Rhodium-Catalyzed Cyclohydrocarbonylation: Application to the Synthesis of (+)-Prosopinine and (−)-Deoxoprosophylline†

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Efficient convergent total syntheses of (+)-prosopinine (**1**) and (−)-deoxoprosophylline (**4**) were accomplished using Rh−BIPHEPHOS complex-catalyzed cyclohydrocarbonylation as the key step. The Rh−BIPHEPHOS complex-catalyzed cyclohydrocarbonylation of **I**, derived from (*R*)-serine, at 65 °C and 4 atm of CO and H_2 (1:1) in ethanol afforded 6-ethoxypiperidine **II**, which was transformed to enantiopure (+)-prosopinine (**1**) in 3 steps. In a similar manner, (−)-deoxoprosophylline was synthesized through cyclohydrocarbonylation of **IV** derived from (*S*)-serine, giving 6-ethoxypiperidine **V**. The key intermediate **V** was transformed to enantiopure (−)-deoxoprosophylline (**4**) in 4 steps. These two short total syntheses clearly demonstrate the usefulness of the extremely regioselective cyclohydrocarbonylation process developed in these laboratories for the concise syntheses of piperidine alkaloids and related compounds.

Multifunctionalized piperidine alkaloids are found abundantly in nature, and many of them exhibit biological activity of medicinal interest.[1] Among these various naturally occurring compounds are (+)-prosopinine (**1**) and (−)-prosophylline (**2**), which are isolated from the leaves of *Prosopis africana* Taub (Figure 1).[2] These alkaloids possess antibiotic and anesthetic properties and have attracted considerable interest as synthetic targets.[3] The reduction analogues of prosopinine and prosophylline, i.e., (+)-deoxoprosopinine (**3**)[4] and (−)-deoxoprosophylline (**4**),[5] also exhibit similar biological properties, and thus, a variety of syntheses have been reported. We describe here new and efficient syntheses of enantiopure **1** and **4**, bearing 2,3-*trans*-3,6-*cis* and 2,3-*trans*-3,6-*trans* configurations, respectively, featuring the Rh-catalyzed cyclohydrocarbonylation of functionalized homoallylic amine intermediates, which was recently developed in these laboratories.[6]

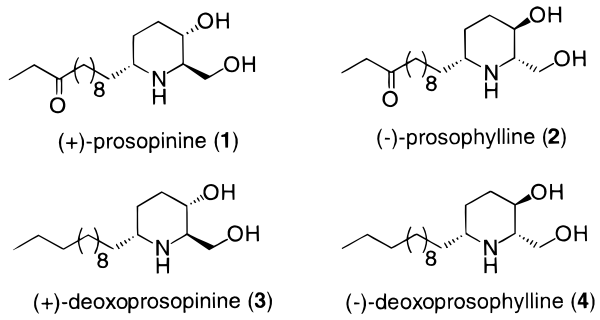

Figure 1.

Our syntheses of these two alkaloids consists of an efficient synthesis of enantiopure piperidine intermediates using our cyclohydrocarbonylation protocol and the subsequent diastereoselective introduction of long alkyl chains at the C-6 position of the piperidine.

The convergent total synthesis of **1** started with the preparation of Garner's aldehydes[7] (**6**) from (*R*)-serine (**5**) (Scheme 1). The aldehyde **6** contains the *R* configuration that is required for the C-2 position of the key intermediate piperidine **11**. Stereoselective addition of vinylmagnesium bromide to **6** afforded a 6:1 mixture of (*S*)-allylic alcohol **7** and (*R*)-allylic alcohol **8**, which were separated by column chromatography to give the desired **7** in 77% isolated yield.[8] Alternatively, a mixture of **7** and **8** was

† This paper is dedicated to the late Dr. Maria Tzamarioudaki, a pioneer of cyclohydrocarbonylation processes, who lost her life in the Swissair flight 111 crash.

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(8) The stereochemistry of **7** was unambiguously assigned on the basis of ^{1}H NMR analysis by converting **7** to **19** (2,3-*trans* (ax−ax), J = 7.2 Hz). Compound **8** was also converted to the corresponding (2*R*,3*R*)-1-Boc-2-TBSO-methyl-3-TBSO-piperidine in the same manner, which showed 2,3-*cis* (ax−eq) relations (J = 1.3 Hz).

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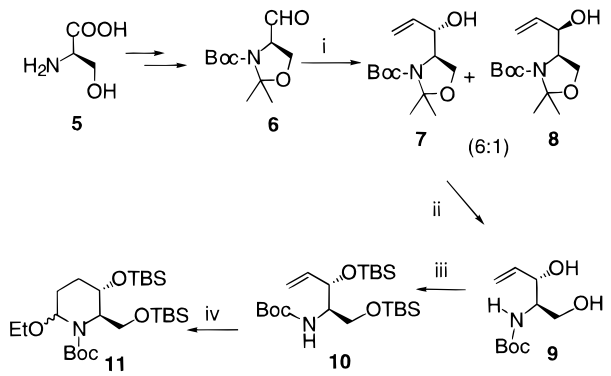
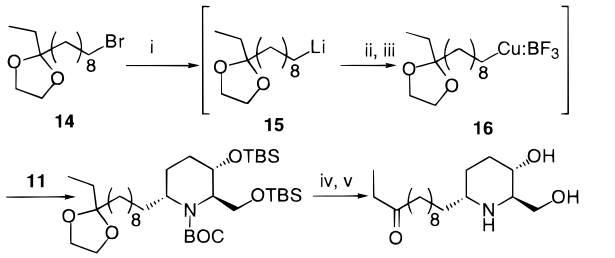
Scheme 1



i) CH_2=CHMgBr (77%); ii) pTSA, MeOH (95%); iii) TBSCl, imidazole, DMF (83%); iv) Rh(acac)$(CO)_2$ (1 mol %), BIPHEPHOS (2 mol%), H_2/CO (1/1, 4 atm), EtOH (92%)

