Linear and cyclic β³-oligopeptides with functionalised side-chains (-CH_2OBn, -CO_2Bn, -$CH_2CH_2CO_2Bn$) derived from serine and from aspartic and glutamic acid

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The natural β-amino acid derivative Boc-Asp(β-OH)-OBn, as well as Boc-β-HGlu(OBn)-OH and Boc-β-HSer(OBn)-OH (prepared from appropriately protected glutamic acid and serine, respectively, by Arndt–Eistert homologation), were employed as building blocks for the synthesis of linear (**11**–**20**) and cyclic (**21**–**23**) β-oligopeptides consisting of two to six β-amino acids [using trichloroethyl (TCE) ester groups for *C*-terminal protection and pentafluorophenyl-ester activation for macrocyclisation]. While the linear derivatives are soluble enough for reactions and structural investigations in solution, the cyclo-β-tri- and -hexapeptides are not (according to FT-IR measurements they form networks of hydrogen bonds, perhaps consisting of so-called *nanotubes*). The CD spectra of the Boc–OTCE-protected (**19**) and of the unprotected (**20**) β-hexapeptides [β-Asp(OBn)-β-HGlu(OBn)-β-HSer(OBn)]$_2$ differ drastically, and only the unprotected form shows the familiar pattern of a negative Cotton effect between 210 and 220 nm (indicative of a 3_{14} helix). An NMR analysis in methanol of the β-hexapeptide **20** with free termini reveals the presence of a single, central, left-handed helix turn (14-membered hydrogen-bonded ring). The results are discussed and compared with those obtained previously for analogous β-peptides carrying non-functionalised side chains.

Introduction

The synthesis and characterisation of peptides consisting of β-amino acids, the so-called β-peptides, is a field of research that has been receiving more and more interest in recent years.[1] Whilst some groups have concentrated their efforts on building β-peptides with cycloalkyl substituents[2,3] or with allyl substituents,[4] we have devoted our attentions to β-amino acids which bear proteinogenic side chains.[1,5] We began initially with simple alkyl side chains and prepared β³-peptides containing β³-HVal-β³-HAla-β³-HLeu subunits[6] and also oligopeptides based entirely on β³-HAla—these being peptidic analogues of oligomers of 3-hydroxybutanoic acid.[7] Our work and that of other groups came to the spectacular conclusion that these short-chain oligomers (6 or 7 residues in length) form remarkably stable 3_{14} helical structures in solution. Further work has shown that other types of structures (a 2.5_1 helix[3] and an irregular helix[5] containing 10- and 12-membered hydrogen-bonded rings) also exist. Early work on polymers based on β-amino acids (the nylon-3 derivatives) has also demonstrated[8,9] the presence of well defined secondary structures. More recently, calculations on poly-β-aspartates have suggested that three different types of helix (17_4, 4_1 and 13_4) could be adopted by these compounds.[10,11] Oligo-β-aspartates have been synthesised; however, no structural characterisation has been performed.[12] Powder X-ray measurements showed that certain cyclic β-peptides form tube-like stacked structures in the solid state,[13] and, recently, cyclic β³-peptides have been shown to induce K^+ conductance through lipid bilayers.[14]

We have also recently demonstrated that the homologation of proteinogenic α-amino acids with functionalised side chains (*e.g.*, Lys, Glu, Thr, Trp) is possible, that these β³-amino acids can be incorporated into β-peptides using standard techniques and that these β³-peptides do not undergo rapid degradation by a variety of enzymes.[15] It is also of interest to note that the biodegradability of poly(α,β-D,L-aspartates) has been studied and the degree of degradation was found to change according to the extent of branching found within the polymer structure.[16]

We now report our findings on the stepwise synthesis of linear and cyclic oligo(β-L-aspartates) and β-peptides containing other functionalised β-amino acids together with an investigation into the structural characterisation of these compounds.

Results and discussion

Synthesis

The first stage of the synthetic strategy design was to identify a suitable set of orthogonal protecting groups. The amino acids Boc-Glu(OBn)-OH **1**, Boc-Ser(OBn)-OH **2** (Scheme 1) and Boc-Asp(OH)-OBn **9** (Scheme 2) are all commercially available and hence provided an attractive starting point. We opted to protect the C-termini as 2,2,2-trichloroethyl (TCE) esters which are easily prepared using standard techniques and deprotection can be achieved by several methods which will leave the Boc group and benzyl ester or ether groups unaffected.[17]

In order to prepare the β³-amino acids derived from glutamic acid and serine, we followed the well established procedures[18] using the Arndt–Eistert homologation protocols. Formation of the diazoketones **3**, **4** proceeded without any difficulties, and homologation with silver trifluoroacetate and triethylamine in aq. THF produced the free amino acids **5**, **6** in excellent yields. Subsequent protection of the C-terminus with trichloroethanol and DCC–DMAP yielded the fully protected amino acids **7**, **8** (Scheme 1). Boc-Asp(OH)-OBn **9** was also subjected to the conditions of the final protection step to give the building block Boc-Asp(OTCE)-OBn **10** in excellent yield, Scheme 2.

The β-peptides derived entirely from aspartic acid or glu-

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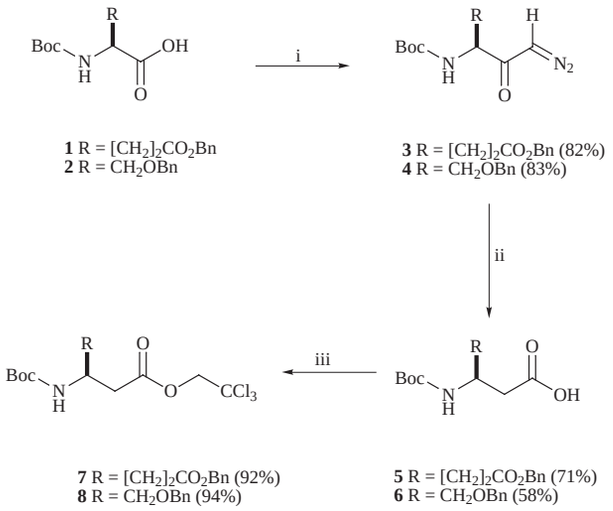
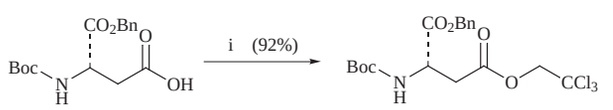


1 R = $[CH_2]_2CO_2Bn$
2 R = CH_2OBn
3 R = $[CH_2]_2CO_2Bn$ (82%)
4 R = CH_2OBn (83%)
7 R = $[CH_2]_2CO_2Bn$ (92%)
8 R = CH_2OBn (94%)
5 R = $[CH_2]_2CO_2Bn$ (71%)
6 R = CH_2OBn (58%)

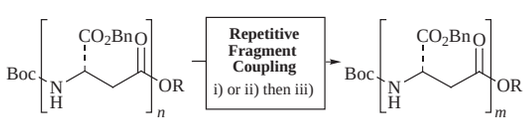
Scheme 1 *Reagents and conditions*: i, (1) $ClCO_2Et$, Et_3N, THF, −20 °C, (2) CH_2N_2, Et_2O; ii, CF_3CO_2Ag, aq. THF; iii, CCl_3CH_2OH, DCC, DMAP, CH_2Cl_2.



9 **10**

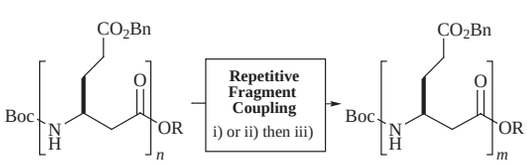
Scheme 2 *Reagents and conditions*: i, CCl_3CH_2OH, DCC, DMAP, CH_2Cl_2.

tamic acid were then readily prepared using a solution-phase block-coupling procedure. This resulted in the formation of the dimer **11**, trimer **12** and hexamer **13** of aspartic acid (Scheme 3) and the analogous oligomers **14**, **15**, **16** of β³-HGlu (Scheme 4).



11 m = 2 (51%)
12 m = 3 (84%)
13 m = 6 (54%)

Scheme 3 *Reagents and conditions*: i, Boc deprotection (CF_3CO_2H); ii, Ester deprotection (Zn, AcOH); iii, Coupling of two half-protected fragments (EDC, HOBt, NEt_3); R = CH_2CCl_3; Bn = CH_2Ph.

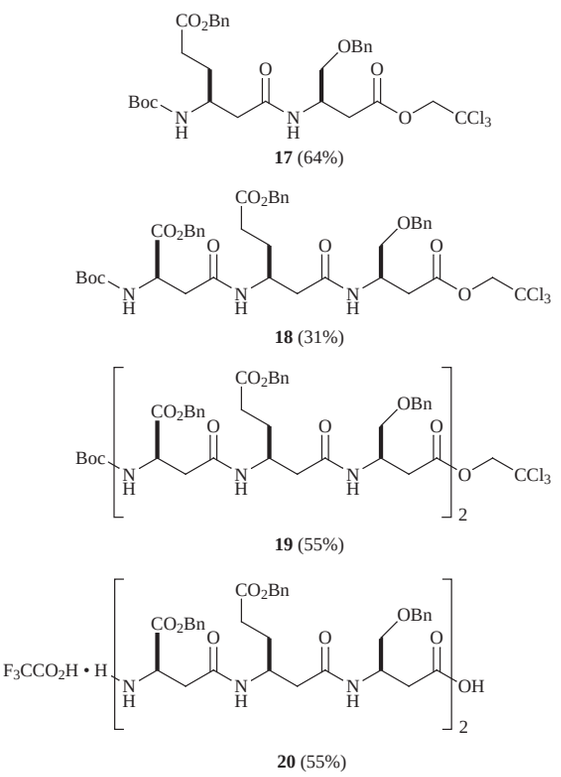


14 m = 2 (83%)
15 m = 3 (81%)
16 m = 6 (72%)

Scheme 4 *Reagents and conditions*: i, Boc deprotection (CF_3CO_2H); ii, Ester deprotection (Zn, AcOH); iii, Coupling of two half-protected fragments (EDC, HOBt, NEt_3); R = CH_2CCl_3; Bn = CH_2Ph.

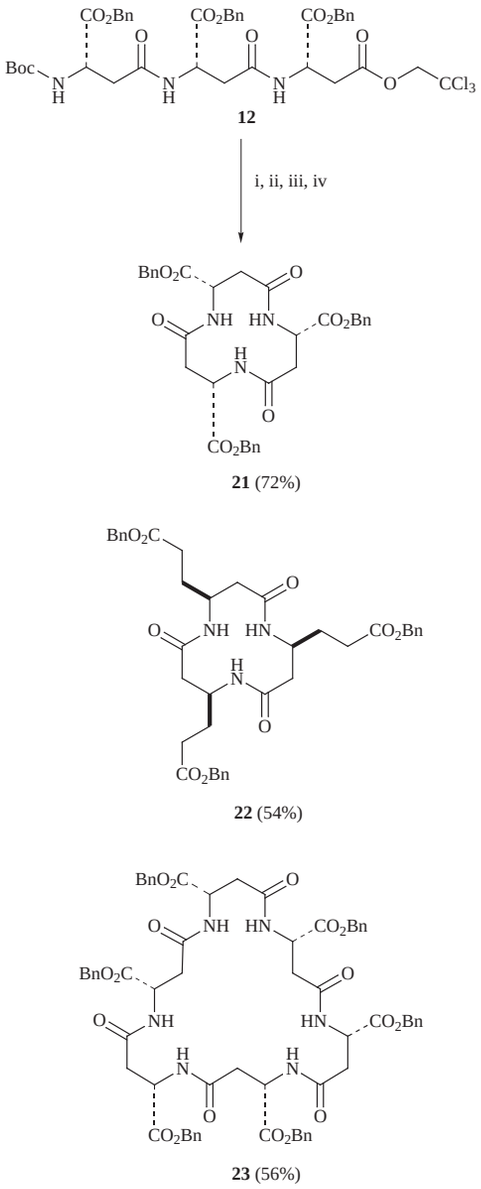
The protecting groups at the N- and C-termini were readily removed under the appropriate conditions. However, all attempts to remove the benzyl protecting groups from the side chains failed; we believe this can be accounted for by the poor solubility of the oligopeptides in the reaction solvent. Given our previous experience of a similar problem,[7] we attempted the hydrogenolysis using trifluoroethanol as the solvent but this also proved to be fruitless. We have still been unable to remove these protecting groups, which is unfortunate as we had hoped to make a direct comparison of the structural characteristics of these oligopeptides with the analogous esters[19] derived from malic acid. However, the previous calculations carried out on poly(β-aspartates) considered[10,11] compounds bearing 'protected' side chains and so we continued to investigate the structures of our protected oligopeptides.

We also felt that the lack of solubility, necessary for the deprotection step, might be overcome by using peptides based on more than one amino acid and therefore we developed a synthesis, based on a strategy analogous to that shown above, of β³-peptides derived from a sequence of β-Asp-β³-HGlu-β³-HSer. These compounds were built up *via* the dimer Boc-β³-HGlu(OBn)-β³-HSer(OBn)-OTCE **17**, the trimer Boc-β-Asp(OBn)-β³-HGlu(OBn)-β³-HSer(OBn)-OTCE **18** and the hexamer Boc-[β-Asp(OBn)-β³-HGlu(OBn)-β³-HSer(OBn)]$_2$-OTCE **19**. Once again, deprotection of the terminal protecting groups of compound **19** proceeded smoothly to yield the hexamer **20** but all attempts to deprotect the side chains (both before and after deprotection of the termini) failed. Undeterred by this, we went on to investigate the structures adopted by these molecules.



17 (64%)
18 (31%)
19 (55%)
20 (55%)

In analogy to our previous work,[6,7,13] we also synthesised the cyclo-β³-peptides based on these β-amino acids. Using the established procedures, we converted the trimers **12** and **15** into pentafluorophenyl esters by deprotection of the trichloroethyl esters and coupling of the resulting acids with pentafluorophenol with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC) in DMF. Subsequent deprotection of the N-terminus and then addition of a dilute solution of the pentafluorophenyl ester in acetonitrile to a solution of ethyldiisopropylamine (DIPEA) in acetonitrile at 70 °C resulted in the formation of the expected cyclo-β³-peptides **21** and **22** in good yields (Scheme 5). The hexamer **13** of aspartic acid was also subjected to the same procedures and this resulted in the formation of the cyclo-β³-peptide **23** in good yield. The analogous compounds based on β³-HAla had been found to be extremely insoluble white powders. We had hoped that these new cyclopeptides would prove to be more soluble given the nature of their aromatic side chains. However, this proved not to be the case, with white precipitates forming as before which proved to be the pure cyclic peptides. These compounds turned out to have very similar properties when compared with the β³-HAla analogues



Scheme 5 *Reagents and conditions*: i, Ester deprotection (Zn, AcOH); ii, C_6F_5OH, EDC, CH_2Cl_2; iii, Boc deprotection (CF_3CO_2H, CH_2Cl_2); iv, Pr^i_2NEt, CH_3CN, syringe pump, several hours, 70 °C.

and we therefore assume that they also adopt a similar stacked tube-like structure[13] and it is conceivable that the side chains also stack in such a way as to increase the insoluble nature of these compounds. There are ongoing attempts being made to analyse the structures of these cyclo-β^3-peptides using powder diffraction techniques.

Spectroscopic characterisation of the β-peptides

So far, we had focused only on β-peptides with β-amino acids corresponding to valine, alanine and leucine, *i.e.* peptides bearing aliphatic and apolar side chains. It was therefore of great importance to investigate the effects of amino acid substitution on the remarkable ability of small β-peptides to form distinct secondary structures in solution. The correlation between the amino acid sequence and induced structure, well known for α-peptides and α-proteins, is yet to be established for β-peptides. We wondered whether small β-peptides composed of protected β-amino acids (Asp, Glu, Ser) with polar groups, hydrogen-bond acceptors and large benzyl-ester side chains would also form stable and distinct secondary structures in solution and in the solid state. Hence, we investigated their structural properties by optical and NMR spectroscopic techniques.

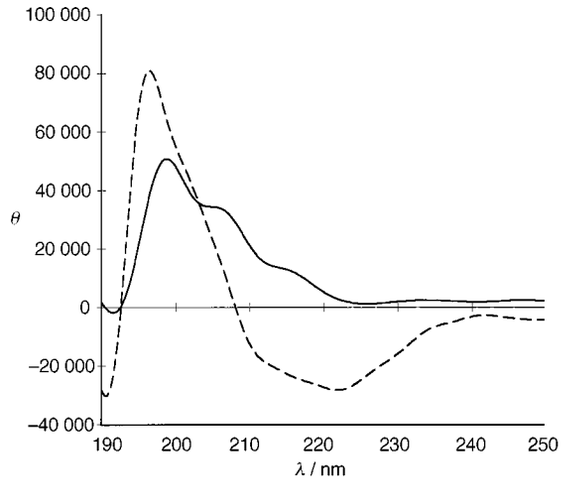


Fig. 1 CD Spectra of β-hexapeptides **19** (solid line) and **20** (dashed line) (~0.2 mM in MeOH; θ in deg cm^2 dmol^{-1}). The β-hexapeptide **19** exhibits a CD pattern that was never observed for β-peptides before; it may be indicative of a new secondary structure in solution.[23] Upon deprotection, the CD spectrum of compound **20** is reminiscent of the CD pattern indicative of a 3_{14} helix.

IR Spectroscopy

It is widely accepted in the literature that Fourier transform (FT)-IR spectroscopy may deliver valuable information about the hydrogen-bonding environment of peptides and proteins, both in solution and in the solid state.[20] In our previous work, we have used powder X-ray techniques[13] to show that cyclic β-peptides composed of β^3-HAla adopt stacked tube-like structures (so-called *nanotubes*) in the solid state. These compounds also exhibit distinct bands in their FT-IR spectra, indicating strong hydrogen bonding in a β-sheet-type manner. FT-IR Spectroscopy on the cyclic β-peptides **21**, **22** and **23** revealed very similar bands when compared with cyclo-β^3-HAla; *i.e.* for **22**, the amide A band, indicative of the hydrogen-bonding status, appears near 3294 cm^{-1}, whereas the Amide I (1648 cm^{-1}) and Amide II (1559 cm^{-1}, shoulders at 1554 and 1535 cm^{-1}) bands are characteristic of β-sheet-type structure.[7,20] These bands indicate the existence of a network of tight hydrogen bonds and, hence, it can be concluded that these cyclic peptides also exist as *nanotubes* in the solid state.[21]

CD Spectroscopy

Due to their low solubility, it proved to be impossible to characterise the cyclic β-peptides by CD-spectroscopy. However, linear β-hexapeptides **19** and **20** were examined. The fully protected β-hexapeptide gave rise to a CD spectrum of a type that had not been previously observed (Fig. 1, solid line). It is characterised by an intense maximum at 198 nm, with two shoulders at 207 and 216 nm.[22] It may be that a novel secondary structure, as indicated by the new CD spectrum of β-hexapeptide **19**, remains yet to be discovered by 2D-NMR analyses.

Upon deprotection of the N- and C-terminal protecting groups, the CD spectrum of the deprotected β-peptide **20** changed dramatically (Fig. 1, dashed line). We observed a minimum at 222 nm with a shoulder at 210 nm, a zero crossing at 208 nm and a maximum at 198 nm. On the one hand, this CD-pattern was somewhat reminiscent of that of a 3_{14} helix (maximum and zero crossing) and on the other hand, more surprisingly to us, of that of an α-helix of α-peptides (line shape and position of the minimum). However, CD cannot give definitive proof of structure and we decided therefore to carry out extensive 2D-NMR studies on β-hexapeptide **20**.

Structure determination by NMR spectroscopy

2D-NMR studies of β-hexapeptide **20** were carried out on a

Table 1 Assignment of all ^{1}H resonances (500 MHz; CD_3OH) and NH, C(β)-H coupling constants for compound **20**. Aromatic protons and NH_3 of the terminal β-HAsp(OBn) have not been assigned (n/a)

Residue	β-D-Asp(OBn)[1]	β-HGlu(OBn)[2]	β-HSer(OBn)[3]	β-D-Asp(OBn)[4]	β-HGlu(OBn)[5]	β-HSer(OBn)[6]
NH, NH_3	n/a	7.87	8.23	8.07	7.82	7.87
C(β)-H	4.34	4.39	4.43	4.98	4.39	4.46
C(α)-H	3.1	2.61	2.67	2.72	2.43	2.53
C(α)-H′	2.13	2.21	2.53	2.49	2.27	2.49
C(γ)-H		2.4	3.41		2.35	3.28
C(γ)-H′		2.39	3.41		2.34	3.28
C(δ)-H		1.86			1.82	
C(δ)-H′		1.75			1.61	
J[NH, C(β)-H]	n/a	9.3	8.9	8.7	9.5	9

Table 2 NOEs extracted from the 150 ms ROESY spectrum (500 MHz; CD_3OH) for compound **20**. The NOEs have been classified in three distance categories according to their relative volume in the contour plot: Strong, medium and weak corresponding to 3.0 Å, 3.5 Å and 4.5 Å. SD stands for sequential difference, an SD of 0 indicating an intraresidual and an SD of 1 a sequential NOE

Residue	Atom	Residue	Atom	Intensity	SD
1	C(α)-H	4	C(β)-H	medium	3
2	C(δ)-H_2	2	C(β)-H	medium	0
2	C(α)-H	3	NH	strong	1
2	C(α)-H	5	C(β)-H	medium	3
3	C(γ)-H_2	3	C(β)-H	strong	0
3	C(α)-H	3	NH	medium	0
3	C(α)-H′	3	NH	weak	0
3	C(α)-H	4	NH	strong	1
4	NH	3	NH	weak	1
4	C(α)-H	4	NH	medium	0
4	C(α)-H	4	C(β)-H	strong	0
4	C(α)-H	5	C(β)-H	medium	1
5	C(β)-H	3	NH	weak	2
5	C(β)-H	5	C(α)-H	medium	0
5	C(α)-H	5	NH	weak	0
5	C(δ)-H_2	5	NH	weak	0
6	C(β)-H	3	NH	medium	3
6	C(β)-H	4	NH	weak	2
6	C(γ)-H_2	6	C(β)-H	medium	0

500 MHz spectrometer for solutions in CD_3OH. We used DQF-COSY§ and TOCSY§ techniques to assign all ^{1}H resonances (except aromatic and benzylic protons) in their respective spin-systems. HSQC¶ and HMBC¶ experiments resulted in assignment of the sequence (long-range C,H correlations across the peptide bond) and the ^{1}H chemical shifts are given in Table 1. From the large ^3J[NH, C(β)-H] coupling constants, ranging from 8.7 to 9.5 Hz (see Table 1), it can be clearly concluded[23] that the NH and C(β)-H protons must be fixed in an anti-periplanar arrangement; this indicates an ordered secondary structure in solution as random rotation around this bond would result in much smaller coupling constants. We therefore decided to perform rotating-frame nuclear Overhauser enhancement (ROESY) experiments to gather information about the three-dimensional structure in solution, and the extracted NOEs are summarised in Table 2. Due to resonance overlap of the NH-resonance of β-HGlu^2(OBn) and β-HSer^6-(OBn), NOEs for these protons could not be properly assigned. From the 19 observed NOEs, 10 were intraresidual, 4 were sequential, 2 were from residue *i* to (*i* + 2) and 3 were from residue *i* to (*i* + 3). This *i*-to-(*i* + 2) and -(*i* + 3) pattern, observed before by us,[6] is charateristic for a 3_{14} helical structure in solution. These NOEs were then classified according to their relative volume in the contour plot of the 150 ms ROESY spectrum in three distance categories with the following upper-bound distance limits: strong < 3.0 Å, medium < 3.5 Å and weak < 4.5 Å. These distance restraints were then used together with 5 dihedral angle restraints for the NH,C(β)-H dihedral angles, derived from the coupling constants, in simulated annealing. This calculation yielded 10 structures, which are superimposed and displayed in Fig. 2. We selected this bundle as representative for the structure in solution.

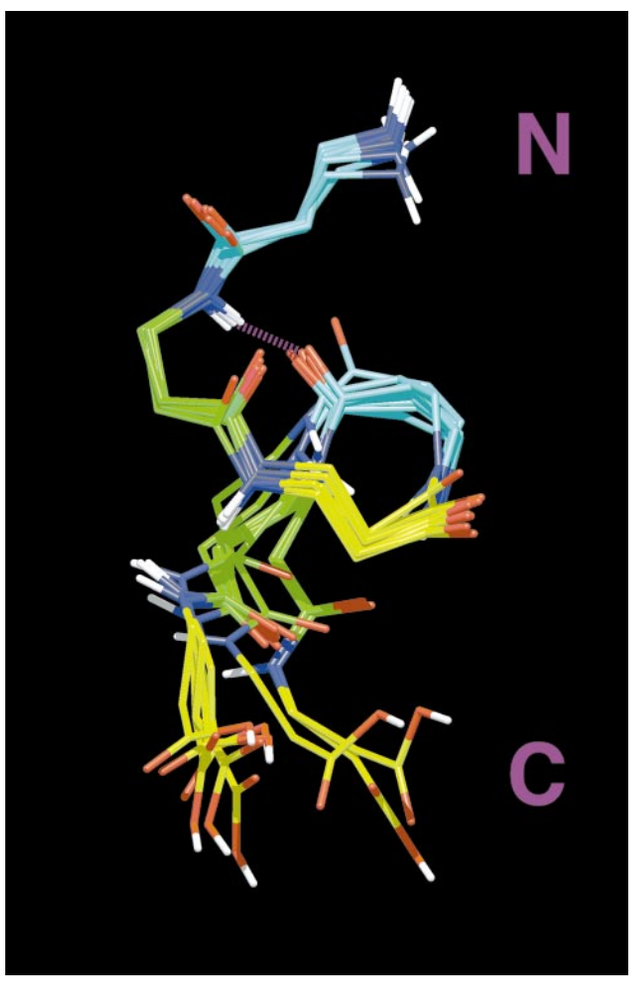


Fig. 2 Side views of the helical conformation of β-hexapeptide **20**. NMR solution structure of β-hexapeptide **20** in MeOH solution. This small β-hexapeptide has a defined, clearly helical structure, with a hydrogen bond from NH of residue 2 to the C=O of residue 4. All carbon-bound hydrogens and all side chains have been omitted for clarity, β-HAsp(OBn) residues are coloured in blue, β-HGlu(OBn) residues coloured in green and β-HSer(OBn) residues are in yellow. This figure was generated using VMD[24] and Raster3D.[25]

The structure is clearly helical, left-handed or (*M*), with a 14-membered hydrogen-bonded ring from NH of residue 2 to C=O of residue 4. The other possible hydrogen bonds, NH of residues 1 and 3 to C=O of residue 3 and 5, that would be closed in the clear 3_{14} helix are not present here. Therefore, the dominant

§ Double-quantum-filtered chemical shift-correlation spectroscopy; phase-sensitive two-dimensional total correlation spectroscopy.
¶ Heteronuclear single-quantum coherence spectroscopy; two-dimensional heteronuclear multiple-bond correlation spectroscopy.

conformational type may be characterised as a transition structure between a random coil and a 3_{14} helix. The additional hydrogen-bond acceptors in or the bulkiness of the side chains appear to weaken the helix. Furthermore the large aromatic groups dominate the structure and may therefore have a destabilising effect on the helix. There is no experimental evidence for aromatic stacking (lack of interresidual side-chain NOEs), and hence this effect appears not to be a stabilising contribution.

Conclusions

A successful strategy for the synthesis of β-peptides with side chains carrying OH and CO_2H functional groups has been developed, using an N-Boc/O-Bn/CO_2-Bn/CO_2-TCE combination of protecting groups, and the derived cyclic β-tri- and -hexapeptides have been shown to be readily available. So far, we have not found conditions for cleavage of the side chain benzyl-ether and -ester groups (LiCl-solubilisation conditions[26] have not yet been tested).

The dramatic influence of terminal protection upon the secondary structure of β-peptides (CD spectra of compounds **19** and **20** in Fig. 1) has been observed before, and it was interpreted as a consequence of pole/charge interaction.[5] The presence of only a single 3_{14}-helical turn in methanol solution of the terminally unprotected β-peptide **20** (Fig. 2) is intriguing, especially since this turn appears to suffice to cause a CD pattern (albeit of weak intensity), typical of the 3_{14}-helix of β-peptides: the NMR structure reported herein may be considered as the first secondary structure on the way from a random-coil to a full-helix structure of a β-peptide, and this is in aggreement with computational results (using the GROMOS96 force field),[27] as well as with our interpretation of thermochemical measurements (temperature-dependent CD and NMR spectroscopy, microcalorimetry),[28] indicating that helical folding/unfolding of β-peptides might occur by a non-cooperative mechanism. Whether the CD spectrum of the protected β-hexapeptide **19** arises from a hitherto unknown β-peptide secondary structure, or from a mixture of different (known and/or unknown) conformations, remains to be seen. Also, it will be exciting to learn about the structure of a fully deprotected, certainly very water-soluble, β-peptide of the series described herein, should we ever obtain it!

The insolubility of the cyclic β-peptides [β-Asp(OBn)]$_{3,6}$ (**21**, **23**), [β-HGlu(OBn)]$_3$ (**22**) as well as FT-IR data compares well with that of the previously reported [β-HAla]$_4$,[7,13] [β-HVal-β-HAla-β-HLeu]$_{1,2}$[6] and [β-HLeu]$_4$.[14] For the cyclo-β-tetrapeptides a stacking of the rings (with formation of tubes, involving an infinite network of hydrogen bonds as in pleated sheets) has been found in the solid state.[7,13] This kind of structure has not yet been demonstrated for cyclo-β-tri- or -hexapeptides,[29] and we have started collaborations with groups specialising in structure determinations by new X-ray and NMR methodologies amenable to substances of which no single crystals can be obtained.

Experimental

General

FAB = fast-atom bombardment; FC = flash chromatography; HV = high vacuum [0.1–0.01 bar (10^3–10^4 Pa)]; β-HXxx = β-Homoamino acid; MALDI-TOF = matrix-assisted laser desorption ionisation-time of flight; TFE = trifluoroethanol.

DMF and acetonitrile were distilled under reduced pressure from CaH_2 and stored over 4 Å molecular sieves. Solvents for chromatography and work-up procedures were distilled from Sikkon (anhydrous $CaSO_4$; Fluka). 'Ether' refers to diethyl ether; other ethers are named systematically. Triethylamine was distilled from CaH_2 and stored over potassium hydroxide. Ethyl chloroformate was distilled, and stored at −25 °C under argon. Amino acid derivatives were purchased from Bachem, Senn or Degussa. All other reagents were used as received from Fluka. Reactions carried out with the exclusion of light were performed in flasks completely wrapped in aluminium foil.

Flash column chromatography was carried out using silica gel (Fluka 60, 0.04–0.053 mm). TLC was carried out on commercially available pre-coated plates (Fluka Kieselgel 60) and the compounds were detected with anisaldehyde (9.2 ml anisaldehyde, 3.75 ml acetic acid, 12.6 ml conc. H_2SO_4, 340 ml ethanol). Analytical HPLC was performed on a Waters HPLC System (pump type 515, automated gradient controller 680, data module type 746, tunable absorbance detector type 484), Macherey-Nagel Nucleosil 5 C18 column. Preparative HPLC was performed on a Knauer HPLC system [pump type 64, programmer 50, UV detector (variable-wavelength monitor)], Macherey-Nagel 7 C18-column. Mps were measured on a Büchi 510 apparatus and are uncorrected. IR spectra were measured on a Perkin-Elmer 782 infrared spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AMX-400 (400 MHz), Varian Gemini 300 (300 MHz) or Gemini 200 (200 MHz) spectrometers: internal standard $CHCl_3$ signal [δ = 7.26 (^{1}H); δ = 77.0 (^{13}C)]. Chemical shifts are quoted in parts per million; *J*-values are given in Hz. Mass spectra were recorded with VG-ZAB2-SEQ (FAB) or Bruker-Reflex-MALDI-TOF (MALDI-TOF) spectrometers. 3-Nitrobenzyl alcohol (3-NOBA) was used as matrix for FAB. Optical rotations were measured with a Perkin-Elmer 241 polarimeter at rt (1 dm cells, concentration *c* in g/100 cm^3). Circular dichroism (CD) spectra were recorded on a Jobin-Yvon Mark III system between 190 and 300 nm (peptide concentration 0.2 mol dm^{-3} in TFE); the molar ellipticity (θ) is reported in deg cm^2 dmol^{-1}. Microanalyses were carried out by the Mikroanalytisches Laboratorium of the Laboratorium für Organische Chemie, ETH-Zürich.

General procedure A: preparation of diazoketones

In a similar fashion to the literature procedure,[18] the N-Boc-protected amino acid was dissolved under argon in THF (0.2 M) and then cooled to −25 °C. Triethylamine (1 equiv.) and ethyl chloroformate were added to the solution. After 15 min the suspension was allowed to warm to 0 °C. A solution of diazomethane in 'ether' was added until the intensive yellow colour persisted over a long period. The mixture was allowed to warm to rt and then stirred for 3 h. Excess of diazomethane was destroyed by addition of a small amount of acetic acid. After aqueous work-up by successive extraction with saturated aq. sodium hydrogen carbonate, aq. ammonium chloride and aq. sodium chloride, the organic layer was separated, dried ($MgSO_4$) and concentrated. Recrystallisation or FC afforded the pure diazoketone.

General procedure B: preparation of the homologated amino acid derivatives

In a similar fashion to the literature procedure,[18] the diazoketone was dissolved in THF (0.1 M) with the addition of 10% (v/v) water under the exclusion of light at −25 °C. Silver trifluoroacetate (0.11 equiv.) dissolved in triethylamine (2.9 equiv.) was added and the resulting mixture was stirred for 3 h as it was allowed to warm to rt. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate. The organic phase was extracted with saturated aq. $NaHCO_3$, and the resulting aqueous phase was adjusted to pH 2 with aq. HCl and extracted with ethyl acetate. The ethyl acetate extracts were washed with saturated aq. sodium chloride, dried ($MgSO_4$) and the solvent was removed under reduced pressure.

General procedure C: Boc deprotection of amino acids

In a similar fashion to the literature procedure,[5] the Boc-protected amino ester was dissolved in CH_2Cl_2 (0.5 M). The

mixture was cooled in an ice-bath and stirred. An equal volume of TFA was added and the solution was stirred for 1 h at 0 °C and for 1 h at rt. The solvent was removed under reduced pressure, the residue was taken up twice in toluene and again the solvent was removed. The residue was then taken up in CH_2Cl_2 and the solvent was removed. The trifluoroacetate salt was dried under HV for 1 h, characterised by ^{1}H NMR and was used for peptide coupling without further purification.

General procedure D: peptide coupling using EDC

The trifluoroacetate salt of the amino ester was dissolved in CH_2Cl_2 (0.2 M) and cooled to 0 °C. This was treated successively with Et_3N (5 equiv.), HOBt (1.2 equiv.), the Boc-protected amino acid (1 equiv.) and EDC (1.2 equiv.). The mixture was stirred at 0 °C for 30 min, then allowed to warm to rt and stirred for 16 h. The solvent was removed under reduced pressure, the residue was taken up in ethyl acetate and washed successively with saturated aq. $NaHCO_3$, aq. $NaHSO_4$ (1 M) and aq. NaCl, and the organic phase was separated, dried ($MgSO_4$) and concentrated. FC or recrystallisation yielded the pure peptide.

General procedure E: cyclisation of oligopeptides

In a similar fashion to the literature procedure,[7] a solution of the carboxylic acid derivative in DMF (0.4 M) was treated at rt with pentafluorophenol (1 equiv.) and EDC (1 equiv.). After 16 h, the mixture was evaporated and the residue was dissolved in $CHCl_3$. The resulting solution was washed successively with 1 M aq. HCl and brine. The org. phase was dried ($MgSO_4$) and evaporated. The residue was dissolved in CH_2Cl_2 (0.5 M) and an equal volume of TFA was added at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and for 1 h at rt. The solvent was evaporated, the residue was taken up twice in toluene and evaporated. The residue was dissolved in CH_3CN (0.025 M) and was slowly added to a solution of Hünig's base (DIPEA) in CH_3CN (3.3 mM) at 70 °C (bath temp.) using a syringe pump over several hours. The resulting precipitate was filtered off and dried under HV.

General procedure F: removal of the trichloroethyl ester protecting group

The peptide was dissolved in 90% (v/v) HOAc (0.03 M). Zn-powder (80 equiv.) was activated using 6 M aq. HCl, filtered off and washed successively with water and 'ether'. The resulting solid was added to the reaction mixture and stirring was continued for 16 h at rt. The resulting suspension was filtered and evaporated. The residue was taken up in ethyl acetate and washed successively with 1 M aq. $NaHSO_4$ and brine. The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure.

(4*S*)-4-*tert*-Butoxycarbonylamino-6-diazo-5-oxohexanoic acid benzyl ester 3. Boc-Glu(δ-OBn)-OH (20 g, 59.3 mmol) **1** was transformed according to general procedure **A**. Recrystallisation from 'ether'–pentane yielded *compound* **3** (17.5 g, 82%) as yellow needles, mp 68–70 °C; $[\alpha]_D^{r.t.}$ −17.1 (*c* 1.07, $CHCl_3$) (Found: C, 59.9; H, 6.2; N, 11.6. $C_{18}H_{23}N_3O_5$ requires C, 59.8; H, 6.4; N, 11.6%); $\nu_{max}(CHCl_3)/cm^{-1}$ 2112, 1712 and 1643; δ_H(300 MHz; $CDCl_3$) 1.41 (9H, s, *t*-Bu), 1.77–1.89 (1H, m, CH*H*), 2.10–2.20 (1H, m, C*H*H), 2.37–2.57 (2H, m, H_2C), 4.24 (1H, br m, *H*CNH), 5.09–5.12 (2H, m, H_2CPh), 5.32 [1H, br d, *J* = 7.5, C(O)NH], 5.47 (1H, br s, N_2CH) and 7.26–7.36 (5H, m, arom. H); δ_C(75 MHz; $CDCl_3$) 27.8, 28.4, 30.2, 54.2, 56.7, 66.7, 80.2, 128.5, 128.5, 128.8, 136.0, 155.8, 173.1 and 193.63; *m*/*z* (FAB) 745.1 [1.2%, $(2M + Na)^+$], 723.3 [2.4, $(2M + 1)^+$], 362.1 [19.6, $(M + 1)^+$], 278.1 (100), 236.1 (18.4), 192.1 (76.4), 154.1 (75.6), 136.0 (86.0) and 107.0 (43.2).

(1*S*)-(1-Benzyloxymethyl-3-diazo-2-oxopropyl)carbamic acid *tert*-butyl ester 4. Boc-Ser(OBn)-OH (5.01 g, 16.9 mmol) **2** was transformed according to general procedure **A**. Recrystallisation from ethyl acetate–diisopropyl ether yielded *compound* **4** (4.5 g, 83%) as yellow needles, mp 87–88 °C; $[\alpha]_D^{r.t.}$ −24.2 (*c* 1.13, $CHCl_3$) (Found: C, 60.0; H, 6.4; N, 13.0. $C_{16}H_{21}N_3O_4$ requires C, 60.2; H, 6.6; N, 13.2%); $\nu_{max}(CHCl_3)/cm^{-1}$ 2112, 1710 and 1639; δ_H(300 MHz; $CDCl_3$) 1.45 (9H, s, *t*-Bu), 3.58–3.63 (1H, m, CH*H*), 3.84–3.87 (1H, m, C*H*H), 4.32 (1H, br m, *H*CNH), 4.52 (2H, s, H_2CPh), 5.42 (1H, br d, N*H*), 5.56 (1H, br s, N_2CH) and 7.27–7.35 (5H, m, Ph); δ_C(75 MHz; $CDCl_3$) 28.4, 54.3, 57.8, 69.9, 73.6, 80.4, 128.0, 128.2, 128.7, 137.7, 155.7 and 193.2; *m*/*z* (FAB) 958 [14%, $(3M + 1)^+$], 639 [47, $(2M + 1)^+$], 320 [97, $(M + 1)^+$], 264 (40.4) and 236.1 (100).

(3*S*)-3-(*tert*-Butoxycarbonylamino)hexanedioic acid 6-benzyl ester 5. The diazoketone **3** (10 g, 27.7 mmol) was transformed according to general procedure **B**. Recrystallisation from ethyl acetate–pentane gave *compound* **5** (6.9 g, 71%) as an amorphous solid, mp 97–98 °C; $[\alpha]_D^{r.t.}$ −12.7 (*c* 1.0, $CHCl_3$) (Found: C, 61.5; H, 7.2; N, 4.0. $C_{18}H_{25}NO_6$ requires C, 61.3; H, 7.2; N, 4.0%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3436, 3032, 2980, 1712, 1501 and 1454; δ_H(300 MHz; $CDCl_3$) 1.42 (9H, s, *t*-Bu), 1.86–1.94 (2H, m), 2.43–2.48 (2H, m), 2.58 (2H, m), 3.95 (1H, br m, *H*CNH), 5.05 [1H, br d, *J* 9.0, C(O)N*H*], 5.12 (2H, s, H_2CPh), 5.96 (1H, br, CO_2H) and 7.29–7.39 (5H, m, arom. H); δ_C(75 MHz; $CDCl_3$) 28.4, 29.4, 31.2, 39.2, 47.1, 66.6, 79.9, 128.5, 128.5, 128.8, 136.1, 155.8, 173.5 and 176.5; *m*/*z* (FAB) 1076.4 [4.4%, $(3M + Na)^+$], 725.2 [45.9, $(2M + Na)^+$], 703.2 [33.9, $(2M + 1)^+$], 374.1 [60.2, $(M + Na)^+$], 352.1 [48.7, $(M + 1)^+$], 296.1 (81.4), 252.1 (100), 192.1 (7.0) and 137.0 (29.56).

(3*R*)-4-Benzyloxy-3-(*tert*-butoxycarbonylamino)butanoic acid 6. The diazoketone **4** (4.25 g, 13.3 mmol) was transformed according to general procedure **B**. Recrystallisation from ethyl acetate–'ether'–pentane yielded *compound* **6** (2.39 g, 58%) as a solid, mp 73–74 °C; $[\alpha]_D^{r.t.}$ +15.1 (*c* 1.05, $CHCl_3$) (Found: C, 61.9; H, 7.4; N, 4.5. $C_{16}H_{23}NO_5$ requires C, 61.9; H, 7.5; N, 4.5%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3438, 2982, 2931, 2865, 1710, 1501 and 1454; δ_H(300 MHz; $CDCl_3$) 1.44 (9H, s, *t*-Bu), 2.68 (2H, d, *J* 9.2), 3.55–3.61 (2H, m), 4.16 (1H, br m, *H*CNH), 4.52 (2H, s, H_2CPh), 5.17 [1H, br d, C(O)N*H*] and 7.29–7.38 (5H, m, arom. H); δ_C(75 MHz; $CDCl_3$) 28.4, 36.2, 47.2, 71.1, 73.4, 80.0, 127.9, 128.0, 128.7, 138.1, 155.8 and 176.2; *m*/*z* (FAB) 619.3 [15.9%, $(2M + 1)^+$], 332.1 [12.8, $(M + Na)^+$], 310.1 [78.9, $(M + 1)^+$], 254.1 (100), 210.1 [96.0, $(M - Boc)^+$], 154.0 (43.9) and 137.0 (38.8).

(3*S*)-3-(*tert*-Butoxycarbonylamino)hexanedioic acid 6-benzyl 1-(2,2,2-trichloroethyl) diester 7. A solution of compound **5** (5.9 g, 16.8 mmol) in CH_2Cl_2 (25 ml) was cooled to 0 °C and 2,2,2-trichloroethanol (1.8 ml, 18.5 mmol), DCC (3.6 g, 18.5 mmol) and DMAP (226 mg, 1.85 mmol) were added. The reaction mixture was allowed to warm to rt and stirring was continued for 16 h. The solvent was evaporated off and the residue was dissolved in ethyl acetate and filtered through Celite. Evaporation of the solvent and purification by FC (ethyl acetate–pentane, 1 : 5) gave *compound* **7** (7.4 g, 92%) as an amorphous solid, mp 65–66 °C; $[\alpha]_D^{r.t.}$ −13.6 (*c* 1, $CHCl_3$) (Found: C, 49.6; H, 5.3; N, 2.9. $C_{20}H_{26}Cl_3NO_6$ requires C, 49.8; H, 5.4; N, 2.9%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1709, 1501 and 1455; δ_H(300 MHz; $CDCl_3$) 1.42 (9H, s, *t*-Bu), 1.88–1.96 (2H, m), 2.47 (2H, t, *J* 7.2), 2.70 (2H, d, *J* 5.5), 4.00 (1H, br m, *H*CNH), ν_A = 4.77, ν_B = 4.73 (2H, AB, J_{AB} 12.1, OCH_2CCl_3), 4.93 [1H, br d, *J* 8.7, C(O)N*H*], 5.12 (2H, s, H_2CPh) and 7.30–7.40 (5H, m, arom. H); δ_C(75 MHz; $CDCl_3$) 28.4, 29.4, 31.1, 39.2, 47.3, 66.6, 74.1, 79.8, 94.9, 128.5, 128.8 (2C), 136.1, 155.6, 170.0 and 173.2; *m*/*z* (FAB) 967.0 [43.8%, $(2M + 1)^+$], 484.0 [35.6, $(M + 1)^+$] and 381.9 [100.0, $(M - Boc)^+$].

2,2,2-Trichloroethyl (3*R*)-4-benzyloxy-3-(*tert*-butoxycarbonylamino)butanoate 8. A solution of compound **6** (4.34 g, 14.0

mmol) in CH_2Cl_2 (25 ml) was cooled to 0 °C and 2,2,2-trichloroethanol (1.56 ml, 16 mmol), DCC (3.3 g, 16 mmol) and DMAP (171 mg, 1.4 mmol) were added. The reaction mixture was allowed to warm to rt and stirring was continued for 16 h. The solvent was evaporated off and the residue was dissolved in ethyl acetate and filtered through Celite. Evaporation of the solvent and purification by FC (ethyl acetate–pentane, 1:5) gave compound **8** (5.8 g, 94%) as a solid, mp 40.5–42.5 °C; $[\alpha]_D^{r.t.}$ +2.3 (*c* 0.84, $CHCl_3$) (Found: C, 49.1; H, 5.6; N, 3.3. $C_{18}H_{24}Cl_3NO_5$ requires C, 49.1; H, 5.5; N, 3.2%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1708, 1499 and 1454; δ_H(300 MHz; $CDCl_3$) 1.46 (9H, s, *t*-Bu), 2.81 (2H, d, *J* 6.2), 3.53–3.68 (2H, m), 4.16–4.24 (1H, br m, *H*CNH), 4.53 (2H, s), $\nu_A = 4.71$, $\nu_B = 4.68$ (2H, AB, J_{AB} 12.0, OCH_2CCl_3), 5.11–5.18 [1H, br m, C(O)N*H*] and 7.29–7.47 (5H, m, arom. H); δ_C(75 MHz; $CDCl_3$) 25.9, 33.7, 44.9, 68.5, 70.9, 71.6, 77.3, 125.4, 125.5, 126.1, 135.4, 152.8 and 167.5; *m*/*z* (FAB) 879.1 [8.6%, $(2M + 1)^+$], 440.0 [62.6, $(M + 1)^+$] and 340 [100.0, $(M - Boc)^+$].

(2*S*)-2-(*tert*-Butoxycarbonylamino)butanedioic acid 1-benzyl 4-(2,2,2-trichloroethyl) diester 10. A solution of compound **9** (1.66 g, 5.0 mmol) in 5:1 CH_3CN–DMF (36 ml) was cooled to 0 °C and 2,2,2-trichloroethanol (0.53 ml, 5.3 mmol), DCC (1.15 g, 5.3 mmol) and DMAP (70 mg, 0.57 mmol) were added. The reaction mixture was allowed to warm to rt and stirring was continued for 16 h. The solvent was evaporated off and the residue was dissolved in ethyl acetate and filtered through Celite. Evaporation of the solvent and purification by FC (ethyl acetate–pentane, 1:5) gave *compound* **10** (2.09 g, 92%) as a solid, mp 52–54 °C; $[\alpha]_D^{r.t.}$ +10.1 (*c* 1.05, $CHCl_3$) (Found: C, 47.7; H, 5.0; N, 3.1. $C_{18}H_{22}Cl_3NO_6$ requires C, 47.4; H, 4.9; N, 3.1%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3437, 2932, 1754 and 1710; δ_H(400 MHz; $CDCl_3$) 1.43 (9H, s, *t*-Bu), 3.02 (1H, dd, J_1 17.1, J_2 4.9), 3.15 (1H, dd, J_1 17.1, J_2 4.6), 4.62–4.71 (3H, m), 5.15–5.23 (2H, m), 5.48 [1H, d, *J* 7.9, C(O)N*H*] and 7.30–7.38 (5H, m, arom. H); δ_C(100 MHz; $CDCl_3$) 28.3, 36.6, 50.0, 67.6, 74.1, 80.3, 94.5, 109.2, 128.4, 128.5, 128.6, 135.1, 155.3, 169.3 and 170.5; *m*/*z* (FAB) 454.2 [13.4%, $(M + 1)^+$], 400.1 (100) and 354.1 [63.7, $(M - Boc)^+$].

Boc-N-β-D-Asp(α-OBn)-β-D-Asp(α-OBn)-OCH_2CCl_3 11. Boc-N-β-D-Asp(α-OBn)-OCH_2CCl_3 **10** (9.78 g, 21.5 mmol) was deprotected according to general procedure **C**. The resulting aminoester and **9** (7.11 g, 22 mmol), Et_3N (11.7 ml, 85.9 mmol), HOBt (3.51 g, 25.8 mmol) and EDC (5.00 g, 25.8 mmol) were transformed according to general procedure **D**. FC (ethyl acetate–hexane 1:2) gave compound **11** (7.37 g, 51%) as an amorphous solid, mp 97–101 °C; $[\alpha]_D^{r.t.}$ +20.4 (*c* 1, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3426, 1752, 1708 and 1498; δ_H(400 MHz; $CDCl_3$) 1.42 (9H, s, *t*-Bu), 2.75 (1H, dd, J_1 15.8, J_2 4.5), 2.89–2.95 (2H, m), 3.12 (1H, dd, J_1 17.4, J_2 4.4), 4.54–4.58 (1H, m, *H*CNH), $\nu_A = 4.53$, $\nu_B = 4.69$ (2H, AB, J_{AB} 11.9, OCH_2CCl_3), 4.85–4.89 (1H, m, *H*CNH), 5.13–5.23 (4H, m, H_2CPh), 5.69 [1H, d, *J* 8.0, O(CO)NH], 6.53 [1H, d, *J* 7.8, C(CO)NH] and 7.28–7.36 (10H, m, arom. H); δ_C(100 MHz; $CDCl_3$) 28.3, 35.91, 37.8, 48.5, 50.4, 67.3, 67.9, 74.1, 80.0, 94.4, 128.5, 128.6, 134.8, 135.4, 155.6, 169.1, 169.8 and 171.1; *m*/*z* (FAB) 1317.4 [1.6%, $(2M + 1)^+$], 659.2 [34.6, $(M + 1)^+$] and 561.2 [100, $(M - Boc)^+$].

Boc-N-β-D-Asp(α-OBn)-β-D-Asp(α-OBn)-β-D-Asp(α-OBn)-OCH_2CCl_3 12. Peptide **11** (2.03 g, 3.08 mmol) was deprotected according to general procedure **C**. The resulting aminoester and compound **9** (1.03 g, 3.20 mmol), Et_3N (1.68 ml, 12.30 mmol), HOBt (504 mg, 3.7 mmol) and EDC (712 mg, 3.7 mmol) were transformed according to general procedure **D**. FC (ethyl acetate–hexane 1:2) gave *compound* **12** (2.24 g, 84%) as an amorphous solid, mp 116–119 °C; $[\alpha]_D^{r.t.}$ +26.2 (*c* 1, $CHCl_3$) (Found: C, 55.5; H, 5.2; N, 4.9. $C_{40}H_{41}Cl_3N_3O_{12}$ requires C, 55.7; H, 4.8; N, 4.9%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3426, 1746, 1677, 1498 and 1456; δ_H(400 MHz; $CDCl_3$) 1.42 (9H, s, *t*-Bu), 2.58 (1H, dd, J_1 15.2, J_2 4.7), 2.65–2.95 (4H, m), 3.09 (1H, br m), 4.54–4.57 (2H, br m), 4.69 (1H, d, *J* 12.0), 4.82 (1H, br s), 4.89 (1H, br s), 5.11–5.21 (6H, m), 5.79 (1H, br m), 6.54 (1H, br m), 6.86 (1H, br m) and 7.27–7.38 (15H, m); δ_C(100 MHz; $CDCl_3$) 28.3, 35.7, 37.6, 48.6, 49.2, 50.5, 67.2, 67.5, 68.0, 74.2, 77.2, 80.0, 94.4, 128.1, 128.3, 128.4, 128.5, 128.5, 128.6, 128.7, 128.8, 134.8, 135.2, 135.5, 155.6, 169.0, 169.8, 170.0 and 170.3; *m*/*z* (FAB) 886.2 [3.4, $(M + Na)^+$], 864.2 [16.5, $(M + 1)^+$] and 764.2 [100, $(M - Boc)^+$].

Boc-N-[β-D-Asp(α-OBn)]$_6$-OCH_2CCl_3 13. Peptide **12** (483 mg, 0.53 mmol) was deprotected in 20 ml 90% (v/v) HOAc with 2 g Zn-powder according to general procedure **F**. A further portion of peptide **12** (484 mg, 0.53 mmol) was deprotected according to general procedure **C**. Both fragments were dissolved in CH_2Cl_2, Et_3N (0.31 ml, 2.24 mmol), HOBt (91 mg, 0.67 mmol) and EDC (130 mg, 0.67 mmol) were added, and the mixture was stirred overnight at rt. The resulting yellow mixture was diluted with $CHCl_3$ and washed successively with 1 M aq. $NaHSO_4$ and saturated aq. $NaHCO_3$. The organic phase was washed with aq. NaCl, dried ($MgSO_4$) and concentrated. Recrystallisation (MeOH–hexane) gave compound **13** (443 mg, 54%) as a solid, mp 138–141 °C (decomp.); $[\alpha]_D^{r.t.}$ +12.9 (*c* 1, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3416, 1744, 1676 and 1498; δ_H(400 MHz; $CDCl_3$) 1.38 (9H, s, *t*-Bu), 2.50–3.10 (12H, m), 4.49–4.69 (3H, m), 4.76–4.89 (3H, m), 5.06–5.18 (12H, m, H_2CPh), 5.93 [1H, d, *J* 8.9, O(CO)NH], 5.79 [1H, d, *J* 7.6, C(CO)NH], 6.98 [1H, d, *J* 7.8, C(CO)NH], 7.05–7.11 [3H, m, C(CO)NH] and 7.26–7.37 (30H, m, arom. H); δ_C(100 MHz; $CDCl_3$) 28.3, 35.7, 37.1, 37.2, 37.3, 48.5, 49.2, 49.4, 50.5, 67.1, 67.4, 67.5, 67.6, 67.7, 68.0, 74.1, 77.2, 79.8, 94.4, 126.96, 127.61, 128.02, 128.11, 128.24, 128.29, 128.47, 128.53, 128.58, 128.66, 128.71, 134.7, 135.1, 135.2, 135.3, 135.4, 135.7, 155.7, 169.1, 169.6, 169.7, 170.1, 170.6, 170.8 and 171.7; *m*/*z* (FAB) 1501.7 [3.1%, $(M + Na)^+$], 1479.8 [3.1, $(M + 1)^+$] and 1381.6 [100, $(M - Boc)^+$].

Boc-N-β-HGlu(OBn)-β-HGlu(OBn)-OCH_2CCl_3 14. Boc-N-β-HGlu(OBn)-OCH_2CCl_3 (7.5 g, 15.6 mmol) **7** was deprotected according to general procedure **C**. The resulting aminoester and **5** (5.5 g, 15.7 mmol), Et_3N (10.9 ml, 78.5 mmol), HOBt (2.54 g, 18.8 mmol) and EDC (3.6 g, 18.8 mmol) was transformed according to general procedure **D**. Recrystallisation (ethyl acetate–pentane 7:3) gave *compound* **14** (9.29 g, 83%) as an amorphous solid, mp 113–114 °C; $[\alpha]_D^{r.t.}$ −16.4 (*c* 1, $CHCl_3$) (Found: C, 55.6; H, 5.8; N, 4.0. $C_{33}H_{41}Cl_3N_2O_9$ requires C, 55.4; H, 5.7; N, 3.9%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3428, 1731 and 1498; δ_H(400 MHz; $CDCl_3$) 1.40 (9H, s, *t*-Bu), 1.73–1.98 (5H, m), 2.25–2.55 (5H, m), 2.63–2.76 (2H, m), 3.80–3.89 (1H, m, *H*CNH), 4.26–4.35 (1H, m, *H*CNH), $\nu_A = 4.78$, $\nu_B = 4.72$ (2H, AB, J_{AB} 12.0, OCH_2CCl_3), $\nu_A = 5.12$, $\nu_B = 5.10$ (4H, AB, J_{AB} 10.9, H_2CPh), 5.29 [1H, s, O(CO)NH], 6.35 [1H, d, *J* 7.8, C(CO)NH] and 7.31–7.38 (10H, m, arom. H); δ_C(100 MHz; $CDCl_3$) 28.4, 28.6, 29.6, 31.1, 38.7, 41.1, 45.9, 47.7, 66.4, 66.6, 74.0, 77.2, 79.4, 94.7, 128.2, 128.3, 128.4, 128.5, 128.6 (3C), 135.7, 135.9, 155.7, 169.6, 170.5, 173.0 and 173.1; *m*/*z* (FAB) 1455.2 [5.8%, $(2M + Na)^+$], 1433.3 [11.8, $(2M + 1)^+$], 739.1 [18.1, $(M + Na)^+$], 717.1 [51.9, $(M + 1)^+$] and 615.0 [100, $(M - Boc)^+$].

Boc-N-β-HGlu(OBn)-β-HGlu(OBn)-β-HGlu(OBn)-OCH_2CCl_3 15. Peptide **14** (7.77 g, 10.2 mmol) was deprotected according to general procedure **C**. The resulting aminoester and compound **5** (3.81 g, 10.9 mmol), Et_3N (7.56 ml, 54.3 mmol), HOBt (1.61 g, 11.9 mmol) and EDC (2.29 g, 11.9 mmol) were transformed according to general procedure **D**. Recrystallisation (ethyl acetate–pentane 4:1) gave *compound* **15** (8.38 g, 81%) as an amorphous solid, mp 129–131 °C; $[\alpha]_D^{r.t.}$ −16.2 (*c* 1, $CHCl_3$) (Found: C, 57.9; H, 5.9; N, 4.5. $C_{46}H_{56}Cl_3N_3O_{12}$ requires C, 58.2; H, 6.0; N, 4.4%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3427, 1732,

1665, 1495 and 1454; δ_H(400 MHz; $CDCl_3$) 1.40 (9H, s, *t*-Bu), 1.80–1.95 (6H, m), 2.24–2.54 (10H, m), 2.70–2.78 (2H, m), 3.86–3.87 (1H, m, *H*CNH), 4.12–4.13 (1H, m, *H*CNH), 4.20–4.30 (1H, m, *H*CNH), $\nu_A = 4.78$, $\nu_B = 4.71$ (2H, AB, J_{AB} 12.0, OCH_2CCl_3), 5.06–5.14 (6H, m, H_2CPh), 5.35 [1H, d, *J* 8.2, O(CO)NH], 6.54 [1H, d, *J* 7.5, C(CO)NH], 6.79 [1H, d, *J* 7.4, C(CO)NH] and 7.31–7.38 (15H, m, arom. H); δ_C(100 MHz; $CDCl_3$) 28.3, 28.7, 28.9, 29.7, 31.0, 31.1, 38.6, 40.5, 41.0, 46.0, 46.6, 47.7, 66.3, 66.4, 66.6, 74.0, 77.2, 79.3, 94.7, 128.2 (2C), 128.3 (2C), 128.4, 128.5, 128.6 (2C), 135.7, 135.8, 135.9, 155.7, 169.7, 170.6, 173.0 and 173.1; *m*/*z* (FAB) 1921.4 [6.2%, $(2M + Na)^+$], 1899.4 [22.0, $(2M + 1)^+$], 972.2 [13.5, $(M + Na)^+$], 950.2 [33.3, $(M + 1)^+$] and 850.1 [100, $(M - Boc)^+$].

Boc-N-[β-HGlu(OBn)]$_6$-OCH$_2$CCl$_3$ 16. Peptide **15** (1.5 g, 1.6 mmol) was deprotected in 90% (v/v) HOAc (66 ml) with zinc powder (10 g) according to general procedure **F**. A further portion of peptide **15** (1.5 g, 1.6 mmol) was deprotected according to general procedure **C**. Both fragments were dissolved in CH_2Cl_2 (30 ml), Et_3N (1.1 ml, 7.9 mmol), HOBt (235 mg, 1.7 mmol) and EDC (333 mg, 1.7 mmol) were added, and the mixture was stirred overnight at rt. The resulting yellow mixture was diluted with $CHCl_3$ and washed successively with 1 M aq. $NaHSO_4$ and saturated aq. $NaHCO_3$. The organic phase was washed with aq. NaCl, dried ($MgSO_4$) and concentrated. Recrystallisation (toluene, 60 °C) gave compound **16** (1.86 g, 72%) as a glass, mp 199–201 °C (decomp.); $[\alpha]_D^{r.t.}$ −14.7 (*c* 0.88, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3366, 1731, 1661 and 1498; δ_H(400 MHz; $CDCl_3$) 1.40 (9H, s, *t*-Bu), 1.60–2.00 (12H, m), 2.17–2.41 (24H, m), 3.80–3.91 (1H, m, *H*CNH), 4.00–4.15 (3H, m, *H*CNH), 4.20–4.40 (2H, m, *H*CNH), $\nu_A = 4.76$, $\nu_B = 4.70$ (2H, AB, J_{AB} 12.0, OCH_2CCl_3), 5.07–5.10 (12H, m, H_2CPh), 5.48 [1H, m, O(CO)NH], 6.64–7.02 [5H, m, C(CO)NH] and 7.29–7.35 (30H, m, arom. H); *m*/*z* (FAB) 1671.5 [13.6%, $(M + Na)^+$], 1649.6 [21.1, $(M + 1)^+$] and 1549.5 [100, $(M - Boc)^+$].

Boc-N-β-HGlu(OBn)-β-HSer(OBn)-OCH$_2$CCl$_3$ 17. Compound **8** (958 mg, 2.17 mmol) was deprotected according to general procedure **C**. The resulting aminoester and compound **5** (763 mg, 2.17 mmol), Et_3N (1.51 ml, 10.85 mmol), HOBt (323 mg, 2.38 mmol) and EDC (458 mg, 2.38 mmol) were transformed according to general procedure **D**. FC (ethyl acetate–pentane 2:3) yielded *compound* **17** (942 mg, 64%) as an amorphous solid, mp 108–109 °C; $[\alpha]_D^{r.t.}$ −5.4 (*c* 1.07, $CHCl_3$) (Found: C, 55.3; H, 5.9; N, 4.3. $C_{31}H_{39}Cl_3N_2O_8$ requires C, 55.2; H, 5.8; N, 4.16%); ν_{max}($CHCl_3$)/cm^{-1} 3648, 3430, 1704 and 1497; δ_H(400 MHz; $CDCl_3$) 1.41 (9H, s, *t*-Bu), 1.82–1.94 (2H, m), 2.31–2.43 (4H, m), 2.77 (2H, d, *J* 6.2), 3.52–3.63 (2H, m), 3.83–3.91 (1H, m, *H*CNH), 4.45–4.54 (3H, m), $\nu_A = 4.67$, $\nu_B = 4.64$ (2H, AB, J_{AB} 12.0, OCH_2CCl_3), 5.07–5.14 (2H, m), 5.32 [1H, d, *J* 7.9, O(CO)NH], 6.33 [1H, d, *J* 8.1, C(CO)NH] and 7.31–7.38 (10H, m, arom. H); δ_C(100 MHz; $CDCl_3$) 28.4, 29.5, 31.1, 35.8, 41.0, 45.9, 47.8, 49.2, 66.4, 70.5, 73.4, 74.1, 79.4, 94.8, 127.9, 128.0, 128.2, 128.3, 128.4, 128.5, 128.6, 135.9, 137.5, 155.6, 169.7, 170.2 and 173.1; *m*/*z* (FAB) 1345.5 [8.3%, $(2M + 1)^+$], 673.2 [77.5, $(M + 1)^+$] and 573.2 [100, $(M - Boc)^+$].

Boc-N-β-D-Asp(α-OBn)-β-HGlu(OBn)-β-HSer(OBn)-OCH$_2$CCl$_3$ 18. Compound **17** (3.47 g, 5.15 mmol) was deprotected according to general procedure **C**. The resulting aminoester and Boc-N-D-Asp(α-OBn)-CO_2H (1.66 g, 5.15 mmol), Et_3N (3.6 ml, 25.7 mmol), HOBt (765 mg, 5.66 mmol) and EDC (1.09 g, 5.66 mmol) were transformed according to general procedure **D**. FC (ethyl acetate–pentane 2:3) with subsequent recrystallisation from ethyl acetate–pentane yielded *compound* **18** (1.39 g, 31%) as an amorphous solid, mp 120–122 °C; $[\alpha]_D^{r.t.}$ −10.1 (*c* 0.75, $CHCl_3$) (Found: C, 57.4; H, 5.7; N, 4.8. $C_{42}H_{50}Cl_3N_3O_{11}$ requires C, 57.4; H, 5.7; N, 4.8%); ν_{max}($CHCl_3$)/cm^{-1} 3430, 1711, 1667, 1498, 1454 and 1368; δ_H(400 MHz; $CDCl_3$) 1.40 (9H, s, *t*-Bu), 1.83–1.86 (2H, m), 2.21–2.41 (4H, m), 2.43–2.54 (1H, m), 2.75 (3H, d, *J* 6.6), 3.56–3.63 (2H, m), 4.07–4.12 (1H, m, *H*CNH), 4.45–4.54 (4H, m), 4.64–4.71 (2H, m, OCH_2CCl_3), 5.07–5.12 (2H, m), 5.13–5.19 (2H, m), 5.87 [1H, d, *J* 8.2, O(CO)NH], 6.33 [1H, d, *J* 8.1, C(CO)NH], 6.65 [1H, d, *J* 7.6, C(CO)NH] and 7.26–7.37 (15H, m, arom. H); δ_C(100 MHz; $CDCl_3$) 28.3, 28.5, 31.1, 35.8, 37.7, 40.1, 45.9, 46.5, 50.6, 66.5, 67.3, 70.6, 73.4, 74.1, 77.2, 79.9, 94.7, 128.0, 128.1, 128.2, 128.3, 128.5, 128.6, 135.5, 135.8, 137.4, 155.7, 169.6, 169.9, 170.2, 171.7 and 173.1; *m*/*z* (FAB) 1759.4 [3.2%, $(2M + 1)^+$], 880.2 [43.3, $(M + 1)^+$] and 780.2 [100, $(M - Boc)^+$].

Boc-N-[-β-D-Asp(α-OBn)-β-HGlu(OBn)-β-HSer(OBn)]$_2$-OCH$_2$CCl$_3$ 19. Peptide **18** (500 mg, 0.57 mmol) was deprotected in 90% (v/v) HOAc (24 ml) with zinc powder (4 g) according to general procedure **F**. A further portion of peptide **18** (501 mg, 0.57 mmol) was deprotected according to general procedure **C**. The fragments were coupled according to general procedure **D** with Et_3N (0.4 ml, 2.85 mmol), HOBt (85 mg, 0.63 mmol) and EDC (120 mg, 0.63 mmol). FC [$CHCl_3$–7% (v/v) MeOH] gave compound **19** (472 mg, 55%) as an amorphous solid, mp 166–176 °C (decomp.); $[\alpha]_D^{r.t.}$ −12.2 (*c* 0.93, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3426, 1733, 1667, 1498 and 1455; δ_H(400 MHz; $CDCl_3$) 1.38 (9H, s, *t*-Bu), 1.75–1.88 (4H, m), 2.20–2.56 (12H, m), 2.64–2.82 (4H, m), 3.48–3.63 (4H, m), 4.10–4.15 (2H, m, *H*CNH), 4.40–4.73 (10H, m), 5.06–5.17 (8H, m), 5.93 (1H, d, *J* 8.4, N*H*), 6.31 (1H, d, *J* 8.7, N*H*), 6.89 (1H, d, *J* 8.4, N*H*), 6.94 (1H, d, *J* 8.4, N*H*) and 7.2–7.38 (30 H, m, arom. H); δ_C(100 MHz; $CDCl_3$) 23.0, 28.3, 28.5, 28.8, 31.1, 35.8, 37.1, 37.3, 37.6, 40.0, 40.3, 45.9, 45.9, 46.3, 46.4, 46.5, 46.7, 49.0, 49.6, 50.6, 66.4, 66.5, 67.2, 67.4, 67.5, 70.6, 71.1, 73.2, 73.4, 74.1, 77.2, 79.8, 94.7, 127.66, 127.86, 127.95, 128.00, 128.02, 128.08, 128.10, 128.15, 128.21, 128.23, 128.30, 128.36, 128.39, 128.42, 128.48, 128.56, 128.58, 128.60, 128.62, 135.36, 135.44, 135.6, 135.8, 135.9, 137.37, 137.43, 137.9, 169.7, 169.8, 169.9, 170.0, 170.2, 170.3, 170.5, 171.25, 171.34, 171.8, 172.9, 173.0 and 173.3; *m*/*z* (FAB) 1531.5 [20.8%, $(M + Na)^+$], 1509.5 [28.4, $(M + 1)^+$] and 1409.4 [100, $(M - Boc)^+$].

H$_2$N-N-[-β-D-Asp(α-OBn)-β-HGlu(OBn)-β-HSer(OBn)]$_2$-OH 20. Peptide **19** (144 mg, 0.095 mmol) was deprotected in 90% (v/v) HOAc (3.3 ml) with zinc powder (500 mg) according to general procedure **F**. The supension was filtered and the residue was taken up in $CHCl_3$ and washed successively with 1 M aq. HCl and brine. The organic layer was dried ($MgSO_4$) and evaporated. The resulting peptide was deprotected according to general procedure **C**. Purification by preparative RP-HPLC [A: water (0.1% TFA); B: CH_3CN; 10 min 60% B, 10 to 15 min 80% B, 15 to 20 min 99% B] yielded compound **20** (66 mg, 55%) as a glass, mp 148–150 °C; δ_H(500 MHz; $CDCl_3$) see Tables 1 and 2.

cyclo[-β-D-Asp(α-OBn)-β-D-Asp(α-OBn)-β-D-Asp(α-OBn)-] 21. Peptide **12** (1.73 g, 2 mmol) was deprotected in 90% (v/v) HOAc (60 ml) with zinc powder (5.5 g) according to general procedure **F**. The resulting peptide was transformed according to general procedure **E** with pentafluorophenol (387 mg, 2.1 mmol) and EDC (402 mg, 2.1 mmol) in CH_2Cl_2. The resulting ester was deprotected according to general procedure **C** in CH_2Cl_2 (80 ml) and TFA (20 ml). The resulting peptide was transformed according to general procedure **E** and the precipitate was collected by filtration to give *compound* **21** (886 mg, 72%) as a powder, mp >300 °C (Found: C, 64.4; H, 5.7; N, 6.8. $C_{33}H_{33}N_3O_9$ requires C, 64.4; H, 5.7; N, 6.8%); ν_{max}(KBr)/cm^{-1} 3288, 1740, 1674, 1560 and 1445; δ_H(400 MHz; $CDCl_3$–TFA) 2.89 (3H, dd, J_1 10.0, J_2 14.4), 3.14 (3H, dd, J_1 5.1, J_2 14.4), 4.77 (3H, br s, HCNH), $\nu_A = 5.24$, $\nu_B = 5.19$ (6H, *AB*, J_{AB} 12.0, H_2CPh), 7.26–7.37 (15H, m, arom. H) and 7.58 (3H, d, *J* 7.6, NH) and 7.37–7.26 (15H, m, arom. H); δ_C(100 MHz; $CDCl_3$–TFA) 37.3, 50.6, 69.1, 133.9, 170.1 and 171.5; *m*/*z* (FAB) 638.2 [96.3%, $(M + Na)^+$] and 616.3 [100, $(M + 1)^+$].

cyclo[-β-HGlu(OBn)-β-HGlu(OBn)-β-HGlu(OBn)-] 22. Peptide **15** (500 mg, 0.53 mmol) was deprotected in 90% (v/v) HOAc (22 ml) with zinc powder (4 g) according to general procedure **F**. The resulting peptide was transformed according to general procedure **E** with pentafluorophenol (97 mg, 0.53 mmol) and EDC (102 mg, 0.53 mmol) in CH_2Cl_2 (29 ml). The resulting ester was deprotected according to general procedure **C** in CH_2Cl_2 (1 ml) and TFA (1 ml). The resulting peptide was transformed according to general procedure **E** and the precipitate was collected by filtration to give compound **22** (200 mg, 54%) as a powder, mp >215 °C; ν_{max}(KBr)/cm^{-1} 3294, 1734, 1687, 1648, 1559 and 1498; δ_H(400 MHz; $CDCl_3$–TFA) 1.97–1.89 (5H, br m), 2.51–2.35 (10H, br m), 2.59–2.57 (3H, br d), 4.21 (3H, br s, HCNH), $\nu_A = 5.18$, $\nu_B = 5.09$ (6H, *AB*, J_{AB} 12.1, H_2CPh), 7.25 (3H, br s, NH) and 7.36–7.33 (15H, m, arom. H); δ_C(100 MHz; $CDCl_3$–TFA) 29.0, 30.9, 40.9, 48.7, 67.8, 128.5, 128.71, 128.74, 134.7, 173.4 and 175.1; *m/z* (FAB) 1421.7 [3.3%, $(2M + Na)^+$], 1399.8 [3.2, $(2M + 1)^+$], 722.4 [79.4, $(M + Na)^+$] and 700.4 [100, $(M + 1)^+$].

cyclo[-β-D-Asp(α-OBn)-]$_6$ 23. Peptide **13** (120 mg, 0.081 mmol) was deprotected in 90% (v/v) HOAc (5 ml) with zinc powder (0.3 g) according to general procedure **F**. The resulting peptide was transformed according to general procedure **E** with pentafluorophenol (17 mg, 0.09 mmol) and EDC (18 mg, 0.09 mmol) in CH_2Cl_2 (5 ml). The resulting ester was deprotected according to general procedure **C** in CH_2Cl_2 (5 ml) and TFA (5 ml). The resulting peptide was transformed according to general procedure **E** and the precipitate was collected by filtration to give compound **23** (55 mg, 56%) as a powder, mp >300 °C; ν_{max}(KBr)/cm^{-1} 3289, 1736, 1544 and 1388; δ_H(400 MHz; $CDCl_3$–TFA) 2.73 (6H, dd, J_1 9.0, J_2 15.4), 2.86 (6H, dd, J_1 4.8, J_2 15.4), 4.75–4.72 (6H, m, HCNH), 5.21–5.13 (12H, m, H_2CPh) and 7.32–7.27 (36H, m); δ_C(100 MHz; $CDCl_3$–TFA) 36.4, 50.5, 69.4, 134.0 and 171.4; *m/z* (FAB) 1254.0 [8.1%, $(M + Na)^+$] and 1232.0 [100, $(M + 1)^+$].

NMR Spectroscopy of β-hexapeptide 20

Sample: 16 mg of compound **20** dissolved in 0.6 ml of CD_3OH. 1D-NMR (AMX500): ^{1}H NMR (500 MHz): 90K data points, 128 scans, 5.6 s acquisition time. 2D-NMR: Solvent peak removed by presaturation DQF.COSY (500 MHz; CD_3OH) with pulsed field gradients (PFG) for coherence pathway selection.[30] Acquisition: 2K(t_2) × 512 (t_1) data points. 1 scan per t_1 increment, 0.21 s acquisition time in t_2; relaxation delay 2.0 s. Time proportional phase incrementation (TPPI) quadrature detection in ω1. Processing: Zero filling and FT to 1K × 1K real/real datapoints after multiplication with sine^2 filter shifted by π/3 in ω_2 and π/2 in ω_1. TOCSY (DIPSI-2 SL; 10 kHz; CD_3OH)[31] (500 MHz; CD_3OH): Acquisition: 2K(t_2) × 512 (t_1) data points. 32 scans per t_1 increment, mixing time 125 ms, TPPI quadrature detection. Processing: Zero filling and FT to 1K × 1K real/real datapoints after multiplication with sine^2 filter shifted by π/3 in ω_2 and π/2 in ω_1. HSQC with PFG[32] (500/125 MHz; CD_3OH): Acquisition: 2K(t_2) × 512 (t_1) datapoints, 2 scans per t_1 increment. ^{13}C-GARP decoupling during t_2. 0.21 s Acquisition time in t_2. Processing: Zero filling and FT to 1K × 1K real/real datapoints after multiplication with sine^2 filter shifted by π/3 in ω_2 and cos filter in ω_1. HMBC with PFG[33] (500/125 MHz; CD_3OH): Acquisition: no ^{13}C-decoupling, 8 scans per t_1 increment, otherwise identical with parameters for HSQC. Processing: Zero filling and FT to 1K × 1K after multiplication with cos^2 filter in ω_2 and Gaussian filter in ω_1; power spectrum in both dimensions. ROESY[34] (500 MHz; CD_3OH). Acquisition: A series of 3 ROESY spectra with mixing times of 50, 100 and 150 ms was acquired. CW-spin lock (3.8 kHz) between trim pulses, 4K(t_2) × 768 (t_1) datapoints, 32 scans per t_1-increment. 0.422 s acquisition time in t_2, other parameters identical with DQF.COSY. Processing: Zero filling and FT to 1K × 1K real/real datapoints after multiplication by sine^2 filter shifted by π/3 in ω_2 and cos^2 filter in ω_1. Baseline correction with 3rd-degree polynomial in both dimensions.

NMR Structure determination

Calculations were performed using AMBER* with BatchMin 5.0[35] on a Silicon Graphics O2 (R 10000) workstation under Irix 6.3. Visualisation and manipulation were carried out using Visual Molecular Dynamics (VMD)[24] and MacroModel 5.0.[35] Structure of β-hexapeptide **20** in CD_3OH: 17 NOEs (Table 2) were ordered according to their cross-peak volume in the contour plot of the 150 ms ROESY in three categories: strong, medium and weak with 3.0 Å, 3.5 Å and 4.5 Å as upper bound distance restraints and their van der Waals radii as lower bound distance restraints together with 4 dihedral angle restraints obtained *via* the Karplus equation.[23] A model of the β-hexapeptide was generated and subjected to a 500-steps energy minimisation. 20 ps Unrestrained molecular dynamics at 500 K yielded 50 starting structures. All restraints were applied and each of these structures was subjected to a simulated annealing calculation from 700 K to 1 K *in vacuo* with subsequent 500-steps energy minimisation. The 10 structures lowest in energy with no violation of constraints converged well to the final structural bundle and were selected as representative for the structure in solution.

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