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Asymmetric total syntheses of hydroxylated piperidine alkaloids via the intramolecular reaction of γ-aminoallylstannane with aldehyde †

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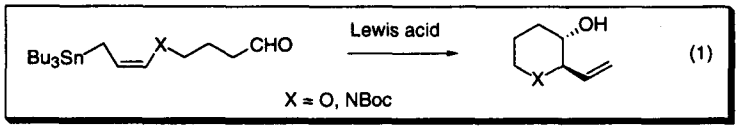
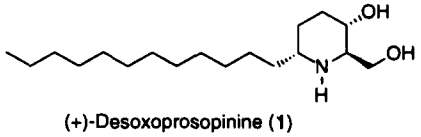
Abstract: Asymmetric total syntheses of (+)-desoxoprosopinine and (−)-desoxoprosophylline were accomplished using L-glutamic acid as the chiral source, in which the intramolecular reaction of a γ-aminoallylstannane with an aldehyde was used as a key step. © 1997 Elsevier Science Ltd. All rights reserved.

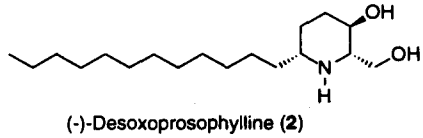
Introduction

During the past several years we have been investigating the stereocontrolled synthesis of polycyclic ethers via the intramolecular reaction of a γ-alkoxyallylstannane with an aldehyde (Eq. 1, X=O).[1] More recently, the methodology has been applied successfully to the synthesis of hydroxylated nitrogen heterocycles by using γ-aminoallylstannane derivatives (Eq. 1, X=NBoc).[2] It occurred to us that certain natural alkaloids could be synthesized by applying the newly developed allylstannane cyclization methodology. Now we report that the stereoselective synthesis of (+)-desoxoprosopinine **1** and (−)-desoxoprosophylline **2**,[3,4] the reduction product of prosopinine, has been achieved via the γ-nitrogen-containing allyltin method.[5]





(+)-Desoxoprosopinine (**1**)



(-)-Desoxoprosophylline (**2**)

Results and discussion

The L-glutamic acid derived starting material **3**[6] was quantitatively converted to the silyl ether **4** by the usual method (Scheme 1). Selective cleavage of the *N,O*-acetal protection of **4** was performed with $PdCl_2(CH_3CN)_2$ in refluxing acetonitrile[7] to give the alcohol **5** in 98% yield. Tosylation of **5** with TsCl/Et_3N/DMAP followed by alkylation with $C_{11}H_{23}Li$/CuI furnished, in 80% overall yield, the compound **7** via the tosylate **6**. Allylation of **7** with allyl bromide/KH gave **8** (92%), which upon desilylation with TBAF led to **9** (74%). Treatment of **9** with *sec*-BuLi/TMEDA followed by the reaction of the corresponding allylic anion with *n*-Bu_3SnCl afforded the allylstannane derivative **10** in 61% yield. Oxidation of **10** with SO_3·py/DMSO/Et_3N produced the cyclization precursor **11** in 92% yield.

† Dedicated to Herbert C. Brown on the occasion of his 85th birthday.

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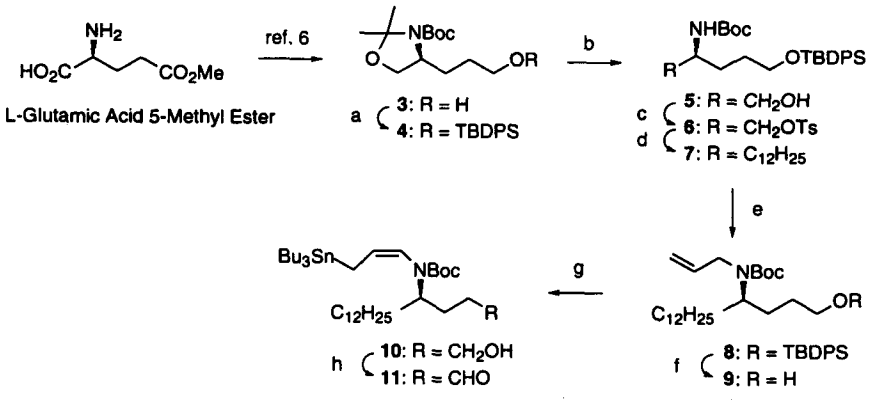
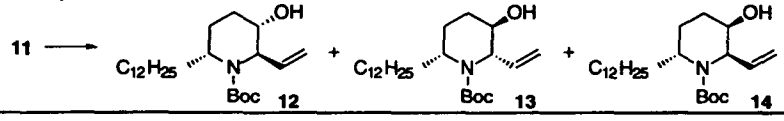


