CHAPTER 3

Asymmetric Synthesis of L-DOPA and Formal Synthesis of Levofloxacin using Proline-Catalyzed α-Functionalization of Aldehydes
SECTION 1:

Enantioselective Synthesis of L-DOPA via Proline-Catalyzed α-Amination of Aldehyde

3.1.1 Introduction

L-DOPA [(5)-3,4-dihydroxyphenylalanine] (1) is a naturally occurring amino acid derived from post-translational modification of tyrosine.\(^1\) It is one of the principal agents administered to patients with Parkinson's disease since 1967.\(^2\) Although rarely found in proteins, L-DOPA (1) was detected in high yield (ca. 10%) in marine mussel adhesive proteins. The ubiquitous nature of (S)-3,4-dihydroxyphenylalanine, \{L-DOPA (1)\}, touches biological fields ranging from medicine to engineering. Most commonly known for pharmacological value, L-DOPA (1) has been the treatment of choice to alleviate Parkinson's disease symptom (Fig. 1).\(^3\)

![Fig. 1 Structure of L-DOPA(1)](image)

Parkinsonism is a chronic neurological disorder characterized by tremor, rigidity of the limbs and poverty of movement (hypokinesia). In most cases, however, no cause can be identified. Pathological examination of the brain reveals widespread degenerative changes in the basal ganglia, particularly the substantia nigra and corpus striatum.
3.1.1.1 Pharmacology of L-DOPA

Parkinson's disease is caused by a shortage of a particular chemical that is produced in the brain. This chemical is called dopamine. Without this chemical messenger, the signals from the brain do not get through to the spinal cord and then to the various muscles of the body, hence muscular function is impaired. Dopamine is synthesized within nerve cells. Chemically, L-tyrosine is converted to (S)-dihydroxyphenylalanine [L-DOPA (1)] and then to dopamine in a two-step process. The symptoms appear when there is not enough dopamine in the brain. Dopamine is a naturally occurring chemical (neurotransmitter) that allows nerve cells to transmit messages between each other and then to muscles to allow normal movement to take place. In Parkinson's disease, many of these cells are dead. The remaining cells cannot produce enough dopamine. Most drug therapy replaces dopamine in the brain. Parkinson's disease is believed to be related to low levels of dopamine in certain parts of the brain. When L-DOPA is taken orally, it crosses through the "blood-brain barrier." Once it crosses, it is converted to dopamine. The resulting increase in brain dopamine concentrations is believed to improve nerve conduction and assist the movement disorders in Parkinson's disease. Carbidopa does not cross the blood-brain barrier and added to L-DOPA (1) to prevent the breakdown of L-DOPA before it crosses into the brain. The addition of carbidopa allows lower doses of L-DOPA to be used. This reduces the risk of side effects from L-DOPA such as nausea and vomiting.

3.1.2 Review of Literature

Literature search reveals that there are various methods available for the enantioselective synthesis of L-DOPA (1). Most of these methods make use of classical kinetic resolution
of diastereomeric derivatives of L-DOPA, others on oxidation of L-tyrosine and probably
the dominating industrial procedure is based upon catalytic asymmetric hydrogenation.
Some of the recent approaches to L-DOPA have been described below.

**Tyagi's approach (1992)**

This approach describes the synthesis of L-DOPA (1) utilizing enzymatic resolution as a
key step. Thus, racemic \( N \)-acetyl-3,4-methylenedioxyphenylalanine methyl ester 2 on
enzymatic hydrolysis by alcalase provided \( (S) \)-\( N \)-acetyl-3,4-methylenedioxyphenylalanine
(3), which was converted to L-DOPA (1) in high optical purity by known sequence of
reactions (Scheme 1).

\[
\begin{align*}
\text{Ar} & \quad \text{CO}_2\text{Me} \quad \text{NHCOCCH}_3 \quad \text{CO}_2\text{H} \quad \text{NHCOCCH}_3 \quad \text{CO}_2\text{H} \\
(\pm)-2 & \quad \text{Ar} = 3,4\text{-methylenedioxyphenyl} \\
3 & \\
\text{Yield: 80%; 96% ee} \\
\text{L-DOPA 1}
\end{align*}
\]

**Scheme 1:** (i) Alcalase, pH: 7.5; (ii) PhOH, HCl, reflux.

**Jung's approach (1997)**

Synthesis of \( N \)-Boc-L-3-[3hydroxy-4-(phenylmethoxy)phenyl]alanine (7) was achieved
via Reimer-Tiemann formylation followed by Dakin reaction as key steps. Thus,
formylation of \( N \)-Boc L-tyrosine (4) provided 2-formyl derivative 5. Further, benzylation
followed by reaction with 30% \( \text{H}_2\text{O}_2 \) in the presence of diphenyl diselenide gave the aryl
formate, which on subsequent treatment with methanolic ammonia afforded the desired
phenol 7 in 78% yield (Scheme 2).

**Chapter III**

105

Antilla and co-workers have synthesized L-DOPA (1) by using asymmetric aziridination approach. Thus, reaction of imine 8 with ethyl diazoacetate (EDA) in the presence of catalytic amount of (R)-VAPOL (11) and triphenylborate afforded the chiral aziridines 9 in 96% ee. Hydrogenation of aziridine 9 at the N-benzylic bond occurred with cleavage of the benzhydral group to give the amino ester 10 in 72% yield. On hydrolysis of 10 L-DOPA (1) was obtained in 60% yield and 98% ee (Scheme 3).


Takashi et al. have described synthesis of L-DOPA ester 15 by using chiral quaternary ammonium salt 16 as a phase-transfer catalyst. Thus, alkylation of imine with bromide 25
in the presence of (R)-16 gave tert-butyl ester 13, which was subsequently treated with 1M citric acid to afford the corresponding amino ester 14 in 81% yield. Debenzylation of amine 14 afforded the desired tert-butyl ester of L-DOPA 15 in 98% ee (Scheme 4).


In this approach, α,β-unsaturated ester 17 was subjected to ADH to give chiral diol 18 in excellent optical purity. The vicinal diol 18 on treatment with SOCl₂ in presence of Et₃N in CH₂Cl₂ at 0 °C gave the corresponding cyclic sulfite 19. Cyclic sulfite 19 was treated with sodium azide, to get azido alcohol 20, which was converted into aziridine 21. Aziridine 21 underwent stereospecific and regioselective ring opening at the benzylic position to produce amine 22. Aminoester 22 was hydrolyzed with acid to furnish L-DOPA (1) in 85% ee (Scheme 5).

---

**Scheme 4:**
(i) (R)-16 (1 mol%), toluene, 50% aq. KOH, 0 °C; (ii) 1M citric acid, THF, 25 °C, 10 h; (iii) 10% Pd-C, 25 °C, THF, 25 °C, 5 h.
Valdes's approach (2004). Valdes et al. have demonstrated the synthesis of L-DOPA (1) by Pd/C catalyzed asymmetric hydrogenation of N-benzoylamino-3-(3',4'-dibenzyloxyphenyl)-2-propenoic acid (25) using cinchonine as ligand (Scheme 6).

Scheme 6: (i) Ac₂O, NaOAc, N-benzoylglycine, 77%; (ii) (a) 2 M NaOH; (b) conc. HCl, 93%; (iii) THF, Pd/C, cinchonine, H₂, 65%; (iv) conc. HBr, 60%.
3.1.3 Present Work

3.1.3.1 Objective

All the reported methods described above for the synthesis of L-DOPA (1) suffer from drawbacks such as use of expensive enzymes and resolving agents, low overall yields, low optical purity, the need for separation of diastereomers etc. As can be seen from the retrosynthetic analysis (Scheme 7), the synthesis of L-DOPA (1) is visualized to be achieved by the D-proline-catalyzed α-amination\(^\text{11}\) of aldehyde 28.

\[
\text{L-DOPA (1)} \quad \xrightarrow{\text{a-amination}} \quad \text{MeO} \quad \text{MeO} \quad \text{H}
\]

Scheme 7: Retrosynthetic analysis for L-DOPA (1)

3.1.4 Results and Discussion

The synthetic route for L-DOPA (1) is shown in Scheme 8.

\[
\text{27} \xrightarrow{\text{i}} \text{28} \xrightarrow{\text{ii}} \text{29} \xrightarrow{\text{iii}} \text{30} \xrightarrow{\text{iv}} \text{31, R = Me, 1, R = H} \xrightarrow{\text{v}} \text{1, R = H}
\]

Scheme 8: (i) allyl alcohol, Pd\(_2\)(dba)\(_3\), P(Cy)\(_3\), K\(_2\)CO\(_3\), DMF, 100 °C, 86%; (ii) dibenzyl azodicarboxylate, D-proline (10 mol%), CH\(_2\)CN, 0-25 °C, 3 h then NaBH\(_4\), EtOH, 62%; (iii) NaClO\(_2\), NaClO, TEMPO, CH\(_2\)CN, phosphate buffer, 25 °C, 78%; (iv) H\(_2\) (70 psig), Raney-nickel, MeOH, AcOH, 25 °C; (v) BBr\(_3\), CH\(_2\)Cl\(_2\), 0 °C, 58%, 94% ee.
Our synthesis started with the preparation of aldehyde 28, which was obtained with a yield of 86% by the arylation of 4-iodo-1,2-dimethoxybenzene (27) with allylic alcohol using Pd$_2$(dba)$_3$ as catalyst. The $^1$H NMR spectrum of aldehyde 28 showed a typical singlet at $\delta$ 9.82 for aldehydic proton; other typical singlets at $\delta$ 3.85 and 3.87 are due to two -OMe protons. Its $^{13}$C NMR spectrum showed an aldehydic carbon at $\delta$ 201.67. Its IR spectrum exhibited a characteristic strong band at 1712 cm$^{-1}$ indicating the presence of a carbonyl group. Aldehyde 28 was then subjected to $\alpha$-amination using D-proline as catalyst, dibenzyl azodicarboxylate as the amine source, followed by its in situ reduction with NaBH$_4$ gave the protected amino alcohol 29 in 62% combined yield. The $^1$H NMR spectrum of 29 showed signals at $\delta$ 5.17 corresponding to -O-CH$_2$ protons of Cbz groups; other multiplet at $\delta$ 4.21 is due to -N-CH proton. Its $^{13}$C spectrum showed signals at $\delta$ 67.9 and 156.38 corresponding to -O-CH$_2$- and carbonyl carbon of Cbz groups respectively (Fig. 2).
Mild oxidation of alcohol 29 was carried out with NaClO₂, NaOCl, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as catalyst to produce the corresponding acid 30. The \(^1\)H NMR spectrum of 30 showed signals at \(\delta\) 5.13 corresponding to -O-CH\(_2\)- protons of Cbz groups. Its \(^{13}\)C spectrum showed signals at \(\delta\) 67.8 and 172.12 corresponding to -O-CH\(_2\)- of Cbz groups and acid carbonyl respectively.

