Total Synthesis of Multiply Substituted, Ion Channel Forming Octi(*p*-Phenylene)s: Theme and Variations

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Supporting Information

General. Reagents for synthesis were purchased from Aldrich or Fluka. Solvents were distilled and dried before use. All reactions were performed under nitrogen atmosphere. Column chromatography was carried out on silica gel 60 (Fluka, 40-63 mm). Analytical (TLC) and preparative thin layer chromatography (PTLC) was performed on silica gel 60 (Fluka, 0.2 mm) and silica gel GF-2 (Aldrich, 1 mm), respectively. UV/VIS spectra were recorded on a Cary UV-vis spectrophotometer and reported as λ in nm (ε in $cm^{-1}mM^{-1}$). IR spectra were recorded on a Perkin Elmer 1660 FT Spectrometer using NaCl solution cells and reported in cm^{-1}. Band intensities are indicated as *vs* (very strong), *s* (strong), *m* (medium), *w* (weak), and *vw* (very weak). ^{1}H NMR spectra were recorded on a Brucker 400 MHz Spectrometer and reported as chemical shifts (δ) in ppm relative to TMS (δ = 0). Spin multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (q) or multiplet (m); coupling constants (*J*) are given in Hz. ^{1}H NMR resonances were assigned with the aid of additional information from pertinent 2D NMR spectra (H, H-COSY, HSQC). The permanent presence of solvent in analytical samples was corroborated by H^1 NMR spectroscopy. EI-MS were performed on VG 7070-E instrument, ESI-MS on a Finnigan MAT SSQ 7000. MALDI-TOF-MS from liquid solution were conducted with a MALDI-TOF mass spectrometer Voyager™ Elite (PerSeptive Biosystems, Framingham MA, USA) equipped with a 337 nm nitrogen laser. The samples for MALDI-TOF-MS were prepared by adding 1 μl of the solubilized compounds in acetonitrile to an air-dried matrix of 1 μl of 5 mg/ml dihydroxy bensoic acid (DHBA) in 30% ACN, 0.1% TFA. Synthetic peptides were added as internal calibrants (monoisotopic MW: 1498.82 and 2095.08).

4,4'-Diiodo-3,3'-dimethoxybiphenyl (5). To a solution of KI (56 g, 0.33 mol) in water (250 ml) was added fast blue B salt (*o*-dianisidine bisdiazotated zinc doublesalt, 8.00 g, 16.82 mmol). The mixture was stirred at 0 °C for 14 h. After dilution with ethyl acetate, the reaction mixture was washed successively with 10% aqueous NaOH, brine, 5% aqueous $Na_2S_2O_5$, and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the crude product on silica gel (CH_2Cl_2 / hexane

1 : 4) gave pure **5** (5.50 g, 70%) as a pale yellow solid. TLC (CH_2Cl_2 / hexane 1 : 4): R_f 0.32. IR ($CHCl_3$): 3009*m*, 2939*w*, 2858*w*, 1850*vw*, 1581*m*, 1555*s*, 1469*s*, 1383*s*, 1248*s*, 1013*s*, 848*m*, 800*s*. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, ^3J = 7.9 Hz, H-C(5), H-C(5')), 6.94 (d, ^4J = 1.9 Hz, H-C(2), H-C(2')), 6.88 (dd, ^3J = 7.9 Hz, ^4J = 1.9 Hz, H-C(6), H-C(6')), 3.93 (s, 2 OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.4 (C(3), C(3')), 142.3 (C(1), C(1')), 139.7 (C(5), C(5')), 121.2 (C(6), C(6')), 109.7 (C(2), C(2')), 85.3 (C(4), C(4')), 56.4 (O*C*H$_3$). EI–MS: 466 (100, $M^{+\cdot}$).

