Improving Foldamer Synthesis through Protecting Group-Induced Unfolding of Aromatic Oligoamides

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Supporting Information

General Methods. Chemicals were purchased from commercial sources and used as received unless otherwise noted. Unless otherwise specified, all solvents were removed with a rotary evaporator. Analytical thin layer chromatography (TLC) was conducted on Analtech Uniplat silica gel plates with detection by UV light.

^1H and ^{13}C NMR analyses were carried out using tetramethylsilane (TMS) as the internal standard. Chemical shifts are reported in ppm values downfield from tetramethylsilane and J values are reported in Hz. For electrospray mass spectrum (ES-MS), the concentration of the samples was about 1.0 mmol/mL. The diluted solution was electrosprayed at a flow rate of $5 \sim 10^{-6}$ L/min with a needle voltage of 4.5 kV. The mobile phase was an aqueous solution of methanol (V/V, 1:1). MALDI experiments were performed using a matrix of 9-nitroanthracene or dithranol. Mass spectra were acquired in positive reflector mode and using an acceleration voltage of 19 kV. External mass calibration was performed using a standard PEG-2000 mixture. Spectra were obtained by setting the laser power close to the threshold of ionization and generally 300 pulses were acquired and averaged.

General Procedure for Preparing Acid Chloride from the Corresponding Acid:¹ To a solution of acid (1.0 equiv) and oxalyl chloride (1.2 to 1.5 equiv) in dry CH_2Cl_2 were added one or two drops of DMF. The mixture was stirred for 20 min at room temperature and then refluxed for an additional 30-50 min. The solvent was evaporated and the resulting acid chloride was dissolved in dry CH_2Cl_2 , then the solvent was evaporated to remove any excess oxalyl chloride. The residue was used for the next coupling step.

General Procedure for the Reduction of Nitro DMB-Oligomers into the Amino Oligomers by Catalytic Hydrogenation: To a mixture of nitro compounds, 10% Pd/C (10-20 wt % of nitro compound) and chloroform, was added methanol (or Ethanol). (Caution! Direct addition of methanol to the Pd/C without wetting the catalyst with solvent may cause fire!) The solution was purged with hydrogen, and shaken under an atmosphere of hydrogen gas at the appropriate temperature for a period of time from one to several hours until only amine appeared on TLC, which is signaled in most cases by the color change of spots caused by oxidation under UV lamp or in air. The mixture was then filtered and the solvent evaporated. The residue consisting usually of both free amine and amine salt was treated according to the following two

procedures: (A) It was dissolved in CH_2Cl_2 , and triethylamine was added to the solution with stirring to convert any amine salt to free amine, followed by immediate coupling with acid chloride. (B) The solution of the residue was washed with aqueous NaHCO_3 and water, dried over Na_2SO_4 , and evaporated to dryness to afford the crude amine (>90%), which was used without further purification for the next step. For each subsequent higher nitro-oligomer an additional 5 °C increment of reaction temperature and an additional 20-30 min of reaction time were required.

I. Preparation of Monomers

The synthesis of two monomer acids bearing a new ether side chain has not been described before and is described below.

2-(3-Methyl-butoxy)-ethanol: To a flask with ethylene glycol (264 g, 4.3 mole) in THF (250 mL) was added NaH (20 g) slowly followed by adding dropwise 1-Bromo-3-methylbutane (50.4 mL, 0.4 mole). The mixture was stirred at room temperature overnight. After removal of the solvent, the residue was treated with water, extracted with Ethyl acetate (200 mL $\times$ 3). The combined organic solvent was dried over anhydrous Na_2SO_4 . The solvent was removed and the residue was distilled to provide colorless oil (45g, 85%). $^1\text{H-NMR}$ (500 MHz, CDCl_3): 3.71 (m, 2H), 3.51 (m, 4H), 1.69 (m, 1H), 1.49 (m, 2H), 0.91 (d, 6H).

Toluene-4-sulfonic acid 2-(3-methyl-butoxy)-ethyl ester: To a flask with 2-(3-Methyl-butoxy)-ethanol (13.2 g, 0.1 mole) in pyridine (40 mL) at 0 °C was added TsCl (21 g, 0.11 mole) and the mixture was stirred at this temperature overnight. The solvent was removed and Methylene Chloride (200 mL) was added. The solution was washed with 1N HCl solution and dried over Na₂SO₄. The solvent was removed and the residue was used for the following step directly. ¹H-NMR (500 MHz, CDCl₃): 7.76 (d, 2H), 7.30 (d, 2H), 3.63 (m, 2H), 3.56 (m, 2H), 3.36 (m, 2H), 2.41 (s, 3H), 1.68 (m, 1H), 1.43 (m, 2H), 0.87 (d, 6H).

