

## Synthesis, Crystal Structure, and Conformation of Methyl 5-*O*-acetyl-5-cyano-6-deoxy-2,3-*O*-isopropylidene- $\beta$ -L-gulofuranoside

Júlia Mičová<sup>1</sup>, Bohumil Steiner<sup>1</sup>, Miroslav Kooš<sup>1\*</sup>, Ján Gajdoš<sup>1</sup>, Vratislav Langer<sup>2</sup>, and Dalma Gyepesová<sup>3</sup>

<sup>1</sup> Institute of Chemistry, Slovak Academy of Sciences, Dúbravská cesta 9, SK-84238 Bratislava, Slovakia. Tel. (421)-2-59410254, Fax (421)-2-59410222

<sup>2</sup> Department of Inorganic Environmental Chemistry, Chalmers University of Technology, SE-41296 Göteborg, Sweden

<sup>3</sup> Institute of Inorganic Chemistry, Slovak Academy of Sciences, Dúbravská cesta 9, SK-84236 Bratislava, Slovakia

\* Author to whom correspondence should be addressed; E-mail: [chemmiro@savba.sk](mailto:chemmiro@savba.sk)

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**Abstract:** Methyl 5-*O*-acetyl-5-cyano-6-deoxy-2,3-*O*-isopropylidene- $\beta$ -L-gulofuranoside was prepared in high yield from methyl 6-deoxy-2,3-*O*-isopropylidene- $\alpha$ -D-*lyxo*-pentodialdo-1,4-furanoside. The configuration at the C5 atom was unambiguously established by single crystal X-ray analysis of the corresponding 5-*O*-acetyl derivative. The conformation of the furanose and 1,3-dioxolane rings is also discussed.

**Keywords:** Saccharide cyanohydrins, methyl 2,3-*O*-isopropylidene- $\beta$ -L-gulofuranoside, X-ray crystallography, conformation.

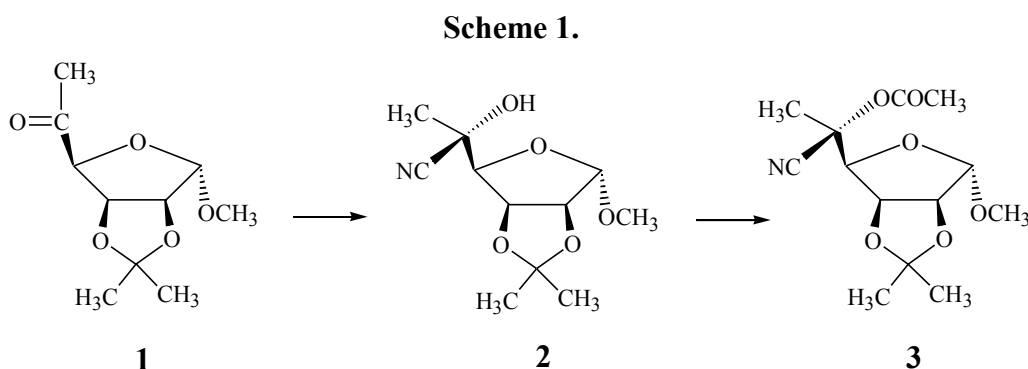
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## Introduction

