Proline-catalyzed asymmetric synthesis of bioactive molecules and synthetic methodologies involving asymmetric additions onto C=N and C=C bonds

A THESIS

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IN

CHEMISTRY

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CERTIFICATE

Certified that the work incorporated in the thesis entitled "**Proline-catalyzed asymmetric synthesis of bioactive molecules and synthetic methodologies involving asymmetric additions onto C=N and C=C bonds**" was carried out by the candidate under my supervision. Such material as had been obtained from other sources has been duly acknowledged in the thesis.

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Pune Research Supervisor

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DECLARATION

I here by declare that the thesis entitled **"Proline-catalyzed asymmetric synthesis of bioactive molecules and synthetic methodologies involving asymmetric additions onto C=N and C=C bonds"** submitted for the degree of Doctor of Philosophy in Chemistry to the University of Pune, has not been submitted by me to any other university or institution. This work was carried out at the National Chemical Laboratory, Pune, India.

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ABBREVATIONS

Ac	Acetyl
Ar	Aryl
Bn	Benzyl
Boc	*N-tert*-Butoxycarbonyl
$(Boc)_2O$	Ditert-butyl dicarbonate
n-Bu	*n*-Butyl
n-BuLi	*n*-Butyl Lithium
CAN	Cerric ammonium nitrate
Cbz	Benzyloxy carbonyl
CH_2Cl_2	Methylene chloride
$CHCl_3$	Chloroform
CH_3CN	Acetonitrile
$CuSO_4$	Copper(II) sulfate
DBAD	Dibenzyl azodicarboxylate
DBU	1,8-Diazabicyclo[5.4.0]undecene-7
DIBAL-H	Diisobutyl alulinum hydride
DET	Diethyl Tartarate
DMF	Dimethyl formamide
DMSO	Dimethyl sulphoxide
DMAP	*N,N*-dimethyl-4-aminopyridine
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
IBX	2-Iodoxybenzoic acid
KHMDS	potassium hexamethyl disilazide
K_2CO_3	Potassium carbonate
KOH	Potassium hydroxide
$LiAlH_4$	Lithium aluminum hydride
LDA	Lithium diisopropyl amide
LiHMDS	Lithium hexamethyl disilazide
M+	Molecular ion
Me	Methyl
MeOH	Methyl alcohol
MOM	Methoxymethyl
min	Minutes

mL	Milliliter
mp	Melting point
MS	Mass spectrum
Ms	Mesyl
$NaBH_4$	Sodium borohydride
$NaHCO_3$	Sodium bicarbonate
NaOH	Sodium hydroxide
Na_2SO_4	Sodium sulfate
NH_4Cl	Ammonium chloride
NH_4OH	Ammonium hydroxide
NIS	*N*-iodosuccinimide
NMR	Nuclear Magnetic Resonance
NMO	*N*-Methyl morpholine *N*-oxide
Pd/C	Palladium on activated charcoal
Pet. ether	Petroleum ether
Ph	Phenyl
p-TSA	*p*-Toluene sulfonic acid
PhNO	Nitrosobenzene
Py	Pyridine
Red-Al	Bis(2-methoxyethoxy)aluminum hydride
TBS	*tert*-Butyldimethylsilyl
TBHP	*tert*-Butyl hydroperoxide
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TBAF	Tetrabutylammonium fluoride
TBDMSCl	*tert*-Butyldimethylsilyl chloride
TBDPSCl	*tert*-Butyldiphenylsilyl chloride
TFA	Trifluoroacetic acid
TMSCN	Trimethylsilyl cyanide
Ts	Tosyl

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, brs = broad singlet, dd = doublet of doublet, dt = doublet of triplet and ddd = doublet of 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. L-proline, D-proline, DL-proline, DBAD, DBU were purchased from Aldrich

ABSTRACT

The thesis entitled "**Proline-catalyzed asymmetric synthesis of bioactive molecules and synthetic methodologies involving asymmetric additions onto C=N and C=C bonds**" is divided into four chapters.

The title of the thesis clearly reflects the objective, which is to synthesize enantiomerically pure bioactive molecules and drugs using organocatalysis, also to develop useful synthetic methodologies. **Chapter 1** deals with enantioselective synthesis of (*S,S*)-ethambutol (**1**), a tuberculostatic antibiotic, using proline-catalyzed asymmetric α-aminooxylation and α-amination of *n*-butyraldehyde and a short enantioselective synthesis of the antiepileptic agent, levetiracetam (**11**) based on proline-catalyzed asymmetric α-aminooxylation approach. **Chapter 2** describes a short asymmetric synthesis of pheromone (*R*)-hexanolide (**21**) and an antitumor marine metabolite (+)-harzialactone A (**24**) using L-proline-catalyzed sequential α-aminoxylation-HWE olefination of the corresponding aldehydes. **Chapter 3** describes synthetic methodologies involving enantioselective synthesis of γ-amino α,β-unsaturated esters *via* tandem α-amination-HWE olefination of aldehydes and its application for the synthesis of substituted 2-pyrrolidones as well as Lewis acid-catalyzed enantioselective addition of cyanide nucleophile onto nitrones. **Chapter 4** presents an efficient synthesis of antihypertensive drug (*S*)-α-methyldopa (**37**) and antidepressant cericlamine (**43**) *via* organocatalytic asymmetric α-amination of α,α-disubstituted aldehydes; also includes a formal synthesis of antibiotic (-)-anisomycin (**48**).

CHAPTER 1

Asymmetric Synthesis of (*S,S*)-Ethambutol and Levetiracetam using Proline-catalyzed α-Functionalization of Aldehydes

The field of asymmetric organocatalysis is rapidly developing and attracts an increasing number of research groups around the world. In particular, organocatalytic asymmetric synthesis have provided several new methods for obtaining chiral compounds.[1] In this connection, proline, an abundant, inexpensive amino acid available in both enantiomeric forms, has emerged as arguably the most practical and versatile organocatalyst.[1,2] Proline

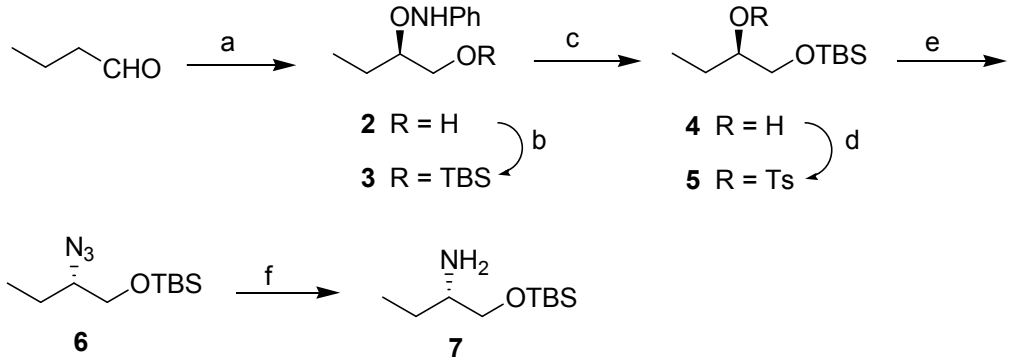
has also been found to be an excellent asymmetric catalyst for α-functionalization[3,4] of carbonyl compounds. This chapter describes proline-catalyzed α-functionalization strategy for the enantioselective synthesis of (*S,S*)-ethambutol (**1**) and levetiracetam (**11**). This chapter is divided into two sections.

SECTION I: Enantioselective Synthesis of (*S,S*)-Ethambutol using Proline-catalyzed Asymmetric α-Aminooxylation and α-Amination

Ethambutol, [(S,S)-2,2'-(ethylenediimino)-di-butanol, **1**], is among the frontline antimycobacterial chemotherapeutic agents, active against nearly all strains of *M. tuberculosis* and *M. kansasii* as well as a number of strains of *M. avium*.[5] Its (*S,S*)-enantiomer is 200-500 times more potent than the (*R,R*)-enantiomer and the meso-isomer.

We envisaged *O*-protected (*S*)-2-amino-1-butanol **7** as the precursor for the asymmetric synthesis of ethambutol. Thus, we have achieved the enantioselective synthesis of (*S,S*)-ethambutol (**1**) by employing proline-catalyzed α-aminooxylation[3] and α-amination[4] of *n*-butyraldehyde; the results of which are presented in this section.

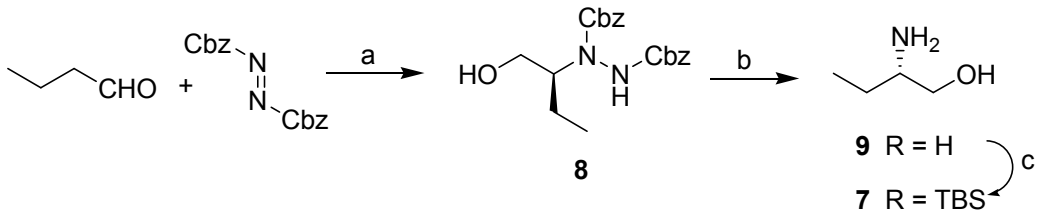
α-Aminooxylation approach: Firstly α-aminooxylation[3a] of *n*-butyraldehyde was carried out using nitrosobenzene and L-proline (25 mol%) at -20 ºC to furnish aminooxy aldehyde which on *in situ* reduction with sodium borohydride afforded the α-aminooxy alcohol **2** in 85% yield; The alcohol **2** was then protected with TBSCl to give the corresponding silyl ether **3** in 90% yield, which on hydrogenation over 10% Pd/C furnished the monoprotected diol **4** in 88% yield. Tosylation of **4** using *p*-toluenesulfonyl



Scheme 1. Reagents and conditions: (a) PhNO, L-proline (25 mol%), -20 ºC, 24 h then MeOH, $NaBH_4$, 85%. (b) TBSCl, imidazole, CH_2Cl_2, 3 h, 90%. (c) H_2 (1atm.), 10% Pd/C, Et_3N, MeOH, 12 h, 88%. (d) *p*-TsCl, Py, 24 h, 95%. (e) NaN_3, DMF, 60 ºC, 30 h, 75%; (f) H_2 (1atm.), 10% Pd-C, Et_3N, MeOH, 6 h, 95%.

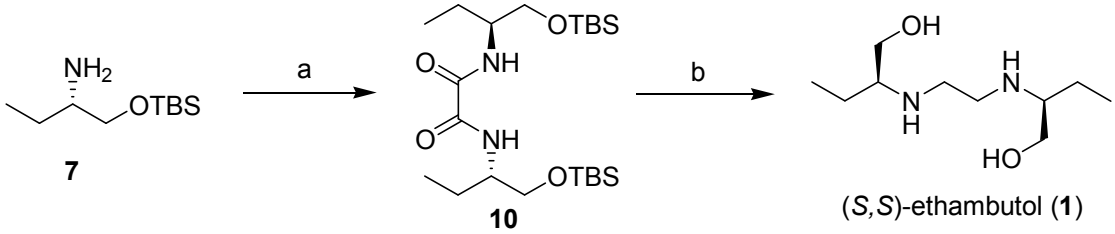
chloride and pyridine followed by displacement of tosyl group with NaN_3 in DMF gave the azido product **6** in 75% yield. Subsequent catalytic hydrogenation of azide with 10% Pd/C-H_2 (1 atm.) afforded the protected amine **7** in 95% yield (**Scheme 1**).

α-Amination approach: In the second approach, α-amination of *n*-butyraldehyde was carried out using List's protocol.[4a] Thus, *n*-butyraldehyde was treated with dibenzyl azodicarboxylate (DBAD) in the presence of D-proline (10 mol%) to furnish aminoaldehyde, which on *in situ* reduction with sodium borohydride afforded the protected amino alcohol **8** in 92% yield. The amino alcohol **8** was then hydrogenated over Raney nickel (H_2) to give (*S*)-2-amino-1-butanol **9** in 70% yield. Protection of the hydroxyl group in the amino alcohol **9** with TBSCl afforded the silyl ether **7** in 85% yield (**Scheme 2**).



Scheme 2. Reagents and conditions: (a) dibenzyl azodicarboxylate , D-Proline (10 mol%), 0-20 ºC, 3 h then $NaBH_4$, EtOH, 92%; (b) H_2 (12 bar), Raney-nickel, MeOH, AcOH, 70%;(c) TBSCl, imidazole, CH_2Cl_2, 0-20 ºC, 3 h, 85%.

Finally, protected aminoalcohol **7** was transformed to (*S,S*)-ethambutol (**1**) in two steps. Thus, amine **7** on treatment with 0.5 equiv. of oxalyl chloride and pyridine furnished oxalyldiamide **10** in 98% yield. The reduction of diamide and TBS deprotection were carried out in one-pot reaction using lithium aluminium hydride at reflux conditions to give (*S,S*)-ethambutol (**1**) in 80% yield and 99% ee (**Scheme 3**).



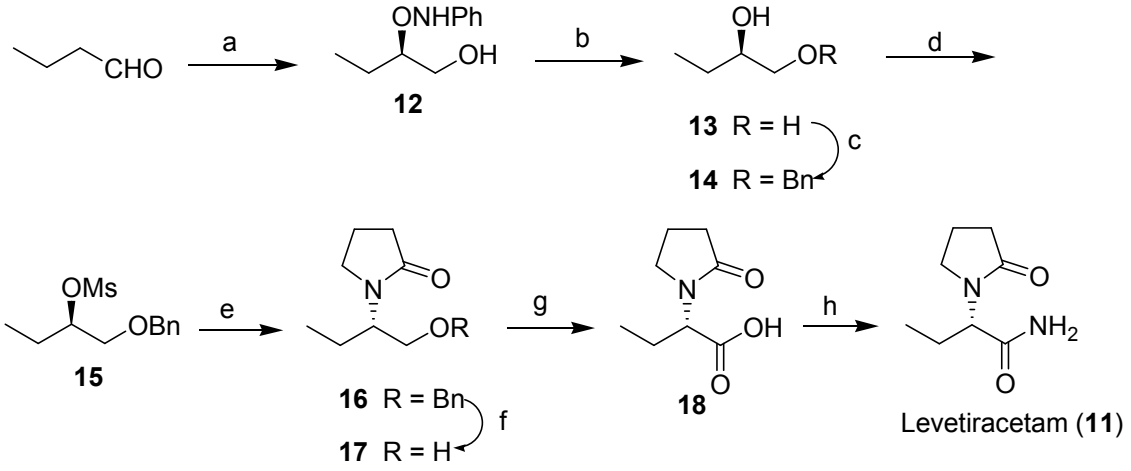
Scheme 3. Reagents and conditions: (a) oxalyl chloride (0.5 equiv.), Py, CH_2Cl_2, 12 h, 98%. (b) $LiAlH_4$, THF, reflux, 24 h, 80%.

SECTION II: A Short Enantioselective Synthesis of the Antiepileptic Agent, Levetiracetam Based on Proline-catalyzed Asymmetric α-Aminooxylation

Levetiracetam, [(*S*)-α-ethyl-2-oxopyrrolidine acetamide, **11**], has recently been approved as an add-on therapy for the treatment of refractory epilepsy.[6] The (*S*)-enantiomer of etiracetam (levetiracetam), has shown outstanding pharmacokinetic and pharmacological activity which has led to the rapid approval of this antiepileptic drug by the FDA.

We have employed L-proline-catalyzed α-aminooxylation coupled with S_N2 displacement of an *O*-mesyl group with 2-pyrrolidone in achieving the enantioselective synthesis of levetiracetam (**11**).

Our synthesis started with α-aminooxylation[3a] of *n*-butyraldehyde, which was carried out using nitrosobenzene and L-proline (25 mol%) at -20 ºC to furnish the aminooxy aldehyde. This was then reduced *in situ* with sodium borohydride to afford (*R*)-α-aminooxy alcohol **12** in 85% yield (**Scheme 4**).



Scheme 4. Reagents and conditions: (a) PhNO, L-proline (25 mol%), -20 ºC, 24 h then MeOH, $NaBH_4$, 85%. (b) H_2 (1 atm.), 10% Pd/C, MeOH, 12 h, 90%. (c) Bu_2SnO, toluene, reflux, 12 h then Bu_4NBr, BnBr, reflux, 24 h, 95%. (d) MsCl, Et_3N, CH_2Cl_2, 0-25 ºC, 4 h, 92%. (e) 2-pyrrolidone, NaH, DMF, 130 ºC, 3 h, 62%. (f) H_2 (1 atm.), 10% Pd/C, MeOH, 6 h, 97%. (g) TEMPO (7 mol%), NaClO-$NaClO_2$, acetonitrile, phosphate buffer (pH 6.8), 25 ºC, 6 h, 90%.(h) $ClCO_2Et$, Et_3N, THF, 0 ºC, 30 min then NH_4OH, 16 h, 75%, 99.5% ee.

The protected alcohol **12** was then hydrogenated over 10% Pd/C; H_2 (1 atm.) to furnish (*R*)-1,2-butanediol **13** in 90% yield. Selective monobenzylation of diol **13** was carried out using Bu_2SnO and benzyl bromide to give **14** in 95% yield. Unfortunately, direct displacement of the secondary hydroxyl group in **14** with 2-pyrrolidone under Mitsunobu conditions failed. Hence, alcohol **14** was treated with methanesulfonyl chloride and

triethylamine to give mesylate **15** in 92% yield. Nucleophilic displacement of mesylate **15** with 2-pyrrolidone in dry DMF at 130 °C proceeded smoothly to give the benzyl ether (*S*)-**16** in 62% yield. Debenzylation of **16** was carried out by catalytic hydrogenation over 10% Pd/C followed by oxidation of the resulting alcohol **17** with sodium hypochlorite-sodium chlorite in the presence of a catalytic amount of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) in acetonitrile-phosphate buffer (pH 6.8) afforded the corresponding acid **18** in 88% overall yield. Acid **18**, on treatment with ethyl chloroformate and ammonium hydroxide, produced levetiracetam (**11**) in 82% yield (75% after recrystallization in acetone) and >99.5% ee (determined by chiral HPLC analysis of the recrystallized sample).

CHAPTER 2

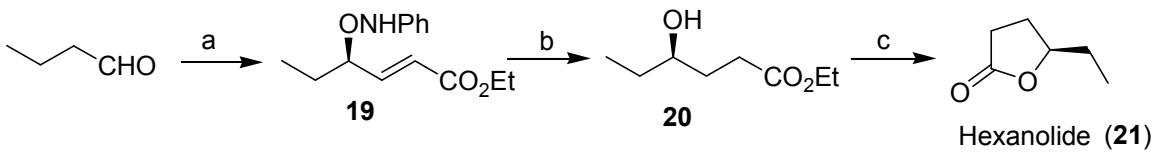
Organocatalytic Asymmetric Synthesis of Hexanolide and Harzialactone A

Proline-catalyzed sequential transformations, is a emerging research field in organic synthesis. In this chapter we employed L-proline-catalyzed sequential aminooxylation-olefination of aldehydes[7] for the asymmetric synthesis of (*R*)-hexanolide and (+)-harzialactone A. The chapter is divided into two sections.

SECTION I: Enantioselective Synthesis of Hexanolide *via* L-proline-catalyzed Sequential Aminooxylation-Olefination

4-Hexanolide (**21**) is a component of attractant pheromone of several *Trogoderma* species of dermestid beetles, such as *T. glabrum* and *T. granarium*.[8] In literature, there are several methods of synthesis of hexanolide have been described, most of them use chiral pool approach. We have achieved highly efficient and short synthesis of (*R*)-4-hexanolide (**21**) *via* L-proline-catalyzed sequential aminooxylation-olefination[9] of *n*-butyraldehyde. Accordingly, synthesis of (*R*)-hexanolide started with α-aminooxylation of *n*-butyraldehyde with nitrosobenzene and L-proline at -20 ^{o}C followed by *in situ* Horner-Wadsworth-Emmons (HWE) olefination with LiCl and DBU (Masamune-Roush protocol) to furnish ester **19** in 75% yield. Reduction of both C=C and anilinooxy group in ester **19** (10% Pd/C, H_2) produced γ-hydroxy ester **20** in 84% yield, which on

subsequent cyclization furnished (*R*)-4-hexanolide (**21**) in 95% yield $[\alpha]^{25}_{D}$ +51.5 (*c* 1, MeOH) { lit.[8b] $[\alpha]^{25}_{D}$ +53.1 (*c* 1, MeOH)} (**Scheme 5**).

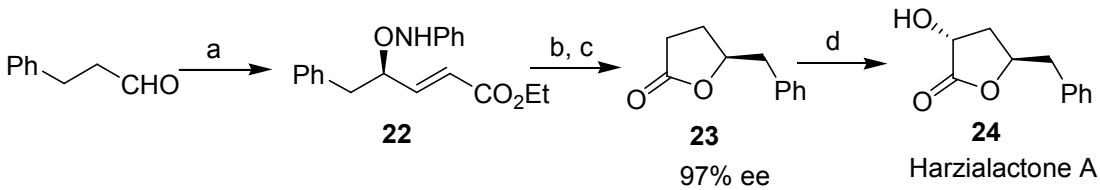


Scheme 5: Reagents and conditions: (a) PhNO, L-proline (25 mol%), CH_3CN, -20 ºC, 24 h then triethyl phosphonoacetate, LiCl, DBU, 1 h, 75%. (b) H_2 (1 atm.), Pd/C (10%), MeOH, 12 h, 84%. (c) EtOH, reflux, 5 h, 95%.

SECTION II: Asymmetric Synthesis of Harzialactone via L-proline-catalyzed Sequential Aminooxylation-Olefination and Diastereoselective α-Hydroxylation

Harzialactone A (**24**) is an antitumor marine metabolite isolated from strain of *Trichoderma harianium* OUPS-N 115 made by Numata and co-workers.[9] In connection with establishing the absolute configuration of harzialactone, Mereyala[10] *et. al*. synthesized this compound from D-glucose and D-xylose in 15% and 24% overall yields respectively. Recently Wu *et. al*.[10c] have synthesized antipode of harzialctone starting from L-malic acid derivative. We have employed L-proline-catalyzed sequential aminooxylation-olefination[9] strategy in the synthesis of harzialactone A (**24**).

Thus, synthesis of (+)-harzialactone A (**24**) started with the same sequential transformation used for hexanolide on hydrocinnamaldehyde to produce **22** in 77% yield. Reduction of C=C and anilinooxy group in **22** (10% Pd/C, H_2) followed by subsequent cyclization gave lactone **23** in 81% yield (over two steps) and with 97% ee (determined by chiral HPLC analysis). Diastereoselective α-hydroxylation of lactone **23** was achieved with



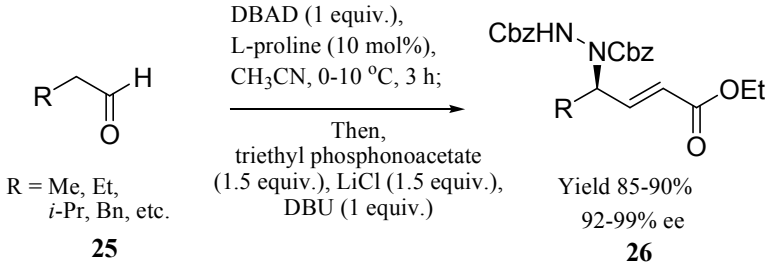
Scheme 6: Reagents and conditions: (a) PhNO, L-proline (25 mol%), CH_3CN, -20 ºC, 24 h then triethyl phosphonoacetate, LiCl, DBU, 1 h, 77%. (b) H_2 (1 atm.), 10% Pd/C, MeOH, 12 h. (c) EtOH, reflux, 5 h, 81% (over two steps), 97% ee. (d) 2-[(4-methylphenyl)sulfonyl]-3-phenyloxaziridine, KHMDS, THF, -78 °C, 1 h, 63%.

KHMDS and 2-[(4-methylphenyl)sulfonyl]-3-phenyloxaziridine as a separable mixture of diastereomers with *trans* lactone **24** (harzialactone A) as a major product (**Scheme 6**) (*dr* 2:1 *trans/cis*, determined by ^{1}H NMR analysis of the crude mixture).

CHAPTER 3

SECTION I: Tandem α-Amination-HWE Olefination of Aldehydes: Enantioselective Synthesis of γ-Amino α,β-unsaturated Esters

Chiral allylic amines, particularly γ-amino-α,β-unsaturated esters **26**, are the key structural elements present in a variety of important naturally occurring molecules and are among the most versatile synthetic intermediates for peptides derivatives, iminosugars, glutamate receptors, amino acids, alkaloids, carbohydrate derivatives, etc. possessing various biological activities such as enzyme inhibitors. Moreover, they could be further functionalized to amino diols, amino epoxy esters, etc. This section describes a one-pot procedure for obtaining highly enantioselective synthesis of γ-amino-α,β-unsaturated esters **26** using tandem α-amination-HWE olefination of aldehydes **25** (**Scheme 7**).



Scheme 7: Asymmetric tandem α-amination/ HWE olefination:

The potential of this reaction has been demonstrated by its easy and efficient incorporation in the synthesis of important optically active 2-pyrrolidinone derivatives such as **27** and **28** and protected amino diol **29** in good yields (**Fig 1**) and by the great substrate generality.

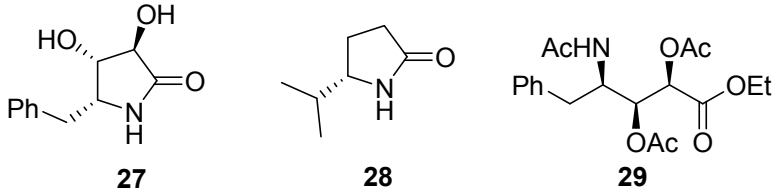


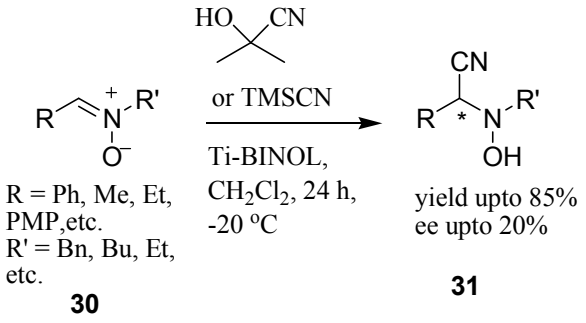
Fig. 1

SECTION II: Chiral Lewis-Acid Catalyzed Asymmetric Cyanide Addition onto Nitrones

Nitrones **30** are highly valuable intermediates for the synthesis of nitrogen containing biologically active compounds, because they are prepared readily by catalytic oxidation of secondary amines, condensation of carbonyl compounds with N-hydroxyl amines, etc. In literature, many methods are reported for stereoselective addition of variety of nucleophiles onto nitrones including diastereoselective addition of chiral enolates, catalytic enantioselective addition of ketene silyl acetals,[11] etc.

This section describes enantioselective addition of cyanide anion onto nitrones **30** catalyzed by chiral Lewis acid such as Ti-BINOL complex (**Scheme 8**).

Accordingly, Ti-BINOL catalyzed addition of cyanide onto nitrones **30** was carried out using trimethylsilyl cyanide or acetone cyanohydrin as cyanide source to get *N*-hydroxylamines **31** in good yields but poor enantioselevtivities. These α-cyano-*N*-hydroxyl amines **31** are direct precursors to the corresponding α-amino acids.



Scheme 8: Lewis acid-catalyzed enantioselective cyanide addition onto nitrones

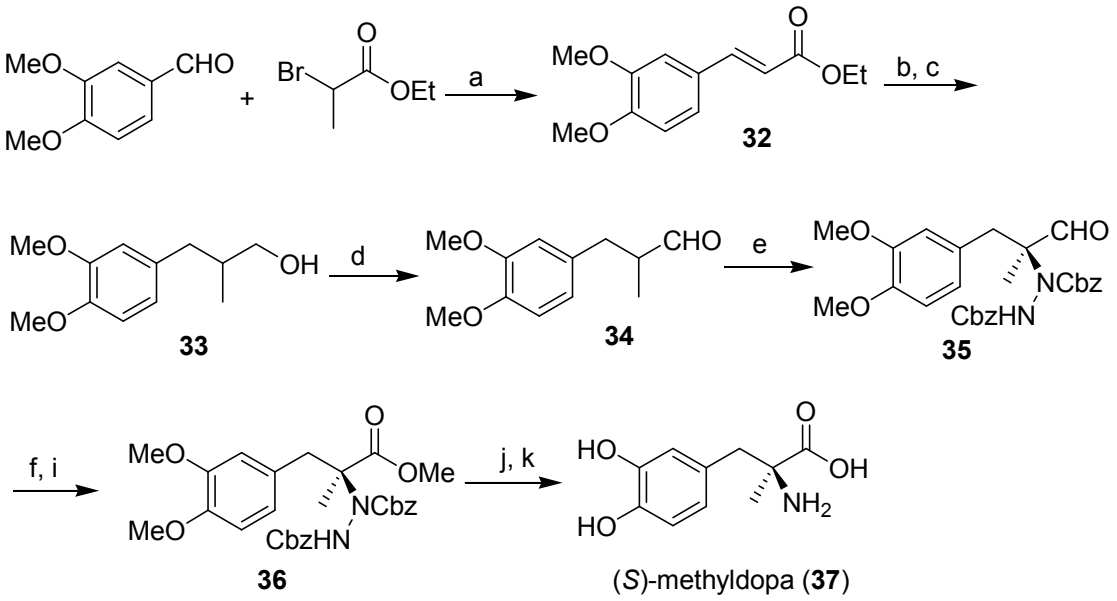
CHAPTER 4

This chapter is divided into three sections.

SECTION I: Organocatalytic Enantioselective Synthesis of Antihypertensive Drug (*S*)-α-Methyldopa

(*S*)-α-Methyldopa (**37**) is a modified unusual amino acid derived from L-Dopa, which is one of the principal agents administered to patients with Parkinson's disease since 1967. Parkinsonism is a chronic neurological disorder characterized by tremor, rigidity of the limbs and poverty of movement (hypokenesia). In literature only few methods are available for the asymmetric synthesis of L-methyldopa (**37**).

Asymmetric α-amination[4] of aldehydes using proline-catalyzed reactions represent a burgeoning field of synthetic research as it has been used to effect such asymmetric transformations as direct Aldol additions, Mannich reactions and conjugate addition reactions, to name only a few. We employed D-proline catalyzed α-amination of corresponding α,α-disubstituted aldehydes for the enantioselective synthesis of L-methyldopa (**37**) (**Scheme 9**).



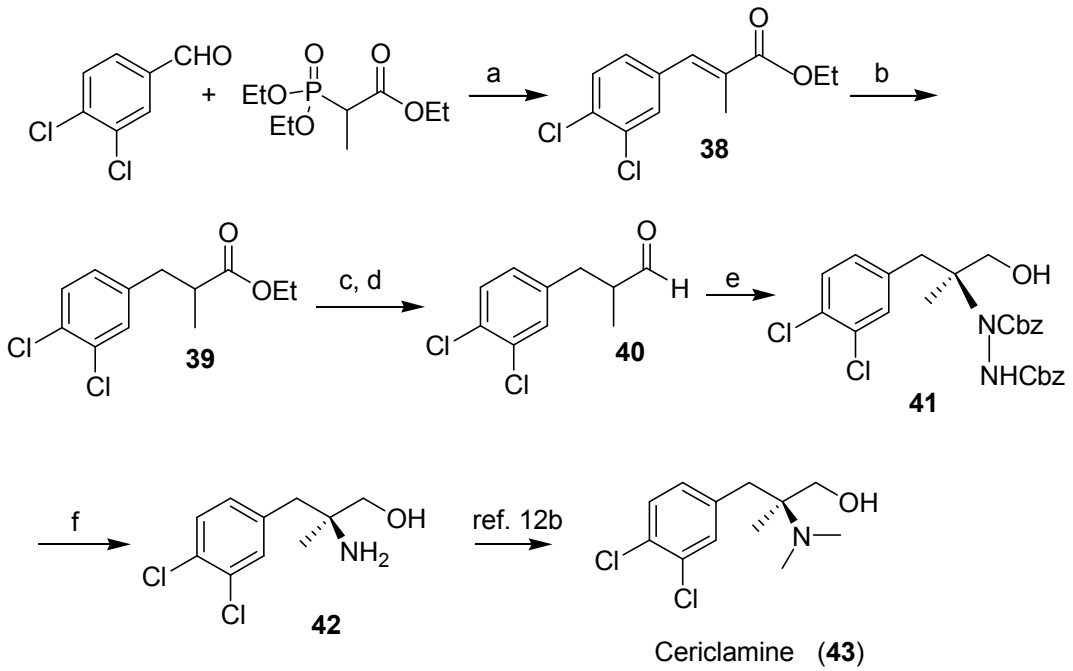
Scheme 9: Reagents and conditions: (a) (i) Zn, C_6H_6, reflux; (ii) cat PTSA, C_6H_6, reflux, 93% for two steps; (b) cat. Pd/C, CH_3OH, H_2 (1atm); (c) LAH, THF, 25 °C, 12 h, 85%.; (d) IBX, DMSO, 30 min., 80%; (e) DBAD, D-Proline, CH_3CN, 10 °C, 30 h, 90%; (f) $NaClO_2$, NaH_2PO_4, DMSO; (i) diazomethane, CH_2Cl_2, 1 h, 82% (over two steps); (j) Raney-Ni, H_2 (60 psig), MeOH, 20 h, 70%; (k) BBr_3, CH_2Cl_2, 60%.

Reformatsky reaction of 3,4-dimethoxybenzaldehyde with α-bromo propionate followed by elimination with *p*-TSA furnished ester **32** in 93% yield. The C=C bond in ester **32** was hydrogenated over (10% Pd/C, H_2) and the resulting saturated ester was subjected to reduction with lithium aluminium hydride to give alcohol **33** in 85% yield, which was oxidized with IBX in DMSO to the corresponding aldehyde **34**. α-Amination of aldehyde **34** with D-proline and DBAD in CH_3CN at 10 °C furnished aldehyde **35** in 80% yield which on oxidation with $NaClO_2$ followed by its treatment with diazomethane gave ester **36** in 82% yield. Reductive removal of both Cbz groups as well as N-N bond cleavage was achieved with Raney-Nickel (H_2, 60 psig). Finally, universal demethylation with BBr_3 furnished (*S*)-α-Methyldopa (**37**) in 60% yield (**Scheme 9**).

SECTION II: Enantioselective Formal Synthesis of Cericlamine

Cericlamine (**43**) is a serotonin reuptake inhibitor which is in clinical trials as an antidepressant.[12a] In literature, few methods of synthesis of Cericlamine are available. This section describes the application of oragnocatalyzed asymmetric α-amination for the enantioselective formal synthesis of Cericlamine (**43**) (**Scheme 10**).

Our synthesis started with ethyl-(3,4-dichloro)-α-methyl cinnamate **38**, which was prepared by Horner-Wadsworth-Emmons olefination of 3,4-dichlorobenzaldehyde with 2-phosphono ester using DBU as a base. Further reduction of C=C in ester **38** was carried out by $COCl_2$ and $NaBH_4$ followed by reduction of ester function with lithium



Scheme 10: Reagents and conditions: (a) LiCl, DBU, CH_3CN, 12 h; (b) $CoCl_2$, $NaBH_4$, 2 h, RT, 85% for two steps; (c) LAH, THF, 12 h, 88%; (d) IBX, DMSO, 30 min., 75%; (e) DBAD, D-proline, CH_3CN, 25 °C, 48 h then MeOH, $NaBH_4$, 53%; (f) Raney-Ni, H_2 (60 psig), MeOH, 65%

aluminium hydride gave the corresponding saturated alcohol, in 88% yield, which on oxidation using IBX in DMSO produced α-methyl aldehyde **40**. The α-methyl aldehyde **40** was subjected to α-amination[4] using D-proline and DBAD in CH_3CN at 25 °C for 48 h to give the α-amination product **41** in average yield. Protected amino alcohol was hydrogenated by Raney Ni to amine **42**, which is direct precursor for the synthesis of cericlamine (**43**) [12b] (**Scheme 10**).

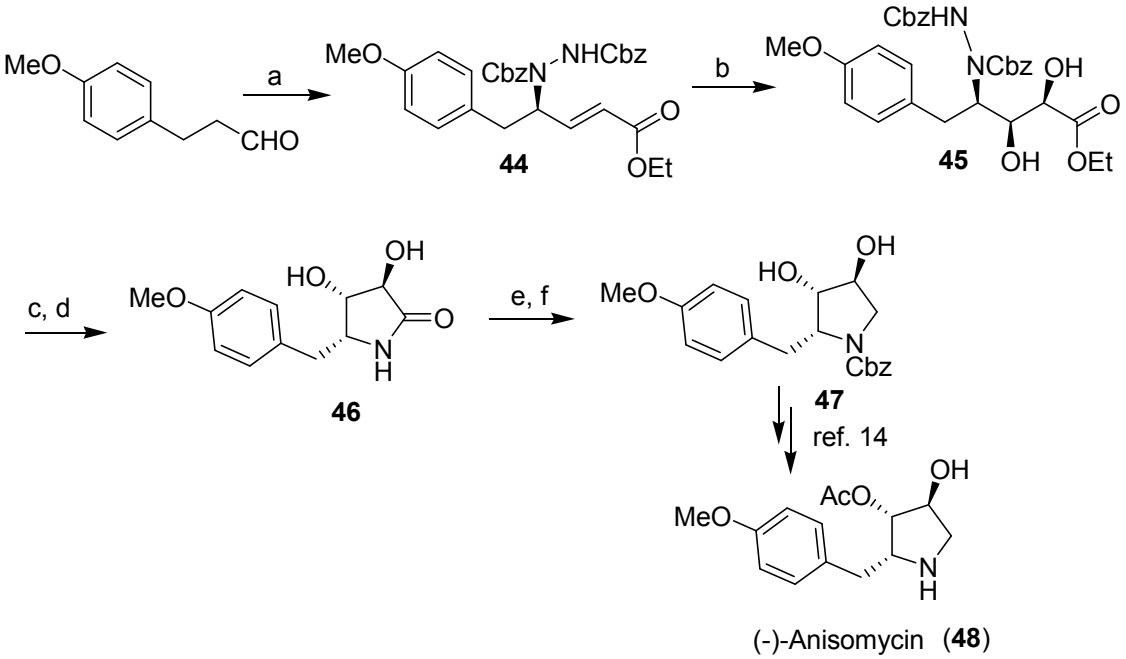
SECTION III: Organocatalytic Formal Synthesis of Antibiotic (-) Anisomycin

The antibiotic (-)-Anisomycin (**48**), isolated from the fermentation broth of Streptomyces sp., exhibits strong and selective activity against pathogenic protozoa and fungi and has clinically been used with success in the treatment of vaginitis due to trichomonas vaginilis and of amoebic dysentery.[13] Both anisomycin and its deacetyl derivative have been used as fungicides in the eradication of bean mildew and for the inhibition of other pathogenic fungi in plants. Anisomycin was also found to inhibit peptide bond formation on eukaryotic ribosomes. Most of the methods reported for the synthesis of anisomycin use chiral pool approach.

We have achieved formal synthesis of (-)-anisomycin (**48**) using two organocatalytic sequential transformations as-

(a) L-proline-catalyzed sequential α-amination-Horner-Wadsworth-Emmons olefination strategy

Firstly, the formal synthesis of (-)-anisomycin **48** was carried out using L-proline-catalyzed sequential α-amination-Horner-Wadsworth-Emmons Olefination of 3-(4-methoxyphenyl) propanal. Accordingly, using the same reaction conditions described in

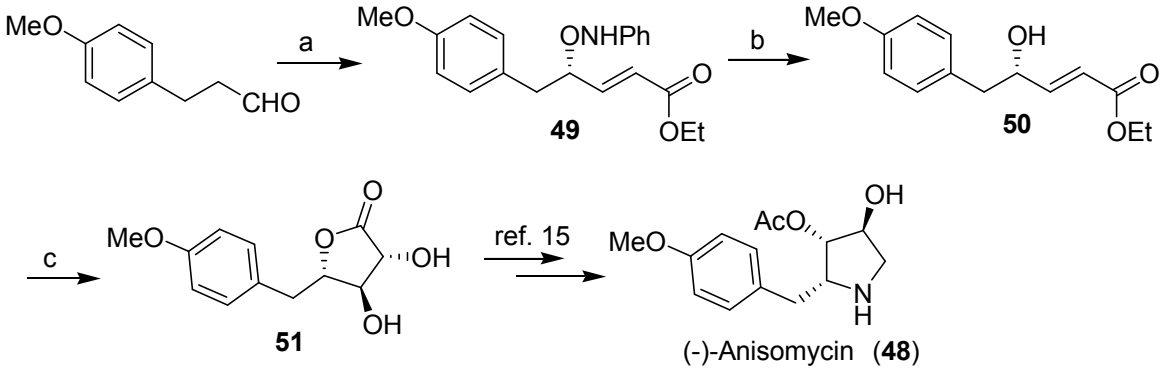


Scheme 11: Reagents and conditions: (a) DBAD, L-proline, CH_3CN, 0-10 °C, 3 h then triethyl phosphonoacetate, LiCl, DBU, 5 °C, 45 min., 88%; (b) OsO_4, NMO, acetone-water; (c) Raney-Ni, MeOH, H_2 (60 psig), 12 h; (d) EtOH, reflux, 4 h, 60% (over two steps); (e) BH_3.THF, THF, reflux, 10 h; (f) aq. Na_2CO_3, Cbz-Cl, CH_2Cl_2, 4 h, 66% (over two steps).

Chapter 3 (section I) we synthesized γ-amino-α,β-unsaturated ester **44** in 88% yield. The Os-catalyzed diastereoselective dihydroxylation of **44** furnished diol **45** in 85% yield (dr 7:1 *syn:anti*). Reductive cyclization was achieved with Raney-Nickel (H_2, 60 psig) in 60% yield. The amide in **46** was reduced with BH_3.THF followed by Cbz protection gave N-Cbz protected diol **47** in 66% yield (**Scheme 11**) from which synthesis of (-)-anisomycin (**48**) has been reported.[14]

(b) D-proline-catalyzed sequential α-aminooxylation-Horner-Wadsworth-Emmons olefination strategy

In the second approach, the synthesis was started where in α-aminooxylation of 3-(4-methoxyphenyl)propanal followed by *in situ* Horner-Wadsworth-Emmons olefination with DBU furnished aminooxy olefinic ester **49** in 85% yield. The deprotection of anilinooxy group to hydroxy group was achieved with $Cu(OAc)_2$ in ethanol. Os-catalyzed diastereoselective dihydroxylation of **50** furnished 3,4-*anti*-γ-lactone **51** in 82% yield (dr *anti:syn* 40:1) (**Scheme 12**). The synthesis of (-)-anisomycin (**48**) has already been reported from lactone **51**.[15]



Scheme 12: Reagents and conditions (a) PhNO, D-proline (20 mol %), CH_3CN, -20 ºC, 24 h then triethyl phosphonoacetate, LiCl, DBU, 1 h, 74%; (b) $Cu(OAc)_2$, EtOH, 25 ºC, 12 h; (c) OsO_4, NMO, acetone-water, 2 h, 82%.

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CHAPTER I

Asymmetric Synthesis of (S,S)-Ethambutol and Levetiracetam using Proline-catalyzed α-Functionalization of Aldehydes

Section I:

Proline-catalyzed asymmetric organic transformations: Review

1.1.1 Introduction to asymmetric organocatalysis

The broad utility of synthetic chiral molecules as single-enantiomer pharmaceuticals, in electronic and optical devices, as components in polymers with novel properties, and as probes of biological function, has made asymmetric catalysis a prominent area of investigation. Until a few years ago, it was generally established that transition metal complexes and enzymes were the two main classes of very efficient asymmetric catalysts. Synthetic chemists have hardly used small organic molecules as catalysts throughout the last century, even though some of the very first asymmetric catalysts were purely organic molecules. Simple organic molecules can be highly effective enantioselective catalysts for a variety of important organic transformations.[1] This rediscovery has initiated an explosive growth of research activities in organocatalysis both in industry and in academia. The 1970s brought a milestone in the area of asymmetric organocatalysis, when two industrial groups led by Hajos and Wiechert published the first and highly enantioselective catalytic aldol reactions using simple amino acid proline as the catalyst.

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

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

Recently, List[1] introduced a system of classification based on the mechanism of catalysis (**Fig. 1**). The four categories are Lewis base, Lewis acid, Bronsted base and Bronsted acid catalysis. Accordingly, Lewis base catalysts (B:) initiate the catalytic cycle via nucleophilic addition to the substrate (S). The resulting complex undergoes a reaction and then releases the product (P) and the catalyst for further turnover. Lewis acid catalysts (A) activate nucleophilic substrates (S:) in a similar manner. Brønsted base and acid catalytic cycles are initiated via a (partial) deprotonation or protonation, respectively.

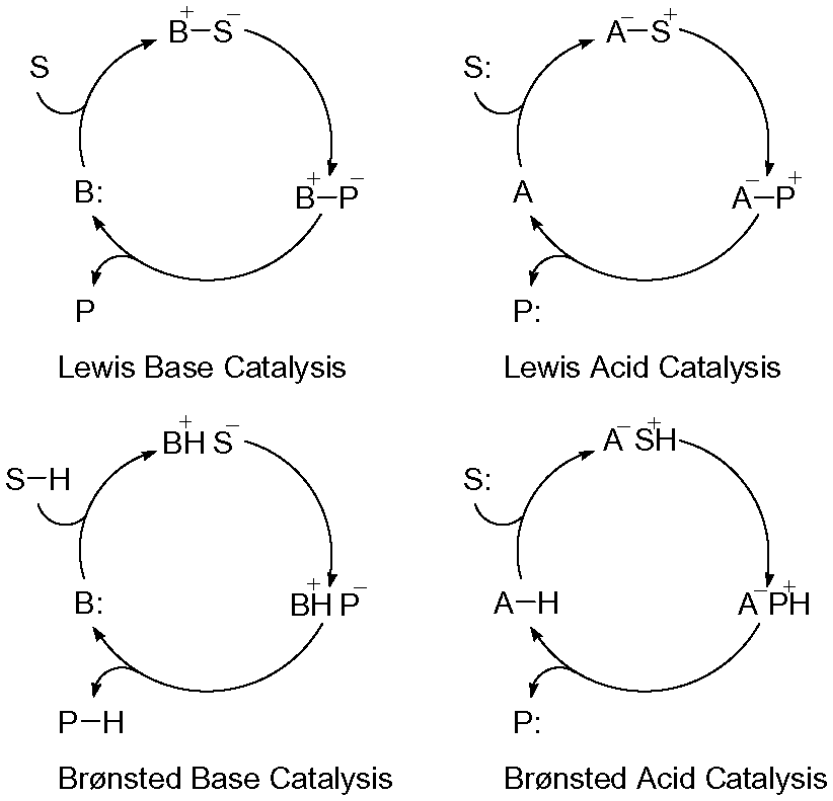


Fig. 1: Organocatalytic cycles

1.1.2 Proline a "Universal catalyst"

Proline (**1**) has been defined as a "universal catalyst" because of its high utility in variety of asymmetric organic transformations. Proline is the only natural amino acid with a secondary amine functionality, which raises the pKa value and better nucleophilicity as compared to other amino acids. It can act as a nucleophile to carbonyl groups (iminium intermediate) or Michael acceptors (enamines).

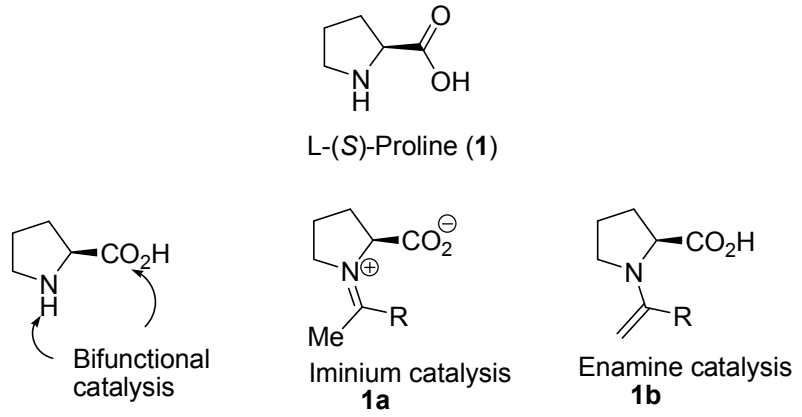


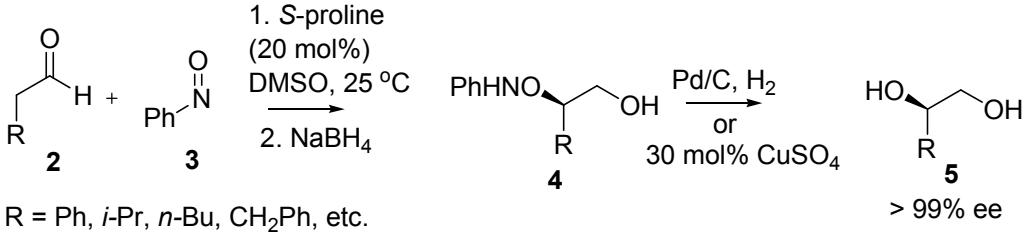
Fig. 2: Modes of proline catalysis

It can be regarded as a bifunctional catalyst as the secondary amine acts as Lewis base and the acid group acts as Bronsted acid (**Fig. 2**). The high stereoselectivity in the proline-catalyzed reactions is possibly due to its formation of organized transition states with many hydrogen bonding frameworks. Proline is not the only molecule to promote catalysis, but it still seems to be one of the best in the diversity of transformations. It is known to catalyze aldol,[2] Diels-Alder,[3] Michael addition[4] and α-functionalization[5] among many other organic transformations.[6] Particularly proline-catalyzed α-aminooxylation[7] and α-amination[8] of carbonyl compounds have emerged as powerful methods because chiral building materials can be synthesized in effective manner starting from easily available materials.

1.1.3 Proline-catalyzed α-Aminooxylation

Optically active α-hydroxyaldehydes and ketones are important intermediates in organic synthesis as they are direct precursors to 1,2-diols. Because of this utility many methods have been developed for their preparation. The more prominent, well-established methods of enantioselective α-oxygenations include the use of Davis oxaziridine,[9a] Sharpless dihydroxylation of enol ethers,[9b] manganese–salen epoxidation of enol ethers,[9c] and Shi epoxidation of enol ethers.[9d] It is only rather recently that direct catalytic, asymmetric variants have been reported.[10] Most of these methods, however, require multiple manipulations and there is no direct method, nor catalytic asymmetric method for their synthesis from the corresponding aldehyde.

Recently, proline has been found to be an excellent asymmetric catalyst for α-aminooxylation[7] of carbonyl compounds. When an aldehyde **2** without substitution at α-position was reacted with nitrosobenzene **3** in presence of L-proline in DMSO at ambient temperature, aminooxylation of the aldehyde takes place at the α-position. Aldehyde can be reduced *in situ* with sodium borohydride and the aminooxyl moiety undergoes hydrogenolysis with Pd/C, H_2 or $CuSO_4$ to give the corresponding diols **5** in very high enantioselectivities (**Scheme 1**).



Scheme 1: α-Aminooxylation of aldehydes

The mechanism of the α-aminooxylation reaction is shown in **Fig. 3**. The observed enantioselectivitiy of the catalytic α-aminooxylation of aldehydes can be rationalized by invoking an enamine mechanism operating through a chair transition state where the *Si* face of an *E*-enamine formed from the aldehyde and L-proline approaches the less-hindered oxygen atom of nitrosobenzene to provide a chiral α-aminoxyaldehyde with *R* configuration. Since proline is commercially available in both enantiopure forms, a one-pot sequential catalytic α-aminooxylation of aldehydes followed by *in situ* reduction with $NaBH_4$ affords *R*- or *S*- configured 1,2-diol units (the secondary alcohol "protected" by an *O*-amino group) with excellent enantioselectivities and in good yields.

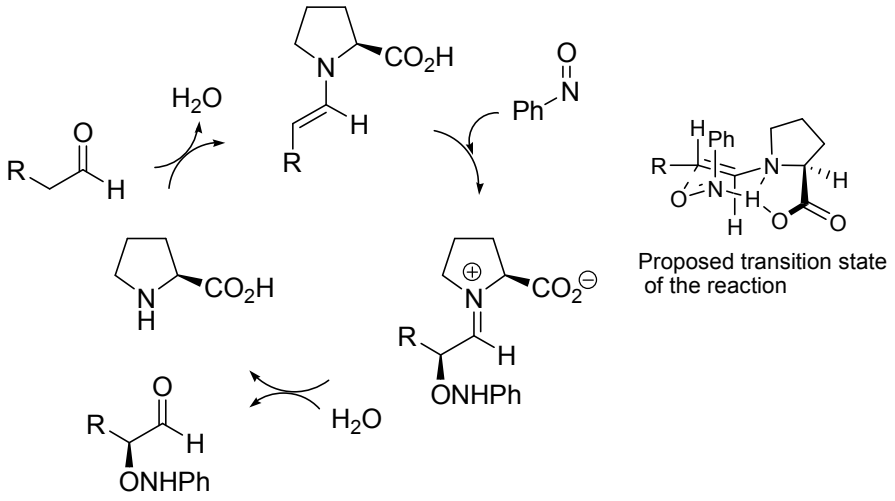


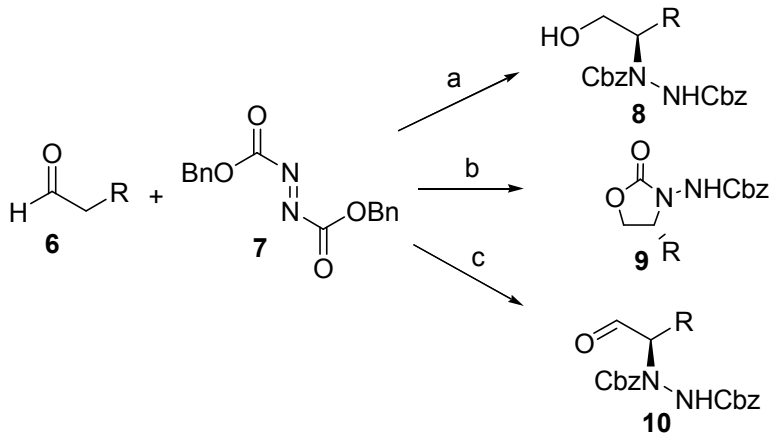
Fig. 3: Proposed mechanism of the α-aminooxylation reaction

1.1.4 Proline-catalyzed α-Amination

The motivation to investigate enantioselective α-amination of carbonyl compounds is provided by valuable synthetic targets such as α-amino acids and α-amino alcohols. The importance of optically active α-amino acids, α-amino aldehydes, and α-amino alcohols, formed by asymmetric catalysis, has stimulated an enormous development in synthetic strategies, and two different catalytic, enantioselective approaches are attractive: the C-C

and the C-N bond-forming reactions. The catalytic enantioselective C-C bond-forming reactions include the addition to imines, such as the Strecker and Mannich reactions. The catalytic, enantioselective, direct C-N bond-forming reaction using aldehydes and a nitrogen source, such as azodicarboxylates, would constitute one of the simplest procedures for the construction of a stereogenic carbon center attached to a nitrogen atom.

Asymmetric α-amination[8] of aldehydes using proline-catalyzed reactions represent a burgeoning field of synthetic research as it is a tool for synthesizing chiral building blocks such as α-amino acids, α-amino aldehydes, and α-amino alcohols. The use of organocatalysis, in particular proline represents a drastic change in approach to asymmetric α-amination. Recently, both List[8a] and Jørgensen[8b] disclosed the asymmetric α-amination of aldehydes (**Scheme 2**) using catalytic quantities of proline. While these approaches parallel each other in many ways, minor variations in reaction conditions result in different products, as well as differences in yields and enantiomeric ratios.



Scheme 2: (a) L-proline (10 mol%), CH_3CN, 0 °C, 3 h; $NaBH_4$, EtOH; (b) L-proline (10 mol%), CH_2Cl_2, 25 °C; $NaBH_4$, MeOH; 0.5 N NaOH; (c) L-proline (10 mol%), CH_2Cl_2, 25 °C; H_2O.

The reaction involves the addition of (*S*)-proline (10 mol%) to a solution of aldehyde and azodicarboxylate ester. List found that optimal enantiomeric enrichment of alcohol product **8** was obtained when the reaction temperature of 0 °C and *in situ* reduction with sodium borohydride was employed. Alternatively, Jørgensen found that aldehydes could be isolated directly, with diminished enantiomeric enrichment as reaction times increased, if the reaction was carried out in methylene chloride at room temperature. This procedure furnishes aldehyde products **10** (path c); these could be converted to the fully protected α-amino acids *via* a multi-step protocol of oxidation, deprotection, protection, and hydrogenolysis. To access *N*-amino oxazolidinones, precursors to α-amino alcohols, Jørgensen's standard proline protocol was used, followed by addition of sodium borohydride and subsequent treatment with sodium hydroxide to facilitate cyclization to the desired product **9** (path b). These additional steps resulted in significantly diminished yields compared to List's route to α-amino alcohol precursors (path a). Both List and Jørgensen were able to achieve high yields and excellent enatiomeric ratios using sterically hindered substrates. This method is easily performed on gram scale using inexpensive chiral catalyst and can be performed in the absence of solvent.

The key shortcoming of this method is that excess aldehyde **6** is required, a serious disadvantage when using valuable aldehydes. Both List and Jørgensen proposed transition states that rationalize the observed stereochemical outcome. While these transition structures involve the anticipated enamine intermediate, they differ substantially in the prediction of the lowest energy conformation of the transition state. Jørgensen proposed a boatlike transition state **11**, whereas List a chairlike transition state **12**, analogous to that proposed for proline-catalyzed intramolecular aldol reaction.[11] It is

worth mentioning that transition structure **12** lacks the hydrogen bond to the proline nitrogen, as Houk and coworkers have recently shown through a series of calculations that the N-H hydrogen bond does not lower the transition state energy in the corresponding aldol reaction[12] (**Fig. 4**).

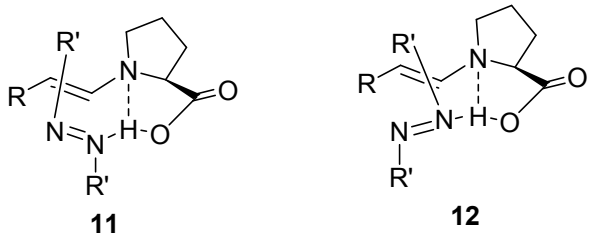


Fig. 4: Transition states for α-amination

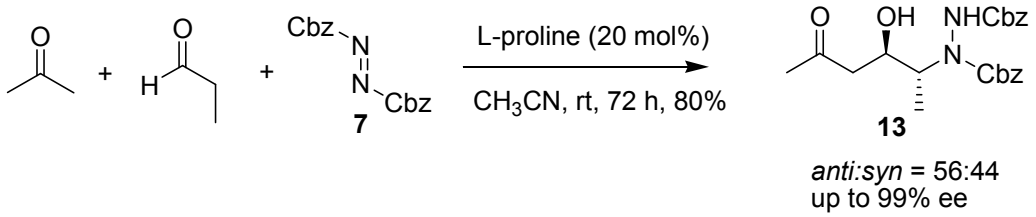
While both transition structures lead to identical products directed by the hydrogen bond from the carboxylic acid of proline, they presumably possess unique energies, so one transition state should be the favored. However, the operative transition state has yet to be established.

1.1.5 Proline-catalyzed sequential transformations

Proline-catalyzed sequential transformations,[13] is a emerging research field in organic synthesis as synthesis of complex organic molecules could be accessible in one-pot procedure. Recently a variety of such transformations has been developed by different research groups some of them are described below

1.1.5.1 Sequential amination-aldol [13a]

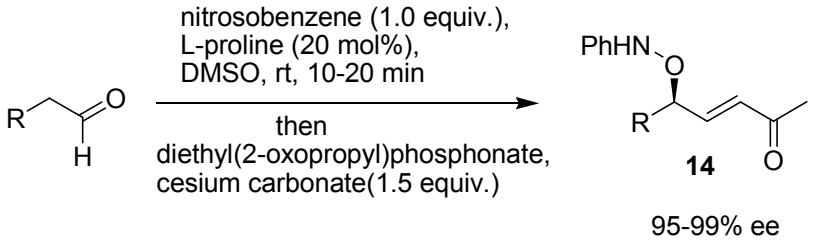
Barbas III *et al*. have developed a one-pot protocol for the synthesis of functionalized β-amino alcohols **13** from aldehydes, ketones and azodicarboxylates (**Scheme 3**).



Scheme 3: Sequential amination-aldol reaction

1.1.5.2 Sequential aminooxylation-olefination[13b]

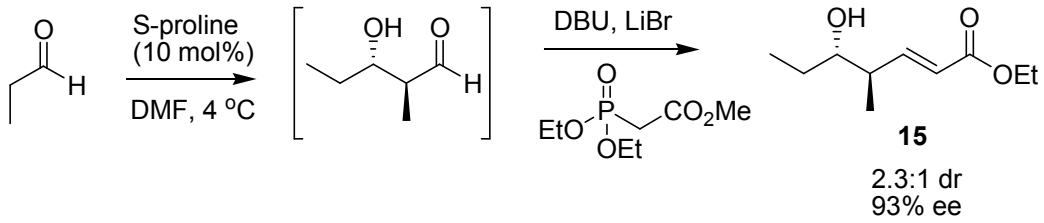
Zhong *et al*. have reported sequential asymmetric α-aminoxylation/Wadsworth-Emmons-Horner olefination of aldehydes for the synthesis of optically active *O*-amino-substituted allylic alcohols **14** in good enantioselectivities using cesium carbonate as base (**Scheme 4**).



Scheme 4: Sequential aminooxylation-olefination

1.1.5.2 Sequential aldol-olefination[13c]

Cordova *et al*. have reported one-pot organocatalytic asymmetric tandem cross-aldol/ Horner-Wittig-Emmons olefination for the synthesis of polyketide and carbohydrate derivatives (**Scheme 5**).



Scheme 5: Sequential aldol-olefination

Apart from this transformation, Cordova *et al*. have also reported tandem Mannich-olefination reaction.[13d]

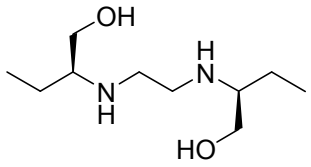
Section II:

Enantioselective Synthesis of (*S,S*)-Ethambutol using Proline-catalyzed Asymmetric α-Aminooxylation and α-Amination

1.2.1 Introduction

Tuberculosis (TB)**,** a human disease caused by Mycobacterial species (such as *Mycobacterium tuberculosis*) is now , and in fact always has been , the predominant cause of human deaths from infectious disease. In developing countries it is rampant and rising infections in developed countries, coupled with the emergence of multi-drug-resistant forms and a synergistic interaction with HIV/AIDS pose a serious future threat. Because of the spectacular success of antitubercular drugs, developed during 1945-65, subsequent research into these drugs, or their replacements, has been neglected. The mode of action of several major antitubercular drugs is even now not properly established, so there is still no basis for rational new-drug design.