[a](a) TBDPSCl, imidazole, CH_2Cl_2, rt, 100%; (b) $PdCl_2(CH_3CN)_2$, CH_3CN, reflux, 98%; (c) TsCl, Et_3N, DMAP, CH_2Cl_2, rt, 98%; (d) $C_{11}H_{23}Li$, CuI, Et_2O, -35 °C, 82%; (e) allyl bromide, KH, THF, 0 °C to rt, 92%; (f) TBAF, THF, rt, 74%; (g) *sec*-BuLi, TMEDA, THF, -78 °C, then *n*-Bu_3SnCl, -78 °C to rt, 61%; (h) SO_3·py, DMSO, Et_3N, CH_2Cl_2, 0 °C, 92%.

Scheme 1. [a]

Table 1. Cyclization of **11**[a]



entry	reagent (eqiv)	temp (°C)	time (h)	ratio (**12**: **13**:**14**)[b]	yield (%)[c]
1	BF_3·OEt_2 (1.5)	-78	1.5	70:30:0	98
2	$TiCl_4$ (1.5)	-78	0.4	68:32:0	93
3	$ZrCl_4$ (1.5)	0	0.5	78:22:0	72
4	$SnCl_4$ (1.5)	-78	0.3	47:53:0	42
5	$MgBr_2$·OEt_2 (1.5)	0	4.0	52:48:0	72
6	HCl (2.0)	-78	4.5	32:0:68	58
7	CF_3CO_2H (2.0)	-78	3.5	22:0:78	72
8	-d	110	4.5	0:0:100	72

[a]The reactions were carried out with 1.0 M substrate in CH_2Cl_2 under the conditions indicated in the table, and quenched with Et_3N at the reaction temperature. [b]Ratios were determined by ^1H NMR analysis. [c]Isolated yields. [d]Toluene was used as a solvent.

The results of the cyclization of **11** are summarized in Table 1. The use of Lewis acids such as BF_3·OEt_2, $TiCl_4$, and $ZrCl_4$ predominantly afforded the 2,3-*trans*-2,6-*trans* isomer **12** in good yields (entries 1–3). The reactions mediated by $SnCl_4$ and $MgBr_2$·OEt_2 gave unsatisfactory results (entries 4 and 5). Interestingly, the reactions mediated by protic acids afforded the 2,3-*cis*-2,6-*trans* isomer **14** as a major product (entries 6 and 7). Although the reason is not clear, the 2,3-*trans*-2,6-*cis* isomer **13** was not detected when the protic acids were utilized. As expected, the thermal cyclization gave **14** with very high stereoselectivity (entry 8).

The stereochemistry of **12**, **13** and **14** was confirmed by the ^1H-NMR analysis and NOE experiments of the corresponding acetate **15**, acetonide **16**, and **17** (Figure 1).[8] The 2,6-*trans* stereochemistry of **15** was determined by observing NOEs between C-6 and olefinic protons. Although the stereochemistry of the C-3 acetoxy group of **15** is not clear, we assumed the *trans* relationship between the C-2 vinyl and C-3 acetoxy group from the comparison with **17**. The 2,3-*trans*-2,6-*cis* stereochemistry of **16** was determined by the coupling constant (J=10.5 Hz) between the C-2 and C-3 protons, and NOE

