

## A Short Synthesis of (*S*)-Pyrrolam A via Domino Oxidation Wittig Reaction

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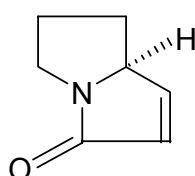
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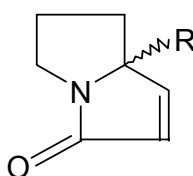
**Abstract:** A short synthesis of (*S*)-Pyrrolam A starting from readily available *N*-benzyloxycarbonyl-L-prolinol is described making use of a domino primary alcohol oxidation Wittig reaction as a key step.

**Keywords:** Domino reaction, Oxidations, Wittig reaction, Assymmetric synthesis, Bicyclic compounds.

Pyrrolizidine and indolizidine alkaloids are important classes of biologically active natural products. The pyrrolizidine skeleton is found in many alkaloids isolated from plant<sup>1</sup> and insects<sup>2</sup>. These alkaloids and their metabolized products serve as pheromones and defensive agents in insect biology and display a range of biological activities in mammals<sup>3</sup>. As a consequence of this bioactivity, efforts have been made during the past two decades, either to isolate new pyrrolizidine alkaloids from nature or design stereocontrolled synthetic routes to these compounds or to their unnatural isomers which might be of interest for SAR studies.



Pyrrolam A



R = OMe

pyrrolam B

R = OH

pyrrolam C

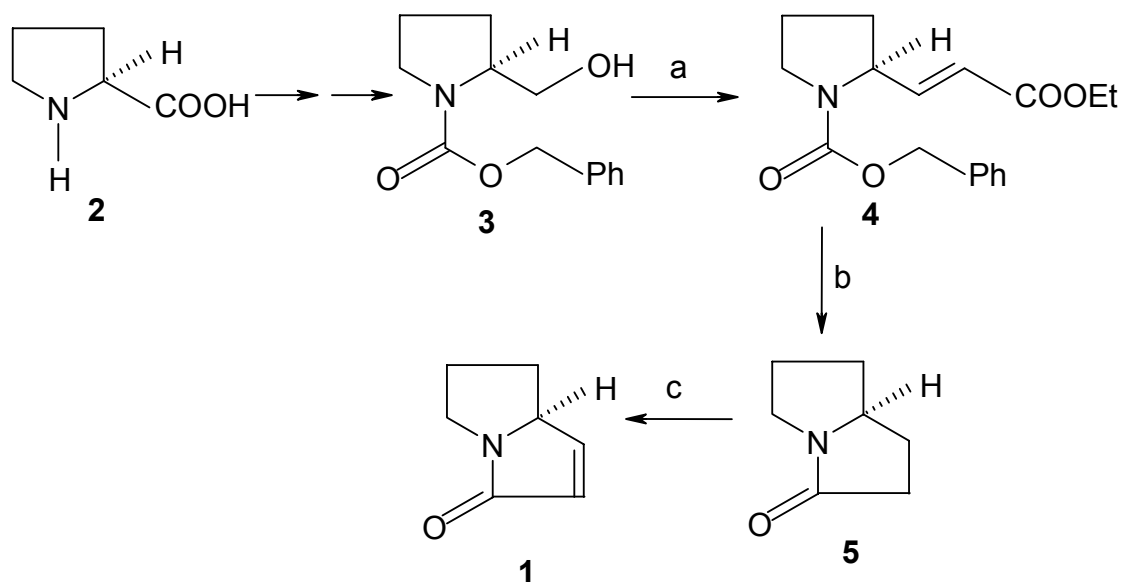
R = OCH(Me)OEt

pyrrolam D

Zeeck and co-workers in 1990 isolated pyrrolam A-D pyrrolizidine alkaloids from the bacterial strain *streptomyces olivaceus* (strain Tu 3082) by elution with methanol from Amberlite XAD-16 resin followed by further purification via column chromatography<sup>4</sup>. Since the initial isolation, several syntheses of pyrrolam A are reported. The first chiral synthesis<sup>5a</sup> utilized a SmI<sub>2</sub> promoted cyclisation, the second approach<sup>5b</sup> uses an intramolecular lactam formation, the third method<sup>5c</sup> uses (*S*)-malic acid as starting compound, the fourth approach<sup>5d,e</sup> utilizes olefin metathesis, fifth uses Dieckmann condensation<sup>5f</sup> and the last utilizes<sup>5g</sup> (-) sparteine for deprotonation for chiral induction.

