Chapter 3

Wittig Approach and Sharpless Asymmetric Dihydroxylation Reaction towards the Synthesis of 3-Hydroxy-L-proline and Tedanalactam
Wittig Approach and Sharpless Asymmetric Dihydroxylation Reaction towards the Synthesis of 3-Hydroxy-L-proline and Tedanalactam

Section A: Synthetic Studies towards trans-3-hydroxy-L-proline

Introduction:

The five-member cyclic α-amino-β-hydroxy acids, namely 3-hydroxy prolines (Figure 1) are important components of various natural products such as mucrorin-D, cyclopeptide antibiotic (teleomycin), polyhydroxylated alkaloids, detoxinine and so forth. They are also used as intermediates in the synthesis of biologically interesting molecules. Both trans and cis-3-hydroxy proline (1 & 2) are components of the cyclopeptide antibiotic teleomycin, which was isolated from a *streptomyces* species.

![Figure 1. Structures of 3-hydroxy proline](image)

Trans-3-hydroxy-L-proline 1 was first isolated from the hydrolysates of Mediterranean sponge and latter from the hydrolysates of the seed of *Delonix regia*. It has also been identified as a component of various collagens and candida. The free amino acids occur in human urine, resulting from collagen metabolism. The other related amino acids includes the dimethylated derivatives i.e. two isomeric 3-hydroxy proline betaines (L-trans and D-cis-3-hydroxystachydrines, 3 & 4) were isolated from *Courbonia virgata*.

Review of Literature:

Various syntheses of cis and trans-3-hydroxy proline have been described, which are based on reductive cyanation, Dieckman-type condensation, diastereoselective amination and the structural manipulation of pyroglutamate. Some
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of these methods, particularly towards the synthesis of trans-3-hydroxy proline are described below.

Hardeis et al. (1994, Scheme 1)\textsuperscript{11}

In this method, enantiopure bicyclic amide 5 was prepared from saturated bicyclic acetal of S-pyroglutaminol. Treatment of bicyclic amide 5 with t-butyl hydroperoxide/ tetrabutyl ammonium fluoride, afforded a single diastereomer of α,β-epoxy amide 6.

Regioselective reductive ring-opening of α,β-epoxy ketone with aluminium amalgam provided the corresponding hydroxy lactam, which on hydroxy protection using TBDMS followed by reduction of amide group using BH\textsubscript{3}S(CH\textsubscript{3})\textsubscript{2} and simultaneous reductive cleavage of the acetal moiety resulted in prolinol derivative 8. N-substituted prolinol 8 on hydrogenolysis using Pd/C in presence of Boc\textsubscript{2}O gave Boc derivative 9, which on oxidation, provided proline derivative 10. Finally, the N-Boc deprotection and TBDMS deprotection followed by ion exchange chromatography on Dowex 50WX2 provided \textit{trans}-3-hydroxy -L-proline 1.
Mulzer J. et al. (1996, Scheme 2)\(^4\)

Alcohol 11 prepared from D-mannitol in 3-steps was subjected to \(O\)-protection, and then ozonolysis followed by NaBH\(_4\) reduction gave the corresponding pentanol derivative 13. Alcohol 13 was converted to corresponding azide 14. Deprotection of the acetonide group followed by the selective protection of 1-OH using TBSCI, and mesylation of 2-OH function generated azide intermediate 16 with high regioselectivity. Staudinger reaction of azide with PPh\(_3\) and hydrolysis of phosphine imine with NaOH provided \(O\)-protected prolinol derivative, which on \(N\)-protection followed by selective desilylation of TBS led to primary alcohol 17.

Oxidation of alcohol 17 followed by desilylation and hydrogenolysis gave trans-3-hydroxy proline 1.

Durand et al. (1998, Scheme 3)\(^12\)

\(L\)-Malic acid 19 was used as the source of chirality to prepare lactam 22. Lactam 22 was subjected to reduction using DIBAL, and then treated with KCN to give trans
nitrile 23 in good yield. The nitrile 23 was hydrolysed, and the hydroxy group was deprotected by using dry HCl in MeOH. Treatment of the crude amide with Amberlyte 15 resin in MeOH at 65 °C led to the conversion of the amide to methyl ester 24.

The allyl group was finally removed using Genet's procedure to give ester 25. Saponification of 25 led to 3-hydroxy proline 1.

Lee, J. H. et al. (2001, Scheme 4)

The diol 27 prepared in five steps from D-glucono-δ-lactone was cleaved with NaIO4, followed by NaBH4 reduction led to the formation of alcohol, which on treatment with MsCl, gave mesylate 28. The mesylate 28 was treated with LiL to give iodide 29 which was treated with nBuLi, to give 2-amino-3-hydroxy-4-pentenoate 30. The pentenoate 30 was subjected to O-protection, followed by hydroboration, and alkaline oxidation furnished 5-hydroxypentanoate 32. The alcohol 32 on mesylation undergoes amination to produce proline ester 33, which on N-deprotection followed by hydrolysis, afforded trans-3-hydroxy-L-proline 1.
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Huang P-Q. et al. (2004, Scheme 5)\textsuperscript{15}

N-substituted-3-hydroxy pyrrolidin-2-one 34 prepared from (S)-malic acid was partially reduced with LAH followed by cyanation gave trans-2-cyano-3-hydroxy pyrrolidine 35, which on acidic hydrolysis and catalytic hydrogenolysis, provided trans-3-hydroxy-L-proline 1.
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Sinha S. et al. (2007, Scheme 6)16

The latest synthesis of trans-3-hydroxyl-L-proline 1 was reported by Sinha S. et al. employing Sharpless epoxidation as a key step. The methyl ester of β-alanine was converted to N-protected methyl ester 37, which on reduction with LAH, followed by oxidation of alcohol, provided aldehyde 38. Aldehyde 38 was treated with phosphorane to give E-olefinic ester, which on reduction with AlH3 gave allylic alcohol 40.

The alcohol 40 was subjected to Sharpless asymmetric epoxidation using (+)-DET to furnish epoxy alcohol 41, which on oxidation with Dess-Martin periodinane followed by treatment with Ag2O provided the epoxy carboxylic acid 42. Acid 42 on esterification followed by detosylation gave N-benzylated-3-hydroxy-L-proline derivative, which on hydrogenolysis, and then saponification gave trans-3-hydroxy-L-proline 1.

Objective:

Most of the methods towards the synthesis of trans-3-hydroxy-L-proline have utilized enzymatic or chiron approach to get the optically pure product. A more practical approach with lesser number of steps for the synthesis of 3-hydroxy proline...
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is highly desirable for further studies. Sharpless asymmetric dihydroxylation (SAD) is the most efficacious method in recent years, for the synthesis of the chiral diols. The objective of the present study is to devise a practical, flexible, and high yielding route to the synthesis of trans-3-hydroxy-L-proline \(1\) employing SAD as the source of chirality. Our retrosynthetic analysis of this approach is depicted in Scheme 7.

\[ \text{Scheme 7. Retrosynthetic analysis of trans-3-hydroxy-L-proline 1} \]

Present Work:

Our proposed retrosynthetic strategy is outlined in Scheme 7. The key disconnection is the ring closure (intramolecular cyclization) of the appropriate diol in order to form the pyrrolidine ring. We thought of achieving it under Mitsunobu condition, or an alternate method using selective monotosylation of diol, followed by cyclization via hydrogenation. The chiral diol can be generated using Sharpless asymmetric dihydroxylation of disubstituted olefin. The olefin in turn can be derived from 3-amino-1-propanol by straightforward synthetic manipulations.

Results and Discussion:

Mitsunobu Cyclization:

The synthesis started from the commercially available 3-amino-1-propanol (Scheme 8). Our choice of selecting N-protective group was based on idea that the selected group should be deprotected easily in the final step of synthesis, to give the pure product (amino acid) without subjecting it to a purification technique such as column chromatography or ion exchange. Hence we decided to use benzylchloroformate (CbzCl) as protecting group, which can be easily removed by hydrogenation.
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Scheme 8. Reagents and condition: a) CbzCl, K₂CO₃; b) PCC/ NaOAc, Ph₃P=CHCOOCH₂Ph; c) OsO₄, NMO; d) DIAD, PPh₃, reflux; e) H₂, Pd/C

Treatment of 3-amino-1-propanol 46 with benzyl chloroformate in the presence of K₂CO₃ afforded carbamate 45. Its IR spectrum showed bands at 3446, 1697 cm⁻¹ indicating the presence of hydroxyl and carbonyl functionalities respectively. The ¹H NMR spectrum (Figure 4) showed a singlet at δ 5.06 integrating for two protons and multiplet at δ 7.27-7.32 integrating for five protons, which indicated the presence of OCH₂Ph. The multiplet at δ 1.61-1.69 (2 protons), a triplet at δ 3.30 (J = 6.0 Hz, 2H), and another triplet at δ 3.62 (J = 5.7 Hz, 2H) were attributed to NCH₂CH₂O fragment. The broad singlet δ 2.59 (1 proton) indicated the presence of OH group. The ¹³C NMR spectrum showed amide carbonyl peak at δ 157.3. The multiplicities of carbon signals were determined by DEPT experiment. Finally the assigned structure 45 was confirmed by recording HRMS, which showed [M+Na]⁺ peak at m/z 232.0936 for C₁₁H₁₅NO₃Na.