Fig. 3: \(^{13}\)C NMR and \(^1\)H spectra of L-DOPA (1)
Reductive removal of both Cbz groups as well as \( N-N \) bond cleavage were achieved with Raney-Nickel (\( H_2, 70 \) psig), followed by demethylation using \( \text{BBr}_3 \), thus afforded L-DOPA (1) in 78\% yield with 94\% ee. The spectral data obtained for L-DOPA were in full agreement with the values reported in the literature\(^9\) (Fig. 3).

### 3.1.5 Conclusion

In conclusion, synthesis of L-DOPA (1) was achieved in 94\% ee via D-proline-catalyzed \( \alpha \)-amination of aldehyde 28. These reactions are operationally simple, rapid and require a relatively low amount of an inexpensive and nontoxic proline-catalyst. Excellent yields, simple and environment friendly procedures and easy availability of starting materials are some of the merits of this synthesis.

### 3.1.6 Experimental Section

3-(3,4-Dimethoxyphenyl)propanal (28):

To a stirred mixture of 4-iodo-1,2-dimethoxybenzene (27) (2.64 g, 10 mmol), \( \text{Pd}_2(\text{dba})_3 \) (0.045 g, 0.5 mol\%), \( \text{P(Cy)}_3 \) (0.028 g, 1 mol \%) and \( \text{K}_2\text{CO}_3 \) (2.76 g, 20 mmol) in DMF (15 mL) was added allyl alcohol (1.68 g, 30 mmol). The resulting mixture was stirred at 100 °C for 6 h. Then the reaction mixture was cooled to 25 °C and extracted with ethyl acetate (3 x 20 mL), washed with brine, dried over anhyd. \( \text{Na}_2\text{SO}_4 \) and concentrated under reduced pressure. The crude product was purified on column chromatography using 5\% ethyl acetate in pet. ether as eluent to afford the pure aldehyde 28 as colorless liquid.
Yield: 1.668 g (86%); colourless liquid; IR: (CHCl₃, cm⁻¹): 757, 831, 1033, 1178, 1247, 1308, 1463, 1514, 1612, 1681, 1712, 2057, 2362, 2837, 2933, 3006; ¹H NMR (200 MHz, CDCl₃): δ 2.73-2.81 (m, 2H), 2.88-2.99 (m, 2H), 3.85 (s, 3H), 3.87 (s, 3H), 6.71-6.82 (m, 3H), 9.82 (s, 1H); ¹³C NMR (50 MHz, CDCl₃): δ 24.3, 45.1, 55.5, 55.6, 111.1, 111.3, 119.8, 132.6, 147.1, 148.6, 201.6; Analysis: C₁₁H₁₄O₃ required C, 68.02; H, 7.27; found C, 67.89; H, 7.45%.

(S)-3-(3,4-Dimethoxyphenyl)-2-(1,2-dibenzyloxycarbonylhydrazinyl)propanol (29):

To a mixture of dibenzyl azodicarboxylate (1.324 g, 4 mmol) and D-proline (0.140 g, 20 mol%) in CH₃CN (200 mL) at 0 °C was added 3-(3,4-dimethoxyphenyl)propanal (1.17 g, 6 mmol) and the reaction mixture was allowed to stir at the same temperature for 2 h and then warmed to 20 °C within 1 h. After the reaction mixture became colorless it was cooled to 0 °C again and then treated with EtOH (20 mL) and NaBH₄ (0.38 g) for 5 min at 0 °C. After completion of reaction, it was quenched with aq. ammonium chloride solution and extracted with ethyl acetate (100 mL X 3). The combined organic layers were dried over anhyd. Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to get 29.

Yield: 1.532 g (62%); [α]D²⁵ +9.6 (c 0.14, CHCl₃); IR: (CHCl₃, cm⁻¹): 665, 929, 1027, 1060, 1217, 1361, 1454, 1514, 1724, 2401, 2937, 2958, 3020; ¹H NMR (200 MHz, CDCl₃): δ 2.04 (t, J = 7.3 Hz, 1H), 2.70 (t, J = 7.4 Hz, 1H), 3.85 (s, 3H), 3.87 (s, 3H), 3.89-3.92 (m, 2H), 4.18-4.24 (m, 1H), 5.17 (s, 4H), 6.67-6.83 (m, 3H), 7.34 (m, 10 H); ¹³C NMR (50 MHz, CDCl₃): δ 31.1, 53.1, 55.8, 55.9, 67.9, 68.7, 111.5, 111.9, 120.3, 128.3, 128.4, 128.6, 132.7, 135.5, 147.6, 149.1, 156.3; Analysis: C₂₇H₃₀N₂O₇ required C, 65.57; H, 6.11; N, 5.66; found C, 65.42; H, 6.13; N, 5.78%.
(S)-3-(3,4-dimethoxyphenyl)-2-(1,2-dibenzyloxycarbonylhydrazinyl)-propanoic acid (30):

To a stirred solution of alcohol 29 (1.48 g, 3 mmol), TEMPO (33 mg, 0.21 mmol), NaClO₂ (0.5 g, 6 mmol) and phosphate buffer (12 mL) in CH₃CN (15 mL) at 25 °C was added NaClO (5%, 0.15 mL). After stirring the reaction mixture for 5 h at 25 °C, 7.2 mL of 2N NaOH was added and the mixture was added to an ice-cold solution of sodium sulfite (92 mg in 30 mL). After stirring for 30 min, the reaction mixture was acidified with 2N HCl to pH 3-4 and extracted with ethyl acetate (50 mL X 3). The combined organic layers were washed with brine, dried over anhyd. Na₂SO₄ and concentrated under reduced pressure to give the acid 30 as a viscous liquid.

Yield: 1.189 g (78%); [α]D²⁵ +5.33 (c 0.36, CHCl₃); IR: (CHCl₃, cm⁻¹): 667, 698, 1027, 1217, 1261, 1514, 1593, 1605, 1633, 2937, 2960, 3018, 3066, 3294; ¹H NMR (200 MHz, CDCl₃): δ 3.05-3.14 (m, 1H), 3.27-3.29 (m, 1H), 3.82 (s, 6H), 5.11-5.20 (m, 4H), 6.63-6.78 (m, 3H), 7.30-7.36 (m, 10H); ¹³C NMR (50 MHz, CDCl₃): δ 34.5, 55.7, 67.8, 68.6, 111.2, 111.9, 120.7, 127.8, 128.3, 128.4, 134.8, 135.3, 147.7, 148.8, 155.19, 172.1;

Analysis: C27H28N₂O₈ requires C, 63.77; H, 5.55; N, 5.51 found C, 63.91; H, 5.38; N, 5.59%.

(S)-2-Amino-3-(3,4-dihydroxyphenyl)propanoic acid (L-DOPA) (1):

The acid 30 (0.763 g, 1.5 mmol) was dissolved in MeOH (20 mL), AcOH (10 drops) and treated with Raney nickel (1 g, excess) for 24 h under 70 psig hydrogen pressure. The reaction mixture was filtered over pad of celite and concentrated. To the crude amino acid dry CH₂Cl₂ (5 mL) was added BBr₃ (1 mL, excess) at 0 °C and stirred for 6 h at 25 °C.
L-DOPA

°C. After completion of reaction, solvents were removed under reduced pressure and purified by column chromatography to get pure product.

Yield: 0.171 g (58%); mp: 298 °C; lit. mp: 295 °C; \([\alpha]_{D}^{25} -12.1\) (c 1.0, 1N HCl); \{lit.\}

\([\alpha]_{D}^{25} -12.3\) (c 1.0, 1N HCl)); \textbf{IR (KBr, cm}^{-1}\): 840, 985, 1245, 1454, 1514, 1591, 1610, 1654, 1696, 2599, 2854, 2925, 3203, 3500; \textbf{\textsuperscript{1}H NMR (200 MHz, D}_{2}O): \(\delta\) 3.20 (dd, \(J = 6.0, 6.0\) Hz, 1H), 3.50 (dd, \(J = 6.0, 6.0\) Hz, 1H), 3.60 (brs, 2H) 4.45 (m, 1H), 6.80-7.05 (m, 3H), 11.8-12.6 (brs, 3H); \textbf{\textsuperscript{13}C NMR (50 MHz, CDCl}_3): \(\delta\) 39.73, 60.20, 119.05, 120.20, 123.87, 128.09, 146.47, 147.43, 164.41. \textbf{Analysis: C}_{9}H_{11}NO_{4} requires C, 54.82; H, 5.62; N, 7.10 found C, 54.69; H, 5.55; N, 6.94%.

Chapter III

115
SECTION 2:  
Formal Synthesis of Levofloxacin via Proline-Catalyzed 
α-Amination and α-Aminoxylation of Aldehydes

3.2.1 Introduction  
3.2.1.1 Quinolone Antibacterial agents  
Quinolone antibacterial agents are among the most attractive drugs in the anti-infective chemotherapy field. A tremendous amount of synthetic effort has been channeled into the synthesis of Quinolone Antibacterial agents. These research efforts have been rewarded by very significant improvements in antibacterial potency that resulted from changes in the basic quinolone nucleus. The contribution of many research facilities have allowed to reach a point where quinolones are some of the potent antibacterial.