Scheme 2



i) Li, Et_2O; ii) CuBr:SMe_2; iii) BF_3:Et_2O (42%); iv) *n*-Bu_4NF, THF; v) TFA/CH_2Cl_2 (48%, 2 steps)

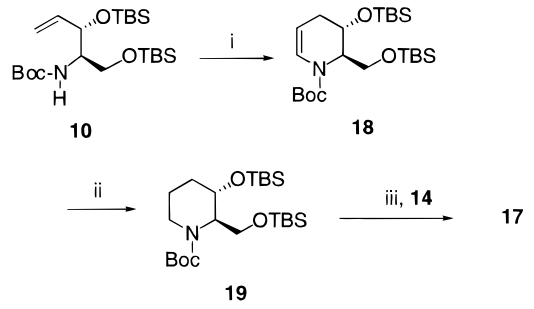
carried over to the next two steps and the diastereomers of **10** were separated by column chromatography. Removal of the acetonide group afforded *N*-Boc-diol **9** which was protected as bis(*tert*-butyldimethylsilyl) ether to give **10.** Rh−BIPHEPHOS[9] complex−catalyzed cyclohydrocarbonylation of **10** at 65 °C and 4 atm of CO and H_2 (1:1) in ethanol afforded 5,6-*trans*-2-ethoxypiperidine **11** in 92% yield, which is the key intermediate in this total synthesis.

The introduction of a 10-oxo-*n*-dodecanyl chain at C-6 of **11** was carried out through the chelation-controlled addition of alkylcopper(I) **16** to the acyliminium ion generated in situ by the reaction of **11** with BF_3, which gave the desired 2,6-*trans* product **17** (Scheme 2). 1-Bromo-10-oxo-decane ketal **14**, the key precusor of the alkylcopper **16**, was prepared in 5 steps from decane-1,-10-diol (**12**) via 10-bromodecan-1-al (**13**).[2]

Lithiation of **14** followed by transmetalation to copper and the subsequent addition of BF_3 etherate generated the alkylcopper·BF_3 complex **16** in situ.[10] The addition of 2-ethoxypiperidine **11** to the ether solution of **16** gave the fully protected (+)-prosopinine **17** in 42% for 4 steps (Scheme 2). Deprotection of TBS ethers using *n*-Bu_4NF as well as removal of the ketal and Boc groups by treating with TFA in dichloromethane afforded (+)-prosopinine (**1**) in 48% yield.

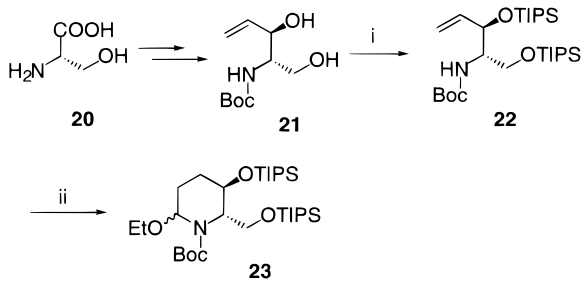
An alternative route to **17** was also examined (Scheme 3), which included the cyclohydrocarbonylation of **10** using THF as the solvent,[5] giving 5,6-didehydropiperidine **18** in 96% yield, followed by hydrogenation on Rh/C,

Scheme 3



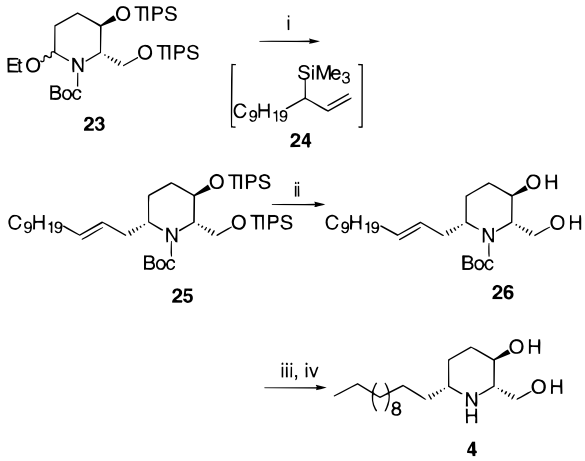
i) Rh(acac)$(CO)_2$ (1 mol %), BIPHEPHOS (2 mol %), H_2/CO (1/1, 4 atm, 65°C, THF (96%); ii) Rh/C, H_2 (1 atm) (>99%); iii) n BuLi, TMEDA

Scheme 4



i) TIPSCl, imidazole, DMF, (72%) ; ii) Rh(acac)$(CO)_2$ (1 mol %); BIPHEPHOS (2 mol %), H_2/CO (1/1, 4 atm), EtOH, 65 °C (96%).

