ASYMMETRIC SYNTHESIS OF BIOACTIVE MOLECULES AND OXYFUNCTIONALIZATION OF ALKENES

A THESIS

SUBMITTED TO THE

UNIVERSITY OF PUNE

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

NARINA V. SRINIVASARAO

Chemical Engineering and Process Development Division

National Chemical Laboratory

Pune-411008, INDIA

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Dedicated to My Teacher
Bhaskar Rama Murthy

NATIONAL CHEMICAL LABOATORY
Dr. A. Sudalai
Scientist
Chemical Engineering & Process Development Division,
Pune – 411 008, India
Phone (O) : 0091-20-25902174, Fax: 0091-20-25902676,
e-mail: a.sudalai@ncl.res.in

CERTIFICATE

Certified that the work incorporated in the thesis entitled "**Asymmetric Synthesis of Bioactive Molecules and Oxyfunctionalization of Alkenes**" was carried out by the candidate under my supervision. Such material as had been obtained from other sources has been duly acknowledged in the thesis.

(Dr. A. Sudalai) **February 2007**

Research Supervisor **Pune**

NATIONAL CHEMICAL LABORATORY

DECLARATION

I here by declare that the thesis entitled **"Asymmetric Synthesis of Bioactive Molecules and Oxyfunctionalization of Alkenes"** 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.

February 2007
Pune

NARINA V. SRINIVASARAO
CE & PD Division
National Chemical Laboratory
Dr. Homi Bhabha Road
Pune – 411 008 INDIA.

CONTENTS

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Narina V. Srinivasarao

ABBREVATIONS

AD	Asymmetric Dihydroxylation
Ac	Acetyl
Ar	Aryl
bp	Boiling Point
Bn	Benzyl
Boc	N-*tert*-Butoxycarbonyl
$(Boc)_2O$	Ditert-butyl dicarbonate
n-BuLi	n-Butyl Lithium
Cbz	Benzyloxy carbonyl
CH_2Cl_2	Methylene chloride
$CHCl_3$	Chloroform
CH_3CN	Acetonitrile
$CuSO_4$	Copper(II) sulfate
DHQ	Dihydoquinine
DHQD	Dihydroquinidine
DIBAL-H	Diisobutyl alulinum hydride
DMF	Dimethyl formamide
DMSO	Dimethyl sulphoxide
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	Infra red
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
p-TSA	*p*-Toluene sulfonic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TBAF	Tetrabutylammonium fluoride
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 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 Brucker FT AC-200 and MSL-300 MHz instruments using TMS as an internal standard. The following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, 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 entitled "**Asymmetric Synthesis of Bioactive Molecules and Oxyfunctionalization of Alkenes**" is divided into four chapters.

The title of the thesis clearly indicates the objective that is to synthesize enantiomerically pure drugs and to interface synthetic organic chemistry for the development of new methodologies. **Chapter 1** deals with enantioselective synthesis of (-)-Cytoxazone (**12**) and (+)-*epi*-Cytoxazone (**16**), (both of which exhibit cytokine-modulating activity) *via* proline-catalyzed asymmetric α-aminooxylation of aldehydes followed by Rh-catalyzed diastereoselective oxidative C-H aminations. **Chapter 2** describes the asymmetric synthesis of two antibacterial agents *i.e* Linezolid (**24**) and Epirezolid (**37**). The stereogenic center in both of them is introduced *via* proline-catalyzed asymmetric α-aminooxylation of aldehydes. **Chapter 3** describes the asymmetric synthesis of (*S*)-Timolol (**43**), β-adrenergic antagonist drug. The stereogenic center in the molecule is introduced by three routes *i.e* OsO_4-catalyzed asymmetric dihydroxylation (AD) of the corresponding allylamine **38**, the hydrolytic kinetic resolution of terminal epoxide **46** and the kinetic resolution of terminal epoxide (epichlorohydrin) *via* enantioselective ring-opening with phenolic substrate **45**. **Chapter 4** deals with synthetic methodologies involving $NaIO_4$-mediated oxidative methoxybromination and dibromination of alkenes and Mn-catalyzed asymmetric epoxidation of alkenes.

CHAPTER 1

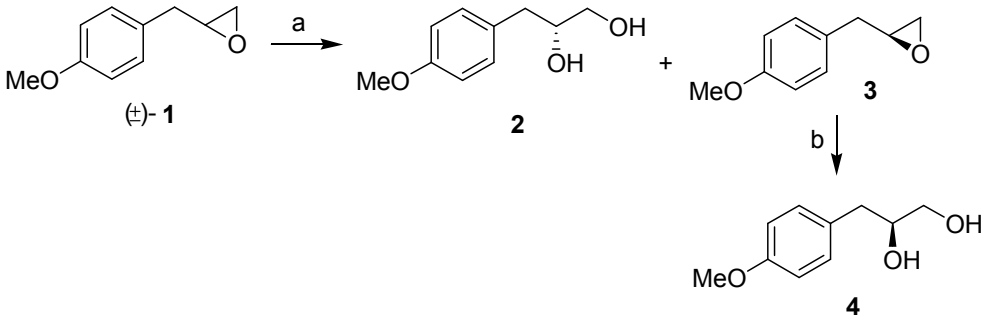
Enantioselective Synthesis of (-)-Cytoxazone and (+)-*epi*-Cytoxazone *via* Proline-Catalyzed α-Aminooxylation of Aldehydes and Rh-Catalyzed Diastereoselective Oxidative C-H Aminations

(-)-Cytoxazone (**12**) and its stereoisomer (+)-*epi*-Cytoxazone (**16**), containing a novel 4,5-disubstituted-2-oxazolidinone moiety were isolated[1] from *Streptomyces* sp., both of which exhibit cytokine-modulating activity by inhibiting the signalling pathway of Th2 cells. Inhibitors of Th2-dependent cytokine production would be potent chemotherapeutic agents in the field of immunotherapy.[1]

Proline, an abundant, inexpensive amino acid available in both enantiomeric forms, has emerged as arguably the most practical and versatile organocatalyst for α-functionalization of carbonyl compounds.[2] Rh-catalyzed diastereoselective intramolecular C-H aminations using either chiral sulfamate or carbamate esters (**8** or

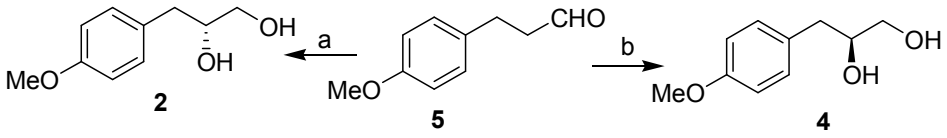
14) gives amines and amine derivatives.[3] In this chapter we have employed both of these reactions for the asymmetric synthesis of bioactive molecules, (-)-Cytoxazone (**12**), and (+)-*epi*-Cytoxazone (**16**)[4].

The synthesis of chiral 1,2-diols **2** and **4**, key intermediates, in the synthesis of (-)-cytoxazone (**12**) and (+)-*epi*-cytoxazone (**16**) respectively, are obtained by two routes, which are presented in **Schemes 1** and **2**. Hydrolytic kinetic resolution (HKR)[5] of the racemic epoxide **1**[6] in presence of (*R,R)*-salen-Co(III)OAc complex gave chiral diol **2** in 44% yield and 98% ee and chiral epoxide **3** in 52% yield and 92% ee. In order to enhance the optical purity of the diol **4**, the epoxide **3** (92% ee) was again subjected to hydrolytic kinetic resolution in presence of (*S,S)*-salen-Co(III)OAc complex with 0.95 eqiuv. of water, which resulted in the formation of diol **4** in 92% yield and 98% ee (**Scheme 1**).



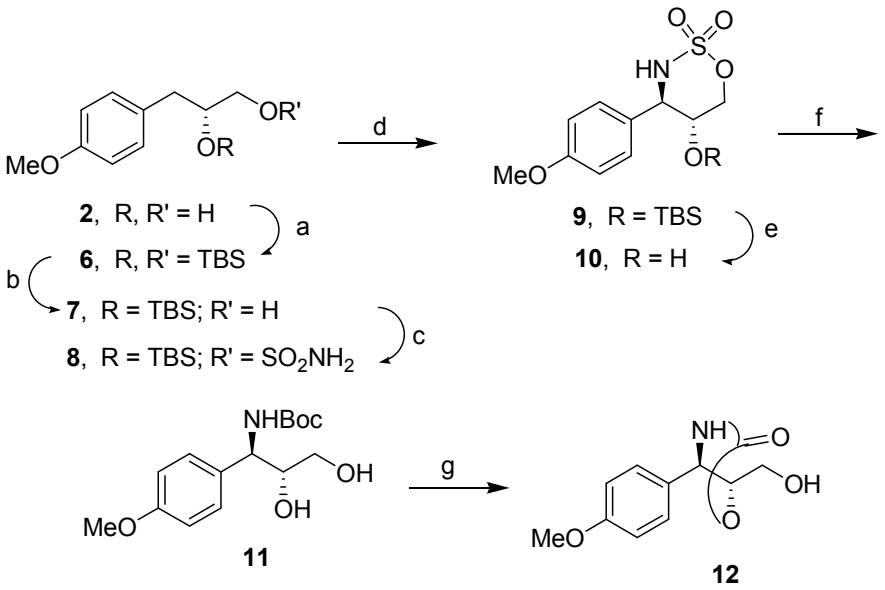
Scheme 1. Reagents and conditions: (a) (*R,R)*-salen-Cobalt(III)OAc (0.5 mol %), THF (0.55 equiv), H_2O (0.45 equiv), 0 ºC, 14 h, (44%, 98% ee for **4** and 52% and 92% ee for **6**); (b) (*S,S)*-salen-Cobalt(III)OAc (0.5 mol %), THF (0.95 equiv), H_2O (0.95 equiv), 0 ºC, 20 h, 92%, 98% ee.

As HKR route generally gives maximum chemical yield up to 50%, we turned our attention to proline-catalyzed asymmetric α-functionalization[2] of aldehydes. Thus, the aldehyde **5**[7] was converted into the corresponding chiral diols **2** and **4** by proline-catalyzed asymmetric α-aminooxylation[2a] in a two-step reaction sequence: (i) reaction of aldehyde **5** with nitrosobenzene as the oxygen source in presence of L or D-proline in CH_3CN at –20 °C, followed by reduction with $NaBH_4$ in MeOH gave the crude aminoxy alcohol and (ii) subsequent reduction of the crude aminoxy alcohol with 10% Pd/C and H_2 (1 atm) to give the chiral diols **2** in 86% yield and 99% ee and **4** in 86% yield and 99% ee respectively (**Scheme 2**).



Scheme 2: (a) (i) PhNO, L-proline (25 mol%), -20 ºC, 24 h then MeOH, $NaBH_4$; (ii) H_2 (1 atm), Pd/C (10%), MeOH, 86% (over two steps); (b) (i) PhNO, D-proline (25 mol%), -20 ºC, 24 h then MeOH, $NaBH_4$; (ii) H_2 (1 atm), Pd/C (10%), MeOH, 86% (over two steps).

Having obtained the diols **2** and **4** in high enantiomeric purity, the second chiral centre was readily generated by Rh-catalyzed diastereoselective intramolecular C-H aminations using either chiral sulfamate or carbamate esters (**8** or **14**). The synthetic route for (-)-Cytoxazone from key intermediate diol **2** is presented in **Scheme 3**.

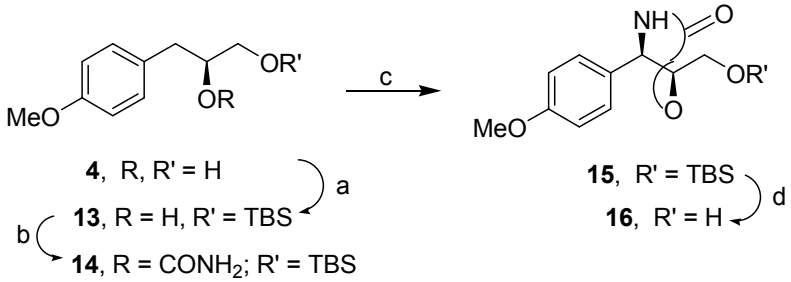


Scheme 3. Reactions and conditions: (a) TBSCl, imidazole, DMF, 25 °C, 4h, 98%; (b) camphor sulfonic acid, MeOH, 95%; (c) HCO_2H, chlorosulfonyl isocyanate, 0 °C, 76%; (d) 2 mol% $Rh_2(OAc)_4$, $PhI(OAc)_2$, MgO, CH_2Cl_2, 40 °C, 82%, *anti*:*syn* (10:1); (e) camphor sulfonic acid, MeOH, 25 °C, 97%; (f) (i) $(Boc)_2O$, DMAP, Et_3N, CH_2Cl_2, 25 °C; (ii) CH_3CN:H_2O (4:3), 60 °C, 84% (over two steps); (g) NaH, THF, 0 °C, 96%.

Thus, synthesis of (-)-cytoxazone starts with di-TBS protected silyl ether **6**. The selective deprotection of TBS group in **6** was achieved using camphor sulfonic acid in MeOH to produce primary alcohol **7** in 95% yield, which was readily converted into sulfamate ester **8** in 76% yield.[3b] The sulfamate ester **8** underwent selective γ-C-H insertion in presence of catalytic amount of $Rh_2(OAc)_4$, $PhI(OAc)_2$ as oxidant, and MgO as additive in CH_2Cl_2 at 40 °C with *anti* (10:1) diastereoselectivity (determined from ^1H NMR analysis) to afford the six-membered ring insertion product **9** in 82%

combined yield. The deprotection of TBS group in **9** using camphor sulfonic acid in MeOH furnished the alcohol **10** in 97% yield. Carbamoylation[3b] of the –NH moiety of oxathiazinane **10** with Boc_2O and Et_3N in CH_2Cl_2 followed by ring opening of the crude *N*-Boc protected oxathiazinane[3b] at 60 °C with aq. CH_3CN gave the *anti*-amino alcohol **11** in 84% yield. Finally, the regioselective intramolecular cyclization[8] of amino alcohol **11** using NaH in THF gave (-)-cytoxazone **12** in 96% yield and 99% ee (**Scheme 3**).

The synthetic route for (+)-*epi*-Cytoxazone from key intermediate diol **2** is presented in **Scheme 4**.



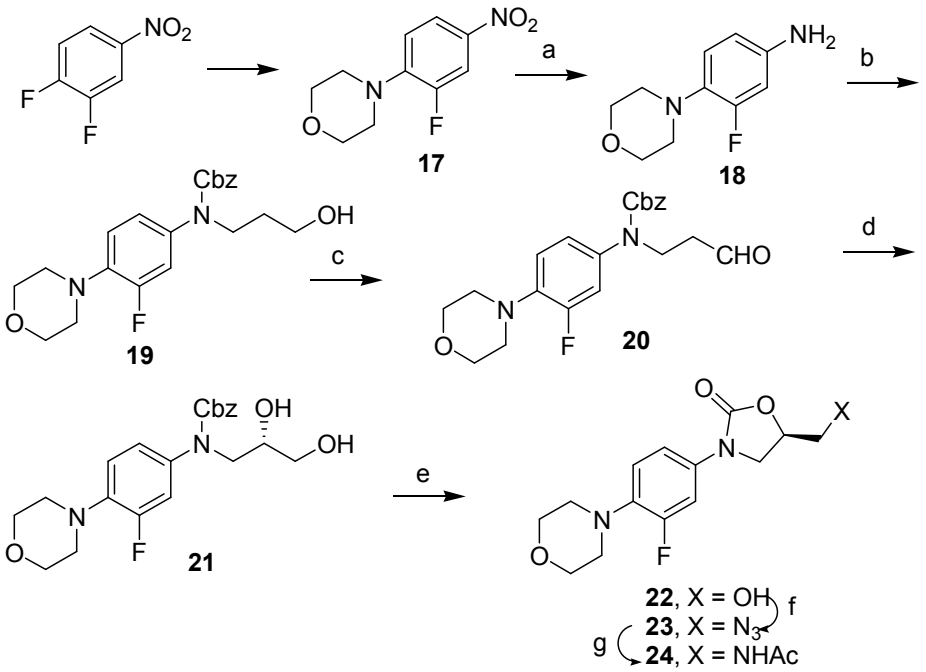
Scheme 4. Reactions and conditions: (a) TBSCl, imidazole, CH_2Cl_2, 25 °C, 98%; (b) trichloroacetyl isocyanate, CH_2Cl_2, 0 ^{0}C-25 ^{0}C, 2 h then K_2CO_3, MeOH, H_2O, 0 ^{0}C-25 ^{0}C, 12h, 92%; (c) 2 mol% $Rh_2(OAc)_4$, $PhI(OAc)_2$, MgO, CH_2Cl_2, 40 °C, 87%, *syn*:*anti* (5.5:1); (d) TBAF, THF, 92%.

The mono protection of primary alcohol of diol **4** with TBSCl gave the secondary alcohol **13**, which was converted into carbamate **14** in 92% yield.[3a] The carbamate **14** underwent C-H insertion on treatment with 2 mol% $Rh_2(OAc)_4$, $PhI(OAc)_2$ and MgO in CH_2Cl_2 at 40 °C to afford the corresponding oxazolidinone **15** with *syn* diastereoselectivity (5.5:1) (determined from ^{1}H NMR analysis) in 87% combined yield.[3a] Finally, the deprotection of TBS group using TBAF in THF furnished (+)-*epi*-Cytoxazone **16** in 92% yield and 99% ee (**Scheme 4**).

CHAPTER 2

Short and Practical Enantioselective Synthesis of Linezolid and Eperezolid *via* Proline-Catalyzed Asymmetric α-Aminooxylation

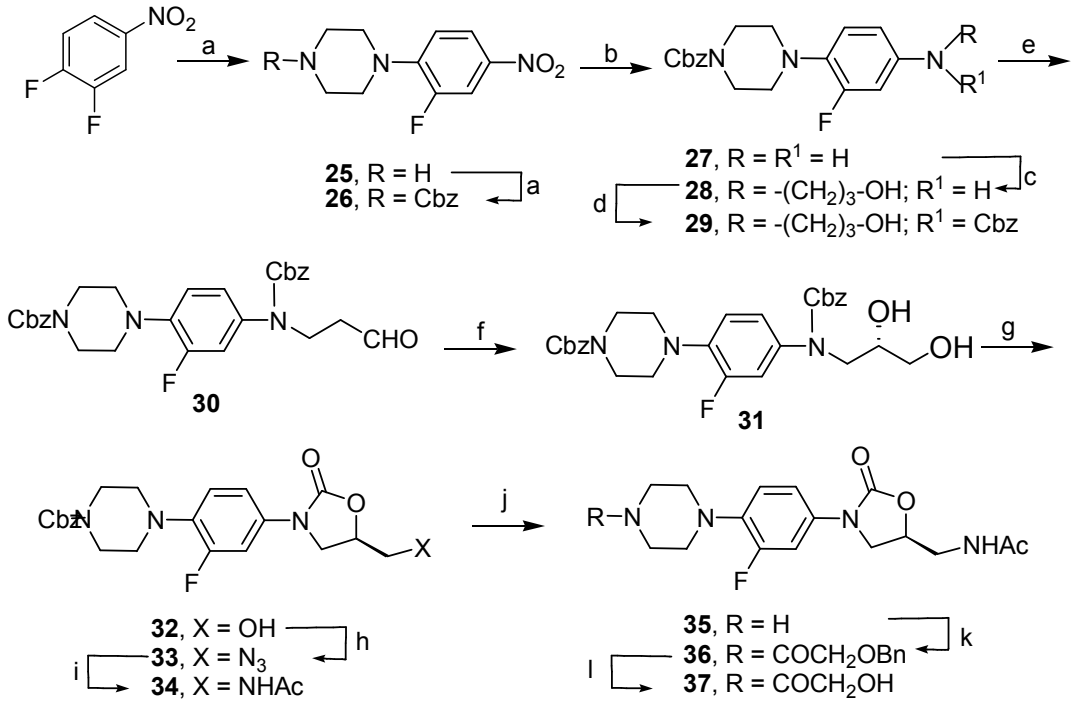
Linezolid (U-100766) **24** (marked as Zyvox^{TM}) and Eperezolid (U-100592) **37**, are a novel and promising class of synthetic antibiotics that have recently emerged as important therapeutic agents, active against numerous multidrug-resistant Gram-positive organisms.[9] The synthetic route for Linezolid is presented in **Scheme 5**.[10]



Scheme 5: (a) TsO-$(CH_2)_3$-OH, NaI, Na_2CO_3, DMF, 65 ºC; (b) Cbz-Cl, $NaHCO_3$, acetone-water, 85% (over two steps); (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ºC to -60 ºC, 95%; (d) (i) PhNO, D-proline (25 mol%), -20 ºC, 24 h then MeOH, $NaBH_4$; (ii) $CuSO_4$ (30 mol%), MeOH, 86% (over two steps); (e) NaH, THF, 0 ºC, 96%; (f) (i) MsCl, Et_3N, CH_2Cl_2, 0 ºC, 4 h; (ii) NaN_3, DMF, 75 ºC, 92% (over two steps); (g) 10% Pd/C, H_2 (1 atm), EtOAc, 12 h then Ac_2O, py, 92%.

The synthesis of Linezolid **24** starts with the nucleophilic reaction of 3,4-difluoronitrobenzene with excess morpholine which selectively gave the *p*-substituted nitrobenzene **17** in 95% yield. The nitro compound **17** (using ammonium formate and Pd/C) was reduced to the corresponding aryl amine **18.** Treatment of arylamine **18** with monotosyl protected 1, 3-propane diol gave the secondary amine, which was then protected using Cbz-Cl to furnish the key intermediate alcohol **19** in 85% overall yield. The alcohol **19** was then oxidized using standard Swern conditions to the aldehyde **20**. It was then converted into the corresponding diol **21** by the reaction of aldehyde **20** with nitrosobenzene as the oxygen source in the presence of D-proline in CH_3CN at -20 ºC,[2a] followed by treatment with $NaBH_4$ in MeOH gave the crude aminoxy alcohol, subsequent reduction of which with 30% $CuSO_4$ yielded the chiral diol **21** in 86% yield. The regioselective intramolecular cyclization[8] of diol **21** using sodium hydride in THF at 0 ^{0}C furnished the desired oxazolidinone **22** in 96% yield and 99% ee (determined by ^{1}H NMR analysis of its Mosher's ester). The oxazolidinone **22** was then converted into the corresponding azide **23** in two steps with 92% overall yield. Finally, the azide function was reduced with H_2 using Pd/C to furnish the crude amine, which was converted (Ac_2O, py) to linezolid **24**.

The synthetic route for Eperezolid **37** is presented in **Scheme 6**.



Scheme 6: (a) Cbz-Cl, $NaHCO_3$, acetone-H_2O, 97%; (b) $CoCl_2$, $NaBH_4$, MeOH, 60 ºC, 95%; (c) TsO-$(CH_2)_3$-OH, NaI, Na_2CO_3, DMF, 65 ºC; (d) Cbz-Cl, $NaHCO_3$, acetone-H_2O, 79% (over two steps); (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ºC to -60 ºC, 94%; (f) (i) PhNO, D-proline (25 mol%), -20 ºC, 24 h then MeOH, $NaBH_4$; (ii) $CuSO_4$ (30 mol%), MeOH, 82% (over two steps); (g) NaH, THF, 0 ºC, 94%; (h) (i) MsCl, Et_3N, CH_2Cl_2, 0 ºC, 4 h; (ii) NaN_3, DMF, 75 ºC, 89% (over two steps); (i) PPh_3, THF-water, 12 h then Ac_2O, py, 96%; (j) 10% Pd/C, H_2 (1 atm), MeOH-CH_2Cl_2 (3:1), 97%; (k) $ClCOCH_2OCH_2Ph$, Et_3N, CH_2Cl_2, 0 ºC, 100%; (l) 10% Pd/C, H_2 (1 atm), MeOH-CH_2Cl_2 (3:1), 89%.

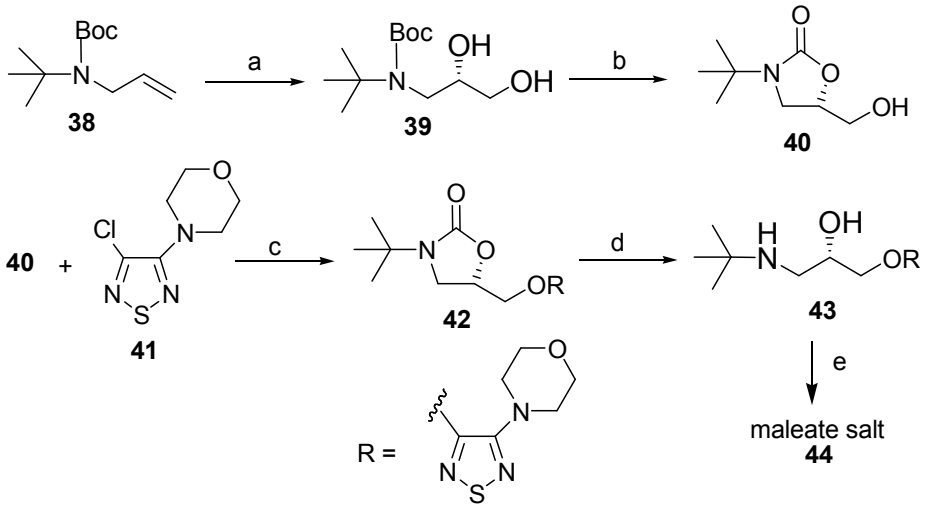
Commercially available 3,4-difluoronitro benzene was converted selectively into *p*-substituted nitrobenzene **25** using excess piperazine. Protection of the secondary amine group of **25** with Cbz-Cl gave **26** in quantitative yield. Reduction of the nitro group in **26** ($NaBH_4$, cobalt chloride, MeOH, 60 ºC)[11] produced arylamine **27,** which was transformed to the alcohol **29** in 79% overall yield in two steps. Swern oxidation of the alcohol **29** gave the aldehyde **30**, which was subjected to D-proline catalyzed asymmetric α-aminooxylation with nitrosobenzene followed by reduction to furnish the chiral diol **31** in 82% yield. Subsequent regioselective intramolecular cyclization[8] of diol **31** (NaH, THF, 0 ºC) gave the oxazolidinone **32** in 94% yield and 99% ee, which was further converted into the corresponding azide **33** in two steps, in 94% overall yield. Reduction of azide **33** to the corresponding amine was readily achieved with PPh_3 in THF-H_2O mixture and the *in situ* generated amine was acetylated (Ac_2O, py) to give acetamide **34** in excellent yield. Deprotection of the Cbz group in **34** under catalytic hydrogenolysis conditions (Pd/C, H_2 (1 atm), MeOH-CH_2Cl_2) provided the

piperazine **35**, which was acylated ($ClCOCH_2OBn$, Et_3N, CH_2Cl_2, 0 ºC) to give **36** in quantitative yield. Finally, debenzylation of **36** (Pd/C, H_2 (1 atm), MeOH-CH_2Cl_2) furnished eperezolid **37** in 89% yield and 99% ee.

CHAPTER 3

Enantioselective Synthesis of (*S*)-Timolol *via* Kinetic Resolution of Terminal Epoxides and Dihydroxylation of Allylamines

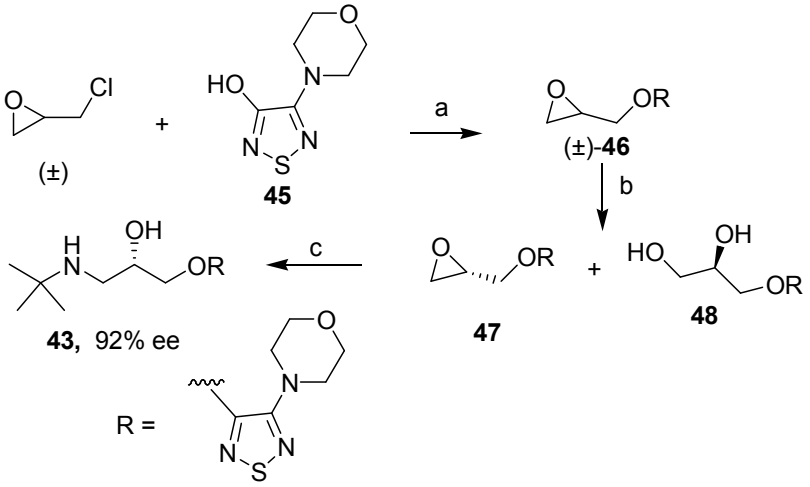
The β-adrenergic antagonist drug Timolol, [(*S*)-(-)-3-(3-*tert*-butylamino-2-hydroxypropoxy)-4-(*N*-morpholino)-1,2,5-thiadiazole, **1**), like propranolol and a number of other β-blockers, has been shown to be effective in humans for the treatment of hypertension and angina pectoris.[12] In addition, Timolol has been marketed recently for the treatment of glaucoma, based on its ability to lower intraocular pressure when administered directly into the eye. The enantioselective synthesis of (*S*)-Timolol **43** using asymmetric dihydroxylation (AD) (**Scheme 7**), Hydrolytic kinetic resolution (**Scheme 8**) and Kinetic resolution of terminal epoxides via enantioselective ring opening with phenol (**Scheme 9**) as key reactions is presented in this chapter. The starting material, *N*-*tert* butyl allylamine (**38**) was readily prepared in 90% overall yield in 2 steps of protection of *tert*-butyl amine with $(Boc)_2O$, followed by its allylation with allylbromide in the presence of NaH. Allyl amine **38** was then subjected to Os-catalyzed asymmetric dihydroxylation using $(DHQ)_2$-PHAL as ligand to produce the corresponding chiral diol **39** in 93% yield and 56% ee.



Scheme 7: (a) cat. OsO_4, $(DHQ)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, *tert*-BuOH:H_2O (1:1), 0-25 ºC, 24 h, 93%, 55.9%ee; (b) K_2CO_3 , MeOH, reflux, 5h, 95%; (c) KO^tBu, ^tBuOH, 25^0C, 12h, 75%; (d) 2N NaOH, MeOH, 90%; (e) maleic acid, THF, 25 ºC, 1h.

The diol **39**, when subjected to treatment with K_2CO_3 in MeOH under reflux, produced 2-oxazolidinone **40** in 95**%** yield. Oxazolidinone **42** was obtained by the *O*-alkylation of hydroxy compound **40** with 3-chloro-4-(*N*-morpholino)-1,2,5-thiadiazole (**41**).[13] It was then hydrolyzed using 1N NaOH in methanol[14] to furnish Timolol (**43**) which was isolated as its maleate salt **44** in 80% yield and 55.9% ee. Although the asymmetric dihydroxylation route to (*S*)-Timolol was facile and high yielding, it suffers from low enantioselectivity. Hence, we focused on a new strategy of preparing the racemic epoxide **46**, which could be then subjected to Jacobsen's hydrolytic kinetic resolution (HKR).[5]

b) Hydrolytic Kinetic Resolution (HKR) Approach: The hydrolytic kinetic resolution (HKR) of terminal epoxides catalyzed by chiral (salen) Co(111) complex **1**.OAc afford both recovered unreacted epoxide and 1,2-diol product in highly enantioenriched form.[5] As such, the HKR provides general access to useful, highly enantioenriched chiral building blocks that are otherwise difficult to access, from inexpensive racemic materials. Thus, the racemic epoxide **46**, prepared by the *O*-alkylation of 3-hydroxy-4-(*N*-morpholino)-1,2,5-thiadiazole (**45)**[13] with epichlorohydrin in excellent yield, was subjected to hydrolytic kinetic resolution[5] [(*S,S)*-Salen-Co(II) (0.5 mol %), AcOH (2 mol%), THF, distilled H_2O (0.55 equiv), 0º C, 14 h] to afford chiral epoxide **47** in 46% yield and 89.9%ee along with its diol **48** in 45% yield.

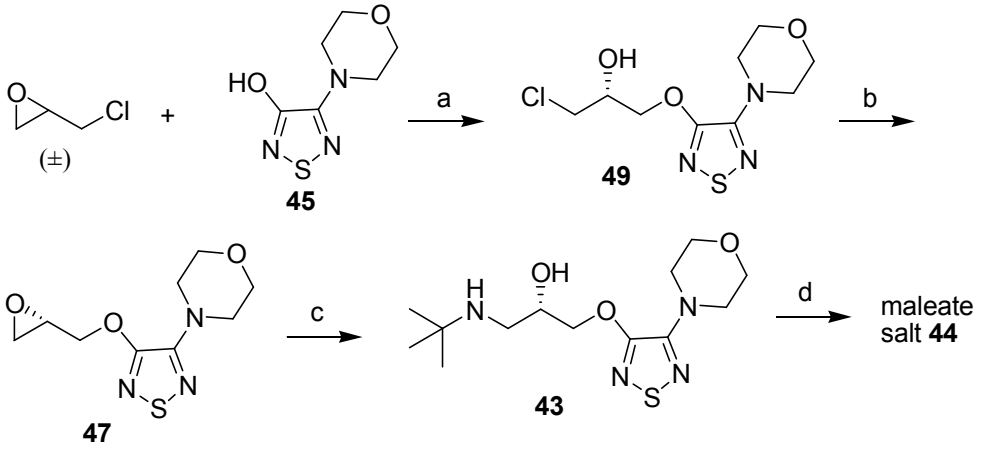


Scheme 8: (a) *tert*-BuOK, THF, 5h, 95%; (b) (*S,S)*-salen-Cobalt(II) (0.5 mol %), AcOH (2 mol%), THF, H_2O (0.55 equiv), 0 ºC, 14 h, (46%, 89.9% ee for **47** and 45% for **48**); (c) *tert*-$BuNH_2$, reflux, 30 h, 66%.

Finally, the regiospecific ring opening of the epoxide **47** with *tert*-butylamine[15] afforded (*S*)-Timolol **43**, which was isolated as its maleate salt **44** in 80% yield and 89.9% ee. Although the optical purity of (*S*)-Timolol has increased considerably in HKR route, the methodology has the disadvantage of losing half of the expensive epoxide **46**. Hence, the recent methodology of kinetic resolution of terminal epoxides *via* enantioselective ring-opening with phenolic substrate[16] was attempted.

c) Kinetic Resolution of Terminal Epoxides via Enantioselective Ring Opening with Phenol Approach:

The ring opening of racemic terminal epoxides with phenols is probably the most versatile and direct method to obtain enantiopure R-aryloxy alcohols (**49**) which are valuable targets for key synthetic intermediates in a variety of pharmaceutically important compounds.[16] The cheaper and ready accessibility of (±)-epichlorohydrin renders kinetic resolution of its epoxide with phenolic substrates as a potentially attractive route for the preparation of chiral epoxide **47** using active Co(salen) complex as the chiral catalyst. Thus, the reaction of 2.5 equiv. of (±)-epichlorohydrin with 3-hydroxy-4-(*N*-morpholino)-1,2,5-thiadiazole (**45**) in the presence of *(R,R)*-(salen)Co[$OC(CF_3)_3$] complex (0.044 equiv) in *tert*-butyl methyl ether at 0 ºC led to isolation of (2*R*)-1-chloro-3-[(4-morpholin-4-yl-1,2,5-thiadiazol-3-yl)oxy]propan-2-ol (**49**) in 86% yield based on hydroxy thiadiazole **45** and 98% enantiomeric excess.



Scheme 9: (a) (*R,R)*-salen-Co[$OC(CF_3)_3$] (0.044 equiv), epichlorohydrin (2.2 equiv), *tert*-butyl methyl ether, 12 h, 86%, 98%ee; (b) *tert*-BuOK, THF, 0º C-25º C, 1 h, 97% (c) *tert*-$BuNH_2$, reflux, 30 h, 66%; (d) maleic acid, THF, 25 ºC, 1h.

The chlorohydrin **49** was then converted to epoxide **47** in 97% yield (Bu^tOK, THF, 0 ºC). Finally, the chiral epoxide **47** was subjected to regiospecific ring opening with

tert-butylamine to afford (*S*)-Timolol **43**, which was isolated as its maleate salt **44** in 80% yield and 98% ee (**Scheme 9**).

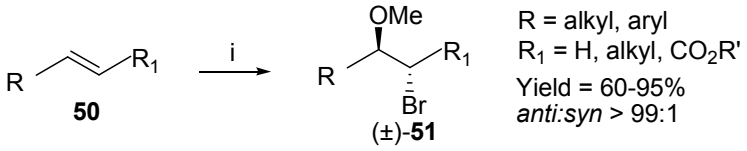
CHAPTER 4

$NaIO_4$-Mediated Regioselective Oxidative Halogenation of Alkenes using Alkali Metal Halides as Halogen Source and Metal-Catalyzed Asymmetric Epoxidation of Olefins

This chapter describes the use of $NaIO_4$ as a novel catalyst in organic synthesis and is divided into three sections. While **Section I** presents the methoxyhalogenation of alkenes, **Section II** presents dibromination of alkenes and **Section III** describes the asymmetric epoxidation of alkenes.

SECTION I: $NaIO_4$-Mediated Regioselective Oxidative Halogenation of Alkenes using Alkali Metal Halide as Halogen Source: A High Yield Preparation of Methoxyhalogens

The functionalization of olefins by addition of the two different functional groups in a single step is an important transformation for e.g. aminohydroxylation, haloazidation, halohydrin, methoxyhalogenation etc. Among all these, methoxyhalogenation is one of the most useful reactions as the halogens can be replaced by a variety of nucleophiles such as N_3, CN, OAc, OMe, NHR, SR etc[17] there-by providing a new class of functionalized reactive intermediates in organic synthesis. This section describes the synthesis of methoxyhalogens **51** from the corresponding alkenes **50** using $NaIO_4$ as the catalyst and metal halide as the halogen source **(Scheme 10**.[18]



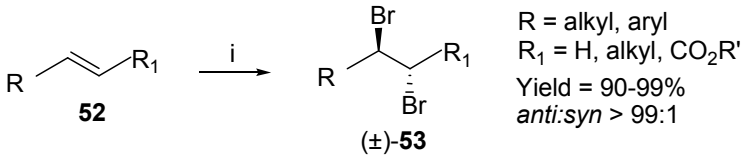
50 (±)-**51**

Scheme 10: (i) $NaIO_4$ (25 mol%), NaBr(1.2 equiv), 30% aqueous H_2SO_4 (1 equiv), MeOH: H_2O (2:1), 25 ºC, 1-3 h, 60-95%.

SECTION II: $NaIO_4$-Mediated Regioselective Oxidative Halogenation of Alkenes using Alkali Metal Halide as Halogen Source: A High Yield Preparation of 1,2-Dibromides

The dibromination of olefins constitute an important method for the synthesis of 1,2-dibromides. The halo compounds have potential utilization in organic synthesis due to their ability to undergo nucleophilic transformation with nucleophiles such as OH,

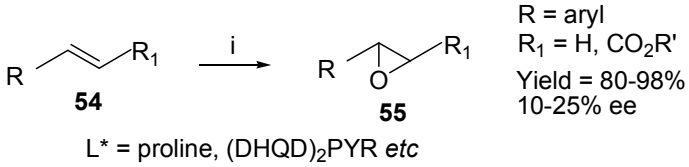
NHR, N_3, CN, OAc, SR, carbanions *etc*. This section describes the synthesis of dibromides **53** from the corresponding alkenes **52** using $NaIO_4$ as the catalyst and metal halide as the halogen source **(Scheme 11)**.[18]



Scheme 11: (i) $NaIO_4$ (25 mol%), NaBr(2.2 mmol), AcOH, 25 ºC, 1-3 h, 95-99%.

SECTION III: Metal-Catalyzed Asymmetric Epoxidation of Olefins

The importance of epoxides in organic synthesis arises partly from the occurrence of the strained three-membered ring unit in a number of interesting natural products.[19] The stereospecific manner in which epoxides generally react renders these compounds attractive chiral building blocks for asymmetric synthesis. This section describes the asymmetric synthesis of epoxides **55** from the corresponding alkenes **54** using variety of ligands (**Scheme 12**).



Scheme 12: (i) $MnCl_2$ (2.5 mol%), L* (2.5 mol%), H_2O_2, $NaHCO_3$ (0.5 equiv), CH_3CN:H_2O (3:1), 0 ºC.

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Chapter I

Enantioselective Synthesis of (-)-Cytoxazone and (+)-epi-Cytoxazone via Proline-Catalyzed α-Aminooxylation of Aldehydes and Rh-Catalyzed Diastereoselective Oxidative C-H Aminations

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"Enantioselective synthesis of (-)-Cytoxazone and (+)-*epi*-Cytoxazone *via* Rh-catalyzed diastereoselective oxidative C-H amination" Narina V. Srinivasarao, Talluri Siva Kumar, Shyla George and Arumugam Sudalai, *Tetrahedron Letters* **2007**, *48*, 65.

Enantioselective Synthesis of (-)-Cytoxazone and (+)-*epi*-Cytoxazone *via* Proline-catalyzed α-Aminooxylation of Aldehydes and Rh-catalyzed Diastereoselective Oxidative C-H Aminations

1.1 Introduction

In 1998, Osada and co-workers reported the isolation of (4*R*,5*R*)-5-(hydroxymethyl)-4-(4-methoxyphenyl)-1,3-oxazolidine-2-one [(–)-**1a**, generic name cytoxazone],[1] which was shown to possess high cytokine modulator activity by acting on the Th2 cells.[2] Because of these biological properties, several total syntheses of (-)-**1a** and its *trans*-diastereoisomer ((+)-*epi*-cytoxazone (**1b**) (**Fig 1)** have been reported.[3, 7-17]

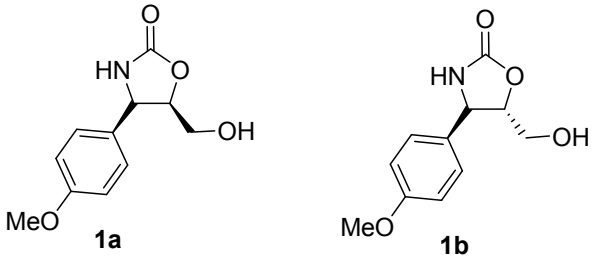


Fig. 1: Structure of (-)-cytoxazone (**1a)** and (+)-*epi*-cytoxazone (**1b)**

Prompted by the first positive biological results, many researchers have also reported the preparation of *cis*- and *trans* isocytoxazones **2a**,**b**, structural isomers of cytoxazone **1a** and its trans epimer **1b** (**Fig 2**).[3]

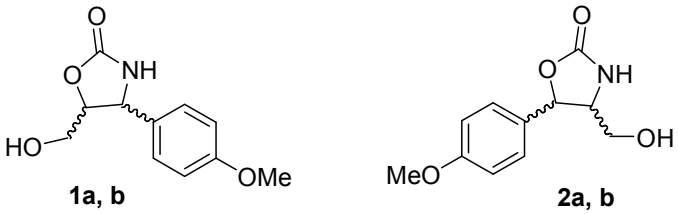


Fig. 2: Structural isomers of cytoxazone

1.2 The Pharmacology of Cytoxazone

It is well established that the induction of humoral or cellular response is influenced by the development of distinct subsets of $CD4^+$ T cells.[4] The Th1 cell subset produces predominately IL-2, GM-CSF, INF-γ, and TNF-β, (type 1 cytokines) and is involved in delayed-type hypersensitivity reactions, whereas the Th2 cell subset secretes IL-4, IL-5, IL-6, IL-10, and IL-13 (type 2 cytokines), which are important factors for B cell growth and differentiation to Ig secretion. The imbalance of cytokine production by $CD4^+$ T cells leads to a wide variety of immunological disorders, i.e. allergy, progressive lymphoproliferation, and severe immunodeficiency.[5] Skin and lung biopsies from allergic patients indicate that the pivotal cells in the allergic site are the Th2 cells.[6] Treatments effectively suppressing the function or the differentiation of these allergen-specific Th2 cells will most likely provide efficient ways to intervene in Ig-mediated allergic diseases.

In the course of screening for chemical immunomodulators that inhibit the type 2 cytokine production in Th2 cells, it was found that cytoxazone (**1a**) containing a 2-oxazolidinone ring, which is rare in microbial metabolites, as a novel cytokine modulator produced by *Streptomyces* sp. Cytoxazone (**1a**) shows a cytokine-modulating activity by inhibiting the signaling pathway of Th2 cells, but not Th1 cells.[1]

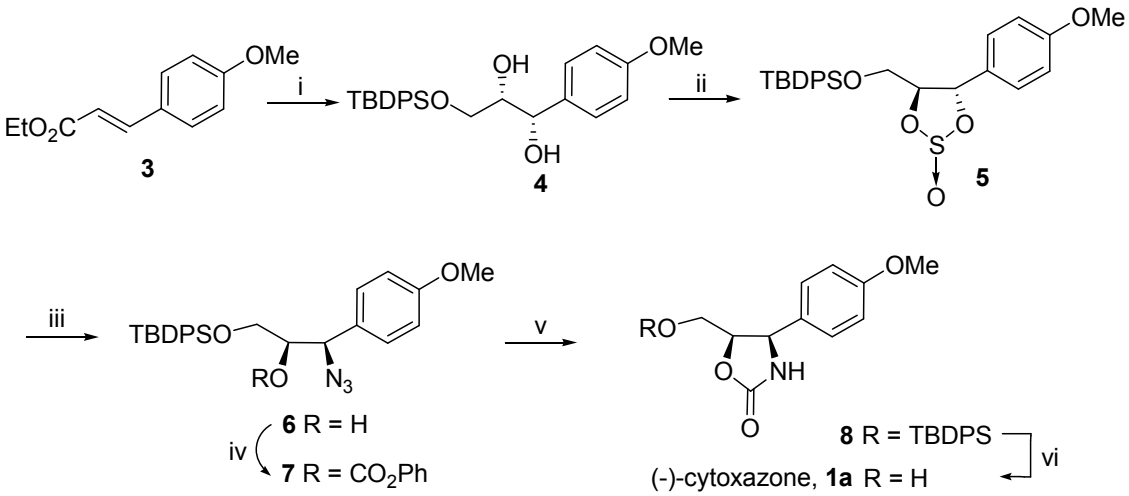
1.3 Review of Literature

Literature search revealed that there are several reports available for the synthesis of cytoxazone (**1a**)[7-17] involving resolution, chemo-enzymatic or enantioselective syntheses, which are described below.

Nakata's approach (1999)[7]

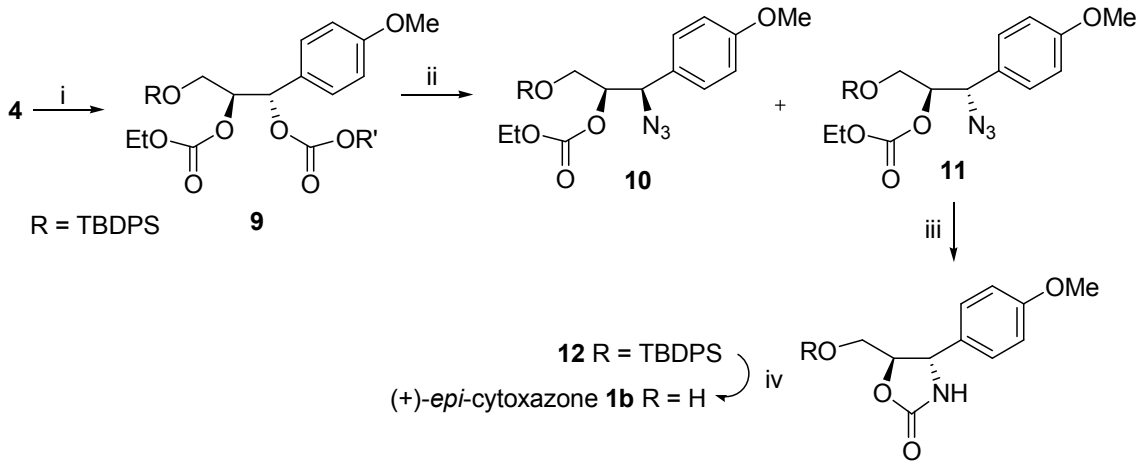
Nakata *et al.* have achieved the synthesis of (-)-cytoxazone (**1a**) using Sharpless asymmetric dihydroxylation of ester **3**. The cyclic sulfite **5** was afforded from ethyl *p*-

methoxycinnamate (**3**) by the Sharpless catalytic asymmetric dihydroxylation followed by treatment with $SOCl_2$ in 99 % yield and 97 % ee. The cycic sulfite **5** was then opened using LiN_3 and the alcohol obtained was protected as the corresponding carbonate **7**. Intramolecular cyclization of carbonate **7** with PPh_3 followed by the deprotection of TBBPS group gave (-)-cytoxazone (**1a**) in 89% ee and 96% yield (**Scheme 1**).



Scheme 1: (i) (a) AD-mix-α, t-BuOH: H_2O (1:1), 25 °C, 93 %, 99% ee. (b) $NaBH_4$, THF, 0 °C, 66%. (c) TBDPSCI, imidazole, DMF, 0 °C, 99%. (ii) $SOCl_2$, Et_3N, CH_2CI_2, 0 °C, 99%. (iii) LiN_3, DMF, 70 °C, 74 %. iv) $ClCO_2Ph$, Py, CH_2CI_2, 25 ºC, 96%. (v) PPh_3, THF/ H_20, 50 °C, 90%. (vi) n-Bu_4NF, THF, 0 °C, 89% ee, 96%.

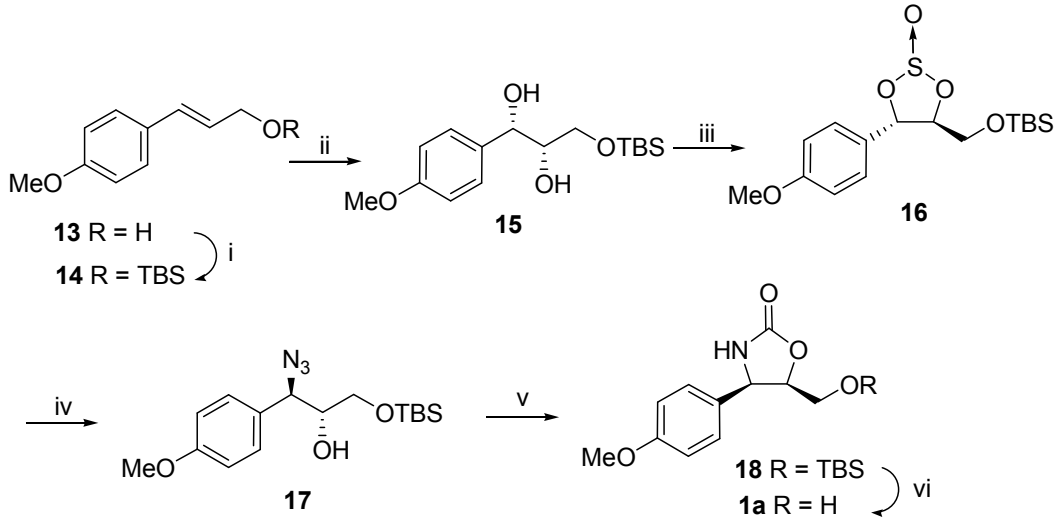
The same group has achieved the synthesis of (+)-*epi*-cytoxazone **1b** from the common intermediate **4** using an efficient one-step method for the stereoselective azidation. Thus, (4*S*,5*S*)-di(ethylcarbonate) **9**, prepared from diol **4**, was treated with $TMSN_3$ (6 eq.) in the presence of TMSOTf to afford a 6:1 mixture of the desired α-azide **11** and its β-isomer **10**. The α-azide **11** was then treated with PPh_3 in THF/H_20 to give 2-oxazolidinone **12**, which was converted to *4-epi*-cytoxazone (**1b**) in 99% yield using tetrabutylammonium fluoride (**Scheme 2**).



Scheme 2: (i) $ClCO_2Et$, Py, CH_2Cl_2, 0 °C, 92%. (ii) $TMSN_3$, TMSOTf, MeCN, -43 °C, 99%. (iii) PPh_3, THF/H_20, 50 °C, 100%. (iv) n-Bu_4NF, THF, 0 °C, 99%.

Mori's approach (1999)[8]

Mori *et al.* have synthesized (-)-cytoxazone (**1a**) employing the Sharpless asymmetric dihydroxylation as the key reaction. Thus, silyl ether **14** was subjected to asymmetric dihydroxylation to give diol **15** in 99% yield, which was further converted to the corresponding azido alcohol **17** via cyclic sulfite **16**. Azido alcohol **17** was converted

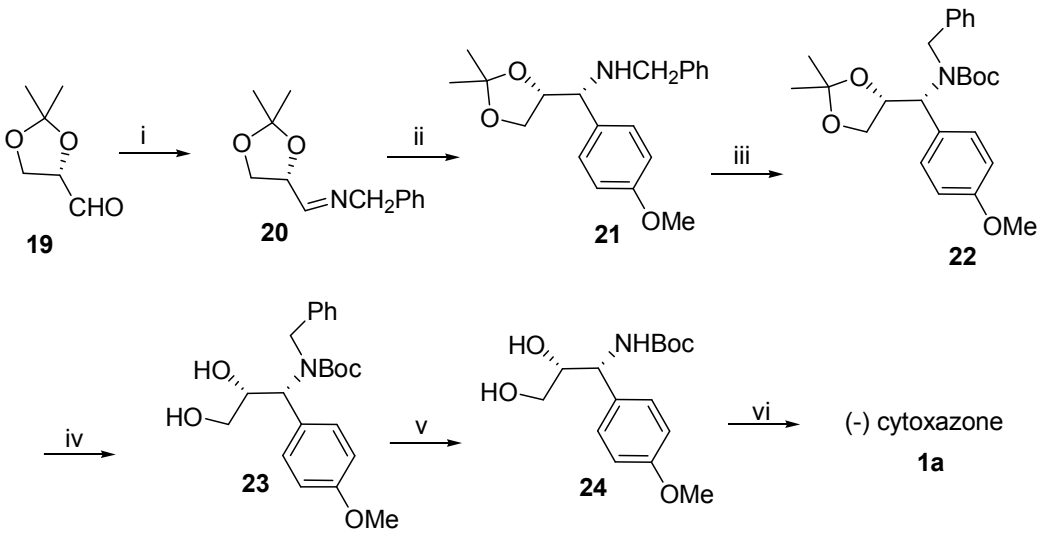


Scheme 3: (i) TBSCl, imidazole, DMF, 97%. (ii) $(DHQD)_2$-PHAL, $K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, *t*BuOH/H_2O, 99%. (iii) $SOCl_2$, Et_3N, CH_2Cl_2, 88%. (iv) LiN_3, DMF, 100 ºC, then H_2O at 0 ºC, 61%. (v) (a) HCO_2NH_4, Pd/C, MeOH, 50 ºC, 87%. (b) $CO(OEt)_2$, K_2CO_3, 66%. (vi) TBAF, THF, 89%.

to (-)-cytoxazone (**1a**) in 3 steps of (i) reduction of azide to amine (ii) formation of oxazolidinone (iii) deprotection of silyl protection (**Scheme 3**).

Rao's approach (2001)[9]

Rao *et al*. have achieved the synthesis of (-)-cytoxazone (**1a**) *via* chiral pool approach starting from aldehyde **19**. Grignard addition of *p*-methoxyphenylmagnesium bromide on to *N*-benzylimine **20** derived from (*S*)-2,3-*O*-isopropylidene glyceraldehyde **19** gave the aminoalcohol **21** which was protected as its carbamate. Reductive removal of the benzyl protection in the carbamate **23** followed by intramolecular cyclization afforded (-)-cytoxazone (**1a**) (**Scheme 4**).

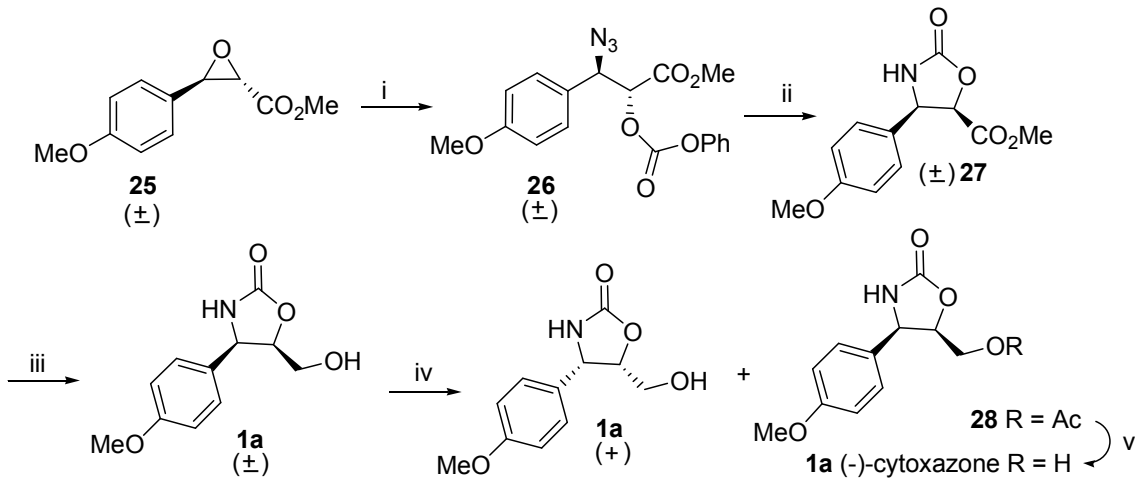


Scheme 4: (i) $PhCH_2NH_2$, dry ether, 0 ºC. (ii) 4-methoxyphenyl magnesium bromide, dry ether. (iii) $(Boc)_2O$, Et_3N, dry ethanol. (iv) PTSA (cat), MeOH. (v) Pd/C (cat), conc.HCl (a drop), EtOH. (vi) NaH, dry THF.

Sunjic's approach (2001)[10]

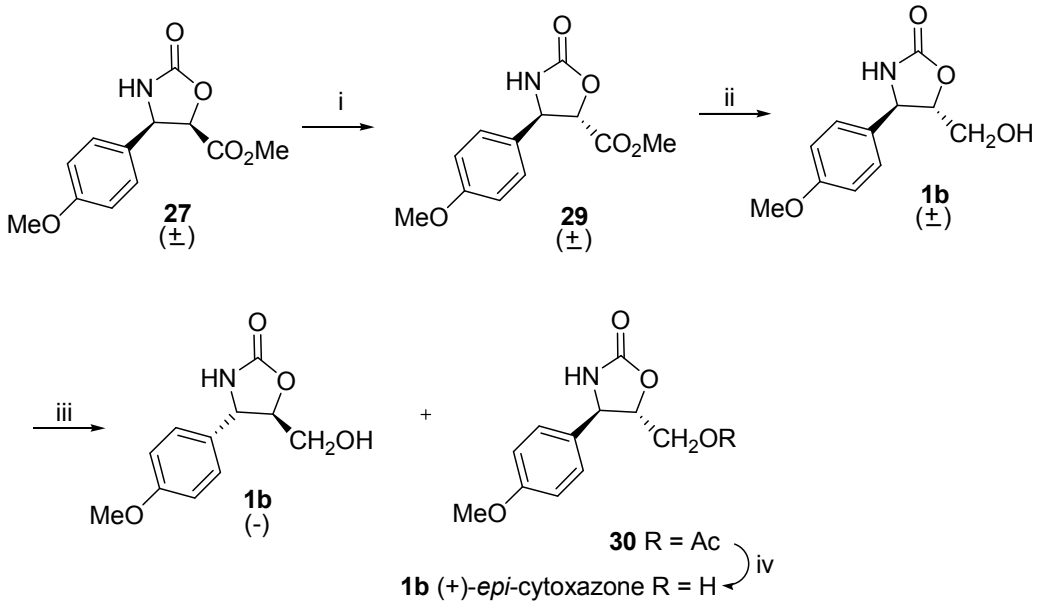
In this approach, synthesis of (-)-cytoxazone (**1a**) was achieved starting from the glycidic ester **25** using enzymatic kinetic resolution. Nucleophilic ring opening of the epoxide **25** with NaN_3, followed by protection of the alcohol and intramolecular cyclization gave ester **27**. Reduction of the ester **27** and the subsequent kinetic

resolution of racemic **1a** using *Penicillium camemberti* lipase (PcamL) afforded (-)-cytoxazone (**1a)** in 33% overall yield and 88.2% ee (**Scheme 5**).



Scheme 5: (i) aq NaN_3, dioxane, 50 °C, 3 h, 56%. (ii) $ClCO_2Ph$, CH_2Cl_2, –5 °C, 1 h, 100%. (iii) (a) Ph_3P, aq THF, 50 °C, 1.5 h, 88%. (b) $NaBH_4$, $CaCl_2$, absolute EtOH, 25 ºC, 20 min, 79%. (iv) PcamL, vinyl acetate, 30 °C. (v) KOH, MeOH, 25 ºC, 1 h.

Also, (±)-*epi*-cytoxazone (±)-**1b** was synthesized from the common intermediate, oxazolidinone (±)-**27** (**Scheme 6**).

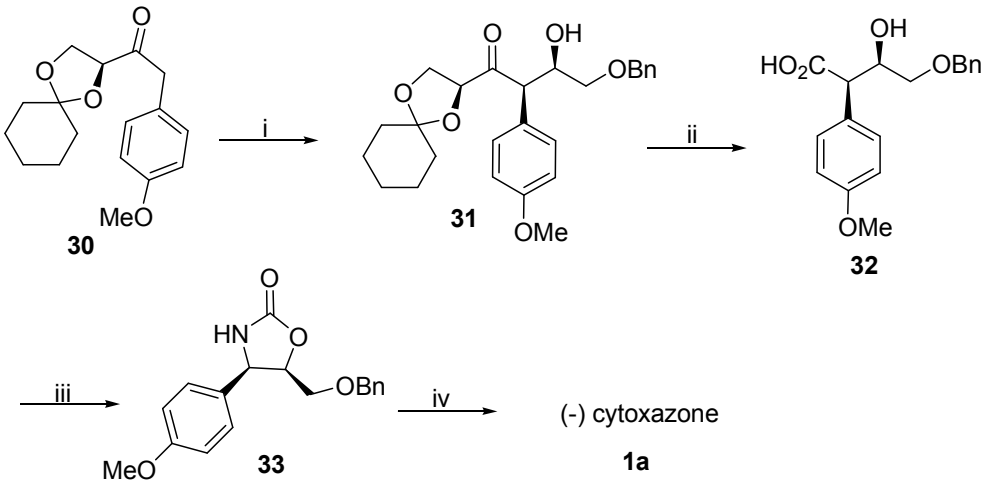


Scheme 6: (i) (a) KOH, EtOH, reflux, 1 h. (b) MeI, K_2CO_3, DMF, 25 ºC, 16 h, 46%. (ii) $NaBH_4$, $CaCl_2$, absolute EtOH, 25 ºC, 20 min., 82%. (iii) CAL in SOL-Gel-AK, vinyl acetate, 30 °C. (iv) KOH, MeOH, 25 ºC, 1 h.

Epimerization at C(5) in oxazolidinone (±)-**27** using potassium hydroxide followed by esterification with methyl iodide gave ester **29**. Reduction of ester **29** with calcium chloride/sodium borohydride and the subsequent kinetic resolution using CAL in SOL-Gel-AK afforded (+)-*epi*-cytoxazone **1b** in 49% overall yield and 87.3% ee.

Carda's approach (2002)[11]

The key steps in Carda's approach are (i) *syn*-stereoselective aldol reaction and (ii) Curtius rearrangement. Aldol reaction of ketone **30** with benzyl protected glycolic aldehyde furnished the expected *syn–syn* aldol adduct **31** in 79% yield. Oxidative cleavage of the acetonide ring in alcohol **31** gave β-hydroxy acid **32** which was subjected to Curtius rearrangement to give the corresponding oxazolidinone **33**. Removal of benzyl group by hydrogenolysis of **33** afforded cytoxazone (-)-**1a** in 78% yield (**Scheme 7**).

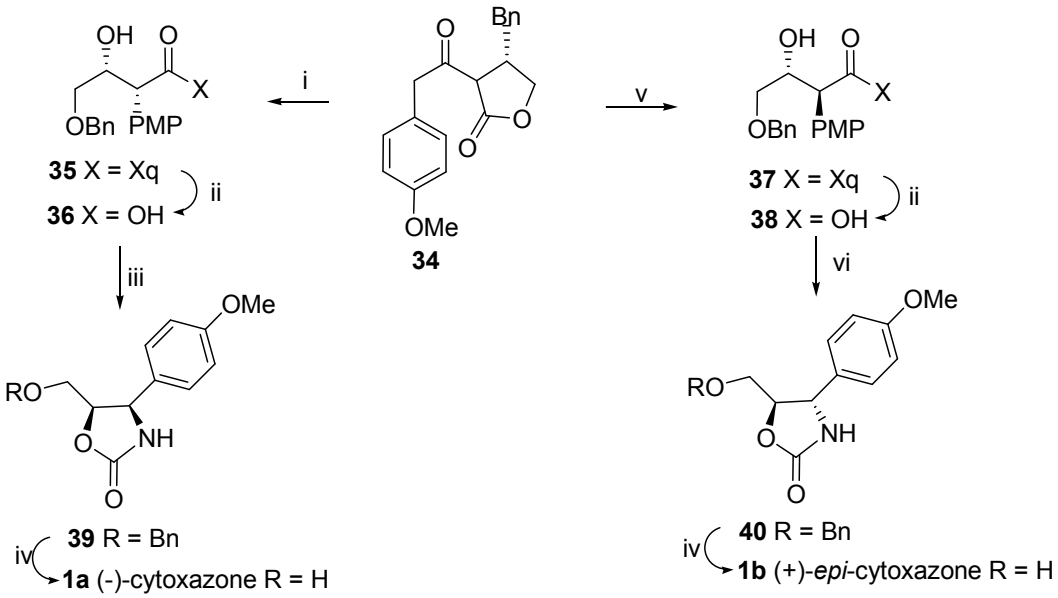


Scheme 7: (i) Chx_2BCl, Et_3N, Et_2O, $BnOCH_2CHO$, -78 ºC to 25 ºC, 79%. (ii) H_5IO_6, Et_2O-EtOAc, 70%. (iii) Et_3N, 4 Å MS, DPPA, toluene, reflux, 12 h, 68%. (iv) EtOH, cat. $Pd(OH)_2$, H_2 (500 psi), 24h, 78%.

Carter's approach (2003)[12]

Carter *et al*. have made use of the Evan's aldol approach as the key reaction for the synthesis of (-)-cytoxazone (**1a**) as well as (+)-*epi*-cytoxazone (**1b**). The reaction of dibutylboron enolate of **34** with the benzyloxyacetaldehyde provided the aldol **35** in

good syn-diastereoselectivity. Removal of the chiral auxiliary from **35** provided the acid **36** which was transformed into the oxazolidinone **39** in a one-pot 3 step procedure: (i) acyl azide formation, (ii) Curtius rearrangement and (iii) isocyanate trapping. Ether **39** was debenzylated using Pearlman's catalyst to provide (-)-cytoxazone (**1a**). The synthesis of (+)-*epi*-cytoxazone required the use of an *anti*-selective aldol product **37** which was obtained by the addition of a pre-complexed solution of benzyloxyacetaldehyde and 0.5 equiv. of $SnCl_4$ to the dibutylboryl enolate of **34**. The same sequence of reactions was used to synthesize (+)-*epi*-cytoxazone (**1b**) starting from aldol product **37** (**Scheme 8**).

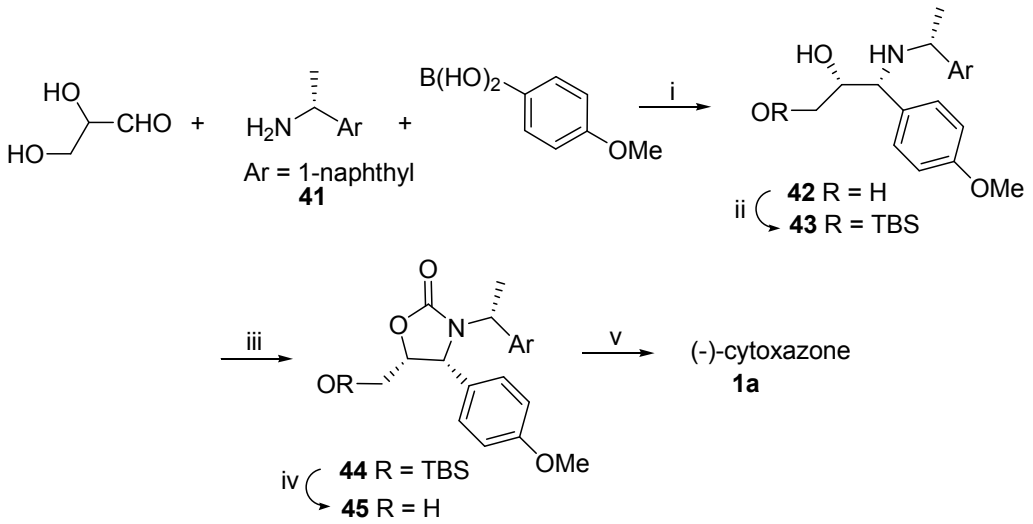


Scheme 8: (i) Bu_2BOTf, i-Pr_2EtN, -78 ºC, 20min.; $BnOCH_2CHO$, -78 ºC to 0 ºC, 1.5 h, 51%. (ii) 4:1 THF:H_2O, H_2O_2, LiOH, 0 ºC, 1 h; $NaHSO_3$, 99%. (iii) $(PhO)_2PON_3$, $PhCH_3$, 23 ºC, 40min., 110 ºC, 3h, 77%. (iv) H_2 (1 atm), $Pd(OH)_2$, MeOH, 23 ^{0}C, 24 h, 84%. (v) Bu_2BOTf, *i*-Pr_2EtN, 0 ºC, 30min.; add $BnOCH_2CHO$ precomplexed w/0.5 equiv $SnCl_4$, -78 ºC, 3 h, 64%. (vi) $(PhO)_2PON_3$, CH_2Cl_2, 23 ºC, 40min.; 45 ºC, 12 h, 61%.

