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New concise asymmetric total synthesis of (+)-desoxoprosophylline and prosophylline

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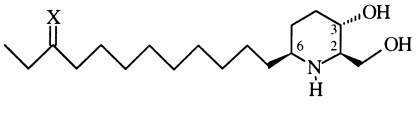
Abstract

Asymmetric total syntheses of (+)-desoxoprosophylline **1** and prosophylline **2** from 1-(α-furyl)-2-phenylmethoxy-*N*-tosylethylamine **3** were accomplished in 10 steps with an overall yield of 4% and in nine steps with an overall yield of 11%, respectively. The oxidation of **3** to dihydropyridone was used as the key step.

1. Introduction

(+)-Desoxoprosophylline **1**, prosophylline **2** and their related compounds are naturally occurring alkaloids isolated from the African mimosa *Prosopis africana* Taub.[1] These polysubstituted piperidine alkaloids exhibit a variety of pharmacological properties such as anesthetic, analgesic and antibiotic activities.[2] Compounds **1** and **2** are particularly intriguing because of their dual physiologically important structural features. The polar head group consists of a piperidine ring similar to the alkaloid deoxynojirimycin, an inhibitor of glucosidase from a variety of sources[3] and potentially valuable therapeutic agent for diabetes mellitus, hyperlipoproteinemia, cancer and arthritis.[4] The lipophilic tail portion, which resembles sphingosine of the membrane sphingolipid, serves to facilitate transfer across membranes. So these alkaloids have become important synthetic targets.[5]



1 X=H,H **2** X=O

During the past several years we have been interested in the preparation of chiral α-furfuryl amine derivatives and the application of these chiral building blocks to the total synthesis of natural products.

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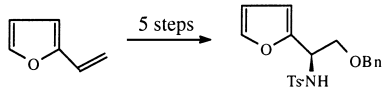
We have developed two methods to prepare these chiral α-furfuryl amine derivatives, one is the kinetic resolution of racemic α-furfuryl amine derivatives using the modified Sharpless asymmetric epoxidation reagent,[6] the other is the diastereoselective addition of organometallic reagents to α-furfuryl imine derivatives.[7] Several natural products and their analogs, such as α-amino acids,[8] δ-hydroxy-α-aminolactones,[9] (+)-azimic acid,[10] dihydropinidine,[11] polyhydroxylated indolizidines[12,13] and 1-deoxyazasugars[14] have been successfully synthesized from the chiral α-furfuryl amine derivatives we have prepared. Very recently, we developed a more convenient method to prepare this chiral α-furfuryl amine derivative **3** from α-furyl ethylene in five steps using Sharpless dihydroxylation as the key step (Scheme 1).[15] This new method could provide a large quantity of **3**, which is a very useful building block for the stereocontrolled synthesis of the polysubstituted piperidines present in a wide variety of natural products. Here we report a full account of the experimental details of the synthesis of (+)-desoxoprosophylline **1**[16] and of prosophylline **2** starting from this building block.



3

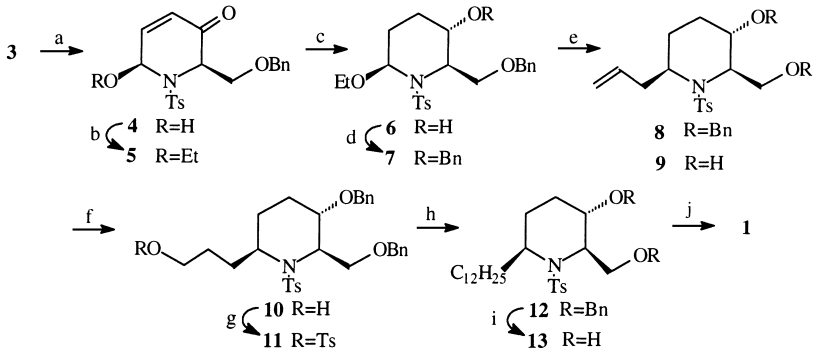
Scheme 1.

