2.1 INTRODUCTION

Boc core 1 (Fig 2.1) is the central core fragment of HIV protease inhibitors, lopinavir & ritonavir (Fig 2.1). Boc core is a chiral 1,4-diamino-3-hydroxy all S-configured intermediate. Boc core has immense importance as it requires tonnage scale and its synthesis involves complexity. It is prepared as succinate salt.

Figure-2.1 Structures of Boc core succinate 1, lopinavir 2 and ritonavir 3

AIDS, a degenerative disease of the immune system, is one of the most challenging problems in medicine. The recent enhance in the AIDS patients has became one of the world’s vital healthcare and social problems. According to the data collected by UNAIDS in 2009,¹ about 35 million people are infected by HIV world wide. Most of them who get infected do not receive therapy because of their economic position.
Figure-2.2 Structures of various HIV protease inhibitors

For approximately a decade, HIV therapy consists of a single nucleoside reverse transcriptase inhibitor (NRTI) such as AZT, d4T, or ddi. In the middle of 1990s, however, a series of HIV protease inhibitors,
which disrupt viral replication, gained approval, and at present, eight such drugs are used in the clinic (Figure 2.2).2

The introduction of these drugs in the developed world, significantly improved the life span of AIDS patient. These drugs having a C2-symmetric homodimeric structure and consist of diaminoalcohols and hydroxyethylene isosteres.3 All of them have chiral center(s) at their core.

HIV paralyzes the immune system of AIDS patients. This immunodeficiency problem among human races has grown up exponentially that led us stride continuously to research and review the science pertaining to the HIV.

2.1.1 Biological activity of HIV protease inhibitors

HIV protease inhibitors play significant role in the cure of HIV related syndromes. HIV invades the cells and directs the cellular machinery to make viral proteins and RNA. Many of the proteins are synthesized in one continuous chain (polyprotein). The polyprotein breaks into smaller chains which can accumulate to form new virus particles. The cleavage, which takes place at specific sites on the polyprotein, is carried out by an enzyme referred as protease. If it is possible to block the activity of the protease the synthesis of new virus can be prevented.4 One of the major limitations of the current therapy is that higher therapeutic doses are necessary because of the presence of ‘peptide-like’ features in the drugs.
Cost effective preparation of these drugs has the extreme importance. All of these inhibitor drugs contain multiple stereo centers, complex heterocycles and functionalities difficult to install. Commercial scale synthesis of these chiral drugs with high chiral purity creates substantial challenge and opportunities for a scientist in the field of organic chemistry.

Ritonavir 3 was approved by the US FDA in 1996 as the 2nd protease inhibitor.\textsuperscript{5,6} Lopinavir 2, contains the identical central core as ritonavir 3, was also approved in 2000 as a 2nd generation HIV protease inhibitor.\textsuperscript{7,8} Co-administration of other drugs with ritonavir 3 in small doses as a combination therapy showed substantial improvements by means of activity and bioavailability.\textsuperscript{9-11}

2.1.2. Product information

M.F : C\textsubscript{23}H\textsubscript{32}N\textsubscript{2}O\textsubscript{3}. Hemi succinic acid
M.Wt : 443
CAS Reg. No : [183388-64-9]
Chemical Name : (2S, 3S, 5S)-2-amino-3-hydroxy-5-t-butyloxycarbonylamino-1,6-diphenylhexane succinate salt

Structure:

\textbf{Figure-2.3} Structure of Boc core hemi succinate 1
2.1.3. Physicochemical properties

- Melting point: 144-146 °C
- Description: White coloured solid
- Solubility: Soluble in methanol, acetone, and practically insoluble in hexane and water

2.2. REVIEW OF LITERATURE

Retrosynthesis of central core of ritonavir:

Since last few decades significant amount of work has been carried out to synthesize 1.\textsuperscript{6,11-16} At first Kempf et al synthesized this molecule. They were synthesized 1 starting from Cbz-phenylalaninol (4, Scheme 2.1).\textsuperscript{17-18} They coupled two molecules of the corresponding aldehyde of 4 by vanadium catalyzed coupling to give diastereomeric mixture of diols to afford 5. Subsequently dehydration of diol and reaction with α-
acetoxyisobutyryl bromide yielded the corresponding bromoacetate $6$. Reductive debromination and further hydrolysis gave the isostere $7$ in 80% yield.

Scheme 2.1 Kempf et al approach for the synthesis of central core

The actual central core synthesis reported by Abbott Laboratories is based on the reduction of an enaminone.$^{19,20}$ Thus phenylalanine $8$ was treated with benzyl chloride in the presence of $\text{K}_2\text{CO}_3$ to yield the corresponding protected benzyl ester (Scheme 2.2) in 94% yield. Acetonitrile anion was generated with sodamide base and added to the benzyl ester to give $9$ in 78% yield. Benzyl magnesium chloride was added to the obtained nitrile yielded the enaminone $10$ in 94% yield. Asymmetric reduction of the enaminone was done by treating the $\text{NaBH}_4$ and methanesulfonic acid complex followed by a 2$^{nd}$ reduction with a complex of $\text{NaBH}_4$ and triethanolamine to provide $11$ with 84% $de$. 

Cbz
Compound 11 was then protected with (Boc)$_2$O and the dibenzyl group was removed by catalytic hydrogenolysis to give the desired core 12. The diamino alcohol consists of several diastereomers as impurities in compound 12, the pure diamino alcohol was afforded by crystallization in isopropylalcohol as succinate salt 1 in 60% yield. This Boc core succinate 1 is very handy because one side of this core is protected with a Boc.

