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Helical secondary structures in 2:1 and 1:2 α/γ-peptide foldamers

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ABSTRACT

Oligomers containing both α- and γ-amino acid residues in a 1:1 alternating pattern have recently been shown by several research groups to adopt helical secondary structures. We have begun to explore the folding behavior of oligomers with different α-residue/γ-residue backbone patterns. Previously we reported that the γ-amino acids bearing a cyclohexyl constraint at the C_β–C_γ bond and a variable side chain at C_α strongly promote a helical conformation containing 12-atom C=O(*i*)···H–N(*i*+3) hydrogen bonds for 1:1 α:γ backbones. Here we report synthesis and crystallographic analysis of 2:1 and 1:2 α/γ-peptides that adopt C=O(*i*)···H–N(*i*+3) hydrogen-bonded helical conformations.

1. Introduction

The ability of biopolymers (proteins and nucleic acids) to adopt a wide variety of specific conformations is essential for many of the complex functions carried out by these macromolecules. The relationship between molecular shape and function has led many researchers to explore unnatural oligomers (foldamers) for the ability to adopt specific conformations,[1,2] which can ultimately provide a basis for activities, such as catalysis, self-assembly, and selective recognition of biopolymers.[3,4] New backbones potentially offer distinct ways to arrange side chains in space, which can widen the range of functions available to foldamers; therefore, efforts to discover new foldamers are underway in many laboratories.

Oligomers constructed from β-amino acid residues ('β-peptides') or from combinations of α- and β-amino acid residues ('α/β-peptides') are among most widely studied foldamers.[1,2,5,6] β-Amino acid residues can be endowed with stronger intrinsic folding propensities than those of α residues by use of cyclic constraints to limit backbone torsional mobility. Analogous benefits should result from the use of constrained γ-amino acid residues in foldamers, but only a few types of ring-containing γ-amino acids are known.[7,8] γ-Peptides containing acyclic subunits, such as γ^4-amino acid residues, $\gamma^{2,4}$-residues, and $\gamma^{2,3,4}$-residues have been shown by Hanessian et al.[7a] and Seebach et al.[7b] to favor a helical conformation defined by 14-atom C=O(*i*)···H–N(*i*+3) hydrogen bonds (designated the '14-helix'). Recently several research groups have explored the folding behavior of short α/γ-peptides containing a 1:1 α/γ backbone pattern.[7f,8a,9] Computational surveys by Hofmann et al. of helical conformations available to the unsubstituted α/γ-peptide backbone have identified a number of possible helical secondary structures.[9c] The helix containing 12-atom-ring C=O(*i*)···H–N(*i*+3) H-bonds, which may be designated the α/γ-peptide '12-helix', is predicted to have *gauche* conformations about the C_α–C_β (ζ) and C_β–C_γ (θ) backbone bonds of each γ-residue. Recent work suggests that oligomers constructed from α- and flexible γ-amino acid subunits can display a variety of discrete folding patterns.[9b,f] In contrast, we found that conformationally restricted γ-residues **I**, bearing a cyclohexyl constraint at the C_β–C_γ bond and a variable side chain at C_α (Fig. 1), strongly promote formation of the α/γ-peptide 12-helix.[9g]

2. Results and discussion

Here we explore foldamers with backbone patterns other than 1:1 alternation of α- and γ-residues; the new oligomers contain either 2:1 or 1:2 α:γ backbone patterns. Fig. 1 shows four new α/γ-peptides (**1**–**4**) for which crystal structures have been obtained. The structure set includes two α/γ-peptides with the 2:1 backbone pattern (**1** and **2**), which contain four and seven residues, respectively, and two α/γ-peptides with the 1:2 backbone pattern (**3** and **4**), containing three and six residues, respectively. Most of the γ-residues are derived from (*R*,*R*,*R*)-γ residue **I**, and the α-residues are derived from D-alanine **III**; however, oligomer **4** contains the (*S*,*S*,*S*)-γ residue **II** and L-alanine. Crystals of α/γ-peptides **1**, **2**, and **4** were grown by slow evaporation of dichloroethane/heptane solutions. Crystals of **3** were grown by slow evaporation of a methanol/dichloromethane solution.