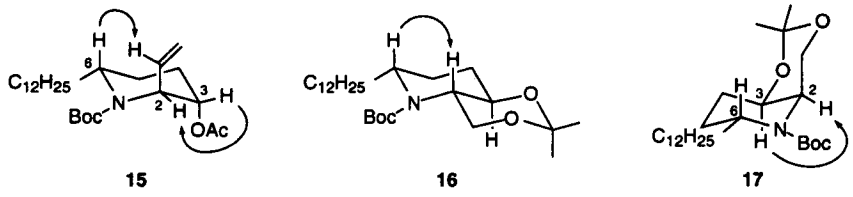
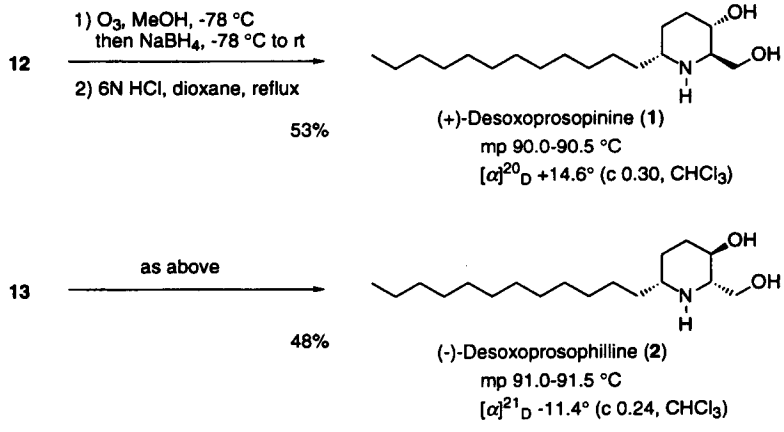


Figure 1. Observed NOEs are shown by arrows.

between C-2 and C-6 protons. Irradiation of the C-3 proton of **17** gave a significant enhancement of the resonance at the C-2 proton, indicating the 2,3-*cis* stereochemistry of **17**.

The hydroxy piperidine derivatives **12** and **13** obtained above were converted to the target molecules **1** and **2**, respectively, as shown in Scheme 2. Ozonolysis of **12** followed by treatment with $NaBH_4$ gave the corresponding diol in 80% yield. The *N*-Boc desoxoprosopinine thus obtained was treated with 6 N HCl in refluxing dioxane, giving the desired (+)-desoxoprosopinine **1**, mp 90.0–90.5°C; $[\alpha]_D^{20}$ +14.6 (c 0.30, $CHCl_3$) {lit.[4b] mp 90.7–91°C; $[\alpha]_D^{18}$ +13 (c 0.31, $CHCl_3$)}, in 66% yield. A similar transformation starting from **13** afforded (−)-desoxoprosophylline **2**, mp 91.0–91.5°C; $[\alpha]_D^{21}$ −11.4 (c 0.24, $CHCl_3$) {lit.[4a] mp 90–91°C; $[\alpha]_D$ −14 (c 0.24, $CHCl_3$)}, in 48% yield. The ^1H NMR spectra of the synthetic **1** and **2** were in good agreement with the literature data.[4a,b]



Scheme 2.

In summary, new and concise syntheses of (+)-desoxoprosopinine **1** and (−)-desoxoprosophylline **2** were accomplished by using the intramolecular reaction of a γ-aminoallylstannane with an aldehyde as a key step. We believe that the strategy developed here is widely applicable to the stereoselective synthesis of naturally occurring nitrogen heterocycles.

Experimental section

General procedure

^1H- and ^{13}C-NMR spectra were recorded on JEOL GSX-270, JNM-LA300, and JNM-A500 spectrometers. Chemical shifts are reported in delta (δ) units, in parts per million (ppm) downfield from tetramethylsilane or in ppm relative to the singlet at 7.26 ppm for chloroform. Coupling constants are reported in hertz (Hz). IR spectra (cm^{-1}) were measured with neat compounds on a Shimadzu FTIR 8200A infra-red spectrophotometer. High resolution mass spectra were obtained with a JEOL JMS-HX110 spectrometer. Optical rotations were recorded on a JASCO DIP-1000 polarimeter. Capillary GC analyses were performed with a Shimadzu GC-14A flame ionization instrument with a CPB1-M25-025 column. All reactions were monitored by thin layer chromatography using Merck precoated

aluminum plates (Kieselgel 60F254, 0.2 mm). Column chromatography was done on Merck silica gel 60 (70–230 mesh ASTM), and for flash chromatography, Merck silica gel 60 (230–400 mesh ASTM) was employed. All solvents were dried immediately before use. Ether and THF were distilled from sodium/benzophenone ketyl; dichloromethane, hexane, benzene, triethylamine, pyridine, DMF, DMSO, and TMEDA were distilled from CaH_2; methanol was distilled from $Mg(OMe)_2$. All reactions involving air- and/or moisture-sensitive materials were carried out in an argon atmosphere.

