Chapter 1

Synthetic Studies towards Pyrrolizidine Alkaloid, (S)-pyrrolam A
Synthetic Studies towards Pyrrolizidine Alkaloid, (S)-Pyrrolam A

Introduction to Pyrrolizidine Alkaloids:

Pyrrolizidine alkaloids (PAs) are a large family of natural products bearing an azabicyclo[3.3.0]octane structural core (Figure 1). PAs are widely distributed in nature and endowed with a vast array of biological and pharmacological activities.\(^1\)

![Figure 1. Structure core of PAs](image)

Most of the PAs have been isolated from flowering and leguminous plants, and some have been found in ants, moths, frogs and butterflies.\(^2\) The classification of pyrrolizidine alkaloids is complicated due to their structural diversities.

![Figure 2. Various PAs containing Necine bases](image)

The vast majority of the PAs are \(\Delta^{1,2}\)-unsaturated-1-methylpyrrolizidine functionalized by hydroxyl or ester moieties, where in the nitrogenous alcohol part are known as necines and the esterifying acid are called the necinic acid components. The necine base of pyrrolizidine alkaloids (Figure 2) exemplified by retronecine, supinidine\(^3\) and...
crotanicine\(^4\) shows acute hepatotoxicity, whereas intermedine, indicine-N-oxide has antitumour activity.\(^5\)

In 1990, four structurally related pyrrolizidinones, namely, pyrrolam A-D (Figure 3) were isolated from \textit{Streptomyces olivaceus}.\(^6\) Among them (\(R\))-pyrrolam A, a structurally simple pyrrolizidone has attracted considerable attention, both due to its bioactivity of causing damage to the fertilized eggs at low concentration and the presence of double bond, which is an important factor to the hepatotoxic, mutagenic and carcinogenic nature\(^{1d,e}\) of various PAs.

\[
\begin{align*}
\text{R} = & \text{OCH}_3 & \text{Pyrrolam B} \\
\text{R} = & \text{OH} & \text{Pyrrolam C} \\
\text{R} = & \text{OCH(CH}_3\text{)OEt} & \text{Pyrrolam D} \\
\text{R} = & \text{H} & \text{Dehydropyrrolam} \\
\end{align*}
\]

\textbf{Figure 3. Examples of pyrrolams}

From a biosynthetic point of view, the necine unit of these PAs is known to be derived from L-ornithine\(^7\) as depicted in Figure 4.

\[
\text{Figure 4. Biosynthetic route of necine unit of PAs from ornithine}
\]

As sugar-mimics, many of the polyhydroxylated PAs have been extensively studied for their potent glycosidase inhibitory activity, which makes them good candidates as new drugs for the treatment of many diseases such as cancer, viral infections and diabetes.\(^8\) This fact, together with their functional stereochemical complexities has

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prompted the development of variety of synthetic routes, from which number of synthetic analogues have been prepared. Not surprisingly, a vast body of research has been conducted regarding the syntheses of these alkaloids. Due to its presence as a core unit in necine bases and the potent biological activities associated with the double bond in strained ring, pyrrolam A has been the focus of extensive synthetic efforts amongst the pyrrolams. Syntheses in this field have followed two distinct approaches. The chiral pool approach exploits proline as a starting material, which has an advantage of being cheap and also exists in both the enantiomeric forms. The other approach involves non-chiral starting materials. The work presented in this chapter describes approaches towards the syntheses of (S)-pyrrolam A, a typical PAs unit.

Review of Literature:

Various synthetic methods for the naturally occurring (R)-pyrrolam A, and its enantiomer have been reported. Most of these approaches start with proline as a starting material. Reported synthetic routes are discussed below.

a) Chiral pool methods
b) The asymmetric method

a) Chiral pool methods:

Aoyagi et al. (1996, Scheme 1) 

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Reduction of d-proline with LAH, followed by cyclization of amino alcohol using diethyl carbonate provided bicyclic oxazolidinone 3, which, when treated with lithium phenyl acetylide, furnished the N-substituted alcohol 4. Conversion of alcohol 4 to bromo compound 5 using NBS/PPh₃ system followed by treatment with SmI₂ provided cyclized pyrrolidone 6. Treatment of 6 with O₃ gave ketoamide 7, which on trifluromethane sulfonylation, provided triflate 8. Reduction of 8 with Bu₃SnH in presence of Pd (PPh₃)₄ produced (R)-pyrrolam A 1 (Scheme 1).

Murray et al. (1996, Scheme 2)¹¹

\[
\begin{align*}
\text{9} & \xrightarrow{\text{LDA or LHMDS}} \text{10} & \xrightarrow{\text{NaBH₄, EtOH, rt}} \text{11} \\
\text{9} & \xrightarrow{\text{MsCl, NEt₃, CH₂Cl₂, 0 °C(2h), rt (3h)}} \text{12} & \xrightarrow{\text{Et₃N, CHCl₃, reflux, 5h}} \text{(-)-1}
\end{align*}
\]

This approach involves cyclization of N-methoxy-N-methyl amide 9 to dione 10, which, on reduction with NaBH₄, provided alcohol 11. Treatment of alcohol 11 with MsCl gave mesylate 12 which on refluxing with NEt₃ in CHCl₃ afforded (S)-pyrrolam A 1.

Giovenzana et al. (1997, Scheme 3)¹²

\[
\begin{align*}
\text{13} & \xrightarrow{(\text{Boc})₂O, \text{CH₂Cl₂, rt}} \text{14} & \xrightarrow{1) \text{TEMT, TPP, DEAD, 2) TFA, CH₂Cl₂, rt}} \text{15} \\
\text{16} & \xrightarrow{12N\text{HCl, reflux}} \text{17} & \xrightarrow{1) \text{LDA, THF (-78 °C), 2) PhSeCl then H₂O₂}} \text{17}
\end{align*}
\]

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Giovenzana et al. have utilized the dehydrative alkylation of protected (R)-prolinol 13 with methanetricarboxylate under Mitsunobu condition to give N-Boc triester. Furthermore, triester was treated with TFA, followed the addition of excess of 12N HCl provided the two carbon homologated L-proline 16. Subsequent cycloamidation using HMDS, and installation of the double bond using selenyl chemistry provided (R)-pyrrolam A 1.

Arisawa et al. (1997 and 2000, Scheme 4)\(^{13}\)

L-proline 2 was converted to methyl-N-Boc-L-prolinate via couple of steps. This was further converted to aldehyde 18 by reduction with DIBAL. Wittig olefination followed by deprotection furnished pyrrolidine which, on acylation with unsaturated acid in the presence of diethylphosphorocyanidate gave chiral diene 20. Chiral diene was subjected to RCM using Grubbs catalyst to give (S)-pyrrolam A 1. The low yield observed in this approach is attributed to the instability of the product under the reaction conditions used.

Schobert et al. (2007, Scheme 5)\(^{14}\)

Benzyl prolinate 21 prepared from D-proline was reacted with the polymer supported cumulated ylide to give the corresponding tetramate. Hydrogenolytic debenzylation furnished dione 23 which, on subsequent reduction using NaBH\(_4\), followed by mesylation, gave sulfonate. Refluxing of the sulfonate with Et\(_3\)N afforded (R)-pyrrolam A 1.
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(Huang et al. (1999, Scheme 6)\textsuperscript{15a}

(S)-Malic acid 25 was converted to (S)-malimide 26 via one-pot procedure reported by Louwrier et al.\textsuperscript{15b} Malimide 26 was subjected to $O$-protection using benzyl bromide to give benzyl ether 27. Reaction of compound 27 with 3-benzyloxy propyl magnesium bromide provided hydroxyl lactam 28, which on reduction with excess of triethylsilane, gave pyrrolidone 29. Selective removal of benzyl group by hydrogenation followed by ditosylation using TsCl, and oxidative N-deprotection using CAN provided ditosylated lactam 31. Finally, base-induced cyclization using NaH provided (R)-pyrrolam A 1.
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b) Asymmetric method:

Watson et al. (2004, Scheme 7)\(^{16}\)

\[
\begin{array}{c}
\text{N} \\
\text{H} \\
\text{32} \\
\end{array}
\xrightarrow{(\text{Boc})_2\text{O}, \text{DMAP}}
\begin{array}{c}
\text{N} \\
\text{Boc} \\
\text{33} \\
\end{array}
\xrightarrow{1)} (-)-\text{sparteine}, \text{sec}-\text{BuLi} (-78^\circ \text{C})
\xrightarrow{2)} \text{CuCN.2LiCl}
\xrightarrow{3)} \text{ICH=CHCOOEt} (-78^\circ \text{C})
\begin{array}{c}
\text{H} \\
\text{34} \\
\end{array}
\]

Watson et al. have utilized α-(N-carbamoyl)alkylcuprate methodology to produce an efficient synthesis of (R)-pyrrolam A. Pyrrolidine amine 32 on protection gave N-Boc carbamate, which was converted to stereogenic organolithium reagent by asymmetric deprotonation. Organolithium reagent was treated with CuCN.2LiCl to give lithium dialkylcuprate reagent, which gave vinylation product 34 upon quenching with (Z)-3-iodopropenate. N-Boc deprotection of 34 followed by cyclization in one-pot using trimethylsilyl chloride (methanolic HCl) afforded (R)-pyrrolam A 1.

