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Note

X-ray diffraction and high-resolution NMR spectroscopy of methyl 3-azido-2,3-dideoxy-α-D-*lyxo*-hexopyranoside

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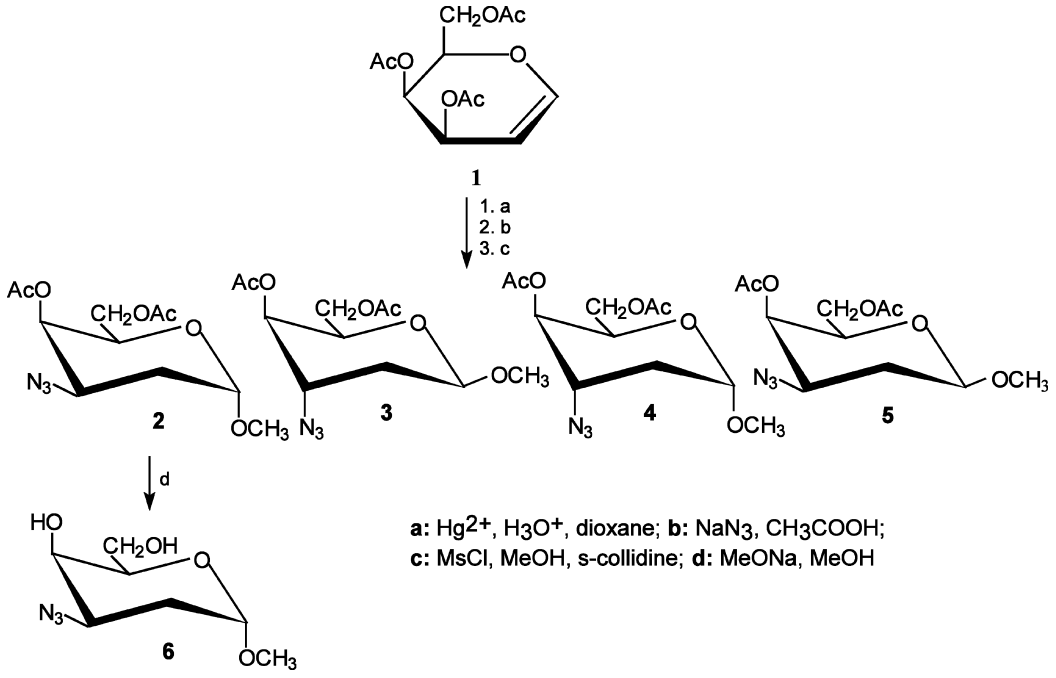
Abstract

The single-crystal X-ray diffraction and high-resolution ^{1}H and ^{13}C NMR spectral data for the title compound are reported. The influence of the ring oxygen atom on the $J_{1,2e}$ and $J_{4,5}$ coupling constants for 2-deoxy-D-*lyxo*- and -D-*xylo*-hexopyranosides is discussed.

Keywords: Methyl 3-azido-2,3-dideoxy-α-D-*lyxo*-hexopyranoside; X-ray diffraction, single-crystal; ^{1}H NMR spectroscopy; ^{13}C NMR spectroscopy; Ring oxygen atom, $J_{1,2e}$ and $J_{4,5}$ coupling constants

As previously reported, addition of hydrazoic acid to the α,β-unsaturated aldehyde derived from tri-*O*-acetyl-D-galactal (**1**), followed by methyl glycosidation led to a mixture of 3-azido-2,3-dideoxy glycosides.[1] Column chromatography of this mixture gave in turn: methyl 4,6-di-*O*-acetyl-3-azido-2,3-dideoxy-α-D-*lyxo*- (**2**), -β-D-*xylo*- (**3**), -α-D-*xylo*- (**4**), -β-D-*lyxo*-hexopyranosides (**5**) (Scheme 1). Deacetylation of methyl 4,6-di-*O*-acetyl-3-



Scheme 1.

