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Versatile Approach to Enantiopure 2,6-Disubstituted Piperidin-3-ol Framework: Application to the Total Synthesis of (+)-Deoxoprosopinine

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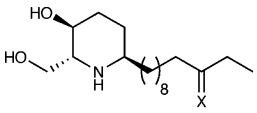
An efficient synthesis of enantiopure 2,6-disubstituted piperidin-3-ol **19** is developed featuring two key steps: (a) Julia olefination of (2*R*)-3-phenylsulfonyl-2-*tert*-butyloxycarbamoylpropanol benzyl ether **9B** and (2*R*,3*S*)-2-*tert*-butyldiphenyl-3,4-*O*-isopropylidine-2,3,4-trihydroxybutyraldehyde **8** and (b) intramolecular *N*-alkylation. A straightforward asymmetric synthesis of (+)-deoxoprosopinine **(2)** from **19** is described demonstrating the versatility of this novel approach.

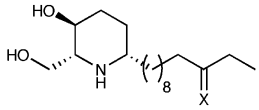
Introduction

Among the multifunctionalized piperidine alkaloids widely found in nature, 3-hydroxy-2,6-disubstituted prosopis alkaloids,[1] such as prosopinine (**1**), prosophylline (**3**), and their deoxo analogues (**2**, **4**) (Figure 1), have attracted much attention because of their interesting biological properties[2] and stereochemical variations at the C-2, C-3, and C-6 positions. Numerous syntheses of this class of compounds have been reported. However, it is still desirable to develop a general synthetic strategy that provides a common pivotal intermediate from which 2,3,6-trisubstituted piperidines with desired stereochemistry can be derived. With this in mind, we envisaged establishing a versatile methodology for the synthesis of an enantiopure 2,6-disubstituted piperidin-3-ol framework starting from chiral building blocks, γ-sulfonyl-β-amino alcohol derivative **I**[3] and aldehyde **II**, easily derived from L-ascorbic acid (Scheme 1).[4]

As shown in Scheme 1, Julia olefination between enantiomerically pure sulfone **I**[3] and aldehyde **II**[4] followed by cyclization are key steps of our projected synthesis. Both enantiomers of **I** are commercially avail-



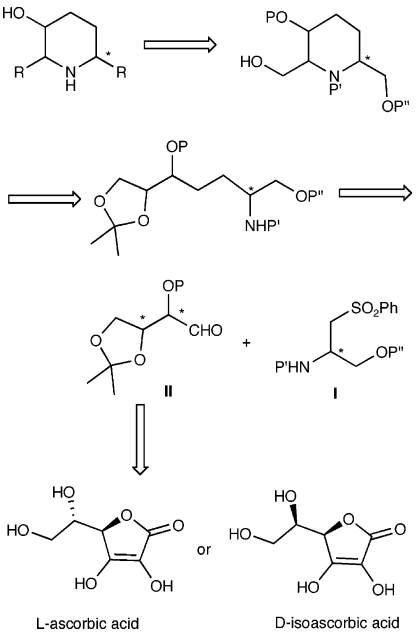
1 X = O, (+)-prosopinine
2 X = H,H, (+)-deoxoprosopinine



3 X = O, (+)-prosophylline
4 X = H,H, (+)-deoxoprosophylline

FIGURE 1. Prosopis alkaloids.

SCHEME 1. Retrosynthetic Analysis of 2,6-Disubstituted Piperidin-3-ol



(1) Prosopis alkaloids from the leaves, stems, and roots of *Prosopis africana*: (a) Ratle, G.; Monseur, X.; Das, B. C.; Yassi, J.; Khuong-Huu, Q.; Goutarel, R. *Bull. Soc. Chim. Fr.* **1966**, 2945−2947. (b) Khuong-Huu, Q.; Ratle, G.; Monseur, X.; Goutarel, R. *Bull. Soc. Chim. Belg.* **1972**, *81*, 425−442, 443−458.

(2) For reviews that include piperidine alkaloids, see: (a) Ayer, W. A.; Habgood, T. E. In *The Alkaloids*; Manske, R. H., Ed.; Academic Press: London, 1968; Vol. 11, p 492. (b) Strunz, G. M.; Findlay, J. A. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1985; Vol. 26, pp 89−183. (c) Foder, G. B.; Colasanti, B. The Pyridine and Piperidine Alkaloids; Chemistry and Pharmacology. In *Alkaloids: Chemical and Biological Perspectives*: Pelletier, S. W., Ed.; Wiley: New York, 1985; Vol. 3, pp 1−90. (d) Numata, A.; Ibuka, T. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 31, pp 193−315 and references therein. (e) Schneider, M. J. Pyridine and Piperidine Alkaloids: An Update. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: Oxford, 1996; Vol. 10, pp 155−299. (f) Wang, C. J.; Wuonola, M. A. *Org. Prep. Proced. Int.* **1992**, *24*, 585−621. (g) Laschat, S.; Dickner, T.; *Synthesis* **2000**, 1781−1813. (h) Weintraub, P. M.; Sabd, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953−2989. Analgesic, antibiotic and anaesthetic properties: (i) Bourrinet, P.; Quevauviller, A. *C. R. Soc. Biol.* **1968**, *162*, 1138−1140. (j) Bourrinet, P.; Quevauviller, A. *Ann. Pharm. Fr.* **1968**, *26*, 787−796.

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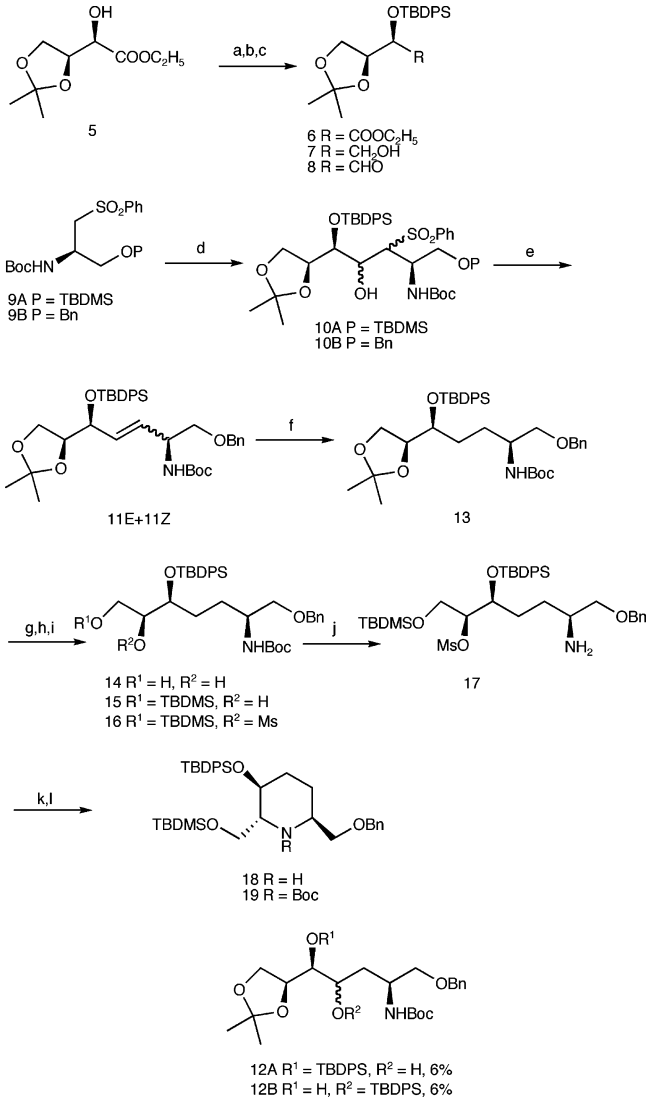
able, while the four diastereomers of aldehyde **II** are readily accessible from L-ascorbic acid and D-isoascorbic acid.[4] This versatile chiral pool approach should enable us to provide a priori any one of eight possible diastereomers of prosopis alkaloids (natural or non-natural) by pairing adequate enantiomers of **I** and diastereomers of **II**.