4,4'-Diiodo-3,3'-di(*tert*-butoxycarbonyl-methoxy)biphenyl (11). To a solution of **5** (2.00 g, 4.2 mmol) in CH_2Cl_2 (100 ml), boron tribromide (16.8 mmol) in CH_2Cl_2 (17 ml) was added at –78 °C. This solution was allowed to reach room temperature over 14 h. Then, the reaction mixture was carefully diluted with ice-water and CH_2Cl_2. The organic phase was washed three times with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was filtered over silica (CH_2Cl_2 / ethyl acetate 9 : 1). The resulting 4,4'-diiodo-3,3'-dihydroxybiphenyl was dissolved in DMF (30 ml), and Cs_2CO_3 (8.21 g, 25.2 mmol) was added. After stirring of the resulting suspension for 1 h at 80 °C, *tert*-butylbromoacetate (2.48 ml, 16.8 mmol) was added. This suspension was stirred for additional 15 min at 60 °C. After cooling to room temperature, the mixture was diluted with ethyl acetate, washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the crude product by column chromatography (CH_2Cl_2 / petroleum ether) gave **11** (2.65 g, 90%) as a pure white solid. TLC (CH_2Cl_2 / petroleum ether 1 : 1): R_f 0.35. IR ($CHCl_3$): 3008*m*, 2982*m*, 2934*w*, 1750*s*, 1724*m*, 1672*w*, 1554*m*, 1469*m*, 1370*m*, 1232*m*, 1154*s*, 1082*m*, 1015*m*, 844*m*, 800*m*. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, ^3J = 7.9 Hz, H-C(5), H-C(5')), 6.86 (dd, ^3J = 7.9 Hz, ^4J = 1.9 Hz, H-C(6), H-C(6')), 6.79 (d, ^4J = 1.9 Hz, H-C(2), H-C(2')), 4.60 (s, 2 OCH_2CO), 1.46 (s, C(CH_3)$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0 (CO), 157.0 (C(3), C(3')), 141.8 (C(1), C(1')), 139.9 (C(5), C(5')), 121.8 (C(6), C(6')), 110.8 (C(2), C(2')), 85.8 (C(4), C(4')), 82.6 (*C*(CH$_3$)$_3$), 66.7 (O*C*H$_2$CO), 27.9 ((C(*C*H$_3$)$_3$). EI-MS: 666 (100, $M^{+\cdot}$).

4,4'-Diiodo-3,3'-di(18-azacrown-6-*N*-carbonylmethoxy)biphenyl (12). Diester **11** (1.00 g, 1.5 mmol) was dissolved in a 1:1-mixture of CH_2Cl_2 and TFA, stirred 30 min at room temperature and concentrated *in vacuo*. The resulting white powder was dissolved in DMF (30 ml), and 18-azacrown-6 (866 mg, 3.3 mmol), PyBOP (1.72 g, 3.3 mmol) and DIPEA (2.1 ml, 12 mmol) were added at room temperature. The mixture was stirred for 3 h at room temperature, diluted with ethyl acetate, washed successively with saturated aqueous $NaHCO_3$, brine, 1M aqueous $KHSO_4$, and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (CH_2Cl_2 / MeOH 95 : 5) gave pure **12** (1.52 g, 95%) as a yellow oil. TLC (CH_2Cl_2 / MeOH 10 : 1): R_f 0.65. UV-vis (CH_2Cl_2): 301 (12.3). IR ($CHCl_3$): 3008*m*, 2874*m*, 1750*w*, 1740*vw*, 1665*s*, 1468*s*, 1240*s*, 1121*s*, 1015*s*, 848*m*, 800*m*. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, ^3J = 8.0 Hz, H-C(5), H-C(5')), 7.07 (br. s, H-C(2), H-C(2')), 6.91 (d, ^3J = 8.0 Hz, H-C(6), H-C(6')), 4.96 (s, 2 OCH_2CO), 3.80-3.60 (m, 8 OCH_2CH_2O, 4 OCH_2CH_2N). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6 (CO), 157.3 (C(3), C(3')), 141.8 (C(1), C(1')), 139.7 (C(5), C(5')), 121.6 (C(6),

C(6')), 111.4 (C(2), C(2')), 85.4 (C(4), C(4')), 71.1-69.4 (8 O*C*H_2*C*H_2O, 4 O*C*H_2CH$_2$N), 68.2 (2 O*C*H_2CO), 48.7 (2 OCH$_2$*C*H_2N$_E$), 46.8 (2 OCH$_2$*C*H_2N$_Z$). ESI-MS ($CHCl_3$): 1067.3 (100, $[M + Na]^+$).

