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Stereoselective total synthesis of (−)-deoxoprosophylline

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Abstract—An efficient synthesis of the prosopis alkaloid (−)-deoxoprosophylline has been developed, utilizing the easily available amino acid L-serine as a chiral pool starting material.

Alkaloids containing multifunctionalized piperidine rings are found abundantly in nature.[1] Prosopis alkaloids, belonging to such a subgroup of alkaloid lipids have been isolated from the leaves, stems and roots of *Prosopis afrikana* and were found to contain a 2,3,6-trisubstituted piperidine framework (Fig. 1).[2] Besides the interesting structural features, these compounds and their synthetic analogs are also of considerable pharmaceutical interest, exhibiting antibiotic, anesthetic and CNS stimulating properties.[1,3] Consequently, several approaches have been developed for the synthesis of these classes of compounds.[4] Described herein is an efficient chiral pool approach for the synthesis of (−)-deoxoprosophylline, starting from the natural amino acid L-serine.

Our retrosynthetic strategy envisions the L-serine-derived homoallylic ketone **2** (Scheme 1) as a key intermediate in the proposed synthesis, wherein, stereoselective reduction of the keto carbonyl will afford the 3*R* secondary hydroxy group, while the terminal alkene can be utilized as a convenient handle towards (i) introduction of the C_{12} side chain, and (ii) forming the piperidine framework. The ketone **2** can in turn be prepared via addition of 3-butenylmagnesium bromide to the known serine-derived Weinreb amide **3**.[5]

1. Results and discussion

In a three-step sequence, the readily available amino acid L-serine was converted to the corresponding *N*,*O*-protected Weinreb amide **3**, following a reported procedure.[5]

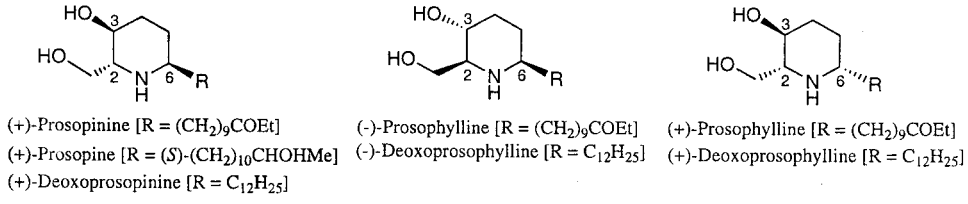
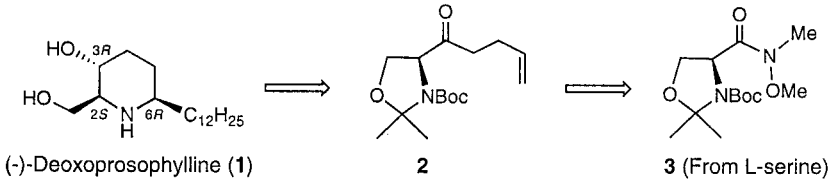


Figure 1. Structures of some prosopis alkaloids and synthetic analogs.



Scheme 1.

Keywords: piperidine alkaloid; chiral pool; chelation control; stereoselection.
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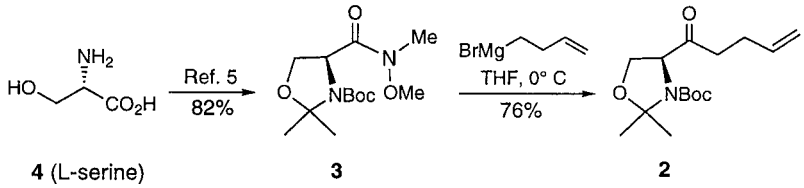
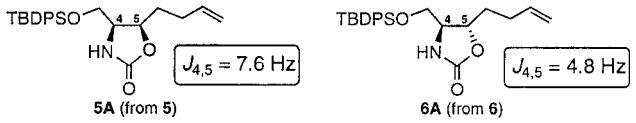


Scheme 2.

