Synthesis of Functionalized Glutamine- and Asparagine-Type Peptoids – Scope and Limitations

by **Carmen Cardenal**[a]), **Sidonie B. L. Vollrath**[a]), **Ute Schepers**[b]), and **Stefan Bräse***[a])[b])

[a]) Karlsruhe Institute of Technology (KIT), Institute of Organic Chemistry, Fritz-Haber-Weg 6, DE-76131 Karlsruhe (phone: +49 721 608 42902; mobile: +49 152 0160 1020; fax: +49 721 608 48581; e-mail: braese@kit.edu)

[b]) Institute of Toxicology and Genetics, KIT, Hermann von Helmholtz Platz 1, DE-76344 Eggenstein-Leopoldshafen

Dedicated with best wishes to Professor *Dieter Seebach* on the occasion of his 75th birthday

N-Alkylated glycine oligomers ('peptoids') can serve as potent peptidomimetic systems. Installing different functional groups can often be a challenge, and minimizes yields and purities. Here, we describe the synthesis of different amide-containing submonomers which were obtained as free bases, as well as their incorporation into peptoids. By using the free amines, the coupling results on solid support could be improved, and various functionalized peptoids were prepared. Additionally, an interesting dimerization side reaction leading to cross-linked peptoids was observed during synthesis.

Introduction. – Peptides play a pivotal role in many biological and pharmacological applications. However, they are sensitive, *e.g.*, to enzymatic degradation or thermal three-dimensional disordering.

Over the past two decades, functional peptidomimetics [1][2] have been shown to display biological activities similar to peptides [3]. Among them, β-peptides (pioneered by *Seebach et al.* [4], and *Gellman* and co-workers [5]) and peptoids (pioneered by *Zuckermann* and co-workers [6]) emerged as potent tools in this area. Peptoids, *i.e.*, *N*-alkylated glycine oligomers, are achiral biopolymers with distinct three-dimensional structures, if appropriately substituted, *e.g.*, with α-chiral aromatic side chains [7]. Although *N*-methylated (poly)peptides are known in nature and can be prepared from peptides by alkylation; peptoids **1** (see *Fig. 1*) with longer side chains are unknown in biological systems.

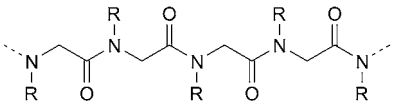

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Fig. 1. *General structure of a peptoid* **1**. R = alkyl or aryl.

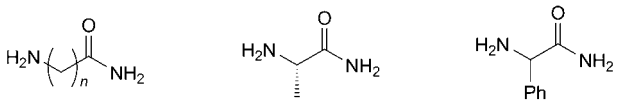
Besides their function as peptidomimetics, peptoids are used as molecular transporters [8], antimicrobials [9], antitumor agents [10], or as conformationally constrained cyclic and also bicyclic structures [11]. In general, peptoids are prepared by

solid-phase synthesis either by assembling *N*-alkylated glycines in analogy to peptide synthesis or by nucleophilic substitution reactions of haloacetates with primary amines (the so-called submonomer method). The latter method is particularly useful to generate peptoid libraries [12][13], because most primary amines can be used directly. Recently, further functionalization of peptoids, for example, by dipolar cycloaddition reactions of azides and alkynes [14] or metathesis reactions [15] have been reported.

Despite the emerging use, the synthesis of peptoids with functionalized side chains other than positively charged residues such as free carboxylic acids [16] or amides [17] is not trivial, and it often lacks proper protocols. The necessity of protecting groups and their quantitative removal in the presence of other functional groups often hamper the synthesis of diverse functional side chains. Due to the fact that solid-phase peptoid synthesis is by far less-established than the corresponding solid-phase peptide synthesis, it often provides products in moderate purities.

During the investigation of the biological activity of peptoids towards tumor-related receptors, we faced the challenge of synthesizing functionalized peptoids containing amide groups in their side chains mimicking glutamine and asparagine.

Results and Discussion. – In this study, we investigated a number of side chains containing amide functionalities in order to mimic proteogenic amino acids. During the submonomer-based synthesis of peptoids with functionalized side chains, we noticed that the use of the amines as free base is necessary in order to obtain the peptoids in good yields. Therefore, we systematically investigated the submonomer-based synthesis of free amines, particularly with amides as functional groups to mimic glutamine and asparagine [18]. For the study of diverse peptidomimetic peptoids, it is also important to synthesize amide-containing side chains with variable length or substitution at the α-C-atom. The building blocks, which are used in this study, **2-NH$_2$** – **5-NH$_2$**, are depicted in *Fig. 2*. The chiral α-amino acid-based submonomers **4-NH$_2$** and **5-NH$_2$** have not been used in peptoid synthesis before. However, at this point it should be noted that the latter submonomers having secondary or tertiary amides are known and peptoids containing these motifs fold in a unique way [19][20].



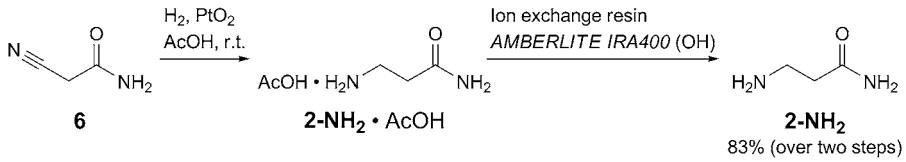
2-NH$_2$ *n* = 2
3-NH$_2$ *n* = 3 (*S*)-**4-NH$_2$** **5-NH$_2$**

Fig. 2. *Submonomers* **2-NH$_2$** – **5-NH$_2$** *used for peptoid synthesis*

Synthesis of Free Amines. β-Alaninamide (**2-NH$_2$**) has been incorporated in peptoid sequences using the monomer approach with prior synthesis of the *N*-alkylated glycine in solution [21a]. *Wenschuh* and co-workers described special conditions for the coupling of the amine hydrochloride on cellulose membranes [21b]. To our knowledge, there is only one example of the submonomer being introduced by standard protocols (amine dissolved in DMF or NMP) [21c]. Both, the free amine and the amine hydrochloride of **2-NH$_2$**, are commercially available, but quite expensive. The free

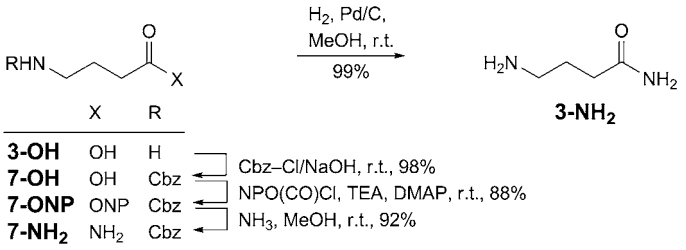
amine could be synthesized from 2-cyanoacetamide **6** adapting a nitrile reduction procedure from *Bartlett* and co-workers[1]) (*Scheme 1*).

