H08094. Intramolecular Wittig Reaction: A New Synthesis of (S)-Pyrrolam A

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A straightforward synthesis of (S)-pyrrolam A is described. The synthesis involves \textit{in situ} generation of the phosphorane 3, followed by an intramolecular Wittig reaction to furnish (S)-pyrrolam A 1.
**Introduction.** – The pyrrolidine motif is found in a wide range of natural products and biologically active compounds including indolizidine and pyrrolizidine alkaloids [1 – 3]. Pyrrolizidine alkaloids such as pyrrolam A 1 and necines 2 have caught our attention as synthetic targets due to their interesting biological activities [3]. The presence of a C=C bond in these ring systems is crucial for the observed pharmacological activities such as hepatotoxic, mutagenic, carcinogenic activities, etc., associated with these molecules. Pyrrolam A 1 is a pyrrolizidine alkaloid belonging to the community of naturally occurring pyrrolams, which was isolated in 1993 by the Zeeck group from the bacterial strain, *Streptomyces olivaceus* along with pyrrolams B – D [4].

**Formulae 1 and 2**

Owing to its interesting structural feature, (S)- and (R)-pyrrolam A has been a popular target and has been prepared via nine different routes ranging from three steps to over twelve steps. The majority (seven routes) of these syntheses exploited the advantage of the pre-existing chiral center of proline or its derivative as chiral pool [5] with the number of synthetic steps ranging from five to seven. Huang et al. [6a] have achieved the synthesis of (R)-pyrrolam A from (S)-malic acid in twelve steps, while Watson et al. have synthesized it via asymmetric deprotonation methodology from N-Boc pyrrolidine in three steps [6b]. Herein, we report a new synthesis of (S)-pyrrolam A by employing an intramolecular Wittig reaction as the key step.

**Results and Discussion.** – Our retrosynthetic path for 1 is shown in Scheme 1. We envisioned that the formation of the bicyclic ring would take place via intramolecular Wittig olefination of 3 as the key intermediate, which in turn would arise from N-substituted prolinol 4. Further, 4 is readily accessible from L-proline (5).

**Scheme 1**

Thus, prolinol 6 [7], which was obtained from L-proline (5), on addition of bromoacetyl chloride in the presence of AcONa provided (S)-N-(bromoacetyl)prolinol (4) in good yield. The latter was treated with PPh3 to give the corresponding phosphonium salt, which, on deprotonation with aqueous NaOH, provided phosphorane 7, which was subjected to our domino primary alcohol oxidation/Wittig reaction protocol using PCC/AcONa [8].
However, we could not isolate any product other than \( \text{Ph}_3\text{PO} \). Similar tandem oxidation procedures (TOP) using \( \text{MnO}_2 \) \[9\], \text{Dess–Martin} \text{ periodinane} \[10\] or \( \text{IBX} \) \[11\] failed also to provide the expected 1. So, 4 was oxidized to \((S)-N-(\text{bromoacetyl})\text{prolinol} \) 8 with PCC, which formed the corresponding phosphonium salt on reacting with \( \text{PPh}_3 \). However, deprotonation of the salt with aq. \( \text{NaOH} \) did not lead to 1. Hence anhydrous conditions using \( \text{NaH} \) as base were used. This provided pyrrolam A 1 along with \( \text{Ph}_3\text{PO} \). In this step, the phosphorane 3 generated \textit{in situ}, reacted intramolecularly with the aldehyde group as envisaged in \textit{Scheme 2}.  

\text{Scheme 2} 

The expected problematic separation \[6b\] of pyrrolam A from \( \text{Ph}_3\text{PO} \) was effected taking advantage of differing solubilities of the products to get partially enriched pyrrolam A. Further purification was done by reverse phase HPLC using 70% MeOH in \( \text{H}_2\text{O} \) as mobile phase to provide pure pyrrolam A in 18.5% overall yield from \((S)\)-prolinol 6. With the aim of avoiding the cumbersome separation step of pyrrolam A from \( \text{Ph}_3\text{PO} \), \((S)-N-(\text{bromoacetyl})\text{prolinal} \) 8 was treated with triethyl phosphite for obtaining the corresponding phosphonate for a \textit{Horner–Wadsworth–Emmons} (HWE) reaction. This provided an inseparable mixture whose \( ^1\text{H}-\text{NMR} \) analysis indicated the presence of only trace amounts of pyrrolam A. Use of polystyrene-bound triphenylphosphine \[12\] also failed in our hands to give 1. Further, our attempt to obtain 1,2-dihydroxyhexahydropyrrolizin-3-one \[13\] from the mixture of pyrrolam A and \( \text{Ph}_3\text{PO} \) or pyrrolam A itself using \textit{Sharpless} asymmetric dihydroxylation was unsuccessful. This may be due to the unstability of 1 at the reaction conditions.  