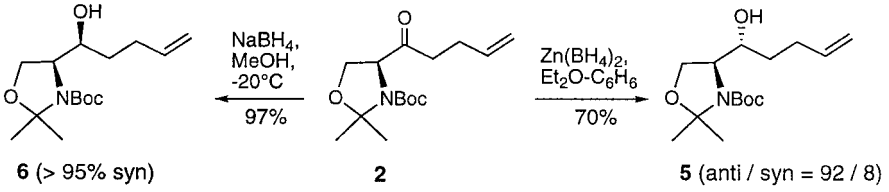
Grignard reaction of the amide **3** with 3-butenylmagnesium bromide uneventfully afforded the pivotal ketone derivative **2** (Scheme 2) in 76% yield.

Having obtained the α-aminoketone **2**, stereoselective reduction of the keto group was then undertaken. Thus, zinc borohydride [$Zn(BH_4)_2$]-mediated chelation-controlled reduction of the ketone **2** was found to form the required amino alcohol derivative **5** (Scheme 3) with good *anti*-selectivity.[6] Interestingly, reduction of the ketone **2** with sodium borohydride ($NaBH_4$) resulted in the exclusive formation of the corresponding 1,2-*syn*-amino alcohol **6** in near-quantitative yield. [The assigned stereochemistry of compounds **5** and **6** were confirmed via their corresponding oxazolidinone derivatives **5A** and **6A** in which the coupling constants between the ring protons (H4–H5) were in good agreement with the assigned structures.]

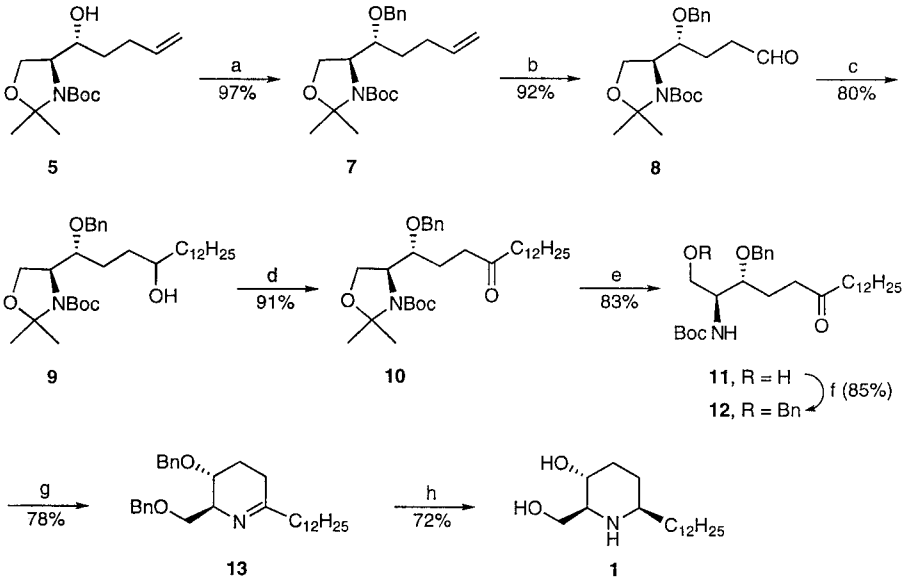


The observed *syn*-selectivity in this reaction is precedented in the literature and has been explained via a non-chelated Felkin–Anh transition state.[7]

Introduction of the dodecyl side chain via functionalization of the terminal olefin was next investigated. Thus, protection of the free hydroxy group of the *anti*-amino alcohol **5** as its benzyl ether derivative **7** (Scheme 4), followed by oxidative degradation of the double bond under standard conditions cleanly afforded the aldehyde **8** in high overall



Scheme 3.



