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PAPER

Effect of capping groups at the *N*- and *C*-termini on the conformational preference of α,β-peptoids†‡

Emiliana De Santis,[a] Thomas Hjelmgaard,[b,c] Cécile Caumes,[b,c] Sophie Faure,[b,c] Bruce D. Alexander,[d] Simon J. Holder,[e] Giuliano Siligardi,[f] Claude Taillefumier*[b,c] and Alison A. Edwards*[a]

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Introduction

Peptoids (*N*-substituted glycines, *i.e.* α-peptoids) are artificial oligoamides which are closely related structurally to α-peptides with the side chains located on the amide nitrogen rather than the α-carbon (Fig. 1).[1] A major advantage of α-peptoids is their ease of synthesis, particularly by the so-called 'submonomer method'.[2] A further benefit is the vast potential for diversity as the side chains on the amide nitrogens are introduced by primary amines. Therefore α-peptoids are particularly well suited for the construction of peptidomimetic libraries in the context of drug discovery[3] as they have been shown to be resistant to proteolytic enzymes.[4]

Peptoids occupy a unique position as peptidomimetic foldamers since their backbones are deprived of free NH amides and thus have decreased capacity to form intramolecular H-bonding interactions. Although unnatural, a peptoid residue is structurally related to a proline as the coupling of residues gives tertiary amide bonds which can populate *cis* and *trans* conformations. These features confer greater flexibility to oligopeptoids but interestingly they maintain the propensity to form ordered secondary structures. α-Peptoids containing aromatic or aliphatic α-chiral side chains can fold into stable helical structures.[5] For example, homo-peptoids with (*S*)-1-cyclohexylethyl or (*S*)-1-naphthylethyl side chains (s1npe) were reported to adopt, both in the solid and solution state, a polyproline type I helix (PPI) featuring only *cis* amide bonds,[6] whilst a polyproline type II helix (PPII) was characteristic of *N*-aryl containing α-peptoids as shown by molecular modelling.[7] A threaded loop conformation was also reported for an α-peptoid nonamer due to H-bonding at the *N*-terminus.[8] By contrast to α-peptoids, there are few literature reports of their β-peptoid homologues (oligomers of *N*-substituted β-alanines) (Fig. 1) and no specific secondary structures have been reported. However they have been shown to be able to adopt ordered conformations by circular dichroism (CD).[9] Furthermore, the conformational properties of their backbone could be more important for folding than the possibility of H-bonding as hypothesized by Hofmann from computation, who showed that β-peptoids could form helices which resemble that of their parent β-peptides.[10]

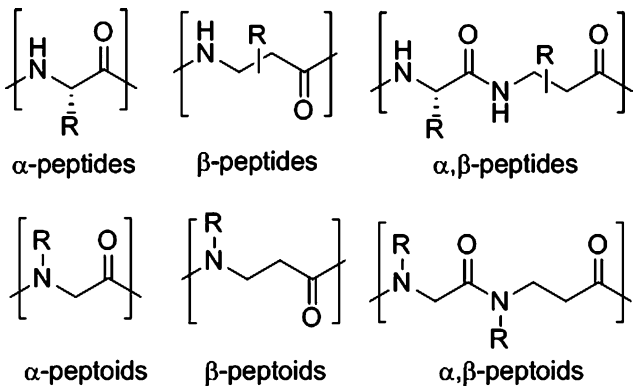

Fig. 1 Peptidomimetic architectures from α- and β-peptide/peptoid monomers.

Early peptidomimetic foldamers focused on the construction of homogeneous backbones and this has now progressed to heterogeneous backbones formed by the combination of at least two different types of building blocks in a defined sequence pattern.[11] This has increased diversity thus allowing greater control of the spatial positioning of side chain pharmacophores when developing peptidomimetic foldamers. Heterogeneous α,β-peptides, with different combinations of α- and β-peptide residues, have been the most extensively studied of this class and have led to the design of foldamers able to form quaternary bundle assemblies.[12] α-Peptide/β-peptoid chimeras with folding propensities that exhibit antimicrobial properties have also been developed.[13] Novel

[a]*Medway School of Pharmacy, Universities of Kent and Greenwich at Medway, Central Avenue, Chatham Maritime, Kent, United Kingdom, ME4 4TB. E-mail: a.a.edwards@kent.ac.uk; Fax: +44 (0)1634 883927; Tel: +44 (0)1634 202947*
[b]*Clermont Université, Université Blaise Pascal, Laboratoire SEESIB, BP 10448, F-63000, Clermont-Ferrand*
[c]*CNRS, UMR 6504, Laboratoire SEESIB, F-63177, AUBIERE cedex, France. E-mail: claude.taillefumier@univ-bpclermont.fr; Fax: +33 (0)4 73 40 77 17; Tel: +33 (0)4 73 40 54 27*
[d]*School of Science, University of Greenwich, Central Avenue, Chatham Maritime, Kent, United Kingdom, ME4 4TB*
[e]*School of Physical Sciences, University of Kent, Canterbury, United Kingdom, CN2 7NZ*
[f]*Diamond Light Source Ltd., Diamond House, Harwell Science and Innovation Campus, Didcot, Oxfordshire, United Kingdom, OX11 0DE*

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linear and cyclic heterogeneous peptoid backbones composed of alternating α- and β-peptoid residues were first reported by us in 2009[14] and also a convenient protocol for gram-scale solution-phase synthesis of α,β-peptoids.[15] Evidence of the conformational stability of cyclic octamers with this backbone, has been recently reported on the basis of CD and NMR studies together with the first X-ray structure for the α,β-peptoid backbone.[16]

To date suitable crystals of linear α,β-peptoids have not been obtained for X-ray structure determination and their solution-phase studies by NMR are limited due to amide *cis*/*trans* isomerism. This leads to increased conformational heterogeneity in solution. Furthermore, the absence of amide protons limits investigation by infrared spectroscopy. However, there are numerous reports of solution-phase study of peptoids using CD spectroscopy to explore their conformational preference.[5,6,8,9,16,17a]

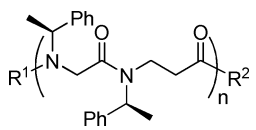
Despite this, there is only one reported study in which the CD spectra are associated with conformationally homogeneous α-peptoids in solution.[6b] There are no characterised reference spectra for β- and α,β-peptoid backbones in contrast to those available for α-peptides and proteins. Therefore interpretation of peptoid CD spectra has to be undertaken with due caution and a combination of independent techniques should be used whenever possible to aid interpretation of spectral features and assign CD spectra to well defined structures. CD alone can give information about the presence of secondary structure by studying the effect of chain length on spectral features. If a chain length dependence is observed then this typically indicates the presence of a secondary structure which may arise from long range interactions. However, the lack of chain length dependence does not exclude the possibility of conformational order arising from short range interactions. The system can be perturbed in different ways to increase information about its conformational behaviour and the presence of ordered structures. For instance, CD experiments at different temperatures will give information about the stability and order of the system. Solvent studies allow evaluation of the nature of the interactions which promote the folding, *e.g.* H-bonding. In addition to this, concentration studies can give an insight into the inter- or intramolecular nature of these. When undertaking CD investigation of peptoids, studies tend to focus on the conformational effect of differing side chains and/or backbone. Most research groups will maintain a consistent protecting group strategy for their peptoids but this can differ between different research groups. The presence, absence and/or type of protecting groups can have significant effects upon conformational preference. For example it has been reported that the threaded loop conformation of the α-peptoid nonamer with (*S*)-1-phenylethyl side chains (spe), H-(*N*spe)$_9$-NH$_2$, was due to the protonated *N*-terminus being involved in H-bonds.[8] The β-peptoids by Olsen[9b] PhCH$_2$CO-(β-*N*rpe)$_5$-NH$_2$ and Norgren[9a] H-(β-*N*spe)$_5$-OH, for the same backbone and side chains, have remarkably different conformational preferences. Firstly, a collapse of secondary structure was observed depending upon the capping groups when in MeCN. A chain length dependence was also observed in MeOH for H-(β-*N*spe)$_n$-NH$_2$ in contrast to H-(β-*N*spe)$_n$-OH.[9a,b] The importance of capping groups for folding has been recently highlighted by Blackwell *et al.* who reported the conformational investigation of *N*s1npe α-peptoids in comparison to that of *N*spe α-peptoids.[6b] Capping groups were carefully chosen to minimise their influence on the peptoid secondary structure, *e.g. via* H-bonding. Therefore the effect of protecting group strategy for peptoids is important to consider when investigating conformational preference. In the present paper we report a study aimed to investigate how capping groups at the *N*- and *C*-termini can influence the CD spectral features of α,β-peptoids and thus conformation. Our study is focused on *N*spe α,β-peptoids. The phenylethyl side chain has been reported to promote helical secondary structure for α-peptoids, on the basis of a combination of NMR, molecular modelling and CD studies.[5c,d,17a] Therefore, this side chain was selected to facilitate interpretation of our results and comparison to CD data of α- and β-peptoid homologues.[9]

Results and discussion

Solution α,β-peptoid synthesis

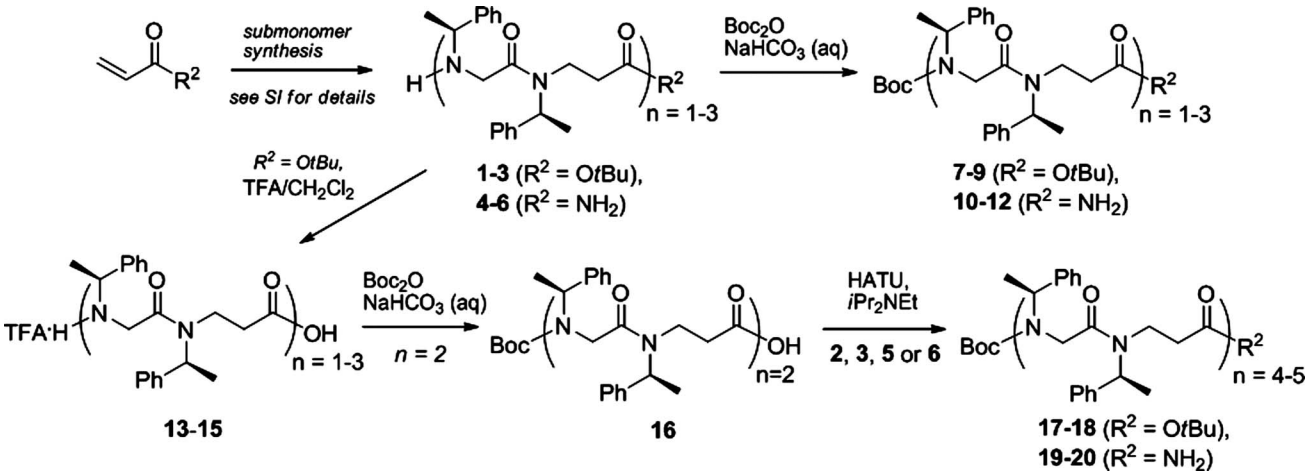
A family of linear α,β-peptoids up to the decamer length was prepared, composed of (*S*)-*N*-(1-phenylethyl)glycine and (*S*)-*N*-(1-phenylethyl)-β-alanine residues in alternation (Table 1), using our recently developed methodology.[14] All the oligomers are composed of α,β-dimeric peptoid repeating units resulting from two coupled 'submonomer' synthetic protocols, one for α-peptoid monomer synthesis and another for β-peptoid monomer synthesis. Due to the significant effect of capping groups observed for β-peptoid pentamers with same backbone and side chains,[9] we synthesised α,β-peptoids with varied capping groups to investigate if this would also be significant in α,β-peptoids. Iteration of

Table 1 α,β-peptoids with different capping groups at the *N*- and *C*-termini studied for conformational preference



Series	Peptoids	R^1	R^2	Chain length (n)[a]	Purity[b] (%)
a	**1**	H	O*t*Bu	1	—
	2	H	O*t*Bu	2	98
	3	H	O*t*Bu	3	94.8
b	**4**	H	NH_2	1	99.9
	5	H	NH_2	2	99.2
	6	H	NH_2	3	96.8
c	**7**	Boc	O*t*Bu	1	97.9
	8	Boc	O*t*Bu	2	98.1
	9	Boc	O*t*Bu	3	94.8
	17	Boc	O*t*Bu	4	99.9
	18	Boc	O*t*Bu	5	99.9
d	**10**	Boc	NH_2	1	99.2
	11	Boc	NH_2	2	97.9
	12	Boc	NH_2	3	97.5
	19	Boc	NH_2	4	93.1
	20	Boc	NH_2	5	93.7
e	**13**	TFA·H	OH	1	98.3
	14	TFA·H	OH	2	96.2
	15	TFA·H	OH	3	93.6

[a] n = 1 dimer, n = 2 tetramer, n = 3 hexamer; n = 4 octamer; n = 5 decamer. [b] As estimated by analytical reversed-phase HPLC of purified products by flash chromatography or preparative HPLC (**17** and **18**) (see ESI).



Scheme 1 Solution-phase synthesis of α,β-peptoid oligomers with different *N*- and *C*-terminal groups.

submonomer methods were used to obtain dimer, tetramer and hexamer (n = 1, 2, 3; Scheme 1 and Table 1) with two *C*-terminal groups (CO_2tBu and $CONH_2$). This generated compounds **1**–**6** and then subsequently all the modified *N*- and *C*-derived α,β-peptoids **7**–**16**. The longer oligomers **17**–**20** (n = 4 octamers and n = 5 decamers) were prepared by peptide-type coupling (HATU/iPr$_2$NEt) of the free acid tetramer **16** with the amine tetramers **2** and **5** or amine hexamers **3** and **6**. All the synthesised peptoids were obtained in excellent purity, as determined by analytical reversed-phase HPLC, after purification by flash chromatography on silica gel or preparative reversed-phase HPLC (see ESI for details).

Conformational studies of dimers

CD in acetonitrile. Comparison between five series (a–e in Table 1) of α,β-peptoid dimers with differing capping groups at the *N*- and *C*-termini showed significantly different CD spectra in MeCN (Fig. 2 and S1).

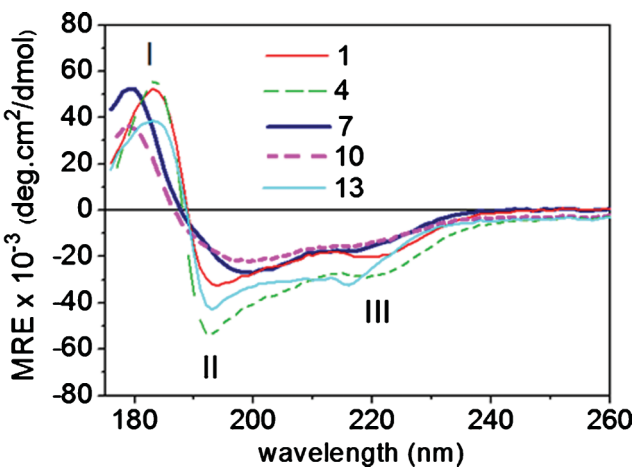


Fig. 2 ECD spectra of dimers in MeCN. All spectra were recorded at 20 °C at known concentrations in the range 650–700 μM.