*(S)-1-(*tert*-Butoxycarbonyl)-5-[3-(*tert*-butyldiphenylsiloxy)propyl]-2,2-dimethyloxazoline* ***4***

To a solution of **3** (3.6 g, 13.9 mmol) and imidazole (1.4 g, 21 mmol) in CH_2Cl_2 (140 mL) at 0°C was added TBDPSCl (4.4 mL, 17 mmol), and the mixture was stirred at rt for 1.5 h. The reaction mixture was diluted with ether, washed with water and brine, dried over $MgSO_4$, and concentrated. Silica gel column chromatography (hexane:AcOEt=20:1) gave **4** (6.9 g, 100%): colorless oil; R_f=0.33 (hexane:AcOEt=10:1); $[\alpha]_D^{26}$ +22.4 (c 1.0, $CHCl_3$); IR (neat) 3071, 3050, 2978, 2958, 2933, 2893, 2859, 1699, 1473, 1428, 1390, 1375, 1366, 1112, 1106, 1091, 702 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.69–7.63 (m, 4H), 7.43–7.33 (m, 6H), 3.93–3.85 (m, 1H), 3.72–3.61 (m, 3H), 3.49 (d, 1H), 1.6–1.5 (m, 4H), 1.5–1.4 (m, 15H), 1.04 (s, 9H). Anal. Calcd for $C_{29}H_{43}O_4NSi$: C, 69.98; H, 8.71; N, 2.81. Found: C, 69.81; H, 8.79; N, 2.86.

*(S)-2-[*N*-(*tert*-Butoxycarbonyl)amino]-5-(*tert*-butyldiphenylsiloxy)pentan-1-ol* ***5***

A mixture of **4** (6.8 g, 13.7 mmol) and $PdCl_2(CH_3CN)_2$ (186 mg, 0.72 mmol) in CH_3CN (140 mL) was refluxed overnight. The reaction mixture was concentrated and the residue was subjected to silica gel column chromatography (hexane:AcOEt=4:1→2:1) to give **5** (5.4 g, 86%) and **4** (850 mg, 13%): colorless oil; R_f=0.33 (hexane:AcOEt=3:1); $[\alpha]_D^{26}$ −5.2 (c 1.0, $CHCl_3$); IR (neat) 3409, 3393, 3370, 3357, 3071, 3049, 2999, 2957, 2932, 2895, 2853, 1735, 1712, 1692, 1507, 1474, 1428, 1392, 1367, 1172, 1112 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.73–7.60 (m, 4H), 7.49–7.32 (m, 6H), 4.82–4.68 (m, 1H), 3.74–3.44 (m, 5H), 2.68–2.56 (m, 1H), 1.8–1.4 (m, 4H), 1.43 (s, 9H), 1.05 (s, 9H). HRMS calcd for $C_{26}H_{39}O_4NSi$ 426.2462, found 426.2462.

*(S)-2-[*N*-(*tert*-Butoxycarbonyl)amino]-5-(*tert*-butyldiphenylsiloxy)propan-1-yl* p*-toluenesulfonate* ***6***

A mixture of **5** (3.0 g, 6,6 mmol), Et_3N (1.8 mL, 13 mmol), TsCl (1.4 g, 7.2 mmol), and a catalytic amount of DMAP in CH_2Cl_2 was stirred at rt overnight. The reaction mixture was diluted with ether, washed with water and brine, dried over $MgSO_4$, and concentrated. Silica gel column chromatography (hexane:AcOEt=5:1) gave **6** (3.9 g, 98%): colorless oil; R_f=0.50 (hexane:AcOEt=3:1); $[\alpha]_D^{24}$ −10.2 (c 1.0, $CHCl_3$); IR (neat) 3393, 3070, 2957, 2931, 1713, 1599, 1507, 1473, 1454, 1428, 1392, 1366, 1246, 1190, 1177, 1112, 1097, 974 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.78 (m, 2H), 7.61 (m, 4H), 7.47–7.29 (m, 8H), 4.61 (m, 1H), 4.05 (dd, J=4.6, 1.5 Hz, 1H), 3.96 (dd, J=4.8, 1.6 Hz, 1H), 3.80–3.66 (m, 1H), 3.62 (t, J=2.7 Hz, 2H), 2.40 (s, 3H), 1.39 (s, 9H), 1.640–1.44 (m, 4H), 1.04 (s, 9H).

