Supporting Information

Formal Total Synthesis of (–)-Lepadiformine

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Full experimental procedures and analytical data of compounds; copies of ¹H NMR and ¹³C NMR spectra of compounds **3**, **12**, **14**, and **18**.

General. All chemicals were reagent grade and used as purchased. All reactions were performed under an inert atmosphere of dry argon or nitrogen using distilled dry solvents. Reactions were monitored through TLC analysis using silica gel 60 F-254 thin layer plates. Compounds were visualized on TLC plate under UV light and by spraying with KMnO_4 or anisaldehyde solutions. Flash column chromatography was carried out on silica gel 60 (230-400 mesh). Melting points are uncorrected. Optical rotations were measured using sodium light (D line 589.3 nm). ^1H NMR and ^{13}C NMR spectra were recorded in δ units relative to deuterated solvent as internal reference by Varian 300 MHz or Bruke 600 MHz NMR instrument. IR spectra were measured on Fourier Transform Infrared spectrometer. Mass spectra (MS) were recorded at 70 or 30 eV using electron impact (EI) or fast atom bombardment (FAB). High-resolution mass spectra (HRMS) were recorded using EI, FAB, or chemical ionization (CI).

(5S)-5-(Benzyloxymethyl)-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxylic Acid (9**).**

To a solution of aldehyde **11** (4.66 g, 14.6 mmol) in CH₃CN/*t*-BuOH/H₂O (2:2:1, 80 mL) were added NaClO₂ (7.92 g, 87.6 mmol) and NaH₂PO₄ (5.26 g, 43.8 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 4 h, diluted with EtOAc, and washed with brine. The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (CH₂Cl₂/MeOH, 10:1) to afford the mixture **9** (4.81 g, 98%) as a colorless oil. Two diastereoisomeric compounds (5*S*,2*S*)-**9** and (5*S*,2*R*)-**9** were isolated for analytical purposes by column chromatography on silica gel.

Less polar (5*S*,2*S*)-**9**: [α]_D²³ -30.7 (*c* 1.65, MeOH); ¹H NMR (300 MHz, CD₃OD; two rotamers in a 3:2 ratio) δ 1.38 (s, 3.6H), 1.41 (s, 5.4H), 1.87-2.12 (m, 3H), 2.37 (m, 1H), 3.43-3.58 (m, 2H), 4.01 (m, 0.4H), 4.11 (m, 0.6H), 4.21 (t, *J* = 8.6 Hz, 1H), 4.48 (d, *J* = 12.3 Hz, 0.6H), 4.51 (s, 0.8H), 4.54 (d, *J* = 12.3 Hz, 0.6H), 7.24-7.33 (m, 5H); ¹³C NMR (75 MHz, CD₃OD; major/minor rotamers) δ 27.4/28.3, 28.6/28.7, 29.8/28.9, 58.95/58.91, 61.5/61.0, 71.6/71.9, 74.3/74.2, 81.5, 128.69/128.6, 128.71/128.8, 129.37/129.44, 139.8/139.7, 155.9/156.1, 176.8/176.3.

More polar (5*S*,2*R*)-**9**: [α]_D²³ -4.38 (*c* 1.01, MeOH); ¹H NMR (300 MHz, CD₃OD; two rotamers are not separable) δ 1.41 (s, 9H), 1.92-1.99 (m, 3H), 2.23 (m, 1H), 3.44 (t, *J* = 8.7 Hz, 1H), 3.73 (m, 1H), 4.05 (m, 1H), 4.18 (m, 1H), 4.49-4.58 (m, 2H), 7.25-7.35 (m, 5H); ¹³C NMR (75 MHz, CD₃OD; major/minor rotamer) δ 28.5, 29.1/28.4, 29.8, 59.0/59.1,

61.4/61.0, 71.3/71.8, 74.2/74.1, 81.7, 128.6, 128.8, 129.3, 139.7, 155.6/155.9, 176.6/176.2; IR (CHCl₃) ν_{max} 2976, 2935, 2878, 1752, 1699, 1393, 1370, 1165, 1100 (cm⁻¹); MS (EI) (*m/z*) 336 ([M + 1]⁺, 1), 190 (33), 114 (66), 91 (100), 57 (90); HRMS (CI) calcd for C₁₈H₂₆NO₅ ([M + H]⁺) 336.1811, found 336.1817.

(5*S*)-(E)-1-*tert*-Butyl 2-[6-(*tert*-Butyldiphenylsilyloxy)hex-2-enyl] 5-(Benzyloxymethyl)pyrrolidine-1,2-dicarboxylate (7**).**

To a solution of **9** (2.23 g, 6.65 mmol) and the allylic alcohol **8** (2.15 g, 6.05 mmol) in CH₂Cl₂ (30 mL) was added DMAP (81 mg, 0.61 mmol) and DCC (1.65 g, 7.25 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h and then diluted with water. The resulting mixture was extracted twice with CH₂Cl₂. The combined organic layers were washed with water, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 10:1) gave the allylic ester **7** (3.59 g, 88%) as a colorless oil. The two diastereisomeric compounds (5*S*,2*S*)-**7** and (5*S*,2*R*)-**7** were isolated for analytical purpose by column chromatography on silica gel.