The different intensities of the dimer spectra in the far UV region may be attributable to the contribution of any chromophore(s) present in the capping groups. To evaluate this possibility, the CD spectra were processed to include the contribution of all the chromophores present (see ESI, Fig. S2, Tables S1 and S2). Despite this, a significant difference was still evident, suggesting that the spectral differences observed in the MRE spectra (Fig. 2) were not solely due to the addition of the chromophores at the terminal capping groups.

Compounds **1** and **4** in Fig. 2 have a positive (I) and two negative (II and III) maxima at 184, 194 and 219 nm respectively (Table S3). Very similar maxima were observed for compound **13**, however the maximum at ~219 nm, was blue shifted by 3 nm in comparison to **1** and **4**. By contrast, different spectral features were observed for compounds **7** and **10**, where one positive (I) and two negative maxima (II and III) were observed at 180, 200 and 217 nm, respectively. The CD spectrum of **4** was found to resemble the spectral features of an α-peptoid hexamer with same side chains and capping groups.[5c,d]

It is of note that compounds **1**, **4** and **13**, which represent one set of distinctive CD spectra, have a free *N*-terminus while **7** and **10** have the *N*-terminus Boc-protected. This suggested that the *N*-terminus is the key structural feature generating the observed difference in the dimer CD spectra, in particular for the wavelength shift of positive and negative maxima. By contrast, changing the terminal groups at the *C*-terminus seemed to determine a change in the intensity (MRE).

^{1}H NMR analyses of the dimers in CD_3CN and $CDCl_3$ also showed the presence of two sub-sets based on the capping group at the *N*-terminus. Peptoids with unprotected *N*-terminus (**1**, **4** and **13**) gave well-resolved NMR spectra which allowed determination of the *cis*/*trans* ratio by integration of the benzylic protons of the spe side chain on the tertiary amide (Table S8). By contrast, the NMR spectra of Boc-protected peptoids **7** and **10** were more complex and showed significant ^{1}H signal overlap due to the simultaneous isomerism of the tertiary amide and carbamate. The values of $K_{cis/trans}$ were in the range of 0.39–0.89 for **1**, **4** and **13** in both solvents. In particular, $K_{cis/trans}$ of 0.61 and 0.64 were measured for dimer **1** in $CDCl_3$ and CD_3CN, respectively. These values were very similar to those measured by Blackwell and co-workers for a monomeric α-peptoid model bearing the phenylethyl side chain and capped at the *N*-terminus by an acetyl group and at the *C*-terminus by a methyl ester ($K_{cis/trans}$ = 0.66–0.67 in $CDCl_3$ and CD_3CN).[18]

Table 2 H-bonding potential of solvents used for CD spectroscopy[18]

Solvent	α-value	β-value
MeCN	0.09	0.31
MeOH	0.35	0.42
TFE	1.51	0.00
HFIP	1.96	0.00

Given the short chain length of the dimers, interpretation of these observations could be complicated by the possibility that R^1 and R^2 may interact with each other. In addition to this, the difference in the CD spectra may arise from short range interactions at the *N*- and *C*-termini, *e.g.* H-bonding, rather than being indicative of secondary structures. Short range interactions at the termini are generally more significant in short oligomers due to the smaller contribution from the 'middle' (*i.e.* the backbone and side chains) – this is known as the 'end effect'. However, it is clear that certain combinations of *N*- and *C*-terminal groups alter conformational preference.

CD in protic *versus* aprotic solvents. CD spectra were also obtained in protic solvents to explore the potential contribution of H-bonding from the *N*- and *C*-termini. Protic solvents with different H-bonding potential were selected for the study (Table 2).[19] MeOH was selected as a good H-bonding acceptor (β-value) and TFE and HFIP as H-bonding donors of differing ability (α-value).

The previously observed trend in MeCN for dimers with different capping groups (*vide supra*) was found to be consistent in all of the solvents investigated (Fig. 3). In each solvent two distinct sets of CD spectra were observed based on the position of the positive and negative maxima. This difference again correlated with the presence of Boc-protected or deprotected *N*-terminus and confirmed that, also in protic solvents, the protecting group at the *N*-terminus has the greatest effect on the spectral features.

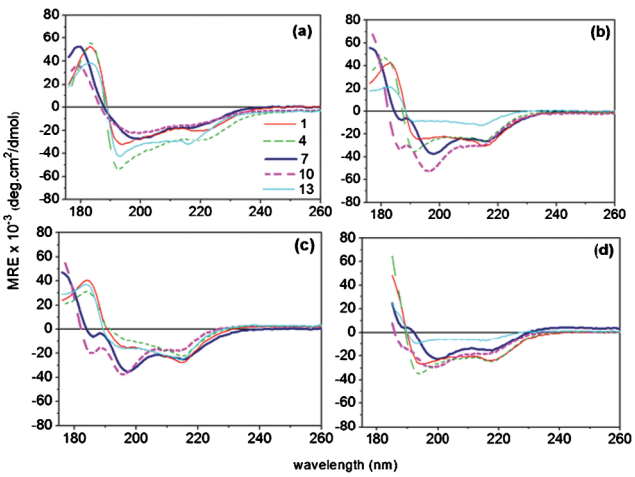


Fig. 3 ECD spectra of dimers in (a) MeCN, (b) TFE, (c) HFIP and (d) MeOH. All spectra were recorded at 20 °C at known concentrations in the range 650–750 μM.

When the *N*-terminus was Boc-protected (**7** and **10**), an additional positive maximum was observed at ~192 nm in protic solvents but not in aprotic (MeCN). The presence of this additional maximum may be indicative of a conformational transition which is promoted in protic solvents. Notably, for Boc-protected oligomers this conformational change was also observed in MeCN upon increase of chain length (*vide infra*).

To investigate the protic/aprotic solvent effect, a solvent titration from MeCN to TFE was undertaken for compound **10** (Fig. 4). A subtle change to the ensemble of conformations adopted occurred when 50% of TFE was added to MeCN, as indicated by the presence of the positive maximum at ~192 nm. This positive maximum and the negative maxima at ~198 and ~218 nm were significantly increased upon further addition of TFE. This suggested an increased population of the conformation(s) observed in MeCN : TFE 1 : 1 and the presence of a conformational transition. It is noted that TFE is known to be structure inducing in peptides[20] mainly by promoting H-bonds. However, these are unlikely to be the main driving forces in the peptoid backbone which has a reduced H-bonding capability. The solvent titration of **7** in MeCN/TFE underwent similar conformational transitions (Fig. S3). The presence of the additional positive maximum at 192 nm clearly relates to the presence of Boc at the *N*-terminus for the dimers (*vide supra*) and is only observed in protic solvents confirming the presence of a H-bonding interaction between the peptoid and protic solvents. This is further supported by the observation that the positive maximum at ~192 nm is less pronounced in MeOH (Fig. 3), which has less H-bonding donor potential than TFE and HFIP. α,β-Dipeptoids with an unprotected *N*-terminus (**1**, **4** and **13**) did not show the additional positive maximum at ~192 nm in protic solvents (Fig. 3 and S4) as their spectra were more comparable to those in MeCN. However, a significantly reduced intensity (MRE) was observed at 190 nm for compound **4** in all protic solvents (Fig. 5a). By contrast, this difference was less pronounced for the spectra of **1** in different solvents (Fig. 5b). It is of note that the CD spectra of **13** are not consistent with the trends observed for the other dimers. This is likely to be due to the presence of the TFA salt at the *N*-terminus which will give rise to different interactions compared to other dimers.

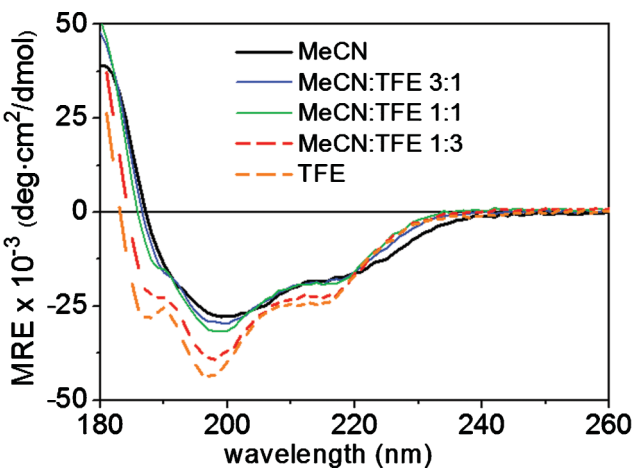


Fig. 4 MeCN/TFE solvent titration of **10** by ECD. All spectra were recorded at 20 °C at 700 μM or 698 μM.

The difference in the response to solvents can be related to the H-bonding acceptors and donors strength of the backbone and terminal capping groups (Table S4). When the peptoid had both strong H-bonding acceptors and donors (**4**), a greater intensity

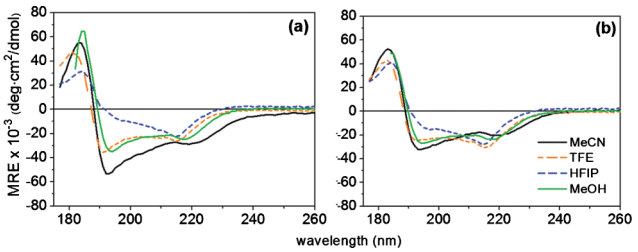


Fig. 5 ECD spectra of dimers (a) **4** and (b) **1** in different solvents. All spectra were recorded at 20 °C at known concentrations in the range 700–780 μM.

in MeCN compared to protic solvents indicated the presence of H-bonding in MeCN. However, when only strong H-bonding acceptors were present in the peptoid structure (**1**), the decrease of intensity in protic solvents, relative to aprotic solvents such as MeCN, was less pronounced (Fig. S4b). The effect of protic solvents, in combination with the greater intensity observed in MeCN for compound **4** in contrast to **1**, suggested the presence of stronger and/or more populated H-bonding interactions for compound **4** in contrast to **1** in MeCN.

Concentration studies were undertaken to establish the nature of the H-bonding interactions. These showed a significant change of the intensity (MRE) with increased concentrations in the range from 5 μM to 1 mM for compound **4** [$\Delta(MRE)_{195nm} = 9 \times 10^3$ deg cm^2 dmol^{-1}] (Fig. S5a), indicating the presence of intermolecular H-bonds in MeCN. A less significant change was observed for **1** in the same concentration range [$\Delta(MRE)_{195nm} = 3.75 \times 10^3$ deg cm^2 dmol^{-1}] (Figure S5b), suggesting that intermolecular H-bonding does not play a role in its conformational stabilization and that the decrease of intensity in protic solvent was likely to be due to intramolecular H-bonds.

Infrared studies. The importance of H-bonding acceptor and donor strength for the folding of α,β-peptoids dimers was further investigated by IR in $CHCl_3$. Possible intramolecular H-bonding relationships for the dimers are shown in Fig. 6. These are based on the H-bonding acceptor and donor strengths,[21] literature precedents and molecular modelling (PM6) from which the H-bonds shown are possible and represent local conformational minima (representative models are shown in Fig. S13). Possible intermolecular H-bonding relationships are not shown but are implied.

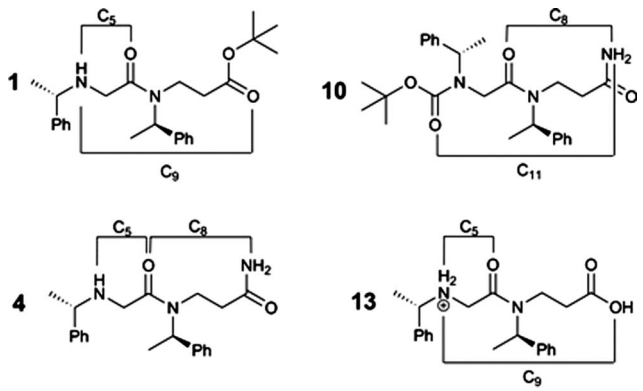


Fig. 6 H-bonding relationship for α,β-peptoid dimers with H-bonding donor and acceptor ability.

It is noticeable that compounds **1**, **4** and **13** all possess the potential for intramolecular H-bonding of the amine (**1** and **4**) or ammonium group (**13**) with the adjacent amide carbonyl (C_5 H-bonding) in contrast to compound **10**.

The N–H and C═O stretching spectral regions for these compounds are shown in Fig. 7. Compound **1** displays a band at 3314 cm^{-1} which can be attributed to the N–H stretch of an amine involved in a H-bond (with a significantly smaller peak at 3420 cm^{-1} attributable to free NH).[22] As expected, its counterpart with Boc-protected *N*-terminus (**7**) displayed no N–H stretch from 3600 to 3200 cm^{-1}. The two potential H-bond acceptors in compound **1** are the tertiary amide carbonyl (β = 0.69–0.78) and the ester ($\beta \sim 0.47$). Comparison of the C═O stretch of compounds **1** and that of **7**, where no intra- or intermolecular H-bonds are possible (due to the absence of H-bonding donors), revealed no significant differences in the C═O stretch peak position for the ester function (1714 cm^{-1} for **1** and 1721 cm^{-1} for **7**) (Table S6). This suggested that the ester was not involved in H-bonding for compound **1**. In contrast, the position of the amide I band (predominantly C═O stretch) was significantly different (1662 cm^{-1} for compound **7** and 1641 cm^{-1} for compound **1**). This was indicative of an H-bonded amide carbonyl.[23]

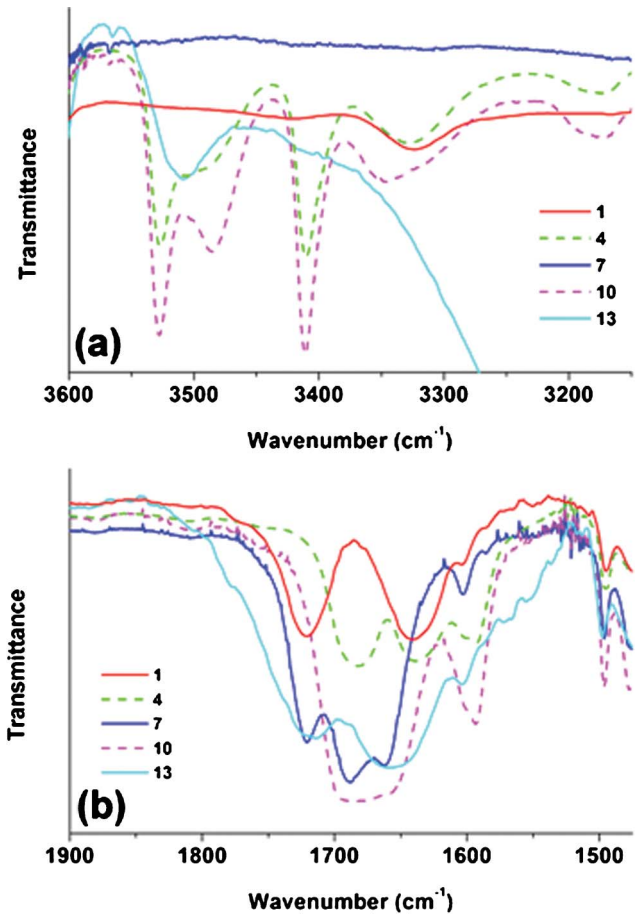


Fig. 7 (a) N–H bonding spectral region and (b) C═O stretching spectral region for α,β-peptoid dimers in $CHCl_3$. All spectra were recorded at room temperature at known concentrations in the range 10–20 mM.