Present Work:

We visualized two different approaches for the synthesis of (S)-pyrrolam A. The first using \textit{in situ} oxidation-intermolecular Wittig reaction and the second via \textit{in situ} oxidation-intramolecular Wittig reaction as depicted in Scheme 8. The two approaches are described in two different sections: Section A and Section B.

\[
\text{Scheme 8. Synthetic strategies of (S)-pyrrolam A}
\]
Section A: Domino Oxidation-intermolecular Wittig Approach to (S)-Pyrrolam A

Objectives:

Most of the syntheses of pyrrolam A as described above are either multi-steps in nature or gives a low overall yield of the desired compound. The objective of the present study is to explore the chemistry of domino oxidation-intermolecular Wittig reaction using PCC/NaOAc, a protocol developed in our laboratory. Further to demonstrate the synthetic utility of our methodology, and to explore its application to the synthesis of the pyrrolizidine alkaloids, the synthetic studies towards (S)-pyrrolam A were investigated. The envisaged strategy is depicted in Scheme 9.

**Scheme 9.** Reagents and conditions: a) LiAlH₄; b) Benzyl chloroformate; c) PCC/NaOAc, CH₂Cl₂, Ph₃P=COOEt; d) H₂, Pd/C; e) LDA, PhSeCl; f) H₂O₂, NaOH

Results and Discussion:

It was visualized that dehydropyrrolam 38 is a key intermediate in the synthesis of pyrrolam A 1 (Scheme 9). Further, dehydropyrrolam 38 could be very easily prepared from N-protected(pyrrolidine) acrylate in one-pot via reduction and cycloamidation reaction, which in turn could be obtained using one-pot oxidation-homologation protocol, developed in our our laboratory using PCC/NaOAc and phosphorane combination. This method would have advantages over the reported method described in Scheme 3, in terms of lesser number of steps, and avoiding the preparation of the labile prolinal intermediate. Thus, the synthesis started from L-proline 2, which on reduction using LAH by a reported method, gave the (S)-prolinol.
35 in 88% yield. The IR spectrum of prolinol 35 showed a broad band in the region 3600-3300 cm\(^{-1}\), confirming the presence of the OH and NH functionality.

The amine group of (S)-prolinol 35 was protected using CbzCl in presence of K\(_2\)CO\(_3\) at 0 °C to give N-benzyloxycarbonyl prolinol 36 in 78% yield. The IR spectrum of 36 showed a band at 3600 cm\(^{-1}\) confirming the presence of OH functionality, and a band at 1700 cm\(^{-1}\) corresponding to carbamate functionality. The \(^1\)H NMR spectrum of 36 (Figure 5) showed a multiplet at \(\delta\) 1.45-2.05 integrating for four protons of CH\(_2\)CH\(_2\) fragment of the pyrrolidine ring. The multiplet at \(\delta\) 3.36-3.39 integrating for four protons indicated the presence of methylene attached to the nitrogen of amide functionality and hydroxyl group, whereas the multiplet at \(\delta\) 4.01 (1H) indicated the presence of CH attached to the nitrogen of amide group. The methylene protons of OCH\(_2\)Ph group appeared as a singlet at \(\delta\) 5.15 (2H), whereas the five protons of the aromatic ring were seen at \(\delta\) 7.26-7.37 as a multiplet. Further the structure 36 was confirmed by \(^13\)C NMR and DEPT experiments, and its spectral properties were in agreement with the literature values.\(^{19}\)

The N-benzyloxycarbonyl prolinol 36 obtained was treated with PCC/NaOAc (2 equiv each) and the stable Wittig reagent (ethoxycarbonylmethylene) triphenylphosphorane (1.5 equiv) to give 37 as colorless viscous liquid in 76% yield, having \([\alpha]_D^{27}\) -42.55 (c 0.094, CHCl\(_3\)). Its IR spectrum showed a strong band at 1716 cm\(^{-1}\) confirming the presence of ester functionality in conjugation with double bond, whereas the strong band at 1708 cm\(^{-1}\) indicated the presence of carbamate group. The \(^1\)H NMR spectrum of 37 (Figure 6) showed a triplet at \(\delta\) 1.30 (\(J = 7.0\) Hz) integrating for three protons which could be assigned to methyl of OCH\(_2\)CH\(_3\) group. The two multiplets at \(\delta\) 1.75-1.90 and \(\delta\) 2.01-2.12 integrating for four protons indicated the presence of CH\(_2\)CH\(_2\) fragment of the pyrrolidine ring, whereas a multiplet at \(\delta\) 3.39-3.76 integrating for two protons suggested the presence of methylene attached to nitrogen of the amide group. The quartet at \(\delta\) 4.20 (\(J = 7.0\) Hz) indicated the presence of methylene of OCH\(_2\)CH\(_3\). The CH proton attached to nitrogen of amide functionality appeared as multiplet at \(\delta\) 4.47-4.54. A doublet integrating for two protons was seen at \(\delta\) 5.04 [5.17] (\(J = 12.6\) Hz), which could be due to the benzylic methylene of the Cbz
The doublets at δ 5.76 [5.86] (J = 15.4 Hz) was seen for one proton whereas a double doublets at δ 6.80 [6.84] (J = 5.6, 15.4 Hz) for another proton. These two protons should be the olefinic protons of the unsaturated ester group with the former being α and the later β—proton. Further, coupling constant confirms the formation of exclusively trans olefin during the Wittig reaction. Due to the presence of rotameric structure at room temperature, the signals for the olefinic protons were seen at two places. A multiplet in aromatic region at δ 7.28-7.35 (5 protons) confirmed the presence aromatic ring of Cbz group. In 13C NMR spectrum (Figure 7), two olefinic carbon peaks appeared at δ 120.8 and δ 147.4 [147.8] respectively. The α,β—unsaturated ester carbonyl showed a peak at δ 166.3 and benzyloxy carbonyl appeared at δ 154.7. Further the structure 37 was confirmed by DEPT experiment indicating the multiplicities of carbon signals, and recording mass spectrum, which showed [M+Na]+ peak at m/z 326.1361 for C17H21NO4Na.

Scheme 10. Reagents and conditions: a) PCC, CH2Cl2, rt, 64%; b) Ph3P=CHCOOEt, CHCl3, rt, 7h, 66% (42% for 2 steps)

In order to check the efficiency of our domino strategy, we also prepared α,β—unsaturated ester [N-benzyloxy carbonyl(pyrrolidine) acrylate] 37 via two step strategy (Scheme 10), wherein N-benzyloxy carbonyl prolinol 36 on oxidation using PCC gave N-benzyloxy carbonyl prolinol 40 having [α]D 27 -60.1 (c 0.521, MeOH) [lit [α]D 26 -63.1 (c 1.44, MeOH)] in 64% yield. Further, the reaction of prolinol 40 with (ethoxycarbonylmethylene)triphenyl phosphorane gave corresponding α,β—unsaturated ester 37 in 66% yield. It was observed that when reaction was carried out in two separate steps, the ester 37 was obtained in only 42% overall yield (76% yield for our domino strategy) with increase in one more step for purification of aldehyde using

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column chromatography. This demonstrates the advantage of the one-pot reaction. The ester 37 was then subjected to catalytic hydrogenation (10% Pd/C, H₂) for the expected reductive cyclization. However, we obtained an uncyclized amine intermediate wherein reduction of double bond took place together with concomitant deprotection. The expected one-pot cyclization did not take place even after carrying out the reaction at higher temperature (70 °C). Hence, the amine intermediate, without purification, was refluxed with the catalytical amount of sodium ethoxide in EtOH to give (S)-dehydroppyrolam 38 as pale yellow oil in 67% yield and having \([\alpha]_D^{27} -20.49\) (c 0.244, CHCl₃) [lit\(^6\) \([\alpha]_D^{20} +23.6\) (c 1.00, CHCl₃) for (R)-dehydroppyrolam].

![Figure 5. Numbering of 38 for NMR description](image)

The IR spectrum of 38 showed a band at 1670 cm\(^{-1}\) corresponding to amide functionality. The \(^1\)H & \(^{13}\)C NMR spectra (Figure 8) of dehydroppyrolam 38 are described in table 1.

**Table 1. NMR spectrum description of dehydroppyrolam 38**

<table>
<thead>
<tr>
<th>(^1)H NMR spectrum of 38</th>
<th>(^{13})C NMR of 38</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.32 (m)</td>
<td>1H H-6</td>
</tr>
<tr>
<td>1.73 (m), 2.3 (m)</td>
<td>2H H-4</td>
</tr>
<tr>
<td>1.96-2.28 (m)</td>
<td>3H Two H-7 &amp; one H-6</td>
</tr>
<tr>
<td>2.44 (ddd, (J = 1.52, 1.56, 1.60) Hz)</td>
<td>1H H-3</td>
</tr>
<tr>
<td>2.75 (m)</td>
<td>1H H-3</td>
</tr>
<tr>
<td>3.06 (m), 3.56 (ddd, (J = 3.9, 7.82, 7.88) Hz)</td>
<td>2H H-8</td>
</tr>
<tr>
<td>3.90 (m)</td>
<td>1H H-5</td>
</tr>
</tbody>
</table>
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The multiplicities of carbon signals were determined from DEPT experiment. Further structure 38 was confirmed by HRMS which showed [M+H]^+ peak at m/z 126.0899 for C_7H_{12}NO.

