Asymmetric Synthesis of Bioactive Molecules and Development of Synthetic Methodologies *via* Enamine Catalysis

Thesis Submitted to the AcSIR For the Award of
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In Chemical Sciences

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DEDICATED TO

MY BELOVED PARENTS,

TEACHERS AND FRIENDS

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Certificate

This is to certify that the work incorporated in this Ph.D. thesis entitled "***Asymmetric Synthesis of Bioactive Molecules and Development of Synthetic Methodologies via Enamine Catalysis***" submitted by **Mr. V.Venkataramasubramanian** to Academy of Scientific and Innovative Research (AcSIR) in fulfillment of the requirements for the award of the Degree of ***Doctor of Philosophy in Chemical Sciences***, embodies original research work under my supervision. I further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material obtained from other sources has been duly acknowledged in the thesis. Any text, illustration, table etc., used in the thesis from other sources, have been duly cited and acknowledged.

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DECLARATION

I hereby declare that the thesis entitled ***"Asymmetric Synthesis of Bioactive Molecules and Development of Synthetic Methodologies via Enamine Catalysis"*** submitted to AcSIR for the award of degree of Doctor of Philosophy in Chemical Sciences, has not been submitted by me to any other university or institution. This work was carried out at the CSIR-National Chemical Laboratory, Pune, India.

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CONTENTS

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V. Venkataramasubramanian

ABBREVATIONS

Ac	Acetyl
Ar	Aryl
Bn	Benzyl
Boc	*N*-*tert*-Butoxycarbonyl
$(Boc)_2O$	Di*tert*-butyl dicarbonate
n-Bu	*n*-Butyl
n-BuLi	*n*-Butyl lithium
t-Bu	*tert*-Butyl
Cbz	Benzyloxy carbonyl
CH_2Cl_2	Methylene chloride
$CHCl_3$	Chloroform
CH_3CN	Acetonitrile
$CuSO_4$	Copper(II) sulfate
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DIBAL-H	Diisobutyl aluminium hydride
DMF	Dimethyl formamide
DMSO	Dimethyl sulphoxide
DMAP	*N,N*-dimethyl-4-aminopyridine
dr	Diastereomeric ratio
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
HNO_3	Nitric acid
imid.	Imidazole
IR	Infra red
IBX	2-Iodoxybenzoic acid
K_2CO_3	Potassium carbonate
KOH	Potassium hydroxide
$LiAlH_4$	Lithium aluminum hydride
LiHMDS	Lithium hexamethyldisilazide
M+	Molecular ion

Me	Methyl
MeOH	Methyl alcohol
MOM	Methoxymethyl
min	Minutes
mg	Miligram
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
NBS	*N*-Bromosuccinimide
NMR	Nuclear Magnetic Resonance
NMO	*N*-Methyl morpholine *N*-oxide
PCC	Pyridinium chlorochromate
Pd/C	Palladium on activated charcoal
PDC	Pyridinium dichromate
$Pd(OH)_2$	Palladium hydroxide
Ph	Phenyl
p-Ts	*p*-Tosyl
p-TSA	*p*-Toluene sulfonic acid
PhNO	Nitrosobenzene
Py	Pyridine
TBS	*tert*-Butyldimethylsilyl
TEMPO	(2,2,6,6-tetramethyl-1-piperidinyl)oxyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TBAF	Tetrabutylammonium fluoride
TBDMSCl	*tert*-Butyldimethylsilyl chloride
TBDPSCl	*tert*-Butyldiphenylsilyl chloride
TFA	Trifluoroacetic acid

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 (230-400 mesh).

5. TLC analyses were performed over aluminum plates coated with silica gel (5-25 m) containing UV active G-254 additive.

6. IR spectra were recorded on a Perkin-Elmer model 683 B or 1605 FT-IR and absorptions were expressed in cm^{-1}.

7. ^{1}H and ^{13}C NMR spectra were recorded on Brucker FT AC-200 MHz, Brucker Avance 500 MHz and JEOL ECX 400 instruments using TMS as an internal standard. The following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet, dd = doublet of doublet, dt = doublet of triplet and ddd = doublet of doublet of doublet.

8. Optical rotations were carried out on JASCO-181 digital polarimeter at 25 °C using sodium D light.

9. Enantiomeric excesses were determined on Agilent HPLC instrument equipped with a chiral column.

10. HRMS data were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump.

11. All melting points and boiling points are uncorrected and the temperatures are in centigrade scale.

12. Elemental analysis was done on Carlo ERBA EA 110B instrument.

13. The compounds, scheme and reference numbers given in each chapter refers to that particular chapter only.

ABSTRACT

Asymmetric Synthesis of Bioactive Molecules and Development of Synthetic Methodologies via Enamine Catalysis

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The thesis entitled **"Asymmetric Synthesis of Bioactive Molecules and Development of Synthetic Methodologies *via* Enamine Catalysis''** is divided into four chapters. The title of the thesis clearly reflects the objective, which is to utilize the enamine catalysis for the enantioselective synthesis of bioactive molecules and their intermediates. **Chapter I** deals with proline - catalyzed α- aminooxylation of β-amino aldehydes and its application for the enantioselective synthesis of 3-aryl-3-amino-1,2- diols and (-)- cytoxazone, a cytokine modulator. **Chapter II** describes a short route for enantioselective synthesis of (+)-sertraline, (+)-tametraline and formal synthesis of (+)-indatraline *via* proline- catalyzed Mannich reaction of acetaldehyde. **Chapter III** deals with the organocatalytic asymmetric synthesis of 4-hydroxypyrazolidines and *L*-carbidopa using α-amination of aldehydes. **Chapter IV** describes an enantioselective synthesis of guggultetrol and D- *ribo*- phytosphingosine tetraacetate *via* L- proline catalyzed sequential α- aminooxylation/ Horner-Wardsworth- Emmons olefination and synthesis of *rac*-clopidogrel *via* CO_2 insertion.

a. Introduction

Over the past 10 years organocatalysis has been extended for discovering novel chemical reactions such as α-functionalization of carbonyl compounds, C-C bond formation *via* enamine and iminium ion catalysis, etc.[1] In particular, these methods are found tremendous applications in the synthesis of various bioactive molecules and drugs with high enantio- and diastereoselectivity.[2] The present work provides for the asymmetric synthesis of various bioactive molecules such as (-)-cytoxazone **4**, (+)-sertraline **5**, tametraline **6**, (+)-indatraline **7**, guggultetrol **15**, D-*ribo*-phytospingosine **16**, and carbidopa **12** and bioactive intermediates such as 4-hydroxypyrazolidines **9**, and 3-amino-1,2-diols **2a-f** *via* enamine catalysis. (-)-Cytoxazone is a microbial metabolite, identified as a selective modulator of T_H2 cytokine secretion,[3] while (+)-sertraline is a potent competitive selective serotonin reuptake inhibitor (SSRI), commonly prescribed for the treatment of depression and other anxiety-related disorders.[4] Tametraline possesses a potent norepinephrine (NE) uptake blocking activity,[5] while (+)-indatraline, a potent psychoactive compound, acts as a monoamine reuptake inhibitor regulating the dopamine and the serotonin transporter.[6] Guggultetrol, a naturally-occurring lipid isolated from the gum-resin of the tree *Commiphorumukul* (guggul) is used in the treatment of arthritis, inflammation, obesity, and disorders of lipid metabolism. D-*ribo*-Phytospingosine regulates cellular growth and mediates the heat stress response of yeast,[7] while drug carbidopa acts against Parkinson's disease.[7c] Also, the synthesis of clopidogrel, an antiaggregatory and antithrombotic drug, has been achieved *via* insertion of CO_2.[8] These bioactive molecules have become popular synthetic targets due to their small but challenging structures.

b. Statement of Problem

The reported synthesis of these highly bioactive molecules suffer from disadvantages such as lengthy reaction sequences including the protection and deprotection of various functional groups, use of chiral auxiliaries, and expensive organomettalic reagents, chiral pool approaches, etc. Hence, the need for a short and protecting group-free method of synthesis from commercially available achiral starting materials is of current interest.

c. Methodology used

1. Several biologically important molecules have been synthesized *via* enamine catalysis involving Mannich[1b], α-aminooxylation, α-amination reaction of aldehydes and their structures characterized by the advanced analytical and spectroscopic techniques such as high field NMR (^{1}H & ^{13}C), FT-IR, LC-MS, HRMS and elemental analysis.

2. Single Crystal X-ray Crystallographic study have been carried out to determine the relative stereochemistry of the intermediates.

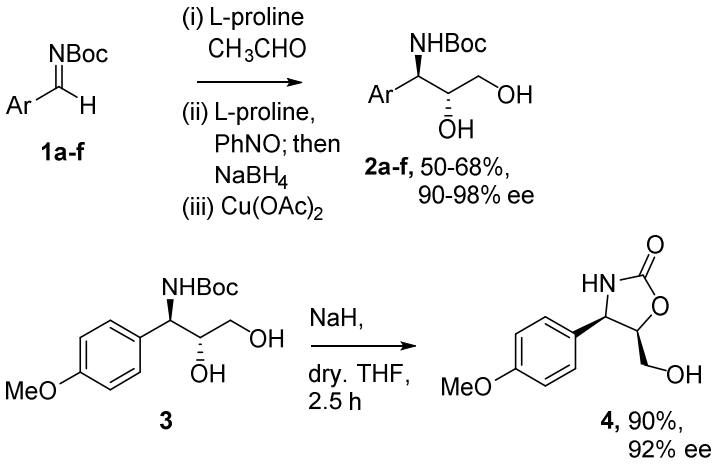
3. The optical purity of chiral intermediates and final drug molecules are determined from chiral HPLC analysis (**Fig.1**) and comparing their specific rotation with those reported in the literature.

c. Sample Results

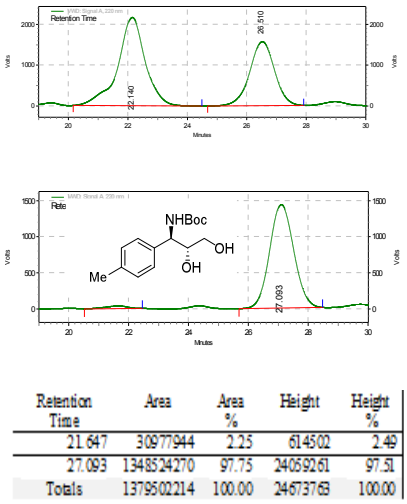
CHAPTER I

Proline - Catalyzed α- Aminooxylation of β- Amino Aldehydes: A Concise Method for the Enantioselective Synthesis of 3-Aryl-3-Amino-1,2- Diols and (-)-Cytoxazone

Chapter I describes the synthesis of various 3-amino-1,2-diols **2a-f** using (i) L-proline catalyzed Mannich reaction of acetaldehyde[1b] with N-Boc arylaldiimines **1a-f**; (ii) α-aminooxylation of resulting chiral β-aminoaldehydes; and (iii) N-O bond cleavage of aminooxy alcohols using $Cu(OAc)_2.2H_2O$ in good yields and excellent ee (**Fig 1**). This strategy has been applied to the synthesis of (-)-cytoxazone (**4**) in a single step starting from the corresponding *anti*-3-amino-1,2-diol, **3 (Scheme 1)**.



Scheme 1: Synthesis of *anti*-3-amino-1,2-diols **(2)** and (-)-cytoxazone **(4)**



Retention Time	Area	Area %	Height	Height %
21.647	30977944	2.25	614502	2.49
27.093	1348524270	97.75	24059261	97.51
Totals	1379502214	100.00	24673763	100.00

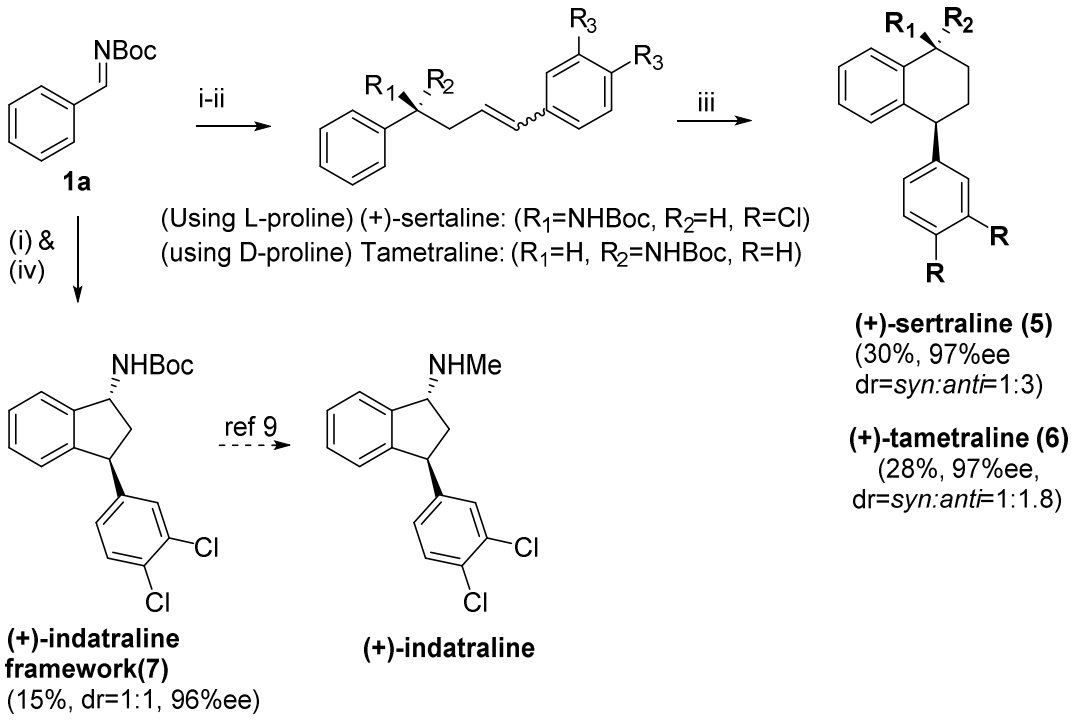
Column :Chiracel AD-H (4.6X250 nm); Mobile Phase :IPA:n-Hexane(10:90)Wavelength:220nm; Flow rate : 0.5ml/min

Fig 1: HPLC chromatogram of *anti*-3-amino-1,2-diol

CHAPTER II

A Short Route for Enantioselective Synthesis of (+)-Sertraline, (+)-Tametraline and Formal Synthesis of (+)-Indatraline *via* Proline- Catalyzed Mannich Reaction of Acetaldehyde

To extend scope of enamine catalysis further, synthetic application of β-aminoaldehydes is widely elaborated for the asymmetric synthesis of various bioactive molecules. Thus, **Chapter II** describes a short route to the synthesis of (+)-sertraline **5**, tametraline **6**, and formal synthesis of (+)-indatraline **7** using proline-catalyzed Mannich reaction of acetaldehyde with N-Boc benzaldiimine **1a** as chiral inducing step in good overall yields and high ees. The synthetic sequence involves Wittig reaction using benzylphosphorous ylide, Grignard reaction using 3,4-dichlorophenyl magnesium bromide and Friedel-Crafts cyclization as the key steps (**Scheme 2**).



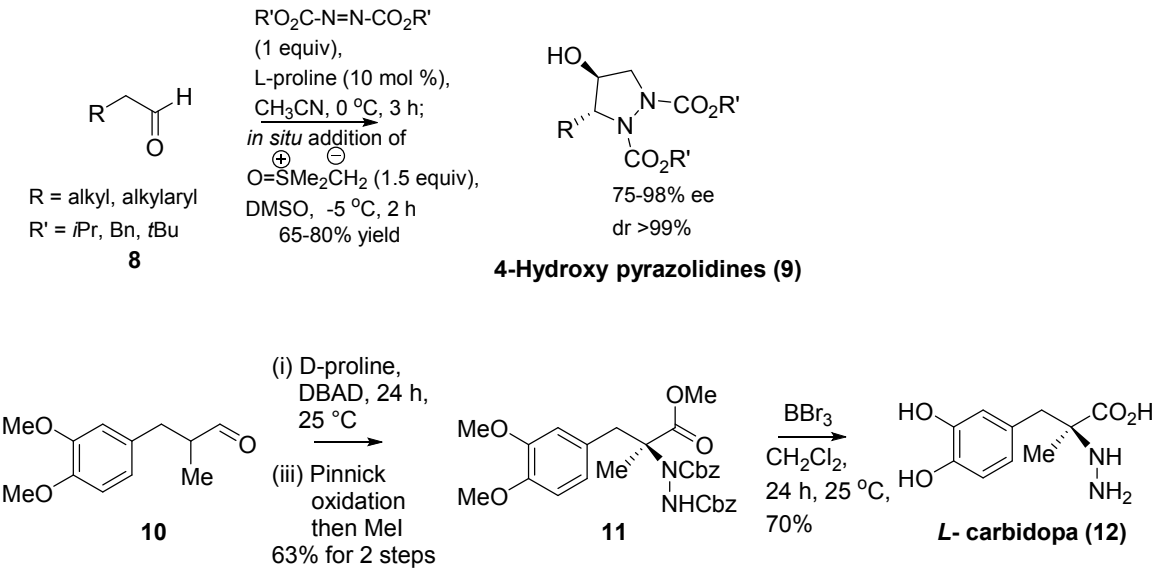
Scheme 2: Reagents and conditions: (i) CH_3CHO (7 equiv), proline (20 mol%), CH_3CN, 0 ^oC, 3 h, 55%; (ii) **A**, *n*-BuLi, dry THF, 1 h, 0 ^oC, 60%;

(iii) a) MeI (2.5 equiv), NaH (2 equiv), dry.THF, 7 h, 0 ^{o}C, 94%; b) PPA (1 equiv), EDC, reflux, overnight, 82%; (iv) $AlCl_3$(3 equiv), CH_3NO_2/CH_2Cl_2(1:1), 25 °C, 40%, 4 h. where, **A**= 3,4-di$ClC_6H_3CH_2PPh_3Br$ (for sertraline) or $C_6H_5CH_2PPh_3Br$ (for Tametraline)

CHAPTER III

Organocatalytic Asymmetric Synthesis of 4-Hydroxypyrazolidines and *L*-Carbidopa using α-Amination of Aldehydes

In this chapter, the utility of enamine catalysis is further extended on the synthesis of 4-hydroxypyrazolidines and *L*-carbidopa under milder reaction conditions. **Chapter III** describes a one-pot procedure of tandem α-amination-Corey-Chaykovsky reaction of aldehydes **8** that proceed to give 4-hydroxypyrazolidine derivatives **9** in high enantio- and diastereoselectivity.[10] Additionally, asymmetric synthesis of *L*-carbidopa **12** is achieved in 7 steps, comprising of D-proline catalyzed α-amination of α-methyl substituted aldehyde **10**, followed by BBr_3-mediated global deprotection as the key steps (**Scheme 3**).

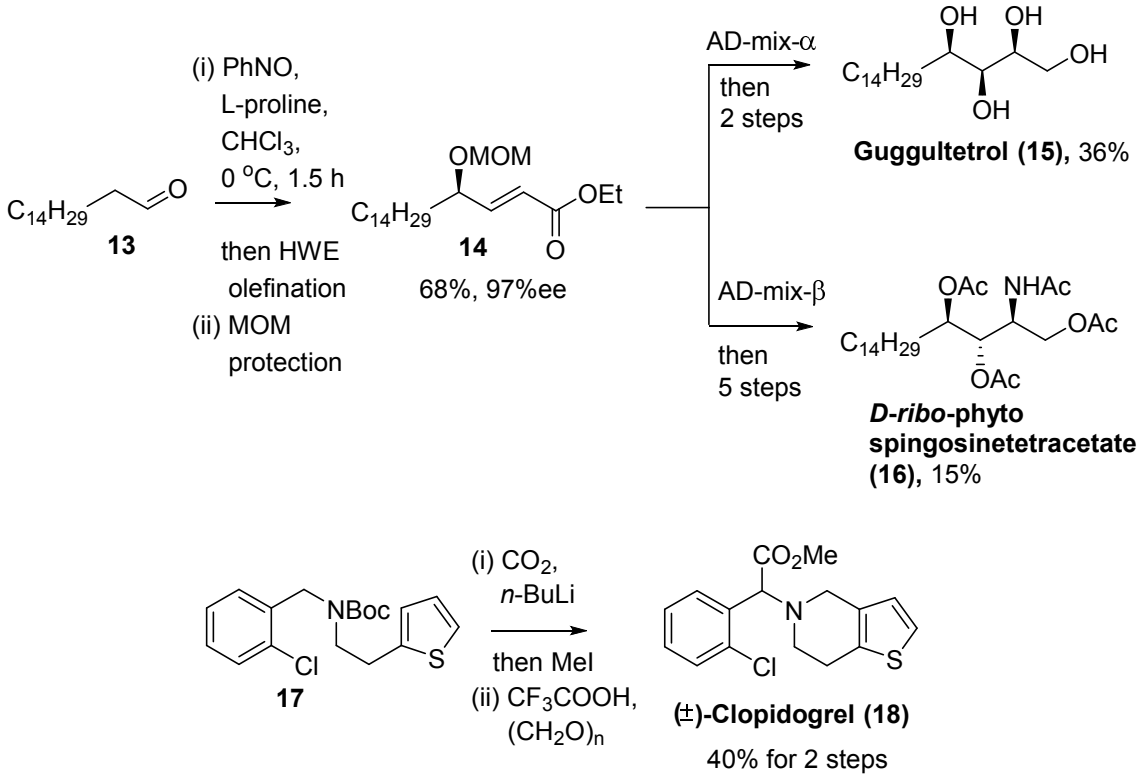


Scheme 3: Synthesis of 4-hydroxypyrazolidines **(9)** and carbidopa **(12)**

CHAPTER IV

Enantioselective Synthesis of Guggultetrol and D- *ribo*- phytosphingosine Tetraacetate *via* L- Proline Catalyzed Sequential α- Aminooxylation/ Horner-Wardsworth- Emmons Olefination and Synthesis of *rac*-Clopidogrel *via* CO_2 Insertion

Chapter IV outlines the synthesis of guggultetrol (**15)** and D-*ribo*-phytospingosine tetraacetate (**16)** *via* enamine catalysis involving tandem L-proline catalyzed α-aminooxylation-Horner-Wardsworth- Emmons olefination of hexadecanal (**13**) to afford γ-hydroxy-α,β-unsaturated ester **14** as a common intermediate for both these molecules. Also the synthesis of clopidogrel **18** has been achieved in good yield *via* insertion of CO_2 at the benzylic position followed by Pictet-Spengler cyclization (**Scheme 4**).



Scheme 4: Synthesis of guggultetrol (**15)** and clopidogrel (**18)**

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CHAPTER I

Proline - Catalyzed α- Aminooxylation of β- Amino Aldehydes: A Concise Method for the Enantioselective Synthesis of 3-Aryl-3-Amino-1,2-Diols and (-)- Cytoxazone

Section I:
Proline-catalyzed Asymmetric Organic Transformations for Highly Enantioselective Synthesis of Bioactive Molecules: Minireview

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.

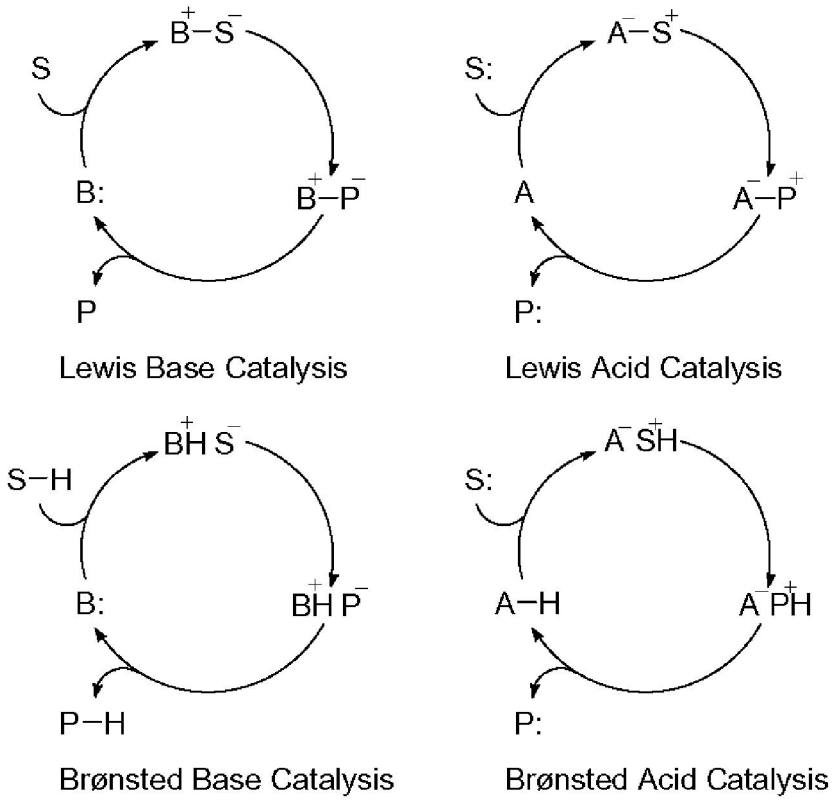


Fig. 1: Organocatalytic cycles

1.1.2 Proline a "Universal catalyst"

Proline (**1**) has been defined as a "universal catalyst" because of its high utility in a variety of asymmetric organic transformations. It 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 both act as acid or base and facilitate many chemical transformations similar to enzymatic catalysis. It can be regarded as a

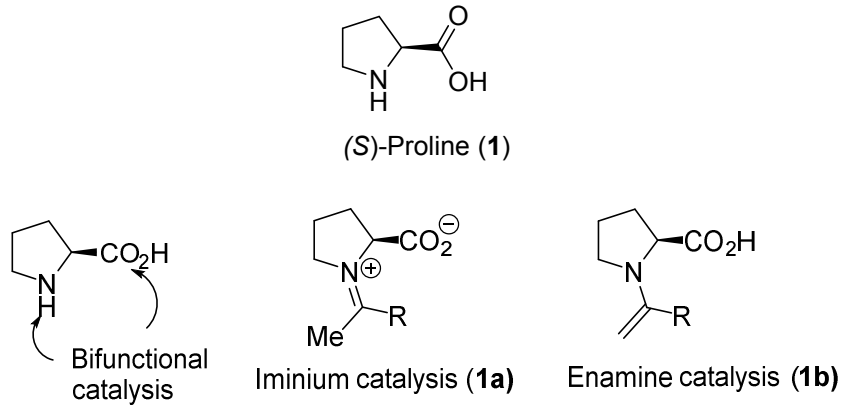


Fig. 2: Modes of proline catalysis

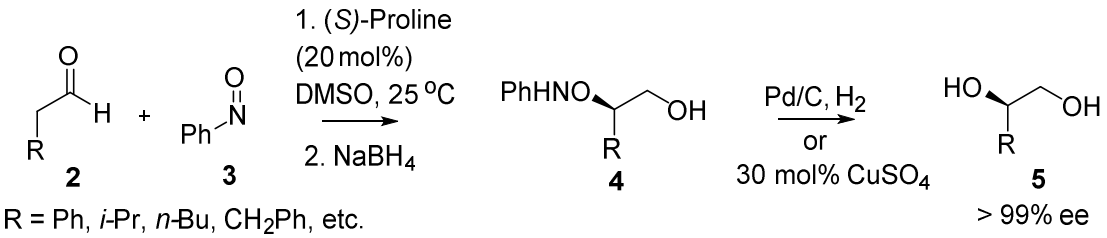
bifunctional catalyst as the secondary amine acts as Lewis base and the acid group acts as Bronsted acid (**Fig. 2**). The high stereoselectivity in the proline-catalyzed reactions is possibly due to its formation of organized transition states with many hydrogen bonding frameworks. Proline is not the 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 an 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 catalytic cycle 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.

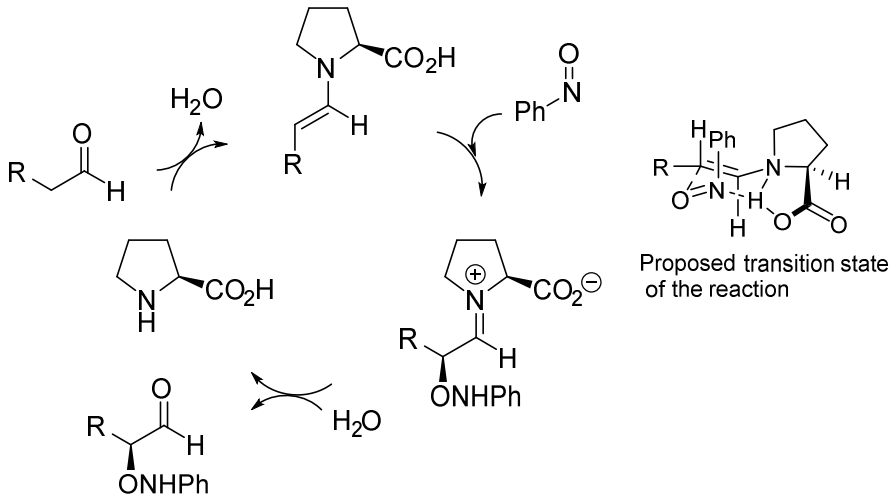


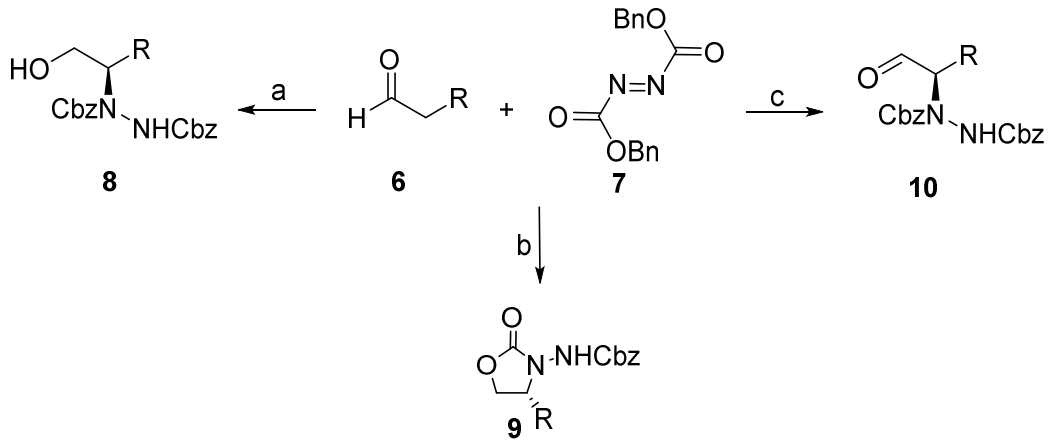
Fig. 3: Proposed mechanism of the α-aminooxylation reaction

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 (**8-10**), 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 **6** and azodicarboxylate ester **7**. 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**).

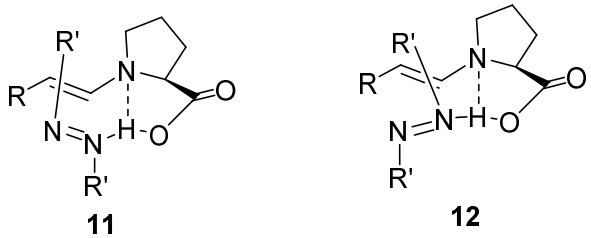


Fig. 4: Transition states for α-amination

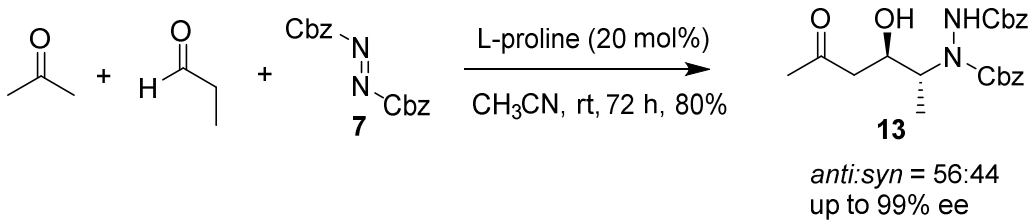
While both transition structures lead to identical products directed by the hydrogen bonding from the carboxylic acid of proline, they presumably possess unique energies, so one transition state should be the favored over the other. However, the operative transition state has yet to be established.

1.1.5 Proline-catalyzed sequential transformations in organic synthesis

Proline-catalyzed sequential transformation,[13] is an emerging area of current research in organic synthesis of complex organic molecules can be synthesized in one-pot procedure. Recently a variety of such transformations has been developed by different research groups, some of which are described below.

1.1.5.1 Sequential amination-aldol[13a]

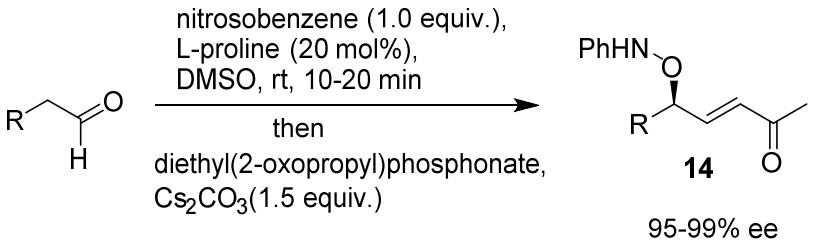
Barbas III *et al*. have developed a one-pot protocol for the synthesis of functionalized β-amino alcohols **13** directly from a mixture containing aldehydes, ketones and azodicarboxylates (**Scheme 3**).



Scheme 3: Sequential amination-aldol reaction

1.1.5.2 Sequential aminooxylation-olefination of aldehydes[13b]

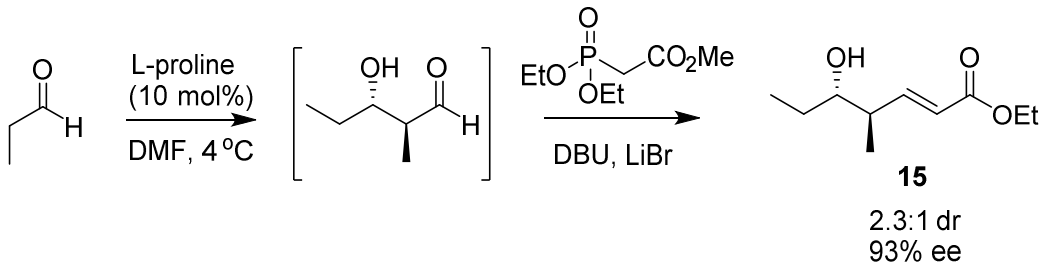
Zhong *et al*. have reported a sequential α-aminoxylation/Wadsworth-Emmons-Horner olefination of aldehydes for the synthesis of optically active *O*-amino-substituted α, β-unsaturated ketones**14** in excellent enantioselectivities using Cs_2CO_3 (**Scheme 4**).



Scheme 4: Sequential aminooxylation-olefination

1.1.5.3 Sequential aldol-olefination of aldehydes[13c]

Cordova *et al*. have reported a one-pot organocatalytic tandem cross-aldol/ Horner-Wittig-Emmons olefination of aldehyde that gave δ-hydroxy α, β-unsaturated ester **15** (**Scheme 5**).

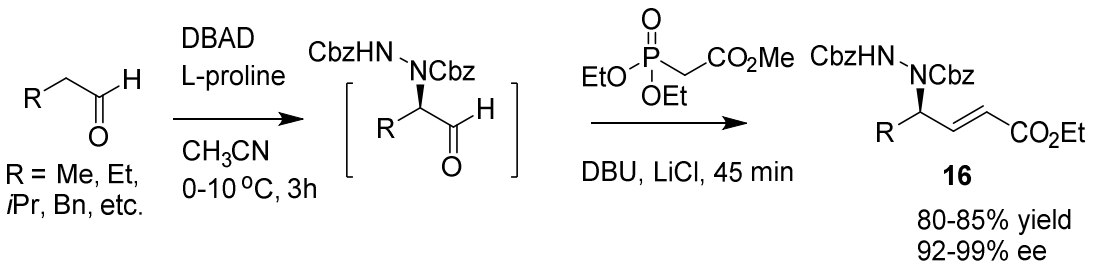


Scheme 5: Sequential aldol-olefination reaction

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

1.1.5.4 Sequential α-amination-olefination[13e]

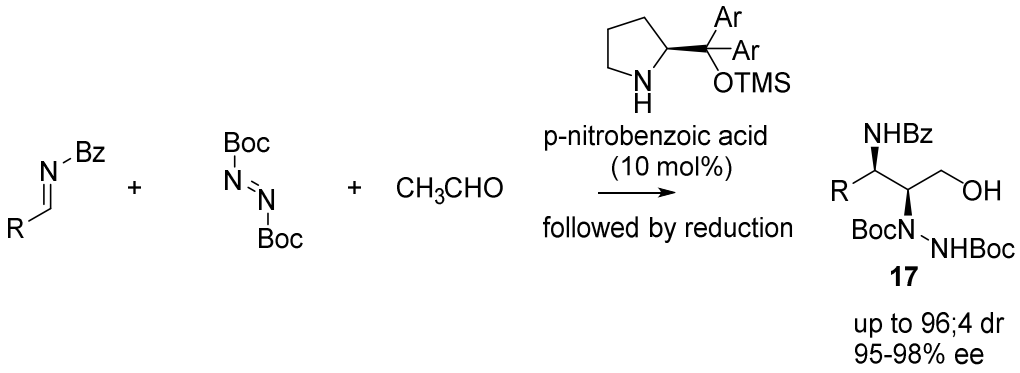
Sudalai *et al*. have reported an organocatalytic sequential α-amination-Horner-Wadsworth-Emmons olefination of aldehydes that produces *γ*-amino-α, *β*-unsaturated esters **16** (**Scheme 6**).



Scheme 6: Sequential α-amination- HWE olefination of aldehydes

1.1.6 Tandem Mannich reaction-electrophilic amination[13f]

Greck *et al*. have disclosed an organocatalytic "one-pot" α, α-bifunctionalization of acetaldehyde by a tandem Mannich reaction/electrophilic amination that leads to the stereoselective synthesis of *syn*-2,3-diaminoalcohols **17** in high yields and excellent enantioselectivities (**Scheme 7**).

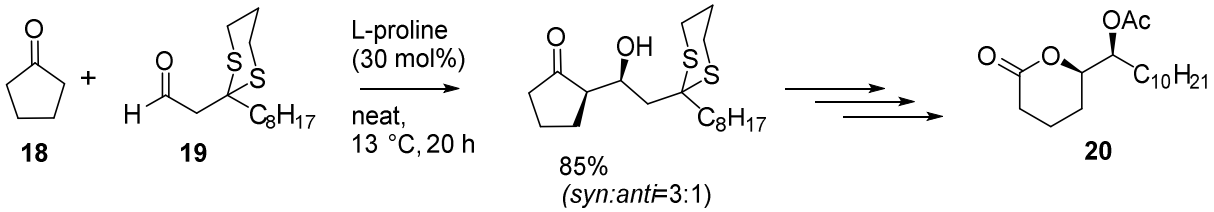


Scheme 7: Tandem Mannich reaction-electrophilic α-amination of aldehydes

1.1.7 Asymmetric synthesis of bio-active molecules using enamine catalysis

1.1.7.1 Synthesis of (-)-(*5R,6S*)-6-acetoxyhexadecanolide *via* crossed-aldol reaction[14a]

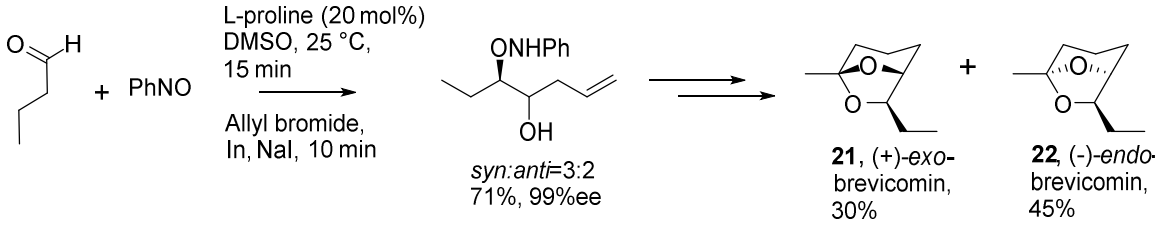
Kotsuki *et al*. have made use of the proline-catalyzed aldol reaction between cyclopentanone **18** and aliphatic aldehyde **19** for the synthesis of (-)-(*5R,6S*)-6-acetoxyhexadecanolide **20**.



Scheme 8: Synthesis of (-)-(*5R,6S*)-6-acetoxyhexadecanolide

1.1.7.2 Synthesis of (+)-*exo* and (-)-*endo*-brevicomin *via* α-aminooxylation[14b]

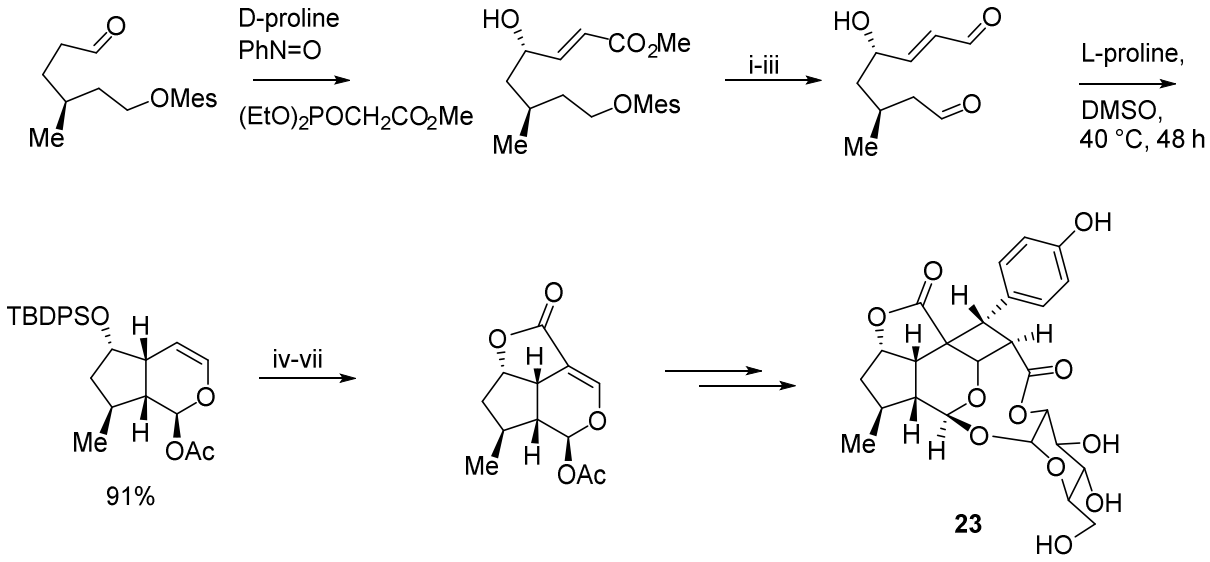
Kim *et al*. demonstrated the utility of tandem aminooxylation-allylation reaction for the short and efficient total synthesis of (+)-*exo* and (-)-*endo*-brevicomin (**21** and **22**), (**Scheme 9**).



Scheme 9: Total Synthesis of Brevicomins

1.1.7.3 Synthesis of (-)-littoralisone *via* sequential aminooxylation-HWE and intramolecular Michael addition reactions[14c]

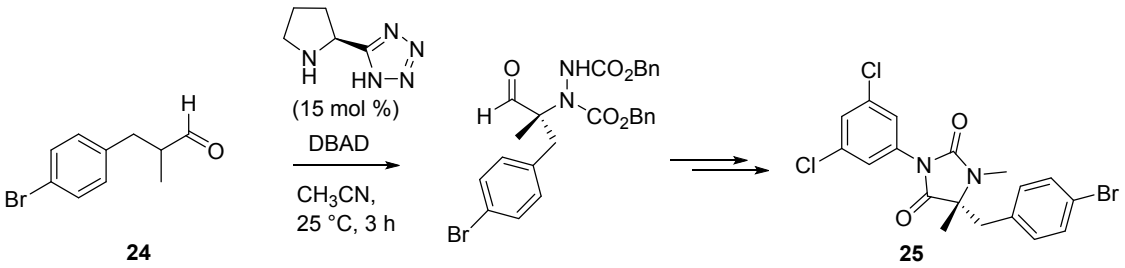
Macmillan *et al*. have reported the total synthesis of (-)-littoralisone **23**, an active agent for increased nerve growth factor (NGF) achieved in 13 steps *via* sequential aminooxylation/ Horner-Wadsworth-Emmons olefination and intramolecular Michael addition reactions with high enantio- and diastereoselectivity, (**Scheme 10**).



Scheme 10: Total synthesis of (-)-littoralisone. (i) TBDPSCl, imidazole, DMF (ii) DIBAL, Et_2O, -78 °C (iii) DMP, CH_2Cl_2 (iv) $POCl_3$, DMF, 40 °C (v) $NaClO_2$, NaH_2PO_4, t-BuOH (vi) HF-pyridine, THF (vii) DCC, CH_2Cl_2.

1.1.7.4 Enantioselective total synthesis of BIRT-377 *via* α-amination[14d]

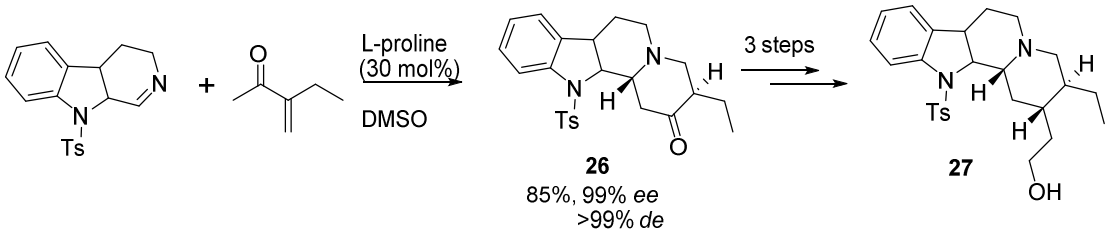
C. F. Barbas, III *et al*. have described the enantioselective total synthesis of BIRT-377 (**25)**, a potential agent for the treatment of inflammatory and immune disorders. The strategy involves the construction of quaternary chiral center *via* L-proline derived tetrazole catalyzed direct α-amination of α-branched aldehyes **24** with dibenzyl azadicarboxylate in good yield and enantiomeric excess upto 80% ee, (**Scheme 11**).



Scheme 11: Enantioselective total synthesis of BIRT-377

1.1.7.5 Stereoselective total synthesis of *ent*-dihydrocorynantheol[14e]

Itoh *et al*. have disclosed the stereoselective total synthesis of the indole alkaloid *ent*-dihydrocorynantheol **27** which exhibits the antiparasitic, antiviral, and analgesic activity. The synthetic route comprising of cascade Mannich-Michael reactions catalyzed by L-proline to **26** exclusively with high stereoselectivity. Then the transformation of **26** into *ent*-dihydrocorynantheol **27** was achieved in 3 steps by standard reaction sequences (**Scheme 12**).



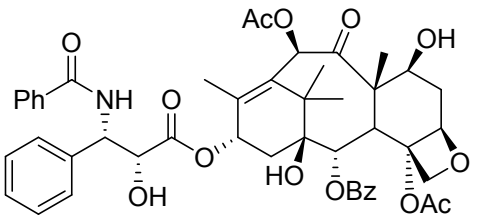
Scheme 12: Stereoselective total synthesis of *ent*-dihydrocorynantheol **27**

Section II:

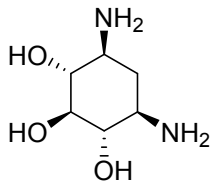
Proline-Catalyzed α-Aminooxylation of β-Aminoaldehydes: A Highly Stereoselective Synthesis of 3-Amino-1, 2-Alkane Diols

1.2.1 Introduction

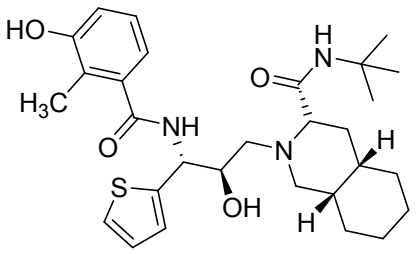
The enantiomerically pure *syn*- and *anti*-3-amino-1,2-alkane diols are ubiquitous substructures associated with biologically active natural products.[15] They are important and versatile 'building blocks' for asymmetric synthesis of bioactive pharmaceuticals and complex bioactive molecules. Some representative examples of biologically active and pharmacologically relevant therapeutic agents, wherein 3-amino-1,2-alkane diols play a vital role as key intermediates in their synthesis are shown in **Fig. 5**. For example, taxol (**28**) is a mitotic inhibitor drug used in cancer chemotherapy and AIDS-related Kaposi's sarcoma.[16]



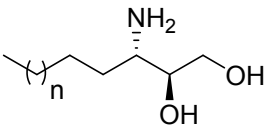
Taxol (**28**)



2-Deoxystreptamine (**29**)



Nelfinavir Analogue (**30**)



n = 11; Amino Diol (**31a**)
n = 15; Amino Diol (**31b**)

Fig. 5: Structures of bioactive 3-amino-1,2-alkane diols

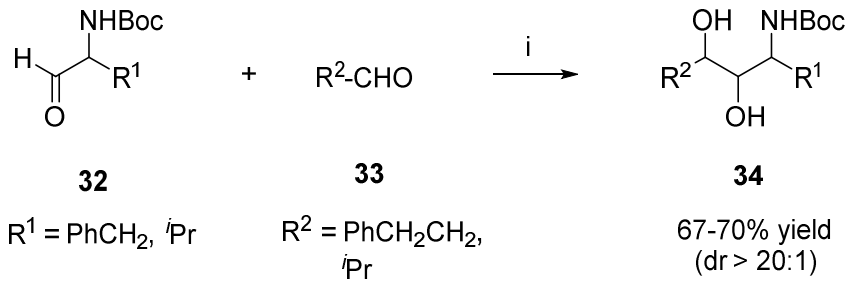
2-Deoxystreptamine **29** is a key structural fragment of aminoglycoside antibiotics, which have broad antibacterial spectrum and proven efficacy in the treatment of serious infections.[17] Nelfinavir analogue **30** showed inhibitory activity against wild type HIV PR with a IC_{50} value of 30μM.[18] Also, long chain 3-amino-1,2-alkane diols (**31a** and **31b**) showed *in vitro* cytotoxicity against six solid tumor cell lines (A2780, H322, LL, WiDr, C26-10 and UMSCC-22B).[19] The wide interest in amino alcohol functionality, as found in chiral auxiliaries, ligands, and in various bioactive compounds has resulted in numerous synthetic strategies for this important class of compounds.[20-31]

1.2.2 Review of Literature

Literature search revealed that there are various methods available for the synthesis of 3-amino-1,2-alkane diols derivatives, some of which are described below.

Pederson's approach (1990)[20]

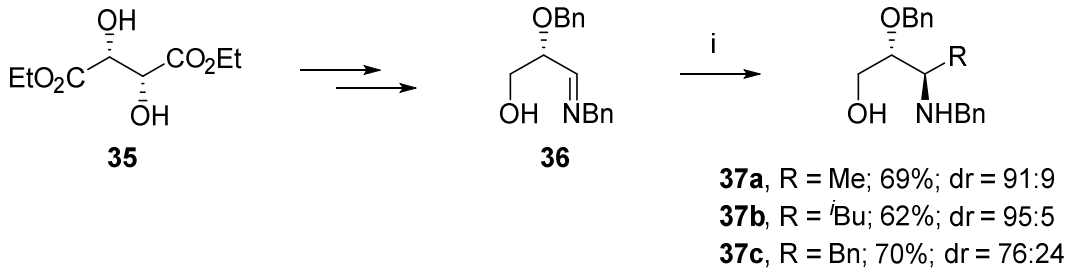
Pederson *et al*. have described the synthesis of *syn*,*syn*-3-amino-1,2-alkane diols **34** *via* chelation-controlled pinacol cross coupling reaction between N-Boc-α-amino aldehydes **32** and aliphatic aldehydes **33** using vanadium(II) reagent {$[V_2C1_3(THF)_6]_2$ $[Zn_2C1_6]$} in 67-70% yield (dr > 20:1) (**Scheme 13**).



Scheme 13: (i) $[V_2C1_3(THF)_6]_2[Zn_2C1_6]$, CH_2Cl_2, 1 h, 10 % aq. sodium tartrate.

Jagers's approach (1994)[21a]

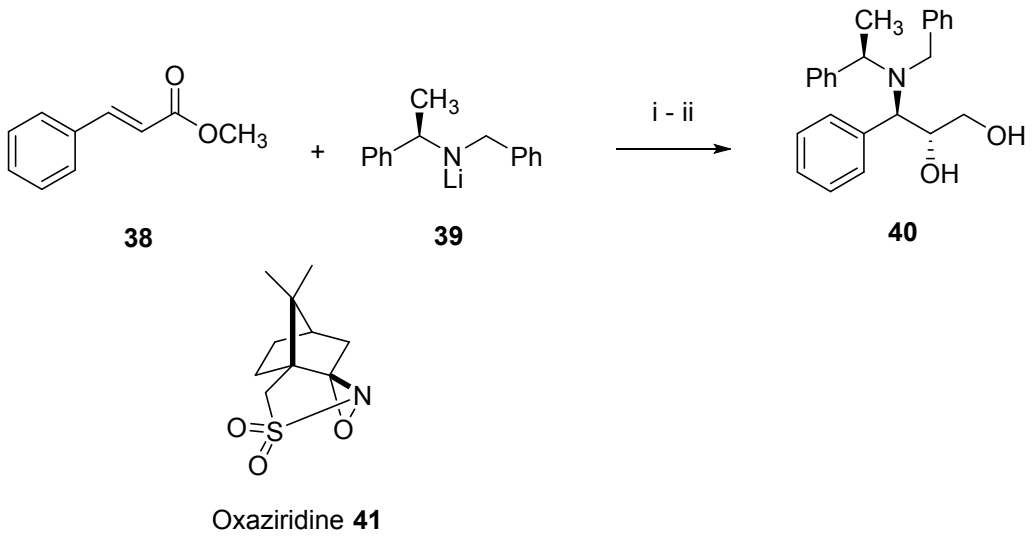
Jagers *et al.* have achieved the synthesis of optically active 3-amino-1,2-alkane diols **37a-c** using a chiral pool approach commencing from (+)-diethyl tartrate (**35**), which was converted to glycerinealdimine **36** using simple standard transformations.[21b] Stereoselective Grignard addition of alkyl magnesium halides onto glycerinealdimine **36** in the presence of $CeCl_3$ provided *anti*-amino diols **37a-c** as major diastereomers (de = 52-90%) in 62-70% yield (**Scheme 14**).



Scheme 14: (i) RMgX, $CeCl_3$, THF, 0 °C to 25 °C, 12 h.

Bunnage's approach (1994)[22]

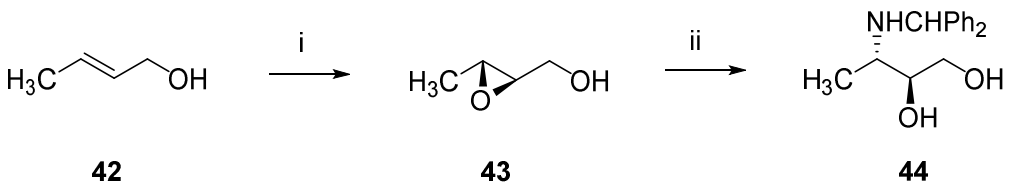
Bunnage *et al*. have reported a useful method for the synthesis of 3-amino-1,2-alkane diol **40** using diastereoselective conjugate addition of amine source with enoate acceptor **38** as key step. Thus, tandem diastereoselective conjugate addition of lithium N-benzylamide **39** with methyl cinnamate **38**, followed by the electrophilic hydroxylation of the resultant β-amino enolates with camphorsulfonyl oxaziridine **41** resulted in β-amino-α-hydroxyester. Subsequent reduction of ester with $LiAlH_4$ provided *anti*-amino diol **40** with good diastereoselectivity (> 90% d.e.) and moderate yield (**Scheme 15**).



Scheme 15: (i) THF, -78 °C, 2 h then oxaziridine (**13**), -78 °C to 0 °C, 1 h, 43%; (ii) $LiAlH_4$, THF, 0 ºC to 25 ºC, 2 h, 72%.

Riera's approach (1995)[23]

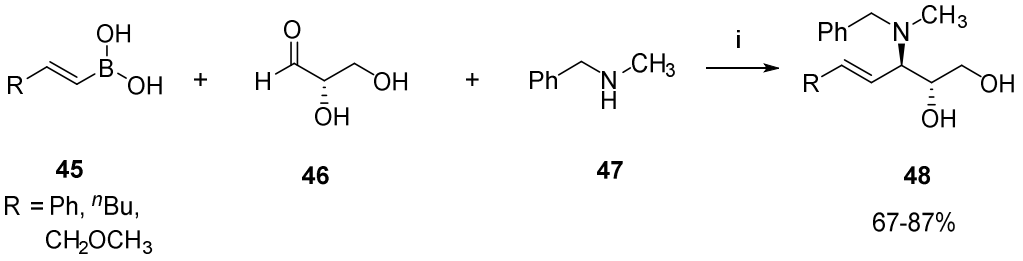
Riera *et al.* have used Sharpless asymmetric epoxidation as the key reaction for the introduction of chirality. Thus, commercially available (*E*)-crotyl alcohol **42** was subjected to Sharpless asymmetric epoxidation with D-(-)-DIPT to give epoxy alcohol **43**. $Ti(O^iPr)_4$ mediated regioselective ring opening of chiral epoxy alcohol **43** by primary amine provided (2*S*, 3*S*)-3-benzhydrylamino-1,2-butanediol (**44**) in 68% yield with 92% ee (**Scheme 16**). Regioselective opening of chiral epoxides with amine source have been extensively used for many bioactive molecule syntheses, especially anti-HIV protease inhibitors.



Scheme 16: (i) D-(-)-DIPT, $Ti(O^iPr)_4$, *tert*-BuOOH, CH_2Cl_2, -25 °C; (ii) Ph_2CHNH_2, $Ti(O^iPr)_4$, CH_2Cl_2, 25 °C, 24 h, 68% (over two steps).

Petasis's approach (1998)[24]

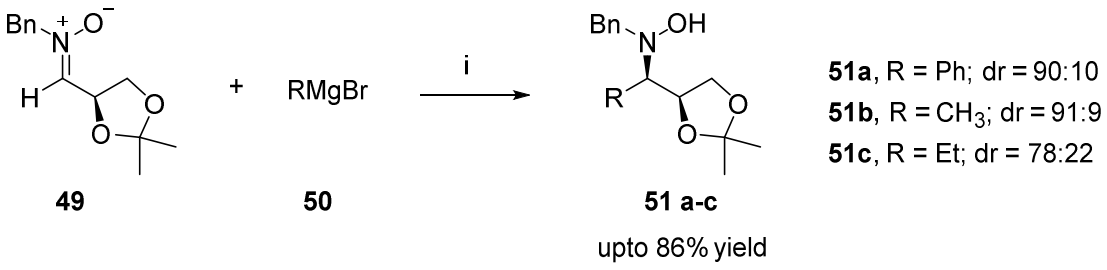
Petasis *et al.* have described the enantioselective synthesis of 3-amino-1,2-alkane diols using chiral pool approach. This method involves one-step three component variant of Mannich reaction involving organoboronic acids **45**, α-hydroxy aldehyde **46** and an amine **47** under milder reaction conditions that gave directly the corresponding *anti*-3-amino-1,2-alkane diols **48** in 99% de and ee (**Scheme 17**).



Scheme 17: (i) EtOH, sealed tube, 25 °C, 24 h.

Merino's approach (1998)[25]

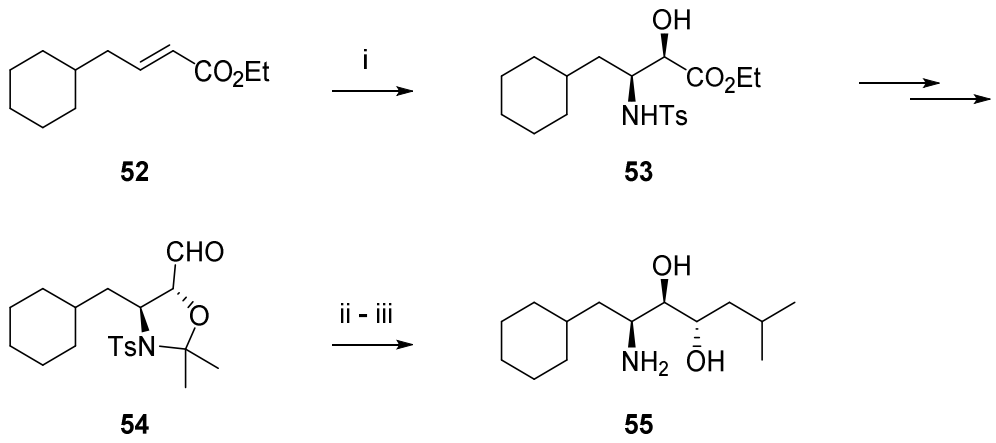
Merino *et al*. have reported the synthesis of *syn*-3-amino-1,2-alkane diols **51** using a chiral pool approach commencing from glyceraldehyde nitrone **49**, which was derived from D-glyceraldehyde by condensation with N-benzyl hydroxylamine. Stereoselective Grignard addition of alkyl magnesium halides **50** onto glyceraldehyde nitrone **49** in the presence of $ZnBr_2$ provided *syn*-amino diols **51a-c** as major diastereomer (de = 66-82%) in 72-86% yield (**Scheme 18**).



Scheme 18: (i) $ZnBr_2$, Et_2O, -60 ºC, 6 h.

Chandrasekhar's approach (1999)[26]

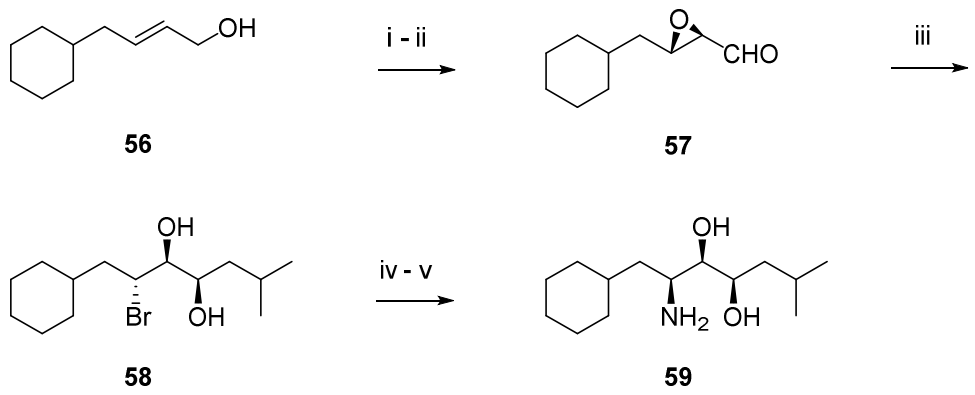
Chandrasekhar *et al.* have reported the synthesis of Abbott amino diol **55** using Sharpless asymmetric aminohydroxylation as the key step. Thus, α,β-unsaturated ester **52** was subjected to asymmetric aminohydroxylation using catalytic amount of quinine derived ligand $(DHQ)_2PHAL$, $K_2OsO_2(OH)_4$ and commercially available Chloramine-T to provide amino alcohol **53** in 65% yield and 89% ee. Acetonide protection of amino alcohol **53** followed by reduction of ester afforded aldehyde **54**, which on reaction with ^{i}BuMgBr followed by deprotection of acetonide with HCl gave *syn*,*anti*-amino diol **55** as major diastereomer (dr = 80:20) (**Scheme 19**). Sharpless asymmetric aminohydroxylation has been extensively used for the introduction of chiral amino alcohols in the synthesis of many bioactive molecules. But the major drawback with this method is the poor regioselectivity of the newly introduced amino alcohol functionality.



Scheme 19: (i) chloroamine-T, $K_2[OsO_2(OH)_4]$, $(DHQ)_2PHAL$, *tert*-BuOH:H_2O (1:1), 12 h, 25 ºC, 65%; (ii) ^{i}BuMgBr, THF, 0 °C to 25 °C, 6 h, 72%; (iii) 6 N HCl, CH_3OH, 25 °C, 4 h, 52%.

Righi's approach (2000)[27]

Righi *et al.* have used Sharpless asymmetric epoxidation as the key reaction for the synthesis of 3-amino-1,2-alkane diol **59**. Thus, allyl alcohol **56** was subjected to Sharpless asymmetric epoxidation using L-(+)-DET to give epoxy alcohol, which on subsequent oxidation provided epoxy aldehyde **57** in 68% yield with 93% ee. One-pot ring opening/organometallic addition of α,β-epoxy aldehyde **57** with ^{t}BuMgBr in the presence of $MgBr_2.Et_2O$ afforded *syn*-diol **58** in stereocontrolled manner. Subsequent substitution of the bromine with azide, followed by catalytic hydrogenation to the amino group, led to *syn*,*syn*-3-amino-1,2-alkane diol **59** in 63% yield (over two steps) (**Scheme 20**).

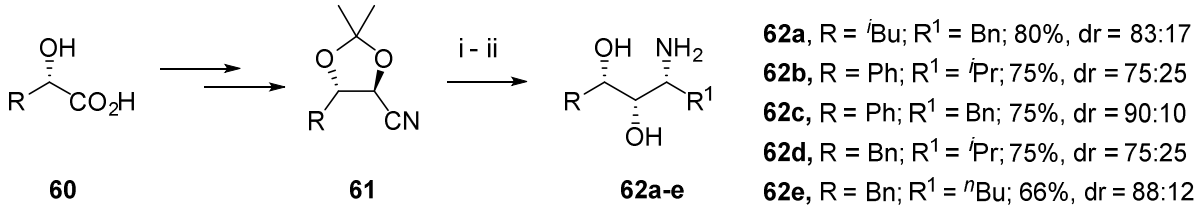


Scheme 20: (i) L-(+)-DET, $Ti(O^{i}Pr)_4$, *tert*-BuOOH, CH_2Cl_2, -25 °C, 24 h; (ii) TEMPO, $PhI(OAc)_2$, dry CH_2Cl_2, 25 ºC, 1 h, 72% (over two steps); (iii) $MgBr_2.Et_2O$, CH_2Cl_2, ^{t}BuMgBr, THF, -50 °C, 24 h, 65%; (iv) NaN_3, DMF, 40 ºC, 24 h, 71%; (v) 10% Pd/C, H_2 (50 psi), EtOAc, 24 h, 89%.

Larcheveque's approach (2000)[28a]

Larcheveque *et al.* have reported the synthesis of *syn*,*syn*-3-amino-1,2-alkane diols **62a-e** using a chiral pool approach commencing from acetonide protected *syn*-2,3-dihydroxynitriles **61**, which were derived from optically active 2-hydroxy acids **60**

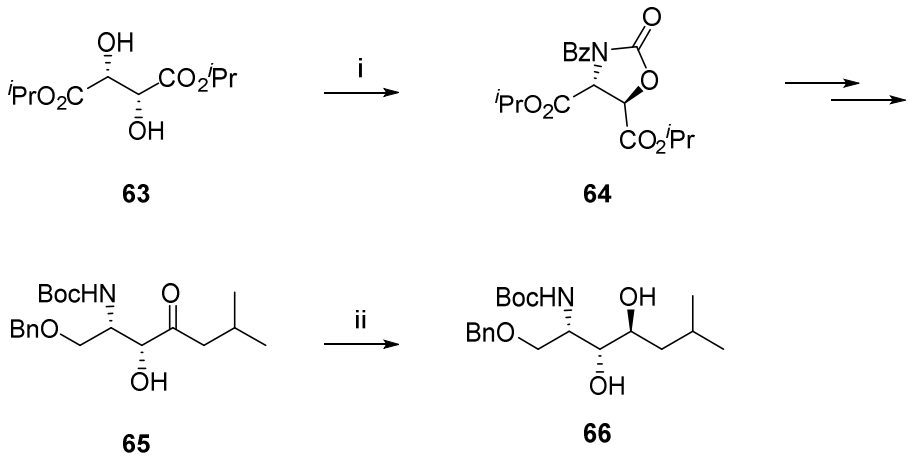
using simple standard transformation.[28b] Stereoselective Grignard addition of alkyl magnesium bromide onto dihydroxynitriles **61,** followed by $NaBH_4$ reduction of the resulting imine, afforded the corresponding *syn*-amino diols **62a-e** as major diastereomer (de = 50-80%) in 66-80% yield (**Scheme 21**).



Scheme 21: (i) R^1MgBr, Et_2O, -15 ºC, 6 h then $NaBH_4$, CH_3OH, 25 ºC, 14 h; (ii) 2 N HCl, CH_3OH, H_2O, 25 °C, 3 h.

Ko's approach (2003)[29]

Ko *et al*. have reported the synthesis of *syn,anti*-3-amino-1,2-alkane diol **66** using a chiral pool approach (**Scheme 22**).



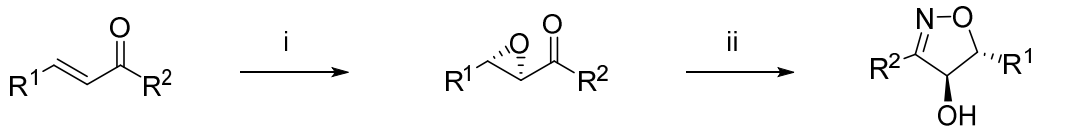
Scheme 22: (i) Bu_2SnO, CH_2Cl_2, reflux, Dean-Stark, 4 h, then BzNCS, Et_3N, Bu_4NBr, reflux, 2 h, 76%; (ii) $NaBH(OAc)_3$, CH_3CN:*n*-hexane (1.2:1), 3 h, 84%.

(+)-Diisopropyl tartrate **63** was converted to protected amino alcohol **65** in 76% yield using a three-step reaction sequence in one pot: (i) activation of diol **63** *via* tin

ketalization; (ii) iminocarbonate formation by treatment of tinketal with BzNCS; (iii) rearrangement of iminocarbonate under nucleophilic condition. Protected amino alcohol **64** was then converted to ketone **65** using simple standard transformations, where regioselective reduction of ester and Weinreb's amide formation served as key steps. Diastereoselective reduction of the carbonyl group **65** with $NaBH(OAc)_3$ afforded *syn,anti*-3-amino-1,2-alkane diol **66** in 8.5:1 diastereoselectivity and 84% yield (**Scheme 22**).

Bickley's approach (2003)[30]

Bickley *et al.* have used *L*-leucine-based chiral epoxidation as the key reaction for synthesis of *anti,anti*-3-amino-1,2-alkane diols **70a-b**.



67a, R^1 = Ph; R^2 = ^{i}Pr — **68a**, 78% yield; 90% ee — **69a**, 73% yield; 89% ee

67b, R^1 = Ph; R^2 = ^{t}Bu — **68b**, 84% yield; 91% ee — **69b**, 76% yield; 94% ee

70a, 73% yield; 89% ee

70b, 75% yield; 90% ee

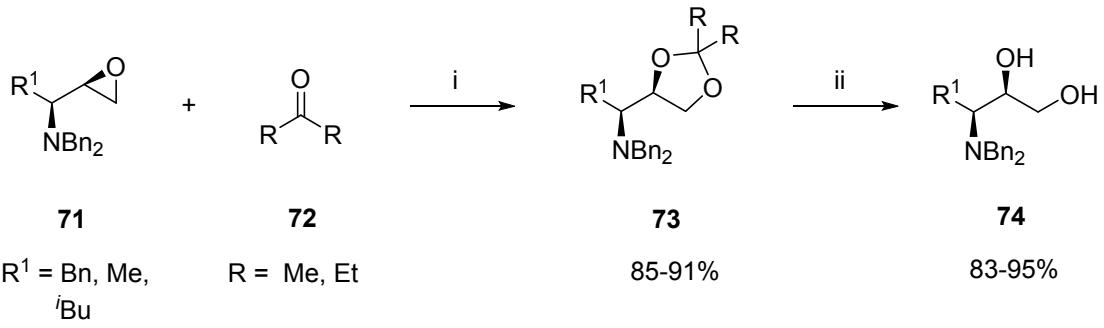
Scheme 23: (i) poly-*L*-leucine, THF, $NH_2CONH_2.H_2O_2$, DBU, 25 ºC, 24 h; (ii) NH_2OH. HCl, EtOH, pyridine, reflux, 14 h; (iii) $LiAlH_4$, THF, 0 ºC to 25 ºC, 2 h.

Thus, enones **67a-b** were epoxidised using urea-hydrogen peroxide complex in the presence of poly-L-leucine supported on silica to yield epoxides **68a-b** in 90% ee. Dihydroisoxazoles **69a-b** were obtained in good yields by treatment of epoxides **68a-b** with hydroxylamine. Subsequent diastereoselective reduction of dihydroisoxazoles

69a-b with $LiAlH_4$ afforded *anti, anti*-3-amino-1,2-alkane diols **70a-b** in good yields (73-75%) with 90% ee (**Scheme 23**).

Concellon's approach (2005)[31]

Concellon *et al.* have reported the synthesis of *syn*-3-amino-1,2-alkane diol **74** using a chiral pool approach commencing from enantiopure *syn*-2-(1-aminoalkyl)epoxides **71**. Thus, epoxides **71** were treated with different ketones **72** in the presence of $BF_3.Et_2O$ to provide the corresponding 4-(1-aminoalkyl)-1,3-dioxolanes **73** in high yields and without epimerization. Finally, deprotection of 1,3-dioxolanes **73** with HCl afforded *syn*-3-amino-1,2-alkane diol **74** (**Scheme 24**).



71 — R^1 = Bn, Me, ^{i}Bu

72 — R = Me, Et

73 — 85-91%

74 — 83-95%

Scheme 24: (i) $BF_3.Et_2O$, CH_2Cl_2, 0 ºC, 1 h; (ii) 1N HCl, CH_3CN, reflux, 1 h.

1.2.3 Present Work

1.2.3.1 Objective

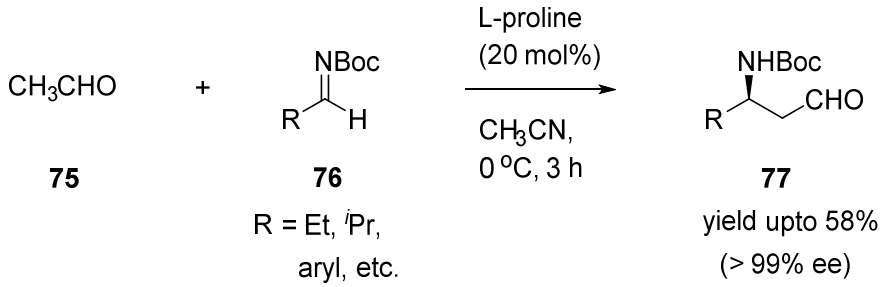
As can be seen from the above discussion, the reported methods of synthesis are quite effective. However, there are certain serious short-comings associated with them such as: (i) dependence on chiral pool resources; (ii) expensive chiral ligands, catalysts and reagents; (iii) multi-step reaction sequences; (iv) lack of broader substrate scope; (v) lack of higher enantio- and diastereoselectivity and (vi) use of protection and deprotection of various functional groups involved in the synthesis thereby limiting

the overall yield of the process, particularly unsuitable for atom economic synthesis. In this regard, a simple metal-free procedure to obtain chiral 3-amino-1,2-alkanediol derivatives in high enantio- and diastereoselectivity is highly desirable. In this section, a highly stereoselective, one-pot procedure for obtaining chiral 3-amino-1,2-alkanediols using proline-catalyzed α-aminooxylation of β-aminoaldehydes is decribed. Since the method involves organocatalysis, especially proline-catalysed Mannich reaction of acetaldehyde[32] for introducing C-N stereogenicity into the prochiral molecule, a brief account of which is described below.

1.2.3.2 Proline-catalyzed Mannich reaction of acetaldehyde

Mannich reaction is enormously useful for the construction of nitrogenous molecules.[33] The increasing popularity of the Mannich reaction has been fueled by the ubiquitous nature of nitrogen in drugs and natural products as well as by the potential of this multi-component reaction to generate molecular diversity. Only a handful of catalytic asymmetric Mannich reactions have been reported.[34] The proline-catalysed Mannich reaction has evolved into a broadly useful transformation that has been applied to the synthesis of natural products, pharmaceuticals, and several classes of chiral amino acids.[35] Quite recently, N-Boc-imines **76** have been introduced to the proline-catalysed Mannich reaction,[36] significantly widening the already large substrate scope and utility of this process. However, acetaldehyde, which would be a particularly useful nucleophile in this reaction, has not been used under proline-catalysed Mannich reactions conditions due to several problems associated with the potential use of acetaldehyde, such as: (i) acetaldehyde rapidly reacting with itself *via* aldol condensation, forming coloured oligomers and polymers if treated with proline and (ii) hypothetical acetaldehyde Mannich products, themselves α-unbranched aldehydes, may undergo further reaction with an additional imine equivalent or

eliminate to form the corresponding unsaturated aldehydes. It was recently found that if a higher excess of acetaldehyde (5-10 equivalents) is used, the yield of Mannich product is increased reasonably.[32] Thus, when N-Boc-imines **76** were treated with acetaldehyde **75** in the presence of L-proline (20 mol%) in CH_3CN at 0 ºC, the desired β-aminoaldehydes **77** were obtained in extremely high enantioselectivities (> 99%) and reasonable yields (**Scheme 25**). The β-amino aldehyde products **77** formed with very high enantioselectivity are highly attractive precursors of chiral β-amino acids, which play a key role in investigations of β-peptides and pharmaceuticals.[37]

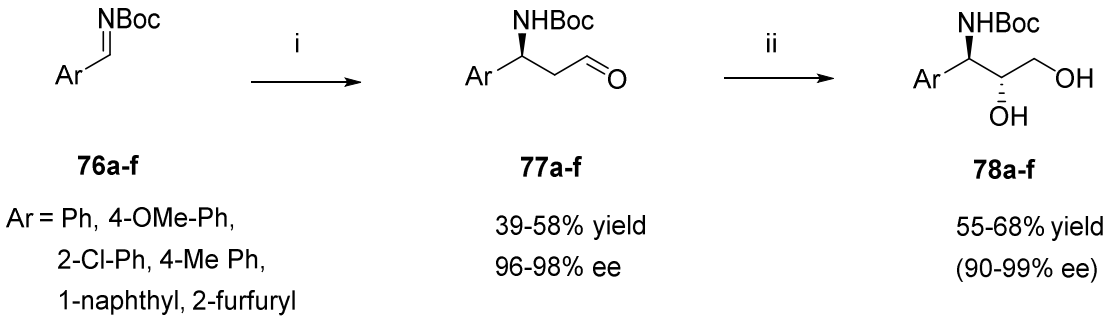


Scheme 25: Mannich reaction of acetaldehyde

1.2.4 Results and Discussion

Considering the high biological importance of chiral 3-amino-1,2-diols, which are also key intermediates in many drugs, we became interested in synthesizing them in one-pot reaction. Based on the literature knowledge of proline-catalyzed Mannich reaction (**Scheme 25**) and α-functionalization of aldehydes, we hypothesized that one pot-synthesis of 3-amino-1,2-alkanediols **78a-f** should be possible through sequential Mannich reaction of Boc-protected benzaldimine **76a-f** with acetaldehyde **75** *via* List's protocol using L-proline providing β-aminoaldehyde **77a-f** *in situ* followed by addition of PhNO and reduction with $NaBH_4$ in the same pot. Accordingly, we

performed several experiments to identify a suitable reaction condition for this sequential α-aminooxylation reaction in one-pot, such as the variation of solvents (CH_3CN, DMSO), temperature, oxygen source (PhNO, benzoyl peroxide) and so on. Unfortunately, we ended up with complex reaction mixtures, often achieving a maximum yield of only 12% of the required product. We then reasoned that low yields may be due to unwanted side reaction of PhNO with the undesired products formed in the Mannich reaction of the first step. To overcome this, we decided to separate pure β-aminoaldehydes **77a-f** after Mannich reaction and then subject it to α-aminooxylation process subsequently (**Scheme 26**).



Scheme 26: (i) CH_3CHO, L-proline (20 mol%), CH_3CN, 0 ^oC, 3 h; (ii) (a) PhNO (0.8 equiv), L-proline (20 mol%), CH_3CN, -10 ^oC, 20 h then $NaBH_4$ CH_3OH, 10 min; (b) $Cu(OAc)_2.H_2O$ (15 mol%), CH_3OH, 25 ^oC, 10 h.

Thus, pure β-aminoaldehydes **77a-f**, the starting materials for α-aminooxylation were efficiently prepared from the corresponding Boc-protected arylaldimines **76a-f** following literature protocol[32] (L-proline, CH_3CN, 0 ºC). The formation of β-aminoaldehydes **77a-f** was confirmed by ^1H and ^{13}C NMR spectroscopy as follows.

Example 1: The ^1H NMR spectrum of β-aminoaldehyde **77a** showed typical proton signals at δ 9.73 (t, J = 1.7 Hz, 1H) and δ 2.83-2.96 (m, 2H) corresponding to

aldehydic and homobenzylic methylene protons respectively. Its ^{13}C NMR showed two characteristic carbon signals at δ 199.8 and 193.3 corresponding to carbamate and aldehyde carbonyl carbons respectively. Its IR spectrum also exhibited a characteristic strong C=O absorption band at 1692 cm^{-1} due to carbamate and aldehydic carbonyl groups (**Fig. 6**).