However whether the H-bonds are due to intra- or intermolecular H-bonding was uncertain. Typically intermolecular H-bonds

are concentration dependent and intramolecular H-bonds are concentration independent. Consequently IR analyses of serial dilutions of compound **1** were carried out from 23 mM to 1.43 mM (Fig. S14 and S15). The C═O stretch at 1640 cm^{-1} displayed almost no change over this concentration and no evidence of any substantial growth of a C═O peak at 1666 cm^{-1} that might correspond to the 'free' C═O stretch. Furthermore no significant change in the relative proportions of free N–H to H-bonded N–H, were observed in the N–H region over the concentration range 5.75 mM to 23 mM. Whilst not conclusive, this evidence could support the occurrence of an intramolecular C_5 N–H—O═C H-bond in compound **1**. C_5 H-bonding between nearest neighbour amino acids in peptides can be energetically less favoured than longer H-bonded chains (such as C_7) and intermolecular H-bonds, due to the parallel alignment of the N–H and C═O vectors and a sharp N—H—O bond angle (~90°).[24] However they have been documented for peptides[25] and recently for α,β-peptides.[26]

Compound **4** displayed the peak for the amide I band and the amine N–H stretch with similar values to those of peptoid **1**, though the amine N–H stretch was partly obscured by the dominant N–H stretches attributable to the primary amide from 3600–3250 cm^{-1}. The sharp peaks at 3527 cm^{-1} and 3410 cm^{-1} can be unequivocally attributed to the anti-symmetric and symmetric N–H stretches respectively, due to unassociated (*i.e.* 'free') N–H bonds. The broad accompanying peaks centred at ~3480–3500 cm^{-1} and 3329 cm^{-1} are attributable to anti-symmetric and symmetric N–H stretches respectively, resulting from associated H-bonded species.[27] Thus intra- or intermolecular H-bonding is present for **4** in solution. The amide I band of **4** occurred at 1638 cm^{-1} which in comparison with **1** and **7** suggests that the tertiary amide bond is again involved in H-bonding. To attempt determining the concentration dependence of the H-bonding, IR analyses of serial dilutions of compound **4**, were carried out from 25 mM to 1.5 mM (Fig. S16 and S17). As with compound **1**, remarkably little change in the relative proportions of the H-bonded to free N–H or C═O bonds was observable over this concentration range. For comparison, no intermolecular H-bonding has been observed for acetamide in $CHCl_3$ at a concentration of 5 mM.[27b] This strongly suggested that the primary amides at the *C*-terminus of compound **4** were likely partaking in intramolecular H-bonds which presumably must be C_8 (Fig. 6). This conclusion however does not preclude the occurrence of intermolecular species altogether, since small but observable changes in the N–H region and particularly the tertiary amide I region were discernible. Given the presence of potentially competitive H-bonds, the question of whether C_5 intramolecular bonds are present in compound **4** remains open.

Similar N–H peaks featured in the N–H stretch region for compound **10** as for compound **4**, however the carbonyl tertiary amide I band for **10** occurred at an almost identical peak position as that of compound **7** (1656 cm^{-1} *versus* 1662 cm^{-1}), suggesting that the tertiary amide was not involved in H-bonding at the concentrations employed or certainly not to the same degree as implied for **4**. However since the N–H stretches of **10** clearly showed H-bonding it is reasonable to deduce that compound **10** is undergoing intermolecular H-bonding and exists as equilibrium of its monomeric form and terminal H-bonded aggregates. It is apparent that for all of these compounds further studies are needed to ascertain the possible H-bonding interactions both inter- and intramolecular.

These results are consistent with observations by CD in MeCN suggesting a small degree of intermolecular H-bonding for compound **4** and none for **1** (Fig. S5). However it must be noted that CH_3CN is a substantially stronger H-bond acceptor than $CHCl_3$ (used in the IR studies) and the degree of H-bonding (between peptoid and solvent) might be expected to differ appreciably.

The combined solvent and concentration studies by CD together with the IR results showed that H-bonding does play an important role in the conformational stabilization for α,β-peptoids and this is closely related to the H-bonding acceptor and donor strength of the terminal protecting groups and tertiary amides.

Conformational studies of longer oligomers

Tetramers and hexamers. In order to identify if the effect observed in dimers also occurred for longer oligomers, corresponding α,β-peptoid tetramers and hexamers were investigated in MeCN. As expected, capping groups were found to affect the CD spectra to a lesser extent for the tetramers (Fig. 8a and S6a) and hexamers (Fig. 8b and S6b), as shown by the correlation between the MRE at 192 nm and the chain length (Fig. 8c).

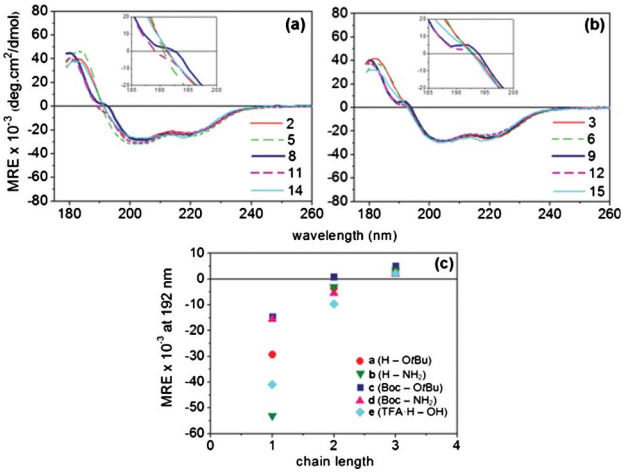


Fig. 8 ECD spectra of (a) tetramers and (b) hexamers in MeCN. (c) Correlation between MRE and chain length at 192 nm. All spectra were recorded at 20 °C at known concentrations in the range 499–500 μM for tetramers and 249–300 μM for hexamers.

Although the effect of terminal groups was less dramatic for the tetramers and hexamers, two different sets of spectral features were evident. This was consistent with observations for the dimers. Peptoids with Boc-protected *N*-terminus can be characterised by the presence of an additional positive maximum at ~193 nm in contrast to their counterparts with an unprotected *N*-terminus (see inset in Fig. 8a and 8b). However, no significant wavelength shift or change in ellipticity of the negative maxima was observed for the longer oligomers which was in contrast to the dimers.

IR studies of the hexamers in $CHCl_3$ solutions showed very similar peak positions to the dimers for the N–H stretching region, 3100–3600 cm^{-1} (Fig. S18) indicating that similar intramolecular and intermolecular H-bonding occurs for longer chains. As for the dimers, this might be responsible for the spectral differences observed by CD between compounds with Boc-protected and

unprotected *N*-terminus. The carbonyl regions for the hexamers were too complex to simply interpret. However, it is worth noting that the relative proportion of H-bonded (~3330 and ~3480 cm^{-1}) to non H-bonded (~3410 and ~3530 cm^{-1}) primary amide for **6** and **12** are considerably larger than for **4** and **10** (compare Fig. 7(a) with Fig. S18). The reason for this is not entirely clear but may be related to the greater intramolecular H-bonding opportunities within the longer chains due to the larger number of tertiary amide H-bond acceptors; *i.e.* between the *C*-terminal amide N–H and the internal C═O amides. Solvent studies on the hexamers revealed that capping groups did not dramatically affect the spectral features of the hexamers in each of the solvents investigated (Fig. 9a, 10 and S7). This was in contrast with results for the dimers and was consistent with a smaller end effect for longer oligomers (*vide supra*). However, a solvent dependence of the conformational preference was observed for all the compounds investigated where spectra in protic solvents were significantly different to those in MeCN (Fig. 9b). The same trend was observed for all the hexamers regardless of the difference in capping groups (Figure S8). This suggested that the minor solvent effect observed for the hexamers was due to the backbone rather than to the presence of differing terminal groups.

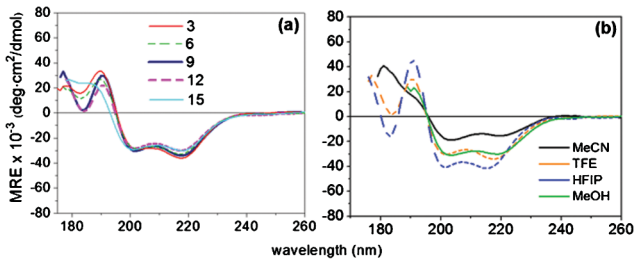


Fig. 9 SRCD spectra of (a) hexamers with different capping groups in TFE and (b) hexamers **9** in different solvents. All spectra were recorded at 20 °C at known concentrations in the range 326–420 μM.

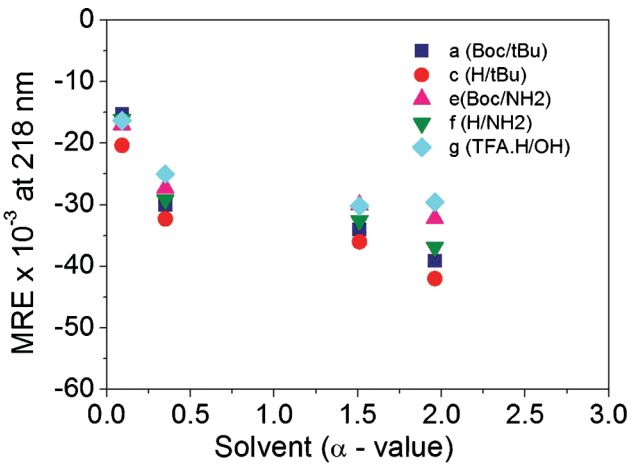


Fig. 10 Correlation between MRE intensity by SRCD and α-values at 218 nm for hexamers with different N- and C-capping groups.

The correlation between the intensity at 218 nm for all the hexamers investigated and the α-value of the solvents showed an increase of the intensity of the negative maxima with increased H-bonding donor potential of the solvent (Fig. 10). This suggested the presence of conformational stabilization due to H-bonding interaction with the solvent.

From the data shown it was clear that the conformational/spectral effects arising from the capping groups were less pronounced for longer oligomers as there was a greater contribution from the backbone and side chains. This was therefore consistent with the presence of an end effect for the dimers.

Investigation of cooperative folding within each series. Each series (a–e in Table 1) was also investigated in MeCN to evaluate the presence of cooperative folding. When processing the molar ellipticity data to MRE, no dramatic intensity difference was observed indicating absence of cooperative folding to increase conformational order (Fig. 11 and S9–12). When going from shorter to longer oligomers, each series had an additional positive maximum at ~192 nm, suggesting that this spectral feature is related to the backbone length. However, depending on the capping groups, this additional maximum was observed at different chain lengths (Fig. S9–12). In particular this was clearly evident when a *tert*-butyl group was present either at the *N*- (series c and d) or at the *C*- (series a) terminus, suggesting that the presence of the *tert*-butyl groups promote adoption of a different confomational preference with increased chain length.

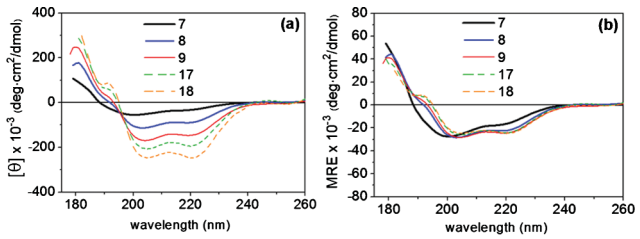


Fig. 11 SRCD spectra of c series in MeCN. (a) Molar ellipticity and (b) MRE spectra. All spectra were recorded at 20 °C at known concentrations in the range 150 μM–2.3 mM.

It is of note that for the series investigated, the dimers had a different spectrum relative to the corresponding longer oligomers. This demonstrated that there was a greater contribution from terminal protecting groups to dimer CD spectra, which was in agreement with previous observations.

The lack of increase in ellipticity associated with the presence of the additional maximum with increased chain length indicates that the order of the system is not altered but the ensemble of conformations adopted is changed. This would be consistent with a change from one ensemble of conformations to another without increase of conformational order. Conformational heterogeneity was also observed by NMR studies showing an average $K_{cis/trans}$ in CD_3CN of 0.92 for tetramer **2** and 1.08 for hexamer **3**. It is important to note that the extent of conformational heterogeneity that is observed is comparable to *N*spe or *N*rch pentamers and hexamers for which the major conformers adopt a PPI like conformation.[6a,17a]

The NMR spectra of compounds **1–3** in CD_3CN were also recorded at 45 °C and 65 °C and the average $K_{cis/trans}$ were measured and compared to the values at room temperature. No collapse of the *cis*/*trans* signals and no change of the amide *cis* and *trans* populations could be observed (Table S9) which indicates slow *cis*/*trans* equilibria on the NMR time scale. On the whole, the *cis*/*trans* conformational heterogeneity ($K_{cis/trans}$) and

cis/*trans* dynamic behaviour of *N*spe α,β-peptoids backbones is comparable to that of *N*spe α-peptoids.

The absence of increased conformational order from cooperative folding for α,β-peptoids with spe side chains was also consistent with literature data on β-peptoids by CD.[9a] This difference certainly arises from a greater flexibility of β-peptoids residues in α,β-peptoids compared to pure α-peptoids.

Conclusions

A family of α,β-alternating peptoids with different chain length and bearing exclusively chiral side chains (spe) was efficiently synthesised by submonomer and block coupling methods. Based on the collapse of secondary structure observed for β-peptoid pentamers with same backbone and side chains but different capping groups,[9] we synthesised five series of α,β-peptoids with different capping groups. This allowed us to investigate if this effect would also occur in α,β-peptoids. No change in conformational order and/or collapse of secondary structure was observed for these systems. Despite this, we were able to ascertain that the presence of different capping groups at the *N*- and *C*-termini has a significant effect on the spectral features, which is more pronounced for shorter oligomers and is also solvent dependent. When studying longer oligomers the contribution of capping groups decreased with increased chain length. However, this is not always the case as reported in literature for β-peptoid pentamers. It is therefore important to compare systems with the same capping groups when undertaking conformational investigation by CD. We hope that this work will raise a greater awareness of the importance of adopting a consistent protecting group strategy for spectroscopic investigation. This is particularly important for more flexible systems, such as peptoids, for which the lack of consistency at the capping groups can lead to false interpretation of their spectral features.

