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Concise asymmetric synthesis of (−)-deoxoprosophylline

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ABSTRACT

An efficient asymmetric synthesis of the 2-hydroxymethyl 3,6-disubstituted piperidine alkaloid, (−)-deoxoprosophylline, is described. The key step of this route is the SmI_2-mediated cross-coupling of chiral *N*-*tert*-butanesulfinyl imine **9** with aldehyde **11** to construct hydroxymethyl-β-amino alcohol **12b** in 83% yield and high diastereoselectivity (>99%, de).

1. Introduction

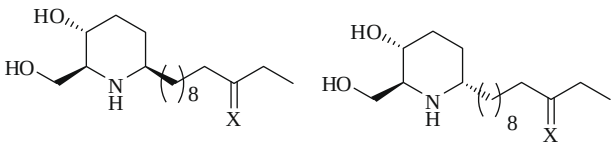
Alkaloids containing multifunctionalized piperidine rings exist abundantly in Nature.[1] Several 2,3,6-trisubstituted piperidines such as prosophyllines **2** and **6**, and prosopinines **4** and **8** have been isolated from the leaves of the West African savanna tree *Prosopis Africana* Taub[2] and the leaves of *Microcos philippinenis* (Perk) Burrentt (*Tiliaceae*).[3] These trisubstituted piperidine alkaloids and their deoxygenated analogues, especially 2-hydroxymethyl-6-alkylated 3-hydroxypiperidines and their deoxygenated derivatives (Fig. 1), have shown anesthetic, analgesic, antibiotic, and CNS stimulating biological properties, and are of considerable pharmacological interest.[4] Structurally, these compounds possess a polar head group and a hydrophobic aliphatic tail, and can be considered as cyclic analogues of the lipid sphingosine membrane.[5] These interesting structural features and therapeutic potential make them attractive synthetic targets. For example, various synthetic strategies for deoxoprosophylline **1** have been reported.[6–8] Although it could be conveniently synthesized based on chiral building blocks from natural amino acids[6] and carbohydrates,[7] there is still a need to develop a general strategy for the asymmetric preparation with desired stereochemistry.[8]

In recent years, chiral *N*-*tert*-butanesulfinamide, as pioneered by Ellman and Davis, is undoubtedly one of the most efficient auxiliaries developed.[9] It enables the preparation of various enantiopure amines, which are ubiquitous in natural products and biologically active substances. Our laboratory has documented the use of *N*-*tert*-butanesulfinyl imines for the synthesis of unsymmetrical vicinal β-amino alcohols,[10a] and applied this method to synthesize several natural products.[10] As a result of our ongoing efforts on developing a method to prepare hydroxymethyl β-amino alcohols, we herein report a novel route to (−)-deoxoprosophylline **1** based on hydroxymethyl β-amino alcohol **12b**, which was synthesized by the reaction of *N*-*tert*-butanesulfinyl imine **9** with aldehyde **11**.

2. Results and discussion

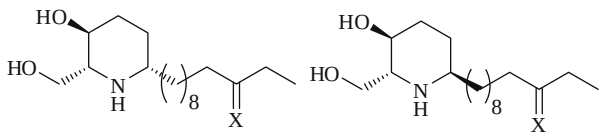
As illustrated in Scheme 1, we envisioned that the stereochemistry of C-2 and C-3 could be constructed by a cross-coupling of aldehydes **10** and **11** with chiral *N*-*tert*-butanesulfinyl imine **9** to form protected hydroxymethyl-β-amino alcohols **12**. To make this synthesis more convergent, we selected methyl 4-oxobutanoate **10** as a starting material.

The SmI_2-induced cross-coupling of **10** with (*S*)-*N*-*tert*-butanesulfinyl imine **9,** which was easily prepared from chiral *N*-*tert*-butanesulfinamide,[11] gave hydroxymethyl β-amino alcohol **12a** with high diastereoselectivity (>99%, de) in 89% yield. After removal of the chiral auxiliary, the resulting amino alcohol was easily cyclized in one pot under TEA conditions to produce **13** in 80%