2. Results and discussion

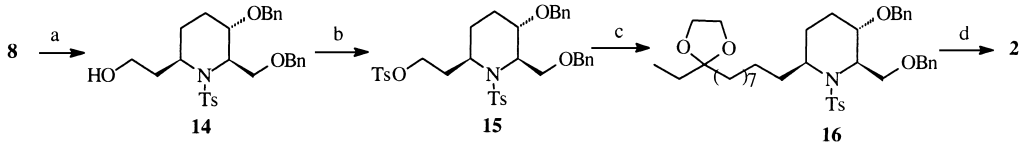
Scheme 2 delineates the synthetic sequence required for the preparation of **1**. Treatment of **3** with *m*-CPBA afforded the dihydropyridone **4**,[17] in which the hydroxyl group was protected with triethyl orthoformate in the presence of $BF_3 \cdot Et_2O$ to give **5**. Reduction of **5** with sodium borohydride in methanol gave the α-hydroxyl product **6**, in which the configuration of C_3 had been proved in our previous report.[11] After protection of **6** with a benzyl group, we initially attempted to introduce the side chain at C_6 directly by reaction of **7** with a Grignard reagent ($C_{12}H_{25}MgBr$), but this reaction gave low stereoselectivity and yield. However treatment of **7** with allyltrimethylsilane in the presence of 0.5 equiv. of titanium tetrachloride at −75°C gave **8** exclusively, this reaction produced **9** as major product when 1.0 equiv. of titanium tetrachloride was present. The stereochemistry of the allyl group was assigned by analogy with the results obtained in allylation of structurally related compounds.[11,18] Hydroboration and oxidation of **8** with a borane–dimethyl sulfide complex, followed by tosylation of the hydroxyl group with tosyl imidazole produced **11**, which was coupled with a Grignard reagent ($C_9H_{19}MgBr$) to afford **12**. Removal of the benzyl group of **12** with Pd–C, H_2 resulted in **13**, the configuration of which was confirmed by 2D-NOESY analysis since there was no NOE correlation between H_2 and H_3. Finally, deprotection of the amino group produced (+)-desoxoprosophylline **1**. Thus the first total synthesis of (+)-**1** was achieved.

In connection with the synthesis of (+)-desoxoprosophylline **1** using this new chiral building block, 1-(α-furyl)-2-phenylmethoxy-*N*-tosylethylamine (**3**),[15] we continued to use this building block for synthesis of a related alkaloid prosophylline **2** as depicted in Scheme 3.

The side chain was introduced by the following procedures: ozonolysis of **8** in CH_2Cl_2:MeOH (9:1) followed by immediate reduction with sodium borohydride in methanol gave the alcohol **14**. Protection of the hydroxyl group of **14** with tosyl imidazole gave the tosylate **15**, which was used to couple with Grignard reagent formed from protected propionylheptyl bromide **17**[5b] and magnesium to afford **16**. Initially, chain extension of the aldehyde through the Wittig method with the ylide formed from **17** afforded very low yield. An attempt to remove simultaneously both the benzyl and tosyl groups of **16**



Scheme 2. (a) *m*-CPBA, CH_2Cl_2, rt, 82%; (b) $HC(OEt)_3$, $BF_3{\cdot}OEt_2$, 4 Å molecular sieves, THF, 0°C, 97%; (c) $NaBH_4$, MeOH, 0°C, 88%; (d) BnBr, NaH, THF, rt, 85%; (e) allyltrimethylsilane, $TiCl_4$, CH_2Cl_2, −78°C, 67%; (f) (i) $BH_3{\cdot}SMe_2$, THF; (ii) NaOH, H_2O_2, 45%; (g) Ts–Im, NaH, THF, 0°C, 87%; (h) $C_9H_{19}MgBr$, Li_2CuCl_4, THF, 0°C, 68%; (i) 10% Pd–C, H_2, EtOH, 84%; (j) liq. NH_3/Na, −78°C, 46%



Scheme 3. (a) (i) O_3, CH_2Cl_2:MeOH (9:1), −78°C; (ii) $NaBH_4$, MeOH, 0°C, 83% from **8**; (b) Ts–Im, NaH, THF, 0°C, 94%; (c) 7-(2-ethyl-1,3-dioxol-2-yl)heptyl bromide **17**/Mg, Li_2CuCl_4, THF, 0°C, 81%; (d) (i) 10% Pd–C, H_2, EtOH; (ii) liq. NH_3/Na, −78°C; (iii) 10% HCl, THF, 75% from **16**

with liq. NH_3 and sodium[19] resulted in a poor yield of **2**, while debenzylation and detosylation proceeded smoothly by separately using Pd–C catalytic hydrogenation and liq. NH_3/Na to give **2**.

In summary, (+)-desoxoprosophylline **1** and prosophylline **2** have been synthesized using a new chiral α-furfuryl amine derivative **3** as a building block, respectively. This chiral building block **3** is very useful for the stereoselective synthesis of the polysubstituted piperidine alkaloids and aza-sugars.

