Cyclization Approaches to the Synthesis of Macrocyclic Bisindolylmaleimides.

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Supporting Information

Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. TLC was performed on Kiesegel 60 F254 plates (Merck) using reagent grade solvents. Flash chromatography was performed using Merck silica gel 60 (230-400 mesh). ^{1}H NMR were performed at 300 MHz and ^{13}C NMR at 75 MHz in $CDCl_3$ unless otherwise specified. Chemical shifts are in ppm downfield from internal tetramethylsilane. Mass spectral, combustion and infrared analysis were performed by the Eli Lilly and Co. Physical Chemistry Department.

1-[2-(2,2-Dimethyl-1,1-diphenyl-1-silapropoxy)ethoxy]-1-[(triphenylmethoxy)methyl]but-3-ene: To a solution of **24** (11.8 g, 31.4 mmol), in CH_2Cl_2 (100 mL) was added imidazole (4.20 g, 62.7 mmol) followed by *tert*-butyldiphenylsilyl chloride (8.60 g, 31.4 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was allowed to stir at room temperature for 24 h, then quenched with saturated aqueous NH_4Cl and diluted with CH_2Cl_2. The organic layer was washed with saturated NaCl, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield 19.6 g (100%) of product as an oil. Thin layer chromatography (TLC, 4:1 hexanes:EtOAc) and ^{1}H NMR indicated a single compound and the material was used directly in the next reaction.

3-[2-(2,2-Dimethyl-1,1-diphenyl-1-silapropoxy)ethoxy]-4-(triphenylmethoxy)butan-1-ol: Ozone was bubbled into a solution of the TBDPS-protected **24**, prepared above, (19.0 g, 30.4 mmol) in CH_2Cl_2:MeOH (1:1, 150 mL) at –78 °C until the pink color, due to the presence of Sudan red indicator, had disappeared. The reaction mixture was quenched with $NaBH_4$ (1.73 g, 45.6 mmol) at –78 °C and allowed to come to room temperature and stir overnight. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted into CH_2Cl_2. The combined organic layers were washed with saturated aqueous NaCl, dried ($MgSO_4$) and the solvent removed *in vacuo* to afford an oil that was purified by column chromatography (4:1 hexanes:EtOAc) to afford 9.8 g of the desired alcohol and 3.9 g of unreduced aldehyde. The aldehyde was reduced using $LiBH_4$ (0.13 g) to afford an additional 3.4 g of alcohol. The overall yield for the reaction was 13.2 g (70%). The alcohol was used directly, without further purifictaion, in the next reaction.

3-[2-(2,2-dimethyl-1,1-diphenyl-1-silapropoxy)ethoxy]-4-(triphenylmethoxy)butyl-4-methane sulfonate (25): To a solution of alcohol, prepared above, (13.2 g, 21.3 mmol) in CH_2Cl_2 (150 mL) at 0 °C was added Et_3N (3.70 mL, 26.6 mmol) and methanesulfonyl chloride (1.80 mL, 23.5 mmol) and the mixture stirred at 0 °C for 3 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with CH_2Cl_2. The organic layer was washed with saturated aqueous NaCl, dried ($MgSO_4$) and the solvent removed *in vacuo* to give 14.1 g **25** (92%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71-7.63 (m, 4H), 7.47-7.17 (m, 21 H), 4.39-4.22 (m, 2H), 3.83-3.70 (m, 3H), 3.61-3.50 (m, 2H), 3.17 (d, 2H, J = 6.5 Hz), 2.85 (s, 3H), 2.07-1.88 (m, 2H), 1.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7, 135.4, 133.5, 129.5, 128.5, 127.7, 127.5, 126.9, 86.6, 75.1, 71.5, 67.3, 65.2, 63.5, 37.1, 35.6, 32.2, 26.9, 19.3. MS (FD) calc'd for $C_{42}H_{48}O_6SSi$ 708.2941, found *m/z* (M+1) 473.2208 (100%).[1]

4-Indolyl-1-(triphenylmethoxy)butan-2-ol: To a solution of diol **35** (2.0 g, 9.75 mmol) in CH_2Cl_2 (20 mL) was added Et_3N (1.5 mL, 10.7 mmol) followed by trityl chloride (2.7 g, 9.75 mmol) and the reaction mixture stirred at room temperature for 24 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with CH_2Cl_2. The organic layer was washed with saturated aqueous NaCl, dried ($MgSO_4$)