(-)-deoxoprosophylline **1** X = H_2
(-)-prosophylline **2** X=O

(-)-deoxoprosopinine **3** X=H_2
(-)-prosopinine **4** X=O



(+)-deoxoprosophylline **5** X=H_2
(+)-prosophylline **6** X=O

(+)-deoxoprosopinine **7** X=H_2
(+)-prosopinine **8** X=O

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

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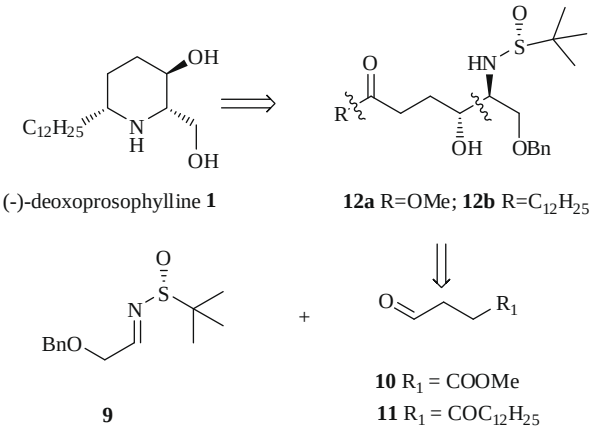
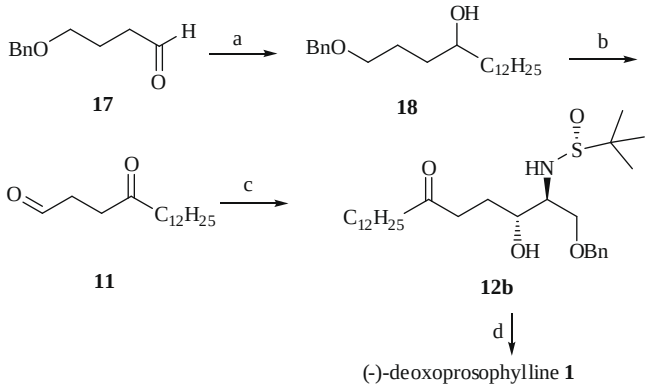


Scheme 1. Retrosynthetic analysis of (−)-deoxoprosophylline **1**.



Scheme 3. Reagents and conditions: (a) $C_{12}H_{25}MgBr$, THF, 88%; (b) (i) Pd/C, H_2, MeOH, rt, 12 h; (ii) PCC, CH_2Cl_2, 5 h, two steps 81%; (c) **9**, SmI_2, *t*-BuOH, THF, 83%; (d) (i) HCl/MeOH, MeOH; (ii) $Pd(OH)_2/C$, H_2, EtOH, 4 h, then concd HCl, 33 h, two steps 58%.

yield. Protection of alcohol **13** (TBSCl, imidazole) and amide **14** (Boc_2O, *n*-BuLi) gave **15** in 66% overall yield. The next step for synthesis of (−)-deoxoprosophylline **1** was to introduce a dodecyl side chain in a *cis*-diastereoselective manner with an organometallic ring-opening method developed by Savoia,[12] which was used by Huang et al.[13] in the total synthesis of 2-*epi*-deoxoprosopinine. N-Deprotection of **16** with TFA, followed by treatment with saturated aqueous $NaHCO_3$ solution led to the cyclic imine, which, without further purification, was hydrogenated under acidic conditions [20% $Pd(OH)_2$, H_2, EtOH and 10% concd HCl, 36 h] and alkalized with an aqueous solution of 1 M sodium hydroxide to afford (−)-deoxoprosophylline **1** as a white solid (Scheme 2).

