ENANTIOSELECTIVE SYNTHESIS OF BIOACTIVE MOLECULES *VIA* ASYMMETRIC HYDROXYLATIONS, AMINOALLYLATION AND SYNTHETIC METHODOLOGIES INVOLVING ACTIVATION OF C-H BONDS

A THESIS

SUBMITTED TO THE

UNIVERSITY OF PUNE

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

By

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UNDER THE GUIDANCE

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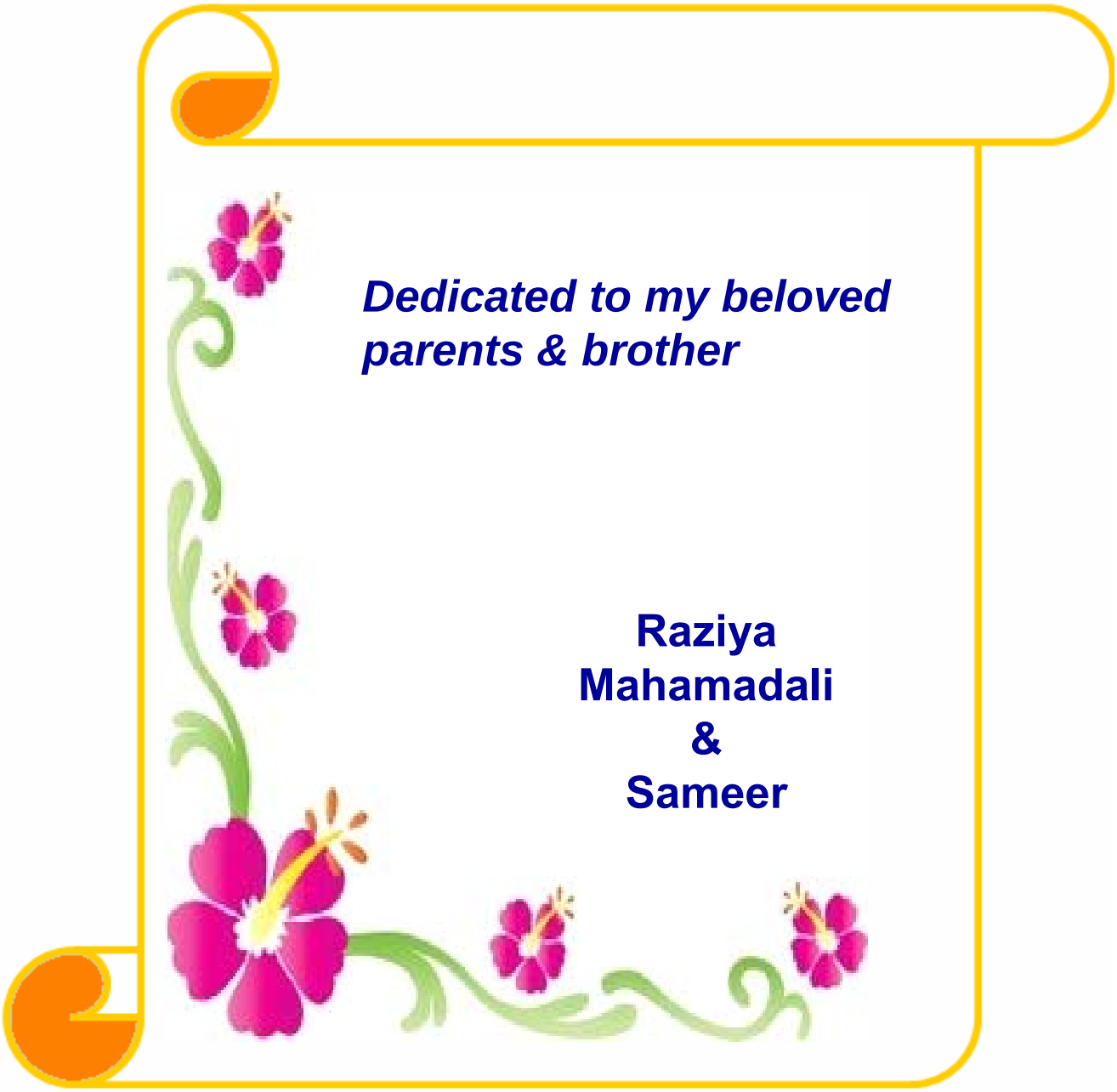
November 2009


Dedicated to my beloved parents & brother
Raziya Mahamadali & Sameer

NATIONAL CHEMICAL LABOATORY

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CERTIFICATE

Certified that the work incorporated in the thesis entitled "**Enantioselective Synthesis of Bioactive Molecules *via* Asymmetric Hydroxylations, Aminoallylation and Synthetic Methodologies Involving Activation of C-H 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.

November 2009 **(Dr. A. Sudalai)**

Pune Research Supervisor

NATIONAL CHEMICAL LABORATORY

DECLARATION

I here by declare that the thesis entitled **"Enantioselective Synthesis of Bioactive Molecules *via* Asymmetric Hydroxylations, Aminoallylation and Synthetic Methodologies Involving Activation of C-H Bonds"** submitted for the degree of Doctor of Philosophy in Chemistry to the University of Pune, has not been submitted by me to any other university or institution. This work was carried out at the National Chemical Laboratory, Pune, India.

November 2009
Pune

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CONTENTS

ACKNOWLEDGEMENT

I wish to express my heartfelt gratitude towards my research supervisor Dr. A. Sudalai sir, whose knowledge and vast experience has inspired me at every stage of my tenure and helped me to achieve this target. His suggestions, criticisms and constant encouragement helped me immensely to grow as a chemist. My everlasting gratitude goes to him.

I thank Dr. B. D. Kulkarni sir, Deputy Director and Head, CE-PD division, for his help and support. My special thanks go to Dr. S. Gurunath for his constant encouragement and moral support. I thank Dr. Ganesh Pandey sir, Head, OCD and Drs. Suresh Iyer, S. N. Kotwal, R. A. Kulkarni, V. G. Kulakarni, S. S. Pardhy, Mrs. S. Mayadevi and S. A. R. Mulla for their help and support.

I am immensely thankful to my seniors Drs. Vinay, Iliyas, Gajanan, Abhimanyu, Shivakumar, Shriram, Srinivas Rao, Ramesh Kumar, Victor Paul, Arun for useful training in the initial phase of my career.

I would like to thank my teachers Zhipre sir, Shirsat, Mrs. Dange, Drs. Patil, Modi sir. I am also grateful to Dr. Md. Qudrathullah Principal, Poona College, Dr. G. M. Nazeruddin, Dr. Alamgir Shaikh, Dr. Rafique Sarkhwas, Dr. Ejazuddin Khan, Dr. Mrs. Mulla, Aziz Mohinuddin for inspiring me towards research.

I thank NMR group Dr. Rajmohan, Jima, Hilda and elemental analysis group for their help in obtaining the analytical data. I am very thankful to Dr. Mrs. S. S. Kulkarni her help in GC-MS analysis and Dr. Vilas Chavan his help in the HPLC analysis. I thank library staff, chemical stores, purchase staff, glass blowing section NCL for their cooperation. I thank PD office staff Mr. Bhosale, Mrs. Puranik and Mr. Kakade for their cooperation. I also thank PG section of Pune University and Dr. Mrs. R. Kusurkar for their cooperation and help. It's my privilege to thank the Director, NCL for giving me this opportunity and providing all necessary infrastructure and facilities. Financial assistance from CSIR, New Delhi is greatly acknowledged.

It's my pleasure to thank all my lab mates Pandurang, Emmanuvel, Shyla, Santhosh, Pratibha, Varun, Dayanand, Narsimha, Chaithanya, Senthil kumar, Dattatraya, Ashish, Venkat, Shukla, Ramachandra, Balaji, Shaheen, Vijay, Hari, Kuppu, Sawant, Divya,

Santosh, Satish, Deepali, Aparna, Nagesh, Nana, Rana for providing a cheerful atmosphere in the lab and in every aspect through out this research. I am very thankful to project students Alka, Mudassir, Baba, Ruchi and Charuta for helping me in this work.

I thank my friends at NCL Bhargava, Raghupati, Bharat, Mehraj, Shafi, Sachin, Nagendra, Amrut, Swaroop, Deepak, Ravi, Nishant, Abhijeet, Sharad, Girish, Namdev, Imran, Muzahid, Suleman, Jayprakash, Tanpreet and Shivranjani for their help.

I acknowledge all my college friends Iqbal, Asgar, Shahbaj, Zubair, Rashid, Khalil, Shabir, Hamid, Hussain.

I thank Wasif for his support during my work. I am greatly indebted to all my childhood friends Pramod, Shivsharan and Pintoo.

I am indeed very grateful to my my parents whose constant love, care, support and encouragement have been the main force and motivation for me. The love and affection showered by my brother on me is magnanimous. My Bhabhi sisterin-law Mehjabeen always supports and encourage me. I have known Arshiya from my childhood days and got married to her. The love, dedication, support and encouragement I received from her helped me to complete this work. My brothers kid Naumaan, Izhaan and my daughter Tasmiya are angels and made my life more beautiful. I am very thankful to my sisters and my brotherin-law, Ishrat-Abdul Sattar, Yasmin-Ayub, Nasreen-Maqdum for their belief in my abilities and constant encouragement. My sister's kids Fahim, Mazhar, Farheen, Naeem, Azahar, Zulfin, Shazia, Sara, Ikra and Tanzim, Asim who always bought a smile on my face.

I wish to thank great scientific community whose achievements are constant source of inspiration for me.

Tanveer Mahamadali Shaikh

ABBREVIATIONS

AD	Asymmetric Dihydroxylation
Ac	Acetyl
Ar	Aryl
bp	Boiling Point
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
$(Boc)_2O$	Di-*tert*-butyl dicarbonate
n-BuLi	n-Butyl Lithium
Cbz	Benzyloxy carbonyl
CH_2Cl_2	Dichloromethane
$CHCl_3$	Trichloromethane
CH_3CN	Acetonitrile
$CuSO_4$	Copper(II) sulfate
DHQ	Dihydoquinine
DHQD	Dihydroquinidine
DIBAL-H	Diisobutylaluminium hydride
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
ee	Enantiomeric excess
Et	Ethyl
Et_3N	Triethylamine
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethyl alcohol
g	Grams
h	Hours
HCl	Hydrochloric acid
HPLC	High pressure liquid chromatography
H_2SO_4	Sulfuric acid
IR	Infrared
K_2CO_3	Potassium carbonate
KF	Potassium fluoride
KOH	Potassium hydroxide
$LiAlH_4$	Lithium aluminum hydride
M+	Molecular ion
Me	Methyl
MeOH	Methyl alcohol
min	Minutes
mL	Milliliter
mp	Melting point
MS	Mass spectrum
$NaBH_4$	Sodium borohydride
$NaHCO_3$	Sodium bicarbonate
NaOH	Sodium hydroxide

Na_2SO_4	Sodium sulfate
NH_4Cl	Ammonium chloride
NH_4OH	Ammonium hydroxide
NMR	Nuclear Magnetic Resonance
NBS	*N*-Bromosuccinimide
Pd/C	Palladium on activated charcoal
Pet. ether	Petroleum ether
Ph	Phenyl
PhNO	Nitrosobenzene
p-TSA	*p*-Toluene sulfonic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TBAF	Tetrabutylammonium fluoride
TBHP	*tert*-Butyl hydroperoxide
TBDMSCl	*tert*-Butyldimethylsilyl chloride

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 °C.
3. Organic layers after every extraction were dried over anhydrous sodium sulfate.
4. Column Chromatography was performed over silica gel (60-120 and 230-400 mesh).
5. TLC analyses were performed over aluminum plates coated with silica gel (5-25 m) 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 Bruker FT AV-200, AV-400 and AV-500 MHz instruments using TMS as an internal standard. The following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = 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 °C using sodium D light.
10. All melting points and boiling points are uncorrected and the temperatures are in centigrade scale.
11. Elemental analysis was 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 ligands $(DHQD)_2$-PHAL, $(DHQ)_2$-PHAL, $(DHQD)_2$-AQN were purchased from Aldrich.

ABSTRACT

The thesis entitiled "**Enantioselective Synthesis of Bioactive Molecules *via* Asymmetric Hydroxylations, Aminoallylation and Synthetic Methodologies Involving Activation of C-H Bonds**" is divided into four chapters.

The title of the thesis clearly reflects the objective, which is to synthesize enantiomerically pure bioactive molecules and also to develop useful synthetic methodologies. **Chapter 1** deals with enantioselective synthesis of (+)-Sertraline and (+)-Lentiginosine using Sharpless Asymmetric Dihydroxylation (ADH) and a*za*-Cope rearrangement respectively. **Chapter 2** describes the enantioselective synthesis of three alkaloids namely (+)-α-Conhydrine, (-)-Sedamine and (-)-Allosedridine. This chapter also describes a short synthesis of two β-blockers namely (*S*)-Betaxolol and (*S*)-Metoprolol *via* Co-salen-catalyzed kinetic resolution of terminal epoxides. **Chapter 3** presents $NaIO_4$-mediated C-H activation of alkylbenzenes, alkanes including oxidative functionalization of C-H, C-Br and C-O bonds. **Chapter 4** describes the application of two heterogeneous catalysts for the oxidative functionalization of C-H, C-O and C=C bonds of alkylarenes, arylketones and olefins respectively.

CHAPTER I

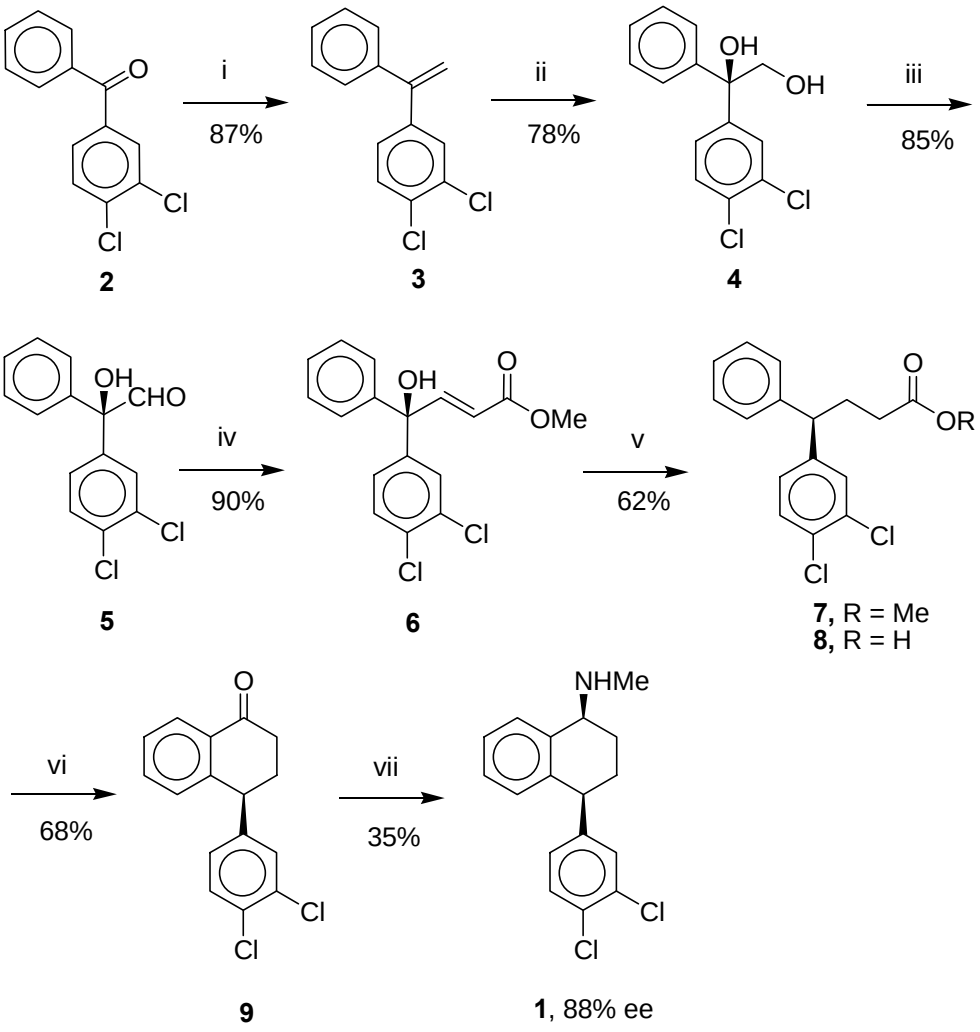
ENANTIOSELECTIVE SYNTHESIS OF (+)-SERTRALINE AND (+)-LENTIGINOSINE

This chapter is divided into two sections. Section I presents the synthesis of (+)-Sertraline, an antidepressant drug while Section II describes the synthesis of (+)-Lentiginosine, an anticancer drug.

Section I: A short Enantioselective Synthesis of (+)-Sertraline *via* Sharpless Asymmetric Dihydroxylation

(+)-Sertraline **1**, a selective competitive inhibitor of synaptosomal serotonin uptake, is an important antidepressant [1] drug discovered by Pfizer chemist Reinhard Sarges in 1970. This section describes an enantioselective synthesis of (+)-Sertraline *via* ADH[2] of 1,1-diaryl olefin. Our approach to the synthesis of (+)-Sertraline **1**, commenced with 3,4-

dichlorobenzophenone **2**, which was subjected to Wittig olefination to give 1,1-diaryl olefin **3**, in 87% yield (**Scheme 1**). Asymmetric dihydroxylation (K_2OsO_4, $(DHQD)_2$-AQN, $K_3Fe(CN)_6$, K_2CO_3, $^tBuOH:H_2O$ (1:1) of olefin **3** gave chiral diol **4** in 78% yield. Selective oxidation of primary alcohol in **4** was achieved with IBX in DMSO to give



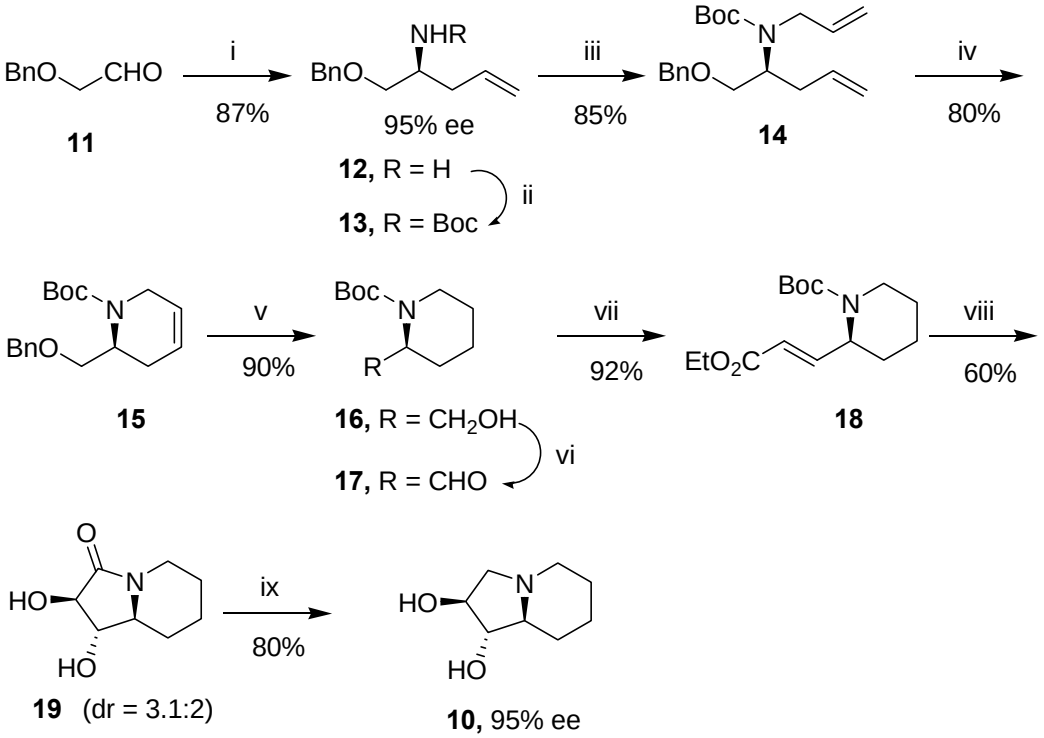
Scheme 1: Reaction conditions: (i) $Ph_3P^+CH_3I^-$, BuLi, THF, -78-0 ^oC, 5 h; (ii) $K_2OsO_4{\cdot}2H_2O$, $(DHQD)_2$-AQN, K_2CO_3, $K_3Fe(CN)_6$, $^tBuOH:H_2O$ (1:1), 24 h; (iii) IBX, dry DMSO, 25 ^oC, 1 h; (iv) $Ph_3P{=}CHCO_2Et$, dry benzene, 25 ^oC, 12 h; (v) 10% Pd/C, H_2 (20 psi), MeOH, 25 ^oC; (vi) 6 N HCl, reflux, 23 h; $ClSO_3H$, CH_2Cl_2, 25 ^oC, 2 h; (vii) $TiCl_4$, excess $MeNH_2$, , $Pd/CaCO_3$, H_2, (50 psi).

aldehyde **5** in 85% yield. Aldehyde **5** was then subjected to Wittig olefination to give the α,β-unsaturated ester **6** in 90% yield. Hydrogenolysis (10% Pd/C, H_2 (20 psi), MeOH) of ester **6** at the benzylic position led to the formation of saturated ester **7** in 62% yield.

Ester **7** was subsequently hydrolysed and cyclised under acidic conditions to give tetralone **9** with an overall yield of 68% and 88% ee. Finally, reductive amination ($TiCl_4$, excess $MeNH_2$, $Pd/CaCO_3$, H_2 (50 psi)) of **9** afforded **1** in 35% yield and 88% ee.

Section II: Enantioselective Synthesis of (+)-Lentiginosine *via* aza-Cope Rearrangement

Hydroxylated indolizidine alkaloids are known to be the potential glycosidase inhibitors. (+)-Lentiginosine **10,** a bicyclic azasugar, was isolated from the leaves of *Astragalus lentiginosis*[3] in 1990 and found to exhibit amyoglucosidase inhibition[4] activity (IC_{50} = 0.43 mg/L) including anticancer and anti HIV activities. Recently, Kobayashi *etal*. have reported a highly enantioselective synthesis of homoallylic primary amines *via* aza-Cope rearrangement.[5] In this section we have made use of this rearrangement protocol for the synthesis of (+)-Lentiginosine **10**.



Scheme 2: Reaction conditions: (i) Camphorsulfonic acid (10 mol%), 1,2-dichloroethane, (1*R*,3*R*,4*S*)-3-allyl-3-amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (1equiv.), $NH_2OH{\cdot}AcOH$, 25 ^oC, 24 h; (ii) $(Boc)_2O$, DMAP (10 mol%), Et_3N, CH_2Cl_2, 25 ^oC, 10 h; (iii) NaH, allylbromide, dry DMF, 0-25 ^oC, 5 h; (iv) Grubbs 2nd generation catalyst (10 mol%), dry CH_2Cl_2, 20 h, reflux; (v) 10% Pd/C, H_2 (20 psi), MeOH, 25 ^oC, 12 h; (vi) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^oC; (vii) $Ph_3P{=}CHCO_2Et$, benzene, 50 ^oC, 14 h; (viii) OsO_4, NMO, $^tBuOH{:}H_2O$, 25 ^oC, 24 h; then TFA, 18 h; (ix) $LiAlH_4$, THF, 12 h, reflux.

Synthesis of (+)-Lentiginosine **10** commenced with the readily available benzyl-protected acetaldehyde **11**, which was subjected to aza-Cope rearrangement using Kobayashi protocol [CSA (10 mol%), (1*R*,3*R*,4*S*)-3-allyl-3-amino-1,7,7-trimethylbicyclo [2.2.1] heptan-2-one (1 equiv.), $NH_2OH{\cdot}AcOH$, 1,2-dichloroethane] to give the homoallylic amine **12** in 87% yield and 95% ee (**Scheme 2**). The Ring Closing Metathesis (RCM)-precursor **14** was prepared in two steps with an overall yield of 85%: Boc protection of amine **12** followed by its N-allylation using allyl bromide. The RCM strategy on **14** was employed using Grubbs 2nd generation catalyst to effect the construction of six-membered dihydropyridine **15** in 80% yield. Catalytic hydrogenation of **15** afforded piperidine derivative **16** in 90% yield and 98% ee (determined from chiral HPLC analysis). Swern oxidation of alcohol **16** produced piperidine carboxaldehyde **17** which underwent Wittig olefination with $Ph_3P{=}CHCO_2Et$ to give the α,β-unsaturated ester **18** in 92% yield. A single-step transformation of ester **18** into diol **19** in 60% yield was achieved using Os-catalyzed dihydroxylation of olefin **18** followed by its treatment with TFA. $LiAlH_4$ reduction of imide carbonyl in **19** was carried out to furnish (+)-Lentiginosine **10** in 80% yield and 95% ee.

CHAPTER II

ENANTIOSELECTIVE SYNTHESIS OF (+)-A-CONHYDRINE, (-)-SEDAMINE, (-)-*ALLO*SEDRIDINE, (*S*)-BETAXOLOL AND (*S*)-METOPROLOL

This chapter is divided into three sections. While Section I presents the enantioselective synthesis of (+)-α-Conhydrine and (-)-Sedamine *via* L-proline-catalyzed α-aminooxylation, Section II describes the enantioselective synthesis of (-)-Allosedridine *via* Sharpless asymmetric epoxidation. Section III also presents the asymmetric synthesis of two β-blockers namely (*S*)-Betaxolol and (*S*)-Metoprolol using Co-salen-catalyzed phenolytic kinetic resolution of terminal epoxides.

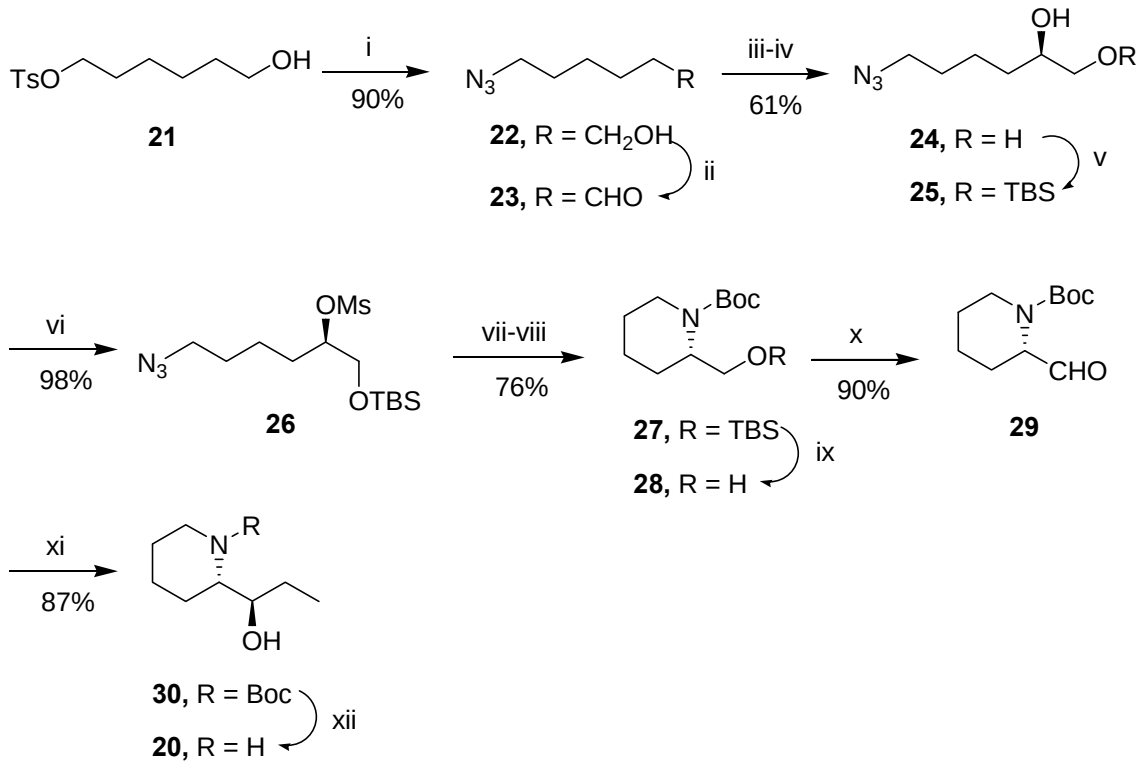
Section I: Enantioselective Synthesis of (+)-α-Conhydrine and (-)-Sedamine *via* L-Proline Catalyzed α-Aminooxylation

Asymmetric synthesis with non-toxic metal salts has been of great importance in organic synthesis. Organocatalyst such as optically active proline, available cheap and

abundantly, has been employed as a universal catalyst because of its high utility in a variety of asymmetric organic transformations. Particularly, proline catalyzed α-aminooxylation[6] and α-amination of carbonyl compounds have emerged as powerful methods since chiral building materials can be synthesized in an effective manner with high enantiopurity.

(+)-α-Conhydrine:

Hydroxylated piperidines represent a structural unit found in many biologically active alkaloids including (-)-Conhydrine **20**, which was isolated from hemlock of poisonous plant *Conium maculatum* L.[7]



Scheme 3: Reactions conditions: (i) NaN_3, dry DMF, 80 °C, 16 h; (ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 1 h; (iii) L-proline (25 mol%), PhNO, CH_3CN, -20 °C, 24 h; then MeOH, $NaBH_4$, 0 °C, 1 h; (iv) $CuSO_4$ (30 mol%), MeOH, 12 h; (v) TBSCl, imidazole, CH_2Cl_2, 0 °C, 1 h; (vi) MsCl, Et_3N, CH_2Cl, 0 °C, 1 h; (vii) 10% Pd/C, H_2 (20 psi), MeOH, Et_3N, 25 °C 5 h; (viii) $(Boc)_2O$, DMAP, Et_3N, CH_2Cl_2, 25 °C, 6 h; (ix) TBAF, THF, 0 °C, 3 h; (x) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 1 h; (xi) excess EtMgBr, -78 °C, 3 h; (xii) TFA:CH_2Cl_2 (1:1), 25 °C, 12 h.

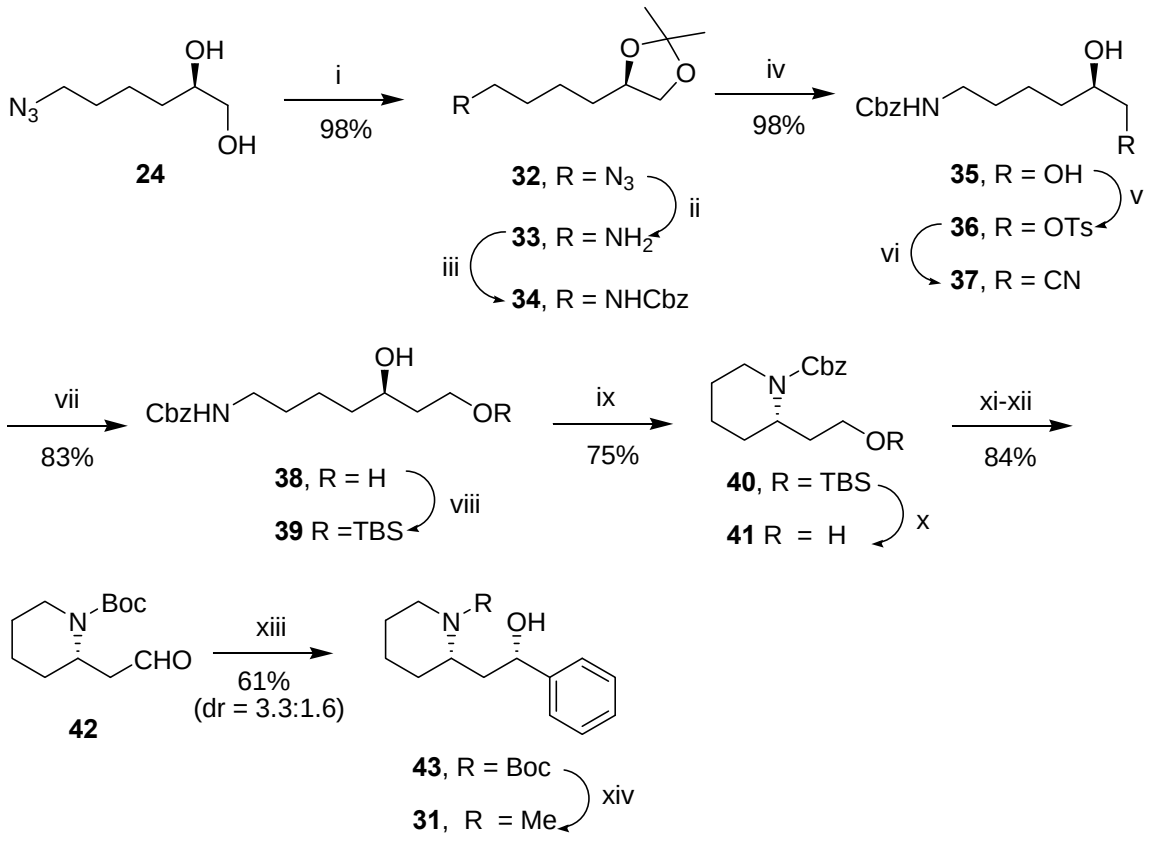
The synthesis of (+)-α-Conhydrine **20** was started with monoprotected 1,6-hexanediol **21**, which was subjected to S_N2 displacement with NaN_3 to produce azidoalcohol **22** in 90% yield (**Scheme 3**). The Swern oxidation of alcohol **22** gave aldehyde **23**, which was

subsequently converted to azidodiol **24** in two steps: (i) L-proline-catalyzed asymmetric aminooxylation using PhNO as electrophile followed by *in situ* reduction of aldehyde with $NaBH_4$ and (ii) reductive cleavage of aminoxy moiety with $CuSO_4$ in MeOH that furnished the diol **24** in 61% overall yield. The selective protection of primary alcohol in diol **24** was achieved giving TBS ether **25** which was protected as its mesylate **26** in quantitative yield. The reductive cyclization (10% Pd/C, H_2 (20 psi) followed by Boc protection of N-H bond resulted in the formation of TBS ether **27** in 76% yield. The hydrolysis of **27** followed by its oxidation under Swern conditions produced aldehyde **29** in 90% yield. Grignard addition of EtMgBr onto aldehyde **29** gave the Boc protected Conhydrine **30**, which was finally hydrolysed to (+)-α-Conhydrine **20** in high optical purity (98% ee).

(-)-Sedamine:

(-)-Sedamine **31** was isolated from *Sedum acre*[8] and other species.[9,10] It has been used for the treatment of respiratory illness such as asthma, bronchitis and pneumonia.[11]

Our synthesis of (-)-Sedamine **31** started with azido diol **24** (*vide infra* for its preparation) which was converted to amino compound **34** in three steps of acetonide protection of diol **24**, reduction of azide function and Cbz protection of its amine function. Amino derivative **34** was subsequently converted to cyano compound **37** again in three steps of acetonide deprotection, selective mono tosylation of primary alcohol **35** and S_N2 displacement of tosylate **36** with CN^- ion. The selective reduction (1.2 M DIBAL-H, CH_2Cl_2) followed by its treatment with $NaBH_4$ in MeOH produced 1,3-diol **38** in 70% yield. The TBS ether **39**, prepared from 1,3-diol **38** *via* selective protection, was directly cyclized under basic conditions to give the piperidine derivative **40** in 76% yield, subsequently hydrolysis of TBS ether gave the piperidine alcohol **41**. The removal of Cbz group and subsequently protection of Boc group followed by its oxidation under Swern conditions produced aldehyde **42** in 84% yield. Grignard addition of PhMgBr onto aldehyde **42** gave a diastereomeric mixture of Cbz protected alcohols **43** in 61% yield (dr = 3.3:1.6) which were readily separated by column chromatography and the required isomer **43** was converted to Sedamine **31** on reduction with $LiAlH_4$ (**Scheme 4**).

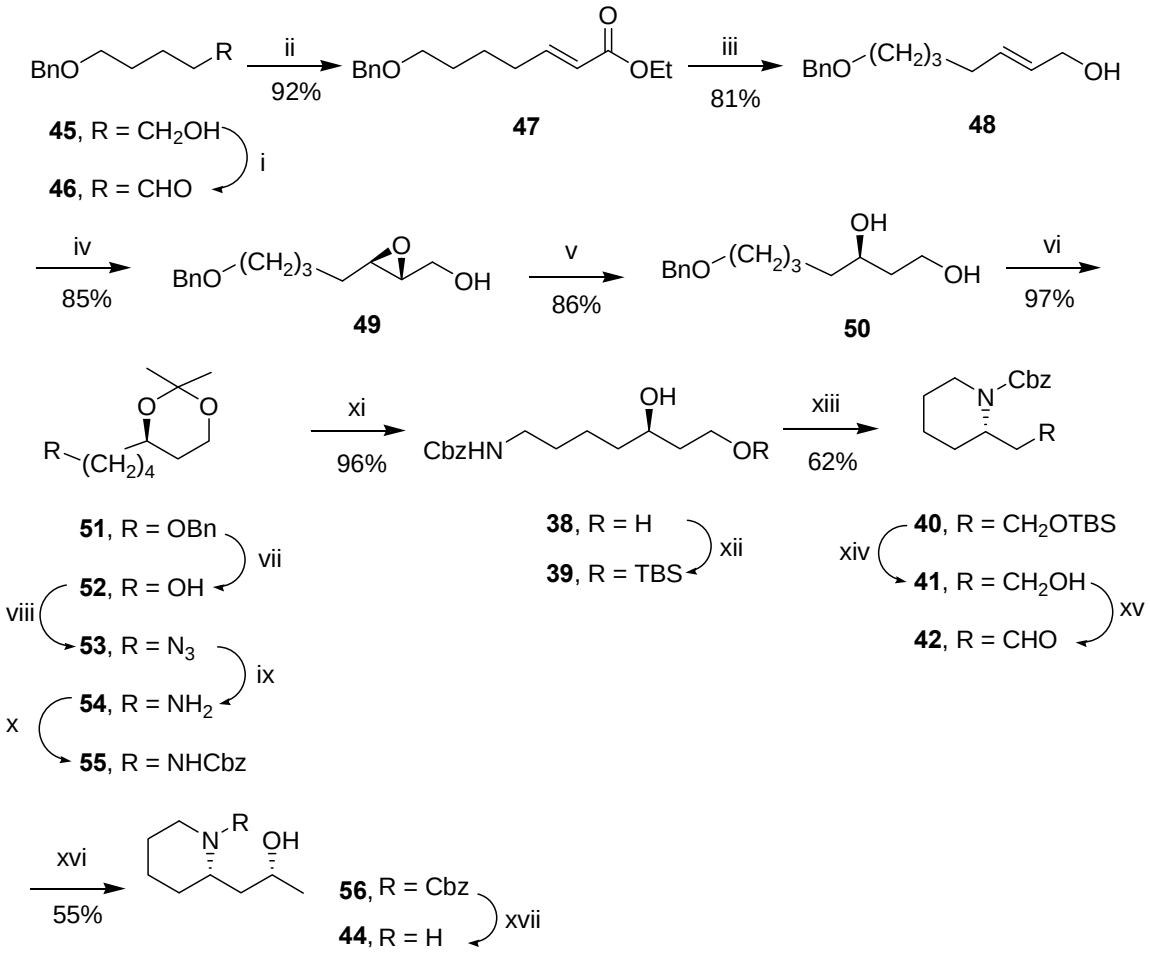


Scheme 4: Reaction conditions: (i) 2,2-dimethoxypropane, *p*-TSA (10 mol%), CH_2Cl_2, 25 ^oC, 12 h; (ii) 10% Pd/C, H_2 (20 psi), MeOH, 25 ^oC, 8 h; (iii) CbzCl, K_2CO_3, CH_2Cl_2:H_2O (1:1), 25 ^oC, 10 h; (iv) excess of 80% aq. AcOH, 25 ^oC 18 h; (v) *p*-TsCl, Et_3N, excess CH_2Cl_2, -20 ^oC, 18 h; (vi) NaCN, EtOH:H_2O (3:2), 0-25 ^oC, 18 h; (vii) 1.2 M DIBAL-H; CH_2Cl_2; then $NaBH_4$, MeOH, 25 ^oC, 2 h; (viii) TBSCl, imidazole, CH_2Cl_2, 0 ^oC, 1 h; (ix) MsCl, Et_3N, CH_2Cl_2, -10 ^oC, 45 min then NaH (1 equiv.), THF, 40 ^oC, 8 h (x) 3N HCl 25 ^oC, 2 h; (xi) 10% Pd/C, H_2 (20 psi), MeOH, 25 ^oC, 5 h, 91%; then $(Boc)_2O$, I_2 (10 mol%), 3 h (xii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^oC, 1 h; (xiii) PhMgBr, dry THF, -20 ^oC, 6 h; (xiv) $LiAlH_4$, THF, 70 ^oC, 15 h.

Section II: Enantioselective Synthesis of (-)-*Allo*sedridine *via* Sharpless Asymmetric Epoxidation

(-)*Allo*sedridine **44** was isolated from *Sedum nudum*.[12] It has shown memory enhancing-properties and may be effective for the treatment of Alzheimer's disease. This section describes the synthesis of (-)-*Allo*sedridine **44** *via* Sharpless asymmetric epoxidation.[13]

The synthesis of (-)-a*llo*sedridine **44** was started with mono protected 1,5-pentanediol **45**, which was subjected to Swern oxidation conditions to give aldehyde **46** in 92% yield (**Scheme 5**). Allylic alcohol **48** was prepared in two steps: Wittig olefination of aldehyde **46** with $Ph_3P{=}CHCO_2Et$ furnished α,β-unsaturated ester **47** in 92% yield. The selective



Scheme 5: Reaction condition: (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^oC, 1 h; (ii) PPh_3=$CHCO_2Et$, dry benzene, reflux, 12 h; (iii) 1.2 M DIBAL-H, CH_2Cl_2, 25 ^oC, 6h; (iv) $Ti(O^ipr)_4$, (-)-DIPT, CH_2Cl_2, 5.5 M TBHP in decane, -23 ^oC, 24 h; (v) Red-Al® (65%) in toluene, 1,2-dimethoxyethane, 25 ^oC, 4 h; (vi) 2,2-dimethoxypropane, CH_2Cl_2, *p*-TSA (10 mol%), 25 ^oC, 10 h; (vii) 10% Pd/C, H_2 (20 psi), MeOH, 25 ^oC,10 h; (viii) (a) MsCl, Et_3N, CH_2Cl_2, 0 ^oC, 45 min; (b) NaN_3, DMF, 80 ^oC, 15 h; (ix) 10% Pd/C, H_2 (20 psi), MeOH, 25 ^oC, 6 h; (x) CbzCl, K_2CO_3, CH_2Cl_2:H_2O (1:1) 25 ^oC, 8 h; (xi) excess 80% aq. AcOH, 25 ^oC, 18 h; (xii) TBSCl, imidazole, CH_2Cl_2, 0 ^oC, 1 h (xiii) (a) MsCl, Et_3N, CH_2Cl_2, 0 ^oC, 45 min; (b) NaH (1 equiv.), THF, 40 ^oC, 10 h; (xiv) 6 N HCl, 25 ^oC, 2 h; (xv) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^oC, 1 h; (xvi) excess MeMgBr, THF, -78 ^oC 4 h; (xvii) 10% Pd/C, H_2 (20 psi), MeOH, 25 ^oC, 10 h.

reduction of α,β-unsaturated ester **47** with 1.2 M DIBAL-H gave allylic alcohol **48** in 81% yield. The Sharpless asymmetric epoxidation of allylic alcohol **48** gave chiral epoxy alcohol **49** in 85% yield and 97% ee (determined from chiral HPLC analysis). Regioselective reduction (Red-Al®, DME) of epoxy alcohol **49** resulted in the formation of 1,3-diol **50**, which was protected as its acetonide **51** in 97% yield. Amino derivative **55** was prepared in three steps: hydrogenolysis of **51**, reduction of azide function and Cbz

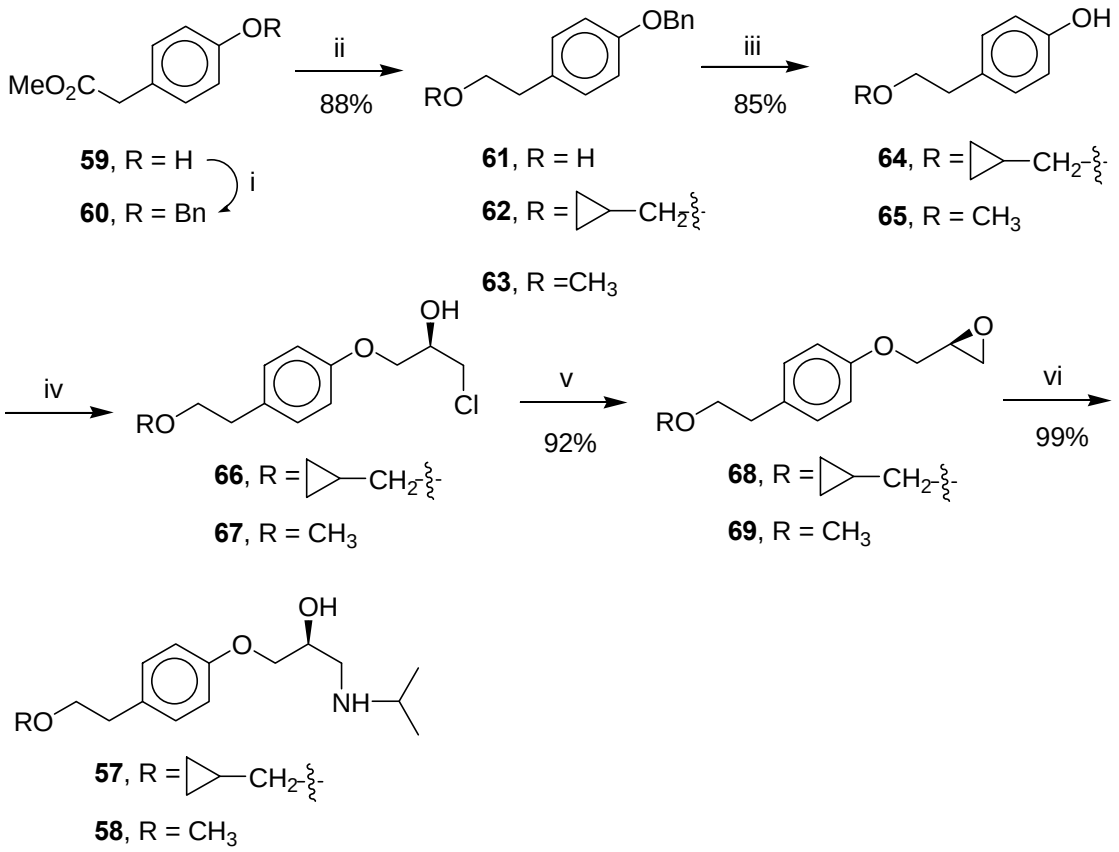
protection of its amine function. Acetonide function in amino derivative **55** was subsequently deprotected under acidic conditions to give 1,3-diol **38**. The TBS ether **39** prepared from 1,3-diol **38** *via* selective protection, was directly cyclized under basic conditions to give piperidine derivative **40** in 62% yield. The hydrolysis of TBS ether **40** followed by its oxidation under Swern conditions produced aldehyde **42** in 90% yield. Grignard addition of MeMgBr onto aldehyde **42** gave a diastereomeric mixture of Cbz protected alcohols **56** in 85% yield (dr = 3.2:1.7) which were readily separated by column chromatography and the required isomer **56** was converted to (-)-allosedridine **44** on hydrogenation with $Pd(OH)_2$, H_2 (20 psi).

Section III: Asymmetric Synthesis of β-Blockers: (*S*)-Betaxolol and (*S*)-Metoprolol

β-Blockers are a group of compounds that competitively inhibit[14] the effects of catecholamine at β-adrenergic receptors and have a diverse range of clinical applications. They lower blood pressure by slowing down the heart rate and decreasing the force of contraction of heart.[15] (*S*)-Betaxolol **57** (trade name Betoptic) is a strong antiglaucoma agent while (*S*)-Metoprolol **58** (trade name Lopressor) is widely used in the treatment of angina hypertension.

The dynamic kinetic resolution of recemic epoxides with phenols is probably the most direct method to obtain enantiopure aryloxy alcohols [$(Ar\text{-}O\text{-}CH_2(OH)CH_2Cl$], which are the key structural units present in a variety of β-blockers. The cheaper and readily available (±)-epichlorohydrin renders kinetic resolution of its epoxide function with phenolic substrates as a potentially attractive route for the preparation of chiral epoxides using Co-salen complex as the chiral catalyst.[16] Our synthesis of (*S*)-Betaxolol **57** and (*S*)-Metoprolol **58** started with commercially available phenolic ester **59**, which was protected as its benzyl ether **60**. Alcohol **61**, obtained from $LiAlH_4$ reduction of ester **60** was O-alkylated with (bromomethyl)cyclopropane and methyl iodide to produce the corresponding ethers **62** and **63** respectively in high yields (**Scheme 6**). Hydrogenolysis [10% Pd/C, H_2 (20 psi)] of ethers **62** and **63** resulted in the formation of phenols **64** and **65** respectively. Thus, the reaction of 2.5 equiv. of (±)-epichlorohydrin with 4-(2-(cyclopropylmethoxy)ethyl)phenol **64** and 4-(2-methoxyethyl)phenol **65** in the presence

of [(*R*, *R*)-(salen)Co(OAc)] complex (0.044 equiv.) in *tert*-butyl methyl ether at 0-25 ^{o}C led to the isolation of (*R*)-1-(4-(2-(cyclopropylmethoxy)ethyl)phenoxy)-3-chloropropan-2-ol **66** and (*R*)-1-(4-(2-methoxyethyl)phenoxy)-3-chloropropan-2-ol **67** in 73 and 71% yield respectively. The chlorohydrins **66** and **67** were then converted to epoxides **68** and **69** (Bu^{t}OK, THF, 0 ^{o}C). Finally, the chiral epoxides **68** and **69** were subjected to regiospecific ring opening with isopropylamine to afford (*S*)-Betaxolol and (*S*)-Metoprolol in high optical purity.



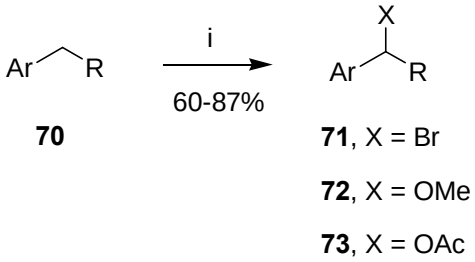
Scheme 6: Reaction conditions: (i) anhyd. K_2CO_3, acetone, BnBr, 0-60 ^{o}C, 6 h; (ii) $LiAlH_4$, dry THF, 65 ^{o}C, 12 h; (iii) 10% Pd/C, H_2 (20 psi), MeOH, 12 h; (iv) for betaxolol: NaH, dry DMF, (bromomethyl)cyclopropane, 0-25 ^{o}C, 6 h; and for metoprolol: NaH, dry DMF, MeI, 0-25 ^{o}C, 3 h; (v) 2.5 equiv. (±)-epichlorohydrin, (*R,R*)-Co-salen, *tert*-butyl methyl ether, MS 4 A$^{\circ}$, 25 °C, 24 h; (vi) K^{t}OBu, THF, 0 °C; (vii) isopropylamine, H_2O, 50 °C.

CHAPTER III

$NaIO_4$-MEDIATED C-H ACTIVATION OF ALKYLARENES AND OXIDATIVE FUNCTIONALIZATION OF C-H, C-Br, C-O BONDS

Section I: $NaIO_4$-Mediated C-H Activation of Alkylarenes: Oxyfunctionalization at the Benzylic Position

The selective and efficient oxyfunctionalization of unreactive C-H bonds in hydrocarbons is challenging. In particular, oxidation at benzylic position of alkylbenzene assumes importance due to their oxygenated derivatives such as alcohols and carbonyl compounds that are useful as specialty chemicals in industry.[17] This section describes a "transition metal free" method for the C-H activation of alkylarenes leading to C-X bonds (**Scheme 7**).



70

71, X = Br

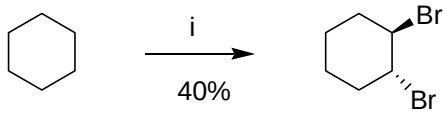
72, X = OMe

73, X = OAc

Scheme 7: Reaction conditions: (i) if X = Br, OMe: alkylarenes (10 mmol), LiBr (11 mmol), H_2SO_4 (20 mmol), MeOH (15 mL), 65 ^oC, 24 h; (i) if X = OAc: alkylarenes (10 mmol), LiBr (11 mmol), $NaIO_4$ (25 mol%), AcOH (15 mL), 90 ^oC, 24 h.

Thus, alkylarenes **70** in combination with $NaIO_4$/LiBr/MeOH/H^+ undergo oxidation smoothly at the benzylic position to give a mixture of benzylic bromides **71** and benzylic methyl ethers **72**. Surprisingly, high yields of benzyl acetates **73** were obtained when $NaIO_4$/LiBr/ AcOH combination[18] was used.

We have observed that $NaIO_4$-mediated oxidative bromination of cycloalkanes takes place with LiBr as bromide source. For example, cyclohexane **74** underwent oxidation moderately to produce *trans*-1,2-dibromocyclohexane **75** in 40% yield in a single step (**Scheme 8**).

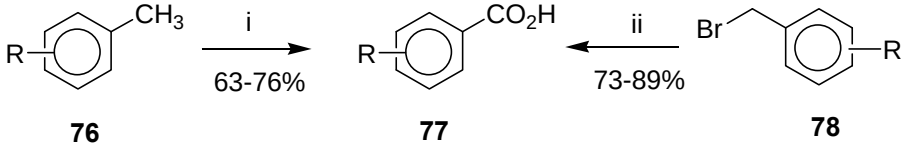


74 **75**

Scheme 8: (i) cyclohexane (10 mmol), LiBr (22 mmol), $NaIO_4$ (25 mol%), AcOH (15 mL), 80 ^oC, 24 h.

Section II: $NaIO_4$-Mediated Selective Oxidation of Benzylic Bromides and Alkylarenes to Benzoic acids in Water as Solvent

Carboxylic acids are of industrial importance since such carbonyl derivatives are versatile building blocks in pharmaceutical and polymer industries.[19] In this section we describe a single-step "transition metal-free" oxidation of alkylarenes and benzylic bromides to the corresponding carboxylic acids in high yields with water as a solvent.[20]



76 **77** **78**

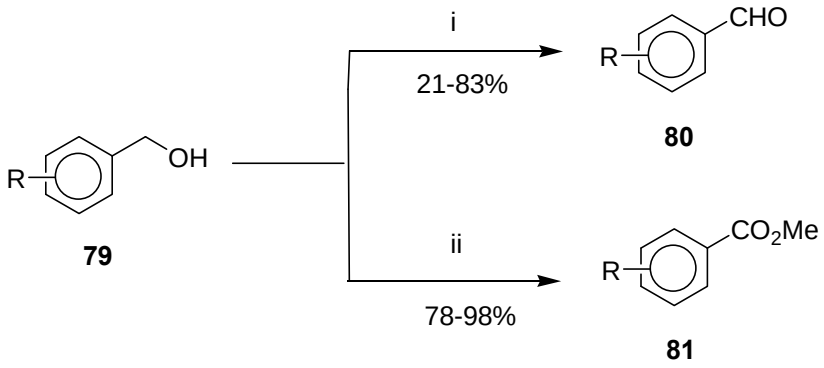
R = alkyl, halogen, NO_2, etc

Scheme 9: Reaction conditions: (i) methylarenes (3 mmol), $NaIO_4$ (3 mmol), LiBr (3.3 mmol) 2% aq. H_2SO_4 (15 mL), 95 ^oC, 18 h; (ii) benzyl bromides (3 mmol), $NaIO_4$ (3 mmol), 2% aq. H_2SO_4 (15 mL), 95 ^oC, 18 h.

Thus, while oxidation of alkylarenes **76** to the corresponding carboxylic acids **77** has been achieved with $NaIO_4/LiBr/H_2O/H^+$ combination, benzylic bromides **78** were oxidized with $NaIO_4/H_2O/H^+$ to give the same carboxylic acids **77** in excellent yields (**Scheme 9**). Several alkylarenes and benzylic bromides with electron-donating and -withdrawing groups underwent oxidation and produced the corresponding carboxylic acids **77**. A noteworthy feature of the present method is the use of water as solvent and the products were isolated by simple filtration followed by crystallization.

Section III: $NaIO_4$-Mediated Selective Oxidation of Benzylic alcohols: High Yield Preparation of Aromatic Aldehydes and Esters

The oxidation of primary aromatic alcohols to the corresponding carbonyl compounds is a fundamental reaction in organic synthesis.[21] Also, direct conversion of alcohols or aldehydes to the corresponding carboxylic esters is often required in organic synthesis particularly in the synthesis of natural products. In general, the synthesis of carboxylic esters is achieved by the oxidation of alcohols to aldehydes or carboxylic acids followed by acid-catalyzed esterification with alcohols. However, the direct conversion of benzylic alcohols to aldehydes or esters minimizes the number of steps in organic synthesis. This section deals with a new procedure involving $NaIO_4/H_2O/H^+$ that oxidizes benzylic alcohols **79** to the corresponding benzaldehydes **80**. Also, this section describes a one-pot conversion of benzylic alcohols to the corresponding aromatic esters **81** in excellent yields[22] (**Scheme 10**).



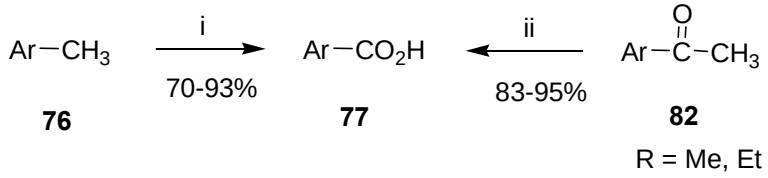
Scheme 10: Reaction conditions: (i) benzyl alcohol (3 mmol), $NaIO_4$ (3 mmol), 2% aq. H_2SO_4 (15 mL), 95 ^oC, 12 h; (ii) benzyl alcohol (3 mmol), $NaIO_4$ (3 mmol), LiBr (3 mmol), H_2SO_4, MeOH (15 mL), 80 ^oC, 24 h.

CHAPTER IV
HETEROGENEOUS CATALYSTS FOR OXIDATIVE TRANSFORMATION OF C-H, C-O AND C=C BONDS

Section I: WO_3-Catalyzed Selective Oxidation of Alkylarenes and Arylketones: High Yield Preparation of Benzoic acids

The oxidation of benzylic C-H bonds to the corresponding oxyfunctionalized products constitutes one of the most fundamental transformations in organic synthesis.[19, 21] In

particular, the direct conversion of methylarenes or aryl ketones to the corresponding benzoic acids assumes greater industrial importance as such carbonyl derivatives are versatile building blocks in pharmaceutical and polymer industries. This section describes a new practical method where in WO_3 acts as a catalyst for the oxidation of methylarenes and for oxidative cleavage of arylketones to the corresponding benzoic acids in the presence of 70% aq. *tert*-butyl hydroperoxide (TBHP) as oxidant with 40% aq. NaOH as additive[23] (**Scheme 11**).

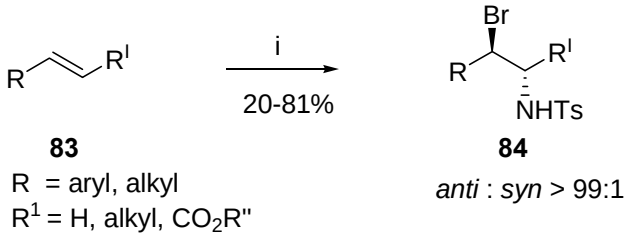


Scheme 11: Reaction conditions: (i) methylarenes (3 mmol), WO_3 (20 mol%), 70% aq. TBHP (24 mmol), 40% aq. NaOH (24 mmol), 80 ^oC, 10 h; (ii) aryl ketones (3 mmol), WO_3 (10 mol%), 70% aq. TBHP (12 mmol), 40% aq. NaOH (12 mmol), 80 ^oC, 8 h.

Several alkylarenes **76** and aryl ketones **82** with electron-donating as well as -withdrawing groups underwent oxidation and produced carboxylic acids **77** in high yields. The important aspects of WO_3-catalyzed oxidation: free from organic solvents, benzoic acids were isolated in pure form without the need for column chromatographic purification, does not generate any hazardous waste, WO_3 could be recovered by filtration.

Section II: Titanium Superoxide: A Heterogeneous Catalyst for Aminobromination of Olefin

The haloamination of olefins by the addition of two different functional groups in a single step is an important transformation.[24] The vicinal haloamine functionality represents a useful structural moiety as well as versatile building blocks in organic and medicinal chemistry.



Scheme 12: Reaction conditions: (i) olefin (3 mmol), *p*-$TsNH_2$ (3.3 mmol), NBS (3 mmol), titanium superoxide (10 wt%), CH_2Cl_2 (20 mL), 25 ^oC, 14 h.

This section describes a new heterogeneous catalytic method for the regiospecific bromoamination of olefins **83** catalyzed by titanium superoxide using NBS (N-bromosuccinimide) as bromine source and *p*-toluene sulfonamide as the nitrogen source[25] (**Scheme 12**). The present method has been demonstrated for several olefins (aliphatic and aromatic) with electron-donating and -withdrawing groups that underwent bromoamination in high yields and diastereoselectivity (>99:1). The protocol makes use of stable, reusable and readily accessible titanium superoxide as solid catalyst, which could be recovered by simple filtration.

References:

1. (a) Welch, W. M.; Harbert, C. A.; Koe, B. K.; Kraska, A. R. European Patent 30081, **1981**; *Chem. Abstr.* **1981**, *95*, 209648; (b) Welch, W. M.; Kraska, A. R.; Sarges, R.; Koe, B. K. *J. Med. Chem.* **1984**, *27*, 1508.
2. Kolb H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev*. **1994**, *94*, 2483.
3. Pastuszak, I.; Molyneux, R. J.; James, L. F.; Elbein, A. D. *Biochemistry* **1990**, *29*, 1886.
4. Mammen, M.; Choi, S.-K.; Whitesides, G. M. *Angew. Chem., Int. Ed.*, **1998**, *37*, 2754.
5. Sugiura, M.; Mori, M.; Kobayashi, S.; *J. Am. Chem. Soc*. **2006**, *128*, 11038 11039.
6. (a) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808; (b) Zhong, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4247; (c) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett.* **2003**, *44*, 8293.
7. Wertheim, T. *Liebigs*. *Ann. Chem*. **1856**, *100*, 328–330.
8. (a) Marion, L. *Can. J. Res*. **1945**, *23B*, 165; (b) Marion, L.; Lavigne, R.; Lemay, L. *Can. J. Chem.* **1951**, *29*, 347; (c) Franck, B. *Chem. Ber*. **1958**, *91*, 2803; (d) Franck, B. *Chem. Ber.* **1960**, *93*, 2360; (e) Fodor, G.; Butruille, D.; Huber, S. C.; Letourneau, F. *Tetrahedron* **1971**, *27*, 2055.
9. Kim, J. H.; Hart, H. T.; Stevens, J. F. *Phytochemistry*, **1996**, *41*, 1319.

10. (a) Wieland, H.; Koschara, K.; Dane, E.; Renz, J.; Schwarze, W.; Linde, W. Liebigs *Ann. Chem.* **1939**, *540*, 103; (b) Schopf, C.; Kauffmann, T.; Berth, P.; Bundshuh, W.; Dummer, G.; Fett, H.; Habermehl, G.; Wieters, E.; Wust, W. Liebigs *Ann. Chem*. **1959**, *626*, 150.
11. Gershwin, M. E.; Terr, A.; *Clin. Rev. Allergy* **1996**, *14*, 241.
12. (a) Strunzand, G. M.; Finlay, J. A. In *The Alkaloids;* Brossi, A., Ed.; Academic Press: New York, **1985**; Vol. *26*, pp 89–174; (b) Buffat, M. G. P. *Tetrahedron,* **2004**, *60*, 1701.
13. Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc*. **1980**, *102*, 5974.
14. Barrett, M. A. *Beta-adrenoceptive agonists; in Recent Advances in Cardiology*, ed. Churchill Livingstone, Edinburgh, London, **1973**; p. 289.
15. (a) Howe, S. *Nature* **1966**, *210*, 1336; (b) Shiratsuchi, M.; Kawamura, K.; Akashi, T.; Ishihama, H.; Nakamura, M.; Takenaka, F. *Chem. Pharm. Bull.* **1987**, *35*, 3691.
16. Ready, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc*. **1999**, *22*, 274.
17. (a) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev*. **1997**, *97*, 2879–2932; (b) Hill, C. L. *Activation and Functionalization of Alkanes*; John Wiley: New York, **1989**; (c) Labinger, J. A.; Bercaw, J. E. *Nature*, **2002**, *417*, 507–514.
18. Shaikh, T. M.; Sudalai, A.; *Tetrahedron Lett*. **2005**, *46*, 5587-5590.
19. (a) Sheldon, R. A.; Kochi, J. K. *Metal Catalyzed Oxidations of Organic Compounds*; Academic press: New York, **1981**; (b) Cainelli, G.; Cardillo, G. *Chromium Oxidations in organic Chemistry*; Springer: Berlin, **1984**; (c) Hudlicky, M. *Oxidations in Organic Chemistry*; American Chemical Society: Washington, DC, **1990**.
20. Shaikh, T. M.; Emmanuvel, L.; Sudalai, L.; *J. Org. Chem*. **2006**, *71*, 5043-5046.
21. (a) *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*; Larock, R. C., Ed.; Wiley-VCH: New York, **1989**; (b) Fisher, C. H. *J. Am. Chem. Soc*. **1934**, *56*, 2056; (c) Kornblum, N.; Jones, W. J.; Anderson, G. J. *J. Am. Chem. Soc.* **1959**, *81*, 4113 ; (d) Suzuki, S.; Onishi, T.; Fujita, Y.; Misawa, H.; Otetra, J. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3287.
22. Shaikh, T. M.; Emmanuvel, L.; Sudalai, A. *Synth. Commun*. **2007**, *37*, 2641-2646.
23. Shaikh, T. M.; Sudalai, A. *Eur. J. Org. Chem*. **2008**, 4877-4880.
24. (a) Kemp, J. E. G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, **1991**; Vol. 3, p 471; (b) Gao, G.-Y.; Harden, J. D.; Zhang, X. P. *Org. Lett*. **2005**, *7*, 3191; (e) Yeung, Y.-Y.; Hong, S.; Corey, E. J. *J. Am. Chem. Soc*. **2006**, *128*, 6310.

CHAPTER I

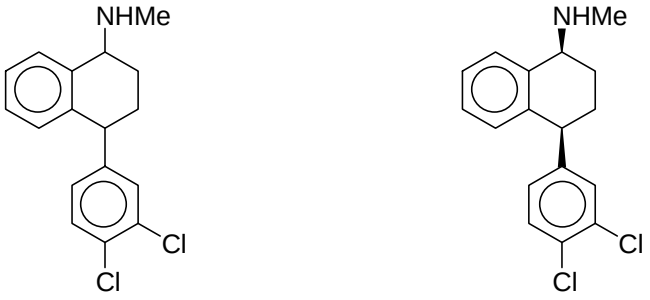
Enantioselective Synthesis of (+) Sertraline and (+)-Lentiginosine

Section I:

A Short Enantioselective Synthesis of (+)-Sertraline *via* Sharpless Asymmetric Dihydroxylation

1.1.1 Introduction

Selective serotonin reuptake inhibitors are a class of antidepressants used for the treatment of depression.[1] Drugs are designed to allow serotonin, the neurotransmitter to be utilized more effectively. Low-level serotonin is currently seen as one of numerous neurochemical symptoms of depression. These low levels of serotonin can be caused by an anxiety disorder, because serotonin is necessary to metabolize stress hormones. A depressive disorder is believed to be caused by a chemical imbalance in the brain. Messages are passed between two nerve cells *via* a small gap between the cells. The nerve cells sending the information release neurotransmitters into that gap.



(±) -1 **(S)-(+)-1a**

Fig. 1: Structures of sertraline

These neurotransmitters are recognized by receptors on the surface of the recipient cell, which relays the signal. Approximately 10% of the neurotransmitters are lost in this process, with the other 90% released from the receptors and taken up again by

monoamine transporters. Depression has been associated with a lack of stimulation of the recipient neuron at the synapse. To stimulate this cell, selective serotonin reuptake inhibitor (SSRI) block the reuptake of serotonin.

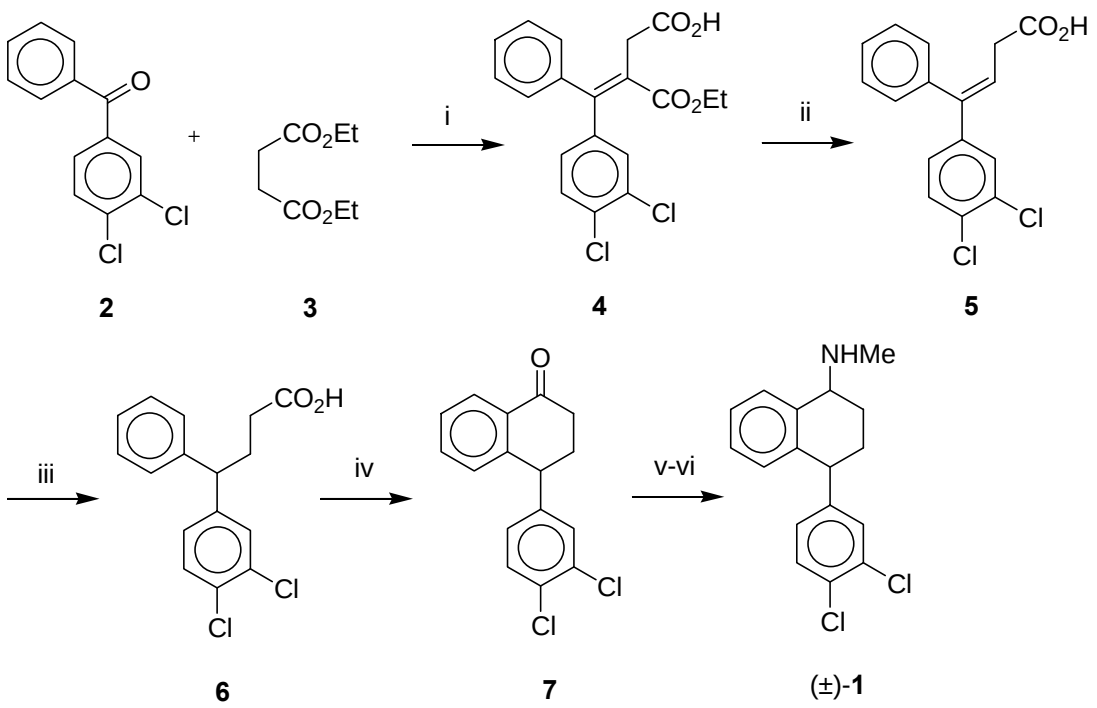
1.1.2 Pharmacology

(+)-Sertraline **1a**, a selective serotonin reuptake inhibitor (SSRI), is an important antidepressant drug discovered by Pfizer chemist Reinhard Sarges in 1970. It is one of the highest selling drugs, sold under the trade name Zoloft®.[2] Medically, sertraline (**1a**) is used for the treatment of depression and anxiety but it is also prescribed for the treatment of obsessive-compulsive disorder, post-traumatic stress disorder, premenstrual dysphoric disorder, panic disorder and bipolar disorder. Administration of sertraline comes with side effects such as gastrointestinal complaints, nervousness and agitation, sexual dysfunction as well as weight gain mainly on long-term users.

1.1.3 Review of literature

Welch's approach (1984)[3]

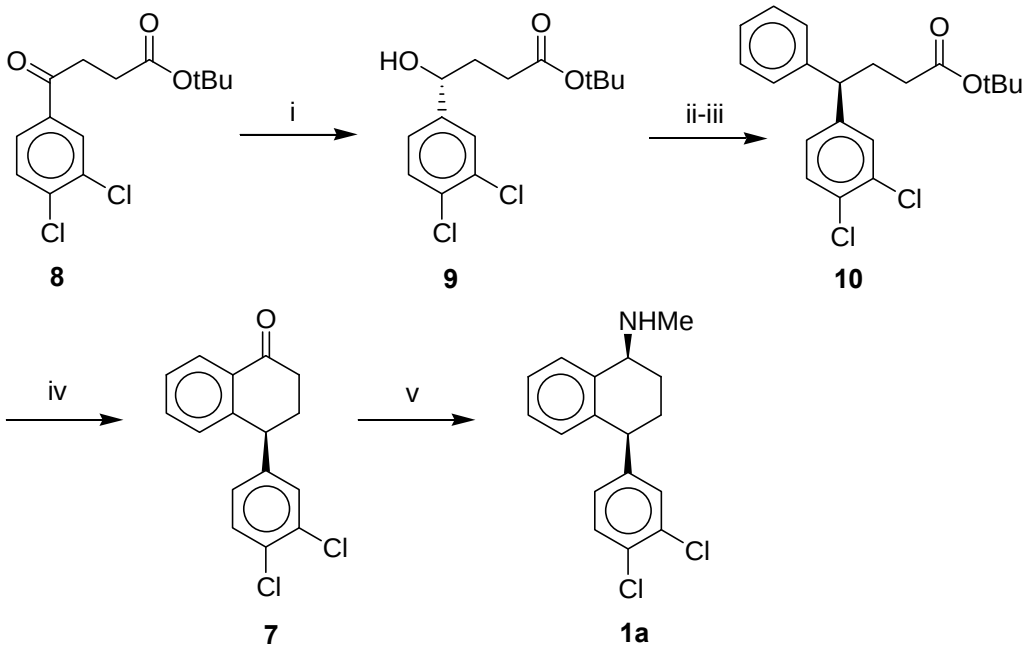
In this route, the synthesis of recemic sertraline (±)-**1** was achieved by following a simple sequence of reactions. Thus, α,β-unsaturated ester **4** was readily prepared by base-catalyzed Stobbe condensation of 3,4-dichlorobenzophenone **2** with diethylsuccinate **3**. Ester **4** was then subjected to acid-catalyzed decarboxylation, followed by catalytic hydrogenation (5% Pd/C) to give the saturated acid **6**. Acid **6** underwent cyclization under Friedel-Crafts' condition (anhyd. $AlCl_3$) to produce tetralone **7**. Finally, reductive amination of tetralone **7** with methylamine ($MeNH_2$, $TiCl_4$; $NaBH_4$, MeOH) afforded (±)-sertraline **1** (**Scheme 1**).



Scheme 1: K^{t}OBu, ^{t}BuOH, reflux, 16 h, 80%; (ii) 48% HBr in glacial AcOH, reflux, 26 h, 50%; (iii) 5% Pd/C, H_2 (1 atm), EtOAc, 24 h, 100%; (iv) $SOCl_2$, toluene, 110 ^{o}C, 1.5 h; anhyd. $AlCl_3$, CS_2, 0-25 ^{o}C, 16 h, 48%; (v) $TiCl_4$, $MeNH_2$, toluene, 25 ^{o}C, 17 h; (vi) $NaBH_4$, MeOH, 0-25 ^{o}C, 1.5 h.

Quallich's approach (1992)[4]

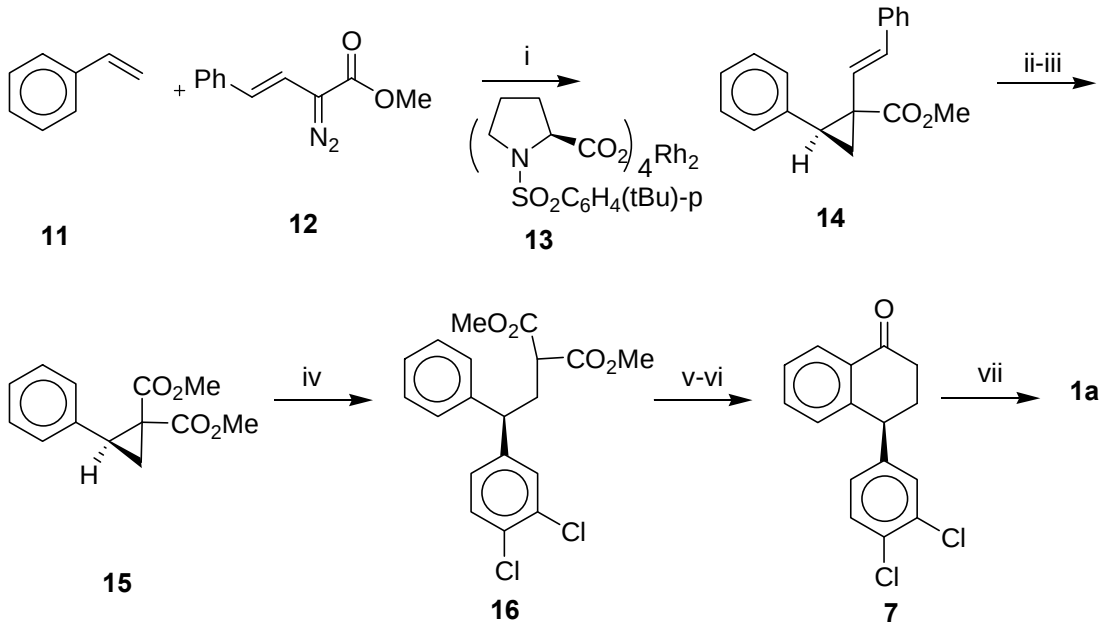
Quallich *et al*. have reported the first asymmetric synthesis of (+)-sertraline **1a**. The asymmetric reduction of γ-keto ester **8** with CBS catalyst constituting the key reaction in their approach gave the hydroxy ester **9** in quantitative yield and 88% ee. Alcohol **9** was mesylated and coupled with higher order phenyl cuprate to give butyrate **10** in 70% yield. The butyl ester **10** was directly cyclized to form tertralone **7** in the presence of triflic acid. Finally, transformation of **7** to (+)-sertraline **1a** was achieved by reductive amination (**Scheme 2**).



Scheme 2: (i) BH_3, (S)-tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrollo [1,2-C][1,3,2] oxazaborole (CBS), THF, 0 ^oC, 100%; (ii) MsCl, Et_3N, CH_2Cl_2, 0 ^oC, 20 min.; (iii) CuCN, PhLi, Et_2O, -45 ^oC, (iv) CF_3CO_2H, benzene, 70 ^oC, 2 h; (v) $TiCl_4$, $MeNH_2$.

Corey's approach (1994)[5]

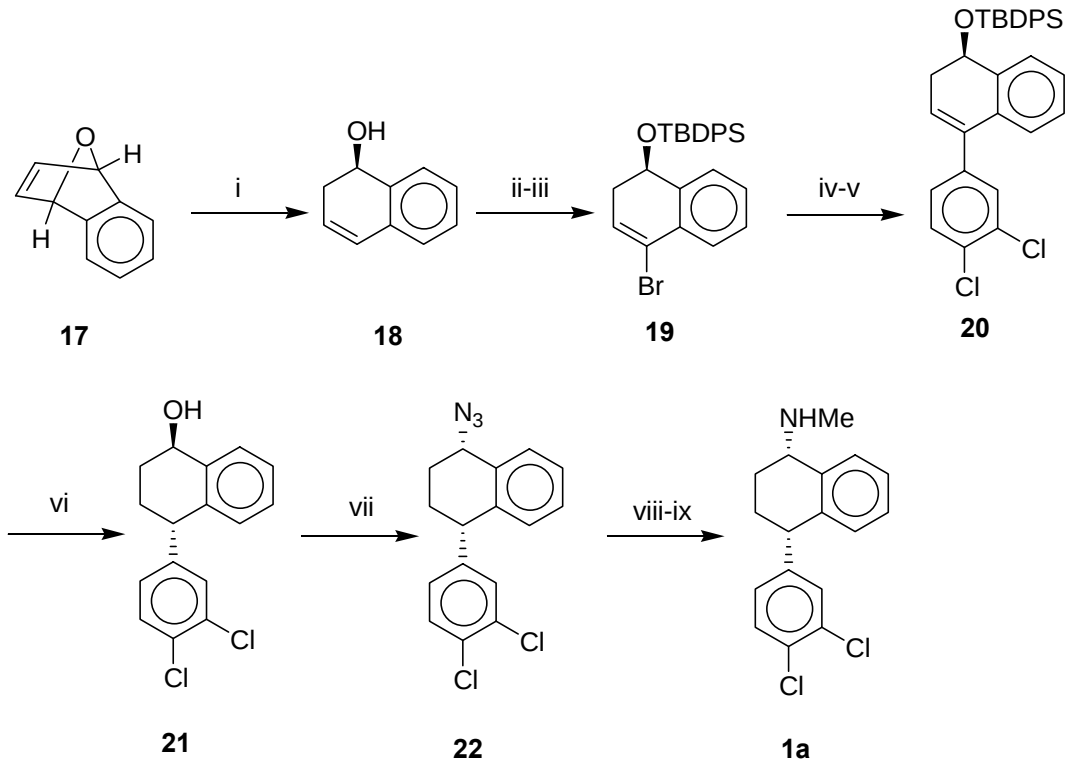
Corey *et al*. have reported the synthesis of (+)-sertraline (**1a**) by employing rhodium-catalyzed asymmetric cyclopropnation reaction. Thus, the diazo butanoate **12** was subjected to asymmetric cyclopropanation with styrene **11** using proline derived catalyst **13** to afford cyclopropane ester **14** in 79% yield and 94% ee. The oxidation of styrenic C=C of **14** with $KMnO_4/NaIO_4$ followed by esterification afforded malonyl ester **15**. Treatment of **15** with cuprate reagent Ar_2CuLi_2CN (prepared from 3,4-dichlorophenyl iodide) led to ring opening of cyclopropane ring to give diester **16** in 82% yield. Hydrolysis of diester **16** with 6N HCl followed by cyclization with chlorosulfonic acid gave tetralone **7**; reductive amination of which resulted in the formation of (+)-sertraline (**1a**) (**Scheme 3**).



Scheme 3: (i) 10 mol% of catalyst **13**, pentane, 25 ^{o}C, 12 h, 79%; (ii) $KMnO_4$, $NaIO_4$, K_2CO_3, ^{t}BuOH, 0.5 h, 25 ^{o}C, 83%; (iii) K_2CO_3, Me_2SO_4, acetone, 3 h, 97%; (iv) BuLi, 3,4-dichlorophenyl iodide, CuCN, Et_2O, 15 min, 82%; (v) 6N HCl, reflux, 20 h then 1N NaOH; (vi) $ClSO_3H$, CH_2Cl_2, 30 min, 84%; (vii) reductive amination using $MeNH_2$.

Lautan's approach (1997)[6]

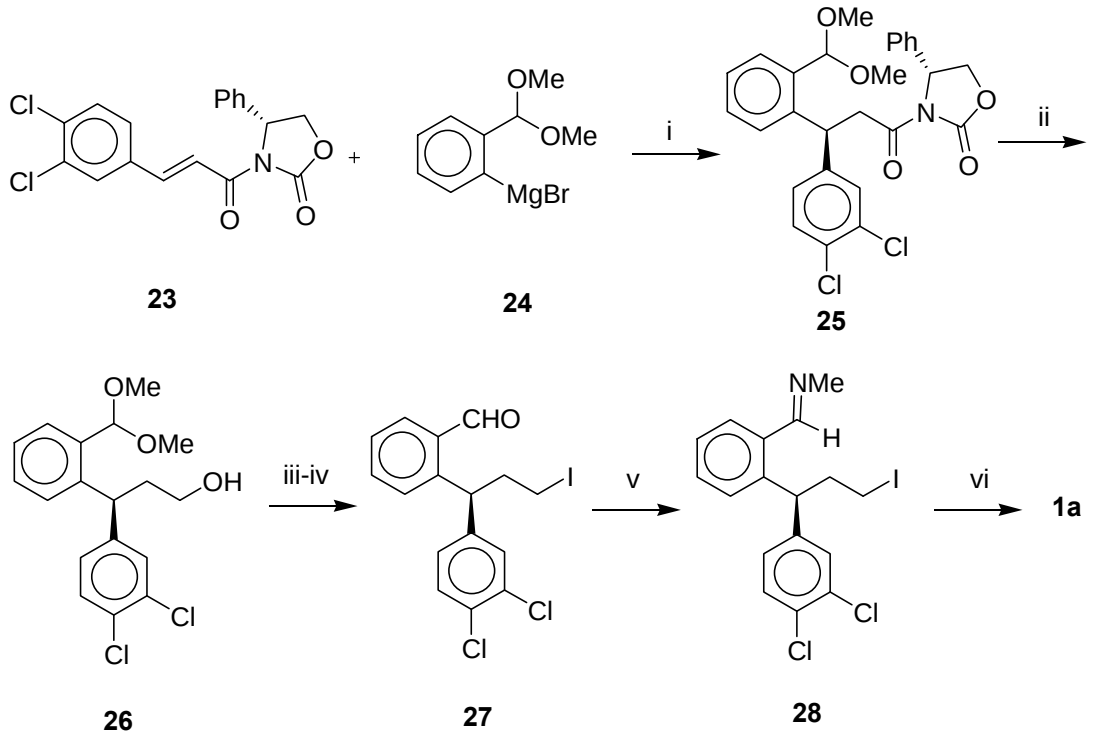
Lautan *et al*. have reported the synthesis of (+)-setraline (**1a**) *via* nickel –catalyzed regio- and enantioselective ring opening of oxabicyclic alkene **17** in the presence of (R)-BINAP to give chiral alcohol **18** in 88% yield. The protection of alcohol **18** as its silyl ether followed by its Pd-catalyzed Stille coupling with $(3,4\text{-}Cl_2)C_6H_3SnMe_3$ gave **20** in 55% yield. Desilylation of **20** (Bu_4NF in THF) followed by reduction of double bond using Crabtree's catalyst {$[Ir(COD)pyPCy_3]PF_6$} produced **21** in 88% yield and 28:1 diastereoselectivity. The direct nucleophilic displacement of alcohol **21** with diphosphoryl azide (dppa) gave azide **22** in 88% yield. The catalytic reduction of azide **22** followed by N-carbethoxylation and its reduction with $LiAl(OMe)_3$ afforded sertraline (**1a**) in 86% yield (**Scheme 4**).



Scheme 4: (i) $Ni(COD)_2$ (14 mol%), (R)-BINAP, 1.1 eq. DIBAL-H, toluene, 25 ^oC, 88%; (ii) TBDPSCl, imid., DMAP, CH_2Cl_2, 86%; (iii) Br_2, Et_3N, CH_2Cl_2, 0 ^oC; then DBU, toluene, 83% (iv) $(CH_3CN)_2PdCl_2$ (5%), $AsPh_3$ (20%), $(3,4\text{-}Cl_2)C_6H_3SnMe_3$, NMP, 80 ^oC, 1.5 h, 55%; (v) TBAF, THF, 0 ^oC; (vi) $[Ir(COD)pyPCy_3]PF_6$ (10 mol%), H_2 (1000 psi), CH_2Cl_2, 88% (vii) dppa, DBU, THF, 88%, 98:2; (viii) (a) 10% Pd/C, H_2, EtOH; (b) K_2CO_3, $ClCO_2Et$, CH_3CN, (ix) $LiAlH(OMe)_3$, THF, reflux, 40 h, 86%.

Chen's approach (1999)[7]

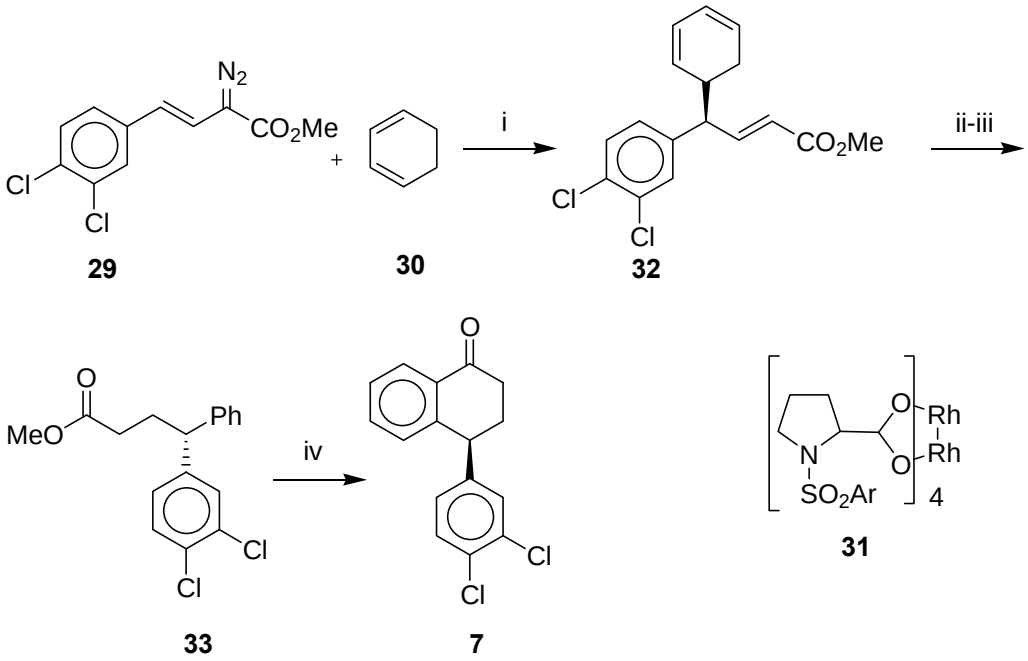
Chen *et al*. have achieved the synthesis of (+)-sertraline (**1a**) by the addition of Grignard reagent **24** onto α,β-unsaturated chiral carbamate **23** to prvide **25** in 90% yield. Reductive removal of chiral auxiliary in **25** using $NaBH_4$ in THF-H_2O gave alcohol **26**. Alcohol **26** was transformed to iodoaldehyde **27** in 85% yield. Iodoaldehyde **27** on treatment with methylamine gave the corresponding imine **28** which was subjected to BuLi-mediated intramolecular ring closing so that a single diastereomer of (+)-sertraline (**1a**) was obtained (**Scheme 5**).



Scheme 5: (i) $CuBrSMe_2$ (20 mol%), THF, -30 ^oC, 90%; (ii) $NaBH_4$, THF-H_2O; (iii) PPh_3, I_2, imid., CH_2Cl_2; (iv) 2N HCl, 85%; (v) 2.0 M $MeNH_2$ in THF, (vi) ^{t}BuLi, THF, toluene, -78 ^oC, 69%.

Davies's approach (1999)[8]

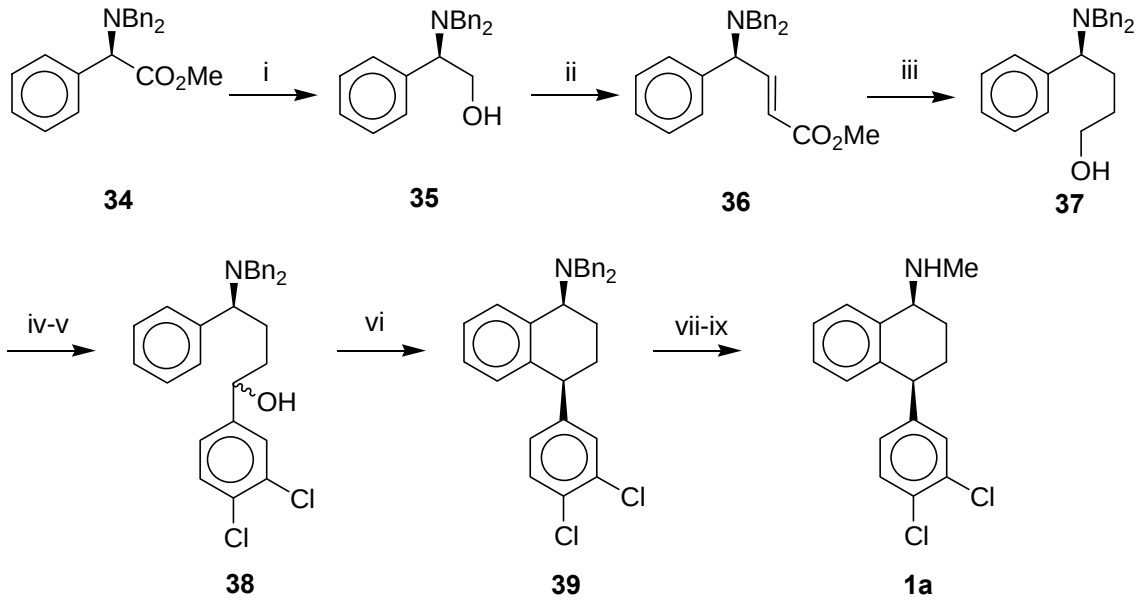
Davies *et al*. have reported a formal synthesis of (+)-sertraline (**1a**) using rhodium-catalyzed C-H insertion as the key step. The diazo ester **29** and cyclohexadiene **30** were exposed to intramolecular C-H insertion using Rh-catalyst **31** that resulted in the formation of α,β-unsaturated ester **32**. Aromatization of **32** using DDQ followed by catalytic hydrogenation afforded saturated ester **33** in 52% yield. Ester **33** was hydrolyzed and cyclized intramolecularly to produce tetralone **7** in 79% yield and 96% ee (**Scheme 6**).



Scheme 6: (i) Rh_2(S-DOSP)$_4$, hexane, 23 ^oC, 59%; (ii) DDQ, toluene; (iii) Pd/C, H_2 (20 psi), EtOH, 52%; (iv) 6N HCl, then $ClSO_3H$, 25 ^oC, 2 h, 79%.

Chandrashekar's approach (2000)[9]

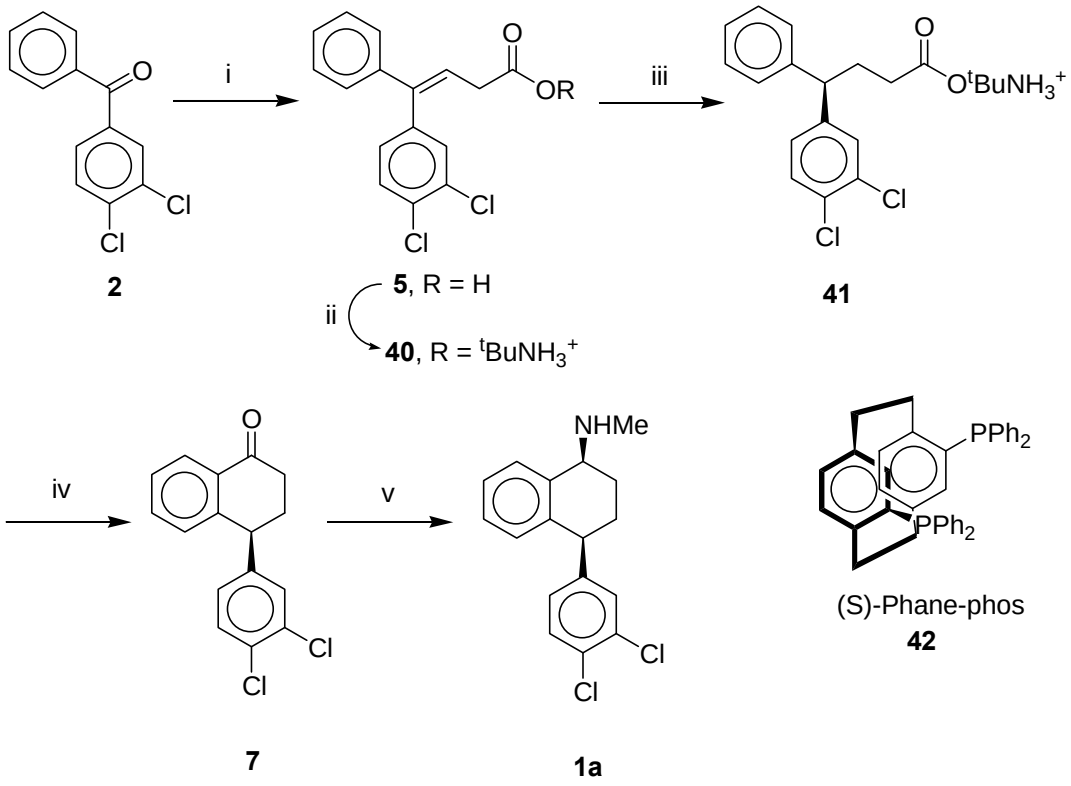
Chandrashekar *et al*. have achieved the synthesis of (+)-sertraline (**1a**) by employing chiral pool strategy. Thus, reduction of ester **34** with $LiAlH_4$ gave alcohol **35**, which was oxidized to aldehyde under Swern's conditions. Aldehyde on subsequent treatment with Wittig reagent namely PPh_3=$CHCO_2Et$ to afforded α,β-unsaturated ester **36** in 72% yield. The complete reduction of α,β-unsaturated ester **36** gave the saturated alcohol **37**. Oxidation of alcohol **37** with Corey's reagent (PCC) followed by its treatment with Grignard reagent, i.e 3,4-dichlorophenylmagnesium bromide, gave the secondary alcohol **38** in 83% yield. Alcohol **38** was cyclized intramolecularly with anhyd. $AlCl_3$, which generated **39** with a second chiral centre of separable diastereomers. The conversion of *cis* isomer **39** to (+)-sertraline (**1a**) was achieved *via* a known series of reactions namely debenzylation, Boc-protection, N-methylation and Boc-deprotection (**Scheme 7**).



Scheme 7: (i) $LiAlH_4$, THF, 0 ^oC, 12 h, 80%; (ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^oC; then $Ph_3P{=}CHCO_2Et$, benzene, 25 ^oC, 15 h, 72%; (iii) (a) Mg, MeOH, 4 h; (b) $LiAlH_4$, THF, 25 ^oC, 12 h, 76%; (iv) PCC, CH_2Cl_2, 5 h; (v) 3,4-dichlorophenylmagnesium bromide, THF, 5 h, 83%; (vi) $AlCl_3$, CH_2Cl_2, 1 h, 78% (vii) $Pd(OH)_2$, MeOH, H_2, 3 h; then $(Boc)_2O$, 3 h; (viii) NaH, MeI, THF, 6 h, 84% ; (ix) CF_3CO_2H, CH_2Cl_2, 25 ^oC, 85%.

Boultan's approach (2003)[10]

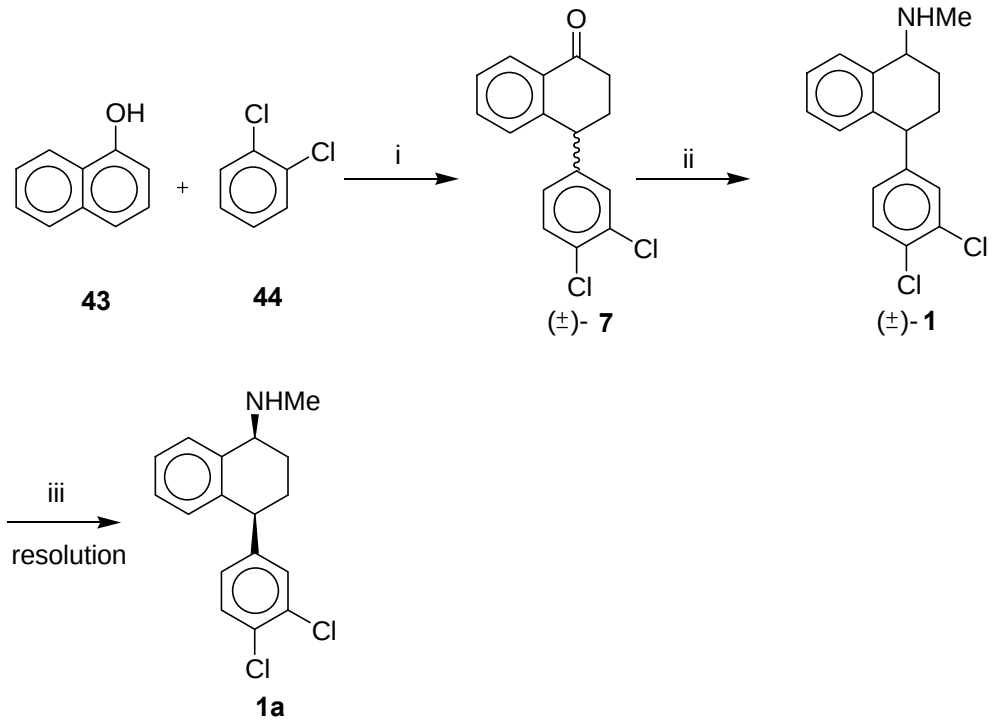
Boultan *et al*. have employed asymmetric hydrogenation as the key reaction. Diarylbutanoate salt **40** was prepared from 3,4-dichlorobenzophenone **2** by Wittig olefination. The compound **40** was subjected to asymmetric catalytic hydrogenation using rhodium-phane-phos catalyst **42** and H_2 (120 psi) to afford enantio-enriched saturated ester **41** in quantitative yield and 90% ee. The synthesis of (+)-sertraline (**1a**) was completed by following the three-step reaction sequences of hydrolysis, cyclization and reductive amination (**Scheme 8**).



Scheme 8: (i) KOBu^t, diethyl succinate, ^{t}BuOH; then 48% HBr, AcOH, 32%; (ii) ^{t}BuNH$_2$, EtOAc, 99%; (iii) [RhCOD]BF$_4$, ligand **42**, H_2 (120 psi), MeOH; (iv) 2M H_2SO_4, EtOAc; then $ClSO_3H$, CH_2Cl_2, 91%; (v) $MeNH_2$, H_2, MeOH.

Colberg's approach (2004)[11]

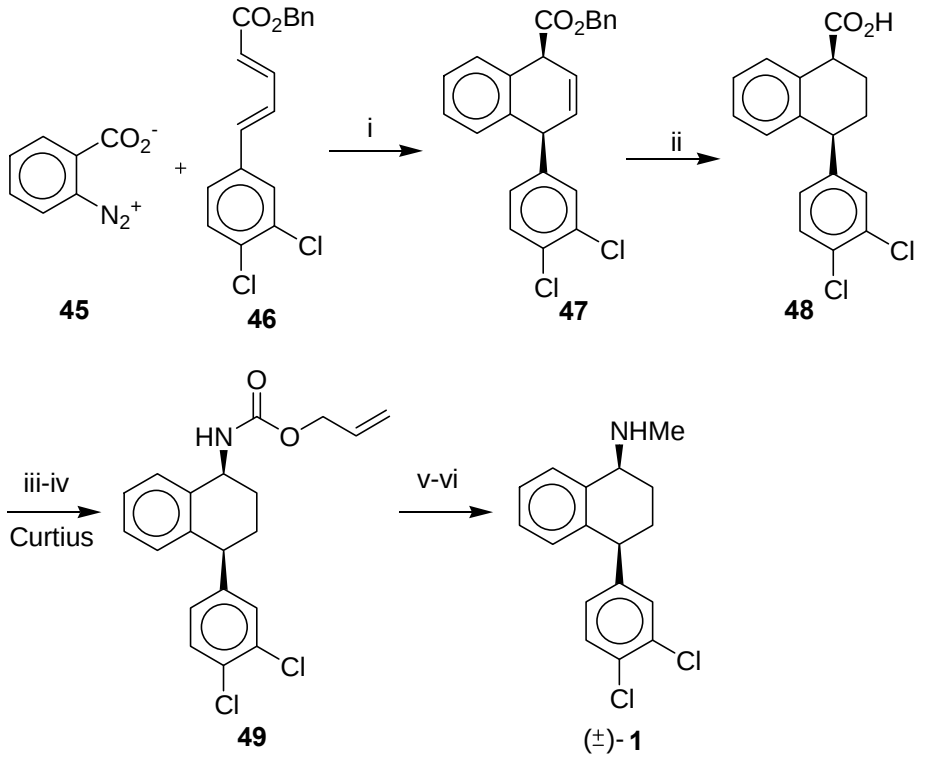
Colberg *et al*. have employed kinetic resolution of recemic (±)-sertraline (**1**) as the key step. α-Napthol **43** and 1,2-dichlorobenzene **44** were reacted in the presence of anhyd. $AlCl_3$ under Friedel-Crafts alkylation conditions to give recemic (±)-tetralone **7** in 95% yield. Treatment of (±)-tetralone **7** with excess of methyl amine in ethanol furnished the corresponding imine, which was then subjected to reductive amination [Pd/$CaCO_3$, H_2 (50 psi)] to yield (±)-sertraline, **1** (*cis:trans* 20:1) with *cis* as the major isomer. The recemic sertraline, **1** was then treated with D-mandelic acid so that the *cis* isomer is resolved selectively in solid form (**Scheme 9**).



Scheme 9: (i) $AlCl_3$; (ii) $MeNH_2$, EtOH, 95%; then $Pd/CaCO_3$ (1% w/w), H_2 (50 psi), 40%; (iii) (D)-mandelic acid, EtOH, reflux then -5 ^oC, 36%.

Lautens's approach (2005)[12]

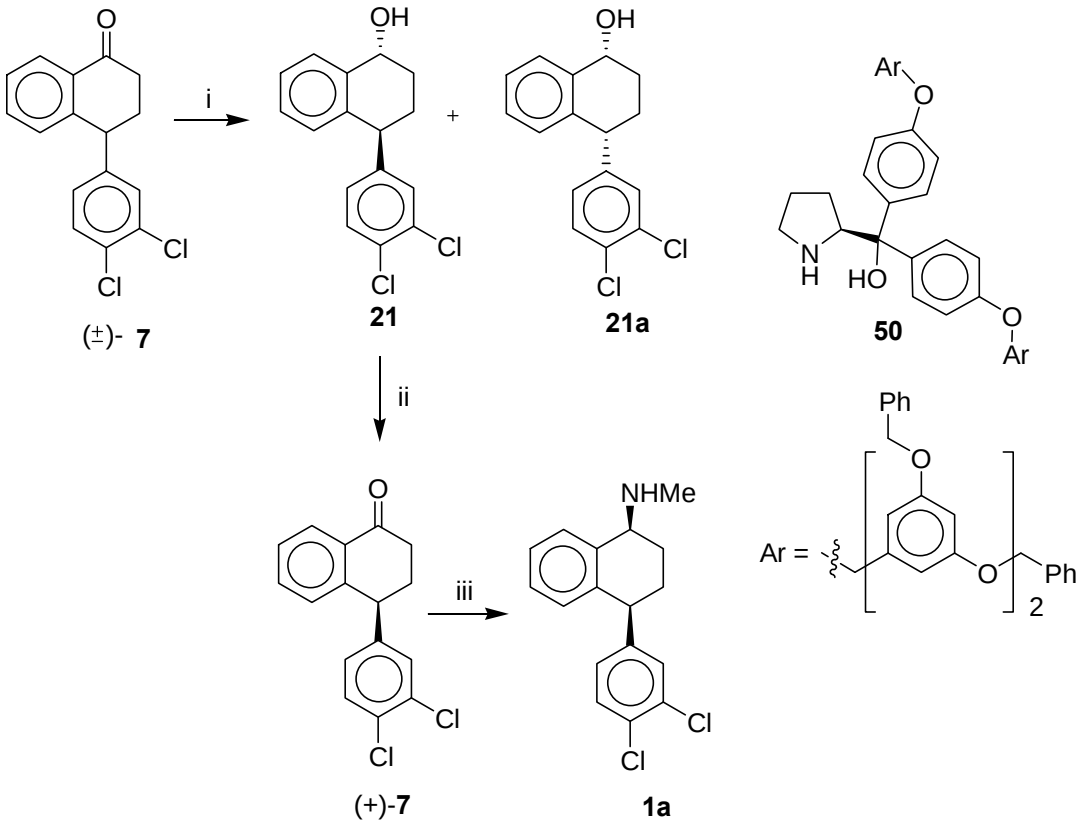
Lautens *et al*. have reported the synthesis of (±)-sertraline (**1)** by employing Diels-Alder reaction between benzenediazonium-2-carboxylate **45**, a benzyne-equivalent and dienyl ester **46** in 1,2-dichloroethane as solvent at 60 ^oC, to give the cycloadduct **47** in 78% yield. Cycloadduct **47** was hydrogenated and the benzyl group deprotected in one-pot using 10% Pd/C and H_2 (4 atm) to give acid **48** in 94% yield. The acid **48** was then subjected to Curtius rearrangement *via* the initial formation of acylazide ($ClCO_2Et$, then NaN_3) followed by the addition of allyl alcohol at 90 ^oC, which afforded allyl carbamate **49** in 65% yield. N-methylation and deprotection of allyl group in **49** resulted in the formation of (±)-sertraline **1** (**Scheme 10**).



Scheme 10: (i) 1,2-dichloroethane, 60 °C, 78%; (ii) 10% Pd/C, H_2 (4 atm), MeOH, 94%; (iii) $ClCO_2Et$, NaN_3, Et_3N, toluene, 25 °C; (iv) allyl alcohol (10 equiv.), toluene, 90 °C, 65%; (v) NaH, MeI, THF, 91%; (vi) $Pd(OAc)_2$, $HNEt_2$, H_2O:CH_3CN, 75%.