Experimental section

Circular dichroism

CD samples were prepared by weighing accurately small amounts of compound and adding the solvent volumetrically to achieve a sample solution of appropriate concentration (Table S5). For the solvent titrations, 5 samples (for each compound) were prepared at similar concentrations with different solvent combinations and an appropriate solvent background recorded at proximal time for each sample. For concentration studies, a stock solution of peptoid was prepared from which samples of appropriate concentrations were obtained by volumetric dilution and recorded by using a quartz cell as follows: 1 cm path length was used for samples at 1 mM and 500 μM, 0.1 cm path length for 100 μM and 50 μM and 0.01 cm pathlength for 10 μM and 5 μM. Circular dichroism analyses were performed either by ECD or SRCD as specified. The effect of radiation for SRCD *versus* ECD has been previously reported and found to be neglegible.[16] ECD spectra were recorded using a Chirascan instrument (Applied Photophysics Ltd.) equipped with a Peltier temperature control system. SRCD spectra were recorded at beamline B23 of the Diamond Light Source, UK using an Olis CD spectropolarimeter (Module B) equipped with a Peltier temperature control system and fitted with a bespoke thermostated cell holder.[28] A quartz Suprasil cylindrical cell with a path length of 0.01 cm was used. Spectra were recorded at 20 °C in acetonitrile (MeCN), methanol (MeOH) or 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) supplied by Romil at super-purity grade and 2,2,2-trifluoroethanol (TFE) supplied by Sigma Aldrich at spectroscopic grade. The following parameters were used: 4 acquisitions, 10 nm min^{-1} scan speed, 0.1 nm data interval, 1.0 nm spectral band width, 4 s time constant, 260 nm–175 nm scan range (depending on solvent transparency). Solvent baseline spectra (4 accumulations) were recorded in the same cell at proximal time averaged to give the baseline spectrum. The spectra were averaged and the solvent baseline subtracted from the resulting spectrum which was normalised for path length and concentration to give the molar ellipticity ([θ], deg cm^2 $dmol^{-1}$). Correction of molar ellipticity spectra by the number or residues provided the mean residue ellipticity spectra (MRE).

Infrared

Infrared (IR) spectra were recorded on a Perkin-Elmer Spectrum One IR Fourier Transform spectrophotometer in chloroform solution ($CHCl_3$) as stated. Spectroscopic grade $CHCl_3$ was dried over 4 Å molecular sieves before use. Solution spectra were recorded at room temperature by using cells equipped of KBr windows and pathlength of 0.1 cm. Spectra were the result of 12 scans obtained with 4 cm^{-1} resolution when recording the entire spectral range (5000–370 cm^{-1}) and 1 cm^{-1} when recording spectra in the N–H (2000–4000 cm^{-1}) and C═O (2000–1200 cm^{-1}) regions. Baseline spectra were recorded at proximal time and subtracted from the peptoid spectrum. Concentrations used are reported in SI (Table S7). For concentration studies spectra were the result of 64 scans obtained with 8 cm^{-1} resolution and recorded in the N–H (2000–4000 cm^{-1}) and C═O (2000–1200 cm^{-1}) regions. The concentrations used are reported in the ESI (Fig. S14–S17).

Molecular modelling

Molecular modelling was performed using version 12 of the MOPAC Interface for ChemDraw3D (CambridgeSoft). A PM6 method was employed to minimise energy/geometry using an Open Shell (Unrestricted) wavefunction, an EF optimizer, minimum RMS of 0.1000 and a dieletric constant of 37.5 (acetonitrile).

Synthesis – general information

Chemicals obtained from commercial sources were used without further purification, unless stated otherwise. THF was distilled from potassium/benzophenone and stored over 4 Å molecular sieves. CH_2Cl_2 and MeOH were distilled from CaH_2 and stored over 4 Å molecular sieves. DMF, Et_2O, Et_3N and iPr_2NEt were dried over 4 Å molecular sieves. (*S*)-1-phenylethylamine 99% (99% ee) was purchased from Acros. Melting points were determined on a Reichert microscope apparatus and are uncorrected. 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 and wavenumbers (ν) are expressed in cm^{-1}. NMR spectra were recorded on a Bruker AC 400 spectrometer. Chemical shifts are referenced to the residual solvent peak and *J* values are given in Hz. The following multiplicity abbreviations are used:

(s) singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet, and (br) broad. Where applicable, assignments were based on COSY, HMBC, HSQC and *J*-mod-experiments. Thin layer chromatography (TLC) was performed on Merck TLC aluminum sheets, silica gel 60, F_{254}. Flash chromatography was performed with Merck silica gel 60, 40–63 μm. HRMS was recorded on a Micromass Q-Tof Micro (3000 V) apparatus.

The synthesis and characterisation of compound **1** from *tert*-butyl acrylate is described in a previous publication.[16] Chemical structures of intermediates **1a**, **2a**, **4a** and **5a** are shown in ESI (Figure S19).

General procedure for chain elongation of one α,β-dimeric peptoid unit using two consecutive submonomer methods (A and B).

β-*Peptoid submonomer synthesis (method A).* To a solution of the secondary amine (*N*-terminus α-peptoidic residue: 1.0 equiv, 0.2 M) in THF at 0 °C under Ar was added Et_3N (1.4 equiv) and then acryloyl chloride (1.2 equiv). After stirring for 1 h at 0 °C the resulting mixture was filtered, washing the solids with THF. The filtrate was then concentrated and dried *in vacuo*, yielding the crude acrylamide. To a solution of the crude acrylamide (0.4 M) in MeOH at rt under Ar was added (*S*)-1-phenylethylamine (2.0 equiv). After stirring 6 h at 50 °C, the mixture was concentrated under reduced pressure. Flash chromatography of the crude yielded the desired secondary amine which was engaged in the α-peptoid submonomer synthesis.

α-*Peptoid submonomer synthesis (method B).* To a solution of the previously obtained secondary amine (1.0 equiv, 0.2 M) in THF at 0 °C under Ar was added Et_3N (1.2 equiv) and then bromoacetyl bromide (1.2 equiv). After stirring for 1 h at 0 °C the resulting mixture was filtered, washing the solids with THF. The filtrate was then concentrated and dried *in vacuo*, yielding the crude bromoacetyl amide. To a solution of the crude bromoacetyl amide (0.2 M) in THF at 0 °C under Ar was added Et_3N (2.0 equiv) followed by (*S*)-1-phenylethylamine (2.0 equiv). After stirring overnight at rt, further Et_3N (3.0 equiv) was added and stirring was continued for 10 min. The resulting mixture was filtered, washing the solids with THF. The filtrate was then concentrated under reduced pressure. Flash chromatography of the residue yielded the desired product (**1–6**).

General procedure for *N*-Boc protection of peptoids (method C). To a solution of the peptoid with a free *N*-terminus (1.0 equiv, 0.2 M) in dioxane at 0 °C was added 0.5 M aq. NaOH (1 mL per 1 mL dioxane) and the resulting mixture was stirred for 5 min. Boc_2O (2 equiv) was then added and stirring was continued overnight while allowing the reaction to warm to rt. The dioxane was then evaporated under reduced pressure and the residue was diluted with water (approx. twice the volume used for the reaction). The aqueous layer was extracted with EtOAc (2×) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash chromatography yielded the desired product (**7–12**).

General procedure for TFA *t*-butyl ester deprotection and isolation of compounds 13–15 as TFA salts (method D). To a solution of the *t*Butyl ester (**1**, **2** or **3**: 1.0 equiv, 0.10 M) in CH_2Cl_2 at 0 °C under Ar was added TFA (1 mL per 1 mL CH_2Cl_2) and the resulting mixture was stirred for 4 h at 0 °C. The solvents were evaporated under reduced pressure and the residue was evaporated several times with CH_2Cl_2. The residue was dried *in vacuo*, yielding the desired TFA salt.

General procedure for coupling of peptoid oligomers using HATU (method E). To a solution of the peptoid with a free *N*-terminus (**2**, **3**, **5** or **6**: 1.0 equiv, 50 mM) and the peptoid **16** with a free *C*-terminus (1.0 equiv) in CH_2Cl_2/DMF 4 : 1 at 0 °C under Ar was added iPr_2NEt (1.2 equiv.) and HATU (1.2 equiv.) The resulting mixture was stirred overnight while allowing to warm slowly to rt. The solvents were evaporated under reduced pressure and the residue was taken up in EtOAc. The organic layer was washed with an equal amount of water and the aqueous layer was extracted with EtOAc (×1). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash chromatography of the residue yielded the desired product (**17–20**).

α,β-Peptoid 2. Reaction of **1** (8.41 g, 20.5 mmol) following method A yielded **1a** (10.8 g, 90%) as a pale yellowish oil. Then reaction of **1a** (5.27 g, 9.00 mmol) following method B and performing the flash column chromatography with EtOAc/MeOH 97 : 3 as eluent until the impurities had passed followed by change to CH_2Cl_2/MeOH 97 : 3 yielded **2** (5.33 g, 79%) as a pale yellowish solid: R_f (CH_2Cl_2/MeOH 97 : 3) = 0.23; $[\alpha]_D^{21}$ −118.8 (*c* 0.74 in $CHCl_3$); mp 36–38 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–6.94 (20H, m, Ph*H*), 6.09–5.69 (1.24H, m, NC*H*CH_3), 5.34–5.05 (0.30H, m, NC*H*CH_3), 4.98–4.50 (1.46H, m, NC*H*CH_3), 4.42–2.98 (9H, m, 2×NCH_2C═O, HNC*H*CH_3 and 2×NC$H_2$$CH_2$C═O), 2.83–1.75 (4H, m, 2×NCH_2CH_2C═O), 1.64–1.26 (21H, m, 4×NCHCH_3 and ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3, 172.1, 171.3, 171.2, 171.1, 171.0, 170.9, 170.8, 170.6, 170.3, 170.2, 170.0, 170.0, 169.7, 168.3, 168.0, 167.9, 167.8, 167.6, 167.4, 167.0, 166.9 (4C, 4×*C*═*O*), 144.8 (C, Ph), 140.6, 140.5, 140.3, 140.2, 140.0, 139.9, 139.7, 139.4, 139.2, 139.0 (3C, Ph), 128.9, 128.6, 128.6, 128.4, 128.0, 127.8, 127.5, 127.4, 127.3, 126.9, 126.8, 126.7, 126.5, 126.4, 126.0, 125.9 (20CH, Ph), 80.4, 80.2 (C, ^{t}Bu), 58.4, 58.4, 58.0, 57.8, 57.8 (CH, HN*C*HCH_3), 55.1, 55.0, 54.5, 54.4, 54.2, 54.1, 54.0 (1.76CH, N*C*HCH_3), 52.0, 51.8, 51.4, 51.3, 51.2, 50.7 (1.24CH, N*C*HCH_3), 49.1, 48.9, 48.7, 48.5 (CH_2, HN*C*H_2C═O), 45.1, 44.9, 44.6, 44.0, 43.9 (CH_2, N*C*H_2C═O), 40.3, 40.2, 39.9, 39.8, 39.6, 39.2, 39.1, 38.8, 38.5, 38.4, 38.3 (2CH_2, 2×N*C*$H_2$$CH_2$C═O), 36.2, 36.1, 35.6, 35.6, 34.1, 34.0, 33.7, 33.6, 33.4, 33.1, 32.7, 32.5 (2CH_2, 2×NCH_2*C*H_2C═O), 27.9, 27.9 (3CH_3, ^{t}Bu), 24.6, 24.6, 24.4 (CH_3, HNCH*C*H_3), 18.6, 18.5, 18.4, 18.3, 18.3, 18.2, 17.8, 16.5, 16.4, 16.2, 16.2, 16.0, 15.8 (3CH_3, 3×NCH*C*H_3); ν_{max}/cm^{-1} 2975, 1724 (C═O, ester), 1642 (C═O, amide), 1496, 1451, 1415, 1393, 1369, 1290, 1257, 1207, 1151, 1074, 1051, 1033, 1007, 991, 914, 846, 788, 755, 700; HRMS (TOF MS ES$^+$) calcd for $C_{46}H_{59}N_4O_5$ $[M + H]^+$ *m*/*z* 747.4485, found 747.4493. HPLC (Water (0.1% TFA)/MeCN 40 : 60, flow = 0.80): t_r = 22.42 min; HPLC (Water (0.1% TFA)/MeOH 20 : 80, flow = 0.60): t_r = 13.57 min, purity = 98.0%.

α,β-peptoid 3. Reaction of **2** (1.50 g, 2.01 mmol) following method A yielded **2a** (1.45 g, 79%) as a pale yellowish solid. Then reaction of **2a** (1.29 g, 1.40 mmol) following method B and performing the flash column chromatography in EtOAc/MeOH 95 : 5 to EtOAc/MeOH 90 : 10 yielded **3** (1.14 g, 75%) as a colorless solid: R_f (EtOAc/MeOH 90 : 10) = 0.64; $[\alpha]_D^{21}$ −120.0 (*c* 0.69 in $CHCl_3$); mp 62–64 °C; ^{1}H NMR (400 MHz,

$CDCl_3$): δ 7.42–6.92 (30H, m, Ph*H*), 6.10–5.61 (2.23H, m, NC*H*CH_3), 5.33–4.53 (2.77H, m, NC*H*CH_3), 4.48–2.95 (13H, m, 3×NC*H*$_2$C═O, HNC*H*CH_3 and 3×NC*H*$_2$$CH_2$C═O), 2.84–1.84 (6H, m, 3×NCH$_2$C*H*$_2$C═O), 1.70–1.20 (27H, m, 6×NCHC*H*$_3$ and ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 172.2, 172.0, 171.5, 171.3, 171.1, 171.0, 170.9, 170.8, 170.6, 170.2, 170.1, 170.0, 168.5, 168.4, 168.1, 168.1, 167.8, 167.8, 167.2, 167.1 (6C, 6×*C*═*O*), 144.8 (C, Ph), 141.0, 140.9, 140.7, 140.6, 140.5, 140.4, 140.3, 140.2, 140.1, 139.9, 139.8, 139.7, 139.4, 139.4, 139.2, 139.1, 139.1 (5C, Ph), 128.6, 128.3, 127.5, 127.3, 126.9, 126.8, 126.6, 126.5, 126.4, 126.3 (30CH, Ph), 80.4, 80.3 (C, ^{t}Bu), 58.4, 57.9, 57.8 (CH, HN*C*HCH$_3$), 55.4, 55.3, 55.2, 55.0, 54.9, 54.7, 54.6, 54.5, 54.4, 54.4, 54.3, 54.0 (2.77CH, N*C*HCH$_3$), 51.8, 51.7, 51.6, 51.6, 51.4, 51.4, 51.2, 51.1, 50.9, 50.8, 50.6, 50.6 (2.23CH, N*C*HCH$_3$), 49.0, 48.9, 48.6, 48.4 (CH_2, HN*C*H$_2$C═O), 45.1, 45.0, 44.9, 44.8, 44.7, 44.6, 44.5, 44.3, 44.3, 44.2, 44.1, 44.0, 43.9 (2CH_2, 2N*C*H$_2$C═O), 40.6, 40.2, 40.1, 39.8, 39.7, 39.5, 39.4, 39.3, 39.2, 39.1, 38.8, 38.8, 38.6, 38.4, 38.2 (3CH_2, 3×N*C*H$_2$$CH_2$C═O), 36.1, 36.1, 35.6, 34.1, 33.9, 33.9, 33.8, 33.6, 33.5, 33.4, 33.3, 33.2, 32.5, 32.4, 32.2 (3CH_2, 3×NCH$_2$*C*H$_2$C═O), 27.9, 27.8 (3CH_3, ^{t}Bu), 24.6, 24.4, 24.2, 24.0 (CH_3, HNCH*C*H$_3$), 18.9, 18.7, 18.5, 18.4, 18.2, 18.1, 18.1, 18.0, 17.9, 17.7, 17.6, 16.5, 16.4, 16.3, 16.1, 16.0, 15.8 (5CH_3, 5×NCH*C*H$_3$); ν_{max}/cm^{-1} 1724 (C═O, ester), 1643 (C═O, amide), 1495, 1449, 1418, 1370, 1288, 1206, 1150, 1074, 1042, 1028, 993, 916, 845, 818, 808, 785, 760, 752, 700; HRMS (TOF MS ES$^+$) calcd for $C_{67}H_{83}N_6O_7$ [M + H]$^+$ *m*/*z* 1083.6318, found 1083.6309. HPLC (Water (0.1% TFA)/MeCN 30 : 70, flow = 0.80): t_r = 26.12 min; HPLC (Water (0.1% TFA)/MeOH 20 : 80, flow = 0.60): t_r = 35.18 min, purity = 94.8%.