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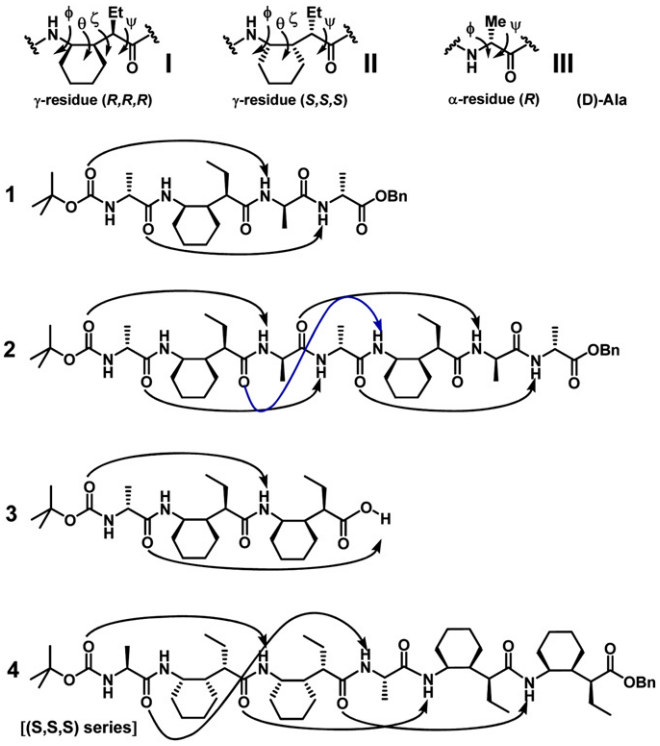

Fig. 1. Structures of α/γ-peptides **1**–**4** (arrows indicate hydrogen bonds in the crystal structures).

2.1. Crystal structures of 2:1 and 1:2 α/γ-peptides

The crystal structures for **1**–**4** are shown in Figs. 2 and 3. Each of the two 2:1 α/γ-peptides (**1** and **2**) displays a fully helical conformation in the solid state, with the maximum number of the C=O(*i*)···H–N(*i*+3) hydrogen bonds (12-atom hydrogen-bonded rings) formed in each case. This internal hydrogen-bonding pattern is comparable to that of the 3_{10}-helix observed for some peptides composed exclusively of α-amino acids. The structure of 1:2 α/γ-peptide trimer **3** reveal a 12-atom hydrogen-bonded ring and a 14-atom hydrogen-bonded ring; in the latter ring the donor is the C-terminal carboxylic acid group. Heptamer **4**, containing α- and γ-residues with *S* configurations, adopts a right-handed helix in the crystalline state as expected given that the other three α/γ-peptides are built from residues with *R* configurations and form left-handed helices. In **4**, all four possible C=O(*i*)···H–N(*i*+3) hydrogen bonds are formed. Three of these hydrogen bonds form 12-atom rings, while the fourth hydrogen bond, across the central γ–γ segment, forms a 14-atom ring. The resulting data set allows us to establish archetypal structural parameters for the *i*,*i*+3 hydrogen-bonded helical secondary structures formed by 2:1 and 1:2 α/γ-peptides and to compare these parameters with those of the α-peptide helices (3_{10}), and the 1:1 α/γ-peptide helix.

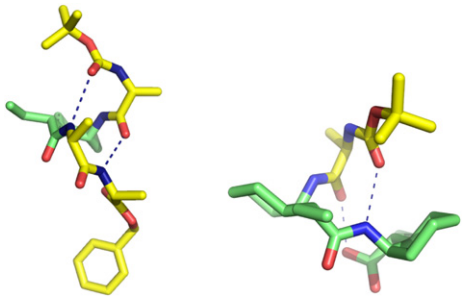

Fig. 2. Crystal structures of **1** (left) and **3** (right); views approximately perpendicular to the helical axes.

