Increasing the Functional Group Diversity in Helical β-Peptoids: Achievement of Solvent- and pH-Dependent Folding

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Abstract: We report the synthesis of a series of bis-functionalized β-peptoid oligomers of the hexamer length. This was achieved by synthesizing and incorporating protected amino- or azido-functionalized chiral building blocks into precursor oligomers by a trimer segment coupling strategy. The resulting hexamers were readily elaborated to provide target compounds displaying amino groups, carboxy groups, hydroxy groups, or triazolo-pyridines, which should enable metal ion binding. Analysis of the novel hexamers by CD spectroscopy and HSQC NMR spectroscopy revealed robust helical folding propensity in acetonitrile. CD analysis showed solvent-dependent degree of helical content in the structural ensembles when adding different ratios of protic solvents including aqueous buffer. These studies were enabled by the substantial increase in solubility compared to previously analyzed β-peptoid oligomers. This also allowed for investigation of the effect of pH on folding propensity of the amino- and carboxy-functionalized oligomers, respectively. Interestingly, we could demonstrate a reversible effect of sequentially adding acid and base, resulting in a switching between compositions of folded ensembles with varying helical content. We envision that the present discoveries can form the basis for the development of functional peptidomimetic materials responsive to external stimuli.

INTRODUCTION

Abiotic oligomers with the ability to adopt secondary structures that either mimic or complement those of biopolymers found in nature have been termed *foldamers*.[1-8] Minimal permutations to the peptide/protein backbone architecture have resulted in the design and intensive investigation of β-peptides[9-15] and α-peptoids,[16-18] which has also led to a combination of these features to garner β-peptoids (oligomers of *N*-alkyl-β-alanine residues)[19-34] (see Figure 1). Peptoids of both the α- and β-type share the tertiary amide bond structural element, which gives rise to isomerization between *transoid* and *cisoid* conformations, termed *trans*-amide and *cis*-amide bonds, respectively. Inspired by detailed studies of the *trans–cis*-amide equilibria of proline residues,[35-38] efforts have also been directed towards the development of methods to control these ratios in α- and β-peptoids.[39-49] Still, only a limited number of examples of high-resolution structures of folded oligomers have been solved,[50-58] underlining the continued challenge of achieving structure-based design of oligomeric peptoids. We reported the *N*-(*S*)-1-(1-naphthyl)ethyl (*N*s1npe, **1**) side chain to promote formation of triangular prism-shaped β-peptoid helical structure of oligomer **2**,[31,53] and recently elaborated upon this highly *cis*-amide bond-inducing side chain to incorporate longer hydrocarbons (**3**) and amino groups.[55] Gratifyingly, this led to oligomers with retained helical content and significantly increased solubility, allowing for more efficient synthesis and characterization in multiple solvents. Here we report considerable expansion of the available selection of functional groups, including an azide-containing building block, which allows for ready functionalization of the foldamer surface by Cu(I)-catalyzed azide–alkyne cycloaddition "click" chemistry (**4**).[59-60] Thus, hexamers containing positive charges, negative charges, hydroxy groups, and metal-chelators were synthesized and evaluated using HSQC NMR spectroscopy to determine $K_{cis/trans}$ overall ratios and by CD spectroscopy. This is the first time that folding behavior of well-defined peptoid helices – designed to display multiple functional groups with high precision in three-dimensional space – has been investigated in response to external stimuli. The folding propensity was perturbed under a variety of conditions, including different solvents, buffer, and acid–base titrations, revealing a varying sensitivity to aqueous medium, acid, and base, depending on the nature of the side chains. We envision that the future development of functional materials or catalysts based on this framework may therefore be designed to be responsive to external stimuli.

Finally, although there is a rich body of literature describing the synthesis of chiral amines,[61-71] only few examples of peptoid syntheses incorporating custom made chiral building blocks have been reported previously and it is therefore our hope that the novel monomer building blocks prepared here, will find use in additional studies of peptoids in the future.

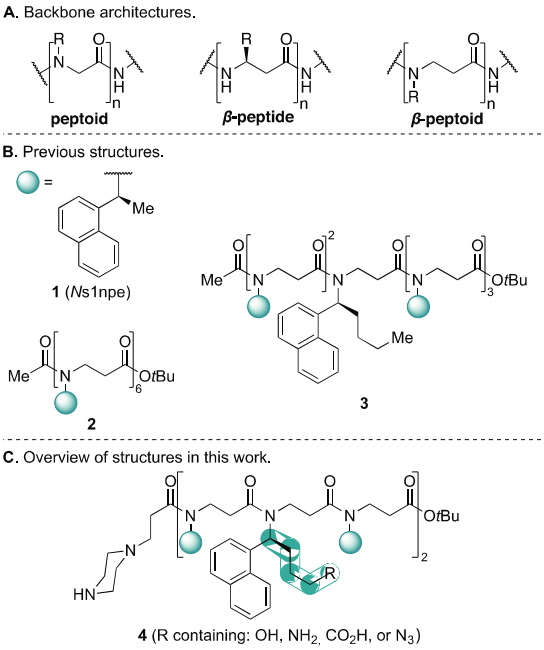
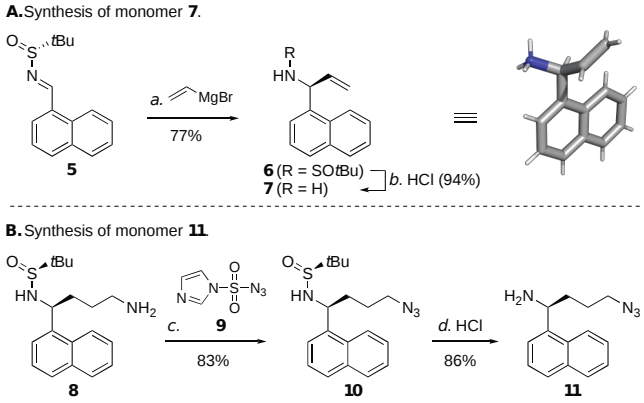


Figure 1. (**A**) Backbone architectures. (**B**) Structures of the *N*s1npe side chain (**1**) and parent compounds (**2** and **3**). (**C**) Current molecular designs (**4**).

RESULTS AND DISCUSSION

Building Block Synthesis. Initially, we designed two building blocks that could be further functionalized, either at building block stage or post-oligomer synthesis. As groups for further elaboration, we chose the olefin **7** and the azide **11**. Similar to our previous synthesis of N^4-Alloc-1,4-diamino-1-(1-naphthyl)-butane,[55] we applied a diastereoselective Ellman-type Mannich reaction[67,72-74] to achieve control of the stereochemistry. For the addition of vinyl Grignard to the *tert*-butylsulfinimine **5** in order to obtain the desired *S*-configuration of the building block **7**, the *R*-configuration of the auxiliary was needed as it leads to the required chelated transition state in non-coordinating solvents.[67] After auxiliary cleavage, the absolute stereochemistry was determined by single crystal X-ray diffraction crystallography (Scheme 1A). To demonstrate the versatility of the vinyl side chain, we performed a cross-metathesis and a hydroboration reaction, leading to a methyl ester-protected (Scheme S1A) and a hydroxy group-containing side chain (Scheme S1B), respectively. However, auxiliary cleavage under acidic conditions was not compatible with the methyl ester and led to deprotection. We therefore decided to continue with a versatile azide-containing building block instead, which we envisioned would be more stable under the applied conditions and eliminate the need for additional protecting groups. Thus, starting from the previously prepared 1,4-diaminobutane (putrescine) precursor (**8**), the azide-containing building block **11** was synthesized in two steps (Scheme 1B). With the building block **11** in hand as well as the previously designed Alloc protected putrescine analogue, we synthesized a series of hexamers, incorporating functional groups with different properties.

Scheme 1. Synthesis of Building Blocks 7 and 11.[a]



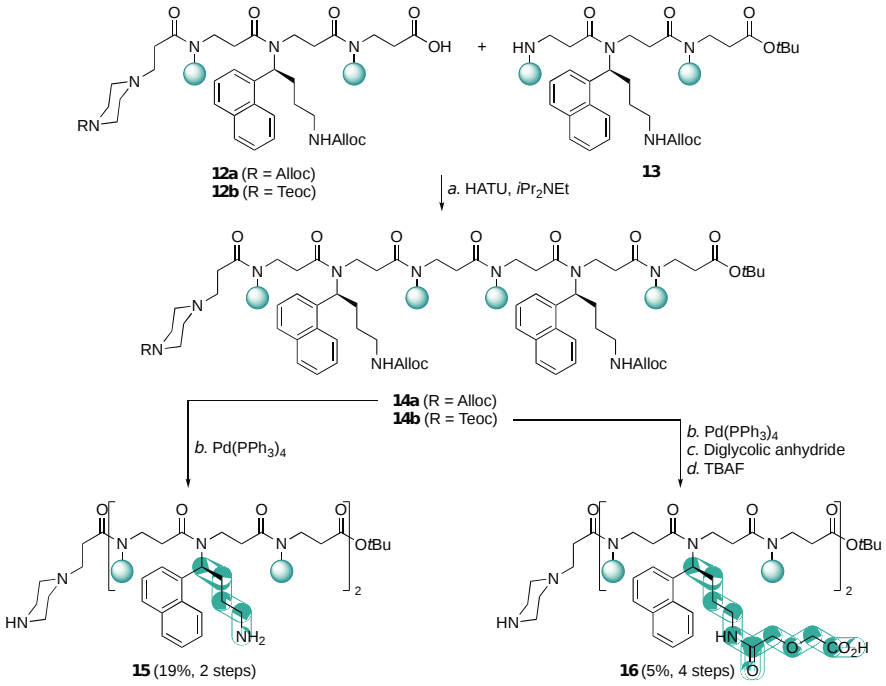
[a]*Reagents and conditions:* (a) Vinylmagnesium bromide (2 equiv), toluene, N_2, –20 °C → rt, 3 h; (b) 2 M HCl in Et_2O–MeOH 1:1, rt, 1 h; (c) **9** (1.7 equiv), K_2CO_3 (1.8 equiv), $CuSO_4$ (0.01 equiv), rt, 18 h; (d) 2 M HCl in Et_2O−MeOH 1:1, rt, 1 h.