Scheme 2.2 Precedented approach for the synthesis of central core fragment 1

Lopinavir 2 was synthesized by coupling both the side chains with this central core 1 or 11. Similarly ritonavir 3 was synthesized by coupling both the side chains to this central core 1.
2.3 PRESENT WORK

The commercial route was developed by Abbott\textsuperscript{20} involves protection of phenyl alanine with benzyl group and deprotection with palladium carbon at the end. Herein we report the innovative approaches to access the central core molecule of the HIV protease inhibitors in a cost effective manner. Unproductive approaches were illustrated below followed by successful approach.

Keeping in view of the cost and toxicity of the Palladium metal, trityl group was selected for the protection of methyl ester of L-phenyl alanine \textbf{13} (Scheme 2.3). We assumed bulky trityl group plays key role to achieve the stereoselectivity in the asymmetric reduction of enaminoketone. In the first step, L-phenyl alanine methyl ester \textbf{13} was protected with trityl\textsuperscript{23} to provide \textbf{14} which was treated with acetonitrile in presence of sodamide to afford \textbf{15}, which was further reacted with benzyl magnesium chloride to provide enaminoketone \textbf{16}. Subsequently \textbf{16} was subjected to asymmetric reduction using sodiumborohydride and methanesulfonic acid at \(-20\) °C showed the formation of \textbf{17} (major isomer, 80% purity by HPLC) which was in situ treated with sodium borohydride and trifluoroacetic acid resulted the compound \textbf{18} rather than the expected compound \textbf{19} (SSS isomer). This is because of cleavage of trityl group immediately in the reaction due to the strong acidity. Same result was observed even at \(-40\) °C.
Scheme 2.3  Trityl protected approach

Thereafter worked on the scheme 2.4. In this scheme, phenyl alanine 8 was reacted with ethylchloroformate to give carbamate\textsuperscript{24} 20 which was treated with PBr\textsubscript{3} to afford cyclic anhydride\textsuperscript{25} 21. To prepare another intermediate\textsuperscript{20} 24, L-phenyl alanine 8 was protected with benzyl chloride to give 22 which was reduced to alcohol\textsuperscript{26} 23 on treating with LiAlH\textsubscript{4}. Thereafter 23 was treated with iodine and triphenyl phosphine (PPh\textsubscript{3}) to afford 24. We have unsuccessfully attempted to couple the two intermediates 21 and 24 using zinc, but the required compound 25 was
not obtained. We found that zinc insertion was not happened in 24, may be because of the steric hindrance caused by the bulky dibenzyl groups.

Scheme 2.4 Cyclic anhydride approach for the synthesis of 1

In order to overcome the steric factors, intermediate 28 was prepared as showed in scheme 2.5. At first L-phenyl alanine 8 was reduced using NaBH₄ and H₂SO₄ to give alcohol 26 which was protected with Boc anhydride followed by treating with iodine resulted the desired iodo compound 28. Thereafter our efforts to couple the intermediate 21 with intermediate 28 were unsuccessful as, 28 was
converted to methyl derivative 29 in presence of zinc which indicates that zinc was inserted in 28 to afford Reformatsky reagent.30

Scheme 2.5 Reformatsky approach for the synthesis of 1

Alternatively when magnesium was used in place of zinc, compound 28 was dimerised and also cyclic anhydride 21 was reverted back to L-phenyl alanine 8, because of its instability in the basic medium. Keeping in view of the instability of cyclic anhydride 21, we have prepared the aldehyde 30 from 23 by following the Swern oxidation method31 as showed in scheme 2.6. Thereafter 28 was treated with zinc followed by the addition of aldehyde 30 resulted the methyl derivative 29 rather than
the expected product 25, because of the instability of zinc inserted compound and also less reactivity of the aldehyde 30.

**Scheme 2.6** Aldehyde approach

Consequently we have explored the following novel scheme 2.7 to prepare the β-Amino aldehyde 34. At first cinnamyl chloride 31 was treated with sodium azide in presence of TBAI32 gave the cinnamyl azide 32, which was further reacted with tert-butanol33 to afford (E)-tert-butyl styryl carbamate 33. Next step was not proceeded in which 33 was treated with acetaldehyde in presence of D-proline catalyst34 in acetonitrile solvent. Hence the required β-Amino aldehyde 34 could not obtain in this route.

**Scheme 2.7** D-Proline catalyzed approach for the synthesis of of β-Amino aldehyde 34
We could able prepared the β-Amino aldehyde compound 34 by following scheme 2.8.

Scheme 2.8  Synthesis of β-Amino aldehyde 34

In this scheme, L-phenyl alanine 8 was protected with Boc anhydride\textsuperscript{35} to afford 37 which was reduced to alcohol 27 by treating with ethyl chloroformate followed by the addition of NABH\textsubscript{4}. 27 was further converted to cyano derivative 39 by reacting with tosyl chloride followed by the addition of NaCN\textsuperscript{36}. Finally 39 was reduced to aldehyde 34 using DIBAL-H at -78° C. Though β-Amino aldehyde 34 was obtained by following above scheme, usage of costly DIBAL-H at -78° C is not favorable conditions for scale up.