Zhao's approach (2006)[13]

Recemic (±)-tetralone **7** was subjected to reduction using L-proline derived catalyst **50** and $Me_2S{\cdot}BH_3$ to give diasteromers **21** and **21a** which were readily separated (in 94% yield and 97% ee). The oxidation of *trans* isomer **21** with PCC give the optically active (+)-tetralone **7**, which was transformed to (+)-sertraline **1a** *via* reductive amination ($MeNH_2$, $TiCl_4$, Raney-Ni) (**Scheme 11**).



Scheme 11: (i) $Me_2S{\cdot}BH_3$, **50** (5 mol%) , THF, reflux, 42%; (ii) PCC, CH_2Cl_2, 25 ^oC; (iii) $TiCl_4$, $MeNH_2$, Et_2O, -78 ^oC; then Raney Ni, H_2, MeOH.

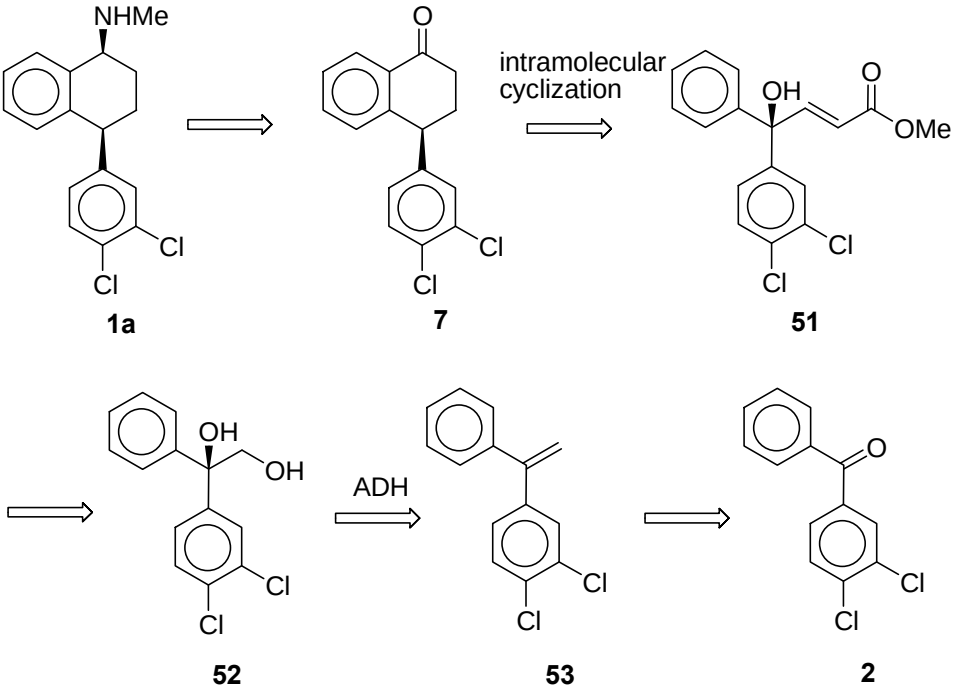
1.1.4 Present Work

1.1.4.1 Objective

As can be seen from the above synthetic studies, the literature methods in the synthesis of (+)-sertraline (**1a**) employ either chiral starting materials or expensive reagents involving longer reaction sequences, often resulting in poor product selectivities. The enantioselective synthesis of (+)-sertraline (**1a**) is thus undertaken to overcome some of the disadvantages associated with the reported methods.

The retrosynthetic analysis of (+)-sertraline (**1a**) is shown in **Scheme 12**. We envisaged that tetralone **7** could serve as a valuable intermediate for the asymmetric synthesis of (+)-sertraline **(1a)**. The tetralone moiety **7** could be constructed by intramolecular

cyclization of unsaturated hydroxy ester **51** after saturation of the C=C bond. The α,β-unsaturated ester **51** can be thought to be obtained from diol **52**, which in turn can be accessible from asymmetric dihydroxylation of styrene **53**. Olefin **53** can be prepared from the corresponding aromatic ketone **2** *via* Wittig olefination. Since the synthetic strategy involves asymmetric dihydroxylation (ADH) as the key chiral inducing reaction, a brief account of ADH is given below.



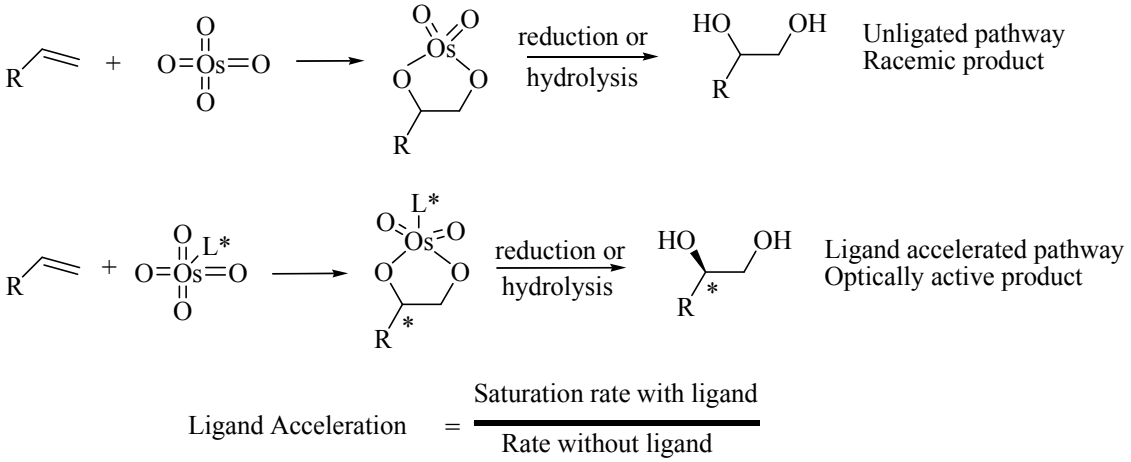
Scheme 12: Retrosynthetic analysis of (+)-sertraline

1.1.4.2 Asymmetric Dihydroxylation

In recent years much attention has been focused on the catalytic asymmetric synthesis. There are several methods to obtain enantiomerically pure compounds that include classical optical resolution, chromatographic separation of enantiomers, enzymatic resolution and asymmetric synthesis.[14] 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).[15] Among all these reactions, Sharpless Catalytic Asymmetric Dihydroxylation (ADH) is one of the most important practical and widely used reactions in organic synthesis. It has become the most general method for the preparation of optically active vicinal *cis*-diols from activated as well as inactivated olefins.[16]

In 1936, Criegee *et al.*[17] have found that addition of pyridine or any other tertiary amine to osmylation of olefins accelerates the rate of reaction considerably. A major breakthrough has occurred in the field of asymmetric oxidation when Sharpless[16b] *et al.*



Scheme 13: Simplified mechanism of achiral and chiral dihydroxylation

demonstrated that asymmetric induction could be achieved when chiral amines were added to OsO_4-mediated asymmetric oxidation of olefins. Among the various ligands screened best results were obtained with ligands which were representatives of the cinchona alkaloid family, dihydroquinidine (DHQD) and dihydroquinine (DHQ).[18] A number of recent methods employ chiral diamine ligands for the asymmetric osmylation

of olefins. The simplified mechanism of achiral and chiral dihydroxylation is given in **Scheme 13.**

Mechanism of OsO_4-catalyzed dihydroxylation of olefin

In order to develop a catalytic method, several co-oxidants such as sodium or potassium chlorate,[19] hydrogen peroxide,[20] *tert*-butyl hydroperoxide[21] and *N*-methylmorpholine *N*-oxide (NMO) [22] were introduced .

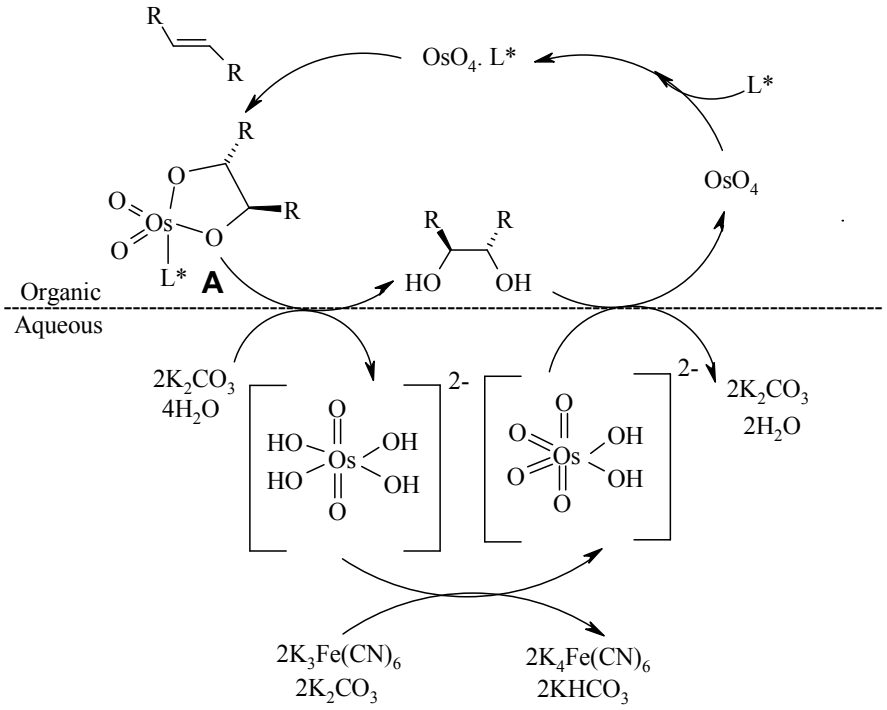
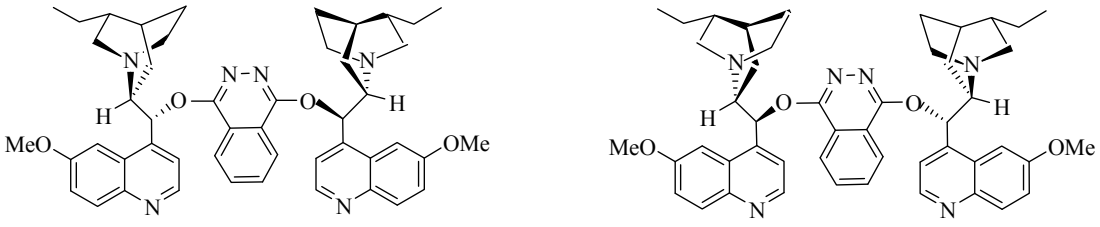


Fig. 2: Catalytic cycle for ADH using $K_3[Fe(CN)_6]$ as co-oxidant.

The idea to use these co-oxidants was to minimize the amount of toxic and costly osmium so as to make the process more economical. Sharpless *et al* [23] have established that the most practical and suitable catalytic method is with NMO as co-oxidant but the ee's of the diol was less than those produced by the stoichiometric reactions (primary catalytic cycle) The reason was thought to be the involvement of second catalytic cycle (secondary catalytic cycle), which results in low or no ee at all. To improve the %ee of

the chiral diol, the second catalytic cycle of AD should be avoided and this was achieved by employing the $K_3[Fe(CN)_6]$ as reoxidant and using biphasic conditions **(Fig. 2)**.[24] These conditions helped in protecting the organic osmate-(VI) monoglycolate ester (species **A**, **Fig. 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. Subsequently, osmium-(VI) gets reoxidized and recycled into the catalytic cycle. Further improvement in the ADH was realized by the addition of methyl sulfonamide ($MeSO_2NH_2$) to the reaction mixture. It also helps to accelerate the hydrolysis of the species **A**, thus facilitating the dihydroxylation smoothly. Addition of methyl sulfonamide also allowed carrying out the reactions of 1, 2-ditri- and tetra- substituted olefins at 0 ^oC, which improved the selectivity as well as %ee. In order to develop the asymmetric version of the Os-catalyzed ADH reaction, Sharpless and coworkers have screened various chiral ligands and found out that the derivatives of cinchona alkaloids gave excellent results. Among all the 250 derivatives of cinchona alkaloid ligands screened, the *bis*-DHQ (**54**) or DHQD (**55**) ethers of phthalazine-1, 4-diol have proven to be the best for obtaining high enantioselectivities of the chiral diols (Fig. 3).[25]



$(DHQ)_2$-PHAL (**54**) $(DHQD)_2$-PHAL (**55**)

Fig. 3: Ligands for asymmetric dihydroxylation reaction

The recent studies have demonstrated the importance of enzyme-like binding pocket of the dimeric cinchona alkaloid for high enantioselectivity of the chiral diols.[26] Sharpless *et*

al have shown that the facial selectivity for both ligands **54** and **55** is different, based on their ability to induce the ee into the diols.

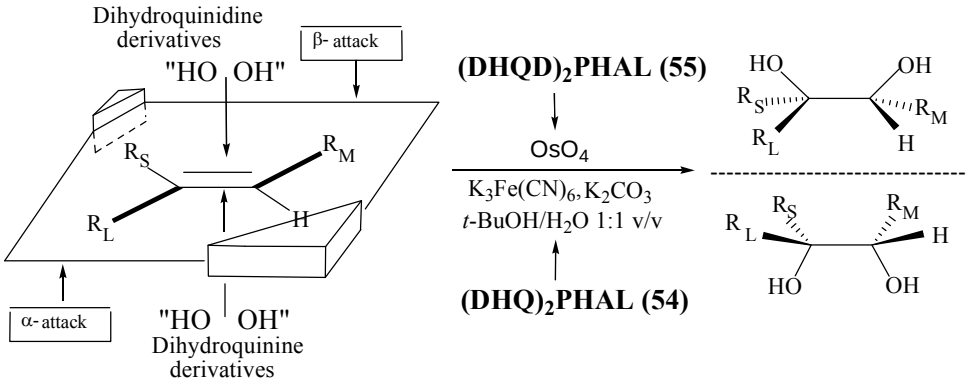
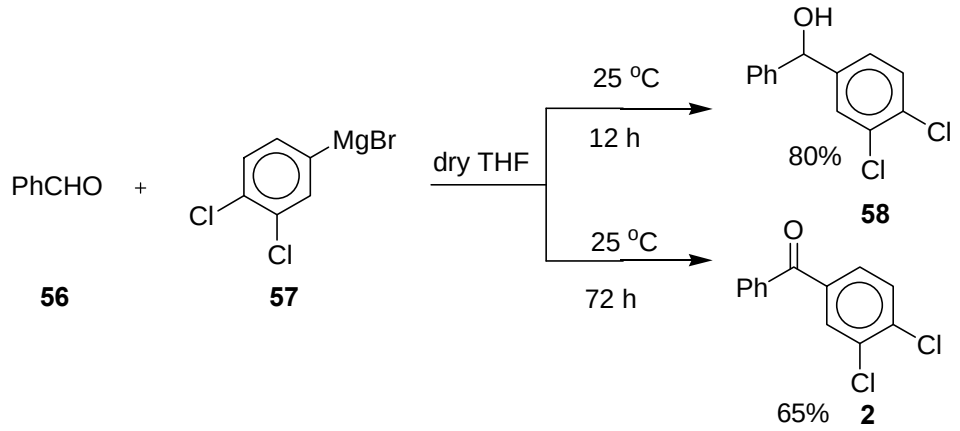


Fig. 4: Enantioselectivity in ADH

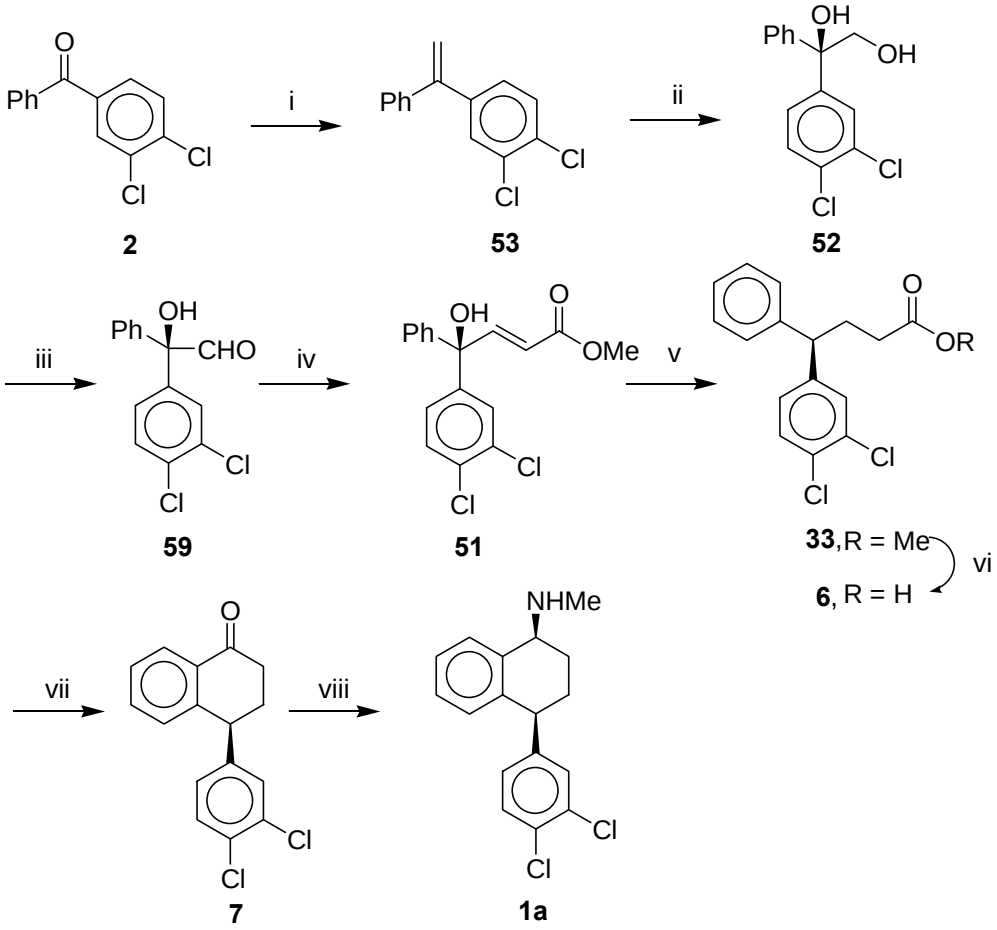
This observation has led to the development of mnemonic model **(Fig. 4)** in which olefin with the constraints will be attacked either from the top (i.e. β) face in the presence of dihydroquinidine (DHQD) derivatives or from the bottom (i.e. α) face in the presence of dihydroquinine (DHQ) derived ligand.

1.1.5 Results and Discussion

Our synthesis of (+)-sertraline (**1a**) commences from benzaldehyde. The addition of arylmagnesium bromide **57**, prepared from the corresponding 3,4-dichlorobromobenzene, onto benzaldehyde **56** furnished the corresponding benzylic alcohol **58** in 80% yield. The oxidation of alcohol **58** with pyridinium chlorochromate (PCC) gave the corresponding benzophenone **2** in 82% yield. Surprisingly, we have observed here an interesting result in which both the Grignard addition onto aldehyde **56** and oxidation of the corresponding alcohol took place simultaneously in a one-pot reaction when the Grignard reaction was conducted for 72 h (3 days) at 25 ^{o}C (**Scheme 14**). This constitutes a direct single-step oxidation to obtain benzophenone **2** obtained in 65% yield.



Scheme 14: Unusual oxidation during Grignard reaction



Scheme 15: Reaction conditions: (i) $Ph_3P^+CH_3I^-$, BuLi, THF, -78 to 0 °C, 5 h, 87%; (ii) $K_2OsO_4 \cdot 2H_2O$, $(DHQD)_2$-AQN, K_2CO_3, $K_3Fe(CN)_6$, $^tBuOH:H_2O$ (1:1), 24 h, 78%; (iii) IBX, dry DMSO, 25 °C, 1 h, 85%; (iv) $Ph_3P{=}CHCO_2Et$, dry benzene, 25 °C, 12 h, 90%; (v) 10% Pd/C, H_2 (20 psi), MeOH, 25 °C, 62%; (vi) 6 N HCl, reflux, 23 h; (vii) $ClSO_3H$, CH_2Cl_2, 25 °C, 2 h, 68%; (viii) $TiCl_4$, $MeNH_2$, Raney-Ni, H_2, (20 psi), 35%.

The Wittig olefination of benzophenone **2** (n-BuLi, $Ph_3P^+CH_3I^-$, THF, -78-0 ^oC) gave olefin **53** in 87% yield (**Scheme 15**). Its ^1H NMR spectrum showed a characteristic olefinic proton signal at δ 5.46 (dd). Its ^{13}C NMR spectrum showed a typical carbon signal at δ 115.4 due to benzylic quaternary carbon (**Fig**. **5**).

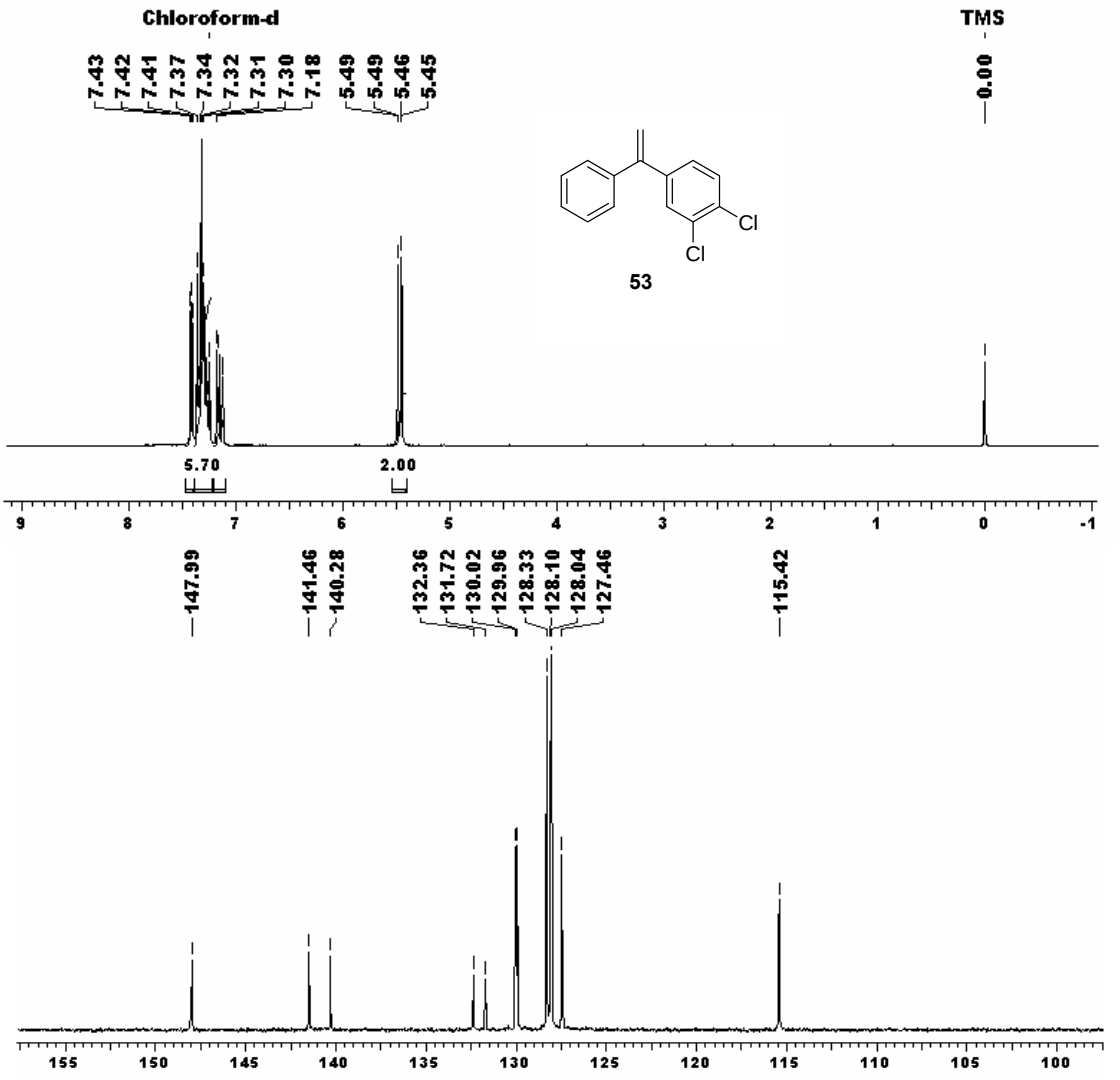


Fig. 5: ^1H and ^{13}C NMR spectra of olefin **53**

It has been well-established that ADH of 1,1-diaryl olefin using anthraquinone (AQN)- and diphenylpyrimidine (PRY)- based ligands produces diols with >90% ee as compared to phthalazine (PHAL)-based ligands. Thus, ADH of olefin **53** was carried out using

potassium osmate [$K_2OsO_2(OH)_4$] as the catalyst and $(DHQD)_2$-AQN as the chiral ligand, which resulted in the formation of the corresponding diol **52** in 78% yield. Its ^1H and ^{13}C NMR spectra confirmed the disappearance of olefinic protons and carbons respectively. The appearance of a multiplet at δ 3.99-4.09 in its ^1H NMR spectrum and a typical carbon signal at δ 77.7 in its ^{13}C NMR spectrum are indicative of formation of diol function (**Fig. 6**).

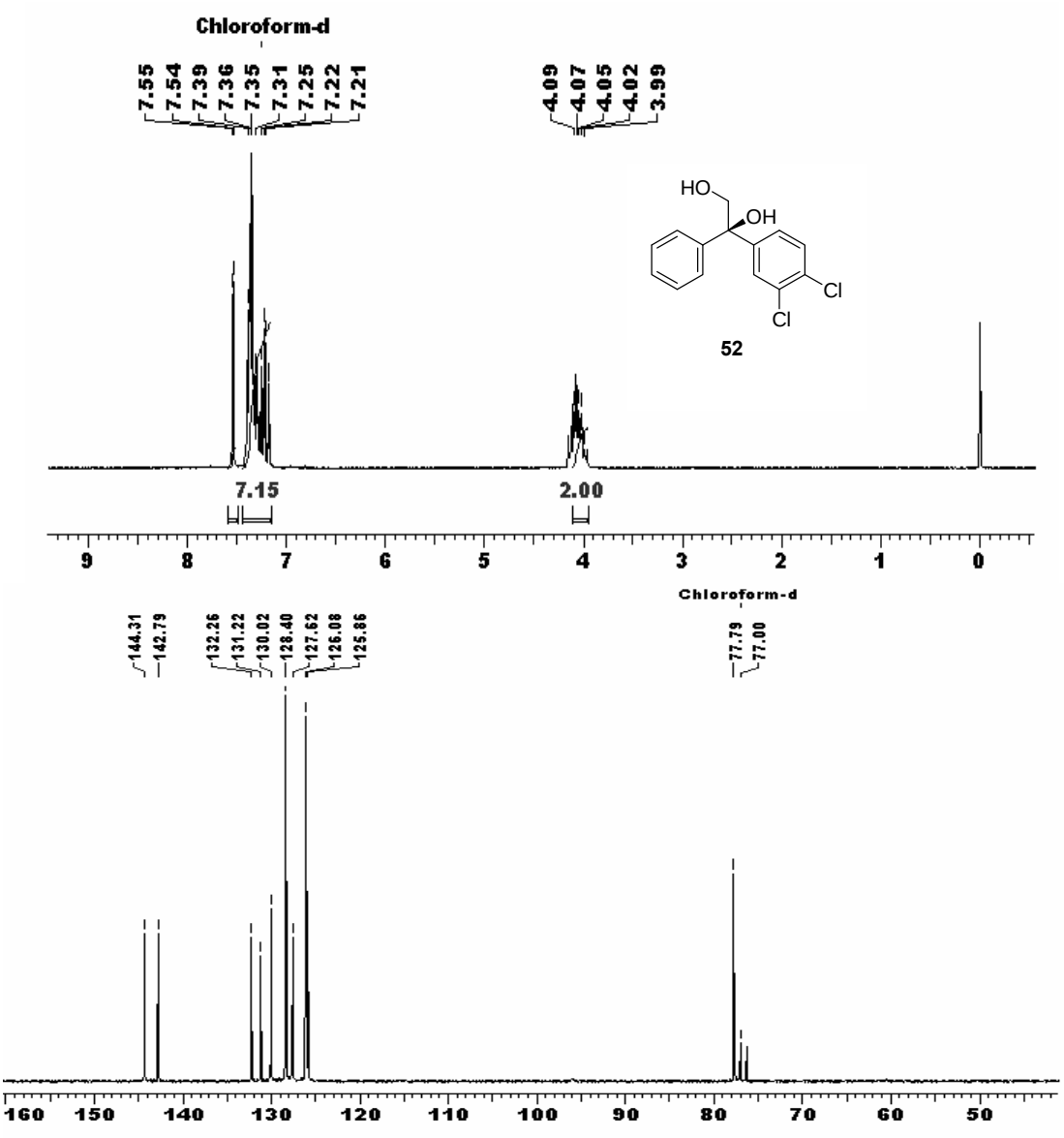


Fig. 6: ^1H and ^{13}C NMR spectra of diol **52**

The IBX oxidation (IBX, DMSO, 25 ^{o}C) of the primary hydroxyl group in diol **52** gave the corresponding aldehyde **59** in 85% yield. Its IR spectrum exhibited a broad band at 3453 cm^{-1} indicating the presence of hydroxyl group whereas the aldehydic carbonyl displayed a strong band at 1725 cm^{-1}. Its ^{1}H NMR spectrum displayed a characteristic singlet at δ 9.92 for aldehydic proton (-C**H**O) while the aromatic protons have displayed signals in the region δ 7.24-7.52 as multiplets. Its ^{13}C NMR spectrum exhibited a typical carbon signal at δ 196.8 corresponding to the carbonyl carbon **(Fig. 7)**.

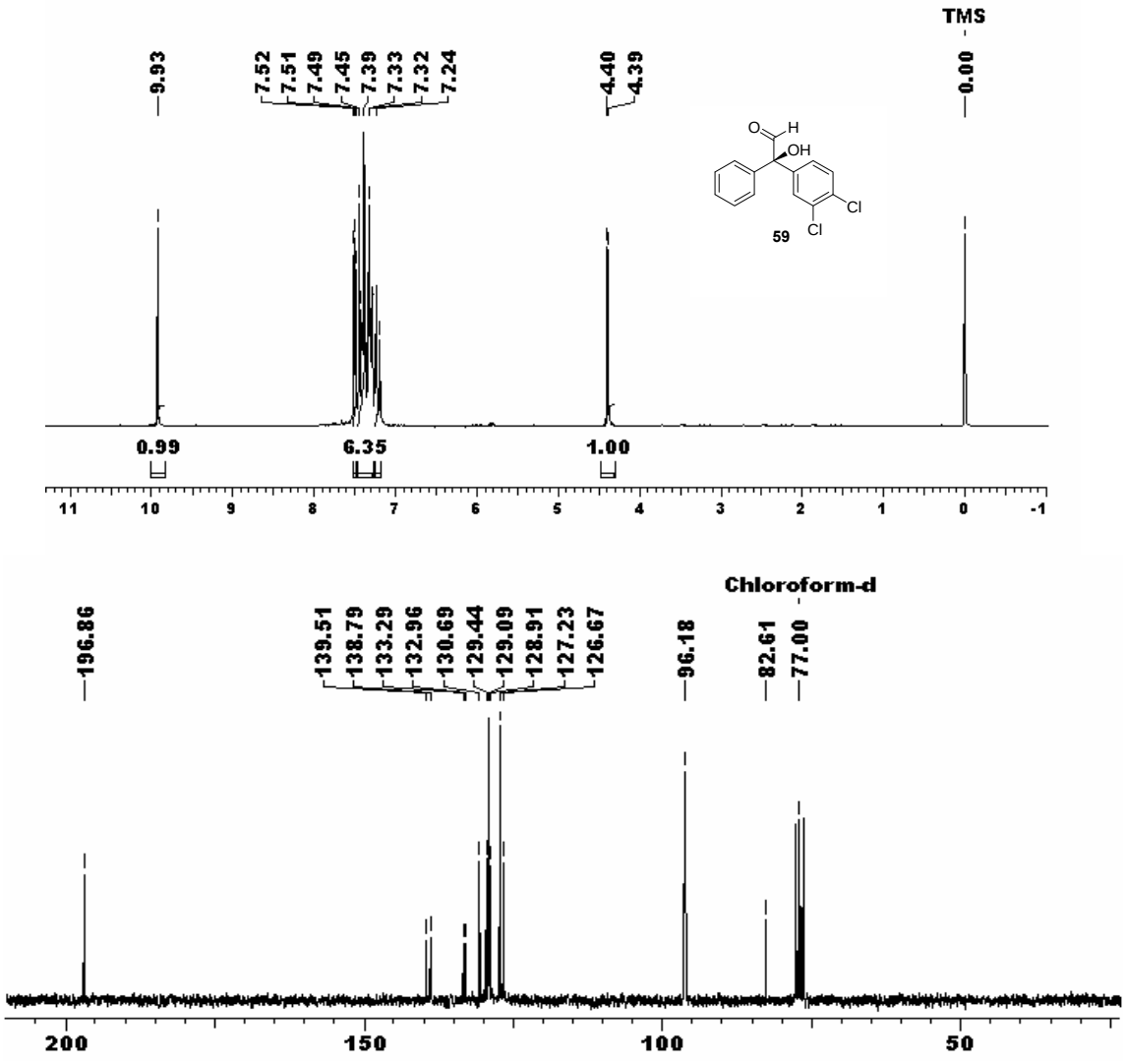


Fig. 7: ^{1}H and ^{13}C NMR spectra of aldehyde **59**

The Wittig olefination ($Ph_3P=CHCO_2Me$, benzene, 25 ^oC) of aldehyde **59** gave the α, β-unsaturated ester **51** in 87% yield. Its ^1H NMR spectrum showed a strong singlet at δ 3.74 due to methoxyl proton a doublet of doublet at δ 6.17 and 7.49 for olefin protons (-C**H**=C**H**-CO_2Me) respectively. Its ^{13}C NMR spectrum displayed typical signals at δ 77.8 119.5 and 143.5 due to quaternary benzylic carbon and α, β-unsaturated olefinic carbons (-**C**H=**C**H-CO_2Me) respectively (**Fig. 8**).

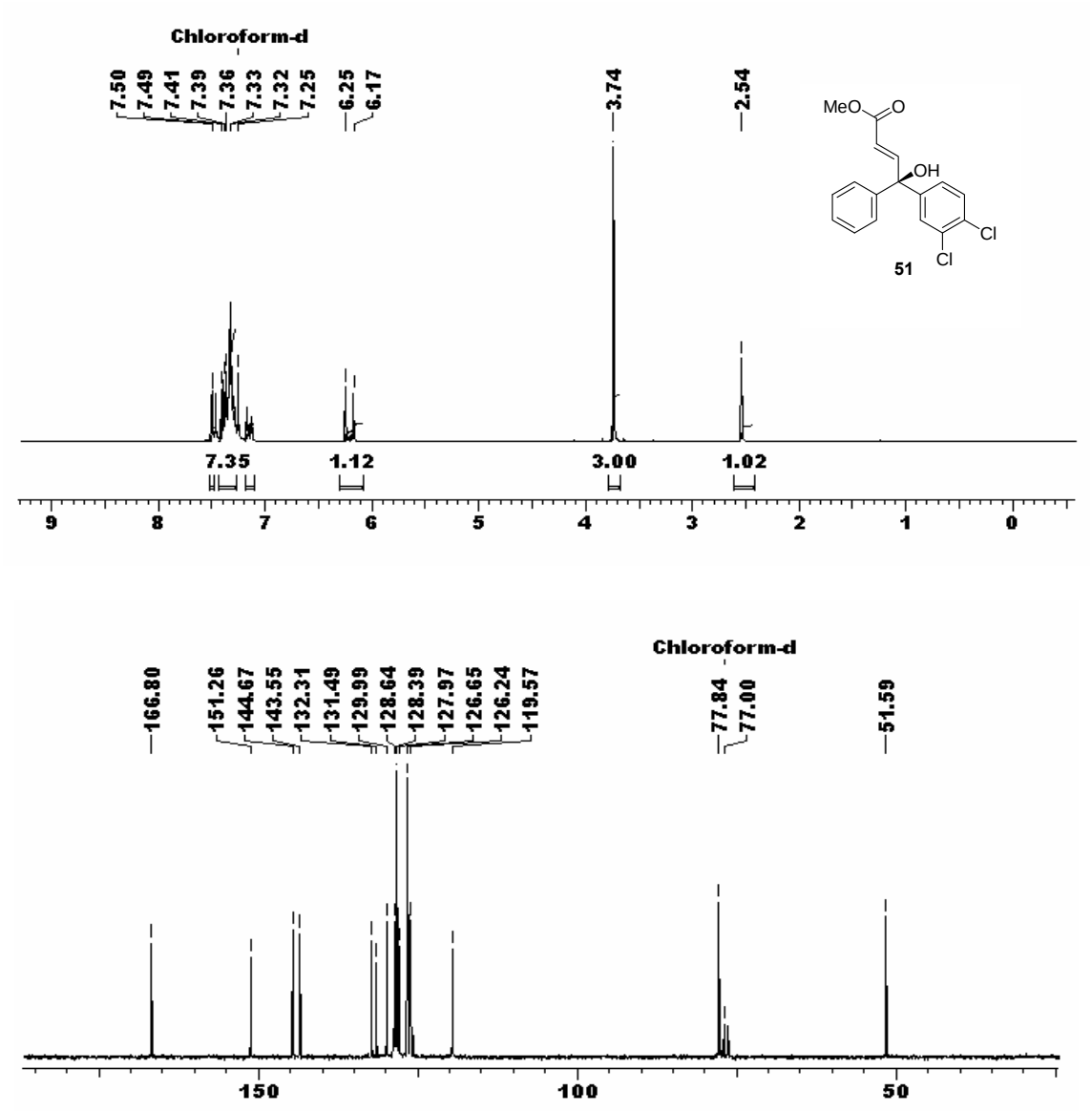


Fig. 8: ^1H and ^{13}C NMR spectra of α, β-unsaturated ester **51**

Catalytic hydrogenation [10% Pd/C, H_2 (20 psi), MeOH] of ester **51** was carried out. It underwent hydrogenolysis at the benzylic position as well as reduction of C=C bond to produce the saturated ester **33** in 62% yield with complete retention of configuration at the benzylic position.[27] Ester **33** was subsequently hydrolyzed in acidic conditions (6N HCl, reflux, 23 h) to give the corresponding carboxylic acid **6**, as confirmed by its IR, which exhibited a broad band at 1715 cm^{-1} due to the presence of carboxylic acid carbonyl function.

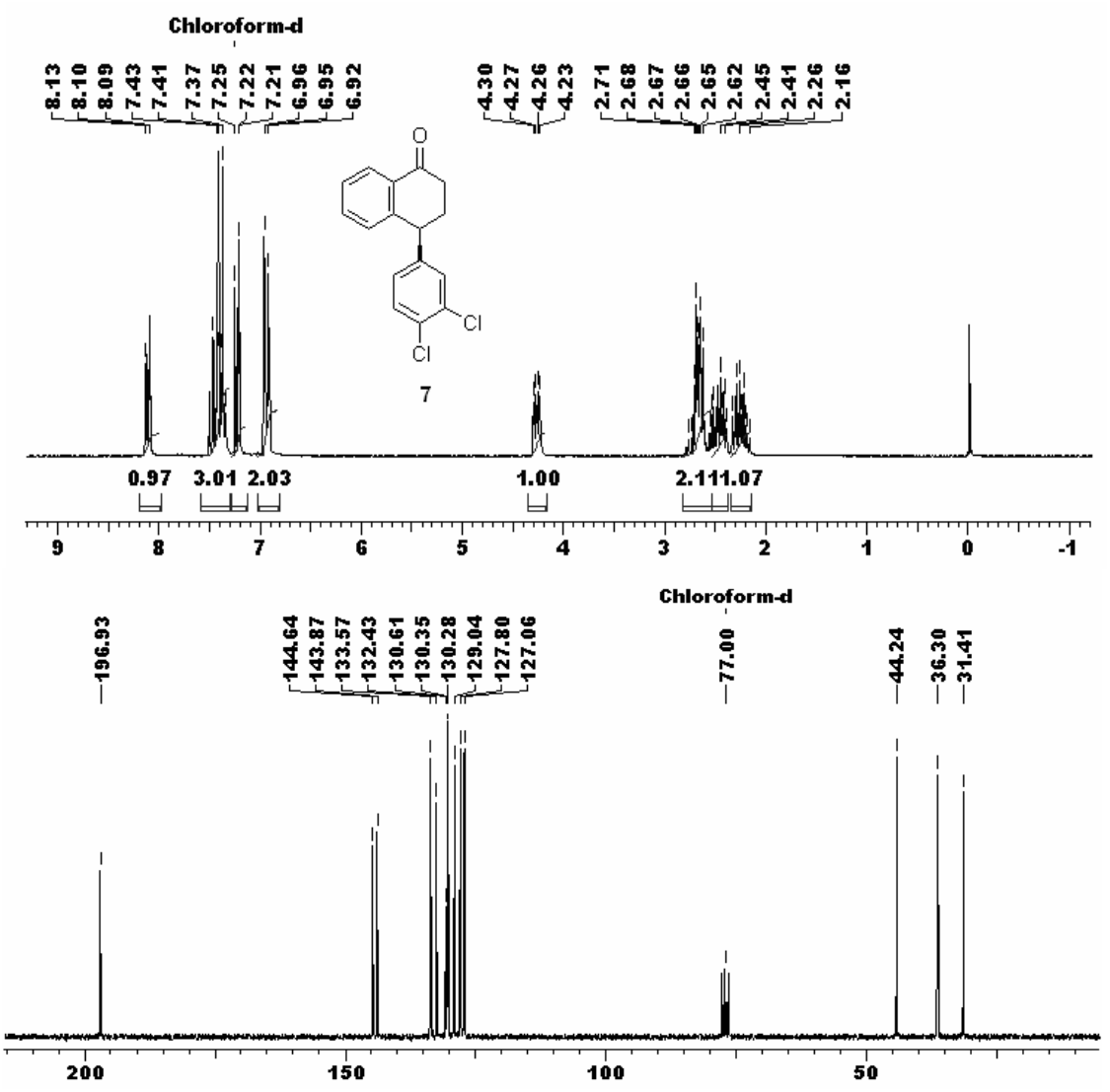


Fig. 9: ^{1}H and ^{13}C NMR spectra of tetralone **7**

Carboxylic acid **6** was subsequently subjected to intramolecular Friedel-Crafts' cyclization ($ClSO_3H$, CH_2Cl_2) to furnish tetralone **7** in 68% yield and 88% ee. Its ^1H NMR spectrum showed a multiplet at δ 2.18-2.71 for -C**H**$_2$-C**H**$_2$- protons. A multiplet at δ 4.28 (dd) is due to benzylic methine proton. Its ^{13}C NMR displayed a typical signal at δ 196.9 for benzylic ketone carbonyl and two signals at δ 143.8 and 144.6 for the aromatic quaternary carbons (**Fig. 9**). Finally, a single-step reductive amination [$TiCl_4$, excess $MeNH_2$, Raney-Ni, H_2 (50 psi)] of tetralone **7** afforded (+)-sertraline **1a** in 35% yield and 88% ee. Sertraline **1a** was recrystallized from chloroform and ethanol. Its ^1H and ^{13}C NMR spectral values and melting point were found to be identical with the reported values[13] (**Fig. 10**).

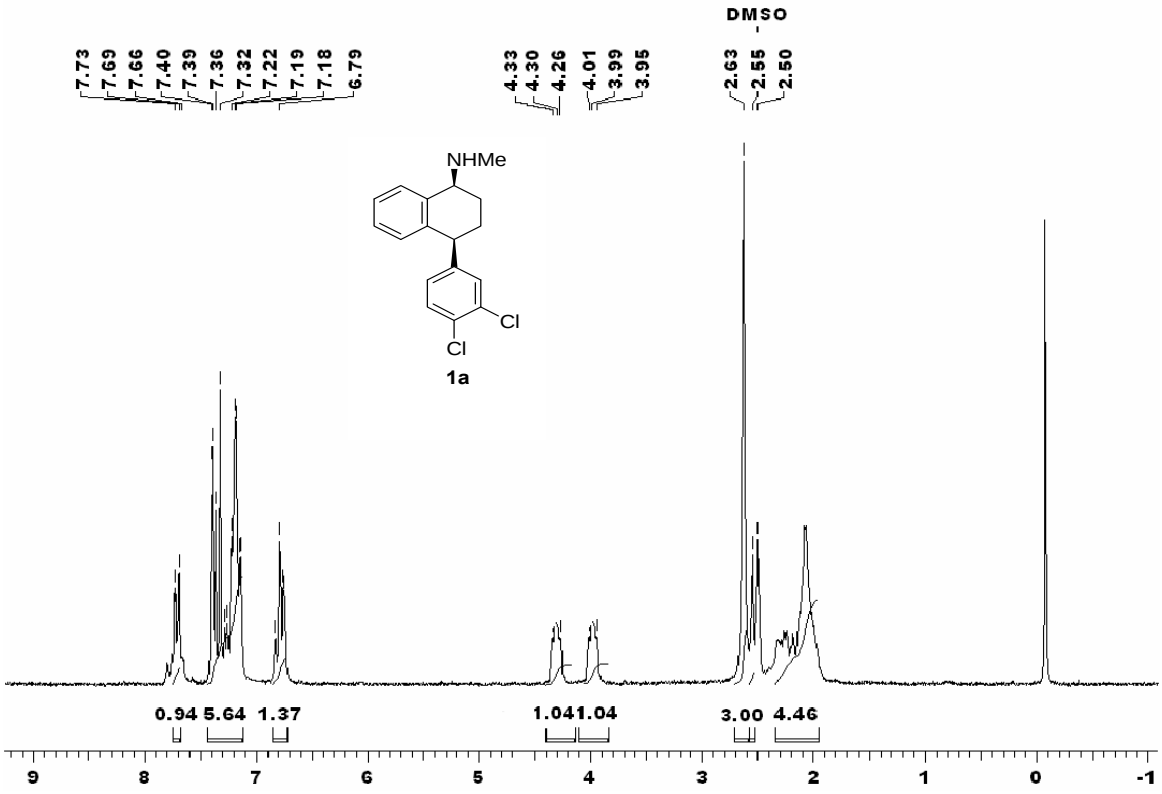


Fig. 10: ^1H NMR spectrum of (+)-sertraline (**1a**)

1.1.6 Conclusion

In summary, we have described an alternative, catalytic method for the enantioselective synthesis of (+)-sertraline (**1a**) that employs Sharpless asymmetric dihydroxylation of 1,1' diaryl olefin as the key step and proceeds in 9 steps with an overall yield of 5.0% and 88% ee.

1.1.7 Experimental section

3,4-Dichlorophenyl(phenyl)methanol (58)

To a stirred suspension of magnesium (1.0 g, 41.13 mmol) and few crystals of iodine in dry THF (100 mL), a solution of 4-bromo-1,2-dichlorobenzene (5g, 22.13 mmol) in 20 mL dry THF was added drop-wise at 25 ^{o}C. It was heated to reflux for 15 min and the reaction mixture was cooled to 0 ^{o}C. To this, a solution of benzaldehyde (2.34 g, in THF 10 mL, 22.05 mmol) was added drop-wise *via* syringe. After stirring at 0 ^{o}C for 10 min and at 25 ^{o}C for 10 h a saturated aqueous NH_4Cl solution was added and the organic layers separated. The aqueous layer was extracted with Et_2O (3x 40 mL) and the combined organic layers were dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure and the crude product purified by column chromatography over silica gel using EtOAc and pet. ether (8:2) as eluant to yield alcohol **58**.

Yield: 80%; **IR** ($CHCl_3$, cm^{-1}): 3305, 2930, 2812, 1460, 1230, 1020, 745, 700, 605; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.38 (br s, 1H), 5.74 (s, 1H), 7.19-7.48 (m, 8H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 74.9, 125.6, 126.4, 128.0, 128.2, 128.6, 130.2, 131.3, 132.4, 142.7, 143.8; **Anal.** Calcd for $C_{13}H_{10}Cl_2O$: C, 61.68; H, 3.98; Cl, 28.01; Found. C, 61.52; H, 3.89; Cl, 27.99%.

3,4-Dichlorophenyl(phenyl)methanone (2)

To a stirred mixture of alcohol **58** (5 g, 19.75 mmol) in dry CH_2Cl_2 (70 mL) was added pyridinium chlorochromate (PCC) (6.3 g, 29.23 mmol) at 0 ^oC. After stirring for 5 min, the reaction mixture was then stirred for 6 h at 25 ^oC. After completion of the reaction monitored by TLC, it was filtered through a funnel, solvent was distilled off under reduced pressure and the crude product purified by column chromatography over silica gel using EtOAc and pet ether (2:8) as eluent to give pure ketone **2**.

Yield: 82.6% (4.1 g); **mp:** 95-96 ^oC; **IR** ($CHCl_3$, cm^{-1}): 2980, 2933, 1710, 1610, 1554, 1410, 1398, 974, 845, 738, 690; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.47-7.66 (m, 5H), 7.76 (dt, *J* = 1.6, 6.5 Hz, 2H), 7.89 (d, *J* = 1.7 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 128.4, 128.9, 129.7, 130.3, 131.7, 132.8, 136.6, 137.1, 193.6; **Anal.** Calcd for $C_{13}H_8Cl_2O$: C, 62.18; H, 3.21; Cl, 28.24; Found. C, 62.11; H, 3.19; Cl, 28.17%.

1,2-Dichloro-4-(1-phenylvinyl)benzene (53)

n-BuLi (19.48 mL, 1.6 M in hexane) was added drop-wise, to a stirred solution of methyltriphenylphosphonium iodide (16.8 g, 41.56 mmol) in THF (100 mL) at 0 ^oC. The reaction mixture was stirred at 0 ^oC for 0.5 h and further cooled to -40 ^oC. To this, a solution of [3,4-dichlorophenyl(phenyl)methanone] **2** (7.0 g, 27.87 mmol) in THF (30 mL) was added drop-wise *via* syringe. The mixture was stirred for further 5 h, quenched by the addition of saturated aq. NH_4Cl, the organic layer separated and the aqueous layer was extracted with CH_2Cl_2 (5 x 50 mL). The combined organic layers was washed with water (50 mL), dried over anhyd. Na_2SO_4, solvent distilled off and the crude product purified by column chromatography over silica gel using EtOAc and Pet.ether (1:9) as eluent to afford olefin **53** as a colorless solid.

Yield: 87.1% (6.05 g); **mp:** 98-99 ^{o}C; **IR** ($CHCl_3$, cm^{-1}): 3100, 2970, 2933, 2852, 1604, 1465, 1056, 930, 669; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.46 (dd, *J* = 6.4 Hz, 2H), 7.15 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.27-7.37 (m, 6H), 7.42 (t, *J* = 2.0 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 115.4, 127.4, 128.0, 128.1, 128.3, 129.9, 130.0, 131.7, 132.3, 140.2, 141.4, 147.9; **Anal.** Calcd for $C_{14}H_{10}Cl_2$: C, 67.49; H, 4.05; Cl, 28.46; Found. C, 67.39; H, 3.99; Cl, 28.21%.

(R)-1-(3,4-Dichlorophenyl)-1-phenylethane-1,2-diol (52)

To a stirred mixture of K_2CO_3 (1.66 g, 12.04 mmol), $K_3[Fe(CN)_6]$ (3.96 g, 12.04 mmol), (DHQD-AQN) (0.034 g, 1 mol%) and methane sulfonamide (0.381 g, 12.01 mmol) in water (10 mL) and *tert*-butanol (10 mL) mixture, was added $K_2OsO_4{\cdot}2H_2O$ (0.4 mol%, 0.0059 g) at 0 ^{o}C. After stirring for 15 min, olefin **53** (1 g, 4.01 mmol) in *tert*-butanol (2 mL) was added. The reaction mixture was then stirred for 24 h at 25 ^{o}C. Reaction was quenched by addition of sodium sulfite and then stirred for further 0.5 h. The organic layer was separated and the aq. layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure and the crude product purified by column chromatography over silica gel using EtOAc and pet. ether (4:6) as eluent to give pure diol **52** as a colorless solid.

Yield: 78% (0.88 g); **mp:** 77-78 ^{o}C; $[\alpha]^{25}_{D}$ = -10 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3390, 3062, 1443, 1371, 1209, 1082, 904, 818, 756, 691; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 4.00-4.10 (m, 2H), 7.20 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.27-7.40 (m, 6H), 7.55 (d, *J* = 2.0 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 77.7, 125.8, 126.0,127.6, 128.4, 130.0, 131.2, 132.2,142.7, 144.3; **Anal.** Calcd for $C_{14}H_{12}Cl_2O_2$: C, 59.39; H, 4.27; Cl, 25.04; Found. C, 59.17; H, 4.31; Cl, 24.99%.

(R)-2-(3,4-Dichlorophenyl)-2-hydroxy-2-phenylacetaldehyde (59)

To a solution of diol **52** (2 g, 7.06 mmol) in dry DMSO (16 mL), was added 2-iodoxybenzoic acid (IBX) (3.99 g, 14.12 mmol) at 25 ^{o}C under nitrogen. The reaction mixture was stirred at 25 ^{o}C for 1 h, and then quenched with water (5 mL). The product was extracted with Et_2O (3 x 15 mL). The organic phase was dried over anhyd. Na_2SO_4 and concentrated under vacuum. The crude product thus obtained was purified by column chromatography on silica gel using ethyl acetate and pet. ether (1:9) as eluent to give **59** as a gum.

Yield: 85% (1.68 g); $[\alpha]^{25}_{D}$ = -16.7 (*c* 1.2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 698, 1030, 1136, 1178, 1380, 1448, 1466, 1725, 2853, 2929, 3453; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 4.40 (brs, 1H), 7.22 (dd, *J* = 1.7, 8.0 Hz, 1H), 7.28-7.45 (m, 6H), 7.51 (t, *J* = 2.8 Hz, 1H), 9.92 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 82.6, 126.6, 127.2, 128.9, 129.0, 129.4, 130.6, 132.9, 133.2, 138.7, 139.5, 196.8; **Anal.** Calcd for $C_{14}H_{10}Cl_2O_2$: C, 59.81, H, 3.59; Cl, 25.22; Found. C, 59.77; H, 3.60; Cl, 25.19%.

(R)-E-Methyl 4-(3,4-dichlorophenyl)-4-hydroxy-4-phenylbut-2-enoate (51)

To a solution of aldehyde **59** (1.0 g, 3.55 mmol) in dry benzene (25 mL), was added $Ph_3P{=}CHCO_2Me$ (1.42 g, 4.26 mmol) at 25 ^{o}C. The reaction mixture was stirred at 25 ^{o}C for 10 h, and then quenched with water (5 mL). The product was extracted with EtOAc (3 x 20 mL) and washed with water (3 x 15 mL). The combined organic phase was dried over anhyd. Na_2SO_4 and concentrated under vacuum. The crude product thus obtained was purified by column chromatography on silica gel using ethyl acetate and pet. ether (1:9) as eluent to give unsaturated **51**.

Yield: 90% (1.07 g); $[\alpha]^{25}_{D}$ = -12.0 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3457, 3063, 2946, 1713, 1652, 1377, 1170, 1130, 1030, 983, 918, 818, 700, 636; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.54 (brs, 1H), 3.74 (s, 3H), 6.21 (d, *J* = 14.0 Hz, 1H), 7.15 (dd, *J* = 2.6, 9.0 Hz, 1H), 7.28-7.41 (m, 7H), 7.50 (d, *J* = 2.0 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 51.5, 77.8, 119.5, 126.2, 126.6, 127.9, 128.3, 128.6, 129.9, 131.4, 132.3, 143.5, 144.6, 151.2, 166.8; **Anal.** Calcd for $C_{17}H_{14}Cl_2O_3$: C, 60.55; H, 4.18; Cl, 21.03; Found. C, 60.11; H, 4.21; Cl, 20.99%.

(R)-Methyl 4-(3,4-dichlorophenyl)-4-phenylbutanoate (33)

To a solution of ester **51** (0.9 g, 2.66 mmol) in methanol (20 mL), was added 10% Pd/C (60 mg) and stirred under hydrogen (20 psi) at 25 ^{o}C. The reaction mixture was further stirred at 25 ^{o}C for 3 h, and the progress monitored by TLC. After completion of reaction, it was filtered through a Celite pad and washed with EtOAc (3 x 20 mL). The combined organic phase was concentrated under vacuum. The crude product thus obtained was purified by column chromatography on silica gel using ethyl acetate and pet. ether (1:9) as eluent to give **33**.

Yield: 62% (0.530 g); $[\alpha]^{25}_{D}$ = -5.2 (*c* 1.2, $CHCl_3$) [lit.[28a] $[\alpha]^{25}_{D}$: -6.1 (*c* 1.12, $CHCl_3$)]; **IR** ($CHCl_3$, cm^{-1}): 2970, 2930, 1722, 1600, 1494, 1365, 1202, 680; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.22-2.38 (m, 4H), 3.64 (s, 3H), 3.85-3.94 (q, *J* = 7.0, 12.0 Hz, 1H), 7.12-7.31 (m, 8H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 30.2, 32.0, 50.4, 51.4, 126.3, 127.1, 127.6, 127.8, 128.4, 128.7, 129.7, 130.4, 132.5, 142.6, 144.5, 173.0; **Anal.** Calcd for $C_{17}H_{16}Cl_2O_2$: C, 63.17; H, 4.99; Cl, 21.94; Found. C, 63.21; H, 4.87; Cl, 21.50%.

(S)-4-(3,4-Dichlorophenyl)-3,4-dihydronaphthalen-1(2*H*)-one (7)

To round bottom flask was charged with **33** (0.3 g, 0.92 mmol) and 6 M HCl (30 mL) and the solution was heated at reflux. After 23 h the reaction was cooled and added H_2O (20 mL) and extracted with EtOAc (3 x 10 mL). The combined organics were dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give corresponding acid **6** (245 mg). **IR** (neat, cm^{-1}): 2975, 2664, 1715, 1470, 1406.

The acid **6** (245 mg) was then dissolved in CH_2Cl_2 (20 mL) and $ClSO_3H$ was added. After 2 h the solution was added to a saturated $NaHCO_3$ solution (75 mL) and extracted with CH_2Cl_2 (2 x 30 mL) followed by ether (1 x 30 mL). The combined organic layers were dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel column chromatography EtOAc:pet. ether (3:7) gave tetralone **7**.

Yield: 68.2% (157 mg); **mp:** 83-84 ^oC [lit.[5] 84 ^oC]; $[\alpha]^{25}_D$ = +62.3 (*c* 1.1, C_6H_6) [lit.[5] $[\alpha]^{25}_D$: +71.3 (*c* 1.1, C_6H_6)]; **IR** ($CHCl_3$, cm^{-1}): 3019, 2984, 1715, 1683, 1599, 1469, 1329, 1284, 1132, 1030, 823, 756, 730, 676; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.16-2.33 (m, 1H), 2.38-2.53 (m, 1H), 2.56-2.77(m, 2H), 4.28 (dd, *J* = 5.0, 8.0 Hz, 1H), 6.93 (dd, *J* = 2.0, 8.0 Hz, 2H), 7.22 (d, *J* = 2.0 Hz, 1H), 7.34-7.50 (m, 3H), 8.11 (dd, *J* = 1.7, 8.0 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 31.4, 36.3, 44.2, 127.0, 127.2, 127.8, 129.0, 130.2, 130.3, 130.6, 132.4, 133.5, 143.8, 144.6, 196.9; **Anal.** Calcd for $C_{16}H_{12}Cl_2O$: C, 66.00; H, 4.15; Cl, 24.35; Found. C, 66.11; H, 4.32; Cl, 23.99%.

(+)-Sertraline (1a)

A stirred solution of tetralone **7** (0.6 g, 2.06 mmol) in a dry diethyl ether (10 mL) was cooled to -78 ^oC. Then methylamine (1.5 mL, excess) was introduced *via* syringe, followed by the addition of $TiCl_4$ (0.33 mL, 3.09 mmol). The reaction mixture was

allowed to warm to 25 ^{o}C slowly and stirred overnight. After the reaction was complete, it was filtered through a pad of Celite and washed with ether (3 x 15 mL). The combined filtrates were concentrated to give imine, which was taken up for further reaction without purification. Imine (0.115 g, 0.37 mmol) formed *in situ* was dissolved in methanol (5 mL) and hydrogenated over Raney-Ni. The reaction was monitored by TLC, as the imine had disappeared. The catalyst was filtered and methanol evaporated. The residue was purified by column chromatography packed with silica gel to give (+)-sertraline **1a**.

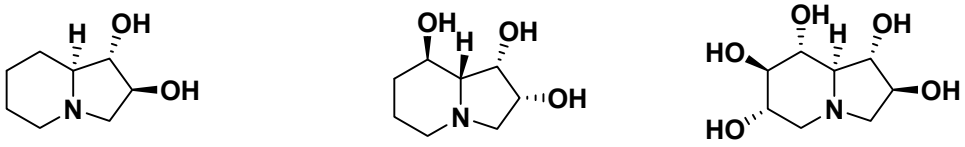
Yield: 35% (40 mg); $[\alpha]^{25}_{D}$ = +32.9 (*c* 1, MeOH) [lit.[13] $[\alpha]^{25}_{D}$ = 36.5 (*c* 1 MeOH)]; **IR** ($CHCl_3$, cm^{-1}): 3438, 3019, 2926, 2749, 1589, 1468, 1401, 1215, 1134, 1028, 669; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.88-2.32 (m, 4H), 2.55 (brs, 1H), 2.63 (s, 3H), 3.99 (t, *J* = 8.0 Hz, 1H), 4.30 (t, *J* = 8.0 Hz, 1H), 6.81 (dd, *J* = 1.7, 8.0 Hz, 1H), 7.14-7.40 (m, 5H), 7.73 (dd, *J* = 7.0, 2.0 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$:DMSO-d_6 1:1) δ 26.0, 29.8, 33.5, 47.4, 58.5, 126.7, 127.2, 129.9, 132.5, 132.8, 133.0, 133.6, 138.5, 139.3, 143.2, 149.9; **Anal.** Calcd for $C_{17}H_{17}Cl_2N$: C, 66.68, H, 5.60; Cl, 23.15; N, 4.57; Found. C, 66.42, H, 5.54; Cl, 23.66; N, 4.12%.

Section II

Enantioselective Synthesis of (+)-Lentiginosine *via* aza-Cope Rearrangement

1.2.1 Introduction

A variety of alkaloids possessing a polyhydroxylated indolizidine structure have been isolated from natural sources, including plants and microorganisms. Some of them are excellent inhibitors of biologically important pathways, including the binding and processing of glycoproteins and show potent glycosidase inhibitory activities.[29] Among naturally occurring polyhydroxylated indolizidines, lentiginosine[30] **60**, swainsonine[31] **61** and catanospermine[32] **62** represent a potent *R*-glycosidase, *R*-mannosidase and amyloglycosidase inhibitors respectively and attracted the greatest attention in terms of both synthetic and biological point of view. These are good examples of dihydroxylated, trihydroxylated and tetrahydroxylated indolizidines respectively (**Fig. 11**).



lentiginosine (**60**) swainsonine (**61**) catanospermine (**62**)

Fig. 11: Structures of indolizidine alkaloids

To study the structure-activity relationships (SAR) in indolizidines, many stereoisomers and analogues have been synthesized and their biological activities tested. These analogues have been used as biochemical tools and are being examined as chemotherapeutic agents against diabetes,[33] cancer[34] and HIV. Their activity is believed to be the result of their ability to mimic the transition state involved in substrate

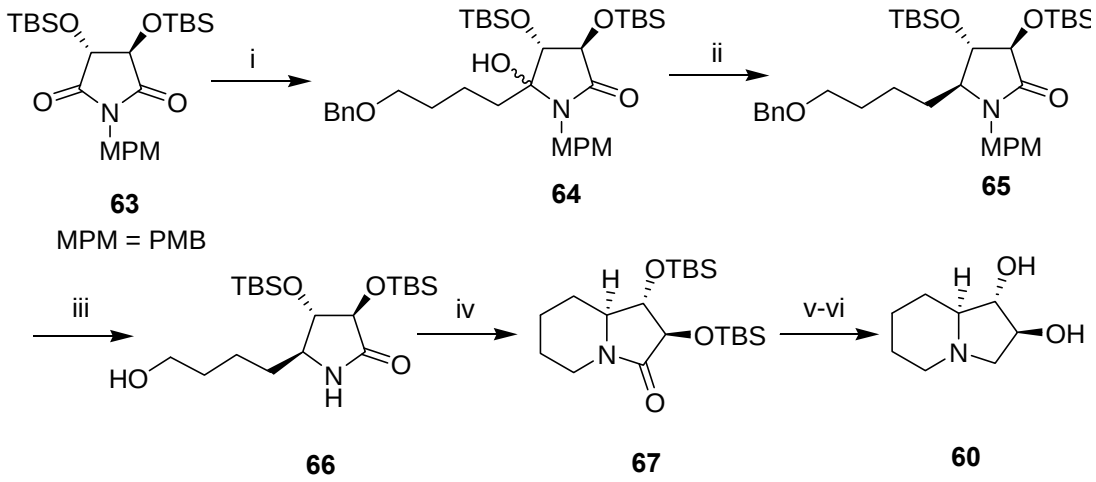
hydrolysis. (+)-Lentiginosine **60**, a dihydroxylated indolizidine alkaloid, isolated from the leaves of *Astragalus lentiginosis*[35] was proven to be a selective inhibitor of amyloglucosidase, an enzyme that hydrolyses 1,4- and 1,6-α-glycosidic linkages.[36]

1.2.2 Review of Literature

Literature search revealed that there are several reports available for the synthesis of (+)-lentiginosine **60** that include chiral pool approach, enantioselective syntheses, etc some of which are described below.

Yoda's approach (1993)[37]

Yoda *et al.* have described the synthesis of (+)-lentiginosine (**60**) starting from TBS protected imide **63**, derived from L-tartaric acid. The imide **63** on treatment with BnO-$(CH_2)_4$-MgBr afforded α-hydroxy lactam **64** in 85% yield. Reductive deoxygenation of **64** using $BF_3{\cdot}OEt$ and Et_3SiH resulted in lactam **65** in 95% yield and 92% ee.

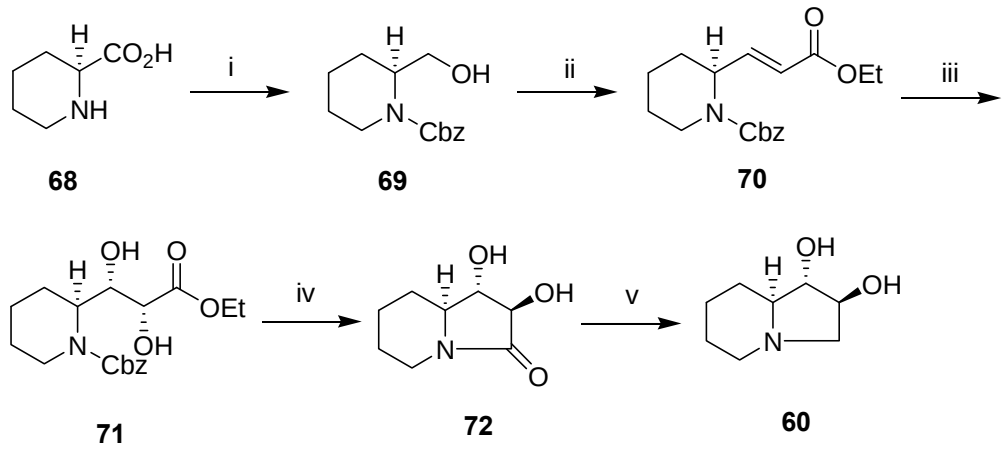


Scheme 16: (i) BnO-$(CH_2)_4$MgBr, THF, -78 ^oC, 85%; (ii) $BF_3{\cdot}OEt_2$, Et_3SiH, CH_2Cl_2, -78 ^oC, 95%; (iii) $Ce(NH_4)_2(NO_3)_6$, CH_3CN, H_2O, 0 ^oC then Pd/C, HCO_2H, *i*-PrOH, 27%; (iv) MsCl, Et_3N, CH_2Cl_2, then NaH, THF, 90%; (v) HCl, MeOH, 100%; (vi) $LiAlH_4$, THF, reflux, 100%.

The compound **65** was subjected to "one-pot" deprotection of benzyl and MPM groups using ceric ammonium nitrate (CAN) and Pd/C respectively to give alcohol **66** in 27% yield. Alcohol **66** was converted into its mesylate followed by intramolecular cyclization afforded indolizidine **67** in 90% yield. Subsequent removal of TBS-ether and reduction of indolizidinone afforded (+)-lentiginosine **60** (**Scheme 16**).

Gurjar's approach (1994)[38]

Gurjar *et al.* have reported the synthesis of (+)-lentiginosine **60** using Sharpless asymmetric dihydroxylation of ester **70** as the key step. The synthesis begins with naturally occurring (S)-pipecolic acid **68**, which was protected as its N-Cbz followed by reduction of acid function using $BH_3 \cdot Me_2S$ giving alcohol **69**.



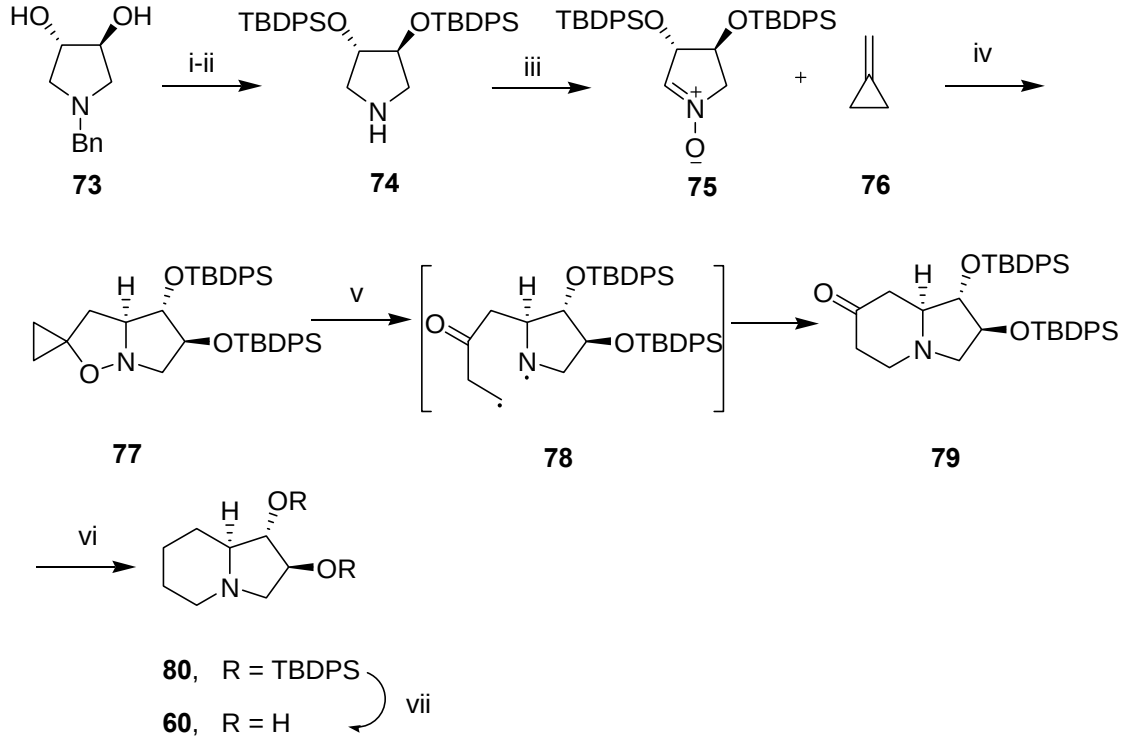
Scheme 17: (i) a) CbzCl, 4N NaOH, 25 °C, 6 h; b) 2M $BH_3 \cdot Me_2S$, THF, 0-25 °C; (ii) a) py:SO_3, DMSO, 0-25 °C, 30 min; (b) $Ph_3P{=}CHCO_2Et$, benzene, 25 °C, 10 h; (iii) AD-mix-α, $^tBuOH{:}H_2O$ (1:1), 25 °C, 24 h; (iv) 10% Pd/C, NaOAc, MeOH, H_2 (1 atm), 12 h; (v) 2M $BH_3 \cdot Me_2S$, THF, 25 °C, 12 h.

The oxidation of alcohol **69** under Parikh-Doering conditions (SO_3:py) gave the corresponding aldehyde, which was subjected to Wittig olefination ($Ph_3P{=}CHCO_2Et$) to produce α,β-unsaturated ester **70**. The ester **70** was then subjected to Sharpless asymmetric dihydroxylation using AD-mix-α which resulted in chiral diol **71**. Finally,

removal of Cbz group leads to the formation of indolizidinone **72**, which on reduction with $BH_3 \cdot Me_2S$ furnished (+)-lentiginosine **60** (**Scheme 17**).

Brandi's approach (1995)[39]

Brandi *et al.* have commenced their synthesis from N-benzyl-3,4-dihydroxypyrrolidine **73**, which was protected as its TBDPS-ether followed by debenzylation to give pyrrolidine **74** in 71% yield. The oxidation of pyrrolidine **74** using SeO_2 and H_2O_2 gave the corresponding nitrone **75** in 58% yield.



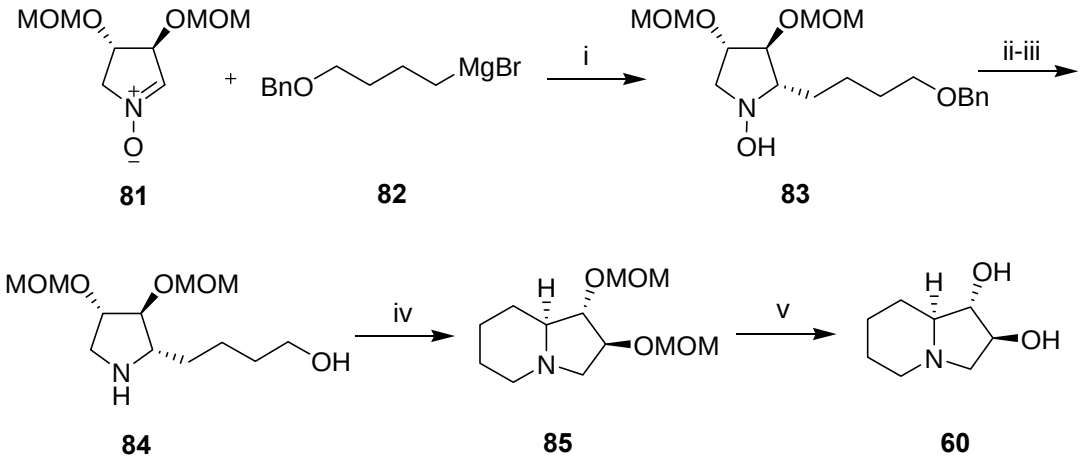
Scheme 18: (i) TBDPSCl, imid., CH_2Cl_2, 100%; (ii) 10% Pd/C, H_2, MeOH, 71%; (iii) SeO_2, 30% H_2O_2, acetone, 20 ^oC, 2 h, 53%; (iv) sealed tube, benzene, 35 ^oC, 8 d; (v) xylene, refluxed, 100 min, 45%; (vi) $NaBH_4$, $TsNHNH_2$, 3 A^o MS, MeOH, 45%; (vii) aq. 40% HF, CH_3CN, 46 h, 85%.

The reaction between nitrone **75** and methylenecyclopropane **76** underwent [3+2] cycloaddition to afford a 12:1 mixture of isooxazolidine **77**. The isooxazolidine **77** was heated in xylene to give di-radical **78** which readily underwent cyclization to produce

indolizidinone **79** in 45% yield. Subsequent reduction of carbonyl group followed by desilylation resulted in the formation of (+)-lentiginosine **60** (**Scheme 18**) in 85% yield.

Petrini's approach (1995)[40]

Petrini *et al.* have synthesized (+)-lentiginosine **60** from optically active nitrone **81**, which was derived from L-tartaric acid. Stereoselective addition of Grignard reagent **82** onto nitrone **81** afforded hydroxylamine **83** in 82% yield. The reduction of hydroxylamine **83** with Raney-Ni followed by its treatment with 10% Pd/C /$HCOONH_4$ furnished amino alcohol **84** in 76% yield. Finally, cyclization of amino alcohol **84** with PPh_3/CCl_4 afforded indolizidine **85**. Subsequent removal of MOM-ether under acidic conditions gave (+)-lentiginosine (**Scheme 19**).

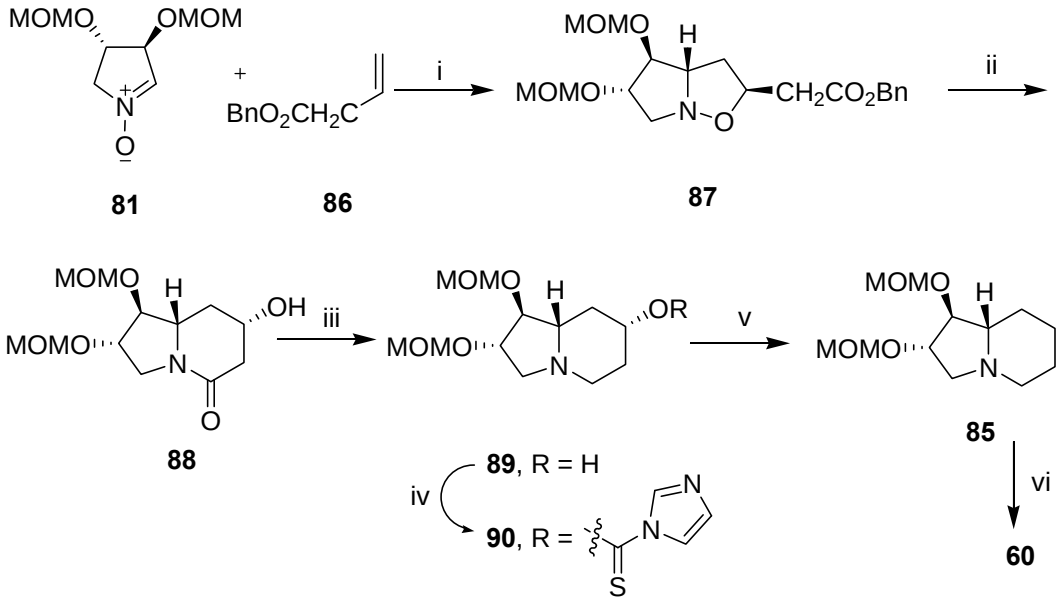


Scheme 19: (i) THF, 25 ^oC, 2 h, 82%; (ii) Raney-Ni, H_2 (1 atm), MeOH, 18 h; (iii) 10% Pd/C, $HCONH_4$, EtOH, 2 h, 76%; (iv) Ph_3P, CCl_4, Et_3N, DMF, 88% yield; (v) 37% aq. HCl, MeOH, reflux, 3 h.

Wightman approach (1998)[41]

Wightman *et al.* also reported the synthesis of (+)-lentiginosine **60** starting from nitrone **81**. The [3+2] cycloaddition of nitrone **81** with olefin **86** afforded cycloadduct **87** in 44% yield. The reductive cleavage of N-O bond was carried out with Zn in AcOH to furnish

lactam **88** in 83% yield. The lactam **88** was subjected to reduction using $BH_3 \cdot Me_2S$ to afford indolizidine **89**, which on treatment with 1,1'-thiocarbonylimidazole in EDC gave imidazolylthiocarbonyl **90** in 80% yield. Finally, the radical deoxygenation of **90** with Bu_3SnH and AIBN followed by deprotection of MOM-ethers under acidic conditions produced (+)-lentiginosine **60** in 76% yield (**Scheme 20**).

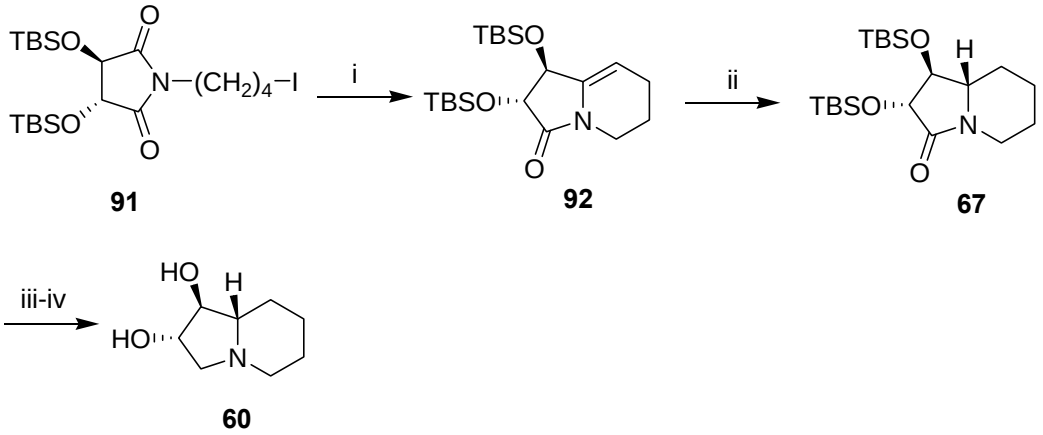


Scheme 20: (i) toluene, reflux, 4 d, 44%; (ii) Zn, AcOH, 60 ^oC, 83%; (iii) $BH_3 \cdot Me_2S$, EtOH, reflux; (iv) 1,1'-thiocarbonyldiimidazole, EDC, reflux, 80%; (v) Bu_3SnH, AIBN, toluene, reflux; (vi) 6M aq. HCl, 76%.

Ha's approach (2000)[42]

Ha *et al.* have achieved the synthesis of (+)-lentiginosine **60** commencing from imide **91**, obtained from L-tartaric acid. Thus, N-(ω-iodobutyl) succinimide **91** was subjected to SmI_2-promoted reductive cyclization in the presence of catalytic amount of tris(dibenzoylmethido)iron(III) [$Fe(DBM)_3$], followed by its treatment with p-TSA to produce enamide **92** in 82% yield. The enamide **92** was then subjected to stereoselective

reduction with Et_3SiH, TFA to produce **67**. Removal of TBS-ether followed by reduction of the resulting amide with $LiAlH_4$ gave (+)-lentiginosine **60** (**Scheme 21**).

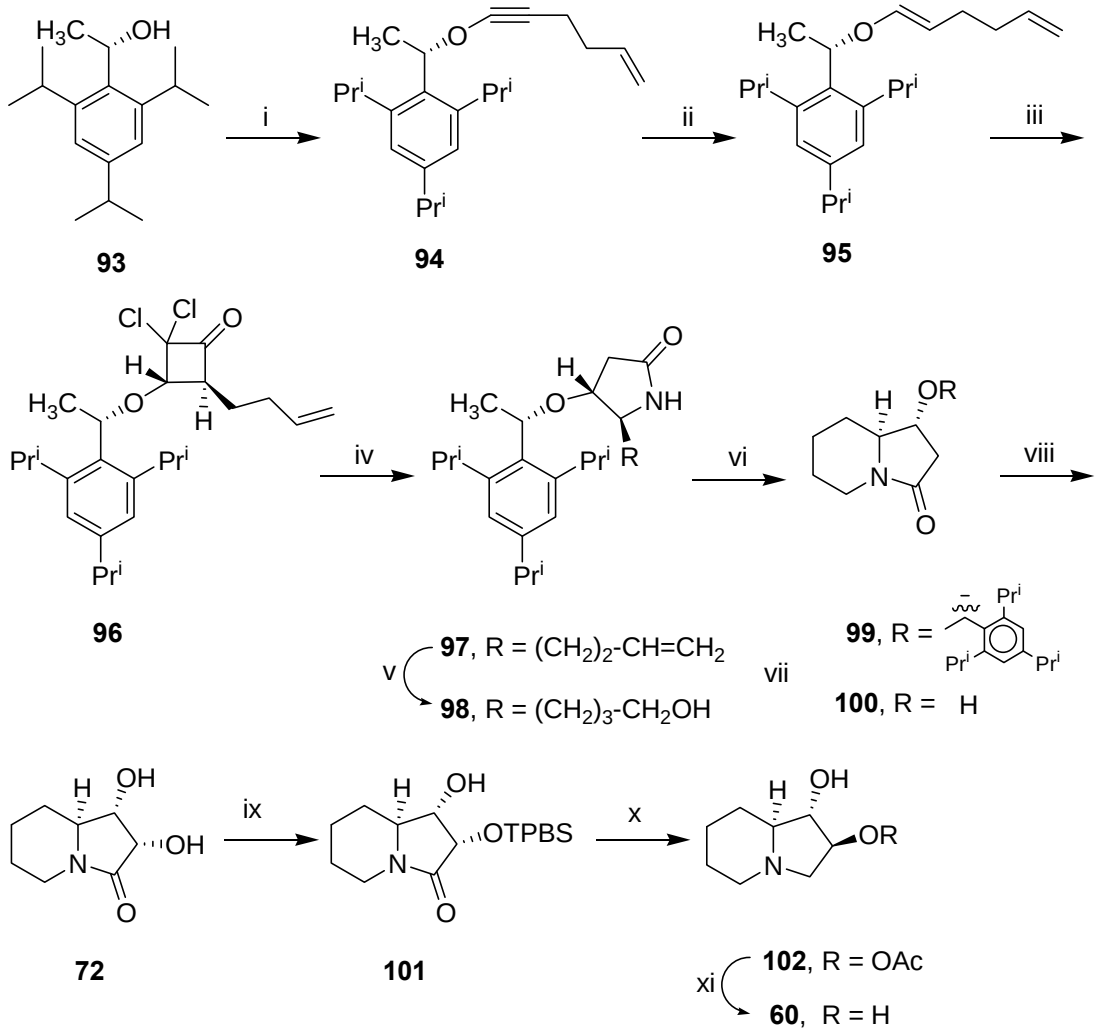


Scheme 21: (i) SmI_2, $[Fe(DBM)_3]$, THF, 0 ^oC, 2 h; then *p*-TSA, CH_2Cl_2, 4 A^o MS, 3 h, 82%; (ii) Et_3SiH, TFA, CH_2Cl_2, 3 h, 93%; (iii) 10% HCl in MeOH, 3 h; (iv) $LiAlH_4$, THF, refluxed, 4 h.

Greene's approach (2001)[43]

This approach describes the synthesis of (+)-lentiginosine **60** starting from chiral alcohol **93** which was subjected to O-alkylation followed by elimination to give ynol ether **94**. Reduction of ynol ether **94** with $LiAlH_4$ produced E-enol ether **95** in 81% yield, which was then subjected to cycloaddition using dichloroketene ($Cl_2C=C=O$) promoted by Zn-Cu to afford cycloadduct **96** in 95:5 dr. The exposure of **96** under Tamura-Beckmann conditions [Al_2O_3, o-mesitylenesulfonyl hydroxylamine] followed by dechlorination gave the corresponding pyrrolidinone **97** in 82% yield. The indolizidine skeleton **99** was constructed from pyrrolidinone **97** through a sequence of reactions which include hydroboration-oxidation, mesylate formation and base-induced cyclization to afford indolizidine skeleton **99** in 88% yield and >99:1 dr. Cleavage of chiral auxiliary in **99** with neat trifluoroacetic acid gave hydroxyl indolizidinone **100** which was then

dehydrated using Martin sulfurane followed by Os-catalyzed dihydroxylation resulted in cis diol **72** in 70% yield.



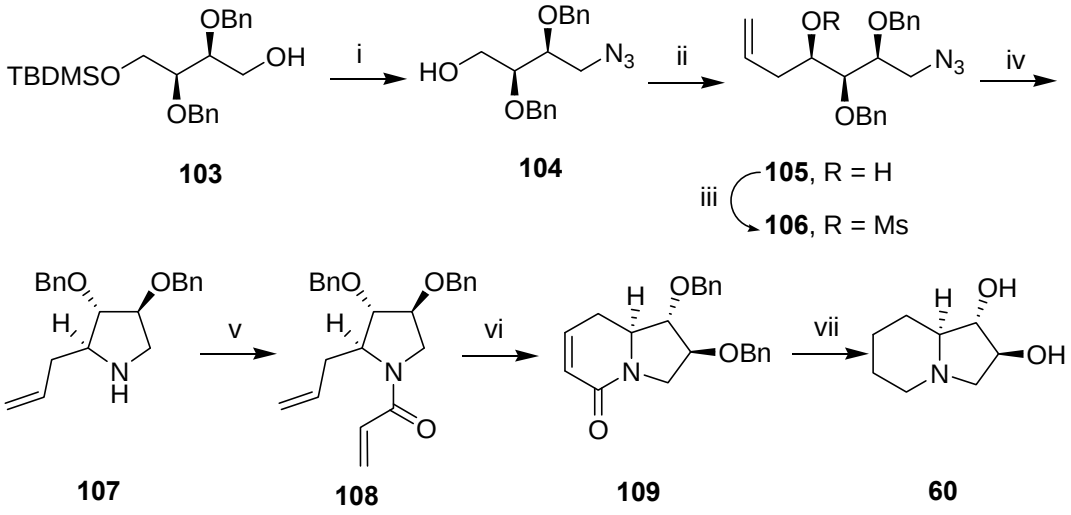
Scheme 22: (i) KH, Cl_2C=CHCl; then *n*-BuLi, 3-butenyl triflate; (ii) $LiAlH_4$, Et_2O, reflux, 1 h, 81%; (iii) Zn-Cu, Cl_3CCOCl, Et_2O, 0 ^oC; (iv) Al_2O_3, *O*-mesitylenesulfonylhydroxylamine, CH_2Cl_2, 4 h; then Zn-Cu, NH_4Cl, 11 h, 82%; (v) 2.6M Sia_2BH, H_2O_2, THF, 5 h; (vi) MsCl, Et_3N, CH_2Cl_2, then NaH, THF, DMF, 88%; (vii) CF_3CO_2H, CH_2Cl_2, 20 ^oC, 3h; (viii) Martin sulfurane, CH_2Cl_2, 25 ^oC, 2 h, 82%; then OsO_4, ^{t}BuOH:H_2O (3:1), trimethylamine N-oxide (TMAO), 25 ^oC, 70%; (ix) Et_3N, 2,4,6-triisopropylbenzenesulfonyl chloride, CH_2Cl_2, 0 ^oC, 20 h, 91%; (x) Bu_4NH_4OAc, toluene, 0 ^oC, 20 h, 70% (xi) $LiAlH_4$, THF, 20 ^oC, 5 h.

Selective protection of one of hydroxyl group in **72** [Et_3N, 2,4,6-triisopropylbenzenesulfonyl chloride (TPBSCl)] gave **101** followed by nucleophilic

displacement in the presence of Bu_4NH_4OAc to afford **102** which was subjected to reduction using $LiAlH_4$ which resulted in lentiginosine **60** (**Scheme 22**).

Sing's approach (2002)[44]

Sing *et al.* have commenced their synthesis from benzyl protected alcohol **103**, derived from tartaric acid. The free hydroxyl group in **103** was protected as its tosylate. Its nucleophilic displacement with NaN_3 followed by deprotection of TBS-ether afforded azido alcohol **104** in 95% yield. The oxidation of alcohol **104** under Corey-Kim's condition (NCS, Me_2S) furnished the corresponding aldehyde which on diastereoselective allylation using $SnCl_4$ and allyltributyltin leads to the formation of syn homoallylic alcohol **105** in 70% yield. The homoallylic alcohol **105** was converted to its mesylate followed by reduction of azide group using $LiAlH_4$, resulted in intramolecular cyclization to produce pyrrolidine **107**. Pyrrolidine **107** was acylated with

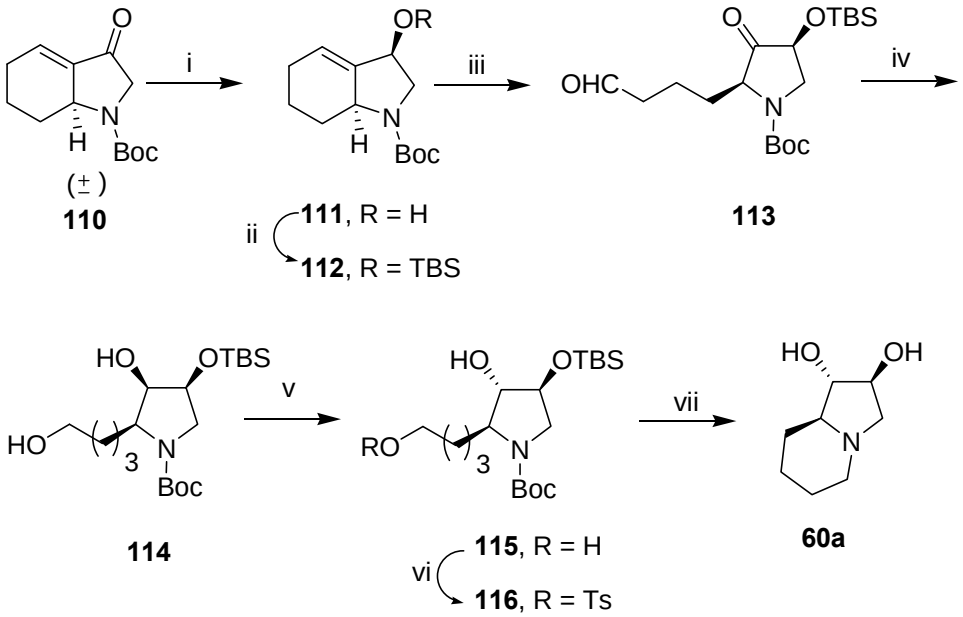


Scheme 23: (i) (a) TsCl, Et_3N, CH_2Cl_2, 12 h; then NaN_3, DMF, 80 ^oC, 12 h, 60%; (b) TBAF, THF, 8 h, 95%; (ii) NCS, Me_2S, CH_2Cl_2, Et_3N, -25 ^oC, 4 h; then $SnCl_4$, allyltributyltin, CH_2Cl_2, -78 ^oC, 1 h, 70%; (iii) MsCl, Et_3N, CH_2Cl_2, 6 h, 92%; (iv) $LiAlH_4$, THF, reflux, 12 h, 68%; (v) acryloyl chloride, Et_3N, CH_2Cl_2, 85%; (vi) 10 mol% Grubbs catalyst, toluene, reflux, 24 h; (vii) 10% Pd/C, H_2, 24 h; then $LiAlH_4$, THF, reflux, 6 h, 97%.

acryloyl chloride in Et_3N to provide the RCM precursor **108** which was subjected to RCM using Grubbs' second generation catalyst to give the cyclized product **109**. Finally, compound **109** was transformed to (+)-lentiginosine **60** in two steps: hydrogenation of benzyl group and double bond followed by reduction of imide function with $LiAlH_4$ (**Scheme 23**).

Sha's approach (2003)[45]

Sha *et al.* have described the recemic synthesis of (±)-lentiginosine **60a**. Boc-protected hexahydro-1H-indol-3-one **110** was subjected to Luche reduction using $CeCl_3.7H_2O$ and $NaBH_4$ to give a single diastereomer **111** which was then protected as its TBS-ether to afford **112** in 95% yield.



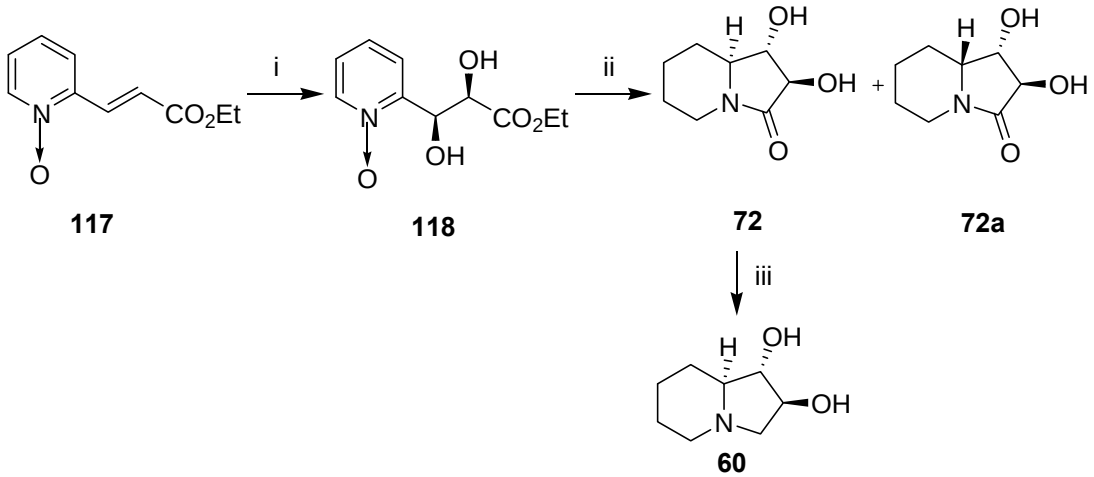
Scheme 24: (i) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, 0 °C, 90%; (ii) TBSCl, imid., DMF, 95%; (iii) O_3, CH_2Cl_2, -78 °C, Me_2S, 92%; (iv) $LiBH_4$, Et_2O, 91%; (v) *p*-NO_2-$C_6H_4CO_2H$, DIAD, Ph_3P, THF, NaOH, MeOH, 55%; (vi) TsCl, pyridine, CH_2Cl_2, 60%; (vii) $BF_3 \cdot OEt_2$, then KOH, MeOH.

The TBS ether **112** was then subjected to ozonolysis to obtain the corresponding aldehyde **113**, the $LiBH_4$ reduction of which gave alcohol **114** in 92% yield. The

configuration of free secondary hydroxyl group in **114** was inverted under Mitsunobu condition [*p*-NO_2-$C_6H_5CO_2H$, DIAD] to afford alcohol **115** in 55% yield. The selective protection of primary alcohol in **115** as its tosylate, Boc-deprotection using $BF_3{\cdot}OEt_2$ and cyclization in the presence of KOH in MeOH resulted in the formation of (±)-lentiginosine **60a** (**Scheme 24**).

Zhou's approach (2003)[46]

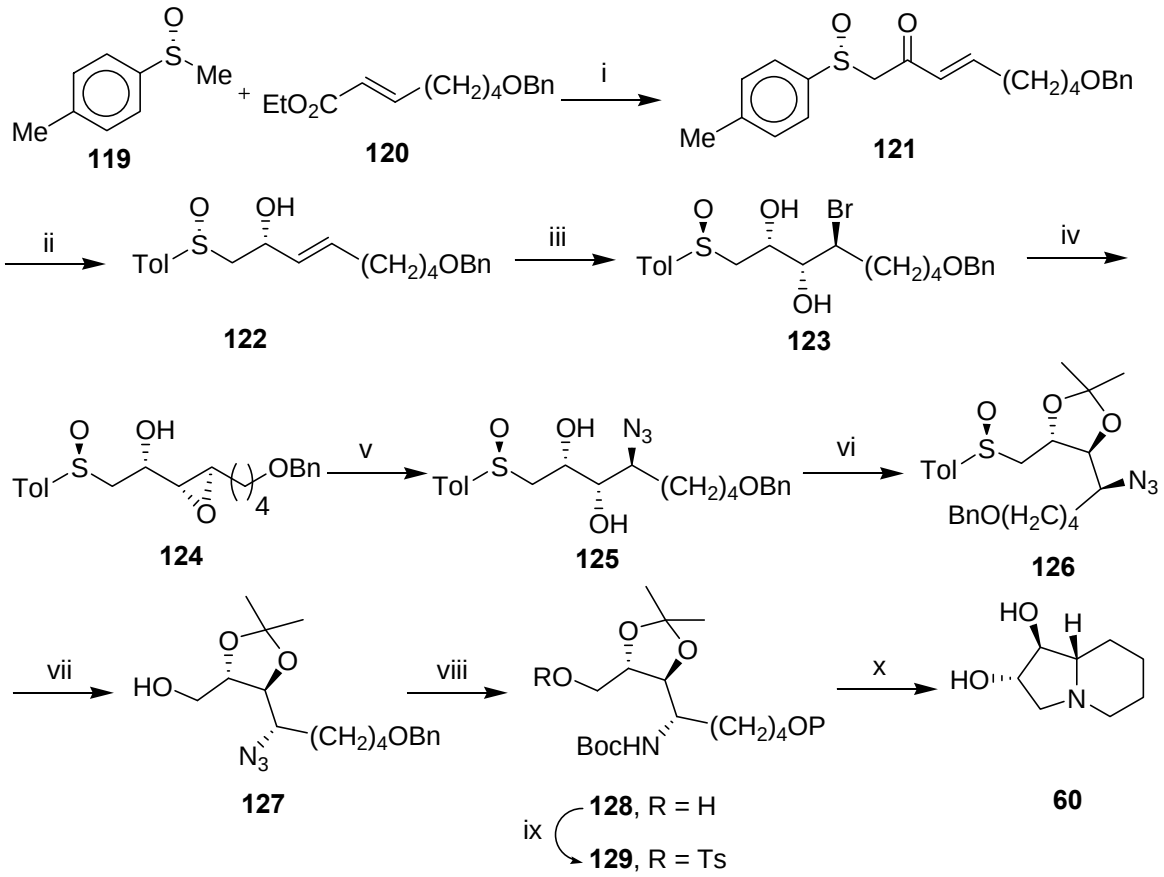
Zhou *et al.* have achieved the synthesis of (+)-lentiginosine **60** using Sharpless asymmetric dihydroxylation as the key step. The α,β-unsaturated ester **117**, prepared from pyridine-2-caboxaldehyde, was subjected to asymmetric dihydroxylation using potassium osmate and $(DHQ)_2$-PHAL as ligand to obtain diol **118** in 62% yield and 99.9% ee. One-pot reduction of pyridine ring followed by intramolecular cyclization using 10% Pd/C, H_2 (10 atm) led to formation of indolizidinones **72** and **72a** in 43% overall yield. The required isomer **72** was however separated by recrystallization and subjected to reduction to give (+)-lentiginosine **60** (**Scheme 25**).



Scheme 25: (i) $K_2[OsO_2(OH)_4]$ (0.4 mol%), $(DHQ)_2$-PHAL (3 mol%), $K_3[Fe(CN)_6]$ (3 equiv.), K_2CO_3 (5 equiv.), $CH_3SO_2NH_2$, H_2O:*tert*-BuOH (1:1), 24 h, 62%; (ii) 10% Pd/C, H_2 (10 atm), MeOH, 24 h, 43%; (iii) $BH_3{\cdot}Me_2S$, THF, 0-25 °C, 10 h, 75%.

Raghavan's approach (2004)[47]

Raghavan *et al.* have reported the synthesis of (+)-lentiginosine **60** commencing from (R)-methyl-*p*-tolyl sulfoxide **119** which was condensed with α,β-unsaturated ester **120** in the presence of lithium diisopropylamide (LDA) to afford β-ketosulfoxide **121** in 70% yield. The β-ketosulfoxide **121** was subjected to reduction with DIBAL-H and $ZnCl_2$ to give allylic alcohol **122**, which on treatment with NBS and H_2O resulted in the formation of bromohydroxylated product **123** in 85% yield.

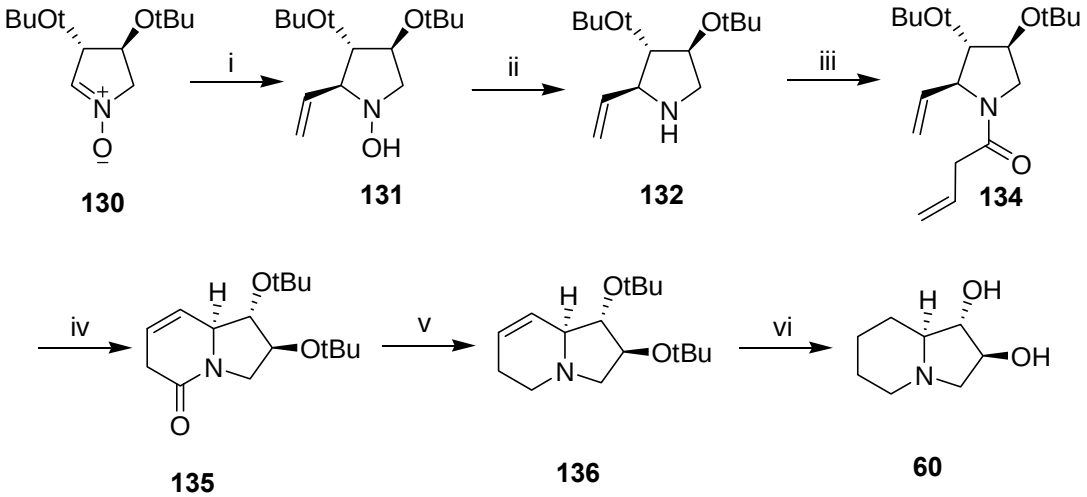


Scheme 26: (i) LDA, THF, -78 °C, 70%; (ii) $ZnCl_2$, DIBAL-H, THF, -78 °C, 91%; (iii) NBS, H_2O, toluene, 25 °C, 85%; (iv) K_2CO_3, MeOH, 0 °C, 83%; (v) NaN_3, NH_4Cl, MeOH:H_2O (8:1), reflux, 81%; (vi) CSA, 2,2-dimethoxypropane, acetone, 25 °C, 87%; (vii) TFAA, Et_3N, CH_2Cl_2, 0 °C, then $NaBH_4$, aq. $NaHCO_3$, 75%; (viii) $Pd(OH)_2$, H_2, $(Boc)_2O$, EtOH, 25 °C, 82%; (ix) TsCl, Et_3N, DMAP, CH_2Cl_2, 75%; (x) TFA:H_2O (95:5), CH_2Cl_2, 0-25 °C; then Et_3N, CH_2Cl_2, 70%.

The bromohydroxylated product **123** on treatment with K_2CO_3 in MeOH afforded epoxide **124** which was then subjected to regioselective opening with NaN_3 to give azido diol **125**. The azido diol **125** was subsequently protected as acetonide to give acetonide **126** in 87% yield. The removal of chiral auxiliary from **126** using trifluoroacetic acid gave triol **127** in 75% yield. The azide group in **127** was then converted to Boc-protected amino-1,8-diol **128** by employing reduction with catalytic amount of $Pd(OH)_2$ and resulted amine was protected with $(Boc)_2O$ in ethanol. The selective protection of primary hydroxyl group in **128** as its tosylate **129** and Boc-deprotection followed by intramolecular cyclization produced (+)-lentiginosine **60** in 70% yield (**Scheme 26**) .

Goti's approach (2005)[48]

Goti *et al.* have achieved the synthesis of (+)-lentiginosine **60** starting from nitrone **130** derived from tartaric acid. Addition of vinylmagnesium bromide onto nitrone **130** gave hydroxyl amine **131** in 96% yield. The RCM precursor **134** was obtained in 71% yield from hydroxylamine **131** by employing indium and zinc catalyzed reductive cleavage of

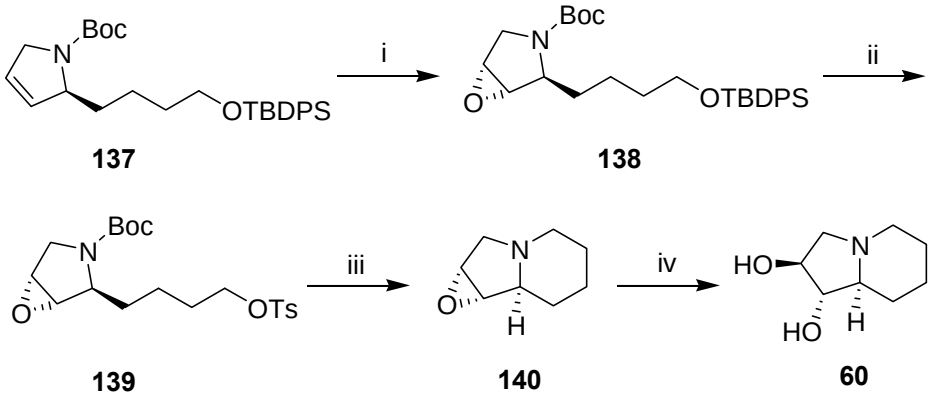


Scheme 27: (i) CH_2=$CHMgBr$, Et_2O, 96%; (ii) In, Zn, MeOH, NH_4Cl, reflux, 84%; (iii) HOBt, DCC, CH_2=$CHCH_2CO_2H$, 71%; (iv) Grubbs' catalyst Ist generation, CH_2Cl_2, reflux, 60%; (v) $LiAlH_4$, THF, 62%; (vi) Pd/C, H_2, MeOH; then TFA, 74%.

N-O bond followed by amidation with but-3-enoic acid using HOBt and DCC as dehydrating agents. Diene **134** was then subjected to RCM using Grubbs' second generation catalyst which resulted in the formation of lactam **135**. Eventually, the synthesis was completed by the standard sequence of reactions: reduction of amide followed by catalytic hydrogenation of double bond and deprotection of *tert*-butyl ether with TFA (**Scheme 27**).

