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Stereoselective Approach to 2,6-Disubstituted Piperidin-3-ol: Synthesis of (–)-Deoxoprosopinine and (+)-Deoxoprosophylline

Vishwajeet Jha,[a] Shruti Vandana Kauloorkar,[a] and Pradeep Kumar*[a]

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A simple and highly efficient approach to an enantioenriched 2,6-disubstituted piperidin-3-ol skeleton is developed from an aldehyde as a starting material by using organocatalytic and asymmetric dihydroxylation as the key steps. Its application to the total synthesis of (–)-deoxoprosopinine and (+)-deoxoprosophylline is also reported.

Introduction

Naturally occurring alkaloids that contain a multi-functionalized piperidine ring system as a key constituent are abundant in nature. Most of them exhibit potent biological activity and are of medicinal and pharmacological interest.[1] Among them, prosopis alkaloids that were isolated from the leaves of *Prosopis afrikana* Taub,[2] exhibit antibiotic, anesthetic, analgesic and central nervous system stimulating properties. Typical representatives include prosopinine **1**, prosophylline **2** and their deoxo analogues deoxoprosopinine **3**, deoxoprosophylline **4**, which all contain a 2,6-disubstituted piperidin-3-ol framework (Figure 1). The unique structural features of these alkaloids are known to resemble the acyclic structure of sphingolipids such as, safingol **5** and sphingosine **6**, which contain a hydrophobic aliphatic tail and a hydrophilic headgroup.[3] The polar headgroup is required for glycosidase inhibition,[4] whereas the hydrophobic tail facilitates transfer across the lipid membrane, which enhances their therapeutic potential for the treatment of diseases such as diabetes, viral infection and cancer.

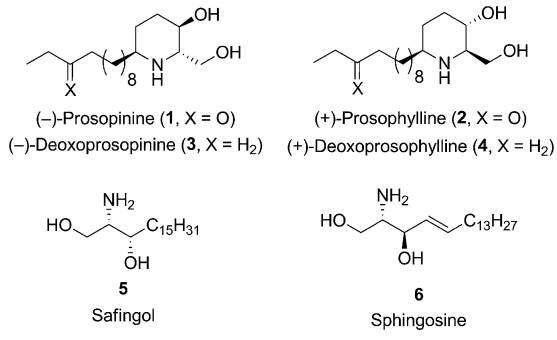

Figure 1. Examples of prosopis alkaloids (**1**-**4**) and sphingoid bases (**5** and **6**).

Owing to their promising biological activities and structural features, these alkaloids have received considerable interest as synthetic targets. Various syntheses[5,6] of this class of compounds have been reported, however the literature describing a general synthetic strategy to construct the 2,6-disubstituted piperidin-3-ols framework is sparse.[5g,5j] Also the majority of the syntheses of deoxoprosopinine and deoxoprosophylline employ chiral-pool starting materials such as sugars and amino acids, which involve a large number of steps, protection-deprotection strategies that result in lower overall yields. Therefore, it is highly desirable to develop a concise, enantioselective and general synthetic route that provides a common pivotal intermediate from which piperidin-3-ol derivatives with desired stereochemical variations can be synthesized.

In continuation of our interest in organocatalysis,[7] we herein describe a general, stereoselective and protecting-group-free synthetic strategy to the 2,6-disubstituted piperidin-3-ols framework, which has led to the total syntheses of (–)-deoxoprosopinine **3** and (+)-deoxoprosophylline **4** by using sequential α-amination and Horner–Wadsworth–Emmons (HWE) olefination reaction catalyzed by proline,[8] as well as asymmetric dihydroxylation[9] as the key steps.

Results and Discussion

Our synthetic approach was envisioned to be through the retro-synthetic route shown in Scheme 1. Amino diol **7** was thought to be a common intermediate for the synthesis of compounds **3** and **4**, which could be synthesized from alcohol **8**. Alcohol **8** could in turn be obtained from sequential α-amination and HWE olefination followed by reduction of aldehyde **9**.

[a] Division of Organic Chemistry, CSIR – National Chemical Laboratory,
Pune 411008, India
E-mail: pk.tripathi@ncl.res.in
http://newhome.ncl.res.in

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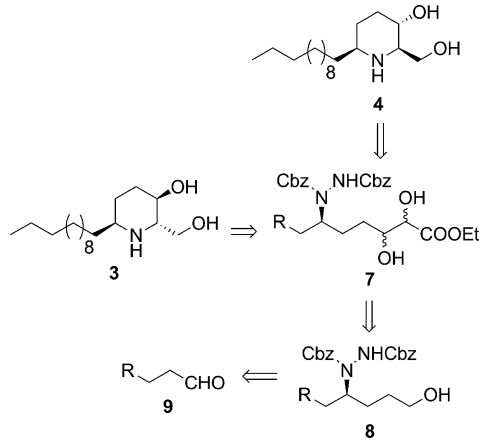


Scheme 1. Retrosynthetic route to the synthesis of 2,6-disubstituted piperidin-3-ols framework.