Scheme 5



i) **24**, BF_3·Et_2O, -78°C; ii) Bu_4NF, THF (38%, 2 steps); iii) Pd/C, H_2; iv) TFA, CH_2Cl_2 (77%, 2 steps)

yielding piperidine **19** quantitatively. The C-6 side chain was introduced to **19** through stereoselective alkylation using alkyl bromide **14** using Beak's directed-lithiation protocol[11] to afford **17** in 36% yield.

The convergent total synthesis of **4** (Schemes 4 and 5) also features a highly efficient synthesis of 6-ethoxypiperidine **23** through cyclohydrocarbonylation of *N*-Boc-homoallylic amine **22** that was prepared from (*S*)-serine (**20**) in a manner similar to the synthesis of **10** mentioned above. The introduction of the C-6 side chain requires 2,6-*cis* stereochemistry in this case. Thus, Speckamp's protocol,[4d] i.e., a Lewis acid−promoted allylsilane addi-

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tion to an acyliminium ion intermediate generated in situ from **23** and BF_3, was employed. The reaction of **23** with allylsilane **24**[12] in the presence of $BF_3{\cdot}Et_2O$ in dichloromethane at −78 °C gave **25**, the TIPS protection of which was removed by adding *n*-Bu_4NF in THF at room temperature to afford dehydrodeoxoprosophylline **26** in 38% for two steps. Hydrogenation of the olefin moiety using Pd/C and deprotection of the Boc group with TFA gave **4** in 77% yield.

In summary, we have demonstrated the usefulness of our Rh-catalyzed cyclohydrocarbonylation process in the concise syntheses of piperidine alkaloids. Further studies on the applications of this protocol are actively underway.

Experimental Section

General Methods and Materials. The ^1H NMR, ^{13}C NMR, COSY, NOSY, and HETCOR NMR spectra were recorded at 250 MHz for ^1H and 62.5 MHz for ^{13}C or at 300 MHz ^1H and 75 MHz for ^{13}C using $CDCl_3$ as the internal standard. The IR spectra were measured with an FT-IR spectrophotometer using samples as neat oils or as KBr disks. High-resolution mass spectra were obtained at the Mass Spectrometry Facility, University of California at Riverside. Analytical gas chromatography was performed with a gas chromatograph equipped with FID detectors using a 30 m DB-17 or a 15 m DB-1 capillary column. Elemental Analyses were performed at the M-H-W Laboratories, Phoenix, AZ. All solvents were reagent grade and distilled before used. Rhodium complex, $Rh(acac)(CO)_2$, was obtained from the Mitsubishi Chemical Corp. and used as received. Silica gel used for chromatography, MN-Kieselgel 60, was purchased from Brinkman Instruments Inc.

Preparation of 3-(*tert*-Butoxycarbonyl)-2,2-dimethyl-4(*R*)-[(*S*)-1-hydroxyprop-2-enyl)oxazolidine (7). To a solution of Garner's aldehyde (*R*)-**6**[7] (0.921 g, 4.3 mmol) in 20 mL of THF at −30 °C was added vinylmagnesium bromide (0.94 M in THF, 9.1 mL, 8.6 mmol) dropwise over a period of 30 min. The solution was then gradually warmed over a period of 1 h to 0 °C and then cooled again to −20 °C. A saturated aqueous solution of NH_4Cl (20 mL) was added and the mixture gradually warmed to room temperature. The mixture was extracted with ethyl acetate (3 × 20 mL), and the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator and the residue chromatographed on a silica gel column using hexane/EtOAc (8:1) as the eluant to give a 6:1 mixture of **7** and **8** as a clear colorless oil (1.057 g, 4.1 mmol, 95%). Compounds **7** and **8** were separated further by column chromatography on silica gel using hexane/EtOAc (16:1) as the eluant. Compound **7** thus obtained was in high purity, i.e., one spot on TLC and one peak in GC (15 m DB-1 capillary column) analysis.

7: ^1H NMR (300 MHz, $CDCl_3$) δ 1.31−1.59 (m, 15 H), 3.87−4.26 (m, 4 H), 5.18−5.38 (m, 2 H), 5.79−5.90 (m, 1 H); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ 18.41, 26.15, 28.22, 61.92, 64.74, 74.17, 74.50, 94.49, 117.90, 134.90, 155.24; IR (neat): 3347, 1694, 1504 cm^{-1}. HRMS: calcd for $C_{13}H_{23}NO_4$ (MH^+), *m/e* 258.1705; found (CI), *m/e* 258.1703 (Δ = 0.9 ppm).

8: ^1H NMR (300 MHz, $CDCl_3$) δ 1.28−1.57 (m, 15 H), 3.85−4.23 (m, 4 H), 5.15−5.36 (m, 2 H), 5.74−5.85 (m, 1 H); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ 18.62, 27.12, 28.01, 60.32, 63.67, 73.33, 74.63, 92.11, 116.31, 134.95, 158.23.