\textbf{Conclusions}. – In conclusion, a new short synthesis of \((S)\)-pyrrolam A comprising of three steps from \((S)\)-prolinol \textit{via} intramolecular \textit{Wittig} reaction has been elaborated. Troublesome separation of pyrrolam A from \( \text{Ph}_3\text{PO} \) using reverse phase HPLC was effected.  

We thank DST, New Delhi for financial support and IISc. Bangalore for HRMS facility.

\textbf{Experimental Part} 

\textit{General}. Solvents were purified and dried by standard procedure before use; column chromatography (CC) was performed on silica gel (\( \text{SiO}_2; \) 60 – 120 mesh). Purification was done on a \textit{Jasco HPLC model MX-2080-31} instrument. Optical rotations: \( \text{NaD-line} \) on an
ADP220 polarimeter. IR Spectra: Shimadzu FT-IR spectrophotometer. $^1$H-NMR and $^{13}$C-NMR spectra: Bruker 300 MHz instrument with CDCl$_3$ as solvent and TMS as internal standard. The multiplicities of the C-atom signals were obtained from DEPT experiments.

(S)-N-(Bromoacetyl)prolinol (4). A soln. of bromoacetyl chloride (3.73 g, 23.7 mmol) in acetone (5 ml) was added dropwise to a stirred soln. of (S)-prolinol 6 (2.19 g, 21.5 mmol) and AcONa (3.53 g, 43.1 mmol) in a mixture of acetone (40 ml) and H$_2$O (20 ml) at 0 – 5°. The mixture was stirred and allowed to reach r.t. over a period of 2 h. The solvent was evaporated under vacuum, the residue was suspended in CHCl$_3$ (50 ml) and washed with H$_2$O. The CHCl$_3$ layer was separated, dried (Na$_2$SO$_4$), evaporated under vacuum, and the crude product was further purified by CC (SiO$_2$; hexane/AcOEt, 1:1) to give 4 as pale yellow oil. Yield: 3.11 g (65%). [$\alpha$]$_D^{28} = -25.85$ (c = 1.18, CHCl$_3$). IR (neat): 3400, 1643. $^1$H-NMR (300 MHz): 1.63 – 1.94 (m, 4 H, CH$_2$(3), CH$_2$(4)); 3.45 – 3.58 (m, 4 H, CH$_2$(5), CH$_2$OH); 3.99 (s, 2 H, CH$_2$Br); 4.02 – 4.09 (m, 1 H, H–C(2)). $^{13}$C-NMR (75 MHz): 24.3 (C(3)); 27.9 (C(4)); 42.4 (C(2')); 47.9 (C(5)); 61.5 (C(2)); 65.4 (OCH$_2$); 167.3 (C=O).

1-[(2S)-2-(Hydroxymethyl)pyrrolidin-1-yl]-2-(triphenylphosphanylidene)ethanone (7). A soln. containing PPh$_3$ (0.824, 3.14 mmol) and 4 (0.664, 2.99 mmol) in benzene (30 ml) was stirred overnight at r.t. Evaporation of benzene gave a white sticky solid which was washed with Et$_2$O. The stirred soln. of the above salt in H$_2$O (50 ml) and benzene (50 ml) was neutralized by aq. 2N NaOH. The benzene layer was separated, dried (Na$_2$SO$_4$), and concentrated to afford the white sticky solid 7. Yield: 0.993 g (82%). IR (neat): 3400, 1616. $^1$H-NMR (300 MHz): 1.83 – 2.05 (m, 4 H, CH$_2$(3), CH$_2$(4)); 2.50 (s, 1 H, CHPPh$_3$); 3.45 – 3.71 (m, 3 H, H–C(2), CH$_2$(5)); 4.18 – 4.21, 5.16 – 5.19 (2m, 2 H, CH$_2$OH); 7.54 – 7.91 (m, 15 H, arom. H). $^{13}$C-NMR (75 MHz): 22.9 (CHPPh$_3$); 24.3 (C(3)); 28.4 (C(4)); 48.9 (C(5)); 63.4 (C(2)); 67.1 (OCH$_2$); 128.4, 128.5, 132.0, 132.1, 133.2 (PPh$_3$); 171.8 (C=O).