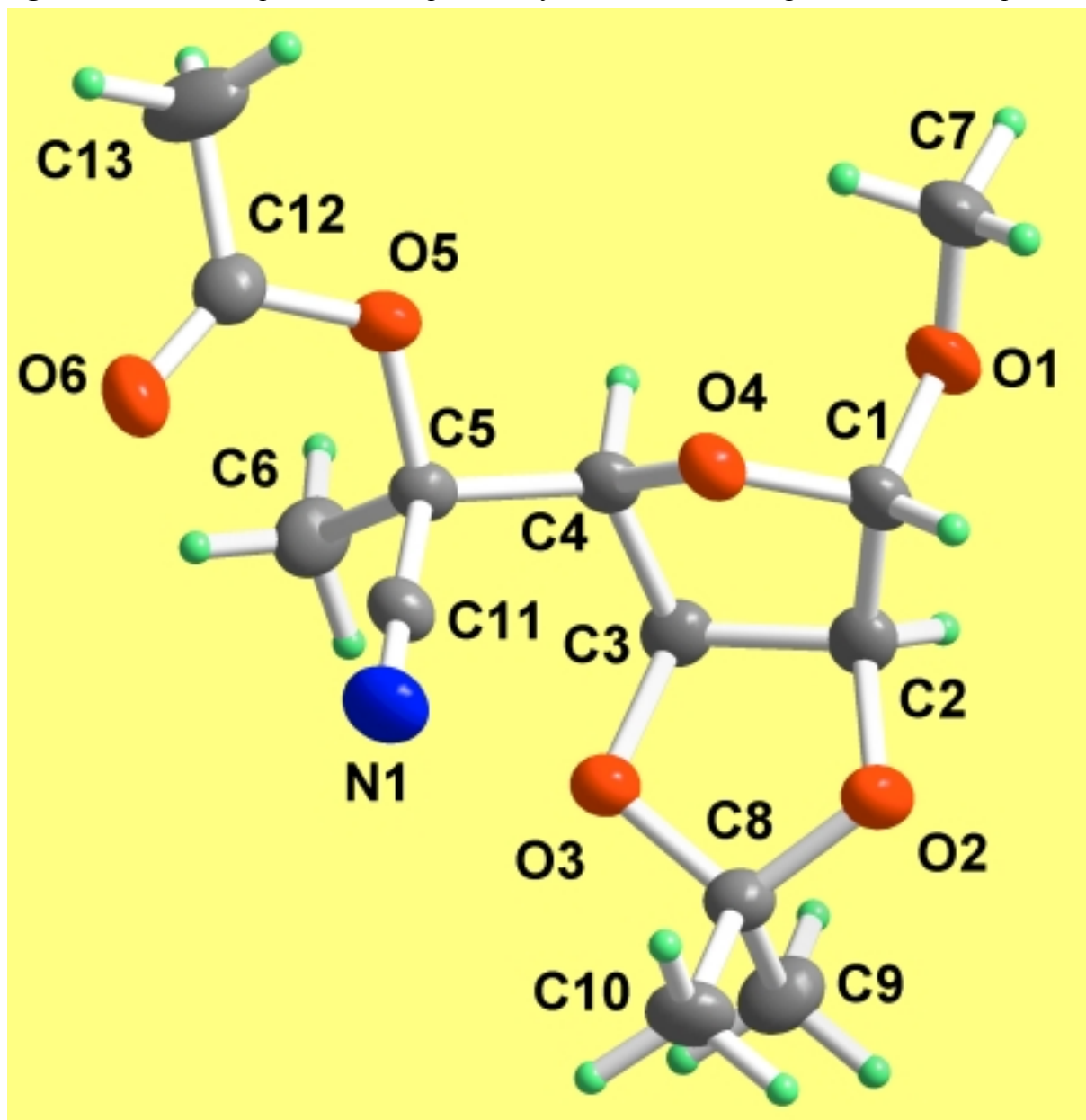
In the framework of our recent research on synthesis and structure determination of some C–C linked sugar  $\alpha$ -amino acids [1–5], we have also prepared several carbohydrate derivatives, including sugar cyanohydrins, amino nitriles, and hydantoin, either as necessary synthetic precursors or suitable models for structural studies. For these model compounds, it is especially important to know their exact structural features with high precision and for this purpose X-ray crystallography was used. This paper reports the preparation of methyl 5-*O*-acetyl-5-cyano-6-deoxy-2,3-*O*-isopropylidene- $\beta$ -L-gulofuranoside and verification of its structure using single crystal X-ray analysis.