Domino reaction<sup>9</sup> are not only important for reducing byproduct formation, solvent consumption and time saving but also helps in handling problem associated with unstable intermediates. In continuation of our research interest in developing domino methodologies using phosphorus ylides and their subsequent application to synthesis of naturally occurring and biologically active compounds<sup>6</sup>, we report here in a short route to the synthesis of the (*S*)-pyrrolam **1** from the naturally occurring (*L*)-proline employing a domino oxidation-Wittig reaction as a key step.

It was visualized that Cbz protected prolinol (Scheme 1) on domino oxidation Wittig reaction would furnish the  $\alpha,\beta$ -unsaturated ester **4**, which on reductive cyclisation would give dehydropyrrolam **5** directly, which would then can be converted to pyrrolam **1** via addition/elimination strategy.



### Scheme 1

a) PCC, NaOAc,  $\text{Ph}_3\text{P}=\text{CHCOOC}_2\text{H}_5$ ,  $\text{CH}_2\text{Cl}_2$ ; b)  $\text{H}_2$ , 10% Pd-C/ EtOH, 10hr. then EtONa (Cat.)/EtOH/ $\Delta$ /6hr.; c) LDA, THF(-78<sup>0</sup>C), PhSeCl, then  $\text{H}_2\text{O}_2$ , THF, 0<sup>0</sup>C.

Thus, (*L*)-Proline **2** was converted to the N-benzyloxycarbonyl-*L*-prolinol **3** using a literature procedure<sup>8</sup>. Our group has earlier reported a domino primary alcohol oxidation Wittig reaction approach<sup>6a</sup> as a simple, efficient and economical solution for handling sensitive aldehydes. Using the same protocol, alcohol **3** was then treated with PCC/NaOAc (2molar) along with the 1.5 equivalent of the stable Wittig reagent (carboethoxymethylene)triphenyl phosphorane, we got exclusively ethyl (*E*)-3-[(2<sup>1</sup>*S*)-N-benzyloxycarbonylpyrrolidine-2<sup>1</sup>-yl]propenoate **4** in 76% yield. When reaction was carried out in two separate steps, we could get the ester **4** only in 42% overall yield. The ester **4** was then subjected to a catalytic hydrogenation (Pd/ C;  $\text{H}_2$ ) for the expected reductive cyclisation. However, we obtained an uncyclised amine intermediate instead. During this reduction step, hydrogenation of the double bond took place along with concomitant deprotection in one pot. The expected one pot cyclization did not take place

even after carrying out the reaction at higher temperature (70<sup>0</sup> C). So, the amine intermediate without purification, was refluxed with a catalytic amount of NaOEt in ethanol leading to (*S*)-dehydropyrrolam **5** in 67% overall yield. The next crucial step was the regioselective dehydrogenation of **5** to **1**. This was done by treatment of **5** with LDA at -78<sup>0</sup> C followed by trapping the enolate with PhSeCl (1.2 eq.) resulted in the formation of a phenyl selenium intermediate that was oxidised<sup>7</sup> with H<sub>2</sub>O<sub>2</sub> at 0<sup>0</sup> C to give the crude pyrrolam A **1**. Attempted purification of **1** via silica gel column chromatography gave instead pyrrolam C. Such rearrangement of pyrrolam A to pyrrolam C is reported in one of the synthetic method<sup>5g</sup>. Therefore, the phenyl selenium intermediate was purified first by column chromatography and then subjected to oxidative elimination to give pure (*S*)-(+)-pyrrolam A **1** having  $[\alpha]_{\text{D}}^{27} +22.37^{\circ}$  (c 0.961, CHCl<sub>3</sub>) whose physical and spectroscopic data is in accordance with reported<sup>5g</sup>. Our attempt to avoid cryogenic condition required during the dehydrogenation step via the use of the corresponding selenated or halogenated phosphorane or phosphonate failed.