Less polar (5*S*,2*S*)-**7**: $[\alpha]_{\text{D}}^{23}$ -16.7 (*c* 2.73, CHCl₃); ¹H NMR (300 MHz, CDCl₃; two rotamers in a 3:2 ratio) δ 1.05 (s, 9H), 1.40 (s, 5.4H), 1.42 (s, 3.6H), 1.60-1.78 (m, 2H), 1.83-2.10 (m, 3H), 2.14-2.38 (m, 3H), 3.38 (dd, *J* = 7.4, 9.3 Hz, 0.4H), 3.51-3.70 (m, 3.6H), 4.09 (m, 0.4H), 4.20-4.32 (m, 1.6H), 4.45-4.62 (m, 4H), 5.55 (m, 1H), 5.76 (m, 1H), 7.27-

7.46 (m, 11H), 7.65-7.68 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3 ; major/minor rotamers) δ 19.2, 26.3/27.1, 26.8, 28.3/28.4, 28.59/27.8, 28.9/28.55, 31.7/31.8, 57.4/57.2, 60.1/59.7, 63.1, 65.6, 70.7/71.0, 73.2, 79.96/80.02, 123.8/123.9, 127.4, 127.5, 127.6, 128.3/128.4, 129.5, 133.91/133.94, 135.5, 136.5/135.9, 138.5/138.3, 153.8/154.2, 173.1/172.6; IR (CHCl_3) ν_{max} 2934, 2859, 1746, 1701, 1387, 1181, 1111, 702 (cm^{-1}); MS (FAB) (m/z) 672 ($[\text{M} + 1]^+$, 5), 572 (15), 460 (15), 337 (15), 190 (30), 135 (30), 81(100); HRMS (FAB) calcd for $\text{C}_{40}\text{H}_{54}\text{NO}_6\text{Si}$ ($[\text{M} + \text{H}]^+$) 672.3720, found 672.3716.

More polar (5*S*,2*R*)-**7**: $[\alpha]_{\text{D}}^{22} +1.44$ (c 1.65, CHCl_3); ^1H NMR (300 MHz, CDCl_3 ; two rotamers in a 3:2 ratio) δ 1.06 (s, 9H), 1.41 (s, 9H), 1.58-1.73 (m, 2H), 1.94-2.09 (m, 3H), 2.12-2.26 (m, 3H), 3.41 (t, $J = 9.0$ Hz, 0.4H), 3.46 (t, $J = 9.0$ Hz, 0.6H), 3.67 (t, $J = 6.5$ Hz, 2H), 3.76 (m, 0.4H), 3.85 (dd, $J = 3.6, 9.0$ Hz, 0.6H), 4.03-4.20 (m, 1.6H), 4.30 (m, 0.4H), 4.50-4.62 (m, 4H), 5.54 (td, $J = 6.6, 15.0$ Hz, 1H), 5.768 (m, 1H), 7.27-7.46 (m, 11H), 7.66-7.69 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3 ; major/minor rotamers) δ 19.2, 26.8, 27.4/28.0, 28.3, 28.6, 28.9, 31.7, 57.4, 60.0/59.6, 63.1, 65.6, 70.4/70.9, 73.2, 80.1, 123.8, 127.4, 127.5, 127.6, 128.3, 129.5, 133.9, 135.5, 136.3/135.8, 138.5, 153.6, 173.0.

(2*S*,5*S*)-5-(Benzyloxymethyl)-1-(*tert*-butoxycarbonyl)-2-[(*R*)-6-(*tert*-butyldiphenylsilyloxy)hex-1-en-3-yl]pyrrolidine-2-carboxylic acid (6**).**

To a solution of the allylic ester **7** (2.32 g, 3.45 mmol) in THF (100 mL) was added LHMDS (10.0 mL, 1.0 M solution in THF, 10.0 mmol) at -78 $^{\circ}\text{C}$. After this mixture had

been stirred for 0.5 h, TBSCl (780 mg, 5.20 mmol) in THF (30 mL) was added slowly. The resulting mixture was warmed to room temperature and stirred for 2 days. The reaction was quenched with aqueous saturated NH_4Cl solution and then the mixture was extracted with twice EtOAc. The organic layers were washed with brine, dried over Na_2SO_4 , and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 6:1, 1% AcOH) afforded the desired isomer **6** (1.63 g, 70%) as a colorless oil and a minor isomer **23** (203 mg, 9%) as a colorless oil. The ratio of the crude mixture of these two stereoisomers was 8:1 (^1H NMR spectrum).

