Abstract

The thesis entitled “Synthetic Strategies Towards (+)-L-733,060, Bruguierols and Natural/Synthetic Lactones And DDQ Mediated Deprotection of N-Allylic Amines” is divided into five chapters.

Chapter 1: Introduction to Sharpless asymmetric epoxidation, Jacobsen’s hydrolytic kinetic resolution (HKR) and proline-catalysed reactions.

Chapter 2: Studies towards enantioselective synthesis of (+)-L-733,060 and (+)-CP-99,994 using Sharpless asymmetric epoxidation.

Chapter 3: Formal synthesis of verbalactone and its monomer via two different hydrolytic kinetic resolution strategies.

Chapter 4: Enantiomeric synthesis of substituted chiral γ-butyrolactones from aldehydes via proline-catalysed sequential lactonization reaction and proline-catalysed enantiomeric synthesis of Bruguierol A and Bruguierol B.

Chapter 5: Chemoselective deprotection of N-Allylic amines using DDQ.

Chapter 1: Introduction to Sharpless asymmetric epoxidation (AE), Jacobsen’s hydrolytic kinetic resolution (HKR) and proline-catalysed reactions.

This chapter gives a brief introduction to Sharpless asymmetric epoxidation (AE), Jacobsen’s hydrolytic kinetic resolution (HKR) and proline-catalysed reactions.

The ultimate goal of organic synthesis is to assemble a given organic compound (target molecule) from readily available starting materials and reagents in the most efficient way.\(^1\) It is more elegant and economical to prepare just wanted isomer by asymmetric synthesis and through inexpensive catalytic processes. It is especially useful in the case of carbon-
hetero atom bond formation reaction, since the resulting functionality can be readily manipulated to produce many important different classes of compounds.

The oxidation of olefins is considered as the single most versatile, powerful and reliable class of transformation in organic synthesis. The Sharpless epoxidation\textsuperscript{2} is a popular laboratory process that is both enantioselective and catalytic in nature. It employs inexpensive reagents and involves various important substrates (allylic alcohols) and products (epoxides) in organic synthesis. It also demonstrates unusually wide applicability because of its insensitivity to many aspects of substrate structure.\textsuperscript{3} The wide scope application of this transformation arises not only from the utility of epoxide compounds but also from the subsequent regiocontrolled and stereocontrolled nucleophilic substitution (ring-opening) reactions of the derived epoxy alcohol. These, through further functionalization, allow access to an impressive array of target molecules in enantiomerically pure form.\textsuperscript{4}

The hydrolytic kinetic resolution\textsuperscript{5} (HKR) of terminal epoxides catalyzed by chiral (salen) Co\textsuperscript{III}(OAc) complex affords both recovered epoxide and 1,2-diol product in highly enantioenriched form. The HKR provides general access to useful, highly enantioenriched chiral building blocks that are otherwise difficult to access, from inexpensive racemic materials. The HKR has seen rapid adoption as the method of choice for the preparation of a variety of terminal epoxides in enantioenriched form, and a large number of applications in target oriented synthesis have been reported already.\textsuperscript{6}

The field of asymmetric organocatalysis is rapidly growing and attracts an increasing number of research groups around the world. In this connection, proline, an abundant, inexpensive amino acid available in both enantiomeric forms, has emerged as arguably the most practical and versatile organocatalyst.\textsuperscript{7-8} The organocatalytic asymmetric \(\alpha\)-aminoxylation of aldehydes and ketones with proline as catalyst is a highly enantioselective means of preparation of \(\alpha\)-hydroxy carbonyl compounds and their derivatives.\textsuperscript{9} Proline-catalyzed sequential transformations is an emerging research field in organic synthesis as synthesis of complex organic molecules could be accessible in one-pot procedure. Recently a variety of such transformations has been developed by different research groups.\textsuperscript{10}
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These methods have contributed to more advances in research not only in chemistry but also in material science, biology and medicine. This work gives access to new molecules needed to investigate hitherto undiscovered and unexplained phenomena in the molecular world. In this chapter, we have described aforementioned catalytic reactions. During the course of our research work we have prepared chiral epoxides and lactones and successfully employed these synthetic intermediate towards the synthesis of (+)-L-733,060, (+)-CP-99,994, Bruguierols A and B, Verbalactone and its monomer.

