Nanoscale Molecular Rods with a new Building Block for Solubility Enhancement

Pablo Wessig and Kristian Möllnitz*

Institut für Chemie, Humboldt-Universität zu Berlin, D-12489 Berlin

pablo.wessig@chemie.hu-berlin.de

Supporting Information

Contents

General Considerations: All reactions using dry solvents were performed under argon in flame-dried flasks. The solvents were dried and distilled prior to use by means of usual laboratory methods. All reagents obtained from commercial sources were used without further purification. Thin-layer chromatography (TLC) was performed on silica gel plates (Silica gel 60 F_{254}), and silica gel (230 – 400 mesh) was used for flash chromatography. IR spectra were recorded as KBr pellets or as films. Chemical shifts are reported in ppm using tetramethylsilane as internal standard. The assignment of the NMR peaks was confirmed by ^{1}H-^{1}H-COSY and HSQC experiments.

1,4-Diethyl-2,3,5,6-tetramethoxy-benzene (15a): To a solution of **14a** (2.15 g, 7.62 mmol) in CF_3COOH (12 mL) was added dropwise $HSiEt_3$ (6.10 mL, 38.51 mmol, 5.0 equiv) and stirred until complete conversion of **14a** controlled by TLC. Water and $NaHCO_3$ solution were added until gas evolution ceased and the resulting mixture was extracted twice with CH_2Cl_2. The combined organic layers was dried, evaporated and purified by flash chromatography (CH_2Cl_2) yielding **15a** as a white solid (1.76 g, 6.92 mmol, 91%). R_f = 0.8 (CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): σ 1.14 ($CH_2C\underline{H}_3$, 6H, t, ^{3}J = 7.5 Hz), 2.61 ($C\underline{H}_2$, 4H, q, ^{3}J = 7.5 Hz), 3.80 ($OC\underline{H}_3$, 12H, s); ^{13}C NMR (75 MHz, $CDCl_3$): σ 15.5 ($CH_2\underline{C}H_3$), 17.7 ($\underline{C}H_2$), 60.6 ($O\underline{C}H_3$), 129.3 ($\underline{C}_{Ar}CH_2$), 147.3 ($\underline{C}OCH_3$); mp 75 – 76°C; IR: 2973, 2936, 1459, 1410, 1103, 1022 cm^{-1}; HRMS (EI): calcd for $C_{14}H_{22}O_4$ [M^+]: 254.1518, found: 254.1519.

[2,5-Diethyl-3,4,6-tris[(trimethylsilyl)oxy]phenoxy]trimethyl-silane (17a): To a solution of **15a** (1.69 g, 6.65 mmol) in CCl_4 (17 mL) was added TMSI (5.50 mL, 40.41 mmol, 6.1 equiv) and the mixture was stirred over night at 70°C. The solvent

was evaporated and the resulting residue was purified by flash chromatography (PE/CH_2Cl_2 5:1) yielding **17a** as a white solid (3.83 g, 7.06 mmol, 89%). R_f = 0.7 (PE:CH_2Cl_2 5:1); ^{1}H NMR (300 MHz, $CDCl_3$): σ 0.18 ($Si(C\underline{H}_3)_3$, 36H, s), 1.07 ($CH_2C\underline{H}_3$, 6H, t, ^3J = 7.4 Hz), 2.52 ($C\underline{H}_2$, 4H, q, ^3J = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): σ 0.7 ($Si(\underline{C}H_3)_3$), 13.5 ($CH_2\underline{C}H_3$), 19.4 ($\underline{C}H_2$), 125.4 ($\underline{C}_{Ar}CH_2$), 139.5 ($\underline{C}OSi(CH_3)_3$); mp 41 – 42°C; IR: 2962, 1442, 1248, 1100, 973, 850 cm^{-1}; HRMS (EI): calcd for $C_{22}H_{46}O_4Si_4$ [M^+]: 486.2473, found: 486.2472.

***N*-Trifluoroacetyl-4-hydroxy-piperidine (21a)**: To a suspension of 4-hydroxypiperidine (3.99 g, 39.45 mmol) and NEt_3 (5.81 mL, 41.61 mmol, 1.05 equiv) in anhyd dioxane (150 mL) was added dropwise at 0°C $(CF_3CO)_2O$ (5.9 mL, 42.42 mmol, 1.08 equiv). After stirring 2h at room temperature Et_2O (200 mL) was added and the organic layer was washed with saturated aq $NaHCO_3$ and brine. The organic layer was dried, evaporated and the resulting residue was purified by flash chromatography (CH_2Cl_2/MeOH 100:3) yielding **21a** as a colorless oil (3.56 g, 18.05 mmol, 46%). R_f = 0.2 (CH_2Cl_2/MeOH 100:3); ^{1}H NMR (300 MHz, $CDCl_3$): σ 1.55 – 1.68 (($C\underline{H}_2)_2CH$, 2H, m), 1.86 – 1.95 (($C\underline{H}_2)_2CH$, 2H, m), 2.62 (O$\underline{H}$, 1H, s), 3.37 – 3.52 (N($C\underline{H}_2)_2$), 2H, m), 3.77 – 3.95 (N($C\underline{H}_2)_2$), 2H, m), 4.00 – 4.01 (C$\underline{H}$, 1H, m); ^{13}C NMR (75 MHz, $CDCl_3$): σ 33.1 (($\underline{C}H_2)_2CH$), 34.0 (($\underline{C}H_2)_2CH$), 40.5 (N($\underline{C}H_2)_2$), 42.5 ((N($\underline{C}H_2)_2$), 65.6 ($\underline{C}H$), 116.4 ($\underline{C}F_3$, q, ^1J = 288 Hz), 155.4 ($\underline{C}O$, q, ^2J = 36 Hz); IR: 3423, 1688, 1675, 1202, 1179, 1141 cm^{-1}; HRMS (EI): calcd for $C_7H_{10}F_3NO_2$ [M^+]: 197.0664, found: 197.0664.

***N*-Chloroacetyl-4-hydroxy-piperidine (21b)**: To a suspension of 4-hydroxypiperidine (5.00 g, 49.43 mmol) and K_2CO_3 (13.66 g, 98.86 mmol, 2.0 equiv) in EtOAc/H_2O (v/v 4:1, 200 mL) was added dropwise at 0°C chloracetyl chloride

(5.10 mL, 51.90 mmol, 1.05 equiv). After stirring 2h at room temperature Et_2O (250 mL) was added and the organic layer was washed with saturated aq $NaHCO_3$ and brine. The organic layer was dried, evaporated and the resulting residue was purified by flash chromatography (CH_2Cl_2/MeOH 100:6) yielding **21b** as a colorless oil (5.64 g, 31.74 mmol, 64%). R_f = 0.4 (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (300 MHz, $CDCl_3$): σ 1.46 – 1.65 ((C$\underline{H}_2$)$_2$CH, 2H, m), 1.81 – 1.95 ((C$\underline{H}_2$)$_2$CH, 2H, m), 3.00 – 3.08 (O$\underline{H}$, 1H, m), 3.23 – 3.32 (N(C$\underline{H}_2$)$_2$, 2H, m), 3.68 – 3.76 (N(C$\underline{H}_2$)$_2$, 1H, m), 3.90 – 3.98 (N(C$\underline{H}_2$)$_2$ + C$\underline{H}$, 1H+1H, m), 4.06 (C$\underline{H}_2$Cl, 2H, s); ^{13}C NMR (75 MHz, $CDCl_3$): σ 33.3 ((C$\underline{H}_2$)$_2$CH), 34.0 ((C$\underline{H}_2$)$_2$CH), 39.4 (N(C$\underline{H}_2$)$_2$), 40.9 (C$\underline{H}_2$Cl), 43.4 ((N(C$\underline{H}_2$)$_2$), 66.1 (C$\underline{H}$), 165.0 (C$\underline{O}$); IR: 3423, 1631, 1453, 1071 cm^{-1}; HRMS (EI): calcd for $C_7H_{12}ClNO_2$ [M$^+$]: 177.0557, found: 177.0557.

