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Some non-anomerically C–C-linked carbohydrate amino acids related to leucine—synthesis and structure determination

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Abstract

(5′*R*)-5′-Isobutyl-5′-[methyl (4*R*)-2,3-*O*-isopropylidene-β-L-erythrofuranosid-4-*C*-yl]-imidazolidin-2′,4′-dione was synthesised starting from methyl 2,3-*O*-isopropylidene-α-D-*lyxo*-pentodialdo-1,4-furanoside via methyl 6-deoxy-6-isopropyl-2,3-*O*-isopropylidene-α-D-*lyxo*-hexofuranosid-5-ulose applying the Bucherer–Bergs reaction. Its 5′-*R* configuration was confirmed by X-ray crystallography. Corresponding α-amino acid–methyl (5*R*)-5-amino-5-*C*-carboxy-5,6-dideoxy-6-isopropyl-α-D-*lyxo*-hexofuranoside (alternative name: 2-[methyl (4*R*)-β-L-erythrofuranosid-4-*C*-yl]-D-leucine) was obtained from the above hydantoin by acid hydrolysis of the isopropylidene group followed by basic hydrolysis of the hydantoin ring. Analogous derivatives with 5*S* configuration, formed in a minority, were also isolated and characterised.

Keywords: Sugar amino acids; Hydantoins, Leucine; Bucherer–Bergs reaction; Methyl 6-deoxy-6-isopropyl-2,3-*O*-isopropylidene-α-D-*lyxo*-hexofuranosid-5-ulose; X-ray crystallography

1. Introduction

Carbohydrate moieties of glycoproteins and glycolipids play an important role in a variety of biological events, especially in recognition phenomena and immune response.[1] Their decisive influence on conformation, solubility and stabilization of proteins is also known.[2] The use of synthetic glycopeptide model compounds became attractive for understanding of the mutual interactions between both moieties with the aim to develop new powerful glycosidase inhibitors and effective compounds for drug design. In this respect, many O- and N-linked (mainly anomerically) glycoproteins have been synthesised and studied intensively especially during the past decade. To improve the metabolic stability of these potential drugs, a lot of more stable glycosyl analogs with a C–C anomeric bond between the carbohydrate moiety and the peptide have been synthesised.[3–18] On the other hand, not too much glycoconjugate analogs with a C–C bond in another glucidic position (excluding anomeric) are described[19–27] until now. Recently, three useful reviews on sugar amino acids have been published by Dondoni and co-workers,[28] Schweizer,[29] and Kessler and co-workers.[30]

In this paper, we present the synthesis and structure determination of some glycoconjugate model compounds having C-2-linked α-amino acid attached to a carbohydrate backbone in the C-5 position. Thus, leucine derivatives branched at C-2 atom are obtained from suitably *O*-protected 6-deoxy-6-isopropyl-hexofuranos-5-ulose. Further studies on the preparation of analogous glycoconjugates of serine and phenylalanine, respectively, are in progress.

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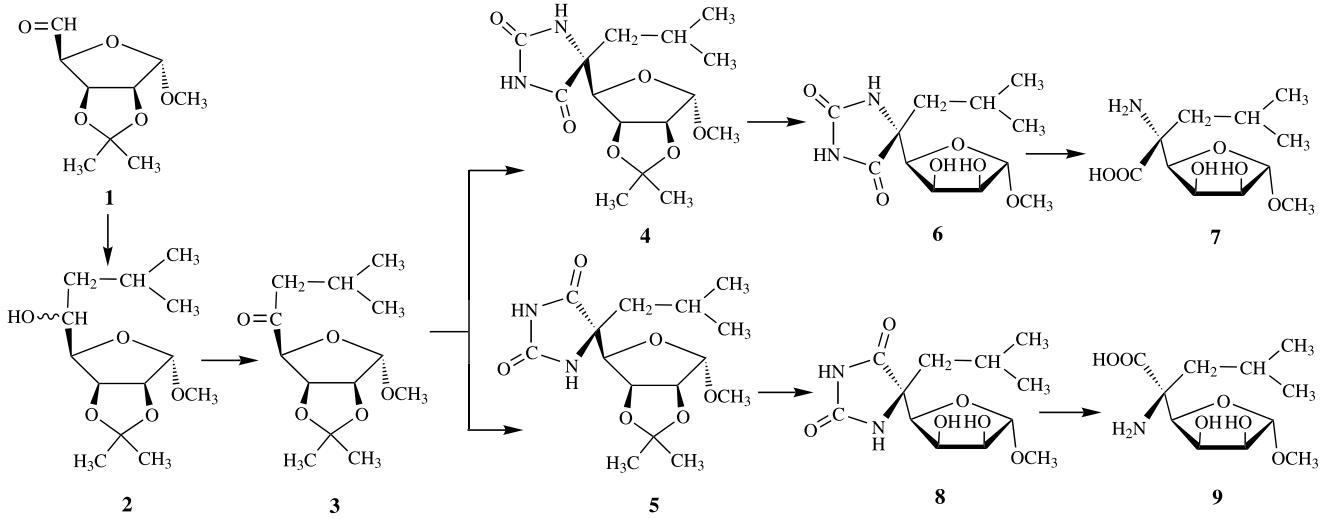
2. Results and discussion

Hydrolysis of hydantoins (imidazolidin-2,4-diones), which can be prepared conveniently by the Bucherer–Bergs reaction, provides a useful route to many α-amino acids. Up to now, many sugar hydantoins have been described.[7,8,19–21,25,26,31–39] However, for their preparation, the Bucherer–Bergs reaction has been applied only several times.[19,20,25,26,32] Recently, we have published[25,26] the synthesis of some sugar α-amino acids via corresponding hydantoin derivatives starting from methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-*lyxo*-hexopyranosid-4-ulose, methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hexofuranosid-5-ulose and methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-*lyxo*-hexofuranosid-5-ulose.