Preparation of (3*S*,4*R*)-4-(*tert*-Butoxycarbonylamino)-3,5-dihydroxypent-1-ene (9). To a solution of **7** (1.057 g, 4.1 mmol) in methanol (20 mL) was added *p*-toluenesulfonic acid (25 mg). The solution was refluxed for 1 h and then cooled to room temperature. Water (50 mL) was added to the reaction mixture and extracted with ether (50 mL × 2). The combined ethereal layers were combined, washed with brine, and dried over anhydrous $MgSO_4$. The solvent was removed on a rotary evaporator and the residue chromatographed on a silica gel column using ethyl acetate as the eluant to yield **9** as a clear colorless oil (0.845 g, 3.89 mmol, 95%): TLC, one spot (AcOEt); ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9 H), 3.62−4.44 (m, 4 H), 5.19−5.41 (m, 2 H), 5.84−5.98 (m, 1 H); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ 28.26, 62.39, 64.18, 74.80, 116.57, 137.53; IR (neat) 3306, 1690, 1594 cm^{-1}. HRMS: calcd for $C_{10}H_{19}NO_4$ (MH^+), *m/e* 218.1395; found (CI), *m/e* 218.1392 (Δ = 1.1 ppm).

Preparation of (3*S*,4*R*)-4-(*tert*-Butoxycarbonylamino)-3,5-bis(*tert*-butyldimethylsiloxy)pent-1-ene (10). To a solution of **9** (1.15 g, 3.5 mmol) and imidazole (0.95 g, 14 mmol) in THF (20 mL) was added chloro(*tert*-butyl)dimethylsilane (1.31 g, 8.75 mmol) in 5 mL of THF at 0 °C with stirring. The mixture was stirred for 2 h while warming to room temperature. The progress of the reaction was periodically checked by TLC. The reaction was quenched with saturated NH_4Cl solution (20 mL). The resulting two layers were separated and the aqueous layer extracted with ether (20 mL × 4). The organic layers were combined, washed with brine, and dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator and the residue chromatographed on a silica gel column using hexane/EtOAc (4/1) as the eluant to yield **10** as a colorless oil (1.27 g, 2.9 mol, 83%): TLC, one spot (hexane/AcOEt = 4/1); ^1H NMR (250 MHz, $CDCl_3$) δ 0.05 (s, 12 H), 0.88−0.89 (m, 18 H), 1.42 (s, 9 H), 3.51−3.60 (m, 2 H), 4.27−4.43 (m, 1 H), 4.51−4.76 (m, 1 H), 5.08−5.27 (m, 2 H), 5.77−5.90 (m, 1 H); ^{13}C NMR (62.7 MHz, $CDCl_3$) δ −5.3, −5.0, 18.1, 25.8, 28.4, 56.4, 61.3, 73.0, 79.1, 115.4, 138.3, 156.0; IR (neat) 3451,1701, 1684 cm^{-1}. HRMS: calcd for $C_{22}H_{47}NO_4Si_2$ (MH^+), *m/e* 46.3121; found (CI), *m/e* 446.3117 (Δ = 1.1 ppm). Anal. Calcd for $C_{22}H_{47}NO_4Si_2$: C, 59.29, H, 10.64. Found: C, 59.50; H, 10.37.

Preparation of (2*R*,3*S*)-2-((*tert*-butyldimethylsiloxy)-methyl)-3-(*tert*-butyldimethylsiloxy)-6-ethoxypiperidine (11). A solution of **10** (142 mg, 0.32 mmol) in ethanol (1 mL) was transferred via syringe to a 10 mL round-bottomed flask with a magnetic stirring bar, containing a solution of $Rh(acac)(CO)_2$ (0.82 mg, 0.0032 mmol) and BIPHEPHOS (4.92 mg, 0.0064 mmol) in ethanol (1 mL) under nitrogen. The reaction flask was placed in a 300 mL stainless steel autoclave and pressurized with 2 atm of carbon monoxide and 2 atm of hydrogen. The autoclave was heated to 65 °C with stirring in an oil bath for 14 h. Then, the autoclave was cooled to room temperature and carefully depressurized. The solvent was removed on a rotary evaporator and the residue chromatographed on a silica gel column using hexane/EtOAc (8/1) as the eluant to yield **11** as a colorless oil (148.1 mg, 0.294 mmol, 92%): TLC, one spot (hexane/AcOEt = 8/1); ^1H NMR (300 MHz, $CDCl_3$) δ 0.02−0.11 (m, 12 H), 0.87−0.93 (m, 18 H), 1.12−1.21(m, 2H),1.26 (t, J = 7.2 Hz, 3 H),1.50 (s, 9 H), 1.94−2.26 (m, 2 H), 3.74 (q, J = 7.2 Hz, 2 H), 3.35−3.62 (m, 2 H), 3.99−4.33 (m, 2 H), 5.34−5.50 (m, 1 H); ^{13}C NMR (62.7 MHz, $CDCl_3$) δ −5.4, −4.9, 15.1, 18.0, 21.5, 23.8,24.0, 28.4, 59.5, 62.4, 63.1, 63.9, 78.9, 157.2; IR (neat) 1697 cm^{-1}. HRMS: calcd for $C_{25}H_{54}NO_5Si_2$ (MH^+), *m/e* 504.3540; found (CI), 504.3536 (Δ = 0.9 ppm). Anal. Calcd for $C_{25}H_{53}NO_5Si_2$: C, 59.60; H, 10.61. Found: C, 59.78; H, 10.42.