Herein we report an improved synthesis for β-amino aldehyde 34 as showed in scheme-2.9. It was almost free from protection-deprotection and the innovative approach which we adopted adds to the expediency of our method to synthesize valuable β-amino aldehydes in an unprecedented manner. Synthesis of 34 starts with the reduction of (S)-phenyl alanine 8 with the use of NaBH\textsubscript{4}/H\textsubscript{2}SO\textsubscript{4} system to afford amino alcohol 26 in 74.3 % of yield and 98 % of purity.\textsuperscript{37} Subsequent
chlorination of alcohol 26 to obtain chlorinated product 40 in excellent yield and purity (79.4 % and 93 %) by following the literature procedure\textsuperscript{38} that utilizes the thionyl chloride for such kind of transformations. Protection of amino group present in 40 with Boc by using (Boc)\textsubscript{2}O and NaOH afforded advanced intermediate 41.\textsuperscript{39} Second order nucleophilic substitution reaction with the use of NaCN on 41 afforded homologated product 39\textsuperscript{40} which was further treated with Raney Ni/Na\textsubscript{2}HPO\textsubscript{4}/pyridine/AcOH/H\textsubscript{2}O\textsuperscript{41} to obtain 34 in 61.3 % yield and 90 % of purity.

\textbf{Scheme 2.9} Synthesis of β-amino aldehyde 34

Analyzing the results obtained from above mentioned different schemes herein, we reported the design, synthetic development, and application of an asymmetric nitroaldol procedure for the C-C bond formation to obtain 1,4-diamino-3-hydroxy all syn functionalized central core 1 (Boc core) as showed in scheme 2.10. The key components are of β-amino aldehyde 34 and 2-phenylnitroethane 35. 2-Phenylnitroethane 35 was prepared by reacting benzaldehyde with nitromethane in
presence of NaOH gives nitrostyrene 43 which was further reduced using NaBH₄ to afford 2-phenylnitroethane 35.⁴²

**Scheme 2.10** Novel asymmetric nitroaldol approach for 1

A key element present in many HIV protease inhibitors is a chiral 1,4-diamino-3-hydroxy containing architecture.⁴³ In general, stereoselective manipulation of two chiral centers, in presence of a systemic predisposed chirality, in a convergent fashion imposes a formidable challenge. The direct nitroaldol reaction between protected amino alcohol and aldehyde is recognized as an economical means to construct chiral C-C bond.⁴⁴ However, despite this importance, in order to access 1,4-diamino-3-hydroxy framework, so far, there is no precedence of asymmetric version describing the reaction of an enantiopure protected β-amino aldehyde
with a nitroalkane derivative. In particular, the development of a catalyst-controlled highly diastereoselective nitroaldol reaction yielding a key component of the biologically active molecules presents a vital pursuit.

Retro-synthetically, 1,4-diamino-2-hydroxy derivative [(2S, 3S, 5S)-2-amino-3-hydroxy-5-tert-butyloxycarbonylamino-1,6 diphenylhexane] 1 may be obtained by employing the nitroaldol strategy. To access the nitroaldol product 36, a catalyst controlled intermolecular nitroalkane 35 (nitronate) addition to the protected β-amino aldehyde 34 was envisioned. Theoretically 4 diastereomers will be formed in this asymmetric nitroaldol reaction which are showed in Fig 2.5.

**Fig 2.5** Possible diastereomers of 36 in the nitro aldol reaction
We have explored various catalysts and ligands for Nitro-Aldol reaction. Initially catalyst made from metal salt and organic base as mentioned below, but no reaction was observed.

\[
\text{Zn(OAc)}_2, 2\text{H}_2\text{O} (0.3 \text{ eq.}), \text{Diisopropylamine (1 eq.)}
\]

\[
\text{Zn(OAc)}_2, 2\text{H}_2\text{O} (0.3 \text{ eq.}), \text{Diisopropylethylamine (1 eq.)}
\]

Later we explored the nitro aldol reaction with metal and amino acid complex as mentioned in table 2.1

**Table 2.1** Nitroaldol reaction with Metal-Amino acids

<table>
<thead>
<tr>
<th>Metal-amino acid complex</th>
<th>Solvent</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zn/L-Arginine complex</td>
<td>THF</td>
<td>No reaction</td>
</tr>
<tr>
<td>Zn/L-Lysine complex</td>
<td>THF</td>
<td>No reaction</td>
</tr>
<tr>
<td>Zn/L-proline complex (0.1 eq.)</td>
<td>THF</td>
<td>No reaction</td>
</tr>
<tr>
<td>Zn/L-proline complex (0.1 eq.)</td>
<td>Ethanol + water</td>
<td>Undesired isomer is major</td>
</tr>
<tr>
<td>Zn/D-proline complex (0.1 eq.)</td>
<td>THF</td>
<td>No reaction</td>
</tr>
<tr>
<td>Zn/D-proline complex (0.1 eq.)</td>
<td>Ethanol + water</td>
<td>Undesired isomer is major</td>
</tr>
</tbody>
</table>

Subsequently explored chiral phase transfer catalyst, but undesired anti isomer was the major product. Results are summarized in table 2.2.

**Table 2.2** Nitroaldol reaction with chiral phase transfer catalysts

<table>
<thead>
<tr>
<th>Chiral phase transfer catalyst</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N)-Benzylcinconidine bromide</td>
<td>Undesired anti isomer is major</td>
</tr>
<tr>
<td>(O)-Benzy1-(N)-benzylcinconidine bromide</td>
<td>Undesired anti isomer is major</td>
</tr>
<tr>
<td>(N)-Benzylcinconine bromide</td>
<td>Undesired anti isomer is major</td>
</tr>
<tr>
<td>(O)-Benzy1-(N)-benzylcinconine bromide</td>
<td>Undesired anti isomer is major</td>
</tr>
</tbody>
</table>
After that screened chiral bases, but again undesired anti isomer was the major product. Results are summarized in table 2.3.