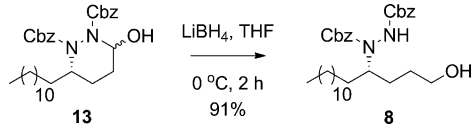
As illustrated in Scheme 2, the synthesis starts with myristyl aldehyde **9**, which on sequential α-amination with DBAD (dibenzyl azodicarboxylate) as a nitrogen source, D-proline as the catalyst, CH_2Cl_2 as the solvent and subsequent HWE olefination with the ylide generated from triethyl phosphonoacetate[10a,10b] furnished γ-amino α,β-unsaturated ester **10** in 82% yield and 94% *ee*.[11] With γ-amino α,β-unsaturated ester **10** in hand, we next reduced the ester group. For this purpose ester **10** was treated with $LiBH_4$, with concomitant reduction of the double bond[7c] to give alcohol **8** in 95% yield. To prepare *trans*-olefin **11**, alcohol **8** was oxidized with Dess–Martin periodinane (DMP)[12] to furnish the aldehyde, which was then subjected to HWE olefination (ylide generated from triethyl phosphonoacetate with NaH as a base), but to our disappointment we obtained hemiaminal **13** as the major product with desired *trans*-olefin **11** in only 18% yield. The formation of **13** was confirmed by using NMR spectroscopy and HRMS. We then tried various other conditions to increase the yield of the *trans*-olefin and the results are summarized in Table 1. There was no substantial increase in yield when different bases [such as 1,8-diazabicycloundec-7-ene (DBU), Cs_2CO_3 and so on] were used to generate the ylide from triethyl phosphonoacetate. When (ethoxycarbonylmethylene)triphenyl phosphorane[10c] was used as the Wittig reagent in THF solvent, we obtained *trans*-olefin **11** in 54% yield along with *cis*-olefin **12** in 26% yield, and cyclized product **13** in 14% yield (Table 1, Entry 4). To reduce the formation of *cis*-olefin **12**, the reaction was carried out in toluene under reflux conditions to provide *trans*-olefin **11** in 70% yield with a small amount of *cis*-olefin **12**. All three products were easily separated by using silica-gel column chromatography (Scheme 2).

Table 1. Optimization of Wittig reaction conditions.

Entry	Wittig reagent	Base	Solvent	**11** [%]	**12** [%]	**13** [%]
1	HWE[a]	NaH	THF	17		75
2	HWE	DBU	CH_3CN	32		60
3	HWE	Cs_2CO_3	CH_3CN	34		57
4	2-C Wittig[b]	–	THF	54	26	14
5	2-C Wittig	–	Toluene (reflux)	70	7	16

[a] HWE: triethyl phosphonoacetate. [b] 2-C Wittig: (ethoxycarbonylmethylene)triphenylphophorane.

Surprisingly, compound **13** was reduced with $LiBH_4$ to reform starting alcohol **8** (Scheme 3).

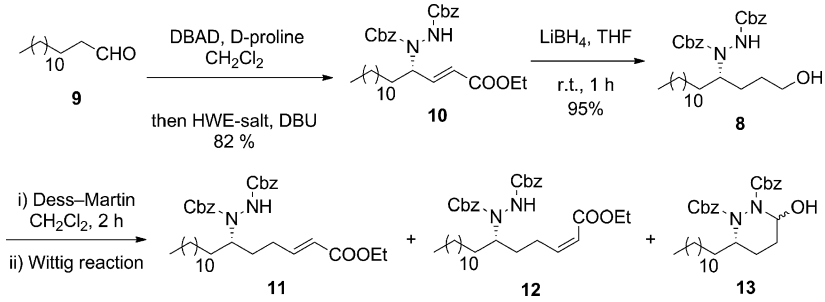


Scheme 3. Reduction of cyclized product **13**.