Results and Discussion

Synthesis of 2,6-Disubstituted Piperidin-3-ol. Our synthesis commenced with the preparation of aldehyde **8**. Ethyl (2*R*,3*S*)-3,4-*O*-isopropylidine-2,3,4-trihydroxybutanoate **5** was prepared from L-ascorbic acid in two steps in 91% yield according to the known procedure (Scheme 1).[4] Protection of the hydroxy group of **5** as TBDPS ether followed by reduction of the ester function ($LiBH_4$−MeOH, Et_2O) provided the primary alcohol **7** that after Swern oxidation afforded aldehyde **8** in 95% overall yields (Scheme 2). The coupling reaction was first investigated using TBDMS protected chiral building block **9A**. Although the coupling intermediate **10A** can be prepared efficiently from **8** and **9A**, the instability of TBDMS group during the deprotection of the isopropylidene function obliged us to use the alternative chiral building block **9B** wherein the primary hydroxy group was protected as a benzyl ether. The coupling of the dianion prepared from chiral sulfone **9B** (2.2 equiv of *n*-BuLi) with aldehyde **8** went smoothly to furnish hydroxysulfone **10B** in 83% yield as a mixture of two diastereoisomers whose signals in ^1H and ^{13}C NMR spectra cannot be differentiated. Reduction of hydroxysulfone **10B** with 6% Na−Hg in methanol at 0 °C gave almost exclusively the *E*-alkene **11E** in 78% yield. *Z*-Alkene **11Z** was also isolated in less than 1% of yield. During this desulfonylation reaction, two byproducts, alcohols **12A** (6%) and **12B** (6%), were formed which were easily removed by chromatography. Selective saturation of the double bond with retention of the benzyl and the TBDMS silyl ether functions was realized under mild hydrogenation conditions (10% Pd−C, methanol, NH_4OAc).[5] The fully protected amino polyol **13** was transformed into mesylate **16** via a standard three-step sequence. Thus, hydrolysis of the isopropylidene under mild acidic conditions ($HOAc/H_2O$ = 4/1, room temperature) provided compound **14**, which after selective protection of the primary hydroxy group (TBDMSCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, 2 h) was converted into mesylate **16** (MsCl, Et_3N, DMAP, CH_2Cl_2, −20 to 0 °C, 2 h) in 92% overall yields. Attempts to convert compound **16** into piperidine ring by intramolecular amide alkylation failed under various conditions (NaH in THF or in DMF). We then turned our attention to the intramolecular alkylation of amine **17**, obtained in turn by removal of the *N*-Boc group under mild conditions (TBDMSOTf, 2,6-lutidine in CH_2Cl_2 at rt, then 1% citric acid)[6] in 99% yield. Eventually, simply refluxing a solution of **17** in methanol in the presence of $^iPr_2NEt$ for 48 h afforded piperidine **18** in 92% yield. The amine group of **18** was then protected with Boc_2O to provide orthogonally protected 2,3,6-trisubstituted piperidine **19** in 99% yield. All three hydroxy groups being differentially protected, the piperidine **19** can serve as a pivotal intermediate not only for the synthesis of various prosopis alkaloids but also of other piperidine alkaloids such as cassia alkaloids (for example, carpamic acid, azimic acid, spectaline)[2] and quinolizidine alkaloids (clavepictine A and B, and pictamine).[7]

SCHEME 2. Synthesis of 2,6-Disubstituted Piperidin-3-ol[a]



[a] Reagents and conditions: (a) TBDPSCl, imidazole, DMF, 0 °C, 15 min; rt, 3 h; (b) $LiBH_4$, MeOH, Et_2O, 0 °C, 3 h, 95% for two steps; (c) $(COCl)_2$, DMSO, CH_2Cl_2, −70 °C, 20 min; Et_3N, −70 °C, 1 h, 100%; (d) BuLi (2.2 equiv), THF, −70 °C, 30 min; **8**, −70 °C, 4 h, 83%; (e) 6% Na−Hg, Na_2HPO_4, MeOH, 0 °C, 2 h, 72%; (f) H_2, 10% Pd−C, NH_4OAc, MeOH, rt, 24 h, 100%; (g) $HOAc-H_2O$ (4/1), rt, overnight, 93%; (h) TBDMSCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, 2 h, 100%; (i) MsCl, Et_3N, DMAP, CH_2Cl_2, −20 to 0 °C, 2 h 99%; (j) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, rt, 1 h; 1% citric acid in MeOH, rt, overnight, 99%; (k) $^iPr_2NEt$, MeOH, reflux, 48 h, 92%; (l) Boc_2O, Et_3N, DMF, rt, overnight, 99%.

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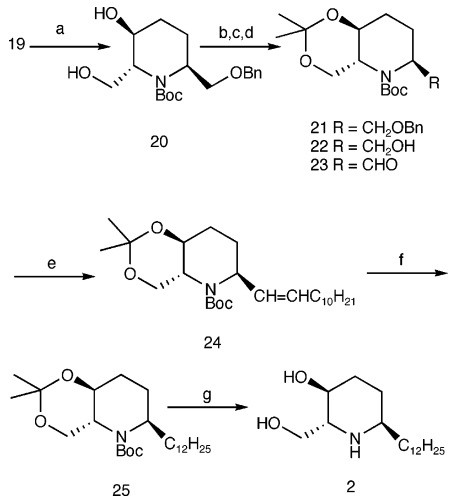
SCHEME 3. Synthesis of (+)-Deoxoprosopinine[a]



[a] Reagents and conditions: (a) Bu_4NF, THF, 0 °C, 10 min; rt, 1 h, 100%; (b) 2,2-dimethoxypropane, TsOH, acetone, rt, 2 h, 93%; (c) H_2 (1 atm), 20% $Pd(OH)_2$−C, EtOAc, rt, 2 h, 96%; (d) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 15 min; Et_3N, 0 °C, 1 h, 100%; (e) $Ph_3PC_{11}H_{23}Br$, KHMDS, THF, −78 °C, 10 min; 0 °C, 1 h; compound **17**, −78 °C, 20 min; 0 °C, 5 h, 87%; (f) H_2 (1 atm), 20% $Pd(OH)_2$−C, EtOAc, rt, overnight, 99%; (g) 1 N HCl−MeOH, rt, 24 h, 79%.

Synthesis of (+)-Deoxoprosopinine. The conversion of **19** into (+)-deoxoprosopinine **(2)** is summarized in Scheme 3.[8,9] Since the essential part of the transformation of **19** to (+)-deoxoprosopinine (**2**) is the conversion of benzyloxymethyl group to $C_{12}H_{25}$ moiety, we first tried the removal of the benzyl group by catalytic hydrogenolysis. A set of hydrogenolysis conditions varying the catalysts [Pd/C, $Pd(OH)_2$/C, Raney-nickel] and the solvents (EtOAc, MeCN, THF) has been investigated. Unfortunately, none of these conditions allowed us to remove the benzyl group selectively. Other conditions including transfer hydrogenolysis and Birch reduction also failed to produce the desired compound. It seems that the TBDMS ether in compound **19** is particularly sensitive to the reductive conditions that we have tried. To overcome this problem, the benzyl group in chiral building block **9B** could be replaced by other protecting groups. In this respect, PMB seems to be the protecting group of choice to obtain a versatile key intermediate analogue of compound **19** with three differentially removable protecting groups on the hydroxyl functionality. Nevertheless, to accomplish the synthesis of (+)-deoxoprosopinine starting from **19**, the silyl ethers were converted to 1,3-*O*-isopropylidene prior to the removal of benzyl group. Thus, alcohol **22** was obtained in 89% overall yield from **19** by a three-step sequence involving (a) TBAF-mediated deprotection of silyl ether; (b) acetonide formation; and (c) removal of benzyl ether under hydrogenolysis conditions. Swern oxidation of **22** to aldehyde followed by Wittig reaction furnished alkene **24** in 87% overall yield. Bases were found to have dramatic effect on the Wittig reaction and higher yield was obtained when KHMDS was used instead of *n*-BuLi. Catalytic hydrogenation of **24** followed by the simultaneous removal of the 1,3-diol protecting group and Boc group (1 N HCl in MeOH) provided (+)-deoxoprosopinine (**2**) in 74% overall yield. The mp, $[\alpha]_D$, and ^1H and ^{13}C NMR spectra of our synthetic material (**2**) are in agreement with that of literature data.[8d,j,m] Starting from fully protected piperidine triol **19**, (+)-deoxoprosopinine (**2**) was obtained in a convenient seven-step sequence in 57% overall yield.

