Highly Convenient Gram-Scale Solution-Phase Peptoid Synthesis and Orthogonal Side-Chain Post-Modification

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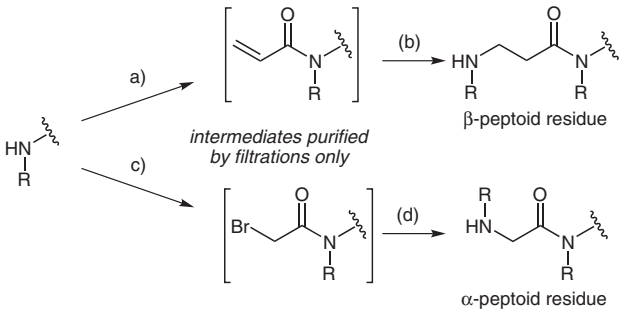
Abstract: This paper describes the development of a highly convenient solution-phase methodology using volatile amines for the synthesis of β-, α,β- and α-tetrapeptoids, as an alternative to solid-phase technologies. Column chromatographic purifications are reduced to a minimum and the majority of the intermediates are purified by filtration and/or evaporation. The method is amenable to gram-scale synthesis of peptoids, and post-modification of a model peptoid by successive and selective ligations, using click thiol–ene coupling, and copper-catalysed azide–alkyne cycloaddition is demonstrated.

Key words: peptoids, oligomers, gram-scale synthesis, thiol–ene coupling, cycloaddition, post-modifications

There has been considerable interest in developing pseudopeptide oligomers with reduced complexity that are able to fulfill the functions of their natural peptide counterparts, without drawbacks such as low half-life and limited bioavailability.[2] Oligomers of N-substituted glycines, or α-peptoids, were developed in the early 1990s as a new type of simple peptidomimetic. They are characterised by resistance to proteases, rapid cellular uptake, a large potential for diversity and straightforward syntheses.[3] The first synthesis of oligomers of N-substituted β-alanines, or β-peptoids, followed later in the same decade.[4] In addition, we have recently communicated our initial studies on a new family of α,β-alternating peptoids.[5] Structurally, peptoids differ from peptides in that the side chains are attached to the amide nitrogen rather than to the α- or β-carbon. The peptoid backbone is therefore achiral and does not contain any amide protons. In spite of this, peptoids can still be driven to form secondary structures such as helices if α-chiral side chains are incorporated.[6] Peptoids have attracted significant interest and have been used in a number of important biological applications.[7]

The structural simplicity of the peptoids allows for their synthesis using a unique 'submonomer' protocol in which the peptoid residues are created directly on a growing chain, in an iterative manner. Highly efficient procedures have been developed for solid-phase synthesis of peptoids. However, our research project aimed at using β- and α,β-peptoids as scaffolds for multivalent ligand display[8] necessitates the development of efficient solution-phase methodologies which are able to provide large quantities of peptoids in a manner competitive with solid-phase synthesis. Accordingly, our published methodology for iterative solution-phase synthesis of peptoids (Scheme 1) has provided improvements, in terms of cost and time, compared to earlier techniques.[5]

Briefly, the peptoid residues are created in two steps by acylation of the N-terminus, followed by reaction of the acylated intermediate with an appropriate amine. By using tetrahydrofuran as the solvent for the acylation steps the formed ammonium salts precipitate, allowing for easy removal by filtration. Evaporation of the filtrate then furnishes the acylated intermediates in sufficiently high purity for direct use in the second step. Thus, only one chromatography operation per synthesised peptoid residue is needed. Nevertheless, further improvements are necessary if this methodology is to emerge as a truly competitive alternative to solid-phase technologies. In this paper, we describe the development of a highly convenient procedure for solution-phase synthesis of tetrapeptoids. The potential of this method is shown by the facile gram-scale synthesis of a multifunctional model peptoid. Successive and selective ligations of this multifunctional tetrapeptoid, as a possible entry to more complex structures, are also demonstrated.



Scheme 1 Solution-phase submonomer synthesis of β- and α-peptoid residues. *Reagents and conditions*: (a) CH_2=CHCOCl (1.2 equiv), Et_3N (1.4 equiv), THF, 0 °C; (b) RNH_2 (2.0 equiv), MeOH, 50 °C then chromatography; (c) $BrCH_2COBr$ (1.2 equiv), Et_3N (1.2 equiv), THF, 0 °C; (d) RNH_2 (2.0 equiv), Et_3N (2.0 equiv), THF, 0 °C to r.t. then chromatography.

The synthetic steps illustrated in Scheme 1 proceed with high efficiency to give crude products which are essentially mixtures of the desired peptoid and unreacted starting amine; the pure peptoid can be isolated by flash chroma-

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tography. We envisaged that by utilising amines that could be removed by evaporation on a standard rotary evaporator, we could potentially optimise our solution-phase method such that flash chromatographic purification could be omitted. The peptoid products would be expected to be sufficiently pure to be used directly in the iterative peptoid synthesis. Initially, we needed to improve the filtration operations. In our previous method (Scheme 1) the ammonium salts were filtered from the reaction mixtures in THF. This gave crude products that still contained small amounts of ammonium salts which could potentially lead to the formation of undesired by-products if continuously returned into the iterative synthesis. We found that dilution of the reaction mixtures with ethyl acetate following the acylation and substitution steps, afforded intermediates of higher purity after filtration and evaporation. Dilution with cyclohexane was also tested, but peptoids longer than two units showed limited solubility in cyclohexane–tetrahydrofuran mixtures which complicated the filtration.

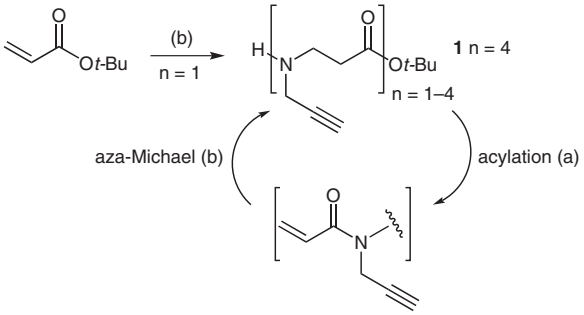
With an improved technique in hand, we next investigated the solution-phase iterative synthesis of β-peptoids without any intermediate chromatographic purifications (Table 1). The synthesis started from *tert*-butyl acrylate and propargylamine was used as a model amine. Using our previously developed reaction conditions for β-peptoid synthesis (Scheme 1), the synthetic cycle shown in Table 1 was repeated until the tetrapeptoid stage, at which point thin layer chromatography showed the presence of non-negligible amounts of impurities.

We were satisfied to find that β-tetrapeptoid **1** could be isolated in 58% overall yield, and in high purity (Table 1, entry 1), after seven steps and a single final flash chromatography.

Encouraged by this initial result we sought to improve the overall yield. Increasing the amount of propargylamine used in the addition step only resulted in a slight increase of the overall yield from 58% to 60% (Table 1, entry 2 vs. 1). The highest overall yield of 65% (HPLC purity = 99%) was obtained by increasing the amount of triethylamine used in the acylation steps (Table 1, entry 3), or by replacing tetrahydrofuran with ethyl acetate as the solvent for the acylation (Table 1, entry 4). For comparison, when each intermediate was purified, tetramer **1** was obtained in 72% overall yield.[8] Hence, by using this new methodology we were able to synthesise the same product in a slightly lower overall yield, but with only one final flash chromatographic purification required; this represents a clear improvement in terms of cost and time. Furthermore, the yield obtained via this methodology was superior to the reported yields for the solid-phase synthesis of β-peptoids.[9]

While working on optimising the two-step iterative process for synthesising β-peptoid units, we were also able to optimise the synthesis of α-peptoid residues. The α,β-alternating tetrapeptoid **2** (Table 2) was chosen as a model target for this study. Thus, while using the initial conditions for chain elongation with a β-peptoid residue (see Table 1, entry 1) the synthetic conditions for α-peptoid residue incorporation were varied (Table 2). Using the initial unoptimised conditions, α,β-tetrapeptoid **2** was isolated in 29% overall yield after seven steps and one final purification (Table 2, entry 1). The lower yield of α,β-peptoid **2**, compared to that of β-peptoid **1**, was anticipated since the solution-phase synthesis of α-peptoid residues proceeds less cleanly than that of β-peptoid residues.[5] Replacing triethylamine in the substitution reaction with a further two equivalents of propargylamine gave reaction mixtures that proved difficult to filter, and consequently, a slightly decreased overall yield was obtained (Table 2, entry 2). A significant improvement in the overall yield to 42% was observed when maintaining the use of triethylamine in the substitution steps, and at the