3-{((*S*)-1-Phenyl-ethyl)-[2-((*S*)-1-phenyl-ethylamino)-acetyl]-amino}-propionamide (4). To a solution of acrylamide (2.13 g, 30.0 mmol) in MeOH (75 mL) at rt under Ar was added (*S*)-1-phenylethylamine (7.65 mL, 60.1 mmol). After stirring overnight, the mixture was concentrated under reduced pressure. Flash chromatography of the crude yielded 3-((*S*)-1-phenyl-ethylamino)-propionamide (5.19 g, 90%) as a colorless oil. It (2.50 g, 13.0 mmol) was then reacted following method B to yield **4** (2.45 g, 53%) as a colorless oil after flash column chromatography in EtOAc/MeOH 95 : 5 until the impurities had passed followed by change to CH_2Cl_2/MeOH 90 : 10: R_f (CH_2Cl_2/MeOH 90 : 10) = 0.53; $[\alpha]_D^{22}$ −135.3 (*c* 0.55 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.09 (10H, m, Ph*H*), 6.35–6.22 (0.70H, br s, N*H*$_2$), 5.96 (0.30H, q, *J* = 7.0 Hz, (c)-NC*H*CH_3), 5.80–5.75 (1.00H, 2×br s, N*H*$_2$), 5.25–5.14 (0.30H, br s, N*H*$_2$), 4.83 (0.70H, q, *J* = 6.9 Hz, (t)-NC*H*CH_3), 3.86–3.75 (1H, m, HNC*H*CH_3), 3.52–3.16 (4H, m, HNC*H*$_2$C═O and NC*H*$_2$$CH_2$C═O), 2.65–2.56 (1H, br s, N*H*), 2.39–2.29 (0.70H, m, NCH$_2$C*H*$_2$C═O), 2.25–2.15 (0.70H, m, NCH$_2$C*H*$_2$C═O), 2.06–1.95 (0.30H, m, NCH$_2$C*H*$_2$C═O), 1.68–1.59 (0.30H, m, NCH$_2$C*H*$_2$C═O), 1.52–1.47 (3H, m, NCHC*H*$_3$), 1.40 (3H, d, *J* = 6.6 Hz, HNCHC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 172.1, 171.2, 171.0 (2C, 2×*C*═*O*), 144.6 (C, Ph), 140.3, 139.4 (C, Ph), 128.7, 128.5, 127.8, 127.5, 127.1, 126.9, 126.7, 126.6 (10CH, Ph), 58.3, 58.0 (CH, HN*C*HCH$_3$), 54.1 (0.70CH, (t)-N*C*HCH$_3$), 51.4 (0.30CH, (c)-N*C*HCH$_3$), 48.9, 48.5 (CH_2, HN*C*H$_2$C═O), 39.8, 38.6 (CH_2, N*C*H$_2$$CH_2$C═O), 35.9, 35.6 ($CH_2$, NCH$_2$*C*H$_2$C═O), 24.5, 24.4 ($CH_3$, HNCH*C*H$_3$), 17.9 (0.70$CH_3$, (t)-NCH*C*H$_3$), 16.4 (0.30$CH_3$, (c)-NCH*C*H$_3$); ν_{max}/cm^{-1} 2972, 1670 (C═O, amide), 1636 (C═O, amide), 1495, 1451, 1416, 1370, 1283, 1252, 1204, 1157, 1121, 1074, 1028, 1005, 914, 762, 700; HRMS (TOF MS ES$^+$) calcd for $C_{21}H_{28}N_3O_2$ [M + H]$^+$ *m*/*z* 354.2182, found 354.2192. HPLC (Water (0.1% TFA)/MeOH 40 : 60, flow = 0.40): t_r = 11.17 min, purity = 99.9%.

α,β-Peptoid 5. Reaction of **4** (2.19 g, 6.20 mmol) following method A yielded **4a** (2.92 g, 89%) as a colorless solid. Then reaction of **4a** (2.00 g, 5.30 mmol) following method B and performing the flash column chromatography in EtOAc/MeOH 95 : 5 until the impurities had passed followed by change to CH_2Cl_2/MeOH 95 : 5 yielded **5** (1.22 g, 33%) as a pale yellowish solid: R_f (CH_2Cl_2/MeOH 95 : 5) = 0.28; $[\alpha]_D^{21}$ −133.1 (*c* 0.58 in $CHCl_3$); mp 46–48 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–6.91 (20H, m, Ph*H*), 6.86–6.70 (0.55H, m, N*H*$_2$), 6.44–6.35 (0.19H, br s, N*H*$_2$), 6.29–6.20 (0.08H, br s, N*H*$_2$), 6.05–5.80 (1.20H, m, NC*H*CH_3), 5.74–5.40 (1.25H, m, 0.07×NC*H*CH_3 and 0.59×N*H*$_2$), 5.30–5.16 (0.29H, m, NC*H*CH_3), 4.92–4.76 (1.19H, m, NC*H*CH_3), 4.68–4.56 (0.25H, m, NC*H*CH_3), 4.32–4.12 (0.84H, m, 0.42×NC*H*$_2$C═O), 3.91–3.10 (8.16H, m, 0.58×NC*H*$_2$C═O, HNC*H*$_2$C═O, HNC*H*CH_3 and 2×NC*H*$_2$$CH_2$C═O), 2.81–1.95 (4H, m, 2×NCH$_2$C*H*$_2$C═O), 1.64–1.29 (12H, m, 4×NCHC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8, 173.7, 173.0, 172.6, 172.1, 171.9, 171.4, 171.2, 171.0, 170.9, 170.8, 170.4, 170.3, 168.6, 168.2, 168.1, 167.7, 167.5, 167.4 (4C, 4×*C*═*O*), 144.7, 144.7, 144.6, 144.1 (C, Ph), 140.7, 140.6, 140.6, 140.5, 140.5, 140.1, 139.9, 139.7, 139.6, 139.2, 139.1, 139.0 (3C, Ph), 128.9, 128.7, 128.6, 128.6, 128.5, 128.4, 128.1, 127.8, 127.7, 127.7, 127.6, 127.5, 127.5, 127.4, 127.3, 127.1, 127.0, 126.9, 126.7, 126.6, 126.5, 126.3, 126.2 (20CH, Ph), 58.4, 58.4, 58.2, 58.0, 57.8, 57.8 (CH, HN*C*HCH$_3$), 55.3, 55.1, 54.8, 54.6, 54.4, 54.3, 54.1 (1.73CH, N*C*HCH$_3$), 52.9, 52.0, 51.8, 51.5, 51.4, 51.1, 51.0, 50.9 (1.27CH, N*C*HCH$_3$), 49.0, 48.9, 48.6, 48.3, 47.9 (CH_2, HN*C*H$_2$C═O), 45.3, 45.1, 45.0, 44.7, 44.4, 44.3, 44.1, 44.0 (CH_2, N*C*H$_2$C═O), 40.5, 40.1, 39.8, 39.0, 38.9, 38.9 (2CH_2, 2×N*C*H$_2$$CH_2$C═O), 36.1, 35.9, 35.7, 35.4, 35.2, 34.9, 34.2, 34.0, 33.9, 33.4, 32.5 (2CH_2, 2×NCH$_2$*C*H$_2$C═O), 24.5, 24.4, 24.3, 24.3, 23.9, 23.5 (CH_3, HNCH*C*H$_3$), 18.7, 18.5, 18.3, 18.2, 18.1, 17.9, 17.7, 16.9, 16.7, 16.5, 16.4, 16.2, 16.1, 16.0 (3CH_3, 3×NCH*C*H$_3$); ν_{max}/cm^{-1} 1653 (C═O, amide), 1647 (C═O, amide), 1640 (C═O, amide), 1494, 1450, 1415, 1293, 1208, 1164, 1071, 1050, 1029, 987, 913, 789, 753; HRMS (TOF MS ES$^+$) calcd for $C_{42}H_{52}N_5O_4$ [M + H]$^+$ *m*/*z* 690.4019, found 690.4016. HPLC (Water (0.1% TFA)/MeOH 30 : 70, flow = 0.50): t_r = 14.49 min, purity = 99.2%.

α,β-Peptoid 6. Reaction of **5** (828 mg, 1.20 mmol) following method A yielded **5a** (975 g, 94%) as a pale yellowish solid. Then reaction of **5a** (813 mg, 0.94 mmol) following method B and performing the flash column chromatography in EtOAc/MeOH 95 : 5 until the impurities had passed followed by change to CH_2Cl_2/MeOH 95 : 5 to 90 : 10 yielded **6** (577 mg, 60%) as a yellowish solid: R_f (CH_2Cl_2/MeOH 90 : 10) = 0.54; $[\alpha]_D^{21}$ −127.0 (*c* 0.61 in $CHCl_3$); mp 65–67 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–6.80 (30H, m, Ph*H*), 6.52–6.10 (0.68H, m, N*H*$_2$), 6.06–5.64 (2.29H, m, NC*H*CH_3), 5.60–5.30 (1.32H, m, N*H*$_2$), 5.30–5.04 (0.53H, m, NC*H*CH_3), 4.96–4.56 (2.18H, m, NC*H*CH_3), 4.52–2.90 (13H, m, 3×NC*H*$_2$C═O, HNC*H*CH_3 and 3×NC*H*$_2$$CH_2$C═O), 2.86–1.94 (6H, m, 3×NCH$_2$C*H*$_2$C═O), 1.70–1.24 (18H, m, 6×NCHC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5, 173.4, 172.7, 172.2, 172.1, 172.0, 171.8, 171.6, 171.6, 171.3, 171.2, 170.7, 170.6, 170.4, 170.3, 168.9, 168.6, 168.3, 168.1, 167.9, 167.7, 167.6, 167.4 (6C, 6×*C*═*O*),

144.5, 144.2 (C, Ph), 140.8, 140.6, 140.5, 140.4, 140.3, 140.2, 140.1, 140.0, 139.9, 139.7, 139.6, 139.4, 139.4, 139.2, 139.2, 139.1, 139.0, 138.6 (5C, Ph), 128.8, 128.6, 128.4, 128.1, 127.7, 127.6, 127.5, 127.4, 127.3, 127.2, 127.1, 126.8, 126.7, 126.6, 126.5, 126.4 (30CH, Ph), 58.5, 58.4, 58.2, 58.0 (CH, HN*C*HCH$_3$), 55.6, 55.5, 55.2, 55.0, 54.9, 54.8, 54.6, 54.6, 54.4, 54.3, 54.3, 54.0, 54.0, 53.8, 53.8 (2.71CH, N*C*HCH$_3$), 52.3, 52.0, 51.9, 51.7, 51.6, 51.6, 51.4, 51.3, 51.0, 50.9, 50.7 (2.29CH, N*C*HCH$_3$), 48.8, 48.8, 48.5, 48.5 (CH$_2$, HN*C*H$_2$C═O), 45.6, 45.3, 45.1, 45.1, 44.9, 44.8, 44.6, 44.3, 44.2, 43.9, 43.8 (2CH$_2$, 2N*C*H$_2$C═O), 41.2, 41.1, 41.0, 40.7, 40.6, 40.3, 40.3, 40.1, 39.9, 39.7, 39.3, 39.2, 39.1, 38.9, 38.8 (3CH$_2$, 3×N*C*H$_2$CH$_2$C═O), 36.5, 36.3, 36.2, 35.9, 35.8, 35.5, 35.4, 35.2, 35.0, 34.9, 34.8, 34.4, 34.2, 34.1, 33.9, 33.8, 33.7, 33.5, 33.4, 33.3, 32.5, 32.3, 32.2, 32.0 (3CH$_2$, 3×NCH$_2$*C*H$_2$C═O), 24.4, 24.3, 24.2, 24.0, 23.9, 23.7 (CH$_3$, HNCH*C*H$_3$), 18.7, 18.6, 18.4, 18.3, 18.2, 18.1, 18.0, 18.0, 17.9, 17.7, 17.4, 17.3, 16.9, 16.9, 16.8, 16.7, 16.6, 16.3, 16.2, 16.1, 16.0, 15.9 (5CH$_3$, 5×NCH*C*H$_3$); ν_{max}/cm^{-1} 1654 (C═O, amide), 1647 (C═O, amide), 1638 (C═O, amide), 1495, 1449, 1421, 1414, 1289, 1205, 1187, 1159, 1054, 1033, 789, 748; HRMS (TOF MS ES$^+$) calcd for $C_{63}H_{76}N_7O_6Na$ [M + H + Na]$^{2+}$ *m*/*z* 524.7877, found 524.7899. HPLC (Water (0.1% TFA)/MeOH 20 : 80, flow = 0.60): t_r = 11.92 min, purity = 96.8%.

3-[{2-[*tert*-Butoxycarbonyl-((*S*)-1-phenyl-ethyl)-amino]-acetyl}-((*S*)-1-phenyl-ethyl)-amino]-propionic acid *tert*-butyl ester (7). *N*-Boc protection of **1** (41 mg, 0.10 mmol) following method C yielded **7** (44 mg, 86%) as a colorless oil: R_f (cyclohexane/EtOAc 70 : 30) = 0.60; $[\alpha]_D^{21}$ −58.1 (*c* 0.52 in CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.37–7.07 (10H, m, Ph*H*), 6.02–5.83 (0.43H, m, NC*H*CH$_3$), 5.70–5.53 (0.55H, m, NC*H*CH$_3$), 5.37–5.21 (0.37H, m, NC*H*CH$_3$), 5.01–4.67 (0.65H, m, NC*H*CH$_3$), 4.30–3.10 (4H, m, NC*H*$_2$C═O and NC*H*$_2$CH$_2$C═O), 2.44–1.76 (2H, m, NCH$_2$C*H*$_2$C═O), 1.60–1.46 and 1.40–1.32 (15H and 9H, 2×m, 2×NCHC*H*$_3$, Boc and ^{t}Bu); ^{13}C NMR (100 MHz, CDCl$_3$): δ 171.1, 169.9, 168.2 (2C, 2×*C*═*O*), 155.7 (C, Boc), 139.6 (2C, Ph), 128.7, 128.5, 128.3, 127.6, 127.5, 127.1, 126.9, 126.5 (10CH, Ph), 80.4, 80.0 (2C, Boc and ^{t}Bu), 54.9, 54.1, 53.1, 53.0, 52.9, 51.7, 51.6, 51.4 (2CH, 2×N*C*HCH$_3$), 45.3, 45.1, 44.8 (CH$_2$, N*C*H$_2$C═O), 39.2, 38.4 (CH$_2$, N*C*H$_2$CH$_2$C═O), 36.3, 34.2 (CH$_2$, NCH$_2$*C*H$_2$C═O), 28.4, 28.0, 27.9 (6CH$_3$, Boc and ^{t}Bu), 18.0, 16.9, 16.5 (2CH$_3$, 2×NCH*C*H$_3$); ν_{max}/cm^{-1} 2976, 1726 (C═O, ester), 1695 (C═O, Boc), 1667 (C═O, amide), 1497, 1472, 1451, 1418, 1393, 1368, 1325, 1277, 1254, 1213, 1163, 1072, 1042, 866, 847, 783, 764, 748, 700; HRMS (TOF MS ES$^+$) calcd for $C_{30}H_{43}N_2O_5$ [M + H]$^+$ *m*/*z* 511.3166, found 511.3172. HPLC (Water (0.1% TFA)/MeCN 20 : 80, flow = 0.80): t_r = 16.18 min, purity = 97.9%.

