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Glucofuranose Analogues of Hydantocidin

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Abstract: Epimeric spirohydantoins of glucofuranose, analogues of hydantocidin, are readily prepared from glucoheptonolactone. No rearrangement of spirohydantoins of glucofuranose to pyranose isomers was observed; a novel rearrangement was observed of a glucofuranose spirohydantoin to an isomeric oxazolidinone, *(3aR,4'R,5S,6S,6aR)*-5-(2',2'-dimethyl-1',3'-dioxolane-4'-yl)-6-hydroxy-3a-N-phenylcarboxamido-tetrahydrofuro[2.3-d]-1,2-oxazolidine-2-one, the structure of which was established by X-ray crystallographic analysis. The X-ray crystal structure of *(1'R,2R,3R,4R,5R)*-6,8-diaza-3,4-dihydroxy-2-(1',2'-dihydroxyethyl)-1-oxa-8-N-phenyl-spiro[4.4]nonane-7,9-dione is reported.
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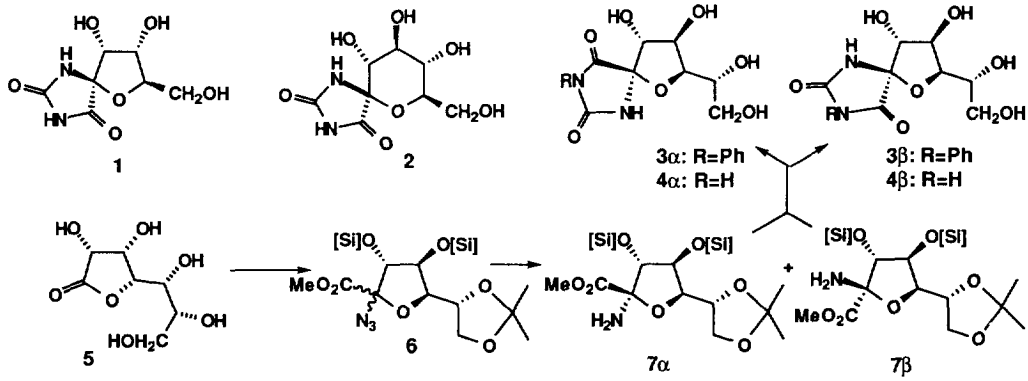
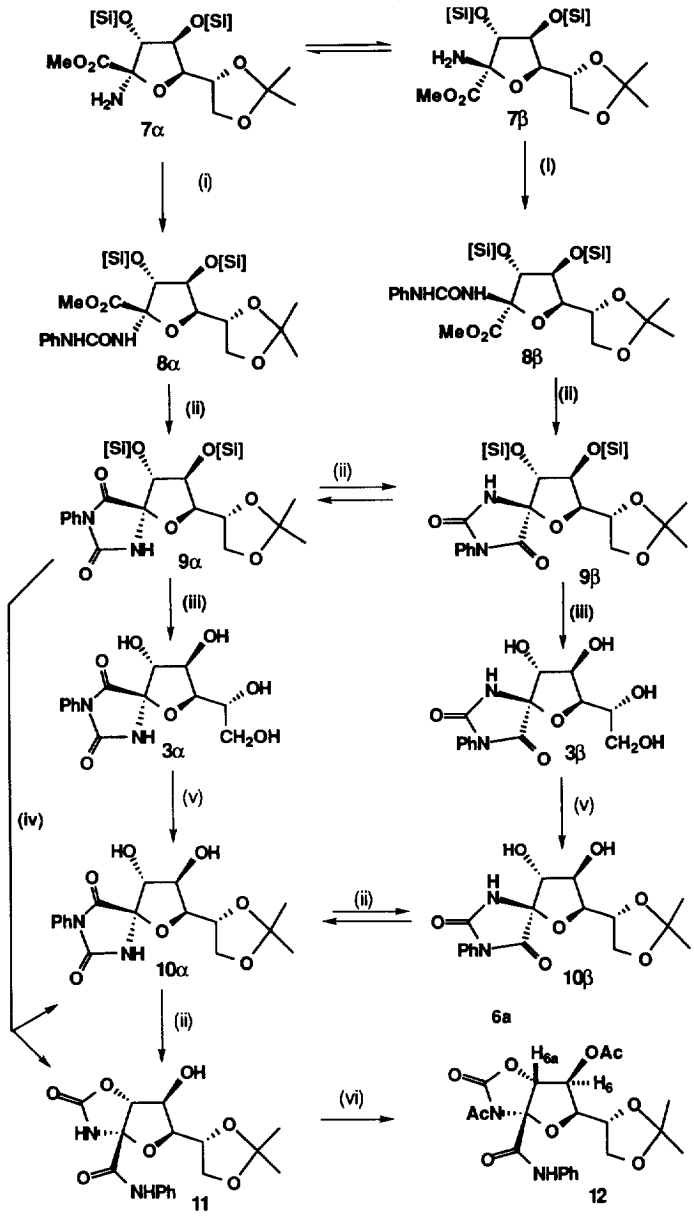
Hydantocidin **1**, isolated from *Streptomyces*,[1] is a potent but non-toxic herbicide with activity similar to that of glyphosate;[2] its mode of action is as a proherbicide of a metabolite that inhibits purine biosynthesis at the site of adenylosuccinate synthetase.[3] The novel spirohydantoin at the anomeric position of a sugar has initiated a number of synthetic studies of the natural product **1**, together with modifications of the hydantoin ring;[4] other furanoses containing anomeric spirohydantoins and related compounds[5] have been reported. Spiroderivatives of pyranoses are much rarer and, in general, it appears that the furanose isomers of both rhamnose[6] and mannose[7] are more thermodynamically stable than the corresponding pyranose forms.[8] Such materials have potential to bind specifically to enzymes or receptors involving carbohydrates and some such rhamnose derivatives interfere with mycobacterial cell growth and may provide a mechanism-based strategy for the chemotherapy of diseases such as tuberculosis and leprosy.[9] A galactopyranose analogue of hydantocidin has been recently described.[10]



Inhibition of glycogen phosphorylase (GP) may provide a new chemotherapeutic strategy for the treatment of late onset diabetes;[11] the glucopyranose hydantoin **2** is a very potent inhibitor of GP.[12] Although there are no examples of furanose analogues of glucose causing any inhibition of GP, the binding provided by

the hydantoin ring in **2** might cause some inhibition when attached to the anomeric position of glucofuranose. This paper reports the synthesis of the four hydantoins **3** and **4** and their complete lack of inhibition of GP; some of this work has been published, in preliminary form.[13] The published route to **2** provides only very small amounts of material at the end of a long synthesis; notwithstanding the previously observed relative stability of spirofuranose to spiropyranose sugars, it was considered that isomerisation of spirohydantoins of the more readily available glucofuranoses **3** and **4** might give easier access to glucopyranoses, such as **2**, in which all the substituents of the pyranose ring are equatorial. However, no evidence was found for the formation of **2** or other pyranose derivatives by base or acid catalysed isomerisations of **3** and **4**. Reduction of the azides **6** gave the epimeric amines **7** as starting materials as described in the preceding paper.[14] In the synthesis of the N-phenylhydantoins **3**, reaction of **7α** with phenyl isocyanate in tetrahydrofuran gave the urea **8α** in 75% yield with only a trace [<5%] of the epimeric urea being formed.



Scheme 1 (i) PhNCO, THF (ii) *tert*-BuOK, DMF [various temp] (iii) dioxan / H_2O/ CF_3COOH 1:1:1 (iv) n-Bu_4NF, THF (v) Me_2CO, CSA (vi)Ac_2O, pyridine

The epimeric amine **7β** under the same conditions afforded **8β** in 63% yield, together with 17% of **8α**. Although the anomeric amines **7** interconvert spontaneously, N-acylation gives rise to stable anomers, and there is no interconversion of the product ureas under the reactions conditions. Thus the urea **8α** was treated with potassium *tert*-butoxide in dimethylformamide at room temperature to give the spirohydantoin **9α** in 88% yield; similar base treatment induced cyclisation of **8β** to give **9β** in 78% yield, with no anomeric

equilibration of either the starting ureas **8** or of the product hydantoins **9** occurring under the cyclisation conditions. The anomeric hydantoins **9** can however be equilibrated under more forcing conditions with *tert*-butoxide in dimethylformamide at 100°C for 96 h. At equilibrium, the approximate ratio of **9α**:**9β** is 7:5 based on 78% recovered yield of material; a small amount of decomposition occurs under these conditions.

Both the ketal and silyl protecting groups can be removed from the hydantoins **9** with aqueous trifluoroacetic acid with only little [<10%] epimerisation of the products occurring. Thus acidic hydrolysis of **9α** gave **3α** in 75% yield and **9β** gave **3β** in 73% yield. The pure hydantoins can readily be isolated by crystallisation. The structure of the unprotected N-phenylhydantoin **3α** was established by single crystal X-ray crystallographic analysis [Figure 1].