N-protected propanol 45 was subjected to domino oxidation-Wittig reaction using PCC/NaOAc and (carbobenzyloxyethylene)triphenyl phosphorane to give α,β-unsaturated ester 47. The reason for choosing the benzyloxy phosphorane was to facilitate the removal of benzyl group in the latter stage during N-deprotection using
hydrogenolysis in one-pot. The IR spectrum of 47 showed bands at 1725, 1712 cm\(^{-1}\), which indicated the presence of carbonyl functionalities. The formation of homologated product was inferred from the disappearance of CH\(_2\)OH proton signals of starting compound, and appearance of the new peaks for olefinic protons at \(\delta\) 5.89 (d, \(J = 15.6\) Hz, 1H) and 6.91 (ddd, \(J = 7.2, 7.5, 15.6\) Hz, 1H), and an additional singlet at \(\delta\) 5.14 corresponding to two protons (OCH\(_2\) of ester) in its \(^1\)H NMR spectrum (Figure 5). Exclusively \textit{trans} olefin was formed during the Wittig reaction, which was indicated by coupling constant (\(J = 15.6\) Hz). Similarly, the \(^{13}\)C NMR and DEPT spectra showed a replacement of peak corresponding to CH\(_2\)OH (\(\delta\) 59.8) by two olefinic carbon peaks at \(\delta\) 145.8 and \(\delta\) 123.2 corresponding to \(\alpha,\beta\)-positions of ester 47 and the additional peaks for OCH\(_2\) (\(\delta\) 66.8) and aromatic carbons (\(\delta\) 128.6-136.4). The HRMS spectrum of 47 showed \([\text{M+Na}^+]\) peak at \(m/z\) 362.1376 for C\(_{20}\)H\(_{21}\)NO\(_4\)Na.

As a model study, initially we decided to prepare a racemic diol to check the feasibility of our proposed strategy. Towards this end, the dihydroxylation of olefin 47 using OsO\(_4\) and NMO as oxidant gave the diol 48 in 80% yield. The IR spectrum of diol 48 showed bands at 3376, 1735, and 1700 cm\(^{-1}\) corresponding to hydroxyl and carbonyl functionalities respectively. The formation of diol 48 was inferred from the appearance of two peaks at \(\delta\) 4.03 (br d, 1H) and \(\delta\) 4.27 (br s, 1H) in its \(^1\)H NMR spectrum (Figure 6), and at \(\delta\) 70.0, 73.7 in \(^{13}\)C NMR spectrum (Figure 7) corresponding to the two newly formed diol CH group, and the disappearance of the C=C peaks. The multiplicities of carbon signals were determined by DEPT experiment. Finally the assigned structure 48 was confirmed by recording HRMS, which showed \([\text{M+Na}^+]\) peak at \(m/z\) 396.1407 for C\(_{20}\)H\(_{21}\)NO\(_6\)Na. With the sufficient amount of the diol 48 in our hand, our next plan was to carry out cyclization to give pyrrolidine skeleton 51. The mechanism for expected cyclization under Mitsunobu condition is outlined in Scheme 9. An oxyphosphonium intermediate formed at \(\alpha\)-hydroxy position of diol 48, which could undergoes cyclization to 51.

The Mitsunobu reagent was found popular and useful in forming pyrrolidines,\(^{17}\) piperidines,\(^{18}\) and azetidines.\(^{19}\) A mixture of PPh\(_3\) and diethylazodicarboxylate (DEAD) is generally used in the Mitsunobu reaction.\(^{17a-c,18,19a}\)
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However, diisopropyl azodicarboxylate (DIAD) is cheaper and less toxic, and works just as well. With DIAD in hand, the Mitsunobu reaction was conducted by treatment of 2,3-dihydroxy ester $\text{48}$ with PPh$_3$ and DIAD in dry toluene.

Scheme 9. Proposed mechanism for the Mitsunobu reaction

The product obtained after purification in its IR spectrum showed bands at 3377, 1745, 1712 and 756 cm$^{-1}$ indicating the presence of hydroxyl, carbonyl, and aromatic functionalities respectively. The multiplets at $\delta$ 1.85 (1 proton), $\delta$ 2.11 (1 proton), $\delta$ 3.29 (2 protons) and a broad singlet at $\delta$ 4.26 (1 proton) and a broad doublet at $\delta$ 4.63 (1 proton) in the $^1$H NMR spectrum (Figure 8) and the carbon peaks at $\delta$ 22.4, 38.4, 72.2, 77.8 in $^{13}$C NMR and DEPT spectrum, indicated the presence of the NHCH$_2$CH$_2$CH(OH)CH(OH) fragment as in the starting diol $\text{48}$. The presence of doublet at $\delta$ 5.20 ($J = 12.0$ Hz, 1H), a doublet at $\delta$ 5.26 ($J = 12.0$ Hz, 1H), and a singlet
at $\delta$ 7.35 (5 protons) in $^1$H NMR spectrum and carbon signals at $\delta$ 67.7, 128.3-128.5 and $\delta$ 135.0 in the $^{13}$C NMR spectrum, indicated the presence of OCH$_2$Ph group. The broad singlet at $\delta$ 6.75 (1 proton) was attributed to the presence of NH group. Hence one benzyloxy group was eliminated during Mitsunobu reaction. Further, $^{13}$C NMR spectrum showed peaks at $\delta$ 154.5 and $\delta$ 171.3 indicating the presence of two carbonyl functionalities. Based on the spectral data, structure 49 was attributed for the product formed under Mitsunobu condition. Further, the assigned structure 49 was confirmed by recording HRMS, which showed [M+Na]$^+$ peak at $m/z$ 288.0861 for C$_{13}$H$_{15}$NO$_5$Na.

Additional proof for the formation of Oxazinane derivative 49 is provided, by subjecting it to hydrogenation reaction using H$_2$, Pd/C for 8 h (Scheme 10). The disappearance of the peaks corresponding to CH$_2$Ph in all NMR spectra indicated the formation of corresponding acetic acid derivative 50 (Figure 9). Further, the assigned structure 50 was confirmed by recording its mass spectrum showing [M+H]$^+$ peak at $m/z$ 176.19 for C$_6$H$_{10}$NO$_5$. Hence we didn't succeed in cyclization of 5-membered pyrrolidine ring, instead we obtained oxazinane derivative.
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*N-Cbz protection and selective tosylation:*

Due to the failure in obtaining the targeted product using Mitsunobu cyclization, we thought of using an alternate method for the pyrrolidine cyclization. Our idea in this approach was to bring a good leaving group at α-position of α,β-substituted ester, and then the nucleophilic displacement of this leaving group would give us the cyclized pyrrolidine (Scheme 11).

![Scheme 11. Reagents and condition: a) TsCl, NEt₃, 0 °C; b) base](image)

With the above objective in our mind, we followed a method reported by Fleming and Sharpless for selective monotosylation of the α-hydroxy group in α,β-dihydroxy ester. Towards this end, the 2,3-dihydroxy ester was treated with TsCl and NEt₃ at 0 °C for 72 h to give the monotosyl compound in 68% yield. Its IR spectrum showed bands at 3315, 1762, 1683, 752 cm⁻¹ indicating the presence of hydroxyl, carbonyl and aromatic functionalities respectively. The ¹H NMR spectrum of 52 (Figure 10), showed the methyl protons at δ 2.43 as a singlet and hydroxyl proton was seen at δ 2.17 as a broad singlet. The CH proton attached to OH group was seen at δ 4.15 (1 proton) as a broad doublet, while the CH proton attached to tosyl group appeared at δ 4.92 as a doublet (J = 3.0 Hz). The multiplet at δ 7.24-7.36 (12 protons), and a doublet at δ 7.79 (J = 8.4 Hz, 2H), indicated the presence of the aromatic rings. Further, the appearance of the new peaks at δ 21.7, 136.3 and 145.2 in ¹³C NMR and DEPT spectrum indicated the presence of tosyl group. The shift of peaks in the diol at δ 70.0 (CH at β-position) and 73.7 (CH at α-position) to 69.1 (CH at β-position) and 79.8 (CH at α-position) in monotosylated compound 52, indicated the presence of tosyl group at α-position of ester. Further, the assigned structure 52

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was proved by mass spectrum, which showed [M+Na]+ peak at m/z 550.1539 for C27H29NO8SNa.

The cyclization of monotosylated compound 52 was attempted under varied basic conditions (Scheme 12). The results are summarized in table 1.

![Scheme 12. Reagents and condition: a) 1.2 equiv K2CO3, MeOH, rt; b) 1.1 equiv Cs2CO3, DMF, rt; c) excess K2CO3, MeOH, reflux; d) excess Cs2CO3, DMF, reflux; e) H2, Pd/C; f) NaH (1 equiv or excess), THF, reflux.](image)

**Table 1.** Conditions and results of attempted cyclization of monotosyl ester 52 to corresponding pyrrolidine skeleton 51.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>1.2 equiv K2CO3, MeOH, rt, 5h</td>
<td>Epoxide 53</td>
</tr>
<tr>
<td>2.</td>
<td>excess K2CO3, MeOH, reflux</td>
<td>Epoxide 53</td>
</tr>
<tr>
<td>3.</td>
<td>excess K2CO3, DMF, reflux</td>
<td>Epoxide 53</td>
</tr>
<tr>
<td>4.</td>
<td>1.1 equiv Cs2CO3, DMF, rt</td>
<td>Epoxide 53</td>
</tr>
<tr>
<td>5.</td>
<td>excess Cs2CO3, DMF, reflux</td>
<td>Epoxide 53</td>
</tr>
<tr>
<td>6.</td>
<td>NaH (1 equiv), THF, reflux</td>
<td>Not isolable</td>
</tr>
<tr>
<td>7.</td>
<td>NaH (excess), THF, reflux</td>
<td>Not isolable</td>
</tr>
</tbody>
</table>

The treatment of compound 52 with K2CO3 (1.2 equiv) in MeOH at room temperature for 5 h, gave an oily compound. Its IR spectrum showed bands at 3300, 1730, 1690 cm⁻¹ indicating the presence of the NH and the carbonyl functionalities.
The disappearance of the peaks at $\delta$ 4.15 (br d, 1H), 4.92 (d, 1H) in $^1$H NMR spectrum, and $\delta$ 69.1, 79.8 in the $^{13}$C NMR, DEPT spectrum of monotosylated compound 52, and the appearance of peaks at $\delta$ 3.56 (br d, 1H), 5.10 (br s, 1H) in the $^1$H NMR spectrum (Figure 11) and $\delta$ 52.3, 55.7 in $^{13}$C NMR and DEPT spectrum of newly formed product, indicated the formation of epoxide ring via detosylation (peaks corresponding to tosyl group disappeared in all the NMR spectra). Further, the assigned structure 53 was confirmed by recording HRMS, which showed [M+Na]$^+$ peak at $m/z$ 396.1407 for C$_{20}$H$_{21}$NO$_5$Na.