Table 1 Optimisation of the Iterative Synthesis of β-Tetrapeptoid **1**



Entry	Acylation (step a)[a]	Aza-Michael (step b)[a]	Yield (%)
1	H_2C=CHCOCl (1.2), Et_3N (1.4), THF, 0 °C, 1 h	propargylamine (2.0), MeOH, 50 °C, overnight	58
2	H_2C=CHCOCl (1.2), Et_3N (1.4), THF, 0 °C, 1 h	propargylamine (4.0), MeOH, 50 °C, overnight	60
3	H_2C=CHCOCl (1.2), Et_3N (2.2), THF, 0 °C, 1 h	propargylamine (2.0), MeOH, 50 °C, overnight	65
4	H_2C=CHCOCl (1.2), Et_3N (1.4), EtOAc, 0 °C, 1 h	propargylamine (2.0), MeOH, 50 °C, overnight	65

[a] Numbers in parentheses are the equivalents used.

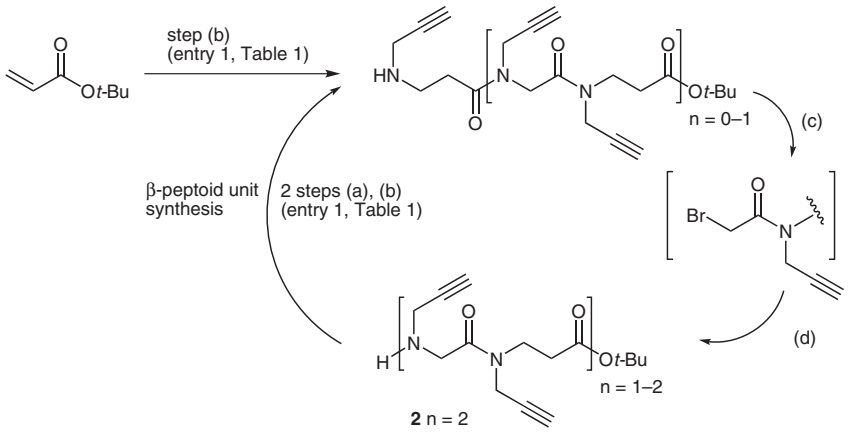
same time, increasing the amount of propargylamine from two to four equivalents (Table 2, entry 3). Increasing the amount of propargylamine to six equivalents raised the overall yield to 46% (Table 2, entry 4). However, the use of eight equivalents of propargylamine did not improve the yield further (Table 2, entry 5). Likewise, other modifications such as decreasing or increasing the temperature of the substitution step (Table 2, entries 6 and 7), replacing tetrahydrofuran with ethyl acetate as the solvent (Table 2, entries 8 and 9), and increasing the amount of triethylamine in the acylation step (Table 2, entry 10) or the use of microwave irradiation[10] (Table 2, entry 11) did not improve the overall yield. As expected, the use of chloroacetyl chloride instead of bromoacetyl bromide in the acylation (step c) gave less reactive intermediates, and heating or microwave activation was necessary for the substitution reactions to proceed (Table 2, entry 12).

Next, we resynthesised the alternating peptoid **2** by combining the optimised conditions for incorporation of both the α- and β-peptoid residues (Table 1, entry 3 and Table 2, entry 3). The reaction conditions listed in Table 2 (entry 3) are not the best in terms of yield (see entry 4), but they were considered the best compromise in terms of both the yield and the number of equivalents of propargylamine used. The α,β-tetrapeptoid **2** was isolated in 45% overall yield (HPLC purity = 95%) after one final flash chromatographic purification. For comparison we synthesised α,β-tetrapeptoid **2** where each amine intermediate was purified; an overall yield of 40% was obtained which demonstrates clearly the efficiency of our methodology.

Using the optimised conditions for α-peptoid residue synthesis we also prepared α-tetrapeptoid **3** in seven steps and 41% overall yield (Scheme 2). Due to difficulties in purifying the final tetramer an additional chromatographic purification of the final bromoacetate intermediate (step six) was necessary in order to obtain the desired product in pure form (HPLC purity = 97%).

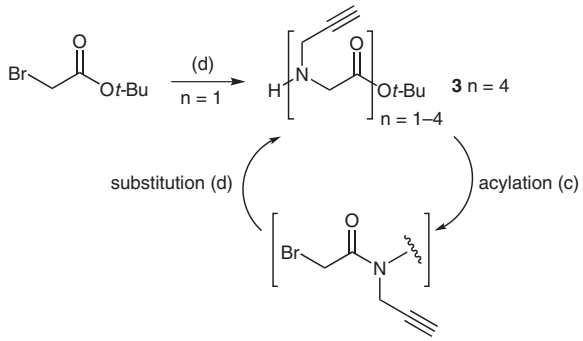
In order to demonstrate the potential of our methodology we easily synthesised 2.5 grams of β-tetrapeptoid **4** (Scheme 3). The product was obtained in high purity (HPLC purity = 98%) and 74% overall yield in seven

Table 2 Optimisation of α-Peptoid Residue Formation for the Synthesis of α,β-Alternating Tetrapeptoid **2**



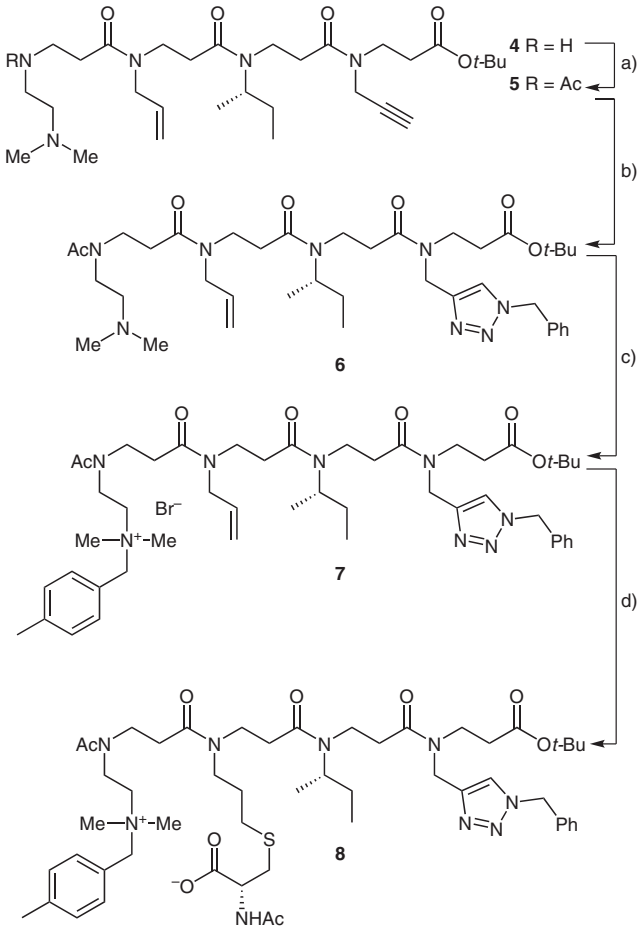
Entry	Acylation (step c)[a]	Substitution (step d)[a]	Yield (%)
1	$BrCOCH_2Br$ (1.2), Et_3N (1.2), THF, 0 °C, 1 h	propargylamine (2.0), Et_3N (2.0), THF, r.t., overnight	29
2	$BrCOCH_2Br$ (1.2), Et_3N (1.2), THF, 0 °C, 1 h	propargylamine (4.0), THF, r.t., overnight	27
3	$BrCOCH_2Br$ (1.2), Et_3N (1.2), THF, 0 °C, 1 h	propargylamine (4.0), Et_3N (2.0), THF, r.t., overnight	42
4	$BrCOCH_2Br$ (1.2), Et_3N (1.2), THF, 0 °C, 1 h	propargylamine (6.0), Et_3N (2.0), THF, r.t., overnight	46
5	$BrCOCH_2Br$ (1.2), Et_3N (1.2), THF, 0 °C, 1 h	propargylamine (8.0), Et_3N (2.0), THF, r.t., overnight	45
6	$BrCOCH_2Br$ (1.2), Et_3N (1.2), THF, 0 °C, 1 h	propargylamine (6.0), Et_3N (2.0), THF, 0 °C, overnight	41
7	$BrCOCH_2Br$ (1.2), Et_3N (1.2), THF, 0 °C, 1 h	propargylamine (6.0), Et_3N (2.0), THF, 40 °C, overnight	40
8	$BrCOCH_2Br$ (1.2), Et_3N (1.2), THF, 0 °C, 1 h	propargylamine (6.0), Et_3N (2.0), EtOAc, r.t., overnight	39
9	$BrCOCH_2Br$ (1.2), Et_3N (1.2), EtOAc, 0 °C, 1 h	propargylamine (6.0), Et_3N (2.0), THF, r.t., overnight	41
10	$BrCOCH_2Br$ (1.2), Et_3N (1.3), THF, 0 °C, 1 h	propargylamine (6.0), Et_3N (2.0), THF, r.t., overnight	44
11	$BrCOCH_2Br$ (1.2), Et_3N (1.2), THF, 0 °C, 1 h	propargylamine (4.0), Et_3N (2.0), THF, 50 °C, MW, 5 min	37
12	$ClCOCH_2Cl$ (1.2), Et_3N (1.2), THF, 0 °C, 1 h	propargylamine (4.0), Et_3N (2.0), THF, 50 °C, overnight	44

