

Toward Large Tubular Helices Based on the Polymerization of Tri(benzamide)s

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ABSTRACT: Herein we present the synthesis and polycondensation of mono- and di-*N*-protected, *bis*-substituted tri(benzamide)s with the aim to create large, tubular helices. We synthesized 2,4-dimethoxy and 2,5-bis-TEGylated aminobenzoic acid derivatives as bent and linear monomers and introduced *p*-methoxybenzyl (PMB) amide protecting groups to the oligobenzamide backbone. An iterative coupling strategy allowed for sequence control, giving rise to oligomers consisting of one bent and two linear monomers. The resulting *meta-para*-linked aromatic trimers carried either one or two PMB-protecting groups. With high organosolubility and flexibility, this synthetic strategy generated suitable precursors for subsequent polycondensation reactions. After polymerization, treatment with acid triggered the cleavage of the *N*-protecting groups. We hypothesize that the hydrogen bonding pattern

generated along the polyamide backbone could lead to the formation of a helical polymer. A drastic change in hydrodynamic volume was observed by gel permeation chromatography and dissolution in a chiral solvent lead to the observation of a circular dichroism signal for this polymer. The results of the polycondensations of *N*-protected oligobenzamides are reported herein. The formation of macrocycles as well as polymers could also be observed, giving a highly interesting insight into the underlying mechanism of the polycondensation of flexible, oligobenzamide-based oligomers. © 2016 Wiley Periodicals, Inc. *J. Polym. Sci., Part A: Polym. Chem.* **2016**, *00*, 000–000

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INTRODUCTION Complex folding processes of supramolecules are plentiful in nature, ensuring the correct function of millions of organisms. They can be found, for example, in the folding of proteins, the DNA double helix or ion channels.¹ In proteins, the information for the self-assembly of the final structure is already encoded in the smallest unit—the amino acid sequence—and their folding is then based on the interplay of multiple noncovalent interactions. Hence, a careful design of the monomer structure is necessary to store information on a molecular level, which is later on transformed into a well-defined structure.² In recent years, various research groups dedicated their work to the synthesis of nature-imitating supramolecules by mimicking the underlying forces: A combination of hydrogen bonds,³ electrostatic,⁴ hydrophobic and solvophobic⁵ interactions, aromatic–aromatic interactions,^{3(i),6} the introduction of sterically demanding side groups,^{4(e),7} and/or metal-coordination⁸ results in the generation of predictable conformations and stabilizes the supramolecule. This allowed for the creation of synthetic single-, double-, or triple-stranded helices,^{4 (d,e),5(e),6(a),9} ion channels,¹⁰ and foldamers.^{3(c),(d,i),9(d),11} However, the majority

of the nonbiological foldamers and helical polymers reported to date do not exhibit an inner cavity.^{11(d),12} Hence, the interest in the construction of synthetic, helical supramolecules containing interior spaces has greatly increased during the past decade.

Bis-Substituted aromatic oligoamide foldamers are especially suitable to approach this task. They exhibit tremendous shape-persistence caused by their aromatic backbone, the double bond character of the amide bonds and the formation of an intramolecular, three-center hydrogen bonding pattern along the amide backbone.^{3(c,i),13} Even though they can theoretically exhibit various conformations, the preference at every rotationally flexible bond forces the supramolecule into one favored conformation. Other factors such as entropy, the influence of functional side chains or solvent effects can thereby be neglected.^{3(d),11(b),14} The first example of a hollow structure constructed from aromatic oligoamides comprised the molecular apple peel described by Huc and his group.¹⁵ The inclusion of small molecules in helical capsules via host-guest interactions has been reported multiple times since then.¹⁶ The group of Gong invented a concept for the

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construction of foldamers and helices with even larger cavities and tunable sizes.^{3(g),13(c),17} The underlying idea is to incorporate *meta*- as well as *para*-linked, *bis*-substituted amino acids in a sequence-controlled manner into the backbone.^{13(c)} The inner diameter thereby increases with an increasing number of *para*-linked amino acids. The largest diameter constructed by alternating *bis*-methoxylated *meta*- and *para*-amino acids reported to date measures 30 Å. The low yields of the coupling steps however limited the number of coupled amino acids to 21, making the creation of a helix with more than one helical turn impossible.¹⁷ To obtain higher molecular weights, an approach via polycondensation of *meta*-diamines and *meta*-diacid chlorides was recently described by the Gong group.¹⁸ The formation of macrocycles could be observed because of the preorganizational effect of the rigid, shape-persistent backbone. However, the polymerization of a *bis*-substituted diacid chloride and a flexibility-inducing mono-substituted diamine resulted in high molecular weight polymers. Their solvophobicity driven folding then led to a racemic mixture of helical (P and M) polyamides with an inner cavity of 8.2 Å and multiple turns. In contrast to conventional organic synthesis, polymerization techniques have the advantage to deliver high molecular weights, however, the monomer sequence within the polymer chain cannot be controlled. Furthermore, the above-described helical polymers exhibit smaller inner diameters than the aromatic oligoamide foldamers prepared by organic synthesis. In conclusion, either high molecular weights or large inner diameters can be generated by the methods described to date.

Based on the studies by our group on substituted oligo- and poly(*p*-benzamide)s from aminosalicylic acid derivatives,¹⁹ we developed a concept for the construction of large, tubular helices combining conventional organic chemistry (*sequence control*) and polymer science (*higher molecular weights*).

We established a synthetic strategy including iterative coupling steps toward a bent tri(benzamide) monomer, which is subsequently polymerized to a coil-like polymer by polycondensation. Acidic cleavage of amide *N*-protecting groups (PG) leads to the formation of the final helical structure. Depending on the size of the precursor, that is, the number of linear monomers within the oligomer (here two), helices with inner cavities of varying diameters can in principle be synthesized. To address the synthetic challenges involved in the formation of helices, the bent oligomeric precursor carries various features. The triethylene glycol monomethyl ether (TEG) side chains ensure excellent organosolubility at all stages of the synthesis. The substitution pattern (2,5-substitution for the *para*-linked ("linear") monomer, 2,4-substitution for the *meta*-linked ("bent") monomer) results in three-center hydrogen bond formation, stabilizing the folded, helical conformation. To avoid macrocyclization during polymerization, one or two amide bonds were chosen to carry a *p*-methoxybenzyl (PMB) *N*-protecting group, leading to an *E*-conformation of the resulting tertiary amide bond and suppression of the hydrogen bond formation. The folding of the helix could

thereby be triggered through the cleavage of the protecting groups upon treatment with acid.^{3(g),20} In that way, the amide backbone undergoes a conformational change from *cis* (*E*) to *trans* (*Z*) (*cis/trans* with respect to the phenyl rings) through the formation of the intramolecular hydrogen bonding pattern.

The results of this new route including the synthesis and characterization of mono- and di-*N*-protected, *bis*-substituted tri(benzamide)s and thorough investigations concerning the polycondensation technique are presented herein.

EXPERIMENTAL

Materials

Solvents of analytical grade were purchased from Honeywell, Acros Organics, Sigma Aldrich, Fisher Scientific, and Fluka and were used without further purification. Solvents of technical grade were purified by distillation, if necessary. Tetrahydrofuran for use in polymerizations was purchased as a sealed bottle from Acros Organics (extra dry, AcroSeal) and transferred into a glove box. Deuterated chloroform (CDCl₃) was purchased from Cambridge Isotope Laboratories. All further chemicals were purchased from Sigma Aldrich, Acros Organics, Alfa Aesar, and Merck and used as received.

Techniques

Standard ¹H and ¹³C nuclear magnetic resonance spectra were recorded on a Bruker Avance III 300 at a frequency of 300 and 75 MHz, respectively, or at 500 MHz (¹H) and 125 MHz (¹³C) on a Bruker Avance III 500 spectrometer. All NMR-signals were referenced internally to residual solvent signals. Electron spray ionization (ESI) mass spectra were recorded on a Bruker-Ion Trap MS esquire HCT mass spectrometer. Matrix assisted laser desorption and ionization time-of-flight (MALDI-ToF) measurements were performed on a Bruker ultrafleXtreme™ MALDI-ToF mass spectrometer. DCTB was used as matrix and sodium trifluoroacetate used as salt. RP-HPLC analysis was performed on a HP 1090 Liquid Chromatograph (Hewlett Packard) using a PerfectSil column (MZ Analysentechnik, Mainz, Germany, 250 × 4.0 mm; 120 ODS-2.5 μm). Samples were dissolved in acetonitrile and eluted with an acetonitrile/water gradient buffered with 0.1% TFA starting from 10% acetonitrile rising to 100% over a period of 40 min. UV signals were detected at 254 nm. For recycling HPLC a Japan Analytical Industry Next System equipped with a preparative MZ Kromasil C18 Column and a UV detector at 254 nm was used. 10 wt-% solutions of the sample in acetonitrile were prepared and eluted in acetonitrile/water (75/25). For gel permeation chromatography in chloroform an instrument consisting of a Dura-tec vacuum degasser, a JASCO PU-2087plus pump and a set of two MZ-Gel SD_{plus} linear columns (300 × 8 mm, 5 μm particle size) was used. Signal detection occurred by use of an Applied Biosystems 759A UV detector (set to 254 nm wavelength) and a Knauer Smartline 2300 RI-Detektor (refractive index). Calibration was done using Malvern Polysciences™ UCS-PS polystyrene standards. UV/Vis spectroscopy

was performed on a JASCO V-630 UV-VIS spectrophotometer, circular dichroism spectra were recorded on a JASCO J-715 spectropolarimeter.