Sugiyama's approach (2004)[13]

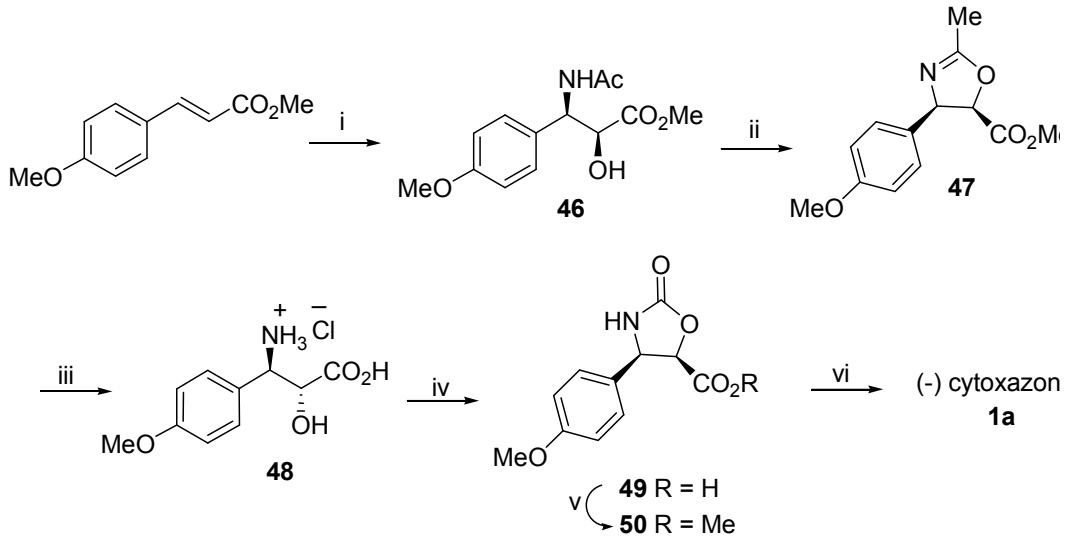
Sugiyama *et al.* have synthesized (-)-cytoxazone **1a** using the Petasis three-component coupling reaction of DL-glyceraldehyde, 4-methoxyphenylboronic acid and (*R*)-1-(1-naphthyl)ethylamine **41**, followed by formation of an oxazolidin-2-one

ring. Separation of the diastereomers by column chromatography and the acidic removal of 1-naphthylethyl group produced (-)-cytoxazone (**1a**) in 13 % overall yield (**Scheme 9**).



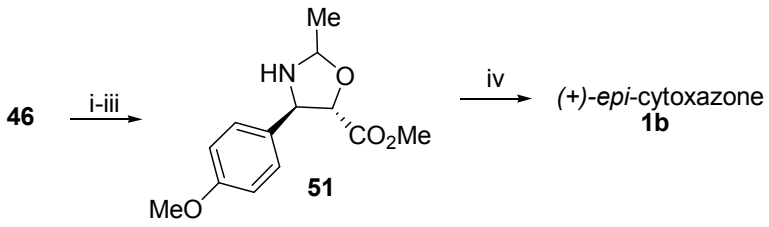
Scheme 9: (i) EtOH, reflux, 3 days, 50%. (ii) TBDMSCl, Et_3N, DMAP, CH_2Cl_2, 25 ºC, 5 h. (iii) DSC, Et_3N, MeCN, 25 ºC, 6 h, 66%. (iv) TBAF, THF, 25 ºC, 63 h and SiO_2 column chromatographic seperation 59%. (v) MsOH, anisole, $MeNO_2$, 50 ºC, 6 h.

Saicic's approach (2004)[14]



Scheme 10: (i) $K_2[OsO_2(OH)_4]$ (4 mol %), BrNHAc, $(DHQD)_2PHAL$ (1 mol%), LiOH, H_2O, t-BuOH, 4 ºC, 20 h, 72%. (ii) Tf_2O, DMAP, CH_2Cl_2, 80%. (iii) 12% HCl, 25 ºC, 1.5 h. (iv) $ClCO_2CCl_3$, NaOH, H_2O, 0 ºC. (v) CH_2N_2, THF, 72%. (vi) $NaBH_4$, THF, 0 ºC, 75%.

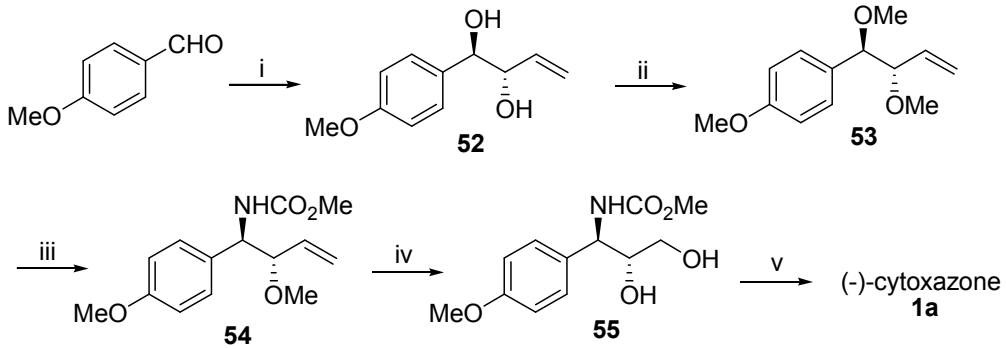
Saicic's approach was based on the Sharpless asymmetric aminohydroxylation reaction, starting from methyl *p*-methoxycinnamate, in six steps and 31% overall yield (**Scheme 10**). The required *anti*-aminoalcohol **48** was synthesized using Sharpless asymmetric aminohydroxylation and subsequent inversion of configuration in amidoalcohol **46** *via* an oxazoline **47**. Submission of amidoalcohol **46** to the sequence of reactions already described for cytoxazone (hydrolysis/cyclization/esterification), gave the methyl ester **51**, which on reduction with sodium borohydride gave (+)-*epi*-cytoxazone (**1b**) (**Scheme 11**).



Scheme 11: (i) 10% HCl, reflux, 4 h. (ii) $ClCO_2CCl_3$, NaOH, H_2O, 0 ºC. (iii) CH_2N_2, THF, 63%. (iv) $NaBH_4$, THF, 0 ºC, 80%.

Jung's approach (2005)[15]

Jung *et al.* have made use of the regio- and diastereoselective introduction of a *N*-protected amine group in to the intermediate **53** with chlorosulfonyl isocyanate (CSI) to obtain *anti*-1,2-aminoalcohol **54**.

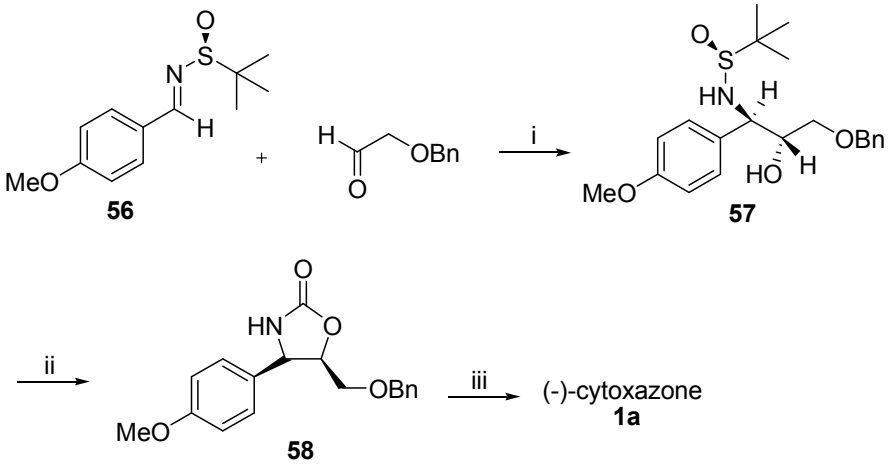


Scheme 12: (i) (a) *B*-[3-((diisopropylamino)dimethylsilyl)allyl]diisopinocampheyl borane, Et_2O, -78 ºC. (b) H_2O_2, KF, $KHCO_3$, THF-MeOH, 25 ºC, 52%. (ii) MeI, NaH, THF, 0 ºC, 96%. (iii) (a) chlorosulfonyl isocyanate, Na_2CO_3, toluene, -78 ºC. (b) Na_2SO_3, KOH, 25 ºC, 95% (dr = 27:1). (iv) (a) O_3, -78 ºC then $NaBH_4$, 0 ºC, CH_2Cl_2-MeOH, 94%. (b) BBr_3, CH_2Cl_2, 0 ºC, 80%; (v) NaH, THF, 0 ºC, 95%.

Thus the treatment of compound **53** with CSI in the presence of sodium carbonate in dry toluene at -78 °C, followed by the reduction of the *N*-chlorosulfonyl group furnished the desired *anti*-1,2-amino alcohol **54** with a high diastereoselectivity (27:1). Ozonolysis of the double bond and intramolecular cyclization of **55** using NaH finally gave (-)-cytoxazone (**1a**) in 95% yield (**Scheme 12**).

Bentley's approach (2005)[16]

Bentley *et al.* have made use of stereoselective cross-coupling of phenyl imine auxiliary **56** and aldehyde in presence of samarium iodide to obtain the corresponding aminoalcohol **57**. Removal of chiral auxiliary and cyclization using triphosgene gave **58**, which on debenzylation afforded (-)-cytoxazone (**1a**) (**Scheme 13**).

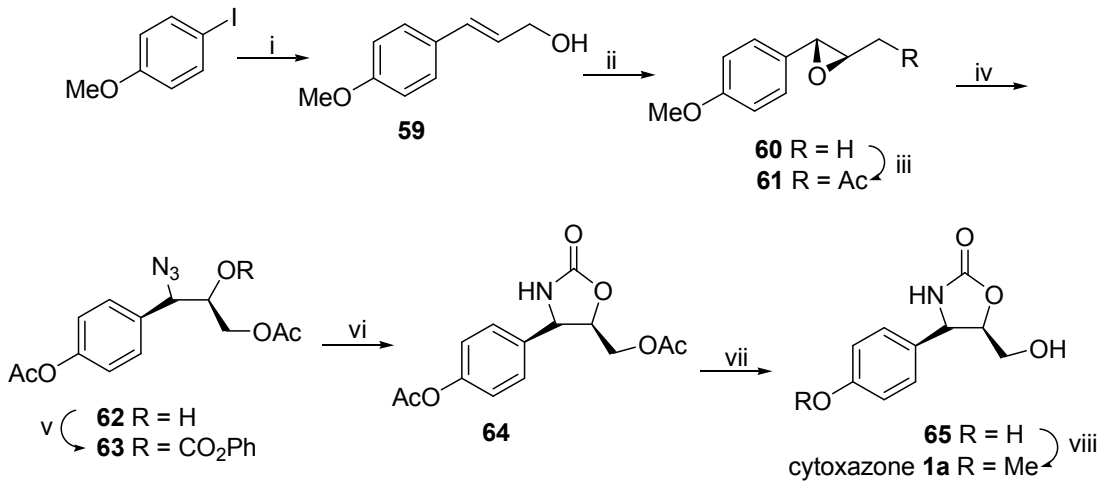


Scheme 13: (i) SmI_2, ^tBuOH, THF, -78 ºC, 83%. (ii) (a) HCl, MeOH, 25 ºC. (b) triphosgene, Et_3N, DCM, 25 ºC, 85%. (iii) $Pd(OH)_2/C$, H_2, MeOH, 86%.

Sudalai's approach (2006)[17]

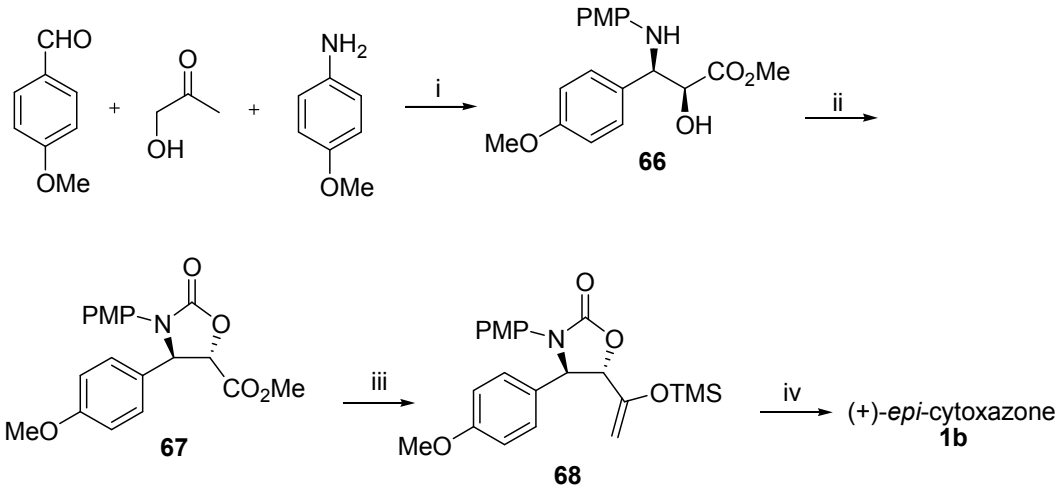
Sudalai *et al*. have developed a simple method for the enantioselective synthesis of (-)-cytoxazone (**1a**) using Sharpless asymmetric epoxidation as the key step. Thus, asymmetric epoxidation of allylalcohol **59** gave chiral epoxide **60**, which was further acylated to give acetate **61**. The nucleophilic opening of the epoxide **61** at the benzylic position with NaN_3 gave azido alcohol **62** in 88% yield. Protection of the alcohol followed by reductive cyclization with PPh_3 gave oxazolidinone **64**, which

was directly subjected to methylation with methyl iodide in the presence of NaH to afford (-)-cytoxazone (**1a**) in 65% yield and 83% ee (**Scheme 14**).



Scheme 14: (i) allyl alcohol, AgOAc, $Pd(OAc)_2$, PPh_3, DMF, 70 ºC, 16 h, 81%. (ii) anhyd. 5.4 M TBHP in CH_2Cl_2, 4Å molecular sieves, $Ti(OiPr)_4$, (+)-DIPT, CH_2Cl_2, -20 ºC, 20 h, 78%. (iii) AcCl, Et_3N, DMAP, CH_2Cl_2, 25 ºC, 87%. (iv) NaN_3, NH_4Cl, THF/H_2O (2:1), 50 ºC, 3 h, 79%. (v) PhOCOCl, pyridine, CH_2Cl_2, -5 to 25 ºC, 1 h, 93%. (vi) PPh_3, THF/H_2O (10:1), 50 ºC, 2 h, 87%. (vii) aq $NaHCO_3$, MeOH, reflux, 1 h. (viii) NaH, MeI, THF, 0–25 ºC, 3 h, 69%, 83% ee.

The same group has achieved the synthesis of (+)-*epi*-cytoxazone (**1b**) using L-proline catalyzed asymmetric Mannich reaction. Thus, key intermediate *syn*-amino alcohol **66** was obtained from L-proline catalyzed asymmetric Mannich reaction of 4-methoxybenzaldehyde, hydroxyacetone and p-anisidine in 76% yield with *syn*/*anti* ratio 2:1. Amino alcohol **66** was then protected with triphosgene to give oxazolidinone **67** in 82% yield. *In situ* generated silyl enol ether **68** was subjected for ozonolysis without purification. Reductive work up of ozonide and PMP deprotection with CAN gave (+)-*epi*-cytoxazone (**1b**) in 59% yield and 81% ee (**Scheme 15**).



Scheme 15: (i) *p*-anisidine, hydroxyacetone,. L-proline, DMSO, 25 ºC, 24 h, 76%. (ii) triphosgene, Et_3N, CH_2Cl_2, -10 to 25 ºC, 82%. (iii) Li-HMDS, TMSCl, THF, -78 ºC. (iv) (a) O_3, PPh_3, CH_2Cl_2, -78 ºC. (b) $NaBH_4$, MeOH, 25 ºC. (c) CAN, CH_3CN, 5 h, 59% (in three steps), 81% ee.

1.4 Present Work:

1.4.1 Objective

Literature search revealed that several methods such as classical resolution, chemo-enzymatic or enantioselective synthesis have been reported for the synthesis of (-)-cytoxazone (**1a**)[3, 7-17] and its epimer (+)-*epi*-cytoxazone (**1b**). However, these methods suffer from many disadvantages such as low over all yields, the need for separation of diastereomers and the use of expensive chiral reagents. The synthetic precursors of (-)-cytoxazone (**1a**) and (+)-*epi*-cytoxazone (**1b**) are 1,2-aminoalcohols, which have been the subject of thorough synthetic efforts in recent years.[18] Most of the syntheses for cytoxazone (**1a**) have made use of indirect methods to establish the *anti*-amino alcohol functionality. In this context, a more practical method for the synthesis of (-)-cytoxazone (**1a**) and (+)-*epi*-cytoxazone (**1b)** is highly desirable.

Retrosynthetic analysis (**Fig. 3**) for (-)-cytoxazone (**1a**) reveals that *anti*-amino alcohol **69** could be visualized as the key intermediate. The *anti*-diastereomer oxathiazinane **69** could be achieved by Rh-catalyzed intramolecular amidation of the

C-H bonds of sulfamate ester **70** at the benzylic position. The sulfamate ester **70** could be prepared from chiral diol **71**, which in turn would be obtained by two routes *i.e.* the hydrolytic kinetic resolution of the racemic epoxide **72** using Co(III)-salen-complex (route 1) and the L-proline-catalyzed α-aminooxylation of aldehyde **73** (route 2).

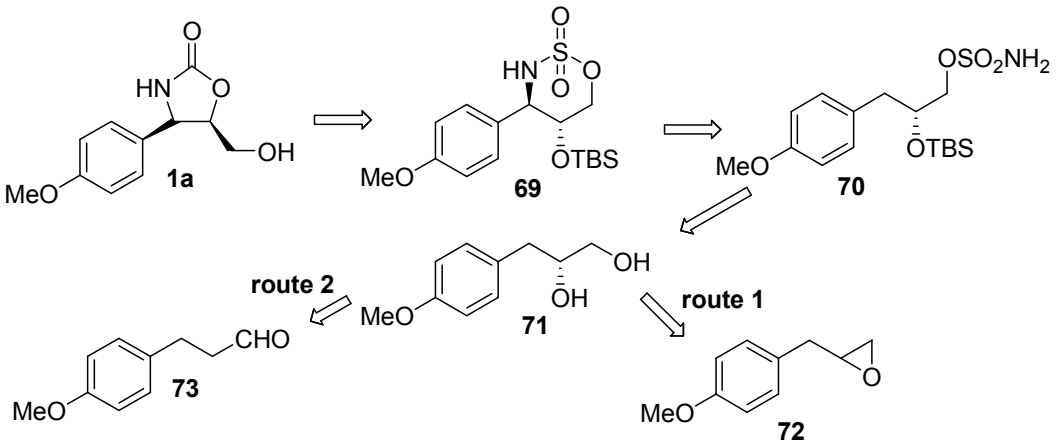


Fig 3: Retrosynthetic analysis of (-)-Cytoxazone (1a)

In case of (+)-*epi*-cytoxazone (**1b**), the retrosynthetic analysis reveals that *syn*-amino alcohol **74** could be visualized as a key intermediate (**Fig. 4**).

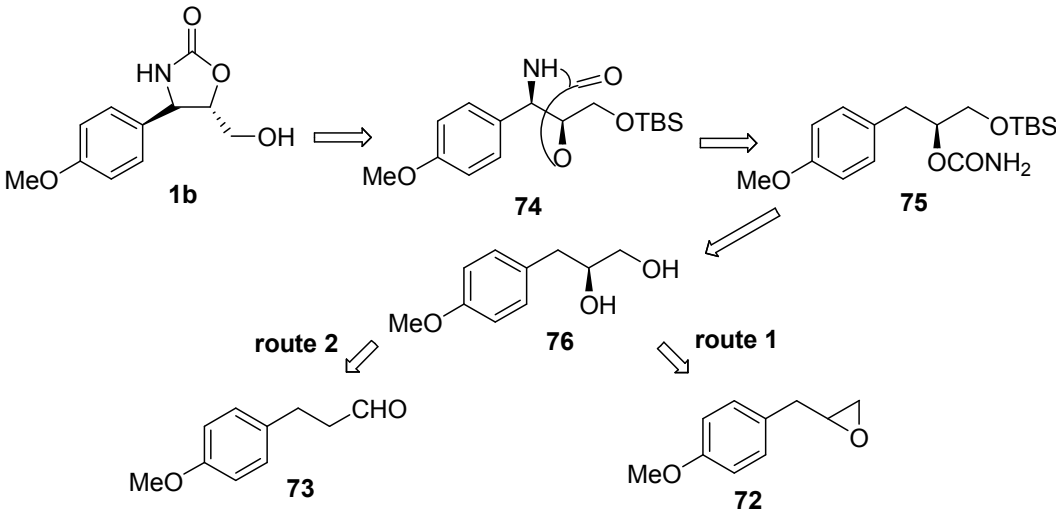


Fig 4: Retrosynthetic analysis of (+)-*epi*-Cytoxazone (1b)

The *syn*-diastereomer, oxazolidinone 7**4**, could be achieved by Rh-catalyzed intramolecular amidation of the C-H bond of carbamate ester **75** at the benzylic

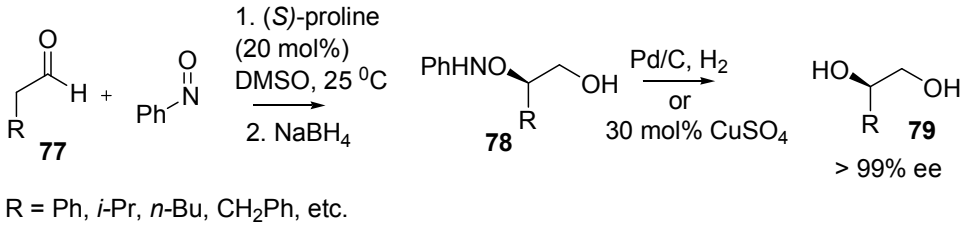
position. The carbamate ester **75** could be prepared from chiral diol **76**, which in turn would be obtained by two routes *i.e* the hydrolytic kinetic resolution of the racemic epoxide **72** using Co(III)-salen-complex (route 1) and the proline-catalyzed α-aminooxylation of aldehyde **73** (route 2).

Since this chapter describes novel strategies for the asymmetric synthesis of (-)-cytoxazone (**1a**) and its *trans* analogue, (+)-*epi*-cytoxazone (**1b**) by employing the proline-catalyzed α-aminooxylation of aldehydes,[19] hydrolytic kinetic resolution of epoxides[20] and diastereoselective oxidative C-H aminations of sulfamate and carbamate esters at the benzylic positions[21] (**Schemes 24**, **25** and **26**) introducing stereogenicity into the prochiral molecule, a brief account of each is presented in the following sections.

1.4.2 Proline-catalyzed α-aminooxylation

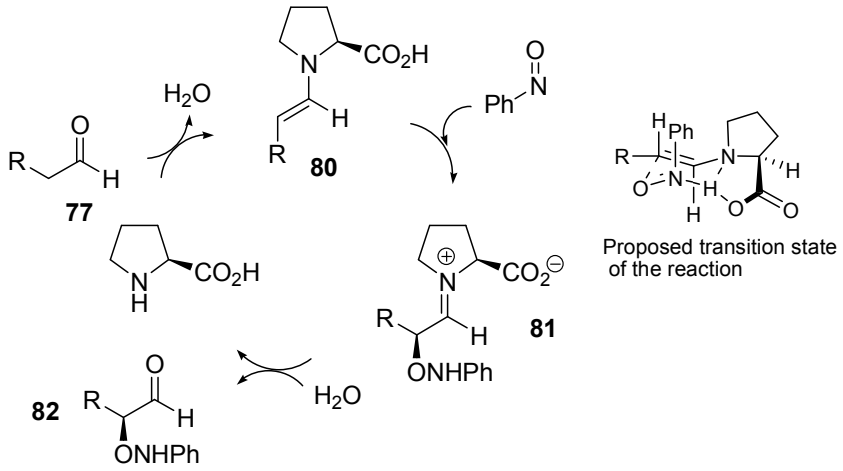
Optically active α-hydroxy carbonyl moieties are commonly found in numerous important natural products and are highly versatile functional synthons. This has led to extensive research into finding new diastereoselective and enantioselective routes for their syntheses.[22] One way of preparing these compounds is asymmetric α-hydroxylation of enolates.[23] In addition, nucleophilic additions to chiral glyoxal derivatives and chiral hydrazones have also been successfully employed.[24] However, these methods are indirect and most of them require multiple manipulations for the desired α-hydroxy products to be obtained. Asymmetric reactions catalyzed by metal-free organic catalysts have experienced a renaissance in recent years. Interestingly, since the discovery of amino acid catalyzed stereoselective Robinson annulations in the early 1970s,[25] there was no intensive research on this concept for other C-C bond-forming reactions for several decades, even though the reaction is frequently used in the preparation of building blocks for the total synthesis

of natural products.[26] The field of asymmetric organocatalysis is rapidly developing and attracts an increasing number of research groups around the world. In particular, organocatalytic asymmetric synthesis have provided several new methods for obtaining chiral compounds in an environmentally benign manner.[27]



Scheme 16 **α-aminooxylation of aldehyde**

In this connection, proline, an abundant, inexpensive amino acid available in both enantiomeric forms, has emerged as arguably the most practical and versatile organocatalyst.[28] Proline has also been found to be an excellent asymmetric catalyst for α-functionalization[19] of carbonyl compounds. When aldehyde **77** without substitution at α-position was reacted with nitrosobenzene in presence of L-proline in DMSO at ambient temperature, aminooxylation of the aldehyde **77** takes place at α-position. The aminooxyl moiety of **78** undergoes hydrogenolysis with Pd/C, H_2 or $CuSO_4$ to give the corresponding diols **79** in very high enantiomeric excess (**Scheme 16**). The mechanism of the α-aminooxylation reaction is given in **Scheme 17**. The highly reactive enamine intermediates **80** formed between aldehydes **77** and proline might serve as nucleophiles and add stereoselectively to the nitroso functional group, either on to the oxygen atom or the nitrogen atom. Nucleophilic O attacks of the enamines **80** on the nitroso double bond might give the aminoxy product **81**.



Scheme 17: Proposed mechanism of the α-aminooxylation reaction

The observed enantioselectivitiy of the catalytic α-aminoxylation of aldehydes can be rationalized by invoking an enamine mechanism operating through a chair transition state where the *Si* face of an *E*-enamine formed from the aldehyde and L-proline approaches the less-hindered oxygen atom of nitrosobenzene to provide the chiral α-aminoxyaldehyde **82** with *R* configuration (**Scheme 17**). Since proline is commercially available in both enantiopure forms, a one-pot sequence-catalytic α-aminoxylation of aldehydes followed by *in situ* reduction with $NaBH_4$ affords *R*- or *S*-configured 1,2-diol units **78** (the secondary alcohol "protected" by an O-amino group) with excellent enantioselectivities and in good yields.

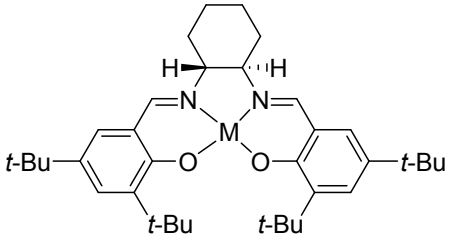
1.4.3 Hydrolytic Kinetic Resolution (HKR)

The importance of epoxides in organic synthesis arises partly from the occurrence of the strained three-membered ring unit in a number of interesting natural products[29] but more so because the ring opening of epoxides allows straightforward elaboration to useful new functionality, often with generation of new carbon-carbon bonds. Indeed, reactions of epoxides with nucleophiles, Lewis acids, radicals, reducing agents, oxidizing agents, acids, and bases have all been well documented and utilized in synthesis.[30] Thus epoxides are versatile building blocks for organic

synthesis. However, terminal epoxides are arguably the most important subclass of these compounds, and no general and practical method exists for their production in enantiomerically pure form. Terminal epoxides are available very inexpensively as racemic mixtures, and kinetic resolution is an attractive strategy for the production of optically active epoxides, given an economical and operationally simple method. Readily accessible synthetic catalysts (chiral cobalt-salen complexes)[31] have been used for the efficient asymmetric hydrolysis of terminal epoxides. This process uses water as the only reagent, no added solvent, and low loadings of a recyclable catalyst (0.5 mol%), and it affords highly valuable terminal epoxides and 1,2-diols in high yields with high enantiomeric enrichment.

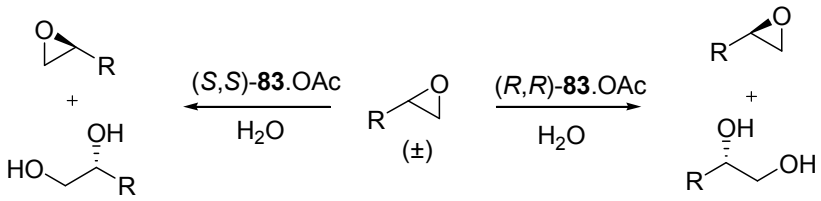
One of the most attractive features of kinetic resolution processes in general is the fact that the enantiomeric composition of unreacted substrate can be controlled by adjusting the degree of conversion, and virtually enantiopure material can be obtained at appropriately high conversions. This is an important consideration in the present case, since low-molecular weight terminal epoxides are typically liquids at room temperature and are not readily derivatized as salts, and therefore it is not a straightforward matter to upgrade their enantiomeric composition by crystallization. However, in the absence of straightforward substrate racemization protocols, kinetic resolutions have the significant disadvantage of a 50% maximum yield of substrate recovery. With a specific interest in devising a practical method for obtaining highly enantioenriched terminal epoxides, the following criteria must be met in order for a kinetic resolution approach to be viable.[32] (1) The racemic epoxides must be inexpensive or easily accessible from inexpensive commercial starting materials. (2) The catalyst for the resolution must be readily available in both enantiomeric forms. In the optimal case, the catalyst would be used in small quantities in the resolution

and would be recyclable. (3) The nucleophile used for the ring opening should be inexpensive and easily handled. (4) The resolved epoxides must be obtained in good yield and very high enantiopurity and must be easily separated from the ring-opened products. (5) Ideally, although not necessarily, the ring-opened byproducts should also be valuable chiral building blocks and be obtainable in high enantiomeric excess. The (salen)Co complex **83** catalyzed the efficient hydrolytic kinetic resolution (HKR) of a variety of terminal epoxides (**Scheme 18**).[31]



M = Co: (*R*,*R*)-**83**

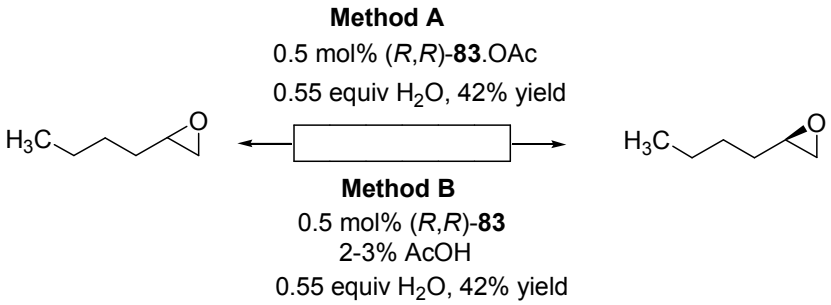
M = Co(OAc): (*R*,*R*)-**83**.OAc



Scheme 18: **Hydrolytic Kinetic Resolution (HKR) Reaction**

This new method appeared to hold considerable promise with regard to meeting all of the criteria outlined above. First, racemic 1,2-epoxides are generally available directly from commercial suppliers at low cost or are obtainable in one step from inexpensive olefins or aldehydes. In fact, certain racemic epoxides, such as propylene oxide, epichlorohydrin, styrene oxide, and butadiene monoepoxide, are commodity chemicals and are no more expensive than common organic solvents. Second, the ligands for catalyst **83** had previously been commercialized and manufactured on a ton scale in the context of (salen)Mn epoxidation catalysts.[33] The cobalt analogues

(*R*,*R*)-**83** and (*S*,*S*)-**83** proved equally accessible, and these are also now available in bulk. Third, water is perhaps the ideal reagent for effecting the resolution reaction: it is inexpensive and safe, and the rate of the ring-opening reaction can be controlled simply by modulating the rate of addition of water to the epoxide-catalyst mixture. Fourth, for those examples that were described in the preliminary report, highly enantioenriched epoxides were recovered from the HKR. Finally, the HKR provided useful enantioenriched 1,2-diols, including many that are otherwise not readily accessible using existing asymmetric dihydroxylation methods.[34]



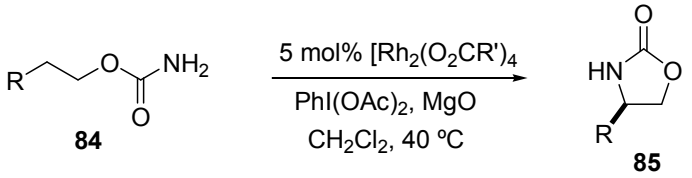
Scheme 19:

Two useful methods for the generation of complex **83.**OAc have been developed (**Scheme 19**). Method A involves isolation of **1.**OAc as a crude solid prior to the HKR. The Co(II) complex **83** is dissolved in toluene to generate ~ 1 M solution, and acetic acid (2 equiv.) is added. The resulting solution is stirred open to air at room temperature for 30 min, during which time the color of the mixture changes from orange to dark brown. All volatile materials are removed *in vacuo*, affording **83.**OAc as a brown solid residue that can be used without further purification. Method B involves in situ generation of **83.**OAc under HKR conditions by suspension of the Co(II) complex **83** in epoxide or epoxide/solvent and addition of HOAc under an aerobic atmosphere.

1.4.4 Rh-catalyzed oxidative C-H amidation

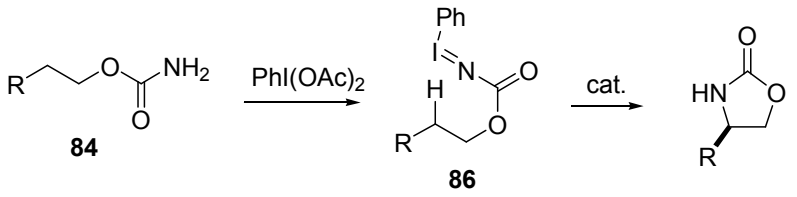
1,2-Difunctionalized amine derivatives:

Vicinal amino alcohols are common structural units in both naturally occurring molecules and pharmaceutical agents.[35] These groups also appear as auxiliaries in asymmetric synthesis and in ligands for metal catalysts.[36,37] The large and varied number of applications for β-hydroxy amines in synthetic, medicinal, materials, and coordination chemistry has fueled interest in the development of methods for their construction.[38] Recently it was found a unique, metal-catalyzed C-H insertion process that makes possible the preparation of such compounds from readily available carbamate starting materials **84** (**Scheme 20**).[21a,e]



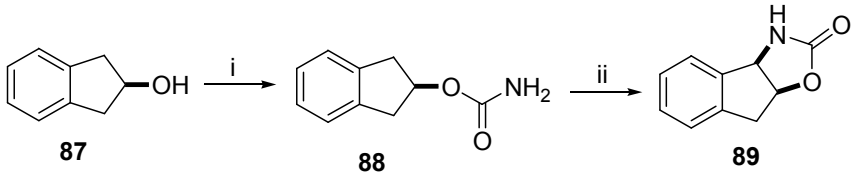
Scheme 20: C-H insertion of carbamates

This methodology utilizes catalytic quantities of Rh^{II} carboxylate complex and an inexpensive commercial oxidant, $PhI(OAc)_2$. The product oxazolidinones **85** are versatile, crystalline materials that can be opened under hydrolytic conditions to furnish 1,2-amino alcohols.[39] Transition metal promoted methods for the oxidative conversion of saturated hydrocarbons to amines or amine derivatives have limited precedence.[40] This reaction is believed to occur through intramolecular metal-nitrene insertion into an methylene C-H bond of **86**, though no mechanistic data has been offered in support of this claim (**Scheme 21**).[41]



Scheme 21: Plausible mechanism

It was explored the use of simple carbamate materials as precursors for the synthesis of substituted oxazolidinones. The crystalline indanol derivative **88** was used for initial studies (**Scheme 22**).[42] Control experiments indicate that **88** does not react with $PhI(OAc)_2$ after >10 hr at 40 °C. However, that a stirred suspension of **88**, $PhI(OAc)_2$, and 5 mol% $Rh_2(OAc)_4$ at 25 °C produced ~15% of the desired oxazolidinone **89**. Analysis of the unpurified reaction mixture by ^{1}HNMR spectroscopy indicated that the sample comprised mostly starting material **88**. Subsequent studies demonstrated that the conversion of **88** into **89** could be improved slightly by warming the mixture of reactants to 40 °C, an observation that intimated a possible problem with slow catalyst turnover.



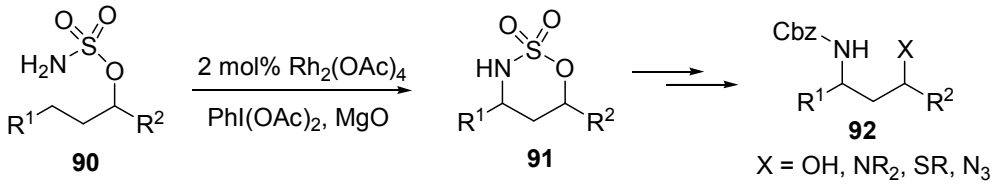
Scheme 22: (i) $CCl_3C(O)NCO$, K_2CO_3/MeOH; (ii) 5 mol% $Rh_2(OAc)_4$, $PhI(OAc)_2$, MgO, CH_2Cl_2, 40 °C, 12 hr.

Following a series of control experiments, it was concluded that AcOH, generated as a by-product from $PhI(OAc)_2$, reduced the catalytic activity of $Rh_2(OAc)_4$. The need to scavenge AcOH from the reaction mixture prompted the screening of K_2CO_3, Na_2HPO_4, 2,6-di-*tert*-butyl-4-methylpyridine, BaO, and MgO as base additives. Of these reagents, MgO proved uniquely effective and, in addition, was the most desirable from a cost and convenience standpoint. Thus, the reaction of **88** performs

optimally when a CH_2Cl_2 suspension containing $PhI(OAc)_2$ (1.4 equivalents), 5 mol% $Rh_2(OAc)_4$, and MgO (2.3 equivalents) is stirred for 12 hr at 40 °C (**Scheme 22**).[21a,e] Substrates containing both benzylic and tertiary C-H centers are cyclized to oxazolidinone products in yields of 74-84%. $Rh_2(OAc)_4$ can be used as the catalyst with a number of these starting materials; in some cases, however, the readily prepared triphenylacetate (tpa) complex, $Rh_2(tpa)_4$,[43] is a more effective promoter at a 5 mol% loading. The enhanced performance of $Rh_2(tpa)_4$ is ascribed to its greater resistance towards oxidation under the reaction conditions.

1,3-Difunctionalized amine derivatives[21b-d]:

Amination reactions of saturated C-H bonds hold great potential as methods for the synthesis of amines and amine derivatives.[44] The conversion of 1° carbamates to oxazolidin-2-ones using dinuclear Rh carboxylate catalysis has been shown in the above discussion. Further explorations of this chemistry have been guided to sulfamate esters **90** (**Scheme 23**). This uniquely reactive class of compounds affords six membered ring insertion products **91** through exclusive γ-C-H bond amination. Such findings contrast distinctly the reactions of carbamates and serve to define a new, exceptionally versatile strategy for the preparation of 1,3-amino alcohols **92** and related α-amino acids.[45]



Scheme 23: Rh-catalyzed oxidative cyclization of sulfamate esters

Additionally, it was demonstrated that these seldom described oxathiazinane heterocycles **91** can be converted following *N*-carbamoylation into reactive alkylating agents. Nucleophilic displacement reactions of these electrophiles afford 1,3-

difunctionalized compounds **92** with marked efficiency. The chemistry described herein thus offers a powerful methodology for the construction of myriad amine-derived materials through selective, intramolecular C-H oxidation.

Reported protocols for the synthesis of sulfamate esters typically employ sulfamoyl chloride, $ClSO_2NH_2$, a convenient reagent for preparative scale use made easily from inexpensive $ClSO_2NCO$ and formic acid.[46] Condensation of $ClSO_2NH_2$ with most 1° and 2° alcohols (pyridine, CH_2Cl_2) furnishes the target sulfamates in 65-75% yield.[47] These substrates react rapidly (<2 h) at 40 °C with $PhI(OAc)_2$, MgO, and 2 mol % $Rh_2(OAc)_4$ to afford the corresponding six-membered ring insertion products through selective γ-C-H insertion.[21b-d] The strong bias for oxathiazinane formation is presumably accounted for by the elongated S-O and S-N bonds (1.58 Å) and the obtuse N-S-O angle (103°) of the sulfamate, which match closely the metrical parameters of the heterocycle.[48]

The C-H amination under Rh-catalysis has general applicability with a range of structurally disparate starting materials. High product yields are obtained for sulfamates possessing 3° and benzylic C-H centers nearly without exception. Although 3° C-H bonds react in preference to 2° -CH_2 units, amination of unactivated –CH_2 groups is catalyzed effectively. Notably, good to excellent levels of 1,3-diastereoselective induction are recorded for substrates derived from 2° alcohols having prochiral –CH_2 centers. Preference for the 1,3-*syn* isomer ranges from 4 to >20:1, and is consistent with the cyclization event proceeding through a chairlike transition state.

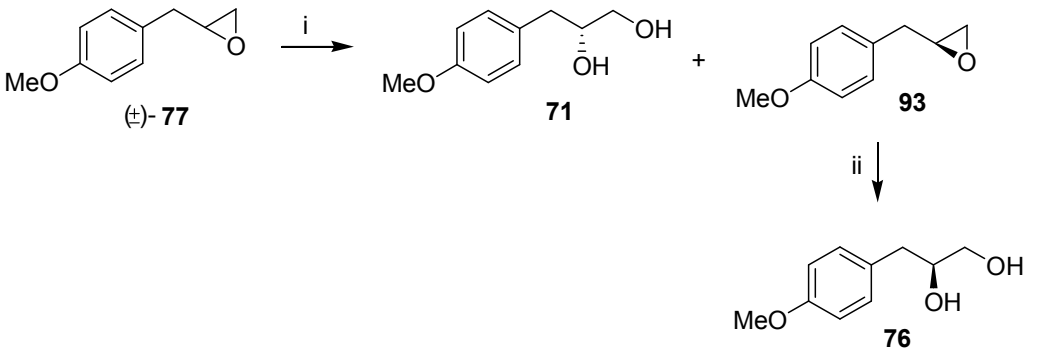
1.5 Results and Discussion

The chiral 1, 2-diols **71** and **76** are the key intermediates in the synthesis of (-)-cytoxazone (**1a**) and (+)-*epi*-cytoxazone (**1b**), respectively. The synthesis of the

chiral 1,2-diols **71** and **76** using hydrolytic kinetic resolution (HKR)[20] of the racemic epoxide (route 1) as well as proline-catalyzed asymmetric α-aminooxylation of aldehydes[19] (route 2) are shown in the **Schemes 24** and **25** respectively.

Enantioselective synthesis of 1,2-diols 71 and 76 (route 1)

The racemic epoxide **77** was prepared in 85% yield by the addition of Grignard reagent, prepared from 4-bromomethoxybenzene (**106**), onto to epichlorohydrin (**Scheme 24**).



Scheme 24: (i) (*R,R)*-salen-Cobalt(III)OAc (0.5 mol%), THF (0.55 equiv), H_2O (0.45 equiv), 0 ºC, 14 h, (44%, 98% ee for **71** and 52% and 92% ee for **78**). (ii) (*S,S)*-salen-Cobalt(III)OAc (0.5 mol %), THF (0.95 equiv), H_2O (0.95 equiv), 0 ºC, 20 h, 92%, 98% ee.

The formation of epoxide **77** was confirmed by the appearance of multiplets at δ 2.79 and 3.10 for methylene and methine protons respectively in its ^{1}H NMR spectrum. Further, its ^{13}C NMR spectrum showed signals at δ 46.7 and 52.6 due to the two carbons of epoxy ring (**Fig. 5**). Racemic epoxide **77** was then subjected to HKR[20] reaction using catalytic amount of (*R,R)*-salen-Co(III)OAc complex to give chiral diol **71** in 44% yield and 98% ee (determined by converting diol **71** into the corresponding 1,2-benzylidene derivative which underwent reduction selectively using DIBAL-H to the benzyl protected 1° alcohol, which was converted into the corresponding Mosher ester **94**) and chiral epoxide **93** in 52% yield and 92% ee.

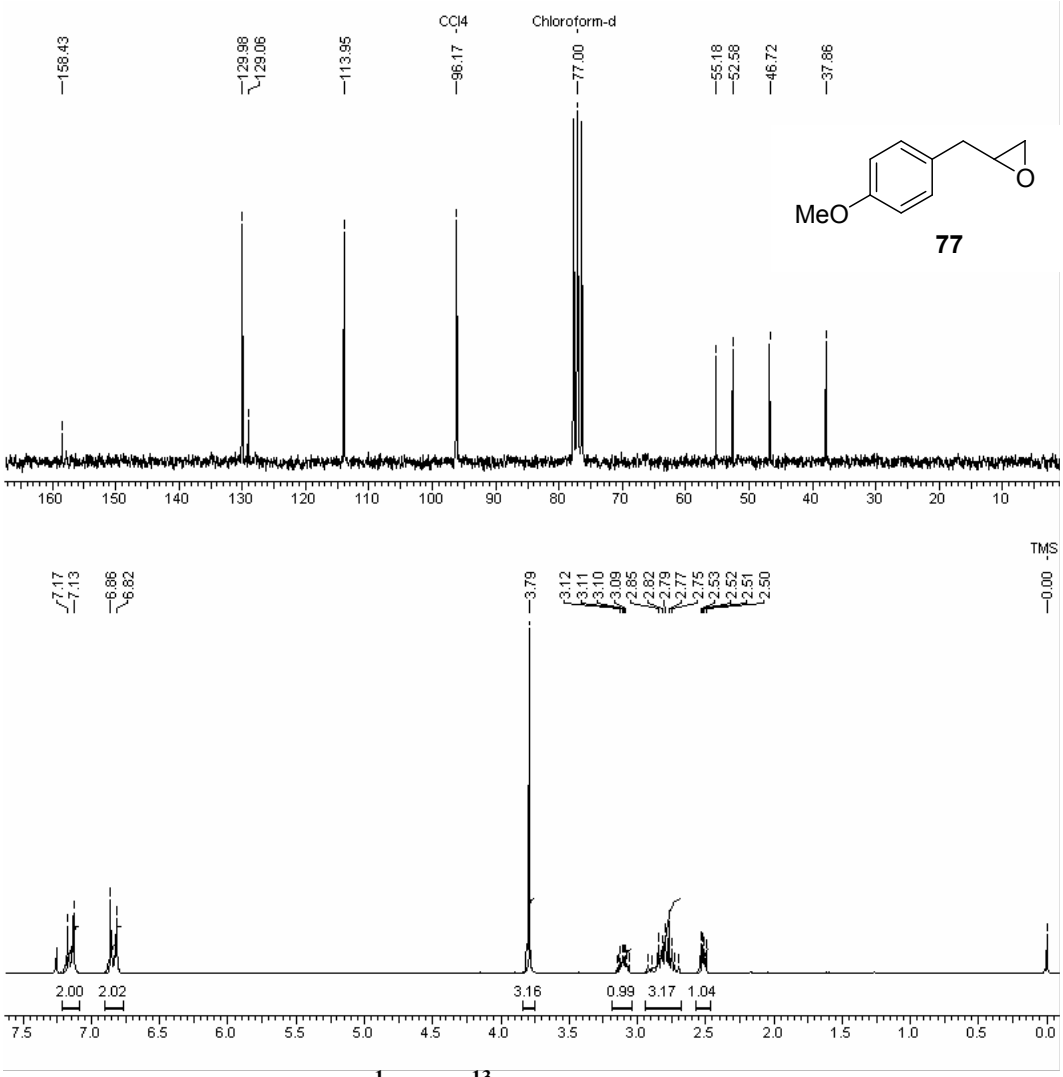


Fig. 5: ^{1}H and ^{13}C NMR spectra of 77

The ee of the chiral epoxide **93** was found to be 92% based on comparison of its optical rotation with that of reported value {$[\alpha]^{25}_{D}$= +0.74 (*c* 1, $CHCl_3$); lit.[49] $[\alpha]^{25}_{D}$= +0.8 (*c* 1, $CHCl_3$)}. The formation of diol **71** was confirmed by the appearance of doublet of doublets at δ 3.49, 3.67 and a multiplet at δ 3.89 for methylene and methine protons respectively in its ^{1}H NMR spectrum. Further, its ^{13}C NMR spectrum showed signals at δ 65.9 and 73.1 due to the two carbons attached to the alcohol groups (**Fig. 6**).

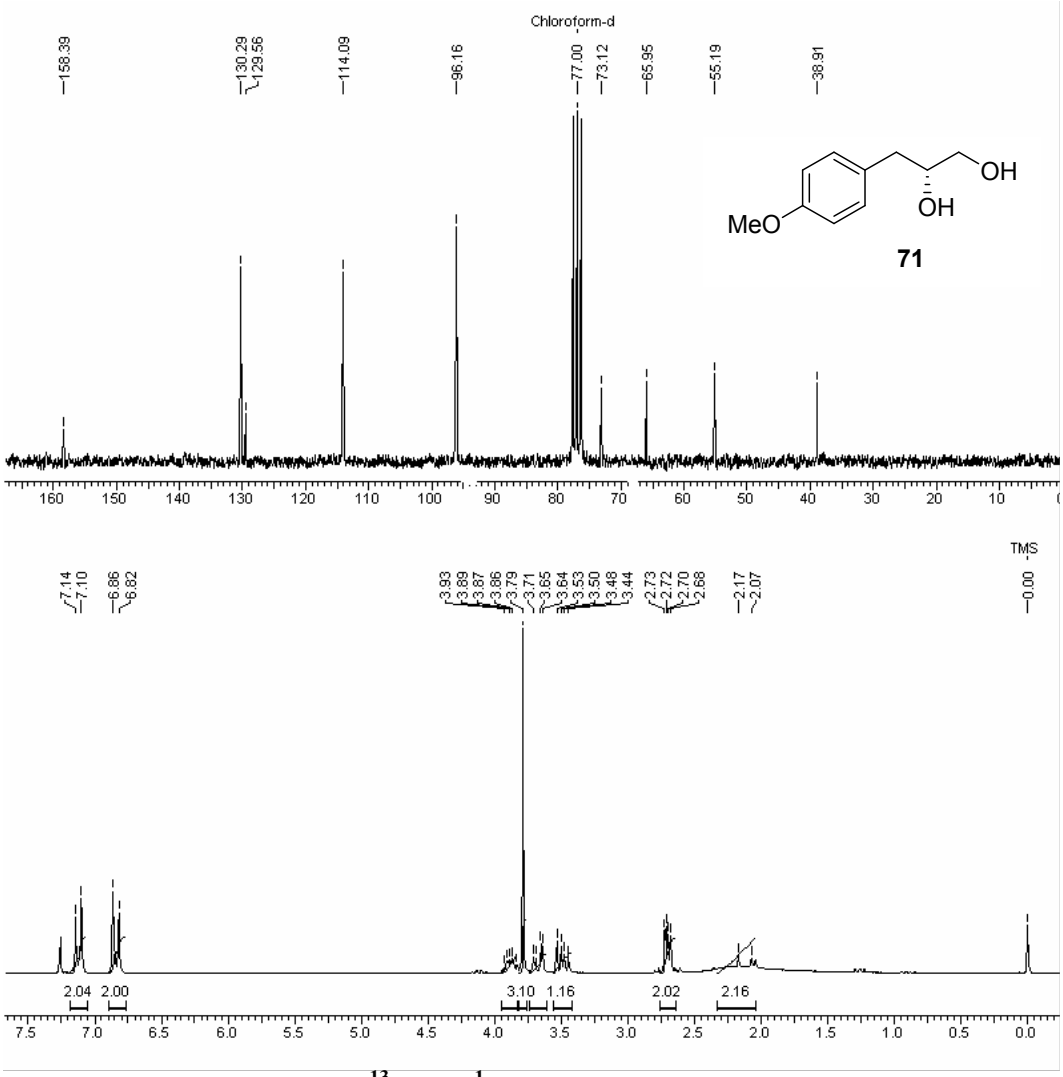


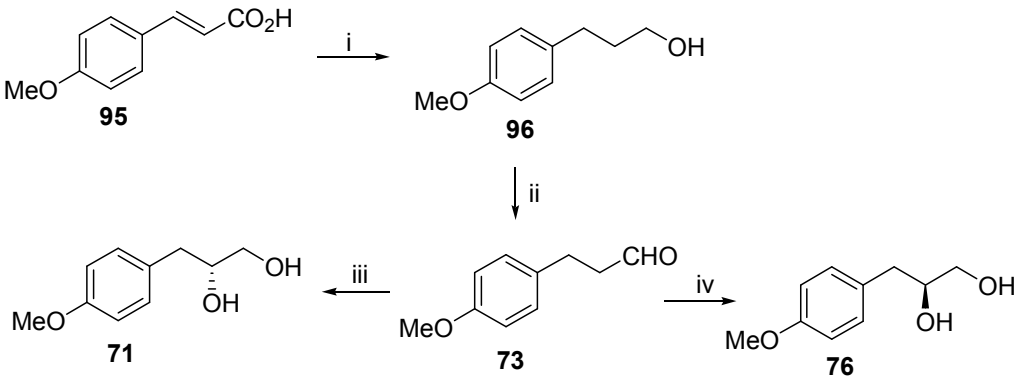
Fig. 6: ^{13}C and ^{1}H -NMR spectra of 71

In order to enhance the optical purity of the diol **76**, the chiral epoxide **93** (92% ee) was again subjected to hydrolytic kinetic resolution in the presence of (*S,S)*-salen-Co(III)OAc complex with 0.95 equiv. of water, which resulted in the formation of diol **76** in 92% yield and 98% ee {$[\alpha]^{25}_{D}$= -12.76 (*c* 2, $CHCl_3$)} (**Scheme 24**).

As HKR generally gives maximum chemical yields up to 50%, we turned our attention to asymmetric α-functionalization[19] of aldehydes by proline, an abundant, inexpensive amino acid available in both enantiomeric forms as a key step in introducing chirality into **71** and **76** (**Scheme 25**).

Enantioselective synthesis of 1,2-diols 71 and 76 (route 2)

Aldehyde **73**, the key intermediate, was obtained in two steps: (i) α,β-unsaturated acid **95**, which was obtained by Doebner modification of Knoevenagel reaction of 4-methoxy-benzaldehyde with malonic acid, was reduced to alcohol **96** in 85% yield; (ii) Swern oxidation[50] of the alcohol **96** gave the key intermediate aldehyde **73** in 96% yield.



Scheme 25: (i) $LiAlH_4$, THF, reflux, 8 h; (ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 0.5 h, 97%; (iii) (a) PhNO, L-proline (25 mol%), -20 ºC, 24 h then MeOH, $NaBH_4$; (b) H_2 (1 atm), Pd/C (10%), MeOH, 86% (over two steps); (iv) (a) PhNO, D-proline (25 mol%), -20 ºC, 24 h then MeOH, $NaBH_4$; (b) H_2 (1 atm), Pd/C (10%), MeOH, 86% (over two steps).

Thus, aldehyde **73** was converted into the corresponding chiral diols **71** and **76** by the proline-catalyzed asymmetric α-aminooxylation[19a] in a two-step reaction sequence: (i) reaction of aldehyde **73** with nitrosobenzene as the oxygen source in presence of L- or D-proline in CH_3CN at –20 °C, followed by its reductions with $NaBH_4$ in MeOH gave the crude aminoxy alcohols and (ii) subsequent reduction of the crude aminoxy alcohol with 10% Pd/C and H_2 (1 atm.) to give the chiral diols **71** in 86% yield and 99% ee (determined by converting diol **71** into the corresponding 1,2-benzylidene derivative which underwent reduction selectively using DIBAL-H to give the benzyl protected 1° alcohol, which was converted into the corresponding Mosher ester **94**) $\{[\alpha]^{25}_D = +12.90$ (*c* 2, $CHCl_3)\}$ and **76** in 86% yield and 99% ee $\{[\alpha]^{25}_D = -12.90$ (*c* 2, $CHCl_3)\}$, respectively (**Scheme 25**).

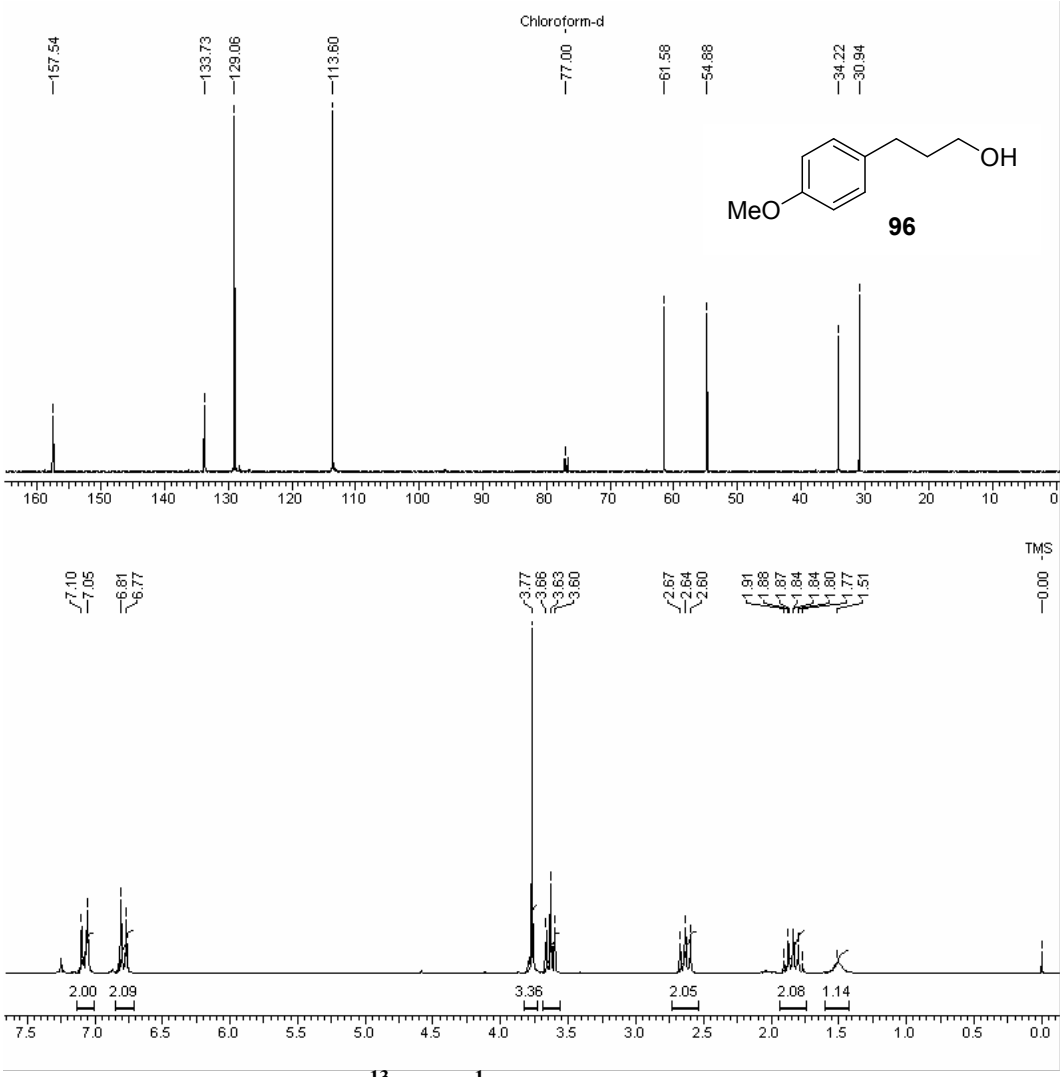
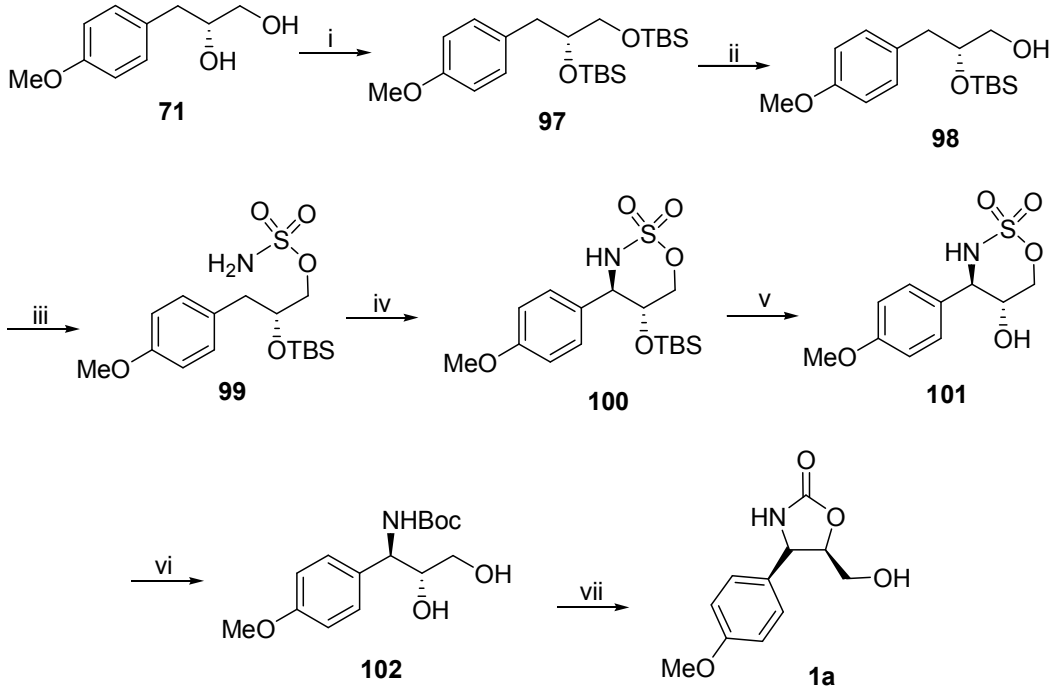


Fig. 7: ^{13}C and ^{1}H -NMR spectra of 96

Having obtained the diols **71** and **76** in high enantiomeric purity, the second chiral centre was readily generated by Rh-catalyzed diastereoselective intramolecular C-H amination using either chiral sulfamate or carbamate esters (**99** or **104**) as such methods have proven reliable for the synthesis of amines and amine derivatives.[21] Selectivity for either *syn* or *anti* 1,2-aminoalcohols was achieved by Rh-catalyzed intramolecular amidation of the C-H bonds of carbamate or sulfamate esters, respectively. The general synthetic schemes employed for the syntheses of (-)-cytoxazone (**1a**) and (+)-*epi*-cytoxazone are presented in **Schemes 26** and **27** respectively.

Enantioselective synthesis (-)-cytoxazone

Synthesis of (-)-cytoxazone started with bis-TBS-protected silyl ether **97** prepared from **71**. The formation of bis-TBS-protected silyl ether **97** was confirmed by the appearance of singlets at δ 0.81 and 0.90 for *t*-butyl protons and at δ -0.25-0.04 for methyl silyl protons in its ^{1}H NMR spectrum.



Scheme 26: (i) TBSCl, imidazole, DMF, 25 °C, 4 h, 98%; (ii) camphorsulfonic acid, MeOH, 95%; (iii) HCO_2H, chlorosulfonyl isocyanate, 0 °C, 76%; (iv) 2 mol% $Rh_2(OAc)_4$, $PhI(OAc)_2$, MgO, CH_2Cl_2, 40 °C, 2 h, 82%, *anti*:*syn* (10:1); (v) camphorsulfonic acid, MeOH, 25 °C, 1 h, 97%; (vi) (a) $(Boc)_2O$, DMAP, Et_3N, CH_2Cl_2, 25 °C, 1 h; (b) CH_3CN:H_2O (4:3), 60 °C, 4 h, 84% (over two steps); (vii) NaH, THF, 0 °C, 1 h, 96%.

The selective deprotection of the primary OH group in **97** was achieved using camphorsulfonic acid in MeOH[51] to produce alcohol **98** in 95% yield. The formation of alcohol **98** was confirmed by the appearance of a singlet at δ 0.79 for *t*-butyl protons in its ^{1}H NMR spectrum (**Fig. 8**).

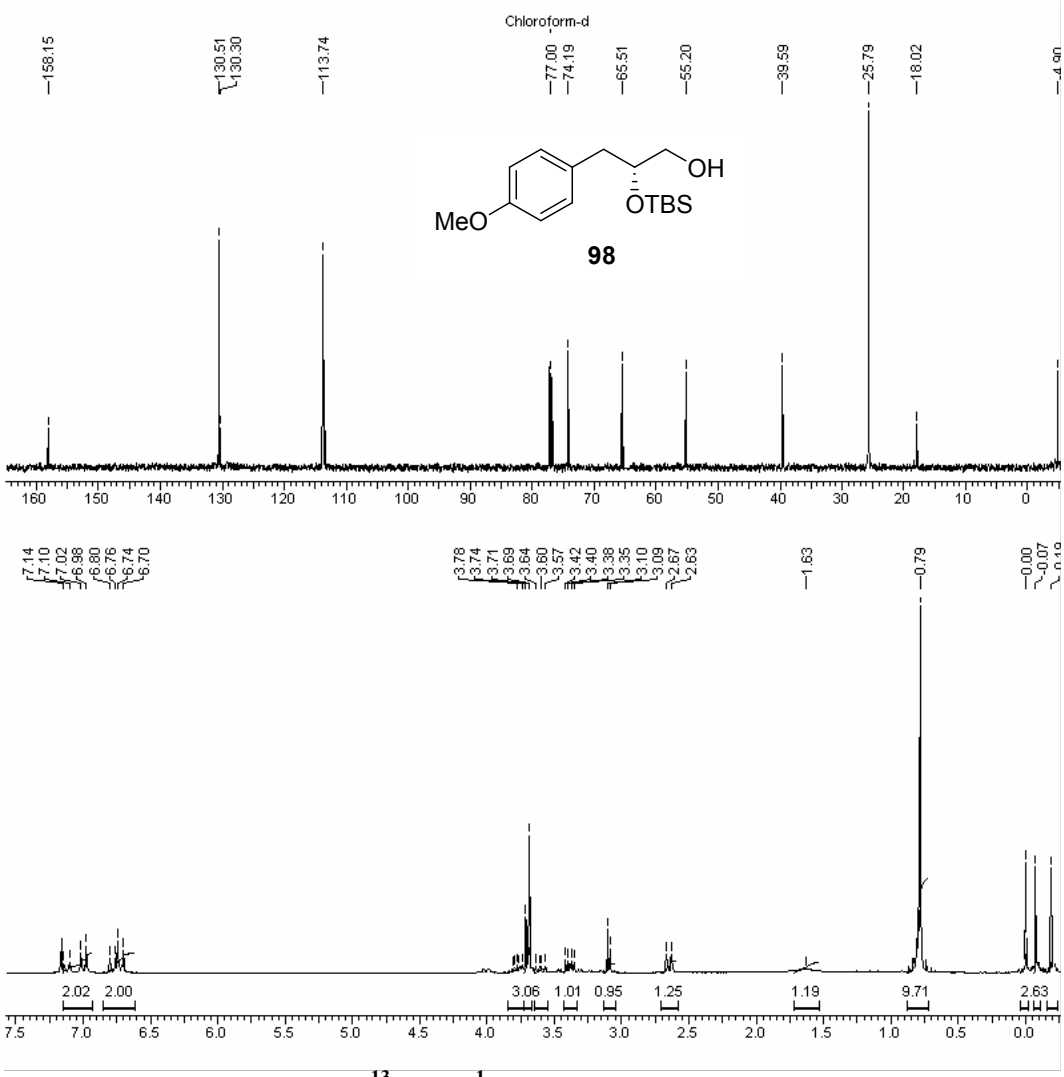


Fig. 8: ^{13}C and ^{1}H -NMR spectra of 98

Alcohol **98** was readily converted into sulfamate ester **99** in 76% yield using reported procedure (HCO_2H, chlorosulfonyl isocyanate, 0 °C).[19b] The ^{1}H NMR of sulfamate ester **99** showed a multiplet at δ 4.14 for methylene protons confirming the presence of OSO_2NH_2 moiety. Its ^{13}C NMR spectrum showed the signal at δ 73.44 due to the carbon attached to the sulfamate moiety (**Fig. 9**).