***N*-(2-Trimethysilylethoxycarbonyl)-4-hydroxy-piperidine (21c)**: A solution of 2-(trimethylsilyl)-1-ethanol (2.04 g, 17.28 mmol), NEt_3 (2.4 mL, 17.28 mmol, 1.0 equiv) and phosgene (20% in toluene, 22.7 mL, 43.19 mmol, 2.5 equiv) was stirred in a sealed flask overnight. The solvent was evaporated and the resulting residue was suspended in dioxane (100 mL) and added to a suspension of 4-hydroxypiperidine (1.76 g, 17.40 mmol, 1.0 equiv) and K_2CO_3 (4.81 g, 34.80 mmol, 2.0 equiv) in dioxane/H_2O (v/v 4:1, 200 mL). The reaction mixture stirred 2h at room temperature, diluted with CH_2Cl_2 and the aq layer was extracted two times with CH_2Cl_2. The combined organic layers were dried, evaporated and the resulting residue was purified by flash chromatography (CH_2Cl_2/MeOH 100:4) yielding **21c** as a colorless oil (1.30 g, 5.29 mmol, 31%). R_f = 0.2 (CH_2Cl_2/MeOH 100:4); ^{1}H NMR (300 MHz, $CDCl_3$): σ 0.03 (Si(C$\underline{H}_3$)$_3$, 9H, s), 0.96 – 1.01 (C$\underline{H}_2$Si, 2H, m), 1.39 – 1.52 ((C$\underline{H}_2$)$_2$CH, 2H, m), 1.81 – 1.87 ((C$\underline{H}_2$)$_2$CH, 2H, m), 2.30 (O$\underline{H}$, 1H, s), 3.03 – 3.12 (N(C$\underline{H}_2$)$_2$, 2H, m), 3.78

– 3.89 (N(C$\underline{H}_2$)$_2$ + C$\underline{H}$, 2H + 1H, m), 4.13 – 4.18 (C$\underline{H}_2$O, 2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): σ –1.53 (Si($\underline{C}H_3$)$_3$), 17.6 ($\underline{C}H_2$Si), 34.0 (($\underline{C}H_2$)$_2$CH), 41.1 (N($\underline{C}H_2$)$_2$), 63.5 ($\underline{C}H_2$O), 67.3 ($\underline{C}$H), 155.6 ($\underline{C}$O); IR: 3428, 2952, 1667, 1432, 1225, 838 cm^{-1}; HRMS (ESI): calcd for $C_{11}H_{24}NO_3Si$ [M+H$^+$]: 246.1521, found: 246.1520.

***N*-Trifluoroacetyl-piperidin-4-one (22a)**: To a solution of DMSO (2.60 mL, 36.64 mmol, 2.1 equiv) in anhyd CH_2Cl_2 (120 mL) was added dropwise at -78°C oxalyl dichloride (2.30 mL, 26.75 mmol, 1.5 equiv). After stirring 30 min **21a** (3.48 g, 17.65 mmol) dissolved in anhyd CH_2Cl_2 (20 mL) was added and stirred 30 min. The reaction mixture was treated with NEt_3 (12.3 mL, 88.25 mmol, 5.0 equiv) and was stirred 15 min during warming up to room temperature. CH_2Cl_2 was added and the organic layer was washed with aq. tartaric acid, the solvent was evaporated and the resulting residue was purified by flash chromatography (CH_2Cl_2/MeOH 100:1) yielding **22a** as a white solid (3.28 g, 16.82 mmol, 95%). R_f = 0.6 (CH_2Cl_2/MeOH 100:4); ^{1}H NMR (300 MHz, $CDCl_3$): σ 2.53 – 2.59 (($C\underline{H}_2$)$_2$CO, 4H, m), 3.87 – 3.96 (N($C\underline{H}_2$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): σ 40.1 (($\underline{C}H_2$)$_2$CO), 40.8 (($\underline{C}H_2$)$_2$CO), 42.6 (N($\underline{C}H_2$)$_2$), 43.9 (N($\underline{C}H_2$)$_2$), 116.2 ($\underline{C}F_3$, q, ^1J = 288 Hz), 155.7 (N$\underline{C}$O, q, ^2J = 37 Hz), 204.6 ($\underline{C}$O); mp 75 – 76°C; IR: 1718, 1715, 1688, 1194, 1179, 1132 cm^{-1}; HRMS (EI): calcd for $C_7H_8F_3NO_2$ [M$^+$]: 195.0507, found: 195.0507.

***N*-Chloracetyl-piperidin-4-one (22b)**: To a solution of **21b** (5.53 g, 31.15 mmol) in anhyd CH_2Cl_2 (220 mL) was added Dess-Martin periodinane (15.87 g, 37.42 mmol, 1.2 equiv) and stirred at room temperature until complete conversion of **21b** controlled by TLC. The organic layer was washed two times with aq $NaHCO_3$/$Na_2S_2O_3$ (125 mL) and once with aq $NaHCO_3$ (100 mL). The solvent was

evaporated and the resulting residue was purified by flash chromatography (CH_2Cl_2/MeOH 100:3) yielding **22b** as a colorless oil (4.55 g, 25.90 mmol, 83%). R_f = 0.35 (CH_2Cl_2/MeOH 100:4); ^{1}H NMR (300 MHz, $CDCl_3$): σ 2.46 – 2.57 (($C\underline{H}_2)_2CO$, 4H, m), 3.78 – 3.88 ($N(C\underline{H}_2)_2$, 4H, m), 4.14 ($C\underline{H}_2Cl$, 2H, s); ^{13}C NMR (75 MHz, $CDCl_3$): σ 40.3 (($\underline{C}H_2)_2CO$), 40.8 (($\underline{C}H_2)_2CO$ + $\underline{C}H_2Cl$), 41.3 ($N(\underline{C}H_2)_2$), 44.6 (($N(\underline{C}H_2)_2$), 165.3 ($N\underline{C}O$), 205.9 ($\underline{C}O$); IR: 1717, 1645, 1446 cm^{-1}; HRMS (EI): calcd for $C_7H_{10}ClNO_2$ [M^+]: 175.0400, found: 175.0401.

***N*-(2-Trimethysilylethoxycarbonyl)-piperidin-4-one (22c)**: To a solution of **21c** (1.25 g, 5.08 mmol) in anhyd CH_2Cl_2 (50 mL) was added Dess-Martin periodinane (2.26 g, 5.33 mmol, 1.05 equiv) and stirred at room temperature until complete conversion of **21c** controlled by TLC. The organic layer was washed two times with aq $NaHCO_3$/$Na_2S_2O_3$ (50 mL) and once with aq $NaHCO_3$ (50 mL). The solvent was evaporated and the resulting residue was purified by flash chromatography (CH_2Cl_2/MeOH 100:2) yielding **22c** as a colorless oil (1.03 g, 4.25 mmol, 84%). R_f = 0.4 (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (300 MHz, $CDCl_3$): σ 0.05 ($Si(C\underline{H}_3)_3$, 9H, s), 1.00 – 1.05 ($SiC\underline{H}_2$, 2H, m), 2.42 – 2.46 (($C\underline{H}_2)_2CO$, 4H, m), 3.74 – 3.78 ($N(C\underline{H}_2)_2$, 4H, m), 4.20 – 4.25 ($C\underline{H}_2O$, 2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): σ –1.5 ($Si(\underline{C}H_3)_3$), 17.7 ($Si\underline{C}H_2$), 41.1 ($N(\underline{C}H_2)_2$), 42.9 (($\underline{C}H_2)_2CO$), 64.1 ($\underline{C}H_2O$), 155.4 ($N\underline{C}O$), 207.4 ($\underline{C}O$); IR: 1691, 1429, 1230, 834 cm^{-1}; HRMS (ESI): calcd for $C_{11}H_{21}NNaO_3Si$ [M+Na^+]: 266.1185, found: 266.1183.

