SUPPLEMENTARY MATERIAL

Asymmetric total syntheses of tuberostemonine, didehydrotuberostemonine and 13-epituberostemonine

Peter Wipf,* and Stacey R. Spencer

Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260

pwipf@pitt.edu

Experimental procedures and spectral data for **1**, **9**-**25**, **28**, **30**, **34**-**37**, **39**, **40a**,**b**, and **42**.

General Methods. All moisture-sensitive reactions were performed under an atmosphere of N_2 and glassware was dried in an oven at 140 °C prior to use. THF and Ether were dried by distillation over Na/Benzophenone and dry CH_2Cl_2 and toluene were obtained by distillation from CaH_2. Unless otherwise stated, solvents or reagents were used as received without further purification. Analytical thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F-254 plates (particle size 0.040-0.055 mm, 230-400 mesh) and visualization was accomplished with a 254 nm UV light and/or by staining with PMA (5 g of phosphomolybdic acid in 100 mL of EtOH), anisaldehyde (2.5 mL of *p*-anisaldehyde in 2 mL of HOAc, 3.5 mL of conc. H_2SO_4, and 92 mL of EtOH), ninhydrin (0.3 g of ninhydrin in 3 mL of conc. HOAc and 100 mL of *n*-butyl alcohol). NMR spectra were recorded at 300 MHz/75 MHz (^{1}H NMR/^{13}C NMR) in $CDCl_3$ using a Bruker AVANCE 300 MHz spectrometer at 21 °C unless stated otherwise. Chemical shifts (δ) are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, b=broad), integration, and coupling constants. IR spectra were obtained on an IBM IR/32 FT-IR spectrometer or on a Nicolet AVATAR 360 FT-IR E.S.P. Spectrometer. Mass spectra were obtained on a VG-70-70-HF. Optical rotations were measured on a Perkin-Elmer 241 polarimeter.

(2*S*,3aR,7a*R*)-3a-Hydroxy-6-oxo-2,3,3a,6,7,7a-hexahydroindole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (1).[1] A solution of Cbz-*L*-tyrosine (**7**, 98 g, 311 mmol) in nitromethane (250 mL) was added dropwise to a solution of iodobenzene diacetate (100 g, 311 mmol) in nitromethane (850 mL) over about 30 min. The reaction mixture was stirred at room temperature for an additional 2.5 h and quenched with saturated $NaHCO_3$. The layers were separated, and the organic layer was washed with saturated $NaHCO_3$, dried ($MgSO_4$), concentrated *in vacuo*, and purified by chromatography on SiO_2 (hexanes/EtOAc, 2:1 to 1:1) to give 34 g (35%) of **8** as a white solid. The spirocycle **8** (36 g, 110 mmol) in MeOH (400 mL) was treated with Na_2CO_3 (12 g, 110 mmol), and the reaction was stirred at room temperature for 3 h and concentrated *in vacuo*. The resulting oil was dissolved in EtOAc (500 mL) and water (500 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (1 x 500 mL), and the combined organic layers were washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated *in vacuo* to give 37 g (97%) of **1** as a crude oil that was used directly in the next step.

(2*S*,3a*R*,7a*R*)-3a-(Hydroxy)-6-oxo-2,3,3a,6,7,7a-hexahydroindole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (9).[1] Crude **1** was dissolved in CH_2Cl_2 (300 mL), and benzoic anhydride (33 g, 150 mmol), dimethylaminopyridine (1.3 g, 5.7 mmol), and pyridine (44 mL, 570 mol) was added. The reaction mixture was heated at reflux for 20 h before 10% HCl (250 mL) was added. The reaction mixture was extracted into $CHCl_3$ (3 x 200 mL). The combined organic layers were washed with 1N HCl, saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The brown residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 5:1 to 2:1 to 3:2) to give 26 g (51% over the two steps) of **9** as a white solid: Mp 118-119 °C (hexanes/EtOAc); $[\alpha]_D$ –114.0 (*c* 0.52, $CHCl_3$, 21 °C); ^{1}H NMR (DMSO-d_6, 373 K) δ 7.89 (d, 2 H, *J* = 7.8 Hz), 7.66 (t, 1 H, *J* = 7.2 Hz), 7.52 (t, 2 H, *J* = 7.4 Hz), 7.33 (bs, 5 H), 7.11 (d, 1 H, *J* = 7.2 Hz), 6.08 (d, 1 H, *J* = 10.4 Hz), 5.12, 5.10 (AB, 2 H, *J* = 12.5 Hz), 4.94 (dd, 1 H, *J* = 9.8, 6.6 Hz), 4.70 (dd, 1 H, *J* = 7.7, 3.8 Hz), 3.51 (s, 3 H), 3.11-2.89 (m, 3 H), 2.76 (dd, 1 H, *J* = 16.5, 9.8 Hz).

(2*S*,3a*R*,6*S*,7aR)-3a-(Benzyloxy)-6-hydroxy-2,3,3a,6,7,7a-hexahydroindole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (10).[1] A solution of **9** (22.0 g, 48.0 mmol) in THF (200 mL) was treated with a solution of cerium (III) chloride heptahydrate

(17.8 g, 48.0 mmol) in MeOH (120 mL). After stirring at room temperature for 5 min, the solution was cooled to 0 °C and NaBH$_4$ (907 mg, 24.0 mmol) was added over a 10 min period. After the addition was complete, the reaction mixture was stirred at 0 °C for 15 h and treated with brine (250 mL) and 1 N HCl (25 mL). The product was extracted into EtOAc (3 x 100 mL). The combined organic layers were washed with brine, dried (MgSO$_4$), and concentrated *in vacuo*. The residue was purified by chromatography on SiO$_2$ (hexanes/EtOAc, 1:1) to give 21.0 g (97%) of **10** as a white solid: Mp 108-111 °C (hexanes/EtOAc); $[\alpha]_D$ –109.0 (*c* 1.02, CHCl$_3$, 21 °C); ^{1}H NMR (DMSO-d$_6$, 373 K) δ 7.83 (d, 2 H, J = 7.3 Hz), 7.63 (t, 1 H, J = 7.1 Hz), 7.50 (t, 2 H, J = 7.9 Hz), 7.34-7.30 (m, 5 H), 5.97-5.84 (m, 2 H), 5.15-5.05 (m, 2 H), 4.87 (bs, 1 H), 4.64-4.60 (m, 2 H), 4.33 (bs, 1 H), 3.35 (s, 3H), 2.89-2.85 (m, 1 H), 2.71-2.67 (m, 2 H), 1.50-1.44 (m, 1 H).

6-Hydroxy-2*S*,6*S*,7,7a*R*-tetrahydroindole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (11). To a base-washed and silylated Schlenk tube was added **10** (1.0 g, 2.2 mmol), THF (10 mL), and Pd$_2$(dba)$_3$CHCl$_3$ (57 mg, 0.055 mmol). The reddish-purple solution was degassed by repetitive freeze-pump-thaw cycles (3 x), and tributylphosphine (0.055 mL, 0.22 mmol) was added. After stirring at room temperature for 1 min, triethylamine (1.0 mL, 7.3 mmol) was added followed immediately by formic acid (0.28 mL, 7.3 mmol). The reaction mixture was again degassed by repetitive freeze-pump-thaw cycles (3 x), heated at 60 °C for 6 h, then concentrated *in vacuo*. The residue was purified by chromatography on SiO$_2$ (hexanes/EtOAc, 2:1) to give 0.68 g (94%) of yellow, solid **11** as a 2:1 mixture of carbamate rotamers: Mp 102-105 °C (hexanes/EtOAc); $[\alpha]_D$ –86.3 (*c* 0.56, CHCl$_3$, 21 °C); IR (neat) 3435, 2954, 1748, 1710, 1408, 1351, 1209 cm^{-1}; ^{1}H NMR δ 7.50-7.44 (m, 5 H), 6.31 (d, 1 H, J = 9.7 Hz), 6.04 (dd, 1 H, J = 15.1, 10.1 Hz), 5.59 (bs, 0.33 H), 5.52 (bs, 0.66 H), 5.36-5.32 (m, 1 H), 5.26-5.22 (m, 1 H), 5.11 (d, 1 H, J = 12.2 Hz), 4.83-4.65 (m, 2 H), 3.84 (s, 1 H), 3.62 (s, 2 H), 3.37-3.31 (m, 0.66 H), 3.17-3.11 (m, 0.33 H), 1.64 (q, 1 H, J = 11.2 Hz); ^{13}C NMR δ 170.6, 170.4, 155.1, 154.3, 140.7, 137.9, 137.3, 136.2, 135.9, 128.4, 128.3, 128.0, 127.8, 121.1, 120.7, 115.1, 114.7, 67.9, 67.6, 67.3, 67.0, 61.8, 52.3, 52.1, 39.4, 38.6; MS (EI) *m/z* (rel. intensity) 329 (M+, 0.3), 311 (57), 270 (80), 208 (23), 176 (11), 91 (100); HRMS *m/z* calculated for C$_{18}$H$_{19}$NO$_5$ 329.1263, found 329.1264.

(2*S*,3,3a*R*,6*S*,7,7a*R*)-Hexahydro-6-hydroxyindole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (12).[1] To a solution of **10** (34 g, 75 mmol) in THF (340 mL) was added Pd$_2$(dba)$_3$CHCl$_3$ (1.6 g, 1.5 mmol) and tribenzylphosphine (1.8 g, 6.0 mmol). The reaction mixture was stirred for one minute, and triethylamine (36 mL, 260 mmol) was added followed immediately by formic acid (9.8 mL, 260 mmol). The solution was then heated at reflux for 16 h. The color changed to a lighter clear-orange-brown color and CO$_2$ gas was evolved upon heating. After 16 h, the mixture was cooled to room temperature and the solvent removed *in vacuo*. The remaining residue was taken up in EtOAc and washed with saturated NaHCO$_3$ (2 x 100 mL), dried (MgSO$_4$), concentrated *in vacuo*, and purified by chromatography on SiO$_2$ (hexanes/EtOAc, 4:1 to 2:1 to 1:1) to give 23 g (93%) of **12** as a yellow foam: ^{1}H NMR (DMSO-d$_6$, 373 K) δ 7.39-7.27 (m, 5 H), 5.73 (bd, 1 H, J = 9.8 Hz), 5.61 (bd, 1 H, J = 9.3 Hz), 5.09, 5.02 (AB, 2 H, J = 12.4 Hz), 4.43-4.31 (m, 2 H), 3.55 (s, 3H), 3.23-3.14 (m, 1 H), 2.50-2.37 (m, 2 H), 1.60-1.36 (m, 2 H).

