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Note

Synthesis, X-ray structure and high-resolution NMR spectroscopy of methyl 3-azido-2,3-dideoxy-α-D-*arabino*-hexopyranoside

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Abstract

The synthesis, crystal structure data and ^{1}H and ^{13}C NMR spectroscopy of methyl 3-azido-2,3-dideoxy-α-D-*arabino*-hexopyranoside (**5b**) is reported. This compound adopts the $^4C_1$ conformation. Hydrogen-bonded molecules of **5b** form helices around the crystallographic 4_1 axis. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: Methyl 3-azido-2,3-dideoxy-α-D-*arabino*-hexopyranoside; Synthesis; X-ray diffraction; Methyl 4,6-di-*O*-acetyl-3-azido-2,3-dideoxy-α-D-*arabino*-hexopyranoside; ^{1}H and ^{13}C NMR

Nitrosoureas are an important class of antitumour agents [1]. If substituted with a sugar moiety, they exhibit powerful cytostatic and oncostatic activities [2]. The nitrosoureido group in these compounds seems to be essential for biological activity, and the carbohydrate moiety might play an important role as a carrier of this group.

The most convenient method for the synthesis of ureido sugars involves the reaction of isocyanates with amino sugars, which are obtained from the corresponding azido sugars. In this paper, we describe the synthesis and crystal structure of methyl 3-azido-2,3-dideoxy-α-D-*arabino*-hexopyranoside (**5b**), a useful intermediate for the synthesis of nitrosoureido derivatives of dideoxy sugars.

The key step in the synthesis of compound **5b** was Michael addition of hydrazoic acid to (*E*)-4,6-di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enose (**2**) generated in situ from per-*O*-acetyl-D-glucal (**1**) [3,4]. In the course of this reaction a mixture of 4,6-di-*O*-acetyl-3-azido-2,3-dideoxy-D-hexopyranoses (**3a**–**d**) was obtained, which in a few subsequent steps [5] and chromatographic separation gave **5b**. This compound, after peracetylation, gave pure **4b** with satisfactory elementary analysis (Scheme 1).

The ^{1}H NMR spectrum of **5b** shows two groups of multiplets at δ 1.72 and 2.19 ppm, characteristic for methylene group protons of the pyranoid ring. The proton signal of H-1 appears at δ 4.83 ppm. The small value of $J_{1,2a}$ and high value of the molar rotation for **5b** indicate the α configuration. The large value of $J_{2a,3} \approx J_{3,4} \approx J_{4,5} \approx 10$ Hz is characteristic of

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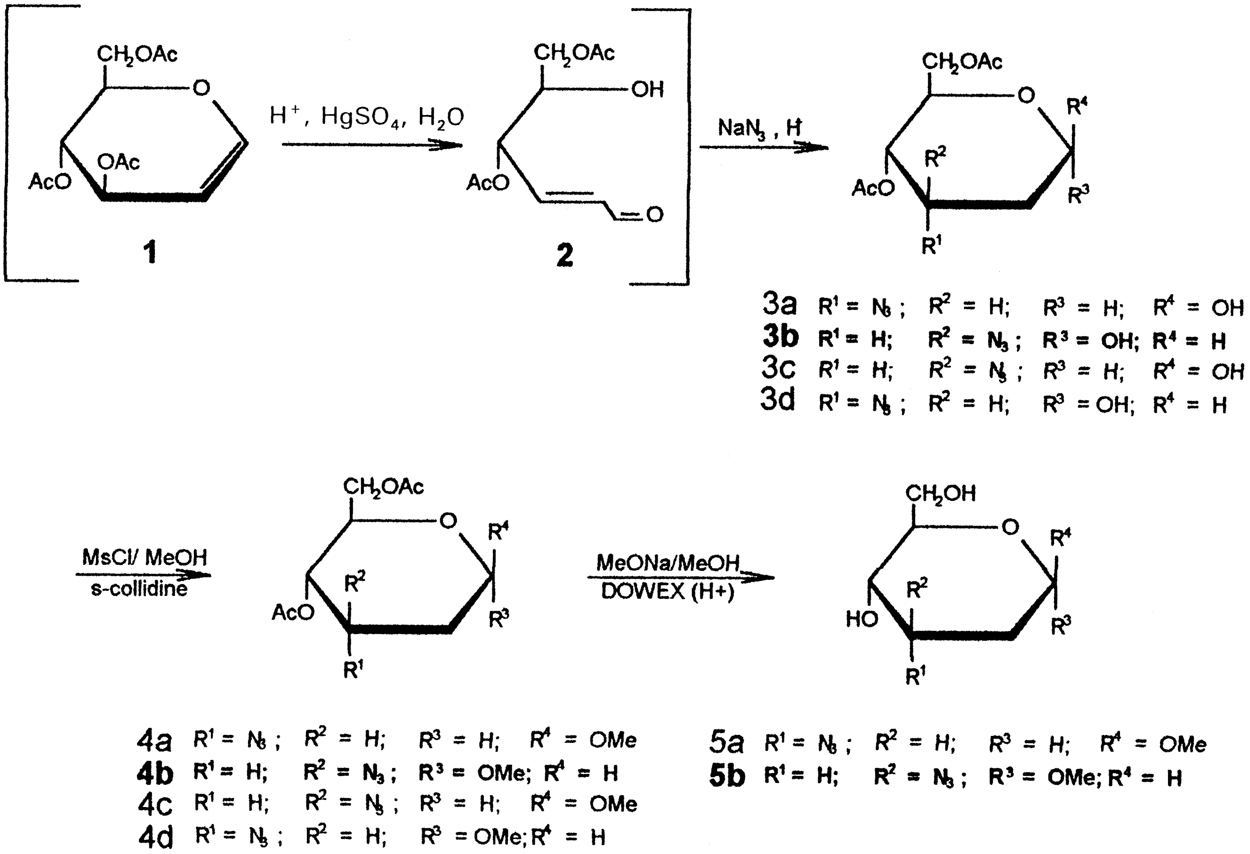