In order to complete the total synthesis of (S)-pyrrolam A 1, we followed a method reported by Giovenzana et al.\textsuperscript{12} for the installation of the double bond in regioselective manner. Towards this end, (S)-dehydropyrrolam 38 was first treated with lithium diisopropylamide at -78 °C and then with phenylselenyl chloride followed by H_2O_2 at 0 °C to afford a yellow colored oily compound. Attempted purification using silica gel column chromatography gave pyrrolam C 43 instead of pyrrolam A 1. Its IR spectrum showed a broad band at 3400 cm\(^{-1}\) indicating the presence of hydroxyl group and a band at 1678 cm\(^{-1}\) indicated the presence of the amide carbonyl functionality. The \(^1\)H NMR spectrum (Figure 9) showed a multiplet at \(\delta\) 1.58-1.65 integrating for one proton of CH\(_2\) (H-7). A multiplet in the region \(\delta\) 2.05-2.43 integrating for six protons was attributed to four protons of two CH\(_2\) (H-4, H-6) and one proton each of CH\(_2\) (H-3, H-7). The other proton of CH\(_2\) (H-3) appeared as a multiplet at \(\delta\) 2.87. The two multiplets at \(\delta\) 3.14-3.20 and 3.38-3.47 integrating for two protons were attributed to CH\(_2\) (H-8). The \(^13\)C NMR spectrum (Figure 10) showed a peak at 174.7 (C-2) corresponding to amide carbonyl. The disappearance of peak at \(\delta\) 62.1 (C-5) of dehydropyrrolam and appearance of a new peak at \(\delta\) 97.7 indicated the presence of the carbon attached to hydroxyl group (C-5) in pyrrolam C 43. Further, the assigned structure 43 was confirmed by recording the multiplicities of carbon signals from DEPT 135 spectrum. The spectral properties (mentioned above) were in close agreement with the literature values.\textsuperscript{16} Hence it was concluded that our attempted purification led to the rearrangement of pyrrolam A to pyrrolam C on silica gel column as depicted in Scheme 11.

![Scheme 11. Rearrangement of pyrrolam A 1 to pyrrolam C 43.](image-url)
1.15-1.12 (m, 1H) 1.72-2.04 (m, 3H) 3.40-3.49 (ddd, J = 2.0, 6.0, 7.8 Hz, 2H) 
2.89-2.97 (m, 1H) 2.15-2.25 & 2.30-2.38 (m, 2H) 3.90 (br d, 1H) 
7.21-7.63 (m, 5H)

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The major drawback in this strategy was the requirement of purification of reaction mixture through a short column of silica, to remove the unreacted selenyl chloride from the pyrrolam A, which was not particularly stable on silica gel. Our such attempt of purification on silica column led to its conversion to pyrrolam C in quantitative yield. Such a rearrangement was reported first time by Watson et al.16 indicating that the double bond in conjugation with carbonyl group in strained ring is highly unstable. To circumvent the problem of rearrangement, it was thought of purifying the selenyl intermediate prior to oxidation reaction (H₂O₂/NaOH) using column chromatography (SiO₂).

Accordingly, dehydropyrrolam 38 was treated with LDA/ -78 °C and the enolate thus formed was trapped using PhSeCl to give crude selenyl intermediate 39 as yellow solid. The selenyl compound was purified at this stage by using column chromatography. The IR spectrum of 39 showed a band at 1685 cm⁻¹ indicating the presence of amide carbonyl. The ¹H NMR spectrum of 39 is described below.

In ¹³C NMR spectrum of 39 (Figure 11), peak at δ 172.1 indicated the presence of the amide carbonyl. Further spectrum is similar to the spectrum of dehydropyrrolam 38 except disappearance of the peak at δ 32.2 (C-3) and appearance of a new peak at δ 45.4 (C-3) in compound 39. The multiplicities of carbon signals were determined by DEPT spectrum. Further, the structure was confirmed by recording HRMS showing [M+H]⁺ peak at m/z 282.0380 for C₁₅H₁₆NOSe.

The selenyl compound 39 was then used to prepare (S)-pyrrolam A 1. Thus, oxidation of 39 using H₂O₂ afforded (S)-pyrrolam A in 80% yield having [α]D²⁷+22.37 (c 0.961, CHCl₃) [lit.¹¹ [α]D²⁰+25.7 (c 1.00, CHCl₃)]. Its IR spectrum showed a strong band at 1678 cm⁻¹ indicating the presence of lactam carbonyl. The ¹H NMR spectrum

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(Figure 12) showed three multiplets at δ 0.95, 1.80 and 2.05 integrating for four protons of CH₂CH₂ fragment of pyrrolidine ring. The methylene attached to the nitrogen of the amide functionality appeared as two multiplets at δ 3.10 and 3.25 integrating for two protons, whereas the CH attached to the nitrogen of the amide functionality appeared as a multiplet at δ 4.20 integrating for one proton. A doublet at δ 5.97 (J = 5.4 Hz) and a double doublet at δ 7.15 (J = 1.5, 5.7 Hz) integrating for one proton each were assigned to the olefinic protons (former is α and later is β). In ¹³C NMR spectrum (Figure 13), the carbon peaks at δ 28.8 and 29.7 is attributed to the CH₂CH₂ fragment of pyrrolidine ring. The peak corresponding to CH₂ and CH attached to the nitrogen of the amide functionality appeared at δ 41.7 and 67.7 respectively. The peaks at δ 128.1 and 148.9 were attributed to C-3 and C-4 (olefinic carbons α, β respectively). The peak at δ 175.4 indicated the presence of the amide carbonyl group. The multiplicities of the carbon signals were determined by DEPT experiment. Further, the structure of (S)-pyrrolam A 1 was confirmed by recording HRMS which showed [M+H]^+ peak at m/z 124.0745 for C₇H₁₀NO. The physical and spectroscopic data were in full agreement with literature data.¹¹

Our Alternate Approach:

During the synthesis of pyrrolam A 1 by using above route, we required to carry out a reaction at -78 °C for the preparation of the selenyl compound 39. To avoid the handling of the cryogenic reaction condition (-78 °C) required during enolate generation and to shorten the route, we thought of modifying our approach towards the synthesis of (S)-pyrrolam A. Our idea was that, if we were able to prepare a Wittig product (α-substituted-α,β-unsaturated ester) from N-Cbz prolinal 40 and α-selenylmethylene phosphorane or α-halomethylene phosphorane, then its cyclization should give 3-substituted dehydropyrrolam which then could be easily transformed to (S)-pyrrolam A 1 as shown in Scheme 12.
Thus, N-Cbz protected prolinol 36 was subjected to domino oxidation-Wittig reaction using PCC/NaOAc and carboethoxymethylene(phenylseleno)triphenyl phosphorane \( \text{Ph}_3\text{P}=\text{C(SePh)}\text{COOEt} \) in \( \text{CH}_2\text{Cl}_2 \) to furnish \( \alpha \)-phenylseleno-\( \alpha,\beta \)-unsaturated ester 44 in 11% yield. Further, to improve the yield of the product, the reaction of N-benzyloxycarbonyl prolinal 40 and selenophosphorane in either refluxing \( \text{CHCl}_3 \) (24 h) or in refluxing toluene (24 h) was attempted, without any improvements in the yield of the product. It was found that the selenophosphorane is very stable and inert for the Wittig-type reaction with carbonyl compounds.

The IR spectrum of the product displayed strong bands at 1735 cm\(^{-1}\) and 1700 cm\(^{-1}\), confirming the presence of carbonyl functionalities. In the \( ^1\text{H} \) NMR spectrum of 44, methyl protons appeared at \( \delta \) 1.20 [1.63] \( (J = 9.0 \text{ Hz}) \) as triplet, while OCH\(_2\) protons appeared as quartet at \( \delta \) 4.12 [4.50] \( (J = 7.2 \text{ Hz}) \). A multiplet at \( \delta \) 1.82-3.79 integrating for seven protons indicated the presence of six protons of CH\(_2\text{CH}_2\text{CH}_2\) fragment of pyrrolidine, and one proton of CH attached to the nitrogen. The benzylic protons appeared as a broad singlet at \( \delta \) 5.03 integrating for two protons. The olefinic proton appeared as a doublet at \( \delta \) 7.54 [7.61] \( (J = 6.9 \text{ Hz}) \), indicating the formation of the E-isomer. The multiplet seen at \( \delta \) 7.25 integrating for ten protons was due to the presence of aromatic ring (SePh and NHCOOCH\(_2\)Ph). In the \( ^{13}\text{C} \) NMR spectrum the peak at \( \delta \) 165.7 and \( \delta \) 175.7 is attributed to carbamate and ester respectively. The \( \alpha,\beta \)-unsaturated carbons appeared at \( \delta \) 98.7 and 147.8 respectively. Further, the assigned
structure 44 was confirmed by recording the multiplicities of the carbon signals using DEPT experiment.

The low yield of Wittig product 44 (α-substituted-α,β-unsaturated ester) obtained using selenophosphorane prompted us to try the Horner-Wittig reaction to prepare α,β-unsaturated ester 44 using the selenophosphonate. Disappointingly, we did not succeed in improving the yield (Scheme 13).

Scheme 13. Reagents and conditions: a) PCC, CH₂Cl₂, rt; b) (EtO)₂POCH(SePh)COOEt, NaH, THF

Having failed to obtain the selenyl compound 44 in good yield, we thought of using α-bromophosphorane in Wittig reaction with N-Chz prolinal 40. Accordingly α-bromo-α,β-unsaturated ester 45 (Scheme 12) was prepared in 70% yield, by reacting N-protected prolinal 36 with PCC/NaOAc and α-bromophosphorane in one-pot. Its IR spectrum showed strong band at 1705 cm⁻¹ indicating the presence of carbonyl functionality. In the ¹H NMR spectrum, methyl protons appeared at δ 1.18-1.29 (J = 7.2 Hz) as two triplets integrating for three protons whereas OCH₂ protons appeared as two quartet at δ 4.05-4.23 (J = 7.2 Hz) integrating for two protons. Two multiplets at δ 1.66-1.86 integrating for four protons indicated the presence of CH₂CH₂ fragment of the pyrrolidine ring. The CH₂ and CH attached to nitrogen of amide functionality appeared as two multiplets at δ 2.18-2.29 and δ 3.42-3.54 integrating for three protons. The benzylic protons displayed as two doublets at δ 5.02 and 5.12 (J = 12.0 Hz). The vinylic proton appeared as doublet at δ 6.53 [7.12] (J = 7.8 Hz), which indicated the formation of E-isomer. The aromatic protons appeared as a multiplet at δ 7.15-7.30 (5H). The multiplicities of the carbon signal were determined by using DEPT experiment.
The $\alpha$-bromo-$\alpha,\beta$-unsaturated ester 45 was subjected to hydrogenation ($H_2$, Pd/C, 2 psi) for 8 h, followed by treatment with catalytic amount of NaOEt to afford a light yellow color oily liquid. Its spectroscopic properties matched with the dehydropyrrolam 38. Further structure was confirmed by recording HRMS that showed $[M+H]^+$ peak at $m/z$ 126.0899 for C$_7$H$_{12}$NO. Hence, during reductive hydrogenation, instead of 3-bromodehydropyrrolam 46, we obtained dehydropyrrolam 38 as product. Thus the synthesis of target compound could not be achieved. The reason for this observation could be attributed to hydrogenolysis of $\alpha$-substituted bromine during hydrogenation step.