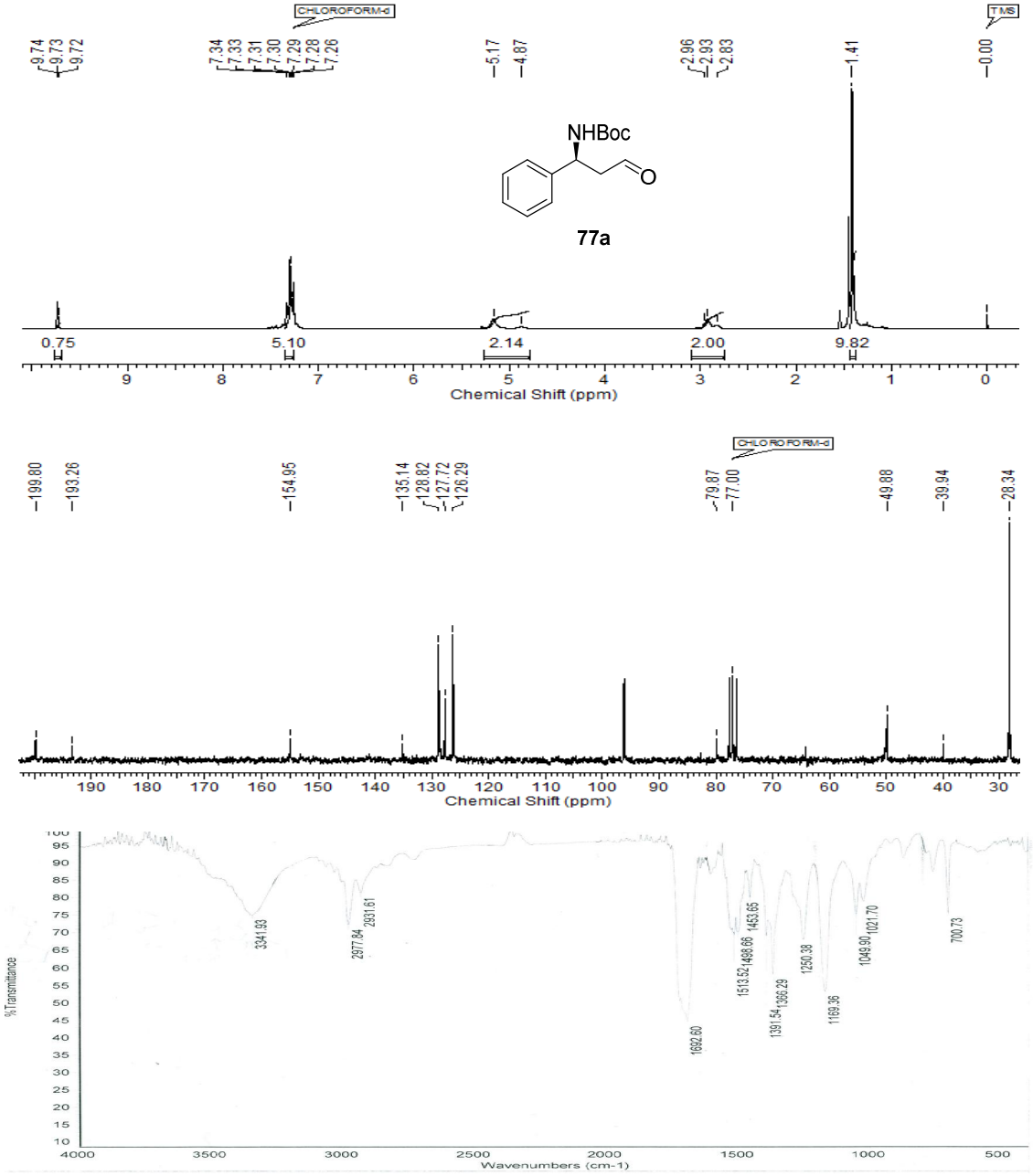


Fig. 6: ^{1}H, ^{13}C NMR and IR spectra of β-aminoaldehyde **77a**

Example 2: The ^{1}H NMR spectrum of β-aminoaldehyde **77e** showed a typical triplet at δ 9.81 (t, J = 2.2 Hz, 1H) and a doublet at δ 3.09 (d, J = 6.5 Hz, 2H) corresponding to aldehydic and homobenzylic methylene protons respectively. Its ^{13}C NMR spectrum showed two characteristic carbon signals at δ 195.4 and 200.2 due to carbamate and aldehydic carbonyl carbons respectively (**Fig. 7**).

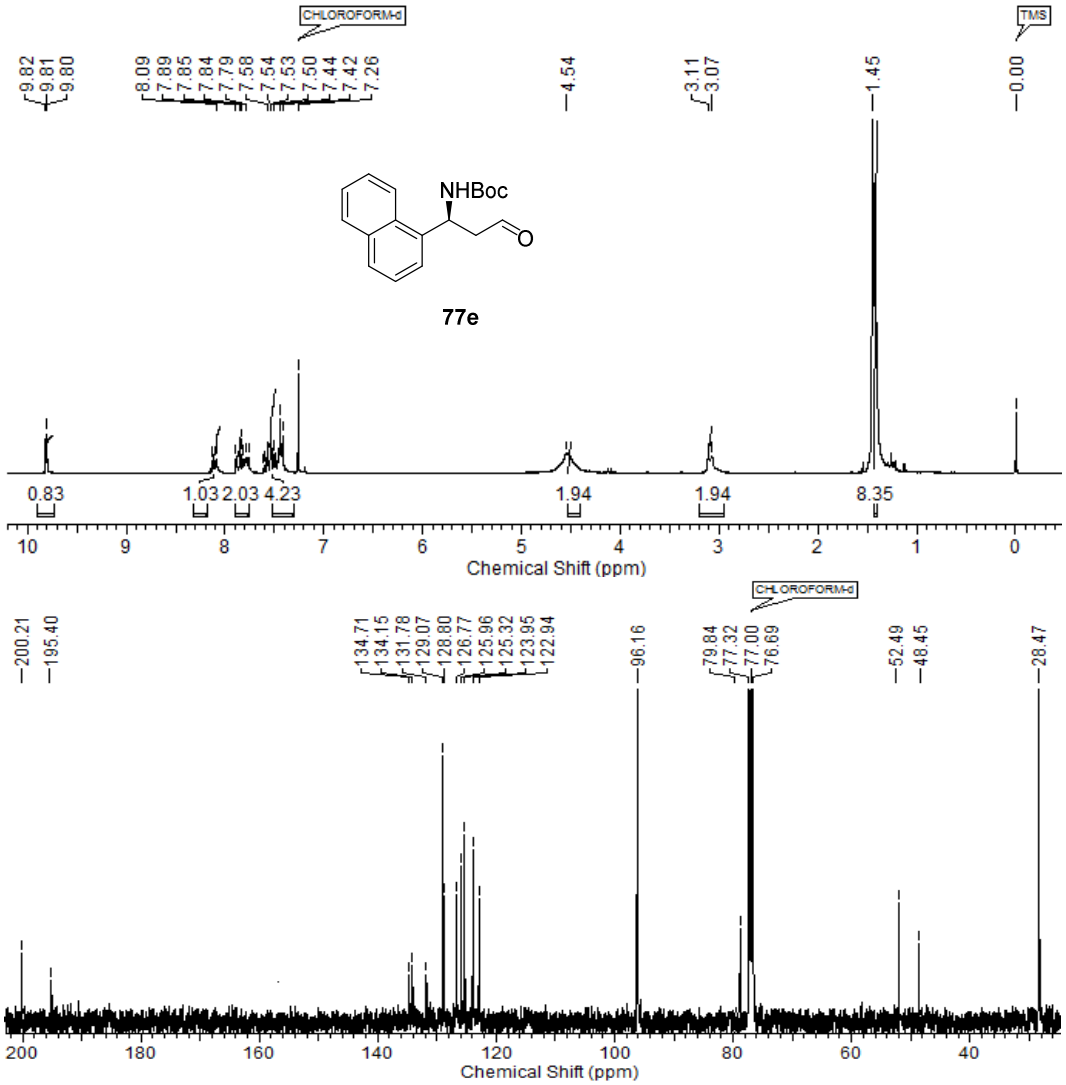


Fig. 7: ^{1}H and ^{13}C NMR spectra of β-aminoaldehyde **77e**

We observed a drastic improvement in the yield of **78a**, when pure β-aminoaldehyde **77a** was subjected to α-aminooxylation separately. The reaction proceeded through α-

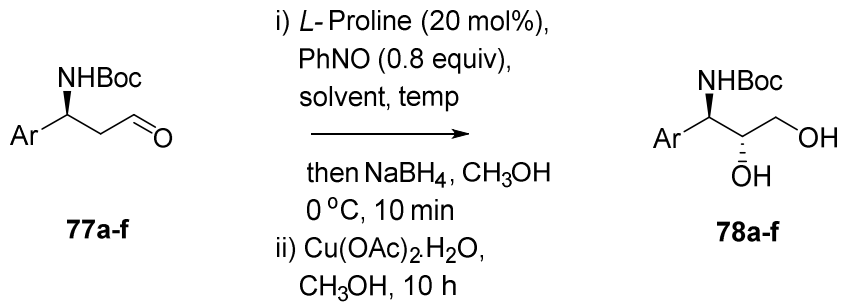
aminoxy aldehyde, which was *in situ* reduced with $NaBH_4$. This was followed by subsequent reduction of the crude aminoxy product with $Cu(OAc)_2.H_2O$ providing >99% diastereomer of *anti*-3-amino-1,2-diol **78a** in 50% yield and 93% ee (**Table 1,** entry 1). The formation of major diastereomer can be explained by the co-ordination *L*-proline *via* hydrogen bonding to the incoming electrophile PhNO and forms the rigid transition state and is not controlled by the substrate.

Encouraged by this result, we became interested to improve the yield further by optimizing the reaction conditions such as variation of solvents and temperatures for the α-aminooxylation step using β-aminoaldehyde **77a** as the model substrate. Among the solvents screened, CH_3CN was found to give a maximum yield as compared to DMSO, $CHCl_3$, CH_2Cl_2 and THF. When the temperature was maintained at -10 ^oC, high yields and high enantiomeric excess were obtained (**Table 1,** entry 2). However, further increase or decrease in the temperature to either 0 ^oC or -20 ^oC had a deleterious effect on the yield.

To determine the scope and generality of the reaction, a variety of β-amino aldehydes **77a-f** were subjected to α-aminooxylation process. In every case, the reaction proceeded smoothly to give a single diastereomer of *anti*-3-amino-1,2-diols **78a-f**, yields ranging from 55-68% with the intact of excellent enantioselectivity. For instance, substrates having electron-rich (entry 9) or electron-deficient (entry 11) substituent on the aromatic ring, 1-naphthyl ring system (entry 12) and heteroaryl (entry 13) gave the desired *anti*-3-amino-1,2-diols in excellent stereoselectivity.

A major advantage of this strategy is that all the four stereoisomers of 3-amino-1,2-diols can be prepared by choosing a suitable L or D-proline for Mannich and subsequent aminooxylation reactions.

Table 1: L-proline-catalyzed α-aminooxylation of β-aminoaldehydes: studies on optimization and substrate scope



entry	substrates **77a-f** (Ar)	solvent	temp (^oC)	time (h)	products **78a-f**	yield (%)[a]	dr (%)[b]	ee %
1	Ph	CH_3CN	-20	22	78a	50	>99	93[d]
2	**Ph**	**CH_3CN**	**-10**	**15**	**78a**	**68**	**>99**	**93**[d]
3	Ph	CH_3CN	0	15	78a	53	>99	90[d]
4	Ph	DMSO	25	0.5	78a	55	>99	93[d]
5	Ph	DMF	25	1	78a	17	>99	nd
6	Ph	$CHCl_3$	25	24	78a	30	>99	nd
7	Ph	CH_2Cl_2	25	20	78a	40	>99	91[d]
8	Ph	THF	25	24	78a	16	>99	nd
9	4-OMe-Ph	CH_3CN	-10	15	78b	65	>99	92[d]
10	4-Me-Ph	CH_3CN	-10	15	78c	63	>99	95[c]
11	2-Cl-Ph	CH_3CN	-10	15	78d	55	>99	>99[c]
12	1-naphthyl	CH_3CN	-10	15	78e	62	>99	92[c]
13	2-furfuryl	CH_3CN	-10	15	78f	58	>99	90[c]

[a]Isolated yield after column chromatographic purification. [b]determined based on [1] HNMR spectrum. [c]determined from HPLC analysis. [d] by comparing with specific rotation reported in the literature.[39]

The formation of all *anti*-3-amino-1,2-diols **78a-f** was established unambiguously from their corresponding ^{1}H & ^{13}C NMR, IR and HRMS spectral data. Their optical purity was established from their chiral HPLC analyses.

Example 1: The ^{1}H NMR spectrum of *anti*-3-amino-1,2-diol **78c** showed two typical signals at δ 2.82 (br s, 1H) and 3.31 (br s, 1H) corresponding to hydroxyl protons while the other signal at δ 2.31 (s, 3H) is due to methyl protons attached to aromatic ring. Its ^{13}C NMR spectrum showed two characteristic carbon signals at δ 62.8 and 73.2 due to methylene and methine carbons attached to hydroxyl groups respectively. Its IR spectrum displayed a characteristic broad absorption band at 3366 cm^{-1} indicating the presence of OH functional group (**Fig. 8**).

The absolute configuration of the newly generated chiral center was assigned on the basis of the previously established configuration of α-aminoxylation of aldehydes.[33] The *anti*-stereochemistry in *anti*-3-amino-1,2-diol **78c** is, however, unambiguously proven from X-ray crystallographic analysis (**Fig. 9**).

Example 2: The ^{1}H NMR spectrum of *anti*-3-amino-1,2-diol **78f** showed a typical broad signal between δ 2.95-3.02 (br s, 2H) corresponding to hydroxyl protons while the other signal at δ 3.67 (br s, 1H) for methylene ($-CH_2-OH$) protons; Its ^{13}C NMR spectrum showed two characteristic carbon signals at δ 62.8 and 73.1 attributed to methylene and methine carbons attached to hydroxyl groups respectively. Its mass spectrum also confirmed the formation of *anti*-3-amino-1,2-diol **78f** (**Fig. 11**).

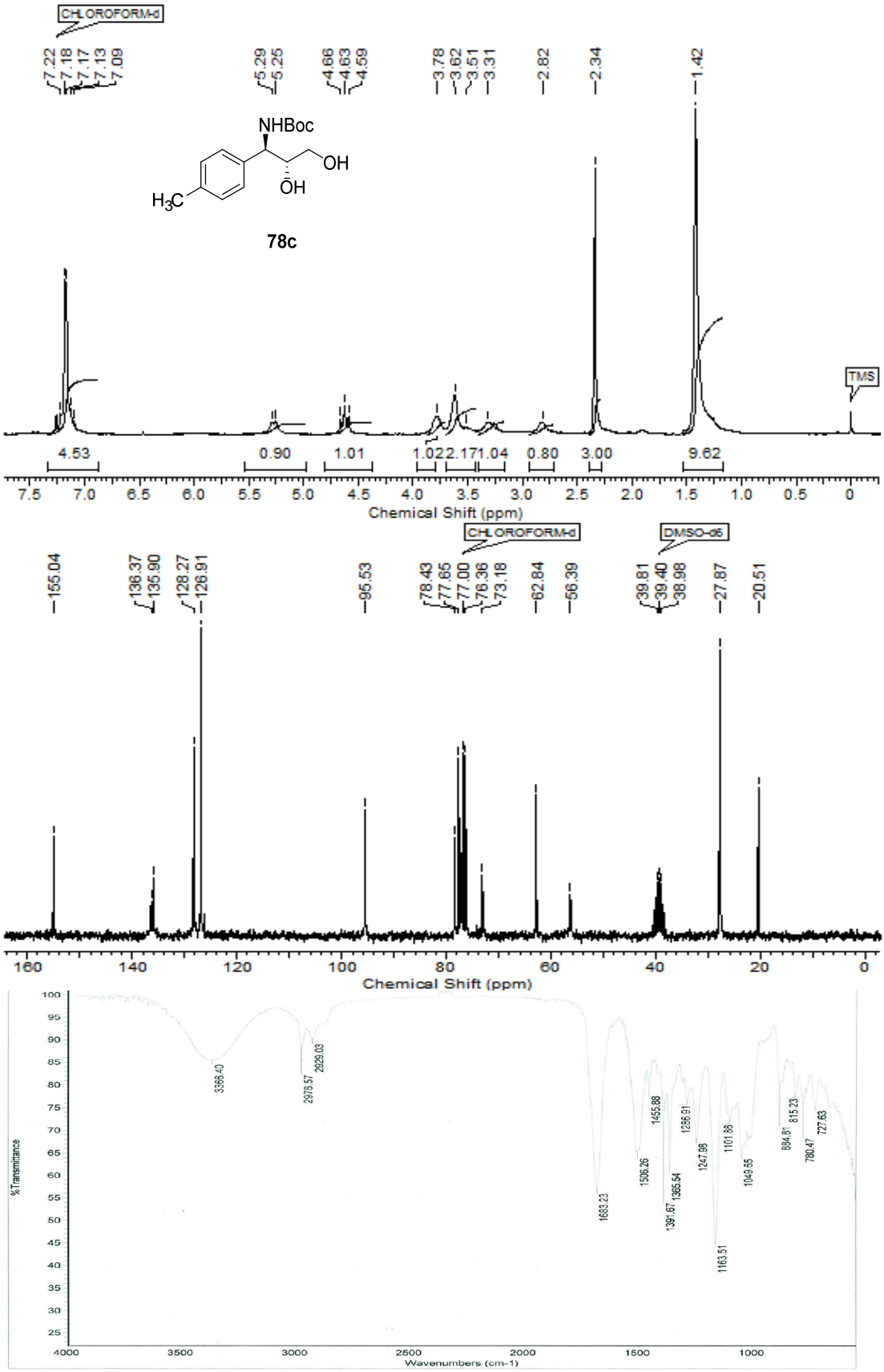


Fig. 8: ^{1}H, ^{13}C NMR and IR spectra of *anti*-3-amino-1,2-diol **78c**

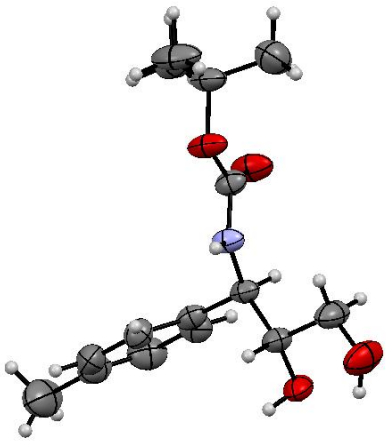
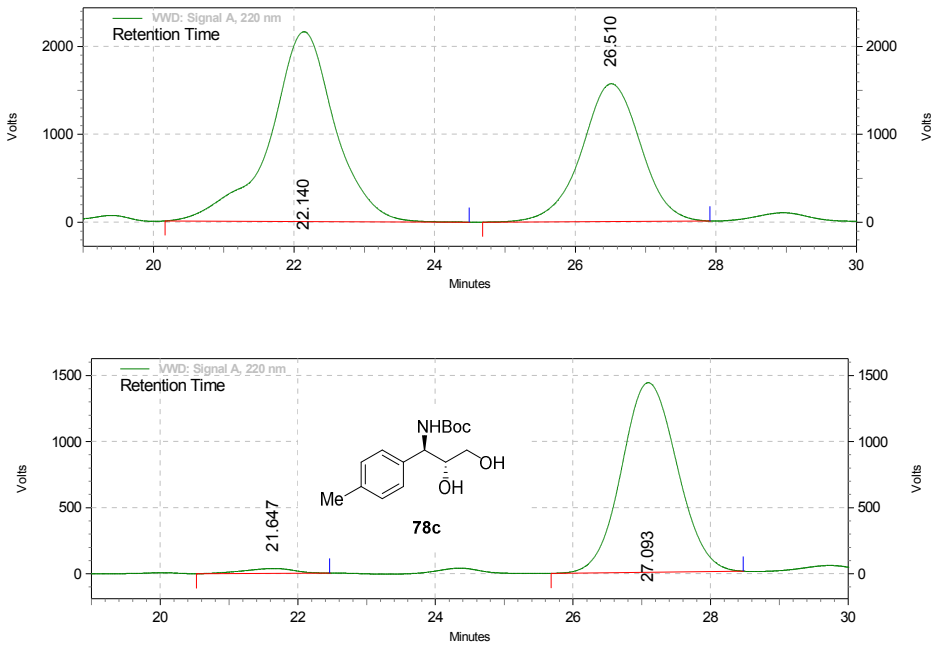


Fig. 9: ORTEP diagram of *anti*-3-amino-1,2-diol **78c**

The optical purity of *anti*-3-amino-1,2-diol **78c** was determined to be 95% ee from chiral HPLC analysis (Chiracel AD-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 21.6 min (2%) and 27.1 min (97%)) (**Fig**.**10**).



Retention Time	Area	Area %	Height	Height %
21.647	30977944	2.25	614502	2.49
27.093	1348524270	97.75	24059261	97.51

Fig. 10: HPLC chromatogram of *anti*-3-amino-1,2-diol **78c**

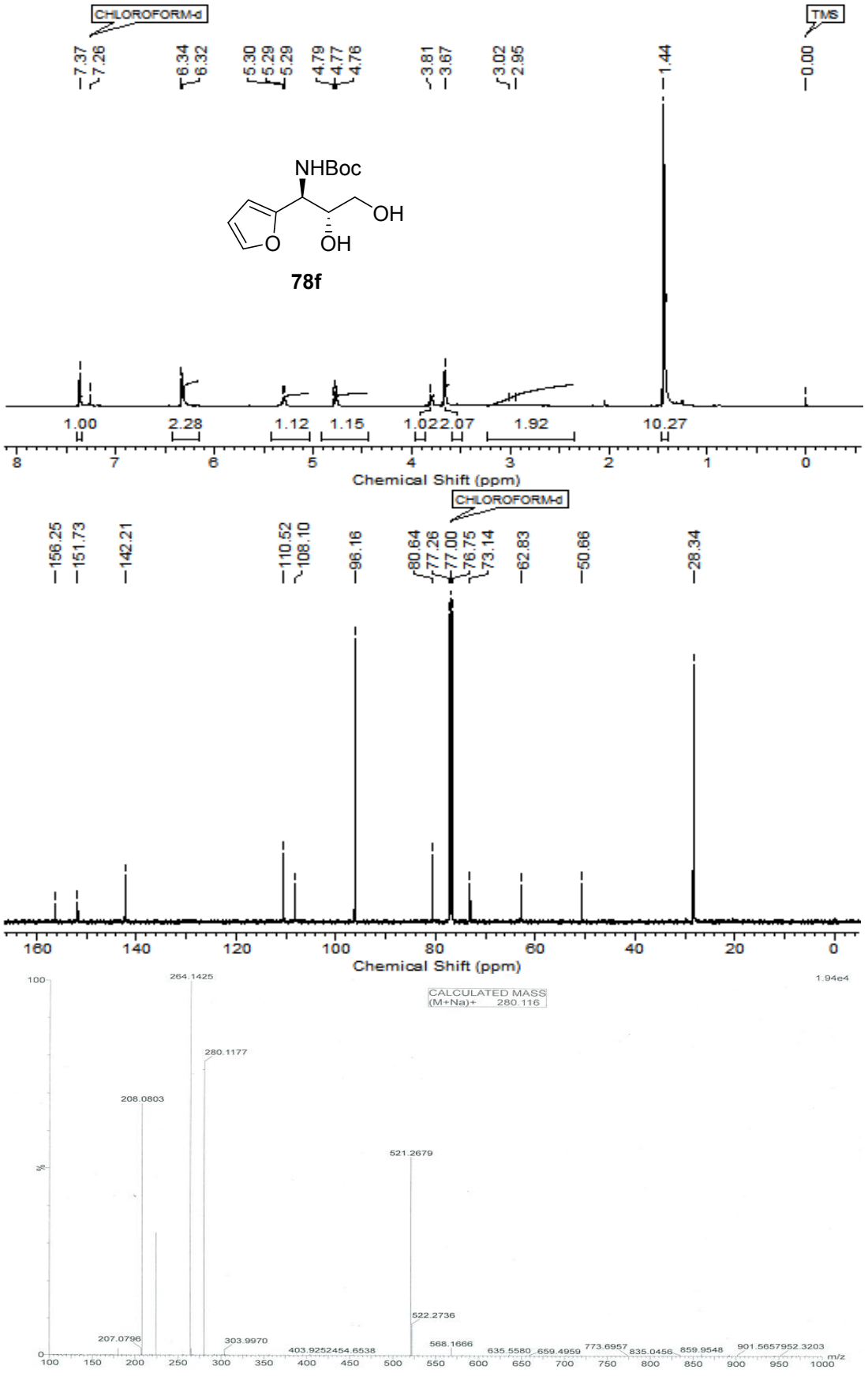


Fig. 11: ^{1}H, ^{13}C NMR and mass spectra of *anti*-3-amino-1,2-diol **78f**

1.2.5 Conclusion

A highly stereoselective route to 3-amino-1,2-diols using proline as catalyst in a single transformation starting from β-aminoaldehydes has been developed. This reaction is also practical in the sense that (i) all the four stereoisomers of 3-amino-1,2-diols can be prepared by choosing a suitable proline as catalyst for Mannich and subsequent aminooxylation reactions; (ii) products were obtained in high optical purities (single diastereomer with 90-99% ee) and moderate yields; (iii) showed broad substrate scope and good functional group tolerance. We believe that this strategy will find applications in the field of asymmetric synthesis of bioactive molecules owing to the flexible nature of the synthesis and the ready availability of proline catalysts in both enantiomeric forms.

1.2.6 Experimental Section

General experimental procedure for the preparation of β-aminoaldehydes (77a-f)

To a stirred solution of aryl N-Boc-imine **76a-f** (1.4 mmol) and redistilled acetaldehyde **75** (0.39 mL, 7 mmol) in CH_3CN (15 mL) at 0 ^oC was added L-proline (0.032 g, 20 mol%) and the mixture stirred further at 0 ^oC for 3 h. After the completion of reaction (monitored by TLC), it was quenched with water and extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4, filtered and concentrated under reduced pressure to give the crude aldehyde. Flash column chromatographic purification [silica gel (230-400 mesh) and pet. ether:EtOAc as an eluent] gave β-aminoaldehydes **77a-f**.

(*S*)-*tert*-Butyl (3-oxo-1-phenylpropyl)carbamate (77a)

Yield: 55%; pale yellow solid; **mp**: 91-94 ºC, (lit.[38] **mp**: 92-93.5 ºC); $[\alpha]^D_{25}$ -30.10 (*c* 1.15, $CHCl_3$); lit.[33] $[\alpha]^D_{25}$ +29.0 (*c* 1.4, $CHCl_3$) for its antipode; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 700, 1021, 1049, 1169, 1250, 1369, 1391, 1498, 1513, 1692, 2977, 3341; **^{1}H NMR**

(200 MHz, $CDCl_3$): δ 1.41 (s, 9H), 2.83-2.96 (m, 2H), 4.87 (br s, 1H), 5.17 (br s, 1H), 7.26-7.34 (m, 5H), 9.73 (t, *J* = 1.7 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 28.3, 39.9, 49.9, 79.9, 126.3, 127.7, 128.8, 135.2, 155.0, 193.3, 199.8; **Analysis**: $C_{14}H_{19}NO_3$ requires C, 67.45; H, 7.68; N, 5.62; found: C, 67.32; H, 7.41; N, 5.46%.

(*S*)-*tert*-Butyl (1-(4-methoxyphenyl)-3-oxopropyl)carbamate (77b)

Yield: 56%; pale yellow viscous liquid; $[\alpha]^{D}_{25}$ -32.90 (*c* 1.1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 690, 1021, 1050, 1170, 1246, 1378, 1387, 1463, 1520, 1689, 2850, 2924, 2978, 3346; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.41 (s, 9H), 2.80-2.94 (m, 2H), 3.78 (s, 3H), 4.90 (br s, 1H), 5.13 (br s, 1H), 6.85 (d, *J* = 8.6 Hz, 2H), 7.21 (d, *J* = 8.6 Hz, 2H), 9.72 (t, *J* = 1.6 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 28.3, 39.8, 49.8, 55.1, 79.6, 114.1, 127.5, 134.9, 154.9, 159.0, 193.4, 200.0; **Analysis**: $C_{15}H_{21}NO_4$ requires C, 64.50; H, 7.58; N, 5.01; found: C, 64.32; H, 7.38; N, 5.06%.

(*S*)-*tert*-Butyl (3-oxo-1-(p-tolyl)propyl)carbamate (77c)

Yield: 58%; pale yellow gum; $[\alpha]^{D}_{25}$ -36.28 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 700, 1026, 1054, 1172, 1242, 1384, 1467, 1518, 1692, 2900, 2982, 3341; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.41 (s, 9H), 2.33 (s, 3H), 2.83-2.96 (m, 2H), 5.15 (br s, 1H), 5.17 (br s, 1H), 7.13-7.26 (m, 4H), 9.73 (t, *J* = 1.7 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.3, 28.4, 50.8, 53.1, 79.6, 125.1, 128.8, 136.9, 140.5, 193.4, 202.2; **Analysis**: $C_{15}H_{21}NO_3$ requires C, 68.42; H, 8.04; N, 5.32; found: C, 68.26; H, 8.01; N, 5.26%.

(*S*)-*tert*-Butyl (1-(2-chlorophenyl)-3-oxopropyl)carbamate (77d)

Yield: 49%; yellowgum; $[\alpha]^{D}_{25}$ -12.32 (*c* 1.6, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 696, 1032, 1061, 1168, 1256, 1376, 1459, 1522, 1698, 2851, 2868, 3347; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.45 (s, 9H), 2.86-2.98 (m, 2H), 4.54 (br s, 2H), 5.26 (br s, 1H), 7.21-7.28 (m, 2H), 7.32-7.40 (m, 2H), 9.73 (t, *J* = 1.5 Hz, 1H); **^{13}C NMR** (50 MHz,

$CDCl_3$): δ 28.4, 46.4, 51.5, 79.4, 126.6, 128.3, 132.2, 136.5, 193.4, 199.7; **Analysis**: $C_{14}H_{18}ClNO_3$ requires C, 59.26; H, 6.39; N, 4.94; found: C, 59.12; H, 6.19; N, 4.82%.

(*S*)-*tert*-Butyl (1-(naphthalen-1-yl)-3-oxopropyl)carbamate (77e)

Yield: 44%; yellow gum; $[\alpha]^{D}_{25}$ -18.71 (*c* 1.9, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 700, 1024, 1053, 1174, 1259, 1398, 1481, 1501, 1626, 2979, 3412; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.45 (s, 9H), 3.09 (d, *J* = 6.5 Hz, 2H), 4.54 (br s, 2H), 7.42-7.61 (m, 4H), 7.76-7.89 (m, 2H), 8.11 (d, *J* = 8.1 Hz, 1H), 9.81 (t, *J* = 2.2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 28.4, 48.4, 52.5, 79.8, 122.9, 123.9, 125.3, 125.9, 126.7, 128.8, 129.1, 131.8, 134.2, 134.7, 195.4, 200.2; **Analysis**: $C_{18}H_{21}NO_3$ requires C, 72.22; H, 7.07; N, 4.68; found: C, 72.12; H, 7.03; N, 4.47%.

(*S*)-*tert*-Butyl (1-(furan-2-yl)-3-oxopropyl)carbamate (77f)

Yield: 39%; yellowish brown gum; $[\alpha]^{D}_{25}$ -18.71 (*c* 1.9, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 690, 1084, 1062, 1174, 1259, 1391, 1467, 1501, 1683, 2824, 2841, 3421; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.44 (s, 9H), 2.91-3.02 (m, 2H), 5.11 (br s, 1H), 5.27 (br s, 1H), 6.30-6.34 (m, 2H), 7.36 (br s, 2H), 9.77 (t, *J* = 2.1 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 28.4, 50.1, 51.5, 79.4, 108.3, 110.6, 142.3, 151.8, 193.6, 200.7; **Analysis**: $C_{12}H_{14}NO_4$ requires C, 60.24; H, 7.16; N, 5.85; found: C, 60.12; H, 7.03; N, 5.76%.

General experimental procedure for the preparation of 3-amino-1,2-alkane diols (78a-f)

To a stirred precooled (-10 °C) acetonitrile (25 mL) solution of β-aminoaldehydes **77a-f** (17 mmol) and nitrosobenzene (1.45 g, 13.6 mmol) was added L-proline (0.039 g, 20 mol%). The reaction mixture was allowed to stir at the same temperature for 20 h followed by the addition of MeOH (10 mL) and $NaBH_4$ (0.97 g, 25 mmol) to the reaction mixture, which was stirred for further 10 min. After addition of phosphate buffer, the resulting mixture was extracted with EtOAc (3 × 30 mL) and the combined

organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude aminooxy alcohol, which was directly taken up for the next step without purification. To a MeOH (25 mL) solution of the above crude aminooxyalcohol was added $Cu(OAc)_2.H_2O$ (0.501 g, 2.6 mmol) at 25 °C and the reaction mixture was allowed to stir for 10 h at that temperature. After addition of phosphate buffer, the resulting mixture was extracted with $CHCl_3$ (3 × 30 mL) and the combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude product, which was then purified by column chromatography over silica gel using pet. ether:EtOAc to give 3-amino-1,2-alkane diols **78a-f**.

(2*R*, 3*R*)-3-(*tert*-Butoxycarbonylamino)-3-phenyl-1,2-propanediol (78a):

Yield: 68%; colourless solid; **mp**: 106-109 ºC,(lit.[39] **mp**: 107-108 ºC); $[\alpha]^D_{25}$ -40.10 (*c* 1.32, $CHCl_3$); lit.[14] $[\alpha]^D_{25}$ +42.90 (*c* 1.4, $CHCl_3$) for its antipode; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 790, 1025, 1056, 1124, 1161, 1369, 1400, 1495, 1696, 2930, 2986, 3370; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.43 (s, 9H), 2.81 (br s, 1H), 3.28 (br s, 1H), 3.64 (br s, 2H), 3.83 (br s, 1H), 4.66-4.70 (m, 1H), 5.29 (br s, 1H), 7.26-7.38 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 28.3, 56.7, 63.2, 73.9, 80.1, 127.4, 127.7, 128.6, 139.0, 156.1; **HRMS** (ESI) *m/z* calcd for $C_{14}H_{21}NO_4$ $[M + Na]^+$: 290.1368, found: 290.1377; **Analysis**: $C_{14}H_{21}NO_4$ requires C, 62.90; H, 7.92; N, 5.24; found: C, 62.78; H, 7.81; N, 5.12%.

(2*R*, 3*R*)-3-(*tert*-Butoxycarbonylamino)-3-(*p*-methoxyphenyl)-1,2-propanediol (78b):

Yield: 65%; colorless solid; **mp:** 114-116 ºC, (lit.[40] **mp**: 116-118 ºC); $[\alpha]^D_{25}$ -49.43 (*c* 0.6, $CHCl_3$); lit.[15] $[\alpha]^D_{25}$ -50.2 (*c* 0.5, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 669, 757, 831, 927, 1035, 1167, 1216, 1368, 1585, 1612, 1701, 2400, 2839, 2981, 3019, 3438, 3682; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.41 (s, 9H), 2.99-3.12 (br m, 2H), 3.61 (br s, 2H), 3.78 (br s, 4H), 4.62 (br s, 1H), 5.36 (br s, 1H), 6.85 (d, *J* = 6.7 Hz, 2H), 7.21 (d, *J* =

6.7 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 28.3, 55.2, 56.1, 63.2, 74.1, 80.1, 114.2, 128.5, 131.1, 156.2, 159.2; **HRMS** (ESI) *m/z* calcd for $C_{15}H_{23}NO_5$ $[M + Na]^+$: 320.1473, found: 320.1485; **Analysis**: $C_{15}H_{23}NO_5$ requires C, 60.59; H, 7.80; N, 4.71; found: C, 60.29; H, 7.62; N, 4.69%.

(2*R*, 3*R*)-3-(*tert*-Butoxycarbonylamino)-3-(*p*-tolyl)-1,2-propanediol (78c):

Yield: 63%; colorless solid recrystallized from $CHCl_3$; **mp:** 126-129 ºC; $[\alpha]^D_{25}$ -57.87 (*c* 2.7, $CHCl_3$); 95% ee from chiral HPLC analysis (Chiracel AD-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 21.6 min (97%) and 27.1 min (2%); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 727, 780, 815, 884, 1049, 1101, 1163, 1247, 1287, 1365, 1391, 1506, 1683, 2929, 2976, 3366; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.42 (s, 9H), 2.34 (s, 3H), 2.82 (br s, 1H), 3.31 (br s, 1H), 3.51-3.62 (m, 2H), 3.78 (br s, 1H), 4.59-4.66 (m, 1H), 5.25 (d, *J* = 6.7 Hz, 1H), 7.09-7.22 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$+DMSO-d_6): δ 20.5, 27.9, 56.4, 62.8, 73.2, 78.4, 127.0, 128.3, 135.9, 136.4, 155.0; **HRMS** (ESI) *m/z* calcd for $C_{15}H_{23}NO_4$ $[M + Na]^+$: 304.1519, found: 304.1514; **Analysis**: $C_{15}H_{23}NO_4$ requires C, 64.04; H, 8.24; N, 4.98; found: C, 63.91; H, 8.12; N, 4.93%.

(2*R*, 3*R*)-3-(*tert*-Butoxycarbonylamino)-3-(*o*-chlorophenyl)-1,2-propanediol (78d):

Yield: 55%; colorless gum; $[\alpha]^D_{25}$ -7.50 (*c* 0.32, $CHCl_3$); 99% ee from chiral HPLC analysis (Chiracel AS-H, *n*-hexane/*i*PrOH, 95:05, 0.5 mL/min) retention time 25.9 min (0.5%) and 28.8 min (99.5%); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 702, 704, 1036, 1164, 1264, 1367, 1393, 1498, 1694, 2928, 3420; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.43 (s, 9H), 2.97 (br s, 1H), 3.39 (br s, 1H), 3.64-3.79 (m, 2H), 3.98-3.99 (m, 1H), 5.15-5.17 (m, 1H), 5.55 (br s, 1H), 7.19-7.25 (m, 2H), 7.27-7.42 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 28.3, 54.1, 62.8, 72.2, 80.4, 127.1, 129.0, 130.1, 133.8, 136.6, 156.3; **HRMS** (ESI) *m/z* calcd for $C_{14}H_{20}ClNO_4$ $[M + Na]^+$: 324.0973, found: 324.0970;

Analysis: $C_{14}H_{20}ClNO_4$ requires C, 55.72; H, 6.68; N, 4.64; found: C, 55.56; H, 6.48; N, 4.47%.

(2*R*, 3*R*)-3-(*tert*-Butoxycarbonylamino)-3-(1-naphthyl)-1,2-propanediol (78e):

Yield: 62%; colorless gum; $[\alpha]^{D}_{25}$ -13.00 (*c* 0.2, $CHCl_3$); 92% ee from chiral HPLC analysis (Chiracel AD-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 12.55 min (3.92%) and 21.64 min (96.1%); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 774, 1019, 1038, 1121, 1159, 1351, 1408, 1499, 1687, 2921, 2991, 3382; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.44 (s, 9H), 2.66 (br s, 1H), 3.48 (br s, 1H), 3.76-3.86 (dd, *J* = 12.0, 29.3 Hz, 2H), 4.10-4.12 (m, 1H), 5.14 (d, *J* = 8.1 Hz, 1H), 5.53-5.57 (m, 1H), 7.48-7.57 (m, 4H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 8.06 (d, *J* = 8.3 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 28.3, 51.7, 62.9, 72.9, 80.6, 122.9, 123.9, 125.3, 125.9, 126.8, 128.8, 129.1, 131.8, 134.2, 134.7, 156.8; **HRMS** (ESI) *m/z* calcd for $C_{18}H_{23}NO_4$ $[M + Na]^+$: 340.1519, found: 340.1515; **Analysis**: $C_{18}H_{23}NO_4$ requires C, 68.12; H, 7.30; N, 4.41; found: C, 67.93; H, 7.12; N, 4.31%.

(2*R*, 3*S*)-3-(*tert*-Butoxycarbonylamino)-3-(furfuryl)-1,2-propanediol (78f):

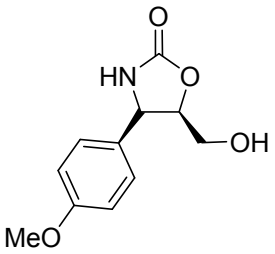
Yield: 58%; colorless gum; $[\alpha]^{D}_{25}$ -44.32 (*c* 0.46, $CHCl_3$); 90% ee; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 784, 1089, 1066, 1178, 1263, 1398, 1469, 1508, 1699, 2824, 2841, 3384, 3421; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.44 (s, 9H), 2.95 (br s, 2H), 3.67 (s, 2H), 3.81 (br s, 1.02), 4.76-4.79 (m, 1H), 5.29 (br s, 1H), 6.32-6.34 (m, 2H), 7.37 (br s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 28.3, 50.7, 62.8, 73.1, 80.6, 108.1, 110.5, 142.2, 151.7, 156.2; **HRMS** (ESI) *m/z* calcd for $C_{12}H_{19}NO_5$ $[M + Na]^+$: 280.1169, found: 280.1177; **Analysis**: $C_{12}H_{19}NO_5$ requires C, 56.02; H, 7.44; N, 5.44; found: C, 56.07; H, 7.36; N, 5.32%.

Section II:

Enantioselective Synthesis of Cytokine Modulator (-)-Cytoxazone

1.3.1 Introduction

In 1998, Osada and co-workers reported the isolation of (4*R*,5*R*)-5-(hydroxymethyl)-4-(4-methoxyphenyl)-1,3-oxazolidine-2-one [(–)-**79**, generic name cytoxazone],[41] which was shown to possess high cytokine modulator activity by acting on the Th2 cells.[42] Because of these biological properties, several total syntheses of (-)-cytoxazone (**79**) (**Fig 12)** have been reported.[46-68]



(-)-cytoxazone (79)

Fig. 12

1.3.2 Pharmacology of Cytoxazone Epimers

It is well established that the induction of humoral or cellular response is influenced by the development of distinct subsets of $CD4^+$ T cells.[43] The Th1 cell subset produces predominantly IL-2, GM-CSF, INF-γ, and TNF-β, (type 1 cytokines) and is involved in delayed-type hypersensitivity reactions, whereas the Th2 cell subset secretes IL-4, IL-5, IL-6, IL-10, and IL-13 (type 2 cytokines), which are important factors for β cell growth and differentiation to Ig secretion. The imbalance of cytokine production by $CD4^+$ T cells leads to a wide variety of immunological disorders, *i.e.* allergy, progressive lymphoproliferation, and severe immunodeficiency.[44] Skin and lung biopsies from allergic patients indicate that the pivotal cells in the allergic site

are the Th2 cells.[45] Treatments effectively suppressing the function or the differentiation of these allergen-specific Th2 cells will most likely provide efficient ways to intervene in Ig-mediated allergic diseases. In the course of screening for chemical immunomodulators that inhibit the type 2 cytokine productions in Th2 cells, it was found that cytoxazone containing a 2-oxazolidinone ring, which is rare in microbial metabolites, as a novel cytokine modulator produced by *Streptomyces sp*. Cytoxazones show a cytokine-modulating activity by inhibiting the signaling pathway of Th2 cells, but not Th1 cells.

1.3.3 Review of Literature

(a) Review of Literature for (-)-Cytoxazone (79)

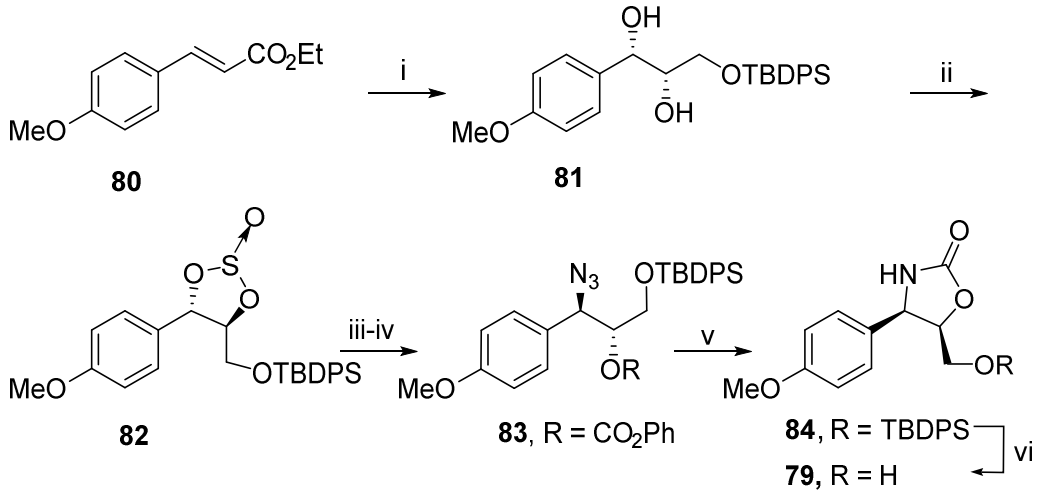
Literature search revealed that there are several reports available for the synthesis of (-)-cytoxazone (**79**), which are described below.

Nakata's approach (1999)[46]

Nakata *et al.* have achieved the synthesis of (-)-cytoxazone (**79)** using Sharpless asymmetric dihydroxylation of cinnamic ester **80**. The cyclic sulfite **82** was obtained (in 99% yield and 97% ee) from ethyl *p*-methoxycinnamate **80** by a two-step process involving the Sharpless catalytic asymmetric dihydroxylation followed by treatment with $SOCl_2$. The cyclic sulfite **82** was then opened using LiN_3 and the alcohol obtained was protected as the corresponding carbonate **83**. Intramolecular cyclization of carbonate **83** with PPh_3 followed by the deprotection of TBDPS group gave (-)-cytoxazone (**79**) in 89% ee and 96% yield (**Scheme 27**).

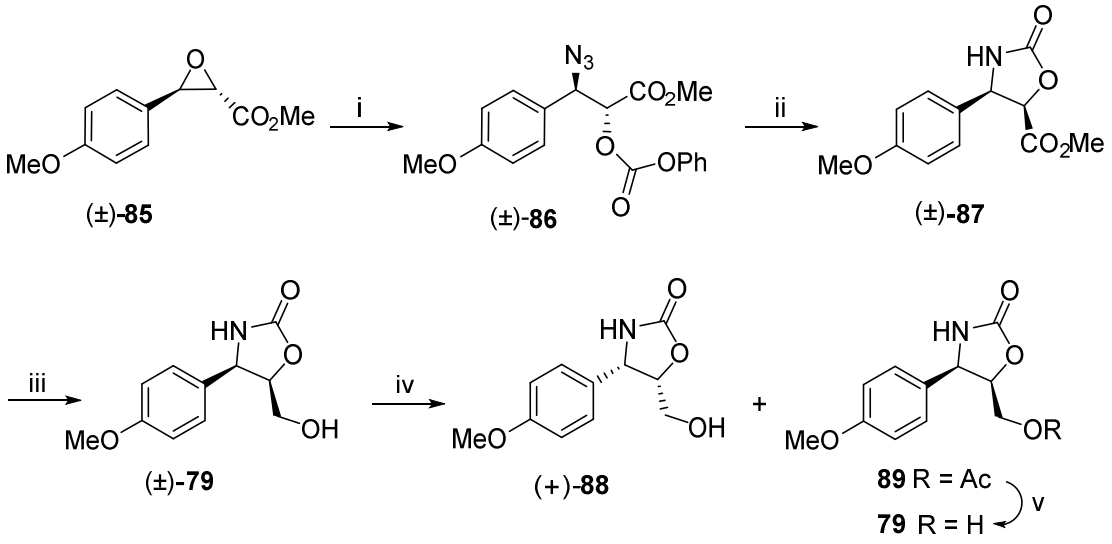
Sunjic's approach (2001)[51]

In this approach, synthesis of (±)-cytoxazone (**79**) was achieved starting from the glycidic ester (±)-**85** using enzymatic kinetic resolution. Nucleophilic ring opening of



Scheme 27: (i) (a) AD-mix-α, *tert*-BuOH: H_2O (1:1), 25 °C, 93 %, 99% ee; (b) $NaBH_4$, THF, 0 °C, 66%; (c) TBDPSCI, imid., DMF, 0 °C, 99%; (ii) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 99%; (iii) LiN_3, DMF, 70 °C, 74 %; iv) $ClCO_2Ph$, Py, CH_2Cl_2, 25 ºC, 96%; (v) PPh_3, THF/ H_2O, 50 °C, 90%; (vi) n-Bu_4NF, THF, 0 °C, 89% ee, 96%.

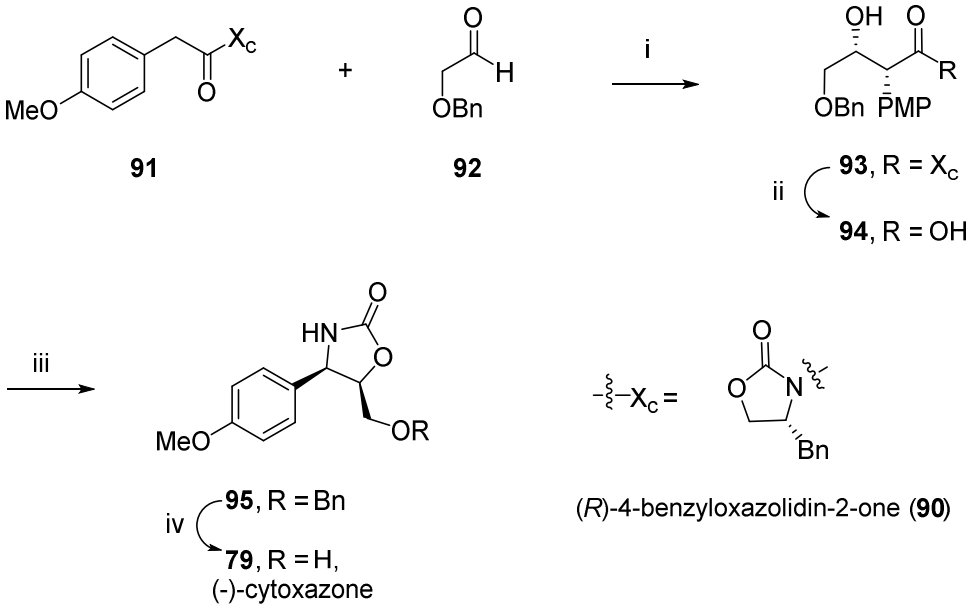
the epoxide (±)-**85** with NaN_3, followed by protection of the alcohol and intramolecular cyclization gave ester (±)-**87**. Reduction of the ester (±)-**87** and the subsequent kinetic resolution of racemic (±)-**79** using *Penicillium camemberti* lipase (PcamL) afforded (-)-cytoxazone (**79)** in 33% overall yield and 88.2% ee (**Scheme 28**).



Scheme 28: (i) (a) aq. NaN_3, dioxane, 50 °C, 3 h, 56%; (b) $ClCO_2Ph$, CH_2Cl_2, –5 °C, 1 h, 100%; (ii) Ph_3P, aq THF, 50 °C, 1.5 h, 88%; (iii) $NaBH_4$, $CaCl_2$, absolute EtOH, 25 ºC, 20 min, 79%; (iv) PcamL, vinyl acetate, 30 °C; (v) KOH, MeOH, 25 ºC, 1 h.

Carter's approach (2003)[53]

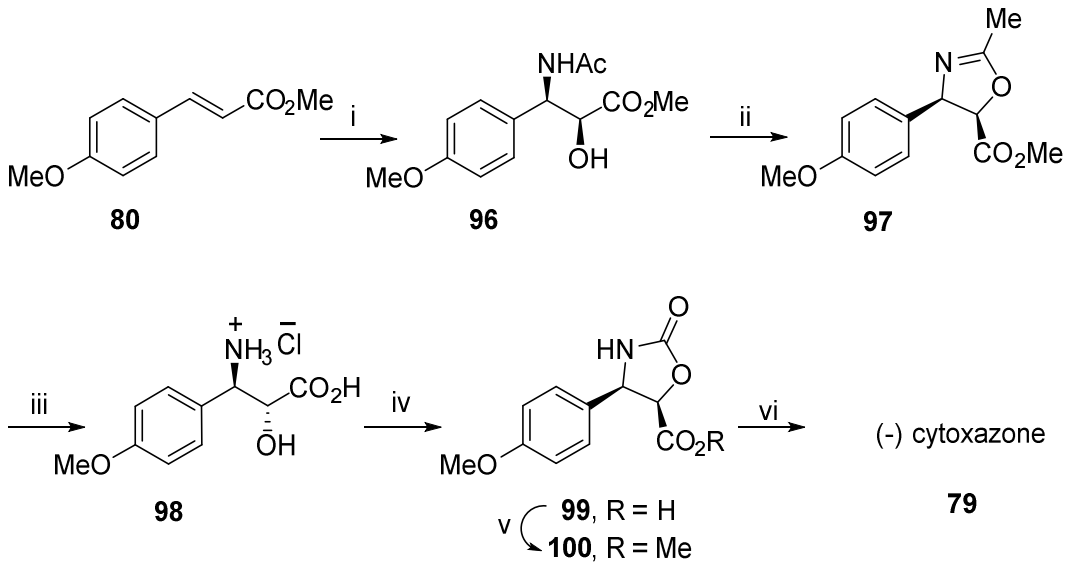
Carter *et. al* have made use of the Evans' *anti*-selective aldol approach as the key reaction for the synthesis of (-)-cytoxazone (**79**). Thus, acylation of the commercially available (*R*)-oxazolidin-2-one **90** with 4-methoxyphenylacetic acid afforded imide **91**. The reaction of dibutylboryl enolate of **91** with benzyloxyacetaldehyde **92** provided the *syn*-aldol **93** (dr = 3:1). Removal of the chiral auxiliary from **93** provided the corresponding acid **94**, which was transformed into the oxazolidinone **95** in a one-pot 3-step procedure: (i) acyl azide formation, (ii) Curtius rearrangement and (iii) isocyanate trapping. Oxazolidinone **95** was debenzylated using Pearlman's catalyst to provide (-)-cytoxazone (**79**) (**Scheme 29**).



Scheme 29: (i) Bu_2BOTf, $^iPr_2EtN$, 0 °C, 30 min, then $BnOCH_2CHO$ precomplexed with 0.5 equiv $SnCl_4$, -78 °C, 3 h, 64%; (ii) H_2O_2, LiOH, THF:H_2O (4:1), 0 °C, 1 h, 99%; (iii) $(PhO)_2PON_3$, CH_2Cl_2, 23 °C, 40 min, 45 °C, 12 h, 61%; (iv) H_2 (1 atm), $Pd(OH)_2$, CH_3OH, 23 °C, 24 h, 84%.

Saicic's approach (2004)[57]

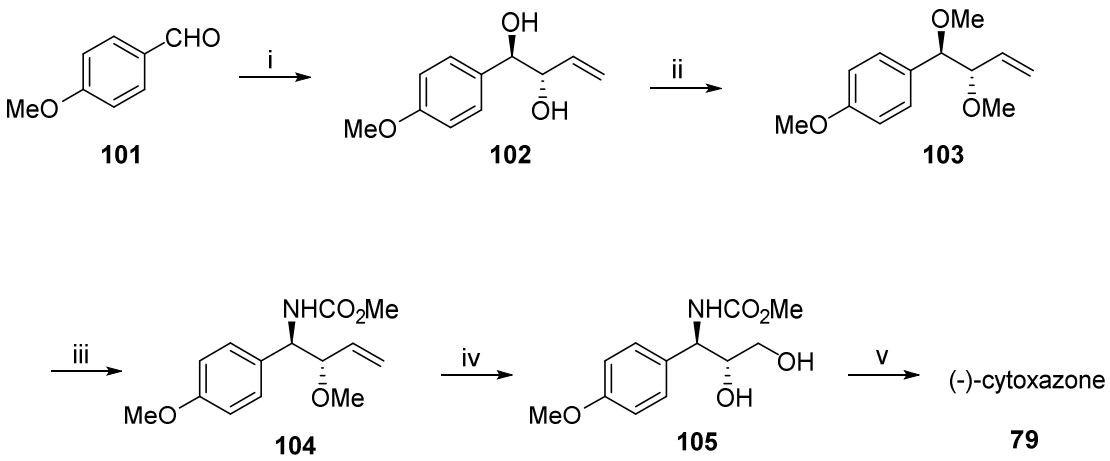
Saicic's approach was based on the Sharpless asymmetric aminohydroxylation reaction, starting from methyl *p*-methoxycinnamate, **80** in six steps and 31% overall yield (**Scheme 30**). The required *anti*-aminoalcohol **98** was synthesized using Sharpless asymmetric aminohydroxylation and subsequent inversion of configuration in amidoalcohol **96** *via* an oxazoline **97**.



Scheme 30: (i) $K_2[OsO_2(OH)_4]$ (4 mol %), BrNHAc, $(DHQD)_2PHAL$ (1 mol%), LiOH, H_2O, t-BuOH, 4 ºC, 20 h, 72%; (ii) Tf_2O, DMAP, CH_2Cl_2, 80%; (iii) 12% HCl, 25 ºC, 1.5 h; (iv) $ClCO_2CCl_3$, NaOH, H_2O, 0 ºC; (v) CH_2N_2, THF, 72%; (vi) $NaBH_4$, THF, 0 ºC, 75%.

Jung's approach (2005)[61]

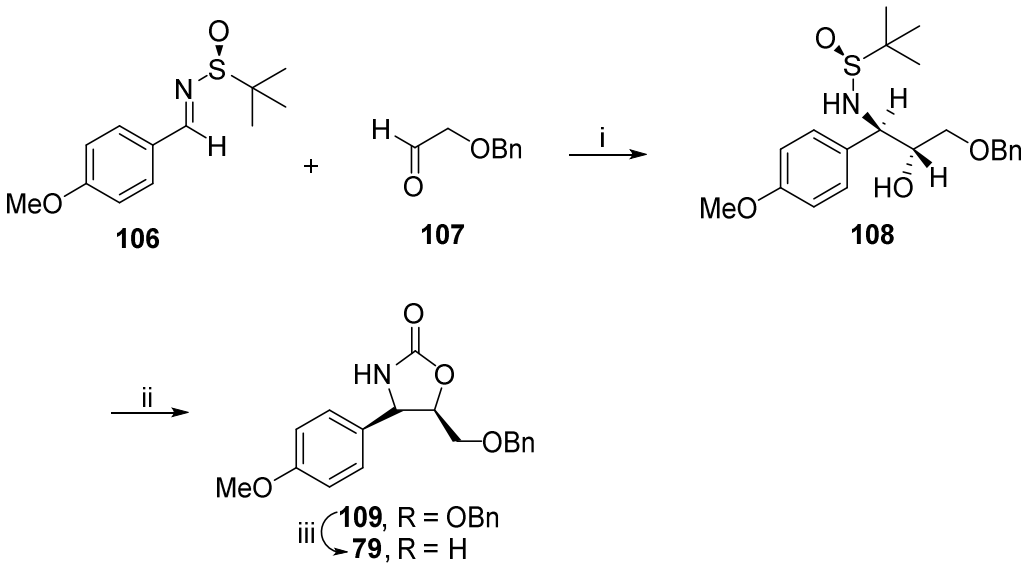
Jung *et al.* have made use of the regio- and diastereoselective introduction of a *N*-protected amine group into the key intermediate **103**. Thus the treatment of ether **103** with chlorosulfonyl isocyanate (CSI) in the presence of sodium carbonate in dry toluene at -78 °C, followed by the reduction of the *N*-chlorosulfonyl group furnished the desired *anti*-1,2-amino alcohol derivative **104** with high diastereoselectivity (27:1). Ozonolysis of the double bond and intramolecular cyclization of **105** using NaH finally gave (-)-cytoxazone (**79**) in 95% yield (**Scheme 31**).



Scheme 31: (i) (a) *B*-[3-((diisopropylamino)dimethylsilyl)allyl]diisopinocampheyl borane, Et_2O, -78 ºC; (b) H_2O_2, KF, $KHCO_3$, THF-MeOH, 25 ºC, 52%; (ii) MeI, NaH, THF, 0 ºC, 96%; (iii) (a) chlorosulfonyl isocyanate, Na_2CO_3, toluene, -78 ºC; (b) Na_2SO_3, KOH, 25 ºC, 95% (dr = 27:1); (iv) (a) O_3, -78 ºC then $NaBH_4$, 0 ºC, CH_2Cl_2-MeOH, 94%; (b) BBr_3, CH_2Cl_2, 0 ºC, 80%; (v) NaH, THF, 0 ºC, 95%.

Bentley's approach (2005)[63]

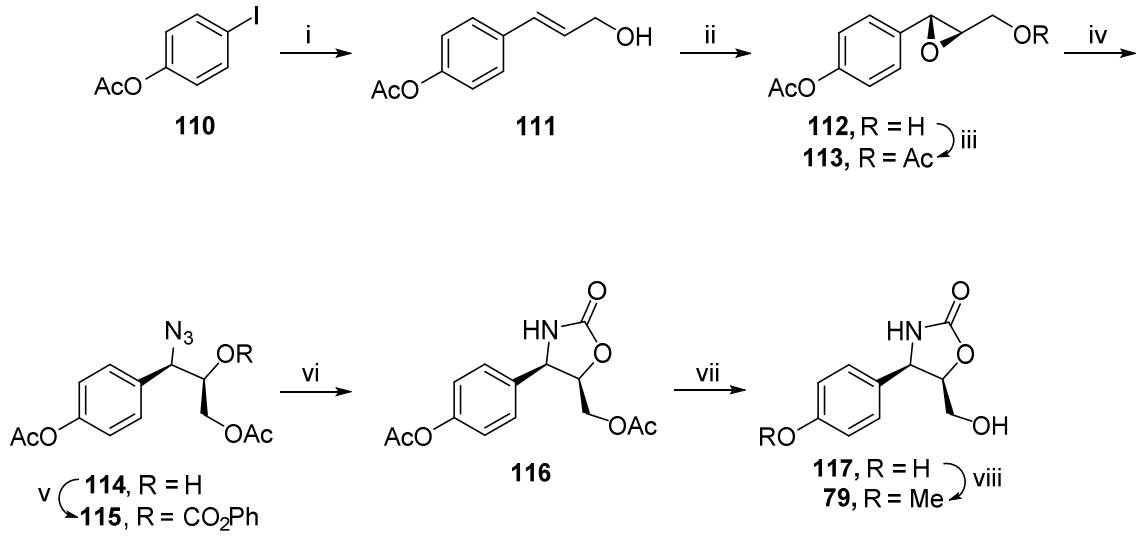
Bentley *et al.* have made use of stereoselective cross-coupling of phenyl imine auxiliary **106** and aldehyde **107** in presence of samarium iodide to obtain the corresponding aminoalcohol **108**. Removal of chiral auxiliary and cyclization using triphosgene gave **109**, which on debenzylation afforded (-)-cytoxazone (**79**) (**Scheme 32**).



Scheme 32: (i) SmI_2, ^tBuOH, THF, -78 ºC, 83%; (ii) (a) HCl, MeOH, 25 ºC; (b) triphosgene, Et_3N, CH_2Cl_2, 25 ºC, 85%; (iii) $Pd(OH)_2/C$, H_2, MeOH, 86%.

Sudalai's approach (2006), (2007)[65,66]

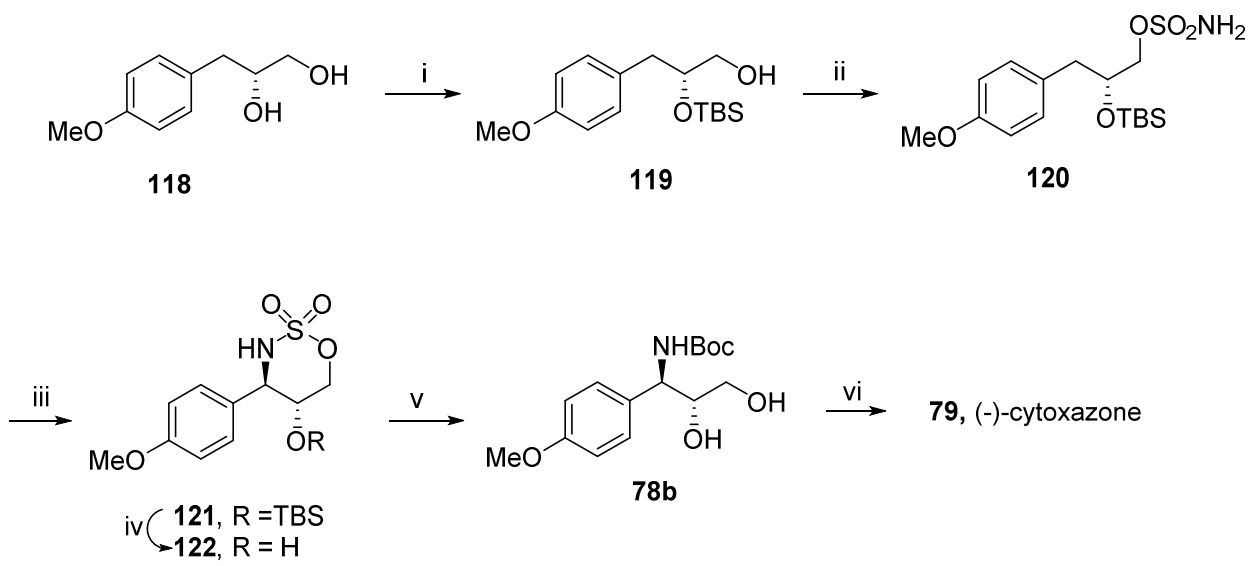
Sudalai *et al*. have developed a simple method for the enantioselective synthesis of (-)-cytoxazone **79** using Sharpless asymmetric epoxidation as the key step. Thus, asymmetric epoxidation of allylalcohol **111** gave chiral epoxide **112**, which was further acylated to give acetate **113**. The nucleophilic opening of the epoxide **113** at the benzylic position with NaN_3 gave azido alcohol **114** in 88% yield. The protection of the alcohol followed by reductive cyclization with PPh_3 and deprotection of acetate group gave oxazolidinone **117**, which was directly subjected to methylation with methyl iodide in the presence of NaH to afford (-)-cytoxazone (**79**) in 65% yield and 83% ee (**Scheme 33**).



Scheme 33: (i) allyl alcohol, AgOAc, $Pd(OAc)_2$, PPh_3, DMF, 70 ºC, 16 h, 81%. (ii) anhyd. 5.4 M TBHP in CH_2Cl_2, 4 Å molecular sieves, $Ti(OiPr)_4$, (+)-DIPT, CH_2Cl_2, -20 ºC, 20 h, 78%. (iii) AcCl, Et_3N, DMAP, CH_2Cl_2, 25 ºC, 87%. (iv) NaN_3, NH_4Cl, THF/H_2O (2:1), 50 ºC, 3 h, 79%. (v) PhOCOCl, pyridine, CH_2Cl_2, -5 to 25 ºC, 1 h, 93%. (vi) PPh_3, THF/H_2O (10:1), 50 ºC, 2 h, 87%. (vii) aq $NaHCO_3$, MeOH, reflux, 1 h. (viii) NaH, MeI, THF, 0–25 ºC, 3 h, 69%, 83% ee.

Sudalai *et al*. have also developed a simple method for the enantioselective synthesis of (-)-cytoxazone (**79**) commencing from the diol **118** obtained by two different

routes: hydrolytic kinetic resolution and proline-catalyzed α-aminooxylation. Diol **118** was converted to *bis*-TBS-protected silyl ether followed by selective deprotection of the primary OH group with camphorsulfonic acid to afford **119** which was converted into sulfamate ester **120** in 76% yield using HCO_2H and chlorosulfonyl isocyanate. The γ-C-H insertion of **120** was carried out with a catalytic amount of $Rh_2(OAc)_4$ (2 mol%), $PhI(OAc)_2$ and MgO in CH_2Cl_2 to give sulfamate ester **121** with *anti* (10:1) diastereoselectivity. The TBS deprotection, carbamoylation and ring opening of *N*-Boc protected oxathiazinane furnished the *anti*-amino alcohol **78b** in 84% yield which was converted to (-)-cytoxazone (**79**) by intramolecular cyclization using NaH in THF (**Scheme 34**).



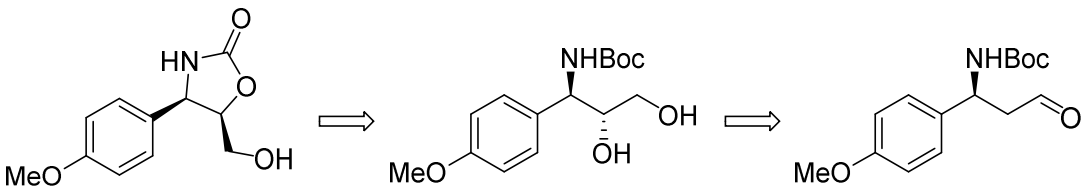
Scheme 34: (i) (a) TBSCl, imidazole, DMF, 25 °C, 4 h, 98%; (b) camphorsulfonic acid, MeOH, 95%; (ii) HCO_2H, chlorosulfonyl isocyanate, 0 °C, 76%; (iii) 2 mol% $Rh_2(OAc)_4$, $PhI(OAc)_2$, MgO, CH_2Cl_2, 40 °C, 2 h, 82%, *anti*:*syn* (10:1); (iv) (a) camphorsulfonic acid, MeOH, 25 °C, 1 h, 97%; (b) (a) $(Boc)_2O$, DMAP, Et_3N, CH_2Cl_2, 25 °C, 1 h; (v) CH_3CN:H_2O (4:3), 60 °C, 4 h, 84%; (vi) NaH, THF, 0 °C, 1 h, 96%.

1.3.4 Present Work:

1.3.4.1 Objective

Literature search revealed that several methods such as classical resolution, chemo-enzymatic or metal-catalyzed enantioselective synthesis have been reported for the synthesis of (-)-cytoxazone (**79**). However, these methods suffer from disadvantages such as low overall yields, the use of expensive chiral reagents, usage of protecting groups, especially the need for separation of diastereomers. The synthetic precursors of (-)-cytoxazone (**79**) are found to be *anti*-amino diols, which have been the subject of thorough synthetic efforts in recent years. We became interested in providing, a more practical method for the synthesis of (-)-cytoxazone (**79**). In this section, we describe a concise protecting group-free enantioselective synthesis of (-)-cytoxazone (**79**) using α-aminooxylation of β-aminoaldehydes as the key reaction.

Retrosynthetic analysis of (-)-cytoxazone (**79**) reveals that *anti*-amino diol **78b** can be visualized as the key intermediate, which in turn can be obtained using α-aminooxylation of β-aminoaldehyde **77b** (**Fig. 13**).



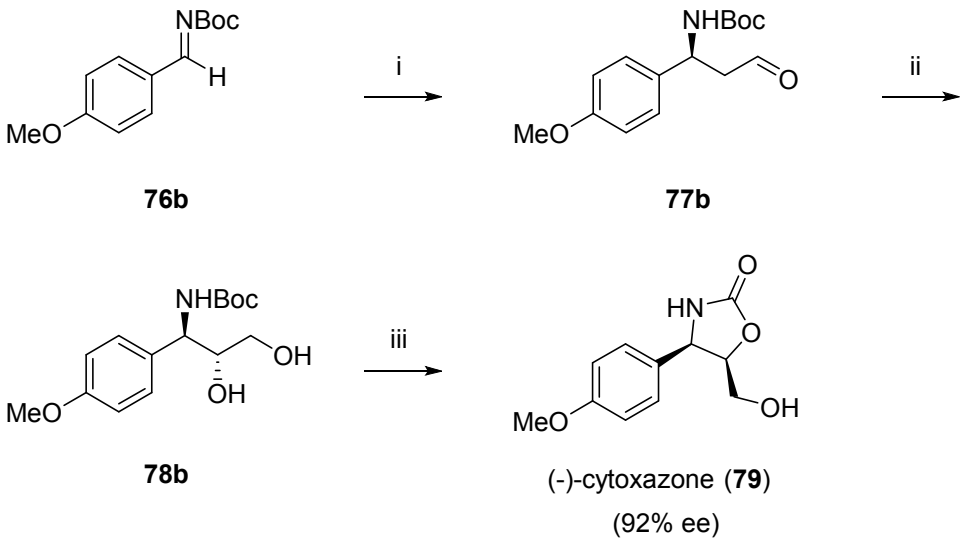
79 **78b** **77b**

Fig. 13: Retrosynthetic analysis of (-)-cytoxazone (**79**)

1.3.5 Results and Discussion

Concise Enantioselective Synthesis of (-)-Cytoxazone (79)

The complete synthetic sequence for (-)-cytoxazone (**79**), wherein α-amino oxylation of β-aminoaldehyde **77b** constitutes a key step, is presented in **Scheme 35**.



76b **77b** **78b**

(-)-cytoxazone (**79**)
(92% ee)

Scheme 35: (i) CH_3CHO, L-proline (20 mol%), CH_3CN, 0 °C, 3 h, 52%; (ii) (a) PhNO (0.8 equiv), L-proline (20 mol%), CH_3CN, -10 °C, 18 h; then $NaBH_4$, CH_3OH, 0 °C, 10 min; (b) $Cu(OAc)_2.H_2O$, CH_3OH, 25 °C, 16 h, 68% (over two steps); (iii) NaH, dry THF, 25 °C, 3 h, 90%.

Accordingly, the synthesis of (-)-cytoxazone (**79**) was undertaken commencing from arylaldimine **76b**, which on subjecting to Mannich reaction with acetaldehyde [L-proline, CH_3CN, 0 °C, 3 h] gave β-aminoaldehyde **77b** in 52% yield. The structure of compound **77b** was confirmed from its ^1H and ^{13}C NMR spectroscopy. The ^1H NMR spectrum of **77b** showed a typical triplet at δ 9.72 (t, J = 1.6 Hz, 1H) and a multiplet at δ 2.80-2.94 (m, 2H) corresponding to aldehydic and homobenzylic protons respectively. Its ^{13}C NMR spectrum showed two characteristic carbon signals at δ 193.4 and 200.0 due to carbamate and aldehydic carbonyl carbons respectively (**Fig. 14**).

β-Aminoaldehyde **77b** was then subjected to α-aminooxylation [L-proline, PhNO] to give α-aminoxyaldehyde, which was *in situ* reduced with $NaBH_4$, followed by subsequent reduction of the crude aminoxy product with $Cu(OAc)_2.H_2O$ that provided a single diastereomer of *anti*-3-amino-1,2-diol **78b** in 68% yield and 92% ee. The formation of *anti*-3-amino-1,2-diol **78b** was confirmed from its ^1H NMR spectrum,

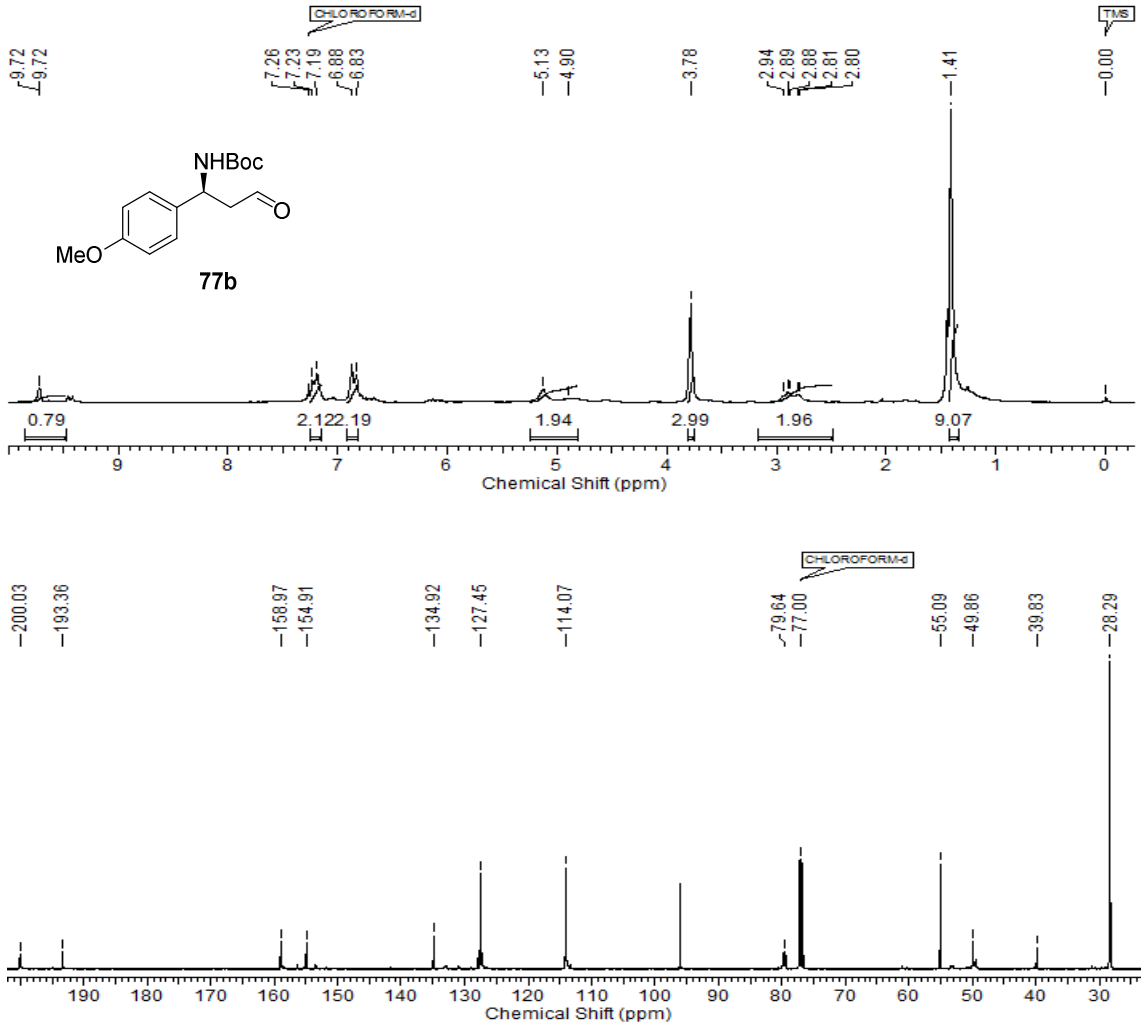


Fig. 14: ^{1}H and ^{13}C NMR spectra of β-aminoaldehyde **77b**

which showed a typical singlet at δ 1.41 (s, 9H) due to *tert*-butyl protons. Its ^{13}C NMR spectrum showed two characteristic carbon signals at δ 63.2 and 74.1 attributed to methylene and methine carbons attached to hydroxyl groups respectively. Its mass spectrum also confirmed the formation of *anti*-3-amino-1,2-diol **78b** (**Fig. 15**).

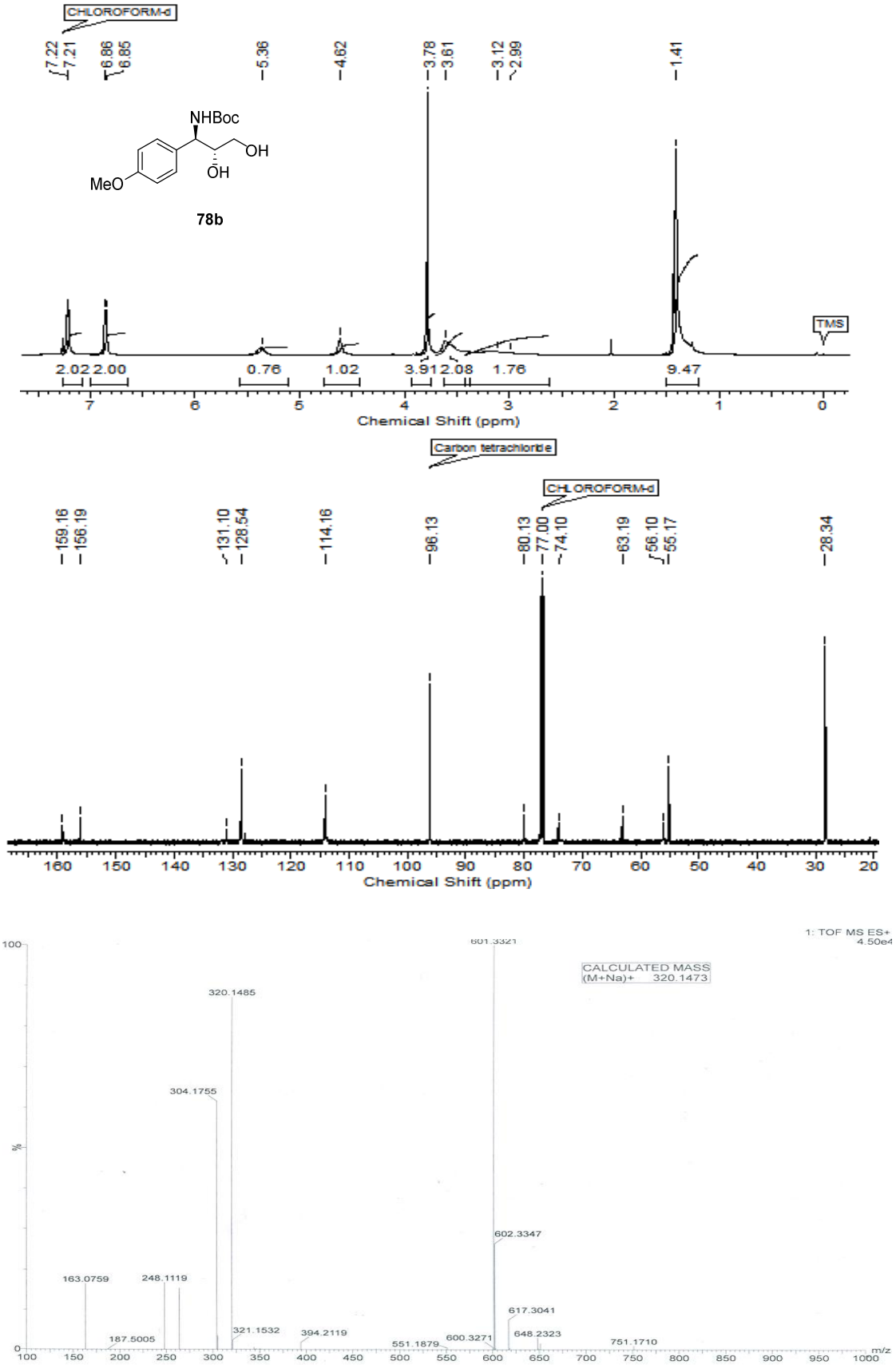


Fig. 15: ^{1}H, ^{13}C NMR and mass spectra of *anti*-3-amino-1,2-diol **78b**

Finally, the regioselective intramolecular cyclization of **78b** using NaH in THF gave (-)-cytoxazone (**79**) in 90 % yield and 92% ee.