Spino's approach (2008)[49]

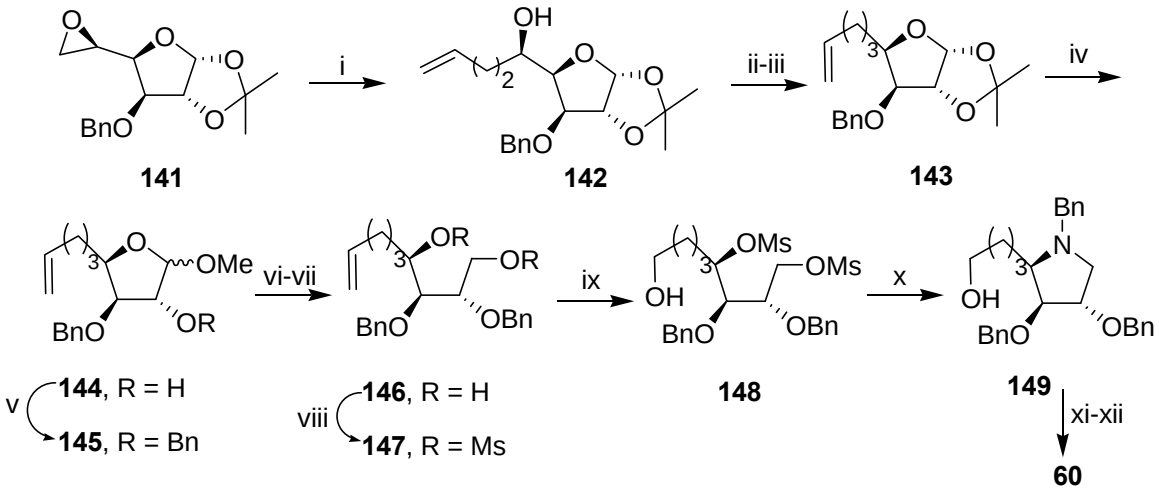
Spino *et al.* have achieved the synthesis of (+)-lentiginosine **60** commencing from chiral Boc-protected pyrrolidine **137**. The stereoselective epoxidation of **137** using oxone produced the corresponding epoxide **138** in 89% yield. Deprotection of TBDPS ether **138** (tetrabutylammonium fluoride, THF) followed by protection of hydroxyl group as tosylate (*p*-toluenesulfonyl chloride, pyridine) afforded tosylate **139**. The Boc group in tosylate **139** was deprotected under acidic conditions followed by its treatment with Et_3N led to the formation of cyclized product **140** in 63% yield. Finally, opening of epoxide **140** with aq. H_2SO_4 resulted in the formation of (+)-lentiginosine **60** in 71% yield (**Scheme 28**).



Scheme 28: (i) oxone, $NaHCO_3$, CF_3COCH_3, CH_3CN, 89%; (ii) TBAF, THF, then TsCl, pyridine, 85%; (iii) TFA, CH_2Cl_2 then Et_3N, 63%; (iv) 10% aq. H_2SO_4, dioxane, 71%

Vankar's approach (2008)[50]

Vankar *et al.* have reported the synthesis of (+)-lentiginosine **60** commencing from epoxide **141** which was derived from D-glucose. The regioselective ring opening of epoxide **141** with allylmagnesium chloride resulted in the formation of homoallylic alcohol **142** in 95% yield. The hydroxyl group in **142** was subjected to deoxygenation under Barton condition [PhOCSCl, Bu_3SnH, AIBN] to give olefin **143** in 75% yield. Olefin **143** was treated with 10% HCl in methanol to give the acetonide-deprotected acetal **144** in 98% yield. Subsequently, the free hydroxyl group in **144** was protected as



Scheme 29: (i) allylMgCl, THF, -20 °C, 1 h, 95%; (ii) PhOCSCl, pyridine, 0 °C, 96%; (iii) Bu_3SnH, AIBN, toluene, reflux, 75%; (iv) 10% HCl in MeOH, 25 °C, 98%; (v) NaH, BnBr, THF, 97%; (vi) 3N HCl, dioxane, reflux, 3 h; (vii) $NaBH_4$, MeOH, 0-25 °C, 88% for two steps; (viii) MsCl, Et_3N, CH_2Cl_2, 0-25 °C, 97%; (ix) (a) OsO_4, NMO, 20 h, 25 °C; (b) $NaIO_4$, MeOH:H_2O (6:1), 0 °C; then $NaBH_4$, MeOH, 1 h, 90%; (x) $BnNH_2$, 80 °C, 20 h, 91%; (xi) MsCl, Et_3N, CH_2Cl_2, 0-25 °C; (xii) 10% Pd/C, H_2 (5 atm), MeOH, 24 h, 81%.

its benzyl ether to give **145** in 97% yield. The acetal moiety in **145** was hydrolyzed using 3M HCl in refluxing dioxane followed by reduction with $NaBH_4$ produced diol **146** in 88% yield. Diol **146** was then treated with MsCl and Et_3N to give the corresponding dimesylate **147** in 96% yield. The double bond was oxidatively cleaved using OsO_4 and $NaIO_4$ followed by reduction with $NaBH_4$ gave hydroxy derivative **148**. Finally,

treatment of dimesylate **148** with benzylamine gave hydroxyl pyrrolididine derivative **149** which was converted to its mesylate. Catalytic hydrogenation with Pd/C and H_2 (5 atm) gave (+)-lentiginosine **60** (**Scheme 29**).

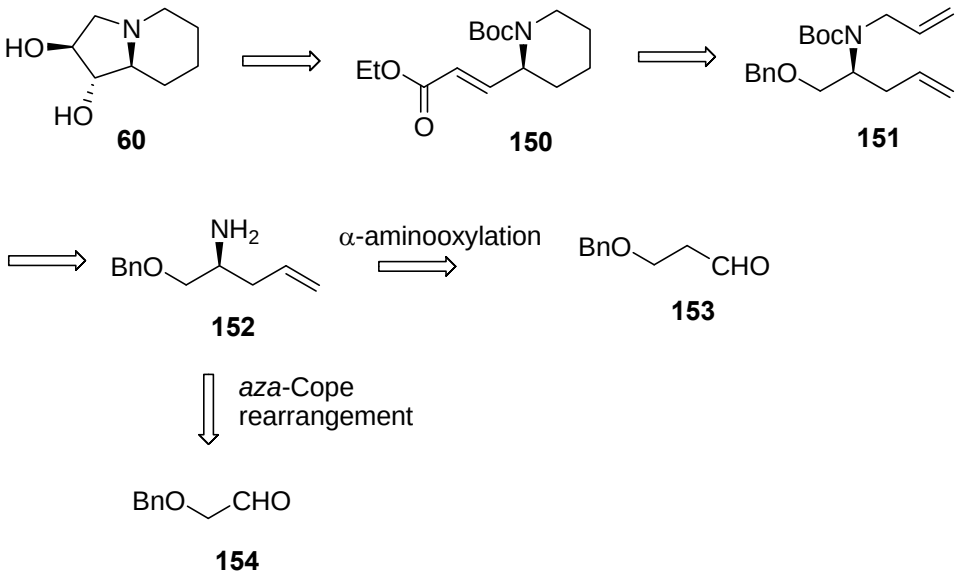
1.2.3 Present Work

1.2.3.1 Objective

As can be seen from the above discussion, the literature methods for the synthesis of (+)-lentiginosine (**60**) employ either chiral starting materials or expensive reagents involving more number of steps, resulting in poor yields. This section describes the enantioselective synthesis of (+)-lentiginosine by employing two approaches: L-proline catalyzed α-aminooxylation and asymmetric *aza*-Cope rearrangement as the chiral inducing reactions.

Retrosynthetic analysis

Retrosynthetic analysis of (+)-lentiginosine (**60)** is outlined in **Scheme 30**. Accordingly, (+)-lentiginosine is visualized to be prepared from α,β-unsaturated ester **150** *via* Os-



Scheme 30: Retrosynthetic analysis of (+)-lentiginosine (60)

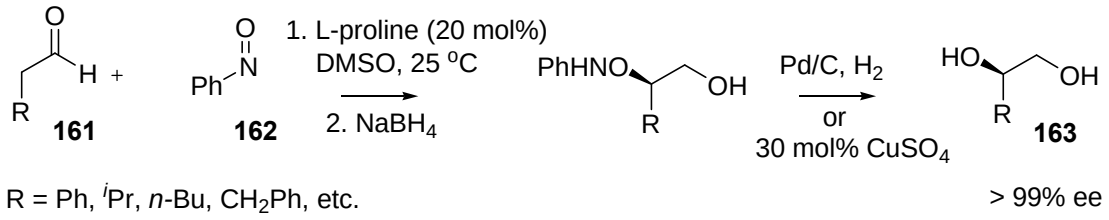
catalyzed diastereoselective dihydroxylation. We further thought that the piperidine core in ester **150** can be constructed from **151** by Ring Closing Metathesis (RCM), which in turn may be obtained from the key amine intermediate **152**. The key intermediate **152** can be thought to be synthesized by two routes of L-proline catalyzed α–aminooxylation and *aza*-Cope rearrangement; a brief account of both is presented below.

1.2.4.1 Proline-catalyzed α-aminooxylation

Optically active α-hydroxy aldehydes and ketones are important intermediates in organic synthesis as they are direct precursors to 1,2-diols. Because of this utility many methods have been developed for their preparation. The more prominent, well-established methods of enantioselective α-oxygenations include the use of Davis oxaziridine,[51a] Sharpless dihydroxylation of enol ethers,[51b] manganese-salen epoxidation of enol ethers, and Shi epoxidation of enol ethers.[51d] It is only rather recently that direct catalytic, asymmetric variants have been reported.[52] Most of these methods, however, require multiple manipulations and there is no direct method, nor catalytic asymmetric method for their synthesis from the corresponding aldehyde.

Organocatalysis is the catalysis of chemical transformations using a purely organic molecule, which is composed of mainly carbon, hydrogen, nitrogen, sulfur and phosphorus and does not contain any metals. The advantages of organocatalysts include their lack of sensitivity to moisture and oxygen, their ready availability, low cost, and low toxicity, which confers a huge direct benefit in the production of pharmaceutical intermediates when compared with transition metal catalysts. Organic molecules not only have ease of manipulation and a "green" advantage but also can be very efficient catalysts. Asymmetric organocatalysis has begun to catch up with the spectacular

advancements of enantioselective transition metal catalysis. In this connection, proline, an abundant, inexpensive amino acid available in both enantiomeric forms has emerged as a practical and versatile organocatalyst.[53] Proline is equally efficient for α-functionalization[54] of aldehydes and ketones. When an aldehyde **155** without substitution at α-position was reacted with nitrosobenzene **156** in presence of L-proline in DMSO at ambient temperature, aminooxylation of the aldehyde takes place at α-position. The aminooxyl moiety undergoes hydrogenolysis with Pd/C, H_2 or $CuSO_4$ to give the corresponding diols **157** in very high enantioselectivities (**Scheme 31**).



Scheme 31: α-aminooxylation of aldehydes

The mechanism of the α-aminooxylation reaction is shown in **Fig. 12**. The observed enantioselectivitiy of the catalytic α -aminooxylation of aldehydes can be rationalized by invoking an enamine mechanism operating through a chair transition state where the *Si* face of an *E*-enamine formed from the aldehyde and L-proline approaches the less hindered oxygen atom of nitrosobenzene to provide a chiral α -aminoxyaldehyde with *R* configuration. Since proline is commercially available in both enantiopure forms, a one-

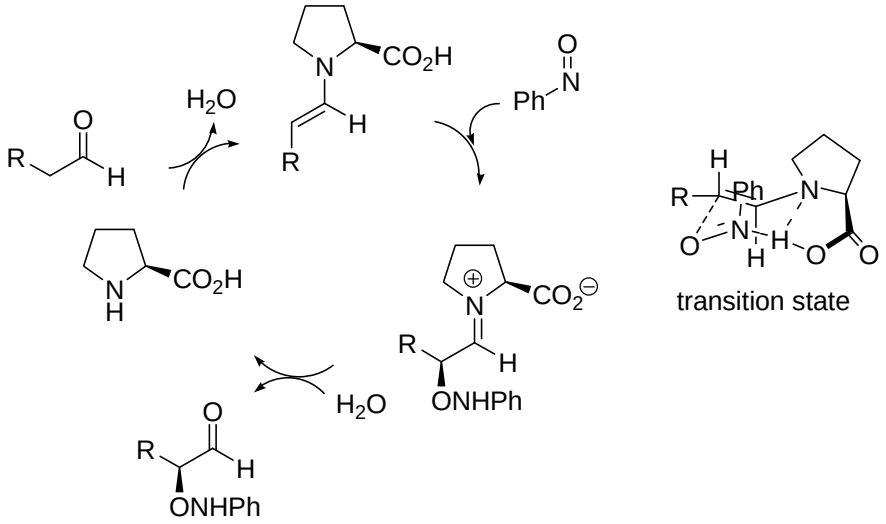


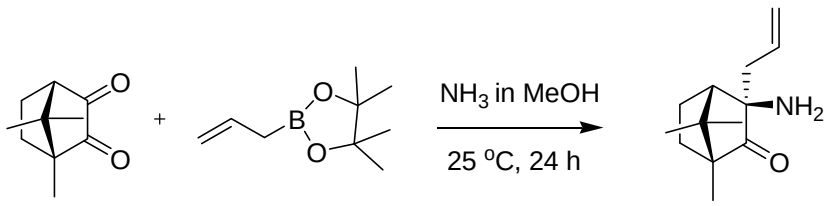
Fig. 12: Proposed mechanism of the α-aminooxylation reaction

pot sequential catalytic α -aminooxylation of aldehydes followed by *in situ* reduction with $NaBH_4$ affords *R*- or *S*- configured 1,2-diol units (the secondary alcohol "protected" by an *O*-amino group) with excellent enantioselectivities and in good yields.

1.2.4.2 Asymmetric *aza*-Cope rearrangement

The Cope rearrangement is an extensively studied reaction involving [3,3]-sigmatropic rearrangement of 1,5-diene. Homoallylic primary amines are of great importance in organic synthesis because allylic C=C can be readily converted to important building blocks. Homoallylic amines could be synthesized effectively by addition of allylic nucleophiles to C=N electrophiles and efficient enantioselective methods including asymmetric catalysis was reported. However, most of those methods require removal of protecting group on the nitrogen to obtain primary amines, and direct routes for optically active homoallylic amines have been limited. Alternatively, allylboration of *N*-silylimines with chiral allylboron reagents reported by Istuno et al.[55] and Brown et al.[56] are applicable for only non-enolizable imines to give high enantioselectivities. Kobayashi *et al*. have recently reported α-aminoallylation of aldehydes with ammonia and

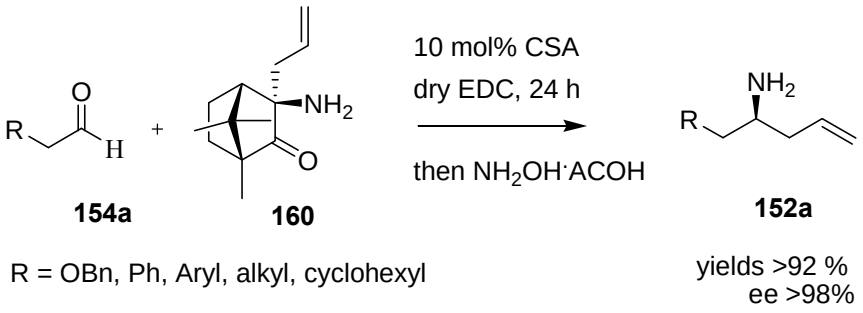
allylboronates for synthesis of homoallylic primary amines[57] while selectivity was unsatisfactory. Further, their study into the allylation of hydroxyglycine[58] have been found that *β*-branched allylglycines isomerized to the corresponding linear isomers *via* imine formation with glyoxylic acid, followed by 2-aza (or azonia)-Cope rearrangement. This type of sigmatropic rearrangement was first reported in 1950[59] and later by Overmann and Kakimoto in 1979, found that [3,3]-sigmatropic shifts for iminium ion and named after then as a 2-azonia-Cope rearrangement.[60] Recently, Kobayashi *et al*. have developed a highly enantioselective synthesis of homoallylic primary amines *via* 2-azonia-Cope rearrangement. The α-aminoketone **160** prepared from camphorquinone and allylboronic acid pinacol ester in ammonia to give 80% yield of reagent **160 (Scheme 32**).



158 **159** **160**

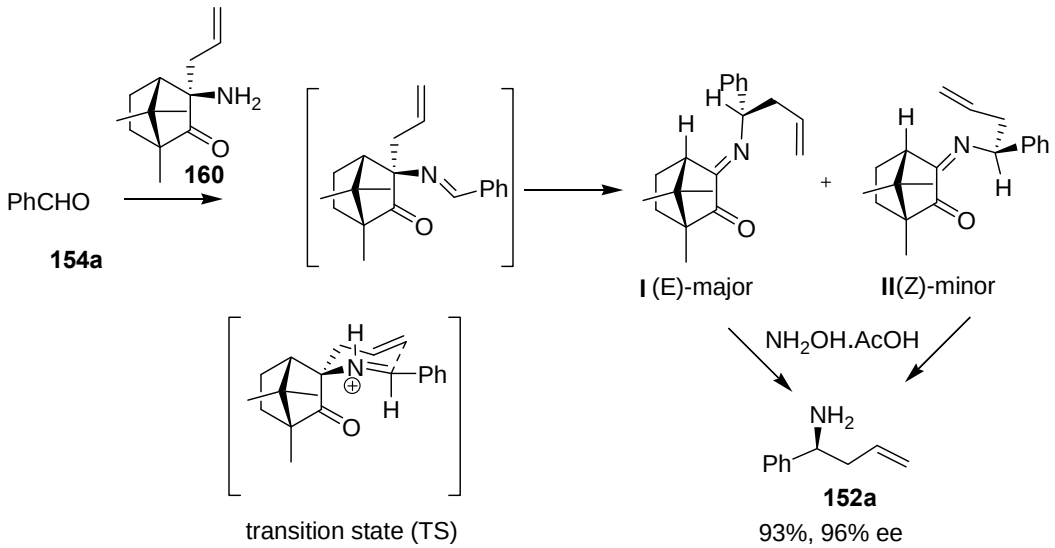
Scheme 32: Preparation of reagent **160**

When an aldehyde **154a** with a variety of substituent at α-position was subjected to asymmetric aza-Cope rearrangement using caphorquinone derived reagent **160** in presence of catalytic amount of camphorsulfonic acid (CSA) in 1,2-dichloroethane at ambient temperature followed by *in situ* imine hydrolysis with $OHNH_2$·AcOH, aminoallylation (rearrangement) takes place at the electrophilic carbon of aldehyde to give **152a** in very high ee and yield (**Scheme 33**).



Scheme 33: Asymmetric *aza*-Cope rearrangement

The mechanisim of the *aza*-Cope rearrangement is given in **Scheme 34**. The observed high enantioselectivity of the aza-Cope rearrangement attempted to isolate the rearranged product **I** and **II**. It was found that **I** (*E*) and **II** (*Z*) isomers was isolated by silica gel chromatography obtained in an 83:17 ratio. The two isomers were simply geometrical isomers of the C=N double bond. Formation of (*S*)-**152a** with high enantiomeric excess from both isomers of **I** (*E*) and **II** (*Z*) strongly supports that the rearrangement proceeded *via* chair-like transition state **TS** to give **I** (*E*) and **II** (*Z*) that is generated through isomerization of **II** (*Z*) under the acidic conditions. Finally, both isomers were converted to (*S*)-**152a** with 96% ee by treatment with hydroxylamine.

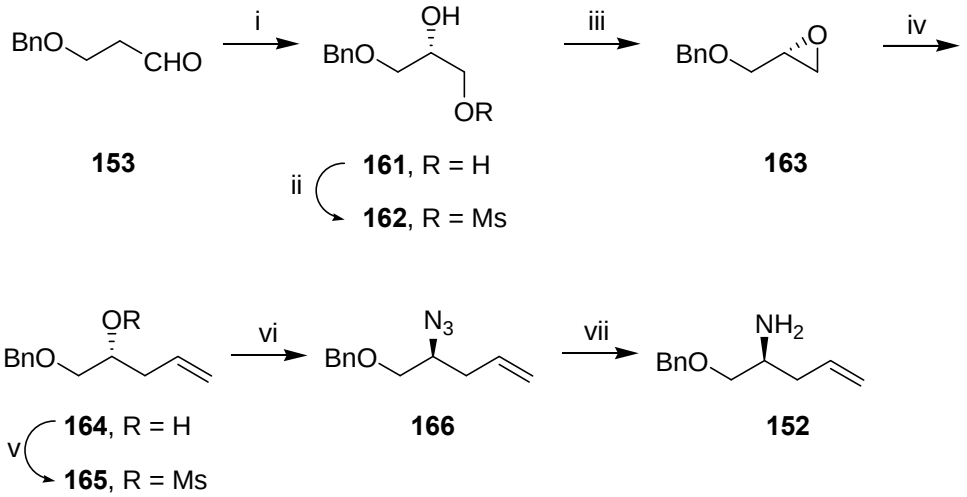


Scheme 34: Mechanistic pathway of aza-Cope rearrangement

1.2.5 Results and Discussion

1.2.5.1 Proline route:

Firstly, our synthesis of (+)-lentiginosine (**60**) had begun with the protected aldehyde **153**, prepared from the corresponding monoprotected 1,3-propanediol followed by its selective oxidation with IBX in DMSO (**Scheme 35**). The proline-catalyzed α-aminooxylation of aldehyde **153** involved a two-step reaction sequence: (i) reaction of aldehyde **153** with nitrosobenzene as electrophile in the presence of L-proline (25 mol%) in CH_3CN at -20 ^oC[54a] followed by reduction with $NaBH_4$ in MeOH to give the crude aminooxy alcohol (ii) subsequent cleavage of aminooxy moiety with 30 mol% $CuSO_4$[61] to yield the chiral diol **161** in 54% yield.



Scheme 35: Reaction conditions: (i) (a) L-proline (25 mol%), PhNO, CH_3CN, -23 ^oC, 24 h; then $NaBH_4$, MeOH, 0 ^oC, 1 h; (b) $CuSO_4$ (30 mol%), MeOH, 12 h, 54%; (ii) MsCl, Et_3N, CH_2Cl_2, 0 ^oC; (iii) K_2CO_3, MeOH, 91% for two steps; (iv) CH_2=CHMgBr, CuI (40 mol%), THF, -40 ^oC, 92%; (v) (a) MsCl, Et_3N, CH_2Cl_2, 45 min, 94%; (vi) NaN_3, DMF, 85 ^oC, 87%; (vii) $LiAlH_4$, THF, 0-25 ^oC, 93%.

The formation of diol **161** was confirmed by its ^1H NMR spectrum, which showed the appearance of typical signals at δ 3.51-3.62 (m, 2H), 3.64-3.74 (m, 2H) and 3.83-3.95 (m, 1H) corresponding to protons attached to diol oxygen atoms. Further, its ^{13}C NMR

spectrum showed characteristic carbon signals at δ 63.7, 70.7, 71.3 and 73.2 corresponding to carbons attached to oxygen atoms (**Fig. 13**).

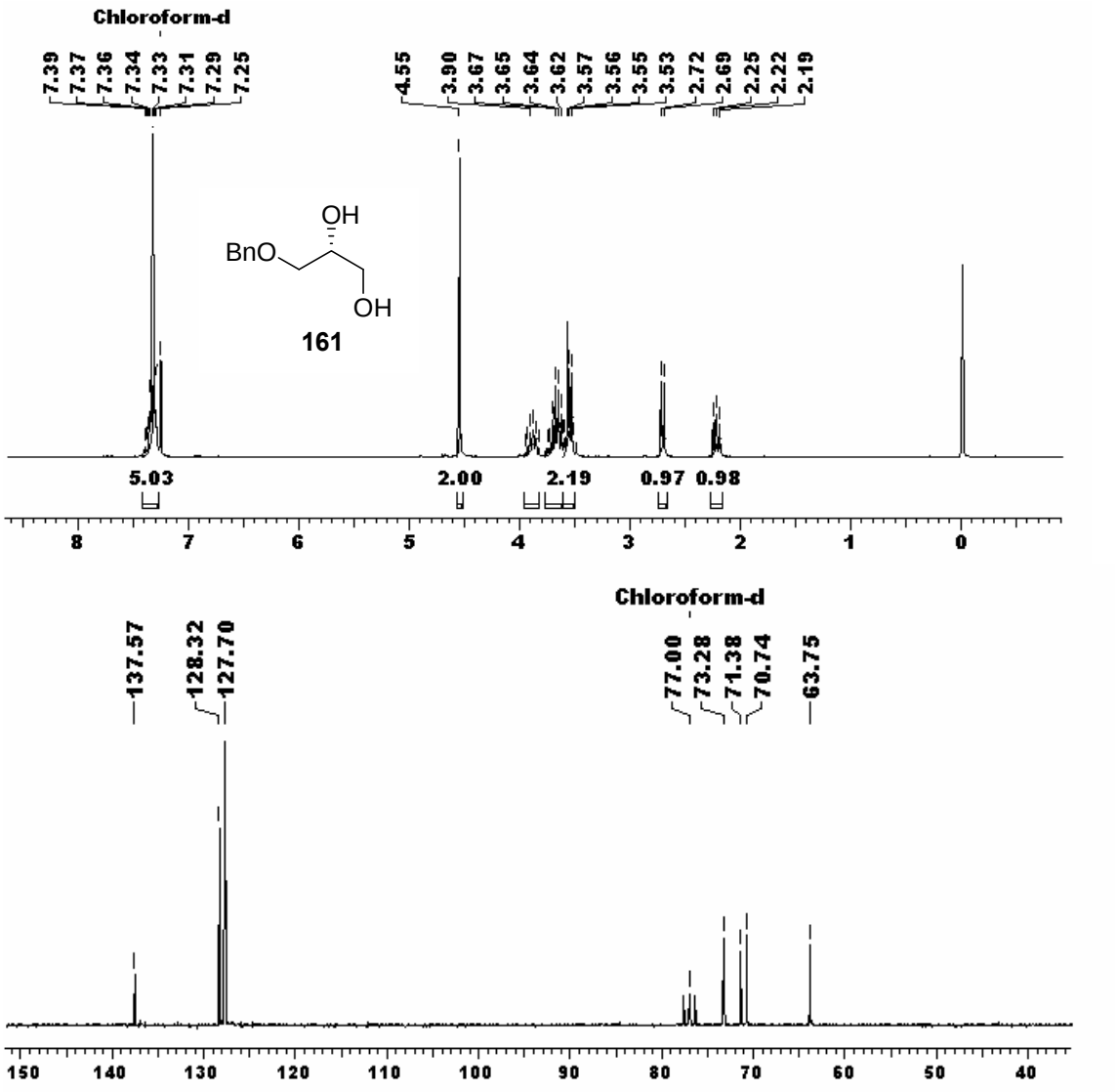


Fig. 13: ^{1}H and ^{13}C NMR spectra of diol **161**

Selective mesylation of diol **161** (MsCl, Et_3N) gave the corresponding mesylate, which on treatment with K_2CO_3 in MeOH yielded the terminal chiral epoxide **163**; $[\alpha]_D^{25}$ –5.3 (*c* 4.5, toluene). Its ^{1}H NMR spectrum showed characteristic proton signals at δ 2.61 (dd, *J*

= 5.4, 1.2 Hz, 1H), 2.79 (dd, *J* = 4.8, 1.0 Hz, 1H) and 3.15-3.22 (m, 1H) due to epoxide moiety. Its ^{13}C NMR spectrum displayed typical signals at δ 44.1 and 50.7 corresponding to methylene and methine carbons respectively of epoxide **163** (**Fig. 14**).

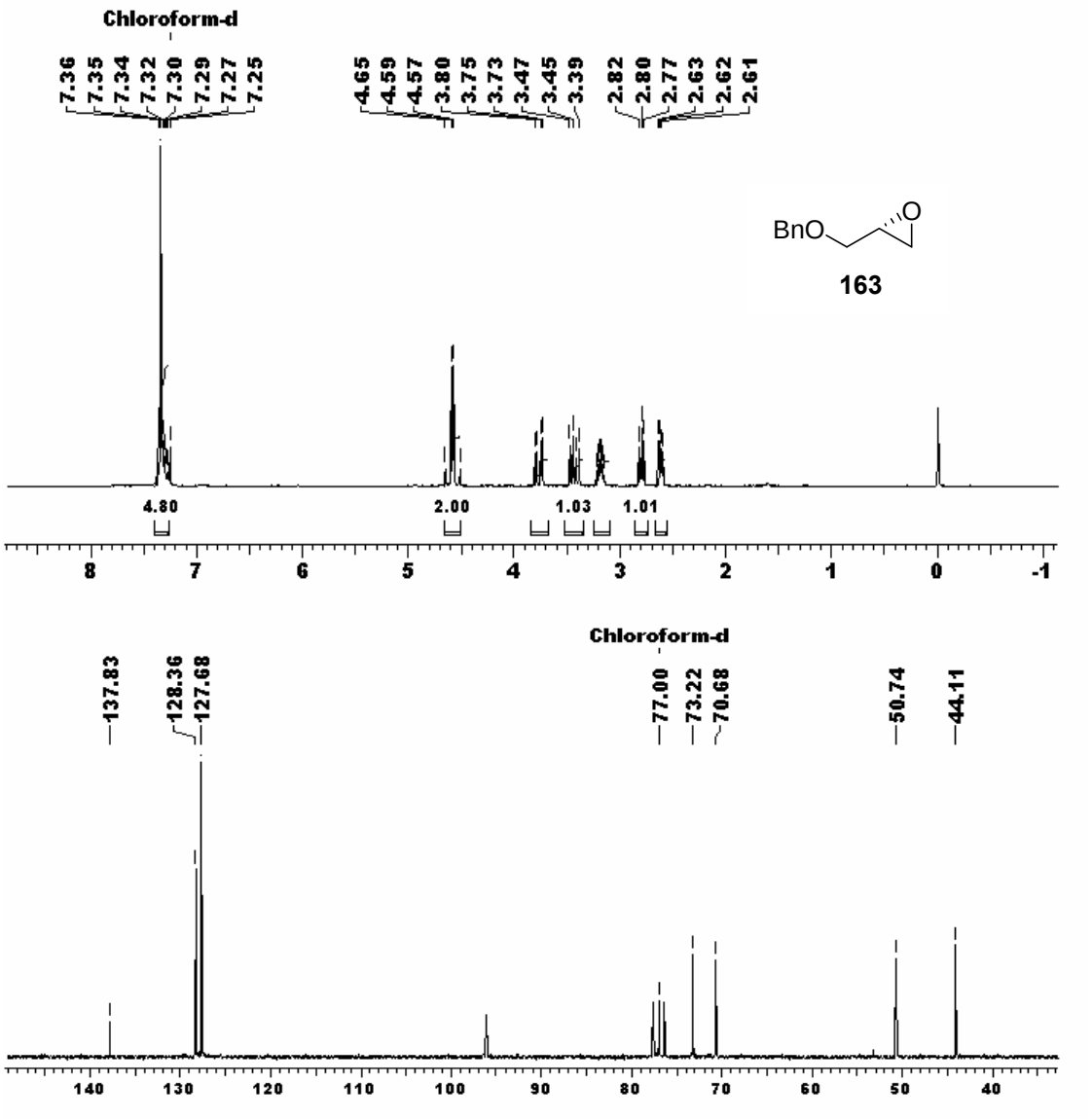


Fig. 14: ^{1}H and ^{13}C NMR spectra of epoxide **163**

Regioselective ring opening of epoxide **163** with vinylmagnesium bromide in the presence of CuI (40 mol%)[62] in THF at -40 ^{o}C gave homoallylic alcohol **164** in 92% yield. Two multiplets shown at δ 5.06 and 5.71 integrating for one proton each, in its ^{1}H

NMR spectrum are due to the presence of olefinic protons. This was further substantiated by the appearance of the typical carbon signals at δ 117.5 and 134.2 in its ^{13}C NMR spectrum (**Fig. 15**).

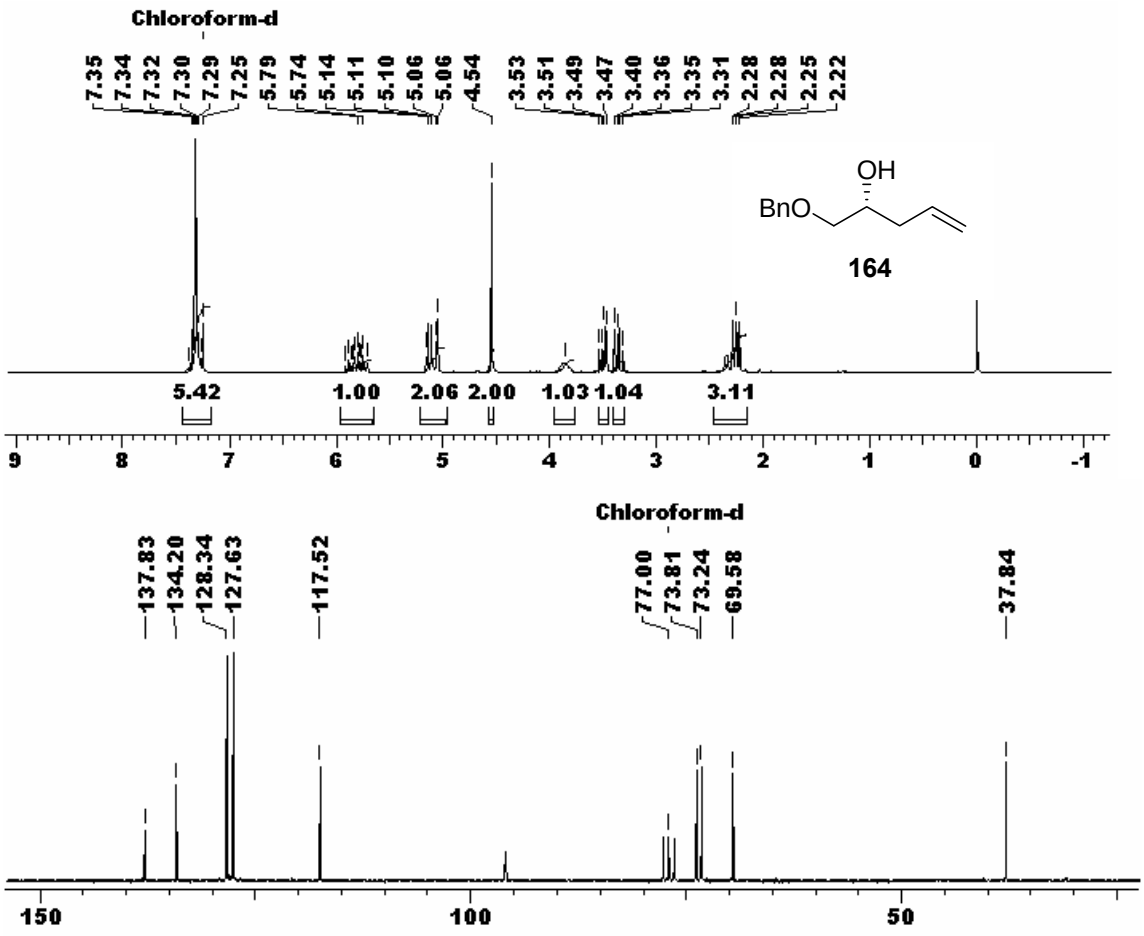


Fig. 15: ^{1}H and ^{13}C NMR spectra of homoallylic alcohol **164**

The nucleophilic displacement of mesylate **165**, obtained from alcohol **164**, with NaN_3 in DMF at 80 ^{o}C yielded the corresponding azide **166** in 87% yield. Its IR spectrum has displayed a characteristic strong band at 2112 cm^{-1} for azide function. The selective reduction of azide function in **166** using $LiAlH_4$ gave homoallylic amine **152** in 93% yield and 95% ee; $[\alpha]^{25}_{D}$ = +7.4 (*c* 1, $CHCl_3$). Its ^{1}H NMR spectrum showed a broad singlet at δ 1.61 due to -N**H**$_2$ function and a multiplet appearing at δ 3.0-3.12 (m) due to

methine proton. Its ^{13}C NMR spectrum showed a typical signal at δ 50.2 due to methine carbon attached to amine (-**C**-NH_2) (**Fig. 16**). Its IR spectrum displayed characteristic absorption bands at 3418 and 3297 cm^{-1} (strong) due to primary amine function. Since the L-proline-based route for obtaining key intermediate **152** involved several steps, thus obtaining an overall reduced yield, an alternative strategy which focused on asymmetric *aza*-Cope rearrangement of aldehyde leading to synthesis of homoallylic amine **152** was developed.

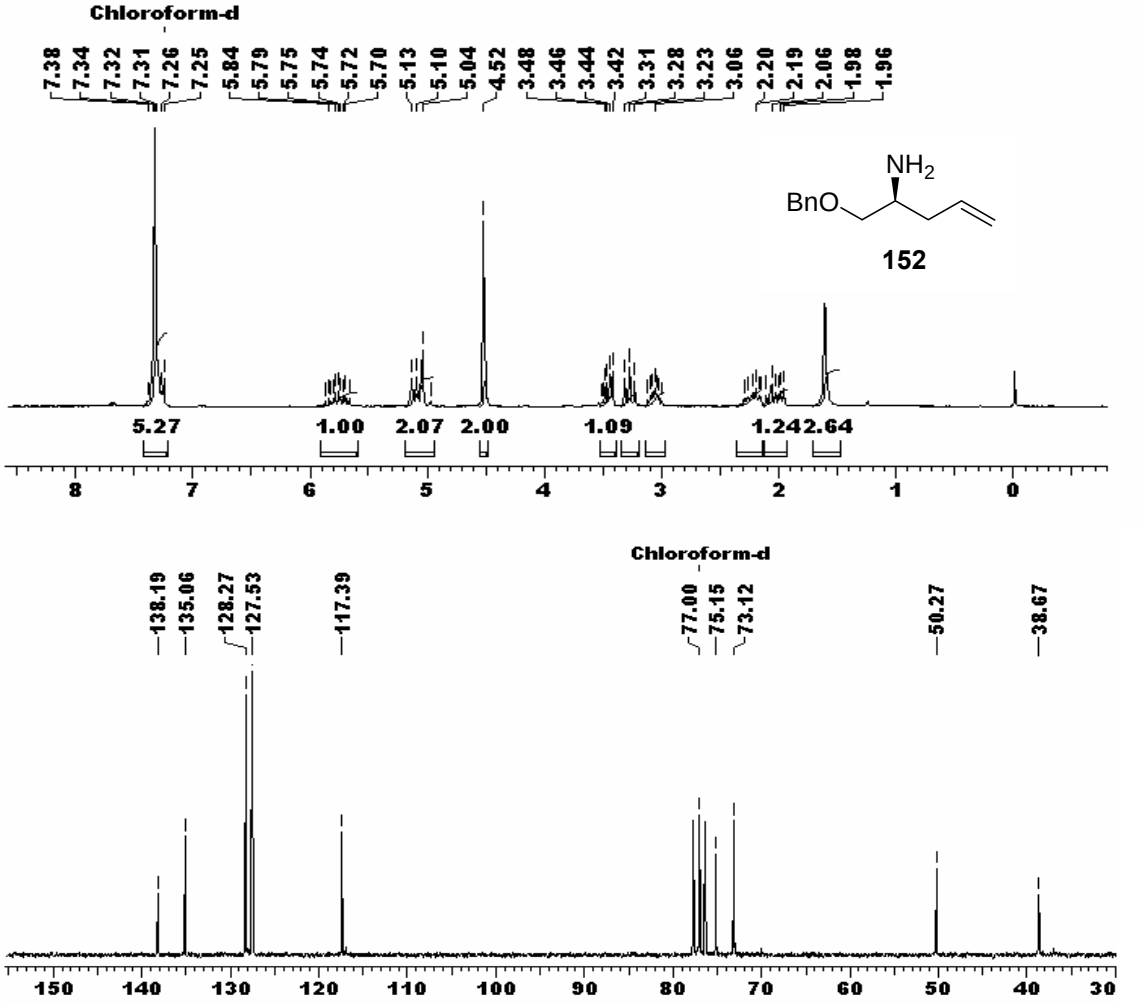
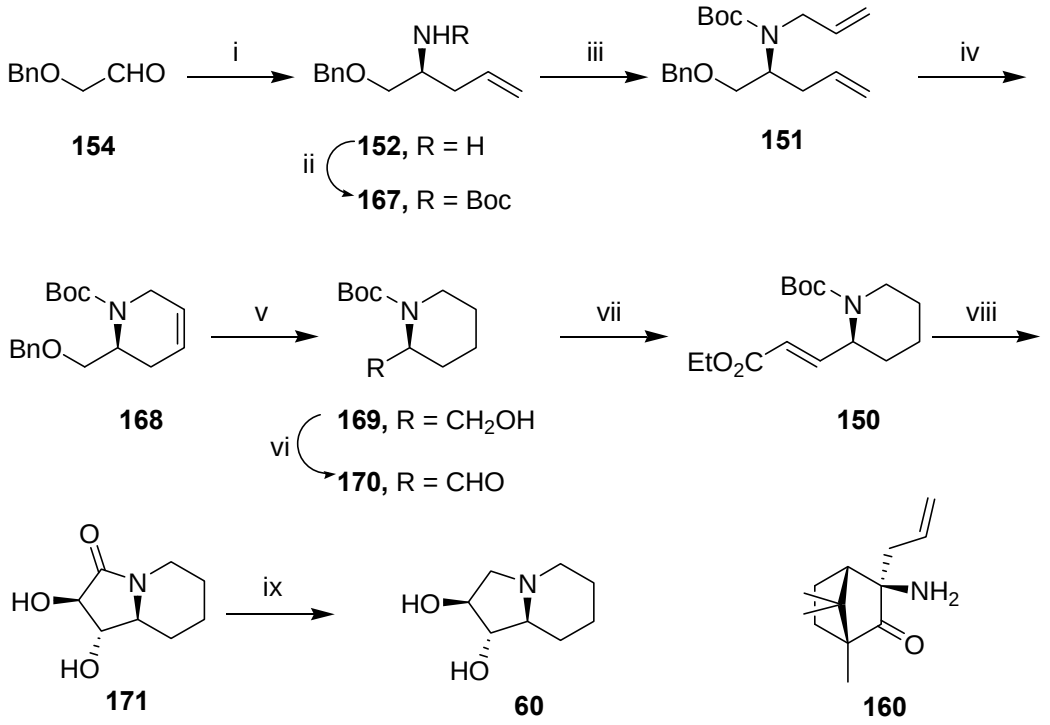


Fig. 16: ^{1}H and ^{13}C NMR spectra of homoallylic amine **152**

1.2.5.2 *Aza*-Cope rearrangement route

In the second route, an elegant synthesis of (+)-lentiginosine **60** has been achieved starting from benzyl protected acetaldehyde **154**. Asymmetric *aza*-Cope rearrangement was performed on aldehyde **154** using Kobayashi protocol[63] [(CSA (10 mol%), chiral auxiliary **160** (1 equiv.), $NH_2OH.AcOH$, 1,2-dichloroethane] exclusively (*S*)-homoallylic amine **152** in 87% yield and 96% ee (**Scheme 36**).



Scheme 36: Reaction conditions: (i) camphorsulfonic acid (10 mol%), (1*R*,3*R*,4*S*)-3-allyl-3-amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (**160**) (1 equiv.), 1,2-dichloroethane, $NH_2OH{\cdot}AcOH$, 25 ^oC, 24 h, 87%; (ii) $(Boc)_2O$, DMAP (10 mol%), Et_3N, CH_2Cl_2, 25 ^oC, 10 h, 95%; (iii) NaH, allyl bromide, dry DMF, 0-25 ^oC, 5 h, 88%; (iv) Grubbs' 2nd generation catalyst (10 mol%), dry CH_2Cl_2, 20 h, reflux, 78%; (v) 10% Pd/C, H_2 (20 psi), MeOH, 25 ^oC, 8 h, 88%; (vi) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^oC; (vii) $Ph_3P{=}CHCO_2Et$, benzene, 50 ^oC, 14 h, 90%; (viii) OsO_4, NMO, ^{t}BuOH:H_2O, 25 ^oC, 24 h; then TFA, 18 h, 58%; (ix) $LiAlH_4$, THF, reflux, 12 h, 82%.

Homoallylic amine **152** was selectively protected as its Boc derivative [$(Boc)_2O$, DMAP, Et_3N, CH_2Cl_2] to give mono-Boc protected amine **167**. A singlet at δ 1.42 in its ^1H NMR spectrum confirmed the presence of *tert*-butyl group (-NH-(C**H$_3$**)$_3$). The display of a

broad singlet at δ 1.64 further indicated the presence of NH proton (-N**H**-Boc). Its ^{13}C NMR spectrum displayed characteristic signals at δ 28.2 and 79.1 due to the [-NH-(C=O)-O-**C**-(**C**H_3)$_3$] methyl and tertiary carbons respectively of *tert*-butyl group. Further, a typical signal at δ 155.4 in its ^{13}C NMR spectrum is due to carbonyl carbon of the Boc moiety.

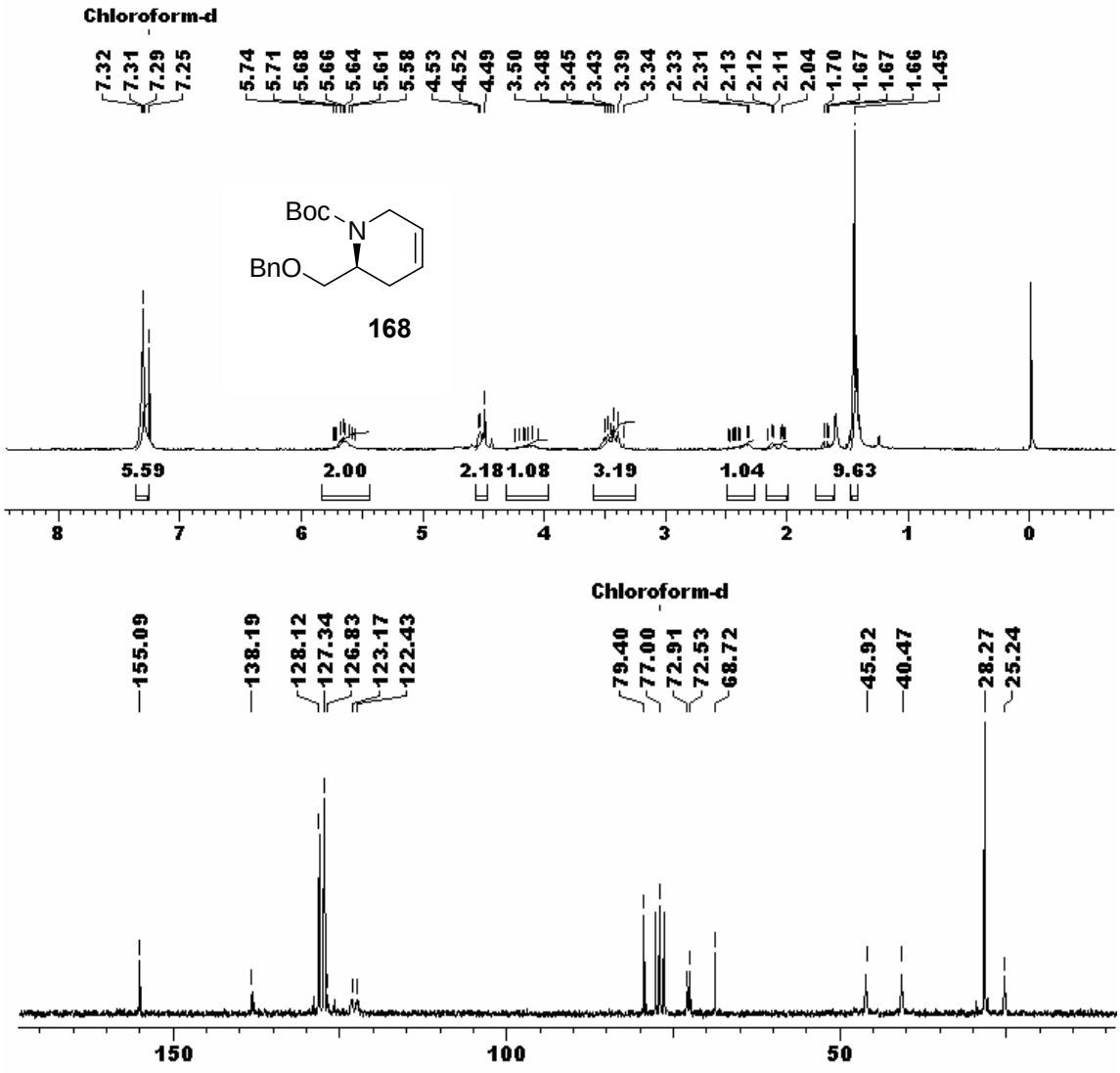
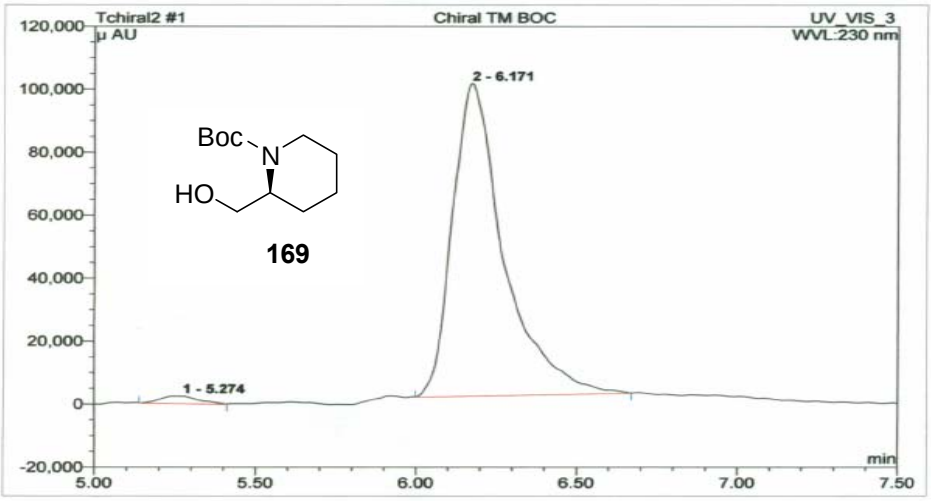


Fig. 17: ^{1}H and ^{13}C NMR spectra of dihydropyridine **168**

The N-allylation of **167** (allyl bromide, NaH) gave the RCM precursor **151** in 88% yield. Ring closing metathesis of diene **151** using Grubbs' second generation catalyst, (10

mol%) in refluxing dichloromethane proceeded smoothly to give dihydropyridine **168** in 78% yield. Its ^{1}H NMR spectrum displayed a typical multiplet at δ 5.56-5.74 for olefinic protons, confirming the formation of dihydropyridine **168**. Its ^{13}C NMR displayed typical signals at δ 122.4 and 123.1 for the **-C=C-** carbons present in dihydropyridine **168**. The other signals appearing at δ 28.2, 79.4, 155.0 and 72.9 are due to the protecting Boc and benzyl groups respectively (**Fig**. **17**).

The hydrogenation of C=C bond coupled with the removal of benzyl group in dihydropyridine **168** was achieved using 10% Pd/C, H_2 (20 psi) to give piperidine alcohol **169** in 88% yield. The enantiomeric purity of alcohol **169** was determined to be 98% ee by HPLC analysis (**Fig. 18**).



#	Name	RT (min)	Area [µV.sec]	% Area
1	T1	5.27	218.92	1.20
2	T2	6.17	18392.14	98.80

Fig. 18: HPLC chromatogram of piperidine alcohol **169**

The Swern oxidation of piperidine alcohol **169** produced piperidine carboxaldehyde **170**, in 93% yield, which on Wittig olefination with stabilized Wittig salt ($Ph_3P=CHCO_2Et$)

gave α, β-unsaturated ester **150** in 90% yield. The IR spectrum of ester **150** showed a strong absorption band at 1730 cm^{-1} that corresponds to the presence of ester carbonyl moiety. Its ^{1}H NMR spectrum displayed two characteristic signals at δ 1.28 (t, J = 7.0 Hz) and 4.17 (q, J = 7.0 Hz) corresponding to -$CO_2C\mathbf{H}_2C\mathbf{H}_3$ group. The olefinic protons of α, β-unsaturated ester have displayed signals at δ 5.77 (dd, J = 2.1, 13.7 Hz) and 6.84 (dd, J = 4.0, 12.0 Hz). Its ^{13}C NMR spectrum displayed carbon signals at δ 166.0 and δ 154.8 due to carbonyl carbons of -$\mathbf{C}O_2$Et and Boc respectively **(Fig. 19)**.

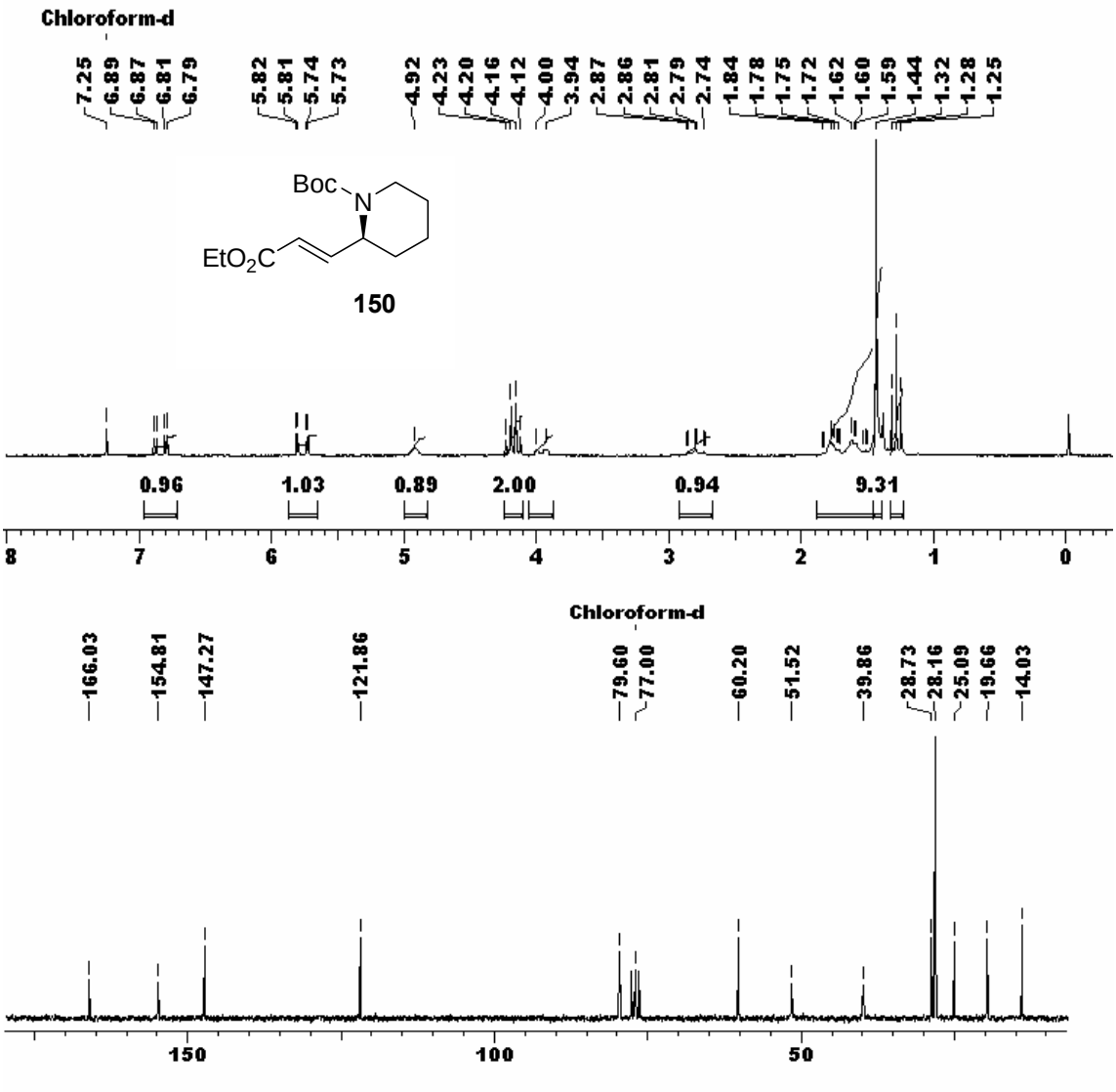


Fig. 19: ^{1}H and ^{13}C NMR spectra of α, β-unsaturated ester **150**

The Os-catalyzed diastereoselective dihydroxylation of α, β-unsaturated ester **150** furnished the corresponding diol *in situ* in 87% yield, which on Boc deprotection followed by refluxing the crude mixture in EtOH produced indolizidinone **171** (dr = 3:2). It was purified by column chromatography followed by repeated recrystallization[46] gave a single diastereomer **171** in 58% overall yield.

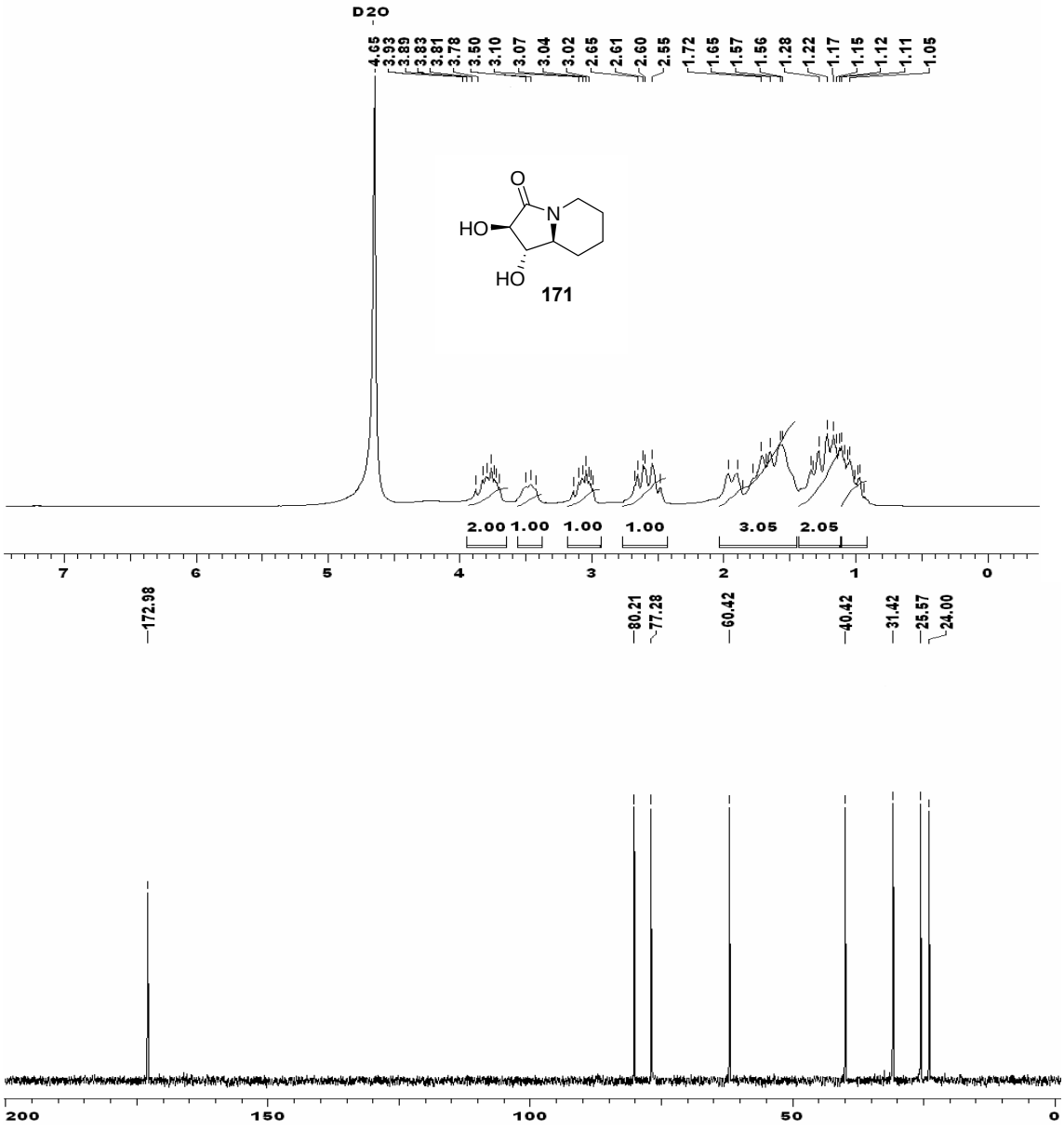


Fig. 20: ^{1}H and ^{13}C NMR spectra of indolizidinone **171**

Its ^{1}H NMR spectrum showed characteristic multiplets at δ 3.02-3.07 (m) and 3.10-3.50 (m); while a characteristic carbon signal at δ 172.0 in its ^{13}C NMR spectrum confirmed

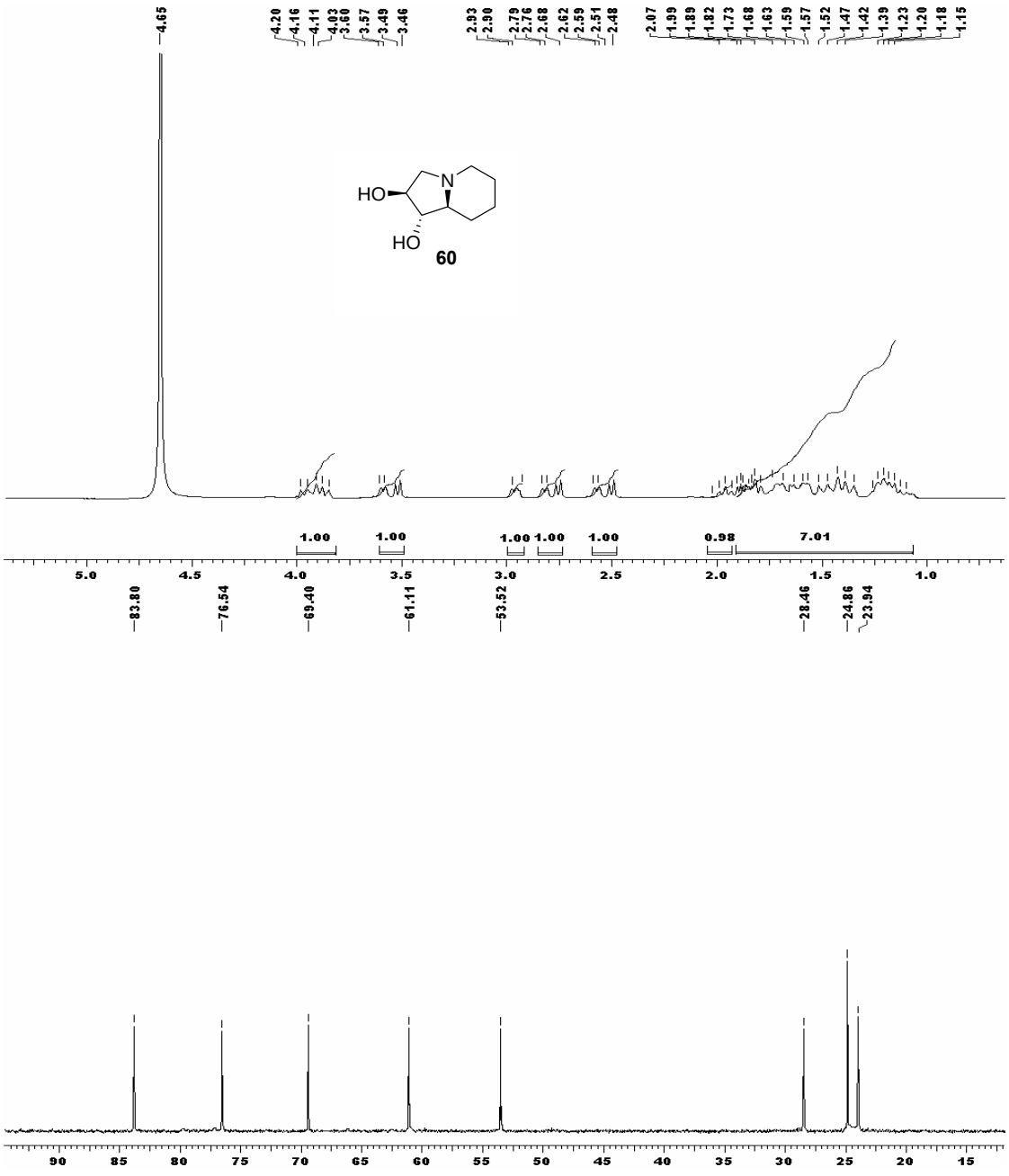


Fig. 21: ^{1}H and ^{13}C NMR spectra of (+)-lentiginosine **60**

the formation of diol with strained five-membered amide of indolizidinone **171 (Fig. 20)**. Finally, $LiAlH_4$ reduction of indolizidinone carbonyl in **171** was carried out that

produced (+)-lentiginosine **60** in 82% yield, whose spectral values (mp ^{1}H and ^{13}C NMR, $[\alpha]_D$, etc) are in complete agreement with the reported values[43,48] (**Fig. 21**).

1.2.6 Conclusion

In conclusion, a short enantioselective synthesis of (+)-lentiginosine **60** has been described based on asymmetric *aza*-Cope rearrangement and L-proline catalyzed α-aminooxylation of aldehydes. Our route to (+)-lentiginosine emphasizes an organocatalytic and metal-free approach demonstrating a shortest route to key intermediate homoallylic amine **152** and should hold promise for the synthesis of similar alkaloids. The synthesis also involves RCM strategy for the construction of piperidine core.

1.2.7 Experimental section

(R)-3-(Benzyloxy)propane-1,2-diol (161)

To a pre-cooled (-20 ^{o}C) acetonitrile (50 mL) solution of aldehyde **153** (5.0 g, 30.4 mmol) and nitrosobenzene (1.68 g, 15.7 mmol) was added L-proline (0.49 g, 25 mol %). The reaction mixture was allowed to stir at the same temperature for 24 h, followed by the addition of MeOH (20 mL) and $NaBH_4$ (2.31 g, 60.9 mmol) to the reaction mixture, which was stirred for 20 min. After the addition of saturated aq. NH_4Cl, the resulting mixture was extracted with EtOAc (3 x 60 mL) and the combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude aminooxy alcohol, which was directly used for the next step without purification. To a MeOH (50 mL) solution of the crude aminooxyalcohol was added $CuSO_4{\cdot}5H_2O$ (1.28 g, 5.1 mmol) at 0 ^{o}C. The reaction mixture was allowed to stir for 10 h at this temperature. After the addition of the phosphate buffer, the resulting mixture was extracted with $CHCl_3$ (3 x 60 mL) and the

combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude diol, which was then purified by column chromatography over silica gel using petroleum ether:EtOAc (6:4) to give diol **161** as a colorless oil.

Yield: 54% (1.5 g); $[\alpha]_D^{25}$ = +5.5 (*c* 10, $CHCl_3$); **IR** ($CHCl_3$ cm^{-1}): 3684, 3615, 3472, 3020, 2927, 2400, 1602, 1521, 1455, 1424, 1216, 1094, 1051, 929, 850, 770, 660; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.22 (dd, *J* = 5.4, 1.2 Hz, 1H), 2.70 (d, *J* = 4.8 Hz, 1H), 3.59-3.60 (m, 2H), 3.62-3.74 (m, 2H), 3.83-3.95 (m, 1H), 4.55 (s, 2H), 7.29-7.39 (m, 5 H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 63.7, 70.7, 71.3, 73.2, 127.7, 128.3, 137.5; **Anal. Calcd for** $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.89, H, 7.68%.

(R)-2-(benzyloxymethyl)oxirane (163)

A solution of diol **161** (1.5 g, 8.2 mmol) in CH_2Cl_2 (40 mL) was treated with methane sulfonyl chloride (0.98 mL, 12.3 mmol) and Et_3N (2.29 mL, 16.48 mmol) at 0 ^oC. After being stirred for 35 min, the mixture was extracted with CH_2Cl_2 (3 x 100 mL), washed with water and the combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude mesylate **162**, which was subjected to epoxidation without further purification. To a solution of mesylate **162** (1.96 g, 7.5 mmol) in MeOH (40 mL) was added anhyd. K_2CO_3 (1.03 g, 7.5 mmol) and the mixture was stirred at 25 ^oC for 1 h. After the reaction was completed (monitored by TLC), the mixture was evaporated and the residue extracted with diethyl ether (3 x 80 mL). The combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude product, which was then purified by column chromatography over silica gel using petroleum ether:EtOAc (8:2) to give epoxide **163** as a colorless oil.

Yield: 91% (1.6 g); $[\alpha]_D^{25}$ = –5.3 (*c* 4.5, toluene); **IR** ($CHCl_3$ cm^{-1}): 877, 985, 1216, 1387, 1452, 1476, 3018, 3435; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.61 (dd, *J* = 2.6, 5.0 Hz, 1H), 2.79 (dd, *J* = 4.2, 1.0 Hz, 1H), 3.15-3.22 (m, 1H), 3.43 (dd, *J* = 5.8, 5.5 Hz, 1H), 3.76 (dd, *J* = 2.9, 8.5 Hz, 1H), 4.58 (d, J = 3.8 Hz, 2H), 7.27-7.36 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 44.1, 50.7, 70.6, 73.2, 127.6, 127.9, 128.3, 137.8; **Anal. Calcd for** $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.20, H, 7.29%.

(R)-1-(benzyloxy)pent-4-en-2-ol (164)

Vinyl bromide (6.44 M in THF, 6 mL, 38.36 mmol) was added slowly to Mg (0.4 g, 19.1 mmol) in THF (20 mL) at 0 ^oC and the mixture was stirred for 10 min; then cooled to -40 ^oC and CuI (0.52 g, 30 mol %) was added. The resulting reaction mixture was stirred for 30 min at -40 ^oC and a solution of epoxide **163** (1.5 g, 9.14 mmol) in THF (25 mL) was added. After being stirred for 3 h, the mixture was quenched with saturated aq. NH_4Cl solution, extracted with diethyl ether (3 X 80 mL), washed with brine and the combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude product, which was then purified by column chromatography over silica gel using petroleum ether:EtOAc (7:3) to give alcohol **164** as a colorless oil.

Yield: 92% (1.6 g); $[\alpha]_D^{25}$ = –2 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$ cm^{-1}): 1243, 1670, 2930, 3010, 3415; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.21-2.29 (m, 1H), 2.34 (bs, 1H), 3.33 (dd, *J* = 7.3, 2.0 Hz, 1H), 4.5 (s, 2H), 5.06-5.16 (m, 2H), 5.71-5.92 (m, 1H), 7.27-7.38 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 37.8, 69.5, 73.2, 73.8, 117.5, 127.6, 128.3, 134.2, 137.8; **Anal. Calcd for** $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.88, H, 8.27%.

(R)-1-(benzyloxy)pent-4-en-2-yl methanesulfonate (165)

To a stirred solution of alcohol **164** (2.5 g, 13 mmol) in CH_2Cl_2 (40 mL) was added Et_3N (3.6 g, 26.0 mmol) at 0 ^oC. After 10 min, methanesulfonyl chloride (1.5 g, 19.5 mmol) was added drop-wise. The reaction mixture was then stirred for another 1 h at 0 ^oC and brought to room temperature. After completion of the reaction as monitored by TLC, it was quenched with water and extracted with CH_2Cl_2 (3 x 50 mL) washed with water, brine and dried over anhyd. Na_2SO_4. The combined organic layer was concentrated under reduced pressure to obtain crude mesylate **165**, which was purified by column chromatography using petroleum ether:ethyl acetate (6:4) to give pure mesylate **165** as a viscous liquid.

Yield: 94% (3.3 g); $[\alpha]_D^{25}$ = –4.76 (*c* 0.84, $CHCl_3$); **IR** ($CHCl_3$ cm^{-1}): 3085, 3031, 2867, 2360, 1647, 1456, 1357, 1174, 1116, 910, 781, 705, 649; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.49 (t, *J* = 6.6, 13.3 Hz, 2H), 3.0 (s, 3H), 3.61 (t, *J* = 3.7 Hz, 2H), 4.51-4.58 (q, *J* = 11.7 Hz, 2H), 4.80-4.85 (m, 1H), 5.14-5.18 (m, 2H), 5.74-5.82 (m, 1H), 7.28-7.36 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 36.2, 38.4, 70.8, 73.2, 81.0, 119.1, 127.6, 127.7, 128.3, 131.7, 137.2; **Anal.** Calcd for $C_{13}H_{18}O_4S$: C, 57.76; H, 6.71; S, 11.86. Found: C, 57.80, H, 6.69; S, 11.79%.

1-[(S-2-azidopent-4-enyloxy)methyl] benzene (166)

To a stirred mixture of crude methane sulfonate ester **165** (2 g, 7.3 mmol) in DMF (30 mL) was added sodium azide (2.4 g, 37 mmol), and the reaction mixture was heated at 80 ^oC for 15 h. After completion of the reaction as monitored by TLC, it was extracted with EtOAc (3 x 50 mL), washed with water, brine and dried over anhyd. Na_2SO_4. The combined organic layer was concentrated under reduced pressure to give the crude

homoallylic azide, which was purified by column chromatography using petroleum ether:ethyl acetate (9:1) to give **166**.

Yield: 87 (1.4 g); $[\alpha]_D^{25}$ = –7.27 (*c* 1.1, $CHCl_3$); **IR** ($CHCl_3$ cm^{-1}): 2959, 2112, 1650, 1216, 640; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.26-2.33 (m, 2H), 3.48-3.61 (m, 3H), 4.56 (s, 2H), 5.08-5.18 (m, 2H), 5.68-5.89 (m, 1H), 7.28-7.36 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 35.2, 60.9, 72.06, 73.2, 118.1, 127.4, 127.6, 128.3, 133.4, 137.7; **Anal.** Calcd for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.34. Found: C, 66.29, H, 6.89; N, 19.30%.

Proline route: (S)-1-(Benzyloxy)pent-4-en-2-amine (152)

To a stirred mixture of $LiAlH_4$ (0.350 g, 9.21 mmol) in anhyd. THF (20 mL) was added homoallylic azide **166** (1 g, 4.60 mmol) in THF (10 mL) at 0 ^oC. The reaction mixture was stirred at 25 ^oC for 10 h. After completion of the reaction as monitored by TLC, it was quenched with ice-cold water and 20% aq. NaOH. This crude mixture was passed through anhyd. Na_2SO_4 and washed thoroughly with EtOAc (3 x 50 mL) and the solvent evaporated under reduced pressure to give the crude homoallylic amine, which was purified by column chromatography using $CHCl_3$: MeOH (9:1) to give **152** as colorless oil.

Yield: 93% (0.820 g); $[\alpha]_D^{25}$ = +7.40 (*c* 1, $CHCl_3$) {lit.[63] $[\alpha]_D^{25}$ = +7.1 (c 1.14, $CHCl_3$)}

Aza-Cope rearrangement: (S)-1-(Benzyloxy)pent-4-en-2-amine (152)

To a solution of chiral amine **160** (2.072 g, 10 mmol) and aldehyde **154** (1.5 g, 10 mmol) in 1,2- dichloroethane (20 mL) was added camphorsulfonic acid (0.232 g, 10 mol%) at 0 °C. The mixture was stirred at the 0 ^oC for 24 h. Then, a solution of $HONH_2$•AcOH in methanol [0.5 M, 2 mL, prepared from $HONH_2$•HCl, NaOH (solid, 1 equiv), and AcOH (1 equiv) in methanol] was added to the solution. After being stirred at 50 °C for 3 h, the

mixture was cooled to 25 ^{o}C, acidified with 1 N aq. HCl (pH = 1). The mixture was washed with dichloromethane (3 x 50 mL), basified with 6 N aqueous NaOH (pH = 10), and extracted with dichloromethane (3 x 50 mL). The combined solvent layers were dried over anhyd. Na_2CO_3, filtered, and evaporated to give amine **152**. The crude product was purified by column chromatography (pet ether:EtOAc = 1:1) to give pure amine **152**.

Yield: 87% (1.65 g); $[\alpha]_D^{25} = +7.1$ (*c* 1.46, $CHCl_3$), {lit.[63] $[\alpha]_D^{25} = +7.1$ (c 1.14, $CHCl_3$)}; **IR** ($CHCl_3$ cm^{-1}): 3418, 3297, 3020, 1618, 761, 670; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.6 (s, 2H), 1.96-2.10 (m, 1 H), 2.16-2.30 (m, 1 H), 3.0-3.12 (m, 1H), 3.28 (t, *J* = 3.0 Hz, 1H), 3.42-3.48 (dd, *J* = 4.3, 4.8 Hz, 1H), 4.52 (s, 1H), 5.10 (t, *J* = 10.3 Hz, 2H), 5.67-5.87 (m, 1H), 7.31-7.38 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 38.6, 50.2, 73.1, 75.1, 117.3, 127.5, 128.2, 135.0, 138.1; **Anal.** Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.29, H, 8.91, N, 7.28%.

***tert*-Butyl (S)-1-(benzyloxy)pent-4-en-2-ylcarbamate (167)**

To a solution of amine **152** (4 g, 20.9 mmol) in dry CH_2Cl_2 (40 mL) were added dry Et_3N (4.3 mL, 31.38 mmol, $(Boc)_2O$ (5.47 g, 25.2 mmol) and DMAP (0.255 g, 10 mol%), and the reaction mixture stirred for 10 h. After completion of the reaction as monitored by TLC, it was extracted with CH_2Cl_2 (3 x 60 mL), washed with brine and dried over anhyd. Na_2SO_4 and concentrated to give the crude product, which was then purified by column chromatography over silica gel using petroleum ether:EtOAc (7:3) to give carbamate **167** as a colorless oil.

Yield: 95% (5.8 g); $[\alpha]_D^{25} = -5.81$ (*c* 0.86, $CHCl_3$); **IR** ($CHCl_3$ cm^{-1}): 3750, 3690, 3021, 2928, 2357, 1708, 1425, 1216, 764, 670; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.42 (s, 9H), 1.64 (brs, 1H), 2.29-2.36 (m, 2H), 3.40-3.53 (m, 2H), 4.50 (d, *J* = 2.4 Hz, 2H), 5.01-5.12

(m, 2H), 5.65-5.86 (m, 1H), 7.27-7.35 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 28.2, 36.3, 49.8, 71.0, 73.0, 79.1, 117.5, 127.5, 128.2, 134.4, 138.0, 155.4; **Anal.** Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.11, H, 8.59; N, 4.78%.

***tert*-Butyl allyl-(S)-1-(benzyloxy)pent-4-en-2-ylcarbamate (151)**

To a solution of NaH (0.494 g, 12.35 mmol) in dry DMF (30 mL) were added Boc protected amine **167** (3 g, 10.29 mmol) at 0 ^{o}C. After 15 min, allylbromide (1 mL, 12.35 mmol) was added drop- wise. The reaction mixture was then stirred for 6 h at 25 ^{o}C. After completion of the reaction as monitored by TLC, it was extracted with CH_2Cl_2 (3 x 50 mL), washed with brine and dried over anhyd. Na_2SO_4 and concentrated to give the crude product, which was then purified by column chromatography over silica gel using petroleum ether:EtOAc (9:1) to give **151** as a colorless oil.

Yield: 88% (3.0 g); $[\alpha]_D^{25}$ = +2.05 (*c* 1.46, $CHCl_3$); **IR** ($CHCl_3$ cm^{-1}): 3780, 3697, 3633, 3019, 2932, 2361, 1682, 1216, 1104, 762, 670; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.43 (s, 9H), 2.33 (t, *J* = 7.0 Hz, 2H), 3.44-3.61 (m, 2H), 3.71-3.81 (m, 2H), 4.05-4.31 (m, 1H), 4.47 (d, *J* = 5.0 Hz, 2H), 4.99-5.11 (m, 4H), 5.63-5.88 (m, 2H), 7.30 (s, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 28.2, 34.1, 47.2, 55.1, 70.9, 72.7, 79.2, 115.1, 116.1, 127.3, 128.1, 135.0, 136.0, 138.1, 155.4; **Anal.** Calcd for $C_{20}H_{29}NO_3$: C, 72.47; H, 8.82; N, 4.23. Found: C, 72.50, H, 8.79; N, 4.19%.

(S)-*tert*-Butyl-6-(benzyloxymethyl)-5,6-dihydropyridine-1(2H)-carboxylate (168)

Olefin **151** (1 g, 3 mmol) was dissolved in dry CH_2Cl_2 (40 mL) and the solution was degassed by bubbling with argon for 10 min. Then, Grubbs' 2nd generation ruthenium catalyst (256 mg, 0.30 mmol) was added. The reaction mixture was stirred for 22 h at 50 ^{o}C and then cooled and solvent was evaporated to give the residue, which was then

directly purified by column chromatography over silica gel using petroleum ether:EtOAc (8:2) to give dihydropyridine **168** as a colorless oil.

Yield: 78% (0.720); $[\alpha]_D^{25}$ = +20.0 (*c* 1.14, $CHCl_3$); **IR** ($CHCl_3$ cm^{-1}): 3443, 2978, 1685, 1413, 1227, 1115, 1028, 909, 698, 648; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.45 (s, 9H), 1.66-1.70 (m, 1H), 2.01-2.16 (m, 1H), 2.31-2.48 (m, 1H), 3.34-3.50 (m, 3H), 4.05-.24 (m, 1H), 4.51 (d, *J* = 5.4 Hz, 2H), 5.56-5.74 (m, 2H), 7.29-7.32 (m, 5 H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 25.2, 28.2, 40.4, 45.9, 68.7, 72.5, 72.9, 79.4, 122.4, 123.1, 127.3, 128.1, 128.9, 138.1, 155.0; **Anal.** Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.30, H, 8.29; N, 4.58%.

(S)-*tert*-Butyl 2-(hydroxymethyl)piperidine-1-carboxylate (169)

Dihydropyridine **168** (0.5 g, 1.65 mmol) was dissolved in MeOH (25 mL), 10% Pd/C (38 mg) was added and the mixture was stirred under H_2 (20 psi) atmosphere for 8 h. The mixture was then filtered over Celite, washed with MeOH (2 x 20 mL) and the solvent was evaporated under reduced pressure to afford alcohol **169**, which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (7:3) to give **169**.

Yield: 88% (0.320 g); Chiral Column: CHIRALCEL OD-H, length 25x4.6 mm, wavelength: 230 nm, flow rate 1.0 mL per min. Mobile phase: 5% isopropyl alcohol in hexane; ee = 98%; $[\alpha]_D^{25}$ = -40.1 (*c* 1, $CHCl_3$), {lit.[64] $[\alpha]_D^{25}$ = -40.5 (*c* 1, $CHCl_3$)}; **IR** ($CHCl_3$ cm^{-1}): 3442, 2940, 2890, 1655, 1422, 1370, 1280, 1170, 1150, 1060, 1050, 870; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.45 (s, 9H), 1.51-1.76 (m, 6 H), 2.11 (brs, 1H), 2.78-2.92 (m, 1H), 3.5-3.6 (m, 1H), 3.74-3.96 (m, 2H), 4.23-4.34 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 18.9, 24.4, 24.9, 28.0, 39.5, 51.7, 60.0, 79.1, 155.5; **Anal.** Calcd for $C_{11}H_{21}NO_3$: C, 61.37; H, 9.83, N, 6.51. Found: C, 61.40, H, 9.79, N, 6.49%.

(S)-*tert*-Butyl 2-[E-2-(ethoxycarbonyl)vinyl] piperidine-1-carboxylate (150)

To a stirred solution of oxalyl chloride (0.825 g, 6.48 mmol) in CH_2Cl_2 (20 mL) at -78 ^oC, was added a solution of DMSO (0.760 g, 9.72 mmol). The reaction mixture was stirred for 20 min. followed by the addition of a solution of alcohol **169** (0.7 g, 3.24 mmol) in CH_2Cl_2 (10 mL). After stirring for 1 h at -78 ^oC, the reaction mixture was quenched by the addition of Et_3N (1.8 mL, 12.96 mmol). The reaction mixture was then stirred for 20 min. followed by the addition of water (20 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (3 x 30 mL), dried over anhyd. Na_2SO_4 and concentrated to give the corresponding crude aldehyde **170** in 0.650 g, which was subjected to Wittig olefination without purification as follows. To a solution of aldehyde **170** in dry benzene (20 mL) was added $Ph_3P{=}CHCO_2Et$ (1g, 3.0 mmol) and the reaction mixture heated at 50 ^oC for 12 h. After completion of the reaction as monitored by TLC, it was cooled to 25 ^oC, extracted with EtOAc (3 x 50 mL), washed with water, brine and dried over anhyd. Na_2SO_4 and concentrated to give the crude product, which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (8:2) to give the unsaturated ester **150** as a gum.

Yield: 90% (0.6 g); $[\alpha]_D^{25}$ = -77.48 (*c* 1.3, $CHCl_3$); **IR** ($CHCl_3$ cm^{-1}): 2940, 2862, 1730, 1700, 1665, 1440, 1410, 1370, 1310, 1280, 1270, 1160, 1050, 870, 770; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.0 Hz, 3H), 1.44 (s, 9H), 1.50-1.84 (m, 6 H), 2.73-2.87 (m, 1 H), 3.97 (d, *J* = 12.0 Hz, 1H), 4.12-4.23 (q, *J* = 7.0 Hz, 2H), 4.92 (s, 1H), 5.77 (dd, *J* = 2.1, 13.7 Hz, 1H), 6.84 (dd, *J* = 4.0, 12.0 Hz); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.0, 19.6, 25.0, 28.1, 28.7, 39.8, 51.5, 60.2, 79.6, 121.8, 147.2, 154.8, 160.0; **Anal.** Calcd for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.60, H, 8.90, N, 4.89%.

(1S,2R,8aS)-Hexahydro-1,2-dihydroxyindolizin-3(5H)-one (171)

To a solution of *tert*-butyl alcohol (5.0 mL) and water (5.0 mL) in THF (5 mL), 4-methylmorpholine N-oxide (0.39 g, 3.34 mmol) and OsO_4 (0.02 g, 0.1 M solution in toluene, 5 mol%) were added and the mixture was stirred at room temperature for 15 min. A solution of ester **150** (0.5 g, 1.76 mmol) in THF (3.0 mL) was added. After 24 h, the reaction mixture was treated with Florisil (2.0 g), and $NaHSO_3$ (1.0 g) and stirring continued for 1 h. The reaction mixture was diluted with EtOAc (20 mL), filtered through Celite and the filtrate distilled *in vacuo* to give a mixture of diols. This crude mixture of diol was stirred in 10 mL of TFA for (Boc deprotection) 10 h and evaporated solvent *in vacuo* followed by refluxing this mixture in ethanol for 6 h gave imide **171** as 3:2 ratio (80% combine yield, determined by ^{1}H and ^{13}C NMR). These compounds were separated by repeated recrystallization followed by flash column chromatographic purification on silica gel ($CHCl_3$: MeOH: Et_3N, 30:68:2) to give pure imide **171** in 58% yield.

Yield: 58%; $[\alpha]_D^{25}$ = +55.2 (*c* 1, MeOH), {lit.[42] $[\alpha]_D^{21}$ +52.3 (*c* 1.99, MeOH)}; **IR** ($CHCl_3$ cm^{-1}): 1685, 1450, 1365, 1280, 640; **^{1}H NMR** (200 MHz, CD_3OD): δ 0.94-1.09 (m, 1H), 1.12-1.22 (m, 2H), 1.28-1.56 (m, 2H), 1.57-1.91 (m, 1H), 2.55-3.08 (m, 1H), 2.55-3.08 (m, 1H), 3.44 (t, *J* = 7.0 Hz, 1H), 3.78-3.94 (m, 2H); **^{13}C NMR** (50 MHz, CD_3OD): δ 25.0, 25.9, 30.4, 41.8, 64.2, 71.2, 72.5, 172.0; **Anal.** Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.20, H, 7.59, N, 8.20%.

(+)-Lentiginosine (60)

To a stirred solution of (0.1 g, 0.584 mmol) of imide **171** in THF (10 mL) at 0 °C was added lithium aluminum hydride (0.044 g, 1.16 mmol). The suspended mixture was stirred at 65 °C for 12 h, cooled to 0 °C, diluted with 2 mL of THF, and then carefully

treated successively with water, 10% aqueous NaOH. The resulting mixture was stirred for 1 h and filtered through pad of sodium sulfate and filtrate was concentrated under reduced pressure. The crude residue was then purified by column chromatography on silica gel ($CHCl_3$: MeOH, 8:2) to give pure lentiginosine **60** as a colourless solid.

Yield: 82% (75 mg); **mp.** 103-105 ^oC [lit.[47] mp. 103-104 ^oC]; $[\alpha]_D^{25}$ = +3.0 (*c* 0.4, MeOH) {lit.[43] $[\alpha]_D^{24}$ = +3.1 (*c* 0.31, MeOH); **IR** ($CHCl_3$ cm^{-1}): 3525, 3515, 3021, 3012, 2932, 2857, 1443, 1210, 1130; **^{1}H NMR** (200 MHz, D_2O): δ 1.15-1.89 (m, 7 H), 1.99-2.07 (m, 1H), 2.55 (dd, *J* = 11.0, 7.4 Hz, 1 H), 2.73 (dd, *J* = 11.0, 2.0 Hz, 1 H), 2.93 (br d, *J* = 11.0 Hz, 1H), 3.53 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.03-4.20 (m, 1H); **^{13}C NMR** (50 MHz, D_2O): δ 23.9, 24.8, 28.4, 53.5, 61.1, 69.4, 76.5, 83.8; **Anal.** Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.20, H, 9.57, N, 8.78%.

1.2.8 Reference:

1. (a) Pinder. R. M.; Bropden, R. N.; Speight. T. M.; Avery, G. S. *Drugs*, **1977**, *13*, 321; (b) Salama, A. I.; Insalaco, J. R.; Maxwell, R. A. *J. Pharmacal. Exp. Ther.* **1971**, *178,* 474; (c) Coppen, A.; Shaw, D. M.; Herzberg, B.; Maggs, R. *Lancet II*, **1967**, 1178; (d) Carlsson, A.; Corrodi, H.; Fuxe, K.; Hokfelt, T. *Eur. J. Pharmacal.* **1969**, *5*, 357.
2. (a) Welch, W. M.; *Adv. Med. Chem*. **1995**, *3*, 113; (b) Sarges, R.; Tretter, J. R.; Tenen, S. S.; Weissman, A. *J. Med. Chem*. **1973**, *16*, 1003.
3. Welch, W. M.; Kraska, A. R.; Koe, K. *J. Med. Chem*. **1984**, *27*, 1508.
4. Quallich, G. J.; Woodwall, T. M. *Tetrahedron*, **1992**, *48*, 10239.
5. Corey, E. J.; Gant, T. G. *Tetrahedron Lett*. **1994**, *35*, 5537.
6. Lautens, M.; Rovis, T. *J. Org. Chem*. **1997**, *62*, 5246.
7. Chen, C-Y.; Reamer, R. A. *Org. Lett*. **1999**, *1*, 293.
8. Davies, H. M. L.; Stafford, D. G.; Hansen, T. *Org. Lett*. **1999**, *1*, 233.
9. Chandrashekhar, S.; Reddy, M. V. *Tetrahedron*, **2000**, *56*, 1111.
10. Boulton, L. T.; Lennon, I. C.; McCague, R. *Org. Biomol. Chem*. **2003**, *1*, 1094.
11. Taber, G. P.; Pfisterer, D. M.; Colberg, J. C. *Org. Process. Res. Dev*. **2004**, *8*, 385.
12. Dockendorff, C.; Sahli, S.; Olsen, M.; Milhau, L.; Lautens, M. *J. Am. Chem. Soc*. **2005**, *127*, 15028.
13. Wang, G.; Zheng, C.; Zhao, G. *Tetrahedron: Asymmetry*, **2006**, *17*, 2074.

14. Johnson, R. A.; Sharpless K. B. In *"*Catalytic Asymmetric Synthesis*"* VCH Publishers (New York), **1993**, Chap. 4, pp. 227-270.
15. (a) Jacobsen E. N.; Marko, I.; France, M. B.; Svendsen, J. S.; Sharpless K. B. *J. Am.Chem. Soc*. **1989**, *111*, 737; (b) Kolb, H. C.; Anderson, P. G.; Bennani, Y. L.; Crispino, G. A.; Jeong, K. S.; Kwong, H. L.; Sharpless, K. B. *J. Am. Chem. Soc*. **1993,** *115*, 12226.
16. (a) Kolb, H. C.; Van-Nieuwenhze, M, S.; Sharpless, K. B. *Chem. Rev*. **1994**, *94*, 2483; (b) Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc*. **1980**, *102*, 4263.
17. (a) Criegee, R.; Justus Liebigs *Ann. Chem***. 1996**, *522*, 75; (b) Criegee, R. *Angew. Chem. Int. Ed. Engl*. **1937**, *50*, 153; (c) Criegee, R.; Marchand, B.; Wannowias, H. Justus *Liegs. Ann. Chem*. **1942**, *550*, 99; (d) Sharpless, K. B.; Teranishi, A. Y.; Backwall, J. E. *J. Am. Chem. Soc*. **1977**, *99*, 3120; (e) Jorgensen, K. A.; Schiott, B. *Chem. Rev*. **1990**, *90*, 1483.
18. Gawley, R. A.; Aube, J. In "Principles of Asymmetric Synthesis" Elsevier Science (Oxford), **1996**, Vol. 14, (Chap. 8), pp 314-350.
19. Hoffman, K. A. *Chem. Ber.* **1912***, 45, 3329***.**
20. (a) Milas, N. A.; Sussman, S. *J. Am. Chem. Soc*. **1936**, *58*, 1302; (b) Milas, N. A.; Trepagnier, J. H.; Nolan, J. T.; Iliopulos, M. I. *J. Am. Chem. Soc*. **1959**, *81*, 4730.
21. Sharpless, K. B.; Akashi, K. *J. Am. Chem. Soc*. **1976**, *98*, 1986.
22. (a) VanRheenen, V.; Kelly, R. C.; Cha. D. Y. *Tetrahedron Lett*. **1976**, *17*, 1973; (b) Schneider, W. P.; Mclntosh, A. V. US 2769284, Nov. 6, **1956**.
23. Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968.
24. Minato, M.; Yamamota, K.; Tsuji, J. *J. Org. Chem*. **1990**, *55*, 766.
25. Sharpless K. B.; Amerg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu. D.; Zhang, X.-L. *J. Org. Chem*. **1992**, *57*, 2768.
26. Amerg, W.; Bennani, Y. L.; Chadha, R. K.; Crispino, G. A.; Davis, W. D.; Hartung, J.; Jeong, K. S.; Ogino, Y.; Shibata, T.; Sharpless K. B. *J. Org. Chem*. **1993**, *58*, 844.
27. Ishibashi, H.; Maeki, M.; Yagi, J.; Ohba. M.; Kanai, T. *Tetrahedron*, **1999**, *55*, 6075-6080.
28. (a) Aleksakis, A. Hajjaji, S. E.; Polet, D.; Rathgeb, X. *Org. Lett*. **2007**, *9*, 3393;
29. (a) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron*: *Asymmetry* **2000**, *11*, 1645-1680; (b) Elbein, A. D.; Molyneux, R. J. Alkaloid Glycosidase Inhibitors In *ComprehensiveNatural Products Chemistry*; Barton, D.; Nakanishi, K.; Meth-Cohn, O.; Eds.; Elsevier: Oxford, **1999**; Vol. 3, p 129; (c) Sears, P.; Wong, C-H. *Chem. Commun.* **1998**, 1161-1170; (d) Ganem, B. *Acc. Chem. Res.* **1996**, *29*, 340-347. (e) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683; (f) Kaushal, G. P.; Elbein, A. D. *Methods Enzymol.* **1994**, *230*, 316; (g) Look, G. C.; Fotsch, C. H.; Wong, C-H. *Acc. Chem. Res.* **1993**, *26*, 182-190; (h) Legler, G. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 319-384.
30. (a) Goti, A.; Cardona, F.; Brandi, A. *Synlett*. **1996**, 761; (b) Goti, A.; Cardona, F.; Brandi, A.;

Picasso, S.; Vogel, P. *Tetrahedron*: *Asymmetry* **1996**, *7*, 1659; (c) Nukui, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 398; (d) Cordero, F. M.; Cicchi, S.; Goti, A.; Brandi, A. *Tetrahedron Lett.* **1994**, *35*, 949.

31. (a) Hohenschutz, L. D.; Bell, E. A.; Jewess, P. J.; Leworth, D. P.; Pryce, R. J.; Arnold, E.; Clardy, J. *Phytochemistry* **1981**, *20*, 811; (b) Nash, R. J.; Fellows, L. E.; Dring, J. V.; Stirton, C. H.; Carter, D.; Hegarty, M. P.; Bell, E. A. *Phytochemistry* **1988**, *27*, 1403.
32. (a) Platt, F. M.; Neises, G. R.; Reinkensmeier, G.; Townsend, M. J.; Perry, V. H.; Proia, R. L.; Winchester, B.; Dwek, R. A.; Butters, T. D. *Science* **1997**, *276*, 428; (b) Robinson, K. M.; Begovic, M. E.; Rhinehart, B. L.; Heinke, E. W.; Ducep, J.-B.; Kastner, P. R.; Marshall, F. N.; Danzin, C. *Diabetes* **1991**, 40, 825; (d) Anzeveno, P. B.; Creemer, L. J.; Daniel, J. K.; King, C.-H.; Liu, P. S. *J. Org. Chem.* **1989**, *54*, 2539.
33. (a) Gross, P. E.; Baker, M. A.; Carver, J. P.; Dennis, J. W. *Clin. Cancer Res.* **1995**, *1*, 935.
34. (a) Ratner, L.; Heyden, N. V.; Dedera, D. *Virology* **1991**, *181*, 180; (b) Wikler, D. A.; Holan, G. *J. Med. Chem.* **1989**, *32*, 2084; (c) Karpas, A.; Fleet, G. W. J.; Dwek, R. A.; Petursson, S.; Namgoog, S. K.; Ramsden, N. G.; Jacob, G. S.; Rademacher, T. W. *Proc. Natl. Acad. Sci. U. S. A.* **1988**, *85*, 9229.
35. Pastuszak, I.; Molyneux, R. J.; James, L. F.; Elbein, A. D. *Biochemistry* **1990**, *29*, 1886.
36. (a) Pastuszak, I.; Molyneux, R. J.; James, L. F.; Elbein, A. D. *Biochemistry* **1990**, *29*, 1886; (b) Brandi, A.; Cicchi, S.; Cordero, F. M.; Frignoli, R.; Goti, A.; Picasso, S.; Vogel, P. *J. Org. Chem.* **1995**, *60*, 6806.
37. Yoda, H.; Kitayama, H.; Katagiri, T.; Takabe, K. *Tetrahedron: Asymmetry*, **1993**, *4*, 1455.
38. Gurjar, M. K.; Ghosh, L.; Syamala, M.; Jayasree, V. *Tetrahedron Lett*. **1994**, *35*, 8871.
39. Brandi, A.; Cicchi, S.; Cordero, F. M.; Frignoli, R.; Goti, A.; Picasso, S.; Vogel, P. *J. Org. Chem*, **1995**, *60*, 6806.
40. Giovannini, R.; Marcantoni, E.; Petrini, M. *J. Org. Chem*. **1995**, *60*, 5706.
41. McCaig, A. E.; Meldrum, K. P.; Wightman, R. H. *Tetrahedron*, **1998**, *54*, 9429.
42. Ha, D-C.; Yun, C-S.; Lee, Y. *J. Org. Chem*. **2000**, *65*, 621.
43. Rasmussen, M. O.; Delair, P.; Greene, A. E. *J. Org. Chem*. **2001**, *66*, 5438.
44. Chandra, K. L.; Chandrashekhar, M.; Singh, V. K. *J. Org. Chem*. **2002**, *67*, 4630.
45. Sha, C-K.; Chau, C-M. *Tetrahedron Lett*. **2003**, *44*, 499.
46. Feng, Z-X.; Zhou, W-S. *Tetrahedron Lett*. **2003**, *44*, 497.
47. Raghavan, S.; Sreekanth, T. *Tetrahedron: Asymmetry*, **2004**, *15*, 565.
48. Cardona, F.; Moreno, G.; Guarna, G.; Vogel, P.; Schuetz, C.; Merino, P.; Goti, A. *J. Org. Chem*. **2005**, *70*, 6552.
49. Lauzon, S.; Tremblay, F.; Gagnon, D.; Godbout, C.; Chabot, C.; Mercier-Shanks, C.; Perreault, S.; Deseve, H.; Spino, C. *J. Org. Chem*. **2008**, *73*, 6239.
50. Alam, M. A.; Vankar, Y. D. *Tetrahedron Lett*. **2008**, *49*, 5534.

51. (a) Davis, F. A.; Bang-Chi, C. *Chem. Rev.* **1992**, *92*, 919; (b) Morikawa, K.; Park, J.; Andersson, P.G.; Hashiyama, T.; Sharpless, K. B. *J. Am. Chem. Soc*. **1993**, *115*, 8463; (c) Adam, W.; Fell, R. T.; Stegmann, V. R.; Saha-Moller, C. R. *J. Am. Chem. Soc.* **1996**, *118*, 708; (d) Zhu, Y.; Tu, Y.; Yu, H.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 7819.
52. Merino, P.; Tejero, T. *Angew. Chem. Int. Ed.* **2004**, *43*, 2995.
53. For a review of proline-catalyzed asymmetric reactions, see: (a) List, B. *Tetrahedron* **2002**, *58*, 5573; (b) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138; (c) Marigo, M.; Jorgensen, K. A. *Chem. Commun*. **2006**, 2001.
54. (a) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett.* **2003**, *44*, 8293; (b) Zhong, G. *Angew. Chem. Int. Ed.* **2003**, *42*, 4247; (c) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2003**, *43*, 1112; (d) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808; (e) Cordova, A.; Sunden, H.; Bøgevig, A.; Johansson, M.; Himo, F. *Chem. Eur. J.* **2004**, *10*, 3673.
55. Itsuno, S.; Watanabe, K.; Matsumoto, T.; Kuroda, S.; Yokoi, A.; El-Shehawy, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2011.
56. Chen, G.-M.; Ramachandran, P. V.; Brown, H. C. *Angew. Chem. Int. Ed.* **1999**, *38*, 825.
57. For aminoallylation with ammonia: (a) Sugiura, M.; Hirano, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 7182; (b) Kobayashi, S.; Hirano, K.; Sugiura, M. *Chem. Commun.* **2005**, 104.
58. Sugiura, M.; Mori, C.; Hirano. K.; Kobayashi, S. *Can. J. Chem.* **2005**, *83*, 937.
59. (a) Horowitz, R. M.; Geissman, T. A. *J. Am. Chem. Soc.* **1950**, *72*, 1518; (b) Przheval'skii, N. M.; Grandberg, I. I. *Usp. Khim.* **1987**, *56*, 814.
60. (a) Overman, L. E.; Kakimoto, M. *J. Am. Chem. Soc.* **1979**, *101*, 1310; (b) Overman, L. E. *Acc. Chem.Res.* **1992**, *25*, 352.
61. Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc*. **2003**, *125*, 6038.
62. Felpin, F.; Lebreton, J. *J. Org. Chem*. **2002**, *67*, 9192.
63. Sugiura, M.; Mori, C.; Kobayashi, S. *J. Am. Chem. Soc*. **2006**, *128*, 11038.
64. Sanchez-Sancho, F.; Herradon, B. *Tetrahedron: Asymmetry*, **1998**, *9*, 1951-1965

CHAPTER II

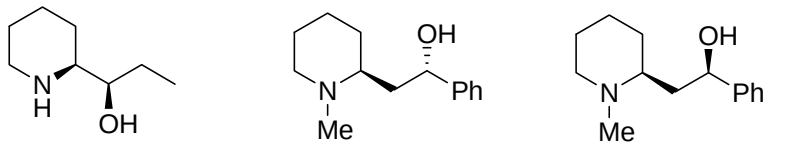
Enantioselective Synthesis of (+)-α-Conhydrine, (-)-Sedamine, (-)-Allosedridine, (*S*)-Betaxolol and (*S*)-Metoprolol

Section I

Enantioselective Synthesis of (+)-α-Conhydrine and (-)-Sedamine *via* L-Proline-Catalyzed Asymmetric α-Aminooxylation

2.1.1 Introduction

Piperidine is a core unit of many alkaloids, which are widespread in nature and occupy an important position in synthetic organic chemistry both as bioactive targets as well as useful synthetic intermediates used for the synthesis of complex molecules. The 1,2- and 1,3-amino alcohols are important functional groups present in a number of bioactive natural products such as alkaloids,[1a–c] amino sugars,[1d] enzyme inhibitors, and antibiotics.[2] The biological and physicochemical specificities of alkaloids are especially due to the properties of the amino alcohol functions. Also, in natural products and pharmaceuticals, the piperidine core is one of the most encountered and has been recognized as a privileged structure in medicinal chemistry.[3] Indeed, over 12,000 discrete piperidine entities have been mentioned in clinical or preclinical studies over the past decade.[4]



(+)-α-conhydrine **1** (-)-sedamine **2** (-)-allosedamine **3**

Fig. 1

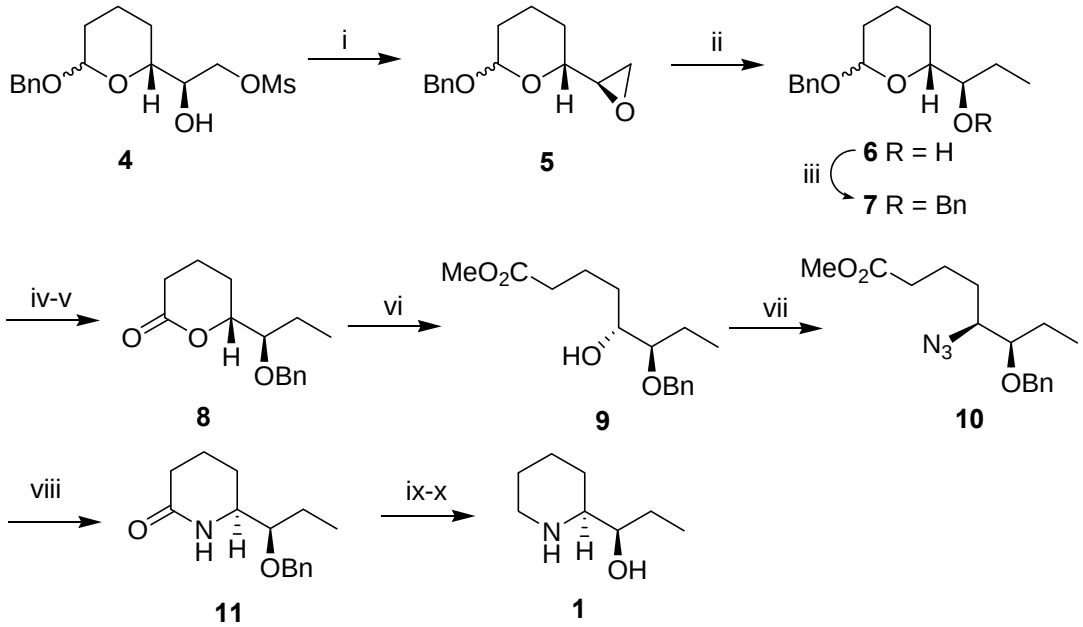
(+)-Conhydrine (**1**) was isolated from seeds and leaves of the poisonous plant *Conium maculatum* L2 in 1856 and its structure was elucidated in 1933. (-)-Sedamine and (−)-allosedamine have been isolated from Sedum acre[3] and *Lobelia inflata* (also known as Indian tobacco) respectively. It has been used for the treatment of respiratory illnesses such as asthma, bronchitis and pneumonia[5] (**Fig. 1**).

