Supporting Information

Experimental

General Methods

All reactions with *s*-BuLi and *n*-BuLi were carried out under a nitrogen atmosphere in glassware that was dried in an oven and cooled under a nitrogen atmosphere. *s*-BuLi in cyclohexane and *n*-BuLi in hexane were titrated against *N*-pivaloyl-*o*-toluidine following the procedure of Suffert.[16] All reagents and solvents were used as provided from commercial sources unless otherwise indicated. DMSO and DMF were purchased as anhydrous reagents from Aldrich Chemical Co. Et_2O and THF were distilled from Na/benzophenone ketyl radical under N_2 prior to use. CH_2Cl_2 was distilled from CaH_2. Dichloro[(*S*)-(-)-2,2'-bis(diphenylphosphino)-binaphthyl]-ruthenium (II) ((*S*)-BINAP-$RuCl_2$) was purchased from Strem Chemicals.

^{1}H NMR spectra were recorded on a Varian U400 at 400 MHz using the $CHCl_3$ signal as an internal standard. ^{13}C-NMR spectra were obtained on a Varian U400 at 100 MHz or a Varian U500 at 125 MHz using carbon signal of $CDCl_3$ as an internal standard. Melting points are uncorrected. Flash chromatography was performed on silica gel (230-400 mesh).

Synthesis of 3-hydroxy-*N*-Boc-piperidine (7).[9] $(Boc)_2O$ (3.16 g, 14 mmol) in $CHCl_3$ (5 mL) was slowly added to a stirred mixture of 3-hydroxypiperidine hydrochloride (**6**) (2.0 g, 14.5 mmol) and triethylamine (2.93 g, 4.07 mmol) in $CHCl_3$ (25 mL). After stirring overnight the solvent was evaporated and the residue was partitioned between water (10 mL) and ether (75 mL). The resulting ether solution was washed with 1 M HCl (4 x 7 mL), water (2 x 7 mL), saturated $NaHCO_3$ (7mL), and brine (7 mL). The solution was dried (Na_2SO_4) and the solvent was evaporated. The solid was recrystallized from hexane to afford 2.44 g (83

%) of **7**. mp 68-69 °C (lit.[17] mp 68-69 °C) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.78-3.57 (m, 2H), 3.56-3.53 (br, 1H), 3.10-2.96 (m, 2H), 1.87-1.77 (br, 1H), 1.76-1.70 (m, 1H), 1.53-1.30 (m,3H), 1.43 (s, 9H).

Synthesis of 3-methoxy-*N*-Boc-piperidine (8).[9] Sodium hydride (1.79 g of a 60% suspension in mineral oil, 42.5 mmol) was slowly added to a rapidly stirred solution of **7** (7.00 g, 34.8 mmol) and iodomethane (6.6 g, 46.5 mmol) in THF (70 mL). The reaction was stirred for 6 h at room temperature. The reaction was quenched by the slow addition of water (30 mL) and diluted with ether (30 mL). The aqueous phase was extracted with ether (2 x 40 mL) and the combined organic phases were dried (Na_2SO_4) and evaporated. The residue was distilled *in vacuo* (bp 78°C/ 0.4 torr) to afford 6.68 g (89%) of **8**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.77 (br, 1H), 3.55 (m, 1H), 3.34 (s, 3H), 3.16 (m, 1H), 3.00 (br, 2H), 1.89 (m, 1H), 1.69 (m, 1H), 1.48-1.32 (m, 2H), 1.42 (s, 9H).

Synthesis of *N*-Boc-δ-valerolactam (10).[18] $(Boc)_2O$ (34.2 g, 156 mmole) was added to a stirred solution of δ-valerolactam (**9**) (12.0g, 121 mmole) and DMAP (.732 g, 6.0 mmol) in acetonitrile (174 mL). Evaporation of the solvent afforded an oil which was dissolved in ether (180 mL) and washed with water (3 x 30 mL) and brine (30 mL). The solvent was evaporated and the residue was distilled *in vacuo* (bp 82-84 °C at 0.3 torr) to provide 19.1 g (79%) of **10**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.62 (m,2H), 2.48 (m, 2H), 1.79 (m, 4H), 1.49 (s, 9H).