Scheme 1. *Synthesis of β-Alaninamide* (**2-NH$_2$**) *as Free Amine*



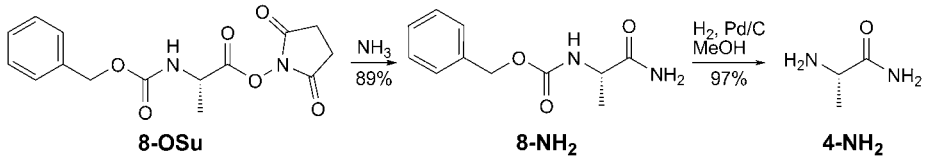
The second functional building block described is 3-aminopropanamide (**3-NH$_2$**), which has not been used in peptoid synthesis before. It was prepared as the free amine using a four-step sequence modified from a literature procedure [23] starting from the acid **3-OH** (*Scheme 2*). After protection of the free amine with Cbz-Cl, the carboxylic acid was converted to a good leaving group, followed by substitution with NH_3. Removal of the Cbz group finally led to the free amine **3-NH$_2$** in good overall yield.

Scheme 2. *Synthesis of 3-Aminopropanamide* (**3-NH$_2$**) *as Free Amine.* Abbreviations: NP, 4-nitrophenyl; Cbz, (benzyloxy)carbonyl; TEA, Et_3N; DMAP, 4-(dimethylamino)pyridine.



α-Alaninamide (**4-NH$_2$**) is only commercially available in its hydrochloride form. Several syntheses have been described to obtain the free base [24]. In this case, it could be prepared in two steps from commercially available Cbz-protected activated L-alanine (*Scheme 3*). In analogy to the last two steps of the synthesis of submonomer **3-NH$_2$**, treatment of the succinyl-activated alanine **8-OSu** with a 7M NH_3 solution in MeOH and final removal of Cbz afforded the free amine in good overall yield. α-Alaninamide (**4-NH$_2$**) has not been used directly as a submonomer, but substituted derivatives are found in some peptoids [18][20].

Scheme 3. *Synthesis of Alaninamide* (**4-NH$_2$**) *as Free Amine.* Su, *N*-Succinyl.

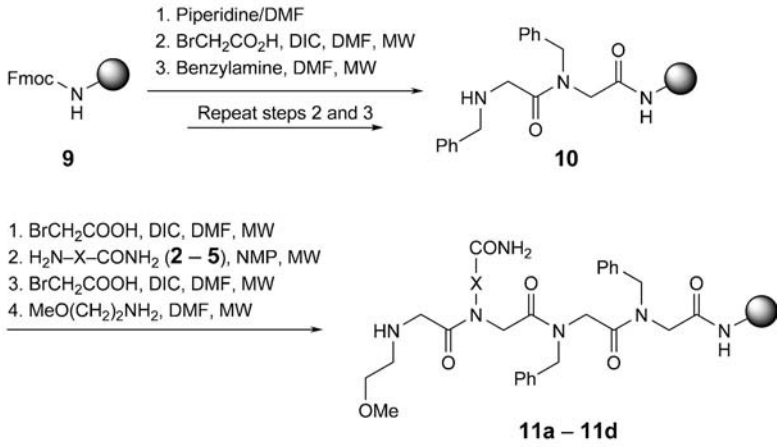


[1]) Synthesis *via* nitrile reduction adapted from [22].

Phenylglycinamide (**5-NH$_2$**) – commercially available as the (*R*)-enantiomer was prepared starting from phenylglycine according to the same procedure used for 4-aminobutanamide (**3-NH$_2$**). This submonomer is so far unknown in peptoid chemistry.

Solid-Phase Synthesis of Functionalized Peptoids. To investigate the scope and limitations of the synthesized submonomers in peptoid synthesis, they were introduced in a test tetramer sequence (*Scheme 4*) by using $PhCH_2NH_2$ and 2-methoxyethylamine as additional side chains. They were chosen because of their high coupling yields. In these experiments, we first tested whether the incorporation of the amide submonomers is possible. After successful coupling, it was tested if the sequence can be elongated by a further coupling step. The peptoids were assembled using standard protocols on a low-loading *Rink* amide resin and were cleaved from the solid support with 95% CF_3COOH (TFA)/CH_2Cl_2. No significant difference in purity was observed between microwave-assisted synthesis or room temperature reactions. However, microwave irradiation led to shorter reaction times.

Scheme 4. *Synthesis of Peptoid Test Sequences for the Different Submonomers.* MW, Microwave; DIC, *N*,*N*′-diisopropylcarbodiimide; NMP, *N*-methylpyrrolidin-2-one.



The four obtained tetrapeptoids **11a**–**11d** are shown in *Fig. 3*. In all cases, a successful incorporation of the submonomers was possible, and the coupling of a new submonomer at the end of the sequence could be achieved in good yields. However, the use of the amines as free bases is crucial. Previous couplings with amine hydrochlorides were completely unsuccessful under various conditions (data not shown). In addition, the use of NMP as a solvent improved the solubility of the amide submonomers.

In peptoids **11c** and **11d**, the final amine reacts within hours with the amide side chain to form a diketopiperazine (DKP). DKP Formation has been mainly described as a side reaction for peptoid dimers [25]. This phenomenon complicates the purification. Together with the higher steric hindrance of submonomers **3-NH$_2$** and **4-NH$_2$** (26% of trimer lacking the last submonomer was isolated for peptoid **11c**), this is responsible for the lower yields of peptoids **11c** and **11d**.