3.2.1.2 Activity of Quinolone Antibacterial agents  
Studies on the N-substituent of the 4-pyridone nucleus showed that an ethyl substituent or some other substituents with comparable steric requirements i.e., vinyl, fluoroethyl, methoxy, methyl amino or cyclopropyl groups were favorable for antibacterial activity. Particularly, N-cyclopropyl derivatives were found to possess excellent antibacterial activity. In the studies of the relationships between physicochemical properties and pharmacokinetics of new compounds, it was found that introduction of fluorine into N-substituent reduced the lipophilicity of the molecules, suggesting that there should be a possibility for preparing less toxic compounds with reduced distribution to the central nervous system (CNS). The series of fluorinated compounds showed lower
Levofoxacin

hydrophobicity than the corresponding nonfluorinated derivatives and some of them retained similar antibacterial activity with that of ciprofloxacin (35).

3.2.1.3 Fluoroquinolones

The first quinolone antibiotic called nalidixic acid (32) was introduced in 1962. Since then, structural modifications have resulted in the second, third and fourth generation of fluoroquinolone antibiotics having excellent activity against gram-positive organisms (Fig. 4-7).

![Fig. 4: 1st Generation Quinolone Antibiotics]

![Fig. 5: 2nd Generation Quinolone Antibiotics]

![Fig. 6: 3rd Generation Quinolone Antibiotics]
Fluoroquinolones were primarily used to treat genitourinary tract infections but now they are used to treat a variety of infections – upper and lower respiratory infections, gastrointestinal infections, gynecologic infections, sexually transmitted diseases, and some skin and soft tissue infections. Most quinolones have excellent oral bioavailability, with few adverse effects. While fluoroquinolones are excellent antibiotics, the organisms it affects are known to develop multi-pathway resistance to fluoroquinolones. This is because, genetic mutations are very rapid and frequent during the course of antibiotic treatment. It is imperative therefore, that fluoroquinolones are used judiciously.

3.2.1.4 Mode of Action of Fluoroquinolones

Quinolones rapidly inhibit DNA synthesis by promoting cleavage of bacterial DNA in the DNA-enzyme complexes of DNA gyrase and type IV topoisomerase, resulting in rapid bacterial death. It has also been established that it binds to Bacterial topoisomerase IV in case of gram-negative organisms while it binds to DNA gyrase in gram-positive organisms. Quinolones are known to bind specifically to single stranded DNA but not to gyrase or double stranded DNA. The excellent potency of quinolones may be attributed to the fact that they are well absorbed following oral administration, with moderate to
excellent bioavailability. Quinolones are effective in the treatment of prostatitis because of their excellent penetration into prostatic tissue.\textsuperscript{14}

3.2.1.5 Importance of fluorine compounds

More than one million compounds containing one or more carbon-fluorine bonds are known, since barely more than ten of those occur natural. Organofluorine chemistry is virtually a completely man-made branch of organic chemistry.\textsuperscript{15} In the medicinal chemistry the introduction of fluorine atoms into molecules of biological interest such as steroids, carbohydrates, antitumor agents, and other biologically important molecules, occupies an increasing position in the recent scientific literature. This growing interest is due to the particular effects that fluorine can exert on the properties of the compound without altering its steric bulk. Electron withdrawal by fluorine results in a strong polarization of the C-F bond and the pronounced electronic effects associated to poor steric demands can have implications for reactions at an adjacent center that is for drug-target interactions.

Many selectively fluoro substituted organic compounds show a peculiar biological activity in fields such as biotechnologies, agriculture, and medicine. In the present case, fluoroamines, fluoroaminoacids and fluorinated peptidomimetics can find use in medicinal field as antitumor, anti-HIV and antithrombotic agents; the chiral fluorinated pheromones can be effective in the integrated biological fight against insects and parasites. The great demand for fluoroaromatics as building blocks in the synthesis of pharmaceuticals and pesticides has led to the search for attractive preparative routes.

Research efforts concerning the use of fluorinated organic compounds are of considerable interest as there are numerous examples wherein fluorine dramatically alters the chemical
Levofloxacin

and biological properties of a molecule. Among the quinolone antimicrobial agents, relatively few fused tricyclic analogues have been found to be possessing outstanding antibacterial activity. Levofloxacin (36) has been developed as a highly active new quinoline antibacterial agent against gram-positive and gram-negative pathogens.\(^{16}\)

### 3.2.2 Review of Literature

Literature search revealed that there are few reports available for the synthesis of (S)-(−)-7,8-difluoro-2,3-dihydro-3-methyl-4H-1,4-benzoxazine (39), the key intermediates for Levofloxacin (36). However, the reports deal with the synthesis of the intermediate using a stoichiometric amount of chiral reducing agents, N-alkylation of sulfonanilides with chiral sulfonates and mitsunobu cyclization, a brief account of which are described below.

**Hayakawa et al (1986)\(^{17}\)**

![Scheme 9]

\(\text{Scheme 9: (i) HPLC separation; (ii) aq. NaHCO}_3, \text{EtOH (iii) P(0Ph)}_3, \text{MeI, DMF; (iv) Bu}_3\text{SnH, EtOH; (v) conc HCl-CH}_3\text{COOH (2:1); (vi) 1-methylpiprazine, DMSO, reflux.}\)

---

*Chapter III 120*
Hayakawa et al. have synthesized both isomers of levofloxacin (36) by HPLC separation of 40 to give optically pure benzoyl esters 41a and 41b. The benzoyl ester 41a was hydrolyzed with an ethanolic aqueous NaHCO₃ solution to yield alcohol 42 which was converted to iodide 43 with triphenylphosphite methiodide in DMF. Reduction of iodide 43 with tri-n-butyltin hydride in ethanol, followed by hydrolysis of resulting ester 44 gave carboxylic acid 45. Finally, acid 45 was treated with 1-methylpiperazine in DMSO yielded (-)-levofloxacin 36 (Scheme 9).

Mitscher et al. (1987)¹³

Mitscher and coworkers have synthesized levofloxacin by condensation of 2,3,4,5-tetrafluorobenzoylacetate (46) with triethyl orthoformate which on reaction with (S)-(+) 2-amino-1-propanol followed by cyclisation with sodium hydride in dimethyl sulfoxide yielded ethyl 1,4-dihydro-fluoroquinoline (49) in 59% yield. Ester 49 on heating with aqueous potassium hydroxide followed by condensation with N-methyl-piperazine yielded levofloxacin (36) (Scheme 10).

![Chemical structure](image)

**Scheme 10:** (i) triethyl orthoformate, Ac₂O, reflux; (ii) (S)-(+) 2-amino-1-propanol, 57%; (iii) NaH, DMSO, 25 °C, 59%; (iv) KOH, THF, 65 °C, 70%; (v) N-methyl-piperazine, pyridine.
Atarashi et al. (1991). Atarashi et al. have synthesized the key intermediate of levofloxacin by asymmetric reduction of imine using chiral sodium triacyloxyborohydride (Scheme 11). Protection of ketone as its ketal with ethyleneglycol and p-toluenesulfonic acid in benzene afforded, which was hydrogenated on 5% palladium on charcoal in methanol gave amine. Deprotection of the ketal in acidic conditions afforded imine, which on asymmetric reduction using in DCM gave in 95% ee.

Scheme 11: (i) ethylene glycol, p-TSA, benzene; (ii) 5% Pd/C, ethanol; (iii) conc. HCl, aqueous ammonia; (iv) CH₂Cl₂, 55.

Kang et al. (1996). Kang et al. have synthesized the key intermediate of levofloxacin (7) by enzymatic reduction of ketone to afford alcohol in 91% yield with >99% ee. Reduction of nitro group with 10% Pd/C followed by Mitsunobu inversion of alcohol gave ester in 95% yield. The mild hydrolysis of with potassium cyanide in MeOH at 25 °C yielded the alcohol with 99% ee. Cyclization of under Mitsunobu reaction conditions afforded benzoxazine in 95% yield (Scheme 12).
Levofloxacin

Scheme 12: (i) Bakers’ yeast, MeOH/H₂O, 35 °C, 91%, 99% ee; (ii) Pd/C, H₂, THF, 25 °C, 99%; (iii) Ph₃P, DEAD, PhCO₂H, THF, 25 °C, 95%; (iv) KCN, MeOH, 25 °C, 99%, 99% ee; (v) Ph₃P, DEAD, ZnCl₂, CH₃CN, reflux, 95%.

Satoh et al. (1998)²⁰

Satoh et al. have synthesized the key intermediate of levofloxacin (36) by enantioselective reduction of imine 54 using [Ir(COD)Cl]₂ and (2S,4S)-BPPM as ligand at 40 bar H₂ pressure (Scheme 13).

Scheme 13: (i) Et₃N, Br₂, EtOAc; (ii) [Ir(COD)Cl]₂, (2S, 4S)-BPPM, benzene: MeOH (1:1), BiI₃, H₂ (40 bar);

3.2.3 Present Work

3.2.3.1 Objectives

As can be seen from the above discussion, most of the methods reported for the synthesis of (-)-levofloxacin (36), either require use of expensive chiral starting materials in

Chapter III
Levofloxacin

stoichiometric amounts or adopt classical resolution strategies. The retrosynthetic analysis of (-)-levofloxacin (36) shows that benzoxazine 39 could serve as the key intermediate, which was visualized to be synthesized by employing proline catalyzed amination (Scheme 14).

\[
\text{Scheme 14: Retrosynthesis of (-)- Levofloxacin}
\]

This section describes the asymmetric synthesis of the intermediate benzoxazine 39 using proline-catalyzed \( \alpha \)-amination as well as \( \alpha \)-aminooxylation of 1-propanal.