Oligomer Design and Synthesis. In our previous study, we observed a positive effect on solubility as well as a retained folding propensity when incorporating a piperazine-containing N-terminal capping group,[55] as originally reported by Maayan and co-workers.[75] We therefore decided to add this feature to all oligomer designs in the current study. It was also decided to apply the previously developed synthetic strategy based on trimer segment couplings. Synthesis of the two bis-functionalized hexamers **15** and **16** was enabled by preparing two N-terminal trimer building blocks with varying protecting groups (**12a** and **12b**) to allow for subsequent diversification (see Scheme S2 and S3 for building block synthesis). Both of these were then coupled to the C-terminal trimer **13** using HATU as the coupling reagent to give **14a** and **14b**, respectively (Scheme 2). Subsequent deprotection of hexamer **14a** gave rise to the amino-functionalized hexamer **15** and removal of the Alloc groups of **14b** allowed for elaboration of the side chains to give carboxy-functionalized hexamer **16** (Scheme 2). Here, we chose diglycolate to increase the solubility further compared to functionalization with purely hydrocarbon-based dicarboxylic acids such as succinate or glutarate. The synthesis of oligomer **16** required three purification steps by preparative HPLC and unexpectedly long reaction times for the removal of the Teoc group using fluoride. Together, these challenges caused the recovery of compound **16** in a somewhat lower yield than usually achieved applying this segment coupling strategy.

Incorporating building block **11** into similarly designed trimers **17** and **18** (Scheme S2 and S3) then enabled synthesis of bis-azide-containing hexamer (**19**) in good yield using HATU as the coupling reagent (Scheme 3). This common intermediate could then undergo Cu(I)-catalyzed azide–alkyne cycloaddition "click" chemistry with different alkynes, followed by N-terminal deprotection, to give hydroxy- and pyridyl-functionalized hexamers **20** and **21** (Scheme 3). It was envisioned that hexamer **20** would exhibit better solubility in polar solvents than the non-functionalized parent oligomer, while not being sensitive to pH with respect to its folding propensity. The compound **21** was designed to enable metal ion binding as previously

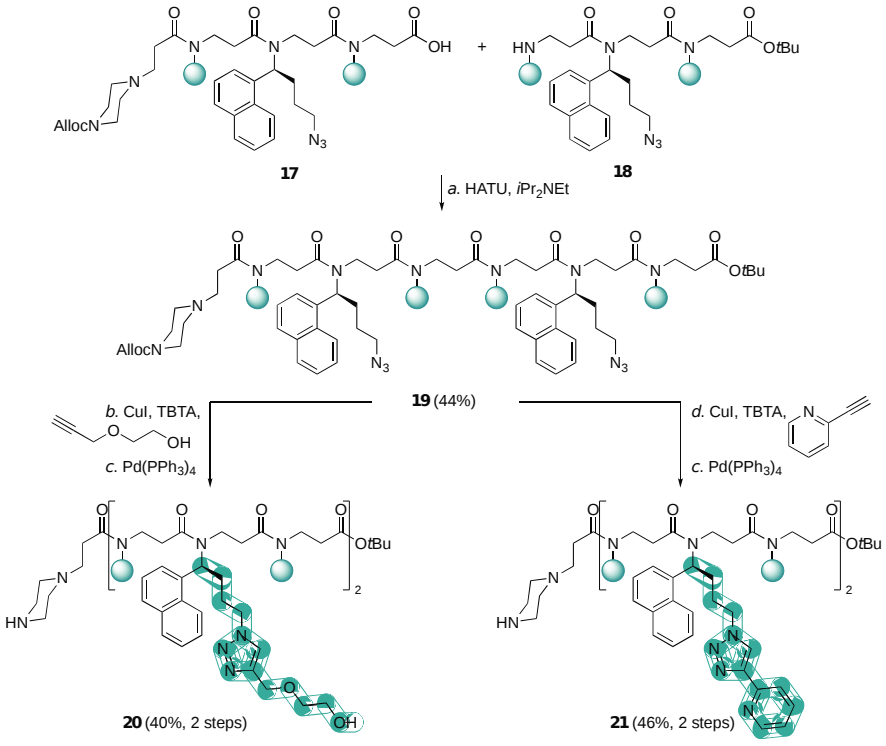
described for α-peptoids.[76] Indeed, all novel analogs exhibited a substantial increase in solubility in polar environment, as indicated by reduced retention times in analytical HPLC chromatograms (Figure S1).

Scheme 2. Synthesis of Amino- and Carboxy-Functionalized β-Peptoid Hexamers 15 and 16.[a]



[a]*Reagents and conditions:* (a) HATU (1.2 equiv), *i*Pr$_2$NEt (3 equiv), DMF–CH$_2$Cl$_2$ 1:1, rt, 18 h; (b) Pd(PPh$_3$)$_4$ (20 mol %), Me$_2$NH•BH$_3$ (20 equiv), CH$_2$Cl$_2$, rt, 4 h; (c) Diglycolic anhydride (4 equiv), *i*Pr$_2$NEt (5 equiv), N$_2$, CH$_2$Cl$_2$, rt, 2 h; (d) TBAF•3H$_2$O (15 equiv), THF, 37 °C, 3 d.

Scheme 3. Synthesis of Hydroxy- and Pyridyl-functionalized β-Peptoid Hexamers.[a]



[a]*Reagents and conditions*: (a) HATU (1.2 equiv), *i*Pr_2NEt (3 equiv), DMF–CH_2Cl_2 1:1, rt, 18 h; (b) 2-hydroxyethyl, 3-propynyl ether (2 equiv), CuI (0.2 equiv), TBTA (0.2 equiv), *i*Pr_2NEt (2 equiv), 2,6-lutidine (2 equiv), N_2, THF, rt, 1.5 h; (c) $Pd(PPh_3)_4$ (20 mol%), $Me_2NH{\bullet}BH_3$ (20 equiv), CH_2Cl_2, rt, 2 h; (d) 2-ethynylpyridine (2 equiv), CuI (0.2 equiv), TBTA (0.2 equiv), *i*Pr_2NEt (2 equiv), 2,6-lutidine (2 equiv), N_2, THF, rt, 1.5 h.

Assessment of Folding Propensity. The extent of helical secondary structure formation was investigated by CD spectroscopy (Figure 2) and the determination of overall $K_{cis/trans}$ values (Table 1). By comparison to data previously generated for parent compounds **2** and **3**, including CD spectroscopy, HSQC NMR spectroscopy, MD simulations and high-resolution X-ray diffraction crystal structures,[53,55] we could assess the propensity of the novel oligomers to adopt helical secondary structures under a range of conditions (i.e., different temperatures, solvents, and pH values).

As previously observed for amino-functionalized *β*-peptoids,[55] it was necessary to add base to a sample of compound **15** in acetonitrile in order to produce the signature CD curve demonstrated for parent compounds **2** and **3** indicating helical folding of the oligomer, i.e., showing a pronounced maximum at a wavelength of 232 nm (Figure S2). This observation is presumably due to the trifluoroacetic acid-containing buffer used for preparative HPLC purification of the final compounds, which leads to protonation of the amine side chains. Deprotonation by triethylamine addition results in a CD trace indicative of helical folding (Figure 2A, orange curve). As also previously demonstrated for amino-functionalized helices,[55] heating to 60 ºC could denature the folded state of **15** and cooling of the sample back to 25 °C resulted in refolding (Figure 2A). For the bis-carboxy-functionalized compound **16**, the structure-indicating maximum at 25 °C was significantly less intense and a new minimum seemed to appear at around 236 nm, even upon addition of acid or base (Figure S3). Interestingly, heating to 60 ºC still appeared to have a denaturing effect and upon cooling, the sample produced a helical signature CD spectrum (Figure 2B). This puzzling observation was reproduced several times and compound integrity upon heating was also demonstrated by LC-MS analysis (Figure S4). We therefore speculate that this carboxylate-containing hexamer may be locked in a non-helical conformation after the purification, which can then be disrupted upon heating to allow for the oligomer to refold into a helical conformation.

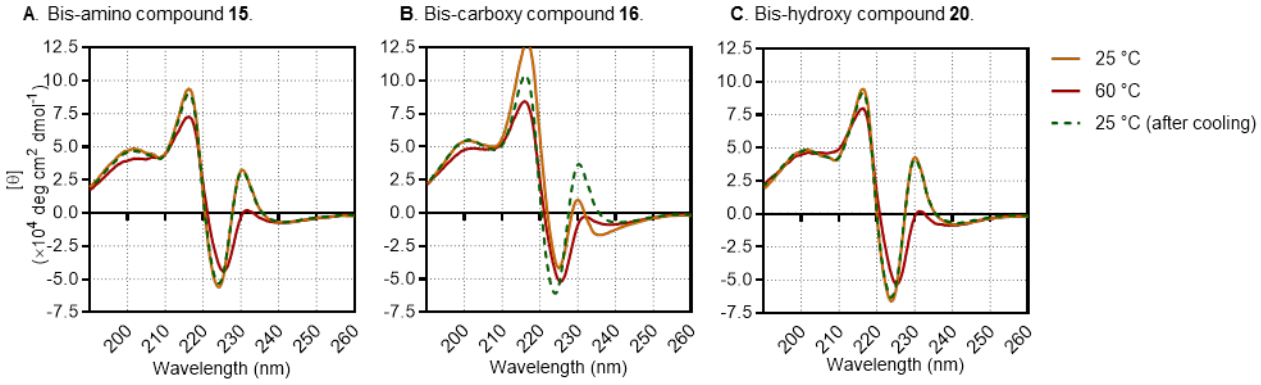


Figure 2. CD spectra of functionalized peptoids **15** (20 equiv. Et_3N added), **16**, and **20** at varying temperatures. All panels contain comparison of spectra measured at 60 °C as well as room temperature before and after heating. The spectra were measured in MeCN (50–59 μM). The mean residue molar ellipticity [θ] is normalized with regards to number of residues and peptoid concentration.

Finally, the bis-hydroxy-containing compound **20** exhibited the expected denaturing and refolding behavior upon heating and cooling of the sample, respectively (Figure 2C). This oligomer did not require addition of either base or acid to afford the CD spectrum expected for a helical β-peptoid (Figure S5). The bis-pyridyl-modified hexamer **21** also demonstrated the anticipated CD spectra of a denatured structure at 60 °C and a refolded helix after cooling (Figure S6A) As expected due to the basicity of the pyridyl groups, addition of triethylamine resulted in a more pronounced helical signal at 232 nm (Figure S6B). Furthermore, we recorded a CD spectrum in THF, which also showed high helical folding propensity, because a non-coordinating polar solvent would be required for future studies of metal chelation due to the solubility of metal-containing salts (Figure S7).

Table 1. Overall $K_{cis/trans}$ Values for Amide Bond Rotamers Measured by HSQC NMR in Acetronitrile-d_3

compound	**15**[a]	**16**	**20**	**21**[a]
$K_{cis/trans}$	25.1	n.d.[b]	all *cis*[c]	46

[a]The samples of compounds **15** and **21** were measured in presence of Et_3N (20 equiv). [b]The signal to noise ratio in the spectra precluded determination of the $K_{cis/trans}$ due to limited solubility of the compound in acetonitrile. [c]The signals from the methine protons of side chains on *trans*–amides were below the detection limit.