4-((4-Methoxybenzyl)amino)-2,5-bis(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)benzoic Acid L-2

4-Amino-2,5-bis(2-(2-(2-methoxyethoxy)-ethoxy)ethoxy)benzoic acid **L-1** (0.95 g, 2.0 mmol) and *p*-anisaldehyde (0.31 g, 2.2 mmol) were dissolved in dry dichloromethane (65 mL) and glacial acetic acid (0.57 mL, 0.01 mol) was added. After stirring at room temperature for 30 min, sodium triacetoxymethylborohydride (1.27 g, 6.0 mmol) was added and the mixture stirred at room temperature overnight. Water was added and the aqueous phase extracted with dichloromethane four times. The combined organic layers were dried over magnesium sulfate. The solvent was removed under reduced pressure to yield a crude oil. Purification by recycling HPLC [acetonitrile/water (75/25)] yielded monomer **L-2** (0.46 g, 0.8 mol) as light brown oil in 40% yield. ^1H NMR (300 MHz, CDCl_3): δ (ppm) = 3.34 (s, 3 H), 3.35 (s, 3 H), 3.47–3.56 (m, 4 H), 3.57–3.71 (m, 13 H), 3.77–3.83 (m, 7 H), 4.16 (t, 3J = 4.40 Hz, 4 H), 4.34 (d, 3J = 5.46 Hz, 2 H), 5.61 (t, 3J = 5.36 Hz, 1 H), 6.06 (s, 1 H), 6.84–6.90 (d, 3J = 8.75 Hz, 2 H), 7.22–7.27 (d, 3J = 8.75 Hz, 2 H), 7.47 (s, 1 H); ^{13}C NMR and APT (75 MHz, CDCl_3): δ (ppm) = 46.50 (+), 55.20 (–), 58.93 (–), 68.64 (+), 68.84 (+), 69.22 (+), 69.51 (+), 70.43 (+), 70.46 (+), 70.49 (+), 70.61 (+), 71.73 (+), 71.77 (+), 94.69 (–), 104.18 (+), 114.04 (–), 114.64 (–), 128.26 (–), 129.83 (+), 140.36 (+), 144.53 (+), 154.41 (+), 158.84 (+), 166.25 (+); HR-MS (ESI+): m/z calculated for $[\text{C}_{29}\text{H}_{44}\text{NO}_{11}]^+ = 582.29144$, found 582.29005; RP-HPLC: 17.87 min.

PMB-Protected Dimer 2

Both monomers were dried at the Schlenk line overnight. Linear monomer **1** (363 mg, 0.74 mmol) was dissolved in NMP (2 mL) and thionyl chloride (0.08 mL, 1.1 mmol) was added dropwise at 0 °C. The ice bath was removed and the reaction was run for 2 h at room temperature after which excess thionyl chloride was removed at the Schlenk line for 1 h. PMB-protected linear monomer **L-2** (430 mg, 0.74 mmol) was dissolved in NMP (2 mL) and added dropwise to the activated acid chloride. The mixture was stirred at room temperature overnight. Ethyl acetate was added, the organic phase washed with water five times, dried over magnesium sulfate and evaporated under reduced pressure. The brown oil was purified via recycling HPLC in acetonitrile/water (85/15) at 40 °C to yield **2** (290 mg, 0.27 mmol, 37%) as an orange oil. ^1H NMR (300 MHz, CDCl_3): δ (ppm) = 3.31 (s, 3 H), 3.32 (s, 3 H), 3.34 (s, 3 H), 3.35 (s, 3 H), 3.45–3.86 (m, 51 H), 3.91–4.08 (m, 6 H), 4.08–4.20 (m, 2 H), 4.44 (d, 2J = 14.35 Hz, 1 H), 5.38 (d, 2J = 14.35 Hz, 1 H), 6.77 (d, 3J = 8.80 Hz, 2 H), 6.84 (s, 1 H), 7.12 (s, 1 H), 7.17–7.19 (d, 3J = 8.80 Hz, 2 H), 7.19 (s, 1 H), 7.43 (s, 1 H); ^{13}C NMR and APT (75 MHz, CDCl_3): δ (ppm) = 50.41 (+), 55.11 (–), 58.86 (–), 58.90 (–), 68.26 (+), 68.77 (+), 69.16 (+), 69.37 (+), 69.46 (+), 70.05 (+), 70.26 (+), 70.31 (+), 70.39 (+), 70.42 (+), 70.45 (+), 70.52 (+), 70.57 (+),

70.65 (+), 70.80 (+), 70.88 (+), 71.74 (+), 71.76 (+), 71.82 (+), 108.70 (–), 113.54 (–), 114.38 (–), 115.27 (–), 116.95 (–), 119.47 (+), 128.71 (+), 130.47 (–), 132.91 (+), 134.72 (+), 139.35 (+), 146.77 (+), 147.27 (+), 149.05 (+), 150.55 (+), 158.94 (+), 164.66 (+), 166.24 (+); HR-MS (ESI+): m/z calculated for $[\text{C}_{50}\text{H}_{74}\text{N}_2\text{O}_{22}\text{Na}]^+ = 1077.46310$, found 1077.46256; RP-HPLC: 19.38 min.

PMB-Protected Trimer 3

Bent monomer **B-1** and protected dimer **2** were dried at the Schlenk line overnight. The protected dimer (420 mg, 0.4 mmol) was dissolved in NMP (3 mL) and thionyl chloride (0.4 mL, 0.6 mmol) was added dropwise at 0 °C. The ice bath was removed and the reaction was run for 2 h at room temperature after which excess thionyl chloride was removed at the Schlenk line for 1 h. The bent monomer (157 mg, 0.4 mmol) was dissolved in NMP (3 mL) and added dropwise to the activated acid chloride. The mixture was stirred at room temperature overnight. Ethyl acetate was added, the organic phase washed with water five times, dried over magnesium sulfate and evaporated under reduced pressure to yield trimer **3** (560 mg, 0.39 mmol, 98%) as a brown oil. HR-MS (ESI+): m/z calculated for $[\text{C}_{73}\text{H}_{95}\text{N}_3\text{O}_{26}\text{Na}]^+ = 1452.61016$, found 1452.60989; RP-HPLC: 24.74 min.

PMB-Protected Trimer T-1

Protected trimer **3** (560 mg, 0.39 mmol) was dissolved in DMF (28 mL) and tin(II) chloride (370 mg, 1.95 mmol) was added. The mixture was stirred at 60 °C overnight, after which 5 eq. were added additionally. The reaction was carried out for two more nights. Ethyl acetate and water were added to the mixture and the aqueous phase was extracted with ethyl acetate four times. The combined organic layers were washed with brine, dried over magnesium sulfate and the solvent removed under reduced pressure. The trimer was purified by recycling HPLC in acetonitrile/water (85/15) at 40 °C to obtain pure **T-1** (105 mg, 0.075 mmol, 19%) as an orange oil. ^1H NMR (500 MHz, 52 °C, CDCl_3): δ (ppm) = 3.34–3.36 (m, 12 H), 3.49–3.75 (m, 50 H), 3.88–3.96 (m, 8 H), 4.27–4.45 (m, 2 H), 5.28–5.31 (m, 1 H), 6.63 (s, 1 H), 6.70–6.76 (m, 2 H), 6.79 (d, 3J = 8.33 Hz, 2 H), 6.88 (s, 1 H), 7.05 (d, 3J = 7.77 Hz, 2 H), 7.14–7.23 (m, 4 H), 7.38 (t, 3J = 7.39 Hz, 2 H), 7.50–7.55 (m, 1 H); ^{13}C NMR and DEPT (125 MHz, 52 °C, CDCl_3): δ (ppm) = 51.28 (–), 55.18 (+), 55.56 (+), 58.83 (+), 58.86 (+), 67.95 (–), 68.14 (–), 69.27 (–), 69.66 (–), 69.85 (–), 70.45 (–), 70.49 (–), 70.53 (–), 70.57 (–), 70.66 (–), 70.69 (–), 70.73 (–), 70.95 (–), 72.00 (–), 77.19 (+), 95.68, 101.47, 110.26, 111.10, 113.59 (+), 113.66 (+), 114.77, 119.45, 121.73 (+), 121.89, 123.19, 125.55 (+), 126.59, 129.28 (+), 129.54, 130.42 (+), 132.30, 133.92, 134.16, 140.06, 147.18, 149.78, 150.98, 158.85, 159.09, 159.84, 161.58, 161.85, 162.68, 168.90, 169.15; HR-MS (ESI+): m/z calculated for $[\text{C}_{73}\text{H}_{97}\text{N}_3\text{O}_{24}\text{Na}]^+ = 1422.63598$, found 1422.63645; RP-HPLC: 20.39 min.