3.2.4 Results and Discussion

We have visualized that benzoxazine 39 and quinoline derivative 61 are the key intermediates in our synthetic strategy. Firstly, we planned to synthesize the intermediate 61 by employing Bayliss-Hillman reaction of 3,4,5-trifluoro-2-nitrobenzaldehyde (67) with methyl acrylate. Initially, a model study was carried out using \( o \)-nitrobenzaldehyde and methyl acrylate as substrates in the presence of DABCO to obtain ethyl 4-hydroxyquinoline-3-carboxylate (62) in 90% yield (Scheme 15). The \( ^1 \)H NMR spectrum
of 62 showed a singlet at δ 3.74 corresponding to methoxy proton; other signals at δ 5.96 and 6.29 are due to olefinic protons. Its IR spectrum exhibited a characteristic strong band at 1720 cm⁻¹ indicating the presence of a carbonyl group. Cyclization of 62 with trifluoroacetic acid resulted in the formation of N-oxide 63 in 85% yield. The ¹H NMR spectrum of N-oxide 63 showed a singlet at δ 8.69 corresponding to the aromatic proton ortho to nitrogen atom; also the disappearance of the signals at δ 5.96 and 6.29 confirmed the nitrone formation. The reduction of N-oxide moiety in 63 using NaBH₄ gave the quinolone 64 in 65% yield. The ¹H NMR spectrum of quinolone derivative 64 showed a typical singlet at δ 8.71 corresponding to an aromatic proton ortho to nitrogen atom.

![Scheme 15](image)

\( \text{Scheme 15: } \) (i) DABCO, methyl acrylate, 25 °C, 90%; (b) CF₃CO₂H, 60 °C, 85%; (c) NaBH₄, MeOH, 25 °C, 24 h, 65%.

Next, the synthesis of fluoro substituted nitrobenzaldehyde 67, the required starting material for the Bayliss-Hillman reaction was envisaged from 1,2,3-trichlorobenzene (Scheme 16). Thus, the nitration of 1,2,3-trichlorobenzene in conc. HNO₃ and H₂SO₄ mixture at 0 °C gave the mono nitrated product 65 in 96% yield. The ¹H NMR spectrum of 65 showed two doublets at δ 7.56 and 7.67 corresponding to two aromatic protons.
Vicarious nucleophilic substitution on nitro compound 65 using K’OBu and CHCl₃ did not give the dichloro intermediate, 66.

\[
\begin{align*}
\text{Scheme 16:} & \quad \text{(i) conc. HNO}_3\text{-H}_2\text{SO}_4, \, 0 \, ^\circ\text{C}, \, 2 \, \text{h}, \, 96\%; \, \text{(ii) K’OBu, CHCl}_3, \, \text{THF-DMF,} \, 25 \, ^\circ\text{C}, \, 3 \, \text{min then AcOH in MeOH.}
\end{align*}
\]

Alternately, L-proline-catalyzed α-aminooxidation²¹ of 1-propanal was carried out using nitrosobenzene and L-proline (25 mol%) at -20 °C to furnish the aminooxy aldehyde, which was reduced in situ with sodium borohydride to afford (R)-α-aminooxy alcohol 68 in 85% yield. The aminooxy alcohol 68 was then hydrogenated over 10% Pd/C to furnish (R)-1,2-propanediol 69 in 90% yield. The \(^1\)H NMR spectrum of diol 69 showed typical signal at \(\delta\) 3.39 (dd) corresponding to the methine proton (-CHOH); other doublet at \(\delta\) 1.15 is due to methyl proton. Its \(^13\)C NMR spectrum displayed signals at \(\delta \) 67.5 and 68.1 due to the methine and methylene carbons respectively. Selective monoprotection of diol 69 was carried out using TBSCI in CH₂Cl₂ to give the TBS ether 70 in 90% yield. The appearance of signals at \(\delta \) 0.06 (s) and 0.89 (s) in the \(^1\)H NMR spectrum of 70 due to methyl and tert-butyl protons of TBS group confirms the formation of silyl ether 70. Mesylation of the silyl protected alcohol 70 using mesyl chloride under basic conditions afforded mesyl compound 71 in 95% yield. The \(^1\)H NMR spectrum of 71 showed typical signal at \(\delta \) 3.01 (s) corresponding to the methyl protons of mesyl group. Its \(^13\)C NMR spectrum displayed signal at \(\delta \) 38.1 corresponding to methyl carbon of mesyl group.
However, \( N \)-alkylation of 2,3,4-trifluoroaniline with chiral mesyl compound 71 under the basic conditions gave mixture of products (Scheme 17).

\[
\begin{align*}
&\text{Scheme 17:} \\
&(i) \text{PhNO, L-proline (25 mol%), CH}_3\text{CN, }-20^\circ\text{C, 24 h then MeOH, NaBH}_4, \\
&\quad 85\%; (ii) \text{H}_2 (1\text{atm.}), 10\% \text{Pd/C, MeOH, 25 }^\circ\text{C, 12 h, 90\%, 98\% ee}; (iii) \\
&\quad \text{imidazole, TBSCI, }\text{CH}_2\text{Cl}_2, \text{0 }^\circ\text{C, 2 h, 90\%}; (iv) \text{Et}_3\text{N, }\text{CH}_3\text{SO}_2\text{Cl, }\text{CH}_2\text{Cl}_2, \text{0 }^\circ\text{C,} \\
&\quad 2 \text{ h, 95\%}; (v) \text{2,3,4-trifluoroaniline, }\text{Et}_3\text{N, DMF, 0-25 }^\circ\text{C.}
\end{align*}
\]

In our next attempt, D-proline-catalyzed \( \alpha \)-aminooxylation\(^1\) of 1-propanal was carried out using nitrosobenzene and D-proline (25 mol\%) at -20 °C to furnish the aminooxy aldehyde, which was reduced \textit{in situ} with sodium borohydride to afford (S)-\( \alpha \)-aminooxy alcohol 73 in 85% yield. The aminooxy alcohol 73 was then hydrogenated over 10% Pd/C to furnish (S)-1,2-propanediol 74 in 90% yield. Selective monobenzylation of diol 74 was carried out with benzyl bromide in presence of Bu\(_2\)SnO and to give 75 in 93% yield. The appearance of signals at \( \delta \) 4.55 (s) and 7.32 (m) in the \(^1\)H NMR spectrum of the 75 corresponding to the benzylic and aromatic protons confirms the benzylic protection. The hydroxy function in alcohol 75 was converted into bromo derivative 76 in 95% yield using CBr\(_4\) and PPh\(_3\) in the presence of imidazole. The \(^1\)H NMR spectrum of bromo intermediate 76 showed typical signal at \( \delta \) 1.70 (d) corresponding to the methyl proton; other signal at \( \delta \) 4.57 is due to benzylic proton. Its \(^{13}\)C NMR spectrum displayed signals at \( \delta \) 67.5 and 68.1 due to the methine and methylene carbons respectively. Among the several conditions tried, \( N \)-alkylation of bromo derivative 76 with 1,2,3-
trifluoroaniline in the presence of NaH, in reflux DMF gave the required product 77 although in low yield (< 5%). The $^1$H NMR spectrum of 77 showed typical singlet at $\delta$ 4.54 corresponding to benzylic protons; other two multiplets at $\delta$ 6.43 and 6.75 corresponding to aromatic protons. At this stage, purification of the required product was not successful to continue the process of debenzylation and cyclization (Scheme 18).

In the new strategy, D-proline-catalyzed $\alpha$-amination$^{11}$ of 1-propanal using dibenzyl azodicarboxylate as the amine source followed by its subsequent reduction with NaBH$_4$ gave the protected amino alcohol 78 in 92% yield. Catalytic hydrogenation of 78 using Raney Ni, H$_2$ (70 psig) produced (S)-2-aminopropan-1-ol (79) in 70% yield and 96% ee (Scheme 19).
In order to complete the synthesis, 1,2,3-trifluoro-4-iodobenzene (81) was prepared in 76% yield by diazotization of the corresponding 2,3,4-trifluoroaniline (80) (Scheme 20). The $^1$H NMR spectrum of 81 showed two multiplets at $\delta$ 6.82 and 6.47 corresponding to aromatic protons. Buchwald amination$^{22}$ (CuI, Cs$_2$CO$_3$, 2-acetylcyclohexanone) of aryl iodide 81 with (S)-2-aminopropan-1-ol (79) was carried out to give the amino alcohol in situ, which was subjected to cyclization under basic conditions to give benzoxazine 39 in 64% yield. The spectral data obtained for benzoxazine 39 were in full agreement with the
values reported in the literature. The synthesis of levofloxacin (36) has already been reported from 39 in six steps.

![Scheme 20:](image)

**Scheme 20:** (i) conc. HCl, NaNO₂, HCl, KI, 76%; (ii) (a) Cul, 2-acetylcyclohexanone, Cs₂CO₃, DMF, 25 °C; (b) KOH, THF, 65 °C. 64%, 96% ee.

3.2.5 Conclusion

In conclusion, we have successfully applied proline-catalyzed α-aminoxylation and α-amination strategies towards the synthesis of the chiral intermediates 71, 76 and 79, in high enantioselectivity (98, 98 and 96%). The reactions are rapid, and require a relatively low amount of an inexpensive and nontoxic proline-catalyst. The synthesis of the intermediate benzoxazine 39 has been achieved in three steps with 96% ee, thus completing the formal synthesis of (-)-levofloxacin (36).

3.2.6 Experimental Section

3-[Hydroxy(2-nitrophenyl)methyl]but-3-en-2-one (62):
Levofoxacin

To a stirred solution of 2-nitrobenzaldehyde (3.02 g, 20 mmol) and methyl acrylate (15 mL) was added DABCO (2.24 g, 20 mmol) at 25 °C and stirred at the same temperature for 24 h. The reaction mixture was poured into water, and extracted with dichloromethane (3 x 25 mL). The combined organic layers were washed with brine (50 mL), dried over anhyd. Na₂SO₄, and evaporated under reduced pressure. The crude product was purified by column chromatography using pet.ether: EtOAc as eluent to give pure hydroxy ester 62.

**Yield:** 3.978 g (90%); IR (CHCl₃, cm⁻¹): 752, 788, 859, 964, 1051, 1082, 1194, 1297, 1351, 1440, 1527, 1633, 1720, 2954, 3004, 3456; **¹H NMR** (200 MHz, CDCl₃): δ 3.64 (brs, 1H), 3.69 (s, 3H), 5.67 (s, 1H), 6.29 (s, 1H), 7.45-7.97 (m, 4H); **Analysis:** C₁₁H₁₄NO₄ required C, 59.73; H, 5.01; N, 6.33; found C, 59.54; H, 5.23; N, 6.52%.