4,4'-Bis(4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane)-3,3'-dimethoxybiphenyl (6). To a solution of **5** (470 mg, 1.0 mmol) in MeCN (4 ml) was added successively $PdCl_2$(dppf) (49 mg, 0.06 mmol), triethylamine (0.83 ml, 6.0 mmol) and 4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (0.43 ml, 3.0 mmol). The mixture was stirred at 80 °C for 4 h. Then the reaction mixture was concentrated *in vacuo*. Purification of the crude product by column chromatography (ether / hexane 1 : 1) gave **6** (277 mg, 59%) as a pure pale pink solid (TLC (ether / hexane 1 : 1): R_f 0.15; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, ^3J = 7.6 Hz, H-C(5), H-C(5')), 7.15 (dd, ^3J = 7.6 Hz, ^4J = 1.6 Hz, H-C(6), H-C(6')), 7.02 (d, ^4J = 1.6 Hz, H-C(2), H-C(2')), 3.88 (s, 2 OCH_3 3H-C(7), 3H-C(7')), 1.34 (s, 4 C(CH_3)$_2$).

6^4,1^4-Diiodo-6^3,5^2,4^3,3^2,2^3,1^3-hexamethoxy-*p*-sexiphenyl (7). To a mixture of **5** (1.00 g, 2.10 mmol), tetrakistriphenylphosphine palladium (145.6 mg, 0.126 mmol), and 2 M aqueous Na_2CO_3 (10.5 ml) in toluene (100 ml) at 80 °C, **6** (2.00 g, 4.2 mmol) in toluene / ethanol (10 : 1, 10 ml) was added *via* syringe during 12 h. The resulting mixture was stirred for additional 12 h at 80 °C. After cooling at room temperature, the product mixture was diluted with ethyl acetate and washed three times with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by column chromatography (CH_2Cl_2 / hexane 3 : 1) gave pure **7** (186 mg, 10%) as a colorless solid (186 mg, 10%). TLC (CH_2Cl_2 / hexane 3 : 1): R_f 0.35. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, ^3J = 7.9 Hz, H-C(1^5), H-C(6^5)), 7.37-7.14 (m, H-C(2^{2,5,6}), H-C(3^{3,5,6}), H-C(4^{2,5,6}), H-C(5^{3,5,6})), 7.05 (d, ^4J = 1.9 Hz, H-C(1^2), H-C(6^2)), 6.98 (dd, ^3J = 7.9 Hz, ^4J = 1.9 Hz, H-C(1^6), H-C(6^6)), 3.95 (s, C(1^3)OCH_3, C(6^3)OCH_3), 3.87 (s, C(2^3)OCH_3, C(3^2)OCH_3, C(4^3)OCH_3 C(5^2)OCH_3). MALDI-TOF-MS: not detectable.

6^4,1^4-Diiodo-6^3,5^2,4^3,3^2,2^3,1^3-hexa(*tert*-butoxycarbonylmethoxy)-*p*-sexiphenyl (8). A (7→8): To a solution of **7** (50 mg, 56.2 μmol) in CH_2Cl_2 (5 ml), boron tribromide (0.67 mmol) in CH_2Cl_2 (0.7 ml) was added at –78 °C. The resulting solution was allowed to reach room temperature within 14 h. Then the reaction mixture was carefully diluted with ice-water and CH_2Cl_2, washed three times with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The resulting crude product was dissolved in DMF (6 ml), and Cs_2CO_3 (220.5 mg, 0.67 mmol) was added at room temperature. After stirring for 1 h at 80 °C, *tert*-butylbromoacetate (0.1 ml, 0.67 mmol) was added. The reaction mixture was stirred for additional 4 h at 60 °C, cooled to room temperature, and diluted with ethyl acetate. The organic phase was washed three times with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by column chromatography (CH_2Cl_2) afforded **8** (16 mg, 20%) as a colorless solid. **B (11→[13]→8):** To a solution of **11** (100 mg, 0.15 mmol) in acetonitrile (2 ml) was added successively $PdCl_2$(dppf) (4 mg, 4.5 μmol), triethylamine (126 μl, 0.9 mmol) and 4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (66 μl,

