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Synthesis of tethered bis-macrocycles by cross-coupling of *N*-(3,5-dibromobenzyl)azacrowns with α,ω-diamino compounds

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14-[(1,4,7,10-Tetraoxa-13-azacyclopentadec-13-yl)methyl]-5,8-dioxa-2,11-diazabicyclo-[10.3.1]hexadeca-1(16),12,14-triene **6b** was synthesized from 37 mg of dioxadiamine **5b**. Eluent CH_2Cl_2/MeOH 3:1. Yield 47 mg (41%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.73 (br.s, 4H, line width 60 Hz), 3.37 (t, J = 4.9, 4H), 3.56-3.63 (m, 14H), 3.65-3.75 (m, 12H), 6.15 (br.s, 2H), 6.86 (br.s, 1H) (NH protons were not unambiguously assigned); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 45.1 (2C), 54.7 (2C, line width 30 Hz), 60.5 (1C, line width 200 Hz), 67.1 (2C, line width 30 Hz), 68.8-69.6 (m, 6C), 70.2 (2C), 72.0 (2C), 98.8 (1C), 106.2 (2C), 149.7 (2C) (one aromatic quaternary carbon was not assigned); MALDI-TOF: M^+ 453.2827; calc. for $C_{23}H_{39}N_3O_6$: 453.2839.

13-[(1,4,7,10-Tetraoxa-13-azacyclopentadec-13-yl)methyl]-2,6,10-triazabicyclo[9.3.1]-pentadeca-1(15),11,13-triene **6c** was synthesized from 33 mg of triamine **5c**. Eluent CH_2Cl_2/MeOH/NH_3-aq 100:20:3. Yield 32 mg (29%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.62 (br.s, 4H, line width 15 Hz), 2.67 (br.s, 4H, line width 15 Hz), 2.79 (br.s, 4H, line width 50 Hz), 3.42 (br.s, 4H, line width 50 Hz), 3.50-3.70 (m, 18H), 5.98 (br.s, 2H), 7.05 (br.s, 1H, line width 30 Hz) (NH protons were not unambiguously assigned); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 30.1 (2C, line width 10 Hz) 39.6 (2C, line width 10 Hz), 45.9 (2C), 54.0 (2C, line width 15 Hz), 60.7 (1C), 69.2 (2C), 70.1 (6C, line width 90 Hz), 94.8 (1C, line width 20 Hz), 103.6 (2C), 149.9 (2C) (one aromatic quaternary carbon was not assigned); MALDI-TOF: $[M+H]^+$ 437.3002; calc. for $C_{23}H_{40}N_4O_4$: 437.3128.

17-[(1,4,7,10-Tetraoxa-13-azacyclopentadec-13-yl)methyl]-2,6,10,14-tetraazabicyclo[13.3.1]-nonadeca-1(19),15,17-triene **6d** was synthesized from 44 mg of tetraamine **5d**. Eluent CH_2Cl_2/MeOH/NH_3-aq 100:25:3. Yield 33 mg (28%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.68 (quintet, J = 5.4, 4H), 2.67 (t, J = 5.6, 4H), 2.68 (s, 4H), 2.74 (t, J = 5.5, 4H), 3.32 (t, J = 6.2,

4H), 3.58-3.67 (m, 14H), 3.65 (s, 4H), 4.88 (br.s, 2H), 5.93 (br.s, 2H), 6.13 (br.s, 1H) (2 NH protons were not unambiguously assigned); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 31.5 (2C), 41.3 (2C), 46.0 (2C), 49.1 (2C), 54.5 (2C), 60.8 (1C), 69.7 (2C), 70.0 (2C), 70.2 (2C), 70.7 (2C), 93.0 (1C), 104.5 (2C), 141.1 (1C), 150.4 (2C); MALDI-TOF: M^+ 479.3407; calc. for $C_{25}H_{45}N_5O_4$: 479.3472.