Compound **6**: $[\alpha]_D^{19} +19.2$ (c 2.17, CHCl_3); ^1H NMR (300 MHz, CDCl_3 ; for major rotamorph) δ 1.05 (s, 9H), 1.21-1.47 (m, 3H), 1.36 (s, 9H), 1.61 (m, 1H), 1.85-1.99 (m, 3H), 2.70 (m, 1H), 3.23 (t, $J = 9.0$ Hz, 1H), 3.33-3.43 (m, 2H), 3.64 (t, $J = 6.3$ Hz, 2H), 4.08 (m, 1H), 4.45 (d, $J = 12.3$ Hz, 1H), 4.52 (d, $J = 12.3$ Hz, 1H), 5.12-5.21 (m, 2H), 5.42-5.54 (m, 1H), 7.26-7.45 (m, 11H), 7.61-7.67 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3 ; for major rotamer) δ 19.2, 24.6, 26.2, 26.9, 28.1, 28.3, 30.5, 45.6, 60.0, 64.0, 70.3, 73.2, 75.5, 83.0, 119.9, 127.6, 127.7, 128.4, 129.5, 133.8, 133.9, 135.5, 135.8, 137.7, 157.4, 172.7; IR (CHCl_3) ν_{max} 3071, 2957, 2932, 2859, 2737, 1759, 1698, 1611, 1395, 1163, 1111, 702 (cm^{-1}); MS (FAB) (m/z) 672 ($[\text{M} + 1]^+$, 1), 572 (30), 526 (20), 135 (25), 91 (100), 57 (30); HRMS (FAB) calcd for $\text{C}_{40}\text{H}_{54}\text{NO}_6\text{Si}$ ($[\text{M} + \text{H}]^+$) 672.3720, found 672.3735.

Compound **23**: $[\alpha]_D^{19} -46.5$ (c 2.73, CHCl_3); ^1H NMR (300 MHz, CDCl_3 ; for major rotamer) δ 1.05 (s, 9H), 1.13-1.68 (m, 4H), 1.42 (s, 9H), 1.86-1.98 (m, 3H), 2.55 (d, $J = 6.0$ Hz, 1H), 3.15 (t, $J = 9.3$ Hz, 1H), 3.33 (t, $J = 8.7$ Hz, 1H), 3.63 (t, $J = 6.3$ Hz, 2H), 3.69 (dd, $J = 3.3, 8.7$ Hz, 1H), 3.96 (m, 1H), 4.44 (d, $J = 12.3$ Hz, 1H), 4.50 (d, $J = 12.3$ Hz, 1H),

5.09-5.15 (m, 2H), 5.40 (ddd, $J = 9.9, 10.2, 16.2$ Hz, 1H), 7.27-7.46 (m, 11H), 7.64-7.70 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3 ; for major rotamer) δ 19.2, 24.2, 25.5, 26.9, 27.3, 28.2, 30.4, 45.9, 59.8, 64.0, 69.6, 73.2, 75.8, 83.2, 119.9, 127.4, 127.6, 128.4, 129.5, 133.78, 133.84, 135.5, 135.9, 137.9, 157.7, 172.2.

(2*S*,5*S*)-1-*tert*-Butyl 2-Methyl 5-(Benzyloxymethyl)-2-[(*R*)-6-(*tert*-butyldiphenylsilyloxy)hex-1-en-3-yl]pyrrolidine-1,2-dicarboxylate (12**).**

To a solution of **6** (1.60 g, 2.38 mmol) in acetone (15 mL) was added K_2CO_3 (360 mg, 2.62 mmol) at room temperature. After stirring the mixture for 1 h, methyl iodide (0.16 mL, 2.62 mmol) was added dropwise. The resulting mixture was heated under reflux for 12 h and then cooled to room temperature. After the white residue had been filtered off, the filtrate was concentrated under reduced pressure. Purification of the resulting residue by flash column chromatography on silica gel (hexane/EtOAc, 4:1) gave the methyl ester **12** (1.52 g, 93 %) as a colorless oil: $[\alpha]_{\text{D}}^{23} -24.7$ (c 1.55, CHCl_3); ^1H NMR (300 MHz, CDCl_3 ; two rotamers in a 1:1 ratio) δ 1.05 (s, 9H), 1.25-1.50 (m, 3H), 1.38 (s, 9H), 1.67 (m, 1H), 1.99 (m, 2H), 2.16 (m, 2H), 3.06 (t, $J = 8.7$ Hz, 0.5H), 3.20 (t, $J = 8.7$ Hz, 0.5H), 3.44-3.71 (m, 3.5H), 3.63 (s, 3H), 3.90 (m, 0.5H), 4.06 (m, 0.5H), 4.20 (m, 0.5H), 4.49-4.64 (m, 2H), 5.08-5.18 (m, 2H), 5.78 (m, 1H), 7.27-7.45 (m, 11H), 7.65-7.68 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3 ; rotamer 1/rotamer 2) δ 18.9, 25.1/25.6, 26.1, 26.6, 28.0, 30.8/30.6, 31.2/31.6, 47.3/46.8, 51.5, 59.0/58.8, 63.8, 69.3/70.0, 71.1/71.8, 72.7, 79.9/79.4, 117.1, 127.2, 127.3,

128.0, 129.2, 133.7, 135.2, 138.2, 138.3, 152.7, 173.8; IR (CHCl₃) $\nu_{\max}$ 2953, 2936, 2859, 1746, 1698, 1383, 1368, 1171, 1111, 702 (cm⁻¹); MS (FAB) (*m/z*) 686 ([M + 1]⁺, 5), 586 (55), 248 (45), 91 (100), 57 (40); HRMS (FAB) calcd for C₄₁H₅₆NO₆Si ([M + H]⁺) 686.3877, found 686.3853.