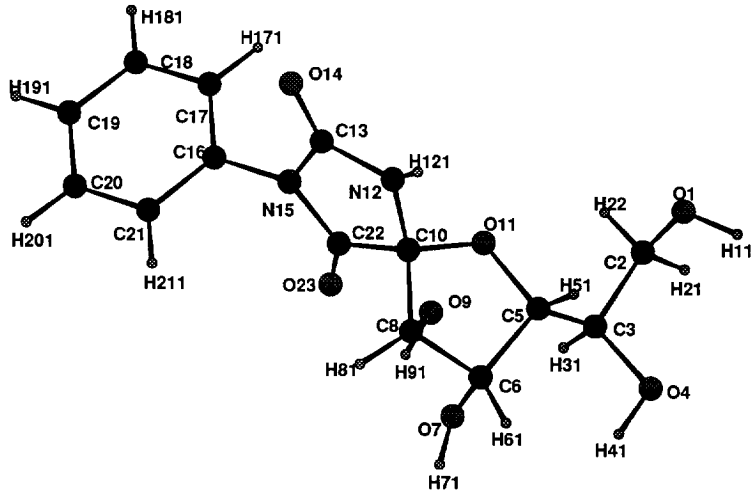


Figure 1 X-Ray structure of *(1'R,2R,3R,4R,5R)*-6,8-diaza-3,4-dihydroxy-2-(1',2'-dihydroxyethyl)-1-oxa-8-N-phenyl-spiro[4.4]nonane-7,9-dione **3α**: showing crystallographic numbering scheme

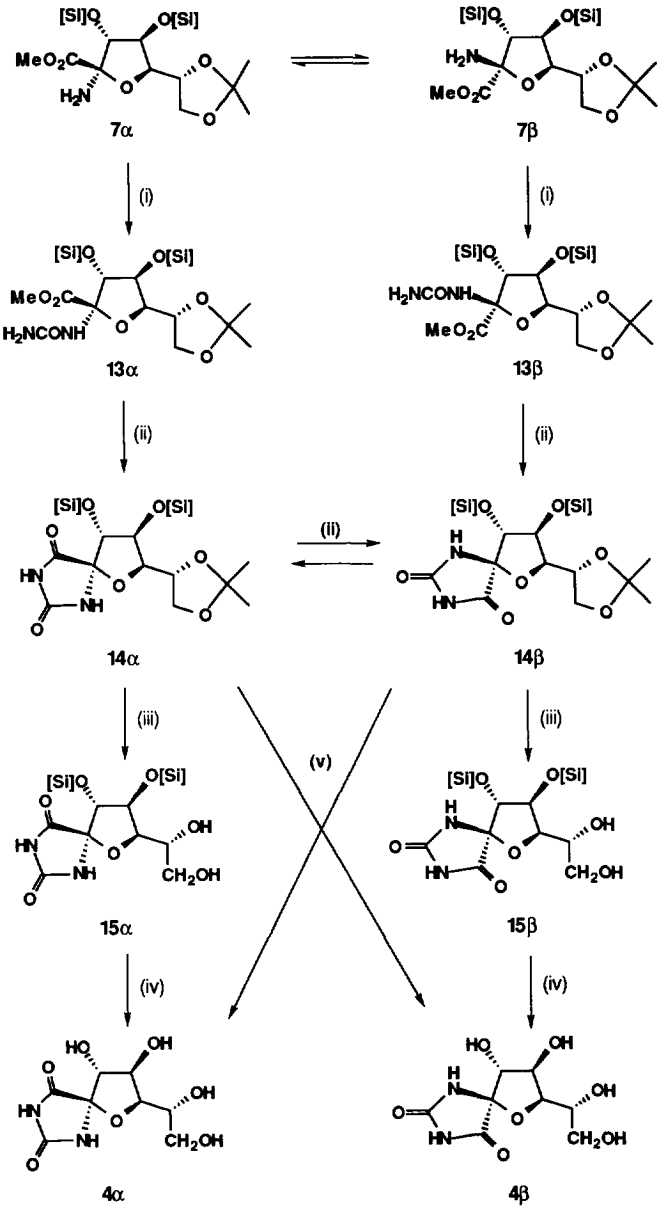
Equilibrations of the unprotected hydantoins gave complex mixtures which were difficult to analyse and accordingly to allow further studies of such equilibrations **3α** and **3β** were converted into the side chain acetonides **10α** and **10β** in yields of 76% and 67%, respectively. In attempting to study the equilibration of the partly protected hydantoins **10**, **10α** was treated with butoxide in dimethyl formamide and instead of observing the formation of an equilibrium mixture of **10**, the oxazolidinone **11** was isolated in 79% yield. This rearrangement presumably occurs by an intramolecular transacylation derived by nucleophilic attack of the C-3 hydroxyl group in **10α** which is *cis* to the α-carbonyl group of the hydantoin ring; no such rearrangements of sugar spirohydantoins have been observed hitherto. Attempted selective deprotection of the silyl ether protecting groups in **9α** by tetrabutylammonium fluoride in tetrahydrofuran also gave **11** together with **10α**. Acetylation of **11** by acetic anhydride in pyridine gave the diacetate **12** in 95% yield.

Comparison of the NMR spectra of **11** and **12** shows a significant downfield shift of H-6 [from δ 4.37 in **11** to δ 5.49 in **12**] whereas there is almost no shift for H-6a [δ 4.89 in **11** to δ 4.87 in **12**] strongly suggesting that OH at 6a was already acylated in **11** [positions 6 and 6a are shown on **12**]. The structure of **11** was confirmed by X-ray crystallographic analysis [Figure 2]. Treatment of **10β** with base gave as the

major product **11**, indicating prior epimerisation to **10α** which is then converted into the thermodynamically more stable oxazolidinone **11**.

Thus all studies to form glucopyranose analogues of the hydantoins by equilibration of the N-phenylfuranoside derivatives were unsuccessful; these studies do not show that the pyranose form of the glucohydantoins are less stable than the furanose forms, merely that an alternative and novel rearrangement to the *cis*-fused oxazolidinone has taken place.

For the synthesis of the glucofuranose analogues of hydantocidin **4**, an anomeric mixture of the amines **7** was treated with potassium cyanate in acetic acid at room temperature to give a separable mixture of the ureas **13α** [26% yield] and **13β** [44 % yield]. Again, potassium *tert*-butoxide in tetrahydrofuran induced cyclisation of the ureas **13** to the hydantoins **14** with essentially no loss of configuration at the anomeric position; **13α** gave **14α** in 87% yield and **13β** gave **14β** in 85% yield. Attempts to remove both the silyl ether and isopropylidene protecting in one step with aqueous trifluoroacetic acid were accompanied by significant epimerisation of the product hydantoins **4** and accordingly the protecting groups were removed sequentially. Thus treatment of **14α** with aqueous acetic acid gave **15α** in 87% yield and similar treatment of **14β** gave **15β** in 83% yield with no comcomitant anomeric equilibration. Removal of the silyl ether protecting groups in **4α** and **4β** with tetrabutylammonium fluoride in tetrahydrofuran gave the unprotected hyanocidin analogues **15α** and **15α** in yields of 95% and 100%, respectively. There is thus a difference in the relative ease of removal of the silyl ethers and rearrangement between **3** and **4**.



Scheme 2 (i) KNCO, MeCOOH (ii) *tert*-BuOK, [various solvents and temp.] (iii) AcOH, H_2O (iv) n-Bu_4NF, THF (v) dioxan / H_2O/ CF_3COOH 1:1:1

Although the hydantoins **14** could be formed by cyclisation of the ureas **13** without significant epimerisation, more vigorous treatment of the individual epimers of **14** with potassium *tert*-butoxide in dimethyl formamide at 100°C caused equilibration to give mixtures of **14**β:**14**α in a ratio of between 1:3 and 1:4. Attempts to study equilibrations of the partly **15** or fully **4** deprotected hydantoins gave no indication of the formation of pyranose hydantoins; the products of base-catalysed reactions were not identified but it was clear that treatment of the epimeric diols **15** lead to significant silyl migrations. Thus, it was not possible to identify whether an analogous rearrangement to that of the N-phenylated hydantoins **10** to **11**, took place in the case of base catalysed isomerisations of **15** and **4**; however, no evidence was found that synthesis of the furanose analogues of hydantocidin would allow later equibration to the the pyranose analogues.

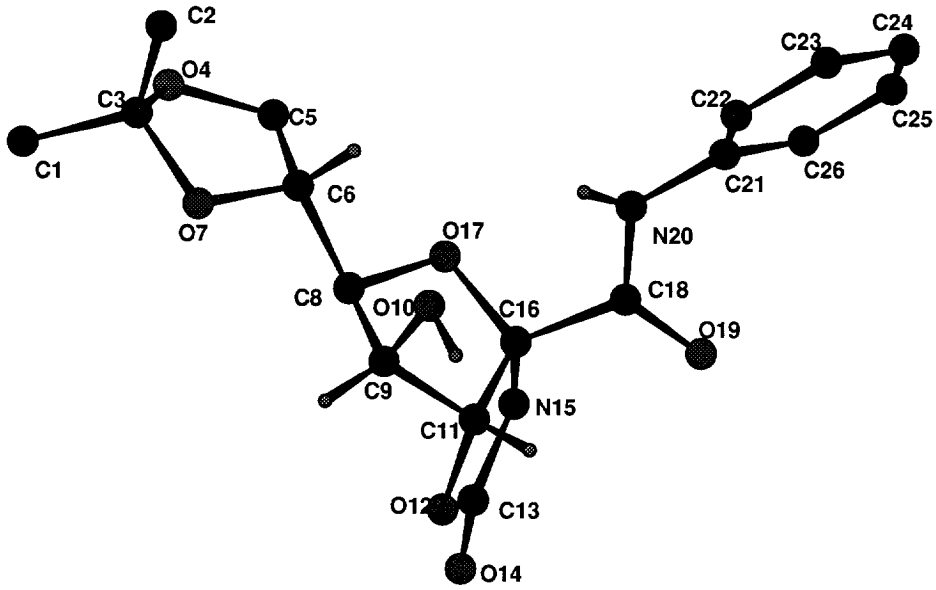


Figure 2 X-Ray structure of *(3aR,4'R,5S,6S,6aR)*-5-(2',2'-dimethyl-1',3'-dioxolane-4'-yl)-6-hydroxy-3a-N-phenylcarboxamido-tetrahydrofuro[2.3-d]-1,2-oxazolidine-2-one **11**: showing crystallographic numbering scheme

The glucohydantoin **2** is among the most potent inhibitors of glycogen phosphorylase (GP) yet discovered, although the hydantoin epimeric at C-2 has essentially no inhibitory effect on the enzyme;[16] all four of the glucofuranose isomers **3** and **4** showed no inhibition of glycogen phosphorylase at 10 mM, showing that phosphorylase does not bind the glucofuranose moiety even if the hydantoin is present in the compound.[15] The complete lack of inhibition by any of the samples of the furanose spirohydantoins **4** also provides support for the observation that none of the samples had isomerised to the pyranose isomers, since the presence of any of 2 at the level of 5% in such mixtures would have caused significant inhibition of GP.

