

## Contents

<b>1</b>	<b>Materials</b>	<b>S2</b>
<b>2</b>	<b>Instrumentation</b>	<b>S2</b>
<b>3</b>	<b>Synthetic procedures</b>	<b>S3</b>
<b>4</b>	<b>Synthetic route</b>	<b>S5</b>
<b>5</b>	<b>Experiments</b>	<b>S9</b>
<b>6</b>	<b>Circular dichroism (CD) spectroscopy</b>	<b>S33</b>
<b>7</b>	<b>Transmission electron microscopy (TEM)</b>	<b>S34</b>
<b>8</b>	<b>References</b>	<b>S40</b>

# Experiments

## 1 Materials

Unless stated otherwise, all reagents and chemicals were obtained from commercial sources at the highest purity available and used without further purification. Water was demineralised prior to use. Some solvents were dried using the following drying agents: Dichloromethane over sodium hydride, tetrahydrofuran over sodium and benzophenone, methanol over molecular sieves 3 Å, *N,N*-dimethylformamide over molecular sieves 3 Å. Purification via flash chromatography was carried out using silica-gel with an average grain size of 15-40  $\mu\text{m}$  (MERCK). Technical grade solvents, which were used as a mobile phase, were distilled before use. Analysis of the collected fractions was performed via TLC on silica coated aluminum sheets (60 F254, MERCK). The solid phase peptide synthesis (SPPS) was carried out on a Peptide Synthesizer CS 136XT (CS Bio) using 2-chloro-tritylchloride resin (1.5 mmol/g loading) and SPPS-grade reagents and solvents.

## 2 Instrumentation

NMR-spectra were recorded on a BRUKER Avance II 400 and BRUKER Avance III 600 spectrometer. All measurements were carried out in deuterated solvents. The chemical shift ( $\delta$ ) is recorded in parts per million (ppm) and relative to the residual solvent protons.<sup>1</sup> The measured coupling constants were calculated in Hertz (Hz). To analyse the spectra the software MESTRENOVA 9.0.1 was used. The signals were quoted as follows: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet and m = multiplet.

Mass spectra were recorded on the electrospray ionization spectrometer (ESI) QTof Ultima 3 (micromass / Waters) using methanol as solvent. Molecules of a high molecular mass were detected using matrix assisted laser desorption ionization-time of flight (MALDITOF) spectrometry using a Shimadzu Axima CFR.

The final compounds **1a**, **1b**, **2a** and **2b** were purified by reversed-phase HPLC on a VariTide RPC semipreparative column (VARIAN). NMR and MALDI-MS were used to identify the purity of the obtained fractions. The acetonitrile content of the combined fractions was removed under reduced pressure before freeze-drying. The acidic monomers **1a** and **2a** were purified under basic conditions with eluents containing 0.1 vol%  $\text{NH}_4\text{OH}$  while the basic monomers **1b** and **2b** were purified under acidic conditions with eluents containing 0.1 vol% TFA applying the following gradient for both monomers:

t [min]	Water /%	Acetonitrile /%
0	95	5
10	95	5
50	57	43
55	0	100
70	0	100

### 3 Synthetic procedures

#### Standard operating procedure for the synthesis of the protected penta and hexapeptides via SPPS (SOP 1)

The loading of the resin was performed according to a procedure described in literature.<sup>2</sup> The appropriate Fmoc-protected amino acid (2.0 eq. relative to resin loading capacity) was dissolved in 10 mL DCM/ g resin and added to the 2-chlorotrityl-chloride resin. Small amounts of DMF can be used to get the amino acid completely dissolved. This is followed by the addition of 2.0 eq. of DIPEA relative to the resin capacity. After shaking for 5 min at room temperature additional 3.0 eq. of DIPEA were added. The reaction mixture was shaken for 1 h at room temperature and afterwards treated with 1 mL MeOH per gram resin and shaken for 15 min. The vessel was drained and the beads were washed consecutively three times each with DCM, DMF, DCM and MeOH. Afterwards the beads were dried under vacuum overnight. The following step-wise chain elongation was performed using the CS 136XT peptide synthesizer, which is an automated batch peptide synthesizer. The procedure is described here.

The dried beads were swollen in DCM p.a. for 10 min while shaking the reaction vessel. After sucking off the solution, piperidine (20% in DMF) was added and the vessel was shaken for 20 min. After draining of the vessel the beads were washed four times with DMF and twice with DCM. The resin was treated with a solution of the corresponding protected amino acid (6.0 mmol, 4.0 eq.), HBTU (4.0 eq.) and DIPEA (6.0 eq.) in DMF. After shaking for 1 h the solution was removed and the resin was washed five times with DMF. This procedure was repeated with the corresponding amino acid for every coupling process, starting with the Fmoc deprotection on the resin. Finally the resin is washed with DCM.

The cleavage of resin-bound peptides was carried out according to a procedure described in the literature.<sup>3</sup> The beads were stirred for 45 min in a solution of 2,2,2-trifluoroethanol (TFE) and DCM (2:8). Afterwards the solution was drained from the reaction vessel and the beads were washed at least two times with a small amount of DCM. The collected solutions were concentrated under reduced pressure and the product precipitated out of a 0 °C solution of diethylether. The whole procedure was repeated three times.

### **Standard operation procedure for the cleavage of the Boc- and *t*-Bu-protection groups (SOP 2)**

The Boc or *t*-Bu protected compound was treated with 8 mL TFA (50%) in DCM. The solution was stirred 1 h at room temperature, concentrated under reduced pressure and another 8 mL of the 1:1 TFA/DCM solution were added. After removal of the solvent via reduced pressure, the desired product was obtained without further purification.

### **Standard operation procedure for the cleavage of Cbz-protection groups (SOP 3)**

The Cbz-protected compound was dissolved in 10 mL MeOH. 10 wt% Pd/C were added and the suspension was stirred under an atmosphere of hydrogen overnight at room temperature. The catalyst was afterwards removed via filtration over Celite<sup>®</sup>. After removal of the solvent via reduced pressure, the desired product was obtained without further purification.

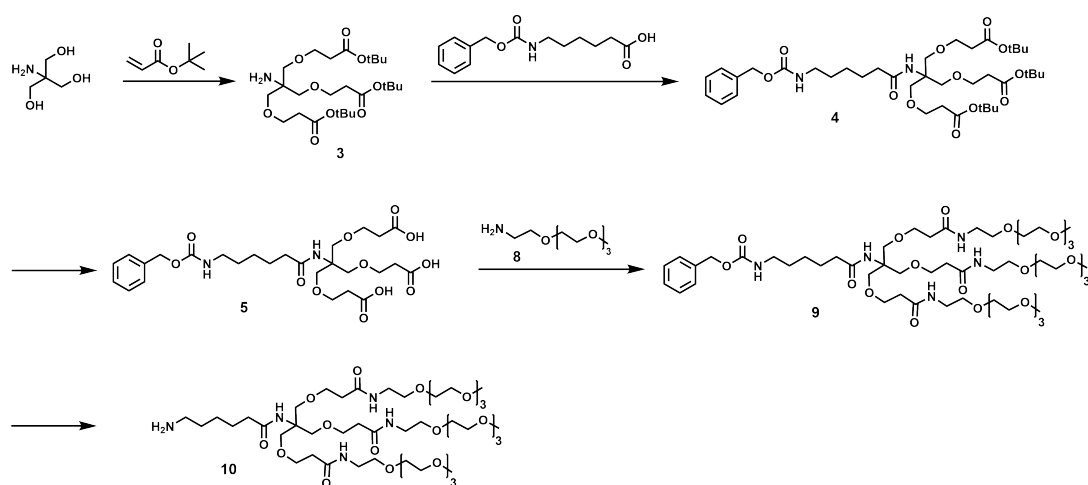
### **Standard operation procedure for the cleavage of Fmoc-protection groups (SOP 4)**

The Fmoc deprotection was carried out based on a literature procedure.<sup>4</sup> The Fmoc-protected compound was dissolved in a 10 vol-% solution of Piperidine in DCM. The reaction was stirred for 30 min at room temperature. After removal of the solvent via reduced pressure, the desired product was precipitated out of diethylether.

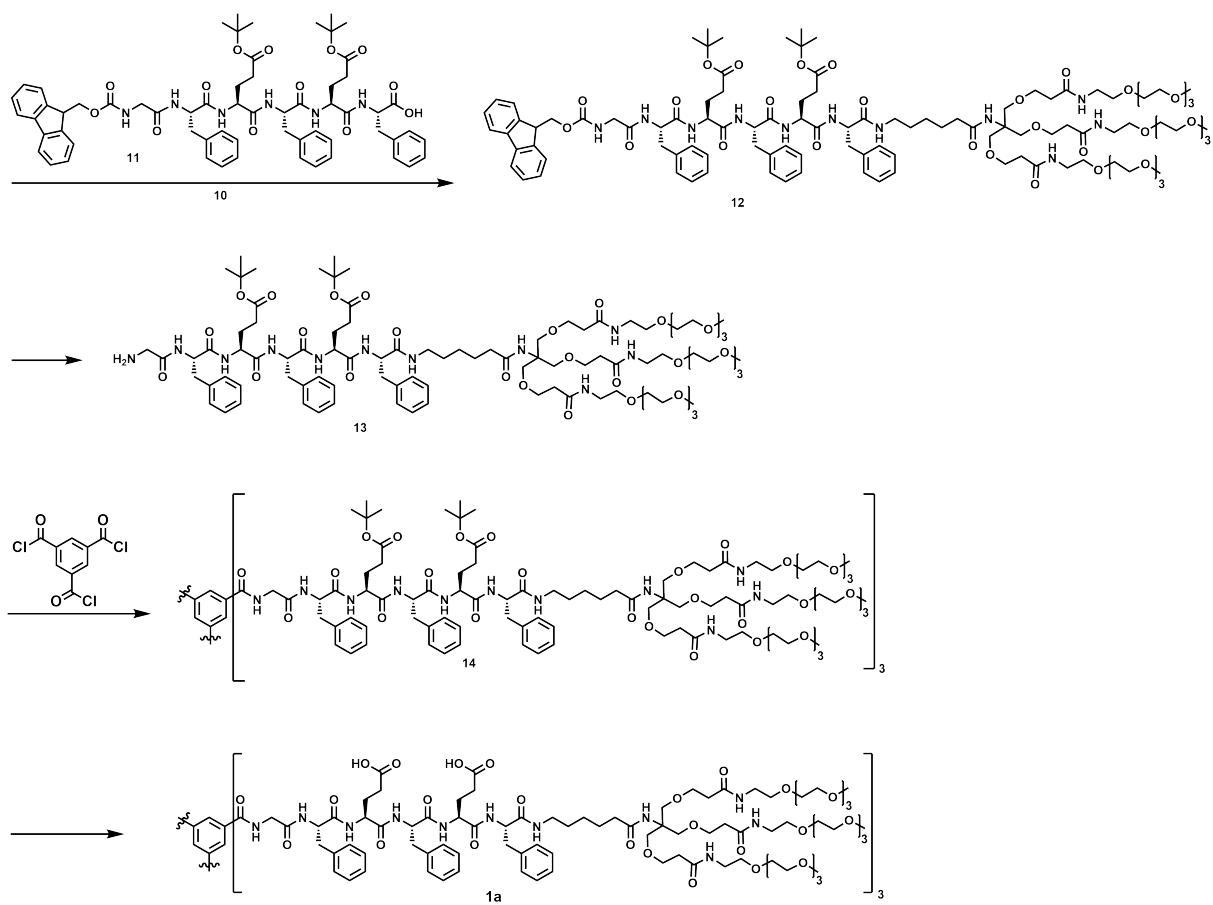


## 4 Synthetic route

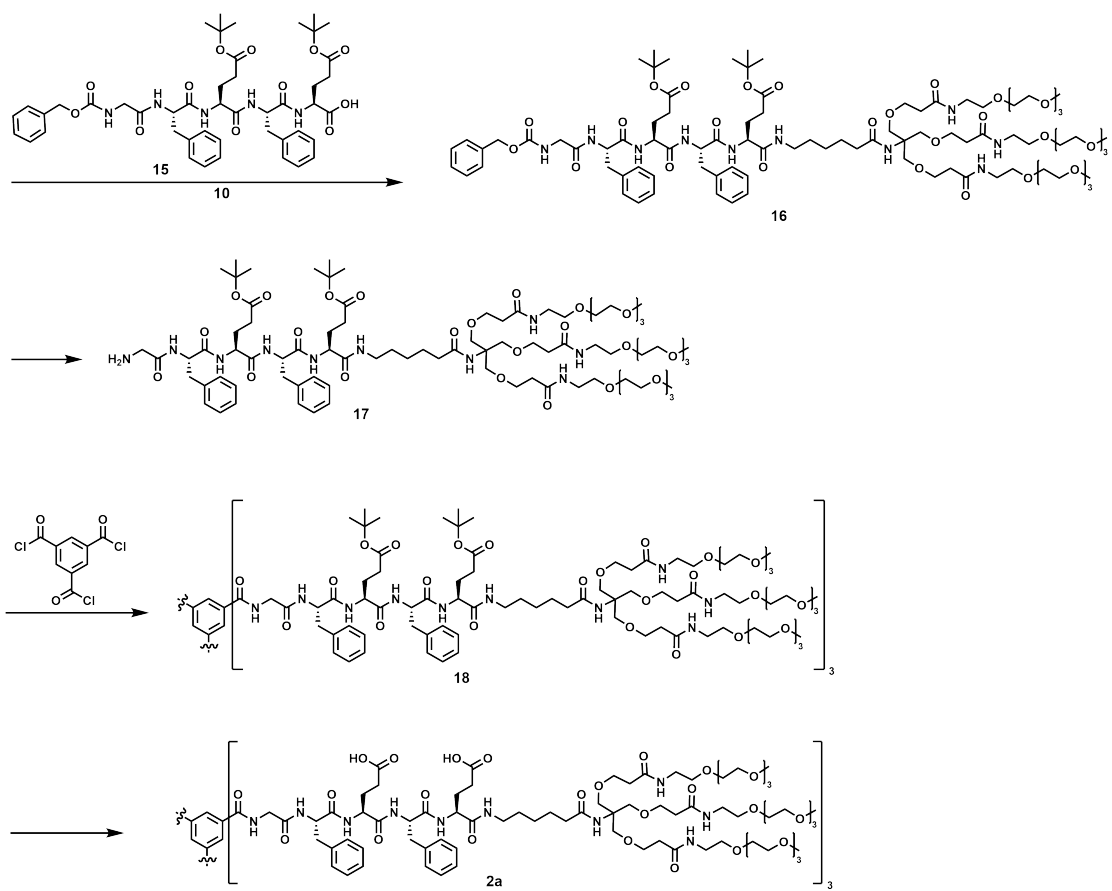
### Synthesis of the hydrophilic dendron (Dnd) 10