3,3-Bis(hydroxymethyl)-9-trifluoroacetyl-1,5-dioxa-9-azaspiro[5.5]undecane (23a): A solution of **22a** (1.00 g, 5.15 mmol), pentaerythritol (1.05 g, 7.71 mmol, 1.5 equiv) and *p*-toluenesulfonic acid mono hydrate (39 mg, 0.21 mmol, 0.04 equiv) in

DMF/benzene (v/v 3:2, 20 mL) was heated under reflux for 2 h. The water formed during the acetalisation was collected in a Dean-Stark trap. Aq $NaHCO_3$ solution was added and the aq layer was extracted several times with CH_2Cl_2. The combined organic layers were dried, evaporated and the resulting residue was purified by flash chromatography (CH_2Cl_2/MeOH 100:6) yielding **23a** as a white solid (494 mg, 1.58 mmol, 31%). R_f = 0.4 (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (300 MHz, $CDCl_3$): σ 1.91 – 1.95 ($N(CH_2C\underline{H}_2)_2$, 4H, m), 2.76 (O<u>H</u>, 2H, s), 3.59 – 3.62 ($N(C\underline{H}_2)_2$, 2H, m), 3.67 – 3.71 ($N(C\underline{H}_2)_2$, 2H, m), 3.73 – 3.79 ($C(C\underline{H}_2O)_4$, 8H, m); ^{13}C NMR (75 MHz, $CDCl_3$): σ 31.7 ($N(CH_2\underline{C}H_2)_2$), 33.1 ($N(CH_2\underline{C}H_2)_2$), 39.3 ($\underline{C}(CH_2O)_4$), 40.4 ($N(\underline{C}H_2)_2$), 42.4 ($N(\underline{C}H_2)_2$), 62.1 ($C(\underline{C}H_2O)_4$), 64.4 ($C(\underline{C}H_2O)_4$), 96.1 ($\underline{C}(CH_2)_2$), 116.5 ($\underline{C}F_3$, q, ^1J = 278 Hz), 155.4 ($\underline{C}O$, q, ^2J = 36 Hz); mp 115 – 116°C; IR: 3327, 1694, 1459, 1140 cm^{-1}; HRMS (ESI): calcd for $C_{12}H_{22}N_2O_5F_3$ $[M+NH_4^+]$: 331.1477, found: 331.1475.

3,3-Bis(hydroxymethyl)-9-chloroacetyl-1,5-dioxa-9-azaspiro[5.5]undecane (23b): A suspension of **23e** (516 mg, 1.47 mmol) and Pd/C (10%, 40 mg) in anhyd THF (70 mL) was stirred under hydrogen atmosphere ($P(H_2)$ 1 atm). After complete conversion of **23e** controlled by TLC hydrogen atmosphere was replaced by argon and 4-nitrophenyl 2-chloroacetate (348 mg, 1.61 mmol, 1.1 equiv) was added at 0°C. The reaction mixture was stirred over night at room temperature, filtered over Celite® and the solvent was evaporated. The resulting residue was purified by flash chromatography (CH_2Cl_2/MeOH 100:7) yielding **23b** as a white solid (382 mg, 1.30 mmol, 89%). R_f = 0.3 (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (300 MHz, CD_3OD): σ 1.83 – 1.95 ($N(CH_2C\underline{H}_2)_2$, 4H, m), 3.52 – 3.62 ($N(C\underline{H}_2)_2$ + $C(C\underline{H}_2O)_4$, 4H + 4H, m), 3.76 ($C(C\underline{H}_2O)_4$, 4H, s), 4.25 ($C\underline{H}_2Cl$, 2H, s); ^{13}C NMR (75 MHz, CD_3OD): σ 33.0 ($N(CH_2\underline{C}H_2)_2$), 34.1 ($N(CH_2\underline{C}H_2)_2$), 40.4 ($N(\underline{C}H_2)_2$), 40.8 ($\underline{C}(CH_2O)_4$), 42.1 ($\underline{C}H_2Cl$),

44.3 (N($\underline{C}H_2)_2$), 62.6 (C($\underline{C}H_2O)_4$), 62.9 (C($\underline{C}H_2O)_4$), 97.2 ($\underline{C}(CH_2)_2$), 167.4 ($\underline{C}O$); mp 114 – 115°C; IR: 3423, 1623, 1472, 1458, 1105 cm^{-1}; HRMS (ESI): calcd for $C_{12}H_{20}NO_5ClNa$ [$M+Na^+$]: 316.0919, found: 316.0922.

3,3-Bis(hydroxymethyl)-9-(2-trimethylsilylethoxycarbonyl)-1,5-dioxa-9-azaspiro[5.5]undecane (23c): A solution of **22c** (991 mg, 4.07 mmol), pentaerythritol (832 mg, 6.11 mmol, 1.5 equiv) and *p*-toluenesulfonic acid mono hydrate (32 mg, 0.17 mmol, 0.04 equiv) in DMF/benzene (v/v 3:2, 15 mL) was heated under reflux for 2 h. The water formed during the acetalisation was collected in a Dean-Stark trap. Aq $NaHCO_3$ solution was added and the aq layer was extracted several times with CH_2Cl_2. The combined organic layers were dried, evaporated and the resulting residue was purified by flash chromatography (CH_2Cl_2/MeOH 100:7) yielding **23c** as a white solid (1.06 g, 2.92 mmol, 72%). R_f = 0.4 (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (300 MHz, $CDCl_3$): σ 0.04 (Si($\underline{C}H_3)_3$, 9H, s), 0.96 – 1.02 (Si$\underline{C}H_2$, 2H, m), 1.82 (N($CH_2\underline{C}H_2)_2$, 4H, bs), 3.12 (O$\underline{H}$, 2H, s), 3.45 – 3.49 (N($\underline{C}H_2)_2$, 4H, m), 3.71 – 3.73 (C($\underline{C}H_2O)_4$, 8H, m), 4.13 – 4.19 ($\underline{C}H_2OC(O)$), 2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): σ –1.4 (Si($\underline{C}H_3)_3$), 17.7 (Si$\underline{C}H_2$), 31.8 ((N($CH_2\underline{C}H_2)_2$), 32.5 ((N($CH_2\underline{C}H_2)_2$), 39.3 ($\underline{C}(CH_2O)_4$), 40.5 (N($\underline{C}H_2)_2$), 62.1 (C($\underline{C}H_2O)_4$), 63.7 ($\underline{C}H_2OC(O)$), 64.4 (C($\underline{C}H_2O)_4$), 96.8 ($\underline{C}(CH_2)_2$), 155.7 ($\underline{C}O$); mp 110 – 112°C; IR: 3285, 2957, 1698, 1229 cm^{-1}; HRMS (EI): calcd for $C_{16}H_{31}NO_6Si$ [M^+]: 361.1921, found: 361.1921.

3,3-Bis(hydroxymethyl)-9-(fluoren-9-ylmethoxycarbonyl)-1,5-dioxa-9-azaspiro[5.5]undecane (23d): A suspension of **23e** (413 mg, 1.18 mmol) and Pd/C (10%, 30 mg) in anhyd THF (40 mL) was stirred under hydrogen atmosphere (p(H_2) 1 atm). After complete conversion of **23e** controlled by TLC hydrogen atmosphere was

replaced by argon, *N*-ethyldiisopropylamine (220 µL, 1.33 mmol, 1.1 equiv) and FmocOSu (440 mg, 1.30 mmol, 1.1 equiv). The reaction mixture was stirred over night, CH_2Cl_2 was added and the organic layer was washed with aq tartaric acid solution. The organic layer was dried, evaporated and the resulting residue was purified by flash chromatography (CH_2Cl_2/MeOH 100:7) yielding **23d** as a white solid (494 mg, 1.12 mmol, 96%). R_f = 0.4 (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (300 MHz, $CDCl_3$): σ 1.82 ($N(CH_2C\underline{H}_2)_2$, 4H, bs), 2.93 (O<u>H</u>, 2H, s), 3.50 ($N(C\underline{H}_2)_2$, 4H, bs), 3.75 ($C(C\underline{H}_2O)_4$, 8H, s), 4.26 (C<u>H</u>, 1H, t, ^3J = 6.8 Hz), 4.44 ($C\underline{H}_2CH$, 2H, d, ^3J = 6.8 Hz), 7.33 ($C\underline{H}_{Ar}$, 2H, dt, ^3J = 7.4 Hz, ^4J = 1.2 Hz), 7.42 ($C\underline{H}_{Ar}$, 2H, dt, ^3J = 7.4 Hz, ^4J = 0.6 Hz), 7.59 ($C\underline{H}_{Ar}$, 2H, d, ^3J = 7.6 Hz), 7.78 ($C\underline{H}_{Ar}$, 2H, d, ^3J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): σ 31.9 ($N(CH_2\underline{C}H_2)_2$), 32.4 ($N(CH_2\underline{C}H_2)_2$), 39.2 ($\underline{C}(CH_2O)_4$), 40.6 ($N(\underline{C}H_2)_2$), 47.2 (<u>C</u>H), 62.0 ($C(\underline{C}H_2O)_4$), 64.4 ($C(\underline{C}H_2O)_4$), 67.3 ($C\underline{H}_2CH$), 96.6 ($\underline{C}(CH_2)_2$), 119.9 ($\underline{C}H_{Ar}$), 124.9 ($\underline{C}H_{Ar}$), 127.0 ($\underline{C}H_{Ar}$), 127.7 ($\underline{C}H_{Ar}$), 141.3 ($\underline{C}_{Ar}$), 143.9 ($\underline{C}_{Ar}$), 155.1 (<u>C</u>O); mp 138 – 140°C; IR: 3423, 1688, 1227, 1098 cm^{-1}; HRMS (EI): calcd for $C_{25}H_{30}NO_6$ [M+H$^+$]: 440.2073, found: 440.2068.