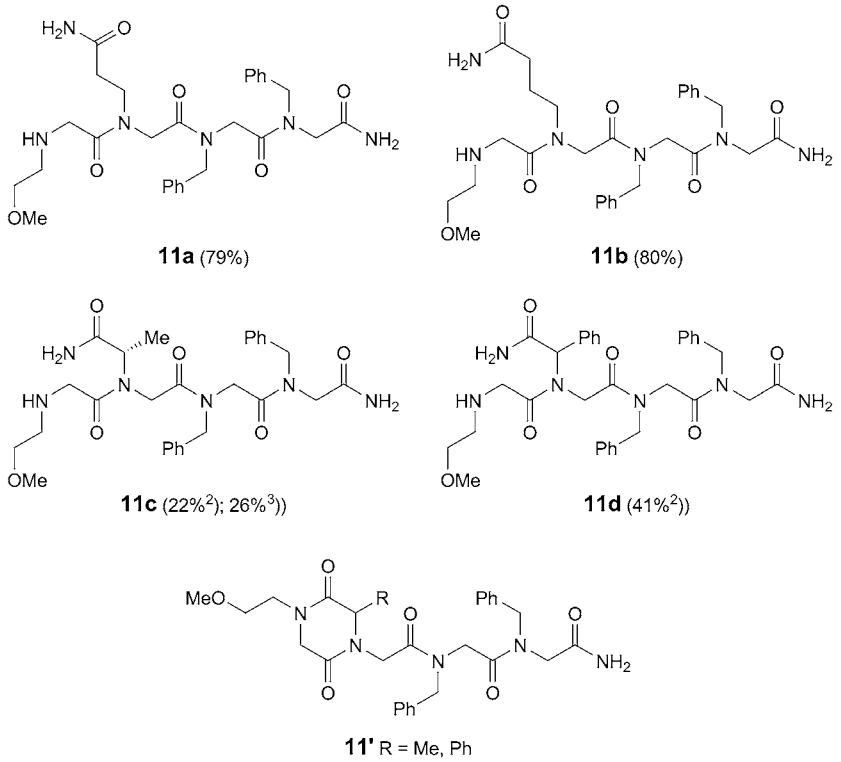


Fig. 3. *Synthesized trial sequences* **11a**–**11d** *and their yields after HPLC purification* (**11′** is the diketopiperazine (DKP) side product)

In some cases, a rarely reported cross-linking reaction was observed during the synthesis which led to a dimerization of the peptoids (*Scheme 5*) on the solid support. Examples for the isolated dimers are shown in *Fig. 4*. It is interesting to note that these types of structures have been prepared for various purposes by other means [26].

Compound **13** represents *ca.* 20% of the overall yield, and the amount of isolated dimers **14a**–**14d** did not exceed 10% in any of the sequences. However, this cross-linking is not characteristic of the reported sequences and has often been observed by our group. It usually takes place in close proximity to the resin. Dimers of short sequences are more abundant than longer ones. In general, the amount of dimers can be reduced by using low-loading resins and increasing the amine concentration. However, this phenomenon was found to be strongly dependent on the nature of the substituents (directionality, flexibility, steric hindrance).

To investigate the coupling potential of alanineamide **4-NH$_2$**, a homopentamer was synthesized, demonstrating that consecutive incorporation of the amides is possible. In

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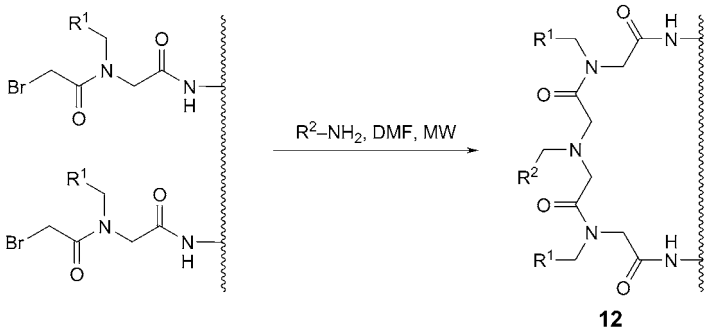
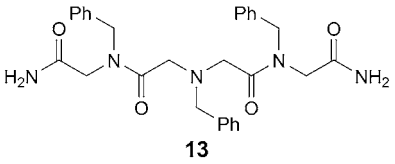
[2]) Inseparable mixture of product and DKP side product.

[3]) Isolated DKP side product.

Scheme 5. *General Cross-Linking Side Reaction*. MW = Microwave.





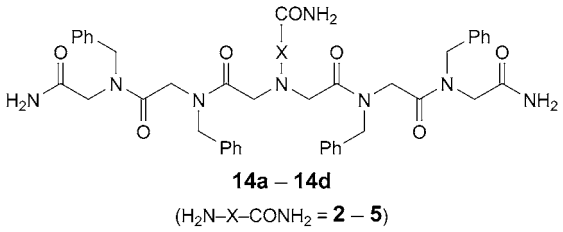


Fig. 4. *Examples of the dimers isolated from the synthesized trial sequences*

addition, this type of α-chiral peptoids is very interesting in terms of their potential to form secondary structures to mimic peptide structures (*Fig. 5*).

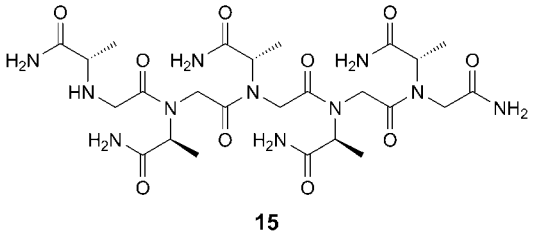


Fig. 5. *Homo-pentapeptoid* **15** *of amide* **4-NH$_2$**

Conclusions. – We reported the straightforward synthesis of diverse amide-containing primary amines which can be used as submonomers in solid-phase peptoid synthesis. All submonomers were obtained as free bases, which finally resulted in better

coupling yields for the peptoid syntheses. It was possible to successfully introduce all submonomers in test sequences as well as the preparation of a homo-oligomer. With this method, the exploration of new amide-containing peptidomimetic peptoids is well accessible, and we will now explore the chemistry and biology of glutamine and asparagine peptidomimetics.