4,6-Bis-[2-(3-methyl-butoxy)-ethoxy]-isophthalic acid (acid-1): A mixture of 4,6-dihydroxy-isophthalic acid (3 g, 13.3 mmol), Toluene-4-sulfonic acid 2-(3-methyl-butoxy)-ethyl ester (15 g, 52 mmol) and anhydrous K₂CO₃ (15 g, 0.11 mol) in DMF (100 mL) was heated at 100 °C for 3 days. After cooling down to room temperature CH₂Cl₂ (200 mL) was added and the mixture was stirred for 20 min and then filtered off. The organic layer was washed with water. After evaporating the solvent, the residue was solved in methanol (50 mL) and 2N NaOH (100 mL) was added. The mixture was refluxed for 2 hours and cooled down to room temperature. The solution was acidified with concentrated HCl and the solid was collected by filtration and dried in the air to give the product as a white solid (4.26 g, 66%); m.p. 149.8 °C. ¹H-NMR (500 MHz, CDCl₃): δδ 8.82 (s, 1H), 6.68 (s, 1H), 4.40 (m, 4H), 3.88 (m, 4H), 3.5 (m, 4H), 1.70 (m, 2H), 1.46 (m, 4H), 0.95 (d, 12H); MS (ESI) m/z, calcd for C₂₂H₃₄O₈ (M⁺) 426.50, found 427.2 (M+H)⁺, 449.1(M+Na)⁺.

2,4-Bis-[2-(3-methyl-butoxy)-ethoxy]-5-nitrophenyl}-oxo-acetic acid (acid-2): A mixture of 2,4-dihydroxy-5-nitro-benzoic acid methyl ester (4.8 g, 22.5 mmol), toluene-4-sulfonic acid 2-(3-methyl-butoxy)-ethyl ester (19.1 g, 66.8 mmol) and anhydrous K₂CO₃ (30 g, 0.22 mol) in DMF (100 mL) was heated at 100 °C for 2 days. After cooling down to room temperature CH₂Cl₂ (200 mL) was added and the mixture was stirred for 20 min and then filtered off. The organic layer was washed with water. After evaporating the solvent, the residue was solved in methanol (50 mL) and 2N NaOH (100 mL) was added. The mixture was refluxed for 2 hours and cooled down to room temperature. The solution was acidified

with concentrated HCl and the solid was collected by filtration and dried in the air to give the product as a white solid (7.8 g, 81%); $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ 8.72 (s, 1H), 6.8 (s, 1H), 4.41 (m, 4H), 3.86 (m, 4H), 3.58 (m, 4H), 1.69 (m, 2H), 1.47 (m, 4H), 0.89 (d, 12H); MS (ESI) m/z , calcd for $\text{C}_{22}\text{H}_{33}\text{NO}_9$ (M^+) 455.5, found 456.4 ($\text{M}+\text{H}$) $^+$.

II. Synthesis of Oligomers

2,4-Dimethoxy-5-nitro-benzoic acid methyl ester (2). This compound was prepared based on procedures we described before.¹ The product was obtained as an off-white solid (21.2 g, 93.8%). m.p. 146.5 $^{\circ}\text{C}$. ^1H NMR (400 MHz, CDCl_3): δ 8.64 (s, 1H), 6.53 (s, 1H), 4.05 (s, 3H), 4.02 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 164.56, 164.42, 158.45, 131.81, 130.46, 111.93, 99.20, 58.02, 57.75, 52.72; MS (ESI) m/z , Calcd for $\text{C}_{10}\text{H}_{11}\text{NO}_6$ (M^+), found 242.0 ($\text{M}+\text{H}^+$). Anal. Calcd. for $\text{C}_{10}\text{H}_{11}\text{NO}_6$: C, 49.80; H, 4.60; N, 5.81. Found: C, 49.61; H 4.40; N, 5.33.

2,4-Diisobutoxy-5-nitrobenzoic acid (6a). Hydrolysis of the corresponding ester¹ (16.3 g, 50.1 mmol) in MeOH (80 mL) with 2N NaOH (50 mL, 50 mmol) under reflux for 2h provided the product as a white solid (15.0 g, 96%). m.p. 178.8 $^{\circ}\text{C}$. ^1H NMR (500 MHz, CDCl_3): δ 8.77 (s, 1H), 6.53 (s, 1H), 4.02 (d, 2H, $J = 6.5$ Hz), 3.92 (t, 2H, $J = 6.5$ Hz), 2.27 (m, 1H), 2.21 (m, 1H), 1.12 (d, 6H, $J = 7.0$ Hz), 1.09 (d, 6H, $J = 6.5$ Hz); ^{13}C NMR (125.7 MHz, CDCl_3) δ 65.03, 162.51, 158.19, 133.16, 132.32, 109.66, 97.61, 76.83, 76.28, 28.21, 28.15, 19.09, 19.00; Anal.

Calcd. for $C_{15}H_{21}NO_6$: C, 57.87; H, 6.80; N, 4.50. Found C, 57.62; H, 6.67; N, 4.42.