Conclusions

A general method for the synthesis of 2,6-disubstituted piperidin-3-ol has been developed featuring key Julia olefination and intramolecular *N*-alkylation reaction. Starting from (2*R*)-3-phenylsulfonyl-2-*tert*-butyloxycarbamoylpropanol benzyl ether **9B** and (2*R*,3*S*)-2-*O*-*tert*-butyldiphenyl-3,4-*O*-isopropylidine-2,3,4-trihydroxybutyraldehyde **8**, (+)-deoxoprosopinine (**2**) has been synthesized in good overall yield. The synthetic strategy should be amenable to the preparation of other piperidine alkaloids with different stereochemistry at C-2, C-3 and C-6 chiral centers.

Experimental Section

(2*R*,3*S*)-Ethyl 2-*O*-*tert*-Butyldiphenylsilyloxy-3,4-*O*-isopropylidene-3,4-dihydroxybutanoate (6). To a solution of **5** (19.01 g, 93.19 mmol) in DMF (93 mL) at 0 °C were added imidazole (15.86 g, 232.97 mmol) and TBDPSCl (28.18 g, 102.50 mmol). The reaction mixture was stirred at 0 °C for 1 h and then at rt for 2 h. Water was added, and the reaction mixture was extracted with ether. The ether extracts were washed with diluted HCl, water, and diluted sodium bicarbonate and brine, dried, and evaporated to give the crude ester **6**, which was used directly for the next reaction without purification. The analytical sample was obtained by flash column chromatography (silica gel, CH_2Cl_2/heptane = 1/1 then CH_2Cl_2/heptane/ethyl acetate = 10/10/1): $[\alpha]_D$ +27 (*c* 4.0, $CHCl_3$); IR ($CHCl_3$) 3074, 3053, 3030, 2989, 2961, 2934, 2896, 2860, 1741, 1590, 1473, 1428, 1382, 1373, 1256, 1227, 1220, 1193, 1154, 1113, 1073, 1029, 966, 940, 881, 856, 823 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70−7.66 (m, 4H), 7.43−7.33 (m, 6H), 4.35 (q, J = 6.0 Hz, 1H), 4.27 (d, J = 5.7 Hz, 1H), 4.05 (dd, J = 5.9, 8.6 Hz, 1H), 4.00 (dd, J = 6.7, 8.8 Hz, 1H), 3.95−3.86 (m, 2H), 1.35 (s, 3H), 1.32 (s, 3H), 1.11 (s, 9H), 1.05 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 136.1, 136.0, 133.1, 133.0, 129.9, 129.8, 127.7, 127.6, 109.8, 77.2, 73.8, 65.4, 60.8, 27.0, 26.3, 25.3, 19.6, 14.0; MS (ESI) *m*/*z* 465 $[M + Na]^+$,

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481 $[M + K]^+$. Anal. Calcd for $C_{25}H_{34}O_5Si$: C, 67.84; H, 7.74; Found: C, 67.85; H, 7.71.

(2*S*,3*S*)-2-*O*-*tert*-Butyldiphenylsilyloxy-3,4-*O*-isopropylidene-3,4-dihydroxybutanol (7). To a solution of crude **6** obtained above (93.19 mmol) in ether (560 mL) at 0 °C was added lithium borohydride (3.04 g, 139.8 mmol) and then methanol (5.66 mL, 139.8 mmol) dropwise. The reaction mixture was stirred at 0 °C for 3 h. The reaction was quenched with 0.5 N HCl with ice-cooling. The mixture was extracted with EtOAc. The extracts were washed with saturated sodium bicarbonate and brine, dried, and evaporated. Flash column chromatography (silica gel, heptane/EtOAc = 10/1 then 3/1) afforded alcohol **7** (35.39 g, 95% for two steps): $[\alpha]_D$ −18 (*c* 3.1, $CHCl_3$); IR ($CHCl_3$) 3568, 3074, 3055, 3017, 2991, 2962, 2934, 2894, 2861, 1473, 1464, 1428, 1383, 1374, 1224, 1218, 1112, 1069, 1050 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.71−7.68 (m, 4H), 7.48−7.35 (m, 6H), 4.22 (dt, *J* = 5.4, 6.6 Hz, 1H), 3.99−3.90 (m, 2H), 3.86 (q, *J* = 4.7 Hz, 1H), 3.64 (dd, *J* = 4.8, 11.7 Hz, 1H), 3.55 (dd, *J* = 4.4, 11.7 Hz, 1H), 2.09 (br s, 1H, OH), 1.38 (s, 3H), 1.29 (s, 3H), 1.08 (s, 9H);^{13}C NMR (62.5 MHz, $CDCl_3$) δ 136.0, 135.8, 133.8, 133.2, 129.9, 127.6, 77.0, 73.4, 65.3, 63.7, 27.0, 26.3, 25.0, 19.4; MS (ESI) *m*/*z* 423 $[M + Na]^+$, 439 $[M + K]^+$. Anal. Calcd for $C_{23}H_{32}O_4Si$: C, 68.96; H, 8.05. Found: C, 68.94; H, 8.22.

(2*R*,3*S*)-2-*O*-*tert*-Butyldiphenylsilyloxy-3,4-*O*-isopropylidene-3,4-dihydroxybutanal (8). To a solution of oxalyl chloride (2.34 mL, 26.85 mmol) in dichloromethane (140 mL) at −70 °C was added dropwise a solution of DMSO (4.16 mL, 58.59 mmol) in dichloromethane (10 mL). The reaction mixture was stirred for 20 min, followed by addition of a solution of **7** (6.51 g, 16.28 mmol) in dichloromethane (10 mL). The stirring was continued for 20 min. Triethylamine (17.01 mL, 122.06 mmol) was added, and the reaction mixture was stirred at −70 °C for 1 h. Water was added. The dichloromethane layer was separated. The aqueous layer was extracted with dichloromethane. The dichloromethane layers were washed with 1 M HCl, water, saturated sodium bicarbonate, and brine, dried, and evaporated to give the crude aldehyde **8** (6.33 g, 98%), which was used directly for the next reaction without purification. The analytical sample was obtained by flash column chromatography (silica gel, heptane/EtOAc = 20/1): $[\alpha]_D$ +11 (*c* 5.0, $CHCl_3$); IR ($CHCl_3$) 3073, 3053, 3029, 3011, 2990, 2933, 2895, 2860, 1734, 1589, 1487, 1472, 1463, 1428, 1382, 1373, 1255, 1229, 1224, 1221, 1212, 1151, 1113, 1076, 998 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.58 (d, *J* = 1.5 Hz, 1H), 7.68−7.65 (m, 4H), 7.49−7.37 (m, 6H), 4.27 (dt, *J* = 4.9, 6.4 Hz, 1H), 4.11 (dd, *J* = 1.4, 4.8 Hz, 1H), 4.00 (dd, *J* = 8.6, 6.3 Hz, 1H), 3.96 (dd, *J* = 8.6, 6.3 Hz, 1H), 1.38 (s, 3H), 1.29 (s, 3H), 1.12 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 201.6, 135.9, 132.8, 132.7, 130.2, 127.9, 109.8, 78.0, 76.6, 65.1, 27.0, 26.1, 25.1, 19.5; MS (ESI) *m*/*z* 421 $[M + Na]^+$. HRMS calcd for $C_{23}H_{30}O_4SiNa$ (M + Na) 421.1811, found 421.1814.