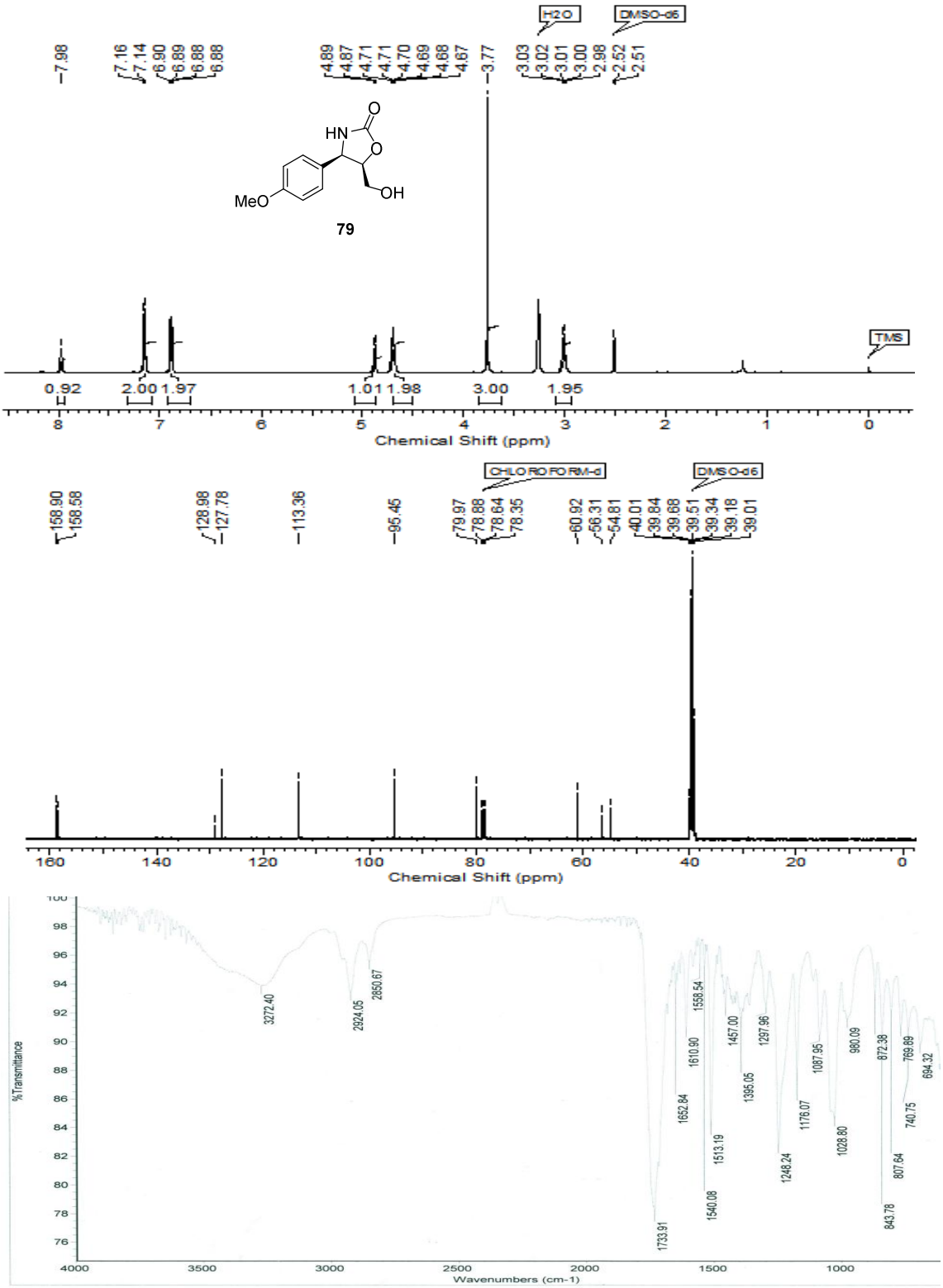


Fig. 16: ^{1}H, ^{13}C NMR and IR spectra of (-)-cytoxazone (**79**)

The ^{1}H, ^{13}C NMR and IR spectra of **79** confirmed the structure of (-)-cytoxazone (**Fig. 16**). The ^{1}H NMR spectrum of (-)-cytoxazone (**79**) showed a typical signal at δ 7.98 (s, 1H) for N-H proton of oxazolidinone ring. Its ^{13}C NMR spectrum showed a characteristic signal at δ 158.9 due to the carbonyl carbon in oxazolidinone ring. Its IR spectrum exhibited a characteristic oxazolidinone carbonyl absorption frequency at 1733 cm^{-1}. The spectral data of (-)-cytoxazone (**79**) were in complete agreement with the reported values.[66]

1.3.6 Conclusion

A short and protecting group-free synthesis of (-)-cytoxazone (**79**) with an overall yield of 32% for three steps has been described. *L*-Proline-catalyzed α-aminooxylation of β-aminoaldehydes was used as the key reaction, which proceeded to give high enantioselectivity. This methodology can be used for a viable synthesis of other diastereomers of (-)-cytoxazone (**79**) family as well by suitably employing *D*-proline as catalyst for α-aminooxylation of β-aminoaldehydes.

1.3.7 Experimental Section

vide supra on section II of the same chapter for experimental procedure and spectral details of compound **77b**.

(2*R*, 3*R*)-3-(*tert*-Butoxycarbonylamino)-3-(*p*-methoxyphenyl)-1,2-propanediol (78b)

To a stirred, precooled (-10 °C) acetonitrile (25 mL) solution of β-aminoaldehyde **77b** (4.78 g, 17 mmol) and nitrosobenzene (1.45 g, 13.6 mmol) was added L-proline (0.039 g, 20 mol%). The reaction mixture was allowed to stir at the same temperature for 18 h followed by the addition of CH_3OH (10 mL) and $NaBH_4$ (0.97 g, 25 mmol) to the reaction mixture. It was stirred for another 10 min. After addition of phosphate buffer, the resulting mixture was extracted with EtOAc (3 × 30 mL) and the combined

organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude aminooxy alcohol, which was directly taken up for the next step without purification.

To a CH_3OH (25 mL) solution of the above crude aminooxy alcohol was added $Cu(OAc)_2.H_2O$ (0.501 g, 2.6 mmol) at 25 °C and the reaction mixture was allowed to stir for 16 h at that temperature. After addition of phosphate buffer, the resulting mixture was extracted with $CHCl_3$ (3 × 30 mL) and the combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude product, which was then purified by column chromatography over silica gel using pet. ether:EtOAc (30:70) as an eluent to give *anti*-amino diol **78b** (2.6 g) as a colorless solid.

Yield: 68%; colorless solid; **mp:** 114-116 ºC, (lit.[67] **mp**: 116-118 ºC); $[\alpha]^D_{25}$ -49.43 (*c* 0.6, $CHCl_3$); lit.[67] $[\alpha]^D_{25}$ -50.2 (*c* 0.5, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 669, 757, 831, 927, 1035, 1167, 1216, 1368, 1585, 1612, 1701, 2400, 2839, 2981, 3019, 3438, 3682; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.41 (s, 9H), 2.99-3.12 (br m, 2H), 3.61 (br s, 2H), 3.78 (br s, 4H), 4.62 (br s, 1H), 5.36 (br s, 1H), 6.85 (d, J = 6.7 Hz, 2H), 7.21 (d, J = 6.7 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 28.3, 55.2, 56.1, 63.2, 74.1, 80.1, 114.2, 128.5, 131.1, 156.2, 159.2; **HRMS** (ESI) *m/z* calcd for $C_{15}H_{23}NO_5$ $[M + Na]^+$: 320.1473, found: 320.1485; **Analysis**: $C_{15}H_{23}NO_5$ requires C, 60.59; H, 7.80; N, 4.71; found: C, 60.29; H, 7.62; N, 4.69%.

(4*R*, 5*R*)-5-(Hydroxymethyl)-4-(4-methoxyphenyl)oxazolidin-2-one: [(-)-cytoxazone] (79)

To a solution of *anti*-3-amino-1,2-diol **78b** (0.3 g, 1.0 mmol) in dry THF (10 mL) was added NaH (0.05 g, 60% w/w, 2.0 mmol) at 25 °C, and the mixture was stirred under nitrogen atmosphere for 3 h. The reaction mixture was concentrated and the resulting mixture was extracted with EtOAc (3 x 10 mL), washed with saturated aq. NH_4Cl (5 mL) and brine solution (5 mL). The organic layers were separated, dried over anhyd.

Na_2SO_4, and concentrated to give the crude product, which was then purified by column chromatography over silica gel using pet. ether:EtOAc (60:40) as an eluent to give **79** (0.20 g) as a colorless solid.

Yield: 90%; colorless solid, **mp:** 116-118 °C, (lit.[67] **mp**: 119-121 °C); $[\alpha]^{25}_D$ -66.0 (*c* 1, MeOH); lit.[67] $[\alpha]^{25}_D$ -71.0 (*c* 0.1, MeOH); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 769, 843, 1028, 1248, 1395, 1513, 1610, 1733, 2580, 2924, 3272; **^{1}H NMR** (500 MHz, $CDCl_3$+ DMSO-d_6): δ 2.98-3.03 (m, 2H), 3.77 (s, 3H), 4.67-4.71 (m, 1H), 4.87-4.89 (d, *J* = 8.24 Hz, 1H), 6.88 (dd, *J* = 2.1, 8.5 Hz, 2H), 7.14 (d, *J* = 8.5 Hz, 2H), 7.98 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$+ DMSO-d_6): δ 54.8, 56.3, 60.9, 79.9, 113.4, 127.78, 128.98, 158.6, 158.9; **Analysis:** $C_{11}H_{13}NO_4$ requires C, 59.19; H, 5.87; N, 6.27; found: C, 59.01; H, 5.69; N, 6.13%.

1.3.8 References

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CHAPTER 2

A Short Route for Enantioselective Synthesis of (+)-Sertraline, (+)-Tametraline and Formal Synthesis of (+)-Indatraline *via* Proline- Catalyzed Mannich Reaction of Acetaldehyde

Section I

A Short Enantioselective Synthesis of (+)-Sertraline and (+)-Tametraline *via* proline catalyzed Mannich reaction of acetaldehyde

2.1.1 Introduction

Optically active 1-amino-4-aryltetralin structural units (**1**-**3**) play a major role in pharmaceutical industries and medicinal chemistry field due to their high profile bioactivity as selective monoamine reuptake inhibitors by inhibiting a particular monoamine neurotransmitter such as serotonin (5-HT) (**4**), dopamine (**5**) and norephinephrine (**6**) (**Fig. 1**). In particular, selective serotonin reuptake inhibitors (SSRI) are a class of antidepressants used for the treatment of depression.[1] Drugs are designed to allow serotonin, the neurotransmitter to be utilized more effectively. Low-level serotonin in the brain is currently seen as one of numerous neurochemical symptoms of depression. The low levels of serotonin is caused by an anxiety disorder, since serotonin is necessary to metabolize stress hormones.

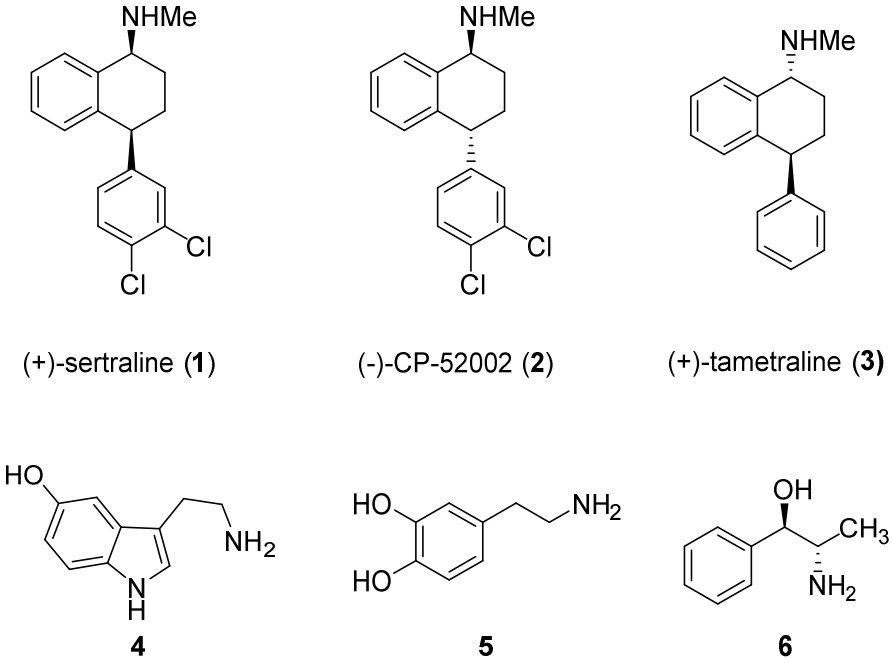


Fig. 1: Structures of 1-amino-4-aryltetralins (**1**-**3**) and monoamine neurotransmiters (**4**-**6**)

A depressive disorder is believed to be caused by a chemical imbalance in the brain. Messages are passed between two nerve cells *via* a small gap *i.e* 'synapse' between the nerve cells. A nerve cell sending the information to the another nerve cell by releasing neurotransmitters into that gap. These neurotransmitters are recognized by receptors on the surface of the recipient cell, which relays the signal. Approximately, 10% of the neurotransmitters are lost in this process, with the other 90% released from the receptors and taken up again by monoamine transporters of first nerve cell. This process is called as 'reuptake'. Depression has been associated with a lack of stimulation of the recipient neuron due to the less availability of serotonin at the synapse. To stimulate this cell, selective serotonin reuptake inhibitor (SSRI) block the reuptake of serotonin by the first nerve cell and allows more serotonin to be available to be taken up by other nerves.

2.1.2 Pharmacology of (+)-Sertraline, CP-52002 and (+)-Tametraline

(+)-Sertraline **1**, a selective serotonin reuptake inhibitor (SSRI), is an important anti-depressant drug with an IC_{50} value of 0.06 μM for the inhibition of 5-HT in rat brain and discovered by Pfizer chemist Reinhard Sarges in 1970. It is one of the highest selling drugs, sold under the trade name Zoloft®.[2] Medically, (+)-sertraline (**1**) is also prescribed for the treatment of post-traumatic stress and panic disorders. Administration of sertraline comes with side effects such as gastrointestinal complaints, nervousness and sexual dysfunction on long-term users. Also, it has been discovered that the C_4 epimer of (+)-sertraline **1** *i.e* CP-52002 [*trans*-(1S,4R)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-l-naphthalenamine (**2**), IC_{50} = 0.45 μM], a potent inhibitor of both dopamine and 5-HT uptake, and its enantiomer (IC_{50} = 0.033 μM) are useful in the treatment of central nervous system disorders such as anxiety, eating and disruptive behaviour disorders.[3] They are also useful for taking the

preventive measurement (prophylaxis) of migraine. Further, (+)-Tametraline[2c] is also known as CP-24441, a norephinephrine-dopamine reuptake inhibitor with an IC_{50} value of 0.018 and 0.15 μM for the inhibition of norephinephrine and dopamine reuptake in rat brain respectively and also administered as psychotropic agent.

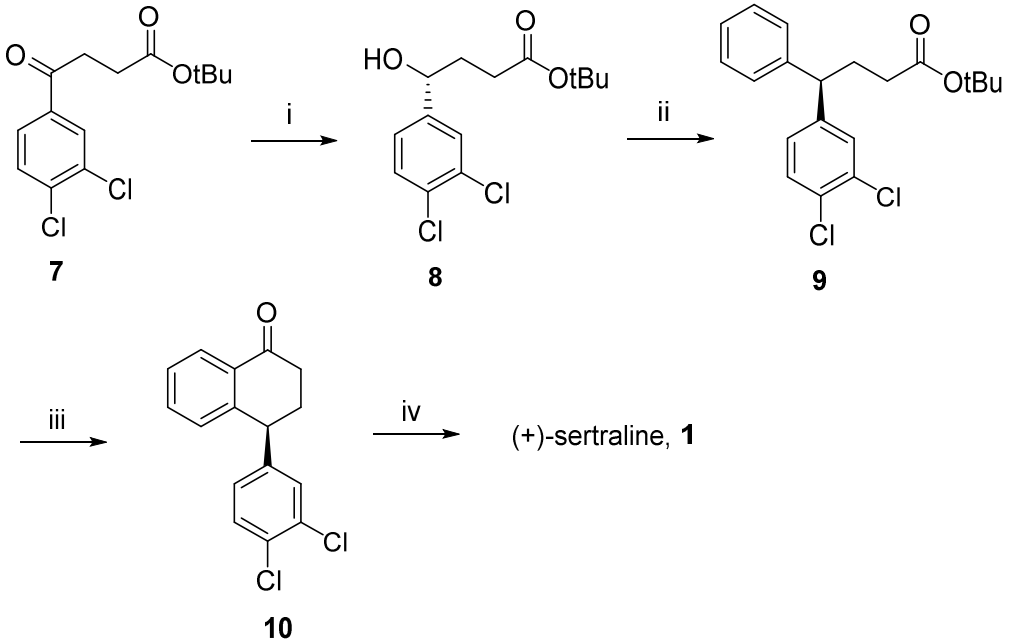
2.1.3 Review of literature

(a) Review of literature of (+)-sertraline

Literature search revealed that there are many reports are available for the synthesis of (+)-sertraline due to its high pharmaceutical importance as a drug and some of which are described below.

Quallich's approach (1992)[4]

Quallich *et al*. have reported the first asymmetric synthesis of (+)-sertraline **1** using asymmetric CBS reduction reaction as key step (**Scheme 1**). Synthesis began with

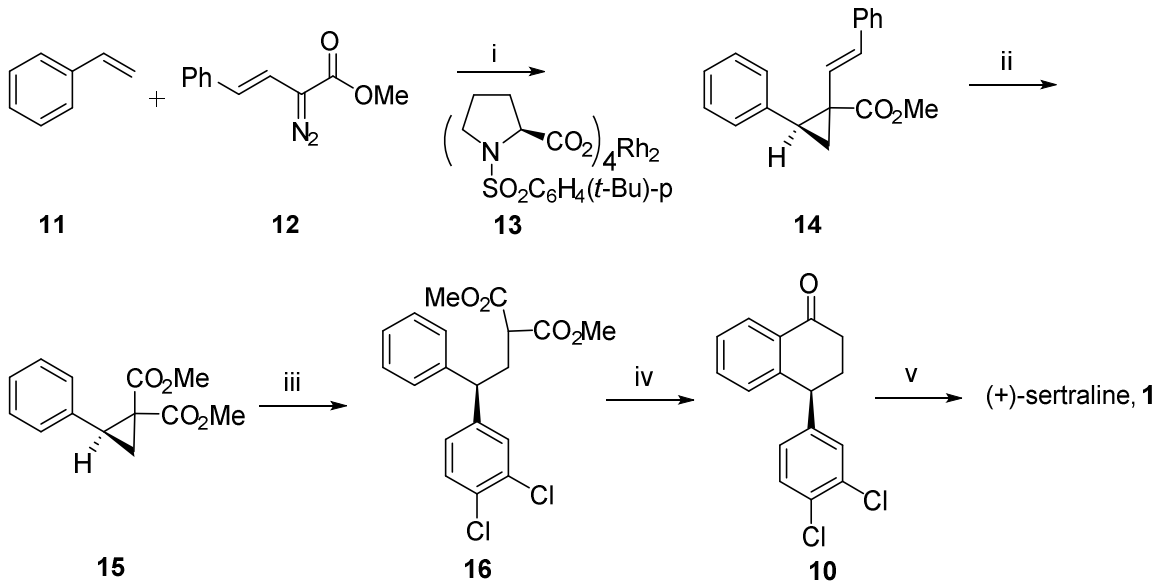


Scheme 1: (i) BH_3, (S)-tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrollo [1,2-C][1,3,2] oxazaborolidine (CBS), THF, 0 ^oC, 100%; (ii) (a) MsCl, Et_3N, CH_2Cl_2, 0 ^oC, 20 min; (b) CuCN, PhLi, Et_2O, -45 ^oC, (iii) CF_3CO_2H, benzene, 70 ^oC, 2 h; (iv) $TiCl_4$, $MeNH_2$ then Raney Ni, H_2 (1 atm), MeOH.

asymmetric reduction of γ-keto ester **7** with CBS catalyst, which gave the hydroxy ester **8** in quantitative yield and 88% ee. Alcohol **8** was mesylated and coupled with higher order phenyl cuprate to give butyrate ester **9** in 70% yield. The butyl ester **9** was directly cyclized to form tertralone **10** in the presence of triflic acid. Finally, transformation of **10** to (+)-sertraline **1** was achieved by reductive amination protocol.

Corey's approach (1994)[5]

Corey *et al*. have reported the synthesis of (+)-sertraline **1** by employing Rh-catalyzed asymmetric cyclopropanation as key step. Thus, diazo butanoate **12** was subjected to asymmetric cyclopropanation with styrene **11** using proline derived catalyst **13** to afford cyclopropane ester **14** in 79% yield and 94% ee. The oxidation of styrenic C=C of **14** with $KMnO_4/NaIO_4$ followed by esterification afforded malonyl ester **15**. Treatment of **15** with Ar_2CuLi_2CN (prepared from 3,4-dichlorophenyl iodide) led to

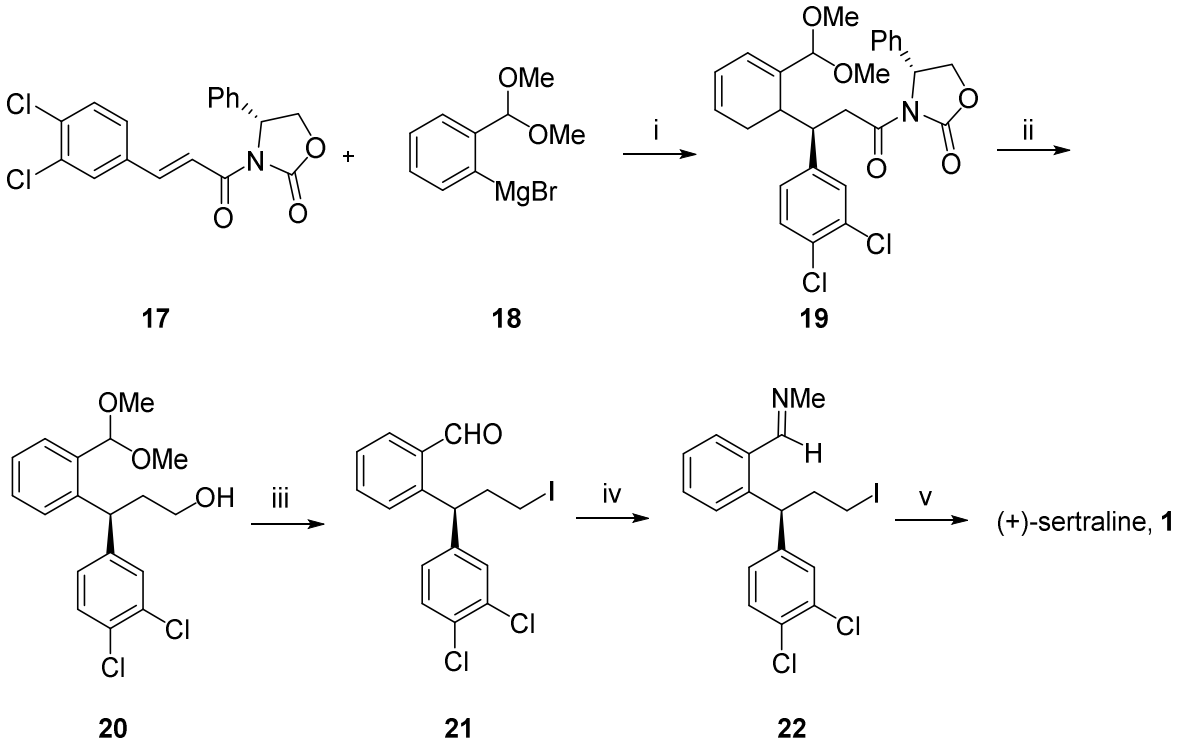


Scheme 2: (i) 10 mol% of catalyst **13**, pentane, 25 ^oC, 12 h, 79%; (ii) (a) $KMnO_4$, $NaIO_4$, K_2CO_3, ^tBuOH, 0.5 h, 25 ^oC, 83%; (b) K_2CO_3, Me_2SO_4, acetone, 3 h, 97%; (iii) BuLi, 3,4-dichlorophenyl iodide, CuCN, Et_2O, 15 min, 82%; (iv) (a) 6N HCl, reflux, 20 h then 1N NaOH; (b) $ClSO_3H$, CH_2Cl_2, 30 min, 84%; (v) reductive amination using $MeNH_2$.

ring opening of cyclopropane ring to give diester **16** in 82% yield. Hydrolysis of diester **16** with 6N HCl followed by cyclization with chlorosulfonic acid gave tetralone **10**; reductive amination of which resulted in the formation of (+)-sertraline **1** (**Scheme 2**).

Chen's approach (1999)[6]

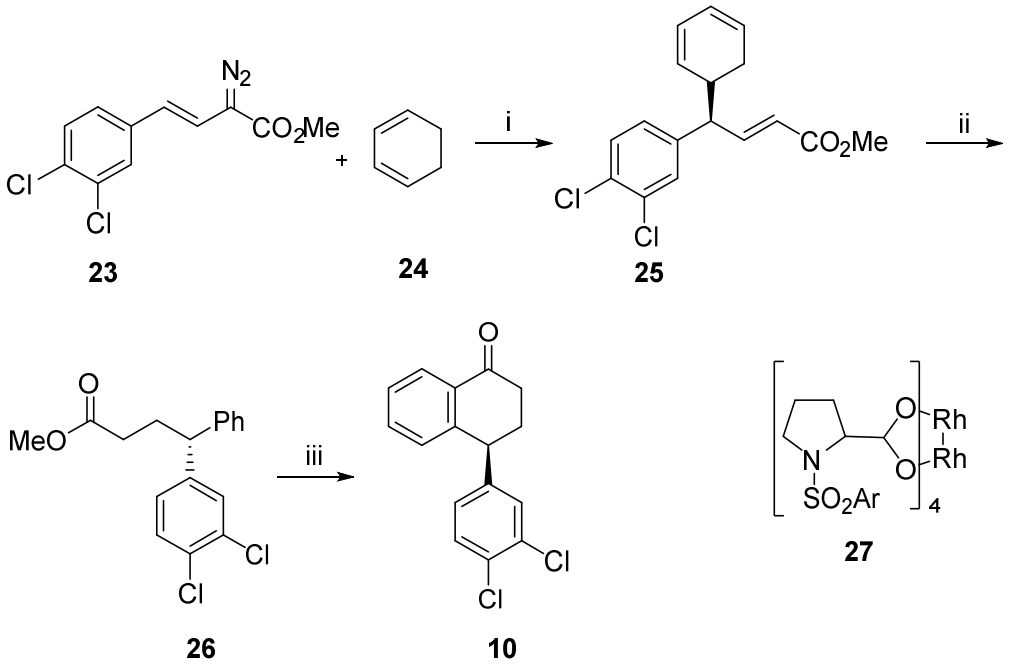
Chen *et al*. have achieved the synthesis of (+)-sertraline **1** by the addition of Grignard reagent **18** onto α,β-unsaturated chiral oxazolidinone **17** to provide **19** in 90% yield. Reductive removal of chiral auxiliary in **19** using $NaBH_4$ in THF-H_2O gave alcohol **20**. Alcohol **20** was transformed into iodoaldehyde **21** in 85% yield, which on treatment with methylamine, gave the corresponding imine **22.** Finally, compound **22** was subjected to *t*-BuLi-mediated intramolecular ring closing to give a single diastereomer of (+)-sertraline **1** (**Scheme 3**).



Scheme 3: (i) $CuBr{\cdot}SMe_2$ (20 mol%), THF, -30 ^oC, 90%; (ii) $NaBH_4$, THF-H_2O; (iii) (a) PPh_3, I_2, imid., CH_2Cl_2; (b) 2N HCl, 85%; (iv) 2.0 M $MeNH_2$ in THF, (v) *t*-BuLi, THF, toluene, -78 ^oC, 69%.

Davies's approach (1999)[7]

Davies *et al*. have reported a formal synthesis of (+)-sertraline **1** using Rh-catalyzed C-H insertion as the key step. The α-diazo ester **23** and cyclohexadiene **24** were exposed to intramolecular C-H insertion using Rh-catalyst **27** that resulted in the formation of α,β-unsaturated ester **25**. Aromatization of **25** using DDQ followed by catalytic hydrogenation afforded saturated ester **26** in 52% yield. Ester **26** was hydrolyzed and cyclized intramolecularly to produce tetralone **10** in 79% yield and 96% ee, which is the key intermediate for the synthesis of (+)-sertraline **1** (**Scheme 4**).

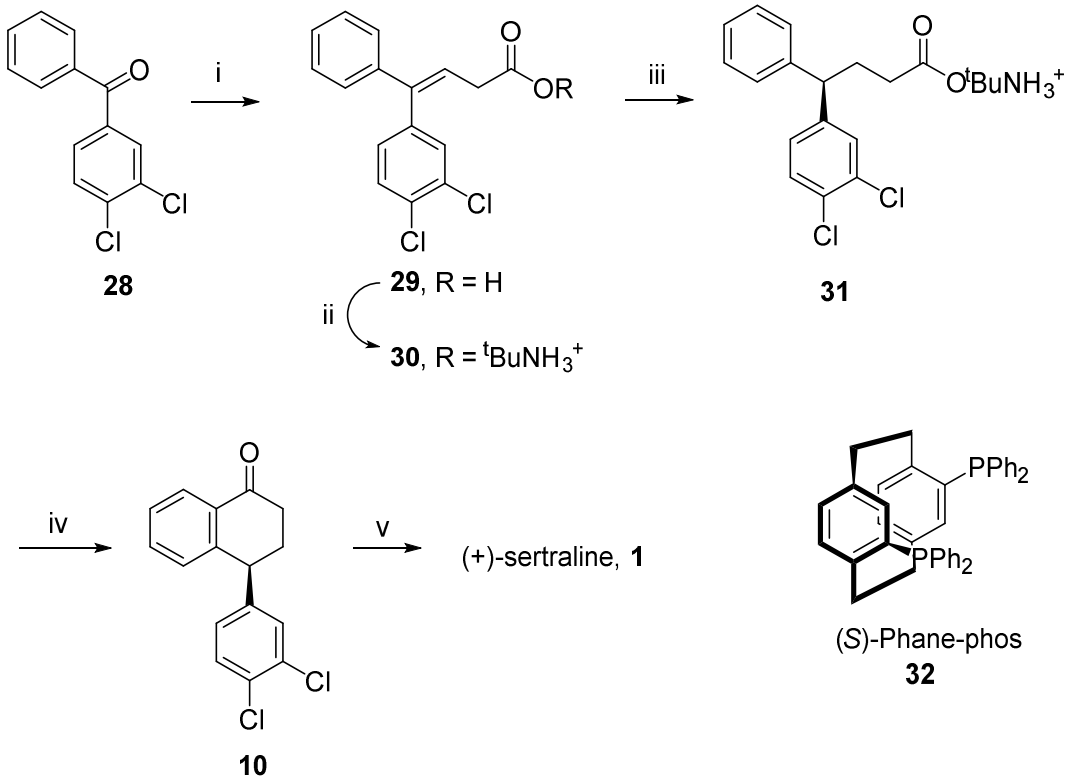


Scheme 4: (i) Rh_2(S-DOSP)$_4$, hexane, 23 ^oC, 59%; (ii) (a) DDQ, toluene; (b) Pd/C, H_2 (20 psi), EtOH, 52%; (iii) 6N HCl, then $ClSO_3H$, 25 ^oC, 2 h, 79%.

Boultan's approach (2003)[8]

Boultan *et al*. have employed asymmetric hydrogenation as the key reaction. Diarylbutanoate salt **30** was prepared from 3,4-dichlorobenzophenone **28** by base mediated condensation. The compound **30** was subjected to asymmetric catalytic hydrogenation using Rh-phane-phos catalyst **32** and H_2 (120 psi) to afford

enantioenriched saturated ester **31** in quantitative yield and 90% ee. Further, the synthesis of (+)-sertraline **1** was completed from **31** by following the three-step reaction sequences of hydrolysis, cyclization and reductive amination (**Scheme 5**).

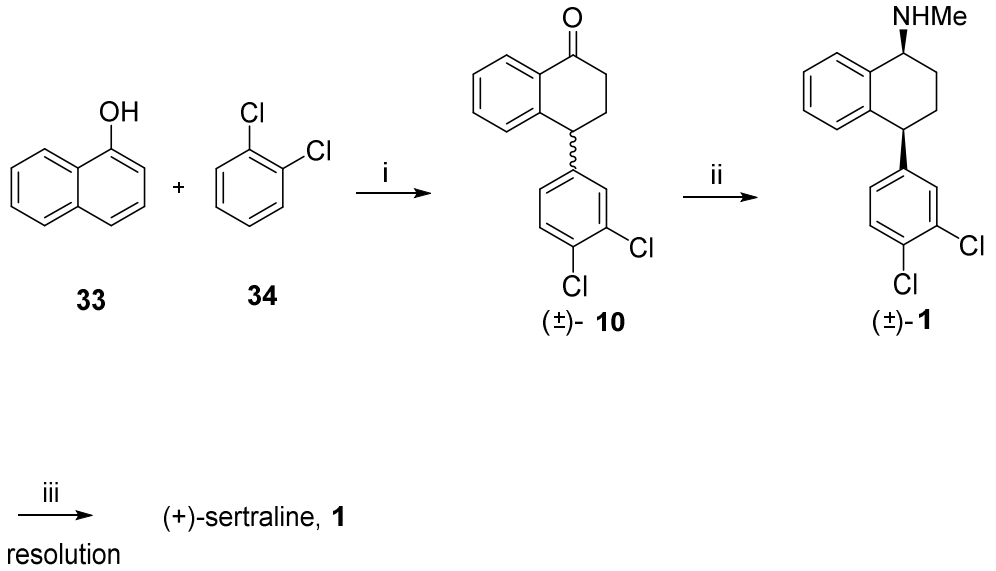


Scheme 5: (i) $KOBu^t$, diethyl succinate, ^tBuOH; then 48% HBr, AcOH, 32%; (ii) $^tBuNH_2$, EtOAc, 99%; (iii) $[RhCOD]BF_4$, ligand **32**, H_2 (120 psi), MeOH; (iv) 2M H_2SO_4, EtOAc; then $ClSO_3H$, CH_2Cl_2, 91%; (v) $MeNH_2$, Ni, H_2(1 atm), MeOH.

Colberg's approach (2004)[9]

Colberg *et al*. have reported a short method of synthesis of (+)-sertraline **1** by employing kinetic resolution of racemic (±)-sertraline **1** as the key step. α-Naphthol **33** and 1,2-dichlorobenzene **34** were reacted in the presence of anhyd. $AlCl_3$ under Friedel-Crafts alkylation conditions to give racemic (±)-tetralone **10** in 95% yield. Treatment of (±)-tetralone **10** with excess of methyl amine in ethanol furnished the corresponding imine, which was then subjected to reductive amination [$Pd/CaCO_3$, H_2 (50 psi)] to yield (±)-sertraline, **1** (*cis:trans* 20:1) with *cis* as the major isomer. The

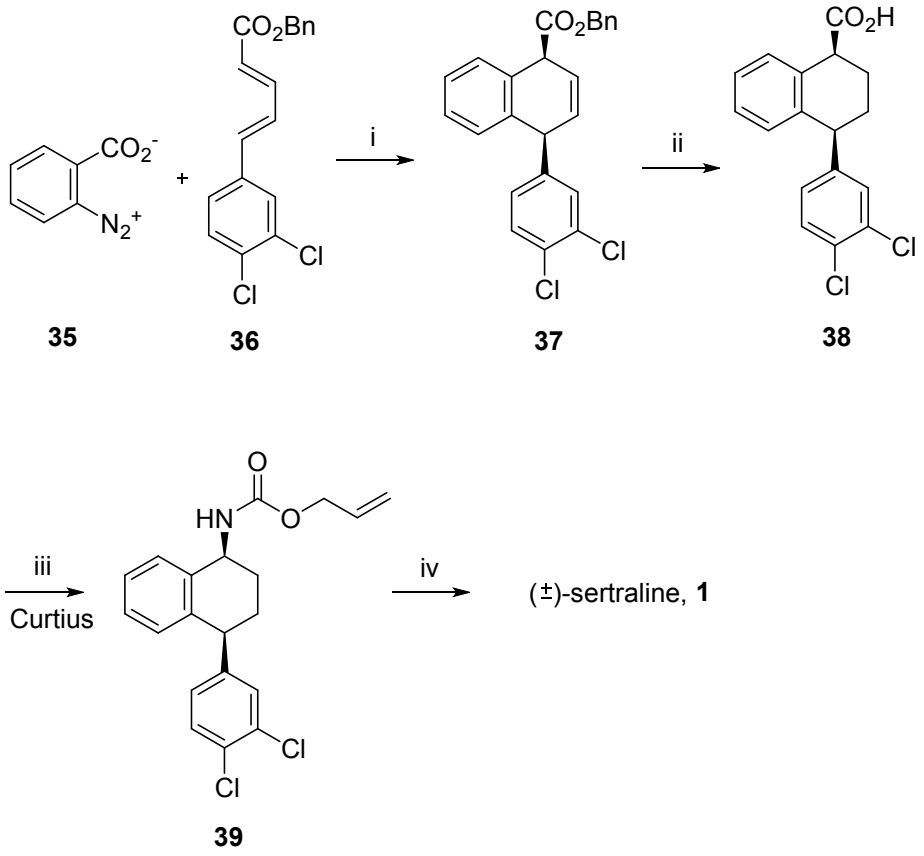
racemic sertraline, was then treated with D-mandelic acid so that the *cis* isomer is resolved selectively in solid form (**Scheme 6**).



Scheme 6: (i) $AlCl_3$; (ii) $MeNH_2$, EtOH, 95%; then $Pd/CaCO_3$ (1% w/w), H_2 (50 psi), 40%; (iii) (D)-mandelic acid, EtOH, reflux then -5 ^oC, 36%.

Lautens's approach (2005)[10]

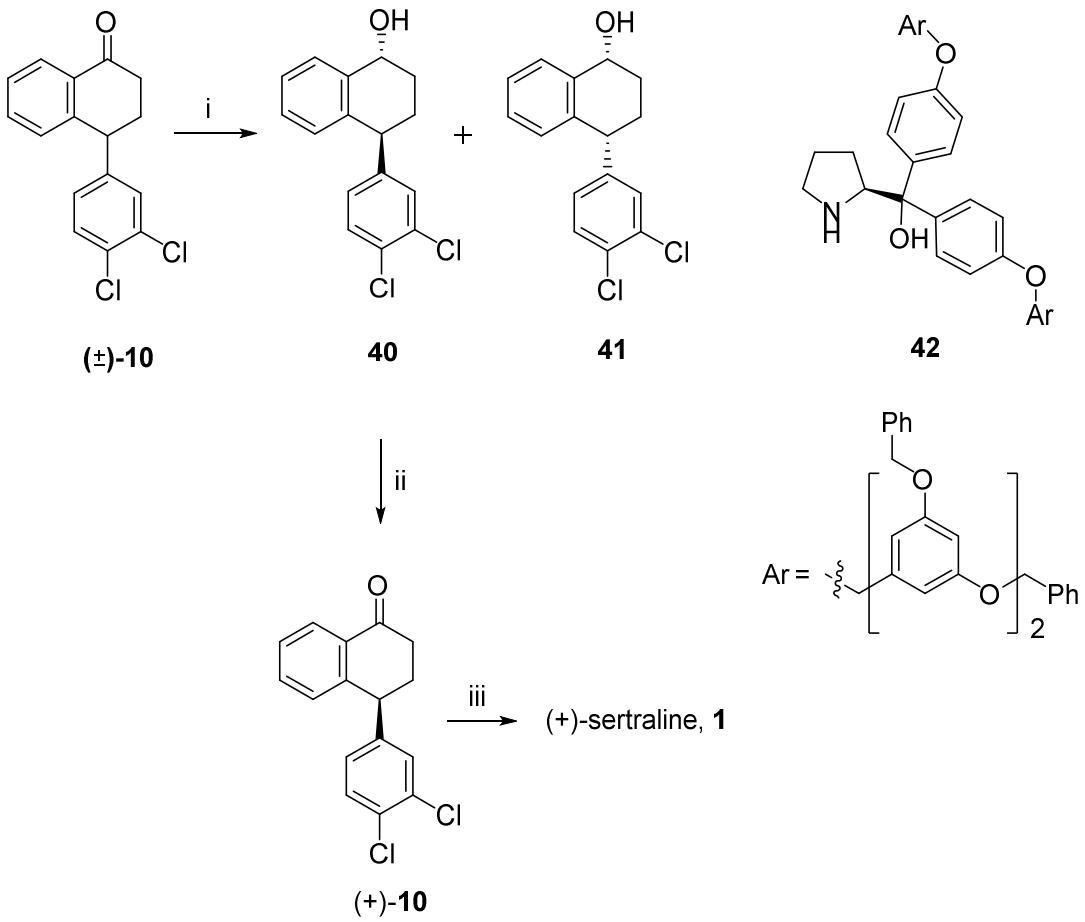
Lautens *et al*. have reported the synthesis of (±)-sertraline **1** by employing Diels-Alder reaction between benzenediazonium-2-carboxylate **35**, a benzyne-equivalent and dienyl ester **36** in 1,2-dichloroethane as solvent at 60 ^oC, to give the cycloadduct **37** in 78% yield. Cycloadduct **37** was hydrogenated and the benzyl group deprotected in one-pot with 10% Pd/C and H_2 (4 atm) to give carboxylic acid **38** in 94% yield. The compound **38** was then subjected to Curtius rearrangement *via* the initial formation of acylazide ($ClCO_2Et$, then NaN_3) followed by the addition of allyl alcohol at 90 ^oC, which afforded allyl carbamate **39** in 65% yield. *N*-Methylation and deprotection of allyl group in **39** resulted in the formation of (±)-sertraline **1** (**Scheme 7**).



Scheme 7: (i) 1,2-dichloroethane, 60 ^{o}C, 78%; (ii) 10% Pd/C, H_2 (4 atm), MeOH, 94%; (iii) (a) $ClCO_2Et$, NaN_3, Et_3N, toluene, 25 ^{o}C; (b) allyl alcohol (10 equiv.), toluene, 90 ^{o}C, 65%; (iv) (a) NaH, MeI, THF, 91%; (b) $Pd(OAc)_2$, $HNEt_2$, H_2O:CH_3CN, 75%.

Zhao's approach (2006)[11]

Zhao *et al.* reported a short synthesis of (+)-sertraline **1,** starting from recemic (±)-tetralone **10**. Compound **10** was subjected to reduction with L-proline derived catalyst **42** and $Me_2S{\cdot}BH_3$ to give diastereomers **40** and **41,** which were readily separated (in 94% yield and 97% ee). The oxidation of *trans* isomer **40** with PCC gave the optically active (+)-tetralone **10**, which was transformed to (+)-sertraline **1** *via* reductive amination ($MeNH_2$, $TiCl_4$, Raney-Ni) (**Scheme 8**).

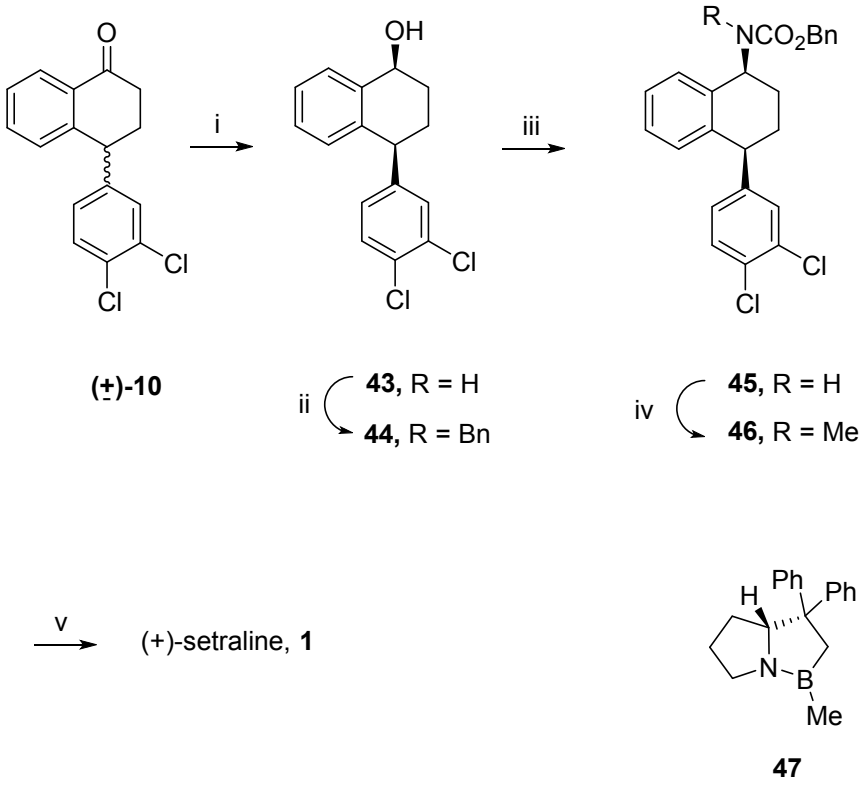


Scheme 8: (i) $Me_2S{\cdot}BH_3$, **42** (5 mol%) , THF, reflux, 42%; (ii) PCC, CH_2Cl_2, 25 ^oC; (iii) $TiCl_4$, $MeNH_2$, Et_2O, -78 ^oC; then Raney Ni, H_2 (1 atm), MeOH.

Jung's approach (2011)[12]

Jung *et al*. have reported synthesis of (+)-sertraline **1** using stereoselective amination of chiral benzylic ethers using chlorosulfonyl isocyanate (CSI). Thus, recemic (±)-tetralone **10** was diastereoselectively converted to the chiral alcohol **43** by employing (*R*)-(+)-2-methyl-CBS-oxazaborolidine as catalyst **(47)** and *N*,*N*-diethylanilineborane as reducing agent. Benzylation of alcohol **43** afforded the ether **44**. Treatment of the benzyl ether **44** with chlorosulfonyl isocyanate and sodium carbonate in anhydrous *n*-hexane at -40 °C for 40 h, followed by reduction of the *N*-chlorosulfonyl group with an aqueous sodium sulfite solution furnished the carbamate **45**. Finally, methylation

of the carbamate **45** and subsequent deprotection of the Cbz group gave (+)-sertraline **1 (Scheme 9)**.



Scheme 9: (i) **47**, *N*,*N*-diethylaniline borane, toluene, 25 ^{o}C, 485; (ii) BnBr, NaH, THF/DMF (4:1), 25 ^{o}C, 82%; (iii) (a) $ClSO_2NCO$ (CSI), Na_2CO_3, *n*-hexane, -40 ^{o}C; (b) sat. Na_2SO_3, 25 ^{o}C, 80%; (iv) MeI, NaH, THF/DMF (4:1), 25 ^{o}C, 99%; (v) (a) Raney Ni, H_2, CH_2Cl_2/MeOH (1:4), 25 ^{o}C; (b) HCl, ether, 25 ^{o}C, 75%.

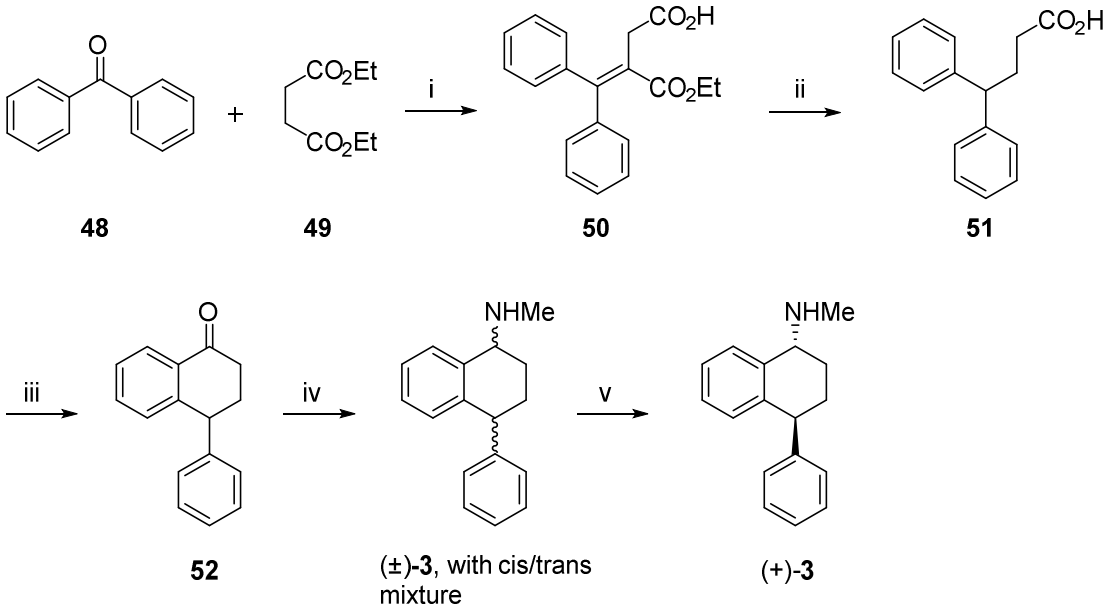
(b) Review of literature of (+)-tametraline

Literature survey revealed that there is only one report available for the synthesis of tametraline in its racemic form and which is described as below.

Sarges approach (1975)[13]

Sarges *et.al* have reported the synthesis of (+)-tametraline (**3**) using intramolecular Friedel Crafts acylation as the key step. Thus, condensation of diethyl succinate **49** with benzophenone **48** gave the diaryl substituted ethylcinnamate **50** in 80% yield. Then ester hydrolysis and decarboxylation followed by hydrogenation of cinnamate

50 provided the butanoic acid **51**. Further, butanoic acid **51** was converted into tetralone **52** using $AlCl_3$ and tetralone **52** was transformed to (±)-tametraline (±)-**3** with its *syn* diasteromer. Finally, separation of diasteromers and resolution of (±)-tametraline (±)-**3** using D-(-)-mandelic acid afforded the (+)-tametraline (+)-**3** in high enantiopurity (**Scheme 10**).



Scheme 10: (i) $KOBu^t$, diethyl succinate, ^tBuOH; (ii) (a) aqueous HBr-glacial acetic acid (1:1), reflux, 36 h, 50%; (b) H_2 (1 atm), 5% Pd/C, EtOAc, 25 °C, 24 h, 99%; (iii) (a) $SOCl_2$, toluene, reflux, 75 min; then $AlCl_3$, CS_2, 25 °C, 16 h, 48%; (iv) (a) $MeNH_2$, $TiCl_4$, toluene, 10 °C, 17 h, 95%; (b) $NaBH_4$, 14-25 °C, 1.5 h, 99%; (v) (a) resolution with D-(-)-mandelic acid then aq. NaOH, 30%.

2.1.4 Present Work

2.1.4.1 Objective

As can be seen, the reported methods for the synthesis of 1-amino-4-aryl tetralins such as (+)-sertraline **1** and (+)-tametraline **3** employ either resolution techniques which lead to lose of one of the enantiomers, chiral starting materials or expensive reagents involving longer reaction sequences, often resulting in poor product selectivities. Thus, there is a need for an efficient and highly enantioselective

synthesis of 1-amino-4-aryltetralins (**1**-**3**) in a lesser number of steps circumventing some of the disadvantages associated with the reported methods. Also no methods are reported so far for their synthesis using enamine catalysis. In this section, we describe a highly enantioselective synthesis of (+)-sertraline **1** and (+)-tametraline **3** using proline catalyzed Mannich reaction of acetaldehyde[14] as the chirality inducing step. Retrosynthetic analysis of (+)-sertraline **1** and (+)-tametraline **3** reveals that both **1** and **3** can be prepared from the intramolecular Friedel-Crafts alkylation of olefins (**56a** and **56b**). These olefins can in turn be derived from the Wittig olefination of β-aminoaldehyde **54** with semi-stabilized benzyl phosphorous ylide of Wittig salts **55a** and **55b** respectively. The β-aminoaldehyde **54** in turn can be obtained from the proline catalyzed Mannich reaction of N-Boc benzaldiimine **53**.

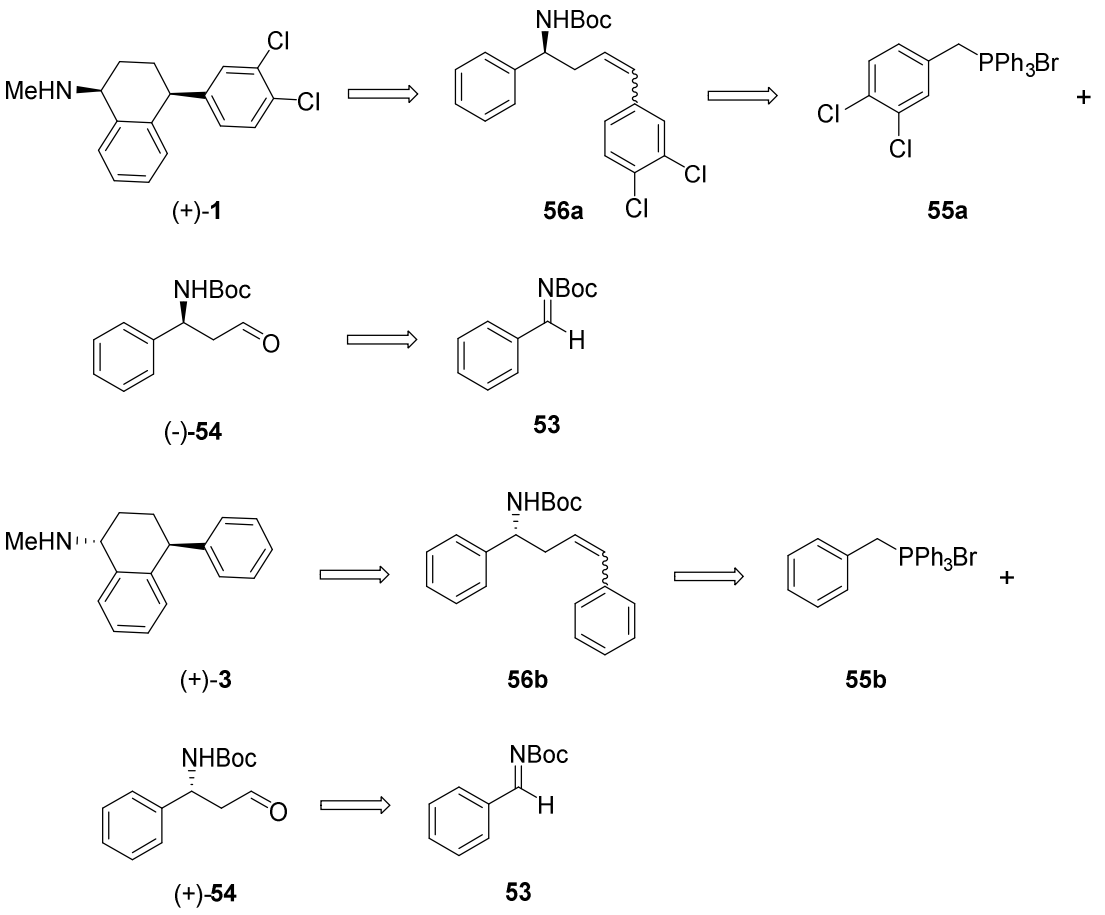
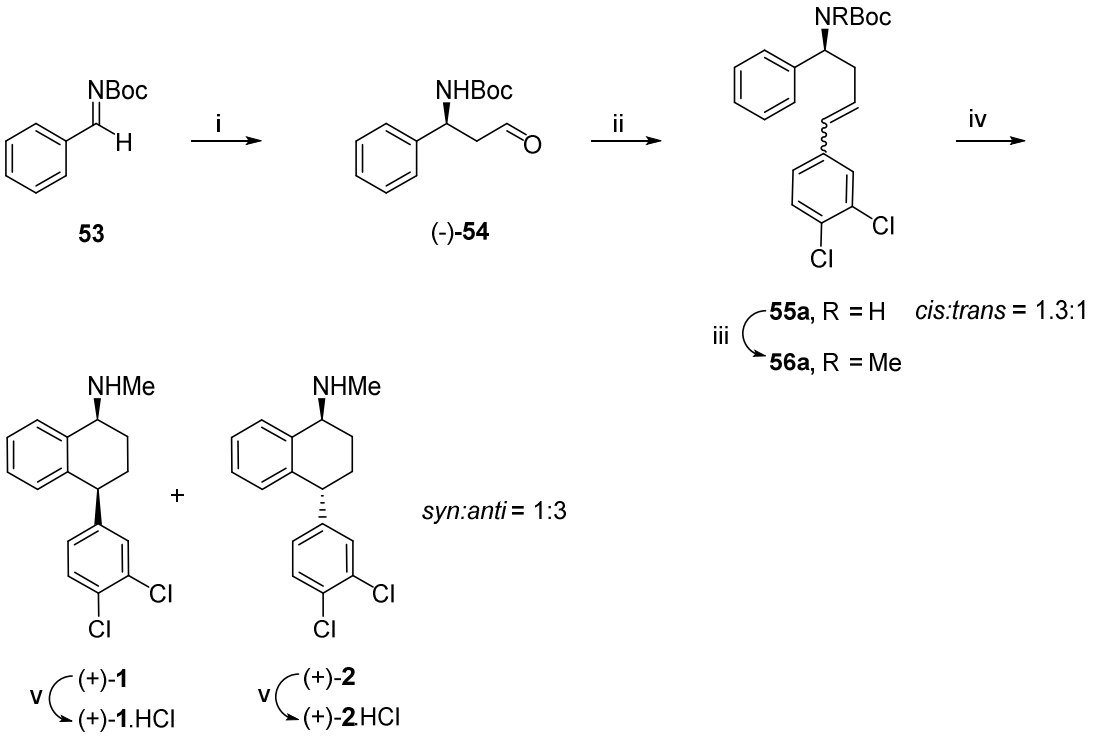


Fig. 2: Retrosynthetic analysis of (+)-sertraline **1** and (+)-tametraline **3**

2.1.5 Results and discussion

(a) Concise enantioselective synthesis of (+)-sertraline *via* L-proline catalyzed Mannich reaction of acetaldehyde

The complete synthetic sequence for (+)-sertraline wherein L-proline catalyzed Mannich reaction of acetaldehyde and acid catalyzed intramolecular Friedel-Crafts alkylation constitute as the key steps is presented in **Scheme 11**.



Scheme 11: (i) CH_3CHO (5 equiv), L-proline (20 mol%), CH_3CN, 0 ^oC, 3 h, 55%; (ii) 3,4-$Cl_2C_6H_3CH_2PPh_3Br$, *n*-BuLi or *t*BuOK, dry THF, 1.5 h, 0 ^oC, 60% with *n*-BuLi or 71% with ^{t}BuOK, 98% ee; (iii) MeI (2.5 equiv), NaH (1.5 equiv), dry THF, 7 h, 0-10 ^oC, 94%; (iv) PPA (1 equiv), EDC, reflux, overnight, 84%; (v) HCl gas, dry Et_2O, ≈97%.

Accordingly, the synthesis of (+)-sertraline (+)-**1** was undertaken starting from the NBoc-benzaldiimine **53** which on subjecting to L-proline catalyzed Mannich reaction with acetaldehyde (5 equiv) provided the β-aminoaldehyde (-)-**54** in 55% yield (**Scheme 11**). Aldehyde (-)-**54** was then treated with semistabilized 3,4-dichlorobenzyl phosphorous ylide[15] [*in situ* derived from the reaction between 3,4-

$Cl_2C_6H_3CH_2PPh_3Br$ Wittig salt and *n*-BuLi or KO*t*Bu] to provide olefin **55a** in 60% yield using *n*-BuLi as base or 71% yield using KO*t*Bu as base with 1.3:1 ratio of *cis:trans* geometrical isomers which were inseparable when attempted to purify through coloumn chromatography. The ^{1}H NMR spectrum of olefin **55a** showed the typical *cis-trans* olefinic signals at δ 5.64-5.69 (dt, *J* = 11.7, 7.2 Hz, 0.6 H), and 6.03-6.10 (dt, *J* = 15.9, 7.1 Hz, 0.4 H) as two doublet of triplets integrating for one of the

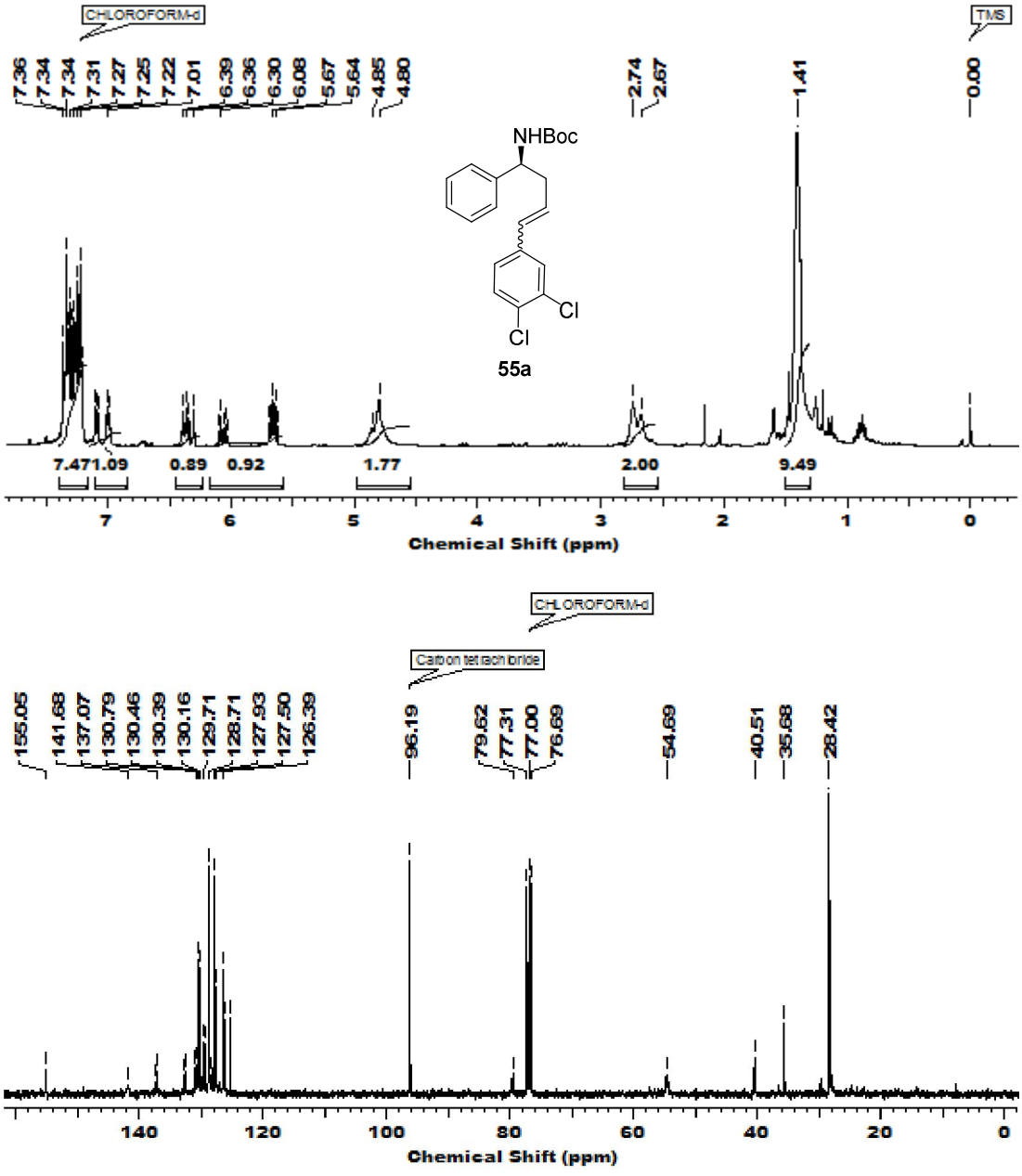
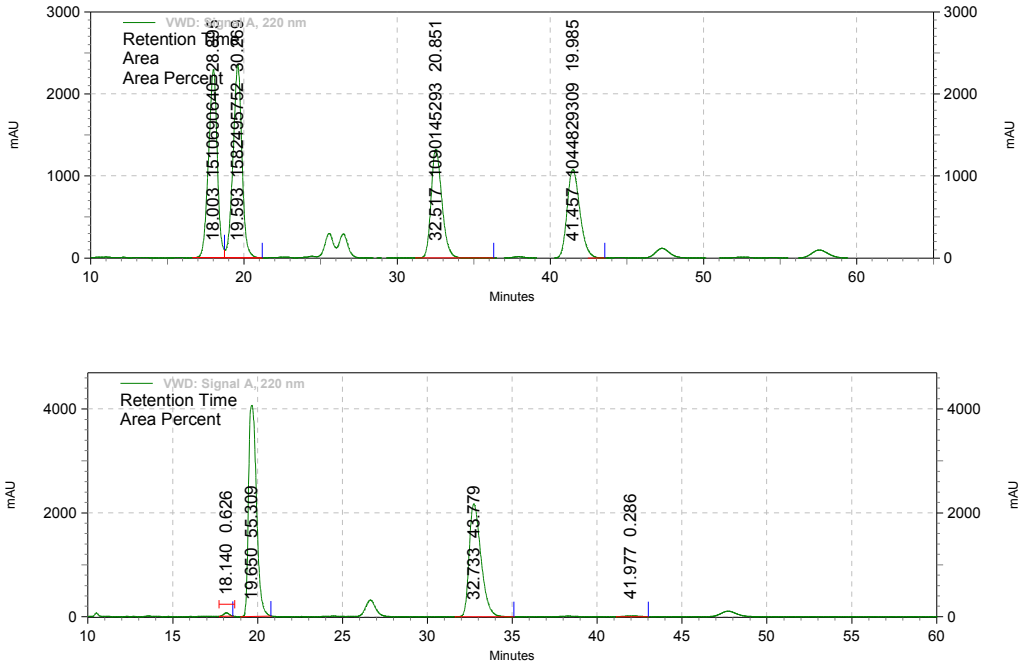


Fig. 3: ^{1}H, and ^{13}C NMR spectra of olefin **55a**

olefinic protons at homobenzylic carbon and a signal at δ 6.30-6.39 (m, 1H) corresponding to another olefinic proton at benzylic position. Its ^{13}C NMR spectrum displayed a characteristic carbon signal at δ 155.1 corresponding to the carbonyl carbon present in the Boc group (**Fig. 3**). The optical purity of olefin **55a** was found to be 99% ee with *cis:trans* isomeric ratio of 1.3:1 determined from chiral HPLC analysis [Chiralpak AD-H, *n*-hexane/*i*PrOH, 95:5, 0.5 mL/min)] retention time 18.14 min (0.63%) and 19.65 min (55.31%) for *cis* isomer] and retention time 32.73 min (43.78%) and 41.98 min (0.286%) for *trans* isomer (**Fig. 4**).



Retention Time	Area	Area %	Height	Height %
18.140	25110890	0.63	1113421	1.05
19.650	2218394046	55.31	68224931	64.34
32.733	1755920230	43.78	36478082	34.40
41.977	11457495	0.29	221136	0.21
Totals	4010882661	100.00	106037570	100.00

Fig. 4: HPLC chromatogram of olefin **55a**

Methylation of olefin **55a** using MeI and NaH at 0 to 10 °C afforded the N-methyl olefin **56a** in 94% yield. The ^{1}H NMR signal showed the proton signals of *cis-trans*

isomeric mixture at δ 2.46 (brs, 1.4H), and 2.56 (brs, 1.5H) as two broad singlets corresponding to three methyl protons (-N**Me**Boc). Its ^{13}C NMR spectrum displayed characteristic carbon signals at δ 28.5, and 155.9 corresponding to methyl and carbonyl carbons present in the Boc group (-NMe**Boc**). Its IR spectrum exhibited a characteristic carbamate –NMe**C**$\mathbf{O_2}$***t*****Bu** absorption bands at 1682 cm^{-1} and also, its mass spectrum with its molecular ion peaks (M) at *m/z* 403.9924 (for ^{35}Cl) and 405.9886 (for ^{37}Cl) confirmed the presence of N-methylated olefin **56a** (**Fig. 5**).

Deprotection of Boc group followed by intramolecular Friedel-Crafts' alkylation of N-methylated olefin **56a** in one pot was then achieved by its treatment with polyphosphoric acid in ethylene dichloride under reflux condition for overnight to deliver (+)-sertraline (+)-**1** (*syn*) and its C_4 epimer CP-52002 (-)-**2** (*anti*) in 84% yield with *syn:anti* ratio of 1:3 after coloumn chromatographic separation. Here, the major '*anti*' isomer is the thermodynamically controlled product[13a] while the minor '*syn*' isomer is the kinetically controlled one. Attempt to increase the ratio of '*syn*' isomer by lowering the temperature *i.e.* at 25 or 50 °C was not fruitful. Also, we observed the complex reaction mixture while treating the N-methylated olefin **56a** with other simple Bronsted acid such as TFA/CH_3CO_2H, and CH_3SO_3H consisting mainly of 1,2-alkene additioned products, whereas using Lewis acid like $BF_3.Et_2O$ at room temperature, we ended up with Boc-deprotected product without affecting the olefin.

Finally, (+)-sertraline (+)-**1** and CP-52002 (-)-**2** were converted into their hydrochloride salts by treating with dry HCl gas in dry Et_2O separately that provided each of (+)-**1**. HCl and (-)-**2**. HCl with 97% yield. The ^{1}H NMR spectrum of (+)-sertraline.HCl (+)-**1**.HCl showed the proton signals at δ 3.97-4.00 (m, 1H), and 4.30 (brs, 1H) for dibenzylic and benzylic (-C**H**NHMe) methine protons respectively. Its ^{13}C NMR spectrum displayed two characteristic carbon signals at δ 45.0, and 56.3

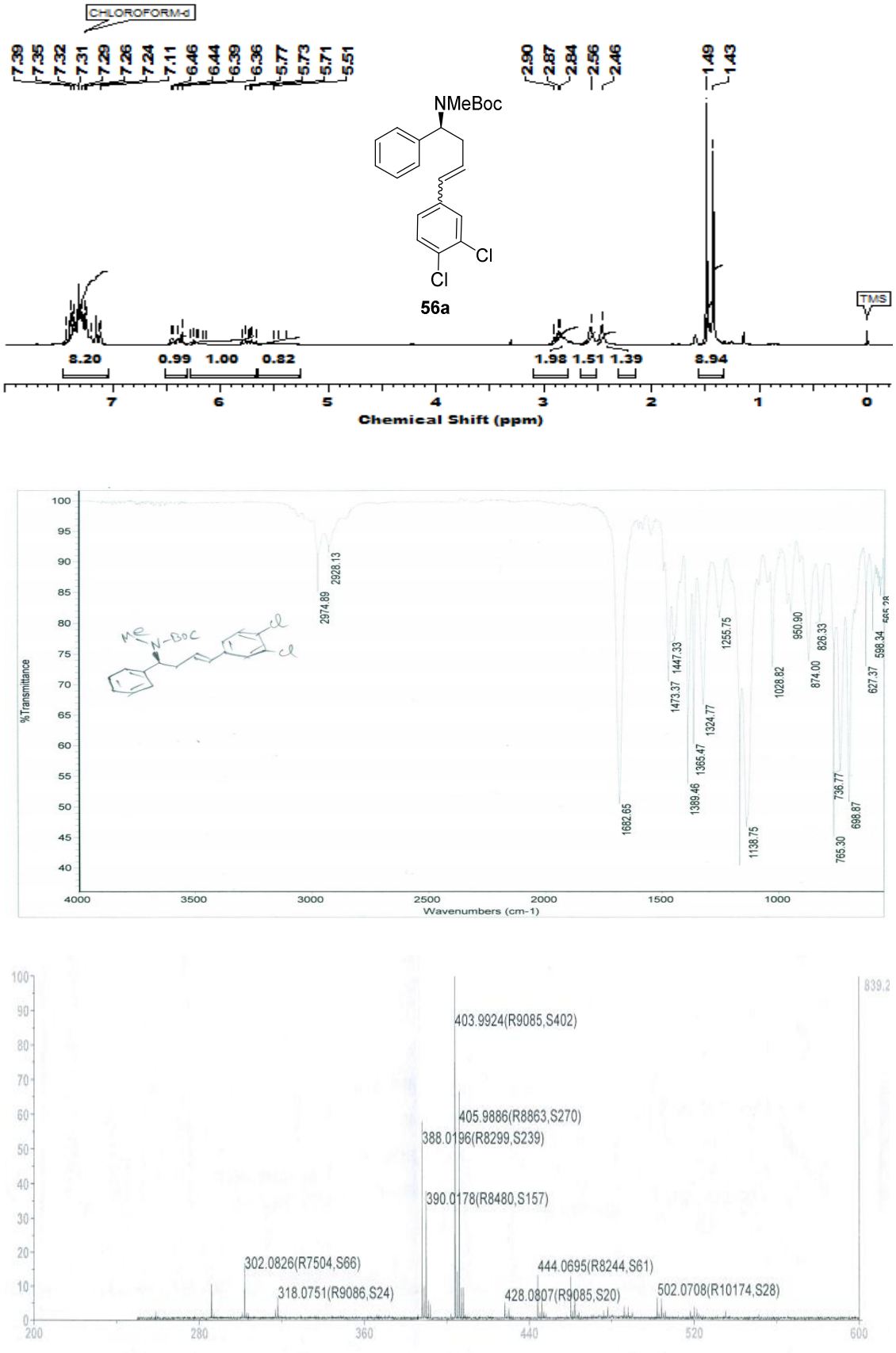


Fig. 5: ^{1}H, ^{13}C NMR, IR and Mass spectra of N-Methylated olefin **56a**

corresponding to dibenzylic and benzylic (-**C**HNHMe) methine carbons respectively (**Fig. 6**).

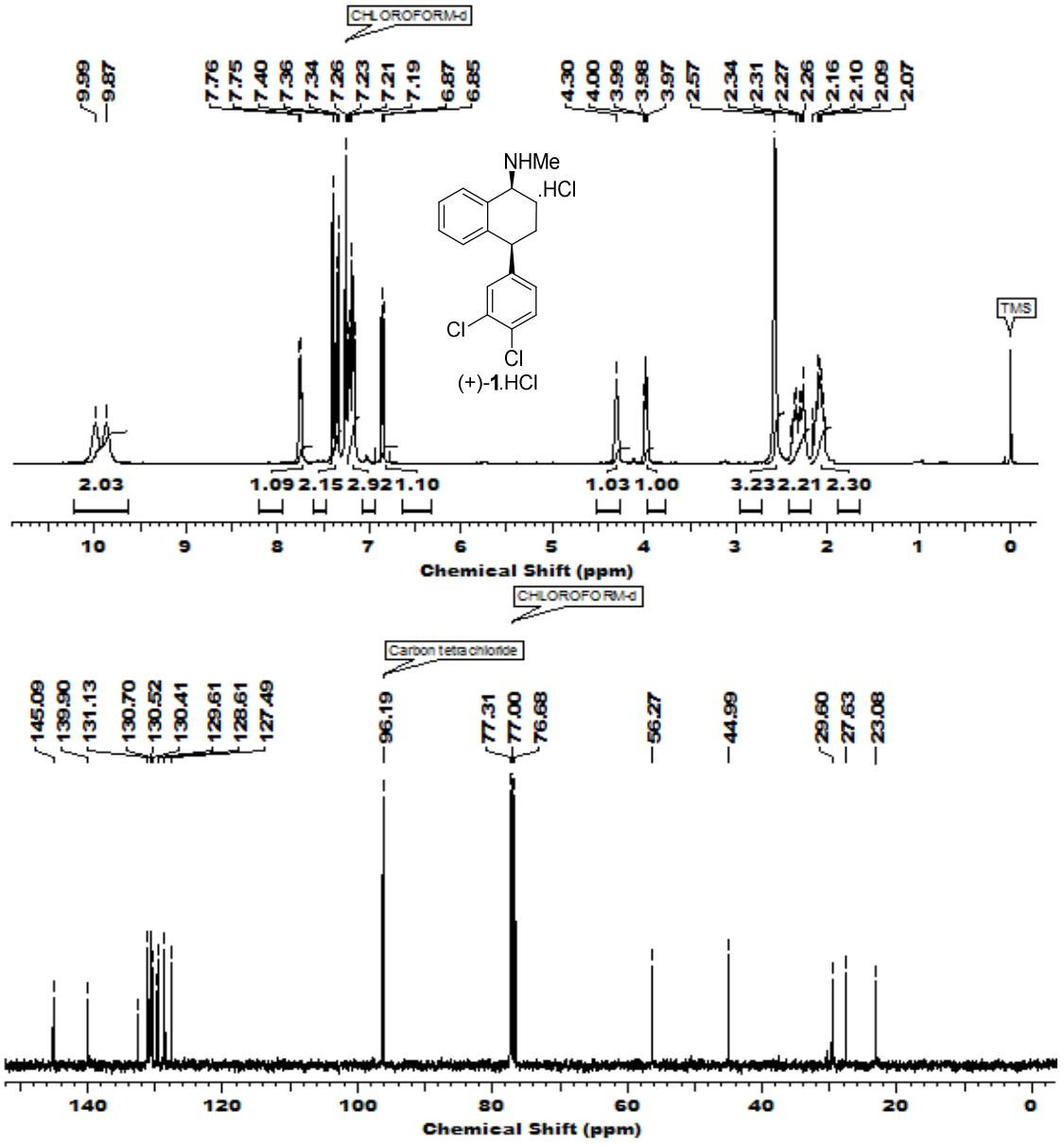


Fig. 6: ^{1}H, ^{13}C NMR spectra of (+)-sertraline.HCl (+)-**1**.HCl

The ^{1}H NMR spectrum of CP-52002.HCl (+)-**2**.HCl showed the proton signals at δ 4.22-4.55 (m, 1H), and 4.55 (brs, 1H) corresponding to dibenzylic and benzylic methine (-C**H**NHMe) protons respectively. Its ^{13}C NMR spectrum displayed two

typical carbon signals at δ 43.1 and 55.0 corresponding to dibenzylic and benzylic methine (-**C**HNHMe) carbons respectively (**Fig.7**).

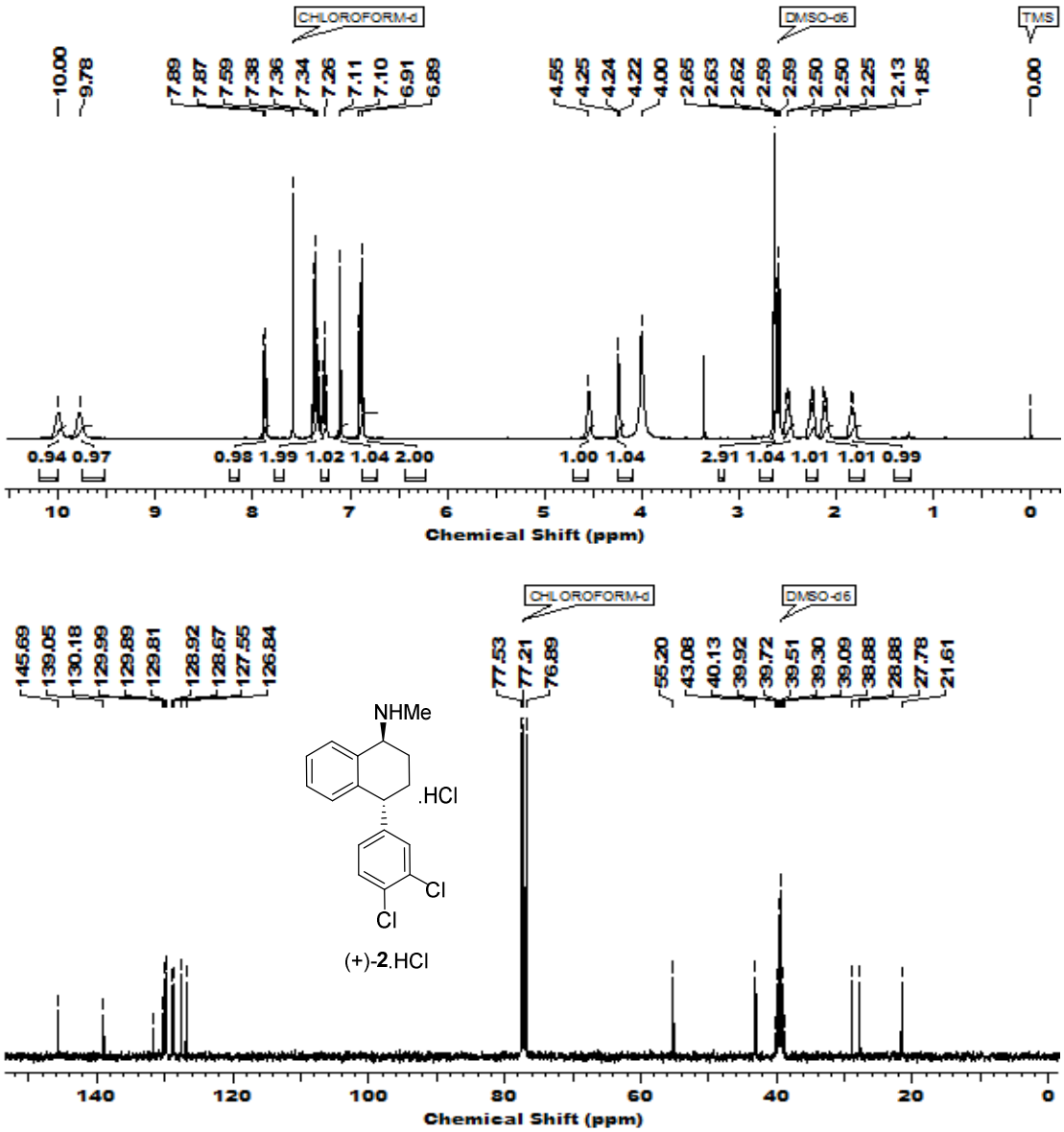
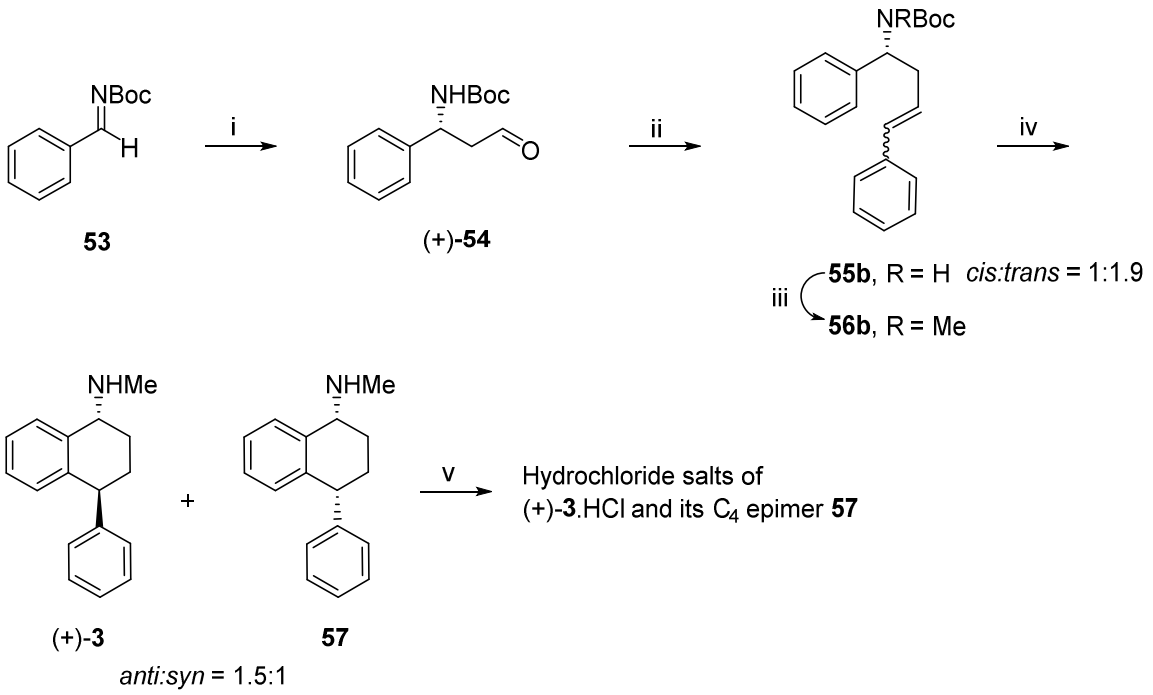


Fig. 7: ^{1}H and ^{13}C NMR spectra of CP-52002.HCl (+)-**2**.HCl

(b) Concise enantioselective synthesis of (+)-tametraline *via* D-proline catalyzed Mannich reaction of acetaldehyde

The complete synthetic sequence for (+)-tametraline (**3**) wherein D-proline catalyzed Mannich reaction of acetaldehyde and intramolecular Friedel-Crafts alkylation constitute as the key steps is presented in **Scheme 12**.