0.45 mmol). The mixture was stirred overnight at 80 °C, and concentrated *in vacuo*. The residue was dissolved in a 10:1-mixture of toluene–ethanol (5 ml) and was added during 12 h to a mixture of **11** (250 mg, 0.375 mmol), $PdCl_2$(dppf) (4.0 mg, 4.5 μmol), and 2M aqueous Na_2CO_3 (1 ml) in 10 ml of toluene at 80°C. After addition, the mixture was stirred for an additional 12 h at 80 °C. After cooling to room temperature, the mixture was diluted with ethyl acetate, washed three times with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by column chromatography (CH_2Cl_2) afforded **8** (20 mg, 10%) as a colorless powder. TLC (CH_2Cl_2): R_f 0.55. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, ^3J = 7.9 Hz, H-C(1^5), H-C(6^5)), 7.48-6.98 (m, H-C($2^{2,5,6}$), H-C($3^{3,5,6}$), H-C($4^{2,5,6}$), H-C($5^{3,5,6}$)), 6.96 (dd, ^3J = 7.9 Hz, ^4J=1.9 Hz, H-C(1^6), H-C(6^6)), 6.90 (d, ^4J = 1.9 Hz, H-C(1^2), H-C(6^2)), 4.63 (s, C(1^3)OCH_2CO, C(6^3)OCH_2CO), 4.55 (s, C(2^3)OCH_2CO, C(5^2)OCH_2CO), 4.54 (s, C(3^2)OCH_2CO, C(4^3)OCH_2CO), 1.49 (s, C(1^3)OCH$_2$COO-C(CH_3)$_3$, C(6^3)OCH$_2$COOC(CH_3)$_3$), 1.45 (s, C(2^3)OCH$_2$COOC(CH_3)$_3$, C(5^2)OCH$_2$-COOC(CH_3)$_3$), 1.44 (s, C(3^2)OCH$_2$COOC(CH_3)$_3$, C(4^3)OCH$_2$COOC(CH_3)$_3$). MALDI-TOF-MS: m/z for $C_{86}H_{98}O_{18}S_2$ calcd 1482.62. found 1482.55.

6^4,1^4-Diiodo-6^3,5^2,4^3,3^2,2^3,1^3-hexa (18-aza-6-*N*-carbonylmethoxy)-*p*-sexiphenyl (10). A (8→10): Hexamer **8** (14.9 mg, 10 μmol) was dissolved in a 1:1-mixture of CH_2Cl_2 and TFA, stirred for 1 h at room temperature and concentrated *in vacuo*. The resulting crude product (~12.4 mg, ~10 μmol) was dissolved in DMF (2 ml), and 18-azacrown-6 (33.7 mg, 0.12 mmol), PyBOP (66.9 mg, 0.12 mmol) and DIPEA (26 μl, 0.14 mmol) were added at room temperature. The mixture was stirred for 3 h at room temperature, diluted with ethyl acetate, washed successively with saturated aqueous $NaHCO_3$, brine, 1 M aqueous $KHSO_4$, and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the crude product by PTLC ($CHCl_3$ / MeOH 95 : 5) gave **10** (14.9 mg, 57%) as slightly yellow residue. **B (12→[14]→10):** To a solution of **12** (300 mg, 0.28 mmol) in acetonitrile (6 ml) was added successively $PdCl_2$(dppf) (7.0 mg, 8.6 μmol), triethylamine (240 μl, 1.68 mmol) and 4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (125 μl, 0.86 mmol). The mixture was stirred at 80 °C over the night, and concentrated *in vacuo*. The crude product was dissolved in a 10:1-mixture toluene–ethanol (10 ml) and slowly added during 12 h to a mixture of **12** (584 mg, 0.56 mmol), $PdCl_2$(dppf) (7.0 mg, 8.6 μmol), and 2 M aqueous Na_2CO_3 (1.4 ml) in toluene (20 ml) at 80 °C. After addition, the mixture was stirred for an additional 12 h at 80 °C. After cooling to room temperature, the mixture was diluted with ethyl acetate and washed three times with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography ($CHCl_3$ / MeOH 95 : 5) afforded pure **10** (87.5 mg, 12%) as a slightly yellow residue. TLC ($CHCl_3$ / MeOH 95 : 5): R_f 0.25. UV-vis (CH_2Cl_2): 310 (15.0). IR ($CHCl_3$): 3009*m*, 2872*s*, 1750*vw*, 1740*vw*, 1651*s*, 1603*w*, 1548*w*, 1471*m*, 1240*m,* 1122*vs*, 945*w*, 848*m*, 800*m*. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, ^3J = 8.0 Hz, H-C(1^5), H-C(6^5)), 7.48-7.40 (m, H-C(2^5), H-C($3^{5,6}$), H-C($4^{5,6}$), H-C(5^6)), 7.35-7.16 (m, H-C(1^2), H-C(2^2), H-C(3^3), H-C(4^2), H-C(5^3), H-C(6^2)), 6.99 (dd, ^3J = 8.0 Hz, ^4J = 0.9 Hz, H-C(1^6), H-C(6^6)), 6.94 (dd, ^3J = 8.0 Hz, ^4J = 0.9 Hz, H-C(2^6), H-C(5^5)), 4.96 (s, C(1^3)OCH_2CO, C(6^3)OCH_2CO), 4.89 (s, C(2^3)OCH_2CO, C(5^2)OCH_2CO), 4.84 (s,