In summary, efficient syntheses of glucofuranose analogues **3** and **4** of hydantocidin are reported; no procedure was found to equilibrate from the spirohydantoins of glucofuranose to the corresponding pyranose, but a hitherto unknown rearrangement of such spirohydantoins to isomeric oxazolidinones was observed. No inhibition of glycogen phosphorylase was found by any of the glucofuranose analogues, indicating that even small amount of glucopyranose analogues were not formed in these syntheses.

X-Ray Crystal Analysis. The absolute configuration of the chiral centres in **3α** and the relative configuration of the chiral centres in **11** were established by X-ray single crystal structure analysis. For both compounds, cell dimensions and intensity data were measured with an Enraf-Nonius CAD4-F Diffractometer, and Lorentz, polarisation and psi scan absorption corrections were applied. All calculations carried out on a 486PC computer. All non-hydrogen atoms were located by SIR92[16] and refined using CRYSTALS.[17] Illustrations produced using CAMERON.[18] Hydrogen atoms were seen in the difference density map but placed geometrically. Non-hydrogen atoms were refined anisotropically using atomic scattering factors from International Tables.[19] Corrections for secondary extinction and anomalous scattering were applied and refinement completed using a 3 term Chebychev polynomial.[20] Structural data for both **3α** and **11** have been deposited at the Cambridge Crystallographic Data Centre.[21]

For **3α** suitable crystal of approximate dimensions 0.1 x 0.5 x 0.8 mm was used. Cell parameters a=5.731(1), b=10.664(1) , c=23.075(3). Orthorhombic P 2_1 2_1 2_1. Molecular formula $C_{14}H_{16}N_2O_7$. Formula weight 324.3. Number of formula units in cell (Z), 4. Calculated density (gcm^{-3}) 1.53. Data collection parameters: h range -7 to 7, -1 to 13, -1 to 28, θ range 0 to 72°, copper radiation, λ = 1.5418. Temperature 294K. 3 intensity standards remeasured every hour, 3.2% decay. Total data collected 3479, number used in refinement 2711, criterion for observed I > 3σ(I). Refinement details: 210 parameters refined, 12.9 observations per parameter, R= 3.2%, R_w= 4.2. Flack Enantiopole parameter = -.2(2)

For **11,** a suitable crystal of approximate dimensions 0.15 x 0.6 x 2.0 mm was used. Cell parameters a=7.123(4) , b=14.133(4) , c=17.118(4). Orthorhombic P 2_1 2_1 2_1. Molecular formula $C_{17}H_{20}N_2O_7$. Formula weight 364.4. Number of formula units in cell (Z), 4. Calculated density (gcm^{-3}) 1.40. Data collection parameters: h range -8 to 8, -6 to 17, -10 to 21, θ range 0 to 72°, copper radiation, λ = 1.5418. Temperature 294K. 3 intensity standards remeasured every hour, 2.9% decay. Total data collected 2631, number used in refinement 1591, criterion for observed I > 3σ(I). Refinement details: 236 parameters refined, 6.7 observations per parameter, R= 5.1%, R_w= 6.9.

Fractional atomic coordinates and equivalent isotropic temperature factors U(iso) with standard deviations in parentheses for the spirohydantoin 3α:

Atom	x/a	y/b	z/c	U(iso)	Occ
O(11)	0.0581(2)	0.2452(1)	0.30146(5)	0.0274	1.0000
O(7)	0.5653(2)	0.2727(1)	0.30795(6)	0.0322	1.0000
O(23)	0.2784(3)	0.3786(1)	0.20481(6)	0.0375	1.0000
O(9)	0.2696(2)	-0.0199(1)	0.26872(6)	0.0329	1.0000
O(14)	-0.2727(3)	0.1053(1)	0.13870(6)	0.0376	1.0000
O(4)	0.3619(2)	0.2558(1)	0.44083(5)	0.0331	1.0000
O(1)	-0.1550(2)	0.2453(2)	0.43555(5)	0.0388	1.0000
N(12)	-0.0691(2)	0.1139(1)	0.22475(6)	0.0265	1.0000
N(15)	0.0111(2)	0.2556(1)	0.15691(6)	0.0277	1.0000
C(10)	0.1206(3)	0.1854(2)	0.24846(7)	0.0238	1.0000
C(6)	0.4315(3)	0.1629(2)	0.31841(7)	0.0259	1.0000
C(13)	-0.1275(3)	0.1506(2)	0.17025(7)	0.0263	1.0000
C(5)	0.2049(3)	0.1993(1)	0.34844(7)	0.0240	1.0000
C(2)	-0.0097(3)	0.3452(2)	0.41626(8)	0.0353	1.0000
C(8)	0.3424(3)	0.1059(2)	0.26115(7)	0.0266	1.0000
C(16)	-0.0034(3)	0.3220(2)	0.10265(7)	0.0283	1.0000
C(22)	0.1542(3)	0.2874(2)	0.20184(8)	0.0268	1.0000
C(3)	0.2255(3)	0.3021(2)	0.39348(7)	0.0274	1.0000
C(21)	0.1828(4)	0.3146(2)	0.06474(9)	0.0431	1.0000
C(20)	0.1667(5)	0.3775(3)	0.0120(1)	0.0510	1.0000
C(17)	-0.2012(4)	0.3890(2)	0.08956(8)	0.0371	1.0000
C(19)	-0.0298(6)	0.4451(2)	-0.0017(1)	0.0480	1.0000

*Fractional atomic coordinates and equivalent isotropic temperature factors U(iso) with standard deviations in parentheses for the oxazolidinone **11**:*

Atom	x/a	y/b	z/c	U(iso)	Occ
O(4)	1.4279(5)	0.3400(3)	0.5451(2)	0.0554	1.0000
O(7)	1.5216(4)	0.4221(2)	0.6510(1)	0.0386	1.0000
O(10)	1.3225(4)	0.4397(2)	0.8343(2)	0.0502	1.0000
O(12)	1.0164(4)	0.6321(2)	0.7815(2)	0.0415	1.0000
O(14)	0.7748(4)	0.6955(2)	0.7165(2)	0.0509	1.0000
O(17)	1.0364(3)	0.4168(2)	0.7154(1)	0.0364	1.0000
O(19)	0.6939(4)	0.4333(2)	0.8624(2)	0.0490	1.0000
N(15)	0.8043(5)	0.5348(2)	0.7333(2)	0.0394	1.0000
N(20)	0.9011(4)	0.3177(2)	0.8332(2)	0.0394	1.0000
C(1)	1.7262(7)	0.4162(4)	0.5398(3)	0.0577	1.0000
C(2)	1.6771(8)	0.2725(4)	0.6244(3)	0.0603	1.0000
C(3)	1.5907(6)	0.3611(3)	0.5897(2)	0.0433	1.0000
C(5)	1.2712(6)	0.3400(3)	0.5952(3)	0.0546	1.0000
C(6)	1.3410(5)	0.3854(3)	0.6716(2)	0.0395	1.0000
C(8)	1.2140(5)	0.4638(2)	0.7012(2)	0.0336	1.0000
C(9)	1.2633(5)	0.5080(3)	0.7803(2)	0.0359	1.0000
C(11)	1.0701(5)	0.5402(3)	0.8094(2)	0.0347	1.0000
C(13)	0.8521(5)	0.6269(2)	0.7411(2)	0.0366	1.0000
C(16)	0.9321(5)	0.4710(2)	0.7699(2)	0.0331	1.0000
C(18)	0.8312(5)	0.4041(2)	0.8264(2)	0.0356	1.0000
C(21)	0.8291(6)	0.2454(2)	0.8822(2)	0.0371	1.0000
C(22)	0.9494(7)	0.1978(3)	0.9323(2)	0.0462	1.0000
C(23)	0.8797(8)	0.1261(3)	0.9791(2)	0.0499	1.0000
C(24)	0.6930(8)	0.1022(3)	0.9765(2)	0.0487	1.0000
C(25)	0.5751(7)	0.1498(3)	0.9262(2)	0.0476	1.0000
C(26)	0.6401(6)	0.2209(3)	0.8792(2)	0.0429	1.0000

Experimental: Melting points were recorded on a Kofler hot block and are corrected. Proton nuclear magnetic resonance (δ_H) spectra were recorded on a Varian Gemini 200 (200 MHz), Bruker AC 200 (200 MHz) or a Bruker AM 500 (500 MHz) spectrometer. ^{13}C Nuclear magnetic resonance (δ_C) spectra were recorded on a Varian Gemini 200 (50 MHz), a Bruker AC 200 (50 MHz) or a Bruker AM 500 (125 MHz) spectrometer and multiplicities were assigned using DEPT sequence. All chemical shifts are quoted on the δ-scale. The following abbreviations were used to explain multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; app, apparent. Infra-red spectra were recorded on a Perkin-Elmer 1750 IR FT spectrophotometer. Mass spectra were recorded on a VG Masslab 20-250, BIO-Q or using desorption chemical ionisation (DCI NH_3), chemical ionisation (CI NH_3), electrospray or thermospray, as stated. Optical rotations were measured on a Perkin-Elmer 241 polarimeter with a path length of 1 dm. Concentrations are given in g/100 ml. Microanalyses were performed by the microanalysis service of the Dyson Perrins laboratory. Thin layer chromatography (t.l.c.) was carried out on aluminium sheets coated with $60F_{254}$ silica, and plates were developed using a spray of 0.2% w/v cerium (IV) sulfate and 5% ammonium molybdate in 2M sulfuric acid. 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; hexane was distilled at 68°C before use to remove less volatile fractions. The anomeric amines were prepared as described in the preceding paper.[14]

Methyl 2-deoxy-3,4-di-O-tert-butyldimethylsilyl-6,7-O-isopropylidene-2-N'-phenylureido-α-D-gluco-2-heptulofuranosonate 8α: Phenyl isocyanate (148 µl, 1.36 mmol) was added to a stirred solution of methyl 2-amino-2-deoxy-3,4-di-*O-tert*-butyldimethylsilyl-6,7-*O*-isopropylidene-α-D-*gluco*-2-heptulofuranosonate **7α**

