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2-*C*-Hydroxymethyl-2,3-*O*-isopropylidene-D-mannono-1,5-lactam

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Key indicators

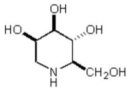
Single-crystal X-ray study
T = 150 K
Mean σ(C–C) = 0.002 Å
R factor = 0.030
wR factor = 0.075
Data-to-parameter ratio = 12.1

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

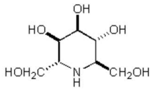
The title compound, $C_{10}H_{17}NO_6$, is an intermediate, with all the stereocentres in place, for a synthesis of a new class of glycosidase inhibitors with a branched carbon chain. Its relative configuration was determined by X-ray crystallography and the absolute configuration by the use of L-sorbose as the starting material.

Comment