Experimental Part

General. The starting materials were purchased from commercial sources and used without further purification. Solid-phase synthesis was performed on a low-loading (0.34 mmol/g) *Rink* amide aminomethyl resin (100–200 mesh) from *Novabiochem*. Peptide-grade DMF was used for peptoid synthesis. Microwave-assisted peptoid synthesis was carried on in a single mode *CEM Discover* microwave. TLC: *MERCK* ready-to-use plates with silica gel *60* (*F254*). Column chromatography (CC): *MERCK* silica gel *60* (SiO_2; 0.04–0.063 mm). Reversed phase (RP) anal. HPLC: *Agilent Series 1100* with a *C18 PerfectSil Target* (*MZ Analytik*, 3–5 μm, 4.0 × 250 mm). Peptoids were purified in a *RP C18* column (19 cm × 3 cm) using a *JASCO* HPLC of the *LC-NetII/ADC* series equipped with a multi-wavelength detector, *PU-2087 Plus* pumps, a *CO2060 Plus* thermostat, and a *CHF-122SC* fraction collector. A H_2O/MeCN gradient (5–95% in 20 min) with 0.1% CF_3COOH was used as eluent. Optical rotations: *Perkin Elmer 241* polarimeter; as $[\alpha]_{21}^{D}$. M.p.: *Stanford Research System* device, model *Opti Melt SRS*; uncorrected. IR Spectra: *Bruker IFS 88*; either as film between KBr plates or by DRIFT technique (diffused reflectance infrared *Fourier*-transform spectroscopy). NMR Spectra: at 25° on a *Bruker Avance 300* (300 (^{1}H) and 75 MHz (^{13}C)) and a *Bruker AM 400* (400 (^{1}H) and 100 MHz (^{13}C)) spectrometer; TMS as the internal standard (δ 0 ppm), by using the signals of the residual protons of $CHCl_3$ (7.26 (^{1}H) or 77.0 ppm (^{13}C)) in $CDCl_3$, or CHD_2OD (3.31 (^{1}H) or 49.1 ppm (^{13}C)) in CD_3OD; coupling constants (*J*) in Hz. MS (EI or FAB): *Finnigan MAT 90* spectrometer; MALDI-TOF-MS: *Bruker Biflex IV* spectrometer with a pulsed ultraviolet nitrogen laser, 200 μJ at 337 nm, and a time-of-flight mass analyzer with a 125-cm linear flight path.

3-Aminopropanamide (=*β-Alaninamide*; **2-NH$_2$**). *2-Cyanoacetamide* (**6**; 303 mg, 3.60 mmol, 1.00 equiv.) and PtO_2 (40.0 mg, 4.68 mmol, 1.30 equiv.) were suspended in AcOH and treated with H_2 at r.t. overnight. The catalyst was filtered off over *Celite*®, and the solvent was removed under reduced pressure by co-evaporation with toluene. The obtained residue was dissolved in H_2O and lyophilized. The amine acetate salt was then filtered over a basic anion-exchange resin (*AMBERLITE® IRA400*; OH) to remove the acetate anions. After lyophilization, 264 mg (3.00 mmol, 83%) of a yellow oil were obtained. IR (KBr): 3357*m*, 3196*m*, 2960*m*, 1666*s*, 1411*m*, 1303*w*, 1157*w*, 1040*w*, 927*w*, 619*w*. ^{1}H-NMR (300 MHz, MeOD): 2.38 (*t*, *J* = 6.6, C*H*$_2$CONH$_2$); 2.90 (*t*, *J* = 6.6, C*H*$_2$NH$_2$). ^{13}C-NMR (75 MHz, MeOD): 38.8 (*C*H$_2$CONH$_2$); 46.3 (*C*H$_2$NH$_2$); 177.2 (*C*O). EI-MS: 88 (7, M^+), 72 (7, $[M-NH_2]^+$), 70 (16), 60 (39), 59 (38, $[CH_2CONH_2+H]^+$), 44 (57, $[CONH_2]^+$), 43 (100, $[COCH_2]^+$). HR-EI-MS: 88.0640 (M^+, $C_3H_8N_2O^+$; calc. 88.0637).

4-{[(Benzyloxy)carbonyl]amino}butanoic Acid (**7-OH**). To a soln. of *4-aminobutanoic acid* (**3-OH**; 1.00 g, 9.70 mmol) in 5 ml 2M NaOH, a suspension of 1.50 ml ClCOOBn (1.78 g, 10.5 mmol) and 25 ml 2M NaOH was added slowly at 0°. Then, the reaction was let warm to r.t. and stirred for 14 h. The crude was washed with Et_2O (3×), acidified to pH 3 with conc. HCl, and cooled in an ice bath. The white precipitate was filtered, washed with cold 0.1M HCl and dried to yield **7-OH** (2.26 g, 9.53 mmol, 98%). White solid. M.p. 69°. IR (ATR diamond): 3335*w*, 2950*w*, 1712*s*, 1537*m*, 1454*m*, 1360*w*, 1261*m*, 1025*w*, 739*w*, 698*w*. ^{1}H-NMR (300 MHz, MeOD): 1.78 (*quint.*, *J* = 7.1, $CH_2CH_2CH_2$); 2.31 (*t*, *J* = 7.1, C*H*$_2$COOH); 3.16 (*t*, *J* = 7.1, C*H*$_2$NH); 5.06 (*s*, C*H*$_2$–Ph); 7.22–7.35 (*m*, 5 arom. H). ^{13}C-NMR (100 MHz, MeOD): 25.1 (CH_2); 31.5 (CH_2); 40.2 (CH_2); 66.7 (CH_2); 128.07 (arom. CH); 128.11 (arom. CH); 128.5 (arom. CH); 136.4 (C_q, arom. *C*CH_2); 156.7 (C_q, COOH); 178.4 (C_q, CONH). EI-MS: 237 (71, M^+), 108 (100, $[BnOH]^+$), 91 (72, $[PhCH_2]^+$). HR-EI-MS: 237.0999 (M^+, $C_{12}H_{15}NO_4^+$; calc. 237.1001).