Polymerization of Trimer T-1

Trimer **T-1** (105 mg, 0.075 mmol) was dried at the Schlenk line overnight and transferred into a glove box. To start the polymerization, 2.2 eq. LiHMDS (0.17 mL, 1 M in THF) were added in one portion under vigorous stirring. After stirring at room temperature overnight, the mixture was quenched by addition of saturated aqueous ammonium chloride solution and extracted with dichloromethane four times. The combined organic layers were washed with water, dried over magnesium sulfate and the solvent removed under reduced pressure to yield the cyclic trimer **P-1** (100 mg, 95%). MALDI-ToF (DCTB, NaTFA): m/z calculated for $[C_{67}H_{91}N_3O_{23}Na]^+ = 1328.5941$, found 1328.5903; GPC (CHCl₃): M_n 840 g/mol, M_w 860 g/mol, D_M 1.02.

Linear Dimer 4

Both monomers were dried at the Schlenk line overnight. Linear monomer **1** (468 mg, 0.95 mmol) was dissolved in NMP (1 mL) and thionyl chloride (0.1 mL, 1.43 mmol) was added dropwise at 0 °C. The ice bath was removed and the reaction was run for 2 h at room temperature, after which excess thionyl chloride was removed at the Schlenk line for 1 h. **L-1** (440 mg, 0.95 mmol) was dissolved in NMP (1.5 mL) and added dropwise to the activated acid chloride. The mixture was stirred at room temperature overnight. Ethyl acetate was added, the organic phase was washed with water five times, dried over magnesium sulfate and evaporated under reduced pressure to give dimer **4** (700 mg, 0.75 mmol) as a brown oil in 79% yield. ¹H NMR (300 MHz, CDCl₃): δ (ppm) = 3.32 (s, 3 H), 3.34 (s, 3H), 3.37 (s, 7 H), 3.43–3.78 (m, 41 H), 3.83–3.87 (m, 3 H), 3.90 (m, 7 H), 4.31 (m, 5 H), 4.42 (m, 3 H), 4.54 (m, 3 H), 7.70 (s, 1 H), 7.77 (s, 1 H), 7.98 (s, 1 H), 8.56 (s, 1 H), 10.80 (s, 1 H); ¹³C NMR and APT (75 MHz, CDCl₃): δ (ppm) = 58.92 (–), 58.94 (–), 58.96 (–), 68.59 (+), 69.05 (+), 69.23 (+), 69.59 (+), 69.70 (+), 70.17 (+), 70.50 (+), 70.55 (+), 70.62 (+), 70.69 (+), 70.80 (+), 71.04 (+), 71.10 (+), 71.78 (+), 71.83 (+), 71.88 (+), 106.14 (–), 112.51 (–), 112.78 (+), 115.17 (–), 118.48 (–), 126.72, 134.06 (+), 141.75, 142.48 (+), 146.46 (+), 150.34 (+), 152.49 (+), 161.79 (+), 165.32 (+); HR-MS (ESI+): m/z calculated for $[C_{42}H_{66}N_2O_{21}Na]^+ = 957.40558$, found 957.40493; RP-HPLC: 18.83 min.

PMB-Protected Trimer 5

Both monomers were dried at the Schlenk line overnight. Linear dimer **4** (650 mg, 0.70 mmol) was dissolved in NMP (2 mL) and thionyl chloride (0.08 mL, 1.04 mmol) was added dropwise at 0 °C. The ice bath was removed and the reaction was run for 2 h at room temperature after which excess thionyl chloride was removed at the Schlenk line for 1 h. Bent phenyl ester **B-1** (275 mg, 0.70 mmol) was dissolved in NMP (1.5 mL) and added dropwise to the activated acid chloride. The mixture was stirred at room temperature overnight. Ethyl acetate was added, the organic phase washed with water five times and twice with saturated aqueous sodium hydrogencarbonate solution. The combined organic layers were dried over magnesium sulfate and

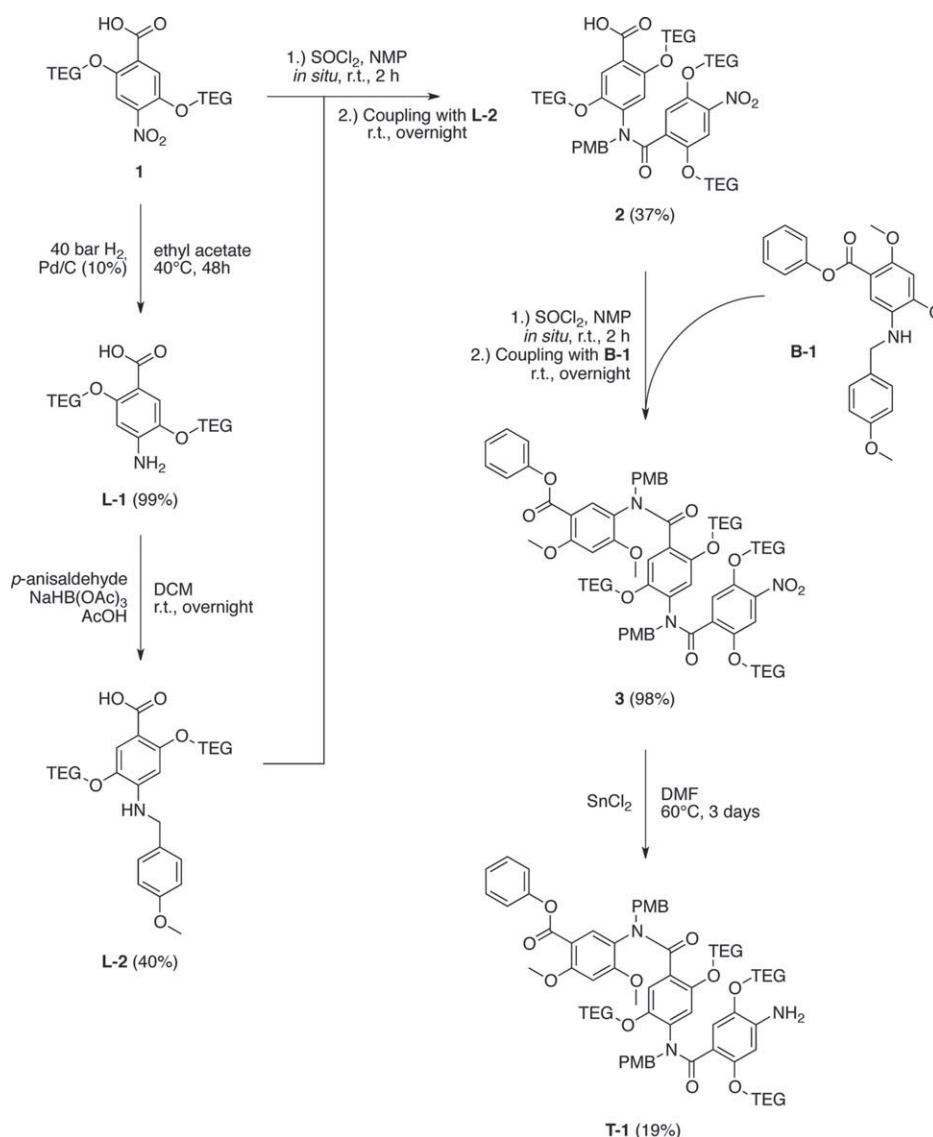
evaporated under reduced pressure to give trimer **5** (790 mg, 0.60 mmol, 86%) as a brown oil. ¹H NMR (300 MHz, CDCl₃): δ (ppm) = 3.33 (s, 3 H), 3.34 (s, 3 H), 3.36 (s, 3 H), 3.37 (s, 3 H), 3.42–4.01 (m, 48 H), 4.29 (t, ³ J = 4.72 Hz, 2 H), 4.39 (d, ² J = 14.35 Hz, 1 H), 4.46 (m, 2 H), 5.38 (d, ² J = 14.16 Hz, 1 H), 6.21 (s, 1 H), 6.81–6.87 (m, 3 H), 7.06 (d, ³ J = 7.37 Hz, 2 H), 7.24 (d, ³ J = 8.50 Hz, 2 H), 7.38 (t, ³ J = 7.56 Hz and 8.05 Hz, 2 H), 7.63 (s, 1 H), 7.72 (s, 1 H), 7.94 (s, 1 H), 8.14 (s, 1 H), 10.44 (s, 1 H); HR-MS (ESI+): m/z calculated for $[C_{65}H_{88}N_3O_{25}]^+ = 1310.57070$, found 1310.57074; RP-HPLC: 23.09 min.