5-[(2,4-Diisobutoxy-5-nitro-benzoyl)-(2,4-dimethoxy-benzyl)-amino]-2,4-dimethoxy-benzoic acid methyl ester (7) To amine **3**, prepared from **2** (7.23 g, 30 mmole) by catalytic hydrogenation in ethanol (150 mL), was added 2,4-dimethoxybenzaldehyde (5.5 g, 33 mmole) and the mixture was stirred overnight at room temperature. $NaBH_4$ (1.7 g, 45 mmole) was added slowly and the reaction mixture was stirred for 12 hours. The reaction was quenched with water and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 , filtrated and the removal of the solvent provided 5-(2,4-Dimethoxy-benzylamino)-2,4-dimethoxy-benzoic acid methyl ester (**5**) as an oil (10.33 g, 95%).

To **5** (4.2 g, 11.6 mmole) and triethylamine (2.1 mL, 1.5 equiv.) in CH_2Cl_2 (50 mL) was added acid chloride **6** in CH_2Cl_2 (50 mL) prepared from acid **6a** (3 g, 9.7 mmol) in CH_2Cl_2 (50 mL) and oxalyl chloride (3 mL) according to the general procedure. The mixture was stirred at room temperature overnight and was then washed with brine, dried over anhydrous Na_2SO_4 . After the removal of the solvent, the residue was purified by chromatography (EtOAc/n-hexane 1: 1) to furnish **7** as a white solid (5.43 g, yield 86%). 1H -NMR (500 MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.41 (d, 1H), 7.38 (s, 1H), 6.43 (s, 1H), 6.32 (s, 1H), 6.20(s, 1H), 6.14(s, 1H), 5.30 (d, J= 14 Hz, 1H), 4.47 (d, J= 14 Hz, 1H), 4.23 (m, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.77 (s, 6H), 3.74 (d, 2H), 3.64 (m, 1H), 3.57 (s, 3H), 2.16 (m, 2H), 1.08 (m, 12H); MS (ESI) m/z, calcd for $C_{34}H_{40}N_2O_{11}K^+$ 691.2.

Methyl 5-{2,4-Bis-[2-(3-methyl-butoxy)-ethoxy]-5-nitrobenzoylamino}-2,4-dimethoxy-benzoate (8). To amine **3**, prepared from **2** (2 g, 8.3 mmol) by catalytic hydrogenation, and triethylamine (2.1 mL, 1.5 equiv.) in CH_2Cl_2 (50 mL) was added acid chloride **6** dissolved in CH_2Cl_2 (50 mL). Compound **6** was prepared from the corresponding acid (3g, 7.03 mmol) in CH_2Cl_2 (50 mL) and oxalyl chloride (2 mL) according to the general procedure. The mixture was stirred at room temperature overnight and then was washed with brine, dried over anhydrous Na_2SO_4 . After the removal of the solvent, the residue was purified by chromatography (EtOAc/n-hexane 1: 1) to supply the tetramer as a white solid **8** (2.96 g, yield 68%). 1H -NMR (500 MHz, $CDCl_3$): δ 9.77 (s, 1H), 8.94 (s, 1H), 8.88 (s, 1H), 6.65 (s, 1H), 6.42 (s, 1H), 4.41 (m, 2H), 4.23 (m, 2H), 3.94 (m, 4H), 3.89 (s, 6H), 3.88 (s, 3H), 3.53 (m, 4H), 1.67 (m, 2H), 1.43 (m,

4H), 0.90 (d, 6H), 0.81 (d, 6H); ^{13}C NMR (75.5 MHz, CDCl_3): 166.29, 161.14, 160.98, 157.89, 156.91, 153.51, 134.05, 131.44, 124.81, 121.14, 115.21, 111.85, 99.80, 95.89, 69.27, 68.98, 56.87, 56.40, 52.28, 38.98, 39.90, 25.55, 25.50, 23.11, 23.01; MS (ESI) m/z for $\text{C}_{25}\text{H}_{32}\text{N}_2\text{O}_9^+$: 541.5, 519.4.

Methyl 5-[5-(2,4-Dimethoxy-benzylamino)-2,4-diisobutoxy-benzoylamino]-2,4-dimethoxy-benzoate (9) To the corresponding amine prepared from **8** (3.65 g, 7.2 mmole) by catalytic hydrogenation in ethanol (150 mL) was added 2,4-dimethoxybenzaldehyde (1.3 g, 7.8 mmole) and the mixture was stirred overnight at room temperature. NaBH_4 (500 mg, 15 mmole) was added slowly and the reaction mixture was stirred for 12 hours. The reaction was quenched with water and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 , filtrated and the removal of the solvent provided **9**, which was purified by recrystallization from methanol as a white solid (3.84 g, 85%). ^1H -NMR (500 MHz, CDCl_3): 10.08 (d, 1H), 9.06 (d, 1H), 7.7 (s, 1H), 7.11 (s, 1H), 6.55 (m, 4H), 4.38 (s, 2H), 3.94 (m, 4H), 3.89 (s, 12H), 3.88 (s, 3H), 2.20 (m, 2H), 1.0 0.81 (d, 12H); MS (ESI) m/z , calcd for $\text{C}_{34}\text{H}_{44}\text{N}_2\text{O}_9^+$ 661.4, 639.3.