Scheme 4. a. NaH, BnBr; b. i) OsO_4, ii) $NaIO_4$ (on silica gel); c. $C_{12}H_{25}MgBr$; d. 2-Iodoxybenzoic acid; e. 80% AcOH in H_2O; f. BnBr, Ag_2O; g. HCO_2H; h. Palladium hydroxide, H_2, EtOH-HCI.

yield. Grignard reaction of the aldehyde **8** with dodecylmagnesium bromide to form the adduct **9** and subsequent oxidation of the resulting hydroxy group afforded the corresponding ketone **10** in good yield. Towards constructing the target piperidine framework, selective hydrolysis of the acetonide linkage and benzyl protection of the primary hydroxy group yielded the open chain ketone **12**. Treatment of this δ-amino ketone with 96% formic acid resulted in simultaneous *N*-Boc-deprotection and cyclodehydration to form the expected Δ^1-piperidine derivative **13** in 78% yield.[8] Finally, in a one-pot reaction, hydrogenation of the imine double bond and reductive removal of the benzyl protecting groups under standard conditions completed the intended synthesis of (−)-deoxyprosophylline (**1**). The specific rotation and spectral data of **1** were in good agreement with the reported values thereby confirming the structure and the assigned stereochemistry of the product. The observed stereoselectivity in the reduction of the imine can be ascribed to the benzyloxymethyl substituent at the 2-position, directing hydrogenation to occur from the less hindered α-face.

In conclusion, the present synthesis compares well with the earlier reported syntheses of enantiopure deoxoprosophylline and offers an efficient alternative route to this important class of piperidine alkaloids. The strategy and the approach described is of general applicability and lends itself well to the preparation of various possible stereoisomers by choice of the starting amino acid (D- or L-serine) and through selective formation of either the *syn*- or *anti*-1,2-amino alcohol fragment as shown above. Moreover, the side chain at C-6 can be easily modified through introduction of alkyl or aryl groups of choice by using the respective alkyl/aryl Grignard reagent. The described method can thus be easily extended towards synthesizing various prosopis alkaloids and other related compounds of structural and biological importance.

1. Experimental

1.1. General

Reagents and solvents were obtained from commercial suppliers and used as received, unless otherwise noted. Moisture- or air-sensitive reactions were conducted under a nitrogen atmosphere in oven dried (120°C) glass apparatus. Diethyl ether and THF were distilled from sodium benzophenone ketyl prior to use. All yields reported refer to isolated material judged to be homogeneous by TLC and NMR spectroscopy. Column chromatography was performed on silica gel 60 (60–120 mesh), using ethyl acetate/hexane mixture as eluent, unless specified otherwise. The NMR spectra were recorded in $CDCl_3$ on a 200 MHz spectrometer with TMS as the internal standard. Elemental analyses were carried out at the Indian Association for the Cultivation of Science, Jadavpur, Calcutta.

1.1.1. *tert*-Butyl (4*S*)-2,2-dimethyl-4-(1′-oxo-4′-pentenyl)-oxazolidine-3-carboxylate (2). To an ice-cold solution of the Weinreb amide **3**[5] (1.2 g, 4 mmol) in 10 mL of anhydrous THF was added dropwise a solution of 3-butenylmagnesium bromide (10 mmol) [prepared from Mg (0.48 g, 0.02 g atom) and 4-bromo-1-butene (1.35 g, 10 mmol)] in ether (15 mL) and stirred at the same temperature for 3 h. The reaction was quenched by careful addition of an aqueous 10% HCl solution (25 mL) and stirred for 5 min. The resulting solution was extracted with ethyl acetate (3×30 mL), the combined extract washed sequentially with water and brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. Purification of the oily residue by column chromatography (ethyl acetate–hexane=1:15) afforded the pure product **2** (0.9 g, 76%) as a colorless oil: $[\alpha]_D^{22}=-64$ (c=1.3, $CHCl_3$); IR (neat) 1725, 1702 cm^{-1}; ^1H NMR δ 1.41 and 1.52 (2s, 12H), 1.74 (s, 3H), 2.34 (m, 2H), 2.59 (m, 2H), 3.86 (m, 1H), 4.11 (m, 1H), 4.32 (m,1H), 5.0 (m, 2H), 5.79 (m, 1H); MS (FAB+) 284 (MH^+); Anal. Calcd for $C_{15}H_{25}NO_4$ (283.18): C, 63.58; H, 8.89; N, 4.94. Found: C, 63.37; H, 8.90; N, 5.28.

