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

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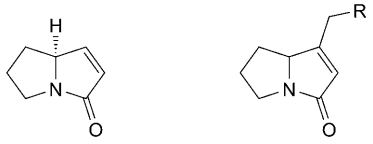
A straightforward synthesis of (*S*)-pyrrolam A is described. The synthesis involves *in situ* generation of the phosphorane **3**, followed by an intramolecular *Wittig* reaction to furnish (*S*)-pyrrolam A.

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 hepatotoxic, mutagenic, and carcinogenic activities 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].

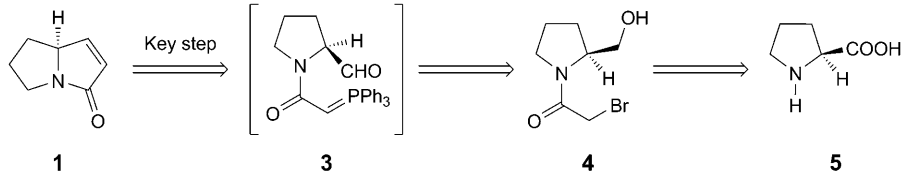


(*S*)-Pyrrolam A (**1**) Necines (**2**)
R= OH or R'COO

Owing to its interesting structural feature, (*S*)- and (*R*)-pyrrolam A have been a popular target and have 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.

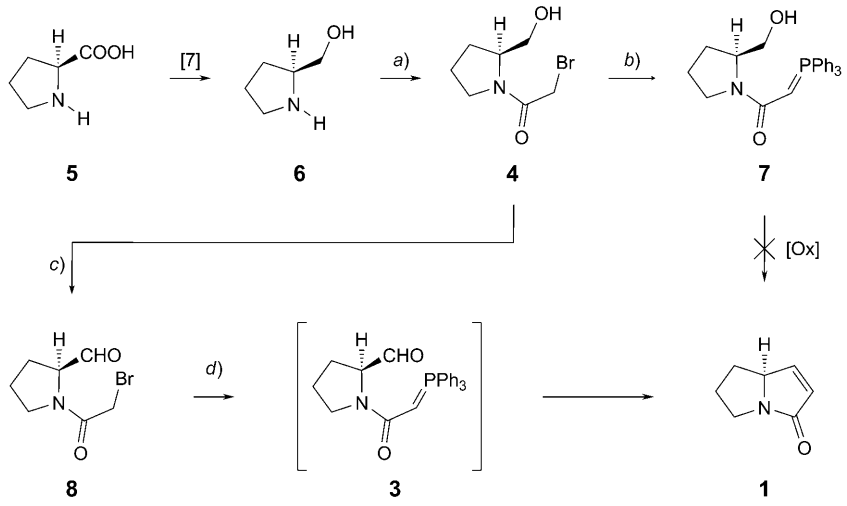
Results and Discussion. – Our retrosynthesic path for **1** is shown in *Scheme 1*. We envisioned that the formation of the bicyclic ring would take place *via* intramolecular *Wittig* olefination of **3** as the key intermediate, which in turn would arise from N-substituted prolinol **4**. Further,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

Scheme 1. *Retrosynthesic Path for* (S)*-Pyrrolam A* (**1**)



Thus, (*S*)-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 PPh_3 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 Ph_3PO. Similar tandem oxidation procedures (TOP) using MnO_2 [9], *Dess–Martin* periodinane [10] or IBX [11] failed also to provide the expected **1**. So, **4** was oxidized to (*S*)-*N*-(bromoacetyl)prolinal (**8**) with PCC, which formed the corresponding phosphonium salt on reacting with PPh_3. However, deprotonation of the salt with aq. NaOH did not lead to **1**. Hence, anhydrous conditions using NaH as base were used. This provided **1** along with Ph_3PO. In this step, the phosphorane **3** generated *in situ*, reacted intramolecularly with the aldehyde group as envisaged in *Scheme 2*.