5-[(2,4-Diisobutoxy-5-nitro-benzoyl)-(2,4-dimethoxy-benzyl)-amino]-2,4-dimethoxy-benzoic acid (10) To a solution of **7** (600 mg, 0.92 mmol) in methanol (20 mL) was added 2N aq. NaOH (20 mL), the mixture was stirred at room temperature overnight. The solution was quenched with 1N HCl, extracted with methylene chloride (30 mL), washed with brine and dried with anhydrous Na₂SO₄. Acid **10** was used without further purification in the next step. ¹H-NMR (500 MHz, CDCl₃): δ 10.03 (s, 1H), 7.85 (s, 1H), 7.76 (s, 1H), 7.40 (d, J = 8 Hz, 1H), 6.41 (dd, J = 8.5, 2.5 Hz, 1H), 6.3 (s, 1H), 6.251 (s, 1H), 6.17 (s, 1H), 5.25 (d, J = 14 Hz, 1H), 4.50 (d, J = 14 Hz, 1H), 4.23 (m, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.77 (s, 6H), 3.74 (d, 2H), 3.64 (m, 1H), 2.24 (m, 1H), 2.11 (m, 1H), 1.08 (m, 12H); ¹³C NMR (75.5 MHz, CDCl₃): 167.77, 164.84, 161.0, 160.78, 160.55, 159.51, 158.97, 156.15, 135.12, 132.14, 131.56, 125.63, 120.06, 117.61, 109.34, 104.68, 98.51, 97.25, 95.17, 76.31, 75.84, 57.28, 56.59, 55.86, 55.55, 46.40, 28.79, 28.68, 19.8, 19.64, 19.58, 19.53; MS (ESI) m/z for C₃₃H₃₈N₂O₁₁⁺ 640.9, 401.2.

Tetramer 12: Hydrogenation of **7** (317 mg, 0.48 mmole) in methanol led to the corresponding amine, which, after removing solvent, was mixed with triethylamine (0.21 mL, 0.48 mmole) in CH₂Cl₂ (30 mL) and treated with the acid chloride in CH₂Cl₂ (50 mL), prepared from acid **10** (320 mg, 0.5 mmol) in CH₂Cl₂ (50 mL) and oxalyl chloride (1 mL) according to the general procedure. The mixture was stirred at room temperature overnight and was then washed with brine, dried over anhydrous Na₂SO₄. After removal of solvent, the residue was purified by chromatography (EtOAc/n-hexane 1: 1) to furnish **12** as a white solid (352 mg, yield 58%). ¹H-NMR (500 MHz, CDCl₃): δ 9.63 (s, 1H), 8.45 (s, 1H), 7.91 (s, 1H), 7.86 (s, 1H), 7.51 (m, 4H), 6.32 (m, 8H), 5.34 (m, 2H), 4.45 (m, 2H), 3.7 (m, 29H), 2.20 (m, 4H), 1.08 (m, 12H); ¹³C NMR (75.5 MHz, CDCl₃): 174.09, 173.98, 173.87, 167.82, 167.11, 165.06, 163.05, 162.97, 182.83, 162.61, 160.72, 160.45, 153.95, 140.26, 140.01, 139.79, 136.81, 136.00, 1365.93, 135.46, 129.12, 129.02, 128.62, 128.24, 127.77, 127.55, 116.74, 115.86, 115.76, 115.37, 114.86, 114.56, 108.51, 98.63, 98.04, 70.61, 70.53, 70.46, 70.25, 69.58, 69.46, 69.10, 68.79, 68.63, 67.29, 60.86, 52.91, 52.85, 49.16, 49.11, 49.02, 48.69, 39.06, 38.78, 38.72, 28.79, 25.52, 25.50, 25.48, 23.13, 23.03, 21.51, 18.77, 18.64; MS (MALDI-TOF) for C₆₇H₈₂N₄O₁₉K⁺: Calcd. 1285.5; Found. 1284.4.

