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A SHORT SYNTHESIS OF (-)-DEOXOPROSOPHYLLINE

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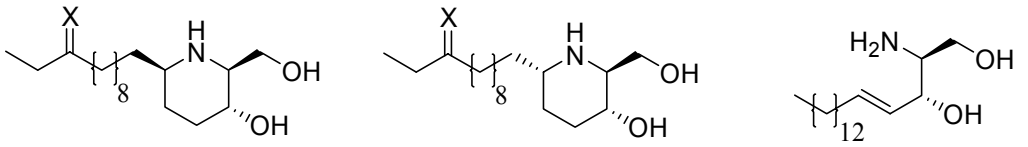
Abstract – Syntheses of (-)-deoxoprosophylline from chiral L-*N*,*N*-dibenzylserine (TBDMS) aldehyde is reported. A highly diastereoselective nucleophilic addition of Büchi's Grignard reagent to chiral serinal followed by an intramolecular reductive amination of ω-oxo amino diol are two key steps of the present synthesis.

This paper is dedicated to Professor Pierre Potier on the occasion of his 70th birthday

INTRODUCTION

2,6-Dialkylated piperidine alkaloids have been found abundantly in nature and are key structural units in many medicinally important compounds.[1] Prosopis alkaloids, isolated from *Prosopis africana*, forms a subgroup possessing a characteristic 3- hydroxy function.[2] Structurally, these compounds, possessing a polar head group and a hydrophobic aliphatic tail, can be considered as cyclic analogues of membrane lipid sphingosine (**5**).[3] Indeed, interesting bioactivities including analgesic, anaesthetic and antibiotic have been reported for prosophylline, prosopinine and their deoxygenated derivatives (**1-4**, Figure 1). Many elegant syntheses of piperidine alkaloids have been developed,[4] including asymmetric syntheses of optically pure prosopis alkaloids.[5] Our approach to deoxoprosophylline (**1**) from L-(*N*,*N*-dibenzylamino)serine (TBDMS) aldehyde (L-**6**),[6,7,8] was depicted retrosynthetically in Scheme 1. Key steps are a highly diastereoselective nucleophilic addition of Büchi's Grignard reagent (**7**) to chiral serinal L-**6** leading to amino diol (**8**) and an intramolecular reductive amination of ω-oxo amino diol (**9**). We detail herein successful implementation of this strategy leading to a short synthesis of **1**.[9] The observation that diastereoselectivity in the reduction of iminium intermediate (**10**) is irrelevant of the *N*-protective group (P) is documented.