3,3-Bis(hydroxymethyl)-9-azidoacetyl-1,5-dioxa-9-azaspiro[5.5]undecane (23f): A suspension of **23b** (694 mg, 2.36 mmol) and NaN_3 (190 mg, 2.92 mmol, 1.2 equiv) in dry DMF (7 mL) was stirred 2 h at room temperature. Brine was added and the aq layer was extracted several times with CH_2Cl_2. The combined organic layers were dried, evaporated and the resulting residue was purified by flash chromatography (CH_2Cl_2/MeOH 100:8) yielding **23f** as a white solid (346 mg, 1.15 mmol, 49%). R_f = 0.35 (CH_2Cl_2/MeOH 10:1); ^{1}H NMR (300 MHz, CD_3OD): σ 1.84 – 1.90 ($N(CH_2C\underline{H}_2)_2$, 4H, m), 3.38 – 3.42 ($N(C\underline{H}_2)_2$, 2H, m), 3.56 – 3.62 ($N(C\underline{H}_2)_2$ + $C(C\underline{H}_2O)_4$, 2H + 4H, m), 3.76 ($C(C\underline{H}_2O)_4$, 4H, s) , 4.11 ($C\underline{H}_2N_3$, 2H, s); ^{13}C NMR (75

MHz, CD_3OD): σ 33.1 ($N(CH_2\underline{C}H_2)_2$), 34.0 ($N(CH_2\underline{C}H_2)_2$), 40.2 ($N(\underline{C}H_2)_2$), 40.8 ($\underline{C}(CH_2O)_4$), 42.9 ($N(\underline{C}H_2)_2$), 51.6 ($\underline{C}H_2N_3$), 62.6 ($C(\underline{C}H_2O)_4$), 62.7 ($C(\underline{C}H_2O)_4$), 62.9 ($C(\underline{C}H_2O)_4$), 97.3 ($\underline{C}(CH_2)_2$), 168.1 ($\underline{C}O$); mp 120 – 121°C; IR: 3412, 2099, 1624, 1235, 1100 cm^{-1}; HRMS (EI): calcd for $C_{12}H_{20}N_4O_5Na$ [$M+Na^+$]: 323.1325, found: 323.1326.

3,3-Bis(hydroxymethyl)-1,5-dioxa-9-azaspiro[5.5]undecane (24): For the determination of analytical data of compound **24** a suspension of **23e** (1015 mg, 2.89 mmol) and Pd/C (10%, 70 mg) in anhyd MeOH (40 mL) was stirred under hydrogen atmosphere ($p(H_2)$ 1 atm). After complete conversion of **23e** controlled by TLC the suspension was filtered by filter-cannula. The solvent was evaporated giving 24 as a white solid (625 mg, 2.88 mmol, >99%). R_f = 0.2 (MeOH/aq NH_3 (25%) 3:1); ^1H NMR (300 MHz, DMSO-D_6): σ 1.64 ($N(CH_2C\underline{H}_2)_2$, 4H, bs), 2.61 ($N(C\underline{H}_2)_2$, 4H, bs), 3.58 ($C(C\underline{H}_2O)_4$, 8H, s); ^{13}C NMR (75 MHz, DMSO-D_6): σ 33.5 ($N(CH_2\underline{C}H_2)_2$), 39.1 ($\underline{C}(CH_2O)_4$), 42.6 ($N(\underline{C}H_2)_2$), 60.6 ($C(\underline{C}H_2O)_4$), 60.8 ($C(\underline{C}H_2O)_4$), 96.1 ($\underline{C}(CH_2)_2$); mp 172 – 174°C; IR: 3272, 2938, 2869, 1630, 1040 cm^{-1}; HRMS (EI): calcd for $C_{10}H_{19}N_1O_4$ [M^+]: 217.1314, found: 217.1314.

General procedure for the Preparation of Octaspiranes 26 (GP1). An ice-cooled solution of **6** in Et_2O was treated with NaH (2.0 equiv) and TMSCl (2.0 equiv) and stirred for 1h. The corresponding diol **25** or **26** (2.0 equiv) and TMSOTf (0.1 equiv) were added and the reaction mixture was stirred at room temperature until complete conversion was indicated by TLC. The solvent was evaporated and the resulting residue was purified by flash chromatography.

4’’’’,8’’’’-Dibutyl-octaspiro[cyclohexane-1,2’-[1,3]dioxane-5’,5’’-[1,3]dioxane-2’’,1’’’-cyclohexane-4’’’,2’’’’-[1,3]dioxolo[4,5-*f*][1,3]benzodioxole-6’’’’,1’’’’’-cyclohexane-4’’’’’,2’’’’’’-[1,3]dioxane-5’’’’’’,5’’’’’’’-[1,3]dioxane-2’’’’’’’,1’’’’’’’’-cyclohexane (26a): According to GP1 ketone **6** (201 mg, 0.45 mmol) and diol **25** (196 mg, 0.91 mmol, 2.0 equiv) in anhyd Et_2O (55 mL) was treated with TMSOTf (3 drops). Purification by flash chromatography (PE/EtOAc 2:1) giving **26a** as a pale yellow solid (155 mg, 0.18 mmol, 41%). R_f = 0.5 (PE/EtOAc 2:1); ^{1}H NMR (300 MHz, $CDCl_3$): σ 0.90 ($C\underline{H}_3$, 6H, t, ^3J = 7.3 Hz), 1.26 – 1.36 ($C\underline{H}_2CH_3$, 4H, m), 1.38 – 1.43 ($C(CH_2CH_2)_2C\underline{H}_2$, 4H, m), 1.50 – 1.60 ($C_{Ar}CH_2C\underline{H}_2$ + $C(CH_2C\underline{H}_2)_2CH_2$, 4H + 8H, m), 1.74 – 1.75 ($C(C\underline{H}_2CH_2)_2CH_2$, 8H, m), 1.97 – 2.05 ($C(C\underline{H}_2C\underline{H}_2)_2C$, 16H, m), 2.47 ($C_{Ar}C\underline{H}_2$, 4H, t, ^3J = 7.2 Hz), 3.75 – 3.78 ($C(C\underline{H}_2O)_4$, 16H, m); ^{13}C NMR (75 MHz, $CDCl_3$): σ 13.8 ($\underline{C}H_3$), 22.1 ($\underline{C}H_2CH_3$), 22.4 ($C(CH_2\underline{C}H_2)_2CH_2$), 23.6 ($C_{Ar}\underline{C}H_2CH_2$), 25.6 ($C(CH_2CH_2)_2\underline{C}H_2$), 28.7 ($C(\underline{C}H_2\underline{C}H_2)_2C$), 30.6 ($C(\underline{C}H_2\underline{C}H_2)_2C$), 30.8 ($C_{Ar}CH_2\underline{C}H_2$), 32.3 ($C(\underline{C}H_2CH_2)_2CH_2$), 32.8 ($\underline{C}(CH_2O)_4$), 63.1 ($C(\underline{C}H_2O)_4$), 63.8 ($C(\underline{C}H_2O)_4$), 97.5 ($C((CH_2O)_2)_2\underline{C}$), 98.6 ($C((CH_2O)_2)_2\underline{C}$), 106.1 ($\underline{C}_{Ar}CH_2$), 116.5 ($(C_{Ar}O)_2\underline{C}(CH_2CH_2)_2$), 138.5 ($\underline{C}_{Ar}O$); mp 280 – 281°C; IR: 2932, 1440, 1378, 1095 cm^{-1}; MS (MALDI): calcd for $C_{48}H_{70}O_{12}$ [M^+]: 838.5, found: 837.1.