Synthesis of 2-ethyl-2-(9-bromononyl)-1,3-dioxolane (14). Preparation of 12-Bromododecan-3-ol. To a magnetically stirred solution of 9-bromodecanal[13] (4.75 g, 19.7 mmol) in THF (20 mL) at −5 °C was added dropwise a 1.3 M ethylmagnesium bromide solution in THF (30 mL, 39.4 mmol). The solution was warmed to room temperature and stirred for 30 min. The reaction mixture was then cooled to 0 °C, and saturated NH_4Cl solution (20 mL) was added dropwise. The resulting two layers were separated and the aqueous layer extracted with 3 × 20 mL portions ether. The combined organic extracts were dried over anhydrous Na_2SO_4 and the solvent removed in vacuo. The residue was purified by column chromatography on silica gel using hexane/EtOAc (4/1) as the

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eluant to give 12-bromododecan-3-ol as a colorless oil (4.7 g, 17.8 mmol, 90% yield): TLC, one spot (hexane/AcOEt = 4/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.935 (t, J = 7.35, 3 H), 1.30−1.56 (m, 14 H), 1.80−1.89 (m, 4 H), 3.40 (t, J = 6.8 Hz, 2 H), 3.48−3.56 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.76, 25.52, 28.05, 21.63, 29.26, 29.38, 29.54, 30.05, 32.72, 33.94, 36.84, 73.3; IR (neat) 3376, 1055 cm^{-1}. HRMS: calcd for $C_{12}H_{25}BrO$ (M^+), *m/e* 264.1089; found, *m/e* 264.1431 (Δ = +0.5 ppm).

Preparation of 12-Bromododecan-3-one. To a mixture of pyridinium chlorochromate (9.58 g, 44.5 mmol), Celite (10 g), and dichloromethane (200 mL) in a 500 mL round-bottomed flask fitted with a magnetic stirring bar and rubber septa was added via syringe a solution 12-bromododecan-3-ol (4.76 g, 17.8 mmol) in 50 mL of dichloromethane at room temperature. After the mixture was stirred for 3 h, the reaction mixture was filtered through a 3 in. Celite pad and the residue washed with dichloromethane. The filtrates was combined and the solvent removed in vacuo. The residue was then purified by column chromatography on silica gel using hexane/EtOAc (8/1) as the eluent to give 12-bromododecan-3-one as a clear colorless oil (2.67 g, 10.15 mmol, 57% yield): TLC, one spot (hexane/AcOEt = 8/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (t, J = 7.4 Hz, 3 H), 1.24−1.31 (m, 8 H), 1.39−1.43 (m, 2 H), 1.54−1.61 (m, 2 H), 1.80−1.89 (m, 2 H), 2.3−2.45 (m, 4 H), 3.40 (t, J = 6.9 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.7, 23.8, 28.6, 29.1, 29.13, 29.2, 32.7, 33.9, 35.8, 42.32, 212.1; IR (neat) 1714 cm^{-1} HRMS: calcd for $C_{12}H_{23}BrO$ (M^+), *m/e* 262.0932; found, *m/e* 263.1024 (Δ = −5.1 ppm).

To a solution of 12-bromododecan-3-one (2.67 g, 8.72 mmol) in toluene (150 mL) was added *p*-toluenesulfonic acid (0.2 g) and 1,2-ethanediol (2.2 g, 38.88 mmol). The mixture was heated under reflux using a Dean−Stark apparatus overnight. The reaction mixture was then cooled to room temperature and washed with a 10% solution of $NaHCO_3$ (100 mL). The organic layer was separated and dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel using hexane/EtOAc (16/1) as the eluent to afford **14** as a clear colorless oil (2.54 g, 8.28 mmol, 95% yield): TLC, one spot (hexane/AcOEt = 16/1); GC, one peak (15 m DB-1 capillary column); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J = 7.5 Hz, 3 H), 1.21−1.43 (m, 12 H), 1.56−1.66 (m, 4 H), 1.82 (p, J = 7.2 Hz, 2 H), 3.40 (t, J = 6.9 Hz, 2H), 3.92 (s, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.0, 23.7, 28.0, 28.6, 29.2, 29.4, 29.7, 29.8, 32.7, 33.9, 36.6, 64.9, 112.1; IR (neat) 1204 (ν_{Br-C}) cm^{-1}. HRMS: calcd for $C_{14}H_{27}BrO_2$ (MH^+), *m/e* 307.1273; found, *m/e* 307.1287 (Δ = −4.7 ppm). Anal. Calcd for $C_{14}H_{27}BrO_2$: C, 54.72; H, 8.86. Found: C, 54.86; H, 8.47.