Scheme 12: i) CH_3CHO (5 equiv), D-proline (20 mol%), CH_3CN, 0 °C, 3 h, 55%; (ii) $C_6H_5CH_2PPh_3Br$, *n*-BuLi, dry. THF, 1.5 h, 0 °C, 58%, 98%ee; (iii) MeI (2.5 equiv), NaH (1.5 equiv), dry.THF, 7 h, 0-10 °C, 92%; (iv) PPA (1 equiv), EDC, reflux, overnight, 82%; (v) HCl gas, dry. Et_2O, ≈97%.

For the synthesis of (+)-tametraline (**3**), a similar reaction sequence was followed as in the case of (+)-sertraline (**1**) except in the type of proline and benzyl Wittig ylide used for the first two steps. Thus, the β-aminoaldehyde (+)-**54** derived from Mannich reaction of acetaldehyde and NBoc-benzaldiimine using D-proline, was treated with semi-stabilized benzyl phosphorous ylide [derived from $C_6H_5CH_2PPh_3Br$ and *n*-BuLi] to provide the olefin **55b** in 58% yield with inseparable *cis/trans* isomers (1:1.9). The ^{1}H NMR spectrum of olefin **55b** showed two typical *cis-trans* olefinic signals at δ 5.59-5.62 (dt, *J* = 7.0, 11.7 Hz, 0.36 H) and 6.03-6.07 (dt, *J* = 7.3, 15.7 Hz, 0.58 H) as two doublet of triplets integrating for one of the olefinic protons at homobenzylic position and two doublets at δ 6.44 (d, *J* = 15.7 Hz, 0.62 H), and 6.52 (d, *J* = 11.7 Hz, 0.38H) thus, integrating for corresponding another olefinic proton at benzylic

position. Its ^{13}C NMR spectrum displayed a characteristic carbon signal at δ 155.1 corresponding to the carbonyl carbon present in the Boc group (**Fig. 8**).

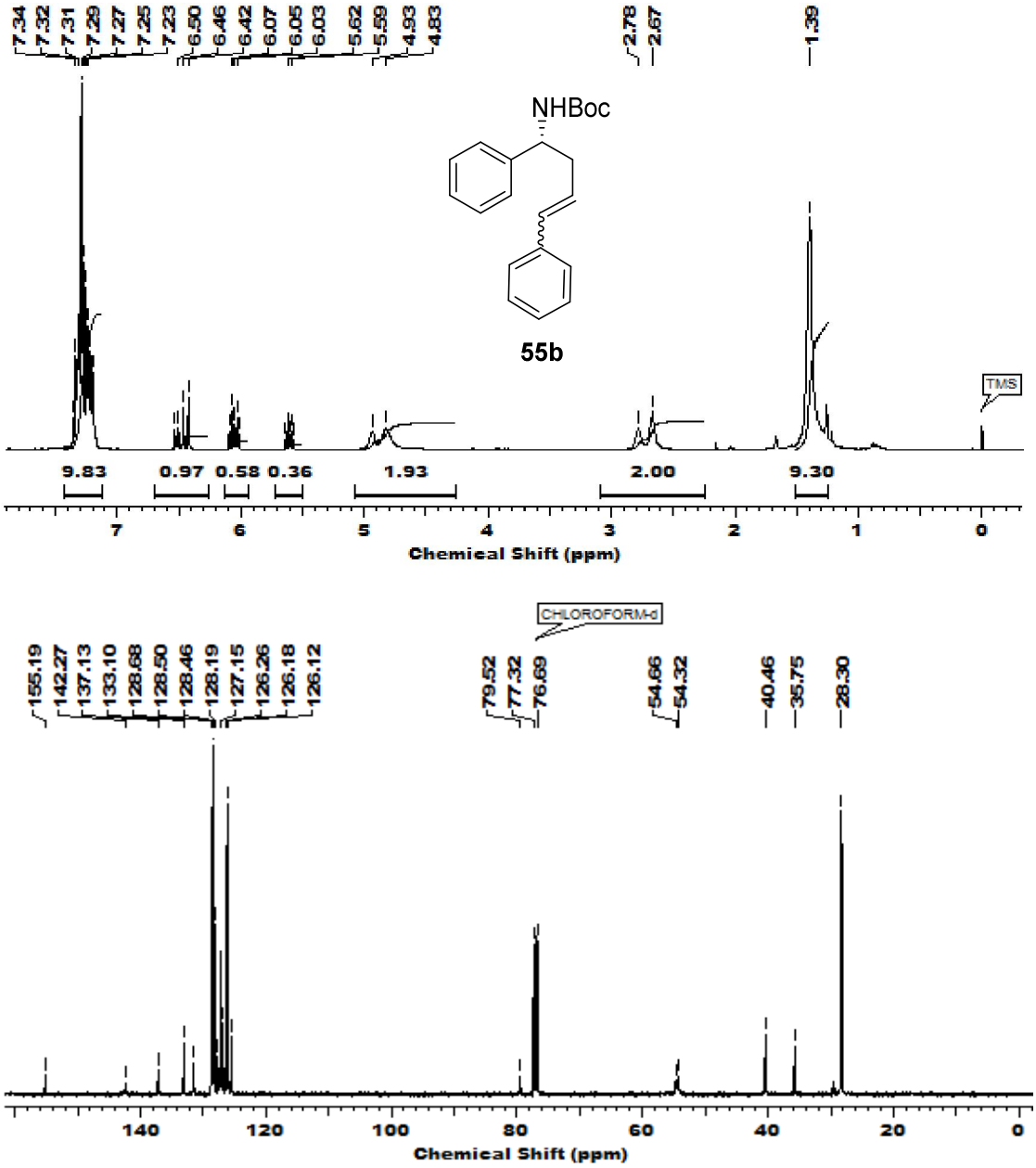
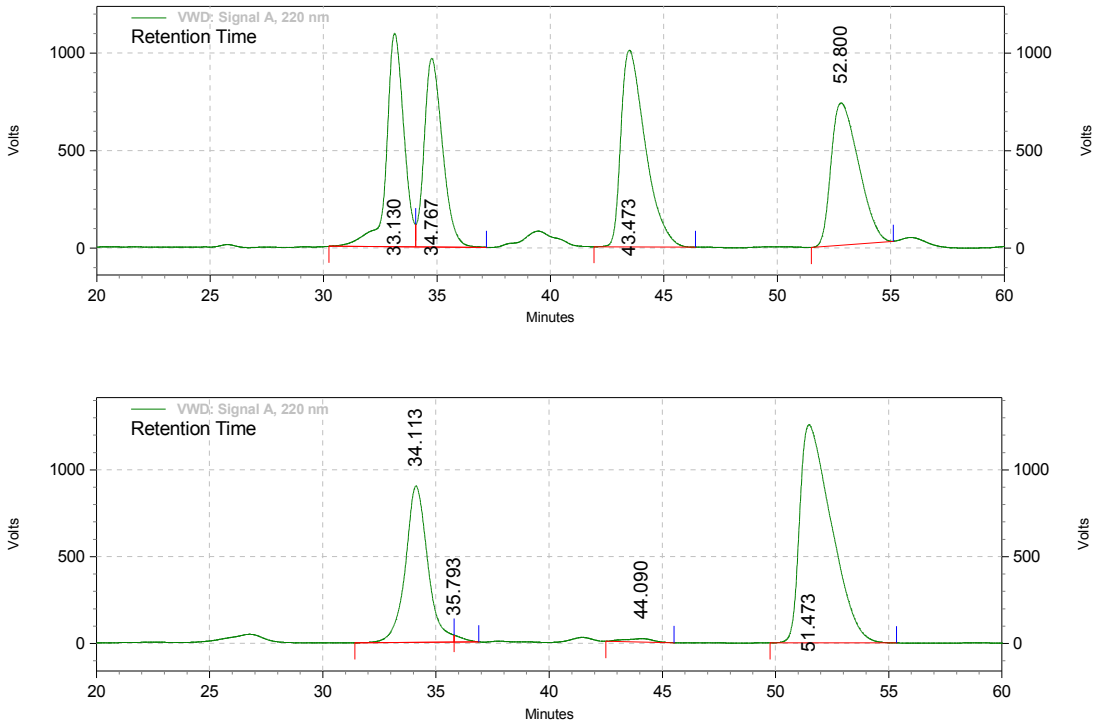


Fig. 8: ^{1}H and ^{13}C NMR spectra of olefin **55b**

The optical purity of olefin **55b** was found to be 99% ee with *cis:trans* isomeric ratio of 1:1.9 determined from chiral HPLC analysis [Chiralpak AD-H, *n*-hexane/*i*PrOH, 98:2, 0.5 mL/min)] retention time 34.113 min (33.14%) and 35.793 min (0.56%) for

cis isomer] and retention time 44.09 min (0.91%) and 51.47 min (65.39%) for *trans* isomer (**Fig. 9**).



VWD: Signal A, 220 nm Results

Retention Time	Area	Area %	Height	Height %
34.113	1036618374	33.14	15115587	40.65
35.793	17627655	0.56	659990	1.77
44.090	28313480	0.91	329039	0.88
51.473	2045245707	65.39	21081832	56.69
Totals	3127805216	100.00	37186448	100.00

Fig. 9: HPLC chromatogram of olefin **55b**

Methylation of olefin **55b** using MeI and NaH at 0 to 10 °C afforded the N-methylated olefin **56b** in 94% yield. Its ^{1}H NMR spectrum showed a typical proton signal at δ 2.6 (brs, 3H) corresponding to three methyl protons (-N**Me**Boc). Its ^{13}C NMR spectrum displayed two characteristic carbon signals at δ 28.5 and 155.7 corresponding to methyl and carbonyl carbons respectively of the Boc group (-NMe**Boc**). Its mass spectrum with its molecular ion peak $(M+K)^{+}$ at *m/z* 376.25 confirmed the presence of N-methylated olefin **56b** (**Fig. 10**).

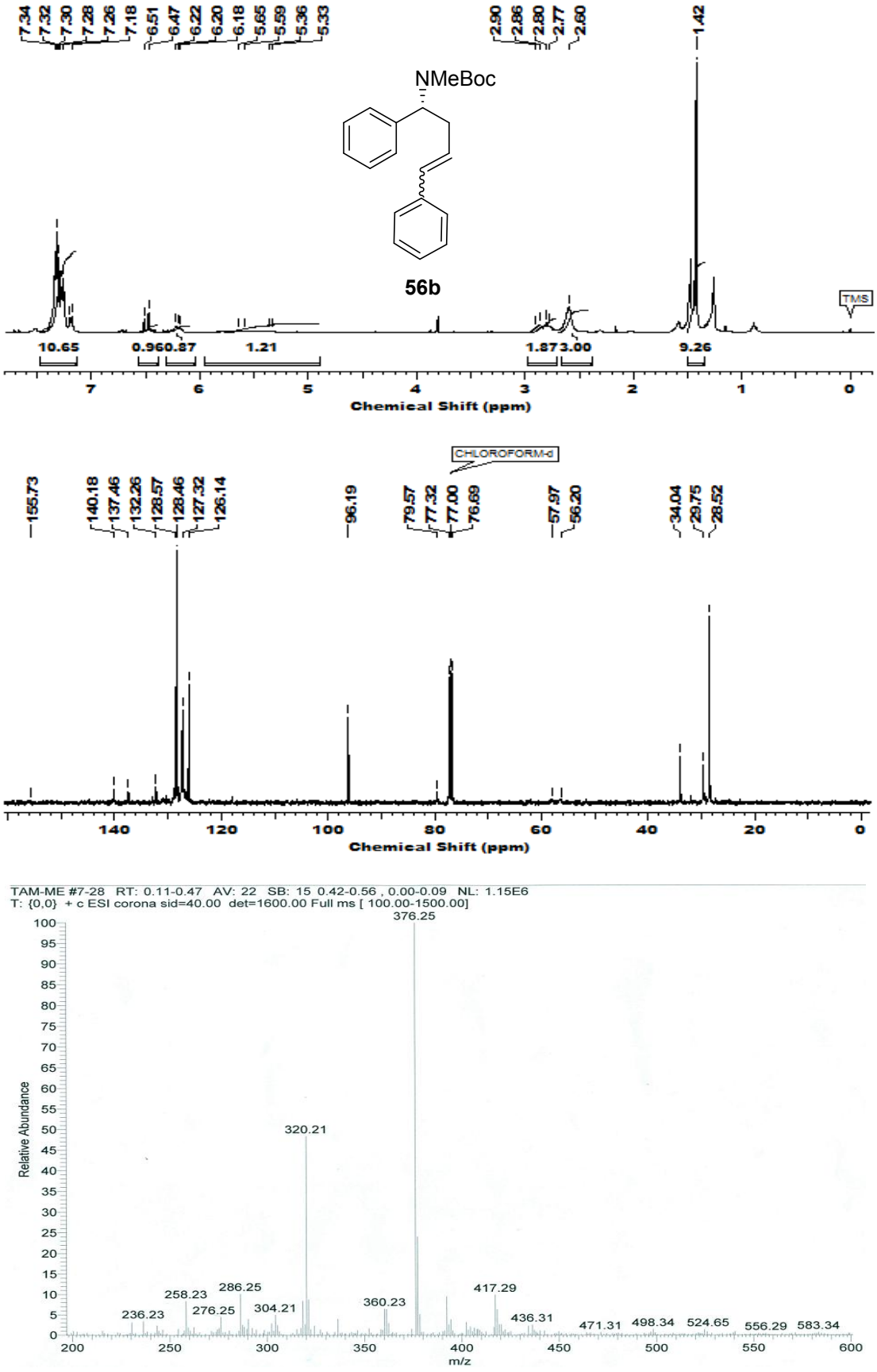


Fig. 10: ^{1}H, ^{13}C NMR and Mass spectra of N-Methylated olefin **56b**

The deprotection of Boc group and intramolecular Friedel-Crafts alkylation of N-methylated olefin **56b** in "one pot" was achieved on treatment with polyphosphoric acid in ethylene dichloride as solvent under reflux condition for 12 h that afforded a mixture of (+)-tametraline [(+)-**3**] and its C_4 epimer **57** in 82% yield, which are inseparable through coloumn chromatography. Hence, to separate the mixture of (+)-**3**

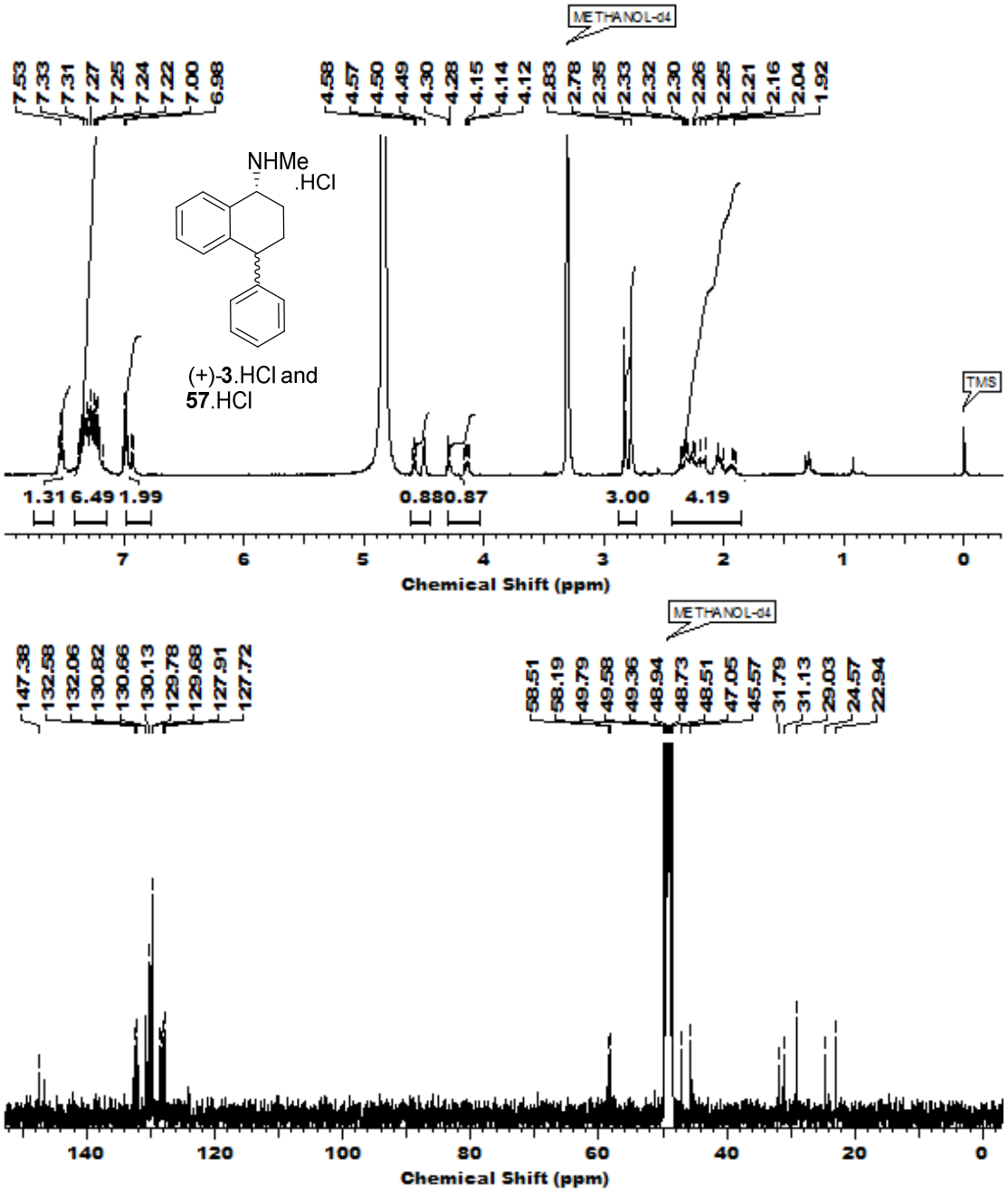


Fig. 11: ^{1}H, and ^{13}C NMR spectra of mixture of HClsalt of (+)-tametraline [(+)-**3**] and its C_4 epimer **57**

from its C_4 epimer **57**, the mixture was converted to the corresponding hydrochlorides which was subjected to fractional crystallization. However, we observed that the crystallization was not successful either. Nevertheless, the mixture can be separated by following the literature protocol[13b] *via* their treatment with D-(-)-mandelic acid to provide the crystals of (+)-tametraline-D-(-)-mandelate selectively. The ^{1}H NMR spectrum of the diastereomeric mixture of (+)-**3** and (-)-**57** showed proton signals at δ 4.12-4.31 (m, 1H) and 4.5-4.6 (m, 1H) for dibenzylic and benzylic (-C**H**NHMe) methine protons respectively. The ^{13}C NMR spectrum of the diastereomeric mixture displayed a set of carbon signals at δ 45.6, 47.1 and δ 58.2, 58.5 corresponding to dibenzylic and benzylic (-**C**HNHMe) methine carbons respectively (**Fig. 11**).

2.1.6 Conclusion

In conclusion, a short and highly enantioselective method for the syntheses of (+)-sertraline (+)-**1**, CP-52002 (+)-**2** and (+)-tametraline (+)-**3** has been described. The strategy employs proline catalyzed Mannich reaction of acetaldehyde and intramolecular Friedel-Crafts alkylation as the key steps. The overall yield of (+)-**1** and (+)-**3** were found to be 31% and 24% respectively with 99%ee and diastereomeric ratio of 1:3 [for (+)-**1** and (-)-**2**] and 1:1 [for (+)-**3** and its C_4 epimer]. The present protocol comprises of less number of steps, use of environmentally benign proline as the catalyst and notably without the use of toxic transition metals. Also, this may provide the flexibility in arriving at all the diasteromers of several biologically active 1-amino-4-aryltetralins with excellent enantioselectivity simply by changing the type of proline used.

2.1.7 Experimental Section

General experimental procedure for the preparation of β-aminoaldehydes

To a stirred solution of aryl N-Boc-imine **53** (1.8 g, 1.4 mmol) in CH_3CN (15 mL) and 0.74 M redistilled acetaldehyde (3.2 mL, 6 mmol) in CH_3CN (60 mL) at 0 ^oC was added L-proline [for (+)-**1**] or D-proline [for (+)-**3**] (202 mg, 20 mol%) as the case may be and the mixture stirred further at 0 ^oC for 3 h. After the completion of reaction (monitored by TLC), it was quenched with water and extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4, filtered and concentrated under reduced pressure to give the crude aldehyde. Flash column chromatographic purification [silica gel (230-400 mesh) and pet. ether:EtOAc (80:20) as an eluent] gave β-aminoaldehyde (-)-**54** or (+)-**54**.

(*S*)-*tert*-Butyl (3-oxo-1-phenylpropyl)carbamate, **[(-)-54]**

Yield: 1.2 g, 55%; pale yellow solid; **mp**: 91-94 ºC, (lit.[14] **mp**: 92-93.5 ºC); $[\alpha]^D_{25}$ -30.10 (*c* 1.15, $CHCl_3$); lit.[14] $[\alpha]^D_{25}$ +29.0 (*c* 1.4, $CHCl_3$) for its antipode; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 700, 1021, 1049, 1169, 1250, 1369, 1391, 1498, 1513, 1692, 2977, 3341; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.41 (s, 9H), 2.83-2.96 (m, 2H), 4.87 (br s, 1H), 5.17 (br s, 1H), 7.26-7.34 (m, 5H), 9.73 (t, *J* = 1.7 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 28.3, 39.9, 49.9, 79.9, 126.3, 127.7, 128.8, 135.2, 155.0, 193.3, 199.8; **Analysis**: $C_{14}H_{19}NO_3$ requires C, 67.45; H, 7.68; N, 5.62; found: C, 67.32; H, 7.41; N, 5.46%.

General experimental procedure for the preparation of olefins (55a and **55b)**

To a stirred solution of 3,4-dichlorobenzyltriphenylphosphonium bromide (1.3 g, 1.2 equiv) [in case of (+)-**1**] or benzyltriphenylphosphonium bromide (1.2 g, 1.2 equiv) [in case of (+)-**3**] in dry THF kept at 0 ^oC added *n*-butyllithium (1.2 equiv, 1.6M solution in *n*-hexane) and allowed to stir for 30 min at the same temperature to generate the ylide. A solution of β-aminoaldehyde **54** (1 equiv) in dry THF was added

to the ylide and the reaction mixture was stirred for 1 h. After completion of reaction, it was quenched with sat. NH_4Cl solution. The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4, filtered and concentrated under reduced pressure to give the crude olefin. Flash column chromatographic purification [silica gel (230-400 mesh) and pet. ether:EtOAc (9:1) as an eluent] gave the desired olefins.

(*S*)-*tert*-Butyl-(4-(3,4-dichlorophenyl)-1-phenylbut-3-en-1-yl)carbamate (55a)

Yield: 60%, pale yellow liquid; 99% ee from **HPLC analysis**; Chiralpak AD-H column (2-propanol:*n*-hexane = 5:95, flow rate 0.5 mL/min, λ = 220 nm). Retention time (min): For *cis*: 18.14 (minor), 19.65 (major); and For *trans*: 32.73 (major), 41.98 (minor), $[\alpha]^{25}_{D}$: -16.5 (c 0.64, $CHCl_3$) (for *trans:cis* = 1:1.3); **IR** ($CHCl_3$, cm^{-1}): 628, 700.25, 830.4, 874.8, 1059, 1142, 1335, 1365, 1394, 1447.26, 1475, 1694, 3357; **^{1}H NMR** ($CDCl_3$, 400MHz): δ 1.41 (br s, 10H), 2.67 (br s, 1H), 2.74 (br s, 1H), 4.80 (br s, 1H), 4.85 (br s, 1H), 5.66 (dt, *J* = 11.7, 7.2 Hz, 1H), 6.24 - 6.46 (m, 1H), 7.00 (d, *J* = 8.1 Hz, 1H), 7.17 - 7.42 (m, 8H); **^{13}C NMR** ($CDCl_3$,125 MHz): δ 28.4, 35.7, 40.5, 54.7, 76.7, 77.3, 79.6, 125.3, 126.3, 126.4, 127.5, 127.9, 128.5, 128.7, 129.3, 129.7, 130.2, 130.4, 130.5, 130.8, 130.9, 132.4, 132.7, 137.1, 137.3, 141.7, 141.9, 155.1. **Analysis:** $C_{21}H_{23}Cl_2NO_2$ requires C, 64.29; H, 5.91; Cl, 18.01; N, 3.57; found: C, 64.5; H, 5.74; Cl, 18.35; N, 3.4%.

(*R*)-*tert*-Butyl-(1,4-diphenylbut-3-en-1-yl)carbamate 55b

Yield: 58%, colorless gum; 99% ee from **HPLC analysis**; Chiralpak AD-H column (2-propanol:*n*-hexane = 2:98, flow rate 0.5 mL/min, λ = 220 nm). Retention time (min): For *cis*: 34.113 (major), 35.793 (minor); and For *trans*: 44.09 (minor), 51.47 (major), $[\alpha]^{25}_{D}$: +25.3 (c 1.2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 790, 1025, 1056, 1124, 1161, 1369, 1400, 1495, 1696, 2930, 2986; **^{1}H NMR** ($CDCl_3$, 200MHz): δ 1.38 (brs, 9H), 2.66 (brs, 1H), 2.77 (brs, 1H), 4.42 - 5.00 (m, 2H), 5.47 - 5.83 (m, 1H), 5.83 -

6.22 (m, 1H), 6.23 - 6.62 (m, 1H), 7.25 (brs, 10H); **^{13}C NMR** ($CDCl_3$,125 MHz): δ 28.4, 35.7, 40.5, 54.8, 76.4, 77.6, 79.4, 96.2, 125.4, 126.2, 126.2, 126.3, 126.8, 127.2, 127.7, 128.2, 128.5, 128.7, 128.9, 129.9, 131.6, 133.2, 137.1, 142.4, 155.1; **Analysis:** $C_{21}H_{25}NO_2$ requires C, 77.98; H, 7.79; N, 4.33; found: C, 78.06; H, 7.90; N, 4.56%.

General experimental procedure for the preparation of N-methylated olefins (56a and **56b)**

To a stirred solution of olefin **55a** or **55b** in anhydrous THF and DMF (4:1) was added NaH (1.5 equiv, 60% in mineral oil) at 0°C. After stirring for 30 min, CH_3I (2.5 equiv) was added at 0 °C under N_2. The reaction mixture was stirred at room temperature for 6 h under N_2 and quenched with H_2O (10 mL). The aqueous layer was extracted with EtOAc (2×25 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography (n-hexane/EtOAc = 97/3) to afford **56a** and **56b** in 94-95% yield.

***tert*-Butyl-(*S*)-(4-(3,4-dichlorophenyl)-1-phenylbut-3-en-1-yl)(methyl)carbamate (56a)**

Yield: 95%, pale yellow viscous liquid; **$[\alpha]^{25}_D$**: -50.77 (c 0.9, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 565.3, 598.3, 627.4, 698.8, 737, 765.3, 826.3, 874, 950.9, 1028.8, 1138.8, 1255.8, 1324.77, 1365.5, 1389.5, 1447.33, 1473.4, 1682, 2928, 2975; **^{1}H NMR** ($CDCl_3$,200MHz): δ 1.43 (s, 4H), 1.49 (s, 5H), 2.46 (brs, 1H), 2.56 (brs, 1H), 2.66 - 2.99 (m, 2H), 5.25 - 5.65 (m, 1H), 5.74 (dt, J = 11.7, 6.8 Hz, 1H), 6.31 - 6.51 (m, 1H), 7.03 - 7.47 (m, 8 H); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 28.3, 28.5, 29.4, 33.8, 57.5, 60.8, 79.7, 124.8, 125.2, 127.3, 127.4, 127.8, 127.9, 128.4, 128.6, 129.1, 129.8, 130.1, 130.3, 130.4, 131.2, 132.4, 132.5, 137.2, 137.5, 139.5, 139.7, 155.9; **Analysis:** $C_{22}H_{25}Cl_2NO_2$ requires C, 65.03; H, 6.20; Cl, 17.45; N, 3.45; found: C, 65.32; H, 6.46; Cl, 17.35; N, 3.57%.

(*R*)-*tert*-Butyl-(1,4-diphenylbut-3-en-1-yl)(methyl)carbamate (56b)

Yield: 94%, colorless liquid; $[\alpha]^{25}_{D}$: +67.0 (c 1.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 200MHz): 1.42-1.49 (br s, 9H), 2.45-2.59 (br s, 3H), 2.8-2.95 (m, 2H), 5.38 (m, 1H), 5.6-6.23 (m, 1H), 6.45-6.55 (m, 1H), 7.14-7.34 (m, 10H); **^{13}C NMR** ($CDCl_3$, 50MHz): δ 28.3, 28.5, 29.4, 33.8, 57.5, 60.8, 79.7, 124.8, 125.2, 127.3, 127.4, 127.8, 127.9, 128.4, 128.6, 129.1, 129.8, 130.1, 130.3, 130.4, 131.2, 132.4, 132.5, 137.2, 137.5, 139.5, 139.7, 155.9; **LCMS (ESI, m/z)**: Calculated for $C_{22}H_{27}KNO_2$ $(M+K)^+$ 376.17; found 376.25; **Analysis:** $C_{22}H_{27}NO_2$ requires C, 78.3; H, 8.06; N, 4.15; found: C, 78.71; H, 8.17; N, 4.45%.

General experimental procedure for the preparation of free base [(+)-1 and (+)-3]

A solution of **56a** or **56b** dissolved in 1,2-dichloroethane was added to liquid of polyphosphoric acid (liquefied after heating the neat polyphosphoric acid at 80 ^oC). The above reaction mixture was stirred overnight at 120 ^oC. Then 1,2-dichloroethane was removed under vaccum and quenched with sat.$NaHCO_3$ solution. The aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography using neutralized silica gel with Et_3N (*n*-hexane/EtOAc/Et_3N = 90/10/1) to afford amine in 82-84% yield.

(*1S, 4S*)-4-(3,4-dichlorophenyl)-N-methyl-1,2,3,4-tetrahydronaphthalen-1-amine (+)-1 and (*1S,4R*)-4-(3,4-dichlorophenyl)-N-methyl-1,2,3,4-tetrahydronaphthalen-1-amine [(-)-2, CP-52002]

Yield: 84% (dr = 1:3 of *syn:anti*), yellow oil; **For *syn* isomer**: **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.25 (br s, 1H), 1.85−2.15 (m, 4H), 2.55 (s, 3H), 3.81 (m, 1H), 3.97-3.99 (dd, *J* = 9.2, 6.1Hz, 1H), 6.79 (d, *J* = 7.6 Hz, 1H), 6.98-7.0 (dd, *J* = 8.2, 1.8 Hz, 1H),

7.1−7.13 (m, 1H), 7.18-7.21 (m, 1H), 7.26-7.27 (m, 1H), 7.33-7.35 (d, *J* = 8.2 Hz, 1H), 7.38-7.39 (d, *J* = 7.6 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 24.0, 28.8, 32.4, 44.2, 56.8, 127.1, 127.8, 128.0, 128.9, 129.7, 130.3, 130.3, 130.4, 130.6, 136.3, 138.6, 147.1; **CP-52002, (-)-2, *anti* isomer**: **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.62 (br s, 1H), 1.74−1.78 (m, 2H), 1.93−2.38 (m, 2H), 2.51 (s, 3H), 3.78-3.8 (m, 1H), 4.12-4.14 (m, 1H), 6.82-6.85 (m, 2H), 7.11-7.14 (m, 2H), 7.21−7.26 (m, 1H), 7.31-7.32 (d, *J* = 8.2 Hz, 1H), 7.44-7.46 (d, *J* = 7.6 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 24.5, 28.7, 33.9, 44.3, 57.1, 126.8, 127.1, 128.1, 128.6, 129.9, 130.1, 130.1, 130.6, 132.2, 138.0, 139.5, 147.5; **Analysis:** $C_{17}H_{17}Cl_2N$ requires C, 66.68; H, 5.60; N, 4.57; found: C, 66.49; H, 5.72; N, 4.63%.

Mixture of (*1R,4S*)-N-methyl-4-phenyl-1,2,3,4-tetrahydronaphthalen-1-amine, [(+)-3] and its C_4 epimer

Yield: 82% (dr = 1:1 of *syn:anti*) inseparable mixture, yellow oil; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.6 - 1.9 (m, 2 H), 2.0 (m, 2H), 2.3 (m, 1H), 2.52-2.54 (br s, 3H), 3.73 - 3.86 (m, 1H), 3.97-4.20 (m, 1H), 6.8 - 6.9 (m, 1H), 7.0 - 7.3 (m, 7H), 7.3 - 7.5 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 20.6, 21.2, 25.2, 25.3, 27.6, 28.1, 42.1, 43.5, 54.4, 54.5, 124.2, 124.4, 126.1, 126.2, 126.6, 127.1, 127.6, 128.3, 129.2, 143.1, 143.4.

Preparation of Hydrochloride salts of (+)-1, (-)-2, and (+)-3

To a solution of free amine base in dry Et_2O, dry HCl gas was passed for 30 min continuously and the precipitate formed was filtered and washed with anhydrous ether and dried to afford the hydrochloride salt in 90-94% yield.

(*1S,4S*)-4-(3,4-Dichlorophenyl)-N-methyl-1,2,3,4-tetrahydronaphthalen-1-amine hydrochloride, [(+)-1.HCl]

Yield: 94%, colorless solid; **mp**: 240-243 °C, (lit.[2c] **mp**: 243-245 °C); $[\alpha]^{25}_{D}$ +46.8 (*c* 0.4, $CHCl_3$); lit.[2c] $[\alpha]^{25}_{D}$ +37.9 (*c* 2, MeOH); **IR** ($CHCl_3$, cm^{-1}): 3380, 2926, 2720,

2459, 1590, 1469, 1452, 1403, 1136, 1029, 953, 825, 740; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.95 - 2.17 (m, 2H), 2.26 (brs, 1H), 2.28 - 2.43 (m, 1H), 2.57 (brs, 3H), 3.85 - 4.06 (m, 1H), 4.30 (brs, 1H), 6.86 (d, *J* = 7.6 Hz, 1H), 7.12 - 7.28 (m, 4H), 7.29 - 7.43 (m, 2H), 7.76 (d, *J* = 7.1 Hz, 1H), 9.87 (brs, 1H), 9.99 (brs, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 23.1, 27.6, 29.6, 45.0, 56.3, 127.5, 128.6, 129.6, 129.7, 130.4, 130.5, 130.7, 130.9, 131.1, 132.6, 139.9, 145.1; **MALDI-MS (ESI, m/z)**: Calculated for $C_{17}H_{16}Cl_2N$ $(M-1)^+$ 304.07; found 304.04.

(*1S,4R*)-4-(3,4-Dichlorophenyl)-N-methyl-1,2,3,4-tetrahydronaphthalen-1-amine hydrochloride, [CP-52002.HCl, (-)-2.HCl]

Yield: 92%, colorless solid; **mp**: 253-255 °C, (lit.[2c] **mp**: 257-258 °C); $[\alpha]^{25}_{D}$ -40.3 (*c* 0.9, $CHCl_3$); lit.[2c] $[\alpha]^{25}_{D}$ -39.2 (*c* 2, MeOH); **^{1}H NMR** (400 MHz, $CDCl_3$ + DMSO-d_6): δ 1.74 - 1.92 (m, 1H), 2.02 - 2.17 (m, 1H), 2.19 - 2.32 (m, 1H), 2.43 - 2.55 (m, 1H), 2.63 (t, *J* = 5.3 Hz, 3H), 4.24 (t, *J* = 6.2 Hz, 1H), 4.55 (brs, 1H), 6.71 - 6.94 (m, 2H), 7.10 (d, *J* = 2.0 Hz, 1H), 7.22 - 7.30 (m, 1H), 7.30 - 7.40 (m, 2H), 7.88 (d, *J* = 7.8 Hz, 1H), 9.78 (brs, 1H), 10.0 (brs, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$ + DMSO-d_6): δ 21.6, 27.8, 28.9, 38.9, 39.1, 39.3, 39.7, 39.9, 40.1, 43.1, 55.2, 126.8, 127.5, 128.7, 128.9, 129.7, 129.8, 129.9, 130.0, 130.2, 131.7, 139.0, 145.7.

Mixture of hydrochlorides of (*1R, 4S*)-N-methyl-4-phenyl-1,2,3,4-tetrahydronaphthalen-1-amine [(+)-3] and its C_4 epimer

Yield: 90%, colorless solid; **mp**: 209-212 °C; **^{1}H NMR** (400 MHz, MeOH-d_4): δ 1.9 - 2.1 (m, 2H), 2.1 - 2.4 (m, 2H), 2.8 (s, 2H), 2.9 (s, 1H), 4.14-4.33 (m, 1H), 4.6 - 4.6 (m, 1H), 6.9 - 7.1 (m, 2H), 7.2 - 7.4 (m, 6H), 7.5 - 7.6 (m, 1H); **^{13}C NMR** (100 MHz, MeOH-d_4): δ 21.4, 23.0, 27.4, 27.5, 29.6, 30.2, 44.0, 45.5, 56.6, 57.0, 126.2, 126.4, 126.8, 126.9, 128.1, 128.2, 128.4, 128.6, 129.1, 129.2, 129.3, 130.5, 131.0, 145.1, 145.8.

Section II

Enantioselective formal synthesis of (+)-indatraline *via* D-proline catalyzed Mannich reaction of acetaldehyde

2.2.1 Introduction

(+)-Indatraline **58** (Lu 19-005) falls under the class of non-selective monamine reuptake blockers (also known as non-selective monoamine transporter inhibitor). Several compounds consisting of 3-aryl-1-amino indane structural motifs (**58**-**60**) possess a high profile biological activity and so attracted the attention of medicinal chemists in synthesizing and studying them.[16] A series of 3-aryl-1-amino indane were thus synthesized and studied by Børgesø *et. al*. for the treatment of depression by inhibiting the reuptake of neurotransmitters such as dopamine (DA), serotonin (5-HT) and norepinephrine (NE) at the pre-synaptic neuron.[17] Among these aryl amino indanes, the *trans* isomer acts as potent inhibitor of reuptake of all these three

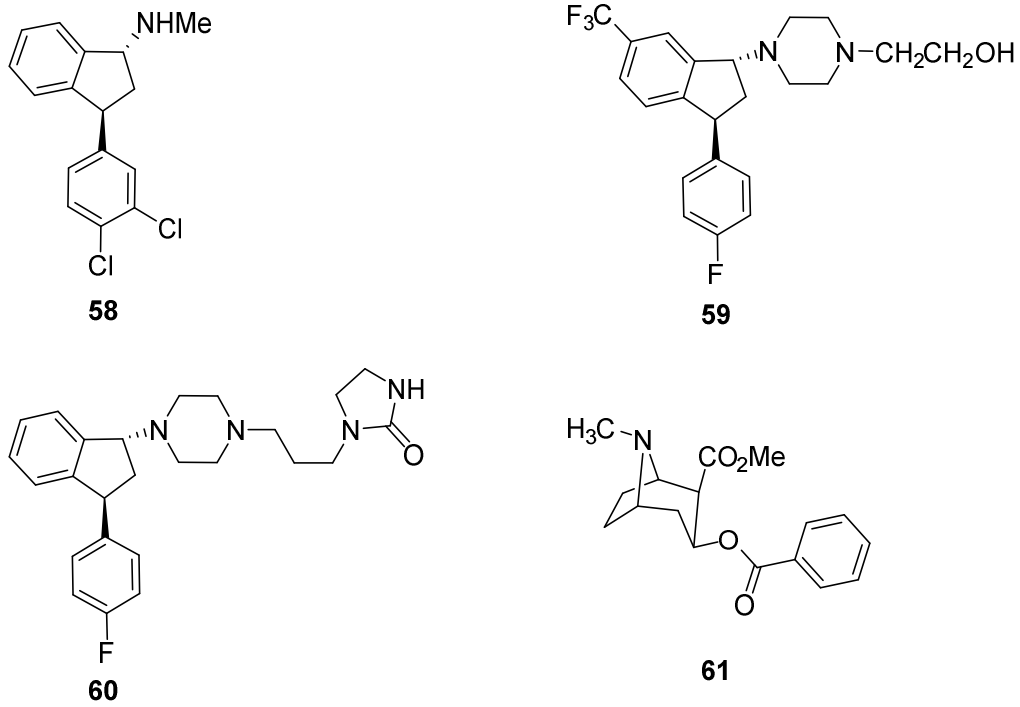


Fig. 11: Structures of various 3-aryl-1-amino indanes [(+)-indatraline **58**, (+)-tefludazine **59**, (+)-irindalone **60**] and cocaine **61**

neurotransmitters, whereas the *cis* isomer is potent in the inhibition of uptake of 5-HT. It was found that the substitutions on aromatic ring also played a major role in the inhibition, hence the 3,4-dichloro substituted 3-aryl-1-amino indane **58** has shown the higher affinity for the site of transporter, which allows the DA uptake.

2.2.2 Pharmacology

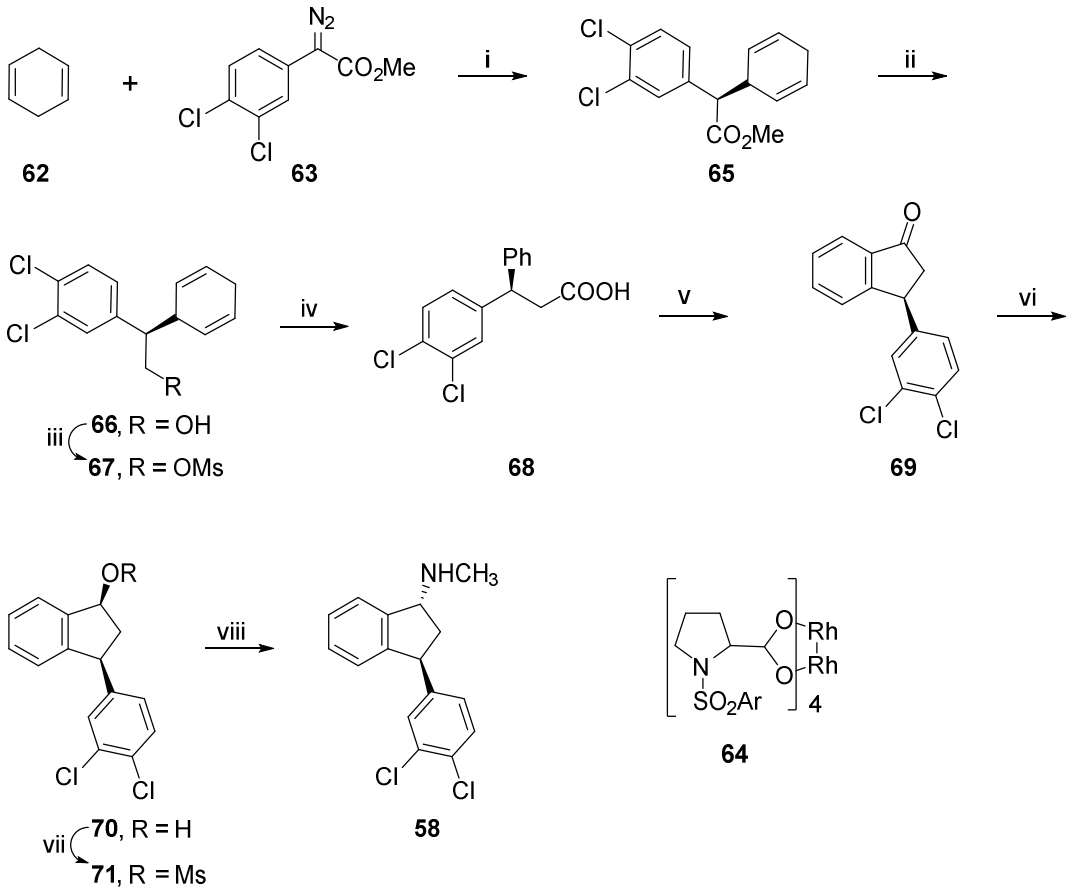
(+)-Indatraline **58** is acting as a potent psychoactive compound and is useful in the treatment of psychostimulant 'cocaine abuse' in rat brain neurons.[18] Cocaine **61** is a strong central nervous system stimulant that increases levels of the neurotransmitter dopamine in brain circuits by regulating pleasure and movement. Normally, dopamine is released by neurons in these circuits and then recycled back into the cell that released it, thus shutting off the signal between neurons. Cocaine **61** prevents the dopamine from being recycled, causing excessive amounts to build up in the synapse, or junction between neurons. This amplifies the dopamine signal and ultimately disrupts normal brain communication. It is this flood of dopamine that causes feeling of excitement and pleasure. In case of cocaine abstinence, at a certain time, the synaptic DA concentration become depleted and hence it increases the urge for taking cocaine and drug seeking behaviour again. Finally, excessive intake of it affects the blood vessels and increase the blood pressure. So there is a need for the treatment of cocaine abuse in many countries. Hence, (+)-indatraline **58** which exhibits as cocaine-like behavior, also has the potential binding affinity than cocaine at the transporter site and excluding it without affecting the DA reuptake. Also, it shows the slow-onset long duration activity as it does not show cocaine like pharmacological effect. The potency of (+)-indatraline was 20 times more than its (−)-(*1S, 3R*) enantiomer while administering in the rhesus monkeys intravenously and showing the reduced cocaine self administration.[19]

2.2.3 Review of literature

Literature survey revealed that there are only six reports[20-25] available for the synthesis of (+)-indatraline **58** which are described below.

Davies's approach (2002)[20]

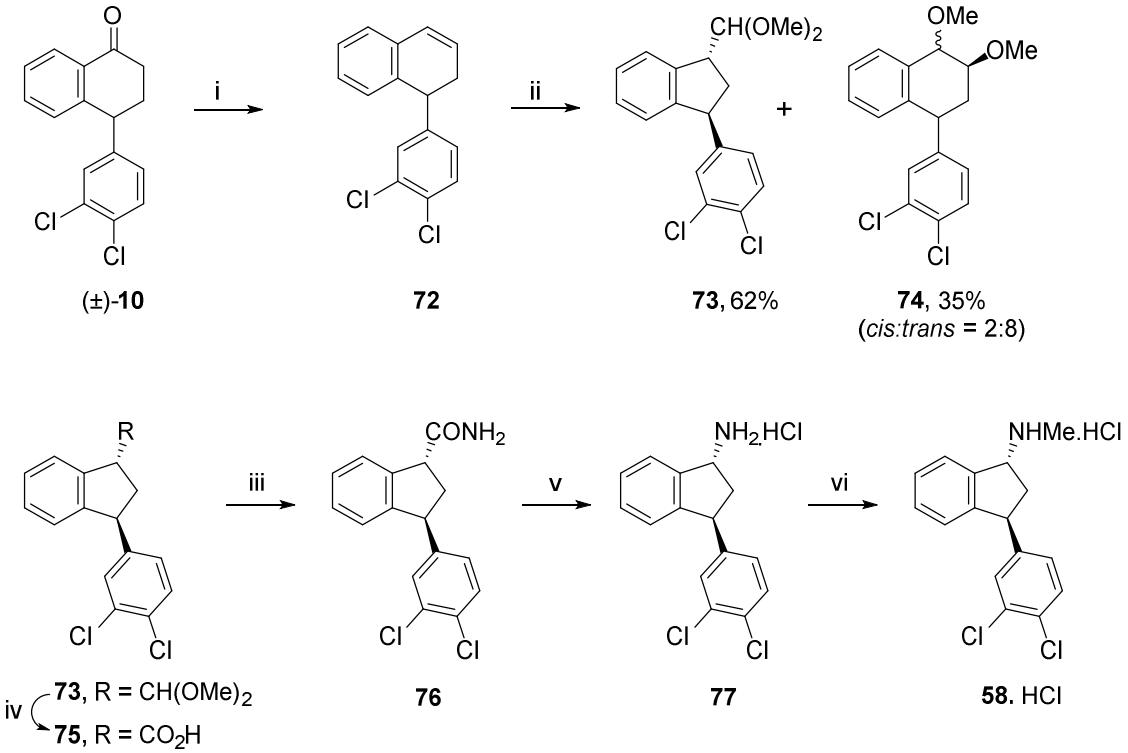
Davies *et al*. have made use of Rh-catalyzed C-H insertion as the key step for the synthesis of (+)-indatraline **58**. Thus, C-H bond of cyclohexadiene **62** was activated by the insertion of Rh-carbene generated from the α-diazo ester **63** and cyclohexadiene Rh-catalyst that resulted in the formation of ester **65**. Reduction of



Scheme 12: (i) Rh_2(S-DOSP)$_4$ (**64**), hexane/$PhCF_3$ (3:1), -20 ^oC, 83%, 93%ee; (ii) $LiAlH_4$, THF, -78 °C; (iii) MsCl, Et_3N; (iv) (a) KCN, 18-crown-6, 90% for three steps; (b) DDQ, benzene; (c) HCl, H_2O; (v) $ClSO_3H$, CH_2Cl_2, then recrystallization with hot heptane, 50% for three steps, 99%ee; (vi) K-Selectride, THF, -10 °C, 93%, *syn:anti* (13:1); (vii) MsCl, Et_3N, THF, -20 °C; (viii) CH_3NH_2, then HCl gas, 67%.

ester **65** with $LiAlH_4$ at −78 °C gave alcohol **66**. Mesylation of alcohol **66** followed by one carbon homologation using KCN provided the nitrile, which was then subsequently hydrolysed with dil.HCl to give the carboxylic acid **68**. Then Intramolecular Friedel-Crafts' acylation of acid **68** was achieved using $ClSO_3H$ to deliver the ketone **69** with 99%ee after recrystallization. Stereoselective reduction of ketone with K-Selectride delivered alcohol **70**, which was then mesylated. Mesylate **71** was displaced with $MeNH_2$ to furnish (+)-indatraline **58**, which was then converted into its salt in 67% yield (**Scheme 12**).

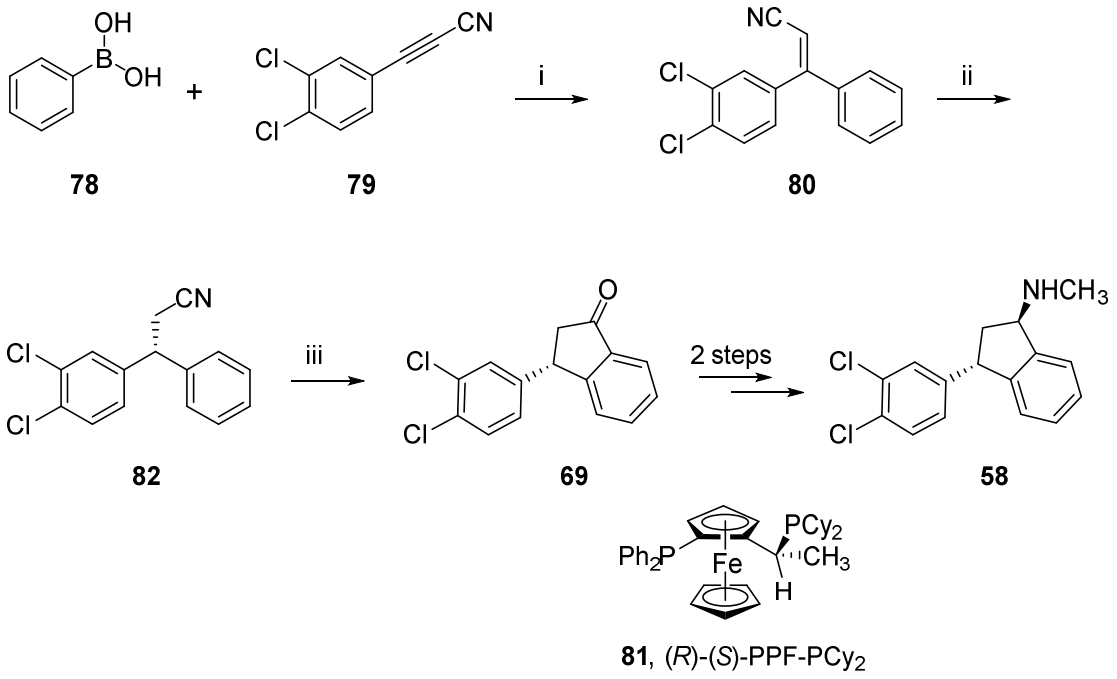
Silva's approach (2007)[21]



Scheme 13: (i) (a) $NaBH_4$, MeOH, 0-25 °C, MeOH, 2 h; (b) *p*-TsOH, dry. toluene, reflux, 1 h, 91%; (ii) HTIB[Hydroxy(tosyloxy)iodobenzene], anhyd. MeOH, 25 °C, 30 min, 62%; (iii) $H_2SO_4/H_2O/CrO_3$ (1:9:1), acetone, 0 °C, 24 h, 83%; (iv) $SOCl_2$, DMF (1 drop), reflux, 1 h, then NH_3, -75-0 °C, 2 h, 80%; (v) $PhI(OCOCF_3)_2$, CH_3CN, H_2O, 25 °C, 6 h, then con. HCl, 90%; (vi) (a) Boc_2O, Et_3N, CH_2Cl_2, 0-25 °C, 2 h, 98%; (b) NaH, MeI, THF/DMF (10:1), -45 °C, 14 h; then CH_3COCl, EtOAc, MeOH, 0-25 °C, 1 h, 85%.

Silva *et.al* have made use of I(III) promoted diastereoselective ring contraction of 1,2-dihydronaphthalenes **72** as the key reaction. Thus, 1,2-dihydronaphthalenes **72** was obtained from tetralone (±)-**10** *via* two-step reaction sequences. Treatment of 1,2-dihydronaphthalene **72** with HTIB [Hydroxy(tosyloxy)iodobenzene] gave a mixture of indan **73** and 1,2-alkene addition product **74**. Acetal in indan **73** was then oxidized to acid **75** using Jones oxidation condition followed by its treatment with $SOCl_2/NH_3$ provided the amide **76**. Hoffman rearrangement of amide **76** using $PhI(OCOCF_3)_2$ furnished the primary amine which was isolated as its hydrochloride salt **77**. Finally, amine salt **77** was converted to (±)-indatraline hydrochloride **58**.HCl *via* three-step reaction sequences in 29% overall yield and excellent diastereoselectivity (**Scheme 13**).

Yun's approach (2009)[22]

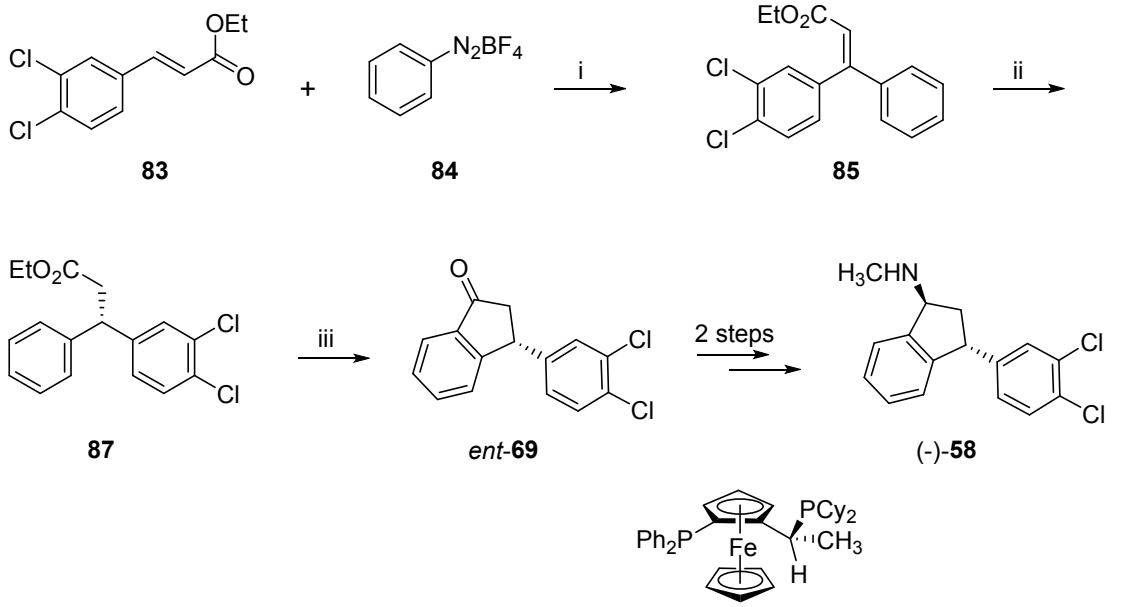


Scheme 14: (i) $Cu(OAc)_2$, MeOH, 25 °C, 6 h, 65%; (ii) $Cu(OAc)_2$, (*R*)-(*S*)-PPF-PCy_2, PMHS, *t*BuOH, toluene, 25 °C, 84%, 95%ee; (iii) H_2SO_4, H_2O, AcOH, reflux, 24 h; then $ClSO_3H$, CH_2Cl_2, 25 °C, 80%.

Yun *et.al*. have reported the formal synthesis of (+)-indatraline **58** by employing Cu(II) catalyzed asymmetric reduction using (*R*)-(*S*)-Josiphos ligand **81**. Thus treatment of phenylboronic acid **78** with 3-(3,4-dichlorophenyl)propynonitrile **79** provided the cinnamonitrile **80**, which was hydrogenated using $Cu(OAc)_2$/(*R*)-(*S*)-PPF-PCy_2 catalytic system and PMHS as reductant to afford the saturated 3,3'-diarylpropanonitrile **82**. Acid hydrolysis of cyano group in nitrile **82** followed by intramolecular Friedel-Crafts' acylation of acid furnished the indanone **69** which was the key interemediate for the synthesis of (+)-indatraline **58** as already reported in the literature. This lead to the formal synthesis of **58** (**Scheme 14**).

Taylor approach (2011) [23]

Taylor *et.al* have described the formal synthesis of (-)-indatraline (-)-**58** through a highly stereoselective synthesis of β,β-disubstituted α,β-unsaturated ester **85** using Pd(0) catalyzed Heck-Matsuda coupling as one of the key steps. Thus, 3,4-dichlorophenyl-α,β-unsaturated ester **83** was treated with benzene diazonium fluoro borate **84** using $Pd(OAc)_2$ as catalyst to form β,β-disubstituted α,β-unsaturated ester **85**. Unsaturated ester **85** was then reduced to its saturated form using $Cu(OAc)_2$/(R)-(S)-Josiphos **86** /PMHS reduction condition to yield the ester **87** in 96% yield with 89%ee. Ester **87** was transformed into indanone *ent*-**69** *via* a two-step reaction sequence which furnished the formal synthesis of (-)-indatraline (-)-**58** (**Scheme 15**).

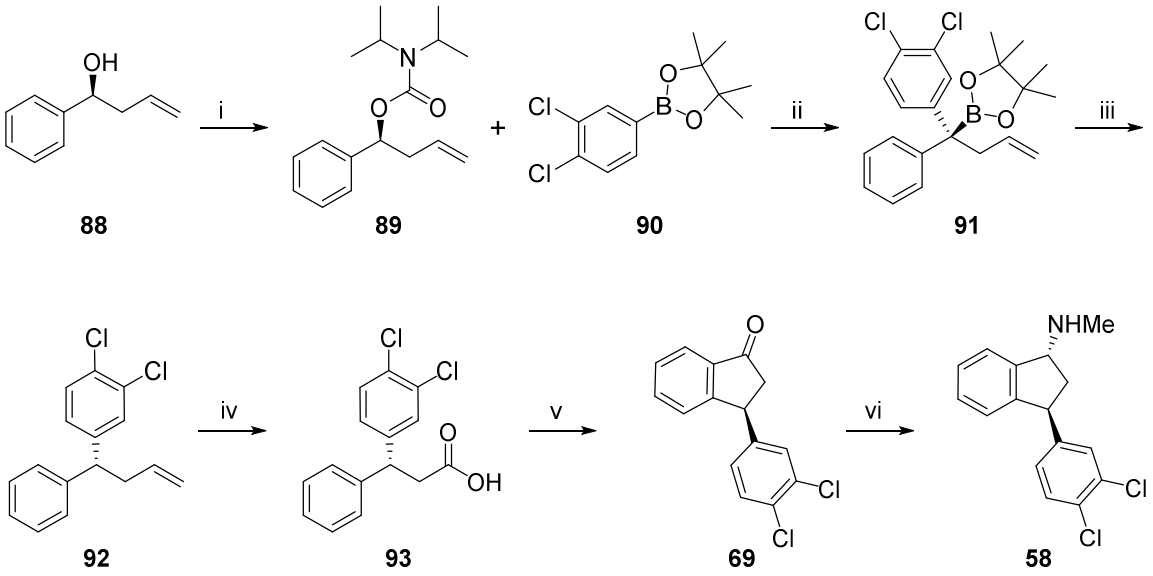


86, (*R*)-Josiphos [(*R*)-(*S*)-PPF-PCy_2]

Scheme 15: (i) $Pd(OAc)_2$, NaOAc, MeOH/CH_3CN (1:1), 60 °C, 15 h; (ii) $Cu(OAc)_2$, (*R*)-Josiphos, PMHS, *t*BuOH, toluene, 25 °C, 84%, 89%ee; (iii) KOH, H_2O/EtOH, reflux, 3h; then $ClSO_3H$, CH_2Cl_2, 25 °C, 55%, 89%ee.

Aggarwal's approach (2011) [24]

Aggarwal *et.al*. have made use of lithiation/borylation-protodeboronation methodology for the synthesis of (+)-indatraline **58**. Thus, homoallylic alcohol **88** was converted to carbmate **89** on its treatment with CbCl (2,2-diisopropylcarbamoyl chloride). Carbamate **89** was then treated with *s*-BuLi and aryl pinacol boronic ester **90** which led to the lithiation/borylation giving the tertiary boronic ester **91** in 81% yield. Protodeboronation of **91** with CsF/H_2O provided the olefin **92**, which was then transformed to acid **93** by a two step reaction sequence, *via* the oxidative C=C bond cleavage. Further, intramolecular Friedel-Crafts' acylation of acid **93** delivered the indanone **69** in 98% yield and 99%ee. Finally, (+)-indatraline **58** was obtained from indanone **69** in two steps involving reduction of ketone **69** followed by displacement of the formed alcohol with methylamine (**Scheme 16**).

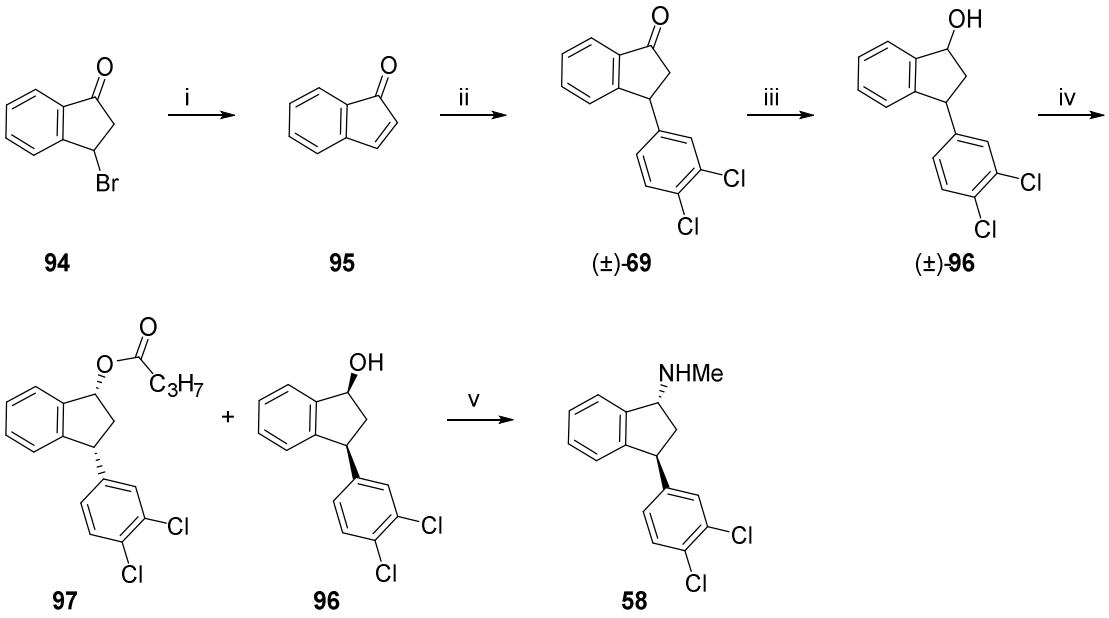


Scheme 16: (i) NaH, CbCl (2,2-diisopropylcarbamoyl chloride), dry. THF, 25 °C to reflux, 24 h; (ii) *sec*-BuLi, boronic ester, dry Et_2O, dry toluene, then 12-crown-4 (1 equiv), H_2O (0.1 equiv), TMSCl, -78 °C, 4 h, 81%, 98%ee; (iii) dry CsF, H_2O, dry CH_2Cl_2, 25 °C, 16 h, 97%; (iv) (a) $K_2OsO_4{\cdot}2H_2O$, $NaIO_4$, 1,4-dioxane/H_2O, 2,6-lutidine, 4 h, 25 °C; (b) $NaH_2PO_4{\cdot}2H_2O$, $NaClO_2$, *t*BuOH, H_2O, 30 min, 25 °C, 95%; (v) $ClSO_3H$, CH_2Cl_2, 1.5 h, 25 °C, 98%, 98%ee; (vi) (a) K-Selectride, dry THF, 4 h, -10 °C; (b) MsCl, Et_3N, dry THF, 1 h, -20 °C; then $MeNH_2$, dry THF, 25 °C, 20 h, 83%.

Norager's approach (2011)[25]

Norager *et.al*. have described the synthesis of (+)-indatraline **58** by employing the rhodium catalyzed conjugate addition of indenone **95**. Thus, indenone **95** was prepared from 3-bromo-1-indanone **94** *via* Et_3N mediated 1,2-elimination. Then, indenone **95** was subjected to Rh(I)-[(±)-BINAP] catalyzed conjugate addition to provide 3-aryl-indanone (±)-**69**. Diastereoselective reduction of indanone (±)-**69** using $NaBH_4$ at -15 °C provided the (±)-indanol (±)-**96** with diastereoselectivity of *syn:anti* (10:1), which was then subjected to enzymatic kinetic resolution using a lipase Novozyme 435® to deliver the enantiomerically pure indanol **96** in 45% yield and

99%ee. Finally, (+)-indatraline **58** was achieved in 80% yield by a one-pot mesylation of **96** followed by nucleophilic displacement with methylamine (**Scheme 17**).



Scheme 17: (i) Et_3N, dry. THF, 25 °C, 1 h, 52%; (ii) 3,4-dichlorophenylboronic acid, bis(norbornadiene)rhodium(I) tetrafluoroborate / (±)-BINAP, 1,4-dioxane-H_2O (9:1), Et_3N, 100 °C, 4 h, 74%; (iii) $NaBH_4$, THF-H_2O (10:1), -15 °C, overnight, 91%, dr = 24:1 (*syn:anti*); (iv) vinyl *n*-butyrate, Novozyme 435®, *i*-Pr_2O, 25 °C, overnight, 45%, 99%ee; (v) MsCl, Et_3N, THF, 1 h, -20 °C; then $MeNH_2$ (20 equiv), 25 °C, overnight, 80%.

2.2.4 Present Work

2.2.4.1 Objective

As can be seen from the above discussion, the reported methods for the synthesis of (+)-indatraline **58** employ either resolution techniques leading to loss of one of the enantiomers, chiral starting materials, or expensive reagents with toxic transition metals especially involving longer reaction sequences. The synthetic precursor of (+)-indatraline **58** is found to be 3-aryl-1-amino indane, which is currently attracting the attention of many medicinal chemists for its synthesis and to check the SAR (strutctural activity relationship) of various other substituted 3-aryl-1-amino indanes. Hence, we became interested to provide a short route for the formal synthesis of (+)-

indatraline **58** using environmentally friendly proline as a catalyst involving the enamine catalysis. In this section, we describe a formal enantioselective synthesis of (+)-indatraline **58** in excellent enantioselectivity *via* D-proline catalyzed Mannich reaction of acetaldehyde and intramolecular Friedel-Crafts alkylation[26] as key reactions.

Retrosynthetic analysis of (+)-indatraline **58** reveals that Boc protected 3-(3,4-dichlorophenyl)-1-aminoindane **100** could be visualized as the key interemediate, which can be obtained *via* intramolecular Friedel-Crafts' alkylation of benzylic alcohol **99**. This in turn could be derived from the Grignard reaction between 3,4-dichlorophenyl magnesium bromide **98** and β-aminoaldehyde (+)-**54** (**Fig. 12**).

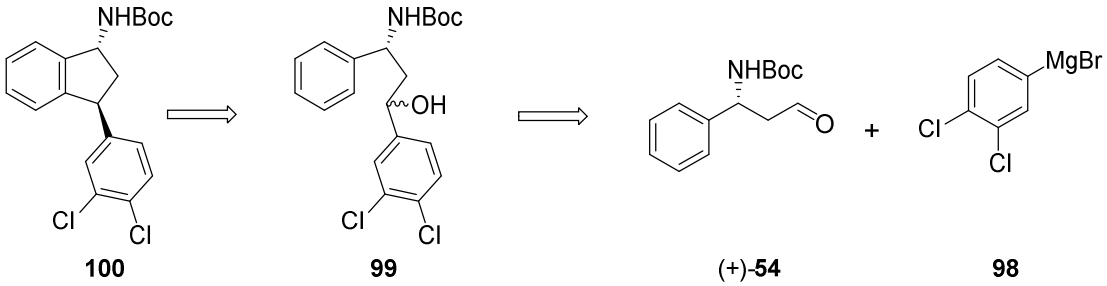
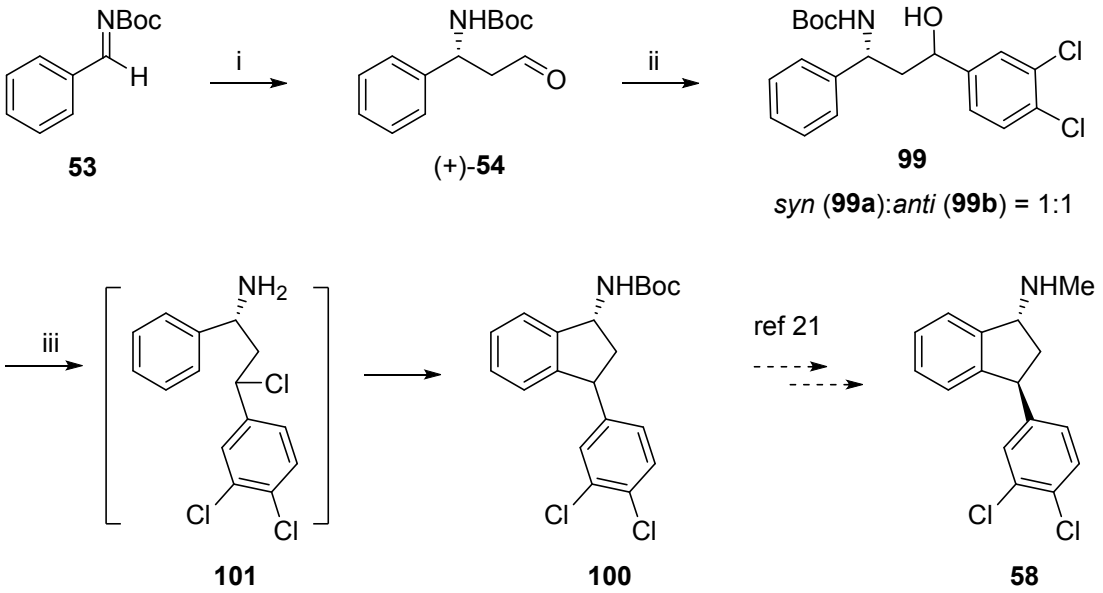


Fig. 12: Retrosynthetic analysis of (+)-indatraline core unit

2.2.5 Results and discussion

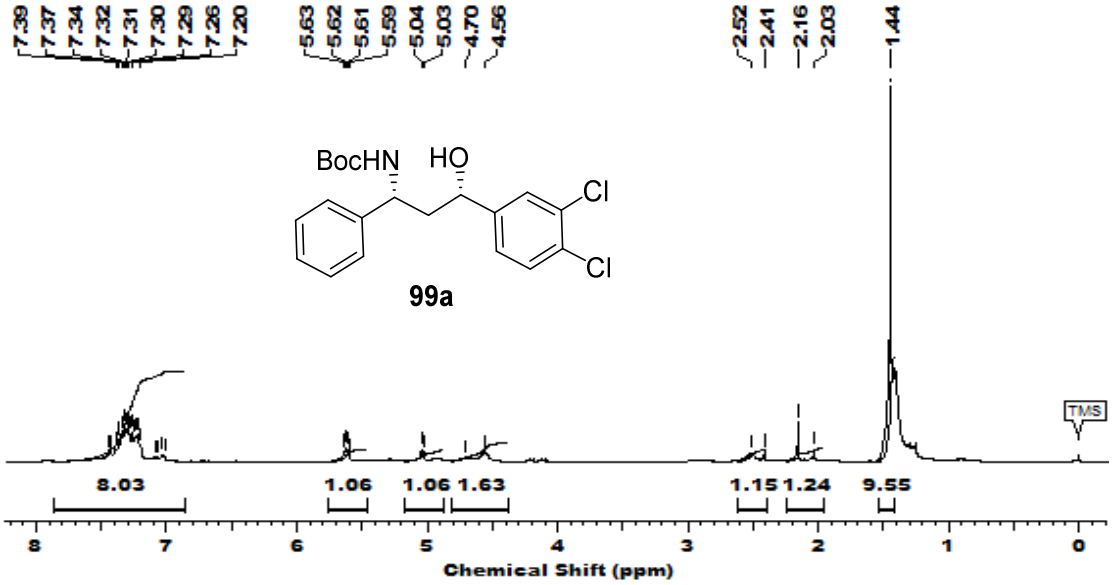
Enantioselective formal synthesis of (+)-Indatraline *via* D-proline catalyzed Mannich reaction of acetaldehyde

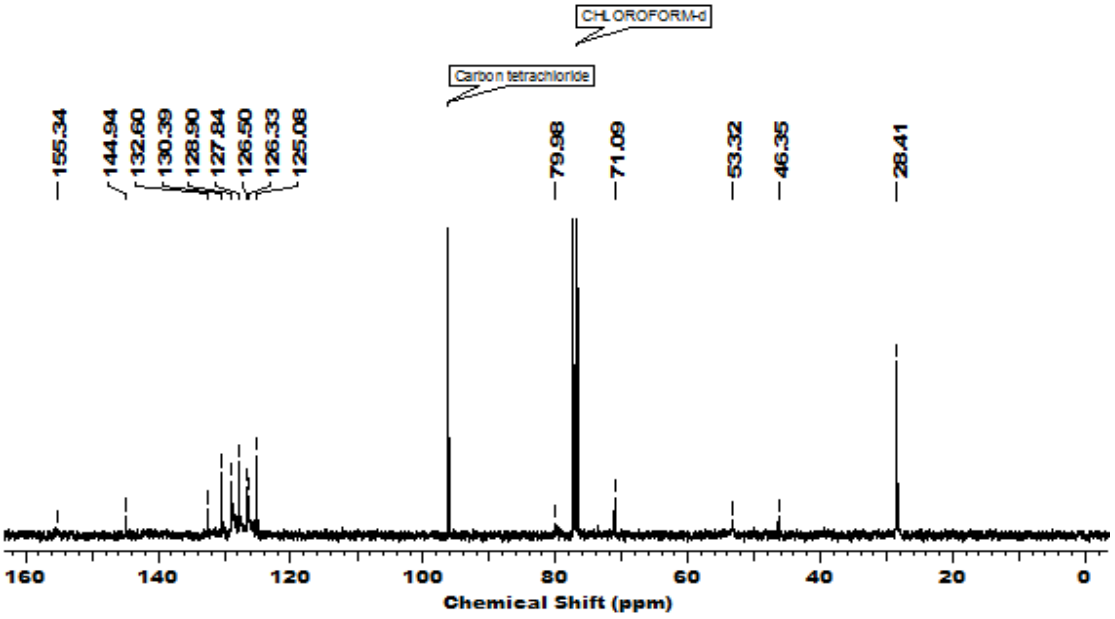
The complete synthetic sequence for (+)-indatraline core unit **100** wherein D-proline catalyzed Mannich reaction of acetaldehyde and intramolecular Friedel-Crafts alkylation constitute the key steps is presented in **Scheme 18**.

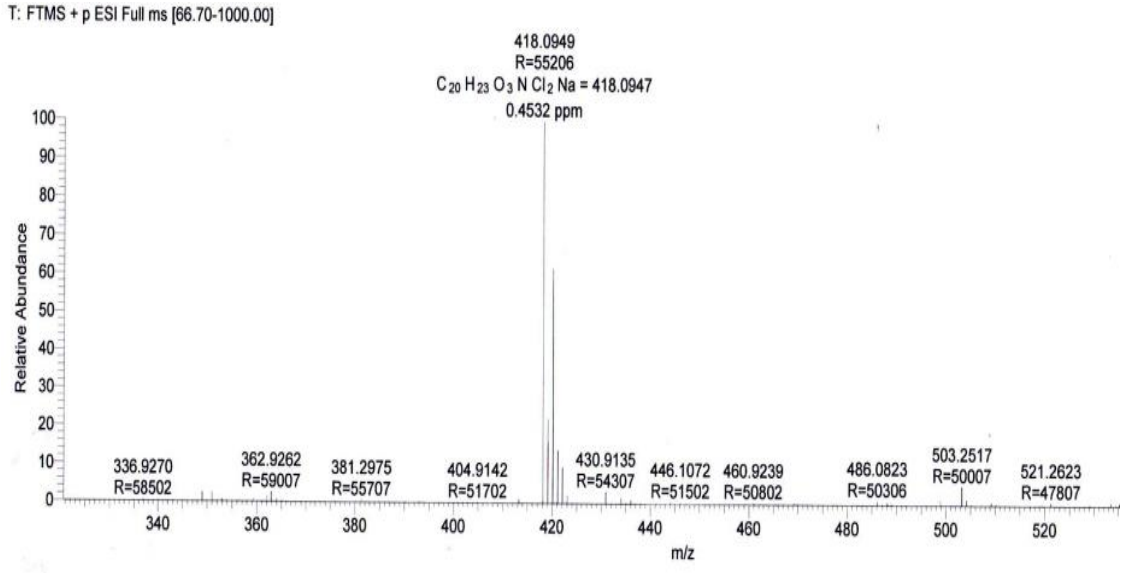


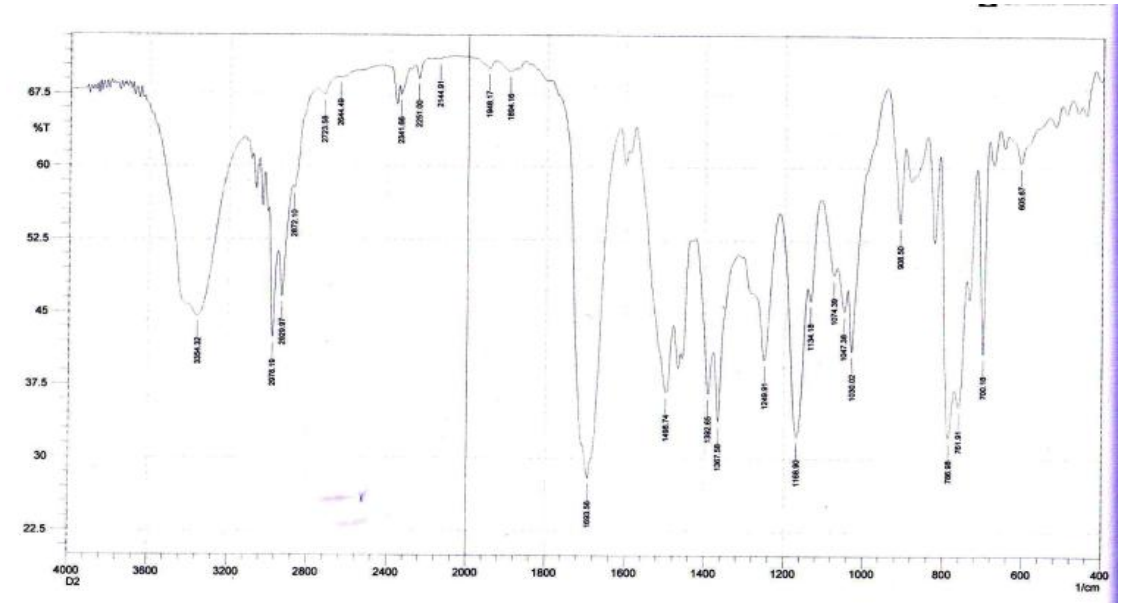
Scheme 18: (i) CH_3CHO (7 equiv), D-proline (20 mol%), CH_3CN, 0 °C, 3 h, 55%; (ii) 0.6 M solution of 3,4-dichlorophenylmagnesium bromide **98** in THF, 25 °C, 4 h, 60%, 99%ee, dr = 1:1; (iii) $AlCl_3$(4 equiv), CH_3NO_2/CH_2Cl_2(1:1), 25 °C, 40%, overnight.