3. Experimental

3.1. General

Melting points were determined with a Büchi 535 melting point apparatus and were uncorrected. All additions were made by syringe. Reactions were monitored by using thin layer chromatography (TLC). The silica gel used in flash chromatography was silica gel H (10 μ) which was produced by the Qingdao Chemical Plant, China. IR spectra were measured on a Shimadzu IR 400 spectrometer. ^{1}H NMR spectra were recorded on a Bruker AM-300 (300 MHz) with $CDCl_3$ as solvent and values were reported in ppm using TMS or residual $CHCl_3$ as internal standard. Mass spectra were obtained on a Finnigan 4021 GC–MS instrument and JMS-01U spectrometer. The optical rotations, $[\alpha]_D^{20}$, were measured on a Perkin–Elmer 241 MC automatic polarimeter in a 1 dm cell and recorded in units of 10^{-1} deg cm^2 g^{-1}. Element analyses were performed by the Analytical Department of this institute. Dichloromethane was distilled from calcium hydride. Tetrahydrofuran was freshly distilled from Na–benzophenone.

3.2. (2R,6S)-1,6-Dihydro-1-tosyl-6-hydroxy-2-phenylmethoxymethyl-3(2H)-pyridinone **4**

To a solution of **3** (1.0 g, 2.69 mmol) in 15 ml of dichloromethane was added *m*-CPBA (1.0 g, 3.23 mmol). After being stirred for 16 h at rt, the solvent was evaporated under reduced pressure to give a solid which was purified by flash column chromatography on silica gel [petroleum ether:ethyl acetate (40:10)] to afford a solid **4** (0.86 g, 82%). M.p. 102–104°C; $[\alpha]_D^{20}$=+3.5 (c=0.8, EtOH); ^{1}H NMR δ: 2.42 (s, 3H, Ts-CH_3), 3.55 (dd, 1H, J=2.6, 9.3 Hz, CH_aH_bOBn), 3.79 (dd, 1H, J=2.2, 9.6 Hz, CH_aH_bOBn), 4.30, 4.42 (ab, 2H, J=11.5 Hz, $PhCH_2$), 4.58 (dd, 1H, J=2.5, 2.2 Hz, 2-H), 4.69 (d, 1H, J=11.8 Hz, OH), 5.94 (dd, 1H, J=4.9, 11.6 Hz, 6-H), 6.10 (d, 1H, J=10.3 Hz, 4-H), 6.92 (dd, 1H, J=5.0, 10.3 Hz, 5-H), 7.10 (m, 2H, Ts), 7.31–7.26 (m, 5H, Ph), 7.77 (d, 2H, J=8.3 Hz, Ts); IR: 3335, 1683 cm^{-1}; MS m/z: 370 (M^++1−H_2O), 263 (M^++1−H_2O−BnO), 155 (Ts), 91 (Bn). HRMS (M^+) calcd for $C_{20}H_{21}NO_5S$: 387.1141. Found: 387.1156.

3.3. (2R,6S)-1,6-Dihydro-1-tosyl-6-ethoxy-2-phenylmethoxymethyl-3(2H)-pyridinone **5**

To 4 Å molecular sieves (0.273 g, 66 mmol) in 15 ml of THF was sequentially added **4** (1.60 g, 4.13 mmol), triethylorthoformate (1.72 ml, 10.3 mmol) and $BF_3\cdot Et_2O$ (57.3 μl) at 0°C. After being stirred for 4 h at 0°C, 5 ml of water was added. The water layer was extracted with ethyl acetate (3×5 ml). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to give an oil which was purified by flash column chromatography on silica gel [petroleum ether:ethyl acetate (40:10)] to afford a solid **5** (1.67 g, 97%). M.p. 106–108°C; $[\alpha]_D^{20}$=−62.6 (c=1.0, EtOH); ^{1}H NMR (600 Hz) δ: 1.197 (t, 3H, J=7.02 Hz, CH_3CH_2), 2.378 (s, 3H, Ts-CH_3), 3.655 (qd, 1H, J=7.02, 9.26 Hz, $CH_3CH_aH_b$), 3.795 (dd, 1H, J=6.71, 10.22 Hz, CH_aH_bOBn), 3.915 (dd, 1H, J=7.66, 10.22 Hz, CH_aCH_bOBn), 3.992 (qd, 1H, J=7.02, 9.42 Hz, $CH_3CH_aH_b$), 4.525, 4.589 (ab, 2H, J=11.8 Hz, $PhCH_2$), 4.632 (dd, 1H, J=6.71, 7.66 Hz, 2-H), 5.641 (d, 1H, J=4.48 Hz, 6-H), 5.826 (d, 1H, J=10.21 Hz, 4-H), 6.754 (dd, 1H, J=4.47, 10.22 Hz, 5-H), 7.221 (d, 2H, J=7.99 Hz, Ts), 7.326 (m, 5H, Ph), 7.587 (d, 2H, J=8.30 Hz, Ts); IR: 1698 cm^{-1}; MS m/z: 415 (M^+), 370 (M^+−EtO), 155 (Ts), 91 (Bn). Anal. calcd for $C_{22}H_{25}NO_5S$: C, 63.59; H, 6.06; N, 3.37. Found: C, 63.52; H, 5.88; N, 3.05.