To prepare the corresponding 5-ulose, we have started from the known methyl 2,3-*O*-isopropylidene-α-D-*lyxo*-pentodialdo-1,4-furanoside (**1**).[40,41] The Grignard reaction of **1** with isobutylmagnesium bromide afforded a mixture of methyl 6-deoxy-6-isopropyl-2,3-*O*-isopropylidene-α-D-mannofuranoside and methyl 6-deoxy-6-isopropyl-2,3-*O*-isopropylidene-β-L-gulofuranoside (**2**) and small amount of methyl 2,3-*O*-isopropylidene-α-D-lyxofuranoside (product of side-reduction of starting aldehyde **1**). A mixture of alcohols **2** was, without separation, subsequently oxidised with pyridinium dichromate to give methyl 6-deoxy-6-isopropyl-2,3-*O*-isopropylidene-α-D-*lyxo*-hexofuranosid-5-ulose (**3**) in high yield. Application of the Bucherer–Bergs reaction to this 5-ulose led to the formation of the corresponding hydantoin derivatives **4** and **5** (Scheme 1). The stereoselectivity of this reaction was higher than 80% (based on the analysis of NMR spectra) in favour of the hydantoin **4** having *R* configuration at C-5 and the isolation and purification of isomer with *S* configuration at C-5 (**5**) was, due to very similar behaviour on chromatography for both **4** and **5**, rather difficult. Therefore, only approx 6% of pure **5** was isolated. Acid hydrolysis of 2,3-*O*-isopropylidene group in **4** and **5** (to increase the solubility of the products **6** and **8** in water) and subsequent basic hydrolysis of the hydantoin afforded the desired amino acids **7** and **9**, respectively. The quaternary C-5 atom of a saccharide moiety coincides in this case with the α-carbon atom of leucine and therefore, in addition to (5*R*)-5-amino-5-*C*-carboxy-5,6-dideoxy-6-isopropyl-α-D-*lyxo*-hexofuranoside (according to carbohydrate nomenclature), compound **7** can be alternatively named as 2-[methyl (4*R*)-β-L-erythrofuranosid-4-*C*-yl]-D-leucine.

Because of the obvious difficulties in unambiguous establishing the configuration at quaternary C-5 atom (*R* versus *S*) by NMR methods, suitable crystals of compound **4** were subjected to X-ray analysis which confirmed 5-*R* configuration relatively to known configuration at C-2, C-3 and C-4. Fig. 1 shows molecule and the numbering scheme of compound **4**. The H-positions have been put at calculated positions and were during refinement riding on their respective pivot atoms. The relevant crystallographic data for **4** are given in Table 1. The bond lengths and bond angles are listed in Table 2. A list of selected torsion angles is given in Table 3. The final positional parameters for compound **4** are summarised in Table 4.

The presence of a 1,3-dioxolane ring fused to a furanose ring at the C-2,3 and the α-glycosidic methyl group imposes some conformational rigidity on **4**. The values of relevant torsion angles O-4–C-1–C-2–C-3 = 17.57(13)°, C-1–C-2–C-3–C-4 = 7.88(13)°, C-2–C-3–C-4–O-4 = −30.45(12)°, C-3–C-4–O-4–C-1 = 43.33(12)°, C-4–O-4–C-1–C-2 = −38.09(13)° and puckering parameters[42] $Q = 0.389(1)$ Å, $\varphi = 348.1(2)°$ indicate that O-4–C-1–C-2–C-3–C-4 furanoside ring adopts the ^{O}E conformation which is significantly



Scheme 1.

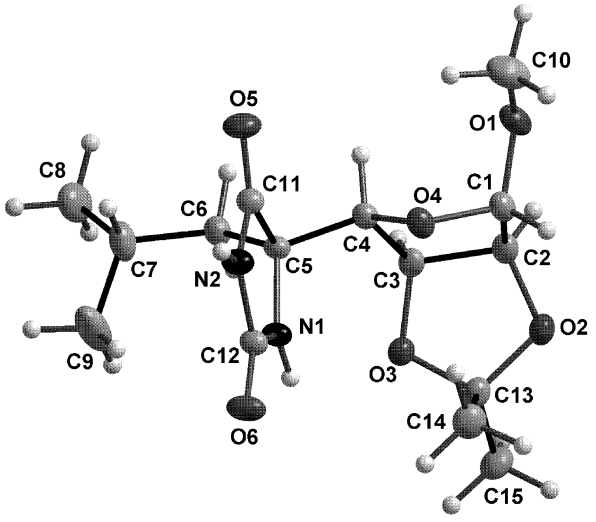


Fig. 1. Numbering scheme and atomic displacement ellipsoids at 50% probability level of compound **4**.

