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Methyl 2,3,4-tri-*O*-acetyl-1-azido-1-deoxy-β-D-glucopyranuronate at room temperature

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The structure of the title compound, $C_{13}H_{17}N_3O_9$, has been determined as part of our continuing investigation into the development of modified sugar amino acid (SAA) scaffolds for dyamic combinatorial libraries of cyclic oligomers. The title compound serves as a viable synthetic precursor and a building block for the synthesis of reversible β-glucosidase inhibitors utilizing target-accelerated *in situ* click methodologies. The overall structure is stabilized by a number of C—H···O interactions.

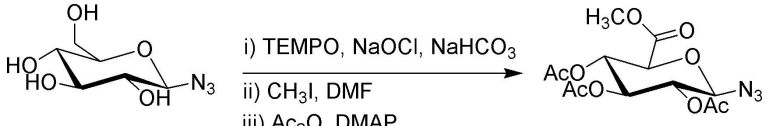
Key indicators

Single-crystal X-ray study
T = 295 K
Mean σ(C–C) = 0.005 Å
R factor = 0.041
wR factor = 0.124
Data-to-parameter ratio = 9.9

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

Comment

As part of our interest in the target-accelerated synthesis of glycosidase inhibitors, as well as the development of dynamic combinatorial libraries of cyclic oligomers based on sugar amino acid scaffolds (Bornaghi *et al.*, 2004), a suitable functionalized glycosyl azide was synthesized as a stable intermediate to a wide variety of potential *N*-glycosides. Glycosyl azides have been the subject of interest in the literature as precursors to 1,2,3-triazole glycosides displaying potential antimicrobial and anticancer properties (Chen *et al.*, 1999; Al-Masoudi & Al-Soud, 2002; Yang *et al.*, 2002). Glycosyl azides are readily prepared from α- or β-azides *via* a modified Staudinger reaction of the azide with an acyl halide in the presence of triphenylphosphine (He *et al.*, 2004; Boullanger *et al.*, 2000). The reaction displays high stereochemical selectivity compared with peptide coupling methodologies on relatively unstable glyocosyl amine intermediates (Boullanger *et al.*, 2000), providing attractive alternative syntheses for glycopeptides of medicinal (Broder & Kunz, 1997; He *et al.*, 2004) and industrial importance (Gyorgydeak & Thiem, 1995).



(I)

The title compound, (I), was selected due to its high stability and the scale-up potential of the synthesis (Gyorgydeak & Thiem, 1995), as well as its relative ease of synthetic manipulation at C6 and C1 to afford the desired target compounds. The azide functionality was incorporated at C1 using a phase-transfer displacement of the α-glucosyl bromide tetraacetate, followed by conventional methoxide deprotection of the acetate protecting groups. The methyl ester group was prepared by a hypochlorite-mediated 2,2,6,6-tetramethylpiperidynyloxy (TEMPO) oxidation of the primary alcohol at

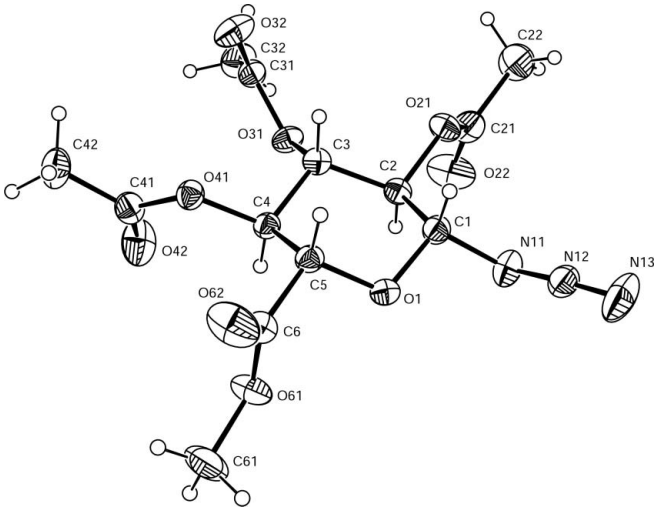


Figure 1
ORTEP-3 (Farrugia, 1997) plot of the title compound, with the atom-numbering scheme. Displacement ellipsoids for non-H atoms are drawn at the 30% probability level.