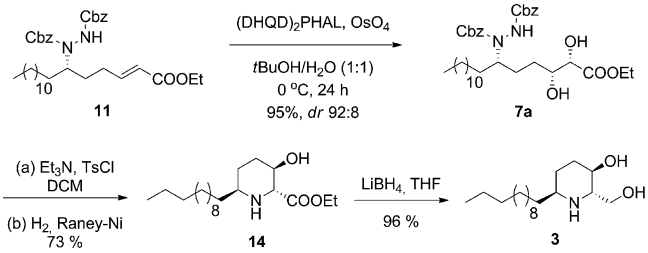
With desired *trans*-olefin **11** in hand, the stage was set to functionalize the double bond. For this purpose, olefin **11** was subjected to Sharpless asymmetric dihydroxylation[9] reaction conditions with $(DHQD)_2PHAL$ as a ligand to give diol **7a** in 95% yield and 92:8 *dr* ratio. Regioselective monotosylation[13] of diol **7a** with tosyl chloride (TsCl) resulted in the α-tosylate that upon concomitant cleavage of the N–N bond with Raney-Ni gave the free amine, which on nucleophilic displacement of the α-tosylate led to the formation of cyclized product **14** in 73% yield. Finally, reduction of **14** with $LiBH_4$ produced (–)-deoxoprosopinine **3** in 96% yield (Scheme 4).

In a similar way, as illustrated in Scheme 5, (+)-deoxoprosophylline (**4**) was synthesized by using $(DHQ)_2PHAL$ as a ligand in the Sharpless asymmetric dihydroxylation reaction step by following a series of reactions analogous to those shown in Scheme 4.

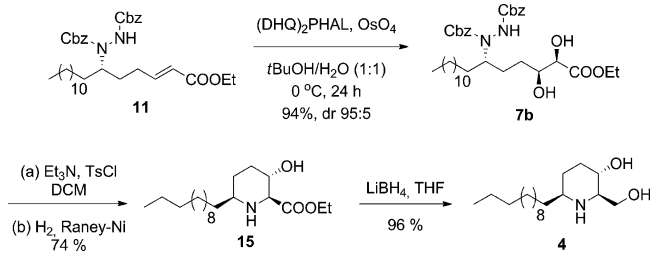
We have successfully completed the total synthesis of (–)-deoxoprosopinine **3** in approximately 33% overall yield



Scheme 2. Synthesis of *trans*-olefin **11**.



Scheme 4. Synthesis of (–)-deoxoprosopinine.



Scheme 5. Synthesis of (+)-deoxoprosophylline.

and (+)-deoxoprosophylline (**4**) in approximately 35% overall yield from commercially available myristyl aldehyde in eight steps. The physical and spectroscopic data of compounds **3** and **4** are in good agreement with the reported data. [For (–)-deoxoprosopinine **3**, m.p. 90 °C, {ref.[5e] 89.5–90 °C}, $[\alpha]_D^{25}$ = –15.8 (*c* = 0.30, $CHCl_3$), {ref.[5e] $[\alpha]_D^{25}$ = –14.7 (*c* = 0.30, $CHCl_3$)}, and for (+)-deoxoprosophylline **4**, m.p. 84 °C, {ref.[6h] 85–86 °C}, $[\alpha]_D^{25}$ = +13.9 (*c* = 0.22, $CHCl_3$), {ref.[6h] +12.50 (*c* 0.22, $CHCl_3$)}.

Conclusions

In conclusion, a simple and highly efficient strategy to 2,6-disubstituted piperidin-3-ol has been developed by employing an α-amination and Sharpless asymmetric dihydroxylation reaction as the key steps. Its usage is illustrated in the total synthesis of (–)-deoxoprosopinine and (+)-deoxoprosophylline. The merits of this synthesis are high enantio and diastereoselectivity with high yielding reaction steps. The synthetic strategy described has significant potential for stereochemical variations at the C-2, C-3 and C-6 positions and further extension to other stereoisomers and analogues.

Experimental Section

General Methods: All reactions requiring anhydrous conditions were performed under a positive pressure of argon with oven-dried glassware (110 °C), which was cooled under argon. Solvents used for chromatography were distilled at respective boiling points by using known procedures.

All commercial reagents were obtained from Sigma–Aldrich Chemical Co. and Lancaster Chemical Co. (UK). Progress of the reactions was monitored by TLC with precoated aluminum plates (Merck kieselgel 60 F_{254}). Column chromatography was performed on silica gel 60–120/100–200/230–400 mesh obtained from S. D. Fine Chemical Co. India or Spectrochem India. Standard syringe and cannula techniques were used to transfer air- and moisture-sensitive reagents.