4-Nitrophenyl 4-{[(Benzyloxy)carbonyl]amino}butanoate (**7-ONp**). To a soln. of **7-OH** (9.80 g, 41.3 mmol, 1.00 equiv.) in 500 ml AcOEt, 4-nitrophenyl chloroformate (9.20 g, 45.5 mmol, 1.10 equiv.),

DMAP (0.500 g, 4.13 mmol, 0.100 mmol), and Et_3N (6.30 ml, 4.60 g, 45.5 mmol, 1.10 equiv.) were added. The mixture was stirred at r.t. for 3 h. After filtering off the precipitated $Et_3N \cdot HCl$, the soln. was concentrated under reduced pressure and washed several times with a total of 3 l half-sat. $NaHCO_3$ soln. The org. phase was dried (Na_2SO_4), and the solvent was evaporated under reduced pressure to yield **7-ONp** (12.1 g, 33.8 mmol, 88%). White solid. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.98 (*quint.*, $J = 7.1$, $CH_2CH_2CH_2$); 2.67 (*t*, $J = 7.1$, $COCH_2$); 3.32–3.38 (*m*, CH_2NH); 5.11 (*s*, $PhCH_2$), 7.32–7.37 (*m*, 5 arom. H); 8.16–8.36 (*m*, 4 arom. H).

Benzyl (4-Amino-4-oxobutyl)carbamate (**7-NH$_2$**). To a soln. of **7-ONp** (12.0 g, 33.8 mmol, 1.00 equiv.) in 5 ml MeOH, 5 ml of a 7N soln. NH_3/MeOH were added, and the mixture was stirred at r.t. for 3 h. After removal of the solvent, the product was purified by CC (5–20% AcOEt in MeOH) to afford **7-NH$_2$** (7.32 g, 31.0 mmol, 92%). White solid. M.p. 127–130°. IR (ATR diamond): 2966*w*, 2537*w*, 2481*w*, 2379*w*, 2334*w*, 1678*m*, 1624*m*, 1576*w*, 1427*m*, 1383*w*, 1359*m*, 1340*m*, 1303*w*, 1279*w*, 1197*w*, 1150*m*, 1060*w*, 1004*w*, 948*w*, 776*w*, 741*w*, 728*w*, 691*w*, 647*w*, 599*w*, 559v*w*, 517*w*. ^{1}H-NMR (300 MHz, MeOD): 1.78 (*quint.*, $J = 6.8$, $CH_2CH_2CH_2$); 2.23 (*t*, $J = 6.8$, CH_2NH); 3.15 (*t*, $J = 6.8$, $COCH_2$); 5.06 (*s*, $PhCH_2$); 7.28–7.35 (*m*, 5 arom. H). ^{13}C-NMR (75 MHz, MeOD): 27.1 (CH_2); 30.21 (CH_2); 33.7 (CH_2); 41.3 (CH_2); 67.4 (CO); 128.8 (arom. C); 128.96 (arom. C); 129.5 (arom. C); 164.3 (CO). EI-MS: 237 (5.3, $[M+H]^+$), 91 (100, $[M - CH_2Ph]^+$). HR-EI-MS: 236.1159 (M^+, $C_{12}H_{16}N_2O_3^+$; calc. 236.1161).

4-Aminobutanamide (**3-NH$_2$**). Amide **7-NH$_2$** (7.32 g, 31.0 mmol, 1.00 equiv.) was dissolved in 140 ml of MeOH, and 10 wt-% of the catalyst (5% Pd/C) were added. The resulting suspension was treated with H_2 at r.t. overnight. After completion of the reaction, the catalyst was removed by filtration over *Celite*®, and the solvent was evaporated to yield **3-NH$_3$** (3.14 g, 30.8 mmol, 99%). Viscous solid. IR (ATR diamond): 3339*m*, 3175*m*, 2944*m*, 2870*w*, 1643*m*, 1465*w*, 1415*m*, 1372*m*, 1320*m*, 1264*w*, 1238*w*, 1149*w*, 1103*w*, 1058*w*, 966*w*, 914*m*, 845*w*, 742*m*, 637*m*, 519*w*. ^{1}H-NMR (300 MHz, MeOD): 1.52 (*quint.*, $J = 7.5$, $CH_2CH_2CH_2$); 2.01 (*t*, $J = 7.5$, $COCH_2$); 2.45 (*t*, $J = 7.5$, CH_2NH_2); 6.05 (br. *s*, CH_2NH_2); 7.06 (br. *s*, NH_2CO). ^{13}C-NMR (75 MHz, MeOD): 29.8 (CH_2); 33.9 (CH_2); 42.0 (CH_2); 178.7 (CO). EI-MS: 103 (17, $[M+H]^+$), 59 (55, $[M - H_2NCO]^+$), 44 (100, $[M - (CH_2)_3NH_2]^+$). HR-EI-MS: 102.0796 (M^+, $C_4H_{10}N_2O^+$; calc. 102.0793).