With the intention of opening the epoxide 53 via intramolecular nucleophillic substitution, we refluxed epoxide 53 in the presence of excess of K$_2$CO$_3$ in different solvents like MeOH, DMF. Mainly the starting epoxide 53 was recovered from these attempted reactions. Hence, we thought of using Cs$_2$CO$_3$, a stronger base than K$_2$CO$_3$. The monotosyl 52 was treated with 1.1 equiv of Cs$_2$CO$_3$ in DMF at room temp. for 8 h. Tlc analysis of the reaction mixture showed the formation of epoxide 53 (after 2 h), which did not disappear even after stirring for additional 6 h. Hence, the excess of Cs$_2$CO$_3$ was added to the same reaction flask containing epoxide 53 and refluxed for 4 h. The analysis of reaction (tlc) showed the disappearance of the epoxide. However, we could not isolate any pure product after work up using different solvents like EtOAc, CHCl$_3$, Et$_2$O. Further, we thought of effecting cyclization$^{21}$ by using stronger base i.e. NaH. Cyclization was attempted using 1 equiv NaH in THF at room temperature, without any success. The excess NaH in refluxing THF, indicated the disappearance of starting material (tlc analysis), but once again we failed to isolate any product after the work up. Hence, the generation of anion at the nitrogen atom (nucleophile) using different bases proved unsuccessful for the used reaction conditions.
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Scheme 12. Hydrogenation of monotosylate 52

With the above failure of cyclization under various reaction conditions, we thought of avoiding the generation of an anion in situ and instead thought to generate nucleophile (NH$_2$) in reaction mixture, which could undergoes SN2 substitution via detosylation to give five member pyrrolidine skeleton (Scheme 12). So, hydrogenation was chosen as preferred method, which on N-deprotection can provide amine, followed by intramolecular SN2 substitution can give the target compound 3-hydroxy proline 1. Hence, the monotosylated compound 52 was subjected to hydrogenation using H$_2$, Pd/C, EtOH for 8 h, led to a complex product mixture, which we could not able to separate by using column chromatography. Tlc analysis indicated the presence of amino acid (ninhydrine test). The separation of p-toluene sulfonic acid from the amino acid was a major problem for us, which were not there during formation of the corresponding epoxide 53 (described earlier in this section). Further, epoxide 53 was subjected to hydrogenation. The heterogeneous solution on filtration, followed by washing with EtOH, gave the thick yellow liquid, whose $^1$H NMR and $^{13}$C NMR spectrum indicated the presence of mixture of compounds. The white crystalline solid (insoluble in EtOH) sticking to the glass bottle of hydrogenator was analyzed. Its $^1$H NMR (D$_2$O) showed two multiplets at $\delta$ 1.76-1.96 integrating for two protons and one multiplet at $\delta$ 3.11-3.16 integrating for 2 protons, indicated the presence of CH$_2$CH$_2$N fragment. The multiplet at $\delta$ 3.24 (1 proton) and a doublet at $\delta$ 3.49 ($J = 3.3$ Hz, 1H), was attributed to the CH of epoxide ring. Further, $^{13}$C NMR spectrum showed peaks at
δ 25.7 and 36.9 for CH₂CH₂N fragment. The peaks at δ 53.8, 54.9 and 174.6, indicated the presence of methine carbons at epoxy ring and carbonyl carbon of acid functionality. Further, the multiplicities of carbons were determined by DEPT experiment. Hence, all the NMR spectra indicated the formation of acyclic epoxy amino acid 54.

**N-Boc protection and selective tosylation:**

The problematic step in the above route was hydrogenation, wherein N-deprotection (Cbz), hydrogenolysis at the side chain of the ester, and the detosylation occurred in one-pot giving amino acid and p-toluenesulfonic acid which was difficult to separate. Additionally, the formation of acyclic epoxy amino acid 54 indicates that, the ring-opening reaction by nitrogen nucleophile in 53 became difficult, once it got converted to acid. To tackle this problem, we thought of using the Boc-protecting group instead of the Cbz, wherein, removal of the N-Boc group followed by treatment of resulting TFA salt with aqueous NH₃, would provided us benzyloxy ester derivative of 3-hydroxy prolinate 60 (Scheme 13).

**Scheme 13. Reagents and condition:** a) Boc₂O, Et₃N; b) PCC/ NaOAc, Ph₃P=CHCOOCH₂Ph; c) OsO₄, NMO; d) TsCl, Et₃N, 0 °C; e) TFA; f) aq. NH₃
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3-Amino-1-propanol 46 was treated with Boc$_2$O in the presence of Et$_3$N to give the corresponding carbamate 55 in 72% yield. Its IR spectrum showed bands at 3612, 1703 cm$^{-1}$ indicating the presence of hydroxyl and carbonyl functionalities. The $^1$H NMR spectrum (Figure 12) of 55 clearly showed a 9 protons singlet for the N-Boc group at $\delta$ 1.45. The triplet at $\delta$ 3.28 ($J$ = 6.0 Hz, 2H) and another triplet at $\delta$ 3.67 ($J$ = 5.7 Hz, 2H), was attributed to CH$_2$NH and CH$_2$OH respectively. In $^{13}$C NMR spectrum, the peaks at $\delta$ 157.6 (C=O), $\delta$ 79.6 (Me$_3$C) and $\delta$ 28.3 (Me$_3$C) was observed corresponding to N-Boc group. Further, the assigned structure 55 was confirmed by HRMS, which showed [M+Na]$^+$ peak at m/z 198.1104 for C$_8$H$_{17}$NO$_3$Na.

The N-Boc alcohol 55 treated with PCC/NaOAc and carbobenzyloxy phosphorane in one-pot, to give the corresponding $\alpha,\beta$-unsaturated ester 56. Its IR spectrum showed bands at 3373, 1712, 1693 cm$^{-1}$, indicating the presence of the NH and carbonyl functionalities. The olefinic peaks at $\delta$ 5.95 ($d$, $J$ = 15.6 Hz, 1H) and $\delta$ 6.96 (ddd, $J$ = 6.9, 7.2, 15.6 Hz, 1H) in the $^1$H NMR spectrum (Figure 13) and the peaks at $\delta$ 123.0 and $\delta$ 146.1 in the $^{13}$C NMR spectrum, indicated the success of the Wittig olefination. Additionally, the new peaks at $\delta$ 5.18 (br s, 2H) and 7.35-7.38 (m, 5H) were observed due to the presence of OCH$_2$Ph group. The multiplicities of the carbon signals were determined using DEPT experiment. Finally, the assigned structure 55 was confirmed by recording HRMS, which showed [M+Na]$^+$ peak at m/z 328.1518 for C$_{17}$H$_{23}$NO$_4$Na.

The most common reagent for syn-dihydroxylation is OsO$_4$ or K$_2$OsO$_4$ as a catalyst and N-methyl morpholine-N-oxide (NMO) as a co-oxidant. Olefin 56 was treated with a catalytic amount of OsO$_4$ (1% aq. solution) in the presence of NMO in a mixture of acetone and water at room temperature for 12 h, to give the desired cis diol 57. Its IR spectrum showed a broad band at 3600-3041 cm$^{-1}$ for the hydroxyl functionality and sharp bands at 1749, 1680 cm$^{-1}$ for carbonyl groups. The success of dihydroxylation was indicated by the disappearance of olefinic peak in all NMR spectra and appearance of the new peaks at $\delta$ 2.84 (br s, 2H), $\delta$ 4.13 ($d$, $J$ = 2.4 Hz, 1H), and $\delta$ 4.0-4.03 (m, 1H) corresponding to hydroxyl, CH(OH)CO, and CH(OH)CH$_2$ group respectively in $^1$H NMR spectrum (Figure 14). Similarly, the new
peaks at $\delta$ 69.7, 73.8 in $^{13}$C NMR were attributed to the CH attached to hydroxyl group at $\beta$ and $\alpha$-position respectively. Further, the multiplicities of the carbon peaks were determined using DEPT experiment and the assigned structure 57 was confirmed by recording HRMS, which showed $[\text{M+Na}]^+$ peak at $m/z$ 362.1579 for $\text{C}_{17}\text{H}_{23}\text{NO}_6\text{Na}$.

The N-Boc-2,3-dihydroxy ester 57 was subjected to the selective monotosylation reaction at 2-position using TsCl, Et$_3$N and CH$_2$Cl$_2$ at 0 °C (72 h) to give 2-tosyloxy-3-hydroxy pentanoate derivative 58. Its IR spectrum showed bands at 3600-3140, 1764, 1685 cm$^{-1}$, which indicated the presence of hydroxyl and carbonyl functionalities. The appearance of new peaks at $\delta$ 2.44 (s, 3H) and 7.80 (d, $J = 8.4$ Hz, 2H) in its $^1$H NMR spectrum (Figure 15) and the peaks at $\delta$ 21.7 (CH$_3$), 134.8 (Ar-C), 145.1 (Ar-C(SO$_3$)), confirmed the presence of tosylo group. The appearance of new peaks at $\delta$ 4.13-4.17 (m, CH(OH), 1H), 4.75 (br s, OH, 1H), and 4.95 (d, $J = 3.3$ Hz, CHO) in the $^1$H NMR and 68.7 (CHOH), 79.9 (CHOTs) in the $^{13}$C NMR spectrum inferred the success of tosylation reaction at 2-position. Its HRMS showed $[\text{M+Nar}]^+$ peak at $m/z$ 516.1658 for $\text{C}_{24}\text{H}_{29}\text{NO}_8\text{SNa}$.