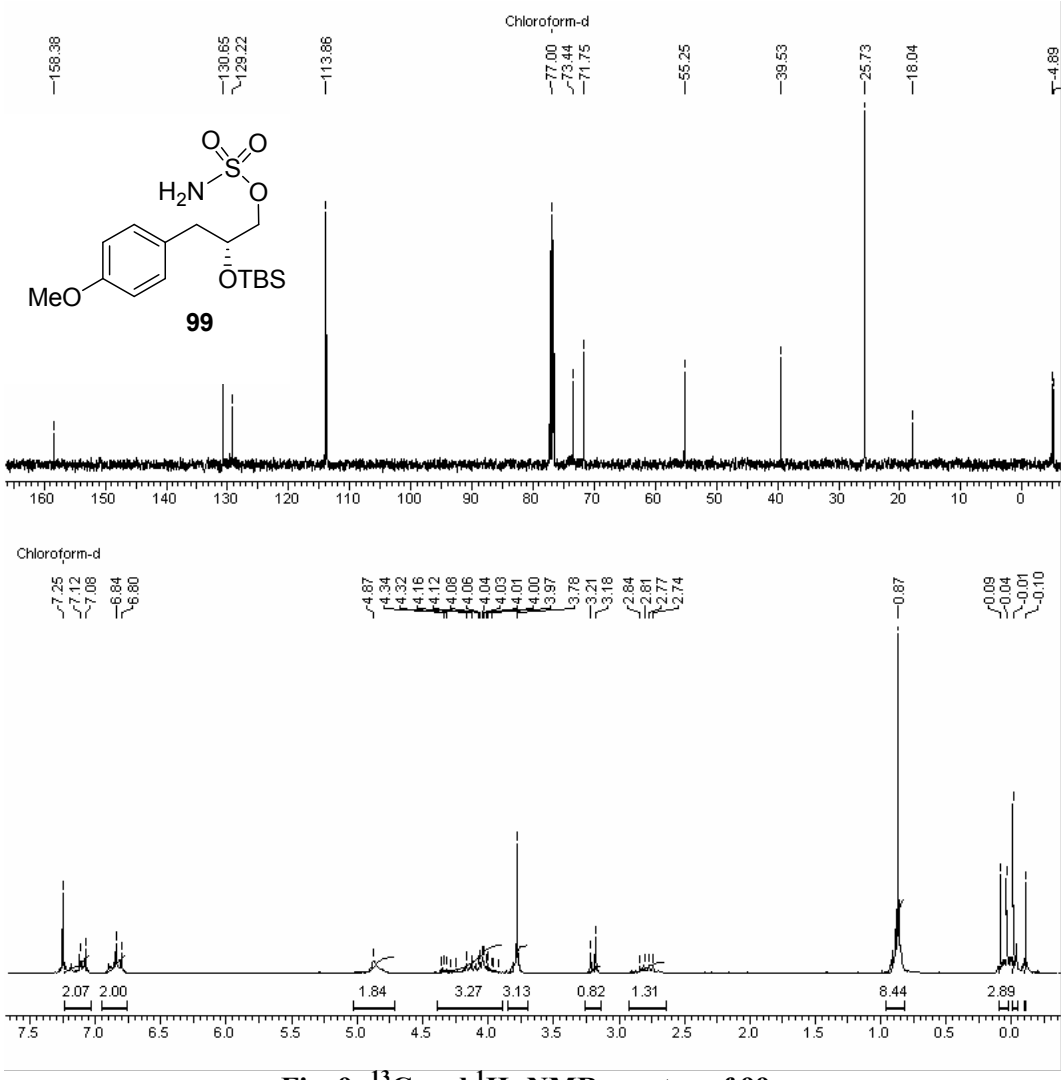


Fig. 9: ^{13}C and ^{1}H -NMR spectra of 99

The NH_2 group of the sulfamate ester **99** underwent selective γ-C-H insertion at the benzylic position in the presence of a catalytic amount of $Rh_2(OAc)_4$ (2 mol%), with $PhI(OAc)_2$ as the oxidant and MgO as additive in CH_2Cl_2 at 40 °C with *anti* (10:1) diastereoselectivity (determined from ^{1}H NMR analysis as well as isolated yields) to afford the corresponding six-membered ring insertion product **100** in 82% combined yield. The *anti*-diastereomer, oxathiazinane **100**, was readily purified by column chromatography. The formation of oxathiazinane **100** was confirmed by the appearance of a doublet of doublet at δ 4.47 due to benzylic proton in its ^{1}H NMR

spectrum. Its ^{13}C NMR spectrum also showed a signal at δ 67.46 due to the benzylic carbon attached to the amine (**Fig. 10**). The *anti*-selectivity of oxathiazinane **100** was deduced by its ^{1}H NMR spectrum, which showed a doublet of doublet at δ 4.47 with coupling constants of J = 10.49 Hz and 7.83 Hz.

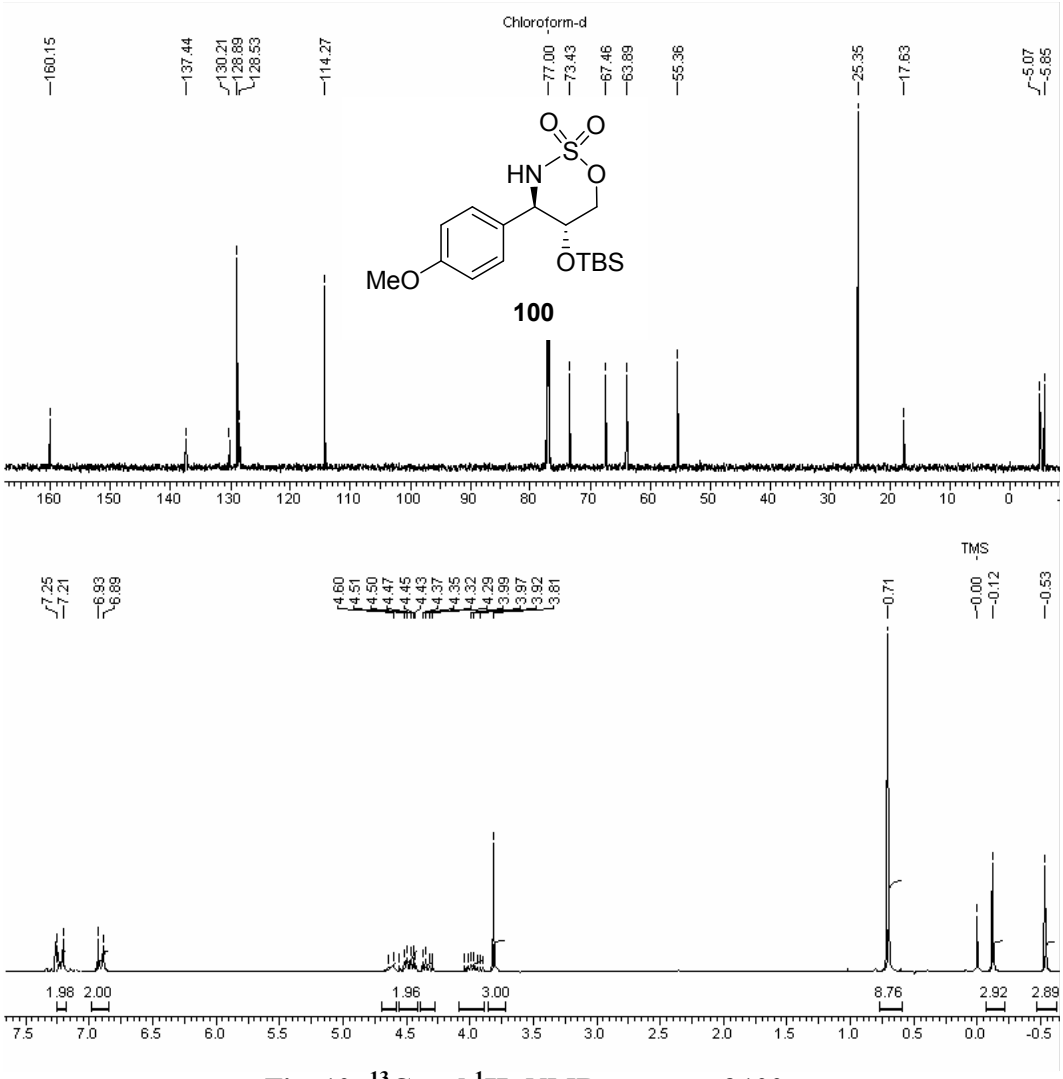


Fig. 10: ^{13}C and ^{1}H -NMR spectra of 100

Deprotection of the TBS group in **100** using camphorsulfonic acid in MeOH furnished the alcohol **101** in 97% yield. The ^{1}H NMR spectrum as well as ^{13}C NMR spectrum of **101** showed the absence of TBS group compared to oxathiazinane **100** (**Fig. 11**).

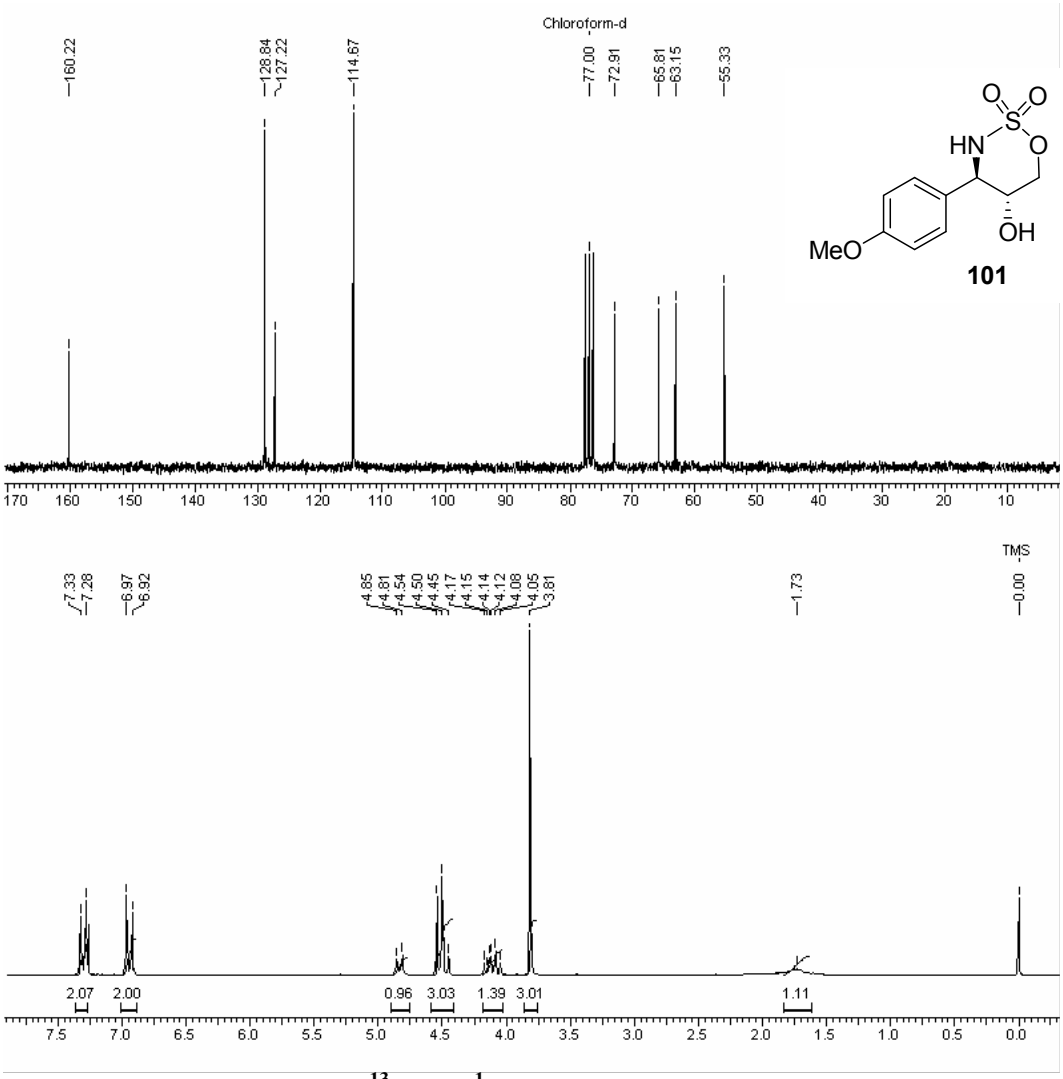


Fig. 11: ^{13}C and ^{1}H -NMR spectra of 101

Carbamoylation[19b] of the –NH moiety in oxathiazinane **101** with Boc_2O, DMAP (cat.) and Et_3N in CH_2Cl_2 followed by ring opening of the crude *N*-Boc protected oxathiazinane[19b] at 60 °C with aq. CH_3CN furnished the *anti*-amino alcohol **102** in 84% yield. The formation of *N*-Boc protected oxathiazinane **102** was confirmed by the appearance of a singlet at δ 1.43 for *t*-butyl protons in its ^{1}H NMR spectrum (**Fig. 12**).

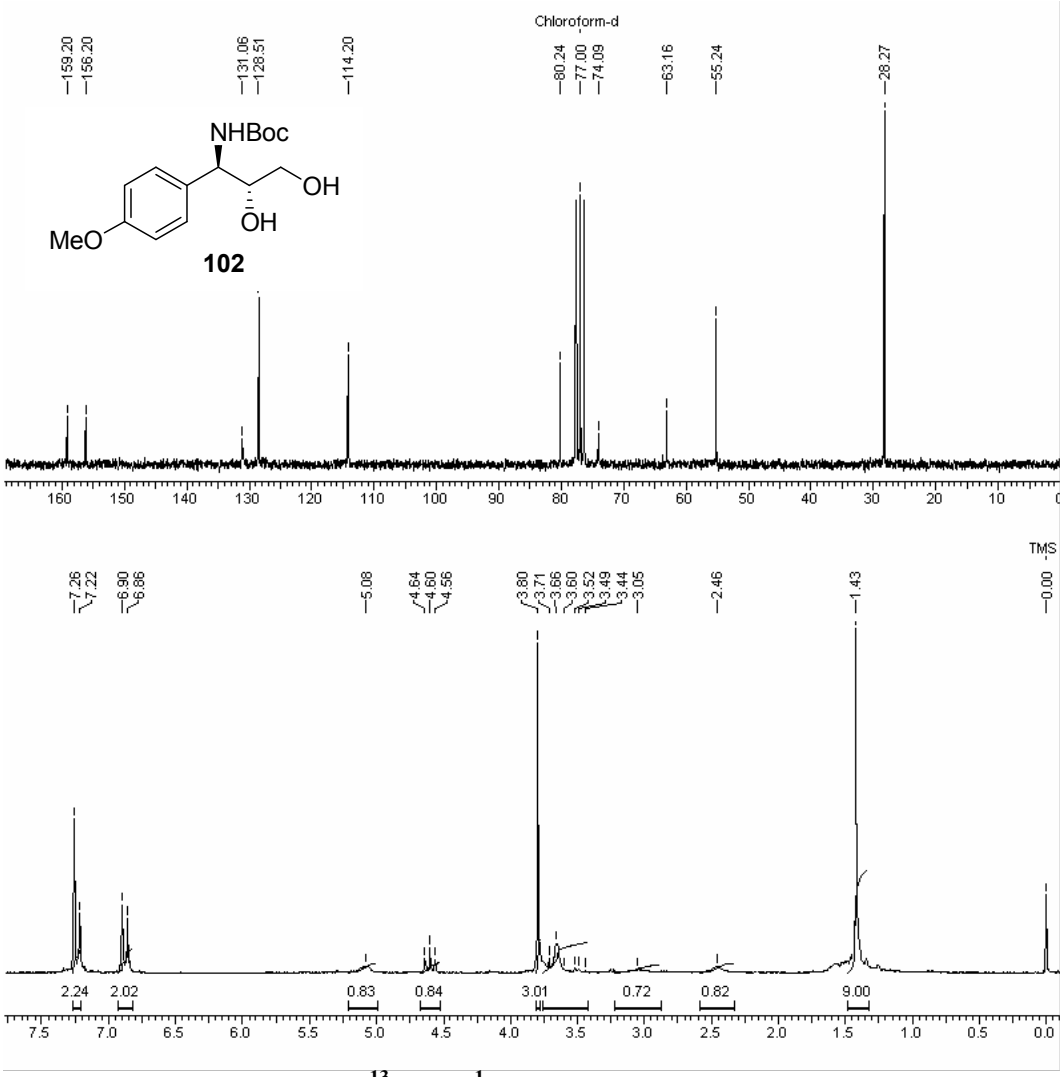
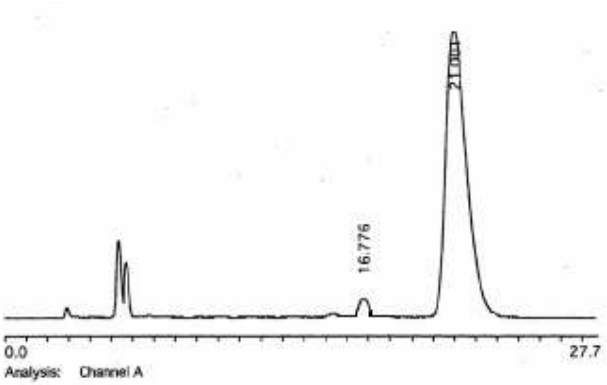


Fig. 12: ^{13}C and ^{1}H -NMR spectra of 102

Finally, regioselective intramolecular cyclization[52] of **102** using NaH in THF at 0 °C furnished (-)-cytoxazone (**1a**) {mp 118-121 ºC; $[\alpha]^{25}_{D}$ -70.3 (*c* 1, MeOH); lit.[1] mp 118-121 ºC; lit.[1] $[\alpha]^{25}_{D}$ -71 (*c* 1, MeOH)} in 96% yield and 99% ee [measured by both chiral HPLC using Chirasphere® column (**Fig. 13**) and $[\alpha]_{D}$].



Peak No.	Retention Time	Area (µV-sec)	Area (%)
1	16.776	10795	0.699
2	21.001	1531408	99.300

Fig. 13: HPLC chromatogram of (-)-cytoxazone (1a)

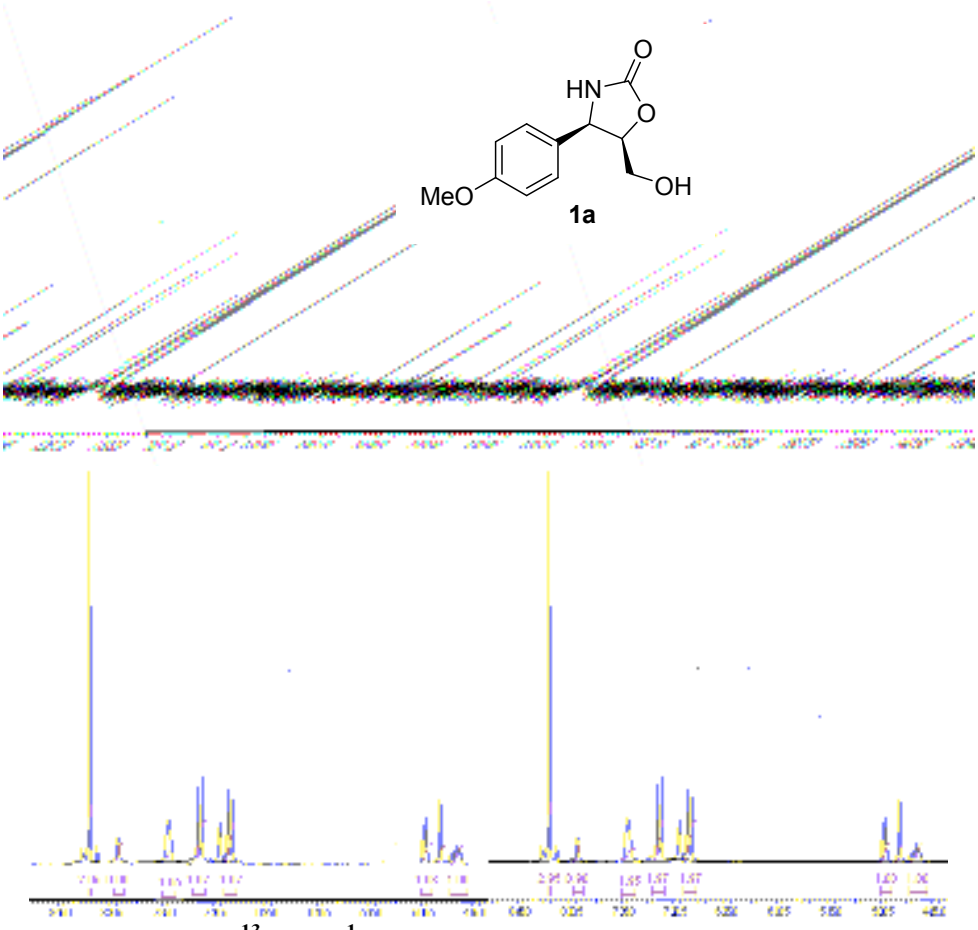


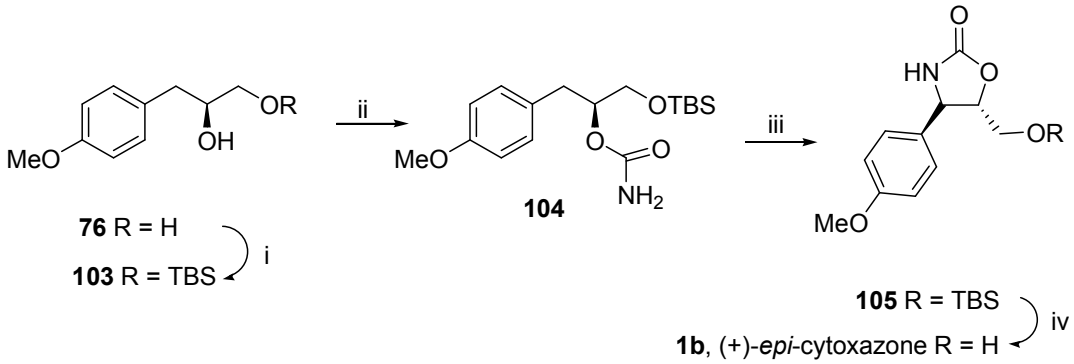
Fig. 14: ^{13}C and ^{1}H NMR spectra of (-)-cytoxazone (1a)

The formation of oxazolidinone in (-)-cytoxazone (**1a)** was confirmed by the appearance of a broad peak at δ 7.92 due to NH proton of oxazolidinone ring in its

^{1}H-NMR spectrum. The signal at δ 160.09 confirms the presence of oxazolidinone carbonyl in its ^{13}C-NMR spectrum (**Fig. 14**). The ^{1}H NMR and ^{13}C NMR spectral data of (–)-cytoxazone (**1a**) matched very well with that of the reported values.[1]

Enantioselective synthesis (+)-*epi*-cytoxazone

In the case of (+)-*epi*-cytoxazone (**1b**), the synthesis was started from the chiral diol **76** in order to obtain epimer of (-)-cytoxazone and the synthetic scheme has been shown in **Scheme 27**.



Scheme 27: (i) TBSCl, imidazole, CH_2Cl_2, 25 °C, 98%; (ii) trichloroacetyl isocyanate, CH_2Cl_2, 0 °C-25 °C, 2 h then K_2CO_3, MeOH, H_2O, 0-25 °C, 12 h, 92%; (iii) 2 mol% $Rh_2(OAc)_4$, $PhI(OAc)_2$, MgO, CH_2Cl_2, 40 °C, 87%, *syn*:*anti* (5.5:1); (iv) TBAF, THF, 92%.

Protection of the primary alcohol of diol **76** with TBSCl gave the secondary alcohol **103** in 98% yield. The formation of secondary alcohol was confirmed by the appearance of signal at δ 0.90 for *t*-butyl protons and δ 0.06 and 0.05 for CH_3-Si protons in its ^{1}H NMR spectrum. The secondary alcohol **103** was then converted into carbamate **104** in 92% yield using the reported conditions (trichloroacetyl isocyanate, CH_2Cl_2 then K_2CO_3, MeOH, H_2O).[19a] The ^{1}H NMR spectrum of carbamate **104** showed the presence of the $CONH_2$ group as evidenced by a broad singlet at δ 4.54. Its ^{13}C NMR spectrum also showed carbon signals at δ 158.1 indicating the presence of $CONH_2$ group (**Fig. 15**).

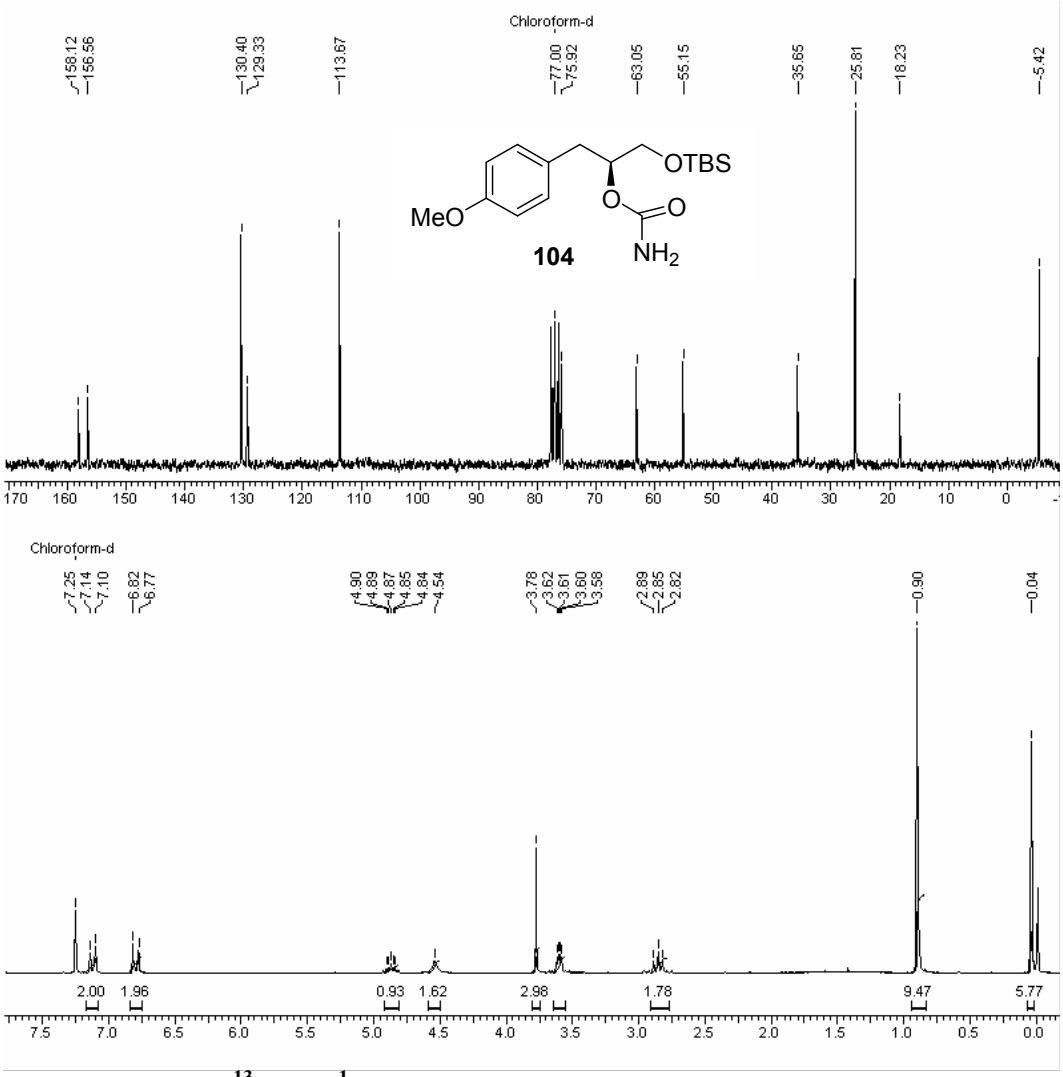


Fig. 15: ^{13}C and ^{1}H NMR spectra of secondary carbamate 104

The carbamate **104** underwent C-H insertion at benzylic position on treatment with 2 mol% $Rh_2(OAc)_4$, $PhI(OAc)_2$ and MgO in CH_2Cl_2 at 40 °C to afford the corresponding oxazolidinone **105** with *syn* diastereoselectivity (5.5:1) (determined from ^{1}H NMR analysis as well as isolated yields) in 87% combined yield.[19a] The *syn*-diastereomer, oxazolidinone **105**, was readily isolated in pure form by column chromatography. The formation of oxazolidinone moiety in **105** was confirmed by the appearance of a broad peak at δ 6.45 due to the typical oxazolidinone ring NH proton in its ^{1}H NMR spectrum. The signal at δ 159.2 confirms the presence of

oxazolidinone carbonyl in its ^{13}C NMR spectrum (**Fig. 16**). The *syn*-selectivity of oxazolidinone **105** was confirmed by the ^{1}H NMR spectrum, which showed a doublet at δ 5.24 with coupling constant J = 4.8 Hz. Finally, deprotection of the TBS group using TBAF in THF furnished (+)-*epi*-cytoxazone (**1b**) {mp 159-160 ºC; lit.[53] mp 158-160 ºC) in 92% yield and 99% ee.

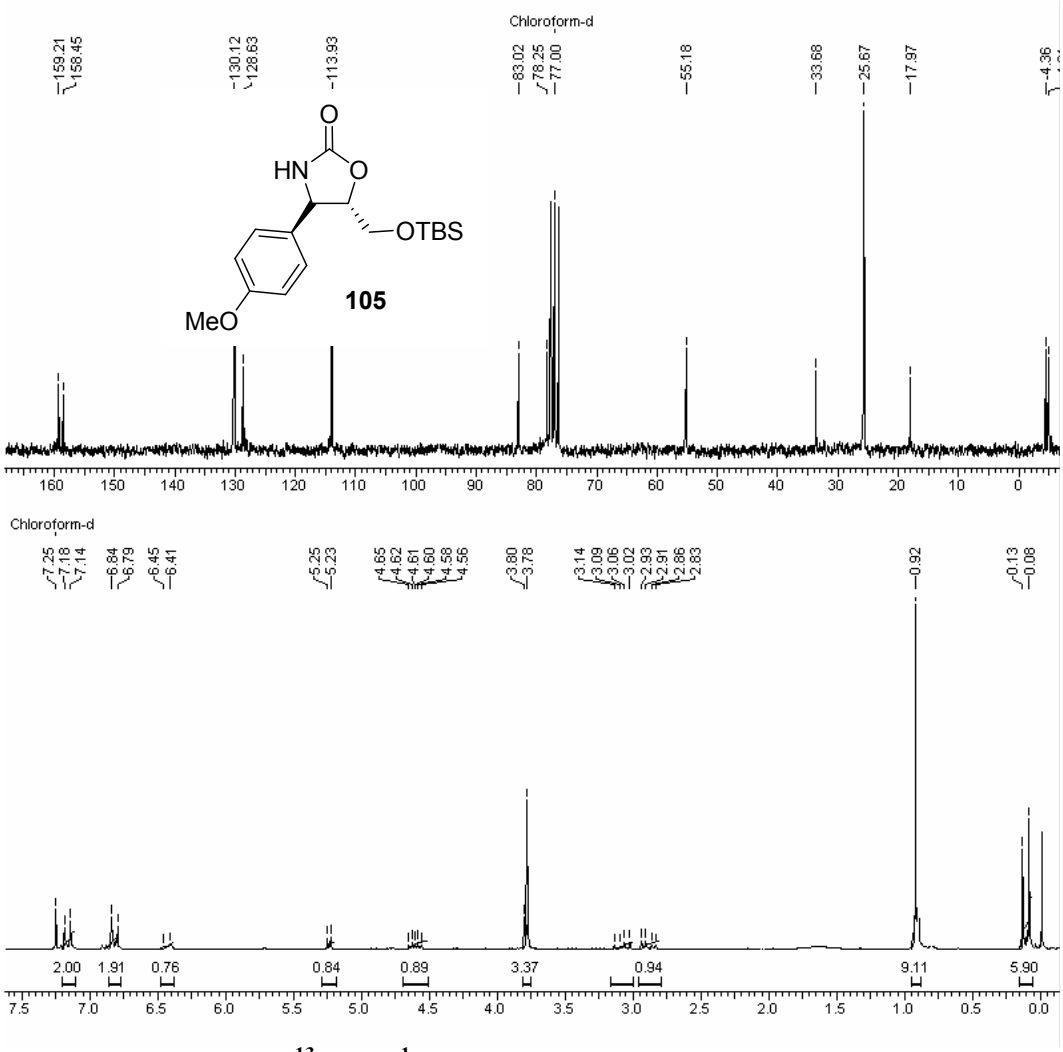


Fig. 16: ^{13}C and ^{1}H-NMR spectra of oxalidinone 105

The ee of (+)-*epi*-cytoxazone (**1b**) was found to be 99% based on comparison of its optical rotation with that of reported value {$[\alpha]^{25}_{D}$ +28.3 (*c* 1, MeOH; lit.[53] $[\alpha]^{25}_{D}$ +28.6 (*c* 1, MeOH)}. The ^{1}H NMR spectrum as well as ^{13}C NMR spectrum of **1b** showed the absence of TBS group compared to oxazolidinone **105** (**Fig. 17**). The

spectral data of (+)-*epi*-cytoxazone (**1b**) matched very well with that of the reported values.[53]

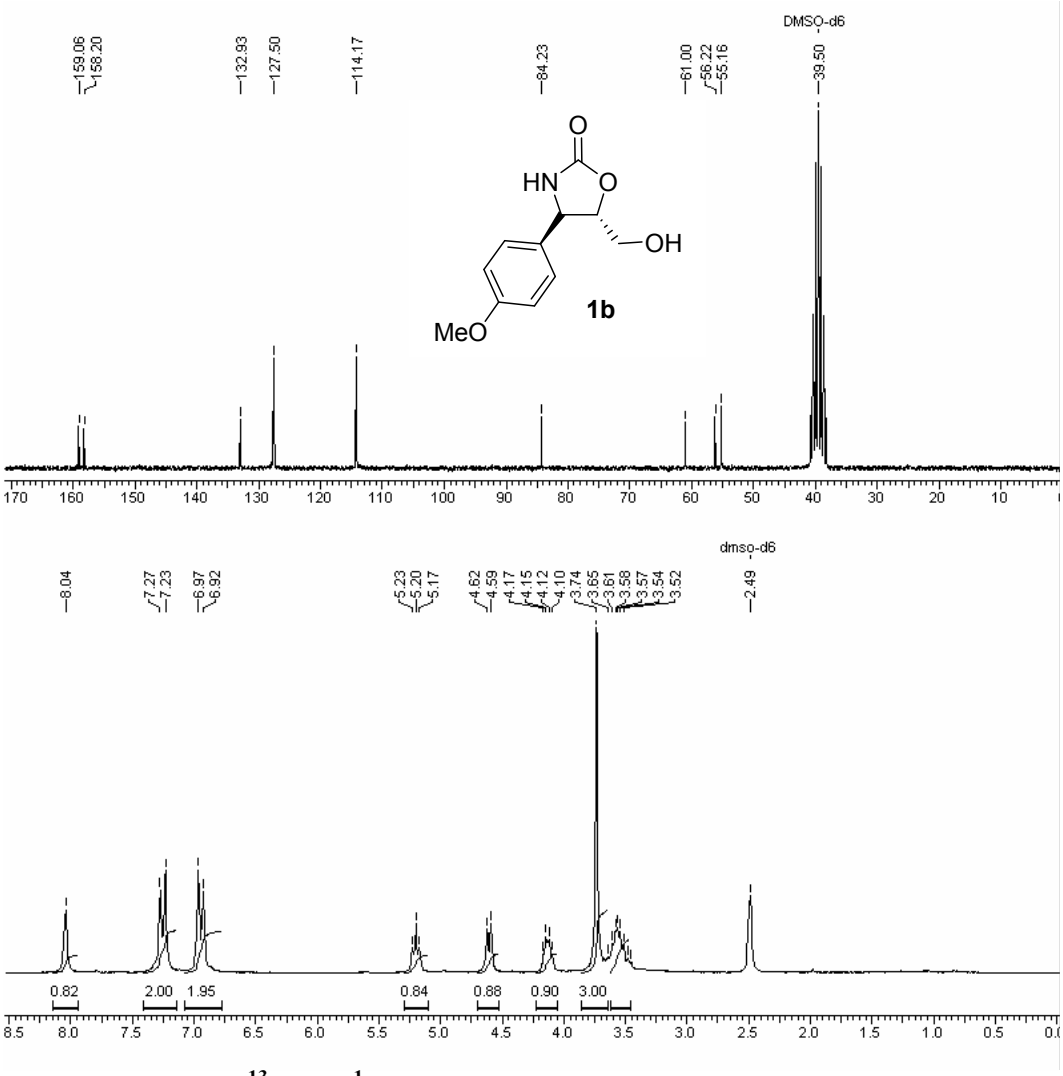


Fig. 17: ^{13}C and ^{1}H-NMR spectra of (+)-*epi*-cytoxazone (1b)

1.6 Conclusion

In conclusion, the enantioselective syntheses of (-)-cytoxazone (**1a**) and (+)-*epi*-cytoxazone (**1b**) were achieved in fewer number of steps. The two powerful methods *i.e.* proline catalyzed asymmetric α-aminooxylation of aldehydes as well as Rh-catalyzed diastereoselective C-H aminations constitute key steps in the synthesis. The selectivity for *syn*- or *anti*-1,2-aminoalcohol products was achieved by Rh-catalyzed

intramolecular amidation of the C-H bonds of carbamates or sulfamate esters with good to excellent diastereoselectivities.

1.7 Experimental Section

4-Bromomethoxybenzene (106):

To a mixture of 4-bromophenol (10.38 g, 60 mmol) and K_2CO_3 (16.56 g, 120 mmol) in dry DMF (100 mL) was added methyl iodide (5.5 mL, 90 mmol) through syringe at 50 °C with vigorous stirring. After completion of reaction (monitored by TLC, 12 h), K_2CO_3 was filterd out. Ethyl acetate (200 mL) and water (200 mL) were added to the filtrate, followed by organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 60 mL). The combined organic extracts were washed with water (80 mL) followed by brine (60 mL) and concentrated *in vacuo* to give the crude product, which was purified by column chromatography packed with silica gel using pet. ether: EtOAc (9.5:0.5) as eluent to afford 4-bromo methoxybenzene (10.98 g) as a colorless liquid.

Yield: 98%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): 804, 822, 1040, 1100, 1170, 1246, 1460, 1490, 1578, 2936, 2956; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 3.78 (3H, s), 6.76 (2H, d, *J* = 8.96 Hz), 7.36 (2H, d, *J = 8.97 Hz*); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 55.24, 112.73, 115.62, 132.13, 158.60; **Analysis**: C_7H_7BrO requires C, 44.95; H, 3.77; Br, 42.72%; found C, 44.93; H, 3.72; Br, 42.70 %.

2-(4-Methoxybenzyl)oxirane (77):

A dry, argon flushed 100 ml round-bottom flask, equipped with a magnetic stirring bar and reflux condenser, was charged with 2-3 crystals of iodine, and magnesium turnings (0.60 g, 25 mmol) in dry Et_2O (20 mL) at 25 °C. Then 4-bromo methoxybenzene **106** (4.67 g, 25 mmol) in Et_2O (10 mL) was added drop wise at 25 ºC. After stirring for 1 h, the reaction flask was cooled to -35 °C, followed by addition

of Et_2O (30 mL) and CuI (0.95 g, 5 mmol) to the reaction mixture. Epichlorohydrin (2.3 g, 25 mmol) in THF (10 mL) was then added to the reaction mixture drop wise by using a syringe and stirred for 1 h at -35 °C. The reaction mixture was then brought to 25 ºC and stirred for 3 h, quenched with saturated solution of NH_4Cl (50 ml) and extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated *in vacuo* to give the crude chloroalcohol which was dissolved in dry THF (50 mL). Powdered NaOH (2 g, 50 mmol) was added to it at 0 °C and stirred for 1.5 h. After completion of the reaction, it was filtered and washed with EtOAc (40 mL), dried over anhyd. Na_2SO_4 and concentrated *in vacuo* to give the crude product, which was purified by column chromatography packed with silica gel using pet. ether: EtOAc (9:1) as eluent to afford the epoxide **77** (3.48 g) as a colorless liquid.

Yield: 85%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): 792, 818, 1034, 1110, 1178, 1246, 1480, 1514, 1612, 2994; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.50 (dd, *J* = 4.92, 2.65 Hz, 1H), 2.70-2.91 (m, 3H), 3.06-3.15 (m, 1H), 3.79 (s, 3H), 6.84 (d, *J* = 8.71 Hz, 2H), 7.15 (d, *J* = 8.59 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 37.9, 46.7, 52.6, 55.2, 113.9, 129.1, 130.0, 158.4; **Analysis:** $C_{10}H_{12}O_2$ requires C, 73.15; H, 7.37%; found C, 73.24; H, 7.29%.

3-(4-Methoxyphenyl)propan-1-ol (96):

To a suspension of $LiAlH_4$ (2.13 g, 56 mmol) in dry THF (60 mL) at 0 °C under N_2 atmosphere was added (*E*)-3-(4-methoxyphenyl)acrylic acid (5 g, 28 mmol) in dry THF (15 mL) drop wise and was refluxed for 12 h. It was cooled to 25 °C and quenched with 4N NaOH (1 mL) and EtOAc (30 mL). The solid formed was filtered and washed with EtOAc. The filtrate was dried over anhyd. Na_2SO_4 and concentrated *in vacuo* to give the crude product, which was purified by column chromatography

packed with silica gel using pet. ether: EtOAc (9:1) as eluent to afford alcohol **96** (4.12 g) as a colorless liquid.

Yield: 91%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): 758, 1084, 1160, 1138, 1564, 1514, 2944, 3338; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.51 (br s, 1H), 1.84 (m, 2H), 2.64 (t, *J* = 7.96 Hz, 2H), 3.63 (t, *J* = 6.44 Hz, 2H), 3.77 (s, 3H), 6.79 (d, *J* = 8.71 Hz, 2H), 7.08 (d, *J* = 8.59 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 30.94, 34.22, 54.88, 61.58, 113.60, 129.06, 133.73, 157.54; **Analysis:** $C_{10}H_{14}O_2$ requires C, 72.26; H, 8.49%; found C, 72.24; H, 8.55%.

(*R*)-3-(4-Methoxyphenyl)propane-1,2-diol (71):

Preparation of Co-salen.OAc complex: To a solution of (*R,R*)-**1** (0.060 g, 0.1 mmol) in toluene (2.5 mL) was added acetic acid (0.063 g, 11 mmol). It was allowed to stir at 25 ºC in open air for 30 min. over which time the color changed from orange-red to a dark brown and it was then concentrated *in vacuo* to get the Co-salen complex as brown colored solid. To solution of Co-salen complex (0.062 g, 0.5 mol%) and epoxide (3.39 g, 20.7 mmol) at 0 °C was added H_2O (0.167 g, 9.3 mmol) drop wise over 5 min. The reaction was allowed to warm to 25 ºC and stirred for 14 h. The reaction mixture was filtered through a pad of silica gel and washed with 50% EtOAc/hexanes (40 mL) and the filtrate was concentrated *in vacuo* to give the crude products, which were purified by column chromatography packed with silica gel using petroleum ether/EtOAc (9:1) to give chiral epoxide **93** (1.765 g, 52%) and using petroleum ether/EtOAc (7:3) to give chiral diol **71** (1.657 g, 44%). The ee of the diol was determined to be 98% ee by Mosher ester **94** (see details in the preparation of Mosher ester). The ee of the chiral epoxide was determined to be 92% ee by optical rotation {$[\alpha]^{25}_D$= +0.74 (*c* 1, $CHCl_3$); lit.[11] $[\alpha]^{25}_D$= +0.8 (*c* 1, $CHCl_3$)}.

Yield: 0.84 g (45%); colorless gum; **$[\alpha]^{25}_{D}$**: +12.76 (*c* 2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 752, 1074, 1110, 1248, 1464, 1514, 2924, 3338 (broad); **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 2.07 (br s, 1H), 2.17 (br s, 1H), 2.71 (m, 2H), 3.49 (dd, *J* = 11.11, 6.94 Hz, 1H), 3.67 (dd, *J* = 11.12, 3.16 Hz, 1H), 3.79 (s, 3H), 3.88 (m, 1H), 6.84 (d, *J* = 8.59 Hz, 2H), 7.12 (d, *J* = 8.59 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 38.91, 55.19, 65.95, 73.12, 114.09, 129.56, 130.29, 158.39; **Analysis: $C_{10}H_{14}O_3$** requires C, 65.96; H, 7.68%; found C, 65.94; H, 7.64%.

Second procedure by α-aminooxylation of aldehydes:

Swern oxidation: To a stirred solution of oxalyl chloride, $(COCl)_2$ (3.81 g, 30 mmol) in CH_2Cl_2 (90 mL) at -78 °C, was added a solution of DMSO (3.18 mL, 45 mmol). The reaction mixture was stirred for 20 min. followed by the addition of a solution of alcohol **96** (2.49 g, 15 mmol) in CH_2Cl_2 (30 mL). After stirring for 0.5 h at -78 °C, the reaction was quenched by the addition of Et_3N (8.4 mL, 60 mmol) and water (100 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 60 mL). The combined organic layers were washed with water (2 x 60 mL), dried over anhyd. Na_2SO_4 and concentrated to give the corresponding aldehyde **73**.

α-Aminooxylation: To a mixture of aldehyde **73** (2.46 g, 15 mmol) and nitrosobenzene (1.6 g, 15 mmol) in CH_3CN (35 mL) was added L-proline (431 mg, 3.72 mmol, 25 mol %) at -20 ºC and stirred for 24 h. Methanol (15 mL) and $NaBH_4$ (1.68 g, 45 mmol) were added to the reaction mixture and stirred for 10 min. After addition of phosphate buffer, the resulting mixture was extracted with EtOAc (30 mL X 3) and the combined organic phases were dried over anhyd. Na_2SO_4 and concentrated *in vacuo* to give the crude product. To the solution of this crude product in MeOH (40 mL) was added 10% Pd/C (100 mg). It was then stirred under the

hydrogen atmosphere (1 atm.) for 12 h. After completion of reaction (monitored by TLC), reaction mixture was filtered through celite pad and concentrated *in vacuo* to give the crude product, which was purified by column chromatography packed with silica gel using EtOAc/ pet. ether (3:7) as eluent to afford pure **71** (2.34 g) as colorless gum. The ee of the diol was determined to be 99% ee by mosher ester **94**.

Yield: 86%; colorless gum; $[\alpha]^{25}_{D}$: +12.90 (*c* 2, $CHCl_3$).

Preparation of Mosher ester of (*R*)-3-(4-Methoxyphenyl)propane-1,2-diol (94):

A two-necked 10 mL flask charged with *N*,*N*'- dicyclohexylcarbodiimide (44 mg, 0.21 mmol), catalytic amount of 4-dimethylaminopyridine (DMAP) and CH_2Cl_2 (2 mL) under argon atmosphere. The flask was cooled to 0 ºC for 10 min. and to this mixture, a solution of benzyl protected alcohol **71** (48 mg, 0.18 mmol) in CH_2Cl_2 (2 mL) was introduced through a syringe. It was allowed to stir for additional 10 min, followed by dropwise addition of (*R*)-α-methoxy-α-trifluoromethylphenyl acetic acid (46 mg, 0.196 mmol) in CH_2Cl_2 (2 mL). This reaction mixture was then stirred at 0 ºC for additional 1h and then at 25 ºC for 12 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with saturated $NaHCO_3$ solution (50 mL), dried over anhyd. Na_2SO_4 and then concentrated *in vacuo* to give Mosher ester of benzyl protected alcohol (59 mg) as a thick syrup.

Yield: 70%; $[\alpha]^{25}_{D}$: –8.6 (*c* 1.12, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3158, 2952, 2927, 2850, 2250, 1753, 1606, 1519, 1495, 1348, 1268, 1242, 1217, 1153, 1122, 1015, 957, 911, 735, 650; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 2.75 (dd, *J* = 13.77, 6.82 Hz, 1H), 2.90 (dd, *J* = 13.77, 5.94 Hz, 1H), 3.50 (m, 1H), 3.56 (s, 3H), 3.69-3.78 (m, 2H), 3.80 (s, 3H), 4.54 (q, 2H), 6.84 (d, *J* = 8.72 Hz, 2H), 7.13 (d, *J* = 8.72 Hz, 2H), 7.44-7.30 (m, 10H).

(*S*)-3-(4-Methoxyphenyl)propane-1,2-diol (76):

Preparation of Co-salen.OAc complex: To a solution of (*S,S*)-1 (0.060 g, 0.1 mmol) in toluene (2.5 mL) was added acetic acid (0.063 g, 11 mmol). It was allowed to stir at 25 ºC in open air for 30 min over which time the color changed from orange-red to a dark brown and it was then concentrated *in vacuo* to get the Co-salen complex as brown colored solid. To solution of Co-salen complex (0.032 g, 0.5 mol%) and chiral epoxide **93** (3.39 g, 20.7 mmol) at 0 °C was added H_2O (0.176 g, 9.8 mmol, 0.95 equiv.) drop wise over 5 min. The reaction was allowed to warm to 25 ºC and stirred for 14 h. The reaction mixture was filtered through a pad of silica gel and washed with 50% EtOAc/hexanes (40 mL) and the filtrate was concentrated *in vacuo* to give the crude product, which was purified by column chromatography packed with silica gel using petroleum ether/EtOAc (7:3) to give chiral diol **76** (1.64 g) as a colorless gum.

Yield: 92%; colorless gum; $[\alpha]^{25}_{D}$: -12.76 (*c* 2, $CHCl_3$).

Second procedure by α-aminooxylation of aldehydes:

To a mixture of aldehyde **73** (2.46 g, 15 mmol) and nitrosobenzene (1.6 g, 15 mmol) in CH_3CN (35 mL) was added D-proline (431 mg, 3.72 mmol, 25 mol %) at -20 ºC and it was stirred for 24 h. Methanol (15 mL) and $NaBH_4$ (1.68 g, 45 mmol) were added to the reaction mixture and stirred for 10 min. After addition of phosphate buffer, the resulting mixture was extracted with EtOAc (30 mL X 3) and the combined organic phases were dried over anhyd. Na_2SO_4 and concentrated *in vacuo* to give the crude product. To the solution of this crude product in MeOH (40 mL) was added 10% Pd/C (100 mg). It was then stirred under the hydrogen atmosphere (1 atm) for 12 h. After completion of reaction (monitored by TLC) the reaction mixture was filtered through celite pad and concentrated in *vacuo to* give the crude product, which was

purified by column chromatography packed with silica gel using ethyl acetate/ pet. ether (3:7) as eluent to afford pure **76** (2.34 g) as colorless gum. The ee of the diol was determined to be 99% ee by optical rotation.

Yield: 86%; colorless gum; $[\alpha]^{25}_{D}$: -12.90 (*c* 2, $CHCl_3$).

(*R*)-1,2-Bis(*tert*-butyldimethylsiloxy)-3-(4-methoxyphenyl)-1,2-propanediol (97):

To a solution of diol **71** (2.074 g, 11.4 mmol) in DMF (40 mL) at 25 ºC was added TBSCl (4.10 g, 27.26 mmol) and imidazole (1.857 g, 27.26 mmol). The resulting solution was stirred at 25 ºC for 24 h, then quenched with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhyd. Na_2SO_4 and concentrated *in vacuo* to give the crude product, which was purified by column chromatography packed with silica gel using pet. ether/EtOAc (9:1) to give pure bis-TBS-protected diol **97** (4.58 g) as a colorless oil.

Yield: 98%; $[\alpha]^{25}_{D}$: +10.26 (*c* 2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 668, 765, 835, 1038, 1111, 1216, 1249, 1464, 1513, 1585, 1612, 2858, 2931, 2955, 3017, 3482; **^{1}H NMR** (200 MHz, $CDCl_3$): δ -0.25 (s, 3H), 0.09 (s, 3H), -0.01 (s, 3H), 0.04 (s, 3H), 0.81 (s, 9H), 0.90 (s, 9H), 2.52 (dd, *J* = 12.56, 7.35 Hz, 1H), 2.89 (dd, *J* = 12.52, 5.34 Hz, 1H), 3.38 (dd, *J* = 10.05, 5.98 Hz, 1H), 3.51 (dd, *J* = 10.01, 6.05 Hz, 1H), 3.78 (s, 4H), 6.79 (dd, *J* = 10.25 Hz, 2H), 7.10 (dd, *J* = 9.25 Hz, 2H); **^{13}C NMR** (50 MHz, CDCl3): δ -5.7, 18.4, 25.8, 41.9, 55.9, 70.9, 77.0, 114.4, 129.2, 130.4, 158.0; **Analysis**: $C_{22}H_{42}O_3Si_2$ requires C, 64.33; H, 10.31%; found C, 64.25; H, 10.39 %.

(*R*)-2-(*tert*-Butyldimethylsiloxy)-3-(4-methoxyphenyl)-1,2-propanediol (98):

To a solution of bis-TBS-protected diol **97** (3.69 g, 9 mmol) in MeOH (30 mL) was added camphorsulfonic acid (2.088 g, 9 mmol) at 0 °C and stirred 2 h. After completion of the reaction (monitored by TLC), it was neutralized with $NaHCO_3$ and concentrated to give the crude product, which was purified by column

chromatography packed with silica gel using pet. ether: EtOAc (9:1) as eluent to furnish **98** (2.5 g) as colorless liquid.

Yield: 95%; colorless liquid; $[\alpha]^{25}_{D}$: +6.56 (*c* 2, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$): δ -0.19 (s, 3H), 0.07 (s, 3H), 0.79 (s, 9H), 1.67 (br s, 1H), 2.65 (d, *J* = 6.82 Hz, 1H), 3.10 (d, *J* = 3.41 Hz, 1H), 3.39 (dd, *J* = 7.96, 3.79 Hz, 1H), 3.69 (s, 3H), 3.60-3.83 (m, 2H), 6.76 (d, *J* = 8.71 Hz, 2H), 7.02 (d, *J* = 8.59 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.9, -4.9, 18.0, 25.6, 25.8, 25.9, 39.6, 55.2, 65.5, 74.2, 113.7, 130.3, 130.5, 158.2; **Analysis**: $C_{16}H_{28}O_3Si$ requires C, 64.82; H, 9.52%; found C, 64.89; H, 9.45 %.

(*R*)-2-(*tert*-Butyldimethylsiloxy)-3-(4-methoxyphenyl)propyl sulfamate (99):

Formic acid (397 μL, 10.5 mmol) was added drop wise to neat chlorosulfonyl isocyanate (0.92 ml, 10.5 mmol) at 0 °C with rapid stirring. Vigorous gas evolution was observed during the addition process. The resulting viscous suspension was stirred for 5 min. at 0 °C during which time the reaction mixture solidified. CH_2Cl_2 (9 mL) was added and it was stirred at 0 °C for 1 h then at 25 °C for 8 h. The reaction mixture was cooled to 0 °C and a solution of alcohol **98** (2.072g, 7 mmol) and pyridine (0.85 mL, 10.5 mmol) in CH_2Cl_2 (8 mL) was added drop wise. The contents were warmed to 25 °C and stirred until TLC indicated complete consumption of alcohol **98** (4 h). The reaction was quenched by the successive addition of EtOAc (20 mL) and H_2O (10 mL). The biphasic mixture was further diluted with EtOAc (50 mL) and H_2O (20 mL). The organic phase was collected and the aqueous layer was extracted with EtOAc (30 mL). The combined organic extracts were washed with brine (40 mL), dried over anhyd. Na_2SO_4 and concentrated *in vacuo* to give the crude product, which was purified by column chromatography packed with silica gel using pet. ether: EtOAc (7 : 3) to afford pure sulfamate ester **99** (2.0 g).

Yield: 76%; colorless liquid; **$[\alpha]^{25}_{D}$**: +8.23 (*c* 2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}) 778, 814, 838, 1112, 1248, 1462, 1514, 1698, 1736, 2928, 2954, 3358; **^{1}H NMR** (200 MHz, $CDCl_3$): δ -0.10 (s, 3H), -0.0 (s, 3H), 0.87 (s, 9H), 2.79 (dd, J = 13.64, 6.06 Hz, 1H), 3.19 (d, J = 7.33 Hz, 1H), 3.78 (s, 3H), 3.93-4.36 (m, 3H), 4.87 (br s, 2H), 6.82 (d, J = 8.71 Hz, 2H), 7.10 (d, J = 8.71 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.2, -4.9, 18.0, 25.7, 39.5, 55.2, 71.7, 73.4, 113.9, 129.2, 130.6, 158.4; **Analysis**: $C_{16}H_{29}NO_5SSi$ requires C, 51.17; H, 7.78; N, 3.73; S, 8.54%; found C, 51.23; H, 7.71; N, 3.68; S, 8.61%.

(4*R*,5*R*)-5-(*tert*-Butyldimethylsiloxy)-4-(4-methoxyphenyl)-2-oxathiazinane (100): To a solution of sulfamate ester **99** (1.5 g, 4 mmol) in CH_2Cl_2 (20 mL) under nitrogen atmosphere were added sequentially MgO (0.371 g, 9.6 mmol), $PhI(OAc)_2$ (1.417 g, 4.48 mmol) and $Rh_2(OAc)_4$ (0.035 g, 2 mol%). It was stirred vigorously at 40 °C for 2 h. The completion of reaction was checked by TLC. After completion of reaction, it was cooled to 25 °C, diluted with CH_2Cl_2 (30 mL), and filtered through a pad of celite, washed with CH_2Cl_2 (2 × 25 mL) and the filtrates were evaporated *in vacuo* to give the crude product, which was purified by column chromatography packed with silica gel using pet. ether: EtOAc (8:2) as eluent to furnish **100** (1.12 g) as a colorless solid.

Yield: 75%; **mp**: 133-135 °C; **$[\alpha]^{25}_{D}$**: + 4.0 (*c* 1.1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3281, 2955, 2931, 2857, 1614, 1518, 1368, 1253, 1193, 1035, 839, 779; **^{1}H NMR** (200 MHz, $CDCl_3$): δ -0.53 (s, 3H), -0.12 (s, 3H), 0.07 (s, 9H), 3.81 (s, 3H), 3.97 (m, 1H), 4.33 (dd, *J* = 11.3, 5.3 Hz, 1H), 4.51-4.43 (m, 2H), 4.62 (d, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 8.7 Hz, 2H), 7.23 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.8, -5.1, 17.6, 25.3, 55.4, 63.9, 67.5, 73.4, 114.3, 128.5, 128.9, 130.2, 137.4, 160.1; **Analysis**:

$C_{16}H_{27}NO_5Ssi$ requires C, 51.45; H, 7.29; N, 3.75; S, 8.58%; found C, 51.58; H, 7.21; N, 3.67; S, 8.49%.

(4*R*,5*R*)-5-Hydroxy-4-(4-methoxyphenyl)-2-oxathiazinane (101):

To a solution of **100** (1.12 g, 3 mmol) in MeOH (15 mL) at 0 °C was added camphorsulfonic acid (0.696 g, 3 mmol) and stirred for 2 h. After completion of reaction (monitored by TLC), it was neutralized with $NaHCO_3$ and organic layer was concentrated *in vacuo* to give the crude product, which was purified by column chromatography packed with silica gel using pet. ether: EtOAc (9:1) as eluent to furnish **101** (0.753 g) as a colorless solid.

Yield: 97%; **mp**: 164-165 °C; **$[\alpha]^{25}_D$**: + 4.0 (*c* 1.1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 669, 761, 1035, 1215, 1373, 1420, 1516, 1613, 2400, 2929, 3020, 3337, 3685; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.73 (br s, 1H), 3.81 (s, 3H), 4.05-4.17 (m, 2H), 4.45-4.54 (m, 3H), 4.83 (d, *J* = 8.46 Hz), 6.94 (d, *J* = 8.84 Hz), 7.30 (d, *J* = 8.72 Hz); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.3, 63.2, 65.8, 72.9, 114.7, 127.2, 128.4, 160.2; **Analysis**: $C_{10}H_{13}NO_5S$ requires C, 46.32; H, 5.05; N, 5.40; S, 12.37%; found C, 46.25; H, 5.01; N, 5.49; S, 12.39%.

***tert*-Butyl (1*R*,2*R*)-2,3-dihydroxy-1-(4-methoxyphenyl) propylcarbamate (102):**

To a solution of alcohol **101** (0.725 g, 2.8 mmol) in THF (10 mL) under nitrogen atmosphere were added sequentially DMAP (0.034 g, 10 mol%), $(Boc)_2O$ (0.732 g, 3.36 mmol) and Et_3N (0.84 mL, 8.4 mmol) and stirred at 25 °C for 12 h. After completion of the reaction the solvent was concentrated to give the residue, which was diluted with CH_3CN (11 mL) and H_2O (6 mL) and stirred vigorously at 65 °C for 12 h. After cooling the solution to 25 °C, CH_3CN was removed from the reaction mixture *in vacuo* and the aqueous layer was extracted with EtOAc (2 x 25 mL). The organic layer was washed with brine (50 mL), dried over anhyd. Na_2SO_4 and

concentrated *in vacuo* to give the crude product, which was purified by column chromatography packed with silica gel using pet. ether: EtOAc (8:2) as eluent to furnish **102** (0.698 g) as a colorless solid.

Yield: 84 %; **mp**: 116 ºC; **[α]$^{25}_{D}$**: -51.0 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): ν 3682, 3438, 3019, 2981, 2839, 2400, 1701, 1612, 1585, 1509, 1392, 1368, 1216, 1167, 1035, 927, 831, 757, 669; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.41 (s, 9H), 2.46 (br s, 1H), 3.05 (br s, 1H), 3.44-3.71 (m, 3H), 3.80 (s, 3H), 4.60 (t, *J* = 7.9 Hz, 1H), 5.08 (br s, 1H), 6.88 (d, *J* = 8.7 Hz, 2H), 7.24 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 28.27, 55.24, 63.16, 74.09, 80.24, 114.20, 128.51, 131.06, 156.20, 159.20; **Analysis**: $C_{15}H_{23}NO_5$ requires C, 60.59; H, 7.80; N, 4.71%; found C, 60.31; H, 8.09; N, 4.60%.

(4*S*,5*R*)-5-Hydroxymethyl-4-(4-methoxyphenyl)-oxazolidin -2-one: (-)-Cytoxazone, (1a):

To a solution of amino alcohol **102** (0.297 g, 1 mmol) in dry THF (8 mL) at 25 º under nitrogen atmosphere was added NaH [0.048 g, 2 mmol (60% w/w in wax)] and stirred for 4 h. The reaction mixture was quenched with H_2O (2 mL) and concentrated to give the residue, which was extracted with CH_2Cl_2 (30 mL), washed with saturated NH_4Cl (20 mL), brine (20 mL) and dried over anhyd. Na_2SO_4. The organic layer was concentrated *in vacuo* to give the crude product, which was purified by column chromatography packed with silica gel using pet. ether/EtOAc (7:3) to afford (-)-cytoxazone **1a** (0.214 g) as a colourless solid.

Yield: 96%; colorless solid; **mp**: 117-120 °C (crystallized from MeOH), (lit.[1] 118-121 °C); **[α]$^{25}_{D}$**: – 60.16 (*c* 0.3, MeOH) {lit.[1] $[\alpha]^{25}_{D}$: –71 (*c* 0.1, MeOH)}; **HPLC**: 99% ee, Chirasphere®, λ = 254 nm, 5% 2-propanol/hexane, 1 mL/min., Retention time: (*S*,*S*) 16.776 min. (*R*,*R*) 21.001 min.; **IR** (KBr, cm^{-1}): 450, 766, 965, 997, 1026, 1041, 1050, 1177, 1215, 1236, 1254, 1398, 1514, 1615, 1712, 1720, 2948, 3228, 3255, 3352,

3476; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 2.95-2.97 (m, 2H), 3.75 (s, 3H), 4.62–4.73 (m, 1H), 4.82 (t, *J* = 5.1 Hz, 1H), 4.90 (d, *J* = 4.37 Hz, 1H), 6.91 (d, *J* = 8.76 Hz, 2H), 7.15 (d, *J* = 8.46 Hz, 2H), 7.92 (br s, 1H); **^{13}C NMR** (50 MHz, , DMSO-d_6): δ 55.17, 56.82, 61.93, 80.48, 113.79, 128.17, 129.45, 158.81, 160.09; **Analysis:** $C_{11}H_{13}NO_4$ requires C, 59.19; H, 5.87; N, 6.27% found C, 59.17; H, 5.80; N, 6.19%.

(*S*)-1-(*tert*-Butyldimethylsiloxy)-3-(4-methoxyphenyl)-1,2-propanediol (103):

To a solution of diol **76** (0.502 g, 2.77 mmol) in dry CH_2Cl_2 (20 mL) under nitrogen atmosphere was added imidazole (0.65 g, 3.6 mmol) and *t*-butyl dimethyl silyl chloride (0.543 g, 3.6 mmol). It was stirred for 0.5 h and quenched with $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL) dried over anhyd. Na_2SO_4 and concentrated *in vacuo* to give the crude product, which was purified by column chromatography packed with silica gel using pet. ether: EtOAc (9:1) as eluent to furnish **103** (0.80 g) as a colorless liquid.

Yield: 98%; **$[\alpha]^{25}_D$**: –9.45 (*c* 4.56, EtOH); **IR** ($CHCl_3$, cm^{-1}): 814, 836, 1006, 1118, 1248, 1388, 1460, 1464, 2996, 3448, 3566 (broad); **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 0.04 (s, 3H), 0.06 (s, 3H), 0.90 (s, 9H), 2.70 (d, *J* = 6.2 Hz, 2H), 1.54 (br s, 1H), 3.56 (dd, *J* = 8.23, 3.12 Hz, 1H), 3.58 (dd, *J* = 10.31, 4.34 Hz, 1H), 3.78 (s, 4H), 6.82 (d, *J* = 8.76 Hz, 2H), 7.12 (d, *J* = 8.96 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: -5.3, 18.3, 25.7, 25.9, 38.7, 55.2, 66.2, 72.9, 113.9, 130.2, 158.2; **Analysis**: $C_{16}H_{28}O_3Si$ requires C, 64.82; H, 9.52%; found C, 64.87; H, 9.46%.

(*S*)-1-(t*ert*-Butyldimethylsiloxy)-3-(4-methoxyphenyl) propan-2-yl carbamate (104):

To a stirred solution of protected diol **103** (0.59 g, 2 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added trichloroacetyl isocyanate (0.56 g, 3 mmol). The resulting solution was stirred for 2 h and then concentrated to give the residue. To a solution of this residue

in MeOH (10 mL) at 0 °C was added a solution of K_2CO_3 (0.83 g, 6 mmol) in water (2 mL) and stirred at 0 °C for 2 h, then at 25 ºC for 16 h. After completion of the reaction, solvent was removed and extracted with CH_2Cl_2 (3 × 15 mL). The organic layer was dried over anhyd. Na_2SO_4 and concentrated *in vacuo* to give the crude product, which was purified by column chromatography packed with silica gel using pet. ether: EtOAc (7:3) as eluent to furnish **104** (0.62 g) as a viscous gum.

Yield: 92%; **$[\alpha]^{25}_D$**: –13.74 (*c* 1.12, EtOH); **IR** ($CHCl_3$, cm^{-1}): 778, 814, 838, 1112, 1248, 1462, 1514, 1698, 1736, 2928, 2954, 3358 (broad), 3476; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 0.04 (s, 6H), 0.90 (s, 9H), 2.85 (t, *J* = 6.95 Hz, 2H), 3.65 (dd, *J* = 4.30, 2.53 Hz, 2H), 3.78 (s, 3H), 4.54 (br s, 2H), 4.87 (m, 1H), 6.80 (d, *J* = 8.72 Hz, 2H), 7.12 (d, *J* = 8.58 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: -5.4, 18.2, 25.8, 35.7, 55.2, 63.1, 75.9, 113.7, 129.3, 130.4, 156.6, 158.1; **Analysis**: $C_{17}H_{29}NO_4Si$ requires C, 60.14; H, 8.61; N, 4.13%; found C, 60.16; H, 8.53; N, 4.10%.