2.1.2 Review of literature

A: For the synthesis of (+)-conhydrine

Masaki's approach (1989)[6]

Masaki *et al*. have described the synthesis of (+)-conhydrine (**1**) *via* chiral pool approach starting from pyranoid acetal **4** which was derived from (S,S)-diethyl tartarate . Pyranoid acetal **4** was treated with K_2CO_3 in methanol to give epoxide **5** in 92% yield. The epoxide **5** was then subjected to regioselective ring opening with Me_2CuLi followed by protection of free hydroxyl group as its benzyl ether to afford **7** in 79% yield. The oxidative cleavage of pyranoid **7** was achieved using $BF_3{\cdot}OEt_2$ in the presence of *m*-CPBA, followed by its treatment with Et_3N gave lactone **8** in 75% yield. Treatment of lactone **8** with K_2CO_3 in MeOH produced δ-hydroxy ester **9** in almost quantitative yield. The azido ester **10** obtained from δ-hydroxy ester **9** was then subjected to reductive cyclization

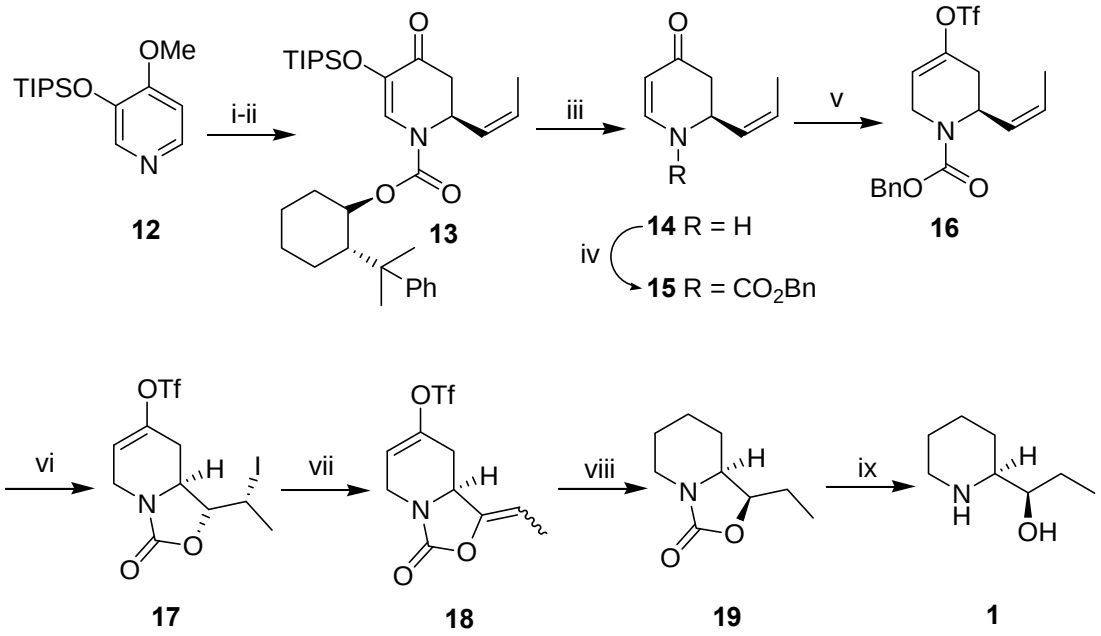


Scheme 1: (i) K_2CO_3, MeOH, 0 ^oC, 0.5 h, 92%; (ii) Me_2CuLi, Et_2O, -5 ^oC, 90%; (iii) NaH, BnBr, DME, 15 h, 79%; (iv) $BF_3{\cdot}Et_2O$, *m*-CPBA, CH_2Cl_2, 2h; (v) Et_3N, 0 ^oC, 1.5 h, 75%; (vi) K_2CO_3, MeOH, 0 ^oC, 2 h, quant.; (vii) PPh_3, HN_3, DEAD, benzene, 2 h, 75%; (viii) (a) 10% Pd/C, H_2, MeOH; (b) toluene, 120 ^oC, 15 h, 82%; (ix) $LiAlH_4$, THF, 25 ^oC, 0.5 h, 80%; (x) 5% Pd/C, H_2, EtOH, con. HCl, 88%.

to produce lactam **11** in 75 % yield. Lactam **11** was then converted to conhydrine **1** using standard reactions *i.e.* reduction of lactam and deprotection of benzyl group (**Scheme 1**).

Comin's approach (2000)[7]

Comin *et al*. have achieved the synthesis of (+)-conhydrine (**1**) starting from pyridine derivative **12**, which was treated with chiral *trans*-2-(α-cumyl) cyclohexylchloroformate [(+)-TCC] followed by addition of allylmagnesium bromide to afford dihydropyridine **13** in 78% yield. The treatment of **13** with NaOMe and 10% HCl resulted in dihydropyridone **14** in 80% yield. It was then treated with *n*-BuLi and benzyl chloroformate to give carbamate **15**, which was subjected to conjugate reduction using L-selectride and its *in situ* treatment with (5-chloro-2-pyridyl)triflamide gave vinyl triflate **16**.

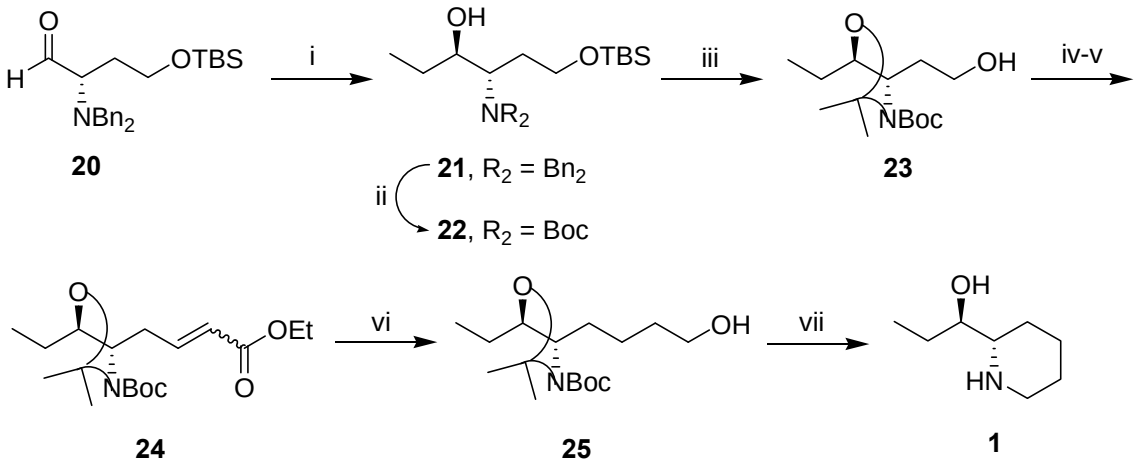


Scheme 2: (i) [(+)-TCC], THF, toluene; (ii) $CH_3CH{=}CH_2MgBr$, H_3O^+, 78%; (iii) NaOMe, MeOH, refluxed then 10% HCl, 80%; (iv) *n*-BuLi, BnOCOCl; (v) L-selectride, N-(5-chloro-2-pyridyl)triflimide, 80%; (vi) I_2, Li_2CO_3, CH_3CN, 70%; (vii) PtO_2, H_2, Li_2CO_3, EtOAc, 75%; (viii) DBU, THF, 25 ^oC, 2h, 99%; (ix) KOH, EtOH, reflux, 79%.

The treatment of triflate **16** with I_2 and Li_2CO_3 gave iodocyclocarbamate **17** in 70% yield. Dehydrohalogenation of iodocarbamate **17** with diaza-bicycloundecane (DBU) gave in enol carbamate **18**. Catalytic hydrogenation of **18** in the presence of PtO_2 and Li_2CO_3 produced oxazolidinone **19** in 75% yield, which was treated with alcoholic KOH to afford conhydrine **1** in 79% yield (**Scheme 2**).

Kumar's approach (2005)[8]

Kumar *et al*. have reported the synthesis of (+)-conhydrine (**1**) commencing from chiral aldehyde **20** derived from L-ascorbic acid. This aldehyde **20** on Grignard addition with ethylmagnesium bromide gave amino alcohol **21** in 73% yield. Debenzylation of **21** was carried out using $Pd(OH)_2$ and *in situ* protection of amine function with $(Boc)_2O$ furnished Boc-protected amino alcohol **22** in 83% yield. Amino alcohol **22** was treated with 2,2-dimethoxypropane in the presence of catalytic amount of p-TSA to afford alcohol **23** in 87% yield.

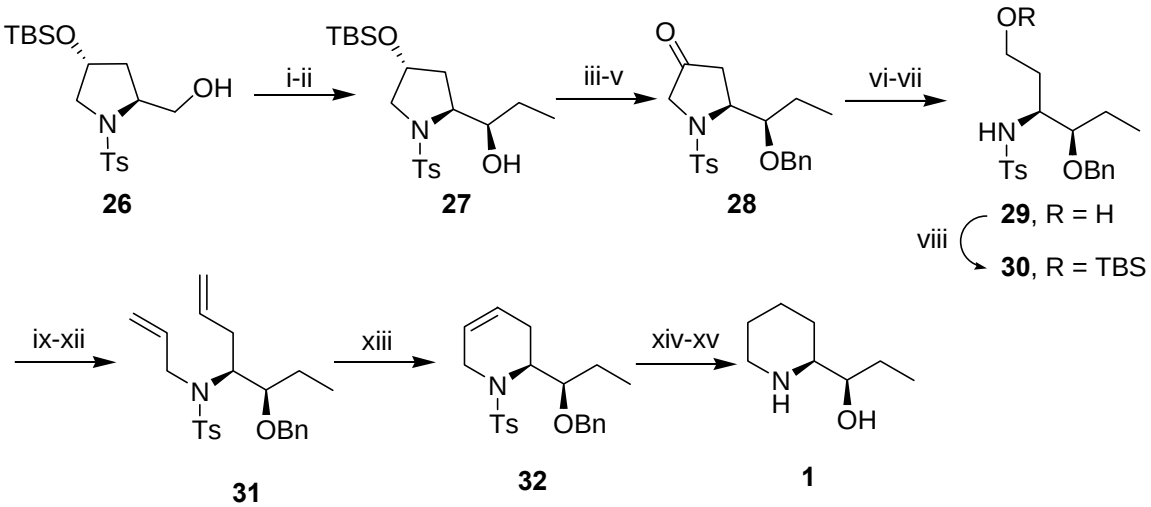


Scheme 3: (i) EtMgBr, Et_2O, 0 ^oC, 2 h, 73%; (ii) $Pd(OH)_2$, H_2, $(Boc)_2O$, EtOAc, 12 h, 83%; (iii) 2,2-dimethoxypropane, p-TSA, CH_2Cl_2, 0-25 ^oC, 87%; (iv) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^oC, 1 h; (v) $Ph_3P{=}CH\text{-}CO_2Et$, THF, 24 h, 96%; (vi) $LiAlH_4$, dry THF, 25 ^oC, 4 h, 78%; (vii) (a) MsCl, Et_3N, -78 ^oC, 1 h; (b) CF_3CO_2H, CH_2Cl_2, 88%.

Alcohol **23** was oxidized under Swern conditions followed by Wittig olefination gave the α,β-unsaturated ester **24**, which on treatment with $LiAlH_4$ resulted in saturated alcohol **25** in 78% yield. The saturated alcohol **25** thus produced was converted to conhydrine **1** by first converting to its mesylate and then Boc-deprotection with TFA in THF which induced an intramolecular cyclization to afford (+)-conhydrine (**1**) (**Scheme 3**).

Chang's approach (2006)[9]

Chang *et al*. have achieved the synthesis of (+)-conhydrine (**1**) commencing from chiral prolinol **26**. The Swern oxidation of prolinol **26**, followed by addition of ethylmagnesium bromide gave a single isomer of **27** in 90% yield. The alcohol **27** was protected as its benzyl ether (NaH, benzyl bromide) followed by desilylation and oxidation with PCC gave ketone **28** in 83% yield. Ketone **28** was subjected to oxidative cleavage with *m*-CPBA and Na_2CO_3 followed by reduction with $LiAlH_4$ produced amino alcohol **29** in 94% yield. Protection of the alcohol **29** as its TBS ether followed by N-allylation provided **31** in 97% yield.

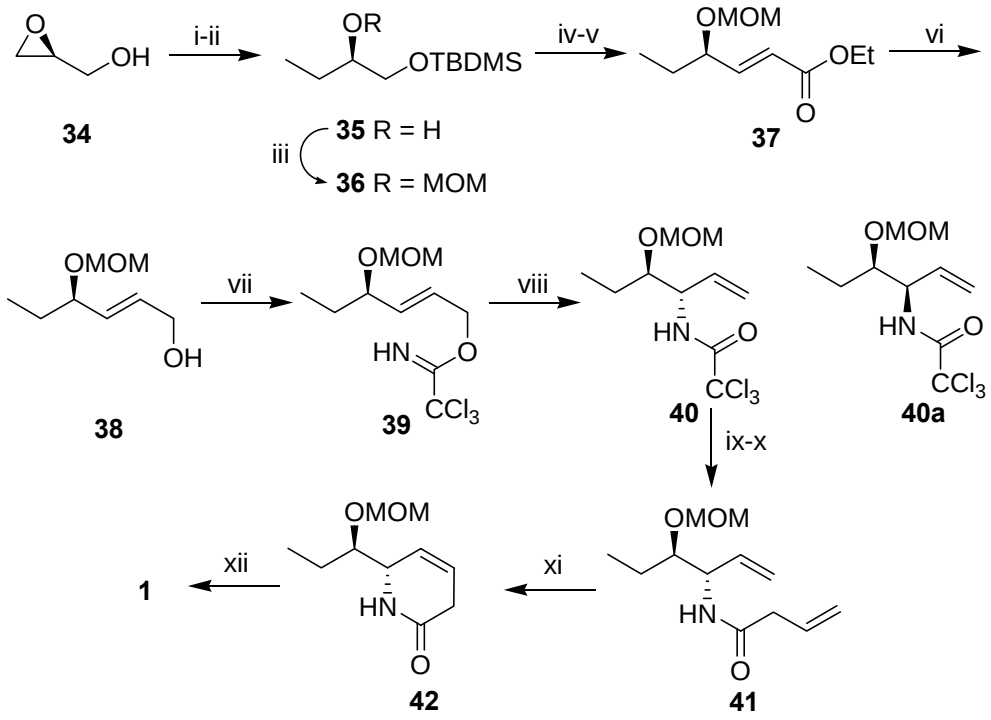


Scheme 4: (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (ii) EtMgBr, Et_2O, 90% for two steps; (iii) NaH, BnBr, 86%; (iv) TBAF, THF, 92%; (v) PCC, CH_2Cl_2, 83%; (vi) m-CPBA, Na_2CO_3, 82%; (vii) $LiAlH_4$, THF, 94%; (viii) TBSCl, imid. 96%; (ix) NaH, allyl bromide, 97%; (x) TBAF, THF, 99%; (xi) PCC, CH_2Cl_2, 97%; (xii) $Ph_3P{=}CH_2$, 82%; (xiii) Grubbs' 2nd generation catalyst, CH_2Cl_2, 92%; (xiv) 10% Pd/C, H_2, 94%; (xv) Na/Hg, MeOH, 80%.

The N-allyl derivative **31** on desilylation, oxidation and Wittig olefination gave the RCM precursor **32** in 82% yield, which was then subjected to ring-closing metathesis with Grubbs' second generation catalyst to produce dihydropiperidine **33** in 92% yield. The dihydropiperidine **33** thus produced was converted to (+)-conhydrine **1** by hydrogenation and reduction of N-Ts bond with Na/Hg (**Scheme 4**).

Sutherland's approach (2007)[10]

Sutherland *et al*. have achieved the synthesis of conhydrine **1** starting from (S)-glycidol **34**, protected as its TBDMS ether, followed by regioselective ring opening of epoxide with methylmagnesium bromide in the presence of $CuBr{\cdot}SMe_2$ produced alcohol **35** in 90% yield. Alcohol **35** was protected as its MOM ether to give **36**, deprotection of TBDMS ether followed by Swern oxidation and Horner-Wadsworth-Emmons (HWE) olefination generated α,β-unsaturated ester **37** in 86% yield. The selective reduction of ester functionality in **37** with DIBAL-H gave allylic alcohol **38**, subsequent protection of hydroxyl function with trichloroacetonitrile gave allylic trichloroacetamide **39**. Trichloroacetamide **39** was then subjected to asymmetric aza-Claisen rearrangement using 10 mol% bis-(acetonitrile)palladium chloride to give *erythro*- and *threo*-allylic trichloroacetamide **40** and **40a** (dr = 16:1). The required isomer **40** was then subjected to hydrolysis using 2M NaOH followed by acylation with 3-butenoyl chloride to give RCM precursor **41** in 72% yield. Finally, ring closing metathesis of **41** using Grubbs' first generation catalyst gave δ-lactam **42**, which was transformed to (+)-conhydrine **1** *via* hydrogenation and deprotection of MOM ether (**Scheme 5**).

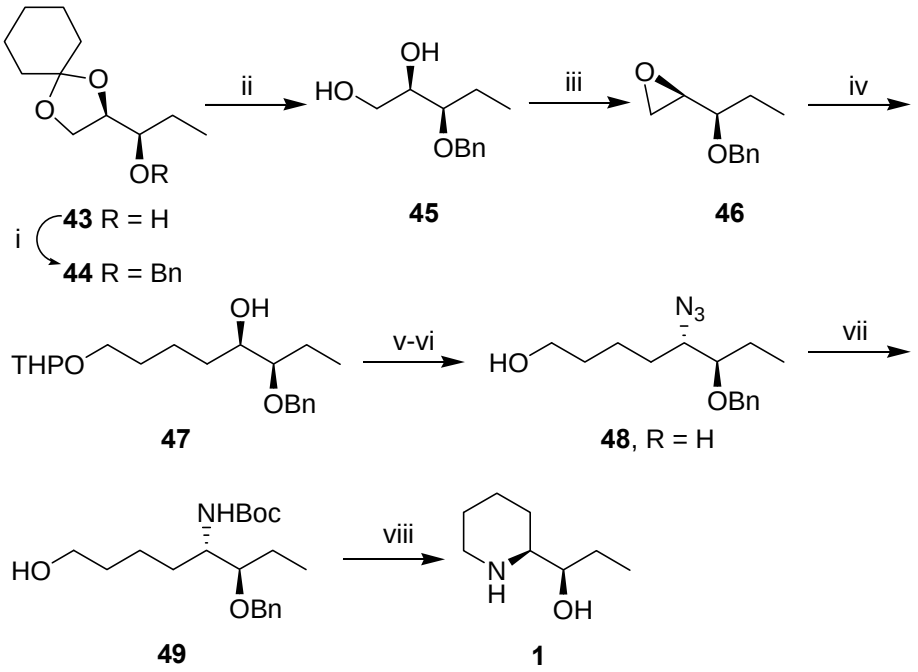


Scheme 5: (i) TBDMSCl, imidazole, THF, 88%; (ii) MeMgBr, CuBr·SMe_2, THF, 90%; (iii) MOMBr, $Et(^iPr)_2N$, CH_2Cl_2, 83%; (iv) TBAF, THF, 59%; (v) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; then $(EtO)_2POCH_2CO_2Et$, DBU, LiCl, CH_3CN, 86%; (vi) DIBAL-H, Et_2O, 95%; (vii) Cl_3CCN, DBU, CH_2Cl_2; (viii) $PdCl_2(CH_3CN)_2$, toluene, dr = 16:1, 55%; (ix) $(Boc)_2O$, 2 M NaOH, 74%; (x) $ClCOCH_2$-CH=CH_2, Et_3N, CH_2Cl_2, 52%; (xi) Grubbs' 1st generation catalyst, CH_2Cl_2, 92%; (xii) 10% Pd/C, H_2, EtOAc, 98%; then 6 M HCl, 100%.

Chattopadhyay's approach (2009)[11]

Chattopadhyay *et al*. have synthesized (+)-conhydrine (**1**) starting from D-mannitol-derived alcohol **43**, which was protected as its benzyl ether **44**; subsequent treatment with $CuCl_2{\cdot}2H_2O$ in methanol gave diol **45** in 92% yield. The diol **45** was subjected to selective monomesylation followed by its treatment with base gave epoxide **46** in 75% yield. This on treatment with Grignard reagent (OTHP-$(CH_2)_3MgBr$) in the presence of $CuBr{\cdot}Me_2S$ gave alcohol **47** in 78% yield. The alcohol **47** was subjected to invertive azidation with diphenylphosphoryl azide (DPPA) in the presence of diethyl azodicarboxylate (DEAD) to furnish the corresponding azide; followed by its treatment with pyridinium p-toluenesulfonate (PPTS) gave azido alcohol **48** in 92% yield. Azido

alcohol **48** was converted into the corresponding amine **49** by a one-pot catalytic hydrogenation in the presence of $(Boc)_2O$. The selective protection of primary hydroxyl group in **49** as its mesylate and subsequently deprotection of Boc group using TFA in THF resulted in (+)-conhydrine **1** (**Scheme 6**).



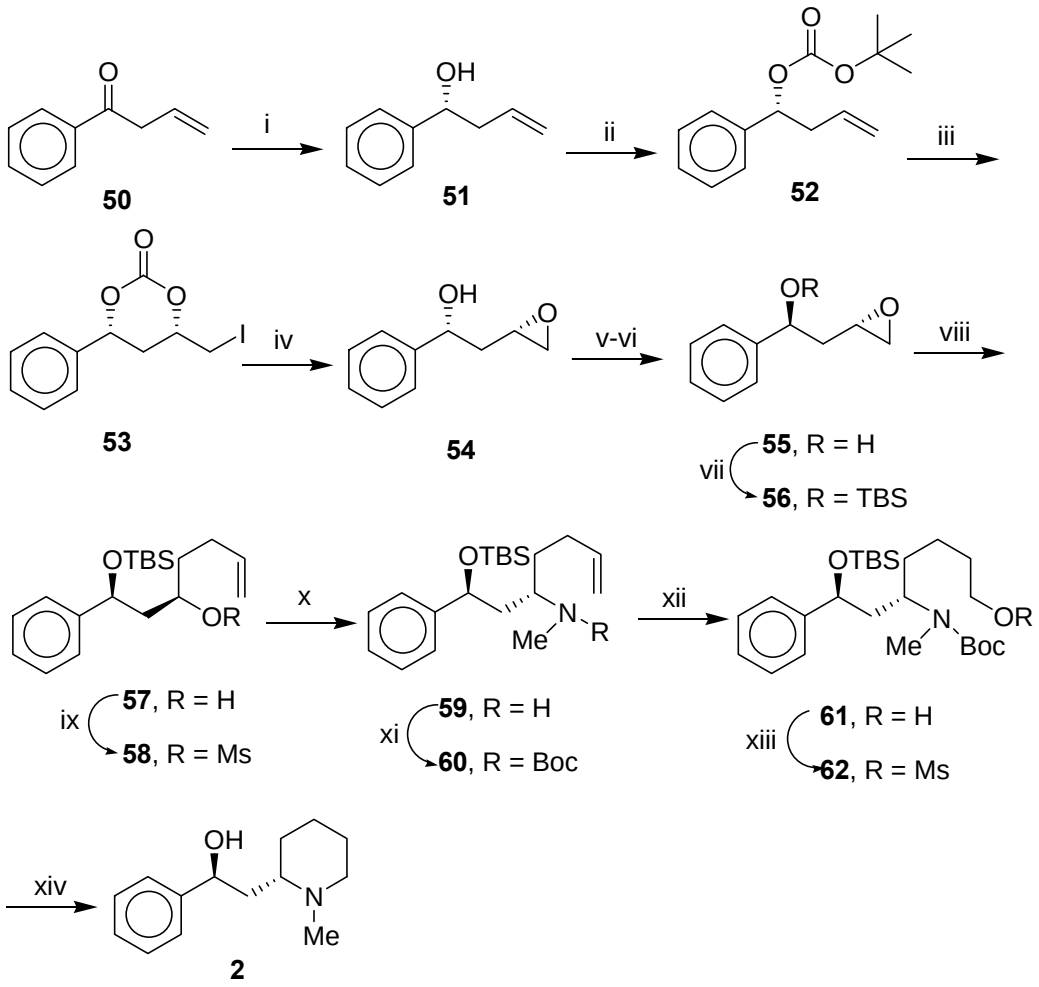
Scheme 6: (i) NaH, BnBr, THF, Δ, 86%; (ii) $CuCl_2 \cdot 2H_2O$, MeOH, Δ, 92%; (iii) K_2CO_3, *p*-TsCl, pyridine, MeOH, 75%; (iv) $CuBr \cdot Me_2S$, Mg, $THPO(CH_2)_3Br$, THF, 78%; (v) PPh_3, DPPA, DEAD, THF, 84%; (vi) PPTS, MeOH, 92%; (vii) 10% Pd/C, H_2, $(Boc)_2O$, EtOAc, 91%; (viii) MsCl, Et_3N, 0 ^oC then TFA, CH_2Cl_2, 67%.

B: For the synthesis of (-)-sedamine:

Lebreton's approach (2002)[12]

Lebreton *et al*. have reported the synthesis of (-)-sedamine **2** starting from ketone **50**, which was subjected to asymmetric reduction using (+)-DIP-Cl in THF to give homoallylic alcohol **51**. It was protected using $(Boc)_2O$ in presence of DMAP to give carbamate **52**, which subsequently underwent intramolecular diastereoselective iodolactonization in presence of IBr to give iodocarbonate **53** in 85% yield.

Iodocarbonate **53** upon exposure to a basic methanolic solution gave the *syn*-epoxy alcohol **54** in 96% yield. S*yn*-epoxy alcohol **54** was treated under Mitsunobu's condition using DEAD and *p*-nitrobenzoic acid to give the desired *anti* epoxy alcohol **55**, protected as its TBS ether to produce **56**.



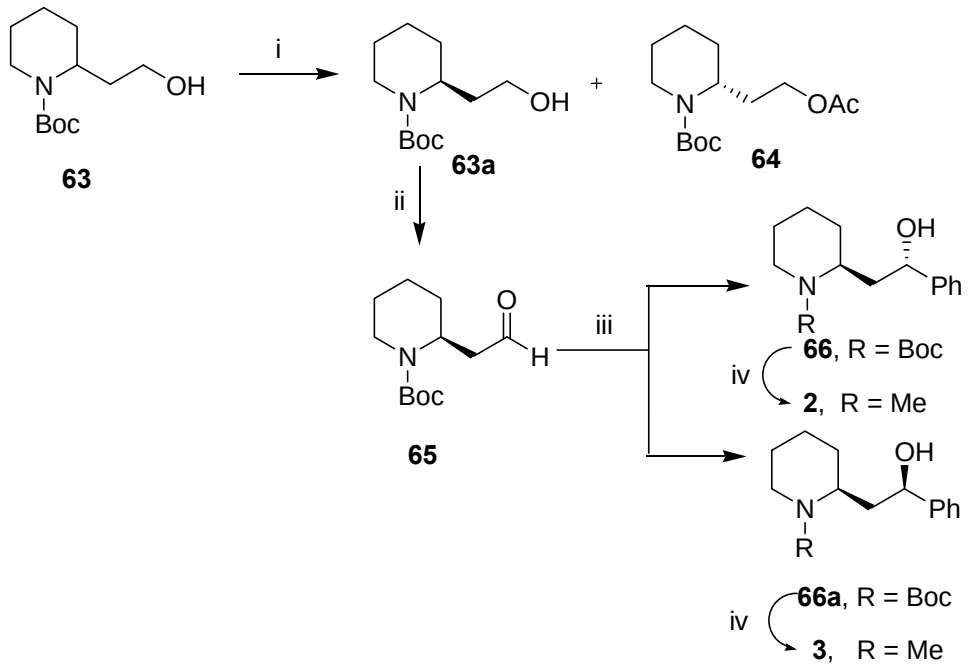
Scheme 7: i) (+)-DIP-Cl, THF, -35 ^{o}C, 84%; (ii) $(Boc)_2O$, DMAP, CH_3CN, 90%; (iii) IBr, PhMe, -85 ^{o}C, 85%; (iv) K_2CO_3, MeOH, 96%; (v) PPh_3, DEAD, *p*-$NO_2C_6H_4CO_2H$, THF, 92%; (vi) K_2CO_3, MeOH, 77%; (vii) TBDMSCl, DMAP, Et_3N, 96%; (viii) CuI, allylmagnesium bromide, Et_2O, -40 ^{o}C, 91%; (ix) MsCl, Et_3N, CH_2Cl_2, 88%; (x) $MeNH_2$, DMF, H_2O, 83%; (xi) $(Boc)_2O$, Et_3N, CH_2Cl_2, 95%; (xii) Cy_2BH, CH_2Cl_2, H_2O_2, NaOH, 90%; (xiii) MsCl, Et_3N, CH_2Cl_2, 88%; (xiv) 1% conc. HCl, MeOH, 94%.

Regioselective ring opening of epoxide with allylmagnesium bromide in presence of CuI afforded alcohol **57**, which was converted to its mesylate **58** in 88% yield. Displacement

of the mesylate group in **58** with methyl amine resulted in **59** in 83% yield, its subsequent treatment with $(Boc)_2O$ produced Boc-protected amine **60**. The olefin functionality in **60** was then subjected to hydroboration-oxidation using dicyclohexylborane in the presence of H_2O_2 and NaOH to give the terminal alcohol **61**, which was converted to its mesylate **62** in 88% yield. The deprotection of Boc group in **62** resulted in intramolecular cyclization readily to produce (-)-sedamine **2** (**Scheme 7**).

Riva's approach (2003)[13]

Riva *et al*. have synthesized (-)-sedamine **2** and (-)-allosedamine **3** by using enzyme-catalyzed kinetic resolution as the key step. Accordingly, the synthesis commenced from



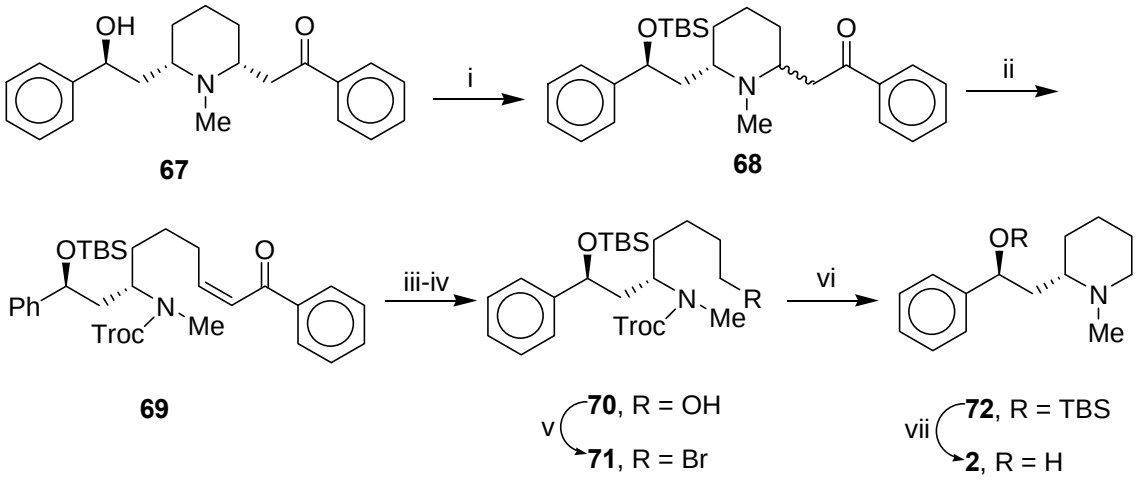
Scheme 8: (i) Lipase PS, $AcOCH=CH_2$, hexane, 20 °C, 190 min., 45%; (ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (iii) PhMgBr, THF, -20 °C; (iv) $LiAlH_4$, THF, reflux.

recemic Boc-protected piperidine alcohol **63**, which was subjected to enzyme-catalyzed resolution using Lipase LS in the presence of vinyl acetate to give the chiral Boc protected piperidine alcohol **63a** and its acetate **64** in 45% yield. The Boc-protected

piperidine alcohol **63a** was oxidized under Swern conditions followed by addition of phenylmagnesium bromide to produce separable diastereomeric mixtures of **66** and **66a** in 2:3 ratio, which on reduction with $LiAlH_4$ afforded (-)-sedamine **2** and (-)-allosedamine **3** (**Scheme 8**).

Crook's approach (2004)[14]

Crook *et al*. have described the synthesis of (-)-sedamine **2** commencing from naturally availabe (-)-lobeline **67**, which was protected as its TBS ether using TBSCl in presence of DMAP to give TBS-protected lobeline **68** in 91% yield. This on further treatment with Troc-Cl in presence of K_2CO_3 afforded **69** in quantitative yield. Bromo compound **71** was obtained from **69** by employing a four-step reaction sequence, which includes OsO_4-catalyzed dihydroxylation followed by cleavage of diol to give the corresponding aldehyde, reduction of aldehyde using $NaBH_4$ and treatment of the resulting alcohol with PPh_3 and CBr_4.

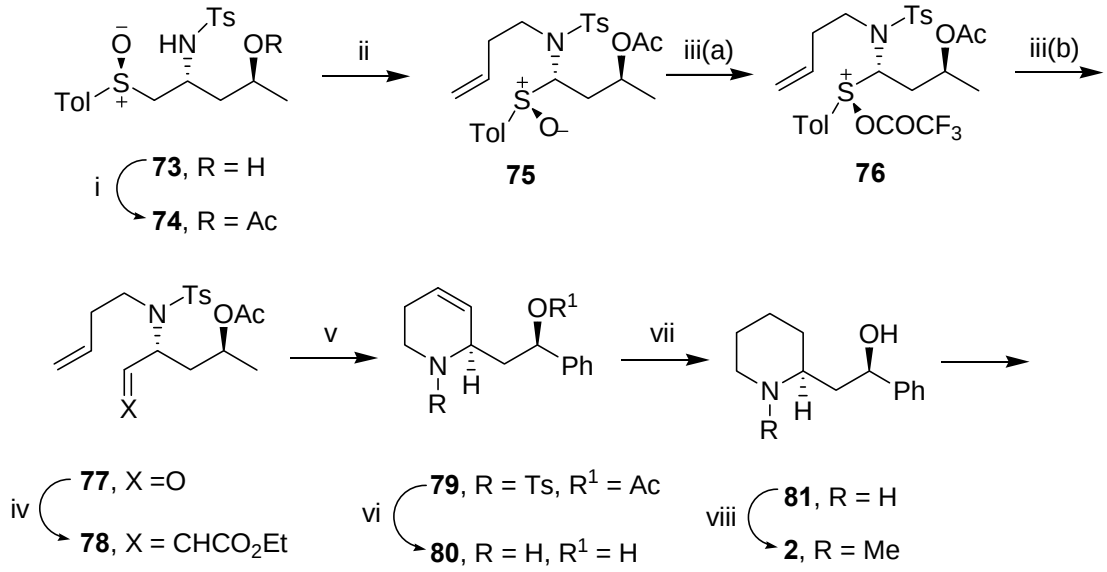


Scheme 9: i) TBSCl, DMAP, Et_3N, CH_2Cl_2, 91%; (ii) TrocCl, K_2CO_3, CH_3CN, 100%; (iii) OsO_4, $NaIO_4$, dioxane:H_2O; (iv) $NaBH_4$, EtOH, 70%; (v) PPh_3, CBr_4, CH_2Cl_2, 93%; (vi) Zn, AcOH, CH_2Cl_2, 96%; (vii) conc. HCl, EtOH, 100%.

The removal of Troc group using zinc in acetic acid induced *in situ* intramolecular cyclization to give adduct **72**, followed by deprotection of TBS ether under acidic conditions resulted in the formation of (-)-sedamine **2** (**Scheme 9**).

Raghavan's approach (2004)[15]

Raghavan *et al*. have reported the synthesis of (-)-*allo*sedamine **3** commencing from chiral amino alcohol **73**, which was protected as its acetate **74** (Ac_2O, pyridine). The nucleophilic displacement of nosylate (CH_2=$CH(CH_2)_2$-ONS) with amine **74** gave the intermediate **75** in 90% yield. The sulfoxide **75** was converted to triflic acetate **76** using trifluoroacetic anhydride in presence of Et_3N, which on hydrolysis with aq. $NaHCO_3$ afforded aldehyde **77**. Wittig olefination of **77** gave ester **78** in 75% yield. The ester **78** was then subjected to ring closing metathesis using Grubbs' first generation catalyst to give dihydropiperidine **79** in 80% yield. Deprotection of N-Ts group using Na-Hg in

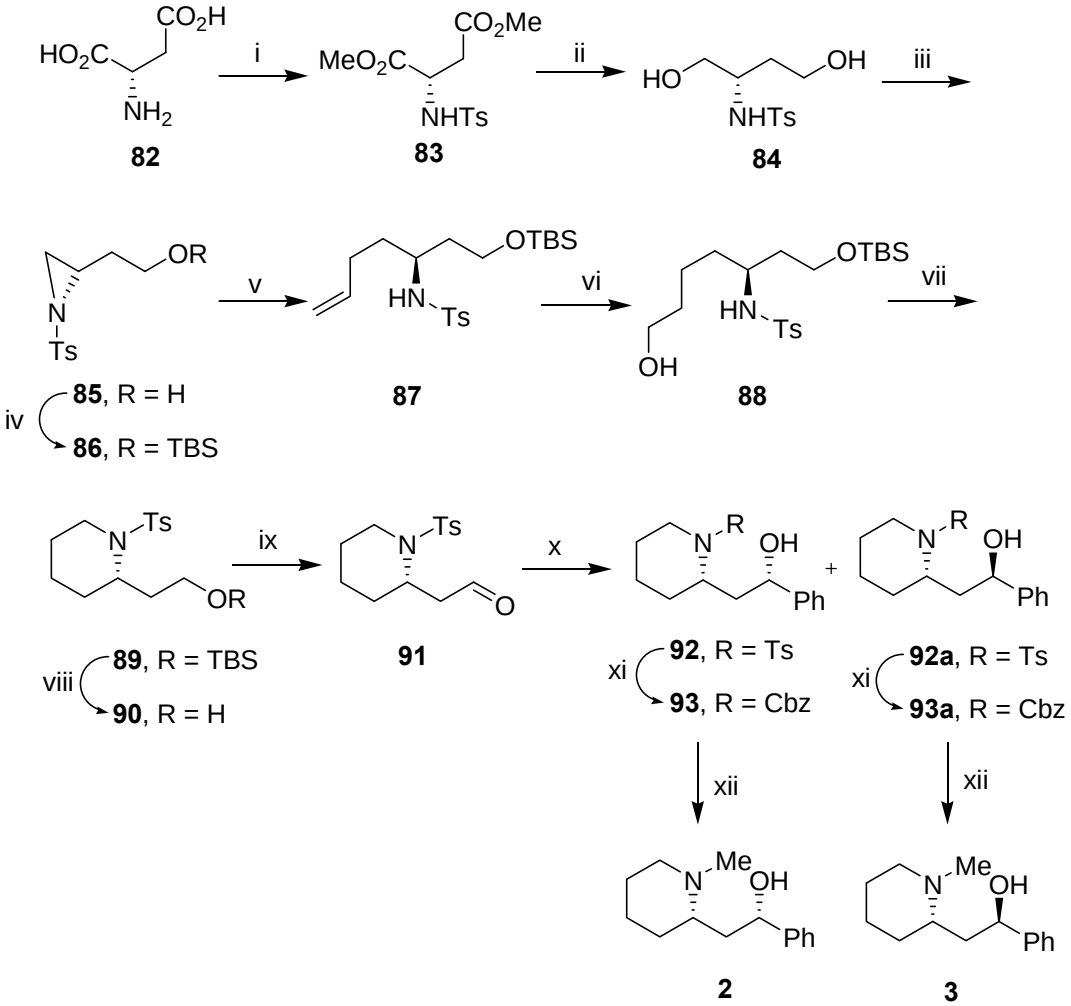


Scheme 10: (i) Ac_2O, pyridine, CH_2Cl_2, 25 ^oC, 4 h, 96%; (ii) CH_2=$CH(CH_2)_2$-ONS, K_2CO_3, CH_3CN, reflux, 2 h, 90%; (iii) (a) TFAA, Et_3N, CH_3CN, 0 ^oC, 50 min; (b) aq. $NaHCO_3$, 0 ^oC, 20 min; (iv) Ph_3PCHCO_2Et, PhH, 25 ^oC, 30 min, 75%; (v) Grubbs' catalyst, toluene, reflux, 16 h, 80%; (vi) Na–Hg, Na_2HPO_4, MeOH, reflux, 6 h, 78%; (vii) Pt/C, H_2, AcOEt, 25 ^oC, 3 h, 90%; (viii) 37% aq. HCHO, $NaCNBH_3$, AcOH, CH_3CN, 25 ^oC, 4 h, 70%.

presence of Na_2HPO_4 gave piperidine **80** in 78% yield. The synthesis of (-)-*allo*sedamine **3** was completed by following a two-step reaction sequence which includes hydrogenation and reductive alkylation (**Scheme 10**).

Singh's approach (2007)[16]

Singh *et al*. have reported the synthesis of (-) sedamine **2** and (-)-*allo*sedamine **3** starting from naturally occurring (S)-aspartic acid **82**, which was esterified ($SoCl_2$, MeOH) to

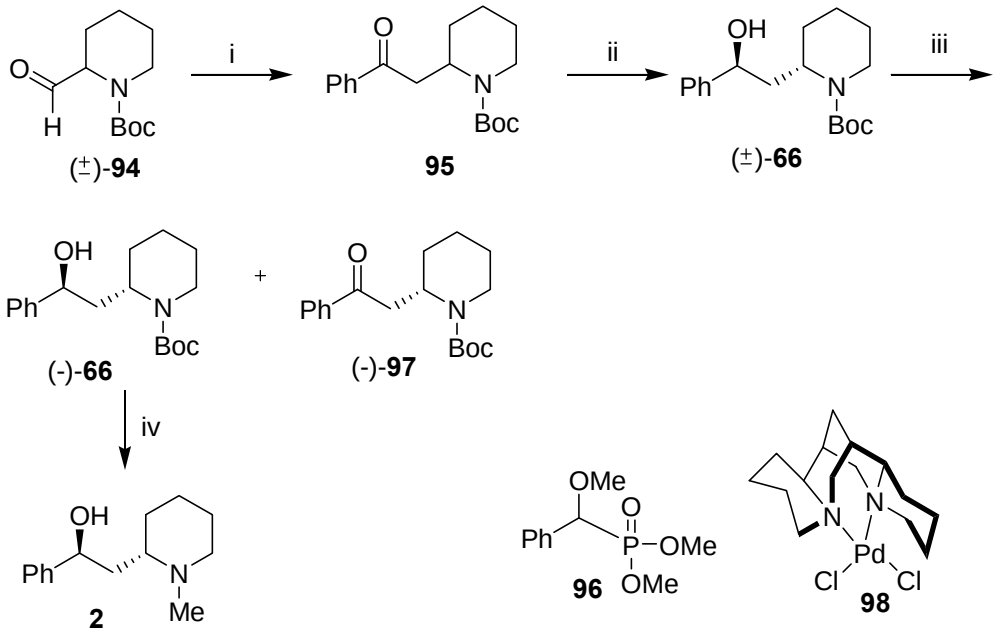


Scheme 11: (i) (a) $SOCl_2$, MeOH, 0–25 ^oC, 12 h; (b) TsCl, Et_3N, 0 –25 ^oC, 12 h, 94%; (ii) $LiAlH_4$, THF, 0–25 ^oC, 12 h, 85%; (iii) ADDP, n-Bu_3P, toluene, 0–25 ^oC, 16 h, 82%; (iv) TBSCl, imidazole, THF, 0–25 ^oC, 8 h; (v) allylmagnesium bromide, THF–Et_2O (1:1), -78–25 ^oC, 6 h, 98%; (vi) $BH_3{\cdot}Me_2S$, THF, -10–25 ^oC, 8 h, then H_2O_2, NaOH, 0–25 ^oC, 2 h, 82%; (vii) DIAD, Ph_3P, THF, 0–25 ^oC, 8 h, 80%; (viii) TBAF, THF, 25 ^oC, 6 h, 99%; (ix) $(COCl)_2$, DMSO, Et_3N, -78–25 ^oC, 8 h, 95%; (x) PhMgBr, THF–Et_2O (1:1), -78–25 ^oC, 6 h; (xi) Na, naphthalene, THF, 0–25 ^oC, 2 h; then $NaHCO_3$, CbzCl, 2 h; (xii) $LiAlH_4$, THF, reflux, 16 h.

give diester, followed by protection of amine as its tosylate **83** in 94% yield. The $LiAlH_4$ reduction of **83** afforded diol **84**, its subsequent treatment with 1,1'-(azodicarbonyl) dipiperidine [ADDP] and *tert*-butyl phosphine resulted in selective formation of aziridine, which was followed by protection of hydroxyl group as its TBS ether that gave N-tosylaziridine **86** in 82% yield. Regioselective ring opening of N-tosylaziridine **86** with allylmagnesium bromide gave olefin **87**, which was subjected to hydroboration-oxidation to give the alcohol **88** in 82% yield. Alcohol **88** readily underwent intramolecular cyclization under Mitsunobu conditions (DIAD, triphenyl phosphine) to give piperidine moiety **89**. Desilylation yielded piperidine-2-ethanol **90** in 99% yield, which was oxidized under Swern conditions to give aldehyde **91**, followed by the addition of phenylmagnesium bromide to give *syn:anti* diastereomeric mixture of **92** and **92a** that could be separated by column chromatography. The synthesis of (-)-sedamine **2** and (-)-*allo*sedamine **3** was completed (the cleavage of N-Ts bond, Cbz protection and reduction with $LiAlH_4$) (**Scheme 11**).

Stoltz's approach (2008)[17]

Stoltz *et al*. have described the synthesis of (-)-sedamine **2** using Pd-catalyzed kinetic resolution of benzylic alcohol as the key step. Addition of anion derived from Horner-Emmons reagent **96** to aldehyde **94** followed by hydrolysis of the resulting methyl enol ether provided (±)-**95** in 82% yield. Reduction of ketone (±)-**95** with DIBAL-H in toluene at -78 ^{o}C gave benzylic alcohol (±)-**66**, which was then subjected to Pd-catalyzed kinetic resolution using sparteine complex **98** in presence of air to produce alcohol (-)-**66** and ketone (-)-**97** in 94% yield and 81% ee respectively. The Boc-protected alcohol (-)-**66** was reduced using $LiAlH_4$ to give (-)-sedamine in 89% yield (**Scheme 12**).



Scheme 12: (i) n-BuLi, THF, -78-23 °C, then Cl_3CCO_2H, acetone, 82%; (ii) DIBAL-H, toluene, -78 -42 °C, 78%, (iii) $PdCl_2$ (7 mol%), (-)-sparteine (9 mol%), MS 3A°, Cs_2CO_3, $CHCl_3$, air, 30 °C, (iv) $LiAlH_4$, THF, 65 °C, 89%.

2.1.3 Present Work

2.1.3.1 Objective

Even though several methods are reported for the synthesis of (+)-conhydrine (**1**) and (-)-sedamine (**2**), several of them suffer from drawbacks such as: use of chiral starting materials, involvement of expensive reagents and also formation of mixture of products. Hence, the synthesis of (+)-conhydrine (**1**) and (-)-sedamine **2**, starting from readily available starting materials and making use of catalytic enantioselective reactions, is highly desirable. The use of catalytic enantioselective reactions are particularly advantageous from synthetic point of view as both the stereoisomers can be synthesized from the same prochiral substrate. In this chapter, the synthesis of (+)-conhydrine (**1**) and (-)-sedamine **2** employing proline-catalyzed α-aminooxylation reaction has been described.

2.1.4 Results and discussion

Retrosynthetic analysis for the synthesis of (+)-conhydrine (**1**) and (-)-sedamine (**2**) is shown in **Fig. 2**.

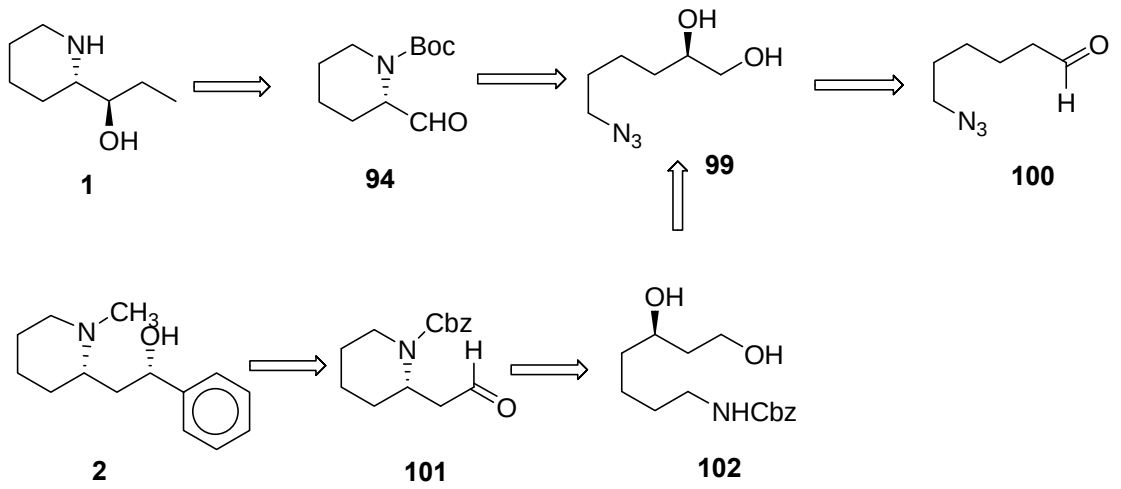
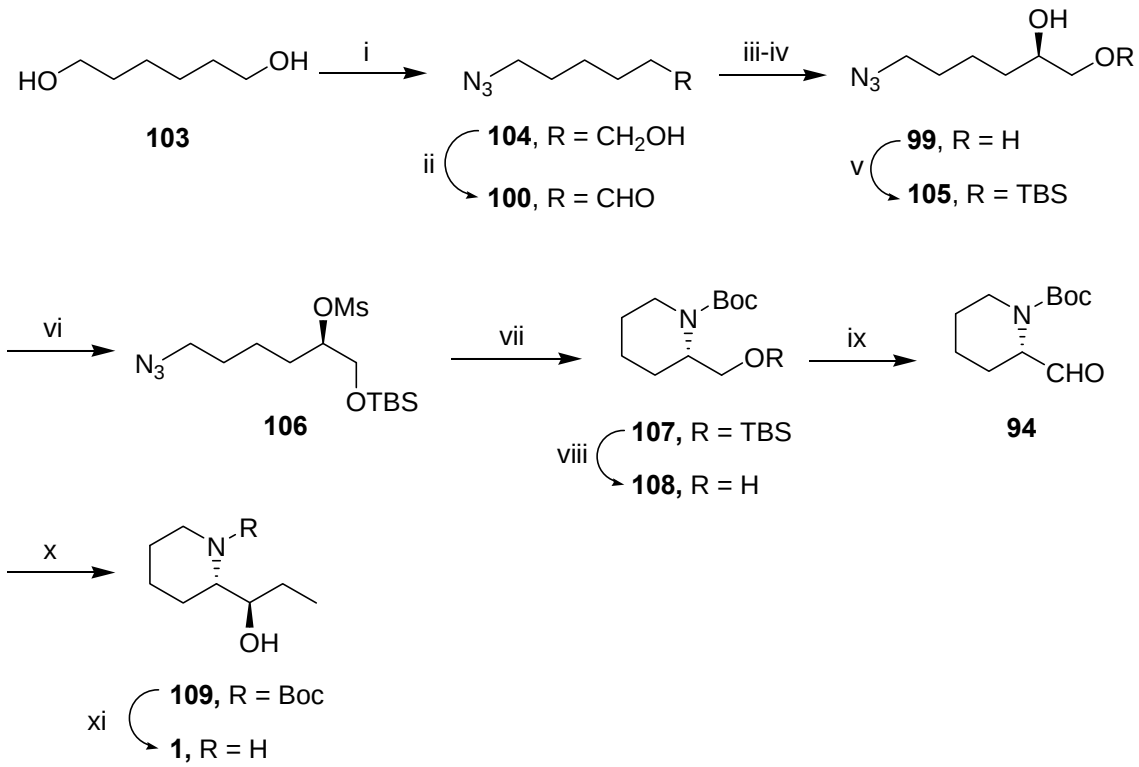


Fig. 2: Retrosynthetic analysis of (+)-conhydrine and (-)-sedamine

The secondary alcohol moiety in (+)-conhydrine (**1**) can be obtained by the addition of ethylmagnesium bromide onto aldehyde **94**, which may be derived from diol **99** *via* intramolecular reductive amination. The diol **99** can *in turn* be obtained from 6-azido-hexanal **100** *via* L-proline catalyzed α-aminooxylation. Similarly (-)-sedamine **2** can be synthesized by the addition of phenylmagnesium bromide onto aldehyde **101**, which may be derived from amino 1,3-diol **102** using intramolecular cyclization. The 1,3-diol **102** can be envisaged from azido 1,2-diol **99**.

2.1.4.1 Enantioselective synthesis (+)-α-Conhydrine

The synthetic scheme for (+)-α-conhydrine (**1**), wherein L-proline-catalyzed α-aminooxylation[18] of aldehyde constitutes a key step for the introduction of chirality, is presented in **Scheme 13**.



Scheme 13: Reactions conditions: (i) TsCl, Et_3N, CH_2Cl_2, 0 ^oC; then NaN_3, dry DMF, 80 ^oC, 16 h, 80%; (ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^oC, 1 h, 96%; (iii) L-proline (25 mol%), PhNO, CH_3CN, -20 ^oC, 24 h; then MeOH, $NaBH_4$, 0 ^oC, 1 h; (iv) $CuSO_4$ (30 mol%), MeOH, 12 h, 61%; (v) TBSCl, imidazole, CH_2Cl_2, 0 ^oC, 1 h, 95; (vi) MsCl, Et_3N, CH_2Cl, 0 ^oC, 1 h; (vii) 10% Pd/C, H_2 (20 psi), MeOH, Et_3N, 25 ^oC 5 h; then $(Boc)_2O$, I_2 (10 mol%), 3 h, 76%; (viii) TBAF, THF, 0 ^oC, 3 h, 92%; (ix) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^oC, 1 h, 90%; (x) excess EtMgBr, Et_2O, -78 ^oC, 3 h, 87%; (xi) TFA:CH_2Cl_2 (1:1), 25 ^oC, 12 h, 86%.

6-Azidohexan-1-ol (**104**) was obtained from 1,6-hexanediol **103** in two steps by following simple organic transformations i.e. selective monotosylation followed by nucleophilic displacement with NaN_3, in overall 80% yield. Its ^1H NMR spectrum showed typical triplets at δ 3.23 and 3.64 corresponding to C**H**$_2$OH and C**H**$_2$N$_3$ protons respectively. Its ^{13}C NMR spectrum showed characteristic peaks at δ 51.1 (**C**H_2OH) and 62.2 (**C**H_2N_3). Azidoalcohol **104** was then subjected to Swern oxidation [$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^oC] to obtain the corresponding aldehyde **100**, which was converted to the azido diol **99** in 61% yield *via* a 2-step reaction sequence: (i) L-proline-

catalyzed asymmetric α-aminooxylation using nitrosobenzene as the oxygen source followed by reduction of aldehyde function with $NaBH_4$ and (ii) cleavage of aminooxy moiety (N-O bond) with $CuSO_4$ in methanol; $[\alpha]^{25}{}_D$: +33.5 (c 0.5, $CHCl_3$). The formation of diol **99**

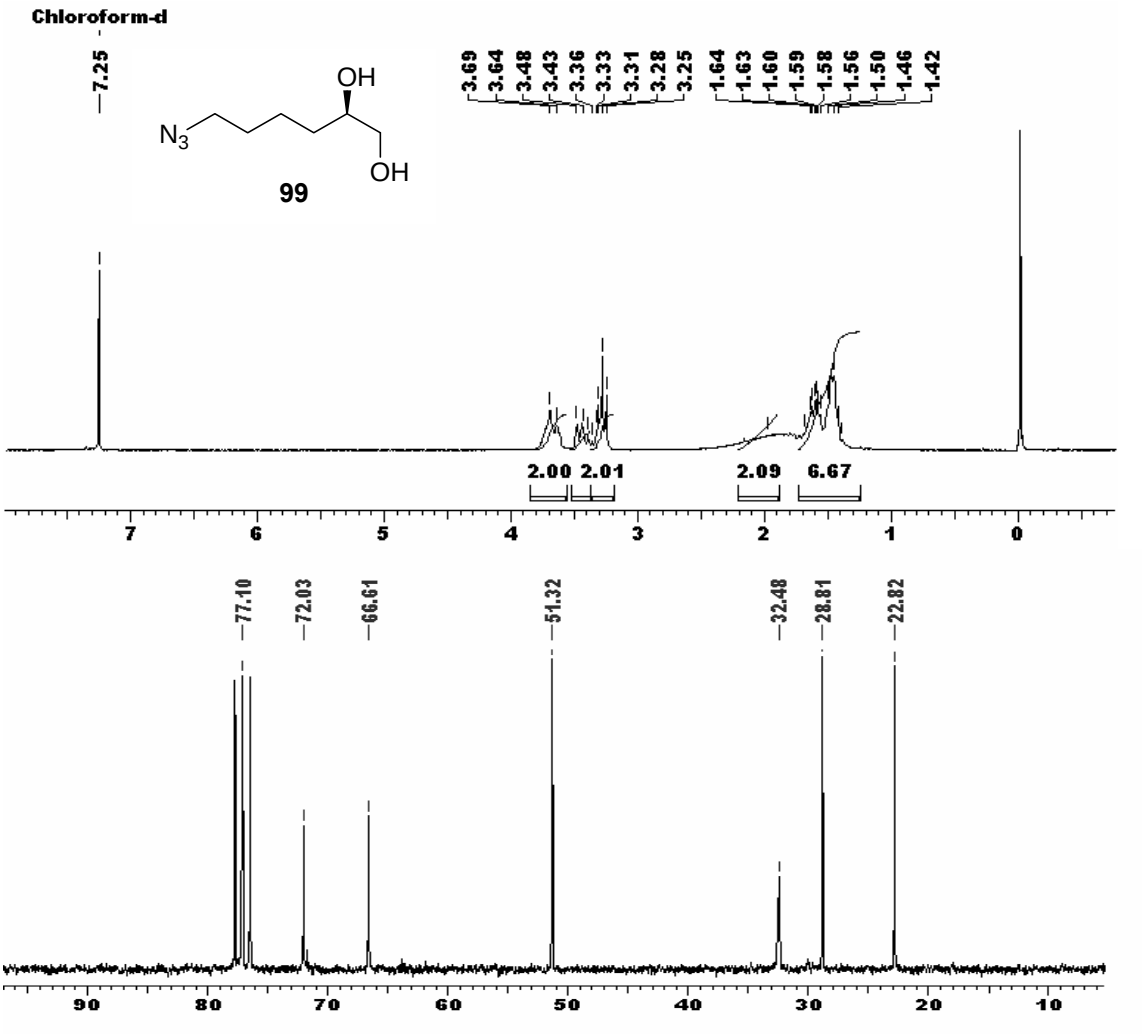


Fig. 3: ^1H and ^{13}C NMR spectra of azido diol **99**

was confirmed by the appearance of typical signals at δ 1.39-1.69 (m), 1.98 (br. s) and 3.66 (br. d) in its ^1H NMR spectrum. Further, its ^{13}C NMR spectrum showed characteristic peaks at δ 66.6 and 72.0, corresponding to the carbons attached to oxygen atoms (**Fig. 3**). The primary hydroxyl group in diol **99** was then protected (TBSCl,

imidazole) selectively to give *tert*-butyldimethylsilyl ether **105** in 95% yield. The ^{1}H NMR spectrum of silyl ether **105** showed two singlets at δ 0.06 (6H) and 0.89 (9H) corresponding to the dimethyl and *tert*-butyl protons of TBS group respectively. Its ^{13}C NMR spectrum displayed carbon signals at δ -5.4 and 25.8 that correspond to the methyl and *tert*-butyl carbons in the silyl protecting group.

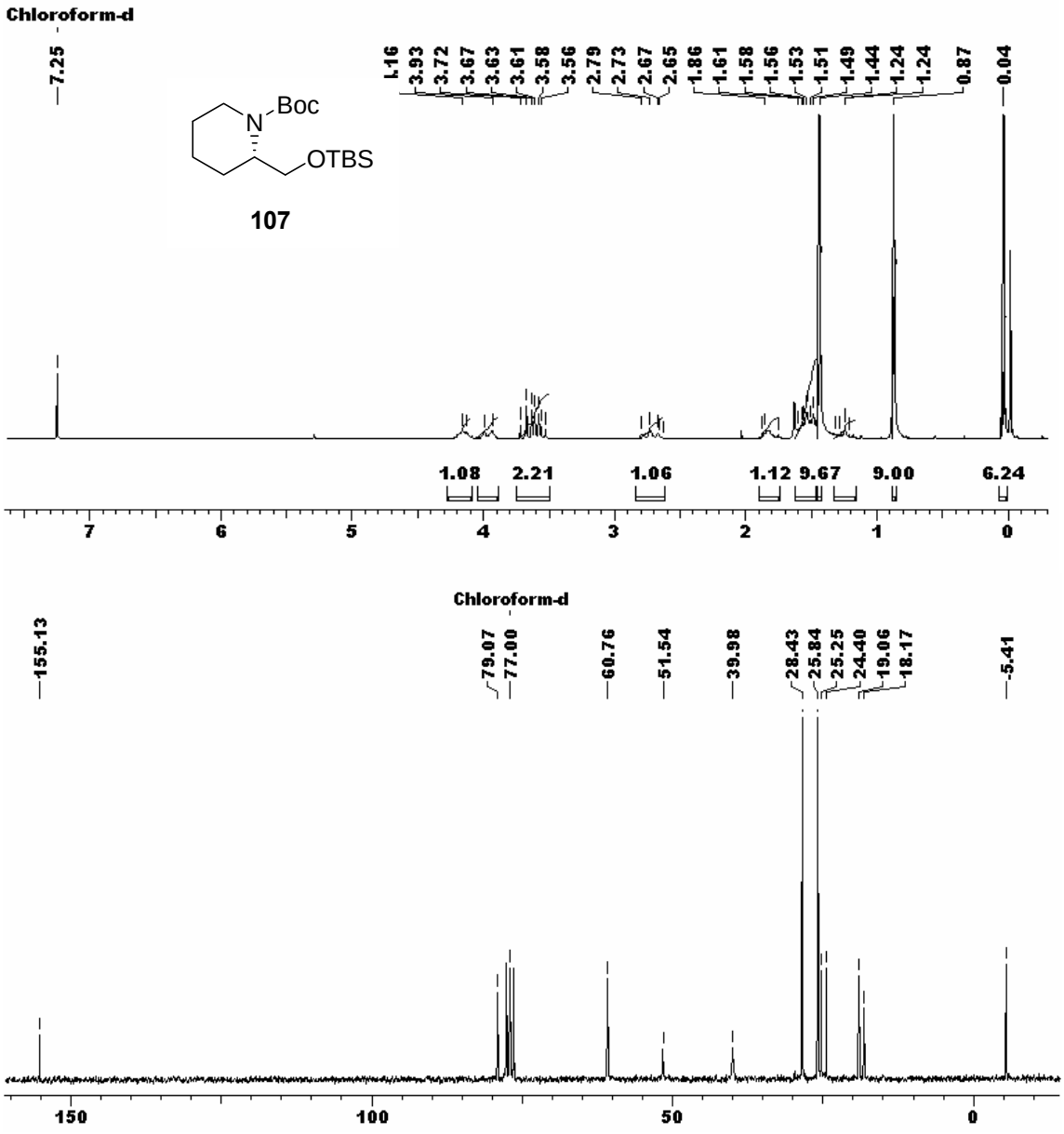


Fig. 4: ^{1}H and ^{13}C NMR spectra of piperidine **107**

The secondary hydroxyl group in TBS ether **105** was then converted to the corresponding mesylate **106** *in situ*, which underwent reductive cyclization with 10% Pd/C and H_2 (20 psi). This was followed by its treatment with $(Boc)_2O$ and I_2 (10 mol%)[19] that resulted in chiral Boc-protected piperidine **107** in 76% yield. The formation of piperidine **107** was confirmed by the signals at δ 3.57 (dd, *J* = 6.9, 9.8 Hz, 1H), 3.67 (dd, *J* = 8.4, 9.6 Hz, 1H), 3.97 (br. d, *J* = 12.10 Hz, 1H) in its ^{1}H NMR spectrum. Its ^{13}C NMR spectrum showed typical signals at δ 39.8, 51.5 and 60.7 corresponding to carbons attached to nitrogen and oxygen atoms respectively (**Fig. 4**).

The deprotection of TBS ether in **107** (TBAF, THF) afforded piperidine alcohol **108** in 92% yield and 98% ee determined by chiral HPLC. The primary hydroxyl group in piperidine alcohol **108** was oxidized using Swern's condition to give aldehyde **94** in 90% yield. The aldehyde **94** was then treated with ethylmagnesium bromide to afford the Boc-protected (+)-conydrine **109** as a single diastereomer in 87% yield. The Boc group in **109** was deprotected under acidic conditions to furnish (+)-α-conhydrine (**1**), $[\alpha]^{25}_D$ = +8.7 (c 0.85, EtOH), {lit.[24c] $[\alpha]^{20}_D$ = +8.9 (EtOH)}.

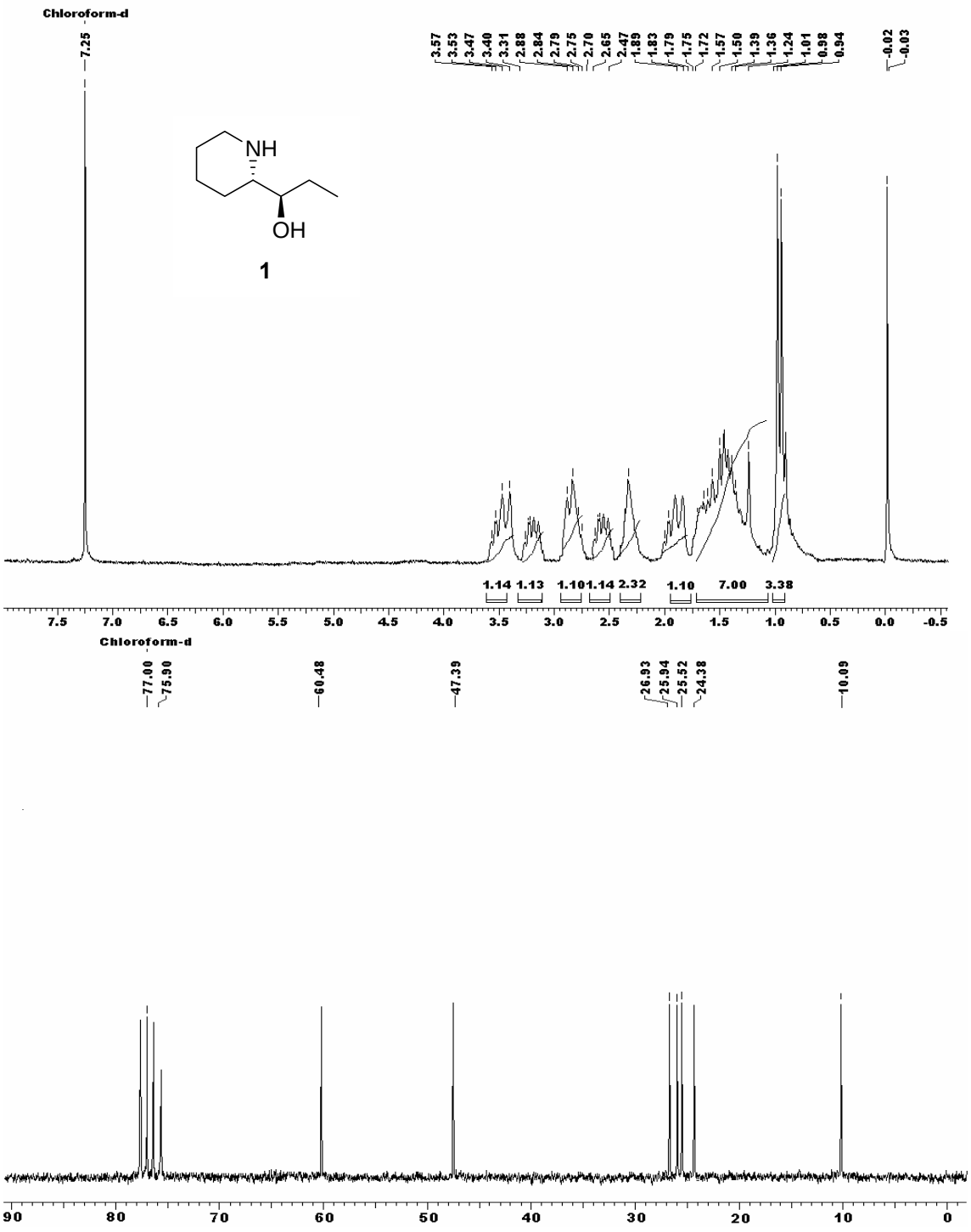
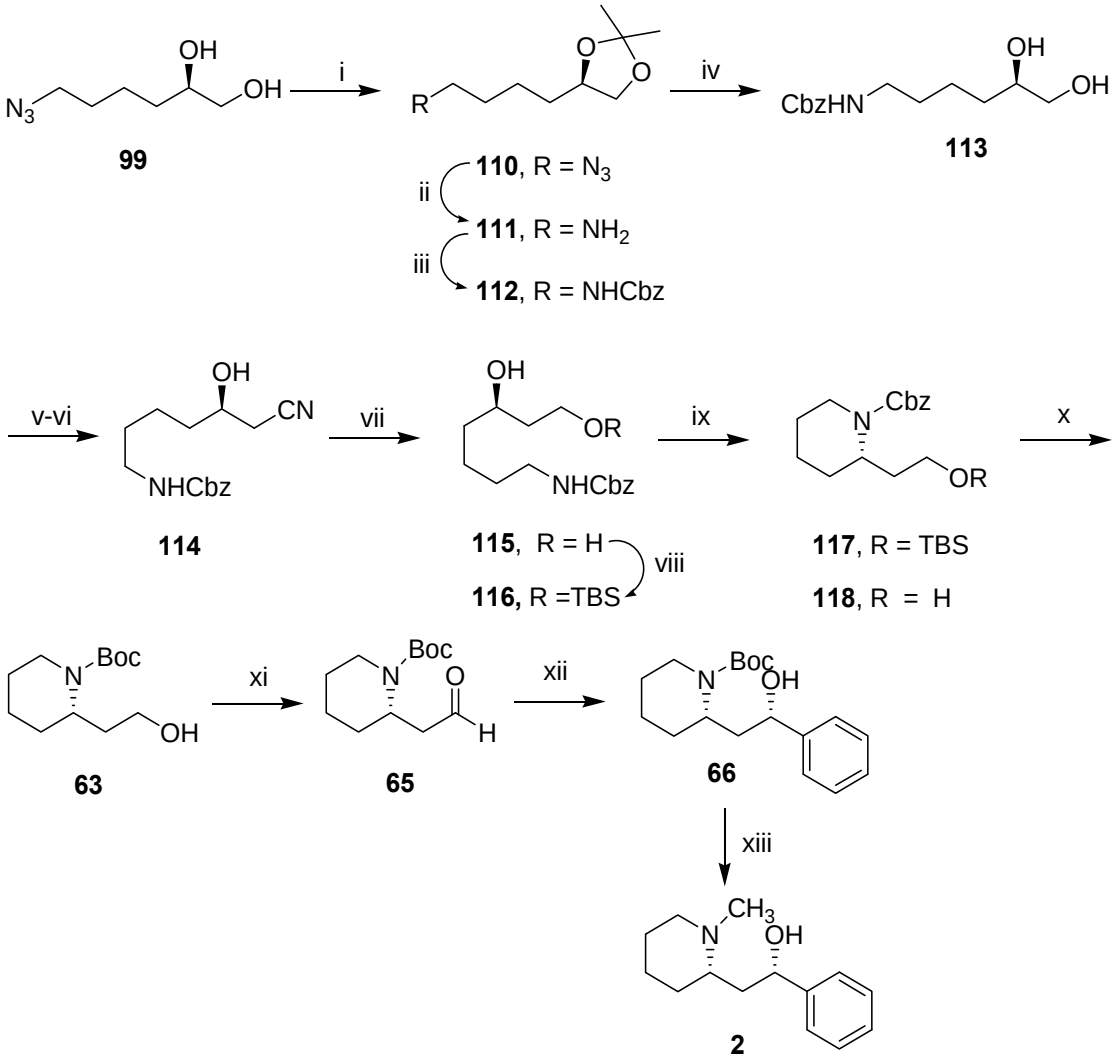


Fig. 5: ^{1}H and ^{13}C NMR spectra of (+)-α-conhydrine (**1**)

2.1.4.2 Enantioselective synthesis of (-)-Sedamine

The complete synthetic sequence for (-)-sedamine (**2**), wherein the intermediate diol **99** derived from L-proline-catalyzed α-aminooxylation reaction has been utilized as a key intermediate, is presented in **Scheme 14**.



Scheme 14: (i) 2,2-dimethoxypropane, *p*-TSA (10 mol%), CH_2Cl_2, 25 °C, 12 h, 98%; (ii) 10% Pd/C, H_2 (20 psi), MeOH, 25 °C, 8 h, 95%; (iii) CbzCl, K_2CO_3, CH_2Cl_2:H_2O (1:1), 25 °C, 7 h, 92%; (iv) excess 80% aq. AcOH, 25 °C 18 h, 98%; (v) *p*-TsCl, Et_3N, CH_2Cl_2, -20 °C, 15 h; (vi) NaCN, EtOH:H_2O (3:2), 0-25 °C, 18 h, 89%; (vii) 1.2 M DIBAL-H; CH_2Cl_2; then $NaBH_4$, MeOH, 25 °C, 5 h, 83%; (viii) TBSCl, imidazole, CH_2Cl_2, 0 °C, 1 h, 85%; (ix) MsCl, Et_3N, CH_2Cl_2, -10 °C, 45 min. then NaH (1 equiv.), THF, 50 °C, 8 h; then 3N HCl in MeOH 25 °C, 2 h, 68%; (x) 10% Pd/C, H_2 (20 psi), MeOH, 25 °C, 5 h, 91%; then $(Boc)_2O$, I_2 (10 mol%), 3 h, 95%; (xi) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 1 h, 84%; (xii) PhMgBr, THF, -78 °C, 4 h, 61%; (xiii) $LiAlH_4$, THF, 70 °C, 8 h, 78%.

Our synthesis of (-)-sedamine (**2**) commenced from diol **99**, which was protected as its acetonide **110** (2,2,-dimethoxypropane, *p*-toluenesulfonic acid)[20]. Its ^{1}H NMR spectrum showed two singlets at δ 1.33 and 1.38 that correspond to dimethyl protons of acetonide moiety. Its ^{13}C NMR spectrum displayed typical signals at δ 25.4, 26.7 and 108.5 corresponding to the dimethyl and quaternary carbons of the acetonide group respectively (**Fig. 6**).

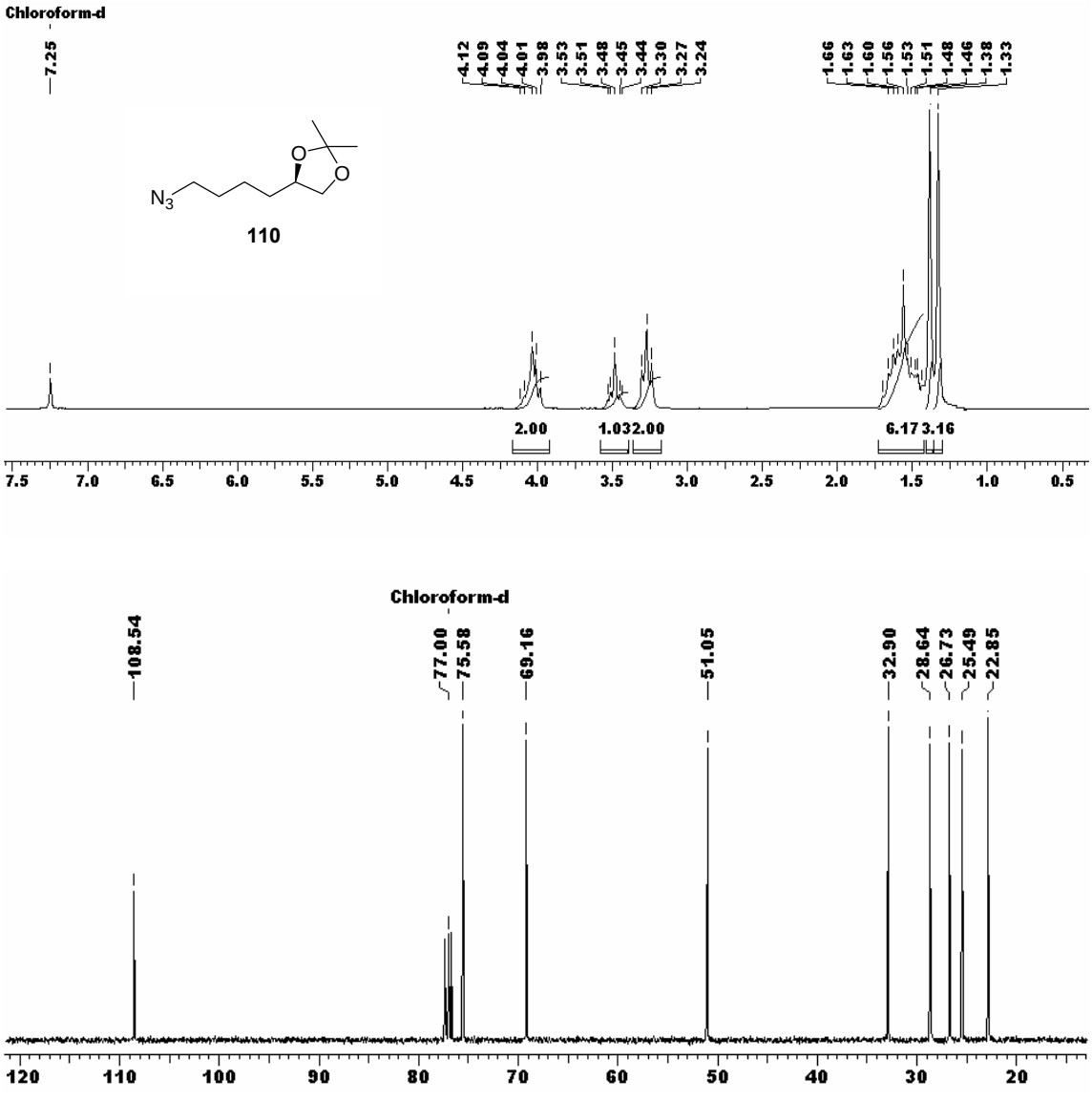


Fig. 6: ^{1}H and ^{13}C NMR spectra of acetonide **110**

Reduction of azide function in **110** under catalytic hydrogenation [10% Pd/C, H_2 (20 psi) in MeOH, 25 ^oC] produced amine **111** in 95% yield. The amine protection [CbzCl (1.5 eq) and K_2CO_3 (2 equiv), CH_2Cl_2:H_2O (1:1)] afforded Cbz-protected[21] amine **112** in 92% yield. Removal of acetonide group in **112** (an excess of 80% aq. AcOH) afforded diol **113**. The ^1H and ^{13}C NMR spectra of **113** showed the disappearance of acetonide group.

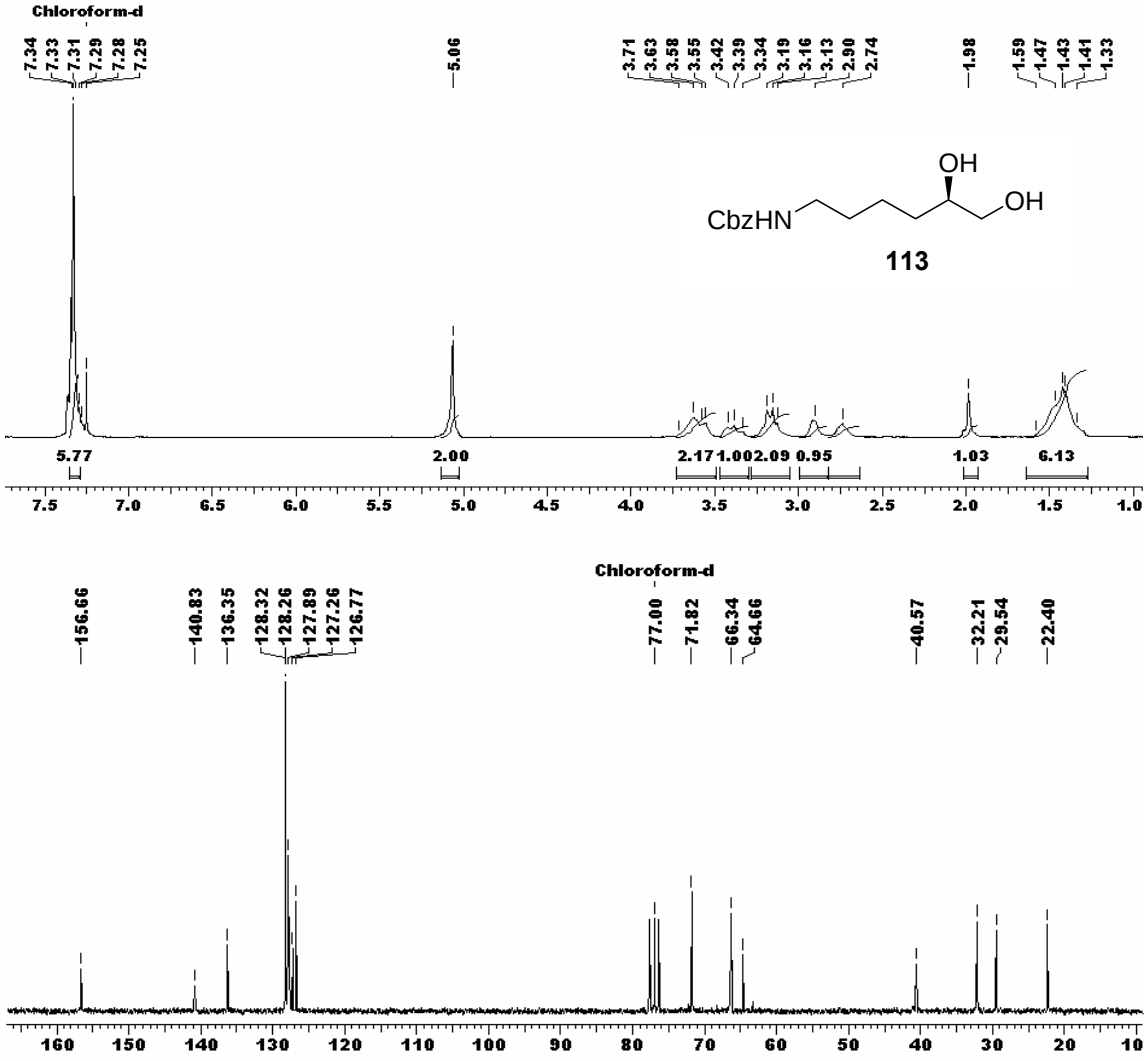


Fig. 7: ^1H and ^{13}C NMR spectra of diol **113**

The formation of diol **113** was further confirmed by two broad singlets at δ 2.74 and 2.90 in its ^1H NMR spectrum corresponding to -CHO**H**-CH_2O**H** protons of diol and further

substantiated by the signals at δ 66.3 and 71.8 in the downfield region of its ^{13}C NMR spectrum that correspond to the carbons attached to oxygen atoms (**Fig. 7**).

The diol **113** was then transformed to cyano derivative **114** in two-steps: selective mono tosylation[22] of primary alcohol and S_N2 displacement of the tosylate with CN^- ion to give nitrile **114** in 89% yield.

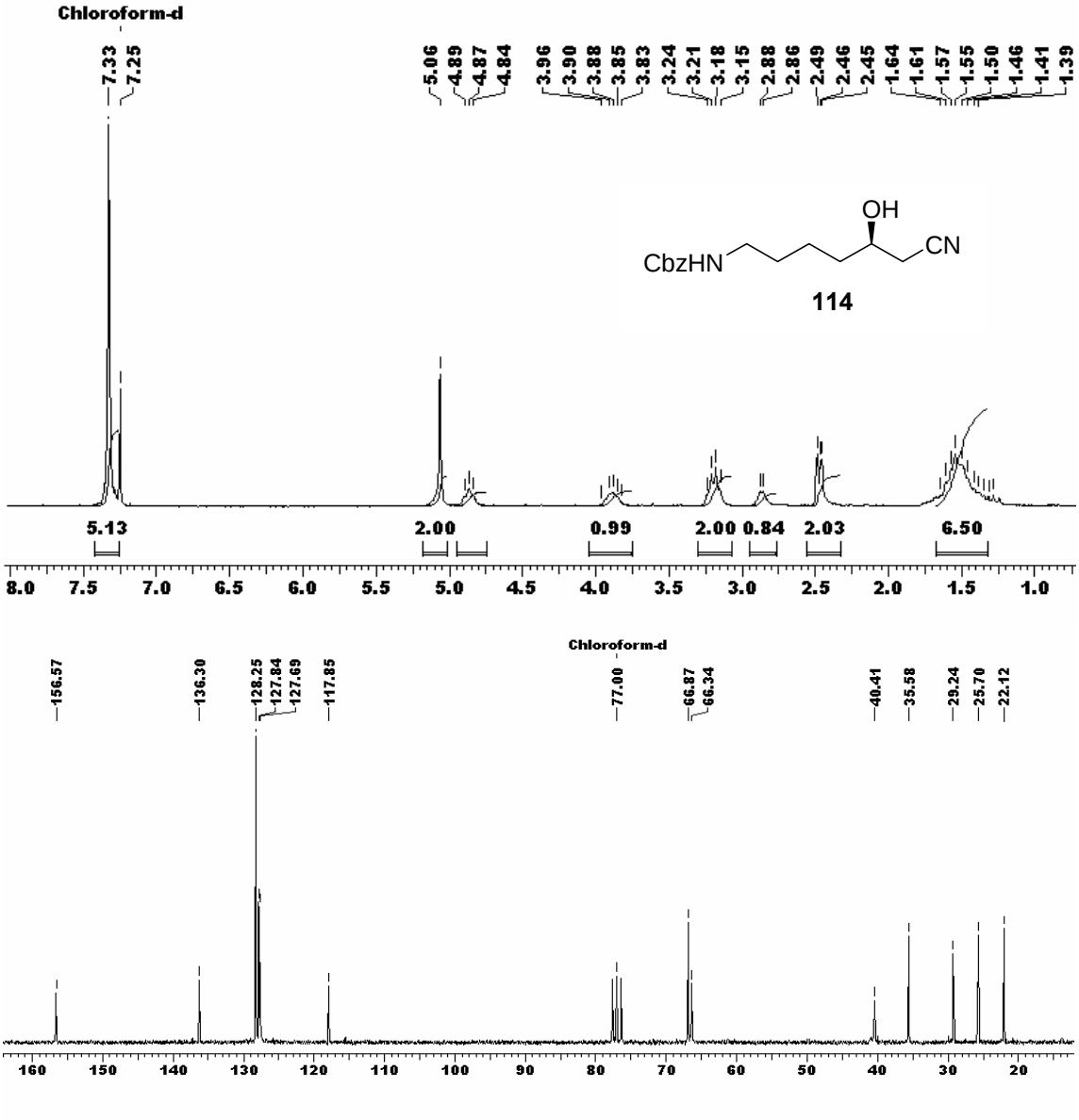


Fig. 8: ^1H and ^{13}C NMR spectra of nitrile **114**

Its ^{1}H NMR spectrum displayed a multiplet at δ 3.15-3.24 for methylene protons of the carbon attached to nitrile (-C**H**$_2$CN). Its ^{13}C NMR spectrum showed a characteristic peak at δ 117.8 that corresponds to nitrile carbon (-CH$_2$**C**N) (**Fig. 8**). The IR spectrum of **114** showed a strong absorption bands at 2249 and 3378 cm^{-1} due to the presence of C≡N and O-H groups respectively. The selective reduction of nitrile **114** (1.2 M DIBAL-H, CH_2Cl_2) to aldehyde *in situ* followed by its treatment with $NaBH_4$ in MeOH produced 1,3-diol **115** in 83% yield. The primary alcohol function in 1,3-diol **115** was selectively protected as its TBS ether (TBSCl, imidazole) to give **116**, followed by the conversion of the secondary free hydroxyl group to its mesylate, which underwent intramolecular cyclization under basic conditions[23] to give the piperidine derivative **117**. The treatment of TBS ether with 3N HCl in MeOH produced piperidine alcohol **118**. Its ^{1}H NMR spectrum displayed typical multiplets at δ 1.37-1.74 (m, 7H), 1.89-2.02 (m, 1H), 2.68-2.82 (m, 1H), 3.26-3.41 (m, 1H), 3.47-3.55 (m, 1H), 4.05 (bd, *J* = 11.2 Hz, 1H), 4.38-4.51 (m, 1H) characteristic of piperidine ring. This was further ascertained by the typical signals at δ 46.7 and 58.3 corresponding to methylene (-CH$_2$**C**H$_2$OH) and methine (-**C**H-NCbz) carbons in its ^{13}C NMR spectrum (**Fig. 9**).

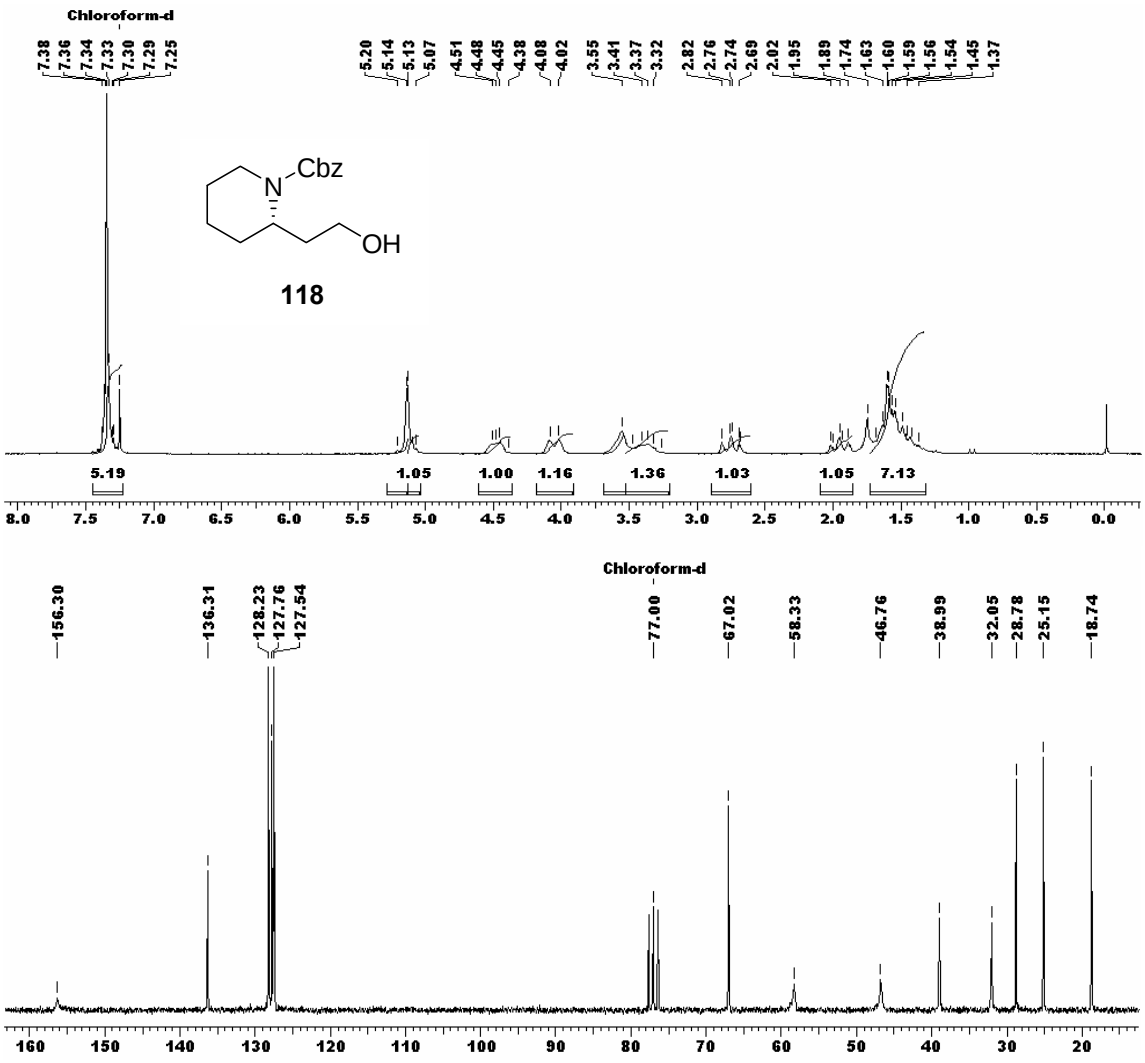


Fig. 9: ^{1}H and ^{13}C NMR spectra of **118**

At this stage, we turned our attention to the stereoselective construction of secondary hydroxyl functionality of (-)-sedamine (**2**). To achieve this, we converted alcohol **118** into the corresponding Boc-protected alcohol **63** in one-pot [catalytic hydrogenation followed by its treatment with [$(Boc)_2O$ and I_2]. Then, piperidine-2-ethanol **63** was subjected to oxidation under Swern condition to give the corresponding aldehyde **65** in 84% yield. Its ^{1}H NMR spectrum showed a triplet at δ 9.73 corresponding to aldehydic

proton (-C**H**O), further substantiated by the appearance of the corresponding carbonyl carbon signal at δ 199.8 in its ^{13}C NMR spectrum (**Fig. 10**).

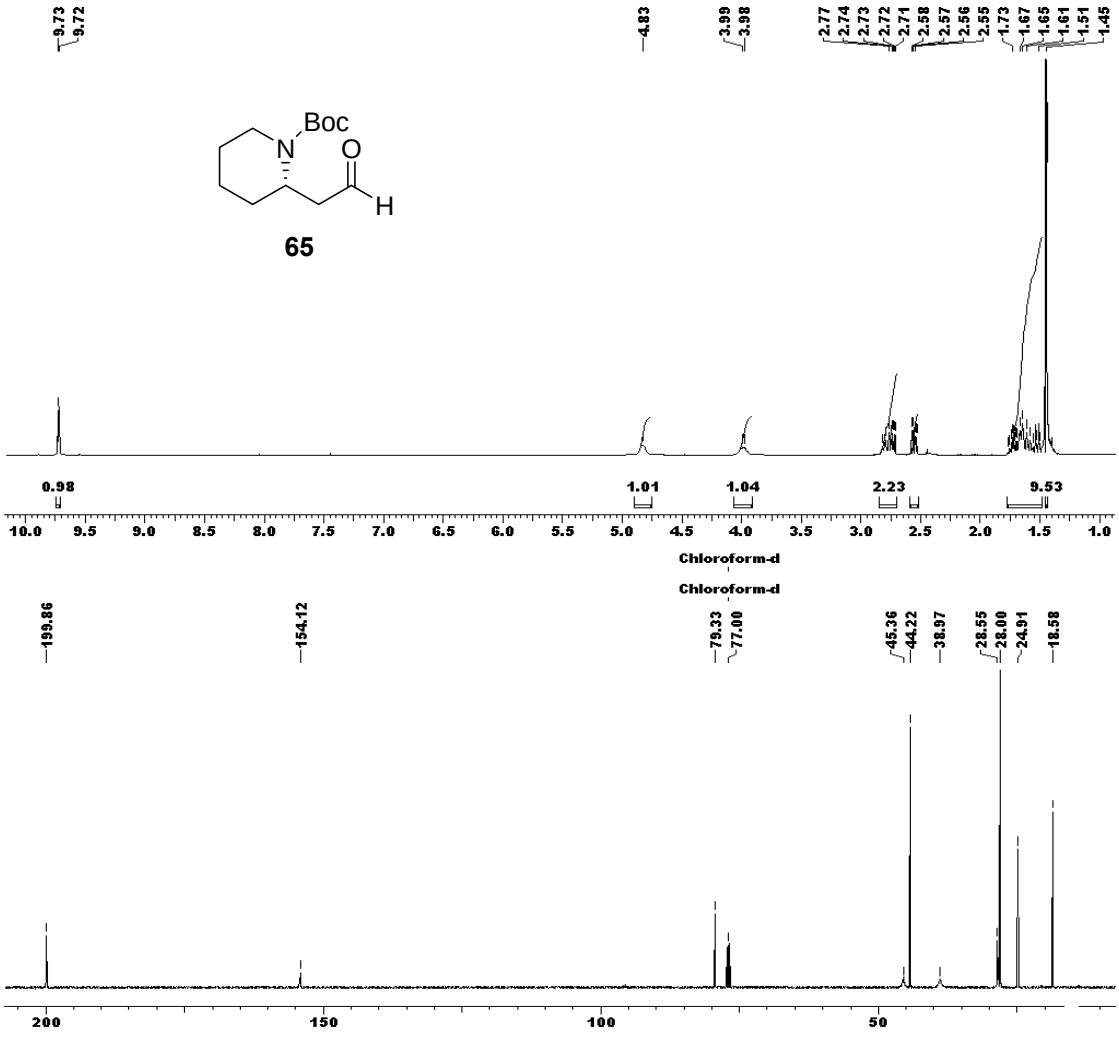


Fig. 10: ^{1}H and ^{13}C NMR spectra of aldehyde **65**

Finally, the addition of PhMgBr to aldehyde **65** resulted in mixtures of *syn* and *anti* alcohols in 2:1 ratio and 90% yield. However, these diastereomers were readily separated by simple column chromatography. The major isomer (61% isolated yield) was subjected to reduction with $LiAlH_4$ to give (-)-sedamine **2** in 86% yield. The spectral data of **2** were in complete agreement with the reported values.[12,14] For example, the ^{1}H NMR spectrum

of **2** displayed a singlet at δ 2.50 corresponding to the methyl protons and a doublet of doublet at δ 4.89 (dd, J = 2.8, 10.7 Hz, 1H) corresponding to benzylic methine protons. The aromatic protons had displayed multiplets at δ 7.28-7.39. Its ^{13}C NMR spectrum showed the presence of methyl carbon (δ 39.9) as well as the methine benzylic carbon attached to oxygen (δ 73.3) (**Fig. 11**).

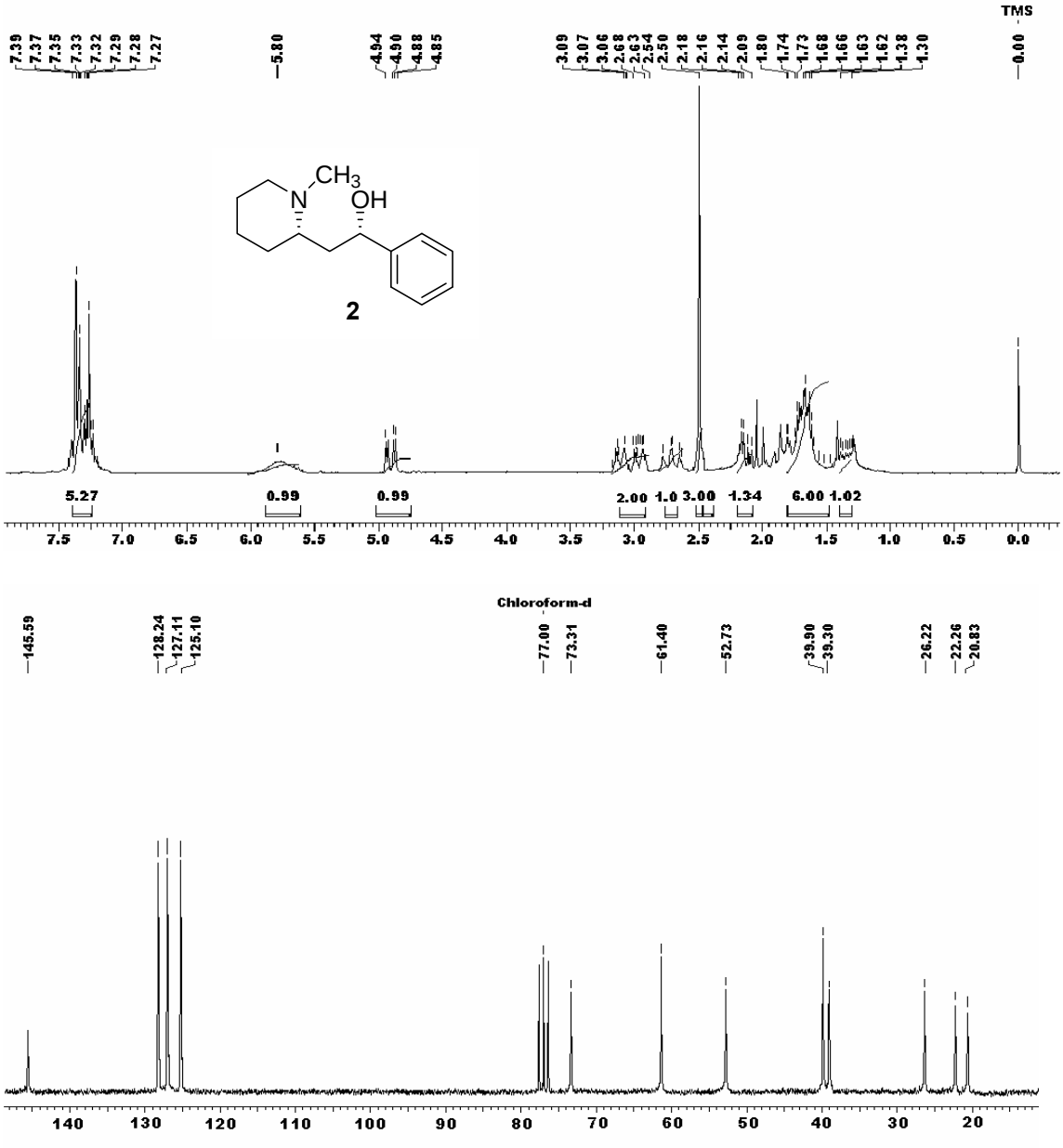


Fig. 11: ^{1}H and ^{13}C NMR spectra of (-)-sedamine **2**

2.1.5 Conclusion

In conclusion, we have achieved an efficient synthesis of (+)-α-conhydrine (**1**) (overall yield 25.0%, 98%ee) and (-)-sedamine (**2**) (overall yield 31.5%, 94% ee). Both the synthesis involved L-proline-catalyzed α-aminooxylation as the key chiral inducing reaction. The synthetic strategy described herein has significant potential for the synthesis of a variety of other biologically important piperidine alkaloids.

2.1.6 Experimental section

6-Azidohexan-1-ol (104)

To a stirred solution of 1,6-hexanediol **103** (7.2 g, 60.9 mmol) and Et_3N (8.4 mL, 60.9 mmol) in CH_2Cl_2 (200 mL), at 0 °C was added *p*-toluenesulfonyl chloride (11.0 g, 57.8 mmol). After stirring for 1 h at 0 °C, the reaction mixture was poured into ice water (150 mL), washed with aq. H_2SO_4 (10%), saturated aq. $NaHCO_3$ and brine, dried over anhyd. Na_2SO_4 and the solvent was distilled off under reduced pressure to give the crude product (12.0 g). The crude tosylate (6.0 g, 22.0 mmol) was then dissolved in DMF (110 mL) followed by the addition of sodium azide (5.7 g, 88.1 mmol). The reaction mixture was then heated at 80 °C for 15 h followed by quenching it with the addition of water. The aqueous layer was extracted with Et_2O (3 x 100 mL) and the combined organic layers were dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure and the crude product purified by column chromatography over silica gel using pet. ether:EtOAc (90:10) as eluent to yield pure azido alcohol **104** in 80% yield.

Yield: 80% (2.52 g); **IR** ($CHCl_3$, cm^{-1}): 3228, 2105, 1452, 1338, 1225, 1110, 1040, 935, 784; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.26 (br s, 1H), 1.33-1.45 (m, 4H), 1.49-1.64 (m, 4H), 3.26 (t, *J* = 6.8 Hz, 2H), 3.64 (t, *J* = 6.2 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ

25.1, 26.3, 28.5, 32.2, 51.1, 62.2; **Anal.** Calcd for $C_6H_{13}N_3O$: C, 50.33; H, 9.15; N, 29.35; Found. C, 49.99; H, 9.30; N, 29.02%.

(R)-6-Azidohexane-1,2-diol (99)

Swern oxidation: To a stirred solution of oxalyl chloride $(COCl)_2$ (4.4 g, 34.9 mmol) in CH_2Cl_2 (30 mL) at -78 °C, was added a solution of DMSO (3.7 mL, 52.3 mmol). The reaction mixture was stirred for 20 min. followed by the addition of a solution of 6-azidohexan-1-ol (**104**) (2.5 g, 17.4 mmol) in CH_2Cl_2 (20 mL). After stirring for 1 h at -78 °C, the reaction was quenched by the addition of Et_3N (9.7 mL, 69.8 mmol). The reaction mixture was then stirred for 30 min. followed by the addition of water (70 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 60 mL). The combined organic layer was washed with water (3 x 30 mL), dried over anhyd. Na_2SO_4 and concentrated to give the corresponding crude aldehyde **100**.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31-1.65 (m, 6H), 2.31-2.48 (m, 2H), 3.26 (t, J = 6.6, 13.2 Hz, 2H), 9.75 (t, J = 1.7 Hz, 1H).

α-Aminooxylation: Aldehyde **100** (2.0 g, 14.16 mmol) was dissolved in CH_3CN (60 mL) and the solution was cooled to -20 °C followed by the addition of nitrosobenzene (1.44 g, 13.45 mmol) and L-proline (407 mg, 25 mol%). After 24 h, the reaction mixture was warmed to 0 °C, followed by dilution with anhyd. methanol (20 mL) and addition of $NaBH_4$ (1.07 g, 28.3 mmol). The reaction was quenched after 20 min. by pouring of the reaction mixture into a vigorously stirred biphasic solution of Et_2O and aqueous NH_4Cl. The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude product which was dissolved in MeOH (40 mL) followed by the

addition of $CuSO_4$ (0.675 g, 4.2 mmol). After stirring for 24 h at 25 °C, the reaction mixture was quenched by the addition of a solution of saturated aq. NH_4Cl (40 mL). The organic layer was separated and the aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude product which was purified by column chromatography over silica gel using pet. ether:EtOAc (60:40) as eluent to give pure diol **99** in 61% yield.

Yield: 61% (0.780 g); $[\alpha]_D^{25}$ +33.5 (*c* 0.5, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3127, 3020, 2115, 1540, 1452, 1330, 1212, 1125, 1035, 932, 775, 669; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.39-1.39 (m, 6H), 1.98 (br s, 2H), 3.28 (t, *J* = 6.3, 2H), 3.33-3.48 (m, 1H), 3.66 (br d, *J* = 11.0 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 22.8, 28.8, 32.4, 51.3, 66.6, 72.0; **Anal.** Calcd for $C_6H_{13}N_3O_2$: C, 45.27; H, 8.23; N, 26.40; Found. C, 45.41; H, 8.17; Cl, 25.98%.

(2R)-1-((*tert*-Butyl)dimethylsilyloxy)-6-azido-hexan-2-ol (105)

To a stirred solution of diol **99** (2.0 g, 12.5 mmol) and imidazole (1.0 g, 15.0 mmol) in CH_2Cl_2 (50 mL) was added TBDMSCl (1.89 g, 12.5 mmol) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C, solvent distilled off under reduced pressure and the crude product purified by column chromatography over silica gel using pet. ether:EtOAc (95:5) as eluent to give TBS-ether **105** in 95% yield.

Yield: 95% (3.26 g); **IR** ($CHCl_3$, cm^{-1}): 3305, 2930, 2812, 1460, 1230, 1020, 745, 700, 605; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.06 (s, 6H), 0.89 (s, 9H), 1.38-1.64 (m, 6H), 2.44 (br d, *J* = 2.9 Hz, 1H), 3.24-3.42 (m, 3H), 3.58-3.69 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.47, 18.23, 22.78, 25.8, 28.8, 32.1, 51.29, 67.11, 71.4; **Anal.** Calcd for $C_{12}H_{27}N_3O_2Si$: C, 52.71; H, 9.95; N, 15.37; Found. C, 52.66; H, 10.01; N, 15.29%.

(2S)-*tert*-Butyl-2-(tert-Butyl)dimethylsilyloxymethyl)-piperidine-1-carboxylate (107)

To a stirred solution of TBS ether **105** (2.5 g, 9.14 mmol) and Et_3N (1.78 mL, 12.7 mmol) in CH_2Cl_2 (60 mL) at 0 °C was added methanesulfonyl chloride (0.707 mL, 9.14 mmol) drop-wise using a syringe. After stirring at 0 °C for 0.5 h, the mixture was poured into ice-water (40 mL), washed with aqueous $NaHCO_3$, and brine, dried over anhyd. Na_2SO_4. Solvent was distilled off under reduced pressure to give the crude mesylate (3.2 g), which was added to a stirred suspension of 10 % Pd/C (40 mg) and Et_3N (1.27 mL, 12.6 mmol) in MeOH (10 mL) under hydrogen atmosphere (H_2, 20 psi) at 25 °C. After 7 h, the mixture was filtered through a pad of celite and rinsed with MeOH (3 x 30 mL). The combined organic layer was concentrated under reduced pressure and the crude product (2.0 g, 8.7 mmol) was stirred with $(Boc)_2O$ (2.0 mL, 8.7 mmol) and I_2 (220 mg, 10 mol%) for 3 h and extracted with EtOAc (3 x 20 mL) and washed with water followed by aq. sodium thiosulphate to give the crude **107**, which was purified by column chromatography using pet. ether:EtOAc (9:1) as eluent to give the pure TBS ether **107**.