(2*S*,5*S*)-1-*tert*-Butyl 2-Methyl 5-(Benzyloxymethyl)-2-[(*S*)-1-(*tert*-butyldiphenylsilyloxy)oct-7-en-4-yl]pyrrolidine-1,2-dicarboxylate (15**).**

To a solution of **12** (345 mg, 0.50 mmol) in THF (1 mL) was added 9-BBN dimer (92 mg, 0.38 mmol), and the mixture was heated at 50 °C for 2 h. The reaction was quenched upon the addition of H₂O (0.05 mL, 2.50 mmol) and then the mixture was treated with TIOEt (0.11 mL, 1.50 mmol). This mixture was transferred to a solution of vinyl bromide (2.5 mL, 2.50 mmol, 1.0 M solution in THF), Pd(dppf)Cl₂ (82 mg, 0.10 mmol), and AsPh₃ (31 mg, 0.10 mmol) in THF (1.5 mL) and DMF (1.0 mL) under a nitrogen atmosphere. After the mixture had been heated at 40 °C for 2 h, the reaction was quenched upon the addition of phosphate buffer solution (pH 7.2, 5 mL) and 30% H₂O₂ (1.6 mL). After being stirred for 0.5 h, the mixture was extracted twice with EtOAc, the combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 5:1) gave the desired product **15** (262 mg, 73%) as a colorless oil: [α]_D¹⁸ -33.0 (c 1.72, CHCl₃); ¹H NMR

(300 MHz, CDCl₃; two rotamers in a 1:1 ratio) δ 1.09 (s, 9H), 1.16-1.29 (m, 3H), 1.40 (s, 9H), 1.48-1.69 (m, 4H), 1.99-2.39 (m, 5.5H), 2.57 (m, 0.5H), 3.51-3.77 (m, 3.5H), 3.66 (s, 1.5H), 3.68 (s, 1.5H), 3.95 (m, 0.5H), 4.08 (m, 0.5H), 4.23 (m, 0.5H), 4.51-4.67 (m, 2H), 4.95-5.07 (m, 2H), 5.87 (m, 1H), 7.30-7.46 (m, 11H), 7.68-7.72 (m, 4H); ¹³C NMR (75 MHz, CDCl₃; rotamer 1/rotamer 2) δ 19.1, 26.8, 27.6/29.4, 28.2, 29.1/30.0, 31.1, 32.1, 34.1, 34.4, 41.2/39.9, 51.8/51.9, 59.1/58.9, 64.4/64.5, 69.5/70.3, 72.6, 72.9, 80.2/79.8, 114.0/113.9, 127.3, 127.4, 127.6, 128.2/128.3, 129.5, 133.9, 135.5, 138.7/138.4, 139.1/139.3, 152.7/152.9, 175.0/175.2; IR (CHCl₃) ν_{max} 2932, 2859, 2361, 1746, 1696, 1387, 1368, 1173, 1111, 702 (cm⁻¹); MS (EI) (*m/z*) 714 ([M + 1]⁺, 1), 600 (40), 554 (30), 492 (100), 432 (25), 91 (25), 57 (25); HRMS (FAB) calcd for C₄₃H₆₀NO₆Si ([M + H]⁺) 714.4190, found 714.4193.

(2*S*,5*S*)-tert-Butyl 5-(Benzyloxymethyl)-2-[(*S*)-1-(tert-butyldiphenylsilyloxy)oct-7-en-4-yl]-2-(hydroxymethyl)pyrrolidine-1-carboxylate (16**).**

A solution of **15** (399 mg, 0.56 mmol) in THF (3 mL) was added to a suspension of LiAlH₄ (32 mg, 0.84 mmol) in THF (5 mL) at 0 °C. The mixture was stirred for 30 min at 0 °C and then quenched upon the addition of an aqueous saturated NaHCO₃ solution. The resulting mixture was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by

flash silica gel column chromatography (hexane/EtOAc, 5:1) to give the alcohol **16** (352 mg, 91 %) as a colorless oil: $[\alpha]_D^{18} -23.1$ (c 0.64, CHCl_3); ^1H NMR (300 MHz, CDCl_3 ; for major rotamer) δ 1.05 (s, 9H), 1.13-1.31 (m, 3H), 1.36 (s, 9H), 1.43-1.69 (m, 4H), 1.80-1.91 (m, 3H), 2.01-2.18 (m, 2H), 2.54 (m, 1H), 3.42 (d, J = 5.1 Hz, 2H), 3.59-3.65 (m, 3H), 3.78 (d, J = 12.0 Hz, 1H), 4.00 (m, 1H), 4.48 (d, J = 12.3 Hz, 1H), 4.55 (d, J = 12.3 Hz, 1H), 4.92 (m, 1H), 4.99 (ddd, J = 1.5, 3.6, 17.1 Hz, 1H), 5.81 (tdd, J = 6.6, 10.2, 17.1 Hz, 1H), 7.27-7.44 (m, 11H), 7.64-7.68 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3 ; for major rotamer) δ 19.0, 26.3, 26.8, 27.7, 28.2, 29.4, 31.5, 31.9, 33.2, 37.1, 59.5, 64.5, 70.0, 71.2, 72.5, 73.0, 80.0, 114.0, 127.4, 127.5, 127.6, 128.2, 129.4, 133.8, 135.3, 137.9, 139.0, 155.3; IR (CHCl_3) ν_{max} 3382, 2957, 2932, 2859, 2363, 1665, 1389, 1366, 1169, 1109, 702 (cm^{-1}); MS (FAB) (m/z) 686 ($[\text{M} + 1]^+$, 2), 586 (15), 220 (20), 154 (40), 91 (100), 57 (50); HRMS (FAB) calcd for $\text{C}_{42}\text{H}_{60}\text{NO}_5\text{Si}$ ($[\text{M} + \text{H}]^+$) 686.4241, found 686.4233.