Octamer 15: To a solution of **12** (150 mg, 0.12 mmol) in methanol (20 mL) was added 2N aq. NaOH (20 mL) and the mixture was stirred at room temperature overnight. The solution was quenched with 1N HCl, extracted with methylene chloride (30 mL), washed with brine and dried with anhydrous Na₂SO₄. Acid **13** was used without further purification in the next step. To amine **14**, prepared by catalytic hydrogenation of **12** (120 mg, 0.1 mmole), and triethylamine (0.21 mL, 0.48 mmole) in CH₂Cl₂ (30 mL) was added the acid chloride in CH₂Cl₂ (50 mL) prepared from acid **13** (123 mg, 0.1 mmol) in CH₂Cl₂ (50 mL) and oxalyl chloride (1 mL) according to the general procedure. The mixture was stirred at room temperature overnight and then was washed with brine, dried over anhydrous Na₂SO₄. After removal of solvent, the residue was purified by chromatography (EtOAc/n-hexane 1: 1) to furnish **15** as a white solid (78 mg, yield 32%). ¹H-NMR (500 MHz, CDCl₃): 9.90 (s, 1H), 9.62 (s, 2H), 9.08 (s, 1H), 7.02-8.4 (m, 16 H), 6.38 (m, 12H), 5.4 (m, 4H), 4.50 (m, 4H), 3.7-4.0 (m, 67H), 2.15 (m, 8H), 1.12 (m, 48H); ¹³C NMR (75.5 MHz, CDCl₃): 160.69, 159.05, 145.39, 125.02, 111.79, 108.93, 108.05, 104.67, 100.47, 98.49, 95.75, 95.17, 93.20, 75.47, 63.41, 56.62, 55.84, 55.58, 31.33, 30.90, 30.05, 28.89, 19.80, 19.58; MS (MALDI-TOF) for C₁₃₃H₁₆₂N₈O₃₅K⁺: Calcd. 2470.1; Found 2469.2.

Pentamer 17. To amine **9** (287 mg, 0.46 mmole) and triethylamine (0.1 mL, 1.5 equiv.) in CH₂Cl₂ (50 mL) was added acid chloride **16** in CH₂Cl₂ (50 mL), prepared from the corresponding acid¹ (62 mg, 0.2 mmol) using oxalyl chloride (1 mL) in CH₂Cl₂ (50 mL) according to the general procedure. The reaction mixture was stirred at room temperature overnight and was then washed with brine, dried over anhydrous Na₂SO₄. After removal of solvent, the residue was purified by chromatography (EtOAc/n-hexane 1: 1) to furnish **17** as a white solid (250 mg, yield 82%), ¹H-NMR (500 MHz, CDCl₃): δ 9.76 (s, 2H), 9.03 (s, 2H), 8.03 (s, 2H), 7.58 (d, J = 8.5 Hz, 2H), 7.05 (s, 1H), 6.52 (s, 2H), 6.42 (dd, J = 8.5, 2 Hz, 2H), 6.34 (dd, J = 2 Hz, 2H), 6.24 (d, 2H), 5.26 (d, J = 15 Hz, 2H), 4.44 (d, J = 15 Hz, 2H), 4.33 (m, 4H), 3.91 (m, 30H), 3.82 (m, 8H), 2.40 (m, 2H), 2.23 (m, 4H), 1.17 (d, 12H), 0.81 (d, 24H). ¹³C NMR

(75.5 MHz, CDCl₃): 170.80, 165.94, 162.88, 160.35, 158.64, 158.48, 157.74, 157.41, 156.42, 153.19, 133.50, 130.98, 125.68, 124.65, 122.03, 119.09, 118.80, 113.38, 112.52, 104.74, 98.51, 96.93, 96.33, 76.49, 75.03, 74.71, 60.87, 57.16, 56.04, 55.80, 55.62, 47.06, 29.06, 28.77, 28.68, 20.21, 20.11, 19.89, 19.86, 19.75, 19.71, 14.86; MS (ESI) m/z, calcd for C₈₄H₁₀₆N₄O₂₂⁺ 1551.5, 1537.6, 1523.6, 1331.4.

Tetramer 19. Catalytic hydrogenation of **18** (232 mg, 0.393 mmol) led to the corresponding amine, which was mixed with triethylamine (0.5 mL, 1.5 equiv.) in CH₂Cl₂ (20 mL) and then treated with the acid chloride, prepared from acid **10** (200 mg, 0.313 mmol) and oxalyl chloride (0.5 mL), and dissolved in CH₂Cl₂ (10 mL). The reaction mixture was stirred at room temperature overnight and was then washed with brine, dried over anhydrous Na₂SO₄. After removal of solvent, the residue was triturated with CH₂Cl₂/n-hexane to provide the tetramer as a white solid **19** (235 mg, yield 62%). m.p. 221.2-222.3 °C ¹H-NMR (500 MHz, CDCl₃): δ 9.99 (s, 1H), 9.93 (s, 1H), 9.24 (s, 1H), 9.01 (s, 1H), 7.97 (s, 1H), 7.87 (s, 1H), 7.46 (d, J = 8 Hz, 1H), 6.60 (s, 1H), 6.50 (s, 1H), 6.44 (d, 1H), 6.34 (s, 1H), 6.21 (d, 2H), 5.30 (d, J = 15 Hz, 1H), 4.50 (d, J = 15 Hz, 1H), 4.20 (m, 4H), 3.93 (d, 4H), 3.92 (s, 21H), 3.86 (d, 8H), 2.27 (m, 1H), 2.09 (m, 1H), 1.67 (m, 2H), 1.43 (m, 4H), 0.90 (d, 12H), 0.81 (d, 12H); ¹³C NMR (75.5 MHz, CDCl₃) 175.79, 168.24, 166.41, 163.33, 161.83, 160.91, 160.80, 158.90, 158.88, 158.58, 157.76, 156.15, 153.84, 153.81, 151.94, 133.88, 131.51, 131.59, 125.54, 125.29, 125.11, 124.76, 123.59, 121.87, 120.19, 117.77, 115.82, 115.78, 114.26, 112.04, 112.01, 104.64, 98.65, 98.60, 98.47, 97.37, 96.25, 95.18, 76.19, 76.03, 70.53, 70.38, 70.28, 69.46, 69.38, 68.89, 60.90, 57.04, 56.56, 56.42, 56.31, 55.84, 55.69, 52.18, 46.86, 38.91, 28.82, 28.74, 25.52, 25.50, 23.03, 21.19, 19.90, 19.66, 19.56, 19.51; MS (ESI) m/z, calcd for C₆₄H₈₄N₄O₁₉Na⁺ 1235.5, 591.2.