Yield: 76% (2.3 g); $[\alpha]_D^{25}$ -35.8 (*c* 0.7, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3442, 2812, 1650, 1020, 745, 700, 605; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.87 (s, 9H), 1.21-1.32 (m, 1H), 1.44 (s, 9H), 1.49-1.61 (m, 4H), 1.75-1.87 (m, 1H), 2.63-2.79 (m, 1H), 3.57 (dd, *J* = 6.9, 9.8 Hz, 1H), 3.67 (dd, *J* = 8.4, 9.6 Hz, 1H), 3.97 (br d, *J* = 12.1 Hz, 1H), 4.16 (br, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.41, 18.1, 19.0, 24.4, 25.2, 25.8, 28.4, 39.9, 51.5, 60.7, 79.0, 155.1; **Anal.** Calcd for $C_{17}H_{35}NO_3Si$: C, 61.96; H, 10.70; N, 4.25; Found. C, 60.99; H, 10.79; N, 4.58%.

(S)-*tert*-Butyl 2-(hydroxymethyl)piperidine-1-carboxylate (108)

To a stirred solution of carbamate **107** (1.5 g, 4.5 mmol) in THF was added a solution of tetrabutylammonium fluoride (TBAF) (1.19 g, 1M in THF, 4.5 mmol) at 0 °C and stirred for 8 h. The reaction mixture was quenched by the addition of water and the organic phase was separated. The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organic layers were dried over anhyd. Na_2SO_4, the solvent distilled off under reduced pressure and the crude product purified by column chromatography over silica gel using pet. ether:EtOAc (7:3) as eluent to give piperidine alcohol **108** as a gum in 92% yield.

Yield: 92% (0.897 g); Chiral Column: CHIRALCEL OD-H, length 25x4.6 mm, wavelength: 230 nm, flow rate 1.0 mL per min. Mobile phase: 5% isopropyl alcohol in hexane; ee = 98%; $[\alpha]_D^{25}$ -40.1 (*c* 1, $CHCl_3$), {lit.[24a] $[\alpha]_D^{25}$ -40.5 (*c* 1, $CHCl_3$)}; **IR** ($CHCl_3$ cm^{-1}): 3442, 2940, 2890, 1655, 1422, 1370, 1280, 1170, 1150, 1060, 1050, 870; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.45 (s, 9H), 1.51-1.76 (m, 6 H), 2.11 (brs, 1H), 2.78-2.92 (m, 1H), 3.5-3.6 (m, 1H), 3.74-3.96 (m, 2H), 4.23-4.34 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 18.9, 24.4, 24.9, 28.0, 39.5, 51.7, 60.0, 79.1, 155.5; **Anal.** Calcd for $C_{11}H_{21}NO_3$: C, 61.37; H, 9.83, N, 6.51. Found: C, 61.40, H, 9.79, N, 6.49%.

(S)-*tert*-Butyl 2-formylpiperidine-1-carboxylate (94)

To a stirred solution of oxalyl chloride $(COCl)_2$ (0.625 mL, 7.24 mmol) in CH_2Cl_2 (25 mL) at -78 °C, was added a solution of DMSO (0.77 mL, 10.86 mmol). The reaction mixture was stirred for 20 min. followed by the addition of a solution of (S)-*tert*-butyl 2-(hydroxymethyl)piperidine-1-carboxylate (**108**) (0.780 g, 3.64 mmol) in CH_2Cl_2 (20 mL). After stirring for 1 h at -78 °C, the reaction was quenched by the addition of Et_3N (2.01

mL, 14.49 mmol). The reaction mixture was then stirred for 30 min. at 25 ^{o}C followed by the addition of water (100 mL). The organic phase was separated and the aq. phase was extracted with CH_2Cl_2 (3 x 60 mL). The combined organic layer was washed with water (3 x 30 mL), dried over anhyd. Na_2SO_4 and concentrated to give the corresponding crude aldehyde which was purified by column chromatography over silica gel using pet. ether:EtOAc (7:3) as a eluent to give piperidine aldehyde **94** as colorless gum in 90% yield.

Yield: 90% (0.7 g); $[\alpha]_D^{25}$ -77.8 (*c* 1.21, $CHCl_3$), {lit.[24b] $[\alpha]_D^{25}$ -77.9 (*c* 1.49, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): 2980, 2940, 2872, 1740, 1702, 1485, 1411, 1372, 1280, 1250, 1167, 1051, 1002, 1062, 871, 778; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.16-1.20 (m, 2H), 1.38 (s, 9H), 1.50-1.62 (m, 3H), 2.06-2.11 (m, 1H), 2.77-2.87 (brs, 1H), 3.80-3.93 (brs, 1H), 4.40-4.53 (brs, 1H), 9.49 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 20.8, 23.3, 24.6, 28.1, 41.7, 42.9, 60.4, 61.4, 80.1, 155.0, 155.6, 200.8; **Anal.** Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57; Found. C, 62.01; H, 8.70; N, 6.45%.

(+)-Conhydrine (1)

A freshly prepared Grignard reagent (EtMgBr) from ethylbromide (0.62 g, 5.68 mmol) and Mg (0.165 g, 6.82 mmol) in diethyl ether (15 mL) at 0 °C was added dropwise to a solution of amino aldehyde **94** (0.5 g, 2.34 mmol) in diethyl ether (7 mL). After stirring at this temperature for 2 h, saturated NH_4Cl (40 mL) was added and the mixture was extracted with diethyl ether (2 x 15 mL). The combined organic layers were washed with brine and dried over anhyd. Na_2SO_4 and the solvent was evaporated under reduced pressure. After flash chromatography using pet.ether/ EtOAc, (6:4), the compound **109** (0.5 g) was obtained as a colorless oil. To a solution of **109** (100 mg, 0.411 mmol) in dry

CH_2Cl_2 (1 mL) at 0 ^oC was added trifluoroacetic acid (1 mL, 8.77 mmol). The reaction mixture was stirred at room temperature for 12 h. After completion of reaction, it mixture was washed with aq. $NaHCO_3$ and the mixture extracted with dichloromethane (3 x 10 mL) and aq. layer extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over anhyd. Na_2SO_4, and concentrated under reduced pressure to give the crude product which was purified by silica gel column chromatography using CH_3OH/CH_2Cl_2 (4:6) as eluent to give(+)-conhydrine, **1**.

Yield: 86% (50 mg); $[\alpha]_D^{25}$ +8.7 (*c* 1.72, EtOH), {lit.[24c] $[\alpha]_D^{25}$ +8.9 (EtOH)}; **IR** ($CHCl_3$, cm^{-1}): 3280, 3110, 2971, 2945, 2815, 1422, 1348, 1250, 1106, 1062, 1005, 972, 940, 811; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.98 (t, *J* = 7.0 Hz, 3H), 1.24-1.57 (m, 7H), 1.62-1.89 (m, 1H), 2.47 (brs, 2H), 2.65-2.72 (m, 1H), 2.73-2.88 (m, 1H), 3.12-3.31 (m, 1H), 3.40-3.57 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 10.0, 24.3, 25.5, 25.9, 29.9, 47.3, 60.4, 75.9; **Anal.** Calcd for $C_8H_{17}NO$: C, 67.09; H, 11.96; N, 9.78; Found. C, 66.99; H, 11.89; N, 9.85%.

(-)-Sedamine 2

(R)-4-(4-Azidobutyl)-2,2-dimethyl-1,3-dioxolane (110)

To a mixture of azido diol **99** (2.5 g, 15.7 mmol), 2,2-dimethoxypropane (7.7 mL, 62.2 mmol) and dry CH_2Cl_2 (25 mL) was added *p*-TSA (0.27 g, 10 mol%) and the reaction mixture was stirred at 25 ^oC for 12 h. After completion of the reaction as monitored by TLC, it was neutralized with triethylamine, concentrated and purified by silica gel chromatography using pet. ether:EtOAc (9:1) as eluent to yield **110** as an oil

Yield: 98% (3.07 g); $[\alpha]_D^{25}$ -20.0 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 2984, 2939, 2864, 2091, 1738, 1457, 1371, 1247, 1216, 1151, 1055, 853; **^{1}H NMR** (200 MHz, $CDCl_3$): δ

1.33 (s, 3H), 1.38 (s, 3H), 1.43-1.70 (m, 6H), 3.27 (t, *J* = 6.5 Hz, 2H), 3.44-3.53 (m, 1H), 3.98-4.12 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 22.8, 25.4, 26.7, 28.6, 32.9, 51.0, 69.1, 75.5, 108.5; **Anal.** Calcd for $C_9H_{17}N_3O_2$: C, 54.25; H, 8.60; N, 21.09; Found. C, 54.50; H, 8.32; N, 20.98%.

4-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)butan-1-amine (111)

To a stirred mixture of azide **110 (**2.8 g 14.0 mmol) in dry methanol (20 mL) was added 10% Pd/C (40 mg), filled with H_2 (20 psi) and the reaction mixture was stirred at 25 ^oC for 8 h. After completion of the reaction as monitored by TLC, mixture was filtered through a pad of celite and rinsed with MeOH (3 x 30 mL). The combined organic layer was concentrated under reduced pressure to give the crude amine **111**, which was purified by column chromatography using $CHCl_3$: MeOH (9:1) to give pure amine **111** as a colorless oil.

Yield: 95% (2.32 g); $[\alpha]_D^{25}$ -16.7 (*c* 2.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3420, 2980, 2932, 2860, 1632, 1559, 1460, 1364, 1251, 1055, 856, 605; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.32 (s, 3H), 1.37 (s, 3H), 1.46-1.68 (m, 6H), 2.77 (t, *J* = 7.3 Hz, 1H), 3.43-3.53 (m, 1H), 3.72 (br s, 2H), 3.97-4.14 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 22.7, 25.3, 26.6, 31.0, 32.9, 40.6, 69.0, 75.4, 108.3; **Anal.** Calcd for $C_9H_{19}NO_2$: C, 62.39; H, 11.05; N, 8.08; Found. C, 62.52; H, 10.97; N, 7.99%.

Benzyl 4-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)butylcarbamate (112)

To a stirred solution of amine **111** (2 g, 11.5 mmol) in a mixture of water (15 mL) and dichloromethane (15 mL), potassium carbonate (3.19 g, 23.0 mmol) was added. After 15 min, benzyl chloroformate (1.97 mL, 13.85 mmol) was introduced with the help of syringe and the reaction mixture was stirred at 25 ^oC for 7 h. After completion of the

reaction, organic layer was decanted separately and the aqueous layer extracted with dichloromethane (3 x 20 mL). The combined organic layer was dried over anhyd. Na_2SO_4, and the solvent was evaporated *in vacuo* and the residue purified by column chromatography using pet.ether:EtOAc (7:3) to give pure carbamate **112** as a colorless oil.

Yield: 92% (3.25 g); $[\alpha]_D^{25}$ -19.0 (*c* 2.1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3347, 3035, 3063, 2977, 2936, 2867, 1710, 1535, 1450, 1367, 1244, 1052, 853, 736; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.33 (s, 3H), 1.38 (s, 3H), 1.44-1.59 (m, 6H), 3.18 (dd, *J* = 6.1, 12.5 Hz, 2H), 3.43-3.52 (m, 1H), 3.97-4.11 (m, 2H), 4.78 (brs, 1H), 5.08 (s, 2H), 7.29-7.39 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 22.8, 25.5, 26.7, 29.7, 32.9, 40.6, 66.3, 69.2, 75.6, 108.5, 127.8, 128.3, 136.4, 156.3, **Anal.** Calcd for $C_{17}H_{25}NO_4$: C, 66.43; H, 8.20; N, 4.56; Found. C, 66.51; H, 7.97; N, 4.49%.

Benzyl (R)-5,6-dihydroxyhexylcarbamate (113)

A solution of acetonide **112** (3.0 g, 9.75 mmol) and 80% aq. AcOH (15 mL) was stirred at 25 ^oC for 18 h. After completion of reaction, acetic acid and water was removed under reduced pressure and the crude mixture was extracted with EtOAc (3 x 20 mL), washed with water 10% $NaHCO_3$. The combined organic layer was dried over anhyd. Na_2SO_4 and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography using pet.ether:EtOAc (5:5) to give pure diol **113**.

Yield: 98% (2.55 g); $[\alpha]_D^{25}$ +18 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3401, 2941, 1640, 1527, 1340, 1066, 1028, 698; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.33-1.59 (m, 6H), 1.98 (brs, 1H), 2.74 (brs, 1H), (2.90 (brs, 1H), 3.16 (t, *J* = 6.0, 12.3 Hz, 2H), 3.34-3.42 (m, 1H), 3.55-3.71 (m, 2H), 5.06 (s, 2H), 7.28-7.34 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ

22.4, 29.5, 32.2, 40.5, 64.6, 66.3, 71.8, 126.7, 127.2, 127.8, 128.2, 128.3, 136.3, 140.8, 156.6; **Anal.** Calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24; Found. C, 63.02; H, 7.58; N, 5.41%.

Benzyl (R)-6-cyano-5-hydroxyhexylcarbamate (114)

To a stirred solution of diol **113** (1.5 g, 5.6 1.3 mmol) and triethylamine (0.858 mL, 6.1 mmol) in dry CH_2Cl_2 (180 mL) at -20 ^oC was added p-toluenesulfonyl chloride (1.1 g, 6.1 mmol) portion-wise using solid addition funnel. After stirring at -20-0 ^oC for 15 h the reaction mixture was poured into ice water (30 mL), washed with 20% aq. H_2SO_4, saturated aq. $NaHCO_3$, brine and dried over anhyd. Na_2SO_4. The solvent was evaporated *in vacuo* to give mono tosylate. The crude tosylate (1 g, 2.37 mmol) was taken up in EtOH:H_2O (3:2 v/v, 15 mL), cooled at 0°C and NaCN (0.697 g, 14.2 mmol) was added. The mixture was slowly allowed to warm to room temperature. After stirring for 18 h, it was diluted with water and extracted with CH_2Cl_2. The organic layer was washed with brine and water, dried over anhyd. Na_2SO_4 and concentrated. The crude product was purified by column chromatography using pet.ether:EtOAc (7:3) to give pure cyano compound **114** as a colorless oil.

Yield: 89% (0.585 mg;) $[\alpha]_D^{25}$ +21.5 (*c* 1.1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3378, 3066, 2936, 2860, 2249, 1704, 1525, 1453, 1254, 1134, 1024, 746, 695; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.28-1.64 (m, 6H), 2.46 (brd, *J* = 2.1, 6.5 Hz, 2H), 2.87 (brs, 1H), 3.15-3.224 (m, 2H), 3.83-3.96 (m, 1H), 4.87 (t, *J* = 5.8, 10.5 Hz, 1H), 5.06 (s, 2H), 7.33 (s, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 22.1, 25.7, 29.2, 35.5, 40.4, 66.3, 66.8, 117.8, 127.6, 127.8, 128.2, 136.3, 156.5; **Anal.** Calcd for $C_{15}H_{20}N_2O_3$: C, 65.20; H, 7.30; N, 10.14; Found. C, 65.39; H, 7.12; N, 9.98%.

Benzyl (R)-5,7-dihydroxyheptylcarbamate (115)

To a stirred solution of nitrile **114** (1.0 g, 3.61 mmol) in CH_2Cl_2 (26 mL) at –78 °C was added dropwise DIBAL-H (4.7 mL, 4.7 mmol, 1.0 M in hexanes). After 5 h, aq. HCl (10%, 10 mL) was added and the mixture was stirred at –78 °C for 30 min, before being allowed to warm to room temperature. After 30 min, aq. HCl (10%, 20 mL) was added, and the mixture was extracted with Et_2O (6 × 30 mL). The organic layers were dried over anhyd. Na_2SO_4 and the solvent was evaporated under reduced pressure to give the crude aldehyde. The aldehyde (0.86 g) was dissolved in MeOH (20 mL) at room temperature and solution cooled to 0 ^oC. Then $NaBH_4$ (380 mg, 10.0 mmol) was added in portions. After being stirred at room temperature for 3 h, the mixture was concentrated. The residue was partitioned between ethyl acetate (40 mL) and water (20 mL). The aqueous layer was extracted with ethyl acetate (3 x 30 mL). The combined organic layer was washed with brine and dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using pet.ether:EtOAc (1:1) to afford diol **115**.

Yield: 83% (0.720 g); $[\alpha]_D^{25}$ +18.7 (*c* 1.04, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 2980, 2940, 2872, 1740, 1702, 1485, 1411, 1372, 1280, 1250, 1167, 1051, 1002, 1062, 871, 778; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.24-1.69 (m, 8H), 2.66 (brs, 2H), 3.18 (dd, *J* = 6.0, 12.2 Hz, 2H), 3.54-3.92 (m, 3H), 4.89 (brs, 1H), 5.06 (s, 2H), 7.27-7.37 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 22.4, 29.6, 36.9, 38.3, 40.7, 60.7, 66.4, 70.7, 127.9, 128.1, 128.3, 136.5, 156.6; **Anal.** Calcd for $C_{15}H_{23}NO_4$: C, 64.03; H, 8.24; N, 4.98; Found. C, 63.97; H, 8.16; N, 5.01%.

Benzyl (R)-5-hydroxy-7-(*tert* butyldimethylsilyloxy)heptyl carbamate (116)

To a stirred solution of diol **115** (1.0 g, 3.5 mmol) and imidazole (290 mg, 4.2 mmol) in CH_2Cl_2 (20 mL) was added TBDMSCl (0.536 g, 3.5 mmol) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C, solvent distilled off under reduced pressure and crude product purified by column chromatography over silica gel using pet.ether:EtOAc (80:20) as eluent to give TBS ether **116** in 85% yield.

Yield: 85% (1.2 g); $[\alpha]_D^{25}$ +21.8 (*c* 1.1, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.07 (s, 6H), 0.89 (s, 9H), 1.31-1.57 (m, 8H), 3.18 (dd, *J* = 6.3, 11.9 Hz, 2H), 3.45-3.63 (m, 1H), 3.76-3.82 (m, 1H), 3.85-3.90 (m, 1H), 4.81 (brs, 1H), 5.06 (s, 2H), 7.28-7.33 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.4, 18.1, 22.6, 25.9, 29.7, 29.9, 37.0, 38.3, 40.9, 62.9, 66.5, 71.9, 128.0, 128.1, 128.4, 136.7, 156.3.

(S)-Benzyl 2-(2-hydroxyethyl)piperidine-1-carboxylate (118)

To a stirred solution of TBS ether **116** (1 g, 2.5 mmol) and Et_3N (0.527 mL, 3.7 mmol) in CH_2Cl_2 (30 mL) at 0 °C was added methanesulfonyl chloride (0.195 mL, 2.5 mmol) drop-wise using a syringe. After stirring at 0 °C for 0.5 h, the mixture was poured into ice-water (30 mL), washed with aqueous $NaHCO_3$, brine and dried over anhyd. Na_2SO_4. Solvent was distilled off under reduced pressure to give the crude mesylate (1.2 g). To a stirred solution of crude mesylate (1 g, 2.11 mmol) at -40 ^oC in THF (200 mL) was added a suspension of NaH (84 mg, 2.11 mmol in THF (10 mL) over a period of 15 min. After stirring for 1 h at that temperature, the mixture was warmed to 50 ^oC and stirred for another 2 h. It was then quenched by the addition of saturated NH_4Cl and the aqueous phase was extracted with brine, dried over anhyd. Na_2SO_4 and concentrated in vacuo. The residue was stirred in 3N HCl in MeOH for 2 h at 25 ^oC then quenched with cold water (5

mL) and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layer was washed with saturated $NaHCO_3$, brine and dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using pet.ether:EtOAc (1:1) to afford pure alcohol **118**.

Yield: 68% (0.45 g); $[\alpha]_D^{25}$ -18.5 (*c* 1, $CHCl_3$), **IR** ($CHCl_3$, cm^{-1}): 3427, 2940, 2864, 1674, 1497, 1429, 1351, 1265, 1172, 1054, 755, 698; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.37-1.74 (m, 7H), 1.89-2.02 (m, 1H), 2.68-2.82 (m, 1H), 3.26-3.41 (m, 1H), 3.47-3.55 (m, 1H), 4.05 (bd, *J* = 11.2 Hz, 1H), 4.38-4.51 (m, 1H), 5.10 (d, *J* = 11.7 Hz, 1H), 5.17 (d, *J* = 12.6 Hz, 1H), 7.29-7.38 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 18.7, 25.1, 28.7, 32.0, 38.9, 46.7, 58.3, 67.0, 127.5, 127.7, 128.2, 136.3, 156.3; **Anal.** Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32; Found. C, 68.39; H, 7.98; N, 5.27%.

(S)-*tert*-Butyl 2-(2-hydroxyethyl)piperidine-1-carboxylate (63)

To a solution of alcohol **118** (0.4 g, 1.5 mmol) in MeOH (10 mL) was added 10 % Pd/C (30 mg) and stirred under hydrogen atmosphere (20 psi) at 25 °C. After 5 h, the mixture was filtered through a pad of celite and rinsed with MeOH (3 x 30 mL). The combined organic layer was concentrated under reduced pressure and the crude product (196 mg) was stirred with $(Boc)_2O$ (0.349 mL, 1.5 mmol) and I_2 (38 mg, 10 mol%) for 3 h and this crude mixture was extracted with EtOAc (3 x 20 mL) and washed with water followed by aq. sodium thiosulphate to give crude **63** which was purified by column chromatography using pet. ether:EtOAc (9:1) as eluent to give the pure Boc alcohol **63**.

Yield: 95% (0.33 g); $[\alpha]_D^{25}$ -19.2 (*c* 1, $CHCl_3$), {lit.[24d] $[\alpha]_D^{25}$ -18.9 (c 1, $CHCl_3$, 95% ee)}; **IR** ($CHCl_3$, cm^{-1}): 3434, 2935, 2864, 1688, 1419, 1391, 1254, 1164, 1254, 1142, 1052, 711; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.44 (s, 9H), 1.48-2.09 (m, 8H), 2.58-2.72 (m,

1H). 3.30 (bt, *J* = 11.6 Hz, 1H), 3.54-3.66 (m, 1H), 3.92 (brd, *J* = 12.6 Hz, 1H), 4.37-4.51 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 19.0, 25.3, 28.2, 29.0, 32.1, 39.0, 45.8, 58.3, 79.7, 155.9; **Anal.** Calcd for $C_{12}H_{23}NO_3$: C, 62.85; H, 10.11; N, 6.11; Found. C, 62.77; H, 9.98; N, 6.27%.

(S)-*tert*-Butyl 2-(formylmethyl)piperidine-1-carboxylate (65)

To a stirred solution of oxalyl chloride $(COCl)_2$ (0.224 mL, 2.6 mmol) in CH_2Cl_2 (15 mL) at -78 °C, was added a solution of DMSO (0.278 mL, 3.92 mmol). The reaction mixture was stirred for 20 min. followed by the addition of a solution of (S)-*tert*-butyl 2-(2-hydroxyethyl)piperidine-1-carboxylate (**63**) (0.3 g, 1.3 mmol) in CH_2Cl_2 (5 mL). After stirring for 1 h at -78 °C, the reaction was quenched by the addition of Et_3N (0.728 mL, 5.22 mmol). The reaction mixture was then stirred for 30 min. at 25 ^oC followed by the addition of water (25 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layer was washed with water (3 x 30 mL), dried over anhyd. Na_2SO_4 and concentrated to give the corresponding crude aldehyde which was purified by column chromatography over silica gel using Pet. ether:EtOAc (7:3) as eluent to give piperidine aldehyde **65** as a colorless oil in 84% yield. **Yield:** 84% (0.250 g); $[\alpha]_D^{25}$ -51.1 (*c* 0.9, $CHCl_3$), **IR** ($CHCl_3$, cm^{-1}): 2980, 2872, 1741, 1700, 1480, 1411, 1372, 1160, 1055, 872, 770; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.45 (s, 9H), 1.50-1.76 (m, 6H), 2.53-2.58 (m, 1H), 2.71-2.82 (m, 2H), 3.98 (bd, *J* = 12.8 Hz, 1H), 4.83 (bs, 1H), 9.73 (t, *J* = 3.1 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 18.5, 24.9, 28.0, 28.5, 38.9, 44.2, 45.3, 79.3, 154.1, 199.8; **Anal.** Calcd for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16; Found. C, 63.28; H, 9.45; N, 5.99%.

(S)-*tert*-Butyl 2-((S)-2-hydroxy-2-phenylethyl)piperidine-1-carboxylate (66)

To a solution of PhMgBr (0.398 g, 2.19 mmol) in THF (20 mL) at – 78 °C was added dropwise a solution of aldehyde **65** (250 mg 1.09 mmol) in THF (5 ml) under nitrogen atmosphere. The solution was allowed to warm up to –20 °C and was left stirring for 4 h. The reaction mixture was quenched with a saturated solution of NH_4Cl (5 ml) and extracted with CH_2Cl_2 (3 x 30 mL). The organic layer was washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the corresponding diastereomeric mixture (90% yield, 305 mg) of *syn* and *anti* alcohol (dr = 2:1) which was purified by column chromatography pet.ether:EtOAc (7:3) as eluent to give major isomer **66** in 61% yield.

Yield: 60.6% (185 mg); $[\alpha]_D^{25}$ -128.3 (*c* 1.5, $CHCl_3$), {lit.[17] $[\alpha]_D^{25}$ -127.2 (c 1, $CHCl_3$, 94.2% ee)}; **IR** ($CHCl_3$, cm^{-1}): 3410, 2943, 1685, 1410, 920, 740; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.49 (s, 9H), 1.57-1.89 (m, 7H), 2.12-2.26 (m, 1H), 2.79 (t, *J* = 13.5 Hz, 1H), 3.88-4.02 (m, 2H), 4.41 (brs, 1H), 4.68-4.81 (m, 1H), 7.21-7.38 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 18.99, 25.3, 28.4, 29.1, 39.2, 40.2, 48.2, 72.3, 79.6, 125.6, 127.1, 128.2, 144.7, 155.3; **Anal.** Calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N, 4.59; Found. C, 70.67; H, 8.77; N, 4.72%.

(-)-Sedamine (2)

To a solution of $LiAlH_4$ (31 mg, 0.81 mmol) in THF (10 mL) was added a solution of *tert*-butyl carbamate **66** (125 mg, 0.40 mmol) in THF (2 mL). The reaction was heated to 70 °C under nitrogen atmosphere for 8 h, then cooled to 0 °C and carefully quenched by the sequential addition of water (0.2 mL), 15% (w/v) aq NaOH (0.2 mL). The resulting mixture was filtered over a pad of Celite and anhyd. Na_2SO_4 to remove solids, rinsing

with ethyl acetate. The mixture was concentrated under reduced pressure and the resulting oil was purified by column chromatography to provide (–)-sedamine **2**.

Yield: 78% (70 mg); mp. 58-59 ^{o}C {lit.[14] mp. 58-60 ^{o}C}; $[\alpha]_D^{25}$ -89.2 (*c* 0.86, EtOH), {lit.[14] $[\alpha]_D^{25}$ -89.4 (c 0.9, EtOH)}; **IR** ($CHCl_3$, cm^{-1}): 3367, 3060, 2928, 2851, 1450, 1264, 1061, 752, 659; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.30-1.63 (m, 1H), 1.66-1.80 (m, 6H), 2.05-2.18 (m, 1H), 2.50 (s, 3H), 2.54-2.68 (m, 1H), 2.98-3.09 (m, 2H), 4.89 (dd, *J* = 2.6 Hz, 1H), 5.80 (brs, 1H), 7.28-7.39 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 20.8, 22.2, 26.2, 39.3, 39.9, 52.7, 61.4, 73.3, 125.1, 127.1, 128.2, 145.5; **Anal.** Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39; Found. C, 76.59; H, 9.72; N, 6.27%.

Section II

Enantioselective Synthesis of (-)-A*llo*sedridine *via* Sharpless Asymmetric Epoxidation

2.2.1 Introduction

The piperidine moiety is frequently found in the structures of many drug candidates and constitutes a large family of compounds that exhibit a broad spectrum of biological activities of medicinal interest.[25] Particularly, alkaloids bearing a substituted piperidine ring have been the objective of considerable synthetic efforts.[26] The sedum alkaloids are an extensive family of 2-substituted and 2,6-disubstituted piperidine, many of which contain the 1,3-aminoalcohol moiety; for example, (-)-*allo*sedridine (**119**), (+)-sedridine (**120**), (-)-halosaline (**122**) (**Fig. 12**). *Allo*sedridine was isolated from *Sedum nudum*[27] which shows memory-enhancing properties and may be effective for the treatment of Alzheimer's disease.[28] Due to the importance in its biological activity, *allo*sedridine **119** became an ideal target for development of asymmetric synthetic methodology and a number of synthetic methods have been reported in the literature.[28-32]

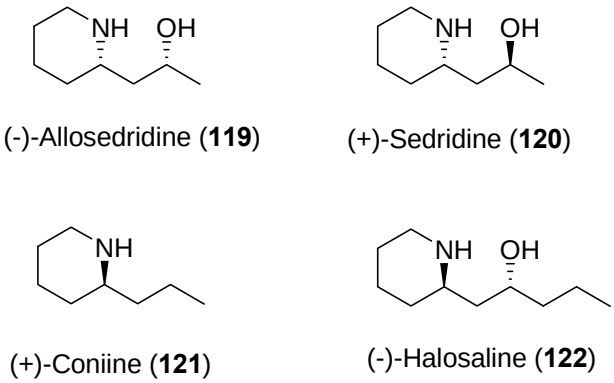
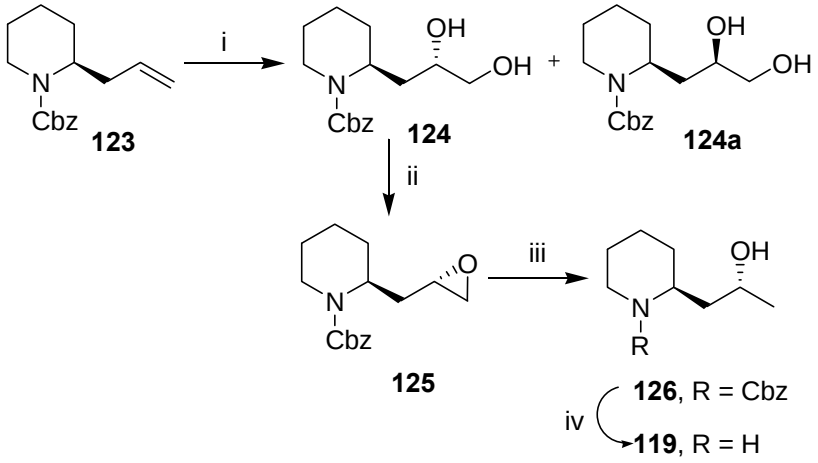


Fig. 12: Structures of piperidine alkaloids

2.2.2 Review of literature

Momose's approach (1997)[29]

Momose *et al.* have achieved the synthesis of (-)-*allo*sedridine (**119**) by employing Sharpless asymmetric dihydroxylation as the key step. Thus, olefin **123** was subjected to asymmetric dihydroxylation using AD-mix-β to give a mixture of diols **124** (98% ee) and **124a** (47% ee) in 74% and 14% yield respectively. The diol **124** was converted to its epoxide **125** under basic conditions followed by regioselective ring opening of epoxide **125** with super-hydride to produce **126** in 77% yield. The resulting Cbz-protected amino alcohol **125** was then subjected to catalytic hydrogenation to afford (-)-*allo*sedridine **119** in 99% yield (**Scheme 15**).

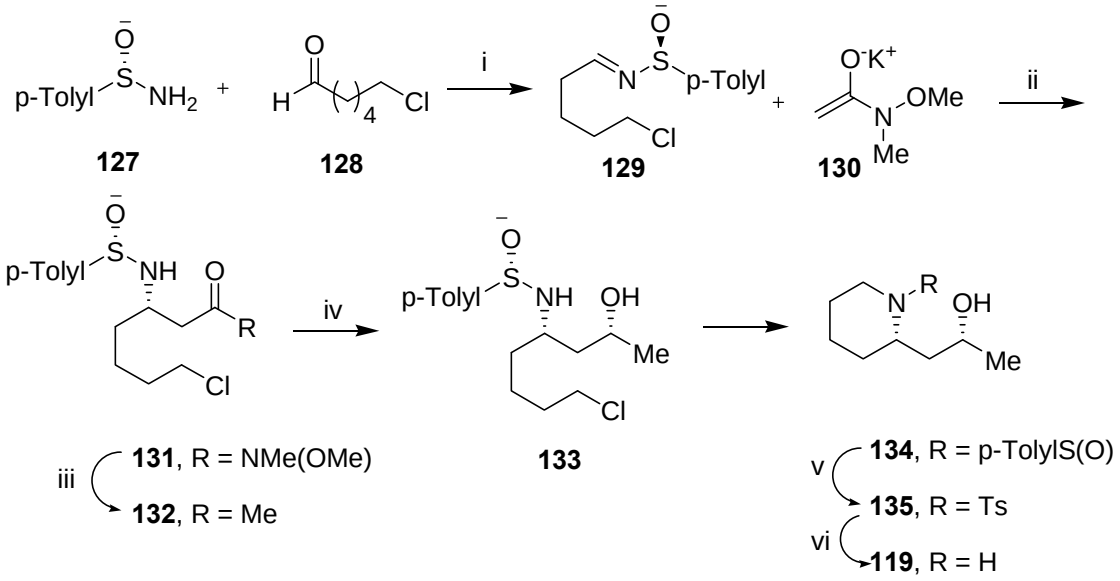


Scheme 15: (i) AD-mix-β $(DHQ)_2$-PYR, 74%; (ii) $CH_3C(OCH_3)_3$, PPTS, CH_3COBr, K_2CO_3, 77%; (iii) super hydride®, (iv) $Pd(OH)_2$, H_2, MeOH, 95%.

Davis' approach (2003)[30]

Davis *et al.* have developed a new methodology involving condensation of sulfinimines with potassium enolate and applied the same to the synthesis of (-)-*allo*sedridine **119**. Aldehyde **128** was condensed with (S)-p-toluene sulfinamide **127** in the presence of

$Ti(OEt)_4$ to produce sulfinimine **129** in 54% yield. Treatment of **129** with potassium enolate **130** gave the corresponding β-amino Weinreb amide **131** in 76% yield and 95% de. Reaction of amide **131** with 5 equiv. of MeMgBr gave the methyl ketone **132**, which was subjected to stereoselective reduction with $LiAlH(O\text{-}t\text{-}Bu)_3$ in THF to give *syn* 1,3-aminoalcohols **133** in 34% yield and 99% ee. The acyclic 1,3-aminoalcohol **133** was cyclized by stirring with NaH in the presence of 18-crown-6 (30 mol%) to give hydroxyl piperidine **134** in 71% yield. The oxidation of sulfinyl group in **134** to the corresponding tosylate **135** was achieved using *m*-CPBA followed by reductive cleavage of the sulfonamides using Na in liq. NH_3, which afforded (-)-*allo*sedridine **119** (**Scheme 16**).

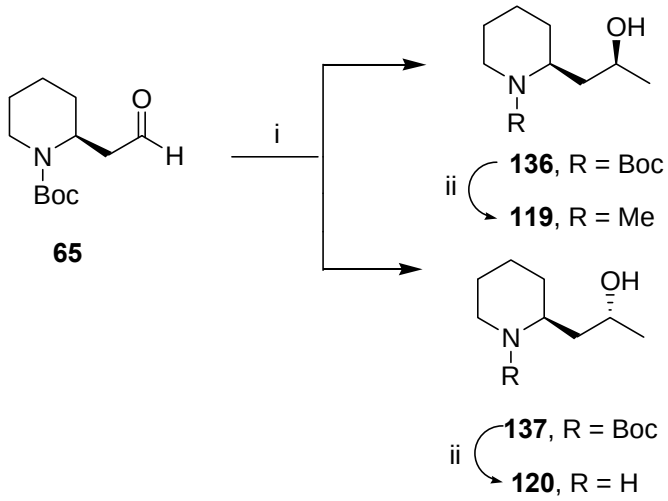


Scheme 16: (i) $Ti(OEt)_4$, 54%; (ii) THF, -78 °C, 76%, (iii) MeMgBr (5 equiv.) THF, -78-25 °C, 77%; (iv) $LiAlH(O\text{-}t\text{-}Bu)_3$, THF, 34%; (v) *m*-CPBA, 74%; (vi) Na, liq. NH_3, 70%.

Riva's approach (2005)[31]

Riva *et al*. also achieved the synthesis of (-)-*allo*sedridine **119** and (+)-sedridine **120** starting from Boc-protected piperidine aldehyde **65**, (see section I for its preparation).

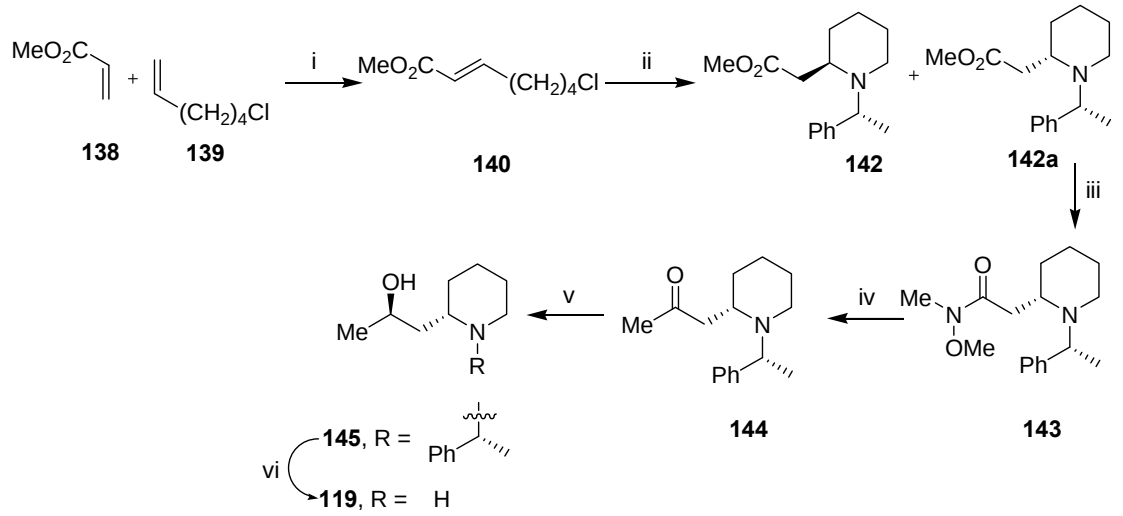
Thus addition of methylmagnesium bromide to aldehyde **65** produced 1:1 diastereomeric alcohols **136** and **137** in 61% yield. After separation of diastereomers **136** and **137**, the cleavage of Boc-group using TFA in CH_2Cl_2 gave (-)-*allo*sedridine **119** (59%) and (+)-sedridine **120** (75%) (**Scheme 17**).



Scheme 17: (i) MeMgBr, THF, -78 ^oC, 1:1, 61%;
(ii) TFA, CH_2Cl_2.

Hou's approach (2008)[32]

Hou *et al* have achieved the synthesis of (-)-*allo*sedridine **119** by employing cross-metathesis of 6-chloro-1-hexene **139** and methyl acrylate **138** to generate α,β-unsaturated ester **140** in 80% yield. Olefin **140** was then subjected to intramolecular Michael addition with chiral amine **141** in presence of phase-transfer catalyst (Bu_4NBr) to give piperidines **142** and **142a** in 2:1 diastereomeric ratio. Piperidine ester **142a** was further converted to Weinreb amide **143**, which was treated with MeMgCl in THF to afford methyl ketone **144**. The diastereoselective reduction of ketone **144** via chelation control using $ZnCl_2$ and $NaBH_4$ resulted in 99% yield of 14:1 syn:anti amino alcohol **145**, which on hydrogenolysis generated (-)-*allo*sedridine **119** (**Scheme 18**).



Scheme 18: (i) Grubbs' 2nd generation catalyst (5 mol%), 80%; (ii) NaI, Na_2CO_3, (R)-α-phenethylamine (**141**), Bu_4NBr, CH_3CN, 82%; (iii) $AlMe_3$, $(CH_3O)CH_3NH_2Cl$, CH_2Cl_2, 75%; (iv) MeMgCl, THF, 25 ^oC, 1.5 h; (v) $ZnCl_2$, $NaBH_4$, MeOH; (vi) Pd/C, H_2, MeOH.

2.2.3 Present Work

2.2.3.1 Objective

In recent years there has been an increased interest in the synthesis of optically active piperidine alkaloids. We find from the literature that the synthesis of (-)-*allo*sedridine (**119**), generally involves use of chiral starting materials. As a part of our research program directed towards expanding the synthetic utility of piperidine alkaloids we became interested in applying Sharpless asymmetric epoxidation for the synthesis of (-)-*allo*sedridine (**119**).

Retrosynthetic analysis of (-)-*allo*sedridine **119** shows that piperidine alcohol **118** emerges as the key intermediate, which could be obtained from Cbz-protected amino 1,3-diol **115** by an intramolecular cyclization. The precursor **115** can be prepared from epoxide **146**, which in turn could be obtained from allylic alcohol **147** by the Sharpless asymmetric epoxidation (**Fig. 13**).

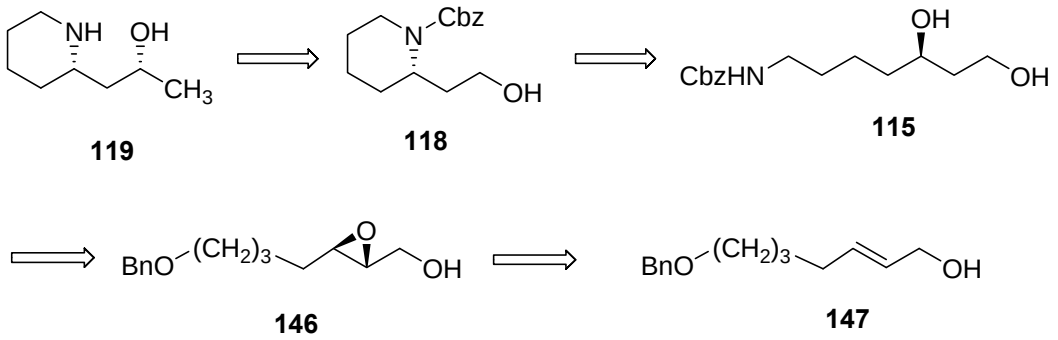


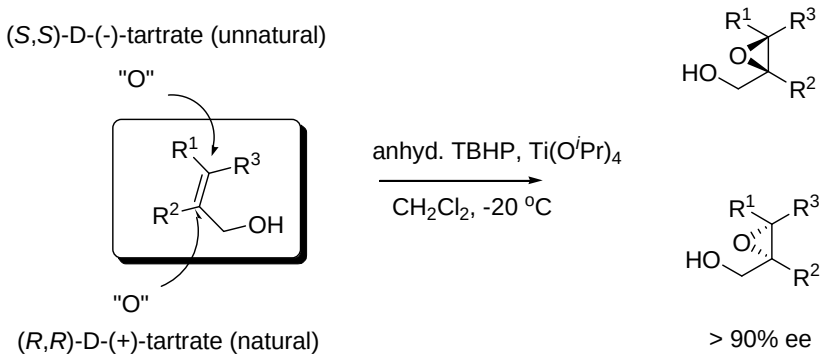
Fig. 13: Retrosynthetic analysis of (-)-*allo*sedridine **119**

2.2.3.2 Sharpless asymmetric epoxidation

Asymmetric epoxidation of allylic alcohols is one of the leading areas of investigation in synthetic organic chemistry, mainly due to the fact that very high enantioselective induction for a wide range of substrates is possible using several classes of reagents. Today, the most successful asymmetric epoxidation reaction is the titanate-mediated epoxidation of allylic alcohols, or Sharpless epoxidation,[33] which enables the achievement of an enantiomeric excess of more than 90% in most cases. The Sharpless epoxidation is a popular laboratory and industrial process due to its both enantioselective and catalytic nature. The reaction mixture includes a titanium tetraalkoxide, a chiral tartrate diester, an allylic alcohol substrate, and an alkyl hydroperoxide as the oxidant. The consistency of the reaction is remarkable, excellent enantiofacial selectivity is realized for allylic alcohol substrates of widely varying structure. In addition to being able to asymmetrically oxidize prochiral substrates to products of predictable absolute configuration, the reaction is extremely sensitive to preexisting chirality in selected positions of the allylic alcohols. For example, kinetic resolution of racemic secondary

allylic alcohols is very efficient since it can be used for generating chiral allylic alcohols as well as *trans*-epoxyalcohols in high enantiomeric excess.

Selection of the proper chirality in the starting tartrate esters and proper geometry of the allylic alcohols allows one to establish both the chirality and relative configuration of the product (**Scheme 19**).



<u>Scheme 19</u>: The Sharpless epoxidation reaction

Since its discovery in 1980, the Sharpless expoxidation of allylic alcohols has become a benchmark classic method in asymmetric synthesis. One factor that simplifies the standard epoxidation reaction is that the active chiral catalyst is generated *in situ*, which means that the pre-preparation of the active catalyst is not required.

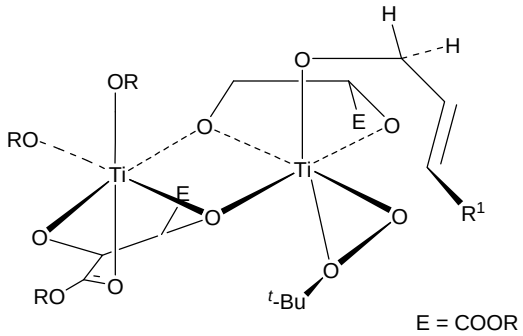
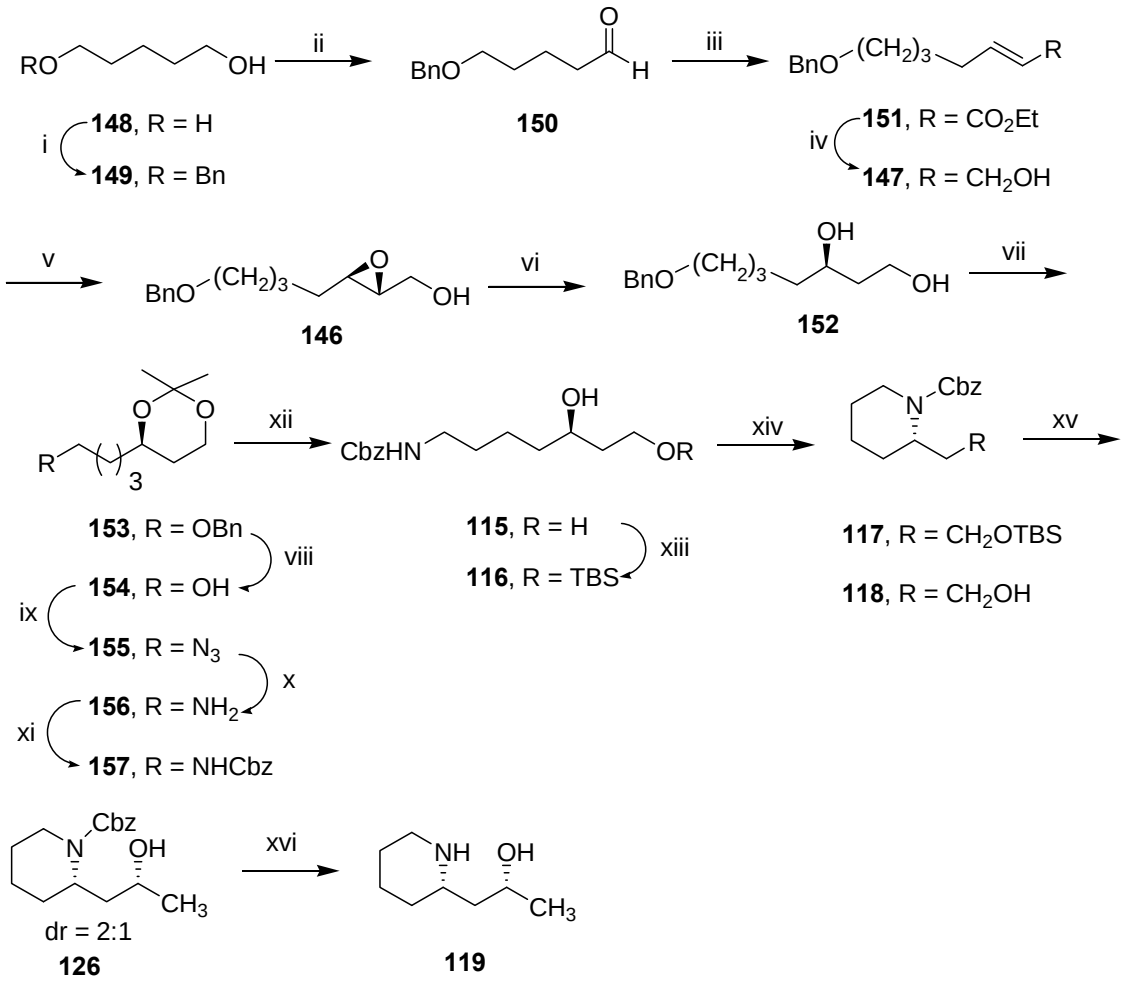


Fig. 14: Structure of dinuclear Ti-tartrate complex

It is believed that the species containing equal moles of Ti and tartrate is the most active catalyst. It promotes the reaction much faster than Ti(IV) tetraalkoxide alone and exhibits

selective ligand-accelerated reaction.[34] Sharpless suggested that epoxidation was catalyzed by a single Ti center in a dimeric complex with a C_2 symmetric axis (**Fig. 14**).[35]

2.2.4 Results and Discussion



Scheme 20: (i) NaH, BnBr, DMF, 5 h, 90%; (ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 1 h, 89%; (iii) PPh_3=$CHCO_2Et$, benzene, 90 °C, 12 h, 92%; (iv) $AlCl_3$ (10 mol%), $LiAlH_4$, Et_2O, 81%; (v) Ti(O*i*-pr)$_4$, (-)-DIPT, 4 A° MS, CH_2Cl_2, 5.5 M TBHP in decane, -20 °C, 24 h, 85%; (vi) Red-Al® (65%) in toluene, THF, -20-25 °C, 12 h, 86%; (vii) 2,2-dimethoxypropane, CH_2Cl_2, *p*-TSA (10 mol%), 25 °C, 12 h, 97%; (viii) 10% Pd/C, H_2 (20 psi), MeOH, 25 °C, 7 h, 85%; (ix) (a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 45 min; (b) NaN_3, DMF, 80 °C, 15 h, 87%; (x) 10% Pd/C, H_2 (20 psi), MeOH, 25 °C, 6 h; (xi) CbzCl, K_2CO_3, CH_2Cl_2:H_2O (1:1) 25 °C, 7 h, 89%; (xii) excess 80% aq. AcOH, 25 °C, 18 h; (xiii) TBSCl, imidazole, CH_2Cl_2, 0 °C, 1 h; (xiv) (a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 45 min; (b) NaH, THF, 40 °C, 10 h; then 3N HCl in MeOH, 25 °C, 2 h, 67%; (xv) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 1 h; then MeMgBr, THF, -78 °C; (xvi) 10% Pd/C, H_2 (20 psi), MeOH.

The complete synthetic sequence for (-)-*allo*sedridine **119** wherein the Sharpless asymmetric epoxidation of allylic alcohol constitutes a key step for the introduction of chirality, is presented in **Scheme 20**.

Our synthesis of (-)-*allo*sedridine **119** started with commercially available 1,5-pentanediol **148**, which was selectively benzylated (BnBr, NaH) to give the benzylated 1,5-penatanediol **149**. The primary alcohol function in **148** was then oxidized

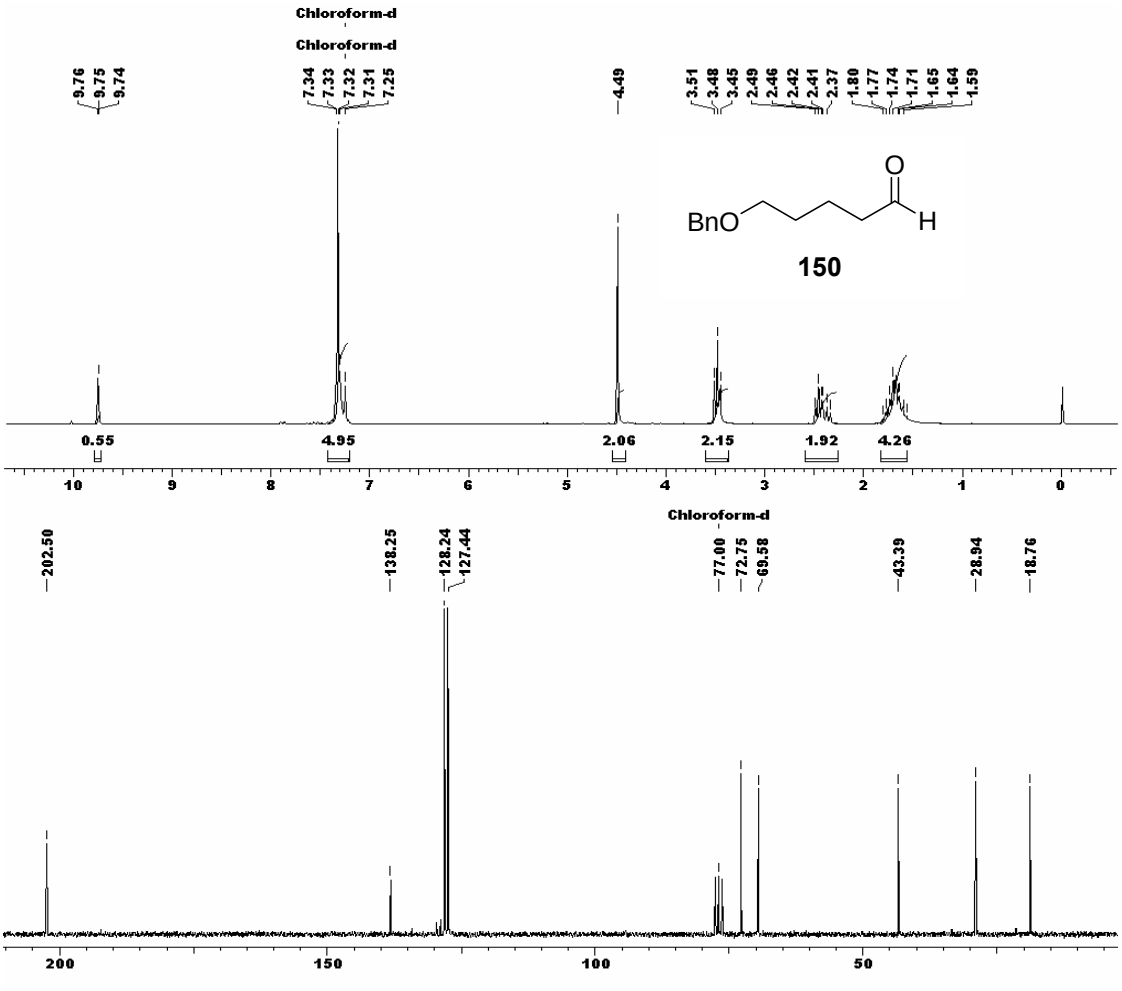


Fig. 15: ^{1}H and ^{13}C NMR spectra of aldehyde **150**

under Swern conditions to provide the corresponding aldehyde **150**. Its ^{1}H NMR spectrum showed a typical triplet at δ 9.75 for the aldehydic proton while its ^{13}C NMR

spectrum displayed a characteristic signal at δ 202.5 due to the aldehydic carbon (-**C**H**O**) (**Fig. 15**). Its IR spectrum showed a strong stretching vibration band at 1725 cm^{-1} for the carbonyl function.

Aldehyde **150** on Wittig olefination with PPh_3=$CHCO_2Et$ in benzene at 80 ^oC produced α, β-unsaturated ester **151** in 92% yield. Its ^1H NMR spectrum

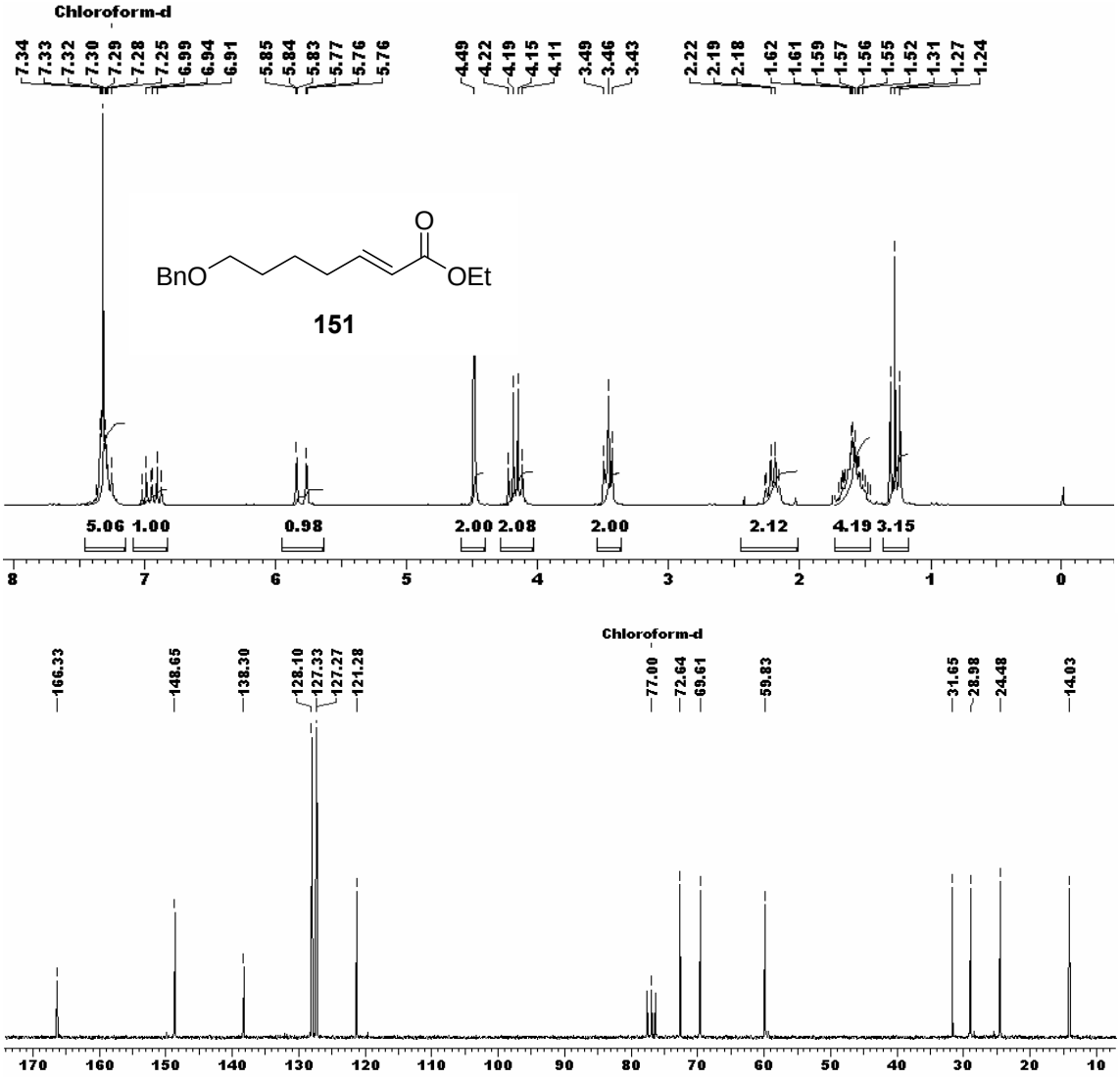


Fig. 16: ^1H and ^{13}C NMR spectra of ester **151**

showed typical signals at δ 1.27 (t, *J* = 7.2, 3H) and δ 4.16 (q, *J* = 7.0, 14.2, 2H) that correspond to -$CO_2C\mathbf{H}_2C\mathbf{H}_3$ ethyl group. It showed two multiplets at δ 5.75-5.84 (m, 1H)

and 6.86-7.01 (m, H) for the olefinic protons (-C**H**=C**H**CO_2Et), Its ^{13}C NMR spectrum showed two typical carbon signals at δ 138.3 and 148.6 (olefinic carbons) and δ 166.3 (carbonyl carbon) (**Fig**. **16**). The IR spectrum of ester **151** showed a strong stretching vibration at 1715 cm^{-1} for the ester carbonyl function.

The selective reduction of ester function in **151** was achieved with $LiAlH_4$ in presence of $AlCl_3$ (10 mol%) in dry diethyl ether[36] to give allylic alcohol **147** in 91% yield.

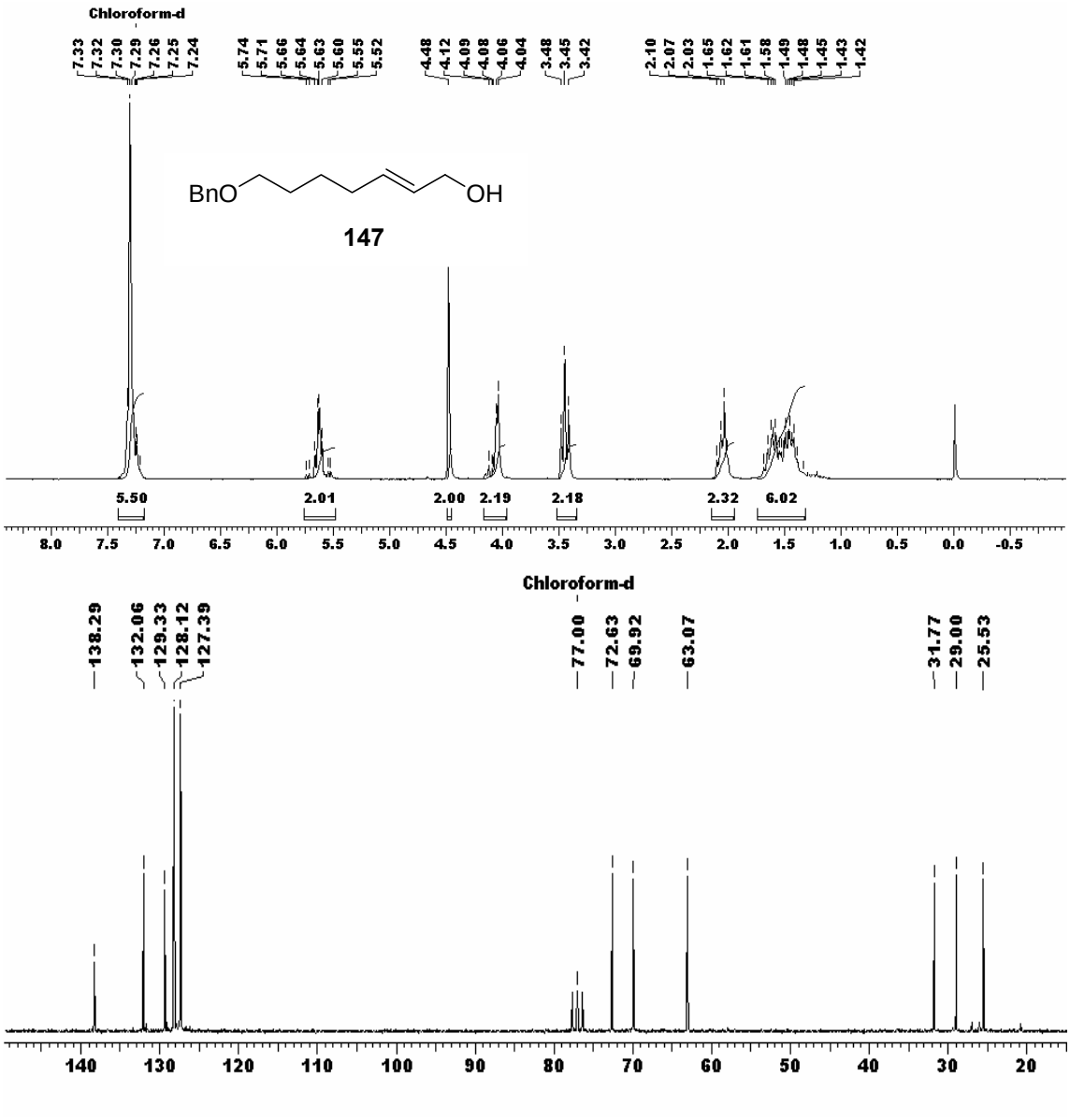
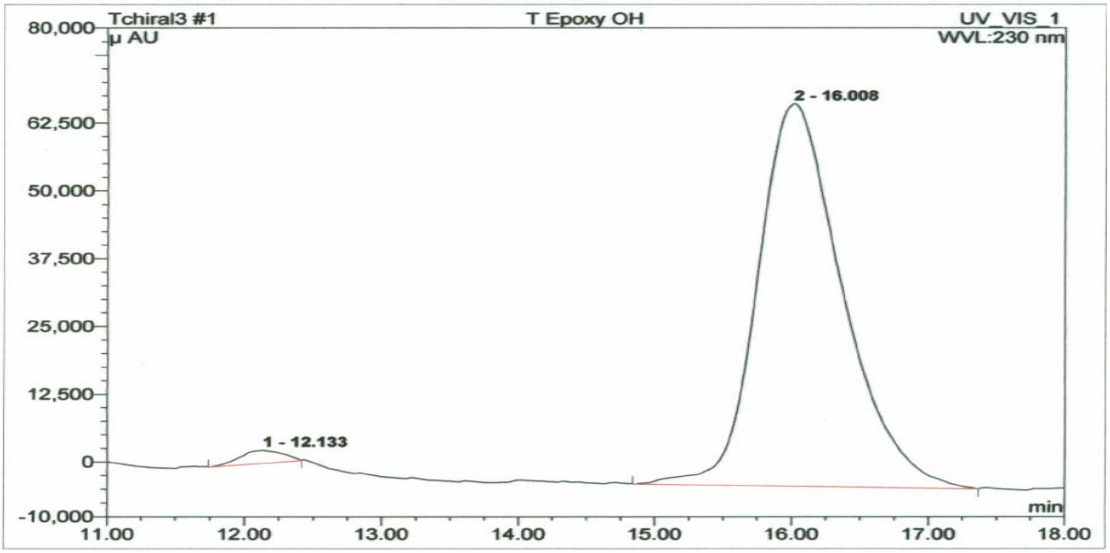


Fig. 17: ^{1}H and ^{13}C NMR spectra of allyl alcohol **147**

Its IR spectrum showed a strong absorption band at 3385 cm^{-1} for the O-H stretching vibrations. The formation of allylic alcohol **147** was also confirmed by the disappearance of ester carbonyl group in its IR spectrum and appearance of typical multiplets at δ 4.04-4.48 (m, 2H) (-CH=CH-C**H**$_2$OH) and δ 5.52-5.74 (m, 2H) (-C**H**=C**H**-CH_2OH) integrating for two protons for allylic group in its ^{1}H NMR spectrum. Its ^{13}C NMR spectrum showed further peaks at δ 129.3 and 132.0 for the olefinic carbons (**Fig. 17**).

Allylic alcohol **147** was then subjected to Sharpless asymmetric epoxidation[37] using (-)-diisopropyl tartarate [(-)-DIPT] to furnish the corresponding chiral epoxide **146** in 85% yield. Its optical purity was determined by HPLC analysis to be 97% ee (**Fig. 18**).



Peak No	Retention Time	Area (µV-sec)	Area (%)
1	12.13	806.78	1.48
2	16.00	50349.87	98.52

Fig. 18: HPLC chromatogram of epoxide **146**

Its ^{1}H NMR spectrum showed characteristic proton signals at δ 3.46 (t, J = 6.2 Hz, 2H), 3.52-3.63 (m, 1H) and 3.85 (bd, J = 12.7 Hz, 1H) for the epoxide function. Its ^{13}C NMR spectrum displayed typical peaks at δ 55.7 and 58.4 corresponding to methine carbons of epoxide moiety (**Fig. 19**).

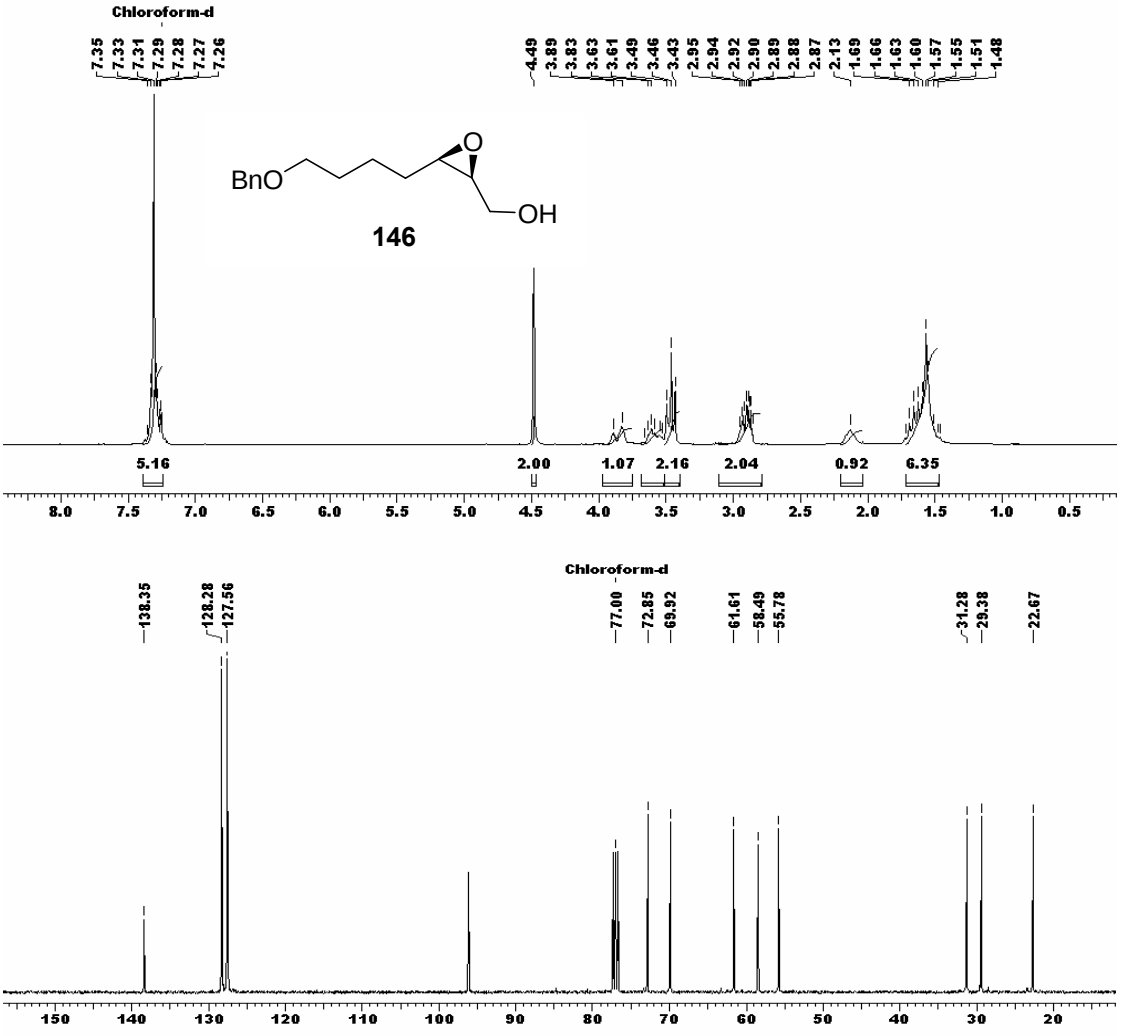


Fig. 19: ^{1}H and ^{13}C NMR spectra of epoxide **146**

Our next task was to construct 1,3-diol **152** from epoxide **146**. In order to achieve this transformation with high regioselectivity and yield, a strategy involving Red-Al®, originally published by Kishi *et al.*, was undertaken.[38] Thus, epoxide **146** was treated

with Red-Al® in THF at -20 °C to give diol **152**. Its ^{1}H NMR spectrum showed typical signals at δ 2.82 (br s, 2H) and δ 3.68-3.88 (m, 3H) due to OH protons and methylene and methine protons respectively (-C**H**OHC**H**$_2$OH). Its ^{13}C NMR spectrum displayed carbon signals at δ 61.1 and 70.2 due to methylene and methine carbons respectively (**Fig. 20**).

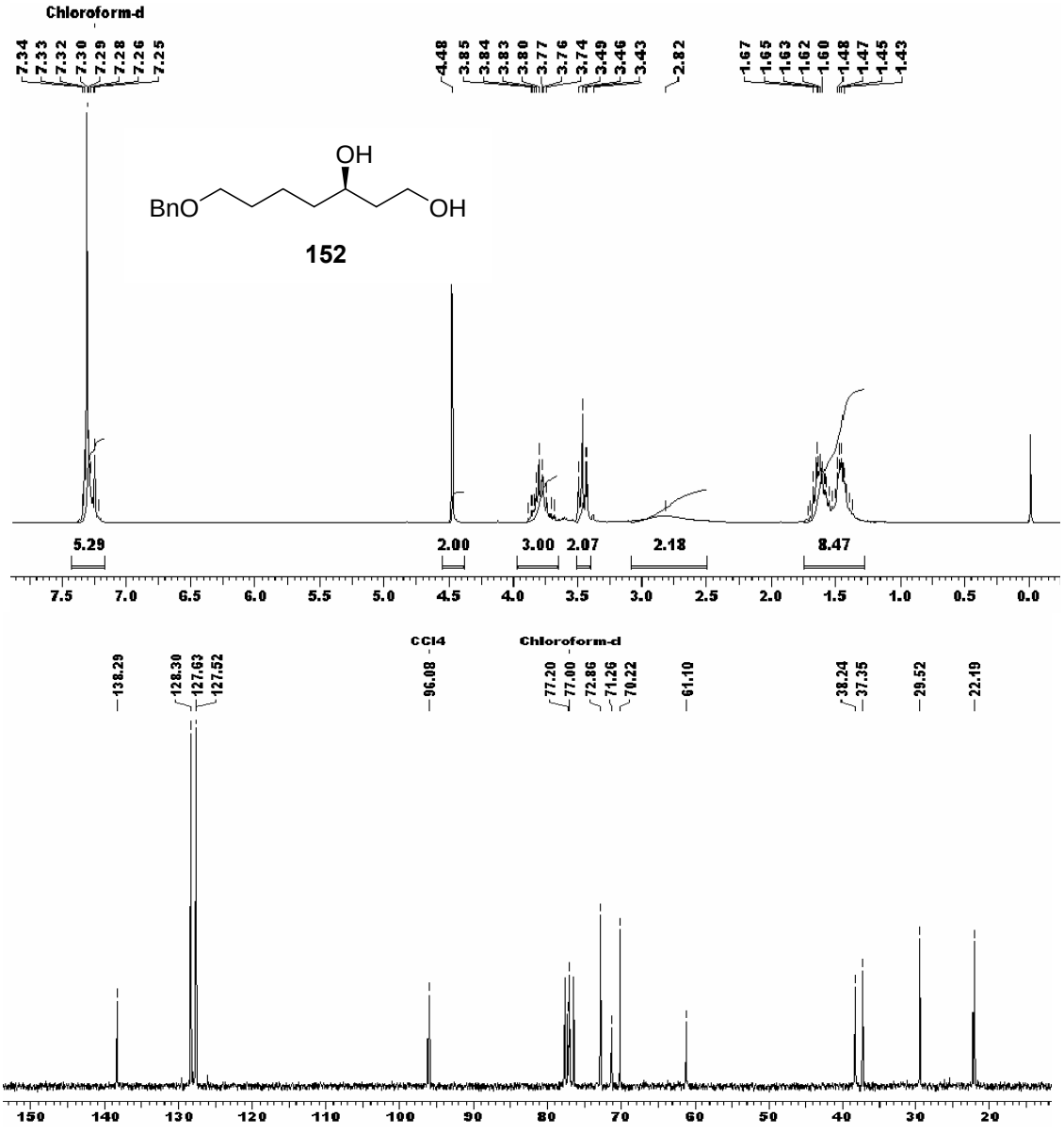


Fig. 20: ^{1}H and ^{13}C NMR spectra of 1,3-diol **152**

1,3-Diol **152** was then protected as its acetonide **153** upon treatment with 2,2-dimethoxypropane in presence of catalytic amounts of p-toluenesulfonic acid. Two singlets at δ 1.35 and 1.45 integrating for three protons each in its ^{1}H NMR spectrum confirmed the formation of acetonide **153**. Its ^{13}C NMR spectrum displayed typical signals at δ 19.1, 21.5 and 97.9 due to methyl and quaternary carbons of isopropylidene group respectively (**Fig. 21**).

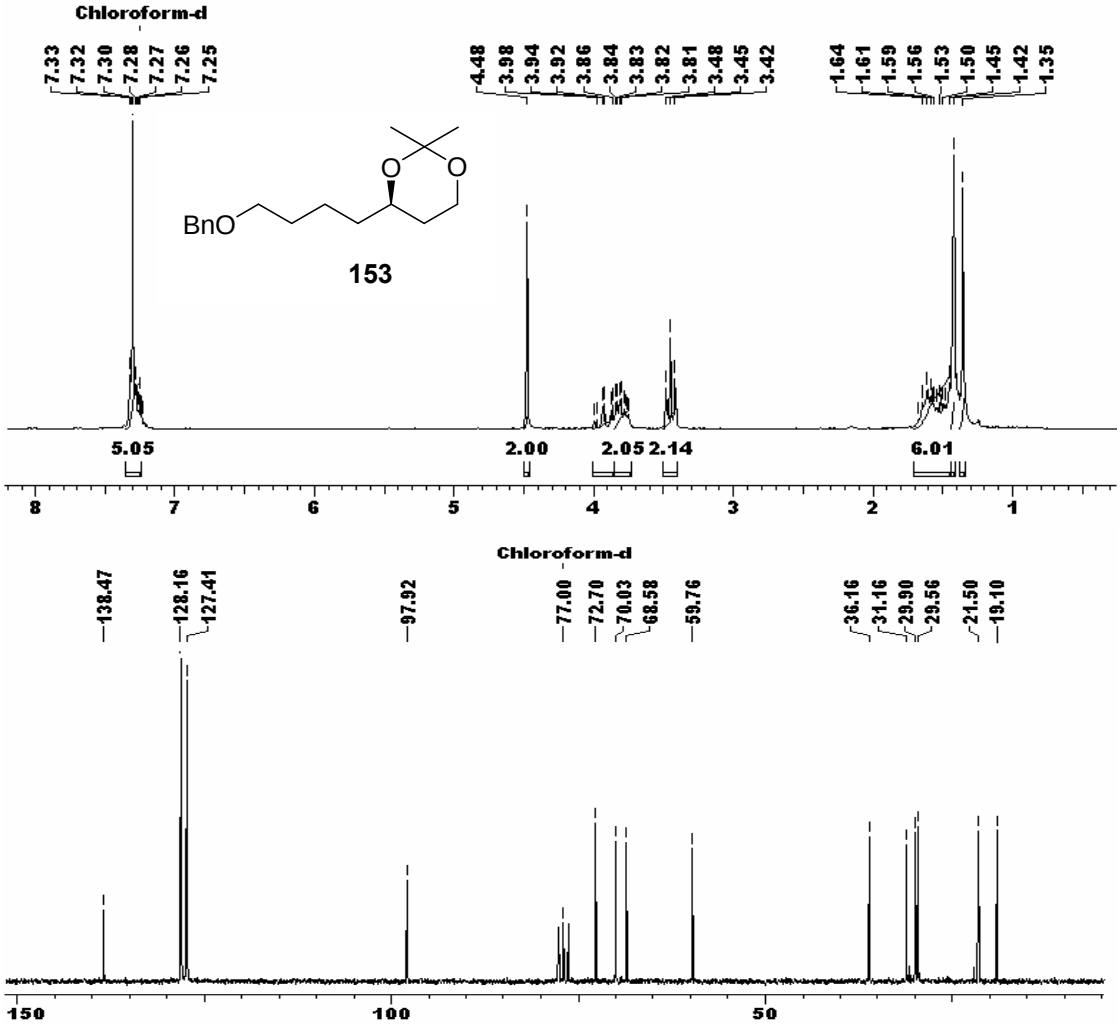


Fig. 21: ^{1}H and ^{13}C NMR spectra of benzyl ether **153**

At this stage, deprotection of the benzyl group in **153** was required. This has been achieved under catalytic hydrogenation conditions [Pd/C, H_2 (20 psi), MeOH] that

provided primary alcohol **154** in 85% yield. The formation of alcohol **154** was confirmed by the disappearance of methylene and aromatic protons signal (δ 4.4 (s, 2H) and 7.26-7.33 (m, 5H)) in its ^{1}H NMR spectrum. A broad singlet at δ 4.8 in its ^{1}H NMR spectrum is due to hydroxyl group. Its ^{13}C NMR spectrum showed a typical peak at δ 69.6 due to carbon attached to oxygen of primary alcohol. The IR spectrum of alcohol **154** displayed a broad absorption band around 3000 cm^{-1} indicating the presence of hydroxyl group.

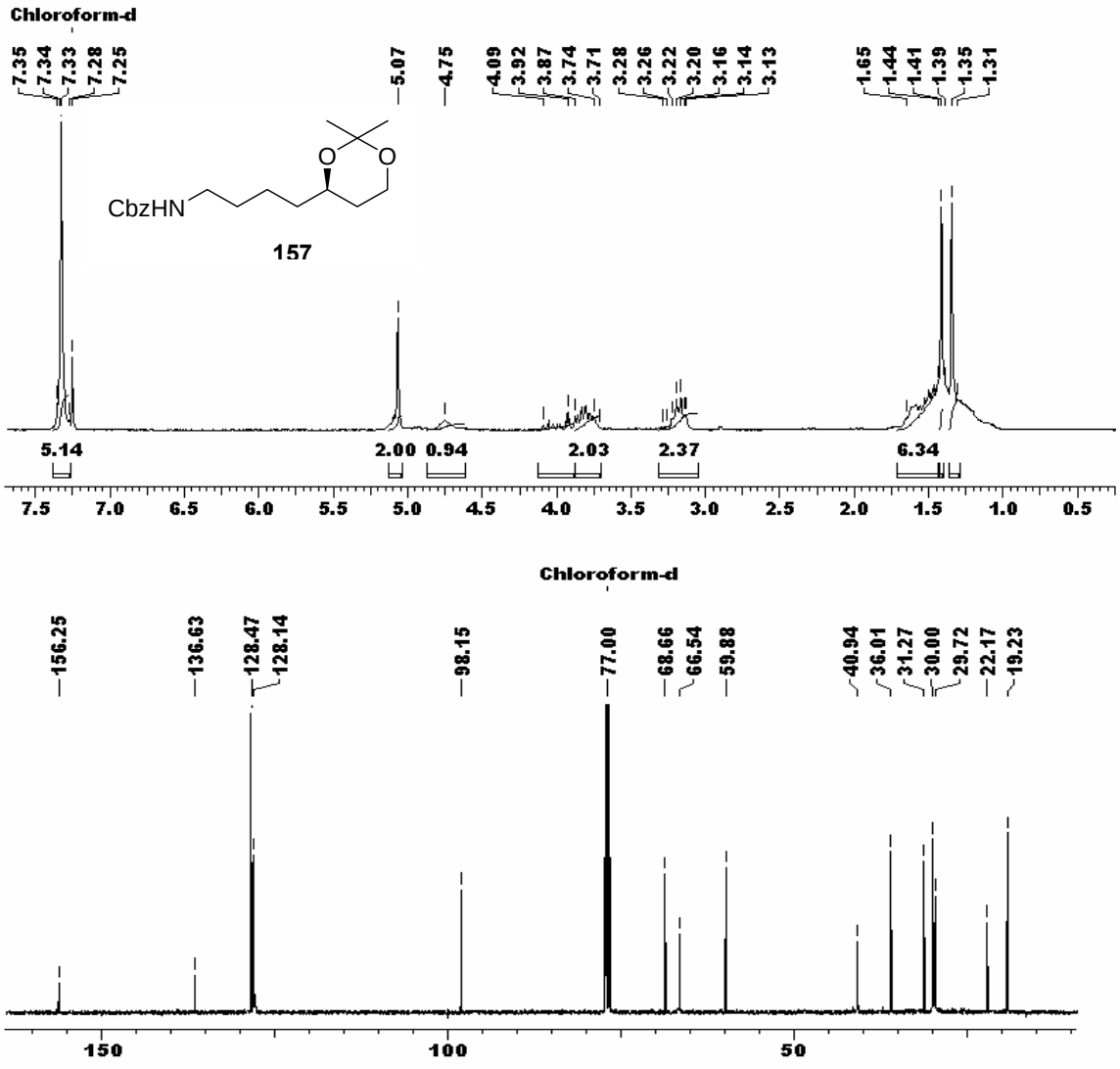


Fig. 22: ^{1}H and ^{13}C NMR spectra of carbamate **154**

The hydroxy group in **154** was then converted to its mesylate followed by its S_N2 displacement with NaN_3 produced the corresponding azide **155** in 87% yield over two steps. The formation of azide **154** was confirmed by IR, ^1H NMR and ^{13}C NMR spectra. For example, its IR showed a strong absorption band at 2091 cm^{-1} due to the presence of azide group. Reduction of azide **155** using 10% Pd/C in methanol and H_2 (20 psi) resulted in the formation of primary amine **156** in good yield, which was then protected as its benzyl carbamate **157** in 96% yield. The formation of carbamate **157** was confirmed by the appearance of signals at δ 5.07 (s, 2H) and 7.28-7.35 (m, 5H) due to methylene and aromatic protons respectively of carbamate moiety in its ^1H NMR spectrum. Its ^{13}C NMR spectrum displayed peaks at δ 66.5 due to methylene and at δ 128.0, 128.1, 128.4 and 136.6 due to aromatic ring carbons. Further, the characteristic carbonyl carbon of carbamate peak displayed at δ 156.2 in its ^{13}C NMR spectrum. (**Fig. 22**).

Treatment of acetonide **157** with 80% of aq. AcOH gave the corresponding 1,3-diol **115** in 97% yield. The synthesis of piperidine-2-ethanol **118**, the key intermediate, was quickly attempted in the subsequent additional steps. Selective protection of diol **115** (TBSCl, imidazole, CH_2Cl_2) furnished silyl protected alcohol **116** followed by conversion of its free secondary hydroxyl group to its mesylate. The mesylate, without purification, was subjected to cyclization intramolecularly under the suspension of NaH in THF, followed by acidic work-up which produced piperidine alcohol **118** in 67% yield. The alcohol **118** was then subjected to Swern oxidation to give the corresponding aldehyde, which on treatment with excess methylmagnesium bromide gave the diastereomeric mixture of *syn* and *anti* alcohols (dr = 2:1) in 85% combined yield. These diastereomers were separated by flash column chromatography to give a major isomer **126** in 55%

isolated yield. Its ^{1}H NMR spectrum displayed characteristic signals at δ 1.17 (t, J = 6.0 Hz, 3H) and 4.51 (br d, J = 10.7 Hz, 1H) due to methyl and methine protons and further substantiated by the typical signals at δ 18.9 and 67.4 in the downfield region of its ^{13}C NMR spectrum that correspond to the methyl and methine carbons attached to oxygen atom respectively.

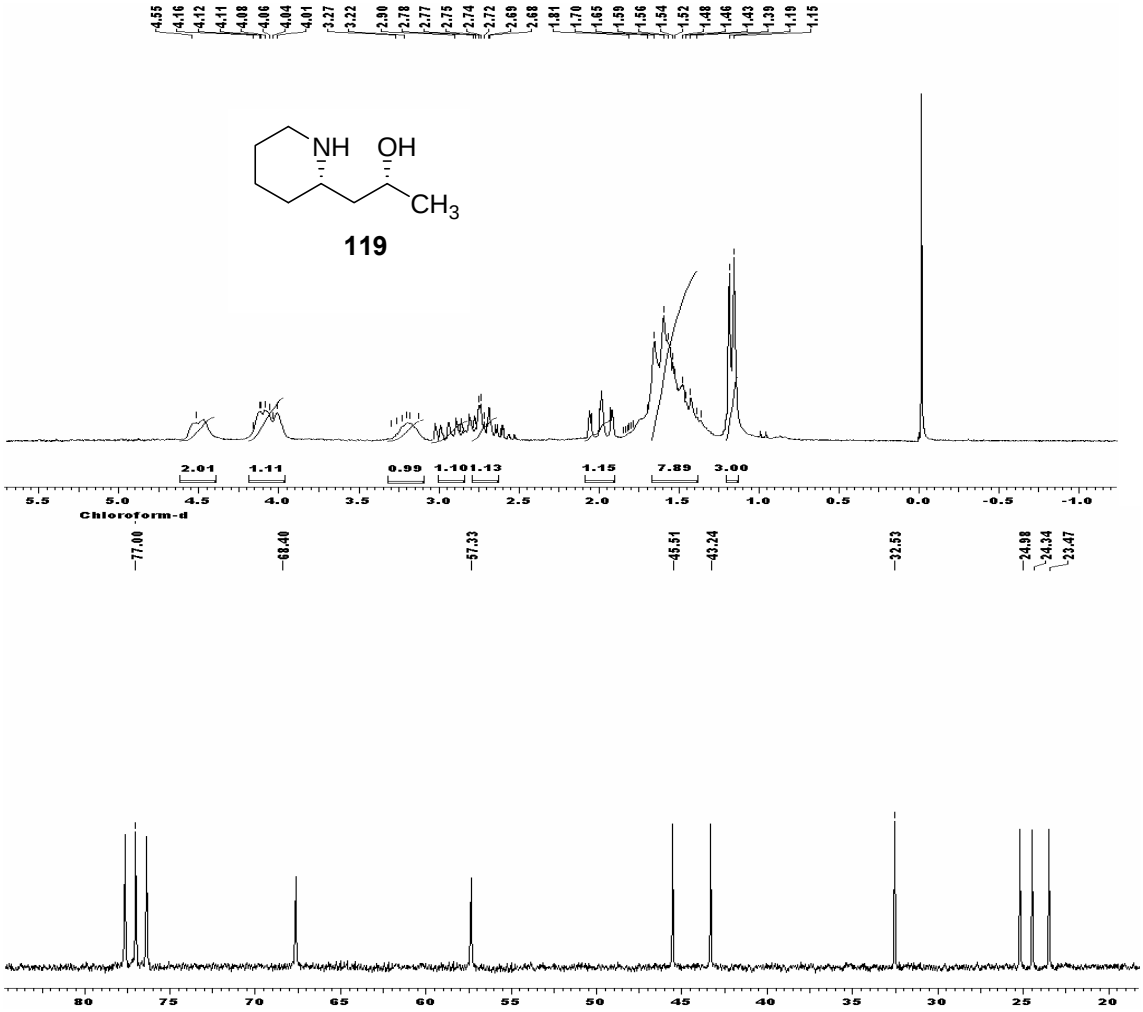


Fig. 23: ^{1}H and ^{13}C NMR spectra of (-)-*allo*sedridine **119**

The major isomer **126** was then hydrogenated to give (-)-*allo*sedridine **119**. The spectroscopic data of **119** was in full agreement with those reported in the literature.[32] Its

^{1}H NMR spectrum showed all the expected peaks. For example: its ^{1}H NMR spectrum showed typical signals at δ 1.13 (d, *J* = 6.0 Hz, 3H), 1.39-1.70 (m, 7H), 1.73-1.81 (m, 1H), 2.68-2.77 (m, 1H), 2.78-3.01 (m, 1H), 3.20-3.27 (m, 1H), 4.01-4.16 (m, 1H) and 4.55 (br s, 2H). Its ^{13}C NMR spectrum showed the characteristic signals at δ 57.3 and 68.4 due to carbons of secondary amine and alcohol respectively (**Fig. 23**).

2.2.5 Conclusion

An enatioselective synthesis of (-)-*allo*sedridine (**119**) has been achieved in 97% ee by employing Sharpless asymmetric epoxidation using (-)-DIPT as the chiral ligand for the induction of chirality in a highly diastereoselective manner. The protocol also demonstrates the synthetic utility of intramolecular cyclization of aminoalcohol **116** to give piperidine core **118**, which can be utilized for synthesis of several piperidine alkaloids.

2.2.6 Experimental section

5-(Benzyloxy)pentan-1-ol (149)

To a solution of NaH (4.6 g, 115.2 mmol) in dry DMF (120 mL) at 0 °C was added 1,5-pentanediol **148** (10 g, 96.0 mmol) in (20 mL) dry DMF over 20 min. The resulting mixture was stirred for an additional 15 min and then benzylbromide (11.4 mL, 96.0 mmol) was added dropwise. The reaction was allowed to warm to room temperature and stirred for 5 h. After completion, the reaction mixture was quenched with cold water (30 mL) and the aq. phase was extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with water followed by brine and dried over anhyd. Na_2SO_4. The solvent was removed under reduced pressure and the crude compound was purified by

column chromatography using petroleum ether/EtOAc (6:4) to afford mono protected alcohol **149** as a colorless liquid.

Yield: 90% (16.8 g); **IR** ($CHCl_3$, cm^{-1}): 3625, 3413, 3015, 2938, 2865, 2401, 1952, 1705, 1495, 1452, 1362, 1211, 1080, 950, 932, 771; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.38-1.67 (m, 6H), 1.73 (brs, 1H), 3.47 (t, *J* = 6.5 Hz, 2H), 3.61 (t, *J* = 6.1 Hz, 2H) 4.49 (s, 2H), 7.28-7.34 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 22.1, 29.1, 32.1, 61.9, 70.0, 72.5, 127.2, 127.3, 128.0, 138.1; **Anal.** Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34; Found. C, 73.99; H, 9.45%.

5-(Benzyloxy)pentanal (150)

To a stirred solution of oxalyl chloride (13.2 mL, 154.4 mmol) in CH_2Cl_2 (120 mL) at -78 °C, was added a solution of dry DMSO (16.4 mL, 231.1 mmol). The reaction mixture was stirred for 20 min followed by the addition of solution of 5-(benzyloxy)pentan-1-ol **149** (15.0 g, 77.2 mmol) in CH_2Cl_2 (40 mL). After stirring for 1 h at -78 °C, the reaction was quenched with the addition of Et_3N (42.9 mL, 308.8 mmol). The reaction mixture was then stirred for 30 min followed by the addition of water (70 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layer was washed with water (3 x 50 mL), dried over anhyd. Na_2SO_4 and concentrated to give the corresponding aldehyde **150**.

Yield: 89.8% (13.3 g); **IR** ($CHCl_3$, cm^{-1}): 3453, 2929, 2853, 1725, 1466, 1448, 1380, 1178, 1030, 698; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.56-1.82 (m, 4H), 2.34-2.49 (m, 2H), 3.48 (t, *J* = 5.7 Hz, 2H), 4.49 (s, 2H), 7.27-7.34 (m, 5H), 9.75 (t, *J* = 1.7 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 18.7, 28.9, 43.3, 69.5, 72.7, 127.4, 127.5, 128.2, 138.2, 202.5; **Anal.** Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39; Found. C, 75.01; H, 8.43%.

(E)-Ethyl 7-(benzyloxy)hept-2-enoate (151)

To a stirred solution of $Ph_3PCH{=}CO_2Et$ (35.3 g, 101.4 mmol) in benzene (120 mL), was added aldehyde **150** (13.0 g, 67.6 mmol) in (30 mL) benzene and heated at 90 ^oC. After 12 h, the solvent was removed under reduced pressure and the crude product was purified by column chromatography using petroleum ether/EtOAc (8:2) to afford α,β-unsaturated ester **151** as a colorless oil.

Yield: 92% (16.1 g); **IR** ($CHCl_3$, cm^{-1}): 2935, 2858, 1715, 1655, 1453, 1367, 1309, 1266, 1196, 1042, 983, 736, 697; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.27 (t, *J* = 7.0, 14.2 Hz, 3H), 1.45-1.70 (m, 4H), 2.16-2.26 (m, 2H), 3.46 (t, *J* = 6.0, Hz, 2H), 4.17 (q, *J* = 7.1, 14.2 Hz, 2H), 4.49 (s, 2H), 5.76-5.85 (td, *J* = 12.6 Hz, 1H), 6.87-7.02 (m, 1H), 7.27-7.37 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.0, 24.4, 28.9, 31.6, 59.8, 69.6, 72.6, 121.2, 127.2, 127.3, 128.1, 138.3, 148.6, 166.3; **Anal.** Calcd for $C_{16}H_{22}O_2$: C, 73.25; H, 8.45; Found. C, 73.19; H, 8.51%.

(E)-7-(Benzyloxy)hept-2-en-1-ol (147)

To a suspension of $LiAlH_4$ (3.2 g, 85.7 mmol) in dry Et_2O (110 mL) at 0 °C under nitrogen atmosphere was added dropwise a solution of $AlCl_3$ (3.8 g, 28.5 mmol) in Et_2O (20 mL). The reaction mixture was stirred at the same temperature for 30 min. To this stirred suspension, ester **151** (15.0 g, 57.17 mmol) in dry Et_2O (20 mL) was added dropwise over a period of 15 min and the mixture stirred at 0 °C for 1 h. It was quenched with ice-water and filtered through Celite. The residue was washed with ethyl acetate. The combined organic layers were dried over anhyd. Na_2SO_4, concentrated and the crude compound was purified by column chromatography using petroleum ether/EtOAc (8:2) to afford allylic alcohol **147** (2.0 g) as a colorless oil.

Yield: 81% (10.2 g); **IR** ($CHCl_3$, cm^{-1}): 3385, 2932, 2857, 1454, 1364, 1095, 1027, 971, 735, 697; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.38-1.69 (m, 5H), 2.01-2.10 (m, 2H), 3.45 (t, *J* = 6.3 Hz, 2H), 4.04-4.15 (m, 2H), 4.48 (s, 2H), 5.52-5.74 (m, 2H), 7.26-7.37 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 25.5, 29.0, 31.7, 63.0, 69.9, 72.6, 127.3, 127.4, 128.1, 129.3, 132.0, 138.2; **Anal.** Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15; Found. C, 76.47; H, 9.01%.

((2S,3R)-3-(4-(Benzyloxy)butyl)oxiran-2-yl)methanol (146)

To a stirred suspension of powdered 4 Å molecular sieves (5 g) in dry CH_2Cl_2 (80 mL), titanium tetraisopropoxide (2.37 mL, 7.80 mmol) was added under nitrogen atmosphere. The reaction mixture was cooled to –20 ºC and (-)-diisopropyl tartrate (1.87 mL, 8.97 mmol) added and stirred for 20 min, after which allyl alcohol **147** (8.6 g, 39.0 mmol) dissolved in CH_2Cl_2 (20 mL) was added and the mixture stirred for 30 min. To the above solution, anhyd. *tert*-butyl hydroperoxide in decane (5.5 M 14.2 mL, 78.07 mmol) was added dropwise over 30 min and stirred at –20 ºC for 24 h. After completion of the reaction (monitored by TLC), it was quenched with water (50 ml) at 20 °C and then allowed to warm to room temperature. A solution of NaOH (30%) in brine (20 ml) was added and the mixture was stirred vigorously for 45 min at room temperature and then diluted with dichloromethane (100 ml). The layers were allowed to separate and the inhomogenous aqueous layer was extracted with dichloromethane (3 × 100 ml). The combined organic extracts were dried over anhyd. Na_2SO_4, and then concentrated *in vacuo* to leave a pale yellow liquid. The crude compound was purified by column chromatography using petroleum ether/EtOAc (8:2) to afford epoxide **146**.

Yield: 85% (7.86 g); $[\alpha]_D^{25}$ +25.1 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3416, 2935, 2861, 1453, 1365, 1027, 737, 698; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.46-1.72 (m, 6H), 2.13 (br

s, 1H), 2.85-2.94 (m, 2H), 3.46 (t, *J* = 6.0 Hz, 2H), 3.52-3.66 (m, 1H), 3.86 (br d, *J* = 12.8 Hz, 1H), 4.48 (s, 2H), 7.26-7.35 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 22.6, 29.3, 31.2, 55.7, 58.4, 61.6, 69.9, 72.8, 127.4, 127.5, 128.2, 138.3; **Anal.** Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53; Found. C, 71.22; H, 8.47%.

(R)-7-(Benzyloxy)heptane-1,3-diol (152)

To a solution of epoxide **146** (4 g, 16.9 mmol) in dry THF (70 mL) at -20 ^{o}C was added a 65 wt% solution of sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al®) in toluene (6.84 g , 33.85 mmol) dropwise under nitrogen. After stirring at room temperature for 12 h, the solution was diluted with ether and quenched with 5% aq. HCl solution. After further stirring at room temperature for 30 min, the white precipitate formed was removed by filtration and the filtrate washed with ethyl acetate (3 x 20 mL). The combined organic extracts were dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by column chromatography using petroleum ether/EtOAc (8:2) to afford diol **152**.

Yield: 86% (3.50 g); $[\alpha]_D^{25}$ +10.0 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3381, 2335, 2861, 1453, 1097, 1051, 735, 697; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.32-172 (m, 8H), 2.82 (br s, 2H), 3.46 (t, *J* = 6.2 Hz, 2H), 3.68-3.88 (m, 3H), 4.48 (s, 2H), 7.26-7.36 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 22.1, 29.5. 37.3, 38.2, 61.1, 70.2, 71.2, 72.8, 77.2, 127.5, 127.6, 128.3, 138.2; **Anal.** Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30; Found. C, 70.39; H, 9.44%.

(R)-4-(4-(Benzyloxy)butyl)-2,2-dimethyl-1,3-dioxane (153)

To a stirred mixture of diol **152** (3 g, 12.58 mmol), 2,2-dimethoxypropane (6.17 mL, 50.35 mmol) and dry CH_2Cl_2 (30 mL) was added *p*-toluenesulfonic acid (0.216 g, 10 mol%) and the mixture was stirred at 25 ^oC for 12 h. After completion of the reaction as monitored by TLC, it was neutralized with triethylamine, concentrated and purified by silica gel chromatography using pet. ether:EtOAc (9:1) as eluent to yield **153** as an oil.

Yield: 97% (3.4 g); $[\alpha]_D^{25}$ +8.6 (*c* 1.1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3610, 3019, 2400, 1716, 1646, 1523, 1456, 1381, 1215, 1097, 929, 758, 669; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.35 (s, 3H), 1.38 (s, 3H), 1.42-1.70 (m, 8H), 3.45 (t, *J* = 6.4 Hz, 2H), 3.75 -3.84 (m, 2H), 3.93 (ddd, *J* = 3.2, 11.6 Hz, 1H), 4.48 (s, 2H), 7.26-7.33 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 19.1, 21.5, 29.5, 29.9, 31.1, 36.1, 59.7, 68.5, 70.0, 72.7, 97.9, 127.3, 127.4, 128.1, 138.4; **Anal.** Calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41; Found. C, 72.99; H, 9.67%.

4-((R)-2,2-Dimethyl-1,3-dioxan-4-yl)butan-1-ol (154)

To a stirred mixture of **153 (**3.0 g 10.7 mmol) in dry methanol (20 mL) was added 10% Pd/C (30 mg), and the mixture exposed to H_2 (20 psi), 2-3 drops Et_3N and the reaction mixture was stirred at 25 ^oC for 7 h. After completion of the reaction as monitored by TLC, mixture was filtered through a pad of celite and rinsed with MeOH (3 x 30 mL). The combined organic layer was concentrated under reduced pressure to give the crude alcohol **154** which was purified by silica gel chromatography using pet. ether:EtOAc (6:4) as eluent to yield **154** as an oil.

Yield: 85% (1.7 g); $[\alpha]_D^{25}$ +24.0 (*c* 0.5, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3502, 3054, 2930, 2103, 1734, 1541, 1427, 1382, 1265, 1201, 1111, 1052, 950, 945, 860, 731; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.35 (s, 3H), 1.42 (s, 3H), 1.46-1.64 (m, 8H), 3.63 (t, *J* = 6.1 Hz,

2H), 3.75-3.88 (m, 2H), 3.93-4.02 (m, 1H), 4.8 (brs, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.4, 31.9, 36.8, 38.4, 49.3, 59.7, 61.6, 69.6, 95.8; **Anal.** Calcd for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71; Found. C, 63.74; H, 10.91%.

(R)-4-(4-Azidobutyl)-2,2-dimethyl-1,3-dioxane (155)

To a stirred solution of alcohol **154** (1.7 g, 9.03 mmol) and Et_3N (1.88 mL, 13.45 mmol) in CH_2Cl_2 (30 mL), at 0 °C was added methanesulfonyl chloride (0.768 mL, 9.93 mmol). After stirring for 1 h at 0 °C, the reaction mixture was poured into ice water (150 mL), washed with aqueous $NaHCO_3$, brine, dried over anhyd. Na_2SO_4 and the solvent was distilled off under reduced pressure to give the crude product. The crude mesylate (2.40 g, 9.0 mmol) was then dissolved in DMF (40 mL) followed by the addition of sodium azide (2.9 g, 45.0 mmol). The reaction mixture was then heated at 80 °C for 15 h followed by quenching it with the addition of water. The aqueous layer was extracted with Et_2O (3 x 100 mL) and the combined organic layers were dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure and the crude product purified by column chromatography over silica gel using pet. ether:EtOAc (95:5) as eluent to yield pure **155**.

Yield: 87% (1.6 g); $[\alpha]_D^{25}$ +12.5 (*c* 1.2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 2984, 2939, 2864, 2091, 1738, 1457, 1371, 1247, 1216, 1151, 1055, 853; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.35 (s, 3H), 1.43 (s, 3H), 1.49-1.67 (m, 8H), 3.26 (t, *J* = 6.5 Hz, 2H), 3.75-3.85 (m, 2H), 3.87-3.94 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 20.8, 25.4, 31.2, 34.2, 39.5, 47.5, 66.9, 71.6, 102.8; **Anal.** Calcd for $C_{10}H_{19}N_3O_2$: C, 56.32; H, 8.98; N, 19.70; Found. C, 56.51; H, 9.01; N, 19.15%.

Benzyl 4-((R)-2,2-dimethyl-1,3-dioxan-4-yl)butylcarbamate (157)

To a stirred mixture of **155 (**1.5 g 7.02 mmol) in dry methanol (20 mL) was added 10% Pd/C (30 mg), and the reaction mixture exposed to H_2 (20 psi), stirred at 25 ^oC for 6 h. After completion of the reaction as monitored by TLC, it was filtered through a pad of celite and rinsed with MeOH (3 x 30 mL). The combined organic layer was concentrated under reduced pressure to give the crude amine **156**.

The crude amine **156** (1.3 g, 6.94 mmol) was dissolved in a mixture of water (15 mL) and dichloromethane (15 mL) followed by the addition of potassium carbonate (1.91 g, 13.88 mmol). After 15 min benzyl chloroformate (1.49 mL, 10.45 mmol) was introduced with the help of syringe and the reaction mixture was stirred at 25 ^oC for 7 h. After completion of the reaction, organic layer decanted separately and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic layer was dried over Na_2SO_4, and the solvent was evaporated *in vacuo* and the residue was purified by column chromatography using pet.ether:EtOAc (7:3) to give pure **157** as a colorless oil.

Yield: 89.6% (2.0 g); $[\alpha]_D^{25}$ +15 (*c* 0.7, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3347, 3035, 3063, 2977, 2936, 2867, 1710, 1535, 1450, 1367, 1244, 1052, 853, 736; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.35 (s, 3H), 1.41 (s, 3H), 1.31-1.65 (m, 8H), 3.13-3.28 (m, 2H), 3.71-3.87 (m, 2H), 3.92-4.09 (m, 1H), 4.75 (br s, 1H), 5.07 (s, 2H), 7.28-7.35 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 19.2, 22.1, 29.7, 30.0, 31.2, 36.0, 40.9, 59.8, 66.5, 68.6, 98.1,128.0, 128.1, 128.4, 136.6, 156.2;

Benzyl (*R*)-5,7-dihydroxyheptylcarbamate (115)

A solution of acetonide **157** (2.0 g, 6.22 mmol) and 80% aq. AcOH (20 mL) was stirred at 25 ^oC for 18 h. After completion of reaction, acetic acid and water were removed under reduced pressure and the crude mixture extracted with EtOAc (3 x 20 mL) and washed

with water 10% $NaHCO_3$. The combined organic layer was dried over anhyd. Na_2SO_4 and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography using pet.ether:EtOAc (5:5) to give pure diol **115** as a gum.

Yield = 96% (1.6 g)

For experimental procedure and spectral details of compounds, **115** to **118** please refer section I of this chapter.