**Chapter 2: Studies towards enantioselective synthesis of (+)-L-733,060 and (+)-CP-99,994 using Sharpless asymmetric epoxidation.**

The search for non-peptide antagonists of the NK1 receptor led to the discovery of 2,3-disubstituted piperidine derivatives L-733,060 2 and CP-99,994 3 (Figure 1). They have excellent affinity and selectivity with human NK1 receptors and possess potent antiemetic activity. They are expected to act as remedy for a wide range of diseases, including arthritis, asthma and migraines. Structure activity relationship studies have shown that the *cis* relationship between C2 and C3 substituents on the piperidine ring of 2 and 3 is required for optimum binding activity. The present study describes our endeavors towards the synthesis of compound 2 and 3 from commercially available cinnamyl alcohol. In this strategy the chirality was introduced by Sharpless asymmetric epoxidation (AE) and piperidine ring formation was achieved by one pot Staudinger/aza-Wittig reaction.

![Figure 1: Structures of 2-aryl-3-hydroxypiperidine and 2-aryl-3-aminopiperidine derivatives](image)

As shown in Scheme 1, the synthesis of 2 and 3 were initiated by AE of commercially available cinnamyl alcohol 4 to afford trans-epoxide 5. The regioselective epoxide opening of 5 with NaN₃ gave a single regio-isomer 6. The regioselective primary monotosylation of diol 6 with tosyl chloride and catalytic Bu₂SnO, furnished compound 7 which on base
treatment in presence of $\text{K}_2\text{CO}_3$ in methanol furnished azido epoxide $\text{8}$. The chain elongation through regioselective ring opening of epoxide $\text{8}$ by allylation is achieved after several trials. Finally we could improve the yield of $\text{9}$ by using 3 equivalents of allylsilane with slow addition of freshly distilled TiCl$_4$.

The subsequent protection of secondary hydroxyl group in $\text{9}$ as TBS ether $\text{10}$ was successfully carried out using TBS triflate and 2,6-lutidine$^{19}$. The oxidation of olefin$^{20} \text{10}$ gave the crucial azido-aldehyde intermediate $\text{11}$ required for the one pot Staudinger/aza-Wittig reaction. Without further purification of aldehyde $\text{11}$, Staudinger reduction was performed. The resulting aza-ylide was condensed intramolecularly with aldehyde to provide a six membered imine $\text{12}$. The \textit{in situ} reduction of imine with NaBH$_4$ and methanol in the same reaction medium provided the free amine $\text{13}$ in good yield. Subsequently the free amine $\text{13}$ was protected as Boc derivative $\text{14}$ and TBS was selectively deprotected using TBAF to obtain compound $\text{15}^{21}$ in 90% yields (Scheme 1).

\begin{center}
\textbf{Scheme 1:} Synthesis of trans-2-aryl-3-hydroxypiperidine
\end{center}
Since various attempts\textsuperscript{22} to make required \textit{cis}-1,2- configuration from 15 failed at this stage (Scheme 2), we decided to invert the hydroxy to the required configuration at the early stage of the synthesis, that is, before the formation of the piperidine ring.

**Scheme 2:** Various attempts to make required \textit{cis}-2-aryl-3-hydroxypiperidine from 15

The desired \textit{cis}-configuration was achieved through a three-step sequence involving the chemoselective pivalation\textsuperscript{23} of diol 6, mesylation of secondary hydroxyl 17 using MsCl and final treatment of crude mesylate 18 with K\textsubscript{2}CO\textsubscript{3} in methanol to furnish the appropriately oriented \textit{cis} azido-epoxide 19 (Scheme 3). Once we accomplished the desired \textit{cis} configuration, we completed the synthesis of N-Boc protected \textit{syn}-3-hydroxy-2-phenylpiperidine 1 from 19 through previously established route.

**Scheme 3:** Synthesis of \textit{cis} azido-epoxide 19

Having constructed the piperidine ring with the desired \textit{syn}-stereochimetry, \textit{O}-alkylation of 1 with 3,5-bis(trifluoromethyl)benzyl bromide in the presence of NaH was performed\textsuperscript{24} to give 20. Finally \textit{N}-Boc deprotection of 20 using TFA furnished the target molecule 2 in good yields (Scheme 4).
Chapter 3: Formal synthesis of verbalactone and its monomer via two different hydrolytic kinetic resolution strategies