α,β-Peptoid 8. *N*-Boc protection of **2** (112 mg, 0.15 mmol) following method C yielded **8** (106 mg, 83%) as a colorless solid: R_f (cyclohexane/EtOAc 60 : 40) = 0.28; $[\alpha]_D^{21}$ −86.9 (*c* 0.62 in CHCl$_3$); mp 57–59 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.41–6.90 (20H, m, Ph*H*), 6.07–5.82 (1.34H, m, NC*H*CH$_3$), 5.78–5.52 (0.66H, m, NC*H*CH$_3$), 5.40–5.13 (0.66H, m, NC*H*CH$_3$), 5.00–4.55 (1.34H, m, NC*H*CH$_3$), 4.41–2.99 (8H, m, 2×NC*H*$_2$C═O and 2×NC*H*$_2$CH$_2$C═O), 2.78–1.82 (4H, m, 2×NCH$_2$C*H*$_2$C═O), 1.61–1.29 (30H, m, 4×NCHC*H*$_3$, Boc and ^{t}Bu); ^{13}C NMR (100 MHz, CDCl$_3$): δ 172.3, 172.3, 171.6, 171.4, 171.2, 171.1, 171.0, 170.8, 170.7, 170.6, 170.4, 170.4, 170.1, 170.0, 169.6, 169.2, 168.6, 168.4, 168.0, 167.9, 167.3, 167.2, 167.0 (4C, 4×*C*═*O*), 155.7, 155.6, 155.5 (C, Boc), 141.4, 141.3, 140.9, 140.8, 140.7, 140.6, 140.3, 139.9, 139.7, 139.4, 139.2, 139.0 (4C, Ph), 128.9, 128.8, 128.6, 128.4, 128.2, 128.0, 127.6, 127.5, 127.5, 127.3, 127.1, 127.1, 126.9, 126.8, 126.7, 126.4, 126.2 (20CH, Ph), 80.3, 79.9, 79.8 (2C, Boc and ^{t}Bu), 55.4, 55.1, 54.7, 54.5, 54.2, 54.1, 54.0, 53.9, 53.2, 52.8, 52.8, 51.9, 51.7, 51.5, 51.3, 51.2, 50.8 (4CH, 4×N*C*HCH$_3$), 45.6, 45.5, 45.2, 45.0, 44.9, 44.6, 44.1, 44.0 (2CH$_2$, 2×N*C*H$_2$C═O), 40.6, 40.1, 39.6, 39.5, 39.3, 39.1, 38.5, 38.3 (2CH$_2$, 2×N*C*H$_2$CH$_2$C═O), 36.2, 36.2, 35.8, 35.6, 34.2, 34.1, 33.9, 33.6, 33.3, 33.3 (2CH$_2$, 2×NCH$_2$*C*H$_2$C═O), 28.3, 28.0, 27.9 (6CH$_3$, Boc and ^{t}Bu), 18.6, 18.5, 18.4, 18.3, 18.1, 17.9, 17.8, 17.2, 17.1, 16.4, 16.2, 16.0, 15.9, 15.8 (4CH$_3$, 4×NCH*C*H$_3$); ν_{max}/cm^{-1} 2976, 1724 (C═O, ester), 1692 (C═O, Boc), 1659 (C═O, amide), 1497, 1451, 1418, 1393, 1368, 1319, 1287, 1277, 1254, 1209, 1165, 1072, 1042, 1028, 993, 864, 847, 783, 752; HRMS (TOF MS ES$^+$) calcd for $C_{51}H_{67}N_4O_7$ [M + H]$^+$ *m*/*z* 847.5010, found 847.5024. HPLC (Water (0.1% TFA)/MeCN 20 : 80, flow = 0.80): t_r = 29.42 min, purity = 98.1%.

α,β-Peptoid 9. *N*-Boc protection of **3** (108 mg, 0.10 mmol) following method C yielded **9** (110 mg, 93%) as a colorless solid: R_f (EtOAc) = 0.82; $[\alpha]_D^{21}$ −90.3 (*c* 0.65 in CHCl$_3$); mp 71–74 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.45–6.88 (30H, m, Ph*H*), 6.10–5.52 (2.88H, m, NC*H*CH$_3$), 5.35–4.50 (3.12H, m, NC*H*CH$_3$), 4.45–2.95 (12H, m, 3×NC*H*$_2$C═O and 3×NC*H*$_2$CH$_2$C═O), 2.77–1.85 (6H, m, 3×NCH$_2$C*H*$_2$C═O), 1.71–1.21 (36H, m, 6×NCHC*H*$_3$, Boc and ^{t}Bu); ^{13}C NMR (100 MHz, CDCl$_3$): δ 172.4, 171.5, 171.3, 171.2, 171.1, 170.7, 170.7, 170.3, 170.0, 169.6, 168.9, 168.9, 168.5, 168.4, 168.1, 167.9, 167.7, 167.3, 167.1, 167.0 (6C, 6×*C*═*O*), 155.7, 155.6, 155.5 (C, Boc), 141.4, 141.3, 141.2, 140.8, 140.6, 140.3, 140.1, 139.8, 139.4, 139.2, 138.9 (6C, Ph), 128.8, 128.8, 128.6, 128.4, 128.2, 128.2, 127.6, 127.5, 127.4, 127.0, 126.9, 126.7, 126.7, 126.5, 126.4, 126.3 (30CH, Ph), 79.9, 79.7, 79.6 (2C, Boc and ^{t}Bu), 55.7, 55.5, 55.3, 55.0, 54.5, 54.5, 54.2, 53.3, 53.2 (3.12CH, N*C*HCH$_3$), 51.8, 51.6, 51.5, 51.4, 51.2, 51.1, 50.9, 50.8, 50.7 (2.88CH, N*C*HCH$_3$), 45.5, 44.9, 44.8, 44.7, 44.5, 44.2, 44.0, 43.9 (3CH$_2$, 3×N*C*H$_2$C═O), 40.7, 40.6, 40.3, 40.1, 39.4, 39.2, 39.1, 39.0, 38.5, 38.3 (3CH$_2$, 3×N*C*H$_2$CH$_2$C═O), 36.2, 35.6, 34.2, 34.0, 33.5, 33.4, 33.3, 33.2 (3CH$_2$, 3×NCH$_2$*C*H$_2$C═O), 28.3, 27.9, 27.9, 27.3 (6CH$_3$, Boc and ^{t}Bu), 18.8, 18.7, 18.6, 18.4, 18.3, 18.2, 18.1, 18.0, 17.9, 17.7, 17.2, 17.1, 16.4, 16.3, 16.2, 16.0, 15.9, 15.8 (6CH$_3$, 6×NCH*C*H$_3$); ν_{max}/cm^{-1} 2978, 1722 (C═O, ester), 1690 (C═O, Boc), 1657 (C═O, amide), 1649 (C═O, amide), 1497, 1449, 1418, 1368, 1281, 1256, 1206, 1165, 1119, 1072, 1028, 993, 914, 845, 783, 752, 700; HRMS (TOF MS ES$^+$) calcd for $C_{72}H_{91}N_6O_9$ [M + H]$^+$ *m*/*z* 1183.6848, found 1183.6898. HPLC (Water (0.1% TFA)/MeCN 10 : 90, flow = 0.80): t_r = 17.82 min, purity = 94.8%.

3-[{2-[*tert*-Butoxycarbonyl-((*S*)-1-phenyl-ethyl)-amino]-acetyl}-((*S*)-1-phenyl-ethyl)-amino]-propionamide (10). *N*-Boc protection of **4** (88 mg, 0.249 mmol) following method C yielded **10** (111 mg, 98%) as a colorless solid: R_f (CH$_2$Cl$_2$/MeOH 90 : 10) = 0.57; $[\alpha]_D^{23}$ −73.0 (*c* 0.64 in CHCl$_3$); mp 44–46 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.36–7.04 (10H, m, Ph*H*), 6.60–6.48 (0.62H, m, N*H*$_2$), 6.01–5.06 (2.51H, m, 0.69×N*H*$_2$ and 1.13×NC*H*CH$_3$), 5.00–4.73 (0.87H, m, NC*H*CH$_3$), 4.22–3.16 (4H, m, NC*H*$_2$C═O and NC*H*$_2$CH$_2$C═O), 2.62–1.90 (2H, m, NCH$_2$C*H*$_2$C═O), 1.62–1.36 (15H, m, 2×NCHC*H*$_3$ and Boc); ^{13}C NMR (100 MHz, CDCl$_3$): δ 173.9, 173.7, 169.1, 168.7 (2C, 2×*C*═*O*), 155.8, 155.6 (C, Boc), 141.6, 141.4, 141.4, 141.3, 139.3

(2C, Ph), 128.7, 128.5, 128.3, 127.8, 127.5, 127.2, 126.8, 126.7, 126.6 (10CH, Ph), 80.5, 80.3, 80.1, 80.0, 79.9, 79.8 (2C, Boc), 55.1, 55.0, 54.4, 54.2, 54.0, 53.2, 52.9, 52.8, 52.7, 51.6, 51.5, 51.4 (2CH, 2×N*C*HCH$_3$), 45.7, 45.5, 45.4, 45.3, 45.0, 44.9, 44.8 (CH$_2$, N*C*H$_2$C═O), 40.1, 38.8 (CH$_2$, N*C*H$_2$CH$_2$C═O), 36.1, 35.9, 35.9, 35.8, 35.7, 35.6, 35.5 (CH$_2$, NCH$_2$*C*H$_2$C═O), 28.4 (3CH$_3$, Boc), 18.1, 17.8, 16.3 (2CH$_3$, 2×NCH*C*H$_3$); ν_{max}/cm^{-1} 2979, 1700 (C═O, Boc), 1665 (C═O, amide), 1654 (C═O, amide), 1496, 1449, 1399, 1365, 1331, 1276, 1254, 1215, 1166, 1136, 1071, 1043, 1028, 997, 953, 918, 864, 811, 787, 762, 748; HRMS (TOF MS ES$^+$) calcd for $C_{26}H_{36}N_3O_4$ [M + H]$^+$ *m*/*z* 454.2706, found 454.2726. HPLC (Water (0.1% TFA)/MeOH 20 : 80, flow = 0.60): t_r = 11.12 min, purity = 99.2%.

α,β-Peptoid 11. *N*-Boc protection of **5** (106 mg, 0.154 mmol) following method C yielded **11** (118 mg, 97%) as a colorless solid: R_f (CH$_2$Cl$_2$/MeOH 95 : 5) = 0.42; $[\alpha]_D^{23}$ −105.8 (*c* 0.62 in CHCl$_3$); mp 56–58 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.38–6.87 (20H, m, Ph*H*), 6.64–6.08 (0.22H, m, N*H*$_2$), 6.08–5.70 (1.49H, m, NC*H*CH$_3$), 5.70–5.10 (2.75H, m, 0.89×N*H*$_2$ and 0.97×NC*H*CH$_3$), 5.00–4.58 (1.54H, m, NC*H*CH$_3$), 4.48–3.02 (8H, m, 2×NC*H*$_2$C═O and 2×NC*H*$_2$CH$_2$C═O), 2.86–2.00 (4H, m, 2×NCH$_2$C*H*$_2$C═O), 1.70–1.23 (21H, m, 4×NCHC*H*$_3$ and Boc); ^{13}C NMR (100 MHz, CDCl$_3$): δ 174.3, 174.0, 172.2, 171.8, 171.5, 171.4, 169.2, 168.9, 168.7, 168.6, 168.0, 167.8, 167.6 (4C, 4×*C*═*O*), 155.9, 155.7, 155.5 (C, Boc), 141.3, 141.1, 141.0, 140.7, 140.5, 139.6, 139.5, 139.2 (4C, Ph), 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.8, 127.7, 127.5, 127.4, 127.3, 127.3, 127.1, 127.0, 126.8, 126.6, 126.4 (20CH, Ph), 80.6, 80.1, 80.0, 79.8 (C, Boc), 55.2, 55.0, 54.9, 54.6, 54.5, 54.4, 54.3, 52.0, 51.5, 51.4, 51.0, 50.9 (4CH, 4×N*C*HCH$_3$), 45.3, 45.2, 45.1, 45.0, 44.5, 44.2, 44.0 (2CH$_2$, 2×N*C*H$_2$C═O), 41.1, 40.9, 40.1, 40.0, 39.0, 38.8 (2CH$_2$, 2×N*C*H$_2$CH$_2$C═O), 36.3, 35.9, 35.4, 35.3, 35.0, 33.6, 33.4 (2CH$_2$, 2×NCH$_2$*C*H$_2$C═O), 28.4, 28.3 (3CH$_3$, Boc), 18.3, 17.9, 17.7, 16.7, 16.2, 16.0 (4CH$_3$, 4×NCH*C*H$_3$); ν_{max}/cm^{-1} 2978, 1683, 1653 (C═O, amide), 1648 (C═O, amide), 1496, 1449, 1412, 1399, 1366, 1334, 1284, 1276, 1254, 1205, 1166, 1128, 1072, 1028, 993, 918, 858, 787, 758, 474; HRMS (TOF MS ES$^+$) calcd for $C_{47}H_{60}N_5O_6$ [M + H]$^+$ *m*/*z* 790.4538, found 790.4520. HPLC (Water (0.1% TFA)/MeOH 20 : 80, flow = 0.60): t_r = 26.56 min, purity = 97.9%.