The Boc group of the monotosylated compound 58 was cleaved by treatment with TFA, to give the corresponding triflouro acetate ammonium salt 59. Its IR spectrum showed bands at 3219, 1759 and 1666 cm$^{-1}$, indicating the presence of hydroxyl and carbonyl functionalities. The success of the reaction was inferred from the disappearance of peak at $\delta$ 1.42 (s, 9H) in $^1$H NMR spectrum and carbon peaks at $\delta$ 28.3, 79.7 in the $^{13}$C NMR and DEPT spectrum, corresponding to the Boc group.

**Scheme 14.** Cyclization under basic condition

Finally, the ammonium salt 59 was treated with aq NH$_3$ to effect cyclization. We expected the formation of amine nucleophile upon neutralization of salt, which could
be easily cyclized intramolecularly to form kinetically favored five member ring via detosylation to give us the desired pyrrolidine skeleton 60 (Scheme 14). The light yellow thick oily compound obtained after column chromatography showed bands at 3268, 1680 cm$^{-1}$ in its IR spectrum, indicated the presence of NH and carbonyl functionalities. The $^1$H NMR spectrum (Figure 16) showed peaks at δ 2.05 (ddd, $J = 6.0, 6.6, 12.3$ Hz, 1H) and δ 2.34-2.90 (m, 1H), which indicated the presence of methylene attached to CH$_2$ and CH. The peaks at δ 3.06 (ddd, $J = 6.0, 6.0, 12.3$ Hz, 1H) and δ 3.34 (dd, $J = 4.2, 12.3$ Hz, 1H) confirms the presence of methylene attached to amine functionality and methylene group. The broad singlet at δ 3.63 and a multiplet at δ 3.42 integrating for one proton each, indicated the presence of two CH attached to oxygen atom (CHOCH). The broad singlet at δ 6.18 (1 proton), confirms the presence of the NH group. Further, the $^{13}$C NMR spectrum (Figure 17) showed peak at δ 23.5 and 35.2 indicated the presence of CH$_2$CH$_2$NH fragment. The peaks at δ 53.1 and 50.6 were attributed to CH of the epoxy ring. The carbon peak at δ 169.1 was attributed to carbonyl group. Spectral analyses indicated the formation of 6-member 3,4-epoxy-2-piperidone 61 during the reaction rather then the pyrrolidine derivative 60. Finally, the assigned structure 61 was confirmed by DEPT experiment and recording the HRMS, which showed [M+Na]$^+$ peak at m/z 136.0374 for C$_5$H$_7$NO$_2$Na and comparing the spectroscopic data with literature report.$^{25}$

Thus, we have achieved a synthesis of 3,4-epoxy-2-piperidone in very short and a simple way. 3,4-Epoxy-2-piperidone also called as tedanalactam, was isolated as natural product. Up-to-date, nor its synthesis, neither its stereochemistry is mentioned in literature. Hence, application of this methodology towards synthesis of both the enantiomers of tedanalactam was undertaken and is discussed in Section B of this chapter.
**Conclusions:**

1) The Mitsunobu cyclization gave 1,3-oxazinan-6-yl derivative which has been further transformed to acetic acid derivative.

2) Under the various reaction conditions employed for the intramolecular cyclization of 2-tosyloxy-3-hydroxy ester to give pyrrolidine skeleton did not work, probably due to the steric hindrance.

3) Boc deprotection of 2-tosyl-3-hydroxy ester undergoes intramolecular cyclization to give 6-membered piperidone ring rather than 5-membered pyrrolidine skeleton, may be again due to steric hindrance.

4) The first total synthesis of (±)-tedanalactam have been accomplished.
**Section B: Synthesis of (-) and (+)-Tedanalactam**

**Introduction:**

Piperidones are widespread in natural products and have been frequently used as convenient building blocks in organic synthesis\(^\text{22}\) and also found as a structural motif in many pharmaceutical leads.\(^\text{23}\) Asymmetric syntheses of substituted piperidine derivatives are receiving considerable attentions.\(^\text{24}\)

Tedanalactam \(62\), a cis-3,4-epoxy-2-piperidone showing a high fungitoxic potential was first isolated from marine sponge\(^\text{25}\) *Tedania ignis* and later from leaves of *Piper crassinervium* (piperaceae).\(^\text{26}\) Related compounds (Figure 2) isolated from other natural sources are piplaroxide \(63\), an ant-repellant alkaloid isolated from *Piper tuberculatum*,\(^\text{27a}\) 3,4-epoxy-8,9-dihydropiplartine \(64\) isolated from leaves and twigs of *Piper verrucosum*,\(^\text{27b}\) 3,4-epoxy-5-pipermethystine \(65\) from roots of the kava shrub (*piper methysticum*).\(^\text{27c}\) The kava shrub is a source of traditional beverage for many South Pacific Island people.

![Figure 2. Examples of epoxy-2-piperidones](image)

Weintraub P. M. *et al.* have published a comprehensive review\(^\text{22c}\) entitled "Recent advances in the synthesis of piperidone and piperidines" covering synthetic efforts in this area from 1999 to 2003. Surprisingly, so far there is no report in literature about the synthesis of tedanalactam and nor is its stereochemistry mentioned. As part of our research program\(^\text{28}\) aimed at developing the synthesis of biologically active compound using tandem (one-pot, domino) strategies, herein, a first highly enantioselective synthesis of (-) and (+)-tedanalactam is described through a common alkene as an intermediate, by employing the Sharpless asymmetric dihydroxylation.
Chapter 3: Wittig Approach and Sharpless Asymmetric Dihydroxylation Reaction towards the Synthesis of 3-Hydroxy-L-proline and Tedanalactam

Present Work:

Objectives:
The objective of the present study is to achieve the first total synthesis of the both enantiomers of tedanalactam and further to demonstrate the synthetic utility of domino oxidation-Wittig reaction protocol. The detailed strategy is depicted in Scheme 15.

Scheme 15. Reagents and condition: a) modified AD-mix α; b) modified AD-mix β; c) TsCl, Et3N, 0 °C, 72 h; d) 1. TFA; 2. aq NH3

Results and Discussion:
The methodology described is analogous to Scheme 13 and 14 discussed in section A of this chapter. Hence this section covers a brief description towards the synthesis of both enantiomers of tedanalactam. As discussed earlier, our synthesis commenced with the protection of the free amine of 3-amino-1-propanol 46 with Boc₂O, followed by domino oxidation-Wittig reaction using PCC/NaOAc and (carbobenzyloxy)methylene)triphenyl phosphorane to furnish the corresponding α,β-unsaturated ester 56. We planned to incorporate the required stereochemistry in early steps of the synthesis employing the Sharpless asymmetric dihydroxylation (SAD).
Chapter 3: Wittig Approach and Sharpless Asymmetric Dihydroxylation Reaction towards the Synthesis of 3-Hydroxy-L-proline and Tedan lactam

**Sharpless Asymmetric Dihydroxylation and Mnemonic Rule:**

The asymmetric dihydroxylation (AD) reaction was developed in early 1990 by Sharpless B. and has emerged as a powerful method for the synthesis of chiral diol from alkene.\(^{29}\) Importantly, the reaction is catalytic in both the osmium and a cinchona alkaloids ligand. The various sources of the nitrogen as a ligand were developed since the reactions discovery. Accordingly, catalyst is prepared and also available commercially as AD-mix: a powder containing an osmium source \(K_2\text{OsO}_4\text{(OH)}_4\), the chiral ligand ([DHQ]_2\text{PHAL} for AD-mix \(\alpha\), [DHQD]_2\text{PHAL} for AD-mix \(\beta\)), a co-oxidant for regeneration of osmium (VIII) is \(K_3\text{Fe(CN)}_6\) and a pH buffer (\(K_2\text{CO}_3\)) to perform the dihydroxylation. In our synthetic endeavors we needed the chiral diol. To predict the enantiofacial selectivity and the ligand needed for the SAD reaction, the mnemonic devise was employed (Figure 3).

![Figure 3. Mnemonic device of Sharpless dihydroxylation.](image)

The alkyl substituent was placed on the south-west quadrant, which is well-suited to accommodate large substituent. The carbonyl group was placed on the north-east quadrant, which is suitable for substituents of moderate size. Both hydrogen atoms were placed on the north-west and south-east quadrants. According to the requirement of the expected diol configuration, an attack from top face was needed, in this case (DHQD)_2PHAL derivative was ligand of choice (AD-mix \(\beta\)). Similarly, AD-mix \(\alpha\) containing (DHQ)_2PHAL as ligand will provide cis diol wherein OH attack from bottom side. Since OsO_4 is an electrophillic reagent, the rate of osmylation of electron deficient disubstituted olefins, such as \(\alpha,\beta\)-unsaturated carbonyl compound is very
low. Sharpless B. and coworkers\textsuperscript{29a} solved the problem with such alkene by using modified AD-mix catalyst which contain little excess amount of osmium source.