*(R)-4-[*N*-(*tert*-Butoxycarbonyl)amino]-1-(*tert*-butyldiphenylsiloxy)hexadecane* ***7***

To a stirred suspension of CuI (495 mg, 2.6 mmol) in ether (10 mL) at −35°C was added $C_{11}H_{23}Li$ (5.1 mL, 1.0 M in ether, 5.1 mmol), and then a solution of **6** (314 mg, 0.51 mmol) dissolved in ether (5 mL) was added. The mixture was stirred at the same temperature for 2 h. The reaction mixture was quenched with saturated aqueous NH_4Cl, filtered through a Celite pad, and extracted with ether. The extract was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. Silica gel column chromatography (hexane:AcOEt=20:1) gave **7** (250 mg, 82%): colorless oil; R_f=0.75 (hexane:AcOEt=3:1); $[\alpha]_D^{24}$ +3.6 (c 1.0, $CHCl_3$); IR (neat) 3448, 3415, 3356, 3135, 3071, 3050, 2999, 2956, 2927, 2855, 1719, 1740, 1502, 1466, 1428, 1389, 1365, 1246, 1174, 1112, 1095, 1008, 988, 824, 741, 701, 614 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.72–7.62 (m, 4H), 7.46–7.33 (m, 6H), 4.34–4.22 (m, 1H), 3.66 (t, J=5.4 Hz, 2H), 3.60–3.46 (m, 1H), 1.63–1.52 (m, 4H), 1.44 (s, 9H), 1.26 (s, 22H), 1.05 (s, 9H), 0.88 (t, J=5.4 Hz, 3H). HRMS calcd for $C_{37}H_{61}O_3NSi$ 595.44174, found 595.4415.

(R)-4-[N-(tert-Butoxycarbonyl)-N′-(2-propenyl)amino]-1-(tert-butyldiphenylsiloxy)hexadecane ***8***

To a stirred suspension of KH (330 mg of a 35% suspension in mineral oil, 2.9 mmol, prewashed with hexane) in THF (5 mL) at 0°C were added allyl bromide (0.25 mL, 2.9 mmol) and a solution of **7** (1.1 g, 1.9 mmol) in THF (5 mL), and the mixture was stirred at rt. After 3 h, the reaction was quenched with MeOH followed by water at 0°C. The mixture was extracted with ether and washed with brine. The organic layer was dried over $MgSO_4$ and concentrated. The residue was subjected to silica gel column chromatography (hexane:AcOEt=20:1) to give **8** (1.1 g, 92%): colorless oil; R_f=0.50 (hexane:AcOEt=10:1); $[\alpha]_D^{22}$ +2.5 (c 1.0, $CHCl_3$); IR (neat) 3071, 3050, 2998, 2956, 2927, 2855, 1692, 1457, 1428, 1403, 1391, 1333, 1247, 1175, 1155, 1112, 701, 614 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.69–7.61 (m, 4H), 7.46–7.32 (m, 6H), 5.94–5.70 (m, 1H), 5.15–4.95 (m, 2H), 3.70–3.50 (m, 4H), 1.54–1.46 (brs, 4H), 1.46 (s, 9H), 1.26 (s, 22H), 1.04 (s, 9H), 0.88 (t, J=7.0 Hz, 3H). Anal. Calcd for $C_{40}H_{65}O_3NSi$: C, 75.54; H, 10.30; N, 2.20. Found: C, 75.60; H, 10.69; N, 2.13.

