ABSTRACT

The thesis entitled “Development of new synthetic route for asymmetric synthesis of (R)-Mexiletine, (R)-Phenoxybenzamine, (S)-Dapoxetine, (R)-Selegiline and (R)-Rasagiline using hydrolytic kinetic resolution and asymmetric epoxidation-reduction strategies” divided into three chapters.

The title of the thesis is clearly reflecting the objective of the Ph. D. work. The overall content of the thesis is mainly consults with the synthesis of an enantiomerically pure drug molecule. The Chapter 1: describes the asymmetric synthesis of anti-arrhythmic drug (R)-Mexiletine and anti-hypertensive drug (R)-Phenoxybenzamine using hydrolytic kinetic resolution (HKR). Chapter 2: represents the asymmetric synthesis of selective serotonin reuptake inhibitor (S)-Dapoxetine and Monoamine Oxidase (MAO-B) Inhibitor (R)-Selegiline using Sharpless asymmetric epoxidation strategy. Chapter 3: deals with asymmetric synthesis of calcium receptor agonist (calcimimetic) (+)-NPS R-568 and Monoamine Oxidase (MAO-B) Inhibitor (R)-Rasagiline via chiral spiroborate catalyzed asymmetric reduction.

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CHAPTER - 1

The Chapter-1 is divided into two sections. This chapter gives an idea about the application of Jacobsen’s Hydrolytic Kinetic Resolution (HKR) strategy. This HKR emerged as an effective method for getting chiral epoxides and 1,2-diols. The value of HKR is being realized looking at its simplicity of the reaction conditions and the availability of the catalyst in the market. As a result this strategy is very effective to obtain chiral building blocks for the asymmetric synthesis of the biologically active compounds such as (R)-Mexiletine (Section-I) and (R)-Phenoxybenzamine in the Section-II.

SECTION - I

Asymmetric Synthesis of anti-arrhythmic drug (R)-Mexiletine:2

Mexiletine is an important class of β-amino aryl ether, which used as drug in the treatment of arrhythmia, allodynia, myotonic syndromes etc. the (R)-isomer of mexiletine is more potent than the (S)-isomer. Therefore, our synthetic planning to (R)-Mexiletine 7 is as indicated in the Scheme 1. The crucial part of the asymmetric synthesis is planning to introduce the chirality and preserve it till the completion of the synthesis of target molecule. In this connection, we adopted Jacobsen’s cobalt-salen based catalytic system as a strategy for hydrolytic kinetic resolution (HKR) to obtain (S)-epoxide 3; as a key intermediate for the synthesis of (R)-Mexiletine 7. The (S)-epoxide 3 was obtained by subjecting the racemic (±)-epoxide 2 to hydrolytic kinetic resolution (HKR) in 44% yield.
and >99% ee. Thus, the key intermediate (S)-epoxide 3 on treatment with lithium aluminum hydride underwent the regioselective reductive ring opening reaction to give chiral secondary alcohol 5 in 92% yield.

![Chemical Structures]

Scheme 1: (i) (±)-epichlorohydrin, K₂CO₃, acetone, reflux, 24 h, 80%; (ii) (R,R)-Salen Co(III)-complex; 0.55 equiv. H₂O; 30 h, 0 °C to rt; (iii) LiAlH₄, THF, 0 °C, 30 min, 92%; (iv) Ph₃P, phthalimide, DIAD, THF, rt, 2 h, 83%; (v) N₂H₄.H₂O, EtOH, reflux, 3h; 86%.

This alcohol 5 was readily transformed into phthalimido ether 6 by Mitsunobu reaction for stereospecific substitution of the hydroxyl group with phthalimide moiety. Finally, the hydrazonolysis of phthalimido ether 6 with hydrazine hydrate resulted in the formation of target molecule (R)-Mexiletine 7 in 86% yield and >99% ee.

**SECTION – II**

**Asymmetric synthesis of anti-hypertensive drug (R)-Phenoxybenzamine:**

The (R)-Phenoxybenzamine 16 is α-adrenergic antagonist and it has been used to treat hypertension & as peripheral vasodilator caused by adrenaline and noradrenaline hormones. Looking at the significant role of the (R)-Phenoxybenzamine 16 in a biological system, we encouraged for developing a new strategy to asymmetric synthesis of (R)-Phenoxybenzamine 16. As a result, we planed to use Jacobson’s HKR strategy to carry out the synthesis of (R)-Phenoxybenzamine 16. Accordingly, we envisioned
glycidol ether 9, as immediate precursor to 16 and it was subjected to HKR in the presence of \((R,R)\)-Salen Co(III)OAc catalyst. The resulting \((S)\)-epoxide 10 was obtained in 47% yield and >99% ee. The other unwanted product \((R)\)-diol 11 was obtained in 43% yield (Scheme 2). The \((S)\)-epoxide 10 is being visualized as key intermediate and it was subjected to regioselective reductive ring opening with lithium aluminum hydride to afford secondary alcohol 12 in 93% yield. Thus, \((S)\)-alcohol 12 was transformed to \((R)\)-sulfonamide derivative 13 under the Fukuyama-Mitsunobu reaction. In order to get free the amino functionality in 13, the nosyl moiety was deprotected using thiophenol to afford the amino ether 14.