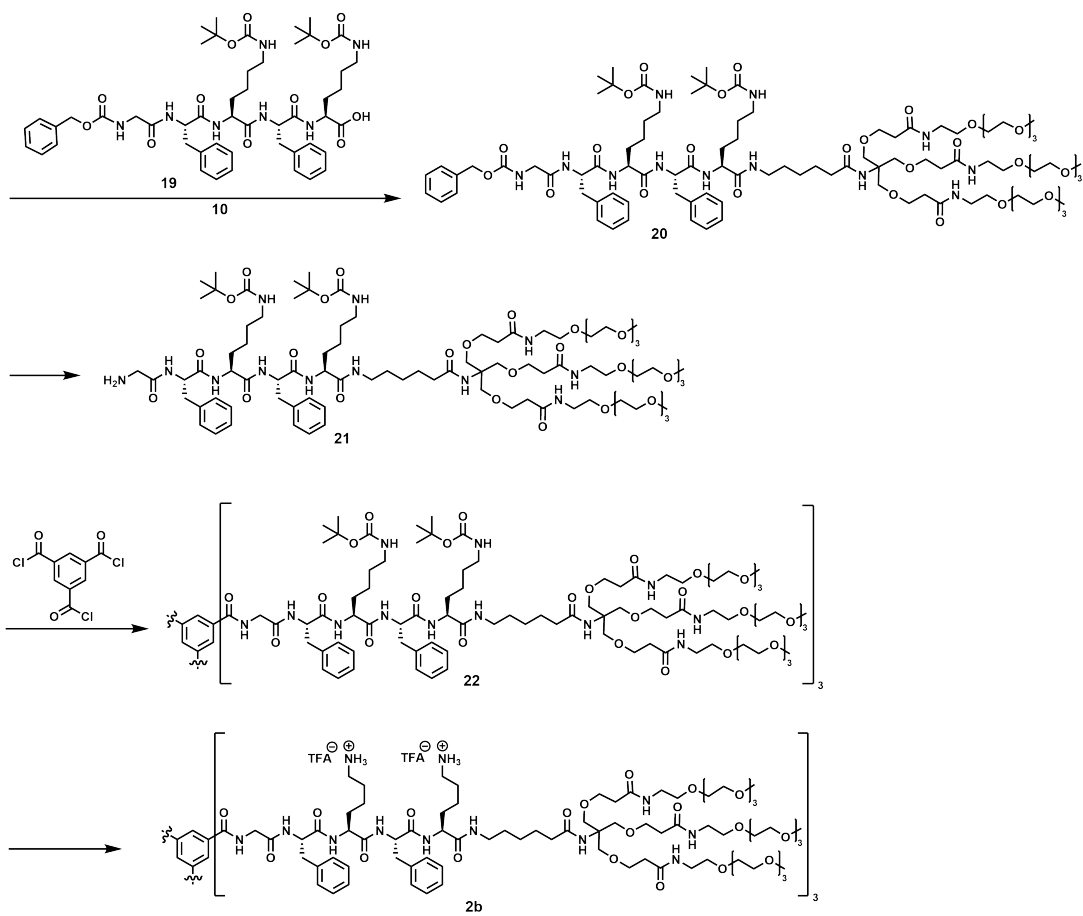
## Synthesis of monomer 1a



## Synthesis of monomer 2a

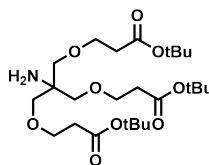


## Synthesis of monomer 2b



## 5 Experiments

### Tris[2-(*tert*-butoxycarbonyl)ethoxy]methylmethanamine (**3**)<sup>5</sup>



**3**

Tris (2.42 g, 20.0 mmol, 1.0 eq.) was suspended in 5 mL DMSO and cooled to 15 °C. Afterwards 5.0 N aq. NaOH (0.4 mL) and *tert*-butyl acrylate (10.00 mL, 68.0 mmol, 3.4 eq.) were added and the solution was stirred overnight at room temperature. The solution was concentrated under reduced pressure and the residue was purified via column chromatography (EtOAc/cyclohexane : 2/1 + 0.05 v/v% NH<sub>4</sub>OH, R<sub>f</sub> = 0.25).

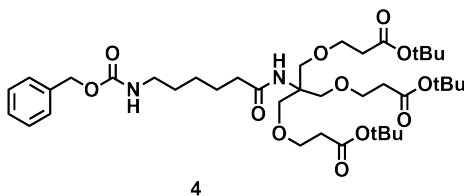
**Yield:** 3.94 g (7.8 mmol, 39%); colourless liquid.

**Molecular formula:** C<sub>25</sub>H<sub>47</sub>NO<sub>9</sub>.

**ESI-HRMS (MeOH) (m/z):** Calculated for [C<sub>25</sub>H<sub>47</sub>NO<sub>9</sub>H]<sup>+</sup>: 506.3324, found: 506.3327; calculated for [C<sub>25</sub>H<sub>47</sub>NO<sub>9</sub>Na]<sup>+</sup>: 528.3143, found: 528.3148.

**<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>, 298 K):** δ = 3.61 (t, *J* = 6.4 Hz, 6H, CH<sub>2</sub>O), 3.27 (s, 6H, CH<sub>2</sub>C<sub>q</sub>), 2.41 (t, *J* = 6.4 Hz, 6H, CH<sub>2</sub>CO<sub>2</sub><sup>*tBu*</sup>), 1.41 (s, 27H, CH<sub>3</sub><sup>*tBu*</sup>).

Cbz-Ahx-Tris[ 2-(*tert*-butoxycarbonyl)ethoxy methyl methylethylamide (4)



PyBOP (5.16 g, 9.9 mmol, 1.3 eq.) was added to a solution of **3** (3.85 g, 7.6 mmol, 1.0 eq.), Cbz-hexanoic acid (Cbz-Ahx) (2.41 g, 9.1 mmol, 1.2 eq.) and DIPEA (5.21 mL, 30.5 mmol, 4.0 eq.) in THF (48 mL). The reaction mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure and the residue was purified via flash chromatography over SiO<sub>2</sub> (EtOAc/DCM : 1/1, R<sub>f</sub> = 0.76).

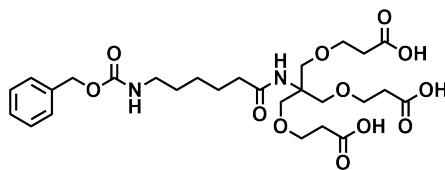
**Yield:** 5.72 g (7.6 mmol, quant.); colourless oil.

**Molecular formula:** C<sub>39</sub>H<sub>64</sub>N<sub>2</sub>O<sub>12</sub>.

**ESI-HRMS (MeOH) (m/z):** Calculated for [C<sub>39</sub>H<sub>64</sub>N<sub>2</sub>O<sub>12</sub>Na]<sup>+</sup>: 775.4359, found: 775.4361.

**<sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>, 298 K):** δ = 7.39 - 7.25 (m, 5H, CH<sup>Cbz</sup>), 7.21 (t, *J* = 5.7 Hz, 1H, NH), 6.90 (s, 1H, NHC<sub>q</sub>), 4.99 (s, 2H, CH<sub>2</sub><sup>Cbz</sup>), 3.60 - 3.47 (m, 12H, OCH<sub>2</sub>), 3.11 - 2.90 (m, 2H, NCH<sub>2</sub>), 2.38 (t, *J* = 6.1 Hz, 6H, OCH<sub>2</sub>CH<sub>2</sub>C=O), 2.03 (t, *J* = 7.4 Hz, 2H, N[CH<sub>2</sub>]<sub>4</sub>CH<sub>2</sub>), 1.51 - 1.41 (m, 2H, N[CH<sub>2</sub>]<sub>3</sub>CH<sub>2</sub>), 1.42 - 1.30 (m, 27H, CH<sub>3</sub><sup>tBu</sup>), 1.29 - 1.14 (m, 4H, NCH<sub>2</sub>CH<sub>2</sub>, N[CH<sub>2</sub>]<sub>2</sub>CH<sub>2</sub>).

### Cbz-Ahx-Tris 2-(carboxyethoxy) methyl methanamide (5)



5

4 (1.97 g, 2.6 mmol) was deprotected according to **SOP 2**.

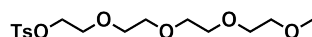
**Yield:** 1.23 g (2.6 mmol, quant.); red oil.

**Molecular formula:** C<sub>27</sub>H<sub>40</sub>N<sub>2</sub>O<sub>12</sub>.

**ESI-HRMS (MeOH) (m/z):** Calculated for [C<sub>27</sub>H<sub>40</sub>N<sub>2</sub>O<sub>12</sub>CF<sub>3</sub>COOH]<sup>+</sup>: 697.2446, found: 697.2446.

**<sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>, 298 K):** δ = 7.41 – 7.27 (m, 5H, CH<sup>Cbz</sup>), 7.21 (t, *J* = 5.7 Hz, 1H, NH<sup>Cbz</sup>), 6.93 (s, 1H, NHC<sub>q</sub>), 5.00 (s, 2H, CH<sub>2</sub><sup>Cbz</sup>), 3.62 – 3.51 (m, 12H, CH<sub>2</sub>OCH<sub>2</sub>), 3.02 – 2.93 (m, 2H, NCH<sub>2</sub>), 2.42 (t, *J* = 6.3 Hz, 6H, OCH<sub>2</sub>CH<sub>2</sub>C=O), 2.04 (t, *J* = 7.4 Hz, 2H, N[CH<sub>2</sub>]<sub>4</sub>CH<sub>2</sub>), 1.49 – 1.33 (m, 4H, NCH<sub>2</sub>CH<sub>2</sub>/N[CH<sub>2</sub>]<sub>3</sub>CH<sub>2</sub>), 1.29 – 1.11 (m, 2H, N[CH<sub>2</sub>]<sub>2</sub>CH<sub>2</sub>).

### Methoxy tetraethylene glycol tosylate (6)



6

Methoxy tetraethylene glycol (16.39 g, 78.7 mmol, 1.0 eq.) was dissolved in a mixture of H<sub>2</sub>O/ THF (120 mL, 3:1) and NaOH (16.37 g, 0.4 mol, 5.2 eq.) was added. At 0 °C Tosylchloride (17.89 g, 93.8 mmol, 1.2 eq.) in THF (110 mL) was added dropwise. The solution was stirred over night at room temperature. The raw product was extracted with Et<sub>2</sub>O, washed with H<sub>2</sub>O and dried over MgSO<sub>4</sub>.

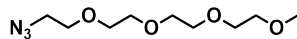
**Yield:** 27.71 g (76.5 mmol, 97%); light yellow oil.

**Molecular formula:** C<sub>16</sub>H<sub>26</sub>O<sub>7</sub>S.

**ESI-HRMS (MeOH) (m/z):** Calculated for [C<sub>16</sub>H<sub>26</sub>O<sub>7</sub>SNa]<sup>+</sup>: 385.1291, found: 385.1287.

**<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>, 298 K):** δ = 7.79 (d, 2H, *J* = 8.2 Hz, *m*-CH), 7.33 (d, 2H, *J* = 8.6 Hz, *o*-CH), 3.70 - 3.50 (m, 16H, CH<sub>2</sub><sup>PEG</sup>), 3.36 (s, 3H, OCH<sub>3</sub>), 2.44 (s, 3H, *p*-CH<sub>3</sub>).

## Methoxy tetraethylene glycol tosylate azide (7)



7

**6** (27.72 g, 76.5 mmol, 1.0 eq.) was dissolved in DMF (30 mL) and sodium azide (15.44 g, 237 mmol, 3.1 eq.) was added. The solution was stirred at 60 °C for three days. Reaction solution was diluted with water and the aqueous layer extracted with CHCl<sub>3</sub> (3x100 mL). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtrated and concentrated in *vacuo*. The residue was purified via column chromatography (EtOAc/pentane : 2/1, R<sub>f</sub> = 0.30).

**Yield:** 16.45 g (70.5 mmol, 92%); colourless oil.

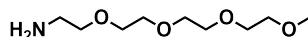
**Molecular formula:** C<sub>9</sub>H<sub>19</sub>N<sub>3</sub>O<sub>4</sub>.

**ESI-HRMS (MeOH) (m/z):** Calculated for [C<sub>9</sub>H<sub>19</sub>N<sub>3</sub>O<sub>4</sub>Na]<sup>+</sup>: 256.1268,

found: 256.1268.

**<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>, 298 K):** δ = 3.73 - 3.45 (m, 16H, CH<sub>2</sub><sup>PEG</sup>), 3.37 (s, 3H, OCH<sub>3</sub>).

## Methoxy tetraethylene glycol tosylate amine (8)



8

**7** (16.45 g, 70.5 mmol, 1.0 eq.) was dissolved in THF (120 mL) and H<sub>2</sub>O (2 mL). Triphenylphosphine (24.04 g, 91.7 mmol, 1.1 eq.) was added and the solution stirred for two days at room temperature. After removing the solvent the residue was dissolved in toluene/H<sub>2</sub>O. The organic layer was washed with H<sub>2</sub>O and concentrated under reduced pressure. After that freeze-dried

**Yield:** 14.61 g (70.5 mmol, quant.); colourless liquid.

**Molecular formula:** C<sub>9</sub>H<sub>21</sub>NO<sub>4</sub>.

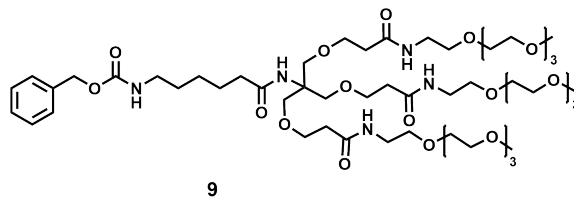
**ESI-HRMS (MeOH) (m/z):** Calculated for [C<sub>9</sub>H<sub>21</sub>NO<sub>4</sub>H]<sup>+</sup>: 208.1543, found: 208.1544,

Calculated for [C<sub>9</sub>H<sub>21</sub>NO<sub>4</sub>Na]<sup>+</sup>: 230.1363, found: 230.1367.

**<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>, 298 K):** δ = 3.73 - 3.45 (m, 14H, CH<sub>2</sub><sup>PEG</sup>), 3.37 (s, 3H, OCH<sub>3</sub>), 2.85 (t, J = 5.2 Hz, 2H, NCH<sub>2</sub>), 2.06 (bs, 2H, NH<sub>2</sub>).



**Cbz-Ahx-Tris[2-(tetraethyleneglycol amido)ethoxy]methylmethanamide (Cbz-Dnd) (9)**



PyBOP (5.34 g, 10.26 mmol, 6.0 eq.) was added to a solution of **5** (1.0 g, 1.71 mmol, 1.0 eq.), **8** (2.69 g, 12.99 mmol, 7.6 eq.) and DIPEA (10.18 mL, 59.87 mmol, 30 eq.) in THF (12 mL). The reaction mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure and the residue was purified via size exclusion chromatography (Sephadex<sup>®</sup> LH 20, MeOH).

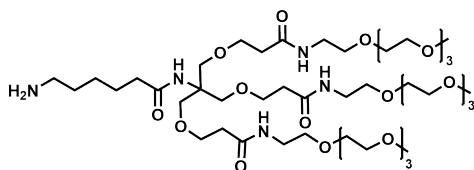
**Yield:** 1.13 g (980  $\mu$ mol, 57%); light red oil.

**Molecular formula:** C<sub>54</sub>H<sub>97</sub>N<sub>5</sub>O<sub>21</sub>.

**ESI-HRMS (MeOH) (m/z):** Calculated for [C<sub>54</sub>H<sub>97</sub>N<sub>5</sub>O<sub>21</sub>Na]<sup>+</sup>: 1174.6568, found: 1174.6612, Calculated for [C<sub>54</sub>H<sub>97</sub>N<sub>5</sub>O<sub>21</sub>K]<sup>+</sup>: 1190.66, found: 1190.69.

**<sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>, 298 K):**  $\delta$  = 7.92 (t, *J* = 5.6 Hz, 3H, NHCH<sub>2</sub>), 7.40 – 7.28 (m, 5H, CH<sup>Cbz</sup>), 7.23 (t, *J* = 5.8 Hz, 1H, NH<sup>Cbz</sup>), 6.99 (s, 1H, NHC<sub>q</sub>), 4.99 (s, 2H, CH<sub>2</sub><sup>Cbz</sup>), 3.60 – 3.34 (m, 54H, CH<sub>2</sub>O), 3.26 – 3.13 (m, 15H, CH<sub>3</sub><sup>TEG</sup>, NCH<sub>2</sub>CH<sub>2</sub>O), 3.05 – 2.91 (m, 2H, NCH<sub>2</sub>[CH<sub>2</sub>]<sub>4</sub>), 2.29 (t, *J* = 6.4 Hz, 6H, OCH<sub>2</sub>CH<sub>2</sub>C=O), 2.05 (t, *J* = 7.4 Hz, 2H, N[CH<sub>2</sub>]<sub>4</sub>CH<sub>2</sub>), 1.50 – 1.30 (m, 4H, NCH<sub>2</sub>CH<sub>2</sub>/ N[CH<sub>2</sub>]<sub>3</sub>CH<sub>2</sub>), 1.29 – 1.13 (m, 2H, N[CH<sub>2</sub>]<sub>2</sub>CH<sub>2</sub>).