3-Methoxycarbonyl-4-hydroxyquinoline N-oxide (63):

A stirred solution of hydroxy ester 62 (1.020 g, 5 mmol) in trifluoroacetic acid (10 mL) was heated at 60-70 °C for 2 h. After cooling to 25 °C, the reaction mixture was poured into water and extracted with chloroform (2 x 30 mL). The combined organic layers were washed with brine (50 mL), dried over anhyd. Na₂SO₄, and evaporated under reduced pressure. The crude product was purified by column chromatography using CH₂Cl₂: MeOH (14:1) as eluent to give nitrone 63.

**Yield:** 0.863 g (85%); colourless solid; **mp:** 182-183 °C; IR (KBr, cm⁻¹): 779, 974, 1057, 1099, 1145, 1227, 1306, 1357, 1421, 1458, 1484, 1536, 1616, 1700, 2563, 2871, 2959, 3106; **¹H NMR** (200 MHz, DMSO-d₆): δ 3.72 (s, 3H), 7.49 (m, 1H), 7.81 (m, 2H), 8.17 (m, 1H), 8.69 (m, 1H); **Analysis:** C₁₁H₉NO₃ required C, 65.02; H, 4.46; N, 6.89; found C, 64.85; H, 4.31; N, 6.97%.

*Chapter III*
Levofloxacin

3-Acetylquinolin-4(1H)-one (64):

A stirred solution of nitrone 63 (0.420 g, 2 mmol) in methanol (8 mL) was added sodium borohydride (0.152 g, 4 mmol) at 25 °C and stirred for 24 h. The reaction mixture was poured into water, and extracted with dichloromethane (3 x 25 mL). The combined organic layers were washed with brine (50 mL), dried over anhyd. Na₂SO₄, and evaporated under reduced pressure. The crude product was purified by column chromatography using pet.ether: EtOAc as eluent to give pure quinolone 64.

Yield: 0.243 g (65%); yellow solid; mp: 204-206 °C; IR (KBr, cm⁻¹): 789, 1056, 1251, 1298, 1497, 1572, 1628, 1717, 2986, 3000, 3082; ¹H NMR (200 MHz, DMSO-d₆): δ 3.77 (s, 3H), 7.38-7.73 (m, 2H), 8.21-8.36 (m, 2H), 8.71 (m, 1H); Analysis: C₁₁H₉NO₂ required C, 70.58; H, 4.85; N, 7.48; found C, 70.41; H, 4.81; N, 7.52%.

1,2,3-Trichloro-4-nitrobenzene (65):

To 1,2,3-trichlorobenzene (10 g, 55 mmol), nitrating mixture (5ml conc. H₂SO₄ + 4ml conc. HNO₃) was added at 0 °C. The reaction mixture was stirred at 25 °C for 10 h and poured carefully onto a mixture of ice/water. The resulting mixture was extracted with dichloromethane (3 x 150 mL) and the combined organic layers were washed with brine (50 mL), dried over anhyd. Na₂SO₄, and evaporated under reduced pressure. The crude product was purified by column chromatography using pet.ether: EtOAc (9:1) as eluent to give pure nitro compound 65.

Yield: 11.98 g (96%); mp: 54-55 °C; IR (KBr, cm⁻¹): 575, 616, 739, 766, 828, 899, 1143, 1173, 1262, 1348, 1432, 1526, 1563, 1911, 2866, 2981, 3078, 3129, 3433; ¹H NMR (200 MHz, CDCl₃): δ 7.54 (d, J = 8.8 Hz, 1H), 7.69 (d, J = 8.8 Hz, 1H); ¹³C NMR (50 MHz,
CDCl₃): δ 123.1, 127.6, 128.5, 134.5, 138.4, 147.7; Analysis: C₆H₂Cl₂NO₂ required C, 31.82; H, 0.89; Cl, 46.97; N, 7.82; found C, 31.95; H, 1.04; Cl, 47.13; N, 7.74%.

(2R)-(N-Phenylaminoxy)propan-1-ol (68):

To a stirred mixture of propanal (5.5 mL, 75 mmol) and nitrosobenzene (2.675 mg, 25 mmol) in CH₃CN (60 mL) was added L-proline (0.575 g, 20 mol%) at -20 °C. The reaction mixture was allowed to stir at the same temperature for 24 h followed by addition of MeOH (75 mL) and NaBH₄ (2.8 g, 75 mmol) to the reaction mixture followed by stirring for 10 min. After addition of phosphate buffer, the resulting mixture was extracted with EtOAc (3 × 60 mL) and the combined organic layers were dried over Na₂SO₄. Purification by column chromatography over silica gel (Pet ether: EtOAc = 80:20) afforded aminoxy alcohol as a brownish liquid.

Yield: 3.55 g (85%); [α]⁰⁺° +4.38 (c 1.2, CHCl₃) {lit.²¹ [α]²⁵° +1.21 (c 0.8, CHCl₃)}; ¹H NMR (200 MHz, CDCl₃): δ 1.25 (d, J = 6.4 Hz, 3H), 2.40 (brs, 1H), 3.70-3.78 (m, 2H); 4.05-4.18 (m, 1H), 6.94-7.01 (m, 3H), 7.24-7.31 (m, 2H); ¹³C NMR (50 MHz, CDCl₃): δ 15.5, 66.5, 80.0, 114.6, 122.3, 128.9, 148.3.

(R)-Propane-1,2-diol (69):

To a solution of alcohol 68 (3.0 g, 18 mmol) in MeOH (15 mL) was added 10% Pd/C (1 g) at 25 °C. The reaction mixture was then stirred in the hydrogen atmosphere (1 atm) for 6 h. After completion of reaction (monitored by TLC) the reaction mixture was filtered through celite pad, concentrated to near dryness. The crude product was then purified by silica gel chromatography using pet ether: EtOAc (30:70) as eluent to afford pure diol 69 as colourless liquid.
Levofloxacin

Yield: 1.23 g (90%); [α]25D -25.22 (c 2.8, CHCl3); IR (CHCl3, cm⁻¹): 811, 922, 1045, 1132, 1264, 1428, 1716, 2933, 3706; ¹H NMR (200 MHz, CDCl3): δ 1.15 (d, J = 6.3 Hz, 3H), 3.39 (dd, J = 8.0, 11.1 Hz, 1H), 3.63 (m, 1H), 3.93 (m, 1H), 4.35 (brs, 2H); ¹³C NMR (50 MHz, CDCl3): δ 18.5, 67.5, 68.1; Analysis: C₃H₈O₂ required C, 47.35; H, 10.6; found C, 47.51; H, 10.69%.

(R)-1-(tert-Butyldimethylsilylhydroxy)propan-2-ol (70):

To a stirred mixture of diol 69 (0.76 g, 10 mmol) and imidazole (0.783 g, 11 mmol) in CH₂Cl₂ was added tert-butyldimethylsilyl chloride (1.73 g, 11 mmol) at 0 °C. The reaction mixture was stirred at same temperature for 1 h and quenched with NaHCO₃ solution. The resulting mixture was extracted with dichloromethane (3 x 150 mL) and the combined organic layers were washed with brine (50 mL), dried over anhyd. Na₂SO₄, and evaporated under reduced pressure. The crude product was purified by column chromatography to give pure silyl protected alcohol 70.

Yield: 1.67 g (90%); [α]25D -4.25 (c 0.9, acetone); ¹H NMR (200 MHz, CDCl3): δ 0.04 (s, 6H), 0.89 (s, 9H), 1.08 (d, 3H), 2.46 (brs, 1H), 3.32 (m, 1H), 3.60 (m, 1H), 3.80 (m, 1H); Analysis: C₉H₂₂O₂Si required C, 56.79; H, 11.65; found C, 56.51; H, 11.52%.

(R)-1-(tert-Butyldimethylsilylhydroxy)-propan-2-yl methanesulfonate (71):

To a stirred mixture of alcohol 70 (0.95 g, 5 mmol) and Et₃N (0.9 mL, 6 mmol) in CH₂Cl₂ (20 mL) was added MeSO₂Cl (0.5 mL, 6 mmol) at 0 °C. The reaction mixture was allowed to stir at 25 °C for 6 h. The solvent was removed under reduced pressure to get crude product. The crude product was purified by silica gel column chromatography using pet ether: ethyl acetate (85:15) to obtain bromo derivative 71.

Chapter III

134
Levofloxacin

**Yield:** 1.27 g (95%); \([\alpha]^D_{25} -6.58 \ (c \ 1.2, \ CHCl_3); ^1H NMR (200 MHz, CDCl_3): \delta 0.05 (s, 6H), 0.88 (s, 9H), 1.37 (d, 3H), 3.01 (s, 3H), 3.66 (m, 2H), 4.72 (m, 1H); ^13C NMR (50 MHz, CDCl_3): \delta 13.3, 14.1, 21.9, 22.8, 28.9, 30.7, 31.8, 33.7, 42.2, 42.3, 42.6;

**Analysis:** C_{10}H_{24}O_{4}SSi required C, 44.74; H, 9.01; S, 11.94; found C, 44.51; H, 9.1; S, 12.08%.

(2S)-(N-Phenylaminooxy)propan-1-ol (73):

To a stirred mixture of propanal (5.5 mL, 75 mmol) and nitrosobenzene (2.675 mg, 25 mmol) in CH_3CN (60 mL) was added D-proline (0.575 g, 20 mol%) at -20 °C. The reaction mixture was allowed to stir at the same temperature for 24 h followed by addition of MeOH (75 mL) and NaBH_4 (2.8 g, 75 mmol) to the reaction mixture followed by stirring for 10 min. After addition of phosphate buffer, the resulting mixture was extracted with EtOAc (3 × 60 mL) and the combined organic layers were dried over Na_2SO_4. Purification by column chromatography over silica gel (Pet ether: EtOAc = 80:20) afforded aminoxy alcohol as a brownish liquid.

**Yield:** 3.55 g (85%); \([\alpha]^D_{25} -4.38 \ (c \ 1.2, \ CHCl_3); \{lit.^{21b} \ [\alpha]^D_{25} -1.21 \ (c \ 0.8, \ CHCl_3)\}.