In conclusion, we have demonstrated utility of domino alcohol oxidation –Wittig reaction approach for a new synthesis of (*S*)-pyrrolam A from L-proline.

Solvent were purified and dried by standard procedure before use; column chromatography was performed on silica gel (60-120 mesh). IR spectra were recorded on Shimadzu FT-IR spectrophotometer. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on a Bruker 300 & 400 MHz instruments using CDCl<sub>3</sub> as solvent and TMS as internal standard. The multiplicities of carbon signals were obtained from Distortionless Enhancement by Polarization Transfer (DEPT) experiment. Optical rotations were measured using sodium D line on ADP220 polarimeter. High resolution mass spectra (HRMS) were recorded on a MicroMass ES-QTOF Mass spectrometer.

#### **Preparation of Ethyl (*E*)-3-[(2<sup>1</sup>*S*)-*N*-benzyloxycarbonylpyrrolidine-2<sup>1</sup>-yl]propenoate (**4**):**

To a magnetically stirred suspension of pyridinium chlorochromate (3.66 g, 17 mmol) and sodium acetate (1.40 g, 17 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (40 mL), Z-prolinol **4** (2.00 g, 8.51 mmol) in anhyd. CH<sub>2</sub>Cl<sub>2</sub> (15 mL) was added, followed by the (carboethoxymethylene)triphenyl phosphorane (4.45 g, 12.8 mmol) in one portion. The mixture was stirred for 7 h at room temp. Et<sub>2</sub>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 using hexanes/ethyl acetate (6:4) as an eluent afforded pure **5** (1.95 g, 76 %) as colorless viscous liquid which had  $[\alpha]_{\text{D}}^{27} -42.553^{\circ}$  (c 0.094, CHCl<sub>3</sub>).

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

<sup>1</sup>H NMR (400 MHz) :  $\delta$  = 1.3 (t, J = 7.0 Hz, 3H, CH<sub>3</sub>), 1.75- 1.90 & 2.01- 2.12 (2m, 4H, H-3<sup>1a</sup>,3<sup>1b</sup>,4<sup>1a</sup>,4<sup>1b</sup>), 3.39- 3.50 & 3.62- 3.76 (2m, 2H, H-5<sup>1a</sup>, 5<sup>1b</sup>), 4.2 (q, J = 7.0 Hz, 2H, OCH<sub>2</sub>), 4.47 & 4.54 (2m, 1H, H-2<sup>1</sup>), 5.07 & 5.14 (2d, J = 12.6 Hz, CH<sub>2</sub>Ph), 5.76 & 5.86

(2d,  $J_{2,3} = 15.4$  Hz, 1H, H-2), 6.80 & 6.84 (2dd,  $J_{2,3}^1 = 5.6$  Hz, 1H, H-3), 7.28-7.35 (m, 5H, Ar-H).

$^{13}\text{C}$  NMR (75 MHz) :  $\delta = 14.0$  ( $\text{CH}_3$ ), 22.5 & 23.7 (C-3<sup>1</sup>), 30.7 & 31.6 (C-4<sup>1</sup>), 46.4 & 46.8 (C-5<sup>1</sup>), 57.7 & 58.0 (C-2<sup>1</sup>), 60.4 ( $\text{OCH}_2$ ), 66.9 ( $\text{CH}_2\text{Ph}$ ), 120.8 (C-2), 127.9, 128.0, 128.9, 136.6(Ph), 147.4 & 147.8 (C-3), 154.7 (Cbz), 166.3 (C-1).

HRMS:  $m/z$  calcd for  $\text{C}_{17}\text{H}_{21}\text{O}_4\text{N}$  (M + Na): 326.1368; found: 326.1361.