Synthesis of (2*R*,3*S*,6*R*)-1-(*tert*-Butoxycarbonyl)-2-((*tert*-butyldimethylsiloxy)methyl)-3-(*tert*-butyldimethylsiloxy)-6-((2-ethyldioxolan-2-yl)nonyl)piperidine (17). To a suspension of lithium powder (301 mg, 90.3 mg Li) (Aldrich Chem Co., 30% suspension in mineral oil, the mineral oil was removed by washing with hexane under N_2) in ether at −30 °C was added a solution of **14** (0.792 g, 2.58 mmol in ether (10 mL). The mixture was stirred for 2 h, warmed to 0 °C, and stirred for additional 30 min. Then, the stirring was stopped and unreacted lithium was allowed to settle at the bottom. The solution was carefully transferred via cannula under nitrogen atmosphere to a dry 100 mL round-bottomed flask containing CuBr·Me_2S (1.06 g, 5.16 mmol) in ether (10 mL), and the mixture was cooled to −78 °C. To this mixture was added dropwise BF_3·Et_2O (366 mg, 0.32 mL, 2.58 mmol) and the solution stirred for 30 min. Then, a solution of **11** (325 mg, 0.645 mmol) in ether (5 mL) was added, and the mixture was stirred for 2 h at −78 °C followed by gradual warming to 0 °C. The reaction was quenched by the addition of 20 mL saturated aqueous solution of NH_4Cl. The mixture was warmed to room temperature and extracted with ether (20 mL × 4). The ethereal layers were combined and dried over anhydrous $MgSO_4$. The solvent was removed on a rotary evaporator and the residue chromatographed on a silica gel column using hexane/EtOAc (8/1) as the eluant to afford **17** as a pale yellow oil (185.1 mg, 0.27 mmol, 42% yield): TLC, one spot (hexane/AcOEt = 8/1); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.03−0.08 (m, 12 H), 0.84−0.92 (m, 21 H), 1.21−1.37 (m, 16H), 1.43 (s, 9 H), 1.55−1.66 (m, 6 H), 1.78−2.03 (m, 2 H), 2.60−2.81 (m, 1H), 3.56−3.68 (m, 2 H), 3.92 (s, 4 H), 4.06 (bs, 2 H); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ −5.39, −4.99, 8.11, 14.10, 18.87, 22.67, 23.80, 25.76, 25.84, 27.24, 28.44, 29.32, 29.42, 29.54, 29.65, 29.78, 29.87, 29.96, 31.88, 36.69, 39.34, 59.13, 61.09, 64.52, 64.93, 112.114; IR (neat) 1693 cm^{-1}. HRMS: calcd for $C_{37}H_{75}NO_6Si_2$ (MH^+), *m/e* 685.5132; found, *m/e* 685.5119 (Δ = 2.0 ppm).

Preparation of (+)-Prosopinine (1).[3a,b] To a solution of **17** (50.1 mg, 108 mmol) in THF (1 mL) was added *n*-Bu_4NF (1M in THF, 0.435 mL, 0.435 mmol) at room temperature. The solution was allowed to stir overnight, and then an aqueous NH_4Cl solution (5 mL) was added. The mixture was extracted with ether (10 mL × 3). The combined ethereal extracts were washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed on a rotary evaporator and the residue dissolved in dichloromethane (1 mL). The solution was then cooled to 0 °C and trifluoroacetic acid (1 mL) added. The mixture was stirred for 30 min, and then the reaction was quenched by adding saturated $NaHCO_3$ solution until the pH of the reaction mixture became pH 8. The reaction mixture was extracted with dichloromethane, the extracts were dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The residue was chromatographed on a silica gel column using hexane/EtOAc (8/1) as the eluant to afford **1** as a pale yellow oil (16.2 mg, 0.052 mmol, 48% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, J = 7.1 Hz, 3H), 1.21−1.37 (m, 13H), 1.54−1.66 (m, 5 H), 1.78−1.83 (m, 2 H), 2.06−2.15 (m, 3H), 2.56−2.68 (m, 2 H), 2.92−3.33 (m, 4 H), 3.43−3.59 (m, 3 H); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 8.14, 22.66, 23.79, 25.74, 27.26, 28.45, 29.38, 29.41, 29.55, 29.83, 29.92, 31.85, 41.66, 49.33, 59.16, 61.18, 64.83, 211.13

Preparation of (2*R*,3*S*)-5,6-Didehydro-2-((*tert*-butyldimethylsiloxy)methyl)-3-(*tert*-butyldimethylsiloxy)piperidine (18). A solution of **10** (142 mg, 0.32 mmol) in THF (1 mL) under nitrogen was transferred via syringe to a 10 mL round-bottomed flask with a magnetic stirring bar, containing a solution of Rh(acac)$(CO)_2$ (0.82 mg, 0.0032 mmol) and BIPHEPHOS (4.92 mg, 0.0064 mmol) in THF (1 mL) under nitrogen. The reaction flask was placed in a 300 mL stainless steel autoclave and pressurized with 2 atm of carbon monoxide and 2 atm of hydrogen. The autoclave was heated to 65 °C with stirring in an oil bath for 14 h. Then, the autoclave was cooled to room temperature and gases were carefully released. The solvent was removed on a rotary evaporator and the residue chromatographed on a silica gel column using hexane/EtOAc (8/1) as the eluant to yield **18** as a colorless oil (140.4 mg, 0.307 mmol, 96% yield): TLC, one spot (hexane/AcOEt = 8/1); GC, one peak (15 m DB-1 capillary column); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00−0.06 (m, 12 H) 0.84−0.88 (m, 18 H), 1.48 (s, 9 H), 1.89−2.28 (m, 2 H), 3.54−4.30 (m, 4 H), 4.60−4.80 (m, 1 H), 6.65−6.81 (m, 1 H); ^{13}C NMR (62.7 MHz, $CDCl_3$) δ −5.4, −4.9, 18.0, 25.8, 28.3, 25.9, 56.9, 61.0, 66.0, 80.3, 101.6, 124.5, 138.3, 156.5; IR (neat) 1691 cm^{-1}. HRMS: calcd for $C_{23}H_{47}NO_4$ (MH^+), *m/e* 458.3121; found (CI), *m/e* 458.3122 (Δ = 1.7 ppm).