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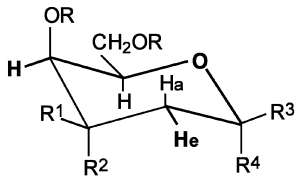

2 R = Ac, $R^1 = N_3$, R^2 = H, R^3 = H, $R^4 = OCH_3$
3 R = Ac, R^1 = H, $R^2 = N_3$, $R^3 = OCH_3$, R^4 = H
4 R = Ac, R^1 = H, $R^2 = N_3$, R^3 = H, $R^4 = OCH_3$
5 R = Ac, $R^1 = N_3$, R^2 = H, $R^3 = OCH_3$, R^4 = H
6 R = H, $R^1 = N_3$, R^2 = H, R^3 = H, $R^4 = OCH_3$

Fig. 1. An anti-periplanar relationship of the H-4 as well as H-2_e proton and ring oxygen atom for compounds **2**–**6**.

Table 1
The ^{1}H–^{1}H coupling constants (Hz) for tri-*O*-acetyl-D-galactal (**1**) (400 MHz)

	$J_{1,2}$	$J_{1,3}$	$J_{2,3}$	$J_{2,4}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$
1	6.4	1.6	2.8	1.2	4.4	1.6	7.2	5.2	11.6

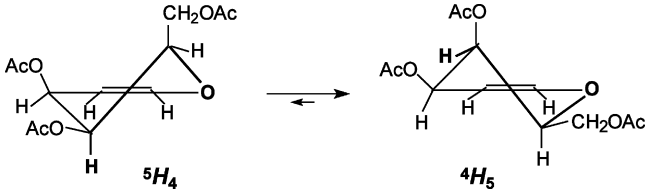

Fig. 2. The half-chair conformations of tri-*O*-acetyl-D-galactal (**1**) with anti-periplanar relationship of the H-4 proton and ring oxygen atom in the case of the $^4H_5$ form.

azido-2,3-dideoxy-α-D-*lyxo*-hexopyranoside (**2**) with a 0.1 M solution of sodium methoxide in absolute methanol, followed by crystallization (ethyl acetate–hexane) yielded methyl 3-azido-2,3-dideoxy-α-D-*lyxo*-hexopyranoside (**6**). The latter compound **6** is our substrate for the synthesis of methyl 3-azido-2,3,6-trideoxy-6-iodo-α-D-*lyxo*-hexopyranoside,[2] a useful intermediate in the synthesis of important bioactive substances such the 3-amino-2,3,6-trideoxyhexopyranoses,[3] aminocyclitols[4] and amino carbasugars.[5,6]

Table 3
Crystal data and structure refinement for **6**

Empirical formula	$C_7H_{13}N_3O_4$
Formula weight	203.20
Temperature (K)	293(2)
Wavelength (Å)	1.54178
Crystal system	monoclinic
Space group	$P2_1$
Unit cell dimensions	
a (Å)	9.182(2)
b (Å)	5.1470(10)
c (Å)	10.187(2)
β (°)	96.29(3)
V (Å^3)	478.54(17)
Z	2
D_{calcd} (Mg m^{-3})	1.410
Absorption coefficient (mm^{-1})	0.992
$F(000)$	216
Crystal size (mm)	$0.3 \times 0.4 \times 0.4$
Θ Range for data collection (°)	4.37–72.10
Limiting indices	$-11 \le h \le 11$, $0 \le k \le 6$, $0 \le l \le 11$
Reflections collected/unique	1095/1038 [$R_{int} = 0.0237$]
Completeness $2\Theta = 144.2°$ (%)	98.7
Refinement method	full-matrix least-squares on F^2
Data/restraints/parameters	1038/1/128
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0411$, $wR_2 = 0.1010$
R indices (all data)	$R_1 = 0.0420$, $wR_2 = 0.1025$
Goodness-of-fit on F^2	1.153
Absolute structure parameter	0.1(3)
Extinction coefficient	0.149(10)
Largest difference peak and hole (e Å^{-3})	0.341 and −0.245

The ^{1}H NMR spectrum of **6** (Table 2) entirely confirmed its α-D-*lyxo* configuration and $^4C_1$ conformation in solution. Thus, the coupling constant $J_{2a,3}$ 12.8 Hz indicates a diaxial orientation of the H-2_a and H-3 protons. The structure of the H-1 signal (d) with only one coupling constant $J_{1,2a}$ 3.6 Hz calls for the α

Table 2
The ^{1}H–^{1}H coupling constants (Hz) for compounds **2**–**6** (400 MHz)