![Chemical structure diagram]

**Scheme 2.** Reagents and conditions: (i) \((\pm)\)-epichlorohydrin, \(\text{K}_2\text{CO}_3\), acetone, reflux, 8 h, 90%; (ii) \((R,R)\)-Salen Co(III)-OAc, 0.55 equiv. \(\text{H}_2\text{O}\), 30 h, 0 °C, rt; (iii) \(\text{LiAlH}_4\), \(\text{THF}\), 0 °C 30 min, 93%; (iv) \(N\)-benzyl-2-nitro-benzenesulfonamide, \(\text{Ph}_3\text{P}\), DIAD, \(\text{THF}\), rt, 2 h, 81%; (v) Thiophenol, \(\text{K}_2\text{CO}_3\), acetonitrile, rt, 2 h, 87%; (vi) bromoethanol, \(\text{K}_2\text{CO}_3\), ethanol, 110 °C, sealed tube, 72 h, 82%; (vii) \(\text{SOCl}_2\), benzene, reflux, 8h, 52%.

Further, alkylation of 14 with bromoethanol was resulted in the formation of amino alcohol 15. The final stage of the synthesis was to incorporate the chloride in place of hydroxyl functionality was carried using thionyl chloride to furnish the synthesis of \((R)\)-Phenoxybenzamine 16 in 52% yield.
CHAPTER - 2

The Sharpless asymmetric epoxidation (AE) reaction is one of his greatest contributions to the chemical science. Therefore, Sharpless rewarded a Nobel Prize in chemistry in 2001 for his achievement in asymmetric catalysis. This catalytic asymmetric epoxidation of allylic alcohol is one of the most favorite reaction to chemists around the world. As a result the asymmetric epoxidation is very effective reaction to obtain chiral building blocks for the asymmetric synthesis of the biologically active compounds.

The beauty of this AE reaction is availability of the tartrate ligand in its both the enantiomeric form. Therefore, it creates a facility to easy access to both the enantiomeric form of the desire product 2,3-epoxy alcohol. Because of the ring strain of an epoxide variety of the nucleophiles are useful to open up the epoxide ring to generate library of compounds. Therefore, epoxides are excellent intermediates for functional group transformations. We used this strategy for asymmetric synthesis of selective serotonin reuptake inhibitor i.e. (S)-Dapoxetine in the Section-I and monoamine oxidase (MAO-B) inhibitor (R)-Selegiline in the Section-II

SECTION - I

Asymmetric Synthesis of Selective Serotonin Reuptake Inhibitor (S)-Dapoxetine:

Dapoxetine is a potent selective serotonin reuptake inhibitor (SSRI) and it is very useful for the treatment of Premature Ejaculation (PE) dysfunctions in men. The (S)-dapoxetine 22 is more potent than (R)-isomer. The (R)-1,3-diol 19 as a key precursor to (S)-dapoxetine 22 (Scheme 3). In order to obtain diol 19, we made use of Sharpless AE reaction for chirality induction in the Dapoxetine 22. In this connection, the trans-cinnamyl alcohol 17 was considered to be the immediate precursor to diol-19 and accordingly it was subjected to Sharpless AE in the presence of (+)-DIPT as a ligand to generate (2S,3S)-epoxycinnamyl alcohol 18 in 89% yield and >98% ee.
Scheme 3: Reagents and conditions: i) (+)-DIPT, Ti(O\text{Pr})_4, TBHP, 4 Å MS, DCM, -20 °C, 3 h, 89%; ii) Red-Al, DME, 0 to 25 °C, 3 h, 93%; iii) 1-naphthol, Ph_3P, DIAD, THF, 20 h, rt, 71%; iv) Phthalimide, Ph_3P, DIAD, THF, 4 h, 82%; v) N_2H_4.H_2O, EtOH, reflux, 3 h; vi) HCHO, HCO_2H, reflux, 6 h, 69% two steps

The epoxy alcohol 18 was then transformed to (R)-1,3-diol 19 through regioselective reductive ring opening with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) to afford 19 in a 93% yield. The Mitsunobu reaction was used to introduce 1-naphthol moiety in the form of ether, thereby generating the compound 20 in a 71% yield as a terminal part of the Dapoxetine 22. Thus, the chiral center possessing the secondary hydroxyl group was then converted to phthalimido ether 21 by Mitsunobu reaction. The phthalimido ether 21 subjected to hydrazonolysis followed by Eschweiler-Clarke reductive methylation reaction to complete the synthesis of (S)-Dapoxetine 22 in 69% yield.