Preparation of (2*R*,3*S*)-2-((*tert*-Butyldimethylsiloxy)-methyl)-3-(*tert*-butyldimethylsiloxy)piperidine (19). To 5% Rh on carbon (145.1 mg) in a 50 mL reaction flask connected to the standard ambient pressure hydrogenation apparatus equipped with a gas bullet with hydrogen was added a solution of **18** (705.2 mg, 1.54 mmol) in EtOAc/MeOH (1:1) (10 mL). The mixture was stirred at room temperature for 4 h. The reaction mixture was filtered through a Celite pad and the residue washed with ethyl acetate. The filtrates were collected and the solvent removed on a rotary evaporator. The residue was chromatographed on a silica gel column using hexane/EtOAc (8/1) as the eluant to afford **19** as a clear colorless oil (0.631 g, 1.37 mmol, 89%): TLC, one spot (hexane/AcOEt = 8/1)); GC, one peak (15 m DB-1 capillary column); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03−0.07 (m, 12 H), 0.87−0.88 (m, 18 H), 1.42−1.45 (m, 9 H), 1.61−1.65 (m, 2 H), 2.61−2.97 (m, 2 H), 3.52−4.15 (m, 6 H); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ −5.09, −5.49, 24.18, 25.69, 25.76 25.87, 28.37, 29.59, 57.83,

61.09, 113.89; IR (neat) 1696 cm^{-1}. HRMS: calcd for $C_{23}H_{49}NO_4$ (MH^+), *m/e* 460.3278; found (CI), *m/e* 460.3254 (Δ = 5.3 ppm).

Synthesis of 17. To a solution of **19** (156.1 mg, 0.34 mmol) in ether (2 mL) at −78 °C was added TMEDA (76.3 mL, 58.8 mg, 0.51 mmol) followed by *n*-BuLi (2.5 M in hexane, 0.204 mL, 0.51 mmol). The solution was gradually warmed to −30 °C and allowed to stir for 2 h. The solution was then cooled to −78 °C followed by slow addition of **14** (178.16 mg, 0.68 mmol) in ether (1 mL), stirred for 3 h, and then allowed to warm to room temperature over the period of 3 h. The reaction mixture was again cooled to −30 °C, and then a saturated aqueous NH_4Cl solution was added to quench the reaction. The reaction mixture was warmed to room temperature and extracted with ether (10 mL × 4). The combined ethereal layers were washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed on a rotary evaporator and the residue chromatographed on a silica gel column using hexane/EtOAc (8/1) as the eluant to afford **17** as a pale yellow oil (83.8 mg, 0.12 mmol, 36% yield). The ^1H and ^{13}C NMR spectra of **17** thus obtained were identical with those of **17** synthesized by the other route mentioned above.

Preparation (3*R*,4*S*)-4-(*tert*-Butoxycarbonylamino)-3,5-bis(triisopropylsiloxy)pent-1-ene (22). (3*R*,4*S*)-4-(*tert*-Butylcarbonylamino)-3,5-dihydroxypent-1-ene (**21**) was prepared from the Garner's aldehyde (*S*)-**6** derived from (*S*)-serine in the same manner as that of **9** (vide supra). To a solution of **21** (0.98 g, 4.5 mmol) and imidazole (0.753 mg, 11.25 mmol) in DMF (30 mL) at 0 °C was added chlorotriisopropylsilane (1.90 g, 9.9 mmol). The progress of the reaction was checked by TLC until completion, and then the reaction was quenched with saturated aqueous NH_4Cl solution. The reaction mixture was extracted with ether (20 mL × 3). The ethereal extracts were combined, washed with brine, and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue chromatographed on a silica gel column using hexane/EtOAc (8/1) as the eluant to afford **21** as a colorless oil (1.71 g, 3.2 mmol, 72% yield): TLC, one spot (hexane/AcOEt = 8/1); GC, one peak (15 m DB-1 capillary column); ^1H NMR (250 MHz, $CDCl_3$) δ 1.00−1.11 (m, 42 H), 1.41−143 (m, 9 H), 4.61−4.78 (m, 3 H), 5.07−5.36 (m, 2 H), 5.81−5.95 (m, 1 H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 11.91, 12.44, 17.97, 18.07, 28.38, 40.91, 62.09, 72.90, 139.11, 113.31, 169.96; IR (neat) 1690 cm^{-1}. HRMS: calcd for $C_{28}H_{59}NO_4Si_2$ (MH^+), *m/e* 530.4060; found (CI), 530.4041 (Δ = −3.8 ppm).

Preparation of (2*S*,3*R*)-2-((Triisopropylsiloxy)methyl)-3-(triisopropylsiloxy)-6-ethoxypiperidine (23). A solution of **22** (142 mg, 0.32 mmol) in ethanol (1 mL) was transferred via syringe to a 10 mL reaction flask with a magnetic stirring bar, containing a solution of $Rh(acac)(CO)_2$ (0.82 mg, 0.0032 mmol) and BIPHEPHOS (4.92 mg, 0.0064 mmol) in ethanol (1 mL) under nitrogen. The reaction flask was placed in a 300 mL stainless steel autoclave and pressurized with 4 atm of carbon monoxide and 4 atm of hydrogen. The autoclave was heated to 65 °C with stirring in an oil bath for 14 h. Then, the autoclave was cooled to room temperature and gases were carefully released. The solvent was removed under reduced pressure and the residue chromatographed on a silica gel column using hexane/EtOAc (8/1) as the eluant to give **23** as a colorless oil (148.1 mg, 0.294 mmol, 92%): TLC, one spot (hexane/AcOEt = 8/1); ^1H NMR (300 MHz, $CDCl_3$) δ 1.03−1.04 (m, 40 H), 1.45−1.46 (m, 14 H), 1.61−2.30 (m, 4 H), 3.40−4.79 (m, 7H); ^{13}C NMR (62.7 MHz, $CDCl_3$) δ −5.4, −4.9, 15.1, 18.0, 21.5, 23.8, 24.0, 28.4, 59.5, 62.4, 63.1, 63.9, 78.9, 157.2; IR (neat) 1697 cm^{-1}. HRMS: calcd for $C_{25}H_{54}NO_5Si_2$ (MH^+), *m/e* 588.4479; found (CI), *m/e* 588.4473 (Δ = −1.0 ppm).