**Conclusion:**

1. (S)-Pyrrolam A, a enantiomer of natural (R)-pyrrolam A has been synthesized using a short new method via domino oxidation-intermolecular Wittig reaction.
2. The synthesis further demonstrate the applicability of domino oxidation-intermolecular Wittig reaction, towards the synthesis of pyrrolizidine alkaloid.
3. Under the various reaction conditions employed, the Wittig reaction of stable selenophosphorane did not give good yield, due to its low reactivity with the carbonyl compounds.
Section B: Intramolecular Wittig Approach to (S)-Pyrrolam A

Objective:

The objective of the present study is to devise a practical, flexible and high yielding route to the synthesis of (S)-pyrrolam A and to check the feasibility of domino oxidation intramolecular-Wittig reaction towards the synthesis of the enantiomer of the naturally occurring pyrrolam A (Scheme 14).

![Scheme 14](image)

Scheme 14. Reagents and conditions: a) i) LiAlH₄; ii) NaOAc, CICOCH₂Br; b) i) PPh₃, benzene; ii) 2N NaOH; c) PCC/NaOAC, CH₂Cl₂

Results and Discussion:

The synthetic route planned towards (S)-pyrrolam A is depicted in Scheme 14. (S)-Prolinol 35 was prepared by reduction of L-proline 2 with LAH in THF at refluxing temperature. The amine group of prolinol was reacted with bromoacetyl chloride in the presence of NaOAc at 0-5 °C, to give (S)-N-bromoacetyl prolinol 47, having [α]D²⁵ -25.85 (c 1.18, CHCl₃). The IR spectrum of 47 showed a broad band at 3400 cm⁻¹ indicating the presence of OH functionality and a strong band at 1643 cm⁻¹ for amide functionality. The ¹H NMR spectrum (Figure 14) of 47 showed peaks corresponding to CH₂CH₂ fragment of pyrrolidine ring at δ 1.63-1.94 as a multiplet integrating for four protons. A multiplet at δ 3.45-3.54 integrating for four protons was attributed to CH₂ attached to nitrogen of amide functionality and CH₂ attached to the hydroxyl group. The singlet at δ 3.99 integrating for two protons was assigned to CH₂Br. The CH attached to the nitrogen atom appeared at δ 4.02-4.09 as a multiplet.
integrating for one proton. In $^{13}$C NMR spectrum (Figure 15), the signals of CH$_2$CH$_2$CH$_2$N fragment appeared at $\delta$ 24.3, 27.9 and 47.9 respectively. The peak of CH attached to the nitrogen appeared at $\delta$ 61.5, whereas CH$_2$Br appeared at $\delta$ 42.4. The peaks at $\delta$ 65.4 and 167.3 were attributed to the CH$_2$OH and the carbonyl carbon respectively. Finally the assigned structure 47 was confirmed by HRMS which showed [M+H]$^+$ peak at $m/z$ 222.0132 for C$_7$H$_{13}$NO$_2$Br.

(S)-N-Bromoacetyl prolinol 47 was treated with triphenylphosphine in benzene at room temperature to give the corresponding phosphonium bromide salt. Its IR spectrum showed a broad band at 3400-3200 cm$^{-1}$ indicating the presence of OH functionality, whereas the band corresponding to 1620 cm$^{-1}$ confirmed the presence of conjugated amide carbonyl group. The $^1$H NMR spectrum showed a multiplet at $\delta$ 1.70-1.94 integrating for four protons of CH$_2$CH$_2$ fragment of pyrrolidine ring. The multiplet seen at $\delta$ 3.30-3.81 integrating for four protons was of NCH$_2$ and OCH$_2$ groups. The CH attached to the nitrogen appeared at $\delta$ 4.03 as a multiplet integrating for one proton, whereas broad singlet seen at $\delta$ 4.70 indicated the presence of hydroxyl group. A doublet at $\delta$ 4.89 ($J = 13.2$ Hz) [$\delta$ 5.53 ($J = 12.6$ Hz)] integrating for 2 protons was attributed to CH$_2$ attached to the phosphorus atom. The multiplets at $\delta$ 7.59 integrating for 15 protons were assigned to the protons of three monosubstituted aromatic rings. In $^{13}$C NMR spectrum, the peaks corresponding to CH$_2$CH$_2$ fragment of pyrrolidine ring appeared at $\delta$ 21.9 [24.5] and 28.14 [28.10]. The peaks at $\delta$ 45.9 [49.7] and 60.6 were attributed to CH$_2$ and CH attached to the nitrogen respectively. The carbon attached to PPh$_3$ showed peaks at $\delta$ 33.5 [34.3] and CH$_2$OH at $\delta$ 64.5. The amide carbon appeared at $\delta$ 162.4. The multiplicities of carbon signals were assigned by DEPT experiment.

The Wittig salt prepared from N-bromoacetyl prolinol was treated with 2N NaOH to give (S)-N-prolinolcarbamoylmethylene triphenylphosphorane 48. Its IR spectrum showed a broad band at 3400 cm$^{-1}$ confirming the presence of hydroxy group, and a band at 1616 cm$^{-1}$ for the carbonyl group. The $^1$H NMR spectrum (Figure 16) showed a multiplet at $\delta$ 1.83-2.05 integrating for four protons of CH$_2$CH$_2$ fragment of pyrrolidine ring. A singlet at $\delta$ 2.50 integrating for one proton indicates
the presence of the CH attached to the phosphorus atom. The CH$_2$ and CH attached to
the nitrogen atom appeared as a multiplet at δ 3.45-3.71 integrating for three protons.
The two multiplets at δ 4.18 and 5.16 integrating for two protons were attributed to
CH$_2$OH, whereas 15 aromatic protons of PPh$_3$ appeared as a multiplet at δ 7.54-7.91.
In the $^{13}$C NMR spectrum (Figure 17), the disappearance of carbon peak at δ 33.5 of
salt, and appearance of a new peak at δ 22.9 indicated the formation of phosphorane.
Further, the assigned structure 48 was confirmed by determining multiplicities of
carbon signals using DEPT experiment.

To finalize the synthesis of (S)-pyrrolam A, we thought of oxidizing prolinol
phosphorane 48 expecting two reactions i.e. oxidation and Wittig reaction to take
place in one-pot in a domino fashion. Towards this end, the prolinol phosphorane 48
was subjected to domino oxidation-Wittig reaction using PCC/NaOAc in CH$_2$Cl$_2$ at
room temperature. We were not able to isolate any product other than OPPh$_3$. Further,
the same reaction was carried out under refluxing condition, but without any success.
We screened different oxidizing agents, such as Dess Martin Periodinane, IBX and
MnO$_2$ in various types of solvents such as CH$_2$Cl$_2$, DMSO and CH$_3$CN at different
temperatures. However, under all these conditions, the reaction failed to give us
targeted compound pyrrolam A. The reason for our failure to get the Wittig product
could be probably due to the unstability of phosphorane and/or instability of product
under the reaction condition employed in the experiment.

Our Alternate Approach using Wittig reaction:

Our initial attempt to synthesise the target compound 1 by domino oxidation-
intramolecular Wittig reaction under varied reaction conditions failed (Scheme 14).
Corresponding to this fact, we modified our approach. We thought of utilizing the
more conventional way to check the feasibility of the intramolecular Wittig reaction
towards the synthesis of pyrrolam A as depicted in Scheme 15. Our idea was that, if
we could prepare the Wittig salt of prolinal, then the resulting phosphorane after the
base treatment should undergo Wittig reaction intramolecularly to effect cyclization of
5-membered ring giving targeted compound 1.
Chapter 1: Synthetic Studies towards Pyrrolizidine Alkaloid, (S)-Pyrrolam A

Accordingly, we started our synthesis from N-bromoacetyl prolinol 47, which was subjected to oxidation using PCC, to give N-bromoacetyl prolinal 50 as viscous oil having $[\alpha]_D^{20} -64.21$ (c 0.366, CHCl$_3$). The IR spectrum showed strong bands at 1743 cm$^{-1}$ and 1647 cm$^{-1}$ indicating the presence of carbonyl functionalities. In the $^1$H NMR spectrum of 50, a multiplet at $\delta$ 1.08-1.91 integrating for four protons was attributed to the CH$_2$CH$_2$ fragment of the pyrrolidine ring. The CH$_2$ and CH attached to the nitrogen atom appeared as a multiplets at $\delta$ 3.56-3.65 (two protons) and at $\delta$ 4.45-4.53 (one proton) respectively. The singlet at $\delta$ 4.05 integrating for two protons was attributed to CH$_2$Br group, whereas appearance of doublet at $\delta$ 9.48 ($J = 1.5$ Hz) integrating for one proton indicated the presence of aldehydic proton (CHO). In $^{13}$C NMR spectrum (Figure 18), the peaks corresponding to CH$_2$CH$_2$CH$_2$N fragment of pyrrolidine ring appeared at $\delta$ 24.8, 25.7 and 47.3 respectively. The peak at $\delta$ 41.6 is attributed to CH$_2$Br, whereas CH attached to the nitrogen of amide group appeared at $\delta$ 65.2. The carbon peaks corresponding to amide and aldehyde functionalities appeared at $\delta$ 165.7 and 198.2 respectively. The multiplicities of the carbon signals were determined by DEPT experiment.

