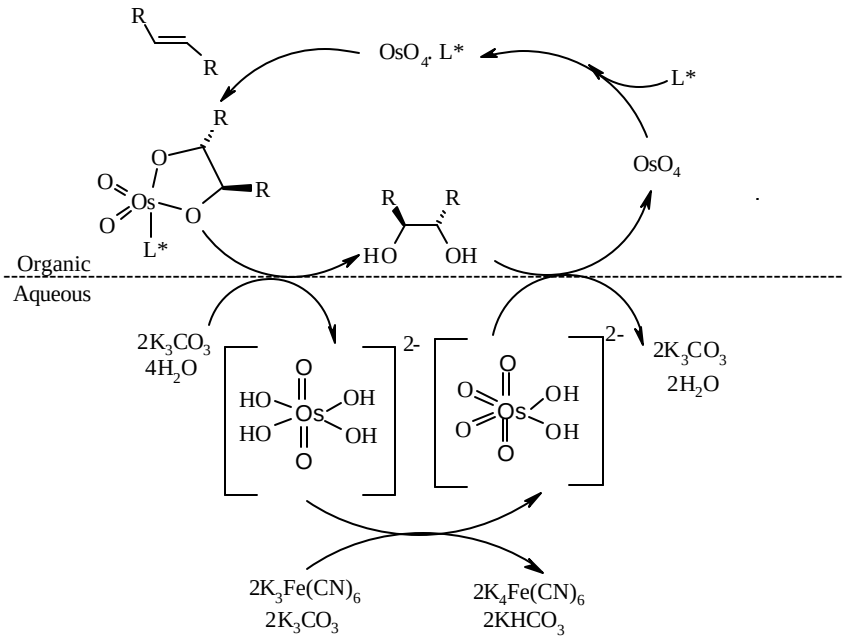
To improve the %ee of the chiral diol, the second catalytic cycle of AD was avoided by employing the $K_3Fe(CN)_6$ as reoxidant and performing the reaction under biphasic

conditions (**Scheme 3**).[1,11] Thus it helps in protecting the organic osmate (VI) monoglycolate ester (species **A**, **Scheme 2**) from inopportune oxidation prior to hydrolysis and thereby releasing the diol and ligand to the organic phase and osmium (VI) to the aqueous phase.



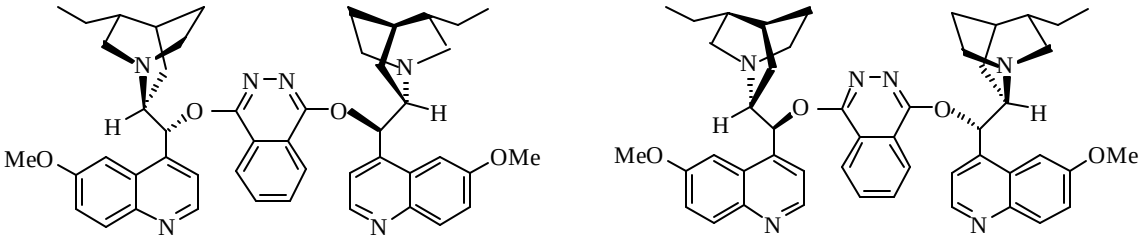
Scheme 2 : Catalytic Cycle for AD using NMO as co-oxidant.

Subsequently, osmium (VI) gets reoxidized and recycled into the catalytic cycle. However, further improvement in the AD was realized by addition of the methyl sulfonamide ($MeSO_2NH_2$) to the reaction mixture. It also helps to accelerate the hydrolysis of the species **A**, thereby increasing the turnover rate of the AD reaction, thus facilitating the dihydroxylation smoothly.[1]



Scheme 3 : Catalytic Cycle for AD using $K_3Fe(CN)_6$ as co-oxidant.

In developing the AD reaction, Sharpless group have screened various chiral ligands and concluded that the derivatives of cinchona alkaloids are found to give excellent results. Among all the 250 derivatives of cinchona alkaloid ligands, the bis-DHQ or DHQD ethers of phthalazine-1,4-diol have proven to be the best for obtaining high enantioselectivities of the chiral diols, thus improving the scope of the AD reaction.[12] Ultimately, it is possible to achieve high ee of the chiral diols derived from a broad range of olefins using ligand **1** or **2** (**Fig. 1**).



$(DHQ)_2$-PHAL (1) **$(DHQD)_2$-PHAL (2)**

Fig. 1 : Ligands for asymmetric dihydroxylation reaction

The recent ligand structure-activity studies have demonstrated that the enzyme-like binding pocket of the dimeric cinchona alkaloid is responsible for high enantioselectivity of the chiral diols.[12,13] Sharpless *et al* have shown that the facial selectivity for both ligands **1** & **2** is different based on their ability to induce the ee into the diols. This observation has led to the development of mnemonic model (**Fig. 2**) in which olefin with the constraints will be attacked either from the top face (i. e. β-face) in the presence of dihydroquinidine (DHQD) derivatives, or from the bottom face (i.e. α-face) in the presence of dihydroquinine (DHQ) derived ligand.[3]

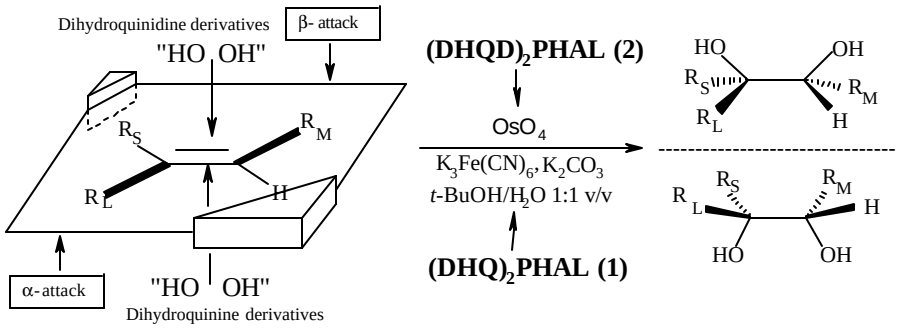


Fig. 2 : Enantioselectivity mnemonic scheme

1.0.2 Lipoic acid:

Lipoic acid (**3**) widely occurs in plants and animals. It was first isolated, characterized and named by Reed.[14] It is surprising to note that nearly ten tones of liver residue was processed to get approximately 30 mg of crystalline *a*-lipoic acid for characterization and structural determination.[15] Golding *et al* have synthesized the unnatural enantiomer (**3a**) of lipoic acid from readily available (S)-malic acid[16] and thereby established the confirmation of (R)-configuration of the naturally occurring lipoic acid.

α-Lipoic acid **3** (R)-(+)-α-Lipoic acid **3a** (S)-(-)-α-Lipoic acid **3b**

Prior to isolation and characterization of lipoic acid (**3**), it was identified as a growth factor for many bacteria and protozoa under the name of "acetate-replacing factor" or "protogen-A".[17] Its multienzyme-complexes act as efficient catalysts in the oxidative decarboxylation of pyruvate to acetate.[18] Its role in phosphorylation as well as detoxyfying effects have been reported.[19] The α-keto acid dehydrogenases is the only enzyme known to contain protein bound lipoic acid. There are two types of α-keto acid dehydrogenases existing in mammalian mitochondria and micro-organisms; one specific for pyruvate and other for the α-ketoglutarate oxidative decarboxylation. Pyruvate is an intermediate in the biosynthesis of fats, carbohydrates and certain amino acids. The pyruvate is a major source of energy, which gained through its complete oxidation *via* tricarboxylic acid cycle. The α-ketoglutarate is a source for protein, porphyrins and nucleic acids.

1.0.3 Biological Significance of Lipoic acid:

The most thoroughly investigated enzyme containing lipoic acid is the pyruvate oxidase of *E. Coli*, a multienzyme complex with a molecular weight of about 4.8 x 10^6. It containes pyruvate decarboxylase, lipoic acid reductase-transacetylase and lipoamide oxidoreductase co-enzymes. The co-enzyme action of lipoic acid in oxidative decarboxylation of pyruvate is presented in the **Eq. 1**. The overall oxidative decarboxylation of pyruvate is accomplished by thiamine pyrophosphate (TPP), Mg^{2+}, nicotinamide adenine dinucleotide (NAD), lipoic acid, co-enzyme (Co-A) and flavin adenine dinucleotide (FAD).[20] The reaction initiates with the formation of "active acetaldehyde",[21] *i.e.* 2-(α-hydroxyethyl)thiamine pyrophosphate (HETPP) *via* a thiamine pyrophosphate (TPP) pyruvate. **Fig. 3** represents the reactions occurring during the oxidative decarboxylation of pyruvate in the presence of pyruvate multienzyme-complex.

$$CH_3\text{-}CO\text{-}CO_2H + NAD^+ + CoA\text{-}SH \xrightarrow[\text{Lipoic acid, FAD}]{\text{TPP, } Mg^{2+}} CH_3\text{-}CO\text{-}SCoA + NADH + H^+ + CO_2 \text{--} \textbf{Eq. 1}$$

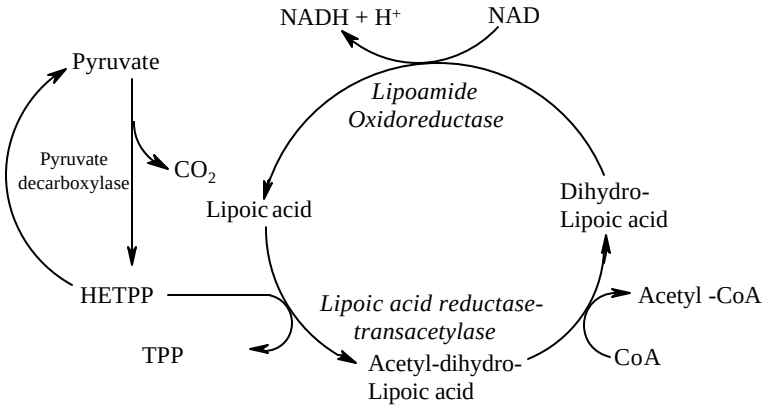


Fig. 3 : Catalytic Oxidative Decarboxylation of Pyruvate

1.0.4 The Pharmacology of Lipoic Acid:

As a result of high biological activity of the lipoic acid, its use in the treatment of various diseases have been investigated. (R) and (S)-*a*-lipoic acid and their salts have a cytoprotective activity and are analgesic and anti-inflammatory,[22] as well as agents for the treatment of retroviral infections, especially infections induced by human immunodeficiency virus. The analgesic activity was tested in mice and the anti-inflammatory activity in the *Carrageenan edema* in rats. The (R)-enantiomer of lipoic acid exhibits anti-HIV activity. The racemic form of *a*-lipoic acid is used for the treatment of liver diseases, poisoning[23] and to enhance the glucose metabolism in insulin-resistant humans and animals.[24] Lipoic acid is initially identified as potent growth promoting factor.[25] It also behaves as radioprotective agent and thereby protects the DNA and its components from the ionizing radiation–inducing damage.[26] Lipoic acid and their derivatives have functioned as hair tonic,[27] thus preventing the loss of hair during the chemotherapy in rats.[28] It is also helpful in reduction of the blood-sugar levels in diabetic rats.[29] The effects of lipoic acid on rats with hepatitis and induced

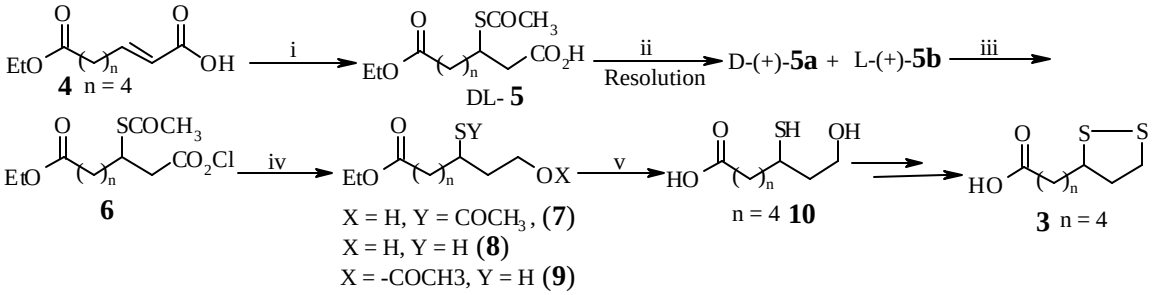
carcinomas have also been investigated with positive results.[30] The deficiency of lipoic acid normally does not occur in humans since it is formed by biosynthesis in vertebrates.[31]

1.0.5 Review of Literature:

A thorough literature search revealed that several reports are available on the synthesis of (R)–lipoic acid, which involves either chiral starting materials, or other methods such as enzymatic resolutions, enzymatic reductions, Sharpless asymmetric epoxidation *etc* for introduction of the chirality. Literature reports are presented as follows.

Walton's approach (1954)[32]

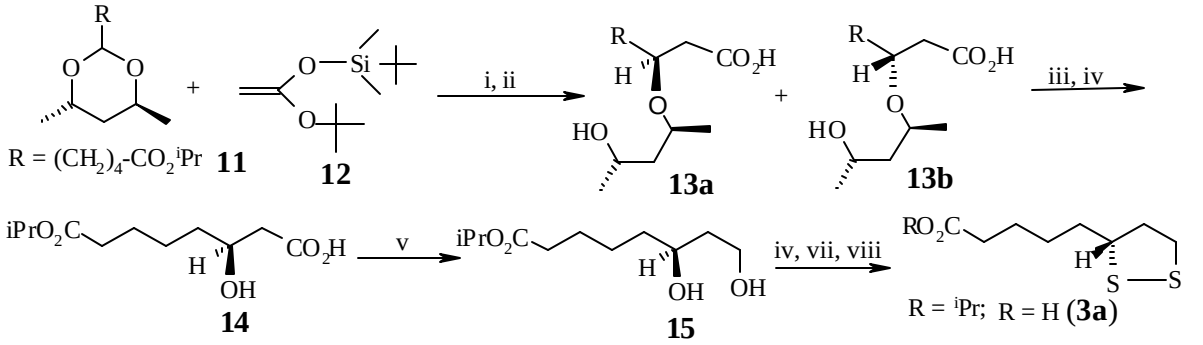
Walton's stratergy for the synthesis of (R)-(+)-lipoic acid involved addition of thioaceticacid to 7-carboethoxy-2-heptenoic acid (**4**) to afford DL-7-carboethoxy-3-acetylthioheptanoic (**5**). It was then resolved by the use of *l*-ephedrine to give D-(**5a**) and L-(**5a**) enantiomers (**Scheme 4**). Each enantiomer on sequence of reactions is transformed into (R)-(+)- and (S)-(-)-lipoic acid (**3a** and **3b**) respectively. During their transformation, the reduction of acid chloride **6** with $NaBH_4$ gave mixture of products (**7**, **8**, **9**), which on alkaline hydrolysis afforded 8-hydroxy-6-thiooctanoic acid (**10**). Finally, the hydroxyl functionality was replaced with sulfuhydryl and then oxidation was performed to give either racemic form of lipoic acid (**3**) or chiral version of it.



Scheme 4: i) CH_3COSH, refluxed; ii) *l*-ephedrine; iii) $SOCl_2$; iv) $NaBH_4$, v) NaOH, dil. HCl; vi) HBr, H_2NCSNH_2, vii) NaOH, viii) O_2, $FeCl_3$, I_2, KI

Elliott's approach (1985)[33]

Elliott's approach for the synthesis of (R)-lipoic acid (**3a**) involved $TiCl_4$ catalyzed aldol type coupling of chiral acetal (**11**) with 1-*t*-butoxy-1-*t*-butyldimethylsilyloxyethene (**12**) to give optically active *b*-alkoxycarboxylates (**13a** & **13b**) in 93% yield with 98:2 diastereoselectivity (**Scheme 5**). The oxidation of **13** followed by *b*-elimination afforded hydroxy acid **14**. It was then transformed into the key intermediate diol **15** by reduction with borane. Subsequently, diol **15** was mesylated, treated with disulfide followed by hydrolysis of the ester group furnished the synthesis of (R)-lipoic acid (**3a**).

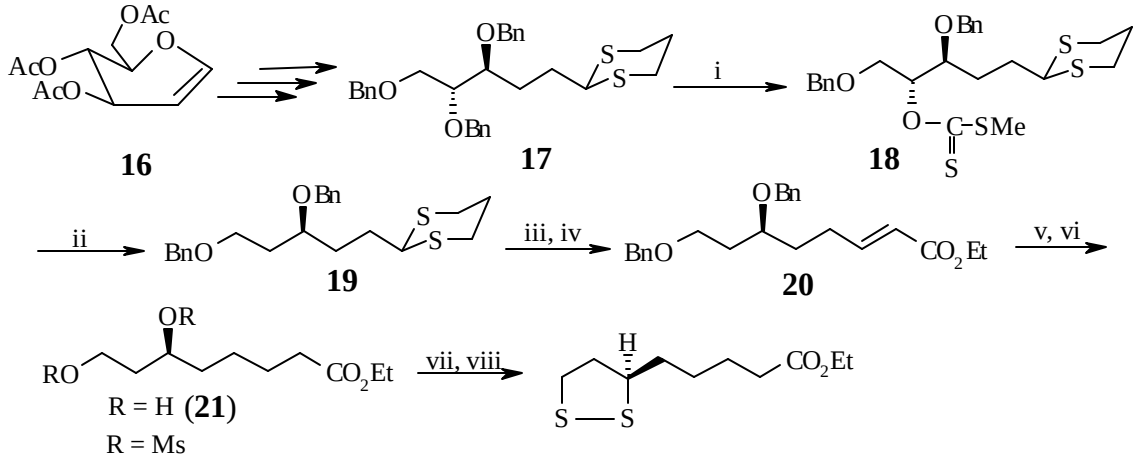


Scheme 5 : i) $TiCl_4$, CH_2Cl_2, -78°C; ii) CF_3CO_2H, H_2O, 22 °C; iii) Jones's oxidation; iv) piperidinium acetate, C_6H_6 , reflux; v) BH_3.THF, aq. (4 M) KOH; vi) $MeSO_2Cl$, Et_3N, 0°C; vii) Na_2S, S, DMF, 80°C; viii) K_2CO_3, MeOH, H_2O

Ravindranathan's approach (1986)[34]

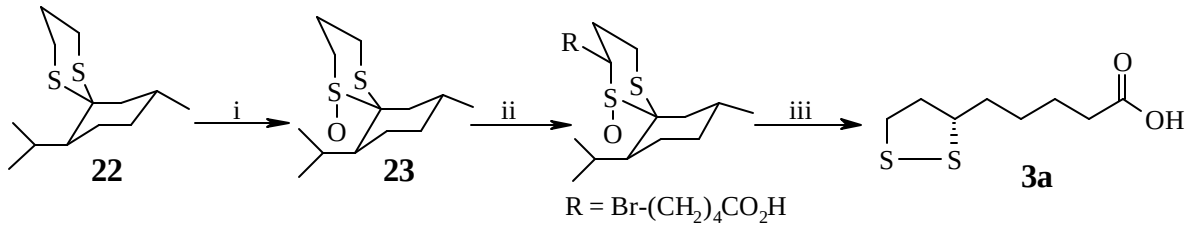
Ravindranathan *et al* have achieved the synthesis of (R)-lipoic acid (**3a**) from the naturally occurring D-glucose (**Scheme 6**). The 3, 4, 6-tri-O-acetyl-D-glucal (**16**) was derived from D-glucose and transformed to dithiane derivative **17** in 5 steps. It was then subjected to Barton-McCombie-deoxygenation with NaH, CS_2 and MeI to give the compound **19** through the formation of intermediate xanthate ester **18**. Subsequent hydrolysis of **19** with mercuric oxide in the presence of boron trifluoride-etherate followed by C_2-homologation using Wittig-Horner reaction afforded the *a*,*b*-unsaturated ester **20**. The Raney-Ni catalyzed hydrogenation

of **20** resulted in the reduction of double bond as well as debenzylation and thus key intermediate, diol **21**, was obtained without racemization. It was then transformed into (R)-lipoic acid by the literature procedures.



Scheme 6: i) NaH, CS_2, MeI, THF, 24h; ii) $(Bu)_3SnH$, AIBN, toluene, 18 h; iii) HgO, $BF_3.Et_2O$, aq. acetone, 20 h; iv) $(EtO)_2P(O)=CH-CO_2Et$, C_6H_6 reflux 10h; v) H_2, Raney-Ni, RT, 18h, vi) $MeSO_2Cl$, NEt_3, CH_2Cl_2, 0^oC, 4h; vii) Na_2S, S, DMF, 90^oC, 24h; viii) KOH, EtOH, RT

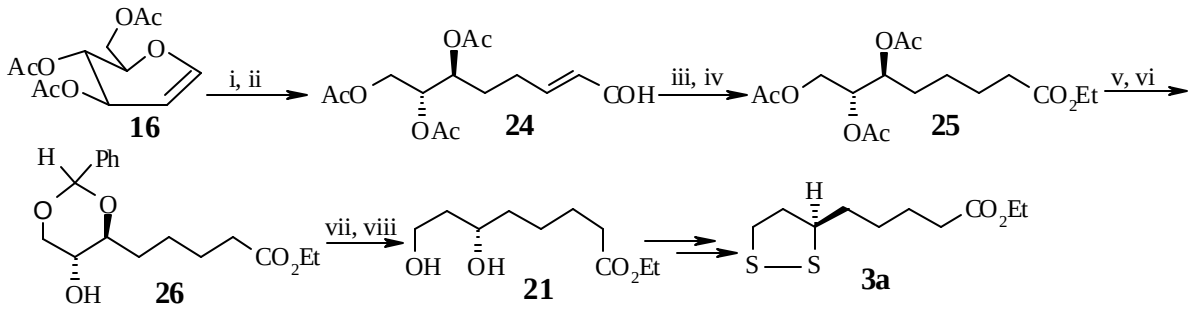
Another strategy of Ravidranathan *et al* [34] for the synthesis of racemic as well as optically active lipoic acid (**3a**) involved 1,3-dithiane derivative of achiral ketone or chiral ketones (**Scheme7**). In case of optically active 1,3-dithiane derivative of *l*-menthone (**22**) stereoselective sulfoxidation gave only the monosulfoxide **23**, which was regioselectively alkylated with 5-bromovaleric acid and cyclized to afford (S)-lipoic acid (**3b**). However, the use of d-menthone led to the formation of (R)-lipoic acid (**3a**).



Scheme 7 : i) $NaIO_4$, MeOH, -5^oC; ii) LDA, TMED, $Br-(CH_2)_4-CO_2H$, THF; iii) aq. HCl : Benzene.

Rao's approach (1987)[35]

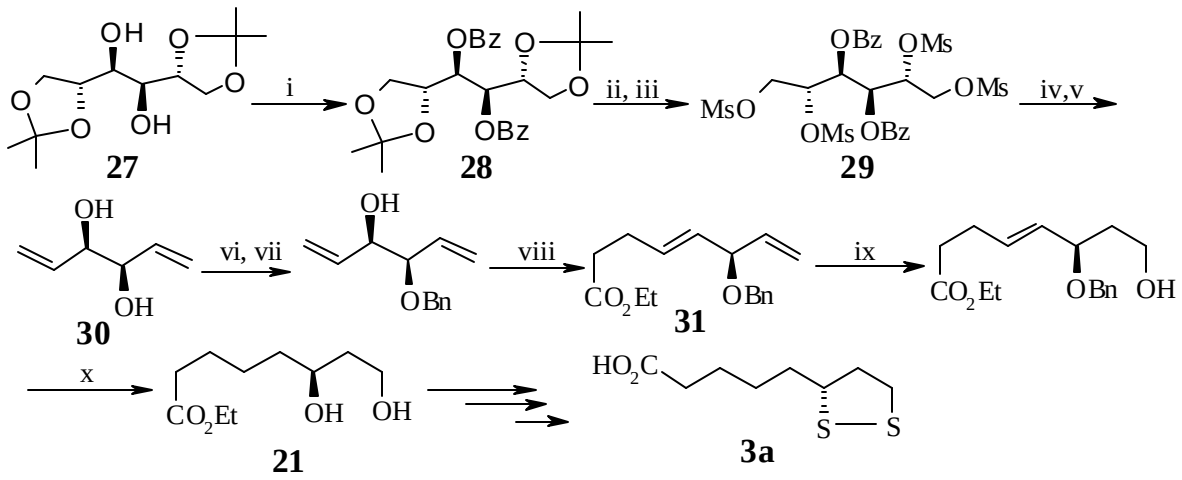
This approach also consists of tri-O-acetyl-D-glucal (**16**) as a chiral starting material. The mercurous-ion catalyzed ring opening of **16** followed by acetylation generated the intermediate aldehyde **24**. Subsequently, it was transformed to 6,7,8-triacetoxy-ethyl octanoate (**25**) by Wittig-Horner olefination and Raney-Ni catalyzed hydrogenation reactions. Further deacetylation and regioselective protection of the diol using α,α-dimethoxytoluene yielded the benzylidene derivative **26**. Under the modified Barton-McCombie reaction, compound **26** was transformed to the key intermediate diol **21**. Further, (R)-lipoic acid was obtained by following the literature procedures (**Scheme 8**).



Scheme 8 : i) $HgSO_4$, H^+, dioxane; ii) Ac_2O, pyridine; iii) $Ph_3P{=}CHCO_2Et$; iv) H_2, Raney-Ni; v) NaOMe, EtOH; vi) $PhCH(OMe)_2$, H^+; vii) Im-C(S)-Im, THF; viii) nBu_3SnH; H_2, Pd/C.

Rao *et al*[36] have used D-mannitol as a chiral starting material in yet another approach for the synthesis of (R)-lipoic acid (**Scheme 9**). 1,2,5,6-Di-O-isopropylidiene-D-mannitol (**27**) was synthesized from the D-mannitol and was subsequently transformed into dibenzoylderivative **28** with benzoyl chloride-pyridine mixture. Hydrolysis of **28** with 50% aq. AcOH followed by mesylation afforded the tetramesylated compound **29**. This upon treatment with Zn dust, NaI and followed by NaOMe was transformed to (3R, 4R)-1,2-divinyl-glycol **30**. Further, its monobenzylation with benzyl bromide through the formation of intermediate dibutyltinglycolate followed by Claisen-ester rearrangement afforded the compound **31**.

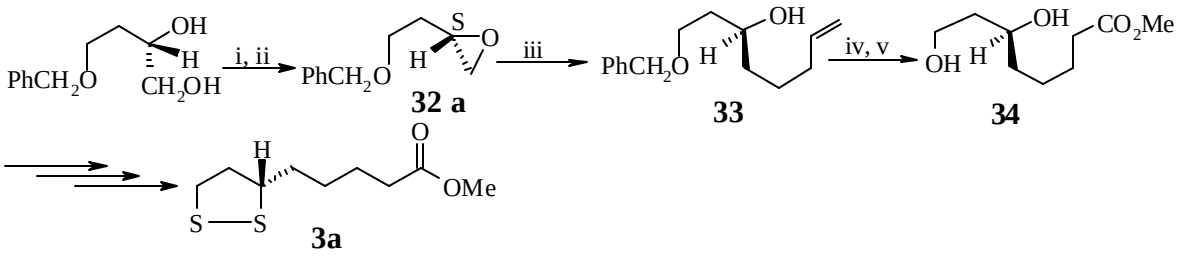
Subsequent selective hydroboration of **31** followed by hydrogenation afforded diol **21**, which was transformed, to (R)-lipoic acid with the reported procedure.



Scheme 9: i) Benzoyl chloride, pyridine, RT, 3 h; ii) aq. AcOH, reflux, 3 h; iii) $MeSO_2Cl$, pyridine, iv) NaI, Zn, dust, DMF, reflux, 2 h; v) NaOMe, MeOH; vi) dibutyltin oxide, toluene, reflux; vii) benzyl bromide, DMF, 100°C, viii) triethylorthoacetate, propionic acid, 145°C, ix) 9-BBN; NaOH, H_2O_2; x) Pd/C, RT, H_2

Golding' approach (1988)[37]

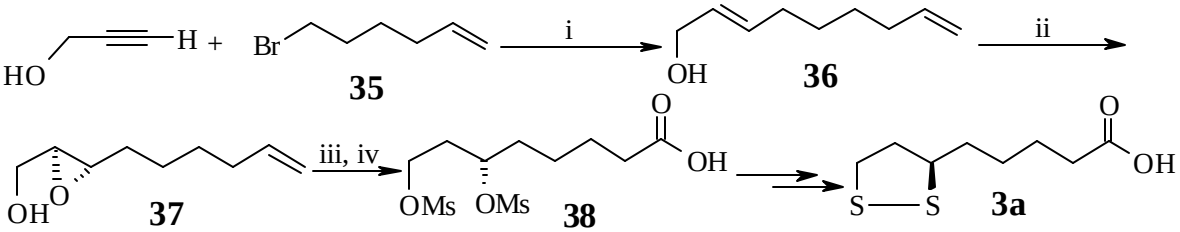
In this approach 2-phenylmethoxyethyl oxirane **32** derived from (S)-malic acid was used as a chiral starting material for the synthesis of both (S) and (R) isomer of the lipoic acid (**Scheme 10**). (S)-1-(Phenylmethoxy)-oct-7-en-3-ol (**33**) was obtained from the Li_2CuCl_4 catalyzed opening of the (S)-epoxide (**32a**) with but-3-ethylmagnesium bromide, which was then transformed to the key intermediate, (S)-methyl 6,8-dihydroxyoctanoate (**34**) through a series of reactions. Finally, ester **34** was transformed to (S)-Lipoic acid (**3b**) by literature procedure. However, for obtaining the (R)-lipoic acid (**33a**), (R)-epoxide was required, which could be obtained by inversion of the (S)-malic acid.



Scheme 10 : i) PhCHO, H^+; ii) NBS, ClF_2CCCl_2F and NaOH, $HO(CH_2)_2OH$, iii) $CH_2=CHCH_2CH_2MgBr$, Li_2CuCl_4, THF, iv) Benzyl bromide, NaH, $HB[Pr^iC(Me)H^-]_2$, THF, aq. H_2O_2, PCC, DMF, v) MeOH-HCl; Pd-C, H_2

Page's approach (1990)[38]

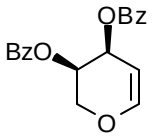
Page *et al* have employed Sharpless asymmetric epoxidation as a key reaction to introduce the chirality for the synthesis of (R)-lipoic acid (**3a**). This synthesis was achieved in six steps, starting from 6-bromohex-1-ene **35** (**Scheme 11**). Alkylation of lithio-dianion of prop-1-yn-3-ol with **35**, followed by *in situ* reduction of the triple bond yielded 100% *trans*-allylic alcohol **36**. The catalytic enantioselective epoxidation of **36** in the presence of L-(+)-diisopropyl tartarate [(+)-DIPT] produced (2S, 3S)-epoxyalcohol **37**. Subsequently, it was transformed to key intermediate (R)-6, 8-dimesyloctanoic acid (**38**) by regioselective ring opening of **37** with Red-Al followed by RuO_4 catalyzed oxidative C=C cleavage. Finally, (R)-lipoic acid was obtained from **38** by following the literature procedures. However, the use of (-)-DIPT as chiral auxiliary for epoxidation led to the formation of (S)-isomer of lipoic acid.



Scheme 11 : i) Li, NH_3; ii) L-(+)-DIPT, $Ti(O^iPr)_4$, *t*-butyl hydroperoxide, Cl-$(CH_2)_2$-Cl, -20°C, 3 days; iii) Red-Al, THF, 0°C; iv) $MeSO_2Cl$, Et_3N, DCM, -5°C; v) $RuCl_3.3H_2O$, $NaIO_4$, CCl_4.

Tolstikov's approach (1990)[39]

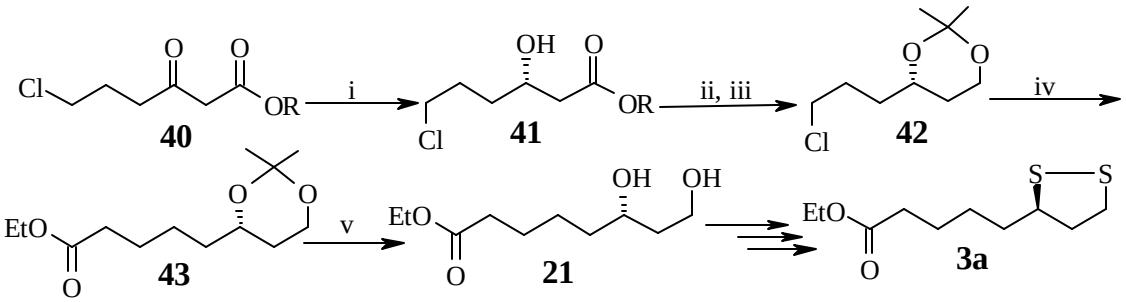
Tolstikov *et al* have been granted a patent for the synthesis of (R)-lipoic acid and its (S)-enantiomer from **39** or L-arabinal *via* methyl (6R, 7) or (6S, 7)-epoxyheptanoate.



39

Gopalan's approach (1990)[40]

Gopalan *et al* have made use of baker's yeast for enantioselective reduction of alkyl-6-chloro-3-oxohexanoate (**40**) and thereby (S)-6-chloro-3-hydroxyhexanoate (**41**) was obtained in 90% ee (**Scheme 12**). The reduction of ester moiety in **41** with $LiBH_4$ followed by acetonide protection of the corresponding diol gave the compound **42**. Subsequent alkylation with diethyl malonate followed by de-ethoxycarbonylation afforded ester **43**. The deprotection of the acetonide led to the formation of key intermediate **21**.



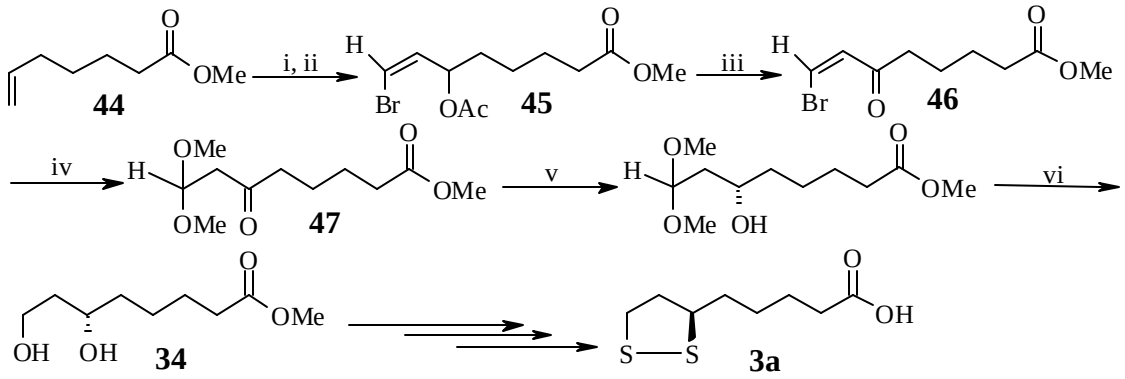
40 **41** **42** **43** **21**

Scheme 12 : i) Baker's yeast, ii) $LiBH_4$, THF, iii) $Me_2C(OMe)_2$, *p*-TsOH, DCM, iv) $CH_2(CO_2Et)_2$, NaH, DMF, 75 ^oC; NaCN, DMSO, 165 ^oC; v) H^+-EtOH

Bhalerao's approach (1990)[41]

In this approach baker's yeast was employed for enantioselective reduction of 8,8-dimethoxy-6-oxo-octonoate (**47**), thereby methyl (S)-6,8-dihydroxyoctanoate (**34**) was obtained. Compound **47** was obtained from methyl-6-heptenoate (**44**) in a sequence of

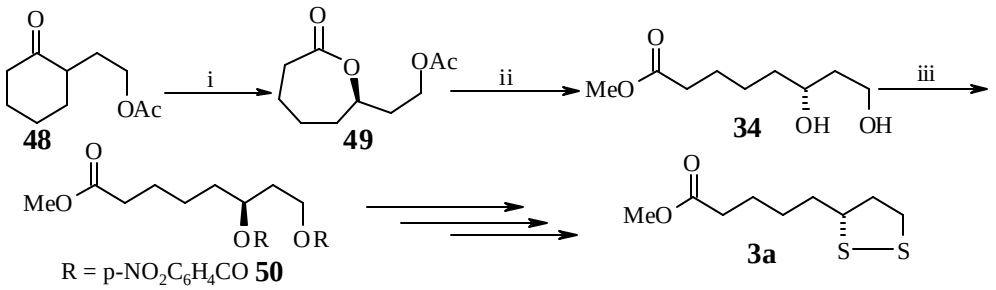
reactions. Initially, **44** was subjected to copper-catalyzed bromoform addition and then treated with KOAc to give intermediate methyl-6-acetoxy-8-bromo-oct-7-enoate (**45**). Subsequently, **45** was hydrolyzed and oxidized to give the ketovinyl bromide (**46**). Further treatment of the **46** with methanol followed by Triton-B gave immediate precursor **47**, which was transformed to (R)-lipoic acid *via* baker's yeast mediated reduction (**Scheme 13**).



Scheme 13 : i) Cu, $CHBr_3$; ii) KOAc, 18-crown-6, DMF; iii) K_2CO_3, MeOH then PCC; iv) Triton B, MeOH; v) baker's yeast, pH 4.5-5; vi) H_3PO_4, MeCOMe, $NaBH_4$.

Adger's approach (1995)[42]

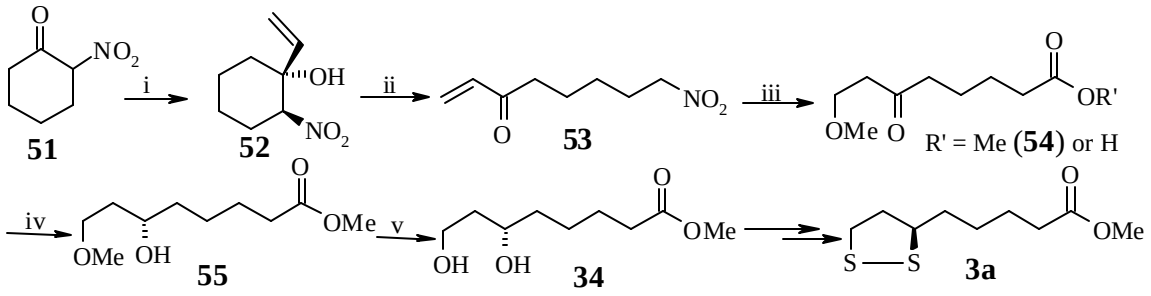
In this approach enantioselective bio Baeyer-Villiger oxidation was employed as a key reaction for introduction of chirality. Thus, ketone **48** was subjected to enantioselective oxidation with monooxygenase (MO_2) derived from *Pseudomonas putida* (NCIMB 10007) and transformed into the *e*-lactone **49**. It was then transesterified with methanol to give key intermediate **34** for the synthesis of (R)-lipoic acid. The (S)-enantiomer of the lipoic acid was obtained from the intermediate **34** by inversion of stereochemistry at C6 by Mitsunobu reaction through the formation of ester **50** (**Scheme 14**).



Scheme 14 : i) MO_2; ii) MeOH, NaOMe; iii) p-$NO_2C_6H_4CO_2H$, PPh_3, diethylazodicarboxylate, THF, iv) K_2CO_3, MeOH.

Barua's approach (1997)[43]

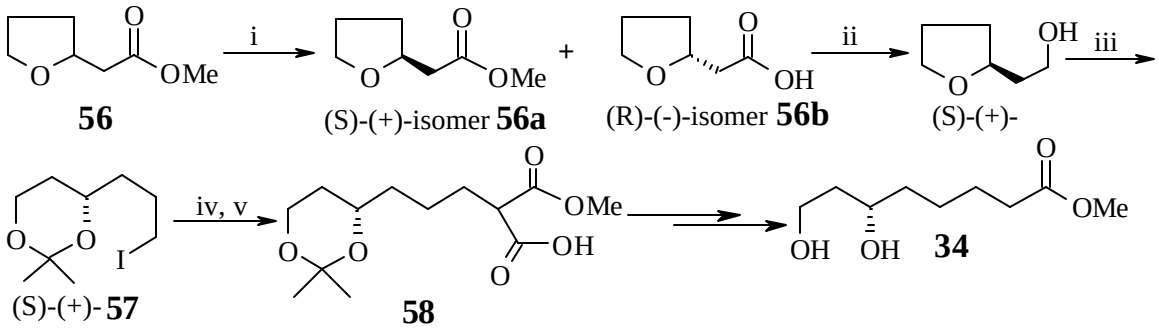
Barua *et al* have synthesized (S)-methyl 6,8-dihydroxyoctanoate (**34**) as key intermediate for (R)-lipoic acid *via* baker's yeast mediated enantioselective reduction of 6-oxoester **54** (**Scheme 15**). Thus 6-oxoester **54** was derived from 2-nitrocyclohexanone (**51**) by a sequence of reactions, wherein Grignard reaction of **51** with vinyl bromide afforded 2-nitro-1-vinylcyclohexanol (**52**). It was then subjected to copper catalyzed retro- Henry reactions and transformed to ω-nitro-α,β-unsaturated ketone **53**. Subsequently, ketone **53** was treated with sodium methoxide followed by sulphuric acid to give immediate precursor **54**. The baker's yeast derived from *Candida cylindracea* was employed for the enantioselective reduction of **54** to give chiral ester **55**, which was subsequently transformed to (R)-lipoic acid by the literature procedure.



Scheme 15 : i) CH_2=CHMgBr, THF, -30°C; ii) $CuSO_4.SiO_2$/ Benzene, reflux; iii) NaOMe, MeOH, H_2SO_4, -30 to 0°C; iv) Baker's yeast, glucose, H_2O, 48 h; v) Bu_4NI, $Et_2O.BF_3$, $CHCl_3$.

Iyengar's approach (1996)[44]

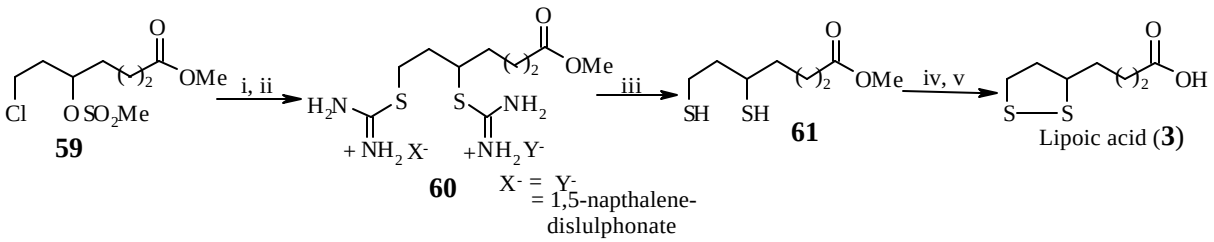
In this approach the key intermediate, (S)-methyl 6,8-dihydroxyoctonoate (**34**) was obtained by lipase mediated resolution of methyl 2-(tetrahydro-2-furyl)acetate (**56**). Thus, reduction of ester moiety in **56a** with $LiAlH_4$ followed by opening of the furan ring with trimethylsilylchloride-NaI in acetone gave the protected 1,3-dihydroxy functionality **57**. Alkylation of the benzyl methyl malonate with **57** followed by hydrogenolysis yielded monoester **58**. It was transformed to the key intermediate **34** in a series of reactions (**Scheme 16**).



Scheme 16 : i) Lipase, phosphate buffer; ii) $LiAlH_4$, Et_2O; iii) TMSCl, NaI, acetone; iv) benzyl methyl malonate, NaH, THF; v) Pd/C, H_2; vi) decarboxylation at 160^oC; MeOH, H^+

Beisswenger's approach (1997)[45]

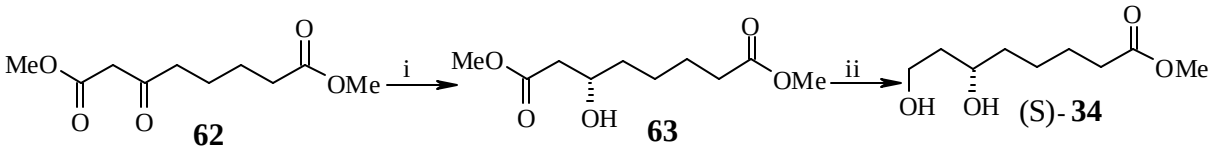
Beisswenger *et al* have filed a patent for the synthesis of racemic as well as chiral lipoic acid (**Scheme 17**). In this approach the key intermediate 6,8-dimercaptooctanoic acid (**61**) was obtained from the chiral or achiral methyl 8-chloro-6-methanesulfonyloxyoctanoate (**59**) as starting material. Thus **59** was treated with thiourea first and then salified with disodium-1,5-napthalenedisulfonate to obtain **60**. Subsequently, compound **60** was hydrolyzed with aq. NaOH to afford **61** as key intermediate. Finally it was transformed to chiral/racemic lipoic acid by oxidative coupling of dithiol with H_2O_2 followed by alkaline hydrolysis of ester.



Scheme 17 : i) H_2NCSNH_2, ii) disodium 1,5-napthalenesulfonate iii) aq. NaOH, iv) aq. H_2O_2, NaOH

Gerald's approach (1998)[46]

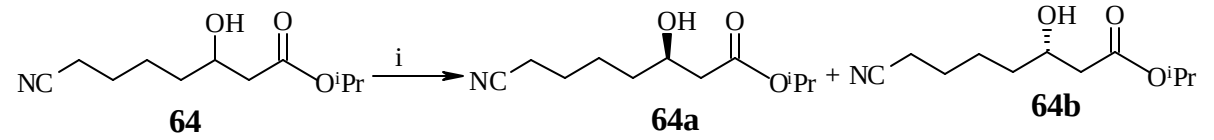
Gerald *et al* have filed a patent for the preparation of key intermediate (S)-methyl 6,8-dihydroxyoctanoate (**34**) *via* Ru-catalyzed asymmetric hydrogenation of methyl 3-oxooctanedioate (**62**) (**Scheme 18**). Thus, **62** on Ru-catalyzed asymmetric hydrogenation in presence of (S)-BINAP gave enantiomerically pure (S)-methyl 3-hydroxyoctanedioate (**63**). It was then transformed to **34** by regioselective reduction of ester with $NaBH_4$.



Scheme 18 : i) Ru(II)-(S)-BINAP, H_2, ii) $NaBH_4$

Lee's approach (1999)[47]

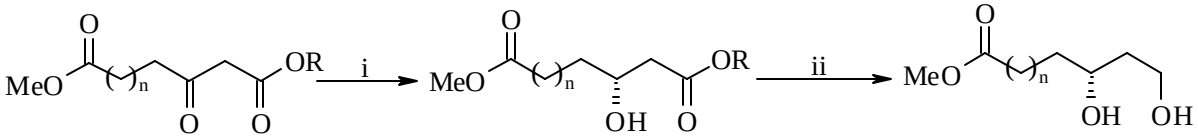
Lee *et al* have synthesized the enantiomerically pure isopropyl-3-hydroxy-7-cyanoheptanoate (**64a** and **64b**), intermediates for the synthesis of (R)-lipoic acid (**3a**) *via* lipase (lipase AK) mediated resolution of **64** in isopropenyl acetate (**Scheme 19**).



Scheme 19 : i) Lipase AK, isopropenyl acetate, 25 ^{o}C, 52 h

Bringmann's approach (1999)[48]

Bringmann *et al* have synthesized (R)-lipoic acid (**3a**) in 7 steps starting from methyl acetylacetoacetate or Meldrum's acid and *mono*-methyl adipate (**Scheme 20**). The enzymatic and catalytic asymmetric hydrogenation approaches were employed for the enantioselective reduction of 3-oxooctanedioate (**65**) to obtain (S)-3-hydroxyoctanedioate (**66**). Subsequently, regioselective reduction of ester in **66** afforded (S)-6,8-dihydroxyoctanoate (**34**), which was transformed further to (R)-lipoic acid by the literature procedure.



n = 2 **65** n = 2 **66** n = 2 **34**

Scheme 20 : i) fermentation/asymmetric reduction ii) $NaBH_4$

1.0.6 Present Work:

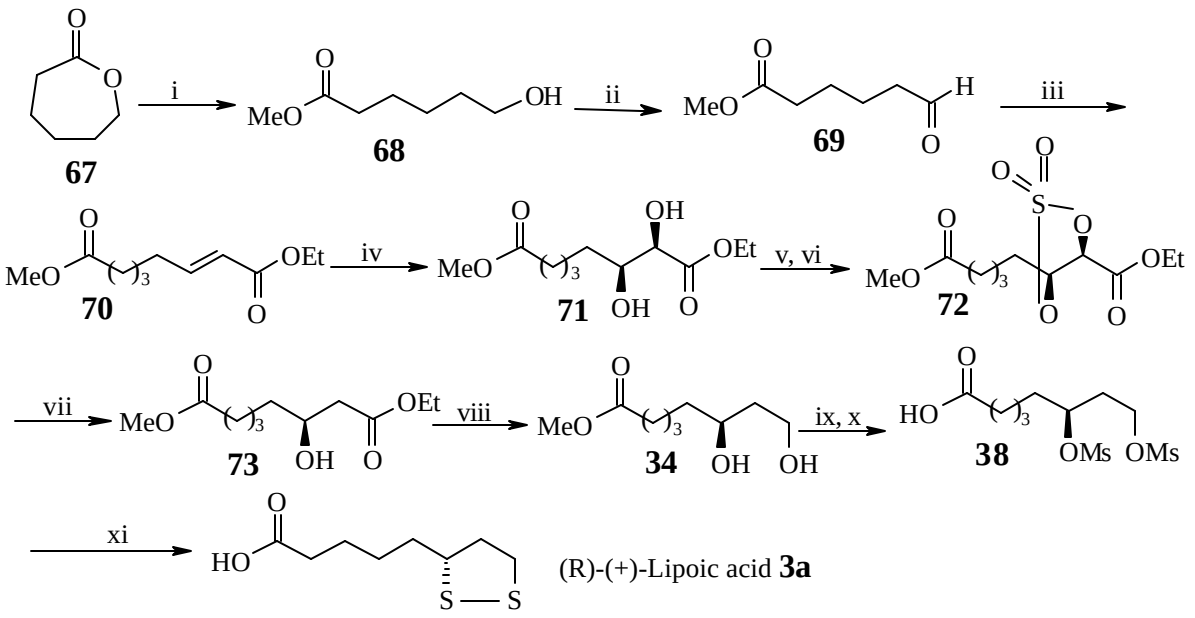
1.0.6.1 Objective:

In a view of high biological activity associated with the naturally occurring (R)-(+)-enantiomer of lipoic acid,[49] a number of methods for its enantioselective synthesis have been reported in the literature.[32-48] However, these methods suffer from disadvantages such as low overall yields, cumbersome resolution procedures, use of expensive reagents or non-availability of the starting materials. In this context, a more practical approach for the synthesis of pure enantiomer from the prochiral substrate is highly desirable. This chapter describes, for the first time, the synthesis of (R)-(+)-lipoic acid (**3a**) using Sharpless asymmetric dihydroxylation (AD) approach.

1.0.7 Results and Discussions:

The present strategy for the synthesis of (R)-(+)-lipoic acid (**3a**) starting from commercially available ε-caprolactone (**67**) is depicted in **Scheme 21**. The disulfide moiety in **3a** was introduced by disulfide dianion[50] through the inversion of configuration at C-6 in order to give (R)-configuration in the final product.

Accordingly, the diester **70** constituting the C_8-carbon unit of the lipoic acid was readily obtained from ε-caprolactone (**67**) and transformed to (S)-3-hydroxyoctanedioate (**73**) with proper stereochemistry at C6 position (**Scheme 21**). ε-Caprolactone (**67**) was subjected to transesterification with MeOH (50% wt/v) in the presence of conc. H_2SO_4 to afford methyl-6-hydroxycaproate (**68**) in 95% yield.[51] The IR spectrum of **68**, showed a broad peak at 3483 cm^{-1} indicating the presence of hydroxyl group. The ^{1}H-NMR showed a strong singlet at δ 3.6 corresponding to the methoxy group of ester. Thereupon, either Swern[52] or pyridinium



Scheme 21: (i) MeOH, conc. H_2SO_4, 60°C, 30 min.; 94% (ii) Swern oxidation / PCC, DCM, 0°C, 1h, 68% (iii) $(EtO)_2POCH_2COOEt$, NaH, THF, -78°C, 1.5 h; 70% (iv) cat. OsO_4, $(DHQD)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, *t*BuOH:H_2O, RT, 18 h; 92%, $[\alpha]^{25}_D$ = +9.39° (c = 1.02 EtOH); (v) $SOCl_2$, Et_3N, DCM, 0°C 45 min.; 94%; (vi) cat. $RuCl_3$, $NaIO_4$, CH_3CN: H_2O, 0°C 30 min., 86%, $[\alpha]^{25}_D$ = +54.25 (c = 1.2 EtOH); (vii) $NaBH_4$, DMAC, 20% H_2SO_4, 2h; 76%, $[\alpha]^{25}_D$ = -13.59° (c = 1.2 EtOH); (viii) $NaBH_4$, Et_3N, MeOH: DMF (2:1), AcOH, 5 h; 65%, $[\alpha]^{25}_D$ = -3.4° (c = 0.14, $CHCl_3$); (ix) $MeSO_2Cl$, TEA, DCM, 0°C, 2h; 90%, -19.0° (c = 1.0, $CHCl_3$); (x) 0.1 M KOH, RT, 20h, 55%; (xi) KOH, H_2O, $Na_2S.9H_2O$, S_8, DMF, HCl, 45%, +96.4° (c = 1.86, C_6H_6).

chlorochromate[53] (PCC) mediated oxidation of **68** afforded methyl-6-oxocaproate (**69**) in 74% and 67% yield respectively. Its IR bands at 2869 (w) and 1712 cm^{-1} are indicative of the presence of aldehyde group, while band at 1739 cm^{-1} is due to ester group. The C_2-homologation of **69** by Wittig-Horner reaction[54] with triethyl phosphonoacetate furnished the octenedioic ester **70** in quantitative yield. The IR spectrum of ester **70** showed a band at 1656 cm^{-1}corresponding to C=C bond. Its ^{1}H-NMR spectrum showed signals at δ 5.8 and 6.8-7.0 indicative of the olefinic protons. In ^{13}C-NMR spectrum the signals at δ 121.84 and 147.58 are due to the olefinic carbons (**Fig. 4**).