PMB-Protected Trimer T-2

Protected trimer **5** (400 mg, 0.3 mmol) was dissolved in DMF (20 mL) and tin(II) chloride dihydrate (690 mg, 3.0 mmol) was added. The mixture was stirred at 40 °C for 72 h. Ethyl acetate was added and the mixture extracted between ethyl acetate and water four times. The combined organic layers were washed with saturated aqueous sodium hydrogencarbonate and brine, dried over magnesium sulfate and the solvent removed under reduced pressure. The product was purified by recycling HPLC in acetonitrile/water (85/15) at 35 °C to give the pure trimer **T-2** (86 mg, 0.067 mmol) as a yellow oil in 22% yield. ¹H NMR (300 MHz, CDCl₃): δ (ppm) = 3.33 (s, 6 H), 3.35 (s, 3 H), 3.37 (s, 3 H), 3.45–3.72 (m, 45 H), 3.75 (s, 4 H), 3.77–3.89 (m, 10 H), 4.04–4.10 (m, 3 H), 4.13–4.16 (m, 3 H), 4.30 (t, ³ J = 5.10 Hz, 2 H), 4.39 (d, ² J = 14.15 Hz, 1 H), 4.51 (br. s., 2 H), 5.36 (d, ² J = 14.15 Hz, 1 H), 6.19 (s, 1 H), 6.41 (s, 1 H), 6.79 (s, 1 H), 6.82 (d, ⁴ J = 2.18 Hz, 2 H), 7.05 (d, ³ J = 7.39 Hz, ⁴ J = 1.26 Hz, 2 H), 7.20 (s, 1 H), 7.23 (d, ² J = 8.65 Hz, 2 H), 7.34–7.39 (m, 2 H), 7.59 (s, 1 H), 7.62 (s, 1 H), 8.18 (s, 1 H), 10.33 (s, 1 H); ¹³C NMR and DEPT (75 MHz, CDCl₃): δ (ppm) = 51.05 (+), 55.08 (–), 55.47 (–), 55.95 (–), 58.81 (–), 58.87 (–), 67.70 (+), 67.87 (+), 69.08 (+), 69.19 (+), 69.29 (+), 69.32 (+), 69.57 (+), 69.83 (+), 70.39 (+), 70.50 (+), 70.56 (+), 70.65 (+), 71.75 (+), 71.77 (+), 71.83 (+), 71.86 (+), 77.20, 95.28 (–), 100.47 (–), 104.30 (–), 109.53, 111.17, 112.37, 113.45 (–), 115.86 (–), 120.30, 121.77 (–), 122.77, 125.44 (–), 129.19 (–), 129.55, 130.42 (–), 131.31 (–), 134.09, 140.31, 140.49, 142.73, 148.91, 150.76, 153.15, 158.82, 159.79, 161.44, 162.61, 163.63, 169.48; HR-MS (ESI+): m/z calculated for $[C_{65}H_{89}N_3O_{23}Na]^+ = 1302.57846$, found 1302.57777; RP-HPLC: 21.27 min.

Polymerization of Trimer T-2

Trimer **T-2** (86 mg, 0.067 mmol) was dried at the Schlenk line overnight and cooled to –10 °C by using a cryostat. To start the polymerization, 3.2 eq. LiHMDS (0.21 mL, 1 M in THF) were added in one portion. Due to the high viscosity, stirring was not possible, and the solution was warmed up to room temperature after 10 min upon which the solution formed a gel. After stirring at room temperature for 1 h, the mixture was quenched by addition of saturated aqueous ammonium chloride solution and extracted with dichloromethane four times. The combined organic layers were washed with water, dried over magnesium sulfate and the solvent



SCHEME 1 Iterative coupling strategy toward the di-PMB-protected trimer **T-1**. PMB, *p*-methoxybenzyl; TEG, triethylene glycol.

removed under reduced pressure to yield a mixture of macrocycles and polymers (80 mg). The higher molecular weight fraction was separated by preparative GPC in chloroform to yield the protected polymer **P-2** (40 mg, 47%). 1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.24–3.39 (m, 13 H), 3.40–4.03 (m, 49 H), 4.10 (br. s, 3 H), 4.24 (br. s, 2 H), 4.45 (br. s, 2 H), 4.92 (br. s, 1 H), 6.17 (br. s, 1 H), 6.80 (d, 3J = 6.05 Hz, 2 H), 6.89 (m, 1 H), 7.24 (d, 3J = 6.79 Hz, 2 H), 7.67 (br. s, 1 H), 8.10 (d, 3J = 9.17 Hz, 2 H), 8.53 (br. s, 1 H), 10.53 (m, 2 H); MALDI-ToF (DCTB): m/z calculated for $[C_{413}H_{583}N_{21}O_{155}Li]^+ = 8323.854$, found 8323.305; $[C_{472}H_{666}N_{24}O_{177}Li]^+ = 9509.401$, found 9509.791; GPC ($CHCl_3$): M_n 6900 g/mol, M_w 11,100 g/mol, D_M 1.6.

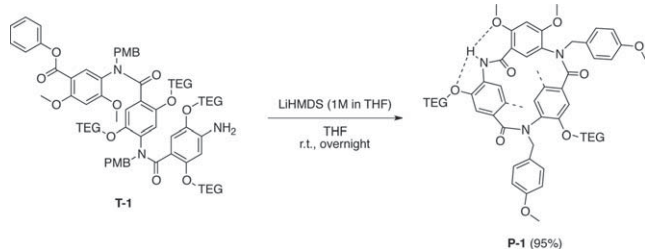
Deprotected Polymer **H-1**

Polymer **P-2** (40 mg) was dissolved in a 1:1-mixture of dichloromethane and trifluoroacetic acid (3 mL). The solution was stirred at room temperature for three days. Trifluoroacetic acid and dichloromethane were removed at the

Schlenk line and the solid washed with dichloromethane three times to yield the deprotected polymer **H-1** as brown solid in quantitative yield (35 mg). MALDI-ToF (DCTB): m/z calculated for $[C_{204}H_{302}N_{12}O_{85}Li]^+ = 4285.982$, found 4285.622; GPC (THF): M_n 5500 g/mol, M_w 6300 g/mol, D_M 1.1.

RESULTS AND DISCUSSION

The syntheses of the oligomers presented here were based on two different monomers: the linear monomer (L), which originated from *p*-aminobenzoic acid, and the bent monomer (B), which derived from *m*-aminobenzoic acid. The synthetic route toward the linear monomer L-1 (Scheme 1) has been described previously.²¹ The preparation of methyl-2,4-dimethoxy-5-nitrobenzoate, a key intermediate in the synthesis of the bent monomer, has been reported elsewhere.¹⁴ The following steps toward the final structure of B-1 (Scheme 1) can be found in the Supporting Information.



SCHEME 2 Polycondensation of the di-PMB-protected trimer **T-1** resulted in the unexpected formation of the cyclic trimer **P-1**. The inner triethylene glycol ether side chains are omitted for clarity. PMB, p-methoxybenzyl; TEG, triethylene glycol.

We previously investigated the Yokozawa-like polycondensation²² of phenyl ester derivatives of **L-1**. In doing so, we could already draw important conclusions with regard to the polycondensation of *bis*-substituted *tri*(benzamide)s and their required constitution: the polymerization of monomers carrying a primary amine resulted in the *in situ* formation of a polyanion, which showed only modest solubility in THF. The introduction of an *N*-amide protecting group to increase the organosolubility during polymerization however led to a sterical hindrance of the reactive center and a deactivation of the monomer. A polycondensation reaction could not take place.

Based on these two facts, we designed the *di*-PMB-protected oligomer **T-1** (Scheme 1), comprised of two *N*-protected amides to avoid polyanion formation upon exposure to strong base during polymerization. Moreover, **T-1** carried a primary amino group at the *N*-terminus to prevent sterical hindrance.

Synthesis and Polymerization of the di-PMB-Protected Trimer **T-1**

In the synthesis of the *di*-PMB-protected trimer **T-1** (Scheme 1) we started from one bent monomer **B-1**, one linear monomer **1** (nitro form of **L-1**) and one linear monomer **L-2**. The iterative coupling strategy is presented in Scheme 1.

The linear monomer **L-1** could be converted to **L-2** with *p*-anisaldehyde in a direct reductive amination by the use of sodium triacetoxy borohydride and glacial acetic acid. Purification via recycling HPLC gave the pure monomer **L-2** in 40% yield. The subsequent reaction between monomers **1** and **L-2** followed the standard coupling protocol, which our group has optimized for the synthesis of oligo(*p*-benzamide)s.²³ The reaction showed a high conversion, the purification of the PMB-protected dimer **2** by recycling HPLC however limited the yield to 37%. Dimer **2** could then be coupled with the bent monomer **B-1** to the trimer **3** in 98% yield. The reduction of the nitro group succeeded using tin(II)chloride in DMF and stirring the reaction mixture at 60 °C for three days. The final compound was purified by recycling HPLC to yield the pure *di*-PMB-protected trimer **T-1** in 19% yield. The formation of all compounds was validated by ¹H and ¹³C NMR spectroscopy, analytical RP-HPLC

and high-resolution ESI-mass spectrometry, which can be found in the Supporting Information.

The polycondensation of trimer **T-1** followed the protocol we reported previously.²¹ In a first attempt, we polymerized **T-1** in dry THF by addition of 2.2 eq. LiHMDS (1M in THF) with a final monomer concentration of 0.25 mol/L (Scheme 2).