N-Bromoacetyl prolinal 50 was treated with triphenyl phosphine in benzene to give the corresponding Wittig salt 51. To complete the synthesis of (S)-pyrrolam A, the Wittig salt 50 of N-bromoacetyl prolinal was treated with aqueous 2N NaOH.

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expecting two reactions to take place in one-pot i.e. the generation of the phosphorane followed by intramolecular Wittig reaction. However, the products obtained were N-acetyl prolinal and triphenylphosphine oxide. Again, the reason for failure could be attributed to the instability of phosphorane 49 in aqueous reaction condition. Further, we thought of avoiding the aqueous condition during the deprotonation step.

Wittig salt 51 was treated with NaH in THF at 0 °C and then stirred at room temperature for 14 h under N₂ atmosphere. Keeping in mind the unstability of pyrrolam A on silica gel, we attempted separation on column using Al₂O₃ (neutral, basic), ODS, as well as flash chromatography using SiO₂. But our attempts to improve separation under various chromatographic techniques were unsuccessful giving either mixture of products (pyrrolam + triphenylphosphine oxide) or rearranged product (pyrrolam C). Thus, triphenylphosphine oxide proved very difficult to remove from the crude product mixture, as it seems to have nearly identical chromatographic mobility. Finally separation was effected taking advantage of the different solubilities of product to get partially enriched pyrrolam A. Thus, crude compound was dissolved in the mixture of diethyl ether and hexanes (2:1) and after keeping in refrigerator, the solution was decanted from solidified triphenylphosphine oxide. The maximum amount of oxide was removed by repeating above step (3 times). Further, purification was done by using reverse phase HPLC to give pyrrolam A 1 having [α]D₂₈ -25.06 (c 0.133, CHCl₃). The spectroscopic properties of pyrrolam A were same to those discussed earlier in Section A of this chapter. Thus, we have synthesized (S)-pyrrolam A via intramolecular Wittig approach in a very simple way.

**Our Alternate Approach using Polymer Supported PPh₃ for Wittig Reaction:**

With the aim of avoiding the cumbersome separation of pyrrolam A from Ph₃P=O, we attempted a different approach (Scheme 16). We thought of modifying our above route using intramolecular Wittig reaction in such way so as to obtain the target compound in solution form (dissolved in solvent) and byproduct (Ph₃P=O) as insoluble solid, and simplify the separation procedure. This could be achieved using polymer supported triphenylphosphine, wherein, polymer supported triphenyl
phosphine oxide formed during Wittig reaction could be removed very easily via filtration giving pyrrolam A in pure form. Thus, the treatment of N-bromoacetyl prolinal 50 with polystyrene supported PPh₃ gave us corresponding Wittig salt 52, but the deprotonation using NaH did not work in our hand.

Scheme 16. Synthesis of (S)-pyrrolam A using polymer support

We also attempted preparation of 3,4-dihydroxy-2-pyrrolizidone 54²⁵ directly from the mixture of Ph₃P=O and pyrrolam A, thinking that the expected product could be easily purified using column chromatography. However, we could not isolate the targeted product. To find out the reason for the failure, we also subjected pyrrolam A to dihydroxylation reaction. Once again we failed to get the expected product. During this reaction condition, pyrrolam A gets decomposed prior to dihydroxylation reaction could take place, may be due to its unstability for the reaction condition (Scheme 17).

Scheme 17. Sharpless asymmetric dihydroxylation of pyrrolam A
Wittig-Horner-Emmons approach towards pyrrolam:

The Wittig-Horner-Emmons reaction is one of the most important reactions for the synthesis of olefins. In this reaction the aldehyde/ ketone is condensed with a phosphonate. We had found that the separation of Ph₃P=O from pyrrolam A during the normal Wittig reaction is problematic. This prompted us to use the Wittig-Horner-Emmons approach. Our idea was to prepare a phosphonate of prolinal which could be cyclized via Wittig-Horner reaction using a base. Further, taking advantage of water soluble byproduct during the reaction, pyrrolam A could be easily separated by chemical treatment (solvent extraction) without subjecting to column chromatographic purification. The details of the proposed synthesis is depicted in Scheme 18.

Scheme 18. Reagents and conditions: a) PCC, CH₂Cl₂; b) P(OEt)₃, reflux, neat, 7 h; c) NaH, THF

The synthesis began with N-bromoacetyl prolinal 50, whose preparation from L-proline is discussed in section B of this chapter. (S)-N-Bromoacetyl prolinal 50 on treatment with triethylphosphite at 95 °C for 7 h furnished a crude product as a viscous oil, whose TLC showed single spot. Its IR spectrum showed strong bands at 1643 cm⁻¹ and 1690 cm⁻¹, indicating the presence of carbonyl functionalities. The ¹H NMR spectrum showed a doublet at δ 5.97 (J = 5.4 Hz) and a double doublet at δ 7.15 (J = 1.5, 5.4 Hz) indicating the presence of vinylic protons. These peaks are characteristic of the double bond of pyrrolam A. We were able to assign the other peaks of pyrrolam in ¹H NMR spectrum, although it was found to be complex spectrum containing the mixture of products. Further ¹³C NMR spectrum showed all the carbon peaks corresponding to pyrrolam A, together with many other carbon peaks. Thus we concluded that, pyrrolam A is formed during the preparation of phosphonate under the refluxing condition. We were not able to proceed further with this route. Thus, our
attempt to prepare phosphonate 55 by reacting N-bromoacetyl prolinal and triethyl
phosphite failed to give us the expected results.

**Conclusion:**

1) Domino oxidation-intramolecular Wittig reaction did not work under various
reaction conditions tried.

2) A concise, new synthesis of (S)-pyrrolam A has been achieved starting from L-
proline using intramolecular Wittig reaction as a key step.
Experimental part of Section A:

1.01 Preparation of (S)-prolinol (35):

(S)-Prolinol 35 was synthesized according to known literature procedure.\textsuperscript{18} To a stirred suspension of LiAlH\textsubscript{4} (2.462 g, 0.065 mol) in dry THF (75 mL) was added L-proline 2 (5.00 g, 0.0432 mol) in three portions under nitrogen atmosphere in 250 mL 3-neck round bottom flask equipped with reflux condenser. The reaction was refluxed for 8 h and then cooled using ice bath. The cold reaction mixture was quenched with sequential addition of H\textsubscript{2}O (2 mL), 10% KOH (5 mL) and H\textsubscript{2}O (3 mL), and refluxed for another 20 min. The white precipitate obtained was filtered and washed with THF (3 \times 20 mL). The combined filtrate was concentrated under reduced pressure to give light yellow color thick liquid (3.860, 87.8%).

IR (neat): \(\nu_{\text{max}}\) 3600-3400 cm\(^{-1}\) (OH).

1.02 Preparation of (S)-N-benzyloxycarbonyl prolinol (36):

A solution of benzyl chloroformate (3.815 g, 22.44 mmol) in acetonitrile (5 mL) was added slowly to a stirred solution of (S)-prolinol 35 (2.070 g, 20.4 mmol) and finely powdered K\textsubscript{2}CO\textsubscript{3} (6.202 g, 44.88 mmol) in dry acetonitrile (20 mL) at \(-10^{\circ}\text{C}\) under N\textsubscript{2} atmosphere. Further, solution was stirred at -10 to 0 \(^{\circ}\text{C}\) for 2 h. H\textsubscript{2}O (50 mL) was added to the reaction mixture and the aqueous layer was extracted with CHCl\textsubscript{3} (3 \times 20 mL). The combined organic extract was washed successively with H\textsubscript{2}O (1 \times 20 mL), 5% HCl (1 \times 20 mL), H\textsubscript{2}O (3 \times 20 mL) and then dried over anhyd Na\textsubscript{2}SO\textsubscript{4}. The solvent was removed under reduced pressure, the crude product was subjected to column chromatography (SiO\textsubscript{2}, hexanes/ EtOAc, 6:4) to give (S)-N-benzyloxycarbonyl prolinol 36 (3.967 g, 82.7%).
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\[ [\alpha]_D^{27} -41.5 \text{ (c 0.448, CHCl}_3) \], [lit.\textsuperscript{19} \[ [\alpha]_D^{27} -40.0 \text{ (c 1.05, CH}_2\text{Cl}_2) \]

IR (neat): \( \nu_{\text{max}} 3600 \text{ (OH)}, 1700 \text{ cm}^{-1} \text{ (C=O)} \).

\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz): \( \delta 1.45-2.05 \text{ (m, 4H, CH}_2\text{CH}_2), 3.36-3.69 \text{ (m, 4H, CH}_2\text{N \& CH}_2\text{OH)}, 4.01 \text{ (m, 1H, CHN)}, 5.15 \text{ (s, 2H, OCH}_2\text{Ph)}, 7.26-7.37 \text{ (m, 5H, Ar-H)} \).

\textsuperscript{13}C NMR (CDCl\textsubscript{3}, 75 MHz): \( \delta 24.0 \text{ (CH}_2), 28.4 \text{ (CH}_2), 47.3 \text{ (CH}_2\text{N)}, 58.7 \text{ (CHN), 66.2 (CH}_2\text{OH), 67.2 (OCH}_2\text{), 127.9-128.3 (Ar-H), 136.0 (Ar-C), 156.9 (CO)} \).