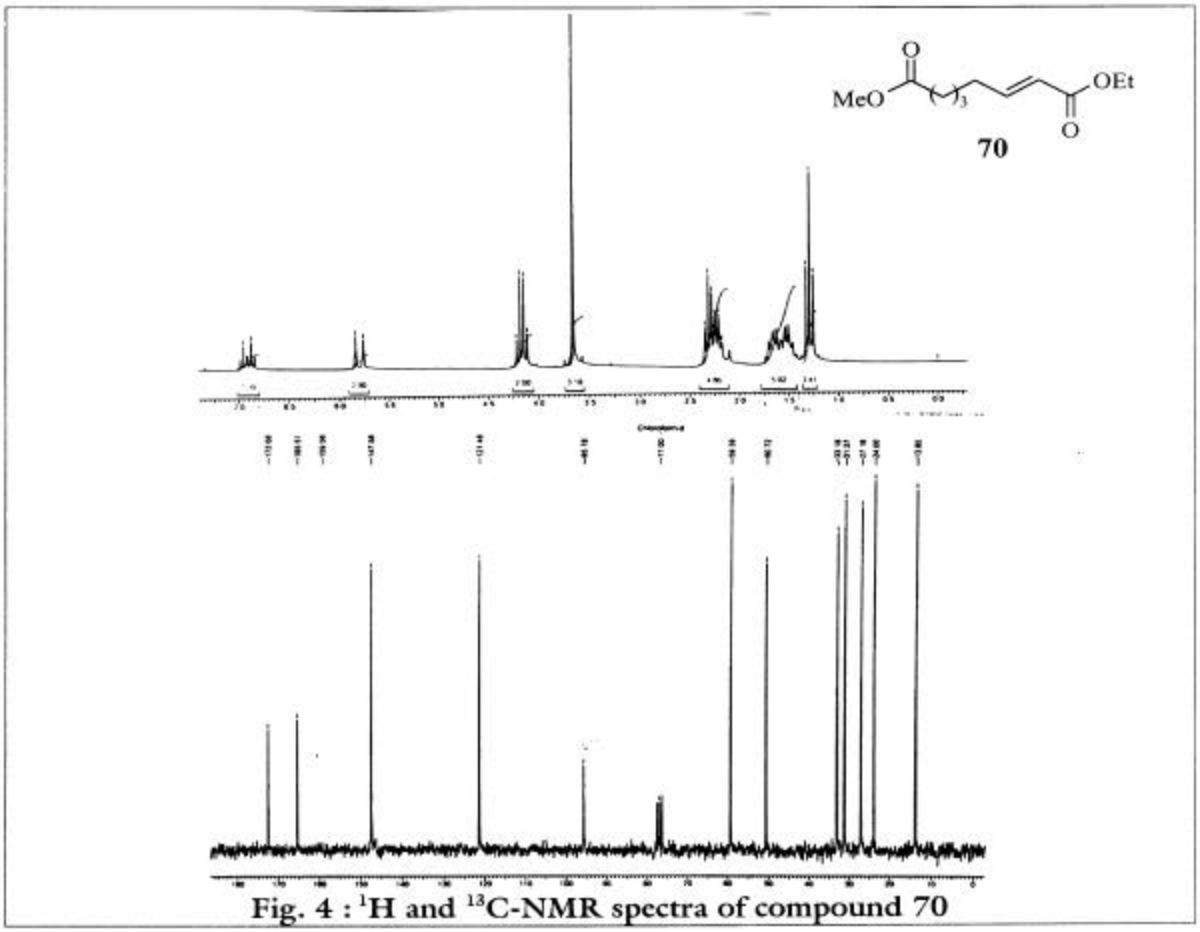


Fig. 4 : ^{1}H and ^{13}C-NMR spectra of compound 70

Olefin **70** was then subjected to AD reaction in presence of $(DHQD)_2$-PHAL to obtain β-diol **71** in 92% yield. The IR spectrum of diol **71** showed bands at 3600-3200 and 1731 cm^{-1}, due to the presence of diol and ester moieties respectively. The ^{1}H-NMR showed the disappearance of olefinic protons and the appearance of signals at δ 3.79 and 4.0 indicative of two CH protons of the diol **71** moiety (**Fig. 5**). These two CH carbons appeared at δ 72.18 and 73.29 in its ^{13}C-NMR spectrum (**Fig. 5**). The diol **71** was converted to its diacetate (86% yield) using acetyl chloride in pyridine and optical purity of the diacetate 96%ee was determined from its ^{1}H-NMR spectrum using Eu(III) chiral shift reagent (Aldrich).

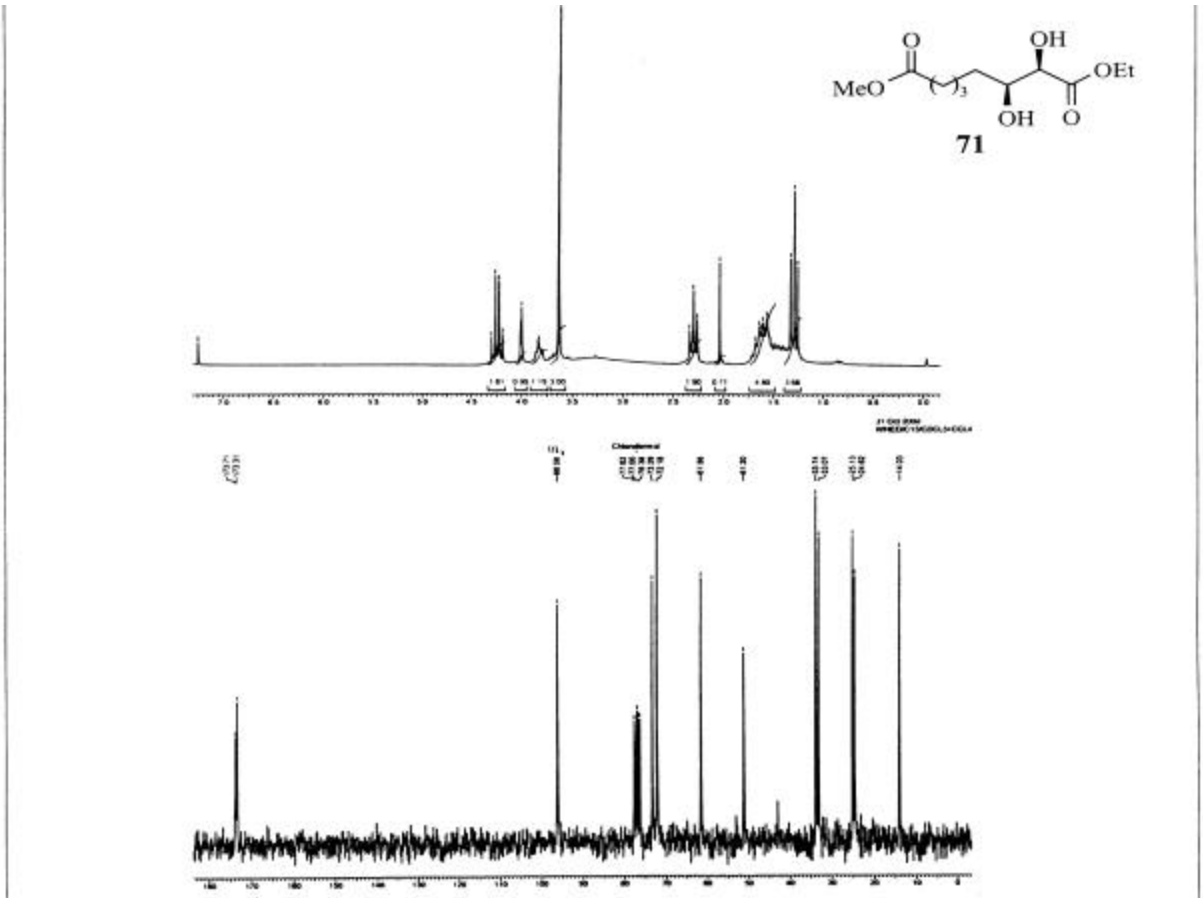


Fig. 5 : ^{1}H and ^{13}C-NMR spectra of compound 71

The diol **71** was then activated by transforming it into the corresponding cyclic sulfate **72** in two steps.[55] Thus, diol **71** was first treated with thionyl chloride to give cyclic sulfite followed by its oxidation with $NaIO_4$ in the presence of catalytic $RuCl_3$ afforded **72** in 86% yield. The IR spectrum of cyclic sulfate **72** showed characteristic bands at 1394 and 1209 cm^{-1} indicative of the presence of cyclic sulfate. Its ^{1}H-NMR spectrum showed two CH signals appearing at δ 4.85-4.96 (m) and at δ 2.35 (t) (**Fig. 6**). Its ^{13}C-NMR spectrum is indicative of the overall downfield shift of the CH carbon signals appearing at δ 79.76 and 83.84.

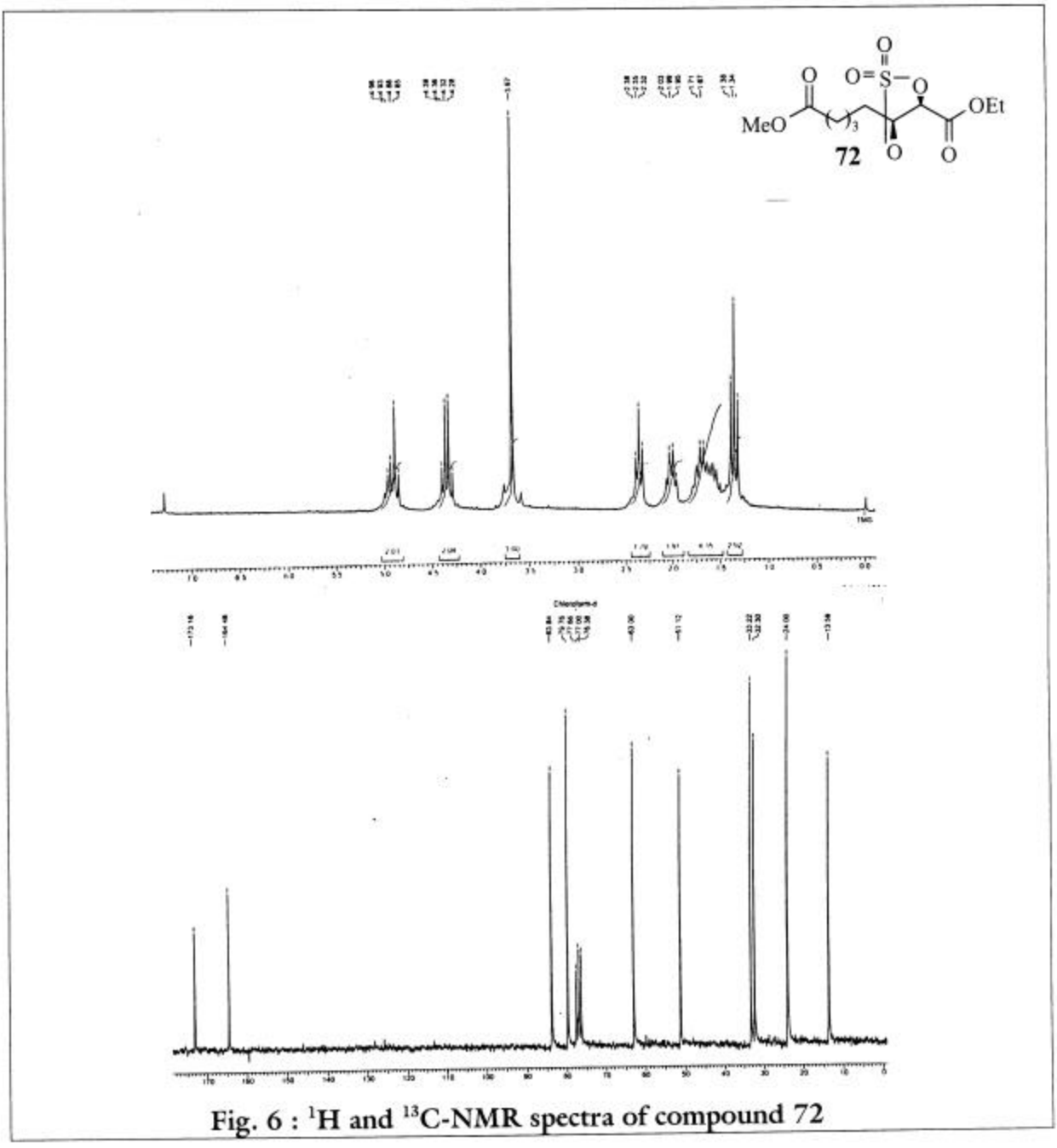


Fig. 6 : ^{1}H and ^{13}C-NMR spectra of compound 72

The treatment of cyclic sulfate **72** with sodium borohydride in N,N'-dimethylacetamide (DMAC) led to the regioselective reductive ring opening of the cyclic sulfate[56] and thereby affording the key intermediate (S)-3-hydroxyoctanedioate (**73**) in good yield. Its IR spectrum shows characteristics bands at 3500 and 1735 cm^{-1} indicative of the

presence of hydroxyl and ester groups respectively. Its ^{1}H-NMR spectrum showed two characteristic signals at δ 2.25-2.50 (m) and 3.9-4.01 (bs) for α-CH_2 and chiral CH protons respectively. Its ^{13}C-NMR spectrum showed a characteristic carbon signal at δ 67.69 corresponding to CH carbon at the chiral center (**Fig. 7**).

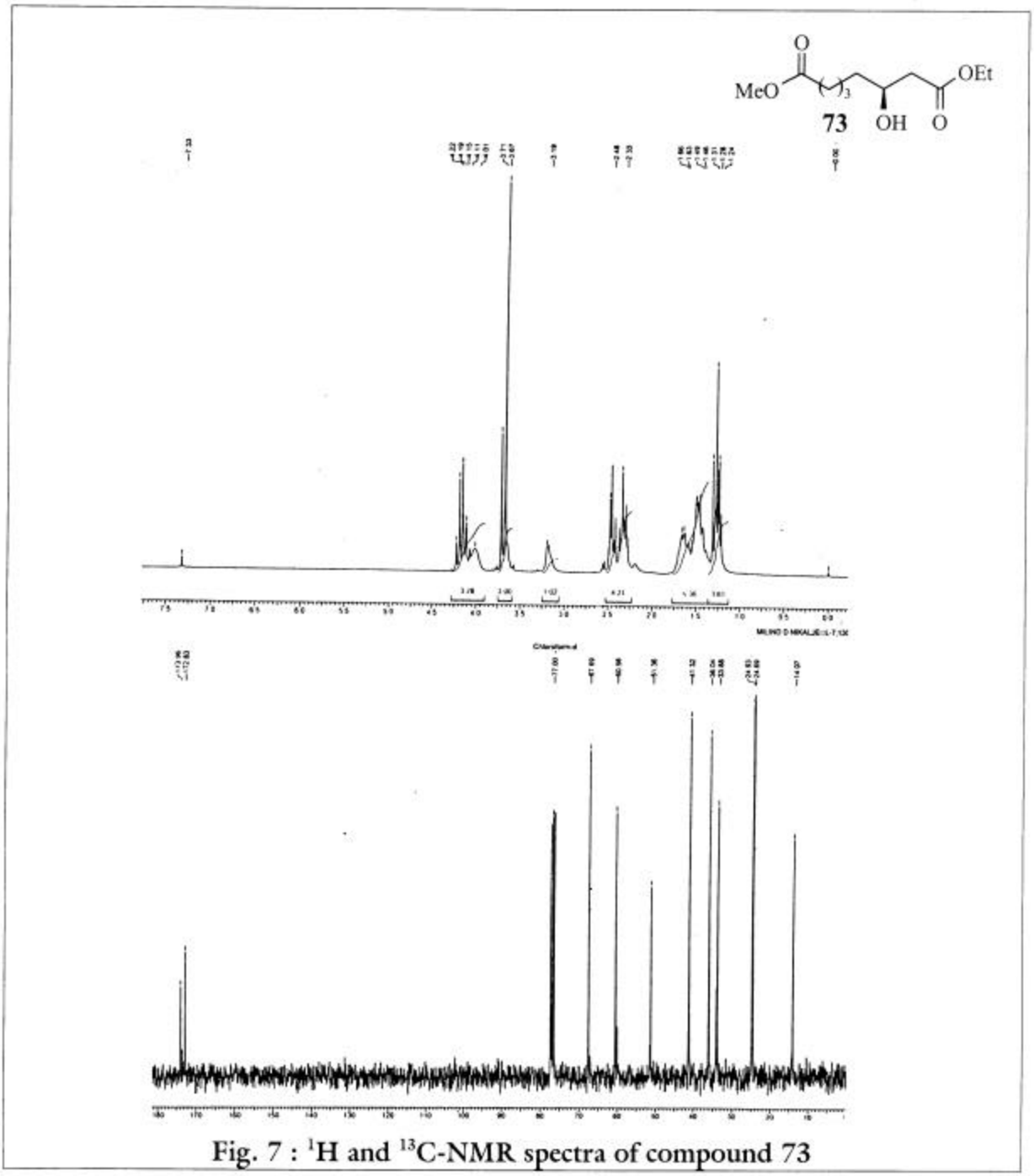


Fig. 7 : ^{1}H and ^{13}C-NMR spectra of compound 73

(S)-3-Hydroxyoctanedioate (**73**) was subjected to regioselective reduction of ethyl ester with sodium borohydride in the presence of triethylamine followed by its treatment with acetic acid gave the key intermediate (S)-methyl 6,8-dihydroxyoctanoate (**34**) in 65% yield and 90%ee.[57, 46, 44] Its IR spectrum showed characteristic broad bands at 3370 and 1731 cm^{-1} indicating the presence of hydroxyl group and ester moiety. The reduction of ethyl ester is confirmed from its ^{1}H-NMR spectrum matching well with the reported value.

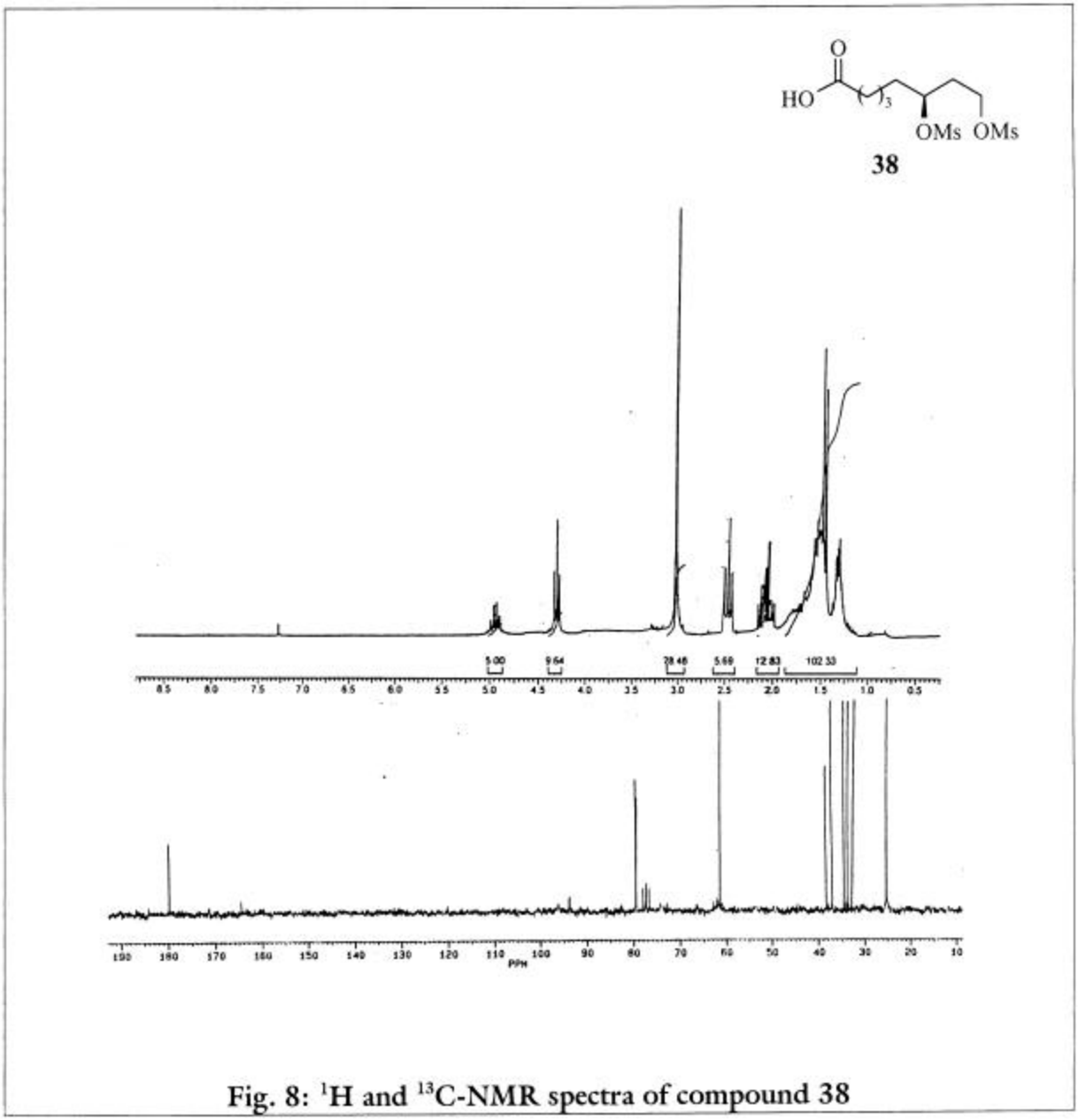


Fig. 8: ^{1}H and ^{13}C-NMR spectra of compound 38

The diol **34** was then mesylated and the crude dimesylated product was carefully treated with 0.1 M NaOH to give the (S)-6,8-dihydroxyoctanoic acid dimesylate (**38**). Its IR spectrum showed broad bands at 3500-3300 and 1728 cm^{-1} indicating the presence of hydroxyl and C=O groups of the acid respectively. Its ^{1}H-NMR showed a characteristic singlet appearing at δ 3.05 corresponding to two CH_3 groups (**Fig. 8**). Its ^{13}C-NMR spectrum indicated the characteristic carbon signals at δ 79.86 and δ 180 corresponding to that of CH carbon at the chiral center and C=O of the acid moiety respectively (**Fig. 8**).

The final step of the synthesis involved disulfide displacement of the acid dimesylate **38**. It was carried out by the initial formation of carboxylate ion using aqueous potassium hydroxide, followed by the addition of suspension of pre-formed disulfide dianion in DMF and heating the mixture at 80^{o}C for 24h. The recrystallization of the crude product gave pure (R)-(+)-lipoic acid (**3a**) in 45% yield and 90% optical purity (%ee was determined by comparison of $[\alpha]_D$ with the literature value[58]). The absolute configuration of **3a** was confirmed to be R by comparison with the literature value of the optical rotation. Hence the predicted stereochemical outcome of asymmetric dihydroxylation is correct. The IR, ^{1}H-NMR and ^{13}C-NMR spectral data of the **3a** matched well with the published values. ^{1}H-NMR of **3a** showed peak at δ 3.2 (t) and δ 3.5 (m) for H-8, 8' and H-6 respectively. The upfield shifts of the signals for these protons were expected because of the shielding effect of the sulfur atom.

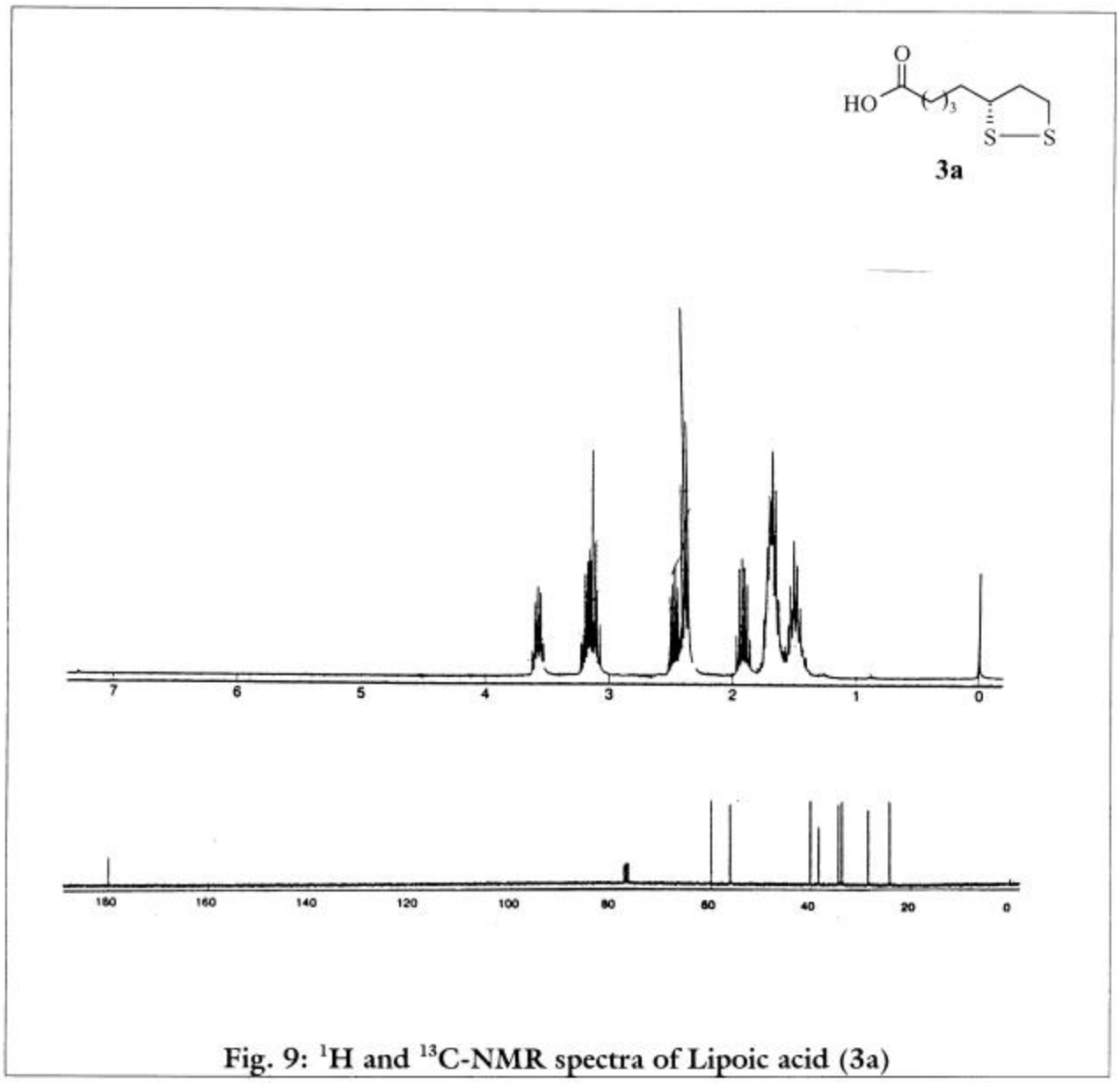


Fig. 9: ^{1}H and ^{13}C-NMR spectra of Lipoic acid (3a)

1.0.8 Conclusion:

We have achieved the synthesis of (R)-(+)-lipoic acid (**3a**) in 90% ee *via* asymmetric dihydroxylation, starting from cheaply available ε-caprolactone. Effectively the present synthesis of (R)-(+)-lipoic acid (**3a**) involved only eight steps starting from olefin **70** in an overall yield of 9%.

1.0.9 Experimental Section:

Preparation of methyl-6-hydroxyhexanoate (68)

To a solution of conc. H_2SO_4 (1.0 ml, 18.78 mmol) and MeOH (10.0 ml), a solution of ε-caprolactone (10.0 g, 87.72 mmol) in MeOH (10.0 ml) was added with stirring at room temperature. After completion of the addition, reaction mixture was heated under reflux for 10 min and allowed to cool to room temperature (RT). It was then neutralized with 10% NaOH (~7 ml) and extracted with ethyl acetate (3 x 50 ml). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give **68**. It was then purified by column chromatography packed with silica gel (10% ethyl acetate in pet. ether) to give pure **68** (12.12 g) as a colorless liquid.

Yield	:	94%
bp	:	82-84^{o}C/ 1 mm Hg
IR (neat cm^{-1})	:	3483, 2947, 1730, 1436-1458, 1367, 1166-1240, 1099, 1047, 964, 860, 756.
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 1.30-1.40 (m, 2H), 1.50-1.75 (m, 4H), 2.20-2.35 (m, 3H), 3.65 (s, 3H), 3.95-4.1 (t, *J* = 2.7 Hz, 2H).
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 24.29, 24.95, 31.82, 33.55, 50.98, 61.75, 173.89.
MS (m/z, %RI)	:	146 (M^+, 3), 128 (35), 115 (62), 101(25), 97 (38), 87 (65), 74 (100), 68 (80), 59 (25), 55 (20).
Analysis	:	$C_7H_{14}O_3$ requires: C, 57.12, H, 10.26%; found: C, 57.02, H, 9.96%

Preparation of methyl-6-oxohexanoate (69)

[A] A solution of dimethyl sulphoxide (5.31 g, 68.03 mmol) in dry CH_2Cl_2 (15 ml) was added dropwise to a solution of oxalyl chloride (5.18 g, 40.81 mmol) in dry CH_2Cl_2 (75 ml) at –48°C under N_2 atmosphere and the reaction mixture was kept under stirring for 30 minutes. Followed by a solution of alcohol **68** (5.0 g, 34.01 mmol) in dry CH_2Cl_2 (25 ml) was added dropwise and the stirring of the reaction mixture continued for another 30 min. Reaction was then quenched by the addition of triethylamine (18.92 ml, 136.05 mmol). The resulting solution was kept under stirring for 10 minutes and diluted with water (75 ml). The aqueous layer was extracted with CH_2Cl_2 (4 x 30 ml). The combined organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and evaporated under reduced to give crude aldehyde **69**. It was then purified by column chromatography packed with silica gel (5% ethyl acetate in pet. ether) to yield pure aldehyde **69** (3.62 g) as a colorless liquid.

Yield	:	74 %
IR (neat, cm^{-1})	:	2952, 2869, 1739, 1712, 1436, 1365, 1172-1240, 1081, 736-756
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 2.1-2.6 (m, 4H), 2.25-2.55 (m, 4H), 3.67 (s, 3H), 9.75 (s, 1H)
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 21.6, 24.5, 33.8, 43.5, 51.5, 172.90, 173.27
MS (m/z, % RI)	:	144 (2), 142 (8), 129 (25), 114 (60), 101 (70), 27 (95), 83 (35), 74 (80), 67 (50), 59 (100), 55 (38)
Analysis	:	$C_7H_{12}O_3$ requires C, 58.32; H, 8.39%; found C, 58.18; H, 8.31%

[B] To a solution of pyridinium chlorochromate (4.38 g, 20.41 mmol) in CH_2Cl_2 (9,0 ml) was added rapidly a solution of alcohol **68** (2.0 g, 13.61 mmol) in CH_2Cl_2 (25 ml) at 0^oC and the reaction mixture brought to RT. After completion of the reaction (monitored by TLC), supernatant solvent was decanted from the black residue and the residue was washed thrice with anhydrous ether (3 x 50 ml). The combined ether layer was then passed through a column packed with celite and the solvent concentrated under reduced pressure to give crude **69**. It was then purified by column chromatography packed with silica gel (5% ethyl acetate in pet. ether) to yield pure **69** (1.33 g) as a colorless liquid in 68% yield. (Characterization of **69** *vide supra* under experimental).

Preparation of ethyl methyl-2-octenedioate (70)

[**A**] A mixture of ethyl bromoacetate (5.0g, 29.94 mmol) and triethyl phosphite (5.46 g, 32.93 mol) was heated in an oil bath at 160^oC for 3h, with generation of ethyl bromide. The crude oil was distilled to give pure triethyl phosphonoacetate (6.50 g) as a colorless liquid. It is characterized by IR, ^{1}H-NMR and mass spectra.

Triethyl phosphonoacetate

Yield	:	97%
IR (neat, cm^{-1})	:	1730, 1450, 1400, 1380, 1280, 1110, 1050, 970, 800
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 1.15-1.25 (m, 9H), 2.8 (d, *J* = 21.0 Hz, 2H) 4.05-4.15 (m, 6H)
MS (m/z, % RI)	:	224 (M^+, 13), 197 (100), 181 (15), 179 (90), 169 (37), 152 (51), 151 (70), 137 (14), 125 (19), 123 (86), 109 (35), 107 (20), 97 (15), 88 (18), 81 (20), 65 (13)

[B] To a mixture of NaH (0.61g, 15.28 mmol) and dry THF (10 ml) was added dropwise triethyl phosphonoacetate with stirring for a period 15 min at RT. Further stirring of the reaction was continued at RT till liberation of H_2 bubble stops (40 min.). It was then cooled to –78°C and a solution of aldehyde **69** (2.0 g, 13.88 mmol) in dry THF (5 ml) was added dropwise over a period of 15 min. After 40 min, the reaction was brought to RT and the stirring continued for 1h (monitored by TLC). Resulting reaction mixture was diluted with water and extracted with ethyl acetate (4 x 30 ml). The combined ethyl acetate layer was washed with water, brine, dried over Na_2SO_4 and concentrated under reduced pressure to give olefin **70**. It was then purified by column chromatography packed with silica gel to yield pure olefinic-diester **70** (2.08 g) as a viscous liquid.

Yield	:	70%
bp	:	Gum
IR ($CHCl_3$, cm^{-1})	:	2952, 1745, 1726, 1656, 1438-1467, 1367, 1271, 1145-1234, 1097, 1043, 983, 900, 850, 811, 711s
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 1.25-1.32 (t, *J* = 7.3 Hz, 3H), 1.45-1.8 (m, 4H), 2.21-2.35 (m, 4H), 3.67 (s, 3H), 4.11-4.22 (q, *J* = 7.3 Hz, 2H), 5.77-5.84 (d, *J* = 15.6 Hz, 1H), 6.80-7.0 (m, 1H)
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 13.85, 24.0, 27.16, 31.27, 33.18, 50.72, 59.39, 121.48, 147.58, 165.51, 172.68
MS (m/z, % RI)	:	214 (M^+, 0.2), 183 (2), 168 (31), 81 (85), 67 (45), 59 (32), 55 (15)
Analysis	:	$C_{11}H_{18}O_4$ requires: C, 61.66; H, 8.47%, found: C, 61. 60, H, 8.44%

Preparation of (2R, 3S)-2,3-dihydroxyoctanedioate (71)

A 100 ml RB flask was charged with $K_3Fe(CN)_6$ (4.61 g, 14.0 mmol), K_2CO_3 (1.93 g, 14.00 mmol), $(DHQD)_2$-PHAL (72 mg, 0.09 mmol, *t*-BuOH : H_2O (1:1, 25 ml) and reaction mixture was mixed well by stirring at 25°C for 5 min followed by a solution of OsO_4 (95 µl, 0.047 mmol, 0.5 M solution in toluene) was added at 0°C. Finally olefin **70** (1.0 g, 4.66 mmol) was added drop wise over a period of 7 minutes at 0°C and stirring of the reaction mixture was continued for 18h (monitored by TLC). Resulting reaction mixture was quenched by the addition of sodium sulfite (1.5 g). The two layers formed were separated. The aqueous layer was extracted with ethyl acetate (4 x 25 ml) and the combined organic extract was washed with brine (30 ml), dried over Na_2SO_4 and evaporated to dryness. The crude product was purified by column chromatography packed with silica gel (ethyl acetate: pet. ether (1:1)) to yield pure diol **71** (1.01 g) as a colorless viscous liquid.

Yield	:	92%
bp	:	Gum
$[\alpha]_D^{25}$	:	+ 9.39° (c = 1.02, EtOH)
IR ($CHCl_3$, cm^{-1})	:	3200-3600, 2948, 2866, 1731, 1633-1645, 1440, 1369, 1120-1269
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 1.26-1.33 (t, 3H, *J* = 7.0 Hz), 1.4-1.7 (m, 7H), 2.05 (s, 1H) 2.27-2.34 (t, 2H, *J* = 7.0 Hz), 3.64 (s, 3H), 3.79-3.87 (m, 1H), 4.00-4.01 (d, 1H, *J*= 2.0 Hz), 4.20-4.30 (q, 2H, *J* = 7.0 Hz)
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 14.03, 24.62, 25.13, 33.07, 33.74, 51.20, 61.56, 72.18, 73.29, 173.31, 173.71
MS (m/z, % RI)	:	248 (M^+, 0.1), 183 (2), 199 (1), 143 (3), 125 (12), 113 (68) 104 (92), 95 (22), 85 (21), 76 (100), 67 (40),57 (18)
Analysis	:	$C_{11}H_{20}O_6$ requires C, 53.22; H, 8.12%; found: C, 53.16, H, 8.07%.

Preparation cyclic sulfate (72) *via* cyclic sulfite.

[A] To a stirred solution of diol **71** (1.0 g, 4.03 mmol) and pyridine (0.70 g, 8.87 mmol) in CH_2Cl_2 (5 ml) at 0 ^oC, was added freshly distilled thionyl chloride (0.523 g, 4.44 mmol) under N_2 atmosphere and the reaction kept under stirring for 45 min (monitored by TLC). It was quenched with ice cold water (10 ml) and extracted with ethyl acetate (3 x 25 ml). Ethyl acetate layer was washed with dil. HCl, saturated $NaHCO_3$ solution, followed by brine (25 ml), dried over Na_2SO_4 and evaporated under reduced pressure to give yellow cyclic sulfite. It was then purified by column chromatography packed with silica gel to afford pure cyclic sulfite (1.11 g) as a colorless viscous liquid in 94% yield.

To a solution of the above cyclic sulfite (1.0 g, 3.40 mmol) in CH_3CN:H_2O (8 ml, 90:10) was added solid sodium periodate (1.09 g, 5.10 mmol) and catalytic amount of $RuCl_3$ (14 mg, 0.068 mmol) at 0^oC. The resulting reaction mixture was kept under stirring for 30 min at 0^oC (monitored by TLC). After completion of the reaction, it was filtered through the sintered funnel packed with pad of celite. The filtrate was evaporated under reduced pressure to dryness. The crude cyclic sulfate **72** was then purified by column chromatography packed with silica gel to afford pure **72** (0.91 g) as a colorless liquid.

Yield	:	86%
bp	:	Gum
$[\alpha]_D^{25}$	:	+ 54.25^o (c = 1.2, EtOH)
IR ($CHCl_3$, cm^{-1})	:	2985, 2954, 2873, 1768, 1737, 1438, 1394, 1302, 1209, 1163, 1041-1029, 948, 885, 842, 651
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 1.31-1.38 (t, *J* = 7.5 Hz, 3H), 1.54-1.74 (m, 4H), 1.95-2.06 (m, 2H), 2.32-2.38 (t, *J* = 6.0 Hz, 2H), 3.67 (s, 3H), 4.28-4.39 (q, *J*=7.5 Hz, 2H); 4.85-4.96 (m, 2H)

^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 13.6, 23.77, 23.99, 32.30, 32.2, 51.1, 63.0, 79.8, 83.8, 164.5, 173.2
MS (m/z, % RI)	:	252 (1), 205 (3), 176 (73), 125 (22), 97 (51), 81 (75), 69 (54), 59 (73), 55 (100)
Analysis	:	$C_{11}H_{18}O_8S$ requires: C, 42.58; H, 5.85; S, 10.32%; found: C, 42.54; H, 5.77; S, 10.27%

Preparation of (S)-3-hydroxyoctanedioate (73)

To a solution of cyclic sulfate **72** (0.500 g, 1.61 mmol) in dry N,N'-dimethylacetamide (DMAC, 2.0 ml) was added a solid $NaBH_4$ (0.061 g, 1.6 mmol) at 25^0C under N_2 atmosphere. The resulting solution was kept under stirring at 25^oC for 2h (monitored by TLC) and then DMAC was removed under reduced pressure. To the resulting residue, 20% aqueous H_2SO_4 (9 ml) and diethyl ether (25 ml) were added and the reaction mixture kept under stirring for 12 h at 25^oC. The two layers were separated and the aqueous layer was extracted with diethyl ether (3 x 10 ml). The combined ether layers, washed with water, brine, dried over Na_2SO_4 concentrated under reduced pressure to give **73**. The crude product **73** was purified by column chromatography packed with silica gel to afford pure hydroxy ester **73** (0.284 g) as a colorless viscous liquid.

Yield	:	76%
bp	:	Gum
$[\alpha]_D^{25}$	:	- 13.59^o (c = 1.2, EtOH)
IR ($CHCl_3$, cm^{-1})	:	3500, 2866, 1768, 1731, 1633-1645, 1440, 1369, 1260, 1120, 1026
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 1.20-1.30 (t, *J* = 7.5 Hz, 3H), 1.60-1.70 (m, 6H), 2.25-2.30 (m, 4H), 3.19 (s, 1H), 3.67 (s, 3H), 4.04-4.20 (m, 3H)
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 14.07, 24.69, 24.93, 33.88, 36.04, 41.32, 51.36, 60.58, 67.69, 172.83, 173.96.
Analysis	:	$C_{11}H_{20}O_5$ requires: C, 56.88; H, 8.68%; found: C, 56.82; H, 8.71%.

Preparation of (S)-methyl 6, 8-dihydroxyoctanoate (34)

A mixture of hydroxyester **73** (0.100 g, 0.431 mmol) and triethylamine (0.065 g, 0.65 mmol) in MeOH: DMF (1.5 ml, 2:1) was cooled to 0^oC. To this was added a solution of $NaBH_4$ (0.020 g, 0.52 mmol) in MeOH (1.0 ml) and the reaction mixture stirred for 5h at 0^oC (monitored by TLC). The resulting solution was brought to RT (25^oC) and the stirring was continued for 2.5h. It was then treated with acetic acid (42 µL, 0.73 mmol) at 0^oC, kept under stirring over a period of 10 min and extracted with ethyl acetate to yield crude **34**. It was then purified by column chromatography packed with silica gel to afford (0.052 g) as viscous liquid.

Yield	:	64%
$[\alpha]_D^{25}$	:	- 3.4^o (c = 0.14, $CHCl_3$) {Lit.[44] $[\alpha]_D^{25} = -3.8^o$ (c = 0.8, $CHCl_3$)}
IR ($CHCl_3$, cm^{-1})	:	3370, 2940, 2870, 1731, 1460, 1435, 1420, 1363, 1195, 1175, 1150, 1095, 1000, 970.
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 1.45-1.51 (m, 8H), 2.26-2.30 (t, *J* = 7.3 Hz, 2H), 3.30-3.36 (m, 3H), 3.62 (s, 3H), 4.2-4.53 (s, 2H)
MS (m/z, % RI)	:	190 (100), 173 (18), 163 (10), 141(22), 130 (3)
Analysis	:	$C_9H_{18}O_4$ requires C, 56.88; H, 9.54%; found C, 56.82; H, 9.71%

Preparation of (S)-6,8-dihydroxyoctanoic acid dimesylate (38)

[**A**] To a solution of diol **34** (0.040 g, 0.21 mmol) and triethylamine (64 µL, 0.46 mmol) in dry CH_2Cl_2 (1 ml) was added methanesulfonyl chloride (36 µL, 0.46 mmol) at 0^oC under N_2 atmosphere. The resulting solution was stirred for 2h (monitored by TLC) and the reaction quenched by the addition of saturated solution of $NaHCO_3$. The product was extracted with

CH_2Cl_2 (3 x 25 ml), washed with brine, dried over anhdy. Na_2SO_4, and concentrated under vacuum to yield almost pure dimesylate ester (0.065 g, 90%). It was subjected to hydrolysis of the ester group without further purification and characterization.

[B] Dimesylate ester (0.050 g, 0.145 mmol) was dissolved in MeOH (0.8 ml) and treated with 0.1 M KOH (2 ml) solution. The resulting solution was stirred at $25^{O}C$ for 20 h (monitored by TLC), neutralized by addition of 0.1 N HCl and extracted with ethyl acetate (3 x 5 ml) to give solid **39** (0.026 g,).

Yield	**:**	55%
mp	**:**	$48^{o}C$ (recrystallized from $CHCl_3$: Pet. ether mixture (40:60))
$[\alpha]_D^{25}$	**:**	- 19.0^{o} (c = 1.0, $CHCl_3$)
IR ($CHCl_3$, cm^{-1})	**:**	3500-3300, 1728, 1697, 1460, 1405, 1380, 1350, 1198, 1178, 1090, 970, 822, 535, 420.
^{1}H-NMR (200 MHz, $CDCl_3$)	**:**	δ 1.2-1.75 (m, 6H), 2.05-2.15 (m, 2H), 2.45 (t, *J* = 6.4 Hz, 2H), 3.05 (s, 6H), 4.25 (t, *J* = 5.0, 2H), 4.75-4.9 (m, 1 H)
^{13}C-NMR (50 MHz, $CDCl_3$)	**:**	δ 24.0, 32.2, 34.0, 34.5, 37.5, 38.6, 64.9, 78.0, 180.0.
Analysis	**:**	$C_{10}H_{20}O_8S_2$ requires C, 36.15; H, 6.02; S, 19.29%. found: C, 36.08; H, 6.10, S, 19.31%.

Preparation of (R)-(+)-Lipoic acid (3a)

To a stirred solution of KOH (0.012 g, 030 mmol) in water (2.5 ml) was added acid dimesylate **38** (0.025g, 0.075 mmol). Then water was removed under reduced pressure at $<40^{o}C$. A slurry of $Na_2S.9H_2O$ (0.039 gm, 0.17 mmol) and sulfur (0.039 g, 0.15 mmol) in

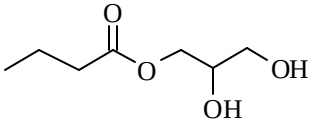
DMF (3 ml) was added to the crude potassium salt of acid and the resulting mixture was then heated under reflux for 28h with vigorous stirring. The reaction mixture was then poured into ice water, acidified with conc. HCl and extracted with ethyl acetate (5 x 30 ml). The combined organic extracts were washed with water, brine, dried over anhy. Na_2SO_4, and concentrated in *vacuo* to afford **3a** in crude form. It was then purified by preparative TLC to give pure (R)-Lipoic acid (0.007 g) as light yellow colored solid.

Yield	:	45%
mp	:	43-45^oC
$[\alpha]_D^{25}$	:	+ 96.4^o (c = 1.86, C_6H_6), {Lit.[37] $[\alpha]_D^{25}$ = + 106^o (c, 0.88 in C_6H_6)
IR ($CHCl_3$, cm^{-1})	:	3600-3350, 1720, 1400, 1255, 1150, 1125, 988, 938, 856, 737, 699, 586.
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 1.2-2.75 (m, 10H), 3.2 (t, *J* = 7.2 Hz, 2H), 3.5 (m, 1H), 4.25 (t, *J* = 5.0, 2H), 4.75-4.9 (m, 1 H).
^{1}H-NMR (50 MHz, $CDCl_3$)	:	δ 24.31, 28.60, 33.83, 34.54, 38.45, 40.18, 56.23, 180.02.

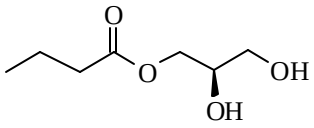
Asymmetric Synthesis of (R)-(+)-Monobutyrin, a Novel Angiogenesis Factor *via* OsO_4-Catalyzed Asymmetric Dihydroxylation

1.1.0 Introduction:

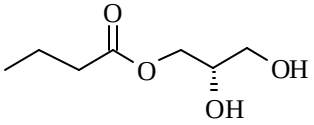
The Monobutyrin (1-Butyrylglycerol, **74**) is a simple lipid and a novel angiogenesis factor secreted by adipocytes. Dobson *et al*, in 1991, isolated the major angiogenesis factor from adipocyte-conditioned medium and identified as a 1-butyrylglycerol (**74**) by GCMS.[59] (R)-Monobutyrin is a naturally occurring lipid and only (R)-isomer is bioactive. It plays an important role in formation of the new blood vessels during the process of embryogenesis, inflammation, wounds, healing neoplasia, ocular diseases and rheumatoid arthritis. The synthetic monobutyrin also shows the same spectrum of biological activities as that of adipocyte-derived factor.



Monobutyrin **74**



(R)-(+)-Monobutyrin **74a**



(S)-(-)-Monobutyrin **74b**

1.2.0 The Pharmacology of Monobutyrin:

Although monobutyrin plays a key role in angiogenic process linked to the normal cellular and tissue level development, it also shows the vasodilatory activity in diabetics of rodent thus controlling the vascular complications.[60] Monobutyrin also acts as cyto-differentiating agents and employed in the treatment of leukemia, thalassemia or sickle cell anemia.[61] It is used as an active ingredient in the preparation of cream, gel and ointment and

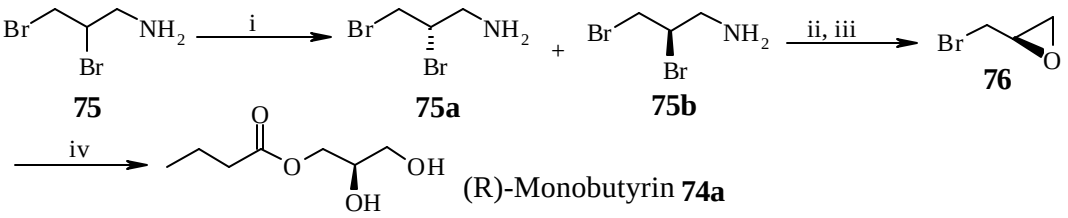
also employed in the treatment of skin disorders.[62] It is an effective inducer of haemoglobin synthesis and shows inhibitory effects on synthesis of DNA in hepatoma cells and cellular proliferation in mouse erythroleukemia cells.[63] It is also used as an active component in hair tonic and growth stimulant. [64]

1.1.1 Review of Literature:

The literature search revealed that there are only a few reports available on asymmetric synthesis of either (R) or (S) isomer of monobutyrin. Among these, only one report employs the preparation of optically active monobutyrin using both D and L-mannitol as a chiral building block, whereas all other reports are concerned with the resolution of racemic starting materials.

Abderhalden's approach (1914)[65]

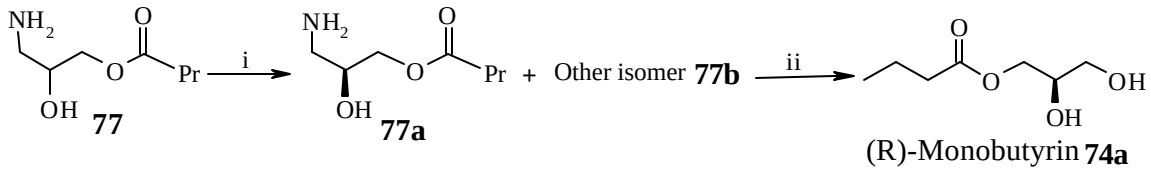
Abderhalden *et al* have synthesized the optically active monobutyrin *via* resolution of 1-amino-2,3-dibromopropane (**75**) in the presence of D-tartaric acid (**Scheme 22**). The enantiomer **75a** on treatment with nitrous acid followed by cyclization with base generated the epibromohydrin **76**. It was subsequently transformed to (R)-monobutyrin (**74a**) by opening with butyric acid. The similar sequence of reaction with **75b** resulted in the formation (S)-isomer of **74b**.



Scheme 22 : i) D-Tartaric acid, ii) HNO_2, ii) K_2CO_3, iv) $CH_3CH_2CH_2CO_2H$

Bergamon's approach (1924)[66]

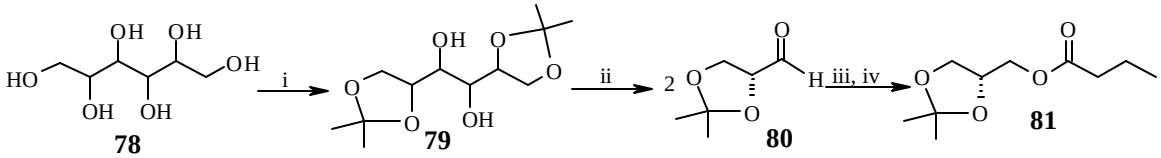
This approach involved the resolution of racemic *a*-acyl ester of *g*-amino propylene glycol (**77**) in the presence of saccharic acid. Thereby both the enantiomers of monobutyrin were synthesized using either chiral **77a** or **77b** as starting material. (**Scheme 23**).



Scheme 23 : i) Saccharic acid ii) Nitrous acid

Bear's approach (1945)[67]

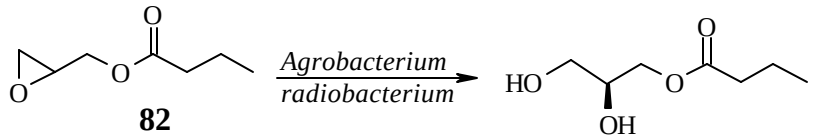
Bear *et al* have used both D and L-mannitol (**78**) as chiral building block for the synthesis of both the isomers of monobutyrin (**Scheme 24**). Thus D-mannitol (**78**) was transformed to 1,2,5,6-diacetone-D-mannitol (**79**) by acetonide protection of the diol with acetone and $ZnCl_2$. The unprotected diol moiety in **79** was oxidatively cleaved with $Pb(OAc)_4$ to produce two molecules of acetonide D-glyceraldehyde (**80**) in a good yield. It was then subjected to Raney-Ni catalyzed hydrogenation followed by acylation with butyryl chloride to afford 1-butyryl-D-acetoneglycerol (**81**). Finally, the deprotection of the diol in **81** with 10% acetic acid or conc. HCl furnished the synthesis of (R)-monobutyrin. The optical purity of the monobutyrin obtained by this method was found to be greater than that of resolution methods. Synthesis of the other isomer of the monobutyrin was achieved starting from L-mannitol.



Scheme 24 : i) Acetone, $ZnCl_2$ ii) $Pb(OAc)_4$, toluene refluxe iii) Raney-Ni, H_2, iv) PrCOCl, pyridine v) 10% acetic acid

Nakamura's approach (1999)[68]

Nakamura *et al* have employed epoxide hydratase of *Agrobacterium radiobacter* strain (DH094) for the resolution of butyryl ester of glycidol (**82**) to obtain the (S)-isomer of monobutyrin (**Scheme 25**).



82

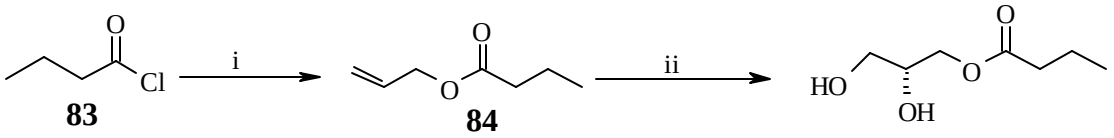
(S)-Monobutyrin **74b**

Scheme 25 :

1.1.2 Present Work:

1.1.2.1 Objective:

Most of the methods described earlier to synthesize (R)-monobutyrin (**74a**) involved resolution of starting materials using chiral materials or enzymes. Only Bear's method constitutes a useful synthetic pathway for obtaining both (R) and (S)-monobutyrin isomers using D and L-mannitol as chiral building blocks. Although the optical purity of (R)-monobutyrin is good, it involves multisteps and thus less attractive. In this context, more practical approach for the synthesis of (R)-Monobutyrin is highly desirable. The objective of the present investigation is to provide a single step synthesis of (R)-(+)-Monobutyrin (**74a**) from allyl butyrate ***via*** Sharpless asymmetric dihydroxylation as a key reaction (**Scheme 26**).



83 **84** (R)-(+)-Monobutyrin **74a**

Scheme 26 : (i) $CH_2=CHCH_2OH$; 82%; (ii) cat. OsO_4, $(DHQD)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3 *t*BuOH:H_2O 20h., 25°C, 96%, $[\alpha]^{25}_D = +0.67^o$ (c = 1.2, C_6H_6).

1.1.3 Results and Discussions:

The present synthetic strategy for the preparation of (R)-Monobutyrin is depicted in **Scheme 26**. Allyl butyrate (**84**) was obtained from the reaction of allyl alcohol with butyryl chloride (**83**). The IR spectrum of **84** showed characteristic bands at 1754 and 1650 cm^{-1} corresponding to the ester carbonyl and C=C functionalities. The ^{1}H-NMR of **84** showed signals appearing at δ 4.57-4.60 (d, *J* = 6Hz, 2H), δ 5.20-5.35 (m, 2H) and δ 5.8-6.1 (m, 1H) respectively, typical of olefinic protons.