Verbalactone 21\textsuperscript{25} is a novel macrocyclic dimer lactone isolated from the roots of *Verbascum undulatum* Lam., a biennial plant that belongs to the family Scrophulariaceae (Figure 2). It is the first example of a 1,7-dioxacyclodecane unit being present in the ring system of a natural product. This compound exhibited interesting antibacterial activity against three Gram-positive bacteria with optimum activity MIC = 62.5 µg/mL and five Gram-negative bacteria with optimum activity MIC = 125 µg/mL\textsuperscript{26} The structure and the absolute stereochemistry of 21 (4\text{\text{R}},6\text{\text{R}},10\text{\text{R}},12\text{\text{R}},4,10-di\text{\text{h}}ydroxy-2,8-dioxo-6,12-di\text{\text{p}}entyl-1,7-dioxocyclodecane) were determined by spectral methods and chemical correlation. Verbalactone 21 is a dimer of lactone 22 [(+)-(3\text{\text{R}},5\text{\text{R}})-3-hydroxy-5-decanolide], a secondary metabolite isolated from *Cephalosporium recifei*\textsuperscript{27} (Figure 2). The lactone moiety 22 is identical to the lactone unit in compactin, mevinolin etc., a potent inhibitor of the enzyme HMG-CoA reductase\textsuperscript{28} Therefore the monomer 22 has also been the synthetic target of considerable interest\textsuperscript{29}

![Figure 2: Structure of Verbalactone and its monomer](image)

This chapter is further divided into two sections.
Section A: Formal synthesis of verbalactone and its monomer via iterative hydrolytic kinetic resolution

The synthesis of verbalactone 21 commenced from commercially available racemic epichlorohydrin 23 as depicted in Scheme 5. Racemic epoxide 25 from epichlorohydrin 23 was prepared by two step process. Then epoxide 25 was resolved with \((R,R)\)-salen-Co-(OAc) complex (0.5 mol\%) and water (0.55 equiv.) in THF (0.55 equiv.) to give the \(R\)-epoxide 26 in 45\% yield with 99\% ee, and \(S\)-diol 27 in 43\% yield with 99.5\% ee (Scheme 5).

Scheme 5. Synthesis of \(R\)-epoxide 26 and \(S\)-diol 27 by HKR

With enantiomerically pure epoxide 26 in hand, our next task was to construct the \(syn\)-1,3-diol. The homoallylic alcohol 29 was prepared by a two-step reaction sequence from 26. The epoxide 26 was treated with excess of lithiumacetylide followed by partial hydrogenation of the resultant acetylene 28 with Lindlar’s catalyst\(^\text{31}\) to afford the homoallylic alcohol 29 in excellent yield. The epoxidation of homoallylic alcohol 29, followed by hydroxyl group protection as the TBS ether produced the epoxide 31 in favour of the desired \(syn\)-isomer (\(syn:anti/\) 1.3:1) (Scheme 6). To synthesise the diastereomerically pure epoxide by means of Jacobson’s hydrolytic kinetic resolution, the epoxide 31 was treated with \((R,R)\)-salen-Co-(OAc) complex (0.5 mol\%) and water (0.55 equiv.) in THF (0.55 equiv.) to afford the epoxide 32 as a single diastereomer in 45\% yield and the diol 33 in 47\% yield. Epoxide 32 could easily be separated from the more polar diol 33 by silica gel column chromatography.
Scheme 6: Synthesis of the epoxide 32 and the diol 33 via HKR.

The regioselective ring opening of epoxide 32 was carried out with NaCN\textsuperscript{33} in the presence of trifluoroacetic acid in ethanol at 50 °C to give the cyanoalcohol 33 with concomitant removal of the TBS group. Finally, the hydrolysis of nitrile was effected by treatment of 33 with 25% aqueous NaOH in methanol followed by acidic work up at pH 5 with HCl to furnish the acid 34 in good yield. As the subsequent transformations of 34 to target molecules 21 and 22 under varied conditions have already been reported\textsuperscript{34}, the formal synthesis of 21 and 22 was completed (Scheme 7).