Scheme 1.

the D-*arabino* configuration. The ^{1}H NMR spectrum of its di-*O*-acetyl derivative **5b** shows two groups of multiplets at the δ 1.77 and 2.33 ppm. The proton signal of H-1 appears at δ 4.87 ppm. In solution, the title compound **5b** and its di-*O*-acetyl derivative **4b** show the same conformation as **5b** in the solid state.

The crystal structure of **5b** was solved by the SHELXS program [6] and refined by SHELXL-97 [7]. A summary of crystallographic data, data collection and structure refinement is presented in Table 1. An ORTEP view [8] of **5b** is shown in Fig. 1. The non-hydrogen atom coordinates and equivalent temperature factors are presented in Table 2, selected bond lengths and bond angles in Table 3 and torsion angles are tabulated in Table 4.

In the crystal, **5b** adopts a chair $^4C_1$ conformation with puckering parameters $Q = 0.564(3)$ and $\theta = 156(6)°$. The values of bond lengths and angles determined in this work for **5b** agree well with the expected ones [9]. Each molecule is involved in four hydrogen bonds in which oxygen atoms O-4 and O-6 act as donors, and oxygen atoms O-5 and O-6-as acceptors. Hydrogen-bonded molecules form helices along the crystallographic 4_1 axis.

1. Experimental

General methods.—NMR spectra were measured with a Varian XL-100 spectrometer at 500 MHz in $CDCl_3$ with Me_4Si as the internal standard. Mass spectra were recorded with a Varian Matt 711 spectrometer with FD ionisation mode. Infrared spectra were recorded in Nujol mulls with a Perkin–Elmer 257 spectrophotometer. The optical rotations were determined with a Hilger and Watts polarimeter in a 1 dm tubes at the D line of sodium at room temperature (rt). The melting points were uncorrected. Reactions were monitored by thin-layer chromatography (TLC) using aluminium-supported plates with Silica Gel 60 (0.08 mm, E. Merck, Darmstadt, Germany)

Table 1
Crystal data and structure refinement for **5b**

Crystal colour/shape	colourless needless
Empirical formula	$C_7H_{13}N_3O_4$
Formula weight	203.20
Temperature (K)	293(2)
Wavelength (Å)	0.71073
Crystal system	tetragonal
Space group	$P4_12_12$
Unit cell dimensions	
a (Å)	15.979(2)
c (Å)	7.445(1)
V (Å^3)	1900.9(4)
Z	8
D_{calcd} (Mg m^{-3})	1.420
Absorption coefficient (mm^{-1})	0.117
$F(000)$	864
Crystal size (mm)	$0.3 \times 0.3 \times 0.7$
θ Range for data collection (°)	1.80–30.00
Index ranges	$0 \leq h \leq 22$, $0 \leq k \leq 22$, $0 \leq l \leq 10$
Reflections collected/unique	3149/2788 [$R_{int} = 0.0165$]
Decay (%)	65
Completeness to $2\Theta = 60.00$ (%)	100.0
Refinement method	full-matrix least-squares on F^2
Data/restraints/parameters	2788/0/138
Goodness-of-fit on F^2	1.108
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0500$, $wR_2 = 0.1218$
R indices (all data)	$R_1 = 0.1089$, $wR_2 = 0.1600$
Absolute structure parameter	0(2)
Extinction coefficient	0.008(2)
Largest difference peak and hole (e A^{-3})	0.194 and −0.156