[a] Numbers in parentheses are the equivalents used.



Scheme 2 Synthesis of α-tetrapeptoid **3**. *Reagents and conditions*: (c) $BrCH_2COBr$ (1.2 equiv), Et_3N (1.2 equiv), THF, 0 °C, 1 h; (d) propargylamine (4.0 equiv), Et_3N (2.0 equiv), THF, 0 °C to r.t., overnight, 41% (over 7 steps).

steps, requiring only a single final flash chromatographic purification. Although our method is limited to the use of volatile amines, it was still possible to install side chains that may serve as entries to more complex structures. Indeed, the model peptoid **4** contains different and useful side chains; an α-chiral *sec*-butyl that can, for example, be used to induce secondary structures, and a dimethylaminoethyl moiety which can be exploited to form an ammonium salt in order to increase the water solubility of the peptoid. Furthermore, the allyl and propargyl side chains can be derivatised successively by click thiol–ene coupling (TEC)[11] and copper-catalysed azide–alkyne cycloaddition (CuAAC).[12] The latter has already been used widely for click ligation on peptoid scaffolds,[8,13] whereas the century-old thiol–ene coupling reaction[14] remains unexploited in this research domain. Recently, thiol–ene coupling and copper-catalysed azide–alkyne cycloaddition have been combined for successive and selective chemical ligations.[15] In order to demonstrate this principle the copper-catalysed azide–alkyne cycloaddition ligation should be carried out first, since otherwise the alkyne would also react with the thiol during irradiation. We then planned to perform the thiol–ene coupling ligation and complete the selective ligations by forming the ammonium salt. However, preliminary studies showed that the thiol underwent rapid deprotonatation by the tertiary amine under the thiol–ene coupling conditions making it inactive. We therefore opted to form the ammonium salt by nucleophilic substitution prior to the thiol–ene coupling ligation. Thus, N-acetylated peptoid **5**, obtained in excellent yield from model peptoid **4**, was subjected to copper-catalysed azide–alkyne cycloaddition with benzyl azide in the presence of copper(II) sulfate (8 mol%) and ascorbic acid (24 mol%) in *tert*-butyl alcohol–water to give **6** in 86% yield. Next, the peptoid ammonium salt **7** was obtained in 87% yield by reaction of **6** with 4-methylbenzyl bromide. Finally, peptoid **7** was subjected to a photoclick thiol–ene reaction in water with *N*-acetyl-L-cysteine in the presence of 2,2-dimethoxy-2-phenylacetophenone (DPAP) as the photoinitiator.[16] The fully functionalised β-tetrapeptoid **8** was isolated in an excellent 86% yield (HPLC purity = 93%) by simple extraction from the aqueous layer.



Scheme 3 Structure of model β-tetrapeptoid **4** and successive post-modifications. *Reagents and conditions*: (a) AcCl, Et_3N, EtOAc, 0 °C, 30 min, 94%; (b) BnN_3, $CuSO_4$, ascorbic acid, *t*-BuOH–H_2O (3:1), r.t., 4 h, 86%; (c) 4-methylbenzyl bromide, CH_2Cl_2, r.t., 2 h, 87%; (d) *N*(Ac)-L-cysteine, DPAP, H_2O, *hν*, Pyrex reactor, 6 h, 86%.

In conclusion, we have developed a highly convenient methodology for the solution-phase synthesis of multifunctional peptoids. Thus, β- and α,β-tetrapeptoids have been synthesised in seven steps and in high purity where only the final products were purified by flash chromatography. All reaction intermediates were isolated by filtration and/or evaporation. The methodology is also applicable to the synthesis of α-tetrapeptoids, in which case, additional purification of the final intermediate by flash chromatography was necessary in order to obtain the pure product. This method is highly suitable for gram-scale synthesis, and although limited to the use of volatile amines, we have shown that various functional groups can be incorporated for further selective transformations. The fully post-modified peptoid **8** was prepared in 45% overall yield in 11 steps starting from *tert*-butyl acrylate. This excellent overall yield demonstrates the efficiency of both the peptoid synthesis and successive post-modifications using click ligation methods. Overall, this methodology should be useful for gram-scale synthesis of relatively short multifunctional peptoids, and is a valuable alternative to solid-phase methods.

THF was distilled from potassium/benzophenone under N_2, and stored over 4 Å molecular sieves. CH_2Cl_2 and MeOH were distilled from CaH_2 under N_2, and stored over 4 Å molecular sieves. EtOAc, CH_2Cl_2, cyclohexane and MeOH for column chromatography were distilled before use. Et_3N was distilled from KOH and stored over 4 Å molecular sieves. (*S*)-(+)-*sec*-Butylamine was obtained by optical resolution of (±)-*sec*-butylamine following a literature procedure.[17]All other solvents and chemicals were obtained from commercial sources and used as supplied. TLC was performed on Merck TLC aluminum sheets, silica gel 60, F_{254}. The extent of reactions was, when applicable, followed by TLC and/or HPLC. Components were made visual with UV light and/or ninhydrin in EtOH/AcOH. Flash chromatography was performed with Merck silica gel 60, 40-63 μm. Unless otherwise stated, flash chromatography was performed using the eluent system for which the R_f values are given. Specific rotations were measured on a Jasco DIP-370 polarimeter using a 10 cm cell. IR spectra were recorded on a Shimadzu FTIR-8400S spectrometer equipped with a Pike Technologies MIRacle™ ATR, or on a Perkin-Elmer 881 spectrometer, and wavenumbers (ν) are expressed in cm^{-1}. NMR spectra were recorded on a 400 MHz Bruker AC 400 spectrometer. Chemical shifts are referenced to the residual solvent peak. The following multiplicity abbreviations are used: (s) singlet, (m) multiplet, and (br) broad. All NMR spectral data are of rotameric mixtures. Where applicable, assignments were based on COSY, HMBC, HSQC and *J*-mod-experiments. HRMS were recorded on a Micromass Q-Tof Micro (3000V) apparatus. HPLC analysis was performed on a Waters 590 instrument equipped with an Acclaim® 120 column (C18, 5 μm, 120 Å, 4.6 × 250 mm) and a Waters 484 UV detector.

Acylation (β-Peptoid Residues, Step a); General Procedure

To a soln of the crude secondary amine (1.0 equiv, 0.2 M) in THF at 0 °C under Ar, were added Et_3N (2.2 equiv) and acryloyl chloride (1.2 equiv). After stirring for 1 h at 0 °C, the resulting mixture was diluted with EtOAc (10 mL per mmol of starting material) and filtered. The solids were rinsed with EtOAc and the filtrate concd and dried in vacuo to yield the crude acrylamide.