(5)-Propane-1,2-diol (74):

To a solution of alcohol 73 (3.0 g, 18 mmol) in MeOH (15 mL) was added 10% Pd/C (1 g) at 25 °C. The reaction mixture was then stirred in the hydrogen atmosphere (1 atm) for 6 h. After completion of reaction (monitored by TLC) the reaction mixture was filtered through celite pad, concentrated to near dryness. The crude product was then purified by silica gel chromatography using pet ether: EtOAc (30:70) as eluent to afford pure diol 74 as colourless liquid.

**Yield:** 1.23 g (90%); \([\alpha]^D_{25} +25.22 \ (c \ 2.8, \ CHCl_3).

---

Chapter III 135
(S)-1-(Benzyloxy)propan-2-ol (75):

A mixture of diol 74 (0.76 g, 10 mmol) and Bu₂SnO (2.98 g, 12 mmol) in toluene (100 mL) was refluxed for 12 h with azeotropic removal of water. Then, tetrabutylammonium bromide (1.6 g, 5 mmol) and benzyl bromide (1.84 g, 12 mmol) were added and the mixture was refluxed for 20 h. The solution was concentrated in vacuo, and silica gel chromatography (pet ether: EtOAc 80:20) afforded alcohol 75.

**Yield:** 1.55 g (93%); \([\alpha]_D^{25} +7.31 (c 1.08, \text{CHCl}_3); \text{IR} (\text{CHCl}_3, \text{cm}^{-1}): 698, 740, 1095, 1253, 2361, 2928, 2967, 3331; ^1H \text{NMR} (200 MHz, \text{CDCl}_3): \delta 1.14 (d, \ J=6.4 \text{ Hz, 3H}), 3.26 (dd, \ J=8.2, 9.3 \text{ Hz, 1H}), 3.46 (dd, \ J=3.1, 9.3 \text{ Hz, 1H}), 3.91-4.06 (m, 1H), 4.55 (s, 2H), 7.32 (m, 5H); ^13C \text{NMR} (50 MHz, \text{CDCl}_3): \delta 18.6, 66.4, 73.3, 75.8, 127.7, 127.8, 128.4, 137.9; \text{MS} (m/z, \% \text{relative intensity}): 166 (11), 107 (18), 91 (100, base peak), 75 (6), 65 (12), 45 (19); Analysis: C₁₀H₁₄O₂ requires C, 72.26; H, 8.49; found C, 72.09; H, 8.54%.

1-[(R)-2-Bromopropoxy]methyl]benzene (76):

To a stirred mixture of alcohol 75 (0.835 g, 5 mmol), PPh₃ (1.44 g, 5.5 mmol) and imidazole (0.37 g, 5.5 mmol) in CH₂Cl₂ (20 mL) was added CBr₄ (1.82 g, 5.5 mmol) at 0 °C. The reaction mixture was allowed to stir at 25 °C for 6 h. the solvent was removed under reduced pressure to get crude product. The crude product was purified by silica gel column chromatography using pet ether: ethyl acetate (85:15) to obtain bromo derivative 76.

**Yield:** 5.4 g (95%); \([\alpha]_D^{25} -6.58 (c 1, \text{CHCl}_3); ^1H \text{NMR} (200 MHz, \text{CDCl}_3): \delta 1.70 (d, \ J=6.7 \text{ Hz, 3H}), 3.56 (dd, \ J=6.8, 10.1 \text{ Hz, 1H}), 3.68 (dd, \ J=5.9, 10.1 \text{ Hz, 1H}), 4.08-4.24 (m, 1H), 4.57 (s, 2H), 7.32 (m, 5H); ^13C \text{NMR} (50 MHz, \text{CDCl}_3): \delta 22.7, 46.3, 73.0,
Levofloxacin

75.4, 127.5, 127.8, 128.4, 137.9; Analysis: C_{10}H_{13}BrO requires C, 52.42; H, 5.72; Br, 34.88; found C, 52.49; H, 5.86; Br, 34.96%.

*N-((S)-1-(benzyloxy)propan-2-yl)-2,3,4-trifluorobenzenamine (77)*:

To a stirred mixture of NaH (0.88 g, 2.2 mmol), 2,3,4-trifluoroaniline (0.516 g, 2.2 mmol) and bromo compound 76 (0.165 g, 2.2 mmol) in DMF (5 mL) was refluxed at 135 °C for 6 h. Solvent was removed under reduced pressure. The resulting residue was purified by column chromatography to obtain 77.

**Yield:** 5%; colorless liquid; \[^1\text{H}\text{ NMR} (200 MHz, CDCl}_3\): \(\delta\) 1.14 (d, \(J = 6.4\) Hz, 3H), 3.28 (dd, \(J = 8.0, 9.2\) Hz, 1H), 3.46 (dd, \(J = 3.2, 9.3\) Hz, 1H), 3.93-4.02 (m, 1H), 4.54 (s, 2H), 6.36-6.46 (m, 1H), 6.71-6.79 (m, 1H), 7.32 (m, 5H).

**(S)-2-((1,2-dibenzyloxycarbonylhydrazinyl)-1-propanol (78):**

To a mixture of dibenzyl azodicarboxylate (8.25 g, 25 mmol) and D-proline (287 mg, 2.49 mmol, 10 mol%) in CH\(_3\)CN (200 mL) at 0 °C was added 1-propanal (2.175 g, 37.5 mmol) and the reaction mixture was allowed to stir at the same temperature for 2 h and then warmed to 20 °C within 1 h. After the reaction mixture became colorless it was cooled to 0 °C again and then treated with EtOH (150 mL) and NaBH\(_4\) (1.2 g) for 5 min at 0 °C. After completion of reaction it was quenched with aq. ammonium chloride solution and extracted with EtOAc (100 mL x 3). The combined organic layers were dried over anhyd. Na\(_2\)SO\(_4\), filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using pet ether: ethyl acetate (85:15) to obtain alcohol 78.

**Yield:** 8.24 g (92%); yellow solid; mp: 82-83 °C; \([\alpha]_D^{25}\) +26.9 (c 0.9, CHCl\(_3\)); IR (CHCl\(_3\), cm\(^{-1}\)): 702, 732, 755, 1049, 1064, 1209, 1264, 1338, 1432, 1702, 1722, 2979.
Levofloxacin

3032, 3252, 3524; \(^1\)H NMR (200 MHz, CDCl\(_3\)): \(\delta\) 1.00 (d, \(J = 6.6\) Hz, 3H), 1.77 (bs, 1H), 3.46 (m, 2H), 4.49 (m, 1H), 5.16 (m, 4H), 6.72 (bs, 1H), 7.34 (m, 10 H); \(^{13}\)C NMR (50 MHz, CDCl\(_3\)): \(\delta\) 13.5, 56.1, 62.9, 68.2, 127.68, 128.1, 128.4, 128.5, 135.0, 135.6, 156.3; Analysis: C\(_{19}\)H\(_{22}\)N\(_2\)O\(_5\) required C, 63.67; H, 6.19; N, 7.82; found C, 63.85; H, 6.05; N, 7.74%.

(S)-2-Aminopropan-1-ol (79):

The alcohol 78 (5.73 g, 16 mmol) was dissolved in MeOH (40 mL), AcOH (10 drops) and treated with Raney nickel (10 g, excess) for 24 h under 5 bar of hydrogen. The reaction mixture was filtered over celite pad and concentrated to give the corresponding amino alcohol 79.

Yield: 0.84 g (70%); colorless liquid; 96% ee; [\(\alpha\)\(^D\)] = +23.02 (c 1.3, MeOH); [\(\alpha\)\(^D\)] = +23.5 (c 1, MeOH) for 98% ee; IR (CHCl\(_3\), cm\(^{-1}\)): 701, 1043, 1376, 1454, 1648, 2873, 2972, 3029, 3296; \(^1\)H NMR (200 MHz, CDCl\(_3\)): \(\delta\) 1.05 (d, \(J = 6.4\) Hz, 3H), 2.55 (bs, 3H), 2.96-3.07 (m, 1H), 3.24 (dd, \(J = 7.8, 10.6\) Hz, 1H), 3.54 (dd, \(J = 3.9, 10.4\) Hz, 1H); \(^{13}\)C NMR (50 MHz, CDCl\(_3\)): \(\delta\) 18.8, 47.8, 67.3; Analysis: C\(_3\)H\(_9\)NO required C, 47.97; H, 12.08; N, 18.65; found C, 47.79; H, 11.88; N, 18.81%.

2,3,4-Trifluoro-iodobenzene (81):

2,3,4-Trifluoroaniline (2.852 g, 19.4 mmol) was dissolved in con. HCl (8.5 mL) and water (8.5 mL). The reaction mixture was cooled to 0-5 °C in an ice-bath and solution of sodium nitrite (2.249 g, 32.6 mmol) in 10.8 mL of water was added in small portions. It was stirred vigorously with a thermometer and the temperature was maintained below 10 °C, but preferably at about 5 °C by adding a little crushed ice to the mixture. To the diazonium mixture was added a solution of KI (5.41 g, 32.6 mmol) in 5 mL of water with

Chapter III
Levofoxacin

shaking and allowed to reflux for 1 h. The reaction mixture was cooled to 25 °C, 10% NaOH was added and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (25 mL), dried over anhyd. Na₂SO₄ and evaporated under reduced pressure. The crude product was purified by column chromatography using pet.ether: EtOAc (9:1) as eluent to give pure iodo compound 81

Yield: 3.8 g (76%); IR (CHCl₃, cm⁻¹): 839, 1023, 1229, 1250, 1501, 2837, 2931, 3076; 

¹H NMR (200 MHz, CDCl₃): δ 6.76-6.90 (m, 1H), 7.41-7.53 (m, 1H); ¹³C NMR (50 MHz, CDCl₃): δ 75.4, 114.0, 132.1, 139.7, 148.9, 153.9; Analysis: C₆H₂F₃I requires C, 27.93; H, 0.78; found C, 27.88; H, 0.75%.