using the following eluent systems (v/v): (A): 3:1 CCl_4–acetone; (B) 2:1 EtOAc–*n*-hexane. Flash chromatography was performed on Silica Gel 60 (0.08 mm, E. Merck). Evaporations were carried out under diminished pressure at 35–40 °C.

*4,6-Di-*O*-acetyl-3-azido-2,3-dideoxy-β-*D-ribo *and α-*D-arabino-*hexopyranoses* (**3a**, **3b**) *and 4,6-di-*O*-acetyl-3-azido-2,3-dideoxy-β-*D-arabino *and α-*D-ribo-*hexopyranoses* (**3c**, **3d**).—3,4,6-Tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol (**1**) [10] (3 g, 0.01 mol) in 1,4-dioxane (15 mL) was stirred with $HgSO_4$ (0.15 g) and a solution of H_2SO_4 (5 mM, 60 mL) for 2 h at rt. Then sodium azide (7.1 g, 0.1 mol) and glacial AcOH (15 mL) were added. After 3 h, the aq phase was extracted with $CHCl_3$ (3×50 mL) and the extract was dried over $MgSO_4$. Evaporation gave a mixture of four isomeric 4,6-di-*O*-acetyl-3-azido-2,3-dideoxy-D-hexopyranoses (**3a**–**d**) (3.95 g).

*Methyl 4,6-di-*O*-acetyl-3-azido-2,3-dideoxy-β-*D-ribo *and α-*D-arabino-*hexopyranosides* (**4a**, **4b**) *and methyl 4,6-di-*O*-acetyl-3-azido-2,3-dideoxy-β-*D-arabino *and α-*D-ribo-*hexopyranosides* (**4c**, **4d**).—To the crude syrupy mixture of **3a**–**d** (3.95 g) in CH_2Cl_2 (70 mL) was added dry *s*-collidine (12 mL) and MsCl (3.5 mL, 0.04 mol) and the reaction

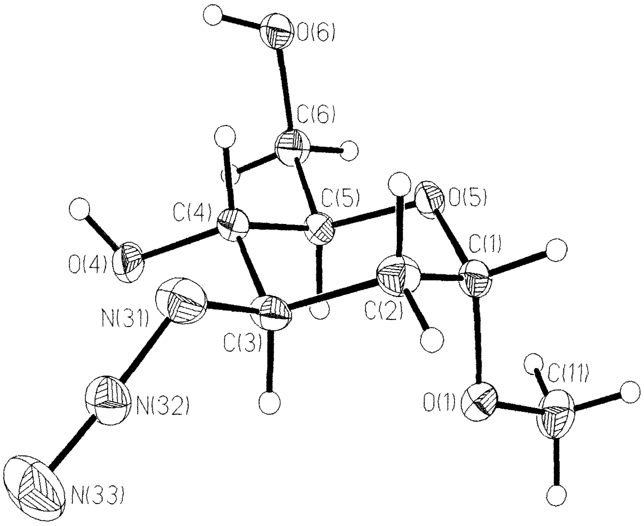

Fig. 1. Structure of methyl 3-azido-2,3-dideoxy-α-D-*arabino*-hexopyranoside (**5b**) showing 50% probability displacement for ellipsoids.

Table 2
Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters (Å$^2 \times 10^3$) for **5b** [a]

Atom	x	y	z	U_{eq}
C-1	2386(2)	6120(2)	−730(4)	42(1)
C-2	1733(2)	6716(2)	−1389(4)	47(1)
C-3	1492(2)	7309(1)	91(4)	43(1)
C-4	1194(2)	6823(2)	1684(4)	38(1)
C-5	1861(2)	6199(1)	2262(4)	36(1)
O-5	2093(1)	5679(1)	789(3)	40(1)
C-6	1592(2)	5639(2)	3775(4)	47(1)
O-6	827(1)	5231(1)	3431(3)	53(1)
O-1	3103(1)	6577(1)	−355(3)	46(1)
C-11	3805(2)	6071(2)	−7(5)	64(1)
N-31	808(2)	7844(2)	−571(4)	61(1)
N-32	893(1)	8586(2)	−316(4)	54(1)
N-33	902(2)	9276(2)	−173(6)	98(1)
O-4	1039(1)	7351(1)	3162(3)	55(1)