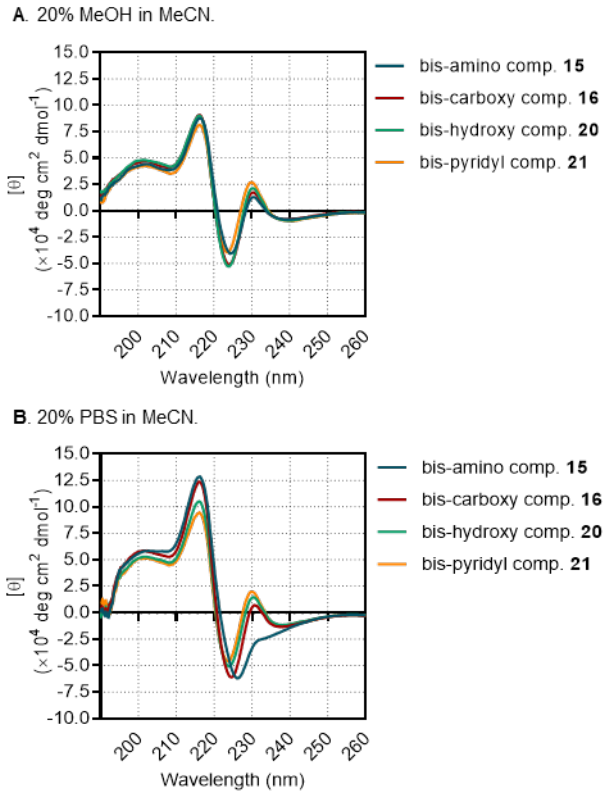


Figure 3. Comparison of CD spectra of **15**, **16**, **20**, and **21** in (**A**) MeCN–MeOH (8:2) and (**B**) MeCN–PBS buffer (8:2). In panel **A** samples of compounds **15** and **21** were measured in presence of Et_3N (20 equiv). The spectra were measured at 45–60 μM concentration at 25 °C. The mean residue molar ellipticity [θ] is normalized with regards to number of residues and peptoid concentration.

The overall *cis–trans* amide bond equilibria determined by NMR spectroscopy also revealed a high degree of *cis*-amide formation for all measurable samples, indicating helical folding (Table 1). Unfortunately, the solubility of compound **16** precluded determination of the equilibrium constant. Next, we investigated the effect of various solvents on folding propensity. We chose to titrate into the acetonitrile either methanol, as previously performed with other oligomers, or aqueous PBS buffer (pH 7.4), which was now possible for the first time due to the increased polarity – and thus solubility – of the oligomers compared to earlier generations. Not surprisingly, there was a denaturing effect that was gradually enhanced with increasing fraction of the protic solvent to 80% MeOH or 60% aqueous PBS buffer as indicated by significant decrease of the helix-indicating maximum at 232 nm (Figure S8). All four oligomers were affected by addition of protic solvents but the amino-functionalized oligomer **15** was particularly sensitive to the addition of buffer (see Figure 3A versus 3B), which is in agreement with its already established requirement for elevated pH to exhibit helical folding. In comparison, carboxy- (**16**), hydroxy- (**20**), and pyridyl-containing (**21**) hexamers all exhibited a more pronounced folding propensity under the addition of buffer. Generally, however, the effect of the protic organic solvent (methanol) was less pronounced than for the aqueous buffer (Figure S8). These investigations indicate that the present design with a triangular prism-shaped helix packed with naphthyl groups along the three faces and functional side chains protruding into space may not see applications in aqueous media due to denaturing. On the other hand, we were excited to learn that the helical content can be affected reversibly by external stimuli, including temperature and solvent composition as this could open up the possibility of designing responsive materials with functions in organic solvent mixtures. Finally, we therefore tested whether acid–base equilibria involving the side chains of amino-functionalized hexamer **15** and carboxy-functionalized hexamer **16** could reversibly affect the helical content.

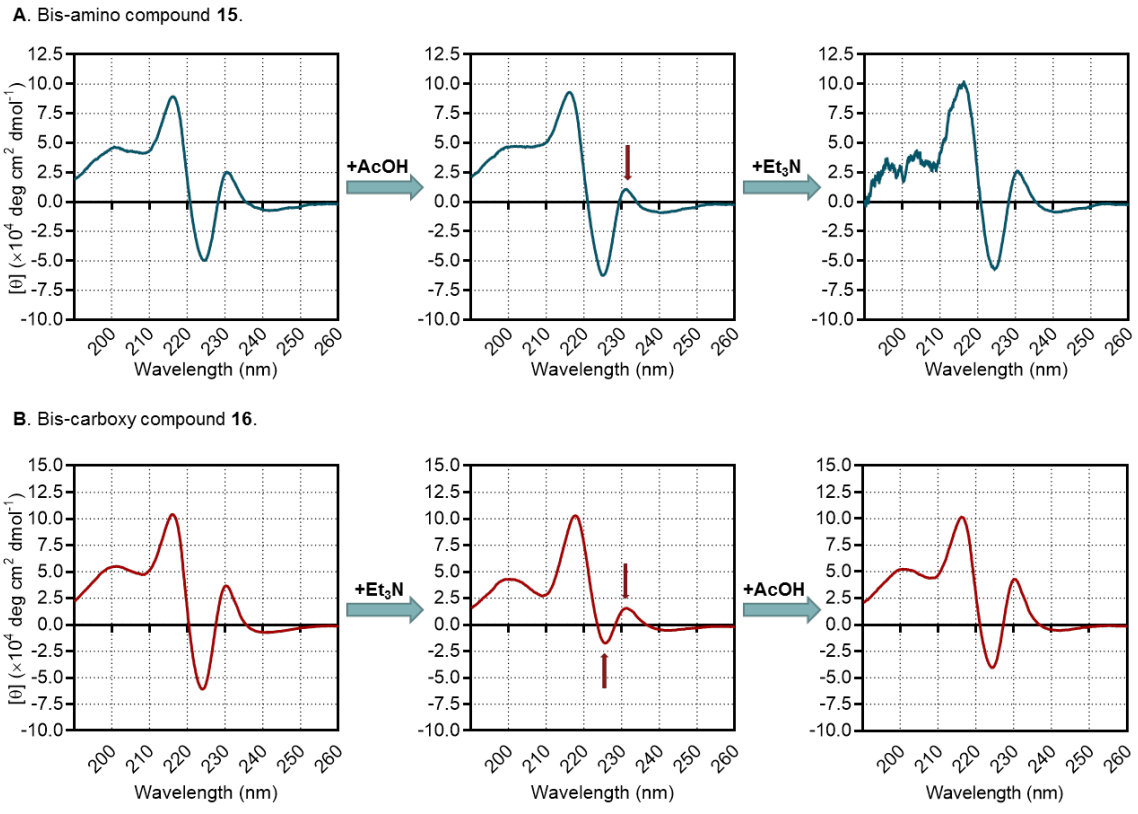


Figure 4. Switching folded ensembles between high and low helical content by addition of acid or base. (**A**) CD traces of **15**, first measurement with addition of Et_3N, then acetic acid, and finally base again. (**B**) CD traces of **16**, first measurement in pure solvent, then in presence of Et_3N, and finally acetic acid. The spectra were measured in MeCN (28–55 μM) at 25 °C with addition of Et_3N (20 equiv) and acetic acid (20 equiv). The mean residue molar ellipticity [θ] is normalized with regards to number of residues and peptoid concentration.

For compound **15**, we first obtained a CD spectrum in the presence of triethylamine, followed by a spectrum after addition of an equal amount of acetic acid, leading to a decrease of the maximum at 232 nm. Upon another addition of triethylamine, we were excited to see that the resulting CD spectrum exhibited a complete rescue of the helix-indicating maximum (Figure 4A). The carboxy-functionalized hexamer **16** demonstrated the same ability to switch between ensembles of conformations in response to addition of acid and base. In this case, with opposite order of addition of triethylamine and acetic acid as would be expected (Figure 4B). Previously, Kirshenbaum and coworkers have reported on α-peptoids containing carboxylic acids in their side chains, which also exhibited pH-dependent CD spetra.[77] However, the current designs allow for switching of the alignment of the functional groups along the helical axis, due to the exquisite precision with which this helical scaffold displays its side chains.

CONCLUSION

In summary, we have developed a strategy for the preparation of helical β-peptoid foldamers with a significantly increased functional group diversity. The strategy is predicated upon incorporation of functionalized monomers containing either a protected amine or an azide into β-peptoid oligomers that adopt robust triangular prism-shaped helical folding in organic solvent. This was achieved by preparation of trimer segments that were joined by peptide couplings to give hexamers. The intermediate hexamers then underwent ready elaboration to furnish the functionalized target compounds. The azide-containing building blocks, in particular, allowed for highly versatile functionalization by applying Cu(I)-catalyzed azide–alkyne cycloaddition "click" chemistry.[59-60] Our collective findings from CD spectroscopy and HSQC NMR spectroscopy provide strong evidence that the novel functionalized oligomers have robust folding propensity in acetonitrile, similar to previously synthesized parent compounds. The substantially improved solubility of the present oligomers also enabled investigation of solvent and pH effects, revealing the ability of the amino- and carboxy-functionalized designs to reversibly respond to the addition of acid and base. Thus, sequential additions of triethylamine and acetic acid to these oligomers (**15** and **16**) resulted in switching between states with varying degrees of helical content. The present work provides responsive three-dimensional foldamer scaffolds that can predictably display pairs of different functional groups in space. Such materials may find use as efficient catalysts as recently demonstrated by Gellman and coworkers.[78-79] The ability to conformationally respond to external stimuli may offer yet another level of sophistication in catalysts design.[80,81] Investigation of metal ion binding properties and potential effects on self-assembly is currently ongoing in our laboratories.