(343 mg, 0.68 mmol) in dry tetrahydrofuran (5 ml) and stirring was continued for 18 h when t.l.c. (ethyl acetate/hexane 1:3) showed no starting material (R_f 0.43) and the formation of one product (R_f 0.28). The solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography (ethyl acetate/hexane 2:7) to afford *the title compound* **8α** (318 mg, 75%) as a white solid, m.p. 72-73°C. (Found: C, 57.60; H, 8.64; N, 4.30%. $C_{30}H_{52}N_2O_8Si_2$ requires C, 57.66; H, 8.39; N, 4.48%). $[\alpha]_D^{25}$ +23.5 (*c*, 1.0 in $CHCl_3$). ν_{max} (film) 3397 cm^{-1} (NH), 1742, 1671 cm^{-1} (C=O). m/z (CI NH_3): 642 ($M+NH_4^+$, 8%), 625 (MH^+, 31%), 593 (MH^+-HOMe, 82%), 94 ($PhNH_3^+$ 100%). δ_H (500 MHz, $CDCl_3$): 0.10, 0.13, 0.14, 0.17 (4 s, 4 x 3 H, SiMe), 0.89, 0.91 (2 s, 2 x 9 H, $SiCMe_3$), 1.33, 1.40 (2 s, 2 x 3 H, CMe_2), 3.78 (s, 3 H, OMe), 4.06 (dd, J = 1.2, 2.9 Hz, 1 H, H-4), 4.09 (dd, J = 4.8, 8.7 Hz, 1 H, H-7), 4.13 (dd, J = 2.9, 8.5 Hz, 1 H, H-5), 4.19 (dd, J = 6.2, 8.7 Hz, 1 H, H-7'), 4.32-4.37 (m, 1 H, H-6), 4.34 (d, J = 1.2 Hz, 1 H, H-3), 5.89, 6.78 (2 s, 2 x 1 H, NH), 7.06-7.10 (m, 1 H, Ph_p), 7.27-7.34 (m, 4 H, $Ph_{o,m}$). δ_C (50 MHz, $CDCl_3$): -5.1, -4.9, -4.5 (3 q, SiMe), 17.7 (s, $SiCMe_3$), 25.3, 25.6, 26.9 (3 q, $SiCMe_3$, CMe_2), 53.0 (q, OMe), 67.8 (t, C-7), 72.3, 76.7, 82.7, 83.3 (4 d, C-3, C-4, C-5, C-6), 90.9 (s, C-2), 108.9 (s, CMe_2), 121.3, 124.1, 129.2 (3 d, $Ph_{o,m,p}$), 138.0 (s, Ph_i), 153.9, 170,0 (2 s, C=O).

Methyl 2-deoxy-3,4-di-O-tert-butyldimethylsilyl-6,7-O-isopropylidene-2-N'-phenylureido-β-D-gluco-2-heptulofuranosonate 8β: Phenyl isocyanate (55 μl, 0.50 mmol) was added to a stirred solution of Methyl 2-amino-2-deoxy-3,4-di-*O-tert*-butyldimethylsilyl-6,7-*O*-isopropylidene-β-D-*gluco*-2-heptulofuranosonate **7β** (167 mg, 0.33 mmol) in dry tetrahydrofuran (5 ml) and stirring was continued for 14 h. The solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography (ethyl acetate/hexane 2:7) to afford *the title compound* **8β** (130 mg, 63%) as a white solid, m.p. 158-160°C. (Found: C, 57.71; H, 8.35; N, 4.45%. $C_{30}H_{52}N_2O_8Si_2$ requires C, 57.66; H, 8.39; N, 4.48%). $[\alpha]_D^{25}$ +107.7 (*c*, 1.0 in $CHCl_3$). ν_{max} (KBr) 3423, 3367 cm^{-1} (NH), 1731, 1712 cm^{-1} (C=O). m/z (CI NH_3): 625 (MH^+, 23%), 593 (MH^+-HOMe, 89%), 94 ($PhNH_3^+$ 100%). δ_H (500 MHz, $CDCl_3$): 0.11, 0.15, 0.18, 0.19 (4 s, 4 x 3 H, SiMe), 0.89, 0.94 (2 s, 2 x 9 H, $SiCMe_3$), 1.32, 1.40 (2 s, 2 x 3 H, CMe_2), 3.80 (s, 3 H, OMe), 4.12 (dd, J = 0.8, 3.1 Hz, 1 H, H-4), 4.15 (dd, J = 6.0, 8.7 Hz, 1 H, H-7), 4.18 (dd, J = 4.6, 8.7 Hz, 1 H, H-7'), 4.22 (d, J = 0.8 Hz, 1 H, H-3), 4.25 (ddd, J = 4.6, 6.0, 9.1 Hz, 1 H, H-6), 4.30 (dd, J = 3.1, 9.1 Hz, 1 H, H-5), 6.07, 6.32 (2 s, 2 x 1 H, NH), 7.03-7.07 (m, 1 H, Ph_p), 7.25-7.32 (m, 4 H, $Ph_{o,m}$). δ_C (50 MHz, $CDCl_3$):-5.9, -5.3, -5.2, -4.6 (4 q, SiMe), 17.7, 18.0 (2 s, $SiCMe_3$), 25.3, 25.4, 25.8, 26.8 (4 q, $SiCMe_3$, CMe_2), 52.7 (q, OMe), 67.7 (t, C-7), 72.7, 77.6, 83.0, 85.1 (4 d, C-3, C-4, C-5, C-6), 94.9 (s, C-2), 109.0 (s, CMe_2), 120.4, 123.8, 129.0 (3 d, $Ph_{o,m,p}$), 137.9 (s, Ph_i), 153.9, 168.1 (2 s, C=O). Further eluation of the column gave methyl 2-deoxy-3,4-di-*O-tert*-butyldimethylsilyl-6,7-*O*-isopropylidene-2-*N'*-phenylureido-α-D-*gluco*-2-heptulofuranosonate **8α** (35 mg, 17%).

(2R,3S,4R,4'R,5R)-6,8-diaza-3,4-di-tert-butyldimethylsilyloxy-2-(2',2'-dimethyl-1',3'-dioxolane-4'-yl)-1-oxa-8-N-phenyl-spiro[4.4]nonane-7,9-dione 9α: A solution of methyl 2-deoxy-3,4-di-*O-tert*-butyldimethylsilyl-6,7-*O*-isopropylidene-2-*N'*-phenylureido-α-D-*gluco*-2-heptulofuranosonate **8α** (260 mg, 0.42 mmol) and potasium *tert*-butoxide (58 mg, 0.52 mmol) in dry dimethylformamide (5 ml) was stirred for 1 h when t.l.c. (ethyl acetate/hexane 1:4) showed no starting material (R_f 0.13) and the formation of one product (R_f 0.41). The solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography (ethyl acetate/hexane 1:4) to afford *the title compound* **9α** (217 mg, 88%) as a white solid, m.p. 142-144°C. (Found: C, 58.61; H, 8.49; N, 4.68%. $C_{29}H_{48}N_2O_7Si_2$ requires C, 58.75; H, 8.16; N, 4.72%). $[\alpha]_D^{25}$ -5.2 (*c*, 1.0 in $CHCl_3$). ν_{max} (KBr) 3297 cm^{-1} (NH), 1798, 1740 cm^{-1} (C=O). m/z (CI NH_3): 593 (MH^+, 100%), 477 (M^+-TBDMS, 39%). δ_H (500 MHz, $CDCl_3$): 0.09, 0.14, 0.15, 0.16 (4 s, 4 x 3 H, SiMe), 0.94, 0.96 (2 s, 2 x 9 H, $SiCMe_3$), 1.35, 1.42 (2 s, 2 x 3 H, CMe_2), 4.01 (dd, J = 6.1, 8.1 Hz, 1 H, H-5'), 4.09 (dd, J = 4.5, 7.9 Hz, 1 H, H-2), 4.13 (dd, J = 6.3, 8.6 Hz, 1 H, H-5"), 4.25 (dd, J = 3.4,

4.5 Hz, 1 H, H-3), 4.34 (d, J = 3.4 Hz, 1 H, H-4), 4.38 (app dt, J = 6.2, 7.8 Hz, 1 H, H-4'), 5.95 (s, 1 H, NH), 7.34-7.47 (m, 5 H, Ph). δ_C (50 MHz, $CDCl_3$): -4.8, -4.7, -4.6 (3 q, SiMe), 17.8, 18.1 (2 s, $SiCMe_3$), 25.5, 25.7, 26.7, 28.8 (4 q, $SiCMe_3$, CMe_2), 66.9 (t, C-5'), 73.1, 77.8, 79.0, 80.7 (4 d, C-2, C-3, C-4, C-4'), 91.1 (s, C-5), 109.3 (s, CMe_2), 125.9, 128.1, 129.0 (3 d, $Ph_{o,m,p}$), 131.1 (s, Ph_i), 154.7, 169.6 (2 s, C=O).

(2R, 3S, 4R, 4'R, 5S)-6,8-diaza-3,4-di-tert-butyldimethylsilyloxy-2-(2',2'-dimethyl-1',3'-dioxolane-4'-yl)-1-oxa-8-N-phenyl-spiro[4.4]nonane-7,9-dione 9β: A solution of methyl 2-deoxy-3,4-di-*O-tert*-butyldimethylsilyl-6,7-*O*-isopropylidene-2-*N*'-phenylureido-β-D-*gluco*-2-heptulofuranosonate **8β** (143 mg, 0.23 mmol) and potasium*tert*-butoxide (32 mg, 0.29 mmol) in dry dimethylformamide (3 ml) was stirred for 30 min when t.l.c. (ethyl acetate/hexane 1:4) showed no starting material (R_f 0.14) and the formation of one product (R_f 0.37). The solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography (ethyl acetate/hexane 1:4) to afford *the title compound 9β* (106 mg, 78%) as a white solid, m.p. 154-156°C. (Found: C, 58.69; H, 8.38; N, 4.62%. $C_{29}H_{48}N_2O_7Si_2$ requires C, 58.75; H, 8.16; N, 4.72%). $[\alpha]_D^{25}$ +9.3 (*c*, 1.0 in $CHCl_3$). ν_{max} (KBr) 3279 cm^{-1} (NH), 1797, 1734 cm^{-1} (C=O). m/z (CI NH_3): 610 ($M+NH_4^+$, 5%), 593 (MH^+, 100%), 535 (M^+- CMe_3, 45%). δ_H (500 MHz, $CDCl_3$): 0.10, 0.11, 0.21, 0.22 (4 s, 4 x 3 H, SiMe), 0.92, 0.98 (2 s, 2 x 9 H, $SiCMe_3$), 1.36, 1.42 (2 s, 2 x 3 H, CMe_2), 4.06 (dd, J = 5.4, 8.6 Hz, 1 H, H-5'), 4.15 (dd, J = 6.1, 8.6 Hz, 1 H, H-5"), 4.23 (dd, J = 1.6, 3.1 Hz, 1 H, H-3), 4.25-4.28 (m, 1 H, H-4'), 4.27 (d, J = 1.6 Hz, 1 H, H-4), 4.38 (dd, J = 3.1, 8.8 Hz, 1 H, H-2), 6.09 (s, 1 H, NH), 7.35-7.38 (m, 3 H, Ph), 7.44-7.47 (m, 2 H, Ph). δ_C (50 MHz, $CDCl_3$): -5.0, -4.9, -4.6 (3 q, SiMe), 17.9, 18.1 (2 s, $SiCMe_3$), 25.4, 25.7, 25.9, 26.7 (4 q, $SiCMe_3$, CMe_2), 67.2 (t, C-5'), 72.8, 76.4, 83.1, 84.0 (4 d, C-2, C-3, C-4, C-4'), 91.7 (s, C-5), 109.3 (s, CMe_2), 126.2, 128.2, 129.1 (3 d, $Ph_{o,m,p}$), 131.2 (s, Ph_i), 153.8, 167.6 (2 s, C=O).

(1'R,2R,3R,4R,5R)-6,8-diaza-3,4-dihydroxy-2-(1',2'-dihydroxyethyl)-1-oxa-8-N-phenyl-spiro[4.4]nonane-7,9-dione 3α: (2R, 3S, 4R, 4'R, 5R)-6,8-diaza-3,4-di-*tert*-butyldimethylsilyloxy-2-(2',2'-dimethyl-1',3'-dioxolane-4'-yl)-1-oxa-8-*N*-phenyl-spiro[4.4]nonane-7,9-dione **9α** (168 mg, 0.28 mmol) was dissolved in dioxane (2 ml). Water (2 ml) and trifluoroacetic acid (2 ml) were added and the mixture was stirred for 26 h when t.l.c. (ethyl acetate/hexane 1:4) showed no starting material (R_f 0.41) and the formation of one product (R_f 0.00). The solvent was removed under reduced pressure and the resulting residue was purified by recrystallisation (ethyl acetate/methanol) to afford *the title comound 3α* (69 mg, 75%) as a white solid, m.p. 199-202°C. (Found: C, 52.05; H, 4.89; N, 8.39%. $C_{14}H_{16}N_2O_7$ requires C, 51.85; H, 4.97; N, 8.64%). $[\alpha]_D^{25}$ +7.2 (*c*, 0.65 in MeOH). ν_{max} (KBr) 3480, 3447, 3352 cm^{-1} (NH, OH), 1793, 1724 cm^{-1} (C=O). m/z (DCI NH_3): 342 ($M+NH_4^+$, 11%), 325 (MH^+, 21%), 222 (100%). δ_H (500 MHz, MeOD): 3.64 (dd, J = 5.8, 11.5 Hz, 1 H, H-2'), 3.79 (dd, J = 3.2, 11.5 Hz, 1 H, H-2"), 3.95 (ddd, J = 3.2, 5.8, 8.1 Hz, 1 H, H-1'), 4.21 (dd, J = 5.0, 8.1 Hz, 1 H, H-2), 4.35 (app t, J = 4.5 Hz, 1 H, H-3), 4.37 (d, J = 4.1 Hz, 1 H, H-4), 7.36-7.49 (m, 5 H, Ph). δ_C (125 MHz, MeOD): 64.6 (t, C-2'), 71.6, 78.2, 79.0, 81.3 (4 d, C-2, C-3, C-4, C-1'), 93.5 (s, C-5), 127.6, 129.4, 130.0 (3 d, $Ph_{o,m,p}$), 132.8 (s, Ph_i), 156.5, 173.6 (2 s, C=O).

(1'R,2R,3R,4R,5S)-6,8-diaza-3,4-dihydroxy-2-(1',2'-dihydroxyethyl)-1-oxa-8-N-phenyl-spiro[4.4]nonane-7,9-dione 3β: (2R, 3S, 4R, 4'R, 5S)-6,8-diaza-3,4-di-*tert*-butyldimethylsilyloxy-2-(2',2'-dimethyl-1',3'-dioxolane-4'-yl)-1-oxa-8-*N*-phenyl-spiro[4.4]nonane-7,9-dione **9β** (127 mg, 0.21 mmol) was dissolved in dioxane (2 ml). Water (2 ml) and trifluoroacetic acid (2 ml) were added and the mixture was stirred for 22 h when t.l.c. (ethyl acetate/hexane 1:4) showed no starting material (R_f 0.37) and the formation of one product (R_f 0.00). The solvent was removed under reduced pressure and the resulting residue was purified by recrystallisation (ethyl acetate) to afford *the title compound 3β* (51 mg, 73%) as a white solid, m.p. 200-

201°C. (Found: C, 52.10; H, 4.44; N, 8.36%. $C_{14}H_{16}N_2O_7$ requires C, 51.85; H, 4.97; N, 8.64%). $[\alpha]_D^{25}$ +16.1 (*c*, 0.5 in water). ν_{max} (film) 3365 cm^{-1} (NH, OH), 1788, 1728 cm^{-1} (C=O). m/z (DCI NH_3): 325 (MH^+, 3%), 194 (69%), 177 (94%), 119 (72%), 94 ($PhNH_3^+$, 100%). δ_H (500 MHz, MeOD): 3.66 (dd, J = 6.0, 11.5 Hz, 1 H, H-2'), 3.78 (dd, J = 3.6, 11.5 Hz, 1 H, H-2''), 3.92 (ddd, J = 3.6, 6.0, 6.9 Hz, 1 H, H-1'), 4.27 (d, J = 6.1 Hz, 1 H, H-4), 4.38 (app t, J = 6.9 Hz, 1 H, H-2), 4.70 (app t, J = 6.4 Hz, 1 H, H-3), 7.33-7.49 (m, 5 H, Ph). δ_C (125 MHz, MeOD): 64.3 (t, C-2'), 73.0, 76.2, 80.3, 81.4 (4 d, C-2, C-3, C-4, C-1'), 93.0 (s, C-5), 127.7, 129.3, 130.0 (3 d, $Ph_{o,m,p}$), 132.8 (s, Ph_i), 156.7, 172.1 (2 s, C=O).

(2S, 3R, 4R, 4'R, 5R)-6,8-diaza-3,4-dihydroxy-2-(2',2'-dimethyl-1',3'-dioxolane-4'-yl)-1-oxa-8-N-phenyl-spiro[4.4]nonane-7,9-dione ***10α****:* (1'R, 2R, 3R, 4R, 5R)-6,8-diaza-3,4-dihydroxy-2-(1',2'-dihydroxyethyl)-1-oxa-8-*N*-phenyl-spiro[4.4]nonane-7,9-dione **3α** (35 mg, 0.108 mmol) was suspended in dry acetone (4 ml). After addition of camphor sulfonic acid (7 mg, 0.030 mmol) the mixture was stirred for 2.5 h when t.l.c. (ethyl acetate) showed no starting material (R_f 0.16) and the formation of one product (R_f 0.68). Sodium bicarbonate (30 mg, 0.36 mmol) was added, the mixture was stirred for 10 min, filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (ethyl acetate/hexane 2:1) to afford *the title compound* ***10α*** (30 mg, 76%) as a colourless foam. (Found: C, 55.73; H, 5.31; N, 7.84%. $C_{17}H_{20}N_2O_7$ requires C, 56.04; H, 5.53; N, 7.69%). $[\alpha]_D^{25}$ -23.3 (*c*, 1.0 in $CHCl_3$). ν_{max} (film) 3407 cm^{-1} (OH, NH), 1792, 1723 cm^{-1} (C=O). m/z (CI NH_3): 382 ($M+NH_4^+$, 33%), 365 (MH^+, 100%). δ_H (500 MHz, $CDCl_3$): 1.39, 1.46 (2 s, 2 x 3 H, CMe_2), 3.54 (s, 1 H, OH), 4.04 (dd, J = 4.6, 8.7 Hz, 1 H, H-5'), 4.15 (dd, J = 6.0, 8.7 Hz, 1 H, H-5''), 4.30 (dd, J = 2.8, 11.7 Hz, 1 H, H-3), 4.37 (s, 1 H, H-4), 4.38 (dd, J = 2.8, 7.9 Hz, 1 H, H-2), 4.42 (ddd, J = 4.6, 6.0, 7.9 Hz, 1 H, H-4'), 4.64 (d, J = 11.7 Hz, 1 H, OH), 6.63 (s, 1 H, NH), 7.37-7.43 (m, 3 H, Ph), 7.45-7.50 (m, 2 H, Ph). δ_C (125 MHz, $CDCl_3$): 25.0, 26.8 (2 q, $C\underline{Me}_2$), 66.7 (t, C-5'), 72.9, 77.4, 83.4 (3 d, C-2, C-3, C-4, C-4'), 93.0 (s, C-5), 109.6 (s, $\underline{C}Me_2$), 125.8, 128.9, 129.2 (3 d, $Ph_{o,m,p}$), 130.1 (s, Ph_i), 154.5, 172.7 (2 s, C=O).

(2S, 3R, 4R, 4'R, 5S)-6,8-diaza-3,4-dihydroxy-2-(2',2'-dimethyl-1',3'-dioxolane-4'-yl)-1-oxa-8-N-phenyl-spiro[4.4]nonane-7,9-dione ***10β****:* (1'R, 2R, 3R, 4R, 5S)-6,8-diaza-3,4-dihydroxy-2-(1',2'-dihydroxyethyl)-1-oxa-8-*N*-phenyl-spiro[4.4]nonane-7,9-dione **3β** (60 mg, 0.185 mmol) was suspended in dry acetone (4 ml). After addition of camphor sulfonic acid (12 mg, 0.05 mmol) the mixture was stirred for 2 h when t.l.c. (ethyl acetate) showed no starting material (R_f 0.14) and the formation of one product (R_f 0.55). Sodium bicarbonate (30 mg, 0.36 mmol) was added, the mixture was stirred for 10 min, filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (ethyl acetate/hexane 2:1) to afford *the title compound* ***10β*** (45 mg, 67%) as a white solid, m.p. 87-88°C. (Found: C, 56.31; H, 5.32; N, 7.39%. $C_{17}H_{20}N_2O_7$ requires C, 56.04; H, 5.53; N, 7.69%). $[\alpha]_D^{25}$ -26.9 (*c*, 1.0 in $CHCl_3$). ν_{max} (film) 3417 cm^{-1} (OH, NH), 1785, 1727 cm^{-1} (C=O). m/z (DCI NH_3): 382 ($M+NH_4^+$, 69%), 365 (MH^+, 100%). δ_H (500 MHz, $CDCl_3$): 1.39, 1.46 (2 s, 2 x 3 H, CMe_2), 2.94, 3.99 (2 s, 2 x 1 H, OH), 4.04 (dd, J = 4.6, 8.8 Hz, 1 H, H-5'), 4.21 (dd, J = 6.0, 8.8 Hz, 1 H, H-5''), 4.35 (ddd, J = 4.6, 6.0, 8.6 Hz, 1 H, H-4'), 4.45 (d, J = 1 Hz, 1 H, H-4), 4.64 (dd, J = 3.5, 8.5 Hz, 1 H, H-2), 4.51 (dd, J = 1.0, 3.5 Hz, 1 H, H-3), 6.59 (s, 1 H, NH), 7.39-7.50 (m, 5 H, Ph), 7.45-7.50. δ_C (50 MHz, $CDCl_3$): 25.1, 26.8 (2 q, $C\underline{Me}_2$), 63.3 (t, C-5'), 73.7, 76.2, 80.9, 84.0 (4 d, C-2, C-3, C-4, C-4'), 89.9 (s, C-5), 109.9 (s, $\underline{C}Me_2$), 126.0, 128.7, 129.2 (3 d, $Ph_{o,m,p}$), 130.4 (s, Ph_i), 153.7, 170.1 (2 s, C=O).

(3aR,4'R,5S,6S,6aR)-5-(2',2'-dimethyl-1',3'-dioxolane-4'-yl)-6-hydroxy-3a-N-phenylcarboxamido-tetrahydrofuro[2.3-d]-1,2-oxazolidine-2-one ***11****: Method I (from* ***10α****):* (2S, 3R, 4R, 4'R, 5R)-6,8-diaza-3,4-dihydroxy-2-(2',2'-dimethyl-1',3'-dioxolane-4'-yl)-1-oxa-8-*N*-phenyl-spiro[4.4]nonane-7,9-dione (33 mg, 0.091 mmol) **10α** was dissolved in dry dimethylformamid (2 ml). After addition of potassium *tert-*

butoxide (2 mg, 0.018 mmol) the solution was stirred for 48 h when t.l.c. (ethyl acetate/hexane 2:1) showed no starting material (R_f 0.23) and the formation of one product (R_f 0.49). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (ethyl acetate/hexane 2:1) to afford *the title compound* **11** (26 mg, 79%) as a white solid, m.p. 218-220°C (decomposition). (Found: C, 56.15; H, 5.27; N, 7.30%. $C_{17}H_{20}N_2O_7$ requires C, 56.04; H, 5.53; N, 7.69%). $[\alpha]_D^{25}$ +25.3 (*c*, 1.0 in MeOH). ν_{max} (KBr) 3394, 3305 cm^{-1} (OH, NH), 1768, 1677 cm^{-1} (C=O). m/z (CI NH_3): 383 ($M+NH_4^+$, 13%), 365 (MH^+, 69%), 161 (100%), δ_H (500 MHz, MeOD): 1.37, 1.44 (2 s, 2 x 3 H, CMe_2), 4.04 (dd, J = 2.6, 7.3 Hz, 1 H, H-5), 4.08 (dd, J = 4.8, 8.8 Hz, 1 H, H-5'), 4.22 (dd, J = 6.3, 8.8 Hz, 1 H, H-5"), 4.37 (d, J = 2.6 Hz, 1 H, H-6), 4.58 (ddd, J = 4.8, 6.3, 7.3 Hz, 1 H, H-4'), 4.89 (s, 1 H, H-6a), 7.16 (dt, J = 1.0, 7.4 Hz, 1 H, Ph_p), 7.34 (dd, J = 7.4, 8.4 Hz, 2 H, Ph_m), 7.57 (dd, J = 1.0, 8.4 Hz, 2 H, Ph_o). δ_C (125 MHz, MeOD): 25.4, 27.1 (2 q, $C\underline{Me}_2$), 68.1 (t, C-5'), 73.5, 73.7, 84.2, 89.5 (4 d, C-4', C-5, C-6, C-6a), 97.1 (s, C-3a), 110.6 (s, $\underline{C}Me_2$), 121.7, 126.2, 129.9 (3 d, $Ph_{o,m,p}$), 138.5 (s, Ph_i), 159.5, 166.6 (2 s, C=O).

Method II (from 9α): (2R, 3S, 4R, 4'R, 5R)-6,8-diaza-3,4-di-*tert*-butyldimethylsilyloxy-2-(2',2'-dimethyl-1',3'-dioxolane-4'-yl)-1-oxa-8-*N*-phenyl-spiro[4.4]nonane-7,9-dione **9α** (48 mg, 0.081 mmol) was dissolved in dry tetrahydrofuran (2 ml). A 1M solution of tetrabutylammonium fluoride in tetrahydrofuran (160 µl mg, 0.16 mmol) was added and the mixture was stirred for 21 h when t.l.c. (ethyl acetate/hexane 2:1) showed no starting material (R_f 0.99) and the formation of two major products (R_f 0.23, R_f 0.49). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (ethyl acetate/hexane 1:1) to afford (3aR, 4'R, 5S, 6S, 6aR)-5-(2',2'-dimethyl-1',3'-dioxolane-4'-yl)-6-hydroxy-3a-*N*-phenylcarboxamido-tetrahydrofuro[2.3-d]-1,2-oxazolidine-2-one **11** (14 mg, 48%). Further eluation with ethyl acetate/hexane 2:1 gave (2S, 3R, 4R, 4'R, 5R)-6,8-diaza-3,4-dihydroxy-2-(2',2'-dimethyl-1',3'-dioxolane-4'-yl)-1-oxa-8-N-phenyl-spiro[4.4]nonane-7,9-dione **10α** (4mg, 13%).

(3aR,4'R,5R,6S,6aR)-6-Acetoxy-3-N-acetyl-5-(2',2'-dimethyl-1',3'-dioxolane-4'-yl)-3a-N-phenylcarboxamido-tetrahydrofuro[2.3-d]-1,2-oxazolidine-2-one ***12****:* (3aR, 4'R, 5S, 6S, 6aR)-5-(2',2'-dimethyl-1',3'-dioxolane-4'-yl)-6-hydroxy-3a-*N*-phenylcarboxamido-tetrahydrofuro[2.3-d]-1,2-oxazolidine-2-one **11** (12 mg, 0.033 mmol) was dissolved in acetic anhydide (1 ml) and pyridine (1 ml). The solution was stirred for 17 h when t.l.c. (ethyl acetate/hexane 1:1) showed no starting material (R_f 0.08) and the formation of one product (R_f 0.60). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (ethyl acetate/hexane 1:2) to afford *the title compound* ***12*** (14 mg, 95%) as a white solid, m.p. 80-82°C. (Found: C, 56.42; H, 4.94; N, 6.11%. $C_{21}H_{24}N_2O_9$ requires C, 56.25; H, 5.39; N, 6.25%). $[\alpha]_D^{25}$ +14.5 (*c*, 0.5 in $CHCl_3$). ν_{max} (film) 3346 cm^{-1} (NH), 1802, 1755, 1728, 1704 cm^{-1} (C=O). m/z (CI NH_3): 466 ($M+NH_4^+$,100%), 449 (MH^+, 63%). δ_H (500 MHz, $CDCl_3$): 1.36, 1.47 (2 s, 2 x 3 H, CMe_2), 2.06 (s, 3 H, OAc), 2.56 (s, 3 H, NAc), 4.14 (dd, J = 3.4, 9.1 Hz, 1 H, H-5'), 4.20 (dd, J = 5.9, 9.1 Hz, 1 H, H-5"), 4.28 (dd, J = 3.1, 7.7 Hz, 1 H, H-5), 4.42 (ddd, J = 3.4, 5.9, 7.7 Hz, 1 H, H-4'), 4.87 (s, 1 H, H-6a), 5.49 (d, J = 3.1 Hz, 1 H, H-6), 7.19 (t, J = 7.9 Hz, 1 H, Ph_p), 7.37 (t, J = 7.9 Hz, 2 H, Ph_m), 7.54 (d, J = 7.9 Hz, 2 H, Ph_o), 8.52 (s, 1 H, NH). δ_C (125 MHz, $CDCl_3$): 20.6, 23.9, 24.9, 26.9 (4 q, Ac, $C\underline{Me}_2$), 66.9 (t, C-5'), 72.0, 73.3, 82.2, 83.7 (4 d, C-4', C-5, C-6, C-6a), 95.7 (s, C-3a), 110.3 (s, $\underline{C}Me_2$), 120.1, 125.5, 129.2 (3 d, $Ph_{o,m,p}$), 136.3 (s, Ph_i), 151.4, 162.5, 168.6, 169.4 (4 s, C=O).

Methyl 2-Deoxy-3,4-di-O-tert-butyldimethylsilyl-6,7-O-isopropylidene-2-ureido-α-D-gluco-2-heptulofuranosonate ***13α*** *and Methyl 2-Deoxy-3,4-di-O-tert-butyldimethylsilyl-6,7-O-isopropylidene-2-ureido-β-D-gluco-2-heptulofuranosonate* ***13β***. Potassium cyanate (400 mg, 4.93 mmol) and a mixture of amines **7α** and **7β** (617 mg, 1.22 mmol) were stirred in glacial acetic acid (9 ml) at room temperature under nitrogen . After 1.5 h, t.l.c. (ethyl acetate/hexane 1:1) showed no starting material (R_f 0.50 and 0.55) and the formation of two products (R_f 0.20 and 0.22). The solution was diluted with water and small portions of $NaHCO_3$ were added

until reaching neutral pH. The mixture was extracted with ethyl acetate. The combined organic extracts were washed with water, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (ether) to afford *the urea 13β* (219 mg, 44%) as a colourless foam (Found: C, 52.37; H, 9.05; N 4.93%. $C_{24}H_{48}N_2O_8Si_2$ C requires C, 52.52; H, 8.82: N, 5.10%). $[\alpha]_D^{22}$ -91.0 (*c*, 0.66 in $CHCl_3$). ν_{max}(film) 3373 cm^{-1} (NH) 1756, 1682 cm^{-1} (CO). m/z (CI NH_3): 549 (MH^+, 28%), 506 (90%), 374 (100%). δ_H(500 MHz, $CDCl_3$): 0.09, 0.14, 0.19, 0.20 (4 s, 4 x 3 H, SiMe), 0.88, 0.97 (2 s, 2 x 9 H, $SiMe_3$), 1.33, 1.39 (2 s, 2 x 3 H, CMe_2), 3.78 (s, 3 H, OMe), 4.10 (d, J = 3.0 Hz, 1 H, H-4), 4.14 (dd, J = 5.2, 8.8 Hz, 1 H, H-7), 4.16 (dd, J = 5.2, 8.8 Hz, 1 H, H-7'), 4.19 (s, 1 H, H-3), 4.23 (app dt, J = 5.2, 9.1 Hz, 1 H, H-6), 4.27 (dd, J = 3.0, 9.1 Hz, 1 H, H-5), 4.43 (s, 2 H, NH_2), 6.01 (s, 1 H, NH). δ_C(50 MHz, $CDCl_3$): -5.4, -5.2, -4.7, -4.7 (4 q, SiMe), 17.7, 18.0 (2 s, $SiCMe_3$), 25.3, 25.4, 25.8, 26.9 (4 q, CMe_2, $SiCMe_3$), 52.6 (q, OMe), 67.7 (t, C-7), 72.7, 77.7, 83.0, 84.9 (4 d, C-3, C-4, C-5, C-6), 94.7 (s, C-2), 109.0 (s, CMe_2), 157.1 (C=O), 167.9 (s, C-1). Further elution gave *the urea 13α* (140 mg, 26%) as a colourless foam. (Found: C, 52.73; H, 8.98; N, 5.37%. $C_{24}H_{48}N_2O_8Si_2$ requires C, 52.52; H, 8.82; N, 5.10%. $[\alpha]_D^{20}$ +21.8 (*c*, 2.05 in $CHCl_3$). ν_{max}(film) 3421, 3365 cm^{-1} (NH), 1741, 1687 cm^{-1} (CO). m/z (CI NH_3) 549 (MH^+, 52%), 517 (100%). δ_H(500 MHz, $CDCl_3$): 0.09, 0.12, 0.19, 0.22 (4 s, 4 x 3 H, SiMe), 0.88, 0.97 (2 s, 2 x 9 H, $SiMe_3$), 1.32, 1.39 (2 s , 2 x 3 H , CMe_2), 3.76 (s, 3H, OMe), 4.03-4.06 (m, 2 H, H-4, H-7), 4.08 (dd, J = 2.9, 8. 5 Hz, 1 H, H-5), 4.16 (dd, J = 6.1, 8.8 Hz, 1 H, H-7'), 4.28-4.32 (m, 1 H, H-6), 4.31 (d, J = 1.4 Hz, 1 H, H-3), 4.86 (s, 2 H, NH_2), 5.75 (s, 1 H, NH). δ_C(50 MHz, $CDCl_3$): -5.2, -5.0, -4.7 (3 q, SiMe), 17.9 (s, $SiCMe_3$), 25.2, 25.5, 25.6, 26.8 (4 q, CMe_2, $SiCMe_3$), 52.6 (q, OMe), 67.5 (t, C-7), 72.2, 76.6, 82.6, 82.9 (4 d, C-3, C-4, C-5, C-6), 90.8 (s, C-2), 108.7 (s, CMe_2), 157.5, 169.8 (2 s, C=O).

*(4'R,2R,3S,4R,5S)-6,8-Diaza-3,4-di-tert-butyldimethylsilyloxy-2-(2',2'-dimethyl-1',3'dioxolan-4'yl)-1-oxaspiro-[4.4]nonane-7,9-dione **14β**.* Urea **13β** (730 mg, 1.33 mmol) was dissolved in dry THF (40 ml), potassium *tert*-butoxide (244 mg, 2 mmol) was added and the mixture was stirred at room temperature under nitrogen for 15 min, when t.l.c. (ethyl acetate/hexane 1:1) showed no starting material (R_f 0.22) and the formation of one product (R_f 0.85). The solvent was removed under reduced pressure, the residue was dissolved in ethyl acetate, washed with water, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography (ethyl acetate/hexane 1:3) to afford *the title compound **14β*** (584 mg, 85%) as a white solid, m.p. 186-187°C (ether/hexane). (Found: C, 53.82; H, 8.76; N 5.07%. $C_{23}H_{25}NO_7$ requires C, 53.46; H, 8.58; N, 5.42%. $[\alpha]_D^{23}$ -6.3 (*c*, 0.53 in $CHCl_3$). ν_{max}(KBr) 3260 cm^{-1} (NH), 1799 1746 cm^{-1} (CO). m/z (electrospray, neg. mode) 515 (M-H^+, 100%). δ_H(500 MHz, $CDCl_3$): 0.18, 0.19 (2 s, 2 x 6 H, SiMe), 0.92, 0.96 (2 s, 2 x 9 H, $SiMe_3$), 1.34, 1.40 (2 s, 2 x 3 H, CMe_2), 4.03 (dd, J = 5.3, 8.6 Hz, 1 H, H-5'), 4.12 (dd, J = 6.0, 8.6 Hz, 1 H, H-5''), 4.16 (dd, = 1.5, 3.0 Hz, 1 H, H-3), 4.19 (d, J = 1.5 Hz, 1 H, H-4), 4.21 (app dt, J = 5.7, 8.9 Hz, 1 H, H-4'), 4.31 (dd, J = 3.0, 8.9 Hz, 1 H, H-2), 5.94 (bs, 1 H, NH), 7.57 (bs, 1 H, NH). δ_C(50 MHz, $CDCl_3$): -5.1, -4.9, -4.8 (3 q, SiMe), 17.8, 18.0 (2 s, $SiCMe_3$), 25.4, 25.6, 25.8, 26.7 (4 q, CMe_2, $SiCMe_3$), 67.2 (t, C-5'), 72.6, 77.3, 83.0, 84.2 (4 d, C-2, C-3, C-4, C-4'), 93.1 (s, C-5), 109.3 (s, CMe_2), 154.7, 169.8 (2 s, C=O).

*(4'R,2R,3S,4R,5R)-6,8-Diaza-3,4-di-tert-butyldimethylsilyloxy-2-(2',2'-dimethyl-1',3'dioxolan-4'yl)-1-oxaspiro-[4.4]nonane-7,9-dione **14** α.* Urea **13α** (533 mg, 1.00 mmol) was dissolved in dry THF (30 ml), potassium *tert*-butoxide (183 mg, 1.5 mmol) was added and the mixture was stirred at room temperature under nitrogen for 15 min, when t.l.c. (ethyl acetate/hexane 1:1) showed no starting material (R_f 0.85) and the formation of one product (R_f 0.20). The solvent was removed under reduced pressure, the residue was dissolved in ethyl acetate, washed with water, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography (ethyl acetate/hexane 1:3) to afford *the title*

compound 14α (453 mg, 87%) as a white solid, m.p. 218°C. (Found: C, 53.76; H, 8.49; N 5.41%. $C_{23}H_{25}NO_7$ requires C, 53.46; H, 8.58; N, 5.42%. $[\alpha]_D^{22}$ +4.4 (*c*, 0.5 in $CHCl_3$). ν_{max}(KBr) 3257 cm^{-1} (NH), 1784, 1739 cm^{-1} (CO). m/z (CI NH_3) 517 (MH^+, 100%). δ_H(500 MHz, $CDCl_3$): 0.07, 0.13 (2 s, 2 x 3 H, SiMe), 0.14, (s, 6 H, SiMe), 0.92, 0.95 (2 s, 2 x 9 H, $SiMe_3$), 1.33, 1.40 (2 s, 2 x 3 H, CMe_2), 3.98 (dd, J = 5.9, 8.6 Hz, 1 H, H-5'), 4.06 (dd, J = 3.9, 7.8 Hz, 1 H, H-2), 4.10 (dd, J = 6.3, 8.6 Hz, 1 H, H-5''), 4.21-4.18 (m, 2 H, H-3, H-4), 4.32 (app dt, J = 6.1, 7.8 Hz, 1 H, H-4'), 5.93 (br s, 1 H, NH), 8.12 (br s, 1 H, NH). δ_C(50 MHz, $CDCl_3$): -5.0, -4.8, -4.7 (3 q, SiMe), 17.7, 18.0 (2 s, $SiCMe_3$), 25.3, 25.6, 25.7, 26.6 (4 q, CMe_2, $SiCMe_3$), 66.8 (t, C-5'), 72.9, 77.9, 79.0, 81.2 (4 d, C-2, C-3, C-4, C-4'), 92.8 (s, C-5), 109.2 (s, CMe_2), 156.0, 171.5 (2 s, C=O).

(1'R,2R,3S,4S,5R)-6,8-Diaza-3,4-di-tert-butyldimethylsilyloxy-2-(1',2'-dihydroxyethyl)-1-oxa-spiro[4.4]-7,9-dione 15β. Acetonide **14β** (483 mg, 0.94 mmol) was dissolved in 80% acetic acid/water (30 ml) and the mixture was heated at 55°C for 1 h, when t.l.c. (ethyl acetate/hexane 2:1) showed no starting material (R_f 0.90) and the formation of one product (R_f 0.20). After cooling to room temperature the solvent was removed under reduced pressure, the residue was coevaporated with ethyl acetate and purified by flash chromatography (ethyl acetate/hexane 2:1) to give *the title compound 15β* (389 mg, 83%) as a white solid, m.p. 174-175°C (ether/hexane). (Found: C, 50.13; H, 8.37; N, 5.58%. $C_{20}H_{40}N_2O_7Si_2$ requires C, 50.39; H, 8.46; N, 5.88%. $[\alpha]_D^{20}$ +34.3 (*c*, 0.35 in acetone). ν_{max}(film) 3306 cm^{-1} (NH, OH), 1733 cm^{-1} (C=O). m/z (DCI NH_3): 494 ($M+NH_4^+$, 9%), 477 (MH^+, 3%), 243 (100%). δ_H(500 MHz, acetone-d_6+D_2O): 0.11, 0.13 (2 s, 2 x 3 H, SiMe), 0.20 (s, 6 H, SiMe), 0.88, 0.95 (2 s, 2 x 9 H, $SiMe_3$), 3.62 (dd, J = 6.1, 11.1 Hz, 1 H, H-2'), 3.72 (dd, J = 3.3, 11.1 Hz, 1 H, H-2''), 3.84 (ddd, J = 3.3, 6.1, 7.3 Hz, 1 H, H-1'), 4.29 (dd, J = 5.5, 7.2 Hz, 1 H, H-2), 4.40 (d, J = 4.9 Hz, 1 H, H-4), 4.62 (app t, J = 5.2 Hz, 1 H, H-3). δ_C(50 MHz, acetone-d_6): -4.4, -4.2 (2 q, SiMe), 18.3, 18.6 (2 s, $SiCMe_3$), 26.1, 26.4 (2 q, $SiCMe_3$), 64.2 (t, C-2'), 71.1, 77.3, 81.8, 81.9 (4 d, C-2, C-3, C-4, C-1'), 93.5 (s, C-5), 156.0, 171.8 (2 s, C=O).

(1'R, 2R, 3S, 4S, 5S) 6,8-diaza-3,4-di-tert-butyldimethylsilyloxy-2-(1',2'-dihydroxyethyl)-1-oxa-spiro[4.4]-7,9-dione 15α. Acetonide **14α** (413 mg, 0.80 mmol) was dissolved in 80% acetic acid/water (25 ml) and the mixture was heated at 55°C for 1 h, when t.l.c. (ethyl acetate/hexane 2:1) showed no starting material (R_f 0.90) and the formation of one product (R_f 0.20). After cooling to room temperature the solvent was removed under reduced pressure, the residue was coevaporated with ethyl acetate and purified by flash chromatography (ethyl acetate/hexane 2:1) to affordthe *title compound 15α* (333 mg, 87%) as a white solid, m.p. 244-245°C (ether/hexane). (Found: C, 50.36; H, 8.62; N, 5.81%. $C_{20}H_{40}N_2O_7Si_2$ requires C, 50.39; H, 8.46; N, 5.88%. $[\alpha]_D^{20}$ +29.2 (*c*, 0.33 in acetone). ν_{max}(film) 3445 cm^{-1} (NH, OH), 1789, 1744 cm^{-1} (C=O). m/z (DCI NH_3): 477 (MH^+, 10%), 243 (55%), 74 (100%). δ_H(500 MHz, acetone-d_6+D_2O): 0.04, 0.13, 0.15, 0.16 (4 s, 4 x 3 H, SiMe), 0.90, 0.94 (2 s, 2 x 9 H, $SiMe_3$), 3.61 (dd, J = 6.1, 11.2 Hz, 1 H, H-2'), 3.73 (dd, J = 3.3, 11.2 Hz, 1 H, H-2''), 3.87 (ddd, J = 3.3, 6.1, 7.1 Hz, 1 H, H-1'), 4.09 (dd, J = 5.5, 7.9 Hz, 1 H, H-2), 4.36 (d, J = 5.1 Hz, 1 H, H-4), 4.47 (app t, J = 5.3 Hz, 1 H, H-3). δ_C(50 MHz, acetone-d_6): -4.7, -4.4, -4.3 (3 q, SiMe), 18.4, 18.6 (2 s, $SiCMe_3$), 26.2, 26.3 (2 q, $SiCMe_3$), 64.1 (t, C-2'), 70.8, 78.4, 79.2, 80.2 (4 d, C-2, C-3, C-4, C-1'), 93.0 (s, C-5), 156.2, 173.1 (2 s, C=O).

(1'R, 2R, 3R, 4R, 5S)-6.8-diaza-3,4-dihydroxy-2-(1',2'-dihydroxyethyl)-1-oxa-spiro[4.4]nonane-7,9-dione 4β. Diol **15β** (149 mg, 0.30 mmol) was dissolved in dry THF (2 ml) and a solution of tetrabutylammonium fluoride in THF (1M, 630 µl, 0.63 mmol) was added. The solution was stirred at room temperature under nitrogen for 24 h, when t.l.c. (ethyl acetate) showed no starting material (R_f 0.50) and the formation of one product (R_f 0.00 (R_f 0.30 ($CHCl_3$/MeOH/HOAc/water 60:30:3:5)). The solvent was removed under reduced pressure and the residue was purified by flash chromatography ($CHCl_3$/MeOH/HOAc/water 60:30:3:5) to

afford *the title compound 4β* (74 mg, 95%), m.p. 181-183°C (methanol). (Found: C, 38.34; H, 5.03; N, 11.16%. $C_8H_{12}N_2O_7$ requires C, 38.72; H, 4.87; N, 11.29%). $[\alpha]_D^{20}$ +40.3 (*c*, 0.31 in methanol). ν_{max}(film) 3316 cm^{-1} (OH, NH), 1783, 1731 cm^{-1} (C=O). m/z (electrospray, neg. mode) 247 ($M-H^+$, 100%). δ_H(500 MHz, MeOD): 3.63 (dd, J = 6.0, 11.5 Hz, 1 H, H-2'), 3.74 (dd, J = 3.5, 11.5 Hz, 1 H, H-2''), 3.87 (ddd, J = 3.5, 6.0, 7.3 Hz, 1 H, H-1'), 4.16 (d, J = 5.7 Hz, 1 H, H-4), 4.30 (app t, J = 6.8 Hz, 1 H, H-2), 4.60 (app t, J = 6.1 Hz, 1 H, H-3). δ_C(50 MHz, MeOD): 64.3 (t, C-2'), 72.8, 76.2, 80.4, 81.2 (4 d, C-2, C-3, C-4, C-1'), 94.3 (s, C-5), 158.4, 174.7 (2 s, C=O).

(1'R, 2R, 3R, 4R, 5R)-6.8-diaza-3,4-dihydroxy-2-(1',2'-dihydroxyethyl)-1-oxa-spiro[4.4]nonane-7,9-dione 4α. Diol **15α** (167 mg, 0.35 mmol) was dissolved in dry THF (2 ml) and a solution of tetrabutylammonium fluoride in THF (1M, 770 µl, 0.77 mmol) was added. The solution was stirred at room temperature under nitrogen for 24 h, when t.l.c. (ethyl acetate) showed no starting material (R_f 0.50) and the formation of one product (R_f 0.00 (R_f 0.30 ($CHCl_3$/MeOH/HOAc/water 60:30:3:5)). The solvent was removed under reduced pressure and the residue was purified by flash chromatography ($CHCl_3$/MeOH/HOAc/water 60:30:3:5) to afford *the title compound 4α* (87 mg, 100%) as a colourless foam, which was freeze-dried. (Found: C, 38.45; H, 4.60; N, 10.53%. $C_8H_{12}N_2O_7$ requires C, 38.72; H, 4.87; N, 11.29%. $[\alpha]_D^{20}$ +5.0 (*c*, 0.36 in methanol). ν_{max}(film) 3369 cm^{-1} (OH, NH), 1786, 1734 cm^{-1} (C=O). m/z (electrospray, neg. mode) 247 ($M-H^+$, 100%). δ_H(500 MHz, MeOD): 3.60 (dd, J = 5.8, 11.5 Hz, 1 H, H-2'), 3.76 (dd, J = 3.1, 11.5 Hz, 1 H, H-2''), 3.90 (ddd, J = 3.1, 5.8, 8.3 Hz, 1 H, H-1'), 4.14 (dd, J = 4.8, 8.3 Hz, 1 H, H-2), 4.22 (d, J = 3.7 Hz, 1 H, H-4), 4.26 (dd, J = 3.7, 4.8 Hz, 1 H, H-3). δ_C(50 MHz, MeOD): 64.7 (t, C-2'), 71.4, 78.2, 78.6, 81.5 (4 d, C-2, C-3, C-4, C-1'), 95.1 (s, C-5), 158.2, 176.6 (2 s, C=O).

EQUILIBRATION OF EPIMERS 14α AND 14β

Compound **14β** (21 mg, 0.04 mmol) was dissolved in dry DMF (1 ml), potassium *tert*-butoxide was added and the mixture was heated at 100°C for 10 h. The solvent was removed under reduced pressure, the residue was dissolved in ethyl acetate, the resulting solution was washed with water, dried ($MgSO_4$), filtered and the solvent concentrated *in vacuo*. The residue was purified by flash chromatography to afford 20 mg of a mixture 1:3 of **14β:14α**. Using the same conditions, **14α** (21 mg, 0.04 mmol) yielded after 20 h a mixture **14β:14α** in a ratio 1:4.

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