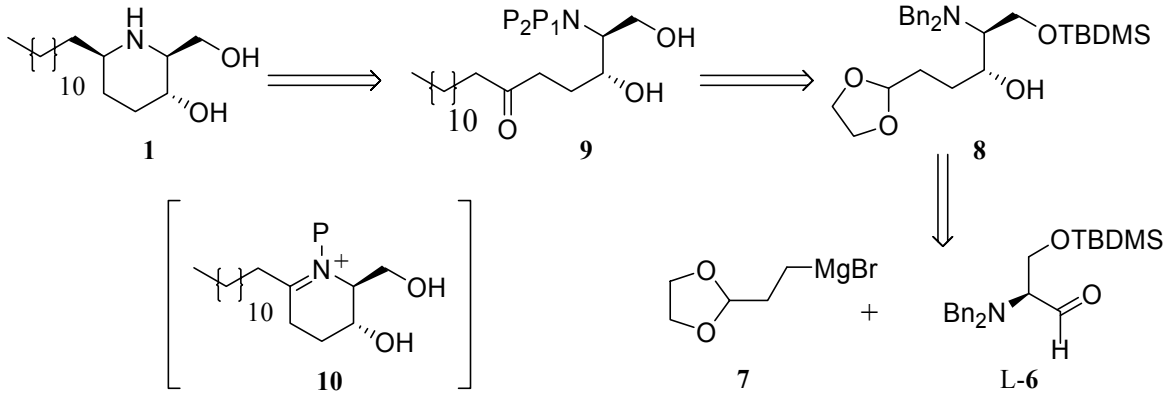


1 X = H, H, (-)-deoxoprosophylline
2 X = O, (-)-prosophylline

3 X = H, H, (-)-deoxoprosopinine
4 X = O, (-)-prosopinine

5 sphingosine

Figure 1



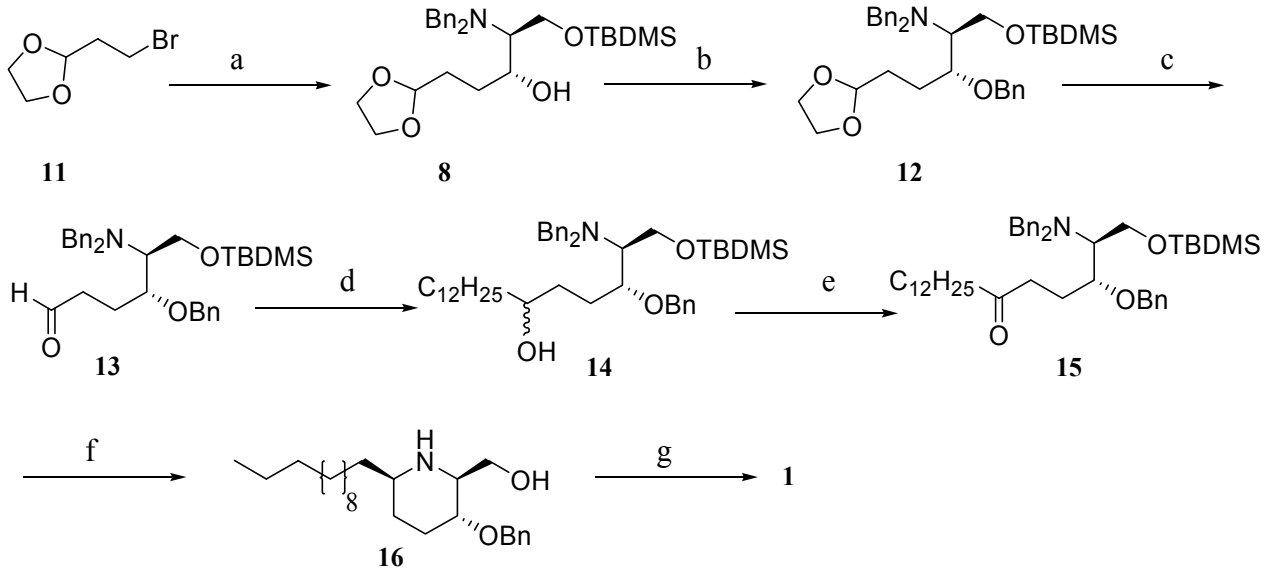
Scheme 1. Retrosynthesis of deoxoprosophylline

RESULTS AND DISCUSSION

Synthesis of (-)-deoxoprosophylline was accomplished as depicted in Scheme 2. Addition of Büchi's Grignard reagent,[10] prepared *in situ* from the corresponding bromide (**11**), to the aldehyde (L-**6**) gave the amino diol (**8**) in excellent yield and diastereoselectivity (*anti/syn* = 15/1). The major stereomer was assumed to be *anti* according to Felkin-Anh model[11] and this is corroborated by the synthesis of final compound. Protection of the secondary hydroxy group as benzyl ether followed by acidic hydrolysis of dioxolane and reprotection of the primary hydroxyl group gave the aldehyde (**13**). Reaction of aldehyde (**13**) with an excess of dodecylmagnesium bromide afforded alcohol (**14**) as a mixture of two diastereomers. This lack of diastereoselectivity was nevertheless of no consequence since the chiral centre in question was anyway thought to be introduced at the end of the synthesis via reduction of a cyclic iminium.

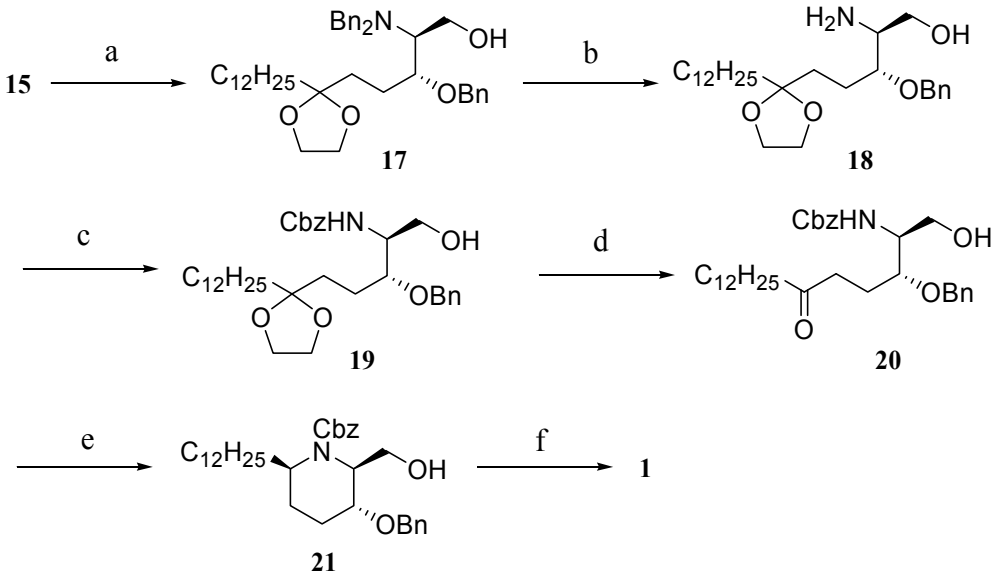
Swern oxidation of alcohol (**14**) afforded ketone (**15**) in 84% yield. Catalytic hydrogenation of **15** under acidic conditions (3N HCl, MeOH, Pd/C, H_2) furnished directly the (-)-deoxoprosophylline (**1**). However, this process is found to be non-reproducible and an alternative two-step process was developed. Thus, under catalytic transfer hydrogenolysis conditions developed by Bajwa and co-workers [$Pd(OH)_2$, cyclohexene, EtOH, HOAc reflux],[12] a chemoselective *N*-debenzylation followed by a reductive amination occurred to provide *O*-benzyldeoxoprosophylline (**16**) which, without purification, was *O*-debenzylated ($Pd(OH)_2$, EtOH, cyclohexene, reflux)[13] to afford (-)-deoxoprosophylline (**1**) in 73% yield. The deoxoprosopinine was not detectable from the ^{1}H NMR spectrum of the crude reaction mixture