6-(*tert*-Butyldimethylsilanyloxy)-2*S*,3,3a*R*,6,7,7a*R*-hexahydroindole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester. A solution of **12** (11 g, 34 mmol) in CH$_2$Cl$_2$ (100 mL) was treated with TBSCl (6.2 g, 41 mmol), imidazole (2.8 g, 45 mmol), and dimethylaminopyridine (410 mg, 3.4 mmol) at 0 °C. After stirring at 0 °C for 2 h, the reaction mixture was poured into water (150 mL) and extracted with ether (3 x 200 mL). The combined organic layers were then washed with 1N HCl, saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 9:1 to 4:1) to give 15 g (97%) of the silyl ether as a colorless oil: $[\alpha]_D$ –82.8 (*c* 1.06, $CHCl_3$, 21 °C); IR (neat) 2916, 1703, 1412, 1333, 1188, 1078, 831, 769 cm^{-1}; ^{1}H NMR (DMSO-d_6, 373 K) δ 7.34 (s, 5 H), 5.77 (d, 1 H, *J* = 9.4 Hz), 5.53 (d, 1 H, *J* = 8.1 Hz), 5.10-4.97 (m, 2 H), 4.54 (bs, 1 H), 4,39 (t, 1 H, *J* = 7.6 Hz), 3.57 (s, 3 H), 3.18 (bs, 2 H), 2.46-2.43 (m, 2 H), 1.59-1.35 (m, 2 H), 0.88 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR δ 173.4, 154.3, 136.5, 133.3, 132.9, 128.6, 128.3, 126.1, 69.4, 67.7, 66.8, 60.9, 60.5, 52.4, 52.2, 44.3, 43.7, 38.6, 37.8, 33.5, 32.9, 26.0, 18.4, -4.4, -7.1; MS (EI) *m/z* (rel. intensity) 445 (M^{+}, 0.5), 430 (0.6), 414 (1), 388 (30), 344 (100), 270 (15), 20 (10), 91 (75); HRMS *m/z* calculated for $C_{24}H_{35}NO_5Si$ 445.2285, found 445.2288.

6-(*tert*-Butyldimethylsilanyloxy)-2*S*,3,3a*R*,6,7,7a*R*-hexahydroindole-2-carboxylic acid methyl ester (13). A suspension of triethylsilane (0.33 mL, 2.0 mmol), palladium (II) acetate (10 mg, 0.044 mmol) and triethylamine (12 μL, 0.088 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature for 15 min. To this black solution was added a solution of the silyl ether (410 mg, 0.93 mmol) in CH_2Cl_2 (5 mL). The resulting mixture was stirred at room temperature for 15 h and quenched with saturated aqueous $NaHCO_3$ (10 mL). The mixture was vigorously stirred for 3 h, and the product was extracted into EtOAc (3 x 30 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 4:1 with 0.5% NEt_3) to give 260 mg (90%) of **13** as a colorless oil: $[\alpha]_D$ –77.2 (*c* 1.00, $CHCl_3$, 21 °C); IR (neat) 2916, 2843, 1725, 1483, 1307, 1244, 1203, 1080, 1030, 860 cm^{-1}; ^{1}H NMR δ 5.82 (d, 1 H, *J* = 9.8 Hz), 5.54 (d, 1 H, *J* = 9.8 Hz), 4.46 (bs, 1 H), 3.96 (t, 1 H, *J* = 8.3 Hz), 3.75 (s, 3 H), 2.76 (dt, 1 H, *J* = 10.0, 2.6 Hz), 2.49-2.40 (m, 2 H), 2.24 (bs, 2 H), 1.66-1.43 (m, 2 H); ^{13}C NMR δ 176.3, 132.6, 127.3, 69.6, 60.4, 57.9, 52.3, 44.0, 39.1, 34.3, 26.0, 25.9, 18.3, -4.6; MS (EI) *m/z* (rel. intensity) 311 (M^{+}, 5), 296 (7), 252 (100), 197 (65), 179 (60), 120 (65); HRMS *m/z* calculated for $C_{16}H_{29}NO_5Si$ 311.1916, found 311.1911.

6-(*tert*-Butyldimethylsilanyloxy)-1-(3-phenylallyl)-2*S*,3,3a*R*,6*S*,7,7a*R*-hexahydro-1*H*-indole-2-carboxylic acid methyl ester. To a solution of **13** (6.26 g, 20.1 mmol) in toluene (250 mL) was added K_2CO_3 (8.42 g, 60.3 mmol) and cinnamyl bromide (12.2 g, 60.3 mmol). This mixture was heated to 60 °C and stirred for 15 h. At this time, the reaction mixture was cooled to room temperature and diluted with ether (250 mL). The etherial layer was washed with water and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 95:5 to 9:1) to give 8.20 g (96%) of the tertiary amine as a colorless oil: $[\alpha]_D$ –72.2 (*c* 0.50, $CHCl_3$, 21 °C); IR (neat) 2922, 1720, 1444, 1242, 1184, 1072, 958, 858, 769 cm^{-1}; ^{1}H NMR δ 7.36-7.22 (m, 5 H), 6.50 (d, 1 H, *J* = 15.9 Hz), 6.26-6.21 (m, 1 H), 5.82 (d, 1 H, *J* = 9.8 Hz), 5.54 (d, 1 H, *J* = 9.7 Hz), 4.50 (bs, 1 H), 3.90 (bt, 1 H, *J* = 6.7 Hz), 3.65 (s, 3 H), 3.50 (d, 2 H, *J* = 4.4 Hz), 2.88 (t, 1 H, *J* = 10.5 Hz), 2.52-2.39 (m, 3 H), 1.55 (t, 2 H, *J* = 8.2 Hz), 0.90 (s, 9 H), 0.08 (s, 3 H); ^{13}C NMR δ 175.0, 137.1, 132.4, 132.2, 128.6, 128.1, 127.8, 127.5, 126.4, 69.9, 63.9, 62.6, 51.7, 51.1, 42.4, 37.3, 34.0, 26.0, 18.4, -4.3, -4.5; MS (EI) *m/z* (rel. intensity) 427 (M^{+}, 6), 368 (55), 341 (10), 117 (100), 91 (20), 75 (45); HRMS *m/z* calculated for $C_{25}H_{37}NO_5Si$ 427.2543, found 427.2542.

1-(3-Phenylallyl)-6-hydroxy-2*S*,3,3a*R*,6*S*,7,7a*R*-hexahydro-1*H*-indole-2-carboxylic acid methyl ester (14). To a 0 °C solution of the amine (9.7 g, 23 mmol) in THF (90 mL) was added a 1.0 M TBAF solution in THF (46 mL, 46 mmol). The reaction mixture was warmed to room temperature and stirred for 3 h. It was then diluted with EtOAc (300 mL) and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oil was purified by chromatography on SiO_2 (hexanes/EtOAc, 1:1 with 0.5% NEt_3) to give 6.9 g (96%) of **14** as a colorless oil: $[\alpha]_D$ –72.6 (*c* 0.35, $CHCl_3$, 21 °C); IR (neat) 3339 (br), 3001, 2922, 2853, 1716, 1442, 1340, 1190, 1016, 960, 742 cm^{-1}; ^{1}H NMR δ 7.32-7.18 (m, 5 H), 6.45 (d, 1 H, *J* = 15.7 Hz), 6.25-6.17 (m, 1 H), 5.85 (d, 1 H, *J* = 9.8 Hz), 5.59 (d, 1 H, *J* = 9.8 Hz), 4.45 (bs, 1 H), 3.90 (t, 1 H, *J* = 7.2 Hz), 3.60 (s, 3 H), 3.47 (d, 2 H), 2.85 (t, 1 H, *J* = 7.6 Hz), 2.60 (ddd, 1 H, *J* = 8.7, 2.6, 1.6 Hz), 2.40-2.33 (m, 2 H), 2.01 (bs, 1 H), 1.55-1.41 (m, 2 H); ^{13}C NMR δ 175.0, 137.2, 132.4, 131.4, 129.2, 128.7, 127.7, 127.6, 126.5, 69.1, 63.9, 62.5, 51.7, 50.9, 42.8, 37.5, 33.7; MS (EI) *m/z* (rel. intensity) 313 (M$^+$, 10), 295 (2), 254 (55), 227 (20), 117 (100), 91 (25); HRMS *m/z* calculated for $C_{19}H_{23}NO_5$ 313.1678, found 313.1675.