IR spectra were recorded with a Perkin–Elmer infrared spectrometer model 599-B and model 1620 FT-IR. ^{1}H NMR spectra were recorded with Bruker AC-200, Bruker AV-400, Jeol-400 and Bruker DRX – 500 instruments and deuterated solvent. Proton coupling constants are reported with multiplicity (br., broadened; s, singlet; d, doublet; t, triplet; m, multiplet). ^{13}C NMR spectra were recorded with Bruker AC-200, Bruker AV-400, Jeol-400 and Bruker DRX-500 instruments operating at 50 MHz, 100 MHz, and 125 MHz, respectively. ^{13}C NMR chemical shifts are reported relative to the central line of $CDCl_3$ (δ = 77.0 ppm). All HPLC analyses used to determine enantiomeric purity were calibrated with a sample of the racemate.

Dibenzyl (*R*,*E*)-1-(1-Ethoxy-1-oxohexadec-2-en-4-yl)hydrazine-1,2-dicarboxylate (10): To a cooled solution of DBAD (0.588 g, 1.97 mmol) and D-proline (0.028 g, 10 mol-%) in CH_2Cl_2 (30 mL) at 0 °C was added aldehyde **9** (0.5 g, 2.4 mmol) and the mixture was stirred for 24 h at 0 °C and further for 6 h at 10 °C. This was followed by addition of lithium chloride (0.125 g, 2.95 mmol), triethyl phosphonoacetate (0.7 mL, 2.95 mmol) and DBU (0.3 mL, 1.97 mmol) in that sequence and the mixture was stirred at 5 °C for 45 min. The reaction was then quenched with aq. ammonium chloride solution (15 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine, dried with anhyd. Na_2SO_4 and concentrated under reduced pressure. Silica gel column chromatography (petroleum ether/ethyl acetate, 9:1) of the crude product gave compound **10** (enantiomeric excess 94%) as a colorless solid (1.121 g, 82%); m.p. 46–48 °C. $[\alpha]_D^{25}$ = –6.26 (*c* = 1.5, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3294, 2981, 1717, 1498, 1219 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.7 Hz, 3 H), 1.25 (m, 23 H), 1.64–1.69 (m, 2 H), 4.18 (q, *J* = 7.1 Hz, 2 H), 4.68–4.75 (m, 1 H), 5.05–5.22 (m, 4 H), 5.90 (d, *J* = 15.6 Hz, 1 H), 6.39 (s, 1 H), 6.85 (dd, *J* = 6.9, 15.8 Hz, 1 H), 7.26–7.38 (m, 10 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0, 14.1, 22.6, 25.9, 29.3, 29.4, 29.6, 30.9, 31.9, 58.9, 60.5, 67.8, 68.3, 122.9, 127.9, 128.1, 128.2, 128.3, 128.5, 135.6, 144.9, 155.6, 156.7, 166.2 ppm. MS (ESI): *m*/*z* = 603.42 [M + Na]$^+$. HRMS: calcd. for $C_{34}H_{48}N_2O_6$ [M + H]$^+$ 581.3585; found 581.3586. calcd. for $C_{34}H_{48}N_2O_6$ [M + Na]$^+$ 603.3405; found 603.3405.

Dibenzyl (*S*)-1-(1-Hydroxyhexadecan-4-yl)hydrazine-1,2-dicarboxylate (8): To a solution of ethyl ester **10** (0.600 g, 1.04 mmol) in THF (8 mL), was added $LiBH_4$ (0.045 g, 2.08 mmol) at 0 °C. The reaction mixture was stirred at room temp. for 1 h. It was then quenched with aq. ammonium chloride solution (1 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine, dried with anhyd. Na_2SO_4 and concentrated under reduced pressure. Silica gel column chromatography (petroleum ether/ethyl acetate, 7:3) of the crude product gave **8** as a colorless solid (0.530 g, 95%); m.p. 85–87 °C. $[\alpha]_D^{25}$ = –5.75 (*c* = 1.0, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3446, 3285, 2927, 1709, 1454, 1221, 1057 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.9 Hz, 3 H), 1.25 (m, 22 H), 1.30–1.53 (m, 4 H), 3.31–3.74 (m, 2 H), 3.96–4.24 (m, 1 H), 5.13–5.18 (m, 4 H), 6.41 (s, 1 H), 7.26–7.36 (m, 10 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 22.7, 26.5, 28.6, 29.3, 29.4, 29.6, 31.9, 32.7, 62.4, 64.7, 67.9, 127.7, 128.2, 128.5, 128.6, 135.5, 156.2, 157.3 ppm. MS (ESI): *m*/*z* = 563.18 [M + Na]$^+$. HRMS: calcd. for $C_{32}H_{48}N_2O_5$ [M + H]$^+$ 541.3636; found 541.3638. calcd. for $C_{32}H_{48}N_2O_5$ [M + Na]$^+$ 563.3455; found 563.3452. HPLC: Chiralcel OD-H (250 × 4.6 mm) (2-propanol: Pet ether = 4:96, flow rate 0.7 mL/min, λ = 254 nm). Retention time