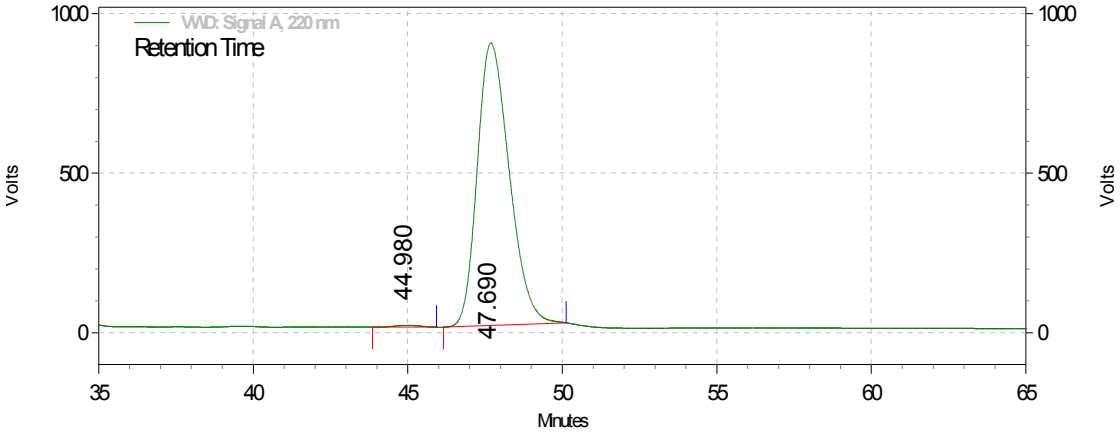
Accordingly, the formal synthesis of (+)-indatraline **58** was started from D-proline catalyzed Mannich reaction of N-Boc benzaldiimine **53** to give β-aminoaldehyde (+)-**54** (see Section I of this chapter). β-Aminoaldehyde (+)-**54** was then subjected to Grignard addition using 0.6 M solution of 3,4-dichlorophenyl magnesium bromide **98** to provide the β-amino alcohol **99** in 60% yield (after coloumn chromatographic separation) with 99%ee and diastereomeric ratio of 1:1.[27] The ^{1}H NMR spectrum of *syn*-β-amino alcohol **99a** showed two typical proton signals at δ 2.16 (br s, 1H), and 2.52 (brs, 1H) corresponding to protons attached to the methylene carbon and a proton signal at δ 5.59-5.62 (m, 1H) corresponding to methine proton attached to benzylic –OH group. Its ^{13}C NMR spectrum displayed two characteristic carbon signals at δ 53.3 and 71.1 corresponding to benzylic methine carbons attached to –NHBoc and –OH groups respectively. Its mass spectrum with its molecular ion peak (M+Na) at *m/z* 418.0949 confirmed the formation of β-amino alcohol **99a**. Its IR spectrum exhibited


7.39
7.37
7.34
7.32
7.31
7.30
7.29
7.26
7.20
5.63
5.62
5.61
5.59
5.04
5.03
4.70
4.56
2.52
2.41
2.16
2.03
1.44
BocHN
HO
Cl
Cl
99a
TMS
8.03
1.06
1.06
1.63
1.15
1.24
9.55
Chemical Shift (ppm)


CHLOROFORM-d
Carbon tetrachloride
155.34
144.94
132.60
130.39
128.90
127.84
126.50
126.33
125.08
79.98
71.09
53.32
46.35
28.41
Chemical Shift (ppm)


T: FTMS + p ESI Full ms [66.70-1000.00]
418.0949
R=55206
C20 H23 O3 N Cl2 Na = 418.0947
0.4532 ppm
Relative Abundance
336.9270
R=58502
362.9262
R=59007
381.2975
R=55707
404.9142
R=51702
430.9135
R=54307
446.1072
R=51502
460.9239
R=50802
486.0823
R=50306
503.2517
R=50007
521.2623
R=47807
m/z





Retention Time	Area	Area %	Height	Height %
44.980	5561227	0.52	95217	0.64
47.690	1071144958	99.48	14857449	99.36
Totals	1076706185	100.00	14952666	100.00

Fig. 13: ^{1}H ^{13}C NMR, mass and IR spectra, HPLC chromatogram of *syn*-β-aminoalcohol **99a**

the characteristic –NH**CO$_2$*t*Bu** and –**OH** absorption bands at 1693 and 3354 cm^{-1} respectively. The optical purity of **99a** was found to be 99%ee determined from chiral HPLC analysis [Chiralpak AD-H, *n*-hexane/*i*PrOH, 85:15, 0.5 mL/min) retention time 44.98 min (0.52%) and 47.69 min (99.48%) for *syn* isomer] (**Fig. 13**). The ^{1}H NMR

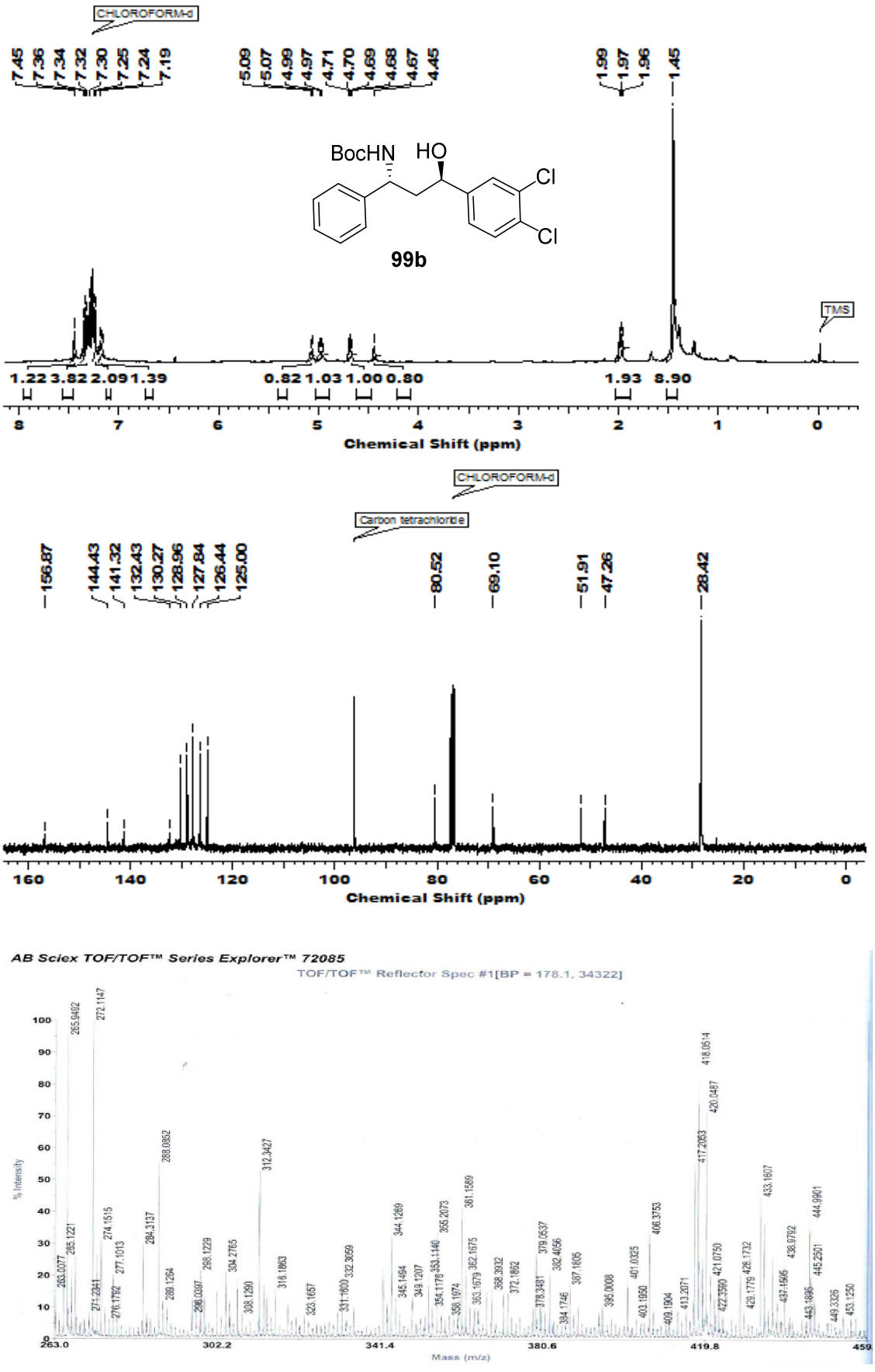
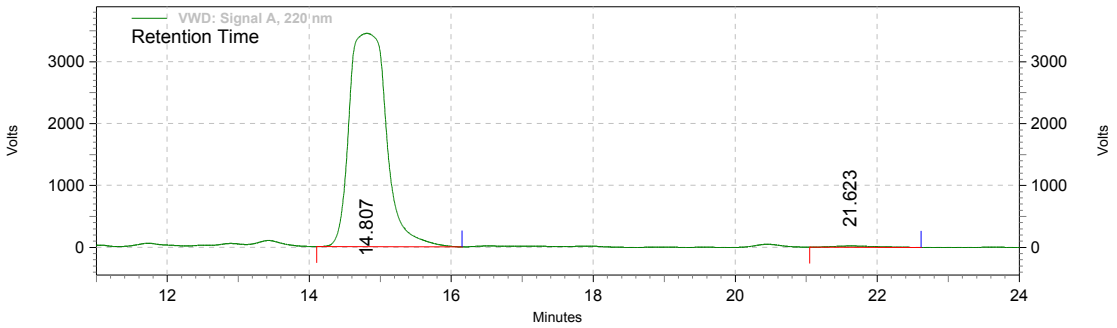


Fig. 14: ^{1}H, ^{13}C NMR, and Mass spectra of *anti*-β-amino alcohol **99b**



VWD: Signal A, 220 nm Results

Retention Time	Area	Area %	Height	Height %
14.807	2094943979	99.31	57797296	99.40
21.623	14456400	0.69	351011	0.60
Totals	2109400379	100.00	58148307	100.00

Fig. 15: HPLC chromatogram of *anti*-β-amino alcohol **99b**

spectrum of *anti*-β-amino alcohol **99b** showed the proton signals at δ 1.96-1.99 (m, 2H) corresponding to two protons attached to the methylene carbon (-C**H**$_2$) and a proton signal at δ 4.97-4.99 (m, 1H) corresponding to methine proton attached to benzylic –OH group. Its ^{13}C NMR spectrum displayed two characteristic carbon signals at δ 51.91 and 69.1 corresponding to benzylic methine carbons attached to –NHBoc and –OH groups respectively. Its mass spectrum with its molecular ion peak (M+Na) at *m/z* 418.0514 confirmed the formation of β-amino alcohol **99b**. The optical purity of **99b** was found to be 99% ee determined from chiral HPLC analysis [Chiralpak AD-H, *n*-hexane/*i*PrOH, 85:15, 0.5 mL/min) retention time 14.807 min (99.31%) and 21.623 min (0.69%) for *anti* isomer] (**Fig. 14**).

Next, we focused on attempting the intramolecular Friedel-Craft's alkylation of β-aminoalcohol **99**. This is unprecedented for the synthesis of indatraline core-unit **100**.

Accordingly, both diastereomers of β-aminoalcohol **99** were treated with anhyd. $AlCl_3$ in CH_2Cl_2 to facilitate the intramolecular Friedel-Crafts' alkylation at room temperature. This was then followed by treating the crude (after the work up) with $(Boc)_2O$ that provided a diastereomeric mixture (≈1:1) of indatraline core unit **100** in 15% combined yield along with simple 1,2-eliminated product. However, by using CH_3NO_2 (10 equiv) as solvent, the reactivity of the $AlCl_3$ is reduced so that 1,2-elimination became less favoured which led to increase in the yield of (+)-indatraline core unit **100** as inseparable diastereomeric mixture having diastereomeric ratio of 1:1 along with the simple chlorosubstituted product **101** at the benzylic position. Further extending the reaction time (in another batch) from 4 h to overnight with treatment of $AlCl_3$ (4 equiv) in CH_3NO_2/CH_2Cl_2 (1:1) followed by the addition of $(Boc)_2O/Et_3N$ (after the work up) afforded the indatraline core unit **100** in 40% yield with diastereomeric ratio of 1:1 determined from ^{1}H NMR spectroscopy. The ^{1}H NMR spectrum of (+)-indatraline core unit **100** showed typical diastereomeric proton signals at δ 4.51-4.79 (m, 2H), corresponding to dibenzylic and benzyl (-C**H**NHBoc) methine protons and a proton signal at δ 1.42 (s, 9H) corresponding to methyl proton present in the Boc group. Its mass spectrum with its molecular ion peak $(M+Na)^+$ at *m/z* 400.0837 confirmed the presence of (+)-indatraline core unit **100** (**Fig. 16**).

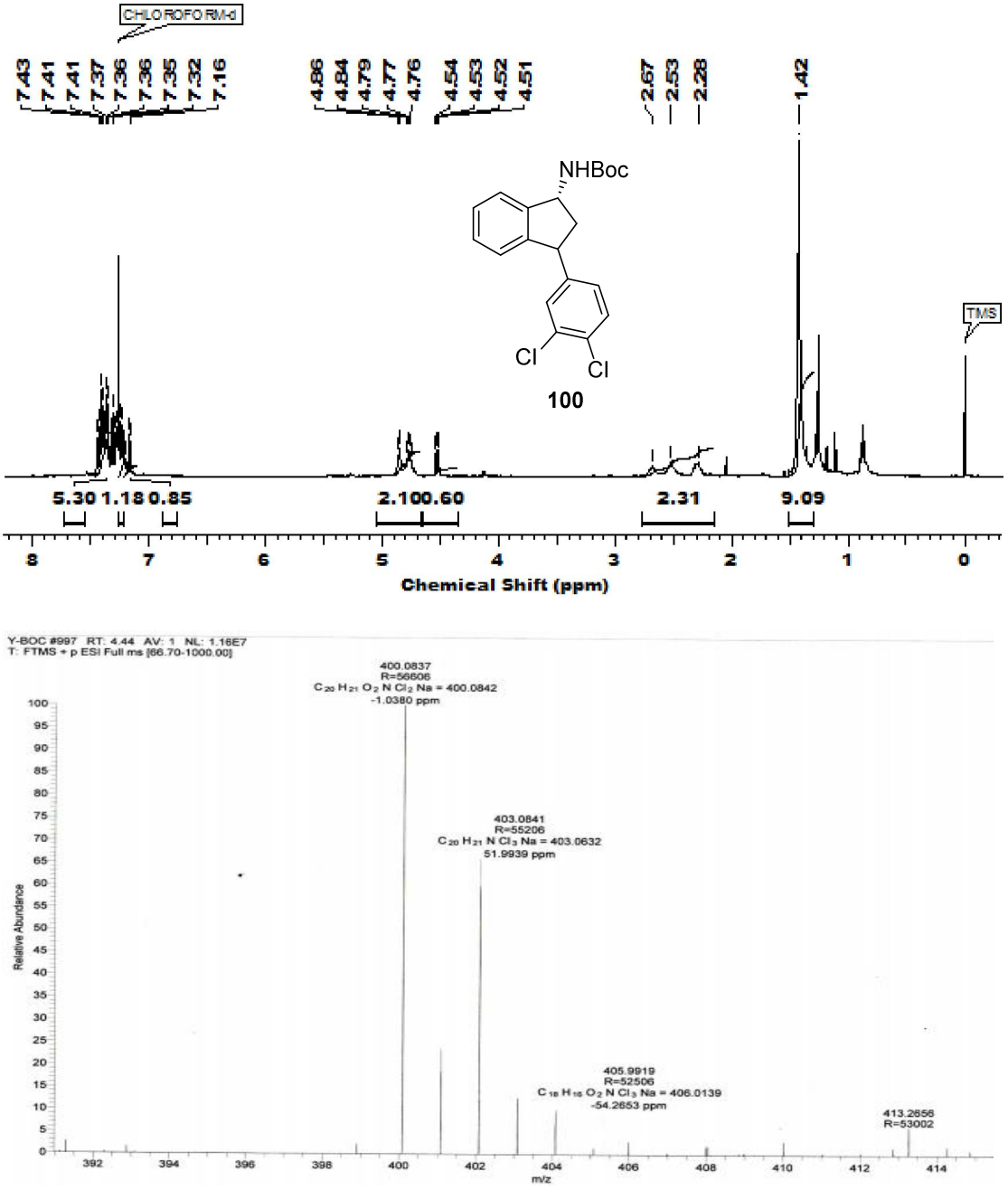


Fig. 16: ^{1}H, and HRMS Mass spectra of (+)-indatraline core unit **100**

2.2.6 Conclusion

In conclusion, we have described a short and efficient route for the high enantioselective formal synthesis of (+)-indatraline **58** using D-proline catalyzed Mannich reaction of acetaldehyde with excellent enantiopurity upto 99% ee. The salient features of this route are mild reaction conditions, and toxic transition metal

free approach which provides flexibility in getting the other various 1-amino-3-aryl indane in less number of steps.

2.2.7 Experimental section

***tert*-Butyl (3-(3,4-dichlorophenyl)-3-hydroxy-1-phenylpropyl)carbamate (99a** and **99b)**

To a stirred solution of 0.5 M 3,4-dichlorophenylmagnesium bromide **98** solution in THF (2.2 g, 18 mL, 8.83 mmol) was added β-aminoaldehyde (+)-**54** (1.1 g, 4.42 mmol) in 25 ml slowly at 10 °C and allowed to stir at room temperature for 4 h. After completion of reaction, it was quenched with sat. NH_4Cl solution. The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4, filtered and concentrated under reduced pressure to give the crude mixture of β-aminoalcohol (**99a-b**). Flash column chromatographic purification [silica gel (100-200 mesh) and pet. ether:EtOAc as an eluent] gave the desired *syn* and *anti* β-aminoalcohols (**99a** and **99b**) in pure form.

Yield: 60%, 1.05 g (for *syn* and *anti*), pale yellow gum;

For ***syn*-β-aminoalcohol (99a)**: 99%ee from **HPLC** analysis; Chiralpak AD-H, (*n*-hexane/*i*PrOH, 85:15, 0.5 mL/min). Retention time (min): 44.98 min (0.52%) and 47.69 min (99.48%); $[\alpha]^{25}_{D}$: +11.92 (c 0.62, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 605, 700, 906, 1030, 1047, 1074, 1134, 1169, 1250, 1367, 1392, 1497, 1693, 1894, 1946, 2145, 2341, 2672, 2929, 2978, 3354; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.45 (s, 9H), 1.87 - 2.03 (m, 2H), 4.45 (brs, 1H), 4.60 - 4.75 (m, 1H), 4.89 - 5.03 (m, 1H), 5.08 (d, J = 8.1 Hz, 1H), 7.14 - 7.21 (m, 1H), 7.24 (d, J = 5.6 Hz, 2H), 7.35 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 7.3 Hz, 2H), 7.45 (brs, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 28.4, 47.3, 51.9, 69.1, 80.5, 125.0, 126.4, 127.8, 129.0, 130.3, 132.4, 141.3, 144.4, 156.9; **HRMS**

(ESI, m/z): Calculated for $C_{20}H_{23}Cl_2NNaO_3$ $(M+Na)^+$ 418.0947, found 418.0949; **Analysis:** $C_{20}H_{23}Cl_2NO_3$ requires C, 60.61; H, 5.85; N, 3.53; found: C, 60.55; H, 5.78; N, 3.48%.

For ***anti*-β-aminoalcohol 99b**: 99%ee from **HPLC** analysis; Chiralpak AD-H, (*n*-hexane/*i*PrOH, 85:15, 0.5 mL/min) Retention time (min): 14.807 min (99.31%) and 21.623 min (0.69%); $[\alpha]^{25}_D$: +38.12 (c 0.54, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 771, 875, 978, 1072, 1168, 1248, 1369, 1500, 1694, 2360, 2855, 2927, 2978, 3355; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.43 (s, 9H), 2.03-2.2 (m, 1H), 2.41-2.5 (brs, 1H), 4.6 (brs, 1H), 4.7 (brs, 1H), 5.0 (d, *J* = 5.4 Hz, 1H), 5.5 - 5.8 (m, 1H), 6.9 - 7.1 (m, 1H), 7.2 - 7.5 (m, 7H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 28.4, 46.3, 53.3, 71.1, 80.0, 125.1, 126.3, 126.5, 127.8, 128.9, 130.4, 132.6, 144.9, 155.7; **MALDI-MS (ESI, m/z)**: Calculated for $C_{20}H_{23}Cl_2NNaO_3$ $(M+Na)^+$ 418.0953, found 418.0514.

tert-Butyl ((*1R,3S*)-3-(3,4-dichlorophenyl)-2,3-dihydro-1H-inden-1-yl)carbamate (100)

To a stirred solution of β-aminoalcohol **99a** or **99b** in dry.CH_2Cl_2 (0.5 mL), was added CH_3NO_2 (0.2 mL) and dry CH_2Cl_2 at 0 °C and the mixture allowed to stir for overnight at 25 °C. The reaction was then quenched with sat. $NaHCO_3$ solution and evaporated under reduced pressure. The aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue obtained was then treated with $(Boc)_2O$ (1 equiv), Et_3N (1 equiv) and DMAP (0.4 equiv) in CH_2Cl_2 and allowed to stir for 4 h at 25 °C. The reaction mixture was then diluted with CH_2Cl_2 and washed with water. The organic layer was then evaporated under vacuum and flash coloumn chromatographic separation of the residue gave the (+)-indatraline core unit **100**.

Yield: 40%, (dr = 1:1 of *syn:anti*) inseparable mixture, colorless oil; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.42 (brs, 9H), 2.28- 2.67 (m, 2H), 4.53 (dd, *J* = 8.9, 5.8 Hz, 1H), 4.66 - 4.82 (m, 1H), 4.85 (d, *J* = 7.6 Hz, 1H), 7.09 - 7.21 (m, 1H), 7.23 (d, *J* = 7.3 Hz, 1H), 7.27 - 7.46 (m, 5 H). **HRMS (ESI, m/z)**: Calculated for $C_{20}H_{21}Cl_2NNaO_2$ $(M+Na)^+$ 400.0842, found 400.0837; **Analysis:** $C_{20}H_{21}Cl_2NO_2$ requires C, 63.50; H, 5.60; N, 3.70; found: C, 63.38; H, 5.51; N, 3.62%.

2.2.8 References

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CHAPTER 3

Organocatalytic Asymmetric Synthesis of 4-Hydroxypyrazolidines and *L*-Carbidopa using α-Amination of Aldehydes

Section I

Organocatalytic Sequential α-Amination/Corey-Chaykovsky Reaction of Aldehydes: A High Yield Synthesis of 4-Hydroxy pyrazolidine Derivatives

3.1.1 Introduction

Pyrazolidines (**1**), pyrazolines (**2**) and pyrazoles are an interesting class of heterocyclic units found in many complex bioactive natural products.[1] Among them chiral hydroxypyrazolidine derivatives represent not only useful building blocks in pharmaceutical industry[2] but also powerful intermediates in the preparation of enantiopure 1,3-diamines (**3**) (**Fig. 1**).[3] More importantly, the derivatives of densely functionalized pyrazolidines exhibit a wide variety of biological acitivities including anticonvulsant,[4] antidepressant[5] and antitumour[6] properties along with other minor uses (**e.g**. as brightening agent).[7]

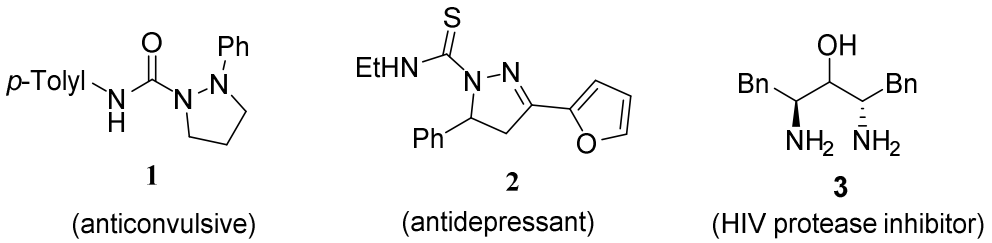


Fig. 1: Some of bioactive molecules

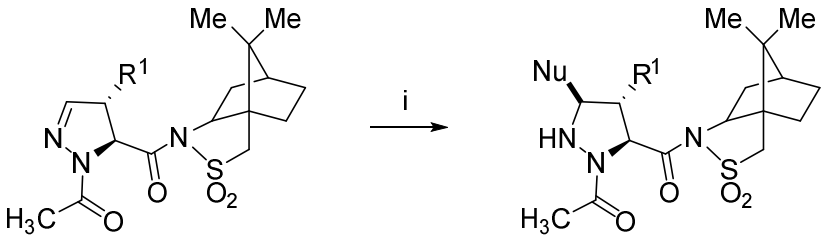
Due to the significance of these chiral pyrazolidines in drug discovery and medicinal chemistry, the development of new methodologies for their synthesis is highly desirable.

3.1.2 Review of literature

Literature search revealed that there are various reports available for the asymmetric synthesis of substituted pyrazolidine derivatives; some of which are described below.

Carreira's approach (2000)[8]

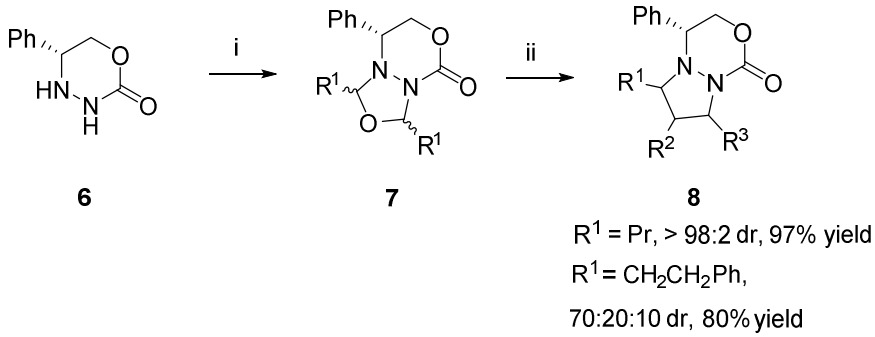
Carreira *et al.* have employed the Lewis acid promoted nucleophilic additions of allyl tributylstannane, the methyl acetate derived silyl ketene acetal, and trimethylsilyl cyanide to a number of chiral *N*-acyl pyrazolines **4** to provide highly functionalized pyrazolidines **5** in a highly diastereoselective fashion (**Scheme 1**).



Scheme 1: $TiCl_4$ (1.2 equiv), **Nu**$^-$ (allyl tributylstannane, methyl acetate derived silyl ketene acetal, and trimethylsilyl cyanide) CH_2Cl_2, –78° C to 23 °C.

Chauveau's approach (2002)[9]

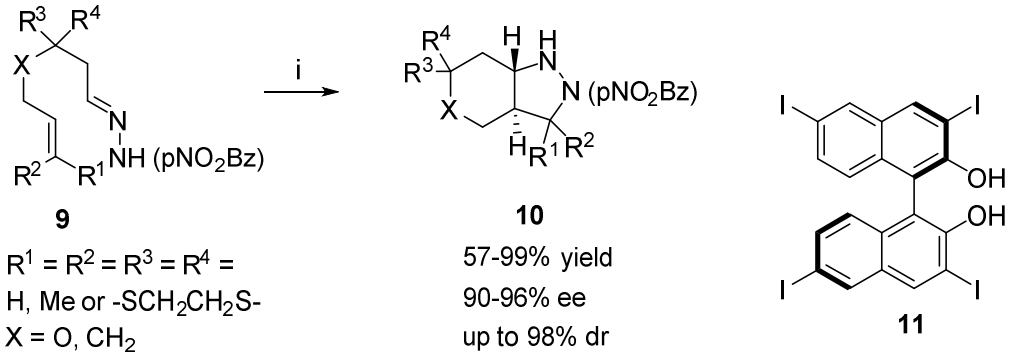
Chauveau *et al.* have described an asymmetric three-component reaction involving a diastereoselective 1,3-dipolar cycloaddition of a chiral non-racemic azomethine imine ylide **7** with dipolarophile for the synthesis of densely functionalized bicyclic hydrazines **8** (**Scheme 2**).



Scheme 2: (i) R^1CHO, $CHCl_3$, 65 °C (ii) dipolarophile, toluene, 80–100 °C, 3 d.

Kobayashi's approach (2002)[10]

Kobayashi *et al*. have reported the asymmetric intramolecular [3 + 2]-cycloaddition reactions of acylhydrazones/olefins **9** employing a chiral zirconium catalyst for the synthesis of pyrazolidine derivatives **10** in high yields with excellent enantio- and diastereoselectivity **(Scheme 3)**.



9

$R^1 = R^2 = R^3 = R^4 =$ H, Me or $-SCH_2CH_2S-$

X = O, CH_2

10

57-99% yield

90-96% ee

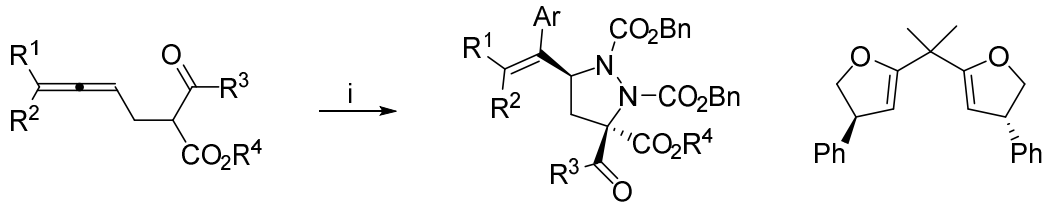
up to 98% dr

11

Scheme 3: $Zr(OPr)_4$ (10 mol %), **11** (12 mol%), PrOH (50 mol %), CH_2Cl_2, 25 °C.

Shengming Ma's approach (2004)[11]

Shengming Ma *et al.* have reported the synthesis of optically active pyrazolidine derivatives **13** in high yields with ees by the Cu- and Pd-catalyzed asymmetric one-pot tandem addition-cyclization reaction of 2-(2',3'-dienyl)-*β*-ketoesters **12**, aryl halides, and dibenzyl azodicarboxylate (**Scheme 4**).



12

13

71-98% yield

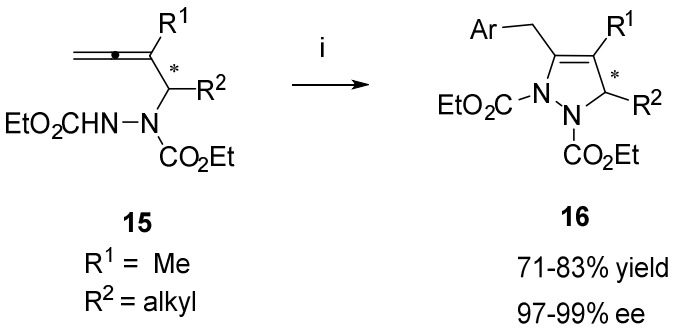
up to 99% ee

up to 3:1 dr

14

Scheme 4: (i) (a) **14** (10 mol%), $Cu(OTf)_2$, ArI, dibenzyl azodicarboxylate, CH_2Cl_2, 0 °C; (b) K_2CO_3 (2 equiv), $Pd(PPh)_4$ (5 mol%), 1,4-dioxane, 100 °C, 4 h.

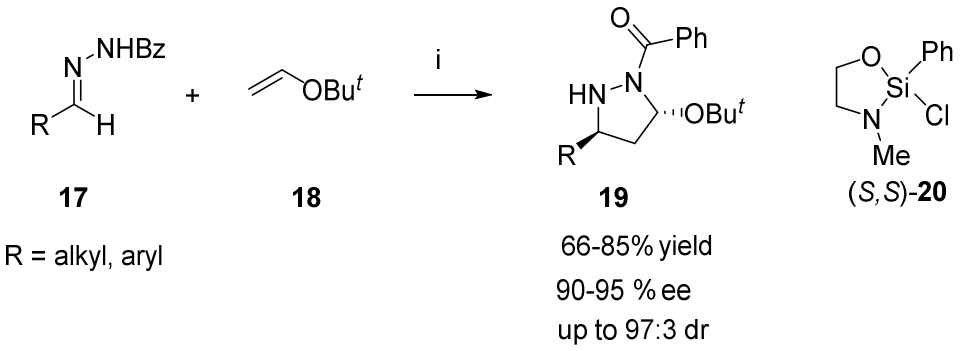
In a similar approach[11b] Shengming Ma *et al.* have developed a method for the regioselective synthesis of 2,3-dihydro-1H-pyrazoles **16** *via* the Pd(0)-catalyzed coupling-cyclization reaction of readily available enantiomerically enriched 2,3-allenyl hydrazines **15** with aryl iodides in moderate to good yields (**Scheme 5**).



Scheme 5: (i) ArI, $Pd(PPh_3)_4$ (5 mol%), Cs_2CO_3 (1.2 equiv), CH_3CN, 80 °C, 3 h.

Leighton's approach (2005)[12]

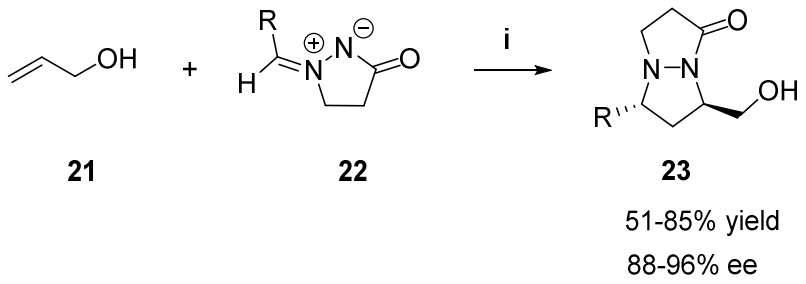
Leighton *et al.* have reported the use of chiral silane Lewis acid **20** for the highly diastereo- and enantioselective synthesis of pyrazolidines **19** *via* [3 + 2]-cycloaddition of benzoylhydrazone **17** with enol ether **18** (**Scheme 6**).



Scheme 6: (i) (*S,S*)-**20** (1.5 equiv), toluene, 23 °C, 24 h.

Inomata's approach (2008)[13]

In this approach Inomata *et al.* have applied the asymmetric 1,3-dipolar cycloaddition of azomethine imines **22** with allyl alcohol **21** by utilizing diisopropyl(*R,R*)-tartrate as a chiral auxiliary to afford the corresponding optically active *trans*-pyrazolidines **23** with excellent regio-, diastereo-, and enantioselectivities (**Scheme 7**).



21 **22** **23**

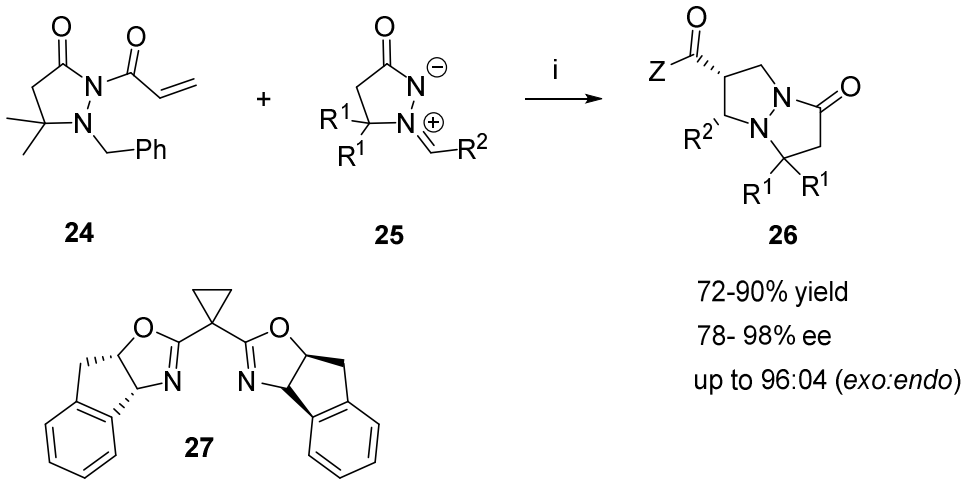
51-85% yield

88-96% ee

Scheme 7: (i) *n*-Bu_2Mg (1 equiv), (*R,R*)-DIPT (1 equiv), *n*-BuMgBr, **22** (1 equiv), CH_3CN, 80 °C, 2 d.

Mukund's approach (2008)[14]

Mukund *et al*. have illustrated an efficient catalytic method for exo and enantioselective cycloaddition of azomethine imines **25** with pyrazolidinone acrylates **24** to give 2-acryloyl-3-pyrazolidinone **26**. The cycloadducts are isolated with high diastereoselectivities (up to >96:4 *exo/endo*) and enantioselectivities (up to 98% ee) (**Scheme 8**).



24 **25** **26**

72-90% yield

78- 98% ee

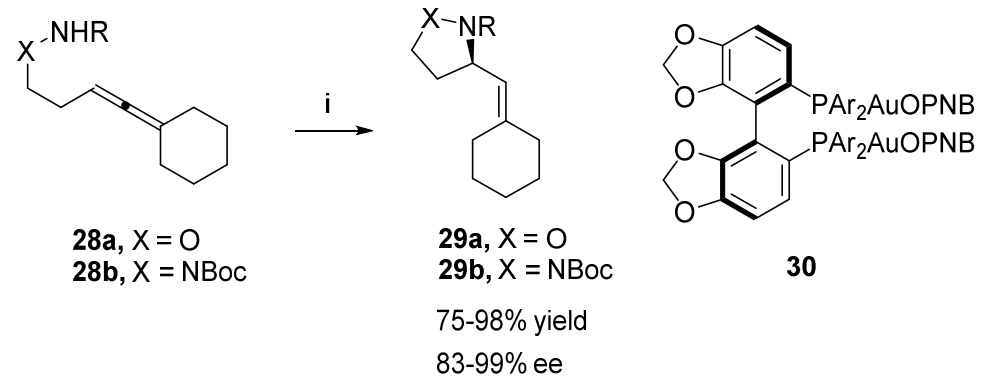
up to 96:04 (*exo:endo*)

27

Scheme 8: (i) **27** (10 mol%), $Cu(OTf)_2$, 4 A° MS, CH_2Cl_2, 0 °C, 6 h.

Toste's approach (2010)[15]

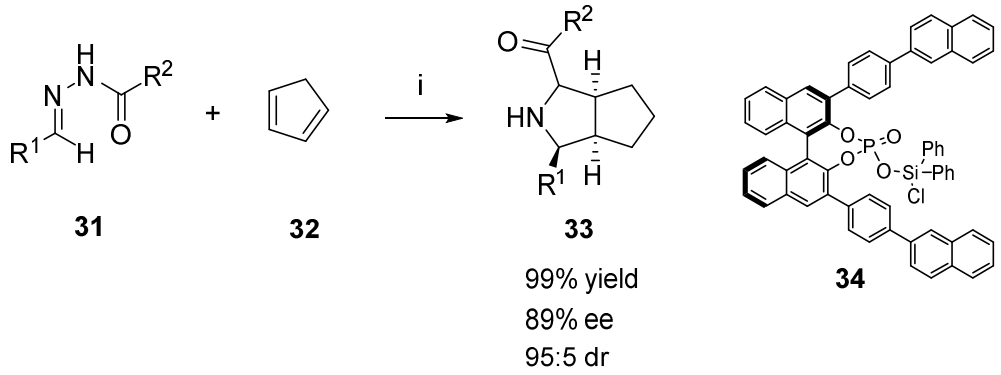
Toste *et al*. have developed an enantioselective gold (I)-catalyzed hydroaminations and hydroalkoxylations of allenes **28** with hydroxylamines and hydrazines using chiral biarylphosphinegold(I) complexes **30** as catalyst (**Scheme 9**). This method allows rapid access to chiral oxazines **29a**, and differentially protected pyrazolidines **29b** in good yields and enantioselectivity (**Scheme 9**).



Scheme 9: (i) **30** (5 mol%), $MeNO_2$, 50 °C, 15 h.

Tsogoeva's approach (2011)[16]

Tsogoeva *et al.* have used BINOL-phosphate-derived silicon Lewis acid **34**, for the [3+2]- cycloaddition of *N*-benzoylhydrazone **31** with cyclopentadiene **32** to afford cycloadduct **33** in high enantiomeric excess (89%) and diastereomeric ratio (*syn*/*anti* = 95:5) (**Scheme 10**).

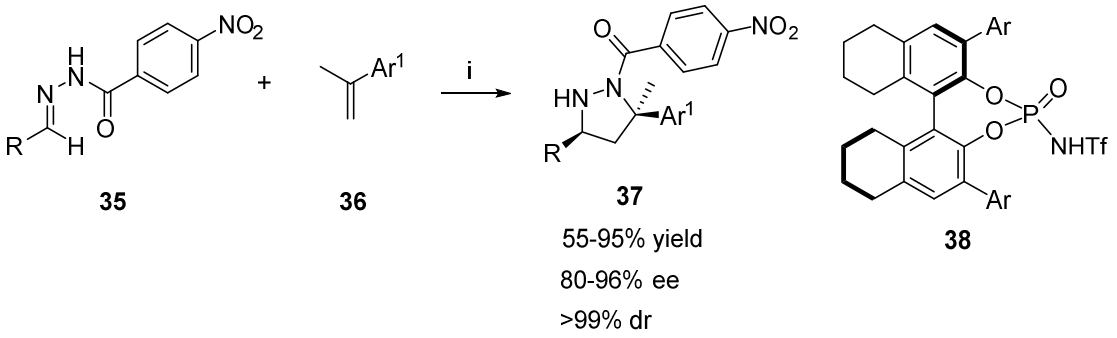


Scheme 10: (i) TMSOTf (10 mol%), CH_2Cl_2, -10 °C, 24 h.

Rueping's approach (2012)[17]

Rueping *et al.* have developed a general metal-free highly enantioselective cycloaddition between hydrazones **35** and alkenes **36** that affords pyrazolidine derivatives **37** in high yields and excellent diastereo- and enantioselectivities. The

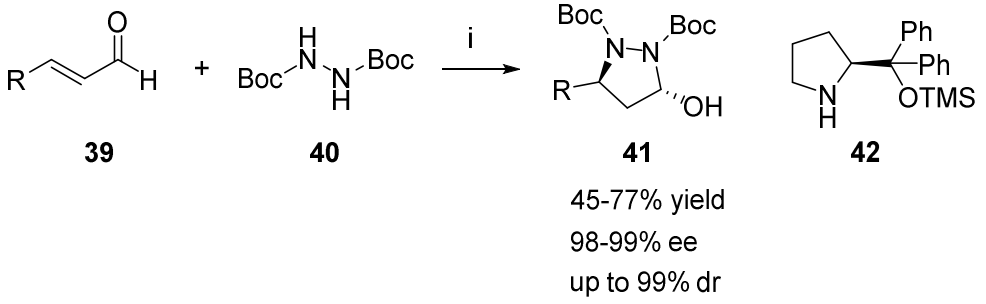
acidic N-triflylphosphoramide Brønsted acid **38** proved to be very effective catalysts and promoted the highly enantioselective cycloaddition reaction (**Scheme 11**).



Scheme 11: (i) **38** (5 mol%), $CHCl_3$, 0-25 °C, 18 h.

Cordova's approach (2012)[18]

Cordova *et al*. have developed a highly chemo- and enantioselective 1,3-diamination of α, β-unsaturated aldehydes **39** with diprotected hydrazine derivatives **40** as the dinitrogen source. The transformation was catalyzed by readily available chiral amine **42** and proceeds *via* a direct catalytic metal-free aza-Michael/hemiaminal cascade sequence and delivers functional 3-hydroxypyrazolidine derivatives **41** with 98–99% ee in one step (**Scheme 12**).

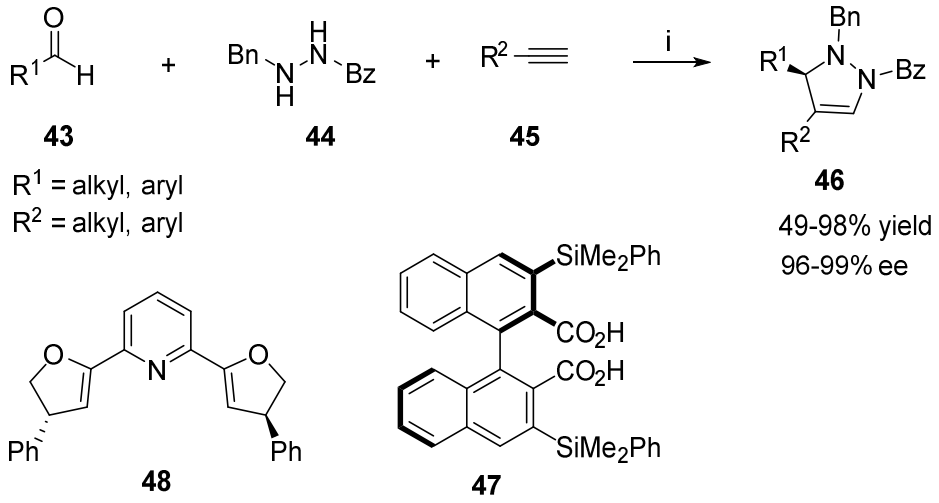


Scheme 12: 39 (1 equiv), **40** (0.8 equiv), **42** (20 mol%), toluene, 4-8 °C, 144 h.

Maruoka's approach (2013)[19]

Maruoka *et al.* have reported the synthesis of substituted pyrazolidines **46** using catalytic asymmetric three-component 1,3-dipolar cycloaddition of aldehydes **43,** hydrazides **44**, and alkynes **45**. The corresponding products were obtained in good yields with high enantioselectivities (**Scheme 13**). The use of CuOAc/Ph-pybox **48**

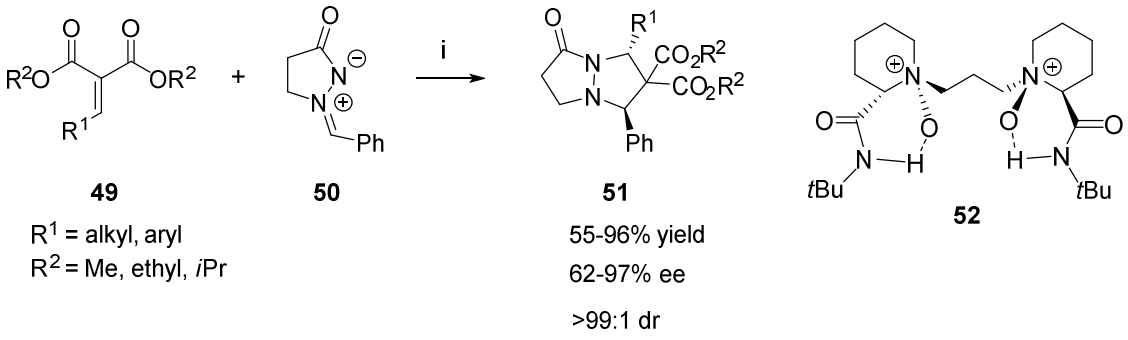
and axially chiral dicarboxylic acid cocatalysts, **47** for the synthesis of variety of 3,4-disubstiuted pyrazolines in high enantioselectivities is demonstrated.



Scheme 13: (i) CuI (10 mol%), **47** (5 mol%), **48** (6 mol%), 4 A° MS, CH_2Cl_2, 40 °C, 3d.

Feng's approach (2013)[20]

Feng *et al.* have demonstrated an asymmetric 1,3-dipolar cycloaddition of azomethine betaines **50** with alkylidene malonates **49** by using a chiral N,N'-dioxide– Ni(II) complex **52** as a catalyst. A range of *trans*-pyrazolone derivatives **51** was exclusively obtained with excellent yields (up to 99% yield) and good enantioselectivities (up to 97% ee) under the reaction conditions (**Scheme 14**).



Scheme 14: (i) **52**–$Ni(ClO_4)_2$ (1:1, 10 mol%), **49** (1 equiv), **50** (1 equiv), CH_2Cl_2, 30 °C.

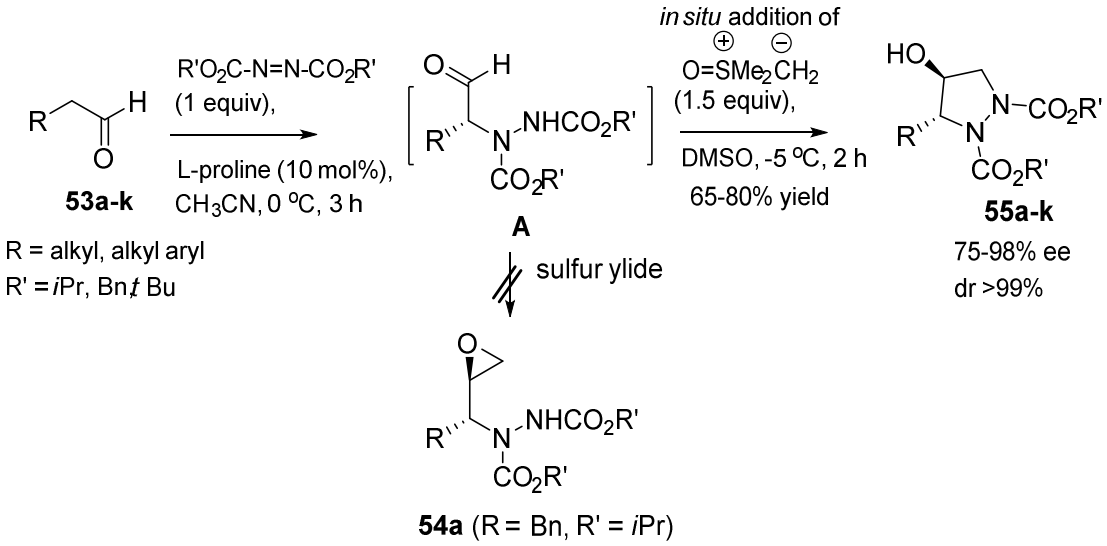
3.1.3 Present Work

3.1.3.1 Objective

The literature survey reveals that there are many methods available for the synthesis of substituted pyrazolidines; most of the strategies involve construction by [3+2]-cycloadditions under strongly acidic as well as thermal conditions. Its asymmetric versions have been reported employing chiral Lewis acid derivatives, and transition metal (Pd, Ni, Au)-catalyzed intramolecular annulations. However, these methods are reasonably limited because of harsh reaction conditions, complex chiral pool resources, expensive chiral ligands and metal catalysts often involving multi-step reaction sequences. Hence, an operationally simple and efficient method, which overcomes the above limitations, is of continuing interest to chemists.

3.1.3.2 Results and Discussion

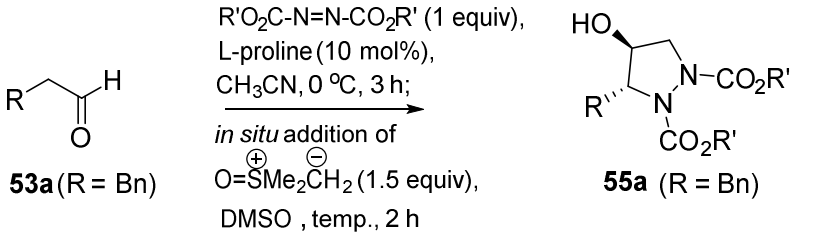
In recent years, proline-catalyzed direct α-amination of aldehydes has emerged as a reliable method for the enantioselective synthesis of α-amino acid derivatives.[21] In this regard, the *in situ* generated amino aldehyde **A**, was readily transformed into several functionalized organic derivatives: e.g. 1,2-aminoalcohols,[21a] 3,6-dihydropyridazines,[22a] functionalized β-aminoalcohols[22b] and γ-amino-α, β-unsaturated esters.[22c] As part of our program directed toward asymmetric synthesis of bioactive molecules employing organocatalysts,[22c,23] we envisaged that *in situ* trapping of amino aldehyde A with Corey's sulfur ylide (dimethyloxosulfonium methylide)[24,27a] under basic conditions should provide the corresponding highly functionalized terminal amino epoxides **54a**. Surprisingly, the reaction took a different course to furnish the corresponding 4-hydroxypyrazolidine derivatives **55a-k** in high yields with excellent ees (**Scheme 15**).



Scheme 15: *in situ* Trapping of α-amino aldehydes **A** with dimethyloxosulfonium methylide

As a model substrate, the amination of hydrocinnamaldehyde **53a** was carried out following the List protocol[21a] that produced the corresponding α-amino aldehyde **A** *in situ*. As the intermediate **A** is prone to racemization[25] under basic conditions, several experiments were conducted to identify the most effective and suitable condition for Corey-Chaykovsky reaction; the results of which are presented in Table 1. Firstly, a solution of dimethyloxosulfonium methylide in DMSO [sulfur ylide (1.5 equiv), prepared *in situ* from $O=SMe_3I$/NaH in DMSO][26a] was added to intermediate **A** at 25 °C, which gave **55a** as a single diastereomer in 80% yield with 5% ee; low % ee may be due to racemization (entry 1). A dramatic improvement in enantioselectivity (75% ee) was however realized by performing the reaction at 10 °C for 2 h. Finally, the best results could be obtained when the addition of ylide was conducted at -5 °C (91% ee with 73% yield). However, further lowering of temperature to either -20 or -40 °C had deleterious effect both in yield and enantioselectivity. Also (*S*)-α,α-diarylprolinol silyl ether as a modified proline catalyst was found to be less effective for the reaction (**Table 1**, foot-note e).

Table 1. Proline-catalyzed α-amination/Corey-Chaykovsky reaction of hydrocinnamaldehyde[a]



53a (R = Bn) **55a** (R = Bn)

no	amine (R')	temp. (°C)	yield of **55a** (%)[b]	ee (%)[c]	de (%)[d]
1	*i*Pr	25	80	5	99
		10	75	75	99
		-5	73 (45)[e]	91 (79)[e]	99
		-20	52	88	99
		-40	48	84	99
2	Bn	-5	71	90	100
3	*t*Bu	-5	60	80	100

[a] aldehyde (5 mmol), amine ($R'O_2C$-N=N-CO_2R') (5 mmol); L-proline (10 mol%); dimethyloxosulfonium methylide (7.5 mmol); [b] isolated yield after column chromatographic purification; [c] determined from chiral HPLC analysis (Chiracel OD-H, Whelk-01columns; n-hexane/2-propanol); [d] Product is obtained as a single diastereomer as determined from ^{1}H,^{13}C NMR and HPLC analysis; [e] refers to 2-[bis(3,5 bistrifluoromethylphenyl) trimethylsilanyloxymethyl] pyrrolidine is used as catalyst.

We then turned our attention to briefly investigate the scope of amine sources; the results of which indicated that diisopropyl- and dibenzylazadicarbxylates were found to be better candidates (entries 2 & 3). Use of other solvents such as THF and CH_2Cl_2 for the tandem protocol resulted in a sluggish reaction with poor yields (~30%). With the optimized reaction conditions in hand,[26b] we next examined the scope of the reaction. Aldehydes bearing bromo, cyano, nitro, methoxy and methylene dioxy groups on the aromatic nucleus and azide and benzyl ether substitutions in aliphatic

compounds were well-tolerated under the reaction conditions. For all the cases studied, the products **55a-k** were indeed obtained in high yields (65-80%), and excellent enantioselectivities (75-98% ee) with dr >99% (**Table 2**).

Table 2. Proline-catalyzed asymmetric tandem α-amination/Corey-Chaykovsky reaction [a]

no	substrates **53a-k** (R)	amine (R')	products[a] **55a-k**	
			yield (%)[b]	ee (%)[c]
1	benzyl (**53a**)	*i*Pr	73	91
2	3,4-dimethylbenzyl (**53b)**	*i*Pr	71	94
3	3,4-methylenedioxybenzyl (**53c**)	Bn	80	90
4	2-Br-4,5-methylenedioxybenzyl(**53d**)	*i*Pr	74	95
5	2-CN-4,5-methylene-dioxybenzyl (**53e**)	*i*Pr	75	75
6	naphthalene-1-yl-methyl (**53f**)	*i*Pr	70	90
7	2-NO_2-4,5-dimethoxybenzyl (**53g**)	*i*Pr	68	90
8	*n*-butyl (**53h**)	Bn	65	92
9	4-azidopropyl (**53i**)	Bn	66	91
10	3-benzyloxymethyl (**53j**)	Bn	70	90
11	3-benzyloxypropyl (**53k**)	*i*Pr	72	98

[a] aldehyde (5 mmol), amine source (R'O_2C-N=N-CO_2R') (5 mmol), L-proline (10 mol%), dimethyloxosulfonium methylide (7.5 mmol); [b] isolated yield after column chromatographic purification;[c] determined from chiral HPLC analysis (Chiracel OD-H, Whelk-01column; n-hexane/2-propanol).

The formation of 4-hydroxypyrazolidines (**55a-k**) was established unambiguously from the corresponding ^{1}H & ^{13}C NMR, IR and HRMS spectral data. Their optical purity was established from their chiral HPLC analyses. For example, the formation of 4-hydroxypyrazolidine **55e** was confirmed from its ^{1}H NMR spectrum, which

showed a doublet of doublet at δ 3.37-3.43 (d, J = 1.8, 12 Hz, 1H) and a doublet of doublet at δ 4.00-4.09 (dd, J = 5.7, 12 Hz, 1H) corresponding to the methylene (-**C**$\mathbf{H_2}$-NR_2) protons. A multiplet at δ 4.33-4.44 (2H) indicated the presence of methine protons (-C**H**-OH and -C**H**-NR_2). Its ^{13}C NMR spectrum displayed two carbon signals at δ 54.0 and 68.6 due to the methylene (-**C**$\mathbf{H_2}$-NR_2) and methine (-**C**H-NR_2) carbons respectively. Also, a characteristic signal at δ 75.0 is due to the methine carbon (-**C**H-OH) attached to the hydroxyl group which proves the formation of cyclized product **55e** (**Fig. 2**).

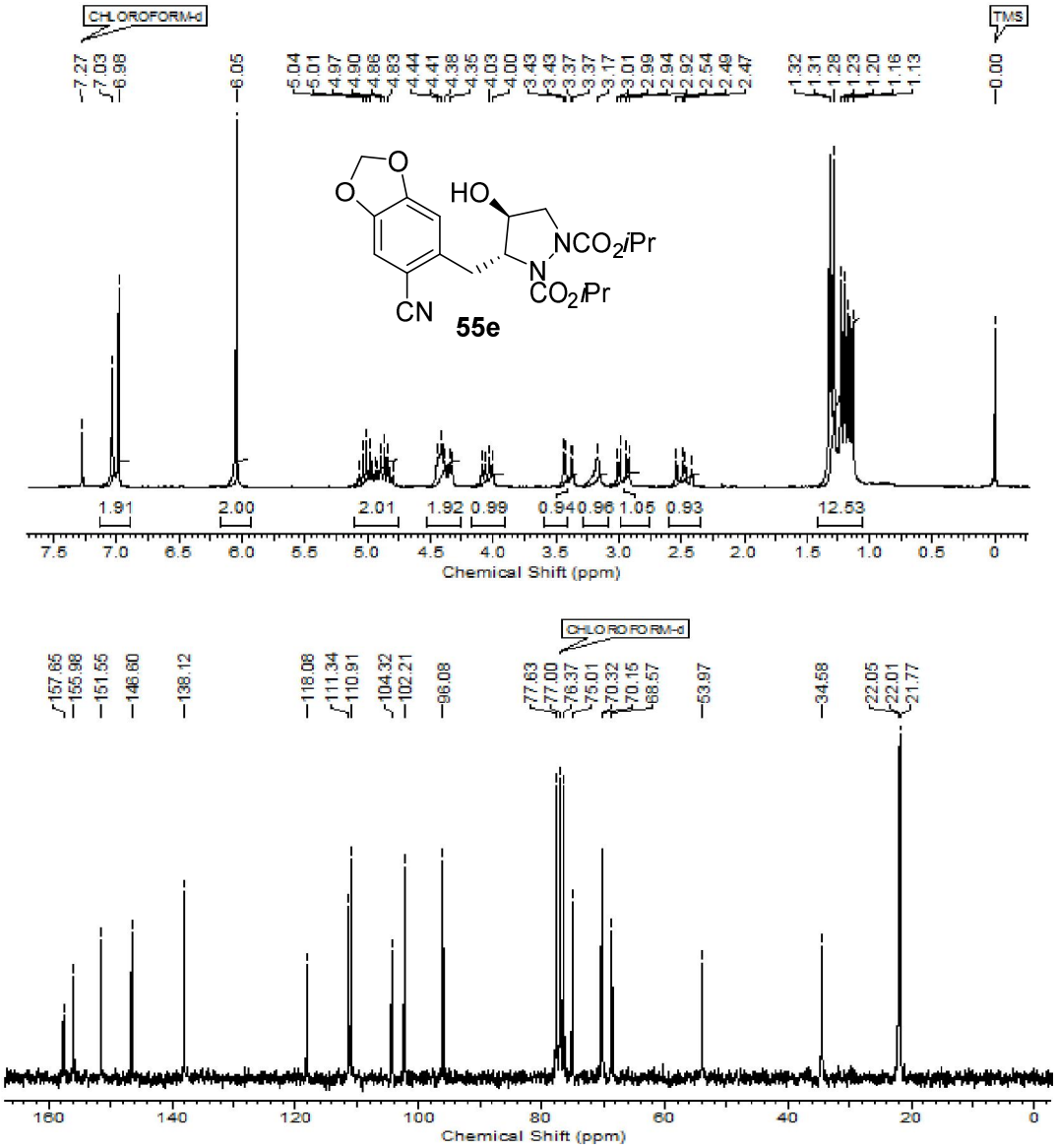


Fig. 2: ^{1}H and ^{13}C NMR spectra of 4-hydroxypyrazolidine derivative **55e**

Similarly, the ^{1}H NMR spectrum of 4-hydroxypyrazolidine **55i** showed a doublet at δ 3.36 (d, *J* = 12.1, 1H) and a doublet of doublet at δ 3.95-4.01 (dd, *J* = 5.4, 12.0 Hz, 1H) corresponding to methylene -**CH_2**-NR_2 protons, while another doublet of doublet

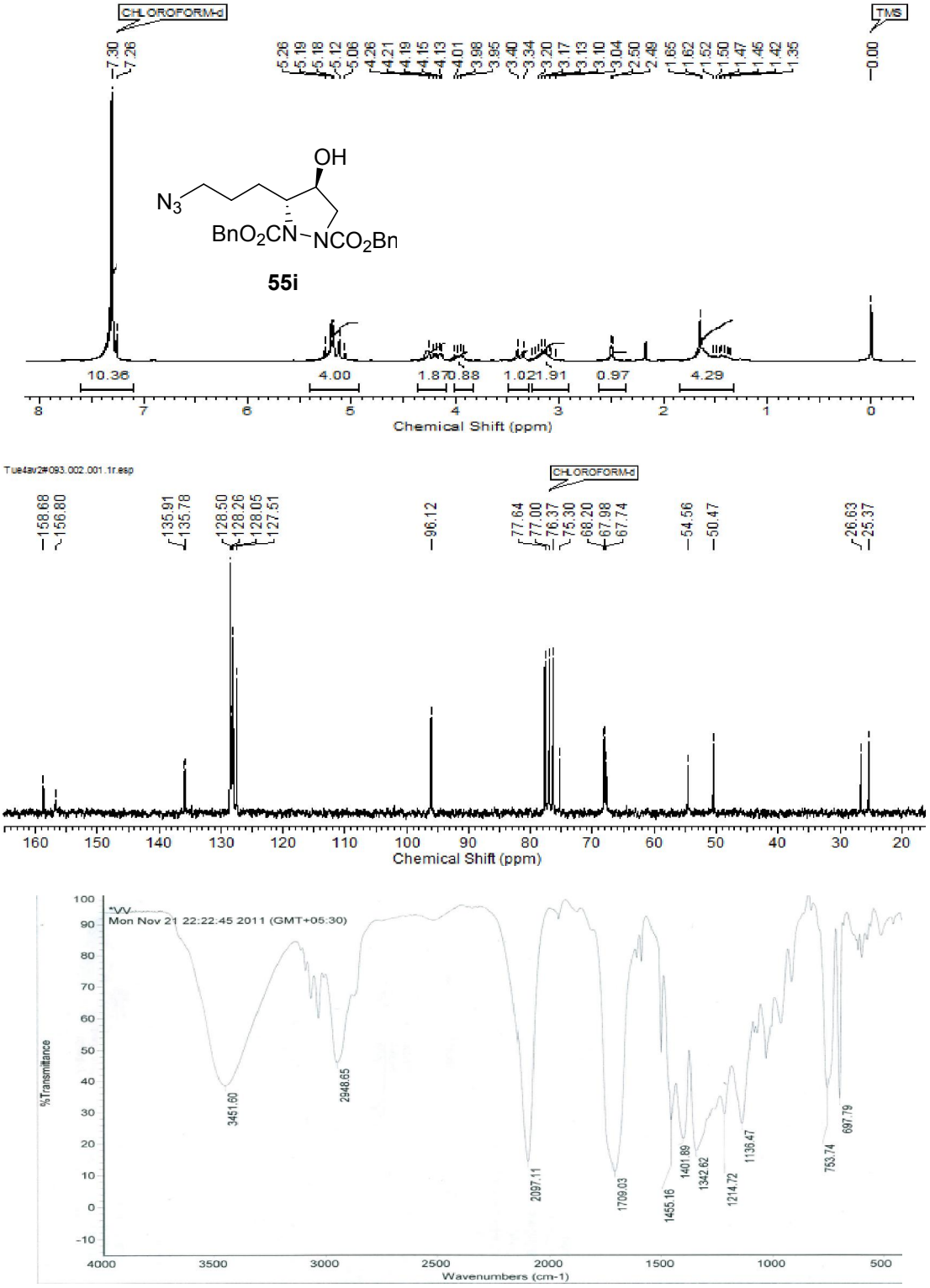
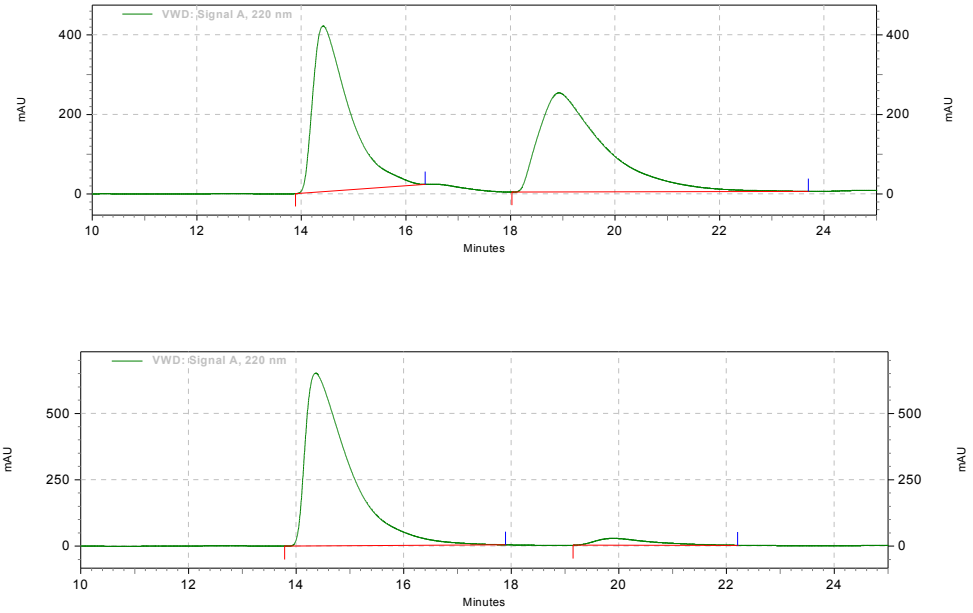


Fig. 3: ^{1}H and ^{13}C NMR and IR spectra of 4-hydroxypyrazolidine **55i**

at δ 4.13-4.21 (dd, *J* = 4.05, 11.37 Hz, 1H) and a typical multiplet at δ 4.26- 4.28 (m, 1H) correspond to the methine (-**C**H-NR_2-) and (-C**H**-OH) protons respectively. Its ^{13}C NMR spectrum displayed a typical carbon signal at δ 54.6 corresponding to methylene carbon **C**H_2-NR_2, while the other carbon signals at δ 68.2 and 75.3 were indicative of two methine (-**C**H-NR_2 and -**C**H-OH) carbons respectively. The other carbon resonance signals at δ 67.7 and 67.9 are due to benzyloxy (Ph-**C**H_2-OR) carbons (**Fig. 3**). Further, the formation of **55i** was substantiated by strong IR absorption bands at 2097 and 3451 cm^{-1} due to the azide and secondary hydroxyl groups respectively (**Fig. 3**). The enantiomeric excess of 4-hydroxypyrazolidine **55i** was determined from chiral HPLC analysis; Whelk-01 column (**Fig. 4**).



Ret. time	Area	Area %	Height	Height %
14.363	618479535	95.55	10915444	96.16
19.887	28817027	4.45	435555	3.84
	647296562	100.00	11350999	100.00

Fig. 4: HPLC chromatogram of 4-hydroxypyrazolidine derivative **55i**

The absolute configuration of the newly generated amine center was assigned on the basis of the previously established configuration of α-amino aldehydes.[12a] The *anti*-stereochemistry in pyrazolidines **55a-k** is, however, proven unambiguously from COSY and NOESY NMR studies,[27] X-ray crystallographic analysis (**Fig. 5**) and also in conformity with Felkin-Ahn model. [28]

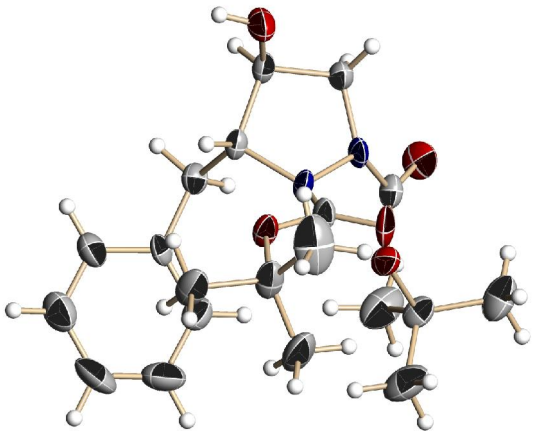
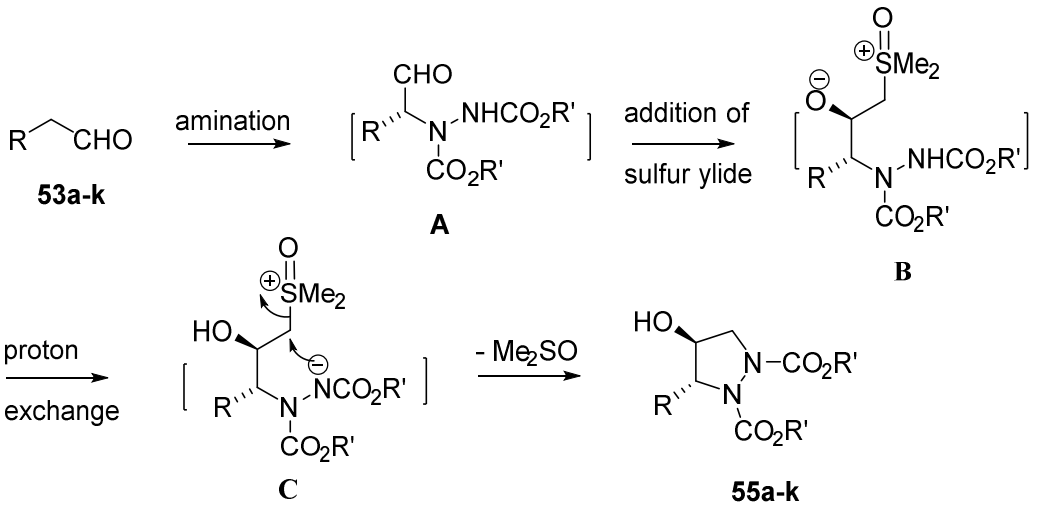


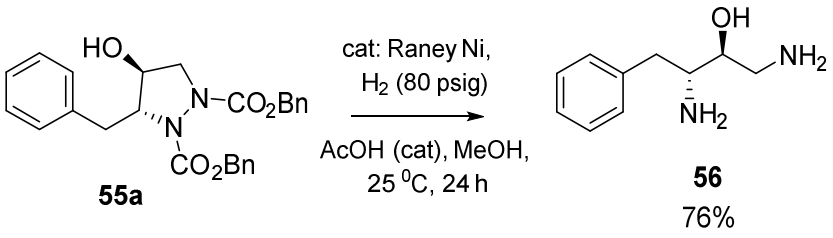
Fig. 5: ORTEP diagram of hydroxypyrazolidine **55a** (R'= *t*Bu)

A probable mechanistic pathway is shown in **Scheme 16**. This pathway is supported by the following experimental facts: (a) no aminoepoxide **54a** was detected (GC & ^{1}H NMR) even at -40 °C when the reaction was monitored every 10 min; (b) alternatively, **54a** was prepared separately in two steps from aldehyde A *via* Wittig reaction ($Ph_3P^+MeI^-$, $KOBu^t$, THF, 0-25 °C, 90%) followed by epoxidation (MCPBA, CH_2Cl_2, 25 °C, 92%) and found to be quite stable under the reaction conditions. This leads us to believe that addition of sulfur ylide onto aldehyde A generates the intermediate B. This in turn is followed by a facile proton exchange[29] from carbamate nitrogen to basic oxide ion to give the stable species C, which then subsequently undergoes intramolecular cyclization with the removal of DMSO to afford the products **55a-k**.



Scheme 16: Probable mechanistic pathway

A single step transformation of **55a** under catalytic hydrogenation conditions [Raney Ni, H_2, (80 psig)] gave the corresponding *anti*-1,2-aminoalcohol **56**, which are common structural subunits present in phytospingosines[30a,b] and HIV protease inhibitors;[30c,d] thus constituting an important application of this methodology (**Scheme 17**).



Scheme 17: Synthesis of *anti*-1,2-aminoalcohol (**56**)

3.1.4 Conclusion

In conclusion, we have described, for the first time, a novel one pot procedure of sequential amination-Corey-Chaykovsky reaction of aldehydes that leads to synthesis of 4-hydroxypyrazolidine derivatives **55a-k** with good yields and excellent enantio-

and diastereoselectivities. The salient features of the methodology are: (1) metal-free synthesis (2) milder reaction conditions (3) functional group tolerance (4) high yields with excellent enantio- and diastereoselectivity.

3.1.5 Experimental Section:

General Experimental Procedure:

(a) **Preparation of sulfur ylide**: 0.18 g (7.5 mmol) of NaH (previously washed with petroleum ether to remove oil) was taken in an oven-dried three-necked flask, followed by the addition of dry DMSO (10 mL) through a septum to it and the the whole slurry was stirred at 25 °C under N_2 atmosphere. Then trimethyloxosulfonium iodide (1.67 g, 7.5 mmol) was added to the slurry over a period of 5 min *via* a solid addition funnel until it becomes a homogenous solution.

(b) **Sequential α-amination-Corey Chaykovsky reaction of aldehydes**: To a cooled solution of azadicarboxylate (5.0 mmol) and L-proline (10 mol%) in dry CH_3CN (20 ml) at 0 ^oC was added α-unsubstituted aldehyde (**53a-k**, 5 mmol) and the mixture was stirred for 3 h at 0 ^oC. This was followed by the addition of a solution of dimethyloxosulfonium methylide in DMSO at -5 °C and allowed to stir for 2 h at the same temperature. The progress of the reaction was monitored by TLC. It was then quenched by the addition of aq. NH_4Cl solution. The mixture was concentrated in vacuum to remove acetonitrile and concentrate extracted with diethylether (3 x 40 ml). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4, and concentrated under reduced pressure to give the crude products, which were then purified by flash column chromatography (100-200 mesh) using petroleum ether and ethyl acetate as eluents to afford the pure products **55a-k**.

(3*R*, 4*S*)-Diisopropyl-3-benzyl-4-hydroxypyrazolidine-1,2-dicarboxylate (R' = *i*Pr) (55a)

Yield: 1.2 g, 73%; colorless liquid; 91% ee from **HPLC analysis**; Column: Chiracel OD-H, (2-propanol:*n*-hexane = 5:95, flow rate 0.5 mL/min, λ = 220 nm). Retention time (min): 22.05 (minor) and 26.25 (major), $[\alpha]^{D}_{25}$ +22.78 (*c* 0.8, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 422, 546, 599, 623, 666, 700, 750, 834, 920, 1000, 1043, 1496, 1585, 1604, 1716, 2936, 2981, 3063, 3087, 3446; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.15-1.30 (m, 12H,), 2.43-2.76 (m, 3H), 3.36 (d, *J* = 11.9 Hz, 1H), 3.94 -4.02 (dd, *J* = 5.43, 11.9 Hz, 1H), 4.33-4.40 (m, 2H), 4.79-5.07(m, 2H), 7.17-7.32 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.5, 21.6, 21.8, 36.2, 53.9, 68.8, 69.7, 69.9, 74.2, 126.3, 128.1, 129.0, 137.1, 156.3, 157.8; ESI-MS: *m*/*z* 373.3294 $[M+Na]^+$ **Analysis**: $C_{18}H_{26}N_2O_5$ requires: C, 61.70; H, 7.48; N, 7.99%; found: C, 61.73; H, 7.44; N, 7.95%.

(3*R*, 4*S*)-Dibenzyl 3-benzyl-4-hydroxypyrazolidine-1,2 -dicarboxylate (When R' = Bn) (55a)

Yield: 1.1 g, 71%; colorless liquid; 90% ee from **HPLC analysis**; Column: Whelk -01 (2-propanol:*n*-hexane = 20:80, flow rate 0.5 mL/min, λ = 260 nm). Retention time (min): 12.77 (major) and 16.71 (major); $[\alpha]^{D}_{25}$ +13.66 (*c* 1.2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 697, 750, 971, 1027, 1077, 1139, 1215, 1343, 1402, 1454, 1497, 1604, 1716, 2955, 3030, 3064, 3450; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.37-2.72 (m, 3H), 3.41 (d, *J* = 11.7 Hz, 1H), 3.95-4.06 (m, 1H), 4.32-4.45 (m, 2H), 5.11-5.24 (m, 4H), 7.10-7.29 (m, 15H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 36.1, 54.2, 67.8, 69.2, 74.1, 76.4, 126.4, 127.1, 127.7, 127.8, 127.9, 128.2, 128.3, 129.0, 135.7, 136.8, 156.5, 158.3; **Analysis**: $C_{26}H_{26}N_2O_5$ requires: C, 69.94; H, 5.87; N, 6.27%; found: C, 69.91; H, 5.85; N, 6.24%.

(3*R*, 4*S*)-Di-*tert*-butyl 3-benzyl-4-hydroxypyrazolidine-1,2-dicarboxylate (When R'= *t*Bu) (55a)

Yield: 0.9 g, 68%; colorless solid; **mp**: 126-128 °C; 80% ee from **HPLC analysis**; Column: Chiracel OD-H (2-propanol:*n*-nexane = 5:95, flow rate 0.5 mL/min, λ = 220 nm). Retention time (min): 14.09 (minor) and 16.47 (major), $[\alpha]^{D}_{25}$ +24.48 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 699, 755, 853, 998, 1033, 1076, 1091, 1142, 1255, 1367, 1455, 1477, 1496, 1697, 2931, 2977, 3444; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.39 (s, 9H), 1.49 (s, 9H), 2.08 (dd, *J* = 2.1, 3.1 Hz, 1H,), 2.46-2.75 (m, 2H), 3.30-3.37 (dd, *J*=1.6, 12.0 Hz, 1H,), 3.95-4.04 (dd, *J* = 5.6, 12.1 Hz, 1H,), 4.26-4.34 (m, 2H), 7.26 (brs, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 28.0, 28.2, 36.6, 53.9, 68.8, 74.6, 80.9, 81.2, 126.4, 128.2, 129.3, 137.5, 155.8, 156.9; **HRMS (ESI, m/z):** Calculated for $C_{20}H_{30}N_2O_5Na$ $(M+Na)^+$ 401.2052, found 401.2060. **Analysis**: $C_{20}H_{30}N_2O_5$ requires: C, 63.47; H, 7.99; N, 7.40% found: C, 63.50; H, 7.93; N, 7.44%.

(3*R*, 4*S*)-Diisopropyl-3-(3,4-dimethylbenzyl)-4-hydroxypyrazolidine-1,2-dicarboxylate (55b)

Yield: 1.8 g, 71%; gum; 94% ee from **HPLC analysis**; Column: Chiracel OD-H (2-propanol:*n*-hexane = 10:90, flow rate 0.5 mL/min, λ = 220 nm). Retention time (min): 8.95 (minor) and 9.95 (major), $[\alpha]^{D}_{25}$ +7.12 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 663,771, 926, 1101, 1211, 1315, 1380, 1697, 2345, 2397, 2973, 3012, 3679; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.19-1.30 (m, 12H), 2.09 (brs, 1H), 2.23 (s, 6H), 2.28-2.40 (dd, *J* = 8.3, 13.9 Hz, 1H), 2.68-2.79 (dd, *J* = 7.1, 13.7 Hz, 1H), 3.33 (d, *J* = 12.1 Hz, 1H), 3.96-4.04 (dd, 1H, *J* = 5.3, 11.9 Hz), 4.30-4.37 (m, 2H), 4.86-5.04 (m, 2H), 6.93-7.05 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 19.1, 19.5, 21.6, 21.7, 21.9, 35.9, 53.9, 68.9, 69.6, 69.9, 74.1, 126.4, 129.4, 130.3, 134.3, 134.5, 136.1, 156.3, 157.9; **HRMS (ESI, m/z):** Calculated for $C_{20}H_{30}N_2O_5Na$ $(M+Na)^+$ 401.2052, found 401.2060. **Analysis**: $C_{20}H_{30}N_2O_5$ requires: C, 63.47; H, 7.99; N, 7.40% found: C, 63.45; H, 7.95; N, 7.45%.

(3*R*, 4*S*)-Dibenzyl-3-((benzo[d][1,3]dioxol-5-yl)methyl)-4-hydroxypyrazolidine-1,2-dicarboxylate (55c)

Yield: 1.9 g, 78%; gum; 90% ee from **HPLC analysis**; Column: Whelk - 01 (2-propanol:*n*-hexane = 20:80, flow rate 0.5 mL/min, λ = 260 nm). Retention time (min): 20.64 (major) and 31.49 (minor),; $[\alpha]^{D}_{25}$ +10.17 (*c* 1.1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 757, 1041, 1216, 1248, 1343, 1444, 1491, 1709, 2929, 3021, 3444; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.33-2.60 (m, 3H), 3.40 (d, *J* = 12 Hz, 1H), 3.93-4.02 (dd, *J* =5.1, 11.8 Hz, 1H), 4.32-4.39 (m, 2H), 5.12-5.24 (m, 4H), 5.88 (s, 2H), 6.53-6.67 (m, 3H), 7.18-7.34 (m, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 35.9, 54.3, 67.9, 69.4, 74.3, 100.8, 108.2, 109.5, 122.2, 127.3, 127.9, 128.1, 128.4, 128.5, 130.5, 135.8, 146.3, 147.6, 156.6, 158.4; **Analysis**: $C_{27}H_{26}N_2O_7$ requires: C, 66.11; H, 5.34; N, 5.71%; found: C, 66.15; H, 5.30; N, 5.74%.