Aza-Michael Addition (β-Peptoid Residues, Step b); General Procedure

To a soln of *tert*-butyl acrylate or the crude acrylamide (1.0 equiv, 0.4 M) in MeOH at r.t. under Ar, was added the appropriate primary amine (2.0 equiv). After stirring overnight at 50 °C, the mixture was concd under reduced pressure. EtOAc was added to the residue which was then concd under reduced pressure. This was repeated twice and the residue dried in vacuo to yield the desired crude secondary amine.

Acylation (α-Peptoid Residues, Step c); General Procedure

To a soln of the crude secondary amine (1.0 equiv, 0.2 M) in THF at 0 °C under Ar, were added Et_3N (1.2 equiv) and bromoacetyl bromide (1.2 equiv). After stirring for 1 h at 0 °C, the resulting mixture was diluted with EtOAc (10 mL per mmol of starting material) and filtered. The solids were rinsed with EtOAc and the filtrate concd and dried in vacuo to yield the crude bromoacetyl amide.

Substitution (α-Peptoid Residues, Step d); General Procedure

To a soln of *tert*-butyl bromoacetate or the crude bromoacetyl amide (1.0 equiv, 0.2 M) in THF at 0 °C under Ar, was added Et_3N (2.0 equiv) followed by the appropriate primary amine (4.0 equiv). After stirring overnight at r.t., the resulting mixture was diluted with EtOAc (10 mL per mmol of starting material) and filtered. The solids were rinsed with EtOAc and the filtrate concd under reduced pressure. EtOAc was added to the residue which was then concd under reduced pressure. This was repeated twice and the residue was dried in vacuo to yield the desired crude secondary amine.

β-Tetrapeptoid 1

Linear β-tetrapeptoid **1** was prepared starting from *tert*-butyl acrylate (384 mg, 3.00 mmol) by application of the appropriate general procedures and using propargylamine as the amine reagent. Flash chromatography of the crude product (EtOAc to EtOAc–MeOH, 90:10) yielded peptoid **1** as a pale-yellowish oil.

Yield: 1.01 g (65%); R_f = 0.22 (EtOAc–MeOH, 95:5).

IR (ATR): 3293, 3249, 2978, 2934, 1722, 1641, 1466, 1442, 1437, 1420, 1209, 1153, 754, 702 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38 (s, 9 H, *t*-Bu), 2.07–2.12 (br s, 1 H, N*H*), 2.15–2.37 (m, 4 H, 4 × $CH_2C{\equiv}CH$), 2.45–2.83 (m, 8 H, 4 × $NCH_2CH_2C{=}O$), 2.88–2.94 (m, 2 H, $HNCH_2CH_2C{=}O$), 3.35–3.39 (m, 2 H, $HNCH_2C{\equiv}CH$), 3.55–3.77 (m, 6 H, 3 × $NCH_2CH_2C{=}O$), 4.03–4.19 (m, 6 H, 3 × $CH_2C{\equiv}CH$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.9 (3 CH_3, *t*-Bu), 31.4, 31.6, 31.7, 31.9, 32.0 (2 CH_2, 2 × $NCH_2CH_2C{=}O$), 32.8, 32.9, 33.1 (CH_2, $NCH_2CH_2C{=}O$), 33.9, 34.0, 34.1, 34.3, 34.4, 34.5, 34.6 (2 CH_2, $CH_2C{\equiv}CH$, $NCH_2CH_2C{=}O$), 38.2, 38.3, 38.4, 38.7, 38.9 (3 CH_2, 2 × $CH_2C{\equiv}CH$, $HNCH_2C{\equiv}CH$), 42.6, 42.8, 43.0, 43.1, 43.3, 43.4, 43.5, 43.6, 43.7 (3 CH_2, 3 × $NCH_2CH_2C{=}O$), 44.0, 44.1 (CH_2, $HNCH_2CH_2C{=}O$), 71.4, 71.6, 71.7, 71.9, 72.0, 72.5, 72.7, 73.1 (4 CH, 4 × $CH_2C{\equiv}CH$), 78.4, 78.7, 78.8, 78.9, 79.1, 79.2, 81.8 (4 C, 4 × $CH_2C{\equiv}CH$), 80.6, 80.7, 80.8, 81.2, 81.4 (C, *t*-Bu), 169.6, 169.7, 169.8, 169.9, 170.0, 170.1, 170.3, 170.7, 170.9, 171.0, 171.3, 171.5, 171.9, 171.9 (4 C, 4 × *C*=O).

HRMS–ESI: *m*/*z* $[M + H]^+$ calcd for $C_{28}H_{38}N_4O_5$: 511.2920; found: 511.2917.

HPLC [H_2O (0.1% TFA)–MeOH, 30:70, flow = 0.50 mL/min]: t_R = 10.33 min, purity = 99%.

α,β-Tetrapeptoid 2

Linear α,β-tetrapeptoid **2** was prepared starting from *tert*-butyl acrylate (384 mg, 3.00 mmol) by application of the appropriate general procedures and using propargylamine as the amine reagent. Flash chromatography of the crude product (EtOAc to EtOAc–MeOH, 90:10) yielded peptoid **2** as a yellowish oil.

Yield: 658 mg (45%); R_f = 0.40 (EtOAc–MeOH, 90:10).

IR (ATR): 3291, 3256, 2979, 2931, 2360, 2342, 1723, 1719, 1653, 1648, 1472, 1465, 1457, 1436, 1420, 1369, 1249, 1211, 1196, 1152, 846, 734, 720 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40–1.41 (2 × s, 9 H, *t*-Bu), 2.15–2.46 (m, 5 H, 4 × $CH_2C{\equiv}CH$, N*H*), 2.46–2.91 (m, 4 H, 2 × $NCH_2CH_2C{=}O$), 3.37–3.51 (m, 2 H, $HNCH_2C{\equiv}CH$), 3.51–3.60 (m, 2 H, $HNCH_2C{=}O$), 3.60–3.81 (m, 4 H, $NCH_2CH_2C{=}O$), 4.05–4.30 (m, 6 H, $NCH_2C{\equiv}CH$), 4.31–4.54 (m, 2 H, $NCH_2C{=}O$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.0 (3 CH_3, *t*-Bu), 31.5, 31.6, 31.7, 32.6, 33.3, 33.7, 33.9, 34.0, 34.1 (2 CH_2, 2 × $NCH_2CH_2C{=}O$), 34.3, 34.4, 34.6, 34.7, 35.3, 35.4, 37.6, 37.7, 37.8, 38.0, 38.1, 38.3 (4 CH_2, 3 × $NCH_2C{\equiv}CH$, $HNCH_2C{\equiv}CH$), 41.7, 41.8, 42.2, 42.4, 42.7, 43.4, 43.5, 43.8, 43.9, 44.1 (2 CH_2, 2 × $NCH_2CH_2C{=}O$), 45.9, 46.0, 46.2, 47.5, 47.6 (CH_2, $NCH_2C{=}O$), 48.6, 48.9, 49.1 (CH_2, $NHCH_2C{=}O$), 71.8, 72.0, 72.2, 72.3, 72.4, 72.5, 72.6, 72.7, 72.9, 73.2, 73.4, 73.5, 73.8 (4 CH, 4 × $CH_2C{\equiv}CH$), 78.1, 78.4, 78.7 (4 C, 4 × $CH_2C{\equiv}CH$), 81.0, 81.4 (C, *t*-Bu), 167.0, 167.4, 167.7, 170.1, 170.4, 170.9, 171.3, 171.4, 171.8 (4 C, 4 × *C*=O).

HRMS–ESI: *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{35}N_4O_5$: 483.2607; found: 483.2603.

HPLC [H_2O (0.1% TFA)–MeOH, 40:60, flow = 0.50 mL/min]: t_R = 8.89 min, purity = 95%.