[min]: 38.850 (major) and 41.108 (minor). The racemic standard was prepared in the same way by using DL-proline as a catalyst, *ee* 94%.

Dibenzyl (*S*,*E*)-1-(1-Ethoxy-1-oxooctadec-2-en-6-yl)hydrazine-1,2-dicarboxylate (11): To a solution of alcohol **8** (0.5 g, 0.93 mmol) in CH_2Cl_2 (8 mL) was added DMP (0.780 g, 1.9 mmol) at 0 °C. The reaction mixture was stirred at room temp. for 2 h. It was then quenched with a 1:1 mixture of (10%) aqueous $Na_2S_2O_3$ solution and saturated $NaHCO_3$ solution and extracted with diethyl ether (3× 5 mL). The combined organic layers were washed with brine, dried with anhyd. Na_2SO_4 and concentrated under reduced pressure to give the aldehyde as a colorless liquid, which was directly used in the next step without further purification.

To a solution of (ethoxycarbonylmethylene)triphenyl phosphorane (0.860 g, 2.47 mmol) in dry toluene (10 mL) was added a solution of the above aldehyde in dry toluene (5 mL). The reaction mixture was stirred at 110 °C (reflux conditions) for 12 h. It was then concentrated and purified by flash silica gel column chromatography EtOAc/petroleum ether (1:9) to give olefin **12** as a waxy white solid (0.040 g, 7%). Continued chromatography with EtOAc/petroleum ether (1:9) gave olefin **11** as a waxy white solid (0.425 g, 70%). Further chromatography with EtOAc/petroleum ether (1:8) gave cyclized product **13** as a waxy solid (0.080 g, 16%). $[\alpha]_D^{25}$ = +2.96 (*c* = 1.0, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3311, 2923, 1717, 1464, 1263 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.1 Hz, 3 H), 1.26 (m, 23 H), 1.42–1.67 (m, 4 H), 2.02–2.45 (m, 2 H), 4.04–4.22 (m, 3 H), 5.02–5.22 (m, 4 H), 5.82–5.85 (m, 1 H), 6.33–6.47 (m, 1 H), 6.94 (m, 1 H), 7.26–7.32 (m, 10 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 14.2, 22.6, 26.4, 29.1, 29.2, 29.3, 29.5, 29.6, 30.9, 31.9, 32.3, 32.5, 33.7, 58.5, 60.1, 67.8, 68.3, 121.4, 127.9, 128.1, 128.2, 128.5, 128.6, 135.5, 135.7, 135.9, 148.5, 156.5, 156.8, 166.6 ppm. MS (ESI): *m*/*z* = 631.15 $[M + Na]^+$. HRMS: calcd. for $C_{36}H_{52}N_2O_6$ $[M + H]^+$ 609.3898; found 609.3896. calcd. for $C_{36}H_{52}N_2O_6$ $[M + Na]^+$ 631.3718; found 631.3712.

Dibenzyl (*S*,*Z*)-1-(1-Ethoxy-1-oxooctadec-2-en-6-yl)hydrazine-1,2-dicarboxylate (12): $[\alpha]_D^{25}$ = +4.78 (*c* = 1.0, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3311, 2923, 1717, 1464, 1263 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.1 Hz, 3 H), 1.26 (m, 23 H), 1.42–1.67 (m, 4 H), 2.02–2.45 (m, 2 H), 4.04–4.22 (m, 3 H), 5.02–5.22 (m, 4 H), 5.82–5.85 (m, 1 H), 6.33–6.47 (m, 1 H), 6.94 (m, 1 H), 7.26–7.32 (m, 10 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 14.2, 22.6, 26.4, 29.1, 29.2, 29.3, 29.5, 29.6, 30.9, 31.9, 32.3, 32.5, 33.7, 58.5, 60.1, 67.8, 68.3, 121.4, 127.9, 128.1, 128.2, 128.5, 128.6, 135.5, 135.7, 135.9, 148.5, 156.5, 156.8, 166.6 ppm. MS (ESI): *m*/*z* = 631.15 $[M + Na]^+$. HRMS: calcd. for $C_{36}H_{52}N_2O_6$ $[M + H]^+$ 609.3898; found 609.3896. calcd. for $C_{36}H_{52}N_2O_6$ $[M + Na]^+$ 631.3718; found 631.3712.

