SYNTHESIS
Journal of
Synthetic Organic
Chemistry
REPRINT

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

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Received 19 October 2006; revised 6 December 2006

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

Keywords: domino reaction, oxidation, Wittig reaction, asymmetric 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 plants[1] and insects.[2] These alkaloids and their metabolized products serve as pheromones and defensive agents in insect biology and display a range of biological activity in mammals.[3] 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 that might be of interest for structure–activity relationship studies.

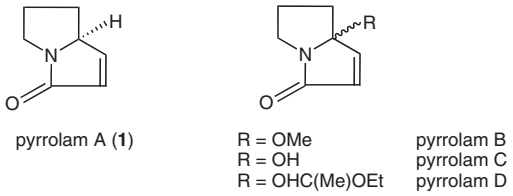
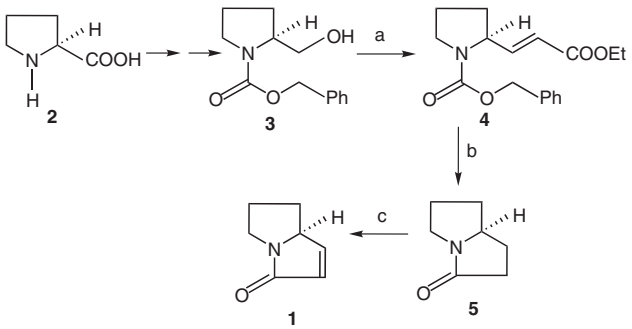


Figure 1

In 1990, Zeeck and co-workers isolated the pyrrolizidine alkaloids pyrrolams A–D from culture broth of the bacterial strain *Streptomyces olivaceus* (strain Tu 3082). The compounds were adsorbed on Amberlite XAD-16 resin, eluted with methanol and subsequently purified by silica gel chromatography (Figure 1).[4] Since initial isolation, several syntheses of pyrrolam A have been reported: (1) the first chiral synthesis by samarium diiodide promoted cyclization;[5a] (2) by intramolecular lactam formation;[5b] (3) using (*S*)-malic acid as the starting compound;[5c] (4) utilizing olefin metathesis;[5d,e] (5) using Dieckmann condensation;[5f] and finally (6) utilizing (–)-sparteine for chiral induction during deprotonation.[5g] Domino reactions[6] are not only important for reducing byproduct formation, solvent consumption, and time saving, but they also assist with respect to handling problems associated with unstable intermediates. In continuation of our research interest in developing domino methodologies using phosphorus ylides, and their subsequent application to the synthesis of naturally occurring and biologically active compounds,[7] herein we report a short synthesis of (*S*)-pyrrolam A (**1**) from naturally occurring L-proline employing a domino oxidation–Wittig reaction as the key step.

It was visualized that domino oxidation–Wittig reaction of benzyloxycarbonyl-protected prolinol **3** would give the α,β-unsaturated ester **4**, which on reductive cyclization would give dehydropyrrolam **5** directly that would then be converted into pyrrolam **1** via an addition–elimination strategy.



Scheme 1 *Reagents and conditions*: (a) PCC, NaOAc, $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 76%; (b) 1. H_2, 10% Pd/C, EtOH, 10 h, 2. NaOEt (cat.), EtOH, heat, 6 h, 67% (2 steps); (c) 1. LDA, THF, –78 °C, 2. PhSeCl, 3. H_2O_2, THF, 0 °C, 61% (2 steps).

Thus, L-proline (**2**) was converted into *N*-(benzyloxycarbonyl)-L-prolinol (**3**) by a literature procedure.[8] Our group earlier reported a domino primary alcohol oxidation–Wittig reaction approach[7a] as a simple, efficient and economical solution for handling sensitive aldehydes. Using the same protocol, alcohol **3** was treated with pyridinium chlorochromate/sodium acetate (2 equiv each) and the stable Wittig reagent (ethoxycarbonylmethylene)triphenylphosphorane (1.5 equiv) to give exclusively ethyl (*E*)-3-[(2*S*)-1-(benzyloxycarbonyl)pyrrolidin-2-yl]prop-2-enoate (**4**) in 76% yield. When reaction was carried out in two separate steps, the ester **4** was obtained in only 42% overall yield. The ester **4** was then subjected to catalytic hydrogenation (Pd/C; H_2) for the expected reductive cyclization. However, we obtained an uncyclized amine