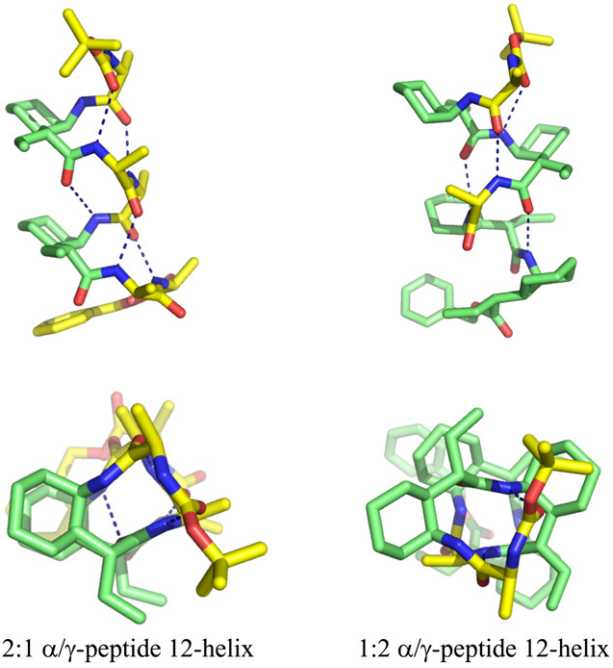

Fig. 3. Crystal structures of **2** (left), **4** (right): (top) views perpendicular to helical axes; (bottom) views along the helical axes.

The crystal structure of α/γ-peptide **2** contains two molecules in the asymmetric unit (1:1 ratio); the two conformations are very similar to one another. Each independent molecule forms all four possible 12-membered-ring hydrogen bonds, and a 10-atom-ring hydrogen bond forms across the central Ala-Ala segment. It is interesting to compare this 12-helix with an ideal 3_{10}-helix among α-peptides. Fig. 4 shows a superimposition of the 12-helical conformation of α/γ-peptide **2** and an idealized 3_{10}-helix (RMSD=1 Å), which demonstrates the similarity of the foldamer helix to a natural prototype.

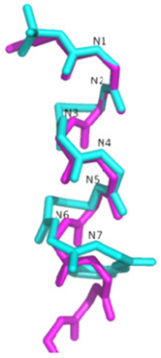

Fig. 4. Superposition of backbone atoms of an ideal 3_{10}-helix (magenta) with α/γ-peptide **2** (molecule A, cyan) backbone.

2.2. Backbone torsion angle analysis

Table 1 compares backbone torsion angles for the α- and γ-residues observed in crystal structures of the four α/γ-peptides described here. Two sets of torsion angles are provided for **2**, because the crystal structure contains two independent molecules. In addition, backbone torsion angles are given for a previously reported 1:1 α/γ-peptide crystal structure;[9g] this example contains the (*R*,*R*,*R*)-γ residue **I** and D-alanine (as do **1**–**3**). All (*S*,*S*,*S*)-γ residues **II** display g^+,g^+ local conformations about the C_α–C_β (ζ) and C_β–C_γ (θ) bonds, and ψ and φ torsion angle near −120°, with a somewhat wider distribution for the latter torsion angle. The