*Benzyl [(2*S*)-1-Amino-1-oxopropan-2-yl]carbamate* (**8-NH$_2$**). (*S*)-Cbz-Ala-OSu (**8-OSu**; 200 mg, 0.624 mmol, 1.00 equiv.) was suspended in 5 ml of 7M NH_3 in MeOH, and stirred overnight at r.t. After evaporation of the solvent, the residue was resuspended in MeOH, and the precipitated solid was filtered off. The solvent was evaporated and the product was purified by CC (cyclohexane/AcOEt 1:2) to yield **8-NH$_2$** (124 mg, 0.558 mmol, 89%). White solid. M.p. 132–134°. $[\alpha]_D^{25} = -3.5$ ($c = 2$, MeOH). IR (ATR diamond): 3373*w*, 3322*w*, 3191*w*, 2986v*w*, 2938v*w*, 1684*m*, 1644*m*, 1523*m*, 1461*w*, 1424*w*, 1377*w*, 1314*m*, 1288*w*, 1252*m*, 1231*m*, 1108*w*, 1064*m*, 1038*w*, 967v*w*, 928v*w*, 841v*w*, 801*w*, 780*w*, 747*m*, 725*w*, 695*m*, 630*m*, 580*m*, 554*w*, 493*w*, 433*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.41 (*d*, $J = 7.0$, Me); 4.22–4.31 (*m*, $MeCH$); 5.12 (*s*, $PhCH_2$); 5.27 (br. *s*, NH); 5.36 (br. *s*, NH); 5.96 (br. *s*, NH); 7.32–7.38 (*m*, 5 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 18.4 (Me); 50.1 (CH_2); 67.1 (CH); 128.1 (arom. C); 128.3 (arom. C); 128.6 (arom. C); 136.0 (C_q, arom. C); 156.0 (C_q, COONH); 174.5 (C_q, $CONH_2$). EI-MS: 222 (13, M^+), 178 (31, $[M - CONH_2]^+$), 91 (100, $[PhCH_2]^+$), 44 (58, $[CONH_2]^+$). HR-EI-MS: 222.1004 (M^+, $C_{11}H_{14}N_2O_3^+$; calc. 222.1004).

L-*Alaninamide* (**4-NH$_2$**). Amide **8-NH$_2$** (1.25 g, 5.63 mmol, 1.00 equiv.) was dissolved in 30 ml of MeOH, and 10 wt-% of the catalyst (5% Pd/C) was added. The obtained suspension was treated with H_2 at r.t. overnight. After completion of the reaction, the catalyst was removed by filtration over *Celite*®, and the solvent was evaporated to yield **4-NH$_2$** (480 mg, 5.45 mmol, 97%). Colorless oil that solidified with time. $[\alpha]_D^{21} = 6.6$ ($c = 1$, MeOH). IR (KBr): 3358*m*, 3203*m*, 2978*m*, 2936*w*, 1668*m*, 1458*w*, 1414*w*, 1371*w*, 1242v*w*, 1134v*w*, 1073v*w*, 960v*w*, 910v*w*, 638*w*. ^{1}H-NMR (300 MHz, MeOD): 1.28 (*d*, $J = 6.9$, Me); 3.41 (*q*, $J = 6.9$, $MeCH$). ^{13}C-NMR (100 MHz, MeOD): 21.6 (Me); 51.3 (CH); 181.3 (C_q, $CONH_2$). EI-MS: 88 (0.8, M^+), 73 (1.2, $[M - Me]^+$), 55 (1), 44 (100, $[CONH_2]^+$). HR-EI-MS: 88.0638 (M^+, $C_3H_8N_2O^+$; calc. 88.0637).

{[(Benzyloxy)carbonyl]amino}(phenyl)ethanoic Acid. From phenylglycine (1.01 g, 6.68 mmol) following the procedure described for the synthesis of **7-OH**. White solid (659 mg, 2.31 mmol, 35%). M.p. 120–124°. IR (ATR diamond): 3577v*w*, 3345*w*, 3033v*w*, 1724*w*, 1682*m*, 1669*m*, 1600*w*, 1496v*w*, 1450*w*, 1411*w*, 1343*w*, 1318*w*, 1298*w*, 1264*w*, 1225v*w*, 1193*w*, 1153v*w*, 1131*w*, 1066*m*, 1026*w*, 967v*w*, 774*w*,

732*w*, 715*w*, 695*m*, 663*w*, 627*w*, 587*w*, 559*w*, 496*w*, 468*w*, 423*w*. ^{1}H-NMR (300 MHz, MeOD): 5.10 (*s*, CH_2); 5.25 (*s*, CH); 7.30–7.44 (*m*, 10 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 57.6 (CH); 67.3 (CH_2); 127.2 (arom. C); 128.2 (arom. C); 128.5 (arom. C); 129.0 (arom. C); 136.2 (arom. C); 155.7 (C_q, COONH); 190.8 (COOH). EI-MS: 285 (3.9, $[M+H]^+$), 240 (10, $[M-CONH_2]^+$), 150 (11, $[M+H-BnOCO]^+$), 104 (25, $[M-H-BnOCO-CONH_2]^+$), 91 (100, $[PhCH_2]^+$), 77 (16, $[Ph]^+$). HR-EI-MS: 285.0999 ($[M+H]^+$, $C_{16}H_{15}NO_4^+$, calc. 285.1001).

4-Nitrophenyl {[(Benzyloxy)carbonyl]amino}(phenyl)acetate. From [(benzyloxy)carbonyl]-amino}(phenyl)ethanoic acid (420 mg, 1.47 mmol) following the procedure described for the synthesis of **7-ONp**. CC (cyclohexane/AcOEt 7:1) resulted in a white solid (252 mg, 0.62 mmol, 42%). ^{1}H-NMR (300 MHz, $CDCl_3$): 5.15 (*s*, CH_2); 5.60 (*d*, $J=6.7$, CH); 5.69 (br. *s*, NH); 7.20 (*d*, $J=8.9$, 2 arom. H); 7.35 (*m*, 5 arom. H); 7.44 (*m*, 5 arom. H); 8.24 (*d*, $J=8.9$, 2 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 58.5 (CH); 67.5 (CH_2); 122.2 (arom. C); 125.2 (arom. C); 127.3 (arom. C); 128.2 (arom. C); 128.4 (arom. C); 128.6 (arom. C); 129.36 (arom. C); 129.43 (arom. C); 134.9 (C_q, arom. C); 135.9 (C_q, arom. C); 145.6 (C_q, arom. C); 154.9 (C_q, arom. C); 155.5 (COONH); 168.8 (*C*OOC).

Benzyl (2-amino-2-oxo-1-phenylethyl)carbamate. From 4-nitrophenyl {[(benzyloxy)carbonyl]amino}(phenyl)acetate (252 mg, 0.62 mmol) following the procedure described for the synthesis of amide **7-NH$_2$**. CC (gradient 20–50% AcOEt in cyclohexane) afforded a white solid (143 mg, 0.50 mmol, 81%). ^{1}H-NMR (300 MHz, $CDCl_3$): 5.10 (*s*, CH_2); 5.25 (*s*, CH); 7.29–7.45 (*m*, 10 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 58.7 (CH); 67.1 (CH_2); 127.3 (arom. C); 128.1 (arom. C); 128.2 (arom. C); 128.5 (arom. C); 128.7 (arom. C); 129.2 (arom. C); 136.1 (C_q, arom. C); 137.8 (C_q, arom. C); 163.5 (COONH); 171.5 (*C*OOC).