Towards this end, the asymmetric dihydroxylation of olefin \textsuperscript{56} using OsO\textsubscript{4} and potassium ferricyanide as co-oxidant in presence of 1,4-bis(dihydroquinin-9-O-yl) phthalazine [(DHQ)\textsubscript{2}PHAL], gave the diol \textsuperscript{66} essentially in 77% yield with 91% ee having [\textalpha]D\textsuperscript{31} -3.93 (c 0.891, CHCl\textsubscript{3}). Its IR spectrum showed strong band at 3600 cm\textsuperscript{-1}, corresponding to the hydroxyl functionality and 1749, 1680 cm\textsuperscript{-1} for carbonyl group. The disappearance of the olefinic peaks and appearance of the new peaks at \delta 2.84 (br s, 2H), \delta 4.13 (d, J = 2.4 Hz, 1H) and \delta 4.0-4.03 (m, 1H) corresponding to OH, CH(OH)COO and CH(OH)CH\textsubscript{2} respectively in the \textsuperscript{1}H NMR spectrum, inferred the success of dihydroxylation reaction. Further, the assigned structure \textsuperscript{66} was confirmed by comparing \textsuperscript{1}H NMR data of (+)-diol \textsuperscript{57} described in section A of this chapter.

The selective conversion of the hydroxy group at 2-position of 2,3-dihydroxy ester \textsuperscript{66} into monotosylate was carried out using TsCl in NEt\textsubscript{3} at 0 °C for 72 h in 65% yield, [\textalpha]D\textsuperscript{31} -13.33 (c 0.1, CHCl\textsubscript{3}) with 91% ee. The IR spectrum of the monotosylate \textsuperscript{67} showed strong bands at 3600, 1764, 1685 cm\textsuperscript{-1}, confirming the presence of hydroxyl and carbonyl functionalities. The \textsuperscript{1}H NMR spectrum of monotosylate \textsuperscript{67} showed new peaks at \delta 2.44 (s, 3H) and 7.80 (d, J = 8.4 Hz, 2H) indicating the presence of the tosyl group. The CH attached to OH appeared at \delta 4.13-4.17 (m, 1H) and the CH attached to OTs at \delta 4.95 (d, J = 3.3 Hz, 1H), which indicated the success of tosylation. Further, the assigned structure \textsuperscript{67} was confirmed by comparing spectra with (+)-monotosylate \textsuperscript{56}. The Boc group of monotosylate \textsuperscript{67} was cleaved by treatment with TFA and the resulting ammonium salt was treated with aqueous NH\textsubscript{3} to effect cyclization. In this final step, three reactions i.e. deprotection, lactamisation and epoxidation took place in one-pot, giving (-)-tedanalactam \textsuperscript{68} having [\textalpha]D\textsuperscript{30} -7.60 (c 0.130, MeOH) \textsuperscript{lit\textsuperscript{25}} [\textalpha]D\textsuperscript{30} -8.90 (c 0.3, MeOH]) in 91% ee and 77% yield. Its IR spectrum showed bands at 3268, 1680 cm\textsuperscript{-1} indicating the presence of NH and carbonyl functionalities. The epoxy CH appeared at \delta 3.63 (br s, 1H) and \delta 3.42 (m, 1H) whereas the peak at \delta 6.18 (br s, 1H) indicated the presence of NH group in its \textsuperscript{1}H
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NMR spectra. The spectral data is consistent with (+)-tedanalactam described in previous section. Similarly, (+)-tedanalactam 71 having $[\alpha]_D^{20} +8.47$ (c 0.118, MeOH) with 94% was prepared via SAD reaction using modified AD-mix $\beta$ with identical overall yield. Thus, disubstituted olefin 64 was subjected to AD reaction using (DHQD)$_2$PHAL as chiral ligand to give 2,3-dihydroxy ester 69 having $[\alpha]^{11}_{D} +4.16$ (c 0.721, CHCl$_3$) in 94% ee and 71% yield. Further, diol 69 was transformed into the corresponding monotosyl compound 70 using TsCl/NEt$_3$ at 0 °C showing $[\alpha]^{11}_{D} +13.42$ (c 0.149, CHCl$_3$), 94% ee and 65% yield. Finally, the Boc-deprotection of monotosylate using TFA, followed by treatment with aqueous NH$_3$ furnished (+)-tedanalactam 71 in 94% ee and 72% yield. The HPLC chromatograms of diol (57,66,69), and piperidone (61,68,71) are shown in figure 18, 19 respectively. The spectroscopic data were in agreement with those previously described in section A of this chapter.

The first total synthesis of (-)-tedanalactam with 91% ee and (+)-tedanalactam with 94% ee has been completed in a simple way from 3-amino-1-propanol in 5 steps. The sign of specific rotation of (-)-tedanalactam is consistent with natural tedanalactam, which reveals the presence of (3S,4S) configuration at epoxy ring of the natural product.

Conclusion:

1. The first total synthesis of (-)-tedanalactam and (+)-tedanalactam have been accomplished in 5 steps starting from 3-amino-1-propanol.
2. Furthermore, a practical and highly enantioselective synthesis of both the isomers of tedanalactam has been achieved using Sharpless asymmetric dihydroxylation as source of chirality.
3. This synthesis demonstrated the feasibility and synthetic utility of one-pot strategies, preferentially, tandem oxidation-Wittig reaction and deprotection-lactamisation-epoxidation sequence for the natural product synthesis.
4. Our successful asymmetric total synthesis of tedanalactam led us to conclude that the natural tedanalactam is having (3S,4S)-configuration.
Experimental Section:
Section A: Synthetic Studies towards trans-3-hydroxy-L-proline
3.01 Preparation of (Carbobenzyloxymethylene)triphenyl phosphorane:

Addition of solution of triphenylphosphine (5.726 g, 0.022 mol) in dry benzene (10 mL) to a solution of benzyl bromoacetate (5.00 g, 0.022 mol) in dry benzene (20 mL) at room temp, resulted in an elevation in temp and precipitation of salt. After allowing the mixture to cool to room temp, it was vigorously shaken and left overnight. The solid obtained was filtered and washed with benzene and dried. Water (150 mL) was added to salt followed by addition of benzene (100 mL) and then neutralized by aqueous NaOH with constant shaking to a phenolphthalein end point. The benzene layer was evaporated, dried over anhyd Na₂SO₄ and concentrated to about 1/3 volume. Addition of n-hexanes (40-60 °C) resulted in separation of white crystalline product which was filtered and dried to afford phosphorane (5.739 g, 64%), mp 118-119 °C.

3.02 Preparation of Benzyl (3-hydroxypropyl)carbamate (45):

A solution of benzyl chloroformate (2.552 g, 15.0 mmol) in acetonitrile (5 mL) was added slowly to a stirred solution of 3-amino-1-propanol 46 (1.025 g, 13.6 mmol) and finely powdered K₂CO₃ (4.150 g, 30.0 mmol) in dry acetonitrile (20 mL) at -10 °C under N₂ atmosphere. Further, the solution was stirred at -10 to 0 °C for 2 h, H₂O (50 mL) was added and the aqueous layer was extracted with CHCl₃ (3 x 20 mL). The combined organic extract was washed successively with H₂O (1 x 20 mL), 5% HCl (1 x 20 mL), H₂O (3 x 20 mL) and then dried over anhyd Na₂SO₄. The solvent was removed under vacuum pump, the crude product was subjected to column
chromatography (SiO$_2$, hexanes/ EtOAc, 1:1) to give benzyl (3-hydroxypropyl)carbamate 45 as a white solid (2.116 g, 74.3%), mp 42-43 $^\circ$C.

IR (neat): 3446-3019 (OH), 1697 (C=O), 755 cm$^{-1}$ (Ar).

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.61-1.69 (m, 2H, H-1-2), 2.59 (br s, 1H, OH), 3.30 (t, $J$ = 6.0 Hz, 2H, H-1), 3.62 (t, $J$ = 6.0 Hz, 2H, H-3), 5.06 (s, 3H, CH$_2$Ph & NH), 7.27-7.32 (m, 5H, Ar-H).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 32.4 (C-2), 37.8 (C-1), 59.7 (C-3), 66.8 (CH$_2$Ph), 128.0, 128.5, 128.1 (Ar-H), 136.5 (Ar-C), 157.3 (C=O).

HRMS: $m/z$ [M+Na]$^+$ calcd for C$_{111}$H$_{115}$NO$_3$Na: 232.0950; found: 232.0936.

3.03 Preparation of Benzyl (2E)-5-[(benzyloxycarbonyl)amino]pent-2-enoate (47):

To a magnetically stirred suspension of PCC (0.591 g, 2.74 mmol) and NaOAc (0.225 g, 2.74 mmol) in anhyd CH$_2$Cl$_2$ (30 mL) was added benzyl (3-hydroxypropyl)carbamate 45 (0.381 g, 1.83 mmol) in anhyd CH$_2$Cl$_2$ (5 mL), followed by addition of (benzyloxycarbonylmethylene) triphenylphosphorane (0.824 g, 2.01 mmol) in one portion. The mixture was stirred at room temp for 8 h. Et$_2$O (50 mL) was added and the supernatant solution was decanted from the black granular solid. The combined organic solutions were filtered through a short bed of celite and the filtrate obtained was evaporated to give a residue that was purified by column chromatography on silica gel (hexanes: EtOAc = 7:3) to give pure benzyl (2E)-5-[(benzyloxycarbonyl)amino]pent-2-enoate 47 (0.465, 72%) as a colorless viscous liquid.

IR (neat): 3343 (NH), 1725 (C=O), 1712 (C=O), 756 cm$^{-1}$ (Ar).

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 2.38-2.40 (m, 2H, H-4), 3.29-3.31 (m, 2H, H-5), 5.06 (s, 2H, H-2'), 5.14 (s, 2H, CH$_2$Ph), 5.89 (d, $J$ = 15.6 Hz, 1H, H-2'), 6.91 (ddd, $J$ = 7.5, 7.5, 15.6 Hz, 1H, H-3), 7.30-7.35 (m, 10H, Ar-H).
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\[ ^{13}\text{C NMR (75 MHz, CDCl}_3\text{): } \delta 32.6 (\text{C-4}), 39.5 (\text{C-5}), 66.2 (\text{C-2'}), 66.8 (\text{CH}_2\text{Ph}), 123.2 (\text{C-2}), 128.1, 128.2, 128.3, 128.5, 128.6 (\text{Ar-H}), 136.0 (\text{Ar-C}), 136.4 (\text{Ar-C}), 145.8 (\text{C-3}), 156.3 (\text{CONH}), 166.0 (\text{C-1}). \]

HRMS: \( m/z [\text{M+Na}^+] \) calcd for C\(_{20}\)H\(_{21}\)NO\(_4\)Na: 362.1368; found: 362.1376.