The polycondensation was carried out at room temperature overnight and the obtained product subsequently characterized by GPC (chloroform). The comparison with the elugram of the starting material (Fig. 1, top, red) revealed a higher molecular weight shoulder after polymerization (Fig. 1, top, blue). The major fraction, however, did not show an increase in molecular weight. MALDI-ToF mass spectroscopic analysis revealed the formation of a cyclic trimer (Fig. 1, bottom and Scheme 2).

All our efforts to polymerize trimer **T-1** gave only the cyclic trimer as the majority compound (see detailed discussion in

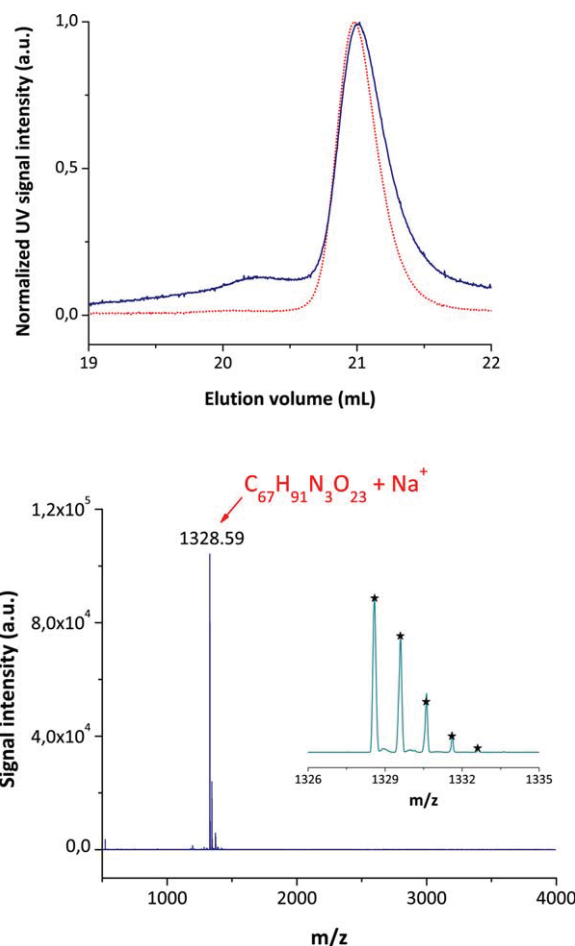
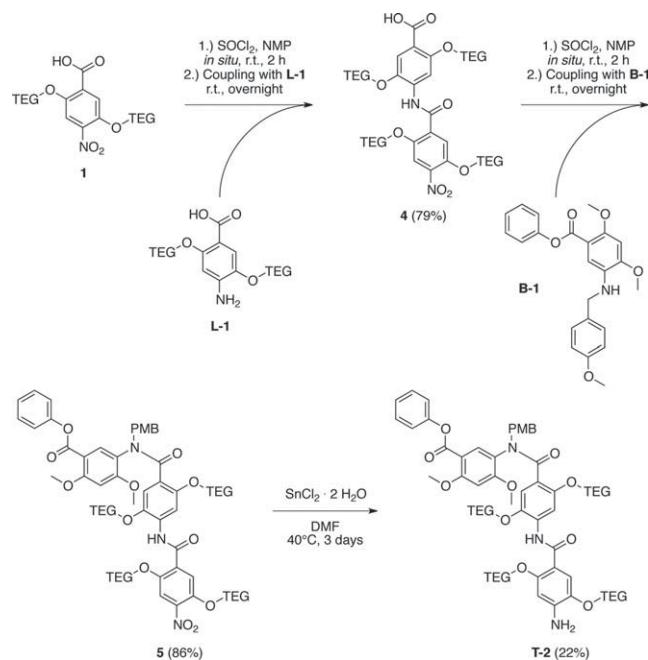


FIGURE 1 Top: GPC elugram in CHCl₃ of the trimer **T-1** (red) and the raw product mixture after polycondensation (blue). Bottom: MALDI-ToF spectrum of the cyclic trimer **P-1** (Na⁺-adduct). Inset: Comparison of the isotope pattern of the cyclic trimer (green) with the calculated one (stars). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



SCHEME 3 Iterative coupling strategy to the mono-PMB-protected trimer **T-2**. PMB, p-methoxybenzyl; TEG, triethylene glycol.

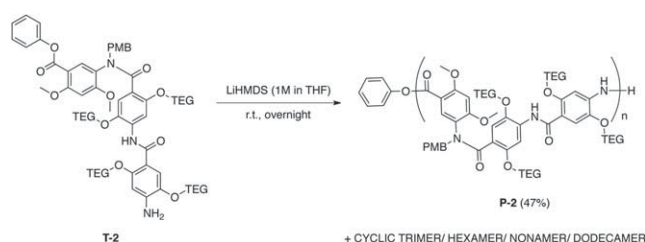
the Supporting Information). To avoid cycle formation we synthesized mono-PMB-protected trimer, **T-2** (Scheme 3) in order to create a longer distance between the reactive centers rendering a macrocyclization geometrically unfavorable. The results of the polycondensation of the mono-PMB-protected oligomer **T-2** are presented in the next section.

Synthesis and Polymerization of the Mono-PMB-Protected Trimer **T-2**

The synthetic route toward the mono-*N*-protected trimer **T-2** (Scheme 3) followed the same iterative coupling strategy as **T-1** (Scheme 1), using two unprotected, linear monomers and one bent monomer. The reaction between **1** and **L-1** yielded the unprotected, linear dimer **4** (79%), which could be coupled with **B-1** to the trimer **5** (86%). **5** was reduced by the use of tin(II)chloride dihydrate in DMF at 40 °C for three days. Purification via recycling HPLC gave the mono-PMB-protected trimer **T-2** in 22% yield. The final product was thoroughly investigated by 1D and 2D NMR spectroscopy and the results can be found in the Supporting Information.

The polycondensation of trimer **T-2** was carried out at a very high monomer concentration: 3.2 eq. of LiHMDS (1M in THF) were added to **T-2** in one portion under vigorous stirring (Scheme 4).

After 18 h of reaction time at r.t., the reaction mixture was analyzed by GPC (chloroform) which revealed the formation of low molecular weight cycles and a higher molecular weight fraction (Fig. 2, red). The comparison with the GPC-elugram of the cyclic trimer **P-1** (Fig. 2, black) emphasizes



SCHEME 4 Polycondensation of the mono-PMB-protected trimer **T-2**, resulting in the formation of macrocycles and polymer **P-2**. PMB, p-methoxybenzyl; TEG, triethylene glycol.

the enhancement of the molecular weight, based on the choice of the trimer. The low molecular weight part of the GPC elugram of **P-2** clearly resolves the formed cyclic oligomers (Fig. 2 red, 19.5–22 min.).

In an attempt to prevent the formation of cycles, a second polymerization of trimer **T-2** was carried out at -10 °C. Unfortunately, efficient stirring of the solution was not possible due to the very high viscosity of **T-2**. After 10 min, we therefore warmed the mixture to room temperature and received a similar result as for the first polymerization. The GPC (chloroform) analysis indicated the formation of both low molecular weight cycles and polymers, the polymer fraction however increased compared to the result of the first polymerization (Fig. S29 in the Supporting Information).

The formation of cycles was confirmed by MALDI-ToF MS analysis (Figs. S30 and S31 in the Supporting Information). Contrary to the polymerization of the di-PMB-protected trimer **T-1**, in which only cyclic trimers were formed, several larger cycles, namely the cyclic hexamer, nonamer, and dodecamer could also be observed.

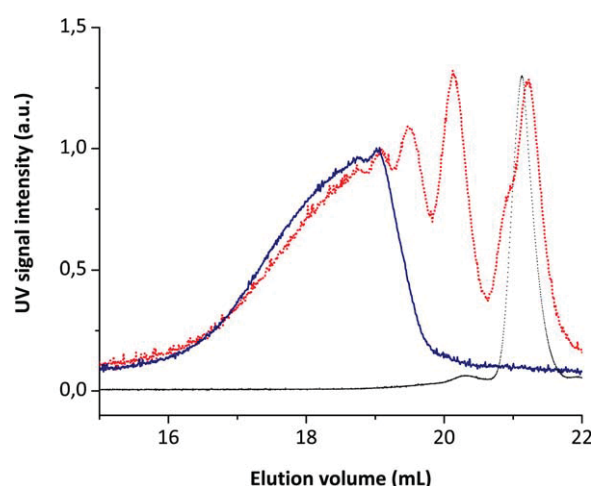


FIGURE 2 Mass distribution of the polymer **P-2** determined by GPC (chloroform) before (red) and after (blue) recycling GPC in comparison with the mass distribution of the cyclic trimer **P-1** (black). [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://www.wileyonlinelibrary.com).]