Although (−)-deoxoprosophylline **1** was synthesized, the method for inducing the chain was a known one, and the overall yield was low. As a result, we turned our attention to study the cross-coupling of 4-oxohexadecanal **11** with chiral *N*-*tert*-butanesulfinyl imine **9**. 4-Benzyloxyl butanal **17**, which was easily prepared from γ-butyrolactone,[14] was treated with dodecylmagnesium bromide to afford the secondary alcohol **18** in 88% yield. Hydrogenation (Pd/C, H_2) of **18** was followed by oxidation (PCC, CH_2Cl_2) to give the aldehyde **11** in 81% overall yield. The SmI_2-induced cross-coupling of **11** with **9** afforded hydroxymethyl β-amino alcohol **12b** with high diastereoselectivity (>99%, de) in 83% yield. Removal of the chiral auxiliary of **12b** with HCl/MeOH, followed by treatment with saturated aqueous $NaHCO_3$ solution led to the cyclic imine, which, without further purification, was hydrogenated under acidic conditions [20% $Pd(OH)_2$, H_2 , EtOH and concd HCl, 33 h] and basified with an aqueous solution of 1 M sodium hydroxide to give (−)-deoxoprosophylline **1** as a white solid (mp 87–88 °C (lit.[6h] 89.5–90 °C); $[\alpha]_D^{25} = -15.1$ (*c* 0.12, $CHCl_3$) {lit.[6d] $[\alpha]_D^{25} = -14.7$ (*c* 0.55, $CHCl_3$)}). The spectroscopic and physical data of the synthetic (−)-deoxoprosophylline **1** were identical with those described in the literature.[6] Thus, a concise method for the synthesis of (−)-deoxoprosophylline was established with an overall yield of 34% from starting material **17** (Scheme 3).

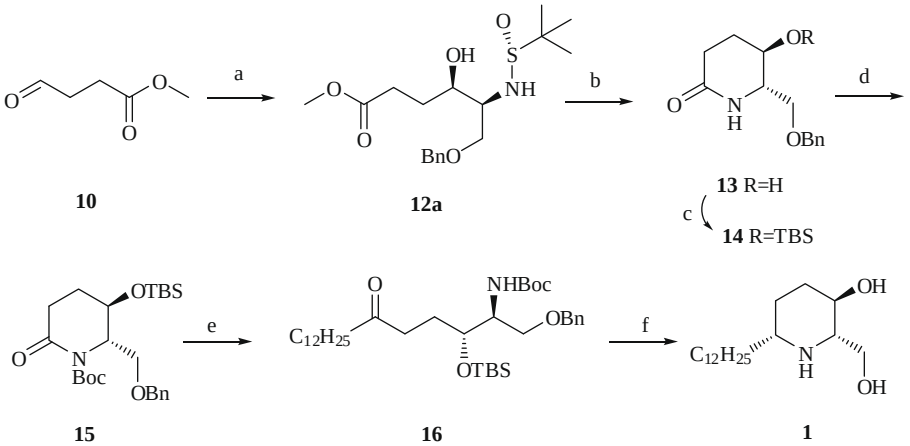
3. Conclusion

In conclusion, hydroxymethyl β-amino alcohol **12b** was prepared by SmI_2-induced cross-coupling of *N*-*tert*-butanesulfinyl imine **9** with 4-oxohexadecanal **11**, in 83% yield and high diastereoselectivity (>99%, de). This is a convenient approach for preparing (−)-deoxoprosophylline **1**. Moreover, the key step might be generally applicable in the synthesis of various 2-hydroxymethyl-6-alkylated 3-hydroxy piperidine alkaloids and their deoxygenated derivatives with structural and biological importance.

4. Experimental

4.1. General methods

Melting points were recorded on a Mel-Temp apparatus and uncorrected. Optical rotations were measured on a P-1020 polarimeter manufactured by JASCO Corporation. IR spectra were re-



Scheme 2. Reagents and conditions: (a) **9**, SmI_2, *t*-BuOH, THF, 89%; (b) (i) HCl/MeOH, MeOH; (ii) TEA, MeOH, two steps 80%; (c) TBSCl, imidazole, DMAP, DMF, 90%; (d) *n*-BuLi, Boc_2O, THF, 73%; (e) $C_{12}H_{25}MgBr$, THF, 66%; (f) (i) TFA; (ii) $Pd(OH)_2/C$, H_2, EtOH–HCl, two steps 47%.

corded using KBr disks or film, on a Fourier Transform Infrared Spectrometer, Type: Avatar 360 E.S.P, manufactured by Thermo Nicolet Corporation, USA. NMR spectra were recorded on Bruker av 400 spectrometer in $CDCl_3$ and chemical shifts were expressed in parts per million relative to internal Me_4Si. Silica gel (300–400 mesh) was used for chromatography, eluting (unless otherwise stated) with an ethyl acetate/petroleum ether mixture. Dichloromethane, DMF, and diisopropylamine were distilled over calcium hydride under N_2. Ether and THF were distilled over sodium benzophenone ketyl under N_2.