3.04 Benzyl-5-[(benzyloxy carbonyl)amino]-2,3-dihydroxypentanoate (48):

To a stirred solution of olefin 47 (0.563 g, 1.66 mmol) in acetone-water 8:1 v/v (9 mL), was added NMO (0.389 g, 3.32 mmol) and aq 1% OsO\(_4\) (2 mL). The mixture was stirred at room temp for 8 h. Na\(_2\)SO\(_3\) (3.2 g) in 5 mL water was added and the mixture was further stirred for 1 h. Concentrated on vacuum pump to remove acetone. EtOAc (30 mL) was added and the aq layer was extracted with EtOAc (3 × 20 mL). The combined organic layer was dried over anhyd Na\(_2\)SO\(_4\), concentrated and purified by column chromatography on silica gel (hexanes: EtOAc = 6:4) to give the rac-diol 48 (0.548 g, 90%) as a white semisolid.

IR (KBr): 3602-3041 (OH), 1735 (COO), 1700 cm\(^{-1}\) (CONH).

\[ ^{1}\text{H NMR (300 MHz, CDCl}_3\text{): } \delta 1.72-1.87 (2\text{m, 2H, H-4}), 3.17-3.48 (2\text{m, 4H, H-5 & OH}), 4.03 (\text{br d, 1H, H-3}), 4.13 (\text{br s, 1H, H-2}), 5.10 (\text{s, 3H, H-2'} & NH), 5.27 (\text{s, 2H, CH}_2\text{Ph}), 7.35-7.38 (\text{m, 10H, Ar-H}). \]

\[ ^{13}\text{C NMR (75 MHz, CDCl}_3\text{): } \delta 33.8 (\text{C-4}), 37.7 (\text{C-5}), 66.9 (\text{C-2'}), 67.6 (\text{OCH}_2\text{H}), 70.0 (\text{C-3}), 73.7 (\text{C-2}), 128.1-128.7 (\text{Ar-H}), 135.0 (\text{Ar-C}), 136.3 (\text{Ar-C}), 157.0 (\text{C-1'}), 172.9 (\text{COO}). \]

HRMS: \( m/z [\text{M+Na}^+] \) calcd for C\(_{20}\)H\(_{23}\)NO\(_6\)Na: 396.1423; found: 396.1407.
3.05 Preparation of Benzyl hydroxyl(2-oxo-1,3-oxazinan-6-yl) acetate (49):

\[
\begin{align*}
\text{HO} & \quad \text{COOCH}_2\text{Ph} \\
5' \quad 4' & \quad \text{Ni} \\
3' \quad 2' & \quad \text{O} \\
1' & \quad \text{N} \\
\end{align*}
\]

Triphenyl phosphate (0.621 g, 2.37 mmol) and diisopropyl azodicarboxylate (0.479 g, 2.37 mmol) was added to a stirred solution of diol 48 (0.736 g, 1.97 mmol) in dry toluene (10 mL) equipped with water condenser, further stirred for 1 h at room temp, and then refluxed at 110 °C for 15 h. The mixture was then concentrated to afford a paste which was dissolved in CHCl₃ (30 mL). The organic phase washed with H₂O (3 × 15 mL), and sat. NaHCO₃ (1 × 20 mL), dried over anhyd Na₂SO₄ and concentrated to afford the crude mixture which was purified by column chromatography on silica gel (MeOH/CHCl₃ = 1:9) to give a thick oily compound 49 (0.234 gm, 44.8%).

IR (neat): 3377 (OH), 1745 (COO), 1712 cm⁻¹ (CONH), 756 (Ar).

¹H NMR (300 MHz, CDCl₃): δ 1.83-1.87 & 2.01-2.11 (m, 3H, H-5' & OH), 3.25-3.33 (m, 2H, H-4'), 4.26 (br s, 1H, H-2), 4.63 (br d, 1H, H-6'), 5.20 (d, J = 12.0 Hz, 1H), 5.26 (d, J = 12.0 Hz, 1H), 6.75 (br s, NH), 7.35 (s, 5H, Ar-H).

¹³C NMR (75 MHz, CDCl₃): δ 22.4 (C-5'), 38.4 (C-4'), 67.7 (OCH₂), 72.2 (C-6'), 77.8 (C-2), 128.3, 128.5, 128.6 (Ar-H), 135.1 (Ar-C), 154.5 (C-2'), 171.3 (COO).


3.06 Preparation of Hydroxyl (2-oxo-1,3-oxazinan-6-yl) acetic acid (50):

\[
\begin{align*}
\text{HO} & \quad \text{COOH} \\
5' \quad 4' & \quad \text{O} \\
3' \quad 2' & \quad \text{N} \\
\end{align*}
\]
Benzyl hydroxyl(2-oxo-1,3-oxazinan-6-yl) acetate 49 (0.043 g, 0.16 mmol) in EtOH (10 mL) was stirred with 10% Pd/C (10 mg) under H₂ atmosphere for 8 h. The mixture was filtered off and then concentrated to give acetic acid derivative 50 as a thick liquid (0.021 g, 75%).

**¹H NMR (300 MHz, DMSO):** δ 1.82-1.84 (m, 2H, H-5'), 3.19 (m, 2H, H-4'), 4.06 (br s, 1H, H-1'), 4.51 (m, 1H, H-6'), 7.13 (br s, NH).

**¹³C NMR (75 MHz, DMSO):** δ 22.8 (C-5'), 35.6 (C-4'), 70.4 (C-6'), 77.9 (C-2), 153.4 (C-2'), 173.3 (COO).

**LCMS:** m/z [M+H]+ calcd for C₁₀H₁₀N₀₅: 176.05; found: 176.19.

### 3.07 Benzyl-5-[(benzyloxy carbonyl) amino]-2-tosyl-3-hydroxypentanoate (52):

To a round bottom flask, the 2,3-dihydroxy ester 48 (0.800 g, 2.15 mmol), CH₂Cl₂ (12 mL, 0.2 M solution in 2, 3-dihydroxy ester 48) and Et₃N (0.326 g, 3.22 mmol) were added. The flask was placed in an ice-water bath, allowed to equilibrate for 20 min and then p-toluenesulfonyl chloride (0.491 g, 2.58 mmol) was added in one portion. The flask was fitted with septum and placed in a refrigerator (0-5 °C) for 72 h. The mixture was then concentrated to afford a paste which was dissolved in CHCl₃ (40 mL). The organic phase washed with 1N HCl (3 × 15 mL), sat. NaHCO₃ (1 × 20 mL) and with brine (2 × 15 mL), dried over anhyd Na₂SO₄ and concentrated to afford the crude mixture which was purified by column chromatography on silica gel (hexanes: EtOAc = 7:3) to give the rac-monotosylate 52 as a white solid (0.888 g, 78.5), mp 89-90 °C.

**IR (KBr):** 3315 (OH), 1762 (COO), 1683 cm⁻¹ (CONH).

**¹H NMR (300 MHz, CDCl₃):** δ 1.64-1.86 (m, 2H, H-4), 2.17 (br s, 1H), 2.43 (s, 3H, CH₃), 3.27-3.46 (m, 2H, H-5), 4.15 (m, 1H, H-3), 4.92 (d, J = 3.0 Hz, 1H, H-2), 5.13 (s, 1H, H-3'), 5.27 (s, 1H, CH₃Ph), 7.24-7.36 (m, 12H, Ar-H), 7.79 (d, J = 8.4 Hz, 2H, Ar-H).
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$^{13}$C NMR (75 MHz, CDCl₃): δ 21.7 (CH₃), 33.2 (C-4), 37.4 (C-5), 67.0 (C-3'), 67.6 (OCH₂Ph), 69.1 (C-3), 79.8 (C-2), 128.1-129.8 (Ar-H), 132.8, 134.8, 136.3 (Ar-C), 145.2 (Ar-CSO₂), 157.3 (C-1'), 167.0 (C-1).


3.08 Benzyl-5-[(benzoyloxycarbonyl)amino]-2,3-epoxypentanoate (53):

Monotosylate 52 (0.888 g, 1.68 mmol) was added to stirred suspension of K₂CO₃ (0.466 g, 3.37 mmol) in DMF (2 mL) and further stirred for 5 h at room temp. Water (20 mL) was added to it and extracted in CHCl₃ (3 x 15 mL). The combined organic layer was dried over anhyd Na₂SO₄, concentrated and were purified by column chromatography on silica gel (hexanes: EtOAc = 7:3) to give the epoxide 53 as a colorless thick liquid (0.245 g, 41%).

IR (neat): 3300 (OH), 1730 (COO), 1690 cm⁻¹ (CONH).

$^1$H NMR (300 MHz, CDCl₃): δ 1.70-1.88 (m, 2H, H-4), 3.25-3.36 (m, 3H, H-5 & H-3), 3.56 (br d, 1H, H-2), 4.86 (br s, 1H, NH), 5.10 (s, 2H, CH₂Ph), 5.18 (d, J = 12.0 Hz, 1H, H-3'), 5.27 (d, J = 11.7 Hz, 1H, H-3'), 7.36-7.37 (m, 10H, Ar-H).

$^{13}$C NMR (75 MHz, CDCl₃): δ 27.8 (C-4), 38.2 (C-5), 52.3 (C-3), 55.7 (C-2), 66.7 (C-3'), 67.3 (OCH₂Ph), 128.1-129.7 (Ar-H), 135.0, 136.1 (Ar-C), 156.1 (C-1'), 167.9 (C-1).