(R)-4-[N-(tert-Butoxycarbonyl)-N′-(2-propenyl)amino]hexadecan-1-ol ***9***

A mixture of **8** (2.5 g, 4.0 mmol) and TBAF (4.8 mL, 1.0 M in THF, 4.8 mmol) in THF (30 mL) was stirred at rt for 2 h. The reaction mixture was concentrated, and the residue was purified by silica gel column chromatography (hexane:AcOEt=20:1→10:1) to give **6** (1.2 g, 74%): colorless oil; R_f=0.11 (hexane:AcOEt=10:1); $[\alpha]_D^{22}$ +3.0 (c 1.0, $CHCl_3$); IR (neat) 3600–3010, 3079, 2955, 2925, 2855, 1694, 1668, 1456, 1405, 1365, 1334, 1267, 1250, 1174, 1145, 1062, 994, 917, 772, 665 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.98–5.74 (m, 1H), 5.18–5.00 (m, 2H), 4.04–4.02 (m, 1H), 3.96–3.75 (m, 1H), 3.72–3.50 (m, 4H), 1.56–1.47 (m, 4H), 1.44 (s, 9H), 1.24 (s, 22H), 0.88 (t, J=7.0 Hz, 3H). Anal. Calcd for $C_{24}H_{46}O_3N$: C, 72.68; H, 11.69; N, 3.53. Found: C, 72.41; H, 11.90; N, 3.66.

(R)-4-[N-(tert-Butoxycarbonyl)-N′-[(Z)-3-tributylstannyl-1-propenyl]amino]hexadecan-1-ol ***10***

To a solution of **9** (1.5 g, 3.8 mmol) in THF (20 mL) at −78°C were added *sec*-BuLi (7.4 mL, 1.1 M in cyclohexane, 8.3 mmol) and TMEDA (1.3 mL, 8.3 mmol), and the resulting yellow solution was stirred at the same temperature. After 0.5 h, *n*-Bu_3SnCl (1.2 mL, 4.5 mmol) was added, the cooling bath was removed, and the reaction mixture was allowed to warm to rt. The mixture was quenched with water and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. Silica gel column chromatography (hexane:AcOEt=20:1→10:1) gave **10** (1.6 g, 61%): colorless oil; R_f=0.31 (hexane:AcOEt=3:1); $[\alpha]_D^{23}$ +5.3 (c 1.0, $CHCl_3$); IR (neat) 2956, 2925, 2871, 2855, 1693, 1666, 1641, 1465, 1406, 1365, 1252, 1153, 1106, 1070 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.48–5.34 (m, 2H), 4.06–3.88 (m, 1H), 3.69–3.60 (m, 1H), 1.45 (s, 9H), 1.70–1.17 (m, 40H), 0.96–0.84 (m, 18H). HRMS calcd for $C_{36}H_{73}O_3NSn$ 687.46086, found 687.4612.

(R)-4-[N-(tert-Butoxycarbonyl)-N′-[(Z)-3-tributylstannyl-1-propenyl]amino]dodecan-1-al ***11***

To a stirred solution of **10** (1.5 g, 2.2 mmol), DMSO (3 mL) and Et_3N (2.1 mL, 15 mmol) in CH_2Cl_2 (10 mL) at 0°C was added SO_3·py (3.3 g, 21 mmol), and the mixture was stirred for 1 h at the same temperature. The reaction mixture was diluted with ether, washed with water and brine, dried over $MgSO_4$, and concentrated. Silica gel column chromatography (hexane:AcOEt=5:1) gave **11** (1.6 g, 61%): colorless oil; R_f=0.81 (hexane:AcOEt=3:1); $[\alpha]_D^{23}$ +16.4 (c 1.0, $CHCl_3$); IR (neat) 2956, 2925, 2870, 2853, 1713, 1729, 1695, 1641, 1465, 1406, 1365, 1252, 1152, 1105, 1073, 882, 757, 665 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 9.76 (t, J=1.2 Hz, 1H), 5.39 (m, 2H), 3.95 (m, 1H), 2.45 (m, 2H), 1.80–1.65 (m, 1H), 1.44 (s, 9H), 1.61–1.21 (m, 34H), 0.93–0.83 (m, 18H). HRMS calcd for $C_{32}H_{71}O_3NSn$ ($M-C_4H_9$) 628.37484, found 628.3749.