C(3^2)OCH_2CO, C(4^3)OCH_2CO), 3.82-3.49 (m, 24 OCH_2CH_2O, 12 OCH_2CH_2N). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3 (C(1^3)OCH$_2$*C*O, C(6^3)OCH$_2$*C*O), 168.2 (C(2^3)OCH$_2$*C*O, C(5^2)OCH$_2$*C*O), 167.2 (C(3^2)OCH$_2$*C*O, C(4^2)OCH$_2$*C*O), 158.5 (C(1^3), C(6^3)), 157.2 (C(2^3), C(5^2)), 156.5 (C(3^2), C(4^3)), 142.7-142.5 (C(1^1), C(2^1), C(3^4), C(4^1), C(5^4), C(6^1)), 139.6 (C(1^5), C(6^5)), 133.8-132.6 (C(2^5), C(3^6), (C(4^5), C(5^6)), 129.6-126.0 (C(2^4), C(3^1), C(4^4), C(5^1)), 121.4-120.2 (C(1^6), C(2^6), C(3^5), C(4^6), C(5^5), C(6^6), 113.0-111.4 (C(1^2), C(2^2), C(3^3), C(4^2), C(5^3), C(6^2), 84.8 (C(1^4), C(6^4), 71.1-69.4 (24 O*C*H$_2$*C*H$_2$O, 12 O*C*H$_2$CH$_2$N), 68.2-66.5 (6 O*C*H$_2$CO), 48.7 (4 OCH$_2$*C*H$_2$N$_E$), 48.4 (2 OCH$_2$*C*H$_2$N$_E$), 46.8 (2 OCH$_2$*C*H$_2$N$_Z$), 46.7 (2 OCH$_2$*C*H$_2$N$_Z$), 46.6 (2 OCH$_2$*C*H$_2$N$_Z$). ESI-MS ($CHCl_3$): 1733 (100), 1732 (45, [M – 3 CH$_2$CO-*N*-crown – 2 H$_2$ + Na]$^+$). MALDI-TOF-MS (DHBA matrix): 1747.7 (5, [M – 3 CH$_2$CO-*N*-crown – 2 H$_2$ + K]$^+$), 1733.7 (25), 1732.7 (50), 1731.7 (60, [M – 3 CH$_2$CO-*N*-crown – 2 H$_2$ + Na]$^+$), 1711.8 (10, [M – 3 CH$_2$CO-*N*-crown – 2 H$_2$ + H$^+$]$^+$), 1710.8 (30, [M – 3 CH$_2$CO-*N*-crown – 2 H$_2$ + H]$^+$), 1709.8 (35, [M – 3 CH$_2$CO-*N*-crown – 2 H$_2$ + H]$^+$), 1623.8 (7, [M – 3 CH$_2$CO-*N*-crown – 2 H$_2$ – I + K]$^+$), 1622.8 (12, [M – 3 CH$_2$CO-*N*-crown – 2 H$_2$ – I + K]$^+$), 1621.8 (15, [M – 3 CH$_2$CO-*N*-crown – 2 H$_2$ - I + K]$^+$), 1607.8 (40, [M – 3 CH$_2$CO-*N*-crown – 2 H$_2$ – I + Na]$^+$), 1606.8 (90, [M – 3 CH$_2$CO-*N*-crown – 2 H$_2$ – I + Na]$^+$), 1605.8 (100, [M – 3 CH$_2$CO-*N*-crown – 2 H$_2$ - I + Na]$^+$), 1604.8 (18), 1603.8 (14), 1685.8 (20, [M – 3 CH$_2$CO-*N*-crown – 2 H$_2$ – I + H]$^+$), 1684.8 (45, [M – 3 CH$_2$CO-*N*-crown – 2 H$_2$ – I + H]$^+$), 1683.8 (55, [M – 3 CH$_2$CO-*N*-crown – 2 H$_2$ - I + H]$^+$), 1682.8 (40), 1681.8 (45).