α-Tetrapeptoid 3

Linear a-tetrapeptoid **3** was prepared starting from *tert*-butyl bromoacetate (585 mg, 3.00 mmol) by application of the appropriate

general procedures and using propargylamine as the amine reagent. Flash chromatography of the crude product (EtOAc to EtOAc–MeOH, 90:10) yielded peptoid **3** as a yellowish oil. In order to obtain a pure product, the final bromoacetyl amide intermediate was purified by flash chromatography (EtOAc–cyclohexane, 60:40) before being subjected to the final substitution step.

Yield: 546 mg (41%); R_f = 0.40 (EtOAc–MeOH, 90:10).

IR (ATR): 3287, 3256, 2979, 2936, 2360, 2343, 1734, 1663, 1653, 1472, 1465, 1457, 1437, 1420, 1369, 1349, 1213, 1153, 961, 750, 740, 668 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.23–1.41 (m, 9 H, *t*-Bu), 2.03 (br s, 1 H, N*H*), 2.09–2.47 (m, 4 H, 4 × $CH_2C{\equiv}CH$), 3.18–3.34 (m, 3 H, 0.5 × $NHCH_2C{\equiv}CH$, $NHCH_2C{=}O$), 3.45–3.55 (m, 1 H, 0.5 × $NHCH_2C{=}O$), 3.89–4.20 (m, 10 H, 2 × $NCH_2C{=}O$, 3 × $NCH_2C{\equiv}CH$), 4.25–4.42 (m, 2 H, $NCH_2C{=}O$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.5, 27.6 (3 CH_3, *t*-Bu), 35.1, 35.2, 35.4, 35.5, 35.6, 35.7, 35.9, 36.6, 36.7, 37.0, 37.3, 37.6 (4 CH_2, $NHCH_2C{\equiv}CH$, 3 × $NCH_2C{\equiv}CH$), 45.7, 45.8, 46.0, 46.2, 46.3, 46.4, 46.5, 46.6, 46.7, 47.5, 47.6, 47.7, 47.8, 48.0, 48.1, 48.6 (4 CH_2, $NHCH_2C{=}O$, 3 × $NCH_2C{=}O$), 71.0, 71.4, 71.5, 71.7, 72.4, 72.5, 72.8, 73.1, 73.2, 73.3, 73.4, 73.5, 73.7, 73.8, 74.0, 74.1, 74.2 (4 CH, 4 × $CH_2C{\equiv}CH$), 76.8, 76.9, 77.1, 77.2, 77.3, 77.7, 77.8, 78.2, 78.3, 78.4 (4 C, 4 × $CH_2C{\equiv}CH$), 81.2, 81.4, 81.6, 81.7, 82.5, 82.6, 82.8, 83.0 (C, *t*-Bu), 167.1, 167.3, 167.4, 167.5, 167.6, 168.0, 168.1, 168.2, 170.5, 170.6, 170.8, 171.1, 171.2 (4 C, 4 × *C*=O).

HRMS–ESI: *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{31}N_4O_5$: 455.2294; found: 455.2301.

HPLC [H_2O (0.1% TFA)–MeOH, 30:70, flow = 0.50 mL/min]: t_R = 6.51 min, purity = 97%.

β-Tetrapeptoid 4

Linear b-tetrapeptoid **4** was prepared starting from *tert*-butyl acrylate (768 mg, 5.99 mmol) by application of the appropriate general procedures and using propargylamine, (*S*)-(+)-*sec*-butylamine, allylamine and *N*,*N*-dimethylethylenediamine as the amine reagents. Flash chromatography of the crude product [EtOAc–MeOH, 80:20 then EtOAc–MeOH–concd NH_3 (aq), 80:20:5] yielded peptoid **4** as a pale-yellowish oil.

Yield: 2.49 g (74%); $[\alpha]_D^{21}$ +3.2 (*c* 0.71, $CHCl_3$); R_f = 0.20 [EtOAc–MeOH–concd NH_3 (aq), 80:20:5].

IR (ATR): 2974, 1726, 1636, 1456, 1445, 1418, 1368, 1287, 1252, 1217, 1153, 1098, 1063, 1030, 993, 924, 845, 754, 731 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.74–0.84 [m, 3 H, $CH(CH_3)CH_2CH_3$], 1.05–1.15 [m, 3 H, $CH(CH_3)CH_2CH_3$], 1.37 (s, 9 H, *t*-Bu), 1.39–1.54 [m, 2 H, $CH(CH_3)CH_2CH_3$], 2.13–2.26 [m, 7 H, $N(CH_3)_2$, $CH_2C{\equiv}CH$], 2.30–2.92 [m, 14 H, $HNCH_2CH_2C{=}O$, $CH_2N(CH_3)_2$, $CH_2CH_2N(CH_3)_2$, 4 × $NCH_2CH_2C{=}O$], 3.24–3.78 [m, 7 H, $CH(CH_3)CH_2CH_3$, 3 × $NCH_2CH_2C{=}O$], 3.85–3.98 (m, 2 H, $CH_2CH{=}CH_2$), 4.03–4.19 (m, 2 H, $CH_2C{\equiv}CH$), 5.02–5.15 (m, 2 H, $CH_2CH{=}CH_2$), 5.64–5.77 (m, 1 H, $CH_2CH{=}CH_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.0, 11.1 [CH_3, $CH(CH_3)CH_2CH_3$], 18.3, 19.2 [CH_3, $CH(CH_3)CH_2CH_3$], 27.1, 27.6 [CH_2, $CH(CH_3)CH_2CH_3$], 27.9 (3 CH_3, *t*-Bu), 32.1, 32.4, 32.7, 32.9, 33.7, 33.9, 34.1, 34.4 (4 CH_2, 4 × $NCH_2CH_2C{=}O$), 33.9, 38.2 (CH_2, $CH_2C{\equiv}CH$), 37.4, 39.3, 39.5 (CH_2, $NCH_2CH_2C{=}O$), 42.5, 42.6, 43.1, 43.5, 43.6 (2 CH_2, 2 × $NCH_2CH_2C{=}O$), 45.43 (CH_2, $NCH_2CH_2C{=}O$), 45.37, 45.6, 45.7, 45.8 [2 CH_3, $N(CH_3)_2$], 47.2 [CH_2, $CH_2CH_2N(CH_3)_2$], 48.0, 48.1, 51.0, 51.1 (CH_2, $CH_2CH{=}CH_2$), 54.4, 54.5 [CH, $CH(CH_3)CH_2CH_3$], 58.5, 58.7 [CH_2, $CH_2N(CH_3)_2$], 71.6, 71.9, 72.5, 73.0 (CH, $CH_2C{\equiv}CH$), 78.6, 78.7, 78.9 (C, $CH_2C{\equiv}CH$), 80.6, 81.1 (C, *t*-Bu), 116.3, 116.4, 116.5, 116.9 (CH_2, $CH_2CH{=}CH_2$), 132.8, 133.0, 133.3 (CH, $CH_2CH{=}CH_2$), 170.0, 170.1, 170.3, 170.8, 170.9, 171.0, 171.1, 171.2, 172.1 (4 C, 4 × *C*=O).

HRMS–ESI: *m*/*z* $[M + H]^+$ calcd for $C_{30}H_{54}N_5O_5$: 564.4119; found: 564.4138.

HPLC [H_2O (0.1% TFA)–MeOH, 30:70, flow = 0.50 mL/min]: t_R = 7.09 min, purity = 98%.

β-Tetrapeptoid 5

To a soln of peptoid **4** (846 mg, 1.50 mmol) and Et_3N (0.50 mL, 3.59 mmol) in EtOAc (30 mL), at 0 °C under Ar, was added AcCl (0.117 mL, 1.65 mmol). After stirring for 30 min at 0 °C the mixture was washed with sat. aq $NaHCO_3$ soln (2 × 15 mL). The combined aq layer was extracted with EtOAc (15 mL) and the combined organic layers dried over Na_2SO_4, filtered and concd under reduced pressure. Flash chromatography (CH_2Cl_2–MeOH, 90:10 to 80:20) of the residue yielded peptoid **5** as a colorless oil.

Yield: 856 mg (94%); $[\alpha]_D^{21}$ +1.1 (*c* 0.74, $CHCl_3$); R_f = 0.38 (CH_2Cl_2–MeOH, 90:10).