Pentamer 21. This oligomer was prepared from tetramer **19** and acid chloride **20** based on procedures we described before.¹ Yield, 74%; ¹H-NMR (500 MHz, CDCl₃): δ 9.96 (s, 1H), 9.88 (s, 1H), 9.52 (s, 1H), 9.23 (s, 1H), 9.04 (s, 1H), 8.80 (s, 1H), 8.38 (s, 1H), 8.05 (s, 1H), 7.59 (d, J = 8 Hz, 1H), 6.59 (s, 1H), 6.52 (s, 1H), 6.49 (d, 1H), 6.46 (s, 1H), 6.38 (s, 1H), 6.21 (s, 1H), 5.96 (s, 1H), 5.39 (d, J = 15 Hz, 1H), 4.47 (d, J = 15 Hz, 1H), 4.20 (m, 4H), 3.93 (d, 4H), 3.92 (s, 27H), 3.86 (d, 8H), 2.27 (m, 1H), 2.09 (m, 1H), 1.67 (m, 2H), 1.43 (m, 4H), 0.90 (d, 12H), 0.81 (d, 12H); ¹³C NMR (75.5 MHz, CDCl₃) 170.34, 163.20, 161.87, 161.57, 160.55, 158.77, 153.60, 151.84, 148.88, 133.03, 130.79, 125.85, 123.82, 122.03, 120.47, 118.31, 98.78, 96.99, 95.68, 91.95, 70.54, 70.37, 69.41, 57.58, 57.13, 56.40, 55.87, 55.71, 52.18, 38.94, 29.07, 28.87, 25.51, 23.04, 20.28, 20.05; MS (ESI) m/z, calcd for C₇₃H₉₃N₅O₂₂Na⁺ 1414.4, 1392.2, 1157.0.

Hexamer 22. This oligomer was prepared from pentamer **21** and acid chloride **6** based on

procedures we described before.¹ Yield, 71%; ¹H-NMR (500 MHz, CDCl₃): δ 9.96 (s, 1H), 9.92 (s, 1H), 9.71 (s, 1H), 9.60 (s, 1H), 9.25 (s, 1H), 9.11 (s, 1H), 9.06 (s, 1H), 8.90 (s, 1H), 8.46 (d, J = 2.5 Hz, 1H), 8.03 (s, 1H), 7.63 (d, J = 6.5 Hz, 1H), 6.58 (s, 1H), 6.51 (s, 1H), 6.47 (s, 1H), 6.44 (s, 1H), 6.40 (s, 1H), 6.36 (s, 1H), 6.30 (s, 1H), 6.24 (s, 1H), 5.10 (d, J = 15 Hz, 1H), 4.52 (d, J = 15 Hz, 1H), 4.20 (m, 4H), 3.93 (d, 8H), 3.92 (s, 27H), 3.86 (d, 8H), 2.27 (m, 2H), 2.09 (m, 2H), 1.67 (m, 2H), 1.43 (m, 4H), 0.90 (d, 36); ¹³C NMR (75.5 MHz, CDCl₃) 173.78, 166.41, 163.28, 162.18, 160.46, 158.33, 157.60, 157.13, 153.54, 151.01, 149.04, 146.04, 145.66, 135.86, 133.74, 131.67, 125.99, 125.06, 123.81, 119.84, 104.61, 98.61, 70.51, 70.37, 69.43, 56.39, 55.86, 55.72, 38.95, 38.88, 29.12, 28.84, 28.54, 25.51, 23.05, 20.18, 19.97, 19.87, 19.74, 19.60; MS (ESI) m/z, calcd for C₈₈H₁₁₄N₆O₂₅Na⁺ 1678.7, 1677.5, 1673.3, 1655.4, 1493.4, 1392.5.