## H-Dnd (10)



10

**9** (661 mg, 0.57 mmol) was deprotected according to **SOP 3**.

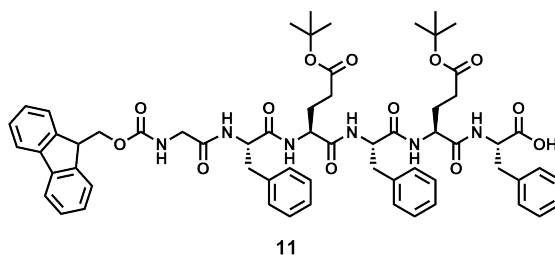
**Yield:** 580 mg (0.57 mol, quant.); light yellow oil.

**Molecular formula:** C<sub>46</sub>H<sub>91</sub>N<sub>5</sub>O<sub>19</sub>.

**ESI-HRMS (MeOH) (m/z):** Calculated for [C<sub>46</sub>H<sub>91</sub>N<sub>5</sub>O<sub>19</sub>H]<sup>+</sup>: 1018.6387, found: 1018.6377, Calculated for [C<sub>46</sub>H<sub>91</sub>N<sub>5</sub>O<sub>19</sub>Na]<sup>+</sup>: 1040.6206, found: 1040.6201.

**<sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>, 298 K):**  $\delta$  = 7.93 (t, *J* = 5.6 Hz, 3H, NHCH<sub>2</sub>), 6.97 (s, 1H, NHC<sub>q</sub>), 3.64 – 3.37 (m, 54H, CH<sub>2</sub>O), 3.28 – 3.13 (m, 15H, CH<sub>3</sub><sup>TEG</sup>, NCH<sub>2</sub>CH<sub>2</sub>O), 3.06 – 2.90 (m, 2H, NCH<sub>2</sub>[CH<sub>2</sub>]<sub>4</sub>), 2.29 (t, *J* = 6.4 Hz, 6H, OCH<sub>2</sub>CH<sub>2</sub>C=O), 2.05 (t, *J* = 7.3 Hz, 2H, N[CH<sub>2</sub>]<sub>4</sub>CH<sub>2</sub>), 1.55 – 1.37 (m, 4H, NCH<sub>2</sub>CH<sub>2</sub>/ N[CH<sub>2</sub>]<sub>3</sub>CH<sub>2</sub>), 1.35 – 1.16 (m, 2H, N[CH<sub>2</sub>]<sub>2</sub>CH<sub>2</sub>).

**Fmoc-Gly-Phe-Glu(*t*Bu)-Phe-Glu(*t*Bu)-Phe-OH (11)**



The synthesis was carried out according to **SOP 1**.

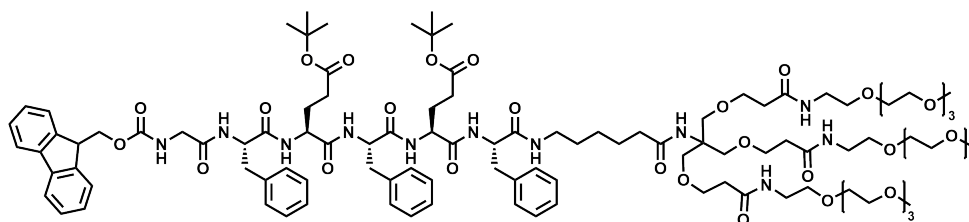
**Yield:** 1.99 g (1,79 mmol); colourless solid.

**Molecular formula:** C<sub>62</sub>H<sub>72</sub>N<sub>6</sub>O<sub>13</sub>.

**ESI-HRMS (MeOH) (m/z):** Calculated for [C<sub>62</sub>H<sub>72</sub>N<sub>6</sub>O<sub>13</sub>H]<sup>+</sup>: 1109.5236, found: 1109.5228.

**<sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>, 298 K):**  $\delta$  = 12.78 (s, 1H, CO<sub>2</sub>H), 8.16 (d, *J* = 8.0 Hz, 1H,  $\alpha$ -NH), 8.12 (d, *J* = 7.6 Hz, 1H,  $\alpha$ -NH), 8.09 (d, *J* = 8.2 Hz, 1H,  $\alpha$ -NH), 8.00 (d, *J* = 8.1 Hz, 1H,  $\alpha$ -NH), 7.88 (d, *J* = 7.5 Hz, 1H,  $\alpha$ -NH), 7.69 (d, *J* = 7.5 Hz, 2H, CHC<sub>q</sub><sup>Fmoc</sup>), 7.61 - 7.53 (m, 2H, CHC<sub>q</sub><sup>Fmoc</sup>), 7.41 (t, *J* = 7.2 Hz, 1H,  $\alpha$ -NH<sup>Gly</sup>), 7.31 (t, *J* = 7.4 Hz, 2H, CHC<sub>q</sub><sup>Fmoc</sup>), 7.27 - 7.06 (m, 17H, CHCH<sup>Fmoc</sup> / CH<sup>Ar</sup>), 4.59 - 4.47 (m, 3H,  $\alpha$ -CH), 4.45 - 4.36 (m, 2H,  $\alpha$ -CH), 3.96 - 3.45 (m, 5H,  $\alpha$ -CH<sub>2</sub><sup>Gly</sup> / CHCH<sub>2</sub><sup>Fmoc</sup> / CH<sub>2</sub><sup>Fmoc</sup>), 3.11 - 2.64 (m, 6H, CH<sub>2</sub><sup>Phe</sup>), 2.22 - 2.06 (m, 4H, CH<sub>2</sub><sup>Glu</sup>), 1.90 - 1.61 (m, 4H, CH<sub>2</sub><sup>Glu</sup>), 1.37 (s, 18H, CH<sub>3</sub><sup>tBu</sup>).

## Fmoc-Gly-Phe-Glu(*t*Bu)-Phe-Glu(*t*Bu)-Phe-Dnd (12)



12

PyBOP (245 mg, 470  $\mu$ mol, 2.4 eq.) was added to a stirred solution of **11** (435 mg, 392  $\mu$ mol, 2.0 eq.), **10** (200 mg, 196  $\mu$ mol, 1.0 eq.) and DIPEA (666  $\mu$ L, 3.9 mmol, 20.0 eq.) in DCM (30 mL). The reaction mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure and the residue was purified via size exclusion chromatography (Sephadex<sup>®</sup> LH 20, MeOH).

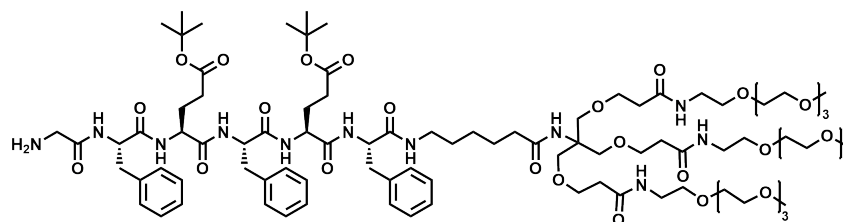
**Yield:** 267 mg (126  $\mu$ mol, 64%); colourless oil.

**Molecular formula:** C<sub>108</sub>H<sub>161</sub>N<sub>11</sub>O<sub>31</sub>.

**MALDI-MS (MeOH) (m/z):** Calculated for [C<sub>108</sub>H<sub>161</sub>N<sub>11</sub>O<sub>31</sub>Na]<sup>+</sup>: 2132.13, found: 2132.13.

**<sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>, 298 K):**  $\delta$  = 8.16 (d, *J* = 8.0 Hz, 1H,  $\alpha$ -NH), 8.12 (d, *J* = 7.9 Hz, 1H,  $\alpha$ -NH), 8.01 (d, *J* = 8.0 Hz, 1H,  $\alpha$ -NH), 7.95 - 7.86 (m, 6H,  $\alpha$ -NH/NHCH<sub>2</sub>), 7.70 (d, *J* = 7.5 Hz, 2H, CHC<sub>q</sub><sup>Fmoc</sup>), 7.66 - 7.53 (m, 2H, CHC<sub>q</sub><sup>Fmoc</sup>), 7.41 (t, *J* = 7.4 Hz, 1H,  $\alpha$ -NH<sup>Gly</sup>), 7.32 (t, *J* = 7.3 Hz, 2H, CHC<sub>q</sub><sup>Fmoc</sup>), 7.26 - 7.10 (m, 17H, CHCH<sup>Fmoc</sup> / CH<sup>Ar</sup>), 6.98 (s, 1H, NHC<sub>q</sub>), 4.59 - 4.41 (m, 5H,  $\alpha$ -CH), 3.96 - 3.33 (m, 60H, CH<sub>2</sub>O /  $\alpha$ -CH<sub>2</sub><sup>Gly</sup> / CHCH<sub>2</sub><sup>Fmoc</sup> / CH<sub>2</sub><sup>Fmoc</sup>), 3.26 - 3.16 (m, 15H, CH<sub>3</sub><sup>TEG</sup>, NCH<sub>2</sub>CH<sub>2</sub>O), 3.06 - 2.90 (m, 2H, NCH<sub>2</sub>[CH<sub>2</sub>]<sub>4</sub>), 2.86 - 2.66 (m, 6H, CH<sub>2</sub><sup>Phe</sup>), 2.30 (t, *J* = 6.4 Hz, 6H, OCH<sub>2</sub>CH<sub>2</sub>C=O), 2.20 - 2.08 (m, 4H, CH<sub>2</sub><sup>Glu</sup>), 2.04 (t, *J* = 7.5 Hz, 2H, N[CH<sub>2</sub>]<sub>4</sub>CH<sub>2</sub>), 1.89 - 1.61 (m, 4H, CH<sub>2</sub><sup>Glu</sup>), 1.55 - 1.37 (m, 22H, NCH<sub>2</sub>CH<sub>2</sub> / N[CH<sub>2</sub>]<sub>3</sub>CH<sub>2</sub> / CH<sub>3</sub><sup>tBu</sup>), 1.35 - 1.16 (m, 2H, N[CH<sub>2</sub>]<sub>2</sub>CH<sub>2</sub>).

### H-Gly-Phe-Glu(*t*Bu)-Phe-Glu(*t*Bu)-Phe-Dnd (13)



**12** (245 mg, 116  $\mu$ mol) was deprotected according to **SOP 4**.

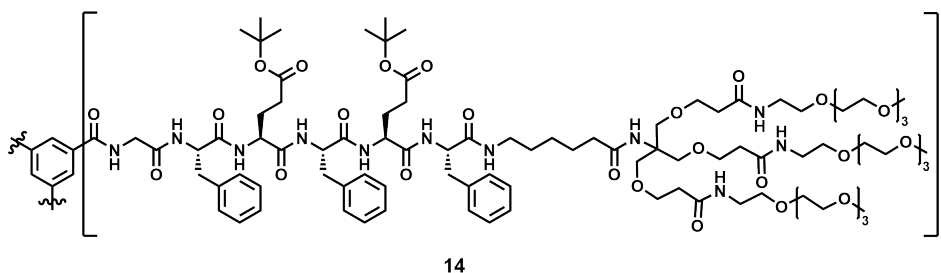
**Yield:** 218 mg (116  $\mu$ mol, quant.); colourless solid.

**Molecular formula:** C<sub>93</sub>H<sub>151</sub>N<sub>11</sub>O<sub>29</sub>.

**ESI-HRMS (MeOH) (m/z):** Calculated for [C<sub>93</sub>H<sub>151</sub>N<sub>11</sub>O<sub>29</sub>H]<sup>+</sup>: 1888.0791, found: 1888.0795.

**<sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>, 298 K):**  $\delta$  = 8.19 (d, *J* = 8.1 Hz, 1H,  $\alpha$ -NH), 8.13 (d, *J* = 7.9 Hz, 1H,  $\alpha$ -NH), 7.97 - 7.85 (m, 7H,  $\alpha$ -NH/ NHCH<sub>2</sub>), 7.28 - 7.12 (m, 15H, CH<sup>Ar</sup>), 6.98 (s, 1H, NHC<sub>q</sub>), 4.63 - 4.40 (m, 3H,  $\alpha$ -CH), 4.27 - 4.16 (m, 2H,  $\alpha$ -CH), 3.60 - 3.28 (m, 56H, CH<sub>2</sub>O/  $\alpha$ -CH<sub>2</sub><sup>Gly</sup>), 3.26 - 3.16 (m, 15H, CH<sub>3</sub><sup>TEG</sup>, NCH<sub>2</sub>CH<sub>2</sub>O), 3.06 - 2.88 (m, 2H, NCH<sub>2</sub>[CH<sub>2</sub>]<sub>4</sub>), 2.86 - 2.64 (m, 6H, CH<sub>2</sub><sup>Phe</sup>), 2.30 (t, *J* = 6.5 Hz, 6H, OCH<sub>2</sub>CH<sub>2</sub>C=O), 2.20 - 2.08 (m, 4H, CH<sub>2</sub><sup>Glu</sup>), 2.07 - 2.01 (m, 2H, N[CH<sub>2</sub>]<sub>4</sub>CH<sub>2</sub>), 1.89 - 1.63 (m, 4H, CH<sub>2</sub><sup>Glu</sup>), 1.63 - 1.34 (m, 22H, NCH<sub>2</sub>CH<sub>2</sub>/ N[CH<sub>2</sub>]<sub>3</sub>CH<sub>2</sub>/ CH<sub>3</sub><sup>tBu</sup>), 1.35 - 1.12 (m, 2H, N[CH<sub>2</sub>]<sub>2</sub>CH<sub>2</sub>).

BTA-[Gly-Phe-Glu(*t*Bu)-Phe-Glu(*t*Bu)-Phe-Dnd]<sub>3</sub> (**14**)



Benzene-1,3,5-tricarboxylchloride (3.2 mg, 12.2  $\mu$ mol, 1.0 eq.) was added to a solution of **13** (138 mg, 73.1  $\mu$ mol, 6.0 eq.) and DIPEA (17  $\mu$ L, 97.5  $\mu$ mol, 8.0 eq.) in DMF (2 mL). The reaction mixture was stirred for 2 d at room temperature. Afterwards PyBop (22 mg, 42.7  $\mu$ mol, 3.5 eq.) and DIPEA (17  $\mu$ L, 97.5  $\mu$ mol, 8.0 eq.) were added. The solvent was removed under reduced pressure and purified via size exclusion chromatography (Sephadex<sup>®</sup> LH 20, MeOH).

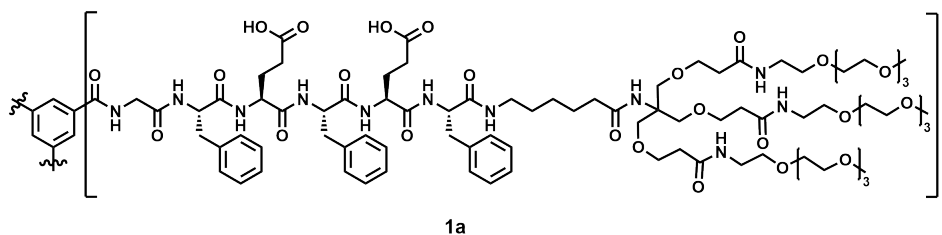
**Yield:** 48.4 mg (8.3  $\mu$ mol, 68 %); colourless oil.

**Molecular formula:** C<sub>288</sub>H<sub>453</sub>N<sub>33</sub>O<sub>90</sub>.

**MALDI-MS (MeOH) (m/z):** Calculated for [C<sub>288</sub>H<sub>453</sub>N<sub>33</sub>O<sub>90</sub>Na]<sup>+</sup>: 5840.2, found: 5840.1.