and the solvent removed *in vacuo* to afford an oil that was purified by column chromatography (4:1 CH_2Cl_2:hexanes) to afford 2.67 g (61%) the trityl protected derivative of **36**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.54 (d, 1H, J = 7.5 Hz), 7.42-7.20 (m, 17H), 7.10 (t, 1H, J = 7.4 Hz), 7.00 (t, 1H, J = 7.1 Hz), 6.41 (d, 1H, J = 2.8 Hz), 5.04 (d, 1H, J = 5.5 Hz), 4.21 (t, 2H, J = 6.8 Hz), 3.68-3.50 (m, 1H), 3.05-2.93 (m, 1H), 2.83-2.75 (m, 1H), 2.17-1.97 (m, 1H), 1.71-1.65 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 143.9, 135.6, 128.6, 128.3, 128.2, 127.9, 127.0, 120.9, 120.5, 118.8, 109.7, 100.4, 85.7, 67.6, 66.7, 42.4, 34.4. IR ($CHCl_3$) v 3060, 3009, 1512, 1490, 1464, 1449, 1317, 1073 cm^{-1}. Anal. calc'd for $C_{31}H_{29}NO_2$ C, 83.19, H, 6.53, N, 3.13, found C, 82.89, H, 6.38, N, 3.18.

***tert*-Butyl 2-{3-indolyl-1-[(triphenylmethoxy)methyl]propoxy}acetate:** To a solution of alcohol (0.5 g, 1.12 mmol), prepared above, in THF (5 mL) was added *tert*-BuOK (0.15 g, 1.34 mmol) and the mixture heated to 45 °C for 1 h. HMPA (214 *u*L, 1.23 mmol) was added followed by *tert*-butyl bromoacetate (331 *u*L, 2.24 mmol) and the reaction mixture heated at 45 °C for 18 h. then cooled to room temperature, quenched with saturated aqueous NH_4Cl and diluted with EtOAc The organic layer was washed with saturated aqueous NaCl, dried ($MgSO_4$) and the solvent removed *in vacuo* to give a brown oil that was purified by column chromatography (4:1 hexanes:EtOAc) to afford 0.36 g (57%) of the ester as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, 1H, J = 7.9 Hz), 7.41-7.06 (m, 19H), 6.46 (d, 1H, J = 3.0 Hz), 4.37-4.24 (m, 2H), 4.13 (d, 1H, J = 16.2 Hz), 3.94 (d, 1H, J = 16.2 Hz), 3.35-3.29 (m, 1H), 3.22-3.11 (m, 2H), 2.07 (q, 2H, J = 6.6 Hz), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 143.6, 135.7, 130.6, 128.5, 127.8, 127.7, 127.2, 126.9, 125.8, 121.1, 120.7, 119.0, 109.4, 100.8, 81.4, 67.9, 65.4, 42.4, 32.5, 28.0, 27.9. IR ($CHCl_3$) v 3008, 1743, 1464, 1449, 1369, 1237, 1159, 1136 cm^{-1}. Anal. calc'd for $C_{37}H_{39}NO_4$ C, 79.12, H, 7.00, N, 2.49, found C, 78.96, H, 7.02, N, 2.78.

2-{3-Indolyl-1-[(triphenylmethoxy)methyl]propoxy}ethan-1-ol (45): To a solution of ester, prepared above, (1.70 g, 3.03 mmol) in Et_2O (15 mL) at 0 °C was added $LiAlH_4$ (0.11 g, 3.03 mmol) and the mixture allowed to warm to room temperature and stir for 2 h. The reaction mixture was quenched with water and

diluted with CH_2Cl_2. The organic layer was washed with saturated aqueous NaCl, dried ($MgSO_4$) and the solvent removed *in vacuo* to give a yellow oil that was purified by column chromatography (4:1 hexanes:EtOAc) to afford 1.15 g **45** (77%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, 1H, J = 7.5 Hz), 7.46-7.36 (m, 6H), 7.35-7.04 (m, 13H), 6.49 (d, 1H, J = 2.7 Hz), 4.30-4.10 (m, 2H), 3.78-3.69 (m, 2H), 3.69-3.60 (m, 1H), 3.51-3.41 (m, 1H), 3.36-3.26 (m, 1H), 3.22 (d, 2H, J = 4.5 Hz), 2.19-2.06 (m, 2H), 2.06-1.96 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 135.7, 128.5, 128.2, 127.7, 127.6, 126.9, 125.8, 121.3, 120.8, 119.1, 109.2, 101.0, 86.7, 76.4, 70.9, 64.9, 62.1, 42.3, 32.3. IR ($CHCl_3$) *v* 3009, 2930, 1512, 1490, 1464, 1449, 1336, 1317, 1184, 1114, 1125, 1087, 1048, 1034 cm^{-1}. HRMS (FAB+) calc'd for $C_{33}H_{33}NO_3$ 491.2460, found *m/z* (M+) 491.2466 (100%).

1. The presence of the *tert*-butyldiphenylsilyl group gave difficulty in obtaining an accurate HRMS.