(2*R*,5*R*,6*S*)-3-Benzenesulfonyl-1-benzyloxy-5-*tert*-butyldiphenylsilyloxy-2-*tert*-butoxycarbonylamino-4-hydroxy-6,7-*O*-isopropylidene-6,7-dihydroxyheptane (10B). To a solution of sulfone **9B** (4.85 g, 11.98 mmol) in THF (110 mL) at −70 °C was added dropwise BuLi (1.6 M in hexane, 16.5 mL, 26.36 mmol). After the mixture was stirred for 30 min, a solution of **8** (6.20 g, 15.58 mmol) in THF (10 mL) was added dropwise. The reaction mixture was stirred at the same temperature for 4 h. Saturated ammonium chloride solution was added. The reaction mixture was extracted with ethyl acetate. The EtOAc extracts were washed with brine, dried, and evaporated. Flash column chromatography (silica gel, heptane/EtOAc = 8/1 then 6/1) afforded hydroxysulfone **10B** (7.98 g, 83%) as a mixture of two diastereoisomers whose signals in ^1H and ^{13}C NMR spectra are not differentiated: IR ($CHCl_3$) 3430, 3072, 3020, 2984, 2961, 2933, 2899, 2861, 1706, 1589, 1497, 1474, 1455, 1449, 1428, 1382, 1369, 1308, 1237, 1221, 1214, 1150, 1113, 1082, 1029, 1000 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.85−7.13 (m, 20H), 5.87 (d, *J* = 7.1 Hz, 0.4H), 5.75 (d, *J* = 10.3 Hz, 0.6H), 4.71−3.41 (m, 12H), 1.41, 1.40 (two s, 9H), 1.04, 1.00, 0.96, 0.91 (four s, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 155.2, 139.8, 138.0, 137.4, 137.2, 136.0, 135.8, 135.7, 134.4, 133.9, 133.8, 133.6, 129.6, 129.5, 129.1, 128.8, 128.3, 127.7, 127.5, 127.4, 109.0, 108.4, 79.7, 79.4, 78.0, 76.4, 75.8, 73.1, 73.0, 72.8, 72.4, 69.3, 68.8, 65.6, 65.3, 64.0, 50.2, 48.8, 28.4, 27.2, 27.1, 25.9, 25.6, 24.8, 24.1, 19.7, 19.6; MS (ESI) *m*/*z* 804 $[M + H]^+$, 826 $[M + Na]^+$. Anal. Calcd for $C_{44}H_{57}NO_9SSi$: C, 65.73; H, 7.15; N, 1.74; S, 3.99. Found: C, 65.89; H, 7.49; N, 1.53; S, 3.64.

(2*R*,5*R*,6*S*)-1-Benzyloxy-2-*tert*-butoxycarbonylamino-5-*tert*-butyldiphenylsilyloxy-6,7-*O*-isopropylidene-6,7-dihydroxyhept-3-ene (11). To a solution of **10B** (13.31 g, 16.58 mmol) in methanol (330 mL) at 0 °C were added Na_2HPO_4 (28.24 g, 198.9 mmol) and 6% Na−Hg (57.20 g, 149.2 mmol). The reaction mixture was stirred at 0 °C for 2 h. Methanol was evaporated. The residue was separated in water and ethyl acetate. The aqueous layer was extracted with ethyl acetate. The ethyl acetate layers were washed with brine, dried, and evaporated. Flash column chromatography (silica gel, heptane/EtOAc = 10/1 afforded compounds **11E** and **11Z** (7.69 g, 72%):

(3*E*,2*R*,5*R*,6*S*)-1-Benzyloxy-2-*tert*-butoxycarbonylamino-5-*tert*-butyldiphenylsilyloxy-6,7-*O*-isopropylidene-6,7-dihydroxyhept-3-ene (11E): $[\alpha]_D$ +20 (*c* 2.5, $CHCl_3$); IR ($CHCl_3$) 3444, 3073, 3054, 3013, 2984, 2961, 2933, 2896, 2861, 1708, 1497, 1474, 1455, 1428, 1392, 1382, 1368, 1248, 1212, 1165, 1112, 1076, 1029 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71-7.65 (m, 4H), 7.44−7.28 (m, 11H), 5.66 (dd, *J* = 6.4, 15.6 Hz, 1H), 5.52 (dd, *J* = 5.1, 15.8 Hz, 1H), 4.54 (d, *J* = 7.8 Hz, 1H), 4.50, 4.45 (AB q, *J* = 12.1 Hz, 2H), 4.30 (t, *J* = 6.1 Hz, 1H), 4.26 (m, 1H), 4.09 (q, *J* = 6.1 Hz, 1H), 3.94 (dd, *J* = 8.0, 6.8 Hz, 1H), 2.16 (dd, *J* = 6.6, 8.5 Hz, 1H), 3.35−3.34 (m, 2H), 1.47 (s, 9H), 1.34 (s, 3H), 1.31 (s, 3H), 1.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 138.0, 136.1, 136.0, 134.0, 133.8, 131.3, 129.7, 129.7, 129.5, 128.4, 127.7, 127.5, 127.5, 109.5, 79.3, 78.4, 74.5, 73.1, 72.1, 65.3, 51.2, 28.5, 27.1, 26.4, 25.3, 19.4; MS (ESI) *m*/*z* 668 $[M + Na]^+$, 684 $[M + K]^+$. Anal. Calcd for $C_{38}H_{51}NO_6Si$: C, 70.66; H, 7.96; N, 2.17. Found: C, 70.49; H, 8.12; N, 2.11.

(3*Z*,2*R*,5*R*,6*S*)-1-Benzyloxy-2-*tert*-butoxycarbonylamino-5-*tert*-butyldiphenylsilyloxy-6,7-*O*-isopropylidene-6,7-dihydroxyhept-3-ene (11Z): $[\alpha]_D$ −2 (*c* 6.0, $CHCl_3$); IR ($CHCl_3$) 3444, 3072, 3053, 3011, 2984, 2962, 2932, 2896, 2859, 1703, 1589, 1496, 1473, 1455, 1428, 1392, 1382, 1368, 1316, 1243, 1219, 1166, 1112, 1069, 1028, 1007, 998 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70−7.67 (m, 4H), 7.39−7.20 (m, 11H), 5.59 (br t, *J* = 10.6 Hz, 1H), 5.41 (dd, *J* = 11.1, 9.0 Hz, 1H), 4.85 (d, *J* = 7.9 Hz, 1H, NH), 4.68 (br dd, *J* = 8.2, 3.6 Hz, 1H), 4.31, 4.22 (AB q, *J* = 11.9 Hz, 2H), 4.15 (dt, *J* = 4.6, 6.7 Hz, 1H), 3.97−3.87 (m, 3H), 3.05 (dd, *J* = 9.4, 4.0 Hz, 1H), 2.78 (dd, *J* = 9.4, 4.1 Hz, 1H), 1.40 (s, 3H), 1.34 (s, 9H), 1.32 (s, 3H), 1.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 138.1, 136.0, 135.9, 134.0, 133.5, 131.0, 129.7, 129.5, 128.3, 127.6, 127.5, 127.4, 109.4, 79.2, 79.0, 73.0, 71.9, 69.8, 65.3, 47.6, 28.3, 26.9, 26.3, 25.5, 19.4; MS (ESI) *m*/*z* 646 $[M + H]^+$, 668 $[M + Na]^+$, 684 $[M + K]^+$; HRMS calcd for $C_{38}H_{51}NO_6SiNa$ (M + Na) 668.3383; found 668.2768.