indicating the high diastereoselectivity in the reduction step. The physical and spectroscopic data of our synthetic material are identical with those described in the literature.[5d] Thus from the serine aldehyde (L-**6**), we were able to synthesize the (-)-deoxoprosophylline (**1**) in 7 steps with a 32% overall yield.



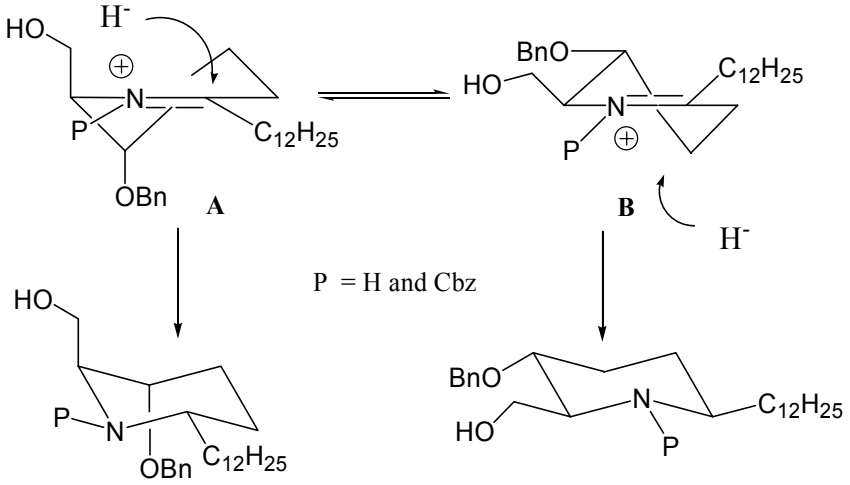
Scheme 2. Reagents and conditions: a) Mg, THF, rt, then L-**6**, 86%; b) NaH, BnBr, Bu_4NI, THF, 0°C, then rt, 85%; c) (i) 3N HCl-THF, (ii) TBDMSCl, imidazole, DMF, 90%; d) $C_{12}H_{25}Br$, Mg, dibromoethane, THF, then **13**, 70°C, 80%; e) DMSO, $(COCl)_2$, then Et_3N, 84%; f) $Pd(OH)_2$, cyclohexene, EtOH, AcOH, reflux, 90%; g) $Pd(OH)_2$, cyclohexene, EtOH, reflux, 81%.

The diastereoselectivity observed in the addition of nucleophiles to substituted iminium is determined by both the conformational preference of the 6-membered iminium intermediate and the reactivity of each conformer as mandated by Curtin-Hammett principle.[14] To probe the influence of the *N*-protective group on the selectivity of the reductive amination process, the *N*-acylated derivative (**20**) was prepared from **15** according to Scheme 3. Protection of the carbonyl function of ketone (**15**) provided the dioxolane (**17**) which was selectively *N*-debenzylated under controlled conditions to afford primary amine (**18**). *N*-Benzyloxycarbonylation followed by hydrolysis of the acetal furnished the cyclization precursor (**20**). Reductive cyclization of **20** was carried out under a variety of conditions varying the reductant, the acid, and the solvent. Under optimal conditions found [$NaBH_3CN$ (2 equiv.), TFA (2 equiv.), CH_2Cl_2, molecular sieve, rt], the desired piperidine (**21**) was obtained in 58% yield. Simultaneous removal of *N*-CBZ and *O*-benzyl groups under transfer hydrogenolysis conditions provided the (-)-deoxoprosophylline (**1**) in 80% yield. Once again, only the 2,6-*cis* derivative (**1**), hence **21**, was obtained from **20** by intramolecular reductive amination process.



Scheme 3. Reagents and conditions: a) ethylene glycol, TMSCl, rt, 12h, 95%; b) $Pd(OH)_2$, cyclohexene, EtOH, 85°C, 4h, 78%; c) CbzOSu, $NaHCO_3$, dioxane-H_2O, 94%; d) 3N HCl, THF, rt, 5h, 85%; e) TFA (2 equiv.), CH_2Cl_2, 4Å molecular sieve, then $NaBH_3CN$ (2 equiv.), rt, 24 h, 58%; f) $Pd(OH)_2$, cyclohexene, EtOH, reflux, 4 h, 80%.