EXPERIMENTAL SECTION

General Methods and Materials. All chemicals and solvents were analytical grade and used without further purification. All reactions under a nitrogen atmosphere were performed in dry solvents. Dichloromethane, *N*,*N*-dimethylformamide (DMF), and tetrahydrofuran (THF) were retrieved from a solvent purification system. All reactions were monitored by thin-layer chromatography (TLC) using silica gel coated plates (analytical SiO_2-60, F-254). Liquid column chromatography was performed either manually on silica gel (particle size 40-63 µm) or with a Büchi Pure C-810 Flash chromatography device. Ultra-high performance liquid chromatography (UPLC)-mass spectrometry (MS) analyses were performed on a Waters Acquity system equipped with a Phenomenex Kinetex C18 column (50 mm × 2.1 mm, 1.7 µm, 100 Å) using a gradient of eluent I (0.1% HCOOH in water) and eluent II (0.1% HCOOH in acetonitrile) rising linearly from 0% to 95% of eluent II during t = 0.00−5.00 min at a flow rate of 0.6 mL/min. Analytical reversed-phase HPLC was performed on an Agilent 1100 LC system equipped with a Phenomenex Kinetex C8 column (250 × 4.6 mm, 5 µm, 100 Å) and a diode-array UV detector, using a gradient of eluent III (water–acetonitrile–TFA, 95:5:0.1) and eluent IV (0.1% TFA in acetonitrile) rising linearly from 5% to 95% of eluent IV during t = 5−30 min (gradient A), from 30% to 95% of eluent IV during t = 5−30 min (gradient B), or from 50% to 95% of eluent IV during t = 5−25 min (gradient C) with a flow rate of 1.2 mL/min at 40 °C. HPLC purification was performed on a Agilent 1260 infinity system equipped with a preparative Phenomenex Luna C8 column (250 × 21.2 mm, 5 µm, 100 Å) or a semi-preparative Waters XBridge C8 column (250 × 10 mm, 5 µm, 130 Å), a diode-array UV detector, and an evaporative light-scattering detector (ELSD) at a flow rate of 20 mL/min. The applied gradients using eluent III (water–acetonitrile–TFA, 95:5:0.1) and IV (0.1% TFA in acetonitrile) are specified for each individual compound. Fractions containing the target compound were identified using UPLC-MS and analytical HPLC. Selected fractions were pooled and lyophilized. ^{1}H NMR and ^{13}C NMR spectra were recorded at 298 K with a cryogenically cooled probe at 600 and 151 MHz, respectively. Chemical shifts are reported in ppm, relative to deuterated solvent as internal standard (δ_H = $CDCl_3$ 7.26 ppm, CD_3OD 3.31 ppm, CD_3CN 1.94 ppm, δ_C = $CDCl_3$ 77.16 ppm, CD_3OD 49.00 ppm, CD_3CN 1.32 ppm). Coupling constants (*J*) are reported in Hertz. Multiplicities of NMR signals are reported as follows: s, singlet; br, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Assignments of peak identities are based on 2D NMR experiments (COSY, HSQC, HMBC). The following abbreviations are used for assignments: CH_{ar}, aromatic proton/carbon; C_q, quaternary carbon. High-resolution mass spectra (HRMS) were recorded using a quadrupole time-of-flight (TOF) mass spectrometer equipped with an electrospray ionization (ESI) source. Alternatively, they were recorded on an UPLC-MS equipped with a diode array detector and coupled to a QTOF mass spectrometer operated in positive electrospray or by either matrix-assisted laser desorption/ionization (MALDI) or ESI.

Circular dichroism spectroscopy. Spectra were acquired with a JASCO J-1500 spectrophotometer equipped with a water-circulating bath and a nitrogen gas flowmeter with sensor. Measurements were carried out in 1 mm quartz cuvettes, and compound solutions in acetonitrile were prepared using the dry weight of the lyophilized material followed by dilution to give the desired concentrations. Concentrations were verified using a NanoDrop to measure the absorbance at λ = 280 nm (A_{280} = ε·c·l). The CD data were obtained at

298 K with a bandwidth of 1.00 nm, a scanning speed of 20 nm/min, three accumulations, and a data integration time of 4 s. The measurements were performed in triplicate. Spectra were recorded in millidegree units (m°), corrected for solvent contributions and normalized to mean residue ellipticity (θ) = 100·m°/l·c·n, with c being the concentration in mM, l being the path length (0.1 cm), and n being the number of peptoid amide bonds.

General procedure for the synthesis of *β*-peptoid oligomers

General procedure A: *Aza*-Michael addition. The respective amine (1.00–2.00 equiv) was added to a solution of the acrylated *β*-peptoid (0.1 M) in MeOH. The reaction mixture was stirred at 50 °C for 18 h. After completion, the solvent was evaporated. In case of the dimeric and trimeric peptoids, the residue was redissolved in EtOAc and washed with 2 M aq. HCl and sat. aq. $NaHCO_3$. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (2% MeOH, 0.25% NH_3 in CH_2Cl_2).

General procedure B: Acryloylation reaction. Under nitrogen atmosphere, the peptoid (1.00 equiv) and Et_3N (1.20 equiv) were dissolved in anhydrous THF (0.05 M) and the mixture was cooled to 0 °C. Acryloyl chloride (1.40 equiv) was added and the solution was stirred for 1 h at this temperature. The reaction mixture was filtered and the filter cake was washed with cold EtOAc. The combined filtrates were concentrated *in vacuo* to give the crude acrylamide, which was used without further purification.

General procedure C: N-terminal acylation. To a solution of the peptoid (1.00 equiv) in anhydrous THF (0.02 M) at –10 °C, Et_3N (1.40 equiv) and 3-chloropropionyl chloride (1.50 equiv) were added. The reaction mixture was stirred for 1 h at –10 °C. After completion, the solution was diluted with EtOAc and washed with water. The organic phase was dried over $MgSO_4$ and the solvent was removed *in vacuo* to give the crude product, which was used without further purification.

General procedure D: Piperazine coupling. The peptoid trimer (1.00 equiv) was dissolved in THF (0.05 M). K_2CO_3 (5.00 equiv), KI (0.1 equiv), *i*$PrNEt_2$ (3.00 equiv) and the protected piperazine·HCl salt (3.00 equiv) were added and the reaction mixture was stirred at 60 °C for 48 h. After completion, the mixture was diluted with EtOAc (15 mL) and washed with 0.1 M aq. HCl (10 mL) and sat. aq. $NaHCO_3$ (10 mL). The organic phase was dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude residue was purified by column chromatography.

General procedure E: C-terminal deprotection. 1) The peptoid trimer (1.00 equiv, 5 mM) was dissolved in MeCN–phosphoric acid (aq., 80%) 1:1 and stirred for 4 h at room temperature. After reaction completion, the solution was diluted with water and extracted with EtOAc. The combined organic phases were washed with sat. aq. $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo*. The product was used without further purification. **2)** A solution of the peptoid (6.00 mM) in 1 M aq. LiOH–MeOH 1:1 was stirred at room temperature for 48 h. After dilution with water, the solution was acidified (pH 1) with aq. conc. HCl. This caused precipitation and the suspension was extracted with EtOAc. The combined organic layers were dried

over $MgSO_4$, filtered, and concentrated. The resulting crude product was purified by column chromatography (1 → 2% MeOH, 0.25% AcOH in CH_2Cl_2).

General procedure F: Amide bond formation. The N-terminal peptoid trimer (1.00 equiv) and the C-terminal peptoid trimer (1.00 equiv) were placed in a vial and dissolved in anhydrous DMF–CH_2Cl_2 1:1 (0.1 M). Subsequently, *i*Pr_2NEt (3.00 equiv) and HATU (1.20 equiv) were added and the reaction was left on a shaker at room temperature for 18–48 h. After reaction completion, the solution was concentrated using a nitrogen stream and either subjected to Alloc-deprotection or purification by preparative HPLC.

(*R*)-2-Methyl-*N*-(naphthalen-1-ylmethylene)propane-2-sulfinimine (5). To a 0.5 M solution of $Ti(OEt)_4$ (5.18 mL, 5.65 g, 24.8 mmol, 1.00 equiv) in anhydrous THF under nitrogen atmosphere were added 1-naphthaldehyde (3.70 mL, 4.25 g, 27.2 mmol, 1.10 equiv) and (*R*)-*tert*-butanesulfinamide (3.00 g, 24.8 mmol, 1.00 equiv). The reaction mixture was stirred at room temperature for 18 h. It was then poured into a flask with brine (100 mL) upon rapid stirring. The suspension was filtered through a pad of Celite, and the filter cake was washed well with EtOAc. The filtrate was washed with brine (2 × 100 mL), and the aqueous layer was extracted with EtOAc (1 × 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified using column chromatography (short flash column as product is labile on silica, 0 → 1.5% MeOH in CH_2Cl_2) to give the sulfinimine **5** as a yellow oil that solidified upon storage at 4 °C (4.95 g, 77%). R_f = 0.18 (CH_2Cl_2). **^{1}H NMR** (600 MHz, CD_3CN): δ = 1.28 (s, 9 H, C(C*H*$_3$)$_3$), 7.61–7.66 (m, 2 H, C*H*$_{ar}$), 7.70 (ddd, *J* = 8.5, 6.8, 1.4 Hz, 1 H, C*H*$_{ar}$), 8.02 (ddt, *J* = 8.1, 1.3, 0.6 Hz, 1 H), 8.08–8.14 (m, 1 H, C*H*$_{ar}$), 9.05 (dq, *J* = 8.6, 0.9 Hz, 1 H, C*H*$_{ar}$), 9.09 (s, 1 H, N=C*H*). **^{13}C {^{1}H} NMR** (151 MHz, CD_3CN): δ = 22.3 (3 × C*C*H$_3$), 57.7 (*C*CH$_3$), 124.9 (*C*H$_{ar}$), 126.0 (*C*H$_{ar}$), 127.2 (*C*H$_{ar}$), 128.8 (*C*H$_{ar}$), 129.5 (*C*H$_{ar}$), 130.0 (naphthyl-*C*$_q$), 131.5 (naphthyl-*C*$_q$), 132.9 (*C*H$_{ar}$), 133.9 (*C*H$_{ar}$), 134.5 (naphthyl-*C*$_q$), 163.2 (N=*C*H). **UPLC-MS** *m/z*: calcd for $[M+H]^+$, $C_{15}H_{18}NOS^+$, 260.11; found 260.14. The data is in agreement with the literature.[82]