(2*S*,5*S*,6*S*)-1-Benzyloxy-5-*tert*-butyldiphenylsilyloxy-2-*tert*-butoxycarbonylamino-6,7-*O*-isopropylidene-6,7-dihydroxyheptane (13). A suspension of **11** (4.98 g, 7.72 mmol), ammonium acetate (595 mg, 7.72 mmol), 10% Pd−C (822 mg) in methanol (154 mL) at rt was hydrogenated at atmospheric pressure for 24 h. The catalyst was removed by filtration, and the solvent was evaporated. The residue was passed through column chromatography on silica gel (heptane/EtOAc = 10 /1 then 5/1) to give compound **13** (4.99 g, 100%): $[\alpha]_D$ +1 (*c* 1.8, $CHCl_3$); IR ($CHCl_3$) 3444, 3073, 3053, 3020, 2984, 2962, 2933, 2895, 2860, 1706, 1502, 1474, 1454, 1428, 1392, 1382, 1368, 1243, 1212, 1208, 1169, 1112, 1074, 1028 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.72−7.68 (m, 4H), 7.44−7.26 (m, 11H), 4.51 (br d, *J* = 9.2 Hz, 1H), 4.47, 4.41 (AB q, *J* = 12.1 Hz, 2H), 4.16−4.10 (m, 1H), 3.91 (dd, *J* = 8.1, 6.7 Hz, 1H), 3.78−7.72 (m, 2H), 3.53 (m, 1H), 3.33−3.24 (m, 2H), 1.46−1.44 (m, 4H), 1.44

(s, 9H), 1.31 (s, 3H), 1.25 (s, 3H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 138.1, 135.9, 135.9, 134.2, 133.9, 129.5, 128.2, 127.4, 127.3, 108.9, 78.7, 78.1, 73.8, 72.9, 72.0, 65.4, 50.1, 29.2, 28.3, 28.1, 27.0, 26.2, 25.1, 19.4; MS (ESI) *m*/*z* 648 $[M + H]^+$, 670 $[M + Na]^+$. Anal. Calcd for $C_{38}H_{53}NO_6Si$: C, 70.44; H, 8.25; N, 2.16; Found: C, 70.81; H, 8.41; N, 2.14.

(2*S*,5*S*,6*S*)-1-Benzyloxy-2-*tert*-butoxycarbonylamino-5-*tert*-butyldiphenylsilyloxy-6,7-dihydroxyheptane (14). A solution of **13** (2.12 g, 3.28 mmol) in HOAc−water (4/1, 65 mL) was stirred at rt overnight. The solvents were evaporated in vacuo. The residue was purified by column chromatography on silica gel (heptane/EtOAc = 2/1) to give diol **14** (1.85 g, 93%): $[\alpha]_D$ +20 (*c* 3.1, $CHCl_3$); IR ($CHCl_3$) 3568, 3442, 3073, 3013, 2960, 2934, 2892, 2861, 1705, 1503, 1473, 1455, 1428, 1393, 1368, 1240, 1219, 1170, 1112, 1074, 1028 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71−7.66 (m, 4H), 7.46−7.25 (m, 11H), 4.57 (d, *J* = 8.8 Hz, 1H), 4.45, 4.37 (AB q, *J* = 12.0 Hz, 2H), 3.83 (m, 1H), 3.66−3.60 (m, 3H), 3.39−3.38 (m, 1H), 3.22 (dd, *J* = 4.0, 9.2 Hz, 1H), 3.13 (dd, *J* = 2.9, 9.2 Hz, 1H), 2.67 (br s, 1H, OH), 2.26 (br s, 1H, OH), 1.69−1.61 (m, 1H), 1.48−1.20 (m, 3H), 1.41 (s, 9H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 138.0, 135.8, 133.8, 133.2, 129.8, 129.7, 128.2, 127.7, 127.5, 127.5, 127.4, 79.0, 73.6, 73.5, 72.9, 71.7, 63.7, 60.2, 49.7, 29.3, 28.3, 27.8, 27.0, 19.4; MS (ESI) *m*/*z* 630 $[M + Na]^+$, 646 $[M + K]^+$; HRMS calcd for $C_{35}H_{49}NO_6SiNa$ (M + Na) 630.3227, found 630.3200.

(2*S*,5*S*,6*S*)-1-Benzyloxy-2-*tert*-butoxycarbonylamino-7-*tert*-butyldimethylsilyloxy-5-*tert*-butyldiphenylsilyloxy-6-hydroxyheptane (15). To a solution of **14** (918 mg, 1.51 mmol) in dichloromethane (15 mL) at 0 °C were added triethylamine (3.07 g, 4.2 mL, 30.2 mmol), DMAP (221 mg, 1.81 mmol), and TBDMSCl (2.28 g, 15.1 mmol) successively. The reaction mixture was stirred at 0 °C for 2 h. Water was added. The aqueous layer was extracted with dichloromethane. The dichloromethane extracts were washed with 1 M HCl, water, saturated sodium bicarbonate, and brine, dried, and evaporated. Flash column chromatography on silica gel (heptane/EtOAc = 10/1 then 5/1) gave compound **15** (1.09 g, 100%): $[\alpha]_D$ +12 (*c* 5.3, $CHCl_3$); IR ($CHCl_3$) 3562, 3443, 3072, 3053, 3019, 3011, 2956, 2931, 2895, 2886, 2859, 1705, 1501, 1472, 1463, 1454, 1428, 1391, 1367, 1256, 1170, 1112, 1085, 1027, 1006 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68−7.65 (m, 4H), 7.43−7.23 (m, 11H), 4.45−4.36 (m, 1H), 4.43, 4.37 (AB q, *J* = 12.0 Hz, 2H), 3.86−3.84 (m, 1H), 3.64−3.61 (m, 2H), 3.58−3.55 (m, 1H), 3.47−3.45 (m, 1H), 3.26−3.17 (m, 2H), 2.43 (d, *J* = 6.3 Hz, 1H, OH), 1.66−1.60 (m, 1H), 1.47−1.13 (m, 3H), 1.40 (s, 9H), 1.05 (s, 9H), 0.85 (s, 9H), 0.019, 0.013 (two s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 138.3, 136.0, 135.9, 134.1, 133.4, 129.8, 129.8, 128.4, 127.7, 127.6, 127.5, 79.0, 73.3, 73.2, 73.0, 71.9, 64.0, 50.2, 29.8, 28.4, 28.1, 27.1, 25.9, 19.6, 18.2, −5.3, −5.3; MS (ESI) *m*/*z* 744 $[M + Na]^+$, 760 $[M + K]^+$; HRMS calcd for $C_{41}H_{63}NO_6Si_2Na$ (M + Na) 744.4091, found 744.4087.