SYNTHESIS 2007, No. 5, pp 0663–0665
Advanced online publication: 08.02.2007
DOI: 10.1055/s-2007-965920; Art ID: Z21406SS

intermediate instead as during this reduction step, hydrogenation of the double bond took place together with concomitant deprotection. The expected one-pot cyclization did not take place even after carrying out the reaction at a higher temperature (70 °C). Hence, the amine intermediate, without purification, was refluxed with a catalytic amount of sodium ethoxide in ethanol leading to (*S*)-dehydropyrrolam (**5**) in 67% overall yield. The next crucial step was the regioselective dehydrogenation of **5** to give **1**. This was done by treatment of **5** with lithium diisopropylamide at –78 °C followed by trapping the enolate with benzeneselenenyl chloride (1.2 equiv) to give a phenylselanyl intermediate that was oxidized[9] with hydrogen peroxide at 0 °C to give the crude pyrrolam A (**1**). Attempted purification of **1** using silica gel column chromatography gave, instead, pyrrolam C. Such rearrangement of pyrrolam A to pyrrolam C has been previously reported.[5g] Therefore, the phenylselanyl intermediate was purified first by column chromatography and then this was subjected to oxidative elimination to give pure (+)-(*S*)-pyrrolam A (**1**) with $[\alpha]_D^{27}$ +22.37 (*c* 0.961, $CHCl_3$) and whose physical and spectroscopic data is in accordance with those reported.[5g] Our attempts to avoid cryogenic conditions required during the dehydrogenation step via the use of the corresponding selenated or halogenated phosphorane or phosphonate failed.

In conclusion, we have demonstrated the utility of the domino alcohol oxidation–Wittig reaction approach for a new synthesis of (*S*)-pyrrolam A (**1**) from L-proline.

Solvents were purified and dried by standard procedures before use; column chromatography was performed on silica gel (60–120 mesh). IR spectra were recorded on Shimadzu FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Brucker 300 MHz and 400 MHz instruments using $CDCl_3$ as solvent and TMS as internal standard. The multiplicities of carbon signals were obtained from DEPT experiments. Optical rotations were measured using sodium D line on ADP220 polarimeter. HRMS were recorded on a MicroMass ES-QTOF.

Ethyl (*E*)-3-[(2*S*)-1-(Benzyloxycarbonyl)pyrrolidin-2-yl]prop-2-enoate (4)

To a magnetically stirred suspension of PCC (3.66 g, 17 mmol) and NaOAc (1.40 g, 17 mmol) in anhyd CH_2Cl_2 (40 mL) was added L-prolinol **3** (2.00 g, 8.51 mmol) in anhyd CH_2Cl_2 (15 mL), followed by the addition of (ethoxycarbonylmethylene)triphenylphosphorane (4.45 g, 12.8 mmol) in one portion. The mixture was stirred at r.t. for 7 h. Et_2O (50 mL) was added and the supernatant solution was decanted from the black granular solid. The combined organic solns were filtered through a short bed of Celite and the filtrate obtained was evaporated to give a residue that was purified by column chromatography (silica gel, hexanes–EtOAc, 6:4) to give pure **4** as colorless viscous liquid; yield: 1.95 g (76%).

$[\alpha]_D^{27}$ –42.553 (*c* 0.094, $CHCl_3$).

IR (neat): 3032 (arom), 1716, 1708, 1699 cm^{-1} (C=O, C=C).

^{1}H NMR (400 MHz): δ = 1.3 (t, *J* = 7.0 Hz, 3 H, CH_3), 1.75–1.90 and 2.01–2.12 (2 m, 4 H, H3′a, H3′b, H4′a, H4′b), 3.39–3.50 and 3.62–3.76 (2 m, 2 H, H5′a, H5′b), 4.20 (q, *J* = 7.0 Hz, 2 H, OCH_2), 4.47 and 4.54 (2 m, 1 H, H2′), 5.07 and 5.14 (2 d, *J* = 12.6 Hz, 2 H, CH_2Ph), 5.76 and 5.86 (2 d, $J_{2,3}$ = 15.4 Hz, 1 H, H2), 6.80 and 6.84 (2 dd, $J_{2',3}$ = 5.6 Hz, 1 H, H3), 7.28–7.35 (m, 5 H, Ar-H).

^{13}C NMR (75 MHz): δ = 14.0 (CH_3), 22.5 and 23.7 (C3′), 30.7 and 31.6 (C4′), 46.4 and 46.8 (C5′), 57.7 and 58.0 (C2′), 60.4 (OCH_2), 66.9 (CH_2Ph), 120.8 (C2), 127.9, 128.0, 128.9, 136.6 (Ph), 147.4 and 147.8 (C3), 154.7 (Cbz), 166.3 (C1).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{21}NNaO_4$: 326.1368; found: 326.1361.