Olefin **84** was subjected to OsO_4 catalyzed asymmetric dihydroxylation in the presence of bis-dihydroquinidine-1,4-phthalazine [$(DHQD)_2$-PHAL] ligand. For the AD reaction, $K_3Fe(CN)_6$ and 4-methylmorpholine N-oxide were used as co-oxidants, wherein (R)-(+)-monobutyrine (**74a**) was obtained in excellent yield with moderate optical purity (50% ee).

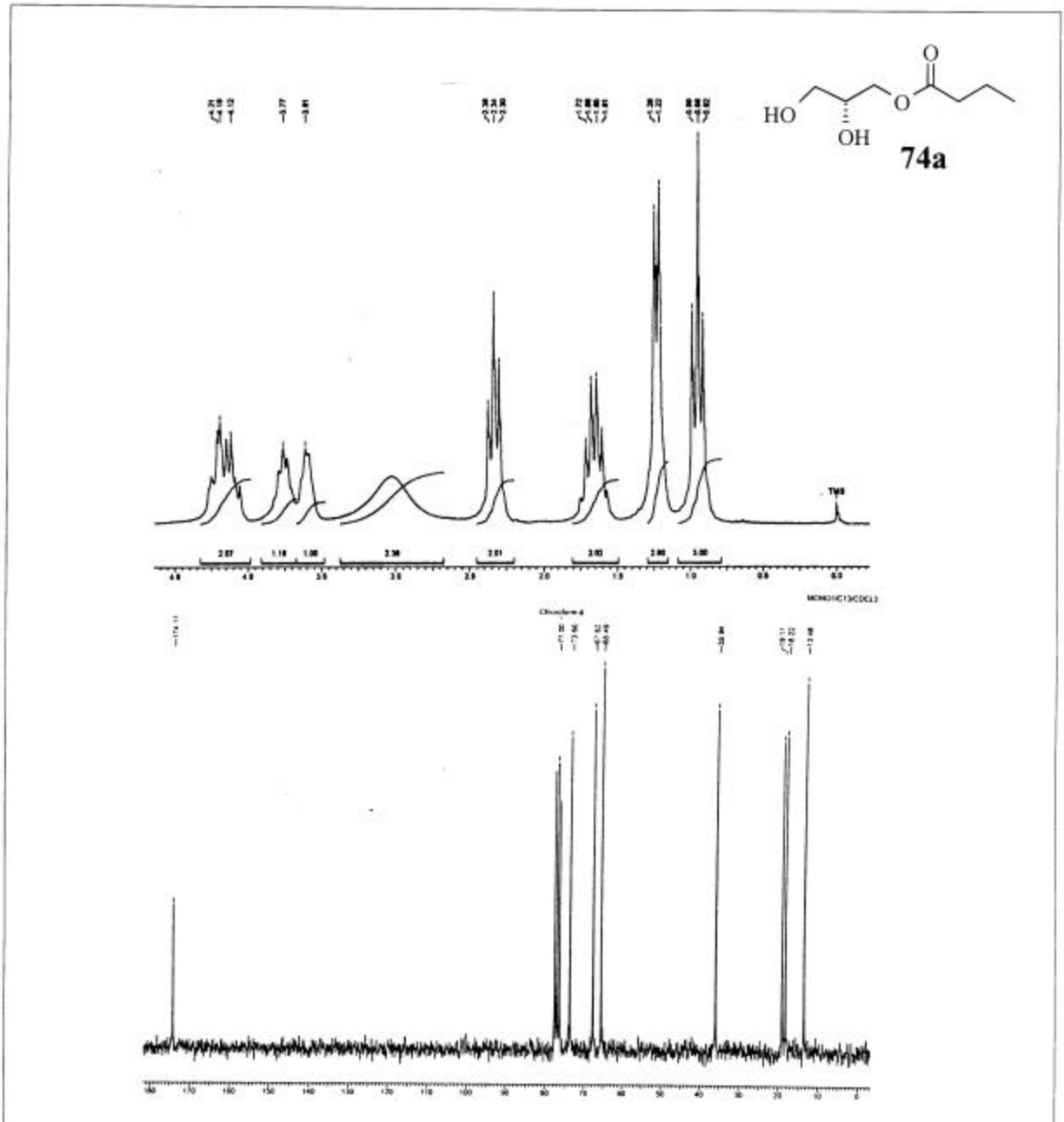


Fig. 10 : ^1H and ^{13}C-NMR spectra of compound 74a

The IR spectrum of **74a** indicated broad peaks at 3443 and 1726 cm^{-1} corresponding to hydroxyl and ester carbonyl groups respectively. Its ^{1}H-NMR indicated characteristic multiplet at δ 3.53-3.87 corresponding to that of CH_2 group attached to n-butyryloxy group (**Fig. 10**). A broad multiplet observed at δ 3.84-3.95 is due to CH-proton. Other two signals at δ 4.32 (s) and 4.12-4.16 (d) are indicative of the presence of hydroxyl and terminal CH_2 groups respectively.

1.1.4 Conclusion:

We have achieved a short and efficient synthesis of (R)-(+)-Monobutyrin (**74a**) employing Sharpless asymmetric dihydroxylation as the key step. As a result **74a** was obtained in a single step with high yield and moderate optical purity. The low optical yield of **74a** is due to Wagner rearrangement[67a] under the basic reaction medium. To overcome this problem we have made use of 4-methylmorpholine N-oxide as co-oxidant instead of $K_3Fe(CN)_6$–K_2CO_3 system. But in both the cases the yield and optical purity of **74a** remained the same.

1.1.5 Experimental Section:

Preparation of Ally butyrate (84)

To a 25ml RB flask charged with butyryl chloride (2.0 g, 18.77 mmol) under nitrogen atmosphere, was added allyl alcohol (1.09 g, 18.77 mmol) under stirring at 0^{o}C. Further stirring of the reaction was continued for 1h (monitored by TLC) and it was quenched with ice cold water (5 ml). The resulting reaction mixture was extracted with diethyl ether (3 x 15 ml). The combined ether layer was washed with 4N $NaHCO_3$ solution followed by water, brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The resulting crude allyl butyrate **84** was then purified by column chromatography packed with silica gel to yield of pure **84** (2.02 g) as a colorless liquid.

Yield	:	84%
bp	:	44 ^{o}C/ 15 mm Hg
IR (neat cm^{-1})	:	3000, 1754, 1650, 1450, 1380, 1240, 1040, 990, 930, 840
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 0.92-0.97 (t, *J* = 8.0 Hz, 3H), 1.62-1.73 (m, 2H), 2.29-2.36 (t, *J* = 8.0 Hz, 2H), 4.57-4.60 (d, *J* = 6.0 Hz, 2H), 5.20-5.35 (m, 2H), 5.8-6.1δ (m,1H)
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 13.19, 18.04, 35.68, 64.47, 117.43, 132.10, 172.79

Preparation of (R)-1-butyrylglycerol (Monobutyrin, 74a)

A 50 ml RB flask was charged with $K_3Fe(CN)_6$ (3.86 g, 11.72 mmol), K_2CO_3 (1.62 g, 11.72 mmol), $(DHQD)_2$-PHAL (61 mg, 0.078 mmol), *t*-BuOH : H_2O (1:1, 20 ml) and stirred at RT for 5 min. It was then cooled to 0^oC and solution of the OsO_4 (79 µl, 0.039 mmol, 0.5 M solution in toluene) followed by olefin **84** (0.5 g, 3.91 mmol) was added under stirring. The resulting reaction mixture was brought to RT and its stirring was continued for further 20 h (monitored by TLC). Reaction was then quenched with sodium sulfite (1.0 g) and extracted with ethyl acetate (3 x 20 ml). Combined organic layer was washed with brine (25 ml), dried over Na_2SO_4 and evaporated under reduced pressure to dryness. The crude product was purified by column chromatography packed with silica gel using ethyl acetate: pet. ether (1:1) to yield pure 0.608 g of (R)-1-Butyrylglycerol (**74a**).

Yield	:	96%
bp	:	101-102^oC/ 6 mm Hg
$[\alpha]_D^{25}$	:	+ 0.67^o (c = 10.2, C_6H_6) {Lit.^{67c} +1.2^0 (c = 10.3, C_6H_6)}
IR (neat, cm^{-1})	:	3443, 3019, 2970, 1726, 1416, 1250, 1208, 916, 750.
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 0.91-0.99 (t, *J* = 7.4 Hz, 3H,), 1.55-1.75 (m, 2H), 2.2-2.4 (t, *J* = 7.9 Hz, 2H), 3.53-3.87 (m, 2H), 3.84-3.95 (m, 1H), 4.12-4.16 (d, *J* = 4.0 Hz, 2H,), 4.32 (s, 2 OH)
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 38.0, 40.13, 49.51, 126.62, 126.92, 128.72, 177.97
MS (m/z, % RI)	:	145 (M^+-OH, 0.2), 131 (54), 114 (14), 102 (52), 89 (70), 87 (45), 71 (100), 60 (5)
Analysis	:	$C_7H_{14}O_4$ requires C, 51.84%; H, 8.70%; found: C, 51.81; H, 8.64%.

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Chiral Cyclic Sulfate Mediated Asymmetric Synthesis of (S)-Xibenolol : A Versatile b-Adrenergic Blocker

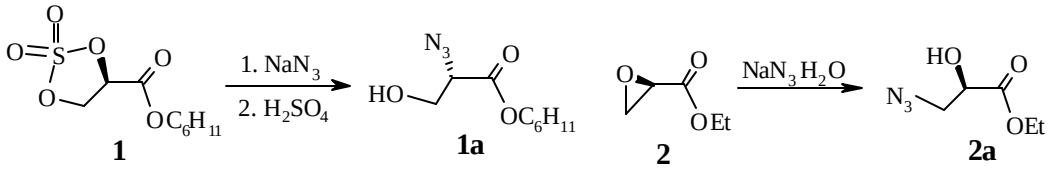
As this chapter is concerned mainly with the application of chiral cyclic sulfites and sulfates, it is necessary to give a brief account of the same in the following section.

2.0.1 Chemistry of Cyclic Sulfites and Sulfates:

The chemistry of cyclic sulfites and sulfates is very old.[1] These are esters of 1,2; 1,3 or 1,4 diols and possess properties similar to epoxides. Unlike epoxide, chemistry of cyclic sulfites and sulfates is less explored in organic synthesis due to lack of an efficient method for their preparation. Several cyclic sulfites and sulfates are of medicinal and biological relevance and of industrially important. The significant role of cyclic sulfates in organic synthesis is realized due to their unique properties such as (i) high reactivity towards nucleophiles compared to epoxide (ii) attack of nucleophile is regiospecific and thereby serving as a protecting group at a second position (iii) nucleophilic opening of five-membered cyclic sulfates generates two contiguous stereocenters.[2] The recent developments in Ru-catalyzed oxidation of the cyclic sulfites with sodium periodate extend the scope of cyclic sulfates in organic synthesis.[3] Cyclic sulfates are important intermediates in obtaining bioactive molecules containing hydroxyl functionality.[2] Chiral cyclic sulfates are easily prepared from the corresponding chiral glycols, which could be obtained from a variety of olefins by OsO_4-catalyzed asymmetric dihydroxylation (see Chapter 1, Section 1.0.1, for AD reaction).

2.0.2 Reactivity of Cyclic Sulfates:

The cyclic sulfates (1, 3, 2-dioxathiolane-2, 2-dioxde) are more reactive than their immediate cyclic sulfites (1, 3, 2-dioxathiolane-2-oxide). The high reactivity of the cyclic sulfate has been attributed to the ring strain and partial double bond character between ring oxygen and sulfur and also due to 2p(O)-3d(S) orbital interaction.[4] The good leaving ability of the $ROSO_3^-$ moiety also enhances the reactivity of cyclic sulfates towards various nucleophilic reagents. The reactivity of cyclic sulfates and epoxides are similar in nature towards nucleophiles but vary in regioselective approach (**Scheme 1**). For example, the reaction of cyclic sulfate **1** with sodium azide in acetone:water system preferentially gave *a*-azido-product (**1a**), whereas epoxyester **2**, under similar reaction conditions gave *b*-azido-product (**2a**).[5]

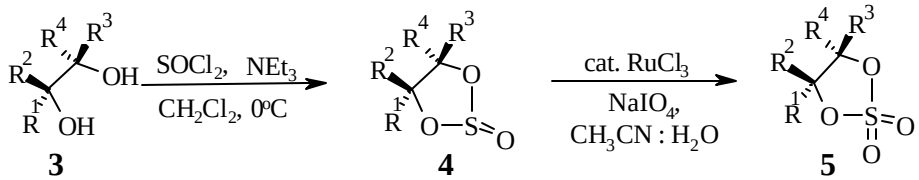


1 **1a** **2** **2a**

Scheme 1 : Reactivity Pattern of Cyclic Sulfate vs Epoxide

2.0.3 Preparation of Cyclic Sulfites and Cyclic Sulfates:

Cyclic sulfites (**4**) are conveniently prepared by condensation of 1, 2-, 1, 3- and 1, 4-diols (**3**) with thionyl chloride (**Scheme 2**).[3,6] In case of acid sensitive substrates, triethyl amine or pyridine is required to scavenge the hydrogen chloride generated in the reaction. It is then transformed to cyclic sulfates (**5**) by Ru-catalyzed oxidation with $NaIO_4$.[2,3]



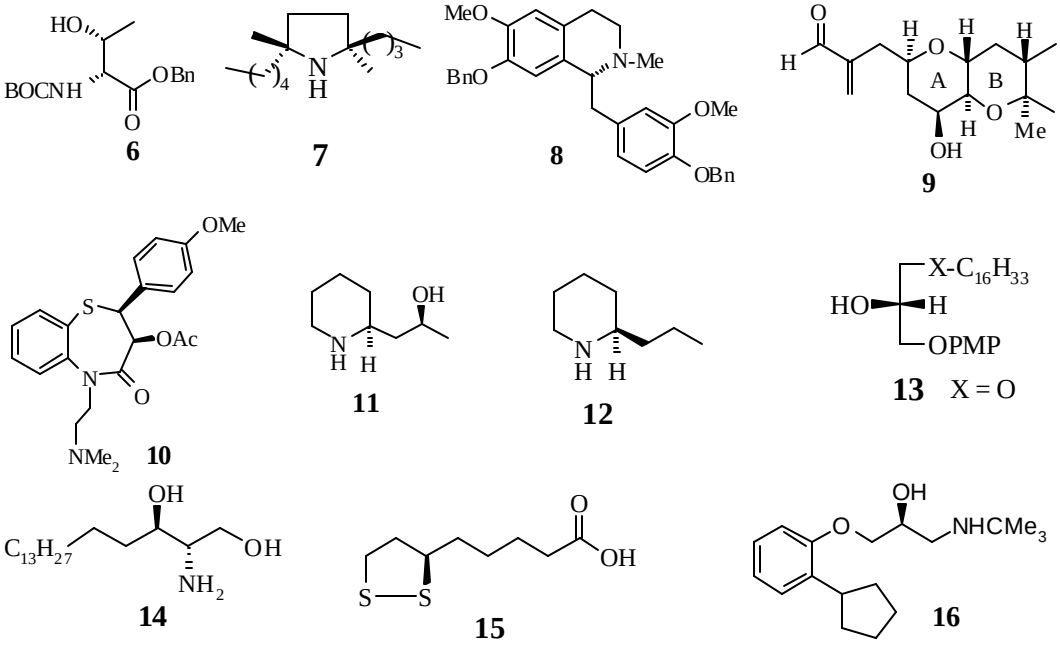
3 **4** **5**

Scheme 2 :

2.0.4 Biological Activities and Applications of Cyclic Sulfites and Sulfates:

The cyclic sulfite derivatives of erythromycin possess anti-microbial properties,[7] while certain cyclic sulfates are found to be bioactive and are anti-fungal, anti-hypertensive or anti-thrombotic agents.[8] Certain five membered cyclic sulfites and sulfates are toxic in nature due to their potential bioalkylating properties. They induce local malignant tumors after subcutaneous injection and are proved to be weak mutagen both *in vivo* and *in vitro*.[9]

Although cyclic sulfites and sulfates are toxic in nature, they act as important chiral synthons in asymmetric synthesis of biologically active compounds such as allo-threonine (**6**),[10] *trans*-2-butyl-5-pentylpyrrolidine (**7**),[11] (R)-reticuline (**8**),[12] *trans-syn-trans* fused AB-bis-pyran ring system of hemibrevotoxine (**9**),[13] (+)-diltiazem (**10**),[14] (+)-sedridine (**11**),[15] coniine (**12**),[15] glycerolipid (**13**),[16] dihydrosphingosine (**14**),[17] (R)-(+)-Lipoic acid (**15**),[18] (S)-penbutolol (**16**)[19] *etc*.

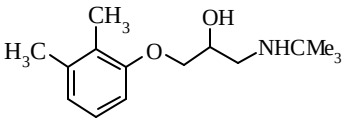


2.0.5 (S)-Xibenolol:

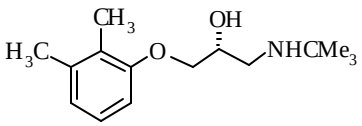
β-Adrenergic blocking agents (β-blockers) are cardiovascular drugs which

exhibit three fundamental functions such as lowering the blood pressure (anti-hypertensive), return of the heart to rhythmic beating (anti-arrhythmics) and the general improvement of the heart muscle tone (cardiotonics).[20] Biochemically, mechanism of action of β-adrenergic system in which the hormonal system provides communication link between the sympathetic nervous system and involuntary muscle.[21] These β-blockers in most of the cases possess a general structure $ArOCH_2CH(OH)CH_2NHR$ and have been used in their racemic form.[22]

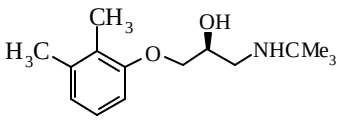
The blocking of β-receptors system reduces the overall activity of sympathetic nervous system. Therefore β-blocking agents are used to increase the life expectancy after heart attack. This property of β-blocking agents is preferentially associated with the (S)-isomer which are much more active (50-500 fold) than (R)-isomers.[21b,c] However, β-adrenergic blocking agents are sold as racemic mixtures in the market. To avoid unnecessary administration or toxicological effect of (R)-isomer, it is essential to use desired (S)-isomer only.[23] (S)-Xibenolol [1-(dimethylethyl)amino)-3-(2,3-dimethylphenoxy)-2-propanol, **17**] is one of the versatile β-adrenergic blocker and exhibits much more potent β-blocking activity than propranolol.[24]



(±)-Xibenolol **17**



(R)-(+)-Xibenolol **17a**

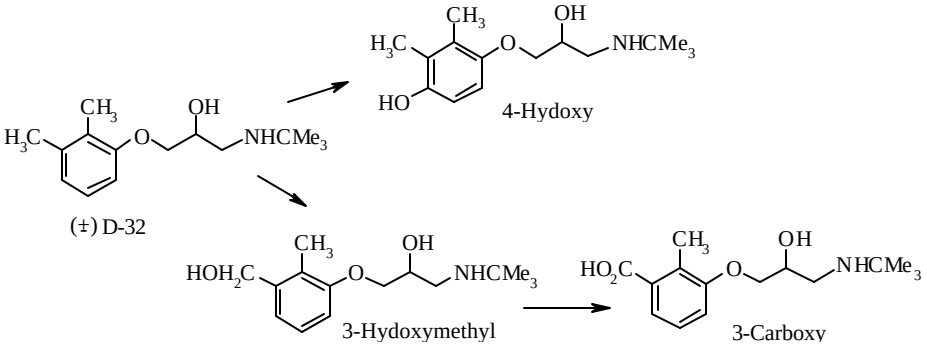


(S)-(-)-Xibenolol **17b**

2.0.6 Pharmacological Effect of Xibenolol in Man:

Honma *et al*[24b] have studied, the stereoselective metabolism of deuterium-labeled psuedoracemic Xibenolol-hydrochloride (D-32) in man by oral administration

(**Scheme 3**). The enantiomeric metabolites identified in plasma and urine were analyzed by gas chromatography-mass spectrometry. It was observed that D-32, biotransformed to 3 major metabolites, 4-hydroxy D-32, 3-hydroxymethyl D-32 and 3-carboxy D-32. The 25% of racemic dose was excreted into the urine as 4-hydroxy D-32, in which 80% of it was derived from (-)-D-32. The 60% of 3-carboxy D-32 in the urine was derived from (+)-D-32. About 1% of the racemic dose was excreted into the urine as unchanged material, in which (+)-D-32 amounted to 3-5 times more than (-)-D-32. The area under the plasma concentration-time curve of (-)-4-hydroxy D-32 was 2.6 times larger than that of (+)-4-hydroxy D-32. The half-lives of (-)-4-hydroxy D-32, (+)-4-hydroxy D-32 and both the enantiomers of D-32 were 3.8, 2.4 and 3h respectively. Thus, a marked difference in the metabolism between (-)-D-32 and (+)-D-32 was found. As 4-hydroxy D-32 and 3-hydroxymethyl D-32 are the active metabolites, the pharmacological effectiveness of D-32 after oral administration is represented by the total amount of (-)-4-hydroxy D-32 and (-)-3-hydroxymethyl D-32.



Scheme 3: Stereoselective metabolism of psuedoracemic Xibenolol-HCl (D-32) in Man

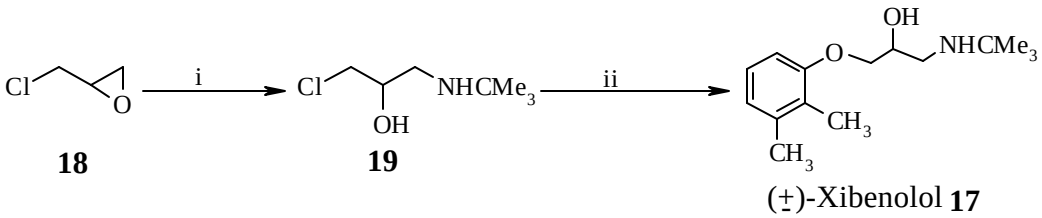
2.0.7 Review of Literature:

Literature search revealed that only few reports are available for the synthesis of Xibenolol (**17**). However, most of the reports are concerned with the synthesis of Xibenolol in their racemic form and only one report highlighted about its asymmetric

synthesis by resolution method.

Suzuki's approach (1968)[25]

It is the first report on synthesis of the Xibenolol in its racemic form (**Scheme 4**). The key intermediate **19** was obtained by the reaction of 1-chloro-2, 3-propyleneoxide (**18**) with *tert* butylamine. It was then alkylated with 2,3-dimethylphenol to afford the (±)-Xibenolol (**17**).

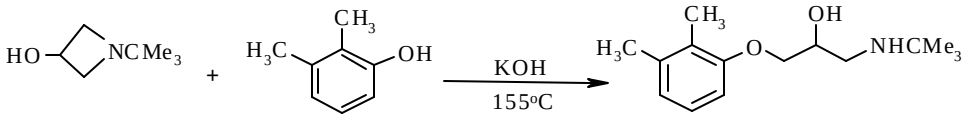


18 **19** (±)-Xibenolol **17**

Scheme 4 : i) 0°C, Me_3CNH_2, ii) KOH, 2,3-dimethylphenol, RT, 12h

Tsukumoto's approach (1971)[26]

Tsukumoto *et al* have synthesized racemic Xibenolol (**17**) by condensation of 1-*tert* butyl-3-azitidinol (**20**) with 2,3-dimethylphenol (**21**) in presence of potassium hydroxide (**Scheme 5**).



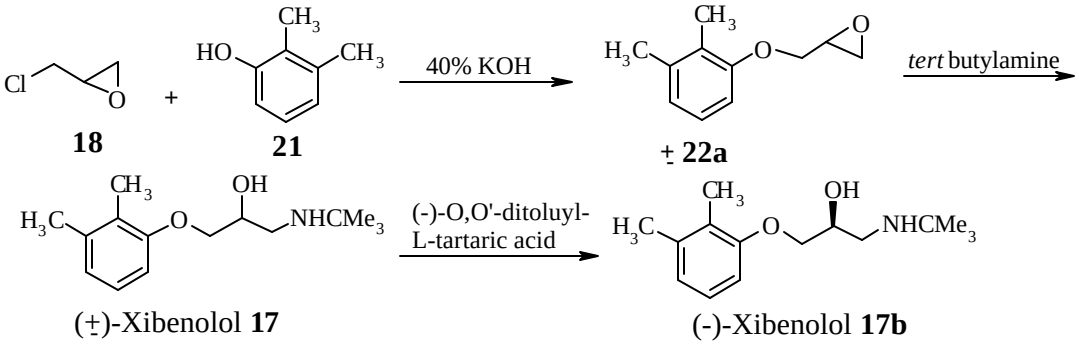
20 **21** (±)-Xibenolol **17**

Scheme 5 :

Honma's approach (1985)[24b]

Honma *et al* have obtained optically active Xibenolol by resolution of its racemate (**Scheme 6**). (-)-O, O'-Ditoluyl-L-tartaric acid was used as a resolving agent and thereby both (+) and (-)-Xibenolol (**17a & b**) were obtained in optically pure form. However, to synthesize the racemic Xibenolol, 1-chloro-2,3-propylene oxide (**18**) condensed with

2,3-dimethylphenol (**21**) in presence of potassium hydroxide. The resulting epoxide **22a** was then treated with *tert* butylamine to get (±)-Xibenolol (**17**).



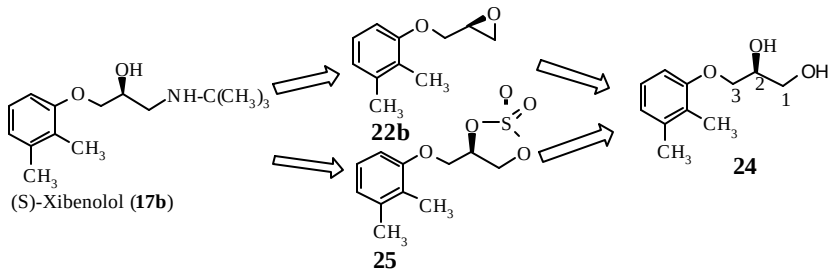
Scheme 6 :

2.0.8 Present Work:

2.0.8.1 Objective:

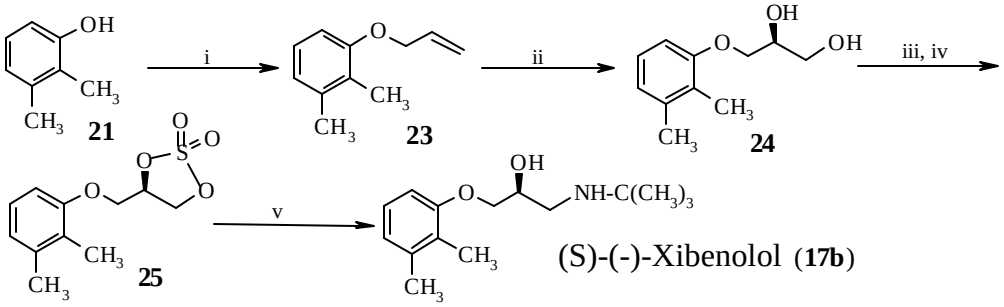
Due to lack of a suitable method for the asymmetric synthesis of Xibenolol and also in view of their high biological activity, its asymmetric synthesis is highly desirable. Consequently, the objective of the present investigation is to synthesize (S)-(-)-Xibenolol

(**17b**) using Sharpless asymmetric dihydroxylation (AD) as a key step.[27] The present strategy for asymmetric synthesis of (S)-(-)-Xibenolol (**17b**) depicted in **Scheme 8** was identified from its retrosynthetic analysis given in **Scheme 7**.



Scheme 7 :Retrosynthetic Analysis of (S)-Xibenolol (17b)

We identified that both the chiral epoxide **22b** and the chiral cyclic sulfate **25** are the intermediates, which could be obtained from the common immediate precursor, chiral diol **24**. We planned to introduce desired chirality in diol **24** at C2 position by Sharpless asymmetric dihydroxylation as presented in **Scheme 8**.



Scheme 7: (i) K_2CO_3, CH_2=$CHCH_2Br$, CH_3COCH_3, 56°C, 12h; 97%; (ii) OsO_4, $(DHQD)_2$-PHAL, K_3FeCN_6, K_2CO_3, *t*BuOH:H_2O, RT, 12h., 94%; $[\alpha]^{25}_D$ = +4.25° (c = 1.0, $CHCl_3$); (iii) $SOCl_2$, Et_3N, DCM, 0°C, 40 min.; 94%, $[\alpha]^{25}_D$ = +24.25° (c = 1.6, $CHCl_3$); (iv) cat. $RuCl_3$, $NaIO_4$, CH_3CN:H_2O, 0°C, 30 min., 86%, $[\alpha]^{25}_D$ = -8.8° (c = 1.0, $CHCl_3$); (v) *t*Bu-NH_2, reflux, 1h, 20% H_2SO_4, Et_2O, 20 h, 90%, $[\alpha]^{25}_D$ = -17.58° (c = 1.0, $CHCl_3$).

2.0.9 Results and Discussion:

As depicted in **Scheme 8**, first step involved alkylation of phenol **21** with allyl bromide in presence of potassium carbonate to afford allyl ether **23** in 95% yield. Subsequently, it was subjected to Os-catalyzed AD in presence of $(DHQD)_2$-PHAL ligand and $K_3Fe(CN)_6/K_2CO_3$ as co-oxidant to give optically active diol **24** in 94% yield. The IR spectrum of diol **24** showed a broad band at 3414-3431 cm^{-1} indicating the presence of

hydroxyl group. Its ^{1}H-NMR spectrum showed the disappearance of olefinic protons (**Fig. 1**). The doublet at δ 3.99-4.02 is due to -CH_2 moiety of ether linkage, while the other -CH_2 group of **24** appeared as multiplet at δ 3.70-3.90. The ^{13}C-NMR spectrum of **24** showed carbon signals at δ 69.28 and 63.80 corresponding to that of -OCH_2- and CH_2-OH carbons respectively. Other characteristic signal appeared at δ 70.68 is due CH carbon at the asymmetric center (**Fig. 1**).

The diol **24** was transformed to chiral cyclic sulfate **25** in two steps. Initially, cyclic sulfite was prepared from the reaction of diol **24** with thionyl chloride followed by its Ru-catalyzed oxidation with $NaIO_4$ afforded cyclic sulfate **25** in 90% overall yield.[2] Its IR spectrum showed absence of hydroxyl groups. Other characteristic IR bands appearing at 1208 and 1374cm^{-1} are indicative of the presence of cyclic sulfate moiety. The ^{1}H-NMR spectrum of **25** showed an overall downfield shift. The characteristic doublet at δ 4.26-4.28 corresponds to CH_2 of the ether linkage (**Fig. 2**), while the other two signals appearing as multiplets at δ 4.78-4.88 and 5.20-5.40 correspond to CH_2 and CH protons of the 5-memebered cyclic sulfate moiety. The ^{13}C-NMR spectrum of **25** indicated an overall downfield shift of the C-signals; wherein the characteristic signals at δ 66.85, 68.62 and 78.10 correspond to O-CH_2, CH_2 and CH carbons respectively (**Fig. 2**).

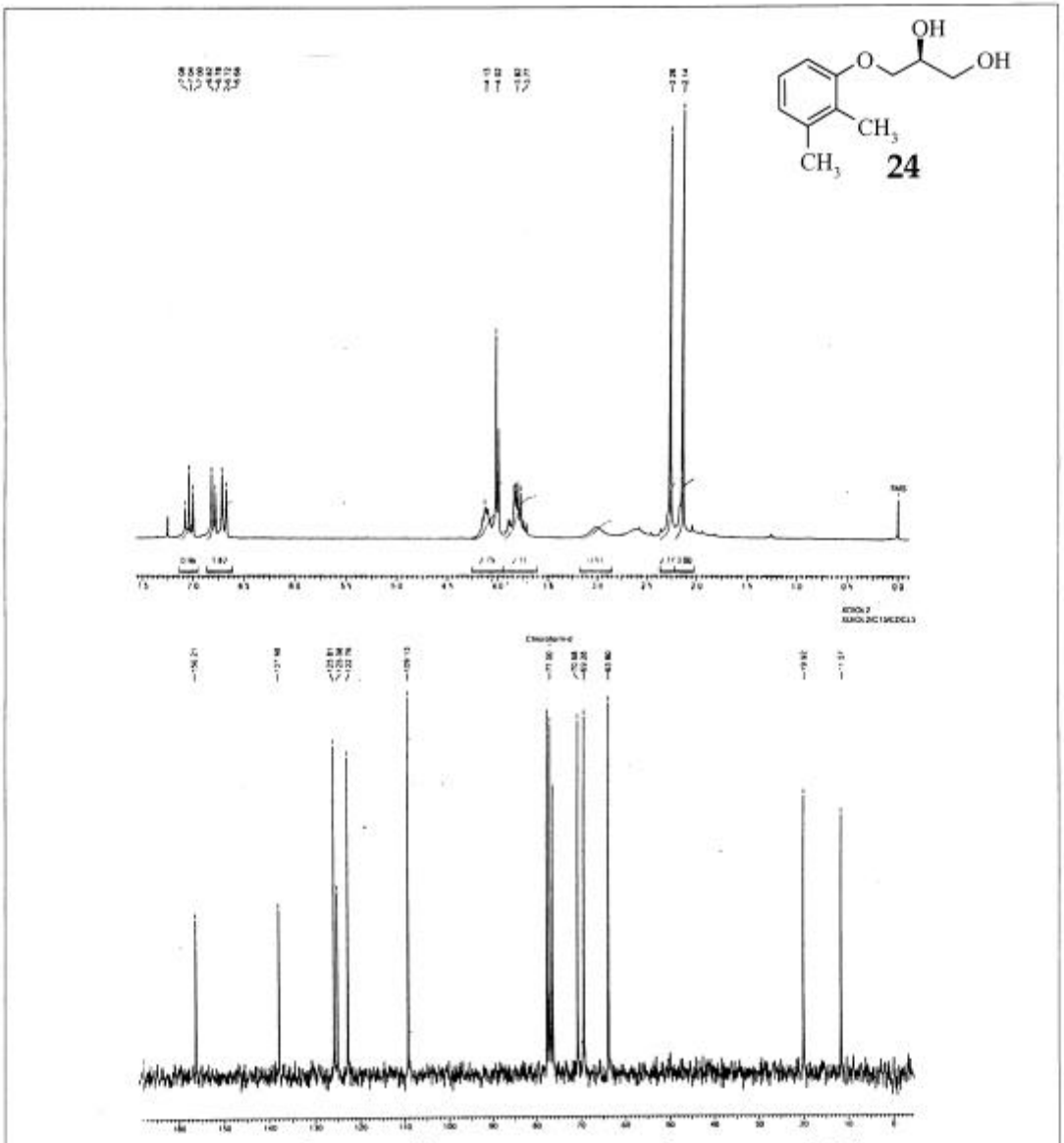


Fig. 1 : ^{1}H and ^{13}C NMR spectra of compound 24

The key intermediate, cyclic sulfate **25**, was then subjected to regioselective ring opening with *tert* butylamine and the resulting sulfated ester moiety was hydrolyzed *in situ* with 20% H_2SO_4 to give (S)-(-)-Xibenolol (**17b**) in 90% yield and 67%ee. The IR spectrum of **17b** showed broad band at 3421-3501 cm^{-1} indicating the presence of OH and NH groups. The ^{1}H-NMR spectrum of **17b** showed an overall upfield shifts (**Fig. 3**). An intense singlet at δ 1.49 indicates the presence of the *tert* butyl-group of *tert* butylamine

part. The two multiplets at δ 3.07-3.36 and 3.90-4.11 correspond to protons of the -OCH_2, CH and N-CH_2 groups respectively. A broad singlet at δ 4.66 indicates the presence of NH

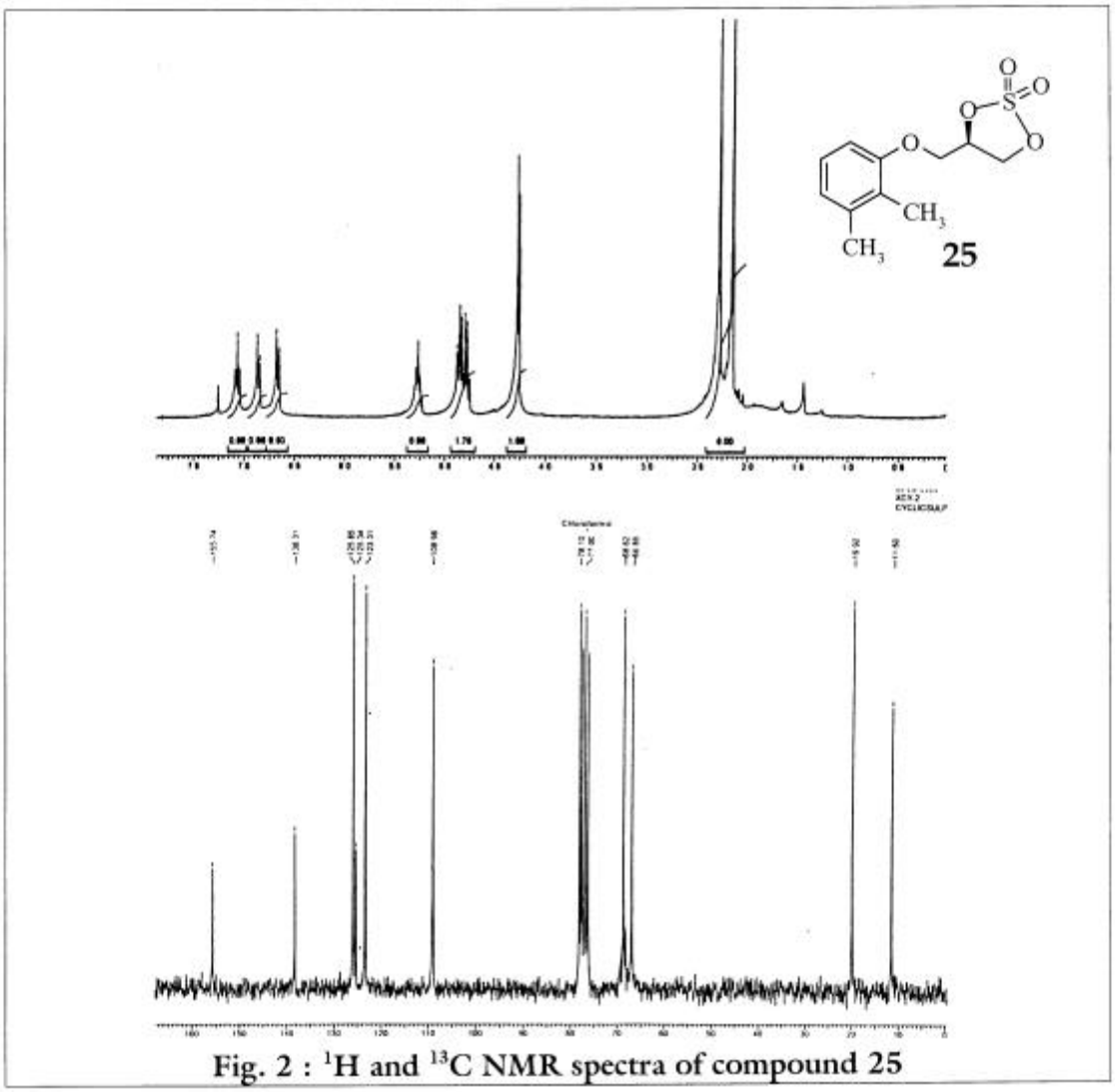


Fig. 2 : ^{1}H and ^{13}C NMR spectra of compound 25

proton. The ^{13}C-NMR spectrum of Xibenolol (**17b**) also indicated the overall upfield shift of the carbon signals. An intense peak appearing at δ 25.61 indicates the presence of methyl groups of *tert* butyl moiety, while its tertiary carbon appears at δ 54.79. The signals at δ 57.48 and 65.79 are due to CH_2 moieties while the other downfield signal at δ 69.91 corresponds to CH carbon at the chiral center (**Fig. 3**).

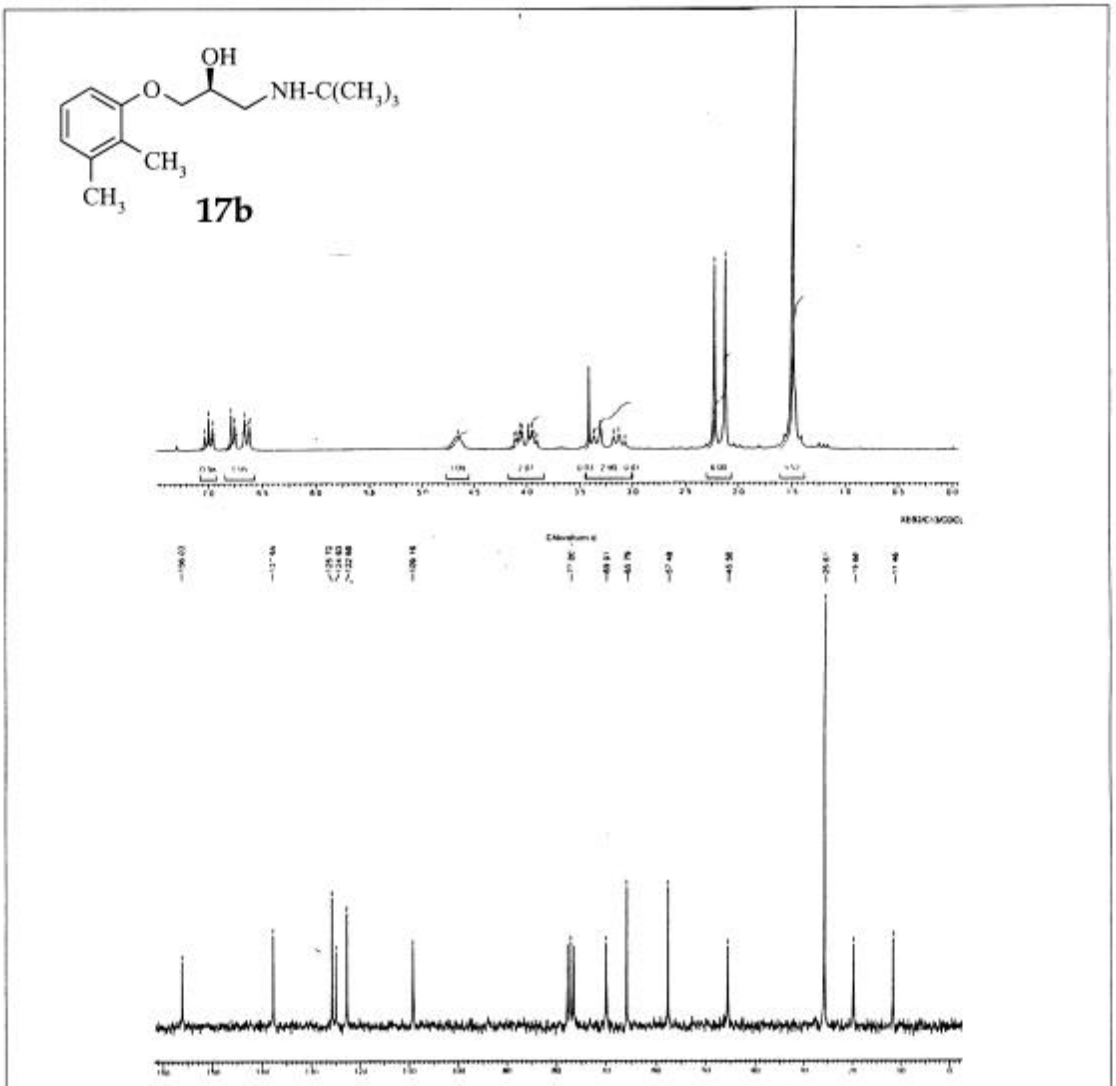
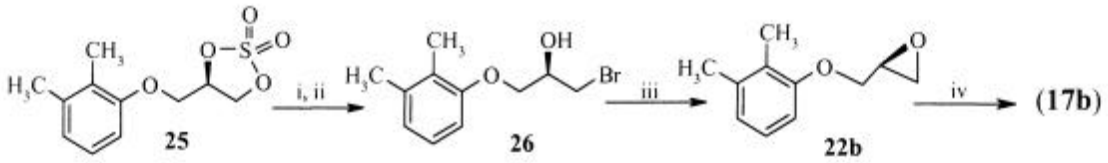


Fig. 3 : ^{1}H and ^{13}C NMR spectra of compound 17b

We envisaged epoxide **22b** as another precursor of (S)-Xibenolol (**17b**). Compound **22b** was prepared from chiral diol **24** *via* its cyclic sulfate **25** which was directly converted into **22b** in a one pot reaction in 54% overall yield (**Scheme 9**).[28] Thus, cyclic sulfate **25** was first treated with anhydrous LiBr in dry THF and then 20% H_2SO_4 and the resulting reaction mixture was diluted with ether. The ether layer was evaporated under reduced pressure to give bromoalcohol **26**, which was then cyclized using potassium carbonate in MeOH to give optically active epoxide **22b**. Its ^{1}H-NMR spectrum showed an overall upfield shift of the protons. The protons of $-CH_2$ of phenolether moiety became

diastereotopic giving rise to ABX pattern in the region δ 3.34-4.23 (**Fig. 4**). The epoxide **22b** was then treated with *tert* butylamine to afford the target molecule (S)-Xibenolol (**17b**) in 80% yield and 55%ee. The spectral data of **17b** was identical in all respect to that of the one discussed as above.



Scheme : 9 (i) LiBr, THF, 45 min.; (ii): 20% H_2SO_4, Et-O-Et, 12h; (iii) K_2CO_3, MeOH, 4h; -6.52° $[\alpha]^{25}_D$ = -6.52° (c = 2.3, $CHCl_3$); 53.3% (overall yield of epoxide) (iv) *tert* butylamine, 80.0%, -$\alpha]^{25}_D$ = -14.12° (c = 1.6, $CHCl_3$)

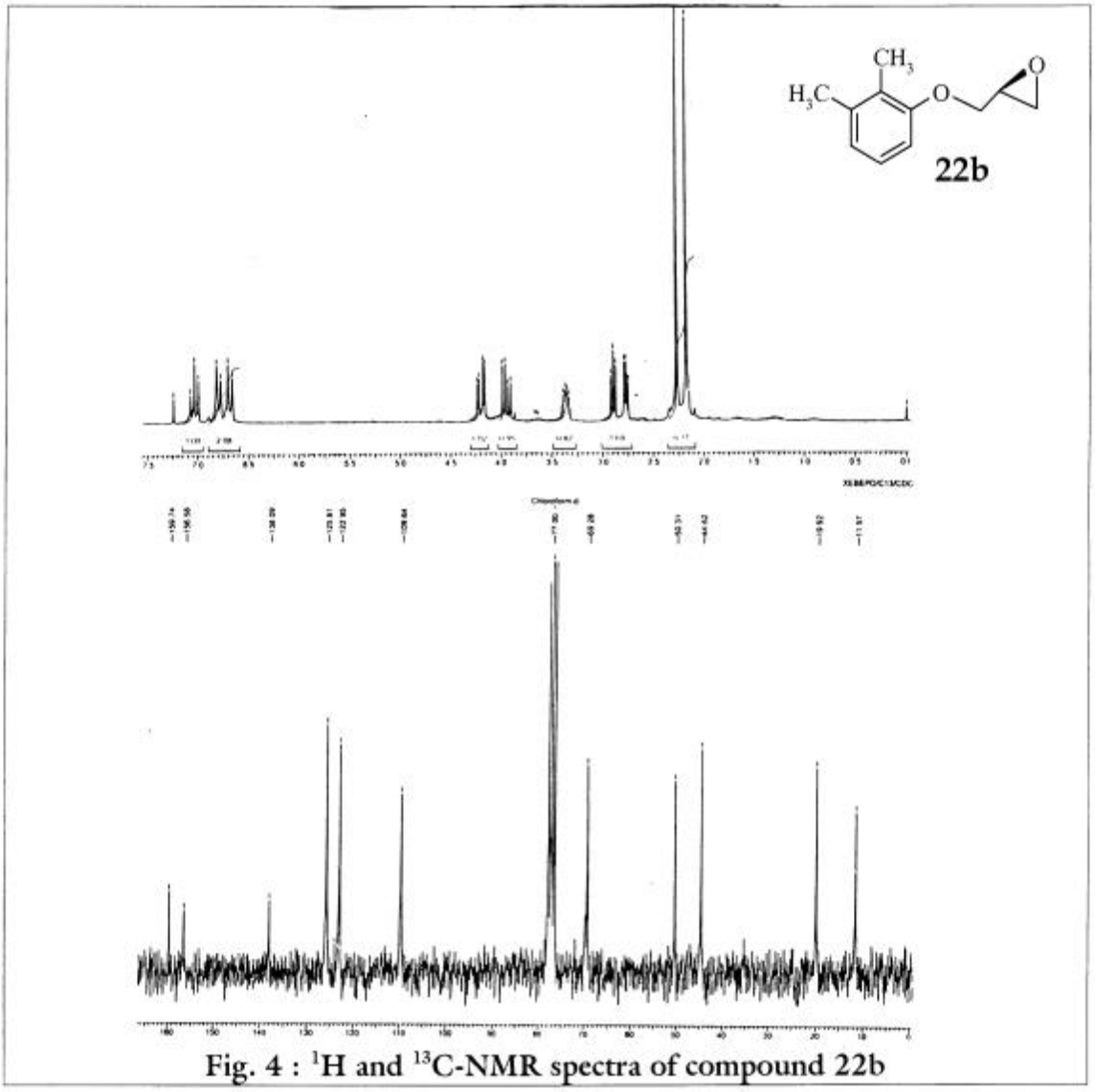


Fig. 4 : ^{1}H and ^{13}C-NMR spectra of compound 22b

2.1.0 Conclusion:

The present synthesis is the first asymmetric synthesis of (S)-Xibenolol (**17b**), achieved by regioselective opening of 5-membered chiral cyclic sulfate (**25**) as well as epoxide **26** with *tert* butylamine. The Sharpless asymmetric dihydroxylation is used as a key reaction for introduction of the chirality into the molecule in presence of bis-dihydroquinidinepthalazine [$(DHQD)_2$-PHAL] as a ligand. Opening of the chiral cyclic sulfate with *tert* butylamine led to 67% ee of (S)-Xibenolol, whereas opening of chiral epoxide **22b** gave only 55% ee of **17b** [determined based on the literature[24b] $[\alpha]_D$ value].

2.1.1 Experimental Section:

Preparation of allyl 2, 3-dimethylphenyl ether (23):

A 25 ml RB flask was charged with 2,3-dimethylphenol (1.22 g, 10 mmol), allyl bromide (1.21 g, 10 mmol), anhydrous K_2CO_3 (2.07 g, 15 mmol) and dry acetone (15 ml). The resulting reaction mixture was refluxed under N_2 for 18h (monitored by TLC). The solution was filtered through sintered funnel and the filtrate was evaporated to dryness. The residue was purified by column chromatography to give pure allyl 2,3-dimethylphenyl ether **23** (1.57 g) as a viscous liquid.

Yield	:	97 %
bp	:	Gum
IR ($CHCl_3$, cm^{-1})	:	2935, 1593, 1503, 1454, 1251, 1224, 1178, 1026, 997, 927, 742
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 2.17 (s, 3H), 2.26 (s, 3H), 4.49-4.51 (d, *J* = 5.0 Hz, 2H), 5.22-5.46 (dd, *J* = 10.0 Hz and *J* = 16.0 Hz, 2H), 5.99-6.13 (m, 1H), 6.66-6.78 (dd, *J* = 8.0 Hz and *J* = 16 Hz, 2H), 6.98-7.02 (m, 1H)
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 11.60, 19.99, 68.94, 109.29, 116.64, 122.38, 125.34, 125.68, 133.80, 137.83, 156.53
MS (m/z, % RI)	:	162 (M^+, 32), 147 (35), 119 (54), 103 (22), 91 (100), 77 (88), 65 (15).
Analysis	:	$C_{11}H_{14}O$ requires C, 81.44; H, 8.70%; found: C, 81.31; H, 8.48%

Preparation of 1-(2,3-dimethylphenoxy)-2,3-dihydroxypropane (24):

A 100 ml RB flask was charged with $K_3Fe(CN)_6$ (3.04 g, 9.26 mmol), K_2CO_3 (1.27 g, 9.26 mmol), $(DHQD)_2$-PHAL (0.096 g, 0.12 mmol) and *t*-BuOH : H_2O (1:1, 20 ml) and stirred for 5 min at RT. It was then cooled to 0°C and a solution of OsO_4 (128 μl, 0.062

mmol, 0.5 M solution in toluene) was added. The resulting reaction mixture was stirred for 5 min and then olefin **23** (0.50 g, 3.08 mmol) was added. The reaction mixture was kept under stirring for 18h at RT (monitored by TLC), quenched with sodium sulfite (1.5 g) and extracted with ethyl acetate (4 x 25 ml). Organic layer was washed with brine (30 ml), dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography (50% ethyl acetate in pet. ether) to yield pure 0.57 g of diol **24** (0.57 g) as a colorless solid.

Yield	:	94 %
mp	:	104-105°C
$[\alpha]^{25}_D$	:	= + 4.25° (c = 1.0, $CHCl_3$)
IR ($CHCl_3$, cm^{-1})	:	3431-3414, , 3019, 2400, 1639, 1215, 751
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 2.14 (s, 3H), 2.27 (s, 3H), 2.55 (bs, OH), 3.0 (bs, OH), 3.77-3.90 (m, 2H), 3.99-4.02 (d, *J* = 6.0 Hz, 2H), 4.05-4.2 (m, 1H), 6.68-6.72 (d, *J* = 8.0 Hz, 1H), 6.78-6.82 (d, *J* = 8.0 Hz, 1H), 7.00-7.08 (t, *J* = 8.0 Hz, 1H)
^{13}C-NMR (50 MHz, $CDCl_3$)	:	11.57, 19.92, 63.80, 69.28, 70.68, 109.13, 122.76, 125.08, 125.81, 137.98, 156.21
MS (m/z, % RI)	:	196 (M^+, 18), 165 (0.2), 147 (8), 123 (100), 107 (40), 91 (12), 77 (8), 65 (0.2)
Analysis	:	$C_{11}H_{16}O_3$ requires: C, 67.32; H, 8.22%; found: C, 67.21; H, 8.16%.

Preparation of cyclic sulfate 25:

[A] To a solution of diol **24** (0.454 g, 23.16 mmol) and triethylamine (0.37 g, [0.5 ml], 37.0 mmol) in CH_2Cl_2 (5 ml) at 0°C was added freshly distilled thionyl chloride (0.31

g [~0.2 ml], 26.6 mmol) under N_2 atmosphere and reaction kept for 45 min under stirring (monitored by TLC). The reaction mixture was quenched with ice cold water (10 ml) and extracted with ethyl acetate (3 x 25 ml). The ethyl acetate layer was washed with dil. HCl, saturated $NaHCO_3$ solution, followed by brine (25 ml) and dried over Na_2SO_4. Evaporation of solvent under reduced pressure to yielded light yellow liquid, which upon purification by column chromatography gave pure cyclic sulfite (0.525 g) as a viscous liquid.