Table 2.3  Nitroaldol reaction with chiral bases

<table>
<thead>
<tr>
<th>Chiral base</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+)-N-Methylephidrine</td>
<td>Undesired anti isomer is major</td>
</tr>
<tr>
<td>(-)-N-Methylephidrine</td>
<td>Undesired anti isomer is major</td>
</tr>
<tr>
<td>Dichloro[(-)-sparteine-(N,N)]copper (II)</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

Thereafter, \(C_2\) symmetric bisoxazoline ligands 44 and 46 (Fig-2.6) were screened. As shown in Scheme 2.11, the chiral ligand was expected to exhibit strong coordination among the metal [Cu(II)], nitronate and aldehyde to effect a Zimmerman-Traxler-type transition state 45, where amino derivative adopts an equatorial position, leading to the desired 3, 4-\textit{syn} product with \(S\) configuration at newly generated chiral centers.

\[
44 \quad 46
\]
\[
R = \text{iPr, tBu, Bn}
\]

Figure 2.6  \(C_2\) symmetric bisoxazoline ligands 44 and 46

It should be noted that this synthetic design relies on chiral center present at \(\beta\)- position in 34. It is also imperative that the existing functional group could cause steric hindrance in stereo space with the group(s) present in the catalyst leading to a moderate diastereoselectivity.
Scheme 2.11 Diastereoselective nitroaldol approach to access 36

As shown in Table 2.4, none of the bisoxazoline variants as a ligand offered excellent diastereoselectivity in the nitroaldol step. The best results in the first screen were obtained with the combination of 5 mol% isopropyl bisoxazoline ligand/Cu(II) catalyst (entry 3) and isopropanol as a solvent affording the desired nitro derivative 36 in promising yield and diastereoselectivity.

In another campaign, (R)-BINOL-Lanthanum-Lithium heterobimetallic catalytic system 47 (Fig-2.7) was employed to obtain enhanced diastereoselectivity.
The catalyst displays basic as well as Lewis acid properties. Such kind of catalytic system, in absence of base, catalyses nitroaldol reaction of aldehydes with nitroalkanes in an excellent enantio/diastereoselective manner in general. With our substrates, the S configuration at both the newly generated stereocenters reflects that the nitronate reacted preferably on the Si face of aldehydes in the presence of (R)-BINOL-La-Li system. However, in general, (R)-BINOL derived catalytic system directs the asymmetric C-C bond formation during nitroaldol on the Re face. Therefore, in our case, plausibly due to the presence of bulky chiral moiety, the diastereotopic face for (S)-β-aminoaldehyde 34 is reversed to that for typical aldehyde which gives enantiomeric nitroaldol products. Preferential syn selectivity in the adduct 36 could be attributed to the sterically hindered transition state as shown in Newman projection analog 48. As shown in Table 2.4, we achieved higher diastereomeric ratio (entry 6) than that with bisoxazoline system.
A nitroaldol reaction of aldehyde 34 with 2-phenylnitroethane 35 was promoted by using 5 mol% of (R)-BINOL-La-Li at -38 °C, and nitroaldol adduct 36 was obtained in 53 % yield and with diastereoselectivity (80:9:10:1) after 24 h. Reaction of 34 with 35 was also alternatively performed using (SS)-isopropylbisoxazoline and Cu(OAc)₂ to obtain 36 in situ in 76 % of yield and with dr (62:29:4:5). We purified the major all syn pair of the nitroaldol adduct 36 and characterized. The anti pair, being minor, was not possible to isolate. Conversion of the nitro derivative 36, as a distereomeric mixture, to the desired core 12 along with other diastereomers of the HIV protease inhibitor was achieved by hydrogenation with Raney Ni under H₂ atmosphere in methanol. After removal of the Raney Ni and distillation of the methanol, the reaction mixture was diluted with isopropanol and subsequently succinic acid was added to obtain Boc core hemisuccinate salt 1 with 40 % of yield.
and 98 % of purity as shown in Scheme 2.12. End game strategy to access 1 hemisuccinate salt.

**Scheme 2.12** Synthesis of 1 via asymmetric nitroaldol reaction

**2.4 CONCLUSION**

In conclusion, we have developed an efficient diastereoselective and operationally simple method for the synthesis Boc core 1 which is a key intermediate of lopinavir 2 and ritonavir 3 drugs. Asymmetric nitroaldol of β-amino aldehyde 34 with 2-phenylnitroethane 35 gave enantiomerically pure diastereomer in good yields and diastereo selectivities. This approach presents the first example of nitroaldol recitating the reaction of an enantiopure protected β-amino aldehyde with a nitroalkane derivative to access 1,4-diamino-3-hydroxy
framework. We believe that this strategy will find applications in synthetic organic chemistry directed to drug research.

2.5. EXPERIMENTAL SECTION

Solvents and regents were used for all the reactions as received. The $^1$H and $^{13}$C NMR spectra were recorded in CDCl$_3$ and CD$_3$OD, using Varian Gemini 200 MHz or 400 MHz FT NMR spectrometer; the chemical shifts are reported in $\delta$ ppm relative to tetramethylsilane TMS (0 ppm). The FT-IR spectra were recorded in the solid state as KBR dispersion using Perkin-Elmer 1650 FT-IR spectrophotometer. Mass spectra were obtained on a low resonance Q-trap machine in electron spray mode. The melting points were determined by using the capillary method on POLMON (model MP-96) melting point apparatus and are uncorrected. Optical rotations were recorded on Perkin Elmer model 341 polarimeter.