1.1.2. *tert*-Butyl (4*S*,1′*R*)-2,2-dimethyl-4-(1′-hydroxy-4′-pentenyl)oxazolidine-3-carboxylate (5). To a stirred solution of the ketone **2** (2.3 g, 8.1 mmol) in anhydrous ether (15 mL) and benzene (5 mL) at room temperature was added dropwise a solution of freshly prepared zinc borohydride (0.66 M solution in THF, 6.2 mL, 4.06 mmol) and stirred for 10 min. The reaction was quenched by addition of saturated NH_4Cl solution and extracted with ethyl acetate (3×50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), solvent was removed under vacuum and the residue purified by column chromatography (ethyl acetate–hexane=1:10) to yield the *anti*-amino alcohol **5** (1.6 g, 70%) as a viscous liquid: $[\alpha]_D^{22}=-3.2$ (c=1, $CHCl_3$); IR (neat) 3456, 1696 cm^{-1}; ^1H NMR δ 1.51 (s, 15H), 1.78 (br s, 2H), 2.19 (m, 1H), 2.42 (m, 1H), 3.74–4.11 (m, 5H), 5.05 (m, 2H), 5.84 (m, 1H); MS (FAB+) 286 (MH^+); Anal. Calcd for $C_{15}H_{27}NO_4$ (285.19): C, 63.13; H, 9.54; N, 4.91. Found: C, 63.07; H, 9.70; N, 5.28.

1.1.3. *tert*-Butyl (4*S*,1′*S*)-2,2-dimethyl-4-(1′-hydroxy-4′-pentenyl)oxazolidine-3-carboxylate (6). To a stirred solution of the ketone **2** (1.1 g, 3.9 mmol) in dry methanol (35 mL) at −20°C was added sodium borohydride (0.3 g, 8 mmol) in one lot and stirring continued at the same temperature for another 2 h. The reaction was then quenched by addition of water (5 mL), concentrated under vacuum, the residue taken up in ethyl acetate (50 mL) and washed sequentially with water and brine. After drying over anhydrous Na_2SO_4 and removal of solvent the residual oil was purified by column chromatography (ethyl acetate–hexane=1:10) to yield the *syn*-amino alcohol **6** (1 g, 97%) as a viscous liquid: $[\alpha]_D^{22}=-41.5$ (c=0.95, $CHCl_3$); IR (neat) 3458, 1692 cm^{-1}; ^1H NMR δ 1.45 (br s, 15H), 1.53 (br s, 2H), 2.13 (m, 2H), 3.60–4.28 (m, 5H), 4.97 (m, 2H), 5.72 (m, 1H); MS (FAB+) 286 (MH^+).

1.1.4. *tert*-Butyl (4*S*,1′*R*)-4-(1′-benzyloxy-4′-pentenyl)-2,2-dimethyloxazolidine-3-carboxylate (7). To a well-stirred solution of the alcohol **5** (2.6 g, 9.1 mmol) in dry DMF (25 mL) was added tetrabutylammonium iodide (6.7 g, 18.2 mmol) followed by benzyl bromide (2.2 mL, 18.2 mmol). The solution was cooled to 0°C and sodium hydride (95%, 0.33 g, 13.6 mmol) added to it. The solution was allowed to warm to room temperature and stirred for 2 h. The reaction was quenched by addition of saturated NH_4Cl solution and extracted thoroughly with diethyl ether (5×50 mL). The combined organic extracts were

washed sequentially with water and brine, dried (Na_2SO_4), solvent was removed under vacuum and the residue purified by column chromatography (ethyl acetate–hexane=1:24) to yield the benzyl ether derivative **7** (3.32 g, 97%) as a pale yellow liquid: $[\alpha]_D^{22}=-36.2$ (c=1.04, $CHCl_3$); IR (neat) 1697 cm^{-1}; ^1H NMR δ 1.54 (br s, 17H), 2.18 (m, 2H), 3.71–4.18 (m, 4H), 4.57 (br s, 2H), 5.0 (m, 2H), 5.76 (m, 1H), 7.30 (s, 5H); MS (FAB+) 376 (MH^+); Anal. Calcd for $C_{22}H_{33}NO_4$ (375.24): C, 70.37; H, 8.86; N, 3.73. Found: C, 70.07; H, 8.40; N, 3.88.