(S)-Benzyl 2-((R)-2-hydroxypropyl)piperidine-1-carboxylate 126

To a stirred solution of oxalyl chloride (0.195 mL, 2.27 mmol) in CH_2Cl_2 (15 mL) at -78 °C, was added a solution of DMSO (0.242 mL, 3.41 mmol). The reaction mixture was stirred for 20 min. followed by the addition of solution of (S)-benzyl 2-(formylmethyl)piperidine-1-carboxylate **149** (300 mg, 1.11 mmol) in CH_2Cl_2 (5 mL). After stirring for 1 h at -78 °C, the reaction mixture was quenched with the addition of Et_3N (0.633 mL, 4.55 mmol). It was then stirred for 30 min followed by the addition of water (10 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layer was washed with water (3 x 10 mL), dried over anhyd. Na_2SO_4 and concentrated to give the corresponding aldehyde **150**. Then aldehyde **150** (290 mg, 1.10 mmol) was dissolved in dry THF (20 mL) and cooled to -78 ^oC. After 15 min, a solution of excess MeMgI in THF was added dropwise using syringe. The solution was finally allowed to warm at 0 ^oC and then left stirring for 4 h. The reaction mixture was finally quenched with saturated NH_4Cl and extracted with EtOAc (3 x 20 mL). The organic layer was washed with water followed by brine and dried over anhyd. Na_2SO_4 and concentrated to give the corresponding mixture of *syn* and

anti (dr = 3.2:1.7) in 85% combined yield. These diastereomers were separated by flash chromatography and **126** were obtained as a major isomer isolated in 55% yield.

Yield: 55% (170 mg); $[\alpha]_D^{25}$ -29.8 (*c* 2.2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3446, 2934, 1684, 1560, 1424 672; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.17 (d, *J* = 6.0 Hz, 3H), 1.20-1.29 (m, 1H), 1.39-1.70 (m, 6H), 1.98 (t, *J* = 13.3 Hz, 1H), 2.68-2.77 (m, 1H), 3.50 (br s, 1H), 4.04 (br d, *J* = 13.4 Hz, 1H), 4.12 (s, 1H), 4.51 (br d, *J* = 10.7 Hz, 1H), 5.11 (br q, 2H), 7.30-7.57 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 18.9, 22.0, 25.3, 29.2, 39.2, 47.5, 63.5, 67.4, 127.8, 128.1, 128.4, 136.3, 156.8; **Anal.** Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05; Found. C, 68.97; H, 8.65; N, 4.99%.

(-)-*Allo*sedridine (119)

A suspension of alcohol **126** (110 mg, 0.39 mmol), $Pd(OH)_2$ (10 mg) in methanol (2 mL) was stirred at 25 ^oC for 7 h under a H_2 (20 psi) atmosphere. After completion of the reaction as monitored by TLC, the mixture was filtered through a pad of celite and rinsed with MeOH (3 x 10 mL). The combined organic layer was concentrated under reduced pressure to give **119**.

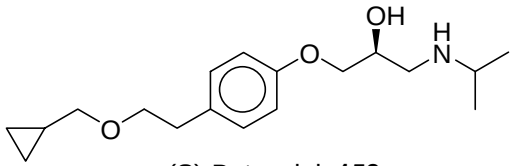
Yield: 90% (62 mg); $[\alpha]_D^{25}$ -16.4 (*c* 1.2, MeOH), {lit.[31b] $[\alpha]_D^{25}$ -16.18 (*c* 1.55, MeOH)}; **IR** ($CHCl_3$, cm^{-1}): 3689, 3676, 2920, 1650, 1431, 1362, 1331, 1050, 790, 635; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.13 (d, *J* = 6.0 Hz, 3H), 1.39-1.70 (m, 7H), 1.73-1.81 (m, 1H), 2.68-2.77 (m, 1H), 2.78-3.01 (m, 1H), 3.20-3.27 (m, 1H), 4.01-4.16 (m, 1H), 4.55 (br s, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 23.4, 24.3, 24.9, 32.5, 43.2, 45.5, 57.3, 68.4; **Anal.** Calcd for $C_8H_{17}NO$: C, 67.09; H, 11.96; N, 9.78; Found. C, 66.99; H, 12.01; N, 9.83%.

Section III

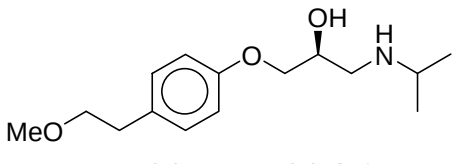
Asymmetric Synthesis of β-Blockers: (*S*)-Betaxolol and (*S*)-Metoprolol

2.3.1 Introduction

The members of a pair of enantiomers often show different pharmacological and metabolic characteristics.[39] Thus one enantiomer may act as a very effective therapeutic drug while the other could be highly toxic. Betaxolol (**158**) and metoprolol (**159**) (**Fig. 24**), very important drugs in this series are used widely for the treatment of angina, hypertension and open angle glaucoma respectively[40]. They are also known to exhibit lower blood pressure, by slowing down the heart rate and increase life expectancy after the heart attack. Although these drugs possess one stereogenic carbon center, they are generally administered as racemates. The biological activity in a racemic drug often resides in a single enantiomer.[41] For instance, the (S)-isomers of betaxolol (**158**) and metoprolol (**159**) are associated with β-blocking activity, while the (R)-isomers are responsible for adverse side effects.[42] The synthesis of drugs in enantiomerically pure form is very important for pharmaceutical industries due to increased demand for more effective and safe single isomers. In the market betaxolol (**158**) is sold under trade names "Betaoptic" or "Kerlone" while metoprolol (**159**) as "Lopressor".



(S)-Betaxolol, **158**



(S)-Metoprolol, **159**

Fig. `24

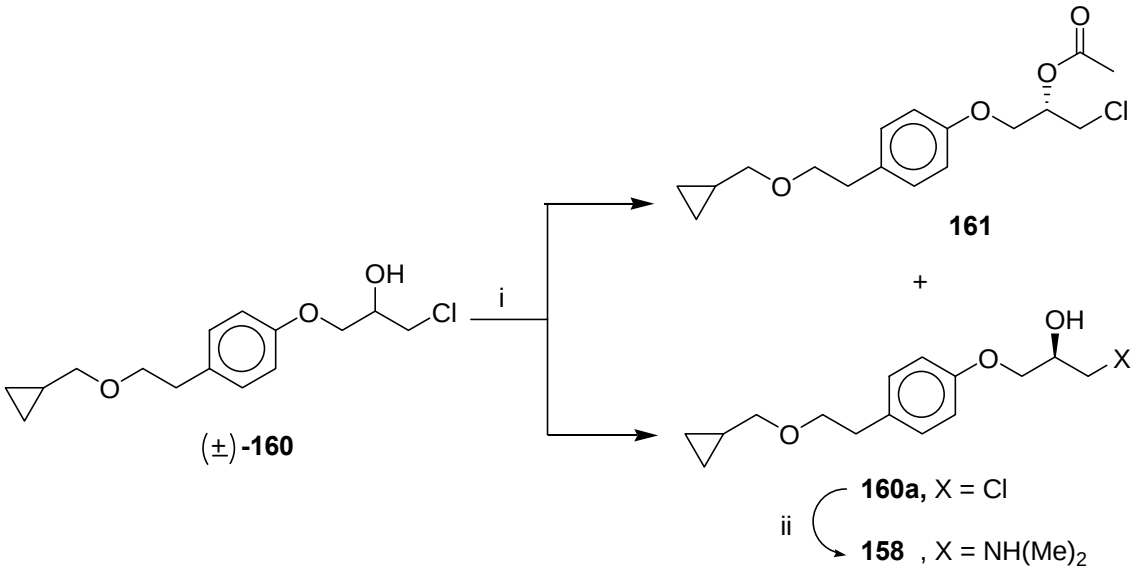
2.3.2 Pharmacology

To examine the physiological effects of betaxolol,[43] a β_1-adrenergic receptor blocker commonly used in the treatment of glaucoma, on retinal ganglion cells and to evaluate its potential to elicit responses consistent with a neuroprotective agent against ganglion cell degeneration and betaxolol lead to reducing neurotoxic effects in ganglion cells, which are the most susceptible retinal neurons to glutamate-induced damages under ischemic and glaucomatous conditions. Therefore, betaxolol (**158**) has the potential to be a neuroprotective agent against retinal degeneration in patients with disorders mediated by such mechanisms. Metoprolol (**159**) is also a β_1-selective adrenergic receptor blocking agent. *In vitro* and *in vivo* animal studies have shown that it has a preferential effect on β_1-adrenoreceptors located in cardiac muscle and it also inhibits β_2-adrenoreceptors located in the bronchial and vascular musculature.[44]

2.3.3 Review of literature

Scilimati's approach (1995)[45]

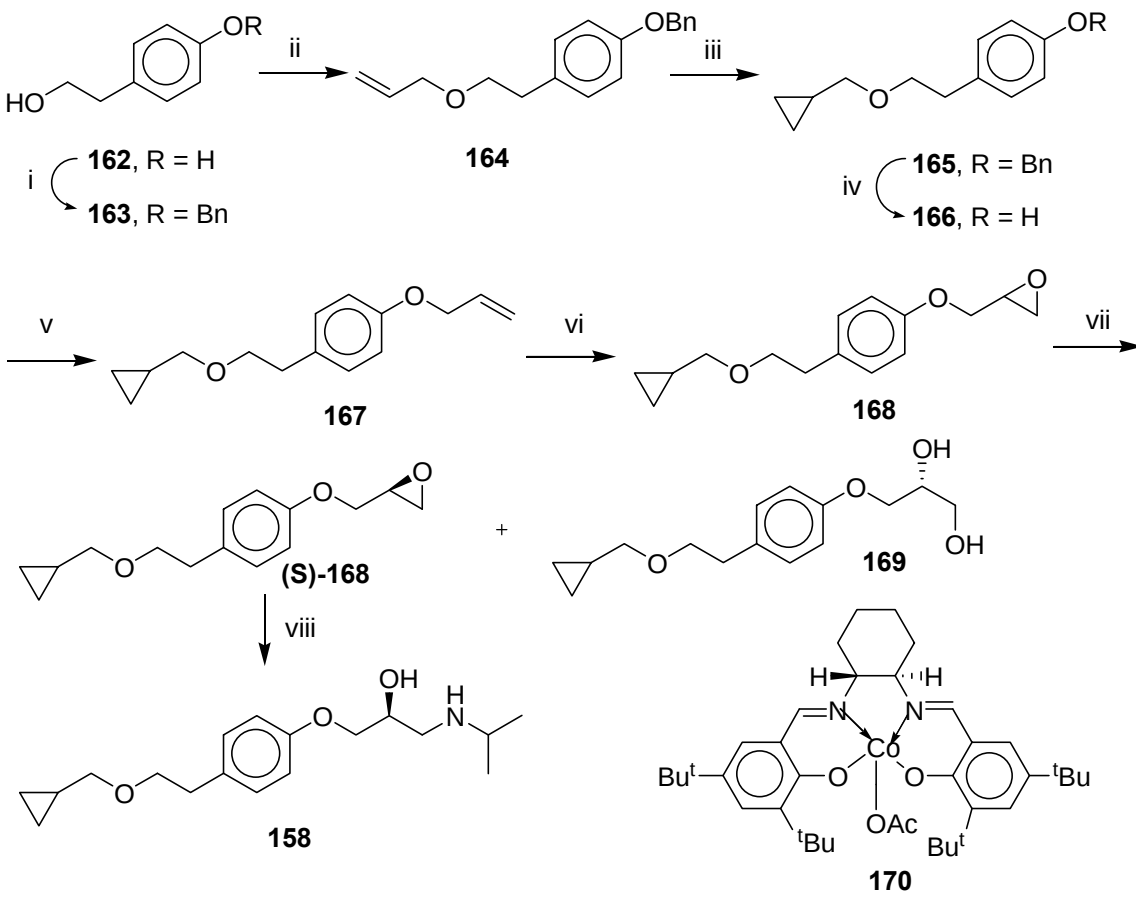
Scilimati *et al.* have reported the synthesis of (S)-betaxolol **158** using enzymatic kinetic resolution of chloro alcohol (±)-**160** in presence of vinyl acetate as acyl donor to give (R)-chloro alcohol **160a** in 83% yield. The chloro alcohol **160a** was then subjected to nucleophilic displacement with isopropyl amine under basic medium (10% NaOH) to afford (S)-betaxolol **158** in 91% yield and 60% ee. The enantiomeric excess was drastically increased to 91% ee, when it was recrystalised in diethyl ether (**Scheme 21**).



Scheme 21: (i) Lipase (SP 435-L); vinyl acetate, MeO^{t}Bu; 83%; (ii) i-PrNH$_2$, 10% NaOH, 83%, 91% ee.

Joshi's approach (2005)[46]

Joshi *et al.* have achieved the synthesis of betaxolol **158** by using hydrolytic kinetic resolution as the key step. The commercially available 4-(2-hydroxyethyl)phenol **162** was selectively benzylated (benzyl bromide, KOH) to afford the benzylated ether **163**, which on treatment with allyl bromide under basic conditions gave **164** in 98% yield. The olefin **164** was subjected to Simon-Smith cyclopropanation (diethylzinc, diiodomethane) to give cycloproyl derivative **165** in 95% yield. Subsequently, its debenzylation (Raney-Ni, H_2) gave phenol **166** which was alkylated (allyl bromide, KOH) to afford allyloxy derivative **167** in 95% yield. The olefin **167** was subjected to epoxidation using m-CPBA to give (±)-epoxide **168**, which on Jacobsen's HKR using (R,R)-salen-Co(OAc) **170** as catalyst produced (S)-epoxide **168** in 43% yield and 99% ee. The regioselective ring opening of epoxide with isopropyl amine resulted in (S)-betaxolol **158** in 76% yield (**Scheme 22**).

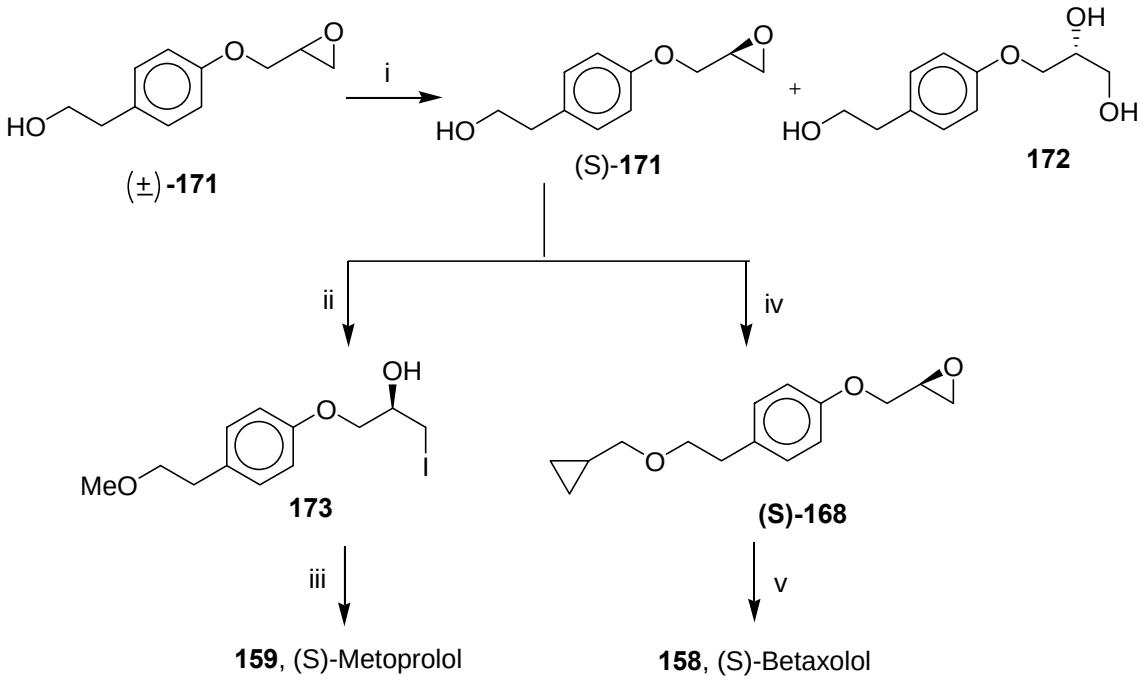


Scheme 22: (i) benzyl bromide, KOH, THF, 90%; (ii) allyl bromide, KO^{t}Bu, DMSO, 40 ^{o}C, 98%; (iii) Et_2Zn, CH_2I_2, hexane, 0 ^{o}C, 95%; (iv) Raney nickel, MeOH, H_2 (65 psi), 86%; (v) allyl bromide, KOH, THF, 95%; (vi) m-CPBA, CH_2Cl_2, 75%; (vii) (R,R)-salen Co(III)-**170**, 43%, 99% ee; (viii) isopropylamine, CH_2Cl_2, 76%.

Muthukrishnan's approach (2007)[47]

Muthukrishnan *et al* also have described the synthesis of (S)-betaxolol **158** and (S)-metoprolol **159** by employing hydrolytic kinetic resolution as the key step. Epoxide (±)-**171** was subjected to Jacobsen's HKR using (R,R)-salen-Co(OAc) **170** as catalyst to give (S)-epoxide **171** in 98% yield. Epoxide (**S**)-**171** was alkylated (MeI, KOBu^t) to produce iodo alcohol **173**, which on treatment with isopropyl amine produced (S)-metoprolol **159** in 97% yield. The synthesis of (S)-betaxolol **158** was achieved by the alkylation of

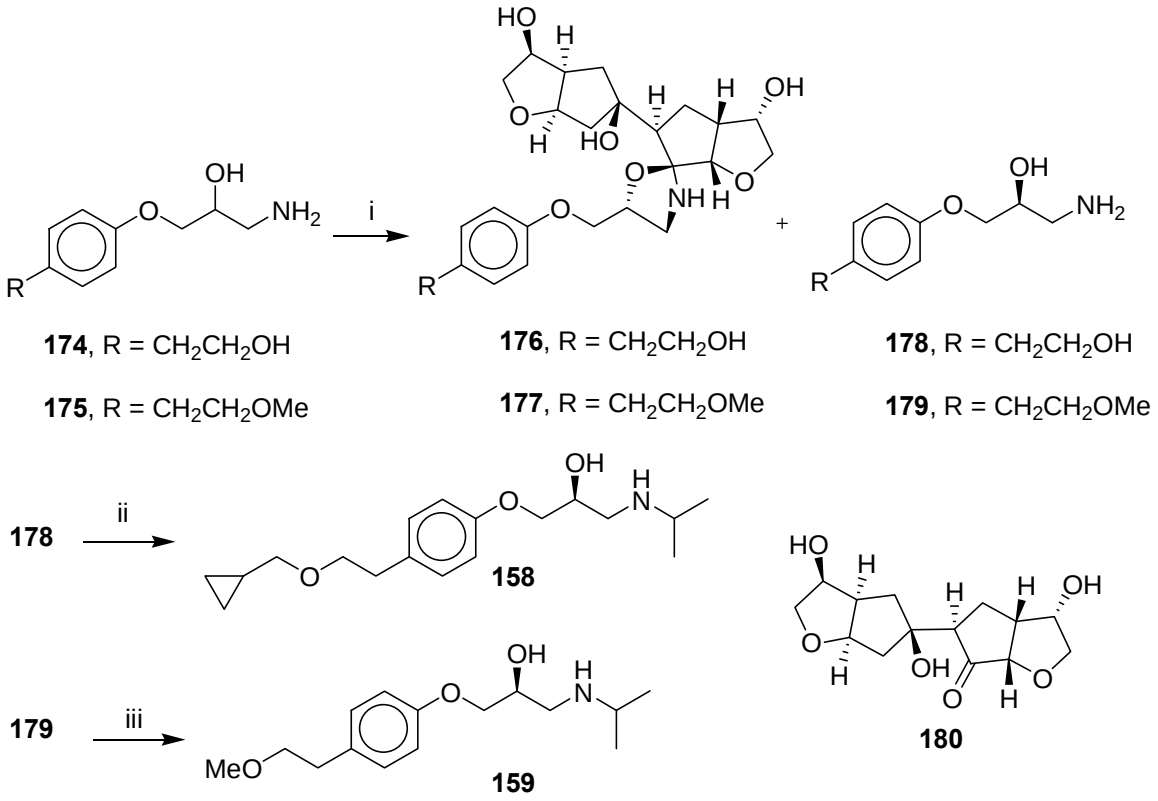
epoxide (**S)-171** (bromomethylcyclopropane, $KOBu^t$) to give (S)-**168**, followed by its nucleophilic ring opening with isopropyl amine (**Scheme 23**).



Scheme 23: (i) (R,R)-salen Co(III)-**170**, i-PrOH, (ii) CH_3I, KO^tBu, N,N-dimethylacetamide, 98%; (iii) isopropylamine, H_2O, reflux, 97%; (iv) bromomethylcyclopropane, KO^tBu, N,N-dimethylacetamide, 96%; (v) isopropylamine, H_2O, reflux, 96%.

Liu's approach (2008)[48]

Liu *et al* have described the synthesis of (S)-betaxolol **158** and (S)-metoprolol **159** by using non-enzymatic kinetic resolution (NKR) as the key step. The β-amino alcohol **174** or **175** was subjected to kinetic resolution using a chiral reagent **180** (derived from sugar) in the presence of p-toluenesulphonic acid to give (S)-isomer of β-amino alcohol **178** (47.8% yield and 99% ee) or **179** (47% yield and 99% ee) respectively. The synthesis of (S)-betaxolol **158** was achieved from β-amino alcohol **178** in one pot by employing sequential reactions of amine protection, o-alkylation and hydrolysis. The alkylation of **179** with isopropyl bromide in presence of K_2CO_3 afforded (S)-metoprolol **159** (**Scheme 24**).



Scheme 24: (i) **180**, methanol, TsOH. 5 ^{o}C; (ii) (a) toluene, phenyl aldehyde, TsOH; (b) DMF, NaH, cyclopropylmethyl bromide; (c) 10% HCl, isopropanol; (d) 10%NaOH, H_2O, toluene; (iii) isopropyl bromide; K_2CO_3, acetone, reflux, 96%.

2.3.4 Present Work

2.3.4.1 Objective

All the reported methods described above for the synthesis of β-blockers suffer from drawbacks such as use of expensive enzymes and resolving agents, low overall yields, low optical purity, etc. In order to develop a new route for the asymmetric synthesis of (S)-betaxolol **158** and (S)-metoprolol **159** with good optical purity and yield, we have decided to make use of Co-catalyzed phenolic kinetic resolution of terminal epoxides as the key reaction. A general retrosynthetic analysis for β-blockers **A** is presented in **Fig. 25**. We envisaged that chiral halohydrine **B** could serve as the key intermediate for the synthesis of β-blockers *via* epoxide opening with amine. We also thought phenolic

kinetic resolution of (±)-epichlorohydrin with Ar-OH **C** would result in the formation of chiral halohydrins with good enantioselectivities.

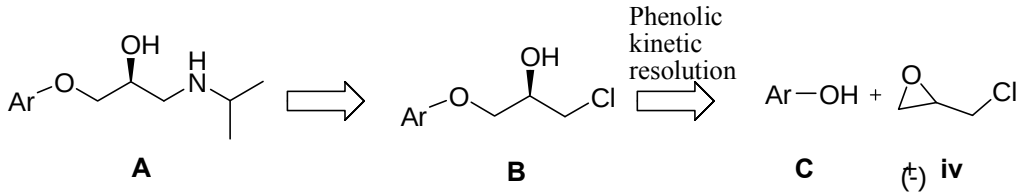


Fig. 25: Retrosynthetic analysis for the β-blockers

A brief account of Co-catalyzed asymmetric kinetic resolution of terminal epoxides is described as follows.

2.3.4.2 Kinetic Resolution

Resolution strategies have always played a central role in the preparation of optically active compounds. Resolutions fall broadly into three classes: (i) *Classical resolutions* involve the use of stoichiometric amount of chiral resolving agent. (ii) *Chiral chromatography* generally relies on the use of chiral stationary phases to resolve enantiomers contained in a mobile phase, and in principal it can be carried out on analytical or preparative scale. (iii) *Kinetic resolution* involves the use of a chiral catalyst or reagent to promote selective reaction of one enantiomer over the other giving a mixture of enantioenriched starting material and product, the desired component is then isolated (**Fig. 26**).

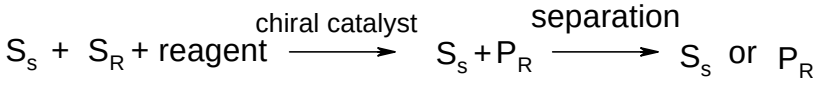


Fig. 26: kinetic resolution

If the undesired resolution byproduct can be racemized or otherwise converted back to the desired enantiomer, then this can improve the yield, and therefore the practicality of the resolution process. In some special circumstances, it is possible to induce substrate racemization under the conditions of resolution. It then becomes possible in principle to convert essentially 100 % of the racemate to the desired product. Such process constitutes a very special subclass of kinetic resolution known as dynamic kinetic resolutions. Kinetic resolutions are particularly attractive, because of the need for only small amounts of chiral "resolving agent". In kinetic resolutions, enantiomers of a racemic substrate (S) react at different rates to form a product (P) that may or may not be a chiral.

2.3.4.3 Kinetic resolution of terminal epoxides via highly enantioselective ring opening with phenols:

Enantiopure α-aryloxy alcohols (**181**) are valuable targets in asymmetric synthesis and as key synthetic intermediates in a variety of pharmaceutically important compounds.[49] In principle, access to these building blocks may be provided by several routes, including asymmetric reduction of aryloxy ketones[50] or the ring opening of enantiopure terminal epoxides with phenols. Of these, the latter is probably the most versatile and direct, but available methods for the addition of phenols to epoxides are extremely limited.

The ready accessibility of terminal epoxides in racemic form renders kinetic resolution of terminal epoxides with phenols a potentially attractive route to **181** (**Fig. 27**). The high selectivities obtained in the recently reported hydrolytic kinetic resolution of terminal epoxides with catalyst **170b**[51] suggested that (salen)Co(III) complexes might also serve as effective catalysts for the enantioselective addition of phenols to epoxides. This

strategy has proven successful and the kinetic resolution of epoxides with phenols has been reported, with the isolation of 1-aryloxy 2-alcohols (**181**) in high ee's and yields.

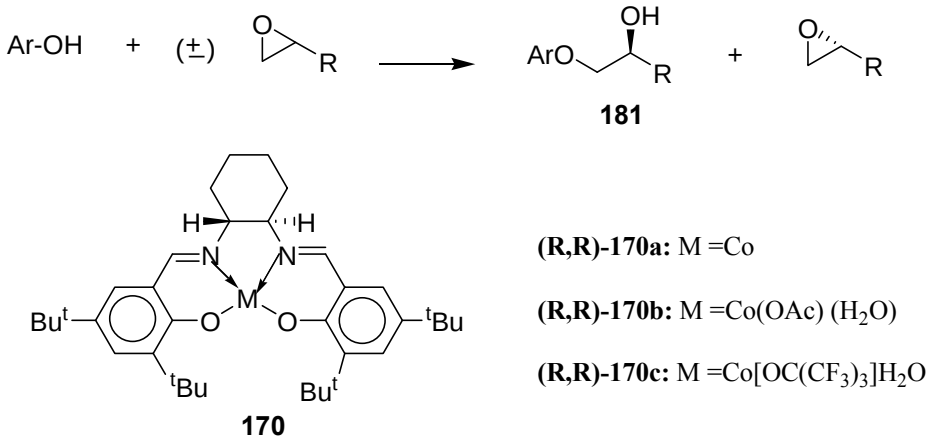


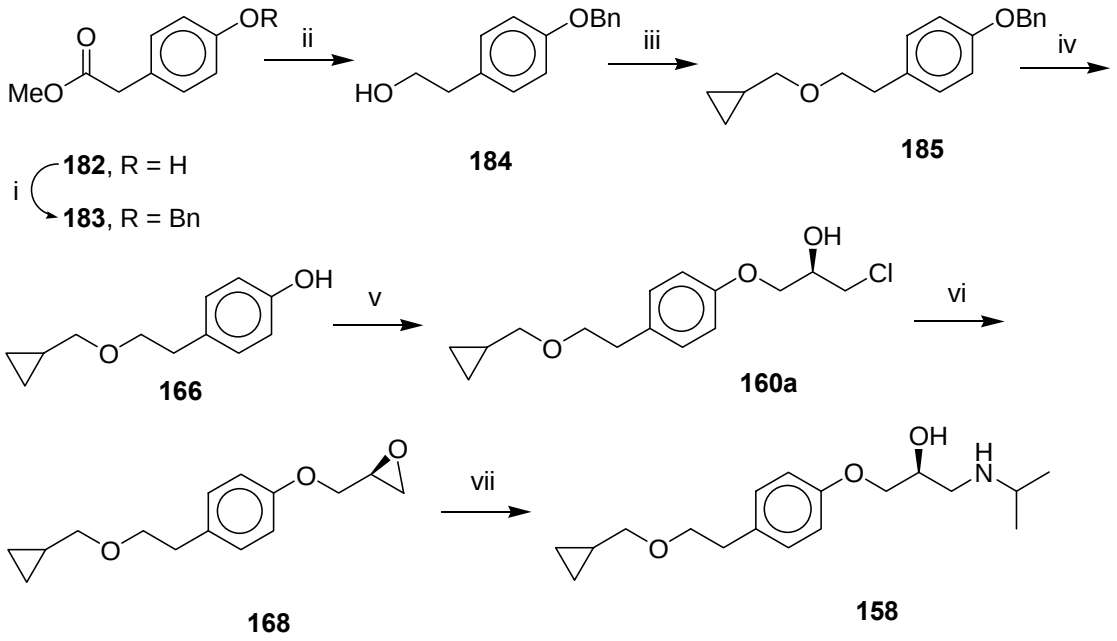
Fig. 27: Kinetic resolution of terminal epoxides with phenols

Reaction of 2.2 equiv of (±)-epoxide with phenol (ArOH) in the presence of (salen)Co(OAc) complex **170b** (0.044 equiv) in *tert*-butyl methyl ether (TBME) led to 61% conversion of phenol after 55 h at room temperature, with 1-aryloxy 2-alcohols generated in 94% ee. Encouraged by the observation of high enantioselectivity in this reaction, a variety of reaction parameters with the goal of identifying a more reactive system has been evaluated. The identity of the counter ion for the (salen)cobalt complex proved to be important in this context, with the perfluoro *tert*-butoxide complex displaying superior reactivity. Thus, the use of complex **170c** under conditions otherwise identical to those outlined above resulted in 80% conversion of phenol in 18 h and formation of 1-aryloxy 2-alcohols (**181**) as the major product in 96% ee. Small amounts of 1,2-diol were also generated, presumably as a result of epoxide hydrolysis with adventitious water, but this pathway could be suppressed easily by the inclusion of 3 A molecular sieves in the reaction mixture.

2.3.5 Results and Discussion

2.3.5.1 Asymmetric synthesis of (S)-betaxolol

The synthesis of (S)-betaxolol **158** commenced from methyl ester **182**, which was prepared from commercially available 4-hydroxyphenylacetic acid on simple esterification (**Scheme 25**).



Scheme 25: (i) anhyd. K_2CO_3, acetone, BnBr, 0-60 ^oC, 8 h, 80%; (ii) $LiAlH_4$, dry THF, 65 ^oC, 8 h, 88%; (iii) NaH, dry DMF, bromomethylcyclopropane, 0-25 ^oC, 10 h, 85%; (iv) 10% Pd/C, H_2 (20 psi), MeOH, 12 h, 88%; (v) 2.5 equiv. (±)-epichlorohydrin, (*R,R*)-Co-salen **170c**, *tert*-butyl methyl ether, MS 3 A°, -15 °C, 24 h, 74%; (vi) K^{t}OBu, THF, 0 °C, 92%; (vii) isopropylamine, H_2O, 50 °C, 99%.

Phenol **182** was protected as its benzyl ether (K_2CO_3, benzyl bromide) to give **183** in 80% yield. The formation of benzyl ether **183** was confirmed by the appearance of a singlet at δ 5.04 (2H) and multiplets at δ 7.31-7.43 (m 5H) due to benzylic methylene and aromatic protons respectively in its ^1H NMR spectrum. Further, its ^{13}C NMR spectrum showed a typical signal at δ 69.8 corresponding to benzylic methylene carbon.

Reduction of ester **183** with $LiAlH_4$ resulted in the formation of primary alcohol **184**, which was subsequently alkylated (bromomethylcyclopropane, NaH) to obtain the corresponding alkyl ether **185** in 85% yields.

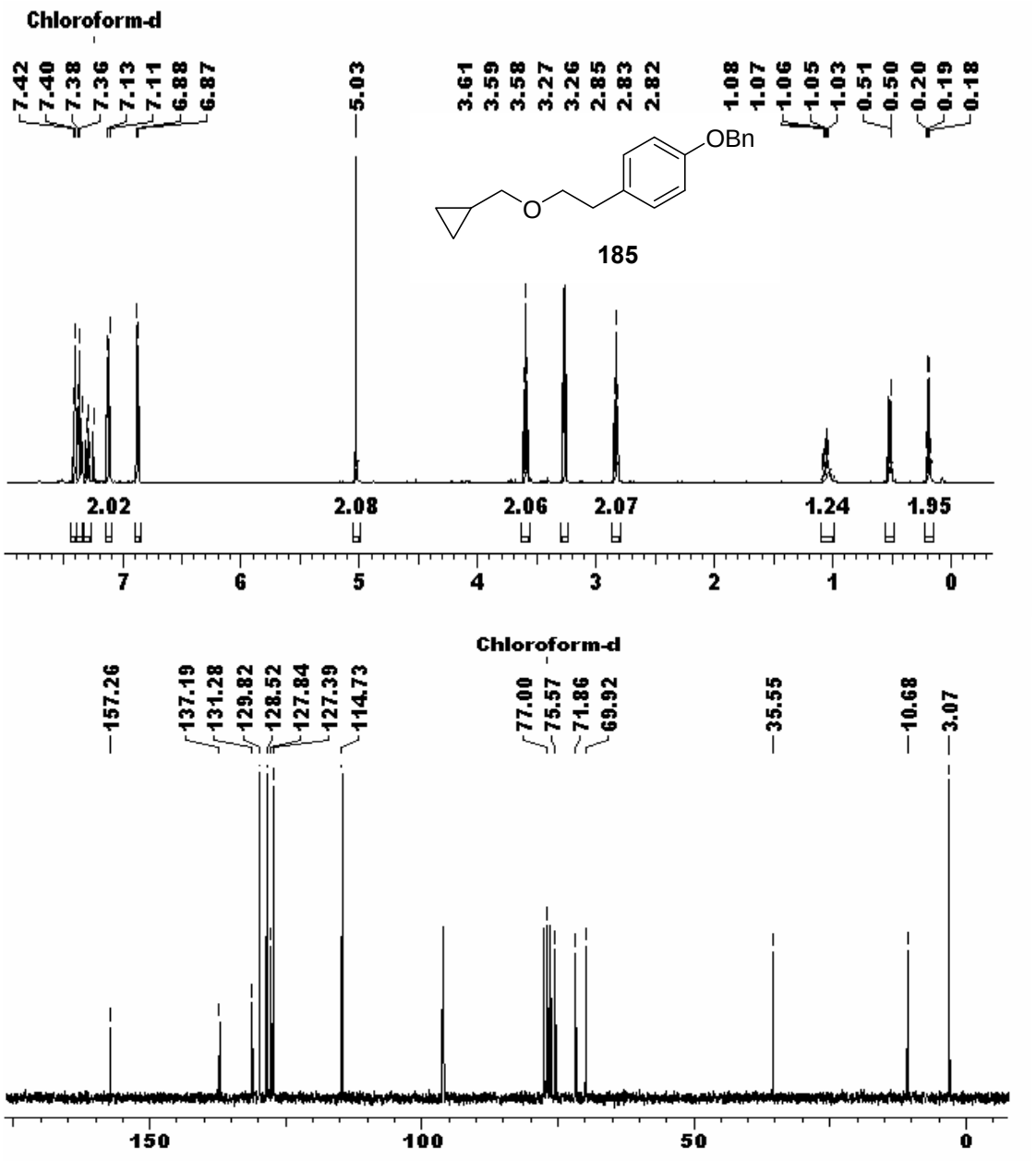


Fig. 28: ^{1}H and ^{13}C NMR spectra of ether **185**

The formation of ether **185** was confirmed, in its ^{1}H NMR spectrum, by the appearance of characteristic signals at δ 0.19 (q, J = 4.7, 10.3 Hz, 2H), 0.50-0.54 (m, 2H) and 1.03-

1.09 (m, 1H) due to cyclopropyl, methylene and methine protons respectively. It was further substantiated by the appearance of typical carbon signals at δ 3.0 and 10.6 in its ^{13}C NMR spectrum (**Fig. 28**).

The deprotection of benzyl group in ether **185** under hydrogenation condition [10% Pd/C, H_2 (20 psi)] was achieved to afford phenol **166**. The phenolytic kinetic resolution of **166** with (±)-epichlorohydrin (2.5 equiv.) in the presence of (R,R)-Co(III)-salen **170c** as catalyst afforded optically active chloroalcohol **160a** in 74% yield.

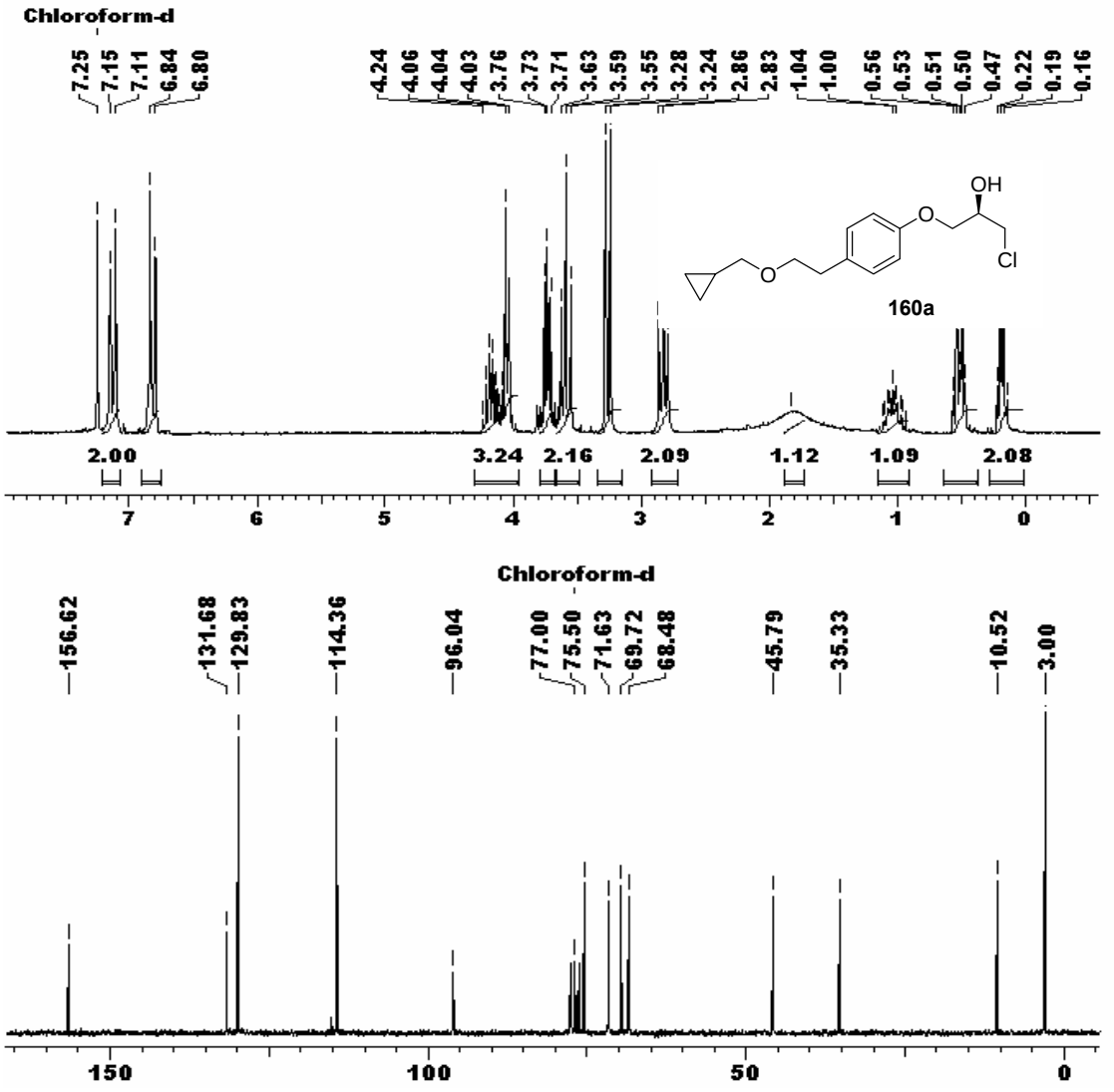


Fig. 29: ^{1}H and ^{13}C NMR spectra of chloroalcohol **160a**

Its ^{1}H NMR spectrum showed typical signals at δ 1.83 (brs) (-O**H**), 3.68-3.81 (m, 2H) (-C**H**$_2$Cl) and 3.98-4.09 (m, 2H), 4.11-4.24 (m, 1H) corresponding to the hydroxyl and the methylene protons of propyl moiety. Its ^{13}C NMR spectrum showed typical signals at δ 45.7 (-**C**H$_2$Cl), 68.4 (-**C**H(OH)-) and 69.7 (-**C**H$_2$O-Ar) corresponding to methylene and methine carbons of the propyl moiety (**Fig. 29**).

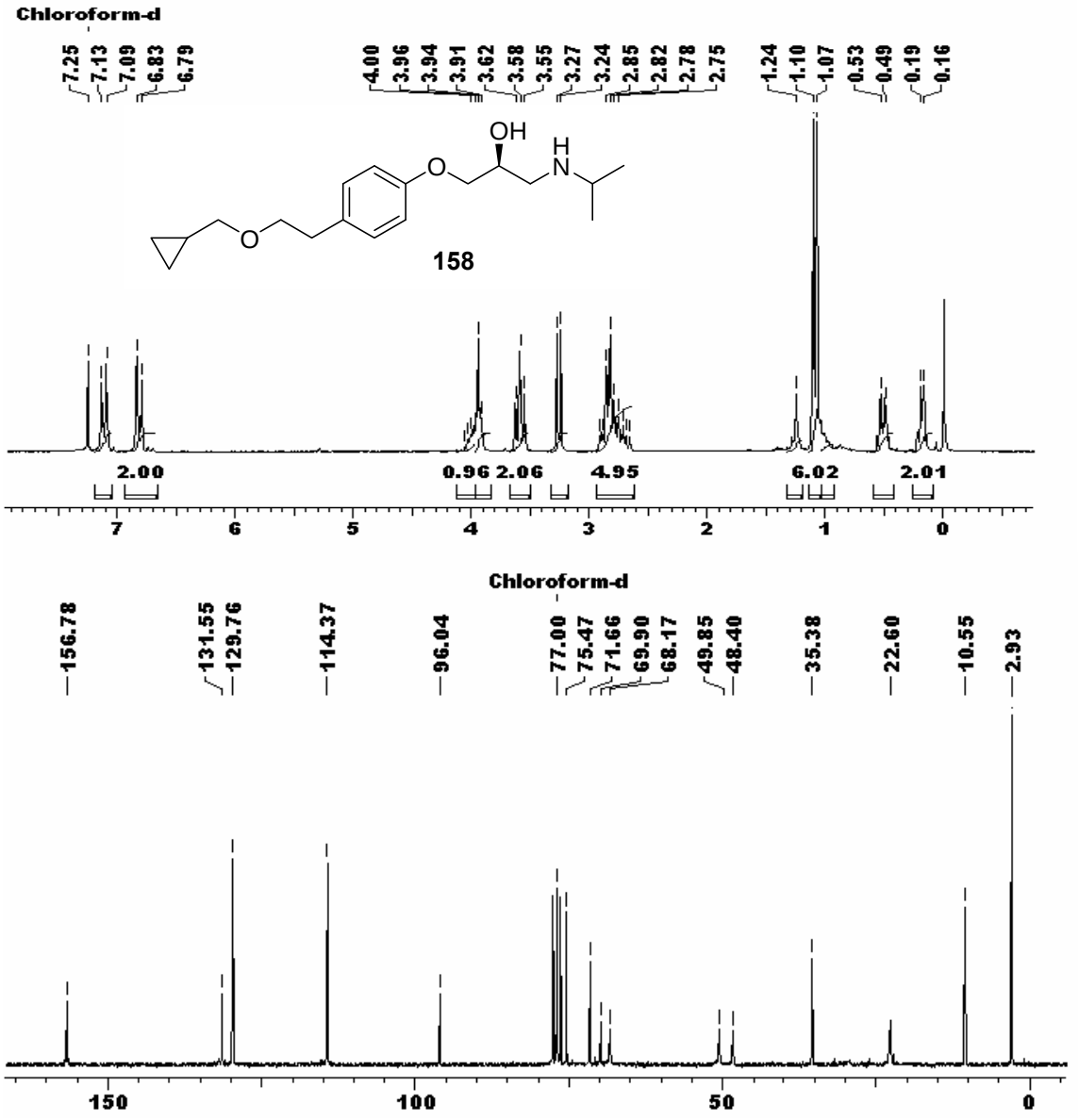
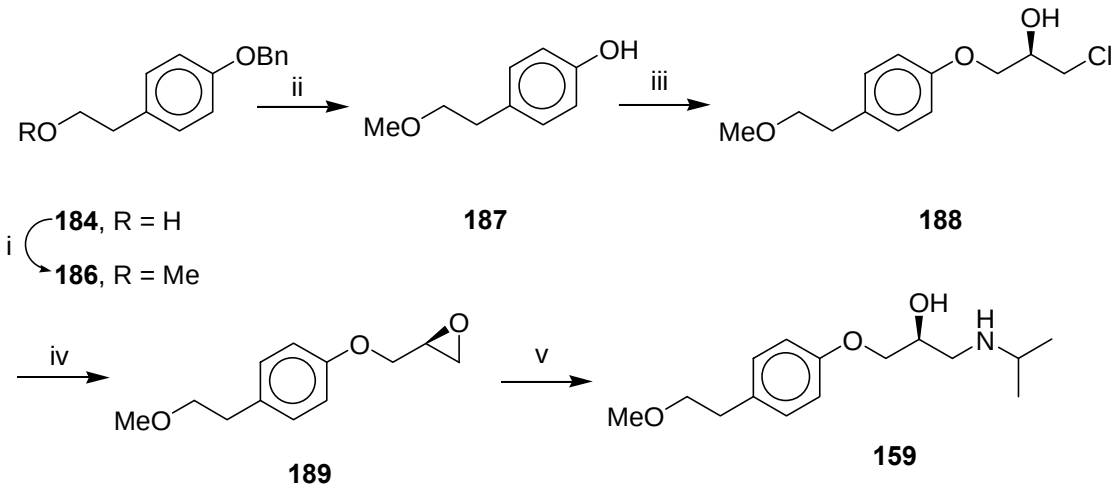


Fig. 30 ^{1}H and ^{13}C NMR spectra of (S)-betaxolol **158**

The choroalcohol **160a** on treatment with KOBu^t gave the corresponding chiral epoxide **168** in 92% yield. The regiospecific ring opening of epoxide **168** with isopropyl amine in the presence of water at 50 ^oC resulted in the formation of (S)-betaxolol **158** in 99% yield. Its ^1H NMR spectrum displayed a typical doublet at δ 1.08 (d, J = 6.4 Hz, 6H) corresponding methyl protons. Multiplets at δ 3.89-3.94 (m, 2H) and 3.96-4.05 (m, 1H) indicate the presence of methylene protons of the aminoalcohol moiety. Further, its ^{13}C NMR spectrum showed characteristic carbon signals at δ 22.6, 48.4 and 49.8 due to the isopropyl carbon and carbons attached to nitrogen atom respectively. The spectral data obtained for (S)-betaxolol **158** were in full agreement with the values reported in the literature (**Fig. 30**).

2.3.5.2 Asymmetric synthesis of (S)-metoprolol (159)

Our synthesis of metoprolol **159** started from alcohol **184**, which on methylation (CH_3I, NaH) gave the methyl ether, **186** in 89% yield (**Scheme 26**).



Scheme 26: (i) NaH, dry DMF, MeI, 0-25 ^oC, 89%; (ii) 10% Pd/C, H_2 (20 psi), MeOH, 10 h, 90%; (iii) 2.5 equiv. (±)-epichlorohydrin, (*R,R*)-Co-salen **170c**, *tert*-butyl methyl ether, MS 3 A$^\circ$, -15 °C, 24 h, 71%; (iv) K^{t}OBu, THF, 0 °C, 90%; (v) isopropylamine, H_2O, 50 °C.

The debenzylation of **186** under hydrogenation conditions [10% Pd/C, H_2 (20 psi)] was achieved to obtain phenol **187**, which was then subjected to phenolytic kinetic resolution with (±)-epichlorohydrin (2.5 equiv.) in the presence of (R,R)-Co(III)-salen **170c** as the chiral catalyst to afford optically active chloroalcohol **188** in 71% yield. Its ^{1}H NMR spectrum displayed typical signals at δ 3.69-3.79 (m, 2H), 4.02-4.09 (m, 2H) and 4.12-4.23 (m, 1H) due to the corresponding methylene and methine protons respectively. Its ^{13}C NMR spectrum displayed carbon signals at δ 45.8 (-**C**H_2Cl), 68.5 (-**C**H(OH)-) and 69.8 (-**C**H_2O-Ar) for the methylene and methine carbons respectively (**Fig. 31**).

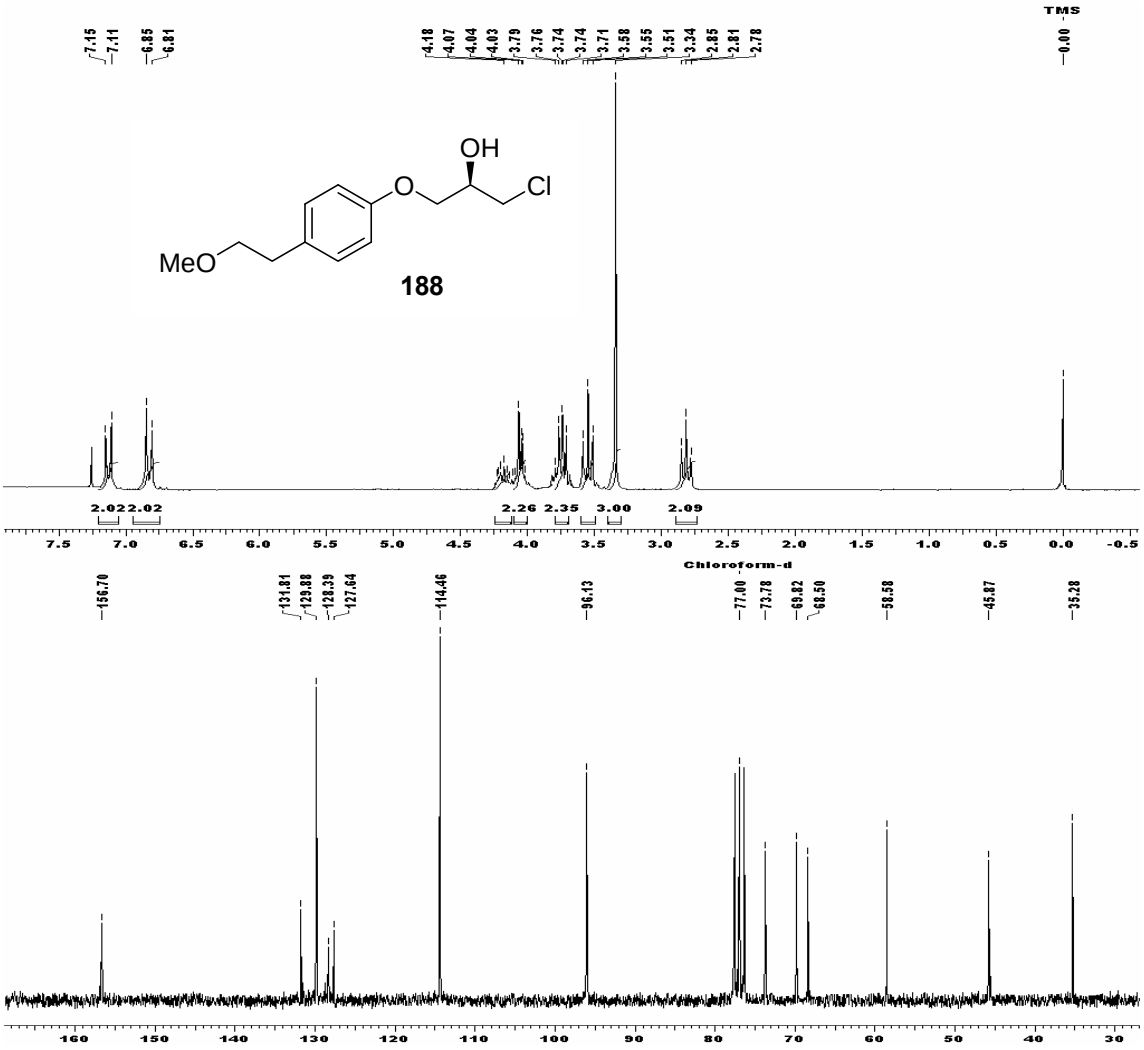


Fig. 31 ^{1}H and ^{13}C NMR spectra of chloroalcohol **188**

The choroalcohol **188** was then converted to the corresponding epoxide **189** (KOBu^t) in 90% yield. Its ^{1}H NMR spectrum displayed an upfield shift in the δ value for the methylene and methine protons [3.28-3.32 (m, 1H), 3.53 (t, *J* = 7.0 Hz, 2H); 3.95 (t, *J* = 5.4 Hz 1H); 4.15 (dd, *J* = 3.4, 10.9 Hz, 1H)] of epoxide moiety. Its ^{13}C NMR spectrum displayed typical carbon signals at δ 44.6 and 50.0 corresponding to the methylene and methine carbons of epoxide moiety (**Fig. 32**).

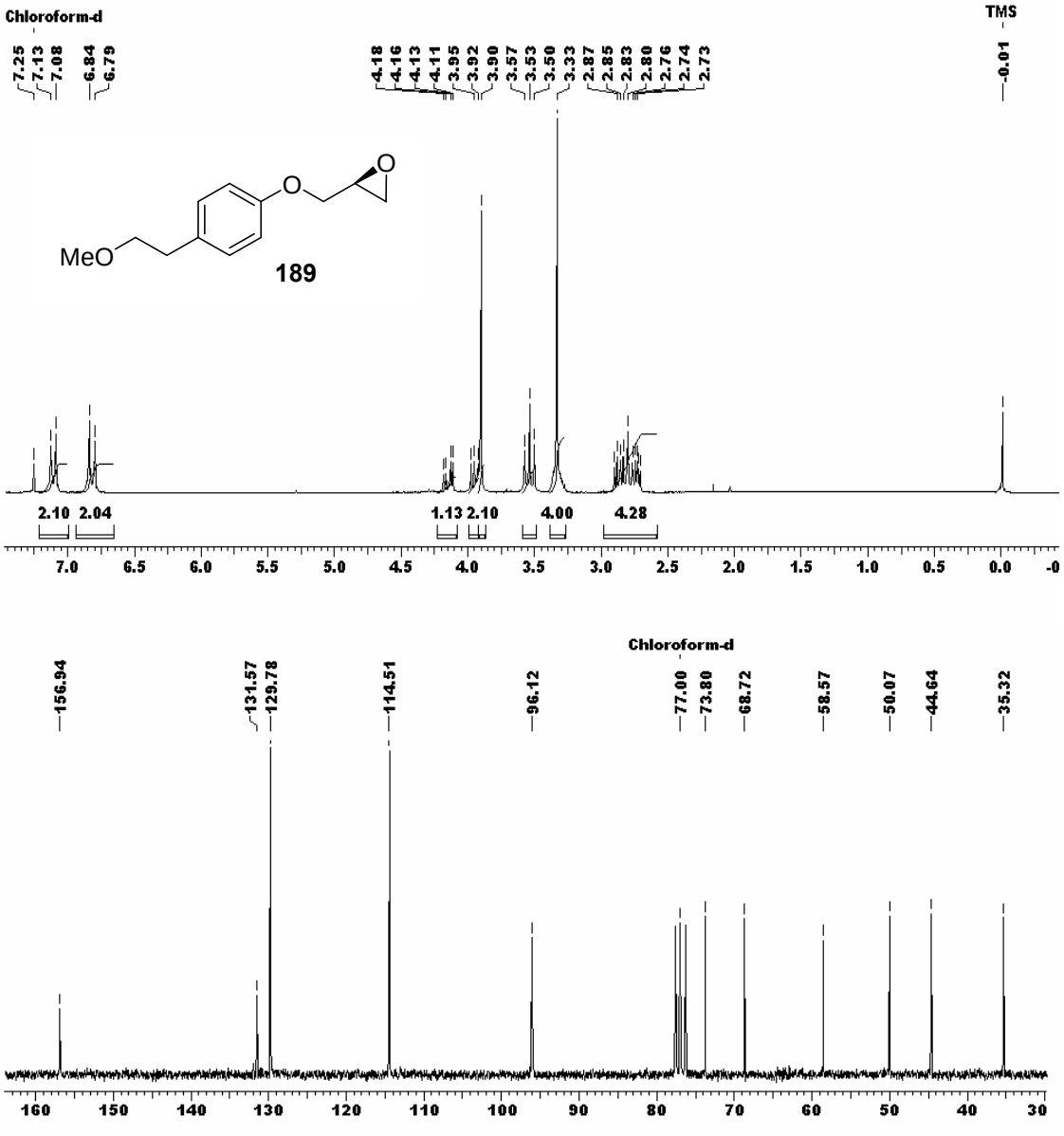


Fig. 32 ^{1}H and ^{13}C NMR spectra of epoxide **189**

The regiospecific ring opening of epoxide **189** with isopropyl amine in the presence of water at 50 ^{o}C resulted in the formation of (S)-metoprolol **159** in 99% yield. Its ^{1}H NMR spectrum showed a doublet at δ 1.07 (d, J = 6.2 Hz, 6H) corresponding to the isopropyl carbons. Further, its ^{13}C NMR spectrum showed typical signals at δ 22.7 and at δ 48.8, 49.3 due to the isopropyl group and carbons attached to nitrogen atom respectively (**Fig. 33**).

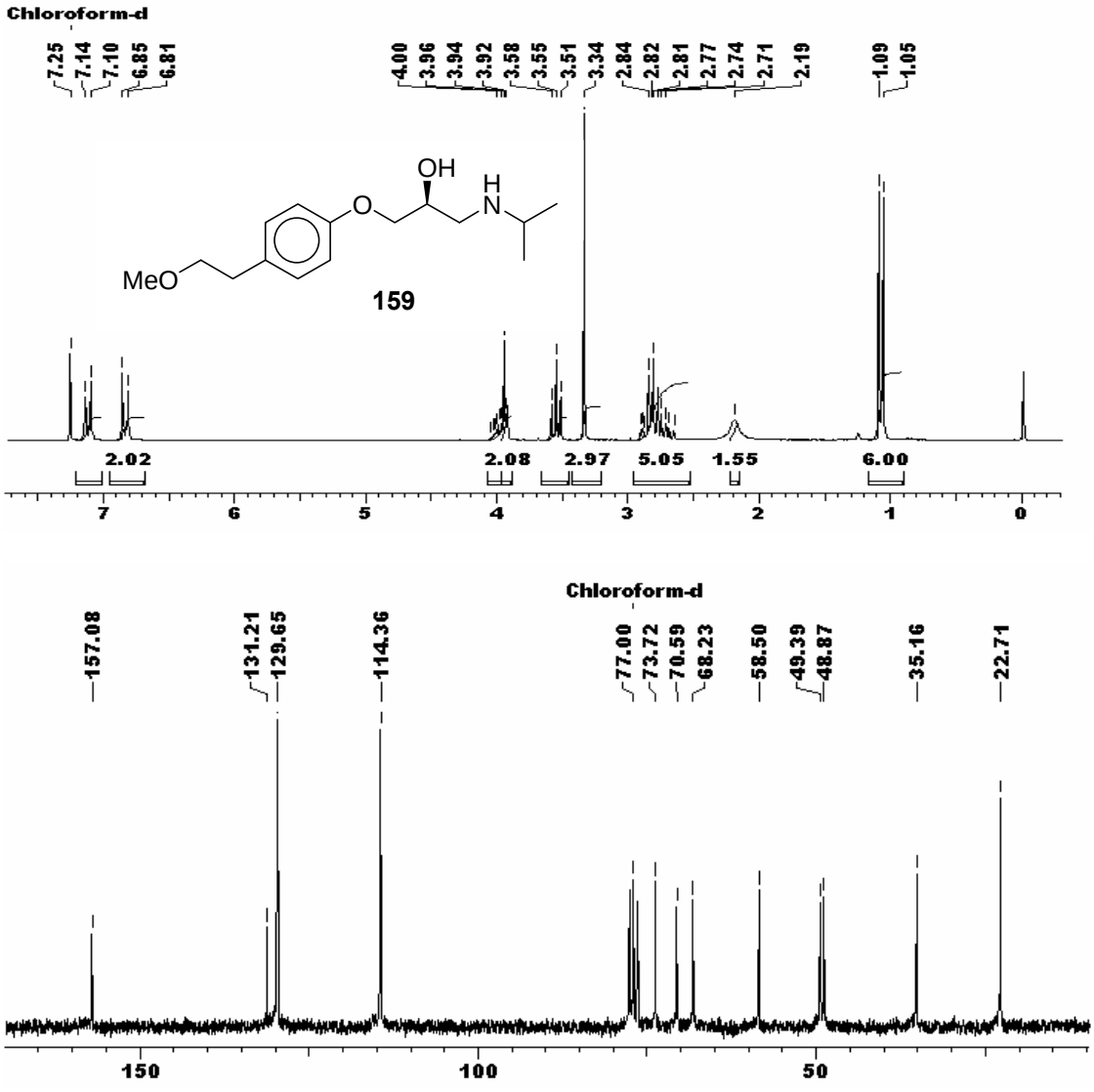


Fig. 33 ^{1}H and ^{13}C NMR spectra of (S)-metoprolol **159**

2.3.6 Conclusion

In conclusion, we have successfully applied Co-catalyzed kinetic resolution of terminal epoxides for the enantioselective synthesis of (S)-betaxolol (**158**) (99% ee) and (S)-metoprolol (**159**) (99% ee). The reactions are rapid and require a relatively low amount of an inexpensive Co-catalyst. The high enantiopurity and yields, less number of steps render our approach a good alternative to the known routes reported in the literature.

2.3.7 Experimental Section

Methyl 2-(4-(benzyloxy) phenyl) acetate (183)

To a solution of methyl 2-(4-hydroxyphenyl) acetate **182** (5.0 g, 30.10 mmol) in dry acetone (40mL) was added anhydrous K_2CO_3 (4.15 g, 30.10 mmol) at room temperature. After 15 min. benzyl bromide (3.5 mL, 30.10 mmol) in 5 mL acetone was added very carefully. The reaction mixture was refluxed for 8 h at 60 ^oC. After completion of the reaction, as monitored by TLC, acetone was evaporated on a rotatory evaporator. The residue was extracted with EtOAc (3 x 50mL) washed with water (3 x 20 mL) and dried over anhyd. Na_2SO_4. The combined organic layers were concentrated under reduced pressure and the product was purified by column chromatography using pet.ether:ethyl acetate (90:10) to give benzyl ether **183**.

Yield: 80% (6.2 g); colorless oil **IR** ($CHCl_3$, cm^{-1}): 3452, 3033, 2925, 2854, 2360, 1735, 1612, 1512, 1456, 1242, 1167, 1076, 1016, 819, 698, 617; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.54 (s, 2H), 3.68 (s, 3H), 5.04 (s, 2H), 6.90 (d, *J* = 8.3 Hz, 2H), 7.17 (d, J = 8.7 Hz, 2H), 7.31 (m, 5H), **^{13}C NMR** (50 MHz, $CDCl_3$): δ 40.2, 51.8, 69.8, 114.8, 126.2, 127.3, 127.8, 128.0, 128.5, 130.2, 136.9, 157.8, 172.0; **Anal.** Calcd for: $C_{16}H_{16}O_3$ requires C, 74.98; H, 6.29; Found C, 75.01, H, 6.05%.

2-(4-(Benzyloxy) phenyl)ethanol (184)

A suspension of $LiAlH_4$ (1.48 g, 39.01 mmol) in THF (50 mL) was cooled to 0 ^oC. To this, a solution of methyl 2-(4-(benzyloxy)phenyl)acetate **183** (5 g, 19.50 mmol) in 15 mL dry THF was added slowly at 0 ^oC over a period of 20 min and then stirred for 8 h at 65 ^oC. Then the reaction mixture was cooled to room temperature and quenched with 20% NaOH followed by EtOAc (5 mL) and extracted with EtOAc (3 x 50 mL) and organic layers were washed with water (3 x 20 mL), dried over anhyd. Na_2SO_4 and solvent was removed under reduced pressure. The crude product was purified by column chromatography pet.Ether:EtOAc (70:30) to give 2-(4-(benzyloxy)phenyl)ethanol **184**.

Yield: 88% (3.9 g); **IR** ($CHCl_3$, cm^{-1}): 3452, 3018, 2945, 2877, 2399, 2380, 1610, 1510, 1380, 752, 669; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.54 (br s, 1H), 2.79 (t, *J* = 6.4 Hz, 2H), 3.81 (t, *J* = 6.4 Hz, 2H), 5.04 (s, 2H), 6.90 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.29-7.44 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 38.1, 63.5, 69.8, 114.8, 127.2, 127.7, 128.4, 129.8, 130.7, 136.9, 157.5; **Anal.** Calcd for: $C_{15}H_{16}O_2$ requires C, 78.92; H, 7.06; Found C, 78.66, H, 6.99%.

1-((4-(2-(Cyclopropylmethoxy)ethyl)phenoxy)methyl)benzene (185)

To a solution of sodium hydride (0.425 g, 10.51 mmol) in dry DMF (30 mL) was added 2-(4-(benzyloxy)phenyl)ethanol **184** (2.0 g, 8.76 mmol) and the reaction mixture was stirred for 15 min at 0 ^oC and then (bromomethyl)cyclopropane (1.0 mL, 10.51) was added drop-wise. The reaction mixture was stirred for 10 h at 25 ^oC. After the completion of the reaction, as monitored by TLC, it was quenched with water and extracted with EtOAc (3 x 50 mL), washed with water followed by brine and dried over anhyd. Na_2SO_4. The combined organic layers were concentrated under reduced pressure to give alkylated

product **185**, which was purified by the column chromatography using pet. ether: EtOAc (90:10) as eluent.

Yield: 85% (2.1 g); **IR** ($CHCl_3$, cm^{-1}): 2923, 2864, 2360, 2343, 1716, 1616, 1512, 1456, 1288, 1265, 1238, 1108, 748; **^{1}H NMR** (200 MHz, $CDCl_3$): 0.19 (q, *J* = 4.7, 10.3 Hz, 2H), 0.50-0.54 (m, 2H), 1.03-1.09 (m, 1H), 2.83 (t, *J* = 7.6 Hz, 2H), 3.26 (d, *J* = 6.8 Hz, 2H), 3.59 (t, *J* = 7.3 Hz, 2H), 5.03 (s, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 7.12 (d, *J* = 8.6 Hz, 2H), 7.30 (t, *J* = 7.3 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.41 (d, *J* = 7.5 Hz, 2H) **^{13}C NMR** (50 MHz, $CDCl_3$): δ 3.0, 10.6, 35.5, 69.9, 71.8, 75.5, 114.7, 127.3, 127.8, 128.5, 129.8, 131.2, 137.1, 157.2; **Anal.** Calcd for: $C_{19}H_{22}O_2$ requires C, 80.82; H, 7.85; Found C, 80.71, H, 7.79%.

4-(2-(Cyclopropylmethoxy)ethyl)phenol (166)

A solution of benzyl ether **185** (1.5 g, 5.3 mmol) was dissolved in MeOH followed by the addition of 10% Pd/C (80mg) to it. The reaction mixture was stirred under hydrogen atmosphere (20 psi) for 12 h. After completion of the reaction, monitored by TLC, it was filtered through celite pad, and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel using pet.ether: EtOAc (70:30) as eluent to give pure product **166**.

Yield: 88% (880 mg); **IR** ($CHCl_3$, cm^{-1}): 3431, 2923, 2864, 2360, 2343, 1716, 1616, 1515, 1456, 1288, 1265, 1238, 1108, 831, 748; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.14-0.22 (m, 2H), 0.47-0.56 (m, 2H), 0.95-1.15 (m, 1H), 2.81 (t, *J* = 7.2 Hz, 2H), 3.29 (d, *J* = 6.8 Hz, 2H), 3.62 (t, *J* = 7.3 Hz, 2H), 5.50 (br s, 1H), 6.70 (d, *J* = 8.5 Hz, 2H), 7.04 (d, *J* = 8.6 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 3.1, 10.4, 35.2, 71.8, 75.7, 115.3, 129.8,

129.9, 154.4; **Anal.** Calcd for: $C_{12}H_{16}O_2$ requires C, 74.97; H, 8.39; Found C, 73.98, H, 8.88%.

(R)-1-(4-(2-(Cyclopropylmethoxy)ethyl)phenoxy)-3-chloropropan-2-ol (160a)

To a stirred mixture of *(*R,R*)*-Co complex **170c** (0.0100 g, 0.044 equiv.), (±)-epichlorohydrin (0.960 g, 10.4 mmol), *tert*-butyl methyl ether (0.15 mL) and 3Å molecular sieve (150 mg) at -15 °C was added phenol **166** (800 mg, 4.16 mmol). The reaction was stirred at -15 °C until GC analysis indicated complete conversion of phenols, at which time pyridinium *p*-toluenesulfonate (52 mg, 5 mol%) was added. The reaction mixture was filtered through a pad of silica and washed with 50% EtOAc/hexanes (25 mL). The filtrate was concentrated *in vacuo* to give the crude product, which was purified by chromatography using pet.ether:EtOAc (70:30) as eluent to give chloroalcohol **160a**.

Yield: 74% (870 mg); $[\alpha]^{25}_{D}$**:** -1.6 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3600, 3212, 3065, 2995, 2900, 2825, 1610, 1511, 1423, 1412, 1366, 1275, 1237, 1175, 1077, 1037, 810; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.14-0.22 (m, 2H), 0.47-0.56 (m, 2H), 0.93-1.14 (m, 1H), 1.83 (br s, 1H), 2.82 (t, *J* = 7.2 Hz, 2H), 3.26 (d, *J* = 6.8 Hz, 2H), 3.59 (t, *J* = 7.3 Hz, 2H), 3.68-3.81 (m, 2H), 3.98-4.09 (m, 2H), 4.11-4.24 (m, 1H), 6.82 (d, *J* = 8.6 Hz, 2H), 7.13 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 3.0, 10.5, 35.3, 45.7, 68.4, 69.7, 71.6, 75.5, 114.3, 129.8, 131.6, 156.6; **Anal.** Calcd for $C_{15}H_{21}ClO_3$: C, 63.26; H, 7.43; Cl, 12.45; Found: C, 63.41; H, 7.33; Cl, 12.38%.

(S)-2-((4-(2-(Cyclopropylmethoxy)ethyl)phenoxy)methyl)oxirane (168)

To a solution of chloroalcohol **160a** (0.5 g, 1.75 mmol) in dry THF (15 mL) at 0 °C was added potassium *tert*-butoxide (394 mg, 3.5 mmol) and stirred for 1 h, diluted with H_2O

(10 mL) and extracted with ether (3 × 20 mL). The collected organic layers were washed with brine and dried over anhyd. Na_2SO_4. Solvent was evaporated *in vacuo* to afford chiral epoxides **168** in high yield.

Yield: 92% (410 mg); $[\alpha]^{25}_{D}$**:** +2.03 (*c* 1, $CHCl_3$), {[lit[47] $[\alpha]^{25}_{D}$**:** +2.05 (*c* 1, $CHCl_3$)]} ; **IR** ($CHCl_3$, cm^{-1}): 3070, 3014, 2920, 2855, 1722, 1610, 1575, 1510, 1452, 1372, 1290, 1240, 1166, 1070, 1022, 935, 826 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.14-0.22 (m, 2H), 0.47-0.56 (m, 2H), 0.95-1.12 (m, 1H), 2.70–2.75 (m, 1H), 2.82 (t, *J* = 7.4 Hz, 2H), 2.86–2.91 (m, 1H), 3.26 (d, *J* = 7.0 Hz, 2H), 3.30–3.36 (m, 1H), 3.59 (t, *J* = 7.6 Hz, 2H), 3.94 (dd, *J* = 5.2, 11.0 Hz, 1H), 4.15 (dd, *J* = 3.6, 11.0 Hz, 1H), 6.82 (d, *J* = 8.5 Hz, 2H), 7.12 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 50 MHz)): δ 2.9, 10.5, 35.3, 44.6, 50.1, 68.7, 71.6, 75.5, 114.4, 129.7, 131.6, 156.8; **Anal.** Calcd for: $C_{15}H_{20}O_3$: C, 72.55; H, 8.12; Found: C, 72.63; H, 7.99%.

(S)-Betaxolol (158)

A solution of epoxide (S)-**168** (0.3 g, 1.2 mmol) in 2-propylamine (2.0 mL) and H_2O (2–3 drops) was refluxed until TLC showed the reaction had gone to completion (12 h). Removal of the solvent yielded the crude (S)-betaxolol **158** as a free base.

Yield: 99% (370 mg); $[\alpha]^{25}_{D}$: -7.39 (*c* 1.1, $CHCl_3$), {[lit[48] $[\alpha]^{25}_{D}$**:** -7.40 (*c* 1, $CHCl_3$)]}; **IR** ($CHCl_3$, cm^{-1}): 3297, 3043, 2978, 2864, 1612, 1555, 1468, 1370, 1244, 1176, 1091, 930, 870; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.14-0.21 (m, 2H), 0.47-0.56 (m, 2H), 0.87-1.04 (m, 1H), 1.08 (d, *J* = 6.4 Hz, 6H), 1.24 (br s, 1H), 2.65-2.91 (m, 5H), 3.26 (d, *J* = 6.8 Hz, 2H), 3.58 (t, *J* = 7.3, 14.4 Hz, 2H), 3.89-3.94 (m, 2H), 3.96-4.05 (m, 1H), 6.82 (d, *J* = 8.6 Hz, 2H), 7.11 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR** ($CDCl_3$): δ 2.9, 10.5, 22.6, 35.3, 48.4,

49.8, 68.1, 69.9, 71.6, 75.4, 114.3, 129.7, 131.5, 156.7; **Anal.** Calcd for: $C_{18}H_{29}NO_3$: C, 70.32; H, 9.51; N, 4.56; Found: C, 70.32; H, 9.51; N, 4.56%.

1-((4-(2-Methoxyethyl)phenoxy)methyl)benzene (186)

To a solution of sodium hydride (0.297 g, 7.42 mmol) in dry DMF (25 mL) was added alcohol **184** (1.5 g, 6.1 mmol) and the reaction mixture was stirred for 15 min at 0 ^oC and then methyl iodide (0.770 mL, 12.38 mmol) was added drop-wise. The reaction mixture was stirred for 6 h at 25 ^oC. After the completion of the reaction, as monitored by TLC, it was quenched with water and extracted with EtOAc (3 x 30 mL) and washed with water followed by brine and dried over anhyd. Na_2SO_4. The combined organic layers were concentrated under reduced pressure to give the methyl ether **186**, which was purified by the column chromatography using pet. ether: EtOAc (90:10).

Yield: 89% (1.41 g); **IR** ($CHCl_3$, cm^{-1}): 2921, 2860, 2357, 2340, 1712, 1611, 1510, 1230, 1176, 748; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.81 (t, *J* = 7.0 Hz, 2H), 3.34 (s, 3H), 3.55 (t, *J* = 7.0 Hz, 2H), 5.03 (s, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 7.11 (d, *J* = 8.6 Hz, 2H), 7.29-7.43 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 35.2, 58.4, 69.7, 73.7, 114.6, 127.2, 127.7, 128.4, 129.6, 131.1, 137.1, 157.2; **Anal.** Calcd for: $C_{16}H_{18}O_2$ requires C, 79.31; H, 7.49; Found C, 78.98, H, 7.62%.

4-(2-Methoxyethyl)phenol (187)

To a solution of benzyl ether **186** (1.0 g, 4.12 mmol) in MeOH (20 mL) was added 10% Pd/C (60 mg). The reaction mixture was stirred under hydrogen atmosphere (20 psi) for 10 h. After completion of the reaction, as monitored by TLC, the reaction mixture was then filtered through celite pad, and the filtrate was concentrated under reduced pressure.

The crude product was purified by column chromatography over silica gel using pet.ether: EtOAc (70:30) as eluent to give pure phenol **187**.

Yield: 90% (570 mg); **IR** ($CHCl_3$, cm^{-1}): 3429, 2920, 2860, 2341, 1722, 1621, 1502, 1451, 1264, 831; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.80 (t, *J* = 7.0 Hz, 2H), 3.35 (s, 3H), 3.56 (t, *J* = 7.0 Hz, 2H), 5.15 (br s, 1H), 6.71 (d, *J* = 8.6 Hz, 2H), 7.05 (d, *J* = 8.6 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 35.0, 58.4, 74.0, 115.3, 129.8, 154.4; **Anal.** Calcd for: $C_9H_{12}O_2$ requires C, 71.03; H, 7.95; Found C, 70.98, H, 8.02%.

(R)-1-(4-(2-Methoxyethyl)phenoxy)-3-chloropropan-2-ol (188)

For experimental details, see the procedure given for compound **160a**

Yield: 71% (578 mg); $[\alpha]^{25}_D$**:** -0.9, (c 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3051, 3000, 2915, 2851, 1720, 1625, 1510, 1430, 1366, 1252, 1080, 932, 826; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.81 (t, *J* = 7.0 Hz, 2H); 3.34 (s, 3H); 3.55 (t, *J* = 7.0 Hz, 2H); 3.69-3.79 (m, 2H); 4.02-4.09 (m, 2H), 4.12-4.23 (m, 1H); 6.82 (dd, *J* = 8.0 Hz, 2H); 7.12 (dd, *J* = 8.0 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 35.2, 45.8, 58.5, 68.5, 69.8, 73.7, 114.4, 127.6, 128.3, 129.8, 131.8, 156.7; **Anal.** Calcd for: $C_{12}H_{17}ClO_3$ requires C, 58.90; H, 7.00; Cl, 14.49; Found C, 58.91, H, 6.99; Cl, 14.57%.

(S)-2-((4-(2-Methoxyethyl)phenoxy)methyl)oxirane (189)

To a solution of chloroalcohol **188** (3 mmol) in dry THF (15 mL) at 0 °C was added potassium *tert*-butoxide (0.673 g, 6 mmol) and the mixture stirred for 1 h, diluted with H_2O (10 mL) and extracted with ether (3 × 20 mL). The collected organic layers were washed with brine and dried over anhyd. Na_2SO_4. Solvent was evaporated *in vacuo* to afford chiral epoxide **189** in high yield.

Yield: 90%; $[\alpha]^{25}_{D}$**:** +11.8, (c 1, MeOH); **IR** ($CHCl_3$, cm^{-1}): 3068, 3011, 2915, 2845, 1718, 1601, 1521, 1452, 1372, 1290, 1240, 1152, 1070, 935, 826; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.70-2.90 (m, 4H); 3.28-3.32 (m, 1H), 3.33 (s, 3H); 3.53 (t, *J* = 7.0 Hz, 2H); 3.95 (t, *J* = 5.4 Hz 1H); 4.15 (dd, *J* = 3.4, 10.9 Hz, 1H), 6.82 (dd, *J* = 8.6 Hz, 2H); 7.11 (dd, *J* = 8.6 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 35.3, 44.6, 50.0, 58.5, 68.7, 73.8, 114.5, 129.7, 131.5, 156.9; **Anal.** Calcd for: $C_{12}H_{16}O_3$ requires C, 69.21; H, 7.74; Found C, 69.33, H, 7.62%.

(S)-Metoprolol (159)

For experimental details, see the procedure given for compound **158**.

Yield: 99%; $[\alpha]^{25}_{D}$: -8.09 (*c* 1, $CHCl_3$); {lit.[47] $[\alpha]^{20}_{D}$: -8.10 (*c* 1, $CHCl_3$}; **IR** ($CHCl_3$, cm^{-1}): 3300, 3012, 2988, 2852, 1602, 1577, 1510, 1462, 1382, 1295, 1244, 1221, 1172, 1088, 927, 820, 752; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.07 (d, *J* = 6.2 Hz, 6H), 2.19 (br s, 1H), 2.65–2.90 (m, 5H), 3.34 (s, 3H), 3.55 (t, *J* = 7.0 Hz, 2H), 3.90–3.94 (m, 2H), 3.98–4.05 (m, 1H), 6.83 (d, *J* = 8.7 Hz, 2H), 7.12 (d, *J* = 8.6 Hz, 2H). **^{13}C NMR** ($CDCl_3$, 50 MHz**)** 22.7, 35.1, 48.8, 49.3, 58.5, 68.2, 70.5, 73.7, 114.3, 129.6, 131.2, 157.0; **Anal.** Calcd for: $C_{15}H_{25}NO_3$ requires C, 67.38; H, 9.42, N, 5.24; Found C, 67.42, H, 9.70, N, 4.99%.

2.3.8 References:

1 (a) Reetz, M.T.; *Angew. Chem. Int. Ed. Engl*. **1991**; *30*, 1531; (b) Ohfune Y. *Acc. Chem. Res*. **1992**, *25*, 360; (c) Yokomatsu, T.; Yuasa, Y.; Shibuya, S.; *Heterocycles*, **1992**, *33*, 1051; (d) Golebiowski, A.; Jurczak, J.; *Synlett*, **1993**, 241.

(a) Umezawa, H.; Aoyagi, T.; Morishima, H.; Matsuzaki, M.; Hamada, M.; Takeuchi, T.; *J. Antibiot.* **1970**, *23*, 259; (b) Aoyagi, T.; Tobe, H.; Kojima, F.; Hamada, M.; Takeuchi, T.; Umezawa, H.; Amastatin, *J. Antibiot.* **1978**, *31*, 636; (c) Gante, J. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1699.

3 Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirshfield, J. *J. Med. Chem.* **1988**, *31*, 2235.

4 Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett.* **2000**, *2*, 3679.

5 Gershwin, M. E.; Terr, A. *Clin. Rev. Allergy Immunol*. **1996**, *14*, 241.

6 Masaki, Y.; Imaeda, T.; Nagata, K.; Oda, H.; Ito, A.; *Tetrahedron Lett*. **1989**, *30*, 6395.

7 Comins, D. L.; Williams, A. L. *Tetrahedron Lett*. **2000**, *41*, 2839.

8 Pandey, S. K.; Kumar, P.; *Tetrahedron Lett*. **2005**, *46*, 4091.

9 Chang, M-Y.; Kung, Y-H.; Chen, S-T. *Tetrahedron*, **2006**, *62*, 10843.

10 Sutherland, A.; Jamieson, A. G. *Org. Lett*. **2007**, *9*, 1609.

11 Roy, S.; Sharma, A.; Mula, S.; Chattopadhay, S. *Chem. Eur. J*. **2009**, *15*, 1713 .

12 Felpin, F-X.; Lebreton, J. *J. Org. Chem*. **2002**, *67*, 9192.

13 Angoli, M.; Barilli, A.; Lesma, G.; Passarella, D.; Riva, S.; Silvani, A.; Danieli, B. *J. Org. Chem*. **2003**, *68*, 9525.

14 Zheng, G.; Dwoskin, L. P.; Crooks, P. A. *J. Org. Chem*. **2004**, *69*, 8514.

15 Raghavan, S.; Rajender, A. *Tetrahedron Lett*. **2004**, *45*, 1919.

16 Bisai, A.; Singh, V. K. *Tetrahedron Lett*. **2007**, *48*, 1907.

17 Krishnan, S.; Bagdanoff, J. T.; Ebner, D. C.; Rantohul, Y. K.; Tamber, U. K.; Stoltz, B. M. *J. Am. Chem. Soc*. **2008**, *130*, 13745.

18 (a) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Angew. Chem Int. Ed*. **2003**, *43*, 1112; (b) Brown, S. P. ; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808.

19 Varala, R.; Nuvula, S.; Adapa, S. R. *J. Org. Chem.* **2006**, *71*, 8283.

20 Gurjar, M. K.; Kumar, V. S.; Rao, B. V. *Tetrahedron*, **1999**, *55*, 12563.

21 Cinquin, C.; Bortolussi, M.; Bloch, R.; *Tetrahedron*, **1996**, *52*, 6943.

22 Fernandes, R. A.; Kumar, P. *Tetrahedron: Asymmetry*, **1999**, *10*, 4349.

23 (a) Fuhshuku, K-i.; Mori, K. *Tetrahedron: Asymmetry*, **2007**, *18*, 2104; (b) Huang, P. Q.; Guo, Z-Q.; Ruan, Y.-P. *Org. Lett*. **2006**, *8*, 1435.

24 (a) Sanchez-Sancho, F.; Herradon, B. *Tetrahedron: Asymmetry*, **1998**, *9*, 1951; (b) Stehl, A.; Seitz, G.; Schulz, K. *Tetrahedron*, **2002**, *58*, 1343; (c) Masaki, Y.; Imaeda, T.; Nagata, K.; Oda, H.; Ito, A. *Tetrahedron Lett*. **1989**, *30*, 6395.

25 (a) Gilligan, P. J.; Cain, G. A.; Christos, T. E.; Cook, L.; Drummond, S.; Johnson, A. L.; Kergaye, A. A.; McElroy, J. F.; Rohrbach, K. W.; Schmidt, W. K.; Tam, S. W. *J. Med. Chem.* **1992**, *35*, 4344; (b) Yang, S. S.; Cragg, G. M.; Newman, D. J.; Bader, J. P. *J. Nat. Prod*. **2001**, *64*, 265; (c) Kennelly, E. J.; Flynn, T. J.; Mazzola, E. P.; Roach, J. A.; McCloud, T. G.; Danford, D. E.; Betz, J. M. *J. Nat. Prod.* **1999**, *62*, 1385; (d) Mill, S.; Hootele´, C. *J. Nat. Prod.* **2000**, *63*, 762.

26 Eibein, A. D.; Molyneux, R. In Alkaloids; Chemical and Biological perspectives; Pelletier, S. W., Ed.; John Wiley and Sons: New York, **1987**; Vol. 57, p 1

27 (a) Strunzand, G. M.; Finlay, J. A. In The Alkaloids; Brossi, A., Ed.; Academic Press: New York, **1985**; Vol. 26, pp 89–174; (b) Buffat, M. G. P. *Tetrahedron,* **2004**, *60*, 1701.

28 (a) Micel, K.-H.; Sandberg, F.; Haglid, F.; Norin, T. *Acta Pharm. Suec*. **1967**, *4*, 97; (b) Micel, K.-H.; Sandberg, F.; Haglid, F.; Norin, T.; Chan, R. P. K.; Craig, J. C. *Acta Chem. Scand*. **1969**, *23*, 3479.

29 Takahata, H.; Kubota, M.; Momose, T. *Tetrahedron Lett*. **1997**, *38*, 3451

30 Davis, F. A.; Prasad, K. R.; Nolt, N. B.; Wu, Y. *Org. Lett.* **2003**, *5*, 925

31 (a) Passarella, D.; Barilli, A.; Belinghieri, F.; Fassi, P.; Riva,S.; Sacchetti, A.; Silvani, A.; Danieli, B. *Tetrahedron: Asymmetry*, **2005**, *16*, 2225; (b) Takahata, H.; Kubota, M.; Ikota, N. *J. Org. Chem*. **1999**, *64*, 8594.

32 Chen, L-J.; Hou, D-R. *Tetrahedron: Asymmetry*, **2008**, *19*, 715

33 (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc*. **1980**, *102*, 5974; (b) Martin, V. S.; Woodward, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc*. **1981**, *103*, 6237.

34 Woodward, S. S.; Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc*. **1991**, *113*, 106.

35 (a) Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc*. **1991**, *113*, 113; (b) Potvin, P. G.; Bianchet, S. J. *J. Org. Chem.* **1992**, *57*, 6629.

36 Yadav, J. S.; Reddy, C. S. *Org. Lett*. **2009**, *11*, 1705.

37 (a) 33; (b) Chattopadhyay, S.; Pattenden, G. *J. Chem. Soc. Perkin. Trans. 1*, **2000**, 2429.

38 Finan, J. M.; Kishi, Y.; *Tetrahedron Lett*. **1982**, *23*, 2719.

39 (a) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev*. **1996**, *96*, 835; (b) Seyden-Penne, J. Chiral Auxiliaries and Ligands in Asymmetric Synthesis; Wiley: New York, **1995**, p 306; (c) Zhong, Y. W.; Tian, P.; Lin, G. Q. *Tetrahedron: Asymmetry*, **2004**, *15*, 771; (d) Faber, W. S.; Kok, J.; De, L. B.; Feringa, B. L. *Tetrahedron*, **1994**, *50*, 4775; (e) Carrillo, L.; Badia, D.; Dominguez, E.; Anakabe, E.; Osante, I.; Tellitu, I. *J. Org. Chem.* **1999**, *64*, 1115.

40 (a) Teerlink, J.; Massie, B. *Am. J. Cardiol*. **1999**, *84*, 94, (b) Messerli, F. H.; Grossman, E. *Drugs* **2001**, *61*, 1531; (c) Ellison, K. E.; Gandhi, G. *Drugs* **2005**, *65*, 787; (d) Baran, D.; Horn, E. M.; Hryniewicz, K.; Katz, S. D. *Drugs* **2000**, *60*, 997.

41 (a) Klibanov, A. M. *Acc. Chem. Res*. **1990**, *23*, 114; (b) Wang, C. H. *Science* **1989**, *244*, 1145; (c) Yamada, H.; Shimizu, S. *Angew. Chem. Int. Ed. Engl*. **1988**, *27*, 622.

42 (a) Berrospi, A. R.; Leibowitz, H. M. *Arch. Opthalmol*. **1982**, *100*, 943; (b) Hussain, S. S.; Aboul-Enein, H. Y.; Al-Dhakan, A.; Hannan, M. *Toxicology* **1989**, *12*, 77.

43 (a) Riddell, J. G.; Shanks, R. G. *Clinical Pharmacology and Therapeutics* **1985**, ***38*,** 554; (b) Chidlow, G.; Melena, J.; Osborne, N. N. *Br J Pharmacol.* **2000**, *130*, 759.

44 Feuerstein, G.; Liu, G-L.; Yue, T-L.; Cheng, H-Y.; Hieble, J. P.; Arch, J. R. S.; Ruffolo, R. R.; Ma, X-L. *Eur. J. Pharm*. **1998**, *351*, 341.

45 Bono, G, D.; Scilimati, A. *Synthesis*, **1995**, 699.

46 Joshi, R. A.; Garud, D. R.; Muthukrishnan, M.; Joshi, R. R.; Gurjar, M. K. *Tetrahedron: Asymmetry*, **2005**, *16*, 3802.

47 Muthukrishnan, M.; Garud, D. R.; Joshi, R. R.; Joshi, R. A. *Tetrahedron*, **2007**, *63*, 1872.

48 Zhang, J-Y.; Liu, H-M.; Wang, X-J.; Wang, P.; Zheng, J-X. *Chirality*, **2009**, *21*, 745.

49 (a) Wright, J. L.; Gregory, T. F.; Heffner, T. G.; MacKenzie, R. G.; Pugsley, T. A.; Meulen, S. V.; Wise, L. D. *Bioorg. Med. Chem. Lett*. **1997**, *7*, 1377; (b) Baker, N. R.; Byrne, N. G.; Economides, A. P.; Javeld, T. *Chem. Pharm. Bull*. **1995**, 1045; (c) Kirkup, M. P.; Rizvi, R.; Shankar, B. B.; Dugar, S.; Clader, J.; McCombie, S. W.; Lin, S.; Yumibe, N.; Huie, K.; Heek, M.; Compton, D. S.; Davis, H, R.; McPhail, A. T. *Bioorg. Med. Chem. Lett*. **1996**, *6*, 2069.

50 (a) Takahashi, H.; Sakuraba, S.; Takea, H.; Achiwa, K. *J. Am. Chem. Soc*. **1990**, *112*, 5877; (b) Gooding, O.; Colin, B.; Cooper, G.; Jackson, D. *J. Org. Chem*. **1993**, *58*, 3681; (c) Yuan, R.; Watanabe, S.; Kuwabata, S.; Yoneyama, H. *J. Org. Chem*. **1997**, *62*, 2494.

51 (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936; (b) Ready, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc*. **1999**, *121*, 6086.

CHAPTER III

$NaIO_4$-Mediated C-H Activation of Alkylarenes and Oxidative Functionalization of C-H, C-Br, C-O bonds

Section I

$NaIO_4$-Mediated C-H Activation of Alkylarenes: Oxyfunctionalization at the Benzylic Position

3.1.1 Introduction

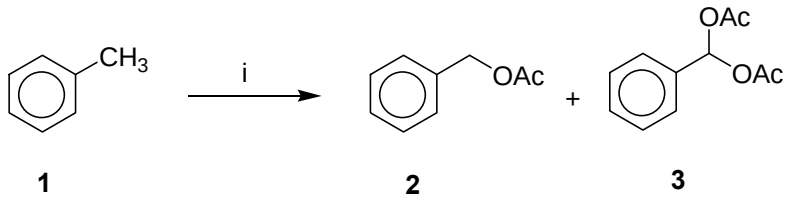
A powerful new class of reactions are emerging that introduce oxidized functionality directly into aliphatic or aromatic (sp^3) C–H bonds. The direct oxidation of benzylic C-H bonds constitutes one of the most fundamental transformations in organic synthesis.[1] Particularly, the benzylic acetoxylation is of great interest from both academic as well as industrial viewpoint as the target product benzyl acetate is widely used in perfumery, food and chemical industries. The importance of aromatic oxyfunctionalized compounds as raw materials has an increasing significance due to the changes in the refinery processes. The chemoselective oxidation of alkylarenes to produce specific oxygenated derivatives is of great importance. 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 is benzylic C-H (~85 k.cal/mol) > tertiary C-H (~91 k.cal/mol) > secondary C-H (~94 k.cal/mol) > primary C-H (~98 k.cal/mol). As a result, benzylic C-H oxidations are complicated due to several competing reactions resulting in a range of oxygenated products. Thus, the development of new catalytic process for such raw materials is indeed more and more attractive. A benzylic oxygenated derivative assumes importance such as alcohols and carbonyl compounds being useful as specialty chemicals in industry.[2] Generally, C–H activation at benzylic position is achieved using a variety of transition metal salts as catalysts or oxidation under high pressure. However, several drawbacks are

associated with these processes which include: (i) the toxicity of some transition metals, (ii) stoichiometric reaction conditions and (iii) non-generality.

3.1.2 Review of literature

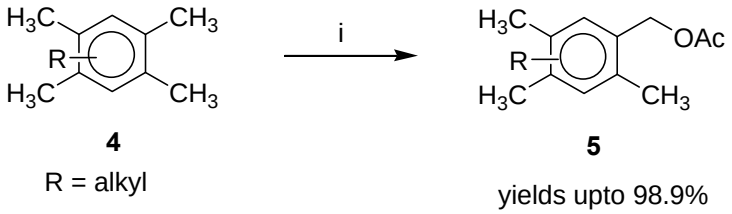
Bryant's approach (1968)[3,4]

Bryant *et al*. have developed an efficient, liquid-phase, catalytic process for the benzylic oxidation, based on the stoichiometric reaction of toluene with palladium(I1) acetate, potassium acetate in acetic acid at 100 ^{o}C. The benzyl esters isolated in 92.5% along with 6.0% of benzylidene diacetate and a trace of benzaldehydes (**Scheme 1**).



Scheme 1: (i) $Pd(OAc)_2$, KOAc, AcOH, 100 ^{o}C

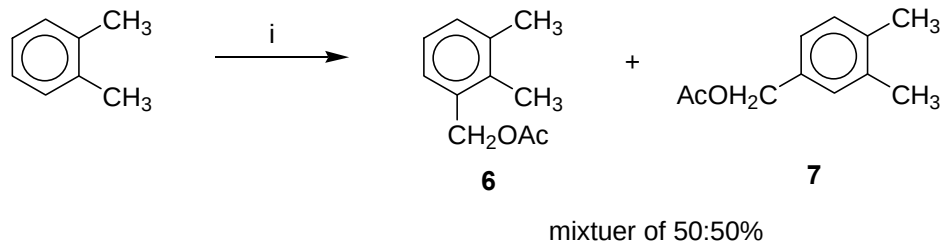
Same author has again reported another method to prepare benzyl esters **5**, which are produced catalytically at moderate temperatures from methylbenzenes **4** in a liquid phase process employing a homogeneous palladium-stannous acetate catalyst and O_2 (1 atm) (**Scheme 2**).



Scheme 2: (i) $Pd(OAc)_2$, $Sn(OAc)_2$, O_2, AcOH, 100 ^{o}C

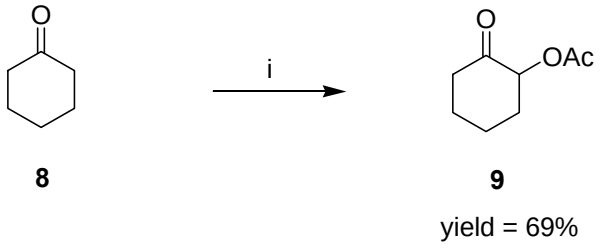
Bergman's approach (1978)[5,6]

Bergman *et al*. have reported TeO_2-catalyzed acetoxylation of alkylarenes using lithium bromide at high temperature to form the corresponding mixture of substituted benzyl acetates **6** & **7** (**Scheme 3**).



Scheme 3: (i) TeO_2, LiBr, AcOH, 120 ^oC

The same author has reported a TeO_2 or $Te(OH)_6$-catalyzed oxidation of alkyl substituted aromatic and aliphatic substrates to give acetoxymethylated product. In the acetoxymethylation reaction TeO_2 apparently slowly oxidized the solvent, HOAc, to a reactive species for e.g., acetoxycarbene, which attacked the aromatic compound. In the side-chain acetoxylations, $Te(OH)_6$ oxidized bromide ions to Br_2, which caused benzylic bromination (**Scheme 4**).

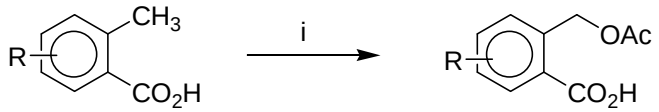


Scheme 4: (i) TeO_2, $Te(OH)_6$, LiBr, AcOH, 160 ^oC

Beek's approach (1978)[7]

Beek *et al*. have employed Cobalt(III) acetate in catalytic amount for aerobic acetoxylation of alkylarenes in acetic acid solution. Under anaerobic conditions the

substituted toluenes were first converted into benzyl acetate and subsequently into benzaldehydes (**Scheme 5**).



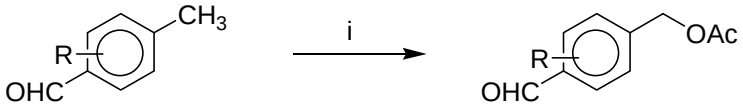
10 **11**

R = alkyl, Br, OMe, CO_2H

Scheme 5: (i) $Co(OAc)_2$, O_2, AcOH, 93 ^oC

Okada's approach (1981)[8]

Okada *et al*. have developed the liquid-phase oxidation of methylbenzenes catalyzed by a catalyst system composed of cobalt(II) and copper(II) acetates and NaBr which was carried out in acetic acid solvent at 150 ^oC. However, ring-bromination observed in case of electron donating methylbenzenes (**Scheme 6**).



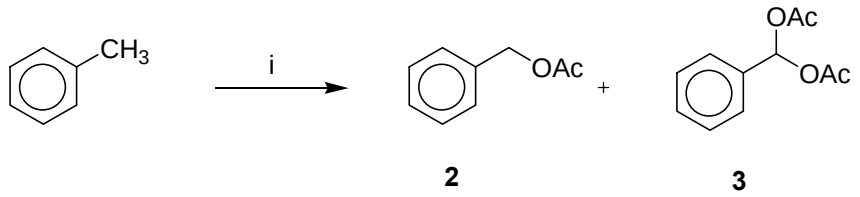
12 **13**

R = alkyl, Cl, OMe yields upto 98%

Scheme 6: (i) $Co(OAc)_2$, $Cu(OAc)_2$, NaBr, AcOH, 150 ^oC

Kaneda's approach (2002)[9]

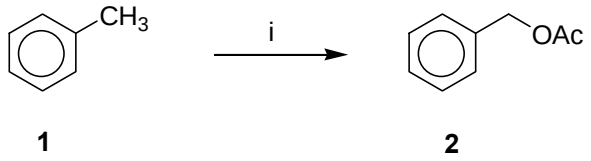
Kaneda *et al*. have described a method to prepare Pd clusters by treatment of palladium carbonyl acetate cluster, $Pd_4(CO)_4(OAc)_4 \cdot 2AcOH$, with metal nitrates, e.g. $Cu(NO_3)_2$, and $Fe(NO_3)_3$, in the presence of 1,10-phenanthroline. Pd cluster showed a high catalytic activity for the oxidative acetoxylation of toluene to give benzyl acetates in the presence of molecular oxygen (**Scheme 7**).



Scheme 7: (i) $Pd_4(CO)_4(OAc)_4 \cdot 2AcOH$, AcOH, 90 ^oC.

Martins's approach (2009)[10]

Martin *et al*. have developed Pd–Sb supported acetoxylation with supports such as TiO_2, γ-Al_2O_3, SiO_2 and ZrO_2 are applied at constant Pd (10 wt%) and Sb (8 wt%) contents. Catalytic performance of these solids is evaluated for the gas phase acetoxylation of toluene to benzyl acetate in >90% conversion (**Scheme 8**).



Scheme 8: (i) Pd-Sb-TiO_2, AcOH, O_2, 75%.

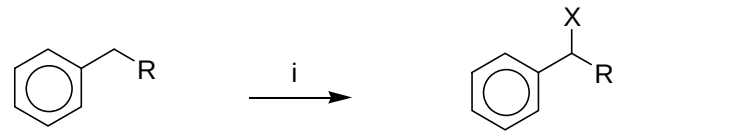
3.1.3 Present Work

3.1.3.1 Objective

From the above discussion it is clear that although there are many methods available for the oxidation of alkylarenes, several of them suffer from certain drawbacks such as low yields, poor regioselectivity, use of toxic metal salts or exotic reagents. This section describes a new method which involves the C-H oxidation of alkanes and alkylarenes into their corresponding oxygenated derivatives using $NaIO_4$ as the oxidizing agent and lithium bromide as the bromide source with acetic acid as solvent.

3.1.4 Results and discussion

In our initial studies, we have found that sodium periodate ($NaIO_4$) oxidizes alkali metal halides efficiently in aqueous medium in halogenating of alkenes and aromatics at 25 ^oC and thus producing the corresponding halo derivatives with excellent regio and stereoselectivity.[11] In this regard, we envisioned that at high temperatures, the oxidative process should result in the formation of benzylic halides. On investigation, we have found that $NaIO_4/LiBr/H^+$ combination oxidatively functionalizes the C–H bonds of alkylarenes.[12] Thus, when toluene was heated with lithium bromide (1.1 equiv) and conc. H_2SO_4 (2 M equiv) in the presence of catalytic $NaIO_4$ (25 mol%) in MeOH at 65 ^oC, the corresponding benzylic bromide **14** and methyl ether **15** were obtained as a mixture in moderate yields (**Scheme 9**).



1

R = Me, alkyl, etc.

14, X = Br; yield = 36%

15, X = OMe; yield = 43%

Scheme 9: (i) $NaIO_4$ (25 mol%), LiBr (5.5 mmol), H_2SO_4, MeOH, 65 ^oC, 24 h.

In order to establish the scope of this reaction, a variety of alkylarenes were screened and the results are presented in **Table 1**. Surprisingly, no reaction took place when other halide sources such as NaBr, NaI, LiCl and KI were employed. In the absence of $NaIO_4$, no reaction took place; lowering the molar ratio of $NaIO_4$ also resulted in reduced yield. In the case of isobutylbenzene it may be noted that the corresponding methyl ether **15** was obtained as the sole product (42%), whereas only benzylic-bromo compound **14** (31%) was obtained when acetonitrile was used as solvent.

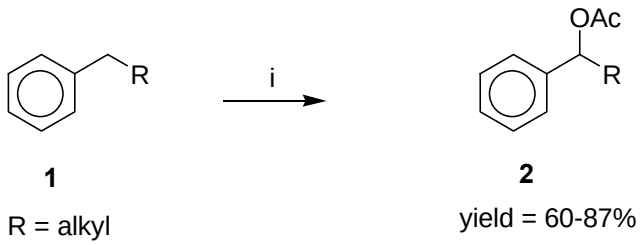
Table 1: $NaIO_4$-mediated oxidative bromination and methoxylation of alkylarenes with metal halides[a]

Entry	Substrate	Metal halide	Solvent	Temp (^oC)	Yield (%)[b]	
					14	**15**
a	Toluene	LiBr	MeOH	65	47	36
		LiBr	CH_3CN	80	31	-
		NaBr	MeOH	65	NR	-
b	Ethylbenzene	LiBr	MeOH	65	36	43
c	*p*-Xylene	LiBr	MeOH	65	45	30
d	Isobutylbenzene	LiBr	MeOH	65	-	42

[a] Conditions: substrate (10 mmol), $NaIO_4$ (25 mol%), metal bromide (11 mmol), conc. H_2SO_4 (0.5 mL, 20 mmol), solvent (15 mL), 24 h.
[b] Isolated yield after chromatographic purification.

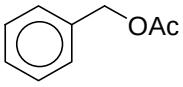
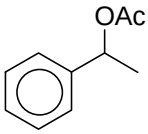
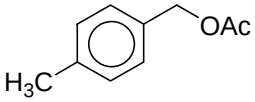
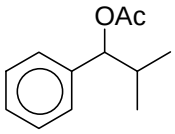
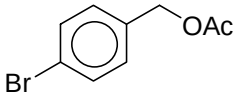
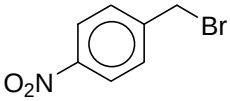
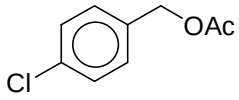
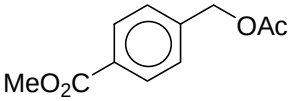
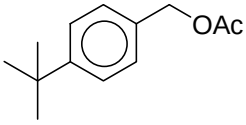
The ^1H NMR spectrum of benzyl methyl ether (**15a**) displayed two singlets at δ 3.42 and δ 4.49 due to methoxyl (-OC**H**$_3$) and benzylic methylene protons respectively. Its ^{13}C NMR spectrum showed characteristic peaks at δ 57.5 and 74.2 (Ph-**C**H_2-O**C**H_3) due to methyl and benzylic methylene carbons respectively.

Reaction condition was optimized so that good selectivity to product was achieved when milder acid like acetic acid was used in place of MeOH/H_2SO_4 (**Scheme 10**). **Table 2** shows the scope of $NaIO_4$-mediated oxidative bromination/acetoxylation of several alkylbenzenes and arenes with LiBr in glacial acetic acid as solvent. Interestingly, high yields (60–87%) and selective acetoxylation at the benzylic position were observed with all the alkylarenes studied except for 4-nitrotoluene (**Table 2**, entry f), where in the



Scheme 10: (i) alkyl arene (3 mmol), $NaIO_4$ (25 mol%), LiBr (3.1 mmol), AcOH, 90-110 ^oC, 24 h.

Table 2: $NaIO_4$-mediated oxidative acetoxylation of alkylarenes with LiBr[a]

Entry	Substrate **1**	Temp[b] (^oC)	Product[c] **2**	Yield[d] (%)
a	Toluene	110		87 (31,[e] 83,[f] 37[g])
b	Ethylbenzene	90		85
c	p-Xylene	100		75
d	Isobutylbenzene	110		80
e	4-Bromotoluene	110		60
f	4-Nitrotoluene	110		80
g	4-Chlorotoluene	110		80
h	Methyl 4-methyl benzoate	110		66
i	4-*tert*-Butyltoluene	110		60

[a] Conditions: substrate (10 mmol), $NaIO_4$ (25 mol%), LiBr (11 mmol), glacial acetic acid (15 mL), 24 h.
[b] Oil bath temperature.
[c] All products were characterized by ^1H and ^{13}C NMR, GC–MS and IR.
[d] Isolated yields after column chromatographic purification.
[e] Yield corresponds to when 20 mol% of LiBr was used.
[f] Yield corresponds to the use of Br_2 (2 equiv) as the halogen source. However, in the absence of $NaIO_4$, only benzyl bromide (60%) was formed.
[g] Yield corresponds to the use of NaBr (1.1 equiv) as halide source.

corresponding benzyl bromide was obtained as the sole product. We observed that both LiBr and $NaIO_4$ were required in the oxidation of the alkylarenes at the benzylic position.

Also when the quantity of $NaIO_4$ was reduced to 5 mol%, the yield of benzyl acetate was reduced considerably (9%). Furthermore, *p*-toluic acid failed to undergo oxidative bromination at the benzylic position.