**<sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>, 298 K):**  $\delta$  = 8.83 - 8.74 (m, 3H,  $\alpha$ -NH<sup>Gly</sup>), 8.45 (s, 3H, CH<sup>BTA</sup>), 8.23 - 8.18 (m, 9H,  $\alpha$ -NH), 8.16 - 8.08 (m, 9H,  $\alpha$ -NH), 7.97 - 7.86 (m, 21H,  $\alpha$ -NH/ NHCH<sub>2</sub>/  $\alpha$ -NH), 7.28 - 7.09 (m, 45H, CH<sup>Ar</sup>), 6.98 (s, 3H, NHC<sub>q</sub>), 4.61 - 4.41 (m, 9H,  $\alpha$ -CH), 4.27 - 4.17 (m, 6H,  $\alpha$ -CH), 3.99 - 3.76 (m, 6H,  $\alpha$ -CH<sub>2</sub><sup>Gly</sup>), 3.60 - 3.28 (m, 162H, CH<sub>2</sub>O), 3.24 - 3.16 (m, 45H, CH<sub>3</sub><sup>TEG</sup>, NCH<sub>2</sub>CH<sub>2</sub>O), 3.13 - 2.86 (m, 6H, NCH<sub>2</sub>[CH<sub>2</sub>]<sub>4</sub>), 2.86 - 2.65 (m, 18H, CH<sub>2</sub><sup>Phe</sup>), 2.29 (t, *J* = 6.4 Hz, 18H, OCH<sub>2</sub>CH<sub>2</sub>C=O), 2.18 - 2.08 (m, 12H, CH<sub>2</sub><sup>Glu</sup>), 2.07 - 2.01 (m, 6H, N[CH<sub>2</sub>]<sub>4</sub>CH<sub>2</sub>), 1.87 - 1.62 (m, 12H, CH<sub>2</sub><sup>Glu</sup>), 1.58 - 1.27 (m, 66H, NCH<sub>2</sub>CH<sub>2</sub>/ N[CH<sub>2</sub>]<sub>3</sub>CH<sub>2</sub>/ CH<sub>3</sub><sup>tBu</sup>), 1.25 - 1.09 (m, 6H, N[CH<sub>2</sub>]<sub>2</sub>CH<sub>2</sub>).

BTA-[Gly-Phe-Glu-Phe-Glu-Phe-Dnd]<sub>3</sub> (1a)



14 (52 mg, 9.2  $\mu\text{mol}$ ) was deprotected according to **SOP 2**.

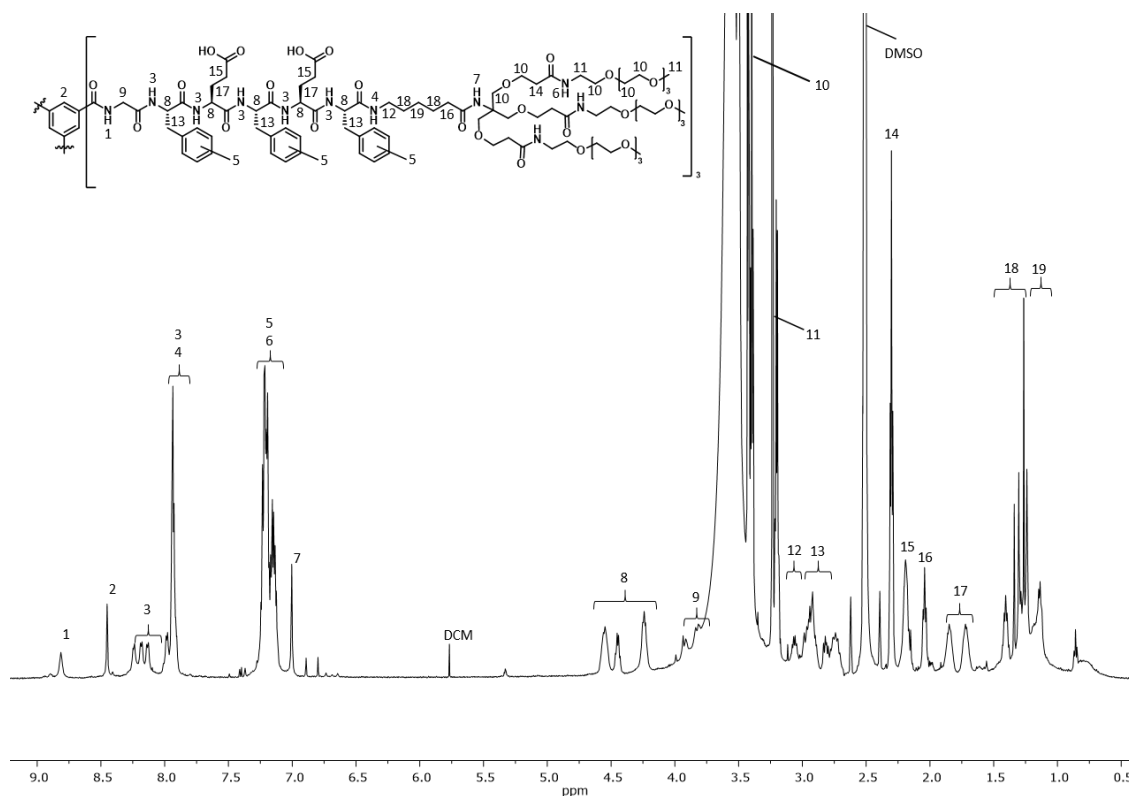
**Yield:** 46 mg (8.1  $\mu\text{mol}$ , 88 %); colourless solid.

**Molecular formula:** C<sub>264</sub>H<sub>405</sub>N<sub>33</sub>O<sub>90</sub>.

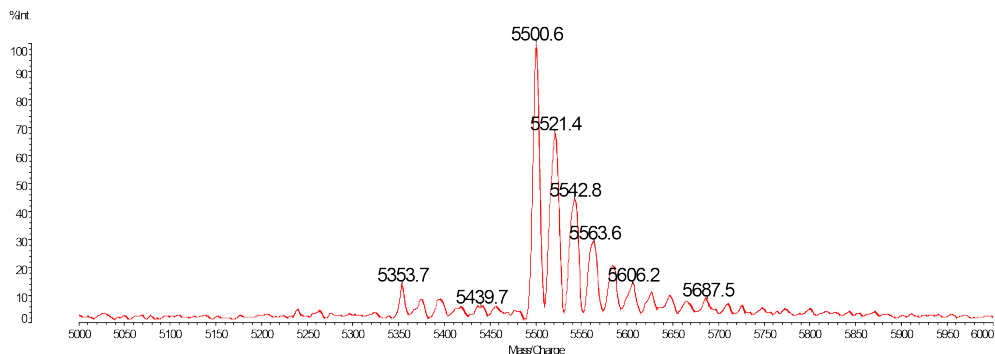
**MALDI-MS (MeOH) (m/z):** Calculated for [C<sub>264</sub>H<sub>405</sub>N<sub>33</sub>O<sub>90</sub>Na]<sup>+</sup>: 5500.8, found: 5500.6.

**<sup>1</sup>H-NMR (600 MHz, DMSO-*d*<sub>6</sub>, 298 K):**  $\delta$  = 8.84 - 8.76 (m, 3H,  $\alpha$ -NH<sup>Gly</sup>), 8.44 (s, 3H, CH<sup>BTA</sup>), 8.23 (d, *J* = 8.0 Hz, 6H,  $\alpha$ -NH), 8.17 (d, *J* = 7.4 Hz, 6H,  $\alpha$ -NH), 8.13 (d, *J* = 7.9 Hz, 6H,  $\alpha$ -NH), 8.02 - 7.87 (m, 21H,  $\alpha$ -NH/ NH), 7.28 - 7.09 (m, 45H, CH<sup>Ar</sup>), 6.99 (s, 3H, NHC<sub>q</sub>), 4.59 - 4.40 (m, 9H,  $\alpha$ -CH), 4.28 - 4.18 (m, 6H,  $\alpha$ -CH), 3.96 - 3.78 (m, 6H,  $\alpha$ -CH<sub>2</sub><sup>Gly</sup>), 3.60 - 3.35 (m, 162H, CH<sub>2</sub>O), 3.24 - 3.16 (m, 45H, CH<sub>3</sub><sup>TEG</sup>, NCH<sub>2</sub>CH<sub>2</sub>O), 3.11 - 2.85 (m, 6H, NCH<sub>2</sub>[CH<sub>2</sub>]<sub>4</sub>), 2.85 - 2.67 (m, 18H, CH<sub>2</sub><sup>Phe</sup>), 2.29 (t, *J* = 6.4 Hz, 18H, OCH<sub>2</sub>CH<sub>2</sub>C=O), 2.21 - 2.11 (m, 12H, CH<sub>2</sub><sup>Glu</sup>), 2.03 (t, *J* = 7.5 Hz, 6H, N[CH<sub>2</sub>]<sub>4</sub>CH<sub>2</sub>), 1.89 - 1.66 (m, 12H, CH<sub>2</sub><sup>Glu</sup>), 1.49 - 1.20 (m, 12H, NCH<sub>2</sub>CH<sub>2</sub>/ N[CH<sub>2</sub>]<sub>3</sub>CH<sub>2</sub>), 1.20 - 1.08 (m, 6H, N[CH<sub>2</sub>]<sub>2</sub>CH<sub>2</sub>).

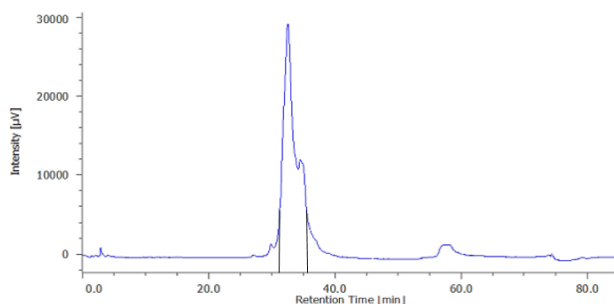
**<sup>1</sup>H-NMR-spectrum of monomer 1a**



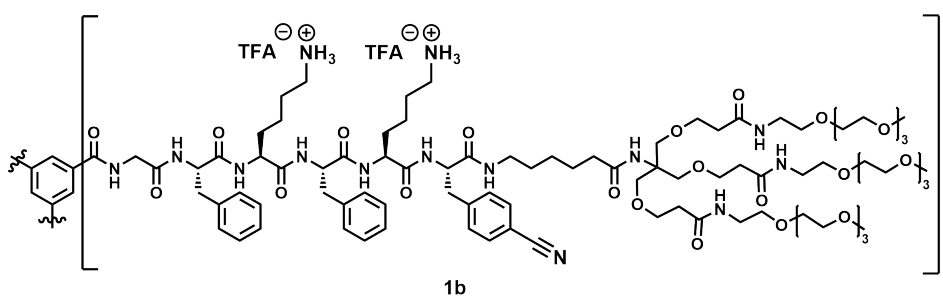
## MALDI-MS spectrum of 1a



## Preparative RP-HPLC trace of 1a recorded at 210 nm



## BTA-[Gly-Phe-Lys-Phe-Lys-Cnf-Dnd]<sub>3</sub> (1b)



The synthesis was carried out according to literature.<sup>6</sup>

**Yield:** 6.8 mg (1.1  $\mu\text{mol}$ ); colourless solid.

**Molecular formula:**  $\text{C}_{273}\text{H}_{432}\text{N}_{42}\text{O}_{78}$ .

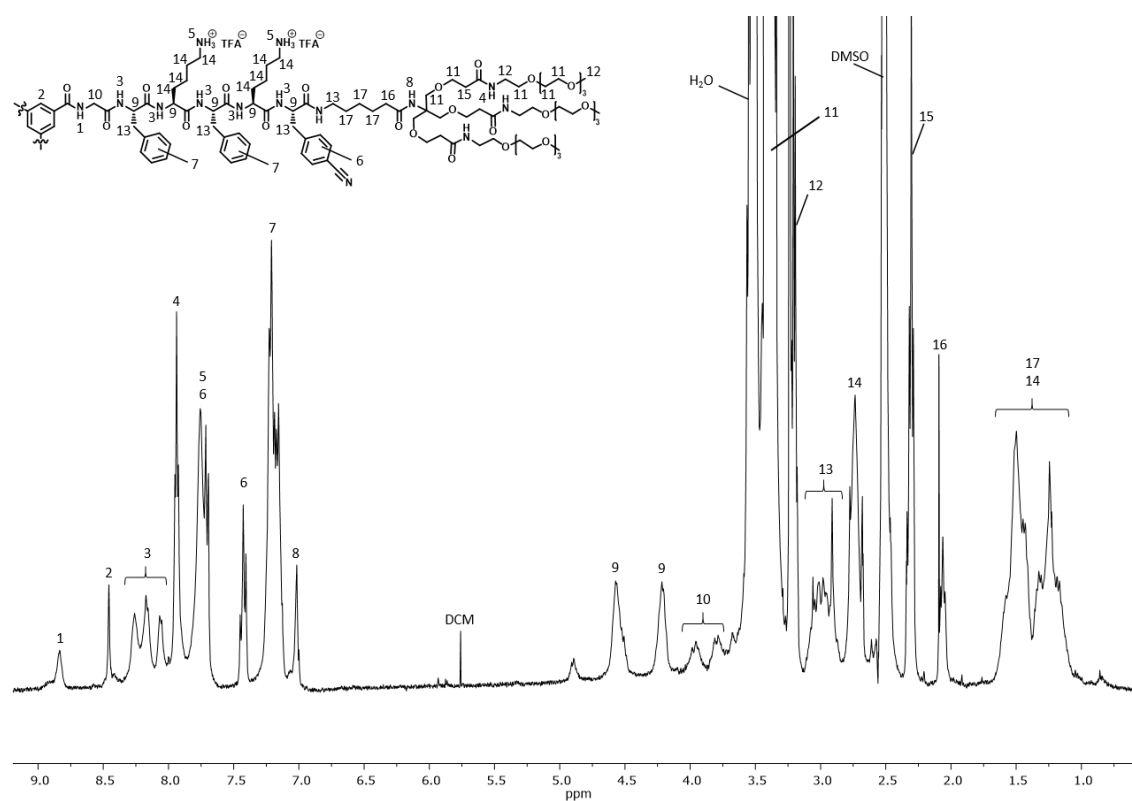
**MALDI-MS (MeOH) (m/z):** Calculated for  $[\text{C}_{273}\text{H}_{432}\text{N}_{42}\text{O}_{78}\text{K}]^+$ : 5588.1, found: 5587.5.

**<sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>, 298 K):**  $\delta$  = 8.97 – 8.77 (m, 3H,  $\alpha\text{-NH}^{\text{Gly}}$ ), 8.45 (s, 3H,  $\text{CH}^{\text{BTA}}$ ), 8.32 – 7.86 (m, 27H, NH), 7.85 – 7.85 (m, 24H,  $\text{CH}^{\text{Cnf}} / \text{NH}_3$ ), 7.47 – 7.37 (m, 6H,  $\text{CH}^{\text{Cnf}}$ ), 7.30 – 7.09 (m, 30H,  $\text{CH}^{\text{Phe}}$ ), 7.01 (s, 3H, NHCq), 4.62 – 4.13 (m, 15H,  $\alpha\text{-CH}$ ), 4.04 – 3.86 (m, 6H,  $\alpha\text{-CH}_2^{\text{Gly}}$ ), 3.64 – 3.27 (m, 162H,  $\text{CH}_2\text{O}$ ), 3.27 – 3.13 (m, 45H,  $\text{CH}_3^{\text{TEG}} / \text{NCH}_2\text{CH}_2\text{O}$ ), 3.10 – 2.83 (m, 24H,  $\text{CH}_2^{\text{Cnf}} / \text{CH}_2^{\text{Phe}} / \text{NCH}_2[\text{CH}_2]_4$ ), 2.82

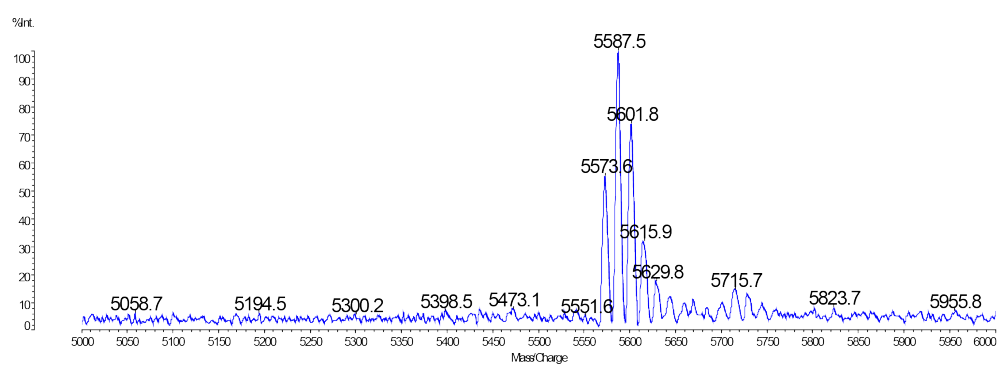


- 2.63 (m, 24H, CH<sub>2</sub><sup>Lys</sup>), 2.29 (t,  $J = 6.4$  Hz, 18H, OCH<sub>2</sub>CH<sub>2</sub>C=O), 2.05 (t,  $J = 7.5$  Hz, 6H, N[CH<sub>2</sub>]<sub>4</sub>CH<sub>2</sub>), 1.66 - 0.95 (m, 42H, CH<sub>2</sub><sup>Lys</sup> / NCH<sub>2</sub>CH<sub>2</sub> / N[CH<sub>2</sub>]<sub>2</sub>CH<sub>2</sub> / N[CH<sub>2</sub>]<sub>3</sub>CH<sub>2</sub>).