1.1.5. *tert*-Butyl (4*S*,1′*R*)-4-(1′-benzyloxy-4′-oxo-butyl)-2,2-dimethyl-oxazolidine-3-carboxylate (8). To a room temperature solution of the pentenyl oxazolidine derivative **7** (1.65 g, 4.4 mmol) and *N*-methylmorpholine-*N*-oxide (60% aq. solution, 5 mL, 51.2 mmol) in acetone (10 mL) and water (2 mL) was added a catalytic amount of OsO_4 solution in toluene (5% solution, 5 mol%) and stirred for 8 h. A saturated aqueous solution of Na_2SO_3 (10 mL) was then added to the mixture and extracted with ethyl acetate (3×50 mL). The combined extracts were dried over Na_2SO_4 and solvent removed under vacuum affording the crude dihydroxylated compound (1.7 g) which was dissolved in CH_2Cl_2 (15 mL) and added in one lot to a vigorously stirred suspension of $NaIO_4$ supported in silica gel (7 g, 20% $NaIO_4$)[9] in CH_2Cl_2 (30 mL) maintained at 0°C. After stirring at the same temperature for 1 h, the solid was removed by filtration, washed with $CHCl_3$ (3×25 mL), combined filtrate concentrated under vacuum and the residue filtered through a pad of silica gel column (ethyl acetate–hexane=1:12) yielding the aldehyde **8** (1.53 g, 92% two steps) as a viscous liquid: $[\alpha]_D^{22}=-32$ (c=3.2, $CHCl_3$); IR (neat) 1726, 1697 cm^{-1}; ^1H NMR δ 1.51 (br s, 15H), 1.78 (m, 2H), 2.46 (m, 2H), 3.81 (m, 3H), 4.15 (br s, 1H), 4.53 (m, 2H), 7.3 (s, 5H), 9.70 (s, 1H); MS (FAB+) 378 (MH^+). This aldehyde was found to decompose slowly on storage and was used immediately for the next reaction.

1.1.6. *tert*-Butyl (4*S*,1′*R*)-4-(1′-benzyloxy-4′-hydroxyhexadecyl)-2,2-dimethyl-oxazolidine-3-carboxylate (9). To an ice-cooled solution of dodecylmagnesium bromide (12 mmol) [prepared from Mg (0.6 g, 0.025 g atom) and dodecyl bromide (3 g, 12 mmol)] in anhydrous ether (30 mL) was added dropwise over 15 min, a solution of the oxazolidine aldehyde **8** (1.5 g, 4 mmol) in ether (20 mL). The mixture was then allowed to warm to room temperature and stirred for another 4 h. The reaction mixture was poured into a saturated aqueous NH_4Cl solution (50 mL). The organic layer was separated, aqueous layer extracted with ethyl acetate (3×50 mL), combined extracts washed with brine, dried (Na_2SO_4) and solvent removed under vacuum. The residue on column chromatography (ethyl acetate–hexane=1:7) afforded the adduct carbinol **9** (1.7 g, 76%) as a colorless oil: IR (neat) 3482, 1694 cm^{-1}; ^1H NMR δ 0.88 (br t, J=7.4 Hz, 3H), 1.20 and 1.47 (2s, 41H), 3.48 (m, 1H), 3.67–4.0 (m, 4H), 4.08 (m, 1H), 4.51 (br s, 2H), 7.29 (s, 5H); MS (FAB+) 548 (MH^+). Anal. Calcd for $C_{33}H_{57}NO_5$ (547.42): C, 72.35; H, 10.49; N, 2.56. Found: C, 72.67; H, 10.40; N, 2.91.