α,β-Peptoid 12. *N*-Boc protection of **6** (103 mg, 0.100 mmol) following method C yielded **12** (108 mg, 96%) as a colorless solid: R_f (CH$_2$Cl$_2$/MeOH 95 : 5) = 0.26; $[\alpha]_D^{22}$ −100.0 (*c* 0.65 in CHCl$_3$); mp 66–68 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.60–6.82 (30H, m, Ph*H*), 6.73–6.12 (0.22H, m, N*H*$_2$), 6.07–4.54 (7.78H, m, 0.89×N*H*$_2$ and 6×NC*H*CH$_3$), 4.47–3.06 (12H, m, 3×NC*H*$_2$C═O and 3×NC*H*$_2$CH$_2$C═O), 3.00–1.85 (6H, m, 3×NCH$_2$C*H*$_2$C═O), 1.70–1.20 (27H, m, 6×NCHC*H*$_3$ and Boc); ^{13}C NMR (100 MHz, CDCl$_3$): δ 172.7, 172.6, 172.3, 171.9, 171.8, 171.7, 171.6, 171.4, 171.3, 168.9, 168.6, 168.4, 168.1, 167.9, 167.7, 167.5 (6C, 6×*C*═*O*), 155.6 (C, Boc), 141.4, 141.0, 140.8, 140.7, 140.5, 140.3, 140.2, 139.9, 139.5, 139.4, 139.1, 139.0 (6C, Ph), 128.7, 128.6, 128.5, 128.4, 128.4, 128.2, 127.9, 127.7, 127.6, 127.5, 127.4, 127.3, 127.1, 127.1, 127.0, 126.8, 126.7, 126.6, 126.5, 126.4 (30CH, Ph), 80.1, 80.0, 79.9, 79.9, 79.8 (C, Boc), 55.6, 55.5, 55.4, 55.3, 55.1, 55.1, 54.9, 54.8, 54.7, 54.5, 54.4, 54.4, 54.2, 54.0, 53.9, 53.8, 53.8, 53.7 (3.27CH, N*C*HCH$_3$), 53.3, 53.3, 53.2, 53.1, 52.4, 52.3, 52.1, 52.0, 51.7, 51.5, 51.5, 51.1, 51.0, 50.8, 50.6, 50.5 (2.73CH, N*C*HCH$_3$), 45.5, 45.3, 45.2, 45.2, 45.1, 45.0, 44.9, 44.8, 44.7, 44.6, 44.5, 44.4, 44.3, 44.1, 44.0 (3CH$_2$, 3×N*C*H$_2$C═O), 40.9, 40.9, 40.7, 40.6, 40.2, 40.0, 39.9, 39.4, 39.2, 39.0, 38.9, 38.8, 38.7, 38.4 (3CH$_2$, 3×N*C*H$_2$CH$_2$C═O), 36.3, 36.1, 35.9, 35.8, 35.7, 35.6, 35.4, 35.2, 35.0, 34.4, 34.2, 34.0, 33.8, 33.7, 33.6, 33.6, 33.5, 33.3, 32.4, 32.3, 32.1, 31.9, 31.8, 29.2 (3CH$_2$, 3×NCH$_2$*C*H$_2$C═O), 28.3 (3CH$_3$, Boc), 18.8, 18.7, 18.5, 18.3, 18.1, 17.9, 17.8, 17.7, 17.4, 17.0, 16.9, 16.8, 16.6, 16.3, 16.1 (6CH$_3$, 6×NCH*C*H$_3$); ν_{max}/cm^{-1} 2976, 1683, 1655 (C═O, amide), 1648 (C═O, amide), 1496, 1449, 1423, 1366, 1331, 1293, 1257, 1207, 1165, 1072, 1063, 1056, 1045, 1028, 996, 918, 786, 757, 750; HRMS (TOF MS ES$^+$) calcd for $C_{68}H_{83}N_7O_8Na_2$ [M + 2Na]$^{2+}$ *m*/*z* 585.8049, found 585.8057. HPLC (Water (0.1% TFA)/MeOH 10 : 90, flow = 0.75): t_r = 10.25 min, purity = 97.5%.

{[(2-Carboxy-ethyl)-((*S*)-1-phenyl-ethyl)-carbamoyl]-methyl}-((*S*)-1-phenyl-ethyl)-ammonium trifluoro-acetate (13·TFA). Reaction of **1** (41 mg, 0.100 mmol) following method D yielded **13**·TFA (47 mg, 100%) as a colorless solid: $[\alpha]_D^{22}$ −91.3 (*c* 0.61 in CHCl$_3$); mp 27–29 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.58–7.06 (10H, m, Ph*H*), 5.77 (0.04H, q, *J* = 6.9 Hz, (c)-NC*H*CH$_3$), 5.58 (0.37H, q, *J* = 6.9 Hz, (c)-NC*H*CH$_3$), 4.85–4.80 (0.07H, m, (t)-NC*H*CH$_3$), 4.67 (0.52H, q, *J* = 6.7 Hz, (t)-NC*H*CH$_3$), 4.58–4.44 (1H, m, HNC*H*CH$_3$), 4.11–3.78 (2H, m, HNC*H*$_2$C═O), 3.51–3.10 (2H, m, NC*H*$_2$CH$_2$C═O), 2.34–2.98 (2H, m, NCH$_2$C*H*$_2$C═O), 1.81–1.73 (3H, m, HNCHC*H*$_3$), 1.64–1.45 (3H, m, NCHC*H*$_3$); ^{13}C NMR (100 MHz, CDCl$_3$): δ 174.9, 173.5, 165.5, 165.1 (2C, 2×*C*═*O*), 161.6 (C, q, *J* = 37.0 Hz, CF$_3$*C*═*O*), 138.7, 138.1, 135.1, 135.0 (2C, Ph), 129.7, 129.7, 129.4, 129.3, 128.9, 128.7, 128.3, 128.0, 128.0, 127.2, 126.6 (10CH, Ph), 116.0 (C, q, *J* = 290.9 Hz, *C*F$_3$C═O), 59.2, 59.1 (CH, HN*C*HCH$_3$), 55.1 (0.59CH, N*C*HCH$_3$), 53.1 (0.41CH, N*C*HCH$_3$), 46.0 (CH$_2$, HN*C*H$_2$C═O), 39.4, 39.0 (CH$_2$, N*C*H$_2$CH$_2$C═O), 33.8, 33.4 (CH$_2$, NCH$_2$*C*H$_2$C═O), 19.6, 19.3, 17.5, 16.3 (2CH$_3$, 2×NCH*C*H$_3$); ν_{max}/cm^{-1} 2983, 1721 (C═O, acid), 1654 (C═O, amide), 1498, 1457, 1426, 1387, 1311, 1193, 1137, 1071, 1033, 916, 835, 798, 765, 720; HRMS (TOF MS ES$^+$) calcd for $C_{21}H_{27}N_2O_3$ [M–TFA + H]$^+$ *m*/*z* 355.2016, found 355.2017. HPLC (Water (0.1% TFA)/MeOH 30 : 70, flow = 0.50): t_r = 7.23 min, purity = 98.3%.

α,β-Peptoid (14·TFA). Reaction of **2** (37 mg, 0.050 mmol) following method D yielded **14**·TFA (40 mg, 100%) as a pale yellowish solid: $[\alpha]_D^{21}$ −101.7 (*c* 0.53 in CHCl$_3$); mp 57–60 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.52–6.85 (20H, m, Ph*H*), 6.04–5.54 (1.49H, m, NC*H*CH$_3$), 5.08–4.60 (1.51H, m, NC*H*CH$_3$), 4.56–2.90 (9H, m, HNC*H*CH$_3$, 2×NC*H*$_2$C═O and 2×NCH$_2$C*H*$_2$C═O), 2.64–2.10 (4H, m, 2×NCH$_2$C*H*$_2$C═O), 1.81–1.20 (12H, m, 4×NCHC*H*$_3$); ^{13}C NMR (100 MHz, CDCl$_3$): δ 174.7, 174.6, 173.5, 173.2, 172.6, 172.2, 171.8, 171.5, 170.9, 168.5, 168.3, 168.2, 167.9, 165.5, 165.4, 164.8 (4C, 4×*C*═*O*), 161.3 (C, q, *J* = 37.4 Hz, CF$_3$*C*═*O*), 140.5, 140.4, 140.1, 140.0, 139.6, 139.4, 139.3, 139.1, 138.7, 135.2, 135.0, 135.0, 134.9, 134.8 (4C, Ph), 130.0, 129.8, 129.8, 129.7, 129.6, 129.4, 129.4, 129.0, 128.9, 128.8, 128.7, 128.6, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.4, 127.1, 126.7, 126.6, 126.5, 126.4, 126.2 (20CH, Ph), 115.9 (C, q, *J* = 289.2 Hz, *C*F$_3$C═O), 59.2, 59.1, 59.0 (CH, HN*C*HCH$_3$), 56.0, 55.5, 55.4, 55.3, 55.2, 55.1, 55.0, 54.5 (1.51CH, N*C*HCH$_3$), 53.5, 53.2, 53.0, 52.9, 51.5, 51.4, 51.3 (1.49CH, N*C*HCH$_3$), 46.1, 46.0, 45.9, 45.8, 45.7, 45.6, 45.5, 45.3,

45.2, 45.1, 45.0, 44.7, 44.5, 44.4, 44.2, 44.0 (CH_2, HN*C*H_2C═O), 41.3, 41.1, 40.7, 40.6, 40.4, 40.2, 40.1, 40.0, 39.8, 39.4, 39.3, 39.3, 39.1, 39.0, 38.9, 38.7 (2CH_2, 2×N*C*H_2CH_2C═O), 34.4, 34.0, 33.9, 33.8, 33.6, 32.6, 32.3, 31.8 (2CH_2, 2×NCH_2*C*H_2C═O), 19.9, 19.6, 19.5, 19.4, 19.3, 18.5, 18.4, 18.1, 18.1, 17.8, 17.7, 16.9, 16.5, 16.3, 16.1, 16.0 (4CH_3, 4×NCH*C*H_3); ν_{max}/cm^{-1} 1728 (C═O, acid), 1654 (C═O, amide), 1647 (C═O, amide), 1497, 1453, 1420, 1383, 1299, 1200, 1183, 1176, 1136, 1073, 1042, 1029, 983, 916, 833, 798, 749; HRMS (TOF MS ES$^+$) calcd for $C_{42}H_{51}N_4O_5$ [M–TFA + H]$^+$ *m*/*z* 691.3859, found 691.3871. HPLC (Water (0.1% TFA)/MeOH 20 : 80, flow = 0.60): t_r = 7.06 min, purity = 96.2%.

α,β-Peptoid (15·TFA). Reaction of **3** (54 mg, 0.050 mmol) following method D yielded **15·TFA** (57 mg, 100%) as a colorless solid: $[\alpha]_D^{21}$ –102.4 (*c* 0.83 in $CHCl_3$); mp 63–66 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52–6.75 (30H, m, Ph*H*), 6.05–5.55 (2.23H, m, NC*H*CH_3), 5.16–4.54 (2.77H, m, NC*H*CH_3), 4.53–3.04 (13H, m, HNC*H*CH_3, 3×NCH_2C═O and 3×NCH_2CH_2C═O), 2.83–1.86 (6H, m, 3×NCH_2CH_2C═O), 1.84–1.20 (18H, m, m, 6×NCHCH_3); Due to the limited amount of product available satisfactory ^{13}C NMR spectra could not be obtained; ν_{max}/cm^{-1} 1728 (C═O, acid), 1654 (C═O, amide), 1651 (C═O, amide), 1646 (C═O, amide), 1497, 1449, 1420, 1380, 1295, 1171, 1076, 1043, 1029, 983, 913, 843, 814, 793, 762; HRMS (TOF MS ES$^+$) calcd for $C_{63}H_{75}N_6O_7Na$ [M–TFA + Na + H]$^{2+}$ *m*/*z* 525.2797, found 525.2808. HPLC (Water (0.1% TFA)/MeOH 20 : 80, flow = 0.60): t_r = 13.55 min, purity = 93.6%.

α,β-Peptoid 16. To a solution of **2** (1.12 g, 1.50 mmol) in CH_2Cl_2 (15 mL) at rt under Ar was added TFA (15 mL) and the resulting mixture was stirred for 1.5 h at rt. The solvents were evaporated under reduced pressure and the residue was dried *in vacuo*. The residue was dissolved in dioxane (8.25 mL)) and 0.5 M aq. NaOH (8.25 mL) at 0 °C. 20% aq. NaOH was added dropwise until the mixture turned basic. Boc_2O (360 mg, 1.65 mmol) was added and stirring was continued overnight while allowing to warm slowly to rt. The dioxane was then evaporated under reduced pressure and 1 M HCl (35 mL) and CH_2Cl_2 (80 mL) were added. The organic layer was isolated and the aqueous layer was extracted with CH_2Cl_2 (2 × 35 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash chromatography of the residue yielded **16** (901 mg, 76%) as a colorless solid: R_f (CH_2Cl_2/MeOH 95 : 5) = 0.41; $[\alpha]_D^{21}$ –97.6 (*c* 0.68 in $CHCl_3$); mp 71–74 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–6.85 (20H, m, Ph*H*), 6.07–5.77 (1.44H, m, NC*H*CH_3), 5.71–5.54 (0.59H, m, NC*H*CH_3), 5.37–5.18 (0.65H, m, NC*H*CH_3), 4.95–4.47 (1.58H, m, 1.32×NC*H*CH_3 and 0.13×NCH_2C═O), 4.37–3.12 (7.74H, m, 1.87×NCH_2C═O and 2×NCH_2CH_2C═O), 2.90–1.95 (4H, m, 2×NCH_2CH_2C═O), 1.66–1.26 (21H, m, 4×NCHCH_3 and Boc); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.6, 174.5, 173.7, 173.3, 172.5, 172.4, 171.7, 169.0, 168.9, 168.5, 168.1, 167.9 (4C, 4×*C*═*O*), 155.8, 155.6 (C, Boc), 141.9, 141.4, 141.1, 140.5, 140.1, 139.7, 139.6, 139.3, 139.2, 139.0, 138.8 (4C, Ph), 128.9, 128.7, 128.7, 128.4, 128.4, 128.3, 127.7, 127.6, 127.4, 127.3, 127.1, 127.0, 126.8, 126.7, 126.5 (20CH, Ph), 81.2, 80.1 (C, Boc), 55.3, 55.2, 55.0, 54.8, 54.8, 54.7, 54.6, 54.4, 54.1, 53.2, 53.1, 52.5, 51.7, 51.5, 51.4, 51.3, 51.0, 50.8 (4CH, 4×N*C*HCH_3), 45.6, 45.5, 45.3, 45.2, 45.0, 44.6, 44.2, 43.9, 43.7 (2CH_2, 2×N*C*H_2C═O), 40.8, 40.0, 39.7, 39.0, 38.8, 38.4 (2CH_2, 2×N*C*H_2CH_2C═O), 34.8, 34.6, 34.4, 33.8, 33.5, 33.2 (2CH_2, 2×NCH_2*C*H_2C═O), 28.3 (3CH_3, Boc), 18.7, 18.5, 18.3, 18.3, 18.0, 17.9, 17.7, 17.6, 17.4, 17.2, 17.1, 16.9, 16.6, 16.4, 16.4, 16.2, 16.0 (4CH_3, 4×NCH*C*H_3); ν_{max}/cm^{-1} 2978, 1730 (C═O, acid), 1692 (C═O, Boc), 1654 (C═O, amide), 1496, 1451, 1399, 1367, 1332, 1284, 1254, 1206, 1164, 1071, 1044, 1028, 994, 916, 862, 793, 751, 700; HRMS (TOF MS ES$^+$) calcd for $C_{47}H_{59}N_4O_7$ [M + H]$^+$ *m*/*z* 791.4384, found 791.4392. HPLC (Water (0.1% TFA)/MeCN 30 : 70, flow = 0.80): t_r = 17.46 min, purity = 99.9%