Ethambutol, [(*S,S*)-2,2'-(ethylenediimino)-di-butanol, **16**], is among the frontline antimycobacterial chemotherapeutic agents, active against nearly all strains of *Mycobacterium tuberculosis* and *Mycobacterium kansasii* as well as a number of strains of *Mycobacterium avium*.[14]



16, (*S,S*)-Ethambutol

1.2.2 Pharmacology of Ethambutol

Ethambutol (**16**) arrests multiplication of Mycobacterium smegmatis cells and eventually affects their death. It has no effect on the survival of nonproliferating cells. It has little or no effect on the metabolism of nonproliferating cells, but cells from cultures whose growth has been inhibited by ethambutol shows evidence of impaired metabolism. Ethambutol exerts its antibacterial effect by interfering with the synthesis of a metabolite(s) needed for multiplication. Depletion of the metabolite(s) results in arrest of multiplication, impairment of metabolism, and loss of viability. Resistance to ethambutol cannot be explained by the failure of the cells to take up the drug, since the drug was equally bound by resistant and sensitive cells. In conclusion, biological activity of ethambutol has been attributed to its inhibition of mycobacterial arabinosyl transferases involved in bacterial cell wall biosynthesis.[15a] From a structure–activity relationship (SAR) viewpoint, the (*S,S*)-absolute configuration as present in ethambutol was found to be essential for optimum activity. For example, compared to the parent (*S,S*)-stereoisomer, the corresponding (*R,R*)-enantiomer and the optically inactive mesoisomer were found to exhibit only 0.2 and 8.3% antibacterial activity, respectively.[15b]

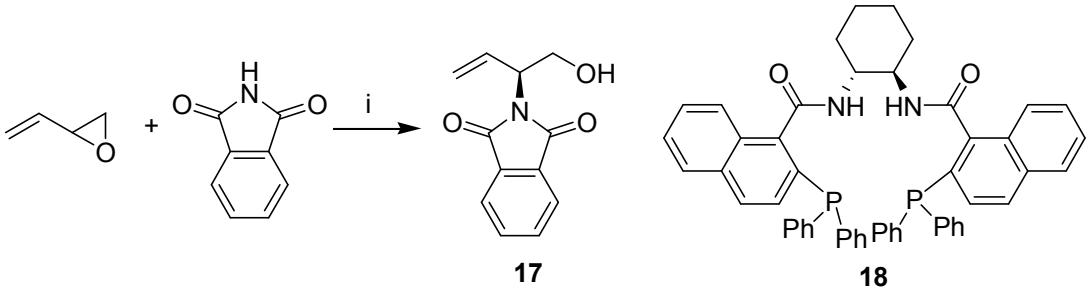
1.2.3 Review of Literature

Literature search reveals that there are only two reports available for the asymmetric syntheses of ethambutol (**16**), which are described below.

Trost's approach (2000)[16]

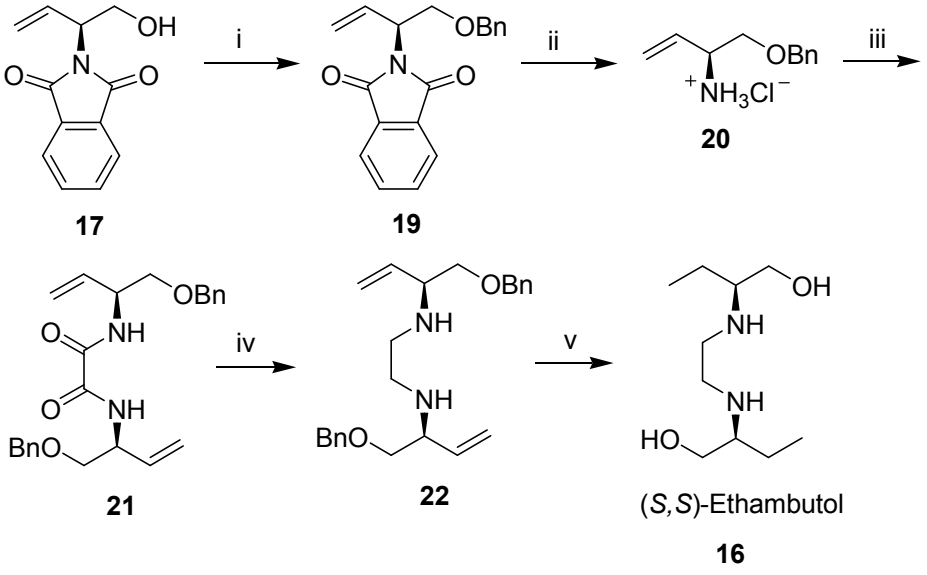
This approach employs dynamic kinetic asymmetric transformation (DYKAT) of butadiene monoepoxide with phthalimide using palladium-catalyzed asymmetric allylic alkylation (AAA) for the synthesis of (*S,S*)-ethambutol (**16**). Accordingly, exposing a

mixture of butadiene monoepoxide and phthalimide to a catalyst formed *in situ* from π-allylpalladium chloride dimer and ligand **18** led to a smooth reaction to get the corresponding alcohol **17** in 99% ee (**Scheme 6**).



Scheme 6: (i) $[\eta^3\text{-}C_3H_5PdCl]_2$, Ligand **18**, rt, 14 h, 98%, 99%ee (after recrysatllization).

Benzyl protection of alcohol **17** followed by removal of phthalimide moiety with ethylenediamine in refluxing ethanol gave protected amino alcohol **20** in 94% yield. Condensation of amine **20** with oxalyl chloride to give oxalamide **21** occurs quantitatively. Further reduction with Red-Al furnished diamine **22** in 78% yield.

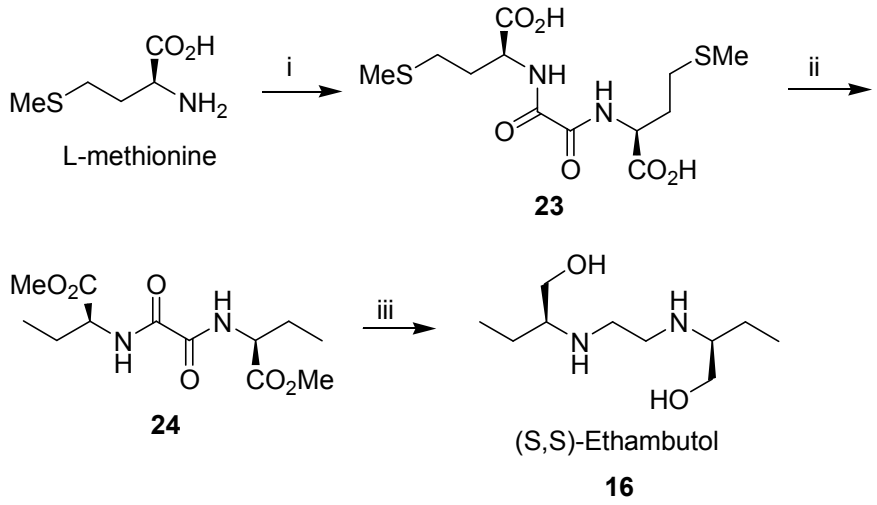


Scheme 7: (i) $PhCH_2Br$, NaH, DMF, 0 °C, 82%; (ii) Ethylenediamine, C_2H_5OH, reflux, then 6 N aqueous HCl, 94%; (iii) $(COCl)_2$, C_5H_5N, CH_2Cl_2, 0 °C, 97%; (iv) Red-Al, $PhCH_3$, 45 °C, 78%; (v) Pd/C, H_2 (1 atm.), CH_3OH, 25 °C; add 1.2 N HCl; ion-exchange resin, 74%.

Hydrogenolysis of **22** with Pd/C, H_2 (1 atm.) followed by purification utilizing ion-exchange resin gave (*S,S*)-ethambutol (**16**) in 74% yield.

Datta's approach (2002)[17]

This approach describes the synthesis of (*S,S*)-ethambutol (**16**) starting from amino acid L-methionine. Esterification of L-methionine under standard reaction conditions (methanol, acetyl chloride) followed by the treatment of the free amine with 0.5 equiv. of oxalyl chloride produced the desired oxalyl diamide derivative **23** in 77% yield over two steps. Raney nickel desulfurization of the terminal thiomethyl groups provided penultimate intermediate **24** in 64% yield. Finally one-pot exhaustive reduction of the diamide and the diester functional groups of **24** with lithium aluminium hydride completed the synthesis of (*S,S*)-ethambutol (**16**).



Scheme 8: (i) MeOH, AcCl ; (ii) $(COCl)_2$ (0.5 equiv.), pyridine, CH_2Cl_2, 77% (over two steps); (ii) Raney Ni (W-4), MeOH–H_2O (9:1), Δ, 64%; (iii) $LiAlH_4$, THF, Δ, 75%.

1.2.4 Present Work

1.2.4.1 Objective

As can be seen from the above descriptions, the literature methods for the synthesis of ethambutol (**16**), employ either chiral starting materials or expensive reagents. Hence, the synthesis of ethambutol (**16**), starting from prochiral substrates using catalytic enantioselective reactions, is still desirable. The use of catalytic enantioselective reactions is advantageous as both the stereoisomers can be synthesized from the same prochiral substrate. Also, the use of oragnocatalysis provides methods for obtaining chiral compounds in environmentally benign manner and from easily available starting materials. Hence, we have decided to synthesize (*S,S*)-ethambutol (**16**) using proline-catalyzed α-aminooxylation[7] as well as α-amination[8] reaction of *n*-butyraldehyde. The retrosynthetic analysis for the synthesis of (*S,S*)-ethambutol (**16**) is shown in **Fig. 5.** We visualize that the key intermediate i.e. protected chiral amino alcohol **25** is readily accessible from both protected diol **26** and the protected amino alcohol **27**. We further envisaged that while the diol **26** can be obtained by L-proline-catalyzed α-aminooxylation, amino alcohol **27** can be prepared by D-proline-catalyzed α-amination of *n*-butyraldehyde.

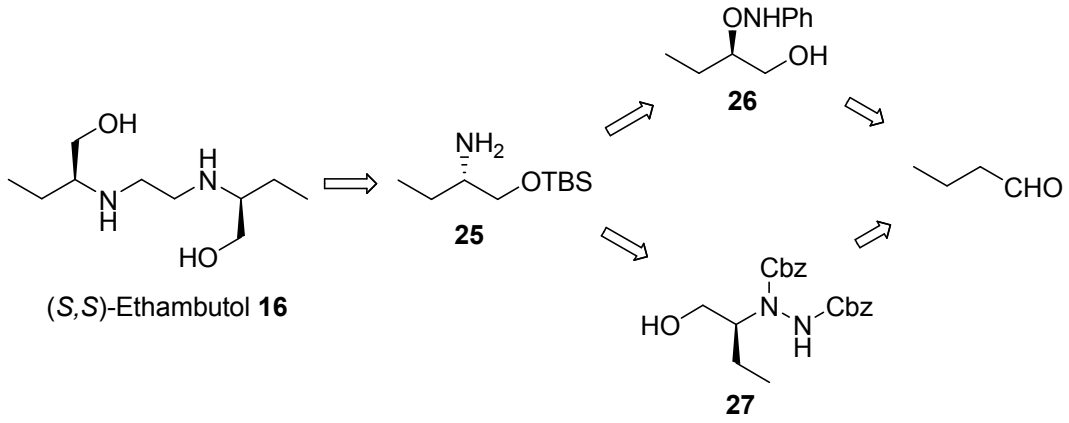


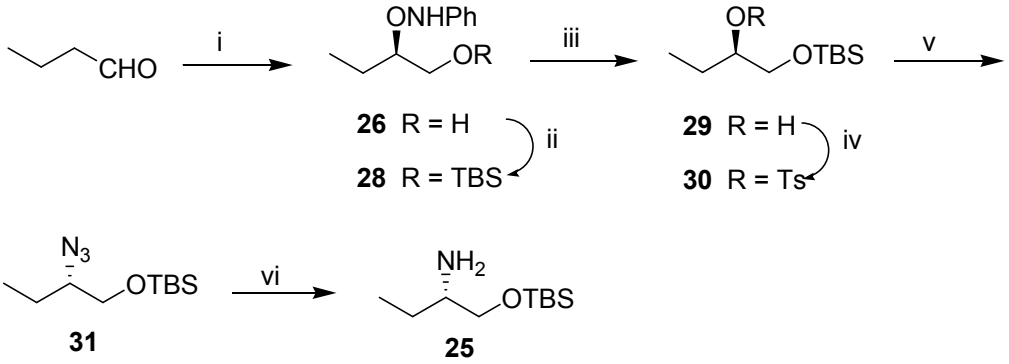
Fig. 5 : **Retrosynthetic analysis for (*S,S*)-ethambutol (16)**

1.2.5 Results and Discussions:

Since *O*-protected (*S*)-2-amino-1-butanol **25** has emerged as the precursor for the asymmetric synthesis of ethambutol, we have achieved the enantioselective synthesis of **25** by employing both proline-catalyzed α-aminooxylation and α-amination of *n*-butyraldehyde as described below.

α-Aminooxylation approach:

We have started the synthesis of **25** by L-proline-catalyzed α-aminooxylation[7] of *n*-butyraldehyde shown in **Scheme 9**.



Scheme 9. Reagents and conditions: (i) PhNO, L-proline (25 mol%), -20 ºC, 24 h then MeOH, $NaBH_4$, 85%; (ii) TBSCl, imidazole, CH_2Cl_2, 3 h, 90%; (iii) H_2 (1atm.), Pd/C (10%), Et_3N, MeOH, 12 h, 88%; (iv) *p*-TsCl, Py, 24 h, 95%; (v) NaN_3, DMF, 60 ºC, 30 h, 75%; (vi) H2 (1atm.), Pd-C (10%), Et_3N, MeOH, 6 h, 95%.

Firstly, α-aminooxylation[7a] of *n*-butyraldehyde was carried out using nitrosobenzene and L-proline (25 mol%) at -20 ºC to provide *in situ* aminooxy aldehyde, which on reduction with $NaBH_4$ afforded the α-aminooxy alcohol **26** in 85% yield; $[\alpha]^{25}_D$ +20.7 (*c* 1, $CHCl_3$); {lit.[7e] $[\alpha]^{25}_D$ +20.5 (*c* 1, $CHCl_3$)}. The ^{1}H NMR spectrum of **26** displayed signals at δ 3.81 (m) and 3.98 (m) corresponding to the methylene group (**CH_2**OH) and a proton at the functionalized carbon (**CH**ONHPh) respectively (**Fig. 6**). Its ^{13}C NMR spectrum showed peaks at δ 64.4 and 85.2 corresponding to the methylene (**CH_2**OH) and methine carbons (**CH**ONHPh) respectively.

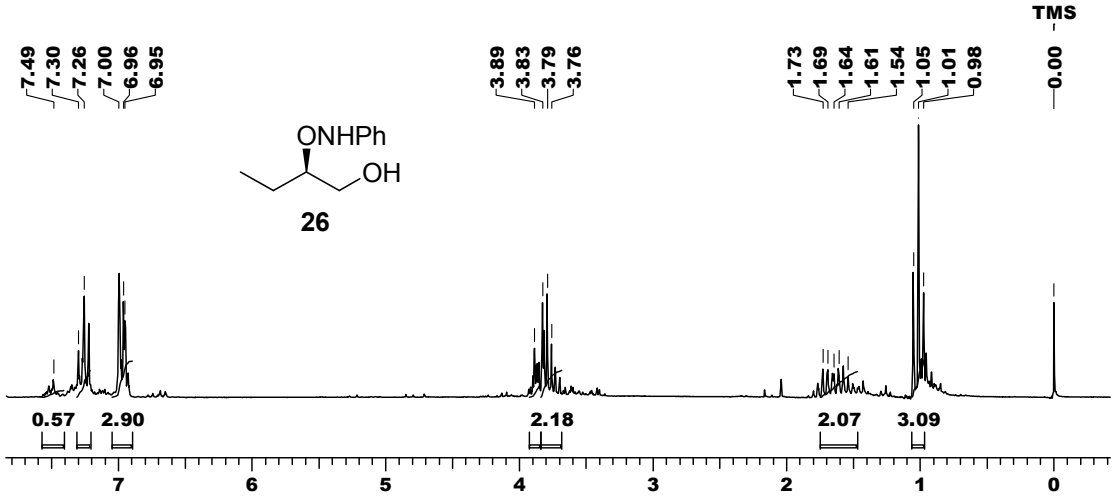


Fig. 6: ^{1}H NMR spectrum of (*R*)-2-(*N*-Phenylaminooxy)butan-1-ol (26)

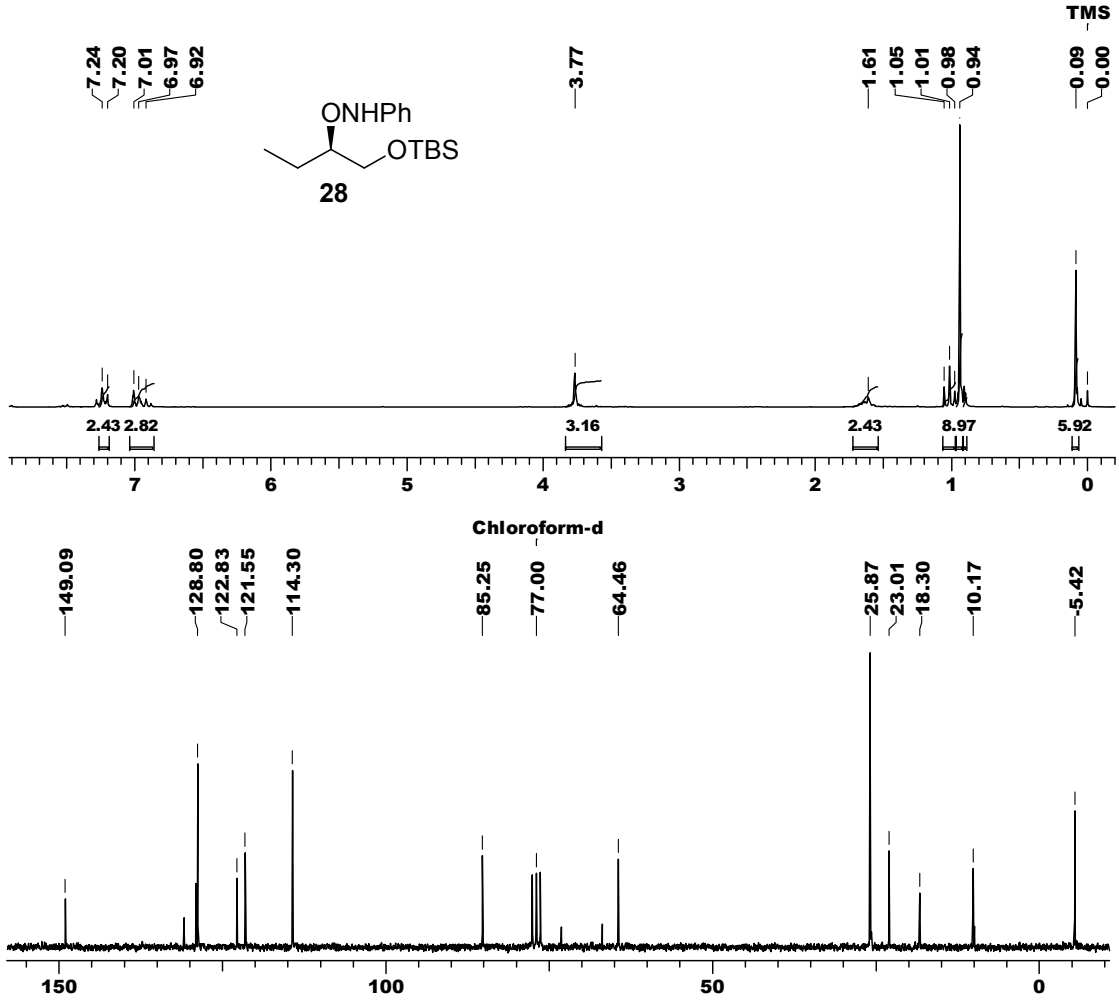


Fig. 7: ^{1}H and ^{13}C NMR spectra of protected diol 28

The alcohol **26** was then protected with TBSCl to give the corresponding silyl ether **28** in 90% yield; $[\alpha]_D^{25}$ +42.35 (*c* 1, $CHCl_3$). The appearance of signals at δ 0.09 (s) and 0.94 (s) in the ^1H NMR spectrum of **28** confirms the TBS protection. Its ^{13}C NMR spectrum showed carbon signals at δ -5.4 and 25.8 corresponding to the methyl and quaternary carbons in the silyl protecting group respectively (**Fig. 7**).

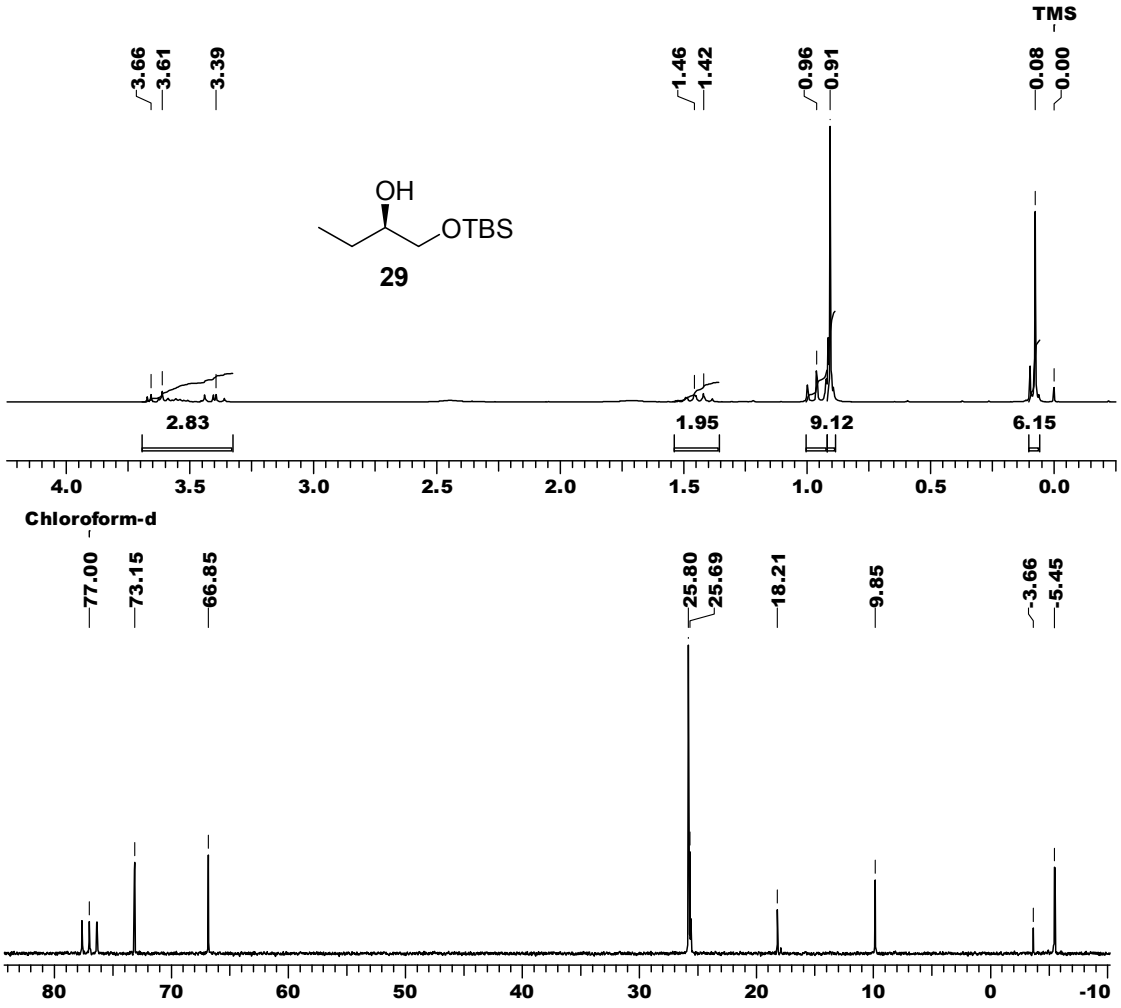


Fig. 8: ^1H and ^{13}C NMR spectra of monoprotected diol 29

Hydrogenation of **28** over 10% Pd/C furnished the monoprotected diol **29** in 88% yield; $[\alpha]_D^{25}$ -9.42 (*c* 1, $CHCl_3$). The disappearance of signals at δ 6.97 (m), 7.24 (m) and 7.25 (brs) in the ^1H NMR spectrum of the prolinol **29** confirmed the deprotection of the

anilinoxy group. Its ^{13}C NMR spectrum showed carbon signals at δ 66.8 and 73.1 corresponding to methylene and methine carbons (**CH**OH) respectively (**Fig. 8**).

Tosylation of secondary alcohol **29** using *p*-toluenesulfonyl chloride and pyridine produced *O*-tosylate **30** in 95% yield; $[\alpha]_D^{25}$ +16.99 (*c* 1, $CHCl_3$). The display of signals at δ 2.42 (s), 7.29 (d) and 7.77 (d) in the ^1H NMR spectrum of **30** confirms the presence of the tosyl moiety (**Fig. 9**).

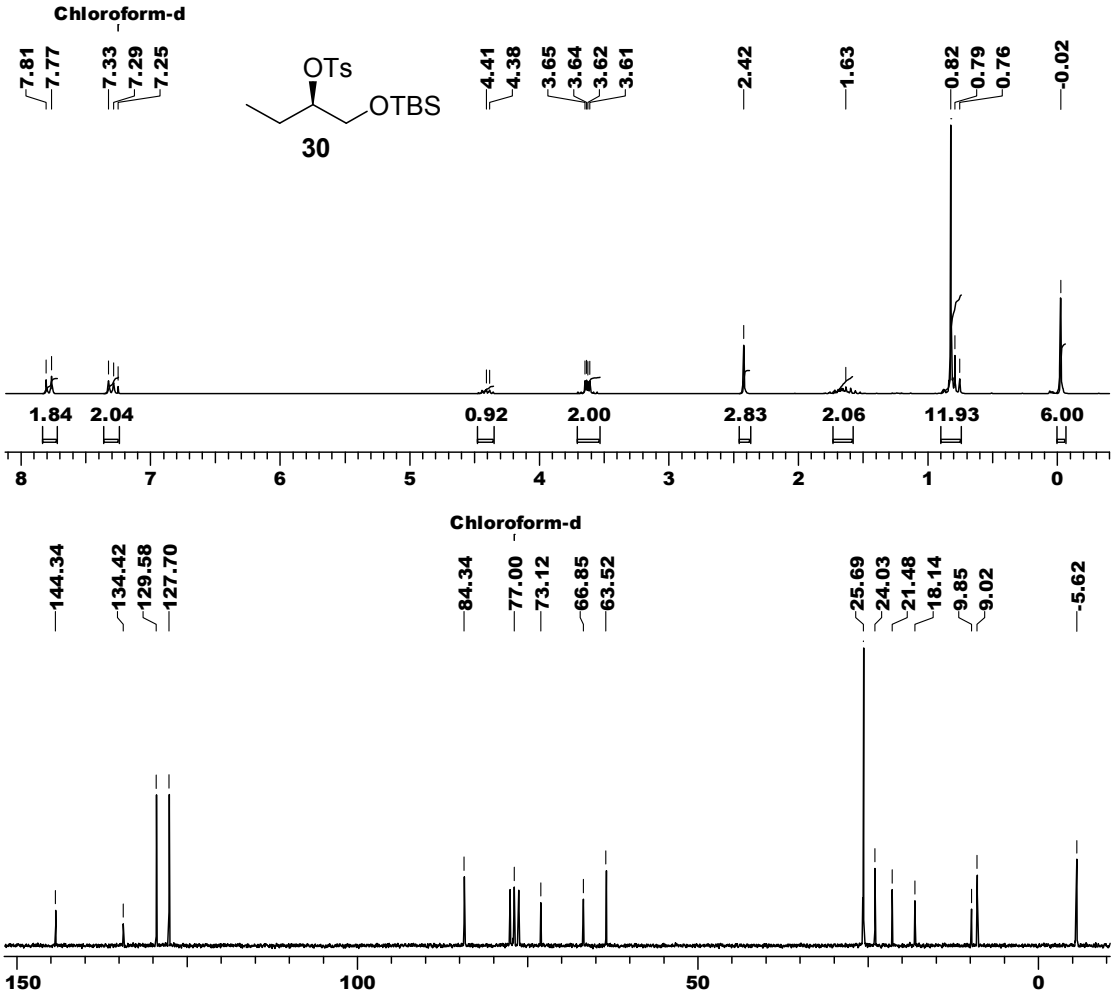


Fig. 9: ^1H and ^{13}C NMR spectra of tosylate 30

Displacement of tosyl group in compound **30** with NaN_3 in DMF gave the azido product **31** in 75% yield with complete inversion of configuration; $[\alpha]_D^{25}$ +21.9 (*c* 1, $CHCl_3$). The

disappearance of signals at 7.29 (d) and 7.77 (d) in the ^{1}H NMR spectrum of the prolinol **31** confirmed the displacement of tosyl group with azide function. Its IR spectrum exhibited a characteristic strong band at 2100 cm^{-1} indicating the presence of azide moiety. The characteristic carbon signal at δ 65.30 (-**C**-N_3) in the ^{13}C NMR spectrum of the azide **31** confirmed the presence of the azide group (**Fig. 10**).

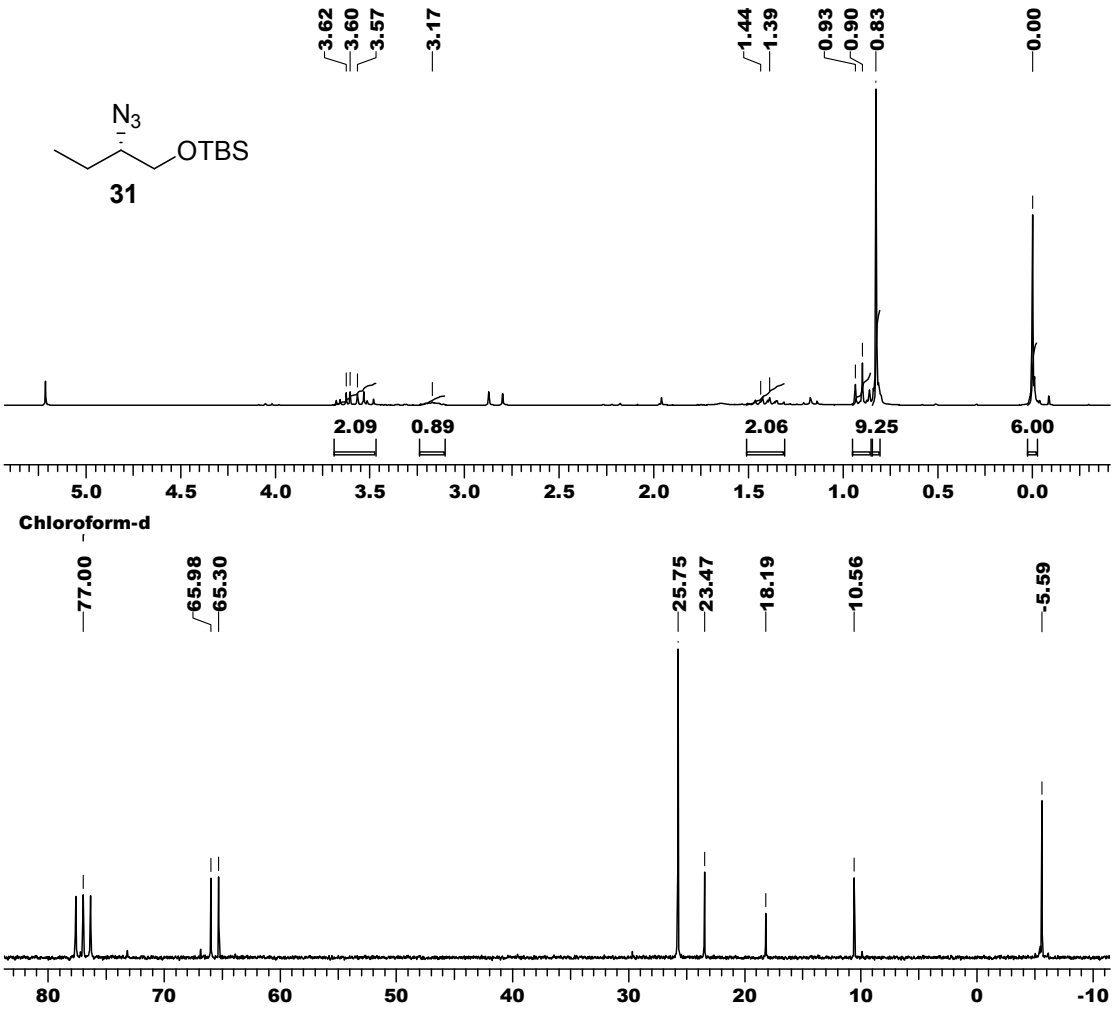


Fig. 10: ^{1}H and ^{13}C NMR spectra of azide 31

Subsequent reduction of the azide group in compound **31** using catalytic hydrogenation with 10% Pd/C-H_2 (1 atm.) afforded the protected amine **25** in 95% yield; $[\alpha]_D^{25}$ +9.7 (*c* 1, $CHCl_3$).

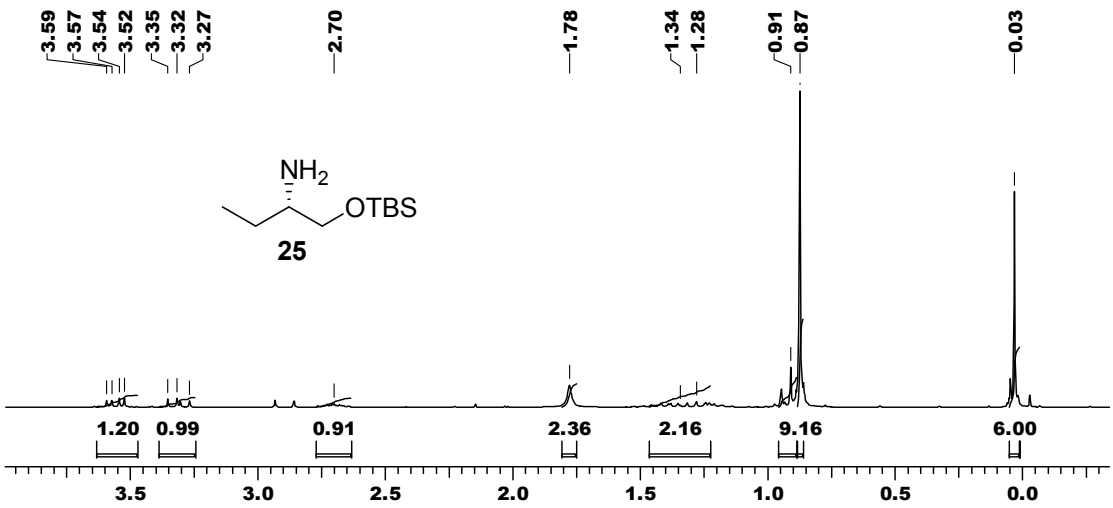
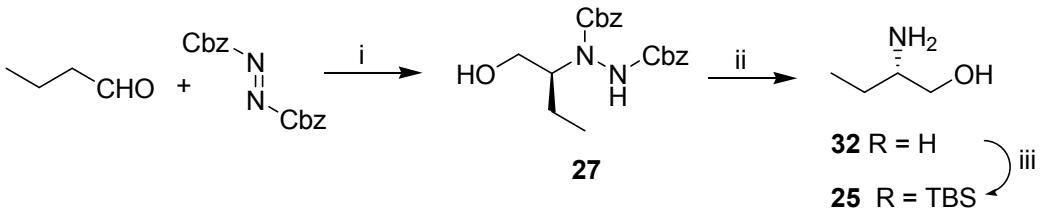


Fig. 11: ^{1}H NMR spectrum of amine 25

The ^{1}H NMR spectrum of the amine **25** showed a characteristic signal at δ 1.78 (brs) corresponding to the amine group of **25**. Its ^{13}C NMR spectrum displayed a typical carbon signal at δ 54.3 due to the carbon attached to amine group (**CH**NH_2) (**Fig. 11**).

α-Amiation approach:

In the second approach, we have carried out the synthesis of intermediate **25** by D-proline-catalyzed α-amination[8] of *n*-butyraldehyde as shown in **Scheme 10**.



Scheme 10. Reagents and conditions: (i) dibenzyl azodicarboxylate (DBAD), D-Proline (10 mol%), 0-20 ºC, 3 h then $NaBH_4$, EtOH, 92%; (ii) H_2 (12 bar), Raney-nickel, MeOH, AcOH, 70%; (iii) TBSCl, imidazole, CH_2Cl_2, 0-20 ºC, 3 h, 85%.

Accordingly, the α-amination of *n*-butyraldehyde was carried out using List's protocol.[8a] Thus, *n*-butyraldehyde was treated with dibenzyl azodicarboxylate in the presence of D-proline (10 mol%) to give *in situ* amino aldehyde, which on subsequent reduction with

$NaBH_4$ afforded the *N*-protected amino alcohol **27** in 92% yield; $[\alpha]_D^{25}$ +14.3 (*c* 1, $CHCl_3$). The ^1H NMR spectrum of the protected amino alcohol **27** showed three multiplets at δ 3.46, 4.27 and 5.15 corresponding to methylene protons (**CH_2**OH), a proton at functionalized carbon (**CH**-NCbz) and benzylic protons of Cbz group respectively. The N-H proton of **NH**Cbz showed a signal at δ 6.53. Its ^{13}C NMR spectrum showed peaks δ 61.7 and 68.0 corresponding to benzylic and methylene carbons (**C**H_2OH) respectively (**Fig. 12**).

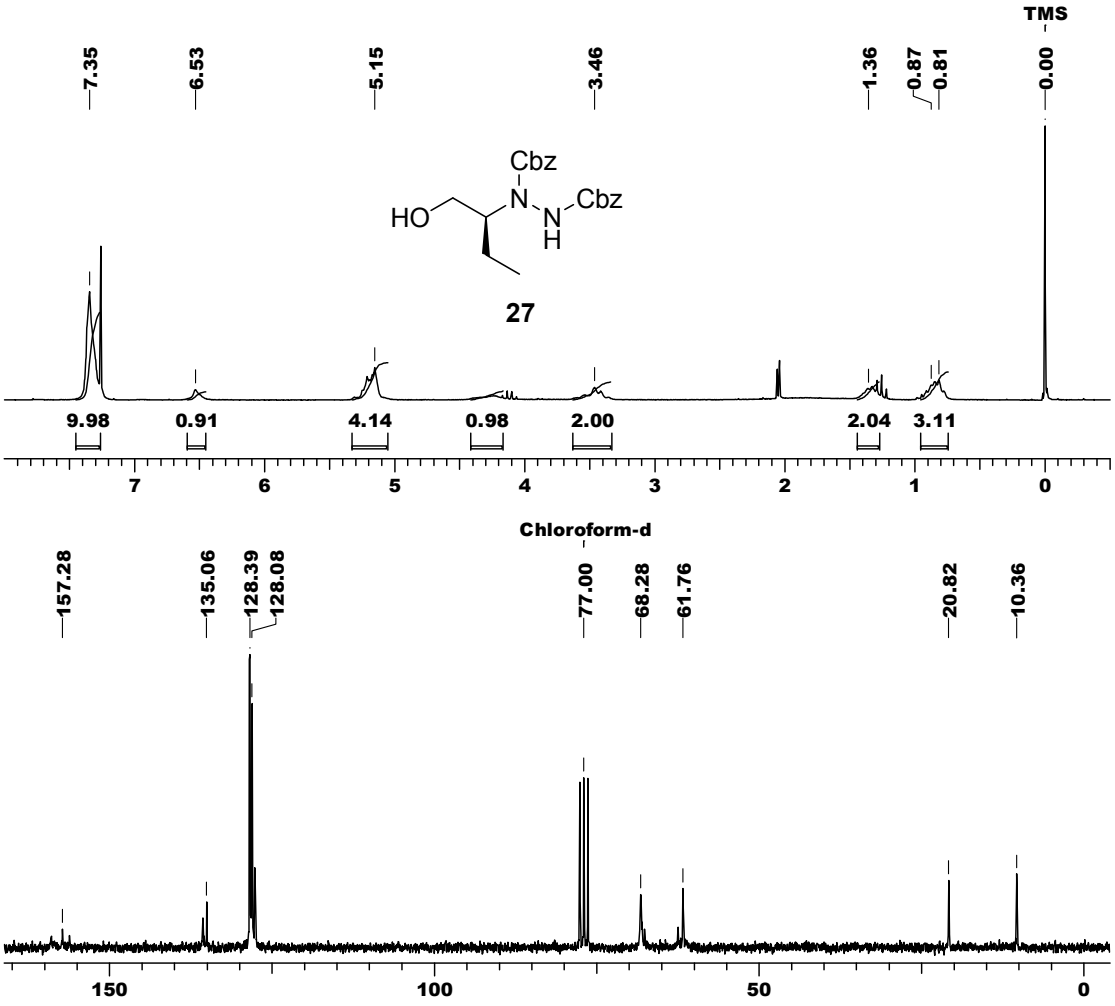


Fig. 12: ^1H and ^{13}C NMR spectra of amino alcohol 27

The amino alcohol **27** was then hydrogenated over Raney nickel (H_2, 12 bar)[17] to give (*S*)-2-amino-1-butanol (**32**) in 70% yield; $[\alpha]^{25}_D$ +12.3 (*c* 2, EtOH); {lit[18] $[\alpha]^{25}_D$ +12.5 (*c* 2, EtOH)}.

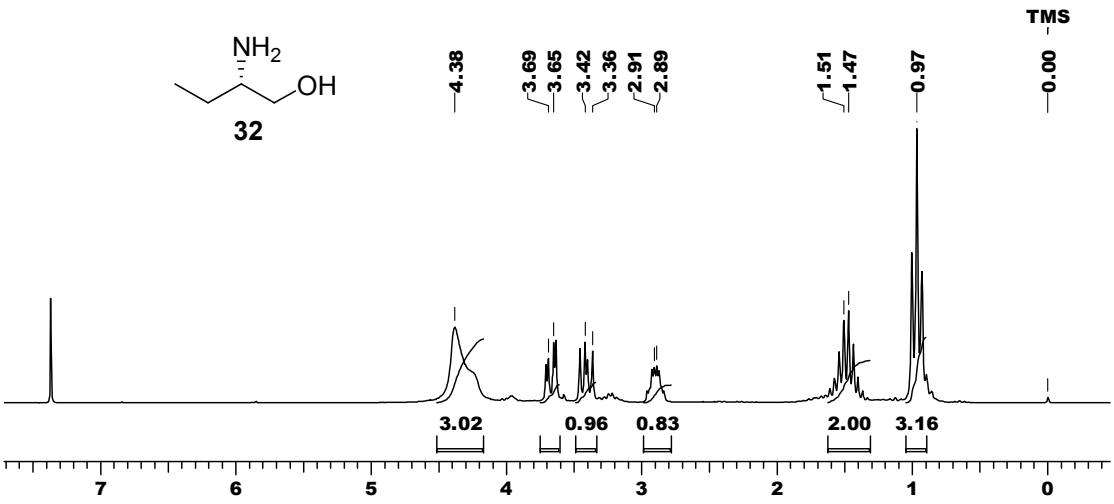
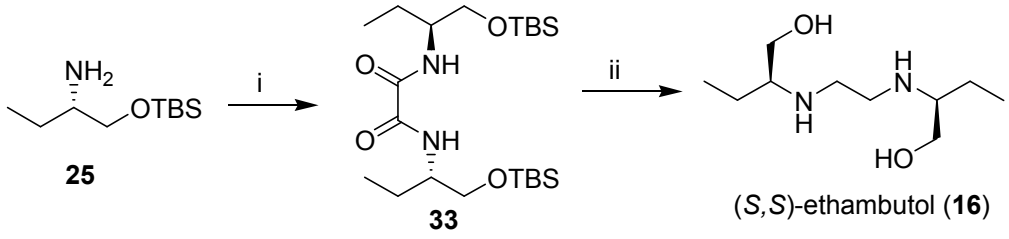


Fig. 13: ^{1}H NMR spectrum of amino alcohol 32

The ^{1}H NMR spectrum of amino alcohol **32** showed three multiplets at δ 2.89, 4.38 and 4.25 corresponding to the methine (**CH**NH_2), NH_2 and OH protons respectively (**Fig. 13**). The ^{13}C NMR spectrum showed carbon signals at δ 66.1 and 73.6 corresponding to the methylene and methine carbons (**CH**NH_2) respectively. Selective protection of the hydroxyl group in the amino alcohol **32** was achieved with TBSCl, imidazole in CH_2Cl_2 to give the silyl ether **25** in 85% yield (**Scheme 10**); $[\alpha]_D^{25}$ +9.5 (*c* 1, $CHCl_3$). Finally, protected amino alcohol **25** was transformed to (*S,S*)-ethambutol (**16**) in two steps (**Scheme 11**).

Thus, amine **25** on treatment with 0.5 equiv. of oxalyl chloride and pyridine furnished oxalyldiamide **33** in 98% yield; $[\alpha]_D^{25}$ -60.3 (*c* 1, $CHCl_3$) for α-aminooxylation and $[\alpha]_D^{25}$ -59.8 (*c* 1, $CHCl_3$) for α-amination approach. The ^{1}H NMR Spectrum of amino



Scheme 11. Reagents and conditions: (i) oxalyl chloride (0.5 equiv.), Py, CH_2Cl_2, 12 h, 98%; (ii) $LiAlH_4$, THF, reflux, 24 h, 80%.

oxalyldiamide **33** showed three multiplets at δ 3.61 and 3.63 corresponding to methine (**CH**NHCO) and methylene protons (**CH_2**OH) respectively.

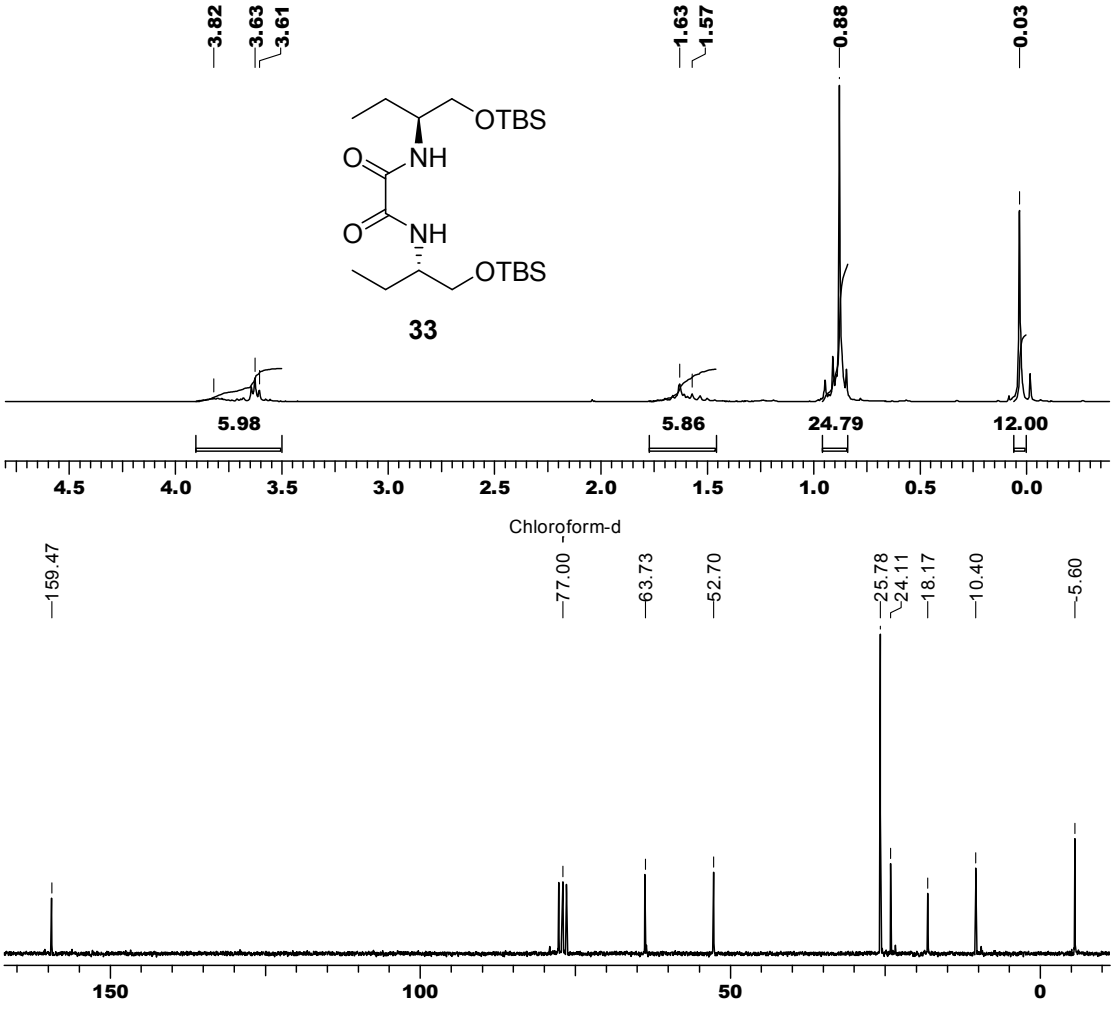


Fig. 14: ^{1}H and ^{13}C NMR spectra of oxalyldiamide 33

The ^{13}C NMR spectrum showed carbon signals at δ 52.7 and 63.7 corresponding to methylene and methine carbons (**CH**NHCO) respectively (**Fig. 14**). Its IR spectrum exhibited a characteristic strong band at 1739 cm^{-1} indicating the presence of amide group.

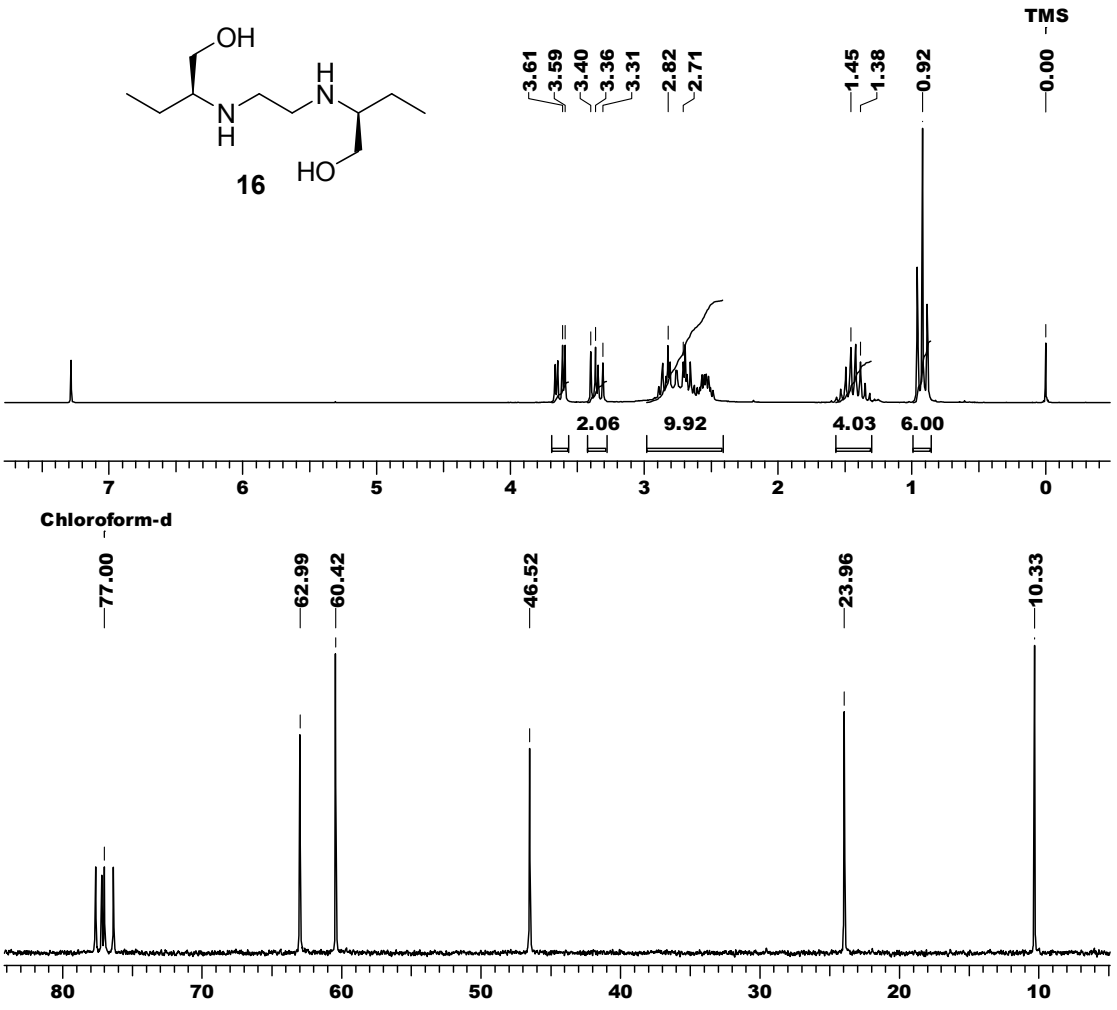


Fig. 15: ^{1}H and ^{13}C NMR spectra of ethambutol (16)

The reduction of diamide and deprotection of TBS group in **33** was achieved by carrying out the one-pot reaction using $LiAlH_4$ at reflux conditions to give (*S,S*)-ethambutol (**16**) in 80% yield and 99% ee (**Scheme 11**); $[\alpha]_D^{25}$ +13.59 (*c* 2, H_2O) (99% ee) for α-aminooxylation and $[\alpha]_D^{25}$ +13.4 (*c* 2, H_2O) (97% ee) for α-amination approach { lit.[14c]

$[\alpha]^{25}_{D}$ +13.7 (c 2, H_2O). The ^{1}H NMR spectrum of (*S,S*)-ethambutol (**16**) showed signals at δ 2.55 (m), 2.71 (m), 2.84 (m) and 2.99 (brs) corresponding to the methylene (**CH$_2$**NH), methine (**CH**NH), **NH** and **OH** protons respectively ((**Fig. 15**). Its ^{13}C NMR showed typical peaks at δ 46.5 and 60.4 corresponding to the methylene (**CH$_2$**NH) and methine carbons (**CH**NH) respectively. The physical and spectroscopic data were in full agreement with the literature values.[16b]

1.2.6 Conclusion:

In conclusion, we have successfully applied proline-catalyzed α-aminooxylation and α-amination strategies towards the synthesis of (*S,S*)-ethambutol (**16**), which was obtained in 99% ee. The operationally simple reactions are rapid, and require a relatively low amount of an inexpensive and nontoxic proline-catalyst that is available in both enantiomeric forms. The high overall yields (35.7% *via* α-aminooxylation and 43% *via* α-amination) and less-number of steps render our approach a good alternative to the known methods.

1.2.7 Experimental Section:

(*R*)-2- (*N*-Phenylaminooxy)butan-1-ol (26):

To a stirred solution of *n*-butyraldehyde (4.5 mL, 50 mmol) and nitrosobenzene (2.67 g, 25 mmol) in CH_3CN (60 mL) was added L-proline (718 mg, 6.2 mmol, 25 mol%) at -20 ºC. The reaction mixture was allowed to stir at the same temperature for 24 h followed by addition of MeOH (25 mL) and $NaBH_4$ (2.8 g, 75 mmol). After stirring for 10 min. it was quenched with phosphate buffer, extracted with ethyl acetate (3 × 60 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. Purification by column

chromatography over silica gel (Pet ether: EtOAc = 80:20) afforded aminooxy alcohol **26** as a brownish liquid.

Yield: 3.8 g, 85% yield; **$[\alpha]^{25}_{D}$** +20.7 (*c* 1, $CHCl_3$) {lit.[7e] $[\alpha]^{25}_{D}$ + 20.5 (*c* 1, $CHCl_3$)}. **IR** ($CHCl_3$) ν_{max} 3375, 3012, 2933, 1955, 1689, 1605, 1596, 1483, 1298, 1217, 1070, 756 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.01 (t, *J* = 6.9 Hz, 3 H), 1.4-1.79 (m, 2H), 3.81 (m, 2H), 3.98 (m, 1H), 6.93 (m, 3H), 7.25 (m, 2H), 7.4 (brs, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 10.1, 26.0, 64.4, 85.2, 114.6, 122.2, 128.9, 148.5. **Analysis:**

$C_{10}H_{15}NO_2$ required C, 66.27; H, 8.34; N, 7.73; found C, 66.15; H, 8.26; N, 7.80%.

(*R*)-2-*N*-Phenylaminooxybutanoxy(tert-butyl)dimethylsilane (28):

To a stirred solution of alcohol **26** (3.0 g, 16.5 mmol) in dry CH_2Cl_2 (30 mL) was added imidazole (1.34 g, 19.8 mmol, 1.2 equiv.) at 0 ºC. After stirring for 10 min., TBDMSCl (2.73 g, 18.2 mmol, 1.2 equiv.) was added and the reaction mixture was stirred at 25 ºC for 3 h. After completion of reaction as monitored by TLC, the reaction mixture was poured into water and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was then purified by column chromatography with silica gel (pet ether: EtOAc = 98: 2).

Yield: 4.4 g, 90%, Brownish liquid; **$[\alpha]_D^{25}$** +42.35 (*c* 1, $CHCl_3$); **IR** (neat) ν_{max} 3412, 2929, 2856, 2360, 1718, 1600, 1471, 1255, 1097, 910, 775 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.09 (s, 6H), 0.94 (s, 9H), 1.01 (t, *J* = 7.45 Hz, 3H), 1.61 (m, 2H), 3.77 (m, 2H), 3.78 (m, 1H), 6.97 (m, 2H), 7.24 (m, 2H), 7.25 (brs, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.4, 10.1, 18.3, 23.0, 25.8, 64.4, 85.2, 114.3, 121.5, 128.8, 149.0; **Analysis:** **$C_{16}H_{29}NO_2Si$** required C, 65.03; H, 9.89; N, 4.74; found C, 65.1; H, 9.85; N, 4.78%.

(*R*)-2-(hydroxy)butanoxy(tert-butyl)dimethylsilane (29):

To a solution of **28** (4.0 g, 13.5 mmol) in MeOH was added 10% Pd/C (200 mg) carefully followed by addition of 5-6 drops of Et_3N. The reaction mixture was then stirred in the hydrogen atmosphere (1 atm. of H_2) for 12 h. After completion of reaction (monitored by TLC) the reaction mixture was filtered through celite pad, concentrated to near dryness. The crude product was then purified by silica gel chromatography (pet ether: EtOAc = 95:5).

Yield: 2.4 g, 88%. Colorless oil; $\mathbf{[\alpha]_D^{25}}$ -9.42 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$) ν_{max} 3569, 3018, 2859, 2957, 2400, 1711, 1460, 1362, 1216, 1093, 927, 837, 669 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.06 (s, 6H), 0.89 (s, 9H), 0.94 (t, *J* = 7.32 Hz, 3H), 1.44 (m, 2H), 2.42 (brs, 1H), 3.39-3.59 (m, 2H), 3.54 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ - 5.4, 9.8, 18.2, 25.6, 25.8, 66.8, 73.1 ppm; **Analysis: $C_{10}H_{24}O_2Si$** required C, 58.77; H, 11.84 found C, 58.66; H, 12.05%.

(*R*)-1-(*tert*-Butyldimethylsilyloxybutan-3-yl) 4-methylbenzenesulfonate (30)

To a solution of alcohol **29** (2.4 g, 11.7 mmol) in pyridine (30 mL) at 0 ºC was added *p*-toluenesulfonyl chloride (2.44 g, 12.8 mmol, 1.1 equiv.) and the reaction mixture was allowed to stir at 25 ºC for 24 h. After completion of reaction (monitored by TLC) pyridine was removed under reduced pressure. To the residue was added water (30 mL) and extracted with ethyl acetate (3 × 30 mL). The crude product was then purified by silica gel chromatography (pet ether: EtOAc = 97:3).

Yield: 4 g, 95%, Colorless oil; $\mathbf{[\alpha]_D^{25}}$ +16.99 (*c* 1, $CHCl_3$). **IR** ($CHCl_3$) ν_{max} 3030 ,2955, 2930, 1598, 1496, 1463, 1362, 1255, 1188, 1099, 915, 835, 758, 665 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ -0.02 (s, 6H), 0.82 (s, 9H), 0.79 (t, *J* = 7.45 Hz, 3H), 1.63 (m, 2H), 2.42

(s, 3H), 3.61-3.65 (m, 2H), 4.38 (m, 1H), 7.29 (d, *J* = 8.34 Hz, 2H), 7.77 (d, *J* = 8.35 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ - 5.6, 9.0, 18.1, 24.0, 25.6, 63.5, 73.1, 84.3, 127.7, 129.5, 134.4, 144.3; **Analysis: $C_{17}H_{30}O_4SSi$** required C, 56.94; H, 8.43 found C, 56.82; H, 8.38%.

((*S*)-2-Azidobutoxy) (*tert*-butyl)dimethyl silane (31):

To a solution of **30** (4.0 g, 11.1 mmol) in DMF (40 mL) was added sodium azide (5.0 g, excess) and the reaction mixture was allowed to stir at 60 ºC for 30 h. After completion of reaction (monitored by TLC) the reaction mixture was poured into 50 mL of water and extracted with diethyl ether (3 × 50 mL) to give the crude product, which was purified, by column chromatography (pet ether).

Yield: 1.91 g, 75%, colorless oil; **$[\alpha]_D^{25}$** +21.9 (*c* 1, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.07 (s, 6H), 0.89 (s, 9H), 0.96 (t, *J* = 7.45 Hz, 3H), 1.45 (m, 2H), 3.24 (m, 1H), 3.63-3.69 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.5, 10.5, 18.1, 23.4, 25.7, 65.3, 65.9; **Analysis: $C_{10}H_{23}N_3OSi$** required C, 52.36; H, 10.11; N, 18.32 found C, 56.25; H, 10.10; N, 18.48%.

((*S*)-2-Aminobutoxy) (*tert*-butyl)dimethyl silane (25):

To a solution of azide **31** (1.9 g, 8.2 mmol) in MeOH (15 mL) was added 10% Pd/C (100 mg) carefully followed by addition of 5-6 drops of Et_3N. The reaction mixture was then stirred in the hydrogen atmosphere (1 atm. of H_2) for 6 h. After completion of reaction (monitored by TLC) the reaction mixture was filtered through celite pad, concentrated to near dryness to get the amine **25** which was purified by column chromatography with neutral Al_2O_3 (pet ether: EtOAc = 70:30).