(5)-7,8-Difluoro-3,4-dihydro-3-methyl-4H-1,4-benzoxazine (39):

To a stirred mixture of copper (I) iodide (0.019 g, 0.1 mmol), aryl iodide 81 (0.516 g, 2 mmol), aminoalcohol 79 (0.165 g, 2.2 mmol) and Cs₂CO₃ (1.3 g, 4.0 mmol) in DMF (5 mL) was added 2-acetylcyclohexanone (56 mg, 0.4 mmol) at 25 °C for 12 h. The reaction mixture was diluted with dichloromethane and filtered to remove inorganic salts and solvent was removed under reduced pressure. To the crude mixture in THF (25 mL) was added 10% aqueous solution of KOH (5 mL), and the reaction mixture was heated at 70 °C for 2 h. The reaction mixture was concentrated under reduced pressure and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (25 mL), dried over anhyd. Na₂SO₄ and evaporated under reduced pressure. The crude product was purified by column chromatography to give amino compound 39

Yield: 0.237 g (64%); colorless liquid; 96% ee; [α]²⁵文化传播 -5.86 (c 3, CHCl₃) (lit²⁰ [α]²⁵文化传播 -5.5 (c 3, CHCl₃) 90% ee); IR (neat, cm⁻¹): 1558, 1610, 1683, 1716, 2871, 2976, 3388; 

¹H NMR (200 MHz, CDCl₃): δ 1.18 (d, J = 6.3 Hz, 3H), 3.43-3.54 (m, 1H), 3.64 (bs, 1H).
Levofloxacin

3.77 (dd, J = 8.3, 10.4 Hz, 1H), 4.26 (dd, J = 2.7, 10.4 Hz, 1H), 6.21-6.34 (m, 1H), 6.54 (m, 1H); Analysis: C9H9F2NO required C, 58.38; H, 4.90; N, 7.56; found C, 58.21; H, 5.04; N, 7.69%.
SECTION 3:
Synthesis of (Z)-Tamoxifen via Palladium-Catalyzed Suzuki coupling

3.3.1 Introduction

Antiestrogens are used clinically for controlling mammary and endometrial carcinomas and managing a number of endocrine disorders.\textsuperscript{24} Tamoxifen (1,2-diphenyl-1-[4[2-dimethylamino)ethoxylphenyl]-1-butene) 82 is a potent antiestrogen, which blocks the action of estrogens. It inhibits the development and growth of mammary tumors in rats and is effective in treating estrogen-dependent, metastatic breast cancer in human.\textsuperscript{25} In vivo, tamoxifen (82) is transformed to hydroxytamoxifen, which has a much higher binding affinity for the estrogen receptor and appears to be the compound responsible, in part, for the biological actions of tamoxifen. (E)-Tamoxifen, usually referred to as cis-tamoxifen has no clinical uses.

Fig. 9: Structures of (Z) and (E)-tamoxifen
3.3.2 Review of Literature

Literature search revealed that there are several reports available for the synthesis of (Z)-tamoxifen (82). However, most of the reports deal with the carbometalation of alkynes with diethylaluminium chloride, triethylaluminium, phenylmagnesium chloride, etc. Other methods produce Z/E mixture of tamoxifen from dehydration of the corresponding tertiary alcohol, a brief account of which is presented below.

**Miller et al (1985)**

In this approach, phenyl(trimethylsilyl)acetylene was carbometalated with diethylaluminium chloride-titanocene to give *in situ* an organometallic intermediate, which was cleaved by NBS at -78 °C to afford the bromo compound 84. Palladium-catalyzed successive Negishi coupling was carried out using arylzinc to give ethyl triaryl olefin 87 in 84% yield. Finally, the methoxy compound 87 was demethylated and the resulting phenol was condensed with 2-(dimethylamino)ethyl chloride to furnish tamoxifen (82) (Scheme 21).

![Scheme 21](image)

**Scheme 21:** (i) Et₂AlCl, Cp₂TiCl₂, CH₂Cl₂; (b) NBS, -78 °C, 85%; (ii) PhZnCl, Pd(PPh₃)₄, THF, 95%; (iii) Br₂, CH₂Cl₂, NaOMe/MeOH, -78 °C, 85%; (iv) p-MeOC₆H₄ZnCl, Pd(PPh₃)₄, THF, reflux, 84%; (v) (a) Na₂S₂O₅, DMF, reflux; (b) ClCH₂CH₂NMe₂.HCl, NaOEt, EtOH, reflux; (c) HCl (g), Et₂O; (d) 0.5 N NaOH, 60%.

*Chapter III* 142
Mohammed et al (1987)\textsuperscript{26}.

In this approach, synthesis of tamoxifen (82) was achieved via carbometallation of diphenylacetylene (88) with trimethyl aluminium followed by palladium-catalyzed cross coupling using 2-(4-bromophenoxy)-1-dimethylaminoethane (Scheme 22).

\[
\begin{array}{c}
\text{88} \quad \text{i} \quad \text{82}
\end{array}
\]

**Scheme 22:** (i) (a) (C\(\text{2}\)H\(\text{3}\))\textsubscript{3}Al, toluene, 90 °C, 24 h; (b) (CH\(\text{3}\))\textsubscript{2}N(CH\(\text{2}\))\textsubscript{2}OC\(\text{6}\)H\(\text{4}\)Br-\(\text{p}\), THF, Pd(0), reflux, 24 h, 35%.

Raymond et al (1987)\textsuperscript{27}

In this approach, tertiary alcohol 90 was prepared by reaction of 1-(p-dimethylamino ethoxy)-2-phenylbutan-l-one (89) with phenyl magnesium bromide. Acid catalyzed dehydration of the tertiary alcohol 90 gave tamoxifen as a Z/E mixture in the ratio of 2: 1 (Scheme 23).

\[
\begin{array}{c}
\text{89} \quad \text{i} \quad \text{90} \quad \text{ii} \quad \text{82}
\end{array}
\]

**Scheme 23:** (i) PhMgBr, Et\(_2\)O; (ii) HCl (aq), EtOH, 80 °C.
In this approach, propylbenzene anion, generated using $n$-BuLi - K'OBU-TMEDA was added on to the substituted benzophenone 91, to give the corresponding carbinol 92. Acid catalyzed dehydration of carbinol 92 gave tamoxifen (82) as a cis/trans mixture in 50% yield (Scheme 24).

Scheme 24: (i) propyl benzene, $n$-BuLi - K'OBU - TMEDA, hexane, 25 °C, then 10, Et₂O, - 70 °C; then 0 °C, 5 h; (ii) 32% H₂SO₄, 16 h, 50 °C.

Brown et al (1997)²⁹

In this approach, alkyne 93 was converted into bis(boryl)alkene 94 by platinum catalyzed addition of diborate. Suzuki coupling of this intermediate 94 with bromobenzene gave the arylated product 95 which was treated with solid supported resin 96 for second Suzuki coupling. Tamoxifen (82) was cleaved from the polymer as amine salts using trifluoroacetic acid (Scheme 25).
In this approach, addition of diphenylzinc on 1-phenyl-1-butyne (93) in the presence of Ni(acac)$_2$ and subsequent iodolysis gave Z alkene 97 in 88% yield (Z:E > 99:1). Then the reaction of alkene 97 with the arylzinc bromide in the presence of Pd$_2$(dba)$_3$ provided tamoxifen (82) in 75% yield (Scheme 26).

**Scheme 26:**

(i) Ph$_2$Zn, THF, NMP, [Ni(acac)$_2$], -35 °C, 3 h; (b) I$_2$, 88%; (ii) (CH$_3$)$_2$Ni(CH$_2$)$_2$OC$_6$H$_4$ZnBr-p, Pd$_2$(dba)$_3$, PPh$_3$, THF, 55 °C, 10 h, then HCl, 75%.
In this approach, Sonogashira cross-coupling of aryl halide 98 with propargyl alcohol gave alkynol 99 in 83% yield. Then carbometallation of 99 with phenylmagnesium chloride followed by the addition of Pd(PPh₃)₄ and phenyl iodide as the cross coupling partner gave alkenol 100 in 72% yield. The alkenol 100 was converted into diene 102 followed by the selective reduction of the less hindered double bond afforded (Z)-tamoxifen (82) in 69% yield (Scheme 27).

Scheme 27: (i) propargyl alcohol, PdCl₂(PPh₃)₂, Cul, THF, 22 °C, 18 h, 83%; (ii) (a) PhMgCl, toluene, reflux; (b) Pd(PPh₃)₄, PhI, 72%; (iii) DMP, CHCl₃, 22 °C, 12 h, 96%; (iv) K'OBu, PPh₃CH₂Br, THF, reflux, 16 h, 81%; (v) H₂, Pd/C, EtOAc, 22 °C, 2 h, 85%.


In this approach, the key intermediate tetrasubstituted alkene was obtained from disubstituted alkyne 103 using nickel catalyzed arylationative carboxylation followed by esterification with diazomethane. Unsaturated ester 104 was reduced into alkenol 100 using DIBAL-H in quantitative yield. The alkenol 100 was converted into diene by
oxidation followed by Wittig olefination. Then the selective reduction of the less hindered double bond afforded \((Z)\)-tamoxifen in 71% yield (Scheme 28).

\[
\begin{align*}
\text{Me}_2\text{N} & \quad \text{O} & \quad \text{Ph} \\
\text{T} & \quad \text{Ph} & \quad \text{Ph} \\
\text{103} & \quad \text{104} & \quad \text{100} \\
\text{i} & \quad \text{ii} & \quad \text{iii}
\end{align*}
\]

Scheme 28: (i) (a) CO\(_2\), Ni(COD), DBU, Ph\(_2\)Zn, THF, 40 °C, 20 h; (b) CH\(_2\)N\(_2\), 63%; (ii) DIBAL-H, CH\(_2\)Cl\(_2\), -78 °C, 2 h, 99%; (iii) (a) DMP, CHCl\(_3\), 22 °C, 12 h, 96%; (b) KO\(_2\)Bu, PPh\(_3\)CH\(_2\)Br, THF, reflux, 16 h, 81%; (c) H\(_2\), Pd/C, EtOAc, 22 °C, 2 h, 85%.