Typical procedure for the cyclization of ***11***

To a stirred solution of **11** (135 mg, 0.2 mmol) in CH_2Cl_2 at −78°C was added BF_3·OEt_2 (0.3 mL, 1.0 M in CH_2Cl_2, 0.3 mmol). After 1.5 h, the reaction mixture was quenched with Et_3N, the cooling bath was removed, and the reaction mixture was allowed to warm to rt. The mixture was diluted with ether and washed with saturated aqueous $NaHCO_3$. The organic solution was vigorously stirred with

saturated aqueous KF at rt overnight. The organic layer was dried over $MgSO_4$, concentrated, and subjected to silica gel column chromatography (hexane:AcOEt=10:1) to give **12** and **13** (78 mg, 98%).

*(2R,3S,6R)-1-(*tert*-Butoxycarbonyl)-5-dodecyl-3-hydroxy-2-vinylpiperidine* ***12***

Colorless oil; R_f=0.36 (hexane:AcOEt=3:1); $[\alpha]_D^{23}$ +1.8 (c 1.0, $CHCl_3$); IR (neat) 3600–3150, 2924, 2870, 2854, 1674, 1456, 1394, 1366, 1253, 1174, 665 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.05 (ddd, J=17.5, 10.5, 7.0 Hz, 1H), 5.19 (m, 2H), 3.96 (m, 1H), 3.81 (ddd, J=7.0, 0.7, 0.7 Hz, 1H), 3.58 (m, 1H), 1.46 (s, 9H), 1.95–1.20 (m, 27H), 0.88 (t, J=7.0 Hz, 3H). HRMS calcd for $C_{24}H_{45}O_3N$ 395.3397, found 395.3400.

*(2S,3R,6R)-1-(*tert*-Butoxycarbonyl)-5-dodecyl-3-hydroxy-2-vinylpiperidine* ***13***

Colorless oil; R_f=0.28 (hexane:AcOEt=3:1); $[\alpha]_D^{24}$ −4.5 (c 1.0, $CHCl_3$); IR (neat) 3600–3050, 2925, 2854, 1687, 1456, 1404, 1363, 1324, 1174, 665 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.81 (ddd, J=17.0, 11.0, 7.0 Hz, 1H), 5.22 (dt, J=17.0, 1.5 Hz, 1H), 5.22 (dt, J=11.0, 1.5 Hz, 1H), 4.67 (brd, 1H), 4.14 (m, 1H), 3.96 (brs, 1H), 1.45 (s, 9H), 1.73–1.10 (m, 27H), 0.88 (t, J=7.0 Hz, 3H). HRMS calcd for $C_{24}H_{45}O_3N$ 395.3397, found 395.3392.

*(2R,3R,6R)-1-(*tert*-Butoxycarbonyl)-5-dodecyl-3-hydroxy-2-vinylpiperidine* ***14***

Colorless oil; R_f=0.36 (hexane:AcOEt=3:1); $[\alpha]_D^{24}$ −0.8 (c 1.0, $CHCl_3$); IR (neat) 3600–3180, 2925, 2855, 1694, 1674, 1467, 1392, 1366, 1175, 1055, 665 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.02 (ddd, J=17.0, 11.0, 6.0 Hz, 1H), 5.25 (m, 2H), 4.28 (m, 1H), 4.11 (m, 1H), 3.86 (m, 1H), 1.45 (s, 9H), 2.10–1.25 (m, 27H), 0.88 (t, J=7.0 Hz, 3H). HRMS calcd for $C_{24}H_{45}O_3N$ 395.3397, found 395.3396.

*(2R,3S,6R)-3-Acetoxy-1-(*tert*-butoxycarbonyl)-5-dodecyl-2-vinylpiperidine* ***15***

Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 5.87 (ddd, J=17.2, 10.8, 4.8 Hz, 1H), 5.18 (m, 2H), 5.09 (m, 1H), 4.52 (brs, 1H), 3.68 (m, 1H), 2.04 (s, 3H), 1.98–1.50 (m, 4H), 1.46 (s, 9H), 1.53 (brs, 22H), 0.88 (t, J=6.8 Hz, 3H).