(S)-2-Amino-3-phenylpropan-1-ol (26)

L-phenylalanine 8 (100 g, 0.60 mol), was added to a slurry of sodium borohydride (65.0 g, 1.70 mol) and tetrahydrofuran (1000 mL) in a round bottom flask and stirred for 10 minutes. The mixture was cooled to 0 °C, followed by drop wise addition of a solution of concentrated H$_2$SO$_4$ (43 mL, 0.23 mol) in tetrahydrofuran (200 mL). The reaction mixture was warmed to 27 °C and maintained for 18 h at 27-30 °C. After the completion of the reaction it was cooled to 0 °C and methanol (100 mL)
was added slowly. Subsequently reaction mixture was distilled at 50 °C under reduced pressure. To the obtained residue, 5N sodium hydroxide solution (650 mL) was added and heated to 75 °C, maintained for 3 h. After that it was cooled to 30 °C and extracted with dichloromethane (4×500 mL). The combined organic layers were dried over anhydrous sodium sulphate, were filtered and evaporated at less than 40 °C under reduced pressure. The resultant residue was dissolved in dichloromethane (200 mL). Dry HCl gas was passed to this solution for 2 h at 30 °C. The precipitated solid was filtered and dried at 60 °C, to afford 26 as white solid (68 g, 74.3 %).

IR (KBr, cm⁻¹): 3357, (NH), 3081 (OH), 1577, 1492 (aromatic C=C), 2939, 753 (Ar-H); ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.36 (m, 5H), 4.57 (bs, 2H), 3.67 (dd, J = 3.1 & 11.4 Hz, 1H), 3.52 (m, 1H), 3.45 (m, 1H), 2.94 (d, J = 7.5 Hz, 2H); MS (ESI): m/z calcd for C₉H₁₃NO (M + H): 152.10; found: (M + H) 152.0.(Fig. 2.8 - 2.10)

**(S)-1-Benzyl-2-chloroethylamine hydrochloride (40)**

To a solution of dimethoxyethane (1650 mL) and thionyl chloride (29 mL, 0.39 mol) was added slowly a solution of 26 (50 g, 0.33 mol) in dimethoxyethane (1950 mL) at 27 °C under nitrogen atmosphere. The reaction mixture was heated to 85 °C and maintained for 4 hours. After the completion of the reaction it was cooled to 55 °C and distilled under reduced pressure. To the resultant residue, ethyl acetate (500 mL) was
added at 30 °C and stirred for 40 min. The obtained solid was filtered and dried at 55 °C under reduced pressure, to afford 40 (54 g, 79.4 %).

IR (KBr, cm⁻¹): 3432 (NH), 2906, 746 (Ar-H), 1573, 1507 (aromatic C=C), 703 (C-Cl); ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.38-7.29 (m, 5H), 3.81 (m, 2H), 3.64 (m, 1H), 3.06-3.03 (m, 2H); MS (ESI): m/z calcd for C₉H₁₂ClN. HCl (M + H): 206.04; found: (M + H) 170.0. (Fig. 2.11 – 2.13)

(S)-1-Chloro-2-tert-butyloxycarbonylamino-3-phenylpropane (41)

To the slurry of 40 (18 g, 0.087 mol) in tetrahydrofuran (90 mL) was added a solution of sodium hydroxide (7.7 g, 0.192 mol) in water (90 mL). The mixture was cooled to 5 °C and (Boc)₂O (21 g, 0.096 mol) was added. Thereafter temperature was raised to ambient temperature and stirred for 20 h. Subsequently the reaction mixture was extracted with ethyl acetate (100 mL). Organic layer was dried over anhydrous sodium sulphate (5 g) and solvent was evaporated at 55 °C under reduced pressure to provide 41 (27.18 g, 95 %).

IR (KBr, cm⁻¹): 3361 (NH), 2983, 746 (Ar-H), 1693 (C=O), 1526 (aromatic C=C), 1167 (C-O), 704 (C-Cl); ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 7.35 (m, 2H), 7.31 (m, 1H), 7.26 (m, 2H), 4.83 (bs, 1H), 4.13 (brs, 1H), 3.62 (dd, J = 3.9 & 10.7 Hz, 1H), 3.48 (dd, J = 3.4 & 11.2 Hz, 1H), 2.88 (m, 2H), 1.43 (s, 9H); MS (ESI): m/z calcd for C₁₄H₂₀ClNO₂ (M + H): 270.12; found: (M - CH₃OH) 300. (Fig. 2.14 – 2.16).
S)-3-[(t-butoxycarbonyl)amino]-4-phenylbutanenitrile (39)

To a solution of 41 (20 g, 0.074 mol), in N,N-dimethylformamide (300 mL) was added sodium cyanide (11 g, 0.224 mol) at 25 °C under a nitrogen atmosphere. The mixture was heated to 100 °C and stirred for 30 min. After that it was brought to room temperature followed by addition of water (500 mL) and ethyl acetate (500 mL). The reaction mass stirred for 10 min and separated the layers. Aqueous layer was extracted with ethyl acetate (200 mL). The combined organic layer was washed with water (500 mL) followed by brine. Solvent was evaporated at 45 °C under reduced pressure, to provide 39 (17.1 g, 88.6 %).