3.09 Preparation of 5-Amino-2,3-epoxypentanoic acid (54):

Epoxide 53 (0.20 g, 0.56 mmol) in EtOH (10 mL) was stirred with 10% Pd/C (0.023 g) under H₂ atmosphere for 15 h. The mixture was filtered off and then concentrated to

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give a sticky liquid (found to be complex mixture). The white solid sticking to the
glass bottle of hydrogenator was manually separated and found to be 5-amino-2,3-
epoxypentanoic acid 54 (0.010 g, 14%).

\[ ^1 \text{H NMR (300 MHz, D}_2\text{O): } \delta \ 1.76-1.96 (m, 2H, H-4), 3.12-3.16 (m, 2H, H-5), 3.24 (m, 1H, H-3), 3.50 (d, J = 3.3 Hz, 1H, H-2). \]

\[ ^{13} \text{C NMR (75 MHz, D}_2\text{O): } \delta \ 25.7 (C-4), 36.9 (C-5), 53.8 (C-3), 54.9 (C-2), 174.6 (C-1). \]

3.10 Preparation of tert-Butyl (3-hydroxypropyl) carbamate (55):

The Boc\(_2\)O (5.83 g, 0.026 mol) was added drop wise to a stirred solution of 3-amino-
1-propanol 46 (1.744 g, 0.023 mol) in dry THF (40 mL) at 0 °C. Then Et\(_3\)N (5.882 g,
0.058 mol) was added drop wise to it. The reaction mixture was stirred at room temp
for 12 h. THF was removed under vacuum, water (30 mL) was added and extracted in
CH\(_2\)Cl\(_2\) (3 x 30 mL). Organic layer was washed with 5% aq HCl (2 x 20 mL), 5% aq
NaHCO\(_3\) (2 x 20 mL), sat. NaCl (20 mL) and then water (30 mL), dried over anhyd
Na\(_2\)SO\(_4\) and concentrated in vacuum. Purification of oily crude product by column
chromatography on silica gel (hexanes: EtOAc = 4:6) afforded tert-Butyl (3-
hydroxypropyl) carbamate 55 (2.929 g, 72 %) as a thick colorless liquid.

\[ \text{IR (neat): } 3612-3115 (\text{OH}), 1703 \text{ cm}^{-1} (\text{CO}). \]

\[ ^1 \text{H NMR (300 MHz, CDCl}_3\): } \delta \ 1.46 (s, 9H, 3xCH}_3\), 1.66-1.70 (m, 2H, H-2), 2.97 (br
s, 1H, OH), 3.30 (q, J = 6.0 Hz, 2H, H-1), 3.68 (t, J = 6.0 Hz, 2H, H-3), 4.79 (br s, 1H).

\[ ^{13} \text{C NMR (75 MHz, CDCl}_3\): } \delta \ 28.3 (CH}_3\), 34.4 (C-2), 37.0 (C-1), 59.7 (C-3), 79.6
(C-3'), 157.1 (C-1'). \]

\[ \text{HRMS: } m/z [M+Na]^{+} \text{ caled for C}_8\text{H}_{17}\text{NO}_3\text{Na: } 198.1106; \text{ found: } 198.1104. \]
3.11 Benzyl (2E)-5-[(tert-butoxycarbonyl)amino]pent-2-enoate (56):

To a magnetically stirred suspension of PCC (3.068 g, 14.2 mmol) and NaOAc (1.167 g, 14.2 mmol) in anhyd CH$_2$Cl$_2$ (40 mL) was added tert-Butyl (3-hydroxypropyl)carbamate 55 (1.556 g, 8.89 mmol) in anhyd CH$_2$Cl$_2$ (5 mL), followed by addition of (benzylxocarbonylmethylene)triphenyl phosphorane (4.014 g, 9.78 mmol) in one portion. The mixture was stirred at room temp for 7 h. Et$_2$O (50 mL) was added and the supernatant soln was decanted from the black granular solid. The combined organic solutions were filtered through a short bed of celite and the filtrate obtained was evaporated to give a residue that was purified by column chromatography on silica gel (hexanes: EtOAc = 7:3) to give pure benzyl (2E)-5-[(tert-butoxycarbonyl)amino]pent-2-enoate 56 (1.955, 72%) as a colorless viscous liquid.

**IR (neat):** 3373 (NH), 1712 (COO), 1693 cm$^{-1}$ (CONH).

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.45 (s, 9H, 3×CH$_3$), 2.42 (q, $J = 6.6$ Hz, 2H, H-4), 3.28 (t, $J = 6.6$ Hz, 2H, H-5), 4.62 (br s, 1H, NH), 5.20 (s, 2H, OCH$_2$Ph), 5.95 (d, $J = 15.6$ Hz, 1H, H-2), 6.96 (ddd, $J = 6.9$, 7.2, 15.6 Hz, 1H, H-3), 7.38-7.39 (m, 5H, Ar-H).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 28.3 (CH$_3$), 32.9 (C-4), 39.0 (C-5), 66.2 (CH$_2$Ph), 79.6 (C-3'), 123.0 (C-3), 128.3, 128.5, 128.6 (Ar-H), 136.0 (Ar-C), 146.1 (C-2), 155.8 (C-1'), 166.0 (C-1).

**HRMS:** $m/z$ [M+Na]$^+$ calcd for C$_{17}$H$_{23}$NO$_4$Na: 328.1525; found: 328.1518.

3.12 Benzyl-5-[(tert-butoxycarbonyl)amino]-2,3-dihydroxypentanoate (57):
Chapter 3: Wittig Approach and Sharpless Asymmetric Dihydroxylation Reaction
towards the Synthesis of 3-Hydroxy-L-proline and Tedanalactam

To a stirred solution of olefin 56 (0.736 g, 2.41 mmol) in acetone-water 8:1 v/v (18 mL), NMO (0.566 g, 4.83 mmol) and aq 1% OsO₄ (2 mL) was added. The mixture was stirred at room temp for 8 h. Na₂SO₃ (3.2 gm) in 5 mL water was added and the mixture was further stirred for 1 h. Concentrated on vacuum pump to remove acetone. EtOAc (30 mL) was added and aq layer was extracted with EtOAc (3 × 20 mL). The combined organic layer was dried over anhyd Na₂SO₄, concentrated and purified by column chromatography on silica gel (hexanes: EtOAc = 6:4) to give the diol 57 (0.679 g, 83%) as a white semisolid.

IR (KBr): 3602-3041 (OH), 1749 (COO), 1680 cm⁻¹ (CONH).

¹H NMR (300 MHz, CDCl₃): δ 1.43 (s, 9H, 3x CH₃), 1.64-1.69 and 1.81-1.91 (2m, 2H, H-4), 2.84 (br s, 2H, OH), 3.15-3.20 and 3.38-3.48 (2m, 2H, H-5), 4.0-4.03 (m, 1H, H-3), 4.13 (d, J = 2.4 Hz, 1H, H-2), 5.26 (s, 3H, CH₂Ph & NH), 7.37 (s, 5H, Ar-H).

¹³C NMR (75 MHz, CDCl₃): δ 28.3 (CH₃), 34.1 (C-4), 37.2 (C-5), 67.6 (OCH₂Ph), 69.7 (C-3), 73.8 (C-4), 79.8 (C-3'), 128.3, 128.5, 128.6 (Ar-H), 135.1 (Ar-C), 157.0 (C-1'), 173.1 (C-1).


3.13 Benzyl-5-[(tert-butoxycarbonyl)amino]-2-tosyl-3-hydroxypentanoate (58):

To a round bottom flask, the 2, 3-dihydroxy ester 57 (0.600 g, 1.77 mmol), [15 mL CH₂Cl₂, 0.2 M solution in 2,3-dihydroxy ester (57)] and Et₃N (0.268 g, 2.85 mmol) were added. The flask was placed in an ice-water bath, allowed to equilibrate for 20 min and then p-toluenesulfonyl chloride (0.371 g, 1.94 mmol) was added in one portion. The flask was fitted with septum and placed in a refrigerator (5 °C) for 72 h. The mixture was then concentrated to afford a paste which was dissolved in CHCl₃ (40 mL). The organic phase washed with 1N HCl (3 × 15 mL), sat. NaHCO₃ (1 × 20 mL) and with brine (2 × 15 mL), dried over anhyd Na₂SO₄ and concentrated to afford
the crude mixture which was purified by column chromatography on silica gel (hexanes: EtOAc = 6:4) to give the rac-monotosylate 58 as a white solid (0.575 g, 66), mp 88-89 °C.

**IR (KBr):** 3621-3140 (OH), 1764 (COO), 1685 cm⁻¹ (CONH).

**¹H NMR (300 MHz, CDCl₃):** δ 1.42 (s, 9H, 3×CH₃), 1.64 (m, 2H, H-4), 2.44 (s, 3H, CH₃), 3.16 (m, 1H, H-5), 3.42 (m, 2H, H-5 & OH), 4.13-4.17 (m, 1H, H-3), 4.75 (br s, 1H, NH), 4.95 (d, J = 3.3 Hz, 1H, H-2), 5.13 (s, 2H, CH₂Ph), 7.26-7.36 (m, 7H, Ar-H), 7.80 (d, J = 8.4 Hz, 2H, Ar-H).

**¹³C NMR (75 MHz, CDCl₃):** δ 21.7 (CH₃), 28.3 (CH₃), 33.5 (C-4), 36.7 (C-5), 67.5 (CH₂Ph), 68.7 (C-3), 79.8 (C-2), 79.9 (C-3’), 128.2, 128.3, 128.4, 128.5, 128.7 (Ar-H), 132.9 (Ar-C), 134.8 (Ar-C), 145.1 (Ar-C), 157.1 (C-1’), 167.0 (C-1).