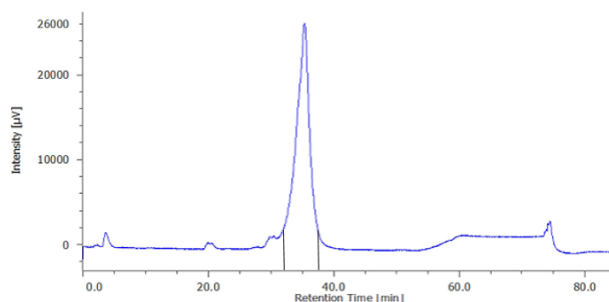
## <sup>1</sup>H-NMR-spectrum of monomer 1b



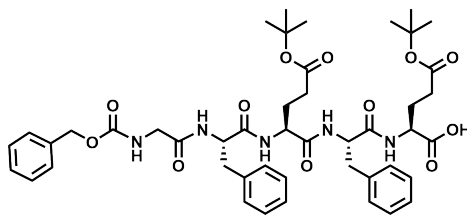
## MALDI-MS spectrum of 1b



## Preparative RP-HPLC trace of 1b recorded at 210 nm



## Cbz-Gly-Phe-Glu(*t*Bu)-Phe-Glu(*t*Bu)-OH (15)



15

The synthesis was carried out according to **SOP 1**.

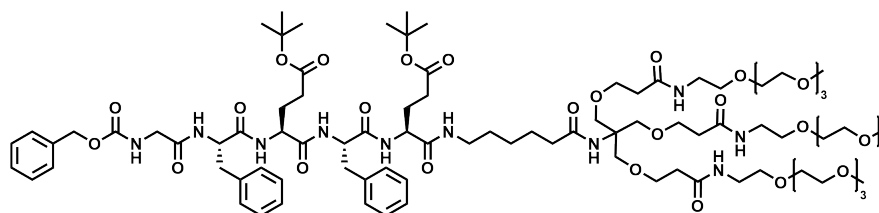
**Yield:** 583 mg (0.67 mmol); colourless solid.

**Molecular formula:** C<sub>46</sub>H<sub>59</sub>N<sub>5</sub>O<sub>12</sub>.

**ESI-HRMS (MeOH) (m/z):** Calculated for [C<sub>46</sub>H<sub>59</sub>N<sub>5</sub>O<sub>12</sub>Na]<sup>+</sup>: 896.4052, found: 896.4040.

**<sup>1</sup>H-NMR (300 MHz, DMSO-*d*<sub>6</sub>, 298 K):**  $\delta$  = 12.72 (s, 1H, CO<sub>2</sub>H), 8.22 (d, *J* = 7.8 Hz, 1H,  $\alpha$ -NH), 8.14 (d, *J* = 7.9 Hz, 1H,  $\alpha$ -NH), 7.99 (d, *J* = 8.2 Hz, 1H,  $\alpha$ -NH), 7.92 (d, *J* = 8.0 Hz, 1H,  $\alpha$ -NH), 7.42 – 7.03 (m, 16H,  $\alpha$ -NH<sup>Gly</sup>/CH<sup>Ar</sup>), 4.98 (s, 2H, CH<sub>2</sub><sup>Cbz</sup>), 4.62 – 4.45 (m, 2H,  $\alpha$ -CH), 4.28 – 4.12 (m, 2H,  $\alpha$ -CH), 3.67 – 3.44 (m, 2H,  $\alpha$ -CH<sub>2</sub><sup>Gly</sup>), 3.11 – 2.60 (m, 4H, CH<sub>2</sub><sup>Phe</sup>), 2.34 – 2.20 (m, 2H, CH<sub>2</sub><sup>Glu</sup>), 2.19 – 2.04 (m, 2H, CH<sub>2</sub><sup>Glu</sup>), 2.03 – 1.57 (m, 4H, CH<sub>2</sub><sup>Glu</sup>), 1.37 (s, 18H, CH<sub>3</sub><sup>tBu</sup>).

**Cbz-Gly-Phe-Glu(*t*Bu)-Phe-Glu(*t*Bu)-Ahx-Dnd (16)**



16

PyBop (226 mg, 432  $\mu$ mol, 2.4 eq.) was added to a stirred solution of **15** (315 mg, 360  $\mu$ mol, 2.0 eq.), **10** (180 mg, 180  $\mu$ mol, 1.0 eq.) and DIPEA (918  $\mu$ L, 5.4 mmol, 30.0 eq.) in DCM (30 mL). The reaction mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure and the residue was purified via size exclusion chromatography (Sephadex<sup>®</sup> LH 20, MeOH).

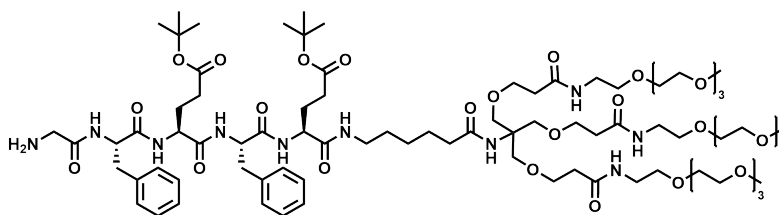
**Yield:** 246 mg (130  $\mu$ mol, 72%); colourless oil.

**Molecular formula:** C<sub>92</sub>H<sub>148</sub>N<sub>10</sub>O<sub>30</sub>.

**ESI-HRMS (MeOH) (m/z):** Calculated for [C<sub>92</sub>H<sub>148</sub>N<sub>10</sub>O<sub>30</sub>Na]<sup>+</sup>: 1896.03, found: 1896.00, Calculated for [C<sub>92</sub>H<sub>148</sub>N<sub>10</sub>O<sub>30</sub>K]<sup>+</sup>: 1912.03, found: 1912.00.

**<sup>1</sup>H-NMR (300 MHz, DMSO-*d*<sub>6</sub>, 298 K):**  $\delta$  = 8.18 (d, *J* = 7.8 Hz, 1H,  $\alpha$ -NH), 8.07 (d, *J* = 8.0 Hz, 1H,  $\alpha$ -NH), 8.00 (d, *J* = 8.2 Hz, 1H,  $\alpha$ -NH), 7.96 - 7.85 (m, 4H, NHCH<sub>2</sub>/ $\alpha$ -NH), 7.44 - 7.05 (m, 16H,  $\alpha$ -NH<sup>Gly</sup>, CH<sup>Ar</sup>), 6.99 (s, 1H, NHC<sub>q</sub>), 5.00 (s, 2H, CH<sub>2</sub><sup>Cbz</sup>), 4.60 - 4.48 (m, 2H,  $\alpha$ -CH), 4.26 - 4.14 (m, 2H,  $\alpha$ -CH), 3.67 - 3.45 (m, 2H,  $\alpha$ -CH<sub>2</sub><sup>Gly</sup>), 3.59 - 3.36 (m, 54H, CH<sub>2</sub>O), 3.25 - 3.13 (m, 15H, CH<sub>3</sub><sup>TEG</sup>, NCH<sub>2</sub>CH<sub>2</sub>O), 3.11 - 2.60 (m, 6H, CH<sub>2</sub><sup>Phe</sup>/NCH<sub>2</sub>[CH<sub>2</sub>]<sub>4</sub>), 2.29 (t, *J* = 6.4 Hz, 6H, OCH<sub>2</sub>CH<sub>2</sub>C=O), 2.21 - 2.00 (m, 6H, CH<sub>2</sub><sup>Glu</sup>/CH<sub>2</sub><sup>Glu</sup>/N[CH<sub>2</sub>]<sub>4</sub>CH<sub>2</sub>), 1.92 - 1.56 (m, 4H, CH<sub>2</sub><sup>Glu</sup>), 1.50 - 1.40 (m, 4H, NCH<sub>2</sub>CH<sub>2</sub>/N[CH<sub>2</sub>]<sub>3</sub>CH<sub>2</sub>), 1.37 (s, 18H, CH<sub>3</sub><sup>tBu</sup>), 1.28 - 1.13 (m, 2H, N[CH<sub>2</sub>]<sub>2</sub>CH<sub>2</sub>).

### H-Gly-Phe-Glu(*t*Bu)-Phe-Glu(*t*Bu)-Ahx-Dnd (17)



17

**16** (155 mg, 82.7  $\mu$ mol) was deprotected according to **SOP 3**.

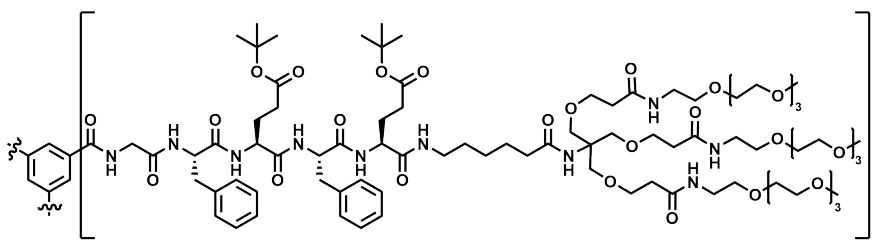
**Yield:** 165 mg (82.7  $\mu$ mol, quant.); colourless oil.

**Molecular formula:** C<sub>84</sub>H<sub>142</sub>N<sub>10</sub>O<sub>28</sub>.

**ESI-HRMS (MeOH) (m/z):** Calculated for [C<sub>84</sub>H<sub>142</sub>N<sub>10</sub>O<sub>28</sub>Na]<sup>+</sup>: 1761.99, found: 1762.02.

**<sup>1</sup>H-NMR (300 MHz, DMSO-*d*<sub>6</sub>, 298 K):**  $\delta$  = 8.29 - 8.15 (m, 1H,  $\alpha$ -NH), 8.12 - 8.04 (m, 1H,  $\alpha$ -NH), 8.03 - 7.97 (m, 1H,  $\alpha$ -NH), 7.94 - 7.85 (m, 4H, NHCH<sub>2</sub>/ $\alpha$ -NH), 7.44 - 7.05 (m, 16H,  $\alpha$ -NH<sup>Gly</sup>, CH<sup>Ar</sup>), 6.99 (s, 1H, NHC<sub>q</sub>), 4.64 - 4.51 (m, 2H,  $\alpha$ -CH), 4.30 - 4.14 (m, 2H,  $\alpha$ -CH), 3.67 - 3.45 (m, 2H,  $\alpha$ -CH<sub>2</sub><sup>Gly</sup>), 3.59 - 3.38 (m, 54H, CH<sub>2</sub>O), 3.25 - 3.13 (m, 15H, CH<sub>3</sub><sup>TEG</sup>, NCH<sub>2</sub>CH<sub>2</sub>O), 3.09 - 2.59 (m, 6H, CH<sub>2</sub><sup>Phe</sup>)/ NCH<sub>2</sub>[CH<sub>2</sub>]<sub>4</sub>), 2.35 - 2.25 (m, 6H, OCH<sub>2</sub>CH<sub>2</sub>C=O), 2.21 - 2.01 (m, 6H, CH<sub>2</sub><sup>Glu</sup>/ CH<sub>2</sub><sup>Glu</sup>/ N[CH<sub>2</sub>]<sub>4</sub>CH<sub>2</sub>), 1.90 - 1.55 (m, 4H, CH<sub>2</sub><sup>Glu</sup>), 1.50 - 1.41 (m, 4H, NCH<sub>2</sub>CH<sub>2</sub>/ N[CH<sub>2</sub>]<sub>3</sub>CH<sub>2</sub>), 1.37 (s, 18H, CH<sub>3</sub><sup>tBu</sup>), 1.28 - 1.13 (m, 2H, N[CH<sub>2</sub>]<sub>2</sub>CH<sub>2</sub>).

BTA-[Gly-Phe-Glu(*t*Bu)-Phe-Glu(*t*Bu)-Ahx-Dnd]<sub>3</sub> (18)



18

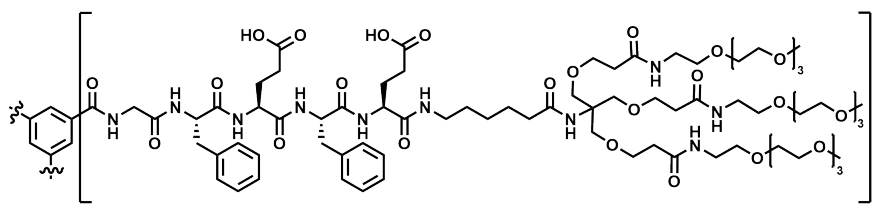
**17** (287 mg, 165  $\mu$ mol, 6 eq.) was added to a stirred solution of benzene tricarboxylchloride (BTA) (7.3 mg, 27.5  $\mu$ mol, 1.0 eq.) and DIPEA (140  $\mu$ L, 825  $\mu$ mol, 30.0 eq.) in DCM (3 mL). The reaction mixture was stirred at room temperature for 48 h and afterwards concentrated slowly under a stream of Argon while PyBop (86 mg, 165  $\mu$ mol, 1.0 eq.) and DIPEA (140  $\mu$ L, 825  $\mu$ mol, 30.0 eq.) was added three times. The obtained residue was purified via size exclusion chromatography (Sephadex<sup>®</sup> LH 20, MeOH).

**Yield:** 148 mg (quant.); colourless wax.

**Molecular formula:** C<sub>261</sub>H<sub>426</sub>N<sub>30</sub>O<sub>87</sub>.

**MALDI-MS (MeOH) (m/z):** Calculated for [C<sub>261</sub>H<sub>426</sub>N<sub>30</sub>O<sub>87</sub>K]<sup>+</sup>: 5412.0, found: 5412.2. **<sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>, 298 K):**  $\delta$  = 8.78 (bs, 3H,  $\alpha$ -NH<sup>Gly</sup>), 8.45 (s, 3H, CH<sup>BTA</sup>), 8.26 - 8.16 (m, 3H,  $\alpha$ -NH), 8.15 - 8.04 (m, 6H,  $\alpha$ -NH), 7.97 - 7.84 (m, 12H, NHCH<sub>2</sub>/ $\alpha$ -NH), 7.39 - 7.08 (m, 33H,  $\alpha$ -NH<sup>Gly</sup>, CH<sup>Ar</sup>), 6.98 (s, 3H, NHC<sub>q</sub>), 4.60 - 4.14 (m, 12H,  $\alpha$ -CH), 3.57 - 3.46 (m, 6H,  $\alpha$ -CH<sub>2</sub><sup>Gly</sup>), 3.45 - 3.25 (m, 162H, CH<sub>2</sub>O), 3.25 - 3.13 (m, 45H, CH<sub>3</sub><sup>TEG</sup>, NCH<sub>2</sub>CH<sub>2</sub>O), 3.07 - 2.58 (m, 18H, CH<sub>2</sub><sup>Phe</sup>)/ NCH<sub>2</sub>[CH<sub>2</sub>]<sub>4</sub>), 2.29 (t, *J* = 6.4 Hz, 18H, OCH<sub>2</sub>CH<sub>2</sub>C=O), 2.05 (t, *J* = 7.4 Hz, 6H, N[CH<sub>2</sub>]<sub>4</sub>CH<sub>2</sub>), 1.90 - 1.60 (m, 12H, CH<sub>2</sub><sup>Glu</sup>), 1.50 - 1.41 (m, 12H, NCH<sub>2</sub>CH<sub>2</sub>/ N[CH<sub>2</sub>]<sub>3</sub>CH<sub>2</sub>), 1.37 (m, 54H, CH<sub>3</sub><sup>tBu</sup>), 1.28 - 1.14 (m, 6H, N[CH<sub>2</sub>]<sub>2</sub>CH<sub>2</sub>).

BTA-[Gly-Phe-Glu-Phe-Glu-Ahx-Dnd]<sub>3</sub> (2a)



2a

18 (53 mg, 9.9  $\mu\text{mol}$ ) was deprotected according to **SOP 2**.