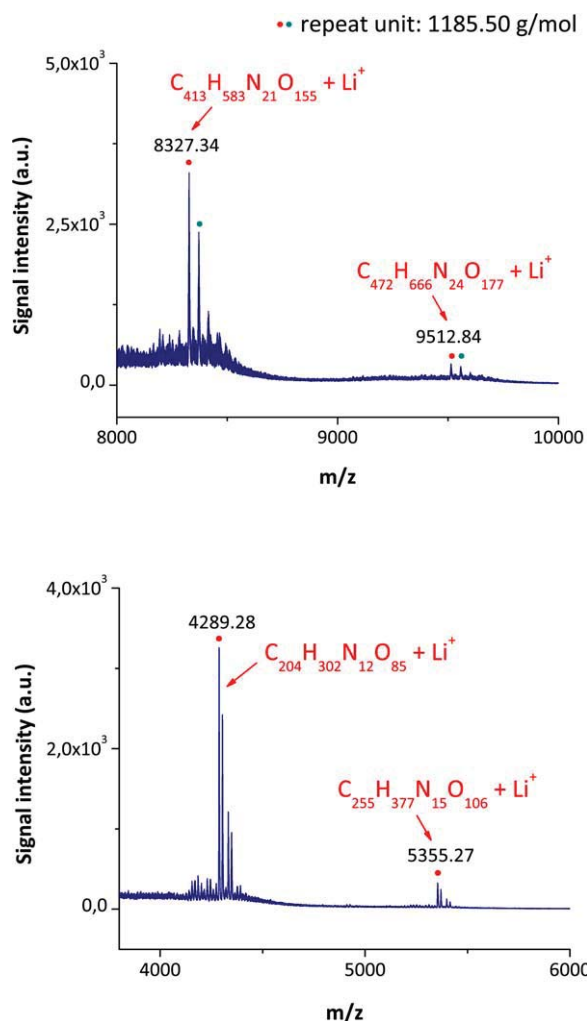


FIGURE 3 Top: MALDI-ToF mass spectrum (section) of the higher molecular weight polymers built in polymerization **P-2** (Li^+ -adducts). The 7-mer and 8-mer of the trimeric monomer are shown. Bottom: MALDI-ToF mass spectrum (section) of the deprotected, helical polymer **H-1** (Li^+ -adducts). The 4-mer and 5-mer of the trimeric monomer are shown. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://www.wileyonlinelibrary.com).]

Two *cis*-amide conformations (with respect to the phenyl rings) are essential for the ring closure of a tribenzamide to occur. We therefore hypothesize that the amide anion, which is formed by deprotonation with LiHMDS during the poly-

condensation, might exist in an *E/Z*-equilibrium (Scheme S2 in the Supporting Information) facilitating the macrocyclization. This phenomenon is currently investigated in our group.

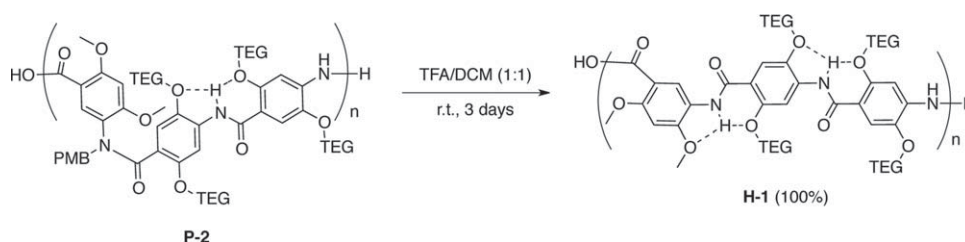
To isolate the higher molecular weight fraction corresponding to the polymer **P-2**, preparative GPC in chloroform was carried out. Analysis of the separated polymer fraction (Fig. 2, blue) via analytical GPC (chloroform), gave a molecular weight of $M_n = 7000$ g/mol and $M_w = 11,100$ g/mol. The MALDI-ToF mass spectrum of the higher molecular weight fraction is shown in Figure 3 (top) and verifies the formation of **P-2** by displaying the exact repeat unit of the trimer **T-2** of 1185.50 g/mol (see also Fig. S32 in the Supporting Information).

The major peaks could be assigned to the Li-salt of the polymer carrying a carboxylic acid and an amine as end groups. The polymer with the isotopic (all ^{12}C) mass of 8327.34 g/mol consists of exactly seven repeat units, the one with the isotopic (all ^{12}C) mass of 9512.84 g/mol exactly of eight repeat units. The longest polymer chain detected by MALDI-ToF MS analysis therefore consists of 24 aromatic amino acids. Further NMR-characterization of the polymer **P-2** is reported in the Supporting Information.

Deprotection of the Polymer

The cleavage of the protecting groups of polymer **P-2** was achieved by treatment with trifluoroacetic acid in dichloromethane [1:1 (vol:vol) mixture] for three days at room temperature (Scheme 5).

After deprotection, the polymer **H-1** showed a drastically modified solubility in organic solvents compared to polymer **P-2**. It was insoluble and swelled in chlorinated solvents such as chloroform and dichloromethane, but it was soluble in THF, DMSO, acetone, and (2R,3R)-butane-2,3-diol. Therefore, a direct comparison of the GPC elugrams in chloroform was not possible. The GPC (THF) elugram of polymer **H-1** shows a significant shift toward higher molecular weights (Fig. 5) compared to the elugram of polymer **P-2**. This shift could be an indication for the proposed structural change from coil-like to helical, which the polymer is expected to undergo upon amide *N*-deprotection. The coil-like structure of polymer **P-2** is expected to convert into a helix through the formation of the intramolecular hydrogen bonding pattern along the backbone of polymer **H-1**. The proposed



SCHEME 5 Cleavage of the amide *N*-PMB-protecting groups by treatment with trifluoroacetic acid. PMB, p-methoxybenzyl; TEG, triethylene glycol.

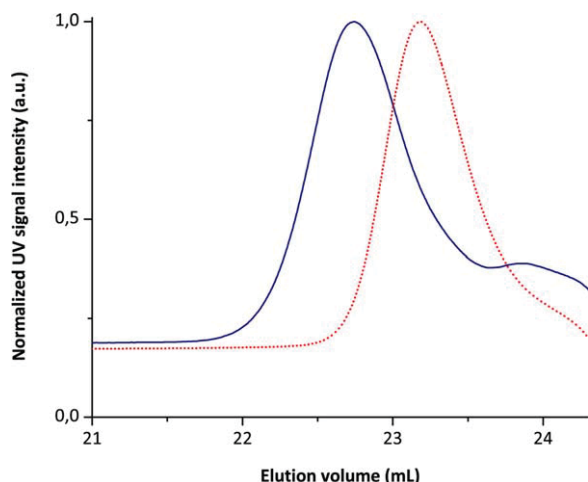


FIGURE 4 GPC (THF) elograms of polymer **P-2** (red) before and polymer **H-1** (blue) after amide *N*-deprotection. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

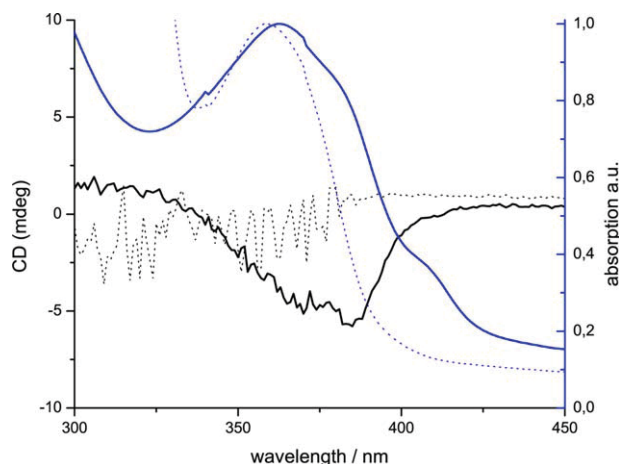


FIGURE 6 Normalized UV absorption (blue) and circular dichroism spectra (black) of polymer **H-1** dissolved in (*2R,3R*)-butane-2,3-diol (1.9 mg/mL, solid lines) and acetone (0.75 mg/mL, dotted lines). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

(rigid) helical polymer even of low molecular weight would exhibit a large excluded inner volume and could thereby elute at an earlier retention time in the GPC run.

In order to obtain further data points that could support the helix hypothesis, we dissolved the polymer **H-1** in acetone (1.7 mg in 1.8 g solvent) and (*2R,3R*)-butane-2,3-diol (2.4 mg in 1.22 g solvent). The solutions were sonicated for 5 min, filtrated through syringe filters (pore size 0.45 μm) and the clear solutions investigated by circular dichroism (CD) and ultraviolet (UV) absorption spectroscopy (normal-

ized), as can be seen in Figure 6. While the acetone solution did not give any significant CD signal, the (*2R,3R*)-butane-2,3-diol solution showed a clear, albeit small circular dichroism signal. We believe that the chiral solvent interacts with the polymer **H-1** thereby slightly favoring the formation of either a plus or minus helix. We believe that this slight enantiomeric excess gives rise to the observed CD-spectrum in Figure 6.

Both, the shift in the gpc elugram (Fig. 5) as well as the CD signal in a chiral solvent (Fig. 5) support the hypothesis of a helical shape of **H-1** but do not provide unambiguous evidence. We are currently investigating the improvement in polymerization conditions to obtain larger sample amounts in the future for more detailed and thorough analytical investigations.

Furthermore, MALDI-ToF MS analysis verified the successful cleavage of the amide *N*-PMB-protecting groups by displaying a repeat unit of 1065.99 g/mol, which corresponds to the *N*-deprotected trimer (Fig. 3, bottom). The polymer was predominantly detected as the Li-ion-adduct.