Yield: 1.6 g, 95%, Colorless oil; $[\alpha]_D^{25}$ +9.7 (*c* 1, $CHCl_3$); **IR** (neat) ν_{max} 3355, 2952, 2927, 2856, 1739, 1589, 1471, 1253, 1103, 837, 775, 667 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.03 (s, 6H), 0.87 (s, 9H), 0.91 (t, *J* = 7.33 Hz, 3H), 1.34 (m, 2H), 1.78 (brs, 2H), 2.70 (m, 1H), 3.27-3.59 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.4, -3.5, 10.4, 18.2, 25.8, 54.3. **Analysis: $C_{10}H_{25}NOSi$** required C, 59.05; H, 12.39; N, 6.89 found C, 59.2; H, 12.44; N, 6.88%.

(*S*)-2-(1, 2-Dibenzyloxycarbonylhydrazinyl)-1-butanol (27):

To a mixture of of dibenzyl azodicarboxylate (90%, 8.25 g, 25 mmol, 1 equiv.) and D-proline (287 mg, 2.49 mmol, 10 mol%) in CH_3CN (200 mL) at 0 ºC was added *n*-butyraldehyde (2.7 g, 37.5 mmol, 1.5 equiv.) and the reaction mixture was allowed to stir at the same temperature for 2 h and then warmed to 20 ºC within 1 h. After the reaction mixture became colorless it was cooled to 0 ºC again and then treated with EtOH (150 mL) and $NaBH_4$ (1.2 g) for 5 min at 0 ºC. After completion of reaction it was quenched by adding half-concentrated aq. ammonium chloride solution and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (pet ether: ethyl acetate = 85:15).

Yield: 8.6 g, 92%, white solid (mp = 65 ºC); $[\alpha]_D^{25}$ +14.3 (*c* 1, $CHCl_3$); **IR** (nujol) ν_{max}: 3550, 3261, 2954, 2875, 1720, 1681, 1537, 1456, 1377, 1263, 1062; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.81 (m, 3H), 1.36 (m, 2H), 3.46 (m, 2H), 4.5 (brs, 1H), 5.15 (m, 4H), 6.53 (s, 1H), 7.35 (m, 10 H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 10.3, 20.8, 61.7, 61.78, 68.0, 68.0, 128.0, 135.0, 157.2; **Analysis: $C_{20}H_{24}N_2O_5$** required C, 64.50; H, 6.50; N, 7.52; found C, 64.52; H, 6.45; N, 7.44.

(*S*)-2-Aminobutan-1-ol (32):

Alcohol **27** (6.0 g, 16 mmol) was dissolved in MeOH (40 mL), AcOH (10 drops) and treated with Raney nickel (10.0 g, excess) for 24 h under 12 bar of hydrogen atmosphere. The reaction mixture was filtered over celite and concentrated to give the corresponding amino alcohol **32.**

Yield: 1.0 g, 70%, colorless oil; $[\alpha]^{25}_{D}$ +12.3 (*c* 2, EtOH) {lit[18] $[\alpha]^{25}_{D}$ +12.5 (*c* 2, EtOH)}; **IR** ($CHCl_3$) ν_{max} 3450, 3560, 2960, 1650, 1420, 1060; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.95 (t, *J* = 7.58 Hz, 3H), 1.44 (m, 2H), 2.89 (m, 1H), 3.40 (m, 1H), 3.57 (m, 1H), 4.07 (brs, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 9.9, 25.8, 66.1, 73.6; **MS** (m/z, % RI) 89 (M+), 71, 60, 58, 56, 41%.

((*S*)-2-Aminobutoxy) (tert-butyl)dimethyl silane (25):

To a solution of amino alcohol **32** (1.0 g, 11.2 mmol) in dry CH_2Cl_2 (50 mL) at 0 ºC was added imidazole (0.916 g, 13.4 mmol, 1.2 equiv.) after stirring for 10 min., TBSCl (1.8 g, 12.3 mmol, 1.1 equiv.) was added and the reaction mixture was stirred at 25 ºC for 3 h. After completion of reaction solvent was removed under reduced pressure and the crude product was then purified by column chromatography on neutral Al_2O_3 (pet ether: EtOAc = 70:30).

Yield: 1.87 g, 85%, Colorless oil; $[\alpha]_D^{25}$ +9.5 (*c* 1, $CHCl_3$).

(*S,S*)-*N*^{1},*N*^{2}-Bis(1-*tert*-butyldimethylsilyloxybutan-3-yl)oxamide (33):

To a solution of amine **25** (1.21 g, 6 mmol) in dry CH_2Cl_2 (10 mL), pyridine (1.04 g, 13.2 mmol) was added and the reaction mixture was cooled to 0 ºC, followed by dropwise addition of oxalyl chloride (378 mg, 3 mmol, 0.5 equiv. dissolved in CH_2Cl_2). After stirring the reaction mixture at 25 ºC overnight it was quenched with water (10 mL)

and was extracted with EtOAc (3 × 20 mL). The crude product was purified by column chromatography over silica gel (pet ether).

Yield: 2.6 g, quantitative, Colorless solid (mp 86 ºC); $[\alpha]_D^{25}$ -60.3 (*c* 1, $CHCl_3$) for α-aminooxylation and $[\alpha]_D^{25}$ -59.8 (*c* 1, $CHCl_3$) for α-amination approach; **IR** ($CHCl_3$) ν_{max} 3629, 3547, 2985, 2086, 1888, 1739, 1507, 1458, 1374, 1241, 1047, 917, 846, 607 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.03 (s, 12H), 0.88 (s, 18 H), 0.90 (t, *J* = 7.3 Hz, 6 H), 1.57 (m, 6H), 3.61 (m, 2H), 3.63 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.6, 10.4, 18.1, 24.1, 25.7, 52.7, 63.7, 159.4; **Analysis: $C_{22}H_{48}N_2O_4Si_2$** required C, 57.34; H, 10.50; N, 6.08 found C, 57.48; H, 10.66; N, 6.24%.

(*S*,*S*)-Ethambutol (16):

To a solution of lithium aluminium hydride (1.2 g, 30 mmol) in dry THF at 0 ºC was added amide **33** (in THF) (2.5 g, 5.4 mmol) carefully. The reaction mixture was refluxed for 24 h. After completion (TLC) the reaction mixture was quenched by 10% aq. NaOH (2 mL) and water (2 mL). The precipitate formed was filtered off and washed with EtOAc (3 × 10 mL). The combined organic layers were concentrated under reduced pressure, dried (Na_2SO_4) and recrystallized (ethyl acetate/hexane) to furnish ethambutol (**16**).

Yield: 0.87 g, 80 %; Colorless solid (mp = 88 ºC, lit.[14c] mp 87.5-88.8 ºC); $[\alpha]_D^{25}$ +13.59 (*c* 2, H_2O) (99% ee) for α-aminooxylation and $[\alpha]_D^{25}$ +13.4 (*c* 2, H_2O) (97% ee) for α-amination approach { lit.[14c] $[\alpha]^{25}_D$ +13.7 (c 2, H_2O)}; **IR** ($CHCl_3$) ν_{max}: 3465, 2984, 1567, 1447, 1374, 1242, 1047, 758 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.92 (t, *J* = 7.55 Hz, 6 H), 1.42 (m, 4H), 2.55 (m, 2H), 2.71 (m, 2H), 2.84 (m, 2H), 2.99 (brs, 4H), 3.34 (dd, *J* = 7.23, 10.88, 2H), 3.59 (dd, *J* = 3.74, 10.97, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 10.3,

23.9, 46.5, 60.4, 62.9; **Analysis: $C_{10}H_{24}N_2O_2$** required C, 58.79; H, 11.84; N, 13.71 found C, 58.85; H, 11.74; N, 13.55%.

Section III:

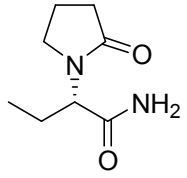
A Short Enantioselective Synthesis of the Antiepileptic Agent, Levetiracetam Based on Proline-catalyzed Asymmetric α-Aminooxylation

1.3.1 Introduction

Epilepsy is a common neurological disorder characterized by recurrent spontaneous seizures and is a major health problem that affects around 1% of the population worldwide.[19] Even though much progress has been made in understanding the pathogenesis of epileptic seizures, the cellular basis of human epilepsy remains a mystery and attempts to drug therapy are still directed toward the control of symptoms, i.e., suppression of seizures. Treatment of epilepsy includes constant administration of antiepileptic drugs (AEDs). The prognosis for seizure control is acceptable in at least 60% of the patients but up to 40% of individuals suffer from intractable pharmacoresistant epilepsy. Furthermore, clinical use of older AEDs is hampered by their limited tolerability, most commonly consisting of central nervous system (CNS)-related adverse effects and idiosyncratic reactions such as skin rashes. Thus the goal of current therapy with an AED is to keep the patient free of seizures without inducing significant side effects. For these reasons, a major goal in epilepsy research is to develop new AEDs combining improved seizure control with better tolerability. The past decade witnessed considerable progress in the pharmacotherapy of epilepsy, including the introduction of several new AEDs and improved formulations of older, "first-generation" drugs, such as phenytoin, carbamazepine, phenobarbital, and valproate. Newer "second-generation"

drugs include lamotrigine, vigabatrin, tiagabine, topiramate, oxcarbazepine, zonisamide, gabapentin, and levetiracetam.[20]

Levetiracetam, [(*S*)-α-ethyl-2-oxopyrrolidine acetamide, **34**], has recently been approved as an add-on therapy for the treatment of refractory epilepsy.[21] The (*S*)-enantiomer of etiracetam (levetiracetam), has shown outstanding pharmacokinetic and pharmacological activity which has led to the rapid approval of this antiepileptic drug by the FDA. Levetiracetam (**34**) offers several advantages over traditional therapy, including twice daily dosing, a wide margin of safety with no requirements for serum drug concentration monitoring, no interactions with other anticonvulsants and has less adverse effects than traditional treatments.[22]



Levetiracetam (**34**)

Indeed, since its launch in the USA in April 2000, levetiracetam has become one of the leading adjunctive antiepileptic drugs prescribed in neurology clinics around the world, in such a way that the worldwide sales of UCB's Keppra have beaten expectations and the growing demand for Keppra has made necessary new production installations and adaptation of existing production plants.

1.3.2 Pharmacology of Levetiracetam

The exact mechanism by which levetiracetam exerts its antiepileptic effect is unknown. The antiepileptic activity of levetiracetam was assessed in a number of animal models of epileptic seizures.[23] Levetiracetam did not inhibit single seizures induced by maximal

stimulation with electrical current or different chemoconvulsants and showed only minimal activity in submaximal stimulation and in threshold tests. Protection was observed, however, against secondarily generalized activity from focal seizures induced by pilocarpine and kainic acid, two chemoconvulsants that induce seizures that mimic some features of human complex partial seizures with secondary generalization. Levetiracetam (**34**) also displayed inhibitory properties in the kindling model in rats, another model of human complex partial seizures, both during kindling development and in the fully kindled state. The predictive value of these animal models for specific types of human epilepsy is uncertain.

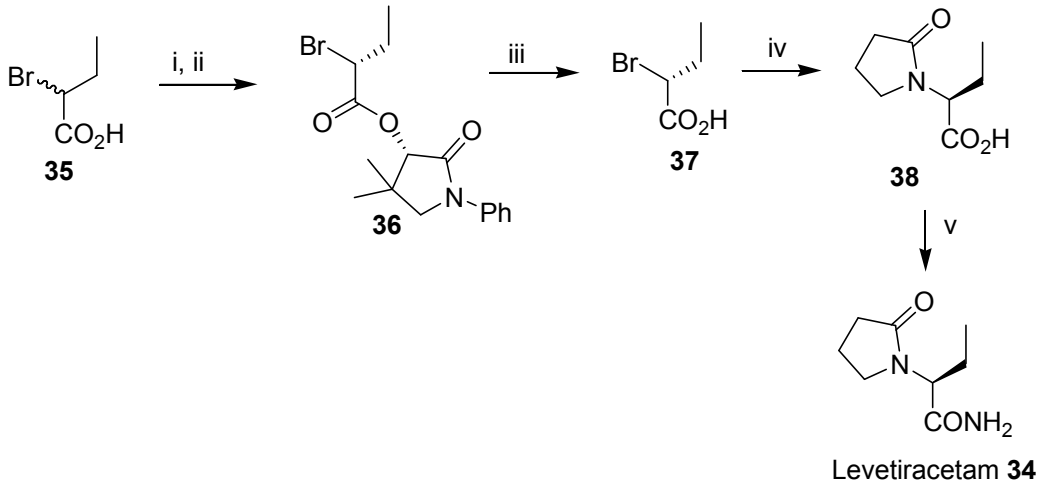
1.3.3 Review of Literature

The literature methods so far known for the synthesis of levetiracetam (**34**) are described below.

Camps Approach (2005)[24]

Camps, *et al*. have reported synthesis of levetiracetam (**34**) based on deracemization of (±)-2-bromobutyric acid (**35**) using (*S*)-*N*-phenylpantolactam as a chiral auxiliary. Accordingly, reaction of (±)-2-bromobutyric acid (**35**) with Cl_2SO, followed by reaction of the resulting racemic 2-bromobutyryl chloride with (*S*)-*N*-phenylpantolactam, gave in a quantitative yield a diastereomeric mixture of esters (α*R*,3*S*)-**36** and (α*S*,3*S*)-**36** in the approximate ratio of 9:1 (^{1}H NMR), which was purified by silica gel column chromatography to get the main diastereomer (α*R*,3*S*)- **36** in 67% isolated yield and with >98:2 dr. Hydrolysis of (α*R*,3*S*)-**36** using $LiOH/H_2O_2$ in THF at 0 °C afforded (*R*)-2-bromobutyric acid (**37**) in 91% yield. The reaction of (*R*)-**37** with the sodium salt of 2-pyrrolidinone in THF at room temperature overnight gave the substitution product (*S*)-**38**

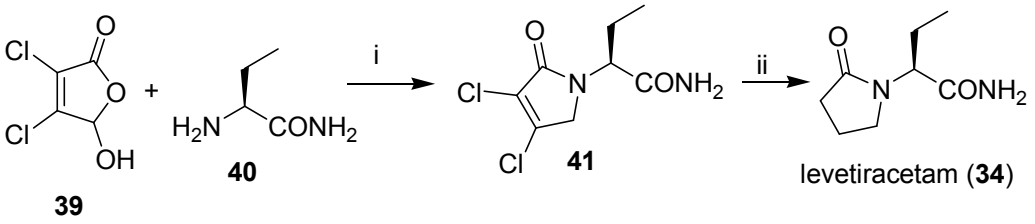
in 55% yield. This compound was transformed into the corresponding amide (*S*)-**34** (levetiracetam) by consecutive reaction with ethyl chloroformate and ammonium hydroxide, following a known procedure. The enantiomeric excess after recrystallization from acetone was >99% with 65% overall yield (**Scheme 12**).



Scheme 12: (i) Cl_2SO; (ii) (*S*)-*N*-phenylpantolactam, CH_2Cl_2, Et_3N, 20 °C, 4 h, 67%; (iii) $LiOH/H_2O_2$/THF, 0 °C, 7 h, 91%; (iv) NaH/2-pyrrolidinone/THF, 25 °C, overnight, 55%; (v) (a) $ClCO_2Et/CH_2Cl_2$, Et_3N, 0 °C, 30 min; (b) NH_4OH, 25 °C, 16 h, 65%.

Zhang's Approach (2006)[25]

Recently, Zhang, *et al*. have reported synthesis of levetiracetam (**34**) using reductive amination of monochloric acid with amino acid amide. Accordingly, reductive amination of monochloric acid (**39**) was carried out with amino acid amide **40** using sodium triacetoxy borohydride to give amide **41** in 62% yield. Dehalogenation of **41** followed by hydrogenation with H_2 afforded levetiracetam (**34**) in 56% yield (**Scheme 13**). Other patented literature methods for the synthesis of levetiracetam (**34**) typically involve chiral pool approaches starting from enantiopure α-amino acids,[26] resolution of etiracetam or advanced racemic intermediates,[26a,27] asymmetric hydrogenaton over Rh(I) or Ru(II) complexes.[28]



Scheme 13: (i) $NaBH(OAc)_3$, $CHCl_3$, HOAc, 62%; (ii) Pd/C, EtOH, Et_3N, H_2, 56%.

1.3.4 Present Work

1.3.4.1 Objective

So far, the methods described in the literature for the synthesis of levetiracetam (**34**) suffer from the following disadvantages: (i) use of chiral starting materials or (ii) expensive reagents. In this section, we describe a new approach to the asymmetric synthesis of levetiracetam using L-proline-catalyzed α-aminooxylation[7] of *n*-butyraldehyde as a key step. Retrosynthetic analysis of levetiracetam (**34**) is shown in **Fig 16** in which we have planned to carry out the asymmetric synthesis of levetiracetam (**34**) from the corresponding chiral alcohol **42** *via* oxidation followed by amidation. Alcohol **42** in turn can be accessible from the mononprotected diol **43** by means of nucleophilic displacement of secondary hydroxyl group. We envisaged that the diol **43** could be synthesized from *n*-butyraldehyde by carrying out L-proline-catalyzed α-aminooxylation.

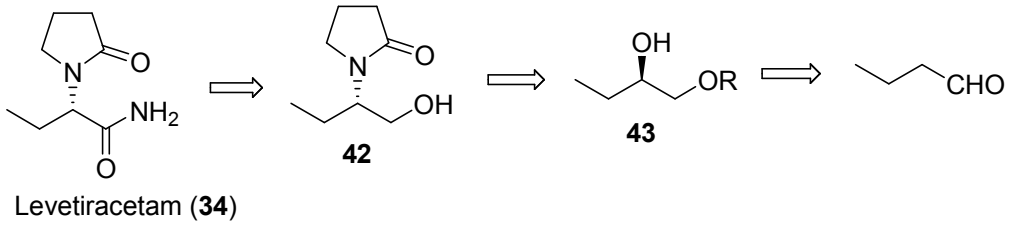
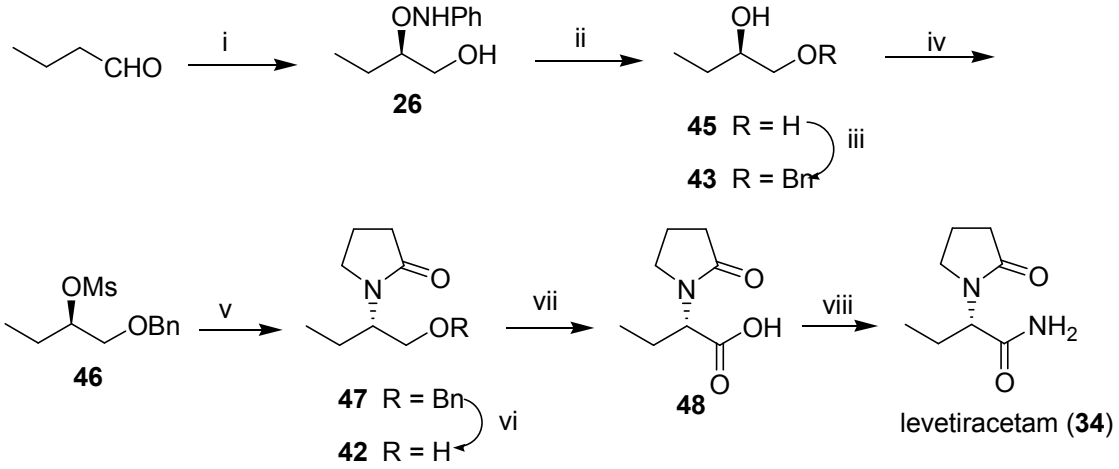


Fig. 16: Retrosynthetic analysis of levetiracetam (34)

1.3.5 Results and Discussions:

For the synthesis of levetiracetam (**34**), L-proline-catalyzed α-aminooxylation of *n*-butyraldehyde is employed as a key step for introduction of chirality (**Scheme 14**). Our synthesis started with α-aminooxylation[7a] of *n*-butyraldehyde which was carried out using nitrosobenzene and L-proline (25 mol%) at -20 ºC to furnish the aminooxy aldehyde **44** [$CH_3CH_2CH(ONHPh)CHO$)] which was reduced *in situ*, with sodium borohydride to afford (*R*)-α-aminooxy alcohol **26** in 85% yield; $[\alpha]^{25}_D$ +20.7 (*c* 1, $CHCl_3$), {lit.[7e] $[\alpha]^{25}_D$ +20.5 (*c* 1, $CHCl_3$)}. The spectral data of the compound have been described in Section I of this Chapter.



Scheme 14: (i) PhNO, L-proline (25 mol%), -20 ºC, 24 h then MeOH, $NaBH_4$, 85%; (ii) H_2 (1 atm.), Pd/C (10%), MeOH, 12 h, 90%; (iii) Bu_2SnO, toluene, reflux, 12 h then Bu_4NBr, BnBr, reflux, 24 h, 95%; (iv) MsCl, Et_3N, CH_2Cl_2, 0-25 ºC, 4 h, 92%; (v) 2-pyrrolidone, NaH, DMF, 130 ºC, 3 h, 62%; (vi) H_2 (1 atm.), Pd/C (10%), MeOH, 6 h, 97%; (vii) TEMPO (7 mol%), NaClO-$NaClO_2$, acetonitrile, phosphate buffer (pH 6.8), 25 ºC, 6 h, 90%; (viii) $ClCO_2Et$, Et_3N, THF, 0 ºC, 30 min then NH_4OH, 16 h, 75%, 99.5% ee.

The anilinooxy alcohol **26** was then hydrogenated over Pd/C (10 mol%) to furnish (*R*)-1,2-butanediol (**45**) in 90% yield; $[\alpha]_D^{25}$ -7.2 (*c* 1, $CHCl_3$). The ^1H NMR spectrum of diol **45** showed peaks at δ 3.40 (m), 3.57 (m) and 4.07 (brs) corresponding to the methine (**CH**OH), methylene (**CH_2**OH) and two hydroxyl protons respectively. Its ^{13}C NMR

spectrum displayed typical peaks at δ 66.1 and 73.6 due to the methine (**C**H**O**H) and the methylene carbons (**C**H_2-OH) respectively (**Fig. 17**).

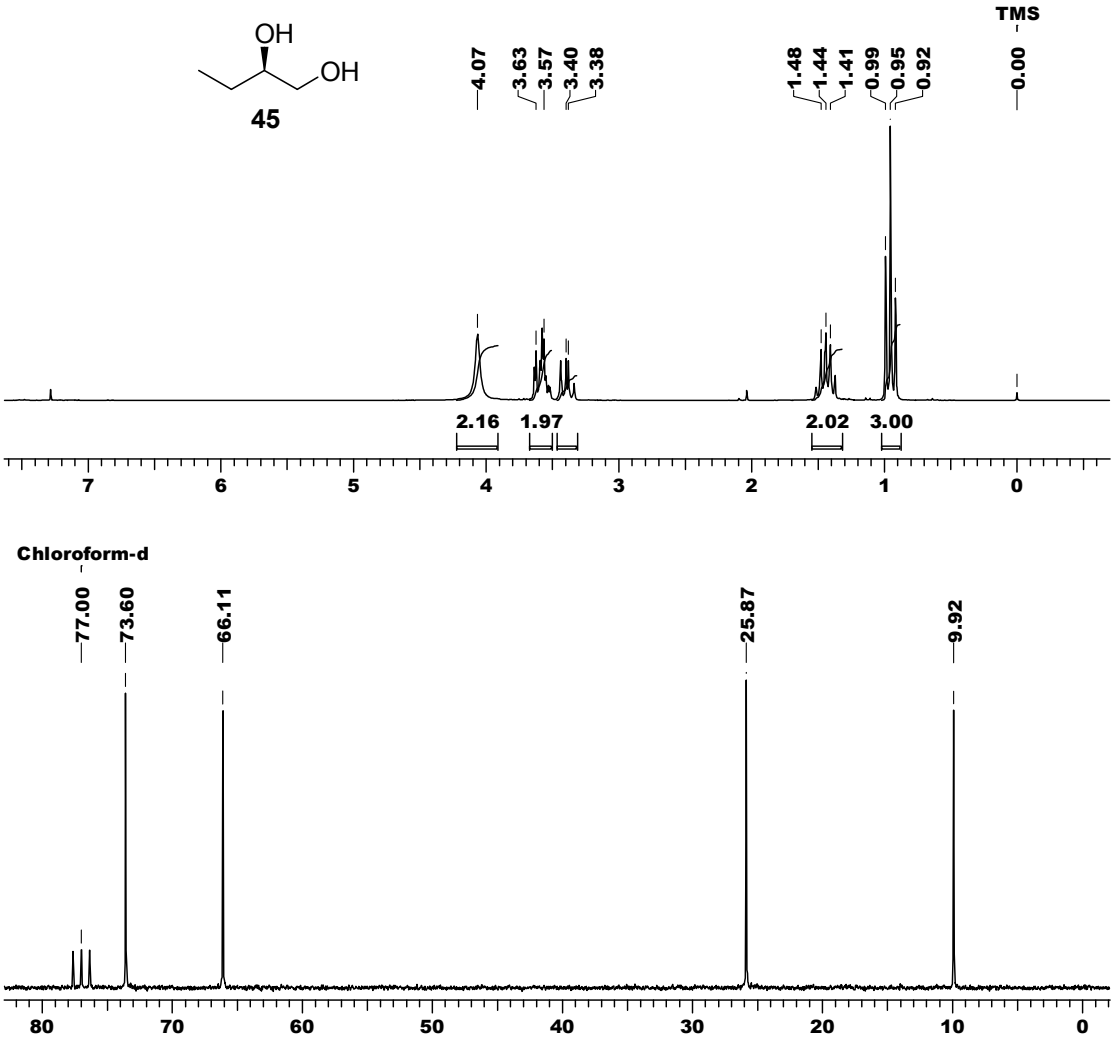


Fig 17: ^{1}H and ^{13}C NMR spectra of diol 45

Selective monobenzylation of diol **45** was carried out using Bu_2SnO and benzyl bromide to give **43** in 95% yield; $[\alpha]_D^{25}$ -10 (*c* 1, $CHCl_3$). The appearance of signals at δ 4.55 (s) and 7.33 (m) in the ^{1}H NMR spectrum of the **43** confirms the presence of benzylic and aromatic protons. The ^{13}C NMR spectrum displayed characteristic carbon signal at δ 71.5 and 73.0 due to the methine and benzylic carbons respectively (**Fig. 18**).

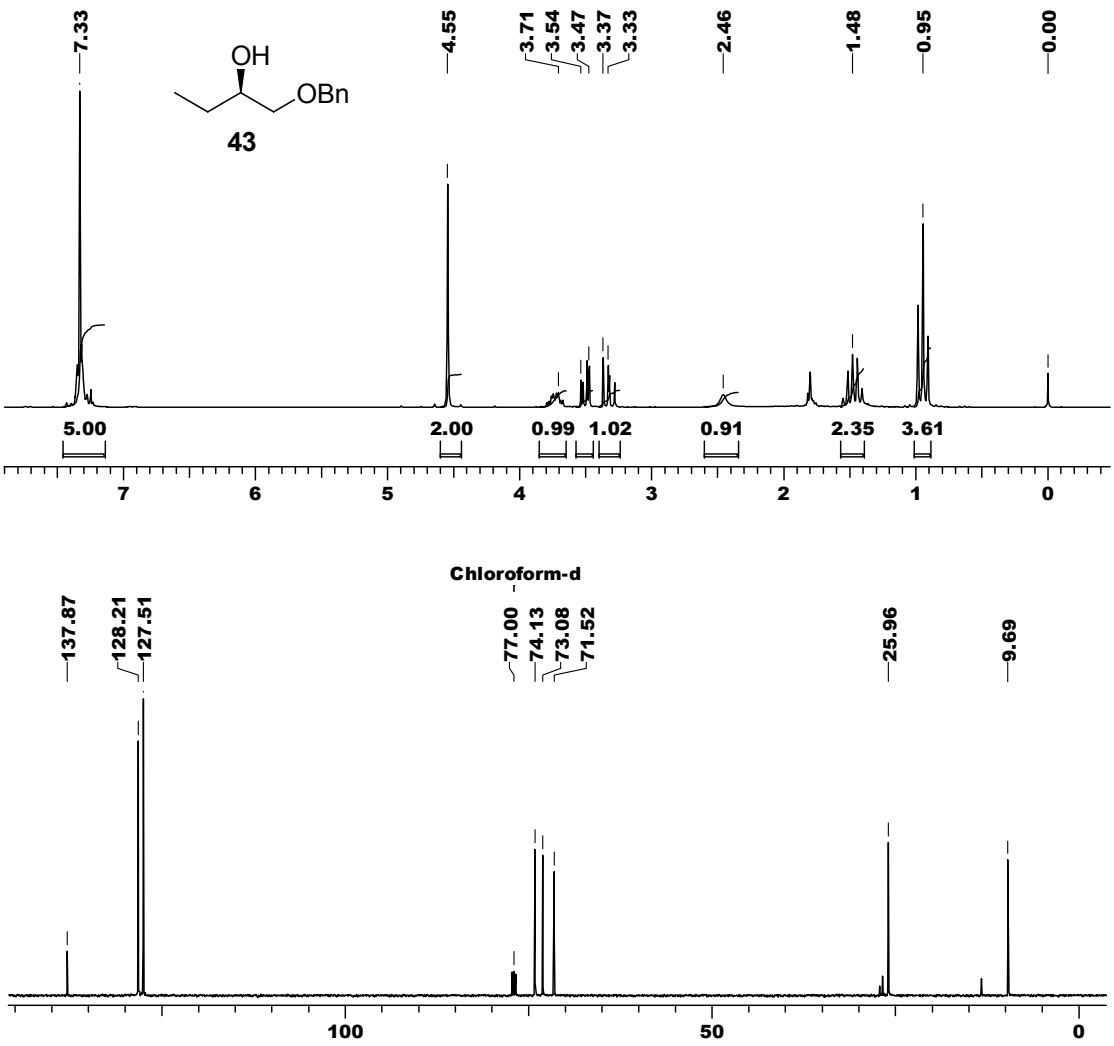


Fig 18: ^{1}H and ^{13}C NMR spectrum of monoprotected diol 43

Unfortunately, the direct displacement of the secondary hydroxyl group in **43** with 2-pyrrolidone under Mitsunobu conditions was unsuccessful. Hence, alcohol **43** was treated with methanesulfonyl chloride and triethylamine to give mesylate **46** in 92% yield. The display of signal at δ 2.97 (s) (**C**$\mathbf{H_3}$$SO_2$) in the ^{1}H NMR spectrum of the **46** confirms the presence of the mesyl group. The ^{13}C NMR spectrum displayed characteristic carbon signal at δ 38.3 due to the mesyl carbon (**C**$\mathbf{H_3}$$SO_2$) (**Fig. 19**).

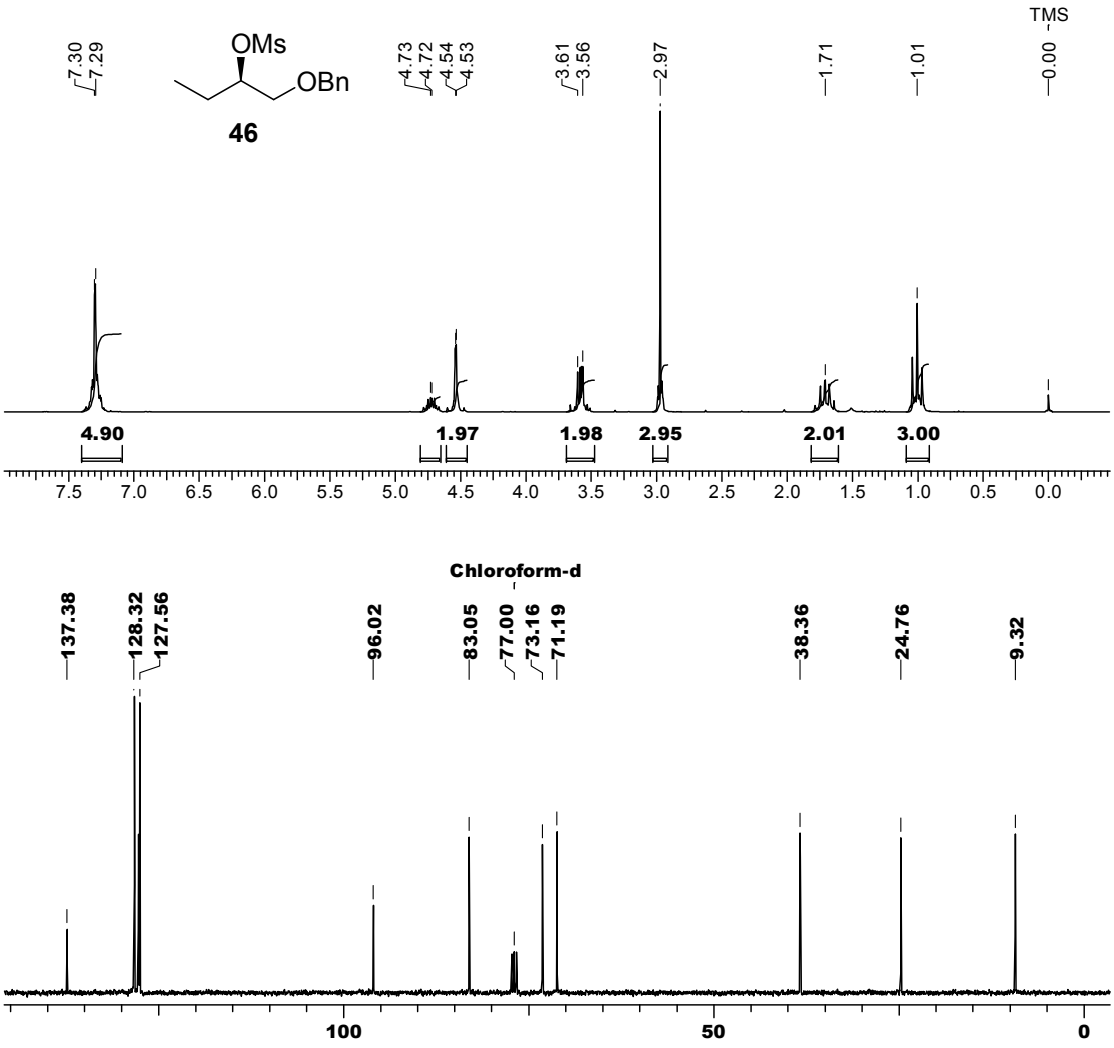


Fig 19: ^{1}H and ^{13}C NMR spectra of mesylate 46

Nucleophilic displacement of mesylate **46** with 2-pyrrolidone in dry DMF at 130 ºC proceeded smoothly to give the benzyl ether (*S*)-**47** in 62% yield; $[\alpha]_D^{25}$ -35.0 (*c* 1, $CHCl_3$). The appearance of signal at δ 1.97 (m) and 2.38 (t) in the ^{1}H NMR spectrum of **47** confirms the displacement of mesyl group with pyrrolidone moiety. Its ^{13}C NMR spectrum displayed peaks at δ 30.9, 43.0 and 174.5 due to the methylene carbons of pyrrolidone moiety and amide carbonyl carbon respectively (**Fig. 20**).

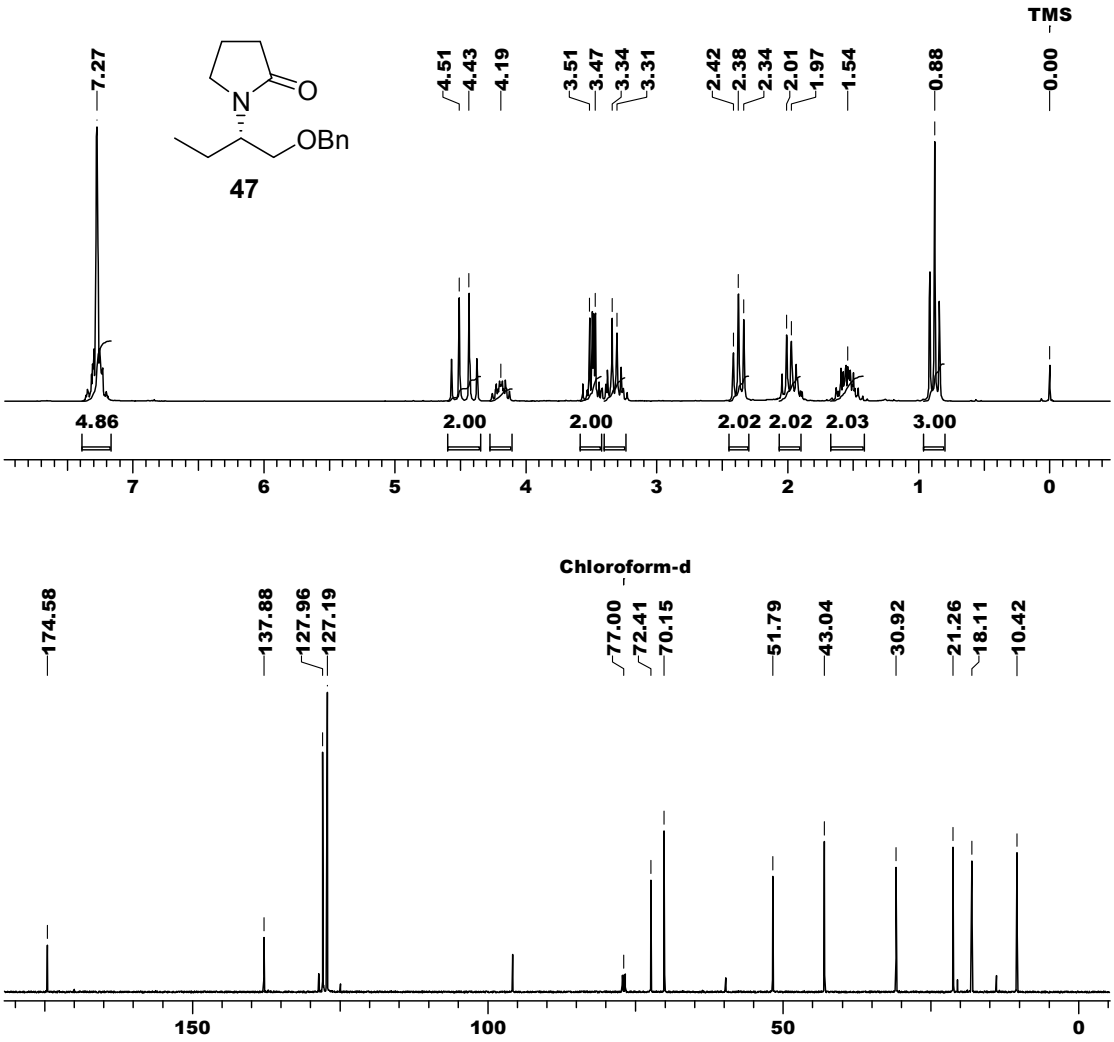


Fig 20: ^{1}H and ^{13}C NMR spectra of benzyl ether 47

Debenzylation of **47** was carried out by catalytic hydrogenation over Pd/C (10 mol%) to give alcohol **42** in 97% yield**;** $[\alpha]_D^{25}$ -19 (*c* 1, $CHCl_3$). Disappearance of signals at δ 4.43 (q) and 7.28 (m, 5H) in the ^{1}H NMR spectrum of alcohol **42** confirmed the deprotection of the benzyl group. Its ^{13}C NMR spectrum displayed peaks at δ 62.1 and 175.8 due to the methylene and amide carbonyl carbons respectively (**Fig. 21**).

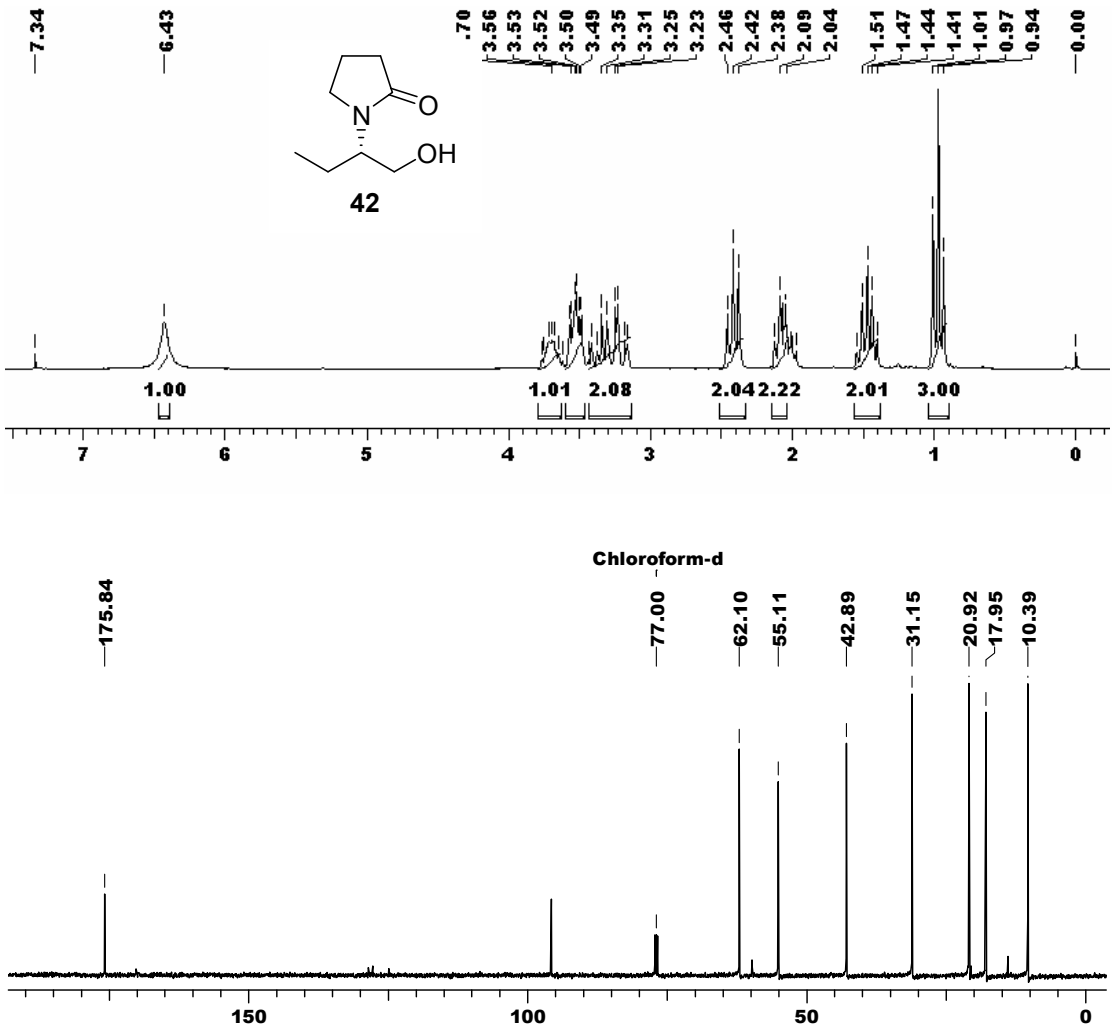


Fig 21: ^{1}H and ^{13}C NMR spectrum of alcohol 42

Oxidation of the resulting alcohol **42** with a mixture containing sodium hypochlorite-sodium chlorite in the presence of a catalytic amount of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO)[29] in acetonitrile-phosphate buffer (pH 6.8) afforded the corresponding acid **48** in 88% overall yield. $[\alpha]_D^{25}$ -28 (*c* 1, $CHCl_3$). The ^{1}H NMR spectrum of alcohol **48** showed characteristic peak at δ 9.66 (brs) for acid proton. Also its ^{13}C NMR spectrum displayed a typical peak at 177.0 (acid carbon), thus confirming the presence of acid carbonyl group (**Fig. 22**).

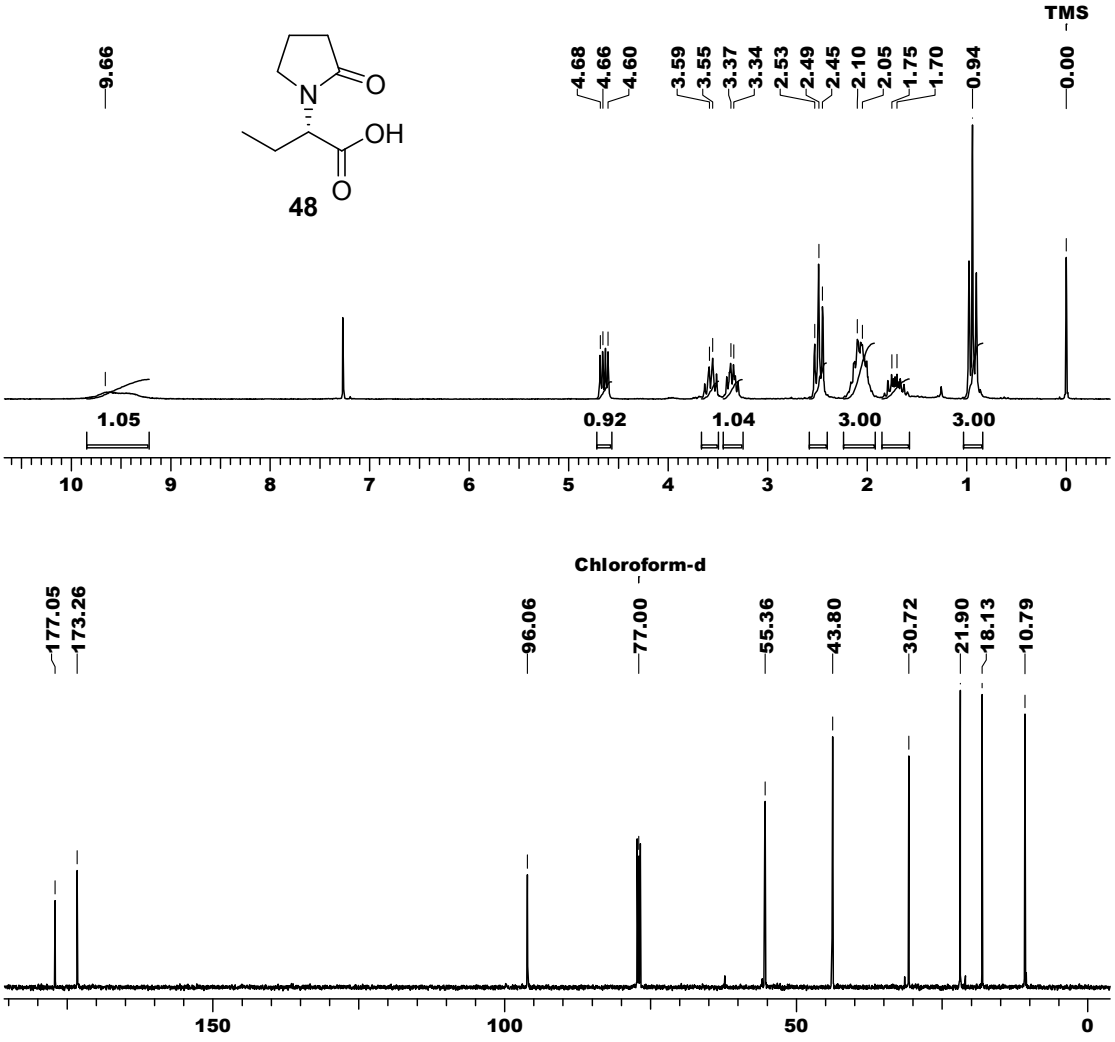


Fig 22: ^{1}H and ^{13}C NMR spectra of acid 48

Acid **48**, on treatment with ethyl chloroformate and ammonium hydroxide, produced levetiracetam (**34)** in 82% yield (75% after recrystallization in acetone). The ^{1}H NMR spectrum of levetiracetam (**34**) showed signals at δ 3.42 (m), 4.42-4.50 (dd), 5.76 (brs, 1H) and 6.52 (brs, 1H) corresponding to the methylene group of pyrrolidone moiety, the methine proton (**CH**NCO) and two amide protons respectively (**Fig. 23**). Its ^{13}C NMR showed typical peaks at δ 55.7, 172.5 and 175.7 corresponding to the methine carbon

attached to the pyrrolidone moiety, amide carbon of pyrrolidone and amide carbon of open chain respectively.

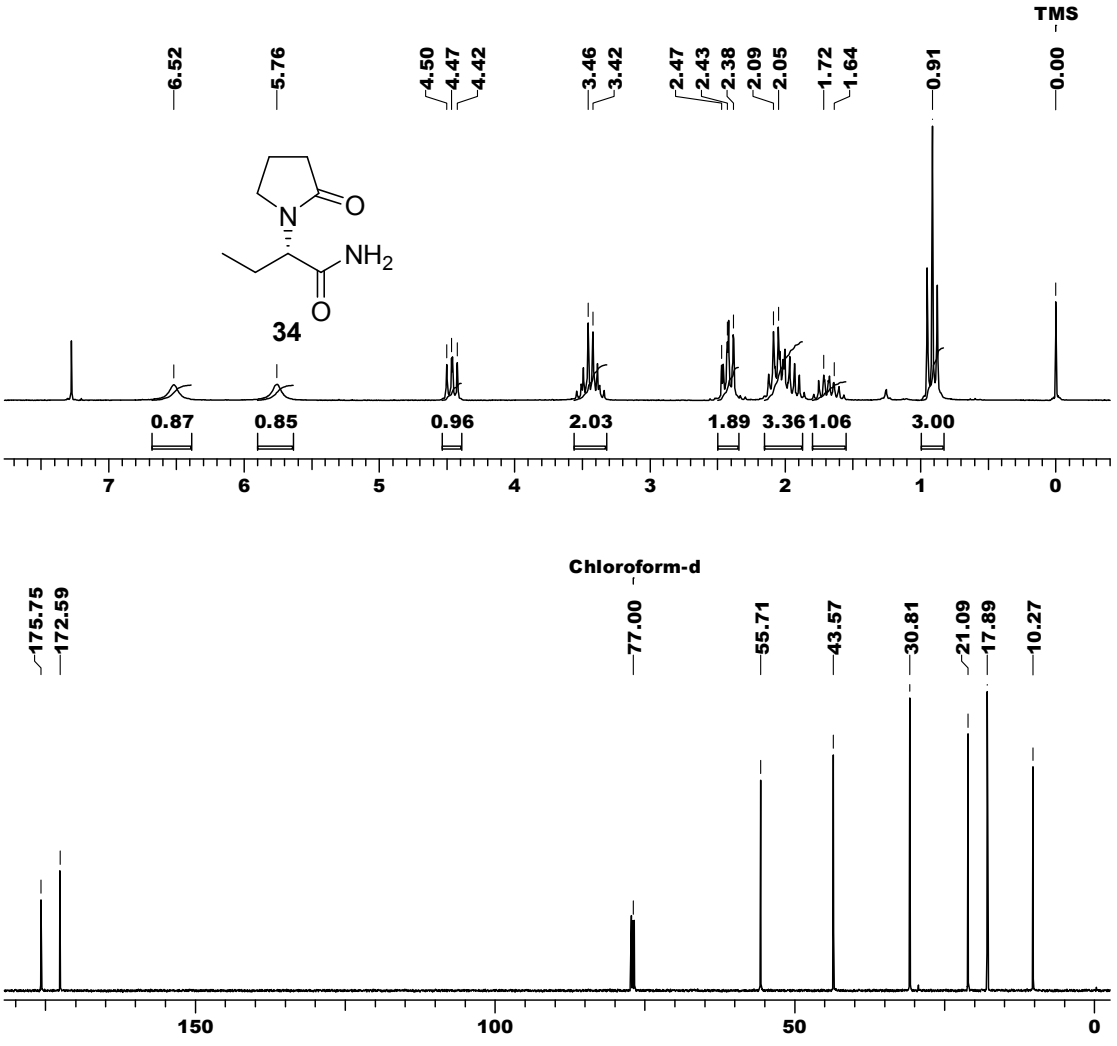
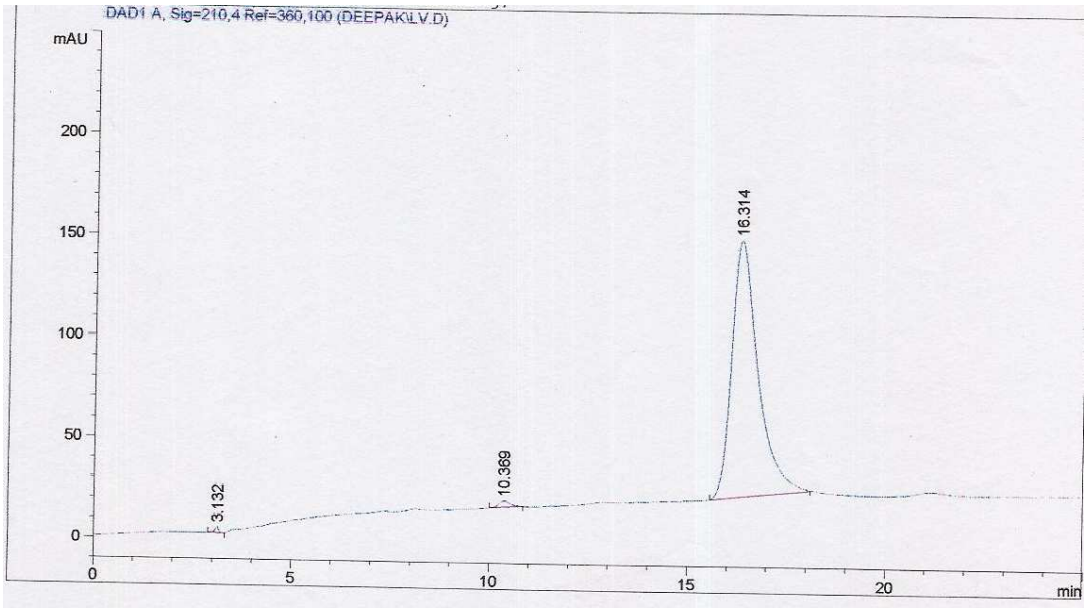


Fig 23: ^{1}H and ^{13}C NMR spectra of levetiracetam (34)

The enantioselectivity of levetiracetam **34** (>99.5% ee) was determined by chiral HPLC analysis (Chiracel OD-H) using hexane and isopropanol (90:10) as eluent. The chiral HPLC chromatogram is shown in **Fig. 24**. The spectral data obtained for levetiracetam (**34**) were in full agreement with the values reported in the literature.[24,25]



Peak No.	Ret. Time (Min.)	Area (mAU*s)	Area (%)
1	10.369	13.3409	0.222
2	16.314	5996.1824	99.778

Fig. 24: HPLC chromatogram of levetiracetam (34)

1.3.6 Conclusion

In conclusion, a practical and short enantioselective synthesis of levetiracetam (**34**), has been achieved successfully by employing proline-catalyzed α-aminooxylation strategy. The reactions are rapid and require a relatively low amount of less expensive and non-toxic proline as a catalyst, which is available in both enantiomeric forms. The merit of the synthesis is that levetiracetam has been obtained with high enantioselectivity (>99.5% ee) and in good overall yield (29.7%).

1.3.7 Experimental Section

(*2R*)- (*N*-Phenylaminooxy) butan-1-ol (26):

(The experimental procedure and spectral data for **26** have been described in Section I of this Chapter).

(*R*)-Butane-1,2-diol (45):

To a solution of alcohol **26** (6 g, 33.1 mmol) in MeOH was added 10% Pd/C (1 g) carefully. The reaction mixture was then stirred in the hydrogen atmosphere (1 atm. of H_2) for 6 h. After completion of reaction (monitored by TLC), the reaction mixture was filtered through celite pad and concentrated to near dryness. The crude product was then purified by column chromatography (pet ether: EtOAc = 30:70).

Yield: 2.68 g, 90%, Colorless oil; $[\alpha]_D^{25}$ -7.2 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$) ν_{max} 3367, 2962, 2933, 2877, 1722, 1666, 1600, 1461, 1251, 1130, 1060, 989, 752 cm^{-1}; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.95 (t, *J* = 7.6 Hz, 3H), 1.44 (p, *J* = 7.3 Hz, 2H), 3.40 (m, 1H), 3.57 (m, 2H), 4.07 (brs, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 9.9, 25.8, 66.1, 73.6 ppm; **Analysis**: **$C_4H_{10}O_2$** requires C, 53.31; H, 11.18 found C, 53.28; H, 11.22%.

(*R*)-1-(Benzyloxy)butan-2-ol (43):

A mixture of diol **45** (3 g, 33 mmol) and Bu_2SnO (9.82 g, 39.6 mmol) in toluene (100 mL) was refluxed for 12 h with azeotropic removal of water. Then, tetrabutylammonium bromide (5.3 g, 16.5 mmol) and benzyl bromide (6.1 g, 39.6 mmol) were added and the mixture was again refluxed for 20 h. The solution was concentrated in *vaccuo* and purified by column chromatography (pet ether: EtOAc = 80:20) to afford alcohol **43**.

Yield: 5.4 g, 95%, Colorless oil; $[\alpha]_D^{25}$ -10 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$) ν_{max} 3442, 2962, 2873, 1452, 1097 cm^{-1}; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.95 (t, *J* = 7.4 Hz, 3H), 1.44 (p, *J* = 7.4 Hz, 2H), 2.46 (brs, 1H), 3.32-3.37 (dd, *J* = 7.7, 9.36 Hz, 1H), 3.47-3.54 (dd, *J* = 3.0, 9.4 Hz, 1H), 3.71 (m, 1H), 4.55 (s, 2H), 7.33 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 9.6, 25.9, 71.5, 73.0, 74.1, 127.5, 128.2, 137.8 ppm; **Analysis: $C_{11}H_{16}O_2$** requires C, 73.30; H, 8.95 found C, 73.29; H, 8.99%.

(*R*)-1-(Benzyloxy)butan-2-yl methanesulfonate (46):

To a solution of alcohol **43** (4 g, 22.3 mmol) in CH_2Cl_2 (50 mL) at 0 ºC was added triethylamine (5.6 g, 55 mmol) followed by addition of methanesulfonyl chloride (2.7 g, 24.5 mmol) and DMAP (122 mg, 1 mmol). The reaction mixture was then stirred at 25 ºC for 4 h. After completion of reaction (TLC), solvents were removed in vaccuo. The residue was extracted with EtOAc (3 × 50 mL), the combined organic layers were dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel (pet ether: EtOAc = 80:20) to give alcohol **46.**

Yield: 5.3 g, 92%, Colorless oil; $\mathbf{[\alpha]_D^{25}}$ -5.45 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$) ν_{max} 3650, 3064, 3031, 2974, 2940, 1724, 1605, 1454, 1351, 1175, 1103, 927, 777 cm^{-1}; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.01 (t, *J* = 7.4 Hz, 3H), 1.71 (p, *J* = 7.4 Hz, 2H), 2.97 (s, 3H), 3.56-3.61 (m, 2H), 4.53 (s, 2H), 4.67-4.78 (m, 1H), 7.29 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 9.3, 24.7, 38.3, 71.1, 73.1, 83.0, 127.5, 127.7, 128.3, 137.3 ppm; **Analysis:** **$C_{12}H_{18}O_4S$** requires C, 55.79; H, 7.02, found C, 55.77; H, 6.99%.

1-((*S*)-1-(Benzyloxy)butan-2-yl)pyrrolidin-2-one (47)

To a solution of NaH (1.1 g, 28.9 mmol) in dry DMF (50 mL) at 0 ºC was added 2-pyrrolidone (7.9 g, 58 mmol) and the reaction mixture was stirred for 30 min. followed by addition of mesylate **46** (5 g, 19.3 mmol). The reaction mixture was then heated at 130 ºC for 3 h. After completion of reaction (TLC), it was cooled to room temperature and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated on rotavapour. The crude product was purified with column chromatography to afford **47**.

Yield: 2.9 g, 62%, Colorless oil; $[\alpha]_D^{25}$ -35.0 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$) ν_{max} 3470, 3062, 2965, 2934, 2875, 1681, 1475, 1455, 1424, 1286, 1270, 1096, 909, 739 cm^{-1}; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.4 Hz, 3H), 1.54 (m, 2H), 1.97 (m, 2H), 2.38 (t, *J* = 8.4 Hz, 2H), 3.27-3.38 (m, 2H), 3.47-3.51 (m, 2H), 4.19 (m, 1H), 4.43 (q, 2H), 7.28 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 10.4, 18.1, 21.2, 30.9, 43.0, 51.7, 70.1, 72.4, 127.1, 127.9, 137.8, 174.5 ppm; **Analysis: $C_{15}H_{21}NO_2$** requires C, 72.84; H, 8.56; N, 5.66 found C, 72.88; H, 8.55; N, 5.63%.

1-((*S*)-1-Hydroxybutan-2-yl)pyrrolidin-2-one (42):

To a solution of alcohol **47** (3 g, 12.1 mmol) in MeOH was added 10% Pd/C (0.4 g) carefully. The reaction mixture was then stirred in the hydrogen atmosphere (1 atm. of H_2) for 10 h. After completion of reaction (monitored by TLC), the reaction mixture was filtered through celite pad, concentrated to near dryness. The crude product was then purified by silica gel chromatography (pet ether: EtOAc 5:95) to furnish alcohol **42.**

Yield: 1.84 g, 97%, gum; $[\alpha]_D^{25}$ -19 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$) ν_{max} 3408, 2965, 2878, 1659, 1464, 1426, 1381, 1291, 1205, 1070, 989, 735 cm^{-1}; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.97 (t, *J* = 7.5 Hz, 3H), 1.47 (p, *J* = 6.7 Hz, 2H), 2.04 (m, 2H), 2.42 (t, *J* = 8.1 Hz, 2H), 3.16-3.38 (m, 2H), 3.52 (m, 2H), 3.70 (m, 1H), 6.43 (brs, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 10.3, 17.9, 20.9, 31.1, 42.8, 55.1, 62.1, 175.8 ppm; **Analysis: $C_8H_{15}NO_2$** requires C, 61.12; H, 9.62; N, 8.91 found C, 61.10; H, 9.62; N, 8.94%.

(*S*)-2-(2-Oxopyrrolidin-1-yl)butanoic acid (48):

To a stirred solution of alcohol **42** (942 mg, 6 mmol), TEMPO (65.6 mg, 0.42 mmol), $NaClO_2$ (1 g, 12 mmol) in CH_3CN (30 mL) and phosphate buffer (22.5 mL) at 25 ºC was added NaClO (5%, 0.15 mL) after stirring the reaction mixture for 5 h at 35 ºC, 7.2 mL of

2N NaOH was added and the mixture was added to ice-cold solution of sodium sulfite solution (183 mg in 30 mL) . After stirring for 30 min, the reaction mixture was acidified with 2N HCl to pH 3-4 and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in *vacuo* to give acid **48**.

Yield: 0.923 g, 90%, White solid (mp 124 °C); $[\alpha]_D^{25}$ -28 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$) ν_{max} 3019, 2975, 1721, 1676, 1642, 1443, 1423, 1291, 1215, 1044, 758 cm^{-1}; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.94 (t, *J* = 7.5 Hz, 3H), 1.63-1.79 (m, 1H), 1.97-2.16 (m, 3H), 2.49 (t, *J* = 7.7 Hz, 2H), 3.37 (m, 1H), 3.55 (m, 1H), 4.66 (dd, *J* = 4.9, 11 Hz, 1H), 9.66 (brs, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 10.79, 18.13, 21.90, 30.72, 43.80, 55.36, 173.26, 177.05 ppm; **Analysis: $C_8H_{13}NO_3$** requires C, 56.13; H, 7.65; N, 8.18 found C, 56.09; H, 7.66; N, 8.22%.