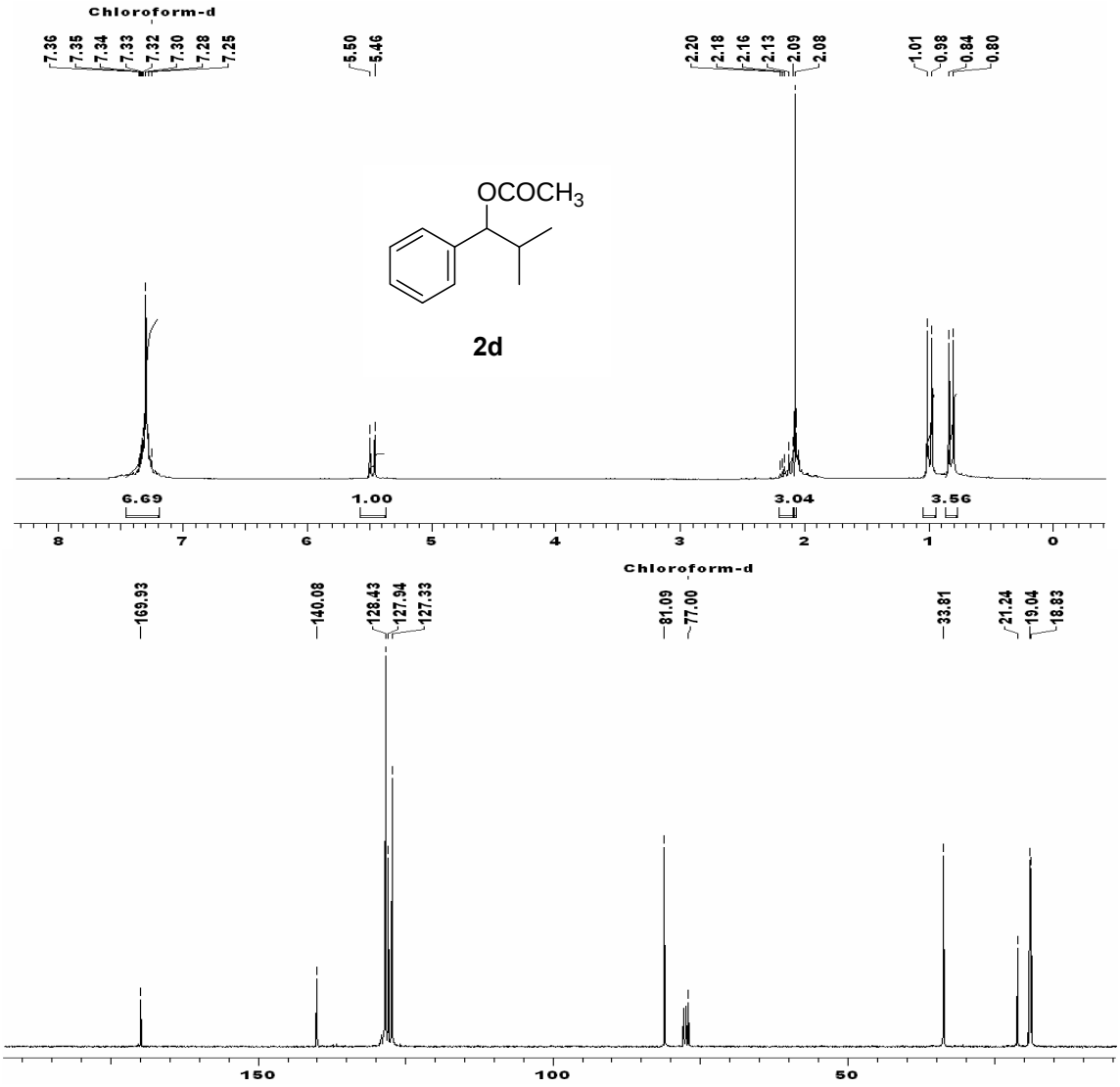


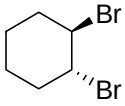
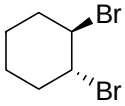
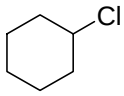
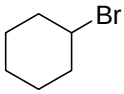
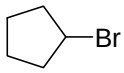
Fig. 1: ^{1}H and ^{13}C NMR spectra of 2-methyl-1-phenylpropyl acetate **2d**

The formation of benzylic acetates was confirmed from ^{1}H NMR, ^{13}C NMR and IR spectra. For example, the ^{1}H NMR of 2-methyl-1-phenylpropyl acetate (**2d**) displayed a singlet at δ 2.08 (s) for methyl protons of acetate (–OCOC**H**$_3$) and a doublet at δ 5.48 (d)

for benzylic protons thereby establishing occurrence of benzylic C-H oxidations. Its ^{13}C NMR spectrum showed typical signals at δ 21.2 and 169.9 for methyl and carbonyl carbons (–O-**C**O**C**H_3) respectively (**Fig. 1**). The IR spectrum of **2d** displayed a strong absorption band at 1740 cm^{-1} indicating the presence of carbonyl group of acetate.

Table 3 shows the results of $NaIO_4$-mediated oxidative bromination of alkanes with LiBr as the bromide source. Surprisingly, cyclohexane underwent oxidative bromination to produce *trans*-1,2-dibromocyclohexane in 28% isolated yield. Notably, a higher isolated

Table 3: $NaIO_4$-mediated oxidative halogenation of alkanes using LiBr[a]

Entry	Substrates	Halides (equiv.)	Temp (°C)	Product **16**	Yield[b] (%)
a	Cyclohexane	LiBr (1.1)	80		28
		LiBr (2.1)	80		40
		LiBr (2.1)	25		-
b	Cyclohexane[c]	Cl_2 excess	80		60
c		Br_2 (2.1)	80		13[d]
d	Cyclopentane	LiBr (2.1)	60		37
e	Octane	LiBr (2.1)	100	Bromooctane[e]	41
f	Heptane	LiBr (2.1)	90	Bromoheptane[e]	30

[a] Conditions: substrate (10 mmol), LiBr (11 or 22 mmol), $NaIO_4$ (25 mol%), glacial AcOH (15 mL), 80 °C, 24 h.
[b] Isolated yield.
[c] $NaIO_4$ (25 mol%) and excess chlorine gas was bubbled through the reaction mixture at 80 °C for 5 h.
[d] Yield of cyclohexyl bromide when no $NaIO_4$ was used.
[e] Isomeric mixtures of bromoalkanes

yield (40%) of *trans*-1,2-dibromocyclohexane was obtained when 2.1 equiv of LiBr were employed (Entry a). However, in the case of cyclopentane (**Table 3**, entry d), only

monobromocyclopentane was obtained in 37% yield. Interestingly, when linear alkanes such as n-octane and n-heptane were subjected to oxidative bromination with equimolar LiBr, a mixture of three bromoalkanes in the ratio 1:1:1 was obtained (confirmed by GC–MS), which were difficult to isolate in pure form.

3.1.5 Mechanism

Our earlier studies[11] had shown that 1 equiv. of $NaIO_4$ was sufficient to oxidize 8 equiv. of Br^- ions, as can be seen from (**Scheme 11**).

$$8\ LiBr + NaIO_4 + 8H^+ \longrightarrow 4\ Br_2 + 4H_2O$$

$$2\ Br^- \longrightarrow Br_2 + 2e$$

$$IO_4^- + 2H + 2e^- \longrightarrow IO_3^- + H_2O$$

$$IO_3^- + 6H + 6e^- \longrightarrow I^- + 3H_2O$$

$$I_2 + 2\ e \xrightarrow{\text{fast}} 2I^-$$

Scheme 11: Steps involving in LiBr oxidation with $NaIO_4$

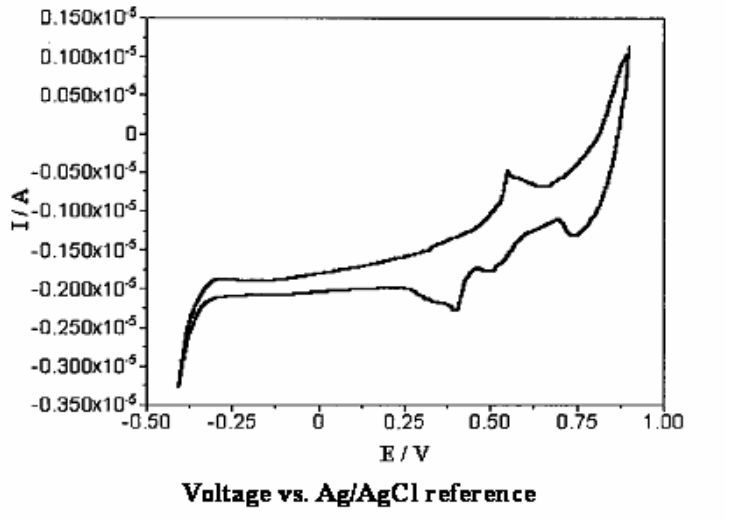


Fig. 2: Cyclic voltagram of LiBr oxidation with $NaIO_4$

The cyclic voltagram (**Fig. 2**) of LiBr oxidation with $NaIO_4$ shows one oxidation peak at Ep_a = 0.565 V and three reduction peaks at Ep_c = 0.720 V, 0.490 V and 0.390 V. The

comparison of this value with the literature values revealed that the reaction involves four steps. Hence, only 30 mol % of $NaIO_4$ was required to bring about 100% conversion. From the above facts and the evidence provided by the cyclic voltammetry study, the proposed reaction pathway for benzylic C-H oxidation is shown in **Scheme 12**. The following experiments were carried out: (i) when benzyl bromide was refluxed with either glacial acetic acid or methanol in the absence of $NaIO_4$, no reaction took place. However, addition of 25 mol% of $NaIO_4$ to the reaction mixture produced benzyl acetate in 72% yield. A further increase in the molar ratio of $NaIO_4$ (>30 mol%) did not produce any significant increase in yield.

$$8\,Br^- \longrightarrow 4Br_2 + 8e^-$$

$$IO_4^- + 8H^+ + 8\,e^- \longrightarrow I^- + 4H_2O$$

$$4\,Ar\text{-}CH_3 + 4\,Br_2 \longrightarrow 4\,Ar\text{-}CH_2Br + 4\,HBr$$

$$4\,Ar\text{-}CH_2\text{-}Br + 4\,AcOH \longrightarrow 4\,Ar\text{-}CH_2OAc + 4\,HBr$$

$$4\,Ar\text{-}CH_3 + IO4^- + 8\,Br^- + 8H^+ + 4\,AcOH \longrightarrow 4\,Ar\text{-}CH_2OAc + I^- + 8\,HBr + 4\,H_2O$$

Scheme 12: Plausible mechanism for the formation of benzyl acetate from toluene

This probably indicates that the first step involves bromination at the benzylic position. (ii) KIO_3 and NaI have been found to be effective in mediating the transformation of benzyl bromide, thus producing benzyl acetate in 47% and 16% yield, respectively. (iii) A cyclic voltammogram study revealed that Br_2 generated in situ oxidation of LiBr with $NaIO_4$, is probably responsible for rapid bromination of the alkyl benzenes to produce

bromo derivatives. Finally, benzyl bromide is solvolyzed with AcOH and a rate enhancement in solvolysis was observed with the addition of either IO_4^-, IO_3^- or I^- salts.

3.1.6 Conclusion

In conclusion, we have described a simple and efficient $NaIO_4$-mediated oxidative bromination as well as acetoxylation procedure that allows the transformation of alkylbenzenes into their corresponding benzyl acetates in excellent yields. A novel feature of the present catalytic process is that cyclohexane could be converted directly into *trans*-1,2-dibromocyclohexane in a single step in 40% isolated yield.

3.1.7 Experimental Section

Typical experimental procedure for the preparation of benzylic acetates

To a stirred mixture of alkylbenzene (10 mmol) and LiBr (11 mmol) in glacial acetic acid (15 mL), $NaIO_4$ (25 mol%) was added and reaction mixture heated to 90–110 ^oC. The progress of the reaction was monitored by TLC. After completion of the reaction, it was diluted with water (30 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with a dilute solution of sodium thiosulfate, 5% $NaHCO_3$ and brine then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was purified by column chromatography (silica gel, petroleum ether and ethyl acetate (9:1) as eluent to afford the pure benzylic acetates.

Benzyl acetate (2a)

Yield: 87%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): 3014, 2921, 1741, 1640, 1350, 1240, 1020, 940, 820, 750, 690; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.10 (s, 3H), 5.10 (s, 2H), 7.30-7.60 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 20.9, 66.1, 128.2, 128.5, 135.9, 170.4; **Anal.** Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 71.65; H, 6.69%.

1-Phenylethyl acetate (2b)

Yield: 85%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): 3010, 2980, 1745, 1620, 1310, 1240, 1105, 1020, 940, 752, 680; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.53 (d, *J* = 7.0 Hz, 3H), 2.05 (s, 3H), 5.87 (q, *J* = 7.0, 13.0 Hz, 1H), 7.28-7.35 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.4, 22.5, 72.4, 126.4, 128.1, 128.7, 142.1, 170.0; **Anal.** Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.66; H, 7.29%.

4-Methylbenzyl acetate (2c)

Yield: 75%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): 3010, 1742, 1640, 1250, 1120, 1010, 860, 830, 670; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.01 (s, 3H), 2.36 (s, 3H), 5.06 (s, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 20.5, 20.9, 65.8, 128.2, 128.9, 132.8, 137.5, 170.0; **Anal.** Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.23; H, 7.40%.

2-Methyl-1-phenylpropyl acetate (2d)

Yield: 80%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): 3008, 1740, 2980, 1610, 1310, 1240, 1100, 1010, 940, 760, 690; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.82 (d, *J* = 7.0 Hz, 3H), 0.99 (d, *J* = 7.0 Hz, 3H), 2.08 (s, 3H), 2.09-2.20 (m, 1H), 5.48 (d, *J* = 8.0 Hz, 1H), 7.28-7.26 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 18.8, 19.0, 21.2, 33.8, 81.0, 127.3, 127.9, 128.4, 140.0, 169.9; **Anal.** Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.86; H, 8.40%.

4-Bromobenzyl acetate (2e)

Yield: 60%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): 3010, 1745, 1640, 1410, 1280, 1100, 1020, 860, 830, 750, 680; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.01 (s, 3H), 4.95 (s, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 20.5, 65.8,

122.2, 128.9, 132.8, 137.5, 170.0; **Anal.** Calcd for $C_9H_9BrO_2$: C, 47.19; H, 3.96; Br, 34.88. Found: C, 47.21; H, 3.84; Br, 34.90%.

4-Chlorobenzyl acetate (2g)

Yield: 80%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): 3012, 1740, 1642, 1410, 1280, 1105, 1020, 860, 830, 755, 680; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.01 (s, 3H), 4.95 (s, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 20.5, 68.0, 128.2, 128.9, 132.9, 137.5, 170.2; **Anal.** Calcd for $C_9H_9ClO_2$: C, 58.55; H, 4.91; Cl, 19.20. Found: C, 58.42; H, 4.89; Cl, 19.18%.

Methyl 4-(acetoxymethyl)benzoate (2h)

Yield: 66%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): 3014, 1728, 1612, 1440, 1240, 1020, 940, 820, 680; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.10 (s, 3H), 3.93 (s, 3H), 5.10 (s, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.89 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 20.0, 52.1, 67.0, 127.2, 129.3, 130.2, 144.8, 166.1, 170.0; **Anal.** Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.39; H, 5.72%.

4-*tert*-Butylbenzyl acetate (2i)

Yield: 60%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): 3009, 1741, 1620, 1220, 1120, 1015, 880, 860, 680; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.34 (s, 9H), 2.01 (s, 2H), 5.02 (s, 2H), 7.11 (d, *J* = 7.8 Hz, 2H), 7.21 (d, *J* = 7.8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 20.7, 31.4, 40.6, 67.8, 125.2, 126.4, 138.1, 148.0, 170.1; **Anal.** Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.55; H, 8.52%.

Typical experimental procedure for the preparation of benzylic methyl ethers

To a stirred mixture of alkylbenzene (10 mmol) and LiBr (11 mmol) in methanol (15 mL), $NaIO_4$ (25 mol%) was added conc. H_2SO_4 (0.5 mL) and the reaction mixture heated

to 70–80 ^{o}C. The progress of the reaction was monitored by TLC. After completion of the reaction, it was diluted with water (30 mL) and extracted with CH_2Cl_2 (50 mL x 3). The combined organic layers were washed with a dilute solution of sodium thiosulfate, 5% $NaHCO_3$ and brine then dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was purified by column chromatography (silica gel, petroleum ether and ethyl acetate (9:1) as eluent to afford benzylic ethers in pure form.

1-(Methoxymethyl)benzene (15a)

Yield: 36%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): 3015, 2980, 1610, 1420, 1160, 1100, 980, 950, 900, 780, 730; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.42 (s, 3H), 4.49 (s, 2H), 7.32-7.38 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 57.5, 74.2, 127.3, 128.0, 138.0; **Anal.** Calcd for $C_8H_{10}O$: C, 78.65; H, 8.25. Found: C, 78.54; H, 8.62%.

1-(1-Methoxyethyl)benzene (15b)

Yield: 43%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): 3010, 2970, 1605, 1420, 1160, 980, 950, 780, 730; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.44 (d, J = 6.3 Hz, 2H), 3.22 (s, 3 H), 4.27 (q, J = 6.0, 13.0 Hz, 1H), 7.28-7.33 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 24.2, 56.6, 80.0, 126.5, 127.7, 128.7, 129.1, 130.1, 134.5, 144.0; **Anal.** Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.40; H, 8.79%.

1-(Methoxymethyl)-4-methylbenzene (15c)

Yield: 30%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): 3016, 2942, 1600, 1205, 1160, 1040, 840, 750; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.51 (s, 3H), 3.51 (s, 3H), 4.56 (s, 2H), 7.27-7.39 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.5, 58.11, 74.89, 128.12, 129.3, 135.6, 137.3; **Anal.** Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.40; H, 8.79%.

1-(1-Methoxy-2-methylpropyl)benzene (15d)

Yield: 42%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): 3012, 2980, 1612, 1420, 1160, 980, 950; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.77 (d, *J* = 7.0 Hz, 3H), 1.02 (d, *J* = 7.0 Hz, 3H), 1.85-2.02 (m, 1H), 3.20 (s, 3 H), 3.77 (d, *J* = 7.0 Hz 1H), 7.27-7.33 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 17.6, 18.0, 33.8, 92.0, 127.3, 127.9, 128.4, 140.0; **Anal.** Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.39; H, 9.78%.

1,2-Dibromocyclohexane (16a)

Yield: 40%; yellow colored liquid; **IR** ($CHCl_3$, cm^{-1}): 2942, 2882, 1425, 1420, 1180, 1001, 900, 840, 822, 671, 652; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.35-1.49 (m, 4H), 1.77-2.04 (m, 4H), 3.71-3.79 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 22.3, 31.3, 55.1; **Anal.** Calcd for $C_6H_{10}Br_2$: C, 29.78; H, 4.17, Br, 66.05. Found: C, 29.80; H, 4.09, Br, 66.12%.

Chlorocyclohexane (16b)

Yield: 60%; liquid; **IR** ($CHCl_3$, cm^{-1}): 2962, 2878, 1422, 1420, 1176, 1012, 900, 840, 820, 670, 652; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.20-1.98 (m, 6H), 2.01-2.22 (m, 4H), 3.98-4.12 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 25.5, 25.7, 37.3, 60.8; **Anal.** Calcd for $C_6H_{11}Cl$: C, 60.76; H, 9.35, Cl, 29.89. Found: C, 60.80; H, 9.41, Cl, 29.77%.

Bromocyclopentane (16d)

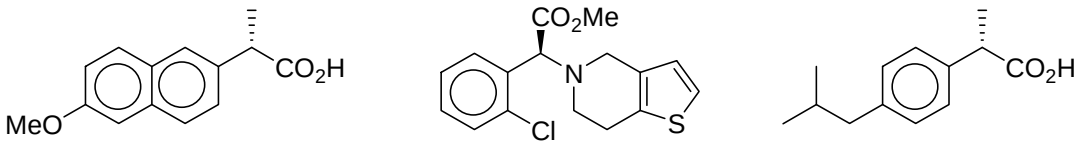
Yield: 37%; liquid; **IR** ($CHCl_3$, cm^{-1}): 2952, 2860, 1428, 1420, 910, 720; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.6-2.2 (m, 8H), 4.01-4.22 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 23.2, 37.8, 53.6; **Anal.** Calcd for C_5H_9Br: C, 40.30; H, 6.09, Br, 53.62. Found: C, 40.29; H, 6.11, Br, 53.59%.

Section II

$NaIO_4$-Mediated Selective Oxidation of Benzylic Bromides and Alkylarenes to Benzoic acids in Water as Solvent

3.2.1 Introduction

Aryl carboxylic acids are important intermediates because these derivatives constitute versatile building blocks in pharmaceutical and polymer industries.[13] They are also present in some drug compounds such as naproxen (1**7**), plavix (1**8**) and ibuprofen (1**9**), etc. (**Fig. 3**). Further, the oxidation of methylarenes to the corresponding carboxylic acids constitutes one of the most fundamental transformations in organic synthesis.[14] While in literature, carboxylic acids are prepared by oxidation of benzylic alcohol or benzaldehydes, the conversion of a $-CH_3$ to –COOH is carried out routinely by a variety of metal-oxo species, enzymes and autoclave oxidations. The laboratory-scale benzylic oxidations are generally carried out with a large excess of metal oxidants such as chromium and manganese reagents. However, the metal residues are environmentally undesirable and often provide problems during reaction and work-up. There are reports of the direct, one-step oxidation of aromatic compounds with peracids in the presence of acid catalysts.



Naproxen (**17**) Plavix (**18**) Ibuprofen (**19**)

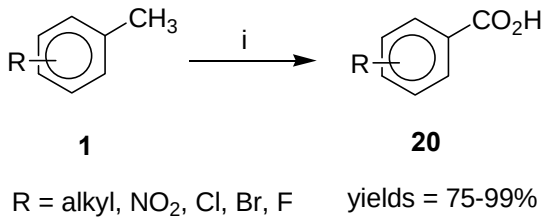
Fig 3: Drugs with aryl carboxylic acid moiety

However, such methods for the oxidation of alkylarenes are not satisfactory in terms of yields and show other disadvantages such as lack of regioselectivity, the need for high pressure and temperature, the undesired side products and the difficulty in handling.

3.2.2 Review of Literature

Friedman's approach (1965)[15]

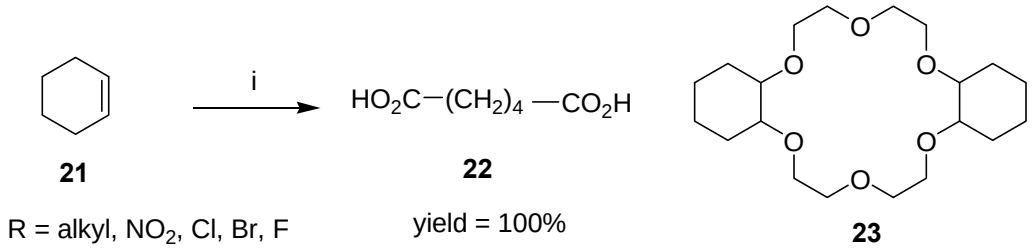
Friedman *et al*. have reported the oxidation of various mono- and polysubstituted methylarenes in water using $Na_2Cr_2O_7$ as a catalyst giving the corresponding carboxylic acids in good yields (**Scheme 13**).



Scheme 13: (i) $Na_2Cr_2O_7$, H_2O, 250 ^oC, 18 h.

Sam's approach (1972)[16]

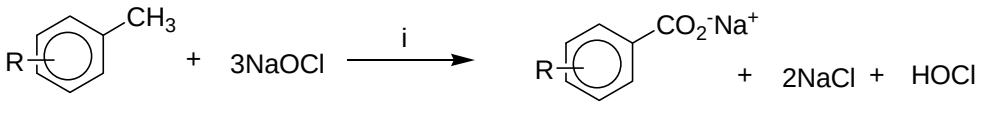
Sam *et al*. have described the oxidation of methylarenes, olefins and benzylic alcohols to the corresponding carboxylic acids with $KMnO_4$ in presence of dicyclohexyl-18-crown-6 **23** and benzene as solvent. By this method, aliphatic substrates like cyclohexene **21** are also converted in to adipic acid **22** in quantitative yields (**Scheme 14**).



Scheme 14: (i) $KMnO_4$, cat. **23**, benzene, 25 ^oC, 72 h.

Sasson's approach (1986)[17]

Sasson *et al*. have reported liquid phase oxidation of various methylarenes with electron-withdrawing substituents to the corresponding carboxylic acids in excellent yields using $RuCl_3 \cdot 3H_2O$ and aq. NaOCl. While in case of electron-donating methylarenes mixture of the corresponding carboxylic acid and ring chlorination was observed (**Scheme 15**).



24

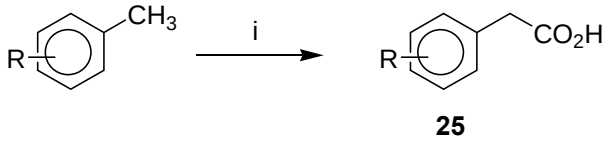
R = alkyl, NO_2, Cl, Br, F

yields upt 99%

Scheme 15: (i) $RuCl_3 \cdot 3H_2O$, NaOCl, (5 mol%) TBAB, 1,2-dichloroethane.

Santamaria's approach (1989)[18]

Santamaria *et al*. have reported a selective and mild photochemical oxidation procedure for the benzylic oxidations with 9,10-dicyanoanthracene (DCA) in the presence of methyl viologen (MV^{2+}) an electron relay. The reaction was carried out with a 500 W high pressure mercury lamp and oxygen bubbling (**Scheme 16**).



25

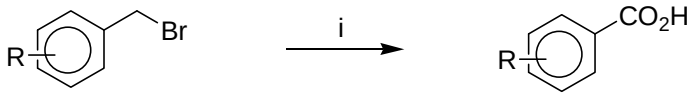
R = alkyl

Scheme 16: (i) hν, O_2, DCA, MV^{2+}.

Shi's approach (2001)[19]

Shi *et al*. have reported the oxidation of various benzylic halides to the corresponding carboxylic acids in good yields with sodium tungstate as an efficient and eco-friendly catalyst. Mechanistically, it was proposed that benzylic halides were first oxidized to

benzyl alcohols and then to the desired benzoic acids by Baeyer-Villiger pathway (**Scheme 17**).



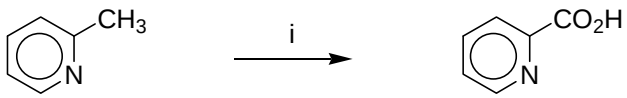
14 **20**

R = alkyl, NO_2, halo yield = 77-99%

Scheme 17: (i) $Na_2WO_4 \cdot 2H_2O$, $[CH_3(n\text{-}C_8H_{17})_3N]^+HSO_4^-$, 4A° MS, 90 °C.

Sen's approach (2003)[20]

Sen *et al*. have reported the oxidation of various methylarenes to the corresponding carboxylic acids in excellent yield using nitrogen oxide as oxidant and selenium as catalyst (**Scheme 18**).



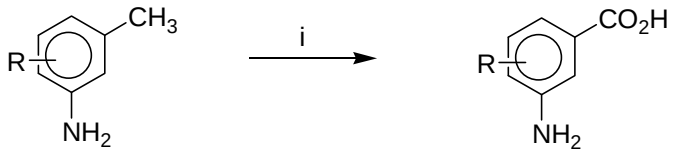
26 **27**

yield = 38%

Scheme 18: (i) Se (5 wt%), $NO:O_2$ (1:1).

Pauls approach (2004)[21,22]

In this approach Paul et al have reported microwave induced oxidation of various alkylarenes to the corresponding carboxylic acids in good yield with urea-hydrogen



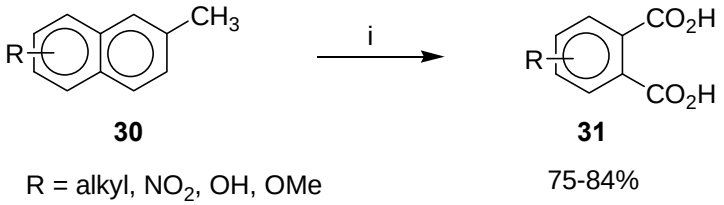
28 **29**

R = alkyl, NO_2, OH, OMe yields upto 83%

Scheme 19: (i) Urea-hydrogen peroxide, MW 300 W.

peroxide complex (UHP) as the stoichiometric oxidant. The reaction proceeded smoothly with both electron-donating and –withdrawing substrates under solvent-free conditions (**Scheme 19**).

Same author described zinc oxide catalyzed oxidation of various alkylbenzenes, naphthalene and 1,2,3,4-tetrahydronaphthalene in air using microwave irradiation or conventional heating in the presence of N,N-dimethylformamide (**Scheme 20**).



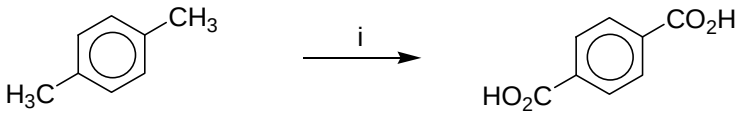
30 **31**

R = alkyl, NO_2, OH, OMe 75-84%

Scheme 20: (i) ZnO, DMF, MW, Δ.

Espenson's approach (2005)[23]

Espenson *et al*. have reported the autooxidation of p-xylene to terphthalic acid with $Co(OAc)_2$ and $Mn(OAc)_2$ as catalysts in strong acid such as trifluoroacetic acid, p-toluenesulfonic acid (**Scheme 21**).

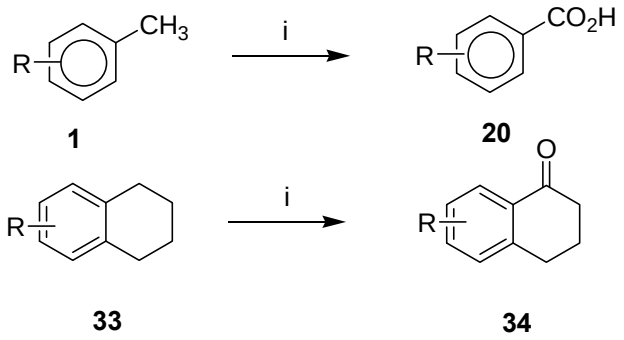


32

Scheme 21: (i) $Co(OAc)_2$, $Mn(OAc)_2$, HBr, TFA, 150-225 ^oC, 85%.

Barrett's approach (2003)[24]

Barrett *et al*. have reported a novel method for the oxidation of various methyl arenes to the corresponding carboxylic acids in good yield using $Bi(OTf)_2$ as catalyst and tert-butyl hydroperoxide as oxidant. While various alkylarenes **33** under similar reaction conditions were selectively oxidized to the corresponding ketones **34** (**Scheme 22**).



Scheme 22: (i) Bi, *t*-BuOOH, picolinic acid, pyridine:AcOH (9:1), 100 ^{o}C, 16 h.

3.2.3 Present Work

3.2.3.1 Objective

Although there are many methods available in the literature for the oxidation of methylarenes and alkylarenes, many of these methods suffer from several disadvantages such as use of heavy metal catalysts, hazardous metal waste, high pressure and temperature. The literature reference for the oxidation of benzylic halides to the corresponding carboxylic acids is scarce.[19] In this section we describe, a transition metal free catalyst for the oxidation of methylarenes and benzylic bromides with $NaIO_4/LiBr/H^+/H_2O$ combination[25] to carboxylic acids.

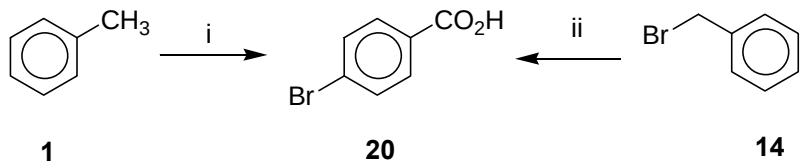
3.2.4 Results and Discussion

In continuation of our interest on $NaIO_4$-mediated oxidations described in earlier section, this section presents a new method of direct oxidation of alkylarenes that produces the corresponding benzylic acetates mediated by $NaIO_4$/LiBr. During our mechanistic investigations, we found that the reaction proceeded through benzylic bromide as intermediate, which was subsequently oxidized by $NaIO_4$ to liberate bromine and benzyl cation; solvolysis of the latter gave benzylic acetates.[12] With this background, we thought

that solvolysis of the benzyl cation with water, instead of acetic acid should give benzylic alcohol.

Unprecedented transformation

Indeed an unprecedented transformation occurred when toluene (**1**) was subjected to oxidation under the same reaction conditions ($NaIO_4/LiBr/H_2O/H^+$) giving 4-bromobenzoic acid (**20**) in 60% isolated yield instead of the expected unsubstituted benzyl alcohol. We also found a similar observation when producing benzyl bromide (**14**) was subjected to oxidation it gave 4-bromobenzoic acid in 79% yield respectively. Additionally, 2-methoxybenzyl bromide under the same reaction conditions gave 5-bromo-2-methoxybenzaldehyde in 18% yield. It may be explained that the intermediate benzyl alcohol, formed by solvolysis, probably underwent nuclear bromination at the para position with Br_2 before itself being oxidized to carboxylic acids (**Schemes 23 and 24**).



Scheme 23: (i) $NaIO_4$, LiBr, 2% aq. H_2SO_4, 95 ^oC, 18 h; (ii) $NaIO_4$, 2% aq. H_2SO_4, 95 ^oC, 12 h.

To explain this observation, the following experiments have been carried out: (1) when 2-nitrotoluene was subjected to oxidation under this reaction condition, 2-nitrobenzoic acid (54%) was obtained, as a side-chain oxidized product; (2) *o*-xylene under the same experimental condition gave only 4-bromo-1,2-dimethylbenzene, a ring-brominated product; (3) a simple competitive experiment was carried out with a mixture of toluene and 2-chlorotoluene where we obtained only 4-bromo- and 2-chlorobenzoic acids

respectively. Notably, we observed that the electrophilic ring bromination was observed only in electron rich methylarenes with an unblocked, sterically favorable *para* position. However, the presence of electron-withdrawing groups such as Br, Cl, NO_2, etc. probably deactivates the ring and also facilitates the oxidation of the intermediate species thereby shortening their lifetime thus resulting in no ring bromination. *ortho* Bromination was not observed possibly because of the steric nature of the bromonium ion.

Encouraged by this result, we subjected a variety of methylarenes (**1**) having both electron-donating and -withdrawing groups to oxidation with $NaIO_4$ (1 equiv) and LiBr (1 equiv) in 2% aq H_2SO_4 (15 mL) at 95 °C and successfully obtained carboxylic acids (**20**) in good yields (**Table 4**). The use of excess $NaIO_4$ (1.2 equiv) did not improve the yield considerably. The yields were found to be higher in the case of methylarenes with electron-withdrawing groups (NO_2, Cl). When highly activating substituents (NH_2, OH) are present, electrophilic ring bromination took place preferentially. Attempts to improve the yields further by using a combination of solvents (*t*-BuOH/H_2O, THF/H_2O, CH_3CN/H_2O, etc.) were not fruitful. When LiBr was replaced by other halogen sources such as NaCl or KI, no reaction took place. Another interesting feature is that, although methyl groups were selectively oxidized to the corresponding carboxylic acids, benzylic methylene groups were oxidized to ketones; the over oxidation of benzylic methylenes to carboxylic acids with carbon C-C bond cleavage a common feature noticed in the case of transition-metal oxides was not observed here (entries m and n, **Table 4**).

The formation of carboxylic acids **20a-n** was confirmed by ^1H, ^{13}C NMR, IR spectroscopy. For example, the ^1H NMR spectrum of **20e** showed signals at δ 1.35 (s) for *tert*-butyl protons ((C**H**$_3$)$_3$C-) and δ 7.43 (d) and 7.94 (d) for aromatic protons

respectively. Its ^{13}C NMR spectrum showed a typical signal at δ 30.5 for (($\mathbf{C}H_3)_3C$-) *tert*-butyl group and δ 167.6 for carbonyl carbon of carboxylic acid (-$\mathbf{C}O_2H$-) (**Fig. 4**).

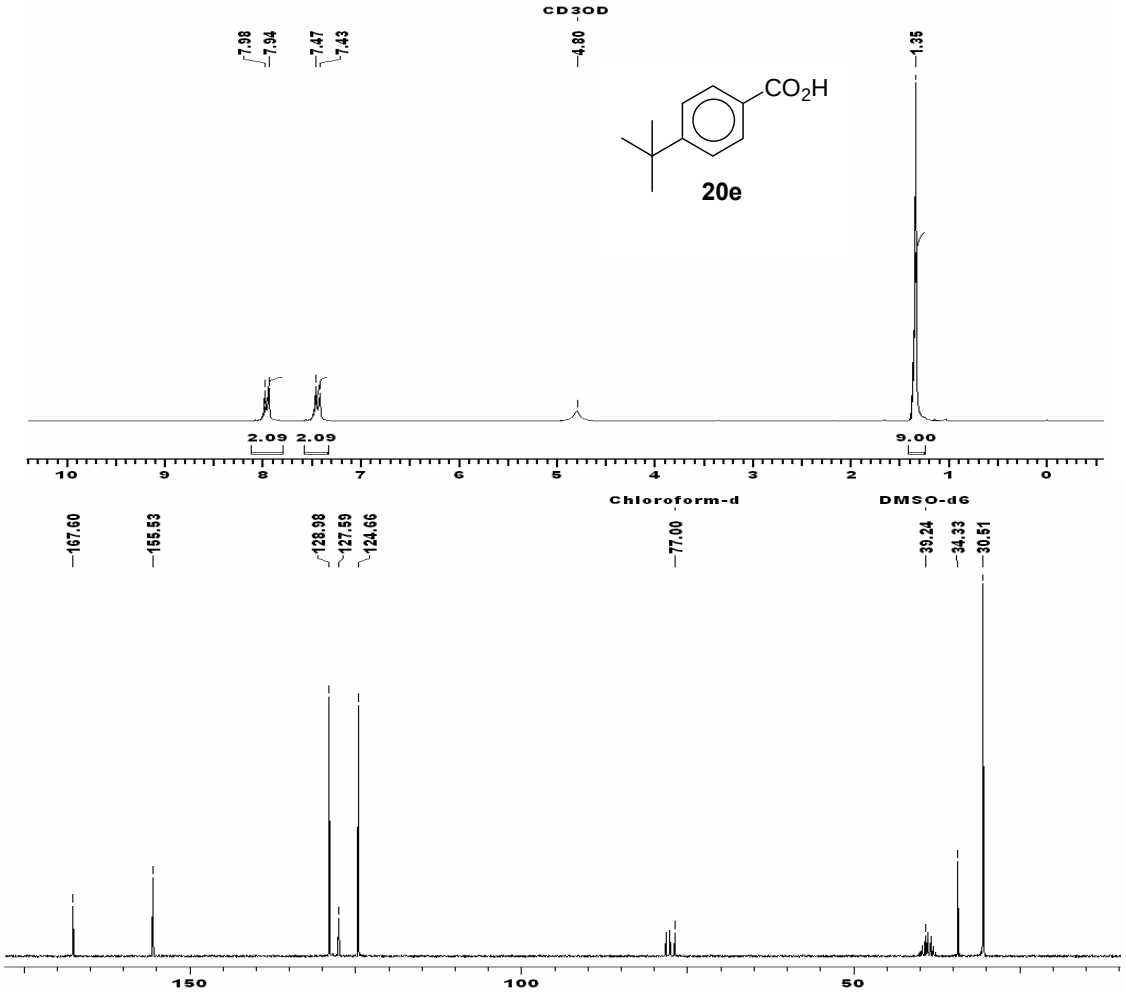
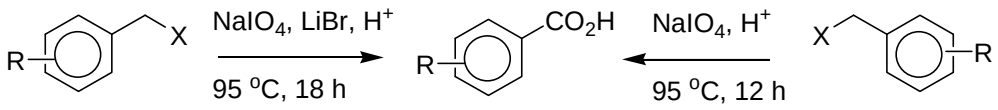


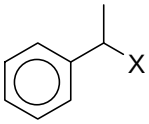
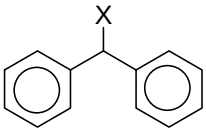
Fig. 4: ^{1}H and ^{13}C NMR spectra of 4-*tert*-butylbenzoic acid **(20e)**

To study its scope, we subjected several benzylic bromides to oxidation with $NaIO_4/H^+$ conditions. Indeed, such oxidations of benzylic bromides with $NaIO_4$ produced the corresponding carboxylic acids in high yields (71-89%). Although a variety of reagents are known to oxidize[19] organic halides to aldehydes, only a few direct one-step

Table 4: $NaIO_4$/LiBr-mediated oxidation of alkylarenes and benzylic bromides in acidic medium[a]



1 **20** **14**

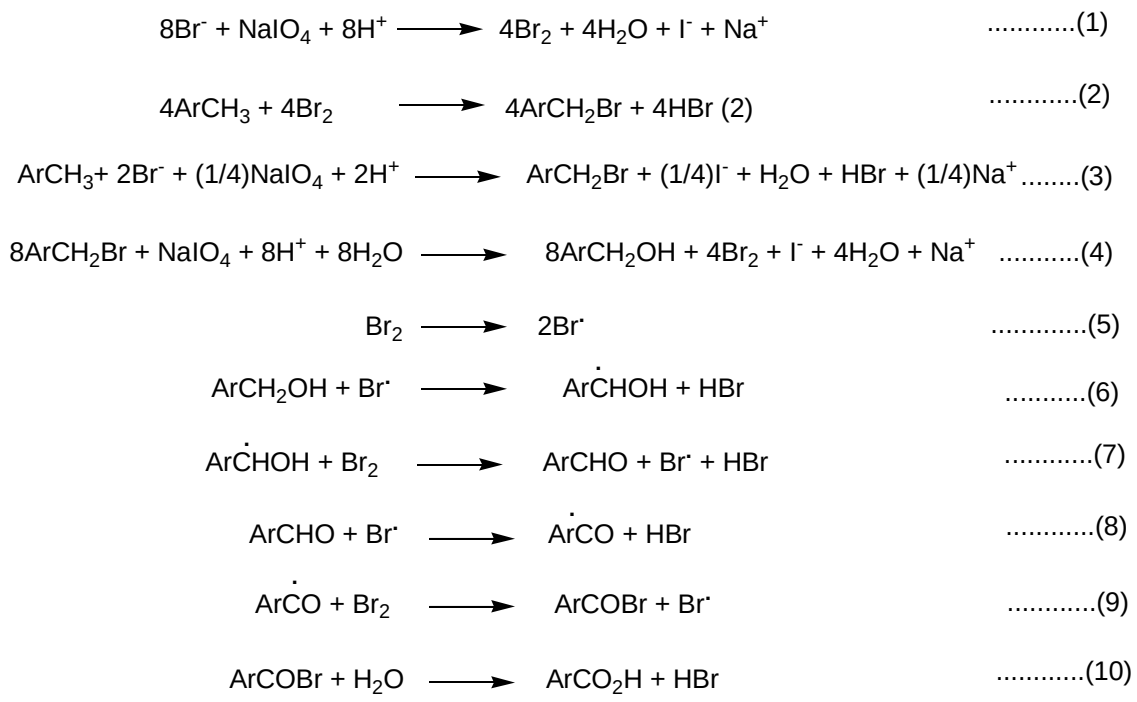
Entry	R	Yield of **20**[b]	
		X = H	**X = Br**
a	4-Br	71, 30[c]	81
b	4-Cl	73	79
c	2-Cl	72	76
d	4-NO_2	76	89 (78)[d]
e	4-$C(CH_3)_3$	63	73
f	4-Me	70	78[e]
g	3,4-Cl	73	88
h	2,3-Cl	75	84
i	3-NO_2	69	81
j	4-Ph	70	83
k	4-F	[g]	86
l	4-CO_2Me	[g]	83[f]
m		72 (X = H)	87 (X = Br)
n		76 (X = H)	85[h] (X = Br)

[a] See Experimental Section for procedure. [b] Isolated yield. [c] 50 mol % of $NaIO_4$ and LiBr were employed. [d] KIO_3 (1.2 equiv) was employed as the oxidant. [e] Terephthalic acid was obtained in 4% yield. [f] Methyl ester is hydrolyzed to form terephthalic acid. [g] Reactions were not done. [h] Yield was 83% with 50 mol % of $NaIO_4$. [i] Corresponding ketones were obtained.

conversion of benzylic bromides to the corresponding carboxylic acids are known. As can be seen from **Table 4**, several benzylic bromides with both electron-withdrawing and -donating groups underwent oxidation with $NaIO_4/H^+$ condition to give the corresponding carboxylic acids in excellent yields. Secondary benzylic bromides were also oxidized to give the corresponding ketones in excellent yields (entries m and n, **Table 4**). The use of a substoichiometric amount of $NaIO_4$ (50 mol %) generally gave poor yields of carboxylic acids except in the case of bromodiphenylmethane (entry n), which gave a comparable yield of benzophenone (83%) due to the easy oxidizability of the C-Br bond. However, benzyl chloride was resistant to undergo oxidation under the reaction conditions, probably because of the higher bond strength of the C-Cl bond. KIO_3 was also found to oxidize benzylic bromides to give benzoic acids in high yields (entry d, **Table 4**). The prolonged oxidation of 4-methylbenzyl bromide led to successive oxidation of benzyl bromide as well as methyl groups to give 4% terephthalic acid (entry f, **Table 4**).

3.2.5 Mechanism

We observed that oxidation of methylarenes to carboxylic acids proceeds *via* intermediates such as benzyl bromide, benzyl alcohol and benzaldehydes in that order respectively as confirmed by GC-MS analysis, in the oxidation of toluene with $NaIO_4/LiBr/H^+$ combinations (**Scheme 24**). Following the concept of side-chain bromination of alkylarenes using metal halide in the presence of an oxidizing agent[6,26a] (H_2O_2, TeO_2, etc.) as reported by others and us,[12] we believe that $NaIO_4$ oxidizes LiBr in the presence of acid to liberate molecular bromine that brominates the side chain of alkylarenes to give the corresponding benzylic bromides (eqs. 1-3). Similar to inorganic



Scheme 24: Mechanism for oxidation of alkylarenes to benzoic acids

halides (LiBr), benzylic bromides are solvolyzed with water in the presence of $NaIO_4$ in acidic medium at elevated temperature (95 °C) to give benzylic alcohols (eq. 4). The fact that the reagent $NaIO_4/H^+$ alone did not oxidize secondary alcohols, whereas the $NaIO_4/LiBr/H^+$ combination did, led to our belief that benzylic alcohols were directly oxidized to the corresponding carboxylic acids with Br_2 *via* a free radical pathway[26b] (eqs 5-10).

3.2.6 Conclusion

In conclusion, we have shown, for the first time, an unprecedented oxidation at the benzylic position coupled with nuclear bromination when toluene, benzyl bromide were subjected to oxidation with $NaIO_4/LiBr/H^+$ at 95 °C to give 4-bromobenzoic acid in up to 79% yield. We have thus developed a mild procedure for the direct conversion of methylarenes and benzyl bromides to the corresponding carboxylic acids in high yields using $NaIO_4/LiBr/H_2SO_4$ conditions.

3.2.7 Experiment Section

Procedure for the oxidation of Alkylarene

To a mixture of alkylarene (3 mmol), $NaIO_4$ (3 mmol) and LiBr (3.3 mmol) was added 2% aq H_2SO_4 (15 mL). The reaction mixture was heated at 95 °C (using an oil bath) for 18 h. The reaction mixture was then cooled to room temperature and extracted with ethyl acetate (40 mL x 3), and the combined organic phase was washed with saturated sodium thiosulfate solution, water, dried over anhyd. Na_2SO_4, and concentrated under reduced pressure to give the crude product; it was washed with cold *n*-hexane and recrystallized to afford a pure product.

Procedure for the oxidation of benzylic halide

Benzylic halides were subjected to the same reaction conditions as given above but without the use of LiBr.

4-Bromobenzoic acid (20a)

colorless solid; **mp:** 252-253 ^oC, [lit.[27] mp: 251-253 ^oC]; **IR** (KBr, cm^{-1}): 3020, 1700, 1640, 1340, 1320, 1200, 1051, 1012, 942, 860, 840, 760; **^{1}H NMR** (200 MHz, CD_3OD): δ 8.04 (d, *J* = 8.0 Hz, 2H), 8.37 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (50 MHz, CD_3OD): δ 126.9, 129.9, 131.0, 131.3, 166.6; **Anal.** Calcd for $C_7H_5BrO_2$: C, 41.82; H, 2.51, Br, 39.75. Found: C, 41.79; H, 2.49, Br, 39.69%.

4-Chlorobenzoic acid (20b)

colorless solid; **mp:** 238-240 ^oC, [lit.[27] mp: 238-241 ^oC]; **IR** (KBr, cm^{-1}): 3015, 1705, 1610, 1415, 1301, 1140, 1032, 930, 870, 820, 790; **^{1}H NMR** (200 MHz, CD_3OD): δ 7.39 (t, *J* = 5.0 Hz, 2H), 7.98 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (50 MHz, CD_3OD): δ 128.3,

129.5, 130.9, 138.0, 166.5; **Anal.** Calcd for $C_7H_5ClO_2$: C, 53.70; H, 3.22; Cl, 22.64. Found: C, 53.68; H, 3.19; Cl, 22.58%.

2-Chlorobenzoic acid (20c)

colorless solid; **mp:** 138-140 ^oC, [lit.[27b] mp: 142 ^oC]; **IR** (KBr, cm^{-1}): 3010, 1710, 1410, 1315, 1050, 905, 740, 690, 660; **^{1}H NMR** (200 MHz, CD_3OD): δ 6.94-7.12 (m, 3H), 7.59 (dd, *J* = 1.6, 5.0 Hz, 1H); **^{13}C NMR** (50 MHz, CD_3OD): δ 126.8, 128.6, 131.4, 131.9, 135.1, 135.4, 166.4; **Anal.** Calcd for $C_7H_5ClO_2$: C, 53.70; H, 3.22; Cl, 22.64. Found: C, 53.69; H, 3.19; Cl, 22.59%.

4-Nitrobenzoic acid (20d)

Yellow colored solid; **mp:** 237-239 ^oC, [lit.[27c] mp: 236-239 ^oC]; **IR** (KBr, cm^{-1}): 3020, 2985, 1700, 1610, 1530, 1400, 1340, 1310, 1005, 920, 840, 800, 730; **^{1}H NMR** (200 MHz, CD_3OD): δ 8.31-8.43 (m, 4H); **^{13}C NMR** (50 MHz, CD_3OD): δ 123.2, 130.5, 136.5, 151.6, 166.7; **Anal.** Calcd for $C_7H_5NO_4$: C, 50.31; H, 3.02; N, 8.38. Found: C, 50.29; H, 3.11; N, 8.40%.

4-*tert*-Butylbenzoic acid (20e)

colorless solid; **mp:** 162-164 ^oC, [lit.[27d] mp: 163-164 ^oC]; **IR** (KBr, cm^{-1}): 3012, 1700, 1600, 1340, 1210, 1110, 940, 840, 780, 710; **^{1}H NMR** (200 MHz, CD_3OD): δ 1.35 (s, 9H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.96 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$+DMSO-d_6): δ 30.5, 34.3, 124.6, 127.5, 128.9, 155.5, 167.6; **Anal.** Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.09; H, 7.88%.

4-Methylbenzoic acid (20f)

colorless solid; **mp:** 177-179 ^oC, [lit.[27] mp: 176-178 ^oC]; **IR** (KBr, cm^{-1}): 3105, 1700, 1600, 1340, 1280, 1100, 940, 850, 760; **^{1}H NMR** (200 MHz, CD_3OD): δ 2.45 (s, 3H),

7.35 (d, *J* = 8.0 Hz, 2H), 8.02 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (50 MHz, CD_3OD): δ 20.1, 126.8, 127.6, 128.2, 144.6, 170.6; **Anal.** Calcd for $C_8H_8O_2$: C, 70.57; H, 5.92. Found: C, 70.49; H, 5.89%.

3,4-Dichlorobenzoic acid (20g)

Yellow colored solid; **mp:** 207-208 ^oC, [lit.[27e] mp: 208-209 ^oC]; **IR** (KBr, cm^{-1}): 3012, 2671, 1710, 1520, 1400, 1340, 1305, 1100, 1050, 920, 850, 760, 740; **^{1}H NMR** (200 MHz, CD_3OD): δ 7.90 (d, *J* = 8.0 Hz, 1H), 8.25 (dd, *J* = 2.0, 8.0 Hz, 1H), 8.48 (d, *J* = 2.0 Hz, 1H); **^{13}C NMR** (50 MHz, CD_3OD): δ 128.8, 130.4, 131.0, 131.2, 131.8, 136.0, 165.5; **Anal.** Calcd for $C_7H_4Cl_2O_2$: C, 44.02; H, 2.11; Cl, 37.12. Found: C, 44.11; H, 2.09; Cl, 37.10%.

2,3-Dichlorobenzoic acid (20h)

Yellow colored solid; **mp:** 168-170 ^oC, [lit.[27f] mp: 164 ^oC]; **IR** (KBr, cm^{-1}): 3020, 1700, 1510, 1400, 1330, 1120, 1050, 930, 860, 760; **^{1}H NMR** (200 MHz, CD_3OD): δ 7.56 (t, *J* = 8.0, 15.9 Hz, 1H), 7.88 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.98 (dd, *J* = 1.6, 8.0 Hz, 1H); **^{13}C NMR** (50 MHz, CD_3OD): δ 126.2, 127.0, 127.7, 131.4, 132.5, 132.7, 165.4; **Anal.** Calcd for $C_7H_4Cl_2O_2$: C, 44.02; H, 2.11; Cl, 37.12. Found: C, 44.09; H, 2.15; Cl, 37.07%.

3-Nitrobenzoic acid (20i)

Yellow colored solid; **mp:** 139-140 ^oC, [lit.[27c] mp: 142 ^oC]; **IR** (KBr, cm^{-1}): 3015, 1712, 1640, 1460, 1420, 1300, 1280, 1130, 910, 720; **^{1}H NMR** (200 MHz, CD_3OD): δ 7.85 (t, *J* = 5.5 Hz, 1H), 8.37 (d, *J* = 8.0 Hz, 1H), 8.46 (d, *J* = 7.8 Hz), 8.62 (s, 1H); **^{13}C NMR** (50 MHz, CD_3OD): δ 123.6, 127.2, 130.3, 132.3, 135.2, 147.7, 165.4; **Anal.** Calcd for $C_7H_5NO_4$: C, 50.31; H, 3.02; N, 8.38. Found: C, 50.29; H, 3.06; N, 8.33%.

4-Phenylbenzoic acid (20j)

colorless solid; **mp:** 226-227 ^{o}C, [lit.[27g] mp: 228 ^{o}C]; **IR** (KBr, cm^{-1}): 3102, 2510, 1700, 1680, 1400, 1340, 1280, 1010, 940, 860, 760, 680; **^{1}H NMR** (200 MHz, CD_3OD): δ 7.80-8.05 (m, 7H), 8.47 (t, *J* = 4.0 Hz, 2H); **^{13}C NMR** (50 MHz, CD_3OD): δ 126.5, 126.8, 127.9, 128.7, 129.6, 129.9, 139.3, 144.4, 167.3; **Anal.** Calcd for $C_{13}H_{10}O_2$: C, 78.77; H, 5.09. Found: C, 78.69; H, 5.11%.

4-Fluorobenzoic acid (20k)

Brown coloured solid; **mp:** 182-183 ^{o}C, [lit.[27h] mp: 185 ^{o}C]; **IR** (KBr, cm^{-1}): 3010, 2912, 1700, 1600, 1415, 1310, 1200, 1110, 920, 840, 760, 640; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.15 (t, *J* = 9.0 Hz, 2H), 8.10-8.17 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 115.7, 115.3, 125.7, 132.8, 166.5, 170.6; **Anal.** Calcd for $C_7H_5FO_2$: C, 60.01; H, 3.60; F, 13.56. Found: C, 60.08; H, 3.57; F, 13.49%.

***p*-Terphthalic acid (20l)**

colorless solid; **mp:** >300 ^{o}C; **IR** (KBr, cm^{-1}): 3010, 2982, 2652, 1706, 1340, 1280, 1121, 1105, 942, 780, 740; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 8.2 (s, 4H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ 129.4, 134.3, 166.6; **Anal.** Calcd for $C_8H_6O_4$: C, 57.84; H, 3.64. Found: C, 57.79; H, 3.66%.

Acetophenone (20m)

Liquid; **IR** (neat, cm^{-1}): 3012, 2992, 1730, 1600, 1410, 1315, 1210, 935, 760, 680; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.58 (s, 3H), 7.40-7.57 (m, 3H), 7.91-7.95 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 26.5, 128.2, 128.5, 133.0, 137.1, 197.9; **Anal. Calcd for** C_8H_8O: C, 79.97; H, 6.71. Found: C, 79.91; H, 6.64%.

Section III:

$NaIO_4$-Mediated Selective Oxidation of Benzylic alcohols: High Yield Preparation of Aromatic Aldehydes and Esters

3.3.1 Introduction

The oxidation of primary aromatic alcohols to the corresponding carbonyl compounds is a fundamental reaction in organic synthesis.[28] Also, direct conversion of alcohols to the corresponding aldehydes or carboxylic esters is often required in organic synthesis particularly in the synthesis of natural products.[29] The processes for the preparation of aldehydes and esters are widespread in industries for synthesis of a variety of end-products such as fragrances, monomers, plasticizers etc, many of which are classed as high production volume (HPV) chemicals. In addition, applications to lower volume, high-value pharmaceutical and fine chemicals targets are prominent, and often require more stringent coupling protocols to achieve the desired chemo- and stereoselectivity. The conventional method for the synthesis of carboxylic esters involves oxidation of aldehydes to carboxylic acids followed by esterification with alcohols catalyzed by either acid or base. However, the direct conversion of benzylic alcohols to aldehydes or esters minimizes the number of steps in organic synthesis.

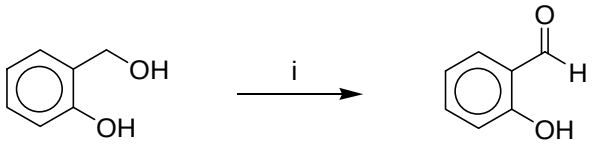
3.3.2 Review of literature

Literature survey revealed that there are numerous methods are available for the direct transformation of alcohols into the corresponding aldehydes. Among them, PCC, PDC Dess-Martin reagent, IBX and TPAP, and Swern oxidations are common and extensively employed. However, the direct transformation of alcohols into esters has been achieved

using a very few reagents such as $NaBrO_2$, Oxone, $Ca(OCl)_2$. Some of the recent developments on these reactions are discussed below.

Harfenist's approach (1956)[30]

Harfenist *et al*. have described the MnO_2-mediated oxidation of benzylic alcohol **21** to afford corresponding benzaldehydes **22** in good yields. Several electron-donating and -withdrawing substituents and the aliphatic allylic alcohols were smoothly oxidized to give the corresponding α,β-unsaturated aldehydes (**Scheme 25**).

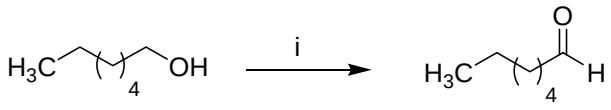


21 **22**

Scheme 25: (i) MnO_2, Et_2O, 47 h, 87%.

Corey's approach (1972)[31,32]

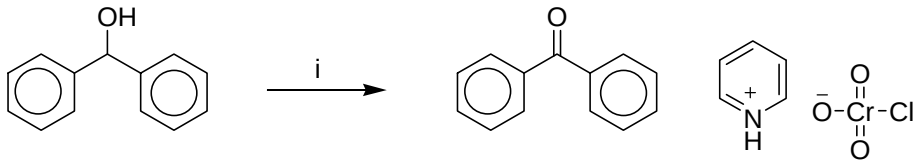
Corey *et al*. have reported that N-iodosuccinimide (NIS) and Me_2S-mediated oxidation of primary as well as secondary alcohols to the respective aldehydes or ketones in good yields. The reaction proceeds with formation of sulfoxonium ion which on treatment with base undergoes elimination to form a carbonyl compound (**Scheme 26**).



23 **24**

Scheme 26: NIS, Me_2S, CH_2Cl_2, -25 ^oC, 1.5 h, 96%.

A stable and mild reagent pyridinium chlorochromate **27** for the oxidation of variety of alcohols to carbonyl compounds with high yield. Reagent can be prepared by reaction of pyridine and CrO_3 in acidic medium (**Scheme 27**).

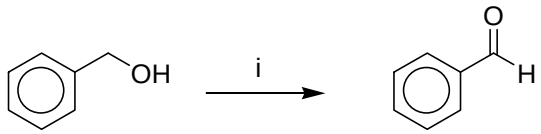


25 **26** **27**

Scheme 27: (i) PCC (**19**), CH_2Cl_2, 2 h, 100%.

Blair's approach (1977)[33]

Blair *et al*. have described a halogen-amine complex 1,4-diazabicyclo [2.2.2]octane·$2Br_2$ for the oxidation of benzylic alcohol to benzaldehydes in excellent yields. However, this reagent is selectively oxidizes secondary alcohol to ketone in presence of primary alcohols (**Scheme 28**).

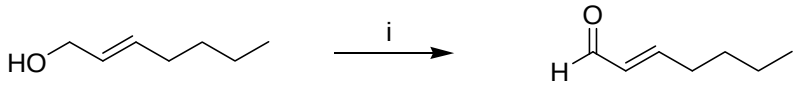


21 **22**

Scheme 28: (i) 1,4-diazabicyclo [2.2.2]octane·$2Br_2$ CH_3CN, reflux, 18 h, 96%.

Swern's approach (1978)[34]

Swern *et al*. have reported a versatile reagent for oxidation of primary, secondary, allylic, benzylic, hindered and bicyclic alcohols to the corresponding carbonyl compounds using activator DMSO and oxalyl chloride (**Scheme 29**).

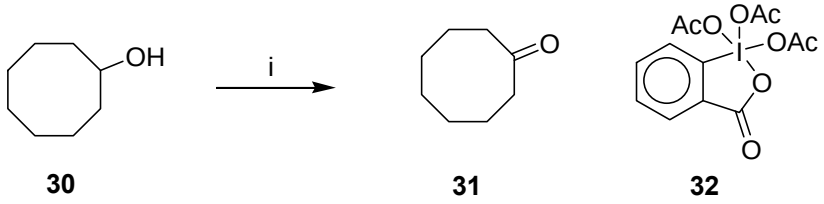


28 **29**

Scheme 29: (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -60 ^oC, 100%.

Martin's approach (1983)[35]

Martin and Dess together have reported a new readily accessible hypervalent-iodine reagent **32**. It is efficient for oxidation of variety of primary and secondary alcohols to the corresponding aldehydes and ketones respectively. The workup procedure is remarkably simple, and the conditions for reaction are very mild (**Scheme 30**).

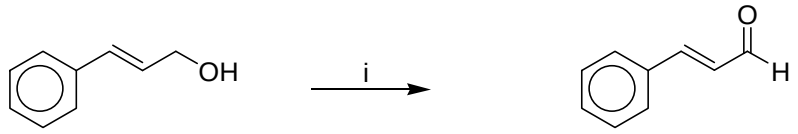


30 **31** **32**

Scheme 30: Dess-Martin periodinane (**32**), CH_2Cl_2, 20 min, 91%.

White's approach (1987)[36]

White *et al*. have described a new mild reagent for the oxidation of various primary and secondary alcohols to carbonyls using *tetra*-n-propylammonium per-ruthenate (TPAP) or *tetra*-n-butylammonium per-ruthenate (TBAP) and *N*-methylmorpholine N-oxide as oxidant (**Scheme 31**).

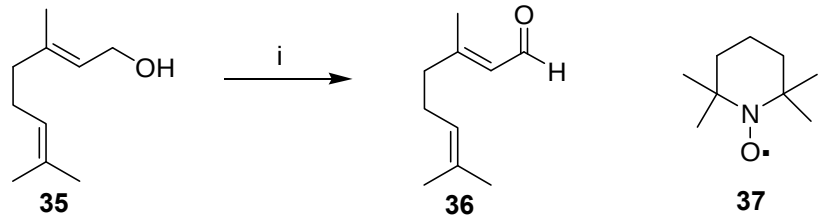


33 **34**

Scheme 31: (i) TPAP, NMO, 4A^o MS, CH_2Cl_2, 91%.

Einhorn's approach (1996)[37]

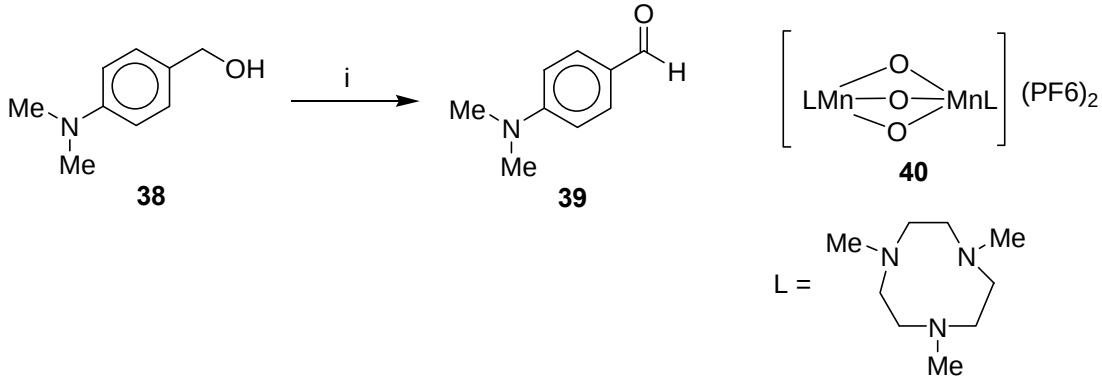
Einhorn *et al*. have described 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) catalyzes efficient oxidation of primary alcohols to aldehydes by *N*-chlorosuccinimide, in a biphasic dichloromethane-aqueous pH 8.6 buffer. A variety of aliphatic, benzylic, allylic alcohols are readily oxidized to aldehydes, while secondary alcohols underwent oxidation with lower efficiency (**Scheme 32**).



Scheme 32: (i) TEMPO, NCS, TBACl, CH_2Cl_2, H_2O, 100%.

Feringa's approach (1997)[38]

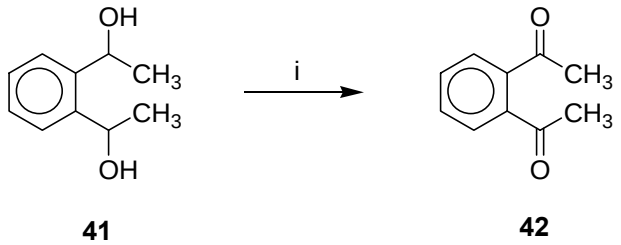
Feringa *et al*. have reported that oxidation of benzylic alcohols to benzaldehydes proceeded with dinuclear manganese (IV) catalyst (**40**). The reaction rate is faster when H_2O_2 or TBHP is used as oxidant with high selectivity (**Scheme 33**).



Scheme 33: (i) Catalyst (**40**), H_2O_2 or TBHP, Me_2CO, 30 min.

Toma's approach (2000)[39]

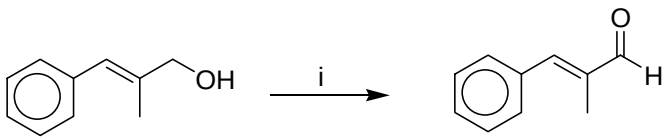
Toma *et al*. have described oxidation of benzyl alcohol to benzaldehydes using a heterogeneous $KMnO_4$ supported copper sulfate pentahydrate as catalyst. Application of ultrasonic irradiation leads to shorter reaction time (**Scheme 34**).



Scheme 34: (i) $KMnO_4$/ $CuSO_4 \cdot 5H_2O$, CH_2Cl_2, 100%.

Kaneda's approach (2000)[40]

Kaneda *et al*. have reported a heterogeneous Ru^{3+} -exchanged hydroxyapatite (RuHAP) catalyzed oxidation of various primary and secondary alcohols to corresponding aldehydes and ketones respectively (**Scheme 35**).

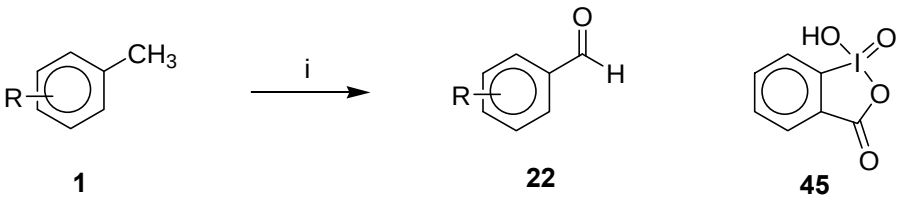


43 **44**

Scheme 35: (i) RuHAP, O_2, toluene, 80 ^oC, 95% by GC.

Nicolaou's approach (2001)[41]

Nicolaou *et al*. have described a novel method for the direct and selective oxidation of benzylic and other activated alcohols to corresponding aldehydes and ketones with 2-iodoxybenzoic acid (IBX) (**22**) as catalyst (**Scheme 36**).



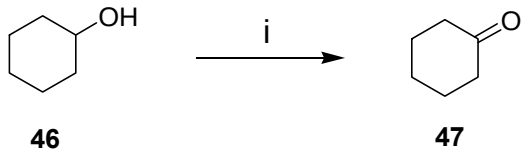
1 **22** **45**

R = 3,5-OMe, 2,5-OMe, Br, etc. yields = 62-95%

Scheme 36: IBX (**22**), DMSO, 85 ^oC, 12 h, 85%.

Mizuno's approach (2002)[42]

Mizuno *et al*. have reported a heterogeneous liquid phase oxidation of benzylic alcohols to benzaldehydes with benzoic acid as side product using $[(n\text{-}C_4H_9)_4N]_4H[SiW_{11}Ru^{III}(H_2O)O_{39}]\cdot 2H_2O$ catalyst. Also, this catalyst is efficient for oxidation of alkanes to the corresponding aldehydes (**Scheme 37**).

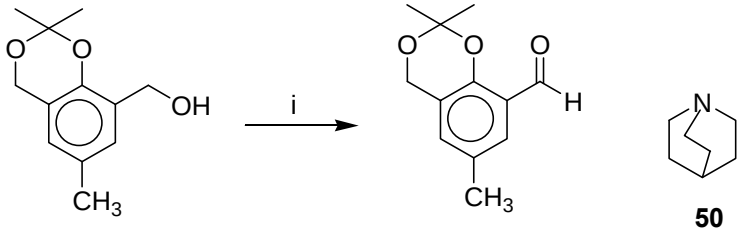


46 47

Scheme 37: (i) $(nC_4H_9)_4N]_4H$ $[SiW_{11}Ru^{III}(H_2O)O_{39}]\cdot 2H_2O$, O_2, 120 h, 81%.

Brown's approach (2002)[43]

Brown *et al*. have developed OsO_4 as catalyst and Cu complex as co-catalyst. A new method for the oxidation of variety of aromatic and aliphatic alcohols to the corresponding carbonyl compounds in good yield (**Scheme 38**).

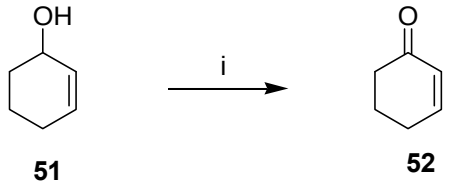


48 49 50

Scheme 38: (i) OsO_4, quinuclidine (**50**), Cu^{II}-2-ethylhexanoate, CH_3CN, O_2, 97%.

White's approach (2003)[44]

White *et al*. have developed zeolite-confined nanometer sized RuO_2 (RuO_2-FAU) a green, selective and efficient catalyst for aerobic oxidation of various primary and secondary alcohols to the corresponding aldehydes and ketones in high yield (**Scheme 39**).



51 52

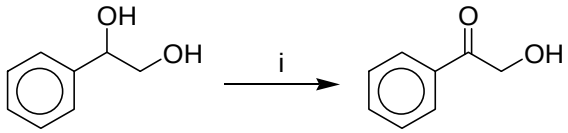
Scheme 39: (i) RuO_2-FAU, O_2, 80 ^oC, 99%.

Trudell[45] *et al*. have reported a new method for the oxidation of alcohols and ketones to the corresponding aldehydes and ketones using 10 mol% of chromium (III) acetylacetone $Cr(acac)_3$ and periodic acid H_5IO_6 as oxidant.

Punniyamurthy *et al*.[46] have described oxidation of benzylic alcohols to aldehydes and ketones using V_2O_5, K_2CO_3 at 100 ^oC. Secondary alcohols underwent oxidation chemoselectively to ketones.

Konwar's approach (2004)[47]

Konwar *et al*. has reported a new alternative system for the oxidation of secondary alcohols to ketones with DMSO/$N_2H_4 \cdot H_2O/I_2/H_2O/ CH_3CN$ in hydrated. The system also selectively oxidizes the secondary alcoholic groups to the corresponding ketones in the presence of primary alcoholic groups present within the same molecule in moderate to very good yields at reflux temperature (**Scheme 40**).

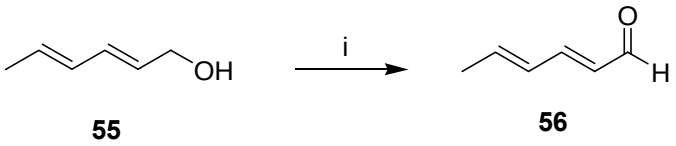


53 **54**

Scheme 40: (i) $N_2H_4.H_2O$, I_2, DMSO, H_2O, CH_3CN, 80 ^oC, 45%.

Ragauskas's approach (2005)[48]

Ragauskas *et al*. have reported a room-temperature aerobic oxidation of primary alcohols to aldehydes catalyzed by the three-component system acetamido-TEMPO/Cu-$(ClO_4)_2$/DMAP in the ionic-liquid [bmpy]PF_6 has been developed, and the catalysts can be recycled and reused for five runs without any significant loss of catalytic activity (**Scheme 41**).



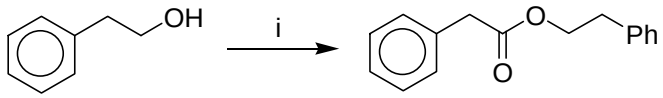
55 **56**

Scheme 41: (i) $Cu(ClO_4)_2$, TEMPO-acetamido, DMAP, O_2, [bmpy]PF_6, 75-92%.

Esters

Kageyama's approach (1983)[49a]

Kageyama *et al*. have reported a method for oxidation of primary alcohol to the corresponding ester using sodium bromite ($NaBrO_2$) in good yields (**Scheme 42**).



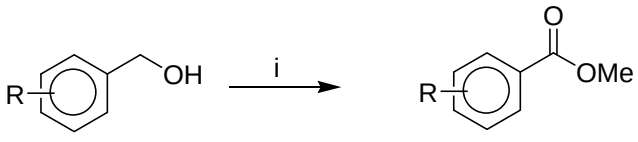
21 **57**

Scheme 42: (i) $NaBrO_2$, aq. AcOH, 25 ^oC, 91%.

Yoshida *et al*.[49b] have reported the oxidation of primary alcohols to the corresponding esters using $Pd(OAc)_2$ as catalyst in the presence of base. The remarkable selectivity achieved with this reagent is an attractive feature of this method.

McDonald's approach (1993)[50]

McDonald *et al*. have described oxidation of benzylic alcohols to the corresponding methyl etser using calcium hypochlorite in good yield. Primary aliphatic alcohols also underwent oxidation; reaction is light sensitive (**Scheme 43**).



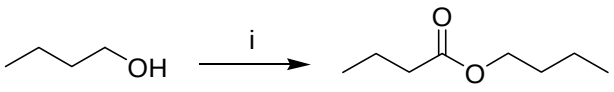
21 **58**

R = alkyl, halo

Scheme 43: (i) $Ca(OCl)_2$, AcOH, CH_3CN,MeOH, 4 A^o MS, dark, 86-89%.

Ishii's approach (1995)[51]

Ishii *et al*. have reported oxidation of primary alcohols to the ester using $NaBrO_3$ combined with $NaHSO_3$. However, aromatic alcohols fail to form esters (**Scheme 44**).

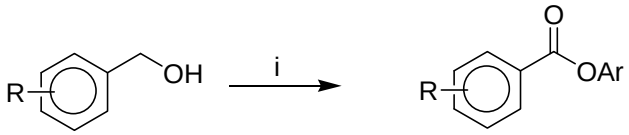


15 **28**

Scheme 44: (i) $NaBrO_3$, $NaHSO_3$, H_2O, 76%.

Lee's approach (1998)[52]

In this approach, esterification of aromatic primary alcohols was carried out with potassium permanganate using phase transfer catalyst (TDA-1) at room temperature. A variety of aromatic alcohols were converted to respective Tishchenko-like dimeric benzoate esters (**Scheme 45**).



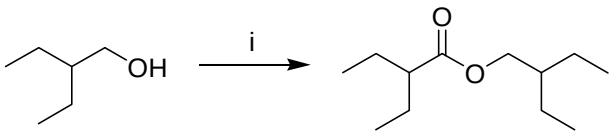
21 **57**

R = alkyl, halo

Scheme 45: (i) $KMnO_4$, tris[2-methoxyethoxy)ethyl] amine (TDA-1), CH_2Cl_2.

Schulze's approach (2005)[53]

Schulze *et al*. has reported an efficient method for the oxidation of alcohols with the catalytic amounts of sodium chloride in combination with oxone allows the conversion primary aliphatic alcohols to symmetric esters (**Scheme 46**).



29 **30**

Scheme 46: (i) Oxone, NaCl, 85%.

3.3.3 Present Work

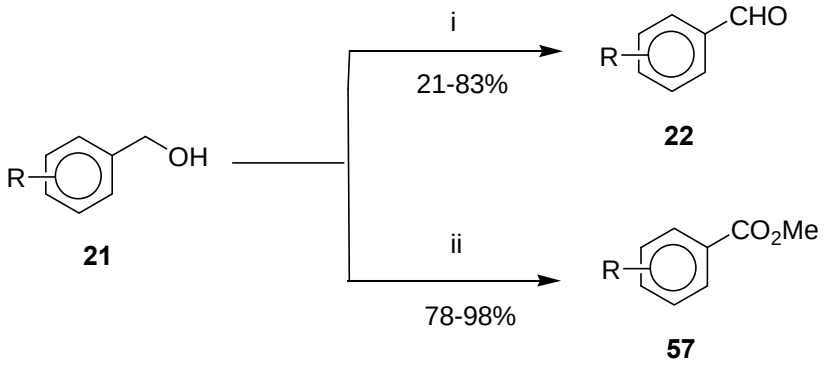
3.3.3.1 Objective

Several reports for alcohols to aldehydes transformation have been reported. These methods usually require harsh conditions and are not cost-effective. In addition, these transformations generally involve an oxidative pathway and require more than stoichiometric amount of oxidants coupled with long reaction times. Also these reagents are unsatisfactorily for alcohols containing electron-withdrawing groups. Since formation of minor amounts of acids often complicates the oxidative process. This section describes a new procedure involving $NaIO_4/H_2O/H^+$ combination that oxidizes benzylic alcohols to the corresponding benzaldehydes. Also, in this section describes a one-pot conversion of benzylic alcohols to the corresponding aromatic esters is described.

3.3.4 Results and discussion

In our earlier section, we have described that $NaIO_4$-mediated oxidations and observed that alkylarenes or benzylic bromides solvolyzed to give oxyfunctionalized product either benzylic acetate or benzoic acid. When benzyl alcohol was subjected to oxidation with $NaIO_4$ (1 equiv) in the presence of acidic medium without LiBr, benzaldehyde **22** was exclusively obtained in 79% yield with no formation of benzoic acid. In this regard, we envisioned that replacing water with alcohol should result in the formation of esters. During this investigation, we found that $NaIO_4$-LiBr-H^+ combination oxidatively

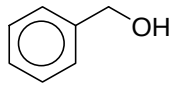
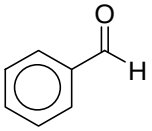
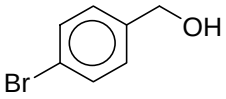
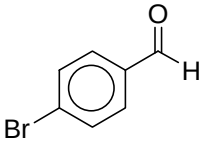
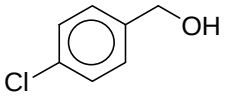
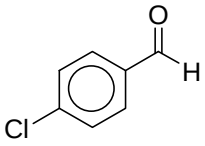
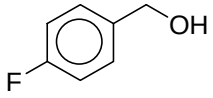
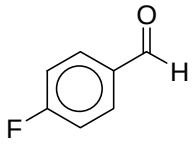
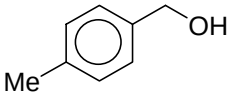
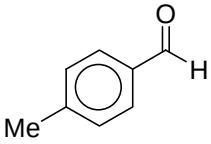
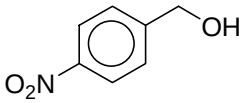
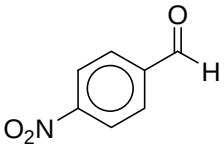
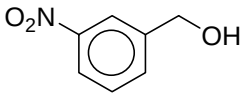
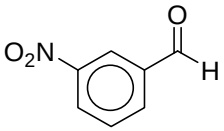
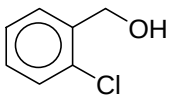
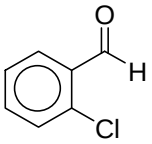
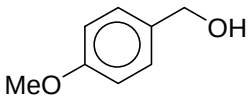
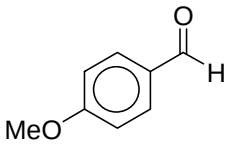
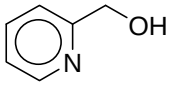
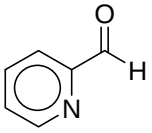
transform aromatic alcohols directly to the corresponding aromatic esters **57** in high yields (**Scheme 47**).



Scheme 47: Reaction conditions: (i) benzyl alcohol (3 mmol), $NaIO_4$ (3 mmol), 2% aq. H_2SO_4 (15 mL), 95 ^oC, 12 h; (ii) benzyl alcohol (3 mmol), $NaIO_4$ (3 mmol), LiBr (3 mmol), H_2SO_4, MeOH (15 mL), 25 ^oC, 18 h.

To study the generality of the reaction, a variety of primary benzylic alcohols were subjected to oxidation with $NaIO_4/H^+$ conditions, and the results are presented in **Table 5**. Among the various solvents screened, H_2O was found to give the best results. However, secondary benzylic alcohols as well as aliphatic alcohols were resistant to oxidation under the reaction conditions. As can be seen, the method worked exceedingly well in the case of aromatic alcohols with electron-withdrawing groups such as halo, nitro, etc. Unfortunately, reaction in the case of benzylic alcohols with electron-donating substitutent as well as aliphatic alcohols did not proceed smoothly. The formation of benzaldehydes **22a-j** was confirmed by ^1H, ^{13}C-NMR and IR spectroscopy. The ^1H NMR spectrum of **22g** showed signals at δ 10.11 (-C**H**O) for aldehydic proton. Its ^{13}C NMR spectrum showed a typical signal at δ 189.64 for the aldehyde carbonyl (-**C**HO) carbon (**Fig. 5**). Its IR spectrum showed a strong band at 1720 cm^{-1} confirming the formation of aldehyde function.

Table 5: Oxidation of Benzylic alcohols to Benzaldehdyes by $NaIO_4$ in acidic medium[a]

Entry	Substrate	Product **22 a-j**	Yield (%)[b]
a			79
b			83
c			80
d			77
e			78
f			67
g			65
h			71
i			21
j			44[c,d]

[a] Reaction conditions: alcohol (3 mmol), $NaIO_4$ (3 mmol), 2% aq H_2SO_4 in water (15 mL), 95 °C, 8 h; [b] Isolated yields after column chromatographic purification; [c] Yield by GC; [d] 2-Pyridinemethanol was employed for oxidation.

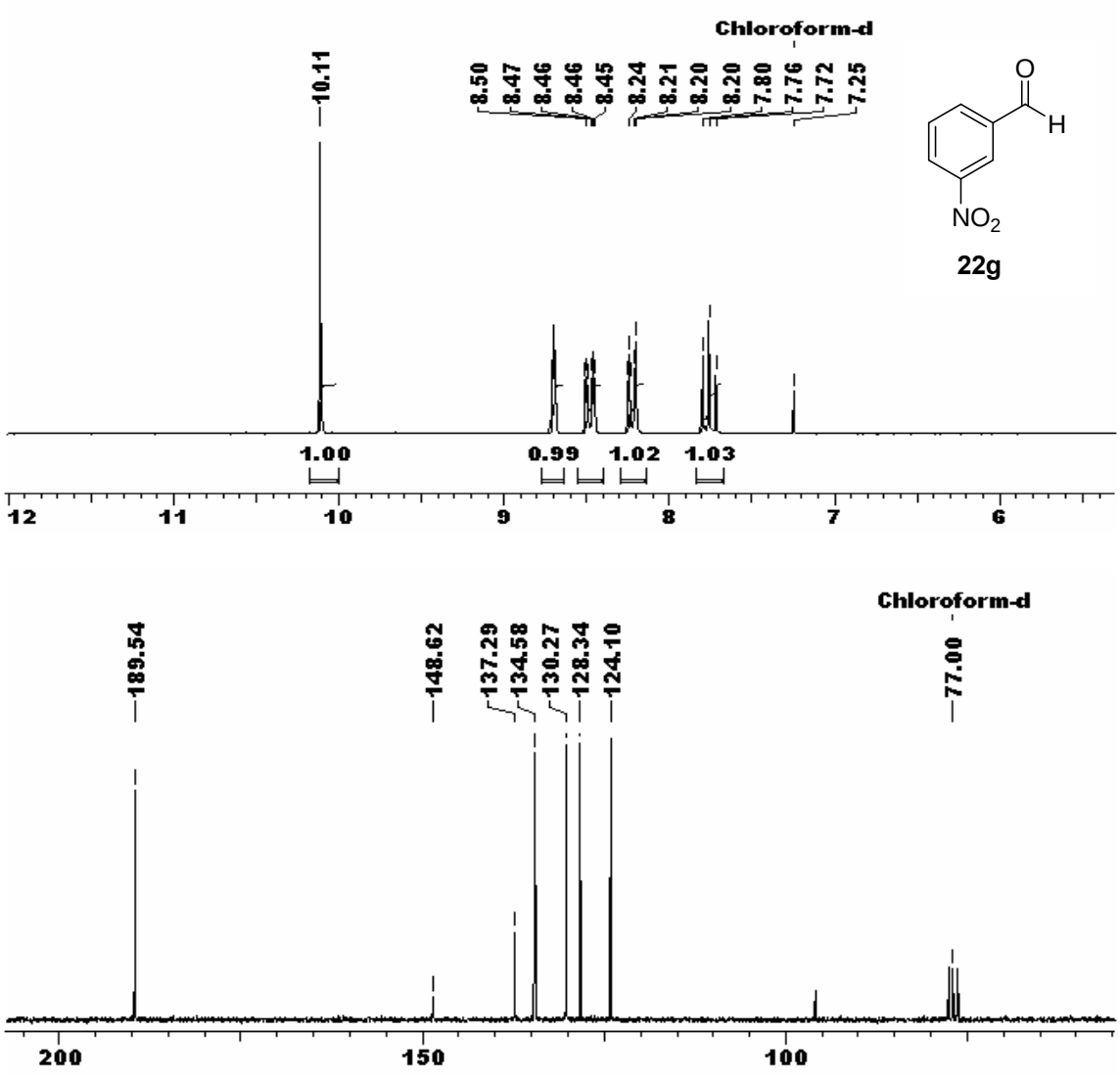
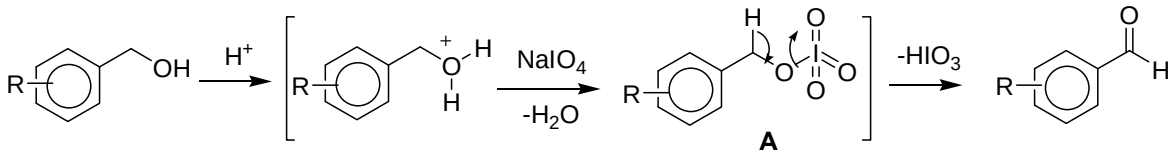


Fig. 5: ^{1}H and ^{13}C NMR spectra of 3-nitrobenzaldehyde (**22g**).

Mechanism

A probable pathway for the oxidation of primary benzylic alcohols to the corresponding aldehydes in the absence of LiBr is shown in (**Scheme 48**). The species **A** formed by

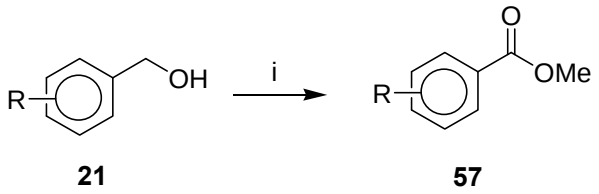
reaction of benzyl alcohol with $NaIO_4$ undergoes oxidation to give benzaldehydes. As further oxidation of aldehydes to acids was not observed, we conclude that $NaIO_4$ was not capable of oxidizing aldehydes to carboxylic acids.



Scheme 48: Possible pathway for the oxidation of alcohol to aldehydes

Direct oxidation of benzylic alcohols to esters

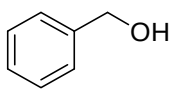
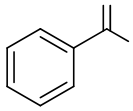
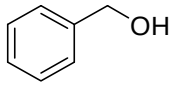
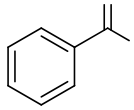
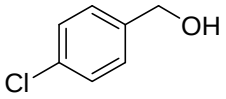
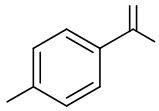
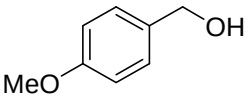
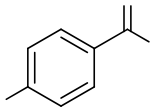
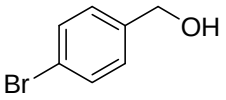
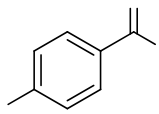
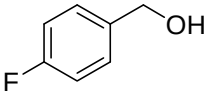
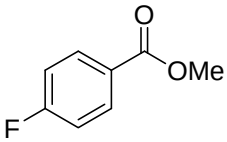
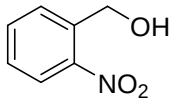
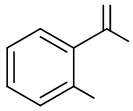
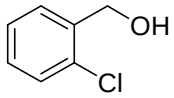
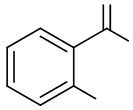
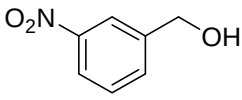
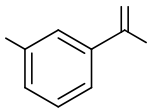
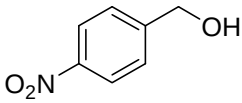
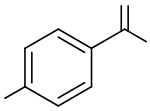
The $NaIO_4$-mediated oxidation of alkylarenes led to high yield preparation of benzoic acids, formed *via* the oxidation of their respective benzyl alcohols and aldehydes when the reaction was carried out in water. In this regard, we envisioned that replacing water with alcohol should result in the formation of esters. During this investigation, we found that $NaIO_4$-LiBr-H^+ combination oxidatively transforms aromatic aldehydes directly to the corresponding aromatic esters in high yields[54] (**Scheme 49**).



Scheme 49: (i) $NaIO_4$ (3 mmol), LiBr (3 mmol), conc. H_2SO_4 (1 mL), MeOH (9 mL), 25 °C, 18 h.

In order to establish the scope of this reaction, a number of aromatic aldehydes were subjected to oxidation and the results are presented in the **Table 6**. As can be seen from **Table 6**, aromatic aldehydes with electron-donating as well as electron-withdrawing

Table 6: Direct conversion of benzylic alcohols to aromatic esters[a]

Entry	Substrate	Product (**57a-j**)	Yield (%)[b]
a			89
b			78[c]
c			86
d			77[d]
e			80
f			73
g			78[e]
h			71[e]
i			73[e]
j			80[e]

[a] Alcohol (3 mmol), $NaIO_4$ (3 mmol), LiBr (3 mmol), conc. H_2SO_4 (1 mL), methanol (9 mL), 25 °C, 18 h; [b] After purification by column chromatography; [c] ethanol was used as the solvent; [d] Yield of the methyl 3-bromo-4-methoxybenzoate when 2 equiv. of LiBr used; [e]

at 65 °C with aq. H_2SO_4 (0.85 N, 1 mL).

substituents on the nucleus underwent oxidative esterification smoothly to give their corresponding aromatic esters in 71-89% yields. In the case of substrates with electron-donating groups, the reaction proceeded at 25 °C while the substrates with electron-withdrawing groups, except 4-chloro aromatics, required higher temperature (65 °C) to achieve excellent conversions. For 4-methoxybenzyl alcohol, the oxidative esterification

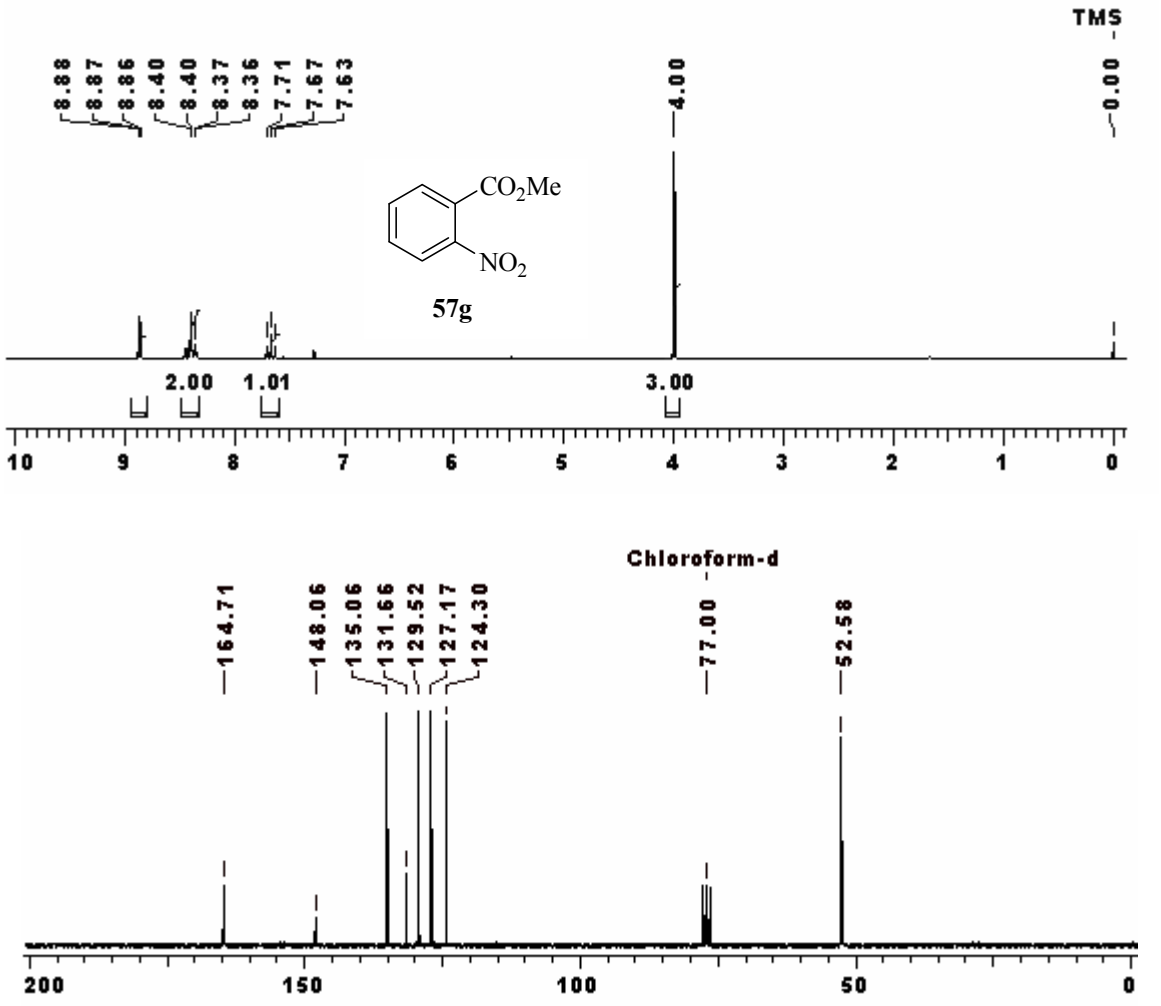
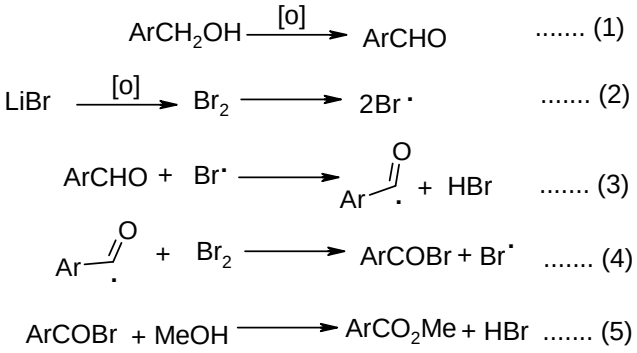


Fig. 6: ^{1}H and ^{13}C NMR spectra of **57g**

occurred along with nuclear bromination when 2 molar equivalents of LiBr was used (entry d). We also observed that use of sub-stoichiometric amount of $NaIO_4$ (25-40 mol%) resulted in poor yields of esters (< 40%). All the aromatic esters synthesized were systematically characterized from IR, ^1H and ^{13}C NMR spectra. For example, the ^1H NMR spectrum of **57g** showed a singlet at δ 4.0 (s) due to methoxyl protons (-$CO_2C\mathbf{H_3}$) of ester moiety. Its ^{13}C NMR spectrum displayed signals at δ 52.5 and 164.7 due to the methoxyl and carbonyl group (-$\mathbf{C}O_2\mathbf{C}H_3$) of ester moiety (**Fig. 6**).

Among the several solvent combinations screened, a mixture of MeOH:H_2SO_4 (9:1, 10 mL) gave the highest yield of esters. Control experiments have shown that both $NaIO_4$ and LiBr are needed to produce esters. Ethanol was also found to give ethyl esters (entry b) while other alcohols such as 2-propanol and benzyl alcohol have failed to give their respective esters probably due to steric hindrance. Aliphatic alcohols or aldehydes were found to be inactive under the reaction conditions, which may be a limitation of this process. Replacing LiBr with other halide sources like tetrabutylammonium bromide or NaBr also brought about this conversion with comparable yield while KI and NaCl failed.



Scheme 50: proposed radical pathway for the direct esterification of aromatic aldehydes and benzylic alcohols.

Based on the observations that no traces of acetal or carboxylic acid was identified in the present study as well as from our earlier work on $NaIO_4$/LiBr mediated reactions,[33] a probable mechanism[46] for the oxidative esterification of aromatic aldehydes and benzylic alcohols has been given in **Scheme 50**. Initially, LiBr is oxidized by $NaIO_4$ in the presence of acetic acid to liberate bromine. Thus, the liberated bromine probably generates bromine radical which then initiates the propagation step by adding to the aldehyde to produce acyl radical. This acyl radical further reacts with bromine to form acylbromide, which upon hydrolysis furnish the corresponding esters.

3.3.5 Conclusion

In conclusion we have developed a new reagent system comprising $NaIO_4$/ LiBr and H_2SO_4 for the direct conversion of aldehydes and alcohols to their corresponding methyl and ethyl esters. The reaction is believed to proceed *via* radical pathway.

3.3.6 Experimental Section

Procedure for the oxidation of primary benzylic alcohols (21a-j)

To a mixture of benzylic alcohols (3 mmol) and $NaIO_4$ (3 mmol) was added 2% aq H_2SO_4 (15 mL). The reaction mixture was heated at 95 °C (using an oil bath) for 12 h. Progress of the reaction was monitored by TLC. The reaction mixture was then cooled to room temperature and extracted with ethyl acetate (40 mL x 3), and the combined organic phase was washed with saturated sodium thiosulfate solution and water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give crude product, which was purified by column chromatography packed with silica gel using *n*-hexane and ethyl acetate (9:1) as eluent to afford pure aldehydes.

Benzaldehyde (22a)

Yield: 79%; colorless liquid; **IR** (neat, cm^{-1}): 3073, 2827, 2745, 1715, 1696, 1012, 720; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.52-7.80 (m, 5H), 9.89 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 128.9, 129.6, 134.3, 136.4, 190.1; **Anal.** Calcd for C_7H_6O: C, 79.22; H, 5.70. Found C, 79.10; H, 5.63%.

4-Bromobenzaldehyde (22b)

Yield: 83%; colorless solid; **mp:** 58-59 ^oC, [lit.[55a] mp: 59-60 ^oC]; **IR** (neat, cm^{-1}): 2910, 2842, 1705, 1600, 1140, 1010, 840, 820; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.67 (d, J = 8.4 Hz, 2H), 7.73 (d, J = 8.4 Hz, 2H), 9.96 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 129.6, 130.8, 132.3, 135.0, 190.8; **Anal.** Calcd for C_7H_5BrO: C, 45.44; H, 2.72; Br, 43.19. Found C, 45.67; H, 2.43; Br, 43.22%.

4-Chlorobenzaldehyde (22c)

Yield: 80%; colorless solid; **mp:** 46-47 ^oC, [lit.[55b] mp: 47 ^oC]; **IR** (neat, cm^{-1}): 3080, 2815, 2720, 1710, 1602, 1389, 1200, 1005, 820; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.51 (d, J = 7.9 Hz, 2H), 7.82 (d, J = 7.5 Hz, 2H), 9.97 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 129.3, 130.8, 137.7, 140.8, 190.6; **Anal.** Calcd for. C_7H_5ClO: C, 59.81; H, 3.59, Cl, 25.22. Found C, 59.90; H, 3.32, Cl, 25.36%.

4-Fluorobenzaldehyde (22d)

Yield: 77%; colorless liquid; **IR** (neat, cm^{-1}): 3060, 2940, 1712, 1600, 1510, 1343, 1140, 750, 715; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.21 (t, J = 8.9 Hz, 2H), 7.87-7.96 (q, J = 5.4 Hz, 2H), 9.96 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 116.1, 116.4, 132.1, 132.3, 133.0, 168.2, 190.3; **Anal.** Calcd for. C_7H_5FO: C, 67.74; H, 4.06. Found C, 67.52; H, 3.99%.

4-Methylbenzaldehyde (22e)

Yield: 78%; colorless liquid; **IR** (neat, cm^{-1}): 2810, 2700, 1705, 1600, 1120, 1110, 720; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.44 (s, 3H), 7.33 (d, *J* = 7.3 Hz, 2H), 7.78 (d, *J* = 7.9 Hz, 2H), 9.96 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.8, 129.6, 129.7, 134.2, 145.4, 191.7; **Anal.** Calcd for. C_8H_8O: C, 79.97; H, 6.71. Found C, 79.45; H, 6.69%.

4-Nitrobenzaldehyde (22f)

Yield: 67%; colorless solid; **mp:** 105-106 ^oC, [lit.[55c] mp: 106 ^oC]; **IR** (neat, cm^{-1}): 2932, 2860, 1706, 1605, 1430, 1320, 1200, 840, 810, 760; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 8.06 (d, *J* = 9.0 Hz, 2H), 8.39 (d, *J* = 7.5 Hz, 2H) 10.15 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 124.2, 130.4, 140.0, 151.1, 190.2; **Anal.** Calcd for. $C_7H_5NO_3$: C, 55.63; H, 3.33; N, 9.27. Found C, 55.58; H, 3.42; N, 9.33%.

3-Nitrobenzaldehyde (22g)

Yield: 65%; colorless solid; **mp:** 58-59 ^oC, [lit.[55d] mp: 58 ^oC]; **IR** (neat, cm^{-1}): 2972, 2952, 1720, 1610, 1445, 1225, 820, 745, 637; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.76 (t, *J* = 7.9 Hz, 1H), 8.20-8.25 (td, *J* = 1.3, 7.6 Hz, 1H), 8.45-8.51 (dddd, *J* = 1.3 Hz, 1H), 8.70 (t, *J* = 1.7 Hz, 1H), 10.11 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 124.1, 128.3, 130.2, 134.5, 137.2, 148.6, 189.5; **Anal.** Calcd for. $C_7H_5NO_3$: C, 55.63; H, 3.33; N, 9.27. Found C, 55.59; H, 3.42; N, 9.41%.

2-Chlorobenzaldehyde (22h)

Yield: 71%; colorless liquid; **IR** (neat, cm^{-1}): 3060, 2820, 2720, 1710, 1602, 1389, 1200, 1015, 826; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.45-7.68 (m, 3H), 7.80 (d, *J* = 8.2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 127.2, 129.3, 130.5, 132.5, 135.0, 137.8, 189.5; **Anal.** Calcd for. C_7H_7ClO: C, 59.81; H, 3.59; Cl, 25.22. Found C, 59.79; H, 3.60; Cl, 25.41%.

4-Methoxybenzaldehyde (22i)

Yield: 21%; colorless liquid; **IR** (neat, cm^{-1}): 2860, 2752,1715, 1610, 1500, 1250, 1120, 1005, 812; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.92 (s, 3H), 6.96 (d, *J* = 5.2 Hz, 2H), 7.80 (d, *J* = 5.5 Hz, 1H), 9.96 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 124.3, 128.5, 130.3, 134.6, 137.4, 148.7, 189.6; **Anal.** Calcd for. $C_8H_8O_2$: C, 70.57; H, 5.92. Found C, 70.60; H, 5.88%.

Typical experimental procedure (57a-j)

To a 50 mL round bottom flask charged with aromatic aldehyde (3 mmol), lithium bromide (3 mmol) sodium metaperiodate (3 mmol), conc. H_2SO_4 (1 mL) in methanol (9 mL) was added at 25 ^oC. The reaction mixture was stirred for 18 h and then excess solvent was removed under reduced pressure. The residue was extracted with ethyl acetate, and the organic phase was washed with water, saturated $Na_2S_2O_3$, brine and dried over anhyd. Na_2SO_4. Concentration of the organic layer gave crude ester, which was subjected to column chromatographic purification using hexane/ethyl acetate (19:1) as eluent to obtain pure aromatic esters.

Methyl benzoate (57a)

Yield: 98%; colorless liquid; **IR** (neat, cm^{-1}): 715, 750, 1140, 134, 1510, 1600, 1732, 2940, 3060; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.87 (s, 3H), 7.38 (t, *J* = 6.2 Hz, 2H), 7.52 (m, 1H), 8.03 (d, *J* = 8.1 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 51.2, 128.3, 129.2, 130.7, 133.1, 148.1, 165.6; **Anal.** Calcd for $C_8H_8O_2$: C, 70.57; H, 5.92. Found C, 70.52; H, 5.97%.

Ethyl benzoate (57b)

Yield: 82%; colorless liquid; **IR** (neat, cm^{-1}): 715, 755, 1040, 1314, 1520, 1600, 1730, 2942, 3055; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.31 (t, *J* = 8.5 Hz, 3H), 4.13 (q, *J* = 7.5 Hz), 7.32-7.42 (t, *J* = 6.5 Hz, 2H), 7.53 (m, 1H), 8.03 (d, *J* = 7.2 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ

14.1, 60.7, 128.1, 128.9, 129.5, 133.3, 166.4; **Anal.** Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 71.52; H, 6.57%.

Methyl 4-chlorobenzoate (57c)

Yield: 91%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): 1127, 1265, 1146, 1510, 1510, 1733, 2304, 2971, 3049; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.89 (s, 3H), 7.83 (d, *J* = 8.6 Hz, 2H), 7.94 (d, *J* = 8.6 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 51.9, 128.6, 129.5, 130.9, 139.2, 165.6; **Anal.** Calcd. for $C_8H_7ClO_2$: C, 56.32; H, 4.14. Found: C, 56.28; H, 4.19%.

Methyl 4-methoxybenzoate (57d)

Yield: 85%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): 1145, 133, 1510, 1603, 1723, 2940, 3060; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.86 (s, 3H), 3.88 (s, 3H), 6.91 (d, *J* =10.2 Hz , 2H), 8.01 (d, *J* = 10.3 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 51.7, 55.3, 113.5, 122.4, 131.5, 163.2, 189.5; **Anal.** Calcd for. $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 65.12; H, 6.01%.

Methyl 4-bromobenzoate (57e)

Yield: 87%; colorless liquid; **IR** (Neat, cm^{-1}): 712, 1236, 1413, 1651, 1739, 2118, 2876, 3062; **^{1}H NMR** (200 MHz, $CDCl_3$,): δ 3.91 (s, 3H), 7.57 (d, *J*= 8.6 Hz, 2H), 7.89 (d, *J* =8.6 Hz, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$,): δ 52.1, 127.9, 129.0, 131.0, 131.6, 165.9; **Anal.** Calcd for. $C_8H_7BrO_2$: C, 44.68; H, 3.28; Found C, 44.62; H, 3.24%.