(*R*)-2-Methyl-*N*-((*S*)-1-(naphthalen-1-yl)allyl)propane-2-sulfinamide (6). Under nitrogen atmosphere, a solution of compound **5** (500 mg, 1.93 mmol, 1.00 equiv) in anhydrous toluene (50.0 mL) at –20 °C was treated with dropwise addition of vinylmagnesium bromide (3.86 mL, 506 mg, 3.85 mmol, 2.00 equiv). The reaction mixture was stirred at –20 °C for 1 h, slowly heated up to reach room temperature and after 3 h quenched by addition of sat. aq. NH_4Cl (10 mL). The mixture was diluted with EtOAc (20 mL) and the organic phase was washed with water (50 mL). The aqueous phase was extracted with EtOAc (2 × 30 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed *in vacuo*. The residue was purified by automated column chromatography (20 → 80% EtOAc in heptane) yielding the product as a clear oil (430 mg, 77%). R_f = 0.37 (heptane−EtOAc, 1:2). **^{1}H NMR** (600 MHz, CD_3CN): δ = 1.13 (s, 9 H, C(C*H*$_3$)$_3$), 4.32 (d, *J* = 5.8 Hz, 1 H, N*H*), 5.22 (dt, *J* = 10.3, 1.3 Hz, 1 H, C=C*H*$_{cis}$), 5.31 (dt, *J* = 17.1, 1.4 Hz, 1 H, C=C*H*$_{trans}$), 5.69 (td, *J* = 5.8, 1.5 Hz, 1 H, NHC*H*), 6.30 (ddd, *J* = 17.1, 10.3, 6.2 Hz, 1 H, C*H*=CH$_2$), 7.46–7.56 (m, 3 H, C*H*$_{ar}$), 7.59–7.64 (m, 1 H, C*H*$_{ar}$), 7.84 (dd, *J* = 8.3, 1.1 Hz, 1 H, C*H*$_{ar}$), 7.89–7.93 (m, 1 H, C*H*$_{ar}$), 8.23 (dt, *J* = 8.0, 1.0 Hz, 1 H, C*H*$_{ar}$). **^{13}C {^{1}H} NMR** (151 MHz, CD_3CN): δ = 23.0 (3 × C*C*H$_3$), 56.4

(*C*CH_3), 59.8 (NH*C*H), 117.0 (CH=*C*H_2), 125.0 (*C*H_{ar}), 126.4 (*C*H_{ar}), 126.7 (*C*H_{ar}), 126.9 (*C*H_{ar}), 127.0 (*C*H_{ar}), 129.2 (*C*H_{ar}), 129.7 (*C*H_{ar}), 131.8 (naphthyl-C_q), 135.0 (naphthyl-C_q), 137.8 (naphthyl-C_q), 140.3 (*C*H=CH_2). **UPLC-MS** *m/z*: calcd for $[M+H]^+$, $C_{17}H_{22}NOS^+$, 288.14; found 288.14. The data is in agreement with the literature.[83]

(*S*)-1-(Naphthalen-1-yl)prop-2-en-1-amine (7). The sulfinamide **6** (0.50 g, 1.74 mmol, 1.00 equiv) was dissolved in a 1:1 mixture of MeOH and 2.0 M HCl in diethylether (10.0 mL) and stirred at room temperature for 1 h. Then the solvent was removed in vacuo and the crude product was purified by automated column chromatography (0 → 10% MeOH, 0.25% NH_3 in CH_2Cl_2). The product was obtained as yellow oil (301 mg, 94%). **^{1}H NMR** (600 MHz, CD_3OD): δ = 5.48–5.51 (m, 2 H, C=C*H*$_2$), 5.88 (d, *J* = 6.1 Hz, 1 H, NC*H*), 6.27 (ddd, *J* = 16.9, 10.4, 6.2 Hz, 1 H, C*H*=CH_2), 7.54–7.66 (m, 3 H, C*H*$_{ar}$), 7.71 (d, *J* = 7.1 Hz, 1 H, C*H*$_{ar}$), 7.95 (d, *J* = 8.1 Hz, 2 H, C*H*$_{ar}$), 8.17 (d, *J* = 8.4 Hz, 1 H, C*H*$_{ar}$). **^{13}C {^{1}H} NMR** (151 MHz, CD_3OD): δ = 53.6 (NH*C*H), 120.7 (CH=*C*H_2), 123.6 (*C*H_{ar}), 125.4 (*C*H_{ar}), 126.4 (*C*H_{ar}), 127.4 (*C*H_{ar}), 128.2 (*C*H_{ar}), 130.1 (*C*H_{ar}), 130.7 (*C*H_{ar}), 131.6 (naphthyl-C_q), 133.0 (naphthyl-C_q), 135.2 (naphthyl-C_q), 135.4 (*C*H=CH_2). **HRMS** (ESI-TOF) *m/z*: calcd for $[M+H]^+$, $C_{13}H_{14}N^+$, 184.1121; found 184.1122. The data is in agreement with the literature.[69]

Imidazole-1-sulfonyl azide (9). To a solution of *N*,*N*'-sulfuryldiimidazole (496 mg, 2.50 mmol, 1.00 equiv) in CH_2Cl_2 (5.00 mL) at 0 °C, methyl triflate (0.25 mL, 369 mg, 2.25 mmol, 0.90 equiv) was added dropwise for 15 min. After 2 h at 0 °C, the solid was filtered and dried under high vacuum to give the triflate salt as a white solid (837 mg, quant.). **^{1}H NMR** (400 MHz, D_2O): δ = 4.04 (s, 3 H, C*H*$_3$), 7.31(s, 1 H, C*H*$_{ar}$), 7.75 (s, 1 H, C*H*$_{ar}$), 7.83 (s, 1 H, C*H*$_{ar}$), 8.20 (s, 1 H, C*H*$_{ar}$), 8.54 (s, 1 H, C*H*$_{ar}$), 9.96 (s, 1 H, C*H*$_{ar}$). **^{13}C{^{1}H} NMR** (101 MHz, D_2O): δ = 37.1 (C*H*$_3$), 118.8 (*C*H_{ar}), 120.6 (*C*H_{ar}), 126.0 (*C*H_{ar}), 131.8 (*C*H_{ar}), 138.5 (2 × *C*H_{ar}). The data is in agreement with the literature.[84]

The triflate salt (822 mg, 2.27 mmol, 1.00 equiv) was dissolved in H_2O (2.70 mL) at 0 °C, and then the equal volume of EtOAc (2.70 mL) was added. After stirring for 0.5 h, NaN_3 (177 mg, 2.72 mmol, 1.20 equiv) was added in portions and the reaction mixture was stirred at 0 °C for 1 h. The aqueous phase was extracted with EtOAc (2 × 2 mL) and the combined organic phases were dried over Na_2SO_4. The crude was used for the diazo transfer reaction directly without further purification, the yield was not determined. The data is in agreement with the literature.[84]

(*S*)-*N*-((*S*)-4-Azido-1-(naphthalen-1-yl)butyl)-2-methylpropane-2-sulfinamide (10). To the *in situ* generated imidazole-1-sulfonyl azide (**9**) in an EtOAc solution (6.00 mL), was sequentially added (*S*)-*N*-((*S*)-4-amino-1-(naphthalen-1-yl)butyl)-2-methylpropane-2-sulfinamide (**8**), previously published,[55] (753 mg, 2.36 mmol, 1.20 equiv) in MeOH (7.60 mL), K_2CO_3 (490 mg, 3.55 mmol, 1.80 equiv), and anhydrous $CuSO_4$ (3.77 mg, 23.6 µmol, cat.). The mixture was stirred at room temperature for 16 h. The crude residue was purified by column chromatography (0 → 10% MeOH, 0.25% NH_3 in CH_2Cl_2) to give the sulfinamide **10** as a yellow oil (561 mg, 83%). R_f = 0.28 (heptane–EtOAc, 2:1). **^{1}H NMR** (600 MHz, CD_3CN) δ = 1.14 (s, 9 H,

C(C*H*$_3$)$_3$), 1.56–1.64 (m, 1 H, CH$_2$C*H*$_2$CH$_2$), 1.69–1.76 (m, 1 H, CH$_2$C*H*$_2$CH$_2$), 2.07–1.98 (m, 2 H, CHC*H*$_2$CH$_2$), 3.30 (td, *J* = 6.8, 2.3 Hz, 2 H, CH$_2$C*H*$_2$N), 4.39 (d, *J* = 6.9 Hz, 1 H, N*H*), 5.14 (q, *J* = 6.9 Hz, 1 H, NC*H*), 7.54–7.49 (m, 2 H, C*H*$_{ar}$), 7.57 (ddd, *J* = 8.5, 6.8, 1.5 Hz, 1 H, C*H*$_{ar}$), 7.63–7.66 (m, 1 H, C*H*$_{ar}$), 7.83–7.85 (m, 1 H, C*H*$_{ar}$), 7.95–7.90 (m, 1 H, C*H*$_{ar}$), 8.21 (d, *J* = 8.5 Hz, 1 H, C*H*$_{ar}$). **^{13}C{^{1}H} NMR** (151 MHz, CD$_3$CN): δ = 23.0 (3 × C*C*H$_3$), 26.5 (CH$_2$*C*H$_2$CH$_2$), 35.2 (CH*C*H$_2$CH$_2$), 51.9 (CH$_2$*C*H$_2$N), 55.7 (*C*(CH$_3$)$_3$), 56.6 (N*C*H), 124.1 (*C*H$_{ar}$), 125.4 (*C*H$_{ar}$), 126.4 (*C*H$_{ar}$), 126.7 (*C*H$_{ar}$), 127.2 (*C*H$_{ar}$), 128.8 (*C*H$_{ar}$), 129.9 (*C*H$_{ar}$), 131.7 (naphthyl-*C*$_q$), 134.9 (naphthyl-*C*$_q$), 140.0 (naphthyl-*C*$_q$). **UPLC-MS** *m/z*: calcd for [M+H]$^+$, C$_{18}$H$_{25}$N$_4$OS$^+$, 345.17; found 345.12.