Synthesis of (2*S*,3*R*,6*S*)-1-(*tert*-Butoxycarbonylamino)-2-(hydroxymethyl)-3-hydroxy-6-(dodec-2-en-1-yl)piperidine (26). To a solution of **23** (0.591 g, 1 mmol) and 3-(trimethylsilyl)dodec-1-ene (**24**)[5d,12] (1.20 g, 5 mmol) in dichloromethane (12 mL) at −78 °C was added $BF_3{\cdot}EtO_2$ (0.423 g, 3 mmol) with stirring. The solution was stirred for 1 h at −78 °C and then gradually warmed to −10 °C over a period of 4 h. The solution was cooled again to −30 °C and then quenched with an aqueous saturated solution of $NaHCO_3$. The reaction mixture was warmed to room temperature and extracted with dichloromethane (20 mL × 3). The extracts were combined, washed with brine, and dried over anhydrous Na_2CO_3. The solvent was removed under reduced pressure to give the crude product as an oil. To a solution of the crude product in THF (10 mL) was added *n*-Bu_4NF (1 M in THF, 3 mL, 3 mmol). The mixture was stirred at room temperature overnight and the reaction quenched by adding a saturated aqueous NH_4Cl solution (10 mL). The reaction mixture was stirred for 10 min and then extracted with dichloromethane (20 mL × 3). The extracts were combined, washed with brine and dried over anhydrous Na_2CO_3. The solvent was removed under reduced pressure and the residue chromatographed on a silica gel column using hexane/EtOAc (4/1) as the eluant to give **26** (151 mg, 0.38 mmol, 38% yield) as a viscous colorless oil: TLC, one spot (hexane/AcOEt = 4/1); ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, J = 6.8 Hz, 3 H), 1.25−1.32 (m, 12H), 1.461 (s, 9 H), 1.52−1.81 (m, 2 H), 1.93−2.20 (m, 8 H), 3.58 (d, J = 7.5 Hz, 2 H), 4.03−4.10 (m, 2 H), 4.21−4.25 (m, 1 H), 5.28−5.48 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.98, 19.58, 21.71, 22.56, 28.33, 29.09, 29.21, 29.36, 29.38, 29.48, 31.79, 32.56, 38.18, 50.23, 59.62, 64.26, 64.49, 80.25, 126.89, 133.62, 156.95; IR (neat) 3030, 1701 cm^{-1}. HRMS: calcd for $C_{23}H_{43}NO_4$ (MH^+), *m/e* 398.3270; found (CI), *m/e* 398.3260 (Δ = −2.6 ppm). Anal. Calcd for $C_{23}H_{43}NO_4$: C, 69.48, H, 10.90. Found: C, 69.70; H, 10.58.

Synthesis of (−)-Desoxyprosophylline (4).[5] To a mixture of 5% Pd on carbon (2.85 g, 0.0136 mmol of Pd) in ethanol (5 mL) in a 25 mL reaction flask connected to the standard ambient pressure hydrogenation apparatus equipped with a gas bullet with hydrogen was added a solution of **26** (54.1 mg, 0.136 mmol) in ethanol (1 mL). The mixture was stirred for 2 h and filtered through a Celite pad. The solvent was removed from the filtrate under reduced pressure to give the crude product. The ^1H NMR analysis of the crude product showed complete hydrogenation. To a solution of the crude product in dichloromethane (0.5 mL) chilled with an ice bath was added trifluoroacetic acid (0.5 mL). The solution was warmed to room temperature and stirred for 4 h. The reaction was quenched with aqueous saturated solution of $NaHCO_3$ and the reaction mixture extracted with dichloromethane (10 mL × 3). The extracts were combined, washed with brine and dried over anhydrouos $MgSO_4$. The solvent was removed under reduced pressure and the residue chromatographed on a silica gel column using hexane/EtOAc as the eluant (1:1) to give **2** as a white solid (31.3 mg, 0.104 mmol): mp 82 °C (lit. mp 83−83.5 °C[5b]); ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, J = 6.9 Hz, 3 H), 1.24−1.31 (m, 22 H), 1.52−1.81 (m, 2 H), 1.68−1.75 (m, 1 H), 1.98−2.11 (m, 1 H), 2.47−2.52 (m, 2H), 3.33 (m, 1 H), 3.58 (d, J = 7.4 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.88, 19.56, 21.75, 22.61, 29.10, 29.17, 29.21, 29.27, 29.38, 29.418, 29.48, 31.77, 32.55, 38.20, 50.21, 59.66, 64.22, 64.44; IR (KBr disk) 3042 cm^{-1}.

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