1.03 (Ethoxycarbonylmethylene)triphenyl phosphorane:

Addition of solution of triphenyl phosphine (10.0 g, 38.1 mmol) in dry benzene (30 mL) to a solution of ethyl bromoacetate (6.367 g, 38.1 mmol) in benzene (10 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 phenolphthaleine end point. The benzene layer was evaporated, dried over anhyd Na\textsubscript{2}SO\textsubscript{4} and concentrated to about 1/3rd volume. Addition of n-hexanes (40-60 °C) resulted in separation of white crystalline product which was filtered and dried to afford phosphorane (10.22 g, 77%).

mp 125-126 °C, [lit.\textsuperscript{26} mp 125-127 °C].

1.04 Preparation of ethyl-(E)-3-[2'S]-N-benzoxycarbonylpyrrolidine-2'-yl propenoate (37):

To a magnetically stirred suspension of pyridinium chlorochromate (3.66 g, 17 mmol) and sodium acetate (1.40 g, 17 mmol) in anhyd CH\textsubscript{2}Cl\textsubscript{2} (40 mL), Z-prolinol \textsubscript{36} (2.00 g,
8.51 mmol) in anhyd CH$_2$Cl$_2$ (15 mL) was added, followed by the addition of (carboethoxymethylene)triphenyl phosphorane (4.45 g, 12.8 mmol) in one portion. The mixture was stirred for 7 h at room temp. Et$_2$O (50 mL) was added and the supernatant solution was decanted from the black granular solid. The combined organic solution were filtered through a short bed of celite and the filtrate obtained was evaporated to give a residue which on purification by silica gel column chromatography (SiO$_2$, hexanes/ EtOAc, 6:4) gave pure 37 as colorless viscous liquid (1.95 g, 76%).

$[\alpha]_D^{27}$ -42.55 (c 0.094, CHCl$_3$).

IR (neat): $\nu_{\text{max}}$ 3032 (aromatic), 1716, 1708, and 1699 cm$^{-1}$ (C=O & C=C).

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 1.3 (t, $J = 7.0$ Hz, 3H, CH$_3$), 1.75- 1.90 & 2.01- 2.12 (2m, 4H, H-3'a,3'b,4'a,4'b), 3.39- 3.50 & 3.62- 3.76 (2m, 2H, H-5'a, 5'b), 4.2 (q, $J = 7.0$ Hz, 2H, OCH$_2$), 4.47 & 4.54 (2m, 1H, H-2'), 5.07 [5.17] (d, $J = 12.6$ Hz, CH$_2$Ph), 5.76 [5.86] (d, $J = 15.4$ Hz, 1H, H-2), 6.80 [6.84] (dd, $J = 5.61$, 15.4 Hz, 1H, H-3), 7.28-7.35 (m, 5H, Ar-H).

$^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 14.0 (CH$_3$), 22.5 [23.7] (C-3'), 30.7 [31.6] (C-4'), 46.4 [46.8] (C-5'), 57.7 [58.0] (C-2'), 60.4 (OCH$_2$), 66.9 (CH$_2$Ph), 120.8 (C-2), 127.9, 128.0, 128.9 (Ar-H), 136.6 (Ar-C), 147.4 [147.8] (C-3), 154.7 (C=O of Cbz), 166.3 (C-1).

HRMS: m/z calcd for C$_{17}$H$_{21}$N$_{10}$O$_4$Na $[M + Na]^+$: 326.1368; found: 326.1361.

1.05 Preparation of (S)-N-benzyloxycarbonyl prolinol (40):

The solution of (S)-N-benzyloxycarbonyl prolinol 36 (1.967 g, 8.37 mmol) in CH$_2$Cl$_2$ (3 mL) was added to a stirred suspension of pyridinium chlorochromate (2.880 g, 13.39 mmol) in dry CH$_2$Cl$_2$ (30 mL) and the reaction mixture was stirred for 5 h at room temp. Et$_2$O (30 mL) was added and stirred for 20 minute at room temp, and the mixture was filtered through a bed of celite and the filtrate obtained was evaporated to give a crude product 40, which was passed through a short bed of silica column using EtOAc (1.248 g, 64%).
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[α]D^27 -60.1 (c 0.521, MeOH), [lit.20 [α]D^26 -63.1 (c 1.44, MeOH)]

IR (neat): ν_max 1730, 1699 cm^-1 (C=O).

1.06 Preparation of (S)-dehydropyrrolam A (38):

A solution of 37 (1.46 g, 4.8 mmol) in EtOH (20 mL) was shaken at room temp with 10% Pd-C (140 mg) in a H₂ atmosphere (4 psi) for 10 h in a parr hydrogenator. The catalyst was filtered off, washed with EtOH and the combined filtrate and washing (50 mL) treated with 2M NaOEt (1 mL) and refluxed for 6 h. The reaction mixture was concentrated and further treated with aqueous 10% HCl (2 x 20 mL), and subsequently extracted with CHCl₃ (4 x 20 mL). The combined organic layer was dried over anhyd Na₂SO₄, concentrated, and purified by silica gel column using ethyl acetate as an eluent to afford 38 as pure pale yellow oil (401 mg, 67%).

[α]D^27 -20.49 (c 0.244, CHCl₃) [lit.5 [α]D^20 +23.6 (c 1.00, CHCl₃) for (R)-enantiomer].

IR (CHCl₃): ν_max 2960, 2890, 1670 cm^-1 (C=O).

¹H NMR (CDCl₃, 400 MHz): δ 1.32 (m, 1H, 6-Hb), 1.73 (m, 1H, 4-Hb), 1.96-2.28 (m, 3H, 6-Ha, 7-H₂), 2.3 (m, 1H, 4-Ha), 2.44 (ddd, J = 1.52, 1.56, 1.6 Hz, 1H, 3-Hb), 2.75 (m, 1H, 3-Ha), 3.06 (m, 1H, 8-Hb), 3.56 (ddd, J = 3.92, 7.84, 7.88 Hz, 1H, 8-Ha), 3.90 (m, 1H, 5-H).

¹³C NMR (CDCl₃, 75 MHz): δ 27.0 (C-7), 27.2 (C-6), 32.2 (C-3), 35.4 (C-4), 41.0 (C-8), 62.1 (C-5), 174.8 (C-2).

HRMS: m/z calcd for C₇H₁₂NO [M + H]⁺: 126.0913; found: 126.0899.
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1.07 Preparation of pyrrolam C (43):

To a stirred solution of diisopropylamine (0.23 mL, 1.54 mmol) in THF (5 mL), n-BuLi (1.0 mL, 1.54 mmol) [1.6 M solution in n-hexane] was added at -78 °C under N₂ atmosphere. The solution of (S)-dehydropyrrolam 38 (0.160 g, 1.28 mmol) in THF (1 mL) was added to reaction mixture over a period of 5 minutes. The solution was further stirred for 10 minute, and then PhSeCl (0.294 g, 1.53 mmol) in THF (1 mL) was added rapidly. The mixture was stirred to attain 0 °C and then water (3 mL), AcOH (0.6 mL) was added followed by slow addition of 30% H₂O₂ (2.47 g, 2.24 mL) keeping the temp. below 25 °C. Further stirred at 25 °C for 30 minutes, the mixture was concentrated under reduced pressure, and then CHCl₃ (25 mL) and 7% NaHCO₃ solution (20 mL) were added. The aqueous layer was extracted with CHCl₃ (4 × 20 mL), the combined organic layer was washed with H₂O (4 × 20 mL), and dried over anhyd Na₂SO₄. The solvent was removed on pump and then crude product was purified by silica gel column chromatography. The first fraction consisted of unreacted PhSeCl was eluted using EtOAc/ hexanes (3:7), while the second fraction eluted using EtOAc, gave pyrrolam C 43 as yellow oil¹⁶ (0.1253, 79%).

IR (CHCl₃): ν_max = 3400, 1678 cm⁻¹.

¹H NMR (CDCl₃, 300 MHz): δ 1.58-1.65 (m, H-7), 2.05-2.43 (m, 6H, four protons of H-4, H-6 & one proton each of H-7 & H-3), 2.87-2.99 (m, 1H, H-3), 3.14-3.20 & 3.38-3.47 (2m, 2H, NCH₂).

¹³C NMR (CDCl₃, 75 MHz): δ 29.4 (C-7), 33.7 (C-6,C-4), 37.7 (C-3), 40.5 (C-8), 97.7 (C-5), 174.7 (C-2).
1.08 Preparation of 3-selenophenyl dehydropyrrolam (39):

To a stirred solution of LDA (2.26 mmol) in THF (10 mL) [prepared by adding 1.6 M n-BuLi in n-hexane (1.41 mL) to diisopropylamine (0.32 mL, 2.26 mmol)] under the N₂ atmosphere at -78 °C, was added dropwise a solution of (S)-dehydropyrrolam 38 (0.235 g, 1.88 mmol) in THF (2 mL) over a period of 5 min. After stirring for additional 10 min, a solution of PhSeCl (0.432 g, 2.26 mmol) in THF (2 mL) was added rapidly. The mixture was stirred to attain room temperature. Solvent was removed under reduced pressure, water (20 mL) was added and the crude mixture was extracted with CHCl₃ (3 x 20 mL), which was then purified by silica gel column chromatography (hexanes/ EtOAc, 6:4) to afford the corresponding pure phenyl selenium intermediate 39 as a yellow colored solid (0.348 g, 66.14%), mp 121-123 °C.

IR (CHCl₃): \( \nu_{\text{max}} \) 1685 cm⁻¹.