Synthesis of 2-hydroxy-*N*-Boc-piperidine (11).[10] *N*-Boc-δ-valerolactam (**10**) (18.0 g, 90.3 mmol) was dissolved in CH_2Cl_2 (156 mL) and cooled to -78 °C. DIBAL-H (107 mL, 1.0 M in hexanes, 107 mmol) was added dropwise with stirring over 1 h and the reaction was stirred an additional 2 h at -78 °C. The cold reaction was poured into water (170 mL). After stirring vigorously for 15 min, 4 M HCl (67 mL) was added in four portions over 20

min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 15 mL). The combined organic phase was washed with water (40 mL) and dried (K_2CO_3). Evaporation of the solvent gave 19.5 g (94%) of crude **11** that was used in the next reaction without purification.

Synthesis of *N*-Boc-1,2,3,4-tetrahydropyridine (12).[10] Dry toluene (93 mL) was added to crude **11** (18.0 g, 89 mmole) followed by *p*-TsOH (70 mg). The solution was refluxed for 20 min and cooled on ice. Triethylamine (2.5 mL) was added and the solvent was evaporated. The resulting oil was dissolved in ether (90 mL) and the solution was washed with water (2 x 20 mL), brine (20 mL), and dried (Na_2SO_4). Evaporation of the solvent left an oil that was distilled *in vacuo* (bp 52-55°C/0.2 torr) to provide **12**,14.3 g (86%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.83 (6.70) (br d, *J* = 8.4 Hz, 1 H), 4.88 (4.78) (m, 1H), 3.54 (m, 2H), 2.01 (m, 2H), 1.79 (m, 2H), 1.47 (s, 9H).

Synthesis of 2-Carboxy-*N*-Boc-1,4,5,6-tetrahyhydropyridine (4) from 8. A solution of 3-methoxy-*N*-Boc-piperidine (**8**) (0.500 g, 2.30 mmol) in THF (6 mL) was cooled to -78°C and stirred for 15 minutes. TMEDA (.454 mL, 3.00 mmol) was added followed by the dropwise addition of s-BuLi (3.70 mL, 5.12 mmol, 1.38 M in cyclohexane). The solution was stirred for 5 h at -78°C. CO_2 (bone dry) was bubbled into the solution for 5 min and the reaction was allowed to warm to 5 °C in an ice bath. A cold 4 M HCl solution (approximately 3.5 mL) was added dropwise with vigorous stirring until the aqueous phase was at pH 3. The aqueous phase was extracted with ether (3 x 1 mL) and the combined ether solution was washed with brine (2 x 1 mL) and dried (Na_2SO_4). Evaporation of the solvent gave the crude product that was purified by flash chromatography with hexane/ ethyl acetate/acetic acid (60:40:10). Residual acetic acid was removed in *vacuo* to afford 0.424 g of **4** as a white solid (80%). An 87% yield was obtained on a larger scale (4.19 g

of **7**). mp 123-124°C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.18 (m, 1H), 3.58 (m, 2H), 2.25 (m, 2H), 1.80 (m, 2H), 1.44 (s, 9 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.6, 153.1, 132.3, 124.2, 81.9, 42.3, 27.9, 23.1, 22.5.

Synthesis of 2-Carboxy-*N*-Boc-1,4,5,6-tetrahyhydropyridine (4) from 12. A solution of *N*-Boc-1,2,3,4-tetrahydropyridine (**12**) (2.00g, 10.9 mmole) in THF (25 mL) was cooled to -65°C. Then TMEDA (2.12 mL, 14.0 mmol) was added followed by the dropwise addition of *n*-BuLi (9.02 mL, 13.1 mmol, 1.45 M in hexane). The solution was allowed to warm to -30 °C and kept at that temperature for 30 min. The solution was cooled to -78 °C and CO_2 (bone dry) was bubbled into the solution for 5 min and the reaction was allowed to warm to 5 °C in an ice bath. Cold 4 M HCl (approximately 13 mL) was added dropwise with vigorous stirring until the aqueous phase was at pH 3. The aqueous phase was extracted with ether (3 x 6 mL) and the combined ether solution was washed with brine (2 x 4 mL) and dried (Na_2SO_4). The solvent was evaporated and the residue was placed on a vacuum line overnight (0.3 torr). The solid was dissolved in ether (25 mL) and filtered through silica gel (10 g) rinsing with additional ether. Evaporation of ether gave a solid that was recrystallized from ethanol-water (7:3) to provide **4** (1.28 g, 52%). mp 110-114 °C. When **4,** prepared according method A (Scheme 2), was recrystallized from ethanol-water (7:3) the same mp was observed. ^{1}H NMR ($CDCl_3$, 400 MHz) was identical to that of **4** prepared from **8**.