8^4,1^4-dithiomethyl-7^3,6^2,5^3,4^2,3^3,2^2-hexa(*tert*-butoxycarbonylmethoxy)-*p*-octiphenyl (9). To a solution of **8** (10.0 mg, 6.70 μmol) in toluene (2 ml) was added successively 4,4,5,5-tetramethyl-2-(4-thiomethylphenyl)-[1,3,2]-dioxaborolane (4.1 mg, 16.7 μmol), $PdCl_2$(dppf) (0.16 mg, 0.5 μmol) and 2 M aqueous Na_2CO_3 (70 μl). The mixture was stirred at 80 °C for 12 h, diluted with ethyl acetate, washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by PTLC (hexane / ethyl acetate 7 : 3) gave pure **9** (3.5 mg, 35%) as a colorless solid. TLC (hexane / ethyl acetate 7 : 3): R_f 0.35. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, ^3J = 8.5 Hz, H-C(2^6), H-C(3^5), H-C(4^6), H-C(5^5), H-C(6^6), H-C(7^5)), 7.52 (dd, ^3J = 7.7 Hz, ^4J = 3.3 Hz, H-C(1^2), H-C(1^6), H-C(8^2), H-C(8^6)), 7.40 (dd, ^3J = 7.7 Hz, ^4J = 3.3 Hz, H-C(1^2), H-C(1^5), H-C(8^3), H-C(8^5)), 7.30 (d, ^3J = 8.5 Hz, H-C(2^5), H-C(3^6), H-C(4^5), H-C(5^6), H-C(6^5), H-C(7^6)), 7.08 (s, H-C(2^3), H-C(3^2), H-C(4^3), H-C(5^2), H-C(6^3), H-C(7^2)), 4.56 (s, C(2^2)OC*H*$_2$CO, C(7^3)OC*H*$_2$CO), 4.55 (s, C(3^3)OC*H*$_2$CO, C(6^2)OC*H*$_2$CO), 4.53 (s, C(4^2)OC*H*$_2$CO, C(5^3)OC*H*$_2$CO), 2.51 (s, 2 SCH$_3$), 1.47 (s, C(2^2)OCH$_2$COOC(C*H*$_3$)$_3$, C(7^3)OCH$_2$COOC(C*H*$_3$)$_3$), 1.46 (s, C(3^3)OCH$_2$COOC-(C*H*$_3$)$_3$, C(6^2)OCH$_2$COOC(C*H*$_3$)$_3$), 1.45 (s, C(4^2)OCH$_2$COOC(C*H*$_3$)$_3$, C(5^3)OCH$_2$-COOC(C*H*$_3$)$_3$),

8^4,1^4-Dithiomethyl-7^3,6^2,5^3,4^2,3^3,2^2-hexa(18-aza-6-*N*-carbonylmethoxy)-*p*-octiphenyl (3). A (9→3): Hexamer **9** (2.0 mg, 1.7 μmol) was dissolved in a 1:1-mixture of CH_2Cl_2 and TFA, stirred for 1 h at room temperature and concentrated *in vacuo*. The resulting crude product was dissolved in DMF (0.5 ml) and 18-azacrown-