(4*S*,5*S*)-5-(*tert*-Butyldimethylsiloxymethyl)-4-(4-methoxyphenyl)oxazolidin-2-one (105):

To a stirred solution of carbamate **104** (0.23 g, 0.68 mmol) in CH_2Cl_2 (8 mL) under nitrogen atmosphere were added sequentially MgO (0.0602 g, 1.56 mmol), $PhI(OAc)_2$ (0.316 g, 1 mmol) and $Rh_2(OAc)_4$ (0.0075 g, 0.034 mmol). It was stirred vigorously at 40 °C for 2 h. The completion of reaction was monitored by TLC. After completion of reaction, the resulting reaction mixture was cooled to 25 °C, diluted with CH_2Cl_2 (15 ml), filtered through a pad of celite and washed with CH_2Cl_2 (30 mL). The combined filtrates were evaporated *in vacuo* to give the crude product, which was purified by column chromatography packed with silica gel using pet. ether: EtOAc (8:2) as eluent to furnish **105** (0.17 g) as a thick gum.

Yield: 74%; **[α]$^{25}_{D}$**: +19.6 (*c* 0.72, EtOH); **IR** ($CHCl_3$, cm^{-1}): 780, 838, 1106, 1248, 1514, 1758, 2928, 2954, 3628, 3648; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.08 (s, 3H), 0.13 (s, 3H), 0.92 (s, 9H), 2.88 (dd, *J* = 14.8, 5.4 Hz, 1H), 3.08 (dd, *J* = 14.7, 8.3 Hz, 1H), 3.78 (s, 3H), 4.60 (m, 1H), 5.24 (d, *J* = 4.8 Hz, 1H), 6.43 (br s, 1H), 6.81 (d, *J* = 8.7 Hz, 2H), 7.16 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 159.21, 158.45, 130.12, 128.63, 113.93, 83.02, 78.25, 55.18, 33.68, 25.67, 17.97, -4.36, -4.91; **Analysis**: $C_{17}H_{27}NO_4Si$ requires C, 60.50; H, 8.06; N, 4.15%; found C, 60.59; H, 7.88; N, 4.25%.

(4*S*,5*S*)-5-(Hydroxymethyl)-4-(4-methoxyphenyl)oxazolidin-2-one:

(+)-*epi*-cytoxazone (1b):

To a solution of oxazolidinone **105** (0.14 g, 0.415 mmol) in dry THF (5 mL) under nitrogen atmosphere was added 1M solution of TBAF (0.83 mL, 0.83 mmol) and stirred at 25 ºC for 0.5 h. After completion of the reaction, it was diluted with water (5 mL), extracted with EtOAc (20 mL), dried over anhyd. Na_2SO_4 and concentrated *in vacuo* to give the crude product, which was purified by column chromatography packed with silica gel using pet. ether: EtOAc (7:3) as eluent to furnish **1b** (0.085 g) as a colorless solid.

Yield: 92%; **mp**: 159-160 °C {lit.[53] **mp**: 158-160 °C}; **[α]$^{25}_{D}$**: +28.30 (*c* 1, MeOH) {lit.[53] **[α]$^{25}_{D}$**: +28.6 (c 1, MeOH)}; **IR** ($CHCl_3$, cm^{-1}): 772, 832, 1104, 1252, 1522, 1570, 1724, 3244; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 3.57 (m, 2H), 3.74 (s, 3H), 4.13 (dd, *J* = 9.85, 3.79 Hz, 1H), 4.61 (d, *J* = 6.32 Hz, 1H), 5.20 (t, *J* = 5.56 Hz, 1H), 6.95 (d, *J* = 8.47 Hz, 2H), 7.25 (d, *J* = 8.59 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 55.16, 55.22, 61.00, 84.23, 114.17, 127.50, 132.93, 158.20, 159.06; **Analysis**: $C_{11}H_{13}NO_4$ requires C, 59.19; H, 5.87; N, 6.27%; found C, 59.20; H, 5.80; N, 6.23%.

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Chapter II

Short and Practical Enantioselective Synthesis of Linezolid and Eperezolid via Proline-catalyzed Asymmetric α-Aminooxylation

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"Short and practical enantioselective synthesis of linezolid and eperezolid via proline-catalyzed asymmetric α-aminooxylation" Narina V. Srinivasarao, Arumugam Sudalai, *Tetrahedron Letters* **2006**, *47*, 6799.

Short and Practical Enantioselective Synthesis of Linezolid and Eperezolid *via* Proline-catalyzed Asymmetric α-Aminooxylation

2.1 Introduction

The increasing incidence of multidrug resistance among Gram-positive bacterial pathogens represents one of the major challenges in the 1990's for health care practitioners.[1] The development of resistance in the Gram-positive pathogenic bacteria to antibiotics over the last twenty years and continuing today has created a need for new antibiotic classes which are unaffected by existing bacterial resistance. In the 1987 Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) workers from DuPont Company formally reported the structure and antibacterial activity profiles of two new antibacterial agents, Dup-105 (**3**) and DuP-721 (**4**).[2] These clinical candidates were the first significant representatives of a totally novel class of antimicrobial compounds, the oxazolidinones. These compounds originated from an iterative medicinal

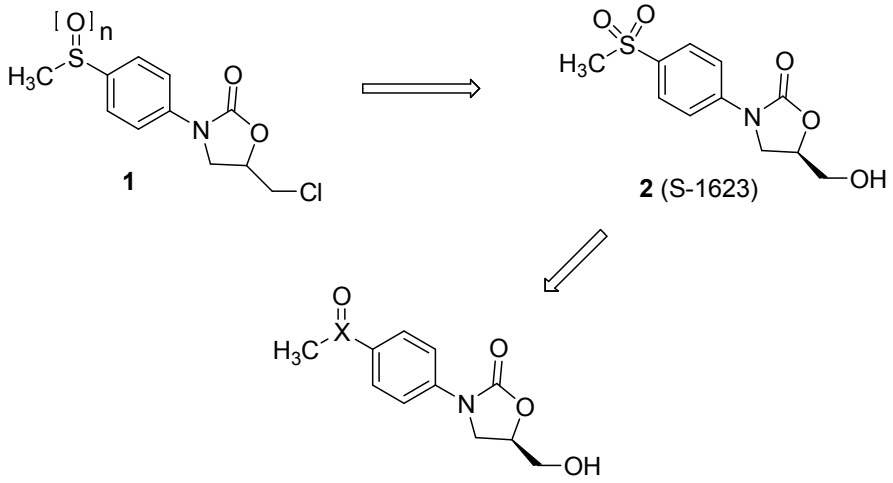
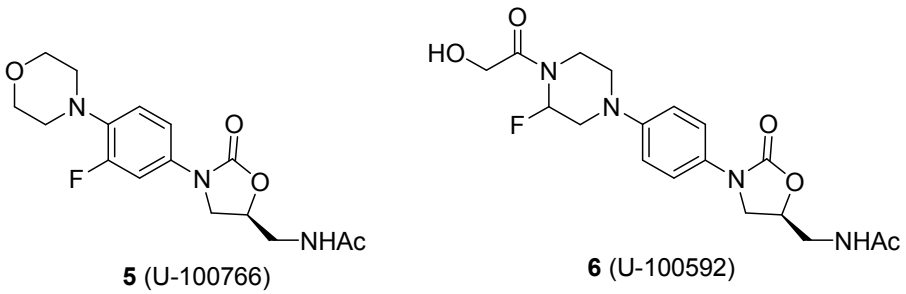


Fig 1: Emergence of the oxazolidinones at DuPont.

chemistry effort starting with a series of racemic 5-halomethyl-3-phenyl-2-oxazolidinones (**1**) with reported utility for treating a variety of plant diseases (**Fig. 1**).[3] Subsequent chemical modification of **1** eventually led to analogues such as S-6123 (**2**), which reportedly exhibited modest *in vitro* activity and *in vivo* efficacy against several Gram-positive and Gram-negative organisms.[4] It was at this time that the absolute configuration of the oxazolidinones at C-5 became evident. Further elaboration of analogues such as **2** eventually led to the identification of the prototypical oxazolidinones, DuP-105 (**3**) and DuP-721 (**4**),[5] which showed significantly improved characteristics relative to their progenitor compounds. While both DuP 105 (**3**) and DuP 721 (**4**) entered into phase I clinical trials, the development of each was subsequently discontinued.[6] In drug safety studies conducted at The Upjohn Co.,[7] it was demonstrated that (±)-DuP 721 (**4**) exhibited lethal toxicity in the rat, when dosed orally at 100 mg/kg b.i.d. for 30 days. Finally, the first oxazolidinones to emerge as potential drug candidates from the testing scheme were linezolid (**5**) and eperezolid (**6**) (**Fig. 2**).

Both linezolid (**5**) and eperezolid (**6**), first clinical candidates, arose from the piperazine subclass with Linezolid (**5**) being chosen for continued development because of its enhanced pharmacokinetic properties. The oxazolidinone moieties in linezolid (**5**) and eperezolid (**6**) were not only a new class with a novel mechanism of action, but importantly were unaffected by existing resistance in Gram-positive agents and were orally active. Linezolid (**5**), approved in the U.S. by the Food and Drug Administration (FDA) in April 2000, subsequently performed exceptionally well in human clinical trials as compared to other marketed antibiotics.



5 (U-100766) **6** (U-100592)

Fig. 2: Structure of linezolid (**5)** and eperezolid (**6)**

2.2 The Pharmacology of linezolid and eperezolid

As depicted in **Fig. 3**, the extensive effort at Pharmacia on the structure–activity relationship of oxazolidinone had prompted several revisions to the dogmas espoused by the earlier DuPont work. Perhaps most interesting was the finding that a suitable electron-donating amino substituent on the phenyl ring can confer excellent antibacterial activity while helping to maintain a good safety profile. Another important result of this investigation was the identification of the potentiating effect of one or two fluorine atoms flanking the morpholine or piperazine ring.

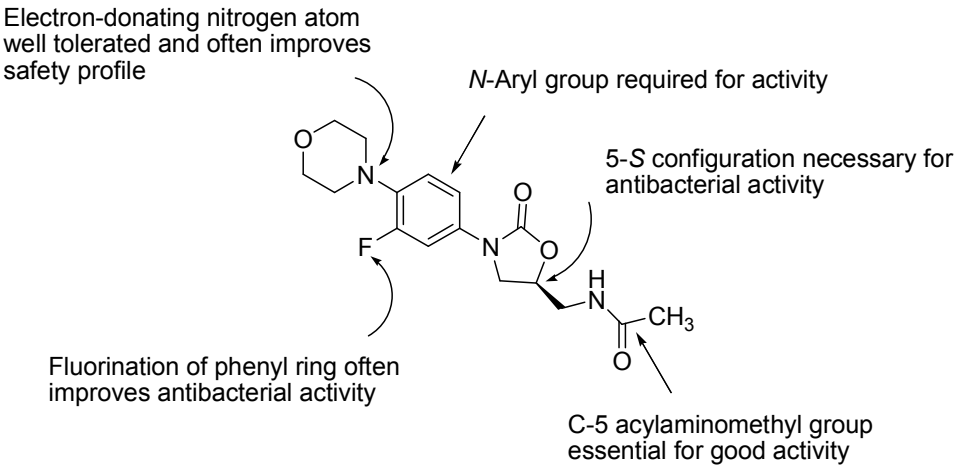


Fig. 3: Structure –activity relationships of oxalidinones identified at Pharmacia

Linezolid also performed well against the *enterococci in vitro*. It inhibited all tested strains of *Enterococcus faecalis* and *Enterococcus faecium* at 4 μgmL^{-1} or less.[8] This observation of enterococcal sensitivity to linezolid (**5**) was very important as the

enterococci had been developing into a therapeutic problem in the 1990s because they were generally antibiotic-resistant and the number of strains possessing vancomycin resistance was growing. The action of linezolid was unaffected by enterococcal resistance to vancomycin and promised welcome relief for physicians with patients who had enterococcal infections untreatable with antibiotics. As with the *staphylococci*, linezolid (**5**) performed identically against geographically diverse enterococcal collections with a large array of antibiotic resistance patterns.

Very importantly, linezolid (**5**) was more than acceptably active against penicillin-sensitive and -resistant *Streptococcus pneumoniae* and *Streptococcus pyogenes*. It was quite active against the *streptococci* and was unaffected by β-lactam resistance. The activity of linezolid against *Streptococcus pyogenes* extends the spectrum of the drug to enable treatment of infections following childbirth. It is also interesting to note that, like many Grampositive antibiotics, linezolid (**5**) covers both the *staphylococci* and the *streptococci*, with more intrinsic activity exhibited against the *streptococci*.

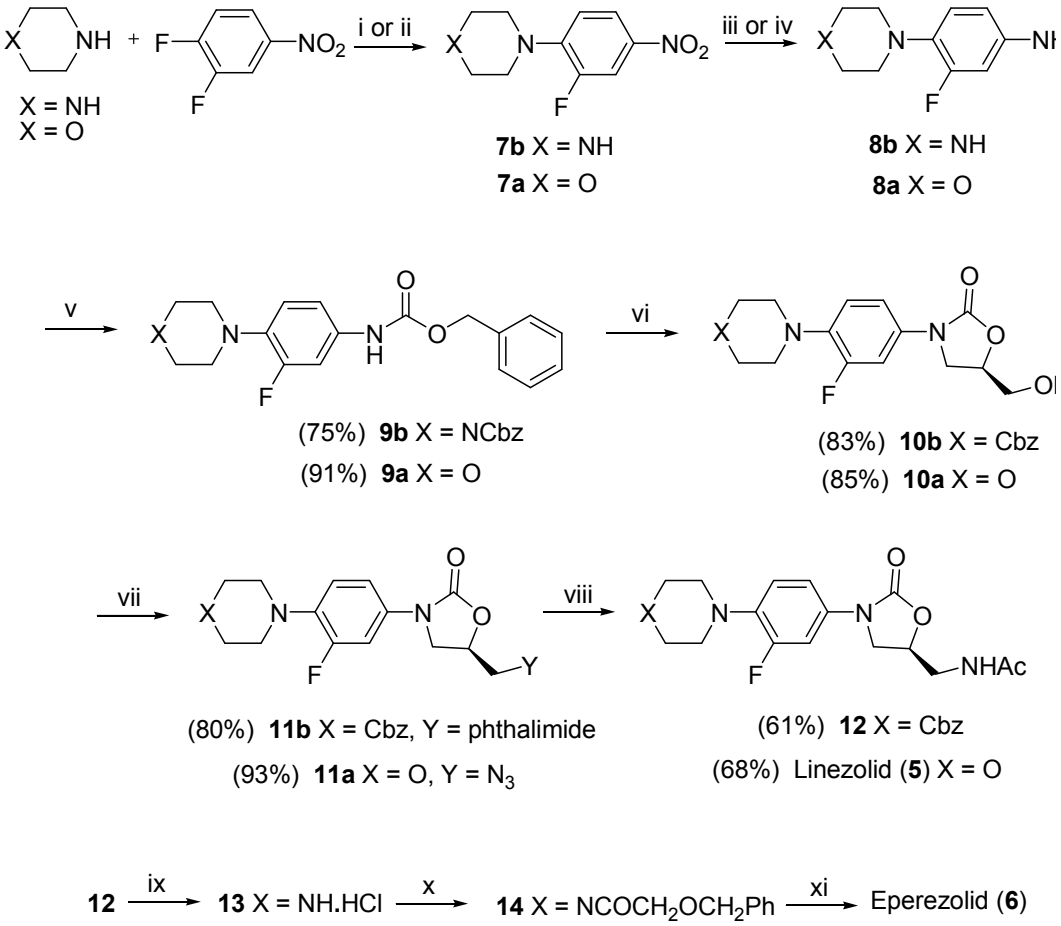
2.3 Review of Literature

Literature search revealed that there are few reports available for the synthesis of linezolid (**5**) and eperezolid (**6**).[7b,9-13] Most of the methods reported for the asymmetric synthesis of linezolid and eperezolid involve either a chiral pool approach or classical resolution of racemates, which are described below.

Brickner's approach (1996)[7b]

In this approach, the syntheses of U-100766 (**5**) and U-100592 (**6**) share a common route, detailed in **Scheme 1**. The key step was the use of (*R*)-glycidyl butyrate, obtained from D-mannitol. Thus, carbamate **9** in THF was reacted with (*R*)-glycidyl butyrate in presence of n-BuLi to give the corresponding (5*S*)-

hydroxymethyloxazolidinone (**10**) in 98% ee. The carbamate **9** in turn was prepared from 3, 4-difluoronitrobenzene in 3 steps: (i) nucleophilic substitution of fluoro with morpholine or piparazine gave the *p*-substituted nitrobenzene **7**. (ii) Reduction of nitro groups in **7** to give thye amino compound **8**. (iii) The amine **8** was protected with Cbz-Cl to give carbamate **9**.



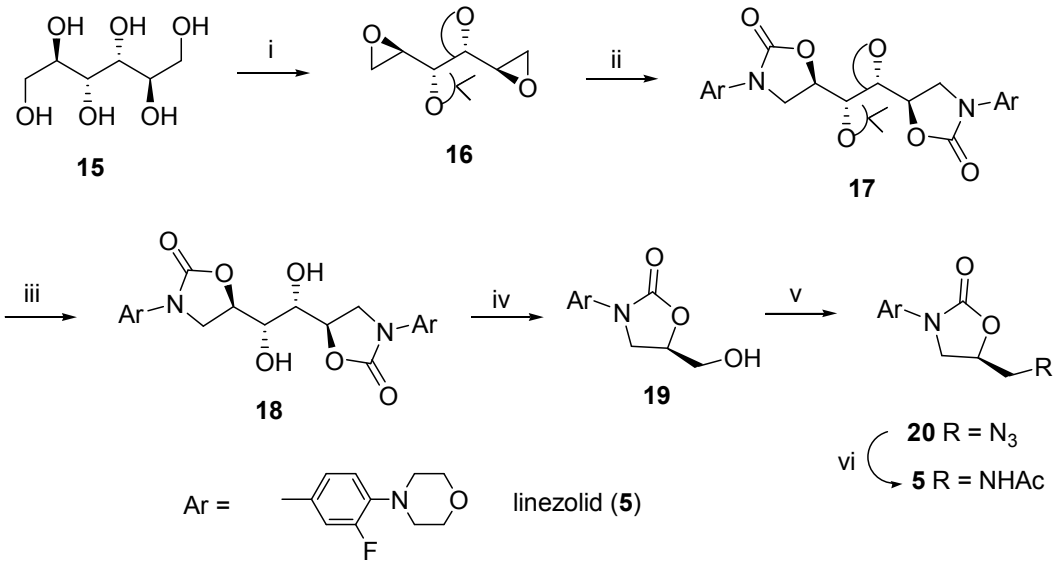
Scheme 1: (i) CH_3CN, reflux or (ii) $(i\text{-}Pr)_2EtN$, EtOAc. (iii) H_2, 5% Pd/C, THF or (iv) HCO_2NH_4, 10% Pd/C, THF/MeOH. (v) Cbz-Cl, $NaHCO_3$ (or Na_2CO_3), acetone-H_2O. (vi) (a) n-BuLi, THF -78 °C. (b) (*R*)-glycidyl butyrate. (f) MsCl, Et_3N, CH_2Cl_2. (g) potassium phthalimide, CH_3CN, H_2O, reflux. (h) NaN_3, DMF, 75 °C. (i) aqueous $MeNH_2$, EtOH, reflux. (j) 10% Pd/C, H_2, EtOAc. (k) Ac_2O, pyr. (l) Pd/C, H_2, $MeOHCH_2Cl_2$. (m) $ClCOCH_2OCH_2Ph$, Et_3N, CH_2Cl_2, 0 ºC. (n) 10% Pd/C, H_2, MeOH-CH_2Cl_2.

Linezolid (**5**) and the Cbz-piperazine **12** were obtained by known sequence of standard reactions: (i) azidation of alcohol **10**, (ii) reduction of azide **11** and *N*-

acetylation of corresponding amine. Catalytic hydrogenolysis of **12** provided the piperazine HCl salt **13**, which was acylated with (benzyloxy) acetyl chloride. Finally, benzylic hydrogenolytic cleavage of **14** gave eperezolid (**6**) in 99.7% ee (**Scheme 1**).

Lohray's approach (1999)[9]

In this approach, bis-epoxide (**16**), obtained from D-mannitol, was used as a key intermediate (**Scheme 2**).[10] The C2-symmetric bis-epoxide **16** was reacted readily with 3-fluoro-4-substituted aniline in isopropyl alcohol at 80-85 ºC to give the crude adduct which was reacted with carbonyldiimidazole in dichloromethane at 25 ºC to furnish the bis-oxazolidinone **17** in 61-70 % yields.

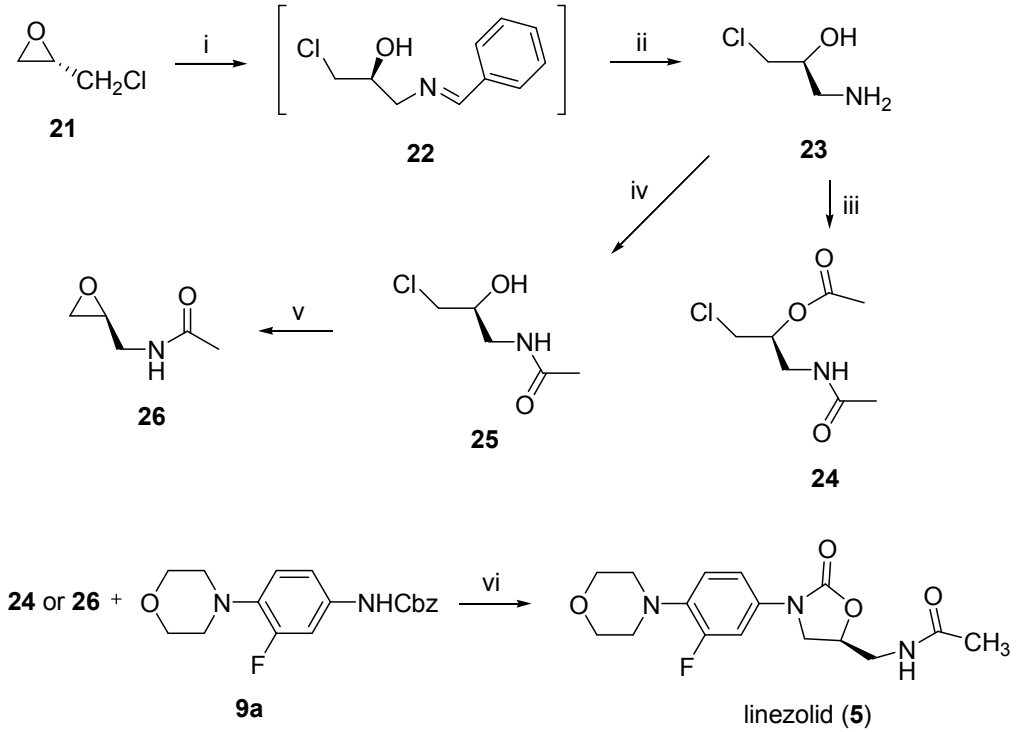


Scheme 2: (i) ref. 19. (ii) (a) $ArNH_2$, isopropyl alcohol, reflux. (b) $(Im)_2$-CO, CH_2Cl_2, 61-70%. (iii) dil. HCl, 95%. (iv) (a) $Pb(OAc)_4$, THF. (b) $NaBH_4$, MeOH, 95%. (v) (a) $MeSO_2Cl$, Et_3N. (b) NaN_3, DMSO, 80 °C, 80-84%. (vi) MeCOSH, 25 ºC.

Selective removal of the acetonide group was achieved with 2N HCI to give the diol **18**. Oxidative cleavage of diol **18** with lead tetra acetate led to the isolation of aldehyde *in situ* which on reduction with sodium borohydride gave alcohol **19**. Following the known procedure, the alcohol **19** was then converted into linezolid (**5**) *via* azide **20**.

Perrault's approach (2003)[11]

The authors have made use of commercially available (*S*)-epichlorohydrin (**21**), which was transformed to *N*-[(2*S*)-2-(acetyloxy)-3-chloropropyl]acetamide (**24**) and epoxide **26** *via* the common intermediate (2*S*)-1-amino-3-chloro-2-propanol hydrochloride (**23**). Finally, coupling of acetamide **24** or epoxide **26** with 1.3 equiv of the benzyl carbamate **9a** under the Manninen conditions gave linezolid (**5**) in 81% yield (**Scheme 3**).

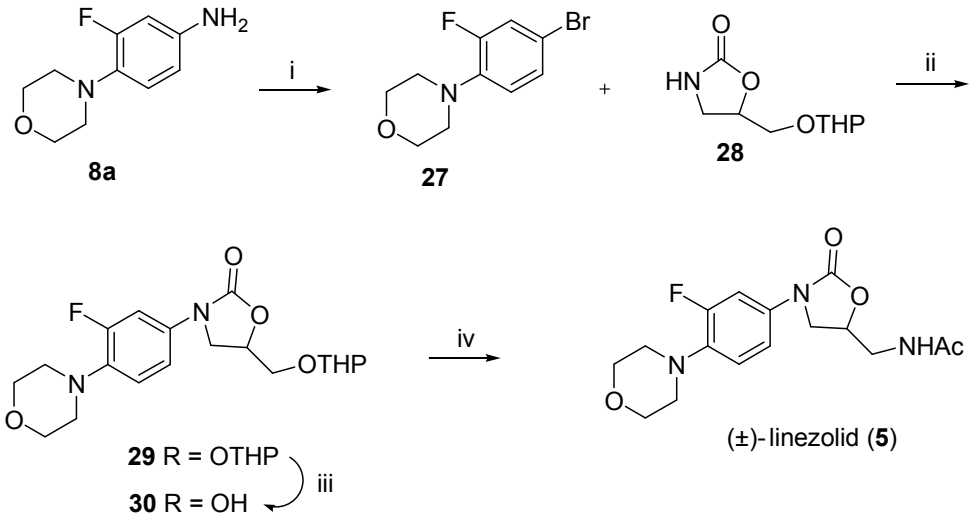


Scheme 3: (i) NH_3 (aq), PhCHO, 25 ºC. (ii) HCl (aq), 25 ºC, 76%; (iii) 2 eq. Ac_2O, pyridine, 25 ºC, 83%. (iv) 1 eq. Ac_2O, pyridine, 25 ºC. (v) 1 eq. KO*t*Bu, THF, -20 ºC, 97%. (vii) 3 eq. LiOMe, 2 eq. MeOH, DMF, 25 ºC, 81%.

Trehan's approach (2003)[12]

The key step in this approach was the coupling of aryl bromide **27** with oxazolidinone **28** using Buchwald's amination protocol. Thus, aryl bromide **27** was prepared from known aniline **8a** *via* Sandmeyer reaction and oxazolidinone **28** was prepared from racemic 5-(hydroxymethyl)-2-oxazolidinone. Deprotection of **29** using PPTS in

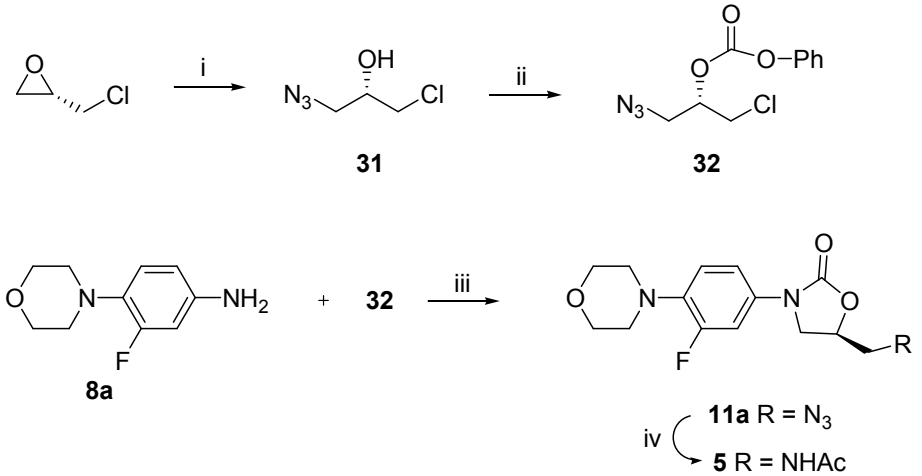
boiling ethanol gave alcohol **30** which was converted to racemic linezolid ((±)-**5**) using a three-step procedure (**Scheme 4**).



Scheme 4: (i) HNO_2, CuBr, HBr; 47%. (ii) CuI (5 mol %), (±)-*trans*-1,2-diaminocyclohexane (10 mol %), dioxane, K_2CO_3, 110 °C, 15 h. (iii) PPTS, EtOH, reflux,1 h. (iv) (a) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0-25 ºC, 1 h. (b) NaN_3, DMF, 70 °C, 2 h. (c) CH_3COSH, 25 °C, 15 h.

Madhusudhan's approach (2005)[13]

In this approach, key intermediate azido alcohol **31**, was obtained by regioselective opening of commercially available (*S*)-epichlorohydrin with sodium azide in 65% yield. Protection of alcohol **31** using phenyl chloroformate gave the corresponding product **32**, which was coupled with amine **8a** to give azide **11a**.



Scheme 5: (i) NaN_3, NH_4Cl, H_2O, EtOH, 0-25 ºC, 65%. (ii) PhOCOCl, Py, CH_2Cl_2, 0 ºC, 91%. (iii) K_2CO_3, Bn-$NEt_3^+Cl^-$ (cat.), DMF, 80 ºC. (iv) CH_3COSH, neat, 25 ºC.

Finally the azide **11a** was converted into linezolid (**5**) in 86% yield with thioacetic acid (**Scheme 5**).

2.4 Present Work

2.4.1 Objective

The reported methods for the enantioselective synthesis of two drugs namely linezolid (**5**) and eperezolid (**6**) involve either a chiral pool approach or classical resolution of racemates. Surprisingly, a catalytic route *via* asymmetric synthesis for the construction of the 2-oxazolidinone moiety has not been reported so far. For the first time, a new catalytic asymmetric system for the synthesis of linezolid (**5**) and eperezolid (**6**) with good optical purity and yields has been developed using proline-catalyzed α-aminooxylation[14] of aldehydes [see **Chapter 1** for its introduction] as the chiral inducing step; the results of which are presented in this chapter.

The retrosynthetic analysis for the syntheses of linezolid **5** and eperezolid **6** is outlined in **Fig. 4**. Oxazolidinones **5** and **6** exhibit structural similarities. The compounds **5** and **6** could be prepared from the corresponding alcohols **36** and **46** by simple functional group transformations. We further envisioned that the oxazolidinones **36** and **46** could be prepared by intramolecular cyclization of diols **35** and **45**, which in turn could be obtained from the corresponding aldehydes **34** and **44** by D-proline-catalyzed-α-aminooxylation.[14] The aldehydes **34** and **44** could be readily obtained from 3,4-difluoronitrobenzene by simple functional group transformations (**Fig. 4**).

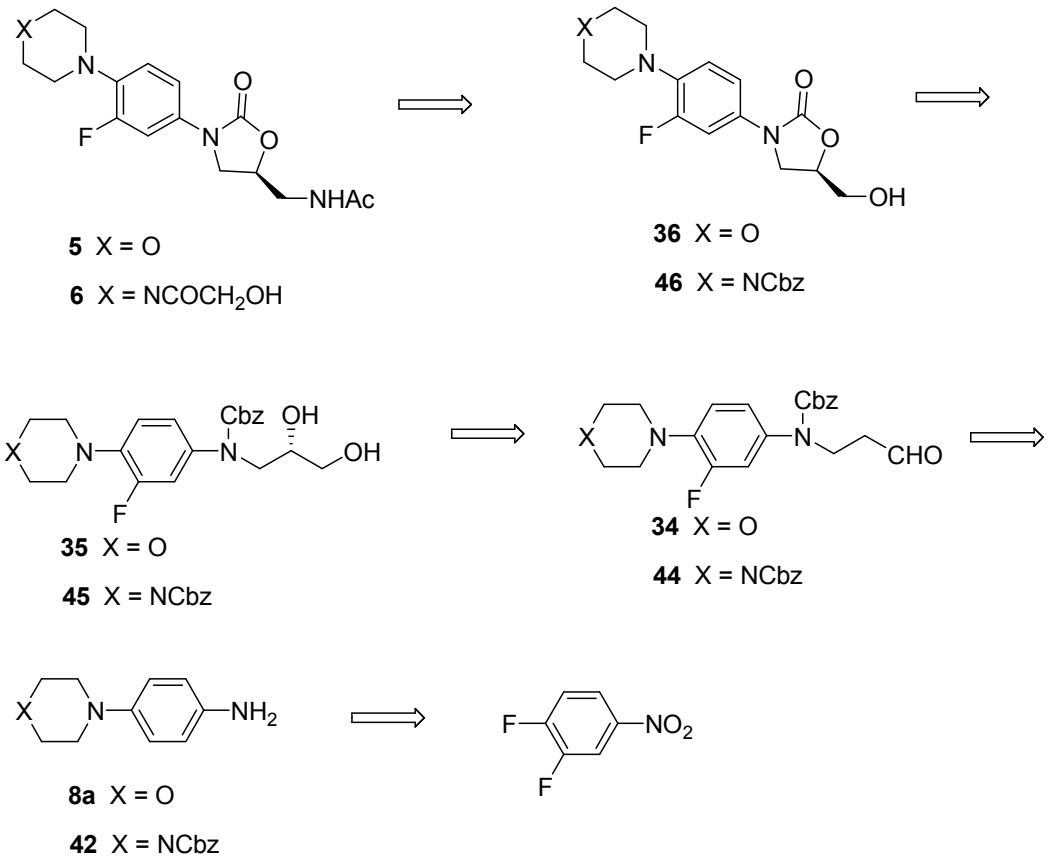


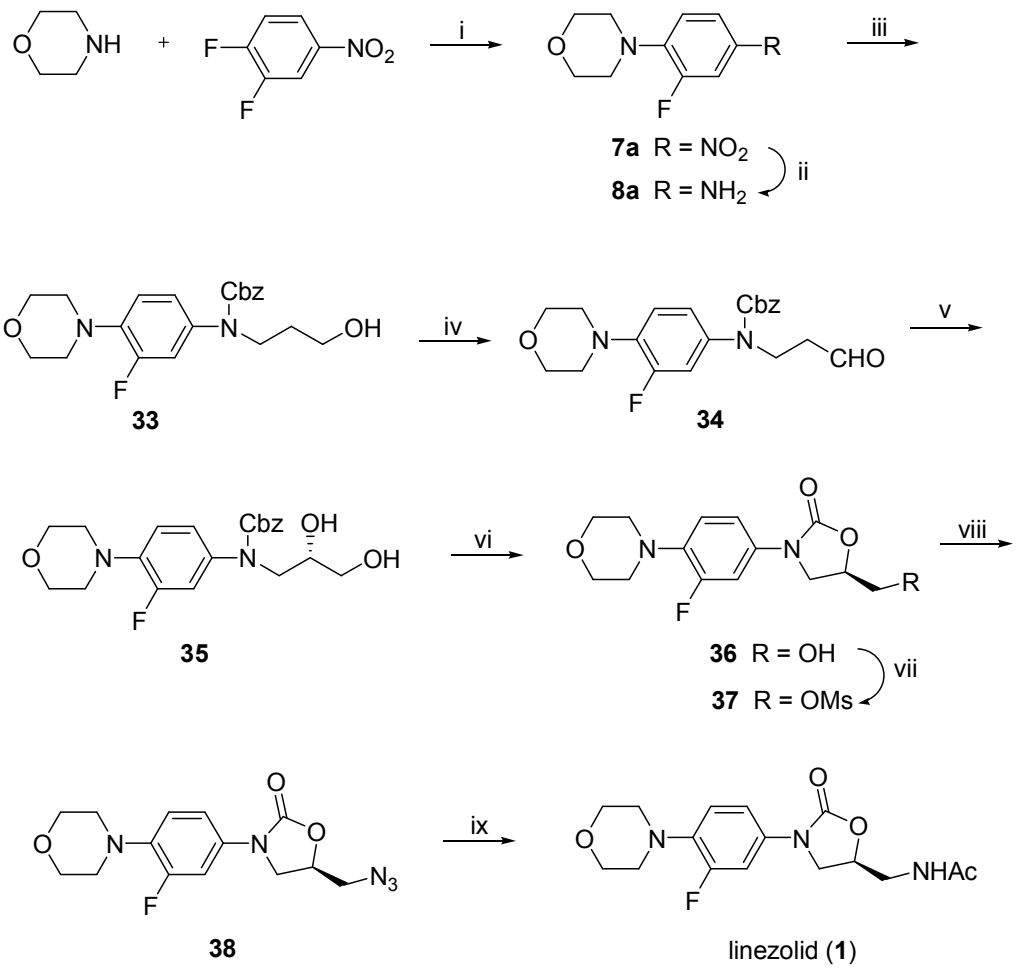
Fig. 4: Retrosynthetic analysis of linezolid (5) and eperezolid (6)

2.5 Results and Discussion

Our approach for the synthesis of linezolid (**5**) and eperezolid (**6**) are based on the disconnection approach, which leads to two chiral synthons (chiral diols **35** and **45**), both of which are accessible using D-proline-catalyzed α-aminooxylation of the corresponding aldehydes **34** and **44**. The general synthetic schemes employed for the synthesis of linezolid (**5**) and eperezolid (**6**) are presented in **Schemes 6** and **7**.

Enantioselevtive synthesis of Linezolid

Amination of 3,4-difluoronitrobenzene with excess morpholine under nucleophilic aromatic displacement at the *para* position, selectively gave the *p*-substituted nitrobenzene **7a** in 98% yield.



Scheme 6: (i) (iPr)$_2$EtN, EtOAc, 0-25 ºC, 12 h, 98%. (ii) (a) TsO-(CH$_2$)$_3$-OH (**39**), NaI, Na$_2$CO$_3$, DMF, 65 ºC; (b) Cbz-Cl, NaHCO$_3$, acetone-H$_2$O, 85% (over two steps). (iii) (COCl)$_2$, DMSO, Et$_3$N, CH$_2$Cl$_2$, -78 ºC to -60 ºC, 95%. (iv) (a) PhNO, D-proline (25 mol%), -20 ºC, 24 h then MeOH, NaBH$_4$. (b) CuSO$_4$ (30 mol%), MeOH, 86% (over two steps). (v) NaH, THF, 0 ºC, 96%. (vi) MsCl, Et$_3$N, CH$_2$Cl$_2$, 0 ºC, 4 h. (vii) NaN$_3$, DMF, 75 ºC, 92% (over two steps). (viii) 10% Pd/C, H$_2$ (1 atm), EtOAc, 12 h then Ac$_2$O, Py, 92%.

The ^{1}H NMR spectrum of **7a** showed two triplets at δ 3.29 and 3.88 due to methylene protons of –CH$_2$NCH$_2$- and –CH$_2$OCH$_2$- respectively confirming the presence of morpholine ring on aromatic system. Its mass spectrum showed the molecular ion peak at *m/z* 226. Reduction of **7a** using 10% Pd/C as catalyst and ammonium formate as hydrogen donor gave amine **8a** in 99% yield. The ^{1}H NMR spectrum of amine **8a** showed a broad singlet at δ 3.56 due to the NH$_2$ moiety. Treatment of arylamine **8a** with mono-tosyl protected 1,3-propane diol (**39**) gave the secondary amine,[15] which

was then *N*-protected using Cbz-Cl to furnish the key intermediate alcohol **33** in 85% overall yield.

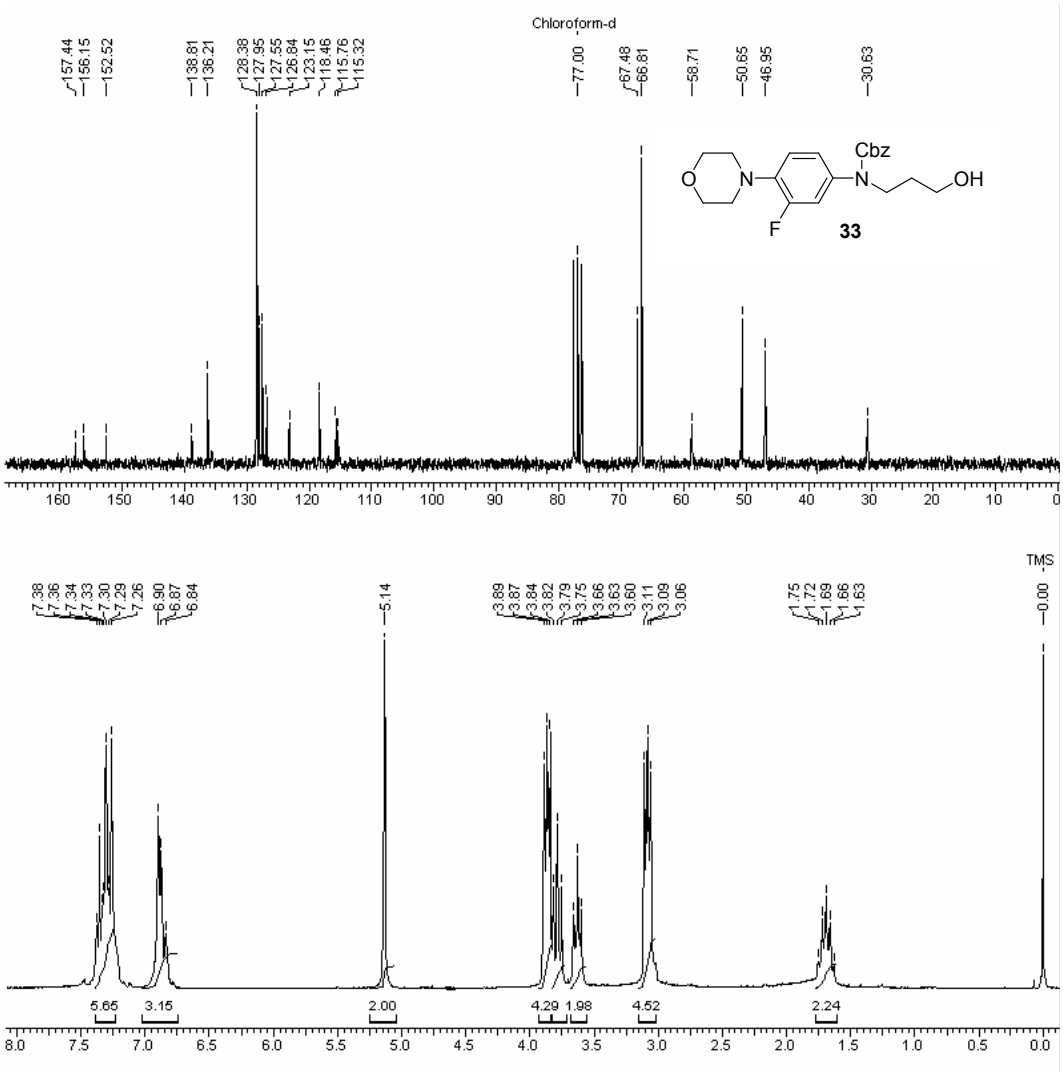


Fig. 5: ^{13}C and ^{1}H NMR spectra of 33

The formation of alcohol **33** was confirmed by the appearance of a multiplet at δ 1.69 and two triplets at δ 3.63 and 3.79 for methylene (-$NCH_2CH_2CH_2OH$) protons and a singlet at δ 5.14 for the benzylic protons in its ^{1}H NMR spectrum. Further, its ^{13}C NMR spectrum showed typical signals at δ 30.63, 46.95 and 58.71 indicating the presence of three-carbon alcohol unit (-$NCH_2CH_2CH_2OH$) (**Fig. 5**). The alcohol **33** was then oxidized to give aldehyde **34** using Swern conditions.[16] The aldehyde **34** was

then subjected to D-proline-catalyzed asymmetric α-aminooxylation[14] in a two-step reaction sequence as follows: (i) reaction of aldehyde **34** with nitrosobenzene as the oxygen source in the presence of D-proline in CH_3CN at -20 ºC[14a] followed by treatment with $NaBH_4$ in MeOH to give the crude aminoxy alcohol and, (ii) subsequent reduction of the crude product with 30% $CuSO_4$ to yield chiral diol **35** in 86% yield; $[\alpha]^{25}_D$ = -4.0 (*c* 1.1, $CHCl_3$). The formation of diol **35** was confirmed by the appearance of multiplets at δ 3.65-3.80 for methylene (CH_2OH) and methine (CHOH) protons in its ^1H NMR spectrum (**Fig. 6b**). Further, its ^{13}C NMR spectrum showed signals at δ 63.76 and 67.53 due to the two carbons attached to hydroxyl groups (**Fig. 6a**).

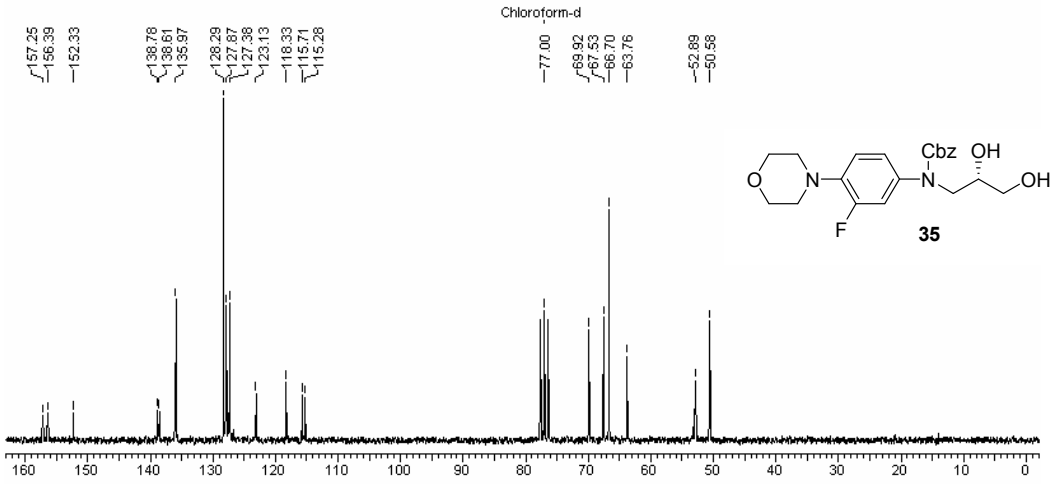


Fig. 6a: ^{13}C NMR spectrum of 35

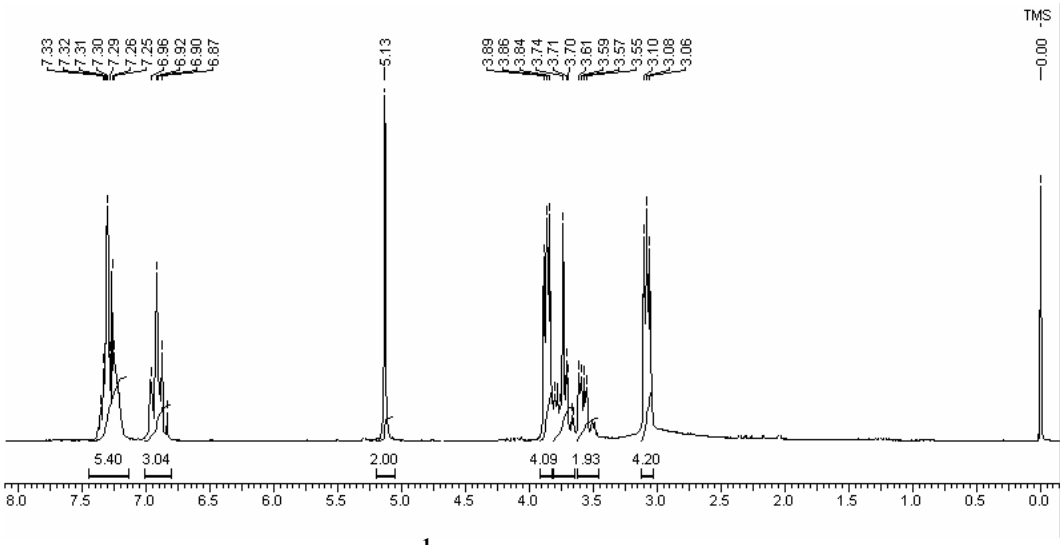


Fig. 6b: ^{1}H NMR spectrum of 35

The regioselective intramolecular cyclization[17] of diol **35** using sodium hydride in THF at 0 ºC furnished the desired oxazolidinone **36** in 96% yield and 99% ee. The optical purity of the oxazolidinone **36** was determined from its ^{1}H NMR analysis of its Mosher ester **40**, which showed the enantiomeric excess to be 99% (see experimental section).

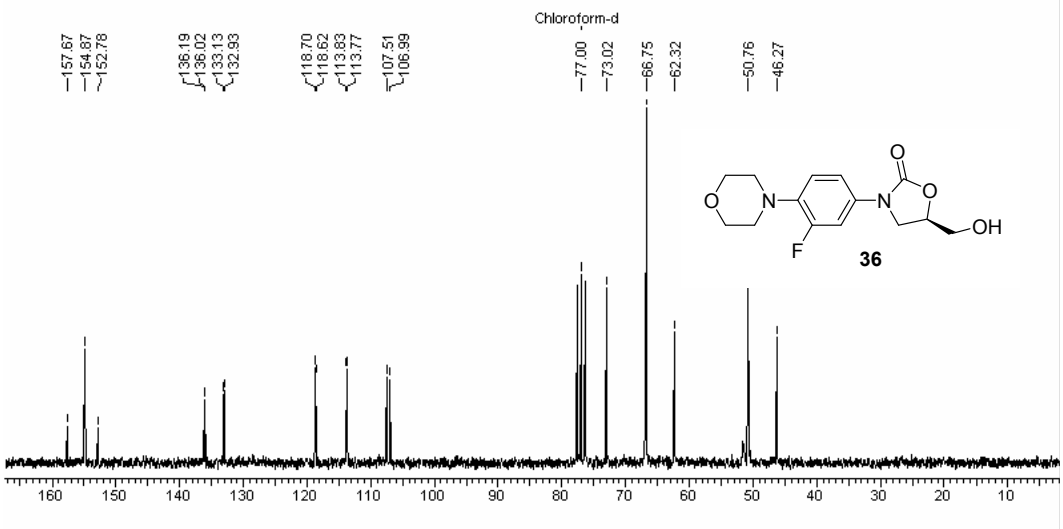


Fig. 7a: ^{13}C NMR spectrum of 36

The formation of oxazolidinone **36** was confirmed by the disappearance of a singlet at δ 5.13 for benzylic protons and a multiplet at δ 7.30 for phenyl protons in its ^{1}H NMR

spectrum (**Fig. 7b**). The typical signal at δ 154.87 in its ^{13}C NMR spectrum confirms the presence of oxazolidinone carbonyl (**Fig. 7a**). Its mass spectrum showed the molecular ion peak at *m/z* 296 confirming the formation of **36**. The physical and spectroscopic data of **36** were in complete agreement with the reported values.[7b]

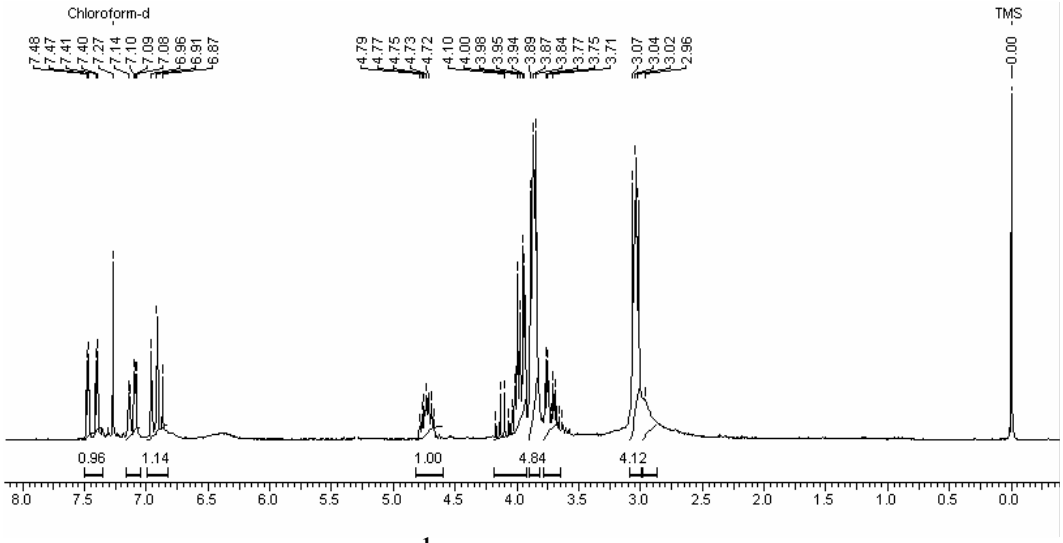


Fig. 7b: ^{1}H NMR spectrum of 36

The oxazolidinone **36** was then converted into the corresponding azide **38** in two steps with 92% overall yield. Thus, alcohol function in oxazolidinone **36** was mesylated using methanesulfonyl chloride in the presence of Et_3N as base in CH_2Cl_2 to give the corresponding mesylated product **37** in quantitative yield. The ^{1}H NMR spectrum of **37** showed a typical singlet at δ 3.25 indicating the presence of OMs moiety. The ^{13}C NMR spectrum of **37** showed peak at δ 36.94 confirming the presence of the OMs moiety (**Fig. 8**). Its mass spectrum showed the molecular ion peak at *m/z* 374 confirming the formation of **37**.

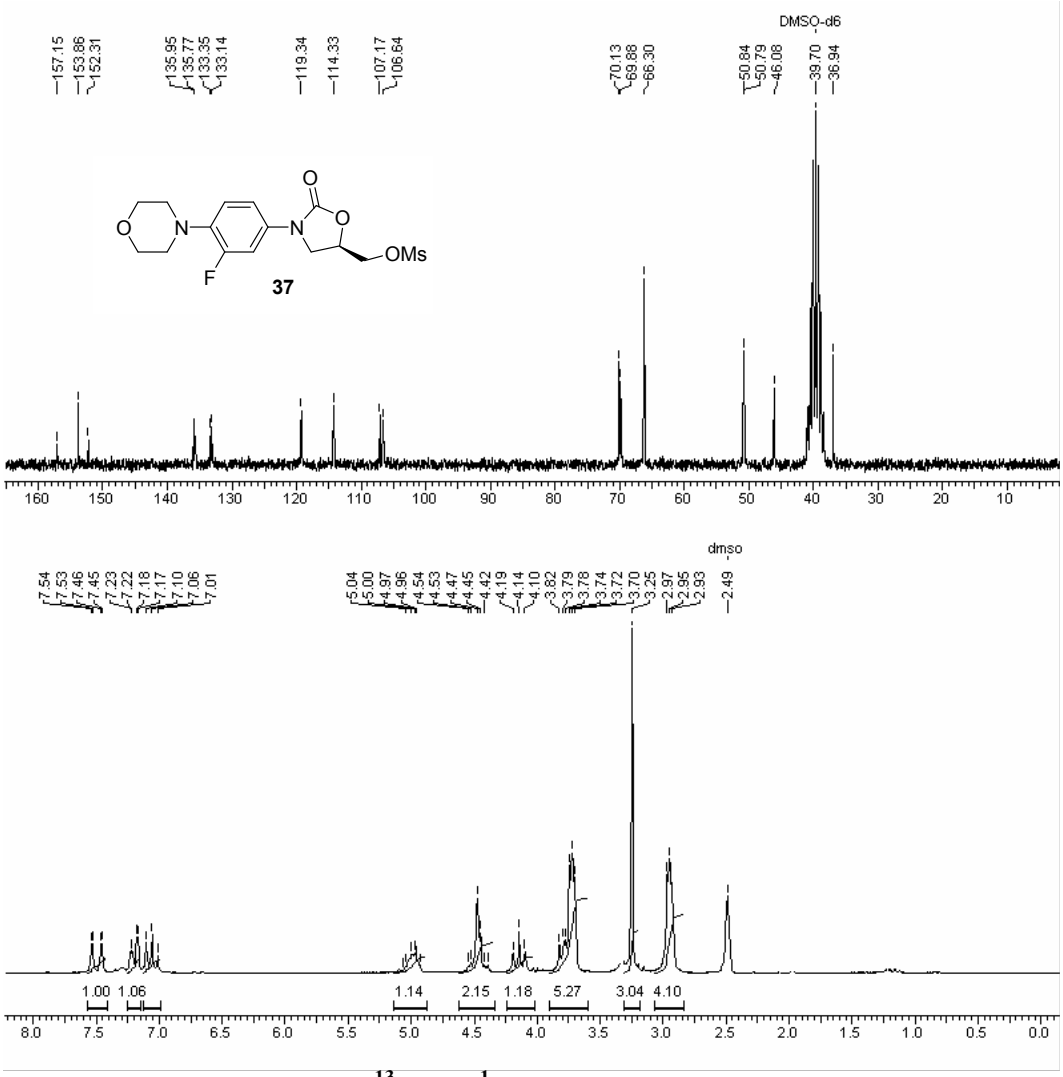


Fig. 8: ^{13}C and ^{1}H NMR spectra of 37

The mesylate **37** was then treated with sodium azide in DMF at 80 ºC to yield the corresponding azide **38** in 92% yield; **$[\alpha]^{25}_{D}$:** - 23.2 (*c* 1, $CHCl_3$). Its IR spectrum showed a band at 2111 cm^{-1} indicating the presence of azide group. The ^{1}H NMR spectrum of **38** showed a doublet of doublet at δ 3.82 and a triplet at δ 4.05 indicating the presence of CH_2N_3 moiety. The ^{13}C NMR spectrum of **38** showed a typical peak at δ 52.92 confirming the presence of the carbon attached to the azide group (**Fig. 9**).

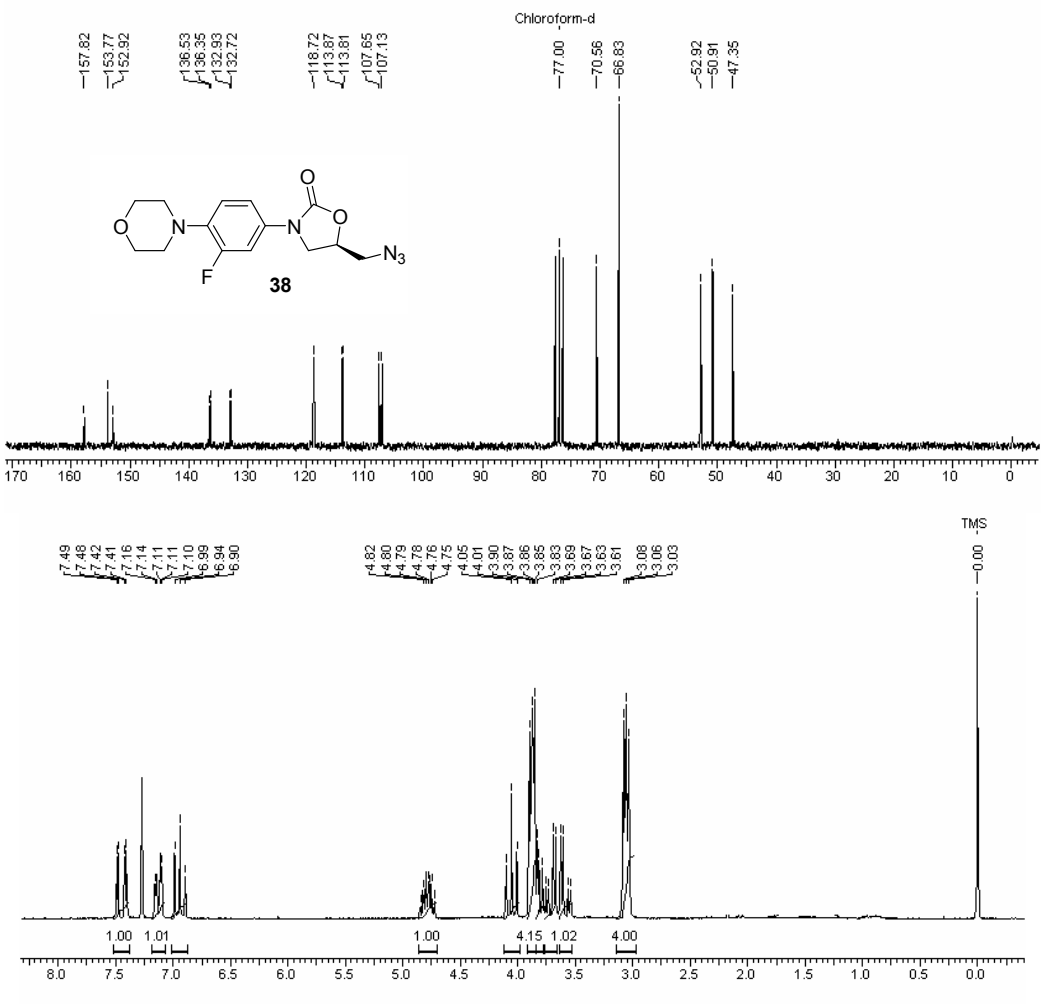


Fig. 9: ^{13}C and ^{1}H NMR spectra of 38

Finally, the azide function in **38** was reduced with H_2 (1 atm.) using 10% Pd/C to furnish the crude amine, which was acylated using acetic anhydride and pyridine to give linezolid (**5**) in 92% yield and 99% ee. **$[\alpha]^{25}_D$:** -8.9 (*c* 1, $CHCl_3$); lit.[7b] $[\alpha]_D$: -9 (*c* 0.919, $CHCl_3$). The ^{1}H NMR spectrum of linezolid (**5**) showed a singlet at δ 2.03 and a triplet at δ 6.43, characteristic of methyl ($COCH_3$) and amine (NH) protons respectively indicating the presence of acetamide (NHAc) moiety.

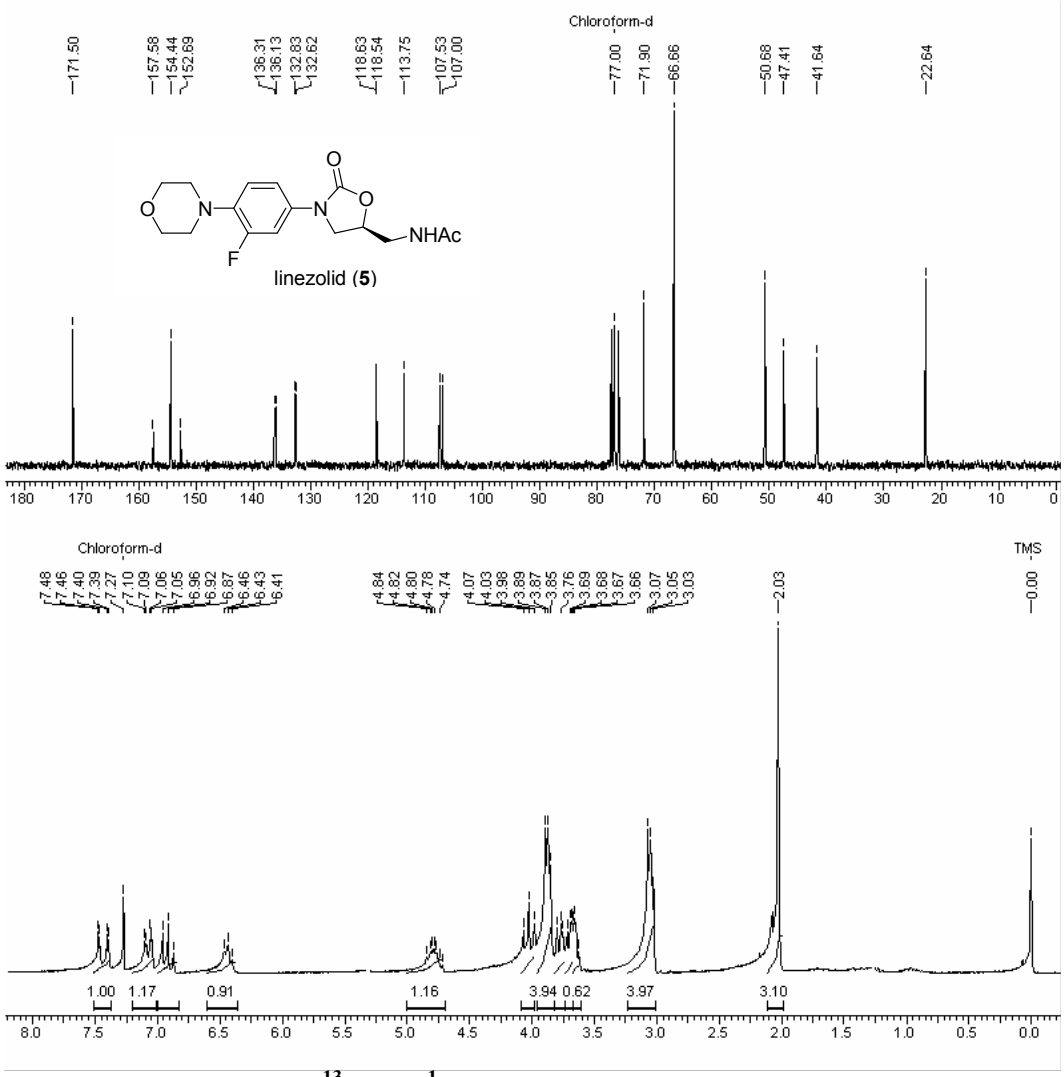
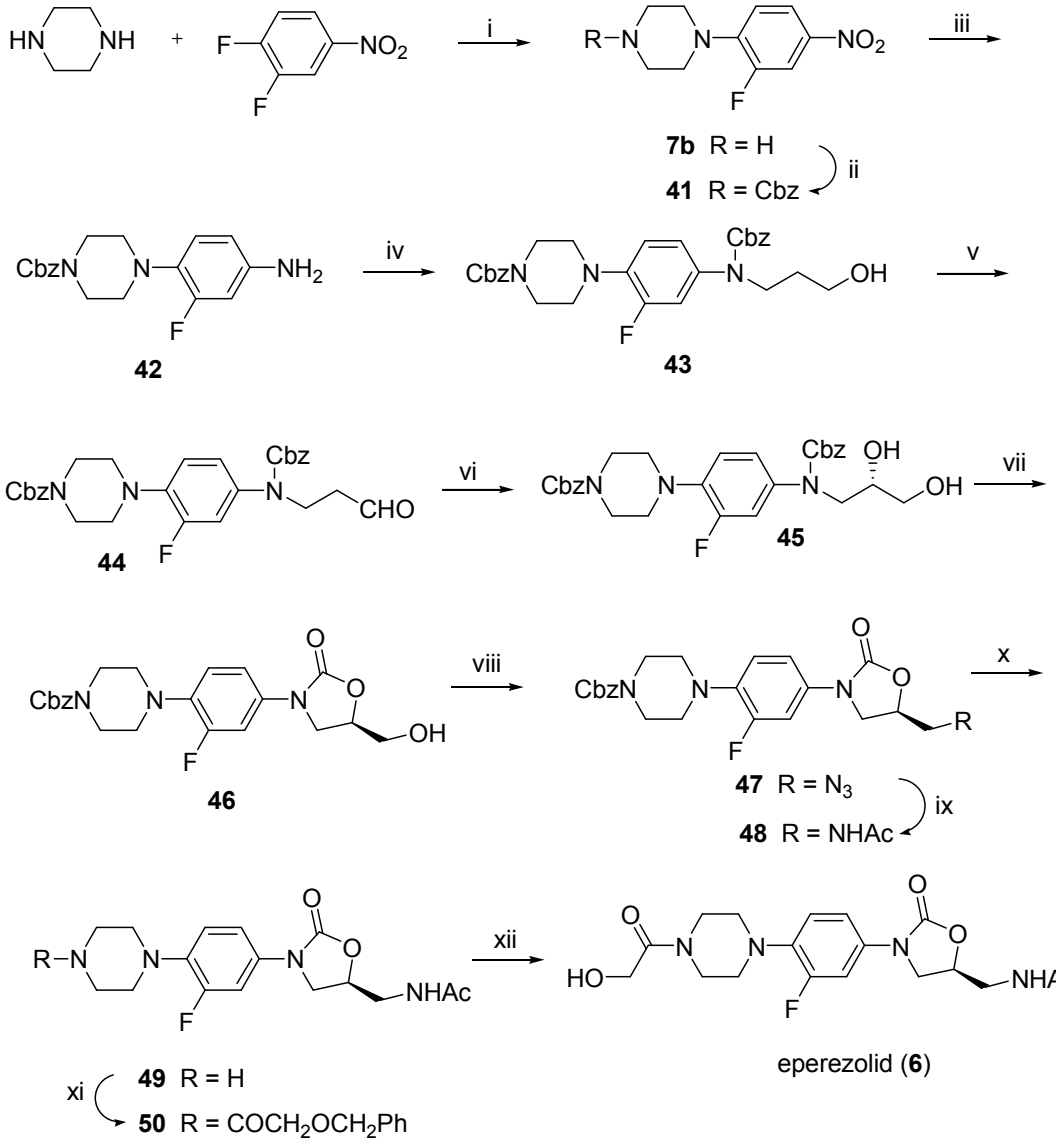


Fig. 10: ^{13}C and ^{1}H NMR spectra of linezolid (1)

Its ^{13}C NMR spectrum exhibited a peak at δ 22.64 due to the acyl methyl group and peak at δ 41.64 due to the carbon attached to the NHAc moiety (**Fig. 10**). The mass spectrum also showed its molecular ion at *m/z* 337 confirming its formation. The analytical and spectroscopic data of linezolid (**5**) were in complete agreement with the reported values.[7b]

Enantioselective synthesis of eperezolid

A similar strategy was extended to the asymmetric synthesis of eperezolid (**6**), of which the synthetic sequences are shown in **Scheme 7**.