(2*S*,5*S*,6*S*)-1-Benzyloxy-2-*tert*-butoxycarbonylamino-7-*tert*-butyldimethylsilyloxy-5-*tert*-butyldiphenylsilyloxy-6-methanesulfonyloxyheptane (16). To a solution of **15** (5.75 g, 7.97 mmol) in dichloromethane (160 mL) at −20 °C were added triethylamine (1.61 g, 2.22 mL, 15.94 mmol), DMAP (1.17 g, 9.56 mmol), and MsCl (1.37 g, 925 μL, 11.96 mmol) successively. The reaction mixture was then stirred at 0 °C for 2 h. Water was added. The aqueous layer was extracted with dichloromethane. The dichloromethane extracts were washed with 1 M HCl, water, saturated sodium bicarbonate, and brine, dried, and evaporated. Flash column chromatography on silica gel (heptane/EtOAc = 10/1 then 8/1) gave compound **16** (6.33 g, 99%): $[\alpha]_D$ −6.9 (*c* 2.7, $CHCl_3$); IR ($CHCl_3$) 3442, 3022, 2957, 2932, 2859, 1705, 1500, 1361, 1264, 1215, 1174, 1112, 930, 910, 838 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69−7.66 (m, 4H), 7.44−7.21 (m, 11H), 4.58−4.53 (m, 1H), 4.49 (d, *J* = 9.0 Hz, 1H), 4.41, 4.36 (AB q, *J* = 12.0 Hz, 2H), 4.00−3.95 (m, 2H), 3.87 (dd, *J* = 11.2, 7.7 Hz, 1H), 3.48 (m, 1H), 3.27 (dd, *J* = 9.2, 4.0 Hz, 1H), 3.20 (dd, *J* = 9.3, 3.8 Hz, 1H), 2.93 (s, 3H), 1.69−1.16 (m, 4H), 1.42 (s, 9H), 1.06 (s, 9H), 0.88 (s, 9H), 0.061 (s, 3H), 0.051 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 155.4, 138.1, 135.9, 133.5, 133.0, 129.9, 129.8, 128.3, 127.8, 127.6, 127.4, 84.9, 78.9, 73.0, 72.5, 71.9, 61.9, 50.1, 38.1, 28.9, 28.3, 27.0, 25.8, 19.4, 18.2, −5.5, −5.6; MS (ESI) *m*/*z* 800 $[M + H]^+$, 822 $[M + Na]^+$, 838 $[M + K]^+$; HRMS calcd for $C_{42}H_{65}NO_8SSi_2Na$ (M + Na) 822.3867, found 822.3836.

(2*S*,5*S*,6*S*)-2-Amino-1-benzyloxy-7-*tert*-butyldimethylsilyloxy-5-*tert*-butyldiphenylsilyloxy-6-methanesulfonyloxyheptane (17). To a solution of **16** (295 mg, 0.37 mmol) in dichloromethane (10 mL) at rt were added 2,6-lutidine (86 μL, 0.74 mmol) and TBDMSOTf (146 mg, 127 μL, 0.55 mmol), successively. The reaction mixture was then stirred at rt for 1 h. After evaporation of dichloromethane, a solution of 1% citric acid in methanol was added, and the mixture was stirred at rt overnight. The solvent was evaporated. The residue was separated into diluted sodium bicarbonate and EtOAc. The aqueous phase was extracted with EtOAc (5×). The organic phases were dried and evaporated. Flash column chromatography on silica gel (CH_2Cl_2/MeOH = 50/1 then 20/1) afforded amine **17** (257 mg, 99%): $[\alpha]_D$ −4 (*c* 3.9, $CHCl_3$); IR ($CHCl_3$) 3376, 3073, 3032, 2956, 2932, 2886, 2859, 1589, 1472, 1463, 1428, 1360, 1259, 1214, 1175, 1112, 931, 910, 838, 822 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67−7.64 (m, 4H), 7.44−7.24 (m, 11H), 4.59−4.54 (m, 1H), 4.39 (s, 2H), 4.24 (br s, 2H, NH_2), 3.98−3.86 (m, 3H), 3.19 (dd, *J* = 9.6, 3.5 Hz, 1H), 3.05 (dd, *J* = 9.6, 7.5 Hz, 1H), 2.96 (s, 3H), 2.78−2.70 (m, 1H), 1.68−1.56 (m, 1H), 1.46−1.33 (m, 1H), 1.29−1.22 (m, 2H), 1.05 (s, 9H), 0.88 (s, 9H), 0.067 (s, 3H), 0.055 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 138.3, 135.9, 133.6, 133.1, 130.0, 129.9, 128.3, 127.8, 127.6, 84.9, 75.0, 73.1, 72.6, 62.0, 50.7, 38.2, 29.7, 28.6, 27.0, 25.9, 19.4, 18.2, −5.4, −5.5; MS (ESI) *m*/*z* 700 $[M + H]^+$; HRMS calcd for $C_{37}H_{58}NO_6SSi_2$ (M + H) 700.3523, found 700.3510.

(2*R*,3*S*,6*S*)-6-Benzyloxymethyl-2-(*tert*-butyldimethylsilanyloxymethyl)-3-(*tert*-butyldiphenylsilanyloxy)piperidine (18). A solution of **17** (264 mg, 0.38 mmol) and diisopropylethylamine (98 mg, 132 μL, 0.76 mmol) in methanol (38 mL) was refluxed for 48 h. The solvent was evaporated. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH = 100/1 then 50/1 then 30/1) afforded amine **18** (209 mg, 92%): $[\alpha]_D$ +17 (*c* 1.7, $CHCl_3$); IR ($CHCl_3$) 3072, 3020, 3016, 3010, 2931, 2858, 1471, 1462, 1428, 1361, 1257, 1221, 1215, 1210, 1111, 1027, 838 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68−7.64 (m, 4H), 7.43−7.28 (m, 11H), 4.58, 4.53 (AB q, *J* = 12.1 Hz, 2H), 3.95 (dd, *J* = 9.5, 4.3 Hz, 1H), 3.66 (t, *J* = 8.8 Hz, 1H), 3.58−3.53 (m, 1H), 3.34 (dd, *J* = 9.1, 4.9 Hz, 1H), 3.27 (t, *J* = 9.0 Hz, 1H), 3.09−3.05 (m, 1H), 2.91 (dt, *J* = 8.0, 4.3 Hz, 1H), 2.81 (br s, 1H, NH), 1.68−1.43 (m, 4H), 1.05 (s, 9H), 0.84 (s, 9H), −0.00012 (s, 3H), −0.014 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 138.5, 135.9, 134.6, 133.9, 129.7, 129.6, 128.4, 127.7, 127.6, 127.5, 73.4, 70.5, 70.4, 64.7, 58.1, 50.3, 29.4, 27.1, 26.0, 24.5, 19.4, 18.3, −5.3; MS (ESI) *m*/*z* 604 $[M + H]^+$; HRMS calcd for $C_{36}H_{54}NO_3Si_2$ (M + H) 604.3636, found 604.3642.

(2*R*,3*S*,6*S*)-6-Benzyloxymethyl-2-(*tert*-butyldimethylsilanyloxymethyl)-3-(*tert*-butyldiphenylsilanyloxy)piperidine-1-carboxylic Acid *tert*-Butyl Ester (19). To a solution of **18** (389 mg, 0.65 mmol) in DMF (2 mL) at 0 °C were added triethylamine (135 μL, 0.97 mmol) and Boc_2O (174 mg, 0.77 mmol) at rt. The reaction mixture was stirred at rt for 24 h. Water was added. The mixture was extracted with ether. The ether extracts were washed with 1 M HCl, water, saturated sodium bicarbonate, and brine, dried, and evaporated. Flash column chromatography on silica gel (heptane/EtOAc = 50/1 then 30/1) gave compound **19** (436 mg, 96%): $[\alpha]_D$ −19 (*c* 2.3, $CHCl_3$); IR ($CHCl_3$) 3072, 3026, 3018, 3008, 2956, 2930, 2884, 2858, 1680, 1471, 1462, 1453, 1427, 1391, 1366, 1340, 1291, 1254, 1220, 1218, 1211, 1171, 1111, 1028, 1006 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64−7.59 (m, 4H), 7.41−7.32 (m, 11H), 4.64−4.50 (m, 2H), 4.27−4.25 (m, 1H), 4.15−4.02 (m, 2H), 3.85−3.77 (m, 1H), 3.56 (dd, *J* = 9.5, 4.5 Hz, 1H), 3.44 (t, *J* = 9.4 Hz, 1H), 2.08−2.04 (m, 1H), 1.79−1.61 (m, 3H), 1.44 (s, 9H), 1.04 (s, 9H), 0.72 (s, 9H), −0.12 (s, 6H); ^{13}C NMR (62.5

MHz, $CDCl_3$) δ 155.5, 138.9, 135.9, 135.8, 134.2, 133.8, 129.7, 129.6, 128.4, 127.7, 127.6, 127.5, 79.5, 73.1, 70.5, 66.7, 63.2, 59.8, 50.8, 28.5, 27.1, 25.9, 24.9, 21.2, 19.3, 18.2, −5.5, −5.6; MS (ESI) *m/z* 726 $[M + Na]^+$; HRMS calcd for $C_{41}H_{61}NO_5Si_2Na$ (M + Na) 726.3986, found 726.3998.