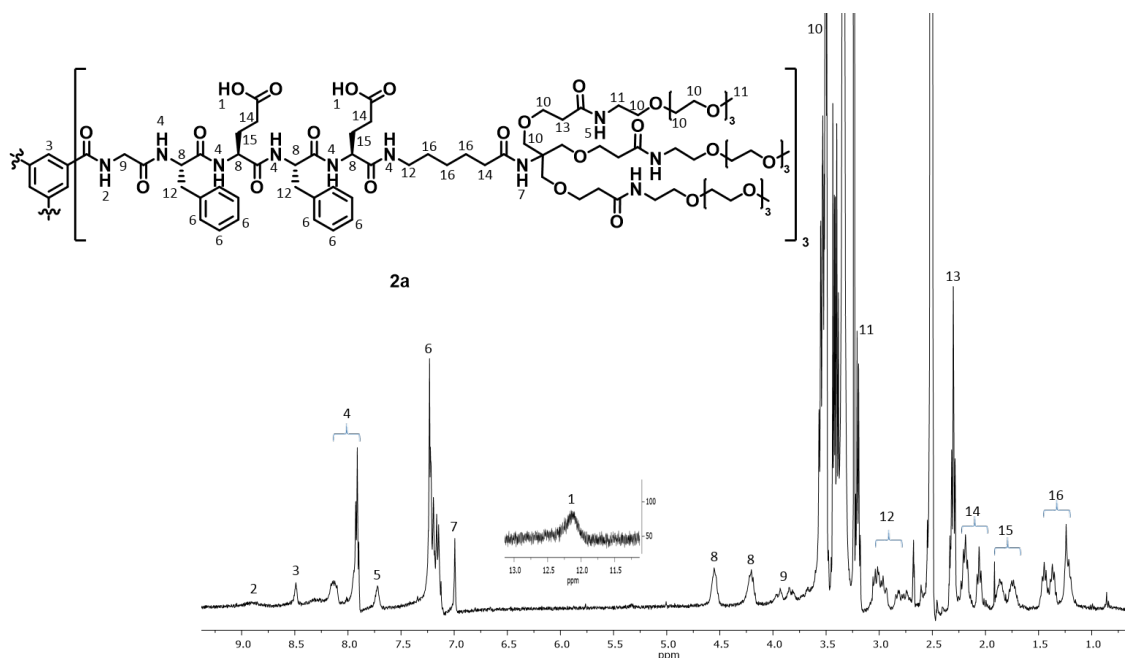
**Yield:** 50 mg (quant.); white solid.

**Molecular formula:**  $\text{C}_{237}\text{H}_{378}\text{N}_{30}\text{O}_{87}$ .

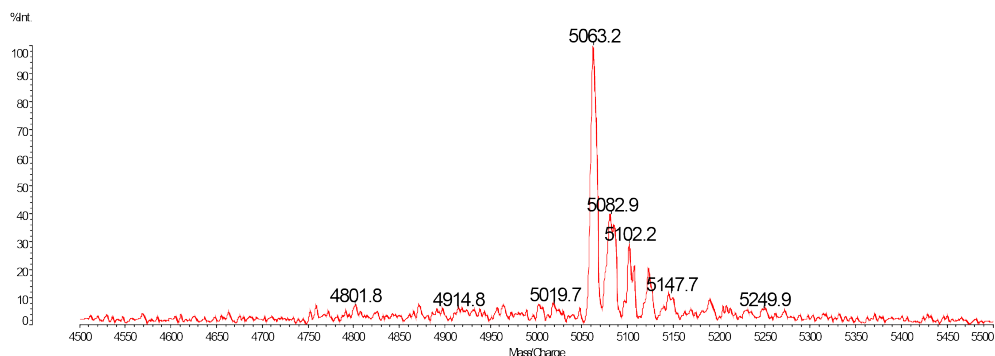
**MALDI-MS (MeOH) (m/z):** Calculated for  $[\text{C}_{237}\text{H}_{378}\text{N}_{30}\text{O}_{87}\text{Na}]^+$ : 5061.6, found: 5063.2.

**$^1\text{H-NMR}$  (400 MHz, DMSO-*d*<sub>6</sub>, 298 K):**  $\delta$  = 12.12 (bs, 6H, CO<sub>2</sub>H), 8.78 (bs, 3H,  $\alpha$ -NH<sup>Gly</sup>), 8.45 (s, 3H, CH<sup>BTA</sup>), 8.26 - 8.16 (m, 3H,  $\alpha$ -NH), 8.15 - 8.04 (m, 6H,  $\alpha$ -NH), 7.97 - 7.84 (m, 12H, NHCH<sub>2</sub>/  $\alpha$ -NH), 7.39 - 7.08 (m, 33H,  $\alpha$ -NH<sup>Gly</sup>, CH<sup>Ar</sup>), 6.98 (s, 3H, NHC<sub>q</sub>), 4.60 - 4.14 (m, 12H,  $\alpha$ -CH), 3.57 - 3.46 (m, 6H,  $\alpha$ -CH<sub>2</sub><sup>Gly</sup>), 3.45 - 3.25 (m, 162H, CH<sub>2</sub>O), 3.25 - 3.13 (m, 45H, CH<sub>3</sub><sup>TEG</sup>, NCH<sub>2</sub>CH<sub>2</sub>O), 3.07 - 2.58 (m, 18H, CH<sub>2</sub><sup>Phe</sup>)/ NCH<sub>2</sub>[CH<sub>2</sub>]<sub>4</sub>), 2.29 (t, *J* = 6.4 Hz, 18H, OCH<sub>2</sub>CH<sub>2</sub>C=O), 2.05 (t, *J* = 7.4 Hz, 6H, N[CH<sub>2</sub>]<sub>4</sub>CH<sub>2</sub>), 1.90 - 1.60 (m, 12H, CH<sub>2</sub><sup>Glu</sup>), 1.50 - 1.41 (m, 12H, NCH<sub>2</sub>CH<sub>2</sub>/ N[CH<sub>2</sub>]<sub>3</sub>CH<sub>2</sub>), 1.28 - 1.14 (m, 6H, N[CH<sub>2</sub>]<sub>2</sub>CH<sub>2</sub>).

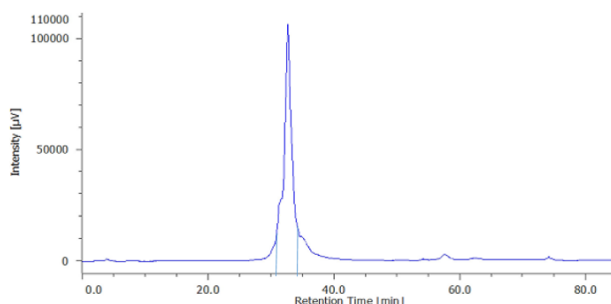
$^1\text{H-NMR}$ -spectrum of monomer 2a



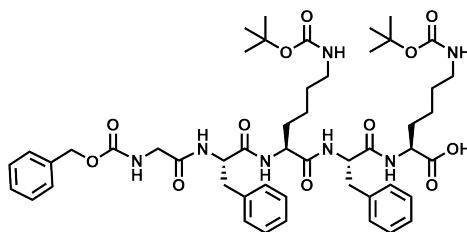
## MALDI-MS spectrum of 2a



## Preparative RP-HPLC trace of 2a recorded at 210 nm



## Cbz-Gly-Phe-Lys(Boc)-Phe-Lys(Boc)-OH (19)



19

The synthesis was carried out according to **SOP 1**.

**Yield:** 676 mg (700  $\mu$ mmol); colourless solid.

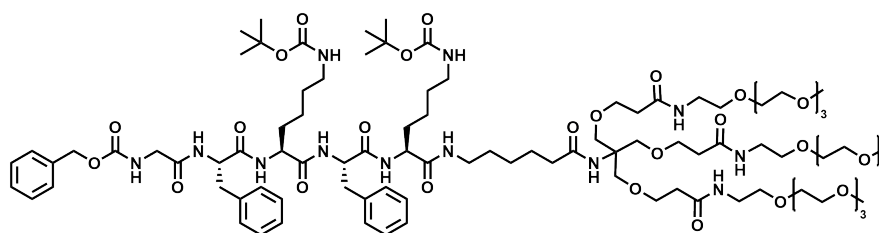
**Molecular formula:** C<sub>50</sub>H<sub>69</sub>N<sub>7</sub>O<sub>12</sub>.

**ESI-HRMS (MeOH) (m/z):** Calculated for [C<sub>50</sub>H<sub>69</sub>N<sub>7</sub>O<sub>12</sub>Na]<sup>+</sup>: 982.4896, found: 982.4864.

**<sup>1</sup>H-NMR (300 MHz, DMSO-*d*<sub>6</sub>, 298 K):**  $\delta$  = 12.61 (s, 1H, CO<sub>2</sub>H), 8.18 (d, *J* = 7.6 Hz, 1H,  $\alpha$ -NH), 8.08 (d, *J* = 8.0 Hz, 1H,  $\alpha$ -NH), 7.98 (d, *J* = 8.2 Hz, 1H,  $\alpha$ -NH), 7.90 (d, *J* = 8.1 Hz, 1H,  $\alpha$ -NH), 7.43 – 7.09 (m, 16H,  $\alpha$ -NH<sup>Gly</sup> / CH<sup>Ar</sup>), 6.82 – 6.70 (m, 2H,  $\epsilon$ -NH<sup>Lys</sup>), 5.00 (s, 2H, CH<sub>2</sub><sup>Cbz</sup>), 4.63 – 4.47 (m, 2H,  $\alpha$ -CH), 4.23 – 4.09 (m, 2H,  $\alpha$ -CH), 3.67 – 3.44 (m, 2H,  $\alpha$ -CH), 3.10 – 2.65 (m, 12H, CH<sub>2</sub><sup>Phe</sup> / CH<sub>2</sub><sup>Lys</sup>), 1.82 – 1.41 (m, 8H, CH<sub>2</sub><sup>Lys</sup>), 1.36 (s, 18H, CH<sub>3</sub><sup>Boc</sup>).



## Cbz-Gly-Phe-Lys(Boc)-Phe-Lys(Boc)-Ahx-Dnd (20)



20

PyBop (113 mg, 216  $\mu\text{mol}$ , 2.4 eq.) was added to a stirred solution of **19** (172 mg, 179  $\mu\text{mol}$ , 2.0 eq.), **10** (90 mg, 90  $\mu\text{mol}$ , 1.0 eq.) and DIPEA (459  $\mu\text{L}$ , 2.7 mmol, 30.0 eq.) in DCM (15 mL). The reaction mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure and the residue was purified via size exclusion chromatography (Sephadex<sup>®</sup> LH 20, MeOH).

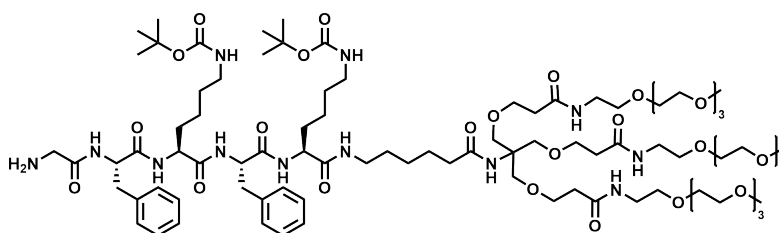
**Yield:** 132 mg (67  $\mu\text{mol}$ , 74%); colourless oil.

**Molecular formula:** C<sub>96</sub>H<sub>158</sub>N<sub>12</sub>O<sub>30</sub>.

**MALDI-HRMS (MeOH) (m/z):** Calculated for [C<sub>96</sub>H<sub>158</sub>N<sub>12</sub>O<sub>30</sub>Na]<sup>+</sup>: 1982.11, found: 1982.05.

**<sup>1</sup>H-NMR (300 MHz, DMSO-*d*<sub>6</sub>, 298 K):**  $\delta$  = 8.18 – 7.84 (m, 8H, NH), 7.44 – 7.07 (m, 16H,  $\alpha$ -NH<sup>Gly</sup> / CH<sup>Phe</sup> / CH<sup>Cbz</sup>), 6.99 (s, 1H, NHC<sub>q</sub>), 6.82 – 6.68 (m, 2H,  $\epsilon$ -NH<sup>Lys</sup>), 4.99 (s, 2H, CH<sub>2</sub><sup>Cbz</sup>), 4.61 – 4.08 (m, 4H,  $\alpha$ -CH), 3.60 – 3.36 (m, 56H  $\alpha$ -CH<sub>2</sub> / CH<sub>2</sub>O), 3.25 – 3.15 (m, 15H, CH<sub>3</sub><sup>TEG</sup> / NCH<sub>2</sub>CH<sub>2</sub>O), 3.08 – 2.63 (m, 14H, CH<sub>2</sub><sup>Phe</sup> / NCH<sub>2</sub>[CH<sub>2</sub>]<sub>4</sub>/CH<sub>2</sub><sup>Lys</sup>), 2.29 (t, *J* = 6.4 Hz, 6H, OCH<sub>2</sub>CH<sub>2</sub>C=O), 2.05 (t, *J* = 7.5 Hz, 2H, N[CH<sub>2</sub>]<sub>4</sub>CH<sub>2</sub>), 1.65 – 0.84 (m, 32H, CH<sub>3</sub><sup>Boc</sup> / CH<sub>2</sub><sup>Lys</sup> / NCH<sub>2</sub>CH<sub>2</sub> / N[CH<sub>2</sub>]<sub>2</sub>CH<sub>2</sub> / N[CH<sub>2</sub>]<sub>3</sub>CH<sub>2</sub>).

## H-Gly-Phe-Lys(Boc)-Phe-Lys(Boc)-Ahx-Dnd (21)



21

**20** (124 mg, 63.3  $\mu\text{mol}$ ) was deprotected according to **SOP 3**.

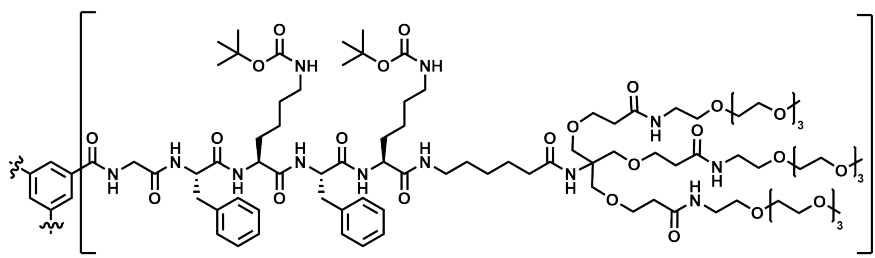
**Yield:** 116 mg (quant.); colourless oil.

**Molecular formula:**  $\text{C}_{88}\text{H}_{152}\text{N}_{12}\text{O}_{28}$ .

**MALDI-HRMS (MeOH) (m/z):** Calculated for  $[\text{C}_{88}\text{H}_{152}\text{N}_{12}\text{O}_{28}\text{Na}]^+$ : 1848.07, found: 1848.09.

**$^1\text{H-NMR}$  (300 MHz,  $\text{DMSO-}d_6$ , 298 K):**  $\delta = 8.18 - 7.84$  (m, 8H,  $\alpha\text{-NH}$ ), 7.44 – 7.07 (m, 11H,  $\alpha\text{-NH}^{\text{Gly}}$  /  $\text{CH}^{\text{Phe}}$ ), 6.99 (s, 1H,  $\text{NHC}_q$ ), 6.82 – 6.68 (m, 2H,  $\epsilon\text{-NH}^{\text{Lys}}$ ), 4.61 – 4.08 (m, 4H,  $\alpha\text{-CH}$ ), 3.60 – 3.36 (m, 56H  $\alpha\text{-CH}_2$  /  $\text{CH}_2\text{O}$ ), 3.25 – 3.15 (m, 15H,  $\text{CH}_3^{\text{TEG}}$  /  $\text{NCH}_2\text{CH}_2\text{O}$ ), 3.08 – 2.63 (m, 14H,  $\text{CH}_2^{\text{Phe}}$  /  $\text{NCH}_2[\text{CH}_2]_4$  /  $\text{CH}_2^{\text{Lys}}$ ), 2.29 (t,  $J = 6.5$  Hz, 6H,  $\text{OCH}_2\text{CH}_2\text{C=O}$ ), 2.09 - 2.00 (m, 2H,  $\text{N}[\text{CH}_2]_4\text{CH}_2$ ), 1.65 – 0.84 (m, 32H,  $\text{CH}_3^{\text{Boc}}$  /  $\text{CH}_2^{\text{Lys}}$  /  $\text{NCH}_2\text{CH}_2$  /  $\text{N}[\text{CH}_2]_2\text{CH}_2$  /  $\text{N}[\text{CH}_2]_3\text{CH}_2$ ).