Table 1
Backbone torsion angles (deg) for α/γ-Peptides **1**–**4**

Peptides	Residues	ϕ	θ	ζ	ψ
2:1 α/γ-Tetramer **1**	α	73.0			27.0
(γ-Residue **I**)	α	130.2	−56.3	−54.8	117.4
	γ	65.1			27.3
	α	142.9			170.1
2:1 α/γ-Heptamer	α	69.6			35.9
(γ-Residue **I**)	γ	133.1	−48.8	−60.5	119.8
Molecule A	α	63.4			29.6
	α	68.7			21.3
	γ	148.2	−56.3	−62.8	117.5
	α	115.8			−8.9
	α	130.2			−23.5
2:1 α/γ-Heptamer **2**	α	75.2			27.9
(γ-Residue **I**)	γ	134.4	−56.5	−51.9	117.3
Molecule B	α	62.5			30.9
	α	65.0			26.8
	γ	148.7	−55.8	−63.3	113.7
	α	123.2			−6.7
	α	124.5			−29.2
1:2 α/γ-Trimer **3**	α	65.7			30.1
(γ-Residue **I**)	γ	155.4	−58.3	−62.2	115.3
	γ	149.7	−52.4	−46.8	140.5
1:2 α/γ-Hexamer **4**	α	−74.0			−19.2
(*S*,*S*,*S*) (γ-Residue **II**)	γ	−139.1	56.2	58.0	−131.1
	γ	−143.8	57.9	53.7	−110.6
	α	−54.1			−35.2
	γ	−145.8	56.5	61.7	−115.5
	γ	−111.4	55.6	60.3	−144.0
1:1 α/γ-Hexamer[9g]	α	75.5			22.8
(γ-Residue **I**)	γ	134.3	−57.7	−50.5	109.4
	α	56.3			41.1
	γ	134.7	−56.7	−55.7	109.8
	α	67.2			45.9
	γ	162.1	−55.4	−51.3	116.0
Computational study	α	72.3			28.8
By Hofmann[9c]	γ	123.4	−52.6	−62.3	124.9
	α	69.8			29.1
	γ	123.3	−52.1	−62.7	122.6
	α	69.6			30.6
	γ	122.8	−53.8	−64.0	129.8

(*R*,*R*,*R*)-γ residues **I** display g^-,g^- local conformations about the C_α—C_β (ζ) and C_β—C_γ (θ) bonds, with torsion angles opposite to those of (*S*,*S*,*S*)-γ residues **II**. These values are consistent with the predictions for a C═O(*i*)···H—N(*i*+3) hydrogen-bonded helical conformation of 1:1 α/γ-peptides from Hofmann et al.[9e] The α-residue ψ torsion angles in our crystal structures (near 30° for D-Ala or the opposite for L-Ala) are similar to those observed for a canonical 3_{10}-helix, which shares the C═O(*i*)···H—N(*i*+3) hydrogen-bonding pattern.

2.3. Helical parameter analysis

Average parameters for the C═O(*i*)···H—N(*i*+3) hydrogen-bonded helices formed by 2:1 and 1:2 α/γ-peptides were derived from the structural data as described previously[10] and are presented in Table 2. Each helical parameter was calculated from a set of four consecutive α-carbons. Nonhelical residues at C-termini were excluded from these calculations. For Cβ of γ-residues was used as an imaginary α-carbon. Table 2 includes for comparison parameters for two other helices that contain C═O(*i*)···H—N(*i*+3) hydrogen bonds: the 1:1 α/γ-peptide 12-helix and the α-peptide 3_{10}-helix. The parameters for all four helices are quite similar. Detailed comparison of the two independent helices observed in the crystal of the 2:1 α/γ-peptide heptamer **2** and the α-peptide 3_{10}-helix reveals further similarities: both helices have a comparable

Table 2
Average parameters for C═O(*i*)···H—N(*i*+3) hydrogen-bonded helices

Backbone	Helix type	Res/turn *n*	Rise/turn *p* (Å)	Rise/res *d* (Å)	Radius *r* (Å)
1:1 α/γ-Peptide	12-Helix	3.0	6.1	2.0	2.5
2:1 α/γ-Peptide	—	3.0	5.7	1.9	2.3
1:2 α/γ-Peptide	—	2.5	5.3	2.0	2.5
α-Peptide	3_{10}-Helix	3.2	5.8	1.8	2.0

number of residues per turn (3.0 vs 3.2), rise per turn (5.7 Å vs 5.8 Å), and rise per residue (1.9 Å vs 1.8 Å). In addition, the radii are similar (2.3 vs 2.0 Å) for these two helices.