The cyclic imminium intermediate (**10**, Scheme 1) can exist in either of the two conformations shown in Scheme 4. In the case of reductive amination of **15**, we speculated that the bis *N*-debenzylation preceded the reduction of iminium. Under this circumstance, conformer **B** would be predominant over conformer **A** since the allylic strain A[1,2] was minimized when P = H and the developing 1,3-diaxial interaction was avoided.[15] Axial attack of nucleophile from the bottom face of the iminium **B** gave the observed lower-energy chair product (**16**) (P = H).



Scheme 4. Conformational biases in the formation of 2,6-*cis*-piperidine (**16**).

The formation of 2,6-*cis*-piperidine (**21**) from amino ketone (**20**) (P = Cbz) on the other hand was intriguing. Both allylic strain and electrostatic stabilization between OBn group and the iminium cation[16] should favor the conformer **A** in case P = Cbz (Scheme 4). This consideration would predict that the

2,6-*trans* isomer would be produced predominantly resulting from the hydride attack from the top face of the iminium if the reaction involved earlier transition states. This was, however, not the case and we hypothesized that the reduction of iminium intermediate under the present reaction conditions may involve a product-like transition state.[17] Hydride attack along the axial trajectory from the bottom face of the less stable iminium B (R = Cbz) is favored leading to the all-equatorial substituted piperidine (**21**).

In summary, we have developed a short synthesis of (-)-deoxoprosophylline from chiral L-*N*,*N*-dibenzylserine (TBDMS) aldehyde. A highly diastereoselective nucleophilic addition of Büchi's Grignard reagent to chiral serinal followed by an intramolecular reductive amination of ω-oxo amino diol are two key steps of the present synthesis.

ACKNOWLEDGEMENT

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EXPERIMENTAL

(2*S*,3*R*)-1-(*tert*-Butyldimethylsilanyloxy)-2-dibenzylamino-5-[1,3]dioxolan-2-yl-pentan-3-ol (8). To the suspension of Mg (221.6 mg, 9.12 mmol) in THF (5 mL) was added 2-(2-bromoethyl)-1,3-dioxolane (1.07 mL, 9,12 mmol) dropwise at 0°C. After being stirred at rt for 1 h, the serinal (L-**6**) (1.17 g, 3.03 mmol) was introduced at 0°C. The resulting reaction mixture was stirred at rt for 1 h and quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with ethyl acetate and the combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The crude mixture was purified by flash chromatograph (SiO_2, eluent: heptane/AcOEt = 8/1) to provide **8** as colorless oil (1.03 g, 86%). $[\alpha]_D$ + 35° (*c* 1.0, $CHCl_3$,); IR ($CHCl_3$) ν 3660, 3066, 2931, 2890, 2859, 1494, 1454, 1259, 1099, 1071 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.09 (s, 3H), 0.10 (s, 3H), 0.81 (s, 9H), 1.34 (m, 1H), 1.60 (m, 2H), 1.85 (m, 1H), 2.55 (td, *J* = 5.4, 7.2, 1H), 3.08 (s, 1H, OH), 3.52 (d, *J* = 13.7, 2H), 3.70-3.90 (m, 7H), 3.73 (d, *J* = 13,7, 2H), 4.75 (t, *J* = 4.6, 1H), 7.18 (m, 10H); ^{13}C NMR ($CDCl_3$, 62,5 MHz) δ -5.3, 18.1, 25.9, 29.0, 29.9, 55.4, 61.3, 61.7, 64.8, 64.9, 71.7, 104.8, 126.9, 128.3, 128.9, 140.1; MS (IC) *m/z* 486 $(M+H)^+$; Anal. Calcd for $C_{28}H_{43}NO_4Si$: C, 69.24; H, 8.92; N, 2.88; Found: C, 69.15; H; 8.99; N, 2.92.

(2*S*,3*R*)-1-(*tert*-Butyldimethylsilanyloxy)-2-dibenzylamino-3-benzyloxy-5-[1,3]dioxolan-2-ylpentane (12). To a suspension of NaH (175.6 mg, 75% w/w, 5.48 mmol) in THF (1.6 mL) was added at 0°C a solution of alcohol (**8**, 2,42 g, 4.99 mmol) in THF (5 mL). The reaction mixture was stirred at the same