BTA-[Gly-Phe-Lys(Boc)-Phe-Lys(Boc)-Ahx-Dnd]<sub>3</sub> (**22**)



22

**21** (296 mg, 162  $\mu\text{mol}$ , 6.0 eq.) was added to a stirred solution of benzene tricarboxylchloride (BTA) (7.1 mg, 27  $\mu\text{mol}$ , 1.0 eq.) and DIPEA (138  $\mu\text{L}$ , 810  $\mu\text{mol}$ , 30.0 eq.) in DCM (3 mL). The reaction mixture was stirred at room temperature for 48 h and afterwards concentrated slowly under a stream of Argon while PyBop (84 mg, 162  $\mu\text{mol}$ , 1.0 eq.) and DIPEA (138  $\mu\text{L}$ , 810  $\mu\text{mol}$ , 30.0 eq.) were added three times. The obtained residue was purified via size exclusion chromatography (Sephadex<sup>®</sup> LH 20, MeOH).

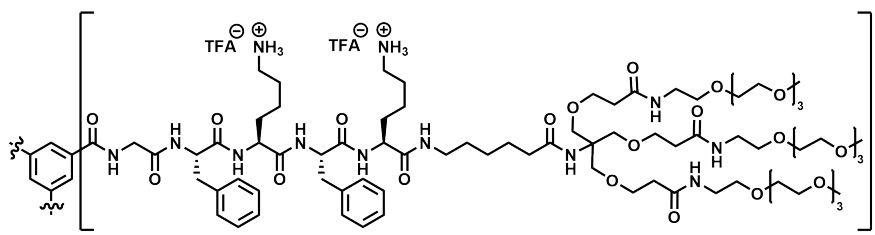
**Yield:** 99.6 mg (17.7  $\mu\text{mol}$ , 65 %); light brown wax.

**Molecular formula:** C<sub>273</sub>H<sub>456</sub>N<sub>36</sub>O<sub>87</sub>.

**MALDI-MS (MeOH) (m/z):** Calculated for [C<sub>273</sub>H<sub>456</sub>N<sub>36</sub>O<sub>87</sub>K]<sup>+</sup>: 5672.2, found: 5671.9.

**<sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>, 298 K):**  $\delta$  = 8.79 (bs, 3H,  $\alpha$ -NH<sup>Gly</sup>), 8.45 (s, 3H, CH<sup>BTA</sup>), 8.22 – 7.61 (m, 24H, NH), 7.28 – 7.03 (m, 30H, CH<sup>Phe</sup>), 6.99 (s, 3H, NHC<sub>q</sub>), 6.78 – 6.61 (m, 6H,  $\epsilon$ -NH<sup>Lys</sup>), 4.66 – 4.06 (m, 12H,  $\alpha$ -CH), 3.99 – 3.70 (m, 6H,  $\alpha$ -CH<sub>2</sub>), 3.58 – 3.35 (m, 162H CH<sub>2</sub>O), 3.25 – 3.15 (m, 45H, CH<sub>3</sub><sup>TEG</sup> / NCH<sub>2</sub>CH<sub>2</sub>O), 3.07 – 2.76 (m, 42H, CH<sub>2</sub><sup>Phe</sup> / NCH<sub>2</sub>[CH<sub>2</sub>]<sub>4</sub> / CH<sub>2</sub><sup>Lys</sup>), 2.29 (t, *J* = 6.4 Hz, 18H, OCH<sub>2</sub>CH<sub>2</sub>C=O), 2.05 (t, *J* = 7.5 Hz, 6H, N[CH<sub>2</sub>]<sub>4</sub>CH<sub>2</sub>), 1.64 – 0.83 (m, 96H, CH<sub>3</sub><sup>Boc</sup> / CH<sub>2</sub><sup>Lys</sup> / NCH<sub>2</sub>CH<sub>2</sub> / N[CH<sub>2</sub>]<sub>2</sub>CH<sub>2</sub> / N[CH<sub>2</sub>]<sub>3</sub>CH<sub>2</sub>).

BTA-[Gly-Phe-Lys-Phe-Lys-Ahx-Dnd]<sub>3</sub>\*6 TFA (2b)



2b

**22** (52 mg, 9.2  $\mu\text{mol}$ ) was deprotected according to **SOP 2**.

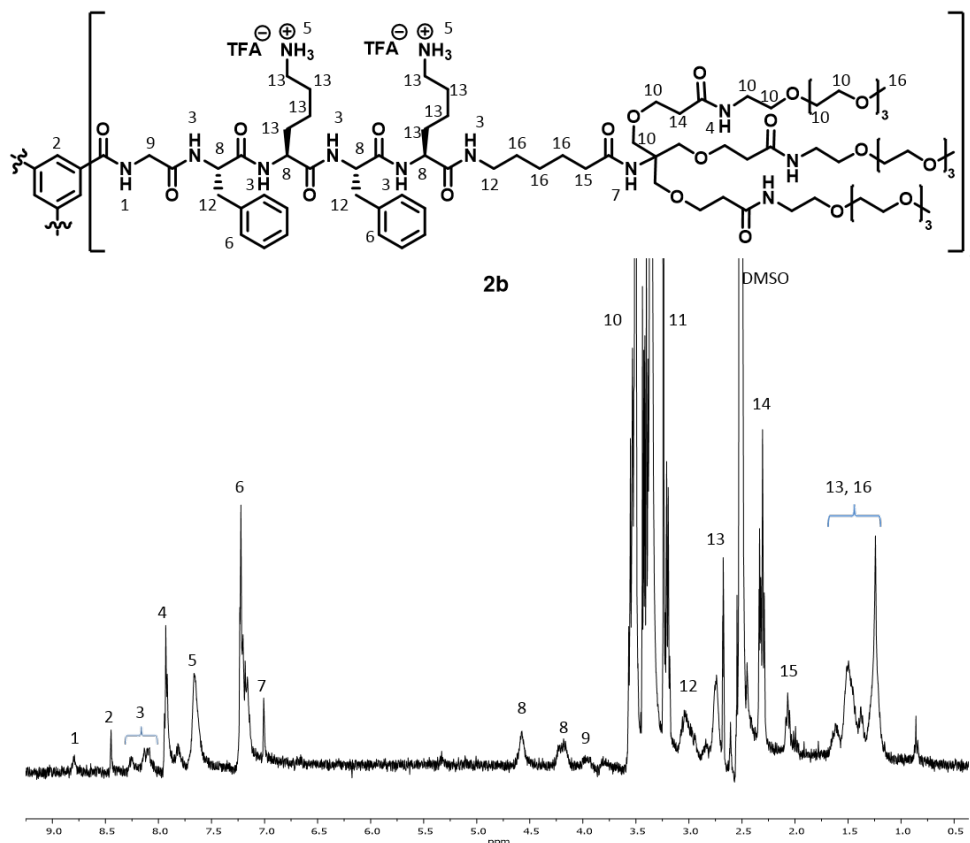
**Yield:** 46 mg (8.1  $\mu\text{mol}$ , 88 %); colourless solid.

**Molecular formula:** C<sub>244</sub>H<sub>416</sub>N<sub>36</sub>O<sub>74</sub>.

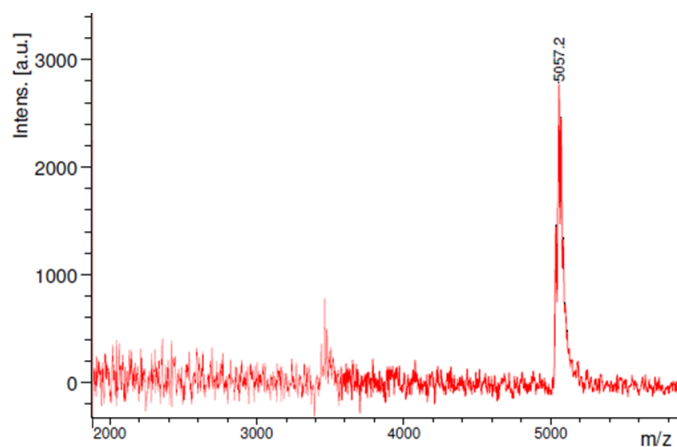
**MALDI-MS (MeOH) (m/z):** Calculated for [C<sub>244</sub>H<sub>416</sub>N<sub>36</sub>O<sub>74</sub>Na]<sup>+</sup>: 5057.9, found: 5057.2.

**<sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>, 298 K):**  $\delta$  = 8.79 (bs, 3H,  $\alpha$ -NH<sup>Gly</sup>), 8.44 (s, 3H, CH<sup>BTA</sup>), 8.27 – 7.49 (m, 24H, NH), 7.28 – 7.03 (m, 30H, CH<sup>Phe</sup>), 7.00 (s, 3H, NHC<sub>q</sub>), 4.64 – 4.09 (m, 12H,  $\alpha$ -CH), 4.02 - 3.62 (m, 6H,  $\alpha$ -CH<sub>2</sub>), 3.59 – 3.25 (m, 162H CH<sub>2</sub>O), 3.25 – 3.15 (m, 45H, CH<sub>3</sub><sup>TEG</sup> / NCH<sub>2</sub>CH<sub>2</sub>O), 3.10 – 2.69 (m, 42H, CH<sub>2</sub><sup>Phe</sup> / NCH<sub>2</sub>[CH<sub>2</sub>]<sub>4</sub> / CH<sub>2</sub><sup>Lys</sup>), 2.30 (t, *J* = 6.4 Hz, 18H, OCH<sub>2</sub>CH<sub>2</sub>C=O), 2.06 (t, *J* = 7.2 Hz, 6H, N[CH<sub>2</sub>]<sub>4</sub>CH<sub>2</sub>), 1.68 – 0.81 (m, 42H, CH<sub>2</sub><sup>Lys</sup> / NCH<sub>2</sub>CH<sub>2</sub> / N[CH<sub>2</sub>]<sub>2</sub>CH<sub>2</sub> / N[CH<sub>2</sub>]<sub>3</sub>CH<sub>2</sub>).

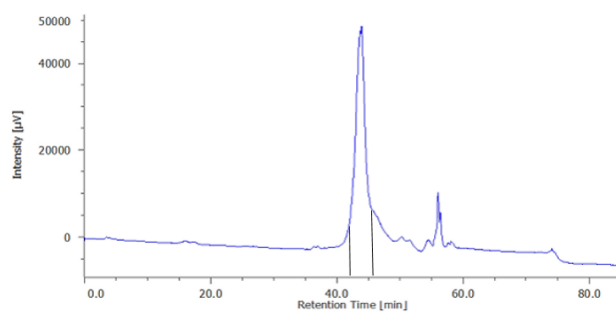
**<sup>1</sup>H-NMR-spectrum of monomer 2b**



## MALDI-MS spectrum of 2b



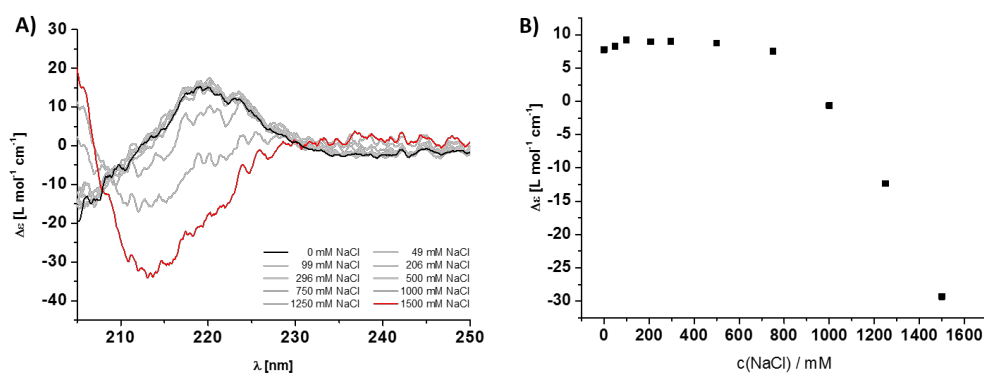
## Preparative RP-HPLC trace of 2b recorded at 210 nm



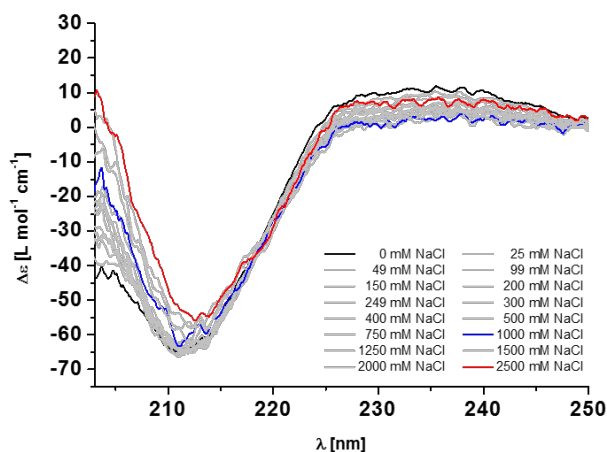
## 6 Circular dichroism (CD) spectroscopy

### General

CD spectra were recorded on a J-815 (JASCO) using the software Spectra Manager 2.08.04 and processed with Origin Pro 9.1 G. All spectra were recorded at 20 °C with a total monomer concentrations of 60  $\mu\text{M}$  in 10 mM phosphate buffer using quartz cells with a path length of 1 mm. The low monomer concentrations made sure that the HT signal was lower than 600 V at all times. In the UV-Vis spectra no evidence for scattering was observed in any of the solutions. The pH values were adjusted by addition of aqueous HCl and NaOH. All Spectra were corrected by subtraction of the background (buffer).



**Figure S1** – A) CD spectra of a 60  $\mu\text{M}$  aqueous solution containing monomer **1a** at pH 6.07 and different NaCl-concentrations. B) contains the corresponding titration curve following the intensity of the CD band at  $\lambda = 216$  nm.



**Figure S2** – CD spectra of a 60  $\mu\text{M}$  aqueous solution containing copolymer **1a-1b** at pH 7.60 and different NaCl-concentrations.

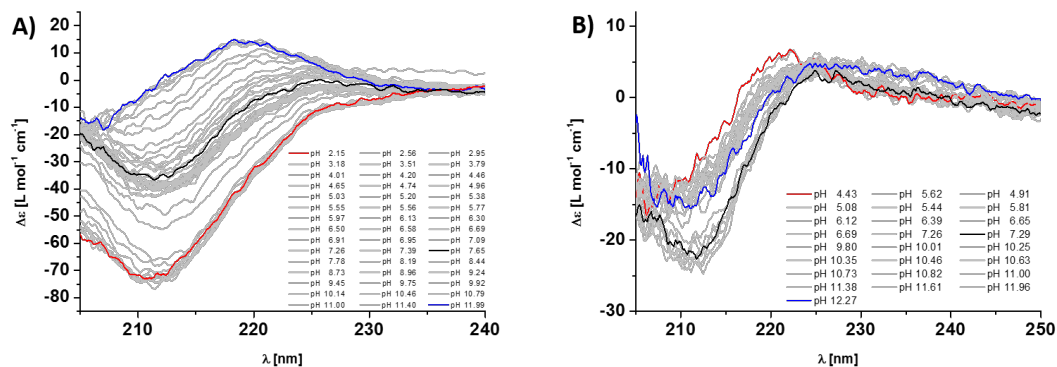


Figure S3 – CD spectra of a 60  $\mu\text{M}$  aqueous solution containing copolymer **1a-2b** (A) and **1a-2b** (B).