Scheme 2. *Synthesis of* (S)*-Pyrrolam A* (**1**)



a) AcONa, $ClCOCH_2Br$, 0°, 2 h, 65%. *b*) 1. PPh_3, benzene, r.t., overnight; 2. 2N NaOH, benzene, 82% (2 steps). *c*) PCC, CH_2Cl_2, r.t., 6 h, 68%. *d*) 1. PPh_3, benzene, r.t., overnight; 2. NaH, THF, 14 h, 41% (2 steps).

The expected problematic separation [6b] of pyrrolam A from Ph_3PO 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 H_2O 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 Ph_3PO, (*S*)-*N*-(bromoacetyl)prolinal (**8**) was treated with triethyl phosphite for obtaining the corresponding phosphonate for a *Horner–Wadsworth–Emmons* (HWE) reaction. This provided an inseparable mixture whose ^{1}H-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 Ph_3PO or pyrrolam A itself using *Sharpless* asymmetric dihydroxylation was unsuccessful. This may be due to the unstability of **1** under the reaction conditions.

Conclusions. – In conclusion, a new short synthesis of (*S*)-pyrrolam A comprising of three steps from (*S*)-prolinol *via* intramolecular *Wittig* reaction has been elaborated. Troublesome separation of pyrrolam A from Ph_3PO using reverse phase HPLC was effected.

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Experimental Part

General. Solvents were purified and dried by standard procedure before use. Column chromatography (CC) was performed on silica gel (SiO_2; 60–120 mesh). Purification was done on a *Jasco HPLC model MX-2080-31* instrument. Optical rotations: Na_D-line on an *ADP220* polarimeter. IR Spectra: *Shimadzu FT-IR* spectrophotometer. ^{1}H- and ^{13}C-NMR spectra: *Bruker* 300 MHz instrument with $CDCl_3$ as solvent and Me_4Si 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_2O (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_2O. The $CHCl_3$ layer was separated, dried (Na_2SO_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), C*H*$_2$OH); 3.99 (*s*, 2 H, CH_2Br); 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-[(2*S*)-2-(Hydroxymethyl)pyrrolidin-1-yl]-2-(triphenyl-λ^5-phosphanylidene)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_2O. The stirred soln. of the above salt in H_2O (50 ml) and benzene (50 ml) was neutralized by 2N aq. NaOH. The benzene layer was separated, dried (Na_2SO_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, C*H*PPh_3); 3.45–3.71 (*m*, 3 H, H–C(2), CH_2(5)); 4.18–4.21, 5.16–5.19 (2*m*, 2 H, C*H*$_2$OH); 7.54–7.91 (*m*, 15 H, arom. H). ^{13}C-NMR (75 MHz): 22.9 (*C*HPPh_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_2Cl_2 (30 ml) was added **4** (0.40 g, 1.80 mmol) in anh. CH_2Cl_2 (10 ml). The mixture was stirred at

r.t. for 6 h. Et_2O (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_2SO_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_2Br); 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* (=*(7a*S*)-5,6,7,7a-Tetrahydro-3*H*-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_2O. 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_2O (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_2SO_4). Evaporation of the solvent under vacuum gave the crude product, which was dissolved in Et_2O (5 ml); hexane (2 ml) was added, and the mixture was kept in refrigerator. After 1 h, the soln. was decanted from solidified Ph_3PO. A maximum amount of Ph_3PO was removed by repeating (3 times) the above step. The decanted soln. containing (*S*)-pyrrolam A (**1**) and a small amount of Ph_3PO was separated by reverse phase HPLC on a *HiQSil* column (C_8–C_{15} on SiO_2, MeOH/H_2O, 70 : 30 (*v*/*v*), flow rate 1.0 ml/min, detection at λ 254 nm). The (*S*)-pyrrolam A eluted first with a retention time of 10.82 min, followed by the Ph_3PO 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

[1] J. R. Liddell, *Nat. Prod. Rep.* **2002**, *19*, 773; J. T. Wroble, in 'The Alkaloids: Chemistry & Pharmacology', Ed. A. Brossi, Academic Press, San Diego, 1985, Vol. 26, Chapt. 7, p. 327, and references cited therein; M. Boppré, *Naturwissenschaften* **1986**, *73*, 17.