1-(3-Phenylallyl)-6-oxo-2*S*,3,3a*R*,6,7,7a*R*-hexahydro-1*H*-indole-2-carboxylic acid methyl ester. A solution of **14** (720 mg, 2.30 mmol) and 4-methylmorpholine N-oxide (297 mg, 2.53 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C and powdered 4 A molecular sieves (720 mg) was added followed by tetrapropylammonium perruthenate (16.0 mg, 46.0 mmol). The reaction mixture was allowed to warm to room temperature, stirred for 15 h, then filtered through a pad of SiO_2 (EtOAc), concentrated *in vacuo*, and purified by chromatography on SiO_2 (hexanes/EtOAc, 2:1) to give 630 mg (88%) of the enone as a white solid: Mp 85-87 °C (hexanes/EtOAc); $[\alpha]_D$ –108.2 (*c* 0.50, $CHCl_3$, 21 °C); IR (neat) 2936, 1705, 1655, 1419, 1334, 1170, 1076, 956 cm^{-1}; ^{1}H NMR δ 7.36-7.23 (m, 5 H), 7.03 (d, 1 H, *J* = 9.8 Hz), 6.49 (d, 1 H, *J* = 15.9 Hz), 6.24-6.17 (m, 1 H), 6.01 (dd, 1 H, *J* = 9.8, 2.5 Hz), 4.06 (t, 1 H, *J* = 7.0 Hz), 3.66 (s, 3 H), 3.53-3.41 (m, 2 H), 3.34 (dt, 1 H, *J* = 9.5, 3.7 Hz), 2.97 (dd, 1 H, *J* = 16.0, 3.8 Hz), 2.70-2.55 (m, 2 H), 2.27 (t, 1 H, *J* = 13.6 Hz), 1.77 (m, 1 H); ^{13}C NMR δ 198.9, 174.5, 149.3, 137.0, 132.7, 130.9, 128.8, 127.8, 126.5, 64.3, 62.3, 51.8, 44.8, 43.2, 32.3; MS (EI) *m/z* (rel. intensity) 311 (M$^+$, 30), 252 (50), 225 (30), 117 (100), 91 (15); HRMS *m/z* calculated for $C_{19}H_{21}NO_5$ 311.1521, found 311.1515.

7-Allyl-1-(3-phenylallyl)-6-oxo-2*S*,3,3a*R*,6,7,7a*R*-hexahydro-1*H*-indole-2-carboxylic acid methyl ester (15). A solution of the enone (3.6 g, 12 mmol) in THF (40 mL) was added to a –90 °C solution of solid KHMDS (3.8 g, 20 mmol) in THF (100 mL). After stirring at –90 °C for 5 min, allyl iodide (13 mL, 120 mmol) was added dropwise over a few minutes. The solution was stirred at –90 °C for an additional 30 min and quenched with EtOAc and saturated aqueous $NaHCO_3$. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 4:1) to give 2.7 g (66%) of **15** as a yellow oil: $[\alpha]_D$ –162.2 (*c* 1.00, $CHCl_3$, 21 °C); IR (neat) 2922, 1716, 1655, 1437, 1344, 1188, 970, 910 cm^{-1}; ^{1}H NMR δ 7.34-7.19 (m, 5 H), 6.92 (d, 1 H, *J* = 10.6 Hz), 6.47 (d, 1 H, *J* = 15.8 Hz), 6.21-6.14 (m, 1 H), 5.92 (d, 1 H, *J* = 10.6 Hz), 5.88-5.79 (m, 1 H), 5.05-4.95 (m, 2 H), 4.07 (t, 1 H, *J* = 7.2 Hz), 3.63 (s, 3 H), 3.50-3.31 (m, 3 H), 2.81-2.78 (m, 2 H), 2.58-2.47 (m, 2 H), 2.13-2.02 (m, 1 H), 1.77-1.71 (m, 1 H); ^{13}C NMR δ 200.8, 174.5, 148.3, 137.0, 135.7, 132.6, 129.8, 128.7, 127.7, 126.8, 126.5, 116.8, 66.3, 61.4, 51.7, 49.8, 49.3, 37.6, 32.1, 27.3; MS (EI) *m/z* (rel. intensity) 351 (M$^+$, 25), 292 (20), 117 (100), 91 (20); HRMS *m/z* calculated for $C_{22}H_{25}NO_5$ 351.1834, found 351.1830.

7-Allyl-1-(3-phenyallyl)-6-hydroxy-2*S*,3,3a*R*,*6S*,7,7a*R*-hexahydro-1*H*-indole-2-carboxylic acid methyl ester (16). To a solution of **15** (1.0 g, 2.8 mmol) in THF (16 mL) was added a solution of cerium (III) chloride heptahydrate (1.0 g, 2.8 mmol) in MeOH (16 mL). After stirring for 5 min at room temperature, the solution was cooled to

0 °C and sodium borohydride (110 mg, 2.8 mmol) was added in 3 portions over a 5 min period. The resulting mixture was allowed to warm to room temperature and stirred for 1.5 h. The reaction mixture was quenched with water (100 mL), and the product was extracted into EtOAc (3 x 100 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 4:1) to give 860 mg (87%) of **16** as a white solid: Mp 80-82 °C (hexanes/EtOAc); $[\alpha]_D$ –111.2 (*c* 0.50, $CHCl_3$, 21 °C); IR (neat) 3399 (br), 2872, 1720, 1421, 1344, 1190, 1066, 1026, 960 cm^{-1}; ^1H NMR δ 7.37-7.20 (m, 5 H), 6.48 (d, 1 H, *J* = 15.9 Hz), 6.25-6.15 (m, 1 H), 6.07-5.95 (m, 1 H), 5.77 (d, 1 H, *J* = 9.9 Hz), 5.56 (d, 1H, *J* = 9.9 Hz), 5.10 (d, 1 H, *J* = 17.1 Hz), 4.97 (d, 1 H, *J* = 10.2 Hz), 4.55 (bs, 1 H), 4.01 (t, 1 H, *J* = 7.0 Hz), 3.63 (s, 3 H), 3.58 (dd, 1 H, *J* = 13.4, 5.0 Hz), 3.38 (dd, 1 H, *J* = 13.5, 7.8 Hz), 2.96 (dd, 1 H, *J* = 9.5, 2.7 Hz), 2.59-2.54 (m, 1 H), 2.44-2.31 (m, 3 H), 2.16-2.06 (m, 1 H), 2.00 (d, 1 H, *J* = 6.8 Hz), 1.60-1.48 (m, 1 H); ^{13}C NMR δ 175.0, 140.5, 137.2, 132.0, 131.1, 128.7, 127.8, 127.6, 127.5, 126.4, 115.3, 72.5, 65.7, 61.2, 51.5, 49.5, 40.3, 37.3, 33.1, 26.9; MS (EI) *m/z* (rel. intensity) 353 (M^+, 65), 336 (40), 294 (100), 214 (35), 133 (80), 117 (80), 105 (65), 91 (90); HRMS *m/z* calculated for $C_{22}H_{27}NO_5$ 353.1991, found 353.1992.

7-Allyl-4-dimethylcarboylmethyl-1-(3-phenylallyl)-(2*S*,3,3a*R*,4*R*,7*S*,7a*R*)-hexahydro-1*H*-indole-2-carboxylic acid methyl ester. A solution of **16** (0.20 g, 0.57 mmol) and *N,N*-dimethylacetamide dimethylacetal (0.70 mL, 4.6 mmol) in xylenes (15 mL) was heated at 130 °C for 19 h. The mixture was cooled to room temperature, concentrated *in vacuo*, and purified by chromatography on SiO_2 (hexanes/EtOAc, 1:1) to give 0.24 g (98%) of the dimethylamide as a yellow oil: $[\alpha]_D$ –99.8 (*c* 0.50, $CHCl_3$, 21 °C); IR (neat) 2874, 1699, 1610, 1466, 1415, 1375, 1149 cm^{-1}; ^1H NMR δ 7.36-7.19 (m, 5 H), 6.49 (d, 1 H, *J* = 15.9 Hz), 6.27-6.18 (m, 1 H), 5.92-5.78 (m, 2 H), 5.59 (d, 1 H, *J* = 9.8 Hz), 5.09-4.99 (m, 2 H), 4.00 (dd, 1 H, *J* = 9.1, 5.5 Hz), 3.63 (s, 3 H), 3.53 (ddd, 1 H, *J* = 14.0, 4.9, 1.4 Hz), 3.36 (dd, 1 H, *J* = 14.0, 8.2 Hz), 3.13 (dd, 1 H, *J* = 10.2, 5.1 Hz), 3.03 (s, 3 H), 2.96 (s, 3 H), 2.70-2.61 (m, 1 H), 2.50-2.34 (m, 4 H), 2.26 (dd, 1 H, *J* = 15.0, 8.6 Hz), 1.84-1.68 (m, 1 H), 1.67-1.57 (m, 2 H); ^{13}C NMR δ 175.1, 171.7, 137.5, 137.2, 132.2., 131.0, 130.4, 128.7, 127.5, 127.4, 126.4, 115.8, 64.8, 61.3, 51.4, 49.4, 40.5, 40.4, 38.0, 37.7, 37.4, 35.7, 33.6, 33.4; MS (EI) *m/z* (rel. intensity) 422 (M^+, 40), 363 (60), 336 (10), 247 (10), 117 (100), 91 (25); HRMS *m/z* calculated for $C_{26}H_{34}N_2O_5$ 422.2569, found 422.2559.

7-Allyl-4-dimethylcarboylmethyl-1-(3-phenylallyl)-(2*S*,3,3a*R*,4*R*,7*S*,7a*R*)-hexahydro-1*H*-indole-2-carboxylic acid methoxymethylamide (17). To a 0 °C suspension of *N,O*-dimethylhydroxyamine hydrochloride (92.3 mg, 0.946 mmol) in CH_2Cl_2 (5 mL) was added a 1.0 M dimethylaluminum chloride solution in hexanes (0.946 mL, 0.946 mmol). The mixture was allowed to warm to room temperature and stirred for 1 h. To this solution was added a solution of the dimethylamide (50.0 mg, 0.118 mmol) in CH_2Cl_2 (1 mL), and the solution was stirred at room temperature for 20 h. The reaction mixture was quenched with an aqueous 10% NaOH solution and the product was extracted into EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), concentrated *in vacuo*, and purified by chromatography on SiO_2 (CH_2Cl_2/MeOH, 50:1) to give 41.0 mg (77%) of **17** as a colorless oil: $[\alpha]_D$ -80.8 (*c* 0.53, $CHCl_3$, 21 °C); IR (neat) 2932, 1647, 1494, 1459, 1410, 1181, 1137, 744 cm^{-1}; ^1H NMR δ 7.33-7.18 (m, 5 H), 6.51 (d, 1 H, *J* = 15.8 Hz), 6.29-6.19 (m, 1 H), 5.93-5.75 (m, 2 H), 5.56 (d, 1 H, *J* = 9.8 Hz), 5.00 (dd, 2 H, *J* = 17.2, 10.0 Hz), 3.57-3.41 (m, 2 H), 3.41 (bs, 3 H), 3.24 (dd, 1 H, *J* = 10.4, 5.0 Hz), 3.07 (s, 3 H), 3.00 (s, 3 H), 2.93 (s, 3 H), 2.58 (m, 1 H), 2.38 (m, 4 H), 2.24 (dd, 1 H, *J* = 14.6, 8.7 Hz), 1.86-1.61 (m, 2 H), 1.54-1.44 (m, 1 H); ^{13}C NMR δ 175.6, 171.8, 137.7, 137.3, 132.1, 130.7, 130.5, 128.6, 128.2, 127.4, 126.3, 115.7, 65.1, 61.4, 56.6, 48.9, 40.7, 38.3, 37.8, 35.6, 33.7, 33.6, 32.1; MS (EI) *m/z* (rel. intensity) 451 (M^+, 4), 420 (10), 363 (23), 334 (5), 117 (100), 91 (25); HRMS *m/z* calculated for $C_{27}H_{37}N_3O_3$ 451.2834, found 451.2834.

1-[2-Bromo-(1*S*)-methyl-ethyl]-5-methyl-2,7,8-trioxa-bicyclo[3.2.1] octane (18). To a –30 °C solution of 3-bromo-2*S*-methyl-propionic acid 2-(2-methyl-oxiranyl)-ethyl ester (5.0 g, 20 mmol) in CH_2Cl_2 (150 mL) was added zirconocene dichloride (0.60 g, 2.0 mmol) and silver perchlorate (50 mg, 0.20 mmol). The reaction mixture was stirred at –30 °C for 1 h and quenched with saturated aqueous $NaHCO_3$ (200 mL). The product was extracted into ether (3 x 100 mL), and the organic layer was washed with saturated $NaHCO_3$ and brine, dried (K_2CO_3), and concentrated *in vacuo* to give 4.7 g (95%) of **18** as a colorless oil. The crude product was used without purification for subsequent transformations.

7-Allyl-4-[2-oxo-4-(2*S*,7,8-trioxa-bicyclo[3.2.1]oct-1-yl)-pentyl]-1-(3-phenylallyl)-2*S*,3,3a*R*,4,7*S*,7a*R*-hexahydro-1*H*-indole-2-carboxylic acid methoxymethyl-amide (19). To a solution of naphthalene (51 mg, 0.40 mmol) in THF (5 mL) was added lithium wire (2.8 mg, 0.40 mmol). The dark green mixture was stirred at room temperature for 6 h, cooled to –78 °C, and a solution of bromo-orthoester **18** (0.050 g, 0.20 mmol) in THF (0.5 mL) was added. The resulting red-brown suspension was stirred at –78 °C for 1 h and treated with a solution of **17** (0.020 g, 0.040 mmol) in THF (0.5 mL). The reaction mixture was stirred at –78 °C for an additional 15 h, diluted with ether (50 mL), and the organic layer was washed with water and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 2:1 to 1:2) to give 11.5 mg (42%) of recovered **17** and 8.4 mg (36%) of **19** as a clear, colorless oil: ^1H NMR δ 7.35-7.18 (m, 5 H), 6.52 (d, 1 H, *J* = 15.9 Hz), 6.323-6.19 (m, 1 H), 5.91-5.75 (m, 2 H), 5.49 (d, 1 H, *J* = 9.9 Hz), 5.08-4.99 (m, 2 H), 4.41 (bs, 1 H), 4.08-4.00 (m, 3 H), 3.99-3.75 (m, 2 H), 3.61-3.45 (m, 4 H), 3.44 (s, 3 H), 3.27-3.19 (m, 1 H), 3.09 (s, 3 H), 2.81-2.69 (m, 1 H), 2.55-2.29 (m, 5 H), 2.09-1.95 (m, 2 H), 1.87-1.35 (m, 3 H), 1.40 (s, 1.5 H), 1.36 (s, 1.5 H), 1.01 (d, 3 H, *J* = 6.8 Hz).

7-Allyl-6-(*tert*-butyldimethylsilanyloxy)-1-(3-phenylallyl)-(2*S*,3,3a*R*,6*S*,7*S*,7a*R*)-hexahydro-1*H*-indole-2-carboxylic acid methyl ester. To a 0 °C solution of **16** (1.6 g, 4.5 mmol) in CH_2Cl_2 (30 mL) was added TBSCl (830 mg, 5.4 mmol), imidazole (380 mg, 5.9 mmol), and dimethylaminopyridine (54 mg, 0.45 mmol). The reaction mixture was warmed to room temperature, stirred for 19 h, poured into water (100 mL), and the product was extracted into ether (3 x 100 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 95:5) to give 1.9 g (91%) of the silyl ether as a colorless oil: $[\alpha]_D$ –96.7 (*c* 0.33, $CHCl_3$, 21 °C); IR (neat) 3021, 2950, 2930, 2884, 2858, 1731, 1634, 1347, 1194, 1081 cm^{-1}; ^1H NMR δ 7.39-7.23 (m, 5 H), 6.48 (d, 1 H, *J* = 15.9 Hz), 6.31-6.09 (m, 2 H), 5.73 (d, 1 H, *J* = 9.9 Hz), 5.46 (d, 1 H, *J* = 9.9 Hz), 5.02 (d, 1 H, *J* = 17.2 Hz), 4.91 (d, 1 H, *J* = 8.0 Hz), 4.54 (bs, 1 H), 4.02 (t, 1 H, *J* = 7.8 Hz), 3.75-3.65 (m, 1 H), 3.63 (s, 3 H), 3.45-3.35 (m, 1 H), 3.00 (d, 1 H, *J* = 9.4 Hz), 2.45-2.08 (m, 5 H), 1.60-1.50 (m, 1 H), 0.95 (s, 9 H), 0.18 (s, 6 H); ^{13}C NMR δ 175.1, 140.5, 137.4, 132.1, 128.6, 127.7, 127.4, 127.0, 126.4, 114.2, 72.1, 65.9, 60.7, 51.4, 49.1, 42.1, 37.2, 33.3, 27.2, 26.2, 26.1, 18.5, -4.4, -4.6; MS (EI) *m/z* (rel. intensity) 467 (M^+, 14), 408 (17), 336 (8), 117 (100), 91 (9), 75 (23); HRMS *m/z* calculated for $C_{28}H_{41}NO_5Si$ 467.2886, found 467.2858.

7-Allyl-6-(*tert*-butyldimethylsilanyloxy)-1-(3-phenylallyl)-(2*S*,3,3a*R*,6*S*,7*S*,7a*R*)-hexahydro-1*H*-indole-2-carboxylic acid methoxymethyl amide (20). To a 0 °C suspension of *N,O*-dimethylhydroxylamine hydrochloride (1.73 g, 18.0 mmol) in CH_2Cl_2 (85 mL) was added a 1.0 M solution of dimethylaluminum chloride in hexane (18.0 mL, 18.0 mmol). This mixture was warmed to room temperature and stirred for 1 h. At this time, a solution of the silyl ether (1.92 g, 4.10 mmol) in CH_2Cl_2 (30 mL) was added, and the resulting mixture was stirred at room temperature for an additional 19 h. The reaction mixture was quenched (slowly) with an aqueous 10% NaOH solution (50 mL), and the product was extracted into EtOAc (3 x 100 mL). The combined organic layers were washed with brine, dried (MgSO4), concentrated *in vacuo*, and purified by chromatography on SiO_2 (hexanes/EtOAc, 4:1) to give 1.98 g (97%) of **20** as a pale yellow oil: $[\alpha]_D$ –70.0 (*c* 0.30, $CHCl_3$, 21 °C); IR (neat) 3058, 3027, 2960, 2925, 2853, 2665, 1465, 1378, 1255, 1081, 1004 cm^{-1}; ^1H NMR δ 7.34-7.18 (m, 5 H), 6.50 (d, 1 H, *J* = 15.8 Hz), 6.24-6.08 (m, 2 H), 5.70 (d, 1 H, *J* = 9.9 Hz), 5.41 (d, 1 H, *J* = 9.9 Hz), 5.03 (d, 1 H, *J* = 10.9 Hz), 4.87 (dd, 1 H, *J* = 9.9, 1.0 Hz), 4.55-4.40 (m, 2 H), 3.70-3.40 (m, 2 H), 3.43 (s, 3 H), 3.11-3.06 (m, 1 H), 3.08 (s, 3 H), 2.40-2.14 (m, 5 H), 1.59-1.40 (m, 1 H), 0.92 (s, 9 H), 0.08 (s, 6 H); ^{13}C NMR δ 175.3, 140.5, 137.2, 131.8, 128.4, 128.2, 127.1, 126.9, 126.1, 113.8, 71.9, 65.9, 61.2, 56.0, 48.4, 41.9, 37.1, 33.0, 31.9, 26.9, 25.9, 18.3, -4.6, -5.0; MS (EI) *m/z* (rel. intensity) 496 (M^+, 29), 465 (10), 408 (7), 158 (6), 117 (100), 91 (17), 75 (38); HRMS *m/z* calculated for $C_{29}H_{44}N_2O_5Si$ 496.3121, found 496.3137.

1-[7-Allyl-6-(*tert*-butyldimethylsilanyloxy)-1-(3-phenylallyl)-2*S*,3,3a*R*,6*S*,7*S*,7a*R*-hexahydro-1*H*-indol-2-yl]-3-(2,7,8-trioxabicyclo[3.2.1]oct-1-yl)-butan-1-one (21). To a solution of naphthalene (2.56 g, 20.0 mmol, 10 eq) in THF (35 mL) was added lithium wire (0.120 g, 17.0 mmol, 8.5 eq). The dark green mixture was stirred at room temperature for 17 h, cooled to –78 °C, and a solution of bromo-orthoester **18** (1.70 g, 6.8 mmol) in THF (7 mL) was added. The resulting red-brown suspension was stirred at –78 °C for 3 h. At this time, a solution of **20** (1.00 g, 2.00 mmol) in THF (3 mL) was added, and the mixture was stirred at –78 °C for an additional 5 min. The reaction mixture was then diluted with ether (50 mL) and the organic layer was washed with water and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 9:1) to give 916 mg (76%) of **21** as a clear, colorless oil: $[\alpha]_D$ –94.8 (*c* 0.80, $CHCl_3$, 21 °C); IR (neat) 3027, 2955, 2930, 2884, 1706, 1634, 1470, 1260, 1076 cm^{-1}; ^1H NMR δ 7.37-7.20 (m, 5 H), 6.44 (d, 1 H, *J* = 15.9 Hz), 6.19-5.99 (m, 2 H), 5.69 (d, 1 H, *J* = 9.9 Hz), 5.42 (d, 1 H, *J* = 9.9 Hz), 4.98 (d, 1 H, *J* = 17.0 Hz), 4.88 (d, 1 H, *J* = 9.9 Hz), 4.50 (bs, 1 H), 4.11 (bt, 1 H, *J* = 7.4 Hz), 4.00-3.89 (m, 2 H), 3.79-3.71 (m, 1 H), 3.60-3.43 (m, 2 H), 3.30 (dt, 1 H, *J* = 7.0, 1.9 Hz), 3.00 (d, 1 H, *J* = 9.9 Hz), 2.70 (t, 1 H, *J* = 15.9 Hz), 2.51-2.18 (m, 1 H), 2.00-1.85 (m, 1 H), 1.41-1.23 (m, 7 H), 0.97-0.89 (m, 9 H), 0.09 (s, 6 H); ^{13}C NMR δ 212.0, 140.6, 137.4, 132.4, 132.1, 128.6, 128.4, 128.2, 127.3, 126.6, 126.4, 121.8, 114.1, 78.7, 73.8, 72.1, 66.0, 64.9, 59.1, 48.4, 44.5, 44.3, 42.1, 37.6, 33.9, 33.2, 32.5, 27.1, 26.2, 22.0, 18.5, 15.4, 14.4, -4.4, -4.7; MS (EI) *m/z* (rel. intensity) 607 (M^+, 1), 595 (1), 550 (2), 490 (2), 408 (100), 117 (72); HRMS *m/z* calculated for $C_{36}H_{53}NO_5Si$ 607.3693, found 607.3697.

(5S)-[7-Allyl-6-hydroxy-1-(3-phenylallyl)-(2*S*,3,3a*R*,6*S*,7*S*,7a*R*)-hexahydro-1*H*-indol-2-yl]-3-methyldihydro-furan-2-one (22). To a –78 °C solution of **21** (190 mg, 0.31 mmol) in THF (10 mL) was added dropwise a 1.0 M solution of L-Selectride in THF (0.50 mL, 0.50 mmol). The reaction was stirred at –78 °C for 1 h, warmed to 0 °C, stirred for 15 h, and quenched with 10% aqueous ethanolamine (10 mL). The product was extracted into ether (2 x 25 mL). The organic layers were washed with brine, dried

($MgSO_4$), and concentrated *in vacuo*. The resulting residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 9:1 to 4:1) to give 160 mg (84%) of 2 alcohols as colorless oils. A solution of those alcohols (130 mg, 0.21 mmol) in MeOH (10 mL) was treated with *p*-toluenesulfonic acid monohydrate (0.080 g, 0.42 mmol), stirred at room temperature for 20 h, and quenched with saturated aqueous $NaHCO_3$ (10 mL). The product was extracted into EtOAc (3 x 25 mL), and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting oil was purified by chromatography on SiO_2 (hexanes/EtOAc, 1:1) to give 59 mg (71%) of the major isomer **22** as a light yellow oil: $[\alpha]_D$ –25.3 (*c* 0.27, $CHCl_3$, 21 °C); IR (neat) 3462 (br), 2966, 2930, 2868, 1767, 1445, 1194, 1009, 748 cm^{-1}; ^{1}H NMR δ 7.39-7.20 (m, 5 H), 6.58 (d, 1 H, *J* = 15.9 Hz), 6.29 (dt, 1 H, *J* = 13.1, 2.7 Hz), 6.05-5.91 (m, 1 H), 5.77 (dd, 1 H, *J* = 9.8, 1.4 Hz), 5.55 (dd, 1 H, *J* = 9.8, 1.9 Hz), 5,11 (d, 1 H, *J* = 16.9 Hz), 4.97 (d, 1 H, *J* = 9.8 Hz), 4.49-4.36 (m, 2 H), 3.80 (dd, 1 H, *J* = 15.5, 6.0 Hz), 3.62-3.48 (m, 2 H), 2.64-2.56 (m, 2 H), 2.43-2.32 (m, 3 H), 2.19-2.07 (m, 2 H), 1.88 (d, 1 H, *J* = 6.2 Hz), 1.46 (dd, 1 H, *J* = 23.0, 12.2 Hz), 1.27 (d, 3 H, *J* = 7.0 Hz), 1.08-0.95 (m, 2 H); ^{13}C NMR δ 179.6, 140.5, 137.5, 131.3, 131.2, 129.0, 128.6, 127.7, 127.3, 126.5, 115.2, 79.0, 72.3, 65.8, 64.1, 48.8, 40.3, 36.8, 34.9, 30.8, 27.3, 15.0; MS (EI) *m/z* (rel. intensity) 393 (M$^+$, 5), 376 (5), 294 (26), 117 (100), 91 (14); HRMS *m/z* calculated for $C_{25}H_{31}NO_5$ 393.2304, found 393.2311.

2-[7-Allyl-2-((4*S*)-methyl-5-oxotetrahydrofuran-2-yl)-1-(3-phenylallyl)-(2*S*,3,3a*R*,4*R*,7*S*,7a*R*)-hexahydro-1*H*-indol-4-yl]-*N*,*N*-dimethylacetamide (23). To a solution of **22** (56 mg, 0.14 mmol) in xylenes (3 mL) was added *N,N*-dimethylacetamide dimethylacetal (0.17 mL, 1.1 mmol). The reaction was heated to 130 °C, stirred for 16 h, cooled to room temperature, concentrated *in vacuo*, and purified by chromatography on SiO_2 (hexanes/EtOAc, 1:4) to give 47 mg (79%) of **23** as a yellow foam: $[\alpha]_D$ –25.0 (*c* 0.20, $CHCl_3$, 21 °C); IR (neat) 3022, 2925, 1772, 1644, 1496, 1393, 1173, 917 cm^{-1}; ^{1}H NMR δ 7.37-7.17 (m, 5 H), 6.60 (d, 1 H, *J* = 15.8 Hz), 6.35-6.33 (m, 1 H), 5.82-5.73 (m, 2 H), 5.53 (d, 1 H, *J* = 9.9 Hz), 5.02 (d, 1 H, *J* = 16.5 Hz), 4.97 (d, 1 H, *J* = 9.8 Hz), 4.50-4.40 (m, 1 H), 3.62-3.57 (m, 3 H), 2.98 (s, 3 H), 2.93 (s, 3 H), 2.80 (dd, 1 H, *J* = 10.3, 5.0 Hz), 2.60-2.10 (m, 8 H), 1.87-1.70 (m, 1 H), 1.70-1.52 (m, 1 H), 1.50-1.28 (m, 1 H), 1.25 (d, 3 H, *J* = 7.0 Hz), 1.10-1.00 (m, 1 H); ^{13}C NMR δ 179.5, 171.7, 137.5, 131.5, 130.8, 130.6, 128.6, 127.2, 126.4, 115.8, 78.8, 64.8, 63.5, 48.3, 40.2, 40.0, 37.6, 35.6, 35.2, 35.0, 33.8, 30.9, 15.0, 14.3; MS (EI) *m/z* (rel. intensity) 462 (M$^+$, 10), 363 (46), 184 (6), 117 (100), 91 (14), 72 (15); HRMS *m/z* calculated for $C_{29}H_{38}N_2O_5$ 462.2882, found 462.2893.

***N*,*N*-Dimethyl-2-[2-((4*S*)–methyl-5-oxotetrahydrofuran-2-yl)-(1,2*S*,3a*R*,4*R*,7*S*,7a*R*,10,10a,10b-octahydroazepino[3,2,1-*hi*]indol-10-yl]acetamide (24).** To a solution of **23** (53 mg, 0.11 mmol) in benzene (8.5 mL) was added bis(tricyclohexylphosphine)benzylidene ruthenium(IV) chloride (Grubbs catalyst) (9.0 mg, 0.010 mmol). The reaction mixture was heated to 60 °C and stirred at that temperature for 24 h. At that time another batch of Grubbs catalyst (9.0 mg, 0.010 mmol) was added, and the mixture was stirred for an additional 16 h, cooled to room temperature and stirred open to air for 2 h. The brown solution was concentrated *in vacuo* and purified by chromatography on SiO_2 (EtOAc) to give 0.010 g (21%) of recovered **23** and 24 mg (61%) of **24** as a yellow foam: IR (neat) 3014, 2927, 1766, 1640, 1453, 1394, 1172, 1018 cm^{-1}; ^{1}H NMR δ 5.70-5.50 (m, 4 H), 4.50-4.20 (m, 1 H), 3.93 (dd, 1 H, *J* = 12.7, 4.9 Hz), 3.43-3.39 (m, 2 H), 3.02 (s, 3 H), 2.96 (s, 3 H), 2.80-2.70 (m, 1 H), 2.63-2.55 (m, 3 H), 2.50-2.20 (m, 5 H), 1.95-1.80 (m, 1 H), 1.50-1.30 (m, 2 H), 1.25 (d, 3 H, *J* = 6.7 Hz), 1.20-1.10 (m, 1 H); ^{13}C NMR δ 179.8, 171.7, 131.2, 130.5, 130.1, 128.5, 78.3, 64.6, 64.3, 48.2, 41.0, 40.3, 38.7, 37.5, 37.2, 35.6, 35.0, 34.8, 30.4, 29.2, 14.9; MS (EI) *m/z* (rel. intensity) 357 ($[M-1]^+$, 6), 259 (100), 198 (11), 190 (23), 167 (57), 117 (39), 91 (13), 72 (13), 55 (15); HRMS *m/z* calculated for $C_{21}H_{29}N_2O_5$(M-H) 357.2178, found 357.2196.

7-([4*S*]-Methyl-5-oxo-tetrahydrofuran-2*S*-yl)-4-phenylselenyl-(1a*R*,3a*S*,4*R*,5*R*,5a*R*,8a*R*)-decahydro-3-oxo-6-azepino[3,2,1-*hi*]-indacen-2-one (25). To a -78 °C solution of **24** (16 mg, 0.040 mmol) in CH_2Cl_2 (0.45 mL) was added phenylselenenyl chloride (13 mg, 0.060 mmol). The reaction mixture was stirred at -78 °C for 2 h, quenched with an aqueous saturated $NaHCO_3$ solution (1 mL) and allowed to warm to room temperature. The product was extracted into $CHCl_3$ (2 x 5 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 2:1 to 0:1) to give 4.0 mg (20%) of **25** as a yellow oil: MS (EI) *m/z* (rel. intensity) 388 ($[M-C_5H_6O_2]^+$, 8), 324 (8), 232 (9), 158 (43), 137 (44), 121 (100), 78 (93); HRMS *m/z* calculated for $C_{20}H_{22}NO_2Se$ (M - $C_5H_6O_2$) 388.0816, found 388.0780.

8-Oxo-1,2*S*,4,7,7a*S*,8,10a*R*,10b*S*-octahydro-azepino[3,2,1-*hi*]indole-2-carboxylic acid methyl ester (30). To a solution of **15** (220 mg, 0.62 mmol) in CH_2Cl_2 (16 mL) was added ruthenium catalyst **32** (28 mg, 0.032 mmol). The reaction was heated at reflux for 2 h, filtered through a pad of SiO_2 (EtOAc), concentrated *in vacuo*, and purified on SiO_2 (hexanes/EtOAc, 4:1 to 2:1) to give 140 mg (92%) of **30** as a tan solid: Mp 96-100 °C (hexanes/EtOAc); $[\alpha]_D$ +6.6 (*c* 1.30, $CHCl_3$, 21 °C); IR (neat) 3018, 2947, 1731, 1663, 1430, 1196 cm^{-1}; ^1H NMR δ 6.98 (dd, 1 H, *J* = 5.8, 1.9 Hz), 5.97 (dd, 1 H, *J* = 9.7, 2.9 Hz), 5.81-5.72 (m, 1 H), 5.60-5.57 (m, 1 H), 4.00 (dd, 1 H, *J* = 8.4, 6.1 Hz), 3.70 (s, 3 H), 3.62-3.54 (m, 2 H), 3.31 (dd, 1 H, *J* = 17.6, 5.8 Hz), 2.92 (ddd, 1 H, *J* = 12.4, 7.1, 2.0 Hz), 2.70-2.54 (m, 3 H), 2.20 (dd, 1 H, *J* = 15.9, 8.1 Hz), 1.81 (dt, 1 H, *J* = 11.7, 5.8 Hz); ^{13}C NMR δ 200.9, 174.2, 148.3, 130.5, 129.1, 128.5, 65.0, 62.9, 51.5, 49.9, 47.2, 37.0, 31.9, 24.0; MS (EI) *m/z* (rel. intensity) 247 (M^+, 8), 188 (100), 145 (6), 117 (8), 79 (6); HRMS *m/z* calculated for $C_{14}H_{17}NO_5$ 247.1208, found 247.1211.

8-Oxo-1,2*S*,4,7,7a*S*,8,10a*R*,10b*S*-decahydroazepino[3,2,1-*hi*]indole-2-carboxylic acid methyl ester (34). To a solution of **30** (2.2 g, 8.9 mmol) in CH_2Cl_2 (80 mL) was added thiophenol (1.0 mL, 10.3 mmol) and triethylamine (190 μL, 1.4 mmol). The reaction mixture was stirred at room temperature for 3 h, concentrated *in vacuo*, and purified by chromatography on SiO_2 (CH_2Cl_2/MeOH, 1:0 to 9:1) to give 2.9 g (91%) of the thiophenol adduct **33** as a white solid that was dissolved in a 4:1 mixture of ethanol and CH_2Cl_2 (220 mL). Chlorotris(triphenylphosphine)rhodium(I) (1.5 g, 1.7 mmol) was added, and the mixture was hydrogenated at room temperature under 1 atm of hydrogen for 15 h. The crude mixture was concentrated *in vacuo* and dissolved in CH_2Cl_2 (220 mL). After addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (1.4 mL, 8.6 mmol), the solution was stirred at room temperature for 3.5 h and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 9:1 to 2:1) to give 1.8 g (89%) of **34** as a yellow oil: $[\alpha]_D$ –69.1 (*c* 0.18, $CHCl_3$, 21 °C); IR (neat) 2923, 2848, 1739, 1667, 1434, 1204 cm^{-1}; ^1H NMR δ 6.86 (dd, 1 H, *J* = 9.7, 1.6 Hz), 5.83 (dd, 1 H, *J* = 9.7, 2.8 Hz), 3.79 (t, 1 H, *J* = 7.9 Hz), 3.60 (s, 3 H), 3.44 (dd, 1 H, *J* = 10.1, 5.9 Hz), 2.85-2.74 (m, 2 H), 2.66-2.55 (m, 2 H), 2.43 (dt, 1 H, *J* = 11.7, 7.0 Hz), 1.83 (dt, 1 H, *J* = 13.4, 3.6 Hz), 1.72-1.47 (m, 4 H), 1.41-1.13 (m, 2 H); ^{13}C NMR δ 201.7, 174.5, 148.0, 130.3, 65.8, 63.6, 51.9, 51.6, 49.0, 38.3, 32.3, 29.5, 28.1, 25.7; MS (EI) *m/z* (rel. intensity) 249 (M^+, 3), 190 (100); HRMS *m/z* calculated for $C_{14}H_{19}NO_5$ 249.1365, found 249.1365.

8-(*tert*–Butyldimethylsilanyloxy)-1,2*S*,4,7,7a*S*,8,10a*R*,10b*S*-decahydro-azepino[3,2,1-*hi*]indole-2-carboxylic acid methyl ester (35). To a solution of **34** (1.2 g, 4.8 mmol) in THF (30 mL) was added a solution of cerium (III) chloride heptahydrate (1.8 g, 4.8 mmol) in MeOH (30 mL). After stirring for 5 min at room temperature, the mixture was cooled to 0 °C and sodium borohydride (190 mg, 4.8 mmol) was added portionwise. After stirring at 0 °C for 10 min, the reaction was quenched with brine and 1N HCl. The solution was then basified to pH>8 with saturated $NaHCO_3$ and extracted into EtOAc (3 x 30 mL) and CH_2Cl_2 (1 x 30 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* giving 850 mg (71%) of a crude solid that was dissolved in CH_2Cl_2 (22 mL). The solution was cooled to 0 °C and TBSCl (610 mg, 3.9 mmol), imidazole (280 mg, 4.4 mmol), and dimethylaminopyridine (42 mg, 0.34 mmol) were added. The mixture was warmed to room temperature and stirred for 14 h, diluted with EtOAc (75 mL) and washed with water and brine. The organic layer was dried ($MgSO_4$), concentrated *in vacuo*, and purified by chromatography on SiO_2 (hexanes/EtOAc, 4:1) to give 1.0 g (79%) of **35** as a colorless oil: $[\alpha]_D$ –62.9 (*c* 0.16, $CHCl_3$, 21 °C); IR (neat) 3022, 2954, 2923, 2855, 1747, 1457, 1251 cm^{-1}; ^1H NMR δ 5.64 (d, 1 H, *J* = 9.9 Hz), 5.35 (d, 1 H, *J* = 9.9 Hz), 4.46-4.44 (m, 1 H), 3.67 (s, 3 H), 3.61 (dd, 1 H, *J* = 10.4, 6.6 Hz), 3.10 (dd, 1 H, *J* = 10.8, 2.4 Hz), 2.95-2.90 (m, 2 H), 2.50-2.39 (m, 1 H), 2.32 (dt, 2 H, *J* = 11.2, 5.8 Hz), 2.06-2.02 (m, 1 H), 1.85 (dt, 1 H, *J* = 13.0, 3.1 Hz), 1.56 (q, 1 H, *J* = 11.1 Hz), 1.43-1.36 (m, 2 H), 1.24-1.09 (m, 2 H), 0.84 (s, 9 H), 0.00 (s, 6 H); ^{13}C NMR δ 175.0, 133.3, 126.0, 71.7, 67.1, 65.3, 52.5, 51.9, 42.1, 38.9, 34.2, 29.3, 25.8, 25.7, 22.4, 18.1, -5.0, -5.1; MS (EI) *m/z* (rel. intensity) 365 (M^+, 2), 306 (100), 231 (12), 172 (83), 130 (29), 73 (22); HRMS *m/z* calculated for $C_{18}H_{32}NOSi(M-CO_2CH_3)$ 306.2253, found 306.2255.

8-(*tert*-Butyldimethylsilanyloxy)-1,2*S*,4,7,7a*S*,8,10a*R*,10b*S*-decahydro-azepino[3,2,1-*hi*]indole-2-carboxylic acid methoxymethyl-amide. To a 0 °C suspension of *N,O*-dimethylhydroxylamine hydrochloride (908 mg, 9.44 mmol) in CH_2Cl_2 (40 mL) was added a 1.0 M solution of dimethylaluminum chloride in hexane (9.44 mL, 9.44 mmol). This mixture was warmed to room temperature, stirred for 1 h, then a solution of **35** (781 mg, 2.14 mmol) in CH_2Cl_2 (15 mL) was added. The reaction mixture was stirred at room temperature for 14 h, cooled in an ice bath, and quenched slowly with 10% aqueous NaOH (50 mL). The product was extracted into EtOAc (3 x 100 mL), and the combined organic layers were dried ($MgSO_4$), concentrated *in vacuo*, and purified on SiO_2 (hexanes/EtOAc, 1:1 to 2:3) to give 794 mg (94%) of the amide as a light yellow oil: $[\alpha]_D$ –55.0 (*c* 0.16, $CHCl_3$, 21 °C); IR (neat) 3022, 2931, 2851, 1671, 1461, 1255, 1089 cm^{-1}; ^1H NMR δ 5.72 (bd, 1 H, *J* = 9.9 Hz), 5.40 (bd, 1 H, *J* = 9.9 Hz), 4.54-4.50 (m, 1 H), 4.02 (dd, 1 H, *J* = 9.5, 6.7 Hz), 3.69 (s, 3 H), 3.21 (s, 3 H), 3.17-3.16 (m, 1 H), 2.86-2.79 (m, 1 H), 2.61-2.51 (m, 1 H), 2.41-2.29 (m, 2 H), 2.11-2.04 (m, 1 H), 1.90-1.85 (m, 1 H), 1.65-1.51 (m, 3 H), 1.37-1.18 (m, 2 H), 0.89 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR δ 175.5, 132.9, 126.3, 71.6, 66.8, 62.8, 61.1, 52.4, 41.9, 38.3, 33.7, 32.3, 28.6, 26.1, 25.6, 21.6, 17.9, -5.1, -5.2; MS (EI) *m/z* (rel. intensity) 393 ($[M-1]^+$, 0.3), 379 (1.5), 363 (13), 306 (100), 172 (27), 130 (6), 73 (18); HRMS *m/z* calculated for $C_{20}H_{35}N_2O_2Si$ $(M-OCH_3)$ 306.2253, found 306.2255.

1-[8-(*tert*-Butyldimethylsilanyloxy)-1,2*S*,4,5,6,7,7a*S*,8*S*,10a*R*,10b*S*-decahydroazepino[3,2,1-*hi*]indol-2-yl]-3*S*-(5*R*,*S*-methyl-2,7,8-trioxa-bicyclo[3.2.1]oct-1-yl)-butan-1-one (36). To a solution of 4,4'-di-*tert*-butylbiphenyl (4.85 g, 18.2 mmol) in THF (35 mL) were added small pieces of lithium wire (106 mg, 15.2 mmol). The reaction was cooled to –15 °C, and the blue-green solution stirred at that temperature for 20 h, cooled to –78 °C, and treated with a solution of orthoester **18**

(ca. 2.6 g, 10.4 mmol) in THF (5 mL) until it turned a deep red color. After stirring for 30 min at –78 °C, a solution of the Weinreb amide (1.00 g, 2.53 mmol) in THF (4 mL) was added. The reaction mixture was stirred at –78 °C for an additional 15 min and quenched with wet ether (50 mL). The organic layer was washed with water and brine, dried ($MgSO_4$), concentrated *in vacuo*, and purified by chromatography on SiO_2 (pretreated with 95:5 hexanes/EtOAc with 0.5% NEt_3) (hexanes/EtOAc, gradient elution from 95:5 to 4:1) to give 1.21 g (95%) of **36** as a light yellow oil: $[\alpha]_D$ -35.5 (*c* 0.20, $CHCl_3$, 21 °C); IR (neat) 2931, 1707, 1465, 1382, 1259, 1093 cm^{-1}; ^{1}H NMR δ 5.71 (bd, 1 H, *J* = 9.9 Hz), 5.41 (bd, 1 H, *J* = 9.9 Hz), 4.55-4.51 (m, 1 H), 4.09-4.00 (m, 2 H), 3.85 (dt, 1 H, *J* = 6.6, 4.6 Hz), 3.63 (ddd, 1 H, *J* = 8.5, 4.7, 1.8 Hz), 3.45 (dt, 1 H, *J* = 2.7, 1.7 Hz), 3.16 (dd, 1 H, *J* = 10.6, 2.4 Hz), 3.02-2.91 (m, 1 H), 2.84-2.75 (m, 2 H), 2.62-2.57 (m, 1 H), 2.50-2.43 (m, 2 H), 2.35-2.30 (m, 2 H), 2.13-1.89 (m, 3 H), 1.46-1.40 (m, 4 H), 1.36 (s, 3 H), 1.33-1.12 (m, 2 H), 1.00 (d, 1.5 H, *J* = 3.6 Hz), 0.97 (d, 1.5 H, *J* = 4.3 Hz), 0.91 (s, 9 H), 0.08 (s, 6 H); ^{13}C NMR δ 211.9, 133.2, 126.2, 121.7, 78.5, 78.4, 77.4, 77.0, 76.6, 73.7, 73.6, 72.5, 71.7, 67.3, 58.9, 52.0, 42.4, 39.7, 38.9, 34.6, 34.5, 33.7, 29.3, 26.1, 25.7, 22.4, 21.8, 18.1, 14.6, 14.4, 14.0, -4.9, -5.0; MS (EI) *m/z* (rel. intensity) 505 (M^+, 2), 490 (4), 306 (100), 172 (56), 130 (8), 73 (50); HRMS *m/z* calculated for $C_{28}H_{47}NO_5Si$ 505.3224, found 505.3233.

5*S*-(8-Hydroxy-1,2*S*,4,5,6,7,7a*S*,8*S*,10a*R*,10b*S*-decahydroazepino[3,2,1-*hi*]indol-2-yl)-3S-methyldihydrofuran-2-one (28). A solution of **36** (1.21 g, 2.39 mmol) in THF (50 mL) was treated at –78 °C dropwise with a 1.0 M solution of lithium tri-*sec*-butylborohydride in THF (4.78 mL, 4.78 mmol). The reaction mixture was stirred at –78 °C for 2 h, then warmed to –15 °C and stirred for 15 h. At that time, the reaction was quenched with 10% aqueous ethanolamine and extracted into EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), concentrated *in vacuo*, and purified on SiO_2 which had been pretreated with 9:1 hexanes/EtOAc containing 0.5% NEt_3 (hexanes/EtOAc, 9:1 to 4:1 to 0:1) to give 970 mg (80%) of a white foam that was dissolved in MeOH (80 mL) and treated with *p*-toluenesulfonic acid monohydrate (551 mg, 2.87 mmol) at room temperature for 20 h. The reaction mixture was concentrated *in vacuo*, diluted with a saturated $NaHCO_3$ solution and extracted into EtOAc (2 x 50 mL) and CH_2Cl_2 (1 x 50 mL). The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo*, and purified by chromatography on SiO_2 (hexanes/EtOAc, 4:1 to 1:1 to CH_2Cl_2/MeOH, 95:5 to 85:15) to give 55 mg (10%) of the minor diastereomer as a white foam and 388 mg (70%) of the major diastereomer **28** as a white foam. **28:** $[\alpha]_D$ -52.8 (*c* 0.65, $CHCl_3$, 21 °C); IR (neat) 3378, 2931, 1758, 1457 cm^{-1}; ^{1}H NMR δ 5.75 (d, 1 H, *J* = 9.9 Hz), 5.50 (d, 1 H, *J* = 9.9 Hz), 4.53-4.51 (m, 1 H), 4.33 (ddd, 1 H, *J* = 13.2, 7.9, 5.5 Hz), 3.22 (dd, 1 H, *J* = 15.2, 6.5 Hz), 3.11 (dt, 2 H, *J* = 9.5, 7.8 Hz), 2.97 (dd, 1 H, *J* = 14.9, 9.5 Hz), 2.63 (ddd, 1 H, *J* = 12.2, 8.3, 7.7 Hz), 2.60-2.34 (m, 3 H), 2.13 (dt, 1 H, *J* = 11.7, 5.7 Hz), 2.05-2.01 (m, 1 H), 1.95-1.91 (m, 1 H), 1.58-1.45 (m, 3 H), 1.37-1.21 (m, 2 H), 1.25 (d, 3 H, *J* = 7.0 Hz), 1.15 (q, 1 H, *J* = 11.3 Hz); ^{13}C NMR δ 179.2, 132.4, 127.0, 82.5, 71.2, 67.8, 67.6, 53.6, 41.1, 38.0, 35.2, 34.1, 31.7, 29.0, 25.6, 22.0, 14.8; MS (EI) *m/z* (rel. intensity) 291 (M^+, 2), 273 (5), 192 (100), 172 (7), 91 (6), 77 (8); HRMS *m/z* calculated for $C_{17}H_{25}NO_3$ 291.1834, found 291.1846. **Minor diastereomer:** $[\alpha]_D$ –63.3 (*c* 0.15, $CHCl_3$, 21 °C); IR (neat) 3386, 2930, 1767, 1186 cm^{-1}; ^{1}H NMR δ 5.77 (dd, 1 H, *J* = 9.9, 2.0 Hz), 5.50 (bd, 1 H, *J* = 9.9 Hz), 4.56-4.46 (m, 2 H), 3.16-2.95 (m, 4 H), 2.76 (dt, 1 H, *J* = 7.3, 1.9 Hz), 2.56-2.46 (m, 2 H), 2.24-2.12 (m, 2 H), 2.03-1.90 (m, 3 H), 1.55-1.47 (m, 2 H), 1.40-1.33 (m, 1 H), 1.32-1.18 (m, 3 H), 1.28 (d, 3 H, *J* = 7.0 Hz); ^{13}C NMR δ 180.0, 132.3, 127.3, 81.4, 71.3, 67.8, 67.5, 54.1, 41.1, 38.1, 34.1, 33.0, 32.1, 28.9, 25.8, 21.9, 16.3; MS (EI) *m/z* (rel. intensity)

291 (M^+, 0.4), 290 (0.4), 271 (2), 192 (100), 172 (42), 106 (16), 91 (38), 84 (29), 73 (47), 61 (52); HRMS *m/z* calculated for $C_{17}H_{24}NO_3$ (M-H) 290.1756, found 290.1751.

N,N**-Dimethyl-2*****R,S*****-[2*****S*****-(4*****S*****-methyl-5-oxotetrahydrofuran-2-yl)-*1*,2*****S*****,4,5,6,7,7a*****S*****,10,10a*****R*****,10b*****S*****-decahydro-azepino[3,2,1-*****hi*****]indol-10-yl)-propionamide (37).** To a solution of **28** (130 mg, 0.45 mmol) in xylenes (12 mL) was added *N,N*-dimethylpropionamide dimethylacetal (0.57 mL, 3.6 mmol). The reaction mixture was heated at 130-140 °C for 19 h, concentrated *in vacuo*, and purified by chromatography on SiO_2 which had been pretreated with 1:1 hexanes/EtOAc containing 0.5% NEt_3 (hexanes/EtOAc, 1:1 to 0:1) to give 110 mg (65%) of **37** as a yellow foam: $[\alpha]_D$ –40.5 (*c* 0.22, $CHCl_3$, 21 °C); IR (neat) 2919, 1774, 1640, 1453, 1156 cm^{-1}; ^1H NMR δ 5.63-5.54 (m, 1.3 H), 5.25-5.20 (m, 0.7 H), 4.23-4.17 (m, 1 H), 3.43 (bd, 1 H, *J* = 13.3 Hz), 3.38-3.27 (m, 1 H), 3.10 (ddd, 1 H, *J* = 16.3, 10.8, 5.6 Hz), 3.00 (s, 1.7 H), 2.99 (s, 1.3 H), 2.89 (s, 1.7 H), 2.89 (s, 1.3 H), 2.74-2.63 (m, 3 H), 2.62-2.49 (m, 1 H), 2.38-2.16 (m, 1 H), 1.99-1.91 (m, 1 H), 1.76-1.65 (m, 2 H), 1.61-1.38 (m, 4 H), 1.22-1.20 (m, 1 H), 1.19 (d, 1.7 H, *J* = 7.0 Hz), 1.19 (d, 1.3 H, *J* = 7.0 Hz), 1.04 (d, 1.3 H, *J* = 6.9 Hz), 0.99 (d, 1.7 H, *J* = 6.8 Hz); ^{13}C NMR δ 179.6, 179.6, 175.4, 175.3, 133.1, 132.4, 128.9, 126.8, 82.9, 82.6, 66.3, 65.9, 64.2, 63.6, 47.6, 47.2, 45.2, 44.4, 41.9, 39.6, 39.1, 37.5, 37.3, 37.1, 35.6, 35.5, 34.6, 34.3, 34.2, 32.8, 31.3, 30.8, 30.7, 29.8, 29.7, 28.0, 14.7, 14.1, 13.1; MS (EI) *m/z* (rel. intensity) 374 (M^+, 2), 302 (5), 275 (100), 198 (12), 172 (39), 130 (18), 91 (8), 72 (13); HRMS *m/z* calculated for $C_{22}H_{34}N_2O_3$ 374.2569, found 374.2561.

2-Cyclohex-2-enyl-***N,N*****-dimethyl-propionamide.** To a solution of cyclohex-2-enol (0.37 g, 3.8 mmol) in xylenes (3.7 mL) was added *N,N*-dimethylpropionamide dimethylacetal (1.8 mL, 11 mmol). The reaction mixture was heated at 130 °C for 15 h, concentrated *in vacuo*, and purified by chromatography on SiO_2 (hexanes/EtOAc, 4:1 to 2:1) to give 460 mg (68%) of the dimethylamide as a yellow oil (ca. 1.6:1 dr) that was used directly in the next step.

N,N**-Dimethyl-2-(7-oxa-bicyclo[4.1.0]hept-2-yl)-propionamide (39).** To a 0 °C solution of the dimethylamide (25 mg, 0.14 mmol) in CH_2Cl_2 (3.8 mL) was added m-CPBA (42 mg, 0.17 mmol). The reaction mixture was stirred at room temperature for 8 h and polymer-bound triphenylphosphine (500 mg, 0.70 mmol) was added. The suspension was stirred at room temperature for 14 h, filtered, and suspended in EtOAc. The organic layer was washed with saturated $NaHCO_3$ (3 x 10 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give 27 mg (100%) of oily **39** as a 2:1 mixture of diastereomers: IR (neat) 2931, 1637, 1398, 1128 cm^{-1}; ^1H NMR δ 3.16-3.13 (m, 1 H), 3.06 (s, 2 H), 3.00 (s, 1 H), 2.89 (s, 2 H), 2.87 (s, 1 H), 2.82-2.72 (m, 1 H), 2.12-2.02 (m, 1 H), 1.88-1.62 (m, 3 H), 1.52-1.33 (m, 2 H), 1.25-1.21 (m, 1 H), 1.17 (d, 1 H, *J* = 7.6 Hz), 1.14 – 1.07 (m, 1 H), 1.03 (d, 2 H, *J* = 6.9 Hz); ^{13}C NMR δ 176.2, 176.0, 54.9, 53.6, 53.4, 38.6, 38.4, 38.2, 37.6, 35.7, 24.5, 24.2, 22.5, 20.4, 19.8, 15.6, 15.5; MS (EI) *m/z* (rel. intensity) 197 (M^+, 5), 182 (5), 168 (6), 164 (7), 154 (9), 152 (11), 140 (6), 126 (45), 107 (14), 101 (100), 84 (33), 74 (57), 72 (75), 59 (75); HRMS *m/z* calculated for $C_{11}H_{19}NO_2$ 197.1416, found 197.1410.

7-Ethyl-3-methyl-hexahydrobenzofuran-2-one (40a,b). To a 0 °C solution of triethylaluminum (22 mg, 0.18 mmol) in CH_2Cl_2 (0.60 mL) was added a solution of **39** (18 mg, 0.091 mmol) in CH_2Cl_2 (0.60 mL). The reaction mixture was stirred at 0 °C for 1 h, then warmed to room temperature and stirred for 17 h. The reaction was quenched with saturated NH_4Cl (3 mL) and EtOAc (5 mL). The organic layer was washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated *in vacuo* to give 20 mg (97%) of a crude clear oil that was heated in toluene (2.8 mL) at 100-110 °C for 22 h. The solvent was removed *in vacuo*, and the resulting residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 4:1) to give 11 mg (69%) of oily **40** as a 4:1 mixture of diastereomers. Major diastereomer **40a**: IR (neat) 2931, 1773, 1461, 1169, 992 cm^{-1}; ^1H NMR δ 4.07 (dd, 1 H, *J* = 9.3, 7.2 Hz), 2.45 (dq, 1 H, *J* = 13.7, 6.9 Hz), 2.28-2.19 (m, 1 H), 1.85-1.75 (m, 3 H), 1.72-1.53 (m, 4 H), 1.33-1.23 (m, 2 H), 1.19 (d, 3 H, *J* = 6.9 Hz), 0.89 (t, 3 H, *J* = 7.4 Hz); ^{13}C NMR δ 179.9, 82.3, 42.6, 41.5, 36.0, 27.6, 25.9, 24.7, 20.1, 13.3, 10.9; MS (EI) *m/z* (rel. intensity) 153 ($[M+H]^+$, 7), 109 (41), 96 (53), 73 (87), 67 (46), 61 (100); HRMS *m/z* calculated for $C_9H_{12}O_2$ 152.0837, found 152.0832.

(-)-8-*Des*-ethyl,8*S*-phenylseleno-13-*epi*tuberostemonine (42). To a 0 °C solution of **39** (330 mg, 0.89 mmol) in MeCN/Water (5:1, 12 mL) was added phenylselenenylchloride (270 mg, 1.4 mmol). The reaction mixture was stirred at 0 °C for 18 h, quenched with a saturated $NaHCO_3$ solution and extracted into EtOAc (3 x 30 mL). The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo*, and purified by chromatography on SiO_2 (hexanes/EtOAc, 9:1 to 1:1) to give 360 mg (81%) of **42** as a white foamy mixture of diastereomers: $[\alpha]_D$ –10.9 (*c* 0.11, $CHCl_3$, 21 °C); IR (neat) 2923, 1774, 1168 cm^{-1}; ^1H NMR δ 7.55-7.46 (m, 2 H), 7.28-7.24 (m, 3 H), 4.58 (t, 0.3 H, *J* = 5.1 Hz), 4.42-4.40 (m, 0.7 H), 4.23-4.15 (m, 1 H), 3.73 (bs, 0.7 H), 3.41 (t, 0.3 H, *J* = 4.3 Hz), 3.36-3.16 (m, 3 H), 2.81-2.68 (m, 2 H), 2.64-2.53 (m, 3 H), 2.42-2.28 (m, 2 H), 2.25-2.06 (m, 2 H), 1.78-1.62 (m, 4 H), 1.51-1.40 (m, 2 H), 1.22 (d, 4.2 H, *J* = 7.2 Hz), 1.21 (d, 1.8 H, *J* = 7.2 Hz), 1.21-1.09 (m, 1 H); ^{13}C NMR δ 179.3, 178.7, 178.1, 134.5, 133.4, 129.7, 129.4, 129.3, 128.9, 128.2, 128.0, 83.4, 82.6, 80.6, 80.2, 65.5, 64.8, 64.4, 64.3, 50.1, 48.9, 48.5, 47.9, 46.0, 44.1, 43.8, 42.5, 41.7, 41.6, 39.3, 35.3, 35.0, 34.8, 34.2, 34.0, 33.2, 32.8, 31.6, 31.5, 29.6, 29.5, 27.5, 26.9, 14.8, 14.3, 11.6; MS (EI) *m/z* (rel. intensity) 503 (M^+, 1), 502 (1), 404 (100), 346 (5), 174 (16), 141 (14), 127 (18), 111 (26), 97 (38), 85 (62), 71 (73); HRMS *m/z* calculated for $C_{26}H_{33}NO_4Se$ 503.1549, found 503.1575.

REFERENCES

1. Wipf, P.; Kim, Y.; Goldstein, D. M. *J. Am. Chem. Soc.* **1995**, *117*, 11106.