Scheme 7: (i) CH_3CN, reflux, 3 h, 81%. (ii) Cbz-Cl, $NaHCO_3$, acetone-H_2O, 97%. (iii) $CoCl_2$, $NaBH_4$, MeOH, 60 ºC, 95%; (iv) (a) TsO-$(CH_2)_3$-OH, NaI, Na_2CO_3, DMF, 65 ºC. (b) Cbz-Cl, $NaHCO_3$, acetone-H_2O, 79% (over two steps). (v) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ºC to -60 ºC, 94%. (vi) (a) PhNO, D-proline (25 mol%), -20 ºC, 24 h then MeOH, $NaBH_4$. (b) $CuSO_4$ (30 mol%), MeOH, 82% (over two steps). (vii) NaH, THF, 0 ºC, 94%. (viii) (a) MsCl, Et_3N, CH_2Cl_2, 0 ºC, 4 h. (b) NaN_3, DMF, 75 ºC, 89% (over two steps). (ix) PPh_3, THF-H_2O, 12 h then Ac_2O, Py, 96%. (x) 10% Pd/C, H_2 (1 atm), MeOH-CH_2Cl_2 (3:1), 97%. (xi) $ClCOCH_2OCH_2Ph$, Et_3N, CH_2Cl_2, 0 ºC, 100%. (xii) 10% Pd/C, H_2 (1 atm), MeOH-CH_2Cl_2 (3:1), 89%.

3,4-Difluoronitrobenzene on nucleophilic displacement with excess piperazine, selectively gave the *p*-substituted nitrobenzene **7b** in 81% yield. The ^{1}H NMR spectrum of **7b** showed two triplets at δ 3.05 and 3.27 (for methylene protons of CH_2NHCH_2 and CH_2NCH_2 respectively) indicating the presence of piperazine ring on aromatic system. Protection of secondary amine of piperazine product **7b** with benzyl chloroformate gave the amine **41** in 97% yield. The formation of compound **41** was confirmed by the appearance of a singlet at δ 5.17 for benzylic protons and multiplet at δ 7.37 for phenyl protons in its ^{1}H NMR spectrum (**Fig. 11**).

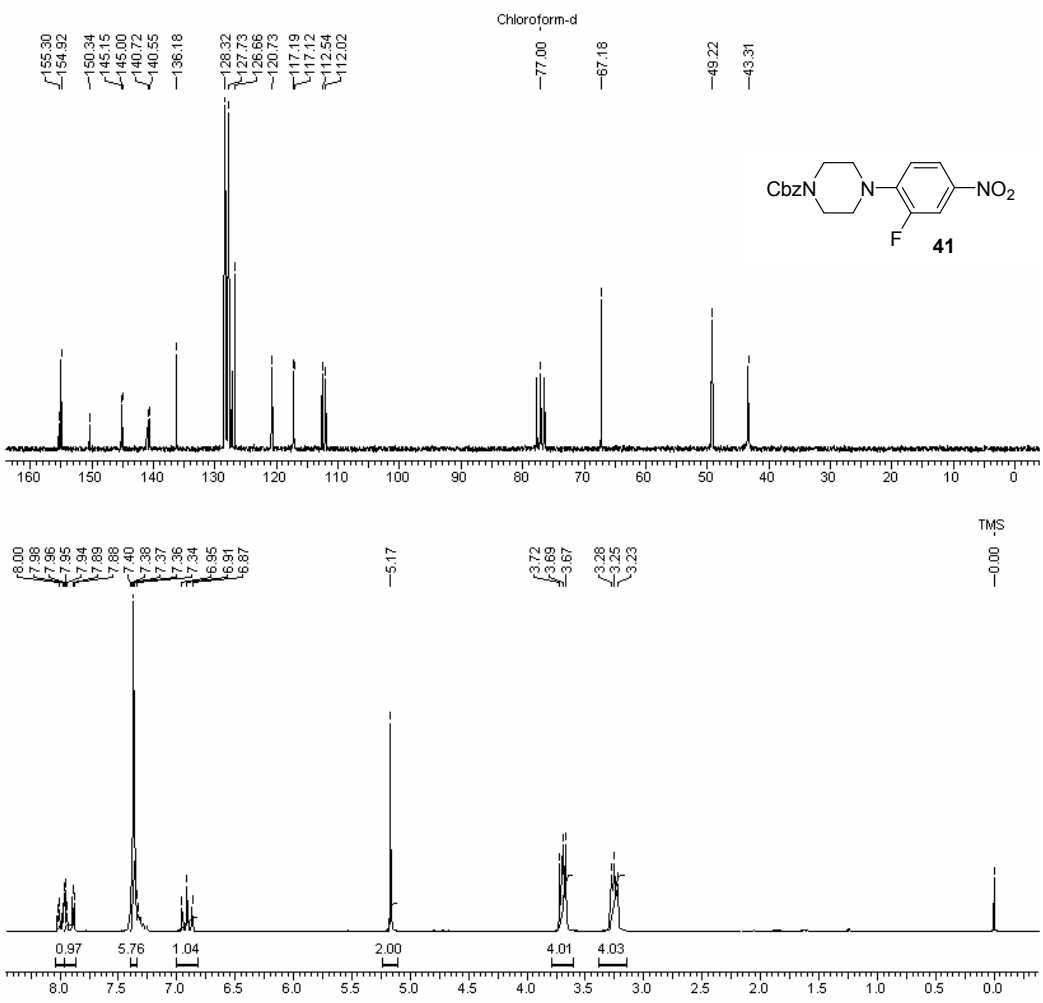


Fig. 11: ^{13}C and ^{1}H NMR spectra of 41

Reduction of the nitro group in **41** ($NaBH_4$, $CoCl_2$ (cat.), MeOH, 60 ºC)[18] produced crude arylamine **42** in 95% yield. Treatment of arylamine **42** with mono-tosyl

protected 1,3-propane diol (**39**) gave the secondary amine[15] *in situ* which was then protected using Cbz-Cl to furnish the key intermediate alcohol **43** in 79% overall yield.

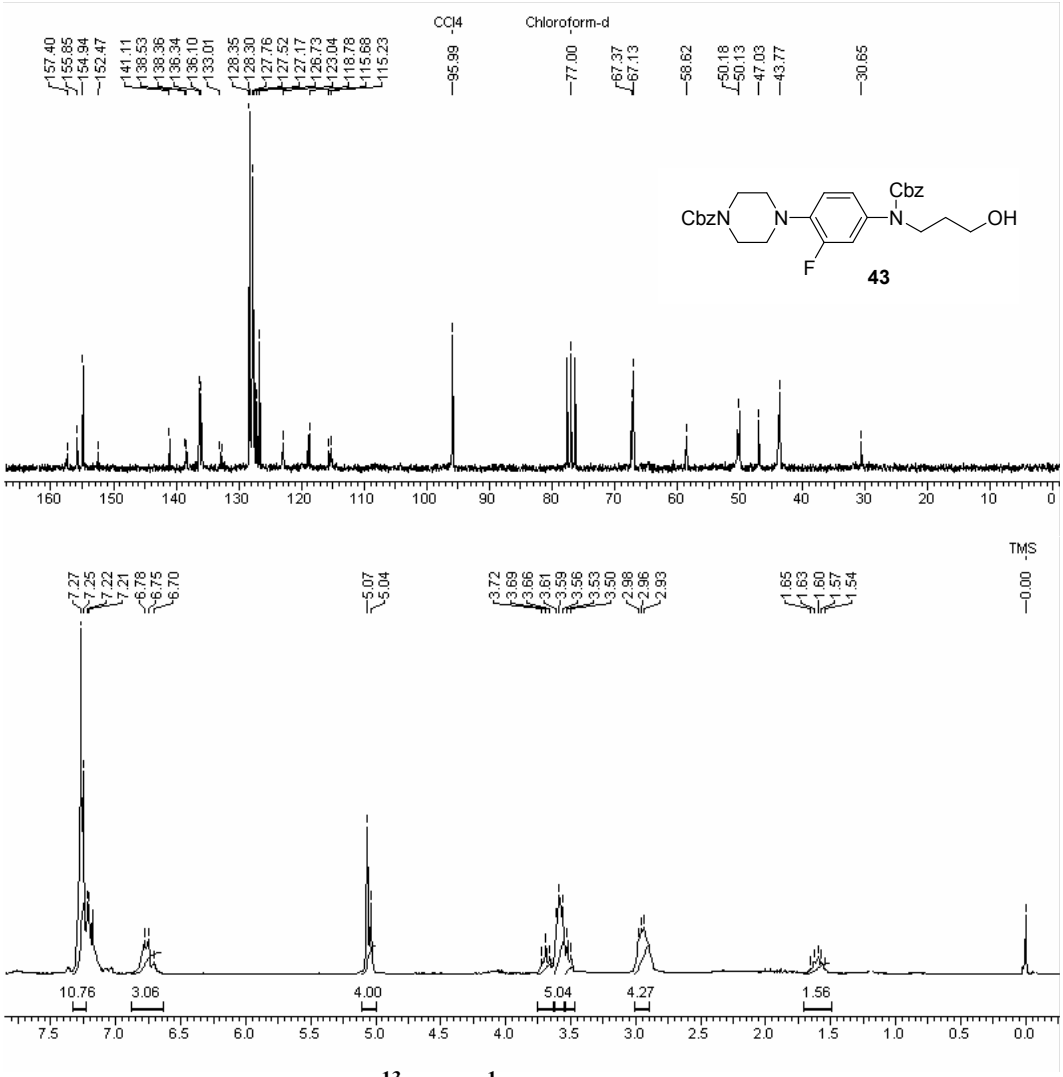


Fig. 12: ^{13}C and ^{1}H NMR spectra of 43

The formation of alcohol 4**3** was confirmed by the appearance of multiplets at δ 1.60 and 3.53 and a triplet at δ 3.69 for methylene (-$NCH_2CH_2CH_2OH$) protons in its ^{1}H-NMR spectrum (**Fig. 12**). Further, its ^{13}C NMR spectrum showed signals at δ 30.65, 47.03 and 58.62 due to the presence of three carbons alcohol unit (-$NCH_2CH_2CH_2OH$) (**Fig. 12**). The alcohol **43** was then oxidized using Swern

conditions[16] to produce the aldehyde **44** which was readily converted into the corresponding diol **45** by proline-catalyzed asymmetric α-aminooxylation in a two-step reaction sequence: (i) reaction of aldehyde **44** with nitrosobenzene as the oxygen source in the presence of D-proline in CH_3CN at -20 ºC[14a] followed by treatment with $NaBH_4$ in MeOH gave the crude aminoxy alcohol and, (ii) subsequent reduction of the crude aminoxy alcohol product with 30% $CuSO_4$ yielded the chiral diol **45** in 82% yield; $[\alpha]^{25}_D$ = - 3.2 (*c* 1.1, $CHCl_3$). The formation of diol 4**5** was confirmed by the appearance of a multiplet at δ 3.74-3.80 for methylene (CH_2OH) and methine (CHOH) protons in its ^1H NMR spectrum (**Fig. 13b**). Further, its ^{13}C NMR spectrum showed typical signals at δ 63.79 and 70.04 due to the two carbons attached to the OH functions (**Fig. 13a**).

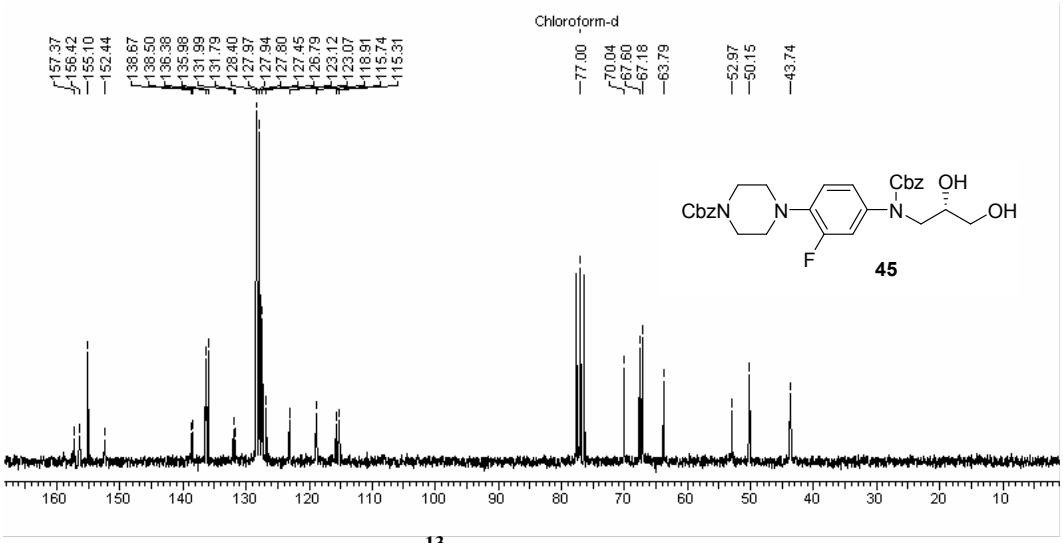


Fig. 13a: ^{13}C NMR spectrum of 45

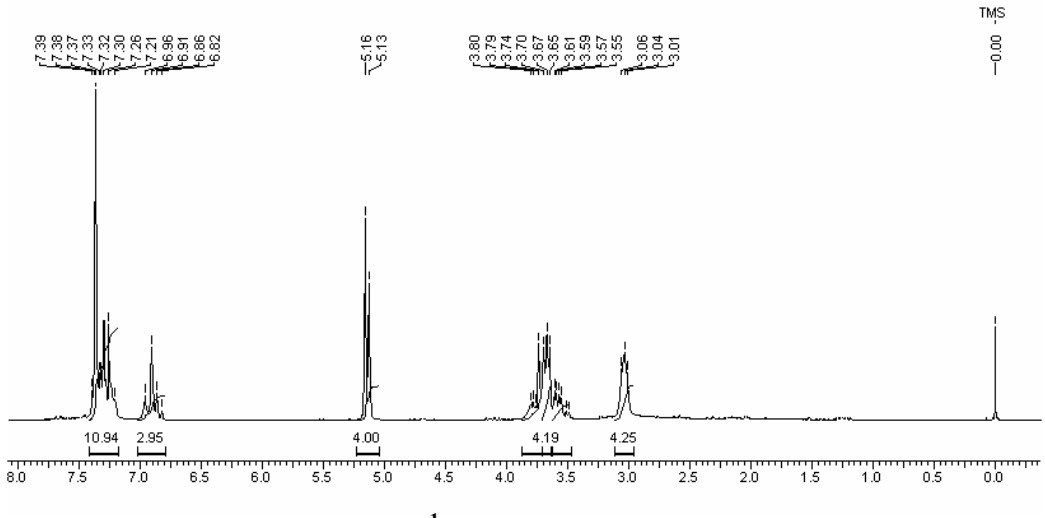


Fig. 13b: ^{1}H NMR spectrum of 45

The regioselective intramolecular cyclization[17] of diol **45** with sodium hydride in THF at 0 ^{0}C furnished the desired oxazolidinone **46** in 94% yield and 99% ee. The optical purity of the oxalidinone **46** was determined from its ^{1}H NMR analysis of its Mosher ester **51**, which showed the ee to be 99% (see experimental section). The formation of oxazolidinone **46** was confirmed by the disappearance of singlet at δ 5.13 for benzylic protons and multiplet at δ 7.30 for phenyl protons in its ^{1}H NMR spectrum (**Fig. 14b**).

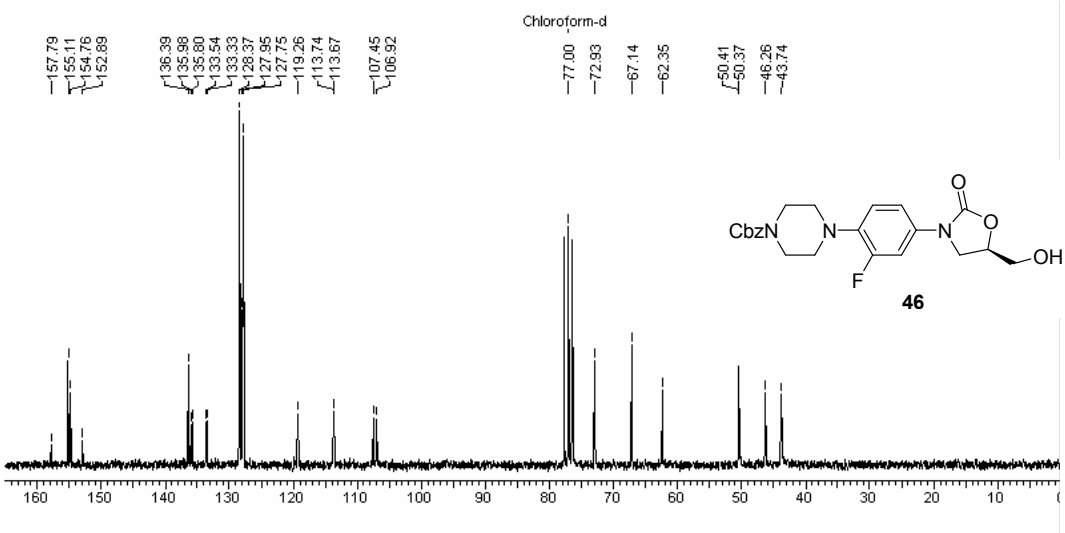


Fig. 14a: ^{13}C NMR spectrum of 46

The signal at δ 154.76 confirms the presence of oxazolidinone carbonyl in its ^{13}C NMR spectrum (**Fig. 14a**). Its mass spectrum showed the molecular ion peak at *m/z* 429 confirming the formation of **46**.

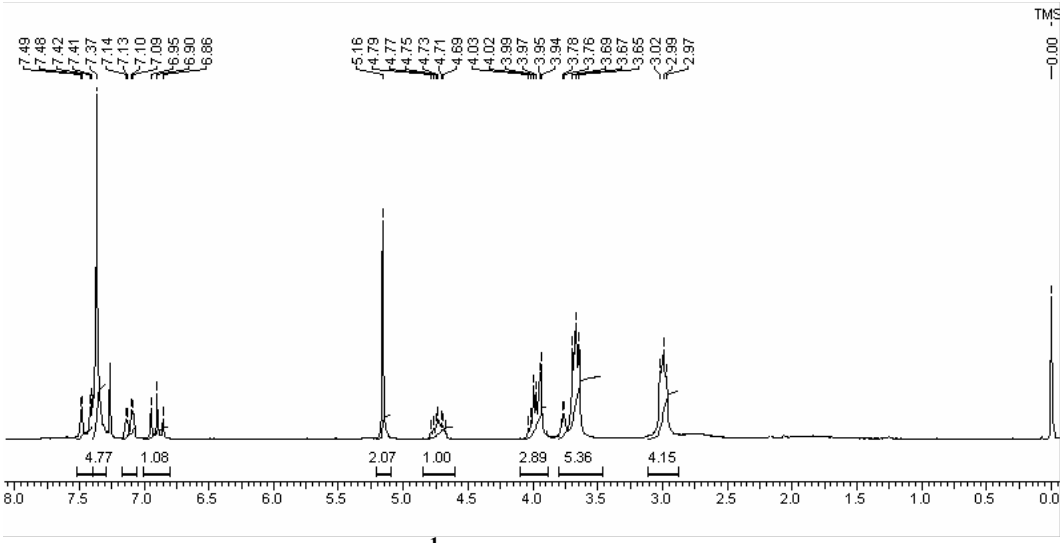


Fig. 14b: ^{1}H NMR spectrum of 46

The oxazolidinone **46** was then transformed into the corresponding azide **47** in two steps with 89% overall yield. Thus, alcohol **46** was mesylated using methanesulfonyl chloride in the presence of triethyl amine as base in CH_2Cl_2 to give the corresponding mesylate *in situ* in 99% yield, which was then subjected to treatment with sodium azide in DMF at 80 ºC to yield the corresponding azide **47** in 89% yield; $[\alpha]^{25}_{D}$: - 24.4 (*c* 1.0, $CHCl_3$). Its IR spectrum showed a band at 2110 cm^{-1} due to the presence of azide group (**Fig. 15**). The ^{1}H NMR spectrum of **47** showed a multiplet at δ 3.91-4.16 indicating the presence of CH_2N_3 moiety. The ^{13}C NMR spectrum of **47** showed a peak at δ 52.90 confirming the presence of carbon attached to the azide group (**Fig. 15**). Its mass spectrum showed the molecular ion peak at *m/z* 454 confirming its formation.

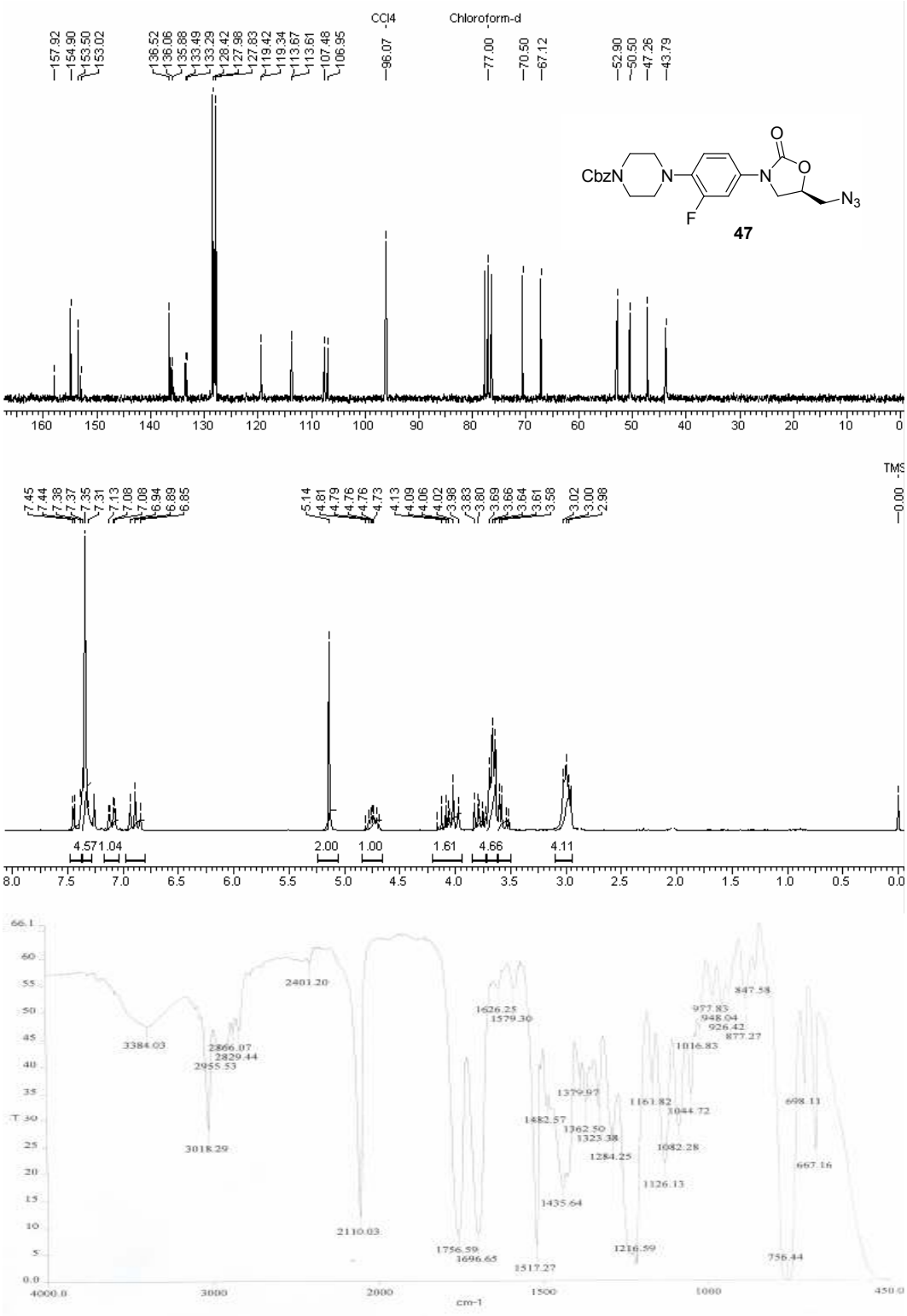


Fig. 15: ^{13}C, ^{1}H NMR and IR spectra of 47

The azide in **47** function was then reduced with triphenylphosphine in THF-H_2O to furnish the crude amine *in situ*, which was the acylated (Ac_2O, pyridine) to give acetamide **48** in 96% yield; $[\alpha]^{25}_{D}$: -18.5º (*c* 1, DMSO). The ^{1}H NMR spectrum of acetamide **48** showed a singlet at δ 2.01 and a broad singlet at δ 6.47 for methyl ($COCH_3$) and amine (NH) protons respectively, thus confirming the presence of acetamide (NHAc) moiety. Further, its ^{13}C NMR spectrum exhibited a peak at δ 22.77 due to the acyl group (**Fig. 16**).

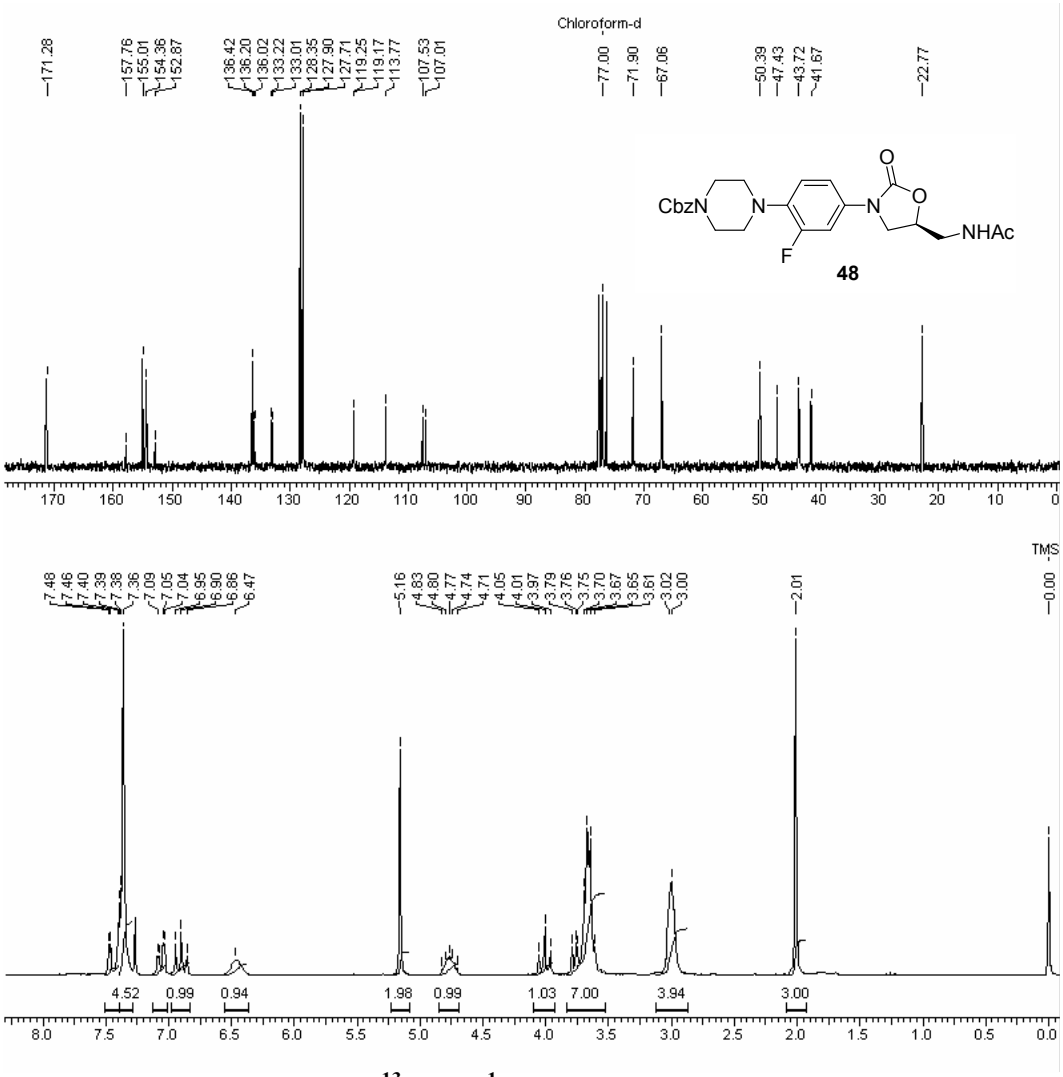


Fig. 16: ^{13}C and ^{1}H NMR spectra of 48

Deprotection of the Cbz group in **48** under catalytic hydrogenolysis conditions (Pd/C, H_2 (1 atm), MeOH-CH_2Cl_2) provided the piperazine **49** *in situ*, which was acetylated (benzyloxy acetyl chloride and Et_3N in CH_2Cl_2 at 0 ºC) to give acetate **50** in quantitative yield. The formation of acetate **50** was confirmed by the appearance of two singlets at δ 4.22 and 4.62 for α-methylene ketone and benzylic protons respectively, in its ^{1}H NMR spectrum.

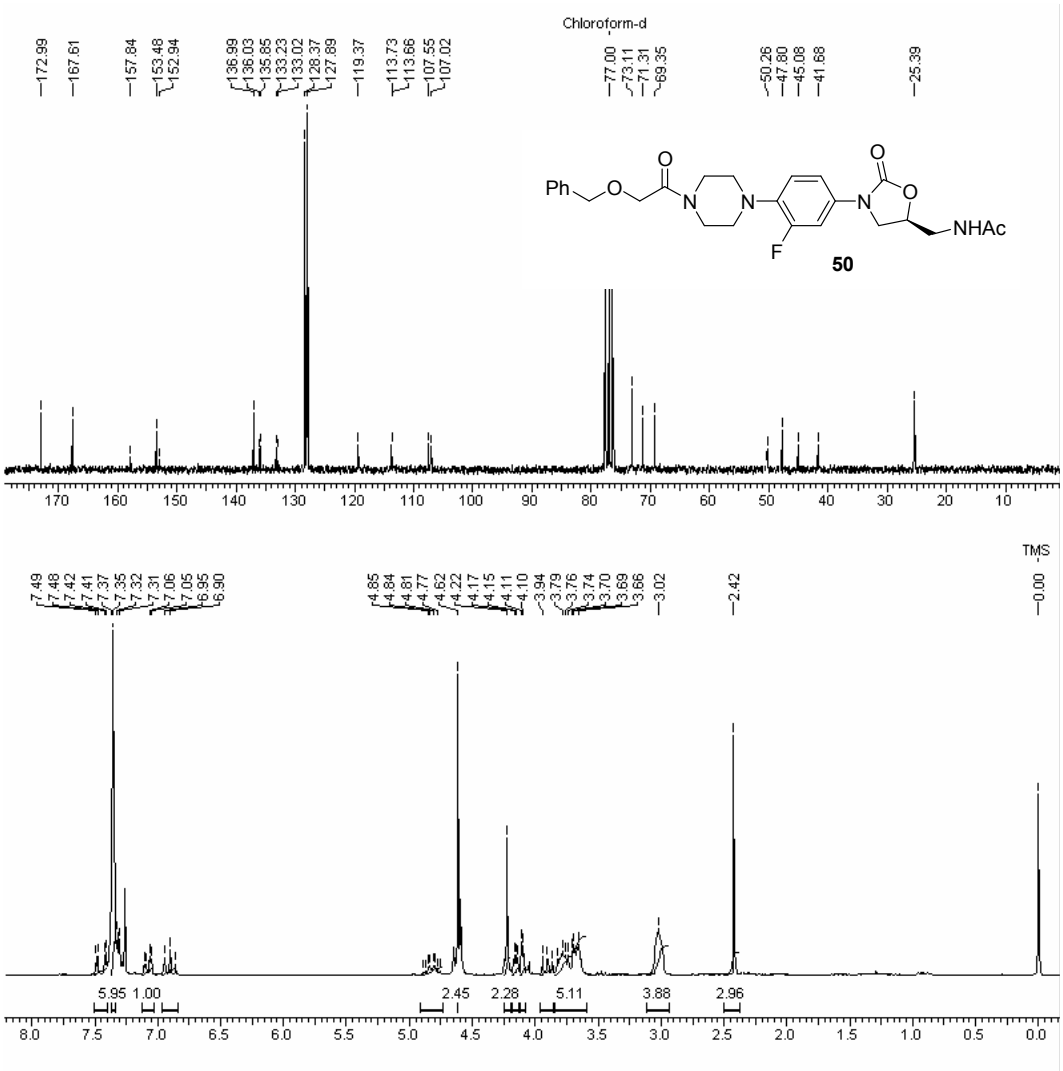


Fig. 17: ^{13}C and ^{1}H NMR spectra of 50

The signals at δ 172.99 and 167.61 in its ^{13}C-NMR spectrum confirm the presence of two amide carbonyls (**Fig. 17**). Finally, debenzylation of **50** using 10% Pd/C and H_2

(1 atm.) in MeOH-CH_2Cl_2 furnished eperezolid (**6**) {**mp** 175-176 ºC; **$[\alpha]^{25}_D$** -20.8 (*c* 1, DMSO); {lit.[7b] mp 175-176 ºC; $[\alpha]^{25}_D$: -21 (*c* 0.853, DMSO)} in 89% yield and 99% ee. The ^{1}H NMR spectrum of eperezolid (**6**) showed a singlet at δ 4.22 for α-methylene ketone ($COCH_2OH$) protons indicating the presence of $NCOCH_2OH$ moiety.

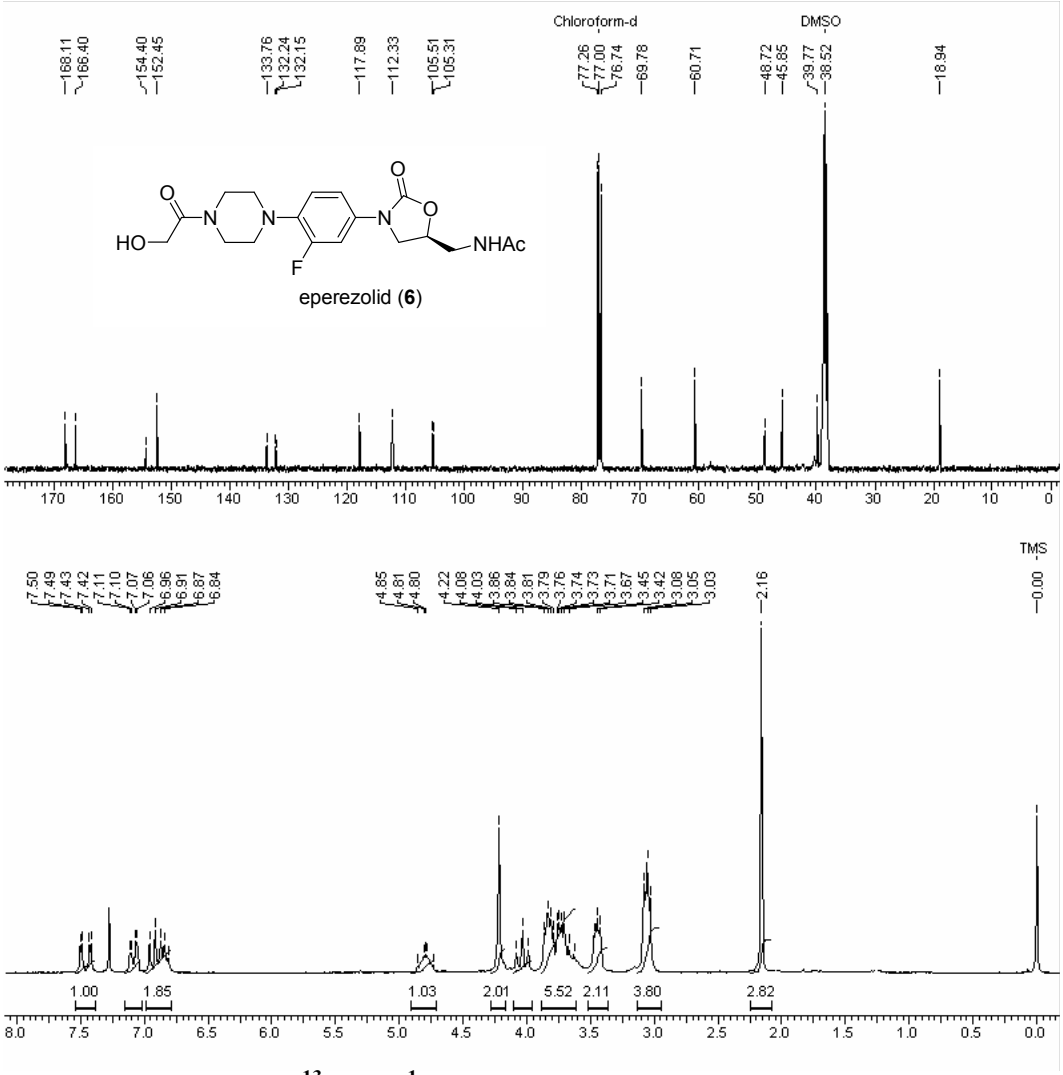


Fig. 18: ^{13}C and ^{1}H –NMR spectra of eperezolid (6)

The signals at δ 168.11 and 166.40 in its ^{13}C-NMR spectrum confirm the presence of two amide carbonyls (**Fig. 18**). The analytical and spectroscopic data of eperezolid (**6**) were in complete agreement with the reported values.[7b]

2.6 Conclusion

In conclusion, the enantioselective syntheses of two antibacterial antibiotics, linezolid (**5**) and eperezolid (**6**) were achieved in nine and fourteen linear steps respectively. The applicability of the D-proline catalyzed asymmetric α-aminooxylation of aldehydes has been demonstrated. The advantages of our syntheses are introduction of chirality using a catalytic amount of D-proline which is cheap and readily available and the high enantioselectivity associated with the process.

2.7 Experimental Section

3-Fluoro-4-morpholinylnitrobenzene (7a):

To a stirred solution of morpholine (8.67 mL, 99 mmol) and *N*,*N*-diisopropylethylamine (17.0 mL, 98 mmol) in EtOAc (150 mL) was added slowly 3,4-difluoronitrobenzene (10.0 mL, 90.3 mmol) *via* an addition funnel. After the addition was *ca.* two-thirds complete, the reaction mixture had warmed to >35 °C. The flask was cooled in an ice bath, the remaining 3,4-difluoronitrobenzene added over the next 30 min, and mixture gradually warmed to room temperature overnight. CH_2Cl_2 (40 mL), EtOAc (100 mL), and H_2O (60 mL) were added to the reaction mixture, which contained a yellow precipitate. The phases were separated, and the aqueous portion was extracted with EtOAc (3 × 50 mL). The combined organic portions were dried over anhyd. Na_2SO_4 and concentrated to give 21.64 g of crude **7a** as a yellow solid, which was recrystallized from acetone and water to give **7a** (20.03 g, 98% yield) as a yellow solid.

Yield: 98%; yellow solid; **mp**: 111-112 °C, (lit.[7b] 111-112 °C); IR ($CHCl_3$, cm^{-1}): 950, 1124, 1245, 1330, 1496, 1517, 1604, 2925; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 3.29 (t, *J* = 4.43 Hz, 4H), 3.88 (t, *J* = 5.75 Hz, 4H), 6.92 (t, *J* = 9.0 Hz, 1H), 7.91 (dd, *J* = 13.2, 2.7 Hz, 1H), 7.99 (ddd, *J* = 9.0, 2.7, 1.2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ:

49.52, 49.57, 66.21, 112.25 (d, J = 26.11 Hz), 116.53 (d, J = 3.6 Hz), 120.666 (d, J = 2.6 Hz), 140.47 (d, J = 7.5 Hz), 145.13 (d, J = 7.7 Hz), 152.75 (d, J = 249.1 Hz); **MS**: *m/z* 226 (89.6, M^+), 168 (100), 138 (23.5), 122 (13.2). **Analysis**: $C_{10}H_{11}FN_2O_3$ requires C, 53.10; H, 4.90; N, 12.38%; found C, 53.23; H, 4.85; N, 12.29%.

3-Fluoro-4-morpholinylaniline (8a):

To a stirred solution of nitro compound **7a** (5.115 g, 22.6 mmol) in THF (15 mL) and MeOH (60 mL) was added ammonium formate (5.67 g, 90 mmol). The flask was alternately evacuated and filled with nitrogen and cooled to 0 °C; then 10% Pd/C (0.132 g) was added, and the system was again evacuated and filled with nitrogen. After stirring for 2 h, the reaction mixture was filtered through a celite, washed with THF (10 mL) followd by EtOAc (20 mL). The volume of the solution was reduced to 60 mL; then water (40 mL) and EtOAc (60 mL) were added and the phases separated, and the aqueous portion was extracted with EtOAc (3 × 50 mL). The combined organic portions were washed with brine (40 mL), dried over anhyd. Na_2SO_4, and concentrated to give crude **8a** (4.88 g) as a yellow solid.

Yield: >99%; yellow solid; **mp**: 135-136 ºC; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.96 (m, 4H), 3.56 (br s, 2H), 3.84 (m, 4H), 6.41 (m, 2H), 6.79 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): 51.70, 51.72, 67.01, 103.81 (d, J = 23.7 Hz), 110.71 (d, J = 2.5 Hz), 120.25 (d, J = 3.9 Hz), 131.30 (d, J = 9.43 Hz), 143.22 (d, J = 10.3 Hz), 156.69 (d, J = 245.0 Hz). **Analysis**: $C_{10}H_{13}FN_2O$ requires C, 61.21; H, 6.68; N, 14.28%; found C, 61.14; H, 6.73; N, 14.15%.

Benzyl 3-fluoro-4-morpholinophenyl-3-hydroxypropyl carbamate (33):

To a stirred solution of amine **8a** (4.88 g, 22.6 mmol) and mono-tosyl protected 1,3-propane diol **39** (5.75 g, 25 mmol) in DMF (60 mL) was added Na_2SO_3 (4.77 g, 45 mmol) and NaI (0.345 g, 2.3 mmol). After the addition was complete, the reaction

mixture was heated to 65 °C and continued for 12 h and cooled to 25 ºC. EtOAc (100 mL) and water (100 mL) were added to the reaction mixture. The phases were separated, and the aqueous portion was extracted with EtOAc (3 × 50 mL). The combined organic portions were dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude secondary amine, which was added to the stirred mixture of Cbz-Cl (3.54 mL, 25 mmol) and $NaHCO_3$ (3.78 g, 45 mmol) in acetone-water (1:1, 60 mL) at 0 °C and stirred for 2 h at 25 °C. After completion of the reaction, EtOAc (100 mL) was added and the phases separated. The aqueous portion was extracted with EtOAc (2 × 50 mL). The combined organic portions were washed with brine (50 mL), 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 : EtOAc (7:3) as eluent to afford alcohol **33** (7.45 g) as a gum.

Yield: 85%; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.63-1.75 (m, 2H), 3.09 (t, J = 4.68 Hz, 4H), 3.63 (t, J = 5.81 Hz, 2H), 3.79 (t, J = 6.32 Hz, 2H), 3.87 (t, J = 4.67 Hz, 4H), 5.14 (s, 2H), 6.84-6.90 (m, 3H), 7.26-7.38 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): 30.63, 46.95, 50.68 (d, J = 3.66 Hz), 58.71, 66.81, 67.48, 115.54 (d, J = 21.95 Hz), 118.41 (d, J = 4.39 Hz), 123.18 (d, J = 2.93 Hz), 126.84, 127.55, 127.95, 128.38, 136.21, 138.72 (d, J = 8.42 Hz), 154.98 (d, J = 247.73 Hz), 156.15; **Analysis**: $C_{21}H_{25}FN_2O_4$ requires C, 64.93; H, 6.49; N, 7.21%; found C, 64.89; H, 6.42; N, 7.36%.

(*S*)-Benzyl 3-fluoro-4-morpholinophenyl-2,3-dihydroxy propyl carbamate (35):

Swern oxidation: To a stirred solution of oxalyl chloride, $(COCl)_2$ (2.54 g, 20 mmol) in CH_2Cl_2 (60 mL) at -78 °C, was added a solution of DMSO (2.12 mL, 20 mmol). The reaction mixture was stirred for 20 min. followed by the addition of a solution of

alcohol **33** (3.88 g, 10 mmol) in CH_2Cl_2 (20 mL). After stirring for 0.5 h at -78 °C, the reaction was quenched by the addition of Et_3N (5.6 mL, 40 mmol) and 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 layers were washed with water (2 x 50 mL), dried over anhyd. Na_2SO_4 and concentrated to give the corresponding aldehyde **34**.

α-Aminooxylation: To a stirred mixture of aldehyde **34** (3.86 g, 10 mmol) and nitrosobenzene (1.07 g, 10 mmol) in CH_3CN (30 mL) was added D-proline (287 mg, 2.48 mmol, 25 mol %) at -20 ºC. The reaction mixture was allowed to stir at the same temperature for 24 h followed by the addition of MeOH (10 mL) and $NaBH_4$ (1.12 g, 30 mmol) with stirring being continued for 10 min. After addition of phosphate buffer, the resulting mixture was extracted with EtOAc (3 X 30 mL) and the combined organic phases were dried over anhyd. Na_2SO_4. Evaporation of solvent gave crude nitroso compound. To a solution of this crude nitroso product in MeOH (20 mL) was added 10% Pd/C (65 mg) carefully followed by the addition of 5-6 drops of Et_3N. The reaction mixture was then stirred under hydrogen atmosphere (1 atm.) for 12 h. After completion of reaction (monitored by TLC), the reaction mixture was filtered through a celite pad and concentrated to give the crude diol, which was purified by column chromatography packed with silica gel using pet. ether: EtOAc (5:5) as eluent to afford pure diol **35** (3.47 g) as brown color gum.

Yield: 86%; $[\alpha]^{25}_{D}$: -4.0 (*c* 1.1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 1117, 1215, 1452, 1514, 1685, 2399, 2862, 2966, 3018, 3433; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.08 (t, J = 4.66 Hz, 4H), 3.49-3.61 (m, 2H), 3.65-3.80 (m, 3H), 3.86 (t, J = 4.83 Hz, 4H), 5.13 (s, 2H), 6.83-6.96 (m, 3H), 7.25-7.35 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): 50.55 (d, J = 3.52 Hz), 52.89, 63.76, 66.70, 67.53, 69.92, 115.49 (d, J = 32.71 Hz), 118.33 (d, J = 3.86 Hz), 123.13 (d, J = 2.92 Hz), 127.38, 127.87, 128.29, 135.97, 138.69 (d, J = 8.95 Hz),

154.79 (d, J = 247.74 Hz), 156.39; **Analysis**: $C_{21}H_{25}FN_2O_5$ requires C, 62.37; H, 6.23; F, 4.70; N, 6.93%, found C, 62.30; H, 6.28; F, 4.81; N, 6.85%.

(*R*)-3-(3-Fluoro-4-morpholinophenyl)-5-(hydroxymethyl) oxazolidin-2-one (36):

To a stirred solution of diol **35** (3.23 g, 8 mmol) in dry THF (60 mL) was added NaH [0.384 g, 16 mmol (60% w/w in wax)] at 25 ºC and the mixture was stirred for 4h. It was quenched with water (10 mL) and concentrated to give residue which was extracted with CH_2Cl_2 (2 × 50 mL), washed with saturated NH_4Cl (30 mL), brine (30 mL), dried over anhyd. Na_2SO_4 and concentrated to give crude product, which was purified by column chromatography packed with silica gel using pet. ether: EtOAc (5:5) to afford oxazolidinone **36** (2.27 g) as a gray solid.

Yield: 96%; gray solid; **mp**: 113-114 °C, {lit.[7b] 112-114 °C}; **$[\alpha]^{25}_D$**: -53.2 (*c* 1, $CHCl_3$), {lit.[7b] $[\alpha]^{25}_D$: -54.0 (*c* 0.99, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): 1231, 1424, 1441, 1454, 1465, 1523, 1734, 1748, 2925, 3263, 3432; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.96 (br s, 1H), 3.04 (t, *J* = 4.8 Hz, 4H), 3.63-3.77 (m, 1H), 3.87 (t, *J* = 4.55 Hz, 4H), 3.94-4.17 (m, 3H), 4.68-4.79 (m, 1H), 6.91 (t, *J* = 9.10 Hz, 1H), 7.11 (ddd, *J* = 8.84, 2.65, 1.01 Hz, 1H), 7.44 (dd, *J* = 14.4, 2.53 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): 46.27, 50.79 (d, *J* = 2.92 Hz), 62.32, 66.75, 73.02, 107.25 (d, *J* = 26.35 Hz), 113.80 (d, *J* = 3.29 Hz), 118.66 (d, *J* = 4.03 Hz), 133.03 (d, *J* = 10.25 Hz), 136.10 (d, *J* = 8.78 Hz), 154.87, 155.22 (d, *J* = 246.27 Hz); **MS**: *m/z* 296 (100, M+), 238 (41.6), 151 (14.2); **Analysis**: $C_{14}H_{17}FN_2O_4$ requires C, 56.75; H, 5.78; F, 6.41; N, 9.45%; found C, 56.89; H, 5.61; F, 6.49; N, 9.57%.

Mosher ester of (*R*)-3-(3-Fluoro-4-morpholinophenyl)-5-(hydroxymethyl) oxazolidin-2-one (40):

A two-necked 10 mL flask was charged with *N*,*N*'- dicyclohexylcarbodiimide (44 mg, 0.21 mmol), catalytic amount of 4-dimethylaminopyridine (DMAP) and CH_2Cl_2 (2

mL) under argon atmosphere. The flask was cooled to 0 ºC for 10 min. and to this mixture, a solution of oxazolidinone **36** (53 mg, 0.18 mmol) in CH_2Cl_2 (2 mL) was introduced through a syringe. It was allowed to stir for additional 10 min., followed by dropwise addition of (*R*)-α-methoxy-α-trifluoromethylphenyl acetic acid (46 mg, 0.196 mmol) in CH_2Cl_2 (2 mL). This reaction mixture was then stirred at 0 ºC for additional one hour and then at 25 ºC for 12 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with saturated sodium bicarbonate solution (20 mL), dried over anhyd. Na_2SO_4 and then concentrated under reduced pressure to give Mosher ester of oxazolidinone **36** (89 mg) as a thick syrup.

Yield: 97%; **$[\alpha]^{25}_D$**: –15.6 (*c* 1.2, $CHCl_3$); **IR** ($CHCl_3$ cm^{-1}): 3158, 2952, 2927, 2850, 2250, 1753, 1606, 1519, 1495, 1348, 1268, 1242, 1217, 1153, 1122, 1015, 957, 911, 735, 650; **^{1}H NMR** ($CDCl_3$) δ: 3.06 (t, *J* = 4.67 Hz, 4H), 3.52 (s, 3H), 3.66 (dd, *J* = 8.97, 6.06 Hz, 1H), 3.87 (t, *J* = 4.55 Hz, 4H), 4.02 (t, *J* = 9.09 Hz, 1H), 4.44 (dd, *J* = 12.26, 3.79 Hz, 1H), 4.66 (dd, *J* = 12.26, 3.29Hz, 1H), 4.85-4.96 (m, 1H), 6.89 (t, *J* = 8.84 Hz, 1H), 7.00 (dd, *J* = 9.10, 2.53 Hz, 1H), 7.22-7.49 (m, 6H).

[(*R*)-3-(3-Fluoro-4-morpholinophenyl)-2-oxazolidin-5-yl]methyl methanesulfonate (37):

To a stirred solution of alcohol **36** (2.072 g, 7 mmol) and Et_3N (2.1 mL, 15 mmol) in CH_2Cl_2 (30 mL) at 0 °C was added MsCl (0.81 mL, 10.5 mmol) over 5 min. After 20 min, the mixture was filtered, and the white solid was filtered, washed with water (3 × 5 mL) and dried in vacuum oven to give mesylate **37** (2.48 g) as a colorless solid.

Yield: 95%; colorless solid; **mp**: 154-155 ºC; **$[\alpha]^{25}_D$**: -49.3 (*c* 1, DMF), {lit.[7b] $[\alpha]^{25}_D$: -50 (*c* 0.998, DMF)}; **IR** ($CHCl_3$, cm^{-1}): 1112, 1183, 1231, 1347, 1356, 1516, 1752, 2925; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 2.95 (t, *J* = 4.42 Hz, 4H), 3.25 (s, 3H), 3.72 (t, *J* = 4.16 Hz, 4H), 3.78-3.82 (m, 1H), 4.14 (t, *J* = 9.35 Hz, 1H), 4.39-4.54 (m, 2H),

4.93-5.06 (m, 1H), 7.06 (t, *J* = 9.35 Hz, 1H), 7.20 (dd, *J* = 8.97, 2.15 Hz, 1H), 7.50 (dd, *J* = 15.03, 2.27 Hz, 1H); **^{13}C NMR** (50 MHz, DMSO-d_6): 36.94, 46.08, 50.82 (d, *J* = 2.56 Hz), 66.30, 69.88, 70.13, 106.90 (d, *J* = 26.35 Hz), 114.36 (d, *J* = 2.92 Hz), 119.38 (d, *J* = 4.03 Hz), 133.34 (d, *J* = 10.61 Hz), 135.86 (d, *J* = 8.78 Hz), 153.86, 154.73 (d, *J* = 243.70 Hz); **MS**: *m/z* 374 (100, M^+), 316 (43.1), 176 (11.9), 150 (12.5), 149 (15.5); **Analysis**: $C_{15}H_{19}FN_2O_6S$ requires C, 48.12; H, 5.12; F, 5.07; N, 7.48; S, 8.56%; found C, 48.19; H, 5.03; F, 5.19; N, 7.55; S, 8.53%.

(*R*)-5-(Azidomethyl)-3-(3-fluoro-4-morpholinophenyl)oxazolidin-2-one (38):

A mixture of mesylate **37** (2.24 g, 6 mmol) and sodium azide (1.56 g, 24 mmol) in DMF (20 mL) was heated at 75 °C for 16 h, at which time, after cooling, water (50 mL) and EtOAc (30 mL) were added. The phases were separated, and the aqueous portion was extracted with EtOAc (2 × 30 mL). The combined organic portions were 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: EtOAc (6:4) to give pure azide **38** (1.73 g) as a brown solid.

Yield: 90%; brown solid; **mp**: 123-124 °C; **$[\alpha]^{25}_D$**: -23.2 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 1117, 1216, 1516, 1758, 2111, 2400, 3019; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.06 (t, *J* = 4.80 Hz, 4H), 3.59 (dd, *J* = 13.26, 4.42 Hz, 1H), 3.71 (dd, *J* = 13.27, 4.55 Hz, 1H), 3.82 (dd, *J* = 9.09, 6.44 Hz, 1H), 3.87 (t, *J* = 4.55 Hz, 4H), 4.05 (t, *J* = 8.84 Hz, 1H), 4.73-4.85 (m, 1H), 6.94 (t, *J* = 9.09 Hz, 1H), 7.13 (ddd, *J* = 8.84, 2.52, 0.88 Hz, 1H), 7.45 (dd, *J* = 14.4, 2.65 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): 47.35, 50.88 (d, *J* = 3.30 Hz), 52.92, 66.83, 70.56, 107.39 (d, *J* = 26.34 Hz), 113.84 (d, *J* = 3.30 Hz), 118.76 (d, *J* = 4.39 Hz), 132.82 (d, *J* = 10.61 Hz), 136.44 (d, *J* = 9.15 Hz), 153.77, 155.37 (d, *J* = 246.27 Hz); **MS**: *m/z* 321 (100, M^+), 191 (80.5), 190 (56.6), 164 (27.8), 150 (54.5), 149 (24.3), 81 (19.3), 42 (18.2); **Analysis**: $C_{14}H_{16}FN_5O_3$

requires C, 52.33; H, 5.02; F, 5.91; N, 21.80%; found C, 52.21; H, 4.89; F, 5.98; N, 21.98%.

(S)-*N*-[[3-(3-Fluoro-4-morpholinylphenyl)-2-oxo-5-xazolidinyl]methyl]acetamide: linezolid (U-100766, 5)

To a stirred solution of azide **38** (0.642 g, 2 mmol) in EtOAc (15 mL) was added 10% Pd/C (0.050 g), and the system was alternately evacuated and filled with nitrogen; then hydrogen was introduced *via* a balloon system, with three cycles of evacuation and filling from the balloon and the mixture was stirred overnight. The reaction mixture was then evacuated and flushed with nitrogen and cooled to 0 °C, and pyridine (0.186 mL, 2.31 mmol) and acetic anhydride (0.708 mL, 7.5 mmol) were added. The mixture was stirred for 30 min and then removed from the ice bath and stirred at room temperature for 1 h; then it was filtered through a celite and concentrated under reduced pressure to give the crude product, which was purified by column chromatography packed with silica gel using MeOH: EtOAc (0.5:9.5) to give linezolid (**5)** (0.62 g) as a colorless solid.

Yield: 92%; colorless solid; **mp**: 181-182 °C (crystallized from EtOAc and hexane), {lit.[7b] 181.5-182.5 °C}; **$[\alpha]^{25}_{D}$**: -8.9 (*c* 1, $CHCl_3$), {lit.[7b] $[\alpha]^{25}_{D}$: -9.0 (*c* 0.919, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): 1435, 1447, 1519, 1565, 1649, 1728, 1753, 3092, 3284; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.03 (s, 3H), 3.05 (t, *J* = 4.67 Hz, 4H), 3.62-3.72 (m, 2H), 3.76 (dd, *J* = 9.09, 6.69 Hz, 1H), 3.87 (t, *J* = 4.30 Hz, 4H), 4.03 (t, *J* = 8.97 Hz, 1H), 4.72-4.84 (m, 1H), 6.43 (br t, *J* = 5.93 Hz, 1H), 6.92 (t, *J* = 9.09 Hz, 1H), 7.08 (dd, *J* = 8.85, 2.53 Hz, 1H), 7.43 (dd, *J* = 14.40, 2.53 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): 22.64, 41.64, 47.41, 50.71 (d, *J* = 3.29 Hz), 66.66, 71.90, 107.27 (d, *J* = 26.35 Hz, 113.79 (d, *J* = 3.29 Hz), 118.59 (d, *J* = 4.40 Hz), 132.73 (d, *J* = 10.62 Hz), 136.22 (d, *J* = 8.78 Hz), 154.44, 155.14 (d, *J* = 246.27 Hz), 171.50; **MS**: *m/z* 337 (100, M^+), 293

(35.8), 234 (35.3), 209 (47.2), 176 (28.4), 164 (24.6), 151 (27.8), 150 (23.1), 138 (22.0), 43 (26.1); **Analysis**: $C_{16}H_{20}FN_3O_4$ requires C, 56.97; H, 5.98; F, 5.63; N, 12.46%; found C, 56.85; H, 5.95; F, 5.67; N, 12.52%.

1-(2-Fluoro-4-nitrophenyl)piperazine (7b):

To a solution of 3,4-difluoronitrobenzene (12.0 g, 75.42 mmol) in CH_3CN (150 mL) was adeed piperazine (16.24 g, 188.6 mmol) and heated to reflux for 3 h. The solution was cooled to 25 °C and concentrated *in vacuo*. The resulting residue was diluted with water (200 mL) and extracted with EtOAc (2 × 250 mL). The combined organic layers were washed with water (200 mL) and brine (200 mL) followed by drying over anhyd. Na_2SO_4. The solution was concentrated *in vacuo* to afford an orange colored oil which was chromatographed over silica gel eluting initially with dichloromethane until the least polar fractions had eluted, and then elution was continued with 2% (v/v) MeOH-CH_2Cl_2 and followed by 10% (v/v) MeOH-CH_2Cl_2. These procedures afforded **7b** (13.83 g) as an orange colored solid.

Yield: 81%; orange solid; **mp**: 69-71 °C (lit.[7b] 68.5-71 °C); **IR** ($CHCl_3$, cm^{-1}): 881, 1203, 1238, 1263, 1330, 1454, 1501, 1508, 1603, 2853, 2924, 2952; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.77 (s, 1H), 3.05 (t, J = 5.17 Hz, 4H), 3.27 (t, J = 4.67 Hz, 4H), 6.92 (t, J = 8.59 Hz, 1H), 7.90 (dd, J = 13.14, 2.53 Hz, 1H), 7.98 (ddd, J = 8.84, 2.53, 0.89 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): 45.68, 50.62 (d, J = 5.12 Hz), 112.22 (d, J = 26.35 Hz), 116.77 (d, J = 4.39 Hz), 120.76 (d, J = 2.93 Hz), 139.95 (d, J = 8.79 Hz), 145.80 (d, J = 7.68 Hz), 152.68 (d, J = 249.20 Hz); **MS**: *m/z* 226 (5), 225 (34, M+), 184 (12), 183 (100), 138 (4), 137 (22); **Analysis**: $C_{10}H_{12}FN_3O_2$ requires C, 53.33; H, 5.37; F, 8.44; N, 18.66%; found C, 53.52; H, 5.39; F, 8.31; N, 18.39%.

Benzyl 4-(2-fluoro-4-nitrophenyl)piperazine-1-carboxylate (41):

To a stirred solution of **7b** (5 g, 22.2 mmol) and $NaHCO_3$ (2.79 g, 33.3 mmol) in acetone-water (1:1, 60 mL) was added Cbz-Cl (4.09 mL, 28.8 mmol) at 5 ºC and stirred at 25 °C for 6 h. EtOAc (60 mL) was added to the reaction mixture. The phases were separated, and the aqueous portion was extracted with EtOAc (2 × 50 mL). The combined organic layers were dried over anhyd. Na_2SO_4 and concentrated to give the crude product, which was purified by column chromatography packed with silica gel using pet. ether: EtOAc (6:4) to afford **41** (7.73 g) as a yellow solid.

Yield: 97%; yellow solid; **mp**: 164-165 °C; **IR** ($CHCl_3$, cm^{-1}): 1254, 1432, 1455, 1465, 1532, 1691, 1713, 3284; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.25 (t, *J* = 5.17 Hz, 4H), 3.69 (t, *J* = 4.92 Hz, 4H), 5.17 (s, 2H), 6.91 (t, J = 8.59 Hz, 1H), 7.33-7.40 (m, 5H), 7.92 (dd, *J* = 12.88, 2.52 Hz, 1H), 7.99 (dd, *J* = 8.86, 3.28 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): 43.31, 49.17 (d, *J* = 4.75 Hz), 67.18, 112.28 (d, *J* = 25.98 Hz), 117.16 (d, *J* = 3.66 Hz), 120.70 (d, *J* = 2.93 Hz), 126.66, 127.73, 128.32,136.18, 140.63 (d, *J* = 8.78 Hz), 145.08 (d, *J* = 7.68 Hz), 152.82 (d, *J* = 249.57 Hz), 154.92; **Analysis**: $C_{18}H_{18}FN_3O_4$ requires C, 60.16; H, 5.05; F, 5.29; N, 11.69%; found C, 60.03; H, 5.10; F, 5.39; N, 11.78%.

Benzyl 4-(4-((benzyloxy)carbonyl)piperazin-1-yl)-3-fluorophenyl-3-hydroxypropylcarbamate (43):

To a stirred solution of nitro compound **38** (5 g, 13.9 mmol) and $CoCl_2$ (0.358 g, 2.8 mmol) in MeOH (150 mL) was added $NaBH_4$ (3.69 g, 97.3 mmol) at 25 ºC and stirred at 60 °C for 6 h. EtOAc (150 mL) and water (80 mL) were added to the reaction mixture. The phases were separated, and the aqueous portion was extracted with EtOAc (2 × 100 mL). The combined organic portions were dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude amine **42** which was

immediately used as such in the next step. To a stirred solution of amine **42** (4.34 g, 13.2 mmol) and monotosyl protected 1,3-propane diol **39** (3.36 g, 14.6 mmol) in DMF (40 mL) was added Na_2SO_3 (2.79 g, 26.31 mmol) and NaI (0.202 g, 1.3 mmol). After the addition was complete, the reaction mixture was heated to 65 °C for 12 h. The reaction mixture was quenched with water and extracted with EtOAc (80 mL). The phases were separated, and the aqueous portion was extracted with EtOAc (2 × 50 mL). The combined organic portions were dried over anhyd. Na_2SO_4 and concentrated to give crude secondary amine prduct, which was added to the solution of Cbz-Cl (2.07 mL, 14.6 mmol) and $NaHCO_3$ (2.21 g, 26.3 mmol) in acetone-water (1:1, 50 mL) at 0 °C and stirred at 25 °C for 2 h. After completion of the reaction, EtOAc (80 mL) was added and the phases separated, and the aqueous portion was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhyd. Na_2SO_4 and concentrated to give the crude product, which was purified by column chromatography packed with silica gel using pet. ether: EtOAc (7:3) as eluent to afford alcohol **43** (5.43 g) as a gum.

Yield: 79%; **IR** ($CHCl_3$, cm^{-1}): 1520, 1647, 1682, 1750, 3256; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.54-1.65 (m, 2H), 1.98 (s, 1H), 2.96 (t, J = 4.67 Hz, 4H), 3.53 (t, J = 5.68 Hz, 2H), 3.59 (t, J = 4.80 Hz, 4H), 3.69 (t, J = 6.19 Hz, 2H), 5.04 (s, 2H), 5.07 (s, 2H), 6.70-6.78 (m, 3H), 7.18-7.36 (m, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$): 30.65, 43.77, 47.03, 50.16 (d, J = 4.75 Hz), 58.62, 67.13, 67.37, 115.46 (d, J = 25.32 Hz), 118.82 (d, J = 4.03 Hz), 123.03 (d, J = 2.46 Hz), 126.73, 127.17, 127.52, 127.76, 128.30, 128.35, 132.91 (d, J = 10.62 Hz), 136.10, 136.34, 138.45 (d, J = 8.42 Hz), 154.93 (d, J = 248.10 Hz), 154.94, 155.85; **Analysis**: $C_{21}H_{26}FN_3O_3$ requires C, 65.10; H, 6.76; F, 4.90; N, 10.85%, found C, 65.23; H, 6.82; F, 4.93; N, 10.72%.

(*S*)-Benzyl 4-(4-((benzyloxy)carbonyl)piperazin-1-yl)-3-fluorophenyl-2,3-dihydroxypropylcarbamate (45):

Swern oxidation: To a stirred solution of oxalyl chloride, $(COCl)_2$ (1.27 g, 10 mmol) in CH_2Cl_2 (30 mL) at -78 °C, was added a solution of DMSO (1.06 mL, 15 mmol). The reaction mixture was stirred for 20 min. followed by the addition of a solution of alcohol **43** (2.6 g, 5 mmol) in CH_2Cl_2 (10 mL). After stirring for 0.5 h at -78 °C, the reaction was quenched by the addition of Et_3N (2.8 mL, 20 mmol) and water (40 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with water (3 x 30 mL), dried over anhyd. Na_2SO_4 and concentrated to give the corresponding aldehyde **44**.

α-Aminooxylation: To a stirred mixture of aldehyde **44** (2.59 g, 5 mmol) and nitrosobenzene (0.535 g, 5 mmol) in CH_3CN (20 mL) was added D-proline (143 mg, 1.24 mmol, 25 mol %) at -20 ºC. The reaction mixture was allowed to stir at the same temperature for 24 h followed by the addition of MeOH (5 mL) and $NaBH_4$ (0.56 g, 15 mmol) with stirring being continued for 10 min. After addition of phosphate buffer, the resulting mixture was extracted with EtOAc (3 X 30 mL) and the combined organic phases were dried over anhyd. Na_2SO_4. Evaporation of solvent gave crude nitroso compound. To the solution of this crude nitroso product in MeOH (15 mL) was added $CuSO_4$ (0.241 g, 1.5 mmol) and stirred at 25 °C for 12 h. After completion of reaction (monitored by TLC) the reaction mixture was filtered through a celite pad and concentrated to give the crude product, which was purified by column chromatography packed with silica gel using pet. ether: EtOAc (4:6) as eluent to afford pure diol **45** (2.20 g) as brown color gum.

Yield: 82%; $[\alpha]_D^{25}$: –3.2 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 758, 1215, 1436, 1514, 1685, 2361, 3018, 3410; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.04 (t, *J* = 5.12 Hz, 4H),

3.49-3.61 (m, 2H), 3.67 (t, J = 5.43 Hz, 4H), 3.74-3.80 (m, 3H), 5.13 (s, 2H), 5.16 (s, 2H), 6.82-6.96 (m, 3H), 7.21-7.39 (m, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 43.74, 50.18 (d, J = 2.84 Hz), 52.97, 63.79, 64.89, 67.18, 67.60, 70,04, 115.52 (d, J = 21.83 Hz), 118.87 (d, J = 3.74 Hz), 123.09 (d, J = 3.01 Hz), 126.79, 127.31, 127.45, 127.80, 127.97, 128.40, 131.89 (d, J = 9.80 Hz), 135.98, 136.38, 138.53 (d, J = 8.45 Hz), 154.90 (d, J = 248.10 Hz), 155.10, 156.42; **Analysis**: $C_{29}H_{32}FN_3O_6$ requires C, 64.79; H, 6.00; F, 3.53; N, 7.82%, found C, 64.72; H, 6.07; F, 3.59; N, 7.81%.