*(1R,6S,8R)-7-(*tert*-Butoxycarbonyl)-3,3-dimethyl-2,4-dioxa-8-dodecyl-7-azabicyclo[4,4,0]decane* ***16***

Colorless oil; R_f=0.69 (toluene:EtOH=5:1); ^1H NMR (400 MHz, $CDCl_3$) δ 4.35–4.27 (m, 1H), 5.25 (m, 2H), 4.03–3.92 (m, 2H), 3.75–3.63 (m, 2H), 1.98–1.88 (m, 1H), 1.79–1.60 (m, 2H), 1.56–1.50 (m, 2H), 1.46 (s, 9H), 1.36 (s, 3H), 1.35 (s, 3H), 1.26 (brs, 20H), 0.88 (t, J=6.8 Hz, 3H). HRMS calcd for $C_{24}H_{45}O_3N$ 395.3397, found 395.3396.

*(1R,6R,8R)-7-(*tert*-Butoxycarbonyl)-3,3-dimethyl-2,4-dioxa-8-dodecyl-7-azabicyclo[4,4,0]decane* ***17***

Colorless oil; R_f=0.69 (hexane:AcOEt=3:1); ^1H NMR (400 MHz, $CDCl_3$) δ 4.49 (dd, J=11.0, 4.5 Hz, 1H), 4.17 (dt, J=11.0, 6.2 Hz, 1H), 3.94 (dq, J=7.5, 2.5 Hz, 1H), 3.63 (d, J=10.5 Hz, 1H), 3.33 (dt, J=10.5, 4.5 Hz, 1H), 2.03 (m, 1H), 1.92 (m, 1H), 1.70 (m, 1H), 1.48 (s, 3H), 1.46 (s, 9H), 1.41 (s, 3H), 1.26 (brs, 22H), 0.88 (t, J=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.12, 22.79, 22.70, 24.17 (sec), 24.25, 27.12, 28.48, 29.16, 29.36, 29.58, 29. 61, 29.65, 29.68, 31.93, 38.59, 51.96, 65.07, 67.44, 77.22, 80.05, 99.01, 156.08.

(+)-Desoxoprosopinine ***1***

To a solution of **12** (100 mg, 0.25 mmol) in MeOH (13 mL) at −78°C was bubbled ozone until a blue color persisted. Excess ozone was removed by bubbling oxygen through the solution until it became colorless. To this solution at −78°C was added $NaBH_4$ (230 mg, 6.1 mmol), and the solution was allowed to warm to rt. The mixture was concentrated, and the residue was extracted with AcOEt (×3). The combined extract was washed with brine, and dried over $MgSO_4$. Concentration and silica gel column chromatography (hexane:AcOEt=2:1) gave *N*-Boc desoxoprosopinine (81 mg, 80%).

A mixture of *N*-Boc desoxoprosopinine (34 mg, 0.085 mmol) and 6 N HCl (2.3 mL) in 1,4-dioxane (2.3 mL) was refluxed overnight. To the reaction mixture was added 2 N NaOH (46 mL), and the resulting mixture was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated. The crude residue was purified by recrystallization (hexane:CH_2Cl_2) to give **1** (17 mg, 66%): colorless needles; mp 90.0–90.5°C; $[\alpha]_D^{20}$ +14.6 (c 0.30, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 3.64 (dd, J=10.5, 7.7 Hz, 1H), 3.59 (dd, J=10.5, 5.7 Hz, 1H), 3.53 (dt, J=5.3, 4.6 Hz, 1H), 2.88 (m, 1H), 2.74 (m, 1H), 1.76–1.47 (m, 4H), 1.24 (brs, 22H), 0.86 (t, J=6.4 Hz, 3H). HRMS calcd for $C_{18}H_{37}O_2N$ 299.2822, found 299.2809.

(−)-Desoxoprosophylline 2

Experimental procedure was followed as described for compound **1**: colorless needles; mp 91.0–91.5°C; $[\alpha]_D^{21}$ −11.0 (c 0.24, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 3.86 (dd, J=10.1, 5.0 Hz, 1H), 3.70 (dd, J=10.8, 5.3 Hz, 1H), 3.44 (dt, J=9.2, 5.0 Hz, 1H), 2.49–2.59 (m, 2H), 2.00–2.04 (m, 1H), 1.86 (m, 2H), 1.69–1.73 (m, 1H), 1.23 (brs, 22H), 0.86 (t, J=6.0 Hz, 3H). HRMS calcd for $C_{18}H_{37}O_2N$ 299.2822, found 299.2851.

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