4.1.1. (4*R*,5*S*)-Methyl-6-(benzyloxy)-4-hydroxy-5-(2-methylpropane-2-ylsulfinamido)hexanoate 12a

To a mixture of 2-benzoxyl ethyl (*S*)-*N*-*tert*-butanesulfinyl imine **9** (1.52 g, 6 mmol), methyl 4-oxobutanoate **10** (2.79 g, 24 mmol), and *t*-BuOH (4.5 mL, 48 mmol) in THF (250 mL) was added a solution of freshly prepared SmI_2 (48 mmol) in THF (250 mL) at −78 °C under an argon atmosphere. After being stirred vigorously for 4 h at the same temperature, the reaction mixture was quenched with saturated $Na_2S_2O_3$ aqueous solution (40 mL). The organic layer was separated, and aqueous layer was extracted with ethyl acetate (200 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (EtOAc/PE) to give **12a** (1.95 g, yield 89%) as a colorless oil. $[\alpha]_D^{25} = -25.5$ (*c* 1.33, $CHCl_3$); IR (film) *v*: 3386, 2953, 2919, 1736, 1454, 1364, 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.36–7.26 (m, 5H), 4.58 (d, *J* = 11.74 Hz, 1H), 4.53 (d, *J* = 11.74 Hz, 1H), 3.97–3.90 (m, 2H), 3.78–3.72 (m, 1H), 3.65 (s, 3H), 3.33–3.26 (m, 1H), 2.86 (m, 1H), 2.53–2.42 (m, 2H), 1.96–1.88 (m, 2H), 1.84–1.78 (m, 1H), 1.24 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.4, 137.5, 128.5 (2C), 127.9 (3C), 73.6, 72.4, 70.3, 59.7, 56.1, 51.7, 30.5, 28.8, 22.6 (3C); MS (ESI): 394.2 (M+Na^+); HRESIMS calcd for ($C_{18}H_{29}NO_5S$ + Na^+): 394.1666, found: 394.1659.

4.1.2. (5*R*,6*S*)-6-(Benzyloxymethyl)-5-hydroxypiperidin-2-one 13

To a solution of **12a** (1.80 g, 4.85 mmol) in MeOH (25 mL) was added a solution of HCl/MeOH (2 M, 13 mL) at room temperature. After stirring for 4 h, the mixture was concentrated under reduced pressure to afford crude intermediate product without further purification, which was dissolved in MeOH (30 mL). Next, TEA (0.68 mL) was added at room temperature. After stirring for 36 h, the mixture was concentrated under reduced pressure. The residue was purified by chromatography on silica gel (EtOAc/PE) to give **13** (915 mg, yield 80% two steps) as a colorless oil. $[\alpha]_D^{25} = -18.5$ (*c* 0.14, $CHCl_3$); IR (film) *v*: 3385, 2920, 1649, 1078 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.35–7.26 (m, 5H), 6.39 (br s, 1H), 3.73–3.65 (m, 2H), 3.50–3.44 (m, 1H), 3.40–3.36 (m, 1H), 2.45 (ddd, *J* = 4.88, 5.68, 17.42 Hz, 1H), 2.28 (ddd, *J* = 6.26, 9.39, 17.42 Hz, 1H), 1.97–1.93 (m, 2H), 1.86–1.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.8, 137.3, 128.5 (2C), 128.0 (2C), 127.7, 73.5, 71.9, 70.7, 63.6, 56.2, 28.4; MS (ESI): 258.1 (M+Na^+). HRESIMS calcd for ($C_{13}H_{17}NO_3$+Na^+): 258.1106, found: 258.1095.