Benzyl 4-(2-fluoro-4-((*R*)-5-(hydroxymethyl)-2-oxazolidin-3-l)phenyl)piperazine-1-carboxylate (46):

To a stirred solution of diol **45** (3.108 g, 6 mmol) in dry THF (50 mL) was added NaH [0.288 g, 12 mmol (60% w/w in wax)] at 0 °C and the mixture was stirred under nitrogen atmosphere at 25 °C for 4h. The reaction mixture was quenched with water (10 mL) and concentrated to give residue which was extracted with CH_2Cl_2 (2 × 50 mL), washed with saturated NH_4Cl (30 mL), brine (30 mL), dried over anhyd. Na_2SO_4 and concentrated to give the crude product, which was purified by column chromatography packed with silica gel using pet. ether: EtOAc (2:8) to afford oxazolidinone **46** (2.42 g) as a colorless solid.

Yield: 94%; colorless solid; **mp**: 156-157 °C {lit.[7b] 156-157 °C}; **$[\alpha]^{25}_D$**: -32.0 (c 1, $CHCl_3$) {lit.[7b] $[\alpha]^{25}_D$: -32.0 (c 0.991, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): 1243, 1451, 1520, 1668, 1745, 3428; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.99 (t, J = 4.55 Hz, 4H), 3.65-3.78 (m, 5H), 3.94-4.03 (m, 3H), 4.67-4.79 (m, 1H), 5.16 (s, 2H), 6.90 (t, J = 9.09 Hz, 1H), 7.12 (dd, J = 8.72, 1.64 Hz, 1H), 7.37 (m, 5H), 7.45 (dd, J = 14.27, 2.52 Hz); **^{13}C NMR** (50 MHz, $CDCl_3$): 43.74, 46.26, 50.39 (d, J = 2.19 Hz), 62.35, 67.14, 72.93, 107.19 (d, J = 26.35 Hz), 113.71 (d, J = 3.30 Hz), 119.22 (d, J = 3.66 Hz), 127.75, 127.95, 128.37, 133.44 (d, J = 10.61 Hz), 135.89 (d, J = 9.14 Hz), 136.39, 154.76,

155.11, 155.34 (d, *J* = 246.27 Hz); **MS**: *m/z* 429 (98.0, M+), 430 (24.8), 294 (22.8), 265 (25.4), 91 (100), 56 (60.0); **Analysis**: $C_{22}H_{24}FN_3O_5$ requires C, 61.53; H, 5.63; F, 4.42; N, 9.78%; found C, 61.65; H, 5.61; F, 4.36; N, 9.62%.

Mosher ester of 46 (51):

A two-necked 10 mL flask was charged with *N*,*N*'- dicyclohexylcarbodiimide (44 mg, 0.21 mmol), catalytic amount of 4-dimethylaminopyridine (DMAP) and CH_2Cl_2 (2 mL) under argon atmosphere. The flask was cooled to 0 ºC for 10 min. and to this mixture, a solution of oxazolidinone **46** (77 mg, 0.18 mmol) in CH_2Cl_2 (2 mL) was introduced through a syringe. It was allowed to stir for additional 10 min., followed by dropwise addition of (*R*)-α-methoxy-α-trifluoromethylphenyl acetic acid (46 mg, 0.196 mmol) in CH_2Cl_2 (2 mL). This reaction mixture was then stirred at 0 ºC for additional one hour and then at 25 ºC for 12 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with saturated $NaHCO_3$ solution (20 mL), dried over anhyd. Na_2SO_4 and then concentrated under reduced pressure to give Mosher ester of the oxazolidinone 4**6** (113 mg) as a thick syrup.

Yield: 98%; $[\alpha]^{25}_{D}$: –17.3 (*c* 1.3, $CHCl_3$); **IR** ($CHCl_3$ cm^{-1}): 3158, 2952, 2927, 2850, 2250, 1753, 1606, 1519, 1495, 1348, 1268, 1242, 1217, 1153, 1122, 1015; **^{1}H NMR** ($CDCl_3$) δ: 3.01 (t, *J* = 4.67 Hz, 4H), 3.52 (s, 3H), 3.61-3.71 (m, 5H), 4.01 (t, *J* = 9.10 Hz, 1H), 4.43 (dd, *J* = 12.12, 3.66 Hz, 1H), 4.66 (dd, *J* = 12.26, 3.29Hz, 1H), 4.84-4.95 (m, 1H), 5.16 (s, 2H), 6.88 (t, *J* = 8.84 Hz, 1H), 6.99 (dd, *J* = 8.97, 2.40 Hz, 1H), 7.27 (dd, *J* = 14.27, 2.53 Hz), 7.33-7.48 (m, 10H).

Benzyl 4-(4-((R)-5-(azidomethyl)-2-oxazolidin-3-yl)-2-fluorophenyl)piperazine-1-carboxylate (47):

To a stirred mixture of **46** (1.59 g, 3.7 mmol) and Et_3N (1.54 mL, 11.1 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added methanesulfonyl chloride (0.4 mL, 5.55 mmol).

The mixture was stirred at 0 °C for 1 h and at 25 °C for 3 h, the mixture was washed with water (20 mL), and the aqueous layer was extracted with CH_2Cl_2 (20 mL). EtOAc (50 mL) was added to the combined organic layers, dried over anhyd. Na_2SO_4 and concentrated to give a yellow foamy solid. This was taken up into the solution of sodium azide (0.721 g, 11.1 mmol) in DMF (30 mL) and it was heated at 75 °C for 16 h, at which time, after cooling, water (50 mL) and EtOAc (50 mL) were added. The phases were separated, and the aqueous portion was extracted with EtOAc (2 × 30 mL). The combined organic portions were dried over anhyd. Na_2SO_4 and concentrated to give the crude product, which was purified by column chromatography packed with silica gel using pet. ether: EtOAc (6:4) to give azide **47** (1.49 g) as a light yellow solid.

Yield: 89%; colorless solid; **mp**: 167-168 °C; **$[\alpha]^{25}_D$**: -24.4 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 756, 1028, 1126, 1217, 1436, 1517, 1697, 1757, 2110, 3018; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.00 (t, *J* = 4.54 Hz, 4H), 3.56 (dd, *J* = 13.14, 4.42 Hz, 1H), 3.66 (t, *J* = 4.29 Hz, 4H), 3.73-3.83 (m, 1H), 3.96-4.16 (m, 2H), 4.69-4.81 (m, 1H), 5.14 (s, 2H), 6.89 (t, *J* = 8.97 Hz, 1H), 7.10 (dd, *J* = 9.60, 2.40 Hz, 1H), 7.31-7.38 (m, 5H), 7.41 (dd, *J* = 14.14, 2.52 Hz); **^{13}C NMR** (50 MHz, $CDCl_3$): 43.79, 47.26, 50.53 (d, *J* = 2.56 Hz), 52.90, 67.12, 70.50, 107.22 (d, *J* = 26.35 Hz), 113.64 (d, *J* = 3.29 Hz), 119.38 (d, *J* = 4.02 Hz), 127.83, 127.98, 128.42, 133.39 (d, *J* = 10.24 Hz), 135.97 (d, *J* = 9.15 Hz), 136.52, 153.50, 154.90, 155.47 (d, *J* = 246.64 Hz); **Analysis**: $C_{22}H_{23}FN_6O_4$ requires C, 58.14; H, 5.10; F, 4.18; N, 18.49%; found C, 58.02; H, 5.15; F, 4.11; N, 18.58%.

(*S*)-*N*-[[3-[3-Fluoro-4-[*N*-1-(4-carbobenzoxy)piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (48):

A mixture of azide **47** (1.543 g, 3.4 mmol) and triphenylphosphine (3.56 g, 13.6 mmol) in THF (30 ml) and water (3 ml) was heated at 50 °C for 3 h. Evolution of N_2 was observed during the first 1h of the reaction. Solvent was evaporated; the solid residue was dissolved in MeOH (20 ml) and cooled to 0 °C, followed by the addition of pyridine (0.55 mL, 6.8 mmol) and acetic anhydride (0.962 mL, 10.2 mmol) under nitrogen atmosphere. The mixture was stirred for 30 min and then removed from the ice-bath and stirred at 25 °C for 1 h; The reaction mixture was concentrated under reduced pressure to give the crude product, which was purified by column chromatography packed with silica gel using MeOH : EtOAc (0.5:9.5) to give acetamide **48** (1.53 g) as a colorless solid.

Yield: 96%; colorless solid; **mp**: 174-175 °C; $\mathbf{[\alpha]^{25}_D}$: -18.5 (*c* 1, DMSO); **IR** ($CHCl_3$, cm^{-1}): 1520, 1647, 1682, 1750, 3306; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.01 (s, 3H), 3.00 (t, *J* = 4.42 Hz, 4H), 3.61-3.79 (m, 7H), 4.01 (t, *J* = 8.97 Hz, 1H), 4.71-4.83 (m, 1H), 5.16 (s, 2H), 6.47 (br s, 1H), 6.90 (t, *J* = 8.97 Hz, 1H), 7.07 (dd, *J* = 8.85, 2.02 Hz, 1H), 7.31-7.38 (m, 5H), 7.43 (dd, *J* = 14.40, 2.40 Hz); **^{13}C NMR** (50 MHz, $CDCl_3$): 22.77, 41.67, 43.72, 47.43, 50.37 (d, *J* = 2.20 Hz), 67.06, 71.90, 107.27 (d, *J* = 25.98 Hz), 113.74 (d, *J* = 3.30 Hz), 119.21 (d, *J* = 4.02 Hz), 127.71, 127.90, 128.35, 133.12 (d, *J* = 10.62 Hz), 136.11 (d, *J* = 9.15 Hz), 136.42, 154.36, 155.01, 155.31 (d, *J* = 246.27 Hz), 171.28; **MS**: *m/z* 470 (43.3, M^+), 426 (17.9), 91 (100), 56 (70.5); **Analysis**: $C_{24}H_{27}FN_4O_5$ requires C, 61.27; H, 5.78; F, 4.04; N, 11.91%; found C, 61.11; H, 5.85; F, 4.18; N, 11.96%.

(*S*)-*N*-[[3-[3-Fluoro-4-(*N*-1-piperazinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide, Hydrochloride (49):

A mixture of **48** (1.109 g, 2.36 mmol) and 10% Pd/C (0.154 g) in MeOH (50 mL) and CH_2Cl_2 (16 mL) was stirred under hydrogen (1 atm, balloon) for 12 h. The mixture was then filtered through celite and washed with 25% CH_2Cl_2 in MeOH (20 mL) followed by EtOAc (10 mL), and the filtrates were concentrated to give **49** (0.930 g) as a white solid. The solid was triturated with 10% MeOH-EtOAc (20 mL) in a warm water bath for 30 min and then cooled to 0 °C to give **49** (0.854 g) as a colorless solid. **Yield**: 97%; colorless solid; **mp**: 215-217 °C {lit.[7b] mp: 214-217 °C}; **$[\alpha]^{25}_D$**: -21.7 (*c* 1, DMSO) {lit.[7b] $[\alpha]^{25}_D$: -22.0 (*c* 0.948, DMSO)}; **IR** ($CHCl_3$, cm^{-1}): 1237, 1517, 1656, 1742; **^{1}H NMR** (200 MHz, $CDCl_3$ + MeOH-d_4): δ 2.01 (s, 3H), 3.20 (s, 8H), 3.57 (dd, *J* = 14.6, 5.7 Hz, 1H), 3.65 (dd, *J* = 11.27, 3.43 Hz, 1H), 3.76 (dd, *J* = 9.27, 6.73 Hz, 1H), 4.04 (t, *J* = 9.16 Hz, 1H), 4.77 (m, 1H), 6.96 (t, *J* = 9.16 Hz, 1H), 7.07 (dd, *J* = 11.52, 9.63 Hz, 1H), 7.45 (dd, *J* = 14.23, 2.57 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): 23.34, 42.13, 45.72, 48.43, 59.37 (d, *J* = 2.20 Hz), 67.06, 107.27 (d, *J* = 25.98 Hz), 113.74 (d, *J* = 3.30 Hz), 119.21 (d, *J* = 4.02 Hz), 127.71, 133.12 (d, *J* = 10.62 Hz), 136.11 (d, *J* = 9.15 Hz), 154.36, 155.31 (d, *J* = 246.27 Hz), 172.34; **MS**: *m/z* 336 (62.4, M+), 294 (100), 250 (24.5), 56 (24.5), 29 (19.6); **Analysis**: $C_{16}H_{22}ClFN_4O_3$ requires C, 51.54; H, 5.95; Cl, 9.51; F, 5.10; N, 15.03%; found C, 51.68; H, 5.87; Cl, 9.56; F, 5.03; N, 15.09%.

(*S*)-*N*-[[3-[3-Fluoro-4-[*N*-1-[(4-benzyloxy)acetyl]piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (50):

To a suspension of **49** (0.854 g, 2.3 mmol) in CH_2Cl_2 (40 mL) at 0 °C were added Et_3N (0.72 mL, 7.08 mmol) and then (benzyloxy)-acetyl chloride (0.56 mL, 3.54 mmol), dropwise over 3 min. The homogeneous mixture was stirred at 0 °C for 2 h

and then at 25 °C for 2.5 h. It was then washed with water (2 × 5 mL), and the combined aqueous layers were extracted with CH_2Cl_2 (20 mL). EtOAc (20 mL) was added to the combined organic layers to provide a homogeneous mixture, which was dried over anhyd. Na_2SO_4 and concentrated to give the crude product, which was purified by column chromatography packed with silica gel using MeOH : EtOAc (1:9) to give **50** (1.1 g) as a colorless solid.

Yield: 99%; colorless solid; **mp**: 164-165 °C; **$[\alpha]^{25}_D$**: -26.3 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 1227, 1521, 1643, 1673, 1757; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.42 (s, 3H), 3.02 (s, 4H), 3.66-3.83 (m, 5H), 3.90 (t, *J* = 7.58 Hz, 1H), 4.06-4.11 (m, 1H), 4.15 (t, J = 2.91 Hz, 1H), 4.22 (s, 2H), 4.59 (s, 2H), 4.62 (s, 2H), 4.76-4.89 (m, 1H), 6.90 (t, *J* = 9.10 Hz, 1H), 7.08 (dd, *J* = 8.84, 1.90 Hz, 1H), 7.31-7.37 (m, 5H), 7.45 (dd, *J* = 14.15, 2.53 Hz); **^{13}C NMR** (50 MHz, $CDCl_3$): 25.39, 41.68, 45.08, 47.80, 50.26, 69.35, 71.37, 73.11, 107.28 (d, *J* = 26.35 Hz), 113.70 (d, *J* = 3.29 Hz), 119.33 (d, *J* = 4.03 Hz), 127.89, 128.37, 133.08 (d, *J* = 10.61 Hz), 135.94 (d, *J* = 9.14 Hz), 136.99, 137.03, 153.48, 155.39 (d, *J* = 246.64 Hz), 167.61, 172.99; **MS**: *m/z* 484 (86.2, M+), 440 (30.1), 306 (66.1), 91 (100), 56 (72); **Analysis**: $C_{26}H_{30}FN_3O_5$ requires C, 64.58; H, 6.25; F, 3.93; N, 8.69%; found C, 64.71; H, 6.31; F, 3.89; N, 8.61%.

(*S*)-*N*-[[3-[3-Fluoro-4-[*N*-1-(4-hydroxyacetyl)piperazinyl]-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (6, U-100592):

A mixture of **50** (1.06 g, 2.2 mmol) and 10% Pd/C (0.280 g) in 33% (v/v) CH_2Cl_2-MeOH (60 mL) was stirred under hydrogen (1 atm., balloon) for 12 h, filtered over celite, and concentrated under reduced pressure to give a solid, which was purified by column chromatography packed with silica gel using MeOH-CH_2Cl_2 (1:10) as a eluent to afford eperezolid (U-100592, **6**) (0.77 g) as a colorless solid.

Yield: 89%; colorless solid; **mp**: 175-176 °C {lit.[7b] mp: 175-176 °C}; **$[\alpha]^{25}_{D}$**: -20.8 (*c* 1, DMSO) {lit.[7b] $[\alpha]^{25}_{D}$: -21.0 (*c* 0.853, DMSO)}; **IR** ($CHCl_3$, cm^{-1}): 1239, 1520, 1647, 1730, 3295, 3453; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.16 (s, 3H), 3.05 (t, J = 4.80 Hz, 4H), 3.45 (t, J = 4.42 Hz, 2H), 3.63-3.86 (m, 5H), 4.03 (t, J = 8.97 Hz, 1H), 4.22 (s, 2H), 4.73-4.85 (m, 1H), 6.84 (t, J = 5.94 Hz, 1H), 6.91 (t, J = 8.97 Hz, 1H), 7.09 (dd, J = 8.72, 1.64 Hz, 1H), 7.46 (dd, J = 14.15, 2.40 Hz); **^{13}C NMR** (50 MHz, $CDCl_3$ + DMSO-d_6): 18.94, 39.77, 45.85, 48.72, 60.71, 69.78, 105.41 (d, J = 24.95 Hz), 112.33, 117.89, 132.20 (d, J = 11.52 Hz), 133.80 (d, J = 9.60 Hz), 152.45, 153.42 (d, J = 245.69 Hz), 166.40, 168.11; **MS**: *m/z* 394 (65.6), 350 (88.3), 306 (72.4), 266 (42.6), 56 (100); **Analysis**: $C_{18}H_{23}FN_4O_5$ requires C, 54.82; H, 5.88; F, 4.82; N, 14.21%; found C, 54.65; H, 5.93; F, 4.97; N, 14.15%.

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Chapter III

Enantioselective Synthesis of (S)-Timolol via Kinetic Resolution of Terminal Epoxides and Dihydroxylation of Allylamines

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"Enantioselective synthesis of (*S*)-timolol via kinetic resolution of terminal epoxides and dihydroxylation of allylamines" Narina V. Srinivasarao and Arumugam Sudalai, *Tetrahedron* **2007**, in press.

Enantioselective Synthesis of (*S*)-Timolol *via* Kinetic Resolution of Terminal Epoxides and Dihydroxylation of Allylamines

3.1 Introduction

β-Adrenergic blockers (**1-7**) were first reported to be useful for the treatment of glaucoma in 1967.[1] In 1978 timolol (**1**) was approved for market use, and since that time, it has become very popular with ophthalmologists as an effective antiglaucoma agent. The members of a pair of enantiomers often show different pharmacological and metabolic characteristics. The synthesis of homochiral drugs has become a key issue not only in academic research but also in the pharmaceutical industry.[2] Biological systems, in most cases, recognize the members of a pair of enantiomers as different substances, and the enantiomers will exhibit different responses. Thus, one enantiomer may act as a very effective therapeutic drug whereas the other enantiomer is highly toxic. It has been shown for many pharmaceuticals that only one enantiomer contains all the desired activity, and the other is either totally inactive or highly toxic.

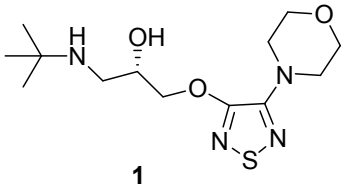

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Fig. 1: Timolol (1)

There are several methods to obtain enantiomerically pure materials, which include classical resolution *via* diastereomers, chromatographic separation of enantiomers, enzymatic resolution, chiral kinetic resolution and asymmetric synthesis.

3.2 β-Adrenergic Blockers

β-Adrenoreceptor antagonists are a group of compounds that competitively inhibit the effects of catecholamines at β-adrenergic receptors.[3] These agents are used widely in clinical medicine for the treatment of various conditions including hypertension,[4] angina pectoris,[5] cardiac arrhythmias,[6] hypothyroidism[7] and glaucoma.[8] As the β-adrenoreceptor antagonists (β-blockers) have such a diverse range of clinical applications, the synthesis of these drugs becomes crucial. Most of the *β*-blockers possess a general structure Ar-O-$CH_2CH(OH)CH_2NHCH(CH_3)_2$ (**Fig. 2**) and have been used in the form of racemic mixtures.[9]

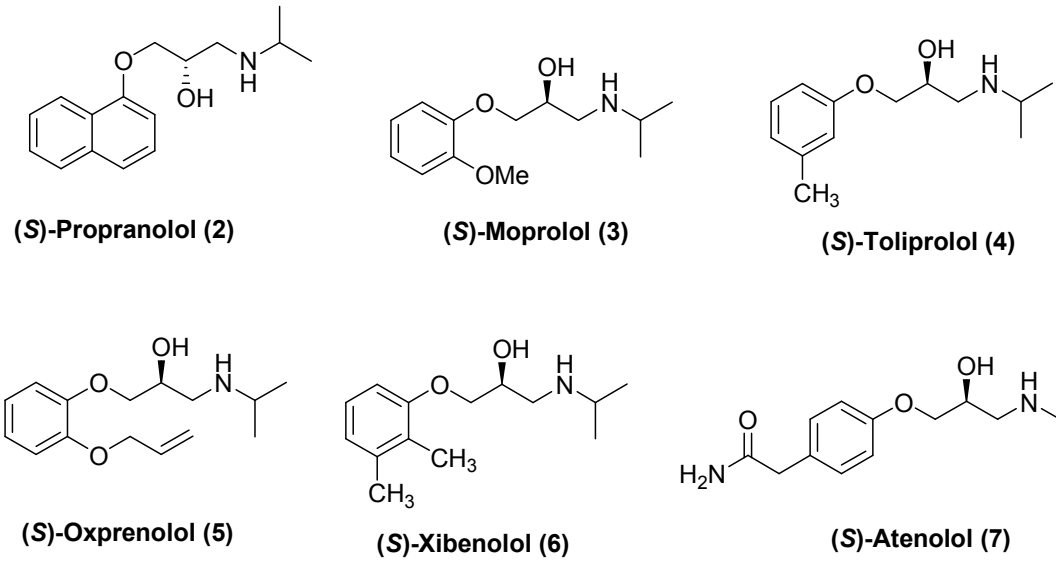


Fig. 2: Structures of various β-blockers

Three fundamental goals of cardiovascular drugs are: the lowering of blood pressure (antihypertensive), return of the heart to rhythmic beating (antiarrhythmics) and the general improvement of the heart muscle tone (cardiotonics).[10] Biochemically, the mechanism of action involves the adrenergic system in which the hormonal system provides the communication link between the sympathetic nervous system and involuntary muscle.[11] There are four types of receptors for these molecules *α1*, *α2*, *β1*

and *β2*. Blocking of *β*-receptor system reduces the overall activity of the sympathetic nervous system. Agents, which are *β*-blockers, are thus used to increase life expectancy after the heart attack. Although (*S*)-isomers are known to be much more effective (100-500 fold) than the (*R*)-isomer,[12] these antihypertensive drugs are presently sold as racemic mixtures. To avoid unnecessary stress or in some case toxicity to an organism caused by the (*R*)-isomers, the administration of optically pure (*S*)-isomer is desirable. The aromatic portion of these compounds is either Ph, naphthyl, or an aromatic ring fused to a 5-membered heterocyclic system containing N and S. Pharmacological investigation has demonstrated that certain members of this series possessed β-adrenergic blocking properties and one of them, maleate salt of timolol (**1**), received detailed pharmacological evaluation. Thus timolol or (S)-1-[(l,l-dimethylethyl)amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3yl]oxy]-2-propanol **(l),** is a non-selective β-adrenergic blocker, and its 1: 1 maleate salt is currently the number one choice in the treatment of glaucoma and ocular hypertension.[13]

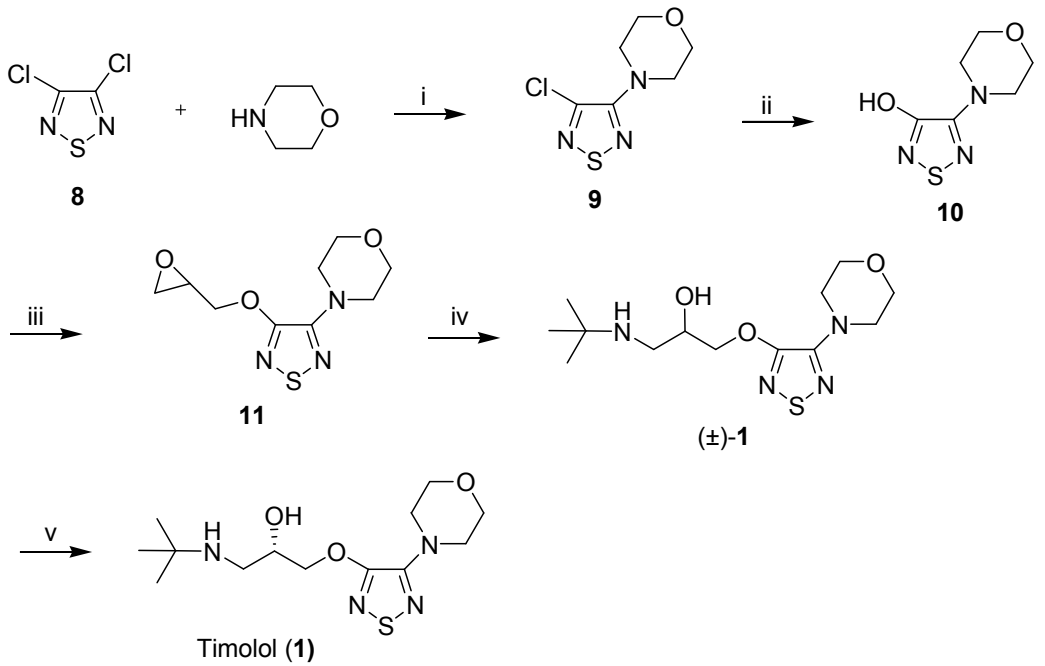
3.3 Review of Literature

Literature search revealed that there are few reports available for the synthesis of timolol (**1**).[14-18] They are concerned mostly with resolution, chemo-enzymatic or enantioselective synthesis, which are described below.

Frosst's approach (1969)[14]

The key step in this approach was the classical resolution of racemic timolol ((±)-**1**) with (+)-tartaric acid. Halo compound **9**, obtained by the coupling of 1,2,5-thiadiazole with morpholine, was converted into hydroxy compound **10** under basic conditions. The racemic timolol ((±)-**1**) was prepared by the *O*-alkylation of 3-hydroxy-4-(*N*-morpholino)-1,2,5-thiadiazole (**10)** with epichlorohydrin in excellent yield and was

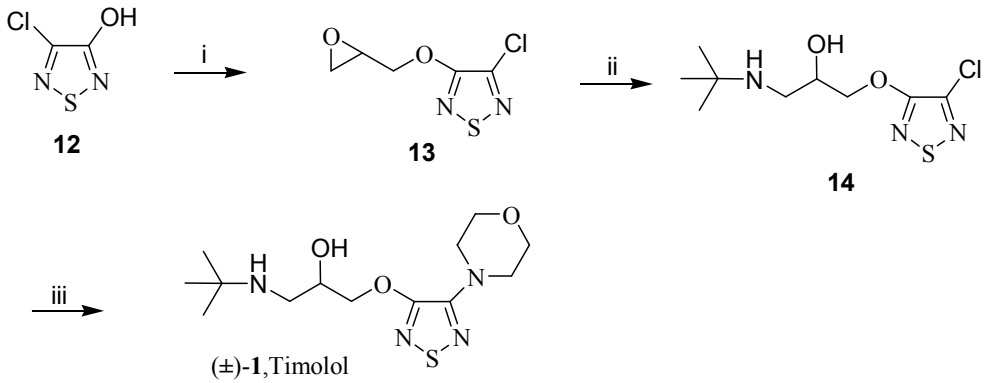
subjected to resolution with (+)-tartaric acid to afford chiral timolol (**1**) in 46% yield and 99% ee.



Scheme 1: (i) morpholine, 105-110 ºC, 2 h, 97%. (ii) 2.5 N NaOH, DMSO, 3 h, 95%. (iii) epichlorohydrin, NaOH, THF, 80%. (iv) *tert*-$BuNH_2$, reflux, 30 h, 66%. (v) 0.5 equiv. (+)-tartaric acid

Wasson's approach (1972)[15]

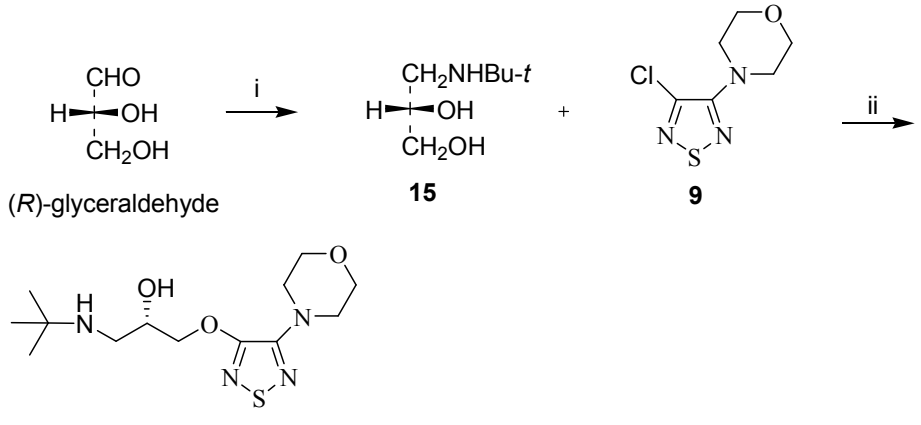
In this approach, racemic timolol ((±)-**1**) was prepared as shown in **Scheme 2**. Thus, epoxide **13** was obtained directly by *O*-alkylation of hydroxy compound **12** with epichlorohydrin. Regiospecific ring opening of the epoxide **13** with *tert*-butylamine afforded **14**, which was heated at 125-135 ºC in morpholine to give racemic timolol ((±)-**1**).



Scheme 2: (i) epichlorohydrin, K_2CO_3, acetone, 25 ºC, 12 h, 75%. (ii) *tert*-$BuNH_2$, 60-70 ºC, 2.5 h, 50%. (iii) morpholine, 125-135 ºC, 4 h.

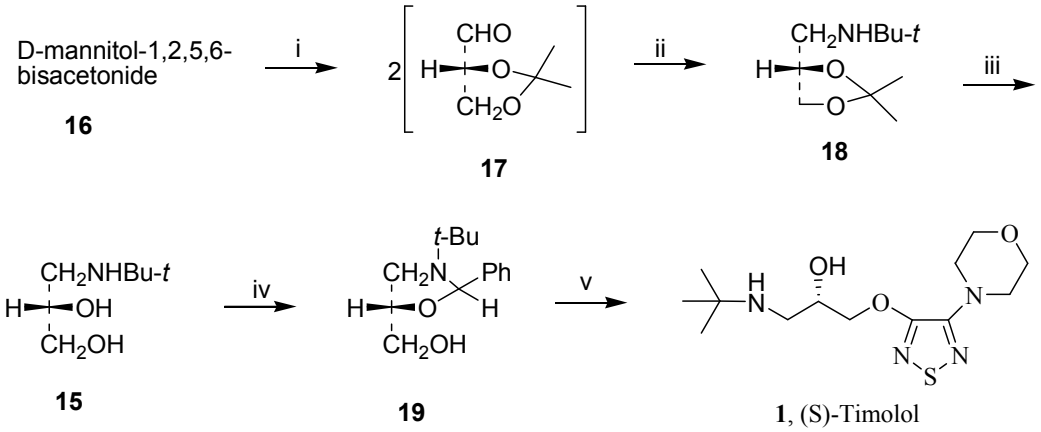
Weinstock's approach (1976)[16]

Weinstock *et al.* have reported the synthesis of (*S*)-timolol from optically active precursors (**Scheme 3**). Catalytic hydrogenation of (*R*)-glyceraldehyde over palladium in the presence of *tert*-butylamine produced (*S*)-3-*tert*-butylamino-1,2-propanedio1 (**15**). This, in turn, was condensed with 3-chloro-4-(*N*-morpholino)-1,2,5-thiadiazole (**9**) in the presence of potassium *tert*-butoxide to afford a low yield of optically pure timolol (**1**), isolated as the levorotatory maleate salt. This procedure was short but suffered from two shortcomings: low yields and the commercial unavailability of glyceraldehyde.



Scheme 3: (i) *t*-$BuNH_2$, H_2 (1 atm.), Pd/C, 24 h, 54%. (ii) t-BuOK, anhyd. *t*-BuOH, 13%.

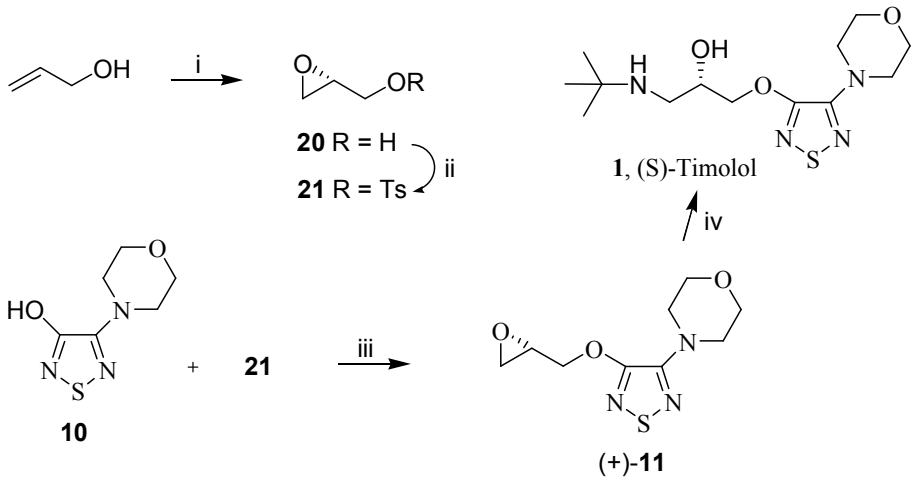
In order to increase the yield of (*S*)-timolol, the secondary alcohol in **15** was protected with benzaldehyde to give oxazolidine **19** (**Scheme 4**). The oxazolidine **19** was obtained in three steps of (i) diol cleavage of **16**, (ii) imine formation of **17** with *tert*-butylamine and (iii) reduction of imine. Reaction of **19** with 3-chloro-4-(*N*-morpholino)-1,2,5-thiadiazole (**9**) in the presence of potassium *tert*-butoxide followed by acid hydrolysis gave (*S*)-timolol (**1**) in 50% yield.



Scheme 4: (i) $Pb(OAc)_4$, CH_2Cl_2, 90%. (ii) t-$BuNH_2$, H_2 (1 atm), Pd/C, 24 h, 92%. (iii) HCl, MeOH, 2 h, 85%. (iv) benzaldehyde, 150 ºC, 77%. (v) (a) **9**, t-BuOK, anhyd. *t*-BuOH. (b) HCl, MeOH, 2h, 50%.

Sharpless' approach (1989)[17]

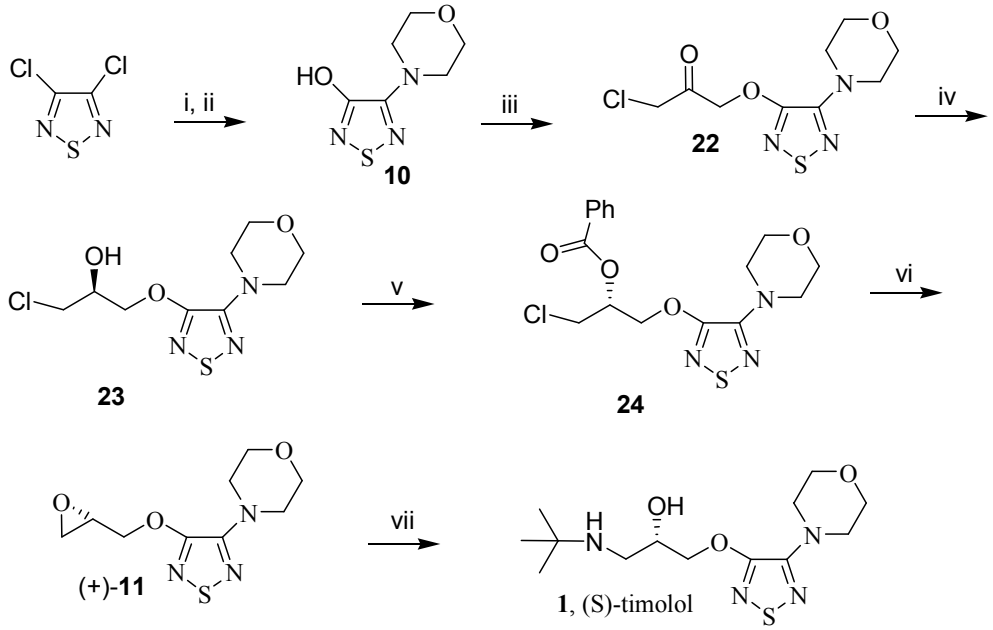
The key step in this approach was Sharpless epoxidation of allylic alcohol to give chiral epoxide **20** in 88% ee. Alcohol in epoxide **20** was tosylated using $(MeO)_3P$, $ArSO_2Cl$ and Et_3N to give the tosylate **21**. Regioselective nucleophilic displacement of **21** by phenol **10** using NaH gave chiral epoxide (+)-**11**. Finally, the chiral epoxide **11** was subjected to regiospecific ring opening with *tert*-butylamine to afford (*S*)-timolol (**1**) in 88% ee (**Scheme 5**).



Scheme 5: (i) $Ti(O^iPr)_4$ (5%), (-)-DIPT (6%), cumene hydroperoxide (2 equiv.), 3Å mol sieves, CH_2Cl_2, 0 ºC. (ii) (a) $(MeO)_3P$. (b) *p*-TsCl, Et_3N. (iii) NaH, DMF, 72%. (iv) *tert*-$BuNH_2$, reflux, 30 h, 66%.

Prati's approach (2004)[18]

The key step in this approach was the asymmetric reduction of the haloketone **22** with baker's yeast as a biocatalyst to afford the halohydrin **23** in 87% ee (**Scheme 6**).



Scheme 6: (i) morpholine, 98%. (ii) 2.5 M NaOH, DMSO, 93%. (iii) dichloroacetone, $NaHCO_3$, DMF, 80%. (iv) baker's yeast, H_2O, 57–74%. (v) PhCOOH, PPh_3, DEAD, THF, 90%. (vi) *t*-BuOK, THF, 97%. (vii) *t*-$BuNH_2$, 66%.

Reaction of **10** with dichloroacetone in dry DMF gave mono-substituted product *i.e.* haloketone **22** in 80% yield. The chiral centre in alcohol **23** was inverted using

Mitsunobu conditions to give the benzoate **24** in 90% yield. Finally, the chiral epoxide **11** was subjected to regiospecific ring opening with *tert*-butylamine to afford (*S*)-timolol (**1**) in 66% yield and in 87% ee.

3.4 Present Work:

3.4.1 Objective

All of the syntheses described in the literature for (*S*)-timolol make use of C_3-synthons such as epichlorohydrin, glycidol and related chirons and chemo-enzymatic approaches. The main drawback of these synthetic methods is the loss of one-half of the expensive 1,2,5-thiadiazole unit during the kinetic resolution step, coupled with low enantiomeric excess of (*S*)-timolol often obtained. In this context, a more practical approach for the synthesis of (*S*)-timolol is highly desirable.

Retrosynthetic analysis (**Fig. 3** and **4**) of (*S*)-timolol (**1**) reveals that either hydroxy oxazolidinone **31** (**Fig. 3**) or epoxide **35** (**Fig. 4**) could be visualized as key intermediates.

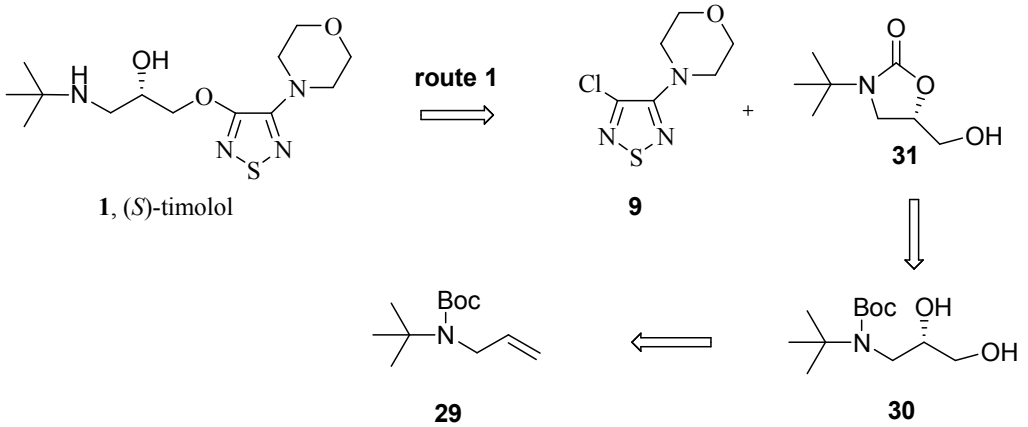


Fig. 3: Retrosynthetic analysis of (*S*)-timolol (1) *via* AD approach

Thus, the key intermediate **31**, can be synthesized using asymmetric dihydroxylation (AD)[19] *via* chiral diol **30** (route 1, **Fig. 3**). On the other hand, the key intermediate **35** can be synthesized by the methods of hydrolytic kinetic resolution (HKR)[20] of racemic epoxide **34** (route 2, **Fig. 4**) and by enantioselective ring opening of epoxides

with phenolic compounds[21] as the chiral inducing steps (route 3, **Fig. 4**). This chapter describes the asymmetric synthesis of (*S*)-timolol (**1**) from **31** and **35** by employing both the AD and kinetic resolution methods (see C**hapter 1** for its introduction) (**Schemes 9**, **10** and **11**).

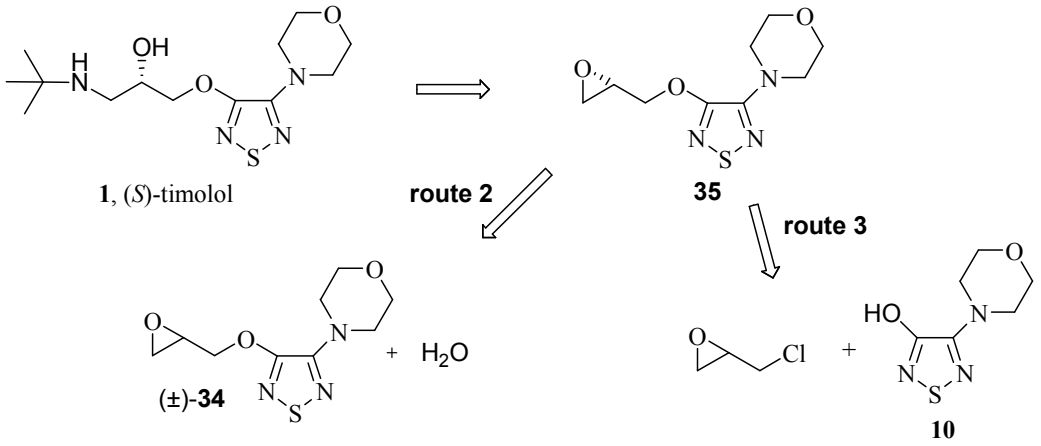


Fig. 4: Retrosynthetic analysis of (*S*)-timolol (1) *via* kinetic resolution approach

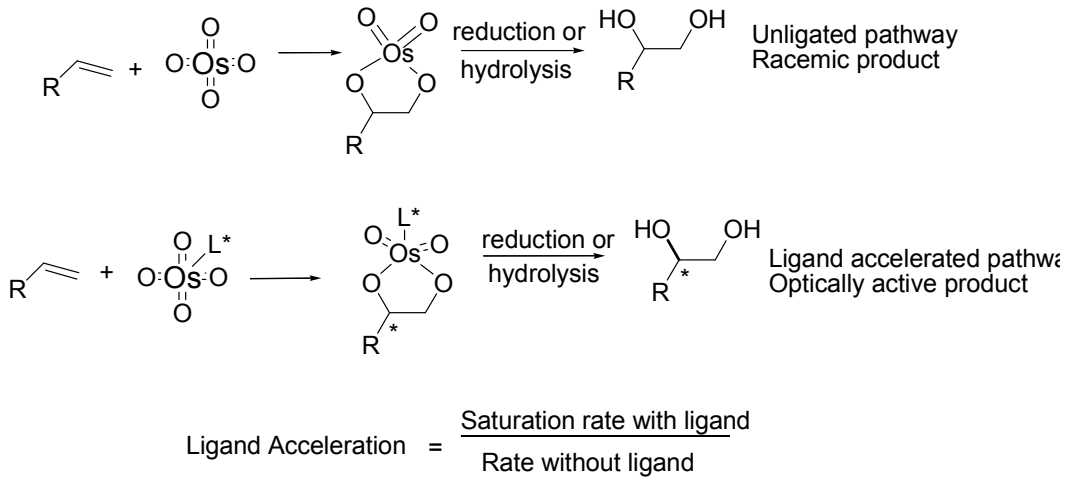
Since this chapter deals with two important asymmetric reactions (AD and kinetic resolutions), which introduce stereogenicity into the prochiral molecule, a brief account of AD is presented in the following sections.

3.4.2 Asymmetric Dihydroxylation (AD):

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.[22] 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).[23] Among all these reactions, Sharpless Catalytic Asymmetric Dihydroxylation (AD) is one of the most important practical and widely used reaction 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.[24]

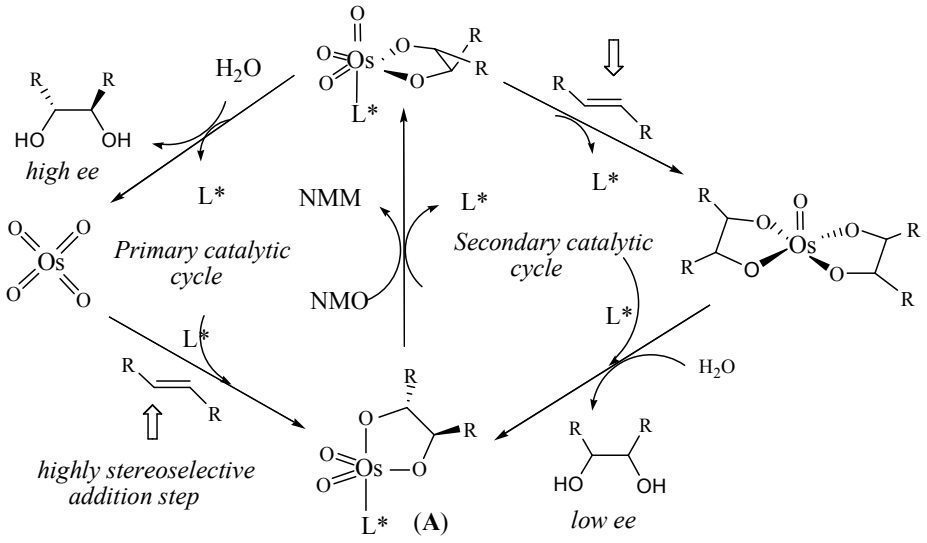
In 1936, Criegee *et al.*[25] have found that addition of pyridine or any other tertiary amine to osmylation of olefins, accelerates the rate of reaction considerably. A major breakthrough has occurred in the field of asymmetric oxidation when Sharpless *et al.*[24b] demonstrated that asymmetric induction 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).[26]



Scheme 7: Mechanism of OsO_4-catalyzed dihydroxylation of olefin

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 7**. In order to develop a catalytic method, several co-oxidants such as sodium or potassium chlorate,[27] hydrogen peroxide,[28] *tert*-butyl hydroperoxide[29] and *N*-methylmorpholine *N*-oxide (NMO)[30] were introduced. 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.



Scheme 8: Catalytic cycle for AD using NMO as co-oxidant.

Sharpless *et al.*[31] 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, **Scheme 8**). The reason was thought to be the involvement of second catalytic cycle (secondary catalytic cycle, **Scheme 8**), 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 $K_3Fe(CN)_6$ as reoxidant and using biphasic conditions **(Fig. 5)**.[22]

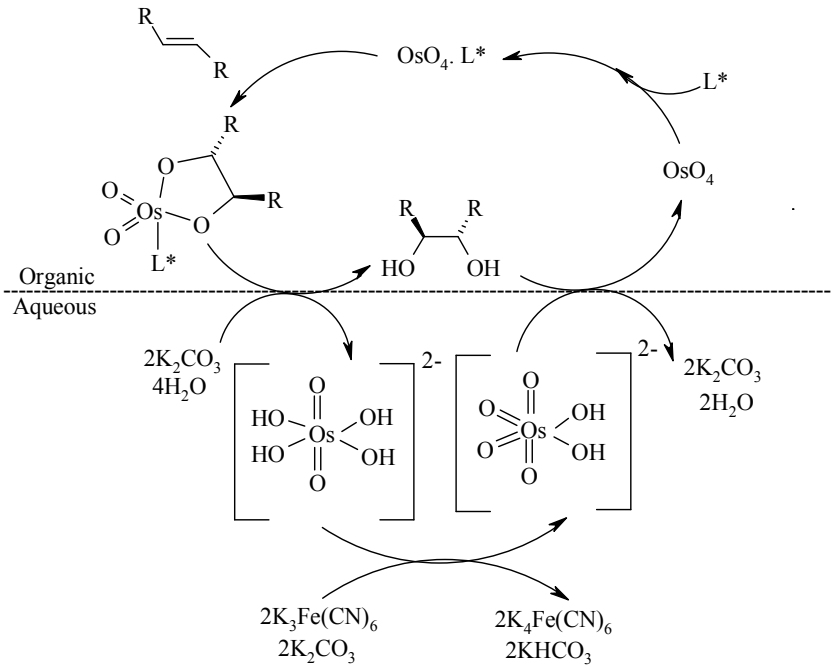


Fig. 5: Catalytic cycle for AD using $K_3Fe(CN)_6$ as co-oxidant.

These conditions helped in protecting the organic osmate-(VI) monoglycolate ester (species **A**, **Scheme 8**) 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 AD 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.[22] Addition of methyl sulfonamide also allowed carrying out the reactions of 1,2-di- tri- 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 AD 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 **25** or DHQD **26** ethers of phthalazine-1, 4-

diol have proven to be the best for obtaining high enantioselectivities of the chiral diols[32] **(Fig. 6)**.

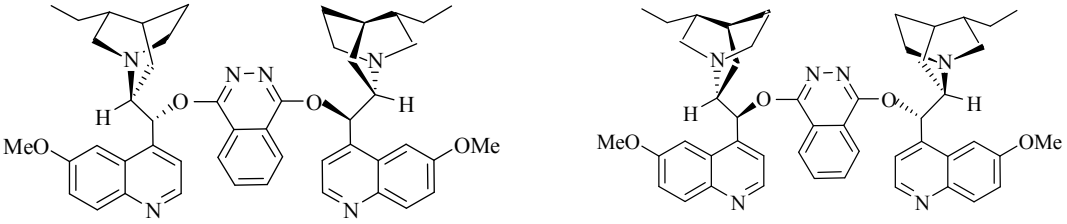


Fig. 6: Ligands for asymmetric dihydroxylation reaction

Studies have demonstrated the importance of enzyme-like binding pocket of the dimeric cinchona alkaloid for high enantioselectivity of the chiral diols.[32,33] Sharpless *et al*.[24] have shown that the facial selectivity for both ligands **25** and **26** is different, based on their ability to induce the ee into the diols. This observation has led to the development of mnemonic model **(Fig. 7)** 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.

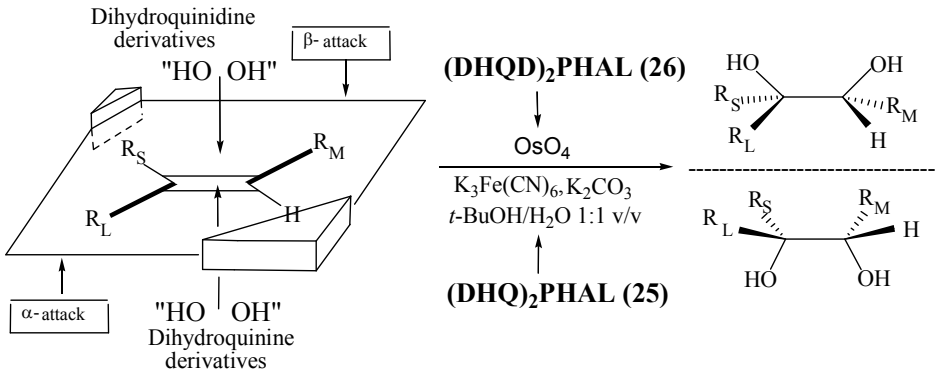
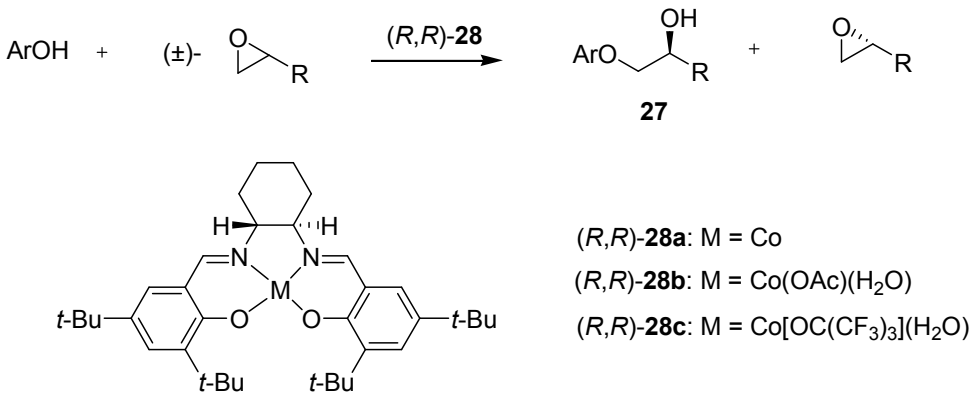


Fig. 7: Enantioselectivity mnemonic scheme

3.4.3 kinetic resolution of terminal epoxides *via* highly enantioselective ring opening with phenols:

Enantiopure α-aryloxy alcohols **27** are valuable targets for asymmetric synthesis as a result of their role as key synthetic intermediates in a variety of pharmaceutically important compounds.[34] In principle, access to these building blocks may be provided by several routes, including asymmetric reduction of aryloxy ketones[35] 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.



Scheme 8a: Kinetic resolution of terminal epoxides with phenols

The ready accessibility of terminal epoxides in racemic form renders kinetic resolution of terminal epoxides with phenols a potentially attractive route to **27** (**Scheme 8a**). The high selectivities obtained in the recently reported hydrolytic kinetic resolution of terminal epoxides with catalyst **28b**[20a] 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 with the isolation of 1-aryloxy 2-alcohols **27** in high ee's and yields. Reaction of 2.2 equiv of (±)-epoxide with phenol (ArOH) in the presence of (salen)Co(OAc) complex **28b** (0.044 equiv) in *tert*-butyl methyl ether (TBME) leads to good conversion of

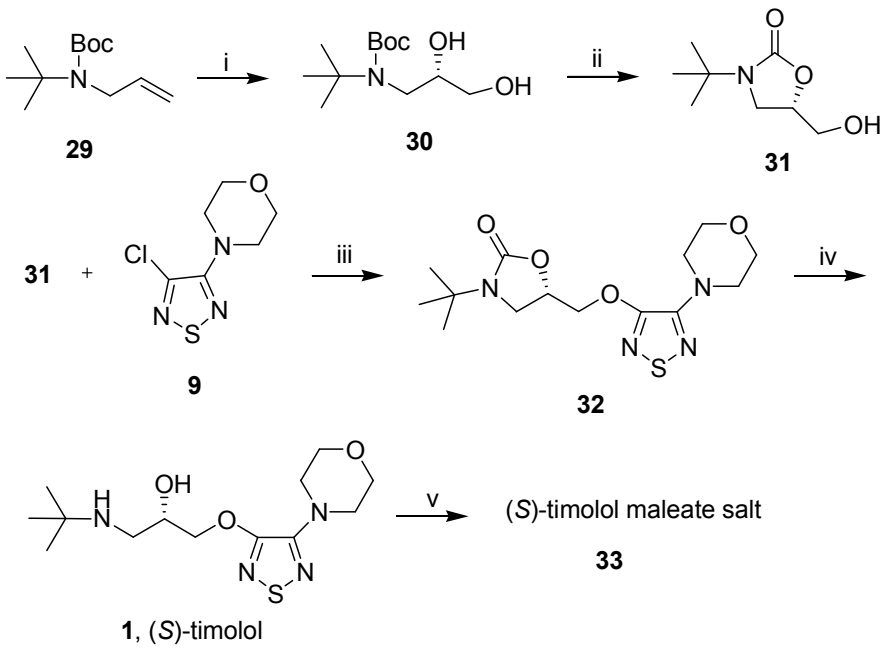
phenol after 55 h at room temperature, with 1-aryloxy 2-alcohols (**27**) generated in 94% ee. The use of complex **28c** under conditions otherwise identical to those outlined above resulted in 80% conversion of phenol in 18 h and formation of 1-aryloxy 2-alcohols **27** as the major product in 96% 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 Å molecular sieves in the reaction mixture.

3.5 Results and Discussion:

The retrosynthetic analyses envisaged for (*S*)-timolol (**1**) are shown in **Fig. 3** and **Fig. 4**. As can be seen, chiral 1,2-diol **30** and chiral epoxide **35** emerge as the key intermediates in the synthesis of (*S*)-timolol (**1**). Thus, route 1 envisages asymmetric didroxylation (AD) (**Scheme 9**), while routes 2 and 3 envisage kinetic resolution (HKR) (**Schemes 10** and **11**) constituting key reactions in introducing chirality into the molecule.

Asymmetric dihydroxylation (route 1):

The synthetic strategy for (*S*)-timolol (**1**) is shown in **Scheme 9**, wherein Os-catalyzed asymmetric dihydroxylation (AD) of olefin **29** constitutes a key step in introducing chirality into the molecule (**Scheme 9**). For the synthesis of (*S*)-timolol, the starting material, *N*-*tert*-butylallylamine (**29**) was readily prepared in 90% overall yield *via* protection of *tert*-butylamine with $(Boc)_2O$, followed allylation with allylbromide in the presence of NaH. Allyl amine **29** was confirmed by the ^{1}H-NMR spectrum, which showed characteristic doublet of doublets at δ 5.15 and 5.17 and a multiplet at δ 5.83 for olefinic protons. Allyl amine **29** was then subjected to Os-catalyzed asymmetric dihydroxylation using $(DHQ)_2$-PHAL as ligand to produce the corresponding chiral diol **30** in 93% yield $\{[\alpha]^{25}_D = -2.90$ (c 2, EtOH)$\}$.



Scheme 9: (i) cat. OsO_4, $(DHQ)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, *tert*-BuOH:H_2O (1:1), 0-25 ºC, 24 h, 93%, 56% ee. (ii) K_2CO_3 , MeOH, reflux, 5 h, 95%. (iii) KO*t*-Bu, *t*-BuOH, 25 ºC, 12 h, 75%. (iv) 2N NaOH, MeOH, 90%. (v) Maleic acid, THF, 25 ºC, 1 h, 85%.

The formation of diol **30** was confirmed by the appearance of proton signals in the region δ 3.31-3.60 for methine and methylene protons in its ^{1}H-NMR spectrum (**Fig. 8b**).

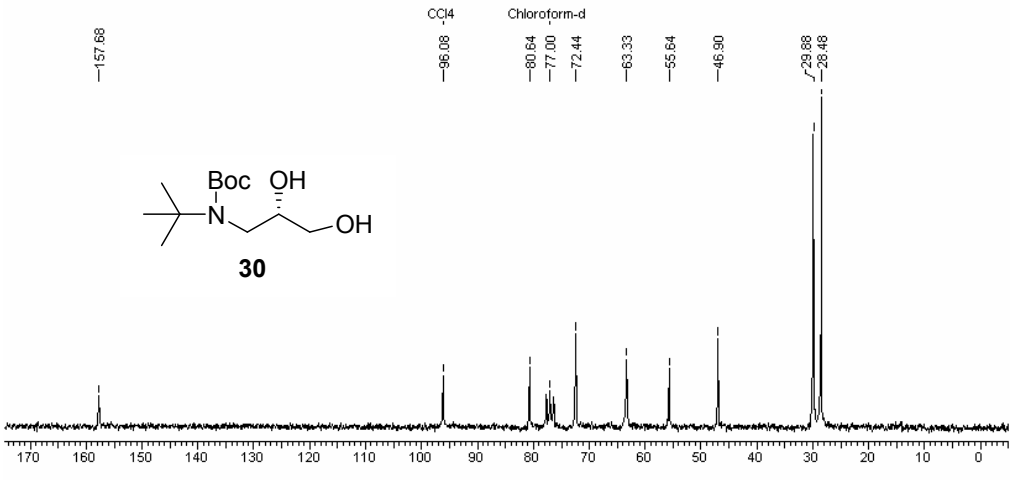


Fig. 8a: ^{13}C NMR spectrum of 30

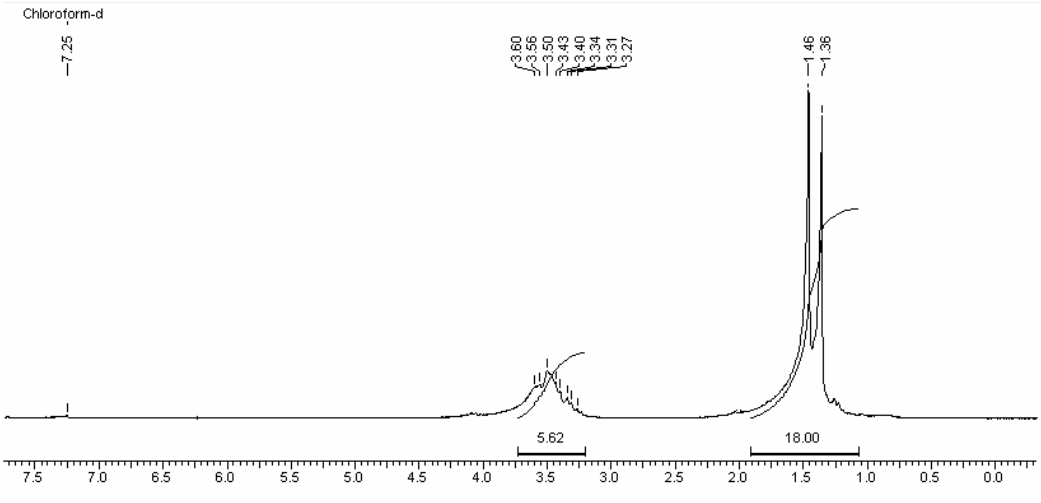


Fig. 8b: ^{1}H NMR spectra of 30

Further, its ^{13}C-NMR spectrum showed signals at δ 63.3 and 55.6 due to the two carbons bearing the OH functions (**Fig. 8a**). Several attempts to prepare the cyclic sulfate[37] from the diol **30** have failed probably due to its unstable nature. However, when the diol **30**, was subjected to treatment with K_2CO_3 in MeOH under reflux, 2-oxazolidinone **31**[19a] was obtained in 95**%** yield and 56% ee. The formation of oxazolidinone **31** was confirmed by the disappearance of singlet at δ 5.13 due to Boc-*t*-butyl protons in its ^{1}H NMR spectrum. The signal at δ 154.87 confirms the presence of oxazolidinone carbonyl in its ^{13}C NMR spectrum. The optical purity of the 2-oxazolidinone **31** was determined from its ^{1}H NMR analysis of its Mosher ester **38**, which showed the enantiomeric excess to be 56% (see experimental section). Oxazolidinone **32** was obtained by *O*-alkylation of the hydroxy compound **31** with 3-chloro-4-(*N*-morpholino)-1,2,5-thiadiazole (**9**)[16]. The ^{1}H NMR spectrum of **32** showed two broad singlets at δ 3.48 and 3.75 indicating the presence of morpholine ring. Its ^{13}C NMR spectrum showed a signal at δ 27.3 confirming the presence of *tert*-butyl moiety (**Fig. 9**).

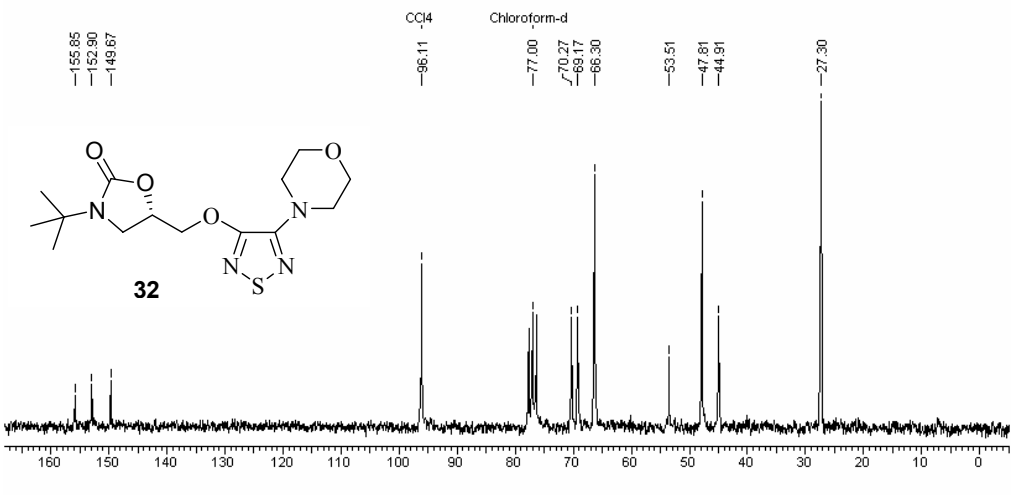


Fig. 9: ^{13}C NMR spectrum of 32

Oxazolidinone **32** was then hydrolyzed using 1N NaOH in methanol[37] to furnish (*S*)-timolol (**1**) in 90% yield. The formation of (*S*)-timolol (**1**) was confirmed by the appearance of a broad singlet at δ 2.09 for NH-proton in its ^{1}H-NMR spectrum (**Fig. 10b**). Its mass spectrum showed the molecular ion peak at *m/z* 316 confirming the formation of (*S*)-timolol (**1**). Further, the formation of (*S*)-timolol (**1**) was confirmed by the disappearance of carbonyl peak in its ^{13}C NMR spectrum (**Fig. 10a**).