(*S*)-2-(2-oxopyrrolidin-1-yl)butanamide (levetiracetam) (34):

To a cold solution (0 ºC) of acid **48** (513 mg, 3 mmol) and Et_3N (3.33 mg, 3.3 mmol) in anhydrous THF (3 mL) was added ethyl chloroformate (3.56 mg, 3.3 mmol) and the reaction mixture was stirred at 0 ºC for 30 min. Ammonium hydroxide (30% aq. solution, 0.57 mL, 4.95 mmol) was added and the reaction mixture was stirred at 25 ºC for 16 h. After addition of K_2CO_3 (0.45 g, 3.3 mmol) the mixture was filtered and concentrated in vaccuo. The residue was extracted with CH_2Cl_2 (3 × 50 mL) and dried over anhydrous Na_2SO_4 and concentrated in *vacuo* to give crude amide **34**, which was recrystallized from acetone in 75% yield.

Yield: 418 mg, 82% (75% after recrystallization); Colorless solid (mp 116 ºC, lit.[26a] mp 117 ºC); $[\alpha]_D^{25}$ -90.3 (*c* 1, acetone) { lit.[26a] $[\alpha]^{25}_D$ -90.0 (*c* 1, acetone)}; **IR** ($CHCl_3$) ν_{max} :

3672, 3332, 3009, 2463, 1668, 1422, 1288, 1043, 754 cm^{-1}, **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.91 (t, *J* = 7.5 Hz, 3H), 1.60-1.75 (m, 1H), 1.90-2.09 (m, 3H), 2.38-2.47 (m, 2H), 3.42 (m, 2H), 4.42-4.50 (dd, *J* = 6.7, 8.6 Hz, 1H), 5.76 (brs, 1H), 6.52 (brs, 1H). **^{13}C NMR** (50 MHz, $CDCl_3$): δ 10.2, 17.8, 21.0, 30.8, 43.5, 55.7, 172.5, 175.7 ppm; **Analysis:** **$C_8H_{14}N_2O_2$** requires C, 56.45; H, 8.29; N, 16.46; found C, 56.49; H, 8.34; N, 16.44.

HPLC conditions: Chiracel OD-H column; hexane: *i*-PrOH (90:10 v/v); flow rate 1.0 mL/min.; UV-210 nm; column temperature 25 ºC; retention time: 10.3 min. (*R*-isomer) and 16.3 min. (*S*-isomer). Compared with reported conditions : Rao, B. M.; Ravi, R.; Reddy, B. S.; Sivakumar, S.; Gopi Chand, I.; Praveen Kumar, K.; Acharyulu, P.V.R.; Om Reddy, G.; Srinivasu, M. K. *J. Pharm. Biomed. Anal.* **2004**, *35*, 1017.

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CHAPTER II

Organocatalytic Asymmetric Synthesis of Hexanolide and Harzialactone A

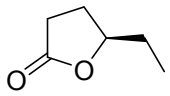
Section I:

Enantioselective Synthesis of Hexanolide *via* L-proline-catalyzed Sequential Aminooxylation-Olefination

2.1.1 Introduction

The dermestid beetles include many economically important insect pests that infest nearly all forms of stored products, including grain, meats, dairy products, carpets and clothing. Among the worst pests in this family are the black carpet beetle, *Attagenus megatoma,* and several species of *Trogoderrna,* including *T. granarium* (the khapra beetle), *T. inclusum, T. glabrum,* and *T. variabile.* Burkholder and Dicke (1966) have reported evidence of sex pheromones for *Attagenus megatoma, T. inclusum,* and *T. glabrum.* Subsequently (*E,Z*)- 3,5-tetradecadienoic acid was identified as the principal sex attractant for *A. megatoma*. Vick and coworkers (1970) then observed considerable pheromone interspecificity among seven *Trogoderma* species and suggested that identical or similar compounds may serve as attractants for these species.[1]

(*R*)-(+)-4-Hexanolide (**1**) is a component of pheromone secreted by the female of dermestid beetles, *Trogoderma glabrum*. The beetle has been reported to respond to the (*R*)-isomer but to neither the (*S*) isomer nor the racemate.[1]



(*R*)-(+)-4-Hexanolide
(**1**)

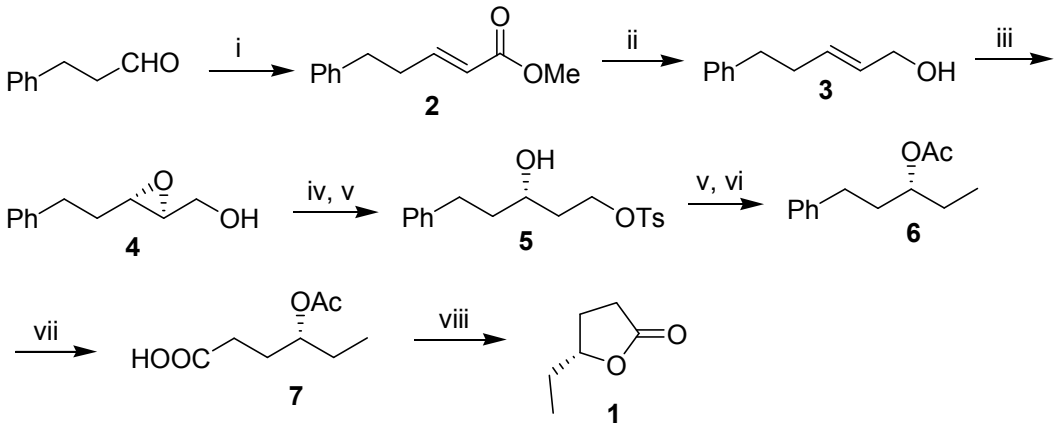
2.1.2 Review of Literature

Several asymmetric syntheses of **1** have been reported,[2-6] which include (i) asymmetric reduction of prochiral ketones with Baker's yeast or chiral reducing agents; (ii)

stereospecific synthesis from chiral building blocks; (iii) resolution of lactones and other catalytic methods. Some of the recent methods are described below.

Martin's approach (1990)[2d]

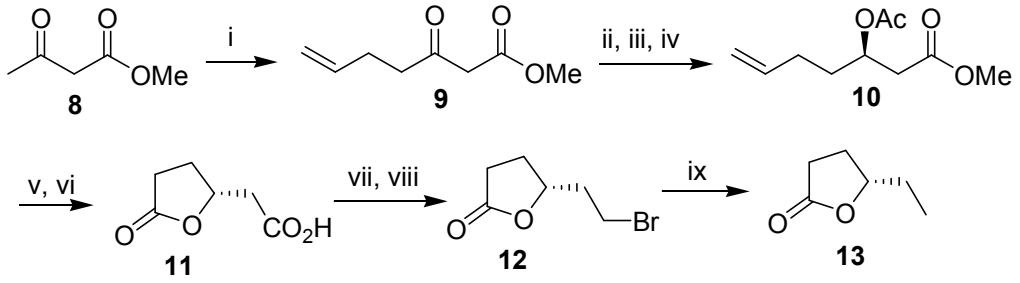
Martin *et al*. have reported the synthesis of hexanolide (**1**) using Sharpless asymmetric epoxidation as a key step. Accordingly, 3-phenylpropanal was subjected to Wittig-Horner olefination using sodium hydride as base to give unsaturated ester **2** in 76% yield. The reduction of **2** was carried out with $LiAlH_4/AlCl_3$ in ether, yielding the (*E*)-allylic alcohol **3,** which was submitted to asymmetric epoxidation using L-(+)-diethyl tartrate [L-(+)-DET] as chiral auxiliary, to afford the 2,3-epoxy alcohol **4** with greater than 95% enantiomeric excess. The reduction of **4** with Red-Al in THF yielded the l,3-diol, which on monotosylation gave **5.** Reduction, without purification, with lithium aluminum hydride in THF led to the chiral alcohol which was acetylated under standard conditions to give acetate **6**. The acetate **6** was oxidized using $RuCl_3$ to afford the acid **7** (72% yield), which after saponification and further acid treatment yielded the (*R*)-hexanolide (**1**) in 73% yield (**Scheme 1**).



Scheme 1: (i) NaH, $(MeO)_2P(O)CH_2COOMe$, benzene, 35 min., 76%; (ii) $LiAlH_4$, $AlCl_3$, ether, 30 min., 91%; (ii) L-(+)-DET, $Ti(O\text{-}i\text{-}Pr)_4$, TBHP, 5 h, CH_2Cl_2, 87%; (iv) Red-Al, THF, 30 min., 75%; (v) *p*-TSA, pyridine, 0 °C, 16 h; (v) $LiAlH_4$, THF, 4 h, 72%; (vi) acetic anhydride, pyridine, 2 h, 96%; (vii) periodic acid, $RuCl_3$, CCl_4, CH_3CN, 3 h, 76%; (viii) 10% NaOH, HCl, 30 min., 73%.

Mamdapur's approach (1991)[3]

Methyl acetoacetate (**8**) was subjected to alkylation to furnish methyl 3-oxo-6-heptenoate (**9**). This on baker's yeast reduction and subsequent esterification with CH_2N_2 furnished methyl (*R*)-3-hydroxy-6-heptenoate, which was acetylated to **10**. The olefinic functionality of the resultant acetate **10** was subjected to oxidative cleavage ($NaIO_4/RuC1_3$), the product thus obtained on alkaline hydrolysis followed by acid treatment gave acid **11**. Selective reduction of its carboxylic acid functionality with BH_3.THF followed by displacement of alcohol with bromine afforded **12** in 82% yield. Reductive bromination of **12** gave (*S*)-hexanolide (**13**) in 80% yield (**Scheme 2**).

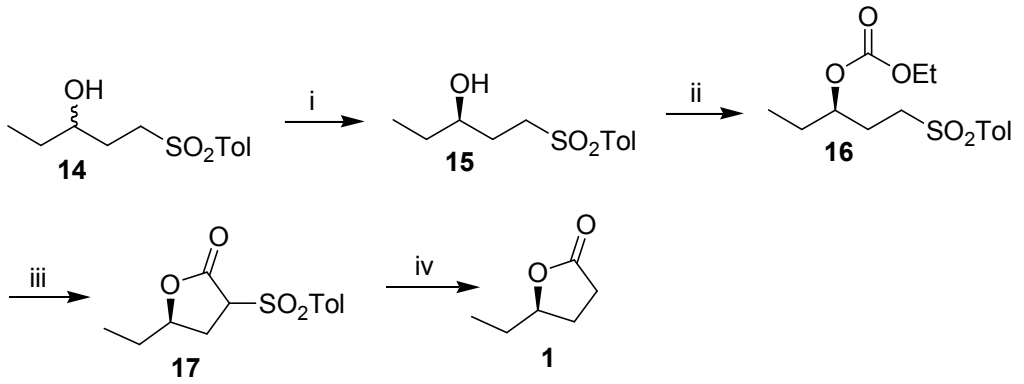


Scheme 2: (i) NaH, allyl bromide, BuLi, THF; (ii) KOH, EtOH, baker's yeast, 25 °C; (iii) CH_2N_2, CH_2Cl_2, 34%; (iv) Ac_2O, pyridine, DMAP, 95%; (v) $RuCl_3$, $NaIO_4$, 24 h, 79%; (vi) NaOH, HCl, 16 h, 64%; (vii) BH_3, THF, 2.5 h, 99%; (viii) $PPh_3.Br_2$, CH_2Cl_2, 1 h, 82%; (ix) *n*-Bu_3SnH, AIBN, 2.5 h, 80%.

Gopalan's approach (1992)[4]

Gopalan *et al*. have reported the synthesis of hexanolide (**1**) using Lipase-catalyzed resolution as key step. Accordingly, resolution of racemic alcohol **14** was carried out with Lipase-30 to give (*R*)-alcohol **15** in 57% yield. Treatment of **15** with ethyl chloroformate in pyridine gave the desired carbonate **16** in 98% yield. Deprotonation of the sulfone **16** with 2.2 eq. lithium hexamethyldisilylamide at -78 °C in THF, leads to a clean intramolecular acylation to yield the lactone **17** in 95% yield. The *p*-toluenesulfonyl

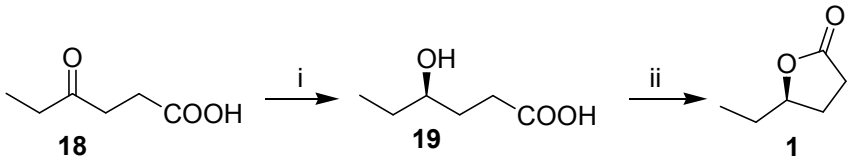
moiety was then reductively removed using standard procedures to give (*R*)-(+)-hexanolide (**1**) in 65% yield.



Scheme 3: (i) Lipase PS-30, isopropenyl actate, ether, 25 °C, 48 h, 57%; (ii) $ClCO_2Et$, pyridine 98%; (iii) LiHMDS, -78 °C, 95%; (iv) Na/Hg, Na_2HPO_4, MeOH, 0 °C, HCl, 65%.

Ramachandran's approach (2001)[5]

Ramachandran *et al*. have used chiral borane-mediated reduction of ketone for the synthesis of hexanolide (**1**). Reduction of γ-ketoacid **18** was carried out with (-)-diisopinocampheylborane to give alcohol **19** in 82% with 95% ee. Lactonization of **19** using trifluoroacetic acid furnished hexanolide (**1**) in 80% yield and 95% ee.

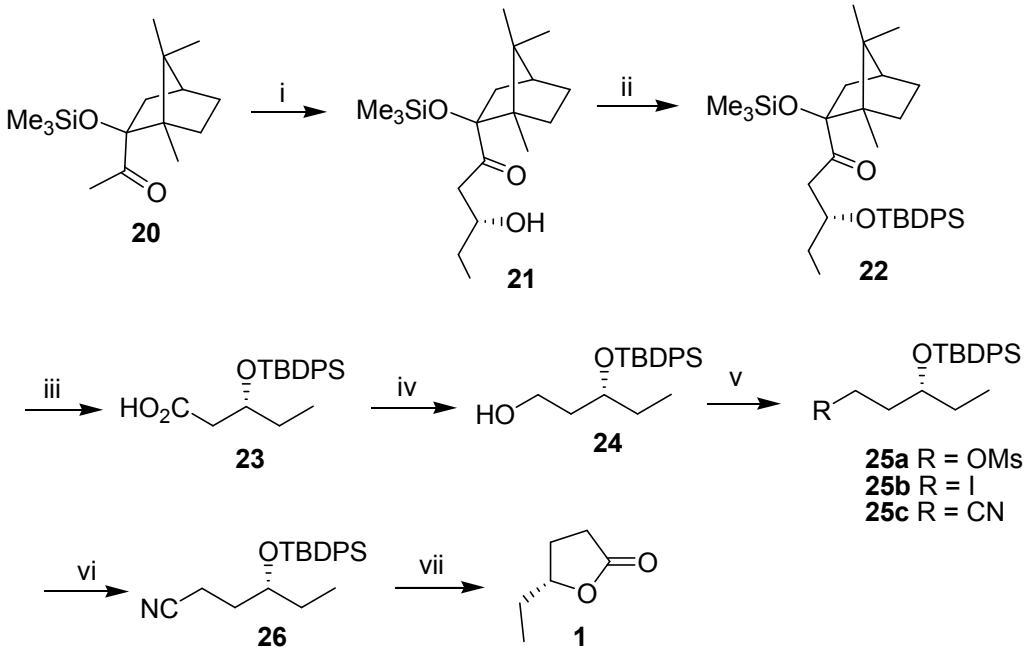


Scheme 4: (i) (-)-diisopinocampheylborane (Ipc_2BH), THF, 0 °C, 48 h, 82%; (ii) CF_3CO_2H, CH_2Cl_2, 6 h, 80%, 95% ee.

Gil's approach (2003)[6]

Gil *et al*. have carried out synthesis of hexanolide (**1**) *via* diastereoselective aldol reaction as a key step. Thus, starting with the camphor-based chiral auxiliary, the asymmetric aldol reaction of its lithium enolate with propanal at −78 °C afforded the aldol product **21** in 93% yield as a diastereomeric mixture (97:3). After desilylation, protection of

secondary hydroxyl group with TBDPS afforded **22** in 94% yield. Cleavage of the chiral auxiliary moiety was accomplished using cericammonium nitrate (CAN) to obtain the protected hydroxy acid **23** in 92% yield. Compound **23** was reduced with BH_3·THF to give the alcohol **24** which was converted to methanesulfonate **25a**, then iodide **25b** and finally nitrile **25c** (80% yield, over three steps). Removal of TBDPS group with Bu_4NF furnished the hydroxy nitrile **26** in 86% yield. Subsequent hydrolysis in aqueous base followed by acidification gave the desired lactone **1** (hexanolide) in 90% yield.



Scheme 5: (i) LDA, −78 °C, then CH_3CH_2CHO, 3 h, 93%; (ii) (a) HF aq., 25 °C, 1.5 h, 96%, (b) TBDPSCl, imidazole, DMF, 25 °C, 12 h, 94%; (iii) CAN, CH_3CN, 0 °C, 20 min, 92%; (iv) BH_3·THF, 0 °C, then 25 °C, 4 h, 95%; (v) (a) MsCl, Et_3N, 0 °C, 3 h, (b) NaI, acetone, reflux, 12 h, (c) NaCN, DMSO, 25 °C, 12 h (80% from **24**); (vi) Bu_4NF, THF, 25 °C, 4 h (86%); (vii) NaOH, 2-methoxyethanol, reflux, 21 h, then HCl (90%).

2.1.3 Present Work

2.1.3.1 Objective

Some of the methods described in literature for the synthesis of hexanolide (**1**) are not amenable to scale up as they involve large number of steps as well as they proceed with

low yields. Hence, the synthesis of hexanolide (**1**) involving less number of steps starting from readily available starting materials is still desirable. In this section, we describe highly efficient and short synthesis of (*R*)-(+)-4-hexanolide (**1**) *via* L-proline-catalyzed sequential aminooxylation-olefination[7] of *n*-butyraldehyde. The retrosynthetic analysis of hexanolide is shown in (**Fig. 1**) wherein we envisaged the L-proline-catalyzed sequential aminooxylation-olefination strategy for introducing chirality into the molecule.

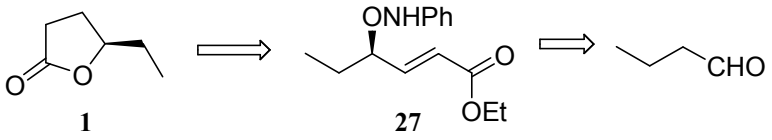
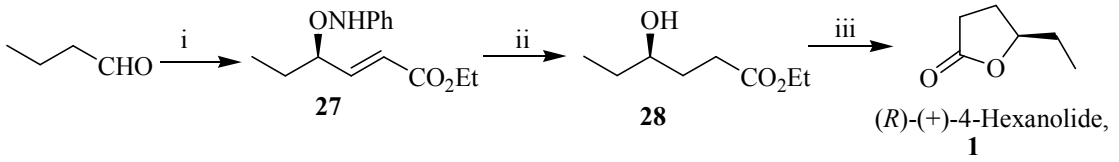


Fig. 1: Retrosynthetic analysis of (*R*)-Hexanolide (1)

2.1.4 Results and Discussions:

The synthetic route for (*R*)-hexanolide (**1**) is presented in **Scheme 6**.



Scheme 6: Reagents and conditions: (i) PhNO, L-proline (25 mol%), -20 ºC, 24 h then triethyl phosphonoacetate, LiCl, DBU, 1 h, 75%. (ii) H_2 (1 atm.), Pd/C (10%), MeOH, 12 h, 84%. (iii) EtOH, reflux, 5 h, 95%.

As can be seen from **Scheme 6**, our synthesis started with α- aminooxylation[8] of *n*-butyraldehyde with nitrosobenzene and L-proline at -20 ^{o}C followed by *in situ* Horner-Wadsworth-Emmons (HWE) olefination with LiCl and DBU (Masamune-Roush protocol)[9] to furnish aminooxy-olefinic ester **27** in 75% yield; $[\alpha]^{25}_{D}$ +88 (*c* 2, $CHCl_3$). The ^{1}H NMR spectrum of **27** showed signals at δ 4.30 (m) and 5.77 (d) corresponding to a proton attached at the functionalized carbon (**CH**ONHPh) and an olefinic proton. Its

^{13}C NMR spectrum showed characteristic peaks at δ 146.9 and 165.9 corresponding to the olefinic and ester carbons respectively (**Fig. 2**).

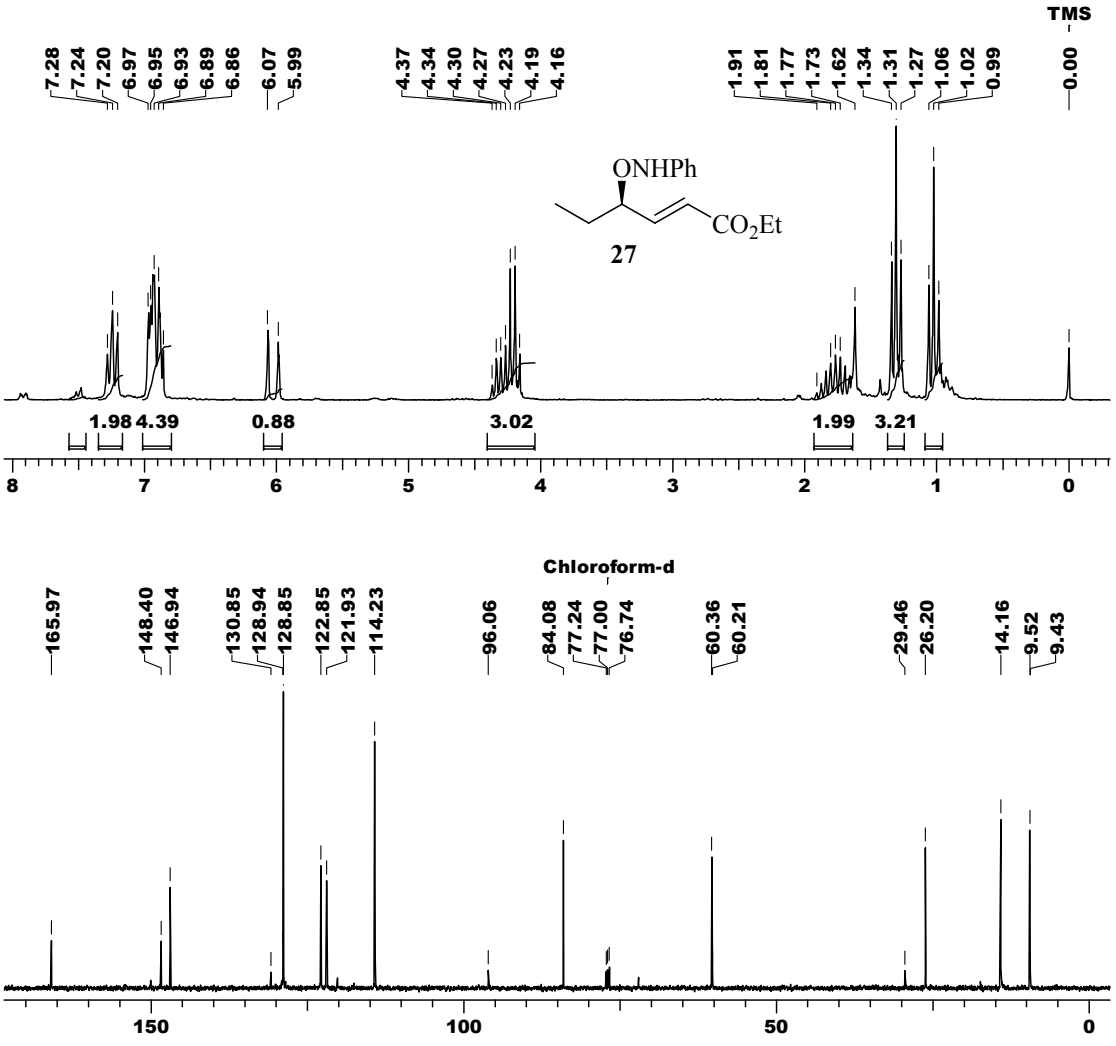


Fig. 2: ^{1}H and ^{13}C NMR spectra of aminooxy-olefinic ester 27

Reduction of both C=C and anilinooxy group in ester **27** with 10% Pd/C, H_2 (1 atm.) proceeded smoothly to give γ-hydroxy ester **28** in 84% yield. The disappearance of signals at δ 5.77 (olefinic proton) and 7.24 (aromatic proton) in the ^{1}H NMR spectrum of ester **28** confirmed the deprotection of the anilinoxy group and reduction of C=C as well

(**Fig. 3**). The ^{13}C NMR spectrum showed typical peaks at δ 71.8 and 173.9 corresponding to the carbons attached to hydroxyl and ester carbonyl groups respectively.

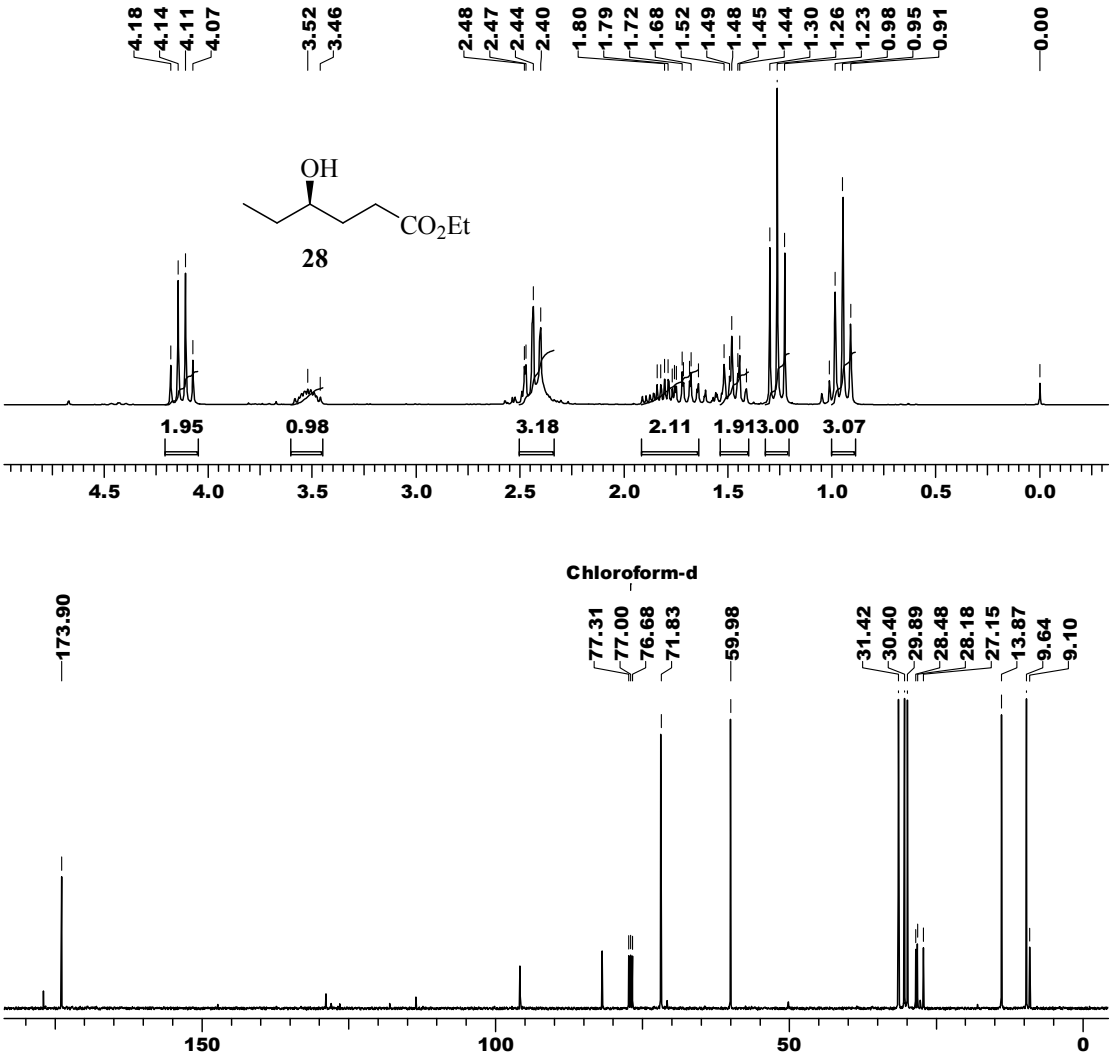


Fig. 3: ^{1}H and ^{13}C NMR spectra of hydroxyl ester 28

Subsequent cyclization of ester **28** in refluxing ethanol furnished (*R*)-4-hexanolide (**1**) in 95% yield $[\alpha]^{25}_{D}$ +51.7 (*c* 1, MeOH) {lit.[6] $[\alpha]^{25}_{D}$ +53.1 (*c* 1, MeOH)} (**Scheme 6**). The ^{1}H NMR spectrum of (*R*)-hexanolide (**1**) showed signals at δ 2.50 (dd) and 4.44 (m) corresponding to the methylene (**CH_2**COO) and the methine protons (**CH**O) respectively (**Fig. 4**). Its ^{13}C NMR showed typical peaks at δ 82.1 and 177.2 corresponding to the

methine carbon in the lactone moiety and ester carbonyl carbon respectively. The physical and spectroscopic data obtained for hexanolide (**1**) were in full agreement with the values reported in the literature.[6]

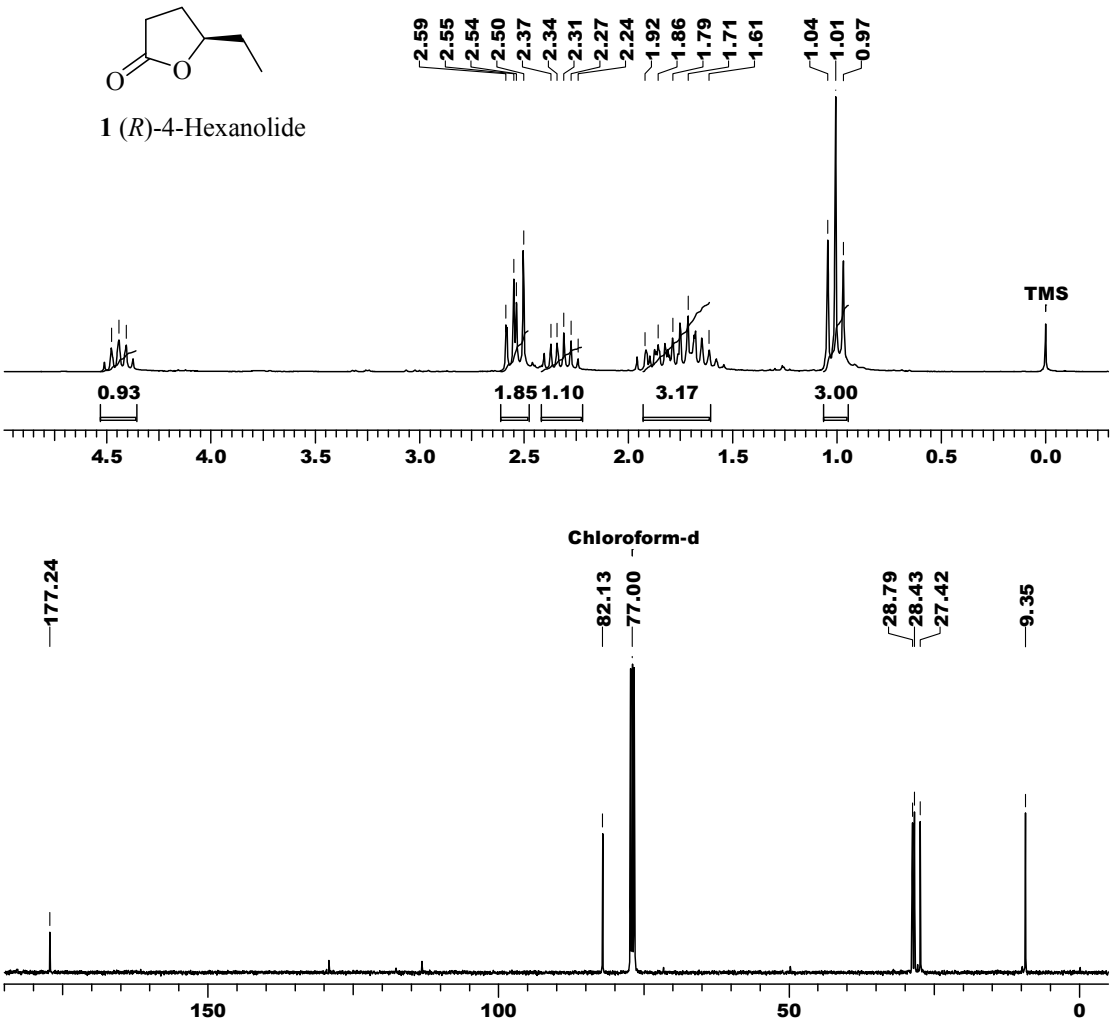


Fig. 4: ^{1}H and ^{13}C NMR spectra of (*R*)-hexanolide (1)

2.1.5 Conclusion:

In conclusion we have achieved a short and efficient synthesis of (*R*)-(+)-4-hexanolide (overall yield 59.8%) by employing proline-catalyzed sequential α-aminooxylation-HWE olefination of *n*-butyraldehyde. Good yields, simple and environment friendly

procedures, easy availability of starting materials, less number of steps are some of the merits of this approach.

2.1.6 Experimental Section:

(*R*)-Ethyl 4-anilinoxyhex-2-enoate (27):

To a solution of nitrosobenzene (3 g, 28 mmol) and L-proline (476 mg, 15 mol%) in CH_3CN (60 mL) was added *n*-butyraldehyde (2.94 mL, 33.6 mmol) at -20 °C. The reaction mixture was stirred at the same temperature for 24 h followed by addition of LiCl (1.7 g, 1.5 equiv.), triethyl phosphonoacetate (9.4 g, 1.5 equiv.) and after stirring for 5 min. DBU (4.2 g, 1 equiv.) was added. The reaction mixture was quenched with half saturated NH_4Cl solution and extracted with ethyl acetate (3 × 60 mL). Combined organic phases were concentrated and dried over anhydrous Na_2SO_4. Purification by flash column chromatography (Pet ether: EtOAc = 90:10) afforded aminooxy olefinic ester **27**.

Yield: 5.2 g, 75% yield, brownish oil; $[\alpha]^{25}_{D}$ +88 (*c* 2, $CHCl_3$); **IR** ($CHCl_3$) ν_{max} 3433, 2975, 2937, 2877, 2360, 1703, 1654, 1454, 1274, 1178, 1039, 777 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.02 (t, *J* = 7.4 Hz, 3 H), 1.31 (t, *J* = 7.1 Hz, 3 H), 1.62 (s, 1H), 1.66-1.99 (m, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 4.30 (m, 1H), 5.77 (d, *J* = 15.9 Hz, 1H), 6.93 (m, 4H), 7.24 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 9.5, 14.1, 26.2, 60.3, 84.0, 114.2, 121.9, 122.8, 128.8, 146.9, 148.4, 165.9 **Analysis: $C_{14}H_{19}NO_3$** required C, 67.45; H, 7.68; N, 5.62; found C, 67.15; H, 7.28; N, 5.80%.

Ethyl 4-hydroxyhexanoate (28):

To a solution of **27** (3.0 g, 12 mmol) in MeOH was added 10% Pd/C (200 mg) carefully. The reaction mixture was then stirred in the hydrogen atmosphere (1 atm. of H_2) for 12 h. After completion of reaction (monitored by TLC) the reaction mixture was filtered

through celite pad, concentrated to near dryness. The crude product was then purified by flash column chromatography (pet ether: EtOAc = 80:20).

Yield: 1.6 g, 84% yield, Colorless oil; **$[\alpha]^{25}_{D}$** +27 (*c* 2, $CHCl_3$); **IR** ($CHCl_3$) ν_{max} 3523, 2970, 2939, 2881, 2358, 2331, 1770, 1602, 1461, 1353, 1182, 960, 850 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.95 (t, *J* = 7.4 Hz, 3 H), 1.26 (t, *J* = 7.1 Hz, 3 H), 1.48 (m, 2H), 1.76 (m, 2H), 2.44 (m, 3H), 3.53 (m, 1H), 4.11 (q, *J* = 7.2 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 9.64, 13.8, 29.8, 30.4, 31.4, 59.9, 71.8, 173.9. **Analysis: $C_8H_{16}O_3$** required C, 59.97; H, 10.07; found C, 59.69; H, 10.3%.

(*R*)-(+)-4-hexanolide (1):

A solution of hydroxyl ester **28** (1 g, 6.2 mmol) in absolute ethanol (20 mL) was refluxed for 5 h. Removal of solvent under reduced pressure and flash chromatographic purification gave hexanolide **1** in 95% yield.

Yield: 676 mg, 95% yield, colorless oil; **$[\alpha]^{25}_{D}$** +51.7 (*c* 1, MeOH) { lit.[6] $[\alpha]^{25}_{D}$ +53.1 (*c* 1, MeOH)}; **IR** ($CHCl_3$) ν_{max} 3020, 2970, 2941, 2360, 1770, 1602, 1458, 1353, 1176, 970, 754 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.01 (t, *J* = 7.4 Hz, 3 H), 1.58-1.96 (m, 3 H), 2.31 (m, 1H), 2.50-2.59 (m, 2H), 4.44 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 9.3, 27.4, 28.4, 28.7, 82.13, 177.2. **Analysis: $C_6H_{10}O_2$** required C, 63.14; H, 8.83; found C, 63.0; H, 8.54%.

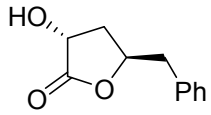
Section II:

Asymmetric Synthesis of (+)-Harzialactone A *via* L-proline-catalyzed Sequential Aminooxylation-Olefination and Diastereoselective α-Hydroxylation

2.2.1 Introduction

Marine microorganisms have been a rich source of bioactive metabolites, especially those with unique structural features that might represent possible leads in the new drug discovery process.[10] The marine environment comprises 71 % of the earth's surface, and consists of extreme and contrasting habitats, ranging from tropical reefs to ice-shelfs of the polar seas, and to black smokers in the deep sea. The biodiversity in the world's oceans is immense, e.g., of 33 known animal phyla 15 are exclusively marine, and 32 of them have marine representatives (Norse, 1995). Some habitats are known to be particularly numerous in species, e.g., tropical marine reefs, which represent one of the most diverse ecosystems encountered on earth, comparable in diversity to tropical rain forests.

(+)-Harzialactone A (**29**), a marine metabolite isolated from the culture broth of a strain of *Trichoderma harzinum* OUPS-N115, exhibited significant antitumor and cytotoxic activities against cultured P388 cells.[11]



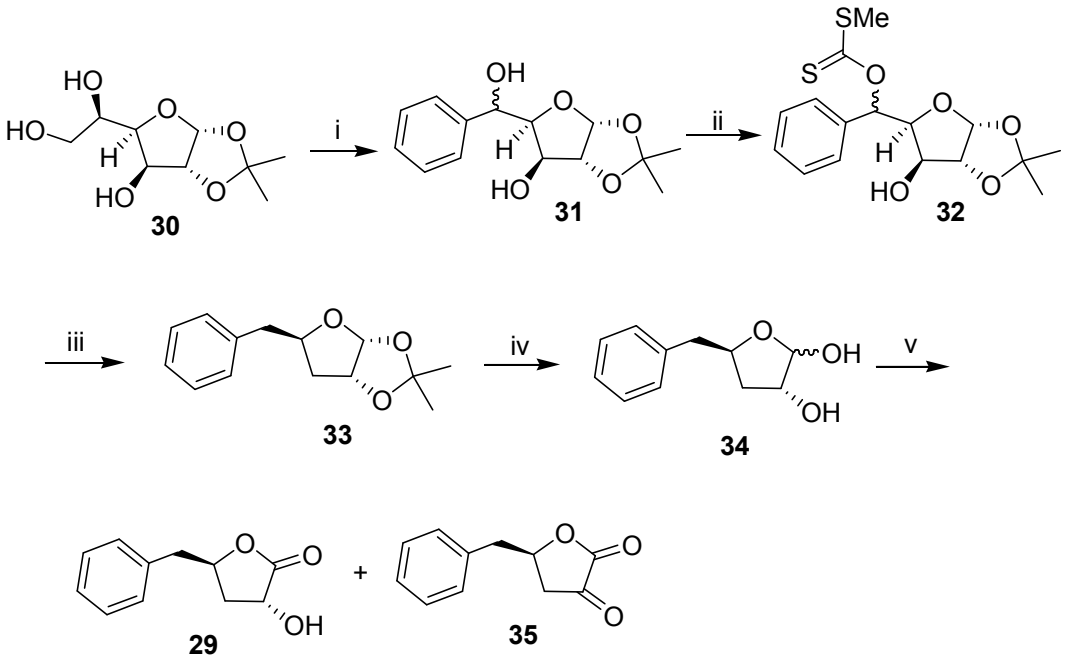
(*R,R*)-(+)-Harzialactone A
(**29**)

2.2.2 Review of Literature

Literature search revealed that there are few methods available for the synthesis of Harzialactone A (**29)**, which are described below.

Mereyala's approach (1999)[12]

Mereyala *et al.* have reported the first synthesis of harzialactone A (**29**), starting from D-glucose derivative. Accordingly, commercially available monoacetone D-glucose **30** was reacted with $NaIO_4$ in CH_2Cl_2/MeOH/saturated aqueous $NaHCO_3$ solution at room temperature for 2 h to obtain the aldehyde, which without purification, was immediately reacted with phenylmagnesium bromide at 0 °C to obtain a diastereomeric mixture of diol (3:1) **31** in 73% yield. Diol **31** was reacted with NaH/CS_2/MeI to obtain the methyl xanthate derivative **32.**

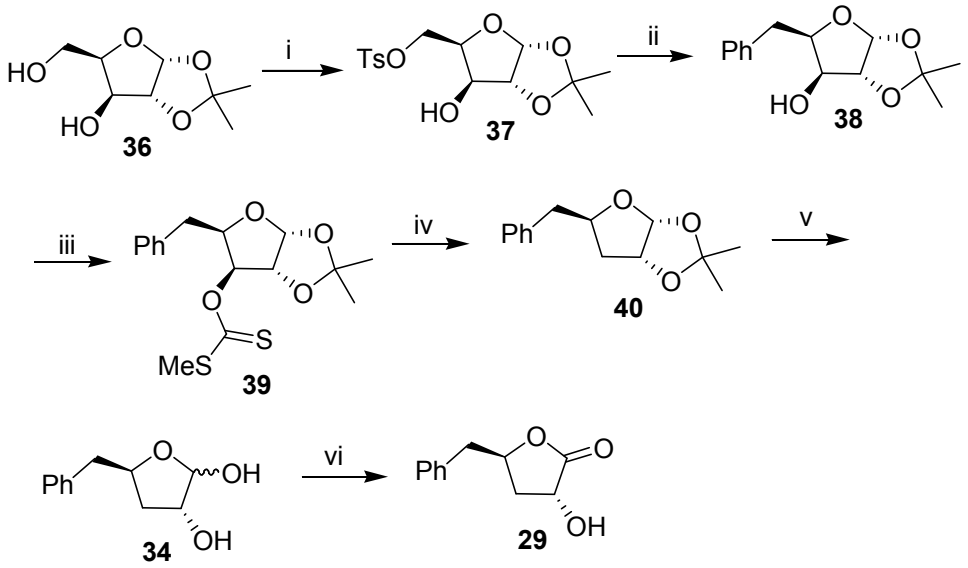


Scheme 7: (1) $NaIO_4$, CH_2Cl_2:MeOH:aq. satd. NaHCO3, 0 °C–25 °C, 2 h; PhMgBr, THF, 0 °C–25 °C, 8 h; (ii) NaH, CS_2, MeI, THF, 0 °C–25 °C, 1 h; (iii) Bu_3SnH, cat. AIBN, toluene, reflux, 6 h; (iv) 60% aq. HOAc, cat. H_2SO_4, 45 °C, 6 h; (v) Ag_2CO_3/Celite, benzene:DMF, reflux, 1 h.

Compound **32** was reduced with Bu_3SnH_6 at reflux temperature in toluene containing a catalytic amount of AIBN for 6 h to obtain dideoxy derivative **33** in 76% yield. Compound **33** was treated with 60% aq. HOAc/cat. H_2SO_4 at 45 °C for 6 h to obtain diol **34** in 79% yield. Regioselective oxidation of the C-1 hydroxyl group of **34** with Ag_2CO_3/Celite gave harzialactone **29** in 71% yield along with undesired product **35** in 11% yield (**Scheme 7**).

Mereyala's approach (2000)[13]

In 2000, Mereyala *et al.* have reported another synthesis of harzialactone A (**29**) starting from D-xylose derivative. Thus, reaction of 1,2-*O*-isopropylidene-α-D-xylofuranose with *p*-toluenesulphonyl chloride gave the mono tosylate **37.**



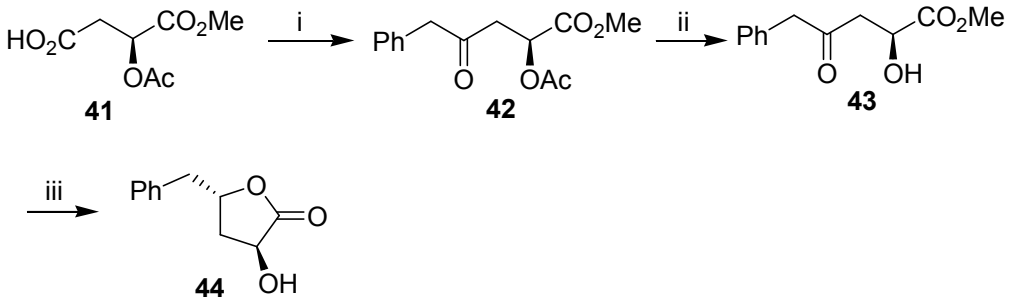
Scheme 8: (i) *p*-toluenesulphonyl chloride, pyridine, 25 °C, 32 h; (ii) phenylmagnesium bromide, THF, 0 °C-25 °C; (iii) NaH, CS_2, MeI, THF, 0 °C-25 °C; (iv) Bu_3SnH, AIBN, toluene, reflux; (v) 60% aq. CH_3CO_2H, cat. H_2SO_4, 45 °C; (vi) Ag_2CO_3–Celite, C_6H_6:DMF (8:1), reflux.

Compound **37** on Grignard reaction with phenylmagnesium bromide gave **38**, which was converted to the methyl xanthate ester **39** and then deoxygenated (Bu_3SnH:AIBN) to obtain the intermediate **40.** Acetonide deprotection of **40** with aq. acetic acid containing a

catalytic amount of conc. H_2SO_4 gave diol **34.** Oxidation of **34** with Ag_2CO_3:Celite in benzene:*N*,*N*-dimethylformamide (DMF) (8:1) at reflux temperature resulted in the formation of the harzialactone (**29**) in 71% yield.

Wu's approach (2005)[14]

Recently, Wu *et al*. have reported the synthesis of antipode of (+)-harzialactone A (**44**) starting from L-malic acid derivative. L-malic acid derivative **41** was treated with $SOCl_2$ followed by BnZnBr and $PdCl_2(PPh_3)_2$ to give keto-ester **42** in 59% isolated yield. The acetyl protecting group was readily removed with a catalytic amount of *p*-TsOH in MeOH, giving **43** in 93% yield. The ketone carbonyl group was then reduced using $NaBH_4/Et_2BOMe$ system to yield an intermediate diol which was directly cyclized on treatment with a catalytic amount of *p*-TsOH in CH_2Cl_2 to furnish (-)-harzialactone A (**44**) in 73% isolated yield.



Scheme 9: (i) (a) $SOCl_2$, 42 °C, 3 h, (b) BnZnBr, $PdCl_2(PPh_3)_2$, THF, 25 °C, overnight, 59% (over two steps); (ii) *p*-TSA, MeOH, 25 °C, overnight, 93%; (iii) (a) Et_2BOMe, THF-MeOH, $NaBH_4$, -78 °C, 5 h, (b) *p*-TSA, CH_2Cl_2, 25 °C, overnight, 73% (two steps).

2.2.3 Present Work

2.2.3.1 Objective

All the literature methods for the synthesis of harzialactone A (**29**), make use of chiral starting materials (chiral pool approach). Hence, the synthesis of harzialactone A, starting

from prochiral substrates using catalytic enantioselective reactions, is highly desirable. In this section, we describe a highly efficient and short synthesis of (+)-harzialactone A (**29**) *via* L-proline-catalyzed sequential aminooxylation-olefination[7] of 3-phenylpropanal. The retrosynthetic analysis for the synthesis of (+)-harzialactone A (**29**) is shown in **Fig. 5**. Accordingly, harzialactone A could be synthesized from lactone **45** by diastereoselctive α-hydroxylation. We further envisaged the L-proline-catalyzed sequential aminooxylation-olefination strategy for the synthesis of lactone **45**.

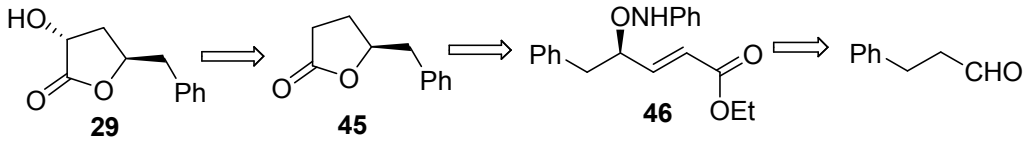
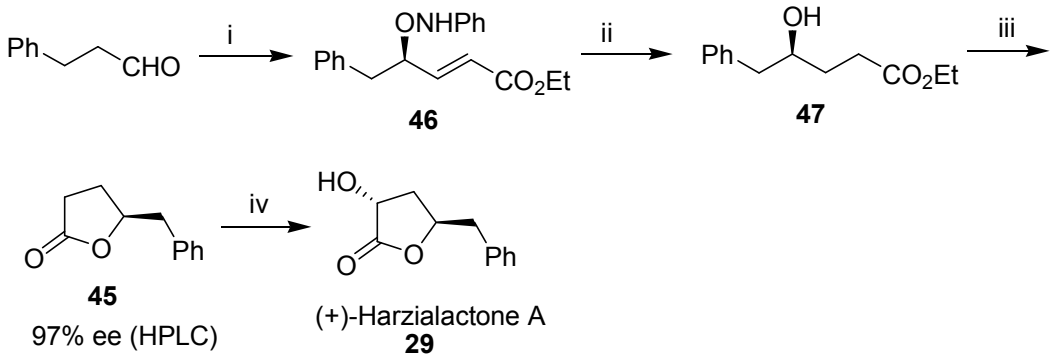


Fig. 5: **Retrosynthetic approach to (+)-harzialactone A (29)**

2.2.4 Results and Discussions:

The synthetic route for (+)-harzialactone A (**29**) is shown in **Scheme 10**, wherein L-proline-catalyzed sequential aminooxylation-olefination[7] reaction has been envisaged as a key step for introduction of chirality into the molecule.



Scheme 10: Reagents and conditions: (i) PhNO, L-proline (25 mol%), CH_3CN, -20 ºC, 24 h then triethyl phosphonoacetate, LiCl, DBU, 1 h, 77%. (ii) H_2 (1 atm.), Pd/C (10%), MeOH, 12 h, 92%. (iii) EtOH, reflux, 5 h, 88%. (iv) 2-[(4-methylphenyl)sulfonyl]-3-phenyloxaziridine, KHMDS, THF, -78 °C, 1 h, 63%.

Thus, 3-phenylpropanal was subjected to α- aminooxylation[8] with nitrosobenzene and L-proline at -20 ^{o}C followed by *in situ* Horner-Wadsworth-Emmons (HWE) olefination with LiCl and DBU (Masamune-Roush protocol)[9] to furnish aminooxy-olefinic ester **46** in 77% yield; $[\alpha]^{25}_{D}$ +47 (*c* 1, $CHCl_3$).

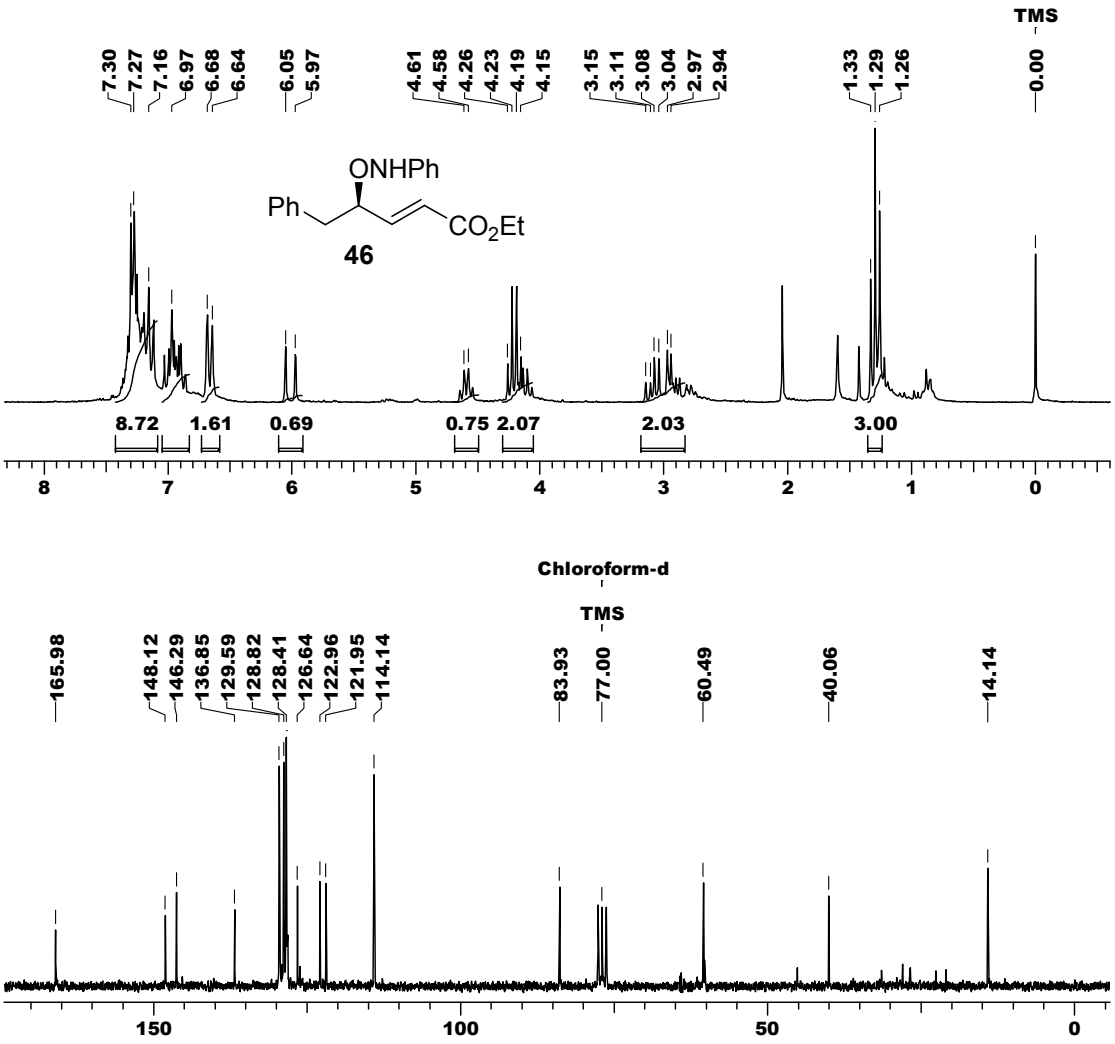


Fig. 6: ^{1}H and ^{13}C NMR spectra of aminooxy-olefinic ester 46

The ^{1}H NMR spectrum of **46** showed signals at δ 4.58 (m) and 5.97 (d) corresponding to a proton at the functionalized carbon (**CH**ONHPh) and the olefinic proton respectively. Its ^{13}C NMR spectrum showed peaks at δ 146.2 and 165.9 corresponding to the olefinic and ester carbonyl carbons respectively (**Fig. 6**).

Simultaneous reduction of both C=C and anilinooxy group in ester **46** was achieved with 10% Pd/C, H_2 (1 atm.) to give γ-hydroxy ester **47** in 92% yield.

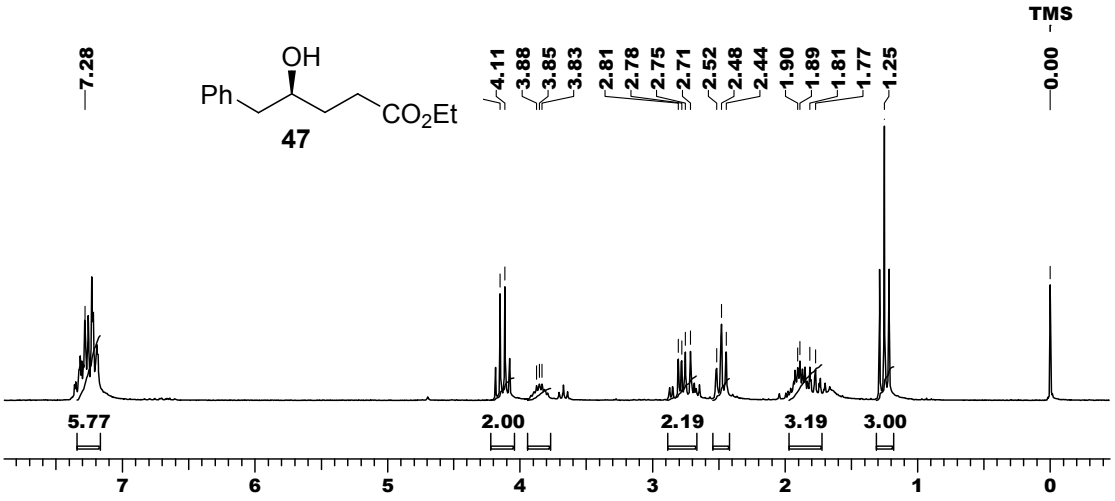
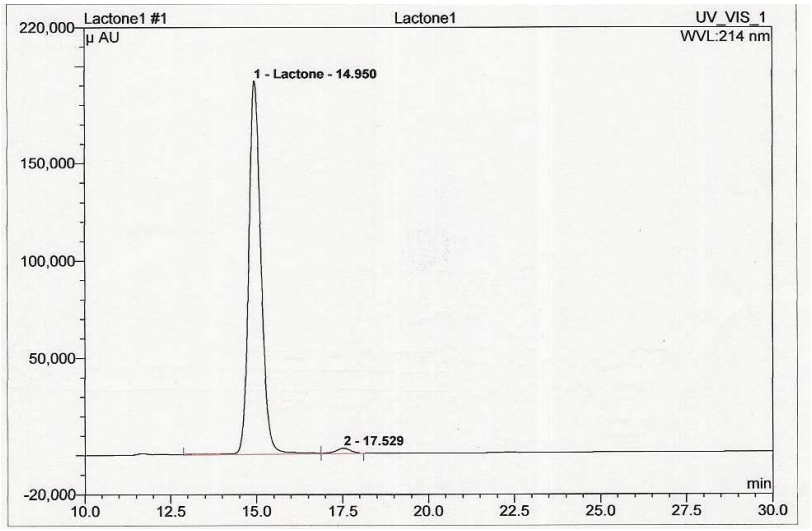


Fig. 7: ^{1}H and ^{13}C NMR spectra of hydroxy ester 47

The disappearance of signals at δ 5.97 (d) (olefinic proton) and 7.27 (aromatic protons) in the ^{1}H NMR spectrum of the ester **47** confirmed the reduction of C=C double bond and deprotection of the anilinoxy group as well (**Fig. 7**).

Subsequent cyclization of ester **47** produced lactone **45** in 88% yield and 97% ee (determined by chiral HPLC analysis, Chiracel OD-H); $[\alpha]^{25}_{D}$ +24.66 (*c* 1, $CHCl_3$). The ^{1}H NMR spectrum of lactone **45** showed signals at δ 2.94 (dd), 3.03 (dd) and 4.74 (m) corresponding to the two benzylic protons and a proton at the methine carbon (**CH**OCO) respectively. Its ^{13}C NMR showed typical peaks at δ 80.5 and 176.9 due to methine (**CH**OCO) and lactone carbonyl carbons respectively (**Fig. 8**).



Peak No.	Ret. Time (Min.)	Area (mAU*s)	Area (%)
1	14.95	78716.84	98.34
2	17.53	1328.757	1.66

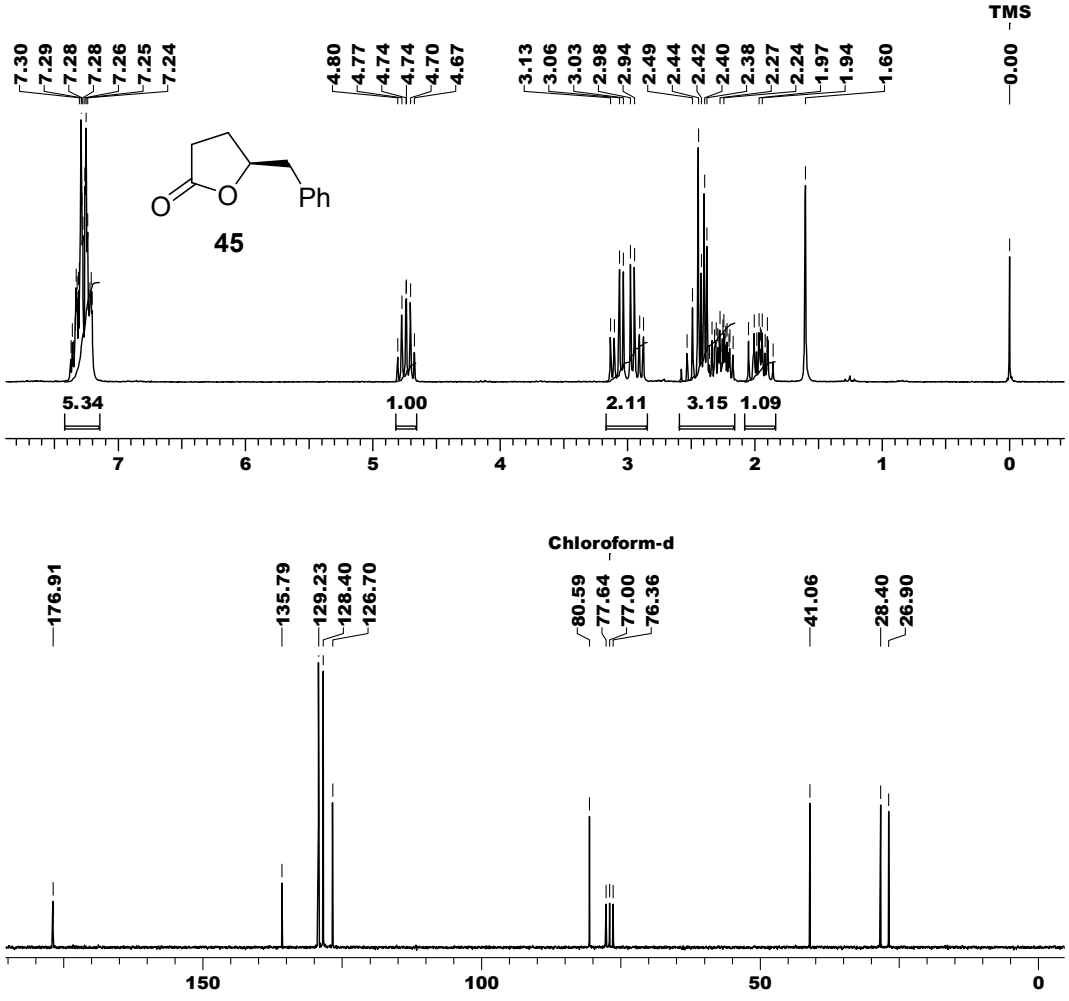


Fig. 8: HPLC chromatogram, ^{1}H and ^{13}C NMR spectra of lactone 45

Diastereoselective α-hydroxylation[15] of lactone **45** was achieved with KHMDS and 2-[(4-methylphenyl)sulfonyl]-3-phenyloxaziridine (Davis oxaziridine) to give *trans* lactone **1** ((+)-harzialactone A) as a separable mixture of diastereomers (*dr* = 2:1 *trans/cis*, determined by ^{1}H NMR analysis of the crude mixture); $[\alpha]^{25}_D$ +40 (*c* 0.3, $CHCl_3$) { lit.[14] $[\alpha]^{25}_D$ -39.6 (*c* 0.32, $CHCl_3$) for antipode of (+)-harzialactone A}.