Methyl 4-fluorobenzoate (57f)

Yield: 80%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): 720, 937, 1172, 1270, 1431, 1619, 1737, 2989, 3079; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.91 (s, 3H), 7.09 (d, *J* = 8.1 Hz, 2H), 8.07 (d, *J* = 8.1 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 52.1, 116.2, 129.8, 131.7, 165.2, 163.9; **Anal.** Calcd for. $C_8H_7FO_2$: C, 62.34; H, 4.58. Found: C,62.39; H, 4.55%.

Methyl 2-nitrobenzoate (57g)

Yield: 78%; yellow colored liquid; **IR** ($CHCl_3$, cm^{-1}): 715, 750, 1140, 134, 1510, 1600, 1732, 2940, 3060; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 4.0 (s, 3H), 7.66 (t, *J* = 8.2 Hz, 1H), 8.40-8.43 (m, 2H), 8.87 (d, *J* = 2.1 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 52.6, 124.3, 127.2, 129.52, 131.7, 135.1, 148.1, 164.7; **Anal.** Calcd for $C_8H_7NO_4$: C, 53.04; H, 3.89; N, 7.73. Found: C, 53.03; H, 3.93; N, 7.78%.

Methyl 3-nitrobenzoate (57i)

Yield: 79%; yellow solid; **mp:** 78-79 ^oC, [lit.[55e] mp: 78 ^oC]; **IR** ($CHCl_3$, cm^{-1}): 715, 750, 1140, 134, 1510, 1600, 1735, 2940, 3060; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.85 (s, 3H), 7.52 (t, *J* = 8.6 Hz, 1H), 8.19-8.30 (m, 2H), 8.75 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 52.3, 124.3, 127.7, 129.7, 129.9, 131.9, 133.1, 164.9; **Anal.** Calcd for. $C_8H_7NO_4$: C, 53.04; H, 3.89; N, 7.73. Found: C, 53.03; H, 3.93; N, 7.78%.

Methyl 4-nitrobenzoate (57j)

Yield: 82%; yellow colored solid; **mp:** 95-96 ^oC, [lit.[55e] mp: 96 ^oC]; **IR** ($CHCl_3$, cm^{-1}): 1112, 1253, 1440, 1612, 1728, 3038; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.97 (s, 3H), 8.16-8.30 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 52.5, 123.4, 130.6, 135.4, 150.8, 164.8; **Anal.** Calcd for. $C_8H_7NO_4$: C, 53.04; H, 3.89; N, 7.73; Found: C, 53.09; H, 3.83; N, 7.71%.

3.3.7 References

1. (a) Shilov, A. E.; Shul_pin, G. B. *Chem. Rev*. **1997**, *97*, 2879; (b) Hill, C. L. *Activation and Functionalization of Alkanes*; John Wiley: New York, **1989**; (c) Crabtree, R. H. *J. Chem. Soc., Dalton Trans.* **2001**, 2437; (d) Schreiner, P. R.; Fokin, A. A. *Chem. Rec*. **2004**, *3*, 247; (e) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507.
2. (a) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res*. **2001**, *34*, 633; (b) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev*. **2002**, *102*, 1731.
3. Bryant, D. R.; McKeon, J. E.; Ream, B. C. *Tetrahedron Lett*. **1968**, *30*, 3371.

4. Bryant, D. R.; McKeon, J. E.; Ream, B. C. *J. Org. Chem*. **1968**, *33*, 4123.
5. Bergman, J.; Engman, L. *Tetrahedron Lett*. **1978**, *35*, 3279.
6. Bergman, J.; Engman, L. *J. Org. Chem*. **1982**, *47*, 5191.
7. Hendriks, C. F.; Beek, H. C. A.; Heertjes, P. M. *Ind. Eng. Chem. Prod. Res. Dev*. **1978**, *17*, 256.
8. Okada, T.; Kamya, Y. *Bull. Chem. Soc. Jpn*. **1981**, *54*, 2724.
9. Ebitani, K.; Choi, K-M.; Mizugaki, T.; Kaneda, K, *Langmuir*, **2002**, *18*, 1849.
10. Benhmid, A.; Narayana, K. V.; Martin, A.; Lucke, B.; *Chem. Commun*. **2004**, 2118.
11. Dewkar, G. K.; Narina, S. V.; Sudalai, A. *Org. Lett*. **2003**, *5*, 4501–4504.
12. Shaikh, T. M.; Sudalai, A. *Tetrahedron Lett*. **2005**, *46*, 5589.
13. (b) Cainelli, G.; Cardillo, G. *Chromium Oxidations in organic Chemistry*; Springer: Berlin, **1984;** (c) Hudlicky, M. *Oxidations in Organic Chemistry*; American Chemical Society: Washington, DC, **1990**.
14. (a) Comprehensive Organic Synthesis; Trost, B. M., Ed.; Pergamon: New York, **1991**; Vol. 7.; (b) Hudlicky, M. Oxidations in Organic Chemistry, ACS Monograph 186; American Chemical Society: Washington, DC, **1990**; (c) Handbook of Reagents for Organic Synthesis: Oxidizing and Reducing Agents; Burke, S. D., Danheiser, R. L., Eds.; John Wiley and Sons: Chichester, UK, **1999**.
15. Friedman, L.; Fishel, D. L.; Shechter, H. *J. Am. Chem. Soc*. **1965**, *30*, 1453.
16. Sam, D. J.; Simmons, H. E. *J. Am. Chem. Soc*. **1972**, 4024.
17. Sasson, Y.; Zappi, G. D.; Neumann, R. *J. Org. Chem*. **1986**, *51*, 2880.
18. Santamaria, J.; Jroundi, R.; Riguady, J. *Tetrahedron Lett*. **1989**, *30*, 4677.
19. Shi, M.; Feng, Y-S. *J. Org. Chem*. **2001**, *66*, 3235.
20. Remias, J. E.; Sen, A. 2003, *J. Mol. Cat*. A. **2003**, *201*, 63-70.
21. Paul, S.; Nanda, P.; Gupta, R. *Synlett*. **2004**, 531.
22. Gupta, M.; Paul, S.; Gupta, R.; Loupy, R. *Tetrahedron Lett*. **2005**, *46*, 4957.
23. Saha, B.; Espenson, J. H. *J. Mol. Catal.* A: **2005**, *241*, 33-38.
24. Bonvin, Y.; Callens, E.; Larrosa, I.; Henderson, D. A.; Oldham, J.; Burton, A. J.; Barrett, A. G. M. *Org. Lett*. **2005**, *7*, 4549.
25. Shaikh, T. M.; Emmanuvel, L.; Sudalai, A. *J. Org. Chem*. **2006**, *71*, 5043.
26. (a) Mestres, R.; Palenzuela, J. *Green Chem.* **2002**, *4*, 314; (b) Amati, A.; Dosualdo, G.; Zhao, L.; Bravo, A.; Fontana, F.; Minisci, F.; Bjorsvik, H. R. *Org. Process Res. Dev.* **1998**, *2*, 261.
27. (a) *Dictionary of Organic Compounds*. *vol. 2*, 936; (b) *Dictionary of Organic Compounds*. *vol. 2*, 1289; (c) *Dictionary of Organic Compounds*. *vol. 5*, 4758; (d) *Dictionary of Organic Compounds*. *vol. 2*, 1161; (e) *Dictionary of Organic Compounds*. *vol. 3*, 2022; (f) *Dictionary of Organic Compounds*. *vol. 3*, 2021; (g) *Dictionary of Organic Compounds*. *vol. 1*, 781; (h) *Dictionary of Organic Compounds*. *vol. 4*, 3173.
28. (a) Hill, C. L. *Advances in Oxygenated Processes*; Baumstark, A. L., Ed.; JAI Press: London, **1988**; Vol. 1, p 1.
29. (a) Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc*. **1968**, *90*, 5616; (b) Sundararaman,

P. Walker, E. C.; Djerassi, C. *Tetrahedron Lett*. **1978**, *19*, 1627; (c) Garegg, P. J.; Olcson, L.; Oscarson, S. *J. Org. Chem.* **1995**, *60*, 2200; (d) Ogawa, T.; Matsui, M. *J. Am. Chem. Soc*. **1976**, *98*, 1629.

30. Harfenist, M.; Bavley, A.; Lazier, W. A. *J. Org. Chem*. **1956**, 1608.
31. Corey, E. J.; Kim, C. U. *J. Am. Chem. Soc*. **1972**, 7586.
32. Corey, E. J.; Suggs, W. *Tetrahedron Lett*. **1975**, *31*, 2647.
33. Blair, L. K.; Baldwin, J.; Smith, W. C. *J. Org. Chem*. **1977**, *42*, 1816.
34. Omura, K.; Swern, D. *Tetrahedron*, **1978**, *34*, 1651.
35. Dess, D. B.; Martin, J. C.; *J. Org. Chem*. **1983**, *48*, 4156.
36. Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc. Chem. Commun*. **1987**, 1625.
37. Einhorn, J.; Einhorn, C.; Ratajczak ,F.; Pierre, J-L. *J. Org. Chem*. **1996**, *61*, 7452.
38. Zondervan, C.; Hage, R.; Feringa, B. L. *Chem. Commun*. **1997**, 419.
39. Meciarova, M.; Toma, S.; Heribanova, A. *Tetrahedron Lett*. **2000**, *56*, 8561.
40. Yamaguchi, K.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc*. **2000**, *122*, 7144.
41. Nicolaou, K. C.; Baran, P. S.; Zhong, Y-L. *J. Am Chem. Soc*. **2001**, *123*, 3183.
42. Yamaguchi, K.; Mizuno, M. *New. J. Chem*. **2002**, *26*, 972.
43. Muldoon, J.; Brown, S. N. *Org. Lett*. **2002**, *4*, 1043.
44. Zhan, B-Z.; White, M. A.; Sham, T-K.; Pincock, J. A.; Doucet, R. J.; Rao, K. V. R.; Robertson, K. N.; Cameron, T. S. *J. Am. Chem. Soc*. **2003**, *125*, 2195.
45. Xu, L.; Trudell, M. L. *Tetrahedron Lett*. **2003**, *44*, 2553.
46. Velusamy, S.; Punniyamurthy, T. *Org. Lett*. **2004**, *6*, 217.
47. Gogoi, P.; Sarmah, G. K.; Konwar, D. *J. Org. Chem*. **2004**, *69*, 5153.
48. Jiang, N.; Ragauskas, A. J. *Org. Lett*. **2005**, *7*, 3689.
49. (a) Kageyama, T.; Kawahara, S.; Kitamura, K.; Ueno, Y.; Okawara, M. *Chem. Lett*. **1983**, 1097; (b) Tamaru, Y.; Yamada, Y.; Inou, K.; Yamamoto, Y.; Yoshida, Z-I. *J. Org. Chem*. **1983**, *43*, 1286.
50. McDonald, C. E.; Nice, L. E.; Shaw, A. W.; Nestor, N. B. *Tetrahedron Lett*. **1993**, *34*, 2741.
51. Takase, K.; Masuda, H.; Kai, O.; Nishiyama, Y.; Sakaguchi, S.; Ishii, Y. *Chem. Lett*. **1995**, 871.
52. Rankin, K. N.; Liu, K.; Hendry, J.; Yee, H.; Noureldin, N. A.; Lee, D. G. *Tetrahedron Lett*. **1998**, *39*, 1095.
53. Schulze, A.; Pagona, G.; Giannis, A. *Synth. Commun*. **2005**, 1147.
54. Shaikh, T. M.; Emmanuvel, L.; Sudalai, A. *Synth. Commun*. **2007**, *37*, 2641.
55. (a) *Dictionary of Organic Compounds*. *vol. 2*, 930; (b) ibid. *vol. 2*, 1282; (c) *vol. 5*, 4749; (d) *vol. 5*, 4448; (e) *vol. 5*, 4758;

CHAPTER IV

Heterogeneous Catalysts for Oxidative Transformation of C-H, C-O and C=C Bonds

Section I

WO_3-Catalyzed Selective Oxidation of Alkylarenes and Arylketones: High Yield Preparation of Benzoic acids

4.1.1 Introduction

The name benzoic acid originates from benzoin, a balsamic resin obtained from a South Asian plant called styrax. The extraction of benzoic acid was carried out by Scheele in 1775 and its structure was determined by Liebig and Wohler in 1832. The initial production methods were developed in the late 1800s. They were based on the hydrolysis of benzotrichloride or the decarboxylation of phthalic anhydride. Also, a variety of substituted benzoic acids are widely used in the pharmaceutical industry as drug intermediates for the synthesis of antirheumatics, antimalarials, tranquilizers etc., in agrochemicals as herbicides and in polymer and dye-stuff industries as modifiers for resins and dye sensitizer respectively.[1]

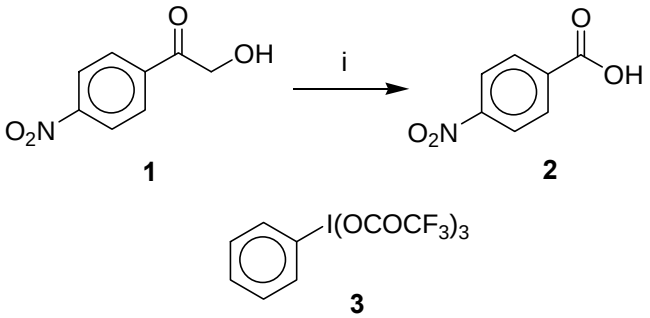
The oxidation of benzylic C–H bonds to the corresponding oxy-functionalized products constitutes one of the most fundamental transformations in organic synthesis.[2] The conventional method for the preparation of carboxylic acid involves oxidation of alcohols or aldehydes catalyzed by either acid or toxic metals. However, stoichiometric use of metallic oxidants generally cause problems associated with either environmental pollution or difficult separation of the metal reagent from the products. In contrast, the direct method of conversion of methylarens or aryl ketones to carboxylic acids holds promise in organic synthesis.

4.1.2 Review of Literature

Literature survey revealed that there are various methods available for the direct transformation of methylarenes into the corresponding carboxylic acids, which has been discussed under section II of Chapter 3. Direct transformation of methylarenes into the corresponding benzoic acids has been achieved using a variety of oxometal oxidants[3] such as $KMnO_4$, $Na_2Cr_2O_7$, CrO_3, CeO_2, TiO_2 or $NaIO_4$ in stoichiometric amounts and $Co(OAc)_2$,[4] Cu–Fe,[5] ZnO,[6] $MnCO_3$,[7] $AlBr_3$,[8] $FeCl_3$[9] and more recently $Ni^{II}(TPA)$,[10] $RuCl_3$,[11] CuCl,[12] and Bi[13] salts in catalytic amounts. Among non-oxometal oxidants, urea hydrogen peroxide, HNO_3, HBr, and CBr_4–PPh_3 are commonly used.[14] Some of the recent developments on oxidation of aryl ketones to carboxylic acids are discussed below.[15-19]

Moriarty's approach (1987)[15]

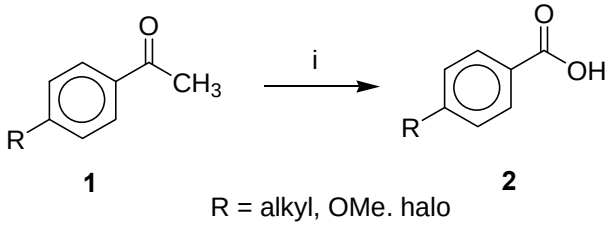
Moriarty *et al*. have reported a method for the oxidative cleavage of acetophenones, α-hydroxyacetophenones, deoxybenzoin, benzoin, and benzil using catalytic amount of hypervalent iodo compound **3** in wet benzene at room temperature to give the corresponding benzoic acids. Also, the method has been demonstrated for the oxidative cleavage of cyclohexanone and dimedone to give adipic acid and 3,3-dimethylglutaric acid respectively (**Scheme 1**).



Scheme 1: (i) cat. **3**, benzene, water, 90%.

Sudalai's approach (1999)[16]

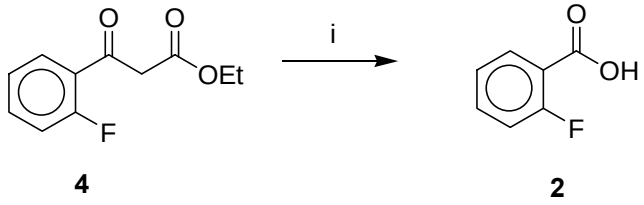
Our group has reported a mild and efficient catalytic method for the C-C bond cleavage of aryl ketones to the corresponding carboxylic acids in good yields using a catalytic amount of Re_2O_7 in presence of 70% *tert*-butyl hydroperoxide (TBHP) as oxidant. The method showed excellent yields for electron-donating substrates (**Scheme 2**).



Scheme 2: Re_2O_7 (6 mol%), TBHP (8equiv.), AcOH, 100 ^oC, 5 h, 25-72%.

Ashford's approach (2001)[17]

Ashford *et al*. have developed a novel method for converting methyl aryl ketones to the corresponding carboxylic acids using oxone® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) in presence of acetone:H_2O. The protocol demonstrates for the oxidative cleavage of 1,3-dicarbonyl compounds and α-hydroxy ketones in excellent yields (**Scheme 3**).

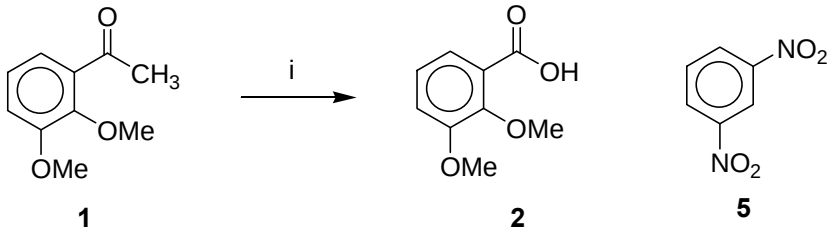


Scheme 3: (i) Oxone®, $NaHCO_3$, acetone+H_2O, 97%.

Bjorsvik's approach (2004)[18]

Bjorsvik *et al*. have reported a new catalytic oxidation method for the preparation of aromatic carboxylic acids from methyl aryl ketones using *m*-dinitrobenzene **5** as catalyst. The method is an alternative to the haloform reaction. The novel features of this protocol

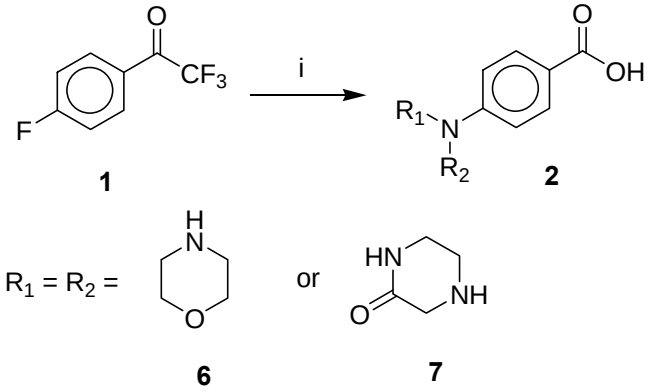
are: (i) no any harmful side products; (ii) use of green oxidants ($Na_2CO_3.1.5\ H_2O_2$) (**Scheme 4**).



Scheme 4: (i) cat. **5**, t-BuOH, K^{t}OBu, $Na_2CO_3 \cdot 1.5\ H_2O_2$, 80 ^oC, 5 h, 73%.

Shinozuka's approach (2006)[19]

Shinozuka *et al*. have described an efficient and practical method for the preparation of 4-amino-substituted benzoic acids in high yields in two steps. The method consists of the aromatic substitution of fluoro with amines **6** or **7**, followed by simultaneous basic hydrolysis to give benzoic acids **2** (**Scheme 5**).



Scheme 5: **6** or **7**, Et_3N, DMSO, 100 ^oC; (ii) NaOH, DMF, H_2O, 100 ^oC, 99%.

4.1.3 Present Work

4.1.3.1 Objective

Although there are many methods available in the literature for oxidation of alkyl arenes, several of them suffer from certain drawbacks like low yields, cumbersome experimental procedures, use of expensive air and moisture sensitive or highly toxic catalysts. Moreover, many of these procedures often require an excess of reagents, long reaction times, expensive heavy metal salts and ionic liquids. Little information is available on the oxidative cleavage of aryl ketones. Hence, there arises a necessity to develop an efficient procedure for the oxidation of methylarenes or aryl ketones to the corresponding benzoic acids, which are industrially useful chemicals.

4.1.4 Results and Discussion

4.1.4.1 Oxidation of methylarenes

Table 1 shows the results of WO_3-catalyzed oxidation of 4-bromotoluene as a model substrate to the corresponding 4-bromobenzoic acid with 70% TBHP as oxidant in the presence of NaOH as additive. When 70% TBHP (1 equiv.) and 40% NaOH (8 equiv.) was used, the corresponding 4-bromobenzoic acid was obtained only in 27% yield. A larger amount of TBHP (4 equiv.) resulted in an improved yield up to 36%. When the reaction was performed with an even larger concentration of TBHP (8 equiv.) and WO_3 (5 mol%), 4-bromobenzoic acid was obtained in moderate yield (42 %). Also, when the quantity of NaOH was reduced to 9 or 15 mmol, the product was obtained in 15 or 57% yield, respectively. Thus, optimal reaction conditions comprised WO_3 (20 mol%), 70% TBHP (8 equiv.), and 40% NaOH (8 equiv.) as additive. This gave 4-bromobenzoic acid in 89% isolated yield. The use of other tungsten-based catalysts like Na_2WO_4 and H_2WO_4

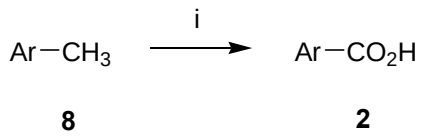
gave poor yields of the product (<15%). Also, the reaction failed when H_2O_2 (aq. 30% or 50%) was used as the oxidant. Control experiments showed that, in the absence of NaOH, no reaction took place.

Table 1: WO_3-catalyzed oxidation of 4-bromotoluene to 4-bromobenzoic acid.[(a)]

Entry	**WO_3** [mol%]	**70% TBHP** [mmol]	**40% NaOH** [mmol]	**Yield[(b)]** [%]
1	20	3	24	27
2	20	12	24	36
3	5	24	15	42
4	20	24	9	15
5	20	24	15	57
6	**20**	**24**	**24**	**89**

Reaction condition: (a) (i) 4-bromotoluene (3 mmol), WO_3, 70% TBHP, 40% NaOH, 80 °C, 10 h; (ii) acidified with 6 N HCl. (b) Isolated yield and product was characterized by m.p. and ^1H and ^{13}C NMR spectroscopy.

For understanding the scope and generality of this oxidation method, several methylarenes were subjected to oxidation (**Scheme 6**) under the optimized conditions, and the results are presented in **Table 2**. Alkylarenes with electron-withdrawing as well as electron-donating substituents underwent oxidation readily to produce the corresponding benzoic acids in excellent yields. It is noteworthy that for substrates with polymethyl groups, one of the methyl groups is selectively oxidized to give monocarboxylic acid (**Table 2**, entries d and i). However, α-picoline failed to undergo oxidation under the reaction conditions.



Scheme 6: (i) (a) methylarene (3 mmol), WO_3 (20 mol-%), 70% TBHP (24 mmol), 40% NaOH (24 mmol), 80 °C, 10 h; (b) acidified with 6 N HCl.

Table 2: WO_3-catalyzed oxidation of methylarenes to benzoic acids with 70% TBHP.[(a)]

Entry	Ar-CH_3 (8)	Ar-CO_2H (2), Yield[(b)] %
a	C_6H_5	85
b	4-Br-C_6H_4	89
c	4-Cl-C_6H_4	84
d	4-Me-C_6H_4	78
e	2-Me-C_6H_4	71
f	4-OMe-C_6H_4	85
g	4-*t*Bu-C_6H_4	74
h	4-NO_2-C_6H_4	93
i	3,5-Me_2-C_6H_3	72
j	2,3-Cl_2-C_6H_3	75
k	2,4-Cl_2-C_6H_3	83
l	3,4-Cl_2-C_6H_3	80
m	2-methylnaphthalene	70

(a) (i) methylarene (3 mmol), WO_3 (20 mol%), 70% TBHP (3 mL, 24 mmol), 40% NaOH (24 mmol), 80 °C, 10 h; (ii) acidified with 6 N HCl. (b) Isolated yields and products were characterized by m.p. and ^1H and ^{13}C NMR spectroscopy.

The formation of carboxylic acids **2** was confirmed by ^1H, ^{13}C NMR and IR spectroscopy. For example, the ^1H NMR spectrum of **2j** showed signals at δ 7.56 (t, J = 8.0 Hz, 1H), 7.88 (dd, J = 1.6, 8.0 Hz, 1H), 7.98 (dd, J = 1.6, 8.0 Hz, 1H) for aromatic

protons. Its ^{13}C NMR spectrum showed a typical signal at δ 165.4 for carbonyl carbon of carboxylic acid (-$\mathbf{C}O_2H$-) (**Fig. 1**). Its IR spectrum showed a broad stretching vibration 1700 cm^{-1} due to the presence of carboxylic acid functional group.

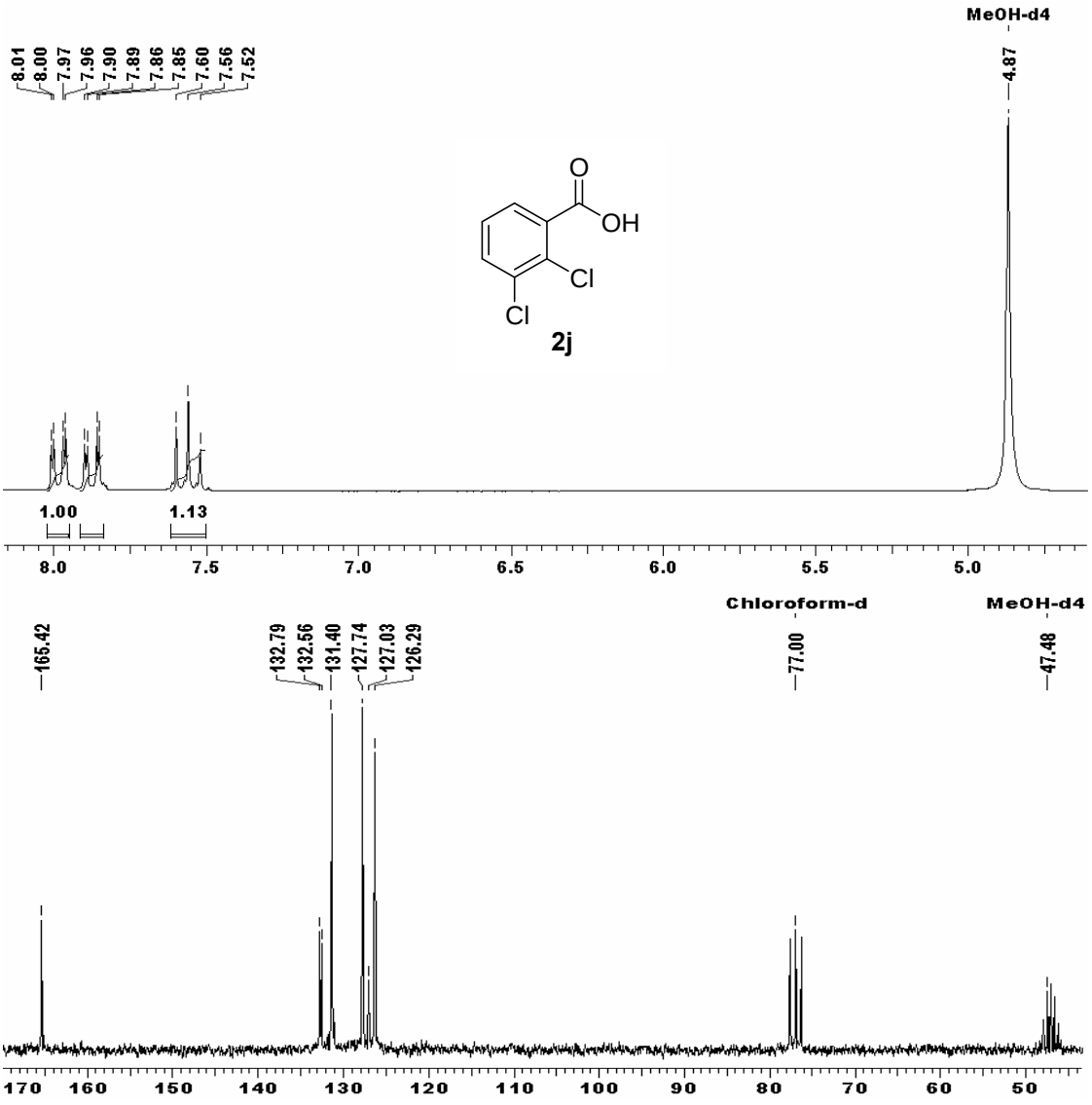
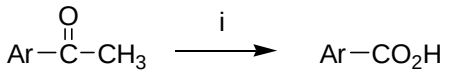


Fig. 1: ^{1}H and ^{13}C NMR spectra of 2,3-dhichlorobenzoic acid **(8j)**

4.1.4.2 Oxidation of aromatic ketones

When we extended the present methodology to aryl ketones, we observed that the corresponding benzoic acids (**Scheme 7**) were formed in high yields, and the results are

presented in **Table 3**. Thus, acetophenone underwent oxidative cleavage with WO_3 (10 mol-%) and 70% TBHP (4 equiv.) and 40% NaOH as additive to give benzoic acid in 89% yield. The reaction was found to be general with other acetophenones as well. When 4-methylacetophenone was subjected to oxidation, *p*-toluic acid was obtained selectively in 83% yield, whereas propiophenone gave benzoic acid in 95% yield (Table 3, entry 3).



1 **2**

Scheme 7: (i) (a) WO_3 (10 mol-%), 70% TBHP (12 mmol), 40% NaOH (12 mmol), 80 °C, 8 h; (b) acidified with 6 N HCl.

Table 3: WO_3-catalyzed oxidative C–C bond cleavage of alkyl aryl ketones.[(a)]

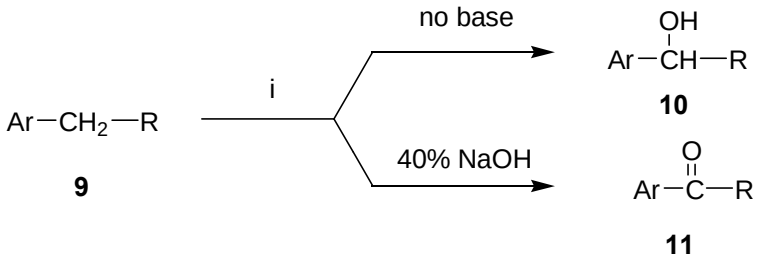
Entry	Alkyl aryl ketones 1	Benzoic acids 2	Yield[(b)] (%)
1	acetophenone	benzoic acid	89
2	4-methylacetophenone	*p*-toluic acid	83
3	Propiophenone	benzoic acid	95
4	4-bromoacetophenone	4-bromobenzoic acid	95
5	2,4-dichloroacetophenone	2,4-dichlorobenzoic acid	92
6	4-nitroacetophenone	4-nitrobenzoic acid	84
7	4-methoxyacetophenone	4-methoxybenzoic acid	85
8	4-fluoroacetophenone	4-fluorobenzoic acid	93
9	4-chloroacetophenone	4-chlorobenzoic acid	94

(a) (i) alkyl aryl ketone (3 mmol), WO_3 (10 mol%), 70% TBHP (1.5 mL, 12 mmol), 40% NaOH (12 mmol), 80 °C, 8 h; (ii) acidified with 6 N HCl. (b) Isolated yields and products were characterized by m.p. and ^1H and ^{13}C NMR spectroscopy.

Upon oxidation, acetophenones with both electron-withdrawing and electron-donating substituents gave the corresponding benzoic acids in high yields. The halo-substituted acetophenones also underwent facile oxidation to give the benzoic acids in high yields.

4.1.4.3 Oxidation of Alkylarenes

Interestingly, alkylarenes when subjected to oxidation with WO_3 (20 mol%) and 70% TBHP (2 equiv.), *in the absence of base*, exhibited an unusual product selectivity (**Scheme 8**).



Scheme 8: (i) (a) WO_3 (20 mol-%), alkyl arenes (3 mmol), 70% TBHP (6 mmol), 80 °C, 12 h.

Table 4: The effect of base in WO_3-catalyzed benzylic C–H oxidation.[(a)]

Entry	Substrate (9)	Yield[b] %	
		alcohol[c] (10)	ketone[d] (11)
1	ethyl benzene	35	48
2	4-bromoethyl benzene	35	40
3	indane	43	58
4	tetraline	40	51
5	fluorene	48	55

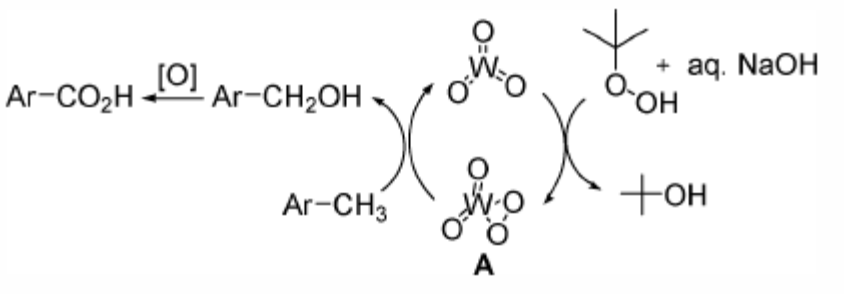
(a) alkylarene (3 mmol), WO_3 (20 mol%), 70% TBHP (6 mmol), 80 °C, 12 h. (b) Isolated yield and products were characterized by m.p. and ^1H and ^{13}C NMR spectroscopy. (c) No base was added. (d) 40% NaOH (0.6 mL) was used.

For example, ethylbenzene on oxidation with the WO_3/TBHP combination gave either acetophenone **11** or benzylic secondary alcohol **10** in moderate yields (48 and 35%,

respectively) depending upon whether NaOH was used or not; the remaining substance was unreacted ethylbenzene. Other alkyl arenes such as indane, tetraline, fluorene, and so on have exhibited similar behavior in terms of product selectivities as well as yields (**Table 4**).

4.1.5 Mechanism

The catalytic cycle for the oxidative process is shown in **Scheme 9**. In the case of methylarenes and aryl ketones, it was observed that no oxidation took place in the absence of base. However, upon the addition of NaOH, WO_3 became homogeneous and readily reacted with TBHP to produce a metal peroxo species, **A**; the evidence for its formation came from its typical IR absorption bands at 495, 640, and 950 cm^{-1}.[20] The metal peroxo species **A** then probably undergoes C–H insertion at benzylic C–H bond of alkylarenes to give the benzylic alcohols. Although none of the benzylic alcohols were isolated during the oxidative process, its formation as an intermediate has been suggested, as 4-nitrobenzyl alcohol when subjected to oxidation [WO_3 (20 mol%), 70% TBHP (8 molar equiv.), no base] gave 4-nitrobenzoic acid (57 %). For aryl ketones, it is established[21] that formation of α-hydroxyacetophenones followed by its facile oxidative cleavage gave benzoic acids.



Scheme 9: Plausible mechanism for WO_3-catalyzed benzylic C–H oxidation of methylarenes.

4.1.6 Conclusion

We have developed a new catalytic method consisting of WO_3/TBHP/NaOH for the oxidation of methyl arenes and alkyl aryl ketones to the corresponding benzoic acids in high yields. Oxidation of alkylarenes to the corresponding secondary alcohols or ketones is dependent upon whether we use alkali or not. In the present protocol benzoic acids were isolated in pure form without the need for column chromatographic purification.

4.1.7 Experimental section

Spectral data: *vide infra* of section II of the Chapter-3 for spectral details.

Typical procedure for oxidation of methylarenes:

To a mixture of toluene (3 mmol), WO_3 (20 mol%), and TBHP (70%, 24 mmol) was added NaOH (40% in water, 24 mmol, 2.4 mL). The reaction mixture was then heated at 80 °C (using oil bath) for 10 h, cooled to room temperature, and acidified by using ice-cold HCl (6 N). The mixture was extracted with ethyl acetate (3 x 40 mL), and the combined organic phase was washed with saturated brine solution, dried with anhyd. Na_2SO_4, and concentrated under reduced pressure to give pure benzoic acid.

General procedure for oxidation aryl alkyl ketones:

To a mixture of aryl alkyl ketone (3 mmol), WO_3 (10 mol%), and TBHP (70%, 12 mmol) was added NaOH (40% in water, 12 mmol, 1.2 mL). The reaction mixture was then heated at 80 °C (using oil bath) for 8 h, cooled to room temperature, and acidified by using ice-cold HCl (6 N). It was extracted with ethyl acetate (3 x 40 mL), and the combined organic phase was washed with saturated brine solution, dried with anhyd. Na_2SO_4, and concentrated under reduced pressure to give pure benzoic acid.

General procedure for oxidation of alkylarenes:

To a mixture of alkylarenes (3 mmol) and WO_3 (20 mol%), was added TBHP (70%, 6 mmol). The reaction mixture was then heated at 80 °C (using oil bath) for 12 h. Progress of the reaction was monitored by TLC. The reaction mixture was then cooled to room temperature and extracted with ethyl acetate (3 x 20 mL), and the combined organic phase was washed with saturated brine solution, dried with anhyd. Na_2SO_4, and concentrated under reduced pressure to give the crude product, which was purified by column chromatography packed with silica gel (*n*-hexane/ethyl acetate, 9:1) to afford pure secondary benzylic alcohol.

Procedure for oxidation of alkylarenes to benzylic secondary ketones:

Alkylarenes were subjected to oxidation as mentioned above with NaOH (40% in water, 0.6 mL, 6 mmol with respect to substrate) to give benzylic secondary ketones.

Section II

Titanium superoxide: a heterogeneous catalyst for *anti*-Markovnikov aminobromination of olefins

4.2.1 Introduction

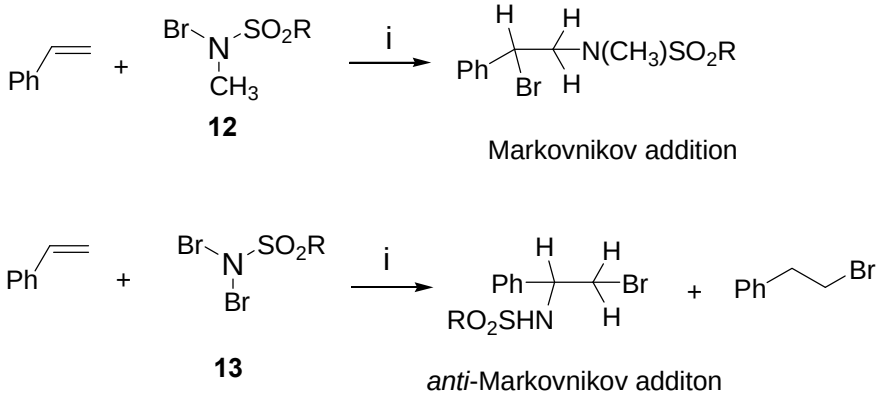
The fuctionalization of olefins by the addition of two different functional groups in a single step provides access to wide range of functional group manipulation in organic synthesis. Variety of reactions such as aminohydroxylation, halohydration, haloazidation, azidohydroxylation and haloamination are some of the examples of this kind of synthetic transformation. The vicinal haloamine functionality presents a very useful structural moiety in synthetic organic chemistry as the halo functionality can be replaced by a variety of nucleophiles such as azido (N_3), cyano (CN), acetate (OAc), alkoxy (OR), amino (NHR), thio (SR), *etc*. thereby providing a new class of functionalized reactive intermediates in organic synthesis. On treatment with base the vicinal haloamines can be converted to the corresponding aziridines, which are important building blocks in organic synthesis. Thus, the vicinal haloamines represents a very useful class of compounds in organic synthesis.[22]

4.2.2 Review of Literature

Literature search revealed that even though the initial work has been started in the late thirties, the progress on direct haloamination of olefins has been quite tardy. Most of these methods, which involve use of *N,N*-dihalo sulfonamides or carbamates as halogen and amine sources, are described below.

Kharasch's approach (1939)[23]

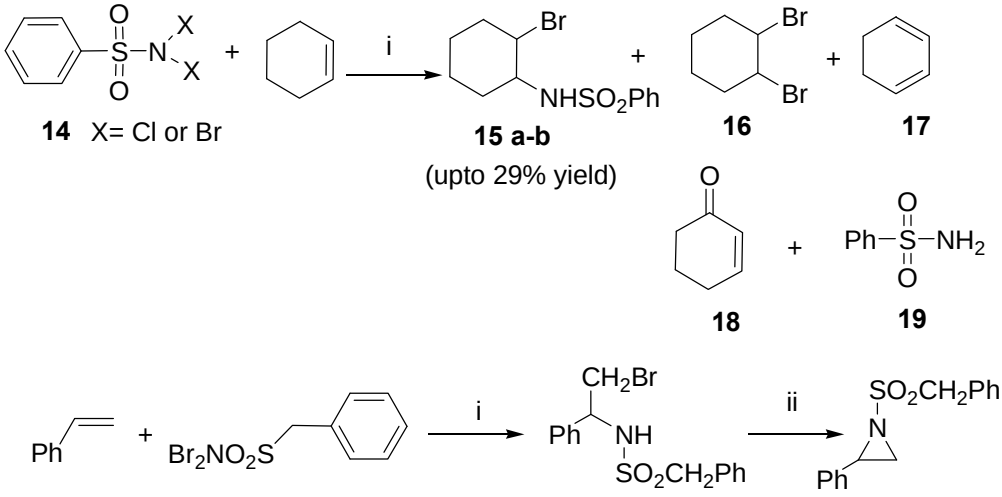
Kharasch *et al*. have studied the addition of sulfonamides **12** and **13** to styrene to give the corresponding bromoamine (**Scheme 10**).



Scheme 10: (i) 25 °C, stirring.

Terauchi's approach (1967)[24]

Terauchi *et al*. have studied the reaction between *N,N*-dihalosulfonamide with cyclohexene and styrene; cyclohexene gave many addition products such as *cis* and *trans*-2-halo-1- benzenesulfonamidocyclohexanes **15a** and **b**,

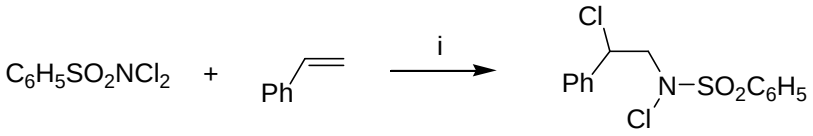


Scheme 11: (i) reflux 10 min. then 50 °C for 30 min; (ii) 5% NaOH.

trans-1,2-dihalocyclohexane (**16**), 1,3-cyclohexadiene (**17**), 1-cyclohexene-3-one (**18**) and benzene sulfonamide (**19**) (**Scheme 11**).

Danither's approach (1968)[25]

In this approach, the addition of *N,N*-dichlorosulfonamides to olefins and conjugated dienes has been examined. The reaction of these reagents with propylene and styrene gave high yields of *N*-chloro-*N*-(*β*-chloroalkyl)sulfonamides **20** which have predominantly *anti*-Markovnikov orientation (**Scheme 12**).



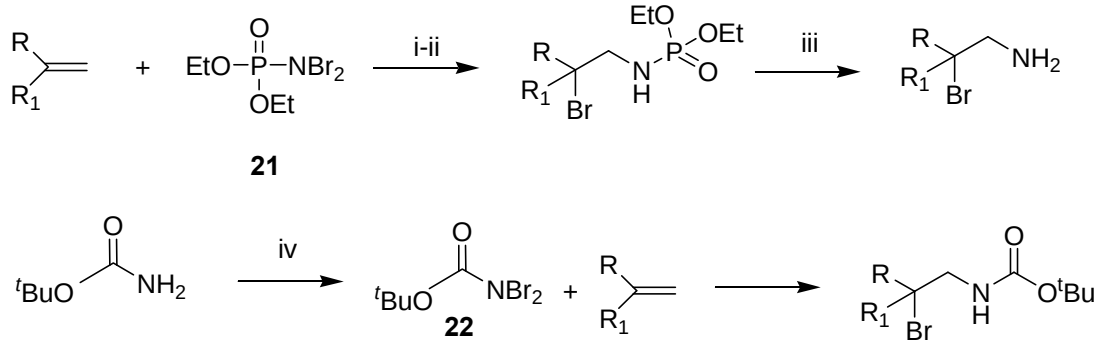
20

yield = 85%

Scheme 12: (i) CH_2Cl_2, 0 - 25 °C

Zwierzak's approach (1981)[26]

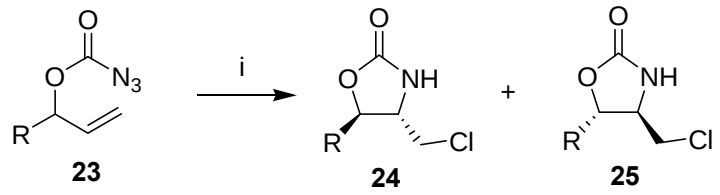
Diethyl *N,N*-dibromophosphoramidate (DBPA, **21**) and *t*-butyl *N,N*-dibromocarbamate (**22**), prepared from *t*-butyl carbamate, was added to phenyl ethylenes and terminal olefins to give *N*-bromo adducts, which were reduced *in situ* ($NaHSO_3$) to give diethyl-*N*-(*β*-bromoalkyl)phosphoramidates and β-bromo-*N*-Boc-amines respectively (**Scheme 13**). The addition followed *anti*-Markovnikov fashion.



Scheme 13: (i) CH_2Cl_2, reflux; (ii) 12% aq. Na_2SO_3, 5-10 °C; (iii) HCl, benzene; (iv) Br_2 (2 equiv.), K_2CO_3, H_2O, 25 °C; (v) CH_2Cl_2, reflux.

Bach's approach (2000)[27]

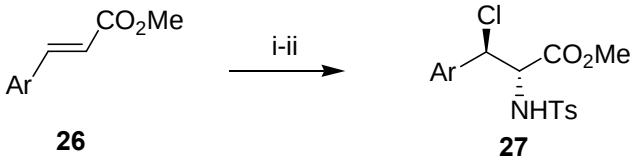
2-Alkenyloxycarbonyl azides **23** underwent an efficient intermolecular aminochlorination with TMSCl catalyzed by $FeCl_2$ to furnish the corresponding 4-(chloromethyl)-oxazolidinones **24-25** in 60-84% yield (**Scheme 14**).



Scheme 14: (i) $FeCl_2$, TMSCl, EtOH, 0 °C to 25 °C.

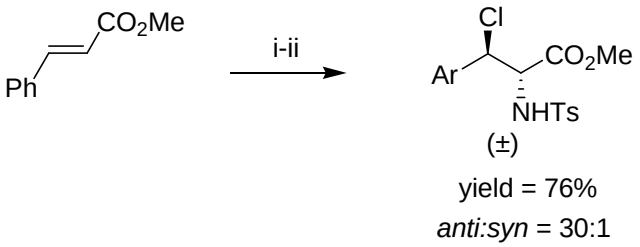
Li's approach (2001)[28]

Recently, Cu or Zn-catalyzed aminochlorination of cinnamic esters **26** has been developed producing vicinal haloamine derivatives **27** in 52-85% yields and >95% regio- and stereoselectivities.[28a] *N,N*-dichloro-*p*-toluenesulfonamide was used as chlorine as well as nitrogen source (**Scheme 15**).



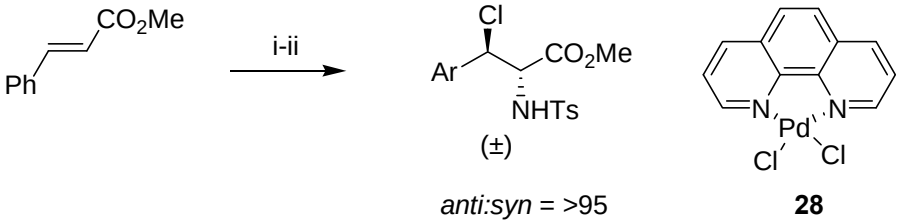
Scheme 15: (i) $TsNCl_2$, 4 Å MS, CuOTf or $ZnCl_2$ (8 mol%), CH_3CN, 25 °C; (ii) Na_2SO_3.

Same authors have developed a new regio- and stereoselective aminohalogenation of cinnamic esters using the combination of 2-$NsNCl_2$/2-NsNHNa (Ns= nitrobenzenesulfonyl) as the nitrogen and chlorine sources respectively and CuOTf as catalyst (**Scheme 16**).[28b]



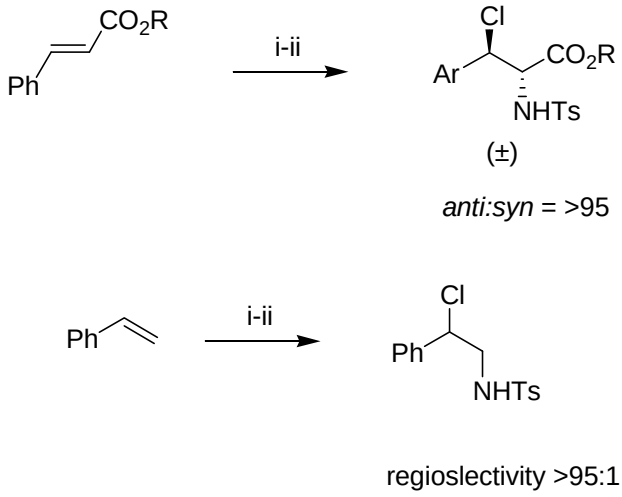
Scheme 16: (i) 2-$NsNCl_2$/2-NsNHNa, CuOTf (10 mol%), CH_3CN, 25 °C; (ii) aq. Na_2SO_3.

Li *et al*.[28c] have used Pd-complex **28** for aminohalogenation of cinnamic esters has been developed using *p*-$TsNCl_2$ as the nitrogen and chlorine sources (**Scheme 17**).



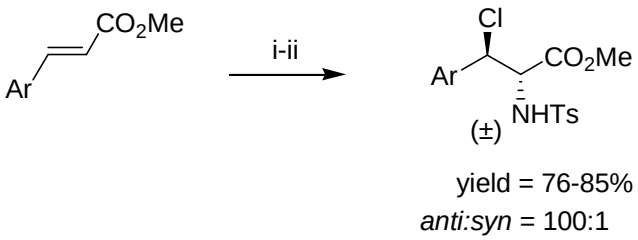
Scheme 17: (i) $TsNCl_2$, Pd-catalyst **14** (8 mol%), CH_3CN; (ii) aq. Na_2SO_3.

N-Chloro-*N*-sodium-sulfonamide was found to react with olefins in the presence of copper catalyst to give vicinal haloamine derivative. (**Scheme 18**).[28d]



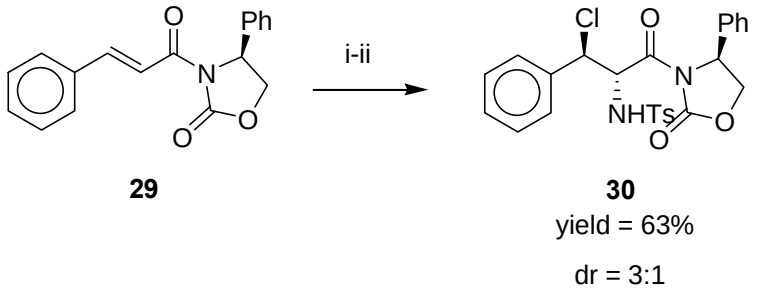
Scheme 18: (i) *o*-NsNClNa, CuOTf (10 mol%), CH_3CN; (ii) aq. Na_2SO_3.

Li *et al*.[28e] have also used ionic liquid butylmethylimidazolium tetrafluoroborate [bmim][BF_4] to reduce the amount of catalyst loading (6 mol% of CuOTf) and enhance the rate of the aminohalogenation of cinnamic esters using *p*-$TsNCl_2$ as the nitrogen and chlorine sources (**Scheme 19**).



Scheme 19: (i) $TsNCl_2$, CuOTf (6 mol%), [Bmim][BF_4], CH_3CN, 25 °C; (ii) aq. Na_2SO_3.

Li *et al*.[28f] have also developed the asymmetric aminohalogentation of chiral α,β-unsaturated *N*-acyl 4-alkyloxazolidinones **29** using $TsNCl_2$ and CuOTf as the catalyst in ionic liquid [bmim][BF_4] to give the corresponding chiral aminohalogens **30** in up to 72% yield and 75% diastereomeric ratio (**Scheme 20**).



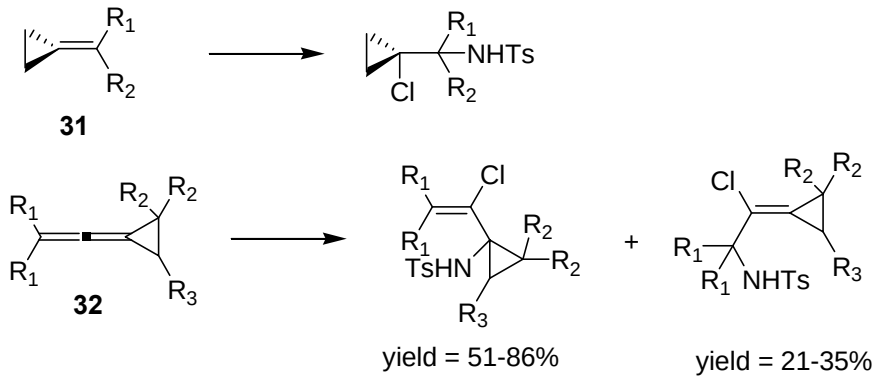
29 **30**

yield = 63%

dr = 3:1

Scheme 20: (i) 4 Å MS, CuOTf (8 mol%), $TsNCl_2$, [Bmim][BF_4]; (ii) Na_2SO_3 (aq.)

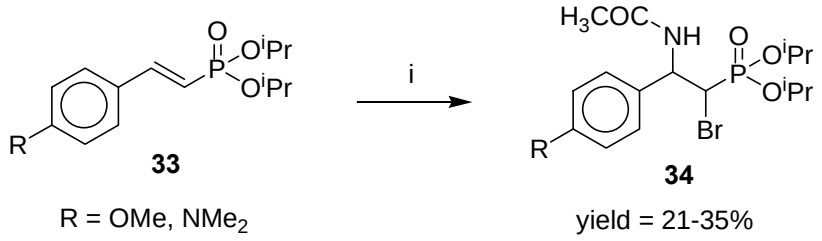
The same group has developed the aminochlorination of arylmethylene cyclopropanes and arylvinylidine cyclopropanes using $FeCl_3$ as the catalyst and $TsNCl_2$ as the nitrogen and chlorine sources (**Scheme 21**).[28g]



Scheme 21: (i) $TsNCl_2$, $FeCl_3$ (20 mol%), CH_3CN, 25 °C; (ii) $TsNCl_2$, $FeCl_3$ (20 mol%), CH_3CN, -15 °C

Yoon's approach (2003)[29]

Yoon *et al.* have developed *syn*-β-amino-α-bromination of unsaturated phosphonates **33** under typical Sharpless asymmetric aminohydroxylation conditions using Os-catalyst, $(DHQD)_2$-PHAL as the ligand and excess *N*-bromoacetamide (**Scheme 22**).

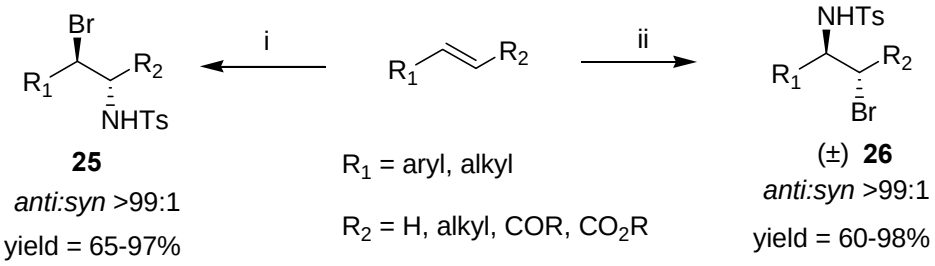


Scheme 22: (i) $BrNHCOCH_3$, 4 % $K_2OsO_2(OH)_4$, 5 % $(DHQD)_2$-PHAL, LiOH, CH_3CN-H_2O, 0– 4 °C

Sudalai's approach (2003)[30]

Our group has reported recently a new synthetic procedure for aminohalogenation of olefins for the preparation of vicinal haloamine derivatives in high yields **25** and **26** by using Cu, Mn, or V catalysts with *p*-toluenesulfonamide ($TsNH_2$) and *N*-bromosuccinimide (NBS) as nitrogen and bromine sources respectively. Unprecedented

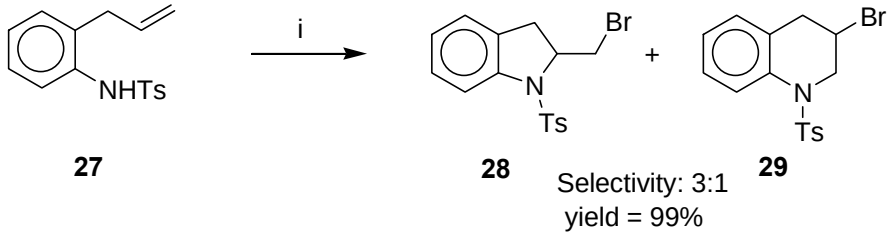
regio- and stereoselectivity (*anti:syn* > 99:1) towards the aminohalogenation process was observed for olefinic substrates as well as for transition metal catalysts (**Scheme 23**).



Scheme 23: (i) $TsNH_2$, NBS, Mn(II) salen, CH_2Cl_2, 25 ^oC; (ii) $TsNH_2$, NBS, CuI, $MnSO_4$ or V_2O_5, CH_2Cl_2, 25 ^oC.

Chemler's approach (2004)[31]

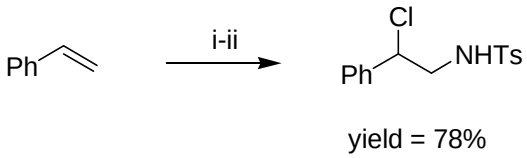
Intramolecular aminobromination of olefins **27** catalyzed by palladium(II) salts using copper (II) halides as the halogen source has been reported (**Scheme 24**).



Scheme 24: (i) $Pd(OCOCF_3)_2$ (10 mol%), $CuBr_2$, K_2CO_3, THF, 0 - 25 °C

Minakata's approach (2006)[32]

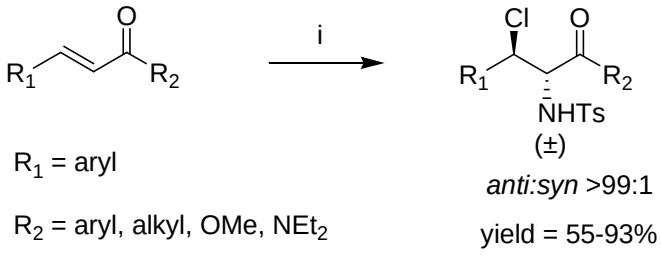
In this method, a new synthetic procedure for the aminochlorination of olefins for the synthesis of vicinal chloroamine derivatives using a combination of chloramine-T and carbon dioxide (10 atm.) is described (**Scheme 25**).



Scheme 25: (i) TsN(Cl)Na, CO (10 atm.), PhH, 25 °C; (ii) Na_2SO_3 (aq.)

Wang's approach (2007)[33]

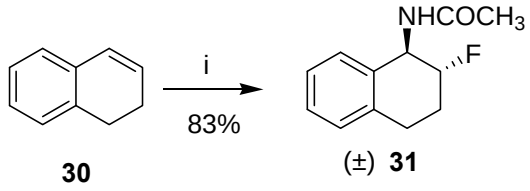
Wang *et al.* have developed a practical and scaleable route for the regio- and diastereoselective synthesis of vicinal chloramines from electron-deficient olefins and Chloramine-T promoted by Bronsted acids in water. The novel features of this protocol: the use of water as a solvent, reaction conditions are mild, ecofriendly, and broadly applicable for the aminochlorination of various electron-deficient olefins including α,β-unsaturated ketones, cinnamates, and amides (**Scheme 26**).



Scheme 26: (i) H_2SO_4, triethylbenzylammonium chloride, H_2O, 25 °C

Yadav's approach (2009)[34]

A variety of alkenes are converted into the corresponding α-fluoroamides in high yields by selectfluor™ in the presence of 10 mol % of InF_3 in nitrile solvent. While α -bromoamides are obtained with NBS in the presence of 10 mol% of $InBr_3$ under similar conditions (**Scheme 27**).



Scheme 27: InF_3, selectfluor™, CH_3CN, 25 °C.

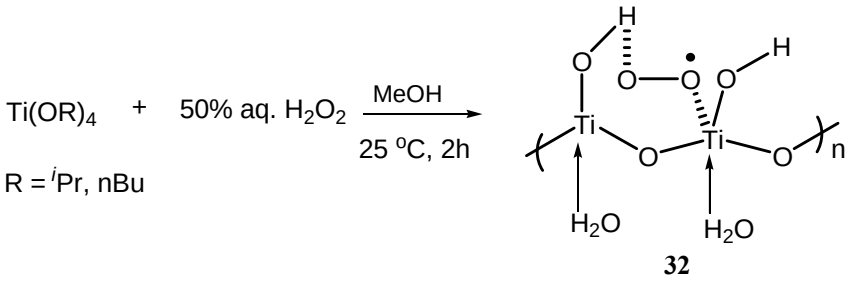
4.2.3 Present Work

4.2.3.1 Objective

Although there are many direct methods available in the literature for haloamination of olefins, they suffer from certain drawbacks like low yields, multi-step reaction sequences, cumbersome experimental procedures and the use of *N,N*-dihalo sulfonamides or carbamates as the nitrogen as well as bromine sources. Our aim was to develop a catalytic, mild and efficient method for the aminobromination of olefins using a heterogeneous catalyst and *N*-bromosuccinnimide (NBS) and *p*-toluenesulfanamide ($TsNH_2$) as the bromo and amine sources respectively.

4.2.4 Results and discussion

Recently, in our laboratory, we have reported the preparation of titanium superoxide (**32**) by treating H_2O_2 with titanium tetraisopropoxide ($Ti(O^iPr)_4$ in dry methanol.[35] Titanium superoxide was filtered as a yellow-colored solid and its structure was proposed to have polymeric Ti oxide matrix as shown in **Fig. 2**.



32

Fig. 2: Preparation of titanium superoxide

We have thoroughly characterized the generation of superoxide species **32** on the hydrated titanium matrix by various spectroscopic techniques such as FTIR, Raman spectroscopy, XRD, ESR, TG/DTA, and chemical analysis as follows. Its IR spectrum showed characteristic absorption bands at 3720 (w), 3665 (w), and 3450 (s) cm^{-1}

indicating the presence of vibrational modes of coordinated water molecules at Ti^{4+} site and of surface Ti-OH groups. The other IR absorption bands at 1027 (s) and 1157 (m) indicate the presence of superoxide radical ion in the solid material. It also has IR absorption bands in the range of 900-538 (m) cm^{-1} corresponding to the presence of Ti-O-Ti linkages. An intense line at 900 cm^{-1} in the Raman spectrum of the catalyst **32** further confirmed the presence of Ti-O-Ti linkages. The other weak Raman lines observed in the range of 1025-1119 cm^{-1} has been assigned for the $O_2^{\cdot}$ species.

A sample of **32** dried at 25 ^oC (3 mm Hg) showed characteristic ESR signals at g_1 = 2.024, g_2 = 2.009 and g_3 = 2.003 (**Fig. 3**), which strongly suggest the presence of unpaired electrons of the stable superoxide radical anion generated by the decomposition of H_2O_2 over Ti-matrix. However, the characteristic ESR signals disappeared when its ESR was recorded at 90 ^oC.

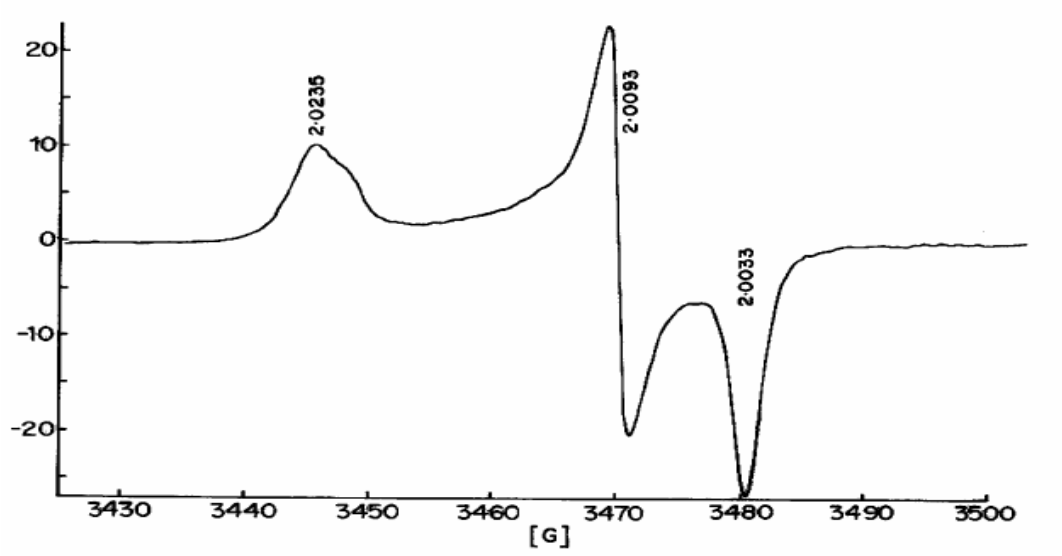
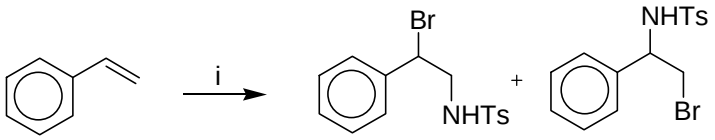


Fig. 3: ESR spectrum of titanium superoxide **32** at 298 K.

During the course of our study on further application of titanium superoxide in organic synthesis,[35] we have now found that olefins can be regiospecifically aminobrominated using *p*-$TsNH_2$ and NBS as nitrogen and bromine sources under ambient conditions. For instance, when styrene **33** was subjected to bromoamination, the corresponding *anti*-Markovnikov product, **25,** was formed in 81% yield; whereas the commercially available TiO_2, under similar conditions, gave the expected Markovnikov product, **26** in 30% yield (**Scheme 28**).



33 **25** **26**

TiO_2	--	30%
titanium superoxide	81%	--

Scheme 28: titanium catalyst (10 wt%), *p*-$TsNH_2$ (1.1 equiv.), NBS (1 equiv.), CH_2Cl_2, 25 ^oC, 14h.

Encouraged by this result, it was of interest to screen several other titanium salts such as titanium silicalite (a zeolite), $TiCl_4$ and titanium isopropoxide under similar reaction conditions; the results of which are presented in **Table 5**. Remarkably, titanium superoxide gave the *anti*-Markovnikov product **25** in 81% yield whereas all other titanium salts furnished the expected Markovnikov product, **26** with low yields.

Among several solvents screened, CH_2Cl_2 was found to be more suitable for titanium superoxide- catalyzed aminobromination of olefins. Thus, the optimal condition for the aminobromination of olefins turned out to be: olefin (3 mmol), *p*-$TsNH_2$ (3.3 mmol), NBS (3 mmol) and titanium superoxide (10 wt %) in CH_2Cl_2 at ambient conditions.

Table 5: Titanium-catalyzed regiospecific aminobromination of styrene[a]

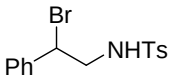
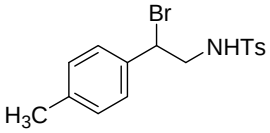
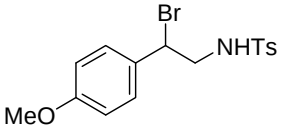
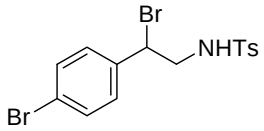
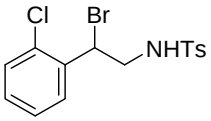
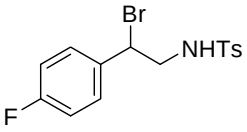
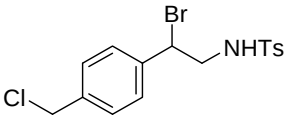
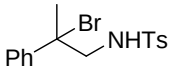
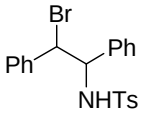
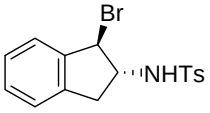
No.	Catalyst	Solvent	Yield (%)[b]	
			25	**26**
1	no catalyst	CH_2Cl_2	-	17
2	TiO_2	CH_2Cl_2	-	38
3	titanium silicate	CH_2Cl_2	-	23
4	$Ti(O^iPr)_4$	CH_2Cl_2	-	24
5	titanium superoxide	CH_2Cl_2	81	-
6	titanium superoxide	$CHCl_3$	61	-
7	titanium superoxide	EDC	58	-

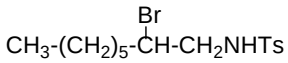
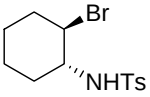
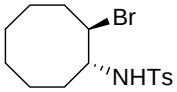
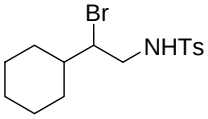
Reaction conditions: [a]olefin (3 mmol), *p*-$TsNH_2$ (3.3 mmol), *N*-bromosuccinimide (3 mmol), titanium catalyst (10 wt%), CH_2Cl_2 (20 mL), 25 ^oC, 14 h;
[b]isolated yield after chromatographic purification.

In order to establish its scope, various olefins were subjected to aminobromination; the results of which are presented in **Table 6**. It is evident that several styrenic substrates including indene underwent the aminobromination regiospecifically to produce the corresponding *anti*-Markovnikov products. No trace of Markovnikov products was, however, observed in the crude product sample (as confirmed by ^1H and ^{13}C NMR and GC analysis). Interestingly, electron-rich olefins gave relatively higher yields of products as compared to electron-deficient olefins. This may be ascribed to the benzylic radical, which abruptly increases its reactivity, thereby resulting in high yields of the aminobrominated product. Also aliphatic olefins underwent aminobromination smoothly to give 1, 2-bromoamines in good yields. After the reaction was complete, solid titanium superoxide was recovered by simple filtration, which on subsequent reuse with styrene as

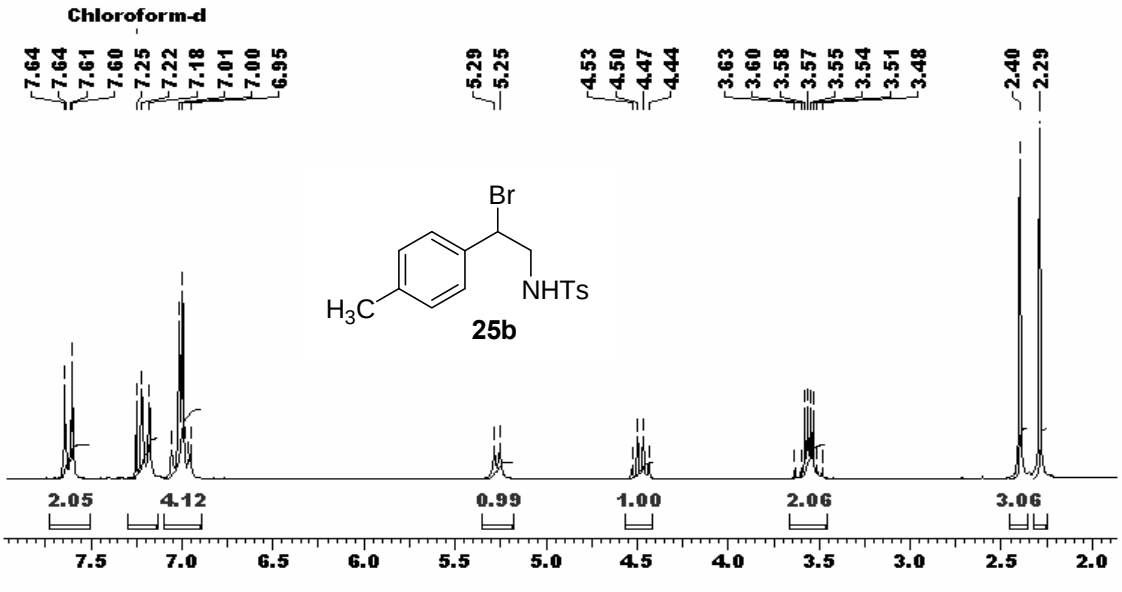
substrate was found to catalyze the aminobromination process with moderate yield (58%). Notably, substrates like indene, cyclohexene and cyclooctene gave the corresponding aminobrominated products with high *anti*-selectivity > 99:1 (**Table 6**, entries j, l & m).

Table 6: Titanium superoxide-catalyzed aminobromination of olefins[a]

No	Substrate	Product[b]	Yield (%)[c]	*anti : syn*
a	styrene		81 (58)[d]	
b	4-methylstyrene		86	
c	4-methoxystyrene		67	
d	4-bromostyrene		69	
e	2-chlorostyrene		68	
f	4-fluorostyrene		78	
g	4-chloromethylstyrene		67	
h	α-methylstyrene		30	
i	*trans*-stilbene		61	
j	indene		80	>99 : 1

k	1-octene		66	
l	cyclohexene		65	>99 : 1
m	cyclooctene		72	>99 : 1
n	vinylcyclohexane		63	

Reaction conditions: [a] olefin (3 mmol), *p*-$TsNH_2$ (3.3 mmol), *N*-bromosuccinimide (3 mmol), titanium superoxide (10 wt%), CH_2Cl_2 (20 mL), 25 ^oC, 14 h;
[b] products were characterized by m.p., IR, ^1H and ^{13}C NMR and elemental analysis;
[c] isolated yield after chromatographic purification;
[d] Yield in parenthesis refers to use of recovered catalyst.



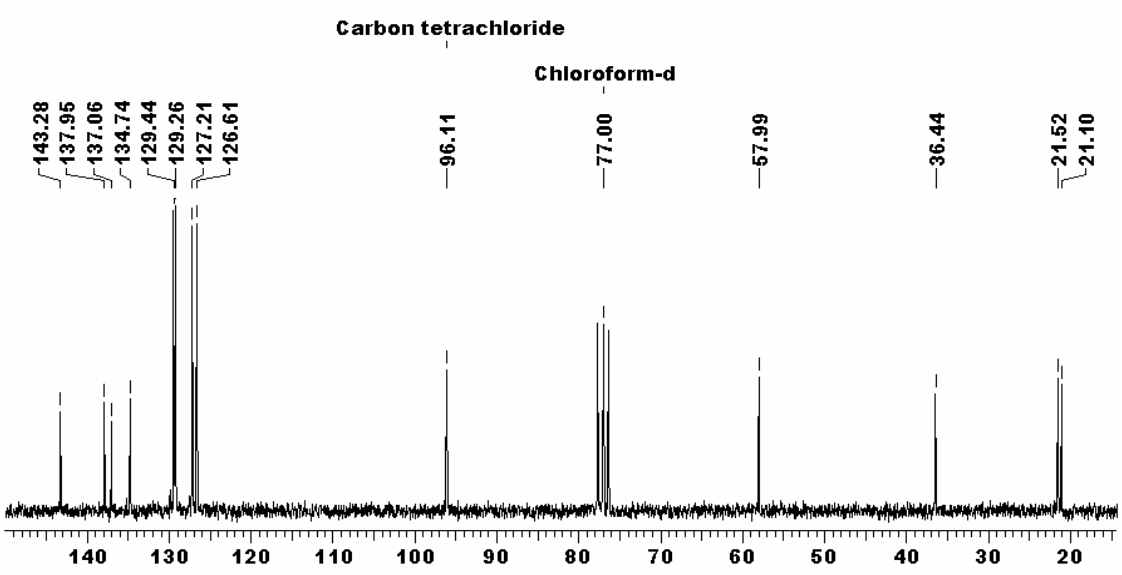


Fig. 4: ^{1}H and ^{13}C NMR spectra of bromoamine **25b**

The structures of regioisomers **25** were confirmed by ^{1}H-NMR and ^{13}C NMR spectroscopy. For example, compound **25b** showed singlets at δ 2.30 (s, 3H) and 2.41 (s, 3H) for methyl protons; δ 3.49-3.64 (m, 2H) for homobenzylic protons; and δ 4.49 (dd, *J* = 6.3, 12.5 Hz, 1H) for benzylic protons. Further a doublet at δ 5.28 (d, *J* = 6.8 Hz, 1H) is due to N-H proton. Its ^{13}C NMR spectrum showed typical carbon signals at δ 36.4 and 57.9 for the homobenzylic and benzylic carbons respectively (**Fig. 4**).

4.2.4.1 Mechanism

A plausible mechanistic pathway is outlined in **Fig. 5** to explain the formation of *anti*-Markovnikov product. Firstly, *p*-toluenesulfonamide reacts with NBS to form *p*-TsNH-Br[3] followed by its interaction with titanium superoxide which facilitates the polarization of the NH-Br bond homolytically. Since the catalyst possesses a stable radical, interaction of which with *p*-Ts-NHBr probably generates *p*-TsNH• radical, which in turn adds on to styrene regiospecifically at the homobenzylic position to form benzylic radical. The

recombination of this radical with Br• radical leads to *anti*-Markovnikov product. The radical pathway proposed here has been supported by the trapping experiment with TEMPO,[36,37] which failed to produce the corresponding haloamine. In the case of other titanium salts, the formation of Markovnikov product **26** can be reasoned on the basis of the formation of bromonium ion followed by its preferential opening at the benzylic position with *p*-toluenesulfonamide.

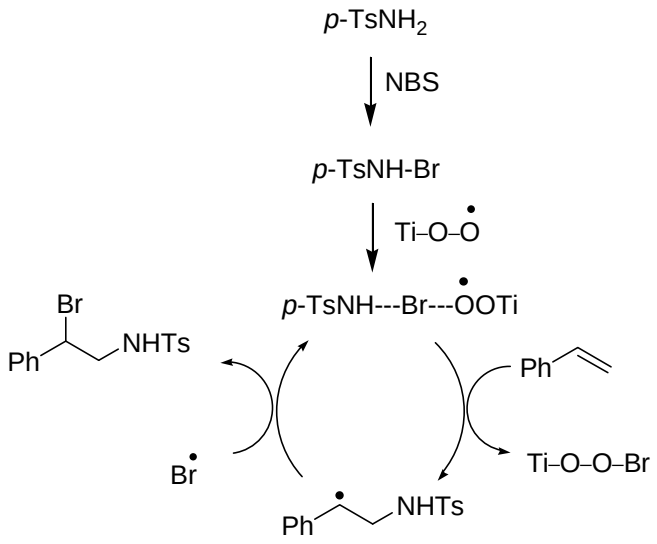


Fig 5: Titanium superoxide catalytic cycle for bromoamination process

4.2.5 Conclusion

In conclusion, we have described a titanium superoxide-catalyzed regiospecific aminobromination of olefins to give exclusively *anti*-Markovnikov products in high yields using *p*-$TsNH_2$ and NBS as amine and bromine sources respectively under ambient conditions. The protocol makes use of stable and readily accessible titanium superoxide as solid catalyst for the aminobromination process.

4.2.6 Experimental section

Preparation of titanium superoxide:

aq. 50% H_2O_2 (5.98 g, 0.175 mol) was added slowly to a solution of titanium isopropoxide (5.0 g, 0.0175 mol) in anhydrous MeOH (50 ml) over 40 min under N_2 with stirring at room temperature. The yellow precipitate formed was collected by filtration on a sintered funnel, washed with anhydrous methanol and dried at room temperature. Yield: 3.94 g (98 %).

Typical experimental procedure for aminobromination of styrene (25a)

To a stirred solution of styrene (0.312 g, 3.0 mmol), titanium superoxide (0.030 g, 10 wt %) and p-$TsNH_2$ (0.564 g, 3.3 mmol) in 25 mL of dry dichloromethane was added NBS (0.534 g, 3.0 mmol) slowly using a solid addition funnel. The reaction mixture was stirred further at 25 ^oC for 14 h. When TLC showed the completion of the reaction, the catalyst was filtered off and the filtrate was diluted with water, extracted with CH_2Cl_2 (20 x 3 mL) and washed with brine. The organic layer was dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was purified by column chromatography packed with silica gel using pet ether and EtOAc as eluents to afford the pure bromoaminated product **25a**.

2-Bromo-2-phenyl-N-tosylethanamine (25a)

Yield: 81%; **mp**: 113-114 ^oC; **IR** ($CHCl_3$, cm^{-1}): 3252, 2985, 2930, 1655, 1593, 1590, 1461, 1340, 1153, 1086, 710, 662; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.43 (s, 3H), 3.50-3.58 (m, 2H), 4.85-4.99 (m, simplifies to triplet with J = 7.12 Hz on D_2O exchange, 2H), 7.24-7.33 (m, 7H), 7.71 (d, J = 8.41 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.4, 49.8, 52.4, 126.8, 127.5, 128.7, 129.7, 136.6, 138.0, 143.6; **MS** m/z (rel. intensity): 354 (M^+,

1), 184 (30), 155 (35), 118 (20), 105 (20), 91 (100), 77 (20), 65 (25); **Anal.** Calcd for $C_{15}H_{16}BrNO_2S$ requires C, 50.86; H, 4.55; Br, 22.56; N, 3.95; S, 9.05; Found C, 50.83; H,4.50; Br, 22.58; N, 3.81; S, 9.12%.

2-Bromo-2-p-tolyl-N-tosylethanamine (25b)

Yield: 86%; **IR** ($CHCl_3$, cm^{-1}): 3268, 2954, 2922, 2851, 1597, 1460, 1377, 1215, 1161, 759, 669; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.30 (s, 3H), 2.41 (s, 3H), 3.49-3.64 (m, 2H), 4.49 (dd, *J* = 6.3, 12.5 Hz, 1H), 5.28 (d, *J* = 6.8 Hz, 1H), 6.96-7.06 (m, 4H), 7.21 (d, *J* = 8.2 Hz, 2H), 7.63 (dd, *J* = 1.7, 6.6 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.1, 21.5, 36.4, 57.9, 126.6, 127.2, 129.2, 129.4, 134.7, 137.0, 137.9, 143.2; **Anal.** Calcd for: $C_{16}H_{18}BrNO_2S$ requires C, 52.18; H, 4.93; Br, 21.70; N, 3.80; S, 8.71; Found: C, 51.99; H, 5.07; Br, 21.81; N, 3.77; S, 8.94%.

2-Bromo-2-(4-methoxyphenyl)-N-tosylethanamine (25c)

Yield: 67%; **IR** ($CHCl_3$, cm^{-1}): 3246, 2923, 2854, 1595, 1461, 1336, 1265, 1163, 1091, 1027, 812, 676; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.41 (s, 3H), 3.55 (q, *J* = 2.8, 6.0 Hz, 2H), 3.76 (s, 3H), 4.48 (q, *J* = 6.1, 12.1 Hz, 1H), 5.24 (d, *J* = 6.4 Hz, 1H), 6.74 (d, *J* = 8.7 Hz, 2H), 7.02 (dd, *J* = 1.8, 6.6 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.62 (dd, *J* = 1.7, 6.7 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.5, 36.4, 55.1, 57.7, 113.9, 127.2, 127.9, 129.4, 129.7, 137.0, 143.2, 159.4; **Anal.** Calcd for: $C_{16}H_{18}BrNO_3S$ requires C, 50.01; H, 4.72; Br, 20.79; N, 3.64; S, 8.34; Found: C, 49.99; H, 4.86; Br, 20.68; N, 3.82; S, 7.99%.

2-Bromo-2-(4-bromophenyl)-N-tosylethanamine (25d)

Yield: 69%; **IR** ($CHCl_3$, cm^{-1}): 3253, 2954, 2923, 2854, 1596, 1458, 1319, 1151, 1091, 825, 765, 565; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.46 (s, 3H), 3.47-3.56 (m, 2H), 4.88 (t, *J* = 7.4 Hz, 1H), 7.14-7.46 (m, 6H), 7.64 (dd, *J* = 8.5 Hz, 2H); **^{13}C NMR** (50 MHz,

$CDCl_3$): δ 21.6, 49.5, 51.2, 123.0, 127.0, 128.5, 129.3, 129.8, 131.6, 132.0, 136.8, 137.3, 143.7; **Anal.** Calcd for: $C_{15}H_{15}Br_2NO_2S$ requires C, 41.59; H, 3.49; Br, 36.89; N, 3.23; S, 7.40; Found: C, 41.61; H, 3.71; Br, 36.68; N, 2.99; S, 7.65%.

2-Bromo-2-(2-chlorophenyl)-N-tosylethanamine (25e)

Yield: 69%; **IR** ($CHCl_3$, cm^{-1}): 3284, 3018, 2925, 2854, 1598, 1456, 1419, 1334, 1215, 1161, 1093, 757, 669, 549; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.45 (s, 3H), 3.51-3.68 (m, 2H), 4.92 (t, *J* = 6.4 Hz, 1H), 5.29-5.40 (m, 1H), 7.22-7.37 (m, 5H), 7.43-7.48 (m, 1H), 7.74 (d, J = 8.2 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.4, 47.7, 48.6, 126.9, 127.4, 128.8, 129.7, 129.8, 133.1, 136.9, 143.4; **Anal.** Calcd for: $C_{15}H_{15}BrClNO_2S$ requires C, 46.35; H, 3.89; Br, 20.56; Cl, 9.12; N, 3.60; S, 8.25; Found C, 46.41; H, 3.96; Br, 20.71; Cl, 8.99; N, 3.55; S, 8.15%.

2-Bromo-2-(4-fluorophenyl)-N-tosylethanamine (25f)

Yield: 78%; **IR** ($CHCl_3$, cm^{-1}): 3281, 3016, 2922, 2853, 1599, 1456, 1419, 1334, 1215, 1161, 1093, 757, 669; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.41 (s, 3H), 3.54 (d, *J* = 6.1 Hz, 2H), 4.56 (q, *J* = 6.1, 12.3 Hz, 1H), 5.42 (d, *J* = 6.4 Hz, 1H), 6.86-6.96 (m, 2H), 7.06-7.13 (m, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.5, 36.3, 57.5, 115.3, 115.7, 127.2, 128.4, 128.6, 129.5, 133.6, 137.0, 143.6; **Anal.** Calcd for: $C_{15}H_{15}BrFNO_2S$ requires C, 48.40; H, 4.06; Br, 21.47; F, 5.10; N, 3.76; S, 8.61; Found C, 48.55; H, 3.98; Br, 21.62; F, 4.97; N, 3.82; S, 8.70%.

1-(4-Chloromethylphenyl)-1-bromo-2-(p-toluenesulfonamido)ethane (25g)

Yield: 67%; **mp**: 111-112 °C; **IR** ($CHCl_3$, cm^{-1}): 3284, 3018, 2925, 2854, 1598, 1456, 1419, 1334, 1215, 1161, 1093, 757, 669, 549; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.43 (s, 3H), 3.51- 3.62 (m, 2H), 4.55 (s, 2H), 4.83 (t, *J* = 7.23 Hz, exchangeable with D_2O, 1H),

4.92 (t, *J* = 7.23 Hz, 1H), 7.25-7.40 (m, 6H), 7.72 (d, *J* = 8.43 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.4, 45.3, 49.7, 51.7, 126.8, 127.9, 128.9, 129.7, 136.6, 138.1, 138.8, 143.7; **MS** m/z (rel. intensity): 403 (M^+, 1), 219 (10), 184 (100), 155 (80), 139 (15), 130 (30), 117 (30), 103 (25), 91 (85); **Anal.** Calcd for: $C_{16}H_{17}BrClNO_2S$ requires C, 47.72; H, 4.25; Br, 19.84; Cl, 8.80; N, 3.48; S, 7.96; Found C, 47.62; H, 4.10; Br, 19.86; Cl, 8.66; N, 3.41; S, 7.89%.

2-Bromo-2-phenyl-N-tosylpropan-1-amine (25h)

Yield: 30%; **IR** ($CHCl_3$, cm^{-1}): 3269, 2954, 2925, 2854, 1598, 1460, 1377, 1215, 1161, 759, 662; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.73 (s, 3H), 2.41 (s, 3H), 3.67 (d, *J* = 10.6 Hz, 1H), 3.87 (d, *J* = 10.6 Hz, 1H), 5.30 (br s, 1H), 7.18-7.32 (m, 7H), 7.60 (d, *J* = 1.8, 6.4 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.4, 25.1, 43.2, 60.5, 126.0, 126.9, 127.6, 128.2, 129.2, 139.3, 140.8, 142.7; **Anal.** Calcd for: $C_{16}H_{18}BrNO_2S$ requires C, 52.18; H, 4.93; Br, 21.70; N, 3.80; S, 8.71; Found C, 52.26; H, 5.01; Br, 21.83; N, 3.77; S, 8.69%.

2-Bromo-1,2-diphenyl-N-tosylethanamine (25i)

Yield: 61%; **IR** ($CHCl_3$, cm^{-1}): 3252, 2985, 2930, 1655, 1593, 1590, 1461, 1340, 1153, 1086, 710, 662; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.34 (s, 3H), 4.72-4.80 (m, 1H), 5.21 (dd, *J* = 6.0. 21.7 Hz, 1H), 5.57 (d, *J* = 5.8 Hz, 1H), 6.84-6.90 (m, 2H), 7.01-7.26 (m, 10H), 7.43 (dd, *J* = 3.4, 8.6 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.4, 58.1, 63.1, 127.0, 127.1, 127.6, 127.7, 127.8, 127.9, 128.0, 128.2, 128.3, 128.4, 128.6, 129.1, 136.4, 137.0, 137.1, 142.9; **Anal.** Calcd for: $C_{21}H_{20}BrNO_2S$ requires C, 58.61; H, 4.68; Br, 18.57; N, 3.25; S, 7.45; Found C, 58.74; H, 4.55; Br, 18.61; N, 3.41; S, 7.37%.

1-Bromo-2,3-dihydro-N-tosyl-1H-inden-2-amine (25j)

Yield: 80%; **mp**: 136-137 °C; **IR** ($CHCl_3$, cm^{-1}): 3274, 3020, 1598, 1429, 1340, 1215, 1161, 1093, 767, 752, 667; **^{1}HNMR** (200 MHz, $CDCl_3$): δ 2.47 (s, 3H), 2.74-2.87 (dd, *J* = 16.10, 10.21 Hz, 1H), 2.93-23.04 (dd, *J* = 6.13, 16.10 Hz, 1H), 3.90-3.99 (m, 1H), 5.13 (d, *J* = 5.55 Hz, 1H), 5.35 (d, *J* = 10.20 Hz, exchangeable with D_2O, 1H), 7.19-7.37 (m, 6H), 7.83 (d, *J* = 8.36 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.5, 36.4, 56.3, 59.5, 125.0, 127.1, 127.6, 129.7, 137.4, 139.4, 140.5, 143.7; **MS** m/z (rel. intensity): 365 (M^{-1}, 1), 286 (30), 196 (15), 155 (20), 130 (100), 115 (25), 103 (40), 91 (38); **Anal.** Calcd for: $C_{16}H_{16}BrNO_2S$ requires C, 52.47; H, 4.40; Br, 21.82; N, 3.82; S, 8.76; Found C, 52.38; H, 4.48; Br, 21.79; N, 3.81; S, 8.74%.

(±)-*trans*-1-(*p*-Toluenesulfonamido)-2-bromocyclohexane (25l)

Yield: 65%; **IR** ($CHCl_3$, cm^{-1}): 3276, 2926, 2862, 1596, 1446, 1321, 1159, 1093, 813, 661; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.19-1.39 (m, 3H), 1.64-1.88 (m, 3H), 2.25-2.34 (m, 2H), 2.44 (s, 3H), 3.09-3.23 (m, 1H), 3.85 (ddd, *J* = 4.2, 9.6 Hz, 1H), 5.08 (d, *J* = 5.5 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.78 (d, *J* = 8.1 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.5, 23.1, 24.8, 32.2, 35.2, 54.6, 58.1, 127.2, 129.4, 137.3, 143.1; **Anal.** Calcd for: $C_{13}H_{18}BrNO_2S$ requires C, 46.99; H, 5.46; Br, 24.05; N, 4.22; S, 9.65%; Found C, 47.01; H, 5.55; Br, 23.99; N, 4.39; S, 9.72%.

(±)-*trans*-1-(*p*-Toluenesulfonamido)-2-bromocyclooctane (25m)

Yield: 72%; **IR** ($CHCl_3$, cm^{-1}): 3280, 3020, 2929, 2860, 1598, 1444, 1328, 1215, 1159, 1091, 757, 669; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.27-1.83 (m, 10H), 1.92-2.34 (m, 4H), 2.45 (s, 3H), 3.38-3.50 (m, 1H), 3.99-4.08 (m, 1H), 4.81 (d, *J* = 4.2 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.77 (d, 8.3 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.5, 24.9, 25.3, 25.6, 31.8, 32.0, 59.3, 60.9, 127.5, 129.4, 136.8, 143.2; **Anal.** Calcd for: $C_{15}H_{22}BrNO_2S$

requires C, 50.00; H, 6.15; Br, 22.18; N, 3.89; S, 8.90%; Found C, 49.98; H, 6.51; Br, 22.21; N, 3.79; S, 8.61%.

2-Bromo-2-cyclohexyl-N-tosylethanamine (25n)

Yield: 63%; **IR** ($CHCl_3$, cm^{-1}): 3275, 3010, 2922, 2858, 1596, 1434, 1321, 1220, 1162, 1080; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.96-1.20 (m, 4H), 1.58-1.78 (m, 5H), 2.44 (s, 3H), 3.12-3.26 (m, 1H), 3.32-3.48 (m, 1H), 3.83-3.92 (m, 1H), 4.69 (d, *J* = 8.8 Hz, 1H), 7.30 (dd, *J* = 3.7, 8.0 Hz, 2H), 7.74 (dd, *J* = 2.8, 8.3 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.5, 25.6, 25.8, 25.9, 29.2, 29.6, 30.6, 41.4, 47.3, 62.1, 127.0, 129.6, 129.7, 136.8, 143.4; **Anal.** Calcd for: $C_{15}H_{22}BrNO_2S$ requires C, 50.00; H, 6.15; Br, 22.18; N, 3.89; S, 8.90%; Found C, 49.98; H, 6.51; Br, 22.21; N, 3.79; S, 8.61%.

4.2.7 References

1 a) L. S. Vondervoort, S. Bouttemy, F. Heu, K. Weissenböck, P. L. Alsters, *Eur. J. Org. Chem.* **2003**, 578; (b) T. Maki, Y. Suzuki in *Ullmann's Encyclopedia of Industrial Chemistry* (Ed.:W. Gerhartz), 5th ed., VCH, **1985**, vol. A3, p. 555; (c) J. Opgrande, E. E. Brown, M. Hesser, J. Andrews, in *Kirk-Othmer Encyclopedia of Chemical Technology*, 5th ed., Wiley, New York, **2004**, vol. 3, p. 625; (d) P. Benz, R. Muntwyler, R. Wohlgemuth, *J. Chem. Technol. Biotechnol.* **2007**, *82*, 1087; (e) G. W. Parshall, S. D. Ittel, *Homogeneous Catalysis*, Wiley, New York, **1992**.

2 (a) D. Dyker (Ed.), *Handbook of C–H Transformations*, Wiley-VCH, Weinheim, **2005**; (b) R. A. Sheldon, J. K. Kochi in *Metal-Catalyzed Oxidation of Organic Compounds*, Academic Press, New York, **1981**; (c) S. D. Burke, R. L. Danheiser, *Handbook of Reagents for Organic Synthesis: Oxidizing and Reducing Agent*, Wiley, Chichester, U. K. **1999**; (d) G. A. Olah, D. G. Parker, N. Yoneda, *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 909; (e) J. Eames, M. Watkinson, *Angew. Chem. Int. Ed.* **2001**, *40*, 3567; (f) F. Kakiuchi, N. Chatani, *Adv. Synth. Catal.* **2003**, *345*, 1077.

3 (a) K. B. Wiberg in *Oxidation in Organic Chemistry*, Academic Press, New York, **1965**, Part A, p. 69; (b) G. Cainelli, G. Cardillo in *Chromium Oxidations in Organic Chemistry*, Springer, New York, **1984**, p. 23; (c) D. J. Sam, H. E. Simmons, *J. Am. Chem. Soc.* **1972**, *94*, 4024; (d) L. Friedman, D. L. Fishel, H. Shechter, *J. Org. Chem.* **1965**, *30*, 1453; (e) J. Muzart, *Tetrahedron Lett.* **1987**, *28*, 2131; (f) S. Yamazaki, *Org. Lett.* **1999**, *1*, 2129; (g) E. Baciocchi, G. C. Rosato, C. Rol, G. V. Sebastiani, *Tetrahedron Lett.* **1992**, *33*, 5437; (h) T. M. Shaikh, L. Emmanuvel, A. Sudalai, *J. Org. Chem.* **2006**, *71*, 5043; (i) W. S. Trahanovsky, L. B. Young, *J. Org. Chem.* **1966**, *31*, 2033; (j)

R. H. Reitsema, N. L. Allphin, *J. Org. Chem.* **1962**, *27*, 27; (k) D. G. Lee, U. A. Spitzer, *J. Org.Chem.* **1969**, *34*, 1493; (l) Q. Z. Shi, J. G. Wang, K. Cai, *Synth. Commun.* **1999**, *29*, 1177.

4 (a) E. Modica, G. Bombieri, D. Colombo, N. Marchini, F. Ronchetti, A. Scala, L. Toma, *Eur. J. Org. Chem.* **2003**, *15*, 2964; (b) R. A. Sheldon, I. W. C. E. Arends, *Adv. Synth. Catal.* **2004**, *346*, 1051; (c) B. Saha, J. H. Espenson, *J. Mol. Catal. A* **2005**, *241*, 33; (d) A. Gizli, G. Aytimur, E. Alpay, S. Atalay, *Chem. Eng. Technol.* **2008**, *31*, 409; (e) T. W. Bastock, J. H. Clark, K. Martin, B. W. Trenbirth, *Green Chem.* **2002**, *4*, 615; (f) N. Hirai, N. Sawatari, N. Nakamura, S. Sakaguch, Y. Ishii, *J. Org. Chem.* **2003**, *68*, 6587; (g) F. Yang, J. Sun, R. Zheng, W. Qui, J. Tang, M. He, *Tetrahedron* **2004**, *60*, 1225.

5 F. Wang, J. Xu, X. Li, J. Gao, L. Zhou, R. Ohnishi, *Adv. Synth.Catal.* **2005**, *347*, 1987.

6 M. Gupta, S. Paul, R. Gupta, A. Loupy, *Tetrahedron Lett.* **2005**, *46*, 4957.

7 (a) J. Gao, X. Tong, X. Li, H. Miao, J. Xu, *J. Chem. Technol. Biotechnol.* **2007**, *82*, 620; (b) X. Li, J. Xu, F. Wang, J. Gao, L. Zhou, G. Yang, *Catal. Lett.* **2006**, *108*, 137; c) N. H. Lee, J. C. Byun, T.-H. Oh, *Bull. Korean Chem. Soc.* **2005**, *26*, 454.

8 K. Nemoto, H. Yoshida, Y. Suzuki, N. Morohashi, T. Hattori, *Chem. Lett.* **2006**, *35*, 820.

9 (a) M. Nakanish, C. Bolm, *Adv. Synth. Catal.* **2007**, *349*, 861; (b) S. S. Kim, S. K. Sar, P. Tamrakar, *Bull. Korean Chem.Soc.* **2002**, *23*, 937.

10 T. Nagataki, Y. Tachi, S. Itoh, *Chem. Commun.* **2006**, 4016.

11 (a) Y. Sasson, G. D. Zappi, R. Neumann, *J. Org. Chem.* **1986**, *51*, 2880; (b) Y. Sasson, A. E.-A. Quntar, A. Zoran, *Chem.Commun.* **1998**, 73; (c) S. I. Murahashi, Y. Oda, T. Naota, T. Kuwabara, *Tetrahedron Lett.* **1993**, *34*, 1299.

12 J. M. Lee, E. J. Park, S. H. Cho, S. Chang, *J. Am. Chem. Soc.***2008**, *130*, 7824.

13 Y. Bonvin, E. Callens, I. Larrosa, D. A. Henderson, J. Oldham, A. J. Burton, A. G. M. Barrett, *Org. Lett.* **2005**, *7*, 4549.

14 (a) S. Paul, P. Nanda, R. Gupta, *Synlett* **2004**, 531; (b) S.-I. Hirashama, A. Itoh, *Synthesis* **2006**, 1757; (c) T. Sugai, A. Itoh, *Tetrahedron Lett.* **2007**, *48*, 9096; (d) B. Srinivasan, S. B. Chandalia, *Indian J. Technol.* **1971**, *9*, 274.

15 Moriarty, R. M.; Prakash, I.; Penmasta, R. *J Chem. Soc. Chem. Commun*. **1987**, 202.

16 Gurunath, S.; Sudalai, A. *Synlett*, **1999**, 559.

17 Ashford, S. W.; Grega, K. C. *J. Org. Chem*. **2001**, *66*, 1523.

18 Bjorsvik, H-R.; Merinero, J. A. V.; Liguori, L. *Tetrahedron Lett*. **2004**, *45*, 8615.

19 Shinozuka, T.; Nakao, A.; Saito, K.; Naito, S. *Chem. Lett*. **2006**, *35*, 1090.

20 (a) Y. Lu, H. Yin, H. Wu, H. Liu, T. Jian, Y. Wada, *Catal.Commun.* **2006**, *7*, 832; (b) R. Vijayalakshmi, M. Jayachandran, C. Sanjeeviraja, *Curr. Appl. Phys.* **2003**, *3*, 171; (c) L. Farrugia, M. L. H. Green, *J. Chem. Soc., Chem. Commun.* **1975**, 416.

21 Y. Ogata, Y. Sawaki, M. Shiroyama, *J. Org. Chem.* **1977**, *42*, 4061.

22 Kemp, J. E. G.; in "Comprehensive Organic Synthesis" Trost, B. M., Ed., Pergmon, Oxford, **1991**,

vol. 7, p 469.

23 Kharasch, M. S.; Priestley. H. M. *J. Am. Chem. Soc*. **1939**, *61*, 3425.

24 (a) Terauchi, H.; Takemura, S.; Ueno, Y. *Chem. Pharm. Bull*. **1975**, *23*, 640; (b) Terauchi, H.; Ando, Y.; Takemura, S.; Ueno, Y. *Chem. Pharm. Bull*. **1967**, *15*, 1193.

25 Danither, F. A. Butler, P. E.; *J. Org. Chem*. **1968**, *12*, 4336.

26 (a) Zawadzki, S.; Zwierzak, A. *Tetrahedron* **1981**, *37*, 2675; (b) Zwierzak, A.; Klepacz, A. *Tetrahedron Lett*. **2001**, *42*, 4539.

27 Bach, T.; Schlummer, B.; Harms, K. *Chem. Commun*. **2000**, 287.

28 (a) Li, G.; Wei, H. -X; Kim, S. H.; Neighbors, M. *Org. Lett*. **1999**, *1*, 395'; (b) Li, G.; Wei, H. -X; Kim, S. H. *Org. Lett*. **2000**, *2*, 2249; (c) Wei, H. -X.; Kim, S. H.; Li, G. *Tetrahedron* **2001**, *57*, 3869; (d) Wei, H. -X.; Kim, S. H.; Li, G. *Tetrahedron* **2001**, *57*, 8407; (e) Kotti, S. R. S. S.; Xu, X.; Wang, Y.; Headley, A. D.; Li, G. *Tetrahedron Lett*. **2004**, *45*, 7209; (f) Xu, X.; Kotti, S. R. S. S.; Liu, J.; Cannon, J. F.; Headley, A. D.; Li, G. *Org. Lett*. **2004**, *6*, 4881; (g) Li, Q.; Shi, M.; Timmons, C.; Li, G. *Org. Lett*. **2006**, *8*, 625.

29 Qi, X.; Lee, S. –H.; Kwon, J. Y.; Kim, Y.; Kim, S. –J.; Lee, Y. -S.; Yoon, J. *J. Org. Chem*. **2003**, *68*, 9140.

30 Thakur, V. V.; Talluri, S. K.; Sudalai, A. *Org. Lett*. **2003**, *5*, 861.

31 Manzoni, M. R.; Zabawa, T. P.; Kasi, D.; Chemler, S. R. *Organometallics* **2004**, *23*, 5618.

32 Minakata, S.; Yoneda, Y.; Oderaotoshi, Y.; Komatsu, M. *Org. Lett*. **2006**, *8*, 967.

33 Wu, X-L.; Wang, G-W. *J. Org. Chem*. **2007**, *72*, 9398.

34 Jadav, J. S.; Reddy, B. V. S.; Chary, D. N.; Chandrakanth, D. *Tetrahedron. Lett*. **2009**, *50*, 1136.

35 (a) Dewkar, G. K.; Nikalje, M. D.; Sayyed, I. A.; Paraskar, A. S.; Jagtap, H. S.; Sudalai, A. *Angew. Chem. Int. Ed*., **2001**, *40*, 405; (b) Dewkar, G. K.; Shaikh, T. M.; Pardhy, S.; Kulkarni, S. S.; Sudalai, A. *Indian J. Chem. B* **2005**, *44*, 1530.

36 (a) Connolly, T. J.; Baldovi, M. V.; Mohtat, N; Scaiano, J. C. *Tetrahedron Lett.* **1996**, *37*, 4919.

37 (a) Kim, T-H.; Dokolas, P.; Feeder, N.; Giles, M.; Holmes, A. B.; Walthar, M. *Chem. Commun*. **2000**, 2419; (b) Beckwith, A. L. J.; Bowry, V. W.; Moad, G. *J. Org. Chem*. **1988**, *53*, 1632.

PUBLICATIONS

1. $NaIO_4$-mediated C-H activation of Alkylbenzenes and alkanes with LiBr. **Tanveer M Shaikh**, A. Sudalai, *Tetrahedron Lett*. **2005**, *33*, 5589-5592.

2. Titanium Superoxide catalyzed selective oxidation of phenols to p-quinones with aq. H_2O_2. G. K. Dewkar, **Tanveer M Shaikh**, S. Pardthy, S. S. Kulkarni, A. Sudalai, *Ind. J. Chem. Section B*, **2005**, *44*, 1530-1532.

3. $NaIO_4$/LiBr-mediated diastereoselective dihydroxylation of olefins: A catalytic approach to the prevost-woodward reaction. Emmanuvel, L., **Tanveer M Shaikh**, Sudalai, A. *Org. Lett*. **2005**, *7*, 5071-5074.

4. $NaIO_4$-mediated selective oxidation of alkylarenes and benzylic bromides/alcohols to carbonyl derivatives using water as solvent. Tanveer M Shaikh., Emmanuvel, L., Sudalai, A. *J. Org. Chem*. **2006**, *71*, 5043-5046.

5. $NaIO_4$/LiBr-mediated direct conversion of benzylic alcohols and aromatic aldehydes to aromatic esters. **Tanveer M Shaikh**, Emmanuvel, L., Sudalai, A. *Synth. Commun*. **2007**, *37*, 2641-2646.

6. WO_3/70%TBHP/aq. NaOH: An Efficient Catalytic Combination for the Selective Oxidation of Methylarenes and Alkylaryl ketones to benzoic acids. **Tanveer M Shaikh**, A. Sudalai, *Eur. J. Org. Chem*. **2008**, *33*, 4877-4880.

7. Titanium superoxide: a heterogeneous catalyst for aminobromination of olefins. **Tanveer M Shaikh**, P. Karabal, S. Gurunath, Sudalai, A. *Tetrahedron Lett*. **2009**, *50*, 2815-2817.

8. Highlights in current synthetic organic chemistry on "Titanium superoxide: a heterogeneous catalyst for aminobromination of olefins". **Tanveer M Shaikh**, P. Karabal, S. Gurunath, Sudalai, A.. *Synfacts* **2009**, *9*, 1009.

9. A concise enantioselective synthesis of (+)-lentiginosine. **Tanveer M Shaikh**, A. Sudalai, *Tetrahedron: Asymmetry*, **2009**, *20*, 2287-2292.

10. Hβ- zeolite: an efficient, reusable catalyst for one-pot synthesis of isatins from anilines. Victor Paul, **Tanveer M Shaikh**, A. Sudalai. (Communicated to *Acta. Chim. Slov*.**2009**).

11. A short Enantioselective synthesis of (+)-α-conhydrine and (-)-sedamine via L-proline catalyzed α-aminooxylation. **Tanveer M Shaikh**, A. Sudalai (Communicated to *Eur. J. Org. Chem*., **2009**).

12. A short enantioselective synthesis of (+)-sertraline via Sharpless asymmetric dihydroxylation. **Tanveer M Shaikh**, A. Sudalai (Manuscript under preparation).

13 Enantioselective synthesis of (-)-allosedridine via Sharpless asymmetric epoxidation **Tanveer M Shaikh**, A. Sudalai (Manuscript under preparation).