Yield	:	94 %
bp	:	Gum
$[\alpha]^{25}_D$	:	+ 24.25° (c = 1.6 $CHCl_3$)
IR ($CHCl_3$, cm^{-1})	:	3020, 2400, 1584, 1470, 1402, 1319, 1277, 1208, 1125, 972, 750,
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 2.13 (s, 3H), 2.27 (s, 3H), 3.95-4.15 (m, 2H), 4.47-4.54 (dd, *J* = 4.0 Hz and *J* = 6.0 Hz, 1H), 4.79-4.87 (dd, *J* = 4.0 Hz and *J* = 6.0 Hz, 1H), 5.21-5.37 (m, 1H), 6.63-6.67 (d, *J* = 8.0 Hz, 1H), 6.81-6.84 (d, *J* = 6.0 Hz, 1H), 7.01-7.1 (t, *J* = 8.0 Hz, 1H)
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 11.36, 19.79, 66.69, 68.44, 78.08, 108.81, 123.11, 125.62, 125.71, 138.10, 155.60
MS (m/z, % RI)	:	242 (M^+, 34), 159 (0.5), 145 (10), 135 (45), 121 (100), 105 (62), 91 (44), 77 (25), 65 (0.2)
Analysis	:	$C_{11}H_{14}O_2S$ requires C, 54.53; H, 5.82, S, 13.23%; found C, 54.51; H, 5.69, S, 13.18%.

[B] To a solution of the above cyclic sulfite (0.525 g, 2.17 mmol) in CH_3CN: H_2O mixture (9:1, 5ml) at 0°C was added solid sodium periodate (0.831 g, 3.90 mmol) and $RuCl_3$ (9 mg, 0.043 mmol). The reaction mixture was stirred for 30 min at 0°C (monitored by TLC) and filtered through a pad of celite. The resulting solution was evaporated

under reduced pressure to give solid cyclic sulfate **25**. It was purified by column chromatography to afford pure **25** (0.480 g) as a colorless solid.

Yield	:	86 %
mp	:	230-231 ^{o}C
$[\alpha]^{25}_{D}$	:	- 8.8^{o} (c = 1.0, $CHCl_3$)
IR ($CHCl_3$, cm^{-1})	:	3020, 2926, 2431, 1584, 1444, 1347, 1291, 1208, 1097, 944, 819, 750, 652
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 2.15 (s, 3H), 2.28 (s, 3H), 4.26-4.28 (d, *J* = 4.0 Hz, 2H), 4.78-4.88 (m, 2H), 5.2-5.35 (m, 1H), 6.65-6.68 (d, *J* = 6.0 Hz, 1H), 6.84-6.87 (d, *J* = 6.0 Hz, 1H), 7.0-7.1 (t, *J* = 8.0 Hz, 1H)
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 11.50, 19.92, 63.85, 68.62, 78.10, 108.98, 123.31, 125.34, 125.85, 138.31, 155.74
MS (m/z, % RI)	:	258 (M^+, 32), 162 (12), 159 (20), 145 (30), 135 (78), 122 (72), 105 (65), 91 (60), 77 (100), 65 (0.5)
Analysis	:	$C_{11}H_{14}O_5S$ requires: C, 51.15; H, 5.46, S, 12.41%; found: C, 51.19; H, 5.39, S, 12.61%.

Preparation of epoxide (22b)[28]

[A] To a solution of cyclic sulfate **25** (0.639 g, 2.47 mmol) in dry THF (15 ml) was added anhydrous LiBr (0.851g, 9.90 mmol) and the resulting reaction mixture stirred for 40 min until the disappearance of cyclic sulfate (monitored by TLC) at RT. After completion of the reaction, the resulting solution was diluted with diethyl ether (40 ml) and treated with 20% H_2SO_4 (40 ml) to hydrolyze the sulfated salt. The reaction was kept under stirring for 4h (monitored by TLC) and then layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 25ml) and the combined organic layer was washed

with 4N $NaHCO_3$ solution, brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure to give crude bromoalcohol **26** (0.484 g) as a viscous liquid.

[B] The crude bromoalcohol **26** (0.484 g, 1.87 mmol) was dissolved in MeOH (20 ml) and treated with anhydrous K_2CO_3 (1.031g, 7.47 mmol) at 0°C. Resulting reaction mixture was then stirred for 2.0 h (monitored by TLC) and quenched by addition of the saturated solution of NH_4Cl (10 ml). The crude product was then extracted with DCM (4x20), washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure to give epoxide **22b**. It was then purified by column chromatography packed with silica gel to give pure epoxide **22b** (0.235 g) as oil.

Yield	:	53.3 % (over all yield of epoxide)
bp	:	Gum
$[\alpha]^{25}_D$	:	- 6.52° (c = 2.3, $CHCl_3$)
IR ($CHCl_3$, cm^{-1})	:	3020, 2926, 2431, 1584, 1444, 1347, 1291, 1208, 1097, 944, 819, 750, 652
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 2.17 (s, 3H), 2.27 (s, 3H), 2.75-2.79 (dd, *J* = 2.0 Hz and *J* = 2.0 Hz, 1H), 2.87-2.92 (t, *J* = 6.0 Hz, 1H), 3.34-3.39 (m, 1H), 3.91-3.99 (dd, *J* = 4.0 Hz and *J* = 6.0 Hz, 1H), 4.16-4.23 (dd, *J* = 4.0 Hz and *J* = 4.0 Hz, 1H), 6.66-6.71 (d, *J* = 10.0 Hz, 1H), 6.78-6.82 (d, *J* = 8.0 Hz, 1H), 7.0-7.08 (t, *J* = 8.0 Hz, 1H)
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 11.57, 19.92, 44.62, 50.31, 69.28, 109.64, 122.95, 125.81, 138.09, 156.58, 159.74
Analysis	:	$C_{11}H_{14}O_2$ requires: C, 74.13; H, 7.92%; found C, 74.41; H, 7.69%.

Preparation of (S)-Xibenolol (17b) *via* opening of cyclic sulfate with *tert* butylamine:

Cyclic sulfate **25** (0.185 g, 0.72 mmol) was dissolved in dry THF (5 ml) under nitrogen atmosphere and treated with an excess of freshly distilled *tert* butylamine (1.06 g, (1.5 ml), 14.0 mmol). The resulting mixture was refluxed for 1h (monitored by TLC) and cooled to RT. It was then diluted with diethyl ether (30 ml) and subjected to hydrolysis of sulfated ester *in situ* with 20% H_2SO_4 (15 ml). Further reaction kept under stirring at RT for 12h (monitored by TLC) and then organic layer was separated from the aqueous layer. The aqueous layer was extracted with ethyl acetate (3 x 20 ml) and the combined organic layers were washed with 4N $NaHCO_3$. It was again washed with water, brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure to give (S)-Xibenolol. It was purified by column chromatography to afford pure (S)-Xibenolol (0.160 g) as a colorless solid in 90% yield and 67% ee.

mp	:	57 ^oC
$[\alpha]^{25}_D$	:	-17.58^o (c = 1.0, $CHCl_3$); {Lit.[24b] $[\alpha]^{25}_D$ = –25.4^o (c = 1.0, $CHCl_3$)}
IR ($CHCl_3$, cm^{-1})	:	3421-3501, 2926, 2928, 2856, 1649, 1580, 1458, 1375, 1263, 1194
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 1.49 (s, 9H), 2.12 (s, 3H), 2.23 (s, 3H), 3.07-3.36 (m, 3H), 3.90-4.11 (m, 2H), 4.66 (bs, 1H), 6.62-6.66 (d, *J* = 8.0 Hz, 1H), 6.75-6.78 (d, *J* = 6.0 Hz), 6.96-7.03 (t, *J* = 8.0 Hz, 1H)
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 11.49, 19.66, 25.61, 45.50, 57.48, 65.79, 69.91, 109.16, 122.69, 124.93, 125.70, 137.69, 156.03
MS (m/z, %RI)	:	233 (M^+-H_2O, 40), 218 (65), 161 (100), 147 (20), 122 (55), 112 (70), 91 (10), 77 (5).
Analysis	:	$C_{15}H_{25}NO_2$ requires: C, 71.67; H, 10.02; N, 5.57%; found: C, 71.51; H, 9.89%; N, 5.51%.

Preparation of (S)-Xibenolol (17b) *via* opening of epoxide (22b) with

tert butylamine:

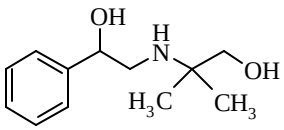
The epoxide **22b** (0.21 g, 1.18 mmol) was dissolved in *tert* butylamine (6 ml) and refluxed in presence of water (0.2 ml, 11.11 mmol) for 40 min (monitored by TLC). Excess of *tert* butylamine was removed under reduced pressure and the resulting solid was purified by column chromatography to give pure (S)-Xibenolol (**17b**) (0.236 g) of as a colorless solid [see vide supra for spectral data].

Yield	:	80.0 %
$[\alpha]^{25}_{D}$	:	-14.12^{0} (c = 1.6, $CHCl_3$) {Lit.[24b] -25.4^{o} (c = 1.6, $CHCl_3$)}

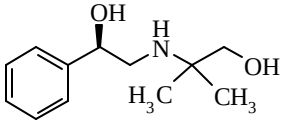
Asymmetric Synthesis of Novel Non-steroidal Anti-inflammatory Agent, (R)-Fepradinol

2.1.2 Introduction:

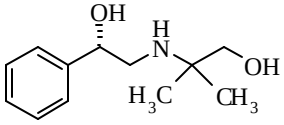
Fepradinol, 1-phenyl-2-(α,α'-dimethylethanolamino)ethanol (**27**), acts as an effective non-steroidal anti-inflammatory agent and tested in its racemic form.[29] It is especially very active against acute inflammations and not chronic inflammations. Unlike other anti-inflammatory agents, it does not show inhibitory effect on prostaglandin-E2 biosynthesis. It also helps to prevent diarrhea in rat. As it possesses structural similarity to that of β-adrenergic blocking agents.[21] It is also useful as diuretic and anti-arrhythmic agents.



(±)-Fepradinol, **27**



(R)-(-)-Fepradinol, **27a**



(S)-(+)-Fepradinol, **27b**

2.1.3 Anti-inflammatory Action of Fepradinol[29a]:

The anti-inflammatory action of fepradinol was compared with that of indomethacin and other non-steroidal anti-inflammatory drugs to investigate its mechanism. It is observed that fepradinol under identical conditions is found to be more effective than indomethacin and piroxicam. The role of fepradinol has proven to be most effective in inhibiting the early and late stages of the concanavalin-A induced edema in rats. However, indomethacin and piroxicam inhibit only the late stage. Both fepradinol and indomethacin are useful to prevent carrageenin-induced inflammation, diarrhea and also suppress the number of leukocytes in rats. Unlike indomethacin, fepradinol did not

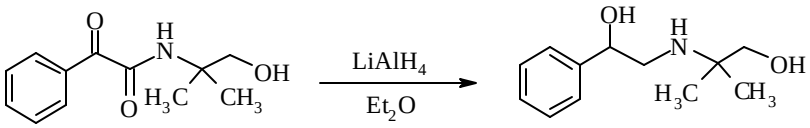
inhibit the prostaglandin-E2 biosynthesis but shows potent inhibitory activity on the acute inflammation in rodents. On increased vascular permeability in the skin, fepradinol (25 mg/kg p.o.) is the only compound that can inhibit the inflammatory actions induced by the three chemical mediators injected (histamine, serotonin and bradykinin).

2.1.4 Review of literature:

Literature search revealed that there are only three reports available on the synthesis of fepradinol (**27**) all of them dealing with the racemic form. Most of the reports emphasized on their biological activity studies, however not much attention has been focused on its asymmetric synthesis. The following reports deal with the synthesis of racemic form of fepradinol (**27**).

Sonnenbichler's approach (1962)[30]

Sonnenbichler *et al* have synthesized the racemic form of fepradinol (**27**) in a single step. The reduction of pheylglyoxylic-[2-hydroxy-1,1'-dimethyl-ethyl] amide (**28**) with $LiAlH_4$ afforded (±)-fepradinol in 65% yield (**Scheme 10**).

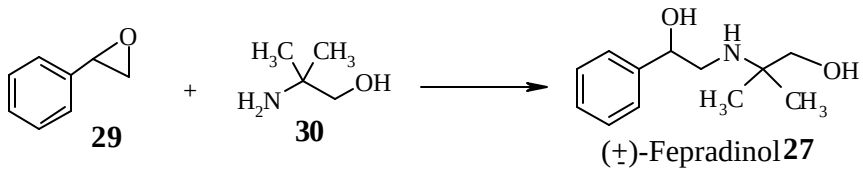


28 (±)-Fepradinol **27**

Scheme 10:

Staibano's approach (1970)[31]

Staibano has patented a process for the production of racemic fepradinol. The condensation of styrene epoxide (**29**) with 2-amino-2-methyl-1-propanol (**30**) yielded (±)-fepradinol in a single step (**Scheme 11**).

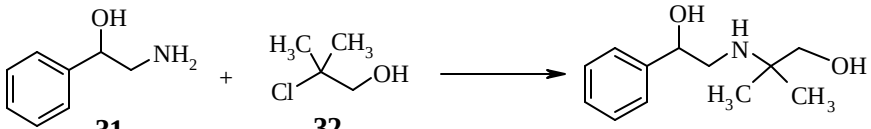


29 **30** (±)-Fepradinol **27**

Scheme 11 :

Staibano's approach (1972)[32]

Staibano has reported another single step procedure for the synthesis of racemic form of fepridinol. In this approach they condensed 2-amino-1-phenylethanol (**31**) with chloroethanol (**32**) to furnish racemic (±)-fepradinol (**Scheme 12**) in a single step.



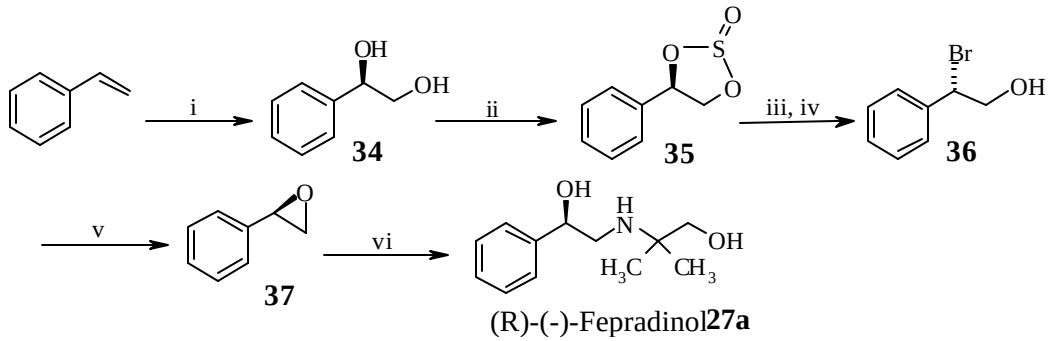
31 **32** (±)-Fepradinol **27**

Scheme 12 :

2.1.5 Present Work:

2.1.5.1 Objective:

Literature search revealed that although there are few reports available on the synthesis of (±)-fepradinol, not much attention has been focused on its asymmetric version. Thus in view of this, the objective of the present work is to synthesize (R)-(-)-fepradinol (**27a**) using Sharpless asymmetric dihydroxylation as a key reaction. Since fepradinol is isostructurally related to that of β-adrenergic blockers and only (-)-isomer is representing the total cardiovascular activity,[21,33] its asymmetric synthesis is highly desirable. Our strategy for asymmetric synthesis of (R)-fepradinol (**27a**) is depicted in **Scheme 13**.

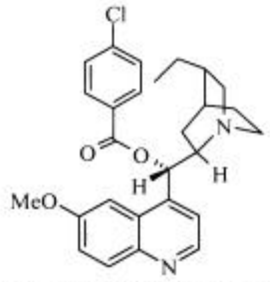


Scheme 13: (i) cat. OsO_4, (-)-DHQD-CLB, $K_3Fe(CN)_6$, K_2CO_3, *t*BuOH:H_2O, RT, 12h, 92%; $[\alpha]^{25}_D$ = -32.3° (c = 1.04, EtOH); (ii) $SOCl_2$, Et_3N, CH_2Cl_2, 0°C, 40min, 78%; $[\alpha]^{25}_D$ = +30.35° (c = 1.12, EtOH); (iii) cat. $RuCl_3$, $NaIO_4$, CH_3CN : H_2O, 0°C, 30min; (iv) anhyd. LiBr, THF, RT, 45min, 20% H_2SO_4, Et_2O, 4h, 58%; (v) K_2CO_3, MeOH, -10°C 2h; 90%, $[\alpha]^{25}_D$ = -17.4° (c = 0.14, $CHCl_3$); (vi) HO-CH_2-$C(CH_3)_2$-NH_2, 90°C, 3h, 55%, $[\alpha]^{25}_D$ = -19.25° (c = 0.5, EtOH);

2.1.6 Result and Discussion:

Sharpless asymmetric dihydroxylation is employed as a key reaction for introduction of the chirality using DHQD-CLB (**33**) as ligand to obtain optically active diol **34** in 92% yield and 80% ee.[34] Its IR spectrum showed a broad band at 3400-3560 cm^{-1}, indicating the presence of hydroxyl group in diol **34**. Its ^{1}H-NMR spectrum showed three characteristic broad signals. Among these, signal appearing at δ 3.64 corresponds to

protons of CH and CH_2 groups, while signals at δ 4.03 and 4.73 are indicative of two OH groups of diol **34**. The ^{13}C-NMR spectrum of diol **34** showed characteristic signals at δ 67.70 and 74.50 corresponding to CH_2 and benzylic CH carbons respectively (**Fig. 5**).



(-)-Hydroquinidine 4-chlorobenzoate (DHQD-CLB, **33**)

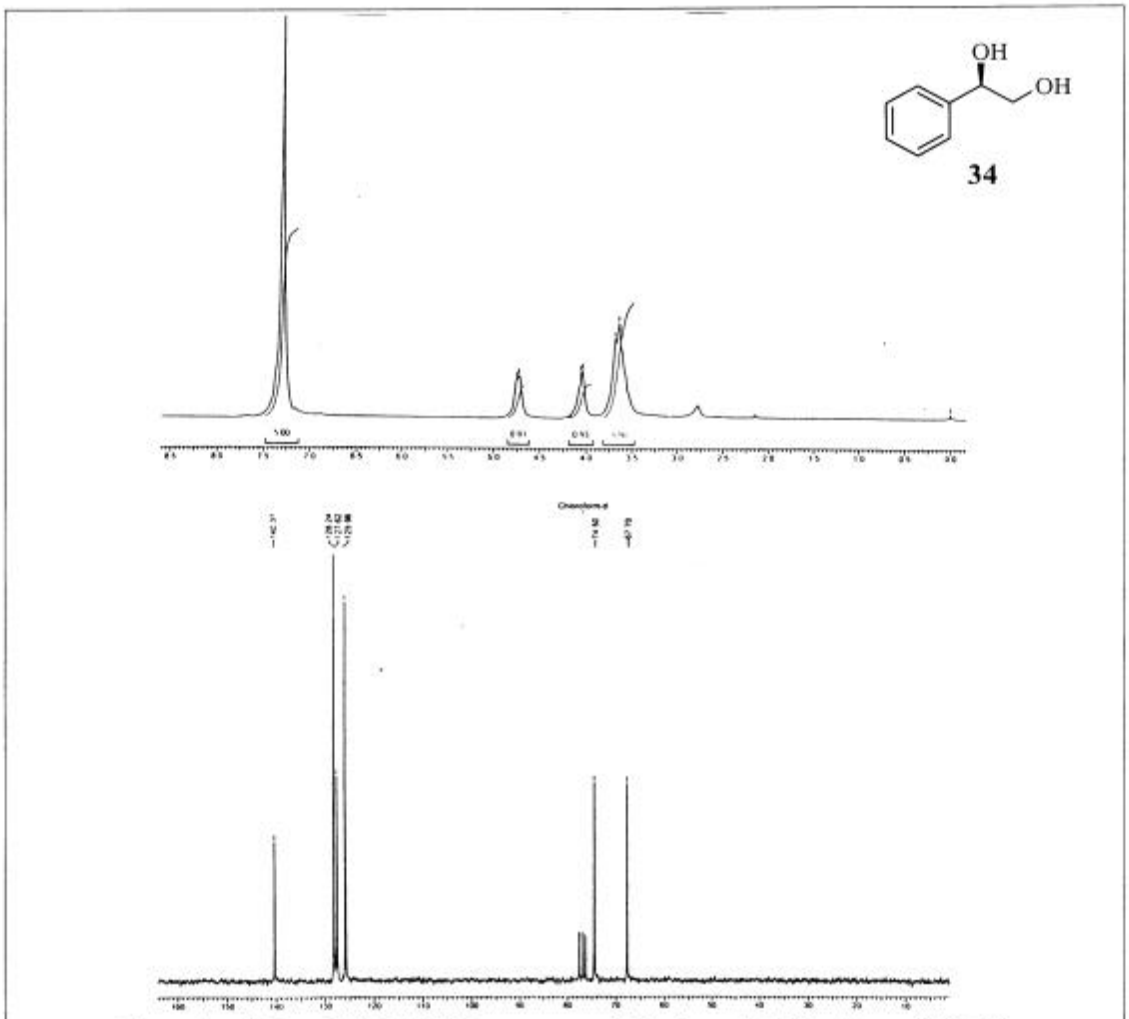


Fig. 5 : ^{1}H and ^{13}C-NMR spectra of 1-phenyl-1,2-ethanediol 34

The diol **34** was then transformed to chiral cyclic sulfite **35** in 78% yield with freshly distilled thionyl chloride in the presence of triethylamine. The IR spectrum of **35** showed absence of hydroxyl groups and the appearance of characteristic band at 1209 cm^{-1} indicative of the presence of cyclic sulfite moiety. The ^{1}H-NMR spectrum of **35** clearly indicates cyclic sulfite formation, wherein the proton signals due to CH and CH_2 groups appearing in duplicate at δ 4.14-7.94. These proton signals in duplicate are due to the diastereisomers, emerging from the adjacent chiral center and sulfoxide. The ^{13}C-NMR spectrum also indicated the characteristic diastereomeric relationship and thereby the CH and CH_2 carbons appeared in duplicate at δ 71.16 (73.29) and 85.30 (80.71) respectively.

When cyclic sulfite **35** was subjected to Ru-catalyzed oxidation with sodium periodate, isolation of the corresponding cyclic sulfate was unsuccessful. This is probably due to the less stable nature of cyclic sulfate. The failure to obtain cyclic sulfate turned our attention to convert diol **34** to chiral epoxide **37**. Consequently, the cyclic sulfate was generated *in situ* and opened with LiBr to afford bromoalcohol **36**.[28] The opening of cyclic sulfate with LiBr was found to be regiospecific, wherein bromide attacks at the benzylic position. This product was further confirmed by comparing the ^{1}H-NMR spectrum of its other regioisomer.

The IR spectrum of **36** showed characteristic bands at 760 and 3400 cm^{-1} indicating the presence of C-Br and hydroxyl moieties respectively. The ^{1}H-NMR spectrum of **36** is characteristic in the region δ 3.91-5.09. The protons in CH_2 group are diastereotopic and hence the compound **36** produced ABX pattern of 12 lines (**Fig. 6**).

The bromoalcohol **36**, was then cyclized with anhydrous potassium carbonate to give epoxide **37** in 90% yield and 76% ee. Its IR spectrum showed absence of hydroxyl group, while other bands at 800, 875 and 1250 cm^{-1} are indicative of epoxide moiety. The

^{1}H-NMR spectrum of **37** showed the typical ABX pattern of 12 lines at δ 2.77-316. Its ^{13}C-NMR spectrum showed the characteristic signal at δ 51.89 due to CH-carbon at chiral center, whereas the adjacent CH_2 carbon appeared at δ 50.68 **(Fig. 7)**.

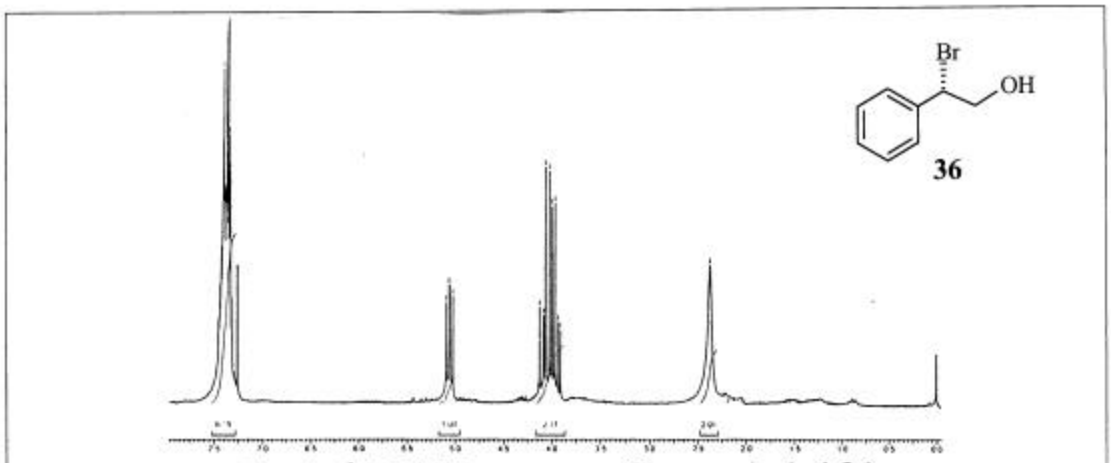


Fig. 6 : ^{1}H-NMR spectrum of bromoalcohol 36

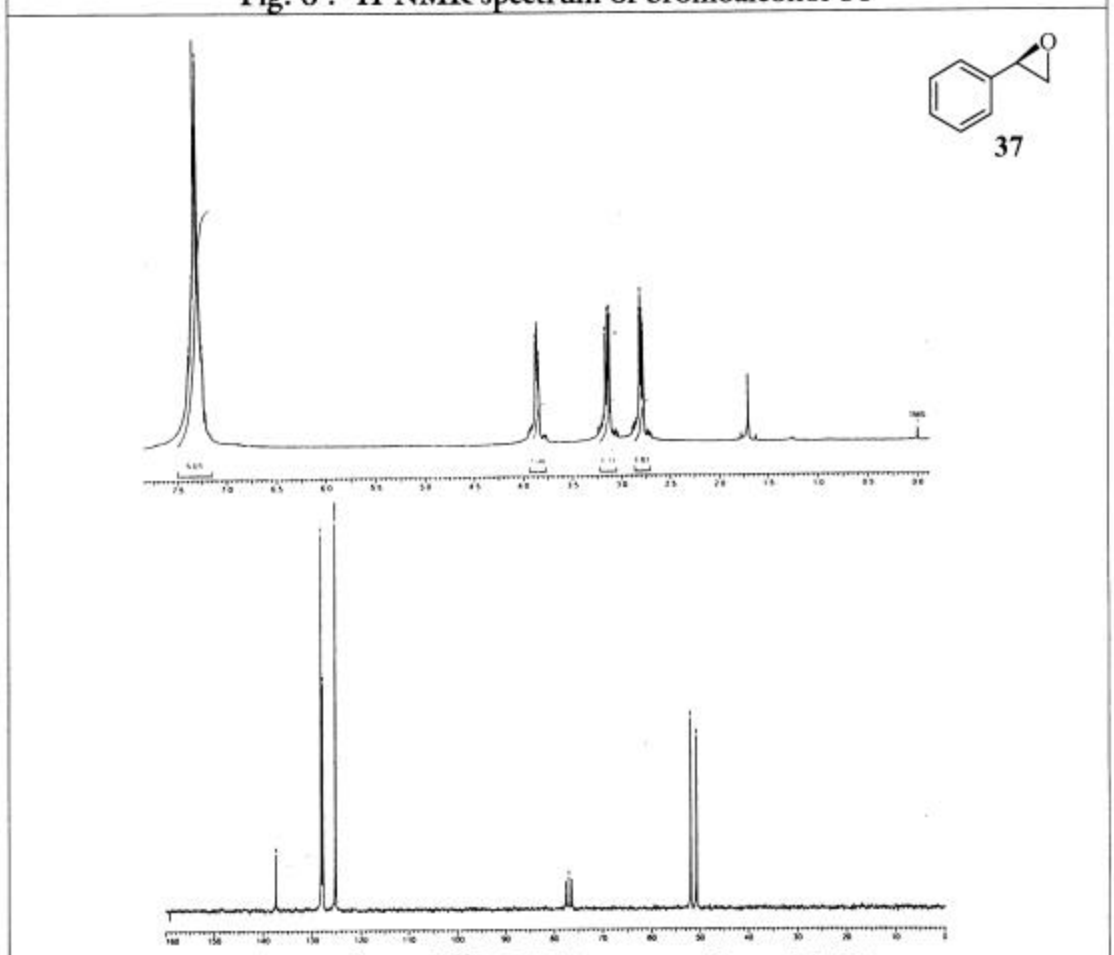
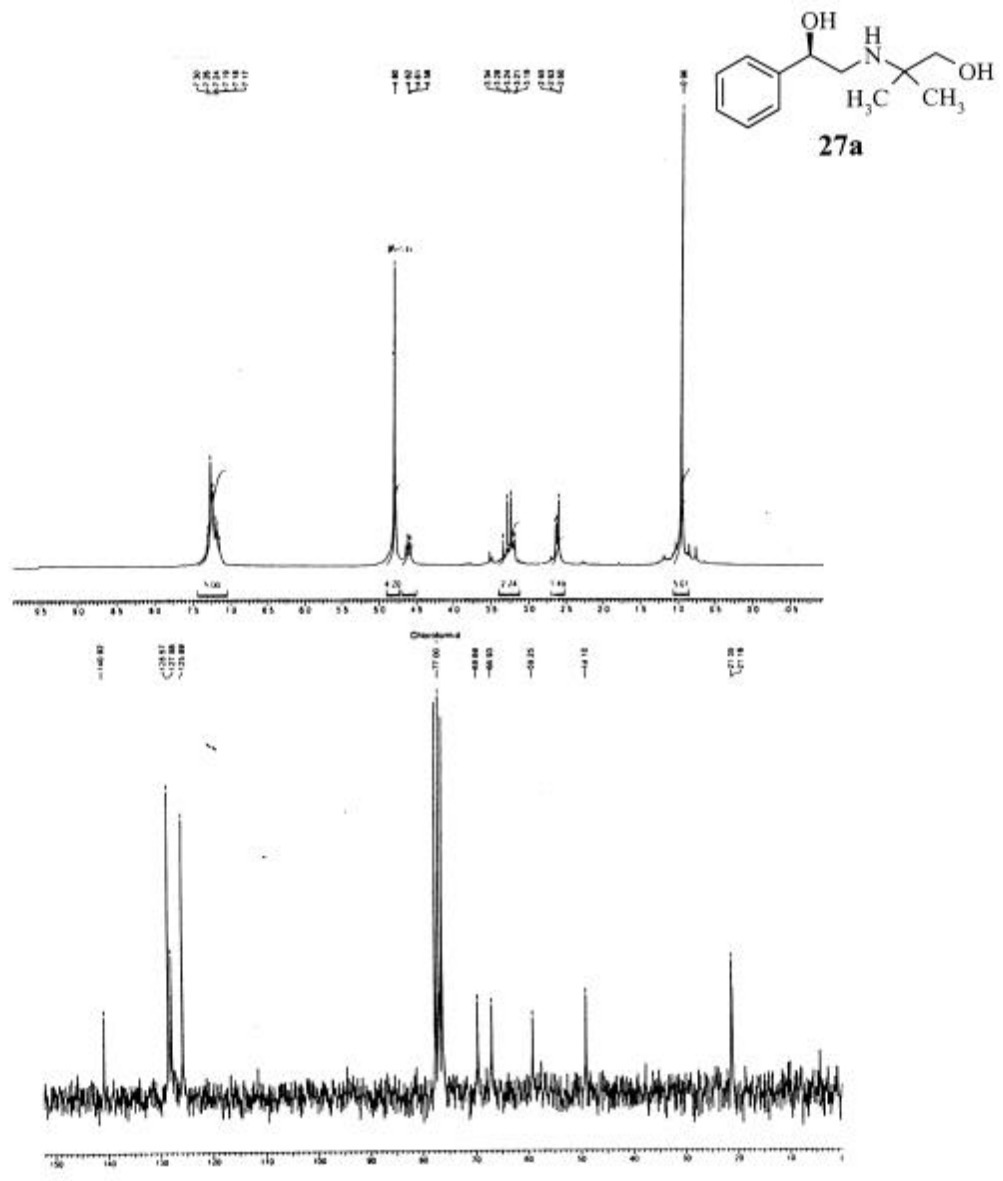


Fig. 7 : ^{1}H and ^{13}C-NMR spectra of epoxide 37

The chiral epoxide **37** was then subjected to regiospecific ring opening with 2-amino-2-methyl-1-propanol (**30**) to afford the optically active (R)-(-)-fepradinol (**27a**). The presence of bulky dimethyl group in aminoalcohol **30** has influenced its attack from the less hindered side of the epoxide **37**. Also the high nucleophilicity of the amino group than hydroxyl moiety in aminoalcohol (**30**) is critical in opening of the epoxide **37** chemoselectively, thus explaining the regiochemistry in the final product **27a**. Its IR



27a

Fig. 8 : ^{1}H and ^{13}C-NMR spectra of (R)-Fepradinol (27a)

spectrum showed a broad band at 3445 cm^{-1} indicating the presence of OH and NH moieties. Its ^{1}H-NMR spectrum showed strong signal at δ 0.96 indicating the presence of two CH_3 groups. The multiplets appearing at δ 2.60-2.65, 3.19-3.44 and 4.48-4.62 are due to CH_2-OH, CH_2NH and CH moieties respectively (**Fig. 8**). The ^{13}C-NMR spectrum showed different carbon signals for the two methyl groups appearing at δ 21.16 and 21.35 respectively. Besides, signals appearing at δ 49.10 and 66.93 are due to CH_2NH and CH_2-OH carbons respectively. The signals at δ 59.25 and 69.69 are due to -$C(Me)_2$- and benzylic CH carbons respectively (**Fig. 8**).

2.1.7 Conclusion:

The present method constitutes the first asymmetric synthesis of (R)-Fepradinol (**27a**) and is achieved starting from easily and cheaply available styrene. The Sharpless asymmetric dihydroxylation has been employed for the induction of chirality into the molecule. The activation of the chiral diol **34** was attempted by transforming it into a reactive intermediate, cyclic sulfate. However this cyclic sulfate was found to be unstable and therefore it was generated *in situ* and transformed to optically active epoxide **37**. The optical purity of the chiral epoxide was 76% based on the comparison of its optical rotation reported in the literature.[35] Opening of the epoxide **37** with 2-amino-2-methy-1-propanol (**30**) resulted in the formation of (R)-(-)-Fepradinol (**27a**).

2.1.8 Experimental Section:

Preparation of (R)-(-)-1-phenyl-1, 2-ethanediol (34)

A 100 ml RB flask was charged with $K_3Fe(CN)_6$ (18.98 g, 57.69 mmol), K_2CO_3 (7.96 g, 57.69 mmol), (-)-hydroquinidine-4-chlorobenzoate (0.178 mg, 0.38 mmol) and *t*-BuOH : H_2O (1:1, 50 ml) and stirred for 5 min at RT. It was then cooled to 0°C and solution of OsO_4 (390 µl, 0.19 mmol; 0.5 M solution in toluene) was added. After 5 min, styrene (2.0 g, 19.23 mmol) was added and the resulting reaction mixture kept under stirring for 12h at RT (monitored by TLC), quenched with sodium sulfite (2.5 g) and extracted with ethyl acetate (4 x 30 ml). Organic layer was washed with brine (2 x 25 ml), dried over Na_2SO_4 and evaporated under reduced pressure. The crude product obtained was purified by column chromatography (50% ethyl acetate in pet. ether) to yield pure diol **34** (2.44 g) as white solid .

Yield	:	92 %
mp	:	66-67°C
$[\alpha]^{25}_D$	:	-32.3° (c = 1.04, EtOH) {Lit.[34] $[\alpha]^{25}_D$ = -39.7° (c = 4.33, EtOH)}
IR ($CHCl_3$, cm^{-1})	:	3560-3400, 3020, 2945, 2880, 2846, 1608, 1496, 1460, 1360
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 3.64 (bs, 3H), 4.03 (bs, OH), 4.73 (bs, OH), 7.29 (s, 5H)
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 67.70, 74.50, 125.96, 127.62, 128.24, 140.37
MS (m/z, %RI)	:	138 (M^+, 7), 107 (100), 91 (6), 79 (78), 76 (77)
Analysis	:	$C_8H_{10}O_2$ requires: C, 69.55; H, 7.29%; found: C, 69.23; H, 6.96%.

Preparation of chiral cyclic sulfite (35)

[A] To a solution of diol **34** (1.0 g, 7.25 mmol) and pyridine (0.69 g, 8.70 mmol) in dry CH_2Cl_2 (5 ml) at 0^oC was added freshly distilled thionyl chloride (0.61 ml, 8.33 mmol) under N_2 atmosphere and the reaction mixture kept under stirring for 40 min (monitored by TLC). Resulting reaction mixture was quenched by adding ice cold water (25 ml) and extracted with ethyl acetate (3 x 30 ml). Ethyl acetate layer was washed with dil. HCl, dil. $NaHCO_3$ solution, followed by brine (25 ml) and dried over anhydrous Na_2SO_4. Ethyl acetate was removed under reduced pressure and crude product purified by column chromatography to give a pure cyclic sulfite **35** (1.04 g) as colorless viscous liquid.

Yield	:	78 %
bp	:	Gum
$[\alpha]^{25}_D$	:	$+30.35^o$ (c = 1.12, EtOH)
IR ($CHCl_3$, cm^{-1})	:	3020, 2400, 1584, 1470, 1402, 1319, 1277, 1209, 1125, 972, 750.
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 4.40-4.46 (m, 1H), 4.70-4.78 (m, 1H), 5.36-5.44 (m, 1H), 7.40 (s, 5H)
^{13}C-NMR (50 MHz, $CDCl_3$)	:	71.16, 85.31, 126.40, 127.28, 128.79, 129.16, 133.72, 134.34
Analysis	:	$C_8H_8O_3S$ requires: C, 52.16; H, 4.37, S, 17.40%; found: C, 52.13; H, 4.13, S, 16.92%.

[B] To a solution of cyclic sulfite **35** (0.533 g, 2.89 mmol) in CH_3CN: H_2O mixture (9:1, 5.5 ml) at 0^oC was added solid $NaIO_4$ (0.93 g, 4.35 mmol) and $RuCl_3$ (12 mg, 0.058 mmol). The reaction mixture was stirred for 5 min at 0^oC and immediately filtered through a pad of mixture of silica and celite directly into the solution of LiBr (1.00 g, 11.57 mmol) in dry THF (20 ml). The resulting solution was stirred at RT for 45 min and diluted with

20% H_2SO_4 (10 ml) and 30 ml diethyl ether. Further stirring of the reaction mixture was continued for 4h and then two layers were separated. The aqueous layer was extracted with diethyl ether (3 x 25 ml) and the combined ether extracts was washed with 4N $NaHCO_3$ solution, water, brine and dried over anhydrous Na_2SO_4. The ether layer was evaporated under reduced pressure. The crude product was purified by column chromatography packed with silica gel to give pure bromoalcohol **36** (0.337 g) as colorless viscous liquid.

Yield	:	58 %
bp	:	Gum
IR (neat, cm^{-1})	:	3400, 1490, 1445, 1210, 1190, 1060, 760, 690
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 3.91-4.00 (dd, J_{AB} = 12.0 Hz, J_{AX} = 6.0 Hz, $1H_A$), 4.03-4.13 (dd, J_{BA} = 12.0 Hz, J_{BX} = 8.0 Hz, $1H_B$), 5.03-5.09 (dd, J_{XA} = 6.0 Hz, J_{XB} = 8.0 Hz, $1H_X$), 7.34-7.41 (m, 5H)
MS (m/z, %RI)	:	200 (M^+-1, 0.6), 121 (31), 104 (100), 91 (35), 77 (29)
Analysis	:	C_8H_9BrO: requires: C, 47.79, H, 4.51, Br, 39.74%; found: C, 47.76, H, 4.23, Br, 39.47%.

Preparation of (S)-phenyloxirane (37)

The bromoalcohol **36** (0.150 g, 0.75 mmol) was dissolved in MeOH (8 ml) and treated with solid K_2CO_3 (0.411 g, 2.98 mmol) at 0°C. The resulting reaction mixture was stirred for 2h (monitored by TLC) and the reaction was quenched by addition of saturated solution of NH_4Cl (10 ml). Then aqueous solution was extracted with CH_2Cl_2 (4 x 20 ml), washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give epoxide **37**. It was then purified by column chromatography packed with silica gel to give pure epoxide **37** (0.081 g) as a colorless liquid.

Yield	:	90 %
bp	:	75°C (3 mm Hg)
$[\alpha]^{25}_D$	:	-19.5° (c = 0.14, $CHCl_3$); {Lit[36] $[\alpha]^{25}_D$ -24.6° (c = 1.34, $CHCl_3$)}
IR (neat, cm^{-1})	:	3010, 1475, 1390, 1310, 1250, 1200, 1070, 1020, 980, 875, 800,
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 2.77-2.81 (dd, J_{AB} = 8.0 Hz, J_{AX} = 4.0 Hz, $1H_A$), 3.11-3.16 (dd, J_{BA} = 8.0 Hz, J_{BX} = 6.0 Hz, $1H_B$), 3.83-3.87 (dd, J_{AX} = 4.0 Hz, J_{BX} = 6.0 Hz, $1H_X$), 7.32 (s, 5H).
^{13}C-NMR (50 MHz, $CDCl_3$)	:	50.68, 51.89, 125.19, 127.80, 128.13,137.39
Analysis	:	C_8H_8O requires: C, 79.97, H, 6.71%; C, 79.78, H, 6.67%.

Preparation of (R)-(-)-Fepradinol (27a)

The solution of epoxide **35** (0.092 g, 0.77 mmol) and 2-amino-2-methyl-1-propanol (0.068 g, 0.77 mmol) in 5 ml RB flask was heated at 90°C for 3h (monitored by TLC). The resulting gummy reaction mixture cooled to RT and purified by column chromatography packed with silica gel to give pure (R)-Fepradinol (0.094 g) as a colorless solid.

Yield	:	55 %
mp	:	142-143 °C, (Lit.[30] for (±)-Fepradinol = 139-141 °C)
$[\alpha]^{25}_D$	:	-19.25° (c = 0.5, EtOH)
IR (nujol, cm^{-1})	:	3445, 3421, 3400, 3385, 3355, 3019, 1618, 1408, 1215, 760, 669
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 0.96 (s, 6H), 2.60-2.65 (m, 2H) 3.19-3.34 (m, 2H), 4.58-4.62 (m, 1H), 7.24 (m, 5H)
^{13}C-NMR (50 MHz, $CDCl_3$)	:	21.16, 21.35, 49.10, 59.25, 66.93, 69.69, 125.89, 127.98, 128.57, 140.92.
MS (m/z, %RI)	:	192 (M^+-OH, 0.6), 178 (58), 160 (56), 102 (99), 91 (41), 77 (100)
Analysis	:	$C_{12}H_{19}NO_2$ requires: C, 63.97; H, 8.50, N, 6.22%; found: C, 63.81; H, 8.39, N, 6.18%

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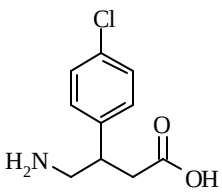
Synthesis of (R)-(-)-Baclofen, a Novel $GABA_B$ Receptor Agonist, *via* Ru(II)-BINAP Catalyzed Asymmetric Hydrogenation

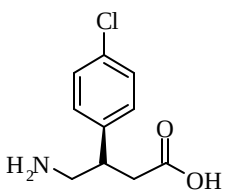
3.0.1 Introduction:

Baclofen [*g*-amino-*b*-(*p*-chlorophenyl)butyric acid, **1**] is a derivative of *g*-aminobutyric acid (GABA). It plays an important role as an inhibitory neurotransmitter in central nervous system (CNS) of mammalians.[1] The simple amino acid has two major receptor subtypes, $GABA_A$ and $GABA_B$. These receptors play a distinct role in central and peripheral nervous system through ion-channel regulation.[2] The overall physiological effects are transmission inhibitions, mediated, pre and post-synaptically by $GABA_A$ sites and pre-synaptically by $GABA_B$ sites. However, baclofen is the only potent and selective $GABA_B$ agonist known so far against bicuculline receptor.[3] In contrast to that of simple GABA, baclofen is the most lipophilic and can penetrate to blood/brain barrier. Consequently, baclofen helps to reduce the excitatory effect of active compounds such as benzodiazepine, barbiturates, *etc*.[4]

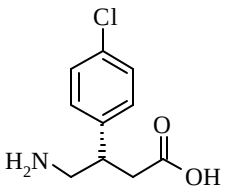
The deficiency of GABA is associated with diseases that exhibit neuromuscular dysfuntions such as epilepsy, Huntigton, Parkinsons' disease, *etc*.[5] Baclofen is one of the promising drugs in treatment of the paroxysmal pain of trigeminal neuralgia[6] as well as spasticity of spinal without influencing the sedation.[7]



(±)-Baclofen **1**



(R)-(-)-Baclofen **1a**



(S)-(+)-Baclofen **1b**

3.0.2 The Pharmacology of Baclofen:

Bowery *et al* have demonstrated that baclofen helps to decrease the neurotransmitter release in mammalian central nervous system by action at the GABA-receptor. This effect is associated with the stereospecificity of baclofen, the (R)-(-)-baclofen (**1a**) isomer being greater than 100-fold more active in producing neural depression than (S)-(+)-baclofen (**1b**) isomer. This effect is clearly marked by the study indicated by radioactive labeling technique, wherein the tritium labeled nor-adrenaline was selected for their neurotransmitter study. It was demonstrated that (S)-(+)-stereoisomer of baclofen failed to reduce the neurotransmitter effect of ^{3}H-adrenaline. However, the effect of (R)-(-)-isomer is comparable to that of racemic form. Similar effect was analyzed with the other neurotransmitter compound such as ^{3}H-labeled dopamine and ^{3}H-labeled serotonine. Baclofen and GABA help to reduce the output of both the neurotransmitter substances.

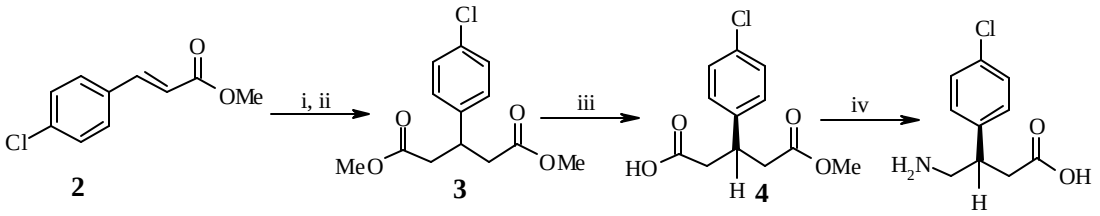
The $GABA_B$ receptor of peripheral and central nervous systems are associated with many biological processes including analgesia, muscle relaxation, hypertension, increased gastric mutility and inhibition of the liberation of corticotropin releasing hormone. There are only few agonist and antagonists available concerning these factors. Baclofen is one of them and used in treatment of spasticity, a serious disease characterized by increase muscle tone, usually perceived muscle tightness or achiness in the limbs.[8] These symptoms are normally associated with multiple sclerosis. Although baclofen is commercially available in its racemic form, only the (R)-enantiomer (**1a**) shows entire medicinal activity. [1,9]

3.0.3 Review of Literature:

Literature search revealed that there are several reports available on the synthesis of (R)-(-)-baclofen (**1a**). They are concerned mostly with resolution and chemo-enzymatic or enantioselective synthesis, which are described as below.

Chenevert's approach (1991)[10]

Chenevert *et al* have achieved the synthesis of both (R) and (S)-enantiomers of baclofen by involving *chymotrypsin* enzyme in their key step reaction (**Scheme 1**). Prior to this, the methyl-4-chlorocinnamate (**2**) was subjected to Michael addition reaction with dimethyl malonate followed by demethoxycarbonylation to give the key intermediate diester **3**. It was then subjected to enantioselective hydrolysis with *chymotrypsin* enzyme to afford chiral mono-ester **4** in 98% ee and 85% yield. The chiral mono-ester **4** upon Curtius rearrangement followed by hydrolysis of intermediate isocyanate with aqueous HCl gave (R)-(-)-baclofen (**1a**).

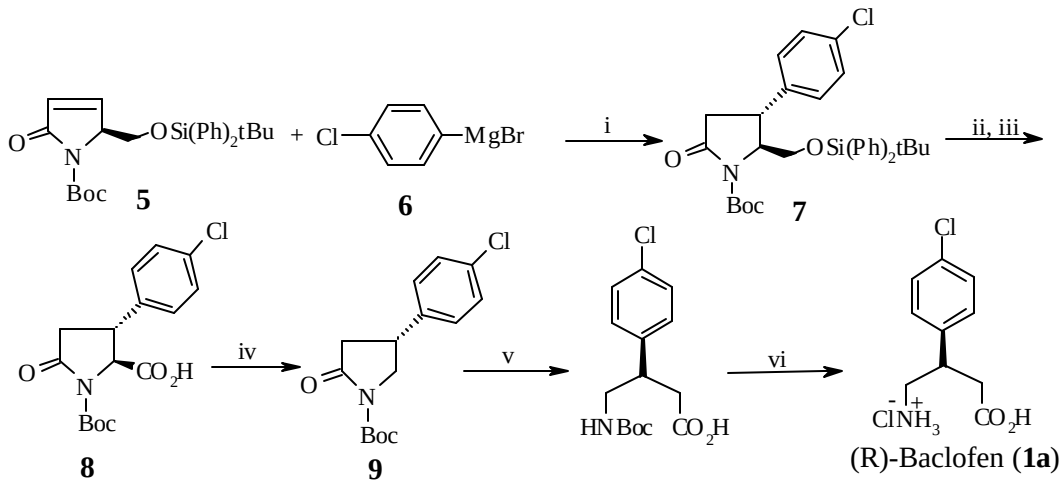


2 **3** **4** (R)-Baclofen **1a**

Scheme 1: (i) Dimethyl malonate, CH_3ONa, THF, reflux; (ii) NaCl, H_2O, DMSO, 160°C; (iii) α-*Chymotrypsin*, phosphate buffer, pH 7.7, 25°C; (iv) **a**: Ethyl chloroformate, Et_3N, acetone, 0°C,; **b**: NaN_3, H_2O, acetone, **c**: toluene, reflux, **d**: HCl, H_2O

Hubmann's approach (1992)[11]

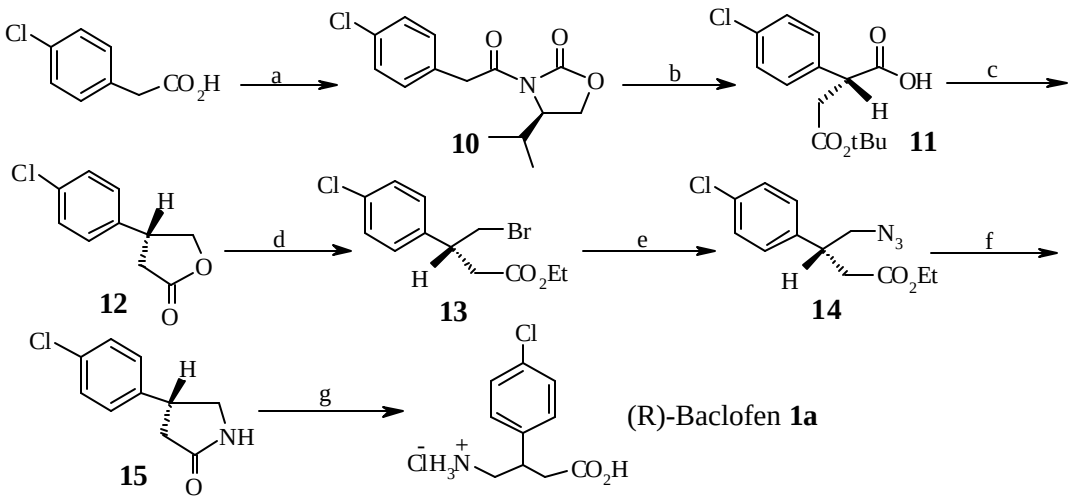
Hubmann's strategy to synthesize (R)-baclofen (**1a**) involved (S)-pyroglutamic acid derivative (**5**) as a chiral precursor (**Scheme 2**). It was subjected to stereoselective Michael addition with Grignard reagent **6** in presence of cuprous bromide as catalyst and thereby pyrrolidone moiety **7** was obtained. The selective deprotection of O-silane moiety by tetraethylammoium fluoride followed by Ru-catalyzed oxidation with $NaIO_4$ afforded the acid moiety **8**. Subsequently, it was transformed to cyclic Boc-derivative of (R)-baclofen (**9**) using Barton's decarboxylation and finally, hydrolyzed with acid to give (R)-baclofen (**1a**), which was isolated as hydrochloride salt.



Scheme 2: (i) CuBr.SMe_2, Et_2O, -35°C, 20 min; -78°C, TMS-Cl, NH_4Cl; (ii) Et_3NHF, THF, RT, 4-5 days; (iii) $RuCl_3$, $NaIO_4$, CH_3CN:CCl_4 (2:1), H_2O; (iv) N-methylmorpholine, isobutyl chloroformate, -15°C, N-hydroxy-2-thiopyridone, Et_3N, THF, 2h; (v) aq. 1M LiOH, 1.5h, (vi) 6M HCl, reflux, 3h

Schoenfelder's approach (1993)[12]

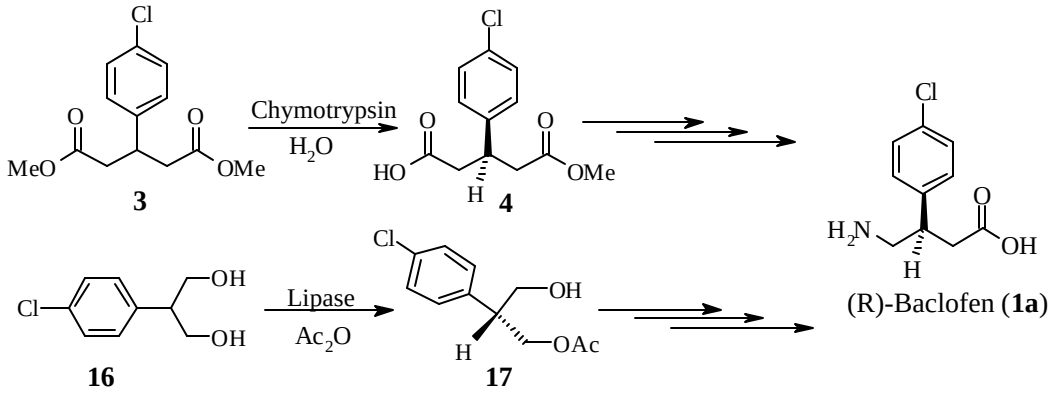
This strategy deals with enantioselective alkylation of chiral 2-(4-chlorophenyl) acetyl oxozolidone (**10**). The oxozolidone **10** was prepared by condensation of mixed anhydride of 2-(4-chlorophenyl)acetic acid with lithium-oxazolidine salt. It was then alkylated with *t*-butyl bromoacetate and subsequently hydrolyzed with H_2O_2-LiOH to give chiral *t*-butyl-2-(4-chlorophenyl)succinate **11**. The acid moiety of **11** was chemoselectively reduced with BH_3.DMS to the corresponding phenethyl alcohol and subsequently cyclized to *g*-butyrolactone **12** using *p*-TSA. The lactone **12** was then transformed to bromoester **13** using ethanol and HBr and subsequently transformed to azidoester **14** with NaN_3. The azido moiety in **14** was reduced to amine by Stuadinger method and then cyclized with N,N-dimethylaminopyridine (DMAP) to give cyclic (R)-baclofen **15**. It was then hydrolyzed with HCl and isolated as (R)-baclofen (**1a**) hydrochloride salt (**Scheme 3**).