IR (KBr, cm\(^{-1}\)): 3345 (NH), 2976 (Ar-H), 2243 (CN), 1690 (C=O), 1530 (aromatic C=C), 1165 (C-O); \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) (ppm). 7.35 (m, 2H), 7.31 (m, 1H), 7.26 (m, 2H), 4.75 (brs, 1H), 4.08 (brs, 1H), 3.02 (dd, \(J = 6.8 & 14.1\) Hz, 1H), 2.89 (dd, \(J = 8.2 & 14.1\) Hz, 1H), 2.68 (dd, \(J = 8.2 & 14.1\) Hz, 1H), 2.44 (dd, \(J = 4.3 & 16.5\) Hz, 1H), 1.43 (s, 9H); MS (ESI): \(m/z\) calcd for C\(_{15}\)H\(_{20}\)N\(_2\)O\(_2\) (M + Na): 283.15; found: (M + Na): 283.1 (Fig. 2.17-2.19)

(S)-3-[(t-butoxycarbonyl)amino]-4-phenyl butanaldehyde (34)

**Method A.** A solution of 39 (10 g, 0.038 mol) in toluene (200 mL) was cooled to -78 °C. To this solution added diisobutylaluminium hydride (20% by weight, 1.4 M in toluene; 108 mL) was added slowly over a period of 2 h. After maintaining the reaction mixture for 30 min at -78 °C, was
quenched with methanol (20 mL) followed by the addition of saturated ammonium chloride solution (200 mL) and ethyl acetate (400 mL). After stirring for 20 min at -50 to -60 °C, was added a solution of 1M HCl (200 mL) followed by 3M HCl (200 mL) until pH of the reaction mixture is 2. Organic layer was separated and washed with 1M HCl solution (200 mL) followed by 10 % sodium bicarbonate solution (200 mL), and with brine (200 mL). Organic layer was evaporated at 45 °C under reduced pressure to afford 34 (5.1 g, 50.4 %).

Method B). To a solution of pyridine (256 mL), water (129 mL), acetic acid (129 mL), was added sequentially Raney nickel (57 g), sodium hypophosphosphate (33.8 g, 0.23 mol) and 39 (10 g, 0.038 mol). After stirring at 25°C for 22 h, was added dichloromethane (250 mL) and stirred for 15 min. After that the mixture was filtered through a celite bed. Organic layers was separated and washed with 15 % sodium bicarbonate solution (250 mL), brine (150 mL), followed by 1 % HCl solution (250 mL). The organic layer was dried over sodium sulphate and evaporated at 35°C under reduced pressure. Toluene (50 mL) was added to the resultant residue and distilled to remove the traces of pyridine. Solid was isolated in a mixture methyl tert-butyl ether (20 mL) and hexane (200 mL) to afford 34 (6.2 g, 61.3 %).

IR (KBr, cm⁻¹): 3356 (NH), 2975 (Ar-H), 1690 (C=O), 1524 (aromatic C=C), 1167 (C-O); ¹H NMR (400 MHz, CDCl₃): δ (ppm). 9.71 (s, 1H), 7.32 (m, 2H), 7.26 (m, 1H), 7.17 (m, 2H), 4.76 (bs, 1H), 4.27 (d, J = 5.8 Hz,
1H), 2.93 (m, 1H), 2.82 (dd, J = 7.5 & 13.4 Hz, 1H), 2.58 (m, 2H), 1.40 (s, 9H); MS (ESI): m/z calcd for C₁₅H₂₁NO₃ (M + H): 264.15; found: (M + H): 265.1 (Fig. 2.20 – 2.22)

(2S,3S,5S)-2-nitro-3-hydroxy-5-(t-butyloxycarbonyl)amino)-1,6-diphenylhexane (36)

**Method-A:** 4, 4'-isopropylisoxazoline 44 (532 mg, 0.002 mol) and Cu(OAc)₂ (362 mg, 0.0018 mol) were added to a 25 mL round bottomed flask containing a stir bar under nitrogen atmosphere. Ethanol (80 mL) was added and the mixture was stirred for 1 h at room temperature. To the resulting blue color solution 2-phenylnitroethane 35 (5.74 g, 0.038 mol) and 34 (10 g, 0.038 mol) were added. After stirring for 48 h the volatile components were removed under reduced pressure and the crude product was purified by column chromatography to afford 36 (10 g, 63.5%).

IR (KBr, cm⁻¹): 3554 (OH), 3376 (NH), 2929 (Ar-H), 1686 (C=O), 1543, 1367 (NO₂), 1518 (aromatic C=C), 1169 (C-O); ¹H NMR (major diastereomer) (400 MHz, CDCl₃) δ (ppm): 7.31-7.22 (m, 6H) 7.17-7.14 (m, 4H), 4.86 (brs, 1H), 4.54 (m, 1H), 4.01-3.93 (m, 2H), 3.36-3.10 (m, 3H), 2.79-2.77 (d, 2H, J = 6.6 Hz ), 1.70-1.61 (m, 2H), 1.37 (s, 9H); MS (ESI): m/z calcd for C₂₃H₃₀N₂O₅ (M + Na): 437.22; found: (M + Na) 437.1. (Fig. 2.23 – 2.26)

A solution of La(OiPr)$_3$ (1.75 mL, 1 mmol, 18 % in xylene) was added slowly to a stirred solution of (R)-binol (859 mg, 3.00 mmol) in THF (8 mL) at 0 °C. The solution was stirred for 30 min at room temperature, then solvent and $^t$PrOH were removed slowly under reduced pressure, and the residue was dried for 2 h under vacuum (10 mm of Hg). The residue was cooled at 0 °C, and THF (8 mL) was added. n-BuLi (1.88 mL, 3.00 mmol, 1.60 M in hexane) was added slowly to the solution. After the mixture was stirred for 1 h at room temperature, the solvent was removed slowly under reduced pressure, and the residue was dried for 3 h under vacuum. The residue was cooled at 0 °C, and THF (7.52 mL) was added. The mixture was stirred at room temperature for 1 h to afford 47 (R)-LLB solution (0.133 M in THF).