(*S*)-4-Azido-1-(naphthalen-1-yl)butan-1-amine (11). The sulfinamide **10** (561 mg, 1.63 mmol, 1.00 equiv) was dissolved in 2 M HCl in diethyl ether–MeOH 1:1 (12 mL) and stirred at room temperature for 1 h. Then the mixture was concentrated *in vacuo* and purified by flash chromatography (0 → 10% MeOH, 0.25% NH$_3$ in CH$_2$Cl$_2$), yielding the product as a light yellow oil (337 mg, 86%). R_f = 0.31 (5% MeOH, 0.25% NH$_3$ in CH$_2$Cl$_2$). **^{1}H NMR** (600 MHz, CD$_3$OD) δ = 1.57 (ddtd, *J* = 13.7, 10.5, 6.8, 5.5 Hz, 1 H, CH$_2$C*H*$_2$CH$_2$), 1.67 (ddtd, *J* = 13.7, 10.6, 6.8, 5.0 Hz, 1 H, CH$_2$C*H*$_2$CH$_2$), 1.92–1.80 (m, 1 H, CHC*H*$_2$CH$_2$), 1.97 (ddt, *J* = 13.6, 10.6, 5.9 Hz, 1 H, CHC*H*$_2$CH$_2$), 3.26 (t, *J* = 6.8 Hz, 2 H, CH$_2$C*H*$_2$N), 4.78 (t, *J* = 6.7 Hz, 1 H, NC*H*), 7.51–7.45 (m, 2 H, C*H*$_{ar}$), 7.53 (ddd, *J* = 8.4, 6.7, 1.4 Hz, 1 H, C*H*$_{ar}$), 7.61 (dd, *J* = 7.2, 1.1 Hz, 1 H, C*H*$_{ar}$), 7.77 (d, *J* = 8.1 Hz, 1 H, C*H*$_{ar}$), 7.87 (dd, *J* = 8.2, 1.4 Hz, 1 H, C*H*$_{ar}$), 8.14 (d, *J* = 8.5 Hz, 1 H, C*H*$_{ar}$). **^{13}C{^{1}H} NMR** (151 MHz, CD$_3$OD): δ = 27.0 (CH$_2$*C*H$_2$CH$_2$), 37.0 (CH*C*H$_2$CH$_2$), 51.1 (CH$_2$*C*H$_2$N), 52.4 (N*C*H), 123.6 (*C*H$_{ar}$), 123.7 (*C*H$_{ar}$), 126.6 (*C*H$_{ar}$), 126.6 (*C*H$_{ar}$), 127.2 (*C*H$_{ar}$), 128.5 (*C*H$_{ar}$), 130.0 (*C*H$_{ar}$), 132.3 (naphthyl-*C*$_q$), 135.4 (naphthyl-*C*$_q$), 142.5 (naphthyl-*C*$_q$). **HRMS** (MALDI-TOF) *m/z*: calcd for [M + H]$^+$C$_{14}$H$_{17}$N$_4^+$ 241.1448, found 241.1447.

***β*-Peptoid trimer 12a.** The peptoid trimer was synthesized from **S12** (72.0 mg, 69.0 µmol, 1.00 equiv) according to general procedure E1. The solvent was removed *in vacuo* and the crude was used for the next reaction without further purification. **HRMS** (ESI-TOF) *m/z*: calcd for [M + H]$^+$ C$_{62}$H$_{73}$N$_6$O$_9^+$ 1045.5434, found 1045.5448.

***β*-Peptoid trimer 12b.** The peptoid trimer was synthesized from **S13** (95.0 mg, 0.08 mmol, 1.00 equiv) according to general procedure E2. The solvent was removed *in vacuo* and the crude was used for the next reaction without further purification. **HRMS** (MALDI-TOF) *m/z*: calcd for [M + H]$^+$ C$_{64}$H$_{81}$N$_6$O$_9$Si$^+$ 1105.5828, found 1105.5820.

***β*-Peptoid hexamer 14b.** The peptoid hexamer **14b** was synthesized according to general procedure F using peptoid trimers **13** (50.0 mg, 0.057 mmol, 1.00 equiv), previously published,[55] and **12b** (75.6 mg, 0.068 mmol, 1.20 equiv). The residual crude product was purified by preparative HPLC (gradient of eluent IV rising linearly from 50 → 95% in eluent III over 25 min, t_R = 29.0 min–30.2 min). The peptoid hexamer

14b was obtained as a white solid (31.6 mg, 28%). **HRMS** (MALDI-TOF) *m/z*: calcd for $[M + H]^+$ $C_{119}H_{143}N_{10}O_{14}Si^+$ 1964.0548, found 1964.0557. Purity according to analytical HPLC (gradient C): 97%.

***β*-Peptoid hexamer 15.** The *β*-peptoid hexamer was synthesized from the trimers **13** (33.6 mg, 0.038 mmol, 1.00 equiv.), previously published,[55] and **12a** (40.0 mg, 0.038 mmol, 1.00 equiv.) according to general procedure F. The reaction mixture was then transferred to an eppendorf tube and the solvent was removed by a nitrogen stream. The residue was redissolved in MeOH and the resulting suspension was centrifuged. The supernatant was removed and the residue was washed with MeOH to give the crude Alloc-protected hexamer **14a**. Under nitrogen atmosphere, the crude **14a** (26.0 mg, 14.0 µmol, 1.00 equiv) was dissolved in 1.00 mL anhydrous CH_2Cl_2 and $Me_2NH{\cdot}BH_3$ (24.1 mg, 410 µmol, 30.0 equiv) was added. $Pd(PPh_3)_4$ (3.16 mg, 2.70 µmol, 0.20 equiv) was added and the mixture was stirred for 2 h. The reaction mixture was then evaporated to dryness and the residue was purified by preparative HPLC (gradient of eluent IV rising linearly from 20 → 95% in eluent III over 25 min, t_R = 21.5 min–22.5 min). The hexamer **15** was obtained as a white solid (11.3 mg, 49% from **14a**). **HRMS** (MALDI-TOF) m/z: calcd for $[M + H]^+$ $C_{105}H_{123}N_{10}O_8^+$ 1651.9520, found 1651.9523. Purity according to analytical HPLC (gradient A): 95%.

***β*-Peptoid hexamer 16.** In a vial, the hexamer **14b** (29.0 mg, 14.8 µmol, 1.00 equiv) was dissolved in 370 µL anhydrous CH_2Cl_2 and $Me_2NH{\cdot}BH_3$ (17.4 mg, 295 µmol, 20.0 equiv) was added. Then, $Pd(PPh_3)_4$ (3.41 mg, 3.00 µmol, 0.20 equiv) was added and the mixture was stirred for 4 h. The residual crude product was purified by preparative HPLC (gradient of eluent IV rising linearly from 30 → 95% in eluent III over 25 min, t_R = 22.3 min–23.2 min). The deprotected peptoid hexamer was obtained as a white solid. **HRMS** (MALDI-TOF) *m/z*: calcd for $[M + H]^+$ $C_{111}H_{135}N_{10}O_{10}Si^+$ 1796.0126, found 1796.0143. Purity according to analytical HPLC (gradient B): 97%.

In a vial, the deprotected hexamer (5.8 mg, 3.20 µmol, 1.00 equiv) was dissolved in 80 µL anhydrous CH_2Cl_2 and *i*Pr_2NEt (2.81 µL, 2.09 mg, 16.0 µmol, 5.00 equiv) was added. Then, diglycolic anhydride (1.67 mg, 12.9 µmol, 4.00 equiv) was added and the mixture was put on a shaker at room temperature for 2 h. The reaction mixture was then evaporated to dryness and the residue was used for the next reaction without further purification. The crude hexamer (6.49 mg, 3.20 µmol, 1.00 equiv) was dissolved in 80 µL anhydrous THF and TBAF·$3H_2O$ (16.8 mg, 48.0 µmol, 15.0 equiv) was added. The mixture was put on a shaker at 37 °C for 3 d. The crude was then purified by semi-preparative HPLC (gradient of eluent IV rising linearly from 30 → 95% in eluent III over 25 min, t_R = 24.3–25.9 min) and the peptoid hexamer **16** was obtained as a white solid (3.10 mg, 5% over 4 steps). **HRMS** (MALDI-TOF) *m/z*: calcd for $[M + H]^+$ $C_{113}H_{131}N_{10}O_{16}^+$ 1883.9738, found 1883.9750. Purity according to analytical HPLC (gradient B): 94%.

***β*-Peptoid trimer 17.** The peptoid trimer was synthesized from **18** (200 mg, 0.24 mmol, 1.00 equiv) according to general procedure C followed by general procedure D using Alloc-piperazine·HCl salt **S10** (149 mg, 0.72 mmol, 3.00 equiv). The peptoid trimer **S14** was obtained as a white foam after automated

column chromatography (0 → 10% MeOH, 0.25% NH_3 in CH_2Cl_2). Trimer **S14** (166 mg, 159 μmol, 1.00 equiv) was then subjected to general procedure E1. The peptoid trimer **17** was obtained as a light yellow foam after column chromatography (58.2 mg, 24% over 2 steps). $\boldsymbol{R_f}$ = 0.28 (5% MeOH, 0.25% NH_3 in CH_2Cl_2). **HRMS** (MALDI-TOF) *m/z*: calcd for $[M + H]^+$ $C_{58}H_{67}N_8O_7^+$ 987.5127, found 987.5112.

***β*-Peptoid trimer 18.** The peptoid trimer was synthesized from **S7** (150 mg, 0.25 mmol, 1.00 equiv) according to general procedure B, followed by general procedure A using (*S*)-1-(1-naphthyl)ethylamine (0.16 mL, 0.17 g, 1.00 mmol, 4.00 equiv). The crude was purified by automated column chromatography (0.5 → 4% MeOH, 0.25% NH_3 in CH_2Cl_2) yielding the product as a yellow foam (90.0 mg, 44%). $\boldsymbol{R_f}$ = 0.30 (3% MeOH, 0.25% NH_3 in CH_2Cl_2). **HRMS** (MALDI-TOF) *m/z*: calcd for $[M + H]^+$ $C_{51}H_{59}N_6O_4^+$ 819.4592, found 819.4593.

***β*-Peptoid hexamer 19.** The peptoid hexamer **19** was synthesized according to general procedure F using peptoid trimers **18** (48.1 mg, 0.059 mmol, 1.00 equiv) and **17** (58.0 mg, 0.059 mmol, 1.00 equiv). The resulting crude product was purified by preparative HPLC (gradient of eluent IV rising linearly from 50 → 95% in eluent III over 25 min, t_R = 29.1 min–30.3 min). The peptoid hexamer **19** was obtained as a white solid (46.0 mg, 44%). **HRMS** (MALDI-TOF) *m/z*: calcd for $[M + H]^+$ $C_{109}H_{123}N_{14}O_{10}^+$ 1787.9540, found 1787.9543. Purity according to analytical HPLC (gradient C): 93%.

***β*-Peptoid hexamer 20.** In a vial, propynol ethoxylate (2.4 μL, 2.46 mg, 24.6 μmol, 2.00 equiv) and the *β*-peptoid **19** (22.0 mg, 12.3 μmol, 1.00 equiv) were dissolved in dry THF (250 μL, 0.05 M). 2.6-Lutidine (2.9 μL, 2.64 mg, 25.0 μmol) and *i*Pr_2NEt (4.3 μL, 3.18 mg, 24.6 μmol), CuI (0.469 mg, 2.50 μmol, 0.20 equiv) and TBTA (1.31 mg, 2.50 μmol, 0.20 equiv) were added. The reaction was stirred at room temperature for 1 h. After completion, the reaction mixture was filtered and the solvent was removed in *vacuo* to give the crude Alloc-protected hexamer. It was dissolved in 0.30 mL anhydrous CH_2Cl_2 and $Me_2NH_2{\cdot}BH_3$ (14.2 mg, 241 μmol, 20.0 equiv) was added. Then, $Pd(PPh_3)_4$ (2.79 mg, 2.40 μmol, 0.20 equiv) was added and the mixture was stirred for 90 min. The reaction mixture was evaporated to dryness and the crude was purified by preparative HPLC (gradient of eluent IV rising linearly from 30 → 95% in eluent III over 25 min, t_R = 22.3 min–23.2 min). The peptoid hexamer **20** was obtained as a white solid (9.20 mg, 40% over 2 steps). **HRMS** (MALDI-TOF) *m/z*: calcd for $[M + H]^+$ $C_{115}H_{135}N_{14}O_{12}^+$ 1904.0377, found 1904.0396. Purity according to analytical HPLC (gradient B): 91%.