Synthesis of (*S*)-*N*-Boc-pipecolic acid (5). (*S*)- BINAP-$RuCl_2$ (.093 g, 0.12 mmole) was added to a solution of **4** (.880 g, 3.87 mmol) in methanol (30 mL). The solution was hydrogenated for 11 h at 45 °C at 1000 psi. The solvent was evaporated and the residue was dissolved in ethyl acetate (24 mL) and extracted with 0.5 M NaOH (5 x 6 mL). The aqueous solution was cooled on ice, acidified with cold 4 M HCl to pH 3 and extracted with

methylene chloride (5 x 6 mL). The solution was dried (Na_2SO_4) and the solvent was evaporated. The resulting solid was recrystallized from heptane to afford 0.771 g **5** (87%). mp = 122-123 °C (lit.[19] mp121-122 °C); $[\alpha]^{20}_D$ -45.7° (*c*= 1.0, MeOH) (lit.[19] $[\alpha]^{24}_D$ -45.1° (*c*= 1.0, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.94 and 4.77 (rotamers, br, s, 1H), 4.02 and 3.93 (rotamers, d, 1H, *J* = 12.0 and 13.4), 2.94 (m, 1H), 2.23 (m, 1H), 1.74-1.22(m, 4H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.5, 156.0 and 155.5 (rotamers), 80.2, 54.6 and 53.5 (rotamers), 42.0 and 41.0 (rotamers), 28.3, 26.6, 24.7 and 24.5 (rotamers), 42.0 and 41.0 (rotamers), 28.3, 26.6, 24.7 and 24.5 (rotamers), 20.8 and 20.6.

Analysis for enantiomeric ratio: (*S*)-*N*-Boc-pipecolic acid (**5**) (.084 g, 0.37 mmol), DCC (.093 g, 0.45 mmol), HOBT (.052 g, 0.38 mmole), CH_2Cl_2 (14.8 mL) and 3,5-dimethylaniline were stirred under N_2 for 12 h. After a standard workup the product was purified by flash chromatography (hexane/ ethyl acetate (75:25)) to afford the amide as a clear, sticky oil (0.068 g, 53%). The enantiomeric purity was determined to be >200:1 by CSP HPLC (1.50 mL/min, 5% IPA/hexane) (minor peak not observed; R_f of major peak:13.2 minutes).

Synthesis of (*S*)-*2*-hydroxymethyl-*N*-Boc-piperidine (13). To a stirred solution of **5** (0.504 g, 2.2 mmol) in THF (2.5 mL) cooled with an ice bath was added BH_3•THF (1.0 M in THF, 3.3 mL, 3.3 mmol). The reaction was warmed to room temperature while stirring. After 3 h the solution was cooled and water (1 mL) was added dropwise. Potassium carbonate (0.5 g) was added and the mixture was vigorously stirred for 30 min. The layers were separated and the aqueous layer was extracted with ether (3 x 1.5 mL). The combined ether layers were washed with brine (1.5 mL) and dried (Na_2SO_4). The solvent was evaporated to give an oil that was filtered through silica gel using ethyl acetate as eluent. The solvent was evaporated to give an oil that crystallized to **13** as a white solid

when placed on a vacuum line overnight (0.471 g, 97%). mp 84-85 °C (lit.[14] 81-83 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.30 (m,1H), 3.94 (d, br, *J* = 12.9, 1H), 3.83 and 3.81 (d, *J* = 9.3 and 9.3), 3.62 and 3.59 (d, J = 6.4 and 6.4, 1 H), 2.87 (m, 1H), 2.00 (br s, 1H), 1.70-1.56 (m, 4H), 1.46-1.39 (m, 2H), 1.46 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.1, 79.6, 61.2, 52.5, 39.8, 28.3, 25.1, 25.0, 10.4. The product was spectroscopically comparable to the ^{1}H NMR and ^{13}C NMR to literature values.[19]