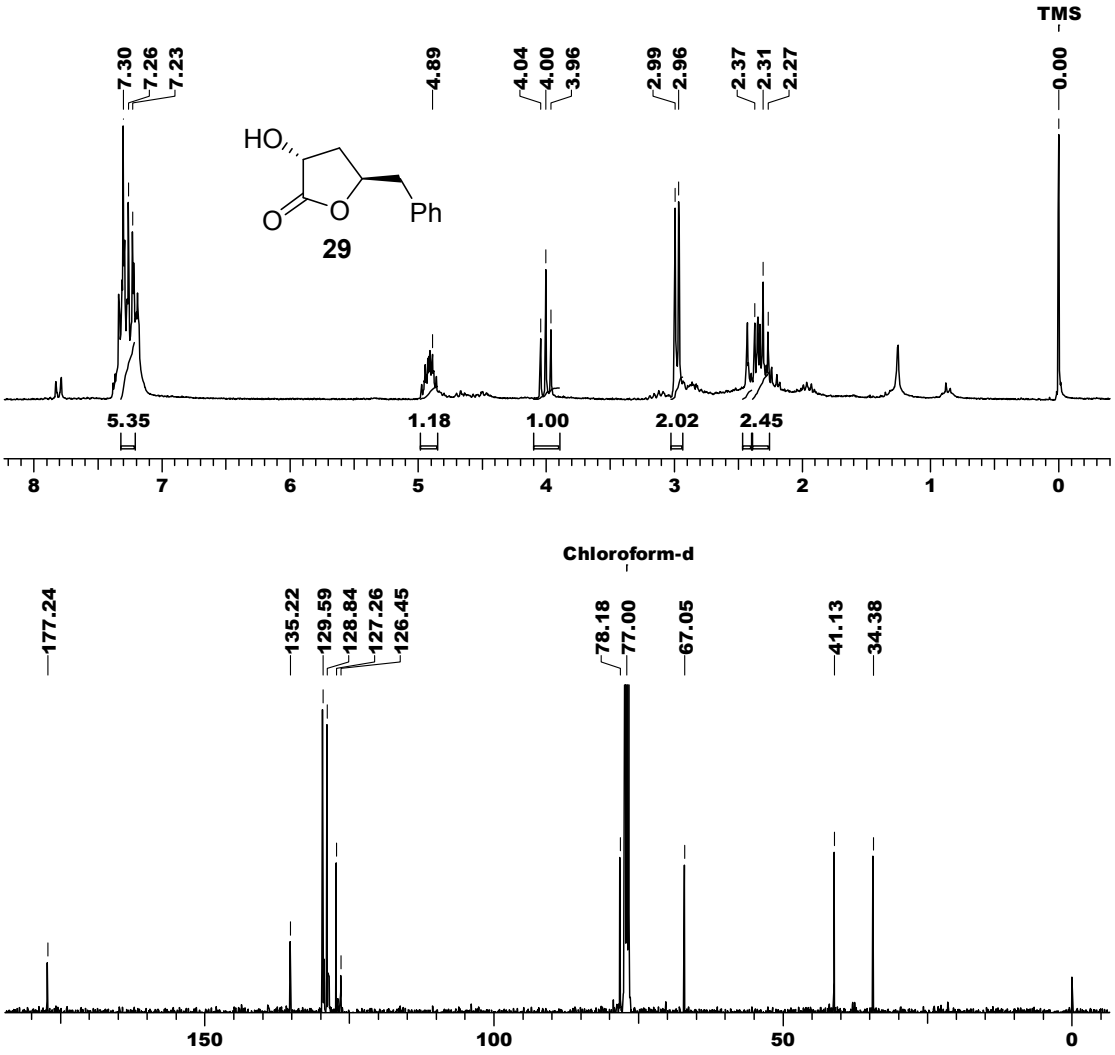


Fig. 9: ^{1}H and ^{13}C NMR spectra of (+)-harzialactone 29

The ^{1}H NMR spectrum of (+)-harzialactone A (**29**) showed characteristic signals at δ 4.0 (t), 4.89 (m) and 7.30 (m) corresponding to the methine protons [(**CH**OH) and

(**CH**CH_2Ph)] and aromatic protons respectively (**Fig. 9**). Its ^{13}C NMR showed typical peaks at δ 78.1 and 177.2 corresponding to methine (**CH**OCO) and lactone carbonyl carbons respectively. The physical and spectroscopic data were in full agreement with the literature values.[14]

2.2.5 Conclusion:

In conclusion we have achieved a short and efficient synthesis of (+)-harzialactone A (overall yield 26.1% and 99% ee) by employing proline-catalyzed sequential α-aminooxylation-HWE olefination of 3-phenylpropanal. Excellent yields, simple and environment friendly procedures, easy availability of starting materials and use of L-proline as a catalyst render our approach a good alternative to known mehods.

2.2.6 Experimental Section:

(*R*)-Ethyl 4-anilinoxy-5-phenylpent-2-enoate (46):

To a solution of nitrosobenzene (3 g, 28 mmol) and L-proline (476 mg, 15 mol%) in CH_3CN (60 mL) was added 3-phenylpropanal (4.5 g, 33.6 mmol) at -20 °C. The reaction mixture was stirred at the same temperature for 24 h followed by addition of LiCl (1.7 g, 1.5 equiv.), triethyl phosphonoacetate (9.4 g, 1.5 equiv.) and after stirring for 5 min DBU (4.2 g, 1 equiv.) was added. The reaction mixture was quenched with half saturated NH_4Cl solution and extracted with ethyl acetate (3 × 60 mL). Combined organic phases were concentrated and dried over anhydrous Na_2SO_4. Purification by flash column chromatography (pet ether: EtOAc = 88:12) afforded aminooxy olefinic ester **46**.

Yield: 6.7 g, 77% yield, brownish oil; $[\alpha]^{25}_{D}$ +47 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$) ν_{max} 3028, 2979, 2937, 2358, 1714, 1600, 1494, 1454, 1369, 1271, 1178, 1029, 910, 754 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.29 (t, *J* = 7.1 Hz, 3H), 2.87-2.97 (dd, *J* = 5.9, 13.8 Hz,

1H), 3.04-3.15 (dd, *J* = 7.6, 13.9 Hz, 1H), 4.19 (q, *J* = 7.1, 2H), 4.58 (m, 1H), 5.97 (d, *J* = 15.8, 1H), 6.64 (d, *J* = 7.9 Hz, 1H), 6.97 (m, 3H), 7.16-7.30 (m, 8H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 40.0, 60.4, 83.9, 114.1, 121.9, 122.9, 126.6, 128.4, 128.8, 129.5, 136.8, 146.2, 148.1, 165.9; **Analysis: $C_{19}H_{21}NO_3$** requires C, 73.29; H, 6.80; N, 4.50; found C, 73.33; H, 6.73; N, 4.67%.

Ethyl 4-hydroxy-5-phenylpentanoate (47):

To a solution of **46** (5.0 g, 16 mmol) in MeOH (10 mL) was added 10% Pd/C (300 mg) carefully. The reaction mixture was then stirred in the hydrogen atmosphere (1 atm. of H_2) for 12 h. After completion of reaction (monitored by TLC) the reaction mixture was filtered through celite pad, concentrated to near dryness. The crude product was then purified by flash column chromatography (pet ether: EtOAc = 75:25).

Yield: 3.28 g, 92% yield, brownish oil; **$[\alpha]^{25}_D$** +14.54 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$) ν_{max} 3488, 2927, 2360, 2331, 1770, 1731, 1602, 1494, 1178, 1022, 923, 750 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.25 (t, *J* = 7.2 Hz, 3H), 1.77-1.90 (m, 2H), 2.48 (dt, *J* = 7.5, 1.3 Hz, 2H), 2.65-2.87 (m, 2H), 3.85 (m, 1H), 4.11 (q, *J* = 7.1, 2H), 7.28 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 30.7, 31.4, 44.0, 60.4, 71.8, 126.4, 128.4, 129.3, 138.1, 174.0; **Analysis: $C_{13}H_{18}O_3$** requires C, 70.24; H, 8.16 found C, 70.14; H, 8.22%.

5-Benzyl-dihydrofuran-2(3*H*)-one (45):

A solution of hydroxyl ester **47** (2 g, 9 mmol) in absolute ethanol (40 mL) was refluxed for 5 h. Removal of solvent under reduced pressure followed by flash chromatographic purification gave lactone **45**.

Yield: 1.39 g, 88% yield, brownish oil; **$[\alpha]^{25}_D$** +24.66 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$) ν_{max} 2925, 2360, 1771, 1602, 1456, 1180, 1022, 912, 734 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$):

δ 1.86-2.05 (m, 1H), 2.17-2.53 (m, 3H), 2.87-2.98 (dd, *J* = 6.29, 14.0 Hz, 1H), 3.03-3.13 (dd, *J* = 6.0, 14.0 Hz, 1H), 4.67-4.80 (m, 1H), 7.21-7.36 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 26.9, 28.4, 41.0, 80.5, 126.7, 128.4, 129.2, 135.7; **Analysis: $C_{11}H_{12}O_2$** requires C, 74.98; H, 6.86 found C, 75.11; H, 6.77%.

HPLC conditions: Chiracel OD-H column; *n*-hexane: i-PrOH (90:10 v/v); flow rate 1.0 mL/min; UV 214 nm; column temperature 25 °C; retention time: 14.95 min. major (*S*-isomer) and 17.53 min minor (*R*-isomer). Compared with reported conditions: (Hoge G. *J. Am. Chem. Soc.* **2003**, *125*, 10219).

(+)-Harzialactone A (29):

To a solution of KHMDS in dry THF (8 mL) at -78 °C was added lactone (0.5 g, 2.8 mmol) in THF and the reaction mixture was stirred for 10 min. followed by addition of -[(4-methylphenyl)sulfonyl]-3-phenyloxaziridine (Davis oxaziridine) (814 mg, 2.8 mmol). After stirring the reaction mixture at same temperature for 1 h it was quenched with aq. NH_4Cl and extracted with ethyl acetate (3 ×15 mL). Purification by flash column chromatography gave **29** as a colorless solid in 63% yield with *dr* = 2:1. The diastereomers were separated by flash column chromatography (pet ether: EtOAc 70:30).

Yield: 229 mg, 42% yield, Colorless solid (after diasteromeric purification); mp = 80 °C (lit.[11] 82-84 °C); **$[\alpha]^{25}_D$** + 40 (*c* 0.3, $CHCl_3$) { lit.[14] $[\alpha]^{25}_D$ -39.6 (*c* 0.32, $CHCl_3$) for antipode of (+)-harzialactone A}; **IR** ($CHCl_3$) ν_{max} 3373, 2921, 2360, 2343, 1772, 1456, 1188, 1031, 700 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.27-2.43 (m, 2H), 2.43 (brs, 1H), 2.96 (d, *J* = 5.8 Hz, 2H), 3.96 (t, *J* = 8.1 Hz, 1H), 4.91 (m, 1H), 7.19-7.34 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 34.3, 41.1, 67.0, 78.1, 127.2, 128.4, 129.5, 135.2, 177.2; **Analysis: $C_{11}H_{12}O_3$** requires C, 68.74; H, 6.29 found C, 68.55; H, 6.58%.

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CHAPTER III

Synthetic Methodologies Involving Asymmetric Additions onto C=N and Formation of C=C bonds

Section I:

Tandem α-Amination-HWE Olefination of Aldehydes: Enantioselective Synthesis of γ-Amino α,β-unsaturated Esters

3.1.1 Introduction

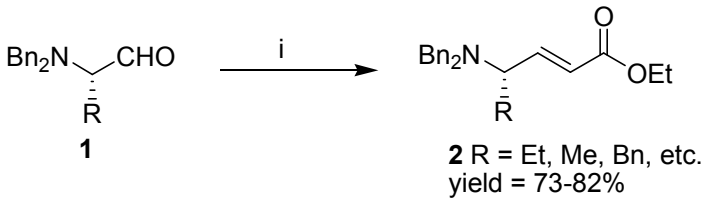
Chiral allylic amines, particularly γ-amino-α,β-unsaturated esters, are the key structural elements present in a variety of important naturally occurring molecules[1] and are among the most versatile synthetic intermediates for peptides derivatives,[2] iminosugars,[3] glutamate receptors,[4] amino acids,[5] alkaloids,[6] carbohydrate derivatives,[7] etc. possessing various biological activities such as enzyme inhibitors.[1a,7] These esters are of synthetic importance because of the presence of multiple functionality consequently, they are important substrates for variety of organic transformations like stereoselective dihydroxylation,[8] epoxidation,[9] selective hydrogenation,[10a] michael addition[10b], etc.

3.1.2 Review of Literature

Few general methods are described in the literature to obtain enantiomerically pure γ-amino-α,β-unsaturated esters, most of them employ Wittig olefination of α-amino aldehydes, that are prepared from naturally occurring α-amino acids.

Reetz's approach (1989)[10b]

Reetz's *et al*. have reported Horner-Wittig olefination of aldehydes **1** for the synthesis of

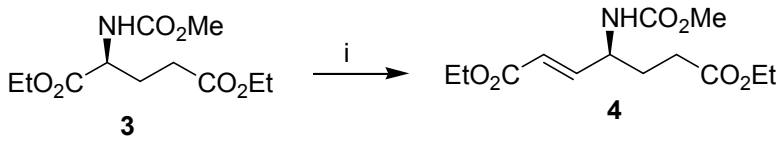


Scheme 1: (i) triethyl phosphonoacetate, NaH.

γ-amino-α,β-unsaturated esters **2** with good yields without any racemization (**Scheme 1**).

Knaus approach (1994)[11]

Knaus *et al*. have reported regioselective tandem reduction-Wittig-Horner olefination of **3** for the synthesis of γ-amino-α,β-unsaturated esters **4** in good yields (**Scheme 2**).

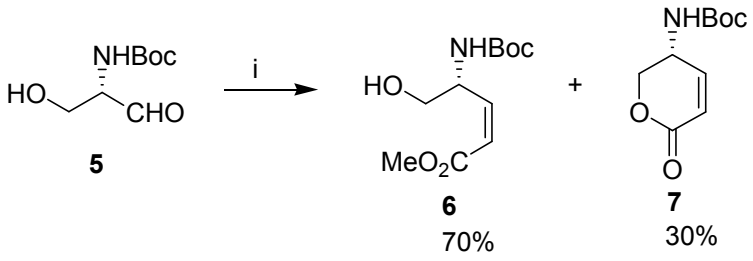


3 **4**

Scheme 2: (i) lithium salt of triethyl phosphonoacetate, DIBAL-H, -78 °C- 25 °C, 64-74%.

Giannis approach (1997)[12]

Giannis *et al*. have described Horner-Wadsworth-Emmons reaction of base sensitive β-hydroxy-α-aminoaldehydes **5**, under mild conditions to give a mixture of **6** and **7** with complete Z-selectivity (**Scheme 3**).

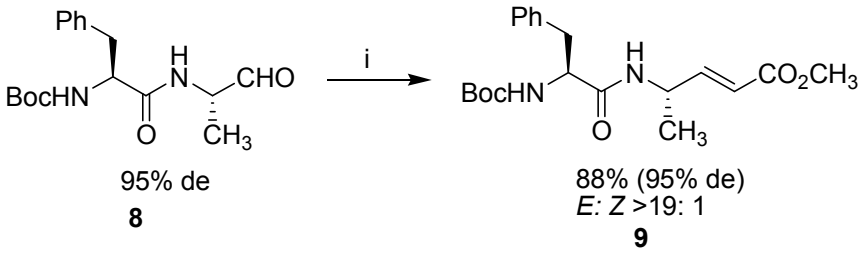


5 **6** 70% **7** 30%

Scheme 3: (i) methyl bis(trifluoroethyl) phosphonoacetate, LiCl, DBU, 0 °C, 1 h

Myers approach (2005)[13]

Recently, Myers *et al*. have developed a system with mild base (lithium 1,1,1,3,3,3-hexafluoroisopropoxide) for Horner-Wadsworth-Emmons (HWE) olefination of epimerizable aldehydes **8** to give olefinic ester **9** with good *E/Z* selectivity (**Scheme 4**).



95% de
8

88% (95% de)
E: Z >19: 1
9

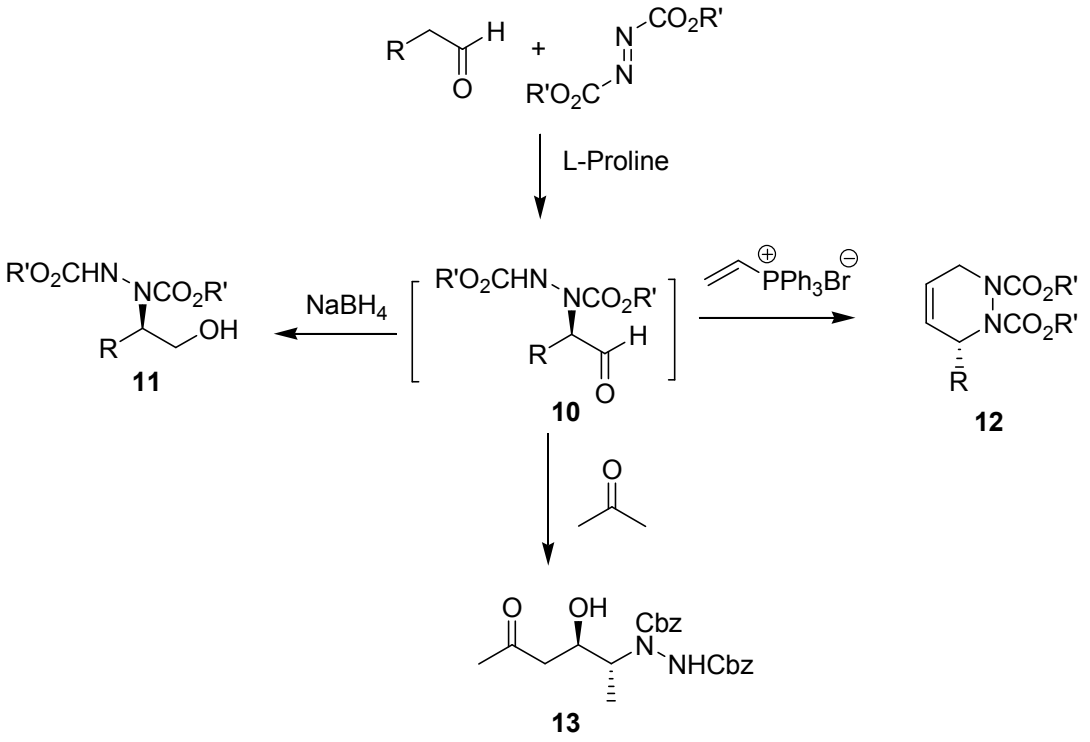
Scheme 4: (i) trimethyl phosphonoacetate, lithium 1,1,1,3,3,3-hexafluoroisopropoxide, DME, -14 °C.

3.1.3 Present Work

3.1.3.1 Objective

Although there are few methods available in the literature for the asymmetric synthesis of γ-amino-α,β-unsaturated esters **15**, these methods are limited by the possibility that racemization may occur during the Wittig reaction.[14] For these reasons, a general synthetic procedure utilizing readily available substrates, overcoming the above difficulties, is still desirable for the enantioselective synthesis of γ-amino-α,β-unsaturated esters **15**.

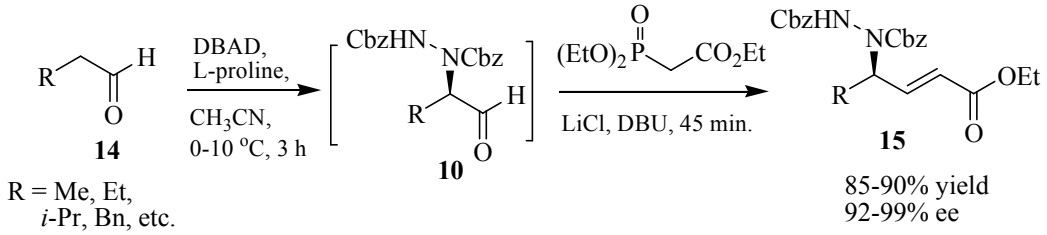
In proline-catalyzed direct α-amination of aldehydes, the reactive intermediate **10**, generated *in situ* was transformed into several functionalized organic derivatives: for instance, it was reduced to 1,2-amino alcohol **11**,[15a] cyclized by intramolecular Wittig olefination to 3,6-dihydropyridazines **12**[15b] or condensed under aldol conditions to form functionalized β-amino alcohols **13**[15c] (**Scheme 5**). In this connection it is of interest to design experiments in trapping intermediate **10** with other reagents such as triethyl phosphonoacetate to obtain the corresponding chiral γ-amino-α,β-unsaturated esters **15**.



Scheme 5: *In situ* Trapping of α-amino aldehydes

3.1.4 Results and Discussions:

In this section, we describe, in detail, a one-pot procedure for obtaining highly enantioselective synthesis of γ-amino-α,β-unsaturated esters **15** using tandem α-amination-HWE olefination of aldehydes **14** (**Scheme 6**).

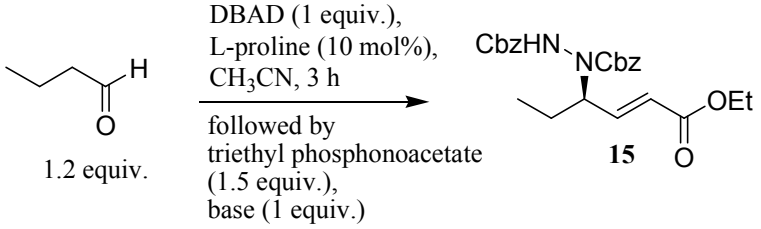


Scheme 6: *in situ* trapping of α-amino aldehydes with triethyl phosphonoacetate

A preliminary study was conducted using *n*-butyraldehyde as a model compound. The α-amination of *n*-butyraldehyde was carried out by following List's protocol.[15a] Thus, a

mixture of *n*-butyraldehyde (1.2 equiv.), dibenzyl azodicarboxylate (DBAD) (1 equiv.) and L-proline (10 mol%) in acetonitrile was stirred for 3 h to obtain *in situ* the intermediate aldehyde **10**. Since these α-amino aldehydes are prone to racemization,[14] we performed several experiments to identify the most effective and suitable base for HWE olefinations. The results of such studies are presented in **Table 1**. Firstly, *in situ* olefination of **10** was started with the addition of triethyl phosphonoacetate (1.5 equiv.) and Cs_2CO_3[16] (1 equiv.). After stirring the reaction mixture for 2 h, subsequent work-up gave **15a** in 80% yield but with very poor enantioselectivity (22% ee). This means that Cs_2CO_3 might have caused racemization in the olefination step. Screening of other bases (entries 2 and 3) has shown that DBU (Masamune-Roush protocol[17]) is quite a suitable base for the desired transformation as enantiomeric excess could be reached up to 88% ee.

Table 1: Proline-catalyzed α-amination/ HWE olefination of *n*-butyraldehyde:



entry	base[a]	temp. (ºC)	time	yield[b] (%)	ee[c] (%)
1	Cs_2CO_3	25	2.5 h	80	22
2	$Ba(OH)_2$	25	2.5 h	78	67
3	DBU	25	2 h	87	88
4	DBU	5	45 min.	84	99

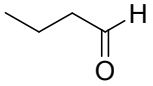
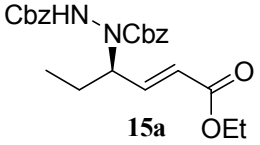
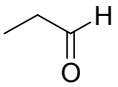
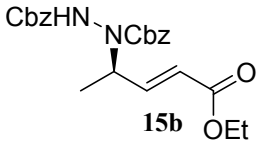
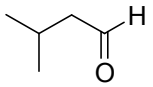
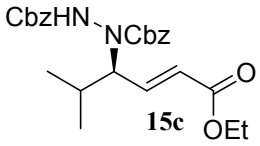
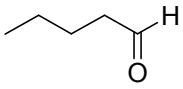
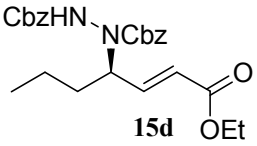
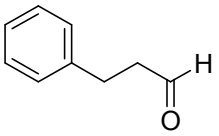
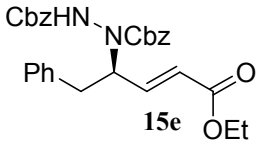
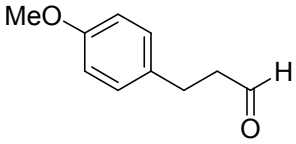
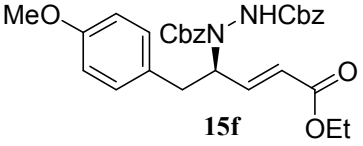
[a] LiCl (1.5 equiv.) was used in case of DBU. [b] yield of isolated product after column chromatography. [c] Enantiomeric excess was determined by chiral HPLC analysis (Chiracel OD-H, hexane: 2-propanol = 4: 96)

We have then decided to optimize the reaction conditions for this sequential protocol using Masamune-Roush conditions (LiCl, DBU) to achieve better enantioselectivities. Due to the epimerizable nature of α-amino aldehydes, we believed that a shorter reaction time and low temperature should provide high enantioselectivities without compromising on the yields. Expectedly, by performing the reaction at 5 ^{o}C for 45 min., **15a** was indeed obtained in 84% yield with excellent enantioselectivity >99% ee (**Table 1**).

We further explored the scope of this novel transformation by subjecting a series of aliphatic aldehydes bearing different functionalities under the optimized reaction conditions. In all cases studied, the desired γ-amino-α,β-unsaturated esters **15(a-f)** were obtained in excellent yields (80-88%) and enantioselectivities (92-99%) (**Table 2**). Purely aliphatic aldehydes as well as aldehydes containing aromatic moieties underwent the reaction smoothly to give **15** in good to excellent enantioselectivity.

However, use of other solvents like THF and CH_2Cl_2 for this tandem protocol resulted in sluggish reaction with poor yields (<50%). The absolute configurations for the newly generated amines were assigned based on previously established configurations of α-amino aldehydes reported by List,[15a] by matching the sign of the optical rotation of pyrrolidone **20** (**Scheme 8**)[18] as well as further confirmed by X-ray crystallographic study of triacetate **19** (**Fig. 8**). The structures of these γ-amino-α,β-unsaturated esters were confirmed by ^{1}H and ^{13}C NMR spectroscopy and the enantiomeric excess was determined by chiral HPLC analysis (Chiracel OD-H column and *n*-hexane-isopropanol as solvent system).

Table 2: Proline-catalyzed asymmetric tandem α-amination/ HWE olefination[a]:

entry	substrates **14(a-f)**	products **(15 a-f)**	yield[b] (%)	ee[c] (%)
1		 **15a**	84	99
2		 **15b**	83	92
3		 **15c**	80	92
4		 **15d**	85	95
5		 **15e**	88	99
6		 **15f**	88	99

[a]Reaction conditions: aldehyde (1.2 equiv.), DBAD (1 equiv.), L-proline (10 mol%), triethyl phosphonoacetate (1.5 equiv.), LiCl (1.5 equiv.) and DBU (1 equiv.) were used. [b]yields of isolated product after column chromatographic purification. [c]Enantiomeric excess was determined by chiral HPLC analysis (Chiracel OD-H column, *n*-hexane-isopropanol as eluents).

Example 1: For instance, the ^{1}H NMR spectrum of **15a** showed a quartet at δ 4.13 for methylene group (**CH$_2$**CH$_3$), a singlet at δ 5.11 for benzylic protons of Cbz group and a doublet at δ 5.85 for the olefinic proton. Its ^{13}C NMR spectrum showed typical peaks at δ

64.7, 144.7 and 166.0 corresponding to benzylic carbon of Cbz group, olefinic carbon and ester carbonyl carbon respectively (**Fig. 1**).

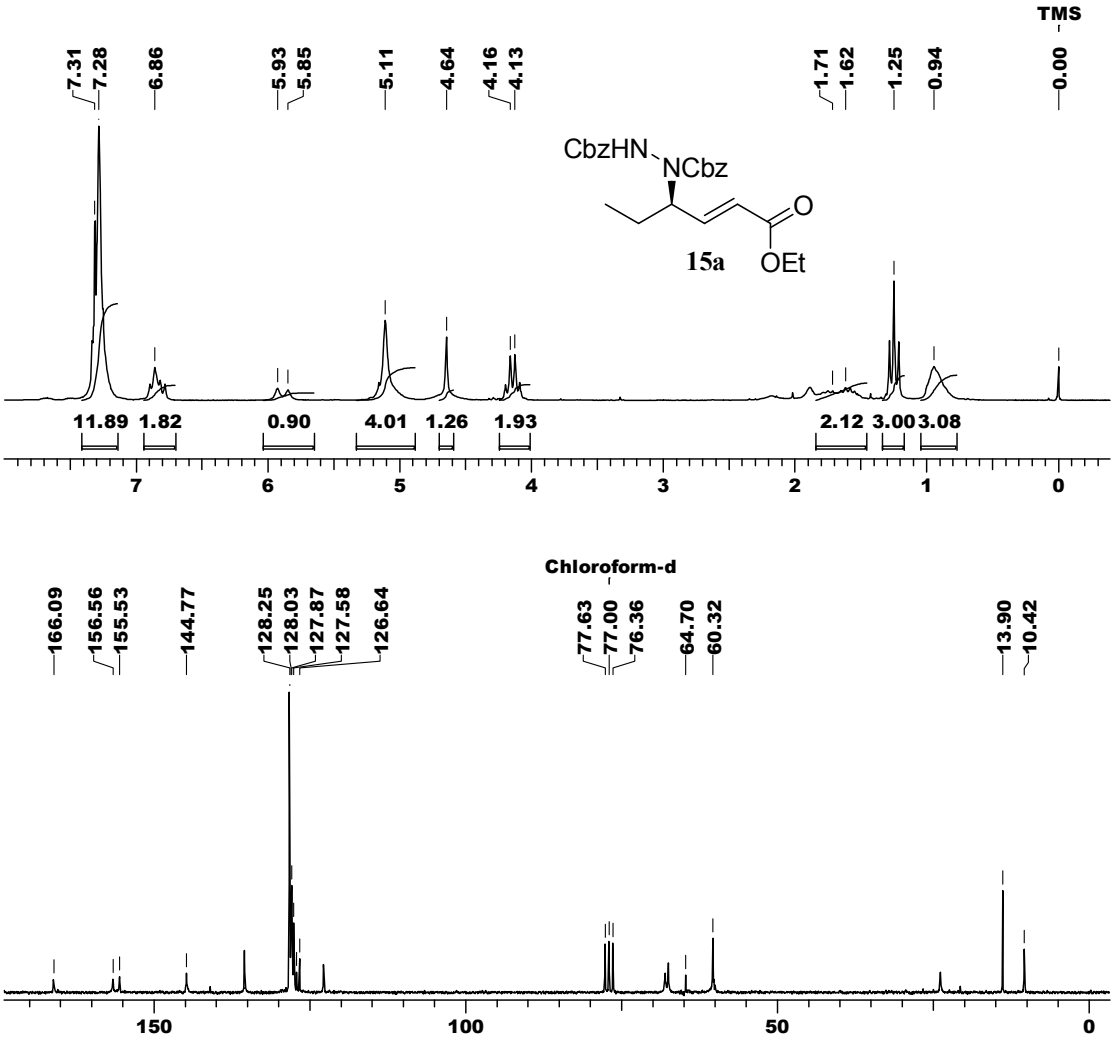
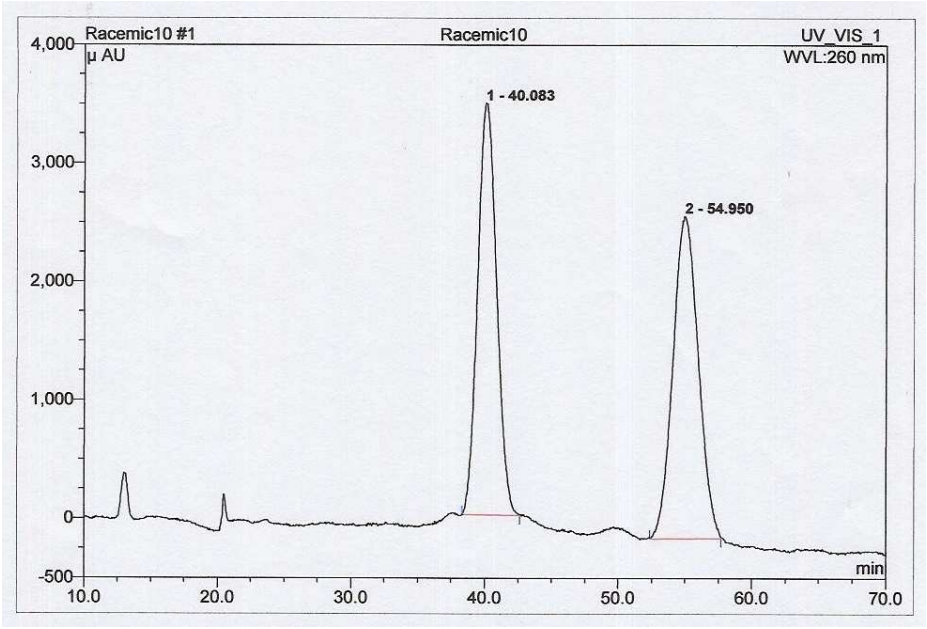


Fig. 1: ^{1}H and ^{13}C NMR spectra of 15a

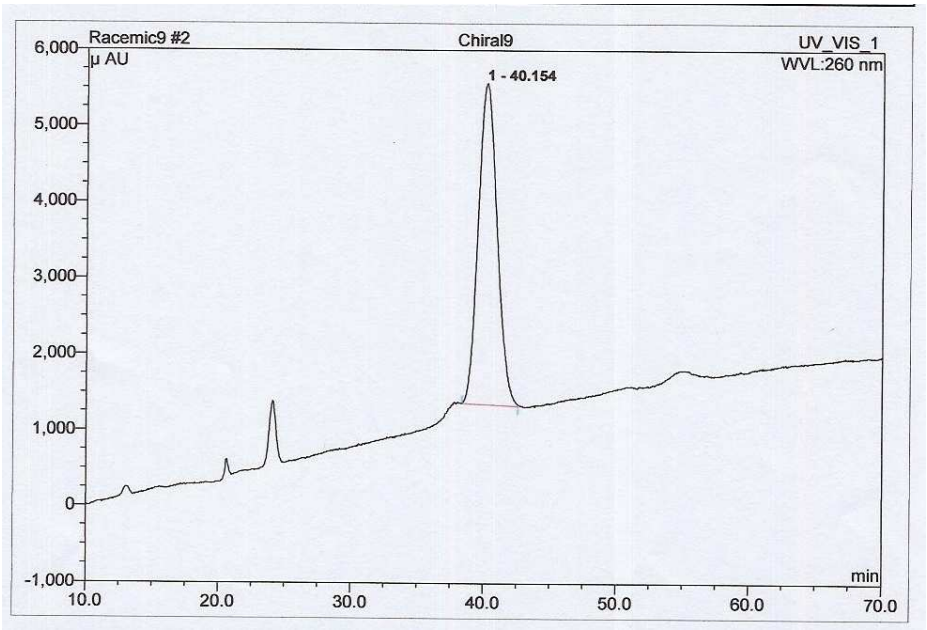
Its enantiomeric excess (>99% ee) was determined by chiral HPLC analysis (Chiracel OD-H). The chiral HPLC chromatogram is shown in **Fig. 2**.

Racemic



Peak No.	Ret. Time (Min.)	Area (mAU*s)	Area (%)
1	40.08	5714.13	48.94
2	54.95	5961.71	51.06

Chiral



Peak No.	Ret. Time (Min.)	Area (mAU*s)	Area (%)
1	40.15	6930	100

Fig. 2: HPLC chromatograms of 15a

Example 2: The ^{1}H NMR spectrum of **15f** showed a singlet at δ 3.76 for methoxy group, a doublet at δ 5.84 for the olefinic proton and a multiplet at δ 7.30 for aromatic protons. Its ^{13}C NMR spectrum showed peaks at δ 156.5, 158.2 and 165.7 corresponding to the amide carbonyl carbons of Cbz groups and ester carbonyl carbon respectively (**Fig. 3**).

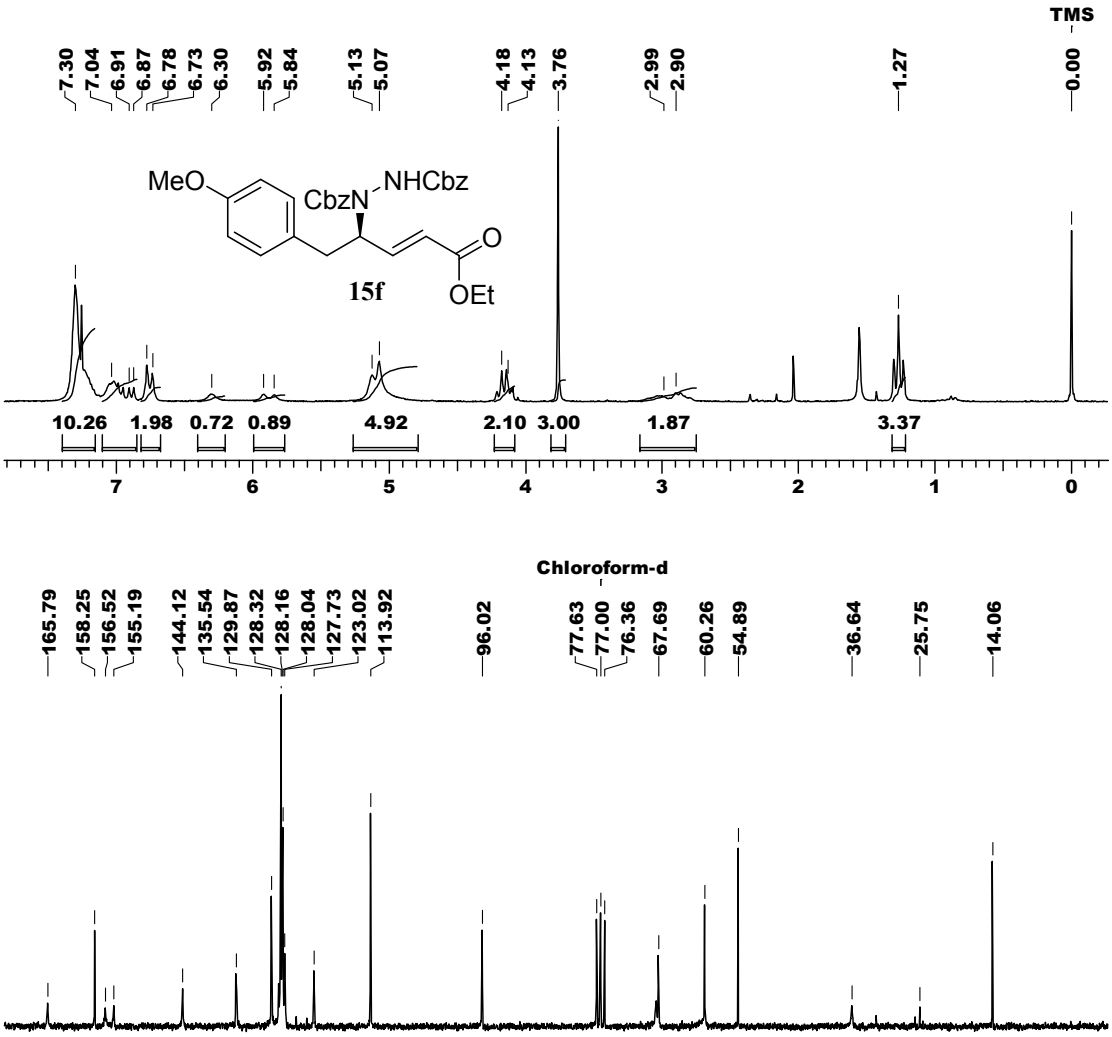
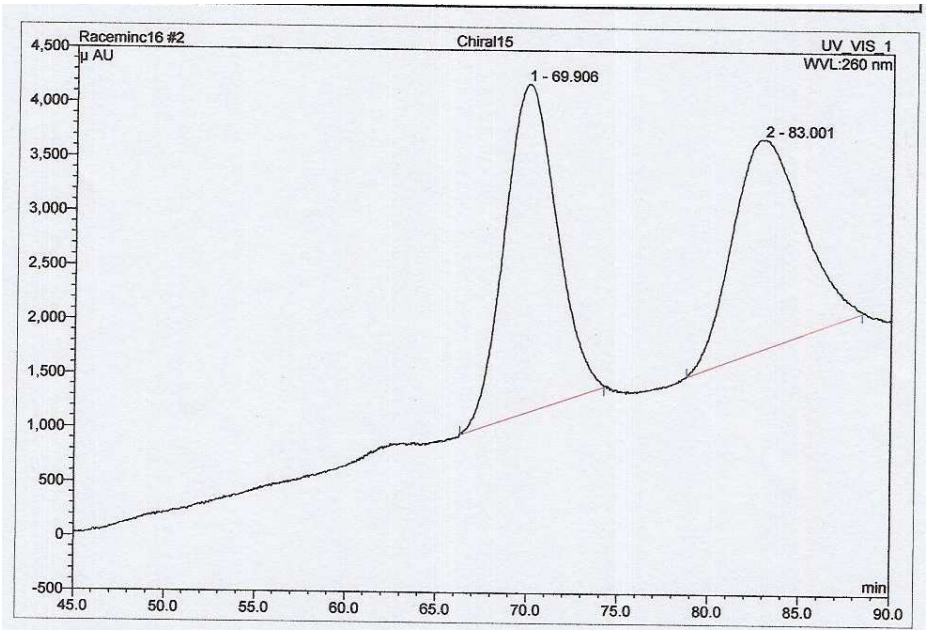


Fig. 3: ^{1}H and ^{13}C NMR spectra of 15f

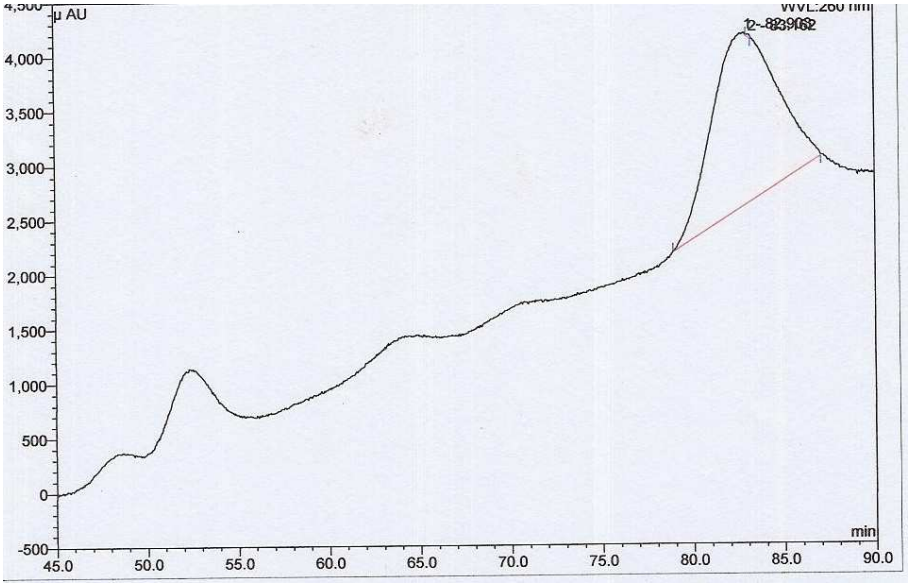
Its enantiomeric excess (99% ee) was determined by chiral HPLC analysis (Chiracel OD-H). The chiral HPLC chromatogram is shown in **Fig. 4**.

Racemic



Peak No.	Ret. Time (Min.)	Area (mAU*s)	Area (%)
1	69.91	8681	49.94
2	83.0	8602	50.06

Chiral

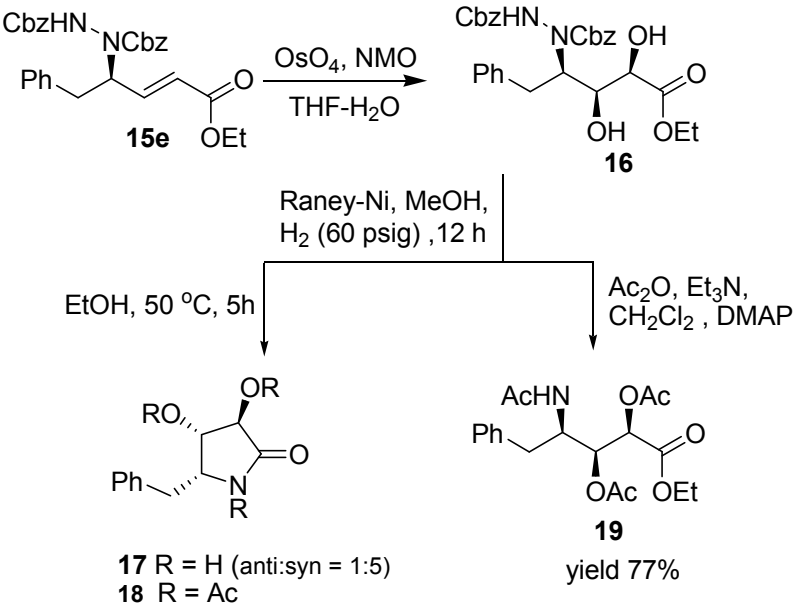


Peak No.	Ret. Time (Min.)	Area (mAU*s)	Area (%)
1	82.90	6573	100

Fig. 2: HPLC chromatograms of 15f

3.1.4.1 Applications: Synthesis of pyrrolidone derivatives and triacetoxy aminodiol

Among the potential applications of this methodology, a short asymmetric synthesis of substituted 2-pyrrolidone derivatives **18** and **20**, common subunits present in a variety of alkaloids,[19] seemed attractive to us due to their chemotherapeutic utilities such as anti-HIV and anti-cancer activities.[20] Also, we have achieved the synthesis of triacetate derivative of amino diol **19,** building block found in sphingosines,[21] depending upon the reaction conditions (**Scheme 7**).



Scheme 7: Synthesis of pyrrolidone derivatives and triacetoxy aminodiol 19

For the synthesis of **17**, amino olefinic ester **15e** was subjected to the Os-catalyzed dihydroxylation in a diastereoselective manner to produce the corresponding amino diol **16** (92% yield), which was hydrogenated over Raney nickel, thus affording the cyclized dihydroxy pyrrolidone **17** (dr = 1:5, 65% yield). The ^{1}H NMR spectrum

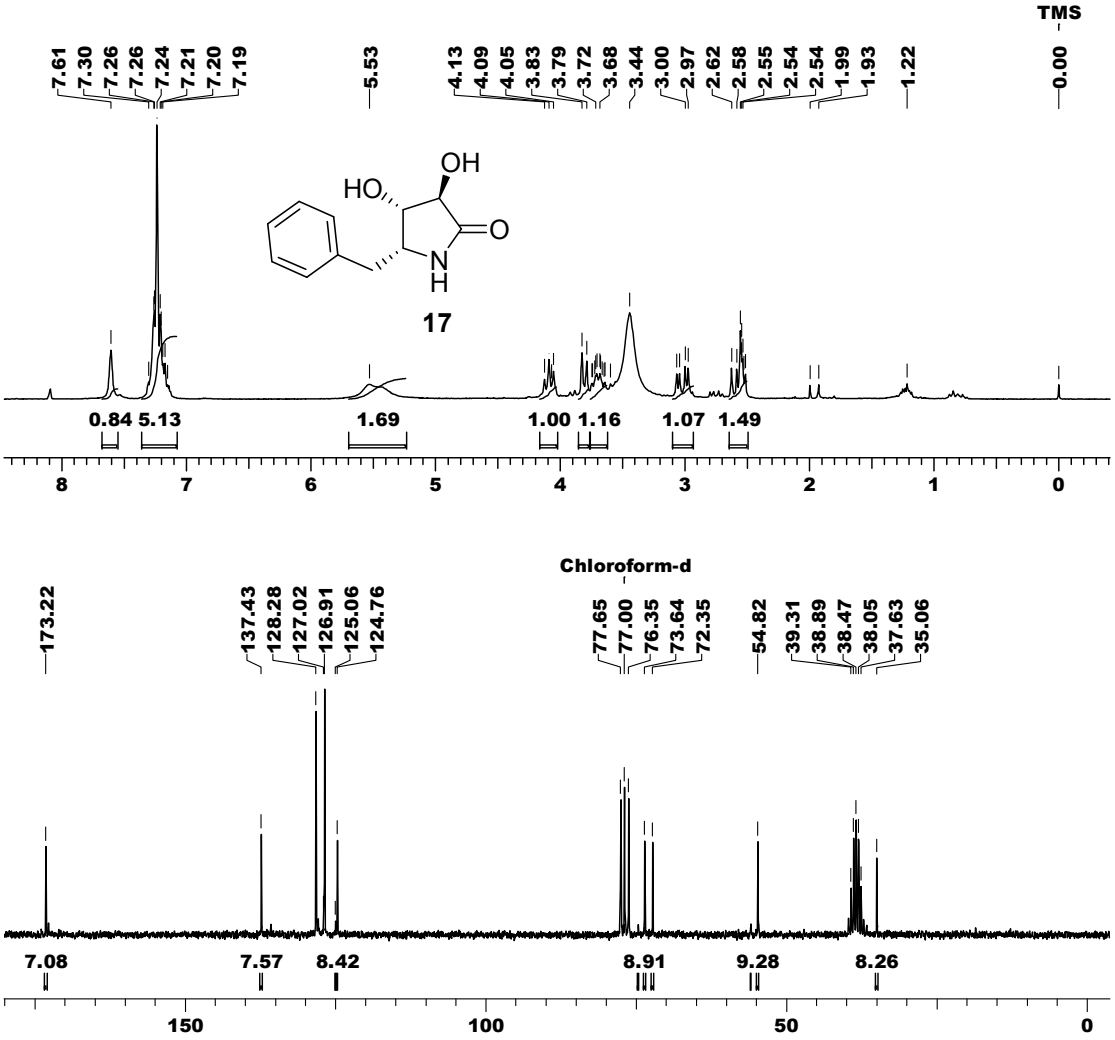


Fig. 5: ^{1}H and ^{13}C NMR spectra of pyrrolidone 17

of dihydroxy pyrrolidone **17** showed peaks at δ 2.97 and 5.53 corresponding to the benzylic and hydroxyl protons. Its ^{13}C NMR spectrum showed peaks at δ 72.3, 73.6 and 173.2 corresponding to the two carbons attached to hydroxyl groups and the amide carbonyl carbon respectively (**Fig. 5**); $[\alpha]^{25}_{D}$ +106 (*c* 1.0, $CHCl_3$). The triacetate derivative **18** was synthesized by acetylation of **17** using acetic anhydride and triethyl amine in 94% yield. The ^{1}H NMR spectrum of **18** showed three singlets at δ 1.94, 2.12 and 2.56 for the three acetate methyl groups. A signal at δ 4.97 (dt) corresponds to the

methine proton (**CH**NAc). Its decoupled spectrum (decoupling of benzylic protons) showed a doublet at δ 4.98 corresponding to the methine proton (**Fig. 6**).

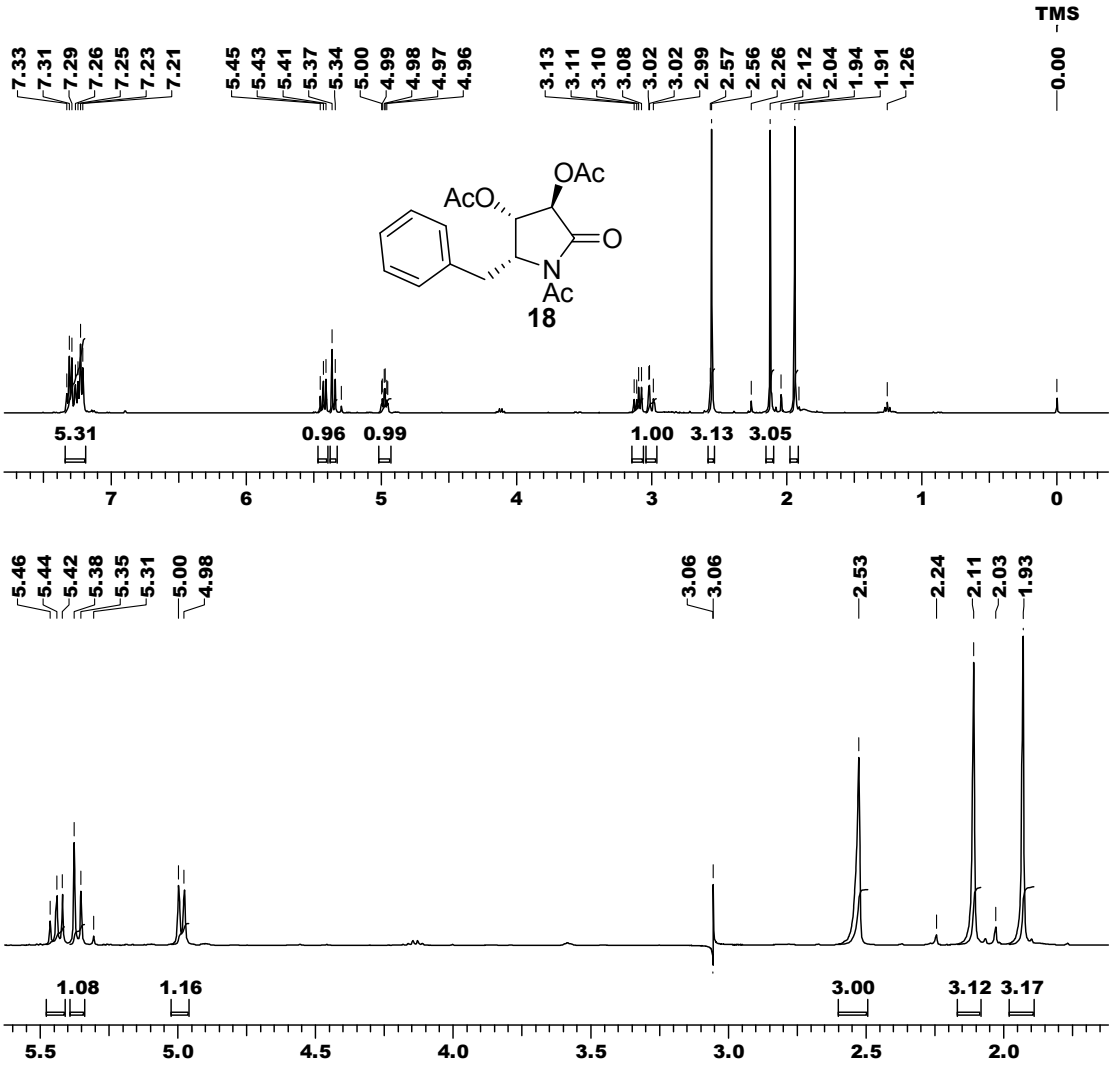


Fig. 6: ^{1}H and Decoupled spectra of triacetate derivative 18

The stereochemistry in **18** is assigned unambiguously based on: COSY, NOESY studies (**Fig. 7)** and X-ray crystallographic analysis (**Fig. 8**) as well as by the literature precedence.[19a]

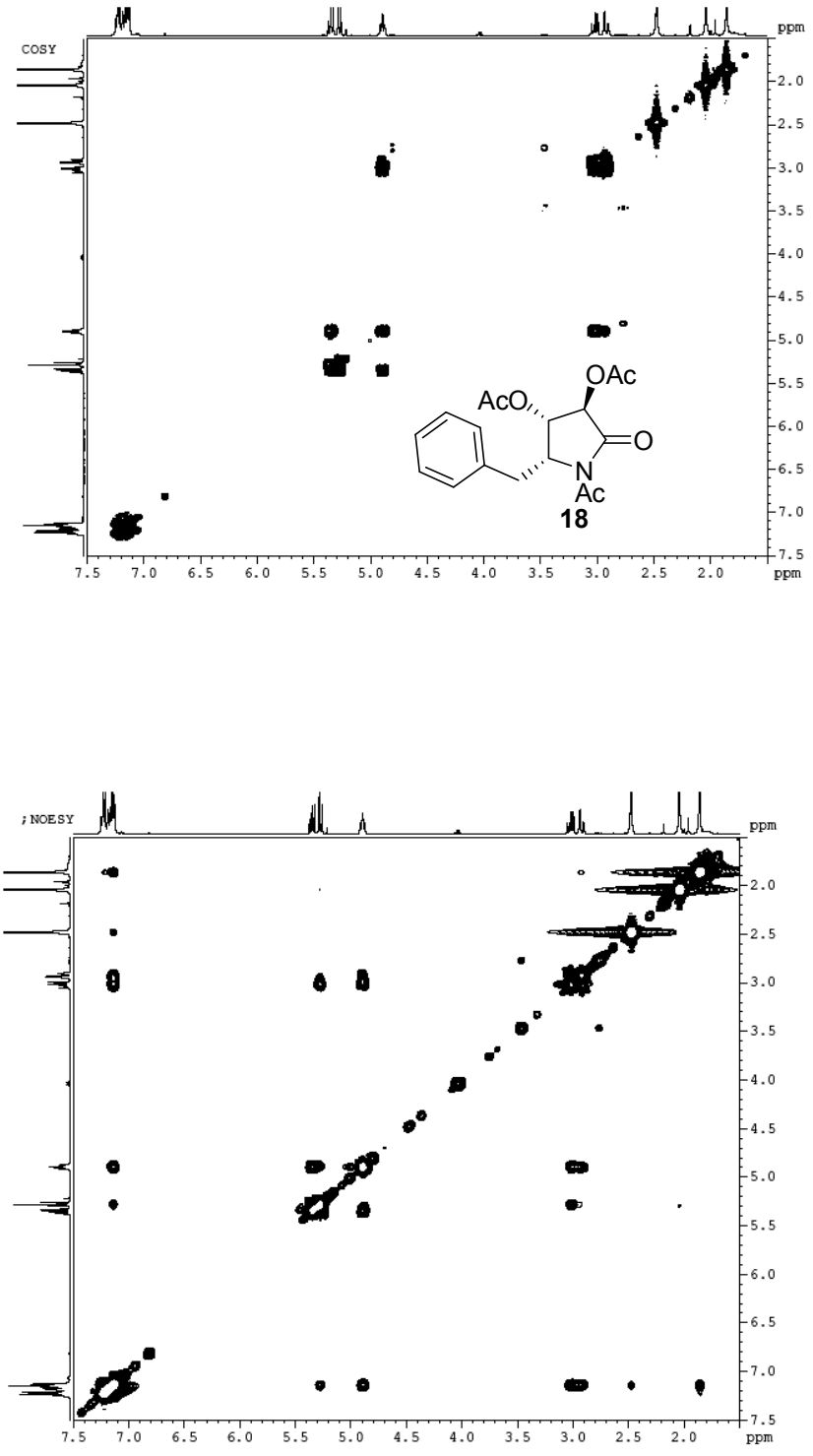
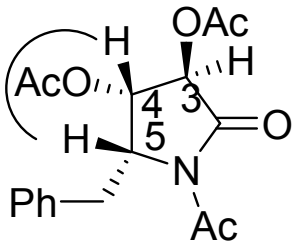


Fig. 7: COSY and NOESY spectra for triacetate 18.



Triacetate 18

The COSY and NOESY spectra of **18** (**Fig 7**) show a significant NOESY correlation between H_4 and H_5. There was no observed correlation between H_3-H_4 and H_3-H_5, thus, confirming *syn* relationship between H_4 and H_5.

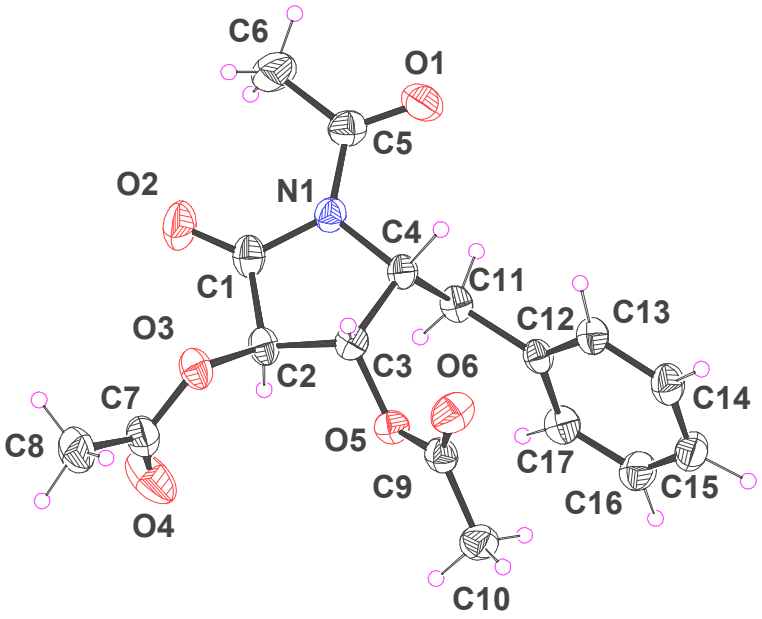


Fig. 8: ORTEP diagram for triacetate 18.