(3*R*, 4*S*)-Diisopropyl-3-((5-bromobenzo[d][1,3]dioxol-6-yl)methyl)-4-hydroxypyrazolidine-1,2-dicarboxylate (55d)

Yield: 1.7 g, 74%; gum; 95% ee from **HPLC analysis**; Column: Chiracel OD-H (2-propanol:*n*-hexane = 10:90, flow rate 0.5 mL/min, λ = 254 nm). Retention time (min): 19.69 (minor) and 22.06 (major), $[\alpha]^{D}_{25}$ +33.19 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 757, 1039, 1106, 1233, 1317, 1384, 1480, 1704, 2984, 3447; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.16-1.30 (m, 12H), 2.46-2.52 (m, 1H), 2.74 -2.79 (dd, *J* = 9.2, 13.5 Hz, 1H), 2.76-2.79 (dd, *J* = 6.1, 14.3 Hz, 1H), 2.95 (brs, 1H), 3.39 (d, *J* = 11.6 Hz, 1H), 4.01-4.05 (dd, *J* = 5.2, 11.6 Hz, 1H), 4.37-4.43 (m, 2H), 4.84-4.90 (m, 1H), 4.96-5.02 (m, 1H), 5.95(s, 1H), 6.85 (s, 1H), 6.98 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.9, 22.1, 36.2, 54.3, 67.9, 70.1, 70.2, 74.6, 101.6, 111.3, 112.5, 114.7, 129.6, 147.3, 156.3, 157.8; **HRMS (ESI, m/z):** Calculated for $C_{19}H_{25}BrN_2O_7Na$ $(M+Na)^+$ 495.0743, found 495.0740. **Analysis**: $C_{19}H_{25}BrN_2O_7$ requires: C, 48.21; H, 5.32; N, 5.92%; found: C, 48.24; H, 5.28; N, 5.88%.

(3*R*, 4*S*)-Diiisopropyl-3-((5-cyanobenzo[d][1,3]dioxol-6-yl)methyl)-4-hydroxypyrazolidine-1,2-dicarboxylate (55e)

Yield: 1.5 g, 75%; gum; 75% ee from **HPLC analysis**; Chiracel OD-H column (2-propanol:*n*-hexane = 10:90, flow rate 0.5 mL/min, λ = 254 nm). Retention time (min): 33.52 (minor) and 37.22 (major), $[\alpha]^{D}_{25}$ +42.19 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): υ_{max} 546, 666, 754, 870, 930, 1035, 1385, 1618, 1715, 2222, 2983, 3440; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.13-1.31 (m, 12H), 2.42-2.54 (dd, *J* = 10.5, 14.3 Hz, 1H), 2.92-3.01 (dd, *J* = 4.3, 14.3 Hz, 1H), 3.17 (bs, 1H), 3.36-3.43 (dd, *J* = 1.8, 12.0 Hz, 1H), 4.00-4.09 (dd, *J* = 5.7, 12.0 Hz, 1H), 4.33-4.44 (m, 2H), 4.83-5.04 (m, 2H), 6.05 (s, 2H), 6.98 (s, 1H), 7.03 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.7, 21.8, 22.0, 22.1, 34.6, 54.9, 68.6, 70.1, 70.3, 75.0, 102.2, 104.3, 110.9, 111.3, 118.1, 138.1, 146.6, 151.6, 155.9, 157.6; **Analysis**: $C_{20}H_{25}N_3O_7$ requires: C, 57.27; H, 6.01; N, 10.02; found: C, 57.20; H, 6.08; N, 10.09 %.

(3*R*, 4*S*)-Diisopropyl-4-hydroxy-3-((naphthalen-2-yl)methyl)pyrazolidine-1,2-dicarboxylate (55f)

Yield: 1.4 g, 70%; gum; 90% ee from **HPLC analysis**; Chiracel OD-H column (2-propanol:*n*-hexane = 6:94, flow rate 0.5 mL/min, λ = 254 nm). Retention time (min): 14.39 (minor) and 16.49 (major), $[\alpha]^{D}_{25}$ +17.29 (*c* 1.2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 757, 1039, 11067, 1233, 1317, 1384, 1480, 1704, 2984, 3447; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.16-1.32 (m, 12H), 2.76-2.88 (dd, *J* = 9.3, 13.9 Hz, 1H), 3.30-3.44 (m, 2H), 4.12-4.20 (m, 1H), 4.37 (brs, 1H), 4.48-4.55 (t, *J* = 7.2 Hz, 1H), 4.86-5.04 (m, 2H), 7.26-7.60 (m, 5H), 7.73-7.88 (m, 2H), 8.12 (d, *J* = 7.8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.7, 21.9, 34.4, 54.1, 67.8, 70.0, 74.6, 123.5, 125.3, 125.6, 126.2, 127.5, 128.8, 131.9, 133.1, 133.8, 156.6, 157.4; **HRMS (ESI, m/z):** Calculated for $C_{22}H_{28}N_2O_5Na$ $(M+Na)^+$ 423.1896, found 423.1893. **Analysis**: $C_{22}H_{28}N_2O_5$ requires: C, 65.98; H, 7.05; N, 7.00% found: C, 65.95; H, 7.01; N, 7.05%.

(3*R*, 4*S*)-Diisopropyl-3-(4,5-dimethoxy-2-nitrobenzyl)-4-hydroxypyrazolidine-1,2-dicarboxylate (55g)

Yield: 1.5 g, 68%; liquid; 90% ee from **HPLC analysis**; Chiracel OD-H column (2-propanol:*n*-hexane = 10:90, flow rate 0.5 mL/min, λ = 260 nm). Retention time (min): 29.78 (minor) and 33.81 (major), $[\alpha]^{D}_{25}$ -6.64 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 666, 756, 797, 870, 939, 1004, 1519, 1581, 1616, 1731, 2852, 2983, 3443; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.04-1.30 (m, 12H), 2.33-2.61 (m, 2H), 3.32-3.47 (m, 2H), 3.94-4.10 (m, 7H), 4.43-4.49 (m, 2H), 4.81-5.04 (m, 2H), 7.08 (s, 1H), 7.62 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.8, 21.8, 22.1, 22.2, 34.2, 54.5, 56.2, 56.8, 68.5, 69.9, 70.2, 76.1, 107.9, 115.3, 128.3, 140.9, 140.7, 153.2, 156.0, 157.3; **HRMS (ESI, m/z):** Calculated for $C_{20}H_{29}N_3O_9Na$ $(M+Na)^+$ 478.1801, found 478.1804. **Analysis**: $C_{20}H_{29}N_3O_9$ requires: C, 52.74; H, 6.42; N, 9.23%; found: C, 52.70; H, 6.37; N, 9.25 %.

(3*R*, 4*S*)-Dibenzyl-3-butyl-4-hydroxypyrazolidine-1,2-dicarboxylate (55h)

Yield: 1.5 g, 76%; gum; 92% ee from **HPLC analysis**; Whelk -01 column (2-propanol:*n*-hexane = 20:80, flow rate 0.5 mL/min, λ = 220 nm). Retention time (min): 10.07 (major) and 14.01 (minor), $[\alpha]^{D}_{25}$ = -1.42 (*c* 0.8, $CHCl_3$, cm^{-1}); **IR** ($CHCl_3$): υ_{max} 756, 1216, 1701, 3021, 3454; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.81 (t, *J* = 7.1 Hz, 3H), 1.02-1.43 (m, 6H), 2.39 (brs, 1H), 3.36 (d, *J* = 12.1 Hz, 1H), 3.91- 4.00 (dd, *J* = 5.4, 12.0 Hz, 1H), 4.13-4.20 (dd, *J* = 4.5, 10.4 Hz, 1H), 4.27 (d, *J* = 5.1 Hz, 1H), 5.07-5.29 (m, 4H), 7.29 (brs, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.9, 22.2, 28.1, 29.4, 54.6, 67.8, 68.0, 68.4, 75.2, 127.4, 127.8, 128.0, 128.1, 128.4, 134.0, 156.9, 158.9; **Analysis**: $C_{23}H_{28}N_2O_5$ requires: C, 66.97; H, 6.84; N, 6.79%; found: C, 66.90; H, 6.89; N, 6.85%.

(3*R*, 4*S*)- Dibenzyl-3-(3-azidopropyl)-4-hydroxypyrazolidine-1,2-dicarboxylate (55i)

Yield: 1.4g, 66%; gum; 91% ee from **HPLC analysis**; Whelk - 01 column (2-propanol:*n*-hexane = 20:80, flow rate 0.5 mL/min, λ = 220 nm). Retention time (min): 14.41 (major) and 18.92 (minor), $[\alpha]^{D}_{25}$ +4.79 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 679, 753, 1136, 1214, 1342, 1401, 1455, 1709, 2097, 2984, 3451; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.35-1.65 (m, 4H), 2.50 (d, *J* = 2.5 Hz, 1H), 3.07-3.26 (m, 2H), 3.34 (d, *J* = 12.1, 1H), 3.92-4.01 (dd, *J* = 5.4, 12.0 Hz, 1H), 4.13-4.21 (dd, *J* = 4.05, 11.4 Hz, 1H), 4.26 (brs, 1H), 5.06-5.26 (m, 4H), 7.30 (s, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 25.4, 25.6, 50.5, 54. 6, 67.6, 68.0, 68.2, 75.3, 127.5, 128.1, 128.3, 128.5, 135.8, 135.9, 156.8, 158.7; **HRMS (ESI, m/z):** Calculated for $C_{22}H_{25}N_5O_5Na$ $(M+Na)^+$ 462.1753, found 462.1751. **Analysis**: $C_{22}H_{25}N_5O_5$ requires: C, 60.13; H, 5.73; N, 15.94%; found: C, 60.21; H, 5.65; N, 15.84%.

(3*R*, 4*S*)-Dibenzyl-3-((benzyloxy)methyl)-4-hydroxypyrazolidine-1,2-dicarboxylate (55j)

Yield: 1.6 g, 70%; gummy liquid; 90% ee from **HPLC analysis**; Whelk-01 column (2-propanol:*n*-hexane = 20:80, flow rate 0.5 mL/min, λ = 254 nm). Retention time (min): 17.45 (major) and 19.64 (minor), $[\alpha]^{25}_{D}$: - 10.45 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 697, 753, 1027, 1141, 1216, 1338, 1402, 1455, 1715, 2953, 3032, 3066, 3446; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 2.43 (d, *J* = 21.2 Hz, 1H), 3.26-3.41 (m, 2H), 3.55-3.62 (dd, *J* = 4.0, 9.9 Hz, 1H,), 4.08-4.16 (dd, *J* = 6.32, 11.1 Hz, 1H), 4.28-4.41 (m, 3H), 4.52 (brs, 1H), 4.96-5.24 (m ,4H), 7.17-7.27 (m, 15H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 55.5, 67.0, 67.7, 68.07, 69.6, 73.4, 73.6, 127.5, 127.7, 128.0, 128.4, 135.9, 136.0, 137.5, 156.8, 157.8; **Analysis:** $C_{27}H_{28}N_2O_6$ requires C, 68.05; H, 5.92; N, 5.88%; found C, 68.15; H, 5.99; N, 5.98%.

(3*R*, 4*S*)-Diisopropyl-3-(3-(benzyloxy)propyl)-4-hydroxypyrazolidine-1,2-dicarboxylate (55k)

Yield: 1.5 g, 72%; gum; 98% ee from **HPLC analysis**; Chiracel OD-H column (2-propanol:*n*-hexane = 5:95, flow rate 0.5 mL/min, λ = 254 nm). Retention time (min): 9.75 (minor) and 11.36 (major), $[\alpha]^{25}_{D}$: +1.33 (*c* 0.9, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 666, 699, 760, 919, 1027, 1105, 1147, 1180, 1219, 1321, 1381, 1690, 2394, 2863, 2936, 2980, 3019, 3434; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.19-1.30 (m, 12H), 1.50-1.83 (m, 4H), 2.55 (brs, 1H), 3.28 (d, *J* = 12.5 Hz, 1H), 3.41-3.60 (m, 2H), 3.91-4.00 (dd, *J* = 5.7, 12.0 Hz, 1H), 4.08-4.16 (dd, *J* = 4.9, 10.7 Hz, 1H), 4.23 (brs, 1H), 4.47 (s, 2H), 4.90-4.98 (m, 2H), 7.23-7.37 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 21.9, 22.0, 26.2, 26.7, 54.2, 67.6, 69.4, 69.6, 70.1, 72.9, 75.3, 127.5, 127.6, 128.3, 138.3, 156.7, 158.3; **HRMS (ESI, m/z)**: Calculated for $C_{21}H_{32}N_2O_6Na$ $(M+Na)^+$ 431.2158, found 431.2160**.** **Analysis:** $C_{21}H_{32}N_2O_6$ requires C, 61.75; H, 7.90; N, 6.86%; found C, 61.75; H, 7.90; N, 6.86%.

Synthesis of *anti*-1, 2-aminoalcohol (56)

A solution of hydroxypyrazolidine (R' = Bn) **55a** (0.805 g, 1.8 mmol) in MeOH (20 ml) and acetic acid (10 drops) was treated with Raney Ni (~ 30 mol%, 20 mg) under H_2 (80 psig) atmosphere for 24 h. After the reaction was complete, it was filtered over Celite and concentrated to give *anti*-1,2-aminoalcohol **56.**

Yield: 0.25 g, 76%, gum; $[\alpha]^{25}_{D}$: + 3.9 (*c* 1.2, MeOH). **^{1}H NMR** (500 MHz, MeOH-d_4): δ 2.16 (brs, 5H), 2.78-3.04 (m, 4H), 3.44 (br s, 1H), 3.93 (brs, 1H), 7.26-7.37 (m, 5H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 37.0, 42.7, 57.3, 69.7, 128.3, 130.2, 130.5, 138.1; **Analysis:** $C_{10}H_{16}N_2O$ requires C, 66.63; H, 8.95; N, 15.54; found C, 66.59; H, 8.93; N, 15.52%.

Synthesis of amino epoxide (54a)

Step 1. Preparation of amino aldehyde (A)

To a cooled solution of diisopropylazadicarboxylate (1.1 g, 5.0 mmol) and L-proline (57.5 mg, 10 mol %) in dry CH_3CN (20 ml) at 0 ^oC was added hydrocinnamaldehyde 53a (670 mg, 5 mmol) and the mixture was stirred for 3 h at 0 ^oC. The progress of the reaction was monitored by TLC. Then the mixture was concentrated in vacuum at room temperature to remove acetonitrile to give the crude product which was then purified by column chromatography with pet-ether/ ethylacetate (80:20) as eluents to afford the amino aldehyde intermediate **A** (1.52 g, 90% yield) **.**

Yield: 1.52 g, 90%, viscous liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 698, 1107, 1180, 1235, 1300, 1385, 1455, 1467, 1496, 1719, 2981, 3286; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.11-1.27 (m, 12H), 2.90-3.11 (m, 1H), 3.21-3.31 (dd, *J* = 5.6, 14.7 Hz, 1H), 4.50-4.77 (m, 1H), 4.84-5.00 (m, 2H), 6.17 (d, *J* = 21.0 Hz, 1H), 7.20- 7.34 (m, 5H), 9.82 (d, *J* = 10.3 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 21.7, 32.3, 70.6, 126.7, 128.5, 128.8, 137.1, 155.2, 198.9; **Analysis:** $C_{17}H_{24}N_2O_5$ requires C, 60.70; H, 7.19; N, 8.33; found C, 60.72; H, 7.17; N, 8.29%.

Step 2. Preparation of amino olefin (epoxide precursor)

To a stirred solution of $Ph_3P^+CH_3I^-$ (3.6 g, 9 mmol) in THF (25 m) was added $KOBu^t$ (1.0 g, 9 mmol) at 0 °C. After 15 min. of stirring, amino aldehyde **A** (1.5 g, 4.5 mmol) in THF (10 ml) was added dropwise over a period of 10 min. The reaction mixture was then stirred for 1 h at 25 °C. After the completion of the reaction, as monitored by TLC, was quenched at 0 °C with aq. NH_4Cl, extracted with diethylether (3X40 ml) and dried over anhyd. Na_2SO_4. The combined organic layer was concentrated under reduced pressure to get the crude product which was then purified by column

chromatography with pet-ether/ ethyl acetate (90:10) as eluents to afford the amino olefin (1.35 g, 90% yield).

Yield: 1.2 g, 90%, viscous liquid; $[\alpha]^{25}_{D}$: + 4.67 (*c* 1.2, $CHCl_3$). **IR** ($CHCl_3$, cm^{-1}): υ_{max} 756, 1037, 1107, 1180, 1216, 1296, 1385, 1706, 2983, 3385; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.15-1.27 (m, 12H), 2.83-3.02 (m, 2H), 4.76-5.02 (m, 3H), 5.13 (d, *J* = 10.4 Hz, 2H), 5.83-6.04 (m, 2H), 7.14-7.31 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.9, 22.0, 37.9, 69.7, 69.9, 116.9, 126.4, 128.4, 129.1, 135.8, 138.0, 155.0, 156.4; **Analysis:** $C_{18}H_{26}N_2O_4$ requires C, 64.65; H, 7.84; N, 8.38; found C, 64.67; H, 7.85; N, 8.35%.

Step 3. Preparation of amino epoxide (54a)

To a stirred solution of amino olefin (200 mg, 0.59 mmol) in CH_2Cl_2 (5 ml) was added mCPBA (154 mg, 0.9 mmol) at 0 °C. The reaction mixture was then stirred for 12 h at 25 °C. After the completion of the reaction, as monitored by TLC, was washed with aq. $NaHCO_3$ and extracted with CH_2Cl_2 (3x5 ml) and dried over anhyd. Na_2SO_4. The combined organic layer was concentrated under reduced pressure to get the crude product which was then purified by column chromatography with pet-ether/ ethylacetate (90:10) as eluents to afford the amino epoxide **54a** (0.189 g, 92%).

Yield: 190 mg, 92%, viscous liquid; $[\alpha]^{D}_{25}$: +2.51 (*c* 1.2, $CHCl_3$). **IR** ($CHCl_3$, cm^{-1}): υ_{max} 756, 1037, 1107, 1180, 1216, 1296, 1385, 1706, 2983, 3385; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.20-1.30 (m, 12H), 2.34-2.39 (m, 1H), 2.64-2.94 (m, 2H), 3.01-3.16 (m, 2H), 4.20-4.30 (m, 1H), 4.81-5.04 (m, 2H), 6.27 (brs, 1H), 7.17-7.32 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.7, 22.0, 35.7, 46.3, 52.7, 60.5, 69.7, 70.1, 126.6, 128.6, 128.7, 129.1, 137.6, 155.2, 156.2; **Analysis:** $C_{18}H_{26}N_2O_5$ requires C, 61.70; H, 7.48; N, 7.99; found C, 61.72; H, 7.58; N, 7.95%.

Section II

Enantioselelctive Synthesis of L-Carbidopa *via* D-Proline Catalyzed α-Amination of Branched Aldehyde

3.2.1 Introduction

The structural units of optically active α-hydrazino acid **57** and α-amino acid **58** (**Fig 5**) are of fundamental interest as they provide a direct route to preparation of a large variety of biologically significant compounds,[31] including the construction of nitrogen containing heterocycles.

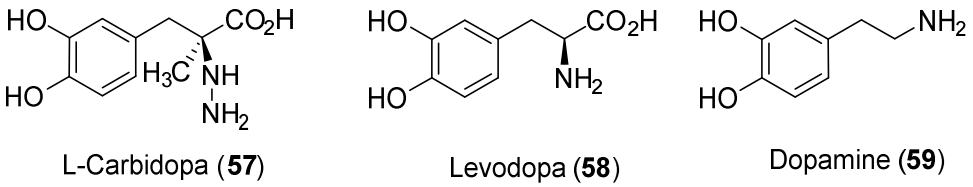


Fig. 5: Structures of L-carbidopa (**61**), Levodopa (**62**), and dopamine (**63**)

L-Carbidopa (**57**) and Levodopa (**58**) are typically used in combination to treat the symptoms of Parkinson's disease like *e.g.* shakiness, stiffness, difficulty moving, *etc*. It is characterized by death of dopaminergic neurons in the *Substantia nigra* of the brain. Parkinson's disease is thought to be caused by the depletion of a naturally occurring substance called dopamine **59** in the brain. Levodopa **58** changes into dopamine **59** in the brain, helping to control the symptoms of this disease.

3.2.2 Pharmacology of L-Carbidopa[32]

Parkinson's disease, caused by the low concentration of the neurotransmitter dopamine **59** in the brain, is the most common neurodegenerative illness. Traditionally, levodopa (L-DOPA), the biogenetic precursor of dopamine, has been used to temporarily diminish the disease's motor symptoms. This treatment, however, is found to be less efficient and produces side effects due to the drug undergoing decarboxylation to dopamine **59** at the peripheral regions. Thus, levodopa **58** is

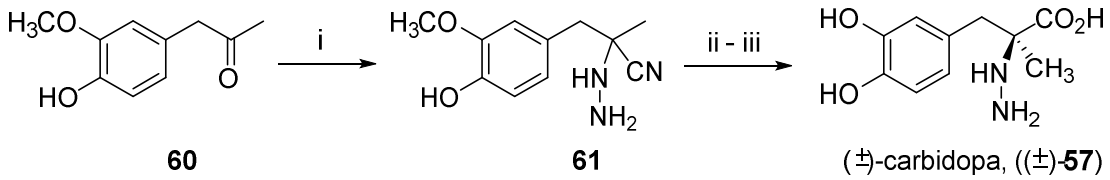
commonly administered in combination with L-carbidopa, an inhibitor of the peripheral aromatic L-amino acid decarboxylase (DDC),[33] an enzyme responsible for the metabolism of levodopa to dopamine. Thus, use of L-carbidopa helps increase the levodopa plasma half-life from 50 min to 1.5 h. Since the L-carbidopa cannot cross the blood brain barrier, only the DDC present in the peripheral region of nervous system is inhibited. This reduces the side effects caused by dopamine on the periphery, as well as increasing the concentration of L-DOPA and dopamine in the brain.

3.2.3 Review of Literature

Literature search reveals that there are only two reports available for the syntheses of L-carbidopa (**57**), which are described below.

Bollinger's Approach (1968)[34]

Bollinger *et al*. have reported the synthesis of (±)-carbidopa (**57**) using the Strecker reaction of ketone **60** with aqueous hydrazine and potassium cyanide to provide α-amino nitrile **61**. This was followed by acid hydrolysis and demethylation to give L-carbidopa (**57**) in 45% yield (**Scheme 18**).



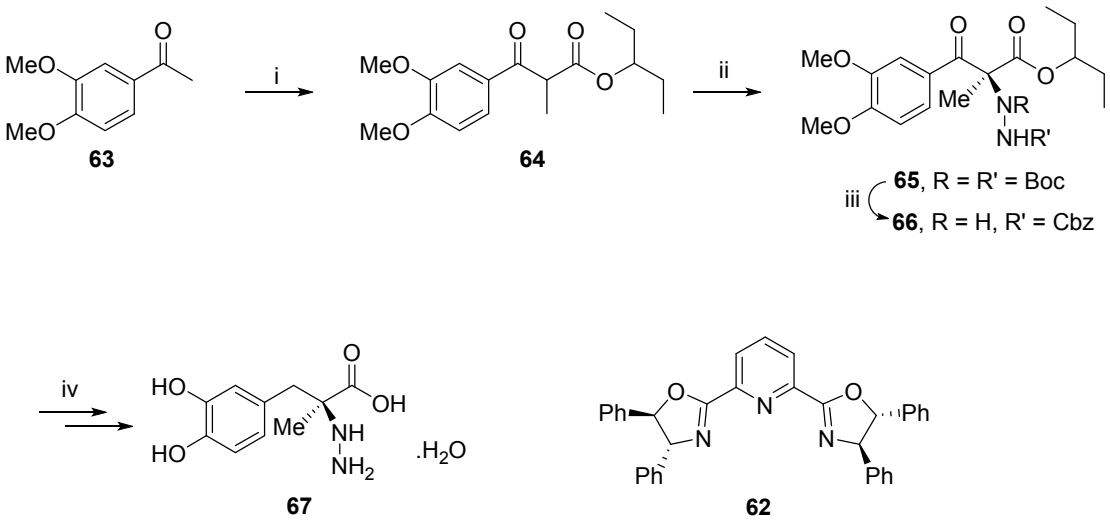
60 **61** (±)-carbidopa, ((±)-**57**)

Scheme 18: (i) NH_2NH_2, KCN, 4 h, 62%; (ii) con. HCl, -10-0 °C then 48% HBr, reflux, 3 h; (iii) $(C_2H_5)_2NH$, benzene, 0 °C, 3 d, 45 %.

Vallribera's approach (2013)[35]

Vallribera *et.al* have made use of enantioselective α-amination of β-ketoester **64** as the key step in the presence of catalytic europium triflate and chiral ligand **62** to obtain the α-aminated product **65**. Then the adduct **65** was deoxygenated by the use of

$Et(Me)_2SiH$/TFA following the removal of Boc-groups and protecting with Cbz-Cl provided the protected hydrazino ester **68**. Thus, carbidopa as its monohydrate (**67**) was finally achieved *via* global deprotection of **66** using BBr_3 in good yield with high enantioselectivity upto 98% ee (**Scheme 19**).



Scheme 19: (i) (a) dimethyl carbonate, NaH, THF, 5 h, reflux, 92%; (b) ZnO (20 mol%), 3-pentanol, toluene, reflux, 99%; (c) MeI, K_2CO_3, acetone, 40 °C, 24 h. (ii) BocN=NBoc, $Eu(OTf)_3$ (10 mol%), **62** (15 mol%), CH_3CN, -20 °C, 2 d, 95%. (iii) (a) trifluoroacetic acid. CH_2Cl_2, 25 °C; (b) CbzCl, $NaHCO_3$, THF, 25 °C, 30 min, 84%; (c) $Et(Me)_2SiH$, trifluoroacetic acid, CH_2Cl_2, 25 °C, 72%. (iv) BBr_3, CH_2Cl_2, -78 °C to 25 °C, 24 h; (b) MeOH, 50 °C, 12 h, 95%; (c) $(CH_3)_2NH$, pH=6.4.

3.2.4 Present Work

3.2.4.1 Objective

In literature, only two methods are available for the synthesis of L-carbidopa (**57**). One of the methods involves the racemic synthesis while other method employs the Eu (III) catalyzed enantioselective α-amination as a key step. However, there is no reports available using enamine catalysis concept with environmentally friendly proline catalytic system. Hence it is our interest to carry out asymmetric synthesis of L-carbidopa (**57**) using D-proline-catalyzed α-amination[21] of the corresponding α-methyl aldehyde **68** which is challenging and rare.[21d] The retrosynthetic analysis for L-carbidopa **57** shows that aldehyde **68** could be an important intermediate which can

be subjected to D-proline-catalyzed α-amination. Aldehyde **68** in turn can be synthesized from the corresponding unsaturated ester, **69 (Fig 6)**.

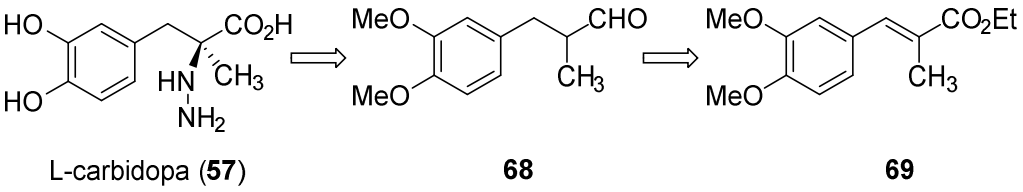
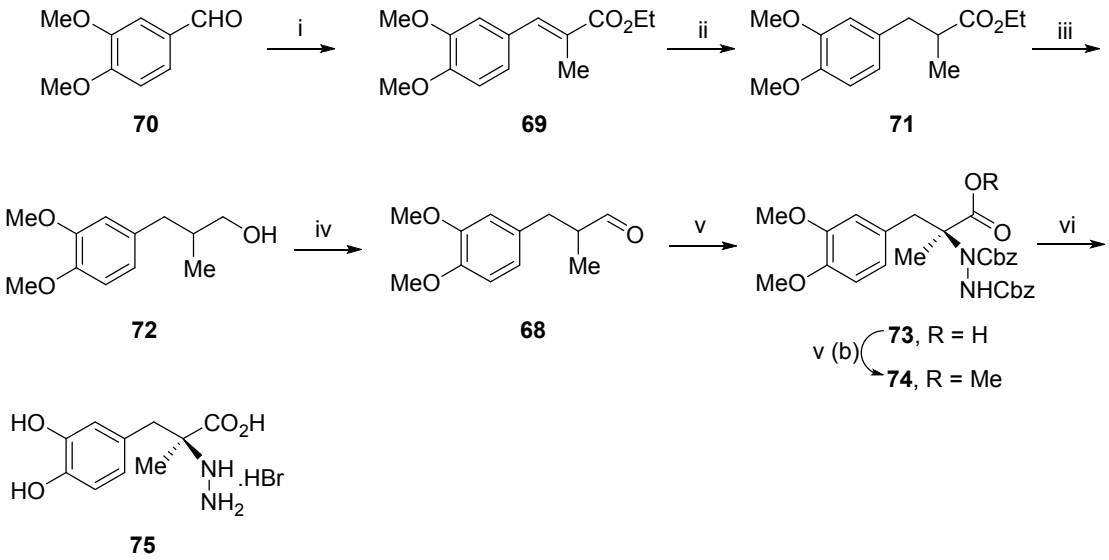


Fig. 6: Retrosynthetic analysis for L-carbidopa (**57**)

3.2.5 Results and Discussions:

We have envisaged D-proline catalyzed α-amination[21] of aldehyde **68** for the synthesis of (*S*)-carbidopa. HBr (**75**). The synthetic sequence is shown in **Scheme 20**.



Scheme 20: (i) (a) $(EtO)_2POCH(Me)CO_2Et$, LiCl, DBU, CH_3CN, 0 °C, to 25 °C, 15 h, 85%; (ii) cat. Pd/C, CH_3OH, H_2 (1 atm), 25 °C; (iii) $LiAlH_4$, THF, 25 °C, 3 h, 90% (over two steps); (iv) PCC, CH_2Cl_2, 25 °C, 3 h, 80%; (v) (a) DBAD, D-proline, CH_3CN, 10 °C, 2 d then $NaClO_2$, NaH_2PO_4, tBuOH/H_2O (5:1), 0 °C, 60 min; (b) MeI, $NaHCO_3$, DMF, 3 h, 25 °C, 67% (over two steps); (vi) BBr_3, CH_2Cl_2, 30 h, 0 °C to 25 °C, 65%.

The synthesis of carbidopa **57** started with Horner-Wardsworth-Emmons olefination reaction of 3,4-dimethoxybenzaldehyde **70** with ethyl 2-(diethoxyphosphoryl) -propanoate that furnished α,β-unsaturated ester **69** in 85% yield. The ^1H NMR spectrum of **69** showed characteristic singlets at δ 3.90 (s, 3H), 3.91 (s, 3H) and 7.61

(s, 1H) corresponding to two methoxy groups (O**C**$\mathbf{H_3}$) and an olefinic proton respectively. Its ^{13}C NMR spectrum displayed two typical carbon signals at δ 55.7 and 138.4 corresponding to methoxy carbon of O**C**H_3 and methine carbons of olefin respectively (**Fig. 7**).

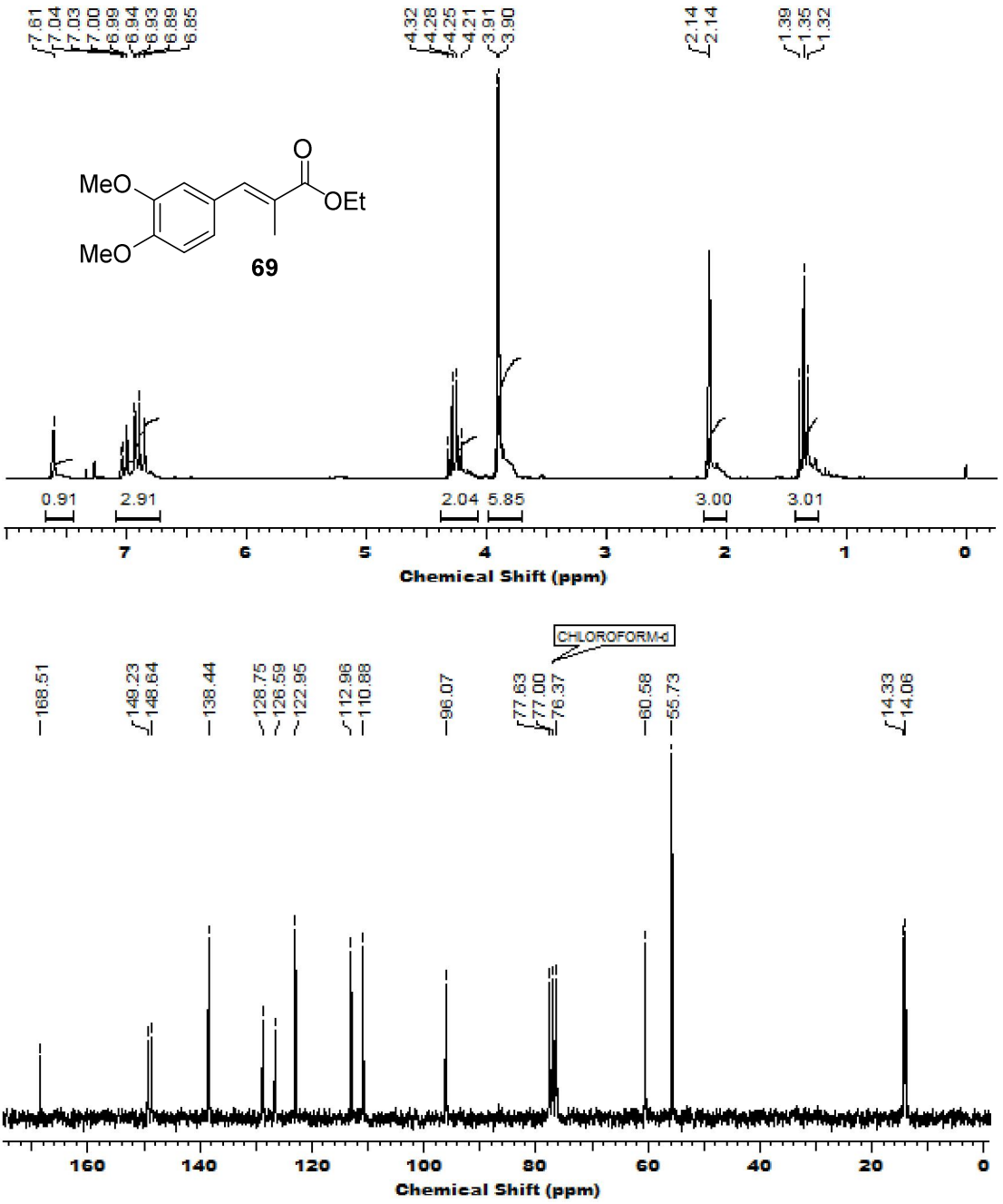


Fig. 7: ^{1}H and ^{13}C NMR spectra of ester **69**

The C=C bond in ester **69** was hydrogenated under catalytic conditions [(10% Pd/C, H_2 (1 atm)] and the resulting saturated ester was subjected to reduction with lithium

aluminium hydride to give alcohol **72** in 90% overall yield for two steps. Alcohol **72** was then oxidized with PCC in CH_2Cl_2 at room temperature to give the corresponding aldehyde **68** in 80% yield. The ^{1}H NMR spectrum of **68** showed characteristic doublet signals at δ 1.07 (d, J = 6.8 Hz, 3H) and δ 9.69 (d, J = 1.4 Hz, 1H) corresponding to

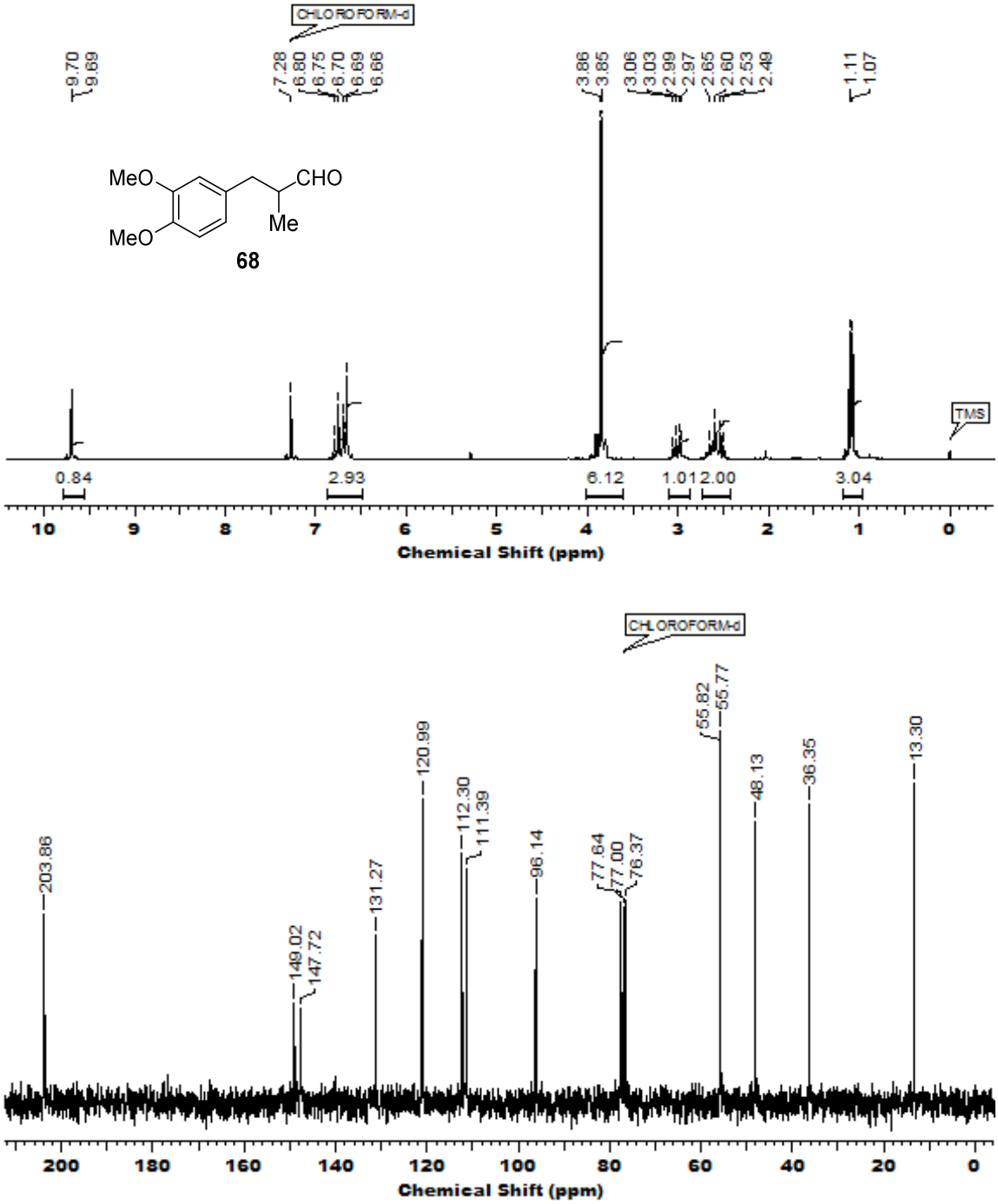


Fig. 8: ^{1}H and ^{13}C NMR spectra of aldehyde **68**

methyl protons and aldehydic proton respectively. Its ^{13}C NMR spectrum displayed typical signals at δ 13.3 and 203.9 confirming the presence of methyl and aldehydic carbons respectively (**Fig 8**).

Aldehyde **68** on D-proline catalyzed α-amination[21] with DBAD in CH_3CN at 10 °C for 2 days resulted in formation of α-aminated aldehyde which is followed by its *in situ* Pinnick-oxidation with $NaClO_2$ furnishing the α-hydrazino acid **72** in 82% crude yield. Then the treatment of crude α-hydrazino acid **72** with MeI, $NaHCO_3$ gave ester **74** in 67% overall yield for two steps. The ^1H NMR spectrum of **74** showed typical signals at δ 2.91 (d, J = 13.5 Hz, 1H), 3.23 (d, J = 13.5 Hz, 1H) and 5.87 (brs) corresponding to benzylic and **NH**Cbz protons respectively. Its ^{13}C NMR spectrum displayed two typical signals at δ 52.31 and 173.32 corresponding to methoxy carbon of ester and ester carbonyl carbon respectively. Its specific rotation was found to be $[\alpha]^{25}_D$ -76 (*c* 1, $CHCl_3$). Its mass spectrum with its molecular ion peak at *m/z* 559.37 confirmed the formation of ester **74** (**Fig. 9**).

The optical purity of ester **74** was found to be 74% ee determined from chiral HPLC analysis [Chiracel AD-H, *n*-hexane/*i*PrOH, 85:15, 0.5 mL/min) retention time 22.05 min (13%) and 26.2 min (87%)] (**Fig**.**10**). The low %ee may be due to the decrease in rate in the formation of less stable enamine from aldehyde **68** and D-proline leading to the formation of α-aminated product with low enantiomeric excess in longer reaction time.

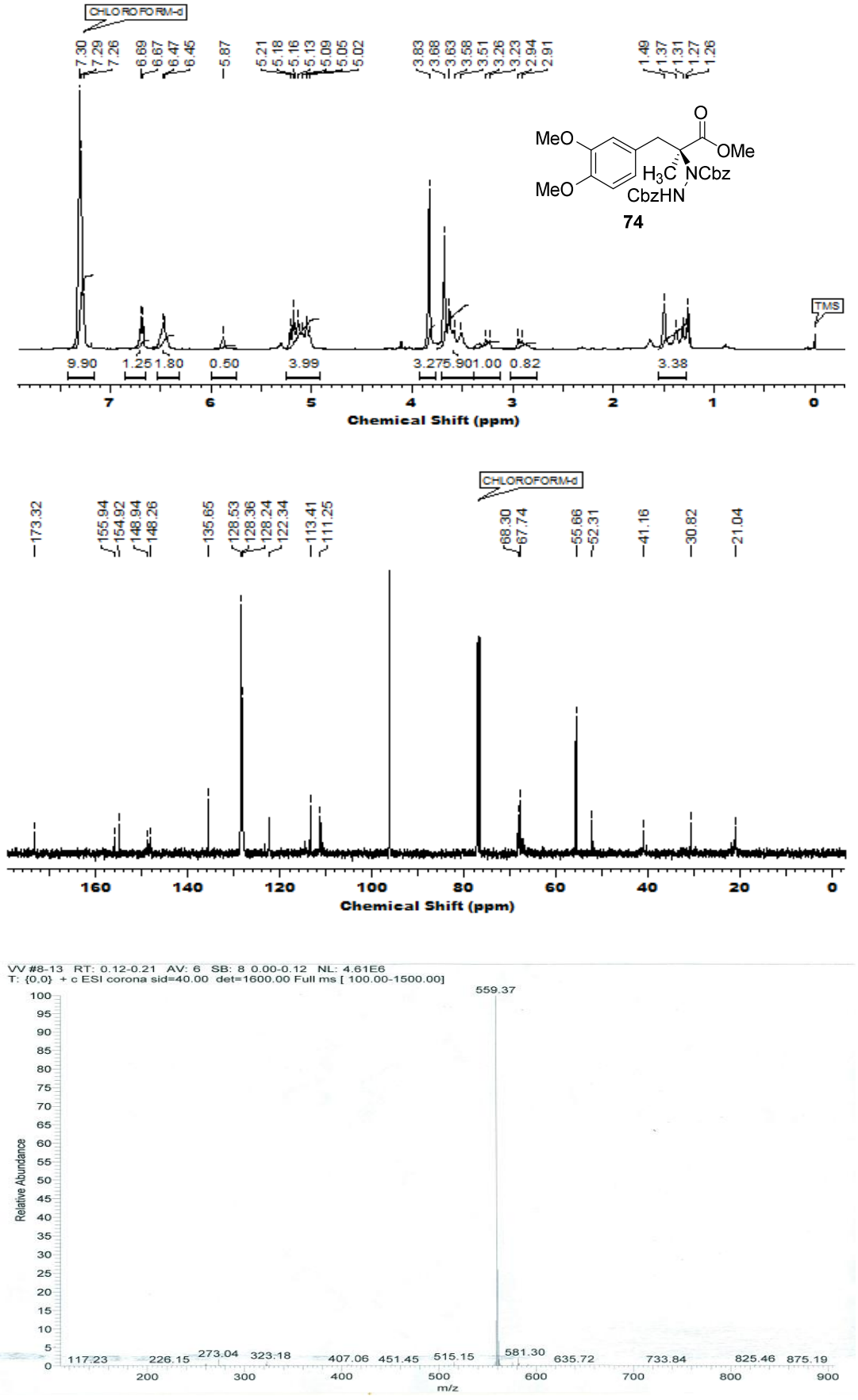
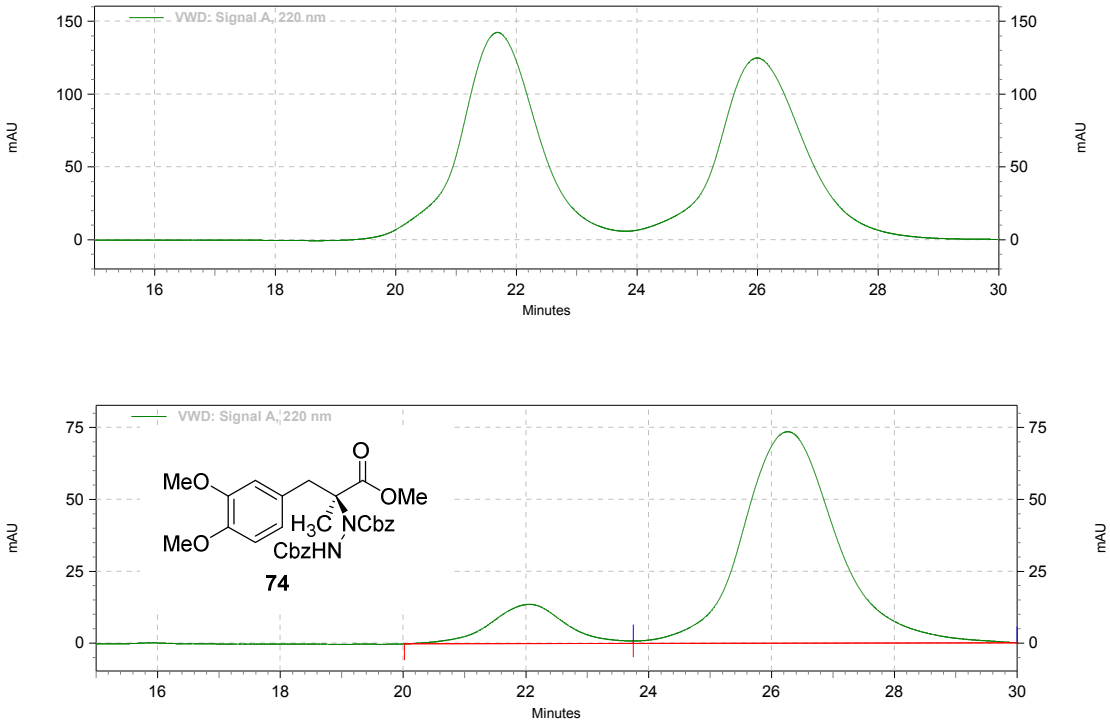


Fig. 9: ^{1}H and ^{13}C NMR and mass spectra of ester **74**



Retention Time	Area	Area %	Height	Height %
22.050	19359335	12.86	229426	15.68
26.257	131143548	87.14	1234100	84.32
Total	150502883	100.00	1463526	100.00

Fig 10: HPLC chromatogram of ester **74**

Finally, global demethylation of ester **74** with BBr_3 at 0-25 °C furnished L-carbidopa (**61**) as its hydrobromide **75** in 65% yield. The ^{1}H NMR spectrum of L-carbidopa hydrobromide **75** showed typical signals at δ 1.45 (s, 3H), 2.85 (d, J = 14.2 Hz, 1H), and 3.08 (d, J = 14.4 Hz, 1H) corresponding to the methyl protons at quaternary carbon and two benzylic protons respectively. Its ^{13}C NMR spectrum displayed the signals at δ 61.7 and 175.83 which confirmed the presence of quaternary and acid carbonyl carbons respectively (**Fig. 11**). Its specific rotation was found to be $[\alpha]^{25}_D$ -6.1 (*c* 0.8, MeOH) with optical purity of 74% ee.

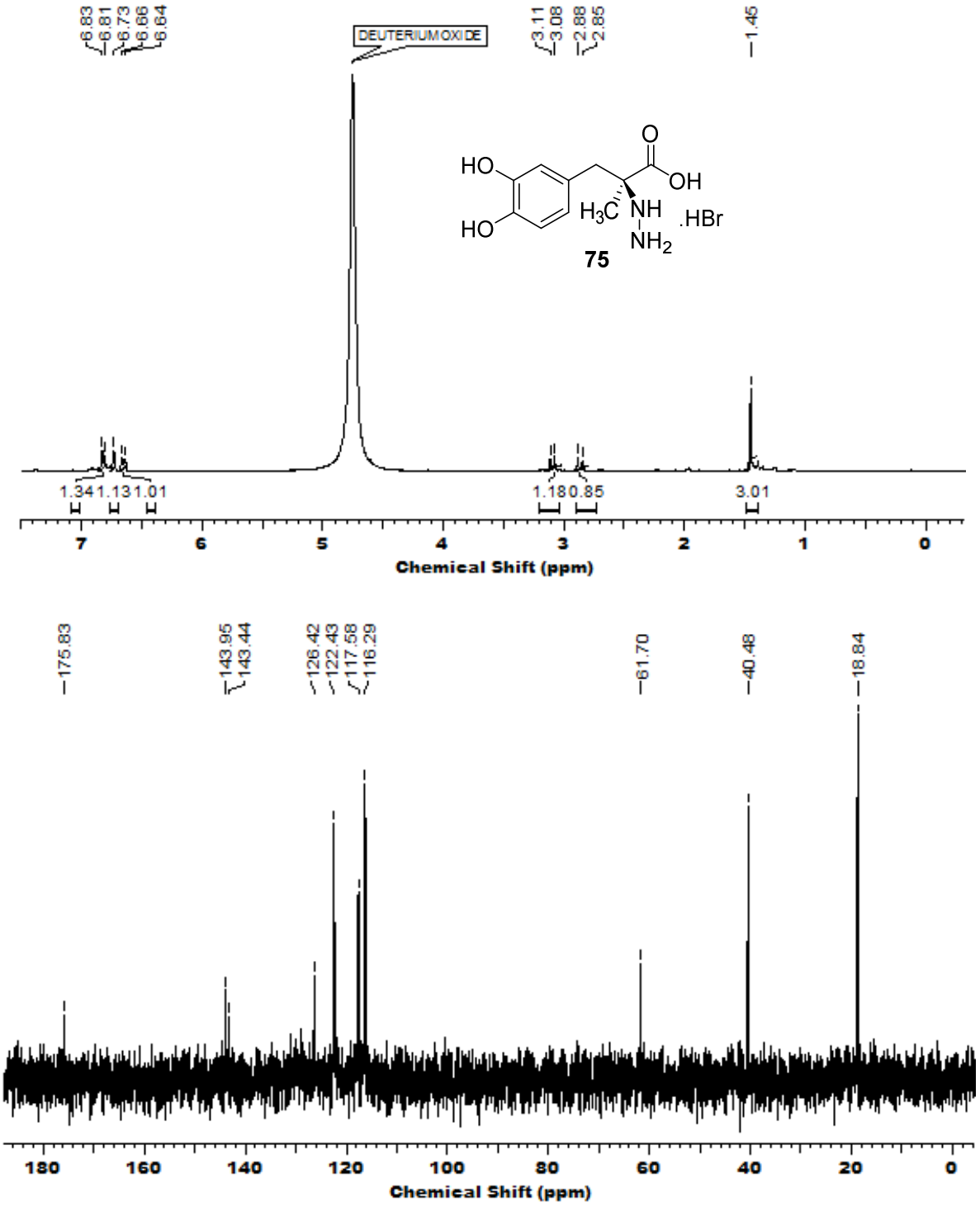


Fig. 11: ^{1}H and ^{13}C NMR spectra of L-carbidopa hydrobromide (**75**)

3.2.6 Conclusion

In conclusion, we have described a new synthesis of L-carbidopa hydrobromide (**75**) *via* D-proline-catalyzed α-amination approach. The overall yield of seven steps is

found to be 26% with 74% ee. The salient features of this strategy are operationally simple reactions, require a relatively low amount of an inexpensive and nontoxic D-proline as catalyst. Good yields, simple, environment-friendly procedures and easy availability of starting materials are some of the merits of this synthesis.

3.2.7 Experimental Section

Ethyl 3-(3,4-dimethoxyphenyl)-2-methylacrylate (69):

To a solution of 3,4-dimethoxybenzaldehyde **70** (6 g, 39.9 mmol) in CH_3CN (60 mL) at 0 °C was added $(EtO)_2POCH(Me)CO_2Et$ (8.4 mL , 44.8 mmol) in CH_3CN (80 mL) followed by addition of 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 NH_4Cl solution, extracted with ethyl acetate (3 × 50 mL), washed with brine and dried over anhydrous Na_2SO_4. After removal of solvents on rotavapour, the crude product was purified by flash chromatography; (Pet ether: EtOAc = 80:20) to give the pure compound **69**.

Yield: 8 g, 85%, Colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 2980, 2959, 2837, 2363, 1703, 1628, 1599, 1464, 1366, 1248, 1142, 1026, 945, 754; **^{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; **Analysis:** $C_{14}H_{18}O_4$ required C, 67.18; H, 7.25; found C, 67.02; H, 7.11%.

3-(3, 4-Dimethoxyphenyl)-2-methylpropan-1-ol (68):

To a solution of ester **69** (10 g, 40 mmol) in 50 mL methanol was added catalytic 10% Pd/C (0.8 g) in catalytic amounts. The reaction mixture was stirred for 12 h under H_2 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) for 3 h. The reaction was quenched with aq. NaOH (3 mL) and water (100 mL) followed by extraction with ethyl acetate (3 × 100 mL) gave the crude product. Purification of crude product by column chromatography gave pure alcohol **72**.

Yield: 7.14 g, 90%, gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3510, 3394, 2929, 2594, 2059, 1737, 1589, 1514, 1263, 1155, 1027, 860, 765; **^{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 16.2, 37.6, 39.00, 55.5, 67.0, 95.9, 111.0, 112.3, 120.8, 133.1, 146.9, 148.5; **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 (68):

To a solution of alcohol **72** (5 g, 23.8 mmol) in CH_2Cl_2 (39 mL) was added PCC (14 g, 36.0 mmol) and the reaction mixture was allowed to stir at 25 °C for 3 h (monitored by TLC), filtered through sintered funnel and solvents were removed on rotavapour and the crude product was purified by column chromatography to give aldehyde **68** in pure form.

Yield: 4 g, 80%, Colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3020, 2360, 1735, 1589, 1517, 1444, 1217, 1060, 1027, 756, 667; **^{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 13.1, 36.1, 47.9, 55.63, 95.9, 111.2, 112.1, 120.8, 131.1, 147.5, 148.8, 203.8.

Methyl-(*S*)-3-(3,4-dimethoxyphenyl)-2-(1,2-dibenzyloxycarbonylhydrazinyl)-2-methylpropionate (74):

To a solution of dibenzyl azodicarboxylate (DBAD) (3.1 g, 9.5 mmol) and D-proline (218 mg, 20 mol%) in CH_3CN (40 mL) at 10 °C, aldehyde **68** (3 g, 14.3 mmol) was added and the reaction mixture was stirred at 10 ^oC for 2 d (monitored by TLC). Then the reaction mixture was diluted with CH_3CN (75 mL) and a mixture of *t*BuOH/H_2O (5:1) was then added, followed by addition of NaH_2PO_4 (5 equiv), $NaClO_2$ (5 equiv) at 0 °C and the contents stirred for 2 h at 25 °C. Then the reaction mixture was acidified with 2M HCl and quenched with saturated solution of Na_2SO_3. After removal of solvents on rotavapour, the aqueous phase was extracted with ethyl acetate (3 × 20 mL) and combined organic layers washed with brine and dried over $MgSO_4$; then concentrated on rotavapour to obtain the crude carboxylic acid **73**. To the crude solution of carboxylic acid **73** in DMF, were added $NaHCO_3$ (1.5 equiv), and MeI (2.5 equiv) and the mixture stirred for 3 h at 25 °C. It was extracted with EtOAc and purified by flash chromatography (Pet ether: EtOAc = 85:15) to give the pure ester **74**.

Yield: 3.5 g, 67%, gum; 74% ee from **HPLC analysis**; Chiracel AD-H column (2-propanol:*n*-hexane = 15:85, flow rate 0.5 mL/min, λ = 220 nm). Retention time (min): 22.05 (minor) and 26.2 (major); $[\alpha]^{25}_D$ -76 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3311, 2985, 2951, 2837, 2255, 1728, 1608, 1590, 1518, 1400, 1348, 1143, 1046, 915, 734; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.45 (m, 3H), 2.91 (d, *J* = 13.5 Hz, 1H), 3.23 (d, *J* = 13.5 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* = 7.9 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; **LCMS (ESI, m/z)**: Calculated for $C_{29}H_{32}N_2NaO_8$ (M+Na) 559.21; found 559.37. **Analysis:** $C_{29}H_{32}N_2O_8$ required C, 64.91; H, 6.01; N, 5.22 found C, 64.55; H, 6.27, N, 5.17%.

(S)-3-(3,4-Dihydroxyphenyl)-2-hydrazinyl-2-methylpropanoicacid hydrobromide (L-carbidopa hydrobromide) (75):

To a solution of ester **74** (506 mg, 2 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C was added BBr_3 (2 mL, excess) and the mixture stirred for 2 h at the same temperature for 30 h at 25 °C. After completion of reaction, solvents were removed under reduced pressure and the crude product was purified by extraction with EtOAc and highly concentrated NaCl ionic solution to give the hydrobromide **75** in 60% yield as a brown solid.

Yield: 0.2 g, 65%; brown solid; **mp:** 201 ºC, (lit.[35] **mp**: 205 ºC); $[\alpha]^{25}_D$ -6.1 (*c* 0.8, MeOH), {lit[35] -7.5 (*c* 1, MeOH); **^{1}H NMR** (400 MHz, D_2O): δ 1.38 (s, 3 H), 2.80 (d, *J* = 14.2 Hz, 1H), 3.03 (d, *J* = 14.4 Hz, 1H), 6.59 (d, *J* = 8.07 Hz, 1H), 6.67 (br s, 1 H), 6.75 (d, *J* = 7.82 Hz, 1H); **^{13}C NMR** (100 MHz, D_2O): δ 18.8, 40.5, 61.7, 116.3, 117.6, 122.4, 126.4, 143.4, 143.9, 175.8; **Analysis:** $C_{10}H_{14}N_2O_4$ required C, 53.09; H, 6.24; N, 12.38 found C, 52.9; H, 6.10, N, 12.12%.

3.2.8. References

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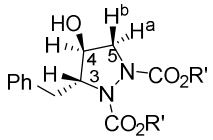
26 Refer experimental section (3.1.5) for general experimental procedure of Sequential α-amination/Corey-Chaykovsky reaction of aldehydes.

27 The relative stereochemistry of **55a (**R = *t*Bu**)** was confirmed by COSY and NOESY studies. A significant NOESY correlation was observed between H_{5a} and H_4. There was no observed correlation between H_3-H_4 confirming *anti* relationship between H_3 and H_4 (see **Fig. 5,** Section I of this chapter)



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CHAPTER 4

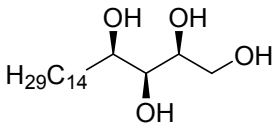
Enantioselective Synthesis of Guggultetrol and D-*ribo*- phytosphingosine Tetraacetate *via* L- Proline Catalyzed Sequential α- Aminooxylation/ Horner-Wardsworth- Emmons Olefination and Synthesis of *rac*-Clopidogrel *via* CO_2 Insertion

Section I

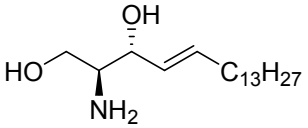
Asymmetric synthesis of guggultetrol and D-*ribo*-phytosphingosine tetraacetate using sequential α-aminooxylation/Horner-Wardsworth-olefination reaction of aldehyde

4.1.1. Introduction

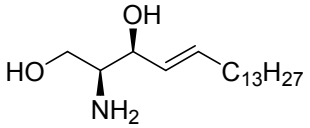
The asymmetric catalysis has emerged as one of the practical, cost effective and efficient methods for the synthesis of biologically active natural products containing multiple stereocenters. Tetrols, in particular, having contiguous stereogenic centers are useful intermediates in the synthesis of a number of biologically active compounds[1] such as phytosphingosines (**Fig. 1**).[2] For instance, guggultetrol (**1**), a naturally occurring lipid isolated from the gum-resin of the tree *Commiphoru mukul (guggul)*,[3] known in Ayurveda, the Indian traditional system of medicine, is used in the treatment of arthritis, inflammation, obesity and disorders of lipid metabolism,[4]



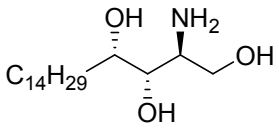
guggultetrol (**1**)



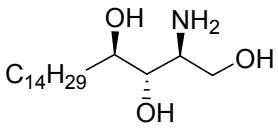
erythro- sphingosine (**2**)



threo- sphingosine (**3**)



lyxo-phytosphingosine (**4**)



D-*ribo*-phytosphingosine (**5**)

Fig. 1: Structures of guggultetrol (**1**), sphingosines (**2 - 3**) and phytosphingosines (**4 - 5**)

whereas sphingolipids such as ceramides, cerebrosides and gangliosides are ubiquitous components of cell membranes present in mammals, plants, fungi, yeast and in some prokaryotic organisms and viruses,[5] They play critical roles in many

physiological processes including cell growth, differentiation, neuronal repair, cell recognition, adhesion, and signalling.[6]

The most important sphingolipids are sphingosines (**2** and **3**) and phytosphingosines (**4** and **5**) which are generally made up of: a) lipophilic part with 18 or 20 carbon atoms and (b) hydrophilic part with 2-amino alcohol functionality as common structural features. Especially, sphingosines (**2** and **3**) possess a 4,5- *trans* double bond while phytosphingosines (**4** and **5**) are the corresponding saturated compounds. The hydrophilic moiety, located on the external surface of the membrane, determines the specificity of interactions, whereas the lipophilic portion, anchored on the outer-leaflet, contributes primarily to the structural rigidity of the membrane.

4.1.2.1 Pharmacology of guggultetrol

The use of plants in the treatment of disease occupies an important place in Ayurveda, the traditional medicine of India. The *Sushruta Samhita* (600 B.C.), a well-known Ayurvedic medical text, describes the usefulness of the gum resin from the tree *Commiphora mukul* in the treatment of a number of ailments, including obesity and disorders of lipid metabolism.[4] *Commiphora mukul* is a member of the *Burseraceae* family and is found in arid areas of India, Bangladesh, and Pakistan.[4] On incision, the plant exudes a yellowish gum-resin, which rapidly solidifies to an agglomerate of tears or stalactitic pieces. This product, called 'guggulu' in Sanskrit, is valued in Ayurveda, for the treatment of several diseases, especially rheumatoid arthritis and lipid disorders. Guggultetrol (**1**) was isolated from guggulu after saponification of its ethyl acetate extract.

4.1.2.2 Pharmacology of phytosphingosines

Phytosphingosines are first detected in fungi, plants, marine organisms, mammalin tissues like kidneys, liver, intestine, etc. They show important biological activities

e.g., antitumor, antiviral, antifungal or cytotoxic properties. Over the past decade, significant strides have been made in the elucidation of biological function of sphingolipids. One of the remarkable findings is the identification of sphingolipid metabolites as second messengers, which provides the basis for the emerging concept of sphingolipid metabolites as therapeutics with clinical potential.[7] In particular, D-*ribo*-phytosphingosine regulates the cellular growth and heat stress response of yeast.

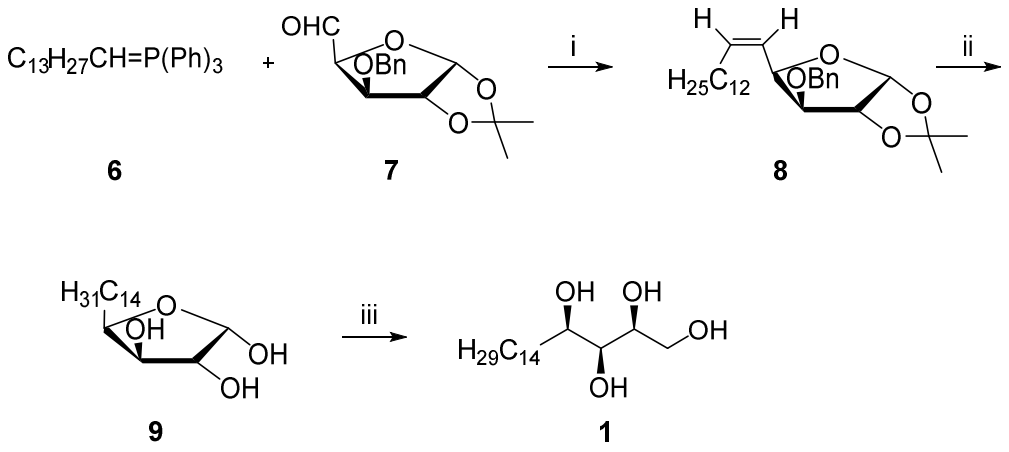
4.1.3 Review of Literature

a) Review of Literature of Guggultetrol

Literature search revealed that there are only few reports[8-11] available for the synthesis of guggultetrol (**1**), all of which utilized chiral pool resources for its asymmetric synthesis.

Kjaer's approach (1986)[8]

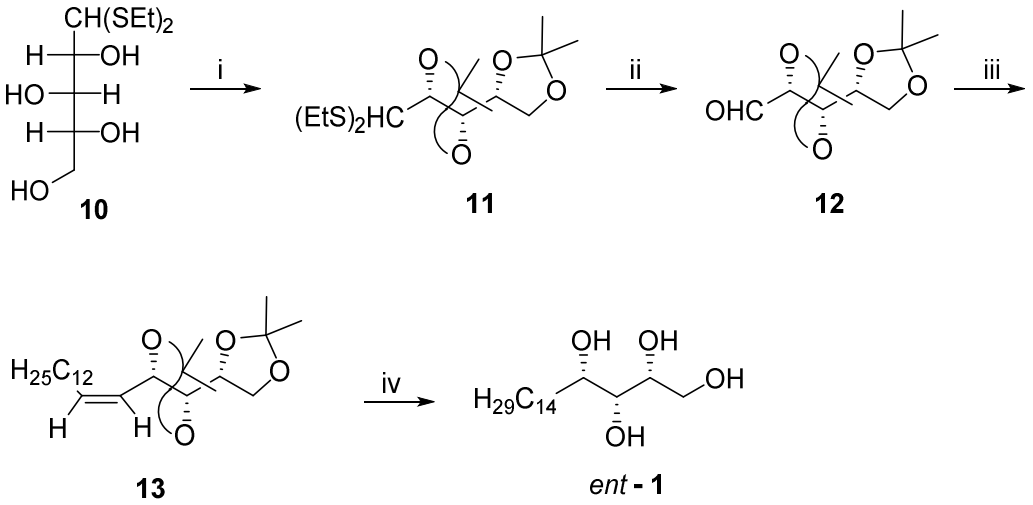
Kjaer *et al.* have achieved the synthesis of guggultetrol (**1**) starting from aldehyde **7** which was subjected to Wittig olefination with ylide **6** in THF and DMSO to give the *Z*-olefin **8**. The olefin **8** was then subjected to catalytic hydrogenation over Pd/C followed by acid hydrolysis to afford triol **9**. The furanoside derivative **9** was then converted to guggultetrol (**1**) on treatment with $NaBH_4$ in EtOH (**Scheme 1**).



Scheme 1: (i) THF, DMSO, 74%; (ii) (a) H_2 (1 atm), 10% Pd/C, EtOH; (b) $HClO_4$, dioxane/H_2O, 69%; (iii) $NaBH_4$, EtOH, 86%.

Sukh Dev's approach (1987)[9]

Sukh Dev *et al.* have described the synthesis of the enantiomer of guggultetrol (**1**) commencing from D-xylose diethyldithioacetal **10**, which was protected as its diacetonide **11** on exposure to acetone in presence of catalytic amounts of $FeCl_3$ in 85% yield. Treatment of diacetonide **11** with mercuric chloride and cadmium carbonate gave the aldehyde **12**, which was subjected to Wittig olefination using tridecyltriphenylphosphonium bromide to afford the *Z*-olefin **13** in 60% yield. Catalytic hydrogenation of the *Z*-olefin **13** followed by acidification provided the enantiomer of guggultetrol (**1**) in quantitative yield (**Scheme 2**).

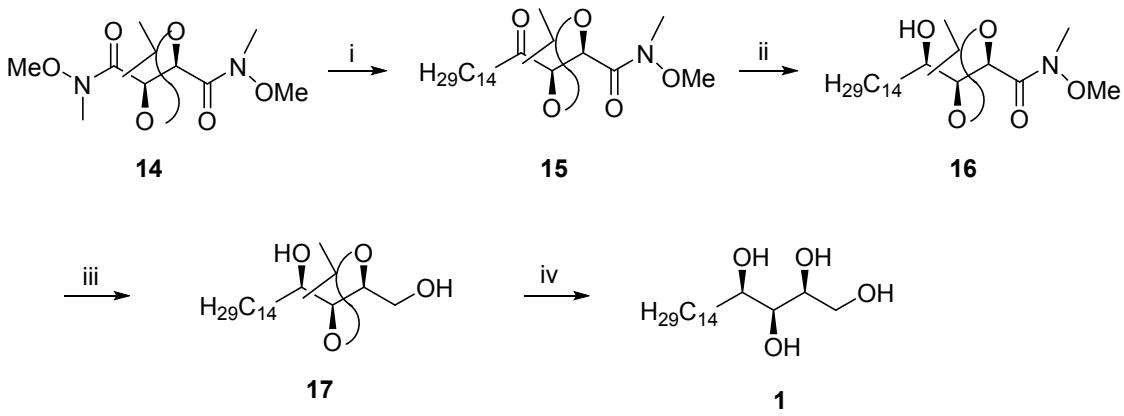


Scheme 2: (i) acetone, $FeCl_3$, 85%; (ii) $HgCl_2$, $CdCO_3$, CH_3CN/H_2O, 70%; (iii) $C_{13}H_{27}PPh_3Br$, PhLi, THF, 60%; (iv) (a) 10% Pd/C, H_2 (1 atm), EtOH; (b) $HClO_4$, dioxane/H_2O, 100%.

Prasad's approach (2007)[10]

Prasad *et al.* have reported the synthesis of guggultetrol (**1**) by the Grignard addition of pentadecanylmagnesium bromide to *bis*-amide **14** derived from L-(+)-tartaric acid. Reduction of ketoamide **15** with K-selectride provided single diastereomer of alcohol **16** in 98% yield. Alcohol **16** was then converted to guggultetrol (**1**) by the reduction

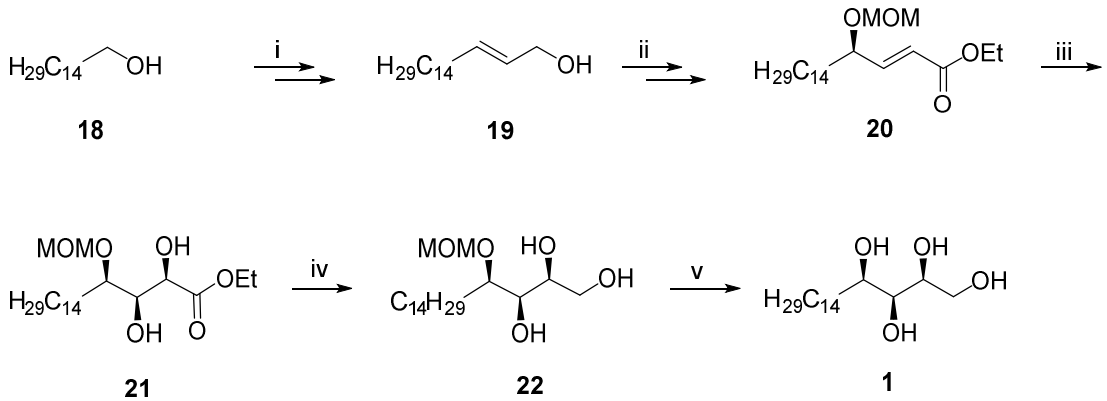
of amide **16** with $NaBH_4$ followed by deprotection of acetonide using $FeCl_3.6H_2O$ (**Scheme 3**).



Scheme 3: (i) $C_{14}H_{29}MgBr$, THF, -15 °C, 0.5 h; (ii) K-selectride, THF, -78 °C, 2 h, 98%; (iii) $NaBH_4$, MeOH, 0 °C to 25 °C, 2 h, 96%; (iv) $FeCl_3.6H_2O$, CH_2Cl_2, 25 °C, 10 min, 71%.

Sudalai's approach (2010)[11]

Sudalai *et. al* have made use of Sharpless asymmetric epoxidation and Sharpless asymmetric dihydroxylation as the key chiral inducing steps for the synthesis of dihydroxy ester intermediate **21**. Finally, dihydroxy ester intermediate **21** was converted to guggultetrol **1** by the reduction of ester **21** with lithium aluminium hydride followed by deprotection of MOM ether using 2M HCl solution (**Scheme 4**).



Scheme 4: (i) (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C to 25 °C, 1 h; (b) PPh_3=$CHCO_2Et$, benzene, reflux, 12 h, 90%; (c) DIBALH, CH_2Cl_2, -78 °C, 2 h, 96%; (ii) (a) (-)-DET, $Ti(O^iPr)_4$, TBHP, CH_2Cl_2, -20 °C, 24 h, 89%, 98%ee; (b) I_2, PPh_3, imidazole, ether/acetonitrile (3:1), 0 °C, 1 h, 83%; (c) Zn, NaI, MeOH,

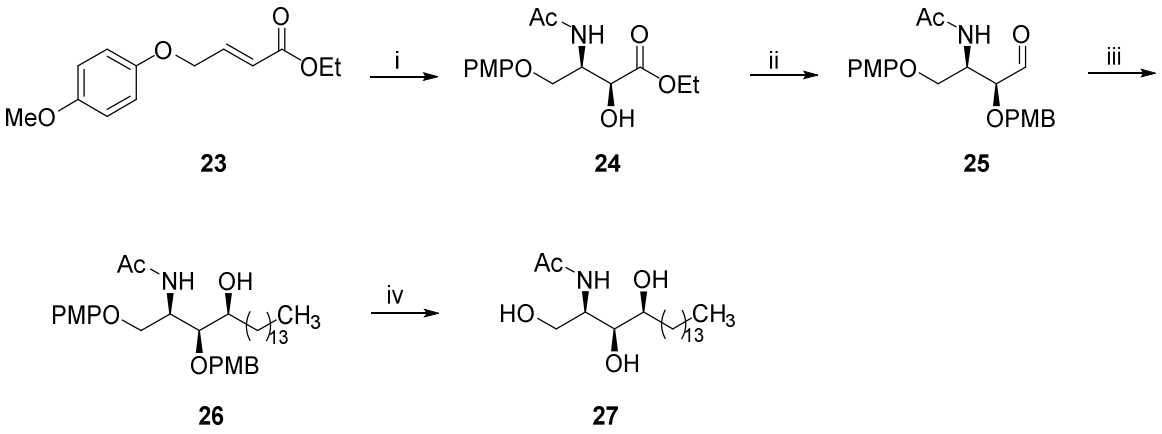
reflux, 6 h, 80%; (d) MOMCl, DIPEA, CH_2Cl_2, 0 °C to 25 °C, 12 h, 91%; (e) OsO_4, 50% aq. NMO, acetone:H_2O (9:1), 25 °C, 12 h; then $NaIO_4$, CH_2Cl_2, 25 °C, 10 min; (f) $Ph_3P{=}CHCO_2Et$, benzene, 50 °C, 1 h, 90%; (iii) $(DHQD)_2PHAL$, K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, *t*-BuOH/ H_2O (1:1), $K_2OsO_2(OH)_4$ (0.2 mol %), 0 °C, 5 h, 86%; (iv) $LiAlH_4$, THF, 0 °C to 25 °C, 5 h, 86%; (v) con. HCl, MeOH, 25 °C, 4 h, 78%.

a) Review of Literature of Phytosphingosines:

Literature survey revealed that there are many reports[12-18] available on the synthesis of various phytosphingosines due to the wide spectrum of their biological activity. Some of the recent methods are described below.

Han's approach (2004)[13]

Han *et.al* have reported the synthesis of *N*-acetyl-L-*xylo*-phytosphingosine (**27**) using regioselective asymmetric aminohydroxylation of α, β-unsaturated ester **23** to give the *syn*-β-amino-α-hydroxy ester **24**. Ester **24** was subjected to reduction using DIBAL-H that afforded aldehyde **25**. Reaction of aldehyde **25** with the slow addition of Grignard reagent provided the alcohol **26** with >10:1 diastereoselectivity; further PMB



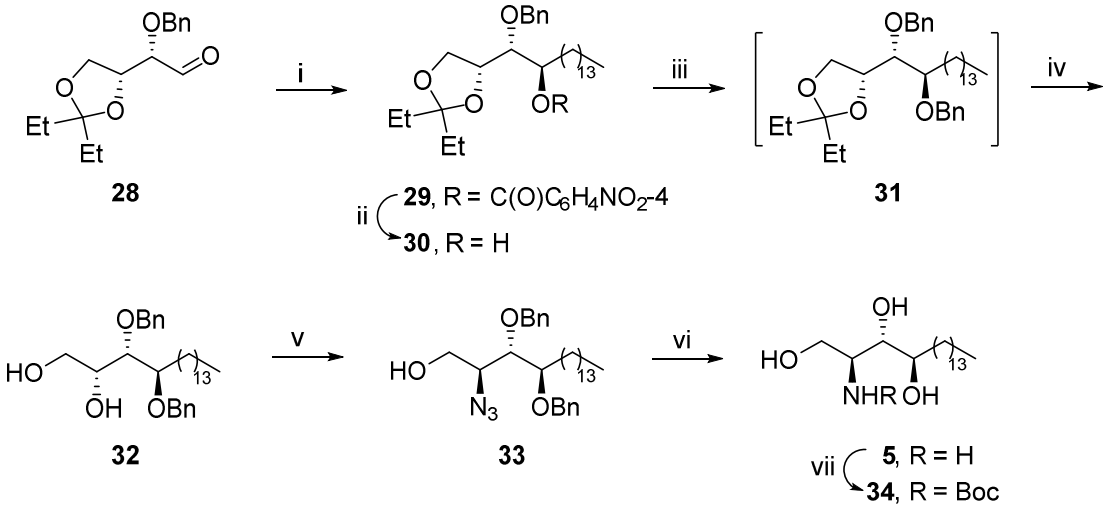
23 **24** **25** **26** **27**

Scheme 5: (i) $K_2OsO_2(OH)_4$, $(DHQD)_2PHAL$, LiOH, AcNHBr, t-BuOH–H_2O 2:1, 4 °C, 70%; (ii) (a) NaH, PMBCl, DMF, 0 °C, 80%; (b) DIBAL-H, CH_2Cl_2, -78 °C, 60%; (iii) $C_{14}H_{29}MgBr$, THF, 30 °C, 1 h then 25 °C, 2h, 88%; (iv) CAN, MeCN–H_2O 4:1, 0 - 25 °C, 75%.

deprotection of alcohol **26** with ceric (IV) ammonium nitrate produced *N*-acetyl-L-*xylo*-phytosphingosine **27** (**Scheme 5**).

Bittman's approach (2005)[14]

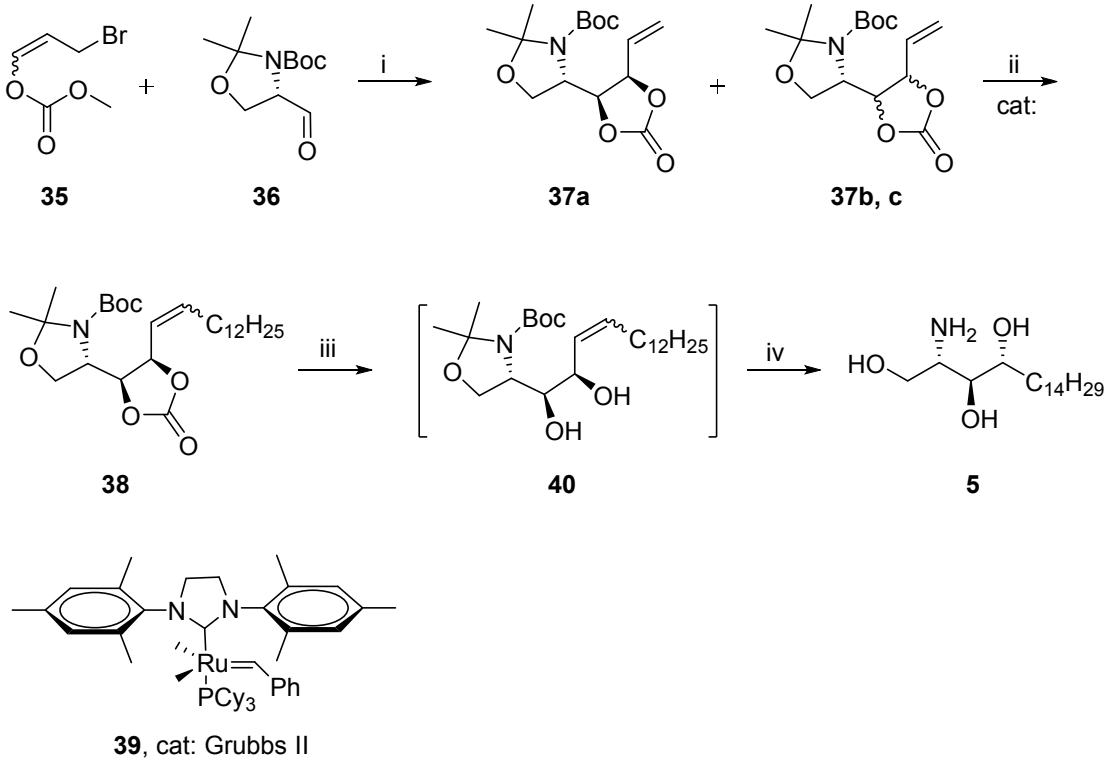
Bittman *et. al.* have made use of chelate controlled Grignard addition on aldehyde **28** derived from D-tartaric acid followed by subsequent Mitsunobu reaction on formed alcohol provided the benzoate ester **29**. Hydrolysis of benzoate ester **29**, benzyl protection with benzyl bromide and deprotection of acetonide using H_2SO_4 gave the diol **32**. Reaction of secondary hydroxyl group in diol **32** on Mitsunobu reaction, with NaN_3 as nucleophile, furnished the azido alcohol **33**. Finally, reduction of azide followed by deprotection of benzyl group in azido alcohol **33** provided the D-*ribo*-phytosphingosine **5,** which is isolated as *N*-Boc- D-*ribo*-phytosphingosine **34** (**Scheme 6**).