3. Conclusions

The set of crystal structures reported here provides atomic resolution structural characterization of two new foldameric secondary structures, the C═O(*i*)···H—N(*i*+3) H-bonded helices formed by backbones that contain either a 2:1 or a 1:2 repeating pattern of α- and γ-amino acid residues. The structural parameters deduced from multiple sets of crystallographic data for each backbone family show that these new folding patterns are comparable to C═O(*i*)···H—N(*i*+3) hydrogen-bonded helices formed by pure α-residue oligomers (the 3_{10}-helix), and by oligomers containing a 1:1 α/γ repeat (the 12-helix). This information should be useful to any researcher who seeks to use these foldamer scaffolds for function-based design.

4. Experimental section

4.1. General procedures for α/γ-peptide synthesis

The α/γ-peptides reported here were prepared via conventional solution-phase methods. As in conventional peptide synthesis, orthogonal amino and carboxyl protecting groups are required for synthesis involving γ-residues. The *tert*-butyloxycarbonyl group (Boc) was used for N-terminal protection, and C-termini were protected as benzyl esters (OBn). Deprotection at the N-terminus was performed using 4 N HCl in dioxane, and hydrogenation was used to remove the C-terminal benzyl esters. α-Amino acid derivatives were purchased from Sigma—Aldrich, NovaBiochem, and Chem-Impex International. Protected forms of γ-amino acids **I** and **II** were prepare according to previously reported procedures.[9g] For peptide coupling, EDCI (1.2 equiv)+HOBt (1.2 equiv)+DIEA (1.2 equiv) or EDCI (1.5 equiv)+DMAP (1.1 equiv) were used. After the coupling reaction was complete, the mixture was diluted with excess EtOAc, and the organic solution was washed with 10% aqueous $NaHSO_4$, saturated aqueous $NaHCO_3$, and then brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated to give a crude product, which was purified by silica gel chromatography.

*4.1.1. Boc-(D)Ala-γ(**I**)-OBn.* Boc-(D)-Ala-OH was coupled to HCl·NH_2-γ(**I**)-OBn to give the desired dipeptide. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37—7.29 (m, 5H), 6.66 (br, 1H), 4.99, 5.20 (AB, J_{AB}=12.3 Hz, 2H), 4.99 (br, 1H), 4.14 (m, 1H), 4.07 (p, *J*=7.2 Hz, 1H), 2.28 (ddd, *J*=4.2, 9.9, 9.9 Hz, 1H), 1.89—1.62 (m, 6H), 1.52 (m, 2H) 1.44 (s, 9H), 1.27 (m, 1H), 1.23 (m, 1H), 1.24 (d, *J*=7.1 Hz, 3H), 1.07 (m, 1H), 0.83 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.55, 171.91, 156.13, 136.37, 128.60, 128.22, 80.26, 77.68, 77.26, 76.83, 66.50, 50.12, 49.63, 46.77, 41.52, 31.11, 28.52, 25.70, 24.82, 23.29, 20.63, 17.40, 11.65; HRMS *m*/*z* (ESI): calcd for: $C_{25}H_{38}N_2O_5Na$ $[M+Na]^+$ 469.2673, found 469.2672.

The dipeptide was dissolved in methanol (10 mL), and the flask was flushed with N_2. To the flask was added 10% Pd/C (0.05 g), and

the flask was attached to a Parr apparatus and shaken for 6–7 h under 10 psi H_2. The reaction mixture was filtered through a pad of Celite and concentrated to give a white solid (Boc-D)Ala-γ(**I**)–OH). The crude product was carried on without purification.

*4.1.2. Boc-(D)Ala-γ(**I**)-(D)Ala-OBn.* Boc-(D)Ala-γ(**I**)–OH was coupled to HCl·NH_2-(D)Ala-OBn by the general procedure described above to give the tripeptide Boc-(D)Ala-γ(**I**)-(D)Ala-OBn. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (br, 1H), 7.39–7.29 (m, 5H), 6.71 (d, J=9.0 Hz, 1H), 5.19 (AB, J_{AB}=12.6 Hz, 2H), 4.89 (br, 1H), 4.57 (p, J=7.1 Hz, 1H), 4.25 (m, 1H), 4.14 (p, J=6.9 Hz 1H), 1.88 (ddd, J=4.2, 10.4, 10.4 Hz, 1H), 1.82–1.62 (m, 5H), 1.58–1.22 (m, 22H) 0.82 (t, J=7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.20, 173.20, 172.51, 156.12, 136.09, 128.68, 128.26, 80.77, 66.93, 51.10, 50.12, 48.75, 47.01, 42.85, 30.89, 28.53, 25.88, 24.39, 22.44, 20.53, 18.12, 17.77, 14.32, 12.21; HRMS m/z (ESI): calcd for: $C_{28}H_{43}N_3O_6Na$ $[M+Na]^+$ 540.3045, found 540.3035.