(Phenylglycine)amide (=*2-Amino-2-phenylacetamide*; **5-NH$_2$**). From Cbz-phenylglycineamide (=benzyl (2-amino-2-oxo-1-phenylethyl)carbamate; 138 mg, 0.49 mmol) following the procedure described for the synthesis of **3-NH$_2$**. White solid (73 mg, 0.49 mmol, quant.). M.p. 125–128°. IR (ATR diamond): 3370*w*, 3294*w*, 3031*w*, 2872*w*, 1641*m*, 1571*m*, 1491*w*, 1453*w*, 1404*w*, 1296*m*, 1202*w*, 1168*w*, 1116*w*, 1024*w*, 982*m*, 918v*w*, 848v*w*, 769*m*, 707*m*, 694*m*, 665*m*, 593*m*, 500*w*, 471*w*. ^{1}H-NMR (300 MHz, MeOD): 4.45 (*s*, CH); 7.30–7.34 (*m*, 3 arom. H); 7.42–7.44 (*m*, 2 arom. H). ^{13}C-NMR (100 MHz, MeOD): 60.1 (CH); 128.0 (arom. C); 128.9 (arom. C); 129.7 (arom. C); 142.7 (C_q, arom. C); 178.4 ($CONH_2$). FAB-MS (3-NBA): 151 (100, $[M+H]^+$), 136 (17), 106 (75, $[M-CONH_2]^+$). HR-FAB-MS (3-NBA): 151.0874 ($[M+H]^+$, $C_8H_{11}N_2O^+$, calc. 151.0871).

Solid-Phase Peptoid Syntheses. Peptoid **10** (starting material for the test sequences). *Rink* Amide aminomethyl resin (905 mg, 0.308 mmol, 1.00 equiv.; 0.34 mmol/g, 100–200 mesh) was swollen in 5 ml of DMF for 2 h. *Deprotection*. The resin was treated with 3 ml of a 20% piperidine in DMF soln. for 5 min at r.t. The procedure was repeated three times, and afterwards the resin was washed with 5 × 5 ml of DMF. *Acylation Step*. $BrCH_2COOH$ (338 mg, 2.43 mmol, 7.90 equiv.) and 378 µl (306 mg, 2.43 mmol, 7.90 equiv.) DIC were dissolved in 2.4 ml of DMF resulting in a 1M soln. The mixture was added to the resin and stirred at 35° under MW irradiation for 1 min. Then, the resin was washed with DMF (4 × 5 ml). *Amination Step*. $PhCH_2NH_2$ (336 µl, 330 mg, 3.08 mmol, 10.0 equiv.) was dissolved in 3 ml of DMF (1M soln.), and added to the resin. The mixture was stirred at 60° under MW irradiation for 30 min. Finally, the resin was washed with DMF (4 × 5 ml). The acylation and amination steps were repeated one more time. The resin was washed with DMF (3 × 5 ml) and CH_2Cl_2 (3 × 5 ml), and dried overnight.

Peptoid **11a** (=N-*(2-Methoxyethyl)glycyl*-N-*(3-amino-3-oxopropyl)glycyl*-N-*benzylglycyl*-N^2-*benzylglycinamide*). The resin-bound peptoid **10** (200 mg, 66.0 µmol, 1.00 equiv.) was swollen in 2 ml of DMF for 2 h. *Acylation Step*. $BrCH_2COOH$ (83 mg, 0.594 mmol, 9.0 equiv.) and 72 µl (58 mg, 0.462 mmol, 7.00 equiv.) DIC were dissolved in 0.6 ml of DMF resulting in a 1M soln. The mixture was added to the resin and stirred at 35° under MW irradiation for 1 min. Then, the resin was washed with DMF (3 × 2 ml) and NMP (1 × 2 ml). *Amination Step*. **2-NH$_2$** (48 mg, 0.548 mmol, 8.30 equiv.) was dissolved in 0.6 ml of NMP (1M soln.), and added to the resin. The mixture was stirred at 60° under MW irradiation for 45 min. Finally, the resin was washed with DMF (3 × 2 ml). The acylation step was performed once more, and the amination step was repeated with 48 µl (41 mg, 0.548 mmol, 8.30 equiv.) 2-methoxyethylamine. *Cleavage from Resin*. The resin was treated at r.t. with 2 ml of 95% TFA in CH_2Cl_2. After 2 h, the cleavage mixture was collected, and the procedure was repeated a second time. Then, the resin was washed several times with CH_2Cl_2 and MeOH. The cleavage solns. and washes were combined,

and the solvent was evaporated. Then, the residue was dissolved in *ca.* 5 ml of H_2O/MeCN and lyophilized. Finally, the peptoid was purified by prep. HPLC (5–95% MeCN in H_2O over 20 min, detector: 218 nm; t_R 10.6 min) to yield **11a** (28.9 mg, 52.1 μmol, 79% yield). Colorless oil (HPLC purity of 92%). MALDI-TOF-MS (DHB, 0.1% TFA): 555 ($[M+H]^+$).

In addition, 2.3 mg (2.9 μmol, 8.8% yield) of dimeric side product **14a** were isolated (t_R 13.4 min; 78% HPLC purity). MALDI-TOF-MS (DHB, 0.1% TFA): 791 ($[M+H]^+$).