(2*R*,5*S*)-*tert*-Butyl 5-(Benzyloxymethyl)-2-[(*S*)-1-(*tert*-butyldiphenylsilyloxy)oct-7-en-4-yl]-2-vinylpyrrolidine-1-carboxylate (14**).**

To a solution of oxalyl chloride (35 μL , 0.40 mmol) in CH_2Cl_2 (1 mL) was added DMSO (71 μL , 1.0 mmol) in CH_2Cl_2 (1 mL) at -78°C . The mixture was stirred for 20 min, and then a solution of **16** (230 mg, 0.34 mmol) in CH_2Cl_2 (1 mL) was added slowly. After the mixture had been stirred for 0.5 h, triethylamine (0.23 mL, 1.7 mmol) was added and then

the mixture was warmed to 0 °C. The residue was diluted with CH₂Cl₂, washed with water and brine, dried over Na₂SO₄, and concentrated in vacuo to give the crude aldehyde. To a solution of methyltriphenylphosphonium iodide (406 mg, 1.0 mmol) in THF (1 mL) was added *n*-BuLi (0.63 mL, 1.0 mmol, 1.6 M solution in hexane) at 0 °C. The mixture was stirred for 30 min at room temperature, and then a solution of the above crude aldehyde in THF (1 mL) was added. After stirring for 1 h, the reaction mixture was quenched with aqueous saturated NH₄Cl solution and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 10:1) afforded the desired product **14** (195mg, 84%) as a colorless oil: $[\alpha]_D^{18}$ -0.84 (*c* 1.00, CHCl₃); ¹H NMR (300 MHz, CDCl₃; two rotamers in a 3:2 ratio) δ 1.05 (s, 9H), 1.13-1.67 (m, 7H), 1.35 (s, 5.4H), 1.42 (s, 3.6H), 1.80-1.93 (m, 3H), 1.98-2.09 (m, 2H), 2.17 (m, 0.4H), 2.46 (m, 0.6H), 3.25 (t, *J* = 9.0 Hz, 0.6H), 3.40 (t, *J* = 9.0 Hz, 0.4H), 3.58-3.75 (m, 3H), 4.02 (m, 0.6H), 4.16 (m, 0.4H), 4.45-4.59 (m, 2H), 4.89-5.06 (m, 4H), 5.75 (tdd, *J* = 6.6, 10.5, 17.1 Hz, 1H), 6.16 (dd, *J* = 10.7, 17.9, 0.4H), 6.36 (dd, *J* = 10.8, 17.7, 0.6H), 7.27-7.44 (m, 11H), 7.65-7.68 (m, 4H); ¹³C NMR (75 MHz, CDCl₃; major/minor rotamers) δ 19.2, 25.9, 26.5, 26.9, 28.1/28.0, 28.4/28.5, 30.1, 31.9/32.3, 34.1/34.6, 41.0/42.2, 58.9/59.3, 64.7/64.5, 71.1/70.3, 71.6/70.9, 72.9, 78.9/79.6, 112.2/112.3, 114.0/114.5, 127.3, 127.4, 127.5, 128.3/128.2, 129.5, 134.0/134.1, 135.5, 138.4/138.7, 139.1/138.8, 142.2/142.6, 152.7/153; IR (CHCl₃) $\nu_{\max}$ 2963, 2932, 2859, 2386, 1692, 1387, 1366, 1173, 1109, 702 (cm⁻¹); MS (EI) (*m/z*) 681 (M⁺, 1), 568 (10), 490 (20), 460 (17), 316 (40), 216 (100), 91(60), 57 (60); HRMS (FAB) calcd for C₄₃H₆₀NO₄Si ([M +

H]⁺) 682.4292, found 682.4282.