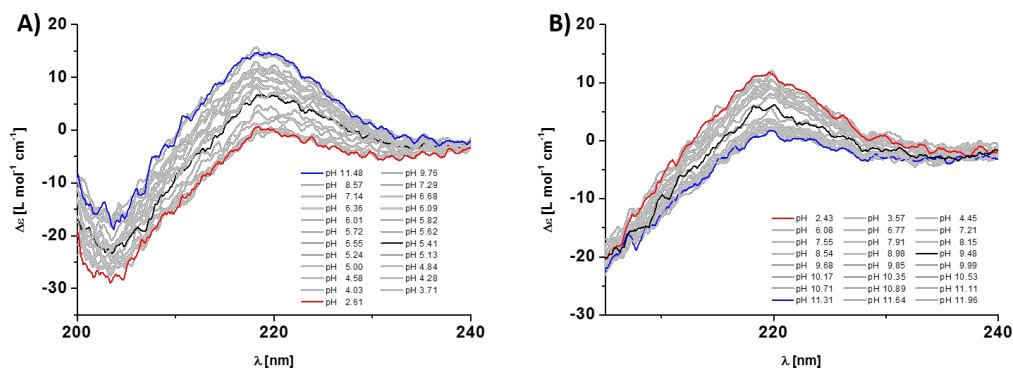


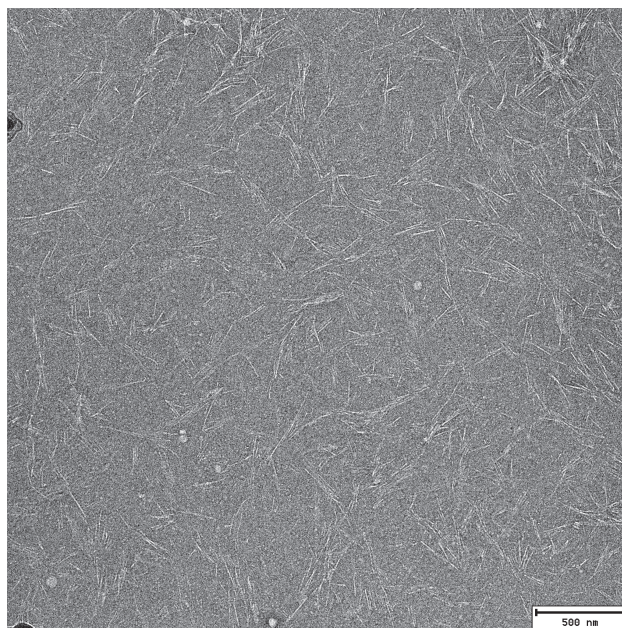
Figure S4 – CD spectra of a 60  $\mu\text{M}$  aqueous solution containing monomer **2a** (A) and **2b** (B).

## 7 Transmission electron microscopy (TEM)

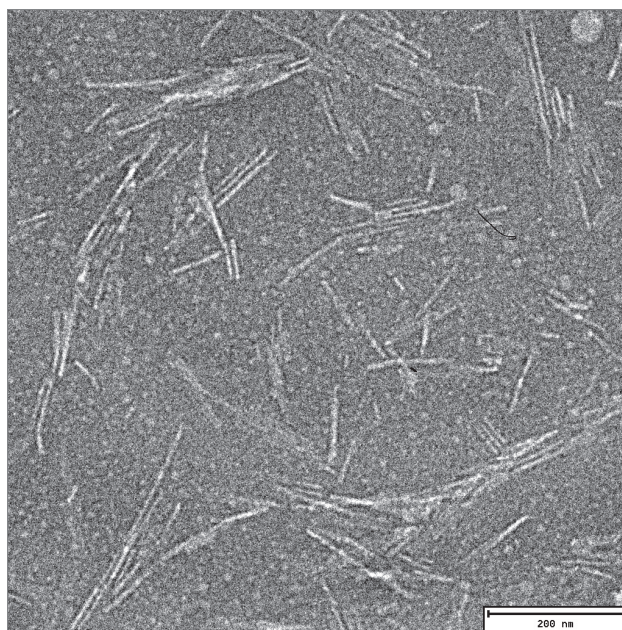
### Negative stain EM: grid preparation and image recording

In brief, 5  $\mu\text{L}$  sample droplets were adsorbed for 2 min on freshly glow-discharged copper grids (Electron Microscopy Sciences; CF300-CU) covered by a thin, continuous carbon film. The grids were then negatively stained with 2.0% uranyl acetate (Polysciences) for 1 min before blotting with filter papers (Whatman no. 4).<sup>7</sup> All images were recorded with a FEI Tecnai T12 electron microscope equipped with a LaB<sub>6</sub> cathode and operated at 120 kV. Digital electron micrographs were recorded with a 4k x 4k CMOS camera (TVIPS) under minimal dose conditions.



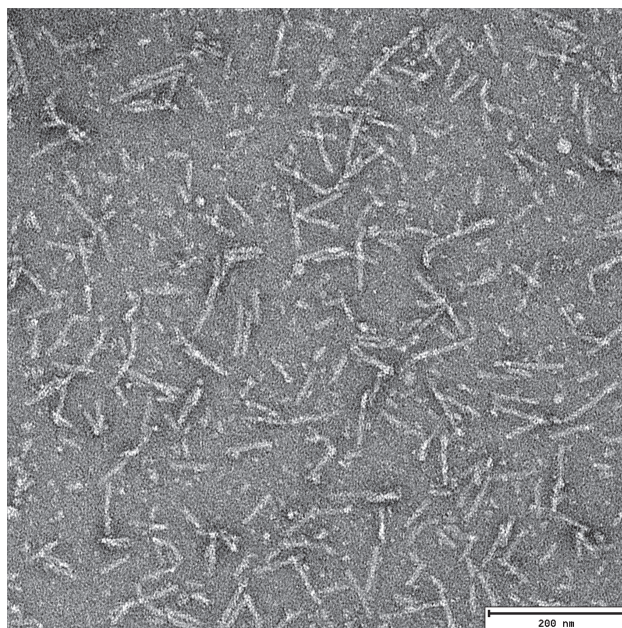


**Figure S5** – TEM image of monomer **1a** at pH 2.0 in 20 mM TRIS-buffer; scale bar: 500 nm.

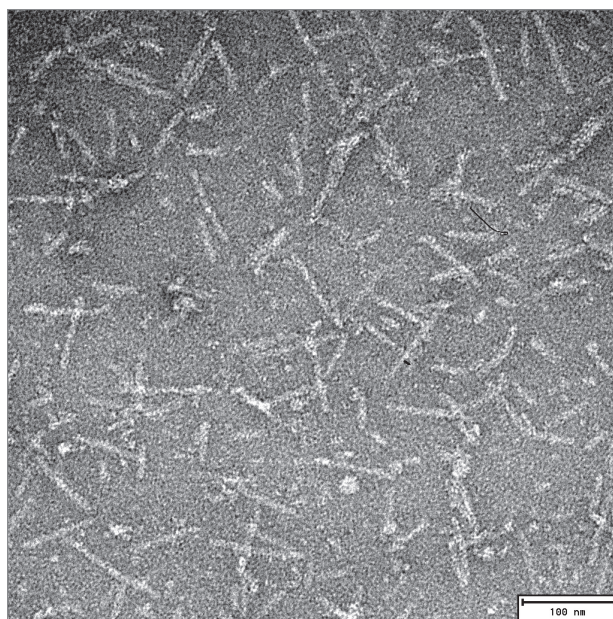


**Figure S6** – TEM image of monomer **1a** at pH 2.0 in 20 mM TRIS-buffer; scale bar: 200 nm.

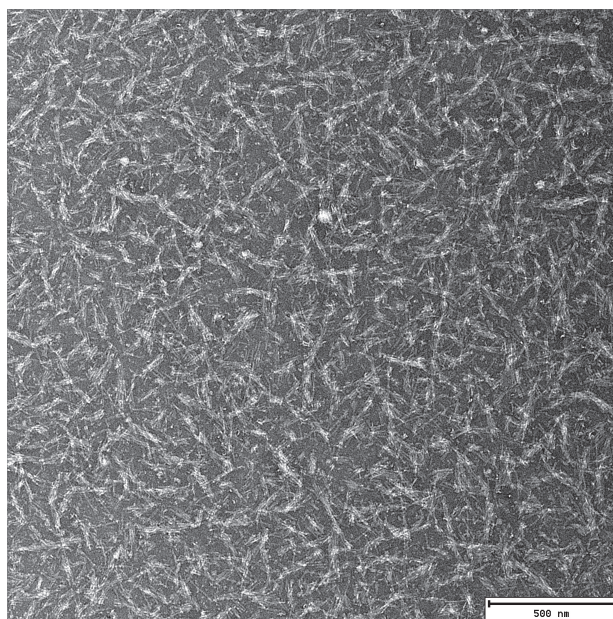




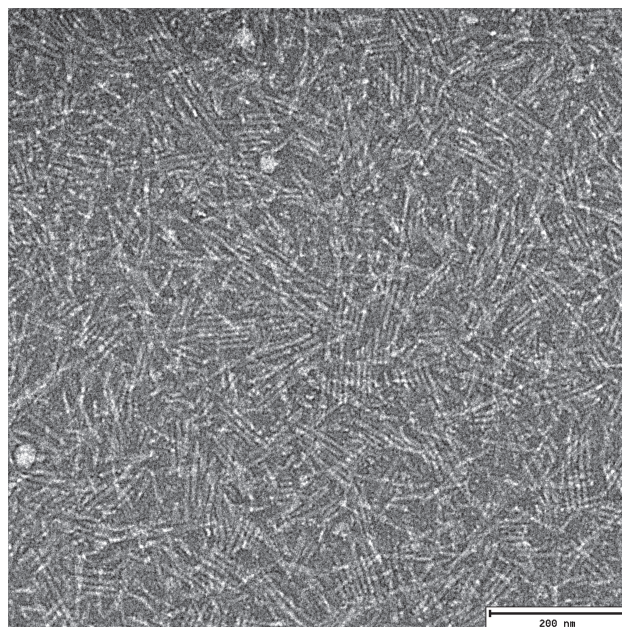
**Figure S7** – TEM image of monomer **1b** at pH 12.0 in 20 mM TRIS-buffer; scale bar: 200 nm.



**Figure S8** – TEM image of monomer **1b** at pH 12.0 in 20 mM TRIS-buffer; scale bar: 100 nm.

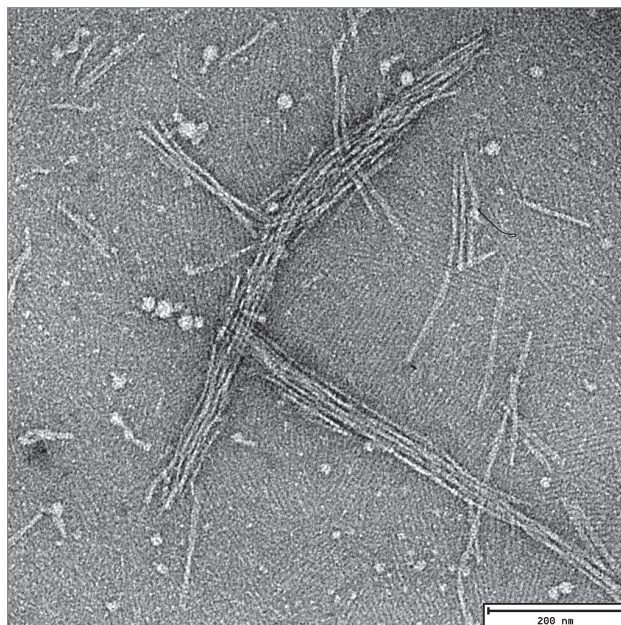


**Figure S9** – TEM images of the copolymer of **1a** and **1b** at pH 7.4 in 20 mM TRIS-buffer; scale bar: 500 nm.

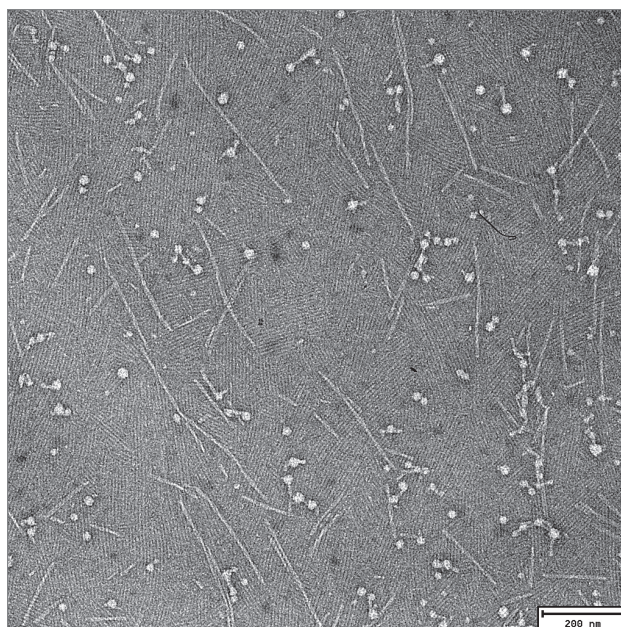


**Figure S10** – TEM images of the copolymer of **1a** and **1b** at pH 7.4 in 20 mM TRIS-buffer; scale bar: 200 nm.

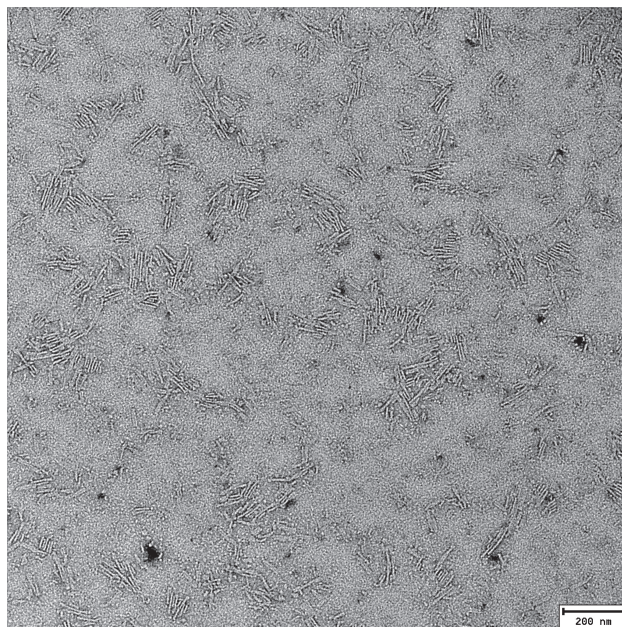




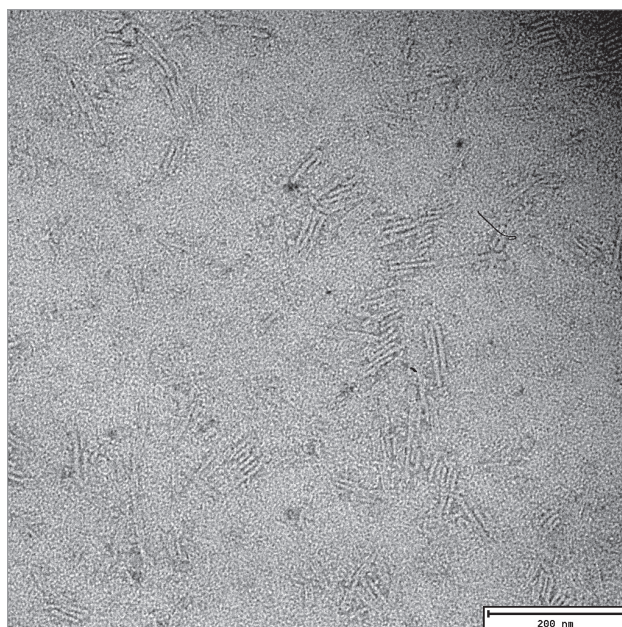
**Figure S11** – TEM image of monomer **2a** at pH 2.0 in 20 mM Phosphate-buffer; scale bar: 200 nm.



**Figure S12** – TEM image of monomer **2a** at pH 2.0 in 20 mM Phosphate-buffer; scale bar: 100 nm.



**Figure S13** – TEM image of monomer **2b** at pH 12.0 in 20 mM Phosphate-buffer; scale bar: 200 nm.



**Figure S14** – TEM image of monomer **2b** at pH 12.0 in 20 mM Phosphate-buffer; scale bar: 200 nm.

## 8 References

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