4.1.3. (5*R*,6*S*)-6-(Benzyloxymethyl)-5-(*tert*-butyldimethylsilyloxy)piperidin-2-one 14

To a mixture of **13** (823 mg, 3.5 mmol) and imidazole (1.70 g, 25.0 mmol) in DMF (30 mL) was added a solution of *tert*-butyldimethylchlorosilane (2.108 g, 14 mmol) in DMF (10 mL). After being stirred for 15 h, the reaction mixture was quenched with water (50 mL) and extracted with ethyl acetate (60 mL × 3). The combined organic layers were washed with brine (30 mL × 3), dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by chromatography on silica gel (EtOAc/PE) to give **14** (1.10 g, yield 90%) as a colorless oil. $[\alpha]_D^{25} = -39.7$ (*c* 0.6, $CHCl_3$); IR (film) *v*: 3211, 2953, 2928, 2856, 1671, 1471, 1098 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.35–7.26 (m, 5H), 6.13 (br s, 1H), 4.52 (d, *J* = 11.84 Hz, 1H), 4.48 (d, *J* = 11.84 Hz, 1H), 3.73 (ddd, *J* = 3.72, 6.66, 9.78 Hz, 1H), 3.59 (dd, *J* = 3.91, 9.00 Hz, 1H), 3.55–3.43 (m, 1H), 3.31 (dd, *J* = 8.21, 9.00 Hz, 1H), 2.43 (ddd, *J* = 5.27, 6.07, 17.80 Hz, 1H), 2.29 (ddd, *J* = 6.26, 9.39, 17.80 Hz, 1H), 1.91–1.75 (m, 2H), 0.84 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.2, 137.4, 128.5 (2C), 127.9 (2C), 127.7, 73.4, 71.3, 66.5, 58.7, 28.4, 28.3, 25.6 (3C), 17.9, −4.4, −5.0; MS (ESI): 372.2 (M+Na^+); HRESIMS calcd for ($C_{19}H_{31}NO_3$-Si+Na^+): 372.1972, found: 372.1971.

4.1.4. (2*S*,3*R*)-*tert*-Butyl 2-(benzyloxymethyl)-3-(*tert*-butyldimethylsilyloxy)-6-oxopiperidine-1-carboxylate 15

To a solution of **14** (800 mg, 2.29 mmol) and Boc_2O (750 mg, 3.44 mmol) in anhydrous THF (25 mL) was slowly dropped a solution of 1.6 M *n*-BuLi (1.36 mL) in hexane at −78 °C under an argon atmosphere. After being stirred for 40 min at the same temperature, the mixture was quenched with saturated NH_4Cl aqueous solution (5 mL) and extracted with ethyl acetate (30 mL × 3). The combined organic layers were washed with brine (15 mL × 3), dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by chromatography on silica gel (EtOAc/PE) to give **15** (714 mg, yield 73%) as a colorless oil. $[\alpha]_D^{25} = -25.2$ (*c* 0.97, $CHCl_3$); IR (film) *v*: 2954, 2929, 1722, 1717, 1367, 1296, 1253, 1154 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.36–7.26 (m, 5H), 4.53 (d, *J* = 12.13 Hz, 1H), 4.48 (d, *J* = 12.13 Hz, 1H), 4.31–4.29 (m, 1H), 4.23–4.21 (m, 1H), 3.55 (dd, *J* = 3.92, 9.98 Hz, 1H), 3.45 (dd, *J* = 8.02, 9.98 Hz, 1H), 2.71 (ddd, *J* = 7.24, 10.95, 17.90 Hz, 1H), 2.37 (ddd, *J* = 2.94, 6.65, 17.90 Hz, 1H), 2.07–1.98 (m, 1H), 1.77–1.72 (m, 1H), 1.48 (s, 9H), 0.89 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.5, 152.7, 137.7, 128.4 (2C), 127.8 (2C), 127.6, 82.8, 73.3, 69.9, 65.4, 61.7, 29.9, 27.9 (3C), 25.7 (3C), 25.6, 17.9, −4.8, −5.0; MS (ESI): 472.2 (M+Na^+); HRESIMS calcd for ($C_{24}H_{39}NO_5Si$+Na^+): 472.2497, found: 472.2490.