**Preparation of (S)-dehydropyrrolam A [(5S)-1-Azabicyclo[3.3.0]octan-2-one] (5):**

A solution of **4** (1.46 g, 4.8 mmol) in EtOH (20 mL) was stirred at room temp. with 10% Pd-C (140mg) in a  $\text{H}_2$  atmosphere (4 psi) for 10 h. The catalyst was filtered off, washed with EtOH and the combined filtrate and washing (50 mL) treated with 2M EtONa (1 mL) and refluxed for 6 h. Then mixture was concentrated and further treated with aq. 10% HCl and subsequently extracted with  $\text{CHCl}_3$  ( $4 \times 20$  mL). The combined organic layer was dried over  $\text{Na}_2\text{SO}_4$ , concentrated and purified by silica gel column using ethyl acetate as an eluent to afford pure pale yellow oil **5** (401 mg, 67%) having  $[\alpha]_{\text{D}}^{27} -20.49^\circ$  (c 0.244,  $\text{CHCl}_3$ )<sup>4</sup>.

IR ( $\text{CHCl}_3$ ):  $\nu_{\text{max}} = 2960, 2890, 1670$   $\text{cm}^{-1}$  (C=O).

$^1\text{H}$  NMR (400 MHz) :  $\delta = 1.32$  (m, 1H, 6-H<sub>b</sub>), 1.73 (m, 1H, 4-H<sub>b</sub>), 1.96-2.28 (m, 3H, 6-H<sub>a</sub>, 7-H<sub>2</sub>), 2.3 (m, 1H, 4-H<sub>a</sub>), 2.44 (dddd,  $J = 1.56, 1.6, 1.52, 1.52$  Hz, 1H, 3-H<sub>b</sub>), 2.75 (m, 1H, 3-H<sub>a</sub>), 3.06 (m, 1H, 8-H<sub>b</sub>), 3.56 (ddd,  $J = 7.88, 3.92, 7.84$  Hz, 1H, 8-H<sub>a</sub>), 3.90 (m, 1H, 5-H).

$^{13}\text{C}$  NMR (75 MHz) :  $\delta = 27.0$  (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  $\text{C}_7\text{H}_{11}\text{ON}$  (M + H): 126.0913; found: 126.0899.

**Preparation of (S)-Pyrrolam A [(5S)-1-Azabicyclo[3.3.0]oct-3-ene-2-one](1):**

To a stirred solution of 2.26 mmol of LDA in 10 mL of THF [prepared by adding 1.6 M n-BuLi in n-hexane (1.41 mL) to diisopropyl amine (0.32 mL, 2.26 mmol)] under the  $\text{N}_2$  atmosphere at  $-78^\circ\text{C}$ , was added drop wise a solution of (S)-dehydropyrrolam **5** (0.235 g, 1.88 mmol) in 2 mL of THF over a period of 5 min. After stirring for additional 10 min., a solution of PhSeCl (0.432 g, 2.26 mmol) in 2 mL of THF was added rapidly. The mixture was stirred to attain room temperature. Solvent was removed under reduced pressure and crude mixture was extracted with  $\text{CHCl}_3$  ( $3 \times 20$  mL) which was then purified by column chromatography using hexanes/ethyl acetate (6:4) as an eluent afforded the corresponding pure phenyl selenium intermediate. To the ice cooled solution ( $0^\circ\text{C}$ ) of this intermediate in 5 mL THF, water (3 mL), acetic acid (0.6 mL) were added followed by slow addition of 2.47 g (2.24 mL) of 30%  $\text{H}_2\text{O}_2$ , keeping the temp. below  $25^\circ\text{C}$ . After stirring for 30 min at  $25^\circ\text{C}$ , the reaction mixture was concentrated under vacuum and then 25 mL of  $\text{CHCl}_3$  and 20 mL of 7%  $\text{NaHCO}_3$  solution was added to it. The aqueous layer was extracted with ( $2 \times 10$  mL)  $\text{CHCl}_3$ , the combined organic layer

was then washed with (2 × 10 mL) water and dried over Na<sub>2</sub>SO<sub>4</sub>. Solvent was removed under vacuum to obtain pure product **1** as a white solid (113 mg, 61 %) having  $[\alpha]_D^{27} +22.37^0$  (c 0.961, CHCl<sub>3</sub>).