(S)-N-(Bromoacetyl)prolinal (8). To a magnetically stirred suspension of PCC (0.62 g, 2.88 mmol) in anh. CH$_2$Cl$_2$ (30 ml) was added 4 (0.40 g, 1.80 mmol) in anh. CH$_2$Cl$_2$ (10 ml). The mixture was stirred at r.t. for 6 h. Et$_2$O (50 ml) was added and the supernatant soln. was decanted from the black granular solid. The combined org. soln. was filtered through bed of Celite and the filtrate obtained was dried (Na$_2$SO$_4$) and evaporated under vacuum to give crude 8 as viscous liquid. Yield: 0.27 g (68%). [$\alpha$]$_D^{29} = -64.21$ (c = 0.366, CHCl$_3$). IR (neat): 1743, 1647. $^1$H-NMR (300 MHz): 1.08 – 1.91 (m, 4 H, CH$_2$(3), CH$_2$(4)); 3.56 – 3.65 (m, 2 H, CH$_2$(5)); 4.05 (s, 2 H, CH$_2$Br); 4.45 – 4.53 (m, 1 H, H–C(2)); 9.48 (d, J = 1.5 Hz, 1 H, CHO).
$^{13}$C-NMR (75 MHz): 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).

(S)-Pyrrolam A (= (7aS)-5,6,7,7a-Tetrahydro-3H-pyrrolo[1,2-a]pyrrol-3-one; 1). A soln. containing PPh$_3$ (90.4 mg, 0.34 mmol) and 8 (68.9 mg, 0.31 mmol) in benzene (20 ml) was stirred overnight at r.t. Evaporation of benzene resulted in a solid which was washed with Et$_2$O. THF (20 ml) was added. The mixture was cooled to 0°. NaH ((22.5 mg, 0.56 mmol) 60% in mineral oil washed with THF) was added and the mixture was stirred for 14 h under N$_2$ atmosphere. H$_2$O (20 ml) was added. The mixture was extracted with CHCl$_3$ (3 × 25 ml). The org. layer was separated, washed with brine and dried over (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 the mixture was kept in refrigerator. After 1 h the soln. was decanted from solidified Ph$_3$PO. A maximum amount of Ph$_3$PO was removed by repeating (3 times) the above step. The decanted soln. containing (S)-pyrrolam A 1 and a small amount of Ph$_3$PO was separated by reverse phase HPLC on a HiQSil column (C$_8$ – C$_{15}$ on SiO$_2$, MeOH/H$_2$O, 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$_3$PO at 20.81 min. Yield: 16 mg (41%). $[\alpha]_{D}^{32} = +25.06$ (c = 0.133, CHCl$_3$); ([5b]: $[\alpha]_{D}^{20} = +25.7$ (c = 1, CHCl$_3$)). IR (CHCl$_3$): 1678. $^1$H-NMR (300 MHz): 0.95 – 1.25 (m, 1 H of CH$_2$(7)); 1.80 – 2.05 (m, 1 H of CH$_2$(7)); 2.05 – 2.50 (m, 2 H, CH$_2$(6)); 3.10 – 3.25 (m, 1 H of CH$_2$(5)); 3.25 – 3.45 (m, 1 H of CH$_2$(5)); 4.20 (m, 1 H, H–C(7a)); 5.97 (dd, J = 5.4, 1.5, 1 H, H–C(2)); 7.15 (dd, J = 5.7, 1.5, 1 H, H–C(1)). $^{13}$C-NMR (75 MHz; CDCl$_3$): 28.8 (C(6)); 29.7 (C(7)); 41.7 (C(5)) 67.7 (C(7a)); 128.1 (C(2)); 148.9 (C(1)); 175.4 (C(3)).
REFERENCES


Received March 11, 2008
Figures

Formulae 1 and 2

Scheme 1. *Retrosynthetic path for Pyrrolam A* 1
Scheme 2. Synthesis of (S)-pyrrolam A

a) AcONa, CICOCH₂Br, 0°, 2 h, 65%.  
b) i) PPh₃, benzene, r.t., overnight; ii) 2N NaOH, benzene, 82% (2 steps).

c) PCC, CH₂Cl₂, r.t., 6 h, 68%.

d) i) PPh₃, benzene, r.t., overnight; ii) NaH, THF, 14 h, 41% (2 steps).