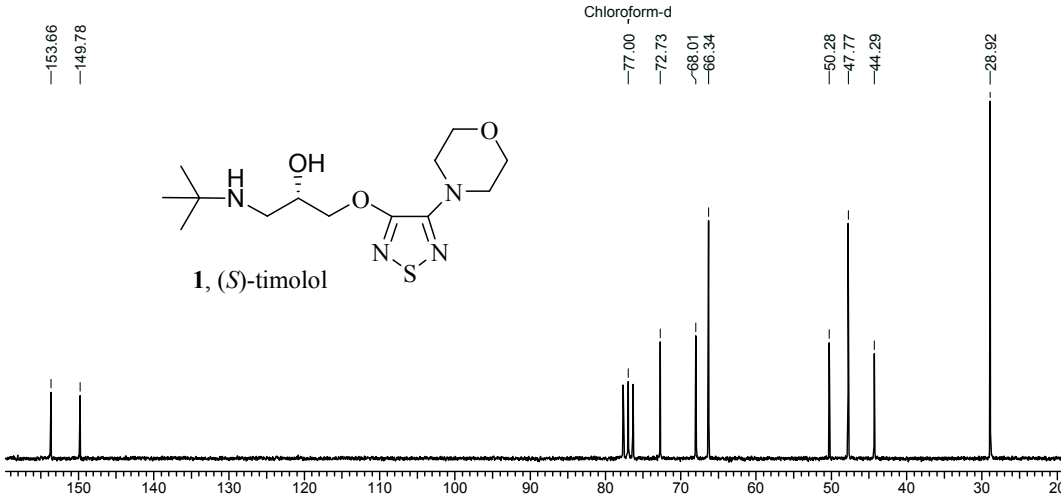


Fig. 10a: ^{13}C NMR spectrum of (*S*)-timolol (1)

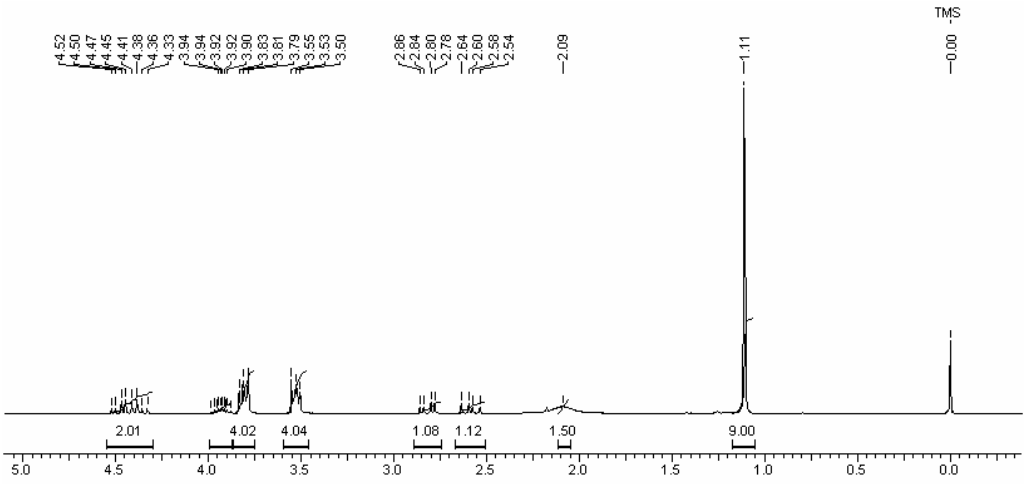
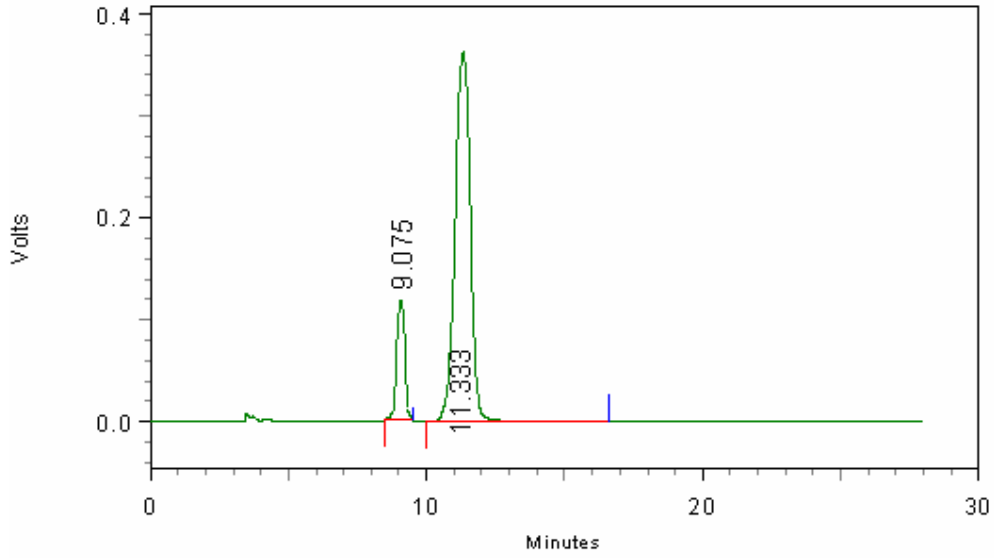


Fig. 10b: ^{1}H NMR spectrum of (*S*)-timolol (1)

(*S*)-Timolol was then isolated as the levorotatory maleate salt **33** {$[\alpha]_D$ = -6.45 (*c* 4, 1 N aq. HCl); lit.[16] $[\alpha]_D$ = -11.52 (c 4, 1 N aq. HCl)} in 85% yield and 56% ee (measured by both chiral HPLC using OD-H column (**Fig. 11**) and $[\alpha]_D$).



Peak No.	Retention Time	Area (µV-sec)	Area (%)
1	9.075	2109616	22.01
2	11.339	7473017	77.98

Fig. 11: HPLC chromatogram of (*S*)-timolol maleate salt 33

The ^{1}H NMR spectrum of (*S*)-timolol maleate salt (**33**) showed a singlet at δ 6.01 for olefinic protons and broad singlet at δ 8.36 indicating the presence of maleic acid moiety (**Fig. 12**). Its ^{13}C NMR spectrum of exhibited peaks at δ 136.08 and 167.5 due to the olefinic and carboxylic acid carbons of maleic acid respectively (**Fig. 12**). The analytical and spectroscopic data of (*S*)-timolol maleate salt (**33**) were in complete agreement with the reported values.[16]

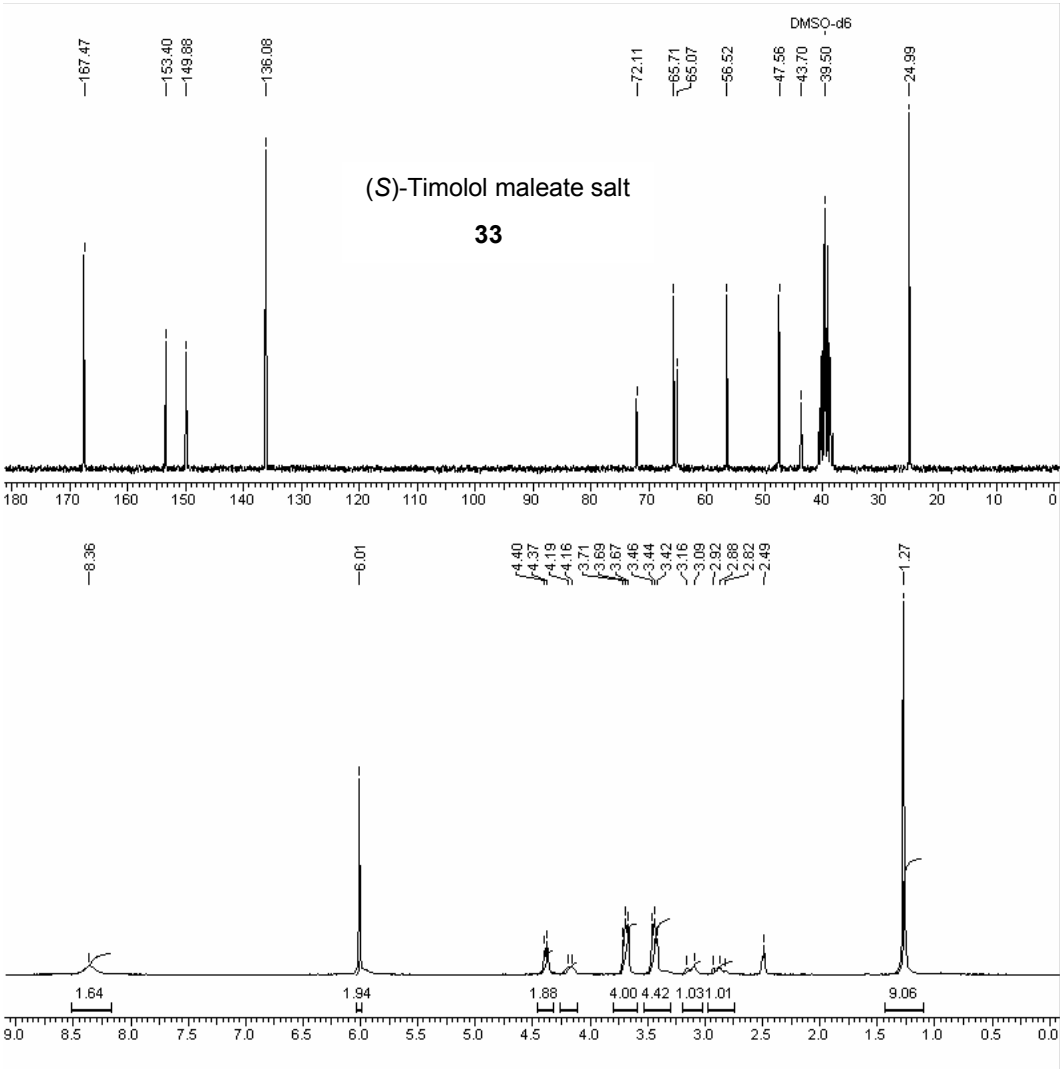


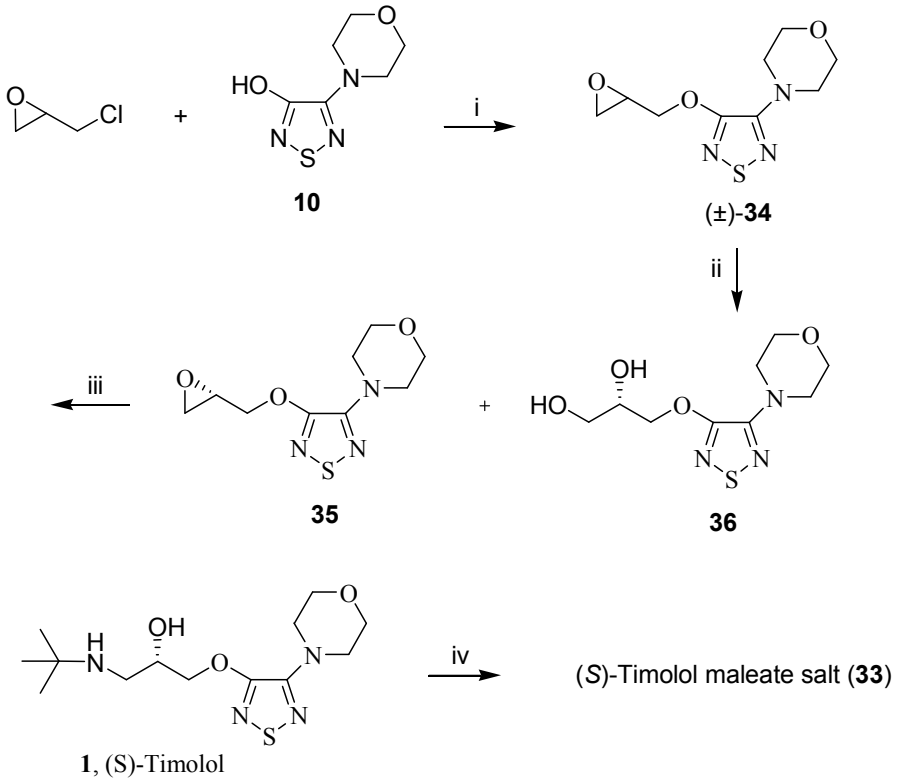
Fig. 12: ^{13}C and ^{1}H NMR spectra of (*S*)-timolol maleate salt (33)

Although the asymmetric dihydroxylation route to (*S*)-timolol was facile and high yielding, it suffers from low enantioselectivity (56% ee). Hence it was of interest to

provide its alternative synthesis by employing hydrolytic kinetic resolution (HKR) route.

Hydrolytic kinetic resolution[20] (route 2):

The HKR strategy for the synthesis of (*S*)-timolol (**1**) is depicted in **Scheme 10**. This strategy involves preparing the racemic epoxide **34**, which will be subjected to Jacobsen's hydrolytic kinetic resolution (HKR).[20]



Scheme 10: (i) KO*t*-Bu, THF, 5 h, 95%. (ii) (*S,S)*-salen-Cobalt(II) (0.5 mol %), AcOH (2 mol%), THF, H_2O (0.55 equiv), 0 ºC, 14 h, (46%, 90% ee for **35** and 45% for **36**). (iii) *tert*-$BuNH_2$, reflux, 30 h, 66%. (iv) Maleic acid, THF, 25 ºC, 1 h, 85%.

Thus, the racemic epoxide **34** was prepared by the *O*-alkylation of 3-hydroxy-4-(*N*-morpholino)-1,2,5-thiadiazole **(10)** with epichlorohydrin in 95% yield. The formation of epoxide **34** was confirmed by the appearance of proton signals in the region δ 2.64–3.37 for methylene and methine protons respectively in its ^{1}H NMR spectrum. Further, its ^{13}C NMR spectrum showed signals at δ 47.8 and 49.2 due to the two

carbons of epoxy ring (**Fig. 13**). Its mass spectrum showed the molecular ion peak at *m/z* 243 confirming the formation of epoxide **34**.

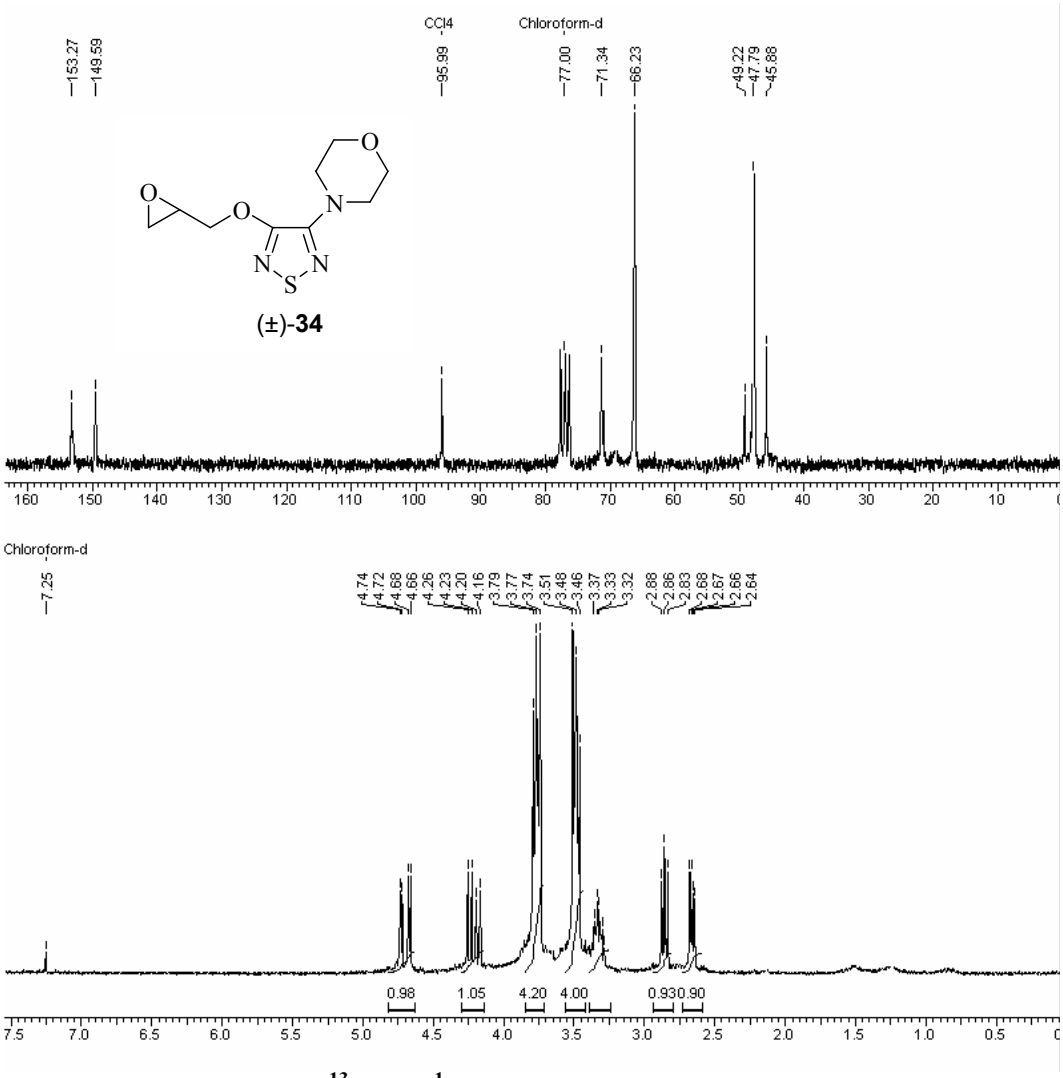
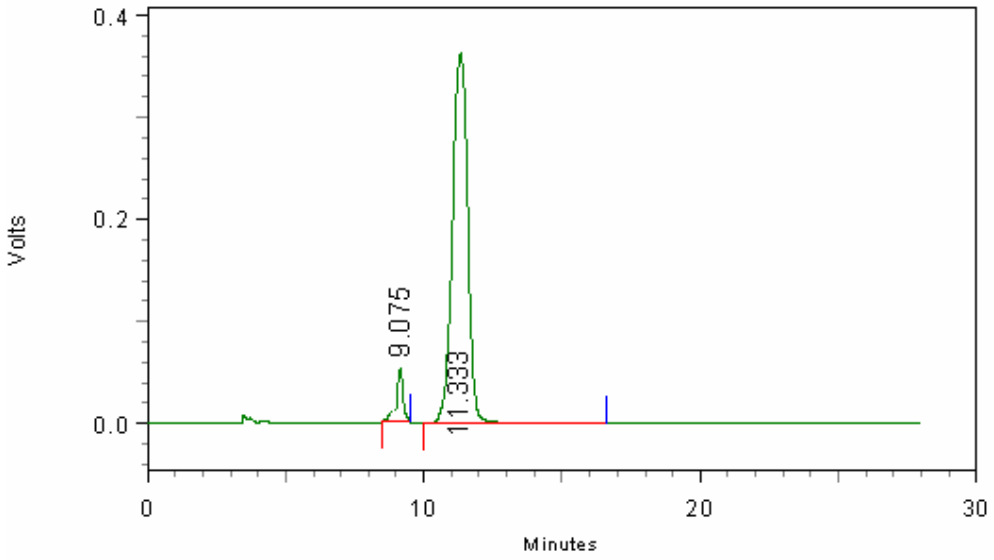


Fig. 13: ^{13}C and ^{1}H NMR spectra of epoxide 34

The racemic epoxide **34** was then subjected to hydrolytic kinetic resolution[20] [(*S,S*)-salen-Co(II) (0.5 mol %), AcOH (2 mol%), THF, distilled H_2O (0.55 equiv), 0 ºC, 14 h] to afford chiral epoxide **35** in 46% yield and 90% ee {$[\alpha]_D$ = +23.0 (c 1, $CHCl_3$); lit.[18,38] $[\alpha]_D$ = +25.6 (c 1, $CHCl_3$)} along with its diol **36** in 45% yield. The chiral epoxide **35** was readily separated from its diol **36** by simple column chromatographic purification. Finally, the regiospecific ring opening of the epoxide **35** with *tert*-

butylamine[18] afforded (*S*)-timolol (**1**), which was isolated as its maleate salt **33** in 85% yield and 90% ee (measured by both chiral HPLC using an OD-H column (**Fig. 14**) and $[\alpha]_D$) {$[\alpha]_D$ = -10.36 (c 4, 1 N aq. HCl); lit.[16] $[\alpha]_D$ = -11.52 (c 4, 1 N aq. HCl)}; [See ***section 3.0.5.1*** for spectral details of (*S*)-timolol (**1**) and (*S*)-timolol maleate salt **33**].



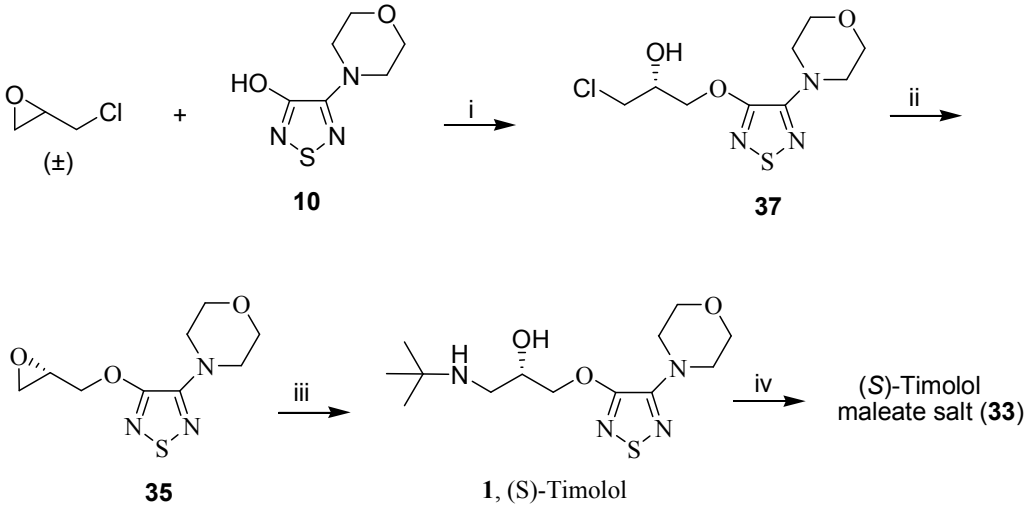
Peak No.	Retention Time	Area (µV-sec)	Area (%)
1	9.075	744357	5.03
2	11.339	14054002	94.97

Fig. 14: HPLC chromatogram of (*S*)-timolol maleate salt 33

Although the optical purity of (*S*)-timolol has increased considerably in HKR route, the methodology has the disadvantage of losing half of the valuable racemic epoxide **34**. Hence, the recent methodology of kinetic resolution of terminal epoxides *via* enantioselective ring-opening with phenolic substrates[21] was attempted.

Kinetic resolution of terminal epoxides *via* enantioselective ring opening with phenolic substrates[21] (route 3):

Kinetic resolution of terminal epoxides *via* enantioselective ring-opening with phenolic substrates strategy for the synthesis of (*S*)-timolol (**1**) is depicted in **Scheme 11**.



Scheme 11: (i) (*R,R*)-salen-Co[$OC(CF_3)_3$] (0.044 equiv), epichlorohydrin (2.5 equiv), *tert*-butyl methyl ether, 12 h, 86%, 98% ee. (ii) KO*t*-Bu, THF, 0-25 ºC, 1 h, 97%. (iii) *tert*-$BuNH_2$, reflux, 30 h, 66%. (iv) Maleic acid, THF, 25 ºC, 1 h, 85%.

The cheaper and ready accessibility of (±)-epichlorohydrin renders kinetic resolution of its epoxide with phenolic substrates as a potentially attractive route for the preparation of chiral epoxide **2** using active Co(salen) complex as the chiral catalyst. Thus, the reaction of 2.5 equiv. of (±)-epichlorohydrin with 3-hydroxy-4-(*N*-morpholino)-1,2,5-thiadiazole (**10**) in the presence of *(R,R)*-(salen)Co[$OC(CF_3)_3$] complex (0.044 equiv) in *tert*-butyl methyl ether at 25 ºC led to isolation of (2*R*)-1-chloro-3-[(4-morpholin-4-yl-1,2,5-thiadiazol-3-yl)oxy]propan-2-ol (**37**) in 86% yield based on hydroxy thiadiazole **10** and 98% enantiomeric excess {$[\alpha]_D$ = +6.88 (c 1, $CHCl_3$); lit.[18] $[\alpha]_D$ = -6.1 (c 1, $CHCl_3$) for the (*S*)-isomer}. The formation of chlorohydrin **37** was confirmed by the appearance of signals at δ 3.65 and 4.23 for CH_2Cl and methine protons respectively in its ^1H NMR spectrum. Further, its ^{13}C

NMR spectrum showed typical signals at δ 46.0 and 69.5 due to the two carbons attached to chloride and alcohol functions (**Fig. 15**). Its mass spectrum showed the molecular ion peak at *m/z* 279-281 confirming the formation of chlorohydrin **37**.

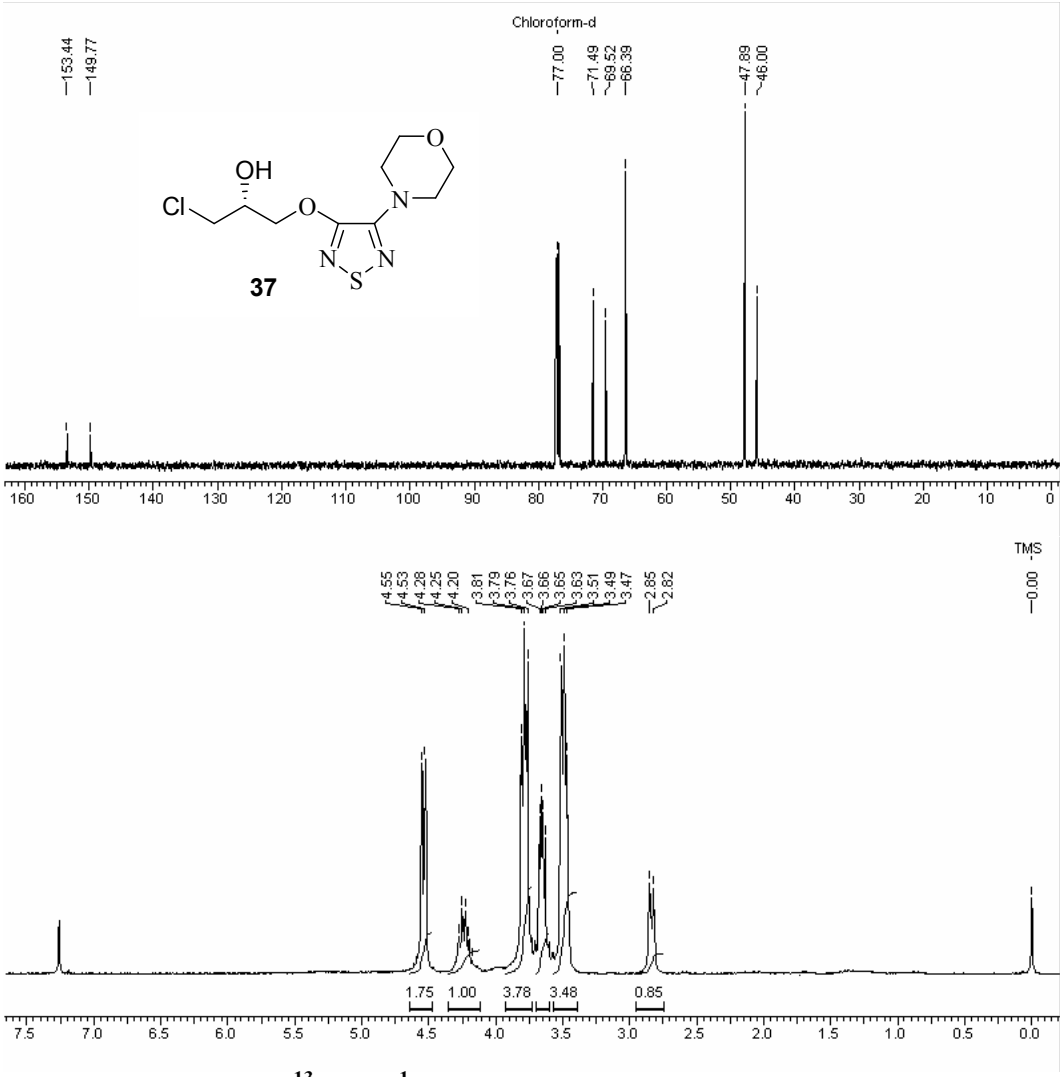
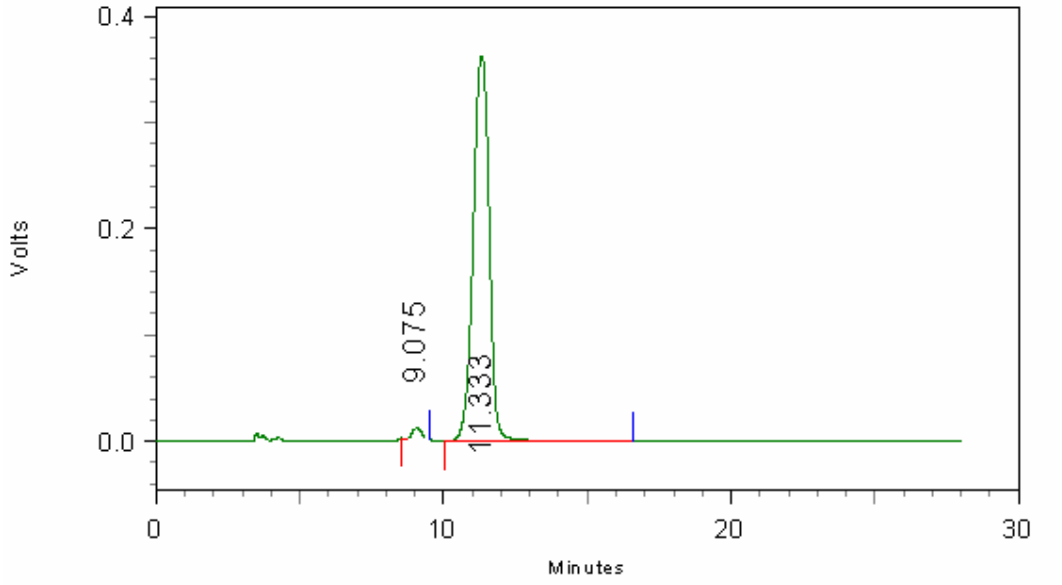


Fig. 15: ^{13}C and ^{1}H NMR spectra of chlorohydrin 37

The chlorohydrin **12** was then converted to chiral epoxide **35** in 97% yield (*t*-BuOK, THF, 0 ºC) and 98% ee; $[\alpha]^{25}_{D}$= +28.9 (*c* 1, $CHCl_3$), {lit.[18,38] $[\alpha]_D$ = +25.6 (*c* 1, $CHCl_3$)}. Finally, the chiral epoxide **35** was subjected to regiospecific ring opening with *tert*-butylamine to afford (*S*)-timolol, which was isolated as its maleate salt **10** in

85% yield and 98% ee (measured by both chiral HPLC using an OD-H column (**Fig. 16**) and $[\alpha]_D$); {$[\alpha]_D$ = -11.3 (c 4, 1 N aq. HCl); lit.[16] $[\alpha]_D$ = -11.52 (c 4, 1 N aq. HCl)}.



Peak No.	Retention Time	Area (µV-sec)	Area (%)
1	9.075	157997	1.04
2	11.339	15034114	98.96

Fig. 16: HPLC chromatogram of (*S*)-timolol maleate salt 33

The physical and spectroscopic data of maleate salt of (S)-timolol (**1**) were in complete agreement with the reported values.[16] [See ***section 3.0.5.1*** for spectral details of (*S*)-timolol (**1**) and (*S*)-timolol maleate salt **33** and ***section 3.0.5.2*** for spectral details of chiral epoxide **35**].

3.6 Conclusion:

In conclusion, the asymmetric synthesis of (*S*)–timolol, an important drug for the treatment of *glaucoma* and *ocular hypertension*, has been achieved in a lesser number of steps with excellent overall yield and high enantiomeric excess using kinetic resolution of cheap and readily available (±)-epichlohydrin with 3-hydroxy-4-(*N*-morpholino)-1,2,5-thiadiazole catalyzed by the *(R,R)*-(salen)Co[$OC(CF_3)_3$] complex.

3.7 Experimental Section:

(*S*)-*tert*-Butyl *tert*-butyl-2,3-dihydroxypropylcarbamate (30):

A mixture of $K_3Fe(CN)_6$ (2.1 g, 6.4 mmol), K_2CO_3 (0.89 g, 6.4 mmol) and $(DHQ)_2$-PHAL (0.038 g, 0.04 mmol) in *t*-BuOH : H_2O (1:1, 40 mL) was stirred for 10 min. at 25 °C. It was then cooled to 0 °C and a solution of OsO_4 (50 μL, 0.02 mmol, 0.5 M solution in toluene) was added. The resulting reaction mixture was stirred at 0 °C for 5 min. and then olefin **29** (0.450 g, 2.1 mmol) was added. The reaction mixture was stirred at 25 °C for 18-24 h (monitored by TLC). It was quenched with sodium sulfite (2.0 g) and extracted with ethyl acetate (4 x 20 mL). Combined organic layers were washed with brine (15 mL), dried over anhyd. Na_2SO_4 and evaporated *in vacuo* to give the crude product, which was purified by column chromatography (30% EtOAc /pet. ether) to give pure diol **30** (0.482 g) as a colorless thick syrup.

Yield: 93%; $[\alpha]^{25}_{D}$: -2.90 (*c* 2, EtOH); **IR** ($CHCl_3$, cm^{-1}): 443, 749, 861, 920, 953, 1285, 1393, 1452, 1688, 1710, 2902, 2977, 3396; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.81-3.32 (m, 5H), 2.99-2.75 (br s, 2H), 1.48 (s, 9H), 1.37 (s, 9H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 157.7, 80.6, 72.4, 63.3, 55.8, 46.9, 29.9, 28.5; **Analysis**: $C_{12}H_{25}NO_4$ requires C, 58.27; H, 10.19; N, 5.66%; found C, 58.20; H, 10.26; N, 5.70%.

(*S*)-3-*tert*-Butyl-5-(hydroxymethyl)oxazolidin-2-one (31):

A mixture of diol **30** (0.988 g, 4 mmol) and K_2CO_3 (0.828 gm, 6 mmol) in dry MeOH (10 mL) was refluxed for 5 h. The resulting reaction mixture was cooled to 25 ºC and the solvent was evaporated *in vacuo*. Work-up (extraction with 30 mL of EtOAc) and purified by column chromatography (30% EtOAc/pet. ether) gave 2-oxazolidinone **31** (0.657 g) as a colorless oil.

Yield: 95%; $[\alpha]^{25}_{D}$: -2.5 (*c* 2, EtOH); **IR** ($CHCl_3$, cm^{-1}): 491, 677, 919, 1066, 1227, 740, 3026; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 4.50-4.39 (m, 1H), 3.85-3.50 (m, 4H),

3.40-3.31 (br s, 1H), 1.36 (s, 9H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 157.0, 72.4, 62.4, 53.2, 44.5, 27.2. **Analysis**: $C_8H_{15}NO_3$ requires C, 55.47; H, 8.73; N, 8.09%; found C, 55.54; H, 8.60; N, 8.14%.

Mosher ester of (*S*)-3-*tert*-butyl-5-(hydroxymethyl)oxazolidin-2-one (38):

A two-neck 10 mL flask with septum was charged with *N*,*N*'-dicyclohexylcarbodiimide (44 mg, 0.21 mmol), catalytic amount of 4-dimethylaminopyridine (DMAP) and CH_2Cl_2 (2 mL) under argon atmosphere. The flask was allowed to cool at 0 ºC for 10 min and a solution of alcohol **31 (**31 mg, 0.18 mmol) in CH_2Cl_2 (2 mL) was introduced through a syringe. It was allowed to stir for additional 10 min, followed by dropwise addition of (*R*)-α-methoxy-α-trifluoromethylphenyl acetic acid (46 mg, 0.196 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was then stirred at 0 ºC for additional 1 h and then at 25 ºC for 12 h. It was diluted with CH_2Cl_2 (50 mL), washed with saturated $NaHCO_3$ solution (50 mL), dried over anhyd. Na_2SO_4 and then concentrated *in vacuo* to give Mosher ester of the alcohol **38** (53 mg) as a colorless thick syrup.

Yield: 70%; **$[\alpha]^{25}_D$** -4.8 (*c* 0.8, MeOH); **IR** ($CHCl_3$ cm^{-1}): 3158, 2952, 2927, 2850, 1753, 1606, 1519, 1495, 1348, 1242, 1217, 1153, 1122, 1015, 957; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 7.32-7.49 (m, 5H), 4.65-4.45 (m, 1H), 3.98-3.55 (m, 4H), 3.52 (s, 3H), 1.38 (s, 9H).

(*S*)-5-((4-Morpholino-1,2,5-thiadiazol-3-yloxy)methyl)-3-*tert*-butyloxazolidin-2-one (32):

To a mixture of 2-oxazolidinone **31** (0.432 g, 2.5 mmol) and 3-chloro-4-morpholino-1,2,5-thiadiazole (**9**)[11] (0.512 g, 2.5 mmol) in *tert*-butyl alcohol (5 mL) at 25 °C was added potassium *tert*-butoxide (0.336 g, 3mmol). The mixture was stirred for 12 h. The solvent was evaporated *in vacuo* and the residue was neutralized by 6N HCl.

Work-up (extraction with 30 mL of EtOAc) and purified by column chromatography using (40% EtOAc/Pet. ether) gave oxazolidinone **32** (0.641 g) as a colorless solid.

Yield: 75%; colorless solid; **mp**: 86-87 °C; **$[\alpha]^{25}_{D}$**: -3.4 (*c* 2, EtOH); **IR** ($CHCl_3$, cm^{-1}): 472, 685, 782, 1227, 1760, 3046; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 4.80-4.65 (m, 1H), 4.54 (br s, 2H), 3.91-3.40 (m, 10H), 1.36 (s, 9H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 155.8, 152.9, 149.7, 70.3, 69.2, 66.3,53.5, 47.8, 44.9, 27.3. **Analysis**: $C_{14}H_{22}N_4O_4S$ requires C, 49.11; H, 6.48; N, 16.36; S, 9.36%; found C, 49.25; H, 6.31; N, 16.42; S, 9.31%.

(2*S*)-1-(*tert*-Butylamino)-3-[(4-morpholin-4-yl-1,2,5-thiadiazol-3-yl)oxy]propan-2-ol (1; (*S*)-timolol):

To a stirred solution of oxazolidinone **32** (0.684 g, 2 mmol) in MeOH (20 mL) was added 2N NaOH (10 mL). The reaction mixture was stirred for 8 h, The residue filtered off and the solvent removed *in vacuo* to give the crude product, which was purified by column chromatography (20% MeOH/Et_2O) to give (*S*)-timolol **1** (0.569 g) as a colorless thick syrup.

Yield: 90%; **$[\alpha]^{25}_{D}$** = -1.93 (*c* 1, $CHCl_3$); **IR** (neat, cm^{-1}): 768, 957, 1122, 1228, 1311, 1497, 2855, 2964, 3295 (br), 3412 (br); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 4.48 (dd, *J* = 11.1, 4.1 Hz, 1H), 4.37 (dd, *J* = 11.1, 5.6 Hz, 1H,), 3.94 (m, 1H), 3.79–3.83 (t, *J* = 4.9 Hz, 4H), 3.50–3.55 (t, *J* = 5.4 Hz, 4H), 2.82 (dd, *J* = 4.0, 12.1 Hz, 1H), 2.59 (dd, *J* = 7.9, 12.1 Hz, 1H), 2.09 (br s, 1H), 1.10 (s, 9H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 153.7, 150.0, 72.7, 68.0, 66.3, 50.3, 47.8, 44.3, 28.9; **MS**: *m*/*z* (%) = 316 (1), 301 (9), 130 (20), 86 (100), 74 (16), 57 (20). **Analysis**: $C_{13}H_{24}N_4O_3S$ requires C, 49.35; H, 7.65; N, 17.71; S, 10.13%; found C, 49.48; H, 7.53; N, 17.79; S, 10.01%.

(*S*)-(-)-3-(3-*tert*-Butylamino-2-hydroxypropoxy)-4-(*N*-morpholino)-1,2,5-thiadiazole ((*S*)-1. hemimaleate salt; 33):

To a stirred solution of (*S*)-timolol (**1**) (0.418 g, 1.3 mmol) in THF (5 mL) was added a solution of maleic acid (0.151 g, 1.3 mmol) in THF (3 mL). The mixture was seeded and aged for 1 h at 25 °C. The resulting salt was filtered, washed with THF (3 mL), and dried at 50 °C *in vacuo* to give hemimaleate salt **33** (0.477 g) as a colorless solid. **Yield**: 85%; **mp**: 198-201 °C {lit.[16] mp 201-202 °C}; **$[\alpha]^{25}_{D}$**: -6.45 (*c* 4, 1N aqueous HCl), 56% ee {lit.[16] $[\alpha]^{25}_{D}$= -11.52 (*c* 4, 1N aqueous HCl)}; HPLC: 56% ee, Chiracel OD-H, λ = 297 nm, diethylamine/2-propanol/hexane (1:40:960), 1 mL/min, retention time: (*R*)-enantiomer 9.07 min, (*S*)-enantiomer 11.33 min; **IR** (neat, cm^{-1}): 443, 749, 861, 920, 953, 1285, 1393, 1452,1562, 1688, 1710, 2902, 2977, 3396; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 8.36 (br s, 1H), 6.01 (s, 2H, CH=CH), 4.38 (m, 2H), 4.19 (m, 1H), 3.69 (t, *J* = 4.2 Hz, 4H), 3.44 (t, *J* = 5.0 Hz, 4H), 3.09-3.16 (m, 1H), 2.82-2.92 (m, 1H), 2.49 (m, 1H), 1.27 (s, 9H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ 167.5, 153.4, 149.9, 136.1, 72.1, 65.7, 65.1, 56.5, 47.6, 43.7, 25; **Analysis**: $C_{17}H_{28}N_4O_7S$ requires C, 47.21; H, 6.53; N, 12.95; S, 7.41%; found C, 47.31; H, 6.54; N, 12.89; S, 7.35%.

4-{4-[Oxiran-2-ylmethoxy]-1,2,5-thiadiazol-3-yl}morpholine (34):

To a stirred solution of (±)-epichlorohydrin (2 g, 21.7 mmol) and 3-hydroxy-4-(*N*-morpholino)-1,2,5-thiadiazole (**10**) (4 g, 21.7 mmol) in dry THF (70 mL) at 0 °C was added potassium *tert*-butoxide (4.8 g, 43.4 mmol). The reaction mixture was stirred at 25 °C for 5 h; diluted with H_2O (30 mL) and extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with brine (50 mL), dried over anhyd. Na_2SO_4 and concentrated to give the crude product, which was purified by column chromatography (10% EtOAc/pet. ether) to give **34** (5 g) as a colorless solid.

Yield: 95%; **mp**: 112-114 °C {lit.[38] mp 113-114 °C}; **IR** (KBr, cm^{-1}): 537, 643, 855, 906, 1117, 1497, 2865, 2925, 2980; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 4.70 (dd, *J* = 11.7, 3.1 Hz, 1H), 4.22 (dd, *J* = 11.7, 6.2 Hz, 1H), 3.77 (t, *J* = 5.1 Hz, 4H), 3.48 (t, *J* = 5.1 Hz, 4H), 3.37-3.29 (m, 1H), 2.86 (t, *J* = 4.7 Hz, 1H), 2.67 (dd, *J* = 4.7, 2.7 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 153.2, 149.6, 71.3, 66.2, 49.2, 47.8, 45.8; **Analysis**: requires $C_9H_{13}N_3O_3S$ C, 44.43; H, 5.39; N, 17.27; S, 13.18%; found C, 44.59; H, 5.50; N, 17.15; S, 13.09%.

4-{4-[(2*S*)-Oxiran-2-ylmethoxy]-1,2,5-thiadiazol-3-yl}morpholine (35):

A mixture of (*S*,*S*)-salen-cobalt(II) catalyst (57 mg, 0.09 mmol), epoxide **34** (4.6 g, 19 mmol) and acetic acid (0.022 g, 0.38 mmol)) was stirred under air at 25 ºC. After the red colored reaction mixture turned to a dark brown solution, the flask was cooled to 0 °C and dry THF (0.2 mL) and H_2O (0.2 mL) were added. After 2 h the reaction was allowed to warm to 25 ºC and stirred for 6 h. The solution of crude products was purified by column chromatography using (10% EtOAc/pet. ether) to give chiral epoxide **35** (2.12 g).

Yield: 46%; **$[\alpha]_D^{25}$**: +23.0 (*c* 1, $CHCl_3$) {lit.[18,38] $[\alpha]_D$ = +25.6 (*c* 1, $CHCl_3$)}.

(2*S*)-1-(*tert*-Butylamino)-3-[(4-morpholin-4-yl-1,2,5-thiadiazol-3-yl)oxy]propan-2-ol (1, (*S*)-timolol):

To a stirred solution of chiral epoxide **35** (0.972 g, 4 mmol) in *tert*-butylamine (10 mL, 95 mmol) was added KI (0.08 g, 0.5 mmol). The reaction mixture was refluxed for 72 h. Thereafter, the solution was cooled, the solvent removed *in vacuo* to give the crude product, which was purified by column chromatography (20% MeOH/Et_2O) to afford (*S*)-timolol **1** (0.834 g) as a colorless thick syrup.

Yield: 66%; **$[\alpha]^{25}_D$**: -3.10 (*c* 1, $CHCl_3$).

(*S*)-(-)-3-(3-*tert*-Butylamino-2-hydroxypropoxy)-4-(*N*-morpholino)-1,2,5-thiadiazole ((S)-1 hemimaleate salt, 33):

Given in the previous experiment **33** was obtained.

$[\alpha]^{25}_D$: -10.36 (*c* 4, 1N aqueous HCl) {lit.[16] $[\alpha]^{25}_D$= -11.52 (*c* 4, 1N aqueous HCl)}; **HPLC**: 90% ee, Chiracel OD-H, λ = 297 nm, diethylamine/2-propanol/hexane (1:40:960), 1 mL/min, retention time: (*R*)-enantiomer 9.07 min, (*S*)-enantiomer 11.33 min.

(2*R*)-1-Chloro-3-[(4-morpholin-4-yl-1,2,5-thiadiazol-3-yl)oxy]-propan-2-ol (37):

To a mixture of *(R,R)*-(salen)Co[$OC(CF_3)_3$] complex (86 mg, 0.100 mmol), epichlorohydrin (0.462 g, 5.00 mmol), TBME (0.15 mL) and 3Å MS (100 mg) at 25 ºC was added phenol **10** (0.374 g, 2.00 mmol). It was stirred at 25 ºC until GC analysis indicated complete conversion of phenol, at which time pyridinium *p*-toluenesulfonate (75 mg, 0.30 mmol) was added. The reaction mixture was filtered through a pad of silica and washed with 50% EtOAc/hexanes (15 mL). The filtrate was concentrated *in vacuo* to give the crude product, which was purified by chromatography (20% EtOAc/pet. ether) to give **37** (0.480 g) as a pale yellow solid.

Yield: 86%; pale yellow solid; **mp**: 59-61 °C {lit.[18] 58-61 °C}; **$[\alpha]_D^{25}$**: +6.88 (*c* 1, $CHCl_3$) {lit.[18] $[\alpha]_D$ = -6.1 (c 1, $CHCl_3$) for the (*S*)-enantiomer}; **IR** ($CHCl_3$, cm^{-1}): 953, 1113, 1298, 1493, 2854, 2923, 2964, 3563; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 4.54 (d, *J* = 4.54 Hz, 2H), 4.17-4.28 (m, 1H), 3.79 (t, *J* = 4.53 Hz, 4H), 3.63-3.67 (m, 2H), 3.49 (t, *J* = 5.03 Hz, 4H), 2.83 (d, *J* = 5.44 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 153.4, 149.8, 71.5, 69.5, 66.4, 47.9, 46.0; **MS** (EI): *m*/*z* (%) = 383–385 (M+, 8), 197–199 (100), 186 (2), 144 (4), 105 (92), 77 (36). **Analysis**: $C_9H_{14}ClN_3O_3S$ requires C, 38.64; H, 5.04; N, 15.02; S, 11.46%; found C, 38.53; H, 5.15; N, 15.14; S, 11.38%.

4-{4-[(2*S*)-Oxiran-2-ylmethoxy]-1,2,5-thiadiazol-3-yl}morpholine (35):

To a stirred solution of **37** (230 mg, 0.82 mmol) in dry THF (5 mL) at 0 °C was added potassium *tert*-butoxide (184 mg, 1.64 mmol) and stirred for 1 h. The reaction mixture was diluted with H_2O (10 mL) and extracted with Et_2O (3 × 10 mL). The collected organic phases were washed with brine (10 mL), dried over anhyd. Na_2SO_4 and evaporated *in vacuo* to afford chiral epoxide **35** (194 mg) as a colorless solid.

Yield: 97%; $[\alpha]^{25}_D$: +28.9 (*c* 1, $CHCl_3$) {lit.[18,38] $[\alpha]_D$ = +25.6 (*c* 1, $CHCl_3$)}.

(2*S*)-1-(*tert*-Butylamino)-3-[(4-morpholin-4-yl-1,2,5-thiadiazol-3-yl)oxy]propan-2-ol (1, (*S*)-timolol):

Following the procedure described in above section, **1** was obtained.

$[\alpha]^{25}_D$: -3.38 (*c* 1, $CHCl_3$).

(*S*)-(-)-3-(3-*tert*-Bbutylamino-2-hydroxypropoxy)-4-(*N*-morpholino)-1,2,5-thiadiazole ((S)-1 hemimaleate salt, 33):

Following the procedure described in the above section, **33** was obtained.

$[\alpha]^{25}_D$: -11.3 (*c* 4, 1N aqueous HCl) {lit.[16] $[\alpha]^{25}_D$= -11.52 (*c* 4, 1N aqueous HCl)}; **HPLC**: 98% ee, Chiracel OD-H, λ = 297 nm, diethylamine/2-propanol/hexane (1:40:960), 1 mL/min, retention time: (*R*)-enantiomer 9.07 min, (*S*)-enantiomer 11.33 min.

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Chapter IV

$NaIO_4$-Mediated Regioselective Oxidative Halogenation of Alkenes using Alkali Metal Halides as Halogen Source and Metal-catalyzed Asymmetric Epoxidation of Olefins

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"$NaIO_4$-Mediated Selective Oxidative Halogenation of Alkenes and Aromatics Using Alkali Metal Halides" Gajanan K. Dewkar, Narina V. Srinivasarao, Arumugam Sudalai, *Org. Lett.* **2003**, *5*, 4501.

SECTION-I

$NaIO_4$-Mediated Regioselective Oxidative Halogenation of Alkenes using Alkali Metal Halide as Halogen source: A High Yield Preparation of Methoxyhalogens

4.1.1 Introduction

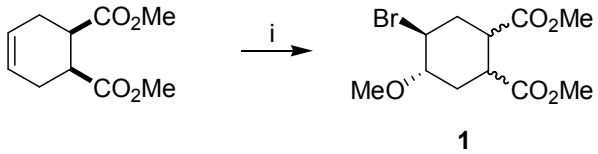
The 1,2-functionalization of olefins by the selective addition of two different functional groups, such as water or alcohols and halogens (halohydroxylation, haloalkoxylation), in a highly regio- and enantioselective manner, remains important and challenging to organic chemists.[1] Such halo derivatives are widely used in the synthesis of pharmaceuticals, dyes, flame-retardants, additives and plasticizers, agrochemicals and speciality chemicals.[2] The vicinal methoxyhalogen 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. Thus, the vicinal halomethoxy represents a very useful class of compounds in organic synthesis.[3]

4.1.2 Review of Literature

Literature search revealed that there are various catalytic as well as non-catalytic methods available for the synthesis of methoxyhalogenation of olefins. All these methods, which involve use of halides, *N*-halides, metal halides and water sources, are described below.

Torii's approach (1981)[4]

In this approach, olefins are converted into the corresponding bromomethoxy compounds **1** with NaBr in MeOH-water-H_2SO_4 electrolysis system in 63-88% yield (**Scheme 1**).

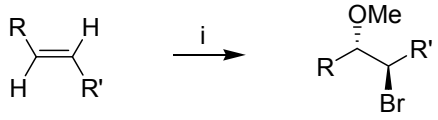


1

Scheme 1: (i) MeOH-H_2O (8:2), NaBr, H_2SO_4, Pt electrodes, 63-88%.

Ruasse's approach (1993)[5]

Ruasse *et al*. have reported the synthesis of bromomethoxy compounds **2** using bromine-methanol system (**Scheme 2**).

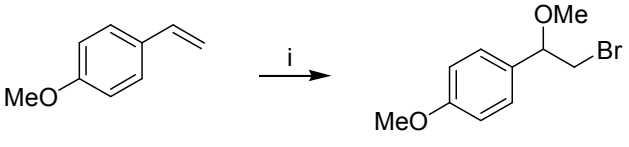


2

Scheme 2: (i) Br_2, MeOH, 25 ºC, 63-85%.

Jacob's approach (2001)[6]

Jacobs *et al.* have developed a new heterogeneous catalyst system such as WO_4^{2-} supported on layered double hydroxides ((Ni,Al)LDH-WO_4^{2-}, which is used for mild oxidative bromination of olefins with H_2O_2 as the oxidant leading to bromomethoxylation **3** (**Scheme 3**).

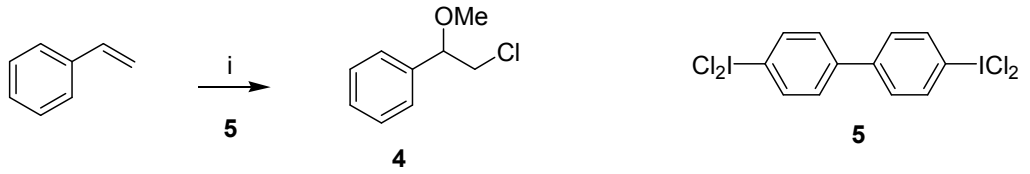


3

Scheme 3: (i) WO_4^{2-} on (Ni, Al) LDH-Cl^-, 25% aq. H_2O_2, NH_4Br, MeOH:H_2O (95:5).

Yasubov's approach (2004)[7]

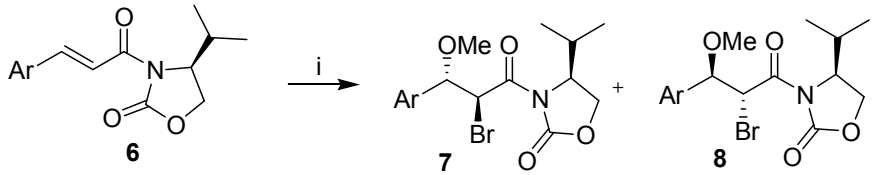
In this approach, hypervalent iodine reagent 4,4'-bis(dichloroiodo)biphenyl (**5**) was used as a halogen source to obtain methoxychloride **4** in 62% yield (**Scheme 4**).



Scheme 4: (i) MeOH, 25 ºC, 2h, 62%.

Hajra's approach (2004)[8]

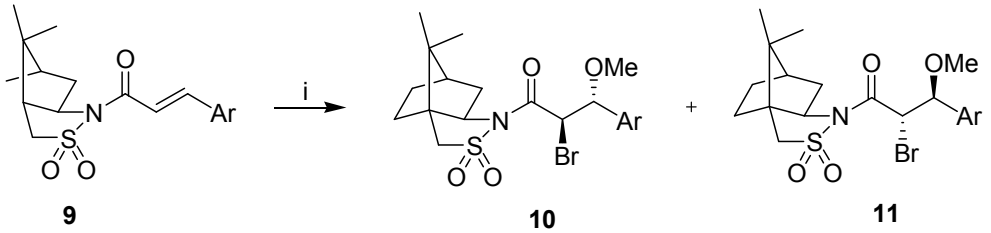
Hajra *et al.* have reported the asymmetric bromomethoxylation of chiral carboxamides **6** with bromine as halogen source promoted by silver nitrate with high regio- and moderate diastereoselectivity (**7**:**8** up to 3:1 ratio) (**Scheme 5**).



Scheme 5: (i) $AgNO_3$, Br_2, MeOH, 0-5 ºC, 0.5 h, 62-91%.

Hajra's approach (2006)[9]

Hajra *et al.* once again have reported the asymmetric bromomethoxylation of chiral carboxamides **9** with NBS as halogen source catalyzed by Lewis acid $Yb(OTf)_3$ with high regio- and moderate diastereoselectivity (**10**:**11** upto 4:1 ratio) (**Scheme 6**).



Scheme 6: (i) $Yb(OTf)_3$ (15 mol%), NBS, MeOH, 25 ºC, 52-97%.

4.1.3 Present Work

4.1.3.1 Objective

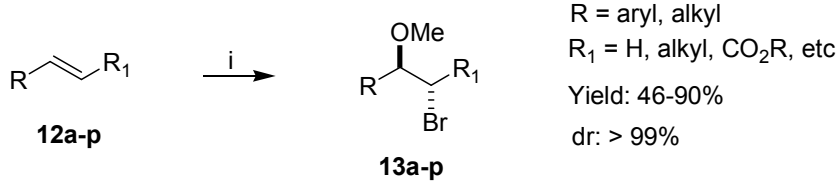
Although there are many methods available in the literature for methoxyhalogenation of olefins, they suffer from certain drawbacks such as use of elemental bromine, which are pollutants, and generate hazardous HX as by-products.[10] In contrast to Br_2, other stoichiometric brominating reagents, such as *N*-bromosuccinimide (NBS), *N*-bromoacetamide, bromodimethylsulfonamide or □romomethox T[11] do not produce HX in halogenation of organic molecules, but they are expensive and generate organic wastes. Recently, the oxidative halogenation of olefins by metal halides has emerged as an important alternative for the synthesis of such halo derivatives.[12] However, such oxidative halogenations involve the use of heavier metals in stoichiometric amounts, often resulting in poor yields and selectivities. Further, catalytic protocols with V-BPO[13] biomimics still have major disadvantages, such as the use of chlorinated solvents and more seriously, when milder pH conditions are required, almost stoichiometric amounts of metals must be used to ensure satisfactory activity.

In this context, $NaIO_4$ is a well-known reagent for oxidation reactions like metal-mediated oxidations,[14a] oxidative cleavage of 1,2-diols,[14b] oxidation of sulfides,[14c] phenols,[14d] indoles,[14e] etc. However, oxidation of alkali metal halides with $NaIO_4$ has not been reported. We have decided to oxidize cheaply available alkali metal halides and use them as a halogen source for selective oxidative halogenation of alkenes. When as a model substrate, we tried to halogenate styrene using $NaIO_4$, in combination with lithium bromide in THF, we got the dibromo product in low yields (10%). We tried to increase the yield by using various solvents such as acetone, acetonitrile, methanol, dimethyl sulfoxide, or acetic acid. We found that acetic acid medium helped to give excellent yield of dibrominated product (98%). We then

thought that use of methanol might produce bromomethoxylated along with bromo-acetate products. We studied this reaction carefully by employing various solvents in combination with methanol, which resulted in very poor yield of □romomethoxylation along with dibrominated products. Then we studied the role of pH in our reaction protocol and found that only in acidic conditions, $NaIO_4$ readily oxidized halides and liberated halogens. After studying various methanol-solvent systems in presence of acidic conditions, we found that methanol-water is the best solvent system for methoxybromination of alkenes and styrenes (up to 90% yield); the results of which are discussed in this section.

4.1.4 Results and Discussion

When styrene was treated with lithium bromide (1.2 equiv.) in the presence of $NaIO_4$ (25 mol%), 30% aq. H_2SO_4/HCl (10 mmol) in methanol/water (3:1) system, the corresponding bromomethoxy product was obtained in good yields (upto 82%) with high regioselectivity (>99%) (**Scheme 7**).[15]

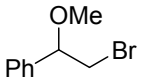
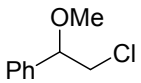
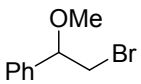
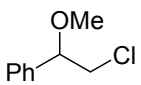
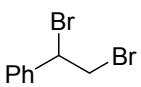
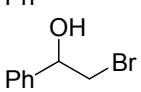


Scheme 7: (i) LiBr (1.2 mmol), $NaIO_4$ (25 mol%), aq. H_2SO_4 (10 mmol), MeOH/H_2O (3:1), 25 ºC, 1-3 h, 46-90%.

As can be seen from **Table 1** we turned our attention to the role of $NaIO_4$ in oxidative halogenation of alkenes in the presence of various alkali metal halides using various solvent systems. When styrene was subjected to oxidative halogenation in presence of 25 mol% of $NaIO_4$, the corresponding halogenated product **13a** was obtained in high yields. In the absence of $NaIO_4$, no reaction took place; lowering the molar ratio of $NaIO_4$ also resulted in the reduced yield. It is found that the use of 25 mol% of $NaIO_4$

and the proper choice of solvent under acidic conditions (H_2SO_4 or HCl) are critical in achieving high conversion level of olefins with excellent product selectivity.

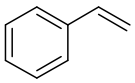
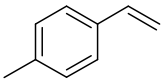
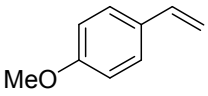
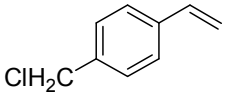
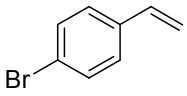
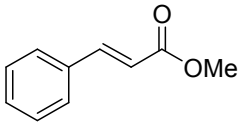
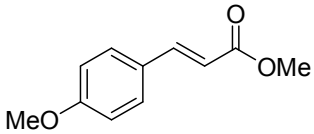
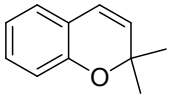
Table 1: $NaIO_4$-mediated oxidative halogenation of styrene using alkali metal halides[a]

Entry	Metal halide	Solvent[b]	Product	Yield (%)[c]
1	LiBr	MeOH/H_2O (3:1)		82[d]
2	LiCl	MeOH/H_2O (3:1)		71[d]
3	NaBr	MeOH/H_2O (3:1)		75d
4	NaCl	MeOH/H_2O (3:1)		69[d]
5	LiBr	AcOH		98
6	LiBr	CH_3CN/H_2O (2:1)		91[d]

a) Reaction conditions: substrate (10 mmol), $NaIO_4$ (25 mol%), metal halides (12 mmol), 30% aq.H_2SO_4 (0.5 mL, 10 mmol); b) solvent 15 mL: CH_3CN:H_2O (2:1), AcOH, MeOH:H_2O (3:1); c) isolated yield after column chromatography; d) 5-10% of the corresponding dihalides and bromohydrins are also formed.

Thus, while a mixture of methanol and water at pH = 6.2 (initial pH = 2.17 rose to 6.2 within 10 min.) was found to be the best solvent for methoxybromine formation, the formation of dibromides was facilitated in presence of acetic acid as solvent requiring no strong acidic conditions. However, when HIO_4 and $PhI(OAc)_2$ were employed in catalytic amounts for the methoxybromination of styrene with LiBr, mixtures of methoxybromins and dibromides were obtained in low yield (25%). As can be seen from **Table 2**, a various substituted styrenes and α,β-unsaturated carbonyl compounds **12a-h** underwent oxidative brominations to give the corresponding methoxybromines **13a-h** in excellent yield. α,β-Unsaturated carbonyl compounds (**12f-g**) also gave excellent yield of methoxybromines **13f-g** but the rate was very slow.

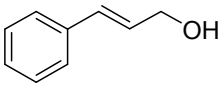
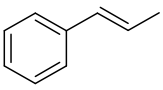
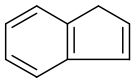
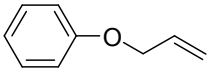
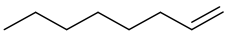
Table 2: $NaIO_4$-mediated oxidative methoxybromination of styrenes and α,β-unsaturated carbonyl compounds with LiBr[a]

No	Olefin	Tine (h)	Product	*anti:syn*[c]	Yield[b] (%)
a		1	**13a**	-	82
b		1	**13b**	-	78
c		1	**13c**	-	80
d		1	**13d**	-	78
e		1	**13e**	-	76
f		3	**13f**	>99:1	80
g		3	**13g**	>99:1	87
h		3	**13h**	>99:1	83

a) Reaction conditions: alkene (10 mmol), $NaIO_4$ (25 mol%), LiBr (12 mmol), 30% aq.H_2SO_4 (0.5 mL, 10 mmol), solvent 15 mL: MeOH:H_2O (3:1); b) yields refers to isolated product after column chromatography; c) determined based on ^1H and ^{13}C NMR.

In all styrenic substrates, the incoming methoxy function entered at the benzylic position exclusively. Remarkably, in the case of 1,2-disubstituted olefins, *anti*-isomers of the corresponding halo derivatives with dr >99% (**13f-h**) were obtained exclusively. As can be seen from **Table 3** a variety of aliphatic olefins and allylic alcohols **12i-o** underwent oxidative bromination with lithium bromide and $NaIO_4$ (25 mol%) to give the corresponding methoxybromines **13i-o** in excellent yields. In case of substrates such as allyl bromide (**12o**), dibromide was obtained in higher yield along with methoxybromine **13o**. For aliphatic olefins the regioisomers were formed nearly in 1:1 ratio as determined from ^1H and ^{13}C-NMR spectra respectively.

Table 3: $NaIO_4$-mediated oxidative bromohydroxylation of olefins with LiBr[a]

No	Olefin	Tine (h)	Product	*anti:syn*[c]	Yield[b] (%)
i		3	**13a**	>99:1	75
j		2	**13b**	>99:1	76
k		1	**13c**	>99:1	90[d]
l		3	**13d**	-	72[d]
m		3	**13e**	>99:1	65[d]
n		1	**13f**	-	84[d]
o		1	**13g**	-	46[d]

a) Reaction conditions: alkene (10 mmol), $NaIO_4$ (25 mol%), LiBr (12 mmol), 30% aq.H_2SO_4 (0.5 mL, 10 mmol), solvent 15 mL: CH_3CN:H_2O (2:1); b) yields refers to isolated product after column chromatography; c) determined based on ^1H and ^{13}CNMR; d) regioisomers were formed nearly in 1:1 ratio as determined from ^1H and ^{13}C NMR.

The formation of methoxybromines **13a-o** was confirmed by ^1H, ^{13}C-NMR, IR and Mass spectroscopy. The ^1H-NMR spectra showed a singlet at δ 3-3.5 due to the presence of methoxy group. For example, the ^1H-NMR spectrum of 2-bromo-1-(4-bromophenyl)ethanol (**13e**) showed a singlet at δ 3.33 for -OMe protons. Its ^{13}C-NMR also showed typical methoxybromo carbon signals at δ 35.58 and 57.10. Its mass spectrum showed the molecular ion peak at m/z 294 (**Fig. 1**).

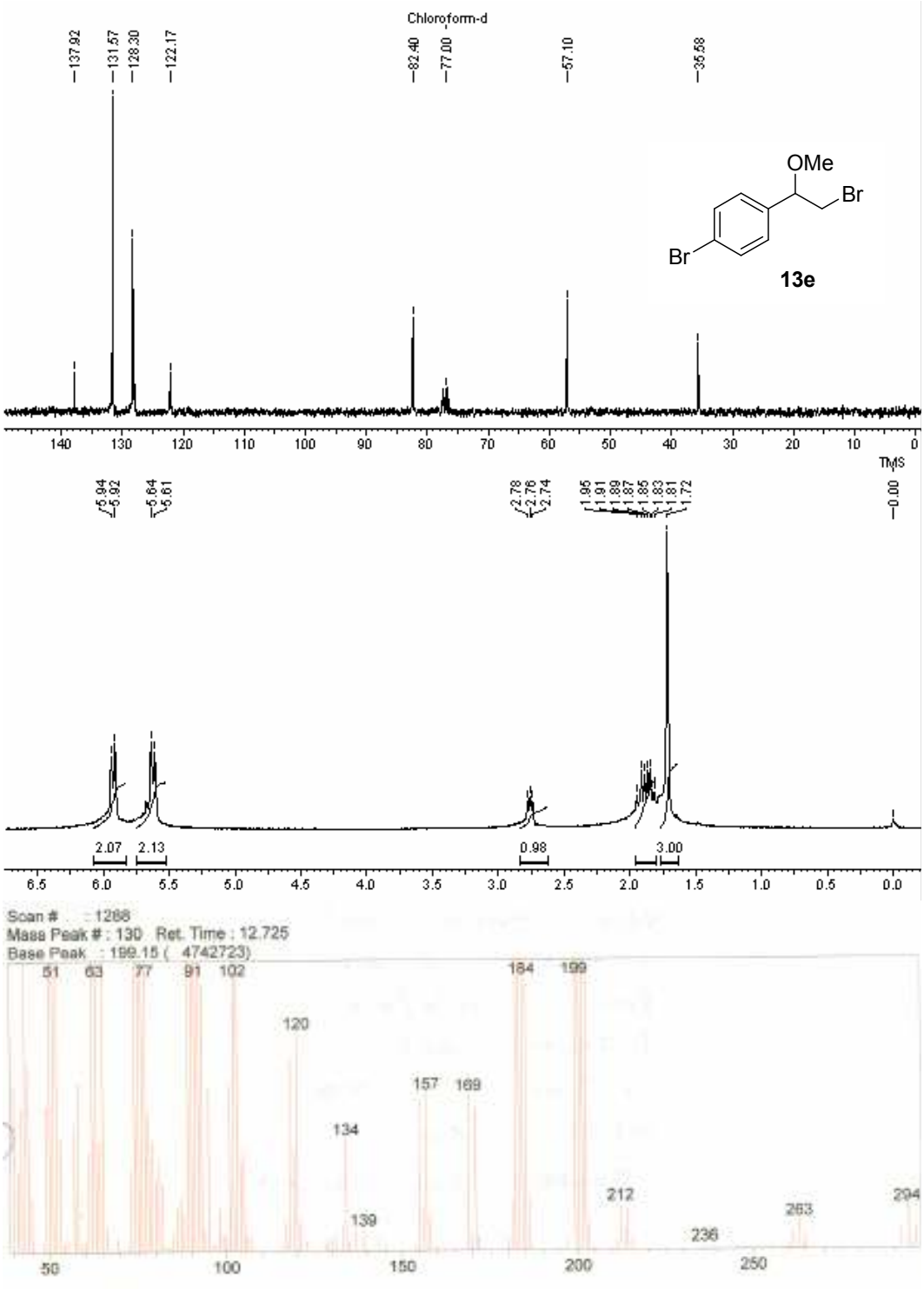
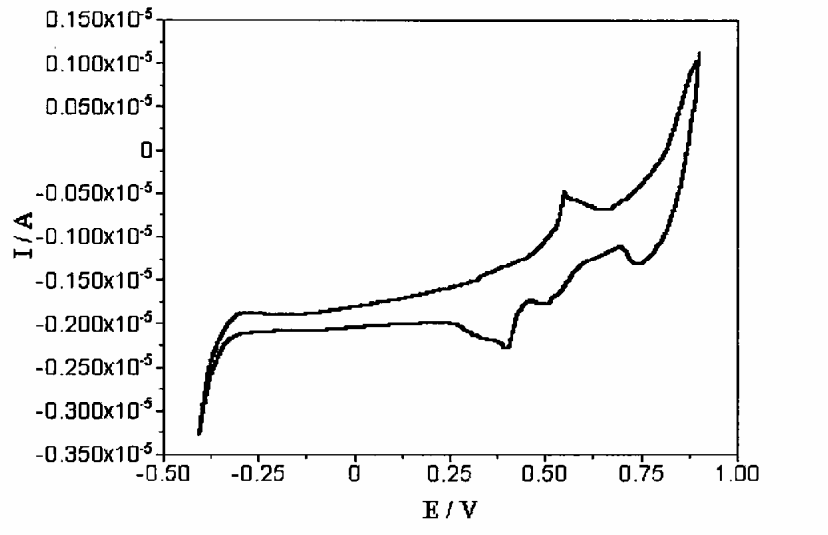


Fig. 1: ^{13}C NMR, ^{1}H and mass spectra of compound 7e

Mechanism

With the help of Cyclic Voltammetry (CV) study, the mechanism of the reaction was deduced. The Cyclic Voltammetry (**Fig. 2**) of the reaction shows, for the forward oxidation scan at 500 mV/s, an irreversible oxidation peak at Ep_a = 0.565 V [$Br^- \rightarrow Br_2$ equn (1)] and, for the reverse reduction scan, three irreversible reduction peaks at Ep_c = 0.720 V, 0.490 V and 0.390 V corresponding to the reduction of IO_4^-, IO_3^- and I_2 respectively [equns (2)-(4)].[16]



Voltage vs. Ag/AgCl reference

Fig. 2: CV of reaction mixture containing $NaIO_4$ (25 mol%), styrene (10 mmol), LiBr (12 mmol), 30% aq. H_2SO_4 (0.5 mL, 10 mmol), CH_3CN/H_2O 2:1 (20 mL) at 25^0C

$$2Br^- \longrightarrow Br_2 + 2e^- \quad \text{----------(1)}$$

$$IO_4^- + 2H^+ + 2e^- \longrightarrow IO_3^- + H_2O \quad \text{----------(2)}$$

$$IO_3^- + 6H^+ + 6e^- \longrightarrow I^- + 3H_2O \quad \text{----------(3)}$$

$$I_2 + 2e^- \xrightarrow{\text{fast}} 2I^- \quad \text{----------(4)}$$

Thus, CV reveals that X_2 (X = Br, Cl) generated *in situ* from metal halides by oxidation with $NaIO_4$, rapidly halogenates olefins to produce the halo derivatives. The fact that such halogenations take place in *anti* fashion in the case of 1,2-disubstituted olefins probably proves the involvement of bromonium ion.