6 (5.4 mg, 20.19 μmol), PyBOP (10.8 mg, 20.19 μmol) and DIPEA (4.2 μl, 23.8 μmol) were added at room temperature. The mixture was stirred for 3 h at room temperature and concentrated *in vacuo*. Purification by PTLC (CH_2Cl_2 / MeOH 10 : 1) gave **3** (1.1 mg, 25%) as a colorless solid. **B (10→3):** To a solution of **10** (50 mg, 19.02 μmol) in toluene (3 ml) tetrakis(triphenylphosphine)palladium (2.53 mg, 1.11 μmol), *p*-thiomethylphenyl boronic acid (9.5 mg, 57.06 μmol) and 2 M aqueous Na_2CO_3 (92 μl, 190.2 μmol) were added successively at room temperature. The mixture was refluxed for 18 h. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate, washed three times with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the crude product by PTLC (CH_2Cl_2 / MeOH 10 : 1) gave **3** (26 mg, 40%) as a colorless solid. TLC (CH_2Cl_2 / MeOH 10 : 1): R_f 0.25. UV-vis (CH_2Cl_2): 324 (30.0). IR ($CHCl_3$): 3008*s*, 2871*s*, 1750*vw*, 1740*vw*, 1648*s*, 1604*m*, 1476*s*, 1352*m*, 1240*s*, 1122*vs*, 945*m*, 850*w*, 800*m* cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, ^3J = 8.4 Hz, H-C(2^6), H-C(3^5), H-C(4^6), H-C(5^5), H-C(6^6), H-C(7^5)), 7.51 (d, ^3J = 6.7 Hz, H-C(1^2), H-C(1^6), H-C(8^2), H-C(8^6)), 7.40 (d, ^3J = 6.7 Hz, H-C(1^2), H-C(1^5), H-C(8^3), H-C(8^5)), 7.33 (d, ^3J = 8.4 Hz, H-C(2^5), H-C(3^6), H-C(4^5), H-C(5^6), H-C(6^5), H-C(7^6)), 7.25 (s, H-C(2^3), H-C(3^2), H-C(3), H-C(5^2), H-C(6^3), H-C(7^2)), 4.86 (s, C(2^2)OCH_2CO, C(7^3)OCH_2CO), 4.84 (s, C(3^3)OCH_2CO, C(6^2)OCH_2CO), 4.80 (s, C(4^2)OCH_2CO, C(5^3)OCH_2CO), 3.80 – 3.50 (m, 24 OCH_2CH_2O, 12 OCH_2CH_2N), 2.52 (s, 2 SCH_3). ^{13}C (100 MHz, $CDCl_3$): δ 168.3-168.0 (C(2^2)OCH$_2$*C*O, C(3^3)OCH$_2$*C*O, (C(4^2)OCH$_2$*C*O, C(5^3)OCH$_2$*C*O), (C(6^2)OCH$_2$*C*O, C(7^3)OCH$_2$*C*O), 158.5 (C(2^2), C(7^3)), 156.0 (C(3^3), C(6^2)), 155.3 (C(4^2), C(5^3)), 141.4-141.1 (C(2^4), C(3^1), C(4^4), C(5^1), C(6^4), C(7^1)), 136.0-134.7 (C(1^1), C(1^4), C(8^1), C(8^4)), 132.4-131.2 (C(2^6), C(3^5), C(4^6), C(5^5), C(6^6), C(7^5)), 131.0-129.9 (C(2^1), C(3^4), C(4^1), C(5^4), C(6^1), C(7^4)), 129.5 (C(1^2), C(1^6), C(8^2), C(8^6)), 126.1 (C(1^3), C(1^5), C(8^3), C(8^5)), 120.4-119.4 (C(2^5), C(3^6), C(4^5), C(5^6), C(6^5), C(7^6)), 114.0-111.7 (C(2^3), C(3^2), C(4^3), C(5^2), C(6^3), C(7^2)), 71.1-69.4 (24 O*C*H$_2$*C*H$_2$O, 12 O*C*H$_2$CH$_2$N), 67.5-67.0 (6 O*C*H$_2$CO), 48.6 (2 OCH$_2$*C*H$_2$N$_E$), 48.5 (2 OCH$_2$*C*H$_2$N$_E$), 48.4 (2 OCH$_2$*C*H$_2$N$_E$), 46.8 (2 OCH$_2$*C*H$_2$N$_Z$), 46.6 (2 OCH$_2$*C*H$_2$N$_Z$), 46.5 (2 OCH$_2$*C*H$_2$N$_Z$), 15.7 (2 SCH_3). ESI-MS ($CHCl_3$): 1729.6, 1728.5, 1727.7 (100, M – 3 CH_2CO-*N*-crown + $Na]^+$). MALDI-TOF-MS (DHBA matrix): 1745.8 (25), 1744.8 (40), 1743.8 (45, [M – 3 CH_2CO-*N*-crown + $K]^+$), 1730.8 (35), 1729.8 (80), 1728.8 (95), 1727.8 (100, [M – 3 CH_2CO-*N*-crown + $Na]^+$), 1707.8 (30), 1706.8 (50), 1705.8 (55, [M – 3 CH_2CO-*N*-crown + $H]^+$), 1697.8 (8, [M – 3 CH_2CO-*N*-crown – SMe + $K]^+$), 1683.8 (20), 1682.8 (30), 1681.8 (35, [M – 3 CH_2CO-*N*-crown - SMe + $Na]^+$), 1659.8 (10, [M – 3 CH_2CO-*N*-crown – SMe + $H]^+$), 1440.6 (5, [M – 4 CH_2CO-*N*-crown + H + $K]^+$), 1424.6 (25, [M – 4 CH_2CO-*N*-crown + H + $Na]^+$), 1402.7 (15, [M – 4 CH_2CO-*N*-crown + 2 $H]^+$), 1378.6 (5, [M – 4 CH_2CO-*N*-crown + H – SMe + $Na]^+$).