Heptamer 23. This oligomer was prepared from hexamer **22** and acid chloride **20** based on procedures we described before.¹ Yield, 63%; ¹H-NMR (500 MHz, CDCl₃): δ 9.96 (s, 1H), 9.92 (s, 1H), 9.89 (s, 1H), 9.77 (s, 1H), 9.71 (s, 1H), 9.24 (s, 1H), 9.18 (s, 1H), 9.15 (s, 1H), 9.05 (s, 1H), 8.84 (s, 1H), 8.49 (s, 1H), 8.06 (s, 1H), 7.66 (d, J = 8 Hz, 1H), 6.51 (s, 1H), 6.48 (s, 1H), 6.45 (s, 1H), 6.37 (s, 1H), 6.36 (s, 1H), 6.34 (s, 1H), 6.32 (s, 1H), 6.30 (s, 1H), 6.21 (s, 1H), 5.44 (m, 1H), 4.52 (m, 1H), 4.20 (m, 4H), 3.93 (d, 8H), 3.92 (s, 33H), 3.86 (d, 8H), 2.27 (m, 2H), 2.09 (m, 2H), 1.67 (m, 2H), 1.43 (m, 4H), 0.90 (d, 36); ¹³C NMR (75.5 MHz, CDCl₃) 174.15, 166.40, 163.38, 162.42, 160.57, 154.89, 151.66, 135.13, 131.49, 125.06, 122.10, 100.43, 98.63, 70.34, 69.38, 56.40, 55.87, 52.15, 38.94, 28.79, 25.59, 25.47, 23.17, 23.02, 20.25, 20.00, 19.84; MS (MALDI-TOF) for C₉₇H₁₂₃N₇O₂₈Na⁺: Calcd. 1856.8; Found 1857.7.

Hexamer 22a. Hexamer **22** (50 mg, 0.03 mmol) dissolved in CH₂Cl₂ (20 mL) was mixed with trifluoroacetic acid (1 mL) and the mixture was stirred at room temperature for 1 h. After removal of solvent, the residue was treated with methanol, refluxed and cooled down. The white solid was filtrated to afford **22a** (43 mg, 94%). ¹H-NMR (500 MHz, CDCl₃): δ 10.13 (s, 1H), 10.05 (s, 1H), 9.95 (s, 1H), 9.84 (s, 1H), 9.69 (s, 1H), 9.1 (s, 1H), 9.04 (s, 1H), 8.96 (s, 1H), 8.94 (s, 1H), 8.81 (s, 1H), 8.77 (s, 1H), 6.47 (s, 6H), 4.20 (m, 4H), 3.93 (d, 8H), 3.92 (s, 21H), 3.86 (d, 8H), 2.27 (m, 2H), 2.09 (m, 2H), 1.67 (m, 2H), 1.43 (m, 4H), 0.90 (d, 36). MS (MALDI-TOF) for C₇₉H₁₀₄N₆O₂₃Na⁺: Calcd. 1527.7; Found 1527.1.

13mer 25. Catalytic hydrogenation of **22** (100 mg, 0.06 mmol) led to the corresponding amine, which was mixed with triethylamine (0.2 mL, 1.5 equiv.) in CH_2Cl_2 (20 mL) and was treated by acid chloride **24** dissolved in CH_2Cl_2 (10 mL). Acid chloride **24** was prepared from the corresponding acid (12 mg, 0.028 mmol) and oxalyl chloride (0.5 mL) according to the general procedure. The mixture was heated under reflux overnight and was then washed with brine, dried over anhydrous Na_2SO_4 . After the removal of the solvent, the residue was recrystallized from Methanol to provide the tetramer as a white solid **25** (47 mg, yield 46%). $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ 9.83 (b, 10H), 9.21 (b, 13H), 8.01 (b, 2H), 7.72 (b, 2H), 6.45 (b, 15H), 5.43 (b, 2H), 4.49 (b, 2H), 3.90 (m, 106H), 2.12 (m, 8H), 1.06 (m, 102H). MS (MALDI-TOF) for $\text{C}_{198}\text{H}_{262}\text{N}_{12}\text{O}_{52}\text{Na}^+$: Calcd. 3662.7; Found 3662.8.

13mer 25a. To Oligomer **25** (40 mg, 0.011 mmol) dissolved in CH_2Cl_2 (20 mL) was added TFA (1 mL) and the mixture was stirred at room temperature for 1h. After removal of solvent, the residue was added to methanol, refluxed and cooled down. The white solid was filtered to afford **25a** as a solid (26 mg, 72%). $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 9.84 (b, 12H), 9.20 (b, 13H), 6.46 (b, 13H), 3.93 (m, 94H), 2.23 (m, 8H), 1.41 (m, 102H); ^{13}C NMR (75.5 MHz, CDCl_3)

164.41, 163.14, 162.06, 157.51, 144.42, 131.08, 126.69, 120.88, 101.89, 98.56, 94.77, 76.79, 59.27, 57.03, 55.73, 52.93, 46.50, 42.48, 40.23, 33.62, 26.57, 24.02, 23.96, 23.73, 22.56, 22.03, 20.68, 17.04, 15.97; MS (MALDI-TOF) for $C_{180}H_{242}N_{12}O_{48}Na^+$: Calcd. 3362.8; Found 3363.2.