Scheme 7: Formal synthesis of verbalactone 21 and monomer 22

Section B: A Revised Strategy for the synthesis of chiral epoxyalcohol, a precursor of verbalactone by combination of diastereoselective iodine induced electrophilic cyclization and hydrolytic kinetic resolution

Our revised strategy initiated with synthesis from Barbier-type\textsuperscript{35} allylation of phenyl acetaldehyde 35 to homoallylic alcohol 36 (Scheme 8). To establish the second stereogenic
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center with an excellent level of diastereoselectivity, we decided to apply a three-step sequence. Accordingly first we prepared the homoallylic tert-butyl carbonate 37 from the corresponding alcohol 36 using BOC₂O and DMAP in CCl₄. With substantial amount of BOC protected homoallylic alcohol 37 in hand we then further proceeded to explore the stereoselective outcome of iodocyclization reaction in different reaction conditions. Cyclic iodo carbonates 38 and 39 were converted into the corresponding epoxy alcohols 40 and 41 by treatment with 3 equiv. of K₂CO₃ in methanol at room temperature (Scheme 8). Reaction was completed after 2 h to furnish the desired syn-epimer 40 with excellent diastereoselectivity.

Scheme 8: Synthesis of the racemic syn-epoxide 40

With syn-racemic epoxide 40 in hand, our next aim was to synthesize the syn-(S,S)-epoxide through the Jacobsen’s hydrolytic kinetic resolution method. Direct introduction of epoxide 40 to HKR reaction was a failure. So we decided to protect the free hydroxyl group of 40 before HKR reaction. We protected the hydroxyl group of homoallylic alcohol 40 as PMB ether 42 using PMB-bromide. In order to get the required (S,S)-hydroxyl epoxide 43, racemic syn-epoxide 42 was treated with (S,S)-salen-Co-(OAc) complex (0.5 mol%) and water (0.7 equiv.) in THF (0.7 equiv.) to afford the epoxide 43 as a single stereoisomer (determined from the ¹H and ¹³C NMR spectral analysis) in 43% yield and the diol 44 in 45% yield. Epoxide 43 could easily be separated from the more polar diol 44 through silica gel column.
chromatography. The enantiomeric purity of the epoxide 43 was estimated to be >98% by chiral HPLC analysis. Compound 43 can lead to a formal synthesis of verbalactone 1.

\[ \text{Scheme 9: Resolution of syn-epoxide 40 by HKR} \]

**Chapter 4: Enantiomeric synthesis of substituted chiral γ-butyrolactones from aldehydes via proline catalysed sequential lactonization reaction and proline catalysed enantiomeric synthesis of Bruguierol A and Bruguierol B**

This chapter is further divided into two sections.

**Section A: Enantiomeric synthesis of substituted chiral γ-butyrolactones from aldehydes via proline catalysed sequential lactonization reaction**

Optically active γ-butyrolactones have attracted much attention owing to their presence in a large variety of biologically active compounds such as alkaloids, antibiotics, pheromones, and flavor components. They have great importance in the areas of pharmaceuticals, agrochemicals, flavor components, material and in polymer productions. Interest in the synthesis of these and other applications of γ-butyrolactones has fueled and stimulated the effort to develop improved methodology for the construction of substituted γ-butyrolactones in an enantioselective manner. Therefore, it is not surprising that various biological and chemical methods have been described in the literature to access the important ring systems in optically active forms.
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**Scheme 10:** Synthetic Strategy for the preparation of substituted chiral γ-butyrolactone 49 from aldehyde 45 via proline catalysed sequential lactonization.

The preparation of optically pure hydroxy esters or acids and their conversion to lactones are important processes in organic syntheses as a result of the significance of such molecules. We have devised a novel and practical sequential asymmetric α-aminoxylation/Wadsworth-Emmons-Horner olefination; tandem reduction/cyclization reaction of aldehydes for the synthesis of optically active substituted γ-butyrolactone (Scheme 10). For making a practical and efficient approach to the stereocontrolled synthesis of γ-butyrolactones, we examined various reaction conditions to standardize our methodology.

The advantages of the sequential process include the following: (1) all starting materials are readily available; (2) the O-amino-substituted unsaturated ester that is formed after sequential α-aminoxylation and HWE olefination can be isolated in good yield and is converted to γ-butyrolactone without requiring a separate column purification step, (3) the procedure is very easy to operate under the ordinary lab conditions; (4) both (R)- and (S)-substituted γ-butyrolactone can be made since either enantiopure form of the proline is commercially available. The synthetic utility of this protocol was further demonstrated by the asymmetric synthesis of Bruguierol A and Bruguierol B (Section B).
Section B: Proline-catalysed enantiomeric synthesis of Bruguierol A and Bruguierol B

In 2005, Sattler and co-workers isolated and disclosed an unusual family of aromatic-C-glycoside natural products termed bruguierols A-C from the stem of the Bruguiera gymnorrhiza mangrove tree\textsuperscript{41} (Figure 3).