(2*R*,3*S*,6*S*)-6-Benzyloxymethyl-3-hydroxy-2-hydroxymethylpiperidine-1-carboxylic Acid *tert*-Butyl Ester (20). To a solution of **19** (2.13 g, 3.03 mmol) in THF (30 mL) at 0 °C was added a solution of Bu_4NF in THF (1 M solution, 6.7 mL, 6.7 mmol). The reaction mixture was stirred at 0 °C for 10 min and then at rt for 1 h. The solvent was evaporated to dryness, and water was added. The mixture was extracted with EtOAc. The organic extracts were washed with brine, dried, and evaporated. Flash column chromatography on silica gel (heptane/EtOAc = 3/1 then 1/2) gave compound **20** (1.06 g, 100%): $[\alpha]_D$ −30 (*c* 3.9, $CHCl_3$); IR ($CHCl_3$) 3673, 3591, 3408, 3031, 3020, 3011, 2980, 2936, 2869, 1674, 1495, 1455, 1428, 1393, 1368, 1334, 1248, 1223, 1163, 1090, 1027, 974 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41−7.29 (m, 5H), 4.85 (br s, 1H, OH), 4.61 (AB q, *J* = 12.1 Hz, 1H), 4.56 (AB q, *J* = 12.1 Hz, 1H), 4.26−4.25 ((m, 2H), 4.02−3.94 (m, 3H), 3.72 (dd, *J* = 7.0, 9.6 Hz, 1H), 3.65 (dd, *J* = 5.8, 9.6 Hz, 1H), 3.34 (m, 1H), 2.00−1.62 (m, 4H), 1.48 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0, 137.9, 128.3, 127.6, 127.5, 80.4, 72.8, 69.3, 65.6, 60.7, 52.5, 28.3, 27.6, 23.0; MS (ESI) *m/z* 374 $[M + Na]^+$; HRMS calcd for $C_{19}H_{29}NO_5Na$ (M + Na) 374.1943, found 374.1960.

(1*S*,4*R*,6*S*)-6-Benzyloxymethyl-2,2-dimethylhexahydro-[1,3]dioxino[5,4-*b*]pyridine-5-carboxylic Acid *tert*-Butyl Ester (21). A solution of **20** (1.06 g, 3.02 mmol), 2,2-dimethoxypropane (0.56 mL, 4.53 mmol), and TsOH (6 mg, 0.030 mmol) in acetone (30 mL) was stirred at rt overnight. Several drops of saturated $NaHCO_3$ were added to neutralize TsOH. The solvent was evaporated, and the residue was separated in $NaHCO_3$ and EtOAc. The aqueous layer was extracted with EtOAc. The organic extracts were washed with brine, dried, and evaporated. Flash column chromatography on silica gel (heptane/EtOAc = 20/1 then 10/1) gave compound **21** (1.095 g, 93%): $[\alpha]_D$ −17 (*c* 3.2, $CHCl_3$); IR ($CHCl_3$) 3009, 2944, 2876, 1689, 1495, 1475, 1454, 1382, 1368, 1309, 1267, 1253, 1203, 1171, 1095, 1030, 989 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39−7.32 (m, 5H), 4.65−4.54 (m, 4H), 4.33 (t, *J* = 11.2 Hz, 1H), 3.71 (dt, *J* = 3.9, 10.3 Hz, 1H), 3.64−3.61 (m, 2H), 3.14 (dt, *J* = 4.8, 10.2 Hz, 1H), 1.92−1.73 (m, 3H), 1.68−1.57 (m, 1H), 1.54 (s, 3H), 1.48 (s, 9H), 1.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.0, 138.2, 128.4, 127.6, 127.5, 98.0, 80.1, 72.9, 71.1, 67.6, 63.1, 54.0, 51.9, 29.5, 28.4, 26.4, 23.3, 19.2; MS (ESI) *m/z* 414 $[M + Na]^+$; HRMS calcd for $C_{22}H_{33}NO_5Na$ (M + Na) 414.2256, found 414.2248.

(1*S*,4*R*,6*S*)-6-Hydroxymethyl-2,2-dimethylhexahydro-[1,3]dioxino[5,4-*b*]pyridine-5-carboxylic Acid *tert*-Butyl Ester (22). A solution of **21** (993 mg, 2.54 mmol) in EtOAc (60 mL) in the presence of 20% $Pd(OH)_2$−C at rt was hydrogenated at atmospheric pressure for 2 h. The catalyst was removed by filtration through Celite, and the solvent was evaporated to dryness. The residue was purified by flash column chromatography on silica gel (heptane/EtOAc = 4/1 then 2/1) to give compound **22** (733 mg, 96%): $[\alpha]_D$ −6 (*c* 3.8, $CHCl_3$); IR ($CHCl_3$) 3673, 3601, 3464, 3010, 2947, 2882, 1689, 1474, 1456, 1446, 1417, 1383, 1368, 1311, 1268, 1253, 1203, 1166, 1096, 1061, 1041 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.45 (dd, *J* = 11.9, 5.1 Hz, 1H), 4.50−4.38 (m, 1H), 4.35 (dd, *J* = 11.9, 10.4 Hz, 1H), 3.87 (ddd, *J* = 10.8, 9.0, 5.7 Hz, 1H), 3.74−3.63 (m, 2H), 3 0.17 (dt, *J* = 10.1, 5.1 Hz, 1H), 2.18 (m, 1H, OH), 1.80−1.67 (m, 3H), 1.60−1.53 (m, 1H), 1.52 (s, 3H), 1.46 (s, 9H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 98.1, 80.7, 70.8, 63.0, 60.2, 54.1, 53.7, 29.3, 28.3, 26.4, 22.8, 19.1; MS (ESI) *m/z* 324 $[M + Na]^+$; HRMS calcd for $C_{15}H_{27}NO_5Na$ (M + Na) 324.1784; found 324.1795.