α,β-Peptoid 17. Coupling of **16** (317 mg, 0.401 mmol) with **2** (299 mg, 0.400 mmol) following method E and performing the flash column chromatography in EtOAc to EtOAc/MeOH 97 : 3 yielded **17** (536 mg, 88%) as a colorless solid: R_f (EtOAc/MeOH 97 : 3) = 0.86. The following analytical data were obtained using a sample purified by prep-HPLC: $[\alpha]_D^{21}$ –94.5 (*c* 0.48 in $CHCl_3$); mp 75–78 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–6.88 (40H, m, Ph*H*), 6.10–5.52 (3.75H, m, NC*H*CH_3), 5.34–4.52 (4.25H, m, NC*H*CH_3), 4.44–2.98 (16H, m, 4×NCH_2C═O and 4×NCH_2CH_2C═O), 2.74–1.79 (8H, m, 4×NCH_2CH_2C═O), 1.71–1.14 (42H, m, 8×NCHCH_3, Boc and ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 172.1, 172.0, 171.8, 171.5, 171.5, 171.2, 171.0, 170.9, 170.8, 170.5, 170.2, 169.9, 169.5, 169.4, 169.3, 168.8, 168.8, 168.7, 168.6, 168.4, 168.3, 168.2, 168.1, 168.0, 167.9, 167.8, 167.6, 167.3, 167.2, 167.1, 166.9, 166.8 (8C, 8×*C*═*O*), 155.5, 155.4 (C, Boc), 141.2, 141.1, 140.9, 140.7, 140.6, 140.4, 140.3, 140.2, 140.0, 139.9, 139.8, 139.6, 139.6, 139.5, 139.4, 139.3, 139.2, 139.0 (8C, Ph), 128.5, 128.3, 128.1, 127.8, 127.4, 127.3, 127.3, 127.2, 127.0, 126.9, 126.6, 126.3, 126.2 (40CH, Ph), 79.7, 79.6 (2C, Boc and ^{t}Bu), 55.6, 55.5, 55.4, 55.3, 55.2, 54.9, 54.8, 54.5, 54.3, 54.2, 54.2, 54.1, 53.3, 53.2, 53.0 (4.25CH, N*C*HCH_3), 51.6, 51.5, 51.3, 51.2, 51.2, 51.1, 51.0, 50.9, 50.7, 50.6 (3.75CH, N*C*HCH_3), 45.4, 44.8, 44.7, 44.5, 44.4, 44.3, 44.2, 44.2, 44.1, 44.0, 43.8 (4CH_2, 4×N*C*H_2C═O), 40.6, 40.4, 40.1, 40.1, 39.9, 39.7, 39.5, 39.3, 39.1, 39.0, 38.9, 38.8, 38.5, 38.3, 38.1, 38.1 (4CH_2, 4×N*C*H_2CH_2C═O), 36.0, 35.9, 35.8, 35.5, 34.0, 33.8, 33.7, 33.4, 33.3, 33.2, 33.0, 32.9, 32.4, 32.2, 31.9 (4CH_2, 4×NCH_2*C*H_2C═O), 28.2, 27.8, 27.8 (6CH_3, Boc and ^{t}Bu), 19.1, 19.1, 19.0, 18.9, 18.7, 18.6, 18.5, 18.4, 18.2, 18.1, 18.0, 17.9, 17.7, 17.6, 17.1, 17.0, 16.7, 16.6, 16.3, 16.2, 16.1, 15.9 (8CH_3, 8×NCH*C*H_3); ν_{max}/cm^{-1} 1724 (C═O, ester), 1718 (C═O, ester), 1691 (C═O, Boc), 1654 (C═O, amide), 1646 (C═O, amide), 1496, 1450, 1420, 1413, 1407, 1367, 1332, 1285, 1253, 1205, 1201, 1164, 1159, 1075, 1045, 1029, 993, 916, 845, 788, 752; HRMS (TOF MS ES$^+$) calcd for $C_{93}H_{114}N_8O_{11}$ [M + 2H]$^{2+}$ *m*/*z* 760.4377, found 760.4440. Original sample: HPLC (Water (0.1% TFA)/MeCN 10 : 90, flow = 0.80): t_r = 28.61 min; HPLC (Water (0.1% TFA)/MeOH 5 : 95, flow = 0.80): t_r = 12.65 min, purity = 81.8%. Sample purified by prep-HPLC: purity = 99.9%.

α,β-Peptoid 18. Coupling of **16** (198 mg, 0.250 mmol) with **3** (271 mg, 0.250 mmol) following method E and performing the flash column chromatography in EtOAc to EtOAc/MeOH 97 : 3 yielded **18** (389 mg, 84%) as a colorless solid: R_f (EtOAc/MeOH 97 : 3) = 0.89. The following analytical data were obtained using a sample purified by prep-HPLC: $[\alpha]_D^{21}$ –98.5 (*c* 0.46 in $CHCl_3$); mp 80–83 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–6.88 (50H, m, Ph*H*), 6.02–5.52 (4.77H, m, NC*H*CH_3), 5.35–4.50 (5.23H, m, NC*H*CH_3), 4.43–2.95 (20H, m, 5×NCH_2C═O and 5×NCH_2CH_2C═O), 2.76–1.30 (10H, m, 5×NCH_2CH_2C═O), 1.71–1.14 (48H, m, 10×NCHCH_3, Boc and ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4, 172.3, 172.2, 172.1, 172.0, 171.6, 171.5, 171.4, 171.3, 171.1, 171.0, 170.9, 170.7, 170.7, 170.6, 170.5,

170.3, 170.0, 169.5, 168.6, 168.5, 168.2, 168.1, 167.9, 167.8, 167.7, 167.5, 167.4, 167.3, 167.2, 167.1, 167.0, 166.9 (10C, 10×*C*═*O*), 155.7, 155.6, 155.5 (C, Boc), 141.5, 141.3, 141.2, 141.1, 140.8, 140.6, 140.5, 140.5, 140.3, 140.2, 140.0, 139.7, 139.6, 139.4, 139.3, 139.1, 139.0 (10C, Ph), 128.6, 128.4, 127.9, 127.5, 127.5, 127.3, 127.0, 126.7, 126.7, 126.4, 126.3 (50CH, Ph), 79.9, 79.7, 79.6 (2C, Boc and ^{t}Bu), 55.5, 55.3, 55.1, 55.0, 54.9, 54.7, 54.5, 54.4, 54.1, 53.9, 53.3, 53.2 (5.23CH, N*C*HCH$_3$), 51.8, 51.6, 51.4, 51.3, 51.1, 51.0, 50.8, 50.7 (4.77CH, N*C*HCH$_3$), 45.5, 45.2, 44.9, 44.8, 44.6, 44.5, 44.4, 44.2, 44.1, 43.9 (5CH$_2$, 5×N*C*H$_2$C═O), 40.8, 40.6, 40.1, 40.0, 39.9, 39.4, 39.2, 39.1, 39.0, 38.8, 38.5, 38.2 (5CH$_2$, 5×NCH$_2$*C*H$_2$C═O), 36.2, 36.1, 35.6, 34.1, 33.9, 33.4, 33.3, 32.4, 32.3, 32.2 (5CH$_2$, 5×NCH$_2$*C*H$_2$C═O), 28.3, 27.9, 27.9 (6CH$_3$, Boc and ^{t}Bu), 19.2, 19.1, 19.0, 18.9, 18.7, 18.6, 18.4, 18.3, 18.2, 18.1, 17.9, 17.8, 17.7, 17.5, 17.2, 17.1, 16.4, 16.3, 16.1, 16.0 (10CH$_3$, 10×NCH*C*H$_3$); ν_{max}/cm^{-1} 1692 (C═O, Boc), 1653 (C═O, amide), 1647 (C═O, amide), 1496, 1451, 1412, 1367, 1285, 1251, 1204, 1162, 1099, 1073, 1045, 1032, 1029, 953, 912, 842, 809, 788, 746, 734; HRMS (TOF MS ES$^+$) calcd for $C_{114}H_{139}N_{10}O_{13}$ [M + 2H]$^{2+}$ *m*/*z* 928.5295, found 928.5291. Original sample: HPLC (Water (0.1% TFA)/MeCN 10 : 90, flow = 0.80): t_r = 42.16 min; HPLC (Water (0.1% TFA)/MeOH 5 : 95, flow = 0.80): t_r = 17.05 min, purity = 85.6%. Sample purified by prep-HPLC: purity = 99.9%.

α,β-Peptoid 19. Coupling of **16** (158 mg, 0.200 mmol) with **5** (139 mg, 0.201 mmol) following method E yielded **19** (277 mg, 95%) as a colorless solid: R_f (CH_2Cl_2/MeOH 95 : 5) = 0.43; $[\alpha]_D^{22}$ −101.0 (*c* 0.74 in $CHCl_3$); mp 68–71 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46–6.80 (40H, m, Ph*H*), 6.06–4.50 (10H, m, N*H*$_2$ and 8×NC*H*CH$_3$), 4.42–3.00 (16H, m, 4×NC*H*$_2$C═O and 4×NC*H*$_2$CH$_2$C═O), 2.75–1.85 (8H, m, 4×NCH$_2$C*H*$_2$C═O), 1.70–1.18 (33H, m, 8×NCHC*H*$_3$ and Boc); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4, 172.2, 171.7, 171.4, 171.2, 170.7, 168.7, 168.5, 168.1, 167.9, 167.7, 167.4, 167.0 (8C, 8×*C*═*O*), 155.6 (C, Boc), 141.0, 140.9, 140.7, 140.7, 140.5, 140.3, 140.1, 140.0, 139.7, 139.5, 139.4, 139.1, 139.0 (8C, Ph), 128.6, 128.5, 128.4, 128.4, 128.2, 127.6, 127.4, 127.1, 127.0, 126.9, 126.7, 126.6, 126.4 (40CH, Ph), 79.9, 79.8, 79.7 (C, Boc), 55.6, 55.5, 55.4, 55.2, 55.1, 55.0, 54.9, 54.8, 54.7, 54.5, 54.4, 54.3, 54.1, 53.9 (4.32CH, N*C*HCH$_3$), 52.0, 51.9, 51.8, 51.6, 51.5, 51.4, 51.3, 51.2, 51.2, 51.0, 50.8 (3.68CH, N*C*HCH$_3$), 45.6, 45.5, 45.4, 45.3, 45.3, 45.1, 44.9, 44.9, 44.6, 44.5, 44.4, 44.3, 44.2, 44.1, 44.0, 43.8 (4CH$_2$, 4×N*C*H$_2$C═O), 41.2, 41.0, 40.9, 40.7, 40.6, 40.6,40.4, 40.1, 39.9, 39.9, 39.4, 39.2, 39.1, 39.0, 39.0, 38.9, 38.8, 38.7 (4CH$_2$, 4×N*C*H$_2$CH$_2$C═O), 34.0, 33.8, 33.8, 33.6, 33.5, 33.3, 32.2, 32.1, 31.9, 31.8 (4CH$_2$, 4×NCH$_2$*C*H$_2$C═O), 28.3 (3CH$_3$, Boc), 18.3, 18.2, 18.1, 18.0, 17.9, 17.7, 17.3, 17.1, 17.0, 16.9, 16.8, 16.7, 16.5, 16.2, 16.1, 16.0 (8CH$_3$, 8×NCH*C*H$_3$); ν_{max}/cm^{-1} 2977, 1686, 1651 (C═O, amide), 1644 (C═O, amide), 1496, 1450, 1418, 1412, 1404, 1366, 1331, 1290, 1253, 1204, 1166, 1072, 1050, 1044, 1028, 992, 786, 750; HRMS (TOF MS ES$^+$) calcd for $C_{89}H_{107}N_9O_{10}Na_2$ [M + 2Na]$^{2+}$ *m*/*z* 753.8968, found 753.8970. HPLC (Water (0.1% TFA)/MeOH 10 : 90, flow = 0.75): t_r = 14.89 min, purity = 93.1%.

α,β-Peptoid 20. Coupling of **16** (95 mg, 0.120 mmol) with **6** (123 mg, 0.120 mmol) following method E yielded **20** (199 mg, 92%) as a colorless solid: R_f (CH_2Cl_2/MeOH 95 : 5) = 0.25; $[\alpha]_D^{22}$ −104.5 (*c* 0.71 in $CHCl_3$); mp 74–76 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.08–5.48 and 5.38–4.50 (12H, m, N*H*$_2$ and 10×NC*H*CH$_3$), 4.46–2.96 (20H, m, 5×NC*H*$_2$C═O and 5×NC*H*$_2$CH$_2$C═O), 2.78–1.78 (10H, m, 5×NCH$_2$C*H*$_2$C═O), 1.72–1.12 (39H, m, 10×NCHC*H*$_3$ and Boc); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3, 172.1, 172.0, 171.7, 171.4, 171.3, 171.1, 171.0, 170.7, 170.6, 170.4, 170.3, 170.2, 170.0, 169.2, 169.0, 168.9, 168.7, 168.7, 168.5, 168.5, 168.3, 168.2, 168.1, 167.9, 167.9, 167.8, 167.7, 167.4, 167.3, 167.2, 167.0 (10C, 10×*C*═*O*), 155.6, 155.6, 155.5 (C, Boc), 141.3, 141.0, 140.9, 140.9, 140.8, 140.7, 140.6, 140.5, 140.4, 140.4, 140.2, 140.1, 139.9, 139.8, 139.7, 139.6, 139.4, 139.3, 139.1, 139.0 (10C, Ph), 128.6, 128.4, 128.2, 128.2, 127.6, 127.4, 127.3, 126.8, 126.7, 126.6, 126.4 (50CH, Ph), 79.9, 79.8, 79.7, 79.7, 79.6 (C, Boc), 55.5, 55.4, 55.3, 55.1, 55.0, 55.0, 54.9, 54.7, 54.6, 54.6, 54.3, 54.2, 54.0 (5.30CH, N*C*HCH$_3$), 53.5, 53.1, 51.9, 51.8, 51.4, 51.3, 51.1, 51.0, 50.9, 50.8 (4.70CH, N*C*HCH$_3$), 45.5, 45.3, 45.2, 44.9, 44.8, 44.5, 44.4, 44.3, 44.3, 44.1, 43.9, 43.8, 43.7 (5CH$_2$, 5×N*C*H$_2$C═O), 41.1, 41.0, 40.9, 40.8, 40.7, 40.6, 40.5, 40.4, 40.0, 39.3, 39.3, 39.2, 39.0, 38.9, 38.8, 38.7, 38.6 (5CH$_2$, 5×N*C*H$_2$CH$_2$C═O), 34.0, 33.9, 33.8, 33.8, 33.7, 33.5, 33.4, 33.3, 33.2, 33.1, 32.4, 32.2, 32.2, 31.9, 31.8 (5CH$_2$, 5×NCH$_2$*C*H$_2$C═O), 28.3 (3CH$_3$, Boc), 19.1, 19.0, 18.9, 18.8, 18.6, 18.5, 18.4, 18.3, 18.2, 18.1, 18.1, 18.0, 17.9, 17.8, 17.7, 17.4, 17.1, 17.0, 16.9, 16.7, 16.7, 16.5, 16.3, 16.3, 16.2, 16.1 (10CH$_3$, 10×NCH*C*H$_3$); ν_{max}/cm^{-1} 2977, 1685, 1647 (C═O, amide), 1642 (C═O, amide), 1638 (C═O, amide), 1495, 1449, 1421, 1405, 1364, 1288, 1207, 1182, 1167, 1071, 1056, 1045, 1028, 997, 784, 746; HRMS (TOF MS ES$^+$) calcd for $C_{110}H_{131}N_{11}O_{12}Na_2$ [M + 2Na]$^{2+}$ *m*/*z* 921.9887, found 921.9893. HPLC (Water (0.1% TFA)/MeOH 10 : 90, flow = 0.75): t_r = 25.03 min, purity = 93.7%.

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