3.3.3 Present Work

3.3.3.1 Objective

As can be seen from the above discussion, many methods are known in the literature for the synthesis of tamoxifen. However, many of these methods have limitations such as producing mixture of \(Z\) and \(E\) isomers of tamoxifen as well as low overall yields. In this section, we have used palladium-catalyzed Suzuki coupling for the synthesis of tamoxifen, the details of which are described as follows.

3.3.4 Results and Discussion

The synthetic route for \((Z)\)-tamoxifen (82) by palladium-catalyzed Suzuki coupling is shown in Scheme 29. Alkylation at the \(\alpha\)-position of ketone 105 under basic conditions
(Z)-Tamoxifen

gave ketone 106 in 91% yield. The $^1$H NMR spectrum of 106 showed typical triplets at $\delta$ 0.90 and 4.40 due to $-\text{CH}_3$ and $-\text{CH}$ protons respectively. Its $^{13}$C NMR spectrum also showed characteristic signals at $\delta$ 12.1 and 55.3 corresponding to methyl and methine carbons respectively.

![Scheme 29:](image)

**Scheme 29:** (i) EtBr, KO'Bu, DMF, 25 °C, 24 h, 91%; (ii) NaH, LiCl, THF, reflux, TsCl, 6 h, 82%; (iii) Pd(_2)(dba)$_3$, Na$_2$CO$_3$, THF, reflux, 12 h, 56%; (iv) dimethyl amine, metanol, reflux, 3 h, 78%.

Ketone 106 was transformed into vinyl tosylate 107 (NaH, TsCl) in 82% yield. The $^1$H NMR spectrum of 107 showed a typical singlet at $\delta$ 2.49 for Ar-CH$_3$ protons. Palladium-catalyzed Suzuki coupling of tosylate 107 with arylboronic acid 109 (prepared from the corresponding bromo compound) in the presence of K$_2$CO$_3$ in THF at 65 °C gave tetra substituted olefin, 108 in 56% yield. The $^1$H NMR spectrum of 108 showed a typical singlet at $\delta$ 2.34 for Ar-CH$_3$ proton; two triplets at $\delta$ 4.17 and 3.91 are due to -O-CH$_2$-CH$_2$-OSO$_2$- protons respectively. Its $^{13}$C NMR spectrum showed characteristic signal at $\delta$
21.4 for Ar-CH₃ carbons; other signals at δ 67.9 and 64.9 are due to -O-CH₂-CH₂-OSO₂- carbons respectively (Fig. 10).

![NMR Spectra of 108](image)

**Fig. 10:** 'H and ¹³C NMR spectra of 108

Nucleophilic displacement of the OTs group with 2 M methanol solution of dimethyl amine resulted in the formation of (Z)-tamoxifen (82) in 78% yield. The spectral data obtained for (Z)-tamoxifen (82) were in full agreement with the values reported in the literature²⁵ (Fig. 11).
3.3.5 Conclusion

Synthesis of (Z)-tamoxifen was achieved in four steps with the overall yield (32.6%) using the palladium catalyzed Suzuki coupling. The reactions are rapid; requiring a relatively low amount of Pd-catalyst.

3.3.6 Experimental Section

1,2-Diphenylbutan-1-one (106):

Fig. 11: \(^1\)H and \(^{13}\)C NMR spectra of (Z)-tamoxifen (82)
To a stirred mixture of 1,2-diphenylethanone (105) (5.88 g, 30 mmol), and K'OBu (6.72 g, 60 mmol) in dry DMF (50 mL) was added ethyl bromide (6.54 g, 60 mmol) at 0 °C. The reaction mixture was stirred at 25 °C for 24 h and extracted with ethyl acetate (3 x 20 mL). The combined ethyl acetate layers were concentrated to give crude product, which was purified by column chromatography using pet.ether: EtOAc (9:1) as eluent to furnish 106.

**Yield:** 6.12 g (91%); **IR** (CHCl₃, cm⁻¹): 669, 1174, 1215, 1263, 1379, 1448, 1490, 1596, 1679, 2875, 2875, 2931, 2968, 3018; **¹H NMR** (200 MHz, CDCl₃): δ 0.90 (t, J = 7.3 Hz, 3H), 1.77-1.92 (m, 1H), 2.13-2.27 (m, 1H), 4.40 (t, J = 7.2 Hz, 1H), 7.14-7.45 (m, 8H), 7.91-7.95 (m, 2H); **¹³C NMR** (50 MHz, CDCl₃): δ 12.1, 27.0, 55.3, 126.8, 128.1, 128.3, 128.5, 128.7, 132.6, 136.9, 139.5, 199.9; **Analysis:** C₁₆H₁₆O requires C, 85.68; H, 7.19; found C, 85.64; H, 7.31%.

**(Z)-1,2-Diphenylbut-1-enyl 4-methylbenzenesulfonate (107):**

To a stirred mixture of NaH (0.22 g, 5.5 mmol), LiCl (0.231 g, 5.5 mmol) in dry THF (25 mL) was added ketone 106 (1.12 g, 5 mmol) at 0 °C. The reaction mixture was stirred for 30 min at the same temperature followed by addition of p-toluenesulfonyl chloride (1.05 g, 5.5 mmol). Then the reaction mixture was refluxed for 6 h, and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over anhyd. Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography to afford 107.

**Yield:** 1.5 g (82%); **¹H NMR** (200 MHz, CDCl₃): δ 0.85 (t, J = 7.5 Hz, 3H), 2.39 (q, J = 7.3 Hz, 2H), 2.49 (s, 3H), 7.23-7.48 (m, 10H), 7.90-7.98 (m, 4H); **¹³C NMR** (50 MHz, CDCl₃): δ 13.4, 21.4, 28.8, 103.5, 126.6, 128.0, 128.4, 129.3, 130.4, 132.9, 134.4, 136.4,
(Z)-Tamoxifen

139.4, 142.2, 146.8, 169.3; Analysis: $\text{C}_{23}\text{H}_{22}\text{O}_{3}\text{S}$ requires C, 72.99; H, 5.86; S, 8.47; found C, 73.12; H, 5.81; S, 8.55%.

2-(4-((Z)-1,2-Diphenylbut-1-enyl)phenoxy)ethyl 4-methylbenzenesulfonate (108):

To the enol tosylate (0.756 g, 2 mmol), arylboronic acid (1.005 g, 3 mmol), and Pd$_2$(dba)$_3$ (0.018 g, 1 mol%), THF (25 mL) was added followed by 2 M Na$_2$CO$_3$ (3.5 mL, 7.5 mmol). The reaction mixture was refluxed for 12 h and product was isolated by extraction with dichloromethane (3 x 25 mL). The combined organic extracts were washed with brine and dried over anhyd. Na$_2$SO$_4$ and concentrated under reduced pressure to give the crude product, which was purified by column chromatography to afford 108.

Yield: 0.558 g (56%); IR (CHCl$_3$, cm$^{-1}$): 669, 929, 1031, 1215, 1508, 1600, 2399, 2927, 2972, 3018; $^1$H NMR (200 MHz, CDCl$_3$): δ 0.84 (t, $J =$ 7.3 Hz, 3H), 2.28-2.44 (m, 5H), 3.86-4.27 (m, 4H), 6.32 (d, $J =$ 8.3 Hz, 2H), 6.65 (d, $J =$ 8.5 Hz, 2H), 7.00-7.08 (m, 6H), 7.21-7.26 (m, 6H), 7.68 (d, $J =$ 7.5 Hz, 2H); $^{13}$C NMR (50 MHz, CDCl$_3$): δ 13.4, 21.4, 28.8, 64.9, 67.9, 113.1, 125.9, 126.4, 127.7, 127.8, 127.9, 129.2, 129.4, 129.6, 130.4, 130.5, 131.7, 132.8, 135.8, 137.8, 141.3, 142.0, 143.4, 144.5, 155.6; Analysis: $\text{C}_{31}\text{H}_{30}\text{O}_{4}\text{S}$ requires C, 74.67; H, 6.06; S, 6.43; found C, 74.59; H, 5.91; S, 6.59%.

1,2-Diphenyl-1-[4-[2-dimethylamino]ethoxylphenyl]-1-butene (Tamoxifen) (82):

A mixture of tosylate 108 (0.498 g, 1 mmol) and 2 M methanol solution of dimethyamine (2.5 mL, excess) was refluxed for 3 h and the excess dimethyamine was distilled off under reduced pressure. The crude product was diluted with water and extracted with ethyl acetate. The organic layers were dried over anhyd. Na$_2$SO$_4$ and
concentrated to obtain the crude product, which was purified by column chromatography to afford tamoxifen \(82\).

**Yield:** 0.29 g (78%); **mp** 95-98 °C; **IR:** (CHCl\(_3\), cm\(^{-1}\)): 667, 703, 1029, 1174, 1215, 1228, 1440, 1461, 1508, 1606, 1672, 2854, 2927, 2964, 3016; \(^1\)H NMR (200 MHz, CDCl\(_3\)):\(\delta\) 0.85 (t, \(J = 7.5\) Hz, 3H), 2.39 (q, \(J = 7.3\) Hz, 2H), 2.49 (s, 6H), 2.92 (t, \(J = 5.0\) Hz, 2H), 4.06 (t, \(J = 5.0\) Hz, 2H), 6.47 (d, \(J = 8.5\) Hz, 2H), 6.71 (d, \(J = 8.5\) Hz, 2H), 7.06-7.28 (m, 10H); \(^1^3\)C NMR (50 MHz, CDCl\(_3\)):\(\delta\) 13.9, 30.7, 45.2, 58.5, 65.3, 114.4, 127.1, 127.6, 128.9, 129.1, 130.4, 130.8, 132.9, 137.1, 139.7, 142.6, 143.6, 144.9, 157.7; **Analysis:** C\(_{26}\)H\(_{29}\)NO requires C, 84.06; H, 7.87; N, 3.77; found C, 83.94; H, 7.81; N, 3.85%.

### 3.3.7 References

10. Valdes, R. H.; Puzer, L.; Gomes, Jr. M.; Marques, C. E. S. J.; Aranda, D. A. G.; Bastos,
(Z)-Tamoxifen


*(Z)-Tamoxifen*