IR (CHCl<sub>3</sub>):  $\nu_{\max} = 1678 \text{ cm}^{-1}$ .

<sup>1</sup>H NMR (300 MHz) :  $\delta = 0.95\text{-}1.25$  (m, 1H, 6-H<sub>a</sub>), 1.80-2.05 (m, 1H, 6-H<sub>b</sub>), 2.05-2.50 (m, 2H, 7-H<sub>2</sub>), 3.10-3.25 (m, 1H, 8-H<sub>a</sub>), 3.25-3.45 (m, 1H, 8-H<sub>b</sub>), 4.20 (m, 1H, 5-H), 5.97 (dd, J = 5.4 & 1.5 Hz, 1H, 3-H), 7.15 (dd, J = 5.7 & 1.5 Hz, 1H, 4-H).

<sup>13</sup>C NMR (75 MHz) in CDCl<sub>3</sub>:  $\delta = 28.8$  (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<sub>7</sub>H<sub>9</sub>ON (M + H): 124.0756; found: 124.0745.

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### References:

- (1) (a) Wroble, J.T. in *The Alkaloids: Chemistry & Pharmacology*, Brossi, A., Ed.; Academic Press: San Diego, **1985**; Vol. 26, Chapter 7, p327 & references cited there in. (b) Robins, D.J. *Fortschr. Chem. Org. Naturst.* **1982**, *41*, 115.
- (2) Boppre, M. *Naturwissenschaften*, **1986**, *73*, 17.
- (3) Mattock, A.R. *Chemistry and Toxicology of Pyrrolizidine Alkaloids*, Academic Press: London, **1986**.
- (4) Grote, R.; Zeeck, A.; Stumpf, J.; Zahner, H. *Liebigs Ann. Chem.* **1990**, 525
- (5) (a) Aoyagi, Y.; Manabe, T.; Ohta, A.; Kurihara, T.; Pang, G.L.; Yuhara, T. *Tetrahedron* **1996**, *52*, 869. (b) Giovenzana, G.; Sisti, M.; Palmisano, G. *Tetrahedron Asymmetry* **1997**, *8*, 515. (c) Huang, P.Q.; Chen, Q.F.; Chen, C.L.; Zhang, H.K. *Tetrahedron: Asymmetry* **1999**, *10*, 3827. (d) Arisawa, M.; Tkezawa, E.; Nishida, A.; Mori, M.; Nakagawa, M. *Synlett* **1997**, 1179. (e) Arisawa, M.; Takahashi, M.; Takezawa, E.; Yamaguchi, T.; Torisawa, Y.; Nishida, A.; Nakagawa, M. *Chem. Pharma. Bull* **2000**, *48*, 1593. (f) Murray, A.; Proctor, G.R.; Murray, P.J. *Tetrahedron* **1996**, *52*, 3757. (g) Watson, R.T.; Gore, V.K.; Chandupatla, K.R.; Dieter, R.K.; Snyder, J.P. *J. Org. Chem.* **2004**, *69*(18), 6105.
- (6) (a) Shet, J.B.; Desai, V.; Tilve, S.G. *Synthesis* **2004**, *11*, 1859. (b) Amonkar, C.P.; Tilve, S.G.; Parameswaran, P.S. *Synthesis* **2005**, *14*, 2341.
- (7) Reich, H.J.; Regna, J.; Reich, I.L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.
- (8) (a) Enders, D.; Eichenauer, *Chem. Ber.* **1979**, *11*, 2933. (b) Yves, S.D.; Tak-Hang, C.; *J. Org. Chem.* **1992**, *57*(11), 3078.
- (9) Tietze, L.F. *Chem. Rev.* **1996**, *96*, 195.