**HRMS:** m/z [M+Na]⁺ calcd for C₂₄H₃₁NO₈SNa: 516.1668; found: 516.1658.

### 3.14 Preparation of 3,4-Epoxy-2-piperidone (61):

To a stirred solution of monotosylate 58 (0.501 g, 1.02 mmol) in CH₂Cl₂ (12 mL) was added TFA (3 mL) at 0 °C. The mixture was stirred at room temp for 2 h and then concentrated under vacuum. Aq. NH₃ (6 mL) was added to the resultant residue in CH₂Cl₂ (10 mL) at 0 °C and stirred for 2 h at room temp. The mixture was diluted with EtOAc (20 mL), washed with aq. NH₄Cl (2 × 15 mL), brine (1 × 15 mL), dried over anhyd Na₂SO₄, concentrated and was purified by column chromatography on silica gel (MeOH: CHCl₃ = 1:19) to give the tedanalactam 61 (0.084 g, 74%) as a pale yellow oil.

**IR (neat):** 3268 (NH), 1680 cm⁻¹ (CO).

**¹H NMR (300 MHz, CDCl₃):** δ 2.05 (dd, J = 6.0, 6.6, 12.3 Hz, 1H, H-5), 2.34-2.90 (m, 1H, H-5), 3.06 (dd, J = 6.0, 6.6, 12.3 Hz, 1H, H-6), 3.34 (dd, J = 4.2, 12.3 Hz, 1H, H-4), 3.42 (m, 1H, H-6), 3.63 (br s, 1H, H-3), 6.18 (br s, 1H, NH).
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$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 23.5 (C-5), 35.2 (C-6), 50.6 (C-4), 53.1 (C-3), 169.1 (C-2).

HRMS: $m/z$ [M+Na]$^+$ calcd for C$_5$H$_7$NO$_2$Na: 136.0351; found: 136.0374.

Section B: Synthesis of (-) and (+)-Tedanalactam

3.15 General Procedure for Dihydroxylation of Alkene (56) with a Chiral Catalyst:

A mixture of K$_3$Fe(CN)$_6$ (2.731 g, 8.36 mmol), K$_2$CO$_3$ (1.142 g, 8.36 mmol) and either (DHQ)$_2$PHAL (0.108 g, 0.139 mmol, AD-mix a) or (DHQD)$_2$PHAL (5 mol%, AD-mix β) were stirred in t-BuOH (10 mL) and H$_2$O (10 mL), after which OsO$_4$ (0.7 mL, 1% aq OsO$_4$ soln.) was added and further stirred for 30 min at room temp. CH$_3$SO$_2$NH$_2$ (0.264 g, 2.78 mmol) was added and the mixture was cooled to 0 °C. Olefin 56 (0.850 g, 2.78 mmol) was added and the heterogeneous slurry was stirred vigorously for 15 h at 0 °C and then 8 h at room temp. Na$_2$SO$_3$ (3.2 g) was added and the mixture was further stirred for 1 h. EtOAc (30 mL) was added and aq layer was extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with 5% KOH (2 x 20 mL), dried over anhyd Na$_2$SO$_4$, concentrated and purified by column chromatography on silica gel (hexanes: EtOAc = 6:4) to give the corresponding diol 66 or 69. IR, $^1$H and $^{13}$C NMR data for 66 and 69 were identical with rac-diol 57 described above in experimental section of this chapter (Exp. No. 3.12).

3.15a Benzy1(2R,3S)-5-{(tert-butoxycarbonyl)amino}-2,3-dihydroxypentanoate (66)

Product 66 obtained as white semisolid (0.730 g, 77% yield) using AD-mix a; [$\alpha$]$^{31}$D - 3.93 (c 0.891, CHCl$_3$); HPLC of diol 66: 91% ee (Rt = 16.0 min for the major enantiomer, Rt = 12.5 min for the minor one, column: Chiralpak AD, UV detector, 254 nm, 20% 2-propanol in n-hexane: flow rate 0.7 mL/min).
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3.15b Benzyl (2S,3R)-5-[(tert-butoxycarbonyl)amino]-2,3-dihydroxypentanoate (69)

Product 69 (0.444 g, 81%) as a white semisolid was obtained from olefin 56 (0.492 g) using AD-mix β; [α]$_{D}^{3}$ +4.16 (c 0.721, CHCl$_{3}$); HPLC of diol 69: 94% ee (Rt = 11.8 min for the major enantiomer, Rt = 17.2 min for the minor one, column: Chiralpak AD, UV detector, 254 nm, 20% 2-propanol in n-hexane: flow rate 0.7 mL/min).

3.16 General Procedure for Monotosylation of Diol (66 & 69):
The procedure is identical as described in experimental part of section A of this chapter for preparation of rac-monotosylate 58. IR, $^{1}$H and $^{13}$C NMR data for 67 and 70 were identical with rac- 58 described above (Exp. No. 3.13).

3.16a Benzyl (2R,3S)-5-[(tert-butoxycarbonyl)amino]-2-tosyl-3-hydroxypentanoate (67):

Product 67 (0.609 g, 65%) was obtained from diol 66 (0.645 g) as a white solid; mp 89-90 °C; [α]$_{D}^{3}$ -13.33 (c 0.150, CHCl$_{3}$); HPLC of monotosylate 67: 91% ee (Rt = 28.1 min for the major enantiomer, Rt = 26.1 min for the minor one, column: Chiralpak AD, UV detector, 254 nm, 10% 2-propanol in n-hexane: flow rate 1.0 mL/min).

3.16b Benzyl (2S,3R)-5-[(tert-butoxycarbonyl)amino]-2-tosyl-3-hydroxypentanoate (70):
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Product 70 (0.437 g, 65%) was obtained from diol 69 (0.460 g) as a white solid; mp 88-89 °C; \([\alpha]^{11}_D +13.42\) (c 0.149, CHCl₃); HPLC of monotosylate 70: 94% ee (Rt = 30.1 min for the major enantiomer, Rt = 27.5 min for the minor one, column: Chiralpak AD, UV detector, 254 nm, 10% 2-propanol in n-hexane: flow rate 1.0 mL/min).

3.17 General Procedure for Preparation of Tedanalactam (68 & 71):
The procedure is identical as described in experimental part of section A of this chapter for preparation of rac-tedanalactam 61. IR, \(^1\)H and \(^13\)C NMR data for 68 and 71 were identical with rac- 61 described above (Exp. No. 3.14).

3.17a Preparation (3S,4S)-epoxy-2-piperidone [(−)-tedanalactam] (68)

Product 68 (0.092 g, 77% yield) was obtained from monotosylate 67 (0.521 g) as a yellow color oil; \([\alpha]^{30}_D -7.60\) (c 0.130, MeOH) [lit\(^25\) \([\alpha]^{30}_D -8.90\) (c 0.3, MeOH)]; HPLC of tedanalactam 68: 91% ee (Rt = 14.5 min for the major enantiomer, Rt = 12.7 min for the minor one, column: Chiralpak AD, UV detector, 206 nm, 10% 2-propanol in n-hexane: flow rate 1.0 mL/min).

3.17b Preparation (3R,4R)-epoxy-2-piperidone [(+)-tedanalactam] (71):

Product 71 (0.031 g, 72% yield) was obtained from monotosylate 70 (0.189 g) as a yellow color oil; \([\alpha]^{30}_D +8.47\) (c 0.118, MeOH); HPLC of tedanalactam 71: 94% ee (Rt = 10.9 min for the major enantiomer, Rt = 12.6 min for the minor one, column: Chiralpak AD, UV detector, 206 nm, 10% 2-propanol in n-hexane: flow rate 1.0 mL/min).
Spectra

Figure 4. $^1$H NMR spectrum of 45

Figure 5. $^1$H NMR spectrum of 47
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Figure 6. $^1$H NMR spectrum of 48

Figure 7. $^{13}$C NMR and DEPT spectrum of 48
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Figure 8. $^1$H NMR spectrum of 49

Figure 9. $^{13}$C NMR & DEPT spectrum of 50
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Figure 10. $^1$H NMR spectrum of 52

Figure 11. $^1$H NMR spectrum of 53
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![Figure 12. $^1$H NMR spectrum of 55](image)

![Figure 13. $^1$H NMR spectrum of 56](image)
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Figure 14. $^1$H NMR spectrum of 57

Figure 15. $^1$H NMR spectrum of 58

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Figure 16. $^1$H NMR spectrum of 61

Figure 17. $^{13}$C NMR & DEPT spectrum of 61
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Figure 18. HPLC Chromatograph of diol 57, 66, 69

File name: Alpha diol(SAD)017.CH1
Control Method: NONE
#  Name  RT  Area[μV.Sec]  %Area
1  Beta  diol  12.583  104812.497  4.48
2  Alpha  diol  16.008  2234133.750  95.52
Total Area of Peak = 2338946.247 [μV.Sec]

File name: diol012.CH1
Control Method: NONE
#  Name  RT  Area[μV.Sec]  %Area
1  beta  12.558  1537905.385  50.20
2  Alpha  16.392  1525393.523  49.80
Total Area of Peak = 3063298.908 [μV.Sec]

File name: Beta diol(SAD)019.CH1
Control Method: NONE
#  Name  RT  Area[μV.Sec]  %Area
1  Beta  diol  11.833  1139780.293  96.88
2  Alpha  diol  17.267  36679.500  3.12
Total Area of Peak = 1176459.793 [μV.Sec]
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Figure 19. HPLC Chromatograph of Tedanalactam 61, 68, 71

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Control Method: NONE

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References:
(6) (a) Sung, M. L.; Fowden, L. Phytochemistry 1968, 7, 2061. (b) Szymanovicz, G.; Mercier, O.; Randoux, A.; Borel, J. P. Biochim. 1978, 60, 499.
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