Synthesis of (*S*)-*N*-Boc-piperidine-2-carboxaldehyde (14). A solution of oxalyl chloride (.218 mL, 2.51 mmol) in methylene chloride (5.7 mL) under nitrogen was cooled to -78 °C and stirred for 15 min. A solution of DMSO (0.323 mL, 4.57 mmol) in methylene chloride .5 mL was added and the solution was stirred for 10 min. A solution of **13** (0.448 g, 2.08 mmol) in methylene chloride (2.3 mL) was added dropwise and the reaction was stirred for 1 h at -78 °C. Diisopropylethylamine (1.43 mL, 8.31 mmol) was added dropwise and the mixture was allowed to warm to room temperature.[11] The mixture was washed with 1 M HCl (2 x 2 mL), water (4 x 2 mL), brine (2 x 2 mL) and dried ($MgSO_4$). Evaporation of the solvent gave 0.433 g (98%) of **14** as a light yellow oil that was used promptly in the next reaction.

Synthesis of *N*-Boc-(*R*)-2-(*cis*-propenyl)-piperidine (15). *n*-BuLi (1.51 mL, 2.29 mmol, 1.51 M) was added dropwise to a stirred suspension of (ethyl)triphenylphosphonium iodide (1.045 g, 2.50 mmol) in THF (7.2 mL) at -78 °C under nitrogen. After stirring 15 min, the solution was cooled with an ice bath for 30 min. The solution was cooled to -78 °C and aldehyde **14** (.444 g, 2.08 mmole) in THF (5 mL) was added. The solution was stirred for 1 h at -78 °C and allowed to warm to room temperature. The reaction was partitioned between water (8 mL) and ether (4 mL). The aqueous layer was extracted with ether (2 x 4 mL). The combined organic phases were washed with brine (2 mL) and dried (Na_2SO_4).

The solvent was evaporated and the residue was mixed well with pentane (11 mL). The solid was filtered and rinsed with additional pentane. The pentane was evaporated to afford an oil that was purified by flash chromatography (hexane/ ethyl acetate (95:5)) to give **15** (0.370 g, 79%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.69 (m, 1H), 5.53 (m, 1H), 5.00 (m, 1H), 3.94 (d, br, *J* = 13.6, 1H), 2.84 (dt, *J* = 13.2, 2.85), 1.66-1.37 (m, 6H), 1.67 (dd, *J* = 6.78, 1.75,), 1.43 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.8, 128.0, 125.8, 79.1, 47.7, 39.5, 30.3, 28.4, 25.5, 19.4, 13.1.

Synthesis of *N*-Boc-2(*R*)-propylpiperidine (16) 0.040 g of 5% Pd/C was added to a solution of **15** (.370 g, 1.64 mmol) in ethyl acetate (8 mL). The flask was repeatedly evacuated and filled with hydrogen (balloon). The mixture was stirred under a hydrogen atmosphere for 24 h and was filtered through a Teflon Millipore filter. The solvent was evaporated to afford the crude product which was dissolved in hexane/ethyl acetate (9:1) and filtered through a silica gel plug. The solvent was evaporated to afford **16** (0.366 g, 98%) as a clear, colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.19 (br, s, 1H), 3.95 (br, s, 1H), 2.73 (t, *J*= 12.9, 1H), 1.69-1.19 (m, 8H), 1.44 (s, 9H), .90 (t, *J* = 7.2, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.2, 78.9, 50.1, 38.4, 31.9, 28.5, 28.4, 25.7, 19.4, 19.0, 14.1. The product was spectroscopically comparable by ^{1}H NMR and ^{13}C NMR to literature values.[2g]

Synthesis of (–)-coniine (1·HCl). *N*-Boc-2(*R*)-propylpiperidine (**16**) (0.345 g, 1.47 mmol) was dissolved in of 2 M HCl-methanol (4.7 mL) and stirred at room temperature for 24 h. The solvent was evaporated and the resulting solid was heated at 70 °C *in vacuo* (0.1 torr) for 3h. 0. 245 g (98%) of **1·HCl** was obtained. mp 219-220 °C (lit.[2c] 218-221 °C); $[\alpha]^{20}_{D}$ -6.7^{o} (*c* = 1.0, EtOH) (lit.[2c] $[\alpha]^{20}_{D}$ -7.3^{o} (*c* = 1.0, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.49 (br s, 1H), 9.19 (br s, 1H), 3.43 (br d, *J* = 12.6, 1H), 2.91 (m, 1H), 2.80 (q, *J* = 12.5, 1H), 2.10-1.55 (m, 7H), 1.50-1.34 (m, 3 H), .93 (t, *J* = 7.3, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ

57.0, 44.7, 35.2, 28.0, 22.3, 22.1, 18.4, 13.6. The product was spectroscopically comparable by ^{1}H NMR and ^{13}C NMR to literature values.[2c]

Synthesis of *N*-Boc-2(*R*)-(*cis*-undecenyl)-piperidine (17). *n*-BuLi (1.72 mL, 2.60 mmole, 1.51 M) was added to a stirred solution of (decyl)triphenylphosphonium bromide (1.36 g, 2.82 mmol) in THF (7.5 mL) under nitrogen at -78°C. The mixture was stirred for 15 min and cooled with an ice bath for 30 min. The solution was cooled to -78°C and aldehyde **14** (.426 g , 2.17 mmole) in THF (5 mL) was added. After stirring for 1 h at -78°C the reaction was allowed to warm to room temperature. The mixture was transferred to a separatory funnel and the flask was rinsed with water (8 mL) and ether (4 mL). The aqueous layer was separated and extracted with ether (2 x 4 mL). The combined organic layer was washed with brine (5 mL) and dried (Na_2SO_4). The solvent was evaporated and the residue was taken up in pentane (10 mL), mixed well, and filtered. The pentane was evaporated to afford a light yellow oil that was purified by flash chromatography (hexane/ethyl acetate (95:5) to give **17** (0. 581 g, 79%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.66 (m, 1H), 5.43 (m, 1H), 5.00 (br, 1H), 3.94 (d,br, J = 13.6, 1H), 2.85 (td, J = 13.2, 2.9, 1H), 2.09 (q, J = 7.0, 2H), 1.69- 1.22 (m, 20H), 1.44 (s, 9H), .87 (t, J = 6.8, 3H) ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.2, 78.9, 31.9, 29.6, 29.3, 28.5, 26.3, 25.7, 22.7, 19.0, 14.1. The product was spectroscopically comparable by ^{1}H NMR and ^{13}C NMR to literature values.[9]

Synthesis of *N*-Boc- 2(*R*)-undecylpiperidine (18) 0.095g of 10% Pd/C was added to a solution of **17** (.581 g, 1.72 mmole) in ethyl acetate (10 mL). The flask was repeatedly evacuated and filled with hydrogen (balloon). The mixture was stirred under a hydrogen atmosphere for 24 h and was filtered through a Teflon Millipore filter. The solvent was evaporated to afford **18** (.552 g, 94%) as a clear, colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz)

δ 4.17 (br s, 1H), 3.94 (br d, J = 11.6 Hz, 1H), 2.73 (t, J = 13.4 Hz, 1H), 1.66-1.15 (m, 26H), 1.43 (s, 9H), .86 (t, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.2, 78.9, 31.9, 29.6, 29.6, 29.3, 28.5, 26.3, 25.7, 22.7, 19.0, 14.1. The product was spectroscopically comparable by ^{1}H NMR and ^{13}C NMR to literature values.[3a]

Synthesis of (2*R*,6*R*)-*N*-Boc-solenopsin A (19) s-BuLi (1.53 mL, 2.11 mmole, 1.38 M) was added to a stirred solution of **18** (.552 g, 1.63 mmole) in ether (5.5 mL) containing TMEDA (.318 mL, 2.11 mmole) at -65 °C. The flask was warmed slowly to -20 °C and held at that temperature for 30 min. The temperature was lowered to -78 °C and dimethylsulfate (.307 mL, 3.24 mmole) was added. The solution was allowed to warm to room temperature gradually. The reaction was partitioned between water (10 mL) and ether (10 mL). The layers were separated and the aqueous layer was extracted with ether (6 x 5 mL). The combined ether solution was washed with brine (2 x 1mL), dried (Na_2SO_4), and the solvent was evaporated. The crude product was purified by flash chromatography (hexane/ethyl acetate (96:4) to give 0.461 g (80%) of **19**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.91 (m, 1H), 3.77 (m, 1H), 1.90-1.73 (m, 2H), 1.69-1.46 (m, 6H), 1.45 (s, 9H), 1.33-1.25 (m, 18H), 1.22 (d, J = 6.7 Hz, 3H), .87 (t, J = 7.1 Hz ,3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.3, 78.7, 51.6, 46.9, 34.4, 31.9, 29.7, 29.6, 29.6, 29.6, 29.4, 29.3, 28.0, 28.0, 27.1, 27.1, 26.9, 26.8, 23.2, 20.8, 14.1, 13.7. The product was spectroscopically comparable by ^{1}H NMR and ^{13}C NMR to literature values.[3a]