Peptoid **11b** (= N-*(2-Methoxyethyl)glycyl*-N-*(4-amino-4-oxobutyl)glycyl*-N-*benzylglycyl*-N^2-*benzylglycinamide*). The resin bound-peptoid **10** (200 mg, 66.0 μmol, 1.00 equiv.) was swollen in 2 ml of DMF for 2 h. Acylation step was performed as described for **11a**. *Amination Step*. **3-NH$_2$** (56 mg, 0.548 mmol, 8.3 equiv.) was dissolved in 0.6 ml of NMP (1M soln.), and added to the resin. The mixture was stirred at 60° under MW irradiation for 45 min. Next, coupling and cleavage from resin were performed as described for **11a**. Finally, the peptoid was purified by prep. HPLC (5–95% MeCN in H_2O over 20 min, detector: 218 nm; t_R 10.8 min) to yield **11b** (30 mg, 52.8 μmol, 80%). Colorless oil (HPLC purity of 95%). MALDI-TOF-MS (DHB, 0.1% TFA): 569 ($[M+H]^+$).

In addition, 2.2 mg (2.7 μmol, 8.3% yield) of dimeric side product **14b** were isolated (t_R 13.4 min; 85% HPLC purity). MALDI-TOF-MS (DHB, 0.1% TFA): 805 ($[M+H]^+$).

Peptoid **11c** (= N-*(2-Methoxyethyl)glycyl*-N-*[(2S)-1-amino-1-oxopropan-2-yl]glycyl*-N-*benzylglycyl*-N^2-*benzylglycinamide*). The resin-bound peptoid **10** (200 mg, 66.0 μmol, 1.00 equiv.) was swollen in 2 ml of DMF for 2 h. Acylation step was performed as described for **11a**. *Amination Step*. **4-NH$_2$** (48 mg, 0.548 mmol, 8.3 equiv.) was dissolved in 0.6 ml of NMP (1M soln.), and added to the resin. The mixture was stirred at 60° under MW irradiation for 45 min. Next, coupling and cleavage from resin were performed as described for **11a**. Finally, the peptoid was purified by prep. HPLC (5–95% MeCN in H_2O over 20 min, detector: 218 nm; t_R 10.8 min) to yield **11c** (8 mg, 14.4 μmol, 22%; including an inseparable DKP side product **11′** (= N-*benzyl*-N-*{[4-(2-methoxyethyl)-2-methyl-3,6-dioxopiperazin-1-yl]acetyl}-glycyl*-N^2-*benzylglycinamide*)). Colorless oil (HPLC purity of 69%). MALDI-TOF-MS (DHB, 0.1% TFA): 555 ($[M+H]^+$), 538 (**11′**, $[M+H]^+$), 560 (**11′**, $[M+Na]^+$). DKP Side product **11′** (R = Me; 9.3 mg (17.3 μmol, 26%) was also isolated (t_R 11.7; 86% HPLC purity). MALDI-TOF-MS (DHB, 0.1% TFA): 538 ($[M+H]^+$), 560 ($[M+Na]^+$).

In addition, 1.9 mg (2.4 μmol, 7.2% yield) of dimeric side product **14c** were isolated (t_R 13.6 min; 85% HPLC purity). MALDI-TOF-MS (DHB, 0.1% TFA): 791 ($[M+H]^+$). Finally, 7.4 mg (16.8 μmol, 26% yield) of the tetramer without the last submonomer could also be isolated in 95% HPLC purity (t_R 10.1 min).

Peptoid **11d** (= N-*(2-Methoxyethyl)glycyl*-N-*(2-amino-2-oxo-1-phenylethyl)glycyl*-N-*benzylglycyl*-N^2-*benzylglycinamide*). The resin bound peptoid **10** (200 mg (66.0 μmol, 1.00 equiv.) was swollen in 2 ml of DMF for 2 h. Acylation step was performed as described for **11a**. *Amination Step*. **5-NH$_2$** (82 mg, 0.548 mmol, 8.3 equiv.) was dissolved in 0.6 ml of NMP (1M soln.), and added to the resin. The mixture was stirred at 60° under MW irradiation for 45 min. Next, coupling and cleavage from resin were performed as described for **11a**. Finally, the peptoid was purified by prep. HPLC (5–95% MeCN in H_2O over 20 min, detector: 218 nm; t_R 12.9 min) to yield **11d** (16.7 mg, 27.1 μmol, 41%; including an inseparable DKP side product **11′** (= N-*benzyl*-N-*{[4-(2-methoxyethyl)-3,6-dioxo-2-phenylpiperazin-1-yl]acetyl}glycyl*-N^2-*benzylglycinamide*)). Colorless oil (HPLC purity of 94%). MALDI-TOF-MS (DHB, 0.1% TFA): 617 ($[M+H]^+$), 600 (**11′**, $[M+H]^+$), 622 (**11′**, $[M+Na]^+$).

Peptoid **15** (= N-*[(2S)-1-Amino-1-oxopropan-2-yl]glycyl*-N-*[(2S)-1-amino-1-oxopropan-2-yl]glycyl*-N-*[(2S)-1-amino-1-oxopropan-2-yl]glycyl*-N-*[(2S)-1-amino-1-oxopropan-2-yl]glycyl*-N^2-*(2-amino-2-oxoethyl)*-L-*alaninamide*). *Rink* amide aminomethyl resin (50 mg, 0.017 mmol, 1.00 equiv.; 0.34 mmol/g, 100–200 mesh) was swollen in 1 ml of DMF for 2 h. *Deprotection*. The resin was treated with 1 ml of a 20% piperidine in DMF soln. for 5 min at r.t. The procedure was repeated three times, and then the resin was washed with 3 × 1 ml DMF. *Acylation Step*. $BrCH_2COOH$ (21 mg, 0.156 mmol, 9.0 equiv.) and 19 μl (15 mg, 0.121 mmol, 7.0 equiv.) of DIC were dissolved in 0.15 ml of DMF resulting in a 1M soln. The mixture was added to the resin and stirred at 35° under MW irradiation for 1 min. Then, the resin was washed with DMF (3 × 1 ml). *Amination Step*. **4-NH$_2$** (12 mg, 0.144 mmol, 8.3 equiv.) was dissolved in 0.15 ml of NMP (1M soln.), and added to the resin. The mixture was stirred at 60° under MW irradiation for 45 min. Finally, the resin was washed with DMF (3 × 1 ml). The acylation and amination steps were

repeated four more times until **15** was obtained. The cleavage from resin was performed as described for **11a**. MALDI-TOF-MS (DHB, 0.1% TFA): 658 ($[M+H]^+$), 680 ($[M+Na]^+$).

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