(*S*)-Dehydropyrrolam A [(5*S*)-1-Azabicyclo[3.3.0]octan-2-one] (5)

A soln of **4** (1.46 g, 4.8 mmol) in EtOH (20 mL) was stirred at r.t. with 10% Pd/C (140 mg) under H_2 atmosphere (0.28 bar) for 10 h. The catalyst was filtered off and washed with EtOH and the combined filtrate and washings (50 mL) were treated with 2 M NaOEt (1 mL) and refluxed for 6 h. Then mixture was concentrated and further treated with aq 10% HCl and subsequently extracted with $CHCl_3$ (4 × 20 mL). The combined organic layers were dried (Na_2SO_4), concentrated and purified by column chromatography (silica gel, EtOAc) to afford **5** as a pale yellow oil; yield: 401 mg (67%).

$[\alpha]_D^{27}$ –20.49 (*c* 0.244, $CHCl_3$).

IR ($CHCl_3$): 2960, 2890, 1670 cm^{-1} (C=O).

^{1}H NMR (400 MHz): δ = 1.32 (m, 1 H, H6b), 1.73 (m, 1 H, H4b), 1.96–2.28 (m, 3 H, H6a, H7), 2.3 (m, 1 H, H4a), 2.44 (dddd, *J* = 1.56, 1.6, 1.52, 1.52 Hz, 1 H, H3b), 2.75 (m, 1 H, H3a), 3.06 (m, 1 H, H8b), 3.56 (ddd, *J* = 7.88, 3.92, 7.84 Hz, 1 H, H8a), 3.90 (m, 1 H, H5).

^{13}C NMR (75 MHz): δ = 27.0 (C7), 27.2 (C6), 32.2 (C3), 35.4 (C4), 41.0 (C8), 62.1 (C5), 174.8 (C2).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_7H_{12}NO$: 126.0913; found: 126.0899.

(*S*)-Pyrrolam A [(5*S*)-1-Azabicyclo[3.3.0]oct-3-en-2-one] (1)

To a stirred soln of LDA (2.26 mmol) in THF (10 mL) [prepared by adding 1.6 M BuLi in *n*-hexane (1.41 mL, 2.26 mmol) to *i*-Pr_2NH (0.32 mL, 2.26 mmol)] under a N_2 atmosphere at –78 °C, was added dropwise a soln of (*S*)-dehydropyrrolam (**5**, 0.235 g, 1.88 mmol) in THF (2 mL) over a period of 5 min. After stirring for an additional 10 min, a soln of PhSeCl (0.432 g, 2.26 mmol) in THF (2 mL) was added rapidly. The mixture was stirred to attain r.t. The solvent was removed under reduced pressure and the crude mixture was extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were evaporated and then purified by column chromatography (hexanes–EtOAc, 6:4) to afford the corresponding pure phenylselanyl intermediate. To the ice-cooled (0 °C) soln of this intermediate in THF (5 mL) was added H_2O (3 mL) and AcOH (0.6 mL) followed by slow addition of 30% H_2O_2 (2.47 g, 2.24 mL), keeping the temperature below 25 °C. After stirring at 25 °C for 30 min, the mixture was concentrated under vacuum and then $CHCl_3$ (25 mL) and 7% $NaHCO_3$ soln (20 mL) were added. The aqueous layer was extracted with $CHCl_3$ (2 × 10 mL), the combined organic layers were then washed with H_2O (2 × 10 mL) and dried (Na_2SO_4). The solvent was removed under vacuum to obtain pure product **1** as a white solid; yield: 142 mg (61%).

$[\alpha]_D^{27}$ +22.37 (*c* O.961, $CHCl_3$).

IR ($CHCl_3$): 1678 cm^{-1}.

^{1}H NMR (300 MHz): δ = 0.95–1.25 (m, 1 H, H6a), 1.80–2.05 (m, 1 H, H6b), 2.05–2.50 (m, 2 H, H7), 3.10–3.25 (m, 1 H, H8a), 3.25–3.45 (m, 1 H, H8b), 4.20 (m, 1 H, H5), 5.97 (dd, *J* = 5.4, 1.5 Hz, 1 H, H3), 7.15 (dd, *J* = 5.7, 1.5 Hz, 1 H, H4).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.8 (C7), 29.7 (C6), 41.7 (C8), 67.7 (C5), 128.1 (C3), 148.9 (C4), 175.4 (C2).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_7H_{10}NO$: 124.0756; found: 124.0745.

Acknowledgment

We thank DST, New Delhi for financial support. We also thank IISc. Bangalore for spectral analysis.

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