Synthesis of (2*R*,6*R*)-solenopsin A·HCl (2·HCl) 2 M HCl-methanol (5 mL) was added to **19** (0.442g, 1.25 mmol) and the mixture was refluxed for 2 h. The solvent was evaporated and the resulting white solid was heated at 70 °C *in vacuo* (0.1 torr) for 3 h to provide .351 g (97%) of **2·HCl**. mp 148.5-149°C (lit.[3c]147-150°C) $[\alpha]_D^{20}$ -8.2 (c = .5, $CHCl_3$) (lit.[3c] $[\alpha]_D^{20}$ –7.7 (c = .51, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.33 (br s, 2H), 3.53 (br s, 1H), 3.27 (br

s, 1H), 2.04-1.88 (m, 3H), 1.73 (m, 1H), 1.64 (br s, 4H), 1.47 (d, J = 6.8 Hz, 3H), 1.38-1.21 (m, 18H), .87 (t, J = 6.6 Hz, 3H) Free base ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.03 (m, 1H), 2.85 (m, 1H), 1.65-1.14 (m, 26H), 1.05 (d, J = 6.5 Hz, 3H), 0.86 (t, J = 6.8 Hz, 1H).). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 50.8, 45.9, 33.6, 32.5, 31.8, 30.2, 29.7, 29.6, 29.6, 29.4, 29.3, 29.1, 26.3, 22.6, 22.5, 22.5, 20.7, 19.5, 14.0. Physical and spectroscopic properties of the free base were identical reported values.[3c]

Synthesis of (6*R*, 2*R*)-6-propyl-*N*-Boc-piperidine-2-carboxaldehyde (20)

To a stirred solution of 2(R)-propyl-N-Boc-piperidine (**16**) (.962 g, 4.23 mmole) in ether (10 mL) under N_2 was added TMEDA (.830 mL, 5.49 mmole). The solution was cooled to -65°C and *s*-BuLi (1.38 M in cyclohexane, 3.98 mL, 5.49 mmole) was added dropwise. The solution was allowed to warm to -30°C and stirred for 30 min. The solution was cooled to -78 °C and DMF (.491 mL, 6.34 mmole) was added. After 10 min the reaction was quenched with saturated NH_4Cl (3.7 mL) and allowed to warm to room temperature. The reaction was diluted with ether (30 mL) and the aqueous layer was extracted with ether (4 x 6 mL). The combined ether solution was washed with brine and dried (K_2CO_3). The solvent was evaporated to afford an oil that was dissolved in hexane/ethyl acetate/triethylamine (90:10:1)(40 mL). Silica gel (6.3 g) was added and the mixture was stirred (53 h). The mixture was filtered and the solvent was evaporated. The residue was chromatographed on silica gel (hexane/ ethyl acetate (92:8)) to afford 0.803 g (74%) of **20**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.60 (d, J = 1.3 Hz, 1H), 4.22 (br s, 1H), 2.31 (d, J = 12.7 Hz, 1H), 1.62-1.25 (m, 9H), 1.48 (s, 9H), .91 (t, J = 6.7 Hz, 3H).

Synthesis of (2*R*, 6*R*)-2-hydroxymethyl-6-propyl-*N*-Boc-piperidine (21)

Aldehyde **20** (.787 g, 3.08 mmole) was dissolved in ethanol (25 mL) and cooled with an ice bath. Sodium borohydride (.157 g, 4.15 mmole) was added over 15 min. The solution

was allowed to warm to room temperature and then heated to 70 °C for 30 min. The solvent was evaporated and the residue was partitioned between brine (10 mL) and ether (40 mL). The aqueous layer was extracted with ether (3 x 19 mL) and the combined ether solution was washed with brine (2 mL) and dried (Na_2SO_4). The solvent was evaporated and the residue was chromatographed (hexane/ethyl acetate (7:3)) to afford 0.671 g (85%) of **21**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.30 (br s, 1H), 4.09 (br s, 1H), 3.63 (m, 2H), 1.73-1.23 (m,10H), 1.47 (s, 9H), .92 (t, J = 7.3 Hz, 3H).