Scheme 6: (i) (a) $C_{14}H_{29}Br$, Mg, $BrCH_2CH_2Br$, Et_2O, 0 °C, 3 h, 75% (dr = 9:1); (b) DIAD, PPh_3, p-nitrobenzoic acid, CH_2Cl_2, 25 °C, 86%; (ii) NaOMe, MeOH, 93%; (iii) BnBr, NaH, THF, 25 °C; (iv) 5% H_2SO_4, MeOH, 82%; (v) (a) PPh_3, DIAD, CH_2Cl_2, 0 °C, (b) $TMSN_3$, 0 - 25 °C, 61%; (c) TBAF, THF; (vi) $Pd(OH)_2/C$, H_2 (1 atm), MeOH; (vii) Boc_2O, Et_3N, dioxane/H_2O, 25 °C, 78%.

Lombardo's approach (2006)[15]

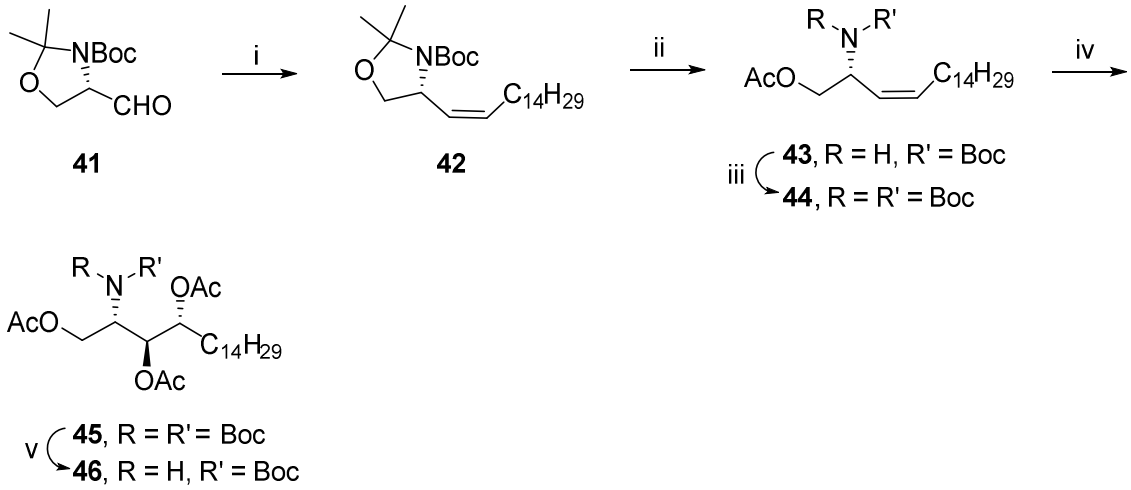
Lombardo *et. al* have described an efficient strategy for the synthesis of D-*ribo*-phytosphingosine **5** by employing α-hydroxyallylation as the key reaction. Thus, Garner aldehyde **36** was subjected to α-hydroxyallylation with 3-bromopropenylmethylcarbonate to afford the cyclic carbonates **37a-c** in 98% overall yield (dr = 91:7:2). Cross metathesis reaction of olefin in cyclic carbonate **37a** with 1-tetradecene using Grubbs 2nd generation catalyst **39** under the microwave condition afforded the long chain alkene **38** in 93% yield. The cleavage of cyclic carbonate in **38**, followed by hydrogenation of olefin in **40** and finally deprotection of Boc group afforded the D-*ribo*-phytosphingosine **5**, in 92% yield (**Scheme 7**).



Scheme 7: (i) In(0), DMF, 0 - 25 °C, 4 h, 98% (dr = 91:7:2); (ii) Grubbs 2nd generation catalyst (3.5 mol%), MW, 90 °C, 15 min, E/Z = 80:20, 93%; (iii) K_2CO_3, CH_3OH/H_2O (4:1), 40 °C, 2 h, 92%; (iv) a) H_2 (1 atm), 10% Pd/C, MeOH, 25 °C, 3 h, then CF_3CO_2H/H_2O, 25 °C, 2 h, 92%.

Kim's approach (2007)[16]

Kim *et. al* have made use of *anti*-selective dihydroxylation of *Z*-olefin **44** as the key step for the synthesis of D-*ribo*-phytosphingosine tetraacetate **46**. Thus, Wittig olefination of Garner aldehyde **41** with phosphonium salt ($Ph_3P^+C_{15}H_{31}Br^-$) furnished the *Z*-olefin **42** with *Z/E* ratio of 16:1. The selective removal of acetonide group in *Z*-olefin **42** under mild acidic condition followed by protection of primary alcohol *via* acylation provided acetate **43**. Further Boc protection of NHBoc present in acetate **43** gave *N, N*-diBoc protected olefin **44**. Then olefin **44** was dihydroxylated and the product diacetylated to yield triacetate **45**. Then removal of diBoc group followed by acylation delivered D-*ribo*-phytosphingosine tetracetate **46** (**Scheme 8**).

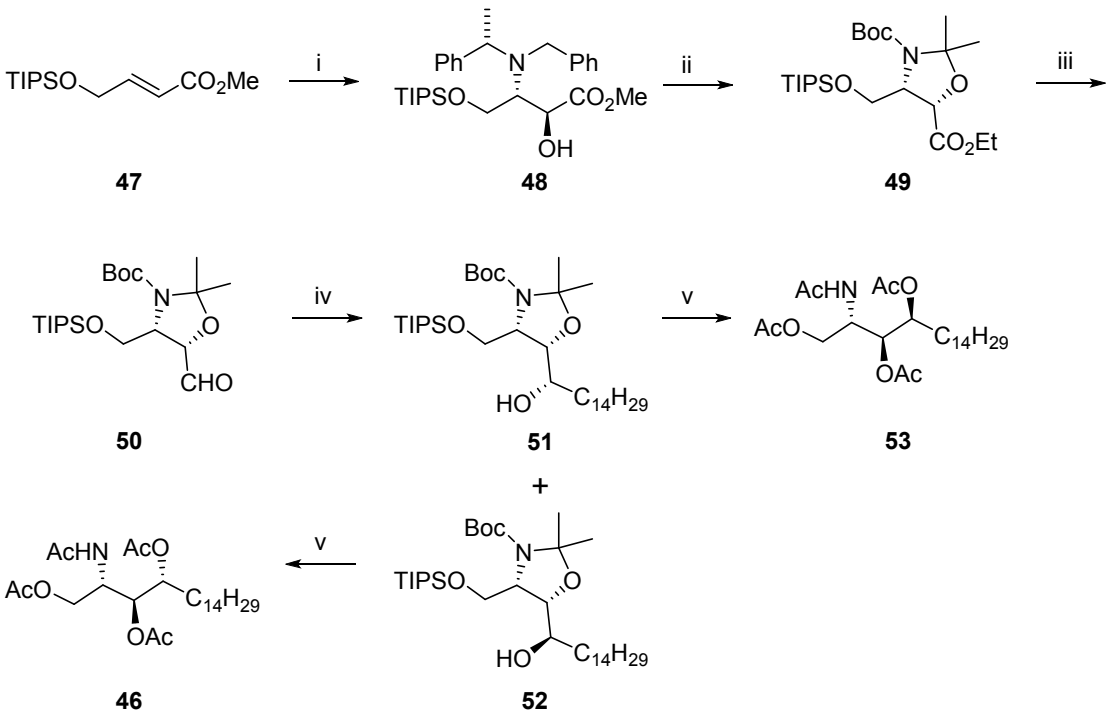


Scheme 8: (i) $Ph_3P^+C_{15}H_{31}Br^-$, KHMDS, -78 °C, 83%, *Z/E* = 16:1; (ii) a) Dowex 50Wx4-100 (H^+ form); b) Ac_2O, Et_3N, DMAP, 25 °C, 94%; (iii) Boc_2O, Et_3N, DMAP, 96%; (iv) a) OsO_4, NMO, CH_2Cl_2, 18 h, 25 °C, 80%, dr = 20:1; b) Ac_2O, Et_3N, DMAP, 25 °C; (v) a) HCl in MeOH; b) Ac_2O, Et_3N, DMAP, 25 °C.

Davies approach (2008)[17]

Davies *et. al* have reported the synthesis of D-*lyso*- and D-*ribo*-phytosphingosines (**4** and **5**) using 1,4-conjugate addition on γ-tri-isopropylsilyloxy-α, β-unsaturated ester **47** as the key step. The enolate formed *in situ* was oxidized with (1*S*)-(+)-(10-

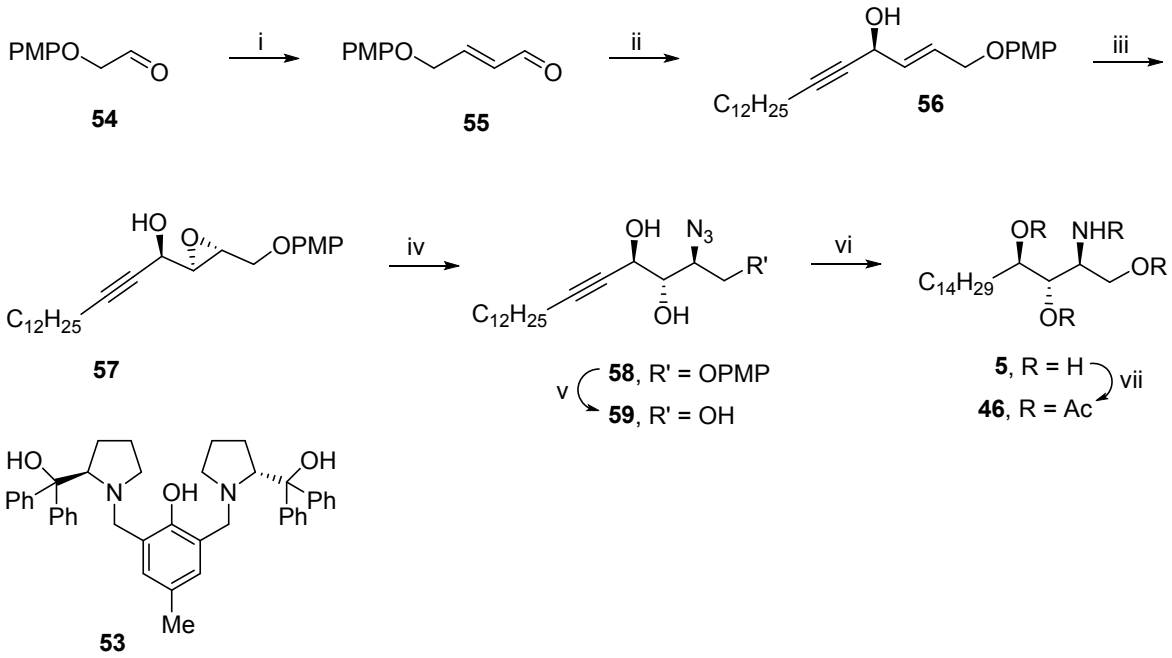
camphorsulfonyl)oxaziridine [*i.e.* (+)-CSO] to give the α-hydroxy-β-amino ester **48**. Protecting froup manipulation of α-hydroxy-β-amino ester **48**, which was converted to oxazolidine ester **49**. Further, DIBAL-H reduction of oxazolidine ester **49** followed by IBX oxidation of alcohol provided the aldehyde **50**. Aldehyde **50** was treated with a solution of tetradecylmagnesium bromide in THF to form alcohols **51**, **52** in 51 and 4% yield respectively with diastereomeric ratio of 90:10. The global deprotection of protecting groups in alcohols **51** and **52** followed by subsequent acetylation of amino triols furnished D-*lyso*- and D-*ribo*-phytosphingosines as their tetraacetates (**53** and **46**) respectively (**Scheme 9**).



Scheme 9: (i) lithium (S)-N-benzyl-N-(methylbenzyl)amide, THF, −78 °C, 2 h, then (+)-CSO, −78 °C to 25 °C, 12 h, 75%, >98% de; (ii) (a) H_2 (5 atm), $Pd(OH)_2/C$, Boc_2O, EtOAc, 25 °C, 12 h, 94%; (b) 2,2-dimethoxypropane, $BF_3 \cdot Et_2O$, acetone, reflux, 12 h, 75%; (iii) (a) DIBAL-H, CH_2Cl_2, 0 °C, 6 h, 98%; (b) IBX, DMSO, 25 °C, 12 h, quant.; (iv) $C_{14}H_{29}MgBr$, THF, 0 °C to 25 °C, 6 h, 56%, dr = 9:1; (ii) aq. 3M HCl, MeOH, 50 °C, 3 h, then Ac_2O, DMAP, pyridine, 25 °C, 12 h, 75% for both the phytosphingosines.

Bittman's approach (2010)[18]

Bittmann's approach was based on the stereoselective alkynylation of enal **55** using the complex formed from (R, R)- ProPhenol **53** as a ligand. Thus allylic propargylic alcohol **56** was subjected to Sharpless asymmetric epoxidation to give the desired propargylic epoxy alcohol **57**. The regioselelctive ring opening of epoxy alcohol **57** by NaN_3/NH_4Cl provided the azido diol **58**. Further, deprotection of PMP using CAN followed by catalytic hydrogenation of azido triol afforded the D-*ribo*-phytosphingosine **5** which was isolated as its tetraacetate **46** on treatment with acetic anhydride.



Scheme 10: (i) (a) $(EtO)_2POCH_2CO_2Et$, K_2CO_3, *i*PrOH/H_2O, 0 °C, 1h, 86%, E/Z = 20:1; (b) $LiAlH_4$, *n*-BuBr, 0 °C, THF, 2 h, 88%; (c) PCC, CH_2Cl_2, MS 4A°, 58%; (ii) 1-tetradecyne, Me_2Zn, (R, R)-ProPhenol (10 mol%), PhMe, 4 °C, 4 d, 86%, 60% ee; (iii) (-)-DIPT, $Ti(O\text{-}iPr)_4$, $PhCMe_2OOH$, MS 4A°, CH_2Cl_2, 75%, 93% de; (iv) NaN_3, NH_4Cl, MeOH/H_2O (8:1), 60 °C, 48 h, 61%; (v) CAN, CH_3CN/H_2O (4:1), 25 °C, 1h; (vi) H_2, $Pd(OH)_2/C$, MeOH, 25 °C, 63%; (vii) Ac_2O, DMAP, pyridine, 25 °C, 12 h, 94%.

4.1.4 Present Work

4.1.4.1 Objective

Acyclic vicinal diols are occasionally encountered as part of many biologically active natural products. Guggultetrol (**1**), a long-chain linear aliphatic tetrol with contiguous stereogenic centers, was isolated by Sukh Dev *et al.* in 1973[3] and is used in the treatment of arthritis, inflammation, obesity and disorders of lipid metabolism in Ayurveda. In spite of its interesting biological activity, there are not many reports available in literature for its asymmetric synthesis and most of the reported syntheses utilized chiral pool approach for establishing the chiral centers. Moreover, D-*ribo*-phytosphingosine **5** and its stereoisomers are attractive synthetic targets for many organic chemists[13-18] due to the highly biological activities such as regulation of cellular growth, anti-tumour, antiviral, cytotoxic properties, etc.[5,6] Hence, most of the methods reported for its synthesis involves the chiral pool starting materials and low stereoselective induction using the chiral ligand. In this context, this section describes a more practical method for the asymmetric synthesis of guggultetrol (**1**) and D-*ribo*-phytosphingosine **5**, starting from readily available linear aldehyde **61** using proline catalyzed α-aminooxylation *via* enamine catalysis as the key chiral inducing step, which is highly desirable.

Retrosynthetic analysis for guggultetrol (**1**) and D-*ribo*-phytosphingosine (**5)** reveals that the target molecules can be synthesized from the common intermediate γ-hydroxy-α,β-unsaturated ester **62**, which in turn can be synthesized from α-aminooxylation of 1-hexadecanal **61** (**Fig. 2**).

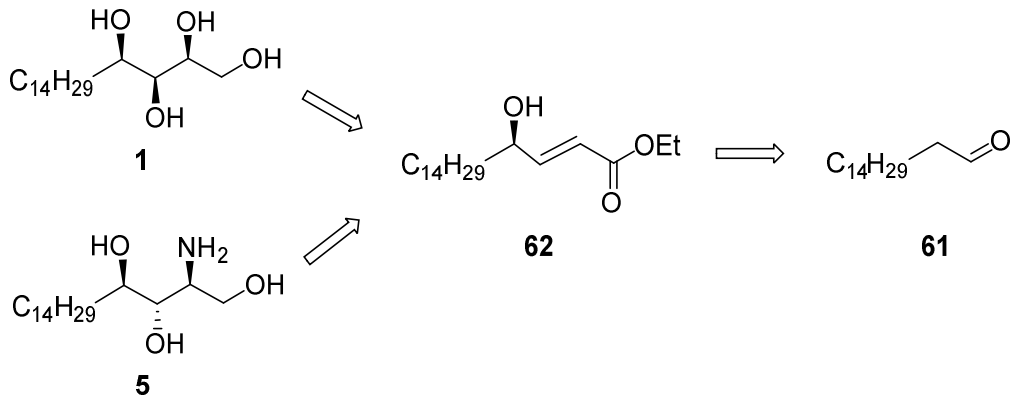


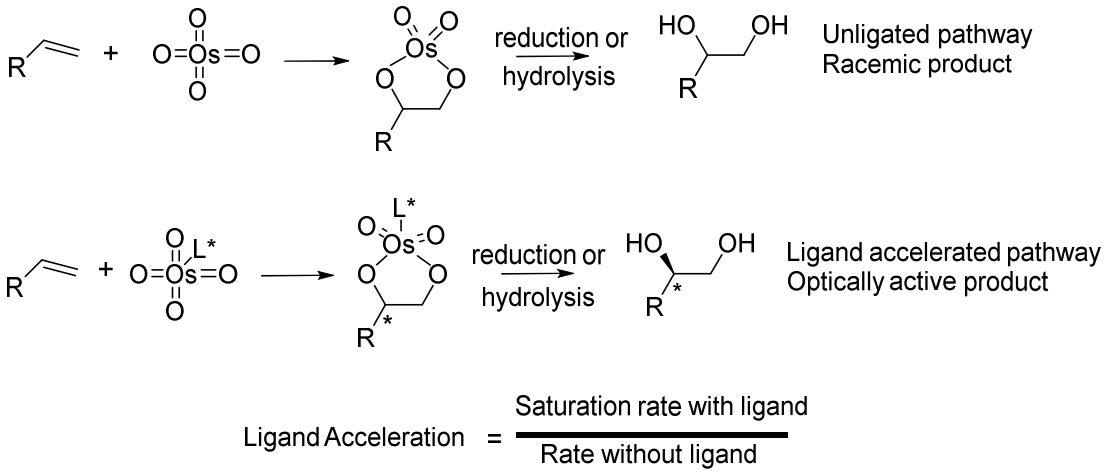
Fig. 2: Retrosynthetic analysis of guggultetrol (**1**) and D-*ribo*-phytosphingosine (**5**)

Since this section utilizes the asymmetric dihydroxylation reaction to introduce two chiral centres, a brief account of Sharpless asymmetric dihydroxylation of olefins is described (a brief account of α-aminooxylation of aldehydes has already been given in Chapter I).

4.1.4.2 Sharpless asymmetric dihydroxylation

In recent years, much attention has been focused on the catalytic asymmetric synthesis. It often has significant economic advantages over stoichiometric asymmetric synthesis for industrial-scale production of enantiomerically pure compounds. All these asymmetric reactions crucially depend on ligand acceleration effect (LAE).[19] Among all these reactions, Sharpless catalytic Asymmetric Dihydroxylation (AD) is one of the most important practical and widely used reaction in organic synthesis. It has become the most general method for the preparation of optically active *vicinal-syn*-diols from activated as well as inactivated olefins.[20]

A major breakthrough has occurred in the field of asymmetric oxidation when Sharpless *et al*.[21] demonstrated that asymmetric induction could be achieved when chiral amines were added to OsO_4-mediated asymmetric oxidation of olefins. Among the various ligands screened best results were obtained with ligands which were representatives of the cinchona alkaloid family, dihydroquinidine (DHQD) and



Scheme 11: Mechanism of OsO_4-catalyzed dihydroxylation of olefin

dihydroquinine (DHQ) (**Scheme 11**).[22] To improve the enantiomeric excess of the chiral diol, the second catalytic cycle of AD should be avoided and this was achieved by employing the $K_3Fe(CN)_6$ as reoxidant and using biphasic conditions **(Fig. 3)**. These conditions helped in protecting the organic osmate-(VI) monoglycolate ester from inopportune oxidation prior to hydrolysis and thereby releasing the diol and ligand to the organic phase and osmium-(VI) to the aqueous phase. Subsequently, osmium-(VI) obtains reoxidized and recycled into the catalytic cycle. Further improvement in the AD was realized by the addition of methyl sulfonamide ($MeSO_2NH_2$) to the reaction mixture. It also helps to accelerate the hydrolysis of the species **A**, thus facilitating the dihydroxylation smoothly. Addition of methyl sulfonamide also allowed carrying out the reactions of 1,2-di- tri- and tetra-substituted olefins at 0 ºC, which improved the selectivity as well as enantiomeric excess.

In order to develop the asymmetric version of the Os-catalyzed AD reaction, Sharpless and coworkers have screened various chiral ligands and found out that the derivatives of cinchona alkaloids gave excellent results. Among all the 250 derivatives of cinchona alkaloid ligands screened, the *bis*-DHQ **72** or DHQD **73**

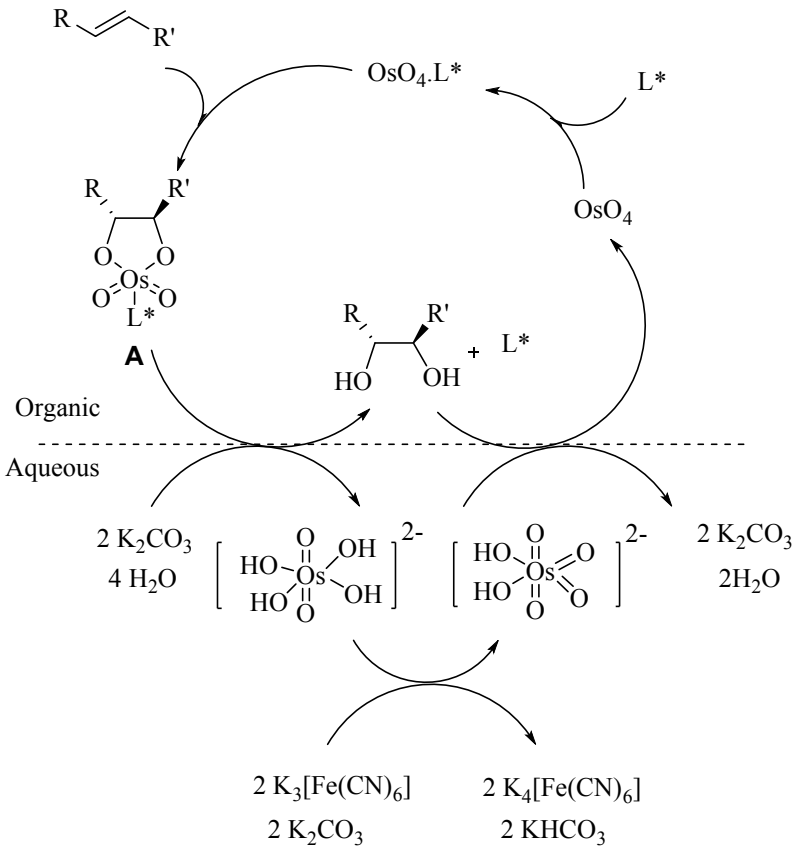


Fig. 3: Catalytic cycle for AD using $K_3Fe(CN)_6$ as co-oxidant

ethers of phthalazine-1, 4-diol have proven to be the best for obtaining high enantioselective diols **(Fig. 4)**. [23]

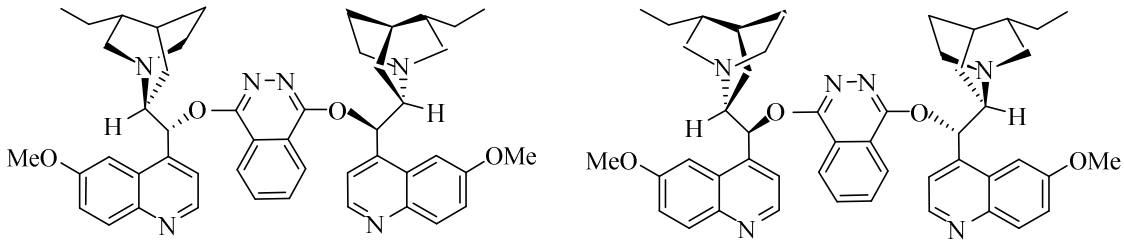


Fig. 4: Ligands for asymmetric dihydroxylation reaction

Studies have demonstrated the importance of enzyme-like binding pocket of the dimeric cinchona alkaloid for high enantioselectivity of the chiral diols.[24] Sharpless *et al*.[21] have shown that the facial selectivity for both ligands **72** and **73** is different,

based on their ability to induce the ee into the diols. This observation has led to the development of mnemonic model **(Fig. 5)** in which olefin with the constraints will be attacked either from the top (i.e. β) face in the presence of dihydroquinidine (DHQD) derivatives or from the bottom (i.e. α) face in the presence of dihydroquinine (DHQ) derived ligand.

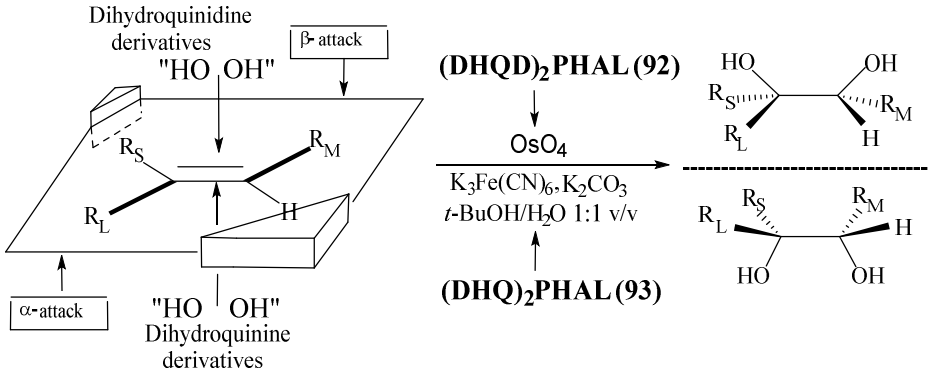


Fig. 5: Enantioselectivity mnemonic scheme

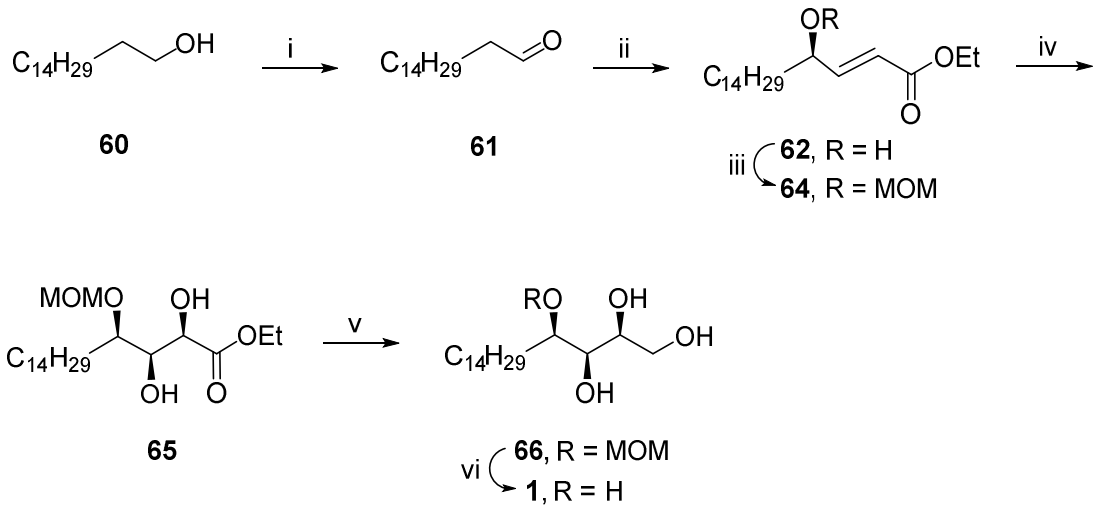
4.1.5 Results and discussion

(a) Enantioselective synthesis of Guggultetrol (1) *via* enamine catalysis

The synthetic sequences of an organocatalytic route for the highly enantioselective synthesis of guggultetrol **1** from the readily available starting material is described in **Scheme 12**.

Accordingly, the enantioselective synthesis of guggultetrol was undertaken starting from easily available 1-hexadecanol **60**. The oxidation of 1-hexadecanol **60** with PCC in CH_2Cl_2 at room temperature gave the corresponding 1-hexadecanal **61** in 94% yield. Aldehyde **61** was then subjected to α-aminooxylation [L-proline (20 mol%), PhNO DMSO, 23 °C] to provide α-aminooxyaldehyde, which was then *in situ* trapped under Horner-Wardsworth-Emmons olefination reaction condition (triethylphosphono acetate, LiCl, and DBU) to give the corresponding γ-aminooxy-α,β-unsaturated ester. It was then followed by the subsequent cleavage of N-O bond

with $Cu(OAc)_2.H_2O$ that provided the γ-hydroxy-α,β-unsaturated ester **62** with 67% yield.



Scheme 12: (i) PCC, MS 4A°, CH_2Cl_2, 25 °C, 3 h, 94%; (ii) (a) PhNO, L-proline (20 mol%), DMSO, 23 °C, 25 min; then triethylphosphono acetate (1.5 equiv), DBU (1 equiv), LiCl (1.5 equiv), CH_3CN, 45 min, 0-25 °C; (b) $Cu(OAc)_2$ (15 mol%), MeOH, 12 h, 67%, 98%ee; (iii) MOMCl, DIPEA, CH_2Cl_2, 0-25 °C, 85%; (iv) $(DHQ)_2PHAL$, $K_3Fe(CN)_6$, $MeSO_2NH_2$, t-BuOH/H_2O (1:1), $K_2OsO_2(OH)_4$ (0.5 mol%), K_2CO_3, 0 °C, 12 h, 86%; (v) $LiAlH_4$, THF, 0 °C, 89%; (vi) conc. HCl, MeOH, 25 °C, 4 h, 78%.

The optical purity of ester **62** was determined as 98%ee by ^{1}H NMR analysis of the corresponding Mosher's ester **63** (**Fig. 6**). The ^{1}H NMR spectrum of **62** showed two characteristic doublet of doublets at δ 6.01 (dd, J = 15.7, 1.6 Hz, 1H) and 6.93 (dd, J = 15.7, 4.9 Hz, 1H) corresponding to two olefinic protons. Its ^{13}C NMR spectrum displayed two typical carbon signals at δ 120.0 and 150.5 corresponding to two olefinic carbons and a signal at δ 166.5 due to ester carbonyl carbon (**Fig. 6**). The γ-hydroxy-α,β-unsaturated ester **62** was then protected as its MOM ether **64** in 85% yield by treating it with MOMCl in presence of diisopropylethylamine. The ^{1}H NMR spectrum of **64** showed two doublets at δ 4.54 (d, J = 6.8 Hz, 1H) and 4.63 (d, J = 6.8 Hz, 1H), which were attributed to the methylene protons of the MOM group while its methyl protons appeared as a singlet at δ 3.37 (s, 3H).

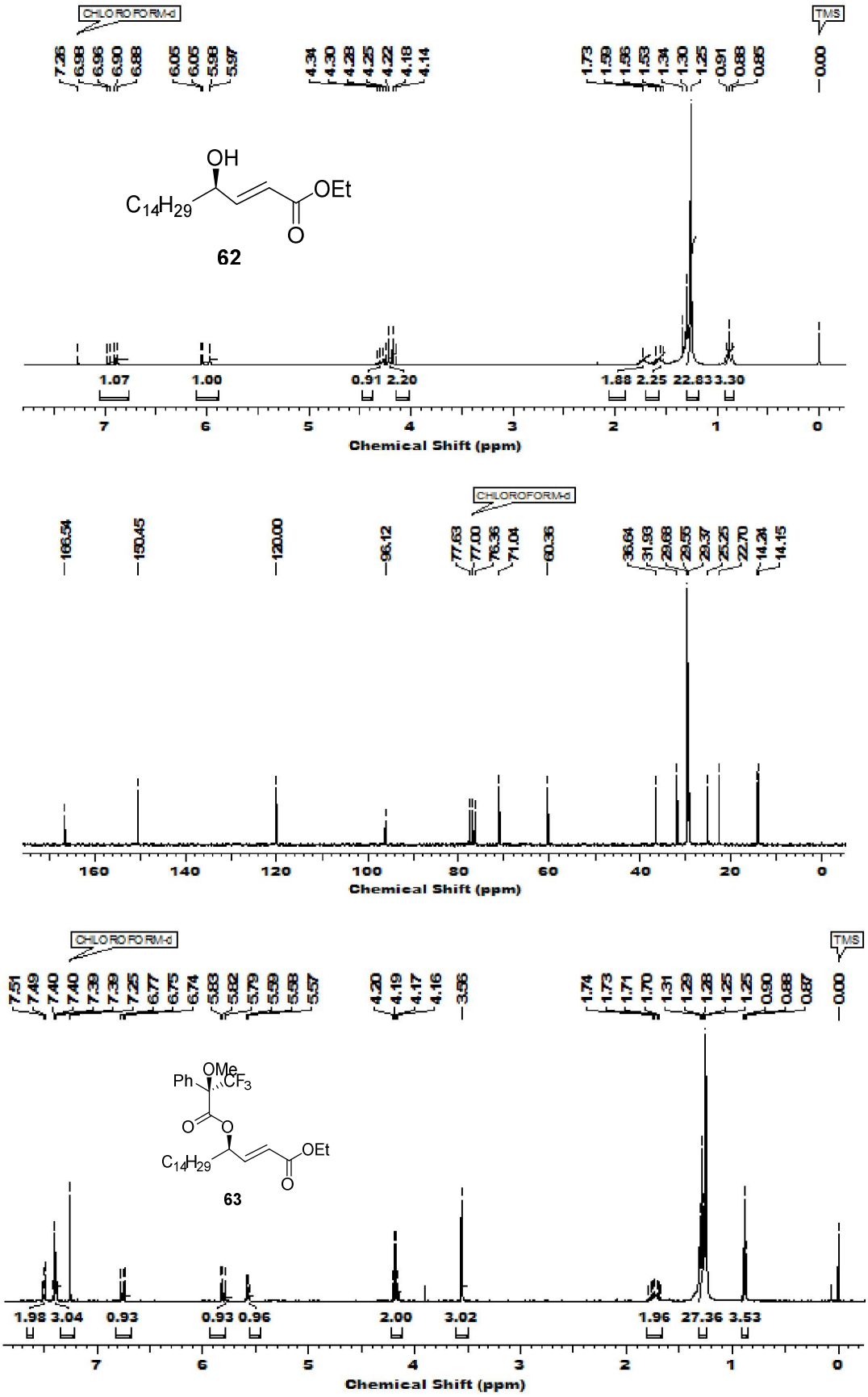
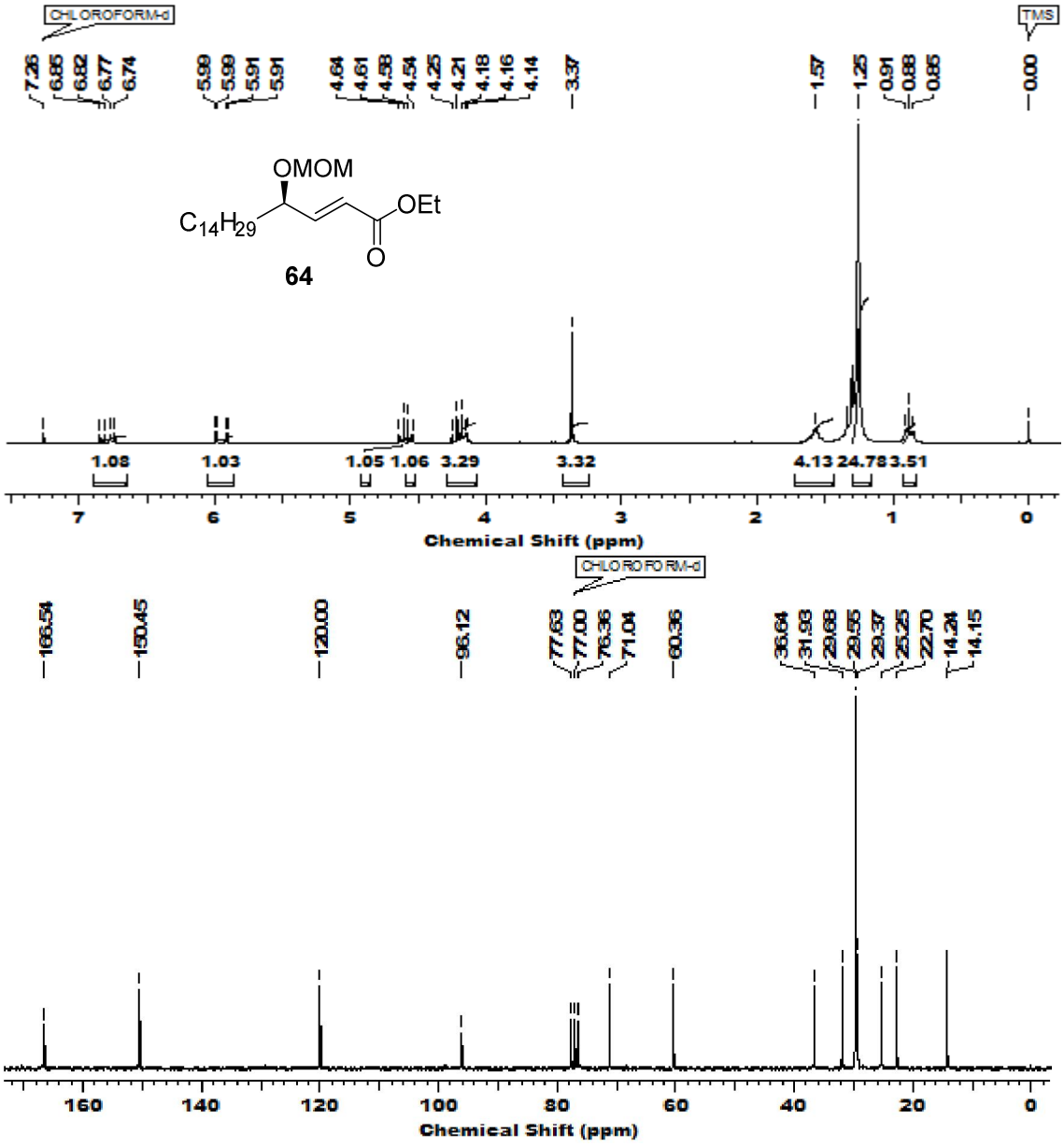


Fig. 6: ^{1}H and ^{13C} NMR spectra of γ-hydroxy-α,β-unsaturated ester **62** and ^{1}H NMR spectrum of its Mosher ester **63**

Its ^{13}C NMR spectrum showed a typical carbon signal at δ 166.5, which confirmed the presence of ester carbonyl carbon. Also, its IR spectrum exhibited a characteristic α, β-unsaturated ester carbonyl absorption band at 1712 cm^{-1} (**Fig. 7**). Earlier, we reported the synthesis of the intermediate **64** with seven linear steps using Sharpless asymmetric epoxidation to introduce the chirality;[11] while the present study employs L-proline catalyzed α-aminooxylation and HWE olefination as the key reactions thereby reducing the number steps to two starting from 1-hexadecanol **60**.



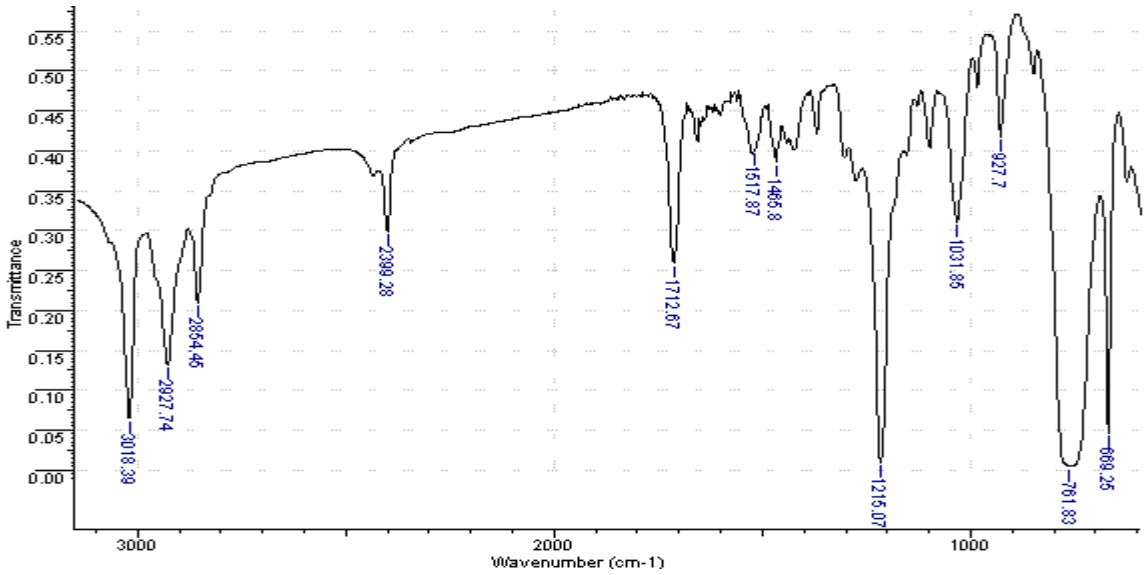


Fig. 7: ^{1}H, ^{13}C NMR and IR spectra of MOM ether **64**

The dihydroxylation of α, β-unsaturated ester **64** was then carried out under Sharpless asymmetric dihydroxylation (SAD) conditions,[21] using catalytic amount of $K_2OsO_2(OH)_4$ and $K_3Fe(CN)_6$ as co-oxidant in the presence of $(DHQ)_2$-PHAL as ligand to give the dihydroxylated ester **65** in 86% yield with a diastereomeric ratio of 11:1 (*syn*:*anti*) determined by its ^{1}H NMR analysis. The ^{1}H NMR spectrum of **65** confirmed the formation of diol **65** as it exhibited typical peak patterns such as δ 3.42 (s, 3H), 3.53-3.68 (m, 2H), 3.79-3.80 (m, 1H), 4.17 (s, 1H), and 4.29 (q, J = 7.1 Hz, 2H). Its ^{13}C NMR spectrum showed a characteristic carbon signal at 173.1 corresponding to the carbonyl carbon, thereby confirming the saturation of double bond. Its mass spectrum with its molecular ion peak (M+Na) at *m/z* 427.34 confirmed the formation of diol ester **65** (**Fig. 8**).

The reduction of the ester function in ester **65** was achieved by its treatment with $LiAlH_4$ in THF at room temperature to afford the triol **66** in 89% yield. Methyl protons of the MOM-group resonated at δ 3.43 while two multiplets at δ 3.56-379 (m, 5H) and at δ 4.64-4.75 (m, 2H) respectively accounted for the rest of the protons of the carbons attached to oxygen atom in its ^{1}H NMR spectrum.

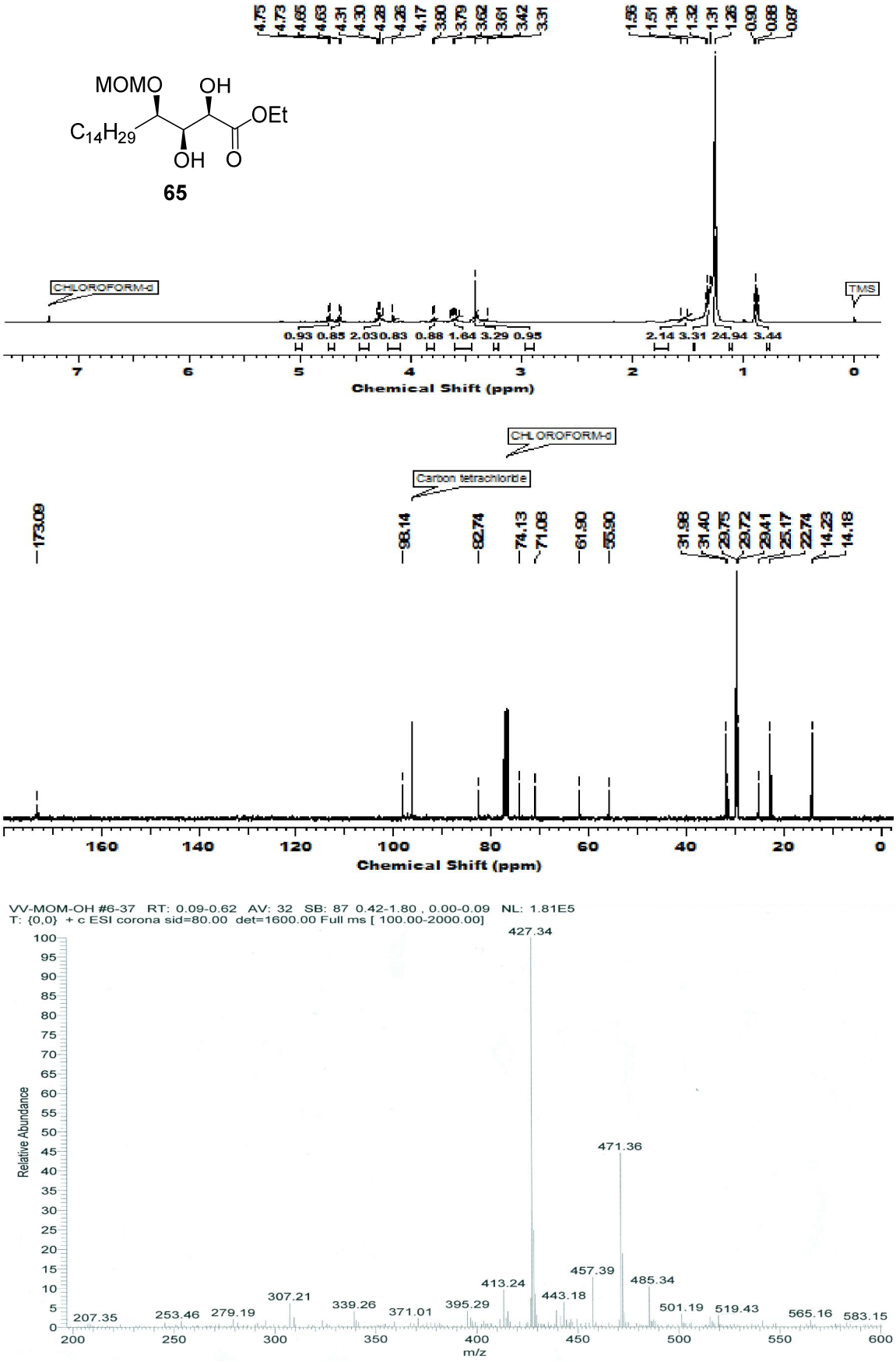


Fig. 8: ^{1}H, ^{13}C NMR and mass spectra of diol ester **65**

The reduction of the ester moiety was further ascertained by the disappearance of carbonyl peak in its ^{13}C NMR spectrum (**Fig. 9**).

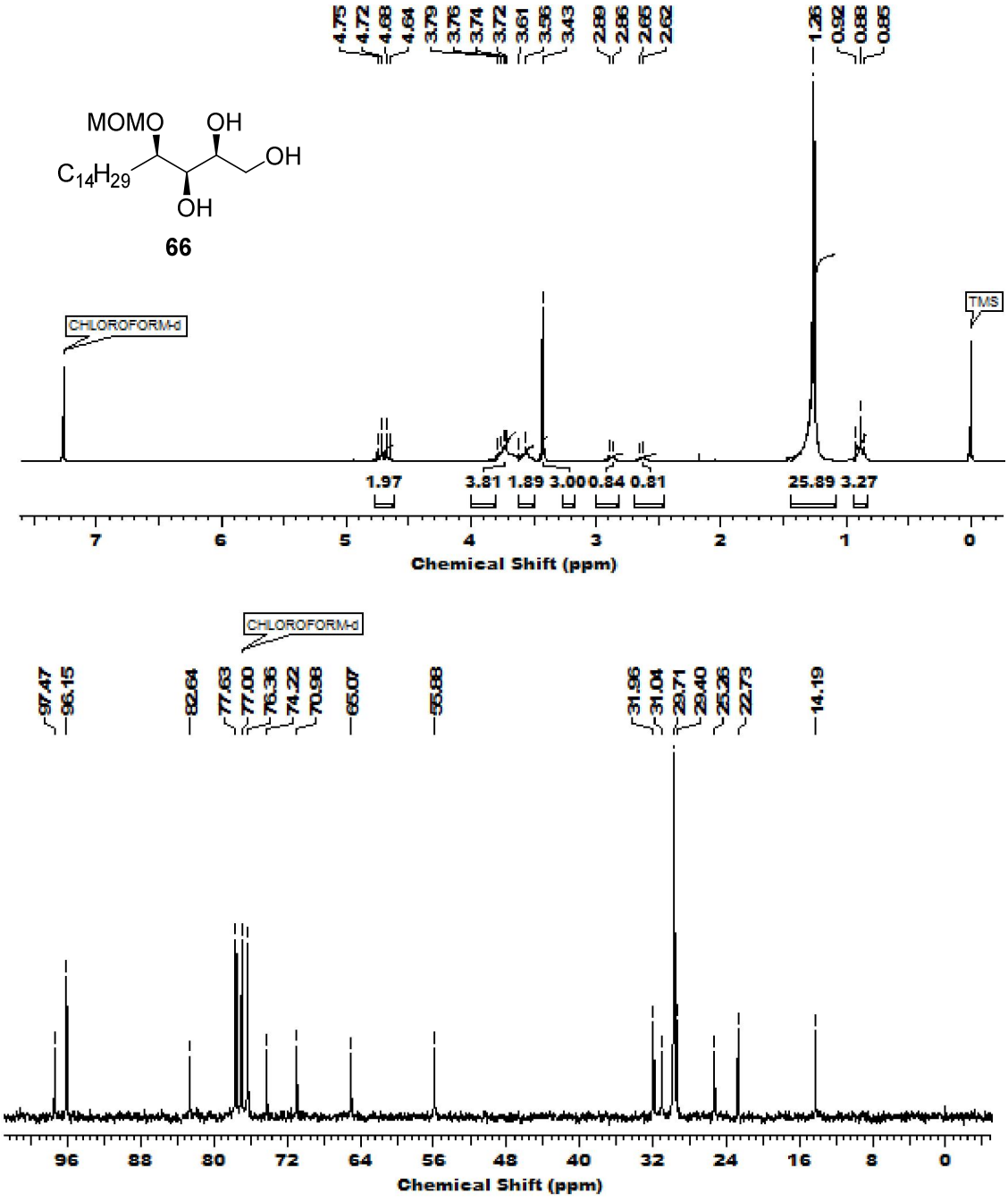


Fig. 9: ^{1}H and ^{13}C NMR spectra of triol **66**

Eventually, deprotection of the MOM group with con. HCl in methanol furnished guggultetrol, **1** in 78% yield, $[\alpha]_D$ = +12 (*c* 0.5, EtOH); {lit.[9,10] $[\alpha]_D$ = +11.4 (*c* 0.34, EtOH)}. The ^{1}H NMR spectrum of **1** displayed signals typical of its structural pattern

such as δ 0.86 (t, *J* = 6.6 Hz, 3H), 1.29-1.59 (s, 26H), and 3.43-3.71 (m, 4H) whereas its ^{13}C NMR spectrum showed characteristic carbon signals at δ 64.6, 73.7, 74.3 and 74.5 for the carbons attached to oxygen atoms (**Fig. 10**). Also, its IR spectrum exhibited a characteristic –OH absorption band at 3382 cm^{-1}.

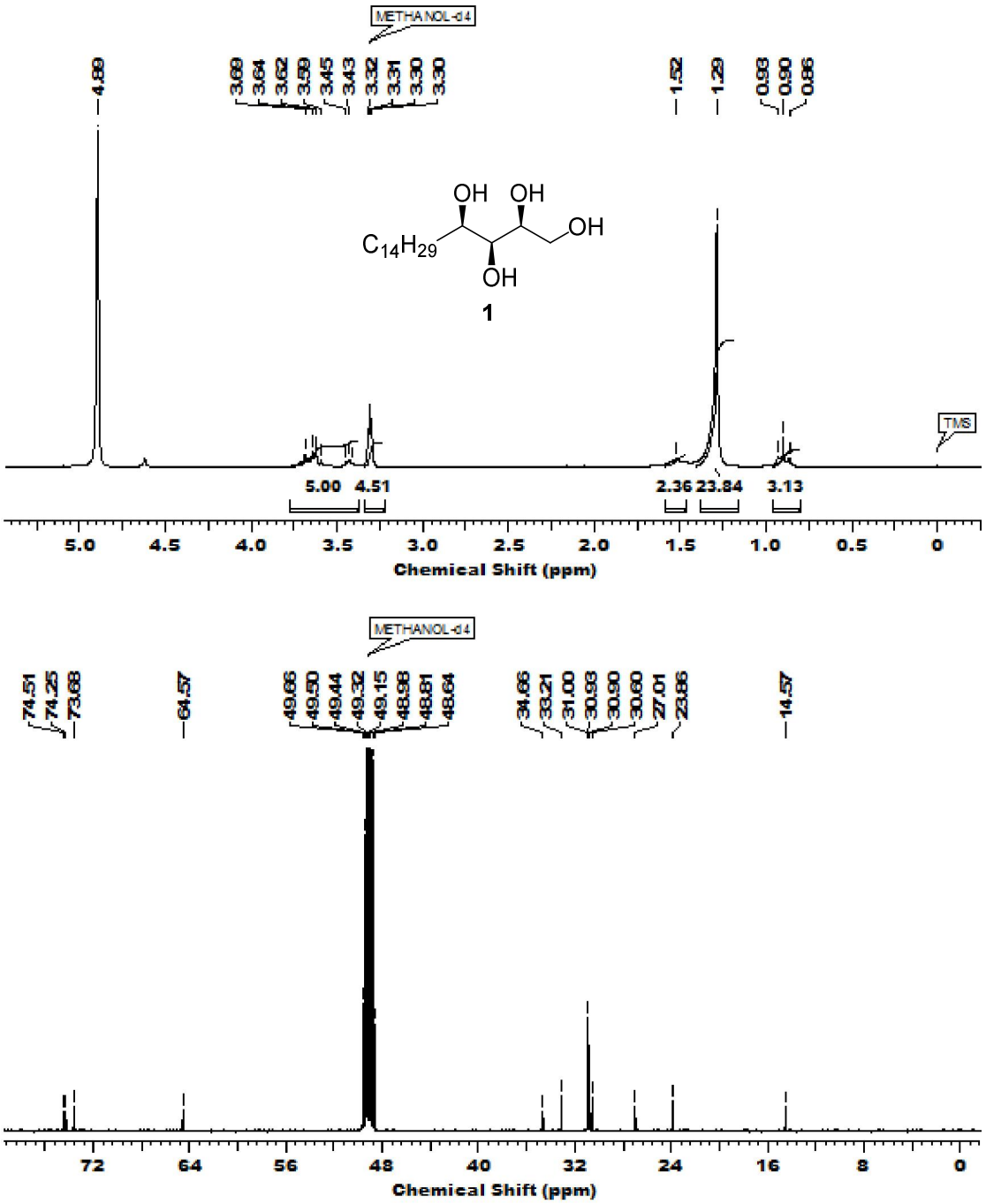
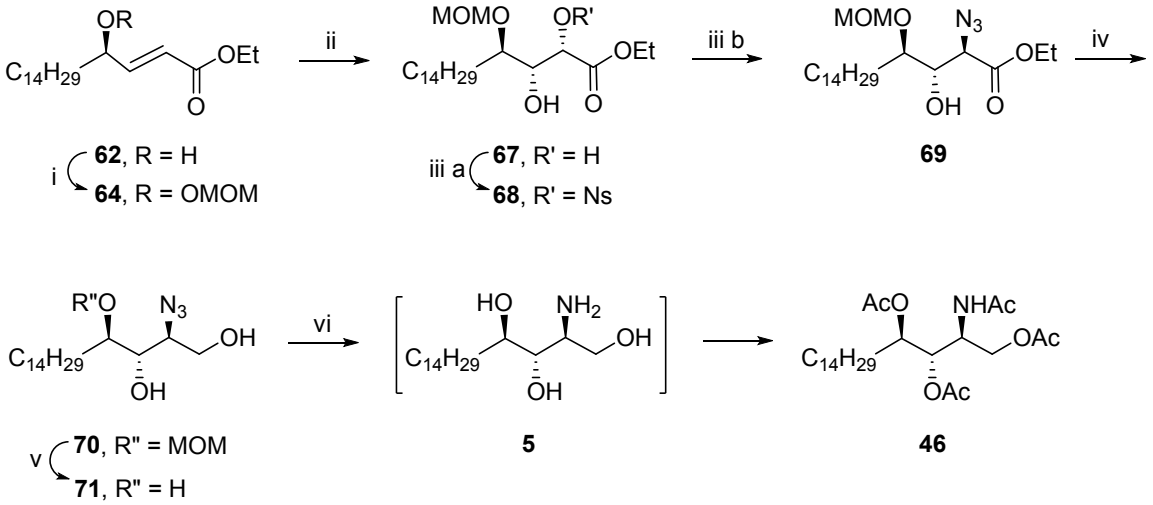


Fig. 10: ^{1}H and ^{13}C NMR spectra of Guggultetrol **66**

(b) Enantioselective synthesis of D-*ribo*-phytosphingosine tetraacetate (46) *via* enamine catalysis:

The synthetic reaction sequence for the enantioselective synthesis of D-*ribo*-phytosphingosine tetraacetate **46** wherein Sharpless asymmetric dihydroxylation and chemoselective displacement of secondary hydroxyl group by N_3 constituting key steps is presented in **Scheme 13**.



Scheme 13: (i) MOMCl, DIPEA, CH_2Cl_2, 0-25 °C, 85%; (ii) $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, $MeSO_2NH_2$, *t*-BuOH/H_2O (1:1), $K_2OsO_2(OH)_4$ (0.5 mol%), K_2CO_3, 0 °C, 12 h, 86%; (iii) (a) NsCl, Et_3N, CH_2Cl_2, 4 °C, 48 h, 62%; (b) NaN_3, dry. DMF, 50 °C, 16 h, 89%; (iv) $LiBH_4$, MeOH, 0-25 °C, 12 h, 89%; (v) conc. HCl, MeOH, 25 °C, 4 h, 80%; (vi) H_2 (1 atm), 10% Pd/C, MeOH, 25 °C, 6 h; then Ac_2O, DMAP, pyridine, 25 °C, 16 h, 85%.

For the synthesis of D-*ribo*-phytosphingosine **5**, MOM ether **64** was chosen as the common intermediate, synthesis of which was presented in this section (see guggultetrol).

Thus, α,β-unsaturated ester **64** was subjected to Sharpless asymmetric dihydroxylation (SAD) conditions,[21] using catalytic amount of $K_2OsO_2(OH)_4$ and $K_3Fe(CN)_6$ as co-oxidant in the presence of $(DHQD)_2$-PHAL ligand to give the dihydroxylated ester **67** in 84% yield with the diastereomeric ratio of 19:1 (*anti*:*syn*) determined by its ^1H

NMR analysis. The specific rotation of the diol was found to be $[\alpha]^{25}_{D}$: −11.5 (*c* 1, $CHCl_3$). The ^1H NMR spectrum of **67** confirmed the formation of diol **67** as it exhibited typical peak patterns such as δ 3.41 (s, 3H), 3.61-3.63 (m, 1H), 3.80-3.82 (m, 1H), 4.29 (q, *J* = 7.2 Hz, 2H), 4.44 (brs, 1H) and 4.66-4.71 (m, 2H). Its ^{13}C NMR spectrum showed a characteristic carbon signal at 173.6 corresponding to the carbonyl carbon (**Fig. 11**).

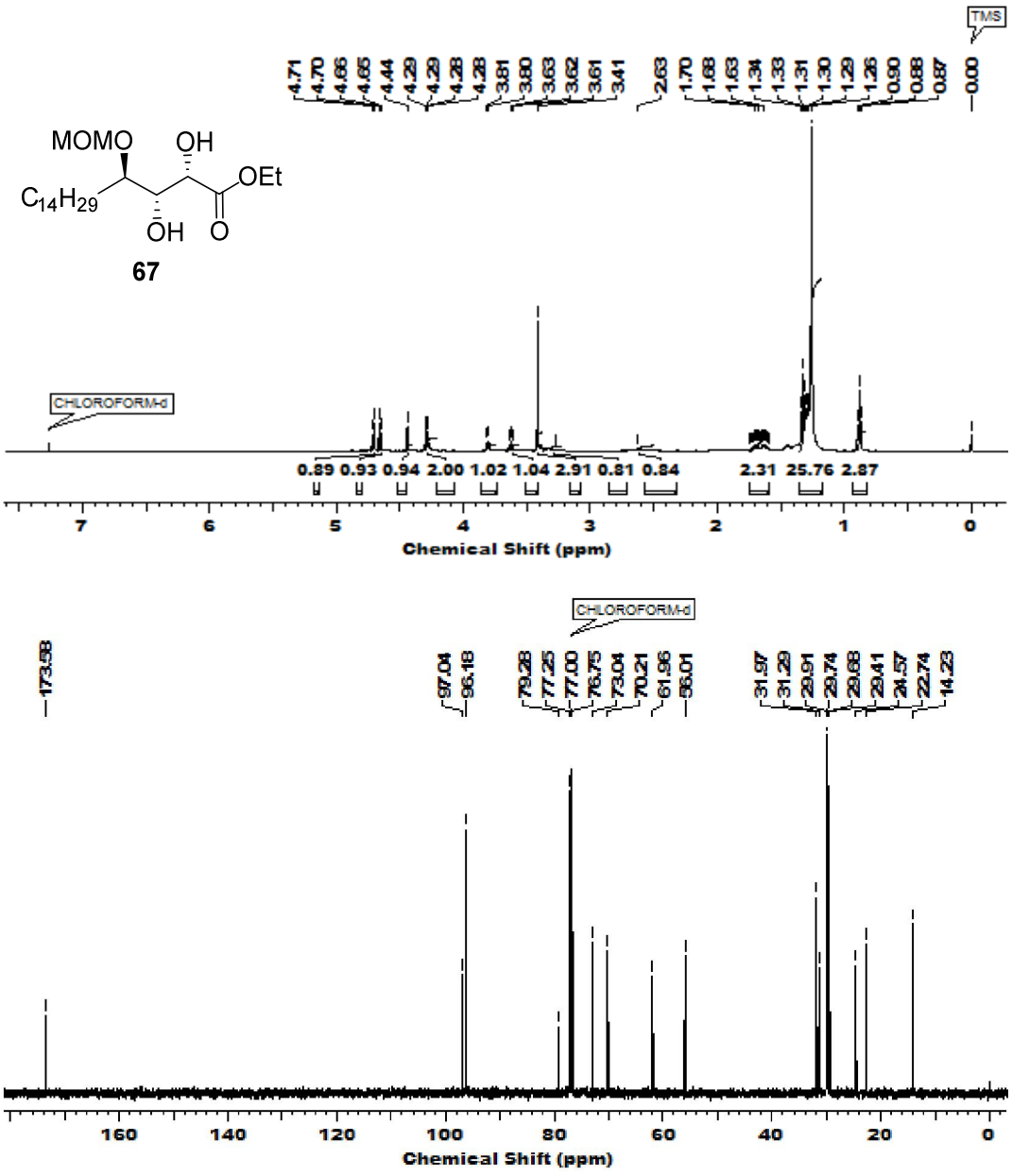


Fig. 11: ^1H, and ^{13}C NMR spectra of diol ester **67**

When the diol ester **67** was treated with p-nitrobenzene sulfonyl chloride (1 equiv), Et_3N in CH_2Cl_2 for 48 h at 25 °C, only the secondary hydroxyl group at the α-position of the ester function in **67** was reacted chemoselectively[25] to provide the nosylate **68** with 62% yield after column chromatographic purification. The ^1H NMR spectrum showed the proton signals at δ 8.17 (d, J = 8.7 Hz, 2H) and 8.38 (d, J = 8.2 Hz, 2H)

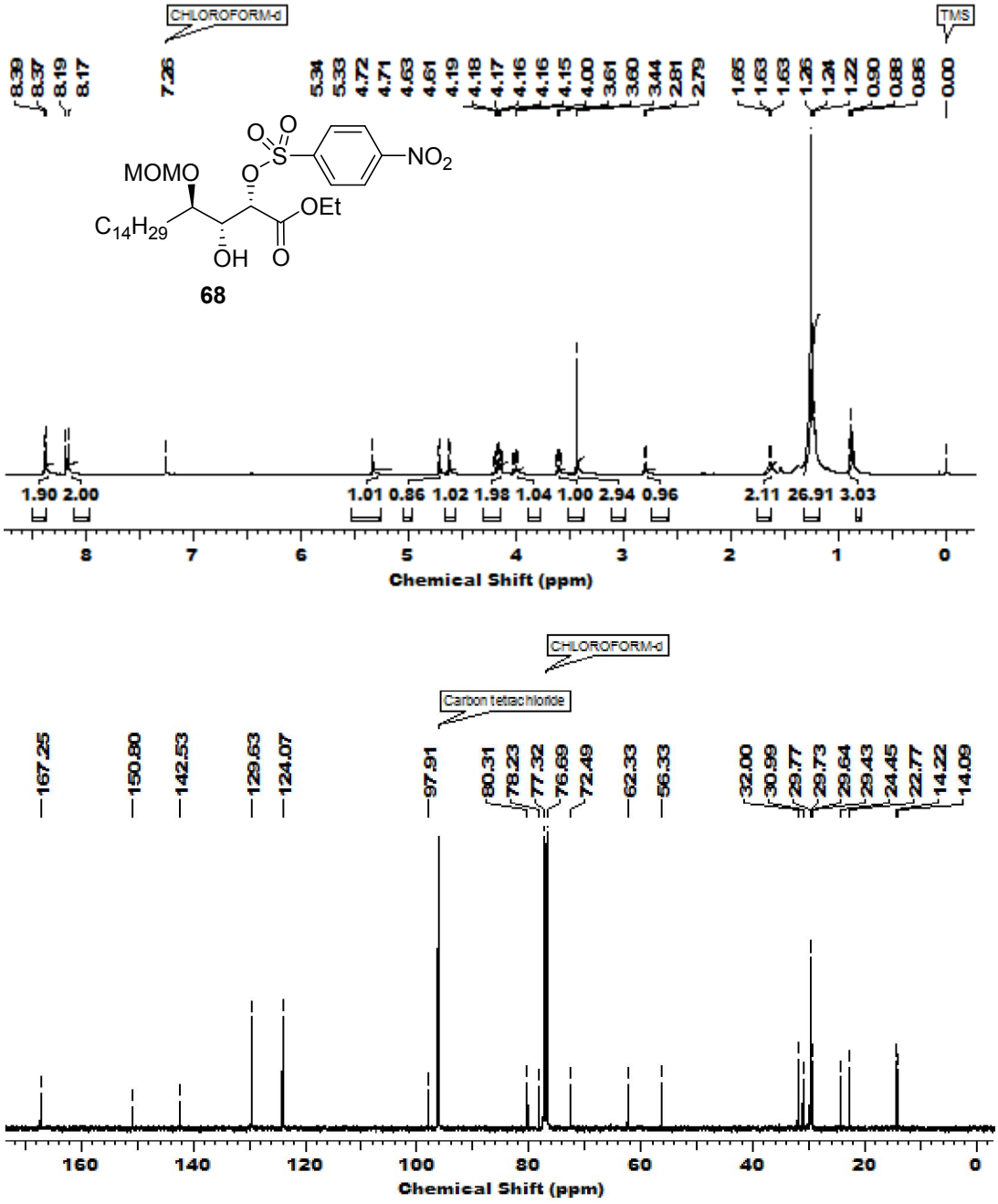


Fig. 12: ^1H, and ^{13}C NMR spectra of nosylate **68**

corresponding to methine protons attached to aromatic carbons present at the ortho position to sulfonyl and nitro groups respectively. Its ^{13}C NMR spectrum displayed typical carbon signals at δ 142.5, 150.8, and 167.3 corresponding to quaternary carbons (–**C**SO_2 and –**C**NO_2) and ester carbonyl carbons respectively (**Fig. 12**).

The nosylate was then subjected to S_N2 displacement with NaN_3, in dry DMF at 50 °C for 16 h that furnished the azido ester **69** in 89% yield. The ^1H NMR spectrum of **69** showed a signal at δ 3.93 (brs, 2H) corresponding to methine (-**CH**N_3) and (-**CH**OH) protons. Its ^{13}C NMR spectrum displayed typical carbon signals at δ 62.34 and 168.95 corresponding to methine carbon (-**C**HN_3) and ester carbonyl carbon respectively. Also, its IR spectrum exhibited a characteristic –OH, -N_3, and CO_2Et absorption bands at 3350, 2112, and 1742 cm^{-1} respectively (**Fig. 13**).

The chemoselective reduction of ester function in azido ester **68** was achieved by its treatment with $LiBH_4$ in MeOH at 25 °C for 8 h to afford the azido diol **70** in 89% yield. The ^1H NMR spectrum of azido diol **70** showed the proton signals at δ 3.51 (m, 1H), 3.70 (m, 2H), and 3.94 (m, 2H) corresponding to five protons present in carbons attached with the heteroatoms (-C**H$_2$**OH, -C**H**N_3, -C**H**OMOM, -C**H**OH,). Its ^{13}C NMR signal displayed four characteristic carbon signals at δ 62.7, 63.0, 72.9, and 81.8 corresponding to the carbons attached to heteroatoms (-**C**HN_3, -**C**H_2OH, -**C**HOH, -**C**HOMOM) (**Fig. 14**).

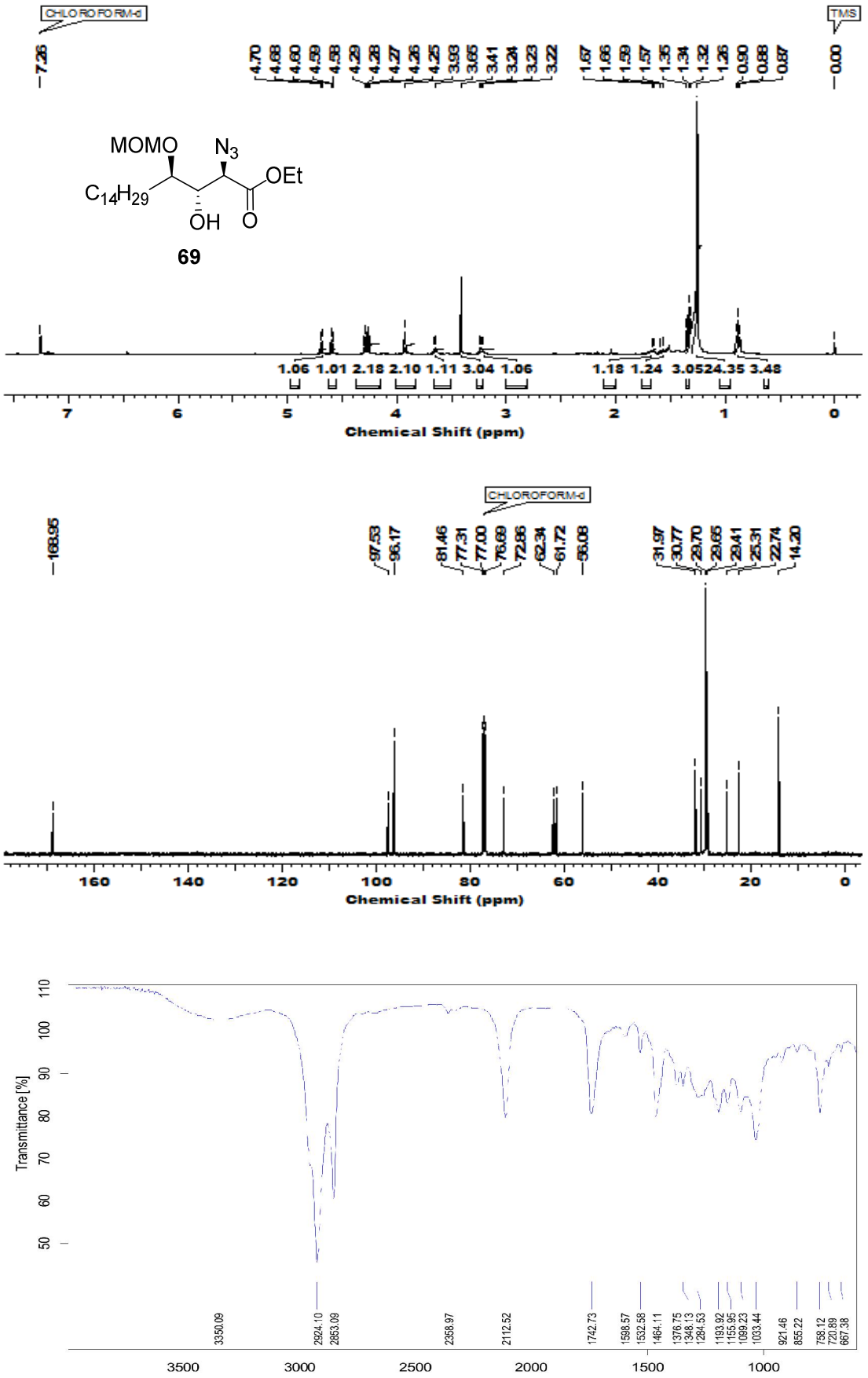


Fig. 13: ^{1}H, ^{13}C NMR and IR spectra of azido ester **69**

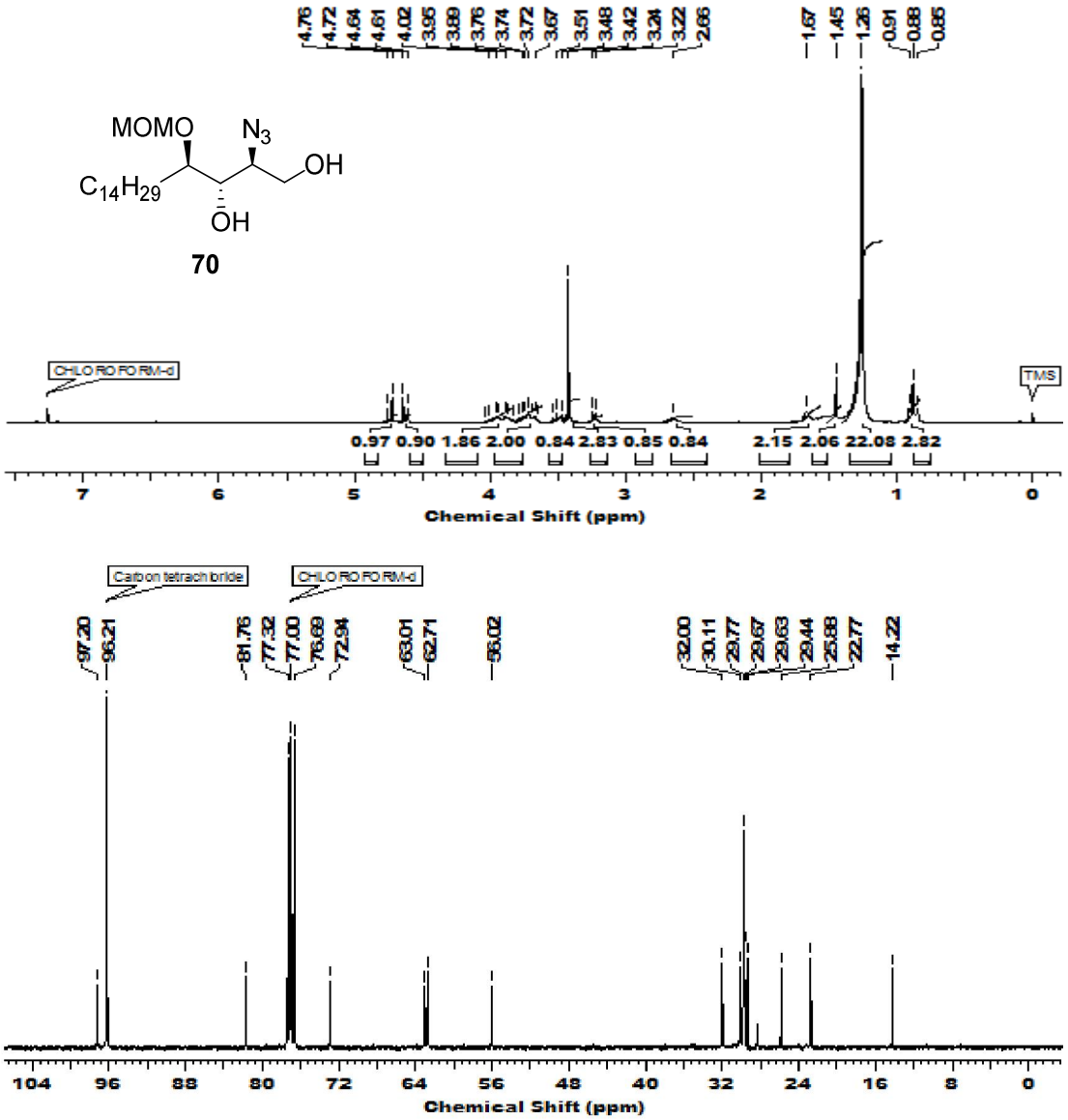


Fig. 14: ^{1}H, and ^{13}C NMR spectra of azido diol **70**

Deprotection of the MOM group in **70** was then achieved with con. HCl in methanol that furnished the azido triol **71** in 80% yield. The ^{1}H NMR spectrum of **71** showed the signals in the range of δ 3.53-3.60 (m, 1H), 3.76-3.78 (m, 1H), and 3.90-3.94 (m, 1H) corresponding to methine and methylene protons attached with all functional groups. Its ^{13}CNMR spectrum confirms the disappearance of signals at δ 56.0 and 97.2 corresponding to the carbons in the MOM group (**C**H_3O**C**H_2O-) (**Fig. 15**).

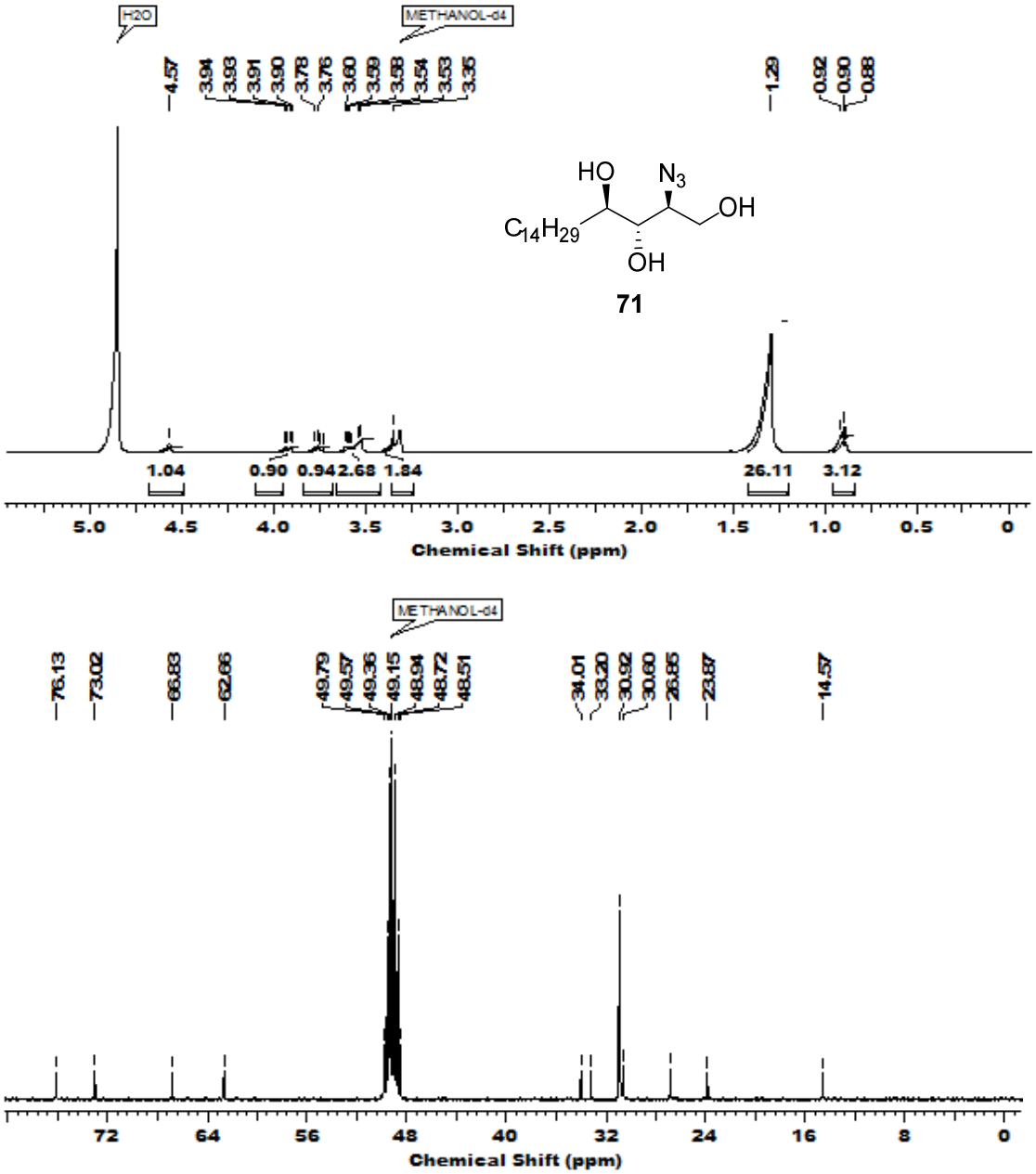


Fig. 15: ^{1}H, and ^{13}C NMR spectra of azido triol **71**

The azido triol **70** was hydrogenated under the catalytic hydrogenation condition [H_2(1 atm), 10% $Pd(OH)_2/C$] to provide D-*ribo*-phytosphingosine (**5**) as colorless solid. Due to the solubility problem, column chromatographic purification of **5** was not carried out and hence, the crude **5** was subsequently treated with Ac_2O, DMAP in pyridine at 25 °C for 16 h that furnished the D-*ribo*-phytosphingosine tetraacetate as

colourless liquid (**46**). Its specific rotation was found to be $[\alpha]^{25}_{D}$: +22.31 (c 0.5, $CHCl_3$) {lit.[18] $[\alpha]^{25}_{D}$: +21.9 (*c* 2, $CHCl_3$)}. The ^{1}H NMR spectrum of **46** showed the typical proton signals at δ 2.02-2.17 (m, 12H) corresponding to the methyl protons of four acetyl -CH_3 groups (C**H$_3$**CO-). Its ^{13}C NMR spectrum displayed typical carbon signals at δ 169.6, 170.0, 170.7, and 171.1 corresponding to the presence of four carbonyl carbons of the acyl groups. Its mass spectrum with its molecular ion peak (M+1) at *m/z* 486.3435 confirmed the formation of D-*ribo*-phytosphingosine tetraacetate **46** (**Fig. 16**).