IR (ATR): 1724, 1635, 1446, 1419, 1368, 1325, 1308, 1289, 1256, 1210, 1153, 1022 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.75–0.85 [m, 3 H, $CH(CH_3)CH_2CH_3$], 1.04–1.16 [m, 3 H, $CH(CH_3)CH_2CH_3$], 1.38 (s, 9 H, *t*-Bu), 1.40–1.57 [m, 2 H, $CH(CH_3)CH_2CH_3$], 2.00–2.09 (m, 3 H, Ac), 2.14–2.30 [m, 7 H, $N(CH_3)_2$, $CH_2C{\equiv}CH$], 2.33–2.79 [m, 10 H, 4 × $NCH_2CH_2C{=}O$, $CH_2CH_2N(CH_3)_2$], 3.10–3.79 [m, 11 H, $CH(CH_3)CH_2CH_3$, 4 × $NCH_2CH_2C{=}O$, $CH_2CH_2N(CH_3)_2$], 3.85–4.00 (m, 2 H, $CH_2CH{=}CH_2$), 4.04–4.20 (m, 2 H, $CH_2C{\equiv}CH$), 5.02–5.19 (m, 2 H, $CH_2CH{=}CH_2$), 5.65–5.80 (m, 1 H, $CH_2CH{=}CH_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.0 [CH_3, $CH(CH_3)CH_2CH_3$], 18.3, 19.2 [CH_3, $CH(CH_3)CH_2CH_3$], 21.4 (CH_3, Ac), 27.1, 27.6 [CH_2, $CH(CH_3)CH_2CH_3$], 27.9 (3 CH_3, *t*-Bu), 31.3, 31.5, 32.0, 32.1, 32.5, 32.7, 33.6, 34.0, 34.1, 34.4 (4 CH_2, 4 × $NCH_2CH_2C{=}O$), 33.9, 38.2 (CH_2, $CH_2C{\equiv}CH$), 37.4, 37.5, 39.3, 39.5 (CH_2, $NCH_2CH_2C{=}O$), 42.5, 42.6, 43.1, 43.2, 43.4, 43.5, 43.6, 43.8, 45.1, 47.9, 48.0 [4 CH_2, 3 × $NCH_2CH_2C{=}O$, $CH_2CH_2N(CH_3)_2$], 45.3, 45.7 [2 CH_3, $N(CH_3)_2$], 48.1, 48.3, 51.0, 51.1 (CH_2, $CH_2CH{=}CH_2$), 54.5, 54.6 [CH, $CH(CH_3)CH_2CH_3$], 56.6, 56.7, 58.0 [CH_2, $CH_2CH_2N(CH_3)_2$], 71.6, 71.9, 72.0, 72.5, 73.0 (CH, $CH_2C{\equiv}CH$), 78.7, 78.8, 78.9 (C, $CH_2C{\equiv}CH$), 80.6, 80.7, 81.1 (C, *t*-Bu), 116.3, 116.9, 117.1 (CH_2, $CH_2CH{=}CH_2$), 132.8, 133.0, 133.1, 133.3 (CH, $CH_2CH{=}CH_2$), 170.0, 170.1, 170.2, 170.3, 170.5, 170.7, 170.8, 170.9, 171.1, 171.2, 171.6 (5 C, 5 × *C*=O).

HRMS–ESI: *m*/*z* $[M + H]^+$ calcd for $C_{32}H_{56}N_5O_6$: 606.4225; found: 606.4233.

HPLC [H_2O (0.1% TFA)–MeOH, 30:70, flow = 0.50 mL/min]: t_R = 9.00 min, purity = 96%.

β-Tetrapeptoid 6

To a soln of peptoid **5** (586 mg, 0.97 mmol) in *t*-BuOH (9 mL, 0.1 M) at r.t. under Ar, were added freshly prepared aq ascorbic acid (0.1 M, 2.32 mL, 0.24 equiv), aq $CuSO_4$ (0.1 M, 0.77 mL, 0.08 equiv) and BnN_3 (258 mg, 2 equiv). After stirring for 4 h at r.t., H_2O (16 mL) was added and the product was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic layer was dried over $MgSO_4$, filtered and concd under reduced pressure. Flash chromatography (CH_2Cl_2–MeOH, 90:10 to 80:20) yielded peptoid **6** as a pale-greenish oil.

Yield: 613 mg (86%); $[\alpha]_D^{21}$ +1.0 (*c* 0.87, $CHCl_3$); R_f = 0.50 (CH_2Cl_2–MeOH, 80:20).

IR (ATR): 2971, 2938, 2876, 2822, 2770, 1724, 1635, 1455, 1448, 1419, 1368, 1328, 1253, 1153, 1047, 1028, 1022, 923, 730 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.73–0.91 [m, 3 H, $CH(CH_3)CH_2CH_3$], 1.01–1.17 [m, 3 H, $CH(CH_3)CH_2CH_3$], 1.38 (s, 9 H, *t*-Bu), 1.36–1.58 [m, 2 H, $CH(CH_3)CH_2CH_3$], 1.98–2.14 (m, 3 H, Ac), 2.24 [s, 3 H, $CH_2CH_2N(CH_3)_2$], 2.35–2.47 [m, 3 H, $CH_2CH_2N(CH_3)_2$], 2.36–2.86 [m, 10 H, 4 × $NCH_2CH_2C{=}O$,

$CH_2CH_2N(CH_3)_2$], 3.25–3.71 [m, 10 H, 4 × NCH_2CH_2C=O, $CH_2CH_2N(CH_3)_2$], 3.61–3.79 [m, 1 H, $CH(CH_3)CH_2CH_3$], 3.90–4.03 (m, 2 H, CH_2CH=CH_2), 4.45–4.67 (m, 2 H, NCH_2-triazole), 5.04–5.21 (m, 2 H, CH_2CH=CH_2), 5.40–5.53 (m, 2 H, $NCH_2C_6H_5$), 5.66–5.81 (m, 1 H, CH_2CH=CH_2), 7.18–7.38 (m, 5 H, $CH_2C_6H_5$), 7.44–7.54 (m, 1 H, C=CHN).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.1 [CH_3, $CH(CH_3)CH_2CH_3$], 18.3, 19.3 [CH_3, $CH(CH_3)CH_2CH_3$], 21.5 (CH_3, Ac), 27.2, 27.7 [CH_2, $CH(CH_3)CH_2CH_3$], 28.0 (3 CH_3, *t*-Bu), 31.3, 31.5, 32.1, 32.4, 32.5, 32.6, 32.7, 33.6, 33.8, 33.9, 34.2, 34.3, 34.5 (4 CH_2, 4 × NCH_2CH_2C=O), 37.5, 37.6, 39.6, 40.4, 40.5, 42.2, 42.4, 42.7, 42.8, 42.9, 43.4, 43.6, 43.8, 45.2, 47.9 [6 CH_2, 4 × NCH_2CH_2C=O, $CH_2CH_2N(CH_3)_2$, NCH_2-triazole], 44.9, 45.7 [2 CH_3, $CH_2CH_2N(CH_3)_2$], 48.3, 48.4, 51.1, 51.2 (CH_2, CH_2CH=CH_2), 54.1 (CH_2, $NCH_2C_6H_5$), 54.5 [CH, $CH(CH_3)CH_2CH_3$], 56.3, 58.0 [CH_2, $CH_2CH_2N(CH_3)_2$], 80.6, 81.0 (C, *t*-Bu), 116.3, 117.0, 117.2 (CH_2, CH_2CH=CH_2), 121.7, 123.2 (CH, C=CHN), 128.0, 128.6, 128.7, 129.0 (5 CH, $CH_2C_6H_5$), 133.0, 133.1, 133.2, 133.4 (CH, CH_2CH=CH_2), 134.5 (C, $CH_2C_6H_5$), 144.5, 144.6 (C, C=CHN), 170.0, 170.2, 170.6, 170.7, 170.9, 171.1, 171.2, 171.3, 171.6 (5 C, 5 × C=O).

HRMS–ESI: *m*/*z* [M + H]$^+$ calcd for $C_{39}H_{63}N_8O_6$: 739.4871; found: 739.4876.

HPLC [H_2O (0.1% TFA)–MeOH, 30:70, flow = 0.50 mL/min]: t_R = 10.29 min, purity = 98%.