4’’’’,8’’’’-Dibutyl-1,1’’’’’’’-bis(trifluoroacetyl)-octaspiro[piperidine-4,2’-[1,3]dioxane-5’,5’’-[1,3]dioxane-2’’,1’’’-cyclohexane-4’’’,2’’’’-[1,3]dioxolo[4,5-*f*][1,3]benzodioxole-6’’’’,1’’’’’-cyclohexane-4’’’’’,2’’’’’’-[1,3]dioxane-5’’’’’’,5’’’’’’’-[1,3]dioxane-2’’’’’’’,4’’’’’’’’-piperidine (26b): According to GP1 ketone **6** (201 mg, 0.45 mmol) and diol **23a** (283 mg, 0.90 mmol, 2.0 equiv) in anhyd Et_2O (55 mL) was treated with TMSOTf (3 drops). Purification by flash

chromatography (PE/EtOAc 2:1) giving **26b** as a pale yellow solid (354 mg, 0.34 mmol, 76%) and **27b** as a yellow solid (49 mg, 0.07 mmol, 15%). R_f = 0.2 (PE/EtOAc 5:2); ^{1}H NMR (300 MHz, $CDCl_3$): σ 0.90 ($C\underline{H}_3$, 6H, t, ^3J = 7.3 Hz), 1.26 – 1.38 ($C\underline{H}_2CH_3$, 4H, m), 1.50 – 1.60 ($C_{Ar}CH_2C\underline{H}_2$, 4H, m), 1.93 – 2.05 (($C\underline{H}_2CH_2)_2N$ + $C(C\underline{H}_2C\underline{H}_2)_2C$, 8H + 16H, m), 2.47 ($C_{Ar}C\underline{H}_2$, 4H, t, ^3J = 7.2 Hz), 3.58 – 3.63 ($N(C\underline{H}_2)_2$, 4H, m), 3.67 – 3.73 ($N(C\underline{H}_2)_2$, 4H, m), 3.75 – 3.82 ($C(C\underline{H}_2O)_4$, 16H, m); ^{13}C NMR (75 MHz, $CDCl_3$): σ 13.8 ($\underline{C}H_3$), 22.1 ($\underline{C}H_2CH_3$), 23.6 ($C_{Ar}\underline{C}H_2CH_2$), 28.7 ($C(\underline{C}H_2\underline{C}H_2)_2C$), 30.6 ($C(\underline{C}H_2\underline{C}H_2)_2C$), 30.8 ($C_{Ar}CH_2\underline{C}H_2$), 32.3 (($\underline{C}H_2CH_2)_2N$), 33.0 ($\underline{C}(CH_2O)_4$), 33.1 (($\underline{C}H_2CH_2)_2N$), 40.3 ($N(\underline{C}H_2)_2$), 42.3 ($N(\underline{C}H_2)_2$), 42.4 ($N(\underline{C}H_2)_2$), 63.5 ($C(\underline{C}H_2O)_4$), 96.2 ($C((CH_2O)_2)_2\underline{C}$), 97.7 ($C((CH_2O)_2)_2\underline{C}$), 106.1 ($\underline{C}_{Ar}CH_2$), 116.4 ($(C_{Ar}O)_2\underline{C}(CH_2CH_2)_2$), 116.5 ($\underline{C}F_3$, q, ^1J = 288 Hz), 138.5 ($\underline{C}_{Ar}O$), 155.3 ($\underline{C}(O)CF_3$, q, ^2J = 36 Hz); mp 255 – 258°C; IR: 2952, 2862, 1694, 1438, 1092 cm^{-1}; HRMS (ESI): calcd for $C_{50}H_{70}N_3O_{14}F_6$ [M+NH$^+$]: 1050.4743, found: 1050.4757.

4’’’’,8’’’’-Dibutyl-1-trifluoroacetyl-octaspiro[piperidine-4,2’-[1,3]dioxane-5’,5’’-[1,3]dioxane-2’’,1’’’-cyclohexane-4’’’,2’’’’-[1,3]dioxolo[4,5-*f*][1,3]benzodioxole-6’’’’,1’’’’’-cyclohexan-4’’’’’-one (27b): R_f = 0.4 (PE/EtOAc 5:2); ^{1}H NMR (300 MHz, $CDCl_3$): σ 0.92 ($C\underline{H}_3$, 6H, t, ^3J = 7.3 Hz), 1.31 – 1.39 ($C\underline{H}_2CH_3$, 4H, m), 1.54 – 1.61 ($C_{Ar}CH_2C\underline{H}_2$, 4H, m), 1.92 – 2.06 (($C\underline{H}_2CH_2)_2N$ + $C(C\underline{H}_2C\underline{H}_2)_2C$, 4H + 8H, m), 2.28 – 2.32 ($C(C\underline{H}_2C\underline{H}_2)_2CO$, 4H, m), 2.51 ($C_{Ar}C\underline{H}_2$, 4H, t, ^3J = 7.4 Hz), 2.59 – 2.63 ($C(C\underline{H}_2C\underline{H}_2)_2CO$, 4H, m), 3.59 – 3.64 ($N(C\underline{H}_2)_2$, 2H, m), 3.68 – 3.73 ($N(C\underline{H}_2)_2$, 2H, m), 3.75 – 3.82 ($C(C\underline{H}_2O)_4$, 8H, m); ^{13}C NMR (75 MHz, $CDCl_3$): σ 13.8 ($\underline{C}H_3$), 22.1 ($\underline{C}H_2CH_3$), 23.7 ($C_{Ar}\underline{C}H_2CH_2$), 28.7 ($C(\underline{C}H_2\underline{C}H_2)_2C$), 30.6 ($C(\underline{C}H_2\underline{C}H_2)_2C$), 30.9 ($C_{Ar}CH_2\underline{C}H_2$), 31.5 (($\underline{C}H_2CH_2)_2N$), 33.0 ($\underline{C}(CH_2O)_4$), 33.2 (($\underline{C}H_2CH_2)_2N$), 33.4 ($C(\underline{C}H_2\underline{C}H_2)_2CO$), 37.3 ($C(\underline{C}H_2\underline{C}H_2)_2CO$), 40.3 ($N(\underline{C}H_2)_2$), 42.4 ($N(\underline{C}H_2)_2$), 42.4

(N($\underline{C}H_2)_2$), 63.5 (C($\underline{C}H_2O)_4$), 63.6 (C($\underline{C}H_2O)_4$), 96.3 (C((CH$_2$O)$_2$)$_2\underline{C}$), 97.6 (C((CH$_2$O)$_2$)$_2\underline{C}$), 106.4 ($\underline{C}_{Ar}CH_2$), 114.7 (($C_{Ar}O)_2\underline{C}(CH_2CH_2)_2$), 116.7 (($C_{Ar}O)_2\underline{C}(CH_2CH_2)_2$), 138.2 ($\underline{C}_{Ar}O$), 138.8 ($\underline{C}_{Ar}O$), 155.2 (N$\underline{C}$O), 209.2 ($\underline{C}$O); mp 134 – 136°C; IR: 2930, 2867, 1717, 1694, 1437, 1092 cm^{-1}; HRMS (ESI): calcd for $C_{38}H_{51}N_1O_{10}F_3$ [M+H$^+$]: 738.3456, found: 738.3460.