4.1.5. *tert*-Butyl (2*S*,3*R*)-1-(benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-6-oxooctadec-2-ylcarbamate 16

To a solution of **15** (600 mg, 1.34 mmol) in anhydrous THF (60 mL) was slowly dropped a solution of 0.3 M *n*-$C_{12}H_{25}MgBr$ in THF (5.8 mL, 1.74 mmol) at −78 °C under an argon atmosphere. After being stirred for 3 h at this temperature, the mixture was slowly warmed to −40 °C and stirred for another 40 min. Then, the reaction mixture was quenched with saturated NH_4Cl aqueous solution (2 mL) and diluted with EtOAc (10 mL). The organic layer was separated and the aqueous phase extracted with EtOAc (10 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by chromatography on silica gel (EtOAc/PE) to give **16** (322 mg) in 66 % yield based on recovered starting material **15** (245 mg). $[\alpha]_D^{25} = -11.0$ (*c* 1.64, $CHCl_3$); IR (film) *v*: 3450, 2926, 2855, 1715, 1498, 1365 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.36–7.26 (m, 5H), 4.82 (d, *J* = 8.80 Hz, 1H), 4.51 (d, *J* = 11.74 Hz, 1H), 4.45 (d, *J* = 11.74 Hz, 1H), 3.90–3.85 (m, 1H), 3.78–3.67 (m, 2H), 3.51 (dd, *J* = 3.72, 9.00 Hz, 1H), 2.64–2.60 (m, 1H), 2.52–2.50 (m, 1H), 2.49–2.35 (m, 2H), 1.82–1.71 (m, 2H), 1.57–1.54 (m, 2H), 1.42 (s, 9H), 1.34–1.25 (m, 19H), 0.88 (s, 9H), 0.89–0.86 (m, 3H), 0.08 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 211.5, 155.5, 138.0, 128.4 (2C), 127.7 (3C), 79.3, 73.1, 70.5, 68.7, 52.8, 43.0, 37.1, 31.9, 29.6, 29.6, 29.5, 29.4(3C), 29.2, 28.3(3C), 26.8, 25.8 (3C), 24.0, 22.7, 18.0, 14.1, −4.4, −5.0; MS (ESI): 620.3 (M+H^+); HRESIMS calcd for ($C_{36}H_{65}NO_5Si$+H^+): 620.4710, found: 620.4718.

4.1.6. 1-(Benzyloxy) hexadecan-4-ol 18

To a solution of 4-(benzyloxy)butanal **17** (4.26 g, 24 mmol) in dry THF (30 mL) was slowly dropped a solution of freshly prepared dode-

cylmagnesium bromide in THF (1.3 M, 30 mL) at 0 °C under an argon atmosphere. After being stirred for 2 h, the reaction mixture was quenched with a solution of 1M HCl and extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with brine (20 mL × 3), dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by chromatography on silica gel (EtOAc/PE) to afford **18** (7.35 g, yield 88%) as a colorless oil. IR (film) ν: 3405, 2924, 2852, 1454, 1362, 1099 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.37–7.26 (m, 5H), 4.52 (s, 2H), 3.66 (br s, 1H), 3.60–3.49 (m, 2H), 1.76–1.60 (m, 4H), 1.56–1.42 (m, 2H), 1.26–1.21 (m, 20H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.1, 128.4 (2C), 127.7 (3C), 73.0, 71.6, 70.5, 37.5, 34.7, 31.9 (2C), 29.7 (4C), 29.6, 29.3, 26.2, 25.7, 22.7, 14.1; MS (ESI): 371.2 (M+Na^+); HRESIMS calcd for ($C_{23}H_{40}O_2$ + Na^+) : 371.2926, found: 371.2927.

4.1.7. (*R*)-*N*-((2*S*,3*R*)-1-(Benzyloxy)-3-hydroxy-6-oxooctadec-2-yl)-2-methylpropane-2-sulfinamide 12b