C6 to afford the sodium uronate, followed by methylation using methyl iodide, and finally a dimethylaminopyridine (DMAP)-catalysed acetylation of the hydroxy groups at C2, C3 and C4.

In the structure of (I) (Fig. 1), the bond lengths and angles (Table 1) are in accord with expected values (Temelkoff *et al.*, 2004). The six-membered carbohydrate ring adopts a chair conformation. As found for other β-glucopyranosides, the non-H substituents are located in equatorial positions. The carbonyl group of the acetate groups on C2, C3 and C4, the methyl ester group on C5 and the azide group on C1 adopt a *cis* conformation with respect to the axial protons with H—C···C═O torsion angles of 8.1 (C2), 21.3 (C3), 19.1 (C4) and 4.8° (C5), and C—H···N—N of 34.7° (C1) (Wiberg & Laidig, 1987). The crystal structure is stabilized by a number of C—H···O contact interactions (Table 2).

The structure of the same compound, determined at 100 K, is reported independently by another research group in the preceding paper (Smith *et al.,* 2005).

Experimental

The title compound, (I), was prepared using a modified version of the literature procedure described by Gyorgydeak & Thiem (1995). A solution of β-D-glucopyranosyl azide (100 mg, 0.49 mmol), KBr (5.0 mg, 0.04 mmol) and TEMPO (5.0 mg, 0.03 mmol) in saturated aqueous $NaHCO_3$ (2.5 ml) was cooled to 290 K. A second solution of NaOCl (100 g l^{-1}, 3.3 ml) was then added dropwise with the temperature maintained below 296–297 K. Once addition was complete, the resulting deep yellow solution was stirred at room temperature for 4 h. The mixture was lyophilized and suspended in dimethylformamide (2.0 ml). CH_3I (65 µl) was added and the suspension stirred overnight at room temperature. DMAP (5 mg) and acetic anhydride (150 µl) were added and stirred at room temperature for a further 2 h. Water (5 ml) was added and the crude product extracted into EtOAc (3 × 7 ml). The organic layers were combined and washed with brine (10 ml), dried over Na_2SO_4, decanted, and evaporated to dryness. Crystals suitable for single-crystal X-ray diffraction were obtained by recrystallization of the crude residue from hot ethanol (m.p. 424–425 K). ^{1}H NMR ($CDCl_3$): δ 5.25 (*m*, 2H, H-2, H-4), 4.96 (*m*, 1H, H-3), 4.72 (*d*, 1H, $J_{4,5}$ = 8.8 Hz, H-5), 4.12 (*d*, 1H, $J_{1,2}$ = 9.2 Hz, H-1), 3.78 (*s*, 3H, OCH_3), 2.08 (*s*, 3H, OAc), 2.03 (*s*, 3H, OAc), 2.02 (*s*, 3H, OAc). ^{13}C NMR ($CDCl_3$): δ 20.63 ($COCH_3$), 20.72 ($COCH_3$), 53.26 (OCH_3), 69.19, 70.60, 72.00, 72.43, 88.26 (C-1, C-2, C-3, C-4, C-5), 166.70, 169.30, 169.46, 170.16 (4 × C═O). MS (LRESI–MS): 360.4 (M + H^+), 382.1 (M + Na^+).