4’’’’,8’’’’-Dibutyl-1,1’’’’’’’-bis(2-trimethylsilylethoxycarbonyl)-octaspiro[piperidine-4,2’-[1,3]dioxane-5’,5’’-[1,3]dioxane-2’’,1’’’-cyclohexane-4’’’,2’’’’-[1,3]dioxolo[4,5-*f*][1,3]benzodioxole-6’’’’,1’’’’’-cyclohexane-4’’’’’,2’’’’’’-[1,3]dioxane-5’’’’’’,5’’’’’’’-[1,3]dioxane-2’’’’’’’,4’’’’’’’’-piperidine (26c): According to GP1 ketone **6** (202 mg, 0.46 mmol) and diol **23c** (330 mg, 0.91 mmol, 2.0 equiv) in anhyd Et_2O (50 mL) was treated with TMSOTf (4 drops). Purification by flash chromatography (PE/EtOAc 2:1) giving **26c** as a pale yellow solid (393 mg, 0.35 mmol, 77%). R_f = 0.2 (PE/EtOAc 5:2); ^{1}H NMR (300 MHz, C_6D_6): σ -0.08 (Si($\underline{C}H_3)_3$, 18H, s), σ 0.84 – 0.91 ($CH_2\underline{C}H_3$ + Si$\underline{C}H_2$, 6H + 4H, m), 1.25 – 1.38 ($C\underline{H}_2CH_3$, 4H, m), 1.59 – 1.69 ($C_{Ar}CH_2\underline{C}H_2$ + ($\underline{C}H_2CH_2)_2$N, 4H + 8H, m), 1.84 – 1.97 (C($C\underline{H}_2C\underline{H}_2)_2$C, 16H, m), 2.59 ($C_{Ar}C\underline{H}_2$, 4H, t, ^3J = 7.2 Hz), 2.59 – 2.63 (C($C\underline{H}_2C\underline{H}_2)_2$CO, 4H, m), 3.40 (N($C\underline{H}_2)_2$ + C($C\underline{H}_2O)_4$, 8H + 16H, bs), 4.12 – 4.18 (C(O)O$C\underline{H}_2$, 4H, m); ^{13}C NMR (75 MHz, C_6D_6): σ -1.77 (Si($\underline{C}H_3)_3$), 13.8 ($CH_2\underline{C}H_3$), 17.6 (Si$\underline{C}H_2$), 22.1 ($\underline{C}H_2CH_3$), 23.8 ($C_{Ar}\underline{C}H_2CH_2$), 28.7 (C($\underline{C}H_2\underline{C}H_2)_2$C), 30.7 (C($\underline{C}H_2\underline{C}H_2)_2$C), 30.9 ($C_{Ar}CH_2\underline{C}H_2$), 32.5 ($\underline{C}(CH_2O)_4$), 33.0 (($\underline{C}H_2CH_2)_2$N), 40.4 (N($\underline{C}H_2)_2$), 63.0 (C($\underline{C}H_2O)_4$), 63.3 (C(O)O$\underline{C}H_2$), 96.7 (C((CH$_2$O)$_2$)$_2\underline{C}$), 97.3 (C((CH$_2$O)$_2$)$_2\underline{C}$), 106.2 ($\underline{C}_{Ar}CH_2$), 116.6 (($C_{Ar}O)_2\underline{C}(CH_2CH_2)_2$), 138.8 ($\underline{C}_{Ar}O$), 155.3 (N$\underline{C}$O); mp 231 – 232°C; IR: 2952, 1693, 1437, 1095 cm^{-1}; HRMS (ESI): calcd for $C_{58}H_{93}N_2O_{16}Si_2$ [M+H$^+$]: 1129.6054, found: 1129.6058.

4’’’’,8’’’’-Dibutyl-1,1’’’’’’’-bis(fluoren-9-ylmethoxycarbonyl)-octaspiro[piperidine-4,2’-[1,3]dioxane-5’,5’’-[1,3]dioxane-2’’,1’’’-cyclohexane-4’’’,2’’’’-[1,3]dioxolo[4,5-*f*][1,3]benzodioxole-6’’’’,1’’’’’-cyclohexane-4’’’’’,2’’’’’’-[1,3]dioxane-5’’’’’’,5’’’’’’’-[1,3]dioxane-2’’’’’’’,4’’’’’’’’-piperidine (26d): According to GP1 ketone **6** (173.5 mg, 0.39 mmol) and diol **23d** (345 mg, 0.79 mmol, 2.0 equiv) in anhyd Et_2O (45 mL) was treated with TMSOTf (3 drops). Purification by flash chromatography (PE/EtOAc 2:1) giving **26d** as a pale yellow solid (213 mg, 0.17 mmol, 42%). R_f = 0.4 (PE/EtOAc 1:1); ^{1}H NMR (300 MHz, $CDCl_3$): σ 0.93 ($C\underline{H}_3$, 6H, t, ^3J = 7.3 Hz), 1.24 – 1.40 ($C\underline{H}_2CH_3$, 4H, m), 1.52 – 1.62 ($C_{Ar}CH_2C\underline{H}_2$, 4H, m), 1.82 (($C\underline{H}_2CH_2)_2N$, 8H, bs), 1.94 – 2.08 ($C(C\underline{H}_2C\underline{H}_2)_2C$, 16H, m), 2.44 – 2.54 ($C_{Ar}C\underline{H}_2$, 4H, m), 3.51 ($N(C\underline{H}_2)_2$, 8H, bs), 3.79 ($C(C\underline{H}_2O)_4$, 16H, s), 4.27 ($C\underline{H}CH_2$, 2H, t, ^3J = 6.7 Hz), 4.45 ($CHC\underline{H}_2$, 4H, d, ^3J = 6.8 Hz), 7.33 ($C\underline{H}_{Ar}$, 4H, dt, ^3J = 7.4 Hz, ^4J = 1.1 Hz), 7.42 ($C\underline{H}_{Ar}$, 4H, t, ^3J = 7.2 Hz), 7.59 ($C\underline{H}_{Ar}$, 4H, d, ^3J = 7.5 Hz), 7.79 ($C\underline{H}_{Ar}$, 4H, d, ^3J = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): σ 13.9 ($\underline{C}H_3$), 22.1 ($\underline{C}H_2CH_3$), 23.7 ($C_{Ar}\underline{C}H_2CH_2$), 28.7 ($C(\underline{C}H_2\underline{C}H_2)_2C$), 30.6 ($C(\underline{C}H_2\underline{C}H_2)_2C$), 30.9 ($C_{Ar}CH_2\underline{C}H_2$), 31.7 (($\underline{C}H_2CH_2)_2N$), 32.5 (($\underline{C}H_2CH_2)_2N$), 32.9 ($\underline{C}(CH_2O)_4$), 40.6 ($N(\underline{C}H_2)_2$), 47.3 ($\underline{C}HCH_2$), 63.4 ($C(\underline{C}H_2O)_4$), 63.6 ($C(\underline{C}H_2O)_4$), 67.2 ($CH\underline{C}H_2$), 96.9 ($C((CH_2O)_2)_2\underline{C}$), 97.6 ($C((CH_2O)_2)_2\underline{C}$), 106.1 ($\underline{C}_{Ar}CH_2$), 116.4 (($C_{Ar}O)_2\underline{C}(CH_2CH_2)_2$), 119.9 ($\underline{C}H_{Ar}$), 124.9 ($\underline{C}H_{Ar}$), 127.0 ($\underline{C}H_{Ar}$), 127.6 ($\underline{C}H_{Ar}$), 138.5 ($\underline{C}_{Ar}O$), 141.3 ($\underline{C}_{Ar}$), 144.0 ($\underline{C}_{Ar}$), 155.0 ($N\underline{C}O$); mp 210 – 211°C; IR: 2957, 2862, 1693, 1438, 1095 cm^{-1}; MS (MALDI): calcd for $C_{76}H_{88}N_2O_{16}$ [M^+]: 1284.6, found: 1284.9.

4’’’’,8’’’’-Dibutyl-1,1’’’’’’’-bis(benzyloxycarbonyl)-octaspiro[piperidine-4,2’-[1,3]dioxane-5’,5’’-[1,3]dioxane-2’’,1’’’-cyclohexane-4’’’,2’’’’-[1,3]dioxolo[4,5-