Dibenzyl (3*S*)-3-Dodecyl-6-hydroxytetrahydropyridazine-1,2-dicarboxylate (13): $[\alpha]_D^{25}$ = +5.21 (*c* = 1.0, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3448, 2932, 1719, 1450, 1232, 1054 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.6 Hz, 3 H), 1.16–1.26 (m, 19 H), 1.49–1.69 (m, 5 H), 1.90–2.11 (m, 2 H), 4.12–4.28 (m, 1 H), 4.98–5.28 (m, 4 H), 5.53–5.56 (m, 1 H), 7.27–7.37 (m, 10 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 22.7, 23.3, 25.7, 26.2, 29.3, 29.5, 29.6, 31.9, 32.7, 54.6, 67.7, 67.8, 68.1, 127.6, 127.9, 128.0, 128.2, 128.5, 128.6, 135.6, 135.8, 136.1, 156.4, 156.6 ppm. MS (ESI): *m*/*z* = 561.01 $[M + Na]^+$. HRMS: calcd. for $C_{32}H_{46}N_2O_5$ $[M + Na]^+$ 561.3299; found 561.3299.

Dibenzyl 1-[(2*S*,3*R*,6*S*)-1-Ethoxy-2,3-dihydroxy-1-oxooctadecan-6-yl]hydrazine-1,2-dicarboxylate (7a): To a mixture of $K_3Fe(CN)_6$ (1.10 g, 3.28 mmol), K_2CO_3 (0.455 g, 3.28 mmol), $(DHQD)_2PHAL$ (10 mg, 1 mol-%) in *t*BuOH/H_2O (1:1, 20 mL) at 0 °C was added osmium tetroxide (0.05 mL, 0.1 M solution in toluene, 0.4 mol-%), followed by methanesulfonamide (0.104 g, 1.09 mmol). After stirring for 5 min at 0 °C, olefin **11** (0.660 g, 1.09 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 24 h and then quenched with solid sodium sulfite (2.0 g). The stirring was continued for additional 15 min and then the solution was extracted with EtOAc (3× 20 mL). The combined extracts were washed with brine, dried with Na_2SO_4 and concentrated. Silica gel column chromatography purification (petroleum ether/EtOAc, 4:6) of the crude product gave **7a** as a white solid (0.63 g, 95%); m.p. 80–82 °C. $[\alpha]_D^{25}$ = –2.78 (*c* = 1.0, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3434, 3018, 1717, 1452, 1218 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 6.7 Hz, 3 H), 1.28–1.31 (m, 27 H), 1.43–1.72 (m, 4 H), 3.81–3.93 (m, 1 H), 3.95–4.82 (m, 4 H), 5.01–5.24 (m, 4 H), 6.65 (m, 1 H), 7.29–7.37 (m, 10 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 22.6, 24.7, 26.4, 29.1, 29.2, 29.3, 29.4, 29.5, 29.6, 30.1, 31.9, 32.7, 33.8, 57.9, 58.9, 61.9, 67.9, 72.3, 73.8, 127.6, 128.0, 128.2, 128.4, 128.5, 135.4, 135.8, 156.2, 156.9, 173.5 ppm. MS (ESI): *m*/*z* = 665.07 $[M + Na]^+$. HRMS: calcd. for $C_{36}H_{54}N_2O_8$ $[M + Na]^+$ 665.3772; found 665.3762.

Diastereomeric ratio was determined by HPLC analysis; *dr* 92:8 Column: Kromasil RP-18, Flow rate: 1.0 mL/min, MeOH:H_2O/85:15; t_R for (*anti*)-isomer = 26.57 min and t_R for (*syn*)-isomer = 29.25 min.