19-[(1,4,7,10,13-Pentaoxa-16-azacyclooctadec-16-yl)methyl]-6,9,12-trioxa-2,16-diazabicyclo-[15.3.1]henicosa-1(21),17,19-triene **7a** was synthesized in the first experiment from 55 mg of trioxadiamine **5a** in the presence of DavePHOS (9 mg, 9 mol%) and in the second experiment from 55 mg of trioxadiamine **5a** in the presence of DavePHOS (18 mg, 18 mol%). Chromatography of combined reaction mixtures was carried out. Eluent CH_2Cl_2/MeOH 10:1. Yield 90 mg (32%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.77 (quintet, J = 5.2, 4H), 2.70 (br.s, 4H, line width 60 Hz), 3.24 (t, J = 6.2, 4H), 3.53 (t, J = 5.1, 4H), 3.55-3.70 (m, 30H), 5.90 (br.s, 2H), 6.04 (br.s, 1H) (NH protons were not unambiguously assigned); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 29.6 (2C), 41.7 (2C), 53.6 (2C), 59.1 br (1C, line width 30 Hz), 67.3 br (2C, line width 50 Hz), 69.2 (2C), 69.3 (4C), 69.4 (4C), 70.0 (2C), 70.8 (2C), 95.6 br (1C, line width 15 Hz), 103.4 (2C), 150.5 (2C) (one aromatic quaternary carbon was not assigned); MALDI-TOF: $[M+K]^+$ 608.3331; calc. for $C_{29}H_{51}KN_3O_8$: 608.3313.

14-[(1,4,7,10,13-Pentaoxa-16-azacyclooctadec-16-yl)methyl]-5,8-dioxa-2,11-diazabicyclo-[10.3.1]hexadeca-1(16),12,14-triene **7b** was synthesized from 37 mg of dioxadiamine **5b**. Eluent CH_2Cl_2/MeOH 5:1-2.5:1. Yield 13 mg (14%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.75 (br.s, 4H, line width 90 Hz), 3.38 (t, J = 4.6, 4H), 3.55-3.71 (m, 30H), 6.08 (br.s, 2H), 6.87 (br.s, 1H) (NH protons were not unambiguously assigned); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 45.0 (2C), 53.6 (2C, line width 12 Hz), 61.2 (1C), 67.4 (2C, line width 80 Hz), 69.4-69.8 (m, 8C), 70.2 (2C), 72.0 (2C), 98.5 (1C), 106.2 (2C), 149.7 (2C) (one aromatic quaternary carbon was not assigned); MALDI-TOF: $[M+Na]^+$ 520.3077; calc. for $C_{25}H_{43}N_3NaO_7$: 520.2999.

13-[(1,4,7,10,13-Pentaoxa-16-azacyclooctadec-16-yl)methyl]-2,6,10-triazabicyclo[9.3.1]penta-deca-1(15),11,13-triene **7c** was synthesized from 33 mg of triamine **5c**. Eluent CH_2Cl_2/MeOH/NH_3-aq 100:20:3. Yield 32 mg (27%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.65 (br.s, 4H, line width 15 Hz), 2.69 (br.s, 4H, line width 15 Hz), 3.25 (br.s, 4H, line width 35 Hz), 3.44 (br.s, 4H, line width 30 Hz), 3.55-3.62 (m, 14H), 3.64 (s, 4H), 3.71 (br.s, 4H, line width 15 Hz), 6.03 (br.s, 2H), 6.95 (br.s, 1H, line width 15 Hz) (NH protons were not unambiguously assigned); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 29.6 (2C, line width 10 Hz), 39.3 (2C), 45.7 (2C),

54.1 (2C, line width 15 Hz), 69.6 (2C), 69.7 (2C), 70.1 (2C), 70.4 (2C), 70.5 (2C), 95.5 (1C, line width 25 Hz), 104.3 (2C), 150.3 (2C) (one aromatic quaternary carbon and one aliphatic tertiary carbon were not assigned); MALDI-TOF: $[M+H]^+$ 481.28; calc. for $C_{25}H_{44}N_4O_5$: 481.34.

17-[(1,4,7,10,13-Pentaoxa-16-azacyclooctadec-16-yl)methyl]-2,6,10,14-tetraazabicyclo[13.3.1]-nonadeca-1(19),15,17-triene **7d** was synthesized from 44 mg of tetraamine **5d**. Eluent CH_2Cl_2/MeOH/NH_3-aq 10:4:1. Yield 26 mg (20%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.67 (quintet, J = 5.2, 4H), 2.68 (t, J = 5.4, 4H), 2.69 (s, 4H), 2.73 (t, J = 5.5, 4H), 3.32 (t, J = 6.2, 4H), 3.55-3.59 (m, 8H), 3.61-3.66 (m, 14H), 5.90 (br.s, 2H), 6.13 (br.s, 1H) (NH protons were not unambiguously assigned); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 31.4 (2C), 41.3 (2C), 46.0 (2C), 48.9 (2C), 54.2 (2C), 59.8 (1C), 69.6 (2C), 70.1 (2C), 70.5 (4C), 70.7 (2C), 92.9 (1C), 104.3 (2C), 141.2 (1C), 150.4 (2C); MALDI-TOF: $[M+H]^+$ 524.3797; calc. for $C_{27}H_{50}N_5O_7$: 524.3812.