***f*][1,3]benzodioxole-6’’’’,1’’’’’-cyclohexane-4’’’’’,2’’’’’’-[1,3]dioxane-5’’’’’’,5’’’’’’’-[1,3]dioxane-2’’’’’’’,4’’’’’’’’-piperidine (26e)**: According to GP1 ketone **6** (200 mg, 0.45 mmol) and diol **23e** (323 mg, 0.92 mmol, 2.0 equiv) in anhyd Et_2O (60 mL) was treated with TMSOTf (3 drops). Purification by flash chromatography (PE/EtOAc 2:1) giving **26e** as a pale yellow solid (259 mg, 0.23 mmol, 52%) and **27e** as a yellow solid (31 mg, 0.04 mmol, 9%). R_f = 0.1 (PE/EtOAc 5:2); ^{1}H NMR (300 MHz, $CDCl_3$): σ 0.91 ($C\underline{H}_3$, 6H, t, ^3J = 7.3 Hz), 1.26 – 1.37 ($C\underline{H}_2CH_3$, 4H, m), 1.52 – 1.59 ($C_{Ar}CH_2C\underline{H}_2$, 4H, m), 1.84 (($C\underline{H}_2CH_2)_2N$, 8H, bs), 1.94 – 2.08 ($C(C\underline{H}_2C\underline{H}_2)_2C$, 16H, m), 2.48 ($C_{Ar}C\underline{H}_2$, 4H, t, ^3J = 7.0 Hz), 3.51 – 3.58 ($N(C\underline{H}_2)_2$, 8H, m), 3.78 ($C(C\underline{H}_2O)_4$, 16H, s), 5.15 ($C(O)OC\underline{H}_2$, 4H, s), 7.31 – 7.38 ($C\underline{H}_{Ar}$, 10H, m); ^{13}C NMR (75 MHz, $CDCl_3$): σ 13.9 ($\underline{C}H_3$), 22.1 ($\underline{C}H_2CH_3$), 23.7 ($C_{Ar}\underline{C}H_2CH_2$), 28.7 ($C(\underline{C}H_2\underline{C}H_2)_2C$), 30.6 ($C(\underline{C}H_2\underline{C}H_2)_2C$), 30.8 ($C_{Ar}CH_2\underline{C}H_2$), 31.5 (($\underline{C}H_2CH_2)_2N$), 32.7 (($\underline{C}H_2CH_2)_2N$), 32.9 ($\underline{C}(CH_2O)_4$), 40.6 ($N(\underline{C}H_2)_2$), 63.4 ($C(\underline{C}H_2O)_4$), 63.6 ($C(\underline{C}H_2O)_4$), 67.1 ($C(O)O\underline{C}H_2$), 96.9 ($C((CH_2O)_2)_2\underline{C}$), 97.6 ($C((CH_2O)_2)_2\underline{C}$), 106.1 ($\underline{C}_{Ar}CH_2$), 116.4 (($C_{Ar}O)_2\underline{C}(CH_2CH_2)_2$), 127.8 ($\underline{C}H_{Ar}$), 128.0 ($\underline{C}H_{Ar}$), 128.5 ($\underline{C}H_{Ar}$), 136.7 ($O\underline{C}H_2C_{Ar}$), 138.5 ($\underline{C}_{Ar}O$), 155.1 ($N\underline{C}O$); mp 221 – 223°C; IR: 2957, 2862, 1696, 1437, 1095 cm^{-1}; HRMS (ESI): calcd for $C_{62}H_{81}N_2O_{16}$ [M+H$^+$]: 1109.5577, found: 1109.5581.

4’’’’,8’’’’-Dibutyl-1-benzyloxycarbonyl-octaspiro[piperidine-4,2’-[1,3]dioxane-5’,5’’-[1,3]dioxane-2’’,1’’’-cyclohexane-4’’’,2’’’’-[1,3]dioxolo[4,5-*f*][1,3]benzodioxole-6’’’’,1’’’’’-cyclohexan-4’’’’’-one (27e): R_f = 0.3 (PE/EtOAc 2:1); ^{1}H NMR (300 MHz, $CDCl_3$): σ 0.92 ($C\underline{H}_3$, 6H, t, ^3J = 7.3 Hz), 1.29 – 1.41 ($C\underline{H}_2CH_3$, 4H, m), 1.53 – 1.63 ($C_{Ar}CH_2C\underline{H}_2$, 4H, m), 1.85 (($C\underline{H}_2CH_2)_2N$, 4H, bs), 1.94 – 2.06 ($C(\underline{C}H_2\underline{C}H_2)_2C$, 8H, m), 2.28 – 2.33 ($C(C\underline{H}_2C\underline{H}_2)_2CO$, 4H, m), 2.52 ($C_{Ar}C\underline{H}_2$,

4H, t, ^{3}J = 7.4 Hz), 2.59 – 2.65 (C(C$\underline{H}_2$C$\underline{H}_2$)$_2$CO, 4H, m), 3.51 – 3.57 (N(C$\underline{H}_2$)$_2$, 4H, m), 3.78 (C(C$\underline{H}_2$O)$_4$, 8H, s), 5.15 (C(O)OC$\underline{H}_2$, 2H, s), 7.31 – 7.39 (C$\underline{H}_{Ar}$, 5H, m); ^{13}C NMR (75 MHz, $CDCl_3$): σ 13.9 (C$\underline{H}_3$), 22.1 (C$\underline{H}_2$CH$_3$), 23.7 (C$_{Ar}$C$\underline{H}_2$CH$_2$), 28.7 (C(C$\underline{H}_2$C$\underline{H}_2$)$_2$C), 30.6 (C(C$\underline{H}_2$C$\underline{H}_2$)$_2$C), 30.9 (C$_{Ar}$CH$_2$C$\underline{H}_2$), 31.5 ((C$\underline{H}_2$CH$_2$)$_2$N), 32.7 ((C$\underline{H}_2$CH$_2$)$_2$N), 33.0 (C(CH$_2$O)$_4$), 33.4 (C(C$\underline{H}_2$C$\underline{H}_2$)$_2$CO), 37.4 (C(C$\underline{H}_2$C$\underline{H}_2$)$_2$CO), 40.7 (N(C$\underline{H}_2$)$_2$), 63.4 (C(C$\underline{H}_2$O)$_4$), 63.6 (C(C$\underline{H}_2$O)$_4$), 67.1 (C(O)OC$\underline{H}_2$), 97.0 (C((CH$_2$O)$_2$)$_2$C), 97.6 (C((CH$_2$O)$_2$)$_2$C), 106.4 (C$_{Ar}$CH$_2$), 114.7 ((C$_{Ar}$O)$_2$C(CH$_2$CH$_2$)$_2$), 116.7 ((C$_{Ar}$O)$_2$C(CH$_2$CH$_2$)$_2$), 128.5 (C$\underline{H}_{Ar}$), 128.0 (C$\underline{H}_{Ar}$), 128.5 (C$\underline{H}_{Ar}$), 136.7 (OCH$_2$C$_{Ar}$), 138.2 (C$_{Ar}$O), 138.9 (C$_{Ar}$O), 155.1 (NCO), 209.2 (CO); mp 105 – 107°C; IR: 2957, 2862, 1701, 1437, 1093 cm^{-1}; HRMS (ESI): calcd for $C_{44}H_{58}N_1O_{11}$ [M+H$^+$]: 776.4000, found: 776.4004.

4’’’’,8’’’’-Dibutyl-1,1’’’’’’’-bis(azidoacetyl)-octaspiro[piperidine-4,2’-[1,3]dioxane-5’,5’’-[1,3]dioxane-2’’,1’’’-cyclohexane-4’’’,2’’’’-[1,3]dioxolo[4,5-*f*][1,3]benzodioxole-6’’’’,1’’’’’-cyclohexane-4’’’’’,2’’’’’’-[1,3]dioxane-5’’’’’’,5’’’’’’’-[1,3]dioxane-2’’’’’’’,4’’’’’’’’-piperidine (26f): According to GP1 ketone **6** (203 mg, 0.46 mmol) and diol **23f** (275 mg, 0.92 mmol, 2.0 equiv) in anhyd Et_2O (65 mL) was treated with TMSOTf (4 drops). Purification by flash chromatography (PE/EtOAc/CH_2Cl_2 2:4:1) giving **26f** as a pale yellow solid (341 mg, 0.34 mmol, 74%) and **27f** as a yellow solid (29 mg, 0.04 mmol, 9%). R_f = 0.2 (PE/EtOAc/CH_2Cl_2 2:4:1); ^{1}H NMR (300 MHz, $CDCl_3$): σ 0.89 (C$\underline{H}_3$, 6H, t, ^{3}J = 7.3 Hz), 1.24 – 1.37 (C$\underline{H}_2$CH$_3$, 4H, m), 1.49 – 1.58 (C$_{Ar}$CH$_2$C$\underline{H}_2$, 4H, m), 1.81 – 1.91 ((C$\underline{H}_2$CH$_2$)$_2$N, 8H, m), 1.91 – 2.05 (C(C$\underline{H}_2$C$\underline{H}_2$)$_2$C, 16H, m), 2.40 – 2.51 (C$_{Ar}$C$\underline{H}_2$, 4H, m), 3.33 – 3.41 (N(C$\underline{H}_2$)$_2$, 4H, m), 3.61 – 3.68 (N(C$\underline{H}_2$)$_2$, 4H, m), 3.69 – 3.84 (C(C$\underline{H}_2$O)$_4$, 16H, m), 3.94 (C$\underline{H}_2$N$_3$, 4H, s); ^{13}C NMR (75 MHz, $CDCl_3$): σ 13.8 (C$\underline{H}_3$),