temperature for 30 min. Bu_4NI (368.6 mg; 0.99 mmol) and BnBr (772.0 μL, 6.49 mmol) were added. After being stirred at rt for 12 h, the reaction was quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with ethyl acetate and the combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The crude mixture was purified by flash chromatograph (SiO_2, eluent: heptane/AcOEt = 15/1) to provide **12** (2.50 g, 85%) as colorless oil: $[\alpha]_D$ + 2° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) ν 2955, 2858, 1454, 1389, 1361, 939, 838 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.09 (s, 3H), 0.10 (s, 3H), 0.98 (s, 9H), 1.50 (m, 2H), 1.88 (m, 1H), 2.01 (m, 1H), 2.76 (m, 1H), 3.75 (d, *J* = 13.4, 2H), 3.85 (m, 5H), 3.94 (d, *J* = 13.4, 2H), 4.12 (dd, *J* = 3.0, 10.6, 1H), 4.45 (d, *J* = 11.1, 1H), 4.55 (d, *J* = 11.1, 1H), 4.85 (t, *J* = 7.0 1H), 7.31 (m, 15H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ -4.8, 19.8, 25.0, 26.7, 28.8, 56.2, 60.2, 60.7, 65.5, 65.5, 72.6, 78.0, 105.5, 127.4, 128.0, 128.3, 128.8, 128.9, 129.7, 141.1; MS (IE) *m/z* 575 $(M)^{+\cdot}$; Anal. Calcd for $C_{35}H_{49}NO_4Si$: C, 73.00; H, 8.58; N, 2.43; Found: C, 72.68; H, 8,26; N, 2.45.

(4*R*,5*S*)-6-(*tert*-Butyldimethylsilanyloxy)-4-benzyloxy-5-dibenzylaminohexanal (13). A solution of acetal (**12**, 2.15 g, 3.73 mmol) in a mixture of solvent HCl (3N, 10 mL)) / THF (10 mL) was stirred at rt for 4 h. The reaction mixture was neutralized by addition of aqueous NaOH (1N) and was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated to give the analytical pure aldehyde which was re-silylated under classic conditions (TBDMSCl, imidazole, DMF, 0.3M, rt) to provide **13** as colorless oil (1.78 g, 90%): $[\alpha]_D$ + 8° (*c* 1.3, $CHCl_3$); IR ($CHCl_3$) ν 3016, 2830, 2726, 1952, 1883, 1813, 1720, 1454, 1214, 526 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.09 (s, 3H), 0.10 (s, 3H), 0.85 (s, 9H), 1.54 (m, 1H), 1.92 (m, 3H), 2.60 (ddd, *J* = 2.8, 6.5, 8.2, 1H), 3.56 (d, *J* = 13.4, 2H), 3.64 (m, 1H), 3.75 (d, *J* = 13.4, 2H), 3.82 (dd, *J* = 6.5, 11.1, 1H), 4.04 (dd, *J* = 2.8, 11.1, 1H), 4.29 (d, *J* = 11.4, 1H), 4.31 (d, *J* = 11.4, 1H), 7.28 (m, 15H), 9.46 (s, 1H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ -5.5, 18.1, 21.8, 26.0, 37.7, 55.4, 58.9, 59.6, 71.9, 76.1, 126.7, 126.9, 127.1, 127.6, 128.2, 129.2, 140.2, 202.8; MS (IE) *m/z* 531 $(M)^+$.

(2*S*,3*R*)-1-(*tert*-Butyldimethylsilanyloxy)-3-benzyloxy-2-dibenzylaminooctadecane-1,6-diol (14). To the suspension of Mg (696.6 mg, 28.9 mmol) in THF (6 mL) were added bromoundecane (8.04 mL, 28.9 mmol) and dibromethane (159.0 μL, 1.61 mmol) dropwise. After being stirred at 70°C for 1 h, a solution of aldehyde (**13**, 1.71 g, 3.22 mmol) in THF (12 mL) was introduced at rt. The resulting reaction mixture was stirred at rt for 3 h and quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with ethyl acetate and the combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The crude mixture was purified by flash chromatograph (SiO_2, eluent: heptane/ Et_2O = 9/ 1) to provide **14** as a mixture of two diastereomers in a ratio of 7/3 (1.82 g, 80%): IR ($CHCl_3$) ν 3630, 2928, 2855, 1718, 1684, 1653, 1360, 1253, 1089 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.09 (s, 3H), 0.10 (s, 3H), 0.75 (t, *J* = 7.1, 3H), 0.79 (s, 9H), 1.15 (m, 20H), 1.50-1.80 (m, 6H), 2.72 (m, 1H), 3.21 (m, 1H), 3.61 (d,

J = 13.6, 2H), 3.75 (d, *J* = 13.6, 2H), 3.76 (m, 2H), 3.98 (dd, *J* = 2.3, 10.6, 1H), 4.26 (d, *J* = 11.1, 1H), 4.28, 4.35 (d, *J* = 11.1), 7.32 (m, 15H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ -5.4, 14.1, 18.1, 22.7, 25.7, 26.0, 29.4, 29.7, 31.9, 37.3, 37.5, 55.4, 59.5, 59.7, 71.8, 72.1, 77.7, 126.8, 127.5, 127.8, 128.2, 129.2, 138.2, 140.4; MS (ES^+) *m/z* 702 $(M+H)^+$.