\(^1\)H NMR (CDCl₃, 300 MHz): \( \delta \) 1.15-1.21 (m, 1H, H-7), 1.72-2.04 (m, 3H, 2 protons of H-6 & 1 proton of H-7), 2.15-2.25 (m, 1H, H-4), 2.30-2.38 (m, 1H, H-4), 2.89-2.97 (m, 1H, CHN), 3.40-3.49 (ddd, \( J = 2.0, 6.0, 7.8 \) Hz, 2H, H-8), 3.92 (br d, 1H, H-3), 7.21-7.63 (m, 5H, Ar-H).

\(^13\)C NMR (CDCl₃, 75 MHz): \( \delta \) 26.8 (C-7), 31.8 (C-6), 36.5 (H-4), 41.0 (C-8), 45.4 (C-3), 60.3 (C-5), 128.1, 128.4, 128.9 (Ar-H), 135.5 [135.3] (Ar-C), 172.0 (C-2).

HRMS: \( m/z \) calcd for C₁₃H₁₄NOSe [M + H]⁺: 282.0391; found: 282.0380.

1.09 Preparation of (S)-pyrrolam A (1):
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To the ice cooled solution (0 °C) of 3-selenophenyl dehydropyrrolam 39 in THF (5 mL), water (3 mL) and acetic acid (0.6 mL) were added followed by slow addition of 30% H$_2$O$_2$ (2.47 g, 2.24 mL), keeping the temp below 25 °C. After stirring for 30 min at 25 °C, the reaction mixture was concentrated under vacuum, and then CHCl$_3$ (25 mL) and 7% NaHCO$_3$ solution (20 mL) was added to it. The aqueous layer was extracted with CHCl$_3$ (2 x 10 mL). The combined organic layer was then washed with water (2 x 10 mL) and dried over anhyd Na$_2$SO$_4$. Solvent was removed under vacuum to obtain pure product 1 as a white semi solid (113 mg, 92.5%).

$[\alpha]_D^{27} +22.37$ (c 0.961, CHCl$_3$) [lit$^{11}$ $[\alpha]_D^{20} +25.7$ (c 1.00, CHCl$_3$)]

IR (CHCl$_3$): $\nu_{\text{max}} = 1678$ cm$^{-1}$

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 0.95-1.25 (m, 1H, H-6), 1.80-2.05 (m, 1H, H-6), 2.05-2.50 (m, 2H, H-7), 3.10-3.25 (m, 1H, H-8), 3.25-3.45 (m, 1H, H-8), 4.20 (m, 1H, H-5), 5.97 (d, $J$ = 5.4 Hz, 1H, H-3), 7.15 (dd, $J$ = 1.5 & 5.4 Hz, 1H, H-4).

$^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 28.8 (C-7), 29.7 (C-6), 41.7 (C-8), 67.7 (C-5), 128.1 (C-3), 148.9 (C-4), 175.4 (C-2).

HRMS: m/z calcd for C$_7$H$_{10}$N$_2$O[M + H]$^+$: 124.0756; found: 124.0745.

1.10 Preparation of carboethoxymethyldene(phenylseleno)triphenyl phosphorane:

![carboethoxymethyldene(phenylseleno)triphenyl phosphorane structure]

The phenylselenyl chloride (2.75 g, 14.3 mmol) in CH$_2$Cl$_2$ (10 mL) was added to a stirred solution of (carboethoxymethylene)triphenyl phosphorane (5.0 g, 14.3 mmol) in CH$_2$Cl$_2$ (10 mL). The mixture was stirred at room temp for 2 h, and solvent was removed under vacuum. The residue was stirred at room temp for 2 h, and solvent was removed under vacuum. The residue was dissolved in water (50 mL), benzene was added (40 mL), followed by 2N NaOH with constant shaking to the phenolphthalein end point. The solvent was removed in vacuum and the addition of n-hexanes resulted in separation of yellow crystalline solid, which was filtered and dried to afford selenophosphorane (4.56 g, 63%). mp 178-179 °C, [lit$^{21}$ mp 182 °C].

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1.11 Preparation of ethyl(phenylseleno)methane triethyl phosphonoacetate:

![Structure of ethyl(phenylseleno)methane triethyl phosphonoacetate]

Seleno phosphonate was synthesized according to known literature procedure. To a round bottom flask containing a suspension of NaH (0.22 g, 5.22 mmol) [60% in mineral oil washed with hexanes] in THF (30 mL), at 0 °C under N₂ atmosphere, triethyl phosphonoacetate (1.112 g, 4.96 mmol) was added, followed by a THF (5 mL) solution of phenylselenyl chloride (1.0 g, 5.22 mmol). Immediate reaction was observed with the disappearance of the deeper color of PhSeCl, leaving the solution yellow. Further the solution was stirred in ice bath for 20 minutes and then concentrated under vacuum to give crude thick syrupy liquid which was subjected to column chromatography (SiO₂, hexanes/ EtOAc, 7:3) to get pure thick liquid (1.586 g, 84.4%).

1.12 Preparation of carboethoxymethylidene(bromo)triphenyl phosphorane:

![Structure of carboethoxymethylidene(bromo)triphenyl phosphorane]

Bromine (1.102 g, 6.9 mmol) in CHCl₃ (5 mL) was added to (carboethoxymethylene)triphenyl phosphorane (2.0 g, 5.7 mmol) in CHCl₃ (20mL), whereupon immediate decolorisation occurred. After allowing it to attain room temp, the solution was concentrated. The residual oil was dissolved in CH₂Cl₂ (30 mL) and solution was extracted three times with an equivalent of Na₂CO₃ in water (10 mL). The organic layer was dried over anhyd Na₂SO₄ and then concentrated. Addition of n-hexane gave bromo phosphorane (1.811 g, 74%). mp 151-152 °C, [lit. mp 155-156 °C].
1.13 Preparation of ethyl-(2E)-phenylseleno-3-[2'S]-N-benzyloxycarbonyl pyrrolidin-2'-yl] propenoate (44):

1.13a Wittig reaction of seleno phosphorane:
To a stirred suspension of pyridinium chlorochromate (0.408 g, 1.90 mmol) and sodium acetate (0.156 g, 1.90 mmol) in anhyd CH₂Cl₂ (40 mL), N-Cbz-prolinol 36 (0.279 g, 1.19 mmol) in anhyd CH₂Cl₂ (15 mL) was added, followed by the addition of carboethoxymethylidene(phenylseleno)triphenyl phosphorane (0.658 g, 1.30 mmol) in one portion. The mixture was stirred for 15 h at room temp. Et₂O (30 mL) was added and the supernatant solution was decanted from the black granular solid. The combined organic solution were filtered through a short bed of celite, and the filtrate obtained was evaporated to give a residue, which on purification by column chromatography (SiO₂, hexanes/EtOAc, 9:1) gave pure 44 as yellow viscous liquid (0.042 g, 11%).

[α]D²⁹ -17.54 (c 0.171, CHCl₃).

IR (neat): v max 1735, 1700 cm⁻¹ (C=O).

¹H NMR (CDCl₃, 300 MHz): δ 1.21 [1.63] (t, J = 9.0 Hz, 3H, CH₃), 1.82- 3.79 (m, 7H, NCH₂CH₂CH₂CH₂CHN), 4.12 [4.50] (q, J = 7.2 Hz, 2H, OCH₂), 5.04 (br s, OCH₂Ph), 7.54 [7.61] (d, 1H, J = 6.9 Hz), 7.25 (m, 10H, Ar-H).

¹³C NMR (CDCl₃, 75 MHz): δ 14.1 (CH₃), 21.5 (C-4'), 37.9 [38.8] (C-3'), 39.8 [40.5] (C-5'), 46.7 [47.7] (C-2'), 69.0 [60.3] (OCH₂), 66.6 [67.1] (OCH₂Ph), 98.7 (C-2), 147.8 (C-3), 120.6-135.0 (Ar-H & Ar-C), 165.8 (CON), 175.7 (COO).

1.13b Horner-Wittig-Emmons reaction of selenophosphonate:
To a suspension of NaH (0.078 g, 1.93 mmol, 60% suspension in mineral oil wash with hexanes) in THF (10 mL) was added phenyl selenophosphonate (0.488 g, 1.29 mmol) at 0 °C under N₂ atmosphere. The mixture was stirred for 30 minutes at 0 °C and then Z-prolinal 40 (0.30 g, 1.29 mmol) was added. The ice bath was removed after
20 minutes and the reaction was heated under reflux for 15 h. The reaction mixture was cooled, treated with H₂O (5 mL), followed by saturated solution of NH₄Cl (50 mL) and extracted with EtOAc (2 × 25 mL). The organic layer was dried over anhyd Na₂SO₄, and the solvent was removed under vacuum. The crude oily compound obtained was purified by column chromatography (SiO₂, hexanes/ EtOAc, 9:1) to give pure 44 as a yellow viscous liquid (0.080 g, 14%).

1.14 Preparation of ethyl-(2E)-bromo-3-[2'-1(2'-N-benzyloxycarbonyl pyrrolidin-2'-yl] propenoate (45):

![Chemical structure of 45]

To a stirred suspension of pyridinium chlorochromate (0.737 g, 3.42 mmol) and sodium acetate (0.280 g, 3.42 mmol) in anhyd CH₂Cl₂ (20 mL), N-Cbz-prolinol 36 (0.502 g, 2.13 mmol) in anhyd CH₂Cl₂ (10 mL) was added, followed by the addition of carboethoxymethylidene(bromo)triphenyl phosphorane (1.0 g, 2.35 mmol) in one portion. The mixture was stirred for 7 h at room temp. Et₂O (30 mL) was added, and the supernatant solution was decanted from the black granular solid. The combined organic solution was filtered through a short bed of celite, and the filtrate obtained was evaporated to give a residue that was purified by column chromatography (SiO₂, hexanes/ EtOAc, 8:2) to give pure 45 as a yellow viscous liquid (0.568 g, 70%).