1^4-thiomethyl-8^4-sulfoxymethyl-7^3,6^2,5^3,4^2,3^3,2^2-hexa(18-aza-6-N-carbonylmethoxy)-*p*-octiphenyl (4). To a solution of **3** (3.0 mg, 1.14 μmol) in a 1:1:1-mixture of THF, methanol and water (1.5 ml), oxone (0.67 mg, 2.28 μmol) was added at room temperature. The mixture was stirred for 14 h. After concentration of the solution, the reaction mixture was diluted with ethyl acetate, washed three times

with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the crude product by PTLC (CH_2Cl_2 / MeOH 10 : 1) gave **4** (1.5 mg, 50%) as a colorless solid. TLC (CH_2Cl_2 / MeOH 10 : 1): R_f 0.20. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, ^3J = 6.8 Hz, H-C(8^3), H-C(8^5)), 7.56 (d, ^3J = 6.8 Hz, H-C(8^2), H-C(8^6)), 7.48–7.35 (m, H-C(1^2), H-C(1^3), H-C(1^5), H-C(1^6)), 7.30-7.15 (m, H-C(2^6), H-C(3^5), H-C(4^6), H-C(5^5), H-C(6^6), H-C(7^5), H-C(2^3), H-C(3^2), H-C(4^3), H-C(5^2), H-C(6^3), H-C(7^2)), 6.92- 6.88 (m, H-C(2^5), H-C(3^6), H-C(4^5), H-C(5^6), H-C(6^5), H-C(7^6)), 4.98-4.85 (m, (C(2^2)OCH_2CO, C(3^3)OCH_2CO, C(4^2)OCH_2CO, C(5^3)OCH_2CO, C(6^2)OCH_2CO, C(7^3)OCH_2CO), 3.85-3.50 (m, 24 OCH_2CH_2O, 12 OCH_2CH_2N), 2.98 (s, SO_2CH_3), 2.52 (s, SCH_3). MALDI-TOF-MS (DHBA matrix): 2692.2 (15), 2691.2 (30), 2690.2 (50), 2689.2 (50), 2688.2 (25, $[M + K]^+$), 2676.2 (40), 2675.2 (70), 2674.2 (95), 2673.2 (100), 2672.2 (60, $[M + Na]^+$), 2654.2 (20), 2653.2 (40), 2652.2 (65), 2651.2 (60), 2650.2 (35, $[M + H]^+$), 2613.2 (7), 2612.2 (12), 2611.2 (15), 2610.2 (8, $[M - SO_2CH_2 + K]^+$), 2597.2 (10), 2596.2 (20), 2595.2 (20), 2594.2 (12, $[M - SO_2CH_2 + Na]^+$), 2575.2 (8), 2574.2 (13), 2573.2 (15), 2572.2 (10, $[M - SO_2CH_2 + H]^+$), 2387.7 (10), 2386.7 (20), 2385.7 (20), 2384.7 (10, [M – CH_2CO-*N*-crown + $K]^+$), 2271.7 (25), 2370.7 (50), 2369.7 (55), 2368.7 (40, [M – CH_2CO-*N*-crown + $Na]^+$), 2349.7 (15), 2348.7 (40), 2347.7 (50), 2346.7 (30, [M – CH_2CO-*N*-crown + $H]^+$), 2308.9 (5), 2307.9 (6), 2306.9 (3, [M – CH_2CO-*N*-crown – SO_2CH_2 + $K]^+$), 2292.9 (10), 2291.9 (12), 2290.9 (7, [M – CH_2CO-*N*-crown – SO_2CH_2 + $Na]^+$), 2270.9 (9), 2269.9 (10), 2268.9 (7, [M – CH_2CO-*N*-crown – SO_2CH_2 + $H]^+$), 2081.9 (2, [M – 2 CH_2CO-*N*-crown + $K]^+$), 2065.9 (4, [M – 2 CH_2CO-*N*-crown + $Na]^+$), 2043.9 (5, [M – 2 CH_2CO-*N*-crown + $H]^+$), 1987.8 (2, [M – 2 CH_2CO-*N*-crown – SO_2CH_2 + $Na]^+$), 1965.9 (2, [M – 2 CH_2CO-*N*-crown – SO_2CH_2 + $H]^+$), 1762.7 (2, [M – 2 CH_2CO-*N*-crown + $Na]^+$), 1740.6 (2, [M – 3 CH_2CO-*N*-crown + $H]^+$). MALDI-TOF-MS (DHBA matrix): m/z for $C_{134}H_{189}N_6O_{44}S_2$ calcd 2650.22; found 2650.24.