Crystal data

$C_{13}H_{17}N_3O_9$
M_r = 359.30
Orthorhombic, $P2_12_12_1$
a = 14.059 (3) Å
b = 16.336 (2) Å
c = 7.356 (3) Å
V = 1689.4 (8) Å^3
Z = 4
D_x = 1.413 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 20 reflections
θ = 12.6–16.3°
μ = 0.12 mm^{-1}
T = 295 K
Prism, colourless
0.30 × 0.20 × 0.15 mm

Data collection

Rigaku AFC-7*R* diffractometer
ω–2θ scans
Absorption correction: none
2779 measured reflections
2227 independent reflections
1346 reflections with $I > 2\sigma(I)$
R_{int} = 0.036
θ_{max} = 27.5°
$h = -8 \rightarrow 18$
$k = 0 \rightarrow 21$
$l = -4 \rightarrow 9$
3 standard reflections
every 150 reflections
intensity decay: 3.2%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.041
$wR(F^2)$ = 0.124
S = 1.01
2227 reflections
226 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0489P)^2 + 0.1669P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.16 e Å^{-3}
$\Delta\rho_{min}$ = −0.22 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

O1—C1	1.426 (4)	O41—C41	1.363 (4)
O1—C5	1.426 (4)	O42—C41	1.186 (5)
O21—C2	1.439 (4)	O61—C6	1.313 (5)
O21—C21	1.379 (4)	O61—C61	1.452 (5)
O22—C21	1.182 (6)	O62—C6	1.190 (5)
O31—C3	1.440 (4)	N11—N12	1.242 (5)
O31—C31	1.345 (4)	N11—C1	1.457 (5)
O32—C31	1.196 (4)	N12—N13	1.108 (5)
O41—C4	1.436 (4)		
C1—O1—C5	110.5 (2)	O41—C4—C5	107.1 (2)
C2—O21—C21	117.6 (3)	O1—C5—C4	107.9 (2)
C3—O31—C31	119.0 (3)	O1—C5—C6	107.9 (2)
C4—O41—C41	117.7 (2)	O61—C6—O62	124.4 (4)
C6—O61—C61	117.4 (3)	O61—C6—C5	111.7 (3)
N12—N11—C1	115.4 (3)	O62—C6—C5	123.9 (4)
N11—N12—N13	171.3 (4)	O21—C21—O22	123.0 (4)
O1—C1—N11	106.8 (2)	O21—C21—C22	110.2 (4)
O1—C1—C2	109.3 (3)	O22—C21—C22	126.8 (4)
N11—C1—C2	107.0 (3)	O31—C31—O32	123.8 (3)
O21—C2—C1	107.0 (3)	O31—C31—C32	110.9 (3)
O21—C2—C3	108.4 (2)	O32—C31—C32	125.3 (3)
O31—C3—C2	105.9 (3)	O41—C41—O42	122.5 (3)
O31—C3—C4	111.3 (3)	O41—C41—C42	109.7 (3)
O41—C4—C3	110.6 (2)	O42—C41—C42	127.7 (4)

Table 2
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
C1—H1···O42^{i}	0.95	2.57	3.177 (5)	122
C2—H2···O22	0.95	2.28	2.705 (5)	106
C3—H3···O32	0.95	2.36	2.725 (4)	103
C4—H4···O42	0.95	2.31	2.682 (4)	102
C22—H22B···O61^{ii}	0.95	2.56	3.458 (6)	158

Symmetry codes: (i) $x, y, z-1$; (ii) $\frac{1}{2}+x, \frac{1}{2}-y, -z$.

H atoms attached to carbon were constrained as riding atoms, with C—H distances set at 0.95 Å. U_{iso}(H) values were set at $1.2U_{eq}$ of the parent atom. In the absence of significant anomalous scattering effects, Friedel pairs were merged. The absolute configuration is assigned on the basis of the known configuration of the starting material.

Data collection: *MSC/AFC-7 Diffractometer Control Software* (Molecular Structure Corporation, 1999); cell refinement: *MSC/AFC-7 Diffractometer Control Software*; data reduction: *TEXSAN for Windows* (Molecular Structure Corporation, 2001); program(s) used to solve structure: *TEXSAN for Windows*; program(s) used to refine structure: *TEXSAN for Windows* and *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3* (Farrugia, 1997); software used to prepare material for publication: *TEXSAN for Windows* and *PLATON* (Spek, 2003).

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