The X-ray crystallographic analysis of **18** further confirmed the *syn* relationship between H_4 and H_5 (**Fig. 8**).

The open-chain triacetate derivative **19** was synthesized by the reductive acetylation of amino diol **16** (Raney-Nickel, H_2).

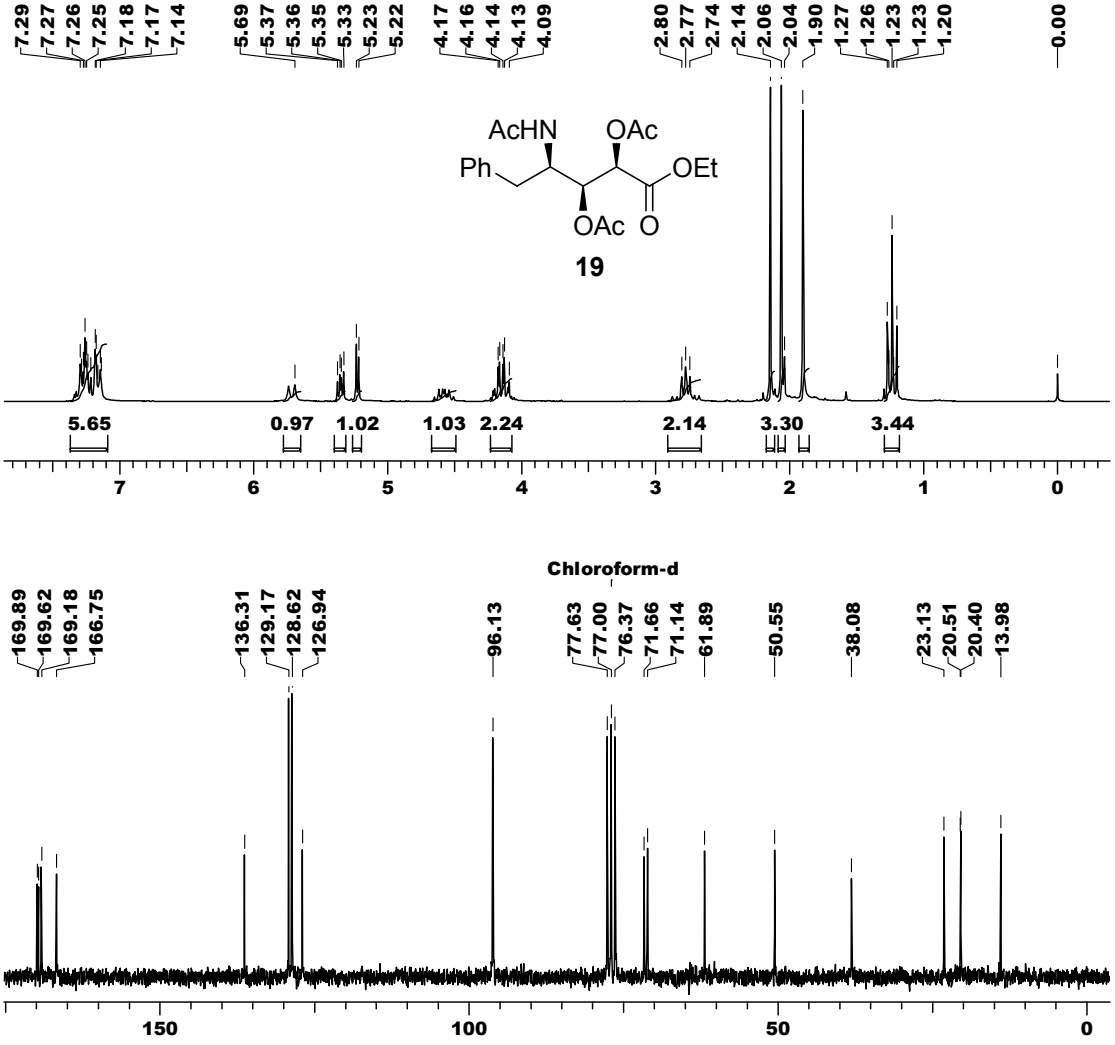
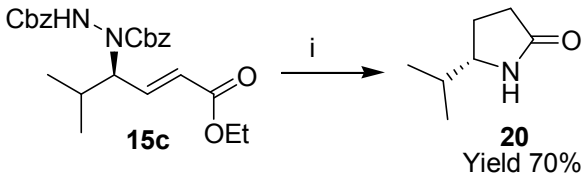


Fig. 9: ^{1}H and ^{13}C NMR spectra of triacetate derivative 19

The ^{1}H NMR spectrum of **19** showed three singlets at δ 1.90, 2.06 and 2.14 for the three acetate groups. A multiplet at δ 4.57 corresponds to methine proton attached to N-Ac group (**CH**NAc). Its ^{13}C NMR spectrum showed typical peaks at δ 166.7, 169.1, 169.6 and 169.8 due to the three ester carbonyls and one amide carbonyl carbons respectively (**Fig. 9**).



Scheme 8: (i) Raney-Ni, MeOH, H_2 (60 psig), 12 h.

The single-step transformation of **15c** under hydrogenation conditions (Raney nickel, H_2, 60 psig) to obtain 2-pyrrolidone **20** (70% yield) constitutes another application of this methodology (**Scheme 8**).

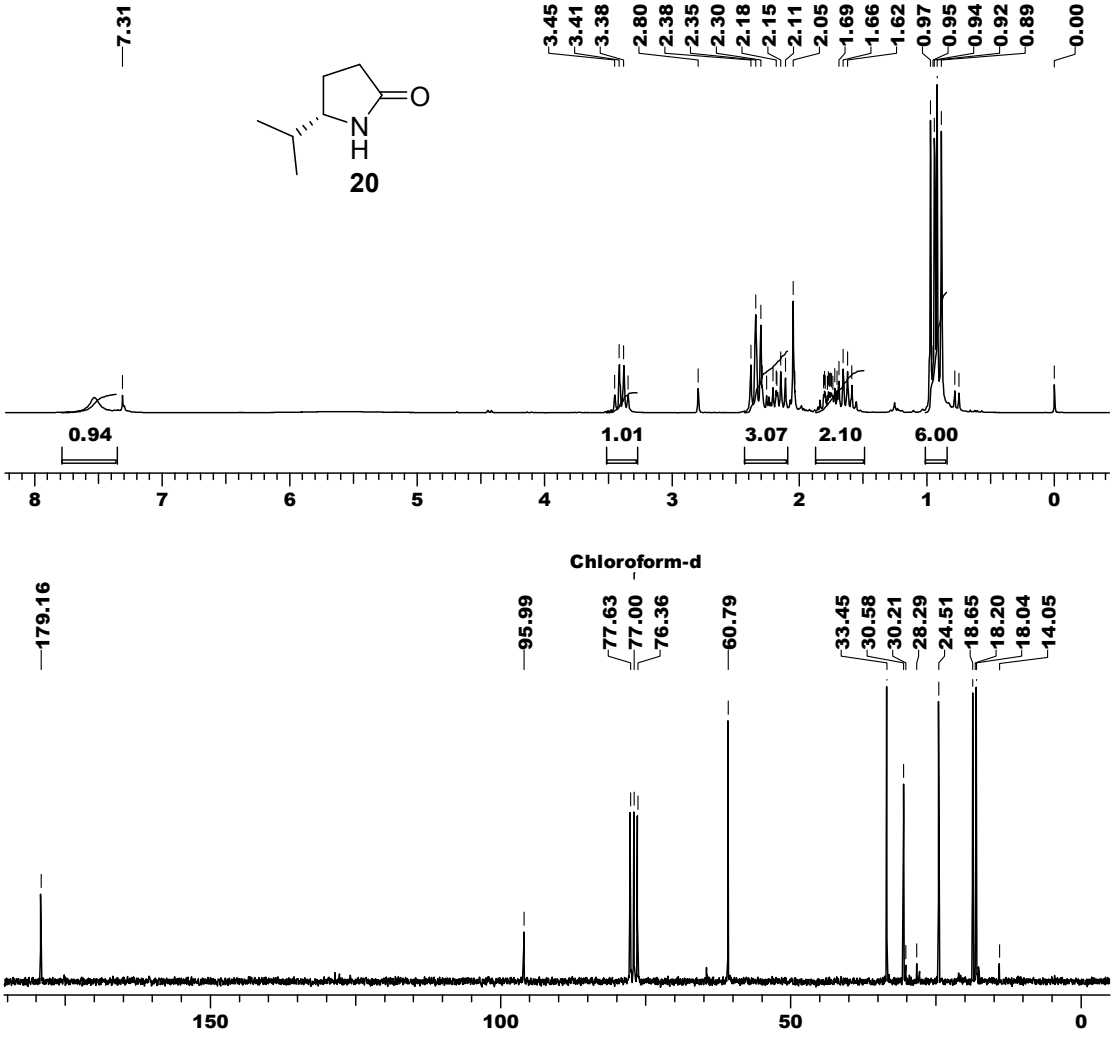


Fig. 10: ^{1}H and ^{13}C NMR spectra of pyrrolidone 20

The ^{1}H NMR spectrum of **20** showed two doublets at δ 0.89 and 0.94 corresponding to two methyl groups of isopropyl moiety. A quartet at δ 3.38 corresponds to amide group (**CH**NHCO). Its ^{13}C NMR spectrum showed typical peaks at δ 60.7 and 179.1 corresponding to carbon attached to amide group (**CH**NHCO) and amide carbonyl carbon respectively (**Fig. 10**).

3.1.5 Conclusion

In summary, we have reported, for the first time, a novel, one-pot procedure of sequential α-amination-HWE olefination of aldehydes that leads to enantioselective synthesis of γ-amino-α,β-unsaturated esters **15** with excellent yields and high enantioselectivities. The potential of this reaction has been demonstrated by its easy and efficient incorporation in the synthesis of important optically active 2-pyrrolidinone derivatives in good yields and by the great substrate generality. The merits of the present protocol are (1) easy availability of starting materials (2) simple environmental-friendly procedure and (3) availability of proline in both enantiomeric forms.

3.1.6 Experimental Section

General experimental procedure for sequential α-amination/ Horner-Wodsworth-Emmons olefination:

To a cooled solution of dibenzyl azodicarboxylate (DBAD) (328 mg, 1 mmol) and L-proline (11.5 mg, 10 mol%) in CH_3CN (10 mL) at 0 °C was added *n*-butyraldehyde (87 mg, 1.2 mmol) and the mixture was stirred for 2 h at 0 °C and further for 1 h at 10 °C. This was followed by addition of lithium bromide (130 mg, 1.5 mmol), triethyl phosphonoacetate (336 mg, 1.5 mmol) and DBU (152 mg, 1 mmol) in that sequence and the whole mixture was stirred at 5 °C for 45 min. It was then quenched with aq.

ammonium chloride solution and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude product **15a**, which was then purified by flash column chromatography (packed with silica gel 60-120 mesh) using petroleum ether and ethyl acetate as eluents to afford the pure product.

(*R*)-Ethyl 4-(dibenzyloxycarbonylhydrazinyl)hex-2-enoate (15a):

Yield: 84%, Viscous liquid; **HPLC:** Chiracel OD-H column (2-Propanol: *n*-Hexane = 4:96, flow rate 1.0 mL/min, λ = 260 nm). Retention time (min): 40.15 (major) and 54.95 (minor). The racemic standard was prepared in the same way with DL-proline as a catalyst, ee 99%; $[\alpha]^{25}_{D}$ +10 (*c* 1.0, $CHCl_3$). **IR** ($CHCl_3$) ν 3389, 3020, 2926, 2852, 1758, 1715, 1289, 1215, 1041, 757 cm^{-1} ; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 0.94 (m, 3H), 1.25 (t, *J* = 7 Hz, 3H), 1.62 (m, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 4.64 (m, 1H), 5.11 (m, 4H), 5.85 (d, *J* = 15.5 Hz, 1H), 6.86 (m, 2H), 7.28 (m, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 10.4, 13.9, 23.8, 60.3, 64.7, 67.4, 68.0, 122.2, 127.4, 127.8, 128.2, 144.7, 155.5, 156.5, 166.0; **Analysis:** $C_{24}H_{28}N_2O_6$ requires C, 65.44; H, 6.41; N, 6.36; found C, 65.25; H, 6.28; N, 6.59%.

(*R*)-Ethyl 4-(dibenzyloxycarbonylhydrazinyl)pent-2-enoate (15b):

Yield: 83%, Colorless solid (mp: 80 °C); **HPLC:** Chiracel OD-H column (2-Propanol: *n*-Hexane = 6:94, flow rate 1.0 mL/min, λ = 260 nm). Retention time (min): 24.39 (minor) and 31.49 (major), ee 92%; $[\alpha]^{25}_{D}$ +5 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$) ν 3301, 3020, 1750, 1713, 1407, 1285, 1216, 1029, 758 cm^{-1} ; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 1.22 (t, *J* = 7.2 Hz, 3H), 1.30 (d, *J* = 6.8 Hz, 3H), 4.11 (q, *J* = 7.2 Hz, 2H), 5.12 (m, 5H), 5.83 (d, *J* = 16.1 Hz, 1H), 6.85-6.96 (dd, *J* = 15.7, 5.3 Hz, 1H), 7.08 (s, 1H), 7.29 (m, 10H); **^{13}C**

NMR (50 MHz, $CDCl_3$): δ 14.0, 16.2, 54.2, 60.4, 66.5, 68.1, 121.8, 127.7, 127.9, 128.1, 128.3, 135.5, 146.5, 152.2, 156.6,166.1; **Analysis:** $\mathbf{C_{23}H_{26}N_2O_6}$ requires C, 64.78; H, 6.15; N, 6.57; found C, 64.59; H, 6.27; N, 6.59%.

(*R*)-Ethyl 4-(dibenzyloxycarbonylhydrazinyl)-5-methylhex-2-enoate (15c):

Yield: 80%, Viscous liquid; **HPLC:** Chiracel OD-H column (2-Propanol: *n*-Hexane = 3:97, flow rate 1.0 mL/min, λ = 260 nm). Retention time (min): 43.39 (major) and 47.94 (minor), ee 92%; $\mathbf{[\alpha]^{25}_D}$ +2 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$) ν 3584, 3295, 3020, 2964, 1753, 1713, 1406, 1286, 1216, 1043, 756 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 0.84 (d, *J* = 6.7, 3H), 1.0 (m, 3H), 1.27 (t, *J* = 7 Hz, 3H), 1.98 (m, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 4.33 (m, 1H), 5.14 (m, 4H), 5.90 (d, *J* = 15.6 Hz, 1H), 6.45 (s, 1H), 6.77-6.89 (dd, *J* = 15.7, 9.1 Hz, 1H), 7.31 (m, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 19.5, 20.0, 29.3, 60.5, 65.5, 67.7, 68.3, 124.2, 127.8, 128.5, 135.7, 143.6, 155.8, 156.5, 166.2; **Analysis:** $\mathbf{C_{25}H_{30}N_2O_6}$ requires C, 66.06; H, 6.65; N, 6.16; found C, 66.17; H, 6.61; N, 6.31%.

(*R*)-Ethyl 4-(dibenzyloxycarbonylhydrazinyl)hept-2-enoate (15d):

Yield: 85%, Colorless solid (mp: 72 °C); **HPLC:** Chiracel OD-H column (2-Propanol: *n*-Hexane = 3:97, flow rate 1.0 mL/min, λ = 260 nm). Retention time (min): 25.79 (minor) and 28.42 (major), ee 95%; $\mathbf{[\alpha]^{25}_D}$ +8 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$) ν 3295, 2936, 2962, 1714, 1407, 1281, 1216, 1042, 756 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 0.90 (m, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.53-1.77 (m, 4H), 4.13 (q, *J* = 7.2 Hz, 2H), 4.77 (m, 1H), 5.11 (m, 4H), 5.85 (d, *J* = 15.5 Hz, 1H), 6.74 (s, 1H), 6.78-6.86 (dd, *J* = 16.1, 7.2 Hz, 1H), 7.28 (m, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.6, 13.9, 19.0, 32.7, 58.3, 60.2, 67.4, 68.0, 122.5, 127.6, 127.7, 128.2, 135.5, 145.1, 155.4, 156.5, 166.0; **Analysis:** $\mathbf{C_{25}H_{30}N_2O_6}$ requires C, 66.06; H, 6.65; N, 6.16; found C, 66.27; H, 6.46; N, 6.35%.

(*R*)-Ethyl 4-(dibenzyloxycarbonylhydrazinyl)-5-phenylpent-2-enoate (15e):

Yield: 88%, Colorless solid (mp 92 °C); **HPLC:** Chiracel OD-H column (2-Propanol: *n*-Hexane = 6:94, flow rate 1.0 mL/min, λ = 260 nm). Retention time (min): 49.18 (minor) and 55.55 (major), ee 99%; $[\alpha]^{25}_{D}$ +8.5 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$) ν 3387, 3020, 1759, 1715, 1285, 1215, 1044, 758 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.1 Hz, 3H), 2.91-3.10 (m, 2H), 4.12 (q, *J* = 7.3 Hz, 2H), 5.16 (m, 5H), 5.83 (d, *J* = 15.4 Hz, 1H), 6.48 (s, 1H), 6.88-7.0 (dd, *J* = 15.7, 6.7 Hz, 1H), 7.21-7.29 (m, 15H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.0, 37.5, 60.3, 61.8, 67.7, 68.1, 123.1, 126.67, 127.7, 128.0, 128.3, 128.4, 128.5, 128.9, 135.5, 136.8, 143.9, 155.1, 156.5, 165.7; **Analysis: $C_{29}H_{30}N_2O_6$** requires C, 69.31; H, 6.02; N, 5.57; found C, 69.25; H, 6.12; N, 5.43%.

(*R*)-Ethyl 4-(dibenzyloxycarbonylhydrazinyl)-5-(4-methoxyphenyl)pent-2-enoate (15f):

Yield: 88%, Colorless solid (mp: 78 °C); **HPLC:** Chiracel OD-H column (2-Propanol: *n*-Hexane = 3:97, flow rate 1.0 mL/min, λ = 260 nm). Retention time (min): 69.9 (minor) and 83.0 (major), ee 99%; $[\alpha]^{25}_{D}$ +4 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$) ν 3384, 3020, 1753, 1715, 1513, 1249, 1216, 1038, 757 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.2 Hz, 3H), 2.90 (m, 2H), 3.76 (s, 3H), 4.13 (q, *J* = 7.2 Hz, 2H), 5.07 (m, 5H), 5.84 (d, *J* = 16.2 Hz, 1H), 6.30 (s, 1H), 6.73 (d, *J* = 8.4 Hz, 2H), 6.87-6.99 (dd, *J* = 16.2, 7.1 Hz, 1H), 7.05 (m, 2H), 7.30 (m, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.0, 36.6, 54.8, 60.2, 60.6, 67.6, 68.1, 113.9, 123.0, 127.7, 128.0, 128.3, 128.6, 129.8, 135.5, 144.1, 155.1, 156.5, 158.2, 165.7; **Analysis: $C_{30}H_{32}N_2O_7$** requires C, 67.66; H, 6.06; N, 5.26; found C, 67.46; H, 6.16; N, 5.13%.

Experimental Procedure for Dihydroxylation:

To a solution of olefin **15e** (1 g, 2 mmol) and NMO (0.702 g, 6 mmol, 3 equiv.) in 20 mL THF-H_2O (1:1) at 0 °C, was added OsO_4 (25.4 mg, 0.1 M in toluene, 5 mol%) and the reaction mixture was stirred at the same temperature for 12 h and at 25 °C for 6 h. The reaction was quenched with sodium bisulfite (0.5 g), diluted with water and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product, which was then purified by flash column chromatography using petroleum ether: ethyl acetate (40:60) to afford pure diol **16**.

(2*R*,3*S*,4*R*)-Ethyl-4-(dibenzyloxycarbonylhydrazinyl)-2,3-dihydroxy-5-phenylpentanoate (16):

Yield: 92%, Colorless solid (mp: 80 °C); $[\alpha]^{25}_{D}$ +16 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$) ν 3390, 3218, 3020, 2929, 2400, 1667, 1427, 1215, 1075, 923, 758 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + DMSO-d_6) δ 1.25 (t, *J* = 7 Hz, 3H), 2.51-2.77 (m, 2H), 3.87 (m, 1H), 4.13-4.24 (q, *J* = 7 Hz, 2H), 4.30 (m, 1H), 4.62-4.96 (m, 5H), 6.94-7.38 (m, 15H); **^{13}C NMR** (50 MHz, $CDCl_3$ + DMSO-d_6): δ 12.6, 31.8, 58.8, 61.6, 65.3, 65.5, 69.3, 69.6, 124.3, 125.4, 125.5, 125.9, 126.0, 126.3, 126.5, 126.7, 127.5, 127.7, 134.3, 134.6, 154.6, 170.7; **Analysis:** $C_{29}H_{32}N_2O_8$ requires C, 64.91; H, 6.01; N, 5.22; found C, 64.55; H, 6.15; N, 5.18%.

Synthesis of (3*R*, 4*S*, 5*R*)-5-benzyl-3,4-dihydroxypyrrolidine-2-one (17):

A solution of diol **16** (0.804 mg, 1.5 mmol) in MeOH (20 mL) and acetic acid (10 drops) was treated with Raney nickel (3 g, excess) under H_2 (80 psig) atmosphere for 24 h. The reaction mixture was filtered over celite and concentrated to give crude aminodiol which

on strirring in EtOH at 50 °C for 5 h cyclized to product **17** (purified by flash chromatography using ethyl acetate as eluent).

(3*R*, 4*S*, 5*R*)-5-Benzyl-3,4-dihydroxypyrrolidine-2-one (17):

Yield: 65%, Colorless solid (mp: 180 °C); **$[\alpha]^{25}_{D}$ +106** (*c* 1.0, $CHCl_3$). IR (nujol) ν 3320, 2918, 2854, 1668, 1461, 1377, 1112, 721 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + DMSO-d_6) δ 2.55 (m, 1H), 2.97-3.07 (dd, *J* = 4.6, 13.7 Hz, 1H), 3.71 (m, 1H), 3.79 (d, *J* = 7.4 Hz, 1H), 4.09 (t, *J* = 7.2 Hz, 1H), 7.24 (m, 5H), 7.61 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+DMSO-d_6): δ 35.0, 54.8, 72.3, 73.6, 124.7, 124.9, 128.2, 137.4, 173.22; **Analysis: $C_{11}H_{13}NO_3$** requires C, 63.76; H, 6.32; N, 6.76; found C, 63.56; H, 6.67; N, 6.88%.

Synthesis of triacetate derivative (18): Acetylation was carried out by treating **17** (207 mg, 1 mmol) with triethyl amine (404 mg, 4 mmol), acetic anhydride (408 mg, 4 mmol) and cat. DMAP in CH_2Cl_2 (8 mL) for 2 h. The crude product was purified by flash column chromatography using pet ether: ethyl aceate (80:20) to afford pure **18**.

(3*R*, 4*S*, 5*R*)-*N*-Methoxycarbonyl-5-benzyl-3,4-diacetoxypyrrolidine-2-one (18):

Yield: 94%, Colorless solid (mp: 105 °C); **$[\alpha]^{25}_{D}$** +44 (*c* 1.0, $CHCl_3$), **IR** ($CHCl_3$) ν 3031, 1751, 1703, 1373, 1215, 1074, 756 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 1.94 (s, 3H), 2.12 (s, 3H), 2.56 (s, 3H), 2.98 (dd, *J* = 14.2, 2.6 Hz 2H), 3.08 (dd, *J* = 14.2, 7.8, 2H), 4.97 (dt, *J* = 7.9, 2.8 Hz, 1H), 5.34 (d, *J* = 9.8 Hz, 1H), 5.41 (dd, *J* = 8, 9.7 Hz, 1H), 7.21-7.33 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 20.3, 25.7, 33.9, 54.5, 71.1, 72.3, 127.1, 128.5, 129.7, 135.9, 167.0, 169.5, 169.8, 170.0; **Analysis: $C_{17}H_{19}NO_6$** requires C, 61.25; H, 5.75; N, 4.20; found C, 61.59; H, 5.40; N, 4.41%.

Synthesis of triacetate 20: Hydrogenation of **16** was carried out using the same procedure as described for **17**, followed by direct acetylation (as described for **18**) using acetic anhydride and triethyl amine gave crude **19** which was purified by flash column chromatography using ethyl aceate as eluent.

(2*R*,3*S*,4*R*)-Ethyl 4-acetamido-2,3-diacetoxy-5-phenylpentanoate (19):

19, **Yield:** 77%, Colorless solid (mp: 85 °C); **[α]$^{25}_{D}$** +30.18 (*c* 1.0, MeOH); **IR** ($CHCl_3$) ν 3019, 1750, 1677, 1513, 1373, 1215, 1047, 756 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.1, 3H), 1.90 (s, 3H), 2.06 (s, 3H), 2.14 (s, 3H), 2.77 (m, 2H), 4.14 (m, 2H), 4.57 (m, 1H), 5.22 (d, *J* = 3.6 Hz, 1H), 5.33 (dd, *J* = 3.5, 5.7 Hz, 1H), 5.69 (d, *J* = 9.3 Hz, 1H), 7.14-7.29 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.9, 20.4, 20.5, 23.1, 38.0, 50.5, 61.8, 71.1, 71.6, 126.9, 128.6, 129.1, 136.3, 166.7, 169.1, 169.6, 169.8; **Analysis: $C_{19}H_{25}NO_7$** requires C, 60.15; H, 6.64; N, 3.69; found C, 60.28; H, 6.78; N, 3.52%.

Synthesis of (*S*)-5-isopropylpyrrolidin-2-one (20):

Hydrogenation of **15c** was carried out using the same procedure described for **17** followed by cyclization in EtOH furnished crude **20**, which was purified by flash chromatography (ethyl acetate).

(*S*)-5-Isopropylpyrrolidin-2-one (20):

Yield: 70%, Colorless solid (mp: 65 °C); **[α]$^{25}_{D}$** -16.5 (*c* 2.0, CH_2Cl_2) [lit[21] $[\alpha]^{25}_{D}$ -18.2 (*c* 2.0, CH_2Cl_2)]; **IR** ($CHCl_3$) ν 3220, 2966, 1697, 1458, 1388, 1271, 754 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 0.89 (d, *J* = 6.7 Hz, 3H), 0.94 (d, *J* = 6.7 Hz, 3H), 1.62 (p, *J* = 6.8 Hz, 1H), 1.77 (m, 1H), 2.11-2.38 (m, 3H), 3.38 (q, *J* = 6.9 Hz, 1H), 7.53 (brs, 1H) ; **^{13}C NMR** (50 MHz, $CDCl_3$): δ 18.0, 18.6, 24.5, 30.5, 33.4, 60.7, 179.1; **Analysis: $C_7H_{13}NO$** requires C, 66.10; H, 10.3; N, 11.01; found C, 65.57; H, 10.33; N, 11.4%.

Section II:

Chiral Lewis-Acid Catalyzed Asymmetric Cyanide Addition onto Nitrones

3.2.1 Introduction

In view of the widespread occurrence of nitrogenated compounds in nature, and the recent demands for the synthesis of enantiomerically pure compounds, it is not surprising that stereoselective additions to C=N bonds are now considered one of the most important and fundamental asymmetric reactions. Among the nitrogenated compounds, nitrones have become highly valuable intermediates for the synthesis of nitrogen-containing biologically active compounds, because they are prepared readily by catalytic oxidation of secondary amines with H_2O_2[22] as well as by condensation of carbonyl compounds with *N*-hydroxyl amines.[23] In literature, many methods are reported for the stereoselective addition of variety of nucleophiles onto nitrones including diastereoselective addition of chiral enolates,[24] catalytic enantioselective addition of ketene silyl acetals,[25] etc. Cyanide nucleophiles are known to add onto nitrones to give α-cyano hydroxylamines, which are precursors to the corresponding α-amino acids.

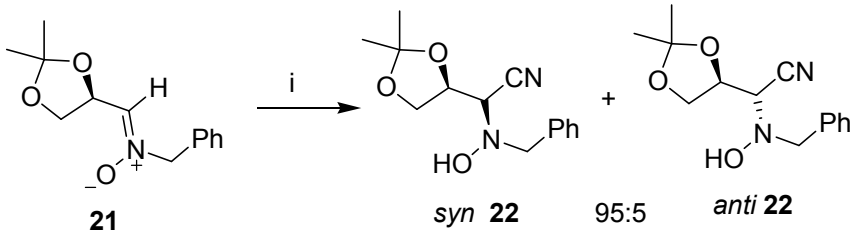
3.2.2 Review of Literature

Few general methods are described in the literature for the addition of cyanide nucleophiles onto nitrones.

Merino's approach (1995)[26]

Merino *et al*. have described for the first time, diastreoselctive addition of cyanide reagents to chiral nitrones **21** to afford a mixture of *syn* and *anti* α-amino nitriles **22** in

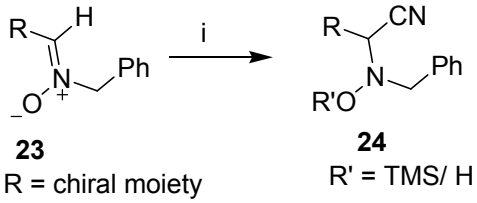
good yields. Trimethylsilyl cyanide was found to the best reagent giving good selectivity (*syn: anti* 95:5) with excellent yields (**Scheme 8**).



Scheme 8: (i) TMSCN, 0 °C, 48 h, 84%.

Merino's approach (1996)[27]

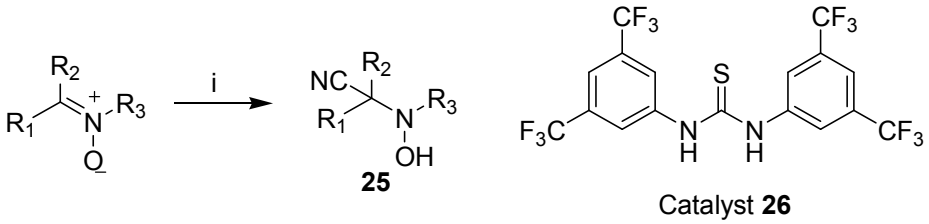
The same group has again reported the stereoselective synthesis of optically active α-(hydroxyamino) nitriles **24**. Thus, addition of both trimethylsilyl cyanide and diethylaluminium cyanide to chiral nitrones **23** proceeded with good to excellent diastereoselectivity (*syn: anti* up to 95:5) and good yields (**Scheme 9**).



Scheme 9: (i) TMSCN or Et_2AlCN, 0 °C to -60 °C, 2-48 h, 64-100%.

Takemoto's approach (2003)[28]

Takemoto *et al*. have described a thiourea-catalyzed (catalyst **26**) addition of cyanide anion onto nitrones to give **25** in good yields (**Scheme 10**).



Scheme 10: (i) TMSCN (5 equiv.), catalyst **26** (0.5 equiv.), -78 to -25 °C, 1.5 h, 75-96% followed by HCl, MeOH.

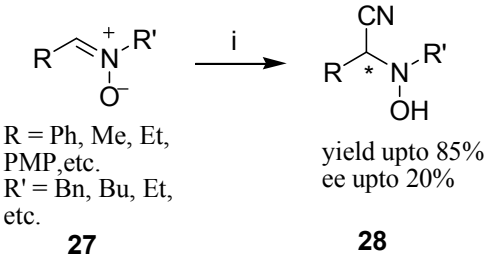
3.2.3 Present Work

3.2.3.1 Objective

Although there are few methods available in the literature for cyanide addition onto nitrones, some of them are racemic while others use chiral nitrones as starting materials. Hence, development of a new protocol starting from prochiral nitrones using catalytic enantioselective reactions is still desirable. In this section, we describe, for the first time, a new approach for enantioselective addition of cyanide ion onto nitrones using chiral Lewis acids as catalysts.

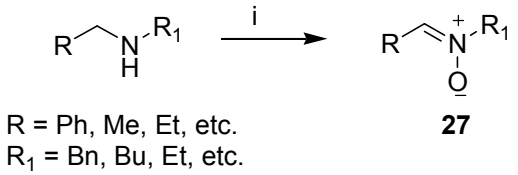
3.2.4 Results and Discussions:

We have developed a new procedure for addition of cyanide anion onto nitrones **27** catalyzed by Ti-BINOL using trimethylsilyl cyanide or acetone cyanohydrin as cyanide source to get α-(hydroxyamino) nitriles **28** in good yields with poor enantioselectivities.



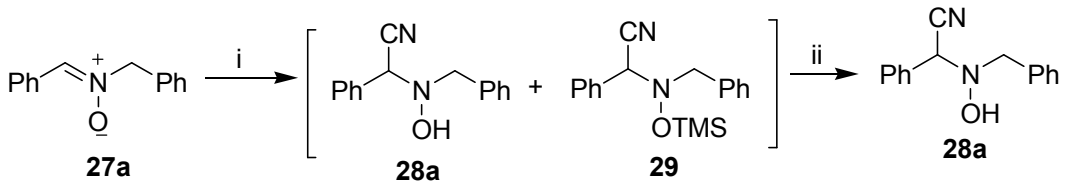
Scheme 11: (i) TMSCN or acetone cyanohydrin, Ti-BINOL (20 mol%), CH_2Cl_2, 24 h, -20 °C.

These α-(hydroxyamino) nitriles **28** are direct precursors to the corresponding α-amino acids (**Scheme 11**). The starting materials, nitrones (**27**), were prepared by the oxidation of the respective secondary amines with Na_2WO_4 and aq. 30% H_2O_2 as oxidants in high yields (62-89%)[29] (**Scheme 12**).



Scheme 12: (i) Na_2WO_4, 30% H_2O_2, MeOH, 0-25 °C, 3 h.

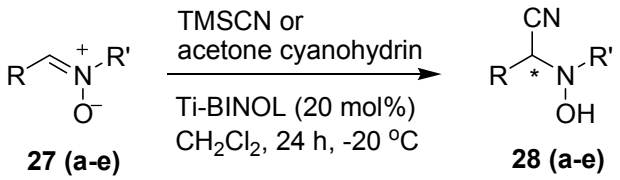
In the preliminary study, acetone cyanohydrin was employed as a cyanide source but due to low yields, it was replaced with trimethylsilyl cyanide. Firstly, nitrone **27a** was reacted with TMSCN in the presence of Ti(O*i*-Pr)$_4$ to give a mixture of products **28a** and **29**, which on treatment with methanolic HCl gave TMS deprotected product **28a** in 90% yield (**Scheme 13**). Encouraged by these results, we wanted to carry out the asymmetric version of this reaction. Thus, use of (+)-diisopropyl tartarate as chiral ligand with titanium tetraisopropoxide as catalyst resulted in low yields (30%) of product **28a**. However, treatment of nitrone **27a** with TMSCN in the presence of (*R*)-BINOL-Ti(O*i*-Pr)$_2$ combination followed by acidification with methanolic HCl gave **28a** in 92% yield; $[\alpha]^{25}_D$ +2.5 (c 1.2, $CHCl_3$).



Scheme 13: (i) TMSCN, Ti(O*i*-Pr)$_4$, CH_2Cl_2, 0 °C, 24 h; (ii) HCl, MeOH, 90%.

Table 3 shows the scope of this reaction, wherein several nitrones underwent this transformation successfully in excellent yields to give **28** (**a-e**).

Table 3: BINOL-Ti(O*i*Pr)$_2$ catalyzed TMSCN addition on to nitrones.[a]



entry	R	R_1	time (h)	yield (%)	$[\alpha]^{25}_D$ (*c* 1, $CHCl_3$)
1	Ph	Bn (**28a**)	24	92	+3.75
2	4-Cl-Ph	^{t}Bu (**28b**)	28	85	+1.4
3	4-OMe-Ph	Bn (**28c**)	24	86	+2.6
4	4-OMe-Ph	^{t}Bu (**28d**)	24	85	+2.3
5	*n*-Pr	*n*-Bu (**28e**)	28	80	+1.75

Reaction conditions: [a]TMSCN (1.2 equiv.), BINOL-Ti (O*i*Pr)$_2$ (20 mol%), CH_2Cl_2, 0 °C.

The structures of these α-(hydroxyamino) nitriles **28** were confirmed by ^{1}H and ^{13}C NMR spectroscopy.

Example 1: For instance, the ^{1}H NMR spectrum of **28a** showed peaks at δ 4.45 (s) and 6.51 (brs) corresponding to methine (**CH**CN) and **OH** protons respectively. Its ^{13}C NMR spectrum showed typical peaks at δ 60.6 and 62.3 corresponding to benzylic and methine (**CH**CN) carbons respectively (**Fig. 11**).

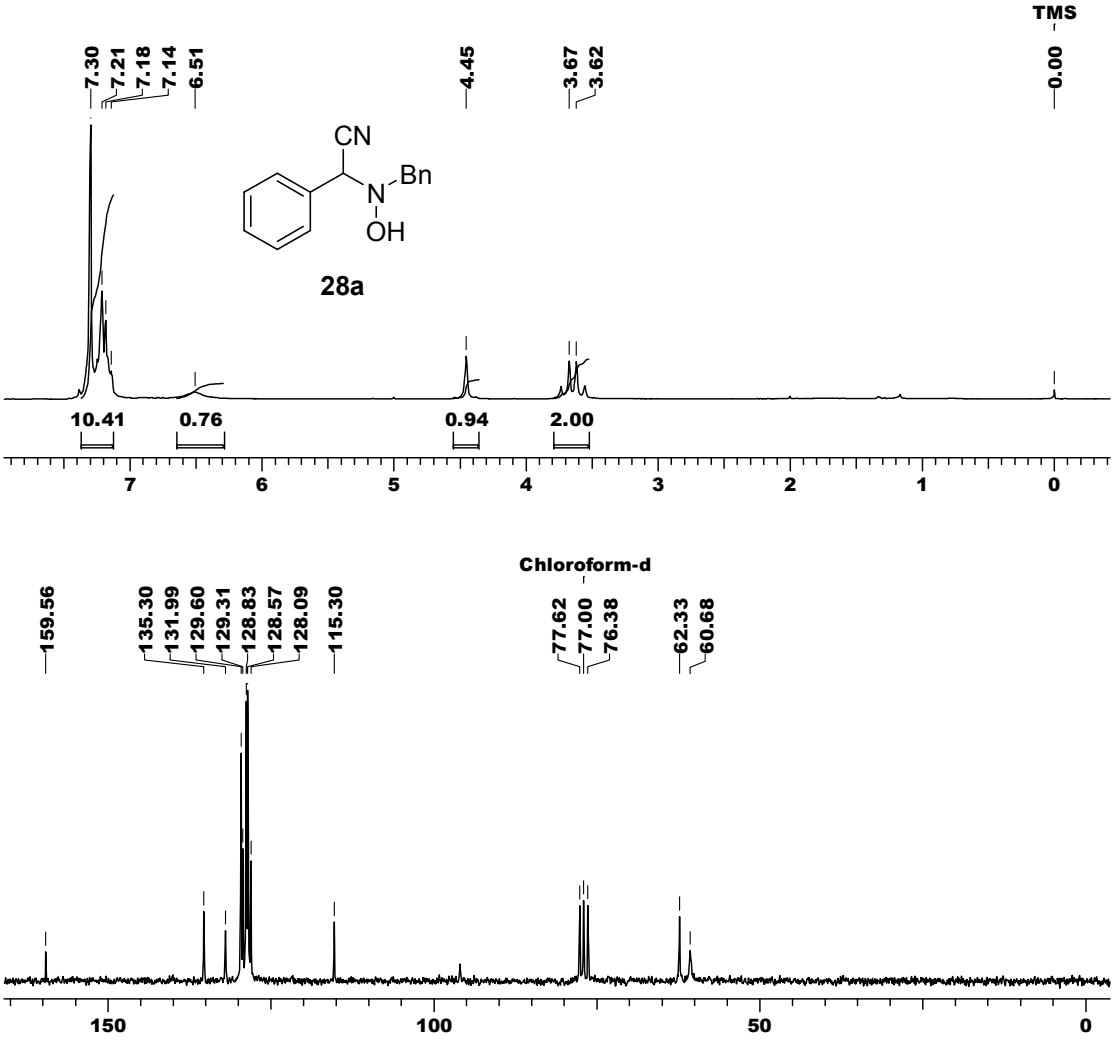


Fig. 11: ^{1}H and ^{13}C NMR spectra of 28a

Example 2: The ^{1}H NMR spectrum of **28d** showed peaks at δ 3.76 (s), 4.94 (s) and 5.12 (brs) corresponding to the methoxyl (O**C**$\mathbf{H_3}$), methine (**CH**CN) and the **OH** protons respectively. Its ^{13}C NMR spectrum showed peaks at δ 25.98 and 113.87 corresponding to quaternary carbon of *t*-butyl group and nitrile carbon respectively (**Fig. 12**).

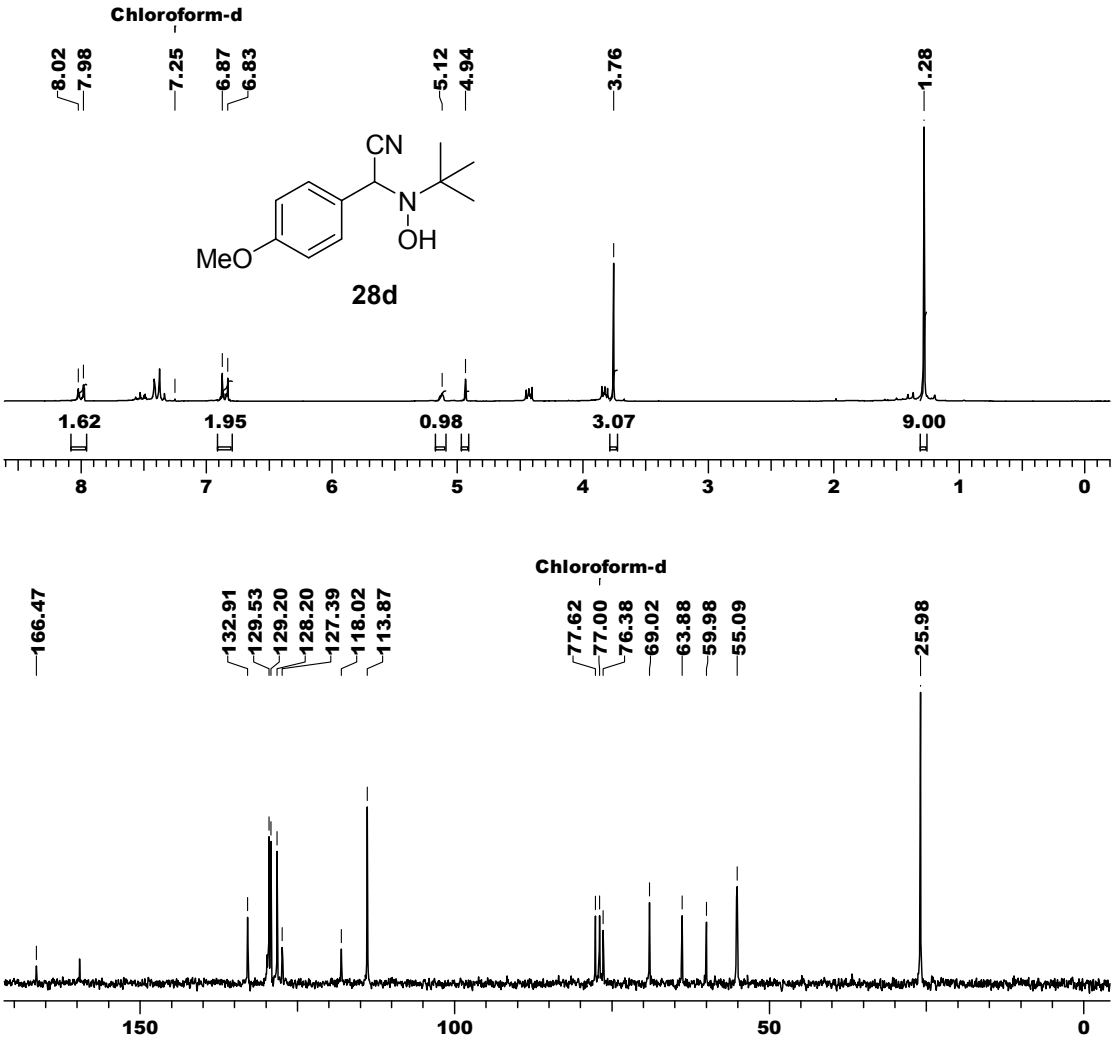


Fig. 12: ^{1}H and ^{13}C NMR spectra of 28d

Screening of other solvents like toluene and CH_2Cl_2 for this transformation resulted in lower yields. Decrease in reaction temperature from 0 °C to -20 °C for entry 1 (Table 3) resulted in increased specific rotation of the product **28a** i.e. $[\alpha]^{25}_{D}$ +3.75 (c 1.2, $CHCl_3$) but still with poor enantiomeric excess i.e. 20% ee (determined by Chiral HPLC analysis, Chiracel OD).

With the negatively charged oxygen, nitrones are known to coordinate effectively to the metallic Lewis acids (LA) to be activated.[30] The chiral Lewis acid might be directing the

incoming cyanide nucleophile through one face of nitrone (chiral induction). The relatively small size of cyanide nucleophile might be responsible for low enantioselectivities.

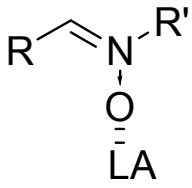


Fig. 13: Presumed activation mechanism of nitrones.

Owing to low enantioselectivities, we did not confirm the absolute configuration of the newly generated center.

3.2.5 Conclusion

In conclusion, we have developed, for the first time, a catalytic enantioselective method for the cyanide addition onto nitrones to give **28** (**a-e**). These cyano hydroxylamines, which are precursors for α-amino acids, are produced in excellent yields with low enantiomeric excess i. e. up to 20% ee.

3.2.6 Experimental Section

General experimental procedure for cyanide addition onto nitrones: To a solution of (*R*)-BINOL (28.6 mg, 20 mol%) in CH_2Cl_2 (10 mL), Ti(O *i*-Pr)$_4$ (28.3 mg, 20 mol%) was added and the reaction mixture was stirred for 1 h followed by addition of TMSCN (1.2 equiv.). The reaction mixture was cooled to -20 °C and nitrone **27a** (105 mg, 0.05 mmol) was added to it. After stirring for 24 h, it was quenched with sat. solution of $NaHCO_3$ and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product (mixture of **28a** and **29**), which was stirred in 0.3 N HCl in methanol for 2

h. After evaporation of solvents, it was again extracted with ethyl acetate (3 × 10 mL). The crude product was then purified by column chromatography using petroleum ether and ethyl acetate as eluents to afford the pure product **28a**.

2-(*N*-benzyl-*N*-hydroxyamino)-2-phenylacetonitrile (28a):

Yield: 109 mg, 92%, Colorless oil; $[\alpha]^{25}_{D}$ +3.75 (*c* 1.2, $CHCl_3$); **IR** ($CHCl_3$) ν 3500, 3200, 3020, 2929, 2235, 1520, 1480, 1075, 758 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 3.62 (m, 2H), 4.45 (s, 1H), 6.51 (brs, 1H), 7.14-7.30 (m, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 60.6, 62.3, 115.3, 128.0, 128.5, 128.5, 128.8, 120.3, 129.6, 131.9, 135.3, 159.5; **Analysis:** **$C_{15}H_{14}N_2O$** requires C, 75.61; H, 5.92; N, 11.76; found C, 75.55; H, 5.85; N, 11.88%.

2-(*N*-tert-butyl-*N*-hydroxyamino)-2-(4-chlorophenyl)acetonitrile (28b):

Yield: 85%, Colorless oil; $[\alpha]^{25}_{D}$ +0.9 (*c* 1.2, $CHCl_3$); **IR** ($CHCl_3$) ν 3520, 3233, 3020, 2929, 2238, 1515, 1490, 1075, 758 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 1.21 (s, 9H), 4.85 (m, 1H), 7.24-7.39 (m, 4H); **Analysis: $C_{12}H_{15}ClN_2O$** requires C, 60.38; H, 6.33; N, 11.74; found C, 60.44; H, 6.56; N, 11.85%.

2-(*N*-benzyl-*N*-hydroxyamino)-2-(4-methoxyphenyl)acetonitrile (28c):

Yield: 86%, Colorless oil; $[\alpha]^{25}_{D}$ +1.8 (*c* 1, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$) δ 3.70 (s, 3H), 3.75 (s, 2H), 4.63 (s, 1H), 5.72 (brs, 1H), 6.75 (d, *J* = 8.2 Hz, 2H), 7.16 (d, *J* = 8 Hz, 2H), 7.32 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.17, 60.1, 62.21, 114.07, 115.30, 127.37, 128.60, 128.86, 129.28, 130.85, 159.48; **Analysis: $C_{16}H_{16}N_2O_2$** requires C, 71.62; H, 6.01; N, 10.44; found C, 71.55; H, 6.12; N, 10.58%.

2-(*N-tert*-butyl-*N*-hydroxyamino)-2-(4-methoxyphenyl)acetonitrile (28d):

Yield: 85%, Colorless oil; $[\alpha]^{25}_{D}$ +1.2 (*c* 1, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$) δ 1.53 (s, 9H), 3.77 (s, 3H), 4.94 (s, 1H), 5.12 (brs, 1H), 6.83 (d, *J* = 8.9 Hz, 2H), 7.98 (d, *J* =

8.1 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 25.98, 55.09, 59.98, 63.88, 69.02, 113.87, 118.02, 127.39, 128.20, 129.20, 129.53, 132.91, 166.47; **Analysis: $C_{13}H_{18}N_2O_2$** requires C, 66.64; H, 7.74; N, 11.96; found C, 66.55; H, 7.52; N, 11.88%.

2-(*N*-butyl-*N*-hydroxyamino)pentanenitrile (28e):

Yield: 85%, Colorless oil; **$[\alpha]^{25}_D$** +1.75 (*c* 1, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$) δ 0.92 (t, *J* = 7.3, 3H), 0.97 (t, *J* = 7.3, 3H), 1.33-1.40 (m, 2H), 1.46-1.58 (m, 4H), 1.75-1.83 (m, 2H), 2.63 (m, 1H), 2.88 (m, 1H), 3.60 (t, *J* = 7.6 Hz, 1H), 5.48 (brs, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.61, 14.01, 19.23, 20.36, 33.17, 57.74, 60.03, 116.89; **Analysis: $C_9H_{18}N_2O$** requires C, 63.49; H, 10.66; N, 16.45; found C, 63.55; H, 10.52; N, 16.68%.

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CHAPTER IV

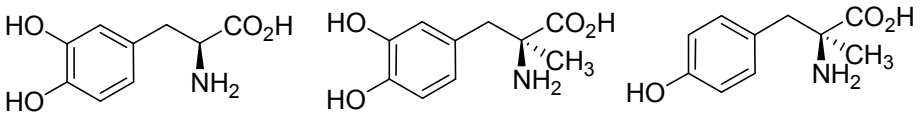
Organocatalytic Synthesis of (S)-α-Methyldopa, Cericlamine and (-) Anisomycin

Section I:

Organocatalytic Enantioselective Synthesis of Antihypertensive Drug (*S*)-α-Methyldopa

4.1.1 Introduction

Syntheses of optically active α-amino acids (**1-3**) are of general interest in that they provide a direct route to preparation of a large variety of biologically significant compounds.[1] Also, these α-amino acids can be used for the construction of nitrogen containing heterocycles.



L-DOPA (**1**) L-Methyldopa (**2**) L-Methyl Tyrosine (**3**)

L-Methyldopa (**2**) is a modified unusual amino acid derived from modification of L-DOPA (3,4-dihydroxy-L-phenylalanine) (**1**), which is one of the principal agents administered to patients with Parkinson's disease since 1967.[2] Only methyldopa, the L-isomer of alpha-methyldopa, has the ability to inhibit dopa decarboxylase and to deplete animal tissues of norepinephrine. In man, the antihypertensive activity appears to be due solely to the L-isomer. About twice the dose of the racemate (DL-alpha-methyldopa) is required for equal antihypertensive effect. Methyldopa (**2**) has no direct effect on cardiac function and usually does not reduce glomerular filtration rate, renal blood flow, or filtration fraction. Cardiac output usually is maintained without cardiac acceleration. In some patients the heart rate is slowed.

4.1.2 Pharmacology of Methyldopa

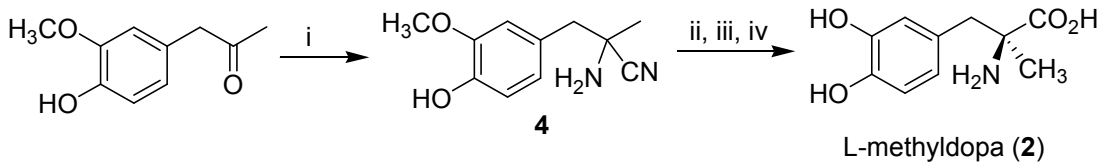
Although the mechanism of action has yet to be conclusively demonstrated, the antihypertensive effect of methyldopa probably is due to its metabolism to α-methylnorepinephrine, which then lowers arterial pressure by stimulation of central inhibitory α-adrenergic receptors, false neurotransmission, and/or reduction of plasma renin activity. It has been shown to cause a net reduction in the tissue concentration of serotonin, dopamine, norepinephrine, and epinephrine. Methyldopa reduces both supine and standing blood pressure. It usually produces highly effective lowering of the supine pressure with infrequent symptomatic postural hypotension. Exercise hypotension and diurnal blood pressure variations rarely occur. Methyldopa is extensively metabolized. The known urinary metabolites are: α-methyldopa mono-*0*-sulfate; 3-*0*-methyl-α-methyldopa; 3,4-dihydroxyphenylacetone; α-methyldopamine; 3-*0*-methyl- α -methyldopamine and their conjugates. Structurally methyldopa (**2**) is an interesting molecule to synthesize as it contains a quaternary chiral amine center.

4.1.3 Review of Literature

Literature search reveals that there are some reports available for the syntheses of L-α-methyldopa (**2**), which are described below.

Reinhold's Approach (1968)[3]

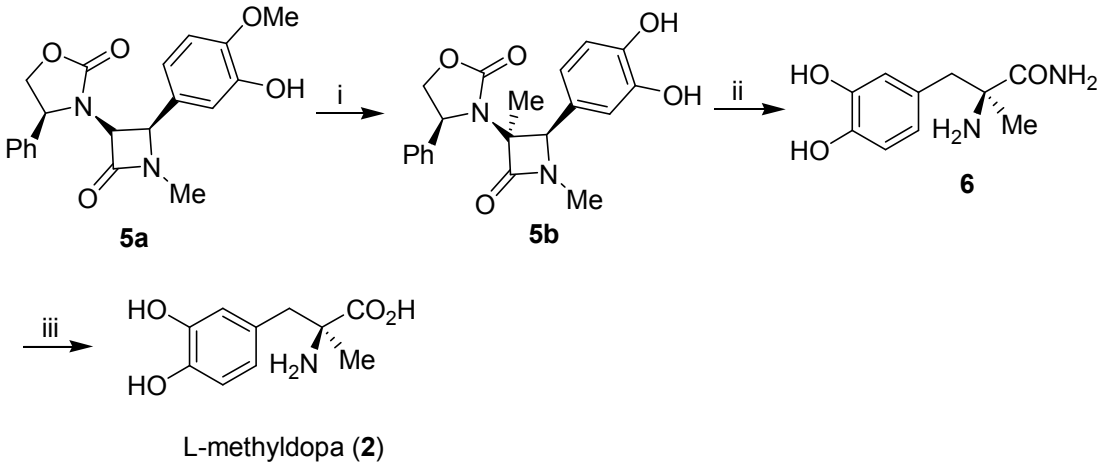
Reinhold *et al*. have reported the synthesis of L-α-methyldopa (**2**) by classical resolution of α-amino nitrile **4** using camphorsulfonic acid. This was followed by acid hydrolysis and demethylation to give L-α-methyldopa (**2**).



Scheme 1: (i) NH_4OH, KCN, 4 h, 89%; (ii) L-camphorsulfonic acid, 5 °C, 16 h; (iii) dioxan, 25 °C, 90 h; (iv) Con. HCl, 130 °C, 5 h .

Ojima's Approach (1995)[4]

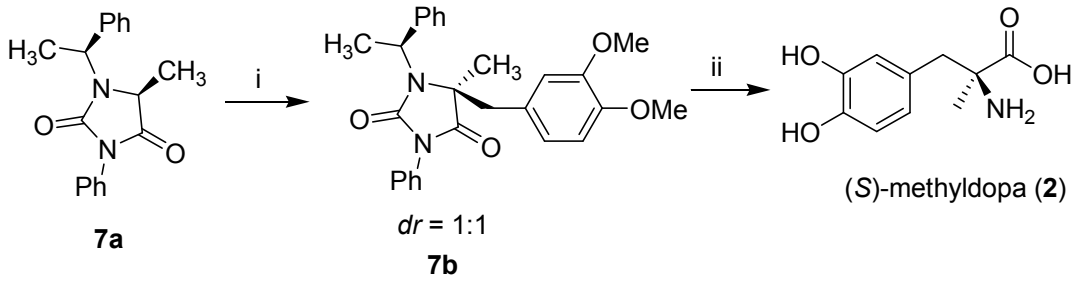
Ojima *et al*. have reported the synthesis of methyldopa (**2**) using asymmetric alkylation of β-lactam. Accordingly, diastereoselective methylation of chiral lactam **5a** was carried out with LiHMDS and methyl iodide in 95% yield and 99.5 % de. The 3-methyl-β-lactum **5b** thus obtained, was subjected to Birch reduction to give the corresponding α-methyl amide **6** in excellent yield. Finally, hydrolysis of amide to acid with 6N HCl gave L-α-methyldopa (**2**) in good yield.



Scheme 2: (i) LiHMDS, THF, -78 °C, 1 h followed by MeI, overnight, 95%; (ii) lithium, *t*-BuOH, THF, -78 °C, 7 min.; (iii) 6N HCl, THF, 110 °C.

Juaristi's approach (2002)[5]

Recetly, Juaristi *et al*. have synthesized L-α-methyldopa (**2**) from chiral hydantoin **7a** by alkylation (*dr* = 1:1) followed by diastereomeric separation to give **7b**. Hydrolysis of hydantoin **7b** with 57% HI afforded **2** in 89% yield.



Scheme 3: (i) LDA, THF, -78 °C followed by 3,4-dimethoxybenzyl chloride, 95%; (ii) 57% HI, 120 °C, 48 h, 89%.

4.1.4 Present Work

4.1.4.1 Objective

In literature, only few methods are available for the asymmetric synthesis of L-methyldopa (**2**). One of the methods uses resolution approach for the induction of chirality into the molecule while other methods employ diastereoselective alkylation as a key step. We have carried out asymmetric synthesis of L-methyldopa (**2**) using proline-catalyzed α-amination[6] of the corresponding α-methyl aldehyde **8**. The retrosynthetic analysis for L-methyldopa **2** shows that aldehyde **8** could turn out to be an important intermediate which can be subjected to D-proline-catalyzed α-amination. Aldehyde **8** in turn can be synthesized from the corresponding ester, **9**.

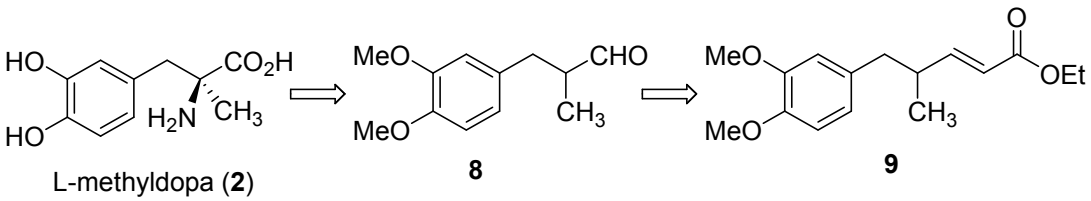
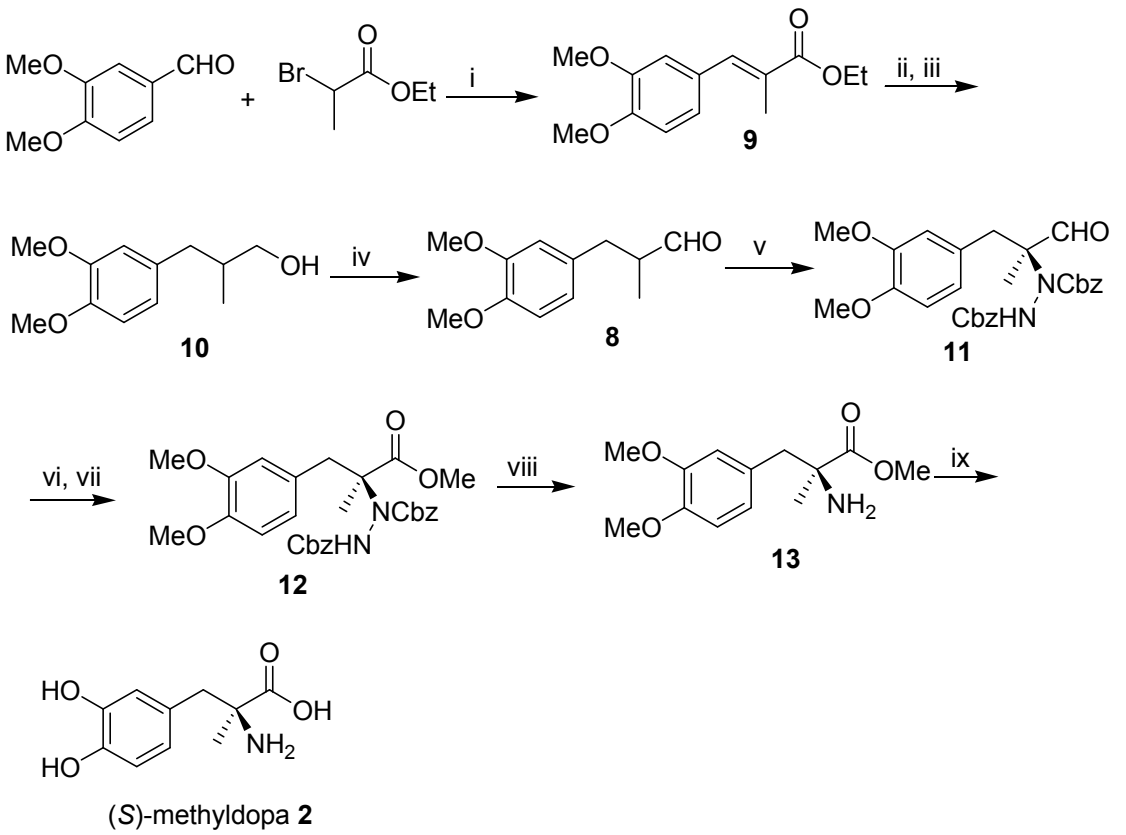


Fig. 1: Retrosynthetic analysis for L-α-methyldopa (2)

4.1.5 Results and Discussions:

We have envisaged D-proline-catalyzed α-amination[6] of aldehyde **8** for the synthesis of (*S*)-α-methyldopa (**2**) as shown in **Scheme 4**.