[2] N. Asano, R. J. Nash, R. J. Molyneux, G. W. J. Fleet, *Tetrahedron: Asymmetry* **2000**, *11*, 1645; S. R. Angle, D. Bensa, D. S. Belanger, *J. Org. Chem.* **2007**, *72*, 5592; J. R. Liddell, *Nat. Prod. Rep.* **1999**, *16*, 499; J. P. Michael, *Nat. Prod. Rep.* **1997**, *14*, 619; R. J. Molyneux, J. E. Tropea, A. D. Elbein, *J. Nat. Prod.* **1990**, *53*, 609.

[3] A. R. Mattock, 'Chemistry and Toxicology of Pyrrolizidine Alkaloids', Academic Press, London, 1986.

[4] R. Grote, A. Zeeck, J. Stümpfel, H. Zähner, *Liebigs Ann. Chem.* **1990**, 525.

[5] a) Y. Aoyagi, T. Manabe, A. Ohta, T. Kurihara, G.-L. Pang, T. Yuhara, *Tetrahedron* **1996**, *52*, 869; b) A. Murray, G. R. Proctor, P. J. Murray, *Tetrahedron* **1996**, *52*, 3757; c) G. B. Giovenzana, M. Sisti, G. Palmisano, *Tetrahedron: Asymmetry* **1997**, *8*, 515; d) M. Arisawa, E. Takezawa, A. Nishida, M. Mori, M. Nakagawa, *Synlett* **1997**, 1179; e) M. Arisawa, M. Takahashi, E. Takezawa, T. Yamaguchi, Y. Torisawa, A. Nishida, M. Nakagawa, *Chem. Pharm. Bull.* **2000**, *48*, 1593; f) M. S. Majik, J. Shet, S. G. Tilve, P. S. Parameswaran, *Synthesis* **2007**, *5*, 663; g) R. Schobert, A. Wicklein, *Synthesis* **2007**, *10*, 1499.

[6] a) P. Q. Huang, Q. F. Chen, C. L. Chen, H. K. Zhang, *Tetrahedron: Asymmetry* **1999**, *10*, 3827; b) R. T. Watson, V. K. Gore, K. R. Chandupatla, R. K. Dieter, J. P. Snyder, *J. Org. Chem.* **2004**, *69*, 6105.

[7] D. Enders, H. Eichenauer, *Chem. Ber.* **1979**, *11*, 2933; Y. St-Denis, T. H. Chan, *J. Org. Chem.* **1992**, *57*, 3078.

[8] J. Shet, V. Desai, S. Tilve, *Synthesis* **2004**, *11*, 1859.

[9] L. Blackburn, X. Wei, R. J. K. Taylor, *Chem. Commun.* **1999**, 1337; S. B. Davies, M. A. McKervey, *Tetrahedron Lett.* **1999**, *40*, 1229.

[10] C. C. Huang, *J. Labelled Compd. Radiopharm.* **1987**, *24*, 675; A. G. M. Barrett, D. Hamprecht, M. Ohkubo, *J. Org. Chem.* **1997**, *62*, 9376.
[11] D. Crich, X.-S. Mo, *Synlett* **1999**, 67; A. Maiti, J. S. Yadav, *Synth. Commun.* **2001**, *31*, 1499.
[12] R. Schobert, C. Jagusch, C. Melanophy, G. Mullen, *Org. Biomol. Chem.* **2004**, *2*, 3524.
[13] I. Izquierdo, M. T. Plaza, J. A. Tamayo, *Tetrahedron: Asymmetry* **2004**, *15*, 3635.

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