(1*S*,4*R*,6*S*)-6-Formyl-2,2-dimethylhexahydro[1,3]-dioxino[5,4-*b*]pyridine-5-carboxylic Acid *tert*-Butyl Ester (23). To a solution of oxalyl chloride in dichloromethane (0.6 M, 2.2 mL, 1.32 mmol) at −78 °C was added dropwise a solution of DMSO in dichloromethane (2.4 M, 1.2 mL, 2.88 mmol). The reaction mixture was stirred for 15 min, followed by addition of a solution of **22** (240 mg, 0.8 mmol) in dichloromethane (5 mL). The stirring was continued for 15 min. Triethylamine (0.84 mL, 6.0 mmol) was added, and the reaction mixture was stirred at 0 °C for 1 h. Water was added. The dichloromethane layer was separated. The aqueous layer was extracted with dichloromethane. The dichloromethane layers were washed with 1 M HCl, water, saturated sodium bicarbonate, and brine, dried, and evaporated to give the crude aldehyde **23** (239 mg, 100%), which was used directly for the next reaction without purification: IR ($CHCl_3$) 3011, 2997, 2982, 2939, 2875, 2802, 1736, 1702, 1682, 1456, 1411, 1381, 1369, 1308, 1263, 1233, 1165, 1136, 1111, 1094 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.54 (s, 1H), 4.67 (d, *J* = 5.0 Hz, 1H), 4.53 (dd, *J* = 11.8, 4.9 Hz, 1H), 4.23 (t, *J* = 11.2 Hz, 1H), 3.59 (dt, *J* = 10.6, 3.7 Hz, 1H), 2.99 (dt, *J* = 10.1, 4.9 Hz, 1H), 2.31−2.24 (m, 1H), 1.79−1.56 (m, 2H), 1.43 (s, 3H), 1.39 (s, 9H), 1.30 (s, 3H), 1.23−1.19 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.9, 155.2, 98.1, 81.3, 70.0, 62.8, 62.8, 56.5, 29.1, 28.1, 27.6, 21.2, 19.2; (MS (ESI) *m/z* 354 $[M + Na + MeOH]^+$; HRMS calcd for $C_{16}H_{29}NO_6Na$ (M + Na + MeOH) 354.1893, found 354.1890.

(1*S*,4*R*,6*S*)-6-Dodec-1-enyl-2,2-dimethylhexahydro[1,3]-dioxino[5,4-*b*]pyridine-5-carboxylic Acid *tert*-Butyl Ester (24). To a solution of $Ph_3PC_{11}H_{23}Br$ (1.60 g, 3.2 mmol) in THF (7 mL) at −78 °C was added KHMDS (0.5 M in toluene, 6.4 mL, 3.2 mmol). The resulting orange-red suspension was stirred at −78 °C for 10 min, then at 0 °C for 1 h, then cooled to −78 °C, and a solution of the aldehyde **23** (480 mg, 1.60 mmol) in THF (5 mL) was added dropwise. After being stirred at −78 °C for 20 min and then at 0 °C for 5 h, the reaction mixture was treated with saturated aqueous ammonium chloride solution and then extracted with ether. The ether extracts were washed with brine, dried, and evaporated. The residue was dissolved in dichloromethane, filtered through a short pad of silica gel, and eluted with heptane/EtOAc = 10/1. The filtrate was evaporated to dryness, and the residue was further purified by flash column chromatography (silica gel, heptane/EtOAc = 20/1) to afford compound **24** (611 mg, 87%): $[\alpha]_D$ +27 (*c* 3.8, $CHCl_3$); IR ($CHCl_3$) 3008, 2928, 2856, 1685, 1458, 1425, 1382, 1368, 1352, 1336, 1309, 1268, 1252, 1203, 1169, 1124, 1093, 1074, 1030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.73−5.67 (m, 1H), 5.58−5.50 (m, 1H), 5.08−5.05 (m, 1H), 4.48 (t, *J* = 11.2 Hz, 1H), 4.29 (dd, *J* = 11.8, 4.8 Hz, 1H), 3.71 (dt, *J* = 10.1, 4.7 Hz, 1H), 3.25 (dt, *J* = 10.3, 4.9 Hz, 1H), 2.13−2.06 (m, 1H), 1.84−1.59 (m, 4H), 1.51 (s, 3H), 1.44 (s, 9H), 1.39 (s, 3H), 1.25 (m, 16H), 0.87 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.5, 134.0, 126.3, 98.3, 80.1, 70.7, 62.9, 54.0, 50.4, 31.9, 29.6, 29.6, 29.5, 29.5, 29.5, 29.4, 29.4, 28.6, 28.5, 27.9, 26.8, 22.7, 19.4, 14.2; MS (ESI) *m/z* 460 $[M + Na]^+$; HRMS calcd for $C_{26}H_{47}NO_4Na$ (M + Na) 460.3403, found 460.3360.

(1*S*,4*R*,6*S*)-6-Dodecyl-2,2-dimethylhexahydro[1,3]-dioxino[5,4-*b*]pyridine-5-carboxylic Acid *tert*-Butyl Ester (25). A suspension of compound **24** (170 mg, 0.39 mmol) in EtOAc (8 mL) in the presence of 20% $Pd(OH)_2$/C (34 mg) at rt was hydrogenated at atmospheric pressure overnight. The catalyst was removed by filtration through Celite. The filtrate was evaporated to dryness. The residue was passed through a flash column chromatography (silica gel, heptane/EtOAc = 20/1) to give compound **25** (170 mg, 99%): $[\alpha]_D$ +6 (*c* 1.7, $CHCl_3$); IR ($CHCl_3$) 3005, 2928, 2856, 1682, 1458, 1417, 1383, 1368, 1310, 1268, 1252, 1203, 1161, 1123, 1092, 1031 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.49 (t, *J* = 11.2 Hz, 1H), 4.36 (dd, *J* = 4.8, 11.8 Hz, 1H), 4.31−4.24 (m, 1H), 3.67 (dt, *J* = 4.3, 10.1 Hz, 1H), 3.13 (dt, *J* = 4.9, 10.3 Hz, 1H), 1.76−1.58 (m, 5H), 1.52−1.40 (m, 1H), 1.52 (s, 3H), 1.45 (s, 9H), 1.40 (s, 3H), 1.27 (m, 20H), 0.89 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 98.3, 79.9, 71.0, 63.1, 53.1, 52.8, 32.0, 29.7, 29.6, 29.6, 29.5, 29.4, 28.5, 26.5, 26.4, 22.7, 19.3, 14.2; MS (ESI) *m/z* 462 $[M + Na]^+$; HRMS calcd for $C_{26}H_{49}NO_4Na$ (M + Na) 462.3559, found 462.3532.

(2*R*,3*S*,6*R*)-6-Dodecyl-2-hydroxymethylpiperidin-3-ol, (+)-Deoxoprosopinine (2). A solution of compound **25** (160 mg, 0.36 mmol) in 1 N HCl−MeOH was stirred at rt for 24 h. The solvent was evaporated to dryness. A solution of 2 N aqueous NaOH was added to the residue, and the reaction mixture was extracted with dichloromethane. The dichloromethane extracts were dried and filtered through Celite. The filtrate was evaporated. Recrystallization from acetone afforded compound **2** as colorless crystals (55 mg). The mother liquor was evaporated to dryness (53 mg) and purified by column chromatography (silica gel, CH_2Cl_2/MeOH/NH_4OH = 10/1/0.5) to give another portion of **2** (30 mg, totally 85 mg, 79%): mp 89−90 °C; $[\alpha]_D$ +15.3 (*c* 0.3, $CHCl_3$); IR ($CHCl_3$) 3606, 3411, 3009, 2928, 2855, 1465, 1240, 1226, 1205, 1050 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.67 (dd, J = 7.4, 10.5 Hz, 1H), 3.61 (dd, J = 5.4, 10.5 Hz, 1H), 3.57−3.52 (m, 1H), 2.87 (dt, J = 5.7, 7.4 Hz, 1H), 2.81−2.73 (m, 1H), 3.12 (br s, 3H), 1.80−1.39 (m, 4H), 1.26 (s, 22H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 68.2, 62.4, 58.1, 49.9, 34.0, 32.1, 29.8, 29.5, 28.7, 27.5, 26.5, 22.8, 14.3; MS (ESI) *m*/*z* 300 $[M + H]^+$; HRMS calcd for $C_{18}H_{38}NO_2$ (M + H) 300.2903, found 300.2883.

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Supporting Information Available: General experimental conditions and copies of ^1H and ^{13}C NMR spectra for all of the compounds described in the Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

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