22.0 ($\underline{C}H_2CH_3$), 23.6 ($C_{Ar}\underline{C}H_2CH_2$), 28.6 ($C(\underline{C}H_2\underline{C}H_2)_2C$), 30.5 ($C(\underline{C}H_2\underline{C}H_2)_2C$), 30.8 ($C_{Ar}CH_2\underline{C}H_2$), 31.0 ($(\underline{C}H_2CH_2)_2N$), 32.9 ($\underline{C}(CH_2O)_4$), 33.5 ($(\underline{C}H_2CH_2)_2N$), 38.8 ($N(\underline{C}H_2)_2$), 41.7 ($N(\underline{C}H_2)_2$), 50.6 ($\underline{C}H_2N_3$), 63.4 ($C(\underline{C}H_2O)_4$), 63.5 ($C(\underline{C}H_2O)_4$), 96.5 ($C((CH_2O)_2)_2\underline{C}$), 97.6 ($C((CH_2O)_2)_2\underline{C}$), 106.0 ($\underline{C}_{Ar}CH_2$), 116.3 ($(C_{Ar}O)_2\underline{C}(CH_2CH_2)_2$), 138.4 ($\underline{C}_{Ar}O$), 165.3 ($N\underline{C}O$); mp > 300°C; IR: 2962, 2862, 2110, 1655, 1438, 1093 cm^{-1}; HRMS (ESI): calcd for $C_{50}H_{71}N_8O_{14}$ [$M+H^+$]: 1007.5078, found: 1007.5084.

4’’’’,8’’’’-Dibutyl-1-azidoacetyl-octaspiro[piperidine-4,2’-[1,3]dioxane-5’,5’’-[1,3]dioxane-2’’,1’’’-cyclohexane-4’’’,2’’’’-[1,3]dioxolo[4,5-*f*][1,3]benzodioxole-6’’’’,1’’’’’-cyclohexan-4’’’’’-one (27f): R_f = 0.5 (PE/EtOAc/CH_2Cl_2 2:4:1); ^{1}H NMR (300 MHz, $CDCl_3$): σ 0.89 – 0.95 ($C\underline{H}_3$, 6H, m), 1.29 – 1.40 ($C\underline{H}_2CH_3$, 4H, m), 1.53 – 1.63 ($C_{Ar}CH_2C\underline{H}_2$, 4H, m), 1.83 – 1.94 ($(C\underline{H}_2CH_2)_2N$, 4H, m), 1.94 – 2.07 ($C(\underline{C}H_2\underline{C}H_2)_2C$, 8H, m), 2.28 – 2.32 ($C(C\underline{H}_2C\underline{H}_2)_2CO$, 4H, m), 2.48 – 2.53 ($C_{Ar}C\underline{H}_2$, 4H, m), 2.59 – 2.64 ($C(C\underline{H}_2C\underline{H}_2)_2CO$, 4H, m), 3.36 – 3.42 ($N(C\underline{H}_2)_2$, 2H, m), 3.63 – 3.69 ($N(C\underline{H}_2)_2$, 2H, m), 3.71 – 3.86 ($C(C\underline{H}_2O)_4$, 8H, s), 4.00 ($C\underline{H}_2N_3$, 2H, s); ^{13}C NMR (75 MHz, $CDCl_3$): σ 13.8 ($\underline{C}H_3$), 22.1 ($\underline{C}H_2CH_3$), 23.7 ($C_{Ar}\underline{C}H_2CH_2$), 28.7 ($C(\underline{C}H_2\underline{C}H_2)_2C$), 30.6 ($C(\underline{C}H_2\underline{C}H_2)_2C$), 30.9 ($C_{Ar}CH_2\underline{C}H_2$), 31.0 ($(\underline{C}H_2CH_2)_2N$), 33.0 ($\underline{C}(CH_2O)_4$), 33.4 ($C(\underline{C}H_2\underline{C}H_2)_2CO$), 33.6 ($(\underline{C}H_2CH_2)_2N$), 37.3 ($C(\underline{C}H_2\underline{C}H_2)_2CO$), 38.9 ($N(\underline{C}H_2)_2$), 41.8 ($N(\underline{C}H_2)_2$), 50.7 ($\underline{C}H_2N_3$), 63.5 ($C(\underline{C}H_2O)_4$), 63.6 ($C(\underline{C}H_2O)_4$), 96.6 ($C((CH_2O)_2)_2\underline{C}$), 97.6 ($C((CH_2O)_2)_2\underline{C}$), 106.4 ($\underline{C}_{Ar}CH_2$), 114.7 ($(C_{Ar}O)_2\underline{C}(CH_2CH_2)_2$), 116.7 ($(C_{Ar}O)_2\underline{C}(CH_2CH_2)_2$), 138.2 ($\underline{C}_{Ar}O$), 138.8 ($\underline{C}_{Ar}O$), 165.4 ($N\underline{C}O$), 209.1 ($\underline{C}O$); HRMS (ESI): calcd for $C_{38}H_{53}N_4O_{10}$ [$M+H^+$]: 725.3756, found: 725.3756.

4’’’’,8’’’’-Dibutyl-4’’’’,8’’’’-octaspiro[piperidine-4,2’-[1,3]dioxane-5’,5’’-[1,3]dioxane-2’’,1’’’-cyclohexane-4’’’,2’’’’-[1,3]dioxolo[4,5-*f*][1,3]benzodioxole-6’’’’,1’’’’’-cyclohexane-4’’’’’,2’’’’’’-[1,3]dioxane-5’’’’’’,5’’’’’’’-[1,3]dioxane-2’’’’’’’,4’’’’’’’’-piperidine (28): A suspension of **26e** (160 mg, 0.14 mmol) and Pd/C (10%, 20 mg) in dry CH_2Cl_2/MeOH (v/v 2:1, 10 mL) was stirred under hydrogen atmosphere ($P(H_2)$ 1 atm). After complete conversion of **26e** controlled by TLC the solvents were evaporated and the resulting residue was purified by flash chromatography (CH_2Cl_2/MeOH/NEt_3 12:3:1) giving a white solid (220 mg). The solid was slurryed several times with CH_2Cl_2/MeOH (v/v 10:1) and filtered by filter-cannula giving **28** as a white solid (99 mg, 0.12 mmol, 82%). R_f = 0.3 (CH_2Cl_2/MeOH/NEt_3 12:3:1); ^{1}H NMR (300 MHz, $CDCl_3$/CD_3OD): σ 0.91 ($C\underline{H}_3$, 6H, t, ^3J = 7.3 Hz), 1.27 – 1.42 ($C\underline{H}_2CH_3$, 4H, m), 1.51 – 1.63 ($C_{Ar}CH_2C\underline{H}_2$, 4H, m), 1.93 – 2.08 ($C(C\underline{H}_2C\underline{H}_2)_2C$, 16H, m), 2.11 – 2.21 ($(C\underline{H}_2CH_2)_2N$, 8H, m), 2.48 ($C_{Ar}C\underline{H}_2$, 4H, t, ^3J = 7.3 Hz), 3.18 – 3.26 ($N(C\underline{H}_2)_2$, 8H, m), 3.80 ($C(C\underline{H}_2O)_4$, 16H, s); ^{13}C NMR (75 MHz, $CDCl_3$/CD_3OD): σ 13.4 ($\underline{C}H_3$), 21.8 ($\underline{C}H_2CH_3$), 23.3 ($C_{Ar}\underline{C}H_2CH_2$), 28.4 ($C(\underline{C}H_2\underline{C}H_2)_2C$), 28.9 ($(\underline{C}H_2CH_2)_2N$), 30.3 ($C(\underline{C}H_2\underline{C}H_2)_2C$), 30.6 ($C_{Ar}CH_2\underline{C}H_2$), 32.6 ($\underline{C}(CH_2O)_4$), 40.9 ($N(\underline{C}H_2)_2$), 63.1 ($C(\underline{C}H_2O)_4$), 63.2 ($C(\underline{C}H_2O)_4$), 94.2 ($C((CH_2O)_2)_2\underline{C}$), 97.5 ($C((CH_2O)_2)_2\underline{C}$), 105.9 ($\underline{C}_{Ar}CH_2$), 116.1 ($(C_{Ar}O)_2\underline{C}(CH_2CH_2)_2$), 138.2 ($\underline{C}_{Ar}O$); mp decomposition >290°C; IR: 3438, 2932, 2682, 1628, 1380, 1099 cm^{-1}; HRMS (ESI): calcd for $C_{46}H_{70}N_2O_{12}$ [M+2H$^+$]: 421.2457, found: 421.2459.