Dibenzyl 1-[(2*R*,3*S*,6*S*)-1-Ethoxy-2,3-dihydroxy-1-oxooctadecan-6-yl]hydrazine-1,2-dicarboxylate (7b): By using the same procedure as described for the synthesis of **7a** and with $(DHQ)_2PHAL$ as ligand in the dihydroxylation step compound **7b** was prepared; m.p. 77–79 °C. $[\alpha]_D^{25}$ = +1.32 (*c* = 1.0, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3434, 3018, 1717, 1452, 1218 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.7 Hz, 3 H), 1.25–1.32 (m, 27 H), 1.53–1.76 (m, 4 H), 3.80–3.94 (m, 1 H), 3.98–4.15 (m, 2 H), 4.25 (q, *J* = 6.7 Hz, 2 H), 5.12–5.23 (m, 4 H), 6.74 (m, 1 H), 7.26–7.43 (m, 10 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0, 22.6, 24.7, 26.4, 29.0, 29.2, 29.3, 29.4, 29.5, 29.6, 31.9, 32.8, 33.8, 43.1, 58.3, 59.4, 61.8, 67.8, 72.4, 72.8, 127.6, 128.0, 128.1, 128.5, 135.5, 135.8, 156.3, 156.9, 173.2 ppm. MS (ESI): *m*/*z* = 665.25 $[M + Na]^+$. HRMS: calcd. for $C_{36}H_{54}N_2O_8$ $[M + Na]^+$ 665.3772; found 665.3764.

Diastereomeric ratio was determined by HPLC analysis; *dr* 95:5 Column: Kromasil RP-18, Flow rate: 1.0 mL/min, MeOH/H_2O/85:15; t_R for (*anti*)-isomer = 23.91 min and t_R for (*syn*)-isomer = 26.34 min.

(2*S*,3*S*,6*S*)-Ethyl 6-Dodecyl-3-hydroxypiperidine-2-carboxylate (14): To a one-neck round-bottomed flask were added diol ester **7a** (780 mg, 1.21 mmol), dry CH_2Cl_2 (10 mL) and Et_3N (178 mg, 0.25 mL, 1.76 mmol). The flask was placed in an ice water bath and allowed to equilibrate for 10–30 min, at which time the *p*-toluenesulfonyl chloride (224 mg, 1.18 mmol) was added in one portion by using a solid addition funnel. The flask was fitted with a serum cap and placed in a refrigerator (5 °C) for 72 h. The mixture was then concentrated to afford a paste, which was dissolved in Et_2O. The organic phase was washed three times with a aqueous HCl (1 N), once with a saturated aqueous $NaHCO_3$ solution, and once with brine, dried with Na_2SO_4, and concentrated to afford the crude tosyl compound, which was directly used in the next step without further purification. The solution of crude tosyl compound in MeOH (10 mL) and acetic acid (5 drops) was treated with Raney nickel (0.8 g, excess) under H_2 (60 psi) atmosphere for 24 h. The reaction mixture was then filtered through Celite and concentrated. The residue was purified by flash column chromatography with silica gel (MeOH/CH_2Cl_2, 1:9) to give compound **14** (301 mg, 73%); m.p. 94–96 °C. $[\alpha]_D^{25}$ = +5.65 (*c* = 0.60, $CHCl_3$). IR

($CHCl_3$): $\tilde{\nu}_{max}$ = 3583, 3436, 3019, 2928, 1725, 1519, 1455, 1215 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.6 Hz, 3 H), 1.26–1.33 (m, 26 H), 1.43–1.56 (m, 2 H), 1.60–1.70 (m, 1 H), 1.72–1.81 (m, 1 H), 2.13 (br. s, 1 H), 2.68–2.76 (m, 1 H), 3.58 (d, J = 4.0 Hz, 1 H), 4.15–4.16 (m, 1 H), 4.22 (q, J = 6.6 Hz, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0, 14.2, 22.6, 25.7, 26.1, 28.0, 29.3, 29.5, 29.6, 31.8, 35.8, 51.6, 60.8, 61.5, 65.5, 172.2 ppm. MS (ESI): m/z = 364.10 $[M + Na]^+$. HRMS: calcd. for $C_{20}H_{39}NO_3$ $[M + Na]^+$ 364.2822; found 364.2821.

Ethyl (2*S*,3*S*,6*S*)-6-Dodecyl-3-hydroxypiperidine-2-carboxylate (15): By using the same procedure as described for the synthesis of **14**, compound **15** was prepared; m.p. 92–94 °C. $[\alpha]_D^{25}$ = +2.47 (c = 0.60, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3583, 3436, 3019, 2928, 1725, 1519, 1455, 1215 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.6 Hz, 3 H), 1.26–1.36 (m, 27 H), 1.68–1.79 (td, J = 3.27, 12.79 Hz, 1 H), 1.99–2.24 (m, 2 H), 2.45–2.65 (m, 2 H), 3.17 (d, J = 9.0 Hz, 1 H), 3.63–3.75 (m, 1 H), 4.26 (dq, J = 3.3, 7.2 Hz, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.9, 22.5, 25.9, 29.2, 29.4, 29.5, 29.6, 30.6, 31.8, 32.3, 36.3, 55.9, 61.3, 64.6, 69.2, 172.6 ppm. MS (ESI): m/z = 364.10 $[M + Na]^+$. HRMS: calcd. for $C_{20}H_{39}NO_3$ $[M + Na]^+$ 364.2822; found 364.2820.