## Results and Discussion

Application of the Kiliani cyanohydrin synthesis to methyl 6-deoxy-2,3-*O*-isopropylidene- $\alpha$ -D-lyxohexofuranosid-5-ulose (**1**) [6] (prepared from methyl 2,3-*O*-isopropylidene- $\alpha$ -D-lyxopentodialdo-1,4-furanoside [7,8] by the Grignard reaction with methylmagnesium iodide and subsequent oxidation of the reaction product with pyridinium dichromate) led to the formation of methyl 5-cyano-6-deoxy-2,3-*O*-isopropylidene- $\beta$ -L-gulofuranoside (**2**) (Scheme 1). The almost 92% isolated yield of **2** indicates a high stereoselectivity for the cyanohydrin formation. Acetylation of **2** under usual conditions afforded methyl 5-*O*-acetyl-5-cyano-6-deoxy-2,3-*O*-isopropylidene- $\beta$ -L-gulofuranoside (**3**).



Compounds **2** and **3** were fully characterized by  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR, EIMS, CIMS,  $[\alpha]_D$ , mp, and elemental analysis data. Because of the obvious difficulties in unambiguously establishing the configuration at C5 (*D-manno* versus *L-gulo* in this case) by NMR methods, suitable crystals of compound **3** were subjected to X-ray analysis. This revealed 5-*R* configuration and because the configuration on positions C1, C2, C3 and C4 did not change, it confirms a *L-gulo* arrangement. Perspective view and the numbering of atoms for compound **3** is depicted in Figure 1. The relevant crystallographic and structure refinement data for **3** 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 are summarized in Table 4. The hydrogen bond geometry for compound **3** is shown in Table 5.

**Figure 1.** Thermal ellipsoids at 50% probability level and numbering of atoms for compound **3**.**Table 1.** Crystal and experimental data for compound **3**<sup>a</sup>

Empirical formula	C <sub>13</sub> H <sub>19</sub> NO <sub>6</sub>
Formula weight	285.29
Temperature, <i>T</i> (K)	193(2)
Wavelength, $\lambda$ (Å)	0.71073
Crystal system	orthorhombic
Space group	<i>P</i> 2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>
Unit cell dimensions (Å)	<i>a</i> = 6.0926(2) <i>b</i> = 9.6035(3) <i>c</i> = 25.5321(7)

Unit cell volume, $V$ ( $\text{\AA}^3$ )	1493.89(8)
Formula units per unit cell, $Z$	4
$D_{\text{calcd}}$ ( $\text{g/cm}^3$ )	1.268
Absorption coefficient, $\mu$ ( $\text{mm}^{-1}$ )	0.101
F(000)	608
Crystal size (mm)	0.80 (max) 0.35 (min)
Diffractometer	Siemens SMART CCD
$\theta$ Range ( $^\circ$ )	2.27–32.79
Range of $h$	–9→9
Range of $k$	–14→14
Range of $l$	–38→38
Reflections	23913
Independent reflections	5203 ( $R_{\text{int}} = 0.0365$ )
Completeness to $\theta = 32.79$ (%)	96.1
Max. and min. transmission	0.9656 and 0.9238
Refinement method	Full-matrix least-squares on $F^2$
Data / restraints / parameters	5203 / 0 / 205
Goodness-of-fit (all)	1.063
Final $R$ indices [ $I > 2\sigma(I)$ ]	$R_1 = 0.0454$ , $wR_2 = 0.1126$
$R$ indices (all data)	$R_1 = 0.0581$ , $wR_2 = 0.1212$
Largest difference peak and hole ( $\text{e/\AA}^3$ )	0.277 and –0.193

<sup>a</sup> Standard deviations in parentheses.

**Table 2.** Selected bond lengths [ $\text{\AA}$ ] and bond angles [ $^\circ$ ] for compound **3**<sup>a</sup>

O1-C1	1.4160(16)	O1-C1-C2	106.88(13)
O1-C7	1.440(3)	O4-C1-C2	105.44(11)
O2-C2	1.4336(17)	O2-C2-C1	109.70(12)
O2-C8	1.4438(17)	O2-C2-C3	104.54(11)
O3-C3	1.4330(16)	C1-C2-C3	104.34(11)
O3-C8	1.4367(16)	O3-C3-C4	110.70(10)
O4-C1	1.4295(18)	O3-C3-C2	104.40(10)
O4-C4	1.4468(17)	C4-C3-C2	103.10(11)
O5-C12	1.3721(18)	O4-C4-C5	109.71(10)
O5-C5	1.4659(16)	O4-C4-C3	104.95(10)
O6-C12	1.209(2)	C5-C4-C3	116.78(11)
N1-C11	1.1476(19)	O5-C5-C11	110.31(11)
C1-C2	1.532(2)	O5-C5-C4	103.84(10)