***β*-Peptoid hexamer 21.** In a vial, ethynylpyridine (2.5 μL, 2.54 mg, 24.6 μmol, 2.00 equiv) and the *β*-peptoid **19** (22.0 mg, 12.3 μmol, 1.00 equiv) were dissolved in dry THF (250 μL, 0.05 M). 2.6-Lutidine (2.9 μL, 2.64 mg, 25.0 μmol, 2.00 equiv) and *i*Pr_2NEt (4.3 μL, 3.18 mg, 24.6 μmol, 2.00 equiv), CuI (0.469 mg, 2.50 μmol, 0.20 equiv) and TBTA (1.31 mg, 2.50 μmol, 0.20 equiv) were added. The reaction was stirred at room temperature for 1 h. After completion, the reaction mixture was filtered and the solvent

was removed in *vacuo* to give the crude Alloc-protected hexamer. The crude was dissolved in 0.30 mL anhydrous CH_2Cl_2 and $Me_2NH{\cdot}BH_3$(14.2 mg, 241 µmol, 20.0 equiv) was added. Then, $Pd(PPh_3)_4$ (2.78 mg, 2.40 µmol, 0.20 equiv) was added and the mixture was stirred for 90 min. The reaction mixture was evaporated to dryness and purified by preparative HPLC (gradient of eluent IV rising linearly from 30 → 95% in eluent III over 25 min, t_R = 20.9 min–22.1 min). The peptoid hexamer **21** was obtained as a light yellow solid (10.7 mg, 47%). **HRMS** (MALDI-TOF) *m/z*: calcd for $[M + H]^+$ $C_{120}H_{128}N_{16}O_8^+$ 1910.0173, found 1910.0198. Purity according to analytical HPLC (gradient B): 94%.

Methyl (*S*)-5-(((*R*)-*tert*-butylsulfinyl)amino)-5-(naphthalen-1-yl)pent-3-enoate (S1). Under nitrogen atmosphere, to a solution of the sulfinamide **6** (400 mg, 1.39 mmol, 1.00 equiv) in anhydrous and degassed CH_2Cl_2 (0.1 M, 14.0 mL), methyl-3-butenoate (0.74 mL, 696 mg, 6.96 mmol, 5.00 equiv), CuI (26.0 mg, 0.14 mmol, 0.10 equiv) and Grubbs II catalyst (295 mg, 0.35 mmol, 0.25 equiv) were added. The reaction mixture was stirred at reflux for 20 h. Upon reaction completion, the solvent was evaporated and the residue was purified by automated column chromatography (20 → 50% EtOAc in heptane). Product **S1** was inseparable from an impurity of remaining catalyst, resulting in a brown oil (240 mg, <48%, 97% *trans*). $\boldsymbol{R_f}$ = 0.11 (heptane−EtOAc, 1:1). **^{1}H NMR** (600 MHz, CD_3CN): δ = 1.12 (s, 9 H, C(CH_3)$_3$), 3.02–3.13 (m, 2 H, CH_2), 3.58 (s, 3 H, OCH_3), 4.35 (d, *J* = 5.1 Hz, 1 H, N*H*), 5.68 (t, *J* = 6.0 Hz, 1 H, NHC*H*), 5.81 (dtd, *J* = 15.4, 6.8, 1.4 Hz, 1 H, C=C*H*CH$_2$), 6.05 (ddt, *J* = 15.4, 6.8, 1.4 Hz, 1 H, CHC*H*=C), 7.47–7.57 (m, 3 H, CH_{ar}), 7.60–7.64 (m, 1 H, CH_{ar}), 7.84 (dt, *J* = 8.3, 1.1 Hz, 1 H, CH_{ar}), 7.89–7.93 (m, 1 H, CH_{ar}), 8.20–8.25 (m, 1 H, CH_{ar}). **^{13}C {^{1}H} NMR** (151 MHz, CD_3CN): δ = 22.9 (3 × CCH_3), 37.7 (*C*H$_2$), 52.2 (O*C*H$_3$), 56.4 (*C*(CH$_3$)$_3$), 59.0 (NH*C*H), 125.0 (*C*H$_{ar}$), 125.8 (C=*C*HCH$_2$), 126.4 (*C*H$_{ar}$), 126.7 (*C*H$_{ar}$), 126.8 (*C*H$_{ar}$), 127.0 (*C*H$_{ar}$), 129.2 (*C*H$_{ar}$), 129.7 (*C*H$_{ar}$), 131.7 (naphthyl-*C*$_q$), 134.9 (naphthyl-*C*$_q$), 135.5 (CH*C*H=C), 137.9 (naphthyl-*C*$_q$), 172.5 (*C*OOCH$_3$). **HRMS** (MALDI-TOF) *m/z*: calcd for $[M+H]^+$, $C_{20}H_{26}NO_3S^+$, 360.1628; found 360.1627.

Methyl (*S*)-5-(((*R*)-*tert*-butylsulfinyl)amino)-5-(naphthalen-1-yl)pentanoate (S2). A solution of **S1** (100 mg, 0.28 mmol, 1.00 equiv) in MeOH (degassed, 6.00 mL, 0.05 M) was purged with nitrogen. Pd/C (30.0 mg, 0.1 equiv, 10 wt%) was added and the flask was evacuated again, before an H_2 balloon was put on. Then the reaction was stirred under H_2 atmosphere for 17 h. The mixture was filtered over Celite and the filter cake was washed thoroughly with CH_2Cl_2. The solvent was evaporated and the procedure was repeated. After the second cycle, pure **S2** was obtained as a brown oil (71.3 mg, 71%). $\boldsymbol{R_f}$ = 0.11 (heptane−EtOAc, 1:1). **^{1}H NMR** (600 MHz, CD_3CN): δ = 1.11 (s, 9 H, C(CH_3)$_3$), 1.49 (ddt, *J* = 17.6, 13.4, 7.2 Hz, 1 H, CH$_2$CH_2CH$_2$), 1.64–1.73 (m, 1 H, CH$_2$CH_2CH$_2$), 1.97–2.07 (m, 2 H, CHCH_2CH$_2$), 2.29 (t, *J* = 7.4 Hz, 2 H, CH$_2$CH_2CO), 3.56 (s, 3 H, OCH_3), 4.17 (d, *J* = 4.6 Hz, 1 H, N*H*), 5.10 (d, *J* = 6.2 Hz, 1 H, NHC*H*), 7.48–7.56 (m, 3 H, CH_{ar}), 7.61 (dd, *J* = 7.4, 1.2 Hz, 1 H, CH_{ar}), 7.83 (dd, *J* = 8.2, 1.1 Hz, 1 H, CH_{ar}), 7.90–7.93 (m, 1 H, CH_{ar}), 8.23 (d, *J* = 8.4 Hz, 1 H, CH_{ar}). **^{13}C {^{1}H} NMR** (151 MHz, CD_3CN): δ = 22.6 (CH$_2$*C*H$_2$CH$_2$), 22.9 (3 × CCH_3), 34.0 (CH$_2$*C*H$_2$CO), 37.7 (CH*C*H$_2$CH$_2$), 51.9 (O*C*H$_3$), 56.1 (*C*(CH$_3$)$_3$), 56.8 (NH*C*H), 124.4 (*C*H$_{ar}$), 126.2 (*C*H$_{ar}$), 126.3 (*C*H$_{ar}$), 126.6 (*C*H$_{ar}$), 127.0 (*C*H$_{ar}$), 128.8 (*C*H$_{ar}$), 129.8 (*C*H$_{ar}$), 132.0 (naphthyl-

C_q), 134.9 (naphthyl-C_q), 139.3 (naphthyl-C_q), 174.4 (COOCH$_3$). **HRMS** (MALDI-TOF) *m/z*: calcd for [M+H]$^+$, $C_{20}H_{28}NO_3S^+$, 362.1784; found 362.1783.

(*R*)-*N*-((*S*)-3-Hydroxy-1-(naphthalen-1-yl)propyl)-2-methylpropane-2-sulfinamide (S3). 9-BBN monomer (0.5 M in THF, 0.70 mL, 42.5 mg, 0.35 mmol, 2.00 equiv) was added dropwise to a solution of the alkene **6** (50.0 mg, 0.17 mmol, 1.00 equiv) in anhydrous THF (1.70 ml) at 0 °C under nitrogen atmosphere. After addition, the mixture was stirred at 0 °C for 30 min, before it was allowed to warm to room temperature and subsequently stirred for further 60 min. NaOH (3 M, 0.07 mL) and 30% H_2O_2 (0.07 mL) were added. The resulting mixture was heated under reflux for 2 h. After reaction completion, the solution was concentrated *in vacuo*. The residue was partitioned between EtOAc (3 mL) and water (3 mL). The separated aqueous layer was extracted with EtOAc (2 x 3 mL). The combined organic extracts were washed with brine (2 x 3 mL), dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by automated column chromatography (0 → 6% MeOH, 0.25% NH_3 in CH_2Cl_2), yielding product **S3** as a white solid (35.5 mg, 67%). R_f = 0.11 (6% MeOH, 0.25% NH_3 in CH_2Cl_2). **^{1}H NMR** (600 MHz, CD_3OD): δ = 1.19 (s, 9 H, C(CH_3)$_3$), 2.12–2.19 (m, 1 H, CHCH_2CH$_2$), 2.19–2.27 (m, 1 H, CHCH_2CH$_2$), 3.68–3.74 (m, 1 H, CH$_2$CH_2OH), 3.75–3.81 (m, 1 H, CH$_2$CH_2OH), 5.32–5.40 (m, 1 H, NHCH), 7.46–7.51 (m, 2 H, CH_{ar}), 7.53 (ddd, *J* = 8.5, 6.8, 1.5 Hz, 1 H, CH_{ar}), 7.63 (dd, *J* = 7.3, 1.2 Hz, 1 H, CH_{ar}), 7.80 (dd, *J* = 8.2, 1.0 Hz, 1 H, CH_{ar}), 7.85–7.94 (m, 1 H, CH_{ar}), 8.26 (d, *J* = 8.5 Hz, 1 H, CH_{ar}). **^{13}C {^{1}H} NMR** (151 MHz, CD_3OD): δ = 23.1 (3 × CCH$_3$), 40.8 (CHCH$_2$CH$_2$), 56.2 (C(CH$_3$)$_3$), 56.8 (NHCH), 60.9 (CH$_2$$CH_2$OH), 124.4 ($CH_{ar}$), 126.1 ($CH_{ar}$), 126.3 ($CH_{ar}$), 126.6 ($CH_{ar}$), 127.1 ($CH_{ar}$), 129.1 ($CH_{ar}$), 130.0 ($CH_{ar}$), 132.2 (naphthyl-$C_q$), 135.5 (naphthyl-$C_q$), 139.5 (naphthyl-$C_q$). **HRMS** (ESI-TOF) *m/z*: calcd for [M+H]$^+$, $C_{17}H_{24}NO_2S^+$, 306.1522; found 306.1528.