(2*S*,3*R*)-1-(*tert*-Butyldimethylsilanyloxy)-3-benzyloxy-2-dibenzylamino-6-oxooctadecan-6-one (15). To a solution of oxalyl chloride (277.9 μL, 3.20 mmol) in CH_2Cl_2, cooled at –78°C, was added DMSO (2.94 mL, 2.4 M in CH_2Cl_2, 7.06 mmol). After 5 min, a solution of alcohol (**14**, 1.5 g, 2.14 mmol) in CH_2Cl_2 (3 mL) was introduced. The reaction mixture was stirred at –78°C for 30 min followed by addition of triethylmine (2.02 mL, 14.5 mmol). The reaction temperature was raised gradually to rt and stirring was continued for 45 min. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The crude mixture was purified by flash chromatograph (SiO_2, eluent: heptane/AcOEt = 11/1) to provide **15** as colorless oil (1.26 g, 84%): $[\alpha]_D$ + 6° (*c* 1.25, $CHCl_3$); IR ($CHCl_3$) ν 2929, 2856, 1707, 1373, 1361, 1256, 724 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.09 (s, 3H), 0.10 (s, 3H), 0.72 (t, *J* = 7.2, 3H), 0.85 (s, 9H), 1.12 (m, 20H), 1.52 (m, 2H), 1.89 (m, 4H), 2.55 (ddd, *J* = 2.3, 6.0, 8.1, 1H), 3.55 (d, *J* = 13.4, 2H), 3.62 (m, 1H), 3.75 (d, *J* = 13.4, 2H), 3.83 (dd, *J* = 6.0, 11.1, 1H), 4.02 (dd, *J* = 2.3, 11.1, 1H), 4.25 (d, *J* = 11.6, 1H), 4.43 (d, *J* = 11.6, 1H), 7.32 (m, 15H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ -5.4, 14.1, 18.1, 22.6, 22.8, 23.7, 26.0, 29.3, 29.4, 29.6, 31.9, 35.8, 42.8, 55.3, 58.9, 59.6, 71.7, 77.4, 126.8, 127.4, 127.7, 128.2, 129.2, 138.5, 140.3, 211.4; MS (ES^+) *m/z* 700 $(M+H)^+$; Anal. Calcd for $C_{45}H_{69}NO_3Si$: C, 77.20; H, 9.93; N, 2.00; Found: C, 76.91; H, 10.05; N, 1.91.

(2*S*, 3*R*, 6*S*)-(3-Benzyloxy-6-dodecylpiperidin-2-yl)methanol (16). A suspension of amino ketone (**15**, 483.0 mg, 0.69 mmol) and $Pd(OH)_2$ (10% on charcon, 102.2 mg) in ethanol (5.3 mL), cyclohexene (2.9 mL) and acetic acid (1.6 mL) were stirred at 85°C for 12 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ and filtered through a short pad of celite. The filtrate was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The crude mixture was purified by flash chromatograph (SiO_2, eluent: CH_2Cl_2/MeOH = 15/1) to provide piperidine (**16**) as colorless oil (242.0 mg, 90%): $[\alpha]_D$ -20° (*c* 0.56, $CHCl_3$); IR ($CHCl_3$) ν 2928, 2855, 1661, 1456, 1074 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.75 (t, *J* = 7.2, 3H), 1.15 (m, 22H), 1.45 (m, 2H), 1.55 (m, 2H), 2.02 (m, 1H), 2.45 (dt, *J* = 5.2, 9.0, 1H), 3.45 (ddd, *J* = 4.6, 9.1, 10.9, 1H), 3.56 (dd, *J* = 5.2, 10.7, 1H), 3.82 (dd, *J* = 4.1, 10.7, 1H), 4.45 (d, *J* = 11.8, 1H), 4.60 (d, *J* = 11.8, 1H), 7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 14.1, 22.6, 24.0, 26.1, 29.2, 29.3, 29.6, 29.8, 31.0, 31.9, 36.6, 40.2, 55.9, 62.0, 64.2, 70.6, 73.3, 127.7, 128.4, 138.4; MS (IE) *m/z* 389 $(M)^{+\cdot}$; HRMS: calcd for $C_{25}H_{43}NO_2$: 390.3372

(M+H), found: 390.3364.

(-)-Deoxoprosophylline (1). A suspension of piperidine (**16**, 50.1 mg, 0.12 mmol) and $Pd(OH)_2$ (10%, 10.0 mg) in ethanol (1.1 mL), cyclohexene (0.5 mL) was stirred at 85°C for 12 h. The reaction mixture was filtered through a short pad of celite and washed thoroughly with ethyl acetate. The filtrate was concentrated and the crude mixture was purified by flash chromatograph (SiO_2, eluent: CH_2Cl_2/MeOH = 15/1) to provide (-)-deoxoprosophylline (**1**) as a white solid (31.2 mg, 81%): mp 85°C; $[\alpha]_D$ -13° (*c* 0.3, $CHCl_3$) {lit., [5d] $[\alpha]_D^{23}$ -14° (*c* 0.24, $CHCl_3$)}; IR ($CHCl_3$): ν 3414, 3024, 2927, 2854, 1466, 1221, 1060 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.88 (t, *J* = 6.7, 3H), 1.00-1.41 (m, 22H), 1.65-1.80 (m, 2H), 1.96-2.04 (m, 2H), 2.41-2.65 (m, 5H), 3.46 (ddd, *J* = 4.3, 9.7, 10.0), 3.70 (dd, *J* = 5.5. 10.7, 1H), 3.84 (dd, *J* = 4.7, 10.7, 1H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 14.1, 22.7, 26.2, 29.4, 29.7, 29.8, 31.1, 31.9, 33.9, 36.6, 56.1, 63.3, 64.6, 70.6; MS (IE) *m/z* 299 $(M)^+$; HRMS calcd for $C_{18}H_{37}NO_2$: 300.2902 (M+H), found: 300.2909.