3.4. (2R,3S,6S)-1-Tosyl-3-hydroxy-6-ethyloxy-2-phenylmethoxymethylpiperidine **6**

To a solution of **5** (1.67 g, 4.02 mmol) in 30 ml of absolute methanol was added $NaBH_4$ (2.14 g, 28 mmol) at 0°C. After being stirred for 3 h, 8 ml of water was added. Work up as usual afforded a crude oil which was purified by flash column chromatography on silica gel [petroleum ether:ethyl acetate (40:10)] to afford an oil **6** (1.48 g, 88%). $[\alpha]_D^{20}$=−21.0 (c=0.4, EtOH); ^{1}H NMR δ: 1.23 (t, 3H, J=7.0 Hz, CH_3CH_2O), 1.51–2.00 (m, 4H), 2.43 (s, 3H, Ts-CH_3), 2.69 (m, 1H), 3.72 (q, 2H, J=7.0 Hz, CH_3CH_2O), 3.78–3.86 (m, 2H), 4.23 (m, 1H), 4.55 (dd, 2H, J=11.8, 16.2 Hz, $PhCH_2$), 5.65 (m, 1H), 7.26–7.38 (m, 7H, Ph), 7.73 (d, 2H, J=8.2 Hz, Ts); IR: 3400, 1600 cm^{-1}; MS m/z: 420 (M^++1), 374 (M^+−OEt), 155 (Ts), 91 (Bn). Anal. calcd for $C_{22}H_{29}NO_5S$: C, 62.98; H, 6.97; N, 3.34. Found: C, 63.45; H, 7.36; N, 2.88.

3.5. (2R,3S,6S)-1-Tosyl-3-phenylmethoxy-6-ethyloxy-2-phenylmethoxymethylpiperidine **7**

To sodium hydride (0.166 g, 6.9 mmol) in 20 ml of DMF at 0°C was added **6** (1.45 g, 3.45 mmol) for 0.5 h, then benzyl bromide (0.49 ml, 4.43 mmol) was added slowly for another 0.5 h. After being stirred for 2 h, 20 ml of aqueous NH_4Cl and 10 ml of water were added sequentially. The mixture was extracted

with ethyl acetate and the combined organic layer was washed with water, dried (Na_2SO_4), evaporated under reduced pressure to afford a crude oil which was purified by flash column chromatography on silica gel [petroleum ether:ethyl acetate (90:10)] to afford an oil **7** (1.48 g, 88%). $[\alpha]_D^{20}$=−27.8 (c=1.5, EtOH); ^{1}H NMR δ: 1.25 (t, 3H, J=7.1 Hz, CH_3CH_2O), 1.74–1.96 (m, 4H), 2.38 (s, 3H, Ts-CH_3), 3.09 (m, 1H), 3.54 (dd, 1H, J=7.8, 10.5 Hz), 3.68–3.76 (m, 2H, CH_3CH_2O), 4.37 (m, 1H), 4.45–4.57 (m, 4H), 4.94 (m, 1H), 6.55 (d, 1H, J=7.7 Hz), 7.11–7.38 (m, 12H, Ph), 7.66 (d, 2H, J=8.4 Hz, Ts); IR: 3050, 1600 cm^{-1}; MS m/z: 464 (M^+−EtO), 402 (M^+−BnO), 308 (M^++1−Ts−EtO), 155 (Ts), 91 (Bn). HRMS (M^++1−Ts−EtO) calcd for $C_{20}H_{22}NO_2$: 308.1650. Found: 308.1629.