Scheme 3: (a) i) $ClCO^tBu$, Et_3N; ii) Li-oxazolidine, THF, -78°C; (b) i) NaHMDS, $BrCH_2CO_2tBu$, -78°C; ii) H_2O_2-LiOH (c) i) BH_3.DMS; ii) pTSA, toluene, reflux; (d) EtOH, HBr; (e) NaN_3, DMSO; (f) i) PPh_3, H_2O; ii) DMAP, toluene, reflux; (g) 6N HCl

Chenevert's approach (1994)[13]

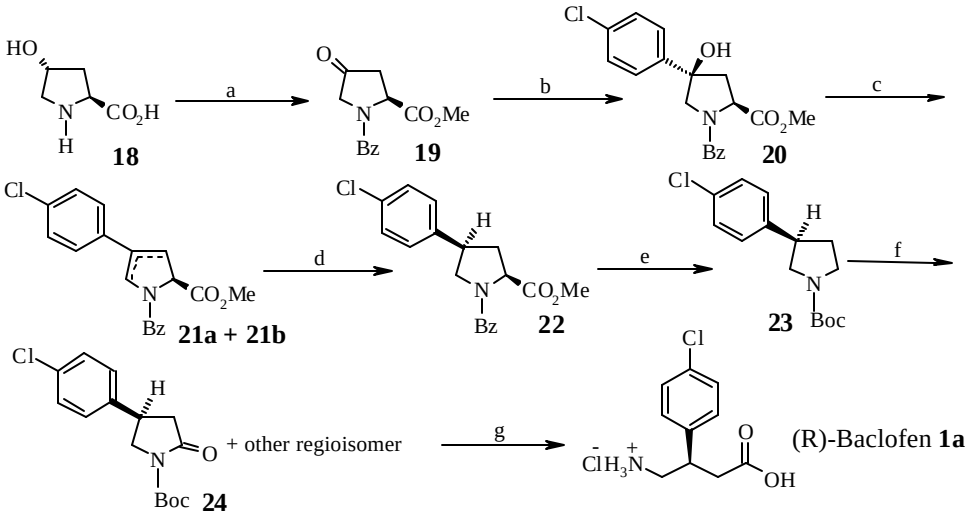
Cheneverts *et al* have developed a novel approach for the synthesis of (R)-baclofen using *chymotrypsin* enzyme in their key step. Herein, the dimethyl-3-(4-chlorophenyl)glutarate (**3**) was subjected to enantioselective hydrolysis with *chymotrypsin* enzyme to obtain the monoglutarate **4**. It was then transformed to (R)-baclofen with similar sequence of reaction as described above. Another approach uses lipase to carry out the enantioselective acetylation of 2-(4-chlorophenyl)-1,3-propane diol (**17**) in their key step reaction for the synthesis of (R)-baclofen (**Scheme 4**).



Scheme 4 :

Yashifuji's approach (1995)[14]

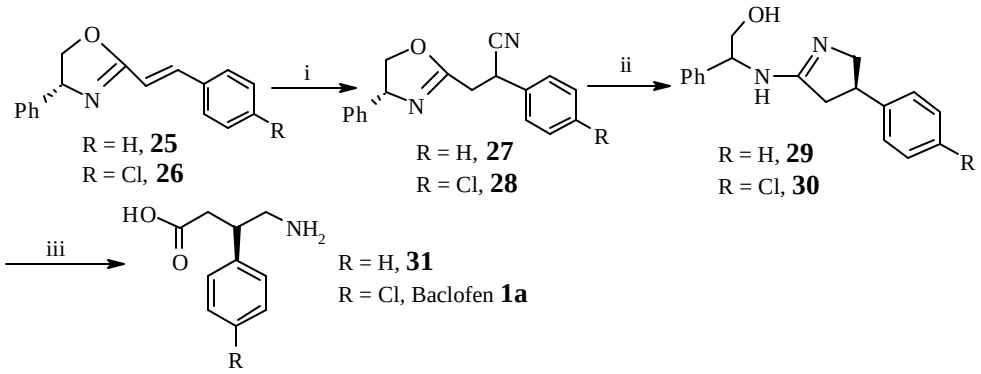
This approach consists of chiral *trans*-4-hydroxy-L-proline (**18**) as a chiral precursor for the synthesis of both (R) and (S)-isomers of baclofen (**Scheme 5**). Their strategy was based on the following two key step reactions (i) a stereoselective hydrogenation of dehydroproline derivative, controlled by C_2-carboxyl functionality (ii) an effective Ru-catalyzed oxidation of pyrrole to pyrrolidone. Thus, the compound **18** was subjected to esterification with MeOH and then transformed to N-benzoyl derivative with benzoyl chloride. Subsequent oxidation with Swern protocol generated the key substrate, 4-ketoproline derivative **19**, which upon stereoselective Grignard reaction with 4-chlorophenylmagnesium bromide in presence of $CeCl_3$ led to the single diastereoisomer **20**. The dehydration of resulting alcohol **20** with $SOCl_2$ and pyridine gave the mixture of olefins (**21a** and **21b**), which were subsequently hydrogenated in presence of platinum to a single diastereoisomer **22** in 84% yield. It was then debenzoylated with 6N HCl-acetic acid followed by decarboxylated with Hashimoto's method to give the pyrrolidine moiety. Furthermore, it was N-protected by *tert* butoxycarbonyl **23** prior to Ru-catalyzed oxidation to give pyrrolidone moiety **24** and finally transformed to (R)-baclofen (**1a**) by hydrolysis with 6N HCl.



Scheme 5: (a) (i) MeOH, (ii) benzoyl chloride, Et_3N; $COCl_2$, DMSO, Et_3N, -78°C, 92%; (b) 4Cl-Ph-Br, Mg, $CeCl_3$, Et_2O, RT, 78%; (c) $SOCl_2$, Pyridine, RT, 79%; (d) H_2, Pt, 1 atm, RT, 6N HCl AcOH, 110°C; (e) (i) cyclohexanol, 2-cyclohexen-1-one, 155°C; (ii) *tert*. Butoxylchloride; (f) RuO_2, aq. $NaIO_4$, AcOEt : H_2O, RT, 3h; (g) 6N HCl, reflux, 18h

Langlois's approach (1997)[15]

Langlois's approach involved asymmetric hydrocyanation of olefin as the key step for the synthesis of (R)-baclofen (**1a**) (**Scheme 6**). Thus, using this method both (R)-4-amino-3-phenylbutyric acid and (R)-baclofen have been synthesized in 50% ee. The chiral precursors, *a,b*-unsaturated oxazoline **25** and **26**, were derived from the reaction of (R)-phenylglycinol with the corresponding cinnamic acids and these were subjected to hydrocyanation reaction with $AlEt_2CN$ to afford 2-(C_2-aryl-2-cyanoethyl) oxazolines **27** and **28** in 40-50% yield and 50% de. Subsequently, these were reduced with $NaBH_4$ in presence of $NiCl_2$ to give imide **29** and **30** respectively. Finally, imide **29** and **30** were hydrolyzed with 2N NaOH followed by acidification with HCl yielded the optically active (R)-4-amino-3-phenylbutyric acid (**31**) and (R)-baclofen (**1a**) respectively.

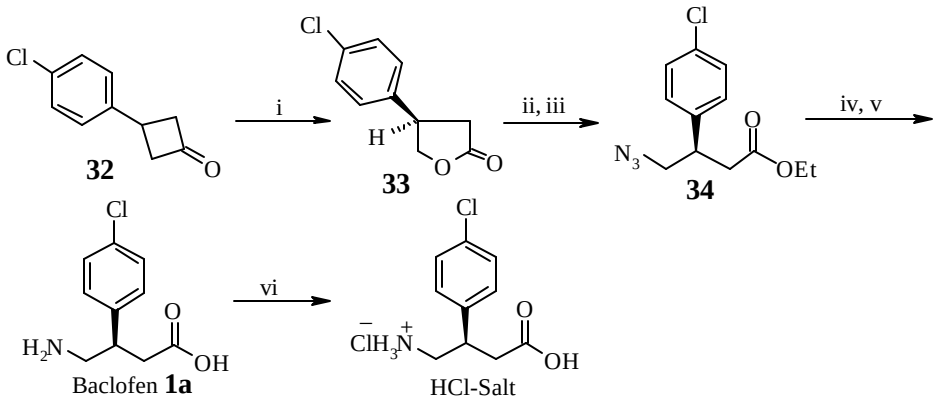


Scheme 6: (i) $AlEt_2CN$, DCM, -30°C, RT, 48h, 30-40%, 50% de; (ii) $NaBH_4$, $NiCl_2$, THF:H_2O (2:1); (iii) 2N NaOH:EtOH, 100°C, 14h, 97%.

Mazzini's approach (1997)[16]

Mazzini *et al* have synthesized (R)-baclofen *via* chemoenzymatic Baeyer-Villiger oxidation as a key step (**Scheme 7**). The 3-(4-chlorophenyl)cyclobutanone (**32**) was subjected to enantioselective Baeyer-Villiger oxidation in presence of *Cunninghamell echinulata* (NRLL 3655) enzyme to obtain (3R)-chlorophenyl-*g*-butyrolactone **33** in 30% yield and >99% ee. Treatment of **33** with iodotrimethylsilane and ethanol followed by NaN_3

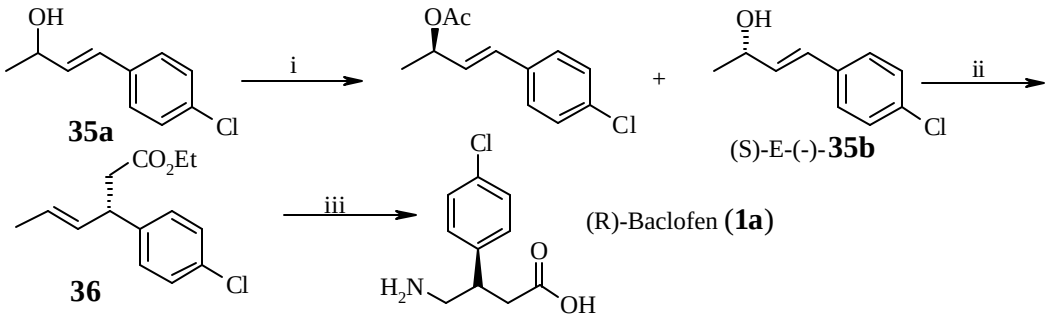
gave the azidoester **34**. Subsequently, it was hydrolyzed with NaOH and subjected to Pd-catalyzed hydrogenation to afford (R)-baclofen (**1a**). However, by the use of *Acinetobactor calcoaceticus* (NCIMB 9871) enzyme it is possible to obtain the (S)-enantiomer of the lactone **33** in 85% ee, which on similar sequence of reactions was transformed to (S)-baclofen (**1b**).



Scheme 7: (i) *Culture C. echinulata*; (ii) Me_3SiI, EtOH, DCM, 0°C to RT, 95%; (iii) NaN_3, DMF, 75°C, 95%, (iv) 2M NaOH, conc. HCl, RT, 95%; (v) Pd-C, H_2, Et_2O/EtOH, RT; (vi) HCl gas 80%.

Brenna's approach (1997)[17]

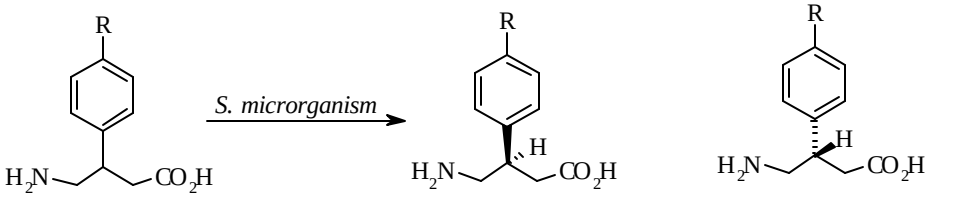
Brenna's approach to synthesis of (R)-baclofen involves enzymatic resolution of substituted allyl alcohol followed by its Claisen orthoester rearrangement as key steps (**Scheme 8**). To obtain allylic alcohol **35a**, acetone was condensed with 4-chlorobenzaldehyde by simple aldol condensation followed by reduction of the ketone with $NaBH_4$. Kinetic resolution of the alcohol **35a** by acetylation in presence of *Porcine pancreas lipase* (PPL, Sigma type II) yielded optically active isomer **35b** in >99% ee. Subsequently, it was transformed to chiral *g, d*-unsaturated ester (**36**) *via* Claisen orthoester rearrangement. Finally, ester **36** on ozonolysis followed by reductive amination with NH_4OAc and $NaCNBH_3$was transformed to (R)-baclofen (**1a**).



Scheme 8: (i) PPL, t-butylmethyl ether, vinyl acetate; (ii) $CH_3C(OEt)_3$ propanoic acid 120-130°C; (iii) O_3, DCM, : MeOH (1:1), NH_4OAc, $NaCNBH_3$, -78°C, 12h, 2N NaOH, HCl, RT, 2h.

Levadoux's approach (1998)[18]

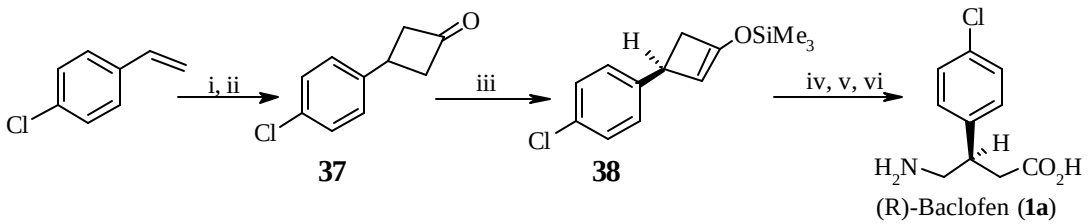
Levadoux *et al* have developed a process for obtaining optically active baclofen and its analogues by *Streptomyces microrganism*-mediated resolution (**Scheme 9**).



Scheme 9:

Resende's approach (1999)[19]

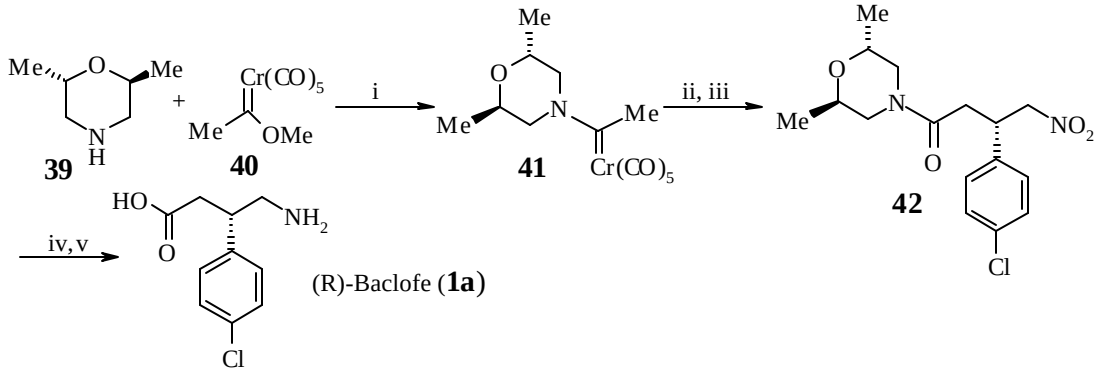
Resende's approach to synthesis of (R)-baclofen (**1a**) involves enantioselective deprotonation of 4-chlorocyclobutanone (**37**) as a key step. The [2+2] cycloaddition of 4-chlorostyrene and dichloroketene followed by reductive dechlorination afforded **37** in 92% yield. Subsequent enantioselective deprotonation with lithium (S, S')-α,α'-dimethylbenzyl-amide followed by silylation using trimethylsilyl chloride afforded the chiral silylenol ether **38** in 70% yield and 98% ee. Finally, it was transformed to (R)-baclofen (**1a**) by simple reductive amination of ozonide with $NaCNBH_4$ and ammonium acetate in presence of dimethyl sulfide (**Scheme 10**).



Scheme 10: (i) Zn-Cu, $POCl_3$, CCl_3COCl, Et_2O, RT, 12h, 91%; (ii) Zn/AcOH, 14h, RT, 93%. (iii) Lithium (S,S')-α,α'-dimethylbenzylamide, THF, TMSCl, -100°C, 15 min 70%; (iv) O_3, DCM, -78°C 40 min; (v) Me_2S, -78°C→ RT, 12h; (vi) $NaBH_3CN$, NH_4OAc, 12h; 6N HCl (one pot sequence)

Licandro's approach (2000)[20]

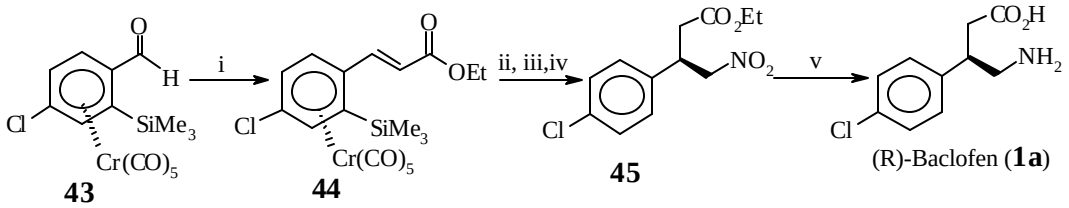
Licandro *et al* have achieved the synthesis of (R)-baclofen using diastereoselective Michael addition of enantiopure carbene to *p*-chloronitrostyrene (**Scheme 11**). The optically active chromium-carbene complex **41** was obtained by condensation of (S, S)-2,6-diemethyl-morpholine **39** with pentacarbonyl(methoxymethylcarbene)chromium **40**. The Michael addition of **41** on *trans p*-chloronitrostyrene using n-butyllithium followed by de-complexation with ceric ammonium nitrate (CAN) yielded compound **42**. The nitro group in **42** was then reduced with Raney-Ni and finally hydrolyzed with 6M HCl to afford (R)-baclofen (**1a**).



Scheme 11: (i) aminolysis (ii) n-BuLi, THF, -97°C, *p*-Cl-PhCH=CHNO$_2$; (iii) CAN, acetone, RT, 4h; (iv) Raney -Ni, dry-MeOH, 5 atm, 1h; (v) 6M HCl, reflux, 8h.

Baldoli's approach (2000)[21]

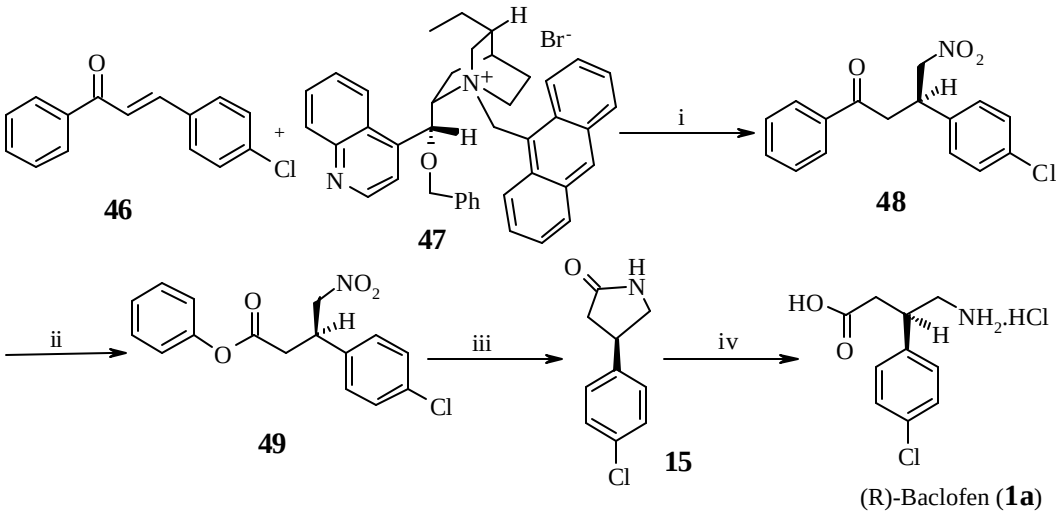
In this approach Baldoli *et al* have employed stereoselective Michael addition of nitromethane to chiral ethyl-4-chlorocinnamate chromium (0) complex as a key step for obtaining (R)-baclofen. This strategy is based on the enantiomerically pure 4-chlorobenzaldehyde chromium (0) complex (**43**). The chiral complex **43** was obtained by resolution of its diastereoisomeric -semioxamazone derivative followed by hydrolysis. Thus, aldehyde **43** was subjected to Wittig-Horner reaction with triethyl phosphonoacetate to obtain ester complex **44** (**Scheme 12**). The Michael addition of nitromethane on ester **44** followed by desilylated and de-complexation transformed to nitroester **45**. Finally, Pt-catalyzed hydrogenation of nitroester **45** resulted in the formation of (R)-baclofen (**1a**).



Scheme 12: (i) $(EtO)_2OPCH_2CO_2Et$, $(Me_3Si)_2NLi$, THF, RT; (ii) CH_3NO_2, K_2CO_3, TEBA, RT; (iii) Bu_4NF, DCM, RT; (iv) hν, air, DCM; (v) PtO_2, H_2, dry MeOH, RT

Coreys' approach (2000)[22]

Corey *et al* have developed a simple method for enantioselective synthesis of (R)-baclofen. Herein the chiral quaternary ammonium salt was used as a chiral catalyst for the enantioselective Michael addition of nitromethane to *a,b*-enones (**Scheme 13**). 4-Chloro-benzylidineacetophenone **46** was subjected to Michael addition with nitromethane in presence of chiral cinchonium salt **47** to obtain nitroketone **48**. Subsequently, it was transformed to nitroester **49** by Baeyer-Villiger oxidation with *m*-chloroperbenzoic acid. Then reduction of nitrogroup in **49** with sodium borohydride gave cyclic (R)-baclofen **15**. Finally, hydrolysis of compound **15** with 5N HCl, followed by removal of water produced (R)-baclofen as a hydrochloride salt.



Scheme 13 : (i) CH_3NO_2, CsF, toluene, -40°C, 36h; (ii) m-CPBA, EDC, reflux, 36h; (iii) $NaBH_4$, $NiCl_2$, MeOH, 23°C, 10 min; (iv) 5N HCl, reflux, 4h.

3.0.4 Present Work:

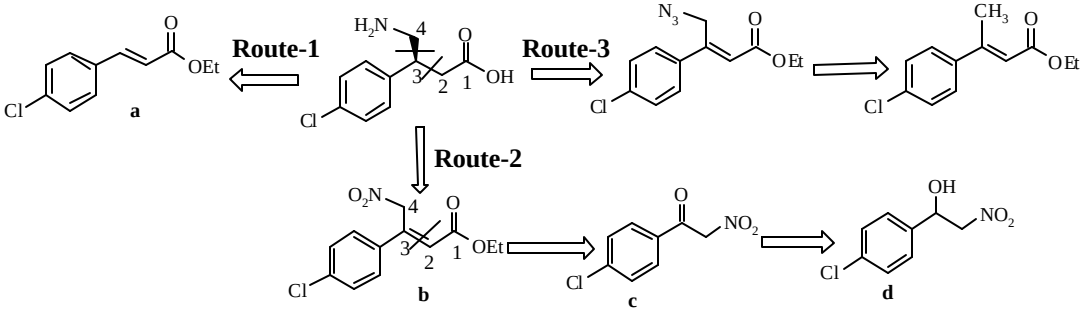
3.0.4.1 Objective:

Although baclofen is commercially available in racemic form, its entire biological activity is associated only with the (R)-enantiomer. In consequence of this various methods such as resolution, chemo-enzymatic or enantioselective synthesis have been developed to synthesize (R)-baclofen (**1a**). However these methods suffer from disadvantages such as low overall yield the need for separation of diastereoisomer and use of expensive reagents. In this context a more practical approach for the synthesis of (R)-baclofen is highly desirable.

In considering the retrosynthetic analysis of (R)-baclofen, special attention is drawn towards bond between C2-C3 and C3-C4 at the chiral center (**Scheme 14**), which establishes the stereochemistry of baclofen. Initially we visualized the disconnection at C3-C4 bond to give a simple precursor (ethyl cinnamate **a**). Based on this, we planned to use asymmetric dihydroxylation (see chapter 1 for AD) approach for the introduction of chirality at C3 carbon. Accordingly AD of ethyl cinnamate has been performed and the resulting chiral diol was transformed to chiral cyclic sulfite, which was expected to be opened by either NaCN or nitromethane anion under standard reaction conditions. However, these reactions have failed to give the desired products. This may be attributed to less reactivity of the cyclic sulfites towards above mentioned nucleophiles (**Scheme 14**, route 2).

According to retrosynthetic analysis, the second approach envisaged was of nitroester **b**, as a key intermediate for asymmetric hydrogenation. In order to obtain **b**, the disconnection of C2-C3 bond of nitroester **b** identifies that ketone **c** is the immediate precursor which can be obtained from the corresponding aryl nitroaldol **d** by oxidation. However, the nitroaldol **d** upon reaction with various oxidizing reagents (see chapt. 4, section III), produced either 4-chlorobenzoic acid or 2-(4-chlorophenyl)-2-oxoacetic acid as the main product. However, we failed to obtain nitroester **b**. So another approach has been employed for the synthesis of (R)-baclofen.

The route 3 in **Scheme 14** is a retrosynthetic outline of baclofen synthesis (see **Scheme 15**), wherein the azidoester **53** was easily obtained from the corresponding bromoester **52**, which in turn could be easily prepared by the following sequence of reactions: Reformatsky reaction of 4-chloroacetophenone, subsequent dehydration and allylic bromination with NBS.



Scheme 14 : Retrosynthetic analysis of (R)-Baclofen

The objective of the present investigation is to synthesize (R)-baclofen *via* Ru(II)-(S)-BINAP (**Fig. 1**, **50**) catalyzed asymmetric hydrogenation of *a*,*b*-unsaturated ester **53**. The Ru-catalyzed asymmetric hydrogenation is distinguished from its ability to produce high degree of enantiomerically pure saturated acid/ester. Since the preparation of the catalyst (**50**) is easy, it turns out to be the most powerful method in organic synthesis.[23]

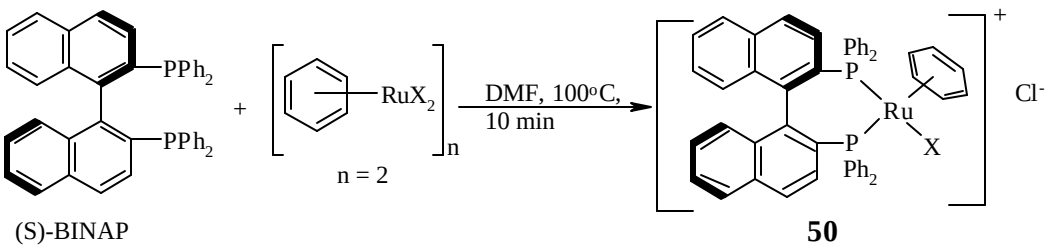


Fig. 1 : Ru(II)-BINAP Complex

3.0.5 Preparation of (S)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl Ruthenium(II) Complex [23]:

A dry, 25 ml two necked, round bottomed flask was charged with $[RuCl_2(benzene)_2]$ (38.3 mg, 0.0765 mmol) and (S)-BINAP (100 mg, 0.16 mmol). The flask was then evacuated, filled with argon and then N,N'-dimethylformamide (2.6 ml) was introduced through syringe. The suspension was stirred under argon atmosphere at 100°C for 10 min the resulting clear reddish brown reaction mixture was cooled and concentrated at 60°C (3 mm Hg) with vigorous stirring. Finally, it was dried at 3 mm Hg for 3h to yield reddish brown solid of Ru(II) (S)-BINAP complex (135 mg). This solid was directly used as catalyst for the asymmetric hydrogenation.

3.0.6 The Mechanistic Aspect of Ru-Catalyzed Asymmetric Hydrogenation of the *a*, *b*-Unsaturated Acids and Esters[24]:

Recently Ashby *et al*[24b] have reported the asymmetric hydrogenation of *a*,*b*-unsaturated acids using Ru(II)-BINAP complex wherein the role of Ru-catalyst has been evaluated to establish the mechanism (**Fig. 2**). The rapid equilibration of Ru-catalyst with an *a*,*b*-unsaturated acid results in the formation of adduct **I** wherein the co-ordination of the carbonyl group with chiral Ru-species is essential to differentiate facial selectivity of the olefin for asymmetric hydrogenation. Subsequently, heterolytic splitting of the H_2 molecule followed by asymmetric insertion of the C=C bond of the substrate to Ru-H bond, leads to the five membered heterometacyclic species **II**, wherein the protonation of Ru-C bond releases the optically active acid by regenerating the Ru-dicarboxylate adduct (species **III**).

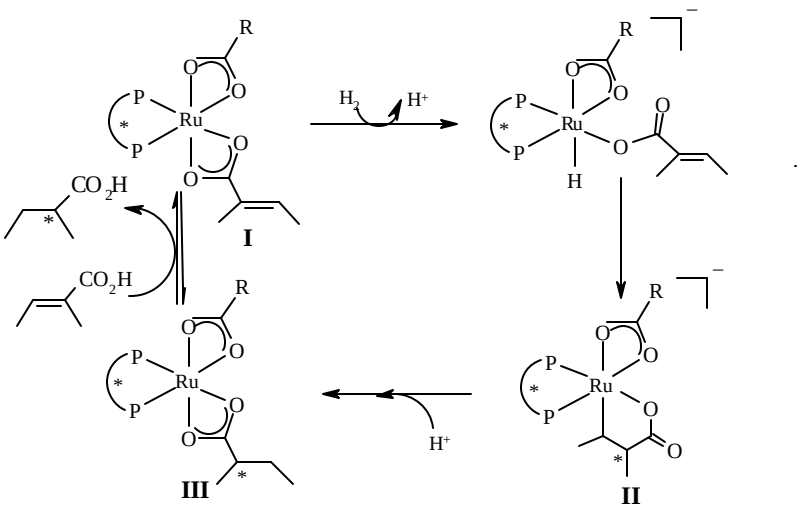
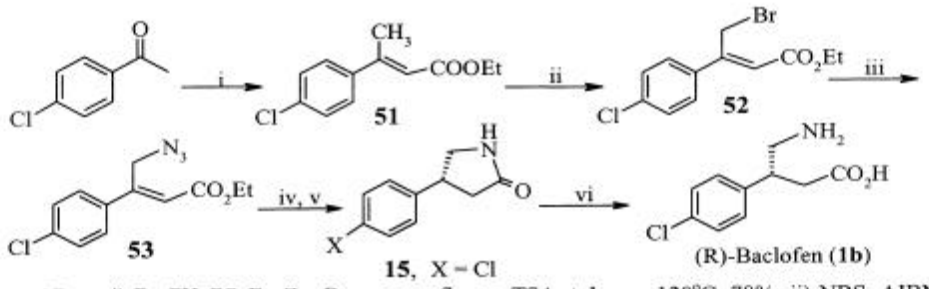


Fig. 2 : Mechanism of Ru(II)-BINAP catalyzed asymmetric hydrogenation

The presence of (S)-BINAP as a ligand indicated clear bias for the delivery of hydride in an asymmetric fashion resulting in the formation of high optically pure acid. On similar basis we applied this method for the asymmetric hydrogenation of ester of *a,b*-unsaturated acid to obtain (R)-baclofen (**1a**).

3.0.7 Results and Discussion:

The present synthetic strategy for the preparation of (R)-baclofen (**1a**) is depicted in **Scheme 15**. The key precursor, ethyl 3-(4-chlorophenyl)-2-butenoate (**51**), was obtained by Reformatsky reaction of 4-chloroacetophenone with ethyl bromoacetate followed by *p*-TSA catalyzed dehydration of the intermediate alcohol in 78% overall yield. The IR spectrum of **51** showed strong bands at 1712 and 1625 cm^{-1} indicating the presence of ester and olefin functionalities. Its ^{1}H-NMR spectrum showed characteristic singlets at δ 2.48 and 6.02 due to the presence of vinylic-methyl group and olefinic proton (=CH) respectively (**Fig. 3**). The ^{13}C-NMR of **51** showed characteristic carbon signals at δ 153.68 and 117.56 corresponding to that of *b*-quaternary carbon and CH carbon of the *a,b*-unsaturated ester respectively. The signal at δ 166.31 confirms the presence of ester carbonyl. The mass spectrum of **51** indicated intense molecular ion peak at 224 (%RI, 97).



Scheme 15 : i) Br-CH_2CO_2Et, Zn, Benzene, reflux, *p*-TSA, toluene; 120°C, 78%; ii) NBS, AIBN, CCl_4, reflux, 10h; 92%; ii) NaN_3, EtOH:H_2O (80:20), 80°C, 8h, 78%; iv) Ru (II)-(S) BINAP, H_2, MeOH, 200 *psi*, 50°C, 20 h; 68%; v) $CoCl_2$, $NaBH_4$, H_2O, 25°C, 30 min; 80%, vi) 20% HCl, 100°C, 3h, 76%.

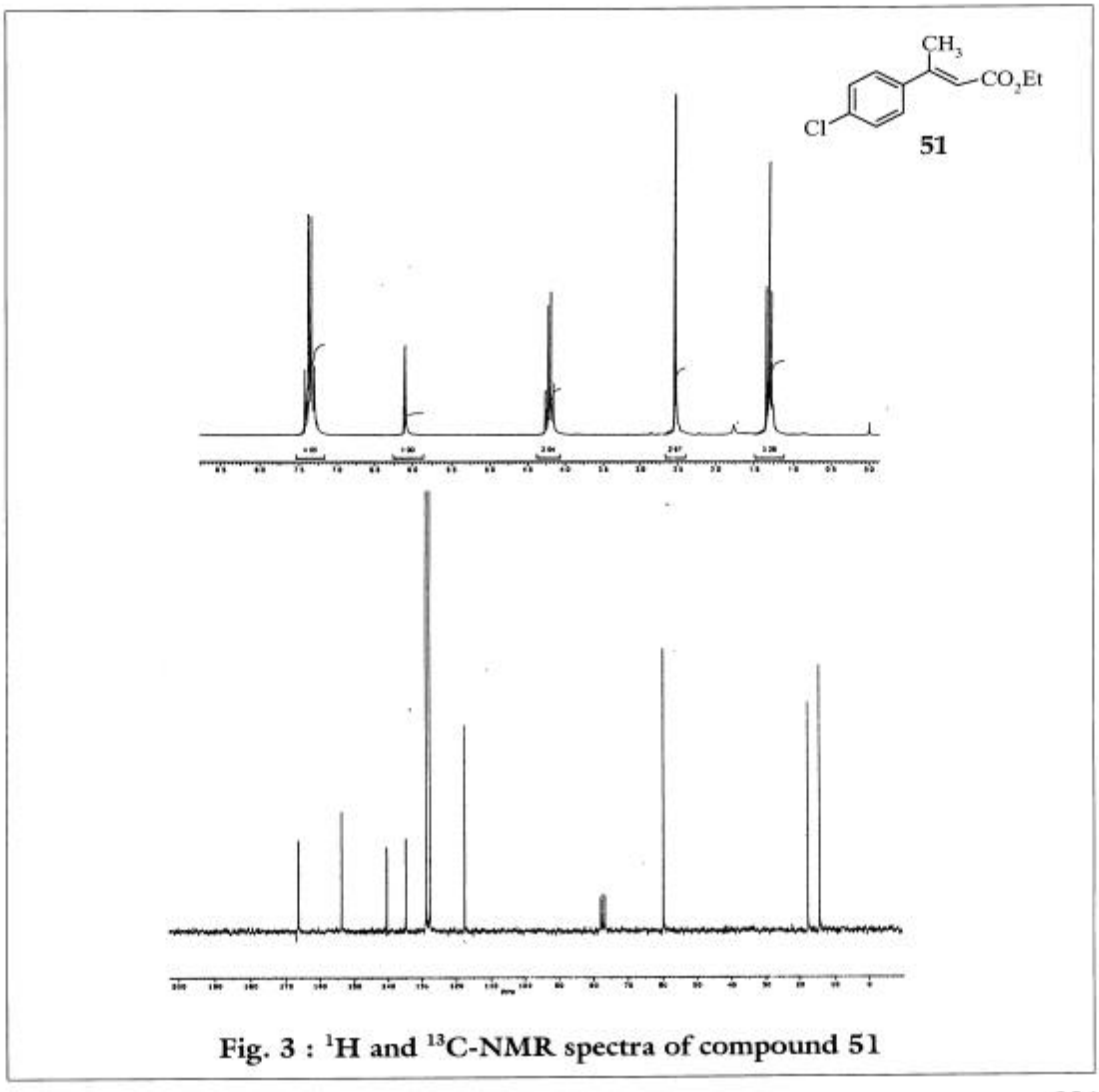


Fig. 3 : ^{1}H and ^{13}C-NMR spectra of compound 51

The allylic bromination of **51** with N-bromosuccinimide (NBS) in presence of 2, 2'-azobisisobutyronitrile (AIBN) resulted in the formation of ethyl 4-bromo-3-(4-chlorophen-yl)-2-butenoate (**52**) in 92% yield. Its IR spectrum showed a characteristic band at 734 cm^{-1}, indicating the presence of C-Br bond. The ^{1}H-NMR spectrum of **52** showed the absence of β-methyl group (**Fig. 4**) and the appearance of signal at δ 4.95 corresponding to CH_2Br moiety. The ^{13}C-NMR spectrum showed a signal at δ 26.09 confirming the presence of CH_2-Br moiety. The mass spectrum of **52** indicated low intensity molecular ion peak at 304.

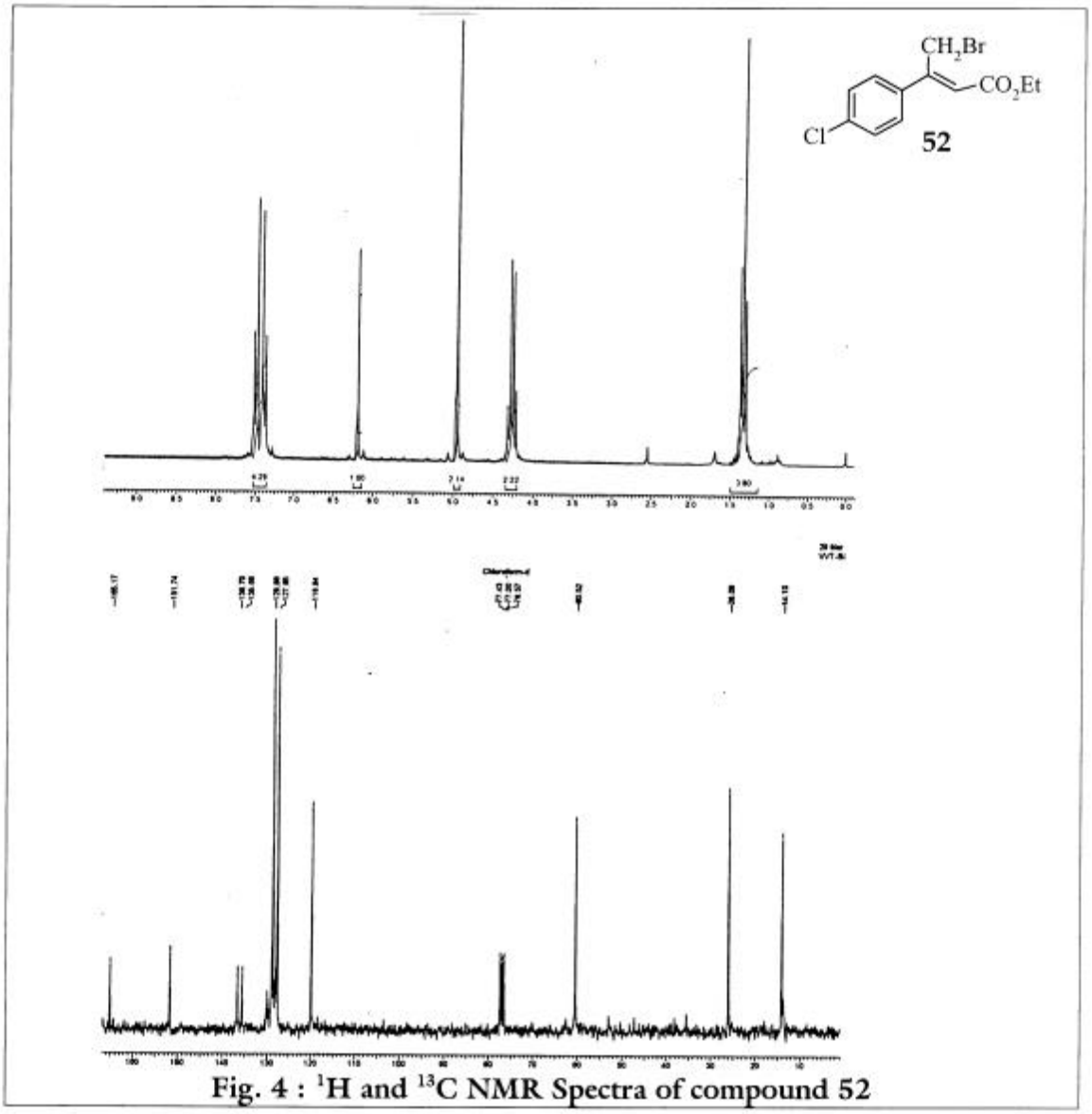


Fig. 4 : ^{1}H and ^{13}C NMR Spectra of compound 52

The bromoester **52** was then transformed to ethyl 4-azido-3-(4-chlorophenyl)-2-butenoate (**53**) by nucleophilic displacement of Br by N_3 using NaN_3. The IR spectrum of **53** showed an intense band at 2104 cm^{-1} indicative of N_3 group. ^{1}H-NMR spectrum of **53** showed a signal at δ 4.71 indicating a slight change in the chemical shift of the CH_2-N_3 protons. This signal is slightly upfield compared to CH_2-Br linkage of the bromoester **52** (**Fig. 4**). However, in ^{13}C-NMR spectrum the signal of CH_2-N_3 moiety appeared at δ 47.92, whereas for CH_2Br at δ 25.73 (**Fig. 5**).

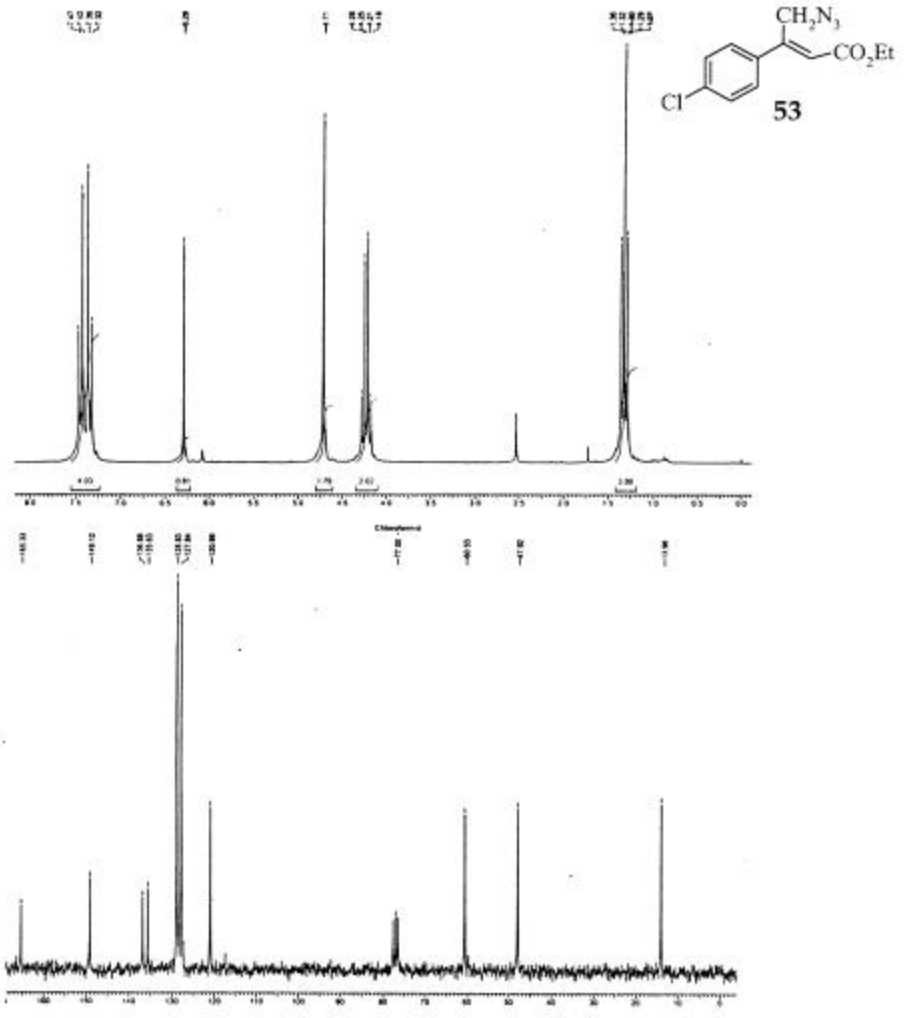


Fig. 5: ^{1}H and ^{13}C-NMR spectra of compound 53

The key intermediate, azidoester **53** was subjected to Ru(II)-(S)-BINAP catalyzed asymmetric hydrogenation in MeOH in a pressure reactor. When the experiment was performed at 200 *psi* and 25°C for 24h, there was no reaction and all the starting material was recovered. However, when the same experiment performed at 50°C and 200 *psi*, it resulted in the formation of mixture of products. These products are the result of reductions of N_3 group, olefin or both the functionalities. However, (R)-ethyl 4-azido-3-(4-chlorophenyl)-1-butanoate (**14**) is the major product obtained in 68% yield through the reduction of olefin. The (R)-ethyl 4-azido-3-(4-chlorophenyl)-1-butanoate (**14**) was analyzed by IR, NMR and Mass spectroscopy. The IR spectrum of **14** shows absorption band at 1730 cm^{-1} due to carbonyl group of saturated ester, derived from the C=C reduction. However, IR band at 2103 cm^{-1} is indicative of N_3 moiety, which shows that it is intact under the reaction

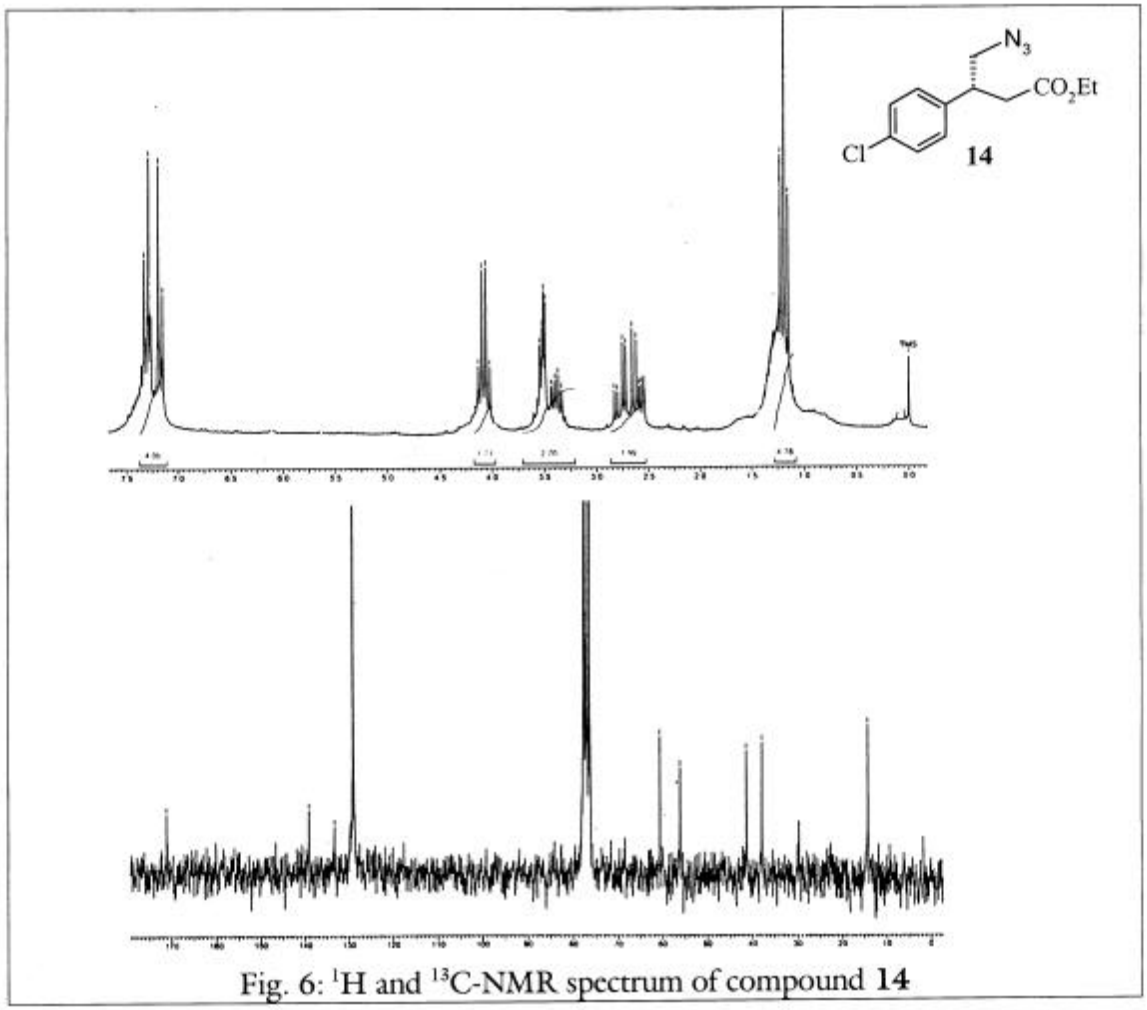


Fig. 6: ^{1}H and ^{13}C-NMR spectrum of compound **14**

condition (50°C, 200 *psi*). The ^{1}H-NMR spectrum of **14** is characteristic in the region δ 2.58-3.54 due to the creation of chiral center into the molecule and thereby indicating the ABX coupling pattern (**Fig. 6**). The ^{13}C-NMR spectrum of **14** indicated that the signal at δ 56.05 is due to the carbon of CH_2-N_3 group, whereas the α-CH_2 group appeared upfield, *i. e.* δ 37.74. The signals at δ 41.27 and 171.21 correspond to that of β-CH and the ester carbonyl group respectively. The mass spectrum of **14** showed molecular ion peak at 239 (**Fig. 7**).

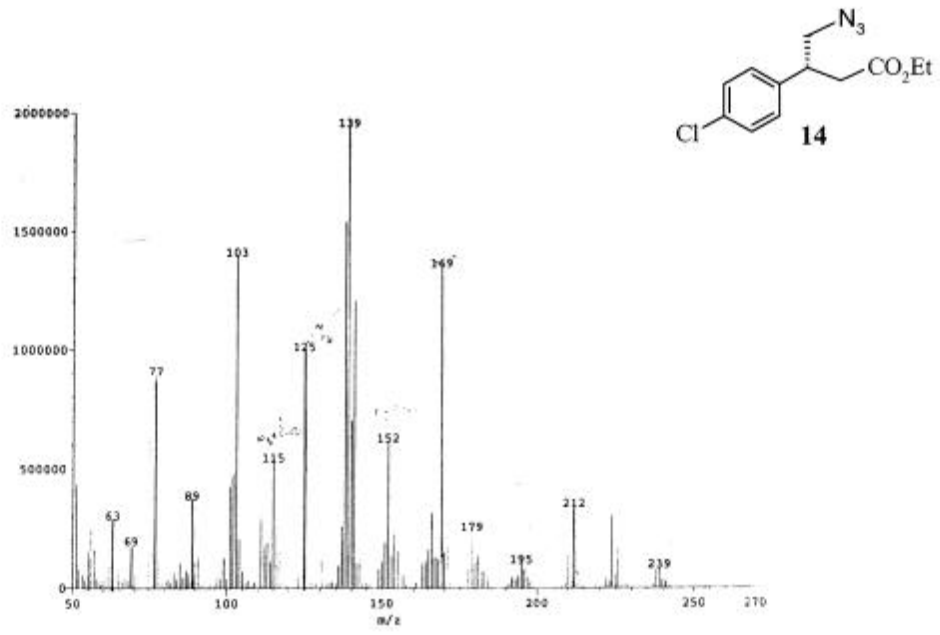


Fig. 7: Mass Spectrum of compound **14**

In order to improve the yield of the C=C reduction and to ensure the further reduction of N_3 moiety, reaction was performed at higher H_2 pressure *i.e.* 300 *psi* and at 50°C. It afforded only a single product **54** (**Scheme 15**, X=H), in which both olefin and azido groups underwent reduction and the chlorine on phenyl moiety was knocked off. Such a possible hydrogenolysis of aryl C-Cl has been known in the literature.[12] The formation of (R)-(-)-3-phenylpyrrolidone (**54**) can be rationalized as a result of reductive cyclization, occurred

during the asymmetric hydrogenation. The compound **54** is obtained in 80% yield and 65% ee (determined by comparison of $[\alpha]_D$ with literature value[25]). The disappearance of 2104 cm^{-1} band in IR spectrum indicates the absence of azide group, while carbonyl absorption band observed at 1692 cm^{-1} indicating the formation of cyclic amide. Due to the presence of chiral center, the ^{1}H-NMR of **54** is characteristic in the region δ 2.46-3.46. The protons of *a*-CH_2 and *g*-CH_2 groups of **54** are diastereotopic and thereby shows the ABX coupling pattern and each proton (H_A and H_B) of these CH_2 groups appearing as a double doublet, while H_x shows multiplet (*e. g.* **Table 1**, shows coupling pattern of *a*-CH_2). In a similar way the protons of γ-CH_2 group represent another ABX pattern. The ^{13}C-NMR spectrum of **54** shows a signal at δ 49.51 due to the *a*-CH_2 group, while the signal at δ 38.00 is due to *g*-CH_2 group. However the signal at δ 40.13 corresponds to *b*-CH carbon. The mass spectrum of **54** (X=H) showed an intense molecular ion peak at 161 (relative intensity %, 52).

Table 1: Chemical shift and coupling constant of ABX pattern of compound **54**:

Protons of *a*-CH_2 group	H_A	H_B	H_X
Chemical shift (δ)	2.44-2.57	2.64-2.80	3.38-3.46
Geminal coupling (*J*)	J_{AB} = 16.6 Hz,	J_{BA} = 16.6 Hz,	-
Vicinal coupling, (*J*)	J_{AX} = 8.3 Hz	J_{BX} = 8.3 Hz	-

Co-catalyzed[26] reduction of N_3 moiety in the compound **14** with $NaBH_4$ gave reductive-cyclized product 4-(4-chlorophenyl)-2-pyrrolidone (**15**) in 80% yield and 67% ee (determined by comparison of $[\alpha]_D$ with literature value[12]). ^{1}H-NMR and ^{13}C-NMR patterns of compound **15** were found to be nearly similar to that of compound **54** as discussed above (**Fig. 8**).