(2*S*, 3*R*)-3-Benzyloxy-2-dibenzylamino[1,3]dioxolan-6-yl-octadecan-1-ol (17). To a solution of amino ketone (**15**, 887.5 mg, 1.27 mmol) in ethylene glycol (6.0 mL) was added TMSCl (0.65 mL, 5.1 mmol). After being stirred at rt for 12 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The crude mixture was purified by flash chromatograph (SiO_2, eluent: heptane/ether = 9/1) to provide dioxolane (**17**, 755.0 mg, 95%) as colorless oil: $[\alpha]_D$ -43° (*c* 0.7, $CHCl_3$); IR ($CHCl_3$) ν 3512, 2930, 2858, 1495, 1454, 1364, 1073, 909, 749, 723 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.78 (t, *J* = 7.3, 3H), 1.21 (m, 20H), 1.48 (m, 2H), 1.65 (m, 2H), 2.68 (q, *J* = 5.9, 1H), 3.49 (d, *J* = 13.2, 2H), 3.75 (d, *J* = 13.2, 2H), 3.80 (m, 7H), 4.35 (d, *J* = 11.0, 1H), 4.55 (d, *J* = 11.0, 1H), 6.55 (m, 15H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 22.6, 23.9, 24.6, 29.3, 29.6, 29.9, 31.4, 31.9, 37.4, 54.3, 58.8, 60.7, 64.9, 71.0, 78.3, 111.6, 127.1, 127.7, 128.3, 128.4, 128.9, 138.0, 139.5; MS (IC) *m/z* 630 $(M+H)^+$; Anal. Calcd for $C_{41}H_{59}NO_4$: C, 78.18; H, 9.44; N, 2.22; Found: C, 77.94; H, 9.65; N, 2.14.

(2*S*,3*R*)-2-Amino-3-benzyloxy[1,3]dioxolan-6-yl-octadecan-1-ol (18). A suspension of dioxolane (**17**, 1.05 g, 1.67 mmol) and $Pd(OH)_2$ (10%, 181.2 mg) in ethanol (13.0 mL), cyclohexene (6.7 mL) was stirred at 85°C for 4 h. The reaction mixture was filtered through a short pad of celite and washed thoroughly with ethyl acetate. The filtrate was concentrated and the crude mixture was purified by flash chromatograph (SiO_2, eluent: toluene/CH_2Cl_2/EtOH = 4/5/1) to provide amino alcohol (**18**) as a white solid (580.0 mg, 78%): mp 50°C; $[\alpha]_D$ -15° (*c* 1, $CHCl_3$); IR ($CHCl_3$) ν 3467, 3020, 2957, 2854, 1601, 1455, 1207, 1072, 948 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.92 (t, *J* = 7.2, 3H), 1.23 (m, 20H), 1.62 (m, 6H), 3.00 (m, 1H), 3.10 (m, 3H), 3.46 (q, *J* = 4.8, 1H), 3.52 (dd, *J* = 6.6, 10.9, 1H), 3.62 (dd, *J* = 3.5, 10.5,

1H), 3.95 (s, 4H), 4.46 (d, *J* = 11.4, 1H), 4.52 (d, *J* = 11.4, 1H), 7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 22.7, 23.9, 24.0, 29.3, 29.6, 32.9, 37.3, 54.2, 63.2, 64.9, 72.0, 81.3, 111.6, 127.8, 128.4, 138.2; MS (ES^+) *m/z* 450 $(M+H)^+$; Anal. Calcd for $C_{27}H_{47}NO_4$: C, 72.12; H, 10.54; N, 3.11; Found: C, 71.97; H, 10.64; N, 3.11.