3.6. (2R,3S,6R)-1-Tosyl-3-phenylmethoxy-2-phenylmethoxymethyl-6-(2-propenyl)piperidine **8**

To a solution of **7** (0.112 g, 1.0 mmol) in 10 ml of dichloromethane was added allyltrimethylsilane (144 μl, 4 mmol). Then $TiCl_4$ (12 μl, 0.5 mmol) was added at −78°C. After being stirred for 45 min, 5 ml of aqueous $NaHCO_3$ was added, then warmed up to rt. The mixture was diluted with 5 ml of Et_2O and 2 ml of 20% KF was added. Work up as usual afforded a crude oil which was purified by flash column chromatography on silica gel [petroleum ether:ethyl acetate (15:1)] to afford an oil **8** (0.12 g, 67%). $[\alpha]_D^{20}$=+6.1 (c=2.0, EtOH); ^{1}H NMR δ: 1.67 (m, 4H), 2.27 (m, 2H), 2.39 (s, 3H, Ts-CH_3), 3.37 (m, 1H), 3.68 (dd, 1H, J=7.0, 10.1 Hz), 3.90 (m, 2H), 4.45–4.65 (m, 4H, $PhCH_2$), 4.73 (m, 1H), 4.96 (m, 2H), 5.64 (m, 1H), 7.15 (d, 2H, J=8.2 Hz, Ts), 7.23 (m, 10H, Ph), 7.71 (d, 2H, J=8.2 Hz, Ts); IR: 3100, 2850 cm^{-1}; MS m/z: 506 (M^++1), 464 (M^+−allyl), 398 (M^+−BnO), 155 (Ts^+), 91 (Bn^+). Anal. calcd for $C_{30}H_{35}NO_4S$: C, 71.26; H, 6.98; N, 2.77. Found: C, 71.21; H, 6.96; N, 3.07.

3.7. (2R,3S,6S)-1-Tosyl-3-phenylmethoxy-2-phenylmethoxymethyl-6-(1-hydroxy-3-propyl)piperidine **10**

To a solution of **8** (0.309 g, 0.61 mmol) in 15 ml of THF was added $BH_3 \cdot SMe_2$ (36 μl, 10 M) at 0°C. After being stirred for 5 h, aqueous sodium hydroxide (105 μl, 3 M) and 30% of H_2O_2 (105 μl) were added. Work up as usual afforded a crude oil which was purified by flash column chromatography on silica gel [petroleum ether:ethyl acetate (70:30)] to afford an oil **10** (0.18 g, 45%). $[\alpha]_D^{20}$=−16.4 (c=2.2, EtOH); ^{1}H NMR δ: 1.26–1.79 (m, 8H), 2.38 (s, 3H, Ts-CH_3), 3.21 (m, 1H), 3.53 (t, 2H, J=6.0 Hz), 3.73 (dd, 1H, J=7.6, 10.4 Hz), 3.83 (dd, 1H, J=5.1, 10.5 Hz), 3.87 (m, 1H), 4.50 (m, 4H, Bn-CH_2), 4.65 (m, 1H), 7.15 (d, 2H, J=8.1 Hz, Ts), 7.32 (m, 10H, Ph), 7.66 (d, 2H, J=8.1 Hz, Ts); IR: 3450, 3100 cm^{-1}; MS m/z: 524 (M^++1), 506 (M^++1−H_2O), 368 (M^+−Ts), 155 (Ts), 91 (Bn). Anal. calcd for $C_{30}H_{37}NO_5S$: C, 68.81; H, 7.12; N, 2.67. Found: C, 68.89; H, 7.21; N, 2.92.

3.8. (2R,3S,6S)-[1-Tosyl-3-phenylmethoxy-2-phenylmethoxymethyl-6-piperidyl]propyl tosylate **11**

To NaH (25 mg, 1 mmol) in 5 ml of THF was added **10** (0.16 g, 0.306 mmol) (dissolved in 4 ml of THF) at 0°C. Then Ts–Im (0.102 g, 0.459 mmol, dissolved in 0.5 ml of THF) was added for 10 min. After being stirred for 2 h, 2 ml of aqueous NH_4Cl was added. Work up as usual afforded a crude oil which was purified by flash column chromatography on silica gel [petroleum ether:ethyl acetate (50:10)] to afford an oil **11** (0.18 g, 87%). $[\alpha]_D^{20}$=−11.4 (c=1.0, EtOH); ^{1}H NMR δ: 1.26–1.78 (m, 8H), 2.38 (s, 3H, Ts-CH_3), 2.43 (s, 3H, Ts-CH_3), 3.15 (m, 1H), 3.64 (dd, 1H, J=7.6, 10.3 Hz), 3.84 (m, 3H), 4.00 (m, 1H), 4.39–4.61 (m, 5H), 7.14 (d, 2H, J=8.2 Hz, Ts), 7.29 (m, 12H, Ph), 7.61 (d, 2H, J=8.2 Hz, Ts), 7.75 (d, 2H, J=8.2 Hz, Ts); IR: 3050, 2900 cm^{-1}; MS m/z: 678 (M^++1), 572 (M^++2−BnO), 465 (M^++2−2BnO), 155 (Ts), 91 (Bn). Anal. calcd for $C_{37}H_{43}NO_7S_2$: C, 65.56; H, 6.39; N, 2.07. Found: C, 65.80; H, 6.44; N, 2.20.

