Synthesis of a Protected δ-Glyco-amino Acid Building Block for Incorporation into Peptide Chains

George Paloumbis,[a] Christos C. Petrou,[a] Berthold Nock,[b] Theodosia Maina,[b] George Pairas,[a] Petros G. Tsoungas,[c] Paul Cordopatis*[a]

[a] Department of Pharmacy, University of Patras, 26504 Patras, Greece
Fax +30(2610)997714; E-mail: pacord@upatras.gr

[b] Institute of Radioisotopes – Radiodiagnostic Products, National Centre for Scientific Research 'Demokritos', Agia Paraskevi Attikis, 15310 Athens, Greece

[c] Ministry of Development, Department of Research and Technology, 14–18 Messogion Ave, 11510 Athens, Greece

Received 11 October 2006; revised 15 November 2006

Abstract: The synthesis of a suitably protected sugar amino acid (δ-glyco-amino acid) as a building block to be incorporated into the peptide chain (N-terminus) of bioactive peptide analogues is described. Its efficient coupling reactions with pilot amino acids as well as dipeptides have been accomplished by standard peptide chemistry.

Key words: carbohydrates, δ-glyco-amino acid, glycosylation, glycopeptides, radiolabelling

Carbohydrates represent an attractive source of readily available stereodefined scaffolds, as they carry easily convertible substituents on a rigid pyran or a more flexible furan ring.[1–4] Their molecular diversity provides a valuable tool for drug discovery. Derivatives bearing an amine and a carboxyl group are non-natural amino acid analogues known as glyco-amino acids or sugar amino acids (SAAs).[5] SAAs attached to peptides give rise to peptidomimetics, hybrid structures with folded conformations.[5–8] Synthetic peptide analogues are widely recognized as important lead compounds for development of new materials[9] and generation of therapeutic agents.[5,10]

Several studies have shown that peptide glycosylation can be used to enhance their resistance to proteolysis and rapid excretion, hence improving their transport across membranes.[11] An example is the incorporation of carbohydrate groups into enkephalin peptides; this influences receptor binding and enhances peptide delivery to the brain or the spinal cord.[12]

Synthetic glycopeptides can be obtained in preparative quantities and can be linked to complex biological carrier molecules. Albert et al.[13] described the synthesis of chemically stable glycated derivatives to produce somatostatin analogues by the Amadori reaction. The in vitro activity of these glycated molecules was shown to be similar to that of the nonglycated parent octreotide. Nonetheless, some of the Amadori products were found to have enhanced bioavailability compared to octreotide. This was thought to be the result of changes in physicochemical properties arising from the incorporation of the carbohydrate structure into the peptide skeleton.

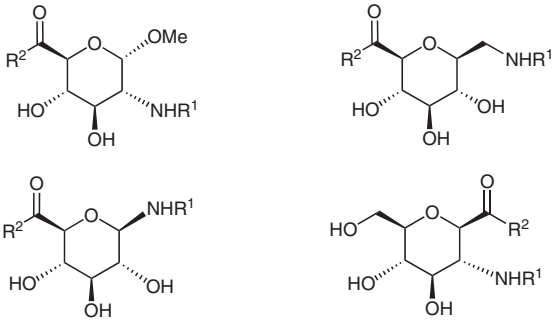


Figure 1 Building blocks of sugar amino acids

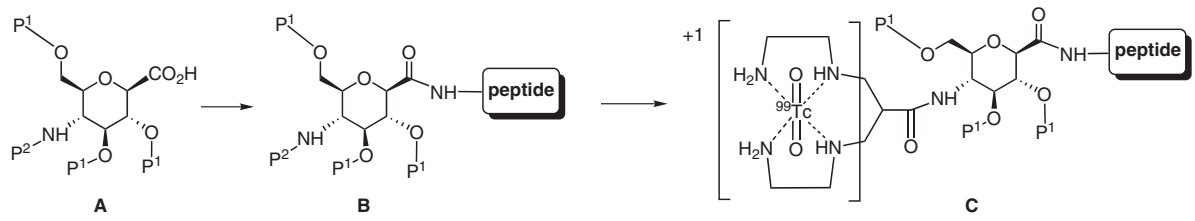
Peptidomimetics incorporating SAAs (Figure 1) have been reported first by Kessler et al.[14] It was demonstrated that the SAA entity triggered constrains on local conformations of the peptide backbone. Furanoid SAAs to be incorporated into peptide side chains have been prepared by other groups.[15–17] Unlike their α-, β-, and γ-peptide-based foldamers, δ-counterparts are somewhat less explored, probably due to their increased backbone flexibility.[8,18]

As part of an ongoing research programme on the study of somatostatin peptidomimetic frameworks, we have embarked on the synthesis of suitably protected δ-glyco-amino acids such as **A** (Scheme 1).

SAA **A**, if incorporated into a peptide sequence, will lead to peptide structure **B** (Scheme 1), which can be selectively deprotected at the N-terminus (base-labile protection) without the other acid-labile protecting groups of the sugar being affected. The released amine can then be coupled with a suitable chelator, e.g. a tetraamine, to further stably bind a metallic radionuclide such as ^{99m}Tc, affording the diagnostic radiopeptide **C** (Scheme 1). Chelator–peptide conjugates labelled with ^{99m}Tc and other radiometals, such as ^{111}In, ^{68}Ga, ^{90}Y, and ^{64}Cu, have been proposed for the scintigraphic imaging or radiotherapy of tumours expressing the corresponding peptide receptors in high density.[19–21]

We report herein the synthesis of **A** as the key building block for our objectives.

SYNTHESIS 2007, No. 6, pp 0845–0852
Advanced online publication: 20.02.2007
DOI: 10.1055/s-2007-965942; Art ID: P12006SS



Scheme 1 Strategy for synthetic targets (P^1 = acid-labile protection; P^2 = base-labile protection)

It is obvious that the key transformations in the synthesis of a molecule such as **A** would be the introduction of the carboxylic acid at C-1 and the amino function at C-4. From a retrosynthetic point of view, the carboxy group can be obtained from the hydrolysis of a nitrile, which in turn can be obtained by a nucleophilic displacement at the anomeric centre with a suitable cyanide reagent. Similarly, the amino group could come from the reduction of an azide derived from a nucleophilic displacement at C-4. Our synthesis was based on a method recently reported by Ichikawa et al.,[22] in which glucose-type amino acids were prepared and combined to form homo-oligomers.

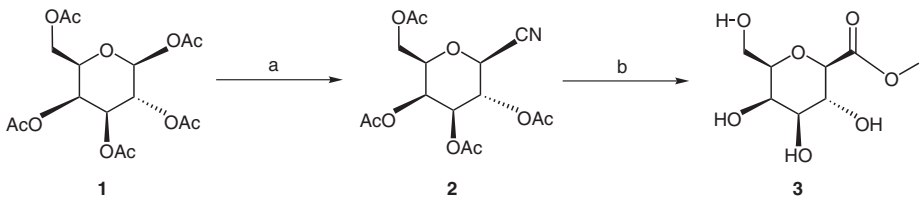
To this end we chose to use the commercially available penta-*O*-acetyl-β-D-galactopyranose (**1**) as our starting galactopyranoside molecule (Scheme 2). This was chosen because the introduction of the amino functionality at C-4 involves an S_N2 displacement of a triflate group by a metal azide, which results in inversion of stereochemistry (see Scheme 4), thus giving the desired glucose configuration. Furthermore, the transformation into the nitrile intermediate **2** is higher-yielding (77%) than when the α-isomer (60%) or the α- and β-glucopyranose derivatives (12% and 15% respectively) are used.[23]

In our case the displacement of the acetoxy group at C-1 with trimethylsilyl cyanide proceeded smoothly, giving nitrile **2** in 70% yield after recrystallisation. Direct hydrolysis of nitrile **2** to the methyl ester derivative **3** with concomitant deprotection of the hydroxy groups can be efficiently effected with either the boron trifluoride–ethanol or –methanol complex[24] or with acetyl chloride/methanol. The latter combination led to a quantitative yield of ester **3**. The assignment of the β-configuration at C-1 was on the basis of the large coupling constant (J = 10.1 Hz) between H-1 (axial) and H-2 (axial) in the ^{1}H NMR spectrum.

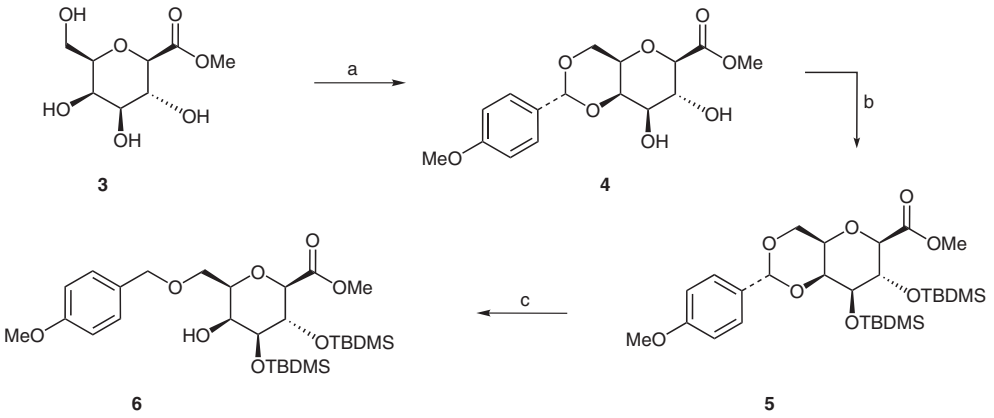
The next set of experiments involved the protection of the free hydroxy functionalities with groups that would allow access to the C-4 position. Benzylidene acetals are most suitable in this respect, since they form a six-membered ring with the hydroxy groups at C-4 and C-6. Subsequent reductive cleavage leaves a free hydroxy group at either position, depending on the conditions used.[25] Our original approach involved benzylidenation of the hydroxy groups at C-4 and C-6 with benzaldehyde dimethyl acetal followed by benzylation of the remaining hydroxy groups with benzyl bromide. Reductive opening of the benzylidene group with hydrogen chloride–sodium cyanoborohydride afforded the C-4-unprotected hydroxy group, which was further functionalised. However, a few steps later we realized that our molecule was unstable to the catalytic hydrogenation conditions used for the removal of the benzyl groups. For this reason we decided to use acid-labile protecting groups on the hydroxy functions from the beginning of our synthesis to avoid this problem.

As before, but now using the *p*-methoxybenzylidene acetal, we prepared the C-4- to C-6-protected diol **4** in 79% yield (Scheme 3). Attempts to protect the remaining hydroxy functions (at C-2 and C-3) also with the *p*-methoxybenzyl group (PMBCl, KI, K_2CO_3) were unsuccessful, and we never managed to obtain the fully protected sugar. As an alternative, the *tert*-butyldimethylsilyl group was used, since the formation of the Si–O bond is much more favourable, and can be readily cleaved under acidic conditions. The α-oxymethyl (formacetal) group ($ROCH_2O$-) is equally effective, hence an efficient surrogate of *tert*-butyldimethylsilyl.[26] The fully protected galactose derivative **5** was obtained in 80% yield (Scheme 3). Regioselective reduction with sodium cyanoborohydride and trifluoroacetic acid afforded the hydroxy ether **6** in 64% yield after chromatography.

With the hydroxy group at C-4 exposed, its triflate analogue was prepared to allow its displacement by the azide group, a commonly used sequence of transformations in glyco-amino acids.[27]



Scheme 2 *Reagents and conditions*: (a) TMSCN, $BF_3{\cdot}OEt_2$, $MeNO_2$, r.t., 23 h, 70%; (b) AcCl, MeOH, 0 °C (15 min) then 60–65 °C (3 d), 100%.



Scheme 3 *Reagents and conditions*: (a) $PMPCH(OMe)_2$, TsOH, MeCN, 2 h, r.t., then Et_3N, 79%; (b) TBDMSCl, imidazole, DMAP, DMF, 65 °C, 24 h, 80%; (c) $NaBH_3CN$, TFA, 4-Å MS, CH_2Cl_2, THF, r.t., 24 h, 64%.

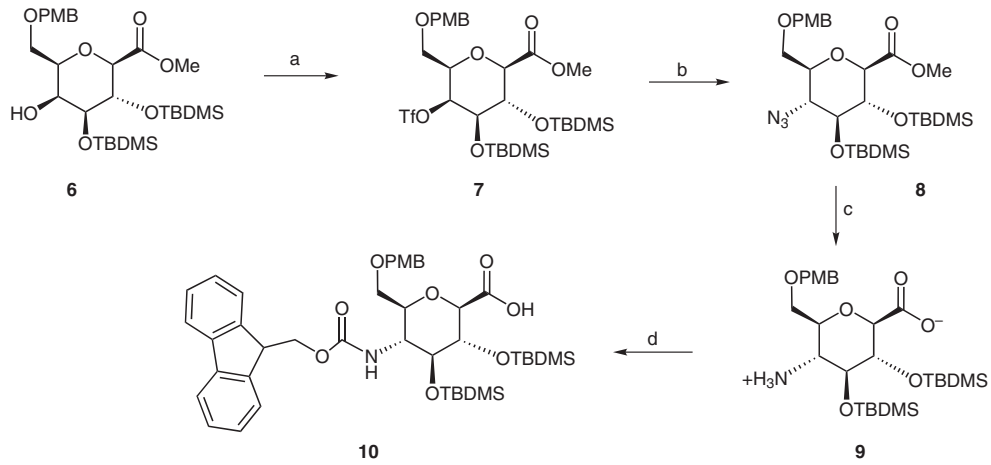
The crude triflate derivative **7** (Scheme 4) was treated with ten equivalents of sodium azide in *N*,*N*-dimethylformamide to give glucose derivative **8** in 89% yield after chromatography. The azide was reduced to the secondary amine **9** by the Staudinger reaction (PPh_3/THF/H_2O), and the ester was hydrolysed in 'one pot' by the addition of lithium hydroxide or sodium hydroxide to the mixture. Finally, the amino terminus was protected with the Fmoc group by treatment of compound **9** with Fmoc-OSu; this gave target molecule **10** in 63% yield.

The penultimate step of our synthetic scheme has been repeated a few times to optimise the conditions. While the formation of the phosphazene and its hydrolysis to the free amine seems to work well, prolonged treatment with lithium hydroxide or sodium hydroxide to facilitate ester hydrolysis sometimes leads to byproducts and reduces the yield.

Finally, to test and establish the conditions of coupling of our glyco-amino acid **10** with bionucleophiles, **10** successfully reacted at the N-terminus of a single amino acid such as H-β-Ala-O*t*-Bu, to give **11**, as well as with the dipeptide H-Ala-Ala-O*t*-Bu, to give **12** (Scheme 5). The coupling reaction was performed by a protocol involving *N*,*N*-diisopropylethylamine combined with *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU); this afforded the desired products cleanly and relatively quickly (0.5–1 h) (Scheme 5).

Table 1 and Table 2 show the correlations between the protons and carbons of compound **10** and **12**, respectively, which helped in the assignment of the spectra.

In summary, we have synthesised a highly functionalised building block, in good overall yield (73%), with orthogonal protecting groups suitable for Fmoc/*t*-Bu peptide synthesis. We decided to introduce acid-labile protecting groups on the free hydroxy functions and a base-labile (Fmoc) protecting group on the free amine (N-terminus). The free carboxy group was successfully coupled with a single non-natural amino acid (β-Ala) as well as a dipeptide (Ala-Ala) by use of standard peptide coupling reactions (HATU/DIPEA protocol).



Scheme 4 *Reagents and conditions*: (a) Tf_2O, py, CH_2Cl_2, r.t., 35 h, 87%; (b) NaN_3, DMF, r.t., 2.5 h, 89%; (c) PPh_3, THF, H_2O, r.t., 45 min, then 50 °C for 1.25 h, then LiOH or NaOH, 16–40%; (d) Fmoc-OSu, MeCN, H_2O, Et_3N, r.t., 17 h, 84%.

Table 1 HMQC Correlations for Compound **10**

No. of hydrogens	δ_H (ppm)	δ_C (ppm)
12	0.07–0.20	–5.27, –4.95, –4.84
9	0.85	25.72
9	0.93	25.93
2	3.63	70.63
2	3.72	72.78
3	3.74	51.07
1	3.86	76.21
1	4.16	47.37
1	4.29	78.04
1	4.31	71.91
2	4.42	66.83
2	4.50	73.35
2	6.84	114.01
4	7.25–7.31	127.15, 129.70
2	7.40	127.87
2	7.54	125.04
2	7.76	120.18

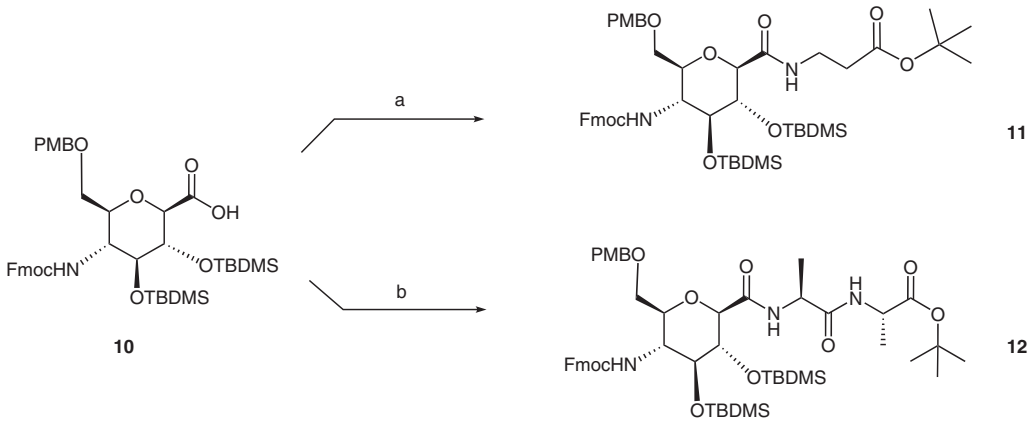
Table 2 HMQC Correlations for Compound **12**

No. of hydrogens	δ_H (ppm)	δ_C (ppm)
12	–0.002 to 0.21	–5.36, –4.98, –4.83
9	0.78	25.66, 25.88
9	0.93	25.66, 25.88
6	1.38	18.0, 18.56
9	1.47	27.98
7	3.63–3.72	51.99, 55.18, 71.8, 71.92, 73.22, 77.23
1	4.13	47.24
1	4.19	80.72
5	4.29–4.44	48.76, 48.80, 66.67, 71.8
2	4.54	74.02
2	6.83	113.80
5	7.29	127.02, 129.4
2	7.38	127.69
3	7.50	125.03
2	7.75	120.0

Future work will involve the coupling of the protected glyco-amino acid with peptide analogues, introduction of a chelator at the amino terminus of the sugar, and binding with a radionuclide to obtain a radiopeptide which will be used for further studies.

This work has demonstrated how the incorporation of pyranoid sugar amino acid based building blocks, in peptides and natural biopolymers, has tapped into new aspects of drug design. Their incorporation into biologically active compounds may directly give rise to highly active and, in some cases, receptor-specific analogues, but, more importantly, assist in tracing the probable conformation of these molecules.

The diversity of sugar molecules can be exploited to create a combinatorial library of sugar-amino-acid-based molecular frameworks predisposed to fold into architecturally beautiful structures, which may also have interesting properties. The protected/unprotected hydroxy groups of sugar rings can also influence the hydrophobic/hydrophilic nature of such molecular assemblies.



Scheme 5 Coupling of SAA **10** with H-β-Ala-O*t*-Bu and H-Ala-Ala-O*t*-Bu. *Reagents and conditions*: (a) H-β-Ala-O*t*-Bu, HATU/DIPEA, $CDCl_3$–DCE, r.t., 30 min, 85%; (b) H-Ala-Ala-O*t*-Bu, HATU/DIPEA, $CDCl_3$–DCE, r.t., 30 min, 80%.

^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker DPX400 spectrometer. For samples in $CDCl_3$, CD_2Cl_2, and DMSO-d_6, TMS was used as an internal reference (δ = 0.00), and for samples in D_2O, the sodium salt of 3-(trimethylsilyl)propionic-2,2,3,3-d_4 acid was used as an internal reference (δ = 0.00), unless otherwise stated. IR spectra were recorded either at NIMS on a Nicolet Avatar 360 FT-IR spectrometer as a film (neat), or by Analytical Services at Novartis Pharma, Basel on a Bruker IFS 66 FT-IR spectrometer, as neat films. Liquid chromatography–mass spectrometetry (LC-MS) was recorded on a Micromass Platform liquid chromatograph with a Gilson LC system [column: CHROMOLITH SpeedROD RP-18e; 50 × 4.6 mm; gradient elution: 5% MeCN in H_2O (with 0.08% formic acid), held for 1 min, then to 100% MeCN over 4 min, and held at 100% MeCN for 1 min at 3.0 mL/min]. Analytical TLC was performed on either Merck or Whatman 0.25-mm silica gel 60-F plates. Flash column chromatography was performed on Biotage FLASH 12i or 40i systems or the Jones Chromatography Personal Flashmaster with Isolute Flash Si SPE cartridges. All reaction mixtures were stirred by a magnetic hotplate and were kept under an atmosphere of either anhyd N_2 or anhyd Ar at r.t., unless otherwise stated.

3,4,5,7-Tetra-*O*-acetyl-2,6-anhydro-D-*glycero*-L-*manno*-heptonitrile (2)

To a stirred soln of **1** (30 g, 76.86 mmol) and TMSCN (2 equiv, 15.26 g, 153.72 mmol) in $MeNO_2$ (250 mL) under argon at r.t. was added $BF_3{\cdot}OEt_2$ (1 equiv, 10 mL, 76.85 mmol) over 5 min. The resulting bright yellow soln was allowed to stir at r.t. for 23 h. The soln was concentrated under reduced pressure. The residue was diluted with $CHCl_3$ (600 mL) and washed with chilled H_2O (4 × 150 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure; this gave a yellow oil, which solidified in vacuo. Recrystallisation of this from CH_2Cl_2–Et_2O (1:1) gave **2**.

Yield: 19.22 g (70%); white crystals.

IR: 2361 (C≡N), 1731 (C=O) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.01 (s, 3 H, CH_3CO), 2.06 (s, 3 H, CH_3CO), 2.12 (s, 3 H, CH_3CO), 2.19 (s, 3 H, CH_3CO), 3.90 (t, 1 H, H-5), 4.10 (d, *J* = 6.4 Hz, 2 H, H-6, H-6′), 4.29 (d, *J* = 10.2 Hz, 1 H, H-4), 5.0 (dd, *J* = 3.3, 10.2 Hz, 1 H, H-2), 5.4 (dd, *J* = 0.82, 3.2 Hz, 1 H, H-1), 5.52 (t, *J* = 10.1 Hz, 1 H, H-3).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 107.7 (CH_3CO), 170.4 (CH_3CO), 170.2 (CH_3CO), 169.2 (CH_3CO), 116.1 (C≡N), 75.8 (C-5), 71.2 (C-3), 67.2 (C-4), 66.4 (C-2), 61.6 (C-6), 21.7 (CH_3CO), 21.0 (CH_3CO), 20.9 (CH_3CO), 20.3 (CH_3CO), 20.0 (CH_3CO).

Methyl 2,6-Anhydro-D-*glycero*-L-*manno*-hepturonate (3)

A soln of **2** (11.05 g, 30.93 mmol) in an HCl–MeOH mixture [prepared by the slow addition of AcCl (8.4 mL) to anhyd MeOH (50 mL) at 0 °C] was heated to 60–65 °C for 3 d. After the mixture had been allowed to cool to r.t., all the volatiles were removed under reduced pressure; this yielded crude **3** as a white foam. ^{1}H NMR spectroscopy showed that a single clean product was obtained. The compound was used without further purification in the next step.

Yield: 6.87 g (100%).

IR: 3108 (OH), 1742 (C=O) cm^{-1}.

^{1}H NMR (400 MHz, D_2O): δ = 4.05 (d, *J* = 10.1 Hz, 1 H, H-1), 4.0 (m, 1 H, H-2), 3.89 (s, 3 H, OCH_3), 3.87–3.70 (m, 5 H, H-3, H-4, H-5, H-6, 6′).

^{13}C NMR (400 MHz, D_2O): δ = 171.1 (CO_2CH_3), 80.1 (C-5), 77.9 (C-1), 76.0 (C-3), 72.5 (C-2), 70.1 (C-4), 60.7 (C-6), 49.8 (CO_2CH_3).

Methyl 2,6-Anhydro-5,7-*O*-(4-methoxybenzylidene)-D-*glycero*-L-*manno*-hepturonate (4)

To a soln of **3** (1.21 g, 5.40 mmol) in anhyd MeCN (35 mL) at r.t. was added $PMPCH(OMe)_2$ (2.5 equiv, 2.32 mL, 13.61 mmol) followed by cat. $TsOH{\cdot}H_2O$ (78 mg, 0.41 mmol). The resulting mixture was stirred at r.t. for 1.67 h, then quenched with Et_3N (0.35 mL, 2.51 mmol), and stirred for a further 10 min. The volatiles were evaporated and the crude product was purified by flash chromatography (silica gel, EtOAc–*n*-hexane, 0:1 to 1:0, 1 h). Evaporation of the desired fractions gave a white solid.

Yield: 1.45 g (79%); R_f = 0.5 (CH_2Cl_2–MeOH, 10:1).

IR: 3429 (br, OH), 1740 (C=O), 1614, 1518 (C=C) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43, 6.87 (2 d, *J* = 8.7 Hz, 4 H, ArH), 5.47 (s, 1 H, CHPh), 4.30 (dd, *J* = 1.3, 12.7 Hz, 1 H, H-1), 4.18 (d, *J* = 3.3 Hz, 1 H, H-3), 4.07 (td, *J* = 2.6, 9.5 Hz, 1 H, H-6), 4.01 (dd, *J* = 1.7, 12.7 Hz, 1 H, H-2), 3.82–3.79 (m, 7 H, 2 × OCH_3, H-6′), 3.68 (td, *J* = 3.7, 9 Hz, 1 H, H-4), 2.94 (d, *J* = 8.7 Hz, 1 H, H-5).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 169.9 (CO_2CH_3), 160.3 (C_{Ar}-OMe), 130.1 (C_{Ar}), 113.6 (C_{Ar}), 101.3 [Ar*C*H(OR)$_2$], 77.9 (C-4), 75.3 (C-5), 73.4 (C-1), 71.2 (C-2), 70.3 (C-3), 69.1 (C-6), 55.3 (ArOCH_3), 52.7 (CO_2CH_3).

LC-MS: *m*/*z* [MH$^+$] = 341.03; t_R = 2.61 min (6 min run).

Methyl 2,6-Anhydro-3,4-bis(*O-tert*-butyldimethylsilyl)-5,7-*O*-(4-methoxybenzylidene)-D-*glycero*-L-*manno*-hepturonate (5)

To a stirred soln of **4** (511 mg, 1.50 mmol) in anhyd DMF (25 mL) was added TBDMSCl (4 equiv, 905 mg, 6.01 mmol), imidazole (8 equiv, 818 mg, 12.01 mmol), and DMAP (15 mol%, 28 mg, 0.23 mmol) at r.t. The mixture was then placed in an oil bath and heated at 65 °C for 24 h. It was then allowed to cool down to r.t., and diluted with EtOAc (150 mL). The organic phase was washed with H_2O (3 × 150 mL) and brine (100 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The yellow oil that was obtained was purified by flash chromatography (silica gel, cyclohexane–EtOAc, 1:0 to 4:1).

Yield: 683 mg (80%); colourless oil; R_f = 0.4 (cyclohexane–EtOAc, 4:1).

IR: 1749 (C=O), 1612, 1518 (C=C), 833, 775 (Si–O) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47, 6.91 (2 d, *J* = 8.7 Hz, 4 H, ArH), 5.40 (s, 1 H, H-7), 4.29 (dd, *J* = 1.3, 12.5 Hz, 1 H, H-1), 4.18 (t, *J* = 9 Hz, 1 H, H-4), 4.08 (d, *J* = 2.8 Hz, 1 H, H-6), 3.97 (dd, *J* = 1.65, 12.5 Hz, 1 H, H-2), 3.81–3.73 (m, 8 H, *p*-CH_3O, CO_2CH_3, H-3, H-6′), 3.4 (d, *J* = 0.8 Hz, 1 H, H-5), 0.92 (s, 9 H, $SiCMe_3$), 0.85 (s, 9 H, $SiCMe_3$), –0.01 to 0.12 (m, 12 H, 2 × $SiMe_2$).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 169.2 (CO_2CH_3), 160.1 (C_{Ar}-OMe), 130.8 (C_{Ar}), 127.7 (C_{Ar}), 113.9 (C_{Ar}), 113.6 (C_{Ar}), 101.3 [Ar*C*H(OR)$_2$], 81.1 (C-4), 80.7 (C-1), 75.8 (C-5), 70.6 (C-3), 69.7 (C-6), 69.2 (C-2), 55.4 (*p*-CH_3OAr), 52.3 (CO_2CH_3), 27.0 [SiC(CH_3)$_3$], 26.5 [SiC(CH_3)$_3$], 26.2 [SiC(CH_3)$_3$], 25.9 [SiC(CH_3)$_3$], 18.8 [Si*C*(CH_3)$_3$], 18.4 [Si*C*(CH_3)$_3$], –2.97 [Si(CH_3)$_2$], –3.0 [Si(CH_3)$_2$], –3.7 [Si(CH_3)$_2$], –4.9 [Si(CH_3)$_2$].

LC-MS: *m*/*z* [MH$^+$] = 586.93; t_R = 5.73 min (6 min run).

Methyl 2,6-Anhydro-3,4-bis(*O-tert*-butyldimethylsilyl)-7-*O*-(4-methoxybenzyl)-D-*glycero*-L-*manno*-hepturonate (6)

A soln of **5** (1.20 g, 2.11 mmol) and $NaBH_3CN$ (10 equiv, 1.33 g, 21.1 mmol) in anhyd CH_2Cl_2 (30 mL) and anhyd THF (5 mL) was cooled to 0 °C, and 4-Å activated powder MS (9.8 g) were added. The resulting mixture was allowed to stir at 0 °C for 40 min and then a soln of TFA (20 equiv, 3.13 mL, 42.19 mmol) in anhyd CH_2Cl_2 (5 mL) was added dropwise over 20 min. The ice bath was removed and the mixture was stirred for 24 h. It was then diluted with EtOAc

(150 mL), neutralised with sat. aq $NaHCO_3$ (200 mL), and filtered through a sintered-glass funnel. The layers were separated and the organic phase was washed with more sat. aq $NaHCO_3$ (100 mL) and brine (100 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The yellow syrup thus obtained was purified by flash chromatography (silica gel, EtOAc–*n*-hexane, 0:1 to 4:1, 50 min).

Yield: 770 mg (64%); colourless oil; R_f = 0.39 (cyclohexane–EtOAc, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26, 6.87 (2 d, *J* = 8.7 Hz, 4 H, ArH), 4.48 (m, 2 H, MeOPhCH_2), 4.02 (t, *J* = 8.8 Hz, 1 H, H-4), 3.86 (m, 1 H, H-1), 3.80 (s, 3 H, PhOCH_3), 3.74 (s, 1 H, CO_2CH_3), 3.71–3.62 (m, 5 H, H-6, H-6′, H-2, H-3, H-5), 2.44 (s, 1 H, OH), 0.94 (s, 9 H, SiCMe_3), 0.86 (s, 9 H, SiCMe_3), 0.16 (s, 3 H, SiMe), 0.13 (s, 3 H, SiMe), 0.08 (s, 3 H, SiMe), –0.05 (s, 3 H, SiMe).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 169.3 (*C*O_2CH_3), 159.4 (C_{Ar}-OMe), 130.2 (C_{Ar}), 129.6 (C_{Ar}), 114 (C_{Ar}), 80.9 (C-3), 77 (C-1), 73.4 (Ar*C*H_2), 70.3 (C-5), 70.1 (C-4), 69.2 (C-6), 55.4 (ArO*C*H_3), 52.3 (CO_2*C*H_3), 26.5 [SiC(*C*H_3)$_3$], 26.1 [SiC(*C*H_3)$_3$], 18.5 [Si*C*(CH$_3$)$_3$], 18.2 [Si*C*(CH$_3$)$_3$], –2.8 [Si(CH$_3$)$_2$], –3.3 [Si(CH$_3$)$_2$], –3.9 [Si(CH$_3$)$_2$], –4.9 [Si(CH$_3$)$_2$].

LC-MS: *m*/*z* [MH$^+$] = 571.86; t_R = 5.55 min (6 min run).

Methyl 2,6-Anhydro-5-azido-3,4-bis(*O*-*tert*-butyldimethylsilyl)-7-*O*-(4-methoxybenzyl)-5-deoxy-D-*glycero*-L-*gulo*-hepturonate (8)

A soln of **6** (752 mg, 1.32 mmol) in anhyd CH_2Cl_2 (20 mL) was cooled to 0°C (ice bath). Py (4 equiv, 427 μL, 5.27 mmol) was added, followed by slow addition of Tf_2O (2 equiv, 445 μL, 2.63 mmol) and DMAP (2 crystals). The mixture was allowed to warm to r.t. and was stirred for 35 h. It was then diluted with H_2O (200 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc–*n*-hexane, 0:1 to 4:1, 1.5 h); this gave **7** as a colourless oil, which was dried under high vacuum.

Yield: 805 mg (87%).

LC-MS: *m*/*z* [MH$^+$] = 703.44; t_R = 5.92 min (7 min run).

Compound **7** (740 mg, 1.05 mmol) was dissolved in anhyd DMF (14 mL) at r.t., and NaN_3 (10 equiv, 685 mg, 10.53 mmol) was added in one portion. The mixture was stirred at r.t. for 2.5 h, and was then quenched with H_2O (150 mL). The aqueous phase was extracted with EtOAc (3 × 60 mL) and the combined extracts were washed with H_2O (50 mL) and brine (60 mL). The organic phase was dried ($MgSO_4$), filtered, and evaporated; this gave a yellow oil which was purified by flash chromatography (silica gel, EtOAc–*n*-hexane, 0:1 to 7:3, 1 h). Azide derivative **8** was obtained as a colourless oil.

Yield: 557 mg (89%).

IR: 2108 (N_3), 1754 (C=O), 1613, 1513 (C=C) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30, 6.89 (2 d, *J* = 8.7 Hz, 4 H, ArH), 4.55 (m, 2 H, ArCH_2), 4.09 (d, *J* = 5.0 Hz, 1 H, H-1), 4.04 (t, *J* = 5.2 Hz, 1 H, H-6), 3.80 (s, 3 H, ArOCH_3), 3.73 (s, 3 H, CO_2CH_3), 3.70 (m, 4 H, H-2, H-4, H-5, H-6′), 3.50 (m, 1 H, H-3), 0.90 (s, 9 H, SiCMe_3), 0.89 (s, 9 H, SiCMe_3), 0.15 (s, 3 H, SiMe_2), 0.13 (s, 3 H, SiMe_2), 0.10 (s, 3 H, SiMe_2), 0.05 (s, 3 H, SiMe_2).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 169.8 (*C*O_2CH_3), 159.2 (C_{Ar}-OMe), 130.0 (C_{Ar}), 129.6 (C_{Ar}), 113.7 (C_{Ar}), 113.6 (C_{Ar}), 79.4 (C-1), 75.8 (C-5), 75.4 (Ar*C*H_2), 73.2 (C-6), 69.7 (C-3), 63.0 (C-2), 55.2 (ArOCH_3), 52.2 (CO_2*C*H_3), 31.6 (C-4), 26 [SiC(*C*H_3)$_3$], 25.9 [SiC(*C*H_3)$_3$], 25.8 [SiC(*C*H_3)$_3$], 22.7 [SiC(*C*H_3)$_3$], 18.1 [Si*C*(CH$_3$)$_3$], 18.0 [Si*C*(CH$_3$)$_3$], 14.1, –3.5 [Si(CH$_3$)$_2$], –3.7 [Si(CH$_3$)$_2$], –4.1 [Si(CH$_3$)$_2$], –4.6 [Si(CH$_3$)$_2$].

LC-MS: *m*/*z* [MH$^+$] = 613.94; t_R = 6.06 min (7 min run).

5-Amino-2,6-anhydro-3,4-bis(*O*-*tert*-butyldimethylsilyl)-7-*O*-(4-methoxybenzyl)-5-deoxy-D-*glycero*-L-*gulo*-heptonic Acid (9)

To a soln of **8** (87 mg, 0.15 mmol) in anhyd THF (1 mL) and H_2O (1 mL) at r.t. was added PPh_3 (42 mg, 0.16 mmol). The resulting mixture was stirred for 45 min and then heated at 50 °C for 1.25 h. LiOH (2.1 equiv, 12.9 mg, 0.31 mmol) was then added and stirring continued for another 2 h at 50 °C. The mixture was allowed to cool to r.t. and was then acidified with citric acid. The aqueous phase was extracted with EtOAc (3 × 30 mL). The combined extracts were washed with brine (30 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The white solid thus obtained was triturated with *n*-hexane, filtered, and dried under suction.

Yield: 12.9 mg (16%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28, 6.89 (2 d, *J* = 8.7 Hz, 4 H, ArH), 4.53 (s, 2 H, ArCH_2), 4.29 (s, 1 H, H-6), 4.27 (d, *J* = 4.0 Hz, 1 H, H-1), 3.82 (m, 1 H, H-3), 3.81 (s, 3 H, ArOCH_3), 3.74 (d, *J* = 4.1 Hz, 1 H, H-2), 3.65 (m, 2 H, H-5, H-6′), 2.74 (d, *J* = 8.9 Hz, 1 H, H-4), 0.91 (s, 9 H, SiCMe_3), 0.86 (s, 9 H, SiCMe_3), 0.18 (s, 3 H, SiMe_2), 0.14 (s, 3 H, SiMe_2), 0.07 (s, 3 H, SiMe_2), 0.06 (s, 3 H, SiMe_2).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 169.8 (*C*O_2CH_3), 159.4 (C_{Ar}-OMe), 130.0 (C_{Ar}), 129.3 (C_{Ar}), 129.1 (C_{Ar}), 113.7 (C_{Ar}), 81.1 (C-5), 79.2 (C-1), 76.0 (PMP*C*H_2), 73.1 (C-3), 71.0 (C-6), 67.6 (C-2), 55.9 (ArOCH_3), 53.8 (C-4), 52.7 (CO_2*C*H_3), 27.2 [SiC(*C*H_3)$_3$], 26.1 [SiC(*C*H_3)$_3$], 26.0 [SiC(*C*H_3)$_3$], 25.7 [SiC(*C*H_3)$_3$], 18.4 [Si*C*(CH$_3$)$_3$], 18.2 [Si*C*(CH$_3$)$_3$], –2.57 [Si(CH$_3$)$_2$], –3.1 [Si(CH$_3$)$_2$], –3.5 [Si(CH$_3$)$_2$], –4.8 [Si(CH$_3$)$_2$].

LC-MS: *m*/*z* [MH$^+$] = 556.84; t_R = 3.54 min (7 min run).

2,6-Anhydro-3,4-bis(*O*-*tert*-butyldimethylsilyl)-5-[(9-fluorenylmethoxy)carbonylamido]-7-*O*-(4-methoxybenzyl)-5-deoxy-D-*glycero*-L-*gulo*-heptonic Acid (10)

To a soln of **9** (12.9 mg, 0.023 mmol) in MeCN (1 mL) and H_2O (1 mL) at r.t., Fmoc-OSu (1.1 equiv, 8.5 mg, 0.025 mmol) was added, followed by Et_3N (2.2 equiv, 8 μL, 0.051 mmol). The mixture was stirred at r.t. for 17 h. The aqueous phase was extracted with EtOAc (3 × 20 mL) and the combined extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure. Flash chromatography (silica gel, EtOAc–*n*-hexane, 0:1 to 1:0, 1.5 h) gave pure **10**.

Yield: 15.1 mg (84%); R_f = 0.47 (CH_2Cl_2–MeOH, 10:1).

IR: 3480 (OH), 1724 (C=O), 1612, 1512 (C=C) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.5 (v br, 1 H, CO_2H), 7.77 (d, *J* = 7.5 Hz, 2 H, ArH), 7.55 (m, 2 H, ArH), 7.42 (t, *J* = 7.3 Hz, 2 H, ArH), 7.27 (m, 4 H, ArH), 6.85 (d, *J* = 8.7 Hz, 2 H, ArH), 5.25 (d, *J* = 10.3 Hz, 1 H, NH), 4.50 (d, *J* = 1.6 Hz, 2 H, H-6′, FmocCH), 4.42 (m, 2 H, PMPCH_2), 4.31 (m, 2 H, H-6, H-1), 4.16 (m, 1 H, H-4), 3.86 (m, 1 H, H-5), 3.75–3.71 (m, 5 H, -OCH_3, H-2, H-3), 3.63 (d, *J* = 5.0 Hz, 2 H, FmocCH_2), 0.93 (s, 9 H, SiCMe_3), 0.85 (s, 9 H, SiCMe_3), 0.20 (s, 3 H, SiMe_2), 0.13 (s, 3 H, SiMe_2), 0.083 (s, 3 H, SiMe_2), 0.082 (s, 3 H, SiMe_2).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 170.3 (CO_2H), 159.6 (C_{Ar}OMe), 155.5 (NHCO), 144.0 (C_{Ar}), 143.9 (C_{Ar}), 141.5 (C_{Ar}), 129.8 (C_{Ar}), 129.7 (C_{Ar}), 127.9 (C_{Ar}), 127.2 (C_{Ar}), 127.1 (C_{Ar}), 120.2 (C_{Ar}), 115.3 (C_{Ar}), 114.0 (C_{Ar}), 113.2 (C_{Ar}), 78.0 (C-1), 76.2 (C-5), 73.3 (C-2), 72.8 (C-3), 71.9 (C-6), 70.6 (FmocCH_2), 66.8 (PMP*C*H_2), 55.4 (FmocCH), 51.1 (CH_3O), 47.4 (C-4), 25.9 [SiC(*C*H_3)$_3$], 25.7 [SiC(*C*H_3)$_3$], 18.1 [Si*C*(CH$_3$)$_3$], 17.9 [Si*C*(CH$_3$)$_3$], –4.8 [Si(CH$_3$)$_2$], –4.9 [Si(CH$_3$)$_2$], –5.3 [Si(CH$_3$)$_2$].

LC-MS: *m*/*z* [MH$^+$] = 779; t_R = 5.79 min (7 min run).

{3,4-Bis(*O*-*tert*-butyldimethylsilyl)-4-[(9-fluorenylmethoxy)carbonylamido]-6-*O*-(4-methoxybenzyl)-4-deoxy-β-D-glucopyranosyl}-*C*-carboxamido-*N*-β-alanine *tert*-Butyl Ester (11)

To a stirred soln of **10** (15.1 mg, 0.019 mmol) in $CDCl_3$ (1 mL) and DCE (0.5 mL) at r.t., HATU (1.1 equiv, 8.12 mg, 0.021 mmol), DIPEA (2.1 equiv, 7.1 μL, 0.041 mmol), and H-β-Ala-O*t*-Bu (1.05 equiv, 0.02 mmol, 2.90 mg) were added. The resulting mixture was stirred at r.t. for 30 min. It was then diluted with CH_2Cl_2 (10 mL), and the organic phase was washed with sat. aq $NaHCO_3$ (10 mL) and brine (10 mL). The organic phase was dried ($MgSO_4$), filtered, and evaporated under reduced pressure. This yielded a brown oil, which was purified by column chromatography (silica gel, EtOAc–*n*-hexane, 0:1 to 3:17, 1 h).

Yield: 14.9 mg (85%); colourless oil; R_f = 0.83 (CH_2Cl_2–MeOH, 10:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 7.5 Hz, 2 H, ArH), 7.57 (m, 2 H, ArH), 7.40 (m, 2 H, ArH), 7.30 (m, 4 H, ArH), 7.01 (m, 1 H, peptide N*H*), 6.83 (d, *J* = 8.6 Hz, 2 H, ArH), 5.16 (d, *J* = 10.4 Hz, 1 H, -N*H*-Fmoc), 4.50 (m, 2 H, H-6′, FmocC*H*), 4.38 (m, 3 H, PMPCH_2, H-1), 4.18 (m, 2 H, FmocCH, H-4), 3.73 (s, 3 H, OCH_3), 3.71–3.51 (m, 5 H, FmocCH_2, H-2, H-3, H-6), 3.15 (m, 1 H, CH_2NHCO), 2.45 (t, *J* = 6.5 Hz, 2 H, CH_2CO_2t-Bu), 1.44 (s, 9 H, $OCMe_3$), 0.93 (s, 9 H, $SiCMe_3$), 0.83 (s, 9 H, $SiCMe_3$), 0.21 (s, 3 H, $SiMe_2$), 0.14 (s, 3 H, $SiMe_2$), 0.07 (s, 3 H, $SiMe_2$), 0.02 (s, 3 H, $SiMe_2$).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 173.4 (CO_2t-Bu), 172.1 (CONH-peptide), 159.7 (C_{Ar}OMe), 155.8 (FmocCONH), 144.1 (C_{Ar}), 143.6 (C_{Ar}), 141.1 (C_{Ar}), 130 (C_{Ar}), 129.4 (C_{Ar}), 128.2 (C_{Ar}), 126.8 (C_{Ar}), 125.7 (C_{Ar}), 114.2 (C_{Ar}), 114.1 (C_{Ar}), 82.2 (CO_2CMe_3), 79.1 (C-5), 75.4 (PMP*C*H_2), 75.2 (C-1), 71.0 (C-3), 70.4 (C-6), 67.7 (C-2), 67.3 (FmocCH_2), 55.8 (OCH_3), 53 (FmocCH), 52.2 (C-4), 38.6 (*C*H_2NHCO), 38.3 (*C*H_2CO_2t-Bu), 28.7 [C(*C*H_3)$_3$], 28.5 [C(*C*H_3)$_3$], 25.9 [SiC(*C*H_3)$_3$], 25.7 [SiC(*C*H_3)$_3$], 19.3 [Si*C*(CH_3)$_3$], 18.6 [Si*C*(CH_3)$_3$], 18.2 [Si*C*(CH_3)$_3$], 17.8 [Si*C*(CH_3)$_3$], –4.8 [Si(CH_3)$_2$], –5.0 [Si(CH_3)$_2$], –5.1 [Si(CH_3)$_2$].

LC-MS: *m*/*z* [MH^+] = 905.8; t_R = 11.22 min (12 min run).

{3,4-Bis(*O*-*tert*-butyldimethylsilyl)-4-[(9-fluorenylmethoxy)carbonylamido]-6-*O*-(4-methoxybenzyl)-4-deoxy-β-D-glucopyranosyl}-*C*-carboxamido-*N*-alanine-alanine *tert*-Butyl Ester (12)

To a stirred soln of **10** (27.8 mg, 0.036 mmol) in $CDCl_3$ (0.5 mL) and DCE (1 mL) at r.t. was added HATU (1.1 equiv, 14.9 mg, 0.039 mmol), DIPEA (2.1 equiv, 13.1 μL, 0.075 mmol), and H-Ala-Ala-O*t*-Bu (1.05 equiv, 8.17 mg, 0.038 mmol). After 30 min, TLC (CH_2Cl_2–MeOH, 10:1) showed that the reaction had gone to completion. The mixture was diluted with CH_2Cl_2 (18 mL) and the organic phase was washed with sat. aq $NaHCO_3$ (20 mL) and brine (15 mL), then dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude product was purified by flash chromatography (silica gel, EtOAc–*n*-hexane, 0:1 to 1:9, 1 h).

Yield: 28 mg (80%); colourless oil; R_f = 0.95 (CH_2Cl_2–MeOH, 10:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 7.5 Hz, 2 H, ArH), 7.56 (m, 2 H, ArH), 7.51 (d, *J* = 6.6 Hz, 1 H, NH-Ala), 7.41 (m, 2 H, ArH), 7.31–7.26 (m, 4 H, ArH), 6.83 (d, *J* = 8.6 Hz, 2 H, ArH), 6.22 (d, *J* = 7.2 Hz, 1 H, NH-Ala), 5.18 (d, *J* = 10.3 Hz, 1 H, Fmoc-NH), 4.54 (m, 2 H, PMPCH_2), 4.48–4.21 (m, 5 H, H-1, FmocCH_2, 2 × H-Ala), 4.19–4.05 (m, 2 H, Fmoc-CH, H-5), 3.72–3.60 (m, 8 H, OCH_3, H-2, H-3, H-4, H-6, H-6′), 1.47 (s, 9 H, CO_2t-Bu), 1.43–1.36 (m, 6 H, 2 × CH_3-Ala), 0.93 (s, 9 H, $SiCMe_3$), 0.78 (s, 9 H, $SiCMe_3$), 0.21 (s, 3 H, $SiMe_2$), 0.14 (s, 3 H, $SiMe_2$), 0.05 (s, 3 H, $SiMe_2$), 0.01 (s, 3 H, $SiMe_2$).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 171.9 (sugar-CONH), 170.9 (Ala-CO-Ala), 169.5 (CO_2t-Bu), 159.2 (C_{Ar}OMe), 155.4 (Fmoc-CONH), 144.0 (C_{Ar}), 143.8 (C_{Ar}), 141.4 (C_{Ar}), 130.2 (C_{Ar}), 130.0 (C_{Ar}), 127.7 (C_{Ar}), 127.0 (C_{Ar}), 114.0 (C_{Ar}), 113.8 (C_{Ar}), 82.2 [$CO_2C(CH_3)_3$], 80.7 (C-5), 74.0 (PMP*C*H_2), 73.2 (C-1), 71.9 (C-3), 71.8 (C-6), 66.7 (C-2), 55.2 (OCH_3), 55.0 (Fmoc-CH), 52.0 (C-4), 48.8 (NH*C*HCH$_3$-Ala), 48.7 (NH*C*HCH$_3$-Ala), 28.5 [C(*C*H_3)$_3$], 26.9 [SiC(*C*H_3)$_3$], 25.9 [SiC(*C*H_3)$_3$], 25.7 [SiC(*C*H_3)$_3$], 19.3, 18.6 [Si*C*(CH_3)$_3$], 18.0 [Si*C*(CH_3)$_3$], 17.8 (NHCH*C*H$_3$-Ala), –4.8 [Si(CH_3)$_2$], –5.0 [Si(CH_3)$_2$], –5.1 [Si(CH_3)$_2$].

LC-MS: *m*/*z* [MH^+] = 977.6; t_R = 10.95 min (12 min run).

Acknowledgment

Dr. A. J. Culshaw and Dr. G. A. Hughes are thanked for allowing G.P. to use the facilities of Novartis Institutes for Biomedical Research in London.

References

(1) Hirschmann, R.; Nicolaou, K. C.; Pietranico, S.; Leahy, E. M.; Salvino, J.; Arison, B.; Cichy, M. A.; Spoors, P. G.; Shakespeare, W. C.; Sprengler, P. A.; Hamley, P.; Smith, A. B. III; Reisine, T.; Raynor, K.; Maechler, L.; Donaldson, C.; Vale, W.; Freidinger, E. M.; Cascieri, M. A.; Strader, C. D. *J. Am. Chem. Soc.* **1993**, *115*, 12550.

(2) Bols, M. *Carbohydrate Building Blocks*; Wiley: New York, **1996**.

(3) Wunberg, T.; Kallus, C.; Opatz, T.; Henke, S.; Schmidt, W.; Kunz, H. *Angew. Chem. Int. Ed.* **1998**, *37*, 2503.

(4) Scgweuzer, F.; Gubdsgayk, O. *Curr. Opin. Chem. Biol.* **1999**, *3*, 291.

(5) (a) Gruner, S. A. W.; Locardi, E.; Lohof, E.; Kessler, H. *Chem. Rev.* **2002**, *102*, 491; and references cited therein. (b) van Well, R. M.; Marinelli, L.; Altona, C.; Erkelens, K.; Siegal, G.; van Raaij, M.; Llamas-Saiz, A. L.; Kessler, H.; Novellino, E.; Lavecchia, A.; van Boom, J. H.; Overhard, M. *J. Am. Chem. Soc.* **2003**, *125*, 10822. (c) Chakraborty, T. K.; Srinivasu, P.; Bikshapathy, E.; Nagaraj, R.; Vairamani, M. J.; Kumar, S. K.; Kunwar, A. C. *J. Org. Chem.* **2003**, *68*, 6257. (d) Grotenbreg, G. M.; Timmer, M. S. M.; Llamas-Saiz, A. L.; Verdoes, M.; van der Marel, G. A.; van Raaij, M. J.; Overkleeft, H. S.; Overhand, M. *J. Am. Chem. Soc.* **2004**, *126*, 3444.

(6) Chakraborty, T. K.; Ghosh, S.; Jayaprakash, S. *Comb. Chem. High Throughput Screening* **2002**, *5*, 373.

(7) Wormald, M. R.; Petrescu, A. J.; Pao, Y.-L.; Glithero, A.; Elliott, T.; Dwek, R. A. *Chem. Rev.* **2002**, *102*, 371; and references cited therein.

(8) Zhao, X.; Jia, M.-X.; Jiang, X.-K.; Wu, L.-Z.; Li, Z.-T.; Chen, G.-J. *J. Org. Chem.* **2004**, *69*, 270.

(9) (a) Kieber-Emmons, T.; Murali, R.; Greene, M. I. *Curr. Opin. Biotechnol.* **1997**, *8*, 435. (b) Kee, S.; Jois, S. D. S. *Curr. Pharm. Des.* **2003**, *9*, 1209.

(10) (a) Schweizer, F. *Angew. Chem. Int. Ed.* **2002**, *41*, 230. (b) Chakraborty, T. K.; Ghosh, S.; Jayaprakash, S. *Curr. Med. Chem.* **2002**, *9*, 421. (c) Geervay-Hague, J.; Weathers, T. M. *J. Carbohydr. Chem.* **2002**, *21*, 867; and references cited therein.

(11) Schottelius, M.; Wester, H. J.; Reubi, J. C.; Senekowitsch-Schmidtke, R.; Schwaiger, M. *Bioconjugate Chem.* **2002**, *13*, 1021.

(12) Bilsky, E. J.; Egleton, R. D.; Mitchell, S. A.; Palian, M. M.; Davis, P.; Huber, J. D.; Jones, H.; Yamamura, H. I.; Janders, J.; Davis, T. P.; Porrera, F.; Hruby, V. J.; Polt, R. *J. Med. Chem.* **2000**, *43*, 2586.

(13) Albert, R.; Marbach, P.; Bauer, W.; Briner, U.; Fricker, G.; Bruns, C.; Pless, J. *Life Sci.* **1993**, *53*, 517.

(14) Graf von Roedern, E.; Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 687.
(15) Chakraborty, T. K.; Jayaprakash, S.; Sharma, J. A.; Ravikanth, V.; Diwan, P.; Nagaraj, R.; Kunwar, A. C. *J. Am. Chem. Soc.* **1998**, *120*, 12962.
(16) Poitout, L.; Le Merrer, Y.; Depezay, J. C. *Tetrahedron Lett.* **1995**, *36*, 6887.
(17) Smith, M. D.; Long, D. D.; Marquess, D. G.; Claridge, T. D. W.; Fleet, G. W. J. *Chem. Commun.* **1998**, 2039.
(18) Rigid glyco- or alkene-based δ-peptide analogues with ordered conformations in solution have been reported, see: (a) Machetti, F.; Ferrali, A.; Menchi, G.; Occhiato, E. G.; Guarna, A. *Org. Lett.* **2000**, *2*, 3987. (b) Gardner, R. R.; Liang, G.-B.; Gellman, S. H. *J. Am. Chem. Soc.* **1999**, *121*, 1806. (c) Wipf, P.; Henninger, T. C.; Geib, S. J. *J. Org. Chem.* **1998**, *63*, 6088. (d) von Rodern, E. G.; Lohof, E.; Hessleer, G.; Hoffmann, M.; Kessler, H. *J. Am. Chem. Soc.* **1996**, *118*, 10156. (e) Jiang, H.; Leger, J.-M.; Huc, I. *J. Am. Chem. Soc.* **2003**, *125*, 3448. Nowick has used ornithine as a scaffold to build hydrogen-bond-mediated folding systems, see: (f) Nowick, J. S.; Brower, I. O. *J. Am. Chem. Soc.* **2003**, *125*, 876.
(19) Maina, T.; Nock, B.; Nikolopoulou, A.; Sotiriou, P.; Loudos, G.; Maintas, D.; Cordopatis, P.; Chiotellis, E. *Eur. J. Nucl. Med.* **2002**, *29*, 742.
(20) Krenning, E. P.; Bakker, W. H.; Breeman, W. A.; Koper, J. W.; Kooij, P. P.; Ausema, L.; Lameris, J. S.; Reubi, J. C.; Lamberts, S. W. *Lancet* **1989**, *1*, 242.
(21) Froidevaux, S.; Eberle, A. N. *Biopolymers* **2002**, *66*, 161.
(22) Ichikawa, Y.; Suhara, Y.; Yamaguchi, Y.; Collins, B.; Schnaar, R. L.; Yanagishita, M.; Hildreth, J. E. K.; Schimada, I. *Bioorg. Med. Chem.* **2002**, *10*, 1999.
(23) Myers, R. W.; Lee, Y. C. *Carbohydr. Res.* **1986**, *154*, 145.
(24) Jayachitra, G.; Yasmeen, Y.; Srinivasa Rao, K.; Ralte, S. L.; Srinivasan, R.; Singh, A. K. *Synth. Commun.* **2003**, *33*, 3461.
(25) Garegg, P. J.; Hultberg, H. *Carbohydr. Res.* **1982**, *110*, 261.
(26) Sawada, D.; Ito, Y. *Tetrahedron Lett.* **2001**, *42*, 2501.
(27) Simiand, C.; Samain, E.; Martin, O. R.; Driguez, H. *J. Carbohydr. Res.* **1995**, *267*, 1.