The tripeptide was dissolved in methanol, and the flask was flushed with N_2. To the flask was added 10% Pd/C, and the flask was attached to a Parr apparatus and shaken for 6–7 h under 10 psi H_2. The reaction mixture was filtered through a pad of Celite and concentrated to give a white solid (Boc-(D)Ala-γ(**I**)-(D)Ala–OH). The crude product was carried on without purification.

*4.1.3. Boc-(D)Ala-γ(**I**)-(D)Ala-(D)Ala-OBn (**1**).* (Boc-(D)Ala-γ(**I**)-(D) Ala–OH) coupled to HCl·NH_2-(D)Ala-OBn by the general coupling method to give the tetrapeptide Boc-(D)Ala-γ(**I**)-(D)Ala-(D)Ala-OBn (**1**). After chromatographic purification, an X-ray quality crystal was grown by slow evaporation of a dichloroethane/heptane solution. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J=7.3 Hz, 1H), 7.37–7.29 (m, 5H), 6.95 (d, J=6.8 Hz, 1H), 6.60 (d, J=9.6 Hz, 1H), 5.14 (AB, J_{AB}=12.4 Hz, 2H), 4.89 (d, J=6.8 Hz, 1H), 4.65 (p, J=7.4 Hz, 1H), 4.46 (p, J=7.1 Hz, 1H), 4.14 (m, J=6.9 Hz 1H), 4.20 (m, 1H), 1.84 (m, 2H), 1.76 (m, 2H), 1.64 (m, 1H), 1.56–1.18 (m, 25H), 0.82 (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.29, 172.86, 172.57, 156.30, 136.17, 128.68, 128.17, 81.20, 66.76, 51.96, 50.55, 50.16, 48.42, 46.86, 42.31, 31.06, 28.54, 25.74, 24.43, 22.97, 20.57, 18.15, 17.98, 17.84, 11.86; HRMS m/z (ESI): calcd for: $C_{31}H_{48}N_4O_7Na$ $[M+Na]^+$ 611.3416, found 611.3391.

*4.1.4. Boc-(D)Ala-γ(**I**)-(D)Ala-(D)Ala-γ(**I**)-(D)Ala-(D)Ala-OBn (**2**).* Tetramer **1** (1 equiv) was treated with 4.0 M HCl in dioxane (~10 equiv). The mixture was stirred for 30 min and then concentrated under a nitrogen gas stream to give the HCl salt form of the amine, which was coupled with Boc-(D)Ala-γ(**I**)-(D)Ala-OH by the general coupling method to give the desired product **2**. After chromatographic purification, an X-ray quality crystal was grown by slow evaporation of a dichloroethane/heptane solution. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (d, J=3.9 Hz, 1H), 7.89 (d, J=7.5 Hz, 1H), 7.47 (d, J=6.1 Hz, 1H), 7.39–7.28 (m, 5H), 7.17 (d, J=8.2 Hz, 1H), 7.01 (br, 1H), 6.64 (d, J=12.7 Hz, 1H), 5.18, 5.13 (AB, J=13.0 Hz, 2H), 5.10 (d, J=2.7 Hz, 1H), 4.63 (p, J=7.4 Hz, 1H), 4.41 (p, J=6.6 Hz, 1H), 4.11 (m, J=6.9 Hz, 3H), 3.97 (m, 2H), 2.31 (ddd, J=3.5, 10.4, 10.4 Hz), 1.92–1.76 (m, 6H), 1.73–1.59 (m, 7H), 1.55–1.14 (m, 34H), 0.81 (m, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 177.30, 177.04, 175.18, 174.01, 172.36, 172.27, 156.34, 137.41, 128.87, 128.36, 127.60, 81.50, 66.03, 52.70, 52.45, 50.41, 49.82, 49.20, 47.59, 47.44, 47.27, 47.03, 46.33, 41.96, 41.33, 39.36, 33.12, 32.69, 32.09, 31.17, 30.68, 28.55, 26.53, 26.46, 26.37, 26.07, 25.58, 24.36, 23.95, 23.68, 23.39, 23.25, 23.14, 22.86, 20.53, 20.36, 20.15, 18.03, 17.93, 12.45, 11.48, 10.85, 10.36; HRMS m/z (ESI): calcd for: $C_{47}H_{75}N_7O_{10}Na$ $[M+Na]^+$ 920.5468, found 920.5466.