1.1.7. *tert*-Butyl (4*S*,1′*R*)-4-(1′-benzyloxy-4′-oxo-hexadecyl)-2,2-dimethyl-oxazolidine-3-carboxylate (10). To a room temperature solution of 2-iodoxybenzoic acid (1.5 g, 5.4 mmol)[10] in anhydrous DMSO (5 mL) was added a solution of the secondary alcohol **9** (1 g, 1.8 mmol) in THF (10 mL) and stirred for 4 h. The reaction was quenched by addition of water (10 mL), the precipitated solid was filtered, filtrate extracted with ether (3×50 mL) and the combined extracts dried over Na_2SO_4. Evaporation of solvent and purification of the crude product by column chromatography (ethyl acetate–hexane=1:12) afforded the pure ketone **10** (0.9 g, 91%) as a colorless oily liquid: $[\alpha]_D^{22}=-21.3$ (c=1.05, $CHCl_3$); IR (neat) 1795, 1694 cm^{-1}; ^1H NMR δ 0.90 (br t, J=7.4 Hz, 3H), 1.29 (br s, 20H), 1.43–1.68 (m, 17H), 2.21–2.52 (m, 4H), 3.58–4.70 (m, 6H), 7.31 (br s, 5H); MS (FAB+) 546 (MH^+); Anal. Calcd for $C_{33}H_{55}NO_5$ (545.41): C, 72.62; H, 10.16; N, 2.57. Found: C, 72.85; H, 10.37; N, 2.88.

1.1.8. (2*S*,3*R*)-3-Benzyloxy-2-(*tert*-butoxycarbonylamino)-1-hydroxyoctadecane-6-one (11). A solution of the ketone **10** (0.82 g, 1.5 mmol) in 80% aqueous acetic acid (10 mL) was stirred at room temperature for 12 h. The reaction mixture was concentrated, residue dissolved in $CHCl_3$ (40 mL), neutralized to pH 7 by careful addition of saturated $NaHCO_3$ solution, organic layer separated, aqueous layer extracted once with $CHCl_3$, combined organic extracts washed with brine and dried (Na_2SO_4). Removal of solvent under vacuum and purification of the residue by column chromatography (ethyl acetate–hexane=1:4) afforded the keto alcohol **11** (630 mg, 83%) as a viscous liquid: $[\alpha]_D^{22}=-4.03$ (c=1, $CHCl_3$); IR (neat) 3451, 1725, 1701 cm^{-1}; ^1H NMR δ 89 (br t, J=7.7 Hz, 3H), 1.30 (s, 20H), 1.41 (br s, 9H), 1.84 (m, 2H), 2.31–2.60 (m, 4H), 3.64 (m, 3H), 3.94 (m, 1H), 4.55 (q, J=6.9 Hz, 2H), 5.15 (br s, 1H), 7.32 (s, 5H); MS (FAB+) 506 (MH^+); Anal. Calcd for $C_{30}H_{51}NO_5$ (505.38): C, 71.25; H, 10.16; N, 2.77. Found: C, 71.52; H, 10.40; N, 2.72.

1.1.9. (2*S*,3*R*)-2-(*tert*-Butoxycarbonylamino)-1,3-dibenzyloxy-octadecane-6-one (12). To a vigorously stirred solution of the alcohol **11** (605 mg, 1.2 mmol) in CH_2Cl_2 (8 mL), at 0°C was added Ag_2O (556 mg, 2.4 mmol) followed by benzyl bromide (0.6 mL, 5 mmol). After stirring at room temperature for 24 h the reaction mixture was filtered, the residual solid washed with CH_2Cl_2 (3×10 mL) and the combined filtrate was concentrated. Purification of the residue by column chromatography (ethyl acetate–hexane=1:9) afforded the benzylated derivative **12** (607 mg, 85%) as a colorless liquid: $[\alpha]_D^{22}=+6.8$ (c=1.2, $CHCl_3$); IR (neat) 1724, 1702 cm^{-1}; ^1H NMR δ 0.88 (br t, J=7.4 Hz, 3H), 1.28 (s, 20H), 1.44 (br s, 9H), 1.71 and 1.92 (2m, 2H), 2.35 (m, 4H), 3.41 (m, 2H), 3.64 (m, 1H), 3.87 (m, 1H), 4.35–4.65 (m, 4H), 4.79 (d, J=9.2 Hz, 1H), 7.27 (s, 10H); MS (FAB+) 596 (MH^+); Anal. Calcd for $C_{37}H_{57}NO_5$ (595.42): C, 74.58; H, 9.64; N, 2.35. Found: C, 74.28; H, 10.01; N, 2.69.