(2*S*,5*R*,10*S*)-*tert*-Butyl **2-(Benzyloxymethyl)-10-[3'-(*tert*-butyldiphenylsilanyloxy)propyl]-1-azaspiro[4,5]dec-6-ene-1-carboxylate (18).**

To a solution of **14** (57 mg, 84 μ mol) in CH₂Cl₂ (20 mL) was added second-generation Grubbs' catalyst **17** (3.9 mg, 4.2 μ mol). The reaction mixture was heated to 40 °C for 1 h and then cooled to room temperature. The mixture was concentrated to dryness. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 10 : 1) to give **18** (54 mg, 98 %) as a colorless oil: [α]_D¹⁹ -53.1 (*c* 0.85, CHCl₃); ¹H NMR (300 MHz, CDCl₃; two rotamers in a 1:1 ratio) δ 1.07 (s, 9H), 1.17-1.99 (m, 11.5H), 1.38 (s, 4.5H), 1.39 (s, 4.5H), 2.17 (m, 0.5H), 2.35 (m, 0.5H), 2.63 (m, 0.5H), 3.38 (t, *J* = 8.7 Hz, 0.5H), 3.55 (m, 1H), 3.67 (m, 2.5H), 4.09 (m, 0.5H), 4.21 (m, 0.5H), 4.49-4.62 (m, 2H), 5.42-5.66 (m, 2H), 7.27-7.45 (m, 11H), 7.66-7.70 (m, 4H); ¹³C NMR (75 MHz, CDCl₃; rotamer 1/rotamer 2) δ 19.2, 25.2/25.5, 26.0/26.2, 26.3/26.6, 26.9, 28.5/28.3, 30.8/31.0, 33.4/34.6, 37.5, 39.6, 59.1/59.2, 64.4/64.3, 67.1/66.9, 71.4/70.6, 73.1/73.0, 79.0/79.2, 125.0/124.0, 127.3/127.4, 127.5, 127.6, 128.4/128.2, 129.5, 134.1, 135.5, 136.8/137.3, 138.4/138.7, 152.5/153.8; IR (CHCl₃) ν_{max} 2957, 2932, 2859, 2384, 2309, 1682, 1387, 1364, 1173, 1111, 702 (cm⁻¹); MS (FAB) (*m/z*) 654 ([*M* + 1]⁺, 5), 554 (35), 432 (27), 135 (27), 91 (100), 57 (35); HRMS (FAB) calcd for C₄₁H₅₆NO₄Si ([*M* + H]⁺) 654.3979, found 654.3983.

(2*S*,5*S*,6*S*)-*tert*-Butyl 2-(Benzyloxymethyl)-6-[3'-(*tert*-butyldiphenylsilyloxy)propyl]-1-aza-spiro[4,5]decane-1-carboxylate (19**).**

To a solution of **18** (50 mg, 76 μ mol) in MeOH (3 mL) was added 10% Pd/C (15 mg, 30 wt %) and triethylamine (1 μ L, 7.6 μ mol) under nitrogen atmosphere. The flask was evacuated, filled with H₂, and stirred at room temperature for 12 h. The mixture was then filtered through Celite and the filtrate was concentrated. The residue was purified by flash column chromatography (hexane/EtOAc, 10:1) to give **19** (47 mg, 95 %) as a colorless oil: $[\alpha]_D^{19}$ -39.8 (c 1.08, CHCl₃); ¹H NMR (300 MHz, CDCl₃; two rotamers in a 3:2 ratio) δ 0.83-1.52 (m, 7H), 1.04 (s, 9H), 1.36 (s, 5.4H), 1.43 (s, 3.6H), 1.57-1.82 (m, 7H), 2.03 (m, 1H), 2.21 (m, 0.6H), 2.49 (m, 1.4H), 3.27 (t, J = 8.7 Hz, 0.6H), 3.40 (t, J = 8.6 Hz, 0.4H), 3.52 (dd, J = 3.3, 8.7 Hz, 0.6H), 3.62 (m, 2.4H), 4.06 (m, 0.6H), 4.20 (m, 0.4H), 4.46-4.60 (m, 2H), 7.27-7.44 (m, 11H), 7.64-7.72 (m, 4H); ¹³C NMR (75 MHz, CDCl₃; major/minor rotamers) δ 19.2, 24.2/24.3, 25.7, 26.2/26.5, 26.9, 27.2, 28.5/28.6, 29.7, 30.8/31.0, 38.4, 39.6, 41.6, 58.9/59.2, 64.7/64.5, 68.5/68.0, 71.4/70.8, 73.0, 78.7/79.3, 127.3, 127.46, 127.55, 128.4/128.3, 129.5, 134.1/134.2, 135.5, 138.5, 152.8; IR (CHCl₃) $\nu_{\max}$ 2932, 2859, 1692, 1391, 1368, 1173, 1109, 702 (cm⁻¹); MS (EI) (m/z) 655 (M⁺, 1), 464 (30), 434 (85), 356 (25), 199 (30), 91 (100), 57(55); HRMS (FAB) calcd for C₄₁H₅₈NO₄Si ([M + H]⁺) 656.4135, found 656.4139.

(2*S*,5*S*,6*S*)-*tert*-Butyl

2-(Benzyloxymethyl)-6-(3'-hydroxypropyl)-1-

azaspiro[4,5]decane-1-carboxylate (**20**).