3.9. (2R,3S,6S)-1-Tosyl-3-phenylmethoxy-2-phenylmethoxymethyl-6-dodecylpiperidine **12**

To a solution of **11** (0.22 g, 0.325 mmol) in 5 ml of THF and Li_2CuCl_4 (1.63 ml, 0.1 M in THF) was added at 0°C nonyl magnesium bromide ($C_9H_{19}MgBr$) (1 ml) prepared from nonyl bromide (0.1 ml) and magnesium (47 mg) in THF (1.5 ml). After being stirred for 1 h, 4 ml of aqueous NH_4Cl was added. Work up as usual afforded a crude oil which was purified by flash column chromatography on silica gel [petroleum ether:ethyl acetate (20:1)] to afford an oil **12** (0.14 g, 68%). $[\alpha]_D^{20}=-7.2$ (c=0.67, EtOH); ^1H NMR δ: 0.88 (t, 3H, J=6.9 Hz, CH_3CH_2), 1.26–1.74 (m, 26H), 2.37 (s, 3H, Ts-CH_3), 3.33 (m, 1H, 6-H), 3.65 (dd, 1H, J=7.2, 10.1 Hz, CH_aH_bOBn), 3.84 (m, 2H), 4.46–4.60 (m, 4H, CH_2Ph), 4.71 (m, 1H, 2-H), 7.13 (d, 2H, J=8.2 Hz, Ts), 7.33 (m, 10H, Ph), 7.70 (d, 2H, J=8.2 Hz, Ts); IR: 3050, 1600 cm^{-1}; MS m/z: 633 (M^+), 477 (M^+-1-Ts), 419 (M^+-2BnO), 155 (Ts), 91 (Bn). Anal. calcd for $C_{39}H_{55}NO_4S$: C, 73.89; H, 8.74; N, 2.21. Found: C, 74.31; H, 9.19; N, 2.42.

3.10. (2R,3S,6S)-1-Tosyl-3-hydroxy-2-hydroxymethyl-6-dodecylpiperidine **13**

To a solution of **12** (0.120 g, 0.190 mmol) in 5 ml of ethanol was added a catalytic amount of 10% Pd/C (12 mg). After the mixture was stirred under H_2 atmosphere (1 atm) at rt for 7.5 h, work up as usual afforded a crude oil which was purified by flash column chromatography on silica gel [petroleum ether:ethyl acetate (30:10)] to afford an oil **13** (72 mg, 84%). $[\alpha]_D^{20}=-4.5$ (c=1.0, EtOH); ^1H NMR δ: 0.88 (t, 3H, J=6.5 Hz, CH_3CH_2), 1.26–1.75 (m, 26H), 2.42 (s, 3H, Ts-CH_3), 3.55 (m, 1H), 3.71 (m, 1H), 3.91 (dd, 1H, J=6.7, 13.3 Hz), 4.13 (dd, 1H, J=6.7, 13.3 Hz), 4.22 (m, 1H), 7.29 (d, 2H, J=8.0 Hz, Ts), 7.73 (d, 2H, J=8.0 Hz, Ts); IR: 3400, 2900 cm^{-1}; MS m/z: 454 (M^++1), 436 (M^++1−H_2O), 422 (M^+-CH_2OH), 155 (Ts). HRMS (M^+-CH_2OH) calcd for $C_{24}H_{40}NO_3S$: 422.2729. Found: 422.2729.