***N*-Benzyloxycarbamate (19)**. A solution of amino alcohol (**18**, 516.7 mg, 1.15 mmol) and CbzOSu (2.07 mmol) in a mixture of solvent (saturated aqueous $NaHCO_3$/1,4 dioxane = 1/ 1, 5 mL each) was stirred at rt for 14 h. The reaction mixture was diluted with saturated aqueous NH_4Cl and was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The crude mixture was purified by flash chromatograph (SiO_2, eluent: heptane/AcOEt = 4/1) to provide carbamate (**19**) as white solid (630.9 mg, 94%): mp 42°C; $[\alpha]_D$ -17° (*c* 0.4, $CHCl_3$); IR ($CHCl_3$) ν 3642, 3436, 2928, 2855, 1717, 1505, 1261, 1069, 948 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.85 (t, *J* = 7.2, 3H), 1.25 (m, 20H), 1.52 (m, 4H), 1.70 (m, 2H), 2.75 (s, 1H), 3.53 (m, 3H), 3.80 (s, 4H), 3.95 (dd, *J* = 3.5, 10.9, 1H), 4.45 (d, *J* = 10.9, 1H), 4.55 (d, *J* = 10.9, 1H), 5.02 (s, 2H), 5.50 (d, *J* = 7.7, 1H), 7.27 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.9, 22.5, 23.6, 24.8, 25.2, 27.0, 29.1, 29.5, 29.7, 31.7, 32.2, 53.8, 61.6, 64.7, 66.5, 72.3, 80.4, 111.3, 127.6, 127.9, 128.3, 128.6, 129.0, 136.3, 137.8, 156.8; MS (ES^+) *m/z* 606 $(M+Na)^+$; Anal. Calcd for $C_{35}H_{53}NO_6$: C, 72.01; H, 9.14; N, 2.40; Found: C, 71.98; H, 9.05; N, 2.24.

Ketone (20). A solution of compound (**19**, 597.2 mg, 1.02 mmol) in a mixture of solvent: HCl (3N)/THF = 1/1 (5 mL) was stirred at rt for 24 h. The reaction mixture was basified with saturated aqueous $NaHCO_3$ and was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The crude mixture was purified by flash chromatograph (SiO_2, eluent: heptane/AcOEt = 9/1) to provide ketone (**20**) as white solid (469.3 mg, 85%): mp 58°C; $[\alpha]_D$ -13° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) ν 3637, 3436, 2928, 2855, 1713, 1507, 1455, 1064, 729 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.82 (t, *J* = 7.4, 3H), 1.22 (m, 18H), 1.45 (m, 2H), 1.81 (q, *J* = 7.1, 2H), 2.26 (t, *J* = 7.3, 2H), 2.41 (q, *J* = 6.7, 2H), 2.62 (br s, 1H, OH), 3.60 (m, 3H), 3.82 (dd, *J* = 2.7, 10.9, 1H), 4.41 (d, *J* = 11.6, 1H), 4.50 (d, *J* = 11.6, 1H), 5.00 (s, 2H), 5.41 (d, *J* = 7.9, 1H), 7.30 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 22.8, 23.9, 24.1, 29.6, 29.3, 29.4, 29.5, 29.7, 32.0, 37.9, 43.1, 53.7, 62.1, 66.9, 72.4, 79.6, 128.1, 128.2, 128.3, 128.5, 128.7, 128.9, 136.5, 137.8, 156.5, 210.8; MS (ES^+) *m/z* 540 $(M+H)^+$, 562 $(M+Na)^+$; Anal. Calcd for $C_{33}H_{49}NO_5$: C, 73.43; H, 9.15; N, 2.59; Found: C, 73.12; H, 9.05, N, 2.67.

Piperidine (21). To a solution of ketone (**20**, 20.0 mg, 0,037 mmol) in CH_2Cl_2 (1 mL) were added TFA (6.0 μL, 0,074 mmol), 4 Å molecular sieve and $NaBH_3CN$ (4.66 mg, 0.074 mmol). After being stirred at rt for 1 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated.

The crude mixture was purified by flash chromatograph (SiO_2, eluent: heptane/AcOEt = 4/1) to provide piperidine (**21**) as colorless oil (11.2 mg, 58%): $[\alpha]_D$ -33° (*c* 0,7, $CHCl_3$); IR ($CHCl_3$) ν 2927, 2854, 1745, 1264, 1220, 778 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.82 (t, *J* = 7.3, 3H), 1.22 (m, 22H), 1.75 (m, 4H), 2.11 (m, 1H), 2.48 (br s, 1H, OH), 2.82 (td, *J* = 2.4, 9.4, 1H), 3.12 (td, *J* = 4.3, 10.5, 1H), 4.02 (dd, *J* = 7.6, 10.5, 1H), 4.32 (d, *J* = 11.4, 1H), 4.49 (dd, *J* = 2.4, 10.5, 1H), 4.52 (d, *J* = 11.4, 1H), 5.11 (s, 2H), 7.30 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 22.7, 26.2, 29.0, 29.4, 29.6, 29.8, 30.9, 31.9, 36.6, 55.9, 59.9, 69.7, 70.6, 75.7, 127.7, 127.8, 128.4, 128.6, 135.2, 138.3, 155.0; MS (IE) *m/z* 523 $(M)^+$; Anal. Calcd for $C_{33}H_{49}NO_4$: C, 75.68; H, 9.43; N, 2.67; Found: C, 75.42; H, 9.31; N, 2.77.

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