C2-C3	1.560(2)	C11-C5-C4	110.95(10)
C3-C4	1.5411(19)	O5-C5-C6	109.02(11)
C4-C5	1.5349(18)	C11-C5-C6	111.87(11)
C5-C11	1.4961(18)	C4-C5-C6	110.54(12)
C5-C6	1.5375(19)	O3-C8-O2	104.43(10)
C8-C10	1.521(2)	O3-C8-C10	108.19(12)
C8-C9	1.526(2)	O2-C8-C10	108.76(12)
C12-C13	1.501(2)	O3-C8-C9	110.44(11)
C1-O1-C7	112.24(15)	O2-C8-C9	111.40(13)
C2-O2-C8	107.64(10)	C10-C8-C9	113.21(13)
C3-O3-C8	107.66(10)	N1-C11-C5	177.77(15)
C1-O4-C4	105.49(10)	O6-C12-O5	123.20(13)
C1-O5-C5	118.74(11)	O6-C12-C13	125.90(15)
O1-C1-O4	111.53(11)	O5-C12-C13	110.90(14)

<sup>a</sup> Standard deviations in parentheses.

**Table 3.** Selected torsion angles [ $^{\circ}$ ] for compound **3**<sup>a</sup>

C7-O1-C1-C2	177.05(12)	C1-O4-C4-C5	167.05(10)
C4-O4-C1-O1	76.03(14)	C1-O4-C4-C3	40.82(12)
C4-O4-C1-C2	-39.62(12)	O3-C3-C4-O4	86.09(12)
C8-O2-C2-C1	130.48(12)	C2-C3-C4-O4	-25.06(12)
C8-O2-C2-C3	19.09(14)	O3-C3-C4-C5	-35.62(15)
O1-C1-C2-O2	152.07(11)	C2-C3-C4-C5	-146.77(11)
O4-C1-C2-O2	-89.14(13)	O4-C4-C5-O5	72.73(12)
O1-C1-C2-C3	-96.41(12)	C3-C4-C5-O5	-168.08(10)
O4-C1-C2-C3	22.38(13)	O4-C4-C5-C11	-45.77(14)
C8-O3-C3-C4	-131.55(11)	C3-C4-C5-C11	73.42(14)
C8-O3-C3-C2	-21.24(14)	O4-C4-C5-C6	-170.48(11)
O2-C2-C3-O3	1.24(14)	C3-C4-C5-C6	-51.29(15)
C1-C2-C3-O3	-113.97(11)	C3-O3-C8-O2	33.46(14)
O2-C2-C3-C4	116.99(11)	C2-O2-C8-O3	-32.57(14)
C1-C2-C3-C4	1.79(13)	C4-C5-C11-N1	-64(4)

<sup>a</sup> Standard deviations in parentheses.

**Table 4.** Atomic coordinates ( $\times 10^4$ ) and equivalent isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for compound **3**<sup>a</sup>

Atom	<i>x</i>	<i>y</i>	<i>z</i>	U(eq)
O1	4992(2)	9235(1)	9060(1)	46(1)
O2	6664(2)	6043(1)	9659(1)	38(1)
O3	7554(2)	5008(1)	8886(1)	33(1)
O4	3751(2)	7059(1)	8757(1)	33(1)
O5	3436(2)	6486(1)	7648(1)	35(1)
O6	2411(2)	4514(1)	7222(1)	47(1)
N1	3034(2)	3574(1)	8438(1)	44(1)
C1	4630(3)	7820(1)	9191(1)	35(1)
C2	6885(2)	7175(1)	9297(1)	35(1)
C3	7528(2)	6467(1)	8769(1)	32(1)
C4	5584(2)	6829(1)	8408(1)	30(1)
C5	4956(2)	5741(1)	7994(1)	29(1)
C6	6985(2)	5298(2)	7676(1)	40(1)
C7	2989(4)	9944(2)	8924(1)	60(1)
C8	7812(2)	4861(1)	9442(1)	32(1)
C9	10240(3)	4881(2)	9590(1)	44(1)
C10	6643(3)	3536(2)	9612(1)	44(1)
C11	3833(2)	4520(1)	8240(1)	31(1)
C12	2457(2)	5772(2)	7246(1)	36(1)
C13	1479(3)	6757(2)	6853(1)	55(1)

<sup>a</sup> Standard deviations in parentheses.**Table 5.** Hydrogen bond geometry in compound **3**<sup>a</sup>

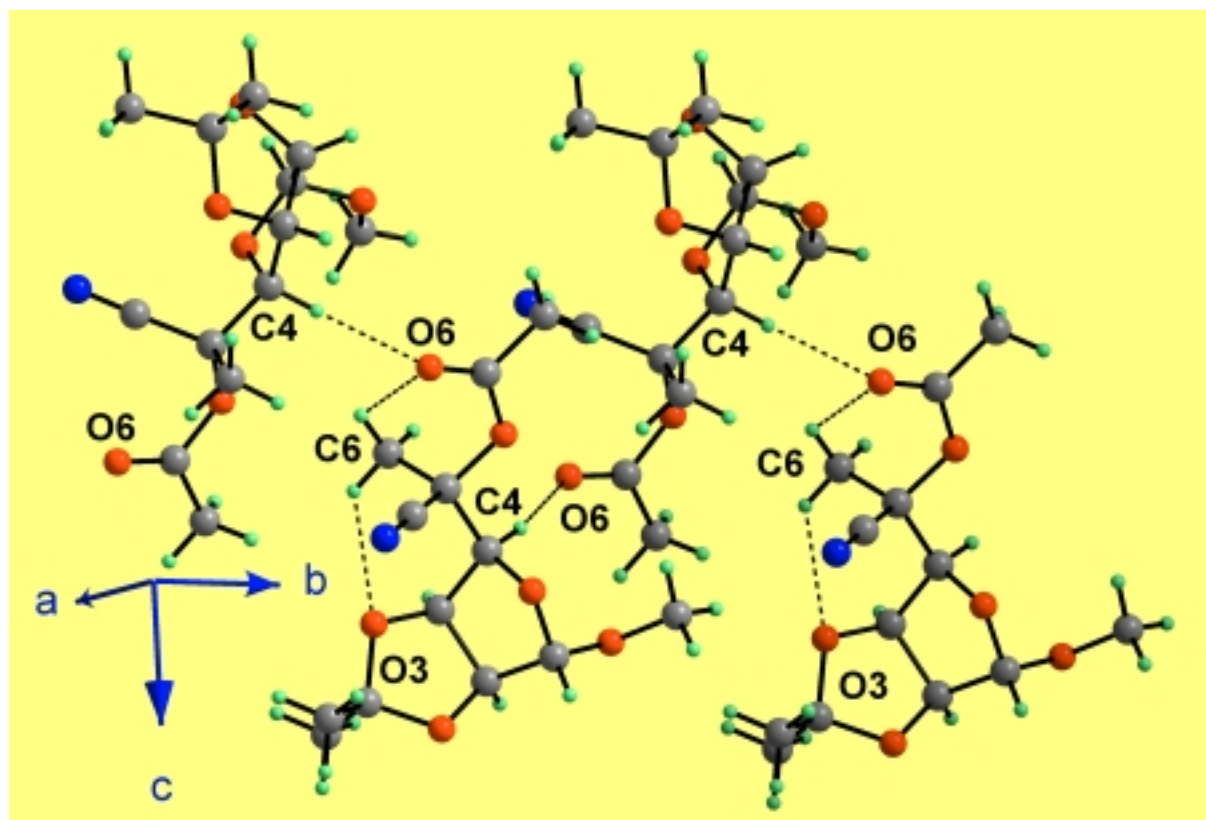
X-H...Y	Symmetry code	X-H (Å)	H...Y (Å)	X...Y (Å)	X-H...Y (°)
C4-H4...O6	$-x+1, y+1/2, -z+3/2$	1.00	2.30	3.2752(17)	164.9
C6-H6A...O6		0.98	2.59	3.111(2)	113.6
C6-H6B...O3		0.98	2.50	3.1202(18)	120.7

<sup>a</sup> Standard deviations in parentheses.

Analysis of the molecular packing in the unit cell revealed two types of hydrogen bonds. In addition to weak intramolecular hydrogen bonds between C6 and O3 and C6 and O6, there are also stronger intermolecular hydrogen bonds involving C4 in one molecule and O6 of the carbonyl group in another molecule, related by a screw axis (Figure 2). The graph-set descriptor of this contact (chain) is C1,1(6). Assignment of the H-bond descriptors are based on the graph-set theory [9]. For convenience, the

notation  $X_{a,d(n)}$  has also been adopted, 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.

**Figure 2.** Crystal packing and hydrogen bonds for compound 3.



The values of calculated puckering parameters [10]  $Q = 0.377(1) \text{ \AA}$ ,  $\varphi = 357.1(2)^\circ$  and selected relevant torsion angles  $C1-C2-C3-C4 = 1.79(13)^\circ$ ,  $C2-C3-C4-O4 = -25.06(12)^\circ$ ,  $C3-C4-O4-C1 = 40.82(12)^\circ$ , indicate that  $O4-C1-C2-C3-C4$  furanoside ring adopts almost perfect  ${}^O E$  conformation with C1, C2, C3 and C4 atoms in a plane and O4 atom directed *endo* to this plane. Analogously, puckering parameters  $Q = 0.307(1) \text{ \AA}$ ,  $\varphi = 141.8(2)^\circ$  and relevant dihedral angles  $O2-C2-C3-O3 = 1.24(14)^\circ$ ,  $C3-O3-C8-O2 = 33.46(14)^\circ$ ,  $C8-O2-C2-C3 = 19.09(14)^\circ$  are indicative of almost perfect  ${}^{C-8} E$  conformation for five-membered 1,3-dioxolane ring ( $O2-C2-C3-O3-C8$ ) with C8 atom lying in the *endo* direction with respect to the plane defined by the atoms O2, C2, C3, and O3.

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## Experimental

### General

$^1\text{H}$ - and  $^{13}\text{C}$ -NMR spectra (in  $\text{CDCl}_3$ , internal standard  $\text{Me}_4\text{Si}$ ) 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 semiselective INEPT experiment and a 1D INADEQUATE pulse sequence technique. The EI and CI (using pyridine as a reactive gas [11]) 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 analyzer. Melting points were determined with a Boetius PHMK 05 microscope. All reactions were monitored by TLC on Silica Gel plates (E. Merck) using 1:3 EtOAc–hexane as solvent. Visualization was affected with iodine vapour or  $\text{H}_2\text{SO}_4$ .

### X-ray techniques

Crystal and experimental data for compound **3** are listed in Table 1. The structure was solved by direct methods and refined by a full-matrix least-squares technique. The crystallographic computations were performed with Bruker SHELXTL [12]. Molecular graphics were obtained using the program DIAMOND [13]. Suitable crystals were obtained by slow crystallization of **3** from a 2:1 (v/v) mixture of EtOAc–hexane.

### Synthetic methods

*Methyl 5-cyano-6-deoxy-2,3-O-isopropylidene- $\beta$ -L-gulofuranoside (2)*: KCN (3.25 g, 50 mmol), water (15 mL) and  $\text{NaHCO}_3$  (4.2 g, 50 mmol) were sequentially added to a stirred solution of 5-ulose **1** (5.4 g, 25 mmol) in ether (150 mL) under cooling at 0 °C, and the stirring at this temperature was continued for 2 h. The ethereal layer was then separated and the water layer was extracted with ether (3 x 50 mL). The combined ethereal solutions were dried ( $\text{Na}_2\text{SO}_4$ ), the solvent was evaporated and the crude product ( $R_f$  0.34) was recrystallized from a 3:1 (v/v) mixture of EtOAc–hexane to afford white needles of cyanohydrin **2** (5.6 g, 92% yield); mp 119–121 °C;  $[\alpha]_D^{25} + 64^\circ$  ( $c$  1, MeOH);  $^1\text{H}$ -NMR:  $\delta$  5.08 (s, 1H, H-1), 4.85 (dd, 1H,  $J_{2,3}$  6.0 Hz,  $J_{3,4}$  4.0 Hz, H-3), 4.62 (d, 1H, H-2), 3.92 (d, 1H, H-4), 3.68 (s, 1H, OH), 3.36 (s, 3H,  $\text{OCH}_3$ ), 1.77 (s, 3H, H-6), 1.60 and 1.33 (2s, each 3H,  $\text{Me}_2\text{C}$ );  $^{13}\text{C}$ -NMR:  $\delta$  120.4 (CN), 114.1 ( $\text{CMe}_2$ ), 107.0 (C-1), 84.6 (C-2), 82.5 (C-4), 79.1 (C-3), 69.6 (C-5), 55.0 ( $\text{OCH}_3$ ), 26.6 (C-6), 24.7 and 24.1 [ $(\text{CH}_3)_2\text{C}$ ]; EIMS:  $m/z$  243  $[\text{M}]^+$ , 228, 212, 185, 183, 173, 114, 113, 87, 73, 43; CIMS:  $m/z$  323  $[\text{M} + \text{C}_6\text{H}_5\text{NH}]^+$ . Anal. Calcd for  $\text{C}_{11}\text{H}_{17}\text{NO}_5$ : C, 54.31; H, 7.04; N, 5.76. Found: C, 54.24; H, 7.10; N, 5.81.

*Methyl 5-O-acetyl-5-cyano-6-deoxy-2,3-O-isopropylidene- $\beta$ -L-gulofuranoside (3)*: Acetylation of **2** (1.22 g, 5 mmol) with  $\text{Ac}_2\text{O}$  (7 mL) in pyridine (15 mL) overnight followed by concentration and co-



evaporation with toluene at diminished pressure gave **3** (1.28 g, 90% yield) as white needles after recrystallization from a 2:1 (v/v) mixture of EtOAc–hexane;  $R_f$  0.48; mp 58–59 °C;  $[\alpha]_D + 43^\circ$  ( $c$  1, MeOH);  $^1\text{H-NMR}$ :  $\delta$  5.05 (s, 1H, H-1), 4.78 (dd, 1H,  $J_{2,3}$  5.9 Hz,  $J_{3,4}$  3.6 Hz, H-3), 4.60 (d, 1H, H-2), 4.18 (d, 1H, H-4), 3.37 (s, 3H, OCH<sub>3</sub>), 2.14 (s, 3H, OCCH<sub>3</sub>), 1.93 (s, 3H, H-6), 1.55 and 1.31 (2s, each 3H, Me<sub>2</sub>C);  $^{13}\text{C-NMR}$ :  $\delta$  168.4 (CO), 116.4 (CN), 113.7 (CMe<sub>2</sub>), 107.0 (C-1), 84.3 (C-2), 81.3 (C-4), 78.6 (C-3), 72.8 (C-5), 54.8 (OCH<sub>3</sub>), 24.7 and 24.3 [(CH<sub>3</sub>)<sub>2</sub>C], 21.2 (OCCH<sub>3</sub>), 20.0 (C-6); CIMS:  $m/z$  365 [M + C<sub>6</sub>H<sub>5</sub>NH]<sup>+</sup>. Anal. Calcd for C<sub>13</sub>H<sub>19</sub>NO<sub>6</sub>: C, 54.73; H, 6.71; N, 4.91. Found: C, 54.62; H, 6.77; N, 4.96.

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