Synthesis of 22. A solution of alcohol **21**(.660 g, 2.56 mmole) and DMAP (1.23 g, 10.2 mmole) in methylene chloride (39 mL) under nitrogen was cooled with an ice bath. Phenylchlorothionoformate (.485 mL, 3.51 mmole) was added and after 30 min the ice bath was removed. The solution was stirred for an additional 5 h. The solvent was evaporated and the residue was partitioned between ethyl acetate (80 mL) and water (20 mL). The layers were separated and the organic layer was washed with 1 M HCl (2 x 8 mL), sat. $NaHCO_3$ (8 mL), and brine (8 mL). The organic layer was dried (Na_2SO_4) and the solvent was evaporated. The resulting oil was purified by flash chromatography on silica gel (hexane/ ethyl acetate (95:5) to afford **22** (.889 g, 88%) as a colorless viscous oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42 (m, 2H), 7.29 (m, 1H), 7.11 (m, 2H), 4.60 (br s, 1H), 4.58 (t, J = 8.7 Hz, 1H), 4.41 (br s, 1H), 4.13 (br s, 1H), 1.81 (m, 1H), 1.69 to 1.24 (m, 9H), 1.48 (s, 9H), .94 (t, J = 7.2 Hz, 3H).

Synthesis of (2*S*,6*R*)-*N*-Boc-dihydropinidine (23) A solution of the phenylthionocarbonate (**22**) (.882 g, 2.24 mmole), toluene (50 mL), Bu_3SnH (1.73 mL, 6.43 mmole), and AIBN (.13 g) was refluxed under N_2 for 3 h. After cooling, TBAF (1.0 M in THF, 4.0 mL) was added and the solution was refluxed for 2h. The solvent was evaporated and the residue was partitioned between ether (50 mL) and water (10 mL).

The aqueous layer was extracted with ether (2 x 10 mL) and the combined organic solution was washed with brine (3 mL) and dried (Na_2SO_4). The solvent was evaporated and the residue was purified by flash chromatography on silica gel (hexane/ ethyl acetate (96:4) to afford .261 g (48%) of **23** a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.28 (m, 1H), 4.04 (m, 1H), 1.71-1.15 (m, 10H), 1.45 (s, sharp, 9H), 1.14 (d, J = 7.1 Hz, 3H) .91 (t, J = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 58.5, 54.6, 35.1, 30.8, 27.5, 22.9, 19.5, 18.8. The product was spectroscopically comparable to ^{1}H NMR and ^{13}C NMR to literature values.[9]

Synthesis of (–)-dihydropinidine·HCl (3·HCl). 2 M MeOH-HCl (6.7 mL) was added to *N*-Boc-dihydropinidine (**23**) (.261 g, 1.08 mmol) and the resulting solution was allowed to stand at room temperature for 24 h. The solvent was evaporated and the residue was heated to 70 °C *in vacuo* (0.1 torr) for 2 h to afford **3·HCl** as a white solid (0.172 g, 90%). mp = 242-242.5°C (lit.[4b] 234°C) $[\alpha]^{25}_D$ -13.3^o (c = 1.0, EtOH) (lit.[4b] -12.74 (c = .47, EtOH) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.445 (br s, 1H), 9.08 (br s, 1H), 3.07 (br s, 1H), 2.91 (m, 1H), 2.14 (m, 1H), 1.92 (t, J = 16 Hz, 1H), 1.78 (m, 4H), 1.67-1.61 (m, 1H), 1.58 (d, J = 6.5 Hz, 3H), 1.44 (m, 2H), 1.32 (m, 1H), .91 (t, J = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 58.5, 54.6, 35.1, 30.8, 27.5, 22.9, 19.5, 18.8, 13.7. The product was spectroscopically comparable by ^{1}H NMR and ^{13}C NMR to literature values.[4b]

References for Supporting Information

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