3.11. (+)-Desoxoprosophylline **1**

To the liquid ammonia (10 ml) was added **13** (50 mg, 0.011 mmol) (dissolved in 2 ml of THF) and sodium to keep the solution a blue color. After being stirred for 5 h, the solid NH_4Cl was added. Warming up to rt under N_2, liquid ammonia was evaporated. HCl (2 M, 2 ml) was added. The water was extracted with dichloromethane and 8 ml of saturated $NaHCO_3$ was added to the water layer, then 5 ml of 3 M NaOH was added to make pH=11. Work up as usual afforded a crude oil which was purified by flash column chromatography on silica gel (first, toluene:ethanol=5:1, then toluene:ethanol=1:5 with 5% of Et_3N) to afford a colorless solid **1** (15 mg, 46%). M.p. 89.5–90°C; $[\alpha]_D^{20}=+14.4$ (c=0.32, $CHCl_3$); ^1H NMR δ: 0.89 (t, 3H, J=6.1 Hz, CH_3), 1.24–1.88 (m, 26H), 1.92–2.00 (m, 1H, N-H), 2.58 (m, 1H), 3.47 (m, 2H), 3.78 (m, 1H), 3.86 (m, 1H); IR: 3338, 3238 cm^{-1}; MS m/z: 300 (M^++1), 282 (M^++1−H_2O), 268 (M^+-CH_2OH), 130 ($M^+-C_{12}H_{25}$). HRMS (M^+) calcd for $C_{18}H_{37}NO_2$: 299.2824. Found: 299.2843. The enantiomer of **1** had m.p. 90.5, $[\alpha]_D^{21}=-14.4$ (c=0.24, $CHCl_3$). The ^1H NMR and the mass spectrum of **1** were identical with the literature data.[5d]

3.12. (2R,3S,6R)-1-Tosyl-3-phenylmethoxy-2-phenylmethoxymethyl-6-(1-hydroxy-2-ethyl)piperidine **14**

A solution of **8** (93 mg, 0.18 mmol) in 5 ml of CH_2Cl_2:CH_3OH (9:1) was bubbled with ozone at −78°C for 5 min until a light blue color appeared. The excess of ozone was removed by passing through N_2 and 1 ml of Me_2S was added. The reaction mixture was stirred at rt for 1 h and evaporated under reduced pressure to give a residue. To a solution of the residue in 5 ml of MeOH was added $NaBH_4$ (46 mg, 1.2 mmol) in portions at 0°C. The reaction mixture was stirred at 0°C for 1 h, 2 ml of aqueous NH_4Cl was

added. Work up as usual afforded a crude oil which was purified by flash column chromatography on silica gel [petroleum ether:ethyl acetate (30:10)] to afford an oil **14** (78 mg, 83%). $[\alpha]_D^{20}$=−37.7 (c=3.8, $CHCl_3$); ^{1}H NMR δ: 1.26–1.66 (m, 6H), 2.39 (s, 3H, Ts-CH_3), 3.11 (m, 1H), 3.58 (m, 1H), 3.70 (dd, 1H, J=7.5, 10.4 Hz, BnOCH_aH_b), 3.81 (dd, 1H, J=5.0, 10.5 Hz, $C_6H_5OCH_aH_b$), 3.91 (m, 1H), 4.10 (m, 1H), 4.53 (m, 5H, 2-H and $PhCH_2$), 7.17 (d, 2H, J=8.0 Hz, Ts), 7.31 (m, 10H, Ph), 7.62 (d, 2H, J=8.2 Hz, Ts); IR: 3537, 1598 cm^{-1}; MS m/z: 510 (M^++1), 492 (M^++1−H_2O), 294 (M^+−1−2BnO), 155 (Ts). HRMS (M^+) calcd for $C_{29}H_{35}NO_5S$: 509.2208. Found: 509.2236.

*3.13. (2*R*,3*S*,6*R*)-[1-Tosyl-3-phenylmethoxy-2-phenylmethoxymethyl-6-piperidyl]ethyl tosylate **15***

To a solution of **14** (130 mg, 0.257 mmol) in 3 ml of THF was added sodium hydride (21 mg, 60% purity, 0.525 mmol) at 0°C. After the reaction mixture was stirred at 0°C for 10 min, Ts–Im (85 mg, 0.383 mmol) was added. The reaction mixture was stirred at 0°C for 3 h and aq. NH_4Cl solution was added. Work up as usual afforded a crude oil which was purified by flash column chromatography on silica gel [petroleum ether:ethyl acetate (50:10)] to afford an oil **15** (161 mg, 94%). $[\alpha]_D^{20}$=−8.2 (c=5.4, $CHCl_3$); ^{1}H NMR δ: 1.26 (m, 6H), 2.38 (s, 3H, Ts-CH_3), 2.44 (s, 3H, Ts-CH_3), 3.23 (m, 1H), 3.70 (m, 2H, CH_2OBn), 4.00 (m, 3H), 4.41∼4.56 (m, 4H, $PhCH_2$), 4.60 (m, 1H, 2-H), 7.13 (d, 2H, J=8.0 Hz, Ts), 7.30 (m, 12H, Ph), 7.60 (d, 2H, J=8.2 Hz, Ts), 7.75 (d, 2H, J=8.3 Hz, Ts); IR: 3064, 1598 cm^{-1}; MS m/z: 665 (M^++2), 542 (M^+−CH_2OBn), 508 (M^+−Ts), 401 (M^+−BnO−Ts), 246 (M^+−OBn−2Ts). HRMS (M^+−OBn−2Ts) calcd for $C_{15}H_{20}NO_2$: 246.1494. Found: 246.1503.