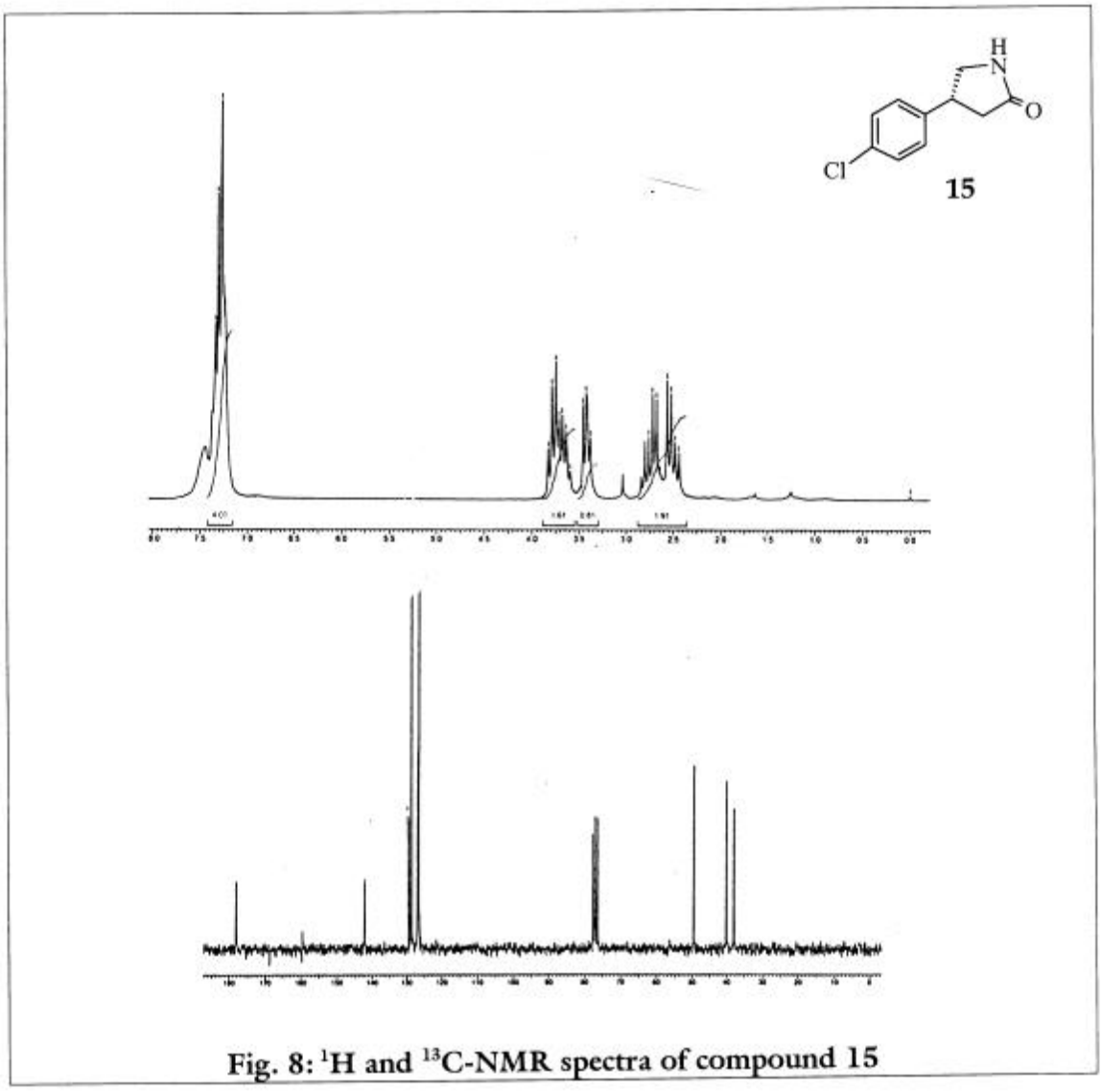


Fig. 8: ^{1}H and ^{13}C-NMR spectra of compound 15

The final step of the synthesis involved hydrolysis of 4-(4-chlorphenyl)-pyrrolidine-2-one (**15**). It was carried out using 20% HCl at 100°C for 3 hrs. The excess of water from the reaction mixture was removed under reduced pressure to afford a white solid of (R)-baclofen hydrochloride **1a** in 76% yield and 67% ee (determined by comparison of $[\alpha]_D$ with literature value[19]). The absolute configuration of **1a** was confirmed to be "R" by comparison with the literature values of its optical rotation. Hence the predication of stereochemical outcome of asymmetric hydrogenation is correct. The IR, ^{1}H-NMR and ^{13}C-NMR spectral data matched well with the published values.[19]

3.0.8 Conclusion:

We have achieved the synthesis of (R)-(-)-baclofen (**1a**) in 24% overall yield and 67% ee *via* the Ru(II)-BINAP catalyzed asymmetric hydrogenation, starting from cheaply available 4-chloroacetophenone.

3.0.9 Experimental Section:

Preparation of ethyl 3-(4-chlorophenyl)-2-butenoate 51:

A 100 ml two necked RB flask was charged with activated zinc (2.32 g, 35.7 mmol), and kept under N_2 atmosphere. Dry benzene (30 ml) was introduced and the reaction mixture was heated to 80^{o}C (oil bath temp.). A solution of ethyl bromoacetate (5.88 g, 35.7 mmol) and *p*-chloroacetophenone (5.0 g, 32.46 mmol) in dry benzene (20 ml) was added dropwise to the reaction mixture. After completion of the addition, the resulting reaction mixture was refluxed for 6 hrs, cooled to RT and quenched by adding ice cold 4N H_2SO_4 (30 ml). The crude hydroxyester was extracted in diethyl ether and then was subjected to dehydration with *p*-toluenesulphonic acid (0.7 g, 3.68 mmol) in toluene at reflux. The water generated during the dehydration was azeotropically separated and then toluene was distilled off. The crude olefinic ester **51** was purified by column chromatography packed with silica gel, eluting with pet. ether to give 5.67 g (78%, *trans*/*cis* = 70/30).

Yield	:	78%
bp	:	154^{o}C at 0.64 mm
IR ($CHCl_3$, cm^{-1})	:	3060, 2982, 1712, 1625, 1577, 1448, 1367, 1344, 1286, 1176, 1047, 879, 769, 696
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 1.21-1.28 (t, *J* = 7.4 Hz, 3H), 2.48 (s, 3H), 4.07-4.18 (q, *J* = 7.4 Hz, 2H), 6.02 (s, 1H), 7.23-7.35 (dd, *J* = 8.0 Hz, 4H)
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 14.14, 17.58, 59.78, 117.56, 127.55, 128.62, 134.93, 140.51, 153.68, 166.31
MS (m/z, % RI)	:	224 (M^+, 96), 209 (8), 195 (55), 179 (100), 152 (32), 115 (92),
Analysis	:	$C_{12}H_{13}ClO_2$ requires: C, 64.15; H, 5.83; Cl, 15.78%, found: C, 63.94; H, 5.81; Cl, 15.72%.

Preparation of ethyl 4-bromo-3-(4-chorophenyl)-2-butenoate 52:

A solution of a,b-unsaturated ester **51** (3.5 g, 15.62 mmol), NBS (2.81 g, 17.2 mmol) and AIBN (0.102 g, 0.62 mmol) in dry CCl_4 (35 ml) was refluxed under nitrogen atmosphere for 10 h. The resulting reaction mixture was cooled to room temperature and then filtered through a sintered funnel to separate succinimide formed during the reaction. The filtrate was concentrated under reduced pressure to obtain bromoester **52**. It was then purified by column chromatography packed with silica gel to give pure 4.37 g of pale yellow colored gum, bromoester **52**.

Yield	:	92%
bp	:	Gum
IR ($CHCl_3$, cm^{-1})	:	3060, 2982, 1710, 1625, 1490, 1369, 1340, 1288, 1182, 1095, 1012, 908, 734, 649
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 1.30-1.37 (t, *J* = 8.0 Hz, 3H), 4.21-4.32 (q, *J* = 8.0 Hz, 2H), 4.94 (s, 2H), 6.19 (s, 1H), 7.36-7.51 (dd, *J* = 8.0 Hz, 4H)
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 14.10, 26.09, 60.52, 119.94, 127.85, 128.88, 135.66, 136.70, 151.74, 165.17
MS (m/z, % RI)	:	304 (M^+, 5), 289 (5), 224 (8), 179 (10), 152 (100), 137 (55), 115 (92), 101 (48), 91 (22), 75 (15)
Analysis	:	$C_{12}H_{12}BrClO_2$ requires: C, 47.48; H, 3.95; Halogens, 37.99%; found: C, 47.75; H, 4.18, Halogens, 37.68%.

Preparation of ethyl 4-azido-3-(4-chlorophenyl)-2-butenoate 53:

A 50 ml RB flask containing a solution of bromoester **52** (1.85 g, 6.1 mmol) and sodium azide (0.594 g, 9.14 mmol) in ethanol: water (80:20, 15ml) mixture was refluxed for 8h. Resulting yellow colour solution was concentrated under reduced pressure to yield crude

azidoester **53**, which was purified by column chromatography packed with silica gel to give pure azidoester **53** (1.26 g) as a colorless viscous liquid.

Yield	:	78%
bp	:	Gum
IR ($CHCl_3$, cm^{-1})	:	2982, 2104, 1712, 1629, 1591, 1492, 1454, 1369, 1249, 1180, 1095, 1012, 910, 831, 732
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 1.29-1.36 (t, *J* = 6.0 Hz, 3H), 4.18-4.28 (q, *J* = 6.0 Hz, 2H), 4.71 (s, 2H), 6.29 (s, 1H), 7.32-7.47 (dd, *J* = 8.0 Hz, 4H)
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 13.96, 47.92, 60.53, 120.96, 127.84, 128.83, 135.63, 136.88, 149.12, 165.33
Analysis	:	$C_{12}H_{12}ClN_3O_2$ requires: C, 54.26; H, 4.52; Cl, 13.34; N, 15.82%; found: C, 54.29; H, 4.24; Cl, 13.31, N, 15.99%.

Asymmetric reduction of azidoester 53 using Ru(II)-BINAP:

[A] A 100 ml autoclave charged with azidoester **53** (0.200 g, 1.88 mmol), Ru(II)-(S)-BINAP (**50**, 10 mg), dry MeOH (40 ml) and the resulting yellowish-orange solution was degassed with N_2. It was then pressurized with H_2 to 200 *psi* and the reaction mixture was vigorously stirred at 50°C for 20h. Resulting solution cooled to room temperature and the excess of H_2 was carefully blend off. The deep reddish-orange colored reaction mixture was transformed to 100 ml round bottomed flask and the solvent was removed under reduced pressure. The residue was purified by column chromatography packed with silica gel to give pure (0.137 g) light yellow colored viscous liquid of ethyl 4-azido-3-(4-chlorophenyl)-1-butanoate **14**.

Yield	:	68%
bp	:	Gum
$[\alpha]^{25}_{D}$	:	-18.66° (c = 0.3, MeOH)
IR ($CHCl_3$, cm^{-1})	:	3020, 2928, 2103, 1730, 1692, 1493, 1374, 1305, 1261, 2151, 1175, 1095, 827, 761, 668.
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 1.14-1.22 (t, *J* = 8.0 Hz, 3H), 2.58-2.66 (dd, J_{Ab} = 16.0 Hz, J_{BX} = 8.0 Hz, 1H); 2.72-2.83 (dd, J_{BA} = 16.0 Hz, J_{BX} = 6.0 Hz, 1H), 3.33-3.54 (m, 3H), 4.02-4.13 (q, *J* = 8.0 Hz, 2H), 7.15-733 (dd, *J* = 8.0 Hz, 4H)
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 14.25, 37.74, 41.34, 56.05, 60.57, 129.01, 133.24, 139.16, 159.89, 171.21,
MS (m/z, %RI)	:	239 (M^+-N_2, 5), 212 (15), 195 (5), 169 (65), 152 (30), 139 (100), 125 (50), 115 (30), 103 (70), 89 (20), 77 (40)
Analysis	:	$C_{14}H_{14}ClN_3O_2$, requires: C, 53.84; H, 5.27; Cl, 13.24; N, 15.70%; found: C, 53.74; H, 5.21; Cl, 13.19; N, 15.68%.

[B] In another experiment, asymmetric hydrogenation of azidoester **53** (0.500 g, 1.88 mmol) in the presence of Ru (II)-(S)-BINAP (**50**, 10 mg) was performed at 50°C and 300 *psi* for 20h. After completion of the reaction, MeOH from the reaction mixture was removed under reduced pressure. The residue was purified by column chromatography packed with silica gel to give pure (R)-4-phenyl-2-pyrrolidone **54** (0.243g) as a light yellow colored solid.

Yield	:	80%
mp	:	91-93°C
$[\alpha]^{D}_{25}$	:	-24.68° (c = 0.89, MeOH) {Lit.$^{25}[\alpha]^{25}_{D}$ = -33.8° (c = 0.89, MeOH)}
IR ($CHCl_3$, cm^{-1})	:	3439, 3228, 3017, 2952, 1692, 1492, 1216, 758, 700, 668.
^{1}H-NMR (200 MHz, $CDCl_3$)		δ 2.44-2.57 (dd, J_{AB} = 16.6 Hz, J_{AX} = 8.3 Hz, 1H), 2.64-2.80 (dd,

		J_{BA} = 16.6 Hz, J_{BX} = 8.3 Hz, 1H); 3.38-3.46 (m, 1H), 3.59-3.83 (AB part of ABX pattern, J_{AB} = 16.6 Hz, J_{AX} = 7.8 Hz, J_{BX} = 6.8 Hz, 2H), 7.27 (bs, 5H)
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 38.00, 40.13, 49.51, 126.62, 126.92, 128.72, 142.13, 177.97.
MS (m/z, %RI)	:	161 (M^+, 52), 133 (8), 104 (100), 91 (8), 77 (10).
Analysis	:	$C_{10}H_{11}NO$ requires: C, 74.51; H, 6.88; N, 8.69%; found: C, 74.35; H, 6.64; N, 8.43%.

[C] **Cobalt (II) catalyzed reduction of azide group in compound 15:**

To a 25 ml RB flask containing a mixture of azidoester **14** (0.100 g, 0.375 mmol) and $CoCl_2.6H_2O$ (0.010 g, 0.042 mmol) in 0.5 ml water, at 25°C was added dropwise under stirring a solution of $NaBH_4$ (0.028, 0.75 mmol) in 0.5 ml H_2O. The resulting reaction mixture was stirred for 30 min in which the appearance of black precipitate indicated the formation of cobalt-boride species. After the reaction was complete, the mixture was extracted with chloroform (10 x 3 ml). The chloroform layer was washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue obtained was then purified by column chromatography to give pure light yellow colored solid of 3-(4-chloropheny)-2-pyrrolidone **15**, 0.058 g.

Yield	:	80%
mp	:	115-117°C
$[\alpha]^{25}_D$	:	-27.35° (c = 1.0, EtOH), {Lit.[12] $[\alpha]^{25}_D$ = -38.3° (c = 0.5, EtOH)}
IR ($CHCl_3$, cm^{-1})	:	3420, 3200, 2103, 1698, 1492, 1090, 1374, 1216, 758, 700, 668
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 2.42-2.50 (dd, J_{AB} = 16.9 Hz, J_{AX} = 8.4 Hz, 1H), 2.70-2.79 (dd, J_{BA} = 16.9 Hz, J_{BX} = 8.7 Hz, 1H); 3.36-3.41 (m, 1H), 3.62-3.73 (AB part of ABX pattern, J_{AB} = 16.6 Hz, J_{AX} = 7.8 Hz, J_{BX} = 6.8 Hz 2H),

		7.27 (m, 4H)
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 38.20, 40.60, 49.51, 126.64, 128.10, 129.01, 139.10, 181.00
Analysis	:	$C_{10}H_9ClNO$, requires C, 61.39, H, 5.15, N, 7.16%; found: C, 61.2, H, 4.98, N, 7.09%.

Preparation of (R)-(-)-Baclofen hydrochloride (1a):

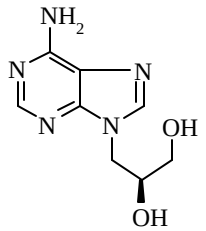
A mixture of compound **15** (0.050g, 0.256 mmol) in aqueous 20% HCl (0.5 ml) was heated at 100°C for 3hr. The excess of water in the reaction mixture was removed under reduced pressure to obtain solid residue, which was triturated in isopropanol affording (R)-baclofen hydrochloride as a colorless solid (0.045 mg).

Yield	:	76%
mp	:	195-197 °C
$[\alpha]^{25}_D$	:	-1.34° (c = 0.6, H_2O), [Lit.[19] $[\alpha]^{25}_D$ = -1.95° (c = 0.6, H_2O]
IR (KBr, cm^{-1})	:	3000-2500, 1620, 1550, 1490, 1090, 758, 700, 668.
^{1}H-NMR (200 MHz, DMSO-d_6)	:	δ 2.65-2.91 (AB part of ABX pattern, J_{AB} = 16.6 Hz, J_{AX} = 6.9 Hz, J_{BX} = 7.7 Hz, 2H), 3.10-3.39 (AB part of ABX pattern, J_{BA} = 12.8 Hz, J_{AX} = 6.0, J_{BX} = 8.9 Hz, 2H); 3.64-3.72 (m, 1H), 7.41-7.43 (m, 4H)
^{13}C-NMR (50 MHz, DMSO-d_6)	:	δ 37.70, 40.22, 48.50, 128.11, 128.93, 131.24, 141.81, 176.00

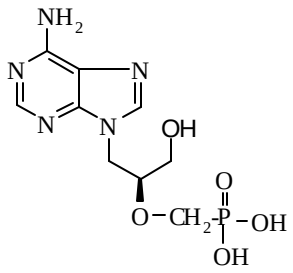
Synthesis of Acyclic Nucleoside Analog, (S)-2,3-Dihydroxy propyl-(9)-adenine, a Novel Anti-Viral Agent

3.1.0 Introduction:

The (S)-2,3-dihydroxypropyl-(9)-adenine (DHPA, **55**) is an acyclic nucleoside analog, in which sugar moiety is replaced by an aliphatic chain.[27] It exhibits broad spectrum of antiviral activity and possesses low acute toxicity. Its potential inhibitory effect on replication of several DNA and RNA viruses such as *vaccinia*, *herpex*, *simplex* (type 1 & 2), *measles* and *Vesicular stomatitis* is highly stereospecific. This entire antiviral action is associated only with the (S)-DHPA and not (R)-DHPA.[27] However, the racemic mixture is almost as effective as (S)-enantiomer. (S)-DHPA is primarily active against (-)-RNA strand of rabies virus, *Vesicular stomatitis*, *Parainfluenza*, *measles* and in certain double stranded RNA viruses such as reo- and rota-viruses.[28] But the (S)-(3-hydroxy-2-posphonylmethoxypropyl)-9-adenine [(S)-HPMPA **56**] derivative of **55** has potent and selective activity against broad spectrum of DNA viruses, including *herpex*, *simplex* virus (type 1 & 2), *Varicella zostar* virus, thymidine kinase deficient (TK^-) mutant of *herpex*, *simplex* and *Varicell zoster* virus, human cytomegalovirus, phocid, smian, suid, bovid and equid herpesviruses, African swine fever virus, vaccinia virus, and human adeno-virus.[28]



(S)-DHPA **55**



(S)-HPMPA **56**

The antiviral gel containing (S)-DHPA has potential curative effect in human against *Herpes facialis*, *H. progenitalis*, *H. glutealis* and other herpetic diseases.[29] Recently it has been identified that derivative of (S)-DHPA is capable of inhibiting the replication of human immuno-deficiency virus type 1 (HIV-1) by inhibiting the hydrolysis mechanism of (S)-adenosyl-L-homocystein hydrolase.[30] The anti-HIV activity is the outcome of blocking the methylation of viral *m*-RNA involved in the long terminal repeat transactivation.[31] Several analog of (S)-DHPA has been synthesized and tested to identify their critical biological activities.[32]

3.1.1 The Pharmacology of (S)-DHPA:

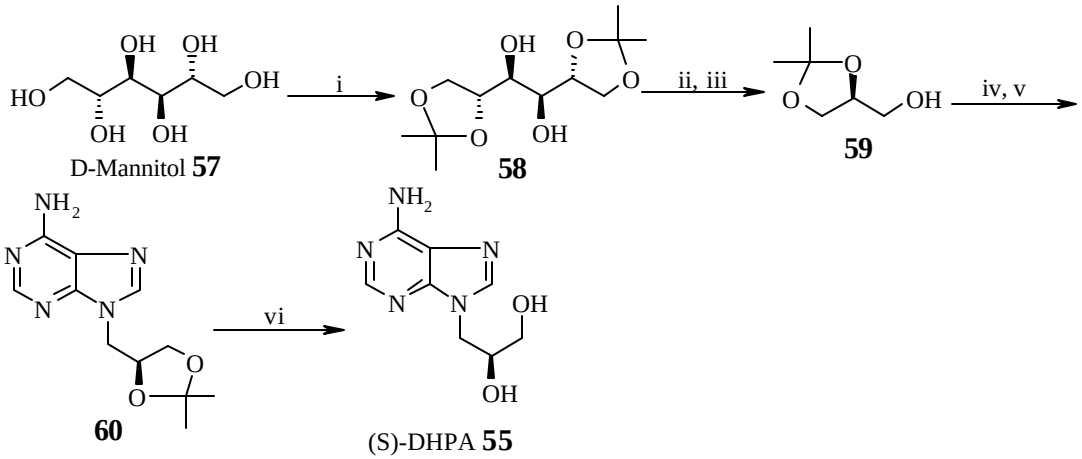
The inhibitory effect of (S)-DHPA on virus induced cytopathogenicity was determined by introducing it to the human skin fibroblast culture, inoculated with *Stomatitis virus*. It has been identified that, (S)-DHPA caused a dramatic decrease of virus titer. The combination of (S)-DHPA and vaccine helps to prevent rabies in mice and thereby help to reduce mortality rate to zero. Therefore, (S)-DHPA is very important and useful in both human and veterinary medicine.[33] The antiviral and antifungal gel containing (S)-DHPA as an active ingredient has shown to have curative effect in human against *Herpes facialis*, *H. progenitalis*, *H. glutealis* and other herpetic diseases.[29] Certain analog of (S)-DHPA has shown to possess anti-HIV activity as well.[30,31] All biological activities of (S)-DHPA are due to their structure and stereoselective orientation.[27b]

3.1.2 Review of Literature:

Literature search revealed that there are only few reports available on asymmetric synthesis of (S)-DHPA as described below:

Holy's approach (1975)[34]

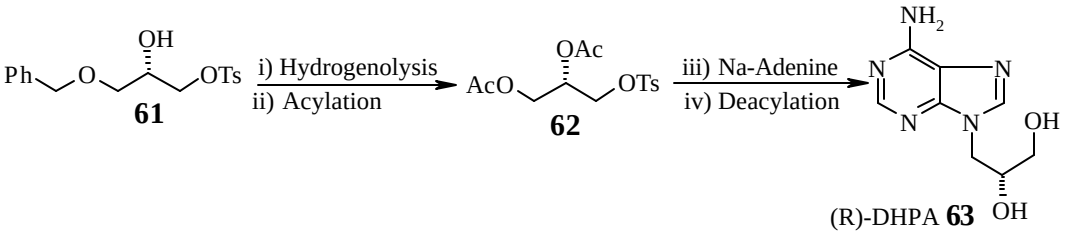
Holy's synthetic strategy for (S)-DHPA involved D-mannitol (**57**) as a chiral building block. Mannitol was subjected to acetonide protection to give bis-O-isopropylidene-D-mannitol (**58**). Subsequently, the unprotected diol moiety in compound **58** was cleaved to give chiral protected glyceraldehyde using $NaIO_4$ and then aldehyde was transformed to chiral 1,2-O-isopropylidene-D-glycerol (**59**) by reduction with $NaBH_4$ *in situ*. The tosylation of free alcohol moiety in **59**, followed by displacement with adenine led to the formation of protected (S)-2,3-dihydroxypropyladenine (**60**), which upon deprotection with 80% aq. acetic acid resulted in the formation of (S)-DHPA (**Scheme 16**).



Scheme 16 : (i) CH_3COCH_3, H^+; (ii) $NaIO_4$, THF, 0°C, 30 min, then RT, 30 min,; (iii) one pot reaction, $NaBH_4$, 0-10°C, 30 min, then RT, 90 min; NH_4Cl, *p*H 8; (iv) Pyridine, TsCl, 0°C, 16h; (v) adenine, NaH, DMF, 100°C, 12h; (vi) 80% aq. acetic acid, reflux.

Kritsyn's approach (1975)[35]

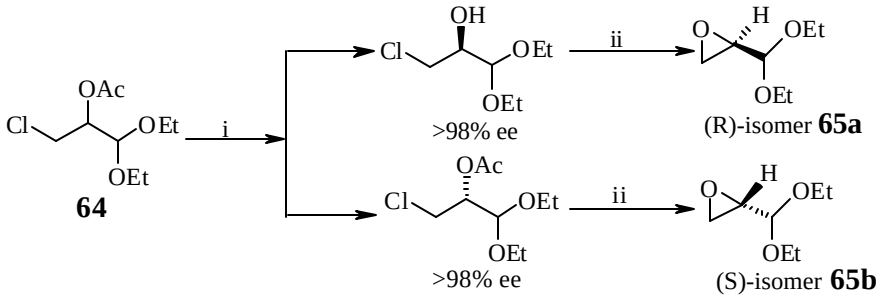
This synthetic strategy also involves 1,2-O-isopropylidene-D-glycerol (**60**) as a chiral C_3-synthon. A similar sequence of reaction as mentioned above was carried out to give (S)-DHPA (**Scheme 16**). But for obtaining the (R)-enantiomer, they subjected 1-benzyl-3-O-tosylglycerine (**61**) to hydrogenolysis and subsequent acetylation to obtain 1,2-diacetyl, 3-O-tosylglycerine (**62**), which upon reaction with sodium salt of adenine followed by deacylation gave (R)-enantiomer **63** (**Scheme 17**).



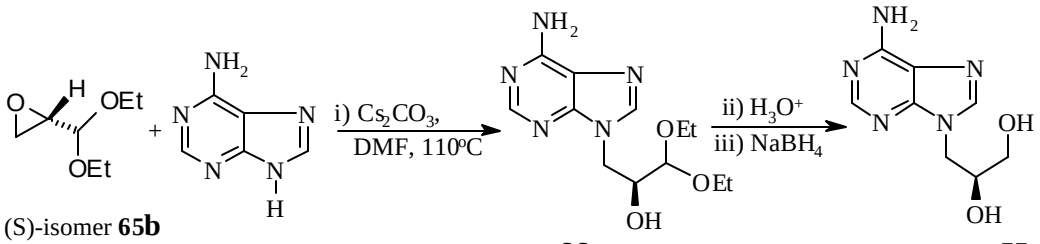
Scheme 17 :

Liu's approach (1992)[36]

This approach involves an optically active (S)-glycidaldehydediethylacetal as chiral starting material **65b**, obtained by lipase (LP-80) catalyzed resolution of 2-acetoxy-3-chloropropanaldiethylacetal **64**, followed by cyclization with KOH (**Scheme18a**). Condensation of **65b** with adenine in presence of Cs_2CO_3 gave 3-adenyl-2-hydroxypropanaldiethylacetal **66** in 54% yield. Subsequent hydrolysis of the diethylacetal followed by *in situ* reduction of aldehyde with $NaBH_4$ gave (S)-DHPA (**55**) **(Scheme 18b**).



Scheme 18a : i) Lipase (LP-80), *p*H = 7, 50% conv. (ii) Anhyd. EtOH, KOH, 0^oC, 3h

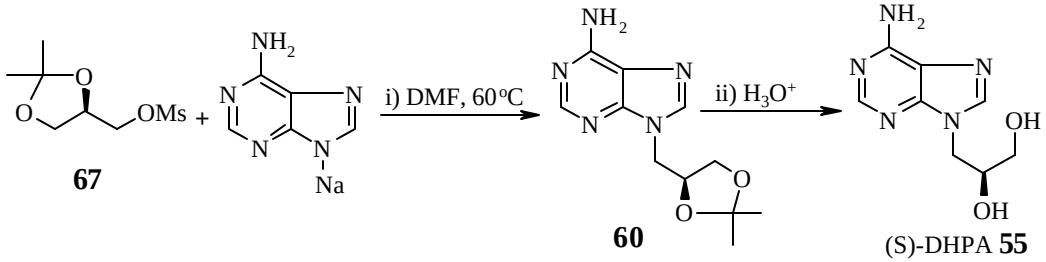


(S)-isomer **65b** **66** >97%ee (S)-DHPA **55**

Scheme 18b:

Wang's approach (1997)[37]

This approach is a modification of Holy's procedure for (S)-DHPA. Compound **59** was mesylated to give **67**, which was then condensed with Na-salt of adenine. Finally diol moiety in **60** deprotected to give (S)-DHPA (**55**) (**Scheme 19**).



67 **60** (S)-DHPA **55**

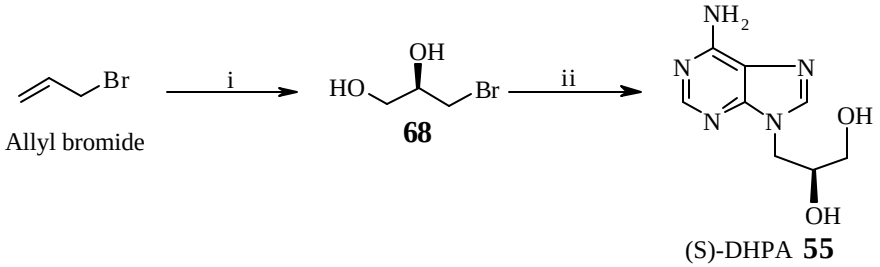
Scheme 19:

3.1.3 Present Work:

3.1.3.1 Objective:

In a view of lack of efficient procedure for asymmetric synthesis of (S)-2,3-dihydroxypropyladenine (DHPA, **55**) also due to its wide range of antiviral activities, we became interested in its short synthesis. Since most of the synthetic methods are based on D-mannitol as a chiral building block to obtain C_3-chiron that has asymmetric center at the central atom *e.g.* protected glyceraldehyde or glycerol. Consequently, carbohydrate-based synthesis tends to be circuitous and/or involved the use of expensive and/or environmentally unacceptable reagents. In this context, a more practical approach with lesser number of steps for the synthesis of (S)-DHPA is strongly desirable.

The objective of the present investigation is to provide a catalytic method based on Sharpless asymmetric dihydroxylation of allyl bromide followed by condensation of resulting bromodiol **68** with sodium salt of adenine (**Scheme 20**).



Scheme 20: (i) cat. OsO_4, $(DHQ)_2$-PHAL, $K_3Fe(CN)_6$, tBuOH:H_2O (1:1), K_2CO_3, 0-4°C, 20h,. 58%, $[\alpha]^{25}_D$ = -5.1° (c = 2.0, $CHCl_3$); (ii) Na-Adenine, 90°C, DMF, 4h. 45%, $[\alpha]^{25}_D$ = -23.2° (c = 0.8, MeOH);

3.1.4 Results and Discussion:

As depicted in **Scheme 20**, the (R)-3-bromo-1,2-propanediol (**68**) was obtained by osmium catalyzed asymmetric dihydroxylation of allyl bromide in presence of $(DHQ)_2$-PHAL as a chiral auxiliary and $K_3Fe(CN)_6$-K_2CO_3 as co-oxidant.[38] The addition of $NaHCO_3$ is essential to avoid the formation of water soluble glycidol.[38b] Although yield of

the diol is poor, the optical purity is found to be 96.63% ee based on comparison of its literature $[\alpha]_D$ value.[38b] The IR spectrum of **68** showed a broad peak at 2935-3367 cm^{-1} indicating the presence of hydroxyl groups of in the diol moiety **68**. In the ^{1}H-NMR spectrum of **68**, protons of CH_2-Br and CH_2-OH groups are diastereotopic and gave multiplets at δ 3.40-3.55 and δ 3.64-3.83 respectively. The CH at δ 3.90-4.00 also appeared as a multiplet (**Fig. 9**). The ^{13}C-NMR spectrum of diol **68** indicated three carbon signals at δ 34.32, 64.20 and 71.41corresponding to CH_2-Br, CH_2-OH and CH groups respectively (**Fig. 9**).

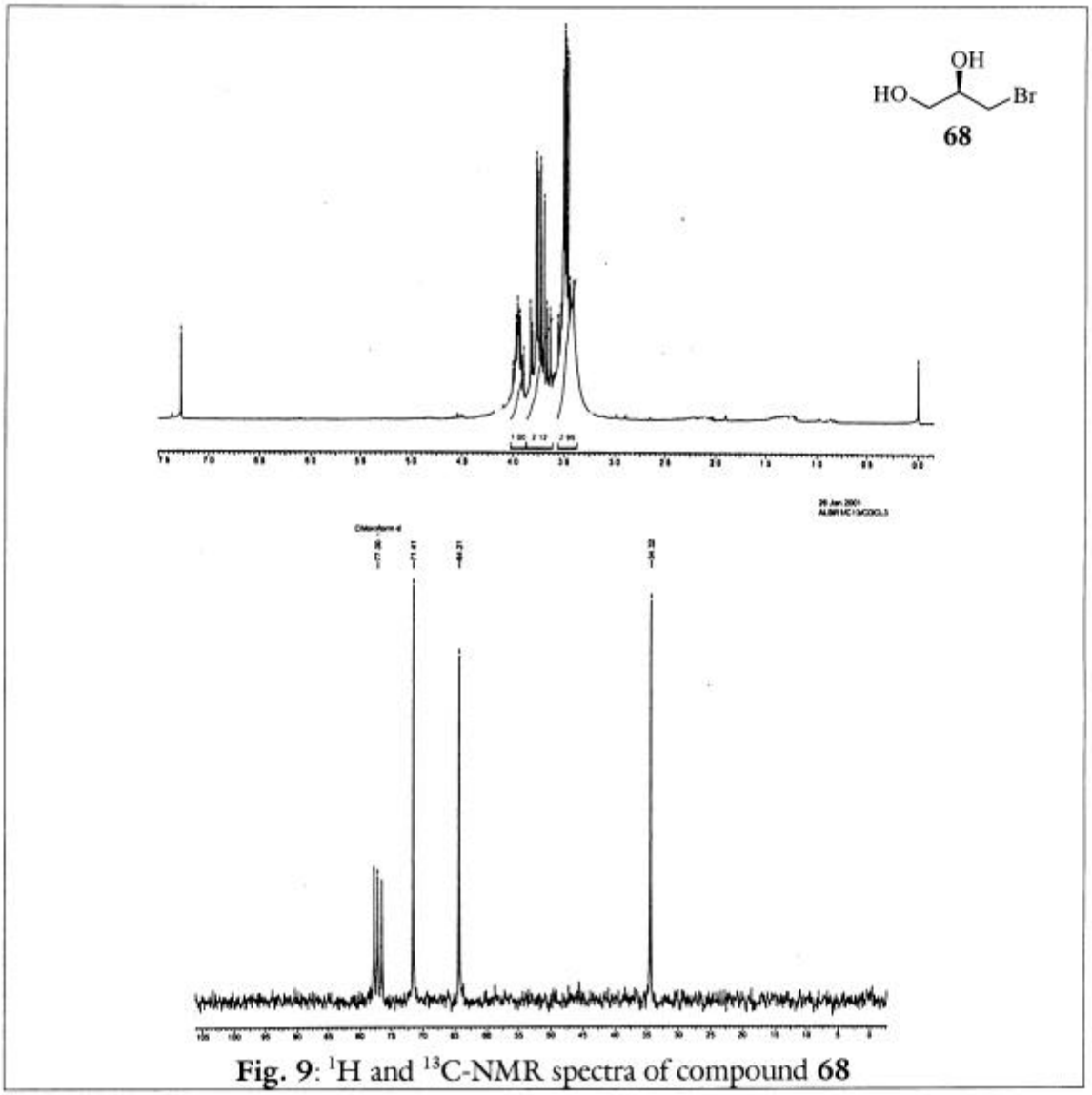
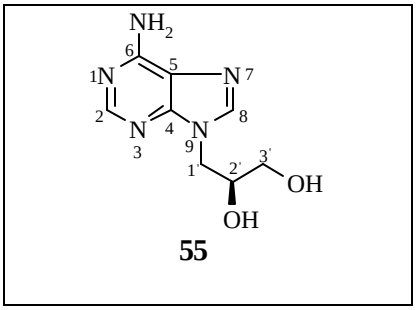


Fig. 9: ^{1}H and ^{13}C-NMR spectra of compound **68**

The sodium salt of adenine generated using sodium hydride in DMF was reacted with bromodiol **68** at 90°C for 4h. The residue formed in the reaction was filtered off and DMF was removed under reduced pressure to give crude product **55**. It was then purified by column chromatography to afford 45% of pure (S)-DHPA **55**, in 96% ee (determined by comparison of $[\alpha]_D^{25}$ with literature value[36a]). The ^{1}H-NMR spectrum of **55** recorded in D_2O indicated that the protons of the CH_2 attached to adenine moiety as well as CH_2-OH groups are diastereotopic and showed multiplets at δ 3.33-3.71 and 4.04-4.31 respectively. The signal due to CH at the chiral center merged into multiplet at δ 4.04-4.31. The sharp singlet at δ 8.02 is due to the protons of C-2 & C-8 of the adenine moiety (**Fig. 10**). The ^{13}C-NMR spectrum of **55** recorded in D_2O+MeOH-d_4 (40:60) solvent system, showed signals as follows: (spectrum in accordance with the numbering in **55** given below): δ 153.58 (C-2); 150.77 (C-4); 119.75 (C-5); 157.12 (C-6); 143.81 (C-8); 47.7 (C-1'); 70.32 (C-2'), 64.2 (C-3') respectively. The mass spectrum of **55** showed the molecular ion peak at M^+ at 209, thereby confirming the structure of (S)-DHPA (**Fig. 10**).



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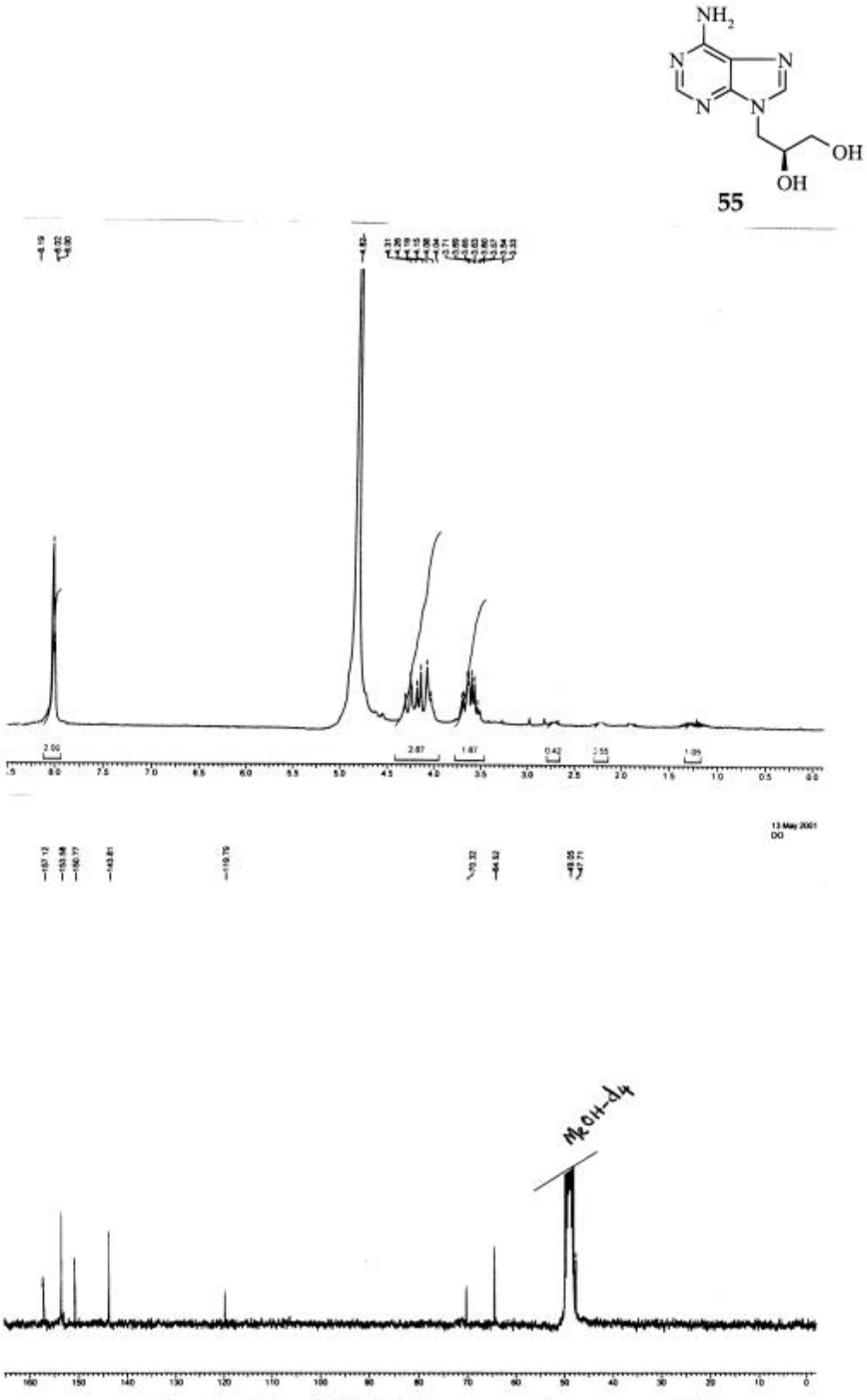

Fig. 10: ^{1}H and ^{13}C-NMR spectra of compound **55**

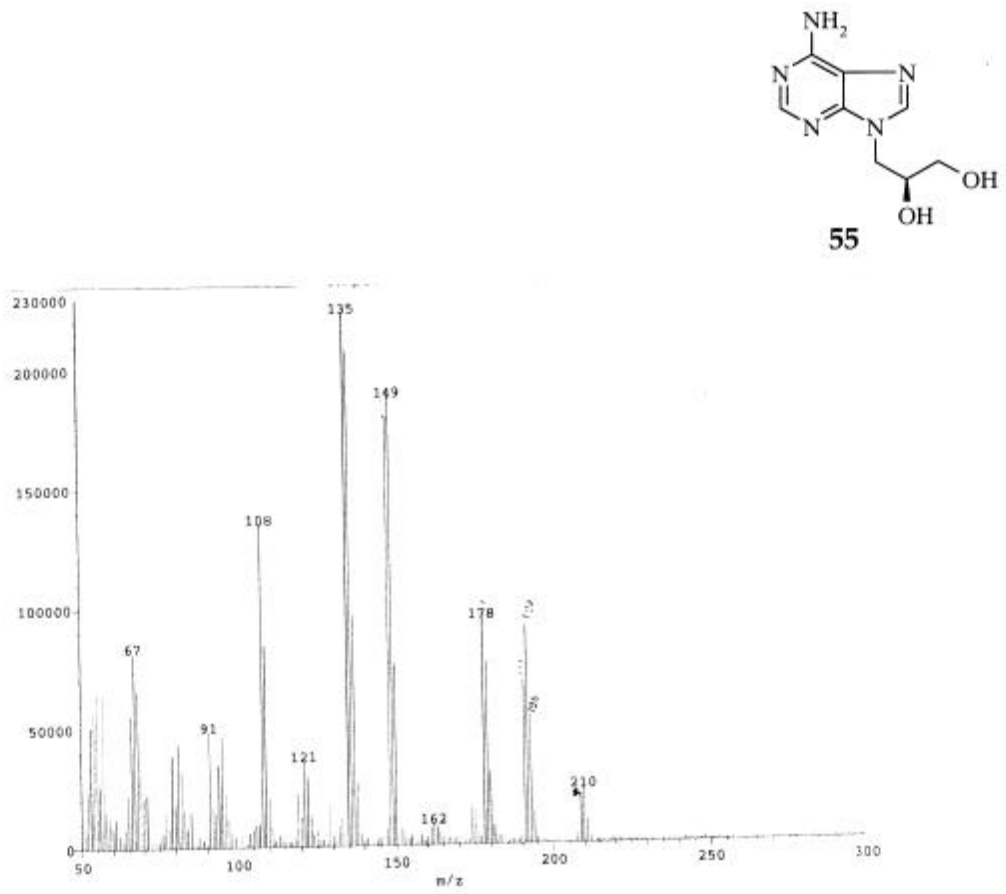

Fig. 11: Mass spectrum of (S)-DHPA

3.1.5 Conclusion:

We have achieved, for the first time, the asymmetric synthesis of (S)-adenyl-2,3-dihydroxypropyl (DHPA, **55**) *via* asymmetric dihydroxylation in a two-step procedure starting from easily available allyl bromide. Although chemical yield of the (S)-DHPA is poor, the optical purity is very high (96% ee).

3.1.6 Experimental Section:

Preparation of (R)-(-)-3-bromopropane-1,2-diol (68):

A 100 ml flask charged with $K_3Fe(CN)_6$ (6.523 g, 19.83 mmol), K_2CO_3 (2.73 g 19.83 mmol), $NaHCO_3$ (1.66 g, 19.83 mmol), $(DHQ)_2$-PHAL (0.103 g, 0.13 mmol), *t*BuOH:H_2O (40 ml, 1:1) mixture and stirred well at RT for 10 min and cooled to 0^oC, thereupon a solution of OsO_4 in toluene (0.5M, 134 μL, 0.06 mmol) was added. Finally, allyl bromide (0.800 g, 6.61 mmol) was added and the resulting reaction mixture was kept under stirring for 20h. It was then quenched by the addition of saturated sodium metabisulfite solution. It was extracted with EtOAc (3 x 25 ml), washed with brine, dried over anhydrous sodium sulfate and the solvent evaporated. The crude product was purified by column chromatography packed with silica gel {EtOAc: pet. ether (40:60)} to yield pure bromodiol **68** (0.594 g) as a colorless liquid.

Yield	:	58%
bp	:	74^oC/ 0.2 mm Hg
$[\alpha]_D^{25}$	:	-5.1 (c = 2.0, $CHCl_3$) {Lit[38b] $[\alpha]_D^{25} = -3.8^0$ (c = 1.75, $CHCl_3$)
IR (neat, cm^{-1})	:	3367, 2935, 2887, 1426, 1100, 1065, 1030,
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 3.40-3.55 (m, 2H), 3.64-3.83 (m, 2H), 3.90-4.07 (m, 1H)
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 34.32, 64.20, 71.41
Analysis	:	$C_3H_7BrO_2$; requires: C, 23.25, H, 4.55, Br, 51.55%; found: C, 23.21, H, 4.34, Br, 51.52%.

Preparation of (S)-(-)-2,3-dihydroxypropyl-(9)-adenine (55):

A flame dried two neck 25 ml RB flask was charged with dry DMF (3 ml) and NaH (0.027 g, 0.65 mmol, 60% dispersion in mineral oil), evacuated and flushed with N_2. Followed by a solution of adenine (0.087 g, 0.65 mmol) in dry DMF (1 ml) was added dropwise and kept under stirring at RT over a period of 10 min. Then solution of bromodiol **68** (0.100g, 0.65 mmol) in dry THF (1 ml) was added and the reaction mixture kept under stirring for 4h at 90°C. The residue formed in the reaction was filtered off and DMF was removed under reduced pressure to give crude product **55**. It was then purified by column chromatography packed with silica gel (MeOH:acetone, 20:80) to yield pure (S)-DHPA (0.060 g) as a white solid.

Yield	:	45%
mp	:	201-203 °C (Lit[34] 202-203°C)
$[\alpha]_D^{25}$	:	-23.2° (c = 0.8, MeOH) {Lit.[36a] -24.0°, c = 0.8, H_2O)
^{1}H-NMR (200 MHz, D_2O)	:	δ 3.33-3.71 (s, 2H), 4.04-4.31 (s, 3H), 8.02 (s, 2H, C-2 and C-8)
^{13}C-NMR (50 MHz, D_2O + MeOH-d_4, 40:60)	:	δ 153.58 (C-2); 150.77 (C-4); 119.75 (C-5); 157.12 (C-6); 143.81 (C-8); 47.7 (C-1'); 70.32 (C-2'), 64.2 (C-3').
MS (m/z, % RI)	:	209 (M^+, 8), 192 (35), 178 (45), 149 (76), 135 (100), 121 (12), 108 (54), 91 (20)

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SECTION-I

Chiral Manganese(III)-Salen as Catalyst in Asymmetric Bromination of Olefins with N-Bromosuccinimide

4.0.1 Introduction:

The dibromination of olefins constitutes an important method for the synthesis of 1,2-dibromides. Usually it is accomplished with molecular bromine[1] and often used as a test, qualitative or quantitative, for identifying the unsaturation.[2] The halo compounds have potential utilization in organic synthesis due to their ability to undergo nucleophilic transformation with nucleophiles such as OH, NHR, N_3, CN, OAc, SR, carbanions *etc*. The convenient sources for achiral dibromination of olefins are the pyridinium bromide perbromide,[3] tetrabutyl ammonium perbromide,[4] Br_2-$CuBr_2$,[5] decylNMe_3MnO_4-Me_3SiBr,[6] N-bromosuccinimide (NBS) in presence of polar solvent or addition of inorganic or ammonium salts.[7] However only few reports are available for the chiral dibromination of olefins, wherein the major emphasis has been given to vapour phase asymmetric bromination of chiral complex of olefins with either a or b-cyclodextrin. The induction of asymmetry into the molecule is due to the cyclodextrin's doughnut shaped hydrophobic pocket, which is capable of binding a variety of organic as well as organometallic molecules (**Fig. 1**). Another report deals with chiral quaternary ammonium bromides, as chiral bromine-transfer agents in asymmetric dibromination of cyclohexene.[8]

The resulting chiral dibromides can be transformed to chiral *vic*-diazides, diamines, diols, dithiols, and aziridines, which are otherwise difficult to prepare, by direct addition to olefins. Thus asymmetric dibromination of olefins can provide a potential route to prepare variety of chiral dibromo-compounds which are useful intermediates in organic synthesis.

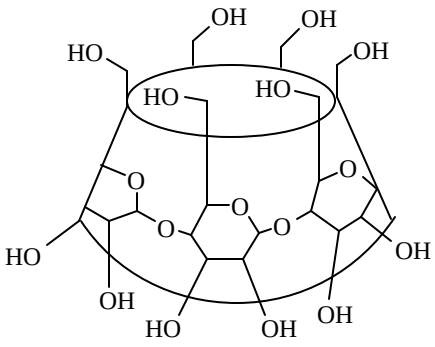


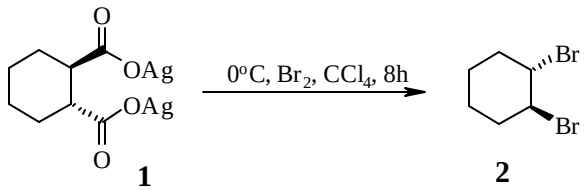
Fig. 1: b-Cyclodextrin's doughnut shaped hydrophobic pocket

Despite the importance of chiral dibromides, the catalytic asymmetric dibromination of olefins is not known in the literature. In view of its wider scope and applicability the present work was undertaken.

4.0.2 Review of Literature:

Applequist's approach (1963)[9]

In this approach Hunsdiecker reaction has been employed to synthesize chiral *trans*-1,2-dibromocylohexane (**2**). To obtain chiral dibromide **2**, the silver salt of chiral *trans*-1,2-cylcohexyldicarboxylate (**1**) was subjected to brominative decarboxylation by addition to a solution of bromine in carbon tetrachloride at 0°C (**Scheme 1**). The formation of optically active dibromide **2** had occurred with inversion of configuration.

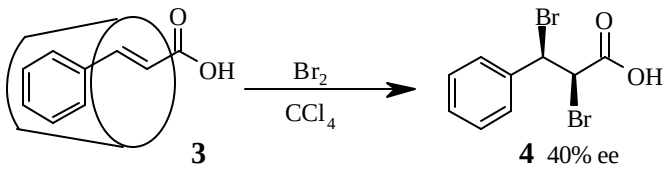


1 **2**

Scheme 1 :

Sakuraba's approach (1984)[10]

Sakuraba's approach involved asymmetric halogenation of *trans*-cinnamic acid in the cavity of *b*-cyclodextrin (**3**). It resulted in the formation of 100% stereospecific *erythro*-2,3-dibromo-3-phenylpropanic acid (**4**) in 40% optical yield. The optical yield of **4** obtained in this way was found to be much higher than *b*-cyclodextrin-assisted resolution method. Therefore, the asymmetric induction in the gas-solid reaction was not due to the optical resolution of *vic*-dibromide but the reaction itself, influenced by the chiral frame of *b*-cyclodextrin (**Fig.1** and **Scheme 2**).

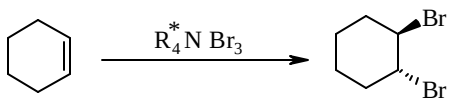


3 **4** 40% ee

Scheme 2 :

Bellucci's approach (1986)[8]

Bellucci *et al* have employed the chiral quaternary ammonium tribromide of cinchona alkaloid and N, N-methylsparteinium dibromide as bromine transfer agents in asymmetric dibromination of cyclohexene. Thereby, optically active (R, R)-(-)- and (S, S)-(+)-*trans*-1,2-dibromocyclohexane (**2**) was obtained in low to moderate yield. The highest optical rotation reported was in CCl_4 {$[a]^{25}_D$ = -8.4°} with N-benzyldihydrocinchonium tribromide and $[a]^{25}_D$ = +16.6° with a N, N-methylsparteinium dibromide for the same system (**Scheme 3**). However, no asymmetric induction was observed with (-)-benzylmethyl-phenylpropylammonium tribromide as the brominating reagent.



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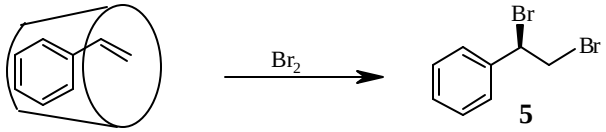
Scheme 3 :

Sakuraba's approach (1987)[11]

This approach deals with asymmetric dibromination of styrene (**Scheme 4**). The gas-solid bromination of styrene-*a* and *b*-cyclodextrin complexes was compared with homogeneous reaction either in aqueous or DMSO solutions. This study demonstrated that, chiral induction due to *a*-cyclodextrin complex was 9 times higher than that of the *b*-cyclodextrin. However, both of them yielded (-)- styrenedibromide (**5**) as a main product. On the contrary, the dibromination of styrene-*a* and *b*-cyclodextrin complexes under homogenous condition afforded racemic bromohydrin exclusively. Therefore, the chiral induction of the gas-solid halogenation using the solid cyclodextrin complexes is mainly attributed to their ability to hold rigidly a chiral conformation of crystal state.



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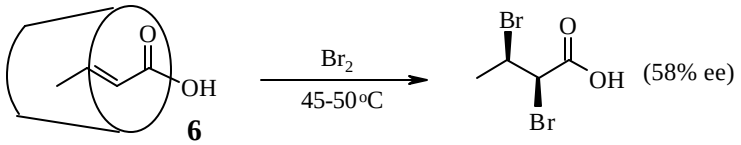
Scheme 4 :

Tanaka's approach (1990)[12]

Tanaka has studied the asymmetric bromination of *trans*-2-butenoic acid (**6**) in crystalline *a*-cyclodextrin complex at 45-50°C. The *erythro*-dibromide was obtained exclusively with low optical purity (**Scheme 5**).