![Figure 3: Structure of Bruguierols](image)

The structure of these natural products is characterized by a 2,3-benzofused 8-oxabicyclo[3.2.1]octane core. Additionally, the aromatic ring is substituted with one (bruguierol A) or two hydroxyl groups (bruguierols B and C). Thus, the development of a flexible strategy to access these natural products or analogues could be highly interesting in finding new broad spectrum antibiotics\textsuperscript{42}.

Synthesis of Bruguierol A

![Scheme 11: syntheses of Bruguierol A](image)
We have developed a new asymmetric synthetic strategy for Bruguierol A 50 and Bruguierol B 51. In this strategy the chirality was introduced by proline catalysed sequential lactonization reaction and 2,3-benzofused 8-oxabicyclo[3.2.1]octane core was achieved by intramolecular Friedel-Crafts alkylation.42b The treatment of lactone 49 with 1.3 equiv. of MeLi in Et₂O quantitatively furnished lactol 57, which was then sequentially treated with BF₃·OEt₂ and allowed to react at -20 °C for 3 h. An intramolecular trap of the incipient oxocarbenium cation by means of a Marson type Friedel-Crafts alkylation43 provided the protected bruguierol A 57 in good yield. Later TBS ether was deprotected using a standard protocol (Scheme 11). We also synthesized Bruguierol B to ensure the flexibility of our synthetic strategy (Scheme 12).

**Synthesis of Bruguierol B**

![Synthesis of Bruguierol B](image)

**Scheme 12:** syntheses of Bruguierol B

**Chapter 5: Chemoselective Deprotection of N-Allyllic Amines using DDQ**

Protecting groups often play a crucial role in many complex synthetic strategies. The proper selection of efficient protecting groups, as well as the search of selective deprotection methodologies, still remains crucial issues in modern organic chemistry.44 In particular, among the plethora of alternatives, the use of allyl moieties for the protection of amines is becoming more and more popular as methods of amines into carbamates or to a lesser extent into amides. In contrast to classical protecting groups such as Boc (tert-butoxycarbonyl),
FMOC (9-fluorenylmethyl carbamate), tosylamide, etc.; allyl groups remain inert under both acidic and basic conditions. But as reported later on, they can be cleaved upon treatment with strong bases.\textsuperscript{45} However, those basic conditions are rather tough and incompatible with base-sensitive functional groups. Except for a few miscellaneous methods, transition-metal-catalyzed reactions (essentially Pd and Rh) are currently the most efficient and selective strategies for the deprotection of N-allylamines\textsuperscript{46}, but selectivity can still be a problem, since O-allyl derivatives are cleaved faster than N-allyl derivatives in most cases. An important drawback of the π-allyl–palladium methodology is the requirement of stoichiometric amounts of a nucleophilic compound, which acts as the allyl group scavenger. New procedures involving Grubbs-type catalysts are also emerged.\textsuperscript{47} But still selectivity remains the problem with these methods. Reductive metals also fall into same position.\textsuperscript{48}

2,3-Dichloro-5,6-dicyanobenzoquinone (DDQ) is a high potential quinone which has found extensive synthetic applications in organic synthesis.\textsuperscript{49} Since O-allyl ethers are cleaved in the presence of DDQ\textsuperscript{50}, this reaction occurs in a rather complex multistep pathway, has not been developed further into a method of synthetic interest for the cleavage of allylic C-N bonds.\textsuperscript{51} Our studies shows that DDQ mediated N-deallylation could be a promising methodology in organic synthesis.

![Chemoselective Deprotection of Allylic Amines using DDQ](image)

Deprotection of N-allyl group was examined in several solvent systems. The best result was obtained using CH\textsubscript{2}Cl\textsubscript{2}-H\textsubscript{2}O (9:1). The reaction in other solvents such as CH\textsubscript{3}CN-H\textsubscript{2}O and Toluene-H\textsubscript{2}O proceeded more slowly. Solvent systems like THF-H\textsubscript{2}O and EtOAc-H\textsubscript{2}O resulted in complex reaction mixtures. This reaction is only achieved in the presence of water. When water was not added, only a trace amount of the desired product was obtained.
This method constitutes a new procedure for deprotection of \( N \)-allyl group with the considerable advantage of being under neutral conditions.

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