4.1.5 Conclusion

In conclusion, we have shown that a stable, commercially available $NaIO_4$ oxidizes alkali metal halides efficiently in aqueous medium to halogenate alkenes and produce the corresponding haloderivatives in excellent region- and diastereoselective fashion.

4.1.6 Experimental section:

General experimental procedure for bromomethoxylation of olefins:

To a stirred mixture of olefin (10 mmol), LiBr (12 mmol) and 30% aq. H_2SO_4 (0.5 mL, 10 mmol) in MeOH:H_2O (3:1, 15 mL) at 10-15 ºC was added $NaIO_4$ (25 mol%) in portion-wise. The reaction was monitored by TLC. After completion of the reaction, it was diluted with water and extracted with CH_2Cl_2 (25 mL x 3). The organic layers were washed with dilute solution of Na_2SO_3 and brine. It was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude products, which were purified on column chromatography packed with silica gel using pet. ether and EtOAc (9:1) as eluent to afford the pure products.

2-Bromo-1-methoxy-1-phenylethane (13a):

Yield: 82%; colorless liquid; **IR** (neat, cm^{-1}): 592, 666, 762, 916, 1026, 1060, 1216, 1296, 1452, 1492, 1758, 2892, 2960; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.30 (s, 3H), 3.56-3.43 (m, 2H), 4.40-4.36 (dd, *J* = 9.23, 3.25 Hz, 1H), 7.37-7.32 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 36.07, 57.07, 83.26, 126.59, 128.33, 138.92; **Analysis**: $C_9H_{11}BrO$ requires C, 50.26; H, 5.15; Br, 37.15%; found C, 50.39; H, 5.31; Br, 37.08%.

2-Bromo-1-methoxy-1-(4-methylphenyl)ethane (13b):

Yield: 78%; colorless liquid; **IR** (neat, cm^{-1}): 682, 764, 818, 916, 1016, 1612, 2920, 2958; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.36 (s, 3H), 3.30 (s, 3H), 3.38 (dd, *J* = 10.58, 5.69 Hz, 1H), 3.53 (dd, *J* = 10.43, 5.49 Hz, 1H), 4.35 (dd, *J* = 5.64, 4.51 Hz, 1H), 7.19

(d, J = 8.45 Hz, 2H), 7.20 (d, J = 8.23 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.06, 36.20, 57.01, 83.35, 126.59, 129.25, 135.96, 138.16; **MS** m/z (% rel. intensity): 314 (M^+, 2), 228 (30), 197 (50), 148 (80), 135 (100), 117 (95), 105 (87), 91 (90), 77 (80), 65 (75), 51 (85). **Analysis**: $C_{10}H_{13}BrO$ requires C, 52.42; H, 5.72; Br, 34.88%; found C, 52.29; H, 5.85; Br, 34.93%.

2-Bromo-1-methoxy-1-(4-methoxyphenyl)ethane (13c):

Yield: 80%; colorless liquid; **IR** (neat, cm^{-1}): 680, 750, 1030, 2930, 2964; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.36 (s, 3H), 3.40 - 3.51 (m, 2H), 3.83 (s, 3H), 4.81 (dd, J = 8.9 and 3.95 Hz, 1H), 7.31 (d, J = 8.5 Hz, 2H), 6.91 (d, J = 8.5 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 36.43, 55.28, 73.73, 114.05, 126.99, 133.31, 164.15; **Analysis**: $C_{10}H_{13}BrO_2$ requires C, 49.00; H, 5.35; Br, 32.60%; found C, 49.21; H, 5.19; Br, 32.69%.

2-Bromo-1-methoxy-1-(4-chloromethylphenyl)ethane (13d):

Yield: 78%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): 654, 744, 838, 916, 1066, 1418, 1512, 2960, 3028; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.32 (s, 3H), 3.52-3.46 (m, 2H), 4.40 (dd, J = 9.23, 3.82 Hz, 1H), 4.6 (s, 2H), 7.43-7.30 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 35.89, 45.63, 57.19, 82.83, 127.02, 128.70, 137.61, 139.23; **MS** m/z (% rel. intensity): 264 (M^+, 5), 252 (10), 229 (60), 197 (50), 183 (20), 169 (100), 147 (70), 134 (75), 117 (85), 105 (90), 91 (75), 77 (90), 63 (85), 44 (85); **Analysis**: $C_{10}H_{12}BrClO$ requires C, 45.57; H, 4.59; Halogen, 43.77%; found C, 45.50; H, 4.45; Halogen, 43.64%.

2-Bromo-1-methoxy-1-(4-bromophenyl)ethane (13e):

Yield: 76%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): 670, 830, 1130, 1212, 1460, 1500, 2960, 3026; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.33 (s, 3H), 3.51-3.44 (m, 2H), 4.36 (dd, J = 9.43, 3.83 Hz, 1H), 7.22 (d, J = 8.92 Hz, 2H), 7.52 (d, J = 8.95 Hz, 2H); **^{13}C NMR**

(50 MHz, $CDCl_3$): δ 35.58, 57.10, 82.40, 128.30, 131.57, 137.92, 138.65; **Analysis**: $C_9H_{10}Br_2O$ requires C, 36.77; H, 3.43; Br, 54.36%; found C, 36.81; H, 3.31; Br, 54.47%.

(±)-*trans*-Methyl-2-bromo-3-methoxy-3-phenylpropionate (13f):

Yield: 80%; gum; **IR** ($CHCl_3$, cm^{-1}): 1017, 1146, 1282, 1454, 1740, 2954, 3032; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.32 (s, 3H), 3.81 (s, 3H), 4.39 (d, *J* = 8.15 Hz, 1H), 5.08 (d, *J* = 8.15 Hz, 1H), 7.4 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 35.64, 47.52, 53.00, 75.61, 126.95, 128.46, 128.68, 139.09, 140.52; **Analysis**: $C_{11}H_{13}BrO_3$ requires C, 48.37; H, 4.80; Br, 29.26%; found C, 48.25; H, 4.79; Br, 29.41%.

(±)-*trans*-Ethyl-2-bromo-3-methoxy-3-(4-methoxyphenyl)propionate (13g):

Yield: 87%; gum; **IR** ($CHCl_3$, cm^{-1}): 668, 770, 833, 1032, 1177, 1216, 1251, 1302, 1514, 1613, 1735, 2984, 3018; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.33 (t, *J* = 8.15 Hz, 3H), 3.20 (s, 3H), 3.82 (s, 3H), 4.20 (d, *J* = 9.45 Hz, 1H), 4.30 (q, 2H), 4.50 (d, *J* = 9.56 Hz, 1H), 6.92 (d, *J* = 8.23 Hz, 2H), 7.29 (d, J = 8.45 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.89, 47.79, 55.15, 57.25, 61.86, 83.71, 113.75, 128.91, 129.16, 159.98, 168.8; **Analysis**: $C_{13}H_{17}BrO_4$ requires C, 49.23; H, 5.40; Br, 25.19%; found C, 49.35; H, 5.28; Br, 25.26%.

3-Bromo-3,4-dihydro-4-methoxy-2,2-dimethyl-2H-chromene (13h):

Yield: 83%; **mp**: 55-56 ºC; **IR** ($CHCl_3$, cm^{-1}): 750, 1054, 1132, 1474, 1592, 2960, 3032; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.34 (s, 3H), 1.53 (s, 3H), 3.23 (s, 3H), 4.08 (d, *J* = 10.15 Hz, 1H), 4.86 (d, *J* = 10.15 Hz, 1H), 6.73 (d, *J* = 10.17 Hz, 1H), 6.91 (m, 1H), 7.14 (m, 1H), 7.41 (d, *J* = 10.17 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 19.78, 28.77, 36.52, 62.88, 70.28, 78.82, 116.93, 121.13, 122.30, 127.52, 129.70, 151.93; **Analysis**: $C_{12}H_{15}BrO_2$ requires C, 53.15; H, 5.58; Br, 29.47%; found C, 53.23; H, 5.41; Br, 29.58%.

(±)-*trans*-2-Bromo-1-methoxy–1-phenylpropanol (13i):

Yield: 75%; gum; **IR** ($CHCl_3$, cm^{-1}): 590, 658, 766, 894, 958, 1078, 1216, 1494, 2932, 3032; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.26 (s, 3H), 3.95 (dd, *J* = 21.21, 5.56 Hz, 2H), 4.22-4.19 (m, 1H), 4.49 (d, *J* = 5.89 Hz, 1H), 7.38-7.35 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 57.42, 57.88, 64.42, 85.78, 127.49, 128.33, 128.45, 138.04; **Analysis**: $C_{10}H_{13}BrO_2$ requires C, 49.00; H, 5.35; Br, 32.60%; found C, 49.18; H, 5.21; Br, 32.65%.

(±)-*trans*-2-Bromo-1-phenyl-1-methoxypropane (13j):

Yield: 76%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): 574, 700, 820, 1068, 1176, 1268, 1450, 1603, 2974, 3030; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.54 (d, *J* = 6.4 Hz, 3H). 3.34 (s, 3H), 4.40-4.43 (m, 1H), 5.00 (d, *J* = 3.5 Hz, 1H), 7.34 – 7.35 (m, 5H), **^{13}C NMR** (50 MHz, $CDCl_3$): δ 18.19, 36.56, 55.09, 76.60, 125.70, 127.25, 127.54, 139.01; **Analysis**: $C_{10}H_{13}BrO$ requires C, 52.42; H, 5.72; Br, 34.88%; found C, 52.29; H, 5.75 Br, 34.97%.

(±)-*trans*-2-Bromo-1-methoxyindane (13k):

Yield: 90%; **mp**: 98-99 ºC; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.29-3.19 (m, 1H), 3.58 (s, 3H), 3.73-3.66 (m, 1H), 4.49-4.46 (m, 1H), 4.98-4.97 (m, 1H), 7.41-7.22 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 25.51, 41.54, 43.40, 50.72, 57.53, 91.62, 93.21, 124.61, 125.10, 127.05, 129.01, 139.90, 140.08, 140.33, 141.24; **Analysis**: $C_{10}H_{11}BrO$ requires C, 52.89; H, 4.88; Br, 35.18%; found C, 52.93; H, 4.73; Br, 35.23%.

1-Phenoxy-3-bromo-2-metoxypropane (13l):

Yield: 72%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): 504, 690, 756, 1074, 1238, 1288, 1460, 1592, 2874, 2930; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.31 (s, 3H), 4.12-4.30 (m, 2H), 4.27-4.57 (m, 1H), 5.17-531 (m, 2H), 7.39 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 36.74, 52.26, 59.25, 64.28, 127.58, 128.42, 128.79, 138.72, 139.64, 159.41;

Analysis: $C_{10}H_{13}BrO_2$ requires C, 49.00; H, 5.35; Br, 32.60%; found C, 49.18; H, 5.28; Br, 32.69%.

(±)-*trans*-1-Bromo-2-methoxycyclooctane (13m):

Yield: 65%**;** gum; **IR** ($CHCl_3$, cm^{-1}): 1050, 1250, 1452, 1510, 1725, 2923, 3030; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.49–1.74 (m, 2H), 1.75–1.95 (m, 8H), 1.98–2.19 (m, 2H), 3.82–3.89 (m, 1H), 3.28 (s, 3H), 4.37–4.75 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.57, 24.25, 32.23, 32.74, 34.47, 36.53, 56.60, 70.79; **Analysis**: $C_9H_{17}BrO$ requires C, 48.88; H, 7.75; Br, 36.13%; found C, 48.93; H, 7.69; Br, 36.04%.

1-Bromo-2-methoxyoctane (13n):

Yield: 84%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): 662, 726, 1030, 1126, 1238, 1376, 1740, 2858, 2928; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.89 (t, J = 6Hz, 3H), 1.29-1.54 (m, 10H), 2.05 (s, 1H), 3.26 (s, 3H), 3.34-3.47 (m, 2H), 3.52 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.92, 22.54, 26.61, 28.37, 31.46, 35.98, 36.20, 36.78, 52.92; **Analysis**: $C_8H_{17}BrO$ requires C, 48.44; H, 8.58; Br, 35.81%; found C, 48.59; H, 8.51; Br, 35.75%.

1,3-Dibromo-2-methoxypropane (13o):

Yield: 46%; gum; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.32 (s, 3H), 3.36-4.01 (m, 4H), 4.03-4.35 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 31.79, 36.54, 53.18, 63.99; **Analysis**: $C_4H_8Br_2O$ requires C, 20.72; H, 3.48; Br, 68.91%; found C, 20.63; H, 3.54; Br, 70.03%.

SECTION-II

$NaIO_4$-Mediated Regioselective Oxidative Halogenation of Alkenes using Alkali Metal Halide as Halogen source: A High Yield Preparation of Dibromides

4.2.1 Introduction

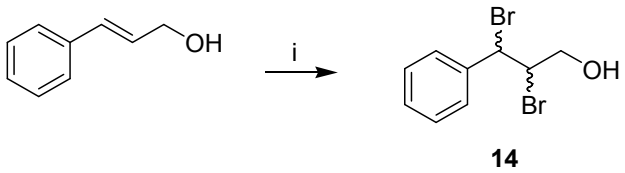
The 1,2-functionalization of olefins by the selective addition of same functional groups, such as halogens, alcohols and amines (dibromination, dihydroxylation and diamination) in stereoselective manner, remains important and challenging to organic chemists.[1] Dihalo derivatives are important compounds in the organic synthesis as well as in analytical chemistry. As an example, the selective determination of alkenes in complex hydrocarbon mixtures, such as air, gasolines etc., by GC-flame ionization detection is indeed difficult. Analysis of alkenes in the presence of alkanes may be however achieved after their transformation into the corresponding dibromo-derivatives using saturated aqueous bromine.[17] More recently, a selective and sensitive method for alkenes determination in different complex matrixes has been obtained by using a GC analysis with element-selective plasma spectroscopic detection of the dibromo derivatives.[18] The resulting dibromides can be transformed to vicinal diazides, diamines, diols, dithiols and aziridines, which are otherwise difficult to prepare, by direct addition to olefins. Thus, the vicinal dibromides represent a very useful class of compounds in organic synthesis.[3]

4.2.2 Review of Literature

Literature search revealed that there are various catalytic as well as non-catalytic methods available for the synthesis of dibromination of olefins. All these methods, which involve use of halides, *N*-halides, metal halides and water sources, are described below.

Strausss's approach (1952)[19]

Strauss *et al.* have reported the dibromination of allyl alcohols in presence of Br_2 in chloroform to give the corresponding mixture of *syn*- and *anti*-dibromide products **14** in 60-70% yield (**Scheme 8**).

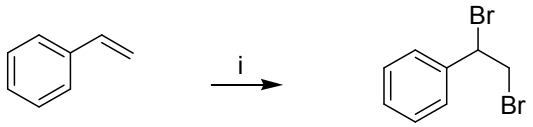


14

Scheme 8: (i) Br_2, $CHCl_3$, 60.70%.

Probst's approach (1957)[20]

In this approach, styrene was converted into the corresponding dibromide **15** using *N*-bromoacetamide and chloroform in moderate yield (**Scheme 9**).

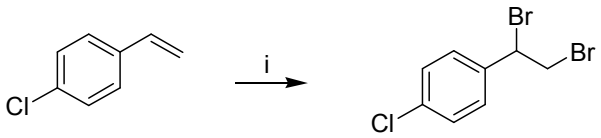


15

Scheme 9: (i) *N*-Bromoacetamide, $CHCl_3$, 2 h, 52%.

Moro's approach (1995)[21]

In this approach, olefins were converted into the corresponding dibromides **16** with H_2O_2 and KBr catalyzed by NH_4VO_3 in moderate to good yields (**Scheme 10**).

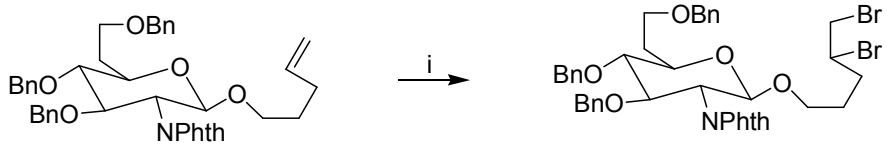


16

Scheme 10: (i) NH_4VO_3, H_2O_2, KBr, CH_2Cl_2/H_2O (1:1), 50-100%.

Snyder's approach (1999)[22]

In this approach, mixture of $CuBr_2$ and LiBr provided the quantitative access to the dibromides **18** from alkenyl sugars **17** that are resistant to straightforward reaction with molecular bromine (**Scheme 11**).

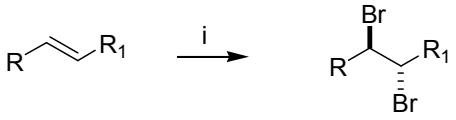


17 **18**

Scheme 11: (i) $CuBr_2$, $LiBr_2$, CH_3CN/THF (3:1), 16 h, 99%.

Pieraccini's approach (2001)[23]

In this approach, olefins were converted into the corresponding dibromides **19** in *anti*-stereoselective manner and good yields using Br_2 in ionic liquid (**Scheme 12**).

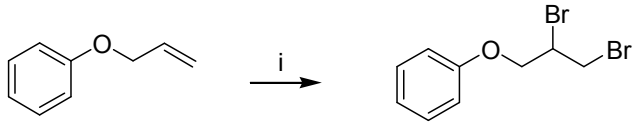


19

Scheme 12: (i) Br_2, [bmim][PF_6], 90-95%.

Hermitage's approach (2004)[24]

Hermitage *et al.* have reported a mild and versatile procedure for the bromination of olefins using expensive (diacetoxyiodo) benzene in stoichiometric amounts and lithium bromide to obtain the corresponding the dibromides **20** (**Scheme 13**).

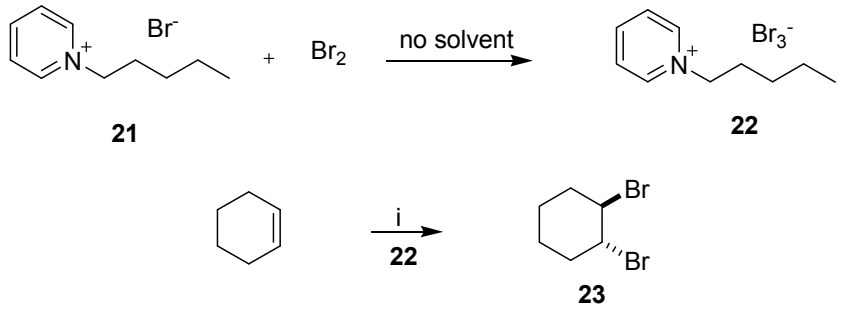


20

Scheme 13: (i) $PhI(OAc)_2$, LiBr, THF, 25 ºC, 0.5 h, 87%.

Dorta's approach (2004)[25]

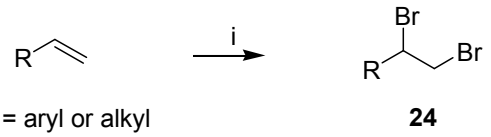
In this approach, an ionic liquid bromine analogue *i.e.* pentylpyridinium tribromide **22**, which was synthesized from pentylpyridinium bromide **21**, was used as a halogen source for 1,2-dibromination of olefins to obtain dibromides **23** (**Scheme 14**).



Scheme 14: (i) 25 ºC, 2 h, 84%.

Shi's approach (2006)[26]

In this approach, olefins were converted into the corresponding dibromides **24** in moderate to good yields (54-82%) using *N*-bromosuccinimide and LiBr (**Scheme 15**).



Scheme 15: (i) *N*-bromosuccinimide, LiBr, THF, 25 ºC, 54-82%.

4.2.3 Present Work

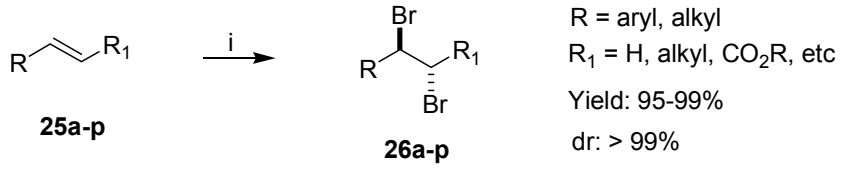
4.2.3.1 Objective

The electrophilic addition of molecular bromine to unsaturated bonds *via* a bromonium ion[27] remains the method of choice for the generation of 1,2-dibrominated compounds. In such a procedure, halogen addition is carried out in CCl_4, one of the common solvents used in bromination. However, CCl_4 is currently on the 'environmental blacklist'. In CCl_4, the electrophilic additions are slow and radical reactions may occur, resulting in a range of products. In addition, despite the widespread use of molecular bromine as an electrophilic reagent it is a toxic, difficult

to handle, low-boiling lachrymatory liquid, which causes severe burns on contact with skin.[28] Moreover, since molecular bromine is a strong oxidizing agent, attempted bromination of complex organic substrates can be hampered by undesired competing oxidation processes.[29] These concerns over selectivity, handling, and toxicity issues associated with Br_2 have fuelled research into new strategies for the bromination of organic substrates. $NaIO_4$ is well-known reagent for oxidation reactions like metal oxidations,[14a] oxidative cleavage of 1,2-diols,[14b] oxidation of sulfides,[14c] phenols,[14d] indoles,[14e] etc. As a model substrate, we tried to halogenate styrene using $NaIO_4$, in combination with lithium bromide in THF, we got the dibromo product in low yield (10%). We tried to increase the yield by using various solvents such as acetone, acetonitrile, methanol, dimethyl sulfoxide, or acetic acid. It became clear that acetic acid medium was found to give excellent yields of dibrominated products (95%).

4.2.4 Results and Discussion

When olefin **25** was treated with lithium bromide (2.4 equiv.) in the presence of $NaIO_4$ (25 mol%) in AcOH, the corresponding 1,2-dibromide products **26** were obtained in excellent yields (upto 99%) with high distereoselectivity (>99%) (**Scheme 16**).[15]



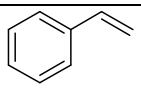
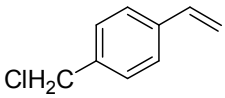
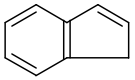
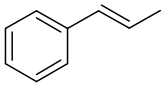
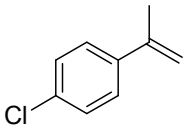
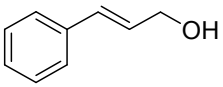
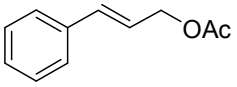
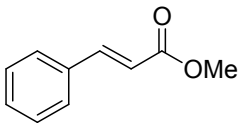
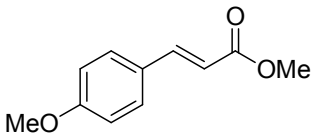
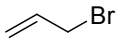
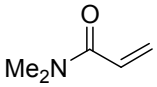
Scheme 16: (i) LiBr (2.4 mmol), $NaIO_4$ (25 mol%), AcOH, 25 ºC, 0.5-1 h, 95-99%.

For a systematic investigation of dibromination, styrene was chosen as a model substrate. To optimize the reaction conditions, various solvents such as acetic acid, acetonitrile, THF, benzene, toluene and various metal halides such as LiBr, NaBr, LiCl, NaCl were tried for the dibromination of styrene at 25 ºC. Among these, acetic

acid and LiBr were proved to be the best solvent and metal halide respectively (see Section I in Chapter 4 for more details). Solvent acetic acid was preferred for the following reasons: (i) reaction was completed within half an hour in quantitative yield and (ii) There was no requirement of other protic acids (H_2SO_4, HCl) for the reaction.

A variety of olefins **25a-p** were then subjected to dibromination using AcOH as solvent (**Scheme 16**), the results of which are summarized in **Table 4**. It can be seen from **Table 4**, various substituted styrenes, α,β-unsaturated carbonyl compounds and olefins **25a-m** underwent oxidative brominations to give the corresponding 1,2-dibromides **26a-m** in quantitative yields. Remarkably, in the case of 1,2-disubstituted olefins, *anti*-isomers of the corresponding dihalo derivatives with dr >99% (**26c-k**) were obtained exclusively. As indicated in **Table 4**, the yields of the dibromides range from 95-99% and are less dependent upon the nature of olefin. Typical substrates such as amides (**25m**) also underwent dibromination in excellent yields; otherwise such amides are resistant to dibromination under normal conditions.

Table 4: $NaIO_4$-mediated oxidative dibromination of olefins with LiBr[a]

No	Olefin	Time (h)	Product	*anti:syn*[c]	Yield[b] (%)
a		1	**26a**	-	95
b		1	**26b**	-	96
c		1	**26c**	>99:1	98
d		1	**26d**	>99:1	99
e		1	**26e**	>99:1	97
f		1	**26f**	>99:1	96
g		1	**26g**	-	95
h		1	**26h**	>99:1	98
i		1	**26i**	>99:1	97
j		1	**26j**	>99:1	98
k		1	**26k**	>99:1	98
l		1	**26l**	-	98
m		2	**26m**	-	93

a) Reaction conditions: alkene (10 mmol), $NaIO_4$ (25 mol%), LiBr (24 mmol), AcOH (15 mL); b) yields refers to isolated product after column chromatography; c) determined based on ^1H and ^{13}C NMR.

The formation of dibromides **26a-m** was confirmed by ^1H, ^{13}C-NMR, IR and Mass spectroscopy. For example, the ^1H-NMR spectrum of 1,2-dibromo-1-phenylpropanol (**26h**) showed a multiplet at δ 4.72 and a doublet of doublet at δ 5.28 for CHBr

protons. Its ^{13}C-NMR also showed typical signals at δ 59.06 and 65.72 for dibromide carbons (**Fig. 3**).

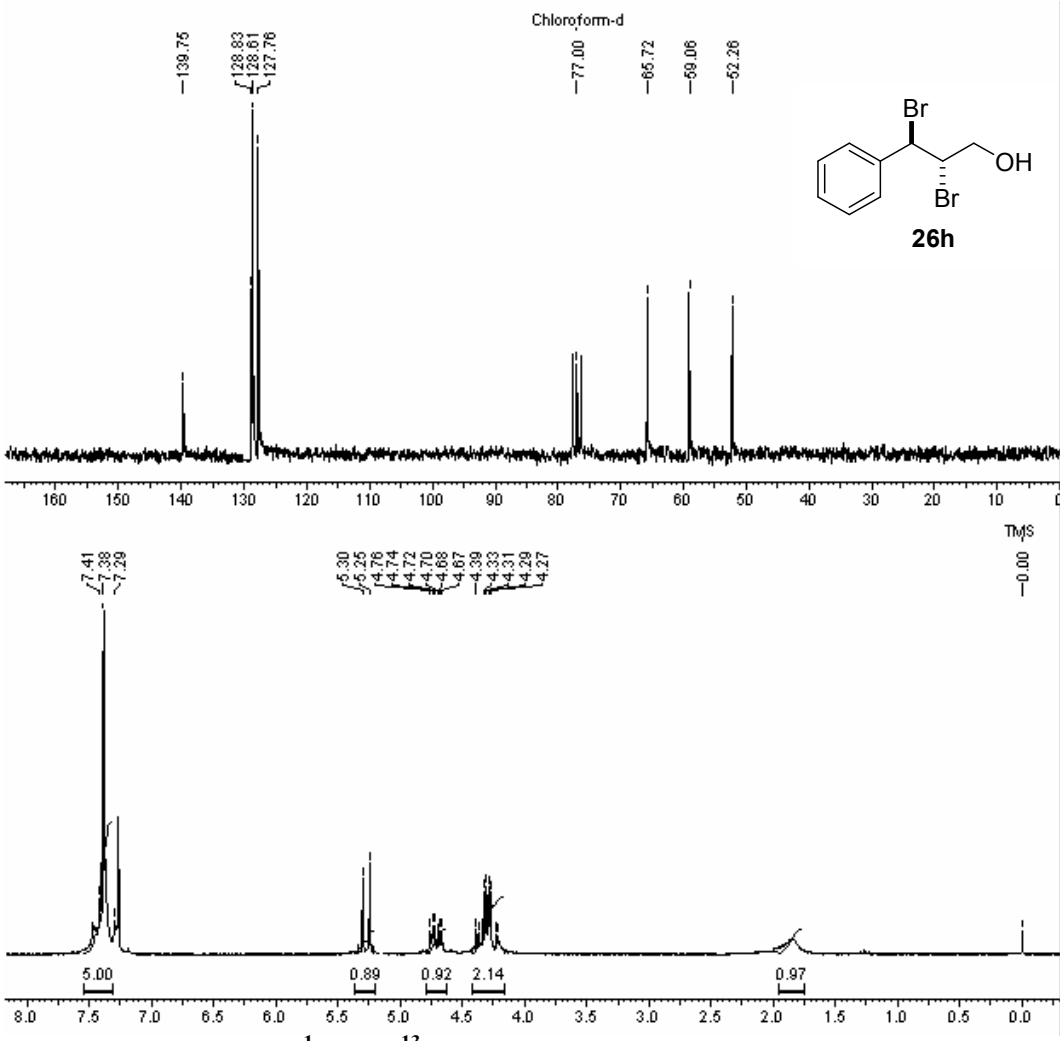


Fig. 3: ^{1}H and ^{13}C NMR spectra of compound 7e

4.2.5 Conclusion

In conclusion, we have described that a stable, commercially available $NaIO_4$ oxidizes alkali metal halides efficiently in AcOH to halogenate alkenes and produce the corresponding dihalo derivatives in quantitative yields and diastereoselective fashion.

4.2.6 Experimental section:

General experimental procedure for dibromination of olefins:

To a stirred mixture of olefin (10 mmol) and LiBr (24 mmol) in acetic acid (15 mL) was added $NaIO_4$ (25 mol%) portion wise. The reaction was monitored by TLC. After completion of the reaction, it was diluted with water and extracted with CH_2Cl_2 (25 mL x 3). The organic layers were washed with dilute solution of $NaHCO_3$, Na_2SO_3 and brine. It was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude products, which were purified on column chromatography packed with silica gel using petroleum ether and ethyl acetate (9:1) as eluent to afford the pure products.

1,2-Dibromo-1-phenylethane (26a):

Yield: 95%; **mp**: 74-75 ºC; **IR** (nujol, cm^{-1}): 554, 680, 725, 840, 914, 1134, 1199, 1265, 1377, 1438, 1463, 1514, 2954; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.98-4.15 (m, 2H), 5.12-5.20 (dd, *J* = 6.52, 6.53 Hz, 1H), 7.40 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 35.02, 50.90, 127.62, 128.76, 129.09, 138.61; **MS** m/z (% rel. intensity): 264 (M+, 5), 185 (96), 183 (100), 77 (45), 63 (8); **Analysis**: $C_8H_8Br_2$ requires C, 36.40; H, 3.05; Br, 60.54%; found C, 36.38; H, 2.98; Br, 60.51%.

1,2-Dibromo-1-(4-chloromethylphenyl)ethane (26b):

Yield: 96%; **mp**: 79-80 ºC; **IR** (nujol, cm^{-1}): 725, 840, 914, 1134, 1199, 1265, 1377, 1438, 1463, 1514, 2954; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 4.0-4.1 (m, 2H), 4.51 (s, 2H), 5.15 (dd, *J* = 6.54, 6.53 Hz, 1H), 7.41 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 34.69, 45.46, 50.02, 128.02, 128.98, 138.00, 138.72; **MS** m/z (% rel. intensity): 312 (M^+, 2), 268 (5), 233 (87), 152 (20), 117 (100), 91 (20); **Analysis**: $C_9H_9Br_2Cl$ requires C, 34.60; H, 2.90; Halogen, 62.50%; found C, 34.46; H, 2.88; Halogen, 62.63%.

1,2-Dibromoindane (26c):

Yield: 98%; gum; **IR** (nujol, cm^{-1}): 545, 685, 732, 750, 817, 896, 946, 1066, 1114, 1170, 1215, 1290, 1346, 1377, 1438, 1463, 2923; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.25 (d, *J* = 7.23 Hz, 1H), 3.82 (dd, *J* = 16.0, 7.15 Hz, 1H), 4.85 (d, J = 7.26 Hz, 1H), 5.65 (s, 1H), 7.3 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 39.06, 53.93, 80.97, 122.93, 125.71, 126.90, 138.25, 141.70; **MS** m/z (% rel. intensity): 276 (M^+, 2), 195 (40), 115 (100), 89 (15); **Analysis**: $C_9H_8Br_2$ requires C, 39.17; H, 2.92; Br, 57.91%; found C, 38.98; H, 2.89; Br, 57.93%.

1,2-Dibromocyclohexane (26d):

Yield: 99%; **mp**: 102-104 ºC/14 mm Hg; **IR** (neat, cm^{-1}): 663, 696, 811, 902, 972, 999, 1161, 1267, 1336, 1357, 1431, 1446, 2860, 2939; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.52-1.59 (m, 6H), 2.30-2.55 (m, 2H), 4.46 (s, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 22.38, 32.01, 55.06; **Analysis**: $C_6H_{10}Br_2$ requires C, 29.79; H, 4.17; Br, 66.05%; found C, 29.76; H, 4.14; Br, 65.98%.

Tetrahydro 2,3-dibromopyran (26e):

Yield: 97%; **mp**: 118-120 ºC; **IR** ($CHCl_3$, cm^{-1}): 871, 972, 1064, 1141, 1218, 1334, 1434, 2854, 2954, 3016; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.7-2.5 (m, 4H), 3.50-3.65 (m, 1H), 3.90-4.21 (m, 2H), 4.99 (d, *J* = 4.12 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 23.19, 29.88, 48.83, 62.90, 96.29; **Analysis**: $C_5H_8Br_2O$ requires C, 24.62; H, 3.31; Br, 65.52%; found C, 24.49; H, 3.28; Br, 65.63%.

1,2-Dibromo-1-phenylpropane (26f):

Yield: 96%; **mp**: 105-106 ºC; **IR** (nujol, cm^{-1}): 696, 769, 817, 850, 1027, 1091, 1157, 1334, 1377, 1429, 1456, 1596, 2921, 2954; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.07 (d, *J* = 6.24 Hz, 3H), 4.55-4.69 (m, 1H), 5.06 (d, *J* = 10.12 Hz, 1H), 7.38 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.45, 49.93, 52.49, 126.93, 127.54, 128.88, 138.10; **MS**

m/z (% rel. intensity): 278 (M^+, 2), 199 (55), 171 (10), 118 (100), 91 (30); **Analysis**: $C_9H_{10}Br_2$ requires C, 38.88; H, 3.63; Br, 57.48%; found C, 38.98; H, 3.78; Br, 57.42%.

1,2-Dibromo-1-methyl-(4-chlorophenyl)ethane (26g):

Yield: 95%; gum; **IR** (nujol, cm^{-1}): 560, 680, 725, 840, 914, 1134, 1199, 1265, 1377, 1438, 1463, 1514, 2954; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.65 (s, 3H), 3.7 (s, 2H), 7.35 (d, *J* = 8.23 Hz, 2H), 7.45 (d, *J* = 8.31 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 27.99, 45.78, 71.25, 126.41, 128.52, 133.37, 142.71; **MS** m/z (% rel. intensity): 232 (M^+-80, 35), 155 (100), 139 (20), 125 (15), 115 (70); **Analysis**: $C_9H_9Br_2Cl$ requires C, 34.59; H, 2.90; Halogen, 62.50%; found C, 34.52; H, 2.78; Halogen, 62.42%.

(±)-*trans*-1,2-Dibromo-1-phenylpropanol (26h):

Yield: 98%; **mp**: 143-144 ºC; **IR** ($CHCl_3$, cm^{-1}): 590, 658, 766, 894, 958, 1078, 1216, 1494, 2932, 3032, 3457; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.84 (br s, 1H), 4.25 (dd, *J* = 12.69, 2.93 Hz, 1H), 4.35 (dd, *J* = 13.18, 3.91 Hz, 1H), 4.67-4.76 (m, 1H), 5.28 (d, *J* = 11.23 Hz, 1H), 7.29-7.47 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 52.26, 59.06, 65.72, 127.76, 128.61, 128.83, 139.75; **Analysis**: $C_9H_{10}Br_2O$ requires C, 36.77; H, 3.43; Br, 54.36%; found C, 36.59; H, 3.49; Br, 54.41%.

(±)-*trans*-2,3-Dibromo-3-phenyl-1-propylacetate (26i):

Yield: 97%; **mp**: 94-95 ºC; **IR** ($CHCl_3$, cm^{-1}): 671, 694, 771, 1056, 1149, 1218, 1365, 1380, 1458, 1751, 3016; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.21 (s, 3H), 4.60-4.81 (m, 3H), 5.21 (d, J = 9.83 Hz, 1H), 7.35 (m, 5H); **Analysis**: $C_{11}H_{12}Br_2O_2$ requires C, 39.32; H, 3.60; Br, 47.56%; found C, 39.19; H, 3.52; Br, 47.61%.

(±)-*trans*-Methyl-2,3-dibromo-3-phenylpropionate (26j):

Yield: 98%; **mp**: 119-120 ºC; **IR** ($CHCl_3$, cm^{-1}): 671, 694, 771, 1056, 1149, 1218, 1365, 1380, 1458, 1751, 3016; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.81 (s, 3H), 4.85 (d, *J*

= 12.12 Hz, 1H), 5.03 (d, *J* = 12.12 Hz, 1H), 7.4 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 46.64, 50.57, 53.36, 128.02, 128.83, 129.34, 137.47, 168.27; **Analysis**: $C_{10}H_{10}Br_2O_3$ requires C, 37.30; H, 3.13; Br, 49.63%; found C, 37.39; H, 3.17; Br, 49.59%.

(±)-*trans*-Ethyl-2,3-dibromo-3-(4-methoxyphenyl)propionate (26k):

Yield: 98%; **mp**: 102-103 ºC; **IR** ($CHCl_3$, cm^{-1}): 668, 770, 833, 1032, 1177, 1216, 1251, 1302, 1514, 1613, 1735, 2984, 3018; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.33 (t, J = 7.15 Hz, 3H), 3.20 (s, 3H), 3.82 (s, 3H), 4.20 (d, *J* = 9.93 Hz, 1H), 4.25-4.34 (m, 2H), 4.50 (d, *J* = 9.93 Hz, 1H), 6.91 (d, *J* = 8.74 Hz, 2H), 7.29 (d, *J* = 8.74 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 13.89, 47.79, 55.15, 57.25, 61.86, 83.71, 113.75, 128.91, 129.16, 159.98, 168.8; **Analysis**: $C_{12}H_{14}Br_2O_3$ requires C, 39.37; H, 3.86; Br, 43.66%; found C, 39.34; H, 3.81; Br, 43.72%.

1,2,3-Tribromopropane (26l):

Yield: 98%; gum; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.80-3.99 (m, 4H), 4.35 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 34.84, 37.19, 48.26; **Analysis**: $C_3H_5Br_3$ requires C, 12.83; H, 1.79; Br, 85.37%; found C, 12.72; H, 1.83; Br, 85.49%.

2,3-Dibromo-*N*,*N*-dimethylpropanamide (26m):

Yield: 93%; **mp**: >210 ºC; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.96 (s, 3H), 1.03 (s, 3H), 1.59 (dd, *J* = 10.56, 6.23 Hz, 1H), 2.07 (t, *J* = 8.34 Hz, 1H), 2.60 (dd, *J* = 12.21, 4.23 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 30.57, 36.20, 37.19, 38.88, 166.17; **Analysis**: $C_5H_9Br_2NO$ requires C, 23.19; H, 3.50; Br, 61.72%; N, 5.41; found C, 23.23; H, 3.55; Br, 61.78; N, 5.38%.

SECTION-III

Metal-catalyzed Asymmetric epoxidation of olefins

4.3.1 Introduction

Barry Sharpless was awarded the 2001 Nobel Prize as a compliment to his great contributions in the field of asymmetric epoxidation, which has been recognized as one of the most important techniques emerging in the last 30 years. These fundamental findings have largely expanded the scope of asymmetric synthesis and allowed a more targeted preparation of pharmaceutical products, such as antibiotics, anti inflammatory drugs and other medicines.

Chiral epoxides are very important building blocks for the synthesis of enantiomerically pure complex molecules, in particular, of biologically active compounds.[30] Catalytic asymmetric epoxidation is an especially useful technique for the synthesis of chiral compounds in both academia and industry because a chiral catalyst molecule can act as an enzyme to induce a million-level chiral product molecules.[31] The development of chiral catalysts capable of inducing asymmetric centers with high efficiency has always been an important task for asymmetric synthesis. The ability to produce desired organic compounds in enantiomerically pure forms from simple and readily available precursors by using extremely small amounts of chiral catalysts, generally with substrate/catalyst molar ratios of 100-1000 or higher, has tremendously practical implications.[32] A variety of carbon-carbon double bonds, for example, those of allylic alcohols, α- and β-unsaturated esters, and simple alkenes, can be catalytically epoxidized with several metal catalysts.[33] The ring strain present in the oxirane system manifests itself through a multitude of ring opening reactions. Biologically important oxiranes include leukotriene A (LTA), the biogenetic precursor of the leukotrienes LTC, LTD and LTE, which are important

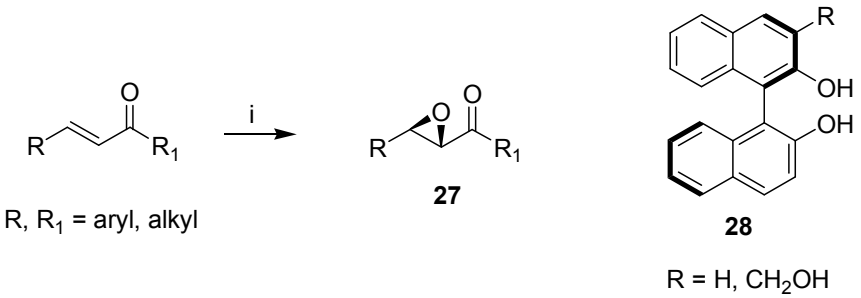
natural mediators of allergic asthma,[34] and arene oxides postulated as intermediates in the metabolism of aromatic compounds to phenols.[35] The ultimate carcinogenic metabolites of polycyclic hydrocarbons are the tetrahydrodiol epoxides.[36] The biological activity aflatoxin B_1, and precocenes are due to the oxiranes derived from them.[37]

4.3.2 Review of Literature

Literature search revealed that there are many methods available for the synthesis of asymmetric epoxidation of olefins.[38] Some of the recent developments on this reaction are discussed below.

Shibasaki's approach (1997)[39]

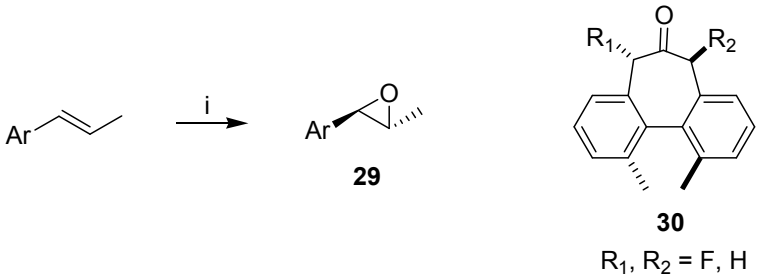
Shibasaki *et al.* have reported that an equimolar mixture of (*R*)-(+)-1,1'-bi-2-naphthol (BINOL) (**28**) and $La(O^iPr)_3$, could catalyze the asymmetric epoxidation of a wide range of (*E*)-enones in the presence of 4 Å molecular sieves to get the corresponding epoxides **27** in good yields (71-93%) and ee (83-94%) (**Scheme 17**).



Scheme 17: (i) $La(O^iPr)_3$ (5 mol%), BINOL **13** (5 mol%), TBHP, THF, 25 ºC, 71-93%, 83-94% ee.

Denmark's approach (1999)[40]

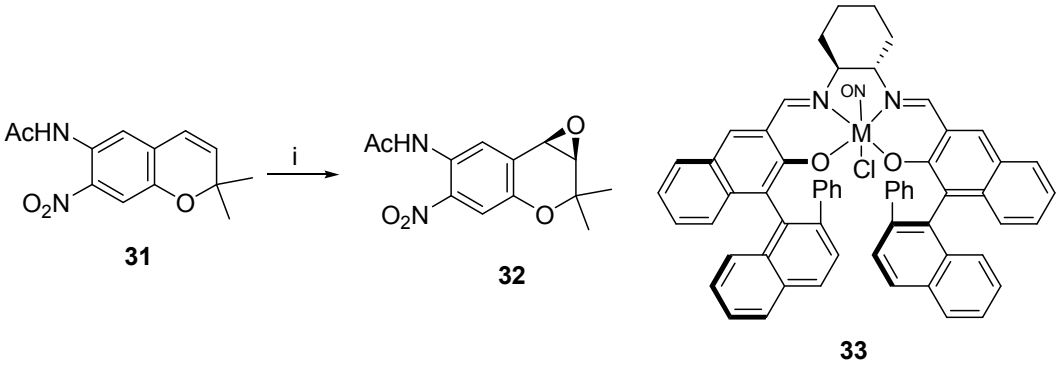
Denmark *et al*. have reported a new, active and enantioselective seven-membered carbocyclic chiral ketone **30** with a chiral center closer to the carbonyl group, in which the lower ee values (35%) and quantitative yields were obtained for the epoxide **29** (**Scheme 18**).



Scheme 18: (i) Catalyst **30** (10 mol%), oxone, $NaHCO_3$, CH_3CN-H_2O, 0 ºC, 100%, 35% ee.

Takeda's approach (1999)[41]

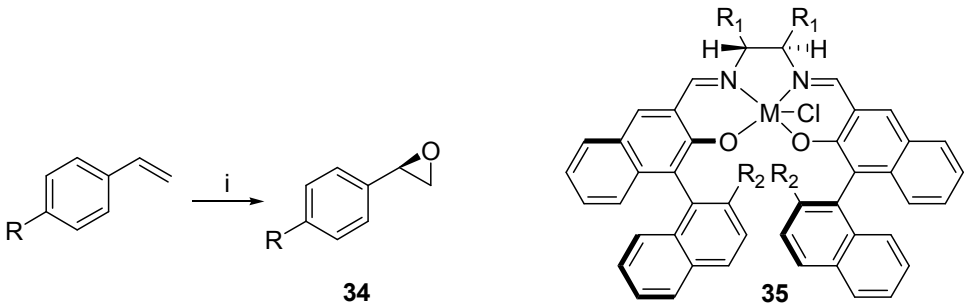
Takeda *et al.* have reported the synthesis and catalytic application of (nitroso)(salen) ruthenium (II) complex [(ON)Ru-salen complex] **33** in the asymmetric epoxidation of 6-acetamido-2,2-dimethyl-7-nitrochromene **31** in the presence of 2,6-dichloropyridine *N*-oxide as an oxidant to get the corresponding epoxide **32** in moderate yield (55%) and good ee (91%) (**Scheme 19**).



Scheme 19: (i) Catalyst **33** (2 mol%), 2,6-dichloropyridine *N*-oxide, CH_2Cl_2, 0 ºC, 55%, 91% ee.

Ahn's approach (2001)[42]

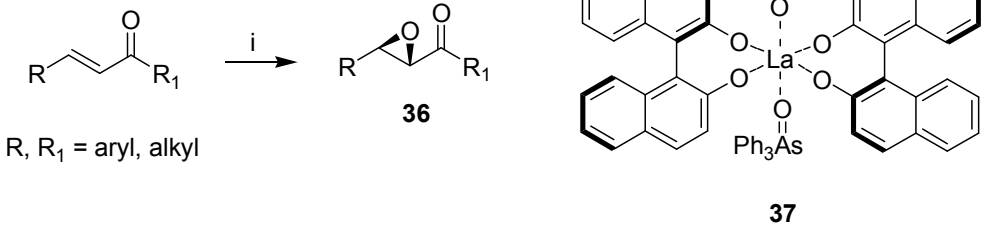
Ahn *et al*. have carried out the asymmetric epoxidation of olefins over the sterically hindered salen-Mn (III) complex **35**, in which moderate to good ee values (53-92%) were obtained for the epoxides **34**. The chirality in diamine moiety of **35** was a requirement for a high enantioselectivity and that the absolute configuration of styrene oxide was controlled by the chirality in the diamine bridge (**Scheme 20**).



Scheme 20: (i) Catalyst **35** (0.02 mmol), NaOCl, CH_2Cl_2, buffer Na_2HPO_4, 0 °C, 50-80%, 53-92% ee.

Nemoto's approah (2001)[43]

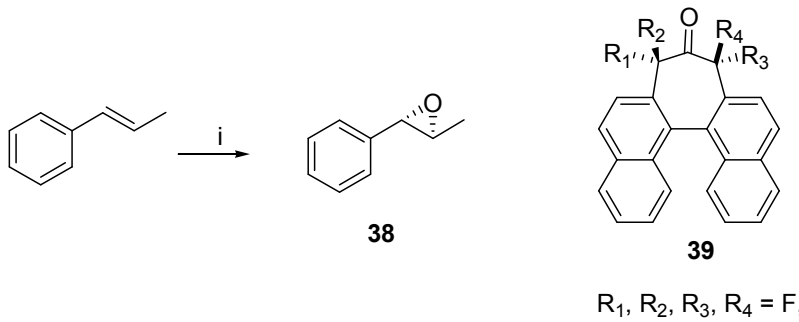
Nemoto *et al.* have reported the application of the asymmetric catalyst, La-BINOL-Ph_3As=O **37**, for the epoxidation of a variety of enones, including dienone and *cis*-enone to get the corresponding epoxide **36** in good yields (85-95%) and ee (92-96%) (**Scheme 21**).



Scheme 21: (i) Complex **37** (5 mol%), TBHP, THF, 25 ºC, 85-95%, 92-96% ee.

Stearman's approach (2002)[44]

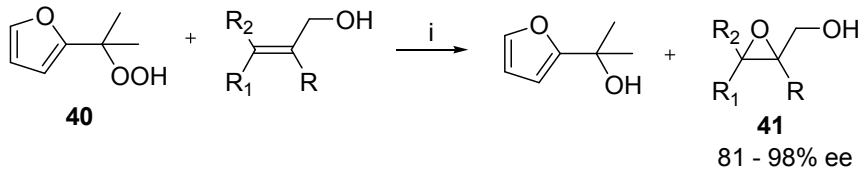
Stearman *et al.* have reported the asymmetric epoxidation of *trans*-*β*-methylstyrene using chiral binaphthyl ketone catalyst **39** with variable distributions of fluorine atoms close to the carbonyl group gave epoxide **38** in quantitative yield and moderate ee (86%) (**Scheme 22**).



Scheme 22: (i) Catalyst **39** (10 mol%), oxone, $NaHCO_3$, CH_3CN-H_2O, -15 ºC, 100%, 86% ee.

Lattanzi's approach (2002)[45]

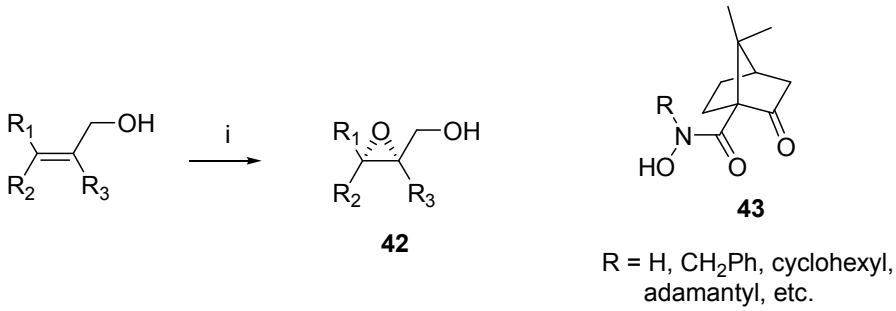
Lattanzi *et al.* have reported that a high enantioselectivity was obtained in the asymmetric epoxidation of allylic alcohols **2** with tertiary furylhydroperoxide **40** as the oxygrn source, $Ti(O^iPr)_4$ as the catalyst and tartarate-based esters as lignads to give epoxides **41** in 90-96% ee (**Scheme 23**).



Scheme 23: (i) $Ti(O^iPr)_4$, L-diethyl tartarate, CH_2Cl_2, 4 Å mol. sieves, -20 ºC, 45-90%, 90-96% ee.

Wu's approach (2002)[46]

Wu *et al.* have reported the synthesis and application of new vanadium catalysts bearing (+)-ketopinic acid-based chiral hydroxamic acid ligands **43** for the asymmetric epoxidation of allylic alcohols. The asymmetric epoxides **42** were obtained in moderate ee (46-89% ee) (**Scheme 24**).



Scheme 24: (i) $VO(O^iPr)_3$ (5 mol%), ligand **43**, TBHP, 0 °C, 70-90%, 46-80% ee.

4.3.3 Present Work

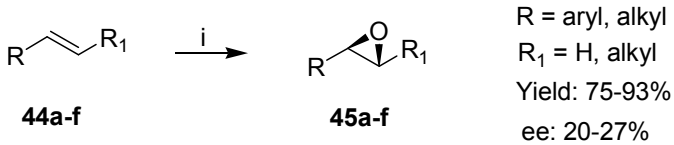
4.3.3.1 Objective

Although there are many methods available in the literature for asymmetric epoxidation of olefins, they suffer from certain drawbacks like use of complex ligands which are costly or difficult to prepare, substrate scope and cumbersome experimental procedures. Our objective is to use simple ligands such as L-proline or $(DHQD)_2$-PYR in presence of metals as catalysts for epoxidation of variety of olefins.

Manganese is a well-known catalyst for asymmetric epoxidation of olefins using variety of complex ligands.[38b] Recently, epoxidation of alkenes catalyzed by simple manganese (II) salts has been reported.[47] Even though manganese salts have excellent ability to catalyze epoxidation reactions, its use in asymmetric epoxidation has not been reported. We have decided to explore the use of manganese salts [such as manganese sulfate ($MnSO_4$) and manganese chloride ($MnCl_2$)] in combination with simple chiral ligands and various oxidants for effecting asymmetric epoxidation of alkenes.

4.3.4 Results and Discussion

When olefins **44** were treated with 30% aq. H_2O_2 (10 equiv.) in the presence of $MnCl_2$ (1 mol%), $(DHQD)_2$-PYR (1.2 mol%) as chiral ligand, $NaHCO_3$ in CH_3CN-H_2O (2:1), the corresponding epoxides **45** were obtained in excellent yields (up to 85%) with low enantioselectivity (20-27% ee) (**Scheme 25**).



44a-f **45a-f**

Scheme 25: (i) $MnCl_2$ (1 mol%), $(DHQD)_2$-PYR (1.2 mol%), $NaHCO_3$ (0.5 equiv.), 30% aq. H_2O_2 (10 equiv.), CH_3CN-H_2O (2:1), 0 ºC, 4-7 h.

Styrene (**44a**) was selected as a model substrate for studying the asymmetric epoxidation reactions (**Scheme 25**). Various catalytic systems were screened for the enantioselective epoxidation of olefins, the results of which are summarized in **Table 5**.

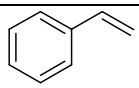
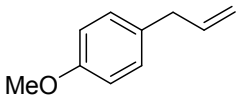
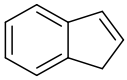
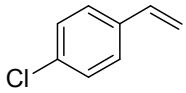
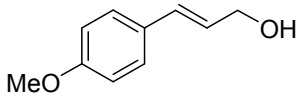
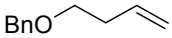
Table 5: Asymmetric epoxidation of phenyl styrene: effect of catalysts and ligands[a]

No	Catalyst	Chiral Ligand	Temp (°C)	Oxidant[f]	Yield[b] (%)	Ee[c] (%) (ac)[d]
1	$Mn(OAc)_2$	L-proline	25	H_2O_2 (30%)	82	8 (*R*)
2	$MnSO_4$	L-proline	25	H_2O_2 (30%)	89	8 (*R*)
3	$MnCl_2$	L-proline	25	H_2O_2 (30%)	92	10 (*R*)
4	$CoCl_2$	L-proline	25	H_2O_2 (30%)	0	-
5	$PdCl_2$	L-proline	25	H_2O_2 (30%)	0	-
6	$MnCl_2$	L-proline	25	H_2O_2-urea[e]	0	-
7	$MnCl_2$	L-proline	25	NMO	0	-
8	$MnCl_2$	L-proline	25	TBHP (70%)	0	-
9	$MnCl_2$	(-)-sparteine	25	H_2O_2 (30%)	0	-
10	$MnCl_2$	$(DHQD)_2$-PYR	25	H_2O_2 (30%)	93	18 (*R*)
11	$MnCl_2$	$(DHQD)_2$-PYR	0	H_2O_2 (30%)	89	25 (*R*)
12	$MnCl_2$	(+)-diisopropyl tartarate	25	H_2O_2 (30%)	88	0
13	$MnCl_2$	(-)-ephedrine hydrochloride	25	H_2O_2 (30%)	85	0
14	$MnCl_2$	D-tyrosine	25	H_2O_2 (30%)	75	0
15	$MnCl_2$	(R)-camphor	25	H_2O_2 (30%)	80	0
16	$MnCl_2$	(-)-quinine	25	H_2O_2 (30%)	86	4 (*S*)
17	$MnCl_2$	hydroquinidine	25	H_2O_2 (30%)	87	5 (*R*)
18	$MnCl_2$	PTC[g]	25	H_2O_2 (30%)	89	8 (*R*)
19	$MnCl_2$	(+)-menthol	25	H_2O_2 (30%)	85	6 (*R*)

a) Reaction conditions: catalyst (1 mol%), ligand (1.2 mol%), oxidant (5-10 equiv.), $NaHCO_3$ (0.5 equiv.), CH_3CN-H_2O (2:1); b) yield refer to isolated yields after column chromatography; c) based on $[\alpha]_D$ with literature values; d) absolute configuration (ac) determined by comparison of $[\alpha]_D$ with literature values; e) solvent is CH_2Cl_2; f) H_2O_2: 10 equiv; g) *N*-benzyl cinconinium chloride

Among all the systems studied, a combination of manganese chloride ($MnCl_2$) and $(DHQD)_2$-PYR (entries 10 and 11) was found to be the best catalytic system (85% yield, 25% ee), which was taken for further studies. The catalytic system consisting of $MnCl_2$ and $(DHQD)_2$-PYR was tested with variety of solvents like CH_3CN, MeOH, acetone, THF, DMF in combination with water and it was found that CH_3CN-H_2O was the best solvent system for epoxidation of alkenes. The epoxidation was carried out at 25 ºC (entry 10) as well as 0 ºC (entry 11) to study the effect of temperature on these catalytic systems. It turned out to give higher ee at lower temperature. Among the various oxidants such as aq. 30% H_2O_2, aq. 70% TBHP, H_2O_2-urea complex *etc*. that were screened for this catalytic system, aq. H_2O_2 was proved to be the best oxidant. After all these initial studies, the combination consisting of $MnCl_2$ (1 mol %), $(DHQD)_2$-PYR (1.2 mol %) and aq. 30% H_2O_2 (10 equiv.) in CH_3CN-H_2O (2:1) has emerged as the best catalytic system for the asymmetric epoxidation of alkenes. Various alkenes, **44a-f** (**Scheme 25**) were subjected to oxidation with this catalytic system to get optically active epoxides, **45a-f** and the results of which are summarized in **Table 6**. It is evident from **Table 6** that a variety of olefins, **44a-f** underwent asymmetric epoxidation under the reaction conditions to yield the corresponding optically active epoxides, **45a-f** in 75-93% yields and 20-27% enantiomeric excess. More substituted olefins showed better enantioselectivity than others. Reactions performed at room temperature (25 ºC) resulted in less enantioselectivity as compared to reactions at 0 ºC. Increasing amount of ligand (upto 5 mol%) does not have any significant effect on the enantiomeric excess of the product.

Table 6: $MnCl_2$-catalyzed asymmetric epoxidation of olefins[a]

No	Olefin	Time (h)	Product	Yield[b] (%)	ee[c] (%)	ac[d]
a		5	**45a**	89	25	*R*
b		4	**45b**	93	23	*R*
c		5	**45c**	92	27	1*S*,2*R*
d		7	**45d**	85	27	*R*
e		5	**45e**	75	24	2*R*,3*R*
f		5	**45f**	90	20	*R*

a) Reaction conditions: a) $MnCl_2$ (1 mol%), $(DHQD)_2$-PYR (1.2 mol%), $NaHCO_3$ (0.5 equiv.), 30% aq. H_2O_2 (10 equiv.), CH_3CN-H_2O (2:1), 0 ºC; b) yields refer to isolated yield after column chromatography; c) %ee was based on comparison of $[\alpha]_D$ values reported in the literature; d) absolute configuration.

4.3.5 Conclusion

In conclusion, we have made an attempt to explore a new metal catalyzed system for the asymmetric epoxidation of alkenes. It turned out that manganese chloride as catalyst in presence of chiral ligand, $(DHQD)_2$-PYR and 30% aq. H_2O_2 as oxidant gave optically active epoxides in 75-93% yield and ee up to 27%.

4.3.6 Experimental section:

General experimental procedure for epoxidation of olefins:

To a cooled (0 ºC) mixture of $MnCl_2$ (0.02 mmol), $(DHQD)_2$-PYR (0.024 mmol) and olefin **44a-f** (2mmol) in CH_2CN-H_2O (2:1, 10 mL), 30% aq. H_2O_2 (20 mmol) was added and the reaction mixture was stirred at 0 ºC. After stirring for the specified time (**Table 6**), the reaction mixture was diluted with EtOAc (10 mL) and washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column

chromatography by using pet. ether and EtOAc as eluent to afford the corresponding pure epoxides **45a-f**.

(*R*)-2-Phenyloxirane (45a):

Yield: 89%; colorless liquid; **[α]$^{25}_{D}$**: +8.8 (neat) {lit.[48] [α]$^{25}_{D}$= +33 (neat)}; **IR** (neat, cm^{-1}): 592, 666, 762, 916, 1026, 1060, 1216, 1296, 1452, 1492, 1758, 2892, 2960; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.56-3.43 (m, 2H), 4.40-4.36 (dd, *J* = 9.23, 3.25 Hz, 1H), 7.37-7.32 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 36.07, 57.07, 83.26, 126.59, 128.33, 138.92; **Analysis**: $C_9H_{11}O$ requires C, 79.97; H, 6.71%; found C, 79.90; H, 6.69%.

(*R*)-2-(4-Methoxybenzyl)oxirane (45b):

Yield: 93%; colorless liquid; **[α]$^{25}_{D}$**: -0.19 (*c* 1.1, $CHCl_3$) {lit.[49] [α]$^{25}_{D}$= +0.8 (*c* 1, $CHCl_3$) for (*S*)-enantiomer}; **IR** ($CHCl_3$, cm^{-1}): 792, 818, 1034, 1110, 1178, 1246, 1480, 1514, 1612, 2994; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.50 (dd, *J* = 4.92, 2.65 Hz, 1H), 2.70-2.91 (m, 3H), 3.06-3.15 (m, 1H), 3.79 (s, 3H), 6.84 (d, *J* = 8.71 Hz, 2H), 7.15 (d, *J* = 8.59 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 37.9, 46.7, 52.6, 55.2, 113.9, 129.1, 130.0, 158.4; **Analysis:** $C_{10}H_{12}O_2$ requires C, 73.15; H, 7.37% found C, 73.24; H, 7.29.

(1*S*,2*R*)-l,2-Epoxyindan (45c):

Yield: 92%; colorless liquid; **[α]$^{25}_{D}$**: +5.6 (*c* 1, $CHCl_3$) {lit.[50] [α]$^{25}_{D}$= +15.7 (*c* 0.94, $CHCl_3$) for 75% ee}; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.99 (dd, *J* = 18.0, 2.9 Hz, 1H), 3.24 (d, *J* = 18.4 Hz, 1H), 4.15 (dd, *J* = 2.9, 2.8 Hz, IH), 4.28 (dd, *J* = 2.6, 1.1 Hz, IH), 7.20-7.35 (m, 3H), 7.52 (d, *J* = 6.8 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 36.12, 57.31, 64.12, 126.19, 128.37, 143.91, 144.43; **Analysis**: C9H8O requires C, 81.79; H, 6.10%; found C, 81.86; H, 6.13%.

(*R*)-2-(4-Chlorophenyl)oxirane (45d):

Yield: 85%; colorless liquid; **$[\alpha]^{25}_{D}$**: -6.4 (*c* 1, $CHCl_3$) {lit.[51] $[\alpha]^{25}_{D}$= -23.8 (*c* 1, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): 670, 830, 1130, 1212, 1460, 1500, 2960, 3026; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.75 (dd, *J* = 5.52, 2.61 Hz, 1H), 3.15 (dd, *J* = 5.43, 4.12 Hz, 1H), 3.84 (dd, J = 4.0, 2.61 Hz, 1H), 7.18-7.26 (m, 2H), 7.30-7.36 (m, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 51.3, 51.8, 126.8, 128.7, 133.9, 136.2, 136.3; **Analysis**: C_8H_7ClO requires C, 62.15; H, 4.56; Cl, 22.93%; found C, 62.23; H, 4.49; Cl, 23.08%.

(2*R*,3*R*)-3-(4-Methoxyphenyl)oxiran-2-yl)methanol (45e):

Yield: 75%; colorless liquid; **$[\alpha]^{25}_{D}$**: -3.0 (*c* 1, $CHCl_3$) {lit.[52] $[\alpha]^{25}_{D}$= -12.45 (*c* 1, $CHCl_3$) for (2*S*,3*S*)-enantiomer}; **IR** ($CHCl_3$): ν 3488, 3019, 2928, 2400, 1603, 1498, 1440, 1259, 1216, 1055, 928, 757 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.13-3.17 (m, 1H), 3.79-3.85 (m, 2H), 3.89 (s, 3H), 3.97-4.06 (m, 1H), 4.24 (d, *J* = 4.6 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 7.13-7.29 (m, 2H), 7.44 (d, *J* = 2.1 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 54.6, 56.2, 61.0, 62.3, 111.7, 126.1, 128.9, 130.5, 133.9, 155.8; **Analysis**: $C_{10}H_{12}O_3$ requires C, 66.65; H, 6.71%; found C, 66.37; H, 7.01%.

(*R*)-2-(2-(Benzyloxy)ethyl)oxirane (45f):

Yield: 90%; colorless liquid; **$[\alpha]^{25}_{D}$** = +3.4 (*c* 3, $CHCl_3$) { lit.[53] $[\alpha]^{25}_{D}$ = + 16.9 (*c* 2.51, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): 3477, 3015, 2925, 2864, 2402, 1725, 1496, 1455, 1362, 1217, 1102, 1028, 910, 831, 766 ; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.62-1.97 (m, 2H), 2.50 (dd, *J* = 2.7, 5.06 Hz, 1H), 2.76 (dd, *J* = 4.06, 4.94 Hz, 1H), 3.01-3.10 (m, 1H), 3.58-3.64 (m, 2H), 4.52 (s, 2H), 7.29-7.35 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 32.76, 46.68, 49.68, 66.76, 72.79, 127.32, 128.13, 128.80, 138.11; **Analysis**: $C_{11}H_{14}O_2$ requires C, 74.13, H, 7.92 found C, 74.46, H, 7.69.

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LIST OF PUBLICATIONS

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