β-Tetrapeptoid 7

To a soln of peptoid **6** (613 mg, 0.83 mmol) in CH_2Cl_2 (5 mL, 0.2 M) at r.t. was added 4-methylbenzyl bromide (161 mg, 1.05 equiv). The resulting mixture was stirred for 2 h and the solvent was evaporated under reduced pressure. Flash chromatography of the residue (CH_2Cl_2–MeOH, 90:10 to 80:20) yielded peptoid **7** as a white foam.

Yield: 669 mg (87%); $[\alpha]_D^{21}$ +0.6 (*c* 0.87, $CHCl_3$); R_f = 0.68 (CH_2Cl_2–MeOH, 80:20).

IR (ATR): 3004, 2975, 2931, 2878, 1724, 1635, 1454, 1419, 1368, 1328, 1247, 1220, 1152, 1048, 846, 819, 789, 751 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.73–0.91 [m, 3 H, $CH(CH_3)CH_2CH_3$], 1.02–1.21 [m, 3 H, $CH(CH_3)CH_2CH_3$], 1.40 (s, 9 H, *t*-Bu), 1.45–1.58 [m, 2 H, $CH(CH_3)CH_2CH_3$], 2.07–2.20 (m, 3 H, Ac), 2.30–2.92 (m, 11 H, $C_6H_4CH_3$, 4 × NCH_2CH_2C=O), 3.12–4.43 [m, 21 H, $N^+(CH_3)_2$, 4 × NCH_2CH_2C=O, $CH(CH_3)CH_2CH_3$, CH_2CH=CH_2, $CH_2CH_2N^+$], 4.44–4.72 (m, 2 H, NCH_2-triazole), 4.72–4.89 (m, 2 H, $N^+CH_2C_6H_4$), 4.96–5.24 (m, 2 H, CH_2CH=CH_2), 5.41–5.60 (m, 2 H, $NCH_2C_6H_5$), 5.66–5.93 (m, 1 H, CH_2CH=CH_2), 7.15–7.73 (m, 10 H, $CH_2C_6H_5$, C=CHN, $N^+CH_2C_6H_4$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.5, 10.6 [CH_3, $CH(CH_3)CH_2CH_3$], 17.7, 18.7 [CH_3, $CH(CH_3)CH_2CH_3$], 20.7, 20.9 (2 CH_3, Ac, $C_6H_4CH_3$), 26.5, 27.1 [CH_2, $CH(CH_3)CH_2CH_3$], 27.4 (3 CH_3, *t*-Bu), 31.3, 31.4, 31.8, 32.1, 33.2, 33.3, 33.7, 33.8, 33.9 (4 CH_2, 4 × NCH_2CH_2C=O), 36.8, 37.0, 39.2, 39.5, 39.7, 39.9, 41.6, 43.0, 44.8 (6 CH_2, 4 × NCH_2CH_2C=O, $CH_2CH_2N^+$, NCH_2-triazole), 47.4, 50.5 (CH_2, CH_2CH=CH_2), 48.9, 49.1 [2 CH_3, $N^+(CH_3)_2$], 53.4 (CH_2, $NCH_2C_6H_5$), 53.8 [CH, $CH(CH_3)CH_2CH_3$], 59.4 (CH_2, $CH_2CH_2N^+$), 67.3 (CH_2, $N^+CH_2C_6H_4$), 79.9, 80.4 (C, *t*-Bu), 115.5, 116.2 (CH_2, CH_2CH=CH_2), 120.6, 123.1 (CH, C=CHN), 123.4 (C, *p*-$N^+CH_2C_6H_4$), 127.4, 128.0, 128.4, 129.2 (9 CH, $CH_2C_6H_5$, $N^+CH_2C_6H_4$), 132.5, 132.8 (CH, CH_2CH=CH_2), 134.0 (C, $CH_2C_6H_5$), 140.3 (C, *ipso*-$N^+CH_2C_6H_4$), 169.5, 169.6, 169.7, 170.0, 170.3, 170.4, 170.5, 170.7, 170.9, 171.0 (5 C, 5 × C=O).

HRMS–ESI: *m*/*z* [M + H]$^+$ calcd for $C_{47}H_{71}N_8O_6$: 843.5497; found: 843.5510.

HPLC [H_2O (0.1% TFA)–MeOH, 30:70, flow = 0.50 mL/min]: t_R = 14.00 min, purity = 93%.

β-Tetrapeptoid 8

To a soln of peptoid **7** (99 mg, 0.11 mmol, 1 equiv) in CH_2Cl_2 (1 mL, 0.1 M) in a Pyrex tube was added *N*(Ac)-L-cysteine (34 mg, 2 equiv), DPAP (8 mg, 0.3 equiv) and H_2O (1 mL). The heterogeneous mixture was degassed with Ar until complete evaporation of CH_2Cl_2. The resulting aq soln was irradiated for 6 h, at r.t. under Ar, using a 400 W medium-pressure Hg lamp fitted with a Pyrex filter. The mixture was diluted with aq NH_4HCO_3 soln (1 M, 20 mL) and extracted with Et_2O (20 mL) and EtOAc (20 mL). The aq layer was then extracted with CH_2Cl_2 (4 × 15 mL). The combined organic layer was dried over $MgSO_4$, filtered and concd under reduced pressure to yield peptoid **8** as an off-white foam.

Yield: 93 mg (86%); $[\alpha]_D^{21}$ +21.7 (*c* 0.95, $CHCl_3$); R_f = 0.33 (CH_2Cl_2–MeOH, 80:20).

IR (ATR): 3398, 2975, 2934, 2874, 1723, 1628, 1623, 1615, 1456, 1429, 1423, 1369, 1326, 1288, 1252, 1223, 1151, 1048, 843, 820, 795, 752, 725 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 0.73–0.95 [m, 3 H, $CH(CH_3)CH_2CH_3$], 1.04–1.23 [m, 3 H, $CH(CH_3)CH_2CH_3$], 1.31, 1.41 (2 × s, 9 H, *t*-Bu), 1.48–1.66 [m, 2 H, $CH(CH_3)CH_2CH_3$], 1.74–1.93 (m, 2 H, $CH_2CH_2CH_2S$), 2.00 (s, 3 H, NHAc), 2.07–2.26 (m, 3 H, Ac), 2.29–2.41 (m, 3 H, $C_6H_4CH_3$), 2.41–2.98 (m, 12 H, 2 × CH_2S, 4 × NCH_2CH_2C=O), 2.99–3.19 [m, 6 H, $N^+(CH_3)_2$], 3.27–4.29 [m, 15 H, 4 × NCH_2CH_2C=O, $CH(CH_3)CH_2CH_3$, $CH_2CH_2CH_2S$, $CH_2CH_2N^+$), 4.35–4.45 (m, 1 H, SCH_2CHNHAc), 4.49–4.77 (m, 4 H, NCH_2-triazole and $N^+CH_2C_6H_4$], 5.52–5.63 (m, 2 H, $NCH_2C_6H_5$), 7.22–7.56 (m, 9 H, $CH_2C_6H_5$, $N^+CH_2C_6H_4$), 7.82–8.05 (m, 1 H, C=CHN).