To a suspension of 10% Pd/C (500 mg) in methanol (60 mL) was added a solution of **18** (3.636 g, 10.45 mmol) in methanol (20 mL) under a H_2 atmosphere. After being stirred for 12 h, the mixture was filtered and concentrated to give crude hexadecane-1,4-diol, which was dissolved in CH_2Cl_2 (40 mL) at room temperature, then PCC (5.72 g, 26.12 mmol) was added. After stirring for 5 h, the mixture was filtered and concentrated to afford crude **11** (2.15 g, yield 81%, two steps) without further purification. To a mixture of 2-benzoxyl ethyl (*S*)-*N*-*tert*-butanesulfinyl imine **9** (536 mg, 2.13 mmol), 4-oxohexadecanal **11** (2.15 g, 8.47 mmol), and *t*-BuOH (2.0 mL, 21 mmol) in THF (105 mL) was dropped a solution of freshly prepared SmI_2 (21 mmol) in THF (42 mL) at −78 °C under an argon atmosphere. After being stirred vigorously for 4 h at the same temperature, the reaction mixture was quenched with saturated $Na_2S_2O_3$ aqueous solution (20 mL). The organic layer was separated, and aqueous layer was extracted with ethyl acetate (100 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (EtOAc/PE) to give **12b** (895 mg, yield 83%) as a colorless oil. $[\alpha]_D^{25} = -13.0$ (c 0.64, $CHCl_3$); IR (film) ν: 3441, 2924, 2853, 1635, 1456, 1043, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.32 (m, 5H), 4.61–4.63 (m, 2H), 3.95–3.91 (m, 2H), 3.79–3.64 (m, 2H), 3.33–3.30 (m, 1H), 2.89 (d, J = 6.62 Hz, 1H), 2.63–2.57 (m, 2H), 2.41 (t, J = 7.2Hz, 2H), 1.98–1.50 (m, 4H), 1.28–1.18 (m, 27H), 0.88 (t, J = 6.65 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 210.8, 136.5, 127.5, 127.4, 126.9 (2C), 126.7, 72.9, 70.4, 69.4, 58.5, 55.1, 42.0, 38.0, 30.9, 29.3, 28.6, 28.5, 28.4, 28.3, 28.2, 26.4, 26.2, 23.5, 22.9, 21.7 (3C), 13.1; MS(ESI): 532.3 (M+Na^+), HRESIMS calcd for ($C_{29}H_{51}NO_4S$+Na^+): 532.3439, found: 532.3465.

4.1.8. (−)-Deoxoprosophylline 1

To a solution of **12b** (368 mg, 0.72 mmol) in MeOH (15 mL) was added a saturated HCl/MeOH solution (5 mL) at room temperature. After being stirred for 4 h, the reaction mixture was concentrated and dissolved in CH_2Cl_2 (100 mL). The resulting solution was washed with saturated $NaHCO_3$ aqueous solution and brine, dried, and concentrated to give a yellow oil, which, without further purification, was stirred in EtOH (20 mL) at room temperature under an argon atmosphere. Next 20% $Pd(OH)_2/C$ (60 mg) was added in one portion, then the argon atmosphere was exchanged with a H_2 atmosphere three times. After stirring for 4 h under a H_2 atmosphere, a solution of concd HCl (2.5 mL) was added dropwise and the mixture was stirred for another 33 h. The reaction mixture was filtered and concentrated. The residue was dissolved in water (20 mL) and extracted with ether (20 mL). Then, the aqueous layer was basified by the addition of 1 M NaOH aqueous solution and extracted thoroughly with $CHCl_3$ (40 mL × 5). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by chromatography on silica gel ($CHCl_3$/MeOH/$NH_3{\cdot}H_2O$ = 100:10:2, V/V/V) to afford a light yellow solid (−)-deoxoprosophylline **1** (125 mg, 58%), which was recrystallized from acetone to give a white solid **1**. Mp 87–88 °C (lit.[6h] 89.5–90 °C); $[\alpha]_D^{25} = -15.9$ (c 0.62, $CHCl_3$) {lit.[6d] $[\alpha]_D^{25} = -14.7$ (c 0.55, $CHCl_3$)}; IR (film) ν: 3343, 3266, 2921, 2851, 1466 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.86 (dd, J = 4.89, 11.06 Hz, 1H), 3.71 (dd, J = 5.28, 10.76 Hz, 1H), 3.47 (ddd, J = 4.89, 10.36, 13.29 Hz, 1H), 2. 60–2.52 (m, 2H), 2.07–2.03 (ddd, J = 3.91, 7.82, 11.53 Hz, 1H), 1.76–1.36 (m, 3H, 2H exchangeable with D_2O), 1.31–1.25 (m, 24H), 0.88 (t, J = 6.65 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 70.9, 64.9, 63.1, 55.9, 36.6, 33.9, 31.9, 31.1, 29.8, 29.7, 29.6 (4C), 29.3, 26.2, 22.7, 14.1 ppm; MS (ESI): 300.2 (M+H^+), HRESIMS calcd for ($C_{18}H_{37}NO_2$+H^+): 300.2903, found: 300.2927.

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