15mer 26. Catalytic hydrogenation of **23** (230 mg, 0.125 mmol) led to the corresponding amine which was mixed with triethylamine (0.2 mL, 1.5 equiv.) in CH_2Cl_2 (20 mL) and was then treated with acid chloride **24** in CH_2Cl_2 (10 mL). Compound **24** was prepared from the corresponding acid (22 mg, 0.051 mmol) in CH_2Cl_2 (10 mL) and oxalyl chloride (0.5 mL) according to the general procedure. The mixture was heated under reflux overnight and then was washed with brine, dried over anhydrous Na_2SO_4 . After the removal of the solvent, the residue was recrystallized from methanol to provide the 15mer **26** as a white solid (81 mg, yield 39%). 1H -NMR (500 MHz, $CDCl_3$): δ 9.85 (b, 12H), 9.23 (b, 15H), 7.97 (b, 2H), 7.66 (b, 2H), 6.44 (b, 17H), 5.44 (b, 2H), 4.50 (b, 2H), 3.88 (m, 118H), 2.10 (m, 8H), 1.06 (m, 102H); ^{13}C NMR (75.5 MHz, $CDCl_3$) 165.84, 163.22, 163.11, 161.08, 156.78, 156.53, 154.76, 154.39, 153.94, 152.87, 132.93, 131.18, 127.47, 126.87, 125.20, 121.87, 121.58, 121.50, 121.42, 121.15, 120.58, 115.42, 115.26, 114.64, 111.78, 98.02, 97.88, 76.58, 75.93, 75.22, 51.46, 28.42, 28.18, 28.16, 28.11, 28.01, 27.59, 19.33, 19.29, 19.26, 19.23, 19.17, 18.99, 18.35; MS (MALDI-TOF) for $C_{198}H_{260}N_{14}O_{54}Na^+$: Calcd. 3720.8; Found 3721.1.

15mer (26a): To a flask with **26** (60 mg, 0.015 mmol) in CH₂Cl₂ (20 mL) was added TFA (1 mL) and the mixture was stirred at room temperature for 1h. After removal of the solvent, the residue was added methanol, refluxed and cooled down. The white solid was filtered to afford the 15mer **26a** (42 mg, 75%). ¹H-NMR (500 MHz, CDCl₃): δ 9.92 (b, 14H), 9.28 (b, 15H), 6.44 (b, 15H), 3.90 (m, 106H), 2.10 (m, 8H), 1.06 (m, 102H); ¹³C NMR (75.5 MHz, CDCl₃) 166.47, 1656.28, 163.66, 159.74, 157.02, 155.54, 141.86, 131.33, 121.23, 114.97, 102.18, 101.31, 100.43, 95.74, 92.53, 69.56, 65.67, 56.35, 47.69, 47.60, 44.23, 38.97, 31.67, 30.22, 28.74, 25.78, 25.50, 23.05, 20.65, 19.83; MS (MALDI-TOF) for C₁₉₈H₂₆₀N₁₄O₅₄Na⁺: Calcd. 3720.8; Found 3721.1.

III. 1D and 2D NMR spectra

Figure 1. ^1H -NMR spectra of 6mer (**22a**), 13mer (**25a**) and 15mer (**26a**).

Figure 2. Expanded ^1H -NMR spectra showing the aromatic and amides signals of ^1H -NMR of 6mer (**22a**), 13mer (**25a**) and 15mer (**26a**).

Figure 3. 2D NOESY spectrum of 15mer **26a** in CDCl_3 (500 MHz, 10 mM, 298K, mixing time: 0.05 sec).

Figure 4 ^{13}C NMR of Compound 17

Figure 5 ^{13}C NMR of Compound 19

S20

Figure 7 ^{13}C NMR of Compound **25a**

Figure 9 ^1H NMR of Compound 26a

S24

Figure 11. The MALDI-TOF of Compound **22a**

Figure 12. The MALDI-TOF Compound **25a**

D:\usr\MaldiTOF\Zam\2006\02172006\02172006_ZAM_12\0_L22_1Ref\data\1\1r (11:05 02/17/06)
 Description: FLEXControl generated XMASS data (c) 2000 Bruker Daltonics

Figure 13. The MALDI-TOF of Compound **26a**

1. Yuan, L. H.; Sanford, A. R.; Feng, W.; Zhang, A. M.; Zhu, J.; Zeng, H. Q.; Yamato, K.; Li, M. F.; Ferguson, J. S.; Gong, B. *J. Org. Chem.* **2005**, *70*, 10660.