^{13}C NMR (100 MHz, CD_3OD): δ = 11.6, 11.7 [CH_3, $CH(CH_3)CH_2CH_3$], 18.7, 19.6, 19.7 [CH_3, $CH(CH_3)CH_2CH_3$], 21.4, 21.6 (2 CH_3, Ac, $C_6H_4CH_3$), 23.0 (CH_3, NHAc), 28.4 (3 CH_3, *t*-Bu), 28.2, 28.6, 28.8, 29.6, 29.8, 30.0, 30.1, 30.4, 30.7, 30.8 [2 CH_2, $CH(CH_3)CH_2CH_3$, $NCH_2CH_2CH_2S$], 32.8, 32.9, 33.0, 33.3, 33.8, 33.9, 34.6, 34.7, 35.1, 35.2, 35.3, 35.9 (4 CH_2, 4 × NCH_2CH_2C=O), 38.7, 38.8, 41.0, 41.2, 41.4, 41.5, 43.6, 43.8, 44.1, 44.2, 44.5, 44.6, 44.7, 45.0, 45.2, 45.4, 45.5, 46.5, 46.7 (9 CH_2, 4 × NCH_2CH_2C=O, $CH_2CH_2N^+$, NCH_2-triazole, $CH_2CH_2CH_2SCH_2$), 49.9, 50.5 [2 CH_3, $N^+(CH_3)_2$], 53.7, 53.9 [CH, $CH(CH_3)CH_2CH_3$], 54.9 (CH_2, $NCH_2C_6H_5$), 55.8, 56.2 (CH, SCH_2CHNHAc), 61.4, 62.1 (CH_2, $CH_2CH_2N^+$), 69.4 (CH_2, $N^+CH_2C_6H_4$), 81.9, 82.1 (C, *t*-Bu), 124.5, 125.0 (CH, C=CHN), 125.7 (C, *p*-$N^+CH_2C_6H_4$), 129.2, 129.6, 130.1, 131.0, 134.2 (9 CH, $CH_2C_6H_5$, $N^+CH_2C_6H_4$), 136.8, 136.9 (C, $CH_2C_6H_5$), 142.5 (C, *ipso*-$N^+CH_2C_6H_4$), 145.5, 145.7 (C, C=CHN), 172.1, 172.4, 172.5, 172.7, 172.8, 173.0, 173.2, 173.3, 173.5, 173.6, 173.7, 174.0, 177.1, 177.3 (7 C, 7 × C=O).

HRMS–ESI: *m*/*z* [M + H]$^{2+}$ calcd for $C_{52}H_{81}N_9O_9S$: 503.7939; found: 503.7934.

HPLC [H_2O (0.1% TFA)–MeOH, 35:65, flow = 0.50 mL/min]: t_R = 15.91 min, purity = 93%.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis. Included are RP-HPLC data for all compounds and NMR spectra of products **1**, **2**, **3**, **4** and **8**.

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References

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(2) (a) *Pseudo-Peptides in Drug Discovery*; Nielsen, P. E., Ed.; Wiley-VCH: Weinheim, **2004**. (b) Patch, J. A.; Barron, A. E. *Curr. Opin. Chem. Biol.* **2002**, *6*, 872.

(3) (a) Simon, R. J.; Kania, R. S.; Zuckermann, R. N.; Huebner, V. D.; Jewell, D. A.; Banville, S.; Ng, S.; Wang, L.; Rosenberg, S.; Marlowe, C. K.; Spellmeyer, D. C.; Tan, R.; Frankel, A. D.; Santi, D. V.; Cohen, F. E.; Bartlett, P. A. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 9367. (b) Patch, J. A.; Kirshenbaum, K.; Seurynck, S. L.; Zuckermann, R. N.; Barron, A. E. In *Pseudo-Peptides in Drug Discovery*; Nielsen, P. E., Ed.; Wiley-VCH: Weinheim, **2004**, 1–31.

(4) Hamper, B. C.; Kolodziej, S. A.; Scates, A. M.; Smith, R. G.; Cortez, E. *J. Org. Chem.* **1998**, *63*, 708.

(5) Hjelmgaard, T.; Faure, S.; Caumes, C.; De Santis, E.; Edwards, A. A.; Taillefumier, C. *Org. Lett.* **2009**, *11*, 4100.

(6) (a) Armand, P.; Kirshenbaum, K.; Falicov, A.; Dunbrack, R. L.; Dill, K. A.; Zuckermann, R. N.; Cohen, F. E. *Folding Des.* **1997**, *2*, 369. (b) Kirschenbaum, K.; Barron, A. E.; Goldsmith, R. A.; Armand, P.; Bradley, E. K.; Truong, K. T. V.; Dill, K. A.; Cohen, F. E.; Zuckermann, R. N. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 4303. (c) Wu, C. W.; Sanborn, T. J.; Huang, K.; Zuckermann, R. N.; Barron, A. E. *J. Am. Chem. Soc.* **2001**, *123*, 6778. (d) Sanborn, T. J.; Wu, C. W.; Zuckermann, R. N.; Barron, A. E. *Biopolymers* **2002**, *63*, 12. (e) Lee, B.-C.; Zuckermann, R. N.; Dill, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 10999. (f) Fowler, S. A.; Luechapanichkul, R.; Blackwell, H. E. *J. Org. Chem.* **2009**, *74*, 1440. (g) Seo, J.; Barron, A. E.; Zuckermann, R. N. *Org. Lett.* **2010**, *12*, 492.

(7) (a) Fowler, S. A.; Blackwell, H. E. *Org. Biomol. Chem.* **2009**, *7*, 1508. (b) Zuckermann, R. N.; Kodadek, T. *Curr. Opin. Mol. Ther.* **2009**, *11*, 299. (c) Yoo, B.; Kirshenbaum, K. *Curr. Opin. Chem. Biol.* **2008**, *12*, 714.

(8) Roy, O.; Faure, S.; Thery, V.; Didierjean, C.; Taillefumier, C. *Org. Lett.* **2008**, *10*, 921.

(9) Norgren, A. S.; Zhang, S.; Arvidsson, P. I. *Org. Lett.* **2006**, *8*, 4533.

(10) (a) Gorske, B. C.; Jewell, S. A.; Guerard, E. J.; Blackwell, H. E. *Org. Lett.* **2005**, *7*, 1521. (b) Olivos, H. J.; Alluri, P. G.; Reddy, M. M.; Salony, D.; Kodadek, T. *Org. Lett.* **2002**, *4*, 4057. (c) Fowler, S. A.; Stacy, D. M.; Blackwell, H. E. *Org. Lett.* **2008**, *10*, 2329. (d) Messeguer, J.; Cortes, N.; García-Sanz, N.; Navarro-Vendrell, G.; Ferrer-Montiel, A.; Messeguer, A. *J. Comb. Chem.* **2008**, *10*, 974. (e) Fritz, D.; Bräse, S. *Synlett* **2010**, 1544.

(11) (a) Dondoni, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 8995. (b) Hoyle, C. E.; Bowman, C. N. *Angew. Chem. Int. Ed.* **2010**, *49*, 1540. (c) Lowe, A. B. *Polym. Chem.* **2010**, *1*, 17.

(12) (a) Huisgen, R. *Pure Appl. Chem.* **1989**, *61*, 613. (b) Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057. (c) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596. (d) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128.

(13) (a) Holub, J. M.; Kirshenbaum, K. *Chem. Soc. Rev.* **2010**, *39*, 1325. (b) Schilling, C.; Jung, N.; Bräse, S. In *Click Chemistry for Biotechnology and Materials Science*; Lahann, J., Ed.; Wiley: Chichester, **2009**, Chap. 2, 9. (c) Jang, H.; Farfarman, A.; Holub, J. M.; Kirshenbaum, K. *Org. Lett.* **2005**, *7*, 1951. (d) Holub, J. M.; Jang, H.; Kirshenbaum, K. *Org. Biomol. Chem.* **2006**, *4*, 1497. (e) Norgren, A. S.; Budke, C.; Majer, Z.; Heggemann, C.; Koop, T.; Sewald, N. *Synthesis* **2009**, 488.

(14) Posner, T. *Chem. Ber.* **1905**, *38*, 646.

(15) (a) Campos, L. M.; Killops, K. L.; Sakai, R.; Paulusse, J. M. J.; Damiron, D.; Drockenmuller, D. E.; Messmore, B. M.; Hawker, C. J. *Macromolecules* **2008**, *41*, 7063. (b) Fiore, M.; Chambery, A.; Marra, A.; Dondoni, A. *Org. Biomol. Chem.* **2009**, *7*, 3910. (c) Nurmi, L.; Lindqvist, J.; Randev, R.; Syrett, J.; Haddleton, D. M. *Chem. Commun.* **2009**, 2727. (d) Iehl, J.; Nierengarten, J.-F. *Chem. Commun.* **2010**, *46*, 4160.

(16) Fiore, M.; Marra, A.; Dondoni, A. *J. Org. Chem.* **2009**, *74*, 4422.

(17) Cohen, S. G.; Chao, H. M. *J. Am. Chem. Soc.* **1968**, *90*, 165.