(–)-Deoxoprosopinine (3): A suspension of $LiBH_4$ (50 mg, 0.147 mmol) in anhydrous THF (10 mL) was stirred for 5 min at 0 °C, and a solution of **14** (65 mg, 0.73 mmol) in THF (5 mL) was then added dropwise. The mixture was stirred for 1 h at room temperature. Excess $LiBH_4$ was destroyed by slow addition of aq. NH_4Cl solution and EtOAc (5 mL). The white precipitate was filtered through a pad of neutral alumina and washed with MeOH (3 × 15 mL). The filtrate was concentrated and the residue was purified by silica gel column chromatography ($MeOH/CH_2Cl_2$, 2:8) to give **3** as a colorless solid (42 mg, 96%); m.p. 90 °C, [ref.[5e] 89.5–90 °C]. $[\alpha]_D^{25}$ = –15. 81 (c 0.30, $CHCl_3$), [ref.[5e] $[\alpha]_D^{25}$ = –14.7 (c = 0.30, $CHCl_3$)]. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3267, 2922, 2852, 1639, 1465, 1376 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.7 Hz, 3 H), 1.26 (m, 20 H), 1.38–1.50 (m, 2 H), 1.53–1.60 (m, 2 H), 1.66–1.77 (m, 2 H), 2.66 (br. s, 3 H), 2.79–2.92 (m, 1 H), 2.86 (q, J = 5.59, 12.73 Hz, 1 H), 3.51–3.59 (m, 1 H), 3.61–3.73 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0, 22.6, 26.4, 27.0, 28.3, 29.3, 29.6, 29.7, 31.9, 33.3, 50.2, 57.9, 62.1, 67.8 ppm. MS (ESI): m/z = 300.16 $[M + H]^+$. HRMS: calcd. for $C_{18}H_{37}NO_2$ $[M + H]^+$ 300.2897; found 300.2895.

(+)-Deoxosoprosophylline (4): By using the same procedure as described for the synthesis of **3**, compound **4** was prepared; m.p. 84 °C, [ref.[6h] 85–86 °C]. $[\alpha]_D^{25}$ = +13.86 (c = 0.22, $CHCl_3$), [ref.[6h] $[\alpha]_D^{25}$ = +12.50 (c = 0.22, $CHCl_3$)]. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3267, 2922, 2852, 1639, 1465, 1376 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.7 Hz, 3 H), 1.23–1.30 (m, 22 H), 1.39–1.51 (m, 2 H), 1.77–1.85 (m, 1 H), 2.03–2.09 (m, 1 H), 2.58–2.66 (m, 2 H), 3.33 (br. s, 3 H), 3.54–3.63 (m, 1 H), 3.84–3.85 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0, 22.6, 26.1, 29.3, 29.6, 29.7, 29.9, 31.9, 33.3, 35.5, 56.4, 62.2, 63.4, 68.2 ppm. MS (ESI): m/z = 300.18 $[M + H]^+$. HRMS: calcd. for $C_{18}H_{37}NO_2$ $[M + H]^+$ 300.2897; found 300.2896.

Supporting Information (see footnote on the first page of this article): Copies of the ^1H and ^{13}C NMR spectra along with *ee* and *dr* chromatograms.

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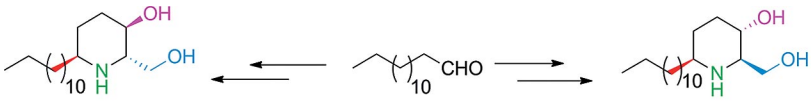

(–)-Deoxoprosopinine (+)-Deoxoprosophylline

A simple and highly efficient approach to an enantioenriched 2,6-disubstituted piperidin-3-ol skeleton is developed from an aldehyde as a starting material by using organocatalytic and asymmetric dihydroxylation as key steps. Its application to the total synthesis of (–)-deoxoprosopinine and (+)-deoxoprosophylline is also reported.

Keywords: Synthetic methods / Alkaloids / Amino alcohols / Amination / Wittig reactions

