EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201200463

Synthesis and Conformational Analysis of Heterogeneous Cyclic Oligomers of 6-Amino-6-deoxygalactonic Acid and Phenylalanine

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Keywords: Peptidomimetics / Cyclopeptides / Amino acids / Carbohydrates / Conformation analysis

A series of heterogeneous oligomers based on the sugar ε-amino acid 6-amino-6-deoxygalactonic acid and D- or L-phenylalanine have been synthesised and cyclised. The resulting cyclic heterogeneous oligomers have been analysed by molecular dynamics and NMR spectroscopy to describe their conformational and topological features. These initial studies have provided valuable insight into the structural properties of these cyclopeptides.

Introduction

Cyclic peptides are widely known as antibiotics and for other chemotherapeutic uses.[1] Accordingly, there has been a great deal of interest in their chemical[2] and enzymatic[3] synthesis. The two most widely used cyclic peptides, gramicidin and cyclosporine, are 30- and 33-membered rings, respectively, and significant activity was also found in a 42-ring analogue of gramicidin.[4] In the past few years, it has become clear that cyclic peptides also have potential applications in nanotube technology.[5] For example, cyclopeptides can adopt the required flat ring-shaped conformations with self-complimentary recognition surfaces, thereby constructing hydrogen-bonded and open-ended hollow peptide nanotubes, which can act as artificial *trans*-membrane ion channels.[6] Bioassays have shown that these cyclic peptides increase membrane permeability because they disrupt the *trans*-membrane ion potential, cause rapid cell death and act preferentially on Gram positive and negative bacterial membranes relative to mammalian cells. The potential biological interest of this type of derivative as antibiotics has led to extensive current studies into cyclopeptide nanotubes.

Sugar amino acids (SAAs) have been reported to be important components for peptidomimetics[7] and, moreover, linear oligomers of conformationally locked[8] SAAs provide many examples in which there is a predisposition towards secondary structures in relatively small molecules.[9] Cyclic peptides that contain SAAs[10] have been used in tissue engineering of cartilage[11] and have provided a set of novel integrin inhibitors.[12]

In the course of our investigations on cyclic peptides containing SAAs, we have synthesised several cyclic homo-oligomers of 6-amino-6-deoxy-D-galactonic acid with different ring sizes.[13] There is a strong predisposition for the macrocyclisation of linear pentafluorophenyl esters of 6-amino-6-deoxy-D-galactonic acid to homooligomers in good yield. Herein, we report the preparation and the conformational study of a series of heterogeneous cyclic oligomers with different ring sizes. The compounds contain 6-amino-6-deoxygalactonic acid and phenylalanine; an α-amino acid with a hydrophobic side chain. It was envisaged that these cyclic peptides could have biological and/or structural properties of interest.

Results and Discussion

Standard peptide coupling methods were employed to couple the galactose-derived azido ester **1**[14] to L-phenylalanine to give dipeptide **2**. Hydrolysis of the methyl ester, followed by reaction of the resulting acid **3** with pentafluorophenol and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI·HCl) in dioxane, afforded the pentafluorophenyl ester. Catalytic hydrogenation of the azido group to an amine led to subsequent cyclisation to the corresponding 10-membered cyclic peptide **4** (Scheme 1).

Catalytic hydrogenation of dimeric azido ester **2** afforded amino ester **5**, which was coupled to dimeric acid **3**. Thus, coupling of the two units of dipeptide afforded tetramer **6**, which was then hydrolysed to the corresponding acid **7**. Compound **7** was then transformed into the cyclic tetramer **8** via the pentafluorophenyl ester.

Linear hexapeptide **9** was synthesised by coupling amine **5** and acid **7**. Hydrolysis of the methyl ester was followed

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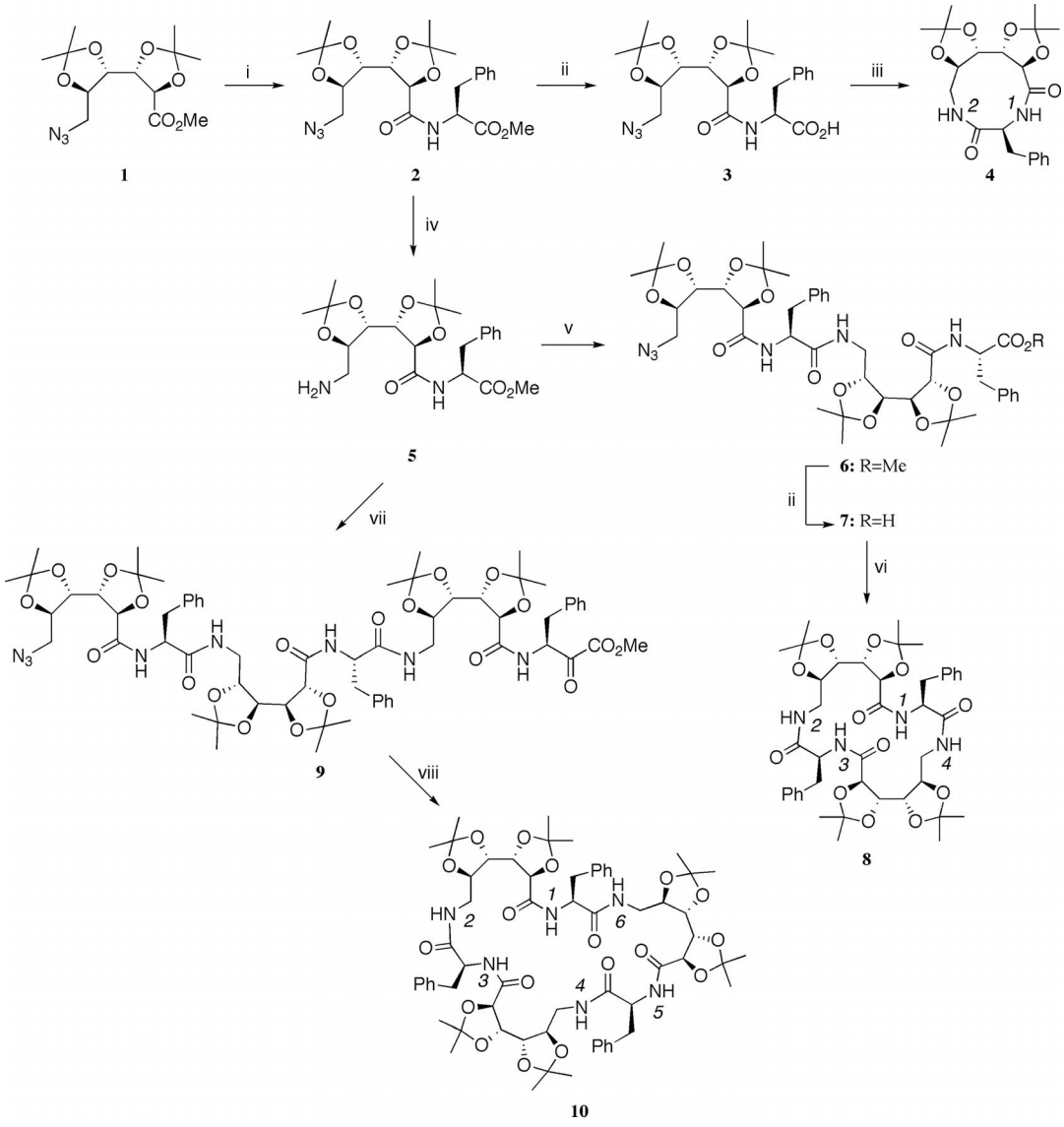
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201200463.



Scheme 1. Reagents and conditions: (i) 1. $Ba(OH)_2$,THF/H_2O. 2. L-Phe-OMe, *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU), Et_3N, DMF, 78% (two steps). (ii) $Ba(OH)_2$, THF/H_2O, quant. (iii) 1. Pentafluorophenol, EDCI·HCl, dioxane. 2. H_2, Pd black, dioxane, 35% (two steps). (iv) H_2, Pd black, dioxane, quant. (v) **3**, TBTU, Et_3N, DMF, 52%. (vi) 1. Pentafluorophenol, EDCI·HCl, dioxane. 2. H_2, Pd black, dioxane, 22% (two steps). (vii) **7**, TBTU, Et_3N, DMF, 38%. (viii) 1. $Ba(OH)_2$, THF/H_2O, quant. 2. Pentafluorophenol, EDCI·HCl, dioxane. 3. H_2, Pd black, dioxane, 14% (two steps).

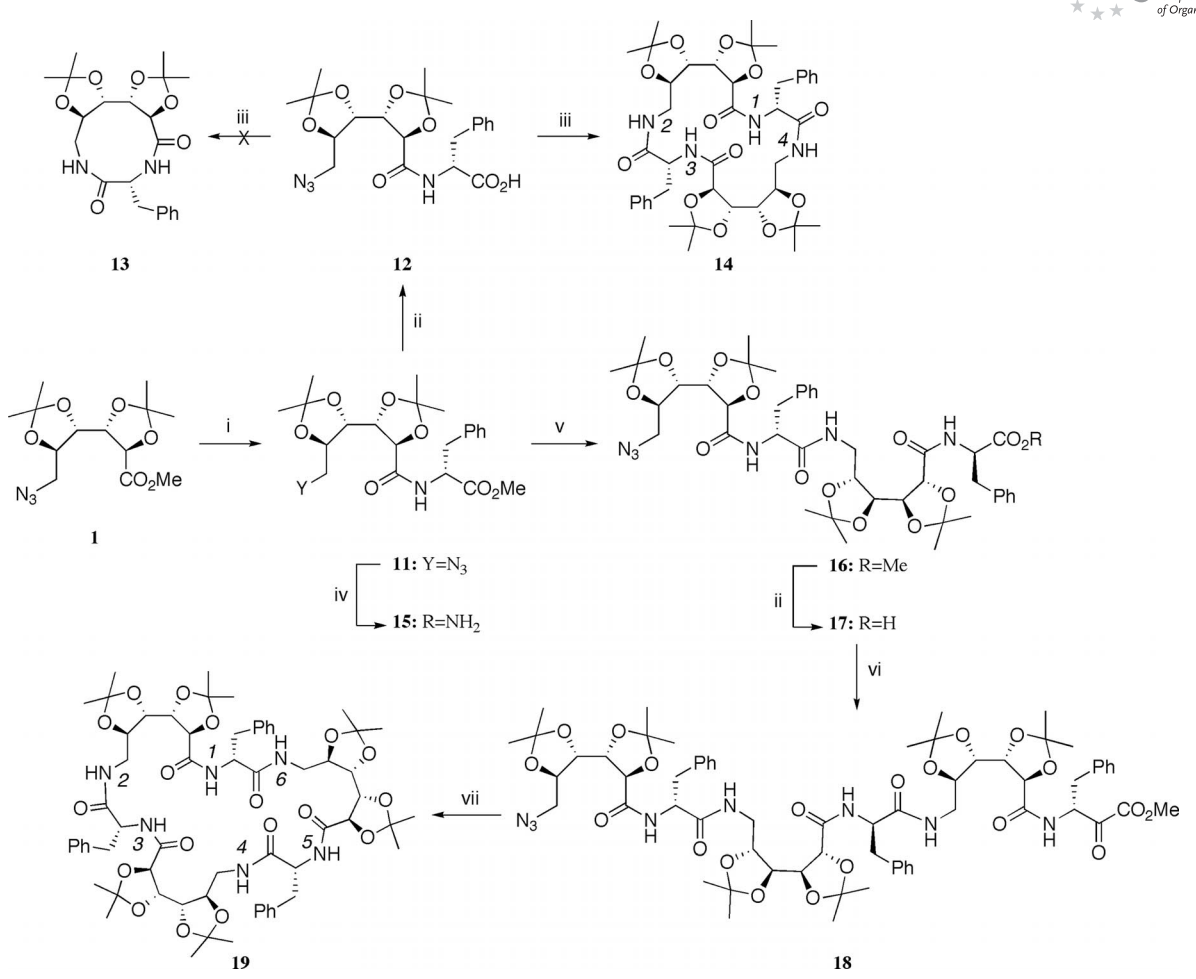
by formation of the pentafluorophenyl ester and catalytic hydrogenation of the azido group afforded cyclic hexamer **10**.

The preparation of cyclic peptides derived from dimer **11**, which is the epimer of **2** obtained by coupling galactose azido ester **1** and D-Phe, was investigated in a similar way (Scheme 2). Interestingly, the synthesis of cyclic dimer **13** was unsuccessful; catalytic hydrogenation of the pentafluorophenyl ester of **12** gave rise to cyclic tetramer **14**. The structure of **14** was unequivocally determined by X-ray crystallographic analysis (see part f of Figure 2).[15] Linear hexamer **18** gave rise to the corresponding cyclic hexamer **19**.

Conformational Analysis of Cyclopeptides

The 3D structures of model compounds **4**, **8**, **10**, **14** and **19** were investigated by NMR spectroscopy and molecular dynamics (MD) simulations. NMR spectroscopic analysis was carried out by using standard techniques at 400 and 500 MHz in $CDCl_3$.

For each peptide, the ^1H NMR spectrum contained a single set of resonances (Figure 1), indicating that the possible conformational equilibria were fast on the NMR chemical shift timescale.[16] COSY analysis allowed unambiguous assignment of the resonances. The molecular backbone conformations were then investigated by analysing the



Scheme 2. Reagents and conditions: (i) 1. $Ba(OH)_2$,THF/H_2O. 2. D-Phe-OMe, TBTU, Et_3N, DMF, 75% (two steps). (ii) $Ba(OH)_2$,THF/H_2O, quant. (iii) 1. Pentafluorophenol, EDCI·HCl, dioxane. 2. H_2, Pd black, dioxane, 38% (two steps); (iv) H_2, Pd black, dioxane, quant. (v) **12**, TBTU, Et_3N, DMF, 55%. (vi) **12**, TBTU, Et_3N, DMF, 30%. (vii) 1. Pentafluorophenol, EDCI·HCl, dioxane; 2. H_2, Pd black, dioxane, 20% (two steps).

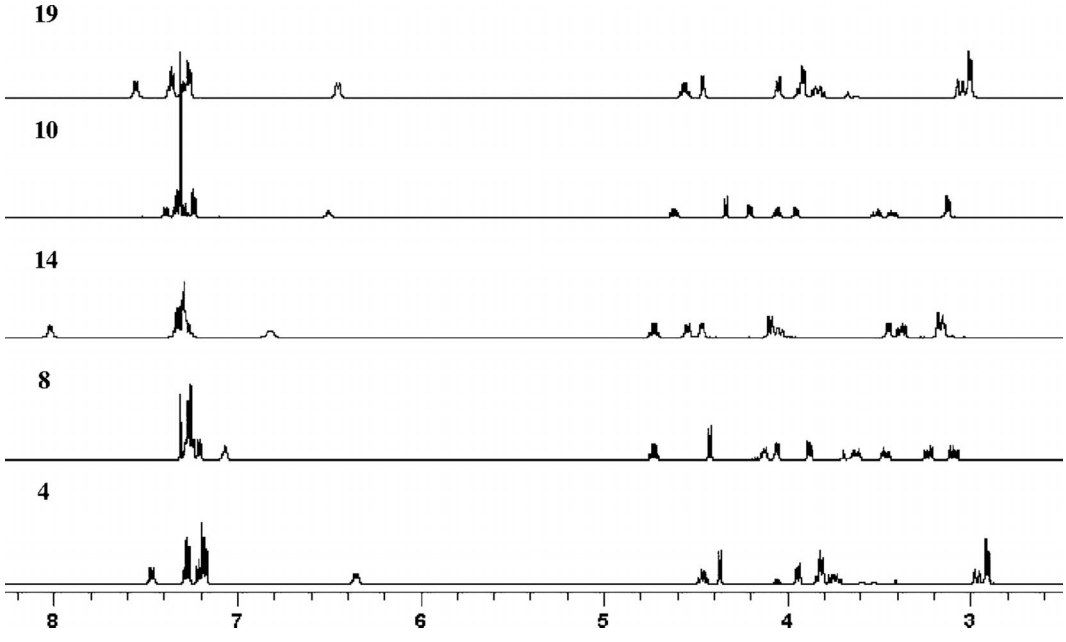


Figure 1. ^1H NMR spectra of cyclic peptides.

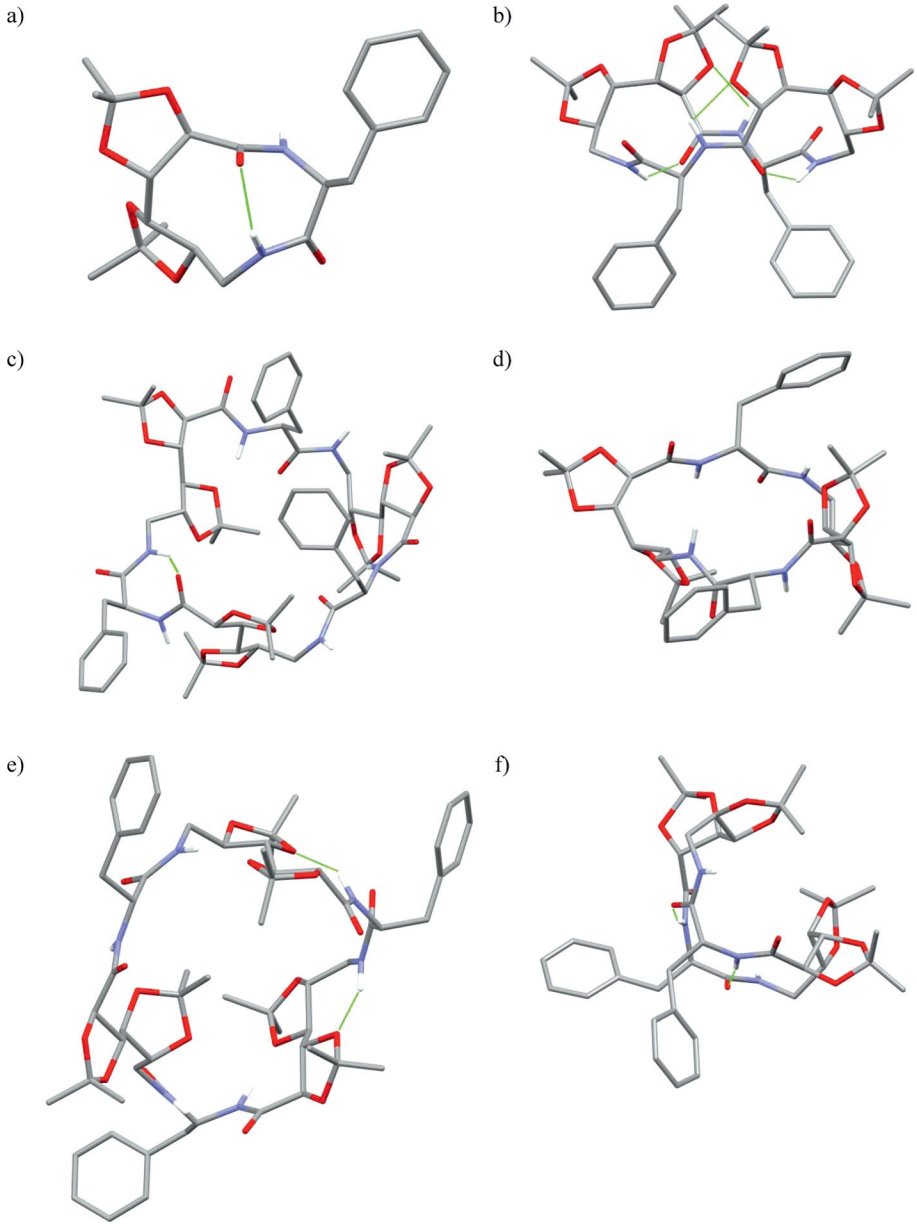


Figure 2. Representative lowest-energy structures of **4** (a), **8** (b), **14** (c), **10** (d) and **19** (e) calculated by ROESY-restrained MD with the fewest violations of ROESY data, and X-ray analysis of cyclopeptide **14** (f).

2D NOESY and ROESY spectra with the aid of molecular modelling protocols. In particular, a set of structures consistent with the NMR spectroscopic analyses were generated by employing restrained MD simulations followed by energy minimisation with the AMBER force field. The conformations with the lowest internal energy and the lowest number of violations were selected from the experimental data and analysed (see Figure 2 and Supporting Information).

The representative structure of dipeptide **4** calculated by MD is the single conformer represented in Figure 2 (a). The calculated coupling constants and NOEs for **4** are in good agreement with the experimental data (Table 1 and the Supporting Information). The structure of this cyclic dipeptide **4** is compatible with an inverse γ-turn centred on the Phe moiety (ϕ: 67.6°; ψ: –55.8°). In this structure, ^{2}Saa NH is involved in an explicit hydrogen bond with ^{2}Saa C=O (2.02 Å) and this stabilises the structure. This situation is also consistent with the chemical shifts of the NH proton. Thus, while ^{1}Phe NH resonates at δ = 6.35 ppm, ^{2}Saa NH (involved in hydrogen bonding) appears downfield at δ = 7.46 ppm (Figure 1).

As far as tetrapeptide **8** is concerned, the conformational analysis protocol predicted the existence of an equilibrium between the three conformers A, B and C (20:20:60). The major conformer is C (Figure 2, b), which has a highly symmetrical structure that is stabilised by hydrogen bonding between all the NH moieties. In particular, ^{2}Saa NH and ^{4}Saa NH are hydrogen-bonded with ^{4}Saa C=O and ^{2}Saa C=O with distances of 1.89 and 1.91 Å, respectively, whereas

Table 1. Experimental and theoretical coupling constants for cyclic peptides **4**, **8**, **10**, **14** and **19**.

Protons	Residue	**4**		**8**				**10**		**14**	
		Exp.	Theor.	Exp.	Theor.	Exp.	Theor.	Exp.	Theor.	Exp.	Theor.
Hα,Hβ	^{2}Saa	6.6	6.5	6.7	6.2	6.5	7.2	9.5	10.3	7.5	6.4
	^{4}Saa	–	–	6.7	6.2	6.5	7.2	9.5	10.3	7.5	9.4
	^{6}Saa	–	–	–	–	6.5	7.2	–	–	7.5	9.9
Hβ,Hγ	^{2}Saa	2.1	2.8	4.1	4.2	3.5	3.8	2.4	2.1	7.2	2.0
	^{4}Saa	–	–	4.1	3.3	3.5	3.4	2.4	1.6	7.2	6.5
	^{6}Saa	–	–	–	–	3.5	3.9	–	–	7.2	9.4
Hγ,Hδ	^{2}Saa	8.3	7.9	8.2	9.3	7.9	8.6	10.1	9.8	10.0	9.7
	^{4}Saa	–	–	8.2	9.3	7.9	8.8	10.1	9.7	10.0	9.9
	^{6}Saa	–	–	–	–	7.9	8.6	–	–	10.0	8.3
Hδ,Hε	^{2}Saa	8.9	9.3	4.9	3.8	5.5	5.4	3.3	1.9	2.2	2.5
	^{4}Saa	–	–	4.9	3.7	5.5	5.0	3.3	4.1	2.2	4.2
	^{6}Saa	–	–	–	–	5.5	5.2	–	–	2.2	2.8
Hδ,H′ε	^{2}Saa	–	–	9.5	10.6	7.9	7.9	9.3	10.2	8.2	9.6
	^{4}Saa	–	–	9.5	10.4	7.9	7.5	9.3	10.4	8.2	11.0
	^{6}Saa	–	–	–	–	7.9	7.8	–	–	8.2	10.9
Hα,CHPh	^{1}Phe	7.8	3.1	6.7	5.2	7.5	7.5	11.3	11.8	11.5	11.8
	^{3}Phe	–	–	6.7	5.2	7.5	7.7	11.3	11.8	11.5	7.1
	^{5}Phe	–	–	–	–	7.5	7.7	–	–	11.5	10.0
Hα,CH′Ph	^{1}Phe	15.4	11.4	8.1	7.2	–	–	3.1	3.1	–	2.9
	^{3}Phe	–	–	8.1	7.4	–	–	3.1	3.0	–	1.8
	^{5}Phe	–	–	–	–	–	–	–	–	–	3.7

^{1}Phe NH and ^{3}Phe NH are hydrogen-bonded to the corresponding O atom of the SAA (2.11 and 2.10 Å, respectively). The structures of the minor conformers are similar and analogous hydrogen bonds are formed. Indeed, the only difference between these conformers is that they have less symmetrical structures than the major conformer.

The MD-derived conformational equilibrium of tetrapeptide **14**, which contains D-Phe instead of the parent L-amino acid residue, shows the presence of two conformers, A and B (60:40). In this case, hydrogen bonds are not observed. The peptide bonds are fairly extended. Short intramolecular CH/Ar distances were found between the isopropylidene protecting group and the aromatic carbon of one phenylalanine residue (2.58 Å). One additional NH/π contact was also found between ^{2}Saa NH and the aromatic ring of Phe (2.7 Å). Thus, the molecule adopts a compact structure that is stabilised by non-polar contacts, without any intramolecular hydrogen bonds (Figure 2, c). It is noteworthy that the crystal structure of peptide **14** is different (Figure 2, f) to that observed in solution. In the solid state, this molecule has a pseudo-chair-like structure stabilised by hydrogen bonding between NH and C=O groups on opposite sides of the ring (^{1}Phe NH–^{3}Phe C=O 1.91 Å; ^{3}Phe NH19–^{1}Phe C=O 1.93 Å). However, the coupling constants calculated for the crystal structure are very different to those observed experimentally; thus confirming the significant differences between the structure of the peptide in solution and that in the solid state.

According to MD calculations for the structure of **14** in solution, the tetrapeptide forms no hydrogen bonds in solution. However, in the NMR spectrum of **14**, the signals of the amide protons are shifted downfield; this is a typical sign of the formation of hydrogen bonds and would mean that the structure in solution would be comparable to that found by crystal analysis. Because it is very difficult to base the existence of hydrogen-bonded species exclusively on chemical shifts and to confirm our hypothesis, we performed H/D exchange experiments. However, the NH exchange behaviour was indeed similar for all of the cyclic peptides and no clear-cut conclusions could be addressed. It is probable that there is certain population of a hydrogen-bonded species for **14**, but its lifetime is short and cannot be experimentally detected.

The hexamer **10** has three slightly different conformers, A, B and C (90:5:5), in equilibrium. Only one hydrogen bond is observed in the major isomer (Figure 2, d) and there are no salient structural features. Folding is again present in the sugar residue, while the peptide bonds are extended.

The representative structure of hexamer **19**, as calculated by MD, involves three conformations in equilibrium, A, B and C (20:20:60). Two hydrogen bonds are observed in the major isomer (Figure 2, e) and, once again, folding is evident in the sugar residue, while the peptide bonds are extended.

Conclusions

We have prepared a variety of cyclopeptides based on alternate units of D- or L-Phe and a galactose-derived ε-amino acid. The conformational properties of these cyclopeptides have been analysed and it was found that they displayed distinct topological features. Cyclodipeptide **4** is a γ-turn mimetic, which could be useful as a template in the preparation of molecular entities with different applications. The L-cyclotetrapeptide has a highly symmetrical structure stabilised by internal hydrogen bonding. In contrast, the D-cyclotetrapeptide has a 3D structure that is largely dominated by the tendency of the sugar residue to

fold, while the amide bonds adopt extended conformations close to antiparallel β sheets. The overall structure thus resembles a β hairpin.[17] Finally, the cyclohexamers also display similar behaviour, with the sugar residue folded back, while the peptide bonds are fairly extended. These different topologies may be employed as templates for further decoration with interacting groups for applications in molecular recognition studies.

Experimental Section

General: TLC was performed on aluminium sheets coated with 60 F_{254} silica, visualised by using a spray of 0.2% w/v cerium(IV) sulfate and 5% ammonium molybdate in 2 M sulfuric acid or 0.5% ninhydrin in methanol. Purification by flash column chromatography was performed on Sorbsil C60 40/60 silica. NMR spectra were recorded on Bruker DPX 400 or DQX 400 spectrometers in the deuterated solvent stated. IR spectra were recorded on a Perkin–Elmer 1750 FTIR spectrophotometer and on a Bruker Tensor 27 FTIR spectrophotometer as thin films on NaCl. Optical rotations were measured on a Perkin–Elmer 241 polarimeter with a path length of 1.0 dm. Concentrations are quoted in g per 100 mL. Low-resolution mass spectra were recorded by using electrospray ionisation (ES) measured on Micromass BioQ II-ZS, Micromass 500 OAT, Micromass TofSpec 2E, Micromass GCT or Micromass Platform 1 mass spectrometers. High-resolution mass spectra were measured on a Waters 2790-Micromass LCT by ES.

Syntheses of the Cyclic Peptides

(6-Azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-L-phenylalanine Methyl Ester (2): Barium hydroxide (1.98 g, 11.56 mmol) was added to a stirred solution of **1** (1.21 g, 3.84 mmol) in THF (37 mL) and water (74 mL). The reaction mixture was stirred for 3 h at room temp. TLC analysis (ethyl acetate/cyclohexane, 1:1) indicated complete conversion of starting material (R_f = 0.4) into one product (R_f = 0.0–0.1). The reaction mixture was acidified by addition of DOWEX 50W (H^+), which was then removed by filtration, and the filtrate was concentrated in vacuo to give 6-azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonic acid. The crude acid was added to a stirred solution of L-phenylalanine hydrochloride methyl ester (1.11 g, 3.84 mmol, quant.) in DMF (35 mL). TBTU (1.85 g, 5.76 mmol) was added and the solution was stirred for 5 min. Triethylamine (1.1 mL, 7.68 mmol) was added and the reaction mixture was stirred at room temp. for 20 h under an atmosphere of argon. TLC analysis (ethyl acetate/cyclohexane, 1:2) indicated complete conversion of the acid starting material (R_f = 0.0) to a major product (R_f = 0.29). The solvent was removed in vacuo (co-evaporation with toluene). The residue was purified by flash column chromatography (ethyl acetate/cyclohexane, 1:2), yielding **2** (1.38 g, 78%) as a colourless oil. R_f = 0.29, ethyl acetate/cyclohexane, 1:2. $[\alpha]_D^{21}$ = +64.9 (c = , 0.5 in $CHCl_3$). $\tilde{\nu}_{max}$ = (NaCl): 3412 (N-H, br.), 2104 (-N_3), 1746 (C=O, CO_2Me), 1684 (C=O, amide) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.31, 1.40, 1.44, 1.48 [4× s, 12 H, 2× C(CH_3)$_2$], 3.16 (ABq, J = 5.8 Hz, 2 H, CH_2Ph), 3.31 (dd, $J_{H\varepsilon,H'\varepsilon}$ = 13.3, $J_{H\delta,H\varepsilon}$ = 4.7 Hz, 1 H, Saa Hε), 3.65 (dd, $J_{H\varepsilon,H'\varepsilon}$ = 13.3, $J_{H\delta,H'\varepsilon}$ = 3.3 Hz, 1 H, Saa H′ε), 3.47 (s, 3 H, CO_2CH_3), 4.06–4.10 (m, 1 H, Saa Hδ), 4.24–4.27 (m, 2 H, Saa Hβ, Saa Hγ), 4.48 (d, $J_{H\alpha,H\beta}$ = 5.8 Hz, 1 H, Saa Hα), 4.86–4.91 (m, 1 H, Phe Hα), 7.05 (d, J = 8.2 Hz, 1 H, NH), 7.12 (ABq, J = 6.8 Hz, 2 H, 2× ArH), 7.25–7.34 (m, 3 H, 3× ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 26.1, 27.3, 27.4, 27.4 [2× C(CH_3)$_2$], 38.2 ($CHPh_2$), 52.1 (C-9), 52.8 (-CH-), 53.0 (CO_2CH_3), 77.3 (C-5), 78.0 (2× -CH), 79.4 (-CH-), 110.8, 112.1 [2× $C(CH_3)_2$], 127.7, 129.1, 129.6, 135.5 (C_6H_5), 170.9 ($CONH$), 171.9 (CO_2CH_3) ppm. MS (ESI^+): m/z (%) = 463.44 (23) $[M + H]^+$. HRMS: calcd. for $C_{22}H_{31}N_4O_7$ $[M + H]^+$ 463.2193; found 463.2190.

(6-Azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-L-phenylalanine (3): Barium hydroxide (1.21 g, 7.09 mmol) was added to a stirred solution of **2** (1.09 g, 2.36 mmol) in THF (37 mL) and water (74 mL). The reaction mixture was stirred for 3 h at room temp. TLC analysis (ethyl acetate/cyclohexane, 1:1) indicated complete conversion of starting material (R_f = 0.4) to one product (R_f = 0.0–0.1). The reaction mixture was acidified by addition of DOWEX 50W (H^+), which was then removed by filtration, and the filtrate was concentrated in vacuo to give **3** (1.02 g, quant.), which was used in the next step without any further purification.

Cyclo[(6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-L-phenylalanine] (4): The crude acid **3** (1.02 g, 2.36 mmol) was dissolved in 1,4-dioxane (8 mL). Pentafluorophenol (870 mg, 2.83 mmol) and EDCI·HCl (543 mg, 4.72 mmol) were added and the mixture was stirred at room temp. under an atmosphere of argon. After 16 h, TLC analysis (ethyl acetate/cyclohexane, 1:2) indicated complete conversion of the starting material (R_f = 0.0) to a major UV-active product (R_f = 0.50). The solvent was removed in vacuo and the residue was dissolved in dichloromethane (50 mL). The solution was washed with an aqueous solution of sodium hydrogen carbonate (5% w/v, 20 mL) and an aqueous solution of citric acid (5% w/v, 20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (ethyl acetate/cyclohexane, 1:4) to yield (6-azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-L-phenylalanine pentafluorophenyl ester (1.14 g, 79%) as a unstable oil. This pentafluorophenyl ester (0.65 g, 1.06 mmol) was dissolved in 1,4-dioxane (60 mL), palladium black (10 mg) was added and the flask was flushed with argon. The reaction mixture was flushed with hydrogen and stirred under a hydrogen atmosphere for 15 h. TLC analysis (ethyl acetate/cyclohexane, 1:1) indicated complete conversion of the starting material (R_f = 0.90 UV) into a major product (R_f = 0.24). The solvent was removed in vacuo and the oil residue was purified by flash column chromatography (ethyl acetate/cyclohexane, 3:2) to yield cyclic dimer **4** (148 mg, 35%) as an off-white solid. R_f = 0.28, ethyl acetate/cyclohexane, 3:2. $[\alpha]_D^{21}$ = +19.9 (c = 2.6 in $CHCl_3$). $\tilde{\nu}_{max}$ = (NaCl): 3383 (N-H, br.), 1668 (C=O, amide) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.32, 1.36, 1.40, 1.47 [4× s, 12 H, 4× C(CH_3)$_2$], 2.90 (d, J = 15.4 Hz, 2 H, CH_2Ph), 2.97–3.04, 3.74–3.77 (2× m, 2 H, Saa Hε, Saa H′ε), 3.80–3.82 (m, 1 H, Saa Hδ), 3.81 (dd, $J_{H\alpha,H\beta}$ = 6.6 Hz, $J_{H\beta,H\gamma}$ = 2.1 Hz, 1 H, Saa Hβ), 3.96 (dd, $J_{H\gamma,H\delta}$ = 8.3 Hz, $J_{H\beta,H\gamma}$ = 2.1 Hz, 1 H, Saa Hγ), 4.36 (d, $J_{H\alpha,H\beta}$ = 6.6 Hz, 1 H, Saa Hα), 4.42–4.49 (m, 1 H, Phe Hα), 6.35 (d, J = 6.4 Hz, 1 H, Phe NH), 7.23–7.36 (m, 5 H, 5× ArH), 7.46 (d, J = 7.5 Hz, 1 H, Saa NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 26.1, 26.5, 26.7, 26.9 [2× C(CH_3)$_2$], 39.8, 40.3 (CH_2Ph, Saa CHδ), 55.1 (Saa CHε), 73.8, 74.2, 79.2, 79.9 (Saa CHα, Phe CHα, Saa CHγ, Saa Hβ), 110.8, 112.1 [2× $C(CH_3)_2$], 127.1, 128.6, 129.2, 136.3 (C_6H_5), 169.7, 172.0 (2× $CONH$) ppm. MS (ESI^+): m/z (%) = 427.18 (29) $[M + Na]^+$. HRMS: calcd. for $C_{21}H_{28}N_2NaO_6$ $[M + Na]^+$ 427.1845; found 427.1851.

(6-Amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-L-phenylalanine Methyl Ester (5): Compound **2** (1.21 g, 2.62 mmol) was dissolved in 1,4-dioxane (60 mL), palladium black (1.21 g) was added and the flask was flushed with argon. The reaction mixture was flushed with hydrogen and stirred under a hydrogen atmosphere for 15 h. TLC analysis (ethyl acetate/cyclohexane, 1:1) indicated complete conversion of the starting material. The solvent was

removed in vacuo to afford **5** (1.10 g, 2.62 mmol), which was used without any further purification.

(6-Azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-L-phenylalanine–(6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-L-phenylalanine Methyl Ester (6): Compound **3** (0.95 g, 2.26 mmol) was added to a stirred solution of **5** (0.91 g, 2.26 mmol) in DMF (18 mL). TBTU (1.02 g, 3.14 mmol) was added and the solution was stirred for 5 min. Triethylamine (0.36 mL, 2.26 mmol) was added and the reaction mixture was stirred at room temp. for 20 h under an atmosphere of argon. TLC analysis (ethyl acetate/cyclohexane, 1:1) indicated complete conversion of the acid starting material (R_f = 0.0) into a major product (R_f = 0.29). The solvent was removed in vacuo. The residue purified by flash column chromatography (ethyl acetate/cyclohexane, 1:1) to yield **6** (1.17 g, 52%) as a colourless oil. R_f = 0.29, ethyl acetate/cyclohexane, 1:1. $[\alpha]_D^{21}$ = +22.9 (c = 1.3 in $CHCl_3$). $\tilde{\nu}_{max}$ = (NaCl): 3321 (N-H, br.), 2103 (-N_3), 1746 (C=O, CO_2Me), 1672 (C=O, amide) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.30, 1.31, 1.32, 1.35, 1.44, 1.46, 1.49 [7× s, 24 H, 8× C(CH_3)$_2$], 3.05–3.09 (m, 2 H, CH_2Ph), 3.16 (ABq, J = 5.6 Hz, 2 H, CH_2Ph), 3.32 (dd, J = 13.6, J = 4.8 Hz, 1 H, ^{2}Saa Hδ), 3.37–3.49 (m, 2 H, ^{1}Saa Hε, ^{1}Saa H′ε), 3.62–3.67 (m, 2 H, ^{1}Saa Hγ, ^{2}Saa Hγ), 3.74 (s, 3 H, CO_2CH_3), 3.96–4.01 (m, 1 H, ^{1}Saa Hδ), 4.07 (dd, $J_{H\varepsilon,H'\varepsilon}$ = 8.0, $J_{H\delta,H'\varepsilon}$ = 5.6 Hz, 1 H, ^{2}Saa H′ε), 4.17–4.28 (m, 3 H, ^{1}Saa Hβ, ^{2}Saa Hβ, ^{2}Saa Hε), 4.41 (d, $J_{H\alpha,H\beta}$ = 6.0 Hz, 1 H, ^{1}Saa Hα), 4.46 (d, $J_{H\alpha,H\beta}$ = 6.0 Hz, 1 H, ^{2}Saa Hα), 4.56–4.62 (m, 1 H, ^{2}Phe Hα), 4.84–4.89 (m, 1 H, ^{1}Phe Hα), 6.07–6.09 (m, 1 H, ^{1}Saa NH), 7.07 (d, J = 8.4 Hz, 1 H, ^{1}Phe NH), 7.11–7.33 (m, 11 H, 10× ArH, ^{2}Phe NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 26.1, 26.3, 27.1, 27.4, 27.5 (8× CH_3), 38.2, 39.2, 41.2, 52.1 (2× CH_2Ph, ^{1}Saa CHε, ^{2}Saa CHε), 52.8, 53.1, 54.8, 76.7, 76.9, 77.4, 77.7, 78.9, 79.1, 79.5 (10× -CH-), 110.1, 110.8, 112.1 [4× C(CH_3)$_2$], 127.6, 127.7, 129.1, 129.2, 129.6, 135.9, 136.7 (2× C_6H_5), 170.6, 170.8, 171.1, 171.8 (3× CONH, CO_2CH_3) ppm. MS (ESI^+): m/z (%) = 865.74 (100) $[M - H]^+$, 866.74 (50) $[M]^+$. HRMS: calcd. for $C_{43}H_{57}N_6O_{14}$ $[M - H]^+$: 865.3984; found 865.3994.

(6-Azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-L-phenylalanine–(6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-L-phenylalanine Pentafluorophenyl Ester (7): Barium hydroxide (59 mg, 0.35 mmol) was added to a stirred solution of **6** (0.10 g, 0.12 mmol) in THF (5 mL) and water (10 mL). The reaction mixture was stirred for 3 h at room temp. TLC analysis (ethyl acetate/cyclohexane, 1:1) indicated complete conversion of starting material (R_f = 0.29) into one product (R_f = 0.0–0.1). The reaction mixture was acidified by addition of DOWEX 50W (H^+), which was then removed by filtration, and the filtrate was concentrated in vacuo to give **7** (0.10 g, quant.), which was used without any further purification.

Cyclo[(6-azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-L-phenylalanine–(6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-L-phenylalanine] (8): The crude acid **7** (101 mg, 0.12 mmol) was dissolved in 1,4-dioxane (2 mL). Pentafluorophenol (43 mg, 0.32 mmol) and EDCI·HCl (27 mg, 0.14 mmol) were added and the mixture was stirred at room temp. under an atmosphere of argon. After 16 h, TLC analysis (ethyl acetate/cyclohexane, 1:1) indicated complete conversion of the starting material (R_f = 0.0) into a major UV-active product (R_f = 0.40). The solvent was removed in vacuo and the residue dissolved in dichloromethane (10 mL). The solution was washed with an aqueous solution of sodium hydrogen carbonate (5% w/v, 5 mL) and an aqueous solution of citric acid (5% w/v, 5 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was filtered through silica to yield (6-azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-L-phenylalanine–(6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-L-phenylalanine pentafluorophenyl ester, which was used without any further purification. This pentafluorophenyl ester was dissolved in 1,4-dioxane (4 mL), palladium black (43 mg) was added and the flask was flushed with argon. The reaction mixture was flushed with hydrogen and stirred under a hydrogen atmosphere for 15 h. TLC analysis (ethyl acetate/cyclohexane, 2:3) indicated complete conversion of the starting material (R_f = 0.31 UV) into a major product (R_f = 0.42). The solvent was removed in vacuo and the oil residue was purified by flash column chromatography (ethyl acetate/cyclohexane, 2:1) to yield cyclic tetramer **8** (21.8 mg, 22%) as an off-white solid. R_f = 0.30, ethyl acetate/cyclohexane, 2:1. ^1H NMR ($CDCl_3$): δ = 1.32, 1.36, 1.40, 1.47 [4× s, 24 H, 8× C(CH_3)$_2$], 3.06–3.12 (dd, 2 H, J = 8.1 Hz, J = 6.7 Hz, 2× CHPh), 3.20–3.25 (dd, J = 8.1 Hz, J = 6.7 Hz, 4 H, 2× CHPh), 3.42–3.49 (dd, 2 H, $J_{H\varepsilon,H\delta}$ = 4.9 Hz, ^{1}Saa Hε, ^{2}Saa Hε), 3.59–3.65 (dd, $J_{H'\varepsilon,H\delta}$ = 9.5 Hz, 2 H, ^{1}Saa H′ε, ^{2}Saa H′ε), 3.87 (dd, 2 H, $J_{H\gamma,H\delta}$ = 8.2 Hz, $J_{H\beta,H\gamma}$ = 4.1 Hz, 2 H, ^{1}Saa Hγ, ^{2}Saa Hγ), 4.05 (dd, $J_{H\alpha,H\beta}$ = 6.7, $J_{H\beta,H\gamma}$ = 4.1 Hz, ^{1}Saa Hβ, ^{2}Saa Hβ), 4.12 (ddd, 2 H, $J_{H\varepsilon,H\delta}$ = 4.9 Hz, $J_{H'\varepsilon,H\delta}$ = 9.5 Hz, $J_{H\gamma,H\delta}$ = 8.2 Hz, ^{1}Saa Hδ, ^{2}Saa Hδ), 4.42 (d, $J_{H\alpha,H\beta}$ = 6.7 Hz, 2 H, ^{1}Saa Hα, ^{2}Saa Hα), 4.73 (dd, J = 6.7, J = 8.1 Hz, 2 H, ^{1}Phe Hα, ^{2}Phe Hα), 7.06 (br. s, 2 H, ^{1}Saa NH, ^{2}Saa NH), 7.20 (br. s, 2 H, ^{1}Phe NH, ^{2}Phe NH), 7.23–7.36 (m, 10 H, 10× ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 26.1, 26.5, 26.7, 26.9 [4× C(CH_3)$_2$], 39.8, 40.3 (2× CH_2Ph, ^{1}Saa CHε, ^{2}Saa CHε), 55.1 (^{1}Saa CHδ, ^{2}Saa CHδ), 73.8, 74.2, 79.2, 80.0 (^{1}Saa CHβ, ^{2}Saa CHβ, ^{1}Saa CHγ, ^{2}Saa CHγ, ^{1}Saa CHα, ^{2}Saa CHα, ^{1}Phe CHα, ^{2}Phe CHα), 110.8, 112.1 [4× C(CH_3)$_2$], 127.1, 128.6, 129.2, 136.3 (2× C_6H_5), 169.7, 172.0 (2× CONH) ppm. MS (ESI^+): m/z (%) = 831.38 (100) $[M + Na]^+$. HRMS: calcd. for $C_{42}H_{56}N_4NaO_{12}$ $[M + Na]^+$: 831.3795; found 831.3788.

(6-Azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-L-phenylalanine–(6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-L-phenylalanine–(6-aAmino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-L-phenylalanine Methyl Ester (9): Compound **7** (724 mg, 0.86 mmol) was added to a stirred solution of **5** (388 mg, 0.86 mmol) in DMF (12 mL). TBTU (334 mg, 1.03 mmol) was added and the solution was stirred for 5 min. Triethylamine (0.12 mL, 0.86 mmol) was added and the reaction mixture was stirred at room temp. for 20 h under an atmosphere of argon. TLC (ethyl acetate/cyclohexane, 2:1) indicated complete conversion of the acid starting material (R_f = 0.0) to a major product (R_f = 0.29). The solvent was removed in vacuo (co-evaporation with toluene). The residue was pre-adsorbed into silica and purified by flash column chromatography (ethyl acetate/cyclohexane, 2:1) to yield **9** (415 mg, 38%) as a colourless oil. R_f = 0.27, ethyl acetate/cyclohexane, 2:1. $[\alpha]_D^{23}$ = +10.7 (c = 0.5 in $CHCl_3$). $\tilde{\nu}_{max}$ = (NaCl): 3317 (N-H, br.), 2103 (-N_3), 1744 (C=O, CO_2Me), 1664 (C=O, amide) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.34, 1.36, 1.37, 1.39, 1.40, 1.40, 1.49, 1.51, 1.53 [9× s, 36 H, 12× C(CH_3)$_2$], 3.08–3.15 (m, 4 H, 2× CH_2Ph), 3.20 (ABq, J = 5.5 Hz, 2 H, CH_2Ph), 3.34–3.66 (m, 6 H, ^{1}Saa Hε, ^{2}Saa Hε, ^{3}Saa Hε, ^{1}Saa H′ε, ^{2}Saa H′ε, ^{3}Saa H′ε), 3.67–3.71 (m, 2 H, ^{1}Saa Hγ, ^{2}Saa Hγ), 3.77 (s, 3 H, COCH_3), 4.01–4.06 (m, 2 H, ^{1}Saa Hδ, ^{2}Saa Hδ), 4.10 (dd, J = 8.0, J = 5.6 Hz, 1 H, ^{3}Saa Hγ), 4.20–4.31 (m, 4 H, ^{1}Saa Hβ, ^{2}Saa Hβ, ^{3}Saa Hβ, ^{3}Saa Hδ), 4.43 (d, $J_{H\alpha,H\beta}$ = 6.0 Hz, 1 H, ^{2}Saa Hα), 4.45 (d, $J_{H\alpha,H\beta}$ = 6.0 Hz, 1 H, ^{1}Saa Hα), 4.50 (d, $J_{H\alpha,H\beta}$ = 5.8 Hz, 1 H, ^{3}Saa Hα), 4.61–4.68 (m, 2 H, ^{2}Phe Hα, ^{3}Phe Hα), 4.89–4.93 (m, 1 H, ^{1}Phe Hα), 6.16–6.19 (m, 2 H, ^{1}Saa NH, ^{2}Saa NH), 7.10 (d, J = 6.8 Hz, 1 H, ^{1}Phe NH), 7.25–7.36 (m, ^{2}Phe NH, ^{3}Phe NH, 15× ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 25.6, 25.8, 26.7, 26.87, 27.02 (12× CH_3), 37.7, 38.8, 40.7, 40.7, 51.7 (3× CH_2Ph, ^{1}Saa CHε, ^{2}Saa CHε, ^{3}Saa CHε), 51.7, 52.3, 52.6, 54.3, 54.4, 76.4, 76.7, 77.0, 77.2, 77.6, 78.3, 78.5,

78.6, 78.7, 80.0 (15× -CH-), 109.6, 109.7, 110.3, 111.6 [6× $C(CH_3)_2$], 127.1, 127.2, 128.6, 128.7, 129.2, 135.4, 136.2 (3× C_6H_5), 170.0, 170.3, 170.4, 170.6, 171.3 (5× *C*ONH, CO_2CH_3) ppm. MS (ESI^+): *m*/*z* (%) = 1270.38 (100) $[M - H]^+$.

Cyclo[(6-Amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-L-phenylalanine–(6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-L-phenylalanine–(6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-L-phenylalanine] (10): Barium hydroxide (77 mg, 0.45 mmol) was added to a stirred solution of **9** (190 mg, 0.15 mmol) in THF (4 mL) and water (8 mL). The reaction mixture was stirred for 3 h at room temp. TLC analysis (ethyl acetate/cyclohexane, 1:1) indicated complete conversion of the starting material into one product. The reaction mixture was acidified by addition of DOWEX 50W (H^+), which was then removed by filtration, and the filtrate was concentrated in vacuo to give (6-azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-L-phenylalanine–(6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-L-phenylalanine–(6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-L-phenylalanine. The crude acid was dissolved in 1,4-dioxane (2 mL). Pentafluorophenol (55 mg, 0.30 mmol) and EDCI·HCl (34 mg, 0.18 mmol) were added and the mixture was stirred at room temp. under an atmosphere of argon. After 16 h, TLC analysis (ethyl acetate/cyclohexane, 1:1) indicated complete conversion of the starting material (R_f = 0.0) into a major UV-active product (R_f = 0.3). The solvent was removed in vacuo and the residue was dissolved in dichloromethane (10 mL). The solution was washed with an aqueous solution of sodium hydrogen carbonate (5% w/v, 5 mL) and an aqueous solution of citric acid (5% w/v, 5 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (ethyl acetate/cyclohexane, 1:1) to yield (6-azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-L-phenylalanine–(6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-L-phenylalanine–(6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-L-phenylalanine pentafluorophenyl ester. This pentafluorophenyl ester was dissolved in 1,4-dioxane (6 mL). Palladium black (57 mg) was added and the flask was flushed with argon. The reaction mixture was flushed with hydrogen and stirred under a hydrogen atmosphere for 15 h. TLC analysis (ethyl acetate/cyclohexane, 1:1) indicated complete conversion of the starting material (R_f = 0.30 UV) into a major product (R_f = 0.1). The solvent was removed in vacuo and the oil residue was purified by flash column chromatography (ethyl acetate/cyclohexane, 3:1) to yield cyclic tetramer **10** (25 mg, 14%) as an off-white solid. R_f = 0.28, ethyl acetate/cyclohexane, 3:2. $[\alpha]_D^{23}$ = +1.2 (*c* = 0.2 in $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 1.41–1.52 [m, 36 H, 12× $C(CH_3)_2$], 3.12 (s, 6 H, 3× CH_2Ph), 3.39–3.45 (m, 3 H, ^{1}Saa H′ε, ^{2}Saa H′ε, ^{3}Saa H′ε), 3.48–3.54 (m, 3 H, ^{1}Saa Hε, ^{2}Saa Hε, ^{3}Saa Hε), 3.94 (dd, 3 H, $J_{H\beta,H\gamma}$ = 3.5 Hz, $J_{H\gamma,H\delta}$ = 7.9 Hz, ^{1}Saa Hγ, ^{2}Saa Hγ, ^{3}Saa Hγ), 4.05 (ddd, $J_{H\gamma,H\delta}$ = 7.9, $J_{H\delta,H\varepsilon}$ = 5.5, $J_{H\delta,H'\varepsilon}$ = 7.9 Hz, 3 H, ^{1}Saa Hδ, ^{2}Saa Hδ, ^{3}Saa Hδ), 4.19 (dd, $J_{H\alpha,H\beta}$ = 6.5, $J_{H\beta,H\gamma}$ = 3.5 Hz, 3 H, ^{1}Saa Hβ, ^{2}Saa Hβ, ^{3}Saa Hβ), 4.32 (d, $J_{H\alpha,H\beta}$ = 6.5 Hz, 3 H, ^{1}Saa Hα, ^{2}Saa Hα, ^{3}Saa Hα), 4.61 (d, *J* = 7.5 Hz, 2 H, ^{1}Phe Hα, ^{2}Phe Hα, ^{3}Phe Hα), 6.50 (br. s, 3 H, ^{1}Phe NH, ^{2}Phe NH, ^{3}Phe NH), 7.23–7.36 (m, 10 H, 10× Ar*H*), 7.38 (br. s, 3 H, ^{1}Saa NH, ^{2}Saa NH, ^{3}Saa NH) ppm. MS (ESI^+): *m*/*z* (%) = 1235.57 (23) $[M + Na]^+$. HRMS: calcd. for $C_{63}H_{84}N_6NaO_{18}$ 1235.5740; found 1235.5745.

(6-Azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-D-phenylalanine Methyl Ester (11): Barium hydroxide (1.98 g, 11.56 mmol) was added to a stirred solution of **1** (1.08 g, 3.42 mmol) in THF (30 mL) and water (60 mL). The reaction mixture was stirred for 3 h at room temp. TLC analysis (ethyl acetate/cyclohexane, 1:1) indicated complete conversion of the starting material (R_f = 0.4) into one product (R_f 0.0–0.1). The reaction mixture was acidified by addition of DOWEX 50W (H^+), which was then removed by filtration, and the filtrate was concentrated in vacuo to give 6-azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonic acid. The crude acid was added to a stirred solution of D-phenylalanine hydrochloride methyl ester (0.74 g, 3.42 mmol, quant.) in DMF (30 mL). TBTU (1.33 g, 4.11 mmol) was added and the solution was stirred for 5 min. Triethylamine (1.0 mL, 6.85 mmol) was added and the reaction mixture was stirred at room temp. for 20 h under an atmosphere of argon. TLC analysis (ethyl acetate/cyclohexane, 1:2) indicated complete conversion of the acid starting material (R_f = 0.0) into a major product (R_f = 0.29). The solvent was removed in vacuo (co-evaporation with toluene). The residue was pre-adsorbed into silica and purified by flash column chromatography (ethyl acetate/cyclohexane, 1:2) to yield **11** (1.18 g, 75%) as a colourless oil. R_f = 0.29, ethyl acetate/cyclohexane, 1:2. $[\alpha]_D^{22}$ = +3.0 (*c* = 1.2 in $CHCl_3$). $\tilde{\nu}_{max}$ = (NaCl): 3412 (N-H, br.), 2104 (-N_3), 1744 (C=O, CO_2Me), 1679 (C=O, amide) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.17, 1.40, 1.43, 1.46 [4× s, 12 H, 2× $C(CH_3)_2$], 3.01–3.33 (m, 2 H, CH_2Ph), 3.63 (dd, $J_{H\varepsilon,H'\varepsilon}$ = 13.3, $J_{H\delta,H\varepsilon}$ = 3.3 Hz, 1 H, ^{1}Saa Hε), 3.65 (dd, $J_{H\varepsilon,H'\varepsilon}$ = 13.3, $J_{H\delta,H'\varepsilon}$ = 3.3 Hz, 1 H, ^{1}Saa H′ε), 3.76 (s, 3 H, CO_2CH_3), 4.04–4.31 (m, 3 H, ^{1}Saa Hγ, ^{1}Saa Hδ, ^{1}Saa Hβ), 4.48 (d, $J_{H\alpha,H\beta}$ = 9.0 Hz, 1 H, ^{1}Saa Hα), 4.83–4.94 (m, 1 H, 2-H), 6.94 (d, *J* = 8.0 Hz, 1 H, NH), 7.10–7.32 (m, 5 H, 5× Ar*H*) ppm. ^{13}C NMR ($CDCl_3$): δ = 26.3, 27.3, 27.3, 27.4 [2× $C(CH_3)_2$], 38.2 ($CHPh_2$), 52.0 (^{1}Saa CHε), 52.9 (-CH-), 53.0 (CO_2CH_3), 77.0, 77.6, 78.0, 79.4 (4× -CH-), 110.7, 111.1 [2× $C(CH_3)_2$], 127.6, 129.1, 129.6, 136.1 (C_6H_5), 170.7 (*C*ONH), 172.0 (CO_2CH_3) ppm. MS (ESI^+): *m*/*z* (%) = 463.44 (25) $[M + H]^+$. HRMS: calcd. for $C_{22}H_{31}N_4O_7$ $[M + H]^+$ 463.2195; found 463.2190.

(6-Azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-D-phenylalanine Acid (12): Barium hydroxide (0.74 g, 4.31 mmol) was added to a stirred solution of **18** (0.66 g, 1.44 mmol) in THF (22 mL) and water (44 mL). The reaction mixture was stirred for 3 h at room temp. TLC analysis (ethyl acetate/cyclohexane, 1:1) indicated complete conversion of the starting material (R_f 0.4) into one product (R_f = 0.0–0.1). The reaction mixture was acidified by addition of DOWEX 50W (H^+), which was then removed by filtration, and the filtrate was concentrated in vacuo to give (6-azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-D-phenylalanine (0.62 g, quant.), which was used without any further purification.

Cyclo[(6-Azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-D-phenylalanine–(6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-D-phenylalanine] (14): The crude acid (0.62 g, 1.44 mmol) was dissolved in 1,4-dioxane (8 mL). Pentafluorophenol (529 mg, 2.87 mmol) and EDCI·HCl (330 mg, 1.72 mmol) were added and the mixture was stirred at room temp. under an atmosphere of argon. After 16 h, TLC analysis (ethyl acetate/cyclohexane, 1:2) indicated complete conversion of the starting material (R_f = 0.0) into a major UV-active product (R_f 0.50). The solvent was removed in vacuo and the residue dissolved in dichloromethane (50 mL). The solution was washed with an aqueous solution of sodium hydrogen carbonate (5% w/v, 20 mL) and an aqueous solution of citric acid (5% w/v, 20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (ethyl acetate/cyclohexane, 1:4) to yield (6-azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-D-phenylalanine pentafluorophenyl ester (0.67 g, 78%) as a unstable oil, which was directly dissolved in 1,4-dioxane (60 mL). Palladium black (67 mg) was added and the flask was flushed with argon. The reaction mixture was flushed with hydrogen and stirred under a hydrogen atmosphere for 15 h. TLC analysis (ethyl acetate/cyclo-

hexane, 1:1) indicated complete conversion of the starting material (R_f = 0.90 UV) into a major product (R_f = 0.24). The solvent was removed in vacuo and the oil residue was purified by flash column chromatography (ethyl acetate/cyclohexane, 3:2) to yield cyclic tetramer **14** (161 mg, 38%) as an off-white solid. R_f = 0.30, ethyl acetate/cyclohexane, 2:1. $[\alpha]_D^{23}$ = +2.8 (c = 0.4 in $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.37, 1.45, 1.46, 1.49 [4× s, 24 H, 4× C(CH_3)$_2$], 3.13–3.17 (m, 4 H, ^{1}Saa Hε, ^{2}Saa Hε, 2× C*H*Ph), 3.37 (dd, J = 8.2 Hz, J = 11.3 Hz, 2 H, C*H*Ph), 3.44 (d, $J_{H\gamma,H\delta}$ = 10.1 Hz, 2 H, ^{1}Saa Hγ, ^{2}Saa Hγ), 4.02–4.06 (m, 2 H, ^{1}Saa H′ε, ^{2}Saa H′ε), 4.09 (d, $J_{H\alpha,H\beta}$ = 9.5 Hz, 2 H, ^{1}Saa Hβ, ^{2}Saa Hβ), 4.46 (d, $J_{H\gamma,H\delta}$ = 10.1 Hz, 2 H, ^{1}Saa Hδ, ^{2}Saa Hδ), 4.54 (d, $J_{H\alpha,H\beta}$ = 9.5 Hz, 2 H, ^{1}Saa Hα, ^{2}Saa Hα), 4.72 (dd, J = 7.2, J = 11.3 Hz, 2 H, ^{1}Phe Hα, ^{2}Phe Hα), 6.82 (d, J = 8.2 Hz, 2 H, ^{1}Saa NH, ^{2}Saa NH), 7.24–7.34 (m, 10 H, 10× Ar*H*), 8.01 (d, J = 7.2 Hz, 2 H, ^{1}Phe NH, ^{2}Phe NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 25.8, 26.1, 26.7, 26.8 [4× C(CH_3)$_2$], 30.3, 39.8 (2× CH_2Ph, ^{1}Saa CHε, ^{2}Saa CHε), 54.6 (^{1}Saa CHδ, ^{2}Saa CHδ), 73.5, 75.2, 76.6, 78.4 (^{1}Phe CHα, ^{2}Phe CHα, ^{1}Saa CHα, ^{2}Saa CHα, ^{1}Saa CHβ, ^{2}Saa CHβ, ^{1}Saa CHγ, ^{2}Saa CHγ), 108.8, 111.9 [4× C(CH_3)$_2$], 127.0, 128.7, 129.2, 136.3 (2× C_6H_5), 169.9, 171.9 (4× *C*ONH) ppm. MS (ESI$^+$): m/z (%) = 831.38 (100) [M + Na]$^+$.

(6-Amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-D-phenylalanine Methyl Ester (15): Compound **11** (1.63 g, 3.52 mmol) was dissolved in 1,4-dioxane (80 mL). Palladium black (0.20 g) was added and the flask was flushed with argon. The reaction mixture was flushed with hydrogen and left stirring under a hydrogen atmosphere for 15 h. TLC (ethyl acetate/cyclohexane, 1:1) indicated complete conversion of the starting material. The solvent was removed in vacuo to afford **15** (1.51 g, quant.), which was used without any further purification.

(6-Azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-D-phenylalanine–(6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-D-phenylalanine Methyl Ester (16): Compound **12** (1.55 g, 3.52 mmol) was added to a stirred solution of **15** (1.51 g, 3.52 mmol) in DMF (20 mL). TBTU (1.37 g, 4.23 mmol) was added and the solution was stirred for 5 min. Triethylamine (0.50 mL, 3.53 mmol) was added and the reaction mixture was left stirring at room temp. for 20 h under an atmosphere of argon. TLC analysis (ethyl acetate/cyclohexane, 1:1) indicated complete conversion of the acid starting material (R_f = 0.0) into a major product (R_f = 0.28). The solvent was removed in vacuo. The residue was purified by flash column chromatography to afford **16** (1.68 g, 55%) as a colourless oil. R_f = 0.28, ethyl acetate/cyclohexane, 1:1. $[\alpha]_D^{21}$ = +22.9 (c = 1.3 in $CHCl_3$); $\tilde{\nu}_{max}$ = (NaCl): 3331 (N-H, br.), 2103 (-N_3), 1744 (C=O, CO_2Me), 1667 (C=O, amide) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.16, 1.17, 1.31, 1.39, 1.43 [5× s, 24 H, 8× C(CH_3)$_2$], 2.99–3.28 (m, 5 H, 2× CH_2Ph, ^{2}Saa Hδ), 3.37–3.48 (m, 2 H, ^{1}Saa Hε, ^{2}Saa Hε), 3.54–3.80 (m, 5 H, ^{1}Saa Hγ, ^{2}Saa Hγ, CO_2CH_3), 4.00–4.24 (m, 5 H, ^{1}Saa Hδ, ^{1}Saa H′ε, ^{2}Saa H′ε, ^{1}Saa Hβ, ^{2}Saa Hβ), 4.37–4.44 (m, 2 H, 5-H, 15-H), 4.66 (dd, J = 1.8, J = 3.7 Hz, 1 H, ^{2}Phe Hα), 4.84 (dd, J = 1.8, J = 3.4 Hz, 1 H, ^{1}Phe Hα), 6.33–6.39 (m, 1 H, ^{1}Phe NH), 6.99 (d, J = 2.0 Hz, 1 H, ^{1}Saa NH), 7.08–7.32 (m, 10 H, 10× Ar*H*) ppm. ^{13}C NMR ($CDCl_3$): δ = 25.6, 26.5, 26.0, 26.8, 26.9 (8× CH_3), 37.6, 38.0, 40.3, 51.5 (2× CH_2Ph, ^{1}Saa CHε, ^{2}Saa CHε), 52.3, 52.5, 53.8, 75.8, 76.0, 76.5, 77.1, 77.4, 78.4, 78.7 (10× -CH-), 109.4, 110.1, 111.2 [4× C(CH_3)$_2$], 127.0, 127.1, 128.5, 128.9, 129.0, 135.4, 136.1 (2× C_6H_5), 170.3, 171.4, 171.8 (3× *C*ONH, CO_2CH_3) ppm. MS (ESI$^+$): m/z (%) = 865.75 (49) [M + H]$^+$. HRMS: calcd. for $C_{43}H_{57}N_6O_{14}$ (M – H)$^+$: 865.3984; found 865.3992.

(6-Azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-D-phenylalanine–(6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-D-phenylalanine Acid) (17): Barium hydroxide (318 mg, 1.83 mmol) was added to a stirred solution of **16** (523 mg, 0.61 mmol) in THF (5 mL) and water (10 mL). The reaction mixture was stirred for 3 h at room temp. TLC analysis indicated complete conversion of starting material into one product. The reaction mixture was acidified by addition of DOWEX 50W (H$^+$), which was then removed by filtration and the filtrate was concentrated in vacuo to give **17** (517 mg, 0.61 mmol). The crude acid was used without any further purification.

(6-Azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-D-phenylalanine–(6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-D-phenylalanine–(6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-D-phenylalanine Methyl Ester (18): Compound **17** (517 mg, 0.61 mmol) was added to a stirred solution of (6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-D-phenylalanine (265 mg, 0.61 mmol) in DMF (10 mL). TBTU (238 mg, 0.73 mmol) was added and the solution was stirred for 5 min. Triethylamine (0.09 mL, 0.61 mmol) was added and the reaction mixture was stirred at room temp. for 20 h under an atmosphere of argon. TLC analysis (ethyl acetate/cyclohexane, 2:1) indicated complete conversion of the acid starting material (R_f = 0.0) into a major product (R_f = 0.29). The solvent was removed in vacuo (co-evaporation with toluene). The residue purified by flash column chromatography to yield **18** (202 mg, 30%) as a colourless oil. R_f = 0.27, ethyl acetate/cyclohexane, 2:1. $[\alpha]_D^{23}$ = +5.7 (c = 2.2 in $CHCl_3$); $\tilde{\nu}_{max}$ = (NaCl): 3324 (N-H, br.), 2104 (-N_3), 1744 (C=O, CO_2Me), 1665 (C=O, amide) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.17, 1.19, 1.20, 1.30, 1.32, 1.33, 1.34, 1.40, 1.45 [9× s, 36 H, 12× C(CH_3)$_2$], 3.03–3.10 (m, 4 H, 2× CH_2Ph), 3.18–2.28 (m, 2 H, CH_2Ph), 3.36–3.60 3.74–3.80 (m, 6 H, ^{1}Saa Hε, ^{2}Saa Hε, ^{3}Saa Hε, ^{1}Saa H′ε, ^{2}Saa H′ε, ^{3}Saa H′ε), 3.74–3.80 (m, 2 H, ^{1}Saa Hγ, ^{2}Saa Hγ), 3.73 (s, 3 H, COCH_3), 3.96–4.26 (m, 7 H, ^{1}Saa Hδ, ^{2}Saa Hδ, ^{3}Saa Hδ, ^{3}Saa Hγ, ^{1}Saa Hβ, ^{2}Saa Hβ, ^{3}Saa Hβ), 4.30–4.43 (m, 3 H, ^{1}Saa Hα, ^{2}Saa Hα, ^{3}Saa Hα), 4.60–4.68 (m, 2 H, ^{2}Phe Hα, ^{3}Phe Hα), 4.85 (dd, J = 7.2, J = 3.2 Hz, 1 H, ^{1}Phe Hα), 6.35–6.39 (m, 2 H, ^{1}Saa NH, ^{2}Saa NH), 7.00 (d, J = 7.2 Hz, 1 H, ^{1}Phe NH), 7.10–7.30 (m, 17 H, ^{2}Phe NH, ^{3}Phe NH, 15× Ar*H*) ppm. ^{13}C NMR ($CDCl_3$): δ = 25.7, 26.6, 26.7, 26.9, 27.0 (12× CH_3), 37.7, 38.9, 40.4, 40.6, 51.6 (3× CH_2Ph, ^{1}Saa CHε, ^{2}Saa CHε, ^{3}Saa CHε), 52.4, 52.6, 53.9, 54.0, 75.9, 76.1, 76.6, 77.2, 77.5, 77.6, 77.8, 78.0, 78.4, 78.5, 78.9 (15× -CH-), 109.4, 109.5, 110.2, 111.2, 111.3, 111.4 [6× C(CH_3)$_2$], 127.0, 127.1, 127.2, 128.6, 128.7, 129.1, 135.5, 136.2 (3× C_6H_5), 170.3, 170.4, 170.7, 171.5 (5× *C*ONH, CO_2CH_3) ppm. MS (ESI$^+$): m/z (%) = 1270.38 (100) [M – H]$^+$.

Cyclo[(6-Amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-D-phenylalanine–(6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-D-phenylalanine–(6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-D-phenylalanine] (19): Barium hydroxide (47 mg, 0.27 mmol) was added to a stirred solution of **18** (117 mg, 0.09 mmol) in THF (2 mL) and water (4 mL). The reaction mixture was stirred for 3 h at room temp. TLC analysis (ethyl acetate/cyclohexane, 1:1) indicated complete conversion of the starting material into one product. The reaction mixture was acidified by addition of DOWEX 50W (H$^+$), which was then removed by filtration, and the filtrate was concentrated in vacuo to give (6-azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-D-phenylalanine–(6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-D-phenylalanine–(6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-D-phenylalanine. The crude acid was dissolved in 1,4-dioxane (1 mL). Pentafluorophenol (34 mg, 0.18 mmol) and EDCI·HCl (21 mg, 0.11 mmol) were added and the mixture was stirred at room temp. under an atmosphere of argon. After 16 h, TLC analysis (ethyl acetate/cyclohexane, 1:1) indicated complete conversion

of the starting material (R_f = 0.0) into a major UV-active product (R_f = 0.3). The solvent was removed in vacuo and the residue dissolved in dichloromethane (10 mL). The solution was washed with an aqueous solution of sodium hydrogen carbonate (5% w/v, 5 mL) and an aqueous solution of citric acid (5% w/v, 5 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (ethyl acetate/cyclohexane, 1:1) to yield (6-azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-D-phenylalanine–(6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-D-phenylalanine–(6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-D-phenylalanine pentafluorophenyl ester (74.5 mg), which was dissolved in 1,4-dioxane (7 mL). Palladium black (74 mg) was added and the flask was flushed with argon. The reaction mixture was flushed with hydrogen and stirred under a hydrogen atmosphere for 15 h. TLC analysis (ethyl acetate/cyclohexane, 1:1) indicated complete conversion of the starting material (R_f = 0.30 UV) into a major product (R_f = 0.1). The solvent was removed in vacuo and the oil residue was purified by flash column chromatography (ethyl acetate/cyclohexane, 3:1) to yield cyclic tetramer **19** (22 mg, 20%) as an off-white solid. R_f = 0.28, ethyl acetate/cyclohexane, 3:2. $[a]_D^{23}$ = +0.8 (c = 0.1 in $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.06, 1.27, 1.31, 1.33 [4× s, 36 H, 12× C(CH_3)$_2$], 2.99–3.07 (m, 9 H, ^{1}Saa Hε, ^{2}Saa Hε, ^{3}Saa Hε, 3× CH_2Ph), 3.80–3.86 (m, 3 H, ^{1}Saa H′ε, ^{2}Saa H′ε, ^{3}Saa H′ε), 3.90–3.94 (m, 6 H, ^{1}Saa Hβ, ^{2}Saa Hβ, ^{3}Saa Hβ, ^{1}Saa Hδ, ^{2}Saa Hδ, ^{3}Saa Hδ), 4.04 (d, $J_{H\gamma,H\delta}$ = 10.0 Hz, 3 H, ^{1}Saa Hγ, ^{2}Saa Hγ, ^{3}Saa Hγ), 4.46 (d, $J_{H\alpha,H\beta}$ = 7.5 Hz, 3 H, ^{1}Saa Hα, ^{2}Saa Hα, ^{3}Saa Hα), 4.56 (dd, J = 8.5, J = 11.5 Hz, 3 H, ^{1}Phe Hα, ^{2}Phe Hα, ^{3}Phe Hα), 6.45 (d, J = 8.4 Hz, 2 H, ^{1}Saa NH, ^{2}Saa NH, ^{3}Saa NH), 7.24–7.34 (m, 10 H, 10× ArH), 7.55 (d, J = 8.5 Hz, 3 H, ^{1}Phe NH, ^{2}Phe NH, ^{3}Phe NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 25.6, 26.5, 26.6, 26.9 [6× C(CH_3)$_2$], 37.7, 41.2 (CH_2Ph, ^{1}Saa CHε, ^{2}Saa CHε, ^{3}Saa CHε), 54.2 (^{1}Saa CHδ, ^{2}Saa CHδ, ^{3}Saa CHδ), 75.3, 75.7, 78.1, 78.3 (^{1}Phe CHα, ^{2}Phe CHα, ^{3}Phe CHα, ^{1}Saa CHα, ^{2}Saa CHα, ^{3}Saa CHα, ^{1}Saa CHγ, ^{2}Saa CHγ, ^{3}Saa CHγ, ^{1}Saa CHβ, ^{2}Saa CHβ, ^{3}Saa CHβ), 109.3, 111.6 [6× C(CH$_3$)$_2$], 127.2, 128.7, 129.1, 136.1 (3× C_6H_5), 170.5, 171.4 (6× CONH) ppm. MS (ESI$^+$): m/z (%) = 1235.57 (21) [M + Na]$^+$. HRMS: calcd. for $C_{63}H_{84}N_6NaO_{18}$ 1235.5740; found 1235.5749.

Conformational Analysis. NMR Spectroscopy: ^{1}H NMR spectroscopic assignments were performed by using standard 1D, 2D-COSY, NOESY, ROESY and HSQC experiments on a Bruker Avance 500 MHz spectrometer at 300 K. The coupling constants were obtained from analysis of the ^{1}H NMR spectra by using MestreNova software. Proton–proton interatomic distances were estimated from the enhancements measured by 2D ROESY experiments, using mixing times of 300 and 400 ms.

Molecular Modelling: Molecular mechanics, MD and Monte Carlo (MC) studies were conducted with the MACROMODEL program as implemented in the Maestro package.[18] The AMBER* force field was used.[19] The energies were minimised by using the Polak–Ribière PR conjugate gradient method. The generalised Born surface area (GB/SA) solvation model[20] was employed for the calculations. The starting coordinates for dynamics calculations were those obtained after energy minimisations. Simulations were carried out over 2 ns at 300 K. MC studies were conducted by using default parameters implemented in MACROMODEL; 300 trial structures were generated for each molecule. Coupling constants were calculated for the obtained structures by using the empirical Karplus equation proposed by Haasnoot et al.[21] and compared to those experimentally available. Interatomic H–H distances and estimated NOEs were calculated by using the Mestrelab program and also compared to those estimated from ROESY experiments as described in ref.[22]

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H and ^{13}C NMR spectra for cyclopeptides **4**, **8**, **10**, **14**, and **19** and results from the MD simulations.

Acknowledgments

Financial support to R. S. provided through the European Community's Human Potential Programme under contract HPRN-CT-2002-00173 is gratefully acknowledged.

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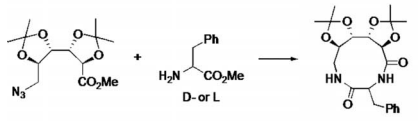
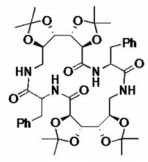
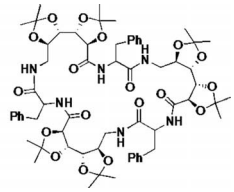
Received: April 11, 2012

Peptide Mimetics







The preparation of a series of cyclopeptides, formed by cyclisation of linear heterogeneous oligomers of 6-amino-6-deoxygalactonic acid and D- or L-phenylalanine, is reported. Molecular dynamics and NMR spectroscopy studies have given valuable insight into their properties, indicating that one of these structures, L-cyclodipeptide, is a peptide mimetic of potential interest in medicinal chemistry.

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Synthesis and Conformational Analysis of Heterogeneous Cyclic Oligomers of 6-Amino-6-deoxygalactonic Acid and Phenylalanine

Keywords: Peptidomimetics / Cyclopeptides / Amino acids / Carbohydrates / Conformation analysis