***β*-Peptoid dimer S7.** The peptoid dimer was synthesized from the peptoid monomer **S4**, previously published,[55] (9.54 g, 31.9 mmol, 1.00 equiv) according to general procedure B. The crude acryloylated peptoid (744 mg, 2.10 mmol, 1.50 equiv) was then reacted with the amine **11** (337 mg, 1.40 mmol, 1.00 equiv) according to general procedure A. The crude was purified by automated column chromatography (0.5 → 4% MeOH, 0.25% NH_3 in CH_2Cl_2), yielding the product as a light yellow foam (400 mg, 48%). R_f = 0.26 (3% MeOH, 0.25% NH_3 in CH_2Cl_2). **UPLC-MS** *m/z*: calcd for [M+H]$^+$, $C_{36}H_{44}N_5O_3^+$, 594.34; found 594.34.

1-Allyl 4-(*tert*-butyl) piperazine-1,4-dicarboxylate (S8). Under nitrogen atmosphere, Boc-piperazine (2.00 g, 10.7 mmol, 1.00 equiv) was dissolved in 85.0 mL anhydrous THF. *i*PrNEt$_2$ (5.63 mL, 4.16 g, 32.2 mmol, 3.00 equiv) and allyl chloroformate (1.37 mL, 1.55 g, 12.9 mmol, 1.20 equiv) were added at 0 °C and the reaction mixture was stirred for 1 h while it was allowed to reach room temperature. Then, the mixture was diluted with EtOAc (30 mL) and washed with water, 0.1 M aq. HCl, and sat. aq. $NaHCO_3$ (70 mL each). The organic phase was dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude product was used for the next reaction without further purification. **^{1}H NMR** (600 MHz, CD_3CN): δ = 1.43

(s, 9 H, 3 × CH_3), 3.33–3.41 (m, 8 H, 2 × NCH_2CH_2N), 4.56 (dt, *J* = 5.4, 1.6 Hz, 2 H, OCH_2CH), 5.19 (dq, *J* = 10.5, 1.5 Hz, 1 H, CH=CH_2), 5.29 (dq, *J* = 17.3, 1.7 Hz, 1 H, CH=CH_2), 5.88–6.01 (m, 1 H, C*H*=CH_2). **^{13}C {^{1}H} NMR** (151 MHz, CD_3CN): δ = 28.5 (3 × *C*H_3), 44.4 (4 × piperazine-*C*H_2), 66.5 (O*C*H_2CH), 80.3 (*C*(CH_3)$_3$), 117.4 (CH=*C*H_2), 134.5 (*C*H=CH_2), 155.4 (N*C*OO), 155.8 (N*C*OO). The data is in agreement with the literature. [85]

1-(*tert*-Butyl) 4-(2-(trimethylsilyl)ethyl) piperazine-1,4-dicarboxylate (S9). Under nitrogen atmosphere, Boc-piperazine (1.50 g, 8.05 mmol, 1.00 equiv) was dissolved in anhydrous CH_2Cl_2 (15.0 mL). Et_3N (2.26 mL, 1.63 g, 16.1 mmol, 2.00 equiv) and a solution of Teoc-ONp (2.28 g, 8.05 mmol, 1.00 equiv) in anhydrous CH_2Cl_2 (4.00 mL) were added and the reaction mixture was stirred for 18 h at room temperature. The mixture was diluted with CH_2Cl_2 (10 mL) and washed with brine (20 mL), 2 M aq. NaOH (2 × 20 mL) and sat. aq. $NaHCO_3$ (3 × 20 mL). The organic phase was dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude was purified by column chromatography (2% MeOH in CH_2Cl_2) and the piperazine derivative **S9** was obtained as a light yellow oil (2.47 g, 93%). R_f = 0.33 (2% MeOH in CH_2Cl_2). **^{1}H NMR** (600 MHz, CD_3OD): δ = 0.1 (s, 9 H, Si(CH_3)$_3$), 1.03–1.10 (m, 2 H, SiCH_2), 1.50 (s, 9 H, 3 × CCH_3), 3.41–3.50 (m, 8 H, 2 × NCH_2CH_2N), 4.22–4.27 (m, 2 H, OCH_2). **^{13}C {^{1}H} NMR** (151 MHz, CD_3OD): δ = 1.5 (Si(*C*H_3)$_3$), 18.6 (Si*C*H_2), 28.6 (3 × *C*H_3), 44.6 (4 × piperazine-*C*H_2), 65.1 (O*C*H_2), 81.6 (*C*(CH_3)$_3$), 156.3 (N*C*OO), 157.2 (N*C*OO). **HRMS** (MALDI-TOF) *m/z*: calcd for [M + Na]$^+$ $C_{15}H_{30}N_2O_4SiNa^+$ 353.1867, found 353.1865.

Alloc-piperazine·HCl-salt (S10). 1-allyl 4-(*tert*-butyl) piperazine-1,4-dicarboxylate **S8** (2.70 g, 9.99 mmol, 1.00 equiv) was dissolved in 2 M HCl in diethyl ether–MeOH 1:1 (25.0 mL) and stirred for 18 h at room temperature. The solvent was removed *in vacuo* and the product was obtained as a yellow solid HCl-salt (2.01 g, 94% over 2 steps). R_f = 0.06 (10% MeOH, 0.5% NH_3 in CH_2Cl_2). **^{1}H NMR** (600 MHz, CD_3OD): δ = 3.27 (t, *J* = 5.3 Hz, 4 H, 2 × NCH_2C*H*$_2$N), 3.78 (br s, 4 H, 2 × NC*H*$_2$CH_2N), 4.66 (dt, *J* = 5.6, 1.5 Hz, 2 H, OC*H*$_2$CH), 5.27 (dq, *J* = 10.7, 1.3 Hz, 1 H, *cis*-C*H*=C), 5.36 (dq, *J* = 17.2, 1.6 Hz, 1 H, *trans*-C*H*=C), 6.00 (ddt, *J* = 17.2, 10.7, 5.6 Hz, 1 H, CH_2=C*H*CH_2). **^{13}C {^{1}H} NMR** (151 MHz, CD_3OD): δ = 41.8 (NCH_2*C*H_2N), 44.3 (N*C*H_2CH$_2$N), 67.8 (O*C*H_2CH), 118.4 (CH=*C*H_2), 133.9 (*C*H=CH_2), 156.2 (N*C*OO). **UPLC-MS** *m/z*: calcd for [M+H]$^+$, $C_8H_{15}N_2O_2^+$, 171.11; found 170.98. The data is in agreement with the literature.[85]

Teoc-piperazine·HCl-salt (S11). Teoc-Boc-piperazine **S9** (2.40 g, 6.64 mmol, 1.00 equiv) was dissolved in 2 M HCl in diethyl ether–MeOH 2:1 (21.0 mL). The reaction mixture was stirred for 18 h at room temperature, then the solvent was removed *in vacuo* and the Teoc-protected piperazine was obtained as the HCl-salt in form of white solids (1.71 g, 87%). R_f = 0.09 (10% MeOH, 0.5% NH_3 in CH_2Cl_2). **^{1}H NMR** (600 MHz, CD_3OD): δ = 0.06 (s, 9 H, Si(CH_3)$_3$), 1.00–1.09 (m, 2 H, SiCH_2), 3.19–3.25 (m, 4 H, N(CH_2)$_2$), 3.71–3.78 (m, 4 H, N(CH_2)$_2$), 4.19–4.29 (m, 2 H, OCH_2). **^{13}C {^{1}H} NMR** (151 MHz, CD_3OD): δ = -1.5 (Si(*C*H_3)$_3$), 18.5 (Si*C*H_2), 41.6 (N(*C*H_2)$_2$), 44.2 (N(*C*H_2)$_2$), 65.7 (O*C*H_2), 156.8 (N*C*OO). **HRMS** (MALDI-TOF) *m/z*: calcd for [M + H]$^+$ $C_{10}H_{23}N_2O_2Si^+$ 231.1523, found 231.1523.

***β*-Peptoid trimer S12.** The peptoid trimer was synthesized from **13**, previously published,[55] (350 mg, 0.40 mmol, 1.00 equiv) according to general procedure C, followed by general procedure D using the crude acylated trimer (90.0 mg, 0.09 mmol, 1.00 equiv) and Alloc-piperazine·HCl salt **S10** (58.0 mg, 0.28 mmol, 3.00 equiv). The crude was purified by automated column chromatography (0.5 → 4% MeOH, 0.25% NH_3 in CH_2Cl_2). R_f = 0.19 (4% MeOH, 0.25% NH_3 in CH_2Cl_2). **HRMS** (MALDI-TOF) *m/z*: calcd for $[M + H]^+$ $C_{66}H_{81}N_6O_9^+$ 1101.6060, found 1101.6050.

***β*-Peptoid trimer S13.** The peptoid trimer was synthesized from **13**, previously published,[55] (350 mg, 0.40 mmol, 1.00 equiv) according to general procedure C, followed by general procedure D using the crude acylated trimer (287 mg, 0.30 mmol, 1.00 equiv) and Teoc-piperazine·HCl salt **S11** (158 mg, 0.59 mmol, 2.00 equiv). The crude was purified by column chromatography (2 → 3% MeOH in CH_2Cl_2) and the product was obtained as a light yellow foam (96.4 mg, 28%). R_f = 0.28 (4% MeOH, 0.25% NH_3 in CH_2Cl_2). **UPLC-MS** *m/z*: calcd for $[M+H]^+$, $C_{68}H_{89}N_6O_9Si^+$, 1161.65; found 1161.86.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website.

Supporting schemes, figures, and tables, experimental procedures, HPLC traces, and copies of NMR spectra (PDF).

Data for compound **7** (CCDC 1988798) (CIF)

Data for compound **S3** (CCDC 1988799) (CIF)

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Notes

The authors declare no competing financial interests

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