Scheme 4: Reagents and conditions: (i) (a) Zn, C_6H_6, reflux; (b) cat PTSA, C_6H_6, reflux, 93% for two steps; (ii) cat. Pd/C, CH_3OH, H_2 (1atm); (iii) $LiAlH_4$, THF, 25 °C, 12 h, 85%.; (iv) IBX, DMSO, 30 min., 80%; (v) DBAD, D-Proline, CH_3CN, 10 °C, 30 h, 90%; (vi) $NaClO_2$, NaH_2PO_4, DMSO; (vii) diazomethane, CH_2Cl_2, 1 h, 82% (over two steps); (viii) Raney-Ni, H_2 (60 psi), MeOH, 20 h, 70%; (ix) BBr_3, CH_2Cl_2, 60%.

The synthesis started with Reformatsky reaction of 3,4-dimethoxybenzaldehyde with α-bromo propionate followed by elimination with *p*-TSA to furnish ester **9** in 93% yield. The ^{1}H NMR spectrum of **9** showed characteristic signals at δ 3.90 (s), 3.91 (s) and 7.33 (s) corresponding to two methoxy groups (O**CH$_3$**) and an olefinic proton respectively (**Fig. 2**).

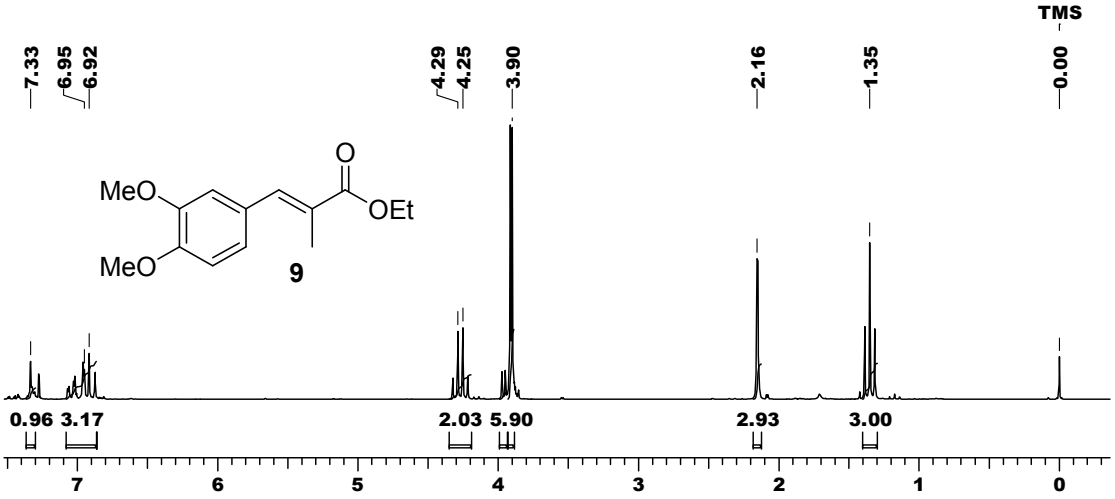


Fig. 2: ^{1}H NMR spectrum of ester 9

The C=C bond in ester **9** was hydrogenated over (10% Pd/C, H_2) and the resulting saturated ester was subjected to reduction with lithium aluminium hydride to give alcohol **10** in 85% yield. The disappearance of signals at δ 1.35 (s) and at 7.33 (s) in the ^{1}H NMR spectrum of **10** confirms the reduction of ester function as well as olefin moiety (**Fig. 3**).

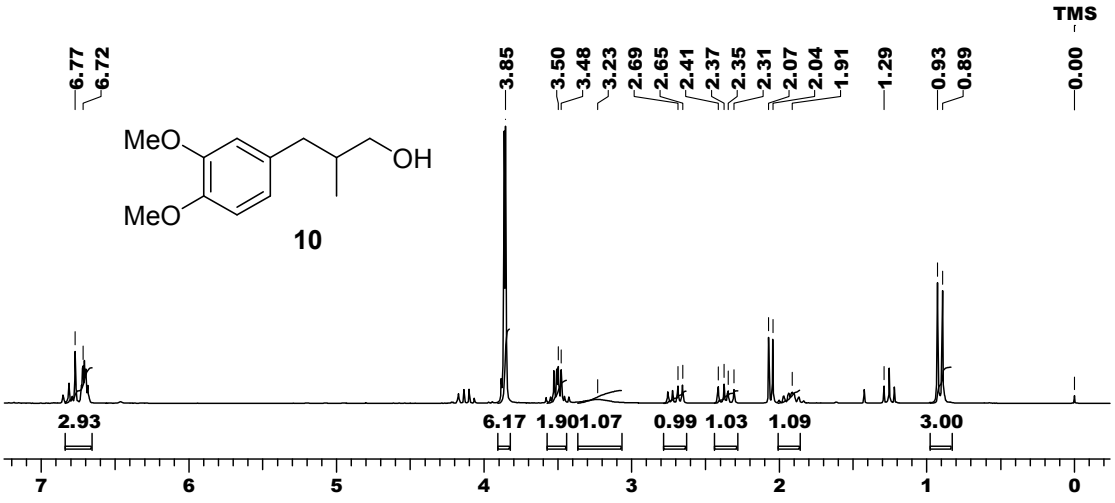


Fig. 3: ^{1}H NMR spectrum of alcohol 10

Alcohol **10** was oxidized with IBX in DMSO to give the corresponding aldehyde **8**, which on α-amination[6] with D-proline and DBAD in CH_3CN at 10 °C furnished aldehyde **11** in 80% yield, $[\alpha]^{25}_D$ -43.42 (*c* 1, $CHCl_3$). The ^1H NMR spectrum of **11** showed signals at δ 5.10 (m), and 9.70 (s) corresponding to benzylic and the aldehydic protons respectively. Its ^{13}C NMR spectrum showed signals at δ 55.3, 55.4 and 198.4 corresponding to methoxy and aldehyde carbons respectively (**Fig. 4**).

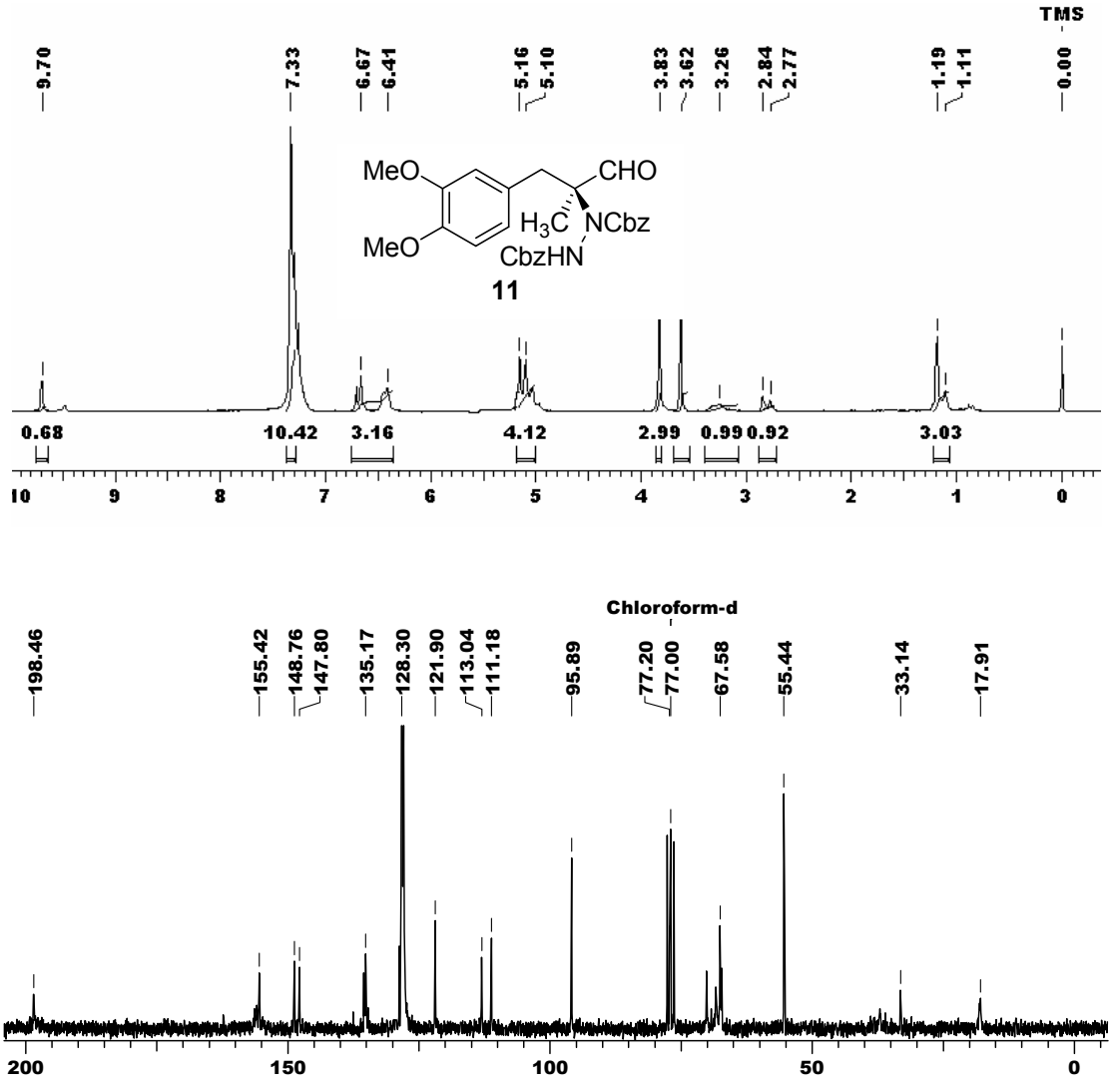


Fig. 4: ^1H and ^{13}C NMR spectra of aldehyde 11

Aldehyde **11** on oxidation with $NaClO_2$ followed by its treatment with diazomethane gave ester **12** in 82% yield. The ^1H NMR spectrum of **12** showed signals at δ 2.89 (d), 3.29 (d) and 5.97 (brs) corresponding to benzylic and **NH**Cbz protons. Its ^{13}C NMR spectrum showed signals at δ 51.7 and 172.0 corresponding to methoxy carbon of ester and ester carbonyl carbon respectively (**Fig. 5**), $[\alpha]^{25}_D$ -77 (*c* 1, $CHCl_3$).

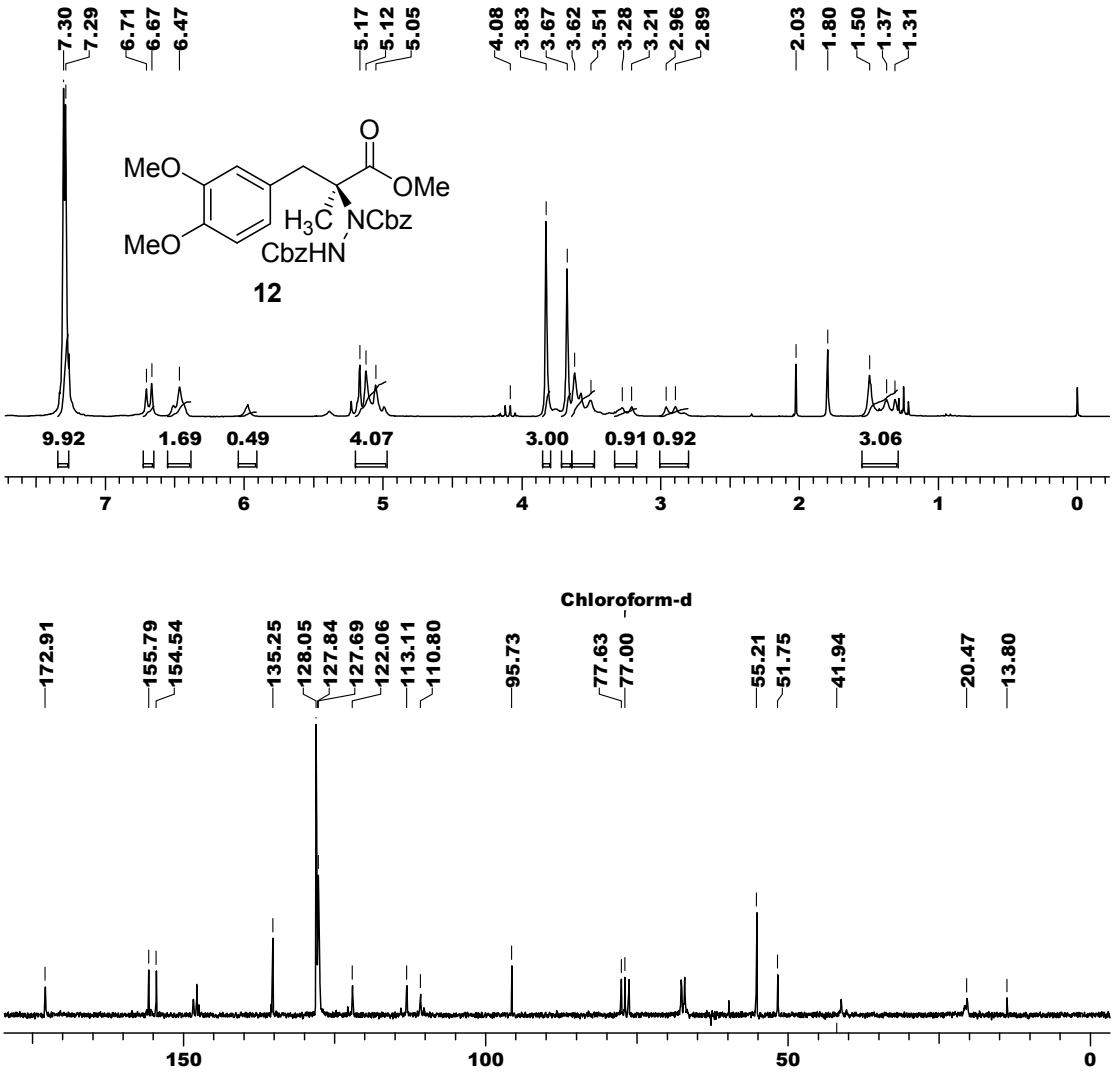


Fig. 5: ^1H and ^{13}CNMR spectra of ester 12

Reductive removal of both Cbz groups as well as *N*-*N* bond cleavage were achieved with Raney-Nickel[7] (H_2, 60 psig) to give the corresponding amine **13** in 70% yield; $[\alpha]^{25}_D$ -18.5 (*c* 1, $CHCl_3$).

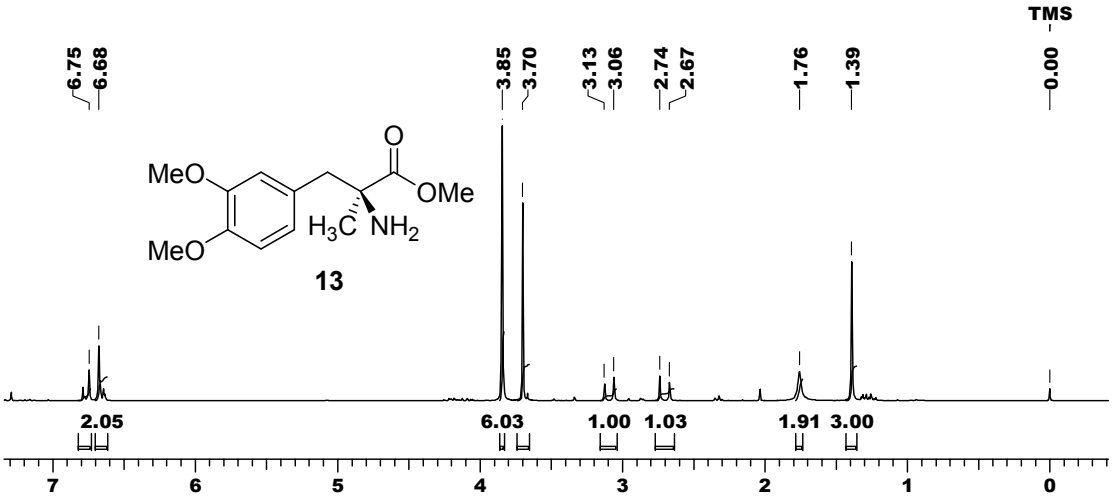


Fig. 6: ^{1}H NMR spectrum of amine 13

The disappearance of signals at δ 5.12 (m) in the ^{1}H NMR spectrum of **13** confirms the deprotection of Cbz groups (**Fig. 6**).

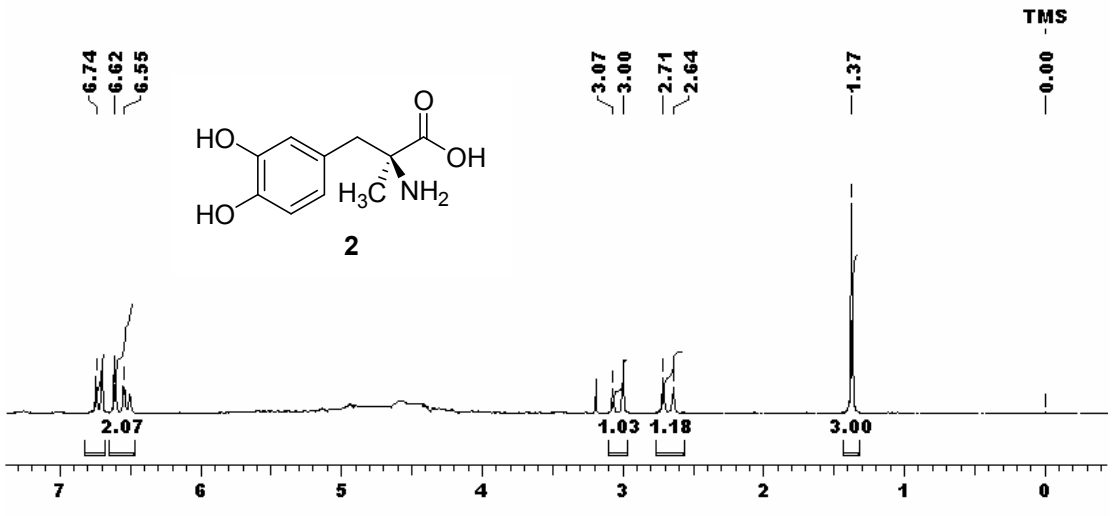


Fig. 6: ^{1}H NMR spectrum of (*S*)-α-Methyldopa (2)

Finally, universal demethylation of **13** with BBr_3 at 0-25 °C furnished (*S*)-α-methyldopa (**2**) in 60% yield (**Scheme 4**). The ^{1}H NMR spectrum of (*S*)-α-methyldopa **2** showed typical signals at δ 1.37 (s), 2.64 (d), and 3.00 (d) corresponding to the methyl group at quaternary carbon and two benzylic protons respectively (**Fig. 6**).

4.1.6 Conclusion

In conclusion, we have achieved the synthesis of (*S*)-α-methyldopa (**2**) *via* D-proline-catalyzed α-amination approach. The operationally simple reactions are rapid, and require a relatively low amount of an inexpensive and nontoxic proline-catalyst. Excellent yields, simple and environment-friendly procedures and easy availability of starting materials are some of the merits of this synthesis.

4.1.7 Experimental Section

Ethyl 3-(3,4-dimethoxyphenyl)-2-methylacrylate (9):

To a mixture of zinc (7.8 g, 120 mmol) and 3,4- dimethoxy benzaldehyde (10 g, 60.2 mmol) in dry benzene (100 mL) was added ethyl 2-bromopropionate (13 g, 9.32 mL, 72 mmol). The reaction mixture was refluxed for 12 h, cooled to room temperature, quenched with ice-cold dil. HCl (50 mL) and extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine (50 mL) and removed under reduced pressure. The crude product was refluxed with catalytic *p*-TSA (0.6 g) in benzene using Dean-Stark apparatus for 24 h. Then reaction mixture was cooled to room temperature and crude product was isolated by extraction and purified by column chromatography using ethyl acetate and petroleum ether as eluents.

Yield: 14 g, 93%, Colorless oil; **IR** ($CHCl_3$) ν_{max} 2980, 2959, 2837, 2363, 1703, 1628, 1599, 1464, 1366, 1248, 1142, 1026, 945, 754 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.35

(t, J = 7.1 Hz, 3H); 2.15 (d, J = 1.4 Hz, 3H); 3.90 (s, 3H); 3.91(s, 3H); 4.25 (q, J =7.1 Hz, 2H); 6.83-7.02 (m, 3H); 7.33 (s, 1H); **^{13}C NMR (**50 MHz, $CDCl_3$**):** δ 13.8, 14.0, 55.5, 60.4, 110.6, 112.7, 122.8, 126.3, 128.5, 138.2, 148.4, 149.0, 168.4; **GCMS** (m/z, %RI) 283(M^+), 250 (base peak), 236, 221, 205, 191, 176, 161, 146, 131, 115, 103, 91, 77, 65, 44.

3-(3, 4-Dimethoxyphenyl)-2-methylpropan-1-ol (10):

To a solution of ester **9** (10 g, 40 mmol) in 50 mL methanol was added catalytic 10% Pd/C (0.8g). The reaction mixture was stirred for 12 h under hydrogen atmosphere (1 atm.) and then it was filtered through celite pad. Solvents were removed under reduced pressure and the crude product was directly subjected to reduction with lithium aluminium hydride (3.8 g, 100 mmol) in dry THF (80 mL). The reaction was quenched with aq. NaOH (3 mL) and water (100 mL) followed by extraction with ethyl acetate (3 × 100 mL) gave crude product. Purification by column chromatography gave pure alcohol **10**.

Yield: 7.14 g, 85%, gum; **IR** ($CHCl_3$) ν_{max} 3510, 3394, 2929, 2594, 2059, 1737, 1589, 1514, 1263, 1155, 1027, 860, 765 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.89-0.93 (d, J = 6.7 Hz, 3H); 1.91 (m, 1H); 2.35 (dd, J = 8.0, 13.5 Hz, 1H); 2.65 (dd, J = 6.2, 13.5 Hz, 1H); 3.23 (brs, 1H), 3.48 (m, 2H); 3.85 (s, 3H), 3.86 (s, 3H), 6.72-6.77 (m, 3H); **^{13}C NMR (**50 MHz, $CDCl_3$**):** δ 16.22, 37.55, 39.00, 55.54, 67.01, 95.86, 111.02, 112.29, 120.83, 133.06, 146.95, 148.50; **Analysis: $C_{12}H_{18}O_3$** required C, 68.54; H, 8.63; found C, 68.55; H, 8.55.

3-(3, 4-Dimethoxyphenyl)-2-methylpropanal (8):

To a solution of alcohol **10** (5 g, 23.8 mmol) in DMSO (39 mL) was added IBX (13.28 g, 47.6 mmol) and the reaction mixture was allowed to stirr at 25 °C for 30 min. (monitored by TLC), quenched by water, filtered through sintered funnel and extracted with EtOAc (3 × 100 mL). Solvents were removed on rotavapour and the crude product was purified by column chromatography.

Yield: 4 g, 80%, Colorless oil; **IR** ($CHCl_3$) ν_{max} 3020, 2360, 1735, 1589, 1517, 1444, 1217, 1060, 1027, 756, 667 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.07 (d, *J* = 6.6 Hz, 3H); 2.59 (m, 2H); 2.96 (m, 1H); 3.84 (s, 6H); 6.67-6.79 (m, 3H), 9.69 (s, 1H); **^{13}C NMR (**50 MHz, $CDCl_3$**):** δ 13.10, 36.14, 47.94, 55.63, 95.96, 111.23, 112.14, 120.84, 131.12, 147.53, 148.8, 203.8.

(*S*)-3-(3,4-Dimethoxyphenyl)-2-(1,2-dibenzyloxycarbonylhydrazinyl)-2-methylpropanal (11):

To a solution of dibenzyldiazodicarboxylate (DBAD) (3.1 g, 9.5 mmol) and D-proline (218 mg, 20 mol%) in CH_3CN at 10 °C, aldehyde **8** (3 g, 14.3 mmol) was added and the reaction mixture was stirred at 10 ^oC for 30 h (monitored by TLC). The reaction mixture was quenched with half saturated ammonium chloride and extracted with ethyl acetate (3 × 20 mL). After removal of solvents on rotavapour, the crude product was purified by flash chromatography (Pet ether: EtOAc = 80:20).

Yield: 6.48 g, 90%, gum; **$[\alpha]^{25}_D$** -43.42 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$) ν_{max} 3020, 2360, 1735, 1598, 1017, 1404, 1217, 1027, 756, 667 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.19 (m, 3H); 2.77 (m, 1H); 3.26 (m, 1H) 3.62 (s, 3H); 3.83 (s, 3H); 5.10 (m, 4H), 6.41-6.67 (m, 3H), 7.33 (m, 10H), 9.70 (s, 1H); **^{13}C NMR (**50 MHz, $CDCl_3$**):** δ 17.91, 33.14, 55.30,

55.44, 67.58, 77.0, 77.20, 95.89, 111.18, 113.04, 121.90, 128.30, 135.17, 147.80, 148.76, 155.42, 198.46; **Analysis:** $\mathbf{C_{28}H_{30}N_2O_7}$ required C, 66.39; H, 5.97; N, 5.53 found C, 66.35; H, 5.77, N, 5.57%.

Methyl-(*S*)-3-(3,4-dimethoxyphenyl)-2-(1,2-dibenzyloxycarbonylhydrazinyl)-2-methylpropionate (12):

To a solution of 1.2 g (7.08 mmol) of 79% $NaClO_2$ in 14 mL of water was added dropwise over 2 h a stirred mixture of 3.6 g (7.08 mmol) of aldehyde **11** in 40 mL DMSO and 0.632 g of NaH_2PO_4 in 14 mL of water. The mixture was left overnight at 25 °C and then 5% aq. solution of $NaHCO_3$ was added to it. The aqueous phase was extracted three times with CH_2Cl_2 (3 × 30 mL) and then acidified with 10 M aq. HCl to give crude acid. The acid was esterified with CH_2N_2 in CH_2Cl_2 for 1 h to give ester **12** which was purified by column chromatography.

Yield: 3.2 g, 82%, gum; $\mathbf{[\alpha]^{25}_D}$ -77 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$) ν_{max} 3311, 2985, 2951, 2837, 2255, 1736, 1608, 1590, 1518, 1400, 1348, 1143, 1046, 915, 734 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.37 (m, 3H); 2.89 (d, *J* = 13.2 Hz, 1H); 3.21 (d, *J* = 13.6 Hz, 1H), 3.57 (m, 3H); 3.67 (s, 3H), 3.83 (s, 3H); 5.12 (m, 4H), 6.47 (m, 2H), 6.67 (d, *J* = 7.87 Hz, 1H), 7.29 (m, 10H); **^{13}C NMR (**50 MHz, $CDCl_3$**):** δ 13.8, 20.4, 41.2, 55.2, 67.1, 67.7, 110.8, 113.1, 122.0, 127.6, 127.8, 128.0, 135.2, 147.8, 148.4, 154.5, 155.7, 172.9; **Analysis:** $\mathbf{C_{29}H_{32}N_2O_8}$ required C, 64.91; H, 6.01; N, 5.22 found C, 64.55; H, 6.27, N, 5.17%.

(*S*)-Methyl 2-(3,4-dimethoxybenzyl)-2-aminopropanoate (13):

A solution of ester **12** (3 g, 5.59 mmol) in MeOH (30 mL) and acetic acid (10 drops) was treated with Raney nickel (5 g, excess) under H_2 (80 psig) for 24 h. The reaction mixture

was filtered over celite and concentrated to give crude aminoester **13** (purified by column chromatography using ethyl acetate as eluent).

Yield: 0.991 g, 70%, Colorless oil; **$[\alpha]^{25}_{D}$** -18.5 (*c* 1, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.39 (s, 3H); 1.76 (brs, 2H), 2.67 (d, *J* = 13.3 Hz, 1H); 3.06 (d, *J* = 13.2 Hz, 1H), 3.70 (s, 3H), 3.87 (s, 6H); 6.68 (m, 2H), 6.75 (m, 1H); **^{13}C NMR (**50 MHz, $CDCl_3$**):** δ 26.5, 46.2, 51.7, 55.5, 58.7, 111.0, 113.0, 121.8, 128.8, 147.9, 148.5, 177.2; **Analysis:** **$C_{13}H_{19}NO_4$** required C, 61.64; H, 7.56; N, 5.53 found C, 61.45; H, 7.57, N, 5.37%.

(*S*)-2-(3,4-Dihydroxybenzyl)-2-aminopropanoic acid (Methyldopa, 2):

To a solution of ester **13** (506 mg, 2 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C was added BBr_3 (2 mL, excess) and stirred for at the same temperature and 6 h at 25 °C. After completion of reaction, solvents were removed under reduced pressure and the crude product was purified by acidic ion exchange resin to give **2** in 60% yield as a white solid.

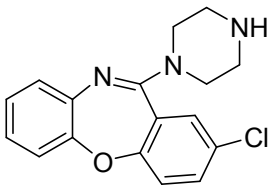
Yield: 0.253 g, 60%; **$[\alpha]^{25}_{D}$** -3.8 (*c* 1, 0.1N HCl), {lit[5] -4.0 (*c* 1, 0.1N HCl); **^{1}H NMR** (200 MHz, D_2O): δ 1.55 (s, 3H); 2.82 (d, *J* = 14.3 Hz, 1H); 3.17 (d, *J* = 14.4 Hz, 1H), 6.67 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.78 (d, *J* = 2.0 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 1H); **^{13}C NMR** (50 MHz, D_2O): δ 22.1, 42.1, 61.7, 117.1, 118.0, 122.8, 126.7, 143.5, 144.0, 172.9; **Analysis: $C_{10}H_{13}NO_4$** required C, 56.86; H, 6.20; N, 6.63 found C, 56.46; H, 6.58, N, 6.38%.

Section II:

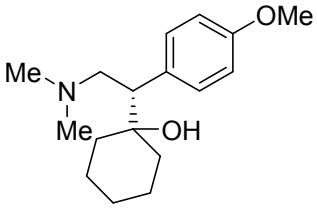
Enantioselective Synthesis of Cericlamine

4.2.1 Introduction

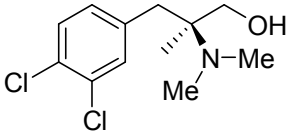
Antidepressants are generally classified into five generations. The first generation antidepressants affect various neurotransmitter systems and are therefore associated with many undesirable effects (e.g. tricyclic antidepressants, maprotiline). The second generation of antidepressants are already devoid of anticholinergic action and their adrenolytic and antihistaminic effects are weaker (e.g. mianserine, mirtazapine, trazodone). The antidepressant action of the third generation is mediated only by one of the three main neurotransmitter systems for depression (5-HT, noradrenaline, and dopamine) and does not affect muscarine, histamine and adrenergic cerebral systems (e.g. SSRI, ipsapirone, viloxazine, reboxetine, bupropione). Recently antidepressants of the fourth generation were synthesized and they influence only serotonin and noradrenaline or dopamine system (e.g. milnacipran, befloxatone). The fifth generation of antidepressants foresees the exclusive action on 5-HT, noradrenaline and dopamine systems of the CNS in varying ratios (e.g. venlafaxine **15**, cericlamine **16**).



Amoxapine **14**



(*S*)-Venlafaxine **15**



(*S*)-Cericlamine **16**

Amoxapine (**14**) and cericlamine (**16**) exert the same effects on the states of vigilance in the rat as do other antidepressants. The effects of cericlamine (**16**) on sleep probably

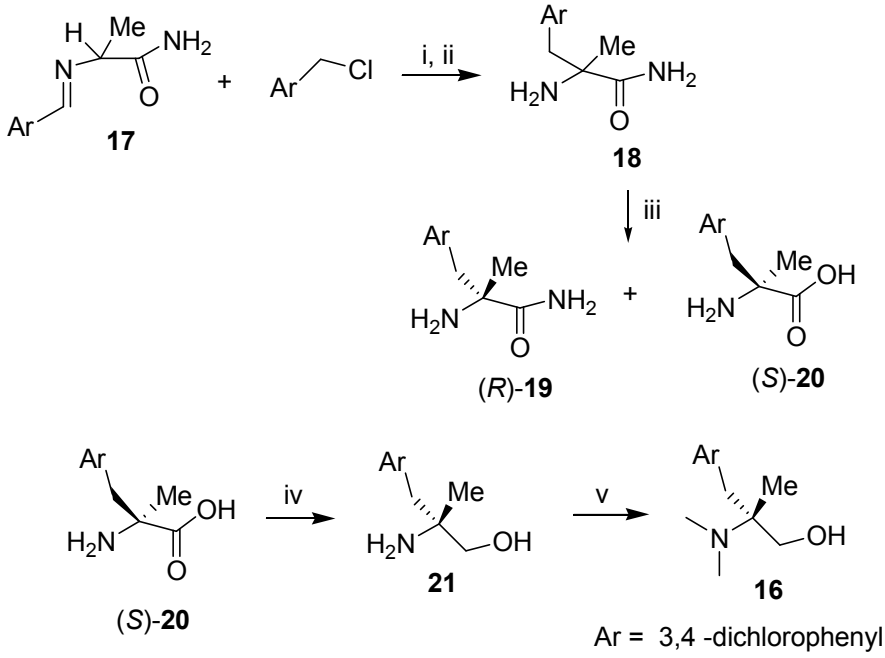
reflect its blocking action on 5-HT uptake. Ericlamine (**16**), is in clinical trials as an antidepressant.[8]

4.2.2 Review of Literature

Literature search revealed that only two reports are available for the asymmetric synthesis of (*S*)-cericlamine (**16**).

Kaptein's approach (1994)[9]

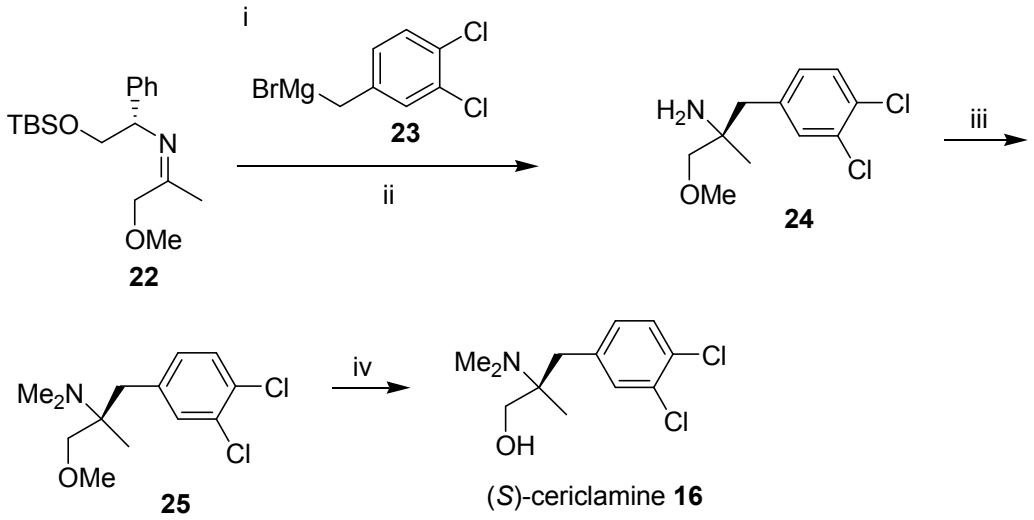
Kaptein *et. al.* have described the synthesis of cericlamine (**16**) starting from α-methyl-3,4-dichlorophenylamine. Accordingly, the phase transfer-catalyzed benzylation of *N*-benzylidenealanine amide **17** followed by acidic work up gave amide **18** in 73% yield. Amide **18** was resolved with *Ochrobactrum anthropi* at pH 5.3 to furnish chiral amide **19** and chiral acid **20** in 93% ee. Reduction of the acid **20** with $NaBH_4$-H_2SO_4 followed by methylation with formaldehyde gave cericlamine (**16**) in 80% yield (**Scheme 5**).



Scheme 5: (i) NaOH (10 mL), CH_2Cl_2, phase-transfer catalysis; (ii) HCl; (iii) amidase from *Ochrobactrum anthropi,* pH *5.3,* 40 °C; (iv) $NaBH_4$, H_2SO_4; (v) HCHO, HCO_2H, 80%.

Spero's approach (1999)[10]

Spero *et al*. have reported the synthesis of cericlamine (**16**) starting from phenylglycinol derivative **22**. Thus diastereoselective Grignard addition of 3,4-dichlorobenzyl magnesium bromide (**23**) onto **22** (95% de) followed by oxidative cleavage with $Pb(OAc)_4$ gave **24** in 73% yield. Dimethylation of **24** with formic acid/formaldehyde gave the amine **25** in 89% yield. Cleavage of the methyl ether with BBr_3 (67%) yielded (*S*)-cericlamine (**16**) in 67% yield (**Scheme 6**).



Scheme 6: (i) **23**, CH_2Cl_2, 12 h, 67%; (ii) 2% HCl, EtOH then $Pb(OAc)_4$, 73%; (iii) aq. HCHO, HCO_2H, reflux, 3 h, 89%; (iv) BBr_3, CH_2Cl_2, 0-20 °C, 6 h, 67%.

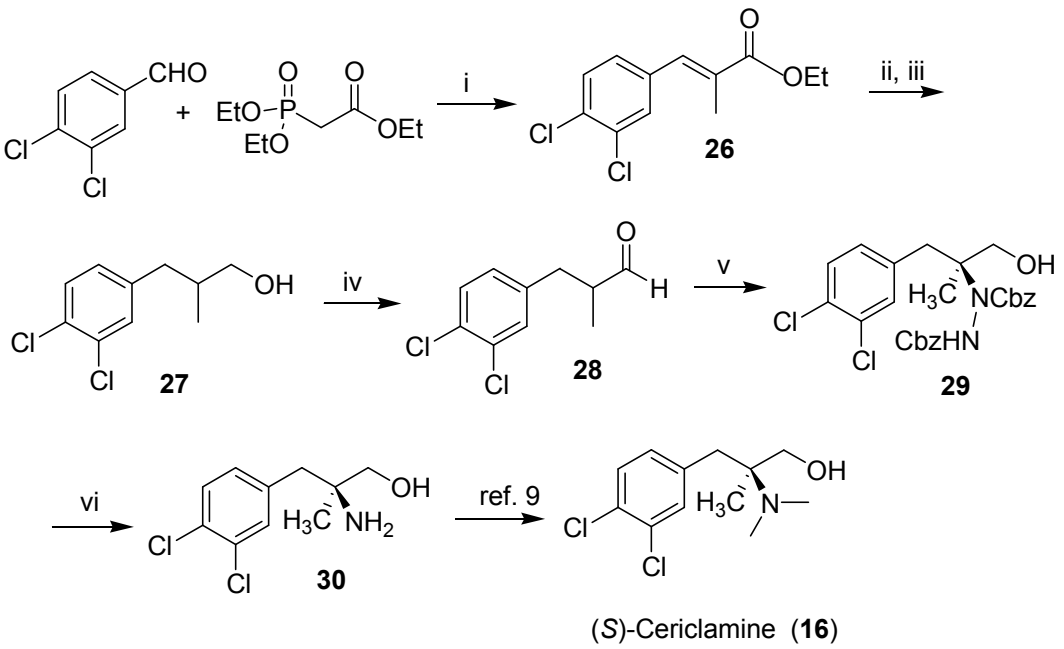
4.2.3 Present Work

4.2.3.1 Objective

In literature only few methods are available for the asymmetric synthesis of (*S*)-cericlamine (**16**). These methods either use resolution or chiral auxillary approach for the asymmetric induction. We have carried out asymmetric formal synthesis of cericlamine (**16**) using proline-catalyzed α-amination[6] of the corresponding α-methyl aldehyde **28**.

4.2.4 Results and Discussions:

The synthetic sequence for the enantioselective formal synthesis of cericlamine (**16**) is presented in **Scheme 7**.



Scheme 7: (i) LiCl, DBU, CH_3CN, 12 h ; (ii) $CoCl_2.6H_2O$, $NaBH_4$, 2 h, 25 ^oC, 85% for two steps; (iii) $LiAlH_4$, THF, 12 h, 88%; (iv) IBX, DMSO, 30 min., 75%; (v) DBAD, D-Proline, CH_3CN, 25 ^oC, 48 h then MeOH, $NaBH_4$, 53%; (vi) Raney-Ni, H_2 (60 psig), MeOH, 20 h, 70%.

The synthesis was started with the preparation of ethyl-(3,4-dichloro)-α-methyl cinnamate (**26**) by carrying out Horner-Wadsworth-Emmons olefination of 3,4-dichlorobenzaldehyde with ethyl phosphonoacetate using DBU as base. The ^1H NMR spectrum of **26** showed signals at δ 2.09 (d), and 7.19 (dd) corresponding to methyl and olefinic protons (**Fig. 7**).

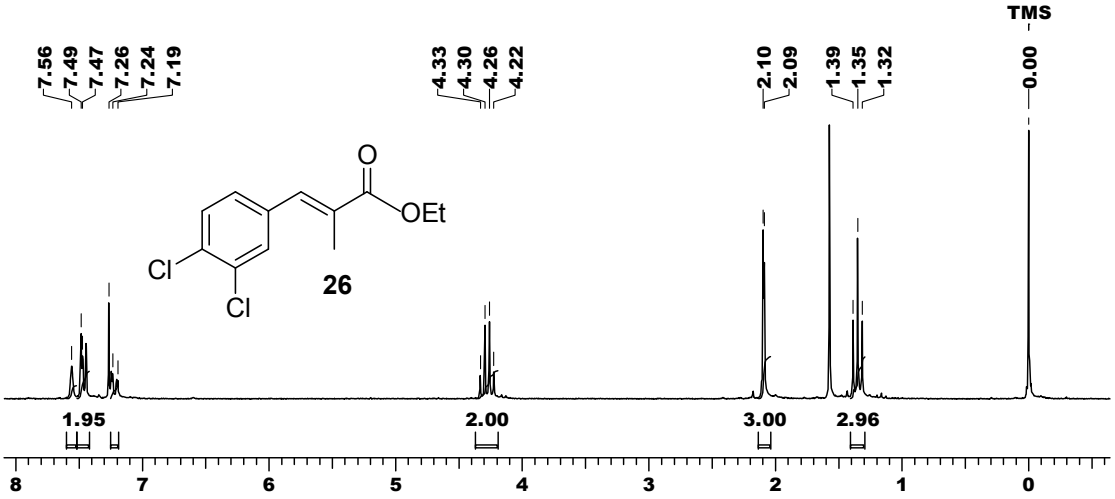


Fig. 7: ^{1}H NMR spectrum of ester 26

Reduction of both olefinic bond and ester group in ester **26** was achieved using $CoCl_2.6H_2O$-$NaBH_4$ and lithium aluminium hydride respectively to give the corresponding saturated alcohol **27** in 88% yield. Two multiplets in the ^{1}H NMR spectrum of **27** at δ 2.30 and 2.71 are due to the benzylic protons. A doublet at δ 3.47 is due to the presence of methylene group (**CH_2**OH) (**Fig. 8**).

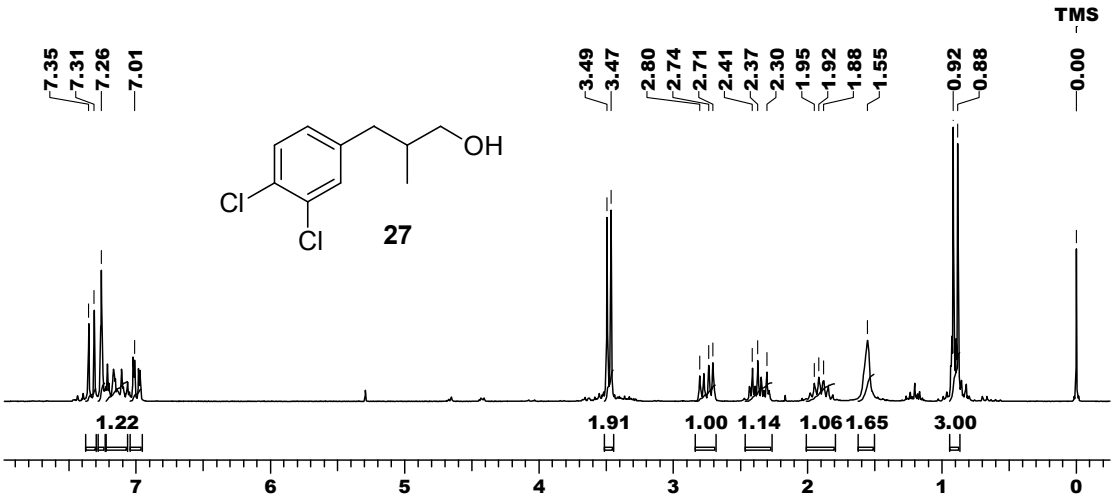


Fig. 8: ^{1}H NMR spectrum of alcohol 27

Oxidation of alcohol **27** to aldehyde **28** has been carried out using IBX in DMSO. α-Methyl aldehyde **27** in hand, we tried α-amination[6] of it using D-proline and DBAD as nitrogen source in CH_3CN at 0 ^oC -25 ^oC for 3 h. However, no reaction took place. Interestingly, increasing the reaction time to 48 h gave α-amination product **29** (after reduction with $NaBH_4$) in 53% yield. The ^1H NMR spectrum of **29** showed signals at δ 2.79 (dd), 3.90 (d) and 4.27 (d) corresponding to benzylic and methylene protons (**CH_2**OH). A multiplet at 5.15 is due to two benzylic groups of Cbz moieties (**Fig. 9**).

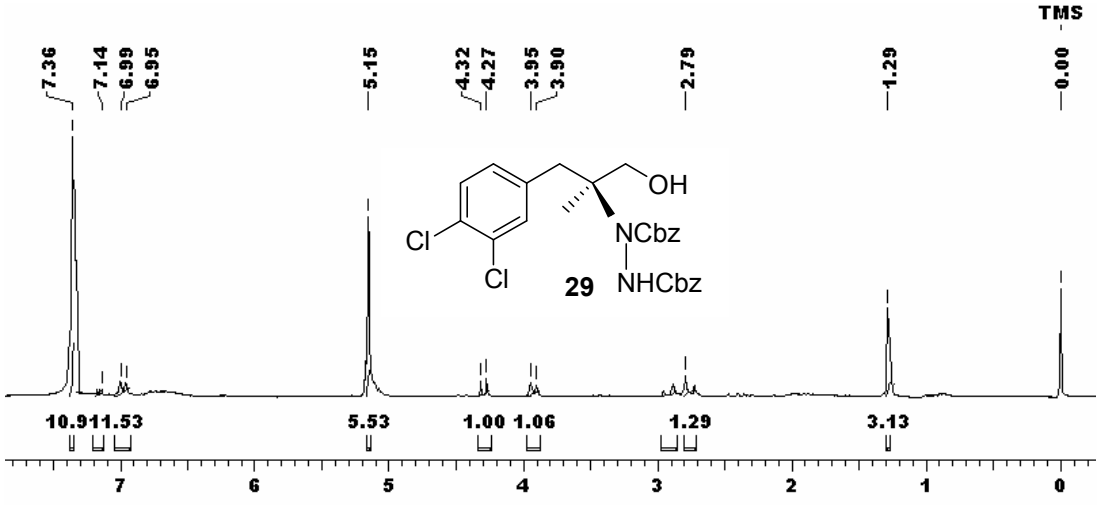


Fig. 9: ^1H NMR spectrum of alcohol 29

Protected amino alcohol was hydrogenated by Raney Ni[7] to amine **30** in 70% yield, which is direct precursor for the synthesis of (*S*)-cericlamine (**16**) [9] (**Scheme 7**) in 85% yield. The spectral data of **30** are in complete agreement with the literature values. Synthesis of (*S*)-cericlamine (**16**) has already been reported from intermediate **30**.[9]

4.2.5 Conclusion

In conclusion, we have achieved the formal synthesis of (*S*)-cericlamine (**16**), a potent antidepressant drug, *via* D-proline-catalyzed for α-amination approach. Good yields,

simple and environment friendly procedures, easy availability of starting materials and use of proline as catalyst render our approach a good alternative to known methods.

4.2.6 Experimental Section

4-(3,4-dichlorophenyl)-3-methylbut-3-en-2-one (26):

To a solution of 3,4-dichlorobenzaldehyde (6 g, 39.9 mmol) in CH_3CN (60 mL) at 0 °C was added phosphonate ester (8.4 mL , 44.8 mmol) in CH_3CN (80 mL) followed by LiCl (2 g, 44.8 mmol) and DBU (7 mL, 44.8mmol). The reaction mixture was stirred overnight. After completion of reaction (TLC), it was quenched with ammonium chloride solution, extracted with ethyl acetate (3 × 50 mL), washed with brine and dried over anhydrous sodium sulphate. After removal of solvents on rotavapour the crude product was purified by flash chromatography; (Pet ether: EtOAc = 80:20).

Yield: 8.3 g, 85%, Colorless oil; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.35 (t, *J* = 7.1 Hz, 3H), 2.1 (d, *J* = 1.5 Hz, 3H), 4.26 (q, *J* = 7.0 Hz, 2H), 7.19 (dd, *J* = 1.8 Hz, 1H), 7.44 (m, 2H), 7.36(s, 1H). **^{13}C NMR** (200 MHz, $CDCl_3$): 14.0, 14.2, 61.1, 128.7, 130.4, 131.4, 131.1, 132.2, 132.5, 135.9, 168.0; **Analysis**: **$C_{13}H_{15}Cl_2O_2$** requires C, 56.95; H, 5.51; found C, 56.85; H, 5.89%;

Ethyl 2-(3,4-dichlorobenzyl)propanoate:

To a solution of ester **26** (5 g, 19.37 mmol) and $CoCl_2.6H_2O$ (0.459 g, 10 wt %) in methanol (50 mL) was added $NaBH_4$ (2 g, 58.1 mmol) in portions with stirring at 20 °C . Evolution of H_2 gas was observed and then black precipitate appeared during the addition of $NaBH_4$. When the addition was complete, stirring was continued for 1 h at 25 °C. After completion of reaction, the mixture was cooled and pored into water and extracted with ethyl acetate (3 × 50 mL). The collected organic layers were washed with water (3 ×

50 mL), brine (50 mL) and dried over anhydrous Na_2SO_4. The organic layers were evaporated under reduced pressure. The crude product was purified by column chromatography (pet ether: EtOAc = 80:20).

Yield: 4.5 g, 90%, Colorless oil; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.18 (m, 6H), 2.66 (m, 2H), 2.94 (m, 1H), 4.01 (q, *J* = 7.1 Hz, 2H), 6.97 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.25 (m, 1H), 7.35 (m, 1H); **^{13}C NMR** (200 MHz, $CDCl_3$): δ 13.8, 16.6, 38.4, 40.8, 60.0, 128.0, 129.9, 130.6, 131.9, 139.3, 174.8; **Analysis**: **$C_{13}H_{17}Cl_2O2$** requires C, 56.54; H, 6.20; found C, 56.48, H 6.66%.

3-(3,4-dichlorophenyl)-2-methylpropan-1-ol (27):

To a solution of $LiAlH_4$ (0.809 g, 30.76 mmol) in THF at 0 ^oC was added ethyl 2-(3,4-dichlorobenzyl) propanoate (4 g, 15.38 mmol) and the reaction mixture was stirred at 25 °C for 12 h. After completion of reaction (TLC), it was quenched with water and the slurry was filtered through sintered funnel. Solvents were removed on rotavapour. Crude product was purified by column chromatography (Pet ether: Ethyl acetate = 70: 30).

Yield: 2.95 g, 88%, Colorless oil; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.88 (d, *J* = 6.7 Hz, 3H), 1.55 (brs, 1H), 1.92 (m, 1H), 2.37 (m, 1H), 2.74 (dd, *J* = 13.5, 6.2 Hz, 1H), 3.47 (d, *J* = 1.91 Hz, 2H), 7.01 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.16 (m, 1H), 7.31 (d, *J* = 8.2 Hz, 1H); **^{13}C NMR** (200 MHz, $CDCl_3$): δ 16.2, 37.5, 38.6, 67.0, 96.15, 128.5, 130.1, 131.0, 132.1, 140.9; **Analysis**: **$C_{10}H_{12}Cl_2O$** requires C, 54.82; H, 5.52; found C, 54.58; H 5.35%.

3-(3,4-Dichlorophenyl)-2-methylpropanal (28):

To a solution of alcohol **27** (2 g, 9.17 mmol) in DMSO (17 mL) was added IBX (5.58 g, 18.26 mmol) and the reaction mixture was allowed to stirr at 25 °C for 50 min. (monitored by TLC), quenched by water and filtered through sintered funnel. Extracted

with ethyl acetate (3 × 25 mL), washed with brine and dried over anhydrous sodium sulphate. Solvents were removed on rotavapour to give **28**, which was directly subjected to α-amination in the next step.

Yield: 1.48 g, 75 %.

(*S*)-3-(3,4-Dichlorophenyl)-2-(1,2-dibenzyloxycarbonylhydrazinyl)-2-methylpropanol (29):

To a solution of dibenzyldiazodicarboxylate (DBAD, 90%) (3.1 g, 9.5 mmol) and D-proline (218 mg, 20 mol%) in CH_3CN at 10 ^oC, aldehyde **28** (3 g, 14.3 mmol) was added and the reaction mixture was stirred at 25 ^oC for 48 h (monitored by TLC). After the reaction mixture became colorless, it was cooled to 0 ºC, treated with EtOH (15 mL) and $NaBH_4$ (0.5 g, excess) and stirred for 10 min. at 0 ºC. The reaction mixture was worked up by adding half-concentrated aq. ammonium chloride solution and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product **29** was purified by silica gel column chromatography (Pet ether: ethyl acetate = 85:15).

Yield: 2.5 g, 53%, gum; **IR** (nujol) ν_{max}: 3550, 3261, 2954, 2875, 1720, 1681, 1537, 1456, 1377, 1263, 1062; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.28 (s, 3H), 2.79 (dd, *J* = 13.6, 14 Hz, 2H), 3.90 (d, *J* = 8.8 Hz, 1H), 4.27 (d, *J* = 8.83 Hz, 1H), 5.15 (m, 5H), 6.96 (m, 2H), 7.14 (m, 1H), 7.33 (m, 10H). **Analysis**: **$C_{28}H_{32}Cl_2N_2O_5$** requires C, 61.43; H, 5.89; N, 5.12 found C, 61.85; H, 5.59; N, 5.66%.

(*S*)-2-amino-3-(3,4-dichlorophenyl)-2-methylpropan-1-ol (30):

Alcohol **29** (2.1 g, 4 mmol) was dissolved in MeOH (40 mL), AcOH (10 drops) and treated with Raney nickel (6.0 g, excess) for 24 h under 60 psig of hydrogen atmosphere.

The reaction mixture was filtered over celite and concentrated to give the corresponding amino alcohol **30**.

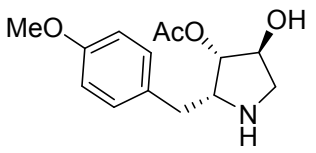
Yield: 0.627 g, 70%, gum; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.05 (s, 3H), 2.3 (brs, 2H), 2.75 (dd, *J* = 13.2, 13.3 Hz, 2H), 3.45 (dd, *J* = 8.9, 9.2 Hz, 2H), 7.1 (m, 1H), 7.75-7.88 (m, 2H). **Analysis**: **$C_{10}H_{13}Cl_2NO$** requires C, 51.30; H, 5.60 found C, 51.65; H, 5.39%.

Section III:

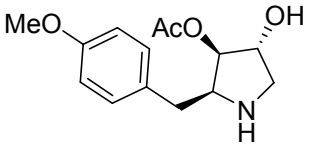
Organocatalytic Formal Synthesis of Antibiotic (-) Anisomycin

4.3.1 Introduction

The antibiotic (-) anisomycin, **39a** (Fig. **1**) isolated from the fermentation broth of *Streptomyces sp.*, exhibits strong and selective activity against pathogenic protozoa and fungi and has clinically been used with success in the treatment of vaginitis due to trichomonas vaginilis and of amoebic dysentery.[11] In addition, both anisomycin and its deacetyl derivative have been used as fungicides in the eradication of bean mildew and for the inhibition of other pathogenic fungi in plants.[12] It was also found to inhibit peptide bond formation on eukaryotic ribosomes.[13] (2*R*,3*S*,4*S*)-(-)-anisomycin (**39a**), also known as Flagecidin, inhibits protein synthesis. Partial inhibition of DNA synthesis occurs at anisomycin concentrations that effect 95% inhibition of protein synthesis. It can activate stress-activated protein kinases, MAP kinase and other signal transduction pathways. It is inactive against bacteria.



(-)-anisomycin (**39a**)



(+)-anisomycin (**39b**)

4.3.2 Pharmacology of Anisomycin

Anisomycin (**39a**) interferes with protein and DNA synthesis by inhibiting peptidyl transferase or the 80S ribosome system. It is also mentioned as a potential psychiatric drug, as it may erase "short-range memory". Injection of anisomycin into the hippocampus has been proposed for selective removal of memories. It is observed that

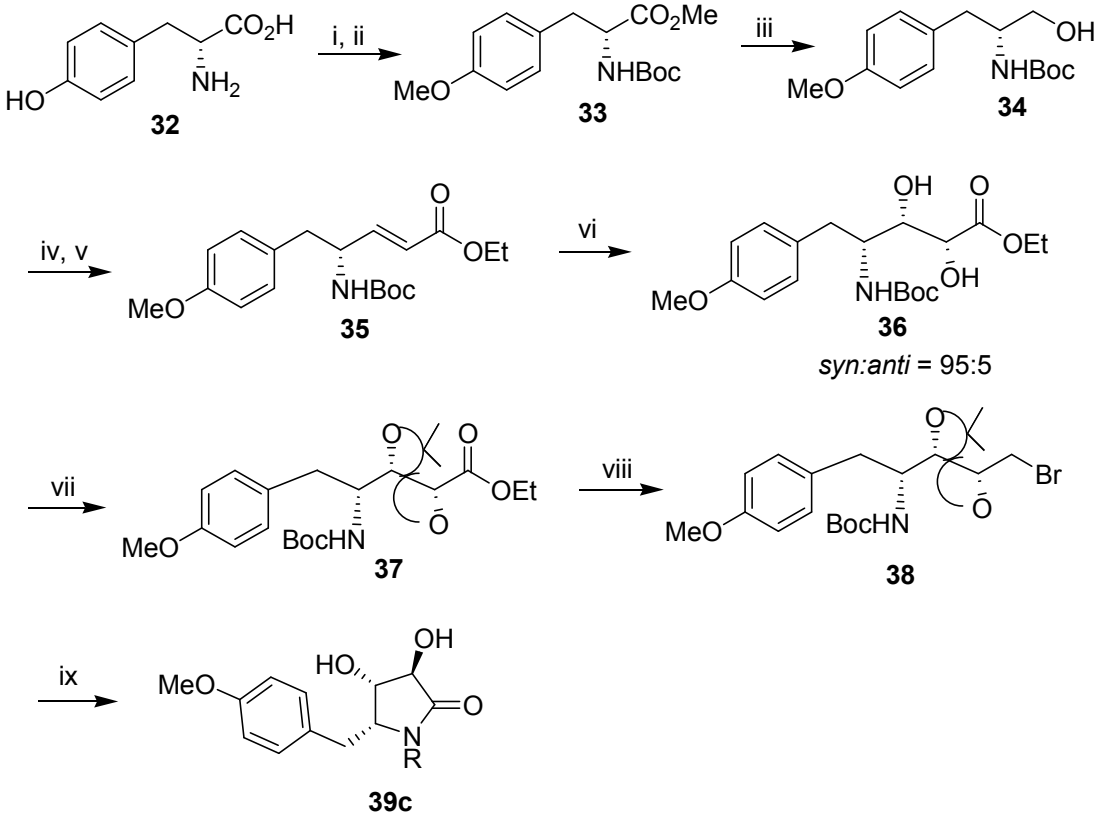
anisomycin interferes with pyrogen induced fever by acting at a site after PGE2 in the pathway to fever.

4.3.3 Review of Literature

In literature, there are many methods available for the synthesis of (-)-anisomycin (**39a**),[14] some of the recent methods are described below.

Chandrasekhar's approach (2002)[14l]

Chandrasekhar *et al*. have used diastereoselective dihydroxylation as a key step for the synthesis of (-)-deacetylanisomycin (**39c**).



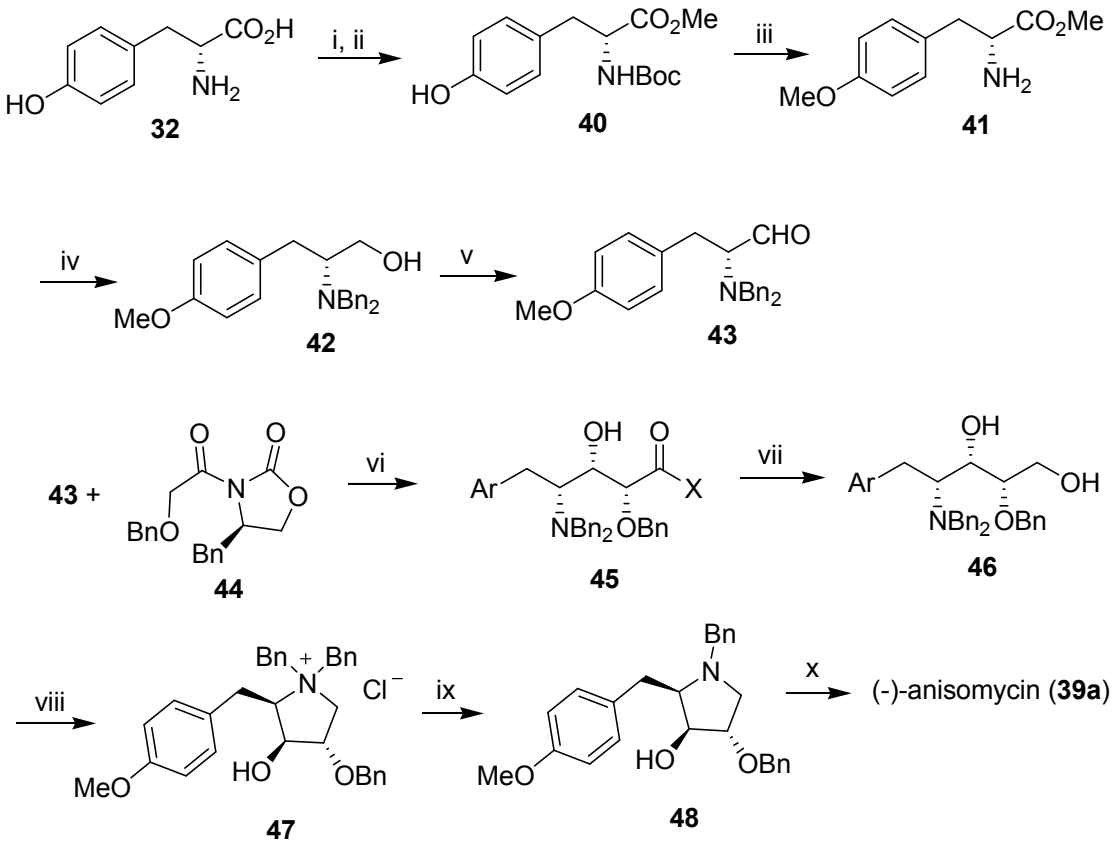
Scheme 8: (i) NaOH, dioxan, H_2O, Boc_2O, 30 min.; (ii) MeI, acetone, K_2CO_3, 8 h (70% over two steps); (iii) $LiBH_4$, Et_2O/MeOH, reflux, 5 h, 72%; (iv) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, -78 °C; (v) Ph_3P=CHCOOEt, CH_2Cl_2, 25 °C, 73%; (vi) AD-mix-α, ^tBuOH-H_2O, 18 h, 60%; (vii) 2,2-DMP, CH_2Cl_2, camphorsulfonic acid, 3 h, 72%; (viii) (a)$LiBH_4$, Et_2O/MeOH, reflux, 5 h, 68%, (b) TsCl, Py, CH_2Cl_2, 10 h, 25 °C, (c) LiBr, DMF, 10 h, 80 °C (65 % over two steps) (ix) TFA, CH_2Cl_2, 10 h, 25 °C, Et_3N, MeOH, 5 h, 25 °C, 70%.