deformed to the $^{O\text{-}4}T_{C\text{-}4}$ direction with O-4 atom oriented *endo* and C-4 *exo* to the reference plane defined by the atoms C-1, C-2, and C-3. Analogously, the puckering parameters $Q = 0.196(1)$ Å, $\varphi = 348.9(4)^\circ$ and the relevant dihedral angles O-2–C-2–C-3–O-3 = 8.76(14)°, C-2–C-3–O-3–C-13 = 4.79(14)°, C-3–O-3–C-13–O-2 = −16.31(15)°, O-3–C-13–O-2–C-2 = 22.27(15)°, C-13–O-2–C-2–C-3 = −19.29(15)° are indicative of $^{O\text{-}2}E$ conformation significantly distorted to the $^{O\text{-}2}T_{C\text{-}13}$ direction for 5-membered 1,3-dioxolane ring (O-2–C-2–C-3–O-3–C-13) with O-2 atom lying in the *endo* and C-13 *exo* direction with respect to the plane defined by the atoms C-2, C-3, and O-3. The 5-membered N-1–C-5–C-11–N-2–C-12 hydantoin ring is almost planar as all relevant torsion angles are close to zero.

Analysis of the molecular packing in the unit cell of the compound **4** (Fig. 2) revealed seven hydrogen mediated interactions (Table 5). First three of them are classical hydrogen bonds, while rest of them are week C···N and C···O interactions. Two of hydrogen bonds, notated as [a] and [d] are intramolecular interactions. Assignment of the H-bond descriptors was based on the graph-set theory.[43] Full set of the first- and second-level descriptors has been obtained using the program PLUTO.[44] For convenience, the notation Xa,d(n) has also been adopted in this paper, in which (X) is the pattern descriptor, (a) is number of acceptors, (d) is number of donors and (n) is the number of atoms comprising the pattern. The first-level descriptors based on the graph-set theory[43] include just two C1,1(4) chains, formed by hydrogen bonds [b] and [c], respectively, while the second-level comprises a chain C1,2(6) and a R2,2(8) ring defined by the hydrogen bonds [b] and [c]. The above mentioned chains and rings are visualised in Fig. 3, where just 5-membered rings of the symmetry related molecules are shown. The other weak C···N and C···O interactions further stabilise the structure.

Table 1
Crystallographic and experimental data for compound **4** [a]

	4
Empirical formula	$C_{15}H_{24}N_2O_6$
Formula weight	328.36
Temperature, T (K)	183(2)
Wavelength, λ (Å)	0.71073
Crystal system	orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	
a (Å)	6.9749(1)
b (Å)	11.1165(1)
c (Å)	21.1876(3)
Unit-cell volume V (Å^3)	1642.81(4)
Formula per unit cell, Z	4
D_{calcd} (g/cm^3)	1.328
Radiation	Mo K_α
Absorption coefficient, μ (mm^{-1})	0.103
$F(000)$	704
Crystal size (mm)	1.00 (max)
	0.10 (min)
Diffractometer	Siemens SMART CCD
θ Range (°)	2.66–33.00
Range of h	−10 → 10
Range of k	−16 → 16
Range of l	−31 → 32
Reflections	29019
Independent reflections	5966 ($R_{int} = 0.0487$)
Refinement method	full-matrix least-squares on F^2
Data/restraints/parameters	5966/0/235
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0452$, $wR_2 = 0.1293$
R indices (all data)	$R_1 = 0.0594$, $wR_2 = 0.1416$
Goodness-of-fit on F^2	1.014
Absolute structure parameter	−0.3 (7)
Largest difference peak and hole (e/Å^3)	0.515 and −0.417

[a] Standard deviations in parentheses.

3. Experimental

3.1. General methods

^{1}H and ^{13}C NMR spectra (in $CDCl_3$ unless specified other, internal standard Me_4Si) were recorded on a Bruker Avance DPX 300 instrument operating at 300.13 and 75.46 MHz working frequencies, respectively. For the assignments of signals, 1D NOESY and C–H heterocorrelated experiments were used. The quaternary carbon atoms were identified on the basis of a semi-selective INEPT experiment and a 1D INADEQUATE pulse sequence technique. The EI and CI (using Py as a

Table 2
Bond lengths (Å) and bond angles (°) for compound **4** [a]

	4
Bond lengths (Å)	
O1–C1	1.4060(17)
O1–C10	1.426(2)
O2–C2	1.4144(18)
O2–C13	1.4393(17)
O3–C3	1.4246(16)
O3–C13	1.4393(16)
O4–C1	1.4223(16)
O4–C4	1.4416(16)
O5–C11	1.2104(17)
O6–C12	1.2363(15)
N1–C12	1.3314(17)
N1–C5	1.4603(16)
N1–H1	0.8800
N2–C11	1.3765(17)
N2–C12	1.3982(17)
N2–H2	0.8800
C1–C2	1.536(2)
C2–C3	1.5471(19)
C3–C4	1.5312(19)
C4–C5	1.5379(18)
C5–C11	1.548(2)
C5–C6	1.5380(18)
C6–C7	1.532(2)
C7–C9	1.481(3)
C7–C8	1.519(2)
C13–C15	1.504(2)
C13–C14	1.520(2)
Bond angles (°)	
C1–O1–C10	112.51(13)
C2–O2–C13	109.66(10)
C3–O3–C13	110.92(10)
C1–O4–C4	105.30(10)
C12–N1–C5	113.29(11)
C12–N1–H1	123.4
C5–N1–H1	123.4
C11–N2–C12	111.49(11)
C11–N2–H2	124.3
C12–N2–H2	124.3
O1–C1–O4	111.46(12)
O1–C1–C2	106.47(11)
O4–C1–C2	105.71(11)
O2–C2–C1	114.02(12)
O2–C2–C3	105.28(11)
C1–C2–C3	104.15(11)
O3–C3–C4	114.01(10)
O3–C3–C2	104.46(10)
C4–C3–C2	103.01(11)
O4–C4–C5	109.43(10)
O4–C4–C3	104.06(10)
C5–C4–C3	117.88(11)
N1–C5–C4	113.13(10)
N1–C5–C11	100.69(10)
C4–C5–C11	107.76(11)
N1–C5–C6	114.04(11)
C4–C5–C6	108.02(10)
C11–C5–C6	113.00(11)
C7–C6–C5	118.28(12)
C9–C7–C8	110.19(17)
C9–C7–C6	115.62(16)
C8–C7–C6	109.53(13)
O5–C11–N2	127.09(13)
O5–C11–C5	126.52(12)
N2–C11–C5	106.39(11)
O6–C12–N1	127.24(13)
O6–C12–N2	124.62(13)
N1–C12–N2	108.13(11)
O3–C13–O2	105.09(11)
O3–C13–C15	108.37(12)
O2–C13–C15	108.52(12)
O3–C13–C14	111.49(12)
O2–C13–C14	110.57(12)
C15–C13–C14	112.48(13)