Figure 5 shows one helical turn of a hypothetical helical polymer **H-1**, for which we calculated an inner diameter of around 4 nm (based on a molecular mechanics model), in accordance with data on helical structures or macrocycles built from *meta-para*-linked oligoamides known from the literature.^{3(g),17}

CONCLUSIONS

A new synthetic strategy toward segmented polyaramides that might adopt a helical shape has been described. We have developed a synthetic route, in which we combined the sequence-controlled synthesis of bent, shape-persistent tri-benzamides with their polycondensation. This combination

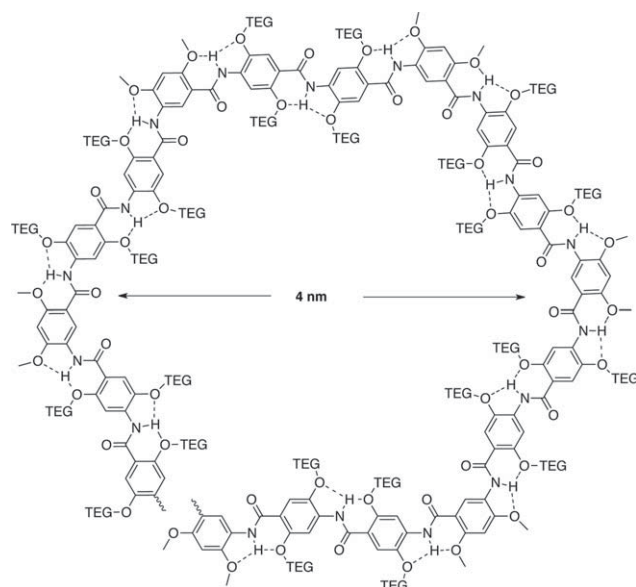


FIGURE 5 Model structure of one helical turn of a hypothetical helical polymer **H-1** with a calculated inner diameter of around 4 nm. In this representation six repeat units are necessary to create one full turn, the presence of eight repeat units was confirmed by MALDI ToF MS (Fig. 3, top). TEG, triethylene glycol.

has the advantage of being able to reach higher molecular weights than organic synthesis alone. Furthermore, it would in principle be possible to determine the inner diameter of such an assumed helix by the number of linear monomers incorporated into the oligomeric precursor. In this publication we report the synthesis and characterization of two *bis*-substituted tribenzamides consisting of one bent and two linear monomers. Triethylene glycol side chains and *N*-amide protecting groups were attached to the oligoaramides to enhance their organo solubility. Moreover, the protecting groups could selectively be cleaved by addition of acid after polymerization of the trimers. The two trimers, namely the mono- and di-PMB-protected *bis*-substituted tri(benz-amide)s showed significantly different results in their polycondensation reactions. The fully protected trimer predominantly formed cyclic trimers upon addition of LiHMDS. The preorganizational effect of the rigid aromatic backbone caused by the preference for the *E*-conformation of the tertiary, protected amide bonds facilitated the macrocyclization reaction. As expected, the polycondensation of the more rigid, mono-protected trimer generated polymers in addition to cycles. Separation of the coil-like polymers by means of preparative GPC and subsequent cleavage of the PMB-protecting groups by treatment with trifluoroacetic acid yielded a polymer for which we hypothesize a helical geometry. The molecular composition of the final compound was validated by MALDI-ToF analysis. A dramatic change in hydrodynamic radius could be observed by gpc analysis upon PMB-deprotection of the obtained polymer. Circular dichroism spectroscopy of the PMB-deprotected polymer in a chiral solvent showed a small but significant CD-signal indicating the formation of an enantiomeric excess of a chiral superstructure in a chiral solvent.

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REFERENCES AND NOTES

- 1 D. Voet, J. G. Voet, C. W. Pratt, *Lehrbuch der Biochemie*, 3rd ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, **2002**.
- 2 (a) J. M. Lehn, *Angew. Chem. Int. Ed.* **1990**, *29*, 1304–1319; (b) D. Philp, J. F. Stoddart, *Angew. Chem. Int. Ed.* **1996**, *35*, 1154–1196; (c) L. Brunsveld, B. J. B. Folmer, E. W. Meijer, R. P. Sijbesma, *Chem. Rev.* **2001**, *101*, 4071–4097; (d) J. M. Lehn, *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 4763–4768; (e) A. R. Sanford, K. Yamato, X. Yang, L. Yuan, Y. Han, B. Gong, *Eur. J. Biochem.* **2004**, *271*, 1416–1425.
- 3 (a) Y. Hamuro, S. J. Geib, A. D. Hamilton, *J. Am. Chem. Soc.* **1996**, *118*, 7529–7541; (b) B. Gong, Y. F. Yan, H. Q. Zeng, E. Skrzypczak-Jankun, Y. W. Kim, J. Zhu, H. Ickes, *J. Am. Chem. Soc.* **1999**, *121*, 5607–5608; (c) I. Huc, *Eur. J. Org. Chem.* **2004**, **2004**, 17–29; (d) I. Huc, L. Cuccia, *Foldamers: Structure, Properties and Applications*; S. Hecht, I. Huc, Eds.; Wiley-VCH Verlag & Co. KGaA: Weinheim, **2007**; (e) J. Zhu, J.-B. Lin, Y.-X. Xu, X.-K. Jiang, Z.-T. Li, *Tetrahedron* **2006**, *62*, 11933–11941; (f) B. Gong, A. R. Sanford, J. S. Ferguson, In *Oligomers Polymer Composites Molecular Imprinting*, *Advances in Polymer Science*, Springer-Verlag Berlin: Berlin, **2007**; Vol. *206*, pp 1–29; (g) B. Gong, *Acc. Chem. Res.* **2008**, *41*, 1376–1386; (h) X. Zhao, Z. T. Li, *Chem. Commun.* **2010**, *46*, 1601–1616; (i) D. W. Zhang, X. Zhao, J. L. Hou, Z. T. Li, *Chem. Rev.* **2012**, *112*, 5271–5316; (j) M. Waki, H. Abe, M. Inouye, *Chem. Eur. J.* **2006**, *12*, 7839–7847.
- 4 (a) C. Dolain, A. Grelard, M. Laguerre, H. Jiang, V. Maurizot, I. Huc, *Chem. Eur. J.* **2005**, *11*, 6135–6144; (b) Y. Tanaka, H. Katagiri, Y. Furusho, E. Yashima, *Angew. Chem. Int. Ed.* **2005**, *44*, 3867–3870; (c) N. Delsuc, T. Kawanami, J. Lefeuvre, A. Shundo, H. Ihara, M. Takafuji, I. Huc, *ChemPhysChem* **2008**, *9*, 1882–1890; (d) E. Yashima, K. Maeda, Y. Furusho, *Acc. Chem. Res.* **2008**, *41*, 1166–1180; (e) E. Yashima, K. Maeda, H. Iida, Y. Furusho, K. Nagai, *Chem. Rev.* **2009**, *109*, 6102–6211; (f) D. Zornik, R. M. Meudtner, T. El Malah, C. M. Thiele, S. Hecht, *Chem. Eur. J.* **2011**, *17*, 1473–1484; (g) H. J. Schneider, *Angew. Chem. Int. Ed.* **2009**, *48*, 3924–3977.
- 5 (a) J. C. Nelson, J. G. Saven, J. S. Moore, P. G. Wolynes, *Science* **1997**, *277*, 1793–1796; (b) T. Nakano, Y. Okamoto, *Chem. Rev.* **2001**, *101*, 4013–4038; (c) D. J. Hill, J. S. Moore, *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 5053–5057; (d) R. W. Sinkeldam, M. H. van Houtem, K. Pieterse, J. A. Vekemans, E. W. Meijer, *Chemistry* **2006**, *12*, 6129–6137; (e) K. Mikami, A. Tanatani, A. Yokoyama, T. Yokozawa, *Macromolecules* **2009**, *42*, 3849–3851; (f) Z. Yu, S. Hecht, *Angew. Chem. Int. Ed.* **2011**, *50*, 1640–1643; (g) T. Qi, V. Maurizot, H. Noguchi, T. Charoenraks, B. Kauffmann, M. Takafuji, H. Ihara, I. Huc, *Chem. Commun.* **2012**, *48*, 6337–6339; (h) K. Mikami, T. Yokozawa, *J. Polym. Sci. Part A: Polym. Chem.* **2013**, *51*, 739–742.
- 6 (a) V. Berl, I. Huc, R. G. Khoury, M. J. Krische, J. M. Lehn, *Nature* **2000**, *407*, 720–723; (b) D. Haldar, H. Jiang, J. M. Leger, I. Huc, *Angew. Chem. Int. Ed.* **2006**, *45*, 5483–5486; (c) N. Delsuc, L. Poniman, J.-M. Léger, Huc, I., *Tetrahedron* **2012**, *68*, 4464–4469; (d) Y. Yang, W. Feng, J. Hu, S. Zou, R. Gao, K. Yamato, M. Kline, Z. Cai, Y. Gao, Y. Wang, Y. Li, Y. Yang, L. Yuan, X. C. Zeng, B. Gong, *J. Am. Chem. Soc.* **2011**, *133*, 18590–18593.
- 7 C. Dolain, H. Jiang, J. M. Leger, P. Guionneau, I. Huc, *J. Am. Chem. Soc.* **2005**, *127*, 12943–12951.
- 8 (a) J.-M. Lehn, A. Rigault, *Angew. Chem.* **1988**, *100*, 1121–1122; (b) R. B. Prince, T. Okada, J. S. Moore, *Angew. Chem. Int. Ed.* **1999**, *38*, 233–236; (c) M. Albrecht, *Angew. Chem. Int. Ed.* **2005**, *44*, 6448–6451; (d) R. M. Meudtner, M. Ostermeier, R. Goddard, C. Limberg, S. Hecht, *Chemistry* **2007**, *13*, 9834–9840.
- 9 (a) G. S. Hanan, J.-M. Lehn, N. Kyritsakas, J. Fischer, *J. Chem. Soc. Chem. Commun.* **1995**, 765; (b) V. Berl, I. Huc, R. G. Khoury, J. M. Lehn, *Chem. Eur. J.* **2001**, *7*, 2798–2809; (c) Y. Ferrand, A. M. Kendhale, J. Garric, B. Kauffmann, I. Huc, *Angew. Chem. Int. Ed.* **2010**, *49*, 1778–1781; (d) G. Guichard, I. Huc, *Chem. Commun.* **2011**, *47*, 5933–5941; (e) M. Banno, T. Yamaguchi, K. Nagai, C. Kaiser, S. Hecht, E. Yashima, *J. Am. Chem. Soc.* **2012**, *134*, 8718–8728; (f) W. Makiguchi, S. Kobayashi, Y. Furusho, E. Yashima, *Angew. Chem. Int. Ed.* **2013**, *52*, 5275–5279.
- 10 (a) N. Sakai, J. Mareda, S. Matile, *Acc. Chem. Res.* **2005**, *38*, 79–87; (b) A. J. Helsel, A. L. Brown, K. Yamato, W. Feng, L. H. Yuan, A. J. Clements, S. V. Harding, G. Szabo, Z. F. Shao, B. Gong, *J. Am. Chem. Soc.* **2008**, *130*, 15784–+; (c) F. Wang, L. Qin, C. J. Pace, P. Wong, R. Malonis, J. Gao, *ChemBioChem* **2012**, *13*, 51–55.
- 11 (a) S. H. Gellman, *Acc. Chem. Res.* **1998**, *31*, 173–180; (b) A. R. Sanford, B. Gong, *Curr. Org. Chem.* **2003**, *7*, 1649–1659; (c) I. Saraogi, A. D. Hamilton, *Chem. Soc. Rev.* **2009**, *38*, 1726–1743; (d) D. H. Appella, L. A. Christianson, I. L. Karle, D. R. Powell, S. H. Gellman, *J. Am. Chem. Soc.* **1996**, *118*, 13071–13072; (e) X.