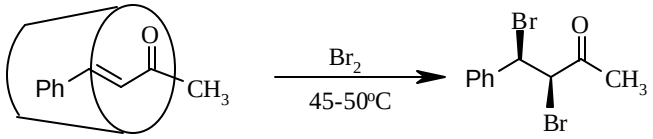
6

Scheme 5

Pitchmuni's approach (1994)[13]

Pitchmuni *et al* have also employed cyclodextrin for the asymmetric dibromination of chalcone and benzylideneacetone (BA) (**Scheme 6**). During their study they observed

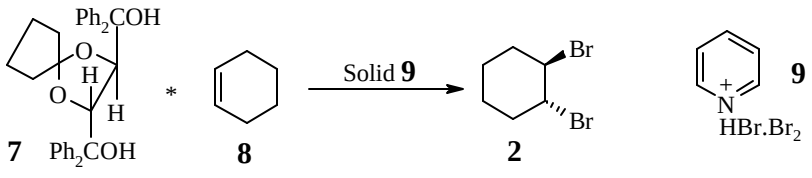
that, the *b*-cyclodextrin-BA complex upon bromination yields exclusively *erythro*-dibromide, which is similar to that of conventional bromination. However, a mixture of *erythro* and *threo*-dibromides were obtained in the ratio of 80:20 respectively in the bromination of *b*-cyclodextrin chalcone complex. This difference in the bromination of the two *b*-cyclodextrin complexes lies in their specific mode of complexation of the substrate into the cyclodextrin cavity.



Scheme 6

Koichi's approach (1999)[14]

Koichi *et al* have studied the asymmetric bromination of cyclohexene in the inclusion crystal of cyclohexene (**8**) with optically active host compound **7**. When a mixture of (-)- **7** and cyclohexene **8** in 2:1 ratio was kept in ether at room temperature for 12 h, an inclusion complex was obtained as a colorless prism in 72% yield. The powder of this complex mixed with solid brominating agent, pyridinium bromide perbromide (**9**), was kept at room temperature in the solid state for 3 days (**Scheme 7**). Upon work up, the (+)-*trans*-1,2-dibromocyclohexane (**2**) was obtained in 56% yield and 12% ee.



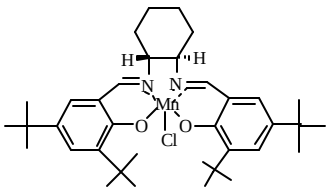
Scheme 7 :

4.0.3 Present Work:

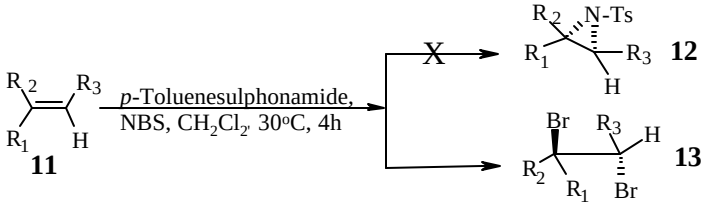
4.0.3.1 Objective:

We envisaged that chiral aziridines (**12**) could be obtained when olefins such as **11** are reacted with *p*-toluenesulphonamide, N-bromosuccinimide (NBS) and Mn(III)-Salen complex **10** (Jacobsen's catalyst, purchased from Aldrich, USA) in dichloromethane at room temperature (**Scheme 8**, R_1 = Ph, R_2 = R_3 = H, **11a**). The logic behind this chemistry was that, upon bromination of *p*-toluenesulphonamide by NBS, the corresponding dibromosulphonamide would be formed. Under the influence of catalyst **10,** the dibromide formed *in situ* is expected to react with olefins to give chiral tosyl aziridines **12**. However, instead of aziridination, styrene underwent asymmetric dibromination (**13**) with the recovery of unreacted sulphonamide (**Scheme 8**). This has prompted us to undertake this study systematically, the results of which are presented in this chapter.

Traditionally, NBS is used for benzylic and allylic bromination, without affecting the C=C. However, it is also possible to brominate C=C with NBS by the use of either polar solvent or addition of inorganic or ammonium salts.[7] We observed that in presence of chiral Mn(III)-Salen catalyst **10**, NBS is useful for asymmetric bromination of C=C (**Scheme 8**). The Jacobsen's catalyst (**10**), has been used extensively for asymmetric epoxidation, aziridination, hydroxylation, *etc*,[15] However, its use as a chiral catalyst for asymmetric dibromination of olefins is not known in the literature.



Jacobson's catalyst (10)



Scheme 8 : Asymmetric dibromination

4.0.4 Result and Discussion:

For a systematic investigation of asymmetric dibromination, styrene was chosen as a model substrate. To optimize the reaction conditions, various solvents such as DCM, acetonitrile, THF, benzene, and toluene were tried for the asymmetric dibromination of styrene at 30°C. Among these, benzene was proved to be the best solvent, where the highest yield and optical rotation of the chiral styrenedibromide was obtained {92%, $[\alpha]^{25}_{D}$ = -1.12° (c = 4.6, C_6H_6)}. Since most of the asymmetric reactions are performed at 0°C and below that temperature to ensure the highest optical activity, we also studied the effect of temperature on optical purity of the dibromide. Accordingly, asymmetric bromination of styrene was studied in toluene at -20°C to 0°C to improve the optical purity. However, no significant increase in optical rotation has been observed. The *cis*-stilbene under identical reaction conditions afforded optically active (-)-1,2-dibromo-1,2-diphenylethane (**Table 1**, **13c**) in 85% yield with high degree of optical rotation {$[\alpha]_D^{25}$ = -6.86° (c = 3.3, C_6H_6)} than dibromostyrene. The optical induction in **13c** is the result of *trans* addition of Br_2 across the C=C. The IR spectrum of **13c** showed intense band at 694 cm^{-1} corresponding to C-Br bond vibration. Its ^{1}H-NMR spectrum indicated sharp singlet at δ 5.50 and 7.19 are due to CH and aromatic protons respectively (**Fig. 2**). Its ^{13}C-NMR showed characteristic signals at δ 59.09 and 137.70 corresponding to that of CH and quaternary carbons respectively (**Fig. 2**).

To explore the scope of this reaction wide range of olefins have been subjected to asymmetric dibromination (**Table 1**). As indicated in **Table 1**, the yields of the chiral dibromides range from 45-90% and are less dependant upon the substituent on the aromatic ring. However, lower yields are also observed with the olefins bearing electron withdrawing groups (**11f**, **i**, **j**). The *anti* addition of bromine across C=C of *cis*-1,2-disubst-

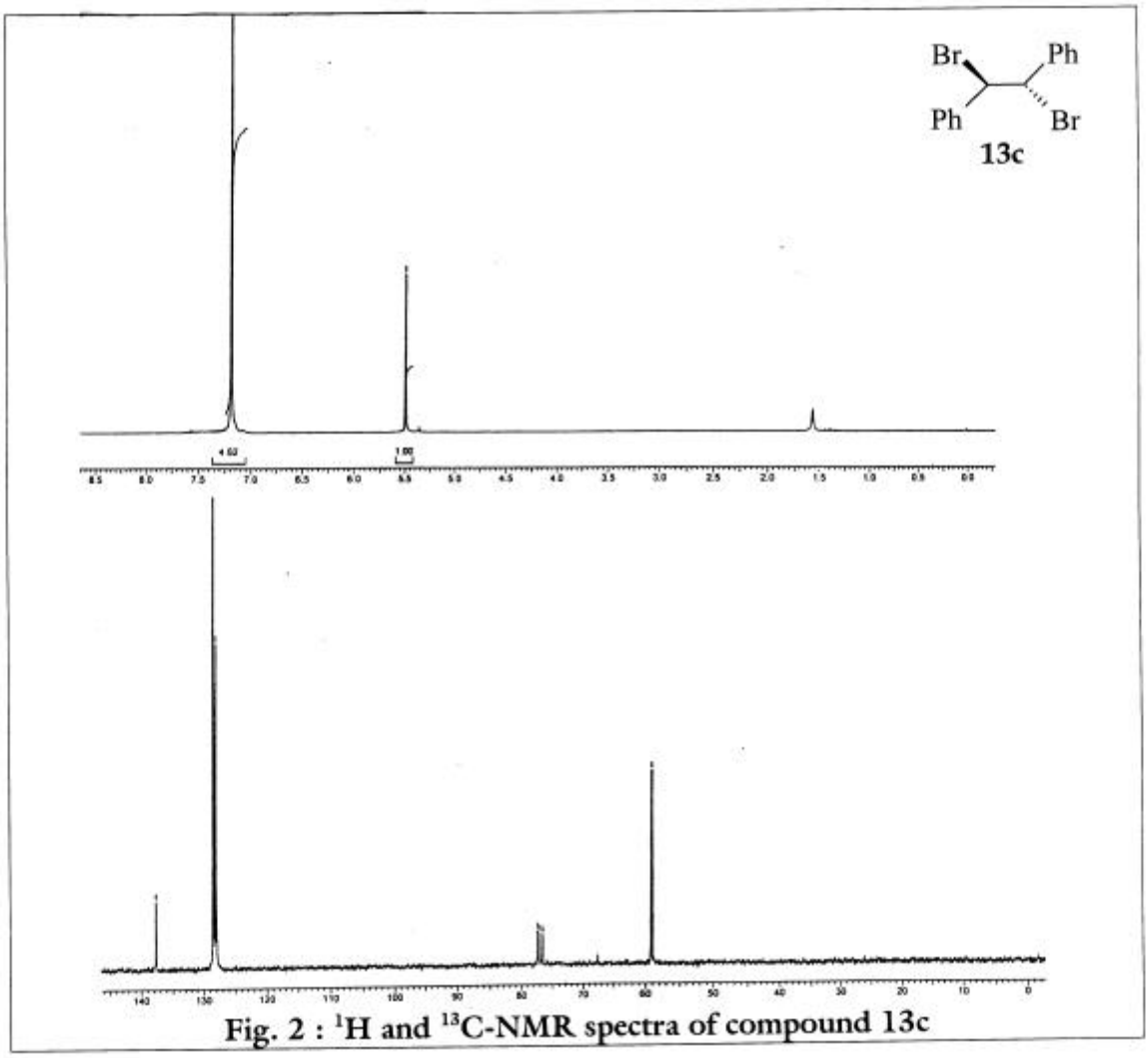


Fig. 2 : ^{1}H and ^{13}C-NMR spectra of compound 13c

ituted olefins (**11c**, **d**, **e**, **f**) led to chiral *threo*-dibromides (**Fig. 3**), while anti addition to *trans*-1,2-disubstituted olefins (**11g**, **h**, **i**, **j**) led to *erythro*-dibromides (**Fig. 4**). In case of *trans*-stilbene (**11h**), the *anti* addition of bromine leads to *meso* dibromide with zero optical rotation. The α-methyl-4-chlorostyrene upon dibromination yielded dibromide with low optical rotation (**11k**).

Fig. 3: Anti-addition of Br_2 to *cis*-olefins

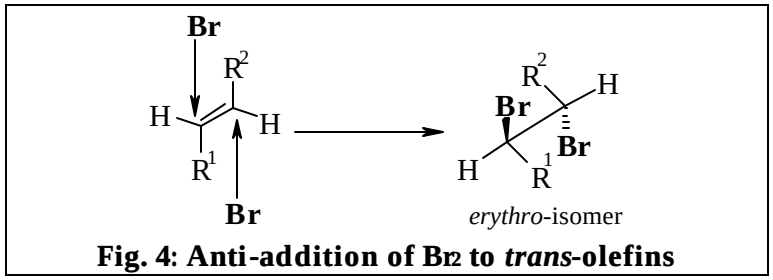
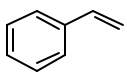
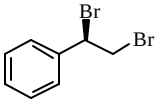
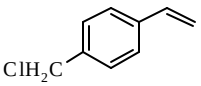
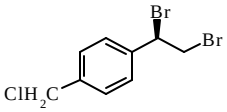
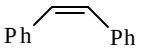
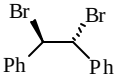
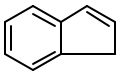
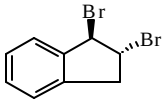
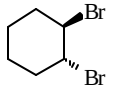
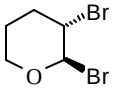
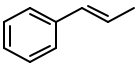
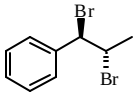
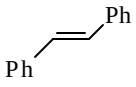
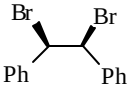
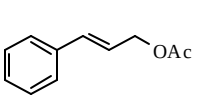
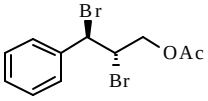
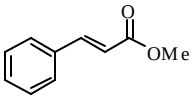
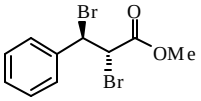
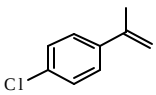
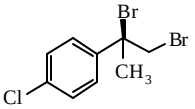


Fig. 4: Anti-addition of Br_2 to *trans*-olefins

Table 1: Chiral Mn(III)-Salen complex (**10**) catalyzed asymmetric bromination of olefins:

No	Substrate (**11**)	Product (**13**)	Yield[a](%)	Mp/bp (°C)	$[\alpha]^{25}_D$
a.			91[b]	73-75	-1.12 (c=4.6, C_6H_6)
b.			85[b]	79-80	-1.44 (c=5.7, C_6H_6)
c.			85[b]	118-120	-6.86 (c=3.3, C_6H_6)
d.			70[b]	126-128	-2.18 (c=2.0, C_6H_6)
e.			85[b]	102-104, 14mm Hg	+6.40 (c=2.5, C_6H_6)
f.			50[c]	gum	+2.68 (c=5.0, C_6H_6)
g.			66[b]	105-106	-7.26 (c=3.7, C_6H_6)
h.			85[b]	>210 dec.	0.0 (c=4.0, C_6H_6)
i.			45[c]	94-95	-2.53 (c=3.0, C_6H_6)
j.			40[c]	119-121	+1.47 (c=1.8, C_6H_6)
k.			45[b]	gum	-0.22 (c=3.6, C_6H_6)

a) Yields refer to isolated *vic*-dibromo compounds after column chromatographic purification; b) reaction completed in 4h; c) reaction for 12 h

Berti and Marsili have reported that optical rotation {$[\alpha]^{25}_{D}$ = +6.4°} for *trans*-1,2-dibromocyclohexane (**13e**) corresponds to ~6% ee.[16] This low ee is associated with the major contribution of the *meso* dibromide as reported by Eliel *et al* by analyzing the IR spectroscopy.[17] Not much data is available on optical purity for other chiral dibromo-compounds.

The plausible explanation for possible chiral induction into the dibromides is the prior coordination of olefin with the chiral catalyst **10**, wherein the incoming bromine atoms are directed in a diastereomeric manner. However no allylic or benzylic bromination is observed under these reaction conditions and therefore the reaction is chemoselective.

4.0.5 Conclusion:

We have developed a new, simple and practical method for the asymmetric dibromination of olefins using commercially available Jacobsen's Mn(III)-Salen catalyst, wherein N-bromosuccinimide is used as a mild brominating agent. The reaction proceeds to give high yields of the dibromides.

4.0.6 Experimental Section:

Typical Experimental Procedure for Preparation of 1,2-Dibromo-1-phenylethane (13a):

A 25 ml dry RB flask charged with styrene (0.500 g, 4.8 mmol), N-bromosuccinimide (1.88 g, 10.6 mmol), catalyst **10** (64 mg, 0.1 mmol), dry benzene (10 ml) and stirred under nitrogen atmosphere at room temperature. After completion of the reaction (monitored by TLC, 5% ethyl acetate in pet. ether), reaction mixture was diluted with ethyl acetate (30 ml), washed with water followed by brine and dried over anhydrous sodium sulfate and evaporated under vacuum. The crude product obtained was crystallized from ethyl alcohol to yield pure 1.15 g of 1,2-dibromo-1-phenylethane.

1, 2-Dibromo-1-phenylethane (13a):

Yield	:	91%
mp	:	73-75°C
$[\alpha]^{25}_D$	:	-1.12° (c = 4.6, C_6H_6)
IR (nujol, cm^{-1})	:	2954, 1514, 1463, 1438, 1377, 1265, 1199, 1134, 914, 840, 725, 680, 554.
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 3.98-4.15 (m, 2H), 5.12-5.20 (dd, *J* = 6.0 Hz, *J* = 6.0 Hz 1H), 7.40 (s, 5H)
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 35.02, 50.90, 127.62, 128.76, 129.09, 138.61
MS (m/z, % RI)	:	264 (M^+, 5), 185 (96), 183 (100), 77 (45), 63 (8)
Analysis	:	$C_8H_8Br_2$, requires: C, 36.40; H, 3.05; Br, 60.54%; found: C, 36.38; H, 2.98; Br, 60.51%.

1, 2-Dibromo-1-(4-chloromethylpenyl)ethane (13b):

Yield	:	85%
mp	:	79-80°C
$[\alpha]^{25}_D$	:	-1.44° (c = 5.7, C_6H_6)
IR (nujol, cm^{-1})	:	2954, 1514, 1463, 1438, 1377, 1265, 1199, 1134, 914, 840, 725.
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 4.0-4.1 (m, 2H), 4.51 (s, 2H), 5.1-5.2 (dd, *J* = 6.0 Hz, *J* = 6.0 Hz, 1H), 7.41 (s, 4H)
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 34.69, 45.46, 50.02, 128.02, 128.98, 138.00, 138.72
MS (m/z, % RI)	:	312 (M^+, 2), 268 (5), 233 (87), 152 (20), 117 (100), 91 (20)
Analysis	:	$C_9H_9Br_2Cl$, requires: C, 34.59; H, 2.90; Halogen, 62.50%, found: C, 34.21; H, 2.88; Halogen, 62.52%.

1, 2-Dibromo-1,2-diphenylethane (13c):

Yield	:	85%
Mp	:	118-120°C
$[\alpha]^{25}_D$	:	-6.86° (c = 3.3, C_6H_6)
IR (nujol, cm^{-1})	:	2956, 2923, 2854, 1496, 1454, 1377, 1199, 1135, 1072, 763.
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 5.5 (s, 2H), 7.2 (s, 10H).
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 59.09, 128.09, 128.49, 137.70.
MS (m/z, % RI)	:	340 (M^+, 2), 261 (30), 180 (100), 165 (25), 152 (10).
Analysis	:	$C_{14}H_{12}Br_2$, requires: C, 49.45; H, 3.57; Br, 46.99%, found: C, 49.39; H, 3.29; Br, 46.62%.

1, 2-Dibromoindane (13d):

Yield	:	70%
mp	:	Gum (Lit. mp = 32°C)
$[\alpha]^{25}_D$	:	-2.18° (c = 2.0, C_6H_6)
IR (nujol, cm^{-1})	:	2923, 1463, 1438, 1377, 1346, 1290, 1215, 1170, 1114, 1066, 946, 896, 817, 750, 732, 685, 545.
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 3.2-3.3 (d, 16.0 Hz, 1H), 3.75-3.9 (dd, *J* = 7.0 Hz, *J* = 16.0 Hz, 1H), 4.8-4.9 (d, *J* = 7.0 Hz, 1H), 5.65 (s, 1H), 7.3 (s, 4H)
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 39.06, 53.93, 80.97, 122.93, 125.71, 126.90, 138.25, 141.70,
MS (m/z, % RI)	:	276 (M^+, 2), 195 (40), 115 (100), 89 (15)
Analysis	:	$C_9H_8Br_2$, requires: C, 39.17; H, 2.92; Br, 57.91%, found: C, 38.98; H, 2.89; Br, 57.93%.

(1S, 2S)-(+)-Dibromocyclohexane (13e):

Yield	:	85%
Mp	:	102-104°C/14 mm Hg
$[\alpha]^{25}_D$	:	+6.40° (c = 3.3, C_6H_6) {Lit.[8] $[\alpha]^{22}_D$ = -27.0 (neat)}
IR (neat, cm^{-1})	:	2939, 2860, 1446, 1431, 1357, 1336, 1267, 1178, 1161, 999, 972, 902, 860, 811, 696, 663.
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 1.52-1.59 (m, 6H), 2.3-2.55 (m, 2H), 4.46 (s, 2H)
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 22.38, 32.01, 55.06
Analysis	:	$C_6H_{10}Br_2$ requires: C, 29.79; H, 4.17; Br, 66.05%; found: C, 29.76; H, 4.14; Br, 65.98%.

Tetrahydro 2, 3-dibromopyran (13f):

Yield	:	66%
mp	:	118-120°C
$[\alpha]^{25}_D$	:	+2.68° (c = 5.0, C_6H_6)
IR ($CHCl_3$, cm^{-1})	:	3016, 2954, 2854, 1434, 1334, 1218, 1141, 1064, 972, 871
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 1.7-2.5 (m, 4H), 3.5-3.65 (m, 1H), 3.9-4.2 (m, 2H), 4.98-5.0 (d, *J* = 4.0 Hz, 1H)
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 23.19, 29.88, 48.83, 62.90, 96.29
Analysis	:	$C_5H_8Br_2O$, requires: C, 24.62; H, 3.31; Br, 65.52%; found: C, 24.48; H, 3.28; Br, 65.48%.

1, 2-Dibromo-1-phenylpropane (13g):

Yield	:	66%
mp	:	105-106°C
$[\alpha]^{25}_D$	:	-7.26° (c = 3.7, C_6H_6)
IR (nujol, cm^{-1})	:	2954, 2921, 1596, 1456, 1429, 1377, 1334, 1157, 1091, 1027, 850, 817, 769, 696
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 2.05-2.08 (d, *J* = 6.0 Hz, 3H), 4.55-4.69 (m, 1H), 5.04-4.09 (d, *J* = 10.0 Hz, 1H), 7.38 (s, 5H)
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 21.45, 49.93, 52.49, 126.93, 127.54, 128.88, 138.10
MS (m/z, % RI)	:	278 (M^+, 2), 199 (55), 171 (10), 118 (100), 91 (30),
Analysis	:	$C_9H_{10}Br_2$ requires: C, 38.88; H, 3.63; Br, 57.48%, found: C, 38.98; H, 3.78; Br, 57.42%.

2, 3-Dibromo-3-phenyl-1-propylacetate (13i):

Yield	:	45%
mp.	:	94-95°C
$[\alpha]^{25}_D$	:	-2.53 (c = 3.0, C_6H_6)
IR ($CHCl_3$, cm^{-1})	:	3016, 1751, 1458, 1380, 1365, 1218, 1149, 1056, 771, 694, 671.
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 2.2 (s, 3H), 4.6-4.8 (m, 3H), 5.18-5.25 (d, *J* = 9.0 Hz, 1H), 7.35 (s, 5H)
MS (m/z, % RI)	:	255 (M^+-80, 20), 213 (25), 197 (60), 183 (30), 133 (20), 115 (80), 105 (100), 91 (40), 77 (60)
Analysis	:	$C_{11}H_{12}Br_2O_2$, requires: C, 39.32; H, 3.60; Br, 47.56%, found: C, 38.98; H, 3.83; Br, 47.52%.

Methyl (2R, 3S)-dibromopropinoate (13j):

Yield	:	40%
mp	:	119-120°C
$[\alpha]^{25}_D$	:	+1.47° (c = 1.8, C_6H_6) {Lit. $[\alpha]^{20}_D$ = +56.8}
IR ($CHCl_3$, cm^{-1})	:	3016, 2954, 1735, 1434, 1373, 1319, 1272, 1218, 1141, 1018, 987, 925, 756, 694, 601
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 3.8 (s, 3H), 4.8-4.9 (d, *J* = 12.0 Hz, 1H), 5.03-5.04 (d, *J* = 12.0 Hz, 1H), 7.4 (s, 5H)
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 46.64, 50.57, 53.36, 128.02, 128.83, 129.34, 137.47, 168.27
Analysis	:	$C_{10}H_{10}Br_2O_2$, requires: C, 37.30; H, 3.13; Br, 49.63%, found: C, 37.38; H, 3.11; Br, 49.59%.

1, 2-Dibromo-1-methyl-1-(4-chlorophenyl)ethane (13k):

Yield	:	45%
$[\alpha]^{25}_{D}$	:	-0.22° (c = 3.6, C_6H_6)
IR (nujol, cm^{-1})	:	2954, 1514, 1463, 1438, 1377, 1265, 1199, 1134, 914, 840, 725, 680, 560.
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 1.65 (s, 3H), 3.7 (s, 2H), 7.3-7.4 (d, *J* = 4.5 Hz, 2H), 7.4-7.5 (d, *J* = 4.5 Hz, 2H)
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 27.99, 45.78, 71.25, 126.41, 128.52, 133.37, 142.71
MS (m/z, % RI)	:	232 (M^+-80, 35), 155 (100), 139 (20), 125 (15), 115 (70),
Analysis	:	$C_9H_9Br_2Cl$, requires: C, 34.59; H, 2.90; Halogen, 62.50%, found: C, 34.52; H, 2.78; Halogen, 62.42%.

Catalytic C-H Oxidation of Alkyl Arenes to Aryl *tert* Butyl Peroxide with TBHP over Ru(III)-Exchanged Montmorillonite K10*

4.0.7 Introduction:

The oxidation of benzylic C-H bond of the alkyl arenes constitutes a potential route to functionalisation of the alkyl arenes into oxygenated derivatives such as peroxides, alcohols, aldehydes, ketones and acids. The chemoselective oxidation of alkyl arenes to produce specific oxygenated derivatives is of crucial importance. Particularly, the benzylic C-H bond exhibits highest reactivity due to its low dissociation energy as compared to other alkyl C-H bonds. The order of reactivity pattern follows: benzylic C-H bonds (~85 k. cal/mol) > tertiary C-H (~91 k. cal/mol) > secondary C-H bonds (~94 k. cal/mol) > primary C-H bonds (~98 k. cal/mol). As a result, benzylic C-H oxidations are complicated due to several competing reaction pathways resulting in the range of oxygenated products.

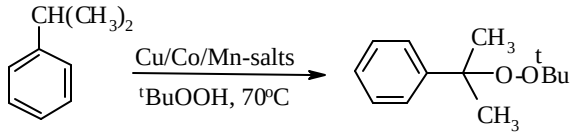
Organic peroxides are involved in many biological processes including development of rancidity in fats, loss of activity of vitamin products and firefly bioluminescence. The synthetic application of these peroxides lies in their ability to decompose to valuable compounds.[18] Some biological products contains a peroxide group *e.g.* the naturally occurring qinghaosu is a 1,2,4-trioxane, possesses antimalarial properties. Whereas endoperoxide, ascardole, possesses sedative, analgesic, antirheumatic and antihelmintic properties. Organic peroxides are also involved in synthetic processes like gum formation in lubricating oils, prepolymerization of some vinyl monomers and degradation of olefin polymers.[19]

*Milind D. Nikalje, A. Sudalai, *Tetrahedron* **1999**, *55*, 5903

4.0.8 Review of Literature:

Kharasch's approach (1959)[20]

The first transition metal catalyzed C-H oxidation of alkyl arenes was proposed by Kharasch *et al* in 1959. Cumene was subjected to oxidation with *tert*. butyl hydroperoxide (TBHP) in presence of homogeneous catalysts such as copper, cobalt or manganese salt at 70°C to obtain *tert*. butyl cumylperoxide **14** (**Scheme 9**). However the reaction suffers from low yield of peroxide **14**, due to the unproductive catalytic decomposition of TBHP.

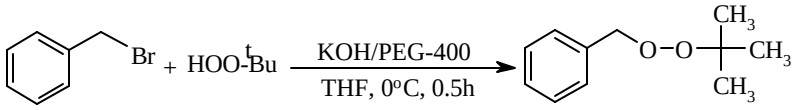


14

Scheme 9 :

Bourgeois's approach (1989)[21]

Bourgeois's approach to obtain unsymmetrical peroxides involved coupling of alkyl bromides or mesylates with TBHP under strong basic conditions. Thus, when benzylbromide is treated with TBHP in the presence of PEG-400 and KOH, benzyl *tert*. butylperoxide (**15**) was formed in 70% yield (**Scheme 10**).



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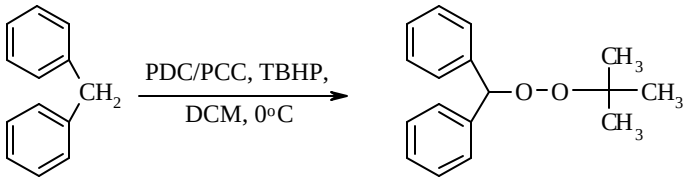
Scheme 10 :

Muzart's approach (1994)[22]

Muzart's work on oxidation of alkyl arenes deals with chromium based catalytic system, wherein the benzylic C-H oxidations with TBHP in presence of chromium catalyst led to the formation of ketones *via* aryl *tert*. butylperoxides as intermediate. However, in

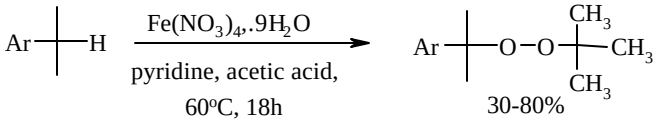
certain cases these intermediates have been isolated and characterized by NMR and IR spectroscopy, *e.g.* during oxidation of fluorene, cumene, indane, diphenylmethane and ethyl benzene, it is possible to isolate peroxides (*e.g.* **Scheme 11**).



Scheme 11 :

Minisci's approach (1994)[23]

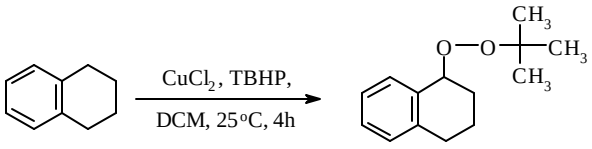
Minisci *et al* have employed Gif-Barton oxidation protocol for oxidation of alkyl arenes. Toluene, ethyl benzene, cumene and p-cymene underwent peroxidation with iron as catalyst in presence of pyridine (**Scheme 12**).



Scheme 12 :

Sasson's approach (1996)[24]

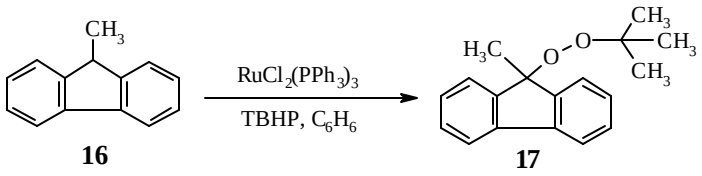
Sasson *et al* have developed a copper based homogeneous catalytic system for *tert.* butyl peroxidation of tetralin with TBHP, wherein improved yield of the *α-tert.* butyl-peroxytetralin formation was observed in presence of phase transfer catalyst (**Scheme 13**).



Scheme 13 :

Murahashi's approach (2000)[25]

Murahashi *et al* have studied the ruthenium catalyzed oxidation of 9-methylfluorene (**16**) with TBHP to give 9-methyl-9-*tert*. butylperoxyfluorene (**17**). The unsymmetrical peroxide **17** was obtained in 98% yield (**Scheme 14**).



16 **17**

Scheme 14 :

4.0.9 Present Work:

4.0.9.1 Objective:

Most of the methods reported in the literature for peroxidation of alkyl arenes suffer from low yields, use hazardous oxidizing reagents and often contaminat with unwanted by-products. Indeed in most of the cases selectivity for peroxide is low, due to the higher oxidation potential of the catalyst.

Kharasch reported that the low yield of the peroxide formation is associated with the unproductive decomposition of the TBHP. Muzart has observed that the over oxidations potential of Cr-based catalyst led to low yield of peroxides with the generation of toxic chromium residues. Sasson has observed that, $CuCl_2$ catalyst under the phase-transfer condition, proceed to give peroxide with the low conversion efficiency. However, under the Gif-Barton oxidation, the substrates to oxidant need to be quite high for a moderate conversion as reported by Minsci *et al*. Furthermore, the coupling of peroxides with alkyl bromides or mesylates requires strong basic condition and did not always lead to pure peroxides. In this context, cleaner, practical and heterogeneous catalytic method assumes great importance.

Accordingly, the objective of the present investigation is to develop a new heterogeneous catalytic method for the chemoselective oxidation of alkyl arenes to aryl *tert* butyl peroxides. The heterogeneous catalyst system has advantages over homogeneous one, as it is possible to bring about high chemical conversion with a small amount of catalyst. In view of this we developed a new Ru(III)-exchanged mont. K10 clay as catalyst for peroxidation of alkyl arenes, the results of which are presented in this chapter.

4.0.9.2 Naturally Occurring Clay Minerals[26b]:

Clay minerals are extremely fine crystals or particles, often colloidal in size and usually plate like in shape (**Fig. 4**). They are predominantly composed of hydrous phyllosilicates of aluminum, magnesium, potassium and iron. They are so finely divided that clay properties are often controlled by the surface properties of the minerals rather than by bulk chemical composition. Particle size, shape, nature and the distribution of amount of both mineral and organic impurities, nature and amount of exchangeable ions and degree of crystal perfection are all known to affect the properties of clays profoundly. Many clay mineral crystals carry an excess negative electric charge owing to internal substitution by lower valent cations, which increase the internal reactivity. Furthermore, these cations can be exchanged with transition metal cations to enhance its reactivity.

The Al^{3+}-cations in clays are bonded to an octahedral arrangement of oxygen anions. Repetition of these AlO_6 units in two dimensions forms an octahedral layer. Likewise, a tetrahedral layer is formed from SiO_4 units. The resulting sheets are planar. These planar clay platelets stack on top of one another. These clays are classified according to the relative number of tetrahedral and octahedral layers (**Fig. 5**).

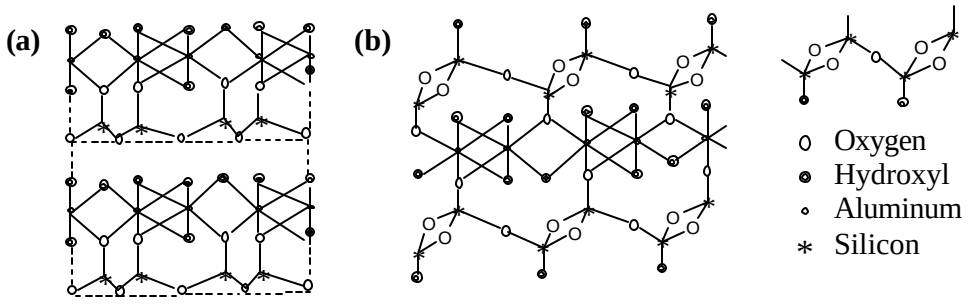


Fig. 5 : Structural arrangement of AlO_4^- and SiO_4^- in (a) Kaolinite and (b)Montmorillonite clay

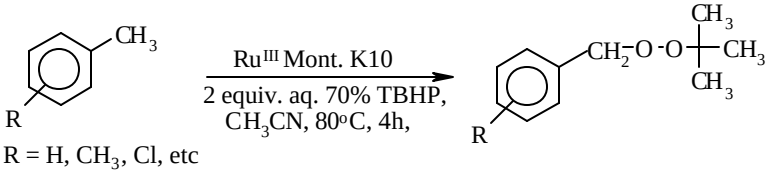
4.0.9.3 Preparation and Characterization of Ru(III), Mn(II) and Cu(II)-Exchanged Montmorillonite K10 Catalysts:

Ru(III), Mn(II), and Cu(II)-exchanged mont. K10 clay catalysts were prepared by exchanging the montmorillonite K10 clay with dilute solutions of $RuCl_3$, $Mn(NO_3)_2.6H_2O$ and $Cu(NO_3)_2$ respectively. In case of Ru-exchanged mont. K10, a mixture containing $RuCl_3$ (0.3 g) and mont. K10 clay (25 g) in distilled water (300 ml) was stirred vigorously at room temperature for 24 h. It was then centrifuged and clay washed repeatedly with distilled water until the discarded filtrate was free from Cl^- ions. Finally it was dried at 110^OC for 12 h and characterized by EDX, XRD, and cyclic voltammetry.

The metal content of all the catalysts was determined by electron disperse X-ray microscope (EDX) (Kevex, US) connected to JEOL (JSM 5200) and scanning electron microscope (SEM). In case of Ru(III)-exchanged mont. K10, it was determined that 5% ruthenium exchanged with the clay. The surface area of the Ru(III), Mn(II) and Cu(II)-exchanged mont. K10 was determined by Brunauer-Emmette-Teller method and are determined as 258, 255 and 238 m^2/g respectively. The XRD pattern of these samples indicated that they were crystalline in nature and no significant differences were observed among their structures. The X-ray photoelectron spectroscopy (XPS) and cyclic voltammetry (CV) were used to determine the nature of the metal species present in the catalyst. The XPS of Ru(III)-exchanged mont. K10 clay indicated two peaks at 282.2 and 286.2 eV, which correspond to Ru-$3d_{5/2}$ and $3d_{3/2}$ levels of Ru(III)-oxidation state. The CV of ruthenium in clay recorded at a scan rate 100 mV/sec shows a reversible peak at E_p = -131.6 mV (vs SCE) which corresponds to that of ruthenium Ru(III) to Ru(IV) redox process.

4.0.9.4 Transition Metal-Exchanged Clays Function as Efficient Catalysts:

The natural and transition metal-exchanged clays possesses Bronsted and Lewis acidic sites, which makes them as efficient catalyst in various organic transformations. [26] From our group various transition metals such as Pd, Cu, Rh, Mn *etc* exchanged mont. K10 clay have been developed for the C-C and C-N bond forming reactions.[27, 28] In continuation of this work, we were interested to study the Ru(III)-exchanged mont. K10 catalyzed oxidation of aryl methyl groups to carboxylic acid with TBHP. However, we observed that the reaction stops at peroxide stage without undergoing further oxidation (**Scheme 15**).



Scheme 15: Peroxidations of alkyl arenes

4.1.0 Results and Discussion:

The Ru(III)-exchanged mont. K10 catalyzed peroxidation of alkyl arenes is depicted in **Scheme 15**. A systematic study on peroxidation of toluene with aq. 70% TBHP in presence of different metal exchanged clays has been carried out and the results are given in **Table 2** The results clearly show that the Ru(III)-exchanged mont. K10-TBHP combination exhibits much higher activity and selectivity for the formation of peroxide as compared to other Mn and Cu-exchanged mont. K10 catalysts. It was also found that both solvent (CH_3CN) and TBHP (2 equiv.) are critical in obtaining high yield. Also, it may be noted that $RuCl_3$ failed to activate toluene and therefore no peroxidation was observed under homogeneous conditions.

Table 2: Effect of catalyst, solvent and oxidant for benzyl *tert* butylperoxide formation:

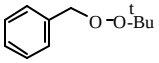
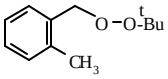
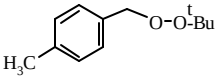
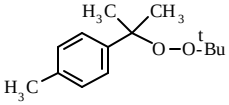
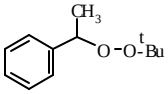
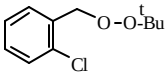
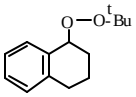
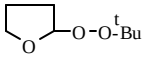
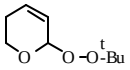
Entry	Catalyst	Surface area[a] (m^2/g)	Solvent	TBHP[b]	Yield[c] (%)
1	Ru-Mont K10	258	CH_3CN	2.0	60
2	Mn-Mont K10	255	CH_3CN	2.0	7
3	Cu-Mont K10	238	CH_3CN	2.0	14
4	$RuCl_3$- hydrate	--	CH_3CN	2.0	0
5	Ru-Mont K10	258	MeOH	2.0	30
6	Ru-Mont K10	258	Acetone	2.0	42
7	Ru-Mont K10	258	CH_3CN	1.1	2
8	Ru-Mont K10	258	CH_3CN	1.7	45
9	Ru-Mont K10	258	CH_3CN	2.2	62

a) Determined by Brunauer-Emmette-Teller (BET) method; b) TBHP equiv. is based on substrate used
c) isolated yield after chromatographic purification (silica gel, pet. ether)

In order to study the scope and limitation of this reaction, various alkyl arenes were subjected to oxidation in presence of Ru(III)-exchanged mont. K10 (**Table 3**) and the reaction are found to be quite general. The reactivity pattern of different arenes and cyclic ethers towards TBHP under the present conditions follows the sequence: $RO\text{-}CH_2 > R_3CH > R_2CH_2 > RCH_3$. A remarkable feature of the present oxidation process is that one of the methyl groups is selectively oxidized in xylenes (entry **b** & **c**), while in the case of *p*-cymene (entry **d**), the oxidation occurs at the C-H group in preference to the CH_3 group. However, electron rich substrates such as isobutylbenzene (entry **j**) and fluorene (entry **k**) are oxidized exclusively at the benzylic positions to give the corresponding ketones in high yields. Also noteworthy is the selective oxidation occurring at the *a*-position of THF (entry **h**) and 3,4-dihydropyran (entry **i**) to give the corresponding *tert.* butyl peroxides in moderate yields (**Table 3**). The isolated yields of the peroxides are generally higher compared to the literature methods.[29]

The catalyst from the reaction mixture was recovered by simple filtration and was successfully reused for oxidation of toluene, although a lower yield (55%) of the product was realized. In order to test the leaching of ruthenium from the catalyst, the aqueous layer of the reaction mixture was analyzed for the Ru metal by atomic absorption spectroscopy and it was found that no Ru had le ached out from the catalyst.

Table 3: Ru^{III}-exchanged mont. K10 catalyzed benzylic oxidation with 70% TBHP:

Entry	Substrate	Products	Product No.	Yield (%)[a]
a.	Toluene		**1**	60
b.	*o*-Xylene		**2**	76
c.	*p*-Xylene		**3**	46.6 (28.8)[b]
d.	*p*-Cymene		**4**	89.6
e.	Ethylbenzene		**5**	54.3 (27.7)[c]
f.	*o*-Chlorotoluene		**6**	76
g.	Tetralin		**7**	50
h.	Tetrahydrofuran		**8**	45
i.	3,4- Dihydropyran		**9**	70
j.	Isobutylbenzene	Isobutyrophenone	-	94
k.	Fluorene	Fluorenone	-	100
l.	*p*-Cresol acetate	4–Acetoxybenzoic acid	-	50
m.	Mesitylene	3,5-Dimethylbenzoic acid	-	94

a) isolated yield after column chromatographic purification. Yield in parenthesis refers to b) *p*-toluic acid c) acetophenone

All benzyl *tert.* butyl peroxides were identified by ^{1}H-NMR, Mass, IR spectroscopy and C-H analysis. For example, the ^{1}H-NMR spectrum of benzyl *tert.* butyl peroxide showed a sharp singlet at δ 1.25 that corresponds to *tert.* butyl group. As a result of peroxidation, the CH_3 of toluene is transformed to CH_2 and showed a downfield shift in the ^{1}H-NMR spectrum and appeared as a singlet at δ 4.95 (**Fig. 6**). The mass spectrometry is very useful in identifying the peroxide linkages, which otherwise are difficult to obtain by other spectroscopic techniques. The mass spectrum of the benzyl *tert.* butyl peroxide showed a molecular ion peak at 180 and thus indicating that peroxides are highly stabile compounds (**Fig. 7**).

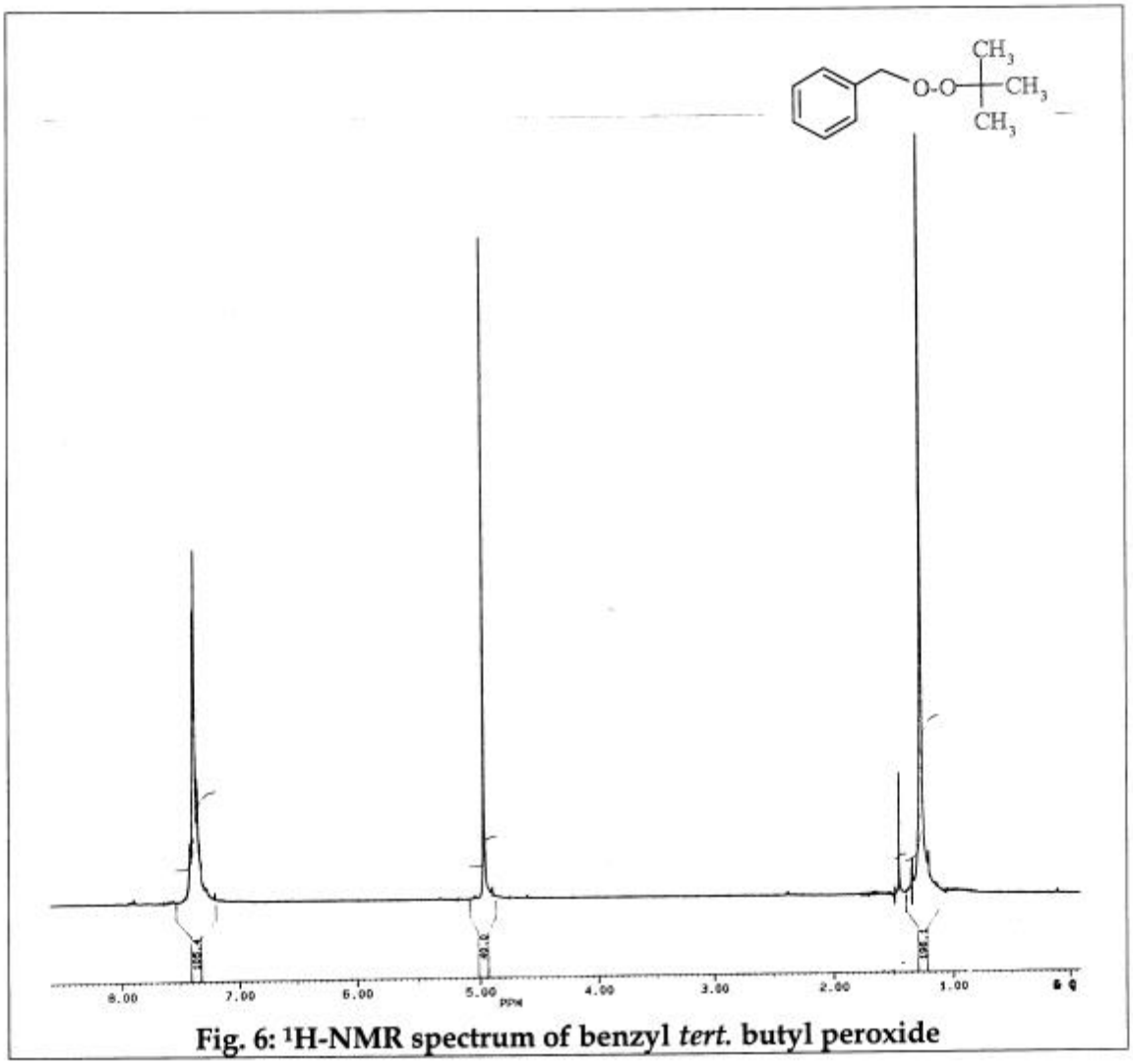


Fig. 6: ^{1}H-NMR spectrum of benzyl *tert.* butyl peroxide

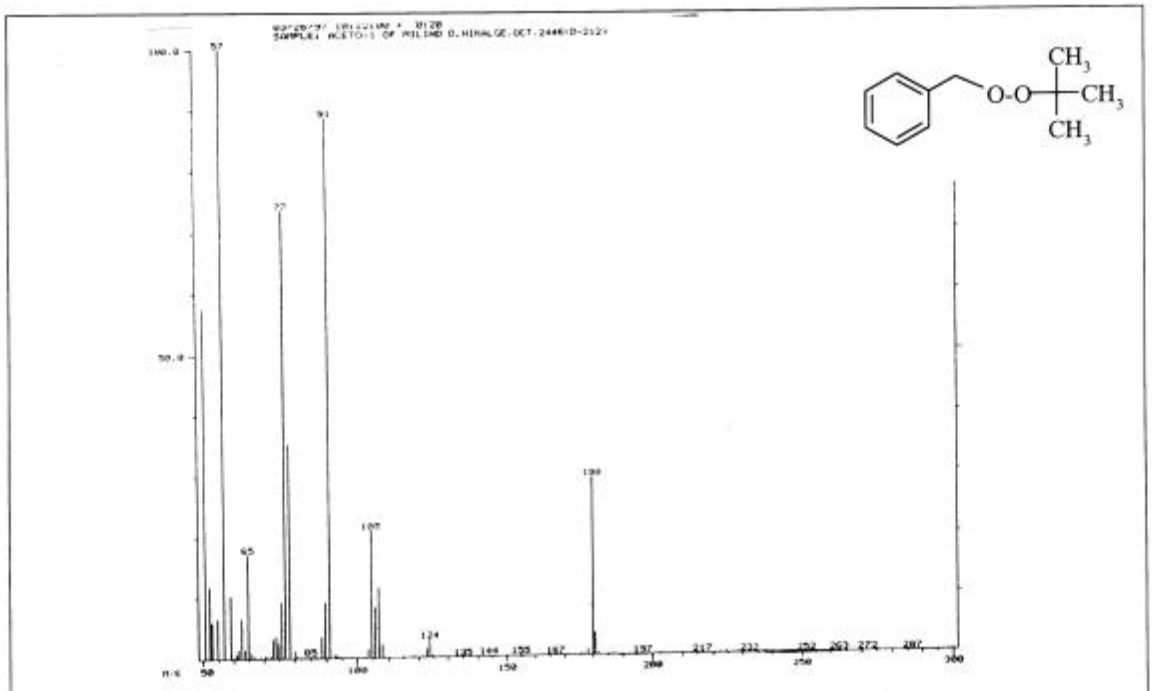
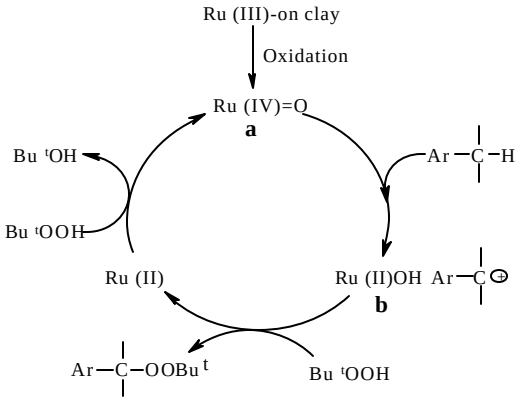


Fig. 7: Mass spectrum of benzyl *tert.* butyl peroxide

4.1.1 Mechanism of Ru(III)-Catalyzed Peroxidation Reaction[30]:

The mechanism proposed for the Ru(III)-catalyzed peroxide formation is depicted in **Scheme 16**. The first step involves the oxidation of Ru metal in Ru(III)-exchanged mont. K10 clay with TBHP to give oxoruthenium (IV) species **a**.[31] Such one electron redox behavior was confirmed by cyclic voltammetry (CV) measurement with a scan rate of 100 mV/sec. Indeed a reversible peak at –131.6 mV (vs SCE) in CV, which we attribute to Ru(III)/Ru(IV) redox process by comparison with the literature value.[32] However the voltammograms were quite stable over many cycles and thus indicating high stability of Ru(III) ions in the clay matrix. The oxoruthenium (IV) species **a** then abstracts hydride ion from the benzylic (C-H) position and thereby Ru(IV) is reduced to Ru(II) species with the simultaneous generation of reactive intermediate carbocation **b**.[33] Subsequently, reaction of **b** with 1 mole equiv. of TBHP affords the aryl *tert.* butyl peroxide. The final step involves the simultaneous oxidation of Ru(II) back to the original Ru(IV) species **a** to complete the

catalytic cycle, thus explaining the overall requirement of 2 molar equiv. of TBHP for oxidations. A similar argument can be made for the oxidation of α-C-H bond of the cyclic ethers (entry **h** & **i**). Further, the formation of both acids and ketones could be explained by oxidation of the corresponding benzylic alcohols presumably formed by the competitive reaction of water molecule with the respective stable carbocation **b** (**Scheme 16**).



Scheme 16: **Ru(III)-Exchanged Mont. K10 Catalytic Cycle for Peroxidation**

4.1.2 Conclusion:

We have developed a new method of peroxidation of alkyl arenes using 70% TBHP as the oxidant. Ru(III)-exchanged mont. K10 has been found to be quite efficient and reusable solid catalyst for the peroxidation of benzylic and α-C-H bonds of cyclic ether to afford unsymmetrical *tert.* butyl peroxide in high yields. In case of electron rich aromatic systems oxidation resulted in >90% yield for the formation of ketones and acids.

4.1.3 Experimental Section:

General Procedure for Peroxidation of Alkyl Arenes with Ru(III)-Exchanged montmorillonite K10:

A mixture of alkyl arene (5 mmol), 70% TBHP (1.3 ml, 10 mmol) and Ru(III)-clay (10 % w/w) in acetonitrile (10 ml) was refluxed for 4h. After completion of the reaction (monitored by TLC, 5% ethyl acetate in pet. ether), catalyst was separated by filtration. The filtrate poured into water (15 ml) and extracted with ethyl acetate (3 x 20 ml), the ethyl acetate layer washed with brine, dried over sodium sulfate and evaporated under vacuum to give the crude product. It was then purified by column chromatography on silica gel (1% ethyl acetate in pet. ether) to afford pure aryl *tert.* butyl peroxide.

1, 1-Dimethylethylphenylmethyl peroxide (1):

Yield	:	60%
bp	:	55-58°C/ 0.2 mm Hg [lit.[29] 60-65°C/0.3mm Hg]
IR ($CHCl_3$, cm^{-1})	:	2960, 2900, 1690, 1450, 1360, 1240, 1200, 1020, 880, 750.
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 1.25 (s, 9H), 4.95 (s, 2H), 7.15 (s, 5H)
MS (m/z, % RI)	:	180 (M^+, 32), 105 (22), 91 (90), 77 (74), 65 (18), 57 (100)
Analysis	:	$C_{11}H_{16}O_2$ requires: C, 73.30; H, 8.95%; found: C, 73.12; H, 8.80%

1,1-Dimethylehtyl-1-(2-methylphenyl)methyl peroxide (2):

Yield	:	76%
Bp	:	78-81°C/ 0.2 mm Hg
IR ($CHCl_3$, cm^{-1})	:	3020, 2980, 1420, 1370, 1260, 1190, 1010, 900, 740.
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 1.25 (s, 9H), 2.4 (s, 3H), 5.0 (s, 2H), 7.2-7.4 (m, 4H)
MS (m/z, % RI)	:	194 (M^+,1), 148(1), 133(2), 119(10), 105(100), 91(55), 77(38)
Analysis	:	$C_{12}H_{18}O_2$ requires: C, 74.19; H, 9.34%; found: C, 74.20; H, 9.26%

1, 1-Dimethylethyl-1-(4-methylphenyl)methyl peroxide (3):

Yield	:	47%
Bp	:	65-68°C/ 0.2 mm Hg [Lit.[20] 65°C/ 0.2 mm Hg]
IR ($CHCl_3$, cm^{-1})	:	3020-2800, 2620, 2440, 1370, 1320, 1220, 1080, 1040, 950, 880,
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 1.25 (s, 9H), 2.35 (s, 3H), 4.8 (s, 2H), 7.2 (d, *J* = 4.7 Hz 2H), 7.4 (d, *J* = 4.7 Hz, 2H)
MS (m/z, % RI)	:	194 (M^+, 20), 178 (1), 137 (2), 119 (38), 105 (100), 91 (80), 77 (42), 73 (20), 65 (45), 57 (73)
Analysis	:	$C_{12}H_{18}O_2$ requires: C, 74.19; H, 9.34%; found C, 74.19; H, 9.25%.