*4.1.5. Boc-(D)Ala-γ(**I**)-γ(**I**)–OH (**3**).* Boc-(D)Ala-γ(**I**)–OH was coupled to HCl·NH_2-γ(**I**)-OBn by using EDCI (1.5 equiv) and DMAP (1.1 equiv) as coupling reagents to give the tripeptide Boc-(D)Ala-γ(**I**)-γ(**I**)-OBn. The tripeptide was dissolved in methanol (10 mL), and the flask was flushed with N_2. To the flask was added 10% Pd/C (0.05 g), and the flask was attached to a Parr apparatus and shaken for 6–7 h under 10 psi H_2. The reaction mixture was filtered through a pad of Celite and concentrated to give the desired product **3** (Boc-(D)Ala-γ(**I**)-γ(**I**)–OH). After chromatographic purification, an X-ray quality crystal was grown by slow evaporation of a methanol/dichloromethane solution.

*4.1.6. Boc-(L)Ala-(S,S,S)γ(**II**)-(S,S,S)γ(**II**)-(L)Ala-(S,S,S)γ(**II**)-(S,S,S)γ(**II**)-OBn (**4**).* (L)-Alanine and (*S*,*S*,*S*)-γ-amino acid **II** were used to synthesize α/γ-peptide **4**, via the fragment approach described above. Trimer Boc-(L)Ala-(*S*,*S*,*S*)γ(**II**)-(*S*,*S*,*S*)γ(**II**)-OBn (1 equiv) was treated with 4.0 M HCl in dioxane (~10 equiv). The mixture was stirred for 30 min and then concentrated under a nitrogen gas stream to give the HCl salt form of the amine, which was coupled with Boc-(L)Ala-(*S*,*S*,*S*)γ(**II**)-(*S*,*S*,*S*)γ(**II**)–OH by the general coupling method to give the desired product **4**. After chromatographic purification, an X-ray quality crystal was grown by slow evaporation of a dichloroethane/heptane solution. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J=10.0 Hz, 1H), 7.74(d, J=9.2 Hz, 1H), 7.62 (br, 1H), 7.46–7.44 (m, 2H), 7.34–7.25 (m, 3H), 6.59 (d, J=10.0 Hz, 1H), 6.53 (d, J=9.1 Hz, 1H), 5.26, 5.06 (AB, J=12.5 Hz, 2H), 4.87 (d, J=10.0 Hz, 1H), 4.43 (m, 1H), 4.25 (m, 1H), 4.12 (m, 1H), 4.03 (m, 2H), 3.91 (m, 1H), 2.91 (m, 1H), 2.17 (ddd, J=3.8, 10.5, 10.5 Hz, 1H), 2.0–1.19 (m, 61H), 0.91–0.79 (m, 12H); HRMS m/z (ESI): calcd for: $C_{58}H_{94}N_6O_9Na$ $[M+Na]^+$ 1041.6975, found 1041.6941.

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Supplementary data

Copies of ^{1}H and ^{13}C spectra for **1**–**4**. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.01.079.

References and notes

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