SECTION – II

Asymmetric Synthesis of Monoamine Oxidase (MAO-B) Inhibitor (R)-Selegiline:

Selegiline is a selective, irreversible inhibitor of monoamine oxidase-B (MAO-B) and is quite effective in the treatment of Parkinson’s disease as well as Alzheimer’s disease when used in combination with L-DOPA. It was observed that only the (R)-Selegiline is associated with the desired biological activity. Therefore, we encouraged to
use Sharpless asymmetric epoxidation reaction to get (R)-isomer of the Selegiline. Thus, our target was (R)-isomer of the selegiline to which (S)-secondary alcohol 24 was imagined to be the key intermediate (Scheme 4). In order to get (S)-secondary alcohol 24, the trans-cinnamyl alcohol 17 was subjected to Sharpless AE to give (2S, 3S)-epoxycinnamyl alcohol 18 in 89% yield and >98% ee. The primary hydroxyl group in the compound 18 was readily transformed to the corresponding iodo derivative 23 in 91% yield.

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\begin{align*}
17 & \xrightarrow{i} 18 & \xrightarrow{ii} 23 & \xrightarrow{iii} 24 \\
& \xrightarrow{iv} 25 & \xrightarrow{v} 26 & \xrightarrow{vi} (R)-Selegiline 27
\end{align*}
\]

**Scheme 4.** i) (+)-DIPT, Ti(O^i-Pr)_3, TBHP, 4 Å MS, DCM, -20 °C, 3 h, 89%; ii) I_2, Ph_3P, imidazole, CH_3CN, Et_2O, 0 °C-rt, 92%; iii) H_2 (2 atm), Pd-C, Et_3N, EtOAc, 10 h, 94%; iv) DIAD, Ph_3P, N-Methyl-2-nitro-benzenesulfonamide, THF, rt, 3 h, 86%; v) PhSH, CH_3CN, rt, 2 h, 87%; vi) propargyl bromide, K_2CO_3, CH_3CN, rt, 3 h, 76%.

Subsequently, the compound 23 was then converted to (S)-secondary alcohol 24 using regioselective reductive ring opening of an epoxide followed by dehalogenation in a one pot reaction (94% yield). The Fukuyama-Mitsunobu reaction was used to replace the hydroxyl functionality by N-methyl in the form of sulfonamide derivative 25. In the presence of thiophenol the nosyl group in compound 25 was deprotected and subsequently the propargylation of the amino functionality in 26 led to the formation of target molecule (R)-Selegiline 27 in 76% yield.
CHAPTER 3

Organoborane reagents, especially oxazaborolidine-borane complexes, are having a very high recognition for enantioselective reduction of ketone.\textsuperscript{10} Therefore, this synthetic strategy is most attracted to the chemist around the world because of their experimental simplicity and easy availability of the reagents. This chapter describes an application of the borane based asymmetric reduction of the ketone in the presence of chiral spiroborate ester catalyst \textsuperscript{35} derived from chiral diphenyl valinol.\textsuperscript{11} This chapter is divided into following two sections. Based on this strategy we carry out the asymmetric synthesis of calcimimetic (+)-NPS R-568 in section-I and (\(R\))-Rasagiline in the section-II.

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\text{Ph} \\
\text{O} \\
\text{O} \\
\text{35}
\end{array}
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SECTION I

Asymmetric synthesis of calcium receptor agonist (Calcimimetic) \((R)-(+)\)-NPS R-568

Hyperparathyroidism is over activity of the parathyroid glands and it led to the production of excess parathyroid hormone.\textsuperscript{12} The calcimimetic is a small organic molecule and it is very useful to treat hyperparathyroidism. The \((R)-(+)\)-NPS R-568 is 10-100 times more potent than the \((S)\)-isomer.\textsuperscript{13} As a result, we were interested to carry out the synthesis of \((+)-(\) isomer of the calcimimetic NPS R-568 \((36)\). We developed the convergent synthetic route to calcimimetic \((R)-(+)\)-NPS R-568 \((36)\). We envisioned fragment \textsuperscript{31} and \textsuperscript{34} are the immediate precursor to \textsuperscript{36}. Accordingly, an individual fragments \textsuperscript{31} & \textsuperscript{34} were synthesized and combined together to get the target molecule via
Fukuyama-alkylation reaction and further deprotection led to the formation of target molecule (Scheme 5 & 6).