1.1.10. (2*S*,3*R*)-3-Benzyloxy-2-benzyloxymethyl-6-dodecyl-2,3,4,5-tetrahydropyridine (13). A solution of the ketone **12** (500 mg, 0.84 mmol) in CH_2Cl_2 (8 mL) was treated with 98% formic acid (12 mL) at 0°C, followed by stirring at room temperature for 6 h. Excess acid was removed under vacuum, the residue diluted with CH_2Cl_2 (25 mL), cooled to 0°C and neutralized to pH 7 by adding aqueous saturated $NaHCO_3$ solution. The layers were then

separated, aqueous layer extracted with CH_2Cl_2 (2×25 mL) and the combined organic extracts were washed with brine. Drying over Na_2SO_4 and removal of solvent under vacuum afforded the crude Δ^1-piperidine derivative **13** (315 mg, 78%) and was used as such for the next reaction. IR (neat) 1645 cm^{-1}; ^1H NMR δ 0.9 (br t, J=7.1 Hz, 3H), 1.25 (br s, 20H), 1.57 (br s, 2H), 1.98–2.51 (m, 4H), 3.72 (m, 2H), 3.91 (br s, 2H), 4.55 (m, 4H), 7.30 (s, 10H).

1.1.11. (−)-Deoxoprosophylline (1). To a room temperature solution of the imine **13** (300 mg, 0.63 mmol) in EtOH (10 mL) and conc. HCl (0.5 mL) was added Pearlman's catalyst (40 mg) and the suspension stirred vigorously under an atmosphere of hydrogen for 24 h. The reaction mixture was then filtered, the catalyst washed with EtOH (3×10 mL) and the combined filtrate concentrated under vacuum. The residue was dissolved in water (5 mL) and extracted once with ether (10 mL). The aqueous layer was made alkaline by addition of 1N NaOH solution and extracted thoroughly with $CHCl_3$ (5×15 mL). The combined extracts were dried over Na_2SO_4 and solvent removed under vacuum. The residual solid was crystallized from acetone to yield (−)-deoxoprosophylline (**1**) as a white solid (135 mg, 72%): mp=85–86°C (lit.[4f] mp 89.5–90°C); $[\alpha]_D^{22}=-15.2$ (c=0.55, $CHCl_3$) {lit.[4f] $[\alpha]_D^{22}=-14.7$ (c=0.3, $CHCl_3$)}; IR (KBr) 3341, 3247 cm^{-1}; ^1H NMR δ 0.88 (t, J=7 Hz, 3H), 1.28 (br s, 24H), 1.75 (m, 3H, 2H exchangeable with D_2O), 2.05 (m, 1H), 2.53(m, 2H), 3.45 (ddd, J=10.5, 8.9, 4.5 Hz,1H), 3.71 (dd, J=10.7, 5.5 Hz,1H), 3.86 (dd, J=11.0, 5.6 Hz,1H); ^{13}C NMR δ 69.7, 63.7, 63.2, 56.1, 38.4, 33.7, 31.8, 30.9, 29.7, 29.6, 29.3, 26.2, 22.6, 14.0; HRMS (FAB+) calcd for $C_{18}H_{38}NO_2$ 300.2902 (MH^+); found 300.2914; Anal. Calcd for $C_{18}H_{37}NO_2$ (299.28): C, 72.19; H, 12.45; N, 4.68. Found: C, 72.47; H, 12.80; N, 4.92.

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