4.1.7 Conclusion

In conclusion, a short and efficient enantioselective syntheses of both the natural products namely guggultetrol and D-*ribo*-phytosphingosine tetraacetate possessing three contiguous stereogenic centers have been described *via* environmentally friendly, L-proline-catalyzed α-aminooxylatin followed by sequential Horner-Wardsworth-Emmons olefination and Sharpless asymmetric dihydroxylation as the key reactions. The overall yields for both the molecules *i.e*. guggultetrol **1** and D-*ribo*-phytospingosine tetraacetate **46** were calculated to be 34% and 16% respectively with excellent enantioselectivity of 98%ee each and high diastereomeric ratio of 11:1 for **1** and 19:1 for **46**.

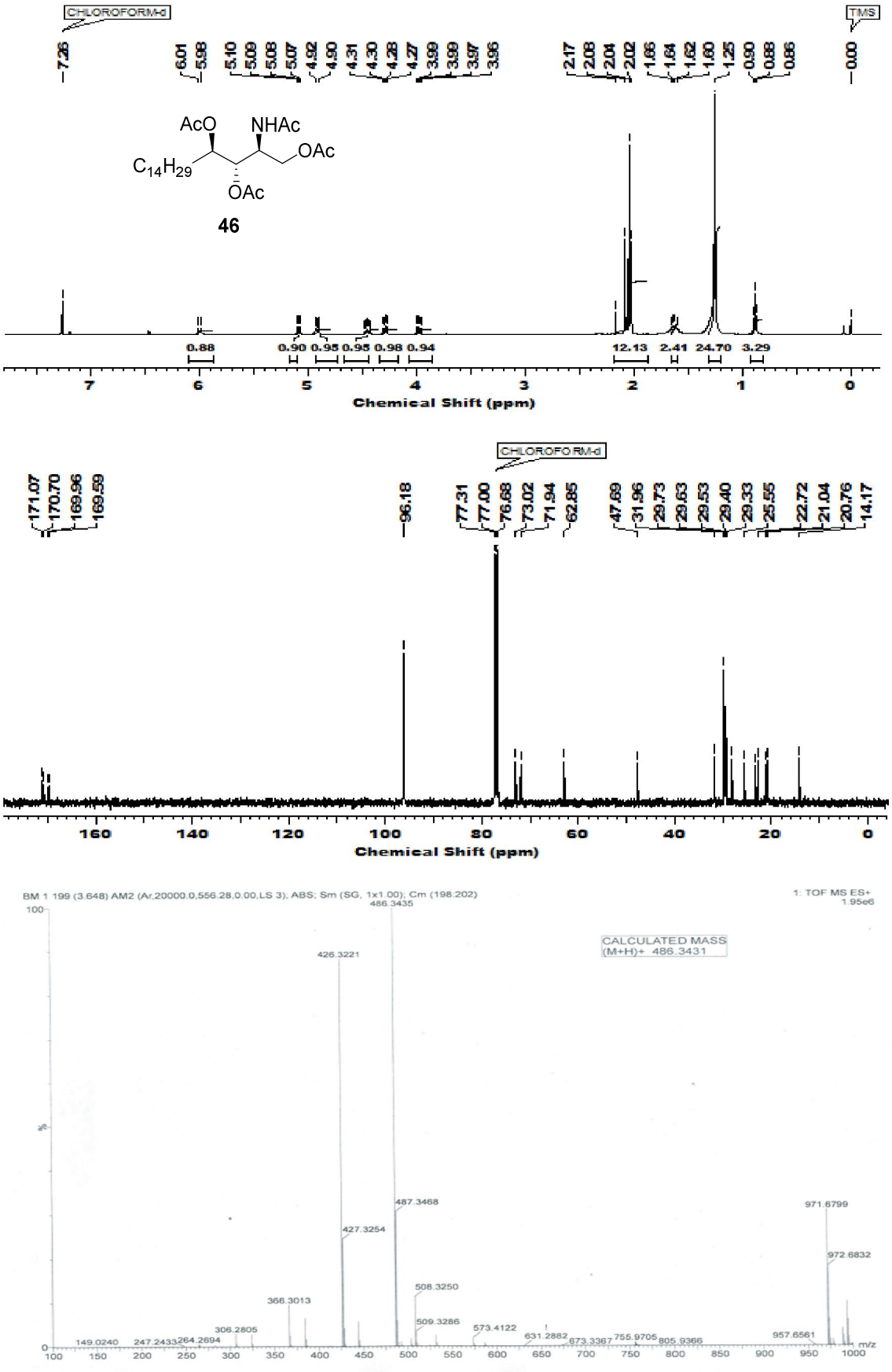


Fig. 16: ^{1}H, and ^{13}C NMR and mass spectra of D-*ribo*-phytospingosine tetraacetate **46**

4.1.8 Experimental Section

***(R,E)*-Ethyl 4-hydroxyoctadec-2-enoate (62)**

To a stirred solution of 1-hexadecanal **61** (5.0 g, 21 mmol) and nitrosobenzene (1.8 g, 17 mmol) in DMSO/*n*-hexane (5:1) (75 mL) at 23 °C was added L-proline (0.488 g, 20 mol%). The reaction mixture was allowed to stir at the same temperature for 25 min. This was followed by addition of lithium chloride (1.5 g, 36 mmol), triethyl phosphonoacetate (7 g, 32 mmol) and DBU (3.5 g, 21 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 × 60 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude α-aminooxy alcohol.

To a MeOH (60 mL) solution of the above crude aminooxyalcohol was added $Cu(OAc)_2.H_2O$ (0.61 g, 3.15 mmol) at 25 °C and the reaction mixture was allowed to stir for 10 h at that temperature. Then MeOH was evaporated using rotavapour and the crude mixture was directly purified by column chromatography over silica gel using pet. ether:EtOAc (95:5) as eluent to give *(R,E)*-Ethyl 4-hydroxyoctadec-2-enoate as a pale yellowish gum **62**.

Yield: 1.9 g, 67%, pale yellowish gum; $[\alpha]^{25}_{D}$: +11.3 (*c* 2.06, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3443, 2924, 2853, 2255, 1723, 1657, 1466, 1388, 1274, 1177, 1095, 1041, 981; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.83 - 0.92 (m, 3H), 1.25 (s, 23H), 1.53-1.73 (m, 4H), 4.20 (q, *J* = 7.1 Hz, 2H), 4.25 - 4.34 (m, 1 H), 6.01 (dd, *J* = 15.7, 1.6 Hz, 1H), 6.93 (dd, *J* = 15.7, 4.9 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.6, 14.2, 22.7, 25.3, 29.4, 29.6, 29.7, 31.9, 36.6, 60.4, 71.0, 120.0, 150.6, 166.5; **Analysis:** $C_{20}H_{38}O_3$ required C, 73.57; H, 11.73; found: C, 73.22; H, 11.43%.

Mosher's ester of *(R,E)*-Ethyl 4-hydroxyoctadec-2-enoate (63)

A two-neck 10 mL flask with septum was charged with (38 mg, 0.18 mmol) *N*,*N*'-dicyclohexylcarbodiimide (DCC), catalytic amount of 4-dimethylaminopyridine (DMAP) and CH_2Cl_2 (2 mL) under argon atmosphere. The flask was allowed to cool at 0 ºC for 10 min and a solution of alcohol **62** (34 mg, 0.16 mmol) in CH_2Cl_2 (2 mL) was introduced through a syringe. It was allowed to stir for additional 10 min, followed by dropwise addition of (*R*)-α-methoxy-α-trifluoromethylphenyl acetic acid (42 mg, 0.176 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was then stirred at 0 ºC for additional 1 h and then at room temperature for overnight. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with saturated $NaHCO_3$ solution (50 mL), dried over anhyd. Na_2SO_4 and then concentrated under reduced pressure to give Mosher's ester **63** (30 mg, 60%) as a thick syrup.

Yield: 30 mg, 60%; $[\alpha]^{25}_{D}$: -58.5 (*c* 0.6, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3156, 3069, 2942, 2868, 2293, 1754, 1721, 1674, 1432, 1351, 1221, 1181, 1046, 1021, 979; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.86 - 0.90 (m, 3H), 1.25-1.31 (m, 27H), 1.66-1.81 (m, 2H), 3.56 (s, 3H), 4.18 (q, *J* = 7.2 Hz, 2H), 5.50 - 5.62 (m, 1H), 5.81 (dd, *J* = 15.7, 1.4 Hz, 1H), 6.76 (dd, *J* = 15.7, 5.7 Hz, 1H), 7.35 - 7.44 (m, 3H), 7.45 - 7.56 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 14.2, 14.3, 22.8, 24.9, 29.3, 29.4, 29.6, 29.7, 32.0, 33.8, 55.5, 60.6, 74.9, 122.7, 127.4, 128.5, 129.7, 132.2, 137.8, 143.5, 165.6, 165.7; **Analysis:** $C_{30}H_{45}F_3O_5$ required C, 66.40; H, 8.36; found: C, 66.25; H, 8.14%.

(*R*,*E*)-Ethyl 4-(methoxymethoxy)octadec-2-enoate (64)

To a solution of the alcohol **62** (1.3 g, 4 mmol) and diisopropylethylamine (2.1 g, 2.7 mL, 16 mmol) in dry CH_2Cl_2 (20 mL) was added methoxymethyl chloride (0.96 g, 1.04 mL, 12 mmol) under nitrogen over 5 min at 0 °C, and the mixture was allowed to warm to room temperature and stirred overnight. After cooling to 0 °C, the reaction mixture was quenched with water and extracted with CH_2Cl_2 (3 × 30 mL). The

combined organic extracts were washed with water (2 × 50 mL) and brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. Silica gel column chromatographic purification of the crude product using petroleum ether gave ether **64** (1.2 g) as a colorless liquid.

Yield: 1.2 g, 85%; **[α]$^{25}_{D}$**: +28 (*c* 0.8, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3018, 2927, 2864, 2399, 1712, 1517, 1466, 1216, 1031, 927, 761, 669; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.85 - 0.91 (m, 3 H), 1.25 (s, 25 H), 1.57 (brs, 4H), 3.37 (s, 3H), 4.14 - 4.25 (m, 3H), 4.54 - 4.64 (m, 2 H), 5.95 (dd, *J* = 15.8, 1.1 Hz, 1 H), 6.79 (dd, *J* = 15.7, 6.4 Hz, 1 H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.2, 14.3, 22.7, 25.2, 29.4, 29.6, 29.7, 32.0, 34.9, 55.5, 60.3, 75.2, 76.4, 77.6, 94.5, 96.2, 121.8, 147.9, 166.1; **Analysis:** $C_{22}H_{42}O_4$ required C, 71.31; H, 11.42; found: C, 71.02; H, 11.73%.

***(2R,3R,4R)*-Ethyl 2,3-dihydroxy-4-(methoxymethoxy)octadecanoate (65)**

To a mixture of $K_3Fe(CN)_6$ (0.59 g, 1.8 mmol), K_2CO_3 (0.25 g, 1.8 mmol) and $(DHQ)_2PHAL$ (5 mg, 1 mol%), in *t*-BuOH/H_2O (1:1, 12 mL) cooled at 0 °C was added $K_2OsO_4.H_2O$ (1 mg, 0.5 mol%) followed by methanesulfonamide (57 mg, 0.6 mmol). After being stirred for 5 min at 0 °C, olefin (0.22 g, 0.6 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 5 h and then quenched with solid sodium sulfite (1 g). The stirring was continued for an additional 45 min, and then the solution was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over anhyd. Na_2SO_4 and concentrated. Silica gel column chromatographic purification of the crude product using petroleum ether/EtOAc (7:3) as eluent gave the diol ester **65** (0.2 g) as a colorless gum.

Yield: 0.2 g, 86%; **[α]$^{25}_{D}$**: −19 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3417, 3018, 2927, 2854, 2399, 1736, 1216, 1126, 1029, 757, 669; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.87 - 0.90 (m, 3H), 1.26 (s, 24H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.4 -1.59 (m, 2H), 3.31 (s, 1H),

3.42 (s, 3H), 3.53-3.68 (m, 2H), 3.79 (m, 1H), 4.17 (s, 1H), 4.29 (q, *J* = 7.1 Hz, 2 H), 4.64 (d, *J* = 6.4 Hz, 1H), 4.74 (d, *J* = 6.6 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.18, 14.23, 22.7, 25.2, 29.4, 29.7, 29.8, 31.4, 32.0, 55.9, 61.9, 71.1, 74.1, 82.7, 98.1, 173.1; **Analysis:** $C_{22}H_{44}O_6$ required C, 65.31; H, 10.96; found: C, 65.62; H, 10.69%.

(2S,3R,4R)-4-(Methoxymethoxy)octadecane-1,2,3-triol (66)

A solution of diol ester **65** (0.16 g, 0.4 mmol) in THF (5 mL) was added to a stirred slurry of $LiAlH_4$ (47 mg, 1.2 mmol) in THF (5 mL). After being stirred for 5 h at 25 °C, the reaction was carefully quenched with water. The reaction mixture was then extracted with EtOAc (2 × 100 mL) and the combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude product, which was then purified by column chromatography using petroleum ether/EtOAc (4:6) to give the triol **66** (130 mg) as a colorless gum.

Yield: 0.13 g, 89%; **$[\alpha]^{25}_D$**: – 40 (*c* 0.4, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3411, 3018, 2926, 2854, 2399, 1216, 1031, 927, 767, 669; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.82-0.95 (m, 3H), 1.26 (s, 26 H), 2.62 (brs, 1H), 2.88 (d, *J* = 6.9 Hz, 1H), 3.43 (s, 3H), 3.56-3.77 (m, 6H), 4.64-4.75 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.2, 22.7, 25.3, 29.4, 29.7, 31.0, 32.0, 55.9, 65.1, 71.0, 74.2, 82.6, 96.2, 97.5; **Analysis:** **$C_{20}H_{42}O_5$** requires C, 66.26; H, 11.68; found: C, 65.95; H, 11.99%.

(2S,3S,4R)-Octadecane-1,2,3,4-tetraol: (Guggultetrol) 1

To a stirred solution of the triol **66** (72 mg, 0.2 mmol) in methanol (5 mL) was added con. HCl and stirred for 4 h. It was then extracted with EtOAc (3 × 10 mL), washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. Silica gel column chromatographic purification of the crude product using petroleum ether/EtOAc (3:7) gave guggultetrol (50 mg) as a colorless solid.

Yield: 0.05 g, 78%; **mp**: 80-133 °C (lit.[10] **mp**: 87-135 °C); **[α]$^{25}_{D}$**: +12 (*c* 0.5, EtOH) {lit.[10,11] **[α]$^{25}_{D}$**: +11.4 (*c* 0.34, EtOH)}; **IR** (MeOH, cm^{-1}): υ_{max} 3382, 2925, 2833, 1448, 1419, 1116, 1027; **^{1}H NMR** (200 MHz, MeOH-d_4): δ 0.86 - 0.93 (m, 3H), 1.29 (s, 24H), 1.52 (brs, 2H), 3.41 - 3.45 (m, 1 H), 3.57 - 3.74 (m, 4H); **^{13}C NMR** (125 MHz, MeOH-d_4): δ 14.6, 23.9, 27.0, 30.6, 30.9, 30.9, 31.0, 33.2, 34.7, 64.6, 73.7, 74.3, 74.5; **Analysis:** $C_{18}H_{38}O_4$ requires C, 67.88; H, 12.03; found: C, 67.59; H, 12.34%.

Enantioselective synthesis of D-*ribo*-Phytosphingosine Tetraacetate (46):

***(2S,3S,4R)*Ethyl-2,3-dihydroxy-4-(methoxymethoxy)octadecanoate (67)**

To a mixture of $K_3Fe(CN)_6$ (3.3 g, 10 mmol), K_2CO_3 (1.4 g, 10 mmol) and $(DHQD)_2PHAL$ (5 mg, 1 mol%), in *t*-BuOH/H_2O (1:1, 65 mL) cooled at 0 °C was added $K_2OsO_4.H_2O$ (5.5 mg, 0.5 mol%) followed by methanesulfonamide (313 mg, 3.3 mmol). After being stirred for 5 min at 0 °C, olefinic ester **64** (1.2 g, 3.3 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 15 h and then quenched with solid sodium sulfite (5 g). The stirring was continued for an additional 45 min, and then the solution was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over anhyd. Na_2SO_4 and concentrated. Silica gel column chromatographic purification of the crude product using petroleum ether/EtOAc (7:3) as eluent gave the diol ester **67** (1.1 g) as a viscous liquid.

Yield: 1.1 g, 86%; **[α]$^{25}_{D}$**: ⁻11.5 (*c* 1, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.26 - 1.34 (m, 27H), 1.63 - 1.70 (m, 2H), 2.63 (brs, 1H), 3.27 (brs, 1H), 3.41 (s, 3H), 3.62 (td, *J* = 6.8, 4.1Hz, 1H), 3.81 (d, *J* = 7.3 Hz, 1H), 4.29 (dd, *J* = 7.3, 1.5Hz, 2H), 4.44 (s, 1H), 4.66 (d, *J* = 6.4 Hz, 1H), 4.71 (d, *J* = 6.7 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 14.2, 14.2, 22.7, 24.6, 29.4, 29.6, 29.7, 29.9, 31.3, 32.0,

56.0, 62.0, 70.2, 73.0, 79.3, 96.2, 97.0, 173.6; **Analysis:** $C_{22}H_{44}O_6$ required C, 65.31; H, 10.96; found: C, 65.62; H, 10.69%.

(*2R,3S,4R*)-Ethyl 2-azido-3-hydroxy-4-(methoxymethoxy)octadecanoate (69)

To a solution of dihydroxy ester **67** (1.1 g, 2.8 mmol) in CH_2Cl_2 (25 mL) was added Et_3N. Then the mixture was stirred at 5 °C for 30 min. This was followed by the addition of p-nitrobenzenesulphonyl chloride (NsCl) (674 mg, 3.05 mmol) in one portion and the mixture was stirred for 48 h at the same temperature; then the reaction mixture was quenched with water and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with water (2 × 20 mL) and brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. Silica gel column chromatographic purification of the crude product using petroleum ether/EtOAc (90:10) gave nosylate **68** (1.2 g) as colourless gum.

Yield: 1.2 g, colourless gum; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.6 Hz, 3H), 1.18-1.33 (m, 27H), 1.56-1.69 (m, 2H), 2.80 (d, *J* = 9.6 Hz, 1H), 3.44 (s, 3H), 3.60 (q, *J* = 5.5 Hz, 1H), 3.92- 4.05 (m, 1H), 4.13-4.23 (m, 2H), 4.62 (d, *J* = 6.9 Hz, 1H), 4.71 (d, *J* = 6.4 Hz, 1H), 5.34 (d, *J* = 1.8 Hz, 1H), 8.18 (d, *J* = 8.7 Hz, 2H), 8.38 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.1, 14.2, 22.8, 24.5, 29.4, 29.6, 29.7, 29.8, 31.0, 32.0, 56.3, 62.3, 72.5, 78.2, 80.3, 97.9, 124.1, 129.6, 142.5, 150.8, 167.3; **Analysis:** $C_{28}H_{47}NO_{10}S$ required C, 57.03; H, 8.03; N, 2.38, S, 5.44; found: C, 56.98; H, 8.10; N, 2.25, S, 5.32%.

Nosylate **68** (1.2 g, 1.36 mmol) was then dissolved in dry.DMF and treated with NaN_3 (90 mg, 1.37 mmol). The mixture was then stirred at 50 °C for 16 h and the solution was extracted with EtOAc (3 × 20 mL) and washed with brine (3 x 10 mL). The combined organic extracts were dried over anhyd. Na_2SO_4 and concentrated. Silica

gel column chromatographic purification of the crude product using petroleum ether/EtOAc (85:15) as eluent gave azido ester **69** (0.7 g) as a pale yellowish liquid.

Yield: 0.7 g, 61%; a pale yellowish liquid; $[\alpha]^{25}_{D}$: -7.1 (c 2.09, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3560, 3401, 2099, 1736, 1216, 1031, 927, 767, 669; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.4 Hz, 3H), 1.26 (s, 24H), 1.34 (t, *J* = 7.3 Hz, 3H), 1.58 (m, 1H), 1.66 (m, 1H), 3.22 - 3.29 (m, 1H), 3.41 (s, 3H), 3.57 - 3.72 (m, 1H), 3.93 (s, 2H), 4.28 (q, *J* = 7.3 Hz, 2H), 4.59 (d, *J* = 6.9 Hz, 1H), 4.69 (d, *J* = 6.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.2, 22.7, 25.3, 29.4, 29.6, 29.7, 30.8, 32.0, 56.1, 61.7, 62.3, 72.9, 76.7, 77.3, 81.5, 96.2, 97.5, 168.9; **Analysis**: $C_{22}H_{43}N_3O_5$ required C, 61.51; H, 10.09, N, 9.78; found: C, 61.35; H, 10.25; N, 9.46%.

(2*S,3S,4R*)-2-Azido-4-(methoxymethoxy)octadecane-1,3-diol (70)

To a stirred solution of azido ester **69** (253 mg, 0.6 mmol) in MeOH (2 mL), was added $LiBH_4$ (32 mg, 1.47 mmol) slowly at 0 °C and the mixture was stirred at 25 °C for overnight, then reaction was quenched with sat.NH_4Cl solution. The solvent was evaporated under reduced pressure then the crude was extracted with EtOAc (2 x 10 mL) and the combined organic extracts were dried over anhyd. Na_2SO_4 and concentrated. Silica gel column chromatographic purification of the crude product using petroleum ether/EtOAc (70:30) as eluent gave the azido diol **70** (0.18 g) as a colourless viscous liquid.

Yield: 0.18 g, 89%; colourless liquid; $[\alpha]^{25}_{D}$: -0.6 (c 0.4, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3401, 2925, 2854, 2362, 2101, 1482, 1373, 1268, 1149, 1097, 1034, 916, 770, 722, 674; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.88 (m, 3H), 1.26 (s, 23H), 1.45 (brs, 2H), 1.67 (brs, 2H), 2.66 (brs, 1H), 3.23 (d, *J* = 5.3 Hz, 1H), 3.42 (s, 3H), 3.51 (m, 1H), 3.70 (m, 2H), 3.94 (m, 2H), 4.62 (d, *J* = 6.7 Hz, 1H), 4.74 (d, *J* = 6.7 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.2, 22.8, 25.9, 29.4, 29.6, 29.7, 29.8, 30.1, 32.0, 56.0,

62.7, 63.0, 72.9, 76.7, 77.3, 81.8, 96.2, 97.2; **Analysis**: $C_{22}H_{43}N_3O_5$ required C, 61.98; H, 10.66, N, 10.84; found: C, 61.74; H, 10.31; N, 10.56%.

(2S,3S,4R)-2-Azidooctadecane-1,3,4-triol (71)

To a stirred solution of alcohol **70** (150 mg, 0.2 mmol) in methanol (5 mL) was added con. HCl and the mixture stirred for 12 h. It was then extracted with EtOAc (3 × 5 mL), washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. Silica gel column chromatographic purification of the crude product using petroleum ether/EtOAc (1:1) gave azido triol **71** (95 mg) as colorless solid.

Yield: 95 mg, 80%; **mp**: 141 °C; **$[\alpha]^{25}_D$**: +8.05 (c 0.3, MeOH); **IR** (MeOH, cm^{-1}): υ_{max} 3445, 2959, 2836, 2387, 2099, 1476, 1363, 1295, 1134, 1082, 916, 795, 652; **^{1}H NMR** (400 MHz, MeOH-d_4): δ 0.90 (m, 3H), 1.29 (brs, 26H), 3.35 (brs, 2H), 3.55 (m, 3H), 3.77 (m, 1H), 3.92 (m, 1H), 4.57 (brs, 1H); **^{13}C NMR** (100 MHz, MeOH-d_4): δ 14.6, 23.9, 26.9, 30.6, 30.9, 33.2, 34.0, 48.5, 48.7, 48.9, 49.4, 49.6, 49.8, 62.7, 66.8, 73.0, 76.1; **Analysis**: $C_{18}H_{27}N_3O_3$ required C, 62.94; H, 10.86, N, 12.23; found: C, 62.80; H, 10.81; N, 11.97%.

2S,3S,4R)-2-Acetamidooctadecane-1,3,4-triyl triacetate:

[D-*ribo*-Phytosphingosine Tetraacetate (46)]

To a solution of 80 mg (0.21 mmol) of azido triol **71** in 10 mL of MeOH was added 25 mg (0.04 mmol) of 20% $Pd(OH)_2/C$. The solution was stirred with H_2 filled balloon (1 atm) overnight, then the crude reaction mixture was filtered through a short pad of Celite, which was washed with 50 mL of MeOH. Then the solvent was evaporated and gave the colorless solid. To the crude solution of colorless solid in pyridine (15 mL), was added Ac_2O (240 μL, 2.4 mmol), catalytic amount of DMAP (4 mg). Then the resulting mixture was stirred at 25 °C, for 16 h. After evaporating the solvent under reduced pressure, the obtained crude was kept in vacuum for 30 min

and then it was directly purified with column chromatography using petroleum ether/EtOAc (80:20) to give D-*ribo*-phytosphingosine tetraacetate **46** (84 mg) as colorless liquid.

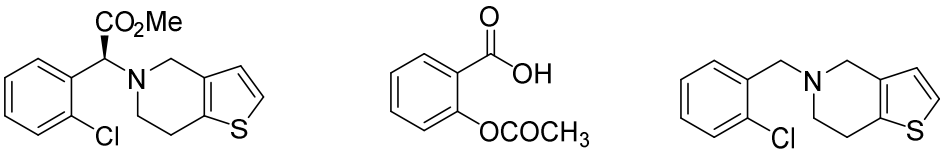
Yield: 84 mg, 85%; $[\alpha]^{25}_{D}$: +22.31 (c 0.5, $CHCl_3$) {lit.[18] $[\alpha]^{25}_{D}$: +21.9 (*c* 1.1, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 3421, 2942, 2872, 1746, 1673, 1496, 1347, 1289, 1178; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.7 Hz, 3H), 1.25 (s, 24H), 1.64 (m, 2H), 2.02 (m, 11H), 2.17 (s, 1 H), 3.98 (dd, *J* = 11.7, 2.9 Hz, 1H), 4.29 (dd, *J* = 11.6, 4.8 Hz, 1H), 4.34 - 4.51 (m, 1H), 4.91 (dt, *J* = 9.8, 3.2 Hz, 1H), 5.08 (dd, *J* = 8.4, 3.1 Hz, 1H), 5.99 (d, *J* = 9.3 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.2, 20.7, 20.8, 21.0, 22.7, 23.3, 25.6, 28.1, 29.3, 29.4, 29.5, 29.6, 29.7, 32.0, 47.7, 62.9, 71.9, 73.0, 169.6, 170.0, 170.7, 171.1; **HRMS (ESI, m/z)**: Calculated for $C_{26}H_{48}NO_7$ $(M+H)^+$ 486.3431, found 486.3435; **Analysis**: $C_{26}H_{47}NO_7$ required C, 64.30; H, 9.75, N, 2.88; found: C, 64.1; H, 9.58; N, 2.96%.

Section II

Concise Synthesis of (±)-Clopidogrel *via* insertion of CO_2 at the benzylic position

4.2.1. Introduction

(S)-Methyl-2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-*c*]pyridin-5(4H)-yl)acetate also known as (S)-clopidogrel (**74**) under international non-proprietry name is marketed as hydrogen sulphate salt. It is a potent antiaggregant and antithrombotic drug demonstrated in several experimental models of thrombosis.[26] It was marketed and licensed by Sanofi in 1986. The drug was launched on the market following a successful clinical evaluation[27] and studies have shown that clopidogrel is more effective in blocking platelet aggregation than aspirin **75** and ticlopidine **76** even at much lower dosage.[28] Clopidogrel has an absolute 'S' configuration at C_7[29]. The corresponding 'R' enantiomer is totally devoid of antiaggregating activity.



74 **75** **76**

Fig. 17: Structure of (S)-clopidogrel (**74**), aspirin (**75**) and ticlopidine (**76**)

4.2.2. Pharmacology

(S)-Clopidogrel **74** is an antiplatelet drug, which was the second top-selling drug worldwide in 2005 with the commercial trade name of 'Plavix'. It is an adenosine diphosphate (ADP) receptor antagonist indicated for the reduction of atherosclerotic events including myocardial infarction, ischemic stroke, and vascular death in patients with atherosclerosis. Clopidogrel works by helping to prevent harmful blood clots

during percutaneous coronary intervention (PCI), which is a non-surgical procedure used to treat the narrowed coronary arteries of the heart found in coronary heart disease. Pharmacologically, clopidogrel is believed to be a pro-drug and during its bio-transformation, it forms 2-oxo-clopidogrel (**77**) which is further transformed into sensitive thiol **78** *via* an incubation of human liver microsomes. Then sensitive thiol **78** then binds covalently by a disulfide bridge to its pharmacological target.[30]

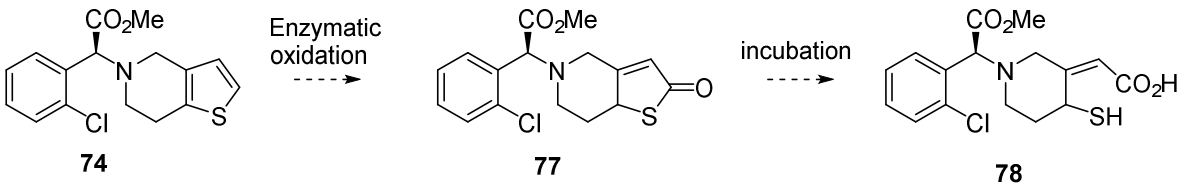


Fig. 18: Enzymatic conversion of clopidogrel (**74**) *via* 2-oxoclopidogrel (**77**) into the active metabolite (**78)**

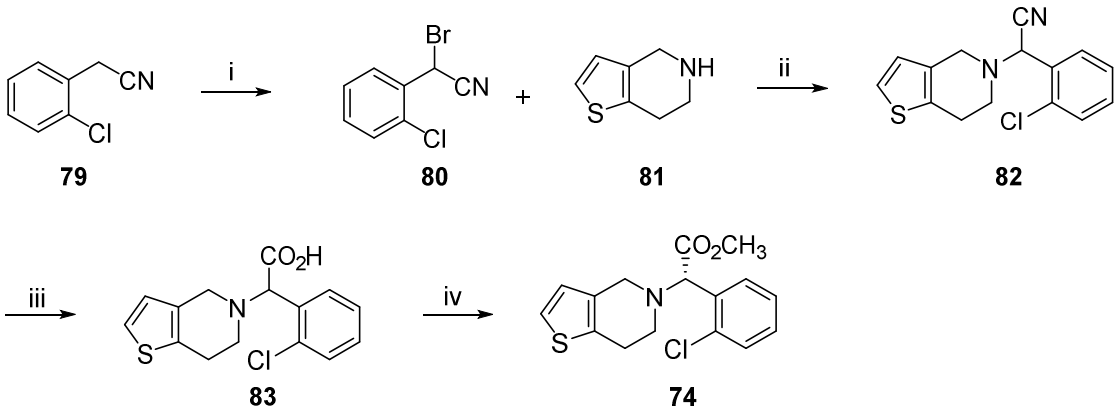
4.2.3. Review of Literature

Literature and patent survey revealed that many methods[31-36] are known for the synthesis of clopidogrel **74** in its racemic as well as chiral forms; Some of which are described below.

Wang's approach (2007)[31]

Wang *et. al*. have developed a useful synthetic method for the synthesis of (S)-clopidogrel **74** in high yield. Reaction of 2-chlorophenyl acetonitrile **79** NBS afforded α-bromo-2-chlorophenyl acetonitrile **80**. Compound **80** was then treated with amine **81** to provide nitrile **82**. Further, nitrile **82** was hydrolysed with con. NaOH and triethylbenzylammonium chloride as phase transfer catalyst to give acid **83** in 95% yield. Esterification of acid in refluxing methanol and con. H_2SO_4 furnished (±)-clopidogrel (±)-**74** in 70% yield. Finally, the resolution of (±)-clopidogrel (±)-**74**

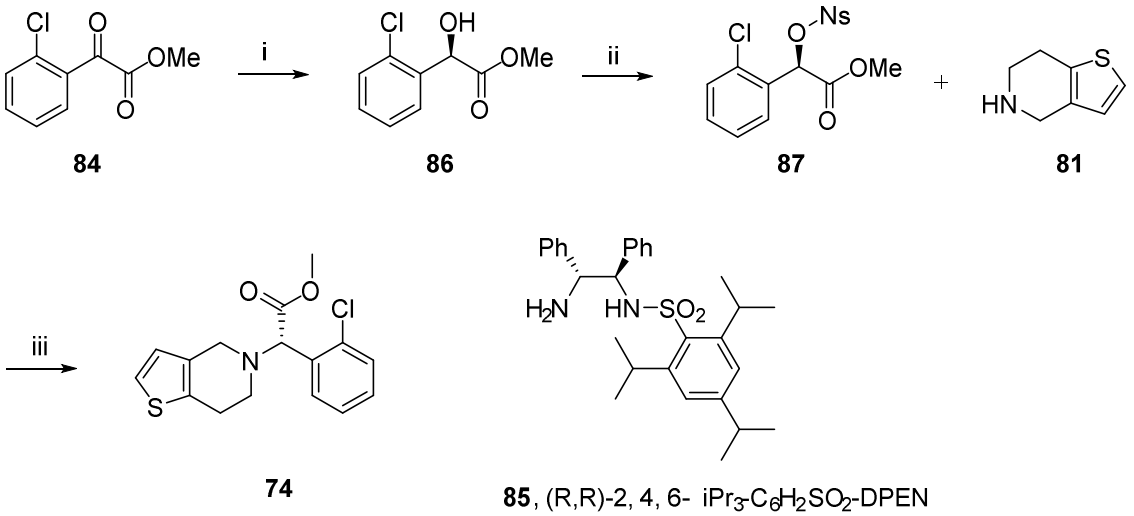
using 10-L-camphorsulphonic acid (L-CSA) furnished (S)-clopidogrel **74** in 88% yield with >98.3%ee (**Scheme 14**).



Scheme 14: (i) Br_2, 100-110 °C, 6 h, 86%; (ii) $NaHCO_3$, methanol, reflux, 3 h, 85%; (iii) TEBA, 40-50% NaOH (aq), methanol, reflux, 12 h, 95%; (iv) (a) TEBA, methanol, NaOH, dimethyl sulfate, 40 °C, 12 h; 87%; (b) L-CSA. H_2O, toluene, 48 h, 93%, >99.5% ee.

Xingshu Li Approach (2009)[32]

Xingshu Li *et. al*. have made use of asymmetric transfer hydrogenation of α-keto ester *i.e*. methyl o-chlorobenzoylformate **84** as the key reaction using the complex formed

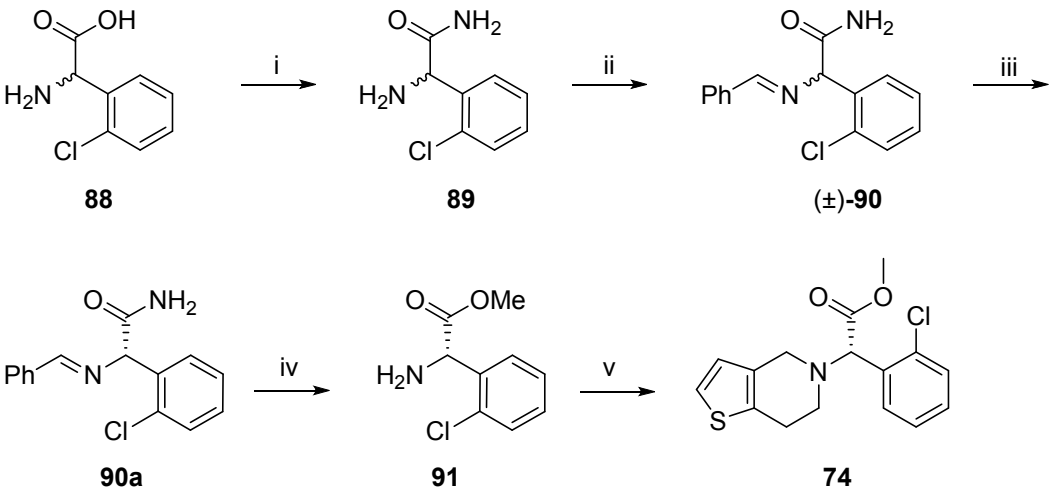


Scheme 15: (i) $[Ru(p\text{-cymene})Cl_2]_2$ (0.5 mol%), L (0.5 mol%), $HCOOH/Et_3N$(5:2), DMF, 80 °C; (ii) 4-nitrobenzenesulphonylchloride, DMAP (10 mol%), Et_3N, CH_2Cl_2, 0 °C, 3 h, 78%; (iii) X, 30% aq. K_2CO_3, CH_2Cl_2, reflux, 2.5 h, 70%.

from [Ru(p-cymene)Cl_2]$_2$ and (R,R)-2,4,6-*i*Pr_3-$C_6H_2SO_2$-DPEN **85**. Thus, alcohol **86** on treatment with p-nitrobenzenesulphonyl chloride produced its nosylate **87** which was subjected to S_N2 displacement reaction with secondary amine **81** to provide the (S)- clopidogrel **74** in good yield and 90% ee (**Scheme 15**).

Kellog's approach (2009)[33]

Kellog's *et. al*. have reported the synthesis of (S)-clopidogrel **74** starting from the (±)-2-chlorophenylglycine **88**. Thus, (±)-2-chlorophenylglycine **88** was transformed into amide **89** followed by the formation of imine (±)-**90** which appeared as the conglomerates. The conglomerates were further carried to a process known as

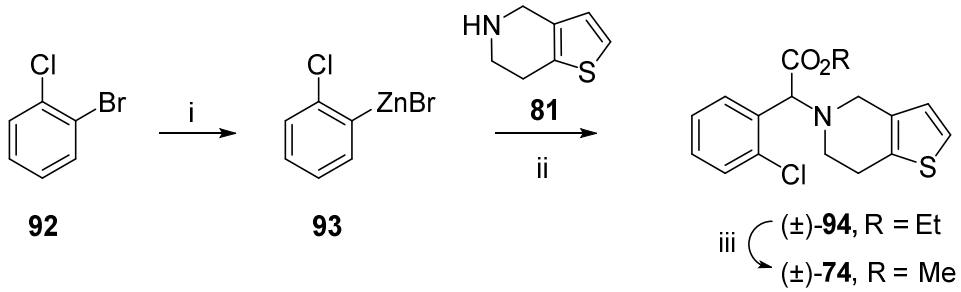


Scheme 16: (i) (a) $SOCl_2$, MeOH, 3 h, 25 °C, 95%; (b) aq. NH_3, 12 h, 25 °C, 81%; (ii) (a) PhCHO, Na_2SO_4, overnight, 25 °C, 90%; (iii) DBU, CH_3CN, sonication, 20 °C, 2 d; (iv) (a) con.HCl, acetone, 1 h, 25 °C, 95%; (b) con. H_2SO_4, MeOH, 4 h, reflux then 12 h at 25 °C, 94%; (v) 2-(2-bromoethyl)-3-(bromomethyl)thiophene, DIPEA, MeCN, reflux, overnight, 95%, >99%ee.

'attrition enhanced deracemization' *via* the treatment with DBU to crystallize the required enantiomer **90a** with >99% ee. Acid hydrolysis and esterification of imine **90a** provided (S)-2-chlorophenylglycine methyl ester **91**. Finally, methyl ester **91** was treated with 2-(2-bromoethyl)-3-(bromomethyl)thiophene to give the target molecule **74** in 95% yield with >99%ee (**Scheme 16**).

Gall's approach (2010)[34]

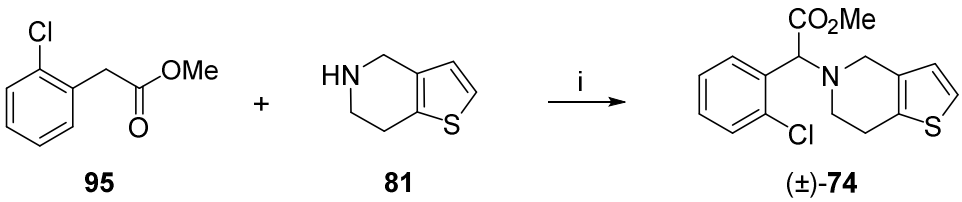
Gall *et. al*. have made use of Mannich-like multicomponent reaction for an efficient synthesis of (±)-clopidogrel (±)-**74**. Thus, 1-bromo-2-chlorobenzene **92** was treated with Zn dust and $CoBr_2$ to form the reagent 2-chlorophenyl zinc bromide **93** in 75% yield. The organozinc compound **93** was treated with ethyl glyoxalate and amine **81** to provide the ethyl ester (±)-**94** in 78% yield. Further transesterificatin of ethyl ester (±)-**94** in MeOH afforded the (±)-clopidogrel (±)-**74** in 52% yield (**Scheme 17**).



Scheme 17: (i) $CoBr_2$ (10 mol%), Zn dust, dodecane, $BrCH_2CH_2Br$, CH_3CN, heat, 45 min, 75%; (ii) ethyl glyoxalate, amine, 60-25 °C, 30 min, 78%; (iii) Na, MeOH, 0-65 °C, 30 min, 52%.

Macmillan's approach (2013)[35]

Macmillan *et. al*. have developed a simple method for the direct coupling of α-carbonyls with functionalized amines using $CuBr_2$ as the catalyst. Thus, methyl 2-(2-chlorophenyl) acetate **95** and amine **81** were successfully coupled in the presence of $CuBr_2$ and oxygen to give (±)-clopidogrel (±)-**74** in one step with 87% yield (**Scheme 18**).



Scheme 18: (i) $CuBr_2$ (10 mol%), O_2 (1 atm), DMSO, 50 °C, 24 h, 87%.

Patented methods[36]

Patented methods mainly involves the resolution of (±)-clopidogrel (±)-**74** using 10-L-camphorsulphonic acid (L-CSA) or its precursor α-amino ester using D- or L-tartaric acid. These intermediates in turn were obtained *via* simple S_N2 displacement reactions, and NaCN addition on imines.

4.2.4. Present work

4.2.4.1. Objective

As can be seen from the above discussion, there are quite efficient strategies available in the literature. Also, there are mainly two kinds of strategies known for the synthesis of clopidogrel, such as (i) from 2-chlorophenylglycine or derivatives of 2-chloromandelic acid; (ii) from α-halogen substituted phenyl acetonitrile; all involving S_N2 substitution reaction. Although many methods are known for the synthesis of clopidogrel such as stereoselective hydrogenation, S_N2 displacement and oxidative coupling reactions, still there is a need for the efficient synthesis of (±)-clopidogrel (±)-**74** with one carbon homologation using insertion of CO_2 at the benzylic position.[37] This is unprecendented till now for its synthesis. Herein, we present a concise synthesis of (±)-clopidogrel (±)-**74** starting from readily available and cheap starting materials.

Retrosynthetic analysis of (±)-clopidogrel (±)-**74** reveals that α-amino ester **99** could be visualized as the key intermediate, which in turn can be obtained from the insertion of CO_2 at the benzylic position in Boc-protected benzylamine **98** derived from 2-chlorobenzaldehyde (**96)** (**Fig. 19**).

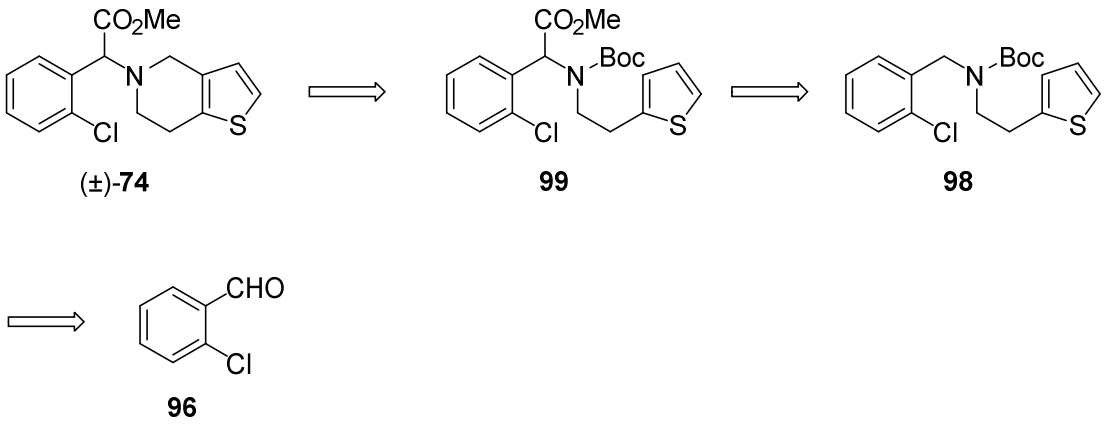


Fig. 19: Retrosynthetic analysis of (±)-clopidogrel (±)-**74**

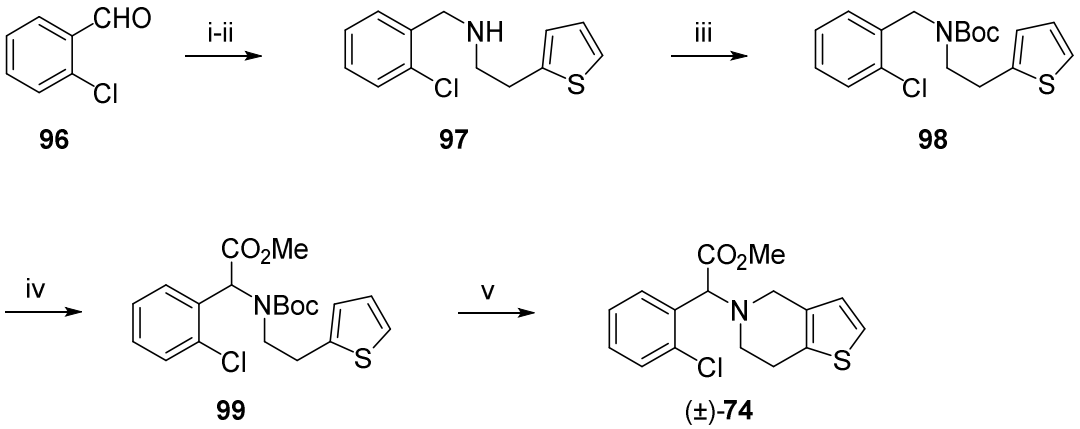
Since this section involves the utilization of CO_2, a brief account on its importance in organic synthesis is given below.

4.2.4.2. CO_2 utilization in organic synthesis

CO_2 insertion for an alternative energy sources is a topic of current interest due to the rise in average global surface temperatures and atmospheric CO_2 concentrations. Hence, this leads to drive the research on the storage of carbon-neutral energy,[38] as various fine chemicals such as cyclic carbonates,[39] alkyl or aryl carboxylic acid,[40] HCOOH[41] and fuels namely methanol[42] and methane. Carbon dioxide is an attractive carbon source for organic synthesis due to its low cost, low toxicity, and ease of handling. Despite the extensive use of carbon monoxide in homo- and heterogeneous catalysis as a C_1 feedstock, *e.g.* hydroformylation,[43] methodology to utilize carbon dioxide under mild conditions remains underdeveloped which is of grand challenge.[44] From the view point of synthetic chemistry, chemically inert CO_2 was transformed to various industrial products.

4.2.5. Results and Discussion

The complete synthetic sequence for synthesis of (±)-clopidogrel **74**, wherein insertion of CO_2 at the benzylic position constitutes a key step, is presented in **Scheme 19**.



96 **97** **98** **99** (±)-**74**

Scheme 19: (i) Thiophene-2-ethanolamine (1.1 equiv), $MgSO_4$ (2 equiv), CH_2Cl_2, 20 min, 25 °C; (ii) $NaBH_4$ (2.5 equiv), MeOH, 15 min, 25 °C, 92% for two steps; (iii) Boc_2O (1.5 equiv), Et_3N (1.5 equiv), DMAP (40 mol%), CH_3CN, 7 h, 25 °C, 85%; (iv) CO_2 (1-2 atm), *n*-BuLi (1 equiv), THF, -78 ^oC, 3 h then MeI (2 equiv), 25 °C, 3 h, 65%; (v) TFA (2.5 equiv), CH_2Cl_2, 0 ^oC, 4 h and paraformaldehyde (1.2 equiv), 24 h, one pot, 68% yield.

Accordingly, the synthesis of (±)-clopidogrel (±)-**74** was undertaken starting from commercially available 2-chlorobenzaldehyde (**96**). The condensation of 2-chlorobenzaldehyde (**96**) with thiophene-2-ethanolamine in CH_2Cl_2 and anhydrous Na_2SO_4 at room temperature provided the corresponding imine. The subsequent reduction of imine using $NaBH_4$ in methanol at 0 °C gave the N-substituted-2-chlorobenzylamine **97**. The ^1H NMR spectrum of **97** showed a typical signal at δ 3.89 (s, 2H) corresponding to benzylic methylene proton while its ^{13}C NMR spectrum displayed a typical carbon signal at δ 50.9, which confirmed the presence of benzylic methylene carbon (**Fig. 20**).

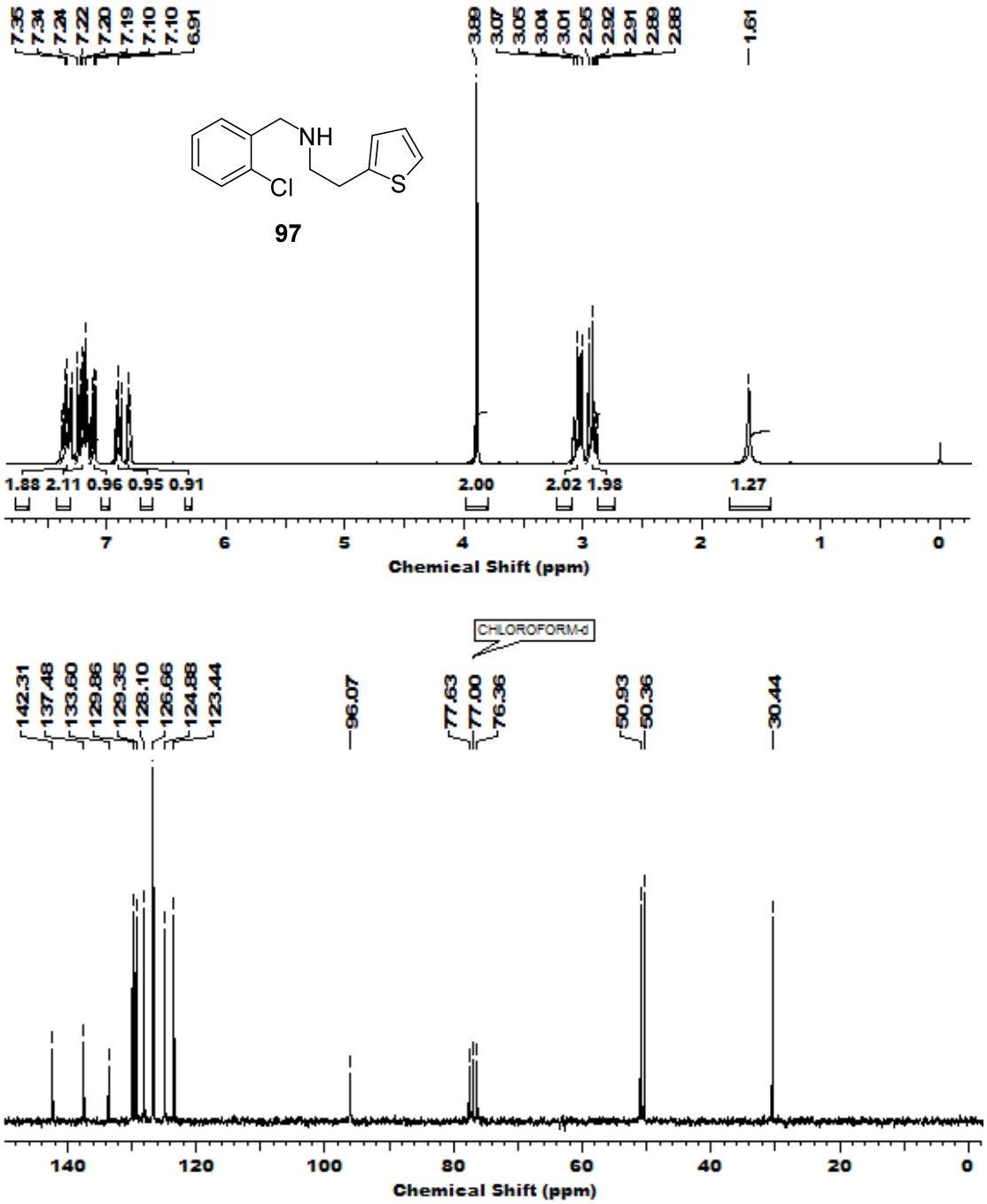


Fig. 20: ^{1}H and ^{13}C NMR spectra of N-substituted-2-chloro benzylamine **97**

The N-substituted-2-chlorobenzylamine **97** was then protected as Boc-carbamate **98** by treating it with $(Boc)_2O$ in CH_3CN at room temperature. The ^{1}H NMR spectrum of **98** showed the presence of rotameric proton signals at δ 1.41 (brs, 4H), and 1.49 (brs, 5H) as two broad singlets for nine Boc-methyl protons and at δ 4.45 (brs, 1H) and

4.55 (brs, 1H) as two broad singlets for two benzylic protons. Its ^{13}C NMR spectrum also displayed the presence of rotameric carbon signals at δ 155.3, and 155.6 for carbonyl carbon present in the Boc group (**Fig. 21**).

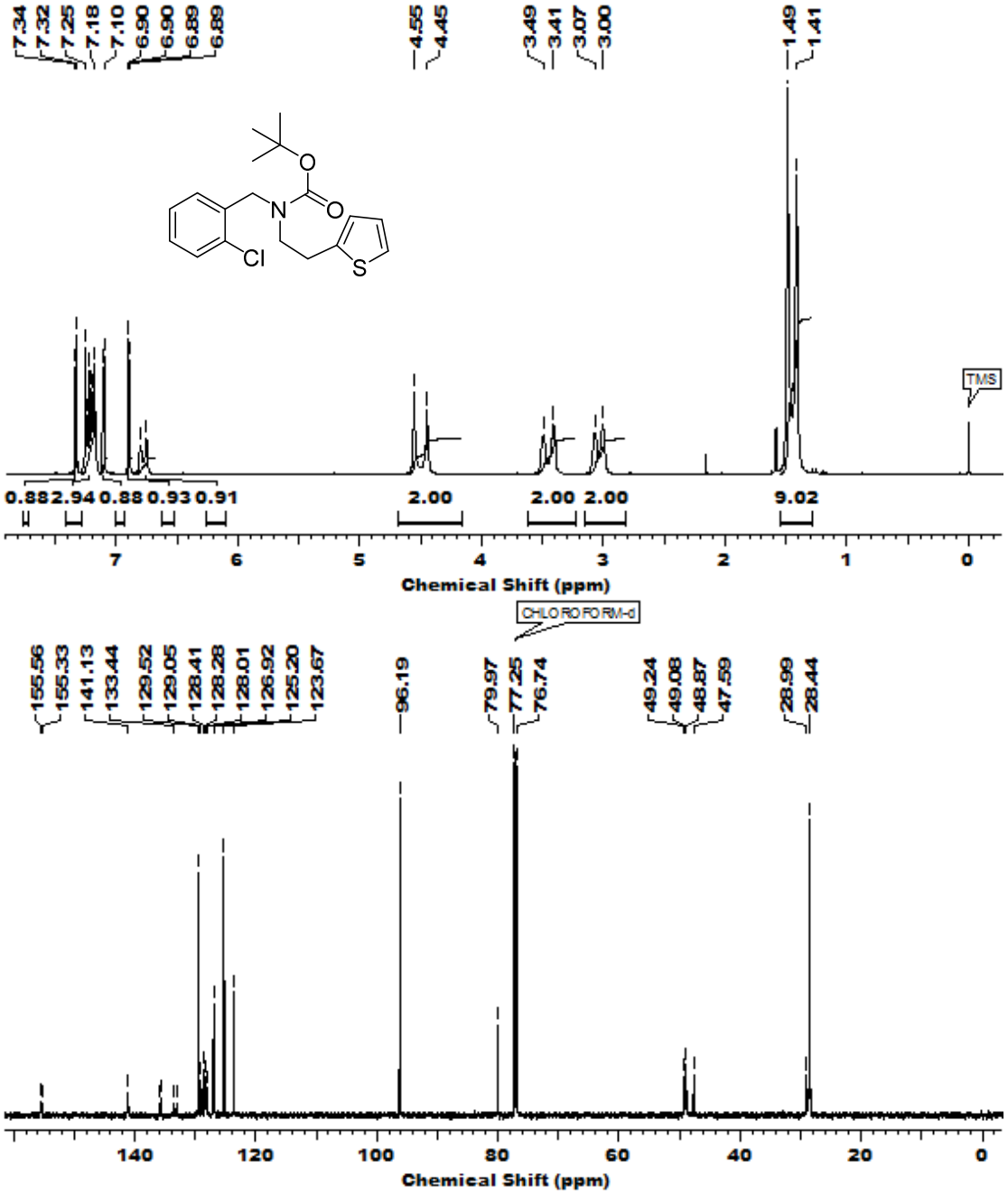
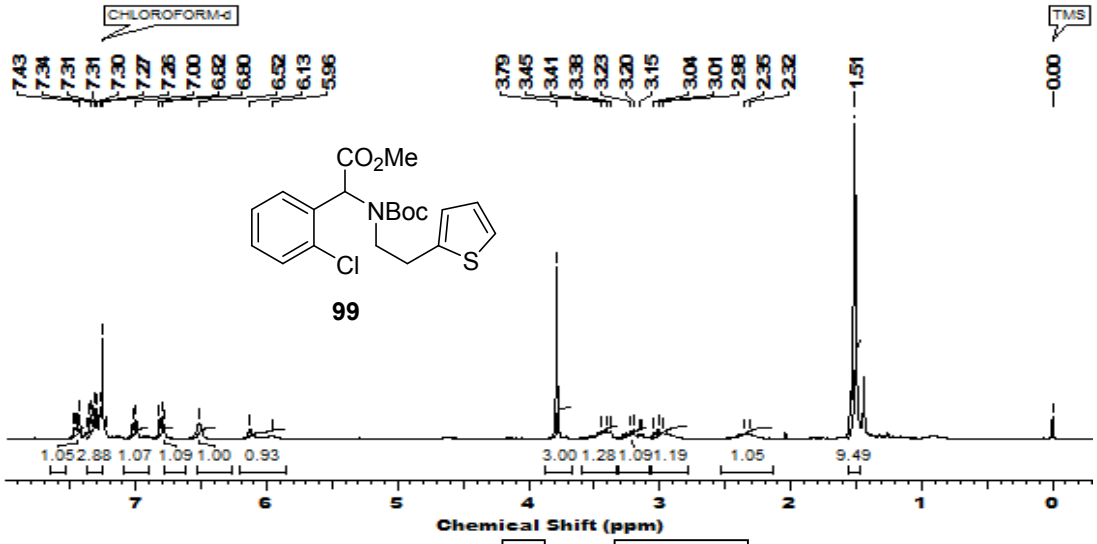


Fig. 21: ^{1}H and ^{13}C NMR spectra of Boc-carbamate **98**

Insertion of CO_2 at benzylic position of carbamate **98** was achieved by using *n*-BuLi as strong base with the bubbling of CO_2 at -78 °C in dry THF to provide the α-amino

acid as its lithium salt indicated by the formation of turbid pale yellow solution after three hours. Subsequently, α-amino acid salt was treated with $NaHCO_3$ and MeI in DMF to furnish the α-amino ester **99** in 65% yield. In order to make this process in an asymmetric fashion, CO_2 was bubbled to solution containing carbamate **98**, (+)-sparteine (1 equiv), *n*-BuLi at -78 °C, we ended up with the α-amino ester **99** in only 3% ee. The ^{1}H NMR spectrum of **99** showed the characteristic proton signals at δ 3.72 (s, 3H) and 6.13 (brs, 1H) for three methyl protons (-$CO_2C\mathbf{H_3}$) and one benzylic proton (-C**H**CO_2Me) respectively. Its ^{13}C NMR spectrum displayed characteristic carbon signals at δ 52.2 and 170.8 corresponding to methyl and carbonyl carbons present in the ester group (-**C**O_2**C**H_3). Its IR spectrum exhibited characteristic absorption bands at 1697 and 1742 cm^{-1} due to (–NCO_2tBu and -CO_2Et) groups respectively. Also, its mass spectrum showing its molecular ion peak (M+Na) at *m/z* 432.1 confirmed the formation of α-amino ester **99** (**Fig. 22**).

The Boc group in α-amino ester **99** was deprotected using trifluoroacetic acid in CH_2Cl_2 at 25 °C; then followed by electrophilic aromatic cyclization on thiophene ring was achieved on its treatment with paraformaldehyde in one pot at 10 °C and then stirring the reaction mixture at room temperature for 24 h. After quenching the reaction mixture with sat. $NaHCO_3$ solution furnished (±)-clopidogrel free base (±)-**74**. The ^{1}H NMR spectrum of **(±)-74** showed the characteristic proton signals at δ 6.65 (d, J = 5.2 Hz, 1H) and 7.04 (d, J = 5.2 Hz, 1H) corresponding to two protons attached to the thiophene ring. The ^{13}C NMR displayed the characteristic carbon signals at δ 50.7 and 171.0 confirming the newly generated methylene carbon and ester carbonyl carbon respectively (**Fig. 23**).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7.34
7.31
7.31
7.30
7.27
7.26
7.00
6.82
6.80
6.52
6.13
5.96
3.79
3.45
3.41
3.38
3.23
3.20
3.15
3.04
3.01
2.98
2.35
2.32
1.51
0.00
CO2Me
NBoc
Cl
S
99
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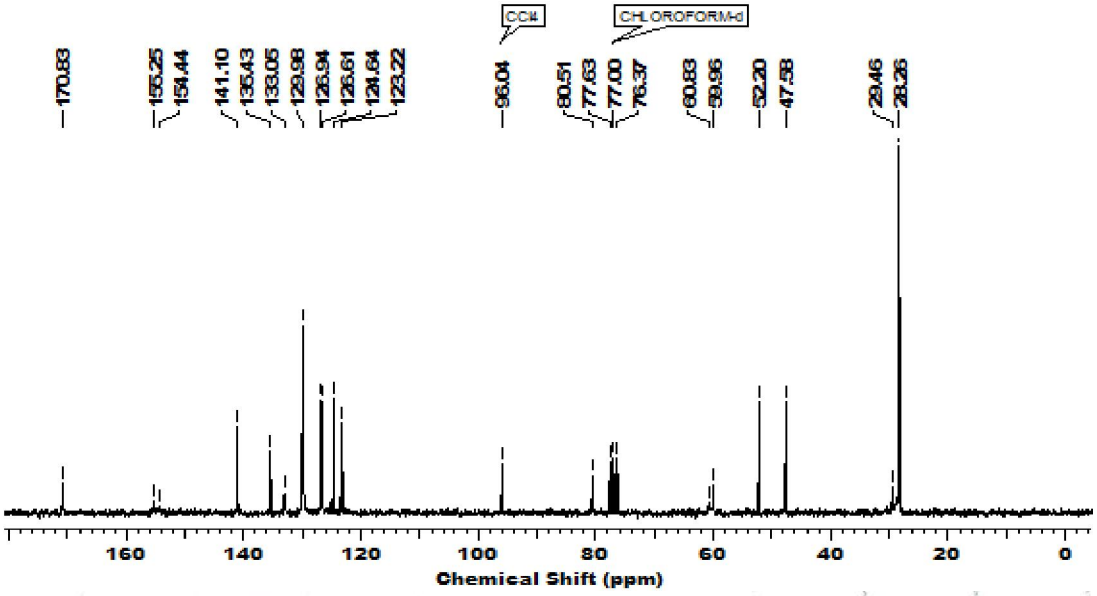
3.00 1.28 1.09 1.19
1.05
9.49
Chemical Shift (ppm)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141.10
135.43
133.05
129.98
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126.61
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123.22
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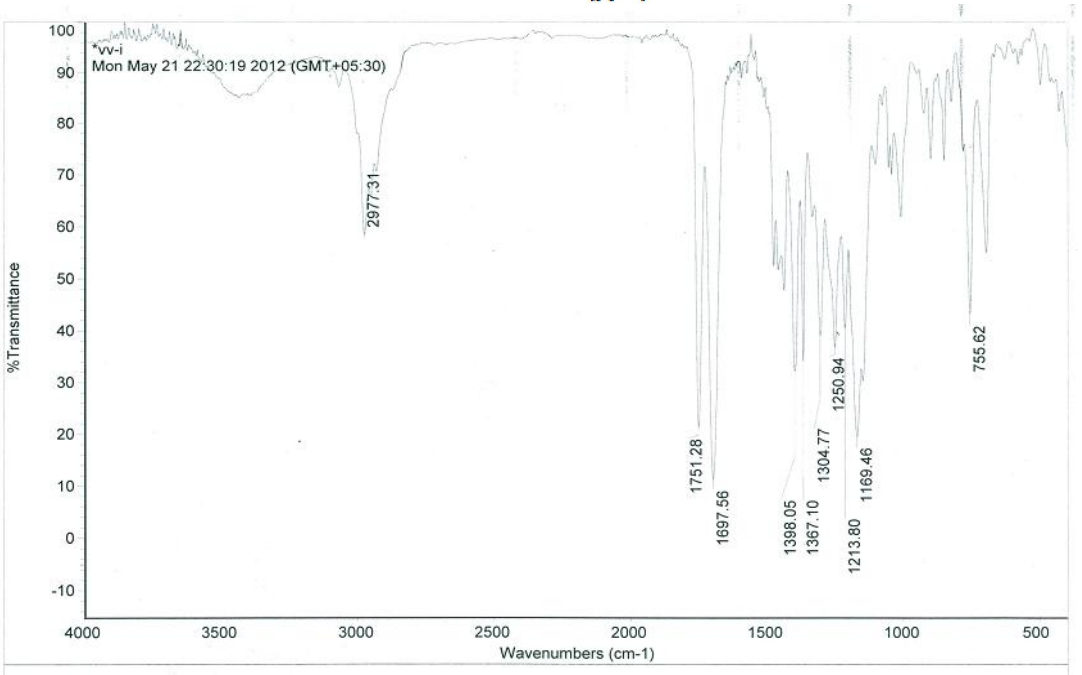
Chemical Shift (ppm)


*vv-i
Mon May 21 22:30:19 2012 (GMT+05:30)
%Transmittance
2977.31
1751.28
1697.56
1398.05
1367.10
1304.77
1250.94
1213.80
1169.46
755.62
Wavenumbers (cm-1)

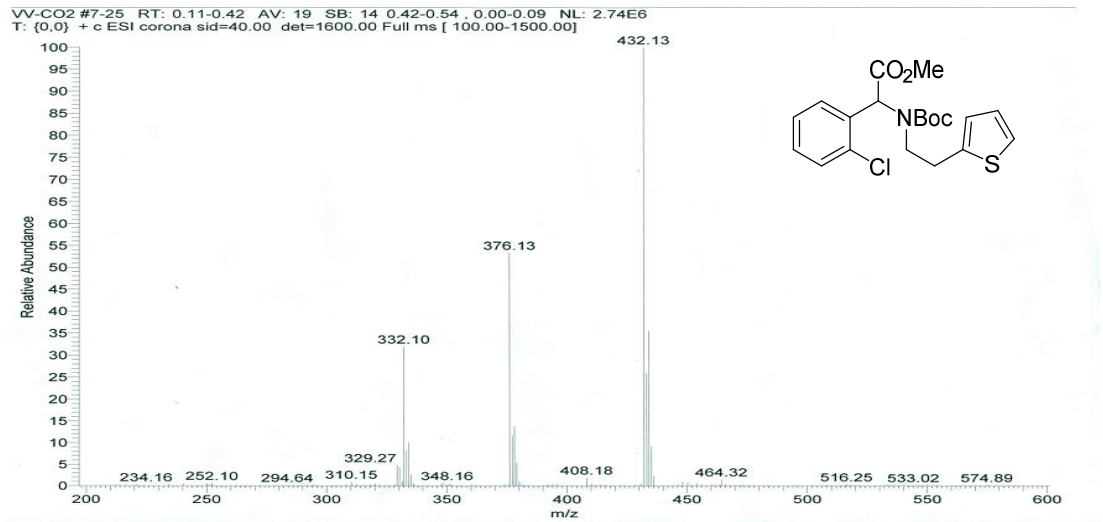


Fig. 22: ^{1}H, ^{13}C NMR, IR and Mass spectra of α-aminoester **99**

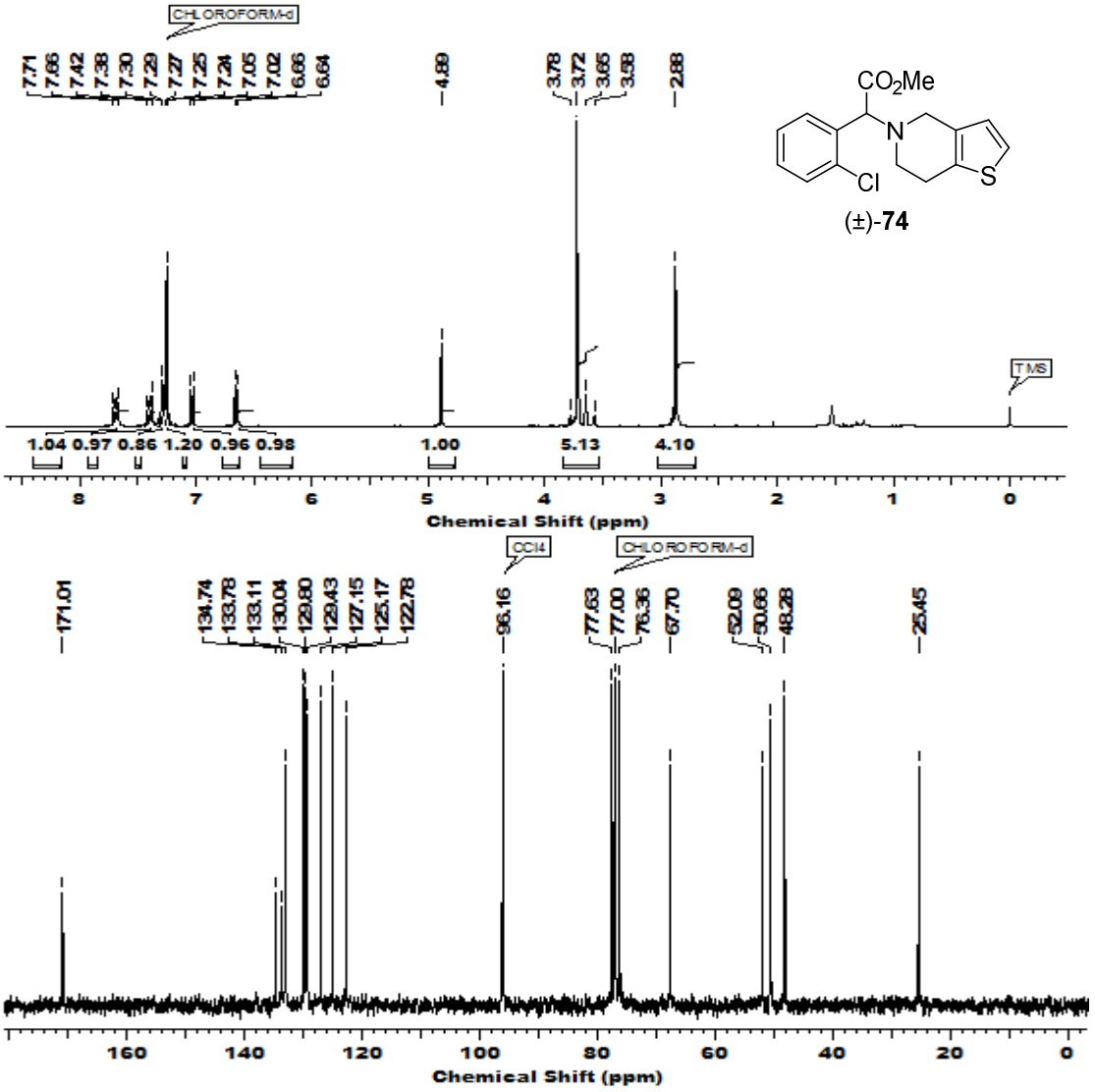


Fig. 23: ^{1}H, ^{13}C NMR spectra of (±)-clopidogrel (±)-**74**

4.2.6. Conclusion

A concise synthesis of (±)-clopidogrel with an overall yield of 38% is described by employing the insertion of CO_2 at the benzylic position as the key reaction without using any toxic transition metals. The salient features include less number of steps and avoiding the usage of toxic transition metals.

4.2.7. Experimental Section

N-(2-chlorobenzyl)-2-(thiophen-2-yl)ethan-1-amine (97)

To a stirred solution of 2-chlorobenzaldehyde (3 g, 21.36 mmol) in CH_2Cl_2 (60 mL), was added 2-(thiophen-2-yl)ethan-1-amine (3.3 g, 25.63 mmol) in CH_2Cl_2 (15 mL) and anhyd. Na_2SO_4 at 25 °C. The reaction mixture was allowed to stir at the same temperature for 30 min. This was followed by the addition of MeOH (30 mL) and $NaBH_4$ (2 g, 53.4 mmol) at 0 °C and this mixture was allowed to stir for 30 min. It was then quenched with sat. NH_4Cl solution. The solvents were evaporated in rotavapour and the residue extracted with CH_2Cl_2 (3 x 60 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude benzylamine. Silica gel column chromatographic purification of the crude product using petroleum ether/EtOAc/Et_3N (70:25:5) gave benzylamine **97** (4.9 g) as a yellow liquid.

Yield: 4.9 g, 92%; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 3440, 3331, 2912, 2826, 1471, 1441, 1049, 1037, 752, 696; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.61 (s, 1H), 2.84-2.98 (m, 2H), 2.99-3.11 (m, 2H), 3.89 (s, 2H), 6.78-6.85 (m, 1H), 6.86 - 6.96 (m, 1H), 7.11 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.15 - 7.26 (m, 2H), 7.28 - 7.40 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 30.4, 50.3, 50.9, 123.4, 124.9, 126.7, 128.1, 129.4, 129.9, 133.6, 137.5, 142.3; **Analysis:** $C_{13}H_{14}ClNS$ required C, 62.02; H, 5.61; N, 5.56; S, 12.73; found: C, 61.89; H, 5.72; N, 5.71; S, 12.65%.

***tert*-Butyl-(N-2-chlorobenzyl)-(N'-2-(thiophen-2-yl)ethyl) carbamate (98)**

To a solution of the benzyl amine **97**, (2.3 g, 9 mmol), triethylamine (1.38 mL, 9.93 mmol), and DMAP (0.6 g, 4.51 mmol) in dry CH_3CN (20 mL), was added $(Boc)_2O$ (3.9 g, 18 mmol) in dry CH_3CN (10 mL) under nitrogen at 0 °C, and the mixture was allowed to warm to room temperature and stirred for 7 h. The reaction mixture was then quenched with water and the solvent was evaporated and the crude product was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with water (2 × 50 mL) and brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. Silica gel column chromatographic purification of the crude product using petroleum ether/EtOAc (95:5) gave carbamate **98** (2.7 g) as a colorless liquid.

Yield: 2.7 g, 85%; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 3019, 2981, 2839, 2400, 1698, 1612, 1585, 1368, 1216, 1035, 1167; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.41 (brs, 4H), 1.49 (brs, 5H), 3.00 (brs, 1H), 3.07 (brs, 1H), 3.41 (brs, 1H), 3.49 (brs, 1H), 4.45 (brs, 1H), 4.55 (brs, 1H), 6.75 (brs, 1H), 6.89 (dd, *J* = 5.0, 3.5 Hz, 1H), 7.10 (d, *J* = 5.2 Hz, 1H), 7.16 - 7.29 (m, 3H), 7.33 (d, *J* = 7.6 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 28.4, 29.0, 47.6, 48.9, 49.1, 49.2, 76.7, 77.3, 80.0, 96.2, 123.7, 125.2, 126.9, 128.0, 128.3, 128.4, 129.1, 129.5, 133.0, 133.4, 135.7, 135.9, 141.1, 155.3, 155.6; **Analysis:** $C_{18}H_{22}ClNO_2S$ required C, 61.44; H, 6.30; N, 3.98; S, 9.11; found: C, 61.26; H, 6.01; N, 3.79; S, 9.02%.

Methyl-2-((*tert*-butoxycarbonyl)(2-(thiophen-2-yl)ethyl)amino)-2-(2-chlorophenyl)acetate (99)

To a stirred solution of carbamate **98** (1.5 g, 4.3 mmol) in dry THF, was added *n*-BuLi (2.96 mL, 4.7 mmol) dropwise at -78 °C under N_2 atmosphere for 15 min. CO_2 (1 atm) gas was bubbled through the reaction mixture and allowed to stir for 3 h until it formed the pale yellow turbid solution. This was followed by the addition of $NaHCO_3$

(540 mg, 6.39 mmol) and MeI (1.5 g, 10.65 mmol) in DMF and stirred for further 3 h at 25 °C. The reaction mixture was quenched with sat. NH_4Cl solution and the solvent was evaporated under reduced pressure. The obtained crude mixture was extracted with EtOAc (3 x 15 mL) and washed with brine (3 x 10 mL). The combined organic extracts were dried over anhyd. Na_2SO_4 and concentrated. Silica gel column chromatographic purification of the crude product using petroleum ether/EtOAc (90:10) as eluent gave α-amino ester **99** (1.13 g) as a colorless liquid.

Yield: 1.13 g, 65%; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 2977, 1751, 1696, 1398, 1367, 1304, 1251, 1214, 1169, 966, 756; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.51 (s, 9H), 2.32-2.35 (m, 1H), 3.01-3.04 (m, 1H), 3.15-3.23 (m, 1H), 3.38-3.53 (m, 1H), 3.79 (s, 3H), 6.13 (brs, 1H), 6.52 (brs, 1H), 6.78-6.82 (m, 1H), 7.01 (d, *J* = 4.9 Hz, 1H), 7.22-7.35 (m, 3H), 7.43 - 7.48 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 28.3, 29.5, 47.6, 52.2, 60.0, 60.8, 80.5, 96.0, 123.2, 124.6, 126.6, 126.9, 130.0, 133.1, 135.4, 141.1, 154.4, 155.3, 170.8; **LCMS (ESI, m/z)**: Calculated for $C_{20}H_{24}ClNO_4SNa$ $(M+Na)^+$ 432.1, found 432.13; **Analysis**: $C_{20}H_{24}ClNO_4S$ required C, 55.49; H, 5.59; N, 3.24; S, 7.41; found: C, 55.38; H, 5.46; N, 3.15; S, 7.37%.

methyl 2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)acetate (±)-Clopidogrel (74)

To a solution of α-amino ester **99** (435 mg, 1.06 mmol) in dry CH_2Cl_2 was added trifluoroacetic acid (0.25 mL, 3.2 mmol) and kept under stirring for 4 h at room temperature. Subsequently, paraformaldehyde (38 mg, 1.3 mmol) was added to the above reaction mixture and allowed to stir for 24 h at room temperature. It was then quenched with sat. $NaHCO_3$ solution at 0 °C and further stirred for 10 min followed by organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with water (2 × 10 mL) and brine, dried over

anhyd. Na_2SO_4 and concentrated under reduced pressure. Silica gel column chromatographic purification of the crude product using petroleum ether/ EtOAc gave (±)-clopidogrel **74** (0.24 g) as a pale yellowish liquid.

Yield: 0.24 g, 70%; **IR** ($CHCl_3$, cm^{-1}): ν_{max} 2977, 1741, 1654, 1434, 1203, 1167, 1042, 755; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.88 (brs, 4H), 3.53 - 3.78 (m, 5H), 4.89 (s, 1H), 6.65 (d, *J* = 5.2 Hz, 1H), 7.04 (d, *J* = 5.2 Hz, 1H), 7.22 - 7.25 (m, 1H), 7.28 - 7.32 (m, 1H), 7.35 - 7.44 (m, 1H) ,7.56 - 7.80 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 25.5, 48.3, 50.7, 52.1, 67.7, 76.4, 77.6, 96.2, 122.8, 125.2, 127.2, 129.4, 129.8, 130.0, 133.1, 133.8, 134.7, 171.0; **Analysis**: $C_{16}H_{16}ClNO_2S$ required C, 59.72; H, 5.01; N, 4.35; S, 9.96; found: C, 59.61; H, 4.95; N, 4.15; S, 9.76%.

4.2.8 References

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