(2S,3S,5S)-2-nitro-3-hydroxy-5-(t-butyloxycarbonylamino)-1,6-diphenylhexane (36)

Diastereoselective nitroaldol reaction catalyzed by (R)-La-Li-BINOL:

To a solution of 34 (3.20 g, 12.2 mmol) in THF (60 mL), was added 2-Phenylnitroethane 35 (2.20 mL, 14.6 mmol) at - 40 °C, and the mixture was stirred for 1 h at - 40 °C. (R)-LLB (0.133 M in THF, 2.8 mL, 5 mol%) was added, and the mixture was stirred for 20 h at - 40 °C. The reaction was quenched with aqueous HCl (1N, 3 mL), and the mixture was
extracted with MTBE (2 x 100 mL). The combined organic layers were washed with saturated NaHCO₃ (2 x 25 mL), water (25 mL), brine (25 mL), dried over anhydrous Na₂SO₄, and evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel) to afford 36 (2.50 g, 53%, syn/anti=80:20) as a colorless liquid.

(2S,3S,5S)-2-amino-3-hydroxy-5-(t-butyloxycarbonyl)amino)-1,6-diphenylhexane hemi succinate (1)

**Method-A:** To a solution of 36 (2 g, 4.8 mmol) in methanol (50 mL) was added zinc (0.6 g, 9.17 mmol) and ammonium formate (0.31 g, 4.92 mmol) at 25 °C. The mixture was maintained at 25 °C for a period of 4-5 hours and filtered through a celite bed. The solvent from the filtrate was evaporated at 45 °C under vacuum and the residue was extracted with ethyl acetate (50 mL). The organic layer was washed with brine solution (25 mL) and finally washed with water (20 mL). Organic layer was evaporated at 45 °C under vacuum to afford 12 as a free base which was dissolved in isopropyl alcohol (20 mL) at 70 °C. To this solution was added succinic acid (0.5 g, 4.23 mmol). After stirring for 1 h at 70 °C it was slowly cooled to room temperature and stirred for overnight. Filtered the solid and washed with isopropyl alcohol (5 mL), dried at 60°C under vacuum to afford 1 (0.43 g, 20 %).

**Method-B:** To a solution of 36 (12 g, 0.028 mol) in methanol (240 mL) was added Raney Ni (3 g, 25 mol %) in a autoclave vessel at 25 °C.
The reaction mass was stirred for a period of 18 h at 25-30 °C maintaining 6-7 kg hydrogen gas pressure and filtered through a celite bed. The solvent from the filtrate was evaporated at 45 °C under vacuum and the residue was dissolved in MTBE (240 mL) and washed with water. Organic layer was dried over sodium sulphate, evaporated at 45 °C under vacuum to afford 12 as a free base which was dissolved in isopropyl alcohol (100 mL) at 70 °C. To this solution was added succinic acid (4.05 g, 0.034 mol). After stirring for 1 h at 70 °C it was slowly cooled to room temperature and stirred for overnight. Filtered the solid and washed with isopropyl alcohol (20 mL), dried at 60 °C under vacuum to afford 1 (5.2 g, 40.3%). M.P: 144-146 °C.

\[\alpha\] \(D\) \(25 = -4.01\) (c = 0.5 in MeOH); IR (KBr, cm\(^{-1}\)): 3391 (OH), 2976 (Ar-H), 1693 (C=O), 1559 (NH\(_2\)), 1508 (aromatic C=C), 1169 (C-O); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) (ppm). 7.33-7.13 (m, 10H), 3.93 (m, 1H), 3.76 (m, 1H), 3.27 (bs, 1H), 2.95 (dd, \(J = 6.3 \& 13.6\) Hz, 1H), 2.85 (m, 2H), 2.64 (m, 1H), 2.49 (s, 4H), 1.75 (m, 2H), 1.32 (s, 9H); MS (ESI): \(m/z\) calcd for C\(_{23}\)H\(_{32}\)N\(_2\)O\(_3\). Succinic acid (M + H): 503.27; found: (M + H) 385.2. (Fig. 2.27-2.30)

\((S)\)-Methyl-3-phenyl-2-(tritylamino)propanoate\(^{23}\) (14)

To a solution of methyl ester of L-Phenylalanine 13 (10 g, 0.046 mol) in dichloromethane, was added triethylamine (9.44 g, 0.093 mol) under nitrogen atmosphere. After stirring for 10 min, trityl chloride (16 g, 0.057
mol) was added lot wise in 5 equal lots for a period of 30 min. Thereafter stirred the reaction mass for 10 h. Subsequently reaction mixture was washed with brine (30 ml). Organic layer was separated and dried over anhydrous sodium sulphate and distilled the solvent completely at 35-40 °C under vacuum. Thereafter the obtained white solid residue was crystallized from methanol (50 mL) to afford 15.6 g (80 %) of the desired product 14 as a white solid.

**{(S)-3-oxo-5-phenyl-4-(tritylamino)pentanenitrile (15)}**

Sodium amide (9.2 g, 0.0237 mol) was charged carefully under nitrogen atmosphere followed by THF (100 ml). It was cooled to 0 °C. Subsequently acetonitrile (17.4 g, 0.332 mol) was added in 2 min. Thereafter the reaction mixture was stirred at 0 °C for 30 min. Subsequently a solution of 14 (20 g, 0.047 mol) in THF (80 mL) of was added over 15 min and the resulting heterogeneous reaction mixture was stirred at -5-0° C for 3 h. Thereafter reaction mass was quenched with 20 % aqueous citric acid (150 mL). After warming to 25 °C separated the layers. To the organic layer, heptane (150 mL) was added and the organic layer was washed with water (100 mL). Thereafter organic layer was dried over sodium sulphate and concentrated in vacuum. The obtained crude was crystallized from diethyl ether (100 mL) of to afford 14.7 g of 15 (72 %).