*3.14. (2*R*,3*S*,6*S*)-1-Tosyl-3-phenylmethoxy-2-phenylmethoxymethyl-6-[9-(2-ethyl-1,3-dioxol-2-yl)-nonyl]piperidine **16***

To a solution of **15** (72 mg, 0.108 mmol) in 1 ml of THF at 0°C was added Li_2CuCl_4 (0.048 ml, 0.114 M in THF) and 7-(2-ethyl-1,3-dioxol-2-yl)heptyl magnesium bromide (0.5 ml) prepared from **20** (0.18 ml) and magnesium (31 mg) in THF (1.5 ml). The reaction mixture was stirred at 0°C for 1 h and aq. NH_4Cl solution was added. Work up as usual afforded a crude oil which was purified by flash column chromatography on silica gel [petroleum ether:ethyl acetate (12:1)] to afford an oil **13** (67 mg, 89%). $[\alpha]_D^{20}$=−5.3 (c=4.1, EtOH); ^{1}H NMR δ: 0.91 (t, 3H, J=7.4 Hz, CH_2CH_3), 1.21–1.65 (m, 24H), 2.39 (s, 3H, Ts-CH_3), 3.31 (m, 1H), 3.66 (m, 1H), 3.84 (m, 2H, CH_2OBn), 3.93 (s, 4H, OCH_2CH_2O), 4.46 (m, 2H, $PhCH_2$), 4.60 (m, 2H, $PhCH_2$), 4.71 (m, 1H, 2-H), 7.12 (d, 2H, J=8.0 Hz, Ts), 7.29 (m, 10H, Ph), 7.69 (d, 2H, J=8.2 Hz, Ts); IR: 3064, 1599 cm^{-1}; MS m/z: 693 (M^++2), 663 (M^+−CH_2CH_2), 536 (M^+−Ts) and 155 (Ts^+). Anal. calcd for $C_{41}H_{57}NO_6S$: C, 71.17; H, 8.30; N, 2.02. Found: C, 71.42; H, 8.67; N, 1.93.

*3.15. Prosophylline **2***

To a solution of **16** (70 mg, 0.102 mmol) in 4 ml of ethanol was added 10% Pd/C (17 mg), and the solution was stirred under H_2 atmosphere (1 atm) for 10 h. The mixture was filtered and concentrated under reduced pressure. The residue was purified by chromatography to give an oil (50 mg) which was added to liquid ammonia and sodium was added. The mixture was kept blue by replenishing sodium. After the reaction mixture was stirred at −55°C for 4 h, NH_4Cl (200 mg) was added. The mixture was warmed up to rt, and ammonia was evaporated. NH_4Cl solution was added. The mixture was extracted with CH_2Cl_2, dried over Na_2SO_4 and concentrated to afford a residue, which was purified by silica gel column chromatography to give an oil (24 mg). To a solution of the oil in THF (2 ml) was added 10% HCl

(0.6 ml). The mixture was stirred at rt for 2 h, neutralized with saturated $NaHCO_3$ (2 ml) and extracted with $CHCl_3$. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give a solid which was purified by flash column chromatography on silica gel [toluene:EtOH (4:1)] to afford crystals (11 mg, 75%). M.p. 79.5–81°C; $[\alpha]_D^{20}$=0 (c=0.5, $CHCl_3$); [lit.[1]: m.p. 79°C; $[\alpha]_D$ 0]; ^{1}H NMR δ: 1.06 (t, 3H, J=7.3 Hz, CH_3CH_2), 1.29–1.61 (m, 20H), 1.90–1.94 (m, 1H, N-H), 2.43 (m, 4H, CH_2COCH_2), 2.56 (m, 1H), 2.75 (m, 1H), 3.74–3.83 (m, 3H); IR: 3350 cm^{-1}; MS m/z: 314 (M^++1), 282 (M^+-CH_2OH), 130 ($M^+-CH_3CH_2CO(CH_2)_9$), 57 ($CH_3CH_2CO^+$). The ^{1}H NMR and the mass spectra of **2** were identical with the literature data.[1]

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