Accordingly, compound **33** was obtained from D-tyrosine by protecting the amino functionality using di-*tert*-butyl dicarbonate, followed by methylation of the acid and phenolic hydroxyl group with MeI/K_2CO_3. Reduction of ester group in **33** with lithium borohydride furnished the alcohol **34** in 72% yield. Swern oxidation of alcohol **34** followed by Wittig olefination with (ethoxycarbonylmethylene)triphenylphosphorane in CH_2Cl_2 yielded the unsaturated ester **35**. Upon reacting the ester **35** with Sharpless asymmetric dihydroxylation conditions using AD-mix-α, the expected *syn* configured ester **36** was obtained with high stereoselectivity (*syn:anti* 95:5). Acetonide protection of diol **36** gave ester **37**. Reduction of ester **37** with $LiBH_4$ furnished alcohol which was tosylated and subsequently displaced with bromine to give **38**. Finally, Boc-deprotection with TFA and cyclisation with triethylamine gave the desired (-)-deacetylanisomycin (**39c**) in 70% yield (**Scheme 8**).

Hulme's approach (2002)[14m]

Hulme *et al*. have reported the synthesis of anisomycin (**39a**), using glycolate aldol coupling. Thus, D-tyrosine was esterified with AcCl in methanol; subsequently *N*-Boc protection gave ester **40**. The free phenolic function was then alkylated with methyl iodide followed by N-Boc deprotection gave amino ester **41** in 100% yield. Subsequent *N,N*-dibenzylation and reduction of the ester with lithium borohydride produced alcohol **42**. Swern oxidation of alcohol **42** gave aldehyde **43**. The *syn* glycolate aldol between aldehydes **43** and Evans oxazolidinone **44** was carried out using Bu_2BOTf to give **45** with 95% de. Aldol adduct **45** was readily reduced to diol **46** with lithium borohydride. Selective tosylation of the primary alcohol resulted in the formation of the pyrrolidinium tosylate salt which was converted to chloride salt **47** using Dowex resin. Then salt **47** was

subjected to hydrogenation under basic conditions to obtain the benzyl-protected pyrrolidone **48** in good yield. Acetylation followed by debenzylation gave anisomycin (**39a**) in excellent yield (**Scheme 9**).

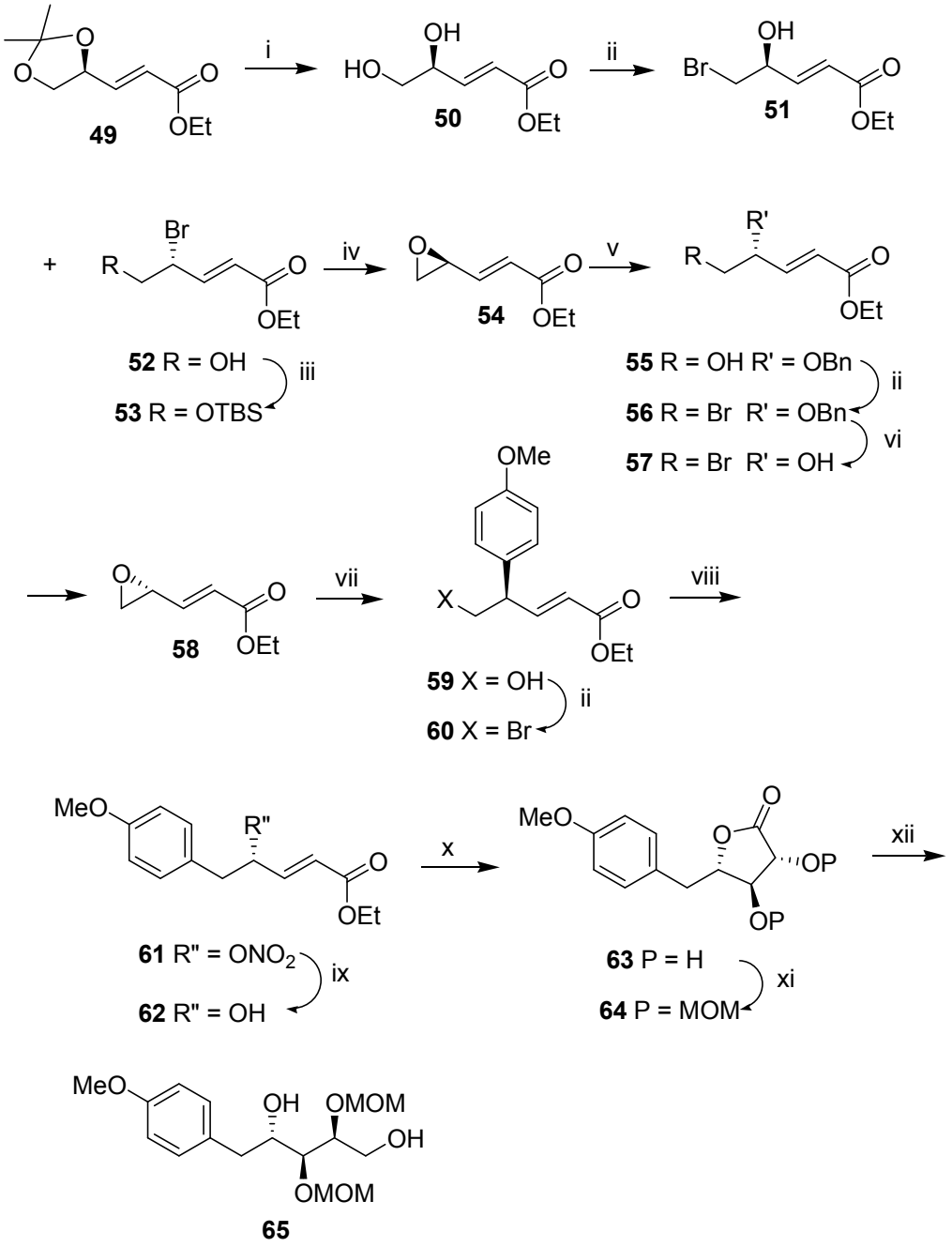


Scheme 9: (i) AcCl, MeOH, 100%; (ii) Boc_2O, $NaHCO_3$, EtOH, 99%; (iii) (a) MeI, K_2CO_3, DMF, 97%, (b) TFA, CH_2Cl_2, 100%; (iv) (a) BnBr, K_2CO_3, CH_3CN, 95%; (b) $LiBH_4$, MeOH, 87%; (v) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, -78 °C; (vi) **13**, Et_3N, Bu_2BOTf, CH_2Cl_2, 75%; (vii) $LiBH_4$, MeOH, 75%; (viii) TsCl, DMAP, CH_2Cl_2, Dowex Cl^-, 85%; (ix) Pd/C (cat.), K_2CO_3, MeOH, 10 min., 94%; (x) (a) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 92% (b) $Pd(OH)_2$, H_2, HCl, MeOH, 100%.

Akita's approach (2004)[14p]

Akita *et al*. have reported formal synthesis of anisomycin (**39a**) based on strategy involving stereoselective nucleophilic substitution and 1,2-aryl migration. Accordingly, commercially available ester **49** was deprotected using 80% aq. AcOH to afford the diol **50** in quantitative yield. Bromination of **50** with CBr_4 gave a mixture of bromohydrins **51**

and **52**. This mixture was subjected to silylation to afford the desired **51** which upon treatment with K_2CO_3 in methanol gave epoxide **54** in 85% yield.

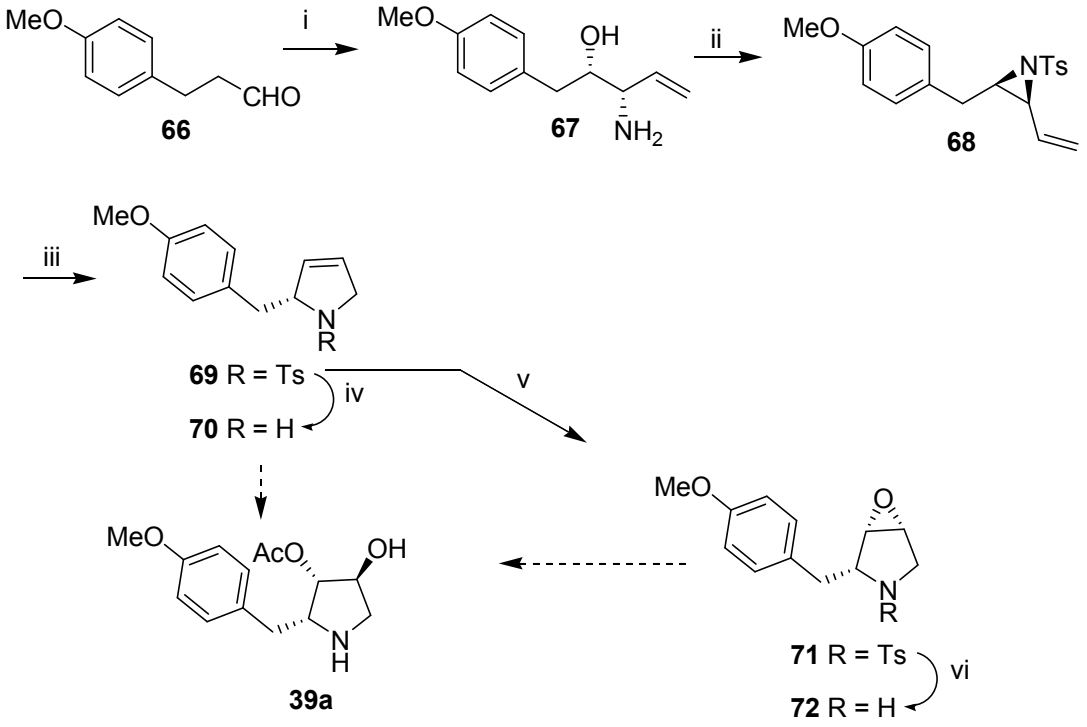


Scheme 10: (i) 80% AcOH, 30 min., 80 °C, quantitative; (ii) CBr_4, PPh_3, CH_2Cl_2, 1 h, reflux; (iii) TBSCl, imidazole, DMF, 2 h, 80 °C; (iv) K_2CO_3, MeOH, 30 min., 0 °C, 85%; (v) $PhCH_2OH$, $BF_3.Et_2O$, CH_2Cl_2, 1.5 h, 0 °C, 55%; (vi) $AlCl_3$, *m*-xylene, CH_2Cl_2, 30 min., -20 °C, 87%; (vii) anisole, $BF_3.Et_2O$, CH_2Cl_2, 1 h, -20 °C, 47%; (viii) $AgNO_3$, MS 4A°, $MeNO_2$, 91%; (ix) Zn, NH_4OAc, MeOH, 1 h, 0 °C, 87%; (x) OsO_4, NMO, acetone-H_2O, 0 °C, 2 h, 78%; (xi) MOM-Cl, diisopropylethylpylamine, CH_3CN, 24 h, 0 °C, 78%; (xii) DIBAL-H, benzene, 1 h, 0 °C, 81%.

Conversion of **54** to **58** was achieved in two steps i.e. bromination, debenzylation followed by alkaline treatment in good yield. The reaction of **58** and anisole in the presence of $BF_3.Et_2O$ followed by enzymatic separation gave **59** in 47% yield, which was converted to bromide **60** using CBr_4. Aryl migration of bromide **60** was carried out with $AgNO_3$ and MS 4 A° in nitromethane to furnish nitrate **61** in 91% yield. Nitrate **61** was converted to alcohol **62** using Zn in ammonium acetate. The Os-catalyzed dihydroxylation followed by treatment with NMO gave 3,4-*anti*-γ-lactone **63** in 78% yield with high diastereoselectivity (*anti:syn* 39:1). Treatment of **63** with chloromethyl methyl ether furnished di-MOM ether **64** in 78% yield. Reduction of **64** with DIBAL-H gave the diol **65** in 81% yield. Synthesis of anisomycin (**39a**) has already been reported from diol **65** (**Scheme 10**).

Somfai's approach (2005)[14q]

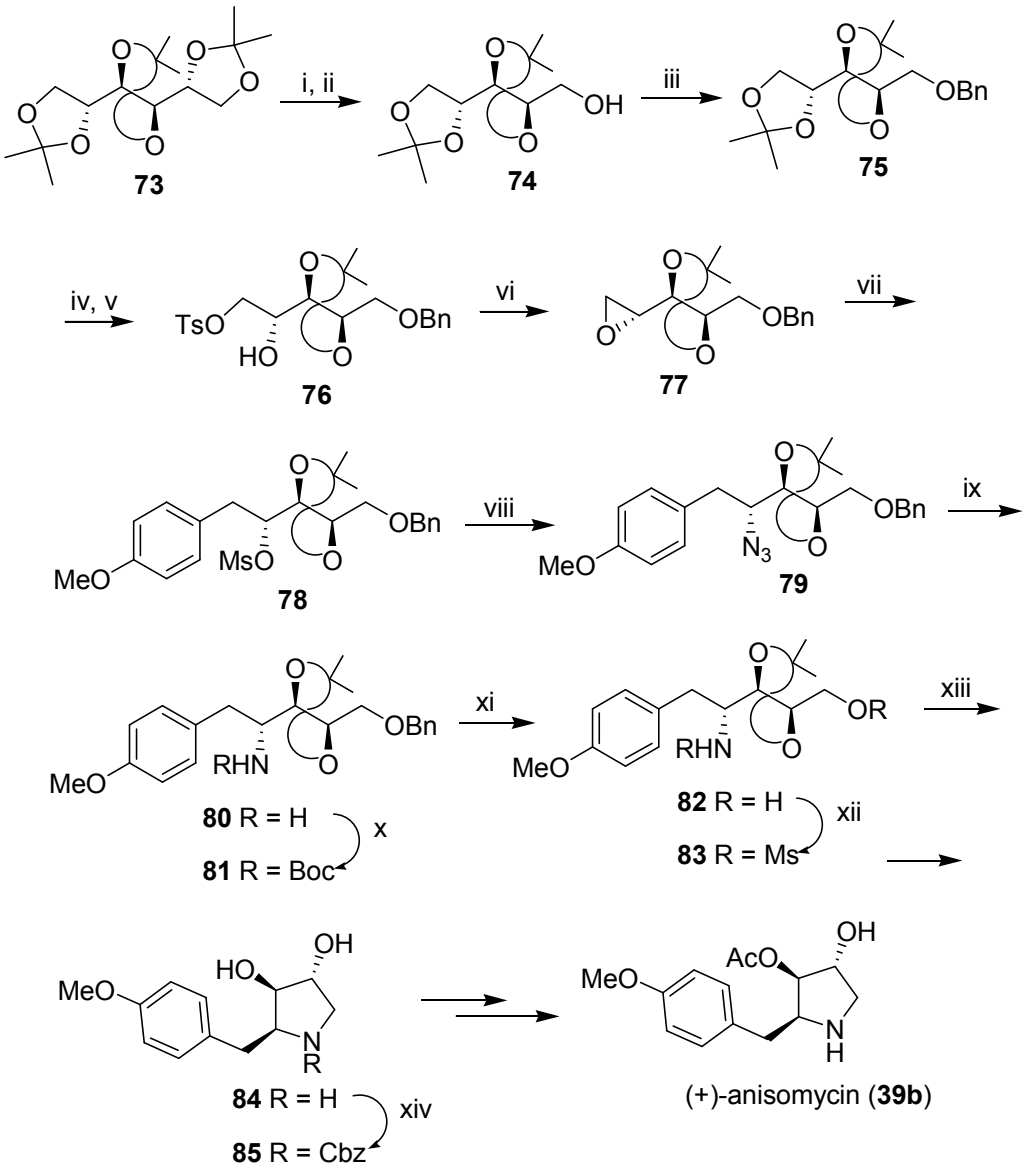
Somfai *et al*. have described a microwave-assisted rearrangement of activated vinylaziridines to 3-pyrrolines to achieve the formal synthesis of anisomycin (**39a**). Accordingly, the synthesis started with Browns allylation of commercially available aldehyde **66** and successive aminolysis of resulting chlorohydrin afforded amino alcohol **67** with excellent enantioselectivity. Tosylation and ring-closure with KOH in THF afforded *cis*-vinylaziridine **68**. Microwave-assisted rearrangement of **68** to pyrroline **69** was achieved in excellent yield. Deprotection of **69** afforded enantiopure secondary amine **70**, which is the precursor for the synthesis of anisomycin (**39a**). Alternatively, iodohydroxylation of pyrroline **69** followed by basic work up afforded epoxide **71**, which was deprotected to **72**. Synthesis of anisomycin (**39a**) has already been known from **72** (**Scheme 11**).



Scheme 11: (i) (a) allyl chloride, $LiNCy_2$, (+)-Ipc_2BOMe, $BF_3.Et_2O$, -95 °C, 6 h; (b) MeOH, NH_4OH, 130 °C, 10 min., 52% (over steps); (ii) TsCl, KOH, THF, 25 °C, 18 h, 93%; (iii) NaI, microwave, CH_3CN, 200 °C, 92%; (iv) Na, naphthalene, THF, -78°C, 84%; (v) NIS, $HClO_4$, THF-H_2O, 1 h then 25 °C, 50%; (vi) MeOH, Mg, 5 h, 91%.

Rao's approach (2005)[14r]

Rao *et al*. have reported a formal synthesis of (+)-anisomycin (**39b**) starting from D-mannitol derivative. A fully protected form of D-mannitol **73** was treated with H_5IO_6 followed by immediate reduction of the resultant crude aldehyde with $NaBH_4$ gave arabinitol derivative **74**. Benzyl protection of **74** with benzyl bromide/NaH furnished benzyl ether derivative **75**. Selective hydrolysis of **75** with 50% aq AcOH followed by subsequent tosylation gave **76**, which on further treatment with K_2CO_3/MeOH yielded epoxide **77**. Reaction of **77** with *p*-methoxyphenylmagnesium bromide in the presence of a catalytic amount of I_2/CuI followed by mesylation gave **78** in good yield.



Scheme 12: (i) H_5IO_6, ether, 0 °C; (ii) $NaBH_4$, MeOH, 3 h, 67% (over two steps); (iii) NaH, BnBr, DMF, 0-25 °C, overnight, 84%; (iv) 50% aq. AcOH, 25 °C, overnight, 84%; (v) *p*-TsCl, Et_3N, CH_2Cl_2, 0 °C, 16 h; (vi) K_2CO_3, MeOH, 30 min, 71% for two steps; (vii) (a) 4-Bromo anisole, Mg, I_2/CuI (cat.), 0-25 °C, overnight, 86%; (b) MsCl, Et_3N, CH_2Cl_2, 25 °C, 1 h; (viii) NaN_3, [18-Crown-6], DMSO, 65 °C, 24 h, 83% for two steps; (ix) $LiAlH_4$, THF, 0-25 °C, overnight; (x) $(Boc)_2O$, Et_3N, THF, 25 °C, 6 h, 81% for two steps; (xi) Li/liq.NH_3, -78 °C, 30 min, 83%; (xii) MsCl, Et_3N, CH_2Cl_2, 25 °C, 1 h; (xiii) (a) TFA, CH_2Cl_2, 0-25 °C, 10 h, (b) Et_3N, MeOH, 0-25 °C, 5 h; (xiv) Cbz-Cl, Na_2CO_3, THF, 2 h, 69% for four steps.

Mesylate **78** on treatment with NaN_3 in DMSO yielded azido derivative **79**. Reduction of the azido functionality with $LiAlH_4$/THF gave amine **80**, which on *in situ* treatment with $(Boc)_2O/Et_3N$ afforded **81**. Deprotection of benzyl group in **81** was achieved using Li/liq.

NH_3 to give **82**. Compound **82** was converted to the corresponding mesyl derivative **83** with MsCl/Et_3N, which without purification was treated with TFA followed by Et_3N to give (+)-deacetyl anisomycin **84**. Further treatment of **84** with Cbz–Cl gave (+)-*N*-benzyloxycarbonyl deacetylanisomycin **85** which is the direct precursor for the synthesis of (+)-anisomycin (**39b**) (**Scheme 12**).

4.3.4 Present Work

4.3.4.1 Objective

As can be seen from the above discussion, many methods are available in literature for the asymmetric synthesis of anisomycin (**39a**). Most of them use chiral pool approaches involving large number of steps for the synthesis. We have employed two approaches for the asymmetric synthesis of (-)-anisomycin (**39a**) using proline-catalyzed sequential transformations.

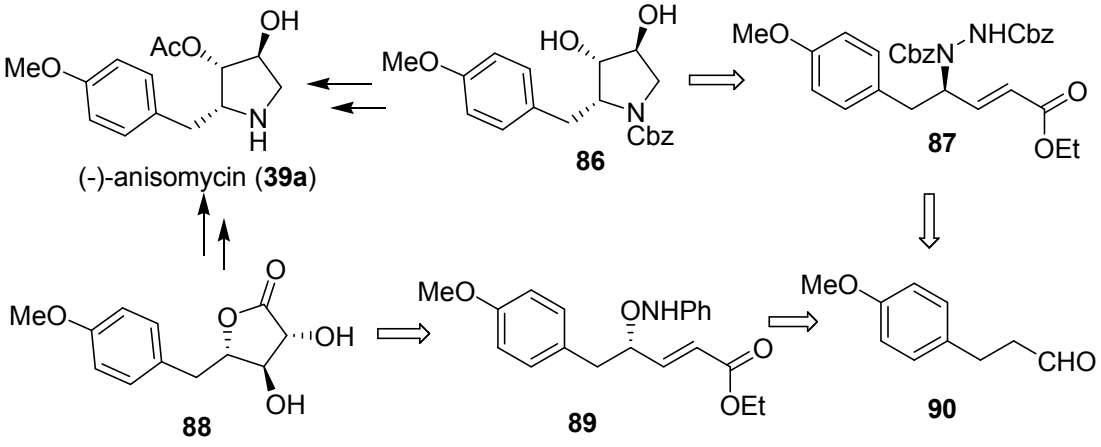


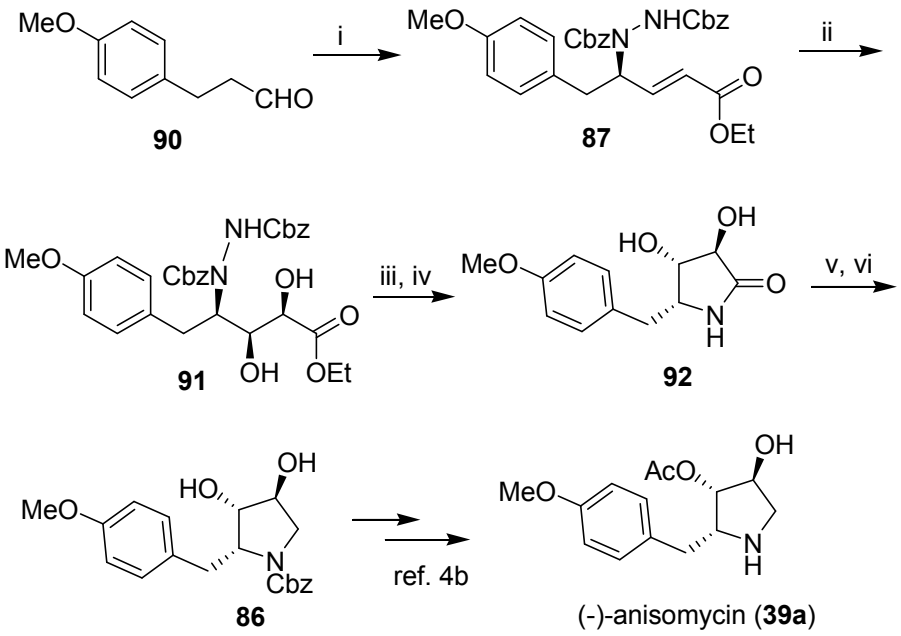
Fig. 10: Retrosynthetic analysis of (-)-Anisomycin (39)

The retrosynthetic analysis for (-)-anisomycin (**39a**) is presented in **Fig. 10** wherein synthesis of anisomycin has already been reported from the key intermediates **86** and **88**. Thus, the retrosynthetic analysis for **86** shows that it could be synthesized from amino

olefinic ester **87**, which in turn can be obtained from aldehyde **90** in a single-step protocol. Lactone **88** can be accessible from aminoxy olefinic ester **89** by means of Os-catalyzed diastereoselctive dihydroxylation. Further, ester **89** can be synthesized readily from aldehyde **90**. In this section, we describe a short and efficient synthesis of key intermediates **86** and **88** using L-proline-catalyzed tandem α-amination-olefination[15a] (Section I, Chapter III) (**Scheme 12**) and D-proline-catalyzed sequential α-aminooxylation-olefination[15b,c] strategies (**Scheme 13**) of 3-(4-methyoxyphenyl)-propanal **90** respectively.

4.3.5 Results and Discussions:

Synthetic route for key intermediate **86** *via* L-proline-catalyzed tandem α-amination-olefination[15a] is presented in **Scheme 13**.



Scheme 13: (i) DBAD, L-proline, CH_3CN, 0-10 °C, 3 h then triethyl phosphonoacetate, LiCl, DBU, 5 °C, 45 min., 88%; (ii) OsO_4, NMO, THF-H_2O, 85%; (iii) Raney-Ni, MeOH, H_2 (60 psig), 12 h; (iv) EtOH, reflux, 4 h, 60% (over two steps); (v) BH_3.THF, THF, reflux, 10 h; (vi) aq. Na_2CO_3, Cbz-Cl, CH_2Cl_2, 4 h, 66% (over two steps).

Accordingly, L-proline-catalyzed sequential α-amination-Horner-Wadsworth-Emmons olefination of 3-(4-methoxyphenyl)-propanal was carried out to obtain γ-amino-α,β-unsaturated ester **87** in 88% yield and 99% ee (determined by chiral HPLC analysis). The spectral data of **87** have been described in detail under Chapter III Section I. Next, the Os-catalyzed diastereoselective dihydroxylation of ester **87** furnished diol **91** in 85% yield.

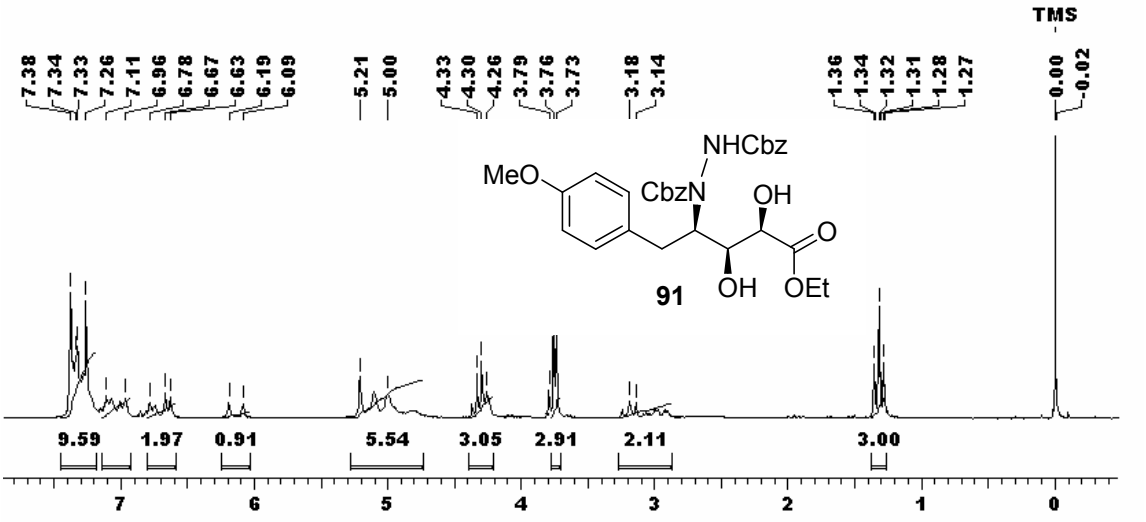


Fig. 11: ^{1}H NMR spectra of diol 91

The ^{1}H NMR spectrum of **91** showed a multiplet at δ 5.0 for the benzylic protons of Cbz group. A doublet at δ 6.09 corresponds to the olefinic proton (**Fig. 11**).

Reductive cyclization of **91** was achieved with Raney-Nickel[7] (H_2, 60 psig) in 60% yield (dr 7:1 *syn:anti* determined by ^{1}H NMR analysis of cyclized product **92** and by analogy with the results obtained for phenyl derivative Chapter III, Section I). The ^{1}H NMR spectrum of **92** showed a typical singlet at δ 3.75 due to methoxy group. A doublet at δ 3.82 corresponds to methine proton on the pyrrolidone ring (**Fig. 12**).

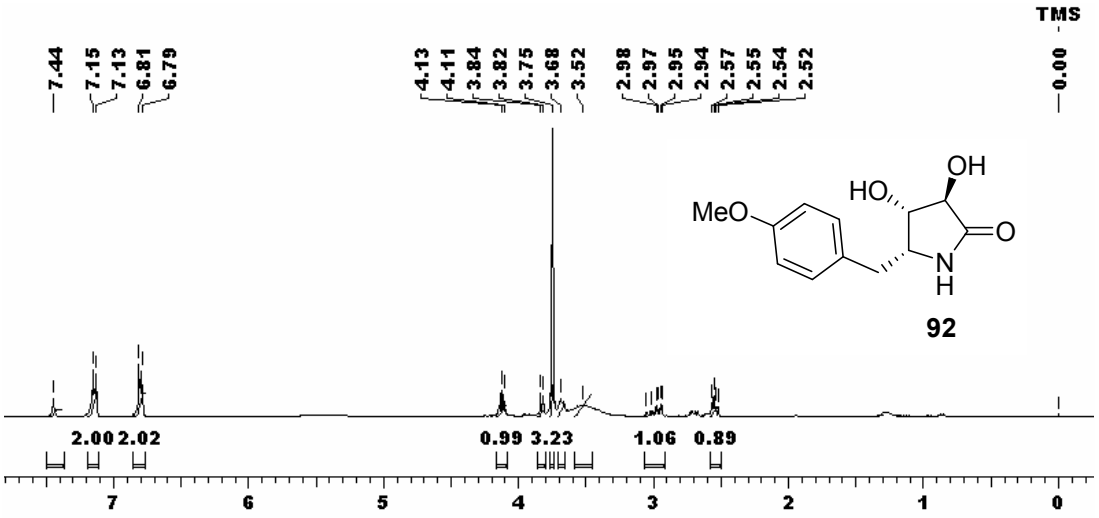


Fig. 12: ^{1}H NMR spectrum of pyrrolidone 92

The amide group in **92** was then reduced with BH_3.THF[16] and the crude product was directly subjected to Cbz protection to give N-Cbz protected diol **86** in 66% yield $[\alpha]^{25}_{D}$ -7.3 (*c* 1, MeOH) { lit.[14b] $[\alpha]^{25}_{D}$ -8.2 (*c* 5.97, MeOH)} (**Scheme 13**). The ^{1}H NMR spectrum of **86** showed a singlet at δ 3.77 corresponding to methoxy group while, two doublets at δ 6.80 amd 7.01 correspond to the aromatic protons (**Fig. 13**).

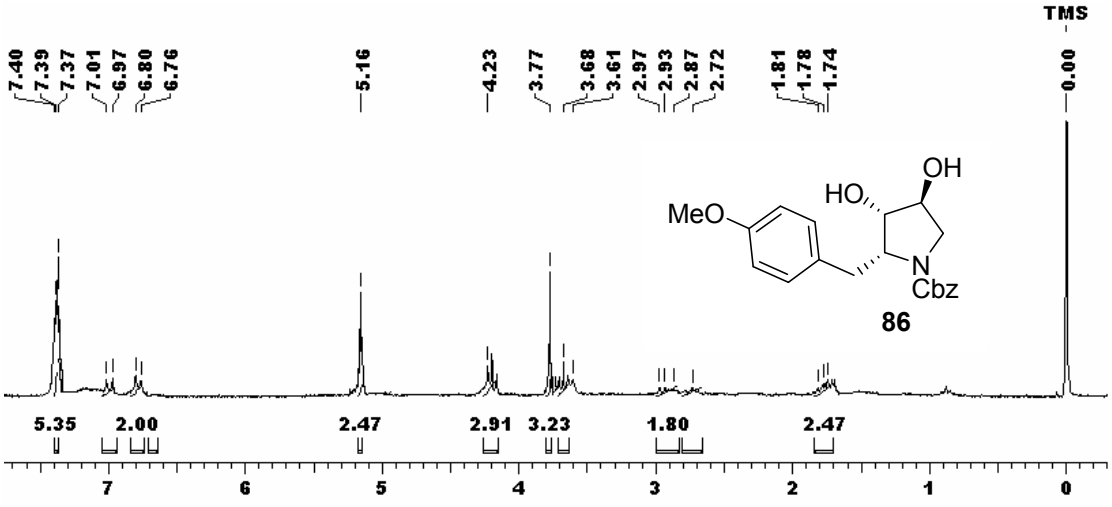
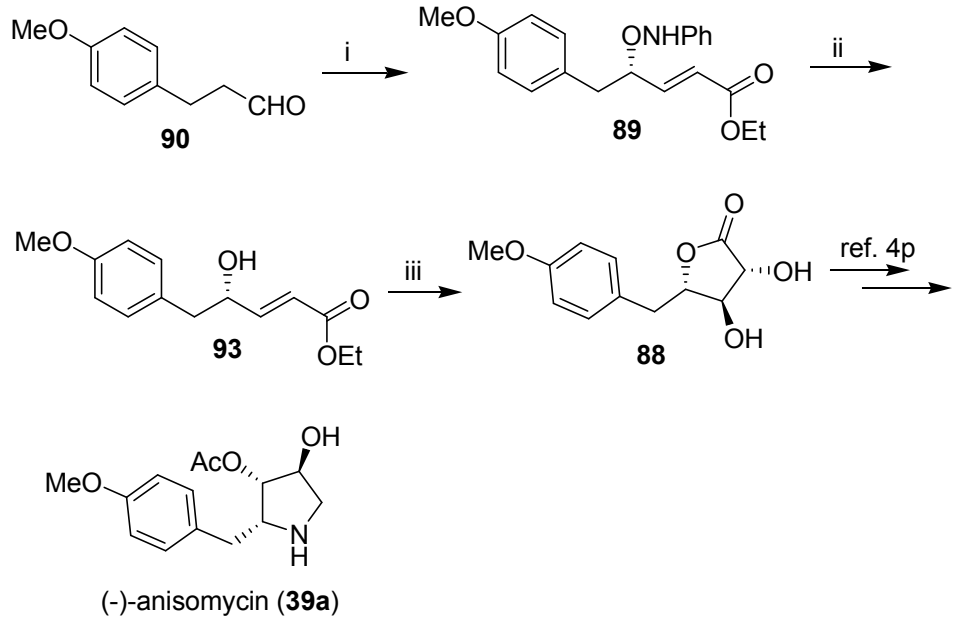


Fig. 13: ^{1}H NMR spectrum of 86

The spectral data of **86** are in complete agreement with the literature values. Synthesis of (-)-anisomycin (**39a**) has already been reported from intermediate **86**.[14b]

In the second approach, we have carried out synthesis of intermediate **88** *via* L-proline-catalyzed tandem α-aminooxylation-olefination[15b,c] strategy (**Scheme 14)**.



Scheme 14: (i) PhNO, D-proline (20 mol %), CH_3CN, -20 ºC, 24 h then triethyl phosphonoacetate, LiCl, DBU, 1 h, 79%; (ii) $Cu(OAc)_2$, EtOH, 25 ºC, 12 h, 70%; (iii) OsO_4, NMO, acetone-water, 2 h, 82%.

The synthesis was started with α-aminooxylation[17] of 3-(4-methoxyphenyl)propanal, **90**. The experiment was conducted using nitrosobenzene as oxygen source followed by *in situ* Horner-Wadsworth-Emmons olefination[15b,c] with DBU as base, which furnished anilinooxy olefinic ester **89** in 79% yield;[9] $[\alpha]^{25}_D$ -25 (*c* 1, $CHCl_3$).

The ^{1}H NMR spectrum of **89** showed singlet at δ 3.81 for the methoxyl group. A doublet at δ 5.95 corresponds to the olefinic proton. Its ^{13}C NMR spectrum showed signals at δ

55.2 and 166.0 corresponding to the methoxy and ester carbonyl carbons respectively (**Fig. 14**).

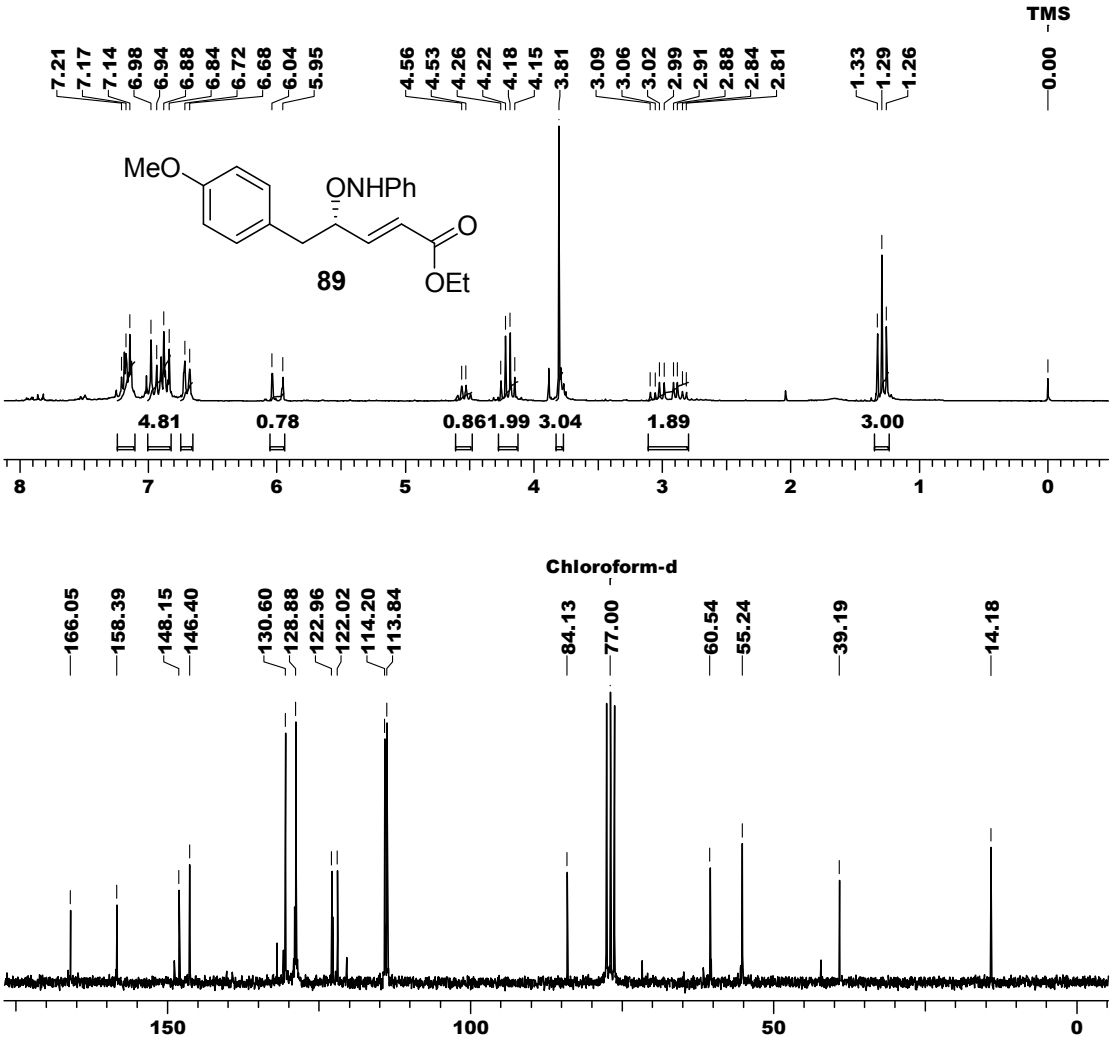


Fig. 14: ^{1}H and ^{13}C NMR spectra of ester 89

The deprotection of anilinooxy group in **89** to hydroxy group, **93**, was achieved with $Cu(OAc)_2$ in ethanol;[15b] $[\alpha]^{25}_{D}$ -10.27 (*c* 1, $CHCl_3$). The ^{1}H NMR spectrum of **93** showed a multiplet at δ 4.47 due to the methine proton (**CH**OH). A doublet at δ 6.0 corresponds to the olefinic proton. Its ^{13}C NMR spectrum showed signals at δ 149.0 and 166.4 corresponding to the olefinic and ester carbonyl carbons respectively (**Fig. 15**).

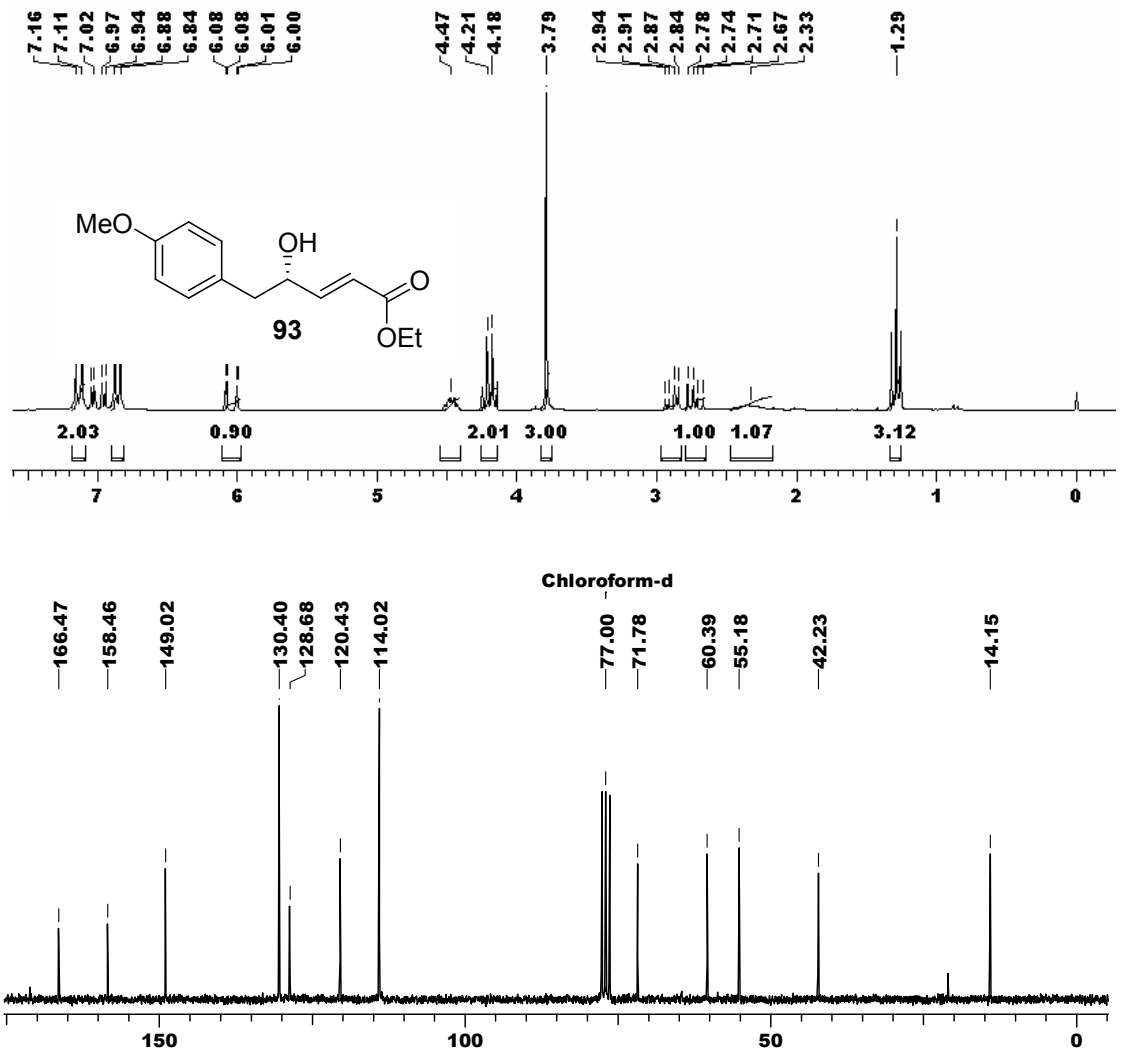


Fig. 15: ^{1}H and ^{13}C NMR spectra of alcohol 93

The Os-catalyzed diastereoselective dihydroxylation[14p] of unsaturated ester **93** gave 3,4-*anti*-γ-lactone **88** as a single diastereomer in 82% yield $[\alpha]^{25}_{D}$ -73 (*c* 1, MeOH) { lit.[14p] $[\alpha]^{25}_{D}$ -72.2 (*c* 0.41, MeOH)} (**Scheme 14**). The ^{1}H NMR spectrum of **88** showed a singlet at δ 3.79 due to the methoxy group. A triplet at δ 3.98 corresponds to the methine proton (**CH**OH). Its ^{13}C NMR spectrum showed signals at δ 80.0 and 173.5 corresponding to the methine **CH**OH) and lactone carbonyl carbons respectively (**Fig.**

16). The spectral data of **86** are in complete agreement with the literature values. The synthesis of (-)-anisomycin (**39a**) has already been reported from lactone **88**. [14p]

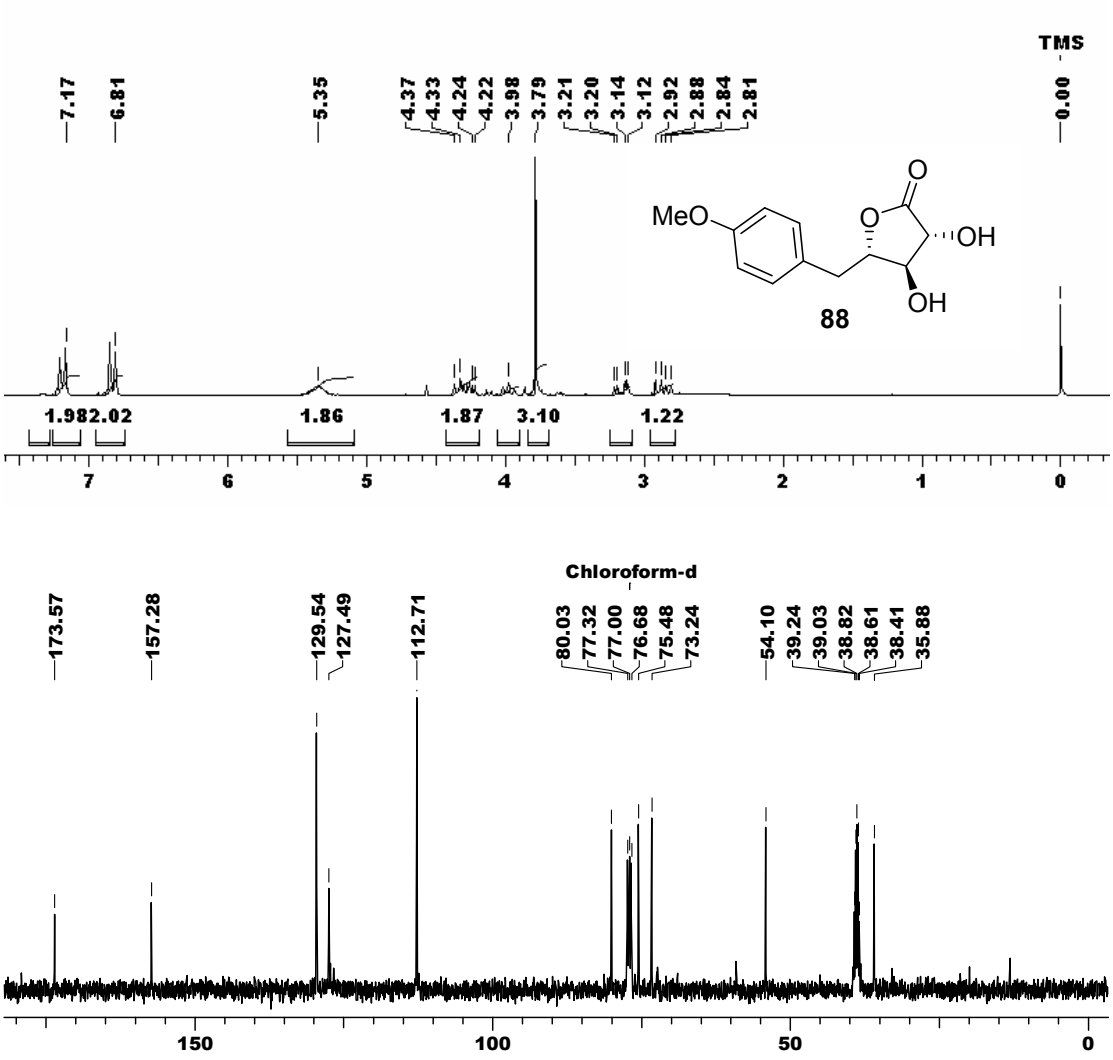


Fig. 16: ^{1}H and ^{13}C NMR spectra of lactone 88

4.3.6 Conclusion

In conclusion we have achieved a short, formal synthesis of (-)-anisomycin (**39a**) employing proline-catalyzed sequential α-aminooxylation/ α-amination-Horner-Wadsworth-Emmons olefination of 3-(4-methyoxyphenyl)-propanal. This is a first organocatalytic approach for the synthesis of anisomycin (**39a**). Operationally simple

procedures with high yields and enantioselectivities, less number of steps, use of inexpensive proline in catalytic amount render our approach a good alternative to known methods.

4.3.7 Experimental Section

(*R*)-Ethyl-4-(*N,N'*-dibenzyloxycarbonylhydrazinyl)-5-(4-methoxyphenyl)pent-2-enoate (87):

(The experimental procedure and spectral data for **87** has been described in Section I of Chapter III).

(2*R*,3*S*,4*R*)-Ethyl-4-(dibenzyloxycarbonylhydrazinyl)-2,3-dihydroxy-5-(4-methoxyphenyl)pentanoate (91):

To a solution of olefin **87** (1.06 g, 2 mmol) and NMO (0.702 g, 6 mmol, 3 equiv.) in 20 mL THF-H_2O (1:1) at 0 °C, was added OsO_4 (25.4 mg, 0.1 M in toluene, 5 mol%) and the reaction mixture was stirred at the same temperature for 12 h and at 25 °C for 6 h. The reaction was quenched with sodium bisulfite (0.5 g), diluted with water and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product, which was then purified by flash column chromatography using petroleum ether: ethyl acetate (35:65) to afford pure diol **91**.

Yield: 0.962 g, 85%, gum; $[\alpha]^{25}_{D}$ +21.66 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$) ν 3400, 3220, 3020, 2929, 2400, 1658, 1429, 1220, 1075, 923, 758 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + DMSO-d_6) δ 1.32 (t, *J* = 7.1 Hz, 3H), 2.90-2.99 (m, 1H), 3.14-3.24 (m, 1H), 3.73 (m, 3H), 4.30 (m, 3H), 5.0 (m, 5H), 6.09 (m, 1H), 6.63 (d, *J* = 7.1 Hz, 1H), 6.74 (d, *J* = 8.2 Hz, 1H), 6.97 (d, *J* = 8.2 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 7.28-7.38 (m, 10H); **^{13}C**

NMR (50 MHz, $CDCl_3$ + DMSO-d_6): δ 13.2, 31.8, 54.0, 60.1, 66.3, 66.5, 70.4, 70.5, 112.5, 126.2, 126.4, 126.7, 126.9, 127, 127.1, 127.2, 127.3, 127.5, 129.1, 129.3, 134.6, 135, 135.2, 154.7, 155.6, 156.9, 171.7; **Analysis: $C_{30}H_{34}N_2O_9$** requires C, 63.59; H, 6.05; N, 4.94; found C, 63.35; H, 6.15; N, 4.68%.

(3*R*,4S,5*R*)-5-(4-Methoxybenzyl)-3,4-dihydroxypyrrolidin-2-one (92):

A solution of diol **91** (0.849 mg, 1.5 mmol) in MeOH (20 mL) and acetic acid (10 drops) was treated with Raney nickel (3 g, excess) under H_2 (80 psig) for 24 h. The reaction mixture was filtered over celite and concentrated to give the crude amino diol, which on strirring in EtOH at 50 °C for 4 h gave the cyclized product **92** (purified by flash chromatography using ethyl acetate as eluent).

Yield: 0.213 g, 60%, gum; **$[\alpha]^{25}_D$** +16.25 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$) ν 3330, 2920, 2864, 1670, 1463, 1377, 1225, 1121, 728 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$ + DMSO-d_6) δ 2.52 (m, 1H), 2.94-3.05 (m, 1H), 3.51 (brs, 2H), 3.68 (m, 1H), 3.75 (s, 3H), 3.82 (d, *J* = 7.5 Hz, 1H), 4.11 (t, *J* = 7.4 Hz, 1H), 6.79 (m, 2H), 7.13 (m, 2H), 7.44 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$ + DMSO-d_6): δ 33.7, 53.4, 54.6, 72.1, 73.3, 112.0, 128.9, 129.1, 129.2, 156.2, 172.85; **Analysis: $C_{12}H_{15}NO_4$** requires C, 60.75; H, 6.37; N, 5.90; found C, 60.45; H, 6.15; N, 5.68%.

(2*R*,3*S*,4*S*)-Benzyl-2-(4-methoxybenzyl)-3,4-dihydroxypyrrolidine-1-carboxylate (86):

To a solution of amide **92** (111 mg, 0.5 mmol) in dry THF (10 mL) was added BH_3.DMS (0.3 mL, excess, 95%) and the reaction mixture was refluxed for 10 h. After completion of reaction (TLC) it was quenched with dil. HCl and solvents were removed under reduced pressure. The crude residue was dissolved in MeOH and treated with Et_3N (2

mL). The solvents were removed under reduced pressure and the crude product was directly used for the next step without purification.

To a solution of the above crude amine in dry THF (10 mL) was added Na_2CO_3 (80 mg, 0.7 mmol) at 0 °C, after stirring for 10 min. Cbz-Cl (85 mg, 0.5 mmol) was added and the reaction mixture was stirred at 25 °C for 2 h. The reaction mixture was extracted with $CHCl_3$, dried over anhydrous Na_2SO_4. Evaporation of solvents under reduced pressure followed by column chromatographic purification gave **86** as a colorless solid.

Yield: 0.110 g, 66%, colorless solid, mp 126 °C (lit.[14b] mp 127-129 °C) ; **$[\alpha]^{25}_D$** -7.2 (*c* 1.0, MeOH) [lit.[14b] $[\alpha]^{25}_D$ -8.2 (*c* 1.0, MeOH)] ; **IR** ($CHCl_3$) ν 3320, 3050, 3022, 2920, 2864, 1670, 1423, 1357, 1235, 1121, 815 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 1.75-1.82 (m, 2H), 2.87 (m, 1H), 2.93 (m, 2H), 3.68 (m, 1H), 3.77 (s, 3H), 4.16-4.23 (m, 3H), 5.16 (s, 2H), 6.76 (d, *J* = 8.2 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 2H), 7.37 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 32.3, 40.3, 55.1, 60.9, 68.9, 70.0, 79.1, 113.8, 128.1, 128.5, 129.8, 136.2, 156.7; **Analysis: $C_{20}H_{23}NO_5$** requires C, 67.21; H, 6.49; N, 3.92; found C, 67.55; H, 6.25; N, 4.73%.

(*S*)-Ethyl 4-anilinoxy-5-(4-methoxyphenyl)pent-2-enoate (89):

To a solution of nitrosobenzene (1 g, 9.3 mmol) and L-proline (158 mg, 15 mol%) in CH_3CN (20 mL) was added 3-(4-methoxyphenyl)propanal (1.8 g, 11.2 mmol) at -20 °C. The reaction mixture was stirred at the same temperature for 24 h followed by addition of LiCl (566 mg, 1.5 equiv.), triethyl phosphonoacetate (3.13 g, 1.5 equiv.) and after stirring for 5 min DBU (1.4 g, 1 equiv.) was added. The reaction mixture was quenched with half saturated NH_4Cl and extracted with ethyl acetate (3 × 20 mL). Combined organic phases

were concentrated and dried over anhydrous Na_2SO_4. Purification by flash column chromatography (Pet ether: EtOAc = 85:15) afforded aminooxy olefinic ester **89**.

Yield: 3 g, 79% yield, brownish oil; **$[\alpha]^{25}_D$** -25.0 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$) ν_{max} 3016, 2935, 2839, 2360, 1716, 1600, 1494, 1512, 1247, 1035, 757 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.29 (t, *J* = 7.1 Hz, 3H), 2.81-2.91 (dd, *J* = 6.1, 13.9 Hz, 1H), 2.99-3.09 (dd, *J* = 7.5, 14.0 Hz, 1H), 3.81 (s, 3H), 4.15 (q, *J* = 7.1 Hz, 2H), 4.53 (m, 1H), 5.95-6.04 (dd, *J* = 1.1, 15.8 Hz, 1H), 6.68 (d, *J* = 7.5 Hz, 2H), 6.84-6.98 (m, 5H), 7.13-7.21 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 39.1, 55.2, 60.5, 84.1, 113.8, 114.2, 122.0, 122.9, 128.8, 130.6, 131.9, 146.4, 148.1, 158.3, 166; **Analysis:**

$C_{20}H_{23}NO_4$ requires C, 70.36; H, 6.79; N, 4.10; found C, 70.63; H, 6.73; N, 4.57%.

(*S*)-Ethyl 4-hydroxy-5-(4-methoxyphenyl)pent-2-enoate (93):

To a solution of ester **89** (2.5 g, 7.3 mmol) in ethanol (25 mL) was added $Cu(OAc)_2$ (488 mg, 0.3 equiv.) and the reaction mixture was stirred at 25 °C for 12 h. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and condensed under vaccum. The crude product was purified by flash column chromatography (Pet ether: EtOAc = 75:25) to give pure **93** in 70% yield.

Yield: 1.2 g, 70% yield, brownish liquid; **$[\alpha]^{25}_D$** -10.27 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$) ν_{max} 3020, 2360, 2343, 1716, 1650, 610, 1512, 1247, 1217, 1178, 1037, 757 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.29 (t, *J* = 7.1 Hz, 3H), 2.34 (brs, 1H), 2.67-2.78 (dd, *J* = 8.1, 13.7 Hz, 1H), 2.84-2.94 (dd, *J* = 5.0, 13.8 Hz, 1H), 3.79 (s, 3H), 4.18 (q, *J* = 7.2, 2H), 4.47 (m, 1H), 6.0 (dd, *J* = 1.6, 15.6 Hz, 1H), 6.84 (d, *J* = 8.6, 2H), 6.94-7.05 (dd, *J* = 4.6, 15.6 Hz, 1H), 7.11 (d, *J* = 8.6, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 42.2, 55.1,

60.3, 71.7, 114.0, 120.4, 128.6, 130.4, 149.0, 158.4, 166.4; **Analysis: $C_{14}H_{18}O_4$** requires C, 67.18; H, 7.25 found C, 67.54; H, 7.62%.

(3*R*,4*R*,5*S*)-5-(4-methoxybenzyl)-dihydro-3,4-dihydroxyfuran-2(3H)-one (88):

To a solution of 50% aq. *N*-methylmorpholine *N*-oxide (0.93 mL, 4 mmol) and osmium tetraoxide (101 mg, 10 mol%) in acetone (10 mL) was added a solution of ester **93** (1 g, 4 mmol) in acetone (10 mL) at 0 °C and the reaction mixture was stirred for 2 h at the same temperature. To the reaction mixture was added 10% Na_2SO_3 at 0 °C and was stirred for 30 min. The generated precipitate was filtered through celite pad and the filtrate was concentrated. The residue was diluted with ether and treated with 10% aq. HCl. The organic layer was dried over anhydrous Na_2SO_4 and evaporated to give the crude product **88**, which was purified by flash column chromatography (Pet ether: ethyl acetate = 55:45) and recrystallized from $CHCl_3$.

Yield: 780 mg, 82% yield, colorless solid (mp = 81 °C, lit.[14p] mp = 81-82 °C); **$[\alpha]^{25}_D$** -72.5 (*c* 1, MeOH), [lit.[14p] $[\alpha]^{25}_D$ -72.2 (*c* 0.41, MeOH); **IR** ($CHCl_3$) ν_{max} 3330, 2920, 2864, 1760, 1465, 1387, 1225, 1131, 728 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.81 (dd, *J* = 7.5, 14.7 Hz, 1H), 3.12 (dd, *J* = 3.3, 14.7 Hz, 1H), 3.79 (s, 3H), 3.98 (t, *J* = 8.4, 1H), 4.22 (dt, *J* = 3.3, 7.6 Hz, 1H), 4.33 (d, *J* = 8.7 Hz, 1H), 5.35 (brs, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 7.17 (d, *J* = 8.7, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 35.8, 54.1, 73.2, 75.4, 80.0, 112.7, 127.4, 129.5, 157.2, 173.5; **Analysis: $C_{12}H_{14}O_5$** requires C, 60.50; H, 5.92 found C, 60.84; H, 5.62%.

4.3.8 References:

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- "Enantioselective synthesis of (*S,S*)-ethambutol using proline-catalyzed asymmetric α-aminooxylation and α-amination" Shriram P. Kotkar and Arumugam Sudalai *Tetrahedron: Asymmetry* **2006**, *17*, 1738-1742.
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- "Organocatalytic Asymmetric Synthesis of Antidepressants (*S*)-α-Methyldopa and Cericlamine" Shriram P. Kotkar and Arumugam Sudalai Manuscript under preparation.