Carbopeptoids: peptides and diketopiperazines incorporating the anomeric centre of mannopyranose

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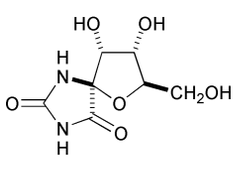
An approach to the synthesis of D-mannopyranose derivatives incorporating an anomeric α-amino acid component is described. An *N*-acylated bicyclic [2.2.2] lactone, formed *via* an oxidative ring closure, provides access to a new class of glycopeptide analogues of D-mannopyranose and determines the anomeric configuration of compounds derived therefrom. The mannopyranose diketopiperazine may be equilibrated to the more stable furanose form under basic conditions; in general, mannopyranose derivatives containing an α-amino acid moiety at the anomeric position are less stable than the mannofuranose isomers.

Introduction

The unique structure of the natural product hydantocidin[1] **1** and its potent herbicidal properties[2] have stimulated considerable interest in both the synthesis of **1** itself[3] and of a wide range of analogues.[4] The D-glucopyranose analogue of hydantocidin, compound **2**, is the most powerful inhibitor of glycogen phosphorylase (GP) known which binds at the active site.[5] The related glucopyranosyl spirodiketopiperazine **3**



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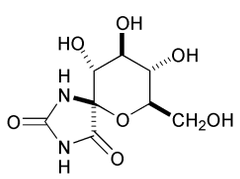

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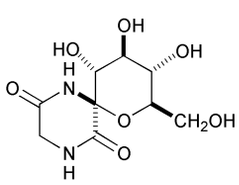

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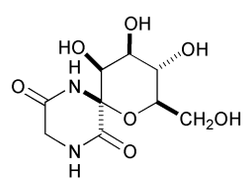

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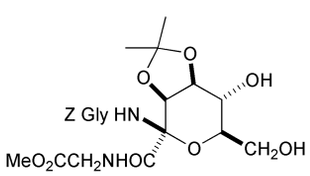

5

has been shown to be a highly specific inhibitor of GP[6] which does not inhibit a range of glucosidases; diketopiperazines in general have a number of potential chemotherapeutic applications.[7,8] Substantial work on thiospirohydantions as GP inhibitors has also been reported.[9]

Carbohydrate analogues possessing both an *N*-acyl group and a carbonyl function at the anomeric carbon are chemically quite stable in regard to both the anomeric configuration and the ring size of the sugar; although harsh treatment with acid or base can cause equilibration to more stable isomers, all these materials are kinetically stable and do not equilibrate under mild conditions.[10] The spirodiketopiperazines of mannofuranose are more stable than the pyranose isomers; treatment of D-mannofuranose diketopiperazines under basic conditions merely induces equilibration to the more stable anomer.[11,12] Oligopeptides **5**, in which the anomeric carbon of a sugar is one of the α-amino acid constituents,[13] form an interesting set of novel *N*-linked glycopeptides, and have been proposed as potential peptidomimetics.[14] Recently, oligomers of furanose derivatives bearing amino-acid functionality have been shown to form helical[15] and β-turn-like secondary structures.[16]

Results and discussion

The strategy employed for the synthesis of D-mannopyranose derivatives bearing an anomeric α-amino acid component involves oxidation of the C-2 nitrogen-bearing substituent of a suitably configured seven-carbon lactone **6** with concomitant closure from the hydroxy group at C-6. This affords a [2.2.2] bicyclic lactone **7** which upon opening gives amino acid derivatives **8** with complete anomeric stereocontrol (Scheme 1). Structures such as the bicycle **7** are attractive intermediates for the synthesis of spiro derivatives of pyranose sugars since the pyranose ring is 'pre-formed' and the configuration at the anomeric position has already been defined by the bicyclic structure. Utilising this strategy, we describe the preparation of the tripeptide **5** and the spirodiketopiperazine **4**, and investigate the relative stabilities and reactivities of bicyclic lactones of this nature in an approach to a mannopyranose spirohydantoin. Certain aspects of this work have been published in preliminary form.[17]

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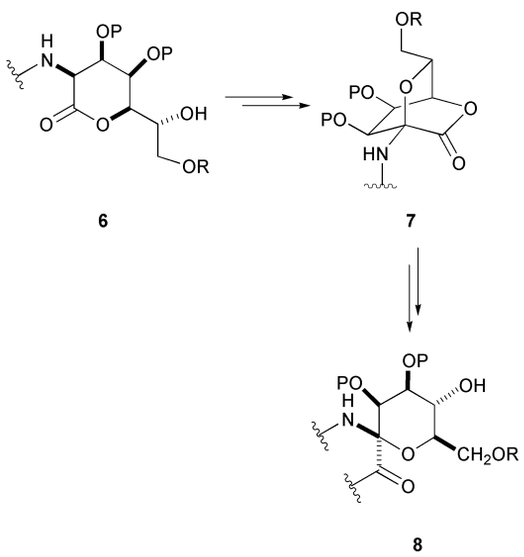
The requisite amino lactone **9** is available by an efficient route[18] from the Kiliani ascension product of diacetone D-mannose.[19] Treatment of the amino lactone **9** with Z-glycine, activated *in situ* as its mixed anhydride with ethyl chloroformate, gave the dipeptide **10** in 86% yield. Selective removal of the primary isopropylidene protecting group was effected with aqueous acetic acid to afford the diol **11** in quantitative yield, which was oxidised with *N*-bromophthalimide in acetonitrile in the presence of sodium acetate to afford the bicycle **13** in 27% yield (54% based on consumed starting material) (Scheme 2). A possible mechanism for this transformation involves initial *N*-bromination and elimination to give a non-isolable imine **12** which is trapped intramolecularly by the free C-6 hydroxy group to afford the bicyclic lactone **13**. Attempts to improve the efficacy of this procedure were unsuccessful, and the yield remains unsatisfactorily low. The bicyclic structure **13** was confirmed by the presence of a long-range 'W' coupling, between H-6 and H-7, characteristic of a rigid system (Fig. 1).

Subsequent hydrogenation of the dipeptide **13** in methanol in the presence of palladium black effected removal of the benzyloxycarbonyl protecting group to give the non-isolable free amine **14** which spontaneously cyclised to give the spirodiketopiperazine **15** in 78% yield. Removal of the isopropylidene group in **15** by hydrolysis in aqueous trifluoroacetic acid (TFA) gave the target unprotected spirodiketopiperazine of mannopyranose, compound **4**, in quantitative yield, the first example of a spiro derivative of mannopyranose. Reaction of **15** with potassium *tert*-butoxide in dimethylformamide (DMF) gave the known mannofuranose **16** in 92% yield; similar equilibration of the unprotected mannopyranose **4** gave the mannofuranose isomer **17**. It is thus clear that the mannofuranose in which the nitrogen is *cis* to the diol unit is the thermodynamically most stable form of all the pyranose and furanose isomers of the anomeric spirodiketopiperazines. The bicyclic lactone **13** could be directly opened with methyl glycinate hydrochloride and sodium acetate in DMF to give the tripeptide **5** (62% yield) in which the α-carbon of the central constituent amino acid is the anomeric position of mannopyranose.

NMR spectroscopy was used to confirm the covalent structure and relative stereochemistry of **15**, **4** and **5**. Complete CH and NH, and partial OH, resonance assignments were obtained for all three compounds. For the protected diketopiperazine **15**, OH resonances were observed for OH-3 and OH-12 but not



Scheme 1 Strategy for the synthesis of mannopyranose anomeric amino acid derivatives.

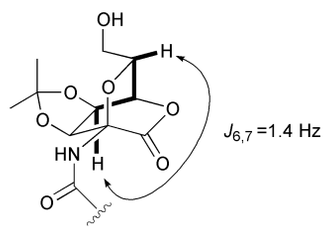
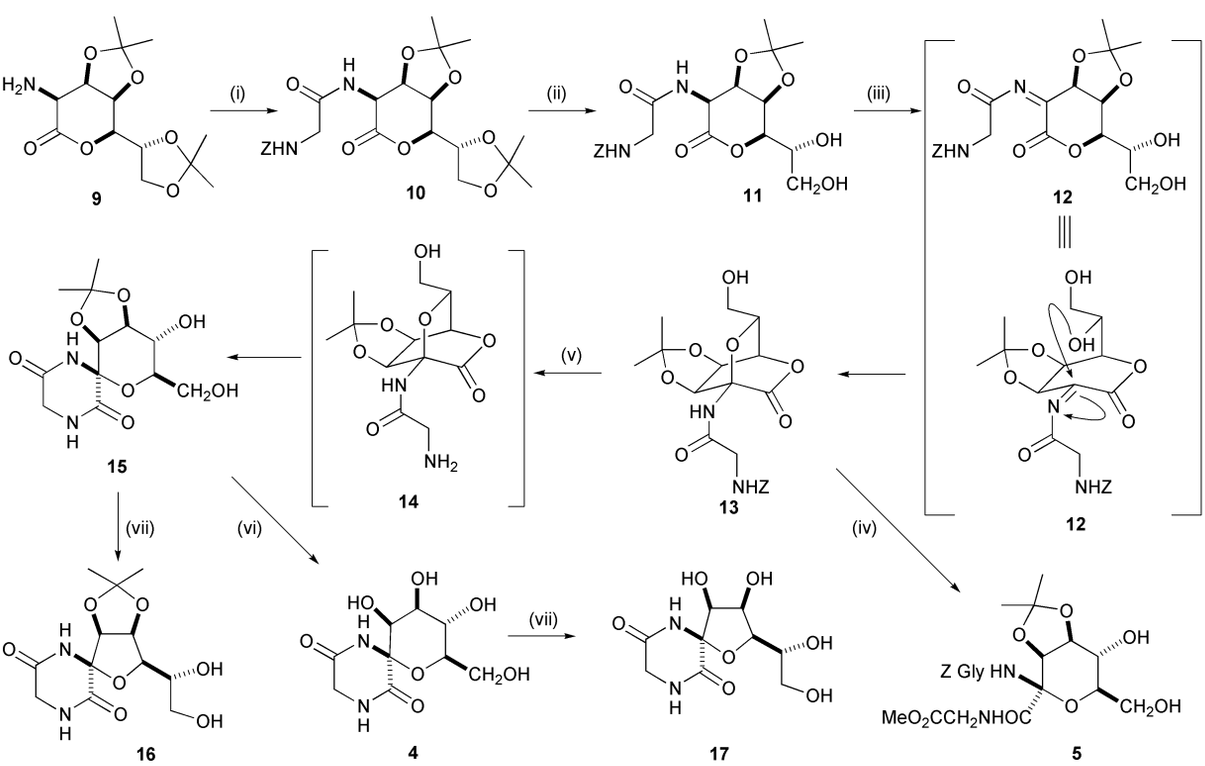


Fig. 1 'W' coupling observed in bicyclic systems.



Scheme 2 *Reagents and conditions*: (i) Z-Gly-OH, $ClCO_2Et$, Et_3N, THF–MeCN (1 : 1) (ii) aq. AcOH (iii) *N*-bromophthalimide, NaOAc, CH_3CN (iv) H-Gly-OMe·HCl, NaOAc, DMF (v) H_2, Pd-black, EtOAc (vi) TFA–water (1 : 1) (vii) KO^{t}Bu, DMF.

Table 1 Proton–proton distances (Å) for **4** and its C-6 epimer, determined by molecular modelling. Proton pairs which would be expected to give strong NOEs are shown in bold

	C2-H	C3-H	C4-H	C5-H
NH-7 ($N7^{eq}$) **4**	4.85	4.39	4.77	3.09
NH-7 ($N7^{ax}$)	**2.53**	4.44	**2.27**	**2.29**

for OH-2, confirming the pyranose ring structure. Full OH assignments could not be made for **4** and **5** because of peak width. The observation of well-separated resonances for H-12 and H′-12 and small $J_{2,12}$ coupling constants in all three compounds indicates hindered rotation about C2–C12, consistent with OH-2 forming part of the ring. Also, the $J_{2,3}$, $J_{3,4}$ and $J_{4,5}$ coupling constants for **4** are fully consistent with a deprotected mannopyranose ring system. The relative stereochemistry at the anomeric centre (C6) of **4** was determined by the pattern of observed nuclear Overhauser effects (NOEs) (Fig. 2).

NH-7 gives a medium-strength NOE to H-5 and a weak NOE to H-3. Molecular modelling of **4** and the other possible anomeric stereochemistry (its C6 epimer) shows both to have a $^4C_1$ ring conformation, and that the configuration with an axial NH-7 would give strong NOEs between NH-7 and H-2, H-4 and H-5 (Table 1). Thus, the observed pattern is only consistent with NH-7 being equatorial and on the same side of the ring as H-3.

The relative stereochemistry at the anomeric centre (C2) of **5** was determined in a similar fashion. The 'anomeric' NH proton gives a strong NOE to H-5 and to the isopropylidene methyl resonance at δ 1.46. This methyl also gives strong NOEs to H-5, whilst the other isopropylidene methyl resonance, at δ 1.31, gives strong NOEs to H-3 and H-4. This allows stereospecific assignment of the two methyl groups, with the group giving a resonance at δ 1.31 being on the same side of the ring as H-3 and H-4, and the group giving a resonance at δ 1.46 being on the same side of the ring as H-5. This then places the 'anomeric' NH group on the same side of the ring as H-5, *i.e.* in an equatorial position.

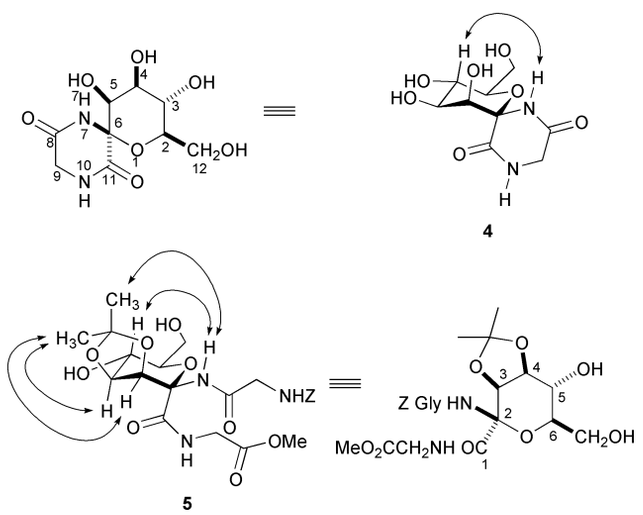


Fig. 2 Significant NOE enhancements for the diketopiperazine **4** and the tripeptide **5** indicating numbering scheme.

An alternative approach to the synthesis of mannopyranose anomeric amino acid derivatives might involve formation of the bicyclic lactone prior to acylation; in the synthesis of 5-*epi*-hydantocidin **21**, the key step was the transformation of the epimeric azido lactones **18** into the bicyclic amine **20** by tetra-*n*-propylammonium perruthenate (TPAP)[20] in the presence of morpholine *N*-oxide (Scheme 3); in this case the equilibrium strongly favours the amine **20** over the imine **19**.[21]

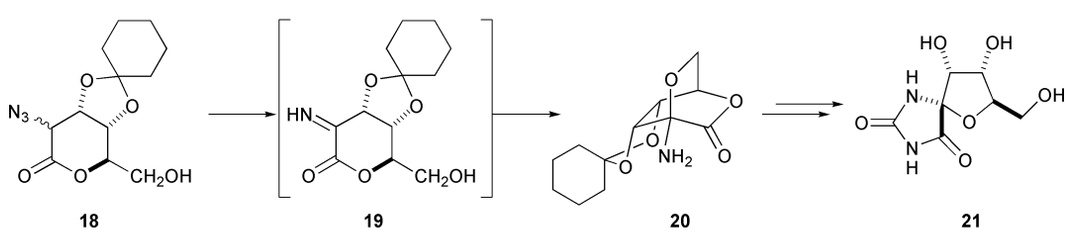
Hydrogenation of the azido lactone **22** in ethyl acetate in the presence of palladium black afforded the 2-amino lactone **24** (Scheme 4). The amino lactone **24** was subjected to the oxidative bromination conditions described previously (in an attempt to isolate the bicycle **27**) gave a complex mixture of decomposition products, although all starting materials were rapidly consumed. Attempts to acylate the putative bicycle **27** *in situ* – for example with methyl chloroformate to afford **28** – were unsuccessful, resulting in intractable mixtures of compounds. The reasons for the instability of this amino bicycle **27** in comparison to the D-*allo*-configured bicycle **20** is not clear; the presence of the free primary alcohol in **27** may allow a number of other equilibrium processes to be established.[22]

In an attempt to circumvent this problem, the primary alcohol in the azido lactone **22** was selectively protected as a silyl ether by reaction with *tert*-butyldimethylsilyl chloride (TBDMSCl) and imidazole in DMF to afford the known monosilyl derivative **23** in 70% yield.[18] Reduction of the azide **23** by hydrogenation in ethyl acetate in the presence of palladium black gave the protected 2-amino lactone **25** (Scheme 4). When the protected amino lactone **25** was submitted to oxidative cyclisation with *N*-bromosuccinimide (NBS), sodium acetate and diisopropylethylamine in acetonitrile, the amino bicycle **29** was isolated in good yield (75%). However, all attempts to acylate **29** proved unsuccessful, giving only low yields of materials which were difficult to characterise.

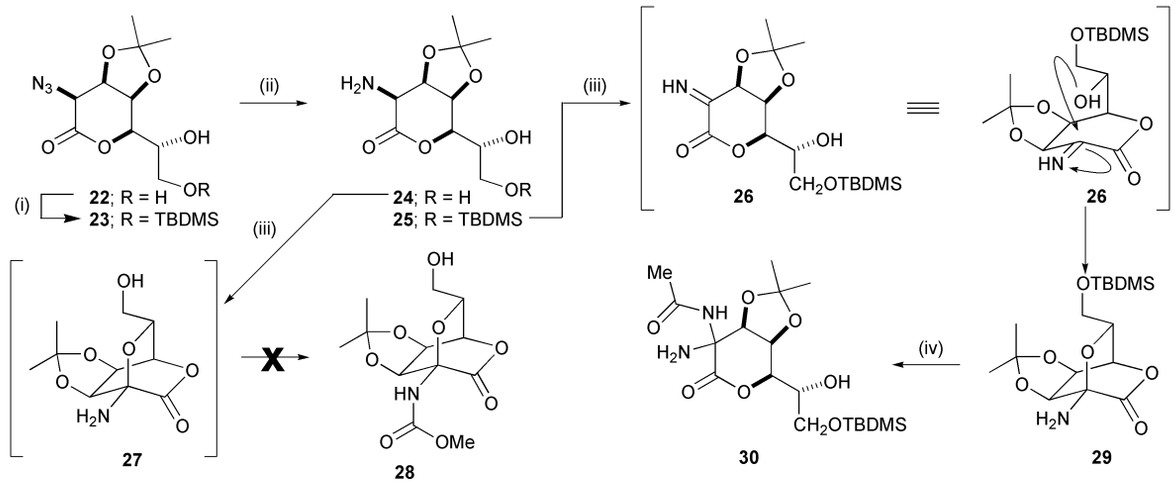
Reaction of the bridgehead amine **20** with cyanate leads to the efficient construction of the spirohydantoin ring system **21** (Scheme 3). It was anticipated that the amine **29** would undergo a similar series of reactions leading to a spirohydantoin at the anomeric position of mannopyranose. However, treatment of the bicycle **29** with potassium cyanate in acetic acid resulted in the isolation of a single amide **30** in 63% yield; the configuration of the C-2 carbon of the monoacetylated aminal **30** was not determined. This product might arise from nucleophilic attack by cyanate ion on the imine tautomer **26** in equilibrium with **29**; the resulting amino isocyanate **31** could react with acetic acid to form a mixed anhydride **32**. Subsequent intramolecular transacylation accompanied by loss of carbon dioxide would yield the monoacylated aminal **30** (Scheme 5).

Conclusions

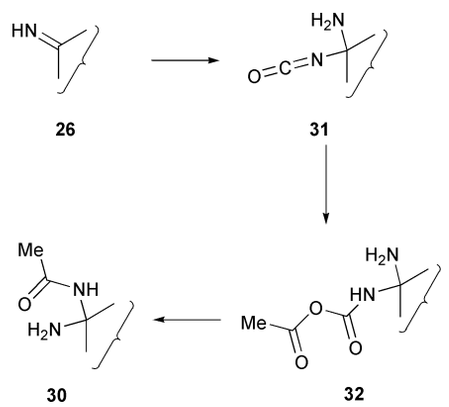
This paper reports a viable route to mannopyranose anomeric amino acid derivatives with complete anomeric stereocontrol *via* a [2.2.2] bicyclic lactone as exemplified by the synthesis of the tripeptide **5** and the spirodiketopiperazine **4**. Although the protected bicyclic amino lactone **29** may be prepared efficiently, further work is required to establish conditions which would



Scheme 3 Previous approach to 5-*epi*-hydantocidin.



Scheme 4 *Reagents and conditions*: (i) TBDMSCl, imidazole, DMF (ii) H_2, Pd-black, EtOAc (iii) NBS, NaOAc, Pr^i_2NEt, CH_3CN (iv) KOCN, AcOH.



Scheme 5 Possible pathway for the formation of **30**.

allow utilisation of this intermediate for the generation of mannopyranosyl amine analogues. It is clear that acylation prior – rather than subsequent – to the generation of the bicyclic amino lactone moiety is a more successful strategy for the synthesis of mannopyranose structures possessing an amino acid residue at the anomeric position.

Experimental

Mps were recorded on a Kofler block and are uncorrected. Proton nuclear magnetic resonance (δ_H) spectra were recorded on a Bruker AMX 500 (at 500 MHz) spectrometer, or where stated, on a Varian Gemini 200 (at 200 MHz). Carbon nuclear magnetic resonance (δ_C) spectra were recorded on a Varian Gemini 200 (at 50.3 MHz) or, where stated, on a Bruker AMX 500 (at 125 MHz) spectrometer; multiplicities were assigned using a DEPT sequence. All chemical shifts are quoted on the δ-scale using residual solvent as an internal standard. *J*-Values are in Hz. Abbreviations a-d and a-t stand for apparent doublet and apparent triplet, respectively, in the ^{1}H NMR multiplicities. ^{1}H NMR spectra of compounds **15** and **4** in dimethyl sulfoxide (DMSO), and **5** in $CDCl_3$, were recorded on a Varian Unity 500, with a probe temperature of 30 °C. Resonance assignments were obtained from the 1D and phase-sensitive 2D COSY spectra, referenced to the residual solvent signal (δ 7.24 for $CDCl_3$, δ 2.49 for DMSO). Unambiguous assignments could be made to all CHs and NHs and to some OHs. The only remaining ambiguities were in the stereospecific assignments of the CH_2 protons, the stereospecific assignments of the protecting-group methyl resonances in **15**, and the assignment of the glycine resonances in **5** to either the equatorial glycine or axial glycine residues. The sequence-specific glycine assignments of **5** were obtained from the pattern of NOEs to the ring protons, resonances of the axial glycine residue giving NOEs to the equatorial Z-Gly-NH, and the amide resonance of the axial glycine residue giving an NOE to C6-H. Phase-sensitive 2D NOESY spectra were recorded with a mixing time of 400 ms without any random variation. Molecular modelling was performed on a Silicon Graphics Indigo 2 workstation using Insight II and Discover software (MSI). IR spectra were recorded on a Perkin-Elmer 1750 IR FT spectrophotometer. Mass spectra were recorded on VG Micromass 20–250, ZAB 1F, Micromass Platform 1 or Trio-1 GCMS (DB-5 column) spectrometers using desorption chemical ionization (DCI, NH_3), chemical ionisation (CI, NH_3), fast-atom bombardment (FAB), atmospheric-pressure chemical ionisation (APCI) or electrospray (ES) techniques, as stated. Optical rotations were measured on a Perkin-Elmer 241 polarimeter with a path length of 1 dm. $[a]_D$-Values are given in units of 10^{-1} deg cm^2 g^{-1}. Concentrations are given in g (100 ml)$^{-1}$. Hydrogenations were executed under an atmosphere of hydrogen gas maintained by inflated balloon. Microanalyses were performed by the microanalysis service of the Dyson Perrins Laboratory. TLC was carried out on aluminium sheets coated with $60F_{254}$ silica or glass plates coated with silica blend 41. Plates were developed 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 (for amines). Flash chromatography was carried out using Sorbsil C60 40/60 silica. Solvents and commercially available reagents were dried and purified before use according to standard procedures; in particular, dichloromethane was refluxed over, and distilled from, calcium hydride, methanol was purchased dry in Aldrich Sure-Seal™ bottles, pyridine was distilled from, and stored over, potassium hydroxide, tetrahydrofuran (THF) was distilled, under nitrogen, from a solution dried with sodium in the presence of benzophenone. Hexane was distilled before use to remove involatile fractions. A solution of KH_2PO_4 (85 g) and NaOH (14.5 g) in distilled water (950 ml) was used as a pH 7 buffer solution.

2-{[*N*-(Benzyloxycarbonyl)glycyl]amino}-2-deoxy-3,4 : 6,7-di-*O*-isopropylidene-D-*glycero*-D-*talo*-heptono-1,5-lactone 10

Triethylamine (1.92 ml, 13.6 mmol) was added to a stirred solution of *N*-(benzyloxycarbonyl)glycine (2.84 g, 13.6 mmol) in acetonitrile–THF (1 : 1; 100 ml) under an atmosphere of nitrogen. The mixture was stirred at room temperature for 5 min and then cooled to 0 °C. Ethyl chloroformate (1.32 ml, 13.6 mmol) was added and the mixture was stirred for a further 10 min. The amine **9** (3.00 g, 10.5 mmol) and pyridine (2.5 ml), in acetonitrile–THF (2 : 1; 45 ml), were added and the mixture was

stirred at 0 °C for 1 h, warmed to room temperature, and stirred for a further 1.5 h, when TLC (hexane–ethyl acetate 1 : 2) indicated complete conversion of the starting material (R_f 0.0) into a major product (R_f 0.3). The solvent was removed *in vacuo* (co-evaporation with toluene) and the residue was preadsorbed onto silica and purified by flash chromatography (hexane–ethyl acetate 1 : 2) to yield *2-{[N-(benzyloxycarbonyl)glycyl]amino}-2-deoxy-3,4 : 6,7-di-O-isopropylidene-D-glycero-D-talo-heptono-1,5-lactone* **10** (4.31 g, 86%) as a white solid, mp 200–202 °C (from ethyl acetate); $[\alpha]_D^{20}$ +98.9 (*c* 1.00, $CHCl_3$); IR (KBr) ν_{max} 3333 (NH), 1768 (C=O, lactone), 1723, 1679 (C=O) cm^{-1}; δ_H ($CDCl_3$; 500 MHz) 1.35, 1.39, 1.42, 1.46 [12H, 4 s, 2 × $C(CH_3)_2$], 4.01–4.02 (2H, m, $CH_2NHCO_2CH_2Ph$), 4.07 (1H, dd, $J_{7,6}$ = 3.7, $J_{7,7'}$ = 9.3, H-7), 4.12 (1H, a-d, H-5), 4.15 (1H, dd, $J_{7',6}$ = 6.0, H′-7), 4.41 (1H, ddd, $J_{6,5}$ = 8.5, H-6), 4.71 (1H, a-d, H-4), 4.83 (2H, a-t, H-2, -3), 5.16 (2H, AB s, $ArCH_2$), 5.40 (1H, br s, NH, exchanges in D_2O), 6.75 (1H, br d, NH, exchanges in D_2O), 7.31–7.39 (5H, m, ArH); δ_C ($CDCl_3$; 50.3 MHz) 24.3, 25.0, 25.8, 27.0 [4 q, 2 × $C(CH_3)_2$], 44.2, 66.5, 67.2 (3 t, C-7, 2 × CH_2), 51.4, 72.2, 72.5, 73.9, 76.7 (5 d, C-2, -3, -4, -5, -6), 110.0, 110.7 [2 s, 2 × $C(CH_3)_2$], 128.1, 128.2, 128.5 (3 d, 5 × ArC), 136.1 (s, ArC), 156.5, 168.0, 169.5 (3 s, 3 × C=O); *m/z* (CI, NH_3) 496 (M + NH_4^+, 19), 479 (M + H^+, 15), 308 (70), 200 (100), 183 (85), 131 (97), 91 (51%) (Found: C, 57.71; H, 6.06; N, 5.81. Calc. for $C_{23}H_{30}N_2O_9$ C, 57.73; H, 6.32; N, 5.85%).

2-{[*N*-(Benzyloxycarbonyl)glycyl]amino}-2-deoxy-3,4-*O*-isopropylidene-D-*glycero*-D-*talo*-heptono-1,5-lactone 11

The glycine derivative **10** (3.00 g, 6.3 mmol) was stirred in acetic acid–water (1 : 1; 110 ml) at 50 °C for 2 h, when TLC (ethyl acetate–methanol 19 : 1) indicated complete conversion of the starting material (R_f 0.7) to a single product (R_f 0.3). The solvent was removed *in vacuo* (co-evaporation with toluene) to give a white solid (2.78 g) which was used without further purification. A quantity was crystallised (ethyl acetate–diethyl ether) to yield *2-{[N-(benzyloxycarbonyl)glycyl]amino}-2-deoxy-3,4-O-isopropylidene-D-glycero-D-talo-heptono-1,5-lactone* **11** as a white solid, mp 162 °C (from ethyl acetate–diethyl ether); $[\alpha]_D^{25}$ +105.9 (*c* 1.00, MeOH); IR (KBr) ν_{max} 3461, 3341, 3289 (NH, OH), 1757 (C=O, lactone), 1717, 1691 (C=O) cm^{-1}; δ_H (CD_3OD; 500 MHz) 1.35, 1.38 [6H, 2 s, $C(CH_3)_2$], 3.69 (1H, dd, $J_{7,6}$ = 4.6, $J_{7,7'}$ = 9.3, H-7), 3.77 (1H, dd, $J_{7',6}$ = 2.5, H′-7), 3.88 (1H, ddd, $J_{6,5}$ = 9.1, H-6), 3.91–3.92 (2H, m, $CH_2NHCO_2CH_2Ph$), 4.39 (1H, a-d, H-5), 4.77–4.86 (2H, m, H-3, -4), 4.97 (1H, a-d, H-2), 5.11 (2H, AB s, $ArCH_2$), 7.27–7.37 (5H, m, ArH); δ_C (CD_3OD; 50.3 MHz) 24.5, 26.4 [2 q, $C(CH_3)_2$], 44.6, 63.8, 67.9 (3 t, C-7, 2 × CH_2), 52.7, 70.1, 73.8, 75.7, 76.8 (5 d, C-2, -3, -4, -5, -6), 111.3 [s, $C(CH_3)_2$], 128.9, 129.1, 129.6 (3 d, 5 × ArC), 138.2 (s, ArC), 159.2, 170.7, 172.3 (3 s, 3 × C=O); *m/z* (DCI, NH_3) 456 (M + NH_4^+, 1), 439 (M + H^+, 2), 308 (60), 183 (63), 108 (93), 91 (100%) (Found: C, 54.67; H, 5.87; N, 6.48. Calc. for $C_{20}H_{26}N_2O_9$ C, 54.78; H, 5.99; N, 6.39%).

(1*R*,4*S*,6*R*,7*S*,8*S*)-4-{[*N*-(Benzyloxycarbonyl)glycyl]amino}-6-hydroxymethyl-7,8-isopropylidenedioxy-2,5-dioxabicyclo[2.2.2]-octan-3-one 13

N-Bromophthalimide (568 mg, 2.5 mmol) and sodium acetate (562 mg, 6.9 mmol) were added to a solution of the diol **11** (1.00 g, 2.3 mmol) in acetonitrile (50 ml). The mixture was warmed to 80 °C and stirred overnight, under an atmosphere of nitrogen. TLC (ethyl acetate–methanol 19 : 1) indicated the presence of starting material (R_f 0.3) and a major product (R_f 0.6). The reaction mixture was cooled to room temperature, filtered, and the solvent removed *in vacuo.* The residue was preabsorbed onto silica and purified by flash chromatography (ethyl acetate) to yield *(1R,4S,6R,7S,8S)-4-{[N-(benzyloxycarbonyl)glycyl]-amino}-6-hydroxymethyl-7,8-isopropylidenedioxy-2,5-dioxabicyclo[2.2.2]octan-3-one* **13** (266 mg, 27%, 54% based on consumed starting material) as a colourless oil, mp 226–228 °C (from acetone); $[\alpha]_D^{22}$ +23.4 (*c* 1.00, MeOH); IR (KBr) ν_{max} 3491, 3321 (NH, OH), 1766 (C=O, lactone), 1726, 1695 (C=O) cm^{-1}; δ_H (CD_3CN; 500 MHz) 1.36, 1.58 [6H, 2 s, $C(CH_3)_2$], 3.09 (1H, br s, OH), 3.81 (2H, a-d, *J* = 6.1, $CH_2NHCO_2CH_2Ph$), 3.84–3.94 (2H, m, CH_2OH), 4.23 (1H, m, H-6), 4.72 (1H, ddd, $J_{7,8}$ = 8.4, $J_{7,1}$ = 4.4, $J_{7,6}$ = 1.4, H-7), 4.77 (1H, d, H-8), 4.86 (1H, dd, $J_{1,6}$ = 1.0, H-1), 5.10 (2H, AB s, $ArCH_2$), 5.93 (1H, br s, NH), 7.09 (1H, br s, NH), 7.32–7.41 (5H, m, ArH); δ_C (d_6-DMSO; 50.3 MHz) 24.3, 24.9 [2 q, $C(CH_3)_2$], 43.3, 60.4, 65.6 (3 t, CH_2OH, 2 × CH_2), 71.2, 72.7, 73.7, 79.6 (4 × d, C-1, -6, -7, -8), 82.0 (s, C-4), 113.9 [s, $C(CH_3)_2$], 127.9, 128.0, 128.5 (3 d, 5 × ArC), 137.2 (s, ArC), 156.6, 166.9, 168.7 (3 s, 3 × C=O); *m/z* (CI, NH_3) 454 (M + NH_4^+, 40), 437 (M + H^+, 74), 108 (100), 91 (75%) (Found: C, 55.34; H, 5.55; N, 6.14. Calc. for $C_{20}H_{24}N_2O_9$ C, 55.04; H, 5.54; N, 6.42%).

(2*R*,3*R*,4*S*,5*S*,6*S*)-3-Hydroxy-2-hydroxymethyl-4,5-isopropylidenedioxy-1-oxa-7,10-diazaspiro[5.5]undecane-8,11-dione 15

A solution of the bicyclic lactone **13** (124 mg, 0.28 mmol) in methanol (14 ml) was stirred under an atmosphere of hydrogen in the presence of palladium black (10 mg). After 48 h, TLC (ethyl acetate–methanol 9 : 1) indicated complete conversion of starting material (R_f 0.7) into a major product (R_f 0.4). The reaction mixture was filtered through Celite (eluted with methanol) and the solvent removed *in vacuo.* The residue was purified by flash chromatography (ethyl acetate–methanol 9 : 1) to yield *(2R,3R,4S,5S,6S)-3-hydroxy-2-hydroxymethyl-4,5-isopropylidenedioxy-1-oxa-7,10-diazaspiro[5.5]undecane-8,11-dione* **15** (66 mg, 78%) as a white solid, mp 125–127 °C (from EtOAc); $[\alpha]_D^{22}$ +45.2 (*c* 0.66, MeOH); IR (KBr) ν_{max} 3399 (NH, OH), 1694 (C=O, amide) cm^{-1}; δ_H (CD_3OD; 500 MHz) 1.39, 1.55 [6H, 2 s, $C(CH_3)_2$], 3.50–3.56 (2H, m, CH_2OH), 3.60 (1H, a-dd, H-2), 3.77 (1H, d, $J_{9,9'}$ = 17.8, H-9), 3.81–3.83 (1H, m, H-3), 4.26 (1H, d, H′-9), 4.36–4.40 (2H, m, H-4, -5); δ_H (500 MHz; DMSO) 1.31, 1.44 [6H, 2 s, 4,5-$C(CH_3)_2$], 3.29 (1H, m, H-3), 3.30 (1H, m, OH-12), 3.38 (1H, dt, $J_{2,12'}$ = 5.4, $J_{12,12'}$ = 12.3, $J_{12',OH}$ = 5.4, H′-12), 3.60 (1H, m, H-9′), 3.61 (1H, m, H-12), 4.11 (1H, d, $J_{9,9'}$ = 17.5, H-9), 4.21 (1H, t, $J_{3,4}$ = $J_{4,5}$ = 5.9, H-4), 4.28 (1H, d, H-5), 4.62 (1H, m, H-2), 5.25 (1H, d, $J_{3,OH}$ = 5.6, OH-3), 7.57 (1H, s, NH-7), 8.51 (1H, d, $J_{9,10}$ < 1, $J_{9',10}$ = 4.2, NH-10); δ_C (CD_3OD; 50.3 MHz) 25.3, 27.0 [2 q, $C(CH_3)_2$], 44.1, 61.3 (2 t, C-9, CH_2OH), 68.4, 73.8, 75.7, 80.0 (4 d, C-2, -3, -4, -5), 82.1 (s, C-6), 109.5 [s, $C(CH_3)_2$], 165.2, 169.9 (2 s, 2 × C=O); *m/z* (CI, NH_3) 320 (M + NH_4^+, 19), 303 (M + H^+, 20), 108 (28), 61 (100%); HRMS (FAB+) Calc. for $C_{12}H_{19}N_2O_7$ (M + H^+): *m/z* 303.1192. Found: *m/z* 303.1192.

Methyl *N*-(2,6-anhydro-2-{[*N*-(benzyloxycarbonyl)glycyl]-amino}-3,4-*O*-isopropylidene-D-*glycero*-D-*talo*-heptonoyl)-glycinate 5

Glycine methyl ester hydrochloride (56 mg, 44.5 mmol) and sodium acetate (73 mg, 0.89 mmol) were added to a solution of the bicyclic lactone **13** (97 mg, 0.22 mmol) in DMF (5 ml). The mixture was warmed to 70 °C under an atmosphere of nitrogen, and stirred overnight. TLC (ethyl acetate–methanol 19 : 1) indicated conversion of the starting material (R_f 0.6) into a major product (R_f 0.2). The solvent was removed *in vacuo* (co-evaporation with toluene) and the residue was preabsorbed onto silica and purified by flash chromatography (ethyl acetate–methanol 19 : 1) to yield *methyl N-(2,6-anhydro-2-{[N-(benzyloxycarbonyl)glycyl]amino}-3,4-O-isopropylidene-D-glycero-D-talo-heptonoyl)glycinate* **5** (72 mg, 62%) as a white solid, mp 80–81 °C (from ethyl acetate–methanol); $[\alpha]_D^{22}$ −3.5 (*c* 1.00, $CHCl_3$); IR (KBr) ν_{max} 3402 (NH, OH), 1740sh (C=O, ester), 1689 (C=O) cm^{-1}; δ_H ($CDCl_3$; 500 MHz) 1.31, 1.46 [6H, 2 s, $C(CH_3)_2$], 3.63 (1H, m, H-6), 3.70 (3H, s, OCH_3), 3.71, 3.83 (2H, 2 m, H_2-7), 3.86, 4.16 (2H, 2 dd, J_{gem} = 18.2, *J* = 6.3,

$CH_2NHCO_2CH_2Ph$), 3.87 (2H, m, $NHCH_2CO_2Me$), 4.06 (1H, m, H-5), 4.24 (1H, a-t, H-4), 4.56 (1H, d, $J_{3,4}$ = 7.5, H-3), 5.07 (2H, AB s, $ArCH_2$), 5.96 (1H, br s, $NHCH_2CO_2Me$), 7.30–7.36 (5H, m, ArH), 7.40 (1H, s, NHGlyZ), 7.61 (1H, br s, CH_2NH-CO_2CH_2Ph); δ_C ($CDCl_3$; 50.3 MHz) 24.4, 26.6 [2 q, $C(CH_3)_2$], 41.1, 45.0, 61.4, 67.4 (4 t, C-7, 3 × CH_2), 67.2, 74.1, 76.0, 78.3 (4 d, C-3, -4, -5, -6), 83.7 (s, C-2), 110.4 [s, $C(CH_3)_2$], 128.3, 128.5 (2 d, 5 × ArC), 135.8 (s, ArC), 156.9 (s, C=O, amide), 168.8, 170.1, 171.1 (3 s, 3 × C=O); *m/z* (CI, NH_3) 543 (M + NH_4^+, 10), 526 (M + H^+, 27), 108 (100), 90 (76%) (HRMS (FAB) Calc. for $C_{23}H_{31}N_3O_{11}$ (*M* + H^+): *m/z*, 526.2037. Found: *m/z*, 526.2025.

(2*R*,3*S*,4*S*,5*S*,6*S*)-3,4,5-Trihydroxy-2-hydroxymethyl-1-oxa-7,10-spiro[5.5]undecane-8,11-dione 4

The diketopiperazine **15** (43 mg, 0.14 mmol) was stirred in TFA–water (3 : 2; 6 ml) at room temperature for 5 h, when TLC (ethyl acetate–methanol 19 : 1) indicated conversion of the starting material (R_f 0.2) into a major product (R_f 0.1). The solvent was removed *in vacuo* (co-evaporation with toluene) to yield *(2R,3S,4S,5S,6S)-3,4,5-trihydroxy-2-hydroxymethyl-1-oxa-7,10-spiro[5.5]undecane-8,11-dione* **4** (36 mg, quantitative) as a white solid, mp 225–226 °C (from methanol); $[\alpha]_D^{21}$ +50.0 (*c* 0.36, H_2O); IR (KBr) ν_{max} 3366, 3288 (NH, OH), 1695, 1667 (C=O, amide) cm^{-1}; δ_H (D_2O; 500 MHz) 3.53 (1H, ddd, J_{2,CH_2OH} = 2.3, J_{2,CH_2OH} = 6.0, $J_{2,3}$ = 9.7, H-2), 3.60 (1H, a-t, H-3), 3.67 (1H, dd, J_{gem} = 12.4, CH_2OH), 3.83 (1H, dd, CH_2OH), 3.88 (1H, d, $J_{9,9'}$ = 8.4, H-9), 4.10 (1H, d, $J_{5,4}$ = 3.7, H-5), 4.24 (1H, d, H′-9), 4.43 (1H, dd, $J_{4,3}$ = 9.4, H-4); δ_H (500 MHz; DMSO) 3.22 (1H, m, H-2), 3.31 (1H, dd, $J_{2,3}$ = 9.2, $J_{3,4}$ = 8.8, H-3), 3.35 (1H, dt, $J_{2,12'}$ = 6.7, H′-12), 3.55 (1H, dd, $J_{9',10}$ = 4.8, H-9′), 3.63 (1H, dd, $J_{2,12}$ = 2.1, $J_{12,12'}$ = 12.1, H-12), 3.80 (1H, d, H-5), 4.07 (1H, d, $J_{9,9'}$ = 17.5, H-9), 4.15 (1H, dd, $J_{4,5}$ = 3.5, H-4), 5.43 (1H, br, OH-5), 7.34 (1H, s, NH-7), 8.29 (1H, d, $J_{9,10}$ < 1, NH-10); δ_C (D_2O, 50.3 MHz) 44.8, 61.3 (2 t, C-9, CH_2OH), 66.7, 69.6, 71.9, 76.8 (4 d, C-2, -3, -4, -5), 83.4 (s, C-6), 166.4, 171.7 (2 s, 2 × C=O); *m/z* (NH_3, CI) 320 (M + NH_4^+, 19), 303 (M + H^+, 20), 245 (11), 108 (21), 100 (29), 98 (36), 78 (39), 61 (100%).

(1′*R*,2*R*,3*S*,4*S*,5*S*)-2-(1′,2′-Dihydroxyethyl)-3,4-isopropylidenedioxy-1-oxa-6,9-diazaspiro[4.5]decane-7,10-dione 16

The diketopiperazine **15** (24 mg, 0.08 mmol) was dissolved in dry DMF, and potassium *tert*-butoxide (10 mg, 0.08 mmol) was added. The mixture was heated at 100 °C for 24 h, concentrated *in vacuo*, and the residue purified by flash column chromatography (chloroform–methanol 17 : 3) to afford *(1′R,2R,3S,4S,5S)-2-(1′,2′-dihydroxyethyl)-3,4-isopropylidenedioxy-1-oxa-6,9-diazaspiro[4.5]decane-7,10-dione* **16** (22 mg, 92%) as a white solid, mp 216–218 °C (from methanol); $[\alpha]_D^{20}$ +88.8 (*c* 0.5, MeOH) identical in all respects to an authentic sample.[11]

(1′*R*,2*R*,3*R*,4*S*,5*S*)-2-(1′,2′-Dihydroxyethyl)-3,4-dihydroxy-1-oxa-6,9-diazaspiro[4.5]decane-7,10-dione 17

The pyranoside **4** (29 mg, 0.11 mmol) was dissolved in dry DMF (3 ml) and potassium *tert*-butoxide (12 mg, 0.11 mmol) was added. The mixture was heated at 100 °C for 24 h, concentrated *in vacuo* and the residue was purified by flash column chromatography (CMAW) to afford (1′*R*,2*R*,3*R*,4*S*,5*S*)-2-(1′,2′-dihydroxyethyl)-3,4-dihydroxy-1-oxa-6,9-diazaspiro[4.5]decane-7,10-dione **17** (15 mg, 50%) as a white solid, mp: 151–153 °C (from MeOH); $[\alpha]_D^{20}$ +10.8 (*c* 0.5 in MeOH), identical in all respects to an authentic sample.[11]

2-Amino-2-deoxy-3,4-*O*-isopropylidene-D-*glycero*-D-*talo*-heptono-1,5-lactone 24

A solution of the azide **22** (404 mg, 1.5 mmol) in ethyl acetate (10 ml) was stirred under an atmosphere of hydrogen in the presence of palladium black (40 mg). After 3 h 30 min, TLC (ethyl acetate) indicated complete conversion of the starting material (R_f 0.4) into a single product (R_f 0.1). The mixture was filtered through Celite (eluted with acetonitrile) and the solvent was removed *in vacuo* to yield *2-amino-2-deoxy-3,4-O-isopropylidene-D-glycero-D-talo-heptono-1,5-lactone* **24**[23] (356 mg, 97%) as a white solid, mp 149–150 °C (from EtOAc); $[\alpha]_D^{22}$ +107.9 (*c* 1.00, CH_3CN); IR (KBr) ν_{max} 3520, 3344, 3289 (NH), 1752 (C=O) cm^{-1}; δ_H ($CDCl_3$; 500 MHz) 1.34 [6H, s, $C(CH_3)_2$], 3.59 (1H, dd, $J_{7,7'}$ = 11.6, $J_{7,6}$ = 4.6, H-7), 3.61 (1H, d, $J_{2,3}$ = 3.5, H-2), 3.69 (1H, dd, H′-7), 3.78 (1H, ddd, $J_{6,5}$ = 8.9, H-6), 4.17 (1H, dd, $J_{5,4}$ = 1.5, H-5), 4.65 (1H, dd, $J_{3,4}$ = 7.9, H-3), 4.73 (1H, dd, H-4); δ_C (d_6-DMSO; 50.3 MHz) 24.2, 26.0 [2 q, $C(CH_3)_2$], 52.1 (d, C-6), 62.4 (t, C-7), 68.4, 72.3, 74.6, 76.0 (4 d, C-2, -3, -4, -5), 108.4 [s, $C(CH_3)_2$], 173.4 (s, C=O); *m/z* (CI, NH_3) M + H^+ (14), 360 (100), 332 (19%) (Found: C, 48.15; H, 6.88; N, 6.08. Calc. for $C_{10}H_{17}NO_6$: C, 48.58; H, 6.93; N, 5.67%).

2-Amino-7-*O*-*tert*-butyldimethylsilyl-2-deoxy-3,4-*O*-isopropylidene-D-*glycero*-D-*talo*-heptono-1,5-lactone 25

A solution of the silylated azide **23** (1.285 g, 3.3 mmol) in ethyl acetate (15 ml) was stirred under an atmosphere of hydrogen in the presence of palladium black (200 mg). After 48 h, TLC (ethyl acetate) indicated complete conversion of the starting material (R_f 0.8) into a single product (R_f 0.2). The mixture was filtered through Celite (eluted with ethyl acetate) and the solvent removed *in vacuo*. The residue was purified by crystallisation (from hexane–ethyl acetate) to yield *2-amino-7-O-tert-butyldimethylsilyl-2-deoxy-3,4-O-isopropylidene-D-glycero-D-talo-heptono-1,5-lactone* **25** (1.159 g, 97%) as a white solid, mp 119–123 °C; $[\alpha]_D^{21}$ +66.6 (*c* 1.00, $CHCl_3$); IR (KBr) ν_{max} 3376 (NH), 1760 (C=O) cm^{-1}; δ_H ($CDCl_3$; 500 MHz) 0.09, 0.10 (6H, 2 s, Me_2Si), 0.90 (9H, s, Me_3CSi), 1.38, 1.43 [6H, 2 s, $C(CH_3)_2$], 3.49 (1H, dd, $J_{2,3}$ = 3.4, H-2), 3.81 (1H, dd, $J_{7,7'}$ = 10.4, H-7), 3.87 (1H, dd, H′-7), 4.00 (1H, m, H-6), 4.07 (1H, dd, $J_{5,4}$ = 1.3, H-5), 4.74 (1H, dd, $J_{3,4}$ = 7.9, H-3), 4.81 (1H, dd, H-4); δ_C ($CDCl_3$; 50.3 MHz) −5.4 (2 q, Me_2Si), 18.3 (s, Me_3CSi), 24.3 [2 q, $C(CH_3)_2$], 25.8, 25.9 [3 q, Me_3CSi], 53.4 (d, C-6), 63.0 (t, C-7), 68.4, 72.4, 75.0, 75.4 (4 d, C-2, -3, -4, -5), 110.2 [s, $C(CH_3)_2$], 172.7 (s, C=O); *m/z* ($APCI^+$, NH_3) 362 (M + H^+, 14), 360 (100), 332 (19%) (Found: C, 52.88; H, 8.91; N, 3.74. Calc. for $C_{16}H_{31}NO_6Si$: C, 53.16; H, 8.64; N, 3.87%).

(1*R*,4*S*,6*R*,7*S*,8*S*)-4-Amino-6-*tert*-butyldimethylsilyloxymethyl-7,8-isopropylidenedioxy-2,5-dioxabicyclo[2.2.2]octan-3-one 29

NBS (490 mg, 2.7 mmol) and sodium acetate (640 mg, 8.3 mmol) were added to a stirred solution of the silylated amine **25** (896 mg, 2.5 mmol) in acetonitrile (8 ml) under an atmosphere of nitrogen. After 1.5 h, TLC (hexane–ethyl acetate 1 : 2) indicated the presence of two major products (R_f 0.7 and R_f 0.6). *N*-Ethyldiisopropylamine (1.29 ml, 8.3 mmol) was added to the mixture. After 30 min, TLC (hexane–ethyl acetate 1 : 2) indicated the presence of a major product (R_f 0.7). The mixture was diluted with pH 7 buffer solution (40 ml) and the aqueous phase was extracted with ethyl acetate (2 × 40 ml). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was preadsorbed onto silica and purified by flash chromatography (hexane–ethyl acetate 4 : 1) to yield *(1R,4S,6R,7S,8S)-4-amino-6-tert-butyldimethylsilyloxymethyl-7,8-isopropylidenedioxy-2,5-dioxabicyclo[2.2.2]octan-3-one* **29** (666 mg, 75%) as a clear oil, $[\alpha]_D^{22}$ +4.18 (*c* 0.79, $CHCl_3$); IR (KBr) ν_{max} 3338 (NH), 1790 (C=O) cm^{-1}; δ_H ($CDCl_3$; 500 MHz) 0.07 (6H, s, Me_2Si), 0.90 (9H, s, Me_3CSi) 1.38, 1.62 [6H, s, 2 $C(CH_3)$], 3.89 (1H, dd, $J_{CHO[Si],CH'O[Si]}$ = 9.7, CHO[Si]), 4.17 (1H, dd, CH′O[Si]), 4.22 (1H, m, H-6), 4.31 (1H, d, $J_{7,8}$ = 8.4, H-8), 4.66 (1H, ddd, $J_{7,1}$ = 4.5, H-7), 4.80 (1H, dd, H-1); δ_C ($CDCl_3$; 50.3 MHz) −5.3, −5.4 (2 q, Me_2Si), 18.2 (s, Me_3CSi), 24.0, 24.9 [2 q, $C(CH_3)_2$], 25.82 (q, Me_3CSi), 69.9 (t, $CH_2O[Si]$), 72.0, 73.3, 76.2, 78.7 (4 d, C-1, -6, -7, -8), 82.4 (s, C-4), 114.5 [s, $C(CH_3)_2$],

168.9 (s, C=O); *m/z* (CI, NH_3) 360 (M + H^+; 100), 332 (19%) (Found: C, 53.54; H, 8.42; N, 3.59. Calc. for $C_{16}H_{29}NO_6Si$: C, 53.46; H, 8.13; N, 3.89%).

The monoacetylated aminal 30

Potassium cyanate (88 mg, 1.07 mmol) was added to a stirred solution of the silylated amino lactone **29** (128 mg, 0.36 mmol) in acetic acid (6 ml). After 40 min, TLC (hexane–ethyl acetate 1 : 1) indicated the absence of starting material (R_f 0.6) and the presence of a major product (R_f 0.1). The mixture was concentrated *in vacuo* (co-evaporation with toluene), pre-adsorbed onto silica, and purified by flash chromatography (hexane–ethyl acetate 2 : 1) to yield a single monoacetylated aminal **30** (89 mg, 63%) as an amorphous solid, IR (film) ν_{max} 3376br (OH, NH), 1752 (C=O, lactone), 1654 (C=O, amide), 1384 (N-CO) cm^{-1}; δ_H ($CDCl_3$; 500 MHz) 0.08, 0.09 (6H, 2 s, Me_2Si), 0.90 (9H, s, Me_3CSi), 1.36, 1.40 [6H, 2 s, $C(CH_3)_2$], 2.03 (3H, s, CH_3CO), 2.49 (2H, s, NH_2), 2.69 (1H, d, OH), 3.83 (1H, dd, $J_{7,7'} = 10.4$, $J_{7,6} = 4.0$, H-7), 3.87 (1H, dd, $J_{7',6} = 3.3$, H′-7), 3.96 (1H, ddd, $J_{6,OH} = 7.3$, $J_{6,5} = 9.3$, H-6), 4.79 (1H, dd, $J_{4,5} = 1.9$, $J_{4,3} = 7.6$, H-4), 5.05 (1H, dd, H-3), 5.27 (1H, dd, H-5); δ_C ($CDCl_3$; 50.3 MHz) −5.5, −5.4 (2 q, Me_2Si), 18.2 (s, Me_3CSi), 24.1, 24.2, 26.1 [3 q, $C(CH_3)_2$, *Me*CO], 25.8 (3 q, Me_3CSi), 62.9 (t, C-7), 68.7, 72.0, 75.7, 75.9 (4 d, C-3, -4, -5, -6), 70.0 (s, C-1), 109.6 [s, $C(CH_3)_2$], 169.0, 171.0 (2 s, 2 × C=O); HRMS (NH_3, Cl) Calc. for $C_{18}H_{35}N_2O_7Si$: *m/z*, 419.221082. Found: $(M + H)^+$, 419.221355.

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References

1 S. Takahasi, M. Nakajima, T. Kinoshita, H. Haruyama, S. Sugai, T. Honma, S. Sato and T. Haneishi, *ACS Symp. Ser.*, 1994, **551**, 74.
2 M. Nakajima, K. Itoi, Y. Takamatsu, T. Kinoshita, T. Okazaki, K. Kawakubo, M. Shindou, T. Honma, M. Tohjigamori and T. Haneishi, *J. Antibiot.*, 1991, **44**, 293; H. Haruyama, T. Takayama, T. Kinoshita, M. Kondo, M. Nakajima and T. Haneishi, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1637.
3 S. Mio, R. Ichinose, K. Goto and S. Sugai, *Tetrahedron*, 1991, **47**, 2111; S. Mio, Y. Kumagawa and S. Sugai, *Tetrahedron*, 1991, **47**, 2133; M. Matsumoto, M. Kirihara, T. Yoshino, T. Katoh and S. Terashima, *Tetrahedron Lett.*, 1993, **34**, 6289; P. Chemla, *Tetrahedron Lett.*, 1993, **34**, 7391; P. M. Harrington and M. E. Jung, *Tetrahedron Lett.*, 1994, **35**, 5145.
4 S. Hanessian, J.-Y. Sanceau and P. Chemla, *Tetrahedron*, 1995, **51**, 6669; H. Sano and S. Sugai, *Tetrahedron: Asymmetry*, 1995, **6**, 1143; H. Sano and S. Sugai, *Tetrahedron*, 1995, **51**, 4635; H. Sano, S. Mio, N. Tsukaguchi and S. Sugai, *Tetrahedron*, 1995, **51**, 1387.
5 C. J. F. Bichard, E. P. Mitchell, M. R. Wormald, K. A. Watson, L. N. Johnson, S. E. Zographos, D. D. Koutra, N. G. Oikonomakos and G. W. J. Fleet, *Tetrahedron Lett.*, 1995, **36**, 2145; C. de la Fuente, T. M. Krülle, K. A. Watson, M. Gregoriou, L. N. Johnson, K. E. Tsitsanou, S. E. Zographos, N. G. Oikonomakos and G. W. J. Fleet, *Synlett*, 1997, 485; T. M. Krülle, C. de la Fuente, K. A. Watson, M. Gregoriou, L. N. Johnson, K. E. Tsitsanou, S. E. Zographos, N. G. Oikonomakos and G. W. J. Fleet, *Synlett*, 1997, 211.
6 T. M. Krülle, K. A. Watson, M. Gregoriou, L. N. Johnson, S. Crook, D. J. Watkin, R. C. Griffiths, R. J. Nash, K. E. Tsitsanou, S. E. Zographos, N. G. Oikonomakos and G. W. J. Fleet, *Tetrahedron Lett.*, 1995, **36**, 8291.
7 C. Prasad, *Peptides* (*N. Y.*), 1995, **16**, 151.
8 L. A. Paquette, S. Brand and C. Behrens, *J. Org. Chem.*, 1999, **64**, 2010.
9 L. Somsak and V. Nagy, *Tetrahedron: Asymmetry*, 2000, **11**, 1719; L. Somsak, V. Nagy, T. Docsa, B. Toth and P. Gergely, *Tetrahedron: Asymmetry*, 2000, **11**, 405 and references cited therein.
10 J. W. Burton, J. C. Son, A. J. Fairbanks, S. S. Choi, H. Taylor, D. J. Watkin, B. G. Winchester and G. W. J. Fleet, *Tetrahedron Lett.*, 1993, **34**, 6119.
11 J. C. Estevez, R. J. Estevez, H. Ardron, M. R. Wormald, D. Brown and G. W. J. Fleet, *Tetrahedron Lett.*, 1994, **35**, 8889.
12 J. C. Estevez, J. W. Burton, R. J. Estevez, H. Ardron, M. R. Wormald, R. A. Dwek, D. Brown and G. W. J. Fleet, *Tetrahedron: Asymmetry*, 1998, **9**, 2137.
13 A. Dondoni and A. Marra, *Chem. Rev.*, 2000, **100**, 4395.
14 M. D. Smith and G. W. J. Fleet, *J. Pept. Sci.*, 1999, **5**, 425; R. M. van Well, H. S. Overkleeft, M. Overhand, E. V. Carstenen, G. A. van der Marel and J. H. van Boom, *Tetrahedron Lett.*, 2000, **41**, 9331.
15 T. D. W. Claridge, D. D. Long, N. L. Hungerford, R. T. Aplin, M. D. Smith, D. G. Marquess and G. W. J. Fleet, *Tetrahedron Lett.*, 1999, **40**, 2199; N. L. Hungerford, T. D. W. Claridge, M. P. Watterson, R. T. Aplin, A. Moreno and G. W. J. Fleet, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3666.
16 M. D. Smith, T. D. W. Claridge, G. E. Tranter, M. S. P. Sansom and G. W. J. Fleet, *Chem. Commun.*, 1998, 2041.
17 J. C. Estevez, D. D. Long, M. R. Wormald, R. A. Dwek and G. W. J. Fleet, *Tetrahedron Lett.*, 1995, **36**, 8287.
18 I. Bruce, G. W. J. Fleet, I. Cenci de Bello and B. Winchester, *Tetrahedron*, 1992, **48**, 10191.
19 I. Bruce, G. W. J. Fleet, A. Girdhar, M. Haraldsson, J. M. Peach and D. J. Watkin, *Tetrahedron*, 1990, **46**, 19.
20 S. V. Ley, J. Norman, W. P. Griffith and S. P. Marsden, *Synthesis*, 1994, 639.
21 A. J. Fairbanks and G. W. J. Fleet, *Tetrahedron*, 1995, **51**, 3881.
22 J. C. Estevez, M. D. Smith, M. R. Wormald, G. S. Besra, P. J. Brennan, R. J. Nash and G. W. J. Fleet, *Tetrahedron: Asymmetry*, 1996, **7**, 391.
23 J. W. Burton, J. C. Son, A. J. Fairbanks, S. Choi, H. Taylor, D. J. Watkin, B. G. Winchester and G. W. J. Fleet, *Tetrahedron Lett.*, 1993, **36**, 6199.