* *p*-Toluic acid was also obtained in 28% yield, confirmed by mp, IR and ^{1}H-NMR.

1, 1-Dimethylethyl-1-methyl(4-methylphenyl)ethyl peroxide (4):

Yield	:	90%
Bp	:	70-73°C/0.2 mm Hg
IR ($CHCl_3$, cm^{-1})	:	2950, 1650, 1350, 1200, 1060, 850, 750.
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 1.25 (s, 9H), 1.4 (s, 3H), 1.65 (s, 3H), 2.4 (s, 3H), 6.25 (d, *J* = 9.4 Hz 2H), 6.85 (d, *J* = 9.4 Hz, 2H).
MS (m/z, %RI)	:	222 (M^+, 8), 172 (15), 147 (24), 133 (100), 119 (28), 105 (20), 91 (30), 77 (4), 65 (10), 57 (8).
Analysis	:	$C_{14}H_{22}O_2$ requires: C, 75.63; H, 9.97%; found: C, 75.66; H, 9.89%

1, 1-Dimethylethyl-1-phenylethyl peroxide (5):

Yield	:	54%
Bp	:	54-57°C/1 mm Hg [Lit.[34] 44-52°C/0.9 mm Hg]
IR ($CHCl_3$, cm^{-1})	:	3100, 2800, 1440, 1370, 1220, 1070, 880, 760.
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 1.25 (s, 9H), 1.2 (d, *J* = 4.7 Hz, 3H), 5.0 (q, *J* = 4.7 Hz, 1H), 7.3-7.4 (s, 5H).
MS (m/z, % RI)	:	194 (M^+, 1), 179 (2), 163 (2), 133 (5), 121 (34), 105 (100), 91 (14), 77 (52), 65 (2), 57 (4).
Analysis	:	$C_{12}H_{18}O_2$ requires: C, 74.19; H, 9.34%; found: C, 74.19; H, 9.25%

* Acetophenone was also obtained in 28% yield, confirmed by IR and ^{1}H-NMR.

1,1-Dimethylethyl-1-phenylethyl peroxide (6):

Yield	:	76%
Bp	:	45-49°C/0.1 mm Hg
IR ($CHCl_3$, cm^{-1})	:	3000, 2900, 1580, 1430, 1350, 1200, 1030, 920, 860.
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 1.25 (s, 9H), 5.2 (s, 2H), 7.05-7.44 (m, 4H).
MS (m/z, % RI)	:	214 (M^+, 12), 124 (1), 125 (40), 110 (8), 111 (18), 89 (5), 77 (25), 57 (100).
Analysis	:	$C_{11}H_{15}ClO_2$, requires: C, 61.54; H, 7.04; Cl, 16.51%; found: C, 61.65; H, 6.99, Cl, 16.56%.

1-(*tert* Butylperoxy)tetralin (**7**):

Yield	:	50%
bp	:	110-112°C/1-2 mm Hg
IR ($CHCl_3$, cm^{-1})	:	3020-2800, 1610, 1440, 1370-1320, 1220, 1080, 1040, 950.
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 1.25 (s, 9H), 1.7-2.0 (m, 2H), 2.3-2.4 (m, 2H), 2.6-2.8 (m, 2H), 5.0 (t, *J* =14.1 Hz, 1H), 7.1-7.3 (m, 3H), 7.5(m, 1H).
MS (m/z, % RI)	:	220 (M^+,1), 146 (4), 130 (100), 115 (10), 103 (1), 91 (20), 77 (2),
Analysis	:	$C_{14}H_{20}O_2$ requires: C, 76.33; H, 9.15%; found: C, 76.34; H, 9.08%

1-(*tert* Butylperoxy)tetrahydrofuran (**8**):

Yield	:	45%
bp	:	40-45°C/8-10 mm Hg
IR ($CHCl_3$, cm^{-1})	:	2960-2840, 1430, 1350, 1220, 1180, 1110, 1060, 960-910.
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 1.25 (s, 9H), 1.7-2.0 (m, 4H), 3.95 (t, *J* = 14.1 Hz, 2H), 5.5 (t, *J* = 14.1 Hz, 1H).
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 24.2, 26.1, 30.3, 67.4, 80.7, 106.8.
MS (m/z, % RI)	:	160 (M^+, 1), 128 (12), 115 (23), 89 (8), 71 (100), 57 (48).
Analysis	:	$C_8H_{16}O_3$ requires: C, 59.98; H, 10.07%; found: C, 59.98; H, 9.97%

2-*(tert* butylperoxy)-3,4-dihydropyran (**9**):

Yield	:	70%
bp	:	58-61^{o}C/8-10 mm Hg
IR ($CHCl_3$, cm^{-1})	:	2910, 1370, 1250, 1200, 1050, 960, 840.
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 1.25 (s, 9H), 1.5-1.75 (m, 4H), 3.6 (m, 1H), 4.0 (m, 1H), 5.0 (t, *J* = 9.4 Hz, 1H).
MS (m/z, % RI)	:	140 (M^+-O_2, 1), 132(5), 119(18), 85(92), 73(25), 67(50), 57(100)
Analysis	:	$C_9H_{16}O_3$, requires: C, 62.76; H, 9.36%; found: C, 62.77; H, 9.28%.

Cu-Catalyzed C-N Oxidation of Aryl Nitroaldols: A High Yield Synthesis of *a*-Aryl Keto Acids*

4.1.4 Introduction:

a-Keto acids plays an important role in biological systems, wherein they act as an enzyme thus participating in various biological functions. Certain *a*-keto acids accumulate in blood and tissues under certain pathological conditions *e. g.* *a*-keto acids have been used in the therapy of uremia and nitrogen accumulation disorders. *a*-Keto acids are of continuing interest as intermediates in chemical syntheses, in the development of enzyme inhibitors and drugs, as model substrates of enzymes *etc*.[34] Pyruvic acid, a form of *a*-keto acid, was first prepared in 1835 by Berzelius,[35] and it was identified as a metabolite involved in a number of enzyme catalyzed intracellular phenomena.

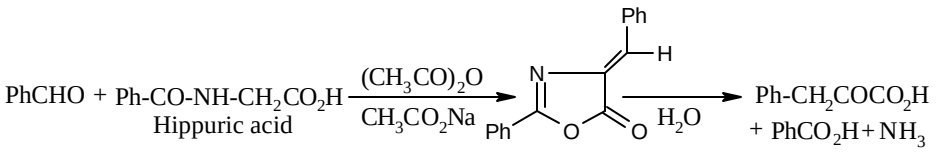
4.1.5 Review of Literature:

The synthesis of *a*-keto acids is known in the literature since long and it is still of interest from synthetic point of view.

Erlenmeyer's approach (1900)[36]

In this approach azlactones (oxazolones) were used for the synthesis of *a*-keto acids. Initially Plochl prepared azlactone,[36a] by condensation of benzaldehyde with hippuric acid. Subsequently, Erlenmeyer has shown the usefulness of these azlactones (**18**) to synthesize *a*-keto and *a*-amino acids respectively (**Scheme 17**).

* Milind D. Nikalje, Iliyas Sayyed Ali, Gajanan K. Dewkar, A. Sudalai, *Tetrahedron Lett.***2000**, *42*, 959.

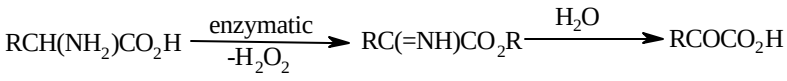


Azlactone **18**

Scheme 17:

Knoop's approach (1910)[37]

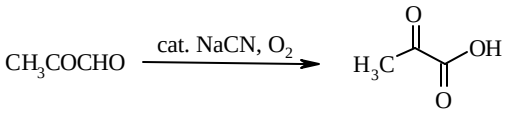
Knoop has shown that amino acid oxidase enzymes are capable of oxidizing the *a*-amino acids to *a*-keto acids by liberating hydrogen peroxide (**Scheme 18**).



Scheme 18 :

Mayerhof's approach (1925)[38]

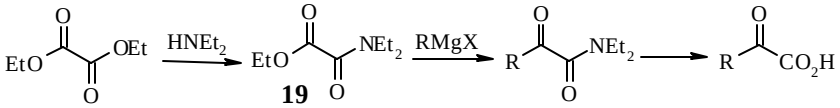
In this approach methylglyoxal is oxidized to pyruvic acid in presence of catalytic amount of alkali cyanide and O_2. (**Scheme 19**).



Scheme 19 :

Barre's approach (1928)[39]

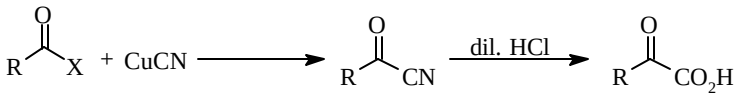
In this strategy diethyl oxalate is reacted with diethyl amine to form compound **19**. Subsequent reaction of **19** with Grignard reagent followed by hydrolysis gave respective *a*-keto acids in 60-70% yield (**Scheme 20**).



Scheme 20 :

Chelinztev's approach (1929)[40]

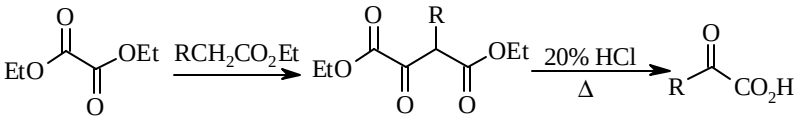
In this approach, acyl cyanides were used to synthesize *a*-keto acids. These acyl cyanides were obtained by refluxing acyl bromide with cuprous cyanide and subsequently transformed to *a*-keto acids by hydrolysis with dilute hydrochloric acid (**Scheme 21**).



Scheme 21 :

Andresen's approach (1943)[41]

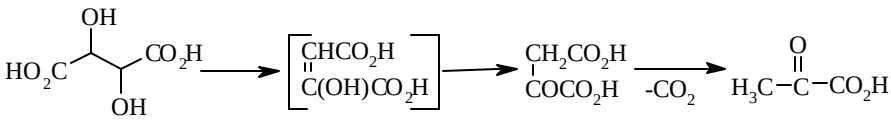
This strategy for the synthesis of *a*-keto acids deals with the hydrolysis of ethyl esters of oxalo-acids. These oxalo-acids were synthesized by condensation of diethyl oxalate with ethyl ester of variety of acids. Subsequently, oxa-acids were hydrolyzed with 20% HCl to provide the respective *a*-keto acids (**Scheme 22**).



Scheme 22 :

Howard's approach (1945)[42]

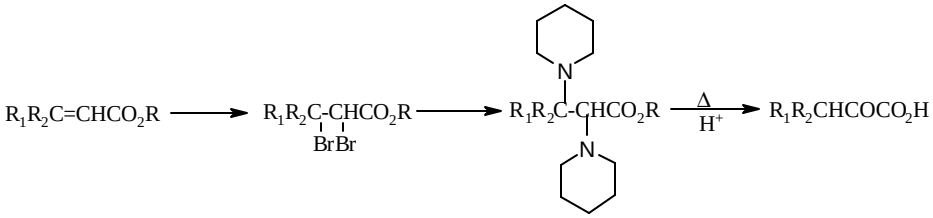
Howard prepared pyruvic acid from tartaric acid *via* distillative dehydration and decarboxylation as given in the **Scheme 23**.



Scheme 23 :

Moureu's approach (1945)[43]

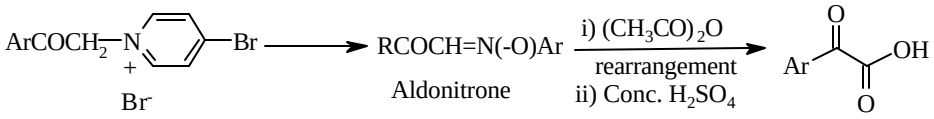
In this approach α,β-unsaturated esters have been employed to synthesize α-keto acids. First, α,β-unsaturated ester was brominated and then treated with piperidine to form mono and di-adduct. This adducts was then hydrolyzed to give α-keto acids (**Scheme 24**).



Scheme 24 :

Krohnke's approach (1947)[44]

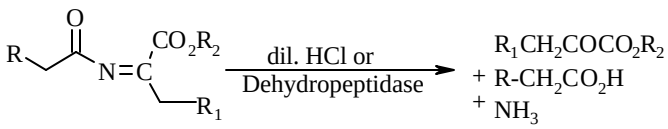
This strategy employed phenacylpyridinium salt (**Scheme 25**), which upon treatment with nitrosoaryl-compounds in presence of solid alkali cyanides or its solution gave the aldonitrone intermediate. Subsequently, it was rearranged and hydrolyzed to give α-keto acids.



Scheme 25 :

Greenstein approach (1948)[45]

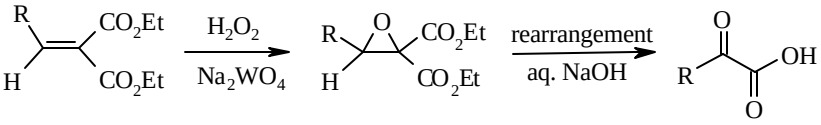
In this approach, α-keto acids were obtained from dehydropeptides. The hydrolysis of dehydropeptides with dilute HCl or by enzymatic methods led to the formation of α-keto acids (**Scheme 26**).



Scheme 26 :

Igarishi and Midorikawa's approach (1964)[46]

This approach involved the rearrangement of epoxide of alkylidenemalonate to afford *a*-keto acids. Epoxide of alkylidenemalonate was obtained from the reaction of hydrogen peroxide with alkylidenemalonate in the presence of sodium tungstate. It was then transformed to *a*-keto acids *via* base catalyzed ring opening followed by decarboxylation (**Scheme 27**).



Scheme 27 :

Rapp's approach (1969)[47]

Rapp's approach made use of *a*-azidoarylacetic acids for the synthesis of *a*-keto acids (**Scheme 28**). These esters were treated with aq. sodium hydroxide to give to *a*-keto acids in 56-89% yield.

$$ArCH(N_3)CO_2H \xrightarrow{NaOH,\ H^+} ArCOCO_2H$$

Scheme 28 :

Anatol's approach (1972)[48]

This approach employed *a*-cyanohydrins (**Scheme 29**). Initially appropriate cyanohydrin was converted to *a*-hydroxy-N-*tert*-butylcarboxamide and subsequently oxidized and hydrolyzed to *a*-keto acids.

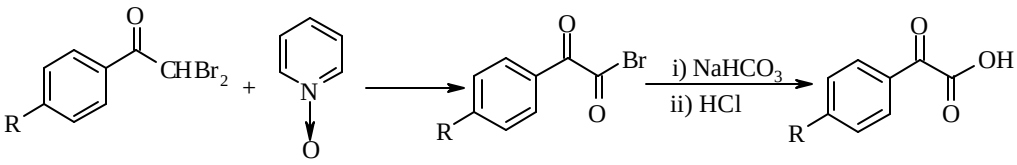
$$RCH(OH)CN \xrightarrow[H_2SO_4]{Me_3COH} RCH(OH)CONHCMe_3 \xrightarrow{CrO_3/HOAc} RCOCO_2H$$

Scheme 29 :

Saldabol's approach (1974)[49]

This strategy deals with synthesis of *para*-substituted phenylglyoxylic acids (**Scheme 30**). When *p*-substituted-phenyl dibromomethyl ketones reacted with pyridine N-oxide, it led

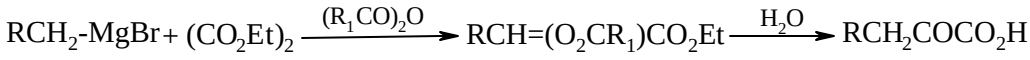
to the formation of intermediate α-keto acyl bromides, which were then hydrolyzed to give α-keto acids in 50-95% yields.



Scheme 30 :

Lapkin's approach (1976)[50]

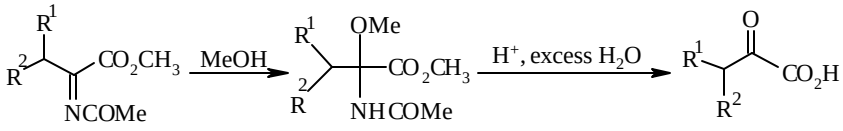
This approach involved addition of Grignard reagent to dialkyloxalate (**Scheme 31**). The intermediate magnesium adduct was dehydrated and subsequently hydrolyzed to give α-keto acids.



Scheme 31 :

Poisel's approach (1978)[51]

In this approach, synthesis of α-keto acids was achieved by hydrolysis of the α-acetylamino-α-methoxy-α-alkyl ester (**20**). However use of 1 equivalent of water resulted in the formation of α-keto ester (**Scheme 32**).



20

Scheme 32 :

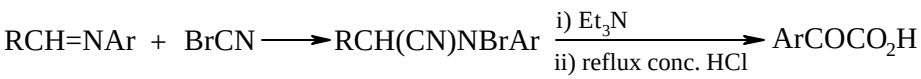
Tanaka's approach (1978)[52]

2,2,2-Trifluoroethyl tosylate was treated with 2 equivalent of lithium diisopropylamide (LDA) to produce the corresponding lithium salt. Subsequently, its reaction with appropriate ketones followed by hydrolysis led to the formation of α-keto acids in 89-95% yield (**Scheme 33**).

Scheme 33 :

Rai's approach (1979)[53]

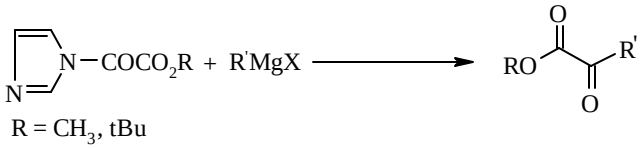
In this approach N-bromo-α-cyano amines, prepared by the addition of BrCN to RCH=NAr is treated with Et_3N and conc. HCl to give the corresponding *a*-keto acids in 71-85% yield (**Scheme 34**).



Scheme 34 :

Nimitz and Mosher's approach (1981)[54]

Nimitz and Mosher have reported that addition of Grignard reagent to acylimidazolides led to the formation of either methyl or *tert.* butyl ester of *a*-keto acids. (**Scheme 35**).



Scheme 35 :

Tanaka's approach (1988)[55]

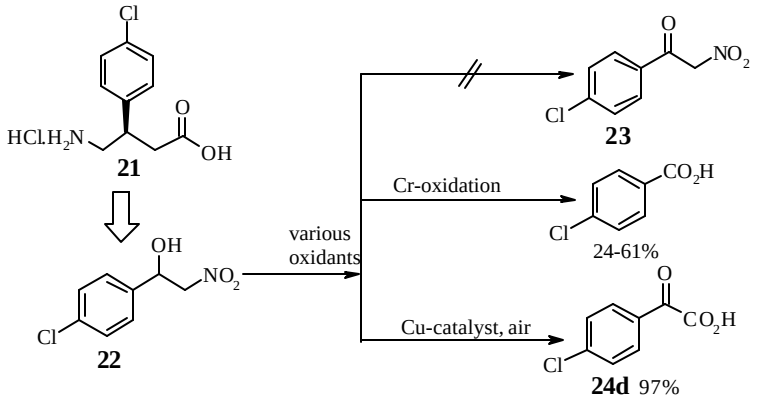
Tanaka *et al* have developed a process for the production of *a*-keto acids. In this strategy, the palladium catalyzed carbonylation of aryl halide in presence of *tert.* butyl alcohol led to the formation of *a*-keto ester, which was then hydrolyzed to the corresponding *a*-keto acids in good yields (**Scheme 36**).

Scheme 36 :

4.1.6 Present Work:

4.1.6.1 Introduction:

We were interested in asymmetric synthesis of baclofen[56] (**21**) (see chapter 3 for its asymmetric synthesis) for which nitroketone **23**, was envisioned as the key intermediate. In order to obtain **23**, aryl nitroaldol **22**, readily prepared by Henry reaction,[57] was subjected to oxidation with various reagents (the results of which are shown in **Table 4**). It was observed that, when chromium-containing oxidants were used (entries 1-3) aryl nitroaldol **22** underwent oxidation to produce 4-chlorobenzoic acid in good yields. However, in presence of milder oxidizing agents like MnO_2 or DMSO/oxalyl chloride/Et_3N, 2-(4-chlorophenyl)-2-oxoacetic acid (**24**) was isolated, although in lower yield. Indeed, a dramatic improvement of the yield (>90%) of the α-keto acid **24** was realized when Cu(II) salts were employed for oxidation in 30% aq. AcOH:MeOH (1:1) as the solvent (**Scheme 37**). Encouraged by this result, we then turned our attention to provide a new method to obtain α-keto acids in a single step from variety of aryl nitroaldols.



Scheme 37: Oxidation of 1-(4-chlorophenyl)-2-nitroethanol (22)

4.1.6.2 Objective:

Although various methods are available in the literature for synthesis of the α-keto acids, only few of them are straightforward and are of synthetic interest. Most of the methods require hazardous chemicals, employ cumbersome procedures, often resulting in

lower yields of the α-keto acids. As a consequence of this, a simple, efficient and catalytic method to synthesize α-keto acids in high yields is highly desirable. In continuation of this objective, we developed a new synthetic method for α-keto acids *via* oxidative conversion of aryl nitroaldols to α-aryl keto acids using cheaply and easily available Cu-salts[58] as catalysts (**Table 5**).

4.1.7 Results and Discussion:

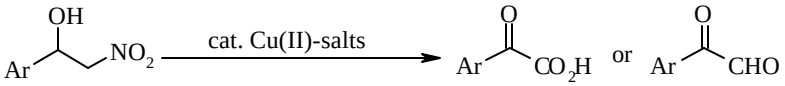
The preliminary results of oxidative conversion of 1-(4-chlorophenyl)-2-nitroethanol (**22**) with various oxidizing agents are presented in the **Table 4** As depicted in the **Scheme 37**, the response of nitroaldol **22** towards different oxidizing agents was found to be different. In case of Cr-based oxidizing agents, 4-chlorobenzoic acid is the only product formed, whereas under Swern's [DMSO, $(COCl)_2$, Et_3N] and MnO_2 oxidation conditions 2-(4-chlorophenyl)-2-oxoacetic acid (**24**) is formed in low yield. However, yield of the α-keto acid **24** is improved in presence of Cu (II)-salts as catalyst and 30% aq. AcOH: MeOH (1:1) as solvent system (**Table 4**).

Table 4: Study of oxidation of 1-(4-chlorophenyl)-2-nitroethanol (**22**)[a]:

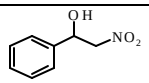
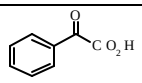
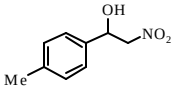
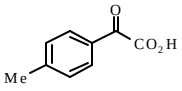
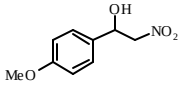
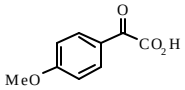
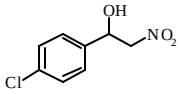
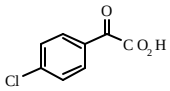
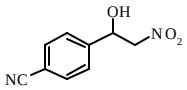
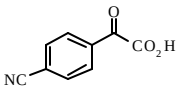
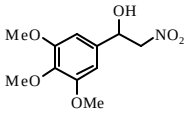
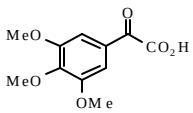
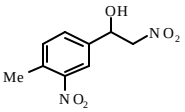
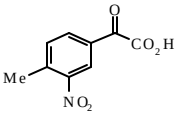
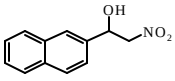
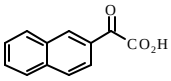
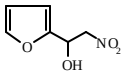
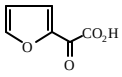
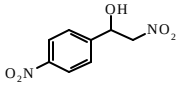
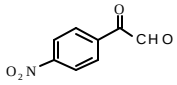
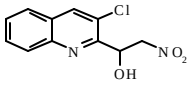
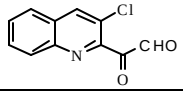
No	Reagents/Catalysts	Condition	T/h	Product	Yield (%)[b]
1	PCC[c]	CH_2Cl_2, 25 °C	24	*p*-Cl-$PhCO_2H$	60
2	PDC[d]	CH_2Cl_2, 25 °C	24	*p*-Cl-$PhCO_2H$	24
3	$H_2Cr_2O_7$	Acetone, 5 °C	1	*p*-Cl-$PhCO_2H$	61
4	MnO_2	Benzene, 80 °C	8	*p*-Cl-$PhCOCO_2H$	46
5	DMSO,$(COCl)_2$, Et_3N	CH_2Cl_2, -43 °C	4	*p*-Cl-$PhCOCO_2H$	60
6	$Cu(OAc)_2.H_2O$	Solvent[e]	4	*p*-Cl-$PhCOCO_2H$	93
7	$CuSO_4.5H_2O$	Solvent[e]	4	*p*-Cl-$PhCOCO_2H$	97
8	$CuCl_2$	Solvent[e]	4	*p*-Cl-$PhCOCO_2H$	90
9	CuI	Solvent[e]	4	*p*-Cl-$PhCOCO_2H$	70

a) Nitroaldol (5 mmol); catalyst (10 mol%); solvent (10 ml); b) isolated yield, after chromatographic purification; c) pyridinium chlorochromate; d) p yridinium dichromate; e) 30% aq. AcOH:MeOH (1:1), 90 °C

Table 5 : Cu(II)–catalyzed oxidative conversion of aryl nitroaldols to *a* -aryl keto acids [a]



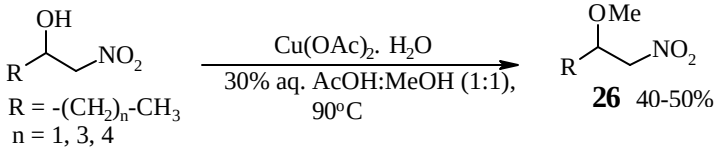
22(a-k) **24(a-i)** **25(j-k)**

No	Substrate Ar (**22**)	t/h	Product (**24** & **25**)	Yield[b] (%) Cu[c]	Cu[d]	mp °C[e]
a.		4		61	45	67-69 (66)
b.		4		88	50	97-99 (97)
c.		4		87	–	93-95 (93)
d.		3		93	97	92-94 (92-93)
e.		5		41	35	138 (dec.)
f.		3		80	41	114-115
g.		4		75	60	165-167
h.		4		59	–	90-92 (91-92)
i.		4		72	–	98-100 (98)
j.		5		50	30	95-97
k.		4		41	–	112-115

a) Nitroaldol (5 mmol); Cu(II) catalyst (10 mol%), 30% aq. AcOH:MeOH (1:1, 15 ml), 90°C; b) isolated yield after column chromatographic purification; c) $Cu(OAc)_2.H_2O$; d) $CuSO_4.5H_2O$; e) number in parenthesis refers to literature mp[59]

In order to study the scope and limitations of the reaction, various aryl nitroaldols were subjected to Cu-catalyzed oxidative conversion to afford *a* -aryl keto acids. The results of oxidative conversion of nitroaldols have been enlisted in **Table 5**. Generally, the catalytic activity of $CuSO_4.5H_2O$ was found to be low as compared to $Cu(OAc)_2.H_2O$ towards the

oxidation of various aryl nitroaldols. It is observed that, for aryl nitroaldols bearing electron-withdrawing groups such as NO_2 and CN, the rate of oxidation is found to be slower as compared to substrates with electron-donating groups. It is remarkable that in case of substrates with NO_2 and quinoline moieties (entries **22j** & **k**), the reaction stops at aldehyde stage without undergoing further oxidation to the corresponding acids. Another novel feature of this catalytic system is that, the aliphatic nitroaldol analogues underwent reaction to produce nitroalkyl ethers **26** in moderate yields (**Scheme 38**).



Scheme 38: Oxidative conversion of aliphatic nitroaldols to nitroethers

The formation of 2-(4-chlorophenyl)-2-oxoacetic acid (**24d**) was confirmed by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectroscopy. The IR spectrum of **24d** showed a characteristic bands at 1775 and 1702 cm^{-1}, which correspond to C=O of acid and ketone moieties respectively. Its ^{1}H-NMR spectrum showed signal at δ 7.37-7.85 (m) due to *para* disubstituted aromatic systems. In ^{13}C-NMR, **24d** showed signals at δ 165 and 191 (**Fig. 8**), indicating the presence of two C=O carbons of acid and keto groups respectively. Its mass spectrum shows a weak molecular ion peak at m/e 184 (**Fig 9**).

In case of aliphatic nitroaldols analog, the formation of nitroalkyl ethers **26** was confirmed by IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy. IR spectrum of **26** showed a sharp band at 1560 cm^{-1}, indicating the presence of $-NO_2$ group. ^{1}H-NMR spectrum of a nitroether (n=1, **Scheme 38**), showed a characteristic singlet at δ 3.35, indicating the presence of OCH_3. The multiplet at δ 4.35-4.45 is due to $-CH_2$ moiety attached to $-NO_2$ group (**Fig. 10**). Its ^{13}C-NMR spectrum indicated that the carbon signals at δ 78.91 and 57.40 are due to -CH and OCH_3 groups respectively. The carbon signal of $-CH_2$ attached to $-NO_2$ group appears downfield at δ 78.09 (**Fig. 10**).

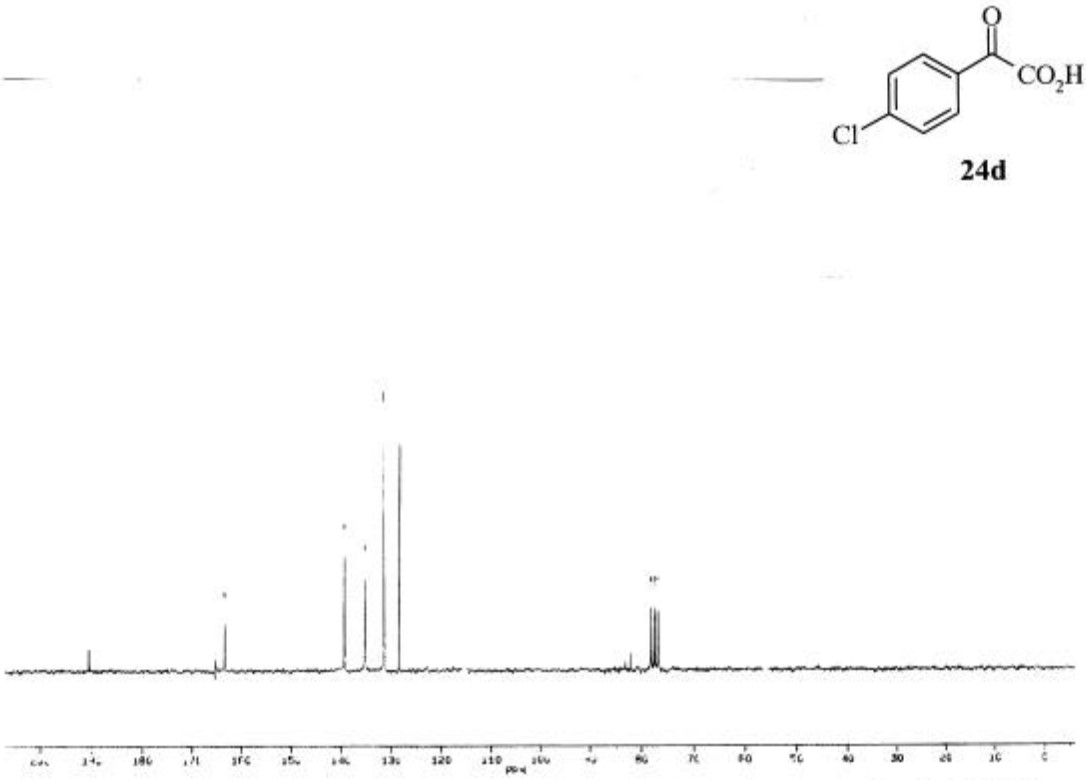


Fig 8: ^{13}C-NMR spectrum of 2-(4-chlorophenyl)-2-oxoacetic acid (24d)

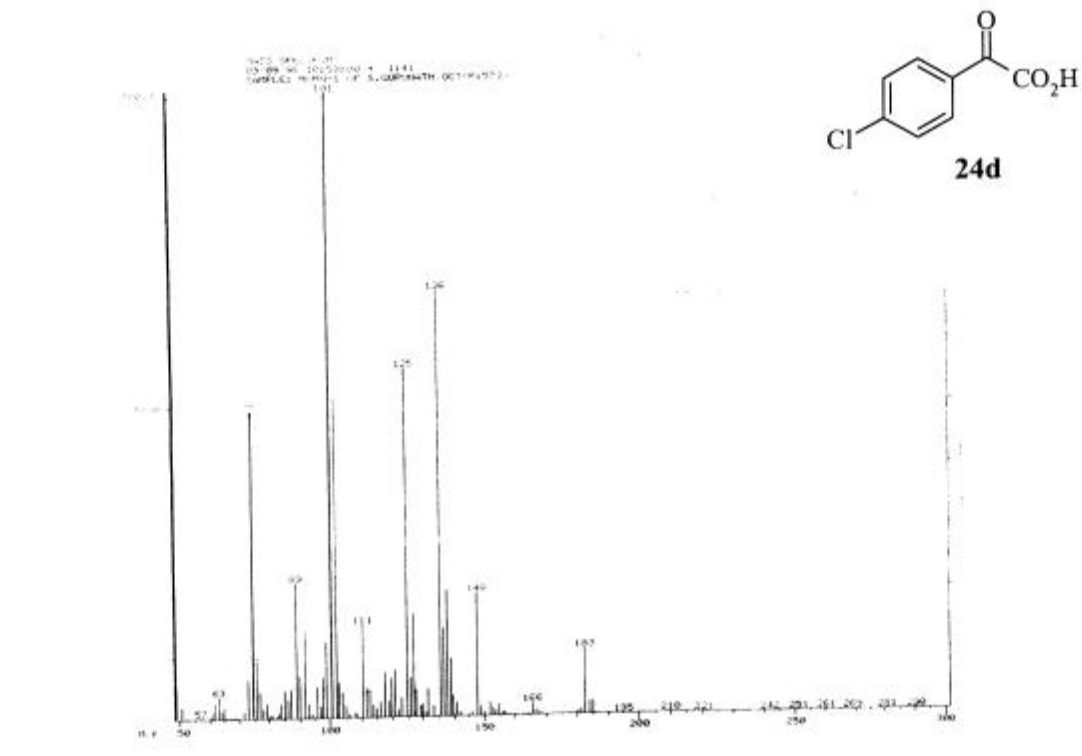


Fig 9: Mass spectrum of 2-(4-chlorophenyl)-2-oxoacetic acid (24d)

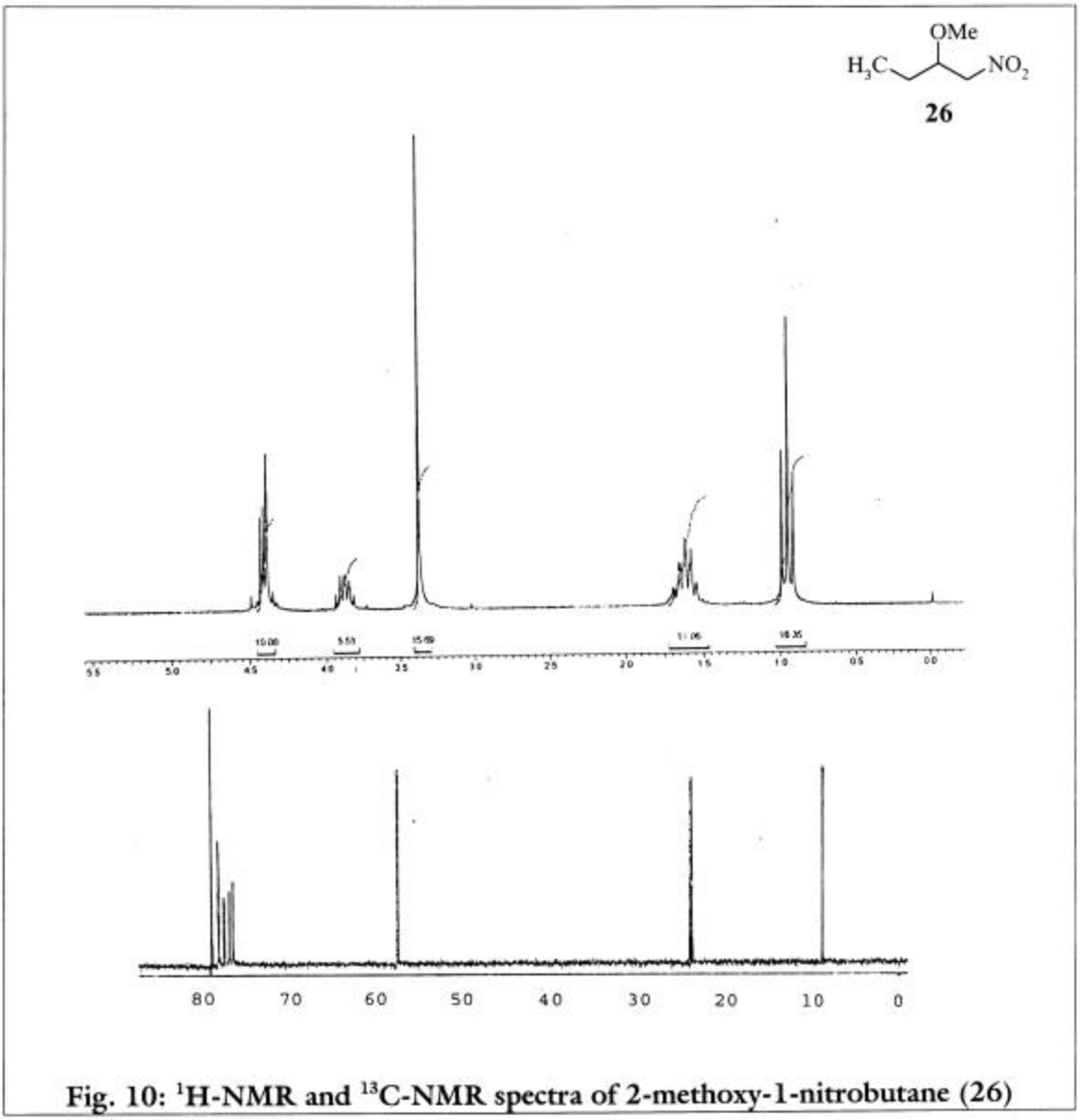
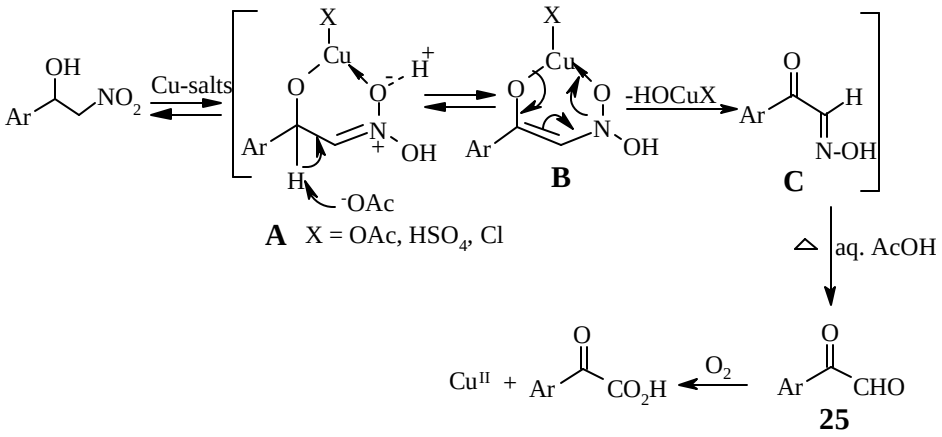


Fig. 10: ^{1}H-NMR and ^{13}C-NMR spectra of 2-methoxy-1-nitrobutane (26)

4.1.8 Mechanism:

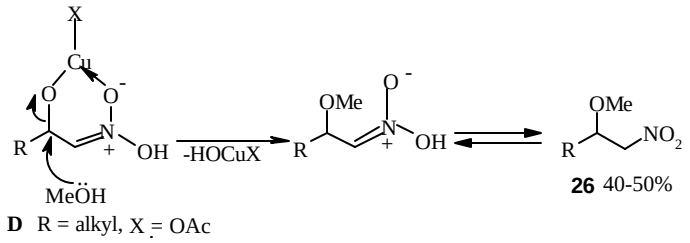
In order to understand the reaction mechanism, analysis of the reaction mixture is done every 1h using ^{1}H NMR spectroscopy. It indicated that the reaction mixture contained α-keto aldehyde (signal at δ 10.0 for CHO is observed) and α-keto acid; as time progresses (in certain cases keto aldehyde has been isolated, **Table 5**, entry **25j** & **25k**), the yield of the α-keto acid increased (signal at δ 10.0 was disappearing). Based on this observation, a

mechanistic pathway for the formation of *a*-keto acid is proposed in **Scheme 39A**. Cu(II) salt, being Lewis acid, is believed to coordinate well with the *aci*- form of the nitroaldols similar to keto carbonyls[60] *via* 6-membered cyclic intermediate to generate species **A** (**Scheme 39A**). The acetate ion, then, abstracts the *b*-proton present in species **A** to produce the species **B**. This is followed by the formation of *a*-keto oxime **C** with the liberation of active species HOCuX. Under aqueous acidic conditions, the oxime **C** undergoes hydrolysis[61] to give *a*-keto aldehyde **25**. In some cases, these keto aldehydes are quite stable and were isolated and characterized (entries **25j** & **25k**) in agreement with literature report.[62] Finally, keto aldehyde **25** undergoes aerial oxidation in the presence of Cu(II) catalyst to give the corresponding *a*-keto acid with the liberation of Cu(I) species which is reoxidized to Cu(II) by air to continue the catalytic cycle.[63]



Scheme 39A: Mechanism of a -keto acid formation

In the case of aliphatic nitroaldol, the species **D** undergoes nucleophilic substitution with MeOH to afford nitroalkyl ether (**26**) instead of yielding *a*-keto acids. This may be explained by the difficulty associated with the abstraction of relatively less acidic nature of the *b*-proton present in species **D** (**Scheme 39B**).



Scheme 39B: Mechanism of nitroalkyl ether formation

4.1.9 Conclusion:

We have developed a new simple, efficient, catalytic method for oxidative conversion of aryl nitroaldols to *a*-aryl keto acids. However in case of aliphatic nitroaldols, reaction failed to give *a*-keto acid under identical conditions, instead it took a different course to provide nitroalkyl ethers in moderate yields.

4.2.0 Experimental Section:

General Experimental Procedure: A mixture of nitroaldol (3.0 mmol), $Cu(OAc)_2.H_2O$ (10 mol%) and 30% aq. AcOH:MeOH (1:1, 10 ml) was heated under reflux at 90°C (oil bath temperature) for 3h. After completion of the reaction (monitored by TLC, 15% EtOAc in pet. ether), reaction mixture was poured into water and extracted with ethyl acetate (3 x 25 ml), washed with brine, dried over anhydrous Na_2SO_4 and evaporated under vacuum. The crude *a*-keto acid was purified by column chromatography.

2-Oxo-2-phenylacetic acid (24a):

Yield	:	61%
mp	:	69-69 °C
IR ($CHCl_3$, cm^{-1})	:	2545-3045, 1735, 1665, 1560, 1340, 1200-1280, 970.
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 7.35-7.65 (m, 3H), 8.05 (d, *J* = 8.0 Hz, 2H).
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 129.52, 130.27, 137.33, 139.20, 165.0, 184.0.
MS (m/z, % RI)	:	150 (M^+, 1), 149 (82), 132 (21), 119 (11), 103 (88), 91(100), 77 (60), 65 (10).
Analysis	:	$C_8H_6O_3$, requires: C, 64.00, H, 4.03%; found: C, 63.97; H, 3.99%.

2-(4-Methylphenyl)-2-oxoacetic acid (24b):

Yield	:	88%
mp	:	97-99 °C
IR ($CHCl_3$, cm^{-1})	:	3105, 3038, 2911, 2853, 1738, 1629, 1601, 1566, 1451, 1375, 1263, 1203, 1181, 963.
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 2.41 (s, 3H), 7.15 (d, *J* = 7.8 Hz, 2H), 7.5 (d, *J* = 7.8 Hz, 1H), 8.0 (d, *J* = 8.0 Hz, 1H).
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 21.85, 127.58, 130.38, 136.57, 139.34, 143.32, 166.1
MS (m/z, % RI)	:	163 (8), 143 (5), 132 (6), 115 (100), 105 (87), 91 (68), 79 (26)
Analysis	:	$C_9H_8O_3$, requires: C, 65.85; H, 4.91%; found: C, 65.79; H, 4.88%

2-(4-Methoxyphenyl)-2-oxoacetic acid (24c):

Yield	:	87%
mp	:	93-95 ^{o}C
IR ($CHCl_3$, cm^{-1})	:	3563-3418, 2932, 1601, 1568, 1493, 1421, 1333, 1251, 1117, 1025, 963, 830.
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 3.85 (s, 3H), 6.95 (d, J = 8.0 Hz, 2H), 8.0 (d, J = 8.0 Hz, 2H).
^{13}C NMR (50 MHz, $CDCl_3$)		δ 55.81, 115.24, 122.85, 131.49, 135.32, 139.28, 163.31.
MS (m/z, % RI)	:	180 (M^+, 1), 179 (79), 162 (6), 149 (5), 132 (100), 121 (30), 103 (10), 96 (3), 89 (41), 77 (27), 63 (21).
Analysis	:	$C_9H_8O_4$ requires: C, 60.00; H, 4.48%; found: C, 59.97; H, 4.43%.

2-(4-Chlorophenyl)-2-oxoacetic acid (24d):

Yield	:	93%
mp	:	92-94 ^{o}C
IR ($CHCl_3$, cm^{-1})	:	3045, 2924, 1775, 1702, 1674, 1576, 1592, 1490, 1206, 1102, 968.
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 7.37 (d, J = 8.0 Hz, 2H), 7.85, (d, J = 8.0 Hz, 2H).
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 129.62, 130.59, 135.19, 141.05, 165.02, 191.13.
MS (m/z, % RI)	:	184 (M^+, 1), 183 (10), 166 (1), 148 (20), 136 (67), 125 (15), 101(100), 89 (21), 75 (50) 63 (3), 57 (1).
Analysis	:	$C_8H_5ClO_3$, requires: C, 52.06, H, 2.73, Cl, 19.20%; found: C, 51.99, H, 2.70, Cl, 19.01%.

2-(4-Cyanophenyl)-2-oxoacetic acid (24e):

Yield	:	41%
mp	:	138^{o}C, dec.
IR ($CHCl_3$, cm^{-1})	:	3572-3431, 3383, 3354, 3221, 1698, 1642, 1610, 1562, 1429, 1392, 1383, 1321, 1292, 1181, 1156, 1116, 1046, 988, 932.
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 7.6 (d, J = 7.8 Hz, 2H), 8.0 (d, J = 7.8 Hz, 2H).

MS (m/z, % RI)	:	147 (M^+-CO, 61), 130 (100), 119 (6), 102 (52), 76 (18), 75 (25).
Analysis	:	$C_9H_5NO_3$, requires: C, 61.72; H, 2.88; N, 7.99%; found: C, 61.68, H, 2.79, N, 7.84%.

2-(3,4,5-Trimethoxyphenyl)-2-oxoacetic acid (24f):

Yield	:	80%
mp	:	114-115 ^oC
IR ($CHCl_3$, cm^{-1})	:	3012, 2939, 2833, 1680, 1576, 1502, 1453, 1417, 1321, 1228, 1132, 757.
^1H-NMR (200 MHz, $CDCl_3$)	:	δ3.85-3.95 (s, 9H) 7.55 (d, *J*=12.0 Hz, 1H), 8.0 (d, *J*=12.0 Hz, 1H)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 50.60, 61.39, 105.04, 125.2, 136.7, 139.59, 154.02.
MS (m/z, % RI)	:	240 (M^+, 3), 239 (46), 211 (10), 192 (18), 177 (25), 163 (13), 149 (31), 134 (18), 125 (23), 118 (27), 107 (52), 92 (100), 79 (50).
Analysis	:	$C_{11}H_{12}O_6$ requires: C, 54.99; H, 5.04%; found: C, 54.48, H, 4.99%

2-(3-Nitro-4-methylphenyl)-2-oxoacetic acid (24g):

Yield	:	75%
mp	:	165-167^oC
IR ($CHCl_3$, cm^{-1})	:	3517-3427, 3392, 3383, 3308, 1680, 1632, 1554, 1520, 1441, 1346, 1255, 1109, 1114, 1075, 1040, 966
^1H-NMR (200 MHz, $CDCl_3$)	:	δ 2.54 (s, 3H), 7.4-7.7 (m, 1H), 8.0(d, *J* = 8.0 Hz, 1H,), 8.15(s, 1H)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 20.25, 124.50, 129.0, 132.30, 133.80, 136.0, 137.01, 168.30
MS (m/z, % RI)	:	209 (M^+, 1), 208 (8), 191 (28), 162 (1), 144 (21), 131 (12), 115 (100), 103 (18), 89 (40), 77 (68), 63 (68).
Analysis	:	$C_9H_7NO_5$, requires: C, 51.68, H, 3.37, N, 6.69%; found: C, 51.64, H, 3.34, N, 6.68%

2-Oxo-2-naphthaleneacetic acid (24h):

Yield	:	59%
mp	:	90-92°C
IR ($CHCl_3$, cm^{-1})	:	3517-3427, 3392, 3383, 3308, 1680, 1632, 1554, 1520, 1441, 1346, 1255, 1109, 1114, 1075, 1040, 966
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 7.5-7.77 (m, 2H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.9 (d, *J* = 8.1 Hz, 1H), 8.0 (d, *J* = 8.0 Hz, 1H), 8.3 (d, *J* = 8.0 Hz, 1H), 8.86 (d, *J* = 8.4 Hz, 1H).
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 125.17, 127.49, 128.85, 131.40, 132.25, 133.64, 135.70, 138.37, 193.01
MS (m/z, % RI)	:	200 (M^+, 1), 199 (25), 182 (4), 171 (27), 152 (100), 141(25), 126 (16), 115 (20), 101 (4), 87 (4), 76 (16), 63 (29)
Analysis	:	$C_{12}H_8O_3$ requires: C, 71.99, H, 4.03%; found: C, 71.94, H, 3.99%.

2-Oxo-2-furanacetic acid (24i):

Yield	:	72%
mp	:	98-100°C
IR ($CHCl_3$, cm^{-1})	:	3524-3416, 3376, 2358, 2332, 1728, 1628, 1493, 1318, 1271, 1192, 1148, 1013, 957, 933, 820.
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 6.00-6.9 (m, 1H), 7.5-7.6 (m, 1H) 7.7 (d, *J* = 8.0 Hz, 1H)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 113.12, 119.51, 134.87, 146.62, 152.14,.
MS (m/z, % RI)	:	140 (1), 139 (73), 92 (41), 83 (95), 68 (33), 65 (100), 53 (57).
Analysis	:	$C_6H_4O_4$, requires: C, 51.44, H, 2.88%; found: C, 51.41, H, 2.85%.

2-(4-Nitrophenyl)-2-oxoacetic acetaldehyde (24j):

Yield	:	50%
mp	:	95-97°C
IR ($CHCl_3$, cm^{-1})	:	2914, 1680, 1623, 1601, 1550, 1494, 1445, 1374, 1329, 1251, 1195, 1098, 1033, 925, 811.
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 8.05 (d, *J* = 7.5 Hz, 2H), 8.45 (d, *J* = 7.5 Hz, 2H), 10.15 (s, 1H)

MS (m/z, % RI)	:	151(M^+-CO, 88), 150 (100) 135 (4), 120 (6) 105 (26), 104 (23), 92 (12), 77 (65), 76 (30), 65 (14).
Analysis	:	$C_8H_5NO_4$, requires: C, 53.64, H, 2.81, N, 7.82%; found: C, 53.62, H, 2.77, N, 7.75%.

2-(3-Chloroquinoline)-2-oxoacetaldehyde (24k):

Yield	:	41%
mp	:	112-115°C
IR ($CHCl_3$, cm^{-1})	:	3307, 2918, 2852, 2357, 1935, 1905, 1837, 1787, 1767, 1740, 1682, 1610, 1573, 1488, 1370, 1328, 1163, 1128, 1043, 755.
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 7.6-7.75 (m, 1H), 7.8-8.1 (m, 3H), 8.75 (s, 1H), 10.05 (s, 1H, CHO)
MS (m/z, % RI)	:	219 (1), 206 (20), 191 (80), 162 (38), 155 (50), 127 (100), 101 (53), 75 (67), 63 (20), 57 (17).
Analysis	:	$C_{11}H_6ClNO_2$, requires: C, 60.16, H, 2.76, N, 6.37, Cl, 16.14%; found: C, 60.09, H, 2.57, N, 6.23, Cl, 16.13%.

2-Methoxy-1-nitrobutane (26, n=1):

Yield	:	41%
bp	:	Gum
IR (neat, cm^{-1})	:	2950, 1560, 1480, 1440, 1400, 1280, 1240, 1200, 1160, 1100, 930, 860, 750.
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 0.93-1.01 (t, *J* = 9.0 Hz, 3H), 1.5-1.7 (m, 2H), 3.35 (s, 3H), 3.85-3.95 (m, 1H), 4.35-4.45 (m, 2H)
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 8.76, 24.06, 57.40, 78.09, 78.91.
MS (m/z, % RI)	:	104 (M^+-C_2H_5, 50), 101 (35), 72 (70), 58 (100)
Analysis	:	$C_5H_{11}NO_3$, requires: C, 45.10, H, 8.33, N, 10.52%; found: C, 44.99, H, 8.27, N, 10.23%.

2-Methoxy-1-nitrohexane (26, n=3):

Yield	:	44%
bp	:	gum
IR (neat, cm^{-1})	:	2936, 2898, 2884, 1556, 1460, 1440, 1424, 1384, 1280, 1086, 1046, 1022, 988, 858, 750.
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 0.87-0.93 (t, *J* = 6.0 Hz, 3H), 1.25-1.40 (m, 4H), 1.49-1.65 (m, 2H), 3.35 (s, 3H), 3.75-3.95 (m, 1H), 4.35-4.45 (m, 2H)
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 13.73, 22.31, 27.09, 31.22, 57.46, 77.97, 78.42
MS (m/z, % RI)	:	114 (15), 104 (50), 101 (35), 83, (30), 72 (70), 69 (45), 58 (100), 55 (88)
Analysis	:	$C_7H_{15}NO_3$, requires: C, 52.16, H, 9.37, N, 8.69%; found: C, 52.11, H, 9.33, N, 8.66%.

2-Methoxy-1-nitroheptane (26, n=4):

Yield	:	51%
bp	:	gum
IR (neat, cm^{-1})	:	2936, 2898, 1556, 1460, 1440, 1424, 1384, 1280, 1100, 1022, 980, 854, 752.
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 0.87-0.93 (t, *J* = 6.0 Hz, 3H), 1.31-1.37 (m, 6H), 1.50-1.65 (m, 2H), 3.39 (s, 3H), 3.85-4.0 (m, 1H), 4.40-4.44 (m, 2H)
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 13.70, 22.12, 24.24, 31.22, 31.54, 57.48, 77.97, 78.42
Analysis	:	$C_8H_{17}NO_3$, requires: C, 54.84, H, 9.77, N, 7.57%; found: C, 54.81, H, 9.74, N, 7.96%.