IR (KBr, cm⁻¹): 3022 (NH), 2257 (CN), 1739 (C=O); ¹H NMR (400 MHz, CDCl₃): δ (ppm). 7.35-7.15 (m, 20 H), 3.71 (t, J = 6.8 Hz, 1H), 3.14 (dd,
6.4 & 13.2 Hz, 1H), 2.86 (dd, 8.3 & 13.1 Hz, 1H), 2.08 (AB quartet, \( J = 20 \) Hz, 2H); \( ^{13}C \) NMR (100 MHz, CDCl\(_3\)): \( \delta \) (ppm) 202.78, 145.76, 136.04, 129.73, 129.06, 128.90, 128.11, 127.42, 126.92, 113.28, 71.14, 63.45, 41.73, 30.31; MS (ESI): \( m/z \) calcd for C\(_{30}\)H\(_{26}\)N\(_2\)O (M + H): 431.2; found: (M + H) 431. (Fig. 2.31 – 2.34)

**(S)-5-amino-1, 6-diphenyl-2-(tritylamino)hex-4-en-3-one (16).**

To a solution of 15 (15 g, 0.035 mole) in tetrahydrofuran (75 mL), was added benzyl magnesium chloride (210 mL, 2M in THF, 0.42 moles). Stirred the reaction mixture for 12 h at 30 °C. Thereafter it was cooled to 5 °C and it was slowly added to a solution of 15 % citric acid (68 mL). Subsequently added the ethylacetate (150 mL), stirred for 10 min and separated the organic layer and washed with 10 % sodium chloride solution (375 mL). The organic layer was separated and dried over sodium sulphate and concentrated in vacuum. The crude thus obtained was crystallized from ethylacetate (75 mL) and hexane (375 mL) to afford 14.8 g of 16 g (81 %). IR (KBr, cm\(^{-1}\)): 3273 (NH\(_2\)), 3026 (NH), 1534 (C=C), 698 (C=CH); \( ^1\)H-NMR (400 MHz, CDCl\(_3\)): \( \delta \) (ppm). 7.41-7.38 (m, 2H), 7.33-7.20 (m, 8H), 7.18-7.11 (m, 8H), 7.10-7.02 (m, 6H), 4.26 (s, 1H), 3.4 (t, \( J = 6.5 \) Hz, 1H), 3.18 (s, 1H), 2.82 (dd, 6.1 & 13.2 Hz, 1H), 2.77 (dd, 8.2 & 13.3 Hz, 1H); MS (ESI): \( m/z \) calcd for C\(_{37}\)H\(_{34}\)N\(_2\)O (M + H): 523.27; found: (M + H) 281.(De-trityl group) (Fig. 2.35 – 2.37)
2.6 REFERENCES


Kowalczyk, W.; Prahl, A.; Derdowska, I.; Slaninova, J.; Zabrocki, J.;


38. Xu, F.; Simmons, B.; Reamer, R. A.; Corley, E.; Murry, J.; Tschaen,

39. Haight, A. R.; Stuk, T. L.; Allen, M. S.; Bhagavatula, L.; Fitzgerald,
**1999**, *3*, 94.

**2003**, 1500.


45. Mihara, H.; Sohtome, Y.; Matsunaga, S.; Shibasaki, M. *Chem. Asian J.*
**2008**, *3*, 359.

**2.7 SPECTRAS:**
Figure-2.8: $^1$H NMR spectrum of compound 26 in CDCl$_3$
Figure-2.9: +ve ESI mass spectrum of compound 26
Figure-2.10: IR spectrum of compound 26
Figure-2.11: $^1$H NMR spectrum of compound 40 in CDCl$_3$
Figure-2.12: +ve ESI mass spectrum of compound 40
Figure-2.13: IR spectrum of compound 40
Figure-2.14: $^1$H NMR spectrum of compound 41 in CDCl$_3$
Figure-2.15: +ve ESI mass spectrum of compound 41
Figure-2.16: IR spectrum of compound 41
Figure-2.17: $^1$H NMR spectrum of compound 39 in CDCl$_3$
**Figure-2.18:** +ve ESI mass spectrum of compound 39
Figure 2.19: IR spectrum of compound 39
Figure-2.20: $^1$H NMR spectrum of compound 34 in CDCl$_3$
Figure-2.21: +ve ESI mass spectrum of compound 34
Figure-2.22: IR spectrum of compound 34
Figure-2.23: $^1$H NMR spectrum of pure diastereomer compound 36 in CDCl$_3$
Figure-2.24: $^1$H NMR spectrum of pure diastereomer compound 36 in CDCl$_3$ (Expansion between 0 - 5.0)
Figure-2.25: +ve ESI mass spectrum of pure diastereomer compound 36
Figure-2.26: IR spectrum of pure diastereomer compound 36
Figure-2.27: $^1$H NMR spectrum of compound 1 in CD$_3$OD
Figure-2.28: $^1$H NMR spectrum of compound 1 in CD$_3$OD (zoomed at $\delta$ 1-6 – 4.0)
Figure-2.29: +ve ESI mass spectrum of pure diastereomer compound 1
Figure-2.30: IR spectrum of pure diastereomer compound 1
Figure-2.31: $^1$H NMR spectrum of compound 15 in CDCl$_3$
Figure-2.32: $^{13}$C NMR spectrum of compound 15 in CDCl$_3$
Figure-2.33: +ve ESI mass spectrum of compound 15
Figure-2.34: IR spectrum of compound 15
Figure-2.35: $^1$H NMR spectrum of compound 16 in CDCl$_3$
Figure-2.36: +ve ESI mass spectrum of compound 16
Figure-2.37: IR spectrum of compound 16