- Li, D. Yang, *Chem. Commun.* **2006**, 3367–3379; (f) J. Fremaux, L. Fischer, T. Arbogast, B. Kauffmann, G. Guichard, *Angew. Chem. Int. Ed.* **2011**, *50*, 11382–11385; (g) W. S. Horne, S. H. Gellman, *Acc. Chem. Res.* **2008**, *41*, 1399–1408.
- 12** (a) J. J. Cornelissen, J. J. Donners, R. de Gelder, W. S. Graswinckel, G. A. Metselaar, A. E. Rowan, N. A. Sommerdijk, R. J. Nolte, *Science* **2001**, *293*, 676–680; (b) L. A. Cuccia, R. Eliseo, J.-M. Lehn, J.-C. Homo, M. Schmutz, *Chem. Eur. J.* **2002**, *8*, 3448–3457; (c) D. Seebach, M. Overhand, F. N. M. Kühnle, B. Martinoni, L. Oberer, U. Hommel, H. Widmer, *Helv. Chim. Acta* **1996**, *79*, 913–941; (d) A. Violette, M. C. Averlant-Petit, V. Semetey, C. Hemmerlin, R. Casimir, R. Graff, M. Marraud, J.-P. Briand, D. Rognan, G. Guichard, *J. Am. Chem. Soc.* **2005**, *127*, 2156–2164; (e) J. M. Rodriguez, A. D. Hamilton, *Angew. Chem. Int. Ed.* **2007**, *46*, 8614–8617; (f) I. Saraogi, C. D. Incarvito, A. D. Hamilton, *Angew. Chem. Int. Ed.* **2008**, *47*, 9691–9694; (g) J. M. Davis, L. K. Tsou, A. D. Hamilton, *Chem. Soc. Rev.* **2007**, *36*, 326–334; (h) Z. Chen, N. D. Urban, Y. Gao, W. Zhang, J. Deng, J. Zhu, X. C. Zeng, B. Gong, *Org. Lett.* **2011**, *13*, 4008–4011.
- 13** (a) R. D. Parra, H. Zeng, J. Zhu, C. Zheng, X. C. Zeng, B. Gong, *Chem. Eur. J.* **2001**, *7*, 4352–4357; (b) L. H. Yuan, H. Q. Zeng, K. Yamato, A. R. Sanford, W. Feng, H. S. Atreya, D. K. Sukumaran, T. Szyperski, B. Gong, *J. Am. Chem. Soc.* **2004**, *126*, 16528–16537; (c) B. Gong, *Chem. Eur. J.* **2001**, *7*, 4336–4342.
- 14** J. Zhu, R. D. Parra, H. Zeng, E. Skrzypczak-Jankun, X. C. Zeng, B. Gong, *J. Am. Chem. Soc.* **2000**, *122*, 4219–4220.
- 15** J. Garric, J. M. Leger, I. Huc, *Angew. Chem. Int. Ed.* **2005**, *44*, 1954–1958.
- 16** (a) J. Garric, J. M. Leger, I. Huc, *Chem. Eur. J.* **2007**, *13*, 8454–8462; (b) H. Juwarker, J. M. Suk, K. S. Jeong, *Chem. Soc. Rev.* **2009**, *38*, 3316–3325; (c) B. Qin, C. L. Ren, R. J. Ye, C. Sun, K. Chiad, X. Y. Chen, Z. Li, F. Xue, H. B. Su, G. A. Chass, H. Q. Zeng, *J. Am. Chem. Soc.* **2010**, *132*, 9564–9566; (d) Q. Gan, Y. Ferrand, C. Bao, B. Kauffmann, A. Grelard, H. Jiang, I. Huc, *Science* **2011**, *331*, 1172–1175; (e) Y. Ferrand, N. Chandramouli, A. M. Kendhale, C. Aube, B. Kauffmann, A. Grelard, M. Laguerre, D. Dubreuil, I. Huc, *J. Am. Chem. Soc.* **2012**, *134*, 11282–11288; (f) Q. Gan, Y. Ferrand, N. Chandramouli, B. Kauffmann, C. Aube, D. Dubreuil, I. Huc, *J. Am. Chem. Soc.* **2012**, *134*, 15656–15659.
- 17** B. Gong, H. Zeng, J. Zhu, L. Yuan, Y. Han, S. Cheng, M. Furukawa, R. D. Parra, A. Y. Kovalevsky, J. L. Mills, E. Skrzypczak-Jankun, S. Martinovic, R. D. Smith, C. Zheng, T. Szyperski, X. C. Zeng, *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 11583–11588.
- 18** J. Cao, M. Kline, Z. Chen, B. Luan, M. Lv, W. Zhang, C. Lian, Q. Wang, Q. Huang, X. Wei, J. Deng, J. Zhu, B. Gong, *Chem. Commun.* **2012**, *48*, 11112–11114.
- 19** (a) H. Seyler, A. Kilbinger, *Tetrahedron Lett.* **2013**, *54*, 753–756; (b) H. Seyler, A. F. M. Kilbinger, *Macromolecules* **2009**, *42*, 9141–9146; (c) H. Seyler, A. F. M. Kilbinger, *Macromolecules* **2010**, *43*, 5659–5664; (d) C. Storz, M. Schulze, A. F. M. Kilbinger, *Macromol. Rapid Commun.* **2011**, *32*, 238–244.
- 20** A. Zhang, J. S. Ferguson, K. Yamato, C. Zheng, B. Gong, *Org. Lett.* **2006**, *8*, 5117–5120.
- 21** M. Schulze, B. Michen, A. Fink, A. F. M. Kilbinger, *Macromolecules* **2013**, *46*, 5520–5530.
- 22** T. Yokozawa, T. Asai, R. Sugi, S. Ishigooka, S. Hiraoka, *J. Am. Chem. Soc.* **2000**, *122*, 8313–8314.
- 23** (a) H. Seyler, E. Berger-Nicoletti, A. F. M. Kilbinger, *J. Mater. Chem.* **2007**, *17*, 1954–1957; (b) H. M. König, R. Abbel, D. Schollmeyer, A. F. M. Kilbinger, *Org. Lett.* **2006**, *8*, 1819–1822.