	$J_{1,2a}$	$J_{1,2e}$	$J_{2a,2e}$	$J_{2a,3}$	$J_{2e,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$
2	3.6	~0	12.8	12.8	4.8	3.2	~0	6.8	4.8	14.4
3	5.6	5.6	[b]	3.6	3.6	3.6	1.6	[a]	[a]	[a]
4	3.6	~0	15.2	4.8	3.2	3.2	1.6	6.4	6.0	11.6
5	9.6	2.0	[a]	12.8	4.8	3.2	1.1	6.6	6.6	[b]
6	3.6	~0	12.8	12.8	4.8	2.4	~0	9.2	5.2	[a]

[a] Not determinated.
[b] Responsive protons are both chemically and magnetically equivalent.

configuration at the anomeric center. The D-*lyxo* configuration and $^4C_1$ form of **6** are also proved by the lack of the coupling between the H-4 and H-5 protons. Single-crystal X-ray diffraction data show that in the crystal **6** also adopts a $^4C_1$ conformation (Fig. 3).

Absence of coupling between H-4 and H-5, as well as between the H-1_e and H-2_e protons, is probably associated with the presence of the ring oxygen atom. It is known that the magnitude of the vicinal coupling constant depends on the electronegative substituents, particularly on the ring oxygen atom. An anti-periplanar orientation of the ring oxygen atom to one of the protons involved in the vicinal coupling considerably reduces the magnitude of this vicinal coupling constant.[7] In the case of **2**–**6** with $^4C_1$ conformations, both H-2_e and H-4 are in an anti-periplanar relationship with the ring oxygen atom (Fig. 1). This relationship is most likely responsible for the lack of the coupling between equatorial H-1 and H-2 in **2**, **4** and **6** (Table 2). From our previous work[1,2,8] and data presented in this paper, it can be summarized that the H-1 proton signal of 2-deoxy-α-D-glycosides with the $^4C_1$ conformation usually appears as a doublet where the H-1 proton is solely coupled with the H-2_a proton, and sometimes as a doublet of doublets with a relatively small coupling constant $J_{1,2e} \sim 1.5$ Hz. Literature studies confirm our observation.[9–11]

The ring oxygen atom has an effect on the $J_{1,2e}$ coupling constant in the case of β glycoside **5** as well. It

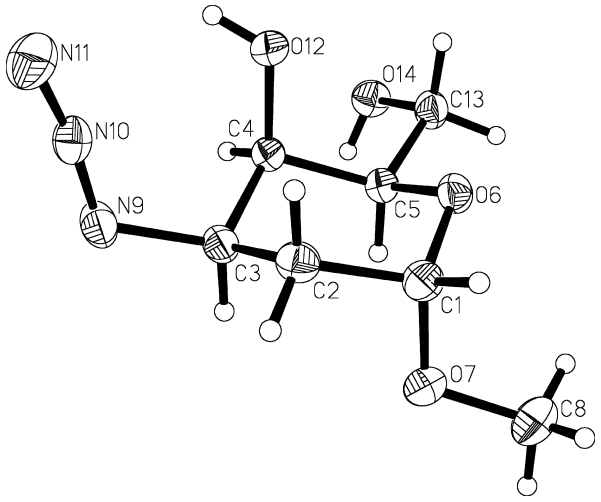

Fig. 3. Structure of **6** showing 50% probability displacements for ellipsoids.

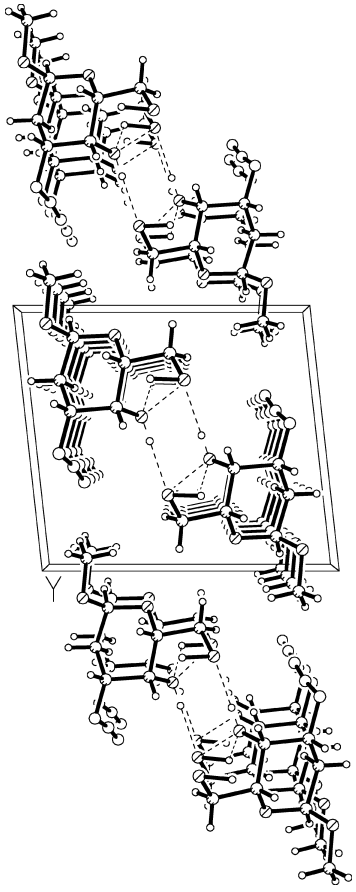

Fig. 4. Molecular packing of **6** (view along *x*-axis).

Table 4
Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for **6**

Atom	*x*	*y*	*z*	U_{eq}
C-1	8604(2)	−710(4)	2056(2)	47(1)
C-2	7075(2)	−1512(4)	1487(2)	47(1)
C-3	5957(2)	553(4)	1750(2)	42(1)
C-4	6089(2)	1201(4)	3227(2)	39(1)
C-5	7661(2)	2033(4)	3643(2)	40(1)
O-6	8655(1)	−18(3)	3413(1)	45(1)
O-7	9036(2)	1361(4)	1296(2)	55(1)
C-8	10,543(3)	2043(9)	1577(3)	82(1)
N-9	4451(2)	−172(4)	1220(2)	54(1)
N-10	3981(2)	−2243(4)	1602(2)	51(1)
N-11	3403(2)	−4099(5)	1850(2)	74(1)
O-12	5769(1)	−1017(3)	3969(1)	49(1)
C-13	7966(2)	2731(5)	5095(2)	48(1)
O-14	7020(2)	4731(4)	5457(1)	52(1)
H-1A	9260	−2141	1977	57
H-2B	7047	−1815	555	56
H-2A	6818	−3104	1896	56
H-3A	6204	2097	1294	50
H-4A	5440	2604	3382	47
H-5A	7873	3508	3119	47
H-8A	10,746	3541	1067	123
H-8B	10,749	2430	2500	123
H-8C	11,140	617	1353	123
H-12A	4901	−997	4092	58
H-13A	7845	1225	5629	57
H-13B	8962	3308	5276	57
H-14A	6907	5815	4865	63

U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

Table 5
Selected bond lengths (Å), valence angles (°) and torsion angles (°) for **6**

Bond lengths	
C-1–O-7	1.400(3)
C-1–O-6	1.424(2)
C-1–C-2	1.516(3)
C-2–C-3	1.522(3)
C-3–N-9	1.476(2)
C-3–C-4	1.533(2)
C-4–O-12	1.418(2)
C-4–C-5	1.521(2)
C-5–O-6	1.431(2)
C-5–C-13	1.518(2)
O-7–C-8	1.424(3)
N-9–N-10	1.229(3)
N-10–N-11	1.135(3)
C-13–O-14	1.421(3)
Valence angles	
O-7–C-1–O-6	111.4(2)
O-7–C-1–C-2	107.6(2)
O-6–C-1–C-2	111.7(2)
C-3–C-2–C-1	110.9(2)
N-9–C-3–C-2	112.5(2)
N-9–C-3–C-4	112.6(2)
C-2–C-3–C-4	110.0(2)
O-12–C-4–C-5	108.9(2)
O-12–C-4–C-3	110.5(2)
C-5–C-4–C-3	107.8(2)
O-6–C-5–C-4	110.5(2)
O-6–C-5–C-13	106.3(2)
C-4–C-5–C-13	114.0(2)
C-1–O-6–C-5	112.9(2)
C-1–O-7–C-8	113.8(2)
N-10–N-9–C-3	116.8(2)
N-11–N-10–N-9	171.8(2)
O-14–C-13–C-5	111.8(2)
Torsion angles	
O-7–C-1–C-2–C-3	−69.9(2)
O-6–C-1–C-2–C-3	52.7(2)
C-1–C-2–C-3–N-9	−179.5(2)
C-1–C-2–C-3–C-4	−53.1(2)
N-9–C-3–C-4–O-12	63.7(2)
C-2–C-3–C-4–O-12	−62.6(2)
N-9–C-3–C-4–C-5	−177.5(2)
C-2–C-3–C-4–C-5	56.3(2)
O-12–C-4–C-5–O-6	59.7(2)
C-3–C-4–C-5–O-6	−60.1(2)
O-12–C-4–C-5–C-13	−59.9(2)
C-3–C-4–C-5–C-13	−179.7(2)
O-7–C-1–O-6–C-5	63.0(2)
C-2–C-1–O-6–C-5	−57.4(2)
C-4–C-5–O-6–C-1	61.9(2)
C-13–C-5–O-6–C-1	−174.0(2)
O-6–C-1–O-7–C-8	67.0(3)
C-2–C-1–O-7–C-8	−170.2(2)
C-2–C-3–N-9–N-10	56.5(2)
C-4–C-3–N-9–N-10	−68.5(2)
C-3–N-9–N-10–N-11	−175.1(2)
O-6–C-5–C-13–O-14	−178.9(2)
C-4–C-5–C-13–O-14	−56.9(2)
H-1A–C-1–C-2–H-2A	53.0
H-1A–C-1–C-2–H-2B	−65.5
H-2A–C-2–C-3–H-3A	−177.0
H-2B–C-2–C-3–H-3A	−59.0
H-3A–C-3–C-4–H-4A	59.1
H-4A–C-4–C-5–H-5A	−60.7
H-5A–C-5–C-13–H-13A	−174.7
H-5A–C-5–C-13–H-13B	−56.4

reduces the axial–equatorial coupling to 2 Hz. An analogous tendency is observed for the other 2-deoxy-β-D-glycosides.[1] Compound **3** is not taken into account since its H-2 protons are both chemically and magnetically equivalent, and in this way are not distinguishable.

Similarly, an anti-periplanar relationship of the H-4 proton and ring oxygen atom has a considerable influence on the $J_{4,5}$ coupling constant. Despite the axial (H-5) and equatorial (H-4) orientation of the responsive protons in the $^4C_1$ form of **2**–**6**, the magnitude of their coupling constant is much smaller than expected and is limited to a range of 0–2 Hz. This small coupling is probably characteristic for galactose and other compounds having an anti-periplanar relationship of the H-4 proton and ring oxygen atom.[1,12–14] It means that for this type of compound, a coupling constant of $J_{4,5} \gg 2$ Hz is rather due to a conformation where this relationship is disturbed.[15,16] Thus, in the case of tri-*O*-acetyl-D-galactal (**1**), the coupling constant $J_{4,5}$ 1.6 Hz (Table 1) confirms its $^4H_5$ conformation, where the ring oxygen atom and H-4 proton are in an anti-periplanar relationship (Fig. 2).

1. Experimental

Complete characterization of **6**: mp 80–81 °C; $[\alpha]_D^{20}$ +138° (*c* 1.0, $CHCl_3$); R_f 0.57 (4:1 petroleum ether–AcOEt); IR: *v* 3432 and 3270 (OH), 2088 (N_3) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.93 (d, 1 H, $J_{1,2a}$ 3.6 Hz, H-1), 4.00 (bs, 1 H, H-4), 3.97–3.85 (m, 2 H, 2 H-6), 3.79 (dk, 1 H, $J_{3,4}$ 2.4 Hz, H-3), 3.76 (k, 1 H, $J_{5,6}$ 9.2, $J_{5,6'}$ 5.2 Hz, H-5), 3.36 (s, 3 H, OCH_3), 2.84 (bs, 1 H, 4-OH), 2.29 (b, 1 H, 6-OH), 2.18 (td, 1 H, $J_{2a,2e} \sim J_{2a,3}$ 12.8 Hz, H-2_a), 1.93 (dd, 1 H, $J_{2e,3}$ 4.8 Hz, H-2_e); ^{13}C NMR (400 MHz, $CDCl_3$): δ 98.32 (C-1), 69.34 (C-5), 68.91 (C-4), 64.11 (C-6), 56.66 (C-3), 55.18 (OCH_3), 28.97 (C-2). Anal. Calcd for $C_7H_{13}N_3O_4$: C, 41.38; H, 6.45; N, 20.68. Found: C, 41.68; H, 6.60; N, 20.61.

Table 6
Hydrogen bonds for **6** with H···A < r (Å) + 2.00 Å and < DHA > 110°

D–H	d(D–H)	d(H···A)	< DHA	d(D···A)	A	Symm. op.
O-12–H-12A	0.82	1.91	168.1	2.715(2)	O14	$[-x+1, y-1/2, -z+1]$
O-14–H-14A	0.82	2.09	150.2	2.833(2)	O12	$[x, y+1, z]$

1.1. Description of the crystal structure

The crystal structure of **6** was solved by the SHELXS program and refined by SHELXL-97.[17,18] A summary of crystallographic data, data collection and structure refinement is presented in Table 3. A view of **6** and its molecular packing in the crystal are presented in Figs. 3 and 4, respectively.[19,20] The coordinates of atoms and their isotropic temperature factors are presented in Table 4. A selection of important geometric parameters of **6** is tabulated in Table 5, and hydrogen bonds are summarized in Table 6.

In the crystal, **6** adopts a $^4C_1$ chair conformation with puckering parameters $Q = 0.573(2)$ and $\Theta = 5.7(3)°$. The values of bond lengths and angles determined in this work for **6** agree well with the expected ones.[21] Both OH groups participate in hydrogen bonding.

2. Supplementary material

Full crystallographic details, excluding structure features, have been deposited with the Cambridge Crystallographic Data Center, CCDC No. 194405. These data may be obtained, on request, from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Tel.: +44-1223-336-408; fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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References

1. Liberek, B.; Dąbrowska, A.; Frankowski, R.; Matuszewska, M.; Smiatacz, Z. *Carbohydr. Res.* **2002**, *337*, 1803–1820.
2. Dąbrowska, A.; Konitz, A.; Smiatacz, Z. *Carbohydr. Res.* **2002**, *337*, 175–181.
3. Hauser, F. M.; Ellenberger, S. R. *Chem. Rev.* **1986**, *86*, 35–67.
4. Frankowski, R.; Smiatacz, Z. *Wiad. Chem.* **2001**, *55*, 821–848.
5. Suami, T. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 21–90.
6. Frankowski, R.; Smiatacz, Z. *Wiad. Chem.* **2001**, *55*, 221–243.
7. Stoddart, J. F. *Stereochemistry of Carbohydrates*; John Wiley & Sons, Inc: Toronto, 1971; pp 137–145.
8. Dąbrowska, A.; Dokurno, P.; Konitz, A.; Smiatacz, Z. *Carbohydr. Res.* **2000**, *323*, 230–234.
9. Bielawska, H.; Michalska, M. *Tetrahedron Lett.* **1998**, *39*, 9761–9764.
10. Yadav, J. S.; Reddy, B. V. S.; Bhaskar Reddy, K.; Satyanarayana, M. *Tetrahedron Lett.* **2002**, *43*, 7009–7012.
11. Constantino, V.; Fattorusso, E.; Imperatore, C.; Mangoni, A. *Tetrahedron* **2002**, *58*, 369–375.
12. Mallet, A.; Mallet, J.-M.; Sinaÿ, P. *Tetrahedron: Asymmetry* **1994**, *5* (2), 2593–2608.
13. Zipser, B.; Bradford, J. J.; Hollingsworth, R. I. *Carbohydr. Res.* **1998**, *308*, 47–55.
14. Qiu, S.-X.; Ge, F.-H.; Zhou, Y.; Jia, J.-S.; Farnsworth, N. R.; Johnson, M. E.; Fong, H. H. S. *Carbohydr. Res.* **1998**, *311*, 85–88.
15. Rubinstein, G.; Esnault, J.; Mallet, J.-M.; Sinaÿ, P. *Tetrahedron: Asymmetry* **1997**, *8*, 1327–1336.
16. Liberek, B.; Konitz, A.; Frankowski, R.; Smiatacz, Z. *Carbohydr. Res.* **2000**, *326*, 151–158.
17. Sheldrick, G. M. *Acta Crystallogr., Sect. A* **1990**, *46*, 467–473.
18. Sheldrick, G.M. *SHELXL-97; Program for the Refinement of Crystal Structures*; University of Goetingen: Goetingen, 1997.
19. Johnson, C.K. *ORTEP II*; *Report ORNL*-5138; Oak Ridge National Laboratory: Oak Ridge, TN, 1976.
20. Motherwell, S.; Clegg S. *PLUTO-78; Program for Drawing Crystal and Molecular Structure*; University of Cambridge: Cambridge, 1978.
21. Allen, F. H.; Kennard, O.; Watson, D. G.; Brammer, L.; Orpen, A. G.; Taylor, R. *J. Chem. Soc., Perkin Trans. 2* **1987**, S1–S19.