![Chemical structure diagram]

Scheme 5. Reagents and conditions: (i) Meldrum’s acid, HCO₂H, Et₃N, DMF, 95-100 °C, 76%; (ii) BH₃. SMe₂, THF, 0 °C, 1 h, 89%; (iii) I₂, PPh₃, imidazole, DCM, rt, 1 h, 91%.

In order to get the fragment 31, the o-chlorobenzaldehyde 28 was subjected to following sequence of reaction i) condensation, in situ reduction, hydrolysis & decarboxylation to give compound 29. The acid functionality in compound 29 was on reduction with borane generating the alcohol 30 in 89% yield. Subsequently, the resulting alcohol 30 was transformed to fragment 31 in the presence of I₂, Ph₃P reagents in 91% yield.

![Chemical structure diagram]

Scheme 6. Reagents and conditions: (i) Cat. 35 (5 mol%), BH₃.SMe₂, THF, rt , 1 h, 95%; (ii) 2-Nitrobenzenesulfonamide, PPh₃,DIAD, THF, rt, 4h, 78%; (iii) 31, K₂CO₃, CH₃CN, 60 °C, 2 h; (iv) PhSH, rt, 2 h, 72%, two steps.

The key intermediate to calcimimetic molecule (R)-(+-)NPS R-568 (36) is compound 34 since it contain the chiral center at benzylic position. In order get this chirality the 3-methoxy acetophenone 32 was subjected to asymmetric reduction in the presence of catalyst 35 via Ortiz-Marciales protocol (Scheme 6). The catalyst 35 was prepared as per the literature procedure from the (R)-Diphenyl valinol, ethylene glycol and triisopropyl borate. The (S)-alcohol 33 was obtained in 95% yield and >99% ee.
Subsequently, alcohol 33 was then converted to sulfonamide derivative 34 under the Fukuyama-Mitsunobu reaction. Finally, in order to complete the synthesis of (R)-(+-)-NPS R-568 (36), the compound 34 was subjected to alkylation reaction with the iodo compound 31 (in one-pot Fukuyama N-alkylation and deprotection of Nosyl moiety) to give target molecule 36 in 72% yield.

**SECTION – II**

**Asymmetric Synthesis of Monoamine Oxidase (MAO-B) Inhibitor (R)-Rasagiline:**

Rasagiline 42 [N-propargyl-1(R)-aminoindan] is a novel drug for the treatment of Parkinson’s disease both as monotherapy in early stages and as an adjunct to L-DOPA.\(^\text{10}\) It is selective and irreversible MAO-B inhibitor. However, the (R)-isomer is more potent than (S)-isomer for preferential inhibition of MAO-B.\(^\text{14}\)

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\text{Scheme 7. } \text{i) } \text{H}_2, \text{Pd-C, MeOH, 30 min, 95%; ii) } (\text{COCl})_2, \text{Cat. DMF, DCM, 0 °C-rt, 1 h; iii) } \text{AlCl}_3, \text{DCM, 0-5 °C, 85%; iv) } \text{Cat. 35 (5 mol%), BH}_3\text{DMS, rt, 1h, 97%; ii) } 2\text{-nitrobenzenesulfonamide, Ph}_3\text{P, DIAD, THF, rt, 4 h, 78%; iii) propargyl bromide, K}_2\text{CO}_3, \text{CH}_3\text{CN, 60 °C, 2 h; iv) PhSH, rt, 2 h, 72% two steps.}
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(R)-Rasagiline 42 was synthesized starting from trans-cinnamic acid 37. The double bond in 37 was hydrogenated over 10% palladium on charcoal to give hydrocinnamic acid 38. It was then transformed to corresponding acid chloride by treating with the oxalyl chloride in the presence of catalytic amount of DMF. The crude
acid chloride was used to Friedel-Crafts intramolecular acylation reaction to afford indanone 39 in 85% yield. Asymmetric reduction of indanone 39 (Scheme 7) using Ortiz-Marciales protocol afforded the (S)-1-indanol 40 in 93% yield and >99%ee. It was then transformed to corresponding nosyl derivative 41 under the Fukuyama-Mitsunobu reaction. The propargylation of the sulfonamide 41 with propargyl bromide followed by one-pot deprotection of the nosyl moiety resulted in the formation of target molecule (R)-Rasagiline 42 in 72% yield.


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LIST OF PUBLICATIONS