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

Table 3
Selected bond lengths (Å) and angles (°) for **5b**

Bond length	
C-1–O-1	1.389(3)
C-1–O-5	1.412(3)
C-1–C-2	1.495(4)
C-2–C-3	1.503(4)
C-3–N-31	1.473(3)
C-3–C-4	1.495(4)
C-4–O-4	1.408(3)
C-4–C-5	1.522(3)
C-5–O-5	1.425(3)
C-5–C-6	1.502(4)
C-6–O-6	1.408(3)
O-1–C-11	1.407(3)
N-31–N-32	1.208(3)
N-32–N-33	1.108(3)
Valence angle	
O-1–C-1–O-5	112.0(2)
O-1–C-1–C-2	107.8(2)
O-5–C-1–C-2	110.4(2)
C-1–C-2–C-3	109.9(2)
N-31–C-3–C-4	109.3(2)
N-31–C-3–C-2	108.1(2)
C-4–C-3–C-2	109.6(2)
O-4–C-4–C-3	111.4(2)
O-4–C-4–C-5	107.2(2)
C-3–C-4–C-5	110.0(2)
O-5–C-5–C-6	107.75(19)
O-5–C-5–C-4	110.3(2)
C-6–C-5–C-4	113.7(2)
C-1–O-5–C-5	114.34(18)
O-6–C-6–C-5	112.8(2)
C-1–O-1–C-11	113.1(2)
N-32–N-31–C-3	115.7(2)
N-33–N-32–N-31	173.3(3)

Table 4
Torsion angles (°) for **5b**

O-1–C-1–C-2–C-3	−65.5(3)
O-5–C-1–C-2–C-3	57.3(3)
C-1–C-2–C-3–N-31	−176.0(2)
C-1–C-2–C-3–C-4	−57.0(3)
N-31–C-3–C-4–O-4	−67.4(3)
C-2–C-3–C-4–O-4	174.3(2)
N-31–C-3–C-4–C-5	174.0(2)
C-2–C-3–C-4–C-5	55.6(3)
O-4–C-4–C-5–O-5	−175.94(19)
C-3–C-4–C-5–O-5	−54.7(3)
O-4–C-4–C-5–C-6	62.9(3)
C-3–C-4–C-5–C-6	−175.9(2)
O-1–C-1–O-5–C-5	61.6(3)
C-2–C-1–O-5–C-5	−58.7(3)
C-6–C-5–O-5–C-1	−178.3(2)
C-4–C-5–O-5–C-1	57.2(3)
O-5–C-5–C-6–O-6	−69.8(3)
C-4–C-5–C-6–O-6	52.7(3)
O-5–C-1–O-1–C-11	68.2(3)
C-2–C-1–O-1–C-11	−170.1(2)
C-4–C-3–N-31–N-32	109.0(3)
C-2–C-3–N-31–N-32	−131.7(3)
C-3–N-31–N-32–N-33	176(3)
H-1–C-1–C-2–H-2a	56
H-1–C-1–C-2–H-2e	−62
H-2a–C-2–C-3–H-3	−175
H-2e–C-2–C-3–H-3	−57
H-3–C-3–C-4–H-4	174
H-4–C-4–C-5–H-5	−176
H-5–C-5–C-6–H-6	−66
H-5–C-5–C-6–H-6′	52

mixture was stirred for 0.5 h at rt. After addition of MeOH (12 mL), stirring was continued for an additional 3 h. The reaction mixture, after dilution with CH_2Cl_2 (20 mL), was washed with 1 M aq HCl, followed by 1 M aq $NaHCO_3$ and cold water. After drying over $MgSO_4$ and evaporation to dryness, a thick syrupy mixture (4.1 g) of four isomeric compounds was obtained. Silica gel chromatography with the eluent system (A) gave two fractions consisting of methyl 4,6-di-*O*-acetyl-3-azido-2,3-dideoxy-D-hexopyranosides (**4a**) and **4b** (1.88 g Fraction I) and **4c** and **4d** (2.0 g, Fraction II).

*Methyl 3-azido-2,3-dideoxy-α-*D-arabino-*hexopyranoside* (**5b**).—To a solution of **4a** and **4b** (1.88 g, Fraction I) in abs MeOH (80 mL) was added NaOMe (1 M) in abs MeOH (0.9 mL). After being kept for 0.5 h at rt, the solution was neutralized with Dowex-50W × 8 (H^+) ion-exchange resin and evaporated. The reaction mixture was treated with 1:3 EtOAc–*n*-hexane (40 mL) and, after cooling, the crystalline product **5b** (1.3 g) was filtered off, washed with cold hexane, and recrystallised from a mixture of EtOAc and *n*-hexane (0.93 g, 49%): mp 117–119 °C; $[\alpha]_D^{20}$ +175° (*c* 1.0, MeOH); R_f 0.3 (solvent B); IR (Nujol); ν 3400 and 3200 (OH), 2900 and 2820 ($–CH_2–$), 2100 (N_3), 1140 (C–O–C eter); ^1H NMR: 4.83 (d, 1 H, $J_{1,2a}$ 3.53 Hz, $J_{1,2e}$ 1.32 Hz, H-1), 3.87 (t, 1 H, $J_{4,5}$ 9.7 Hz, H-4), 3.86 (m, 1 H, $J_{6,6'}$ 13 Hz, H-6), 3.83 (m, 1 H, $J_{3,4}$ 9.7 Hz, $J_{3,2a}$ 12.36 Hz, $J_{3,2e}$ 5.08 Hz, H-3), 3.66 (m, 1 H, H-6′), 3.55 (m, 1 H, $J_{5,6}$ 7.5 Hz, $J_{5,6'}$ 3.08 Hz, H-5), 3.37 (s, 3 H, OCH_3), 2.19 (m, 1 H, $J_{2a,2e}$ 13.02, H-2e), 1.72 (m, 1 H, H-2a); ^{13}C NMR: 97.855 (C-1), 71.351 (C-4), 71.147 (C-6), 62.704 (C-5), 60.545 (C-3), 55.094 (C-11, OCH_3), 34.984 (C-2). FDMS: *m*/*z* 203 [M^+]. Anal. Calcd for $C_7H_{13}N_3O_4$ (203.19): C, 41.38; H, 6.45; N, 20.68. Found: C, 42.04; H, 6.63; N, 20.16.

*Methyl 4,6-di-O-acetyl-3-azido-2,3-dideoxy-α-*D-arabino-*hexopyranoside* (**4b**).—To a solution of **5b** (0.93 g, 4.57 mmol) in CH_2Cl_2 (50 mL) was added anhyd pyridine (9 mL) and Ac_2O (9 mL). The mixture was held for 24 h at rt, then ice was added and the mixture extracted with $CHCl_3$. The organic phase was washed with satd $NaHCO_3$ (3×20 mL) and water, and dried over $MgSO_4$. After evaporation under diminished pressure, the syrupy product **4b** (1.13 g, 3.94 mmol, 86%) was obtained: $[\alpha]_D^{20}$ $+81°$ (*c* 1.0, $CHCl_3$); R_f 0.72 (solvent A); IR (Nujol); *v* 2900 and 2820 ($-CH_2-$), 2100 (N_3), 1720, 1280 (C=O ester), 1140 (C–O–C eter); ^{1}H NMR: 4.95 (t, 1 H, $J_{4,5}$ 10 Hz, H-4), 4.87 (dd, 1 H, $J_{1,2a}$ 4 Hz, $J_{1,2e}$ 1.5 Hz, H-1), 4.28 (dd, 1 H, $J_{6,6'}$ 12 Hz, H-6), 4.04 (dd, 1 H, H-6′), 3.95 (m, 1 H, $J_{3,4}$ 10 Hz, $J_{3,2a}$ 12 Hz, $J_{3,2e}$ 5 Hz, H-3), 3.88 (m, 1 H, $J_{5,6}$ 5 Hz, $J_{5,6'}$ 2 Hz, H-5), 3.37 (s, 3 H, OCH_3), 2.33 (m, 1 H, $J_{2a,2e}$ 12, H-2e), 2.01–2.02 (s, 6 H, OAc), 1.77 (m, 1 H, H-2a). Anal. Calcd for $C_{11}H_{17}N_3O_6$ (287.27): C, 45.99; H, 5.96; N, 14.62. Found: C, 45.83; H, 5.99; N, 14.69.

2. Supplementary material

Tables of atomic coordinates, bond lengths, and bond angles have been deposited with the Cambridge Crystallographic Data Centre. These may be obtained on request from The Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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