IR (neat): ν max 1705 cm⁻¹ (C=O).

¹H NMR (CDCl₃, 300 MHz): δ 1.18-1.29 (2t, J = 7.2 Hz, 3H, CH₃), 1.66-1.86 (2m, 4H, H-3'& H-4'), 2.18-2.90 (m, 2H, NCH₂), 3.42-3.53 (m, 1H, NCH), 4.05-4.23 (2q, J = 7.2 Hz, 2H, OCH₂), 5.02-5.12 (2d, J = 12.0 Hz, 2H, CH₂Ph), 6.53 [7.13] (d, J = 7.8Hz, 1H, H-3), 7.15-7.30 (m, 5H, Ar-H).

¹³C NMR (CDCl₃, 75 MHz): δ 15.5 (CH₃), 25.3 (C-4'), 25.9 (C-3'), 48.5 (CH₂N), 58.5 (CHN), 63.9 (OCH₂), 68.3 (CH₂Ph), 116.4 (CBr), 129.2-129.8 (Ar-H), 137.9 (Ar-C), 148.1 (=CH), 156.3 (CON), 163.4 (COO).
Experimental part of Section B:

1.15 Preparation of (S)-N-bromoacetyl prolinol (47):

A solution of bromoacetyl chloride (3.73 g, 23.7 mmol) in acetone (5 mL) was added dropwise to a stirred solution of (S)-prolinol 35 (2.19 g, 21.5 mmol) and NaOAc (3.53 g, 43.1 mmol) in a mixture of acetone (40 mL) and water (20 mL) at 0-5 °C. The mixture was stirred, and allowed to reach room temp over a period of 2h. The solvent was evaporated under vacuum, residue was suspended in CHCl₃ (50 mL), and washed with water (2 × 25 mL). The CHCl₃ layer was separated, dried over anhyd Na₂SO₄, evaporated under vacuum and the crude product was further purified by column chromatography (SiO₂, hexanes-EtOAc, 1:1) to give 47 as a pale yellow oil (3.11 g, 65%).

\[ [\alpha]_D^{28} = 25.85 \text{ (c 1.18, CHCl}_3) \].

IR (neat): 3400, 1643 cm⁻¹.

\(^1H\) NMR (CDCl₃, 300 MHz): \( \delta 1.63-1.94 \text{ (m, 4H, H-3 & H-4), 3.45-3.58 \text{ (m, 4H, H-5 & CH}_2\text{OH), 3.99 \text{ (s, 2H, CH}_2\text{Br), 4.02-4.09 \text{ (m, 1H, H-2).} } \)

\(^13C\) NMR (CDCl₃, 75 MHz): \( \delta 24.3 \text{ (C-3), 27.9 \text{ (C-4), 42.4 \text{ (C-2), 47.9 \text{ (C-5), 61.5 \text{ (C-2), 65.4 \text{ (OCH}_2), 167.3 \text{ (C=O).} } } \)

HRMS: \( m/z \text{ calcd for C}_7H_{13}O_2N^{79}\text{Br [M + H]}^+ = 222.0129; \text{ found: 222.0132.} \)

1.16 Preparation of (S)-N-prolinolcarbamoylmethylene-triphenyl phosphorane (48):

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A solution containing PPh₃ (0.824 g, 3.14 mmol) and N-bromoacetyl prolinol 47 (0.664 g, 2.99 mmol) in benzene (30 mL) was stirred for 8 h at room temp. Evaporation of benzene resulted in white sticky solid which was washed with Et₂O. The stirred solution of above salt in water (50 mL) and benzene (50 mL) was neutralized by aqueous 2N NaOH to a phenolphthalein end point. The benzene layer was separated, dried over anhyd Na₂SO₄, and concentrated to afford white sticky solid phosphorane 48 (0.993 g, 82%).

IR (neat): 3400, 1616 cm⁻¹.

¹H NMR (CDCl₃, 300 MHz): δ 1.83-2.05 (m, 4H, H-3 & H-4), 2.50 (s, 1H, CHPPh₃), 3.45-3.71 (m, 3H, H-2 & H-5), 4.18-4.21 & 5.16-5.19 (2m, 2H, CI-120H), 7.54-7.91 (m,15H, Ar-H).

¹³C NMR (CDCl₃, 75 MHz): δ 22.9 (CHPPh₃), 24.3 (C-3), 28.4 (C-4), 48.9 (C-5), 63.4 (C-2), 67.1 (OCH₂), 128.4, 128.5, 132.0, 132.1, 133.2 (PPh₃);171.8 (C=O).

1.17 Preparation of (S)-N-bromoacetyl prolinal (50):

To a stirred suspension of PCC (0.62 g, 2.88 mmol) in anhyd CH₂Cl₂ (30 mL) was added N-bromoacetyl prolinol 47 (0.40 g, 1.80 mmol) in anhyd CH₂Cl₂ (10 mL). The mixture was stirred at room temp for 6h. Et₂O (50 mL) was added, and the supernatant solution was decanted from the black granular solid. The combined organic solution were filtered through a bed of celite, and the filtrate obtained was dried over anhyd Na₂SO₄ and evaporated under vacuum to give crude 50 as viscous liquid (0.27 g, 68%).

[α]D²⁹ -64.21 (c 0.366, CHCl₃).

IR (neat): 1743, 1647 cm⁻¹.
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$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 1.08-1.91 (m, 4H, H-3 & H-4), 3.56-3.65 (m, 2H, H-5), 4.05 (s, 2H, CH$_2$Br), 4.45-4.53 (m, 1H, H-2), 9.48 (d, $J = 1.5$ Hz, 1H, CHO).

$^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 24.8 (C-3), 25.7 (C-4), 41.6 (C-2), 47.3 (C-5), 65.2 (C-2), 165.7 (C=O), 198.2 (CHO).

1.18 Preparation of (S)-pyrrolam A (1):

A solution containing PPh$_3$ (90.4 mg, 0.34 mmol) and N-bromoacetyl prolinal 50 (68.9 mg, 0.31 mmol) in benzene (20 mL) was stirred overnight at room temp. Evaporation of benzene resulted in a solid, which was washed with Et$_2$O. THF (20 mL) was added, and the reaction mixture was cooled to 0°C. Sodium hydride [(22.5 mg, 0.56 mmol) 60% in mineral oil washed with THF] was added, and the reaction mixture was stirred for 14 h under N$_2$ atmosphere. Water (20 mL) was added and the reaction mixture was extracted with CHCl$_3$ (3x 25 mL). The organic layer was separated, washed with brine and dried over anhyd Na$_2$SO$_4$. Evaporation of the solvent under vacuum gave the crude product, which was dissolved in Et$_2$O (5 mL), hexane (2 mL) was added and kept in refrigerator. After 1 h, the solution was decanted from solidified Ph$_3$P=O. Maximum amount of Ph$_3$P=O was removed by repeating (3 times) above step. The decanted solution containing (S)-pyrrolam A 1 and little amount of Ph$_3$P=O was separated by reverse phase HPLC on a HiQSil column [C$_8$-C$_{18}$ on silica gel, MeOH/ water, 70:30 (v/v), flow rate = 1.0 mL/min., detection at $\lambda = 254$ nm]. The (S)-pyrrolam A eluted first with a retention time of 10.82 min. followed by the Ph$_3$P=O at 20.81 min.; yield: 16 mg (41%).

$[\alpha]_D^{20} +25.06$ (c O.133, CHCl$_3$) [Lit.$^{11}$ $[\alpha]_D^{20} +25.7$ (c 1, CHCl$_3$)]
1.19 Preparation of polymer bounded Wittig salt of (S)-N-bromoacetyl prolinal (52):

![Chemical Structure](image)

To a stirred suspension of polymer bounded triphenyl phosphine (0.606 g, 3.0 mmol/g) in dry DMF (7 mL), (S)-N-bromoacetyl prolinal 50 (0.5 g, 2.27 mmol) was added, and stirred for 24 h under argon atmosphere. Supported polymer (resin) obtained was filtered off under argon atmosphere, washed with dry toluene (40 mL), dry CH$_2$Cl$_2$ (40 mL), Et$_2$O (60 mL) to give brown powder resin (0.80 g).

1.20 Reaction of N-bromoacetyl prolinal with triethyl phosphite:

![Chemical Structure](image)

Triethyl phosphite (0.661 g, 3.97 mmol) was added to (S)-N-bromoacetyl prolinal 50 (0.875 g, 3.97 mmol), and heated under refluxed temp for 7 h. The crude product obtained was subjected to column chromatography (SiO$_2$, EtOAc) to give yellow oily compound (0.329 g).
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Spectra:

Figure 5. $^1$H NMR spectrum of 36

Figure 6. $^1$H NMR spectrum of 37
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Figure 7. $^{13}$C NMR spectrum of 37

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Figure 8. $^{13}$C NMR spectrum of 38

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Figure 9. $^1$H NMR spectrum of 43

Figure 10. $^{13}$C NMR and DEPT spectrum of 43
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Figure 11. $^{13}$C NMR & DEPT spectrum of 39

Figure 12. $^1$H NMR spectrum of 1
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Figure 13. $^{13}$C NMR and DEPT spectrum of 1

Figure 14. $^1$H NMR spectrum of 47
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Figure 15. $^{13}$C NMR and DEPT spectrum of 47

Figure 16. $^1$H NMR spectrum of 48

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Figure 17. $^{13}$C NMR spectrum of 48

Figure 18. $^{13}$C NMR and DEPT spectrum of 50
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References:


