An Approach to the Synthesis of Stenine (supporting information)

Liang Zhu, Ryan Lauchli, Mandy Loo and Kenneth J. Shea*

Department of Chemistry, 1102 Natural Sciences II, University of California, Irvine,
Irvine, CA 92697-2025

Instrumentation: NMR measurements were conducted with Bruker instruments at 500 MHz for proton spectra and 125 MHz for carbon spectra. Chemical shifts are given in ppm values referenced to residual solvent peaks.

General Procedures: Toluene, THF, and dichloromethane were purified by passage through alumina columns. Isopropanol, triethylamine, and benzene were distilled from CaH₂. Methanol was distilled from its magnesium alkoxide. DMF was dried over 4Å molecular sieves. All reactions were performed under N₂ using flame dried glassware and standard syringe and septa techniques. Removal of solvent *in vacuo* refers to use of a Büchi rotary evaporator. Reagents were purchased from VWR, Fisher, or Aldrich and generally used without purification. TLC was performed with aluminum-backed silica gel 60 F₂₅₄ analytical plates from EMD. Visualization of compound spots was done with a short wave UV lamp followed by staining with either anisaldehyde or Seebach's stain (phosphomolybdic acid and Ce₂(SO₄)₃). Flash chromatography was performed on Geduran silica gel 60 (40-63 µm) from EMD.

5-(*tert*-Butyl-dimethyl-silanyloxymethyl)-cyclohex-2-enone (9)¹: To a cooled solution of 3,4,5-trimethoxybenzoic acid (10.77 g, 50.8 mmol) in 75 mL of absolute ethanol at -78 °C was added 400 mL of freshly distilled anhydrous liquid ammonia. Small pieces of sodium metal (6 g) were added until the solution remained dark blue for 5 min. The reaction mixture was stirred at -78 °C for additional 45 min. Excess sodium was then quenched by the addition of solid ammonium chloride (25 g), and the ammonia was allowed to evaporate overnight under a stream of nitrogen. The mixture was acidified

¹ Smith III, A. B.; Richmond, R. E. *J. Am. Chem. Soc.* **1983**, *105*, 575.

with 150 mL of 2 N HCl to pH 2. An additional 50 mL of ethanol was added, and the resultant mixture was heated at reflux for 20 min. After cooling, the reaction mixture was extracted with ethyl acetate, dried, and the solvent evaporated *in vacuo* to yield 10.47 g of a yellow residue, which was shown by NMR to be a mixture of ketones. In practice, the mixture was esterified without separation or purification. To a solution of the above mixture in 150 mL of benzene and 30 mL of absolute ethanol was added a catalytic amount (300 mg, 1.58 mmol) of *p*-toluenesulfonic acid. The reaction mixture was heated at reflux for 48 h with water separation (Dean-Stark trap). The solution was cooled, filtered, and washed with saturated aqueous sodium bicarbonate and brine, followed by drying. Removal of the solvent *in vacuo* and Kugelrohr distillation (0.5 mmHg, 125-126 °C) afforded 7.10 g of ester (66% from 3,4,5-trimethoxybenzoic acid) as a viscous colorless oil, which solidified upon standing at 4 °C. The spectrum matches the data previously reported for this compound. To a suspension of lithium aluminum hydride (374 mg, 10 mmol) in 50 mL of ether was added ester (2.09 g, 10 mmol) in 10 mL of ether in a dropwise fashion. The solution was stirred at 25 °C for 1.5 h. The excess lithium aluminum hydride was destroyed by adding Na₂SO₄·10H₂O until gas was no longer evolved. The alumina salts were removed by filtration, and the solvent was concentrated *in vacuo* to afford an oily residue. Without purification, the unstable enol (1.61 g) was dissolved in 5 mL of tetrahydrofuran and 5 mL of 10% acetic acid followed by stirring for 3 h. The reaction mixture was poured into ether, washed with brine, dried, and concentrated *in vacuo*. Any residual acetic acid was removed via azeotrope with heptane. The enone was afforded as a pale yellow oil in 89% from previous ester. Without purification, a mixture of *tert*-butyldimethylsilyl chloride (4.22 g, 28 mmol), triethylamine (4.68 mL, 46 mmol), and a catalytic amount of dimethylaminopyridine (137 mg, 0.04 equiv) were stirred in 30 mL of dry methylene chloride for 10 min. To this mixture was added a solution of enone (3.53 g, 28 mmol) in 5 mL of methylene chloride. The reaction was stirred overnight at 25 °C under an argon atmosphere. The mixture was diluted with methylene chloride, washed with saturated ammonium chloride, water, and brine, and dried. Removal of the solvent *in vacuo* and Kugelrohr distillation (1 mmHg, bp 120-121 °C) afforded **9** (5.88 g, 90%) as a colorless oil. The spectrum matches previously reported for this compound.

Trifluoro-methanesulfonic acid 3-(*tert*-butyl-dimethyl-silanyloxymethyl)-cyclohexa-1,5-dienyl ester (10**):** To a solution of LDA (18.8 mmol) in THF (20 mL) was prepared from diisopropylamine (2.63 mL, 18.8 mmol) and *n*-butyllithium (2.5 M in Hexane, 7.52 mL) at -78 °C under N₂. The resulting solution was added **9** in THF (20 mL) dropwise and the reaction mixture was stirred at this temperature for 30 min. A solution of Tf₂NPh (6.5 g, 18.3 mmol) in THF (20 mL) was then added. After complete addition, the reaction mixture was warmed to 0 °C and stirred at this temperature for 2 h. The solvent was

evaporated, and the crude material was dissolved in ether and washed with water. The aqueous phase was extracted with ether, and the combined organic layers were dried and evaporated. The oil was chromatographed to afford ester **10** as a colorless oil (3.64 g, 58 %). ^1H NMR (CDCl_3) 6.02 (m, 1 H), 5.88 (m, 1 H), 5.69 (m, 1 H), 3.61 (m, 2 H), 2.81 (m, 1 H), 2.32 (m, 2 H), 0.95 (s, 9 H), 0.11 (s, 6 H); ^{13}C NMR (CDCl_3) δ 146.8, 131.3, 121.1, 116.7, 64.7, 36.8, 26.3, 26.2, 24.9, 18.7, -5.0; IR (KBr) 2955, 2931, 2859, 1655, 1423, 1212, 1144, 838 cm^{-1} ; HRMS (EI) calculated for $\text{C}_{14}\text{H}_{23}\text{O}_4\text{SiF}_3$ ($\text{M}+\text{H}$) $^+$ 373.1117, observed 373.1110.

4-[3-(*tert*-Butyl-dimethyl-silanyloxymethyl)-cyclohexa-1,5-dienyl]-butyric acid ethyl ester (11**):** To a solution of **10** (3.64 g, 9.8 mmol), $\text{Pd}_2(\text{dba})_3$ (632 mg, 0.69 mmol), dppf (383 mg, 0.69 mmol) and tetrabutylammonium iodide (10.9 g, 29.4 mmol) in THF/NMP (20 ml, 1:1) was added organozinc halide (31.4 ml, 0.5M in THF). The reaction mixture was stirred at 70 $^\circ\text{C}$ for 2 h. The mixture was cooled to rt and quenched with saturated NH_4Cl solution (20ml). The aqueous phase was extracted with ether (3 x 200 ml), and the combined organic layers were dried and evaporated. The oil was chromatographed to afford ester **11** as a colorless oil (2.7 g, 82 %). ^1H NMR (CDCl_3) 5.78 (d, J = 1.5 Hz, 2 H), 5.37 (m, 1 H), 4.13 (dd, J = 8.9, 4.2 Hz, 2 H), 3.49 (d, J = 8.9 Hz, 2 H), 2.45 (m, 1 H), 2.28 (t, J = 9.3 Hz, 1 H), 2.25-2.03 (m, 4 H), 1.75 (m, 1 H), 1.26 (t, J = 8.9 Hz, 3 H), 0.90 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (CDCl_3) δ 174.0, 135.4, 126.4, 126.1, 122.2, 65.0, 60.1, 36.1, 34.7, 33.5, 25.8, 25.2, 23.4, 18.3, 14.2, -5.4; IR (KBr) 2955, 2930, 2857, 1737, 1599, 1463, 1253, 1104, 838 cm^{-1} .

10-(*tert*-Butyl-dimethyl-silanyloxymethyl)-2-oxa-3-aza-tricyclo[6.3.1.0^{3,9}]dodec-8(12)-en-4-one (6**):** To a solution of hydroxylamine hydrochloride (4.6 g, 65.1 mmol) in MeOH (15 mL) at 0 $^\circ\text{C}$ was added a solution of KOH (7.3 g, 130.2 mmol) in MeOH (30 mL) dropwise. The solution was stirred 20 min after the addition was complete, then compound **11** (2.2 g, 6.51 mmol) dissolved in MeOH (15 mL) and added dropwise. The white solution was stirred for 2 h, and added water (5 mL). The pH was adjusted to 6 with concentrated HCl. The mixture was extracted with CHCl_3 (8 x 100 mL) and the extracts were dried (MgSO_4) and concentrated. The product **8** was used for next step without further purification. To a stirred suspension of Bu_4NIO_4 (3.83 g, 8.84 mmol) in CHCl_3 (340 mL) at 0 $^\circ\text{C}$ was added a solution of **8** (2.2 g, 6.8 mmol) dissolved in CHCl_3 (150 mL). The solution was stirred for 30 min then washed with aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution, H_2O , dried (MgSO_4), and concentrated to a yellow oil. The oil was chromatographed to afford cycloadduct **6** as a colorless oil (945 mg, 50 % for two steps).

^1H NMR (CDCl_3) 5.98 (dd, $J = 7.4, 2.3$ Hz, 1 H), 4.78 (t, $J = 6.5$ Hz, 1 H), 4.58 (s, 1 H), 3.52 (dd, $J = 12.8, 6.2$ Hz, 1 H), 3.09 (t, $J = 12.53$ Hz, 1 H), 2.96 (m, 1 H), 2.56 (m, 1 H), 2.38 (m, 3 H), 2.24 (m, 2 H), 1.86 (m, 1 H), 0.92 (s, 9 H), 0.72 (dd, $J = 15.3, 7.1$ Hz, 1 H), 0.05 (s, 6 H); ^{13}C NMR (CDCl_3) δ 184.8, 146.3, 120.3, 73.0, 64.9, 57.3, 35.8, 33.2, 32.0, 27.5, 25.8, 25.7, 18.1, -5.5, -5.7; IR (KBr) 2930, 2858, 1715, 1250, 1095 cm^{-1} ; HRMS (ESI) calculated for $\text{C}_{17}\text{H}_{29}\text{NO}_3\text{Si}$ ($\text{M}+\text{Na}$) $^+$ 346.1814, observed 346.1805.

9-(tert-Butyl-dimethyl-silanyloxymethyl)-7-hydroxy-1,3,4,5,7,8,9,9a-octahydrobenzo[b]azepin-2-one (12): To a solution of compound **6** (945 mg, 2.91 mmol) and Na_2HPO_4 (2.08 g, 14.5 mmol) in EtOH (38 ml) at 0 $^\circ\text{C}$ was added Na/Hg (2.27 g, 20% Na). The solution was stirred for 2h and brine (10 drops) was added followed by CH_2Cl_2 (50 ml). The mixture was filtered through celite and concentrated. The residue was purified by chromatography to yield **12** (500 mg, 51%). mp: 140.1-143.8 $^\circ\text{C}$; ^1H NMR (CDCl_3) 5.75 (m, 1 H), 5.67 (s, 1 H), 4.29 (s, 1 H), 3.90 (t, $J = 6.8$ Hz, 1 H), 3.79 (dd, $J = 10.2, 4.4$ Hz, 1 H), 3.60 (dd, $J = 10.2, 5.0$ Hz, 1 H), 2.56-2.48 (m, 3 H), 2.35 (m, 1 H), 2.05 (m, 1 H), 1.96-1.65 (m, 5 H), 0.94 (s, 9 H), 0.10 (s, 6 H); ^{13}C NMR (CDCl_3) δ 176.0, 141.0, 125.6, 64.4, 64.1, 53.1, 38.9, 34.1, 33.2, 26.3, 22.7, 18.7, -5.0, -5.01; IR (KBr) 3420, 3255, 2938, 2858, 1665, 1426, 1250, 1099, 836 cm^{-1} ; HRMS (ESI) calculated for $\text{C}_{17}\text{H}_{31}\text{NO}_3\text{Si}$ ($\text{M}+\text{Na}$) $^+$ 348.1971, observed 348.1982.

Synthesis of Alcohol 13 by Blechert's procedure (slight modifications).²

Step A: To a solution of NaOMe (0.2 g) in 300 ml MeOH was cooled to 0 $^\circ\text{C}$ and added dimethylmalonate (135 g) followed by adding cyclohexenone (87 g in 100 ml MeOH). The suspension was allowed to warm to room temperature and was stirred for 6 h. MeOH was removed *in vacuo* and the reaction mixture was taken up in EtOAc, washed with 1N HCl and dried over sodium sulfate. The solvent was removed *in vacuo* the residue was distilled to afford the product (174 g, 80%). Spectral data (NMR) matches that previously reported for this compound.

Step B: To a solution of ketone from last step (52 g, 0.22 Mol) in toluene (150 ml) was added ethyleneglycol (38.1 mL, 0.68 Mol) and *para*-toluenesulfonic acid (4.3 g, 22.78 mmol) and the resulting mixture was refluxed with a Dean Stark apparatus for 18 h. The reaction mixture was cooled to room temperature, quenched by addition of saturated NaHCO_3 and diluted with Et_2O , washed several times with water, brine and dried over sodium sulfate. The solvent was removed *in vacuo* and the residue was purified by kugelrohr distillation to give the product (54 g, 88%) as a colorless oil. Spectral data (NMR) matches that previously reported for this compound.

Step C: To a solution of ketal from last step in DMSO (100 mL, 2.0 M) and water (4 mL, 0.28 mol, 1.4 equiv), then LiCl (18 g, 0.42 mol, 2.1 equiv) was added. The reaction mixture was stirred for 17 h at 140 °C, cooled to rt, quenched by H_2O , and extracted with EtOAc (twice). The combined organic layers were washed with 1N HCl aqueous solution, saturated NaHCO_3 aqueous solution and brine, dried over sodium sulfate, and concentrated. The residue was purified by kugelrohr distillation to give the product (30 g, 59%) as a colorless oil. Spectral data (NMR) matches that previously reported for this compound.

Step D: To a solution of lithium aluminiumhydride (6.22 g, 0.15 mol) in diethyl ether was cooled to 0 °C. The methylester from last step (30 g, 0.14 mol) was dissolved in 200 ml diethylether and was added dropwise to the suspension. After complete addition, the mixture was refluxed for 8 h. The reaction mixture was cooled to room temperature and water was carefully added until a white solid precipitated and hydrogen evolution was completed. The diethylether was decanted and the white solid was washed several times with Et_2O . The combined organic layers were washed with water, brine and dried over sodium sulfate. The solvent was removed *in vacuo* and the crude oil was purified by kugelrohr distillation to give the product (21 g, 77%) as a colorless oil. Spectral data (NMR) matches that previously reported for this compound.

Step E (13): To a solution of ketal from last step (21 g, 0.105 Mol) dissolved in acetonitrile (500 mL) and 1N HCl (300 mL) was added at room temperature. The reaction mixture was stirred for 24 h. The reaction mixture was extracted with dichloromethane several times. The combined organic layers were washed with an aqueous saturated NaHCO_3 solution, brine and dried over sodium sulfate. The solvent was removed *in vacuo* and the crude oil was purified by column chromatography to yield **13** (13.2 g, 89%) as a colorless oil. Spectral data (NMR) matches that previously reported for this compound.

5-[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-cyclohex-2-enone (14): To a solution of TBSCl (13.9 g, 0.092 mol) dissolved in dichloromethane (100 mL) was added ketone **13**²

² This compound was made according to: Jiricek, J.; Blechert, S. *J. Am. Chem. Soc.* **2004**, *126*, 3534.

(13.02 g, 0.092 mol), DMAP (450 mg, 3.7 mmol) and Et₃N (16 ml) in 20 ml dichloromethane at room temperature. The reaction mixture was stirred for 24 h. The reaction mixture was quenched by addition of saturated NH₄Cl and extracted with dichloromethane several times. The combined organic layers were washed with brine and dried over sodium sulfate. The solvent was removed *in vacuo* and the crude oil was purified by column chromatography to yield the product (19 g, 80%) as a colorless oil. ¹H NMR (CDCl₃) 3.68 (t, *J* = 6.44 Hz, 2 H), 2.46 (d, *J* = 11.58 Hz, 1 H), 2.39 (d, *J* = 14.25 Hz, 1 H), 2.30 (m, 1 H), 2.07-1.95 (m, 4 H), 1.73-1.45 (m, 3 H), 1.40 (m, 1 H), 0.91 (s, 9 H), 0.07 (s, 6H); ¹³C NMR (CDCl₃) δ 212.1, 60.9, 48.5, 41.9, 39.7, 36.2, 31.7, 26.4, 25.7, 18.7, -4.9; IR (KBr) 2953, 2930, 1715, 1470, 1254, 1102, 838 cm⁻¹; HRMS (ESI) calculated for C₁₄H₂₈O₂Si (M+Na)⁺ 279.1756, observed 279.1751.

5-[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-cyclohex-2-enone (16): To a solution of 2,2,6,6-tetramethylpiperidine (20.5 g, 0.146 mol, 1.5 equiv) in THF (300 mL) was added a 2.5 N hexane solution of *n*-BuLi (54.3 mL, 0.136 mol, 1.4 equiv) at 0°C (ice-water bath). After stirring for 1 h at the same temperature, the reaction mixture was cooled to -78 °C. TMSCl (14.8 g, 0.136 mol, 1.4 equiv) was then added, followed by addition of a solution of ether from the last step (25 g, 0.097 mol) in THF (450 mL) via cannula. After stirring for 2 h at the same temperature, the reaction mixture was quenched by addition of saturated NaHCO₃ aqueous solution, extracted with Et₂O, dried over sodium sulfate, and concentrated to afford crude enol silyl ether, which was used for the next step without further purification. The residue was dissolved with CH₃CN (750 mL, 0.130 M), then diallyl carbonate (19.5 g, 0.137 mol, 1.4 equiv) and Pd₂(dba)₃ (6.35 g, 7 mol %) were added at rt. After stirring for 12 h at the same temperature, the reaction mixture was quenched by addition of saturated NaHCO₃ aqueous solution, extracted with dichloromethane, dried over sodium sulfate, and concentrated. The residue was purified by flash column chromatography to afford **16** (13.1 g) in 64% for two steps. ¹H NMR (CDCl₃) 7.02 (m, 1 H), 6.08 (d, *J* = 10.04 Hz, 1 H), 3.73 (t, *J* = 6.30 Hz, 2 H), 2.61-2.51 (m, 2 H), 2.35-2.30 (m, 1 H), 2.24-2.17 (m, 2 H), 1.69-1.61 (m, 2 H), 0.95 (s, 9 H), 0.10 (s, 6 H); ¹³C NMR (CDCl₃) δ 200.3, 150.3, 130.2, 60.7, 44.8, 38.9, 32.7, 32.5, 26.4, 18.7, -4.9; IR (KBr) 2953, 2858, 1684, 1470, 1388, 1253, 1102, 836 cm⁻¹; HRMS (ESI) calculated for C₁₄H₂₆O₂Si (M+Na)⁺ 277.1600, observed 277.1597.

Trifluoro-methanesulfonic acid 3-[2-(*tert*-butyl-dimethyl-silanyloxy)-ethyl]-cyclohexa-1,5-dienyl ester (17): To a solution of LDA (63.4 mmol) in THF (60 ml) was prepared from diisopropylamine (8.9 ml, 63.4 mmol) and *n*-butyllithium (2.5 M in hexane, 23.4 ml) at -78 °C under N₂. The resulting solution was added **16** (12.4 g, 48.8 mmol) in THF (60 ml) dropwise and the reaction mixture was stirred at this temperature for 30 min. A solution of Tf₂NPh (18.7 g, 52.5 mmol) in THF (60 ml) was then added. After complete addition, the reaction mixture was warmed to 0 °C and stirred at this temperature for 2 h. The solvent was evaporated, and the crude material was dissolved in ether and washed with water. The aqueous phase was extracted with ether, and the combined organic layers were dried and evaporated. The oil was chromatographed to afford ester **17** as a colorless oil (15 g, 79 %). ¹H NMR (CDCl₃) 5.98 (m, 1 H), 5.82 (d, *J* = 10.05 Hz, 1 H), 5.69 (d, *J* = 4.5 Hz, 1 H), 3.66 (m, 2 H), 2.78 (m, 1 H), 2.38 (m, 1 H), 2.11 (m, 1 H), 1.75-1.57 (m, 2 H), 0.91 (s, 9 H), 0.06 (s, 6 H); ¹³C NMR (CDCl₃) δ 145.9, 131.0, 120.8, 119.6, 60.4, 36.7, 30.1, 28.1, 26.1, 18.5, -5.2 (CF₃ carbon not observed); IR (KBr) 2955, 2859, 1422, 1211, 1144, 1098, 837 cm⁻¹.

4-{3-[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-cyclohexa-1,5-dienyl}-butyric acid ethyl ester (18): To a solution of **17** (16.66 g, 44.8 mmol), Pd₂(dba)₃ (2.93 g, 3.2 mmol), dppf (1.78 mg, 3.2 mmol) and tetrabutylammonium iodide (80 g, 135 mmol) in THF/NMP (98 ml, 1:1) was added organozinc halide (144 ml, 0.5 M in THF). The reaction mixture was stirred at 70 °C for 2 h. The reaction mixture was cooled to rt and quenched with saturated NH₄Cl (20 ml). The aqueous phase was extracted with ether (3 x 300 ml), and the combined organic layers were dried and evaporated. The crude oil was purified by column chromatography to yield ester **18** as a colorless oil (12 g, 76 %). ¹H NMR (CDCl₃) 5.78 (s, 2 H), 5.38 (d, *J* = 3.72 Hz, 1 H), 4.13 (dd, *J* = 14.27, 7.13 Hz, 2 H), 3.66 (m, 2 H), 2.41 (m, 1 H), 2.29-2.19 (m, 3 H), 2.05 (t, *J* = 7.15 Hz, 1 H), 1.91 (m, 1 H), 1.76-1.50 (m, 4 H), 1.26 (t, *J* = 7.14 Hz, 3 H), 0.90 (s, 9 H), 0.05 (s, 6 H); ¹³C NMR (CDCl₃) δ 173.9, 134.6, 126.8, 126.6, 126.3, 61.2, 60.4, 37.8, 35.0, 33.8, 30.0, 29.0, 26.2, 23.8, 18.6, 14.5, -5.1; IR (KBr) 2954, 2857, 1738, 1472, 1254, 1099, 836 cm⁻¹; HRMS (ESI) calculated for C₂₀H₃₆O₃Si (M+Na)⁺ 375.2332, observed 375.2326.

10-[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-2-oxa-3-aza-tricyclo[6.3.1.0^{3,9}]dodec-8(12)-en-4-one (19): To a solution of hydroxylamine hydrochloride (7 g, 100 mmol) in MeOH (20 mL) at 0 °C was added a solution of KOH (11.2 g, 200 mmol) in MeOH (50 mL) dropwise. The solution was stirred 20 min after the addition was complete, then

compound **18** (3.52 g, 10 mmol) dissolved in MeOH (20 mL) and added dropwise. The white solution was stirred for 2 h, and added water (10 mL). The pH was adjusted to 6 with concentrated HCl. The mixture was extracted with CHCl₃ (8 x 100 mL) and the extracts were dried (Na₂SO₄) and concentrated. The product was used for next step without further purification. To a stirred suspension of Bu₄NIO₄ (6.5 g, 15 mmol) in acetone (650 mL) at -78 °C was added a solution of hydroxamic acid (3.52 g, 10 mmol) dissolved in acetone (250 mL). The solution was stirred for 30 min then washed with aqueous Na₂S₂O₃ solution, H₂O, dried (MgSO₄), and concentrated to an yellow oil. The oil was chromatographed to afford cycloadduct **19** as a colorless oil (1.74 g, 50 % for two steps). ¹H NMR (CDCl₃) 6.05 (d, *J* = 4.1 Hz, 1 H), 4.80 (t, *J* = 5.5 Hz, 1 H), 4.48 (s, 1 H), 3.75-3.67 (m, 2 H), 2.99 (m, 1 H), 2.60 (dd, *J* = 12.33, 6.83 Hz, 1 H), 2.47-2.35 (m, 4 H), 2.23 (m, 1 H), 1.90 (m, 1 H), 1.53 (m, 1 H), 1.36 (m, 1 H), 0.92 (s, 9 H), 0.10 (s, 6 H); ¹³C NMR (CDCl₃) δ 185.1, 146.8, 121.4, 73.5, 61.5, 60.2, 38.6, 36.2, 33.8, 32.4, 32.2, 28.6, 26.4, 18.8, -4.9; IR (KBr) 2931, 2858, 1712, 1252, 1095 cm⁻¹; HRMS (ESI) calculated for C₁₈H₃₁NO₃Si (M+Na)⁺ 360.1971, observed 360.1979.

9-[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-7-hydroxy-1,3,4,5,7,8,9,9a-octahydro-benzo[*b*]azepin-2-one (20**):** To a solution of compound **19** (1.7 g, 4.9 mmol) and Na₂HPO₄ (3.8 g) in EtOH (70 ml) at 0°C was added Na/Hg (4.1 g, 20% Na). The solution was stirred for 2 h and brine (10 drops) was added followed by CH₂Cl₂ (50 ml). The mixture was filtered through celite and concentrated. The residue was purified by chromatography to yield **20** (1.05 mg, 61%). Recrystallization in EtOAc may be used at this point to isolate the major diastereomer in approximately 70% yield from the mixture of diastereomers. Mp: 163.1-164.2 °C; ¹H NMR (CDCl₃) 6.14 (s, 1 H), 5.58 (d, *J* = 2.95 Hz, 1 H), 4.21 (s, 1 H), 3.73-3.62 (m, 3 H), 2.57-2.41 (m, 3 H), 2.34-2.24 (m, 2 H), 2.03 (m, 1 H), 1.90-1.50 (m, 6 H), 0.93 (s, 9 H), 0.05 (s, 6 H); ¹³C NMR (CDCl₃) δ 176.4, 139.1, 126.5, 64.4, 61.1, 55.1, 36.1, 34.8, 34.7, 34.5, 33.9, 26.2, 22.9, 18.5, -5.1; IR (KBr) 3423, 3267, 2931, 2857, 1661, 1470, 1426, 1252, 1099, 833 cm⁻¹; HRMS (ESI) calculated for C₁₈H₃₃NO₃Si (M+Na)⁺ 362.2127, observed 362.2134.

9-[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-7-(4-methoxy-benzyloxy)-1,3,4,5,7,8,9,9a-octahydro-benzo[*b*]azepin-2-one (21**):** To a solution of compound **20** (144 mg, 0.4 mmol) in anhydrous ether (8 ml) was added freshly prepared 4-methoxybenzyl trichloroacetimidate (282 mg, 1 mmol), followed by triphenylcarbenium tetrafluoroborate (5 mg, 0.015 mmol). After 5 h, 5 ml of saturated NaHCO₃ was added and the mixture was extracted with EtOAc. The organic extracts were washed with brine,

dried, and evaporated, and the residue was purified by chromatography to yield the 4-methoxybenzyl ether **21** (110 mg, 60%). ^1H NMR (CDCl_3) 7.26 (d, $J = 7.26$ Hz, 2 H), 6.88 (d, $J = 8.61$ Hz, 2 H), 5.71 (d, $J = 5.29$ Hz, 1 H), 5.64 (s, 1 H), 4.49 (dd, $J = 26.9$, 11.5 Hz, 2 H), 3.94 (m, 1 H), 3.81 (s, 3 H), 3.69 (m, 3 H), 2.50 (m, 3 H), 2.25 (m, 1 H), 1.98-1.50 (m, 7 H (one extra H assigned to water in NMR solvent)), 0.90 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR (CDCl_3) δ 175.9, 159.4, 140.0, 130.9, 129.5, 124.2, 114.1, 70.6, 70.3, 61.0, 55.7, 55.5, 35.5, 34.7, 34.6, 34.4, 30.8, 26.2, 22.7, 18.5, -5.1; IR (KBr) 3209, 2930, 2857, 1663, 1462, 1441, 1248, 1098, 1037, 836 cm^{-1} ; HRMS (ESI) calculated for $\text{C}_{26}\text{H}_{41}\text{NO}_4\text{Si}$ ($\text{M}+\text{Na}$) $^+$ 482.2703, observed 482.2698.

9-(2-Hydroxy-ethyl)-7-(4-methoxy-benzyloxy)-1,3,4,5,7,8,9,9a-octahydro-benzo[b]azepin-2-one: To a solution of compound **21** (30 mg, 0.066 mmol) in THF (0.1 ml) was added HF/pyridine in THF (0.1 ml, 1.263 M). The 1.263 M HF/pyridine in THF was prepared by dissolving 0.1 ml Aldrich 70% HF/pyridine in 0.98 ml pyridine and 1.8 ml THF. After 28 h, 2 ml CH_2Cl_2 was added and the mixture was washed with saturated CuSO_4 solution, and then saturated NaHCO_3 solution. The organic layer was dried over Na_2SO_4 , and evaporated. The residue was purified by chromatography to yield the alcohol (16 mg, 70%). ^1H NMR (CDCl_3) 7.26 (d, $J = 8.36$ Hz, 3 H, (amide H resonance overlaps in this case, but changes with concentration), 6.88 (d, $J = 8.49$ Hz, 2 H), 5.64 (s, 1 H), 4.53 (dd, $J = 26.9$, 11.5 Hz, 2 H), 3.92 (m, 1 H), 3.80 (s, 3 H), 3.72 (m, 3 H), 3.62 (br.s, 1 H (OH resonance, changes with concentration), 2.52-2.45 (m, 3 H), 2.27 (m, 1 H), 2.00 (m, 1 H), 1.98-1.50 (m, 6 H); ^{13}C NMR (CDCl_3) δ 176.4, 159.4, 140.7, 130.9, 129.5, 123.9, 114.1, 70.32, 70.29, 59.7, 56.4, 55.4, 34.9, 34.1, 33.9, 32.7, 31.4, 22.3; IR (KBr) 3380, 3286, 2935, 2869, 1651, 1512, 1441, 1248, 1063, 1035, 822 cm^{-1} ; HRMS (ESI) calculated for $\text{C}_{20}\text{H}_{27}\text{NO}_4$ ($\text{M}+\text{Na}$) $^+$ 368.1838, observed 368.1844.

Toluene-4-sulfonic acid 2-[7-(4-methoxy-benzyloxy)-2-oxo-2,3,4,5,7,8,9,9a-octahydro-1H-benzo[b]azepin-9-yl]-ethyl ester: To a stirred solution of alcohol from last step (16 mg, 0.0464 mmol) in CH_2Cl_2 (0.5 ml) at 0°C was sequentially added Et_3N (7 mg), *p*-toluenesulfonyl chloride (10.6 mg), and DMAP (2.8 mg). The mixture was stirred at 0°C for 7 h and water (1 ml) was added. The layers were separated and the aqueous layer was extracted with CHCl_3 (3 x 2ml). The combined organic layers were washed with water, dried, and concentrated *in vacuo*. The residue was purified by chromatography to yield the product (18 mg, 78%). ^1H NMR (CDCl_3) 7.84 (d, $J = 8.24$ Hz, 2 H), 7.40 (d, $J = 8.49$ Hz, 2 H), 7.30 (d, $J = 8.56$ Hz, 2 H), 6.93 (d, $J = 8.37$ Hz, 2 H), 5.88 (d, $J = 5.69$ Hz, 1 H), 5.67 (d, $J = 3.18$ Hz, 1 H), 4.53 (dd, $J = 24.7$, 11.1 Hz, 2 H), 4.15 (m, 2 H), 3.95 (m,

1 H), 3.86 (s, 3 H), 3.54 (t, $J = 6.25$ Hz, 1 H), 2.48 (m, 6 H), 2.24 (m, 1 H), 2.10-1.65 (m, 7 H); ^{13}C NMR (CDCl_3) δ 176.3, 159.7, 145.5, 139.9, 133.3, 131.0, 130.5, 129.8, 128.4, 124.4, 114.3, 70.7, 70.3, 68.4, 55.8, 55.6, 35.3, 34.6, 34.1, 31.2, 30.6, 22.7, 22.1; IR (KBr) 3210, 3063, 2930, 2864, 1654, 1511, 1359, 1247, 1175, 818 cm^{-1} ; HRMS (ESI) calculated for $\text{C}_{27}\text{H}_{33}\text{NO}_6\text{S}$ ($\text{M}+\text{Na}$) $^+$ 522.1926, observed 522.1927.

9-(4-Methoxy-benzyloxy)-1,2,6,7,9,10,10a,10b-octahydro-5H-azepino[3,2,1-*hi*]indol-4-one (22): To a stirred suspension of 60% NaH in mineral oil (2 mg, 0.04 mmol) in THF (1 ml) at 0°C was added slowly a solution of the product from last step (9 mg, 0.018 mmol) in THF (1 ml), and the mixture was stirred for 3 h and carefully diluted with water (1 ml) and extracted with CHCl_3 (3 x 2ml). The organic extracts were washed with brine, dried, and evaporated, and the residue was purified by chromatography to yield **22** (5.3 mg, 90%). ^1H NMR (CDCl_3) 7.27 (d, $J = 8.48$ Hz, 2 H), 6.88 (d, $J = 8.55$ Hz, 2 H), 5.52 (s, 1 H), 4.53 (dd, $J = 26.9, 11.5$ Hz, 2 H), 3.89 (m, 1 H), 3.87 (m, 1 H), 3.80 (s, 3 H), 3.54 (d, $J = 10.4$ Hz, 1 H), 3.44 (m, 1 H), 2.62-2.40 (m, 4 H), 2.17 (m, 2 H), 2.00-1.40 (m, 5 H); ^{13}C NMR (CDCl_3) δ 173.2, 159.5, 142.0, 130.7, 129.5, 123.3, 114.1, 72.1, 70.8, 63.9, 55.5, 48.6, 41.3, 37.3, 34.5, 31.9, 28.2, 21.2; IR (KBr) 2930, 2869, 1733, 1612, 1513, 1453, 1246, 1039, 910, 725 cm^{-1} ; HRMS (ESI) calculated for $\text{C}_{20}\text{H}_{25}\text{NO}_3$ ($\text{M}+\text{Na}$) $^+$ 350.1732, observed 350.1730.