To a solution of **19** (75 mg, 0.11 mmol) in THF (3 mL) was added tetrabutylammonium fluoride (0.15 mL, 0.15 mmol, 1.0 M solution in THF). The solution was stirred for 12 h at room temperature, and then the reaction mixture was quenched with aqueous saturated NH_4Cl and extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/EtOAc, 1:1) to afford alcohol **20** (47 mg, 99%) as a colorless oil: $[\alpha]_D^{19} -57.7$ (c 2.03, CHCl_3); ^1H NMR (300 MHz, CDCl_3 ; two rotamers in a 3:1 ratio) δ 0.89-1.45 (m, 7H), 1.40 (s, 6.75H), 1.48 (s, 2.25H), 1.61-1.85 (m, 8H), 2.03 (m, 1H), 2.23-2.41 (m, 1.25H), 2.66 (m, 0.75H), 3.30 (t, $J = 8.7$ Hz, 0.75H), 3.42 (t, $J = 8.4$ Hz, 0.25H), 3.53 (dd, $J = 3.3, 9.0$ Hz, 0.75H), 3.57-3.65 (m, 2.25H), 4.09 (m, 0.75H), 4.23 (m, 0.25H), 4.47-4.61 (m, 2H), 7.28-7.37 (m, 5H); ^{13}C NMR (75 MHz, CDCl_3 ; major/minor rotamers) δ 24.1/24.2, 25.6, 25.67/25.72, 26.2/26.1, 28.5/28.6, 29.0/29.4, 29.3/31.0, 30.6/32.1, 38.4/39.1, 38.5/41.5, 59.1/59.2, 62.2/63.3, 68.6/68.0, 71.2/70.7, 73.0, 79.1/79.5, 127.5/127.3, 127.6, 128.4/128.3, 138.4/138.7, 153.4; IR (CHCl_3) ν_{max} 3441, 2967, 2932, 2861, 1690, 1676, 1391, 1370, 1171, 1111 (cm^{-1}); MS (EI) (m/z) 417 (M^+ , 1), 296 (15), 216 (18), 196 (100), 91 (60), 57 (50); HRMS (CI) calcd for $\text{C}_{25}\text{H}_{40}\text{NO}_4$ ($[\text{M} + \text{H}]^+$) 418.2957, found 418.2950.

(2*S*,5*S*,6*S*)-*tert*-Butyl 2-(Benzyloxymethyl)-6-(3'-oxo-propyl)-1-azaspiro[4,5]decane-1-carboxylate (21).

To a solution of **20** (30 mg, 72 μ mol) in CH_2Cl_2 (2 mL) at 0 °C was added NaHCO_3 (15 mg, 0.22 mmol) and Dess-Martin periodinane (61 mg, 0.14 mmol). After stirring for 30 min at 0 °C, the reaction mixture was quenched upon the addition of isopropyl alcohol (1 mL) and then warmed to room temperature. The resulting mixture was filtered through Celite and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 3:1) to afford the aldehyde **21** (29 mg, 96 %) as a colorless oil: $[\alpha]_D^{19} -55.9$ (*c* 1.01, CHCl_3); ^1H NMR (300 MHz, CDCl_3 ; two rotamers in a 2:1 ratio) δ 0.83-1.45 (m, 7H), 1.40 and 1.48 (each s, total 9H in a 2:1 ratio), 1.62-1.87 (m, 7H), 2.00-2.06 (m, 1H), 2.22-2.62 (m, 4H), 3.30 (t, $J = 8.7$ Hz, 2/3H), 3.45 (t, $J = 8.7$ Hz, 1/3H), 3.52 (dd, $J = 3.3, 9.0$ Hz, 2/3H), 3.62 (dd, $J = 3.3, 9.3$ Hz, 1/3H), 4.09 (m, 2/3H), 4.25 (m, 1/3H), 4.47-4.61 (m, 2H), 7.27-7.37 (m, 5H), 9.74 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3 ; major/minor rotamers) δ 22.7, 24.0/24.1, 25.6/25.8, 26.3/26.0, 28.5/28.6, 29.3, 30.8/32.2, 38.1/39.0, 39.5/41.2, 42.3/42.1, 58.9/59.3, 68.4/67.8, 71.3/70.7, 73.0, 79.0/79.7, 127.5, 127.6/127.4, 128.4/128.3, 138.4/138.6, 152.8, 203.0/202.7; IR (CHCl_3) ν_{max} 2930, 2859, 1725, 1690, 1391, 1368, 1173, 1113 (cm^{-1}); MS (EI) (m/z) 415 (M^+ , 1), 216 (20), 194 (95), 166 (19), 91 (100), 57 (85); HRMS (CI) calcd for $\text{C}_{25}\text{H}_{38}\text{NO}_4$ ($[\text{M} + \text{H}]^+$) 416.2801, found 416.2805.

(3*S*,5*S*,7*aS*,11*aS*)-3-(Benzyloxymethyl)decahydro-1*H*-pyrrolo[1,2-*j*]quinoline-5-

carbonitrile (3).

To a solution of **21** (18 mg, 43 μ mol) in a mixture of acetone (1.2 mL) and H₂O (0.8 mL) was added *p*-TsOH·H₂O (10 mg, 53 μ mol) at room temperature and stirred under reflux for 5 h. The resulting mixture was diluted with saturated aqueous NaHCO₃ solution and extracted twice with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure to give the unstable enamine **22** as a yellow oil: ¹H NMR (300 MHz, CDCl₃) δ 1.12-2.09 (m, 15H), 3.30 (m, 1H), 3.41 (dd, *J* = 6.3, 9.3 Hz, 1H), 3.54 (dd, *J* = 7.5, 9.3 Hz, 1H), 4.50 (d, *J* = 12.3 Hz, 1H), 4.57 (td, *J* = 4.5, 7.8 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 5.80 (d, *J* = 8.1 Hz, 1H), 7.27-7.34 (m, 5H); ¹³C NMR (75 MHz, CDCl₃) δ 23.6, 25.2, 25.3, 25.4, 26.1, 31.1, 37.1, 41.5, 64.6, 65.3, 73.1, 76.4, 100.9, 127.4, 127.6, 128.3, 138.6, 140.2.

To a solution of the above enamine **22** in a mixture of acetone (0.15 mL) and water (1.35 mL) was added KCN (80 mg, 1.23 mmol) and aqueous 1N HCl (0.12 mL, 0.12 mmol) at room temperature. The solution was stirred at room temperature for 5 h. The resulting mixture was diluted with saturated aqueous NaHCO₃ solution, extracted twice with CH₂Cl₂, dried over Na₂SO₄ and filtered. The residue was concentrated under reduced pressure to afford **3** (9.8 mg, 70 %) as a colorless oil: $[\alpha]_D^{25}$ -44.2 (*c* 0.50, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 1.09-1.15 (m, 2H), 1.23-1.41 (m, 3H), 1.45-1.54 (m, 3H), 1.56-1.67 (m, 4H), 1.72 (m, 1H), 1.79 (dd, *J* = 7.7, 12.2 Hz, 1H), 1.86 (m, 1H), 2.02 (m, 1H), 2.22 (td, *J* = 4.8, 7.9 Hz, 1H), 3.37 (app. t, *J* = 8.2 Hz, 1H), 3.46 (m, 1H), 3.72 (dd, *J* = 5.7, 9.2 Hz, 1H), 4.18 (dd,

$J = 3.5, 8.1$ Hz, 1H), 4.52 (d, $J = 12.1$ Hz, 1H), 4.60 (d, $J = 12.1$ Hz, 1H), 7.28 (m, 1H), 7.32-7.36 (m, 4H); ^{13}C NMR (150 MHz, CDCl_3) δ 22.9, 23.8, 26.0, 26.1, 26.6, 27.4, 30.7, 39.4, 40.6, 50.2, 63.4, 67.7, 73.2, 76.1, 121.3, 127.4, 127.6, 128.3, 138.6; IR (CHCl_3) ν_{max} 2930, 2859, 2361, 2338, 1101 (cm^{-1}); MS (EI) (m/z) 324 (M^+ , 1), 296 (20), 203 (80), 176 (100), 105 (40), 91 (80), 57 (50); HRMS (EI) calcd for $\text{C}_{21}\text{H}_{28}\text{N}_2\text{O}$ (M^+) 324.2202, found 324.2203.

Comparison of the spectral data

¹ H NMR of 3			¹³ C NMR of 3		
Weinreb ¹	3	Δδ	Weinreb ¹	3	Δδ
	1.09-1.15 (2H)		22.9	22.9	0
	1.23-1.41 (3H)		23.8	23.8	0
	1.45-1.54 (3H)		26.0	26.0	0
1.08-1.87 (15H)	1.56-1.67 (4H)		26.1	26.1	0
	1.72 (1H)		26.6	26.6	0
	1.79 (1H)		27.4	27.4	0
	1.86 (1H)		30.7	30.7	0
			39.4	39.4	0
2.00 (1H)	2.02 (1H)	+0.02	40.6	40.6	0
2.20 (1H)	2.22 (1H)	+0.02	50.1	50.2	+0.1
3.34 (1H)	3.37 (1H)	+0.03	63.4	63.4	0
3.44 (1H)	3.46 (1H)	+0.02	67.7	67.7	0
3.70 (1H)	3.72 (1H)	+0.02	73.1	73.2	+0.1
4.16 (1H)	4.18 (1H)	+0.02	76.1	76.1	0
			121.3	121.3	0
	4.52 (1H)		127.5	127.4	-0.1
4.54 (2H)	4.60 (1H)	+0.02	127.6	127.6	0
	7.28 (1H)		128.3	128.3	0
7.22-7.33 (5H)	7.32-7.36 (4H)		138.6	138.6	0

¹ (a) Sun, P.; Sun, C.; Weinreb, S. M. *J. Org. Chem.* **2002**, 67, 4337–4345. (b) Sun, P.; Sun, C.; Weinreb, S. M. *Org. Lett.* **2001**, 3, 3507–3510.

Current Data Parameters
NAME jul11-snu-1m
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20050711
Time 15.41
INSTRUM spect
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TD 65536
SOLVENT CDCl3
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FIDRES 0.133381 Hz
AQ 3.7487664 sec
RG 20.2
DM 57.200 usec
DE 6.00 usec
TE 298.0 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRR 0.01500000 sec

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P1 10.30 usec
PL1 -5.00 dB
SF01 600.1336696 MHz

F2 - Processing parameters
SI 32768
SF 600.1300163 MHz
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SSB 0
LB 0.30 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
CY 8.00 cm
F1P 9.000 ppm
F1 5401.17 Hz
F2P -0.300 ppm
F2 -180.04 Hz
PPMCM 0.46500 ppm/cm
HZCM 279.06046 Hz/cm