[a] Standard deviations in parentheses.

Table 3
Selected torsion angles (°) for compound **4** [a]

	4
C1–C2–C3–C4	7.88(13)
O4–C1–C2–C3	17.57(13)
C2–C3–C4–O4	−30.45(12)
C1–O4–C4–C3	43.33(12)
C4–O4–C1–C2	−38.09(13)
O2–C2–C3–O3	8.76(14)
C13–O3–C3–C2	4.79(14)
C3–O3–C13–O2	−16.31(15)
C2–O2–C13–O3	22.27(15)
C13–O2–C2–C3	−19.29(15)
C11–N2–C12–N1	0.16(16)
C5–N1–C12–N2	−0.85(15)
N1–C5–C11–N2	−0.93(13)
C12–N2–C11–C5	0.53(15)
C12–N1–C5–C11	1.10(14)
N1–C5–C11–O5	179.45(14)
C5–N1–C12–O6	178.25(14)
C3–C4–C5–C6	−67.16(14)
C4–O4–C1–O1	77.19(14)
C10–O1–C1–O4	60.90(17)
C2–O2–C13–C15	138.03(13)
C3–O3–C13–C14	103.51(13)

[a] Standard deviations in parentheses.

reactive agent) mass spectra (70 eV) were obtained on a Finnigan MAT SSQ 710 instrument. Specific rotations were determined on a Perkin–Elmer 241 polarimeter (10 cm cell). Microanalyses were performed on a Fisons EA 1108 analyser. Melting points were determined with a Boetius PHMK 05 microscope. All reactions were monitored by thin-layer chromatography (TLC) on

Table 4
Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for compound **4** [a]

Atom	*x*	*y*	*z*	U_{eq}
O-1	8194(2)	8101(1)	6913(1)	29(1)
O-2	4318(2)	6542(1)	7633(1)	29(1)
O-3	4104(2)	7837(1)	8467(1)	22(1)
O-4	8224(2)	7854(1)	8009(1)	23(1)
O-5	10702(2)	10120(1)	8598(1)	30(1)
O-6	8710(2)	7304(1)	10043(1)	28(1)
N-1	7073(2)	8401(1)	9296(1)	20(1)
N-2	10203(2)	8680(1)	9372(1)	22(1)
C-1	7526(2)	7409(1)	7423(1)	24(1)
C-2	5342(2)	7581(1)	7445(1)	24(1)
C-3	5028(2)	8504(1)	7981(1)	21(1)
C-4	7072(2)	8899(1)	8145(1)	20(1)
C-5	7470(2)	9323(1)	8823(1)	19(1)
C-6	6380(2)	10508(1)	8929(1)	22(1)
C-7	6835(3)	11243(2)	9522(1)	32(1)
C-8	5980(3)	12494(2)	9459(1)	43(1)
C-9	6239(6)	10691(2)	10128(1)	78(1)
C-10	10234(3)	8094(2)	6866(1)	40(1)
C-11	9668(2)	9459(1)	8898(1)	21(1)
C-12	8628(2)	8048(1)	9610(1)	20(1)
C-13	3970(2)	6584(1)	8302(1)	24(1)
C-14	5446(2)	5834(1)	8654(1)	30(1)
C-15	1950(2)	6170(2)	8424(1)	32(1)

[a] Standard deviations in parentheses.

Silica Gel 60 plates (E. Merck) using the following solvents: 1:2 EtOAc–hexane (eluent A), 3:2 EtOAc–hexane (eluent B), 10:1 $CHCl_3$–MeOH (eluent C), 1:2 $CHCl_3$–MeOH (eluent D). Visualisation was affected with iodine vapour or H_2SO_4. Column chromatography was performed as flash chromatography on Silica Gel 60 (E. Merck, 0.063–0.200 mm).

3.2. X-ray techniques

Crystal and experimental data for **4** are summarised in Table 1. Preliminary orientation matrix was obtained from the first frames using Siemens SMART software.[45] Final cell parameters were obtained by refinement of 7690 reflections using Siemens SAINT software.[45] The data were empirically corrected for absorption and other effects using SADABS program[46] based on the method of Blessing.[47] The structures were solved by direct methods and refined by full-matrix least-squares on all F^2 data using Bruker SHELXTL.[48] The non-H atoms were refined anisotropically. Hydrogen atoms were constrained to the ideal geometry using an appropriate riding model. Molecular graphics were obtained using the program DIAMOND.[49]

3.3. Methyl 6-deoxy-6-isopropyl-2,3-*O*-isopropylidene-α-D-*lyxo*-hexofuranosid-5-ulose (3)

Aldehyde **1** (10.11 g, 50 mmol) in dry ether (90 mL) was added dropwise to the Grignard reagent prepared from magnesium turnings (3.65 g, 150 mmol) and isobutyl bromide (20.55 g, 150 mmol) in dry ether (90 mL) and the reaction mixture was heated under reflux for 1 h. After cooling to rt, it was poured into cold saturated aqueous solution of NH_4Cl (250 mL) and the product

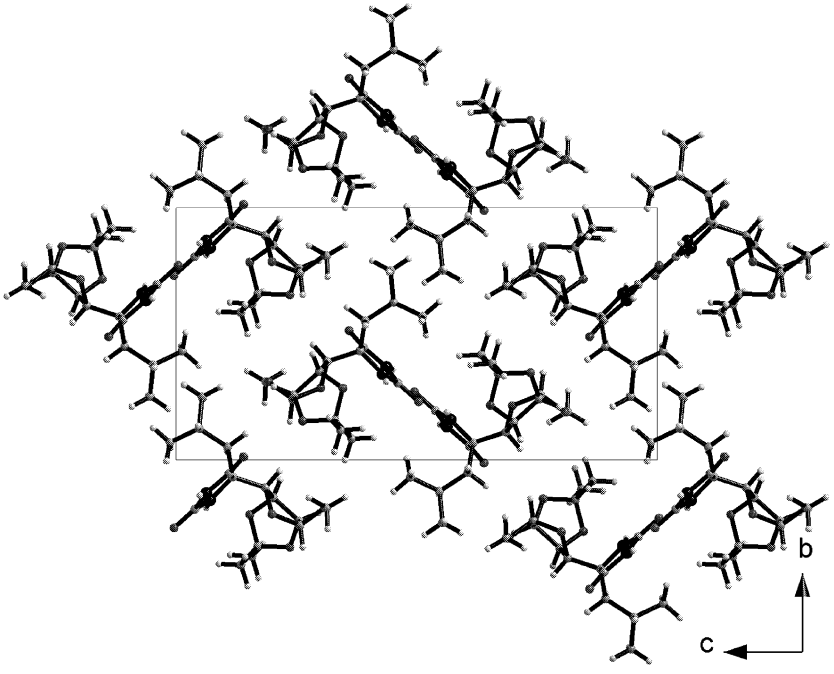


Fig. 2. Molecular packing in the unit cell of compound **4**.

Table 5
Hydrogen bond geometry in compound **4** [a]

Notation	X–H···Y	Symmetry code	X–H (Å)	H···Y (Å)	X···Y (Å)	X–H···Y (°)
a	N1–H1···O3		0.88	2.31	2.7869(15)	114.1
b	N1–H1···O6	$x-1/2,\ -y+3/2,\ -z+2$	0.88	2.04	2.8421(15)	151.6
c	N2–H2···O6	$x+1/2,\ -y+3/2,\ -z+2$	0.88	2.13	2.9525(16)	156.0
d	C9–H9B···N1		0.98	2.58	3.150(3)	116.9
e	C14–H14A···O4		0.98	2.47	3.266(2)	138.6
f	C15–H15B···O1	$-x+1,\ y-1/2,\ -z+3/2$	0.98	2.52	3.487(2)	171.2
g	C15–H15C···O4	$x-1,\ y,\ z$	0.98	2.40	3.322(2)	156.5

[a] Standard deviations in parentheses.

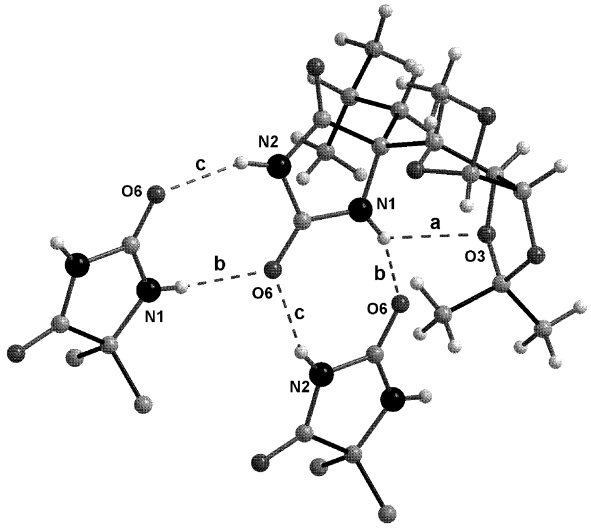


Fig. 3. The most significant hydrogen bonds in compound **4** with codes referring to those in Table 5. Parts of the symmetry related molecules are omitted for clarity.

was extracted with ether (3×100 mL). The combined ethereal extracts were dried (Na_2SO_4), filtered and the solvent was evaporated under reduced pressure to afford the crude product. This was chromatographed on a column of silica gel using solvent A as an eluent. The fractions having R_f 0.72 were collected and evaporated to give a mixture of methyl 6-deoxy-6-isopropyl-2,3-*O*-isopropylidene-α-D-mannofuranoside and methyl 6-deoxy-6-isopropyl-2,3-*O*-isopropylidene-β-L-gulofuranoside (**2**, 8.84 g, 68%). The fractions with R_f 0.17 afforded methyl 2,3-*O*-isopropylidene-α-D-lyxofuranoside (1.23 g); EIMS (70 eV): *m/z* 189 $[M-Me]^+$, 173, 129, 113, 85, 68, 59, 43 (100%). The above mixture of alcohols **2** (8.84 g, 34 mmol) in CH_2Cl_2 (120 mL) was added dropwise to a stirred mixture of pyridinium dichromate (9.03 g, 24 mmol), CH_2Cl_2 (120 mL) and Ac_2O (9.5 mL) and the mixture was heated under reflux for 2.5 h. After cooling and addition of EtOAc (170 mL), the precipitated chromium salts were removed by filtration and CH_2Cl_2 was distilled off under reduced pressure. The separated chromium salts were again filtered off and the solvents were evaporated under diminished pressure to give the crude product. This was purified on a column of silica gel using EtOAc as an eluent. Evaporation of the solvent and recrystallisation of the product (R_f 0.84, solvent A) from ether–hexane afforded ketone **3** (8.07 g, 92%) as colourless crystals with melting point (mp) 34–35 °C; $[\alpha]_D$ −3° (*c* 1, $CHCl_3$), +21° (*c* 1, MeOH); NMR: ^1H (300 MHz, $CDCl_3$): δ 5.03 (s, 1 H, H-1), 5.00 (dd, 1 H, $J_{2,3}$ 5.8, $J_{3,4}$ 4.1 Hz, H-3), 4.56 (d, 1 H, H-2), 4.39 (d, 1 H, H-4), 3.34 (s, 3 H, OCH_3), 2.48 (m, 2 H, CH_2), 2.23 (m, 1 H, CH of isopropyl), 1.41 and 1.27 (2 s, each 3 H, Me_2C), 0.95 and 0.94 (2 d, each 3 H, $J_{CH,Me}$ 6.7 Hz, Me_2C of isopropyl); ^{13}C (75.5 MHz, $CDCl_3$): δ 203.1 (C-5), 112.6 (CMe_2), 107.2 (C-1), 84.6 (C-4), 83.9 (C-2), 80.7 (C-3), 54.5 (OCH_3), 48.7 (CH_2), 25.5 and 24.3 [$(CH_3)_2C$], 23.1 [$CH(CH_3)_2$], 22.4 [$(CH_3)_2CH$]; EIMS (70 eV): *m/z* 259 $[M+1]^+$, 243 $[M-Me]^+$, 227, 173, 169, 158, 127, 115, 113, 99, 87, 85 (100%), 59, 57, 43. Anal. Calcd for $C_{13}H_{22}O_5$: C, 60.40; H, 8.58. Found: C, 60.68; H, 8.62.

3.4. (5′*R*)-5′-Isobutyl-5′-[methyl (4*R*)-2,3-*O*-isopropylidene-β-L-erythrofuranosid-4-*C*-yl]-imidazolidin-2′,4′-dione (4)

To a solution of 5-ulose **3** (7.75 g, 30 mmol) in 50% aq EtOH (50 mL) was added NaCN (2.94 g, 60 mmol) and $(NH_4)_2CO_3$ (13.45 g, 140 mmol) and the mixture was stirred at 60 °C for 6 h. Ethanol was then evaporated and after cooling to room temperature (rt), the first portion (2.64 g) of **4** crystallised from the aqueous solution. This was filtered off, the aqueous solution concentrated under diminished pressure and the residue chromatographed on a column of silica gel with eluent B. The fractions having R_f 0.69 were collected and evaporated to give further portion (1.69 g) of **4**. The combined portions of **4** were recrystallised from EtOAc–hexane affording white needles (4.13 g, 42%) with mp 268–269 °C; $[\alpha]_D$ +140° (*c* 1, MeOH). Recrystallisation from water afforded **4** as a hydrate having mp 130–131 °C; NMR: ^1H (300 MHz, $CDCl_3$): δ 7.81 (bs, 1 H, NH), 5.83 (bs, 1 H, NH), 4.90 (s, 1 H,

H-1), 4.82 (dd, 1 H, $J_{2,3}$ 5.9, $J_{3,4}$ 3.4 Hz, H-3), 4.55 (d, 1 H, H-2), 4.04 (d, 1 H, H-4), 3.24 (s, 3 H, OCH_3), 1.82 (m, 1 H, CH of isobutyl), 1.75 (d, 2 H, CH_2), 1.54 and 1.32 (2 s, each 3 H, Me_2C), 1.00 and 0.92 (2 d, each 3 H, $J_{CH,Me}$ 6.1 Hz, Me_2C of isobutyl); ^{13}C (75.5 MHz, $CDCl_3$): δ 175.2 (CO at C-4 of hydantoin), 156.4 (CO at C-2 of hydantoin), 113.1 (CMe_2), 106.3 (C-1), 84.6 (C-2), 79.6 (C-3 and C-4), 67.4 (C-5), 54.6 (OCH_3), 40.6 (CH_2), 25.8 and 24.1 [$(CH_3)_2C$], 24.2 [CH and one of $(CH_3)_2CH$], 23.6 [one of $(CH_3)_2CH$]; EIMS (70 eV): *m/z* 328 $[M]^+$, 313 $[M-Me]^+$, 297, 210, 173 (100%), 115, 113, 87, 85, 59, 43. CIMS: *m/z* 408 $(M+C_5H_5NH)^+$. Anal. Calcd for $C_{15}H_{24}N_2O_6$: C, 54.90; H, 7.37; N, 8.53. Found: C, 54.79; H, 7.43, N, 8.59.

3.5. (5′*S*)-5′-Isobutyl-5′-[methyl (4*R*)-2,3-*O*-isopropylidene-β-L-erythrofuranosid-4-*C*-yl]-imidazolidin-2′,4′-dione (5)

The fractions having R_f 0.59 (eluent B) from the above column chromatography were collected and evaporated. Recrystallisation of the product from EtOAc–hexane gave pure **5** as white needles (590 mg, 6% yield); mp 197–198 °C; $[\alpha]_D$ +7° (*c* 1, MeOH); NMR: ^1H (300 MHz, $CDCl_3$): δ 8.58 (bs, 1 H, NH), 5.80 (bs, 1 H, NH), 4.95 (s, 1 H, H-1), 4.73 (dd, 1 H, $J_{2,3}$ 5.9, $J_{3,4}$ 3.5 Hz, H-3), 4.54 (d, 1 H, H-2), 3.94 (d, 1 H, H-4), 3.34 (s, 3 H, OCH_3), 1.99 (m, 1 H, H_a of CH_2), 1.80 (m, 2 H, CH and H_b of CH_2 in isobutyl), 1.42 and 1.22 (2 s, each 3 H, Me_2C), 0.97 and 0.93 (2 d, each 3 H, $J_{CH,Me}$ 6.1 Hz, Me_2C of isobutyl); ^{13}C (75.5 MHz, $CDCl_3$): δ 175.5 (CO at C-4 of hydantoin), 157.2 (CO at C-2 of hydantoin), 113.1 (CMe_2), 106.6 (C-1), 84.8 (C-2), 80.2 (C-4), 79.4 (C-3), 65.8 (C-5), 54.9 (OCH_3), 45.6 (CH_2), 25.4 and 23.4 [$(CH_3)_2C$], 24.6 (CH of isobutyl), 24.1 and 23.9 [$(CH_3)_2CH$]; EIMS (70 eV): *m/z* 328 $[M]^+$, 313 $[M-Me]^+$, 297, 210, 173 (100%), 157, 115, 113, 87, 85, 59, 43, CIMS: *m/z* 408 $(M+C_5H_5NH)^+$. Anal. Calcd for $C_{15}H_{24}N_2O_6$: C, 54.90; H, 7.37; N, 8.53. Found: 54.81; H, 7.41; N, 8.49.

3.6. (5′*R*)-5′-Isobutyl-5′-[methyl (4*R*)-β-L-erythrofuranosid-4-*C*-yl]-imidazolidin-2′,4′-dione (6)

A suspension of hydantoin **4** (3.28 g, 10 mmol) in diluted AcOH (70%, 50 mL) was heated at 80 °C for 75 min. The reaction mixture became clear during the first 15 min. The solvent was evaporated to dryness under diminished pressure and co-evaporated twice with toluene. The residual white solid was dissolved in EtOAc (30 mL), treated with charcoal, filtered and solvent evaporated. Recrystallisation of the product from EtOAc–hexane afforded pure **6** (R_f 0.37, solvent C) as white needles (1.93 g, 67%); mp 186–188 °C; $[\alpha]_D$ +148° (*c* 1, MeOH); NMR: ^1H (300 MHz, D_2O): δ 4.97 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 4.32 (dd, 1 H, $J_{2,3}$ 4.9, $J_{3,4}$ 4.5 Hz, H-3), 4.20 (d, 1 H, H-4), 4.03 (dd, 1 H, H-2), 3.43 (s, 3 H, OCH_3), 2.02 (dd, 1 H, J_{CH,H_a} 5.2, J_{H_a,H_b} 14.3 Hz, H_a of CH_2), 1.76 (dd, 1 H, J_{CH,H_b} 6.8 Hz, H_b of CH_2), 1.65 (m, 1H, CH of isobutyl), 0.92 and 0.86 (2 d, each 3 H, $J_{CH,Me}$ 6.5 Hz, Me_2C); ^{13}C (75.5 MHz, D_2O): δ 180.2 (CO at C-4 of hydantoin), 160.0 (CO at C-2 of hydantoin), 108.7 (C-1), 82.0 (C-4), 76.1 (C-2), 72.0 (C-3), 69.2 (C-5), 56.8 (OCH_3), 44.4 (CH_2), 24.4 and 23.7 [$(CH_3)_2CH$], 24.2 ($CHMe_2$); EIMS (70 eV): *m/z* 289 $[M+1]^+$, 257, 156, 133, 113, 87, 73, 45 (100%), 43. Anal. Calcd for $C_{12}H_{20}N_2O_6$: C, 50.00; H, 6.99; N, 9.72. Found: C, 50.11; H, 7.05; N, 9.69.

3.7. Methyl (5*R*)-5-amino-5-*C*-carboxy-5,6-dideoxy-6-isopropyl-α-D-*lyxo*-hexofuranoside (7)

A mixture of hydantoin **6** (1.44 g, 5 mmol), barium hydroxide octahydrate (4.73 g, 15 mmol) and water (50 mL) was heated under reflux for 6 h. Carbon dioxide gas was then passed to the hot reaction mixture. The separated barium carbonate was removed by filtration and washed with hot water. Carbon dioxide gas was again passed to the hot solution and after cooling to rt, another portion of barium carbonate separated. Filtration and decolourising with charcoal gave clear solution. Water was evaporated under diminished pressure and the residual solid was purified on a short column of silica gel (eluent D). Fractions with R_f 0.50 (eluent D) were collected and evaporated to afford **7** (474 mg, 36%). Analytical sample (white solid) was obtained by recrystallisation from water–methanol; mp 195 °C (dec); $[\alpha]_D$ +20° (*c* 0.5, H_2O); NMR: ^1H (300 MHz, D_2O): δ 5.01 (d, 1 H, $J_{1,2}$ 4.5 Hz, H-1), 4.53 (d, 1 H, $J_{3,4}$ 2.9 Hz, H-4), 4.45 (dd, 1 H, $J_{2,3}$ 4.5 Hz, H-3), 4.15 (t, 1 H, H-2), 3.43 (s, 3 H, OCH_3), 1.85–1.70 (m, 3 H, CH and CH_2 of isobutyl), 0.98 and 0.92 (2 d, each 3 H, $J_{CH,Me}$ 6.3 Hz, Me_2C); ^{13}C (75.5 MHz, D_2O): δ 174.7 (CO), 108.7 (C-1), 81.5 (C-4), 77.2 (C-2), 71.9 (C-3), 63.5 (C-5), 56.9 (OCH_3), 40.4 (CH_2), 24.5 and 23.0 [$(CH_3)_2CH$], 24.4 ($CHMe_2$); EIMS (70 eV): *m/z* 218 $[M-COOH]^+$, 144, 116, 102, 87, 86 (100%), 74, 73, 57, 44, 43, 42. Anal. Calcd for $C_{11}H_{21}NO_6$: C, 50.20; H, 8.04; N, 5.32. Found: C, 50.32; H, 8.13; N, 5.28.

3.8. (5′*S*)-5′-Isobutyl-5′-[methyl (4*R*)-β-L-erythrofuranosid-4-*C*-yl]-imidazolidin-2′,4′-dione (8)

Starting from **5** (657 mg, 2 mmol) and application of the same reaction procedure as described for the preparation of **6** afforded **8** (R_f 0.22, solvent C) as white crystals (1.93 g, 67%); mp 260–262 °C; $[\alpha]_D$ +9° (*c* 1, H_2O), +18° (*c* 1, MeOH); NMR: ^1H (300 MHz, D_2O): δ 4.81 (s, 1 H, H-1), 4.29 (dd, 1 H, $J_{2,3}$ 4.6, $J_{3,4}$ 7.6 Hz, H-3), 4.11 (d, 1 H, H-4), 3.99 (d, 1 H, H-2), 3.29 (s, 3 H, OCH_3), 1.83–1.60 (m, 3H, CH and CH_2 of isobutyl), 0.94 and 0.87 (2 d, each 3 H, $J_{CH,Me}$ 6.3 Hz, Me_2C); ^{13}C (75.5

MHz, D_2O): δ 180.4 (CO at C-4 of hydantoin), 160.1 (CO at C-2 of hydantoin), 108.4 (C-1), 84.7 (C-4), 75.3 (C-2), 71.8 (C-3), 70.1 (C-5), 56.0 (OCH_3), 39.5 (CH_2), 24.9 ($CHMe_2$), 24.1 and 23.6 [$(CH_3)_2CH$]; EIMS (70 eV): m/z 289 $[M+1]^+$, 257, 156, 133, 113, 87, 73, 45 (100%), 43. Anal. Calcd for $C_{12}H_{20}N_2O_6$: C, 50.00; H, 6.99; N, 9.72. Found: C, 50.11; H, 7.05; N, 9.69.

3.9. Methyl (5*S*)-5-amino-5-*C*-carboxy-5,6-dideoxy-6-isopropyl-α-D-lyxo-hexofuranoside (9)

Starting from **8** (288 mg, 1 mmol) and application of the same reaction procedure as described for the preparation of **7** afforded **9** (100 mg, 38%); mp 196 °C (dec); $[\alpha]_D$ −57° (c 0.5, H_2O); NMR: ^1H (300 MHz, D_2O): δ 4.90 (s, 1 H, H-1), 4.27 (dd, 1 H, $J_{2,3}$ 4.6, $J_{3,4}$ 7.4 Hz, H-3), 4.14 (d, 1 H, H-4), 4.00 (t, 1 H, H-2), 3.29 (s, 3 H, OCH_3), 1.82–1.63 (m, 3 H, CH and CH_2 of isobutyl), 0.96 and 0.91 (2 d, each 3 H, $J_{CH,Me}$ 6.3 Hz, Me_2C); ^{13}C (75.5 MHz, D_2O): δ 175.2 (CO), 108.0 (C-1), 83.5 (C-4), 77.4 (C-2), 70.6 (C-3), 66.2 (C-5), 56.6 (OCH_3), 40.6 (CH_2), 24.7 and 23.1 [$(CH_3)_2CH$], 24.6 ($CHMe_2$); EIMS (70 eV): m/z 218 $[M-COOH]^+$, 144, 116, 102, 87, 86 (100%), 74, 73, 57, 44, 43, 42. Anal. Calcd for $C_{11}H_{21}NO_6$: C, 50.20; H, 8.04; N, 5.32. Found: C, 50.30; H, 8.10; N, 5.30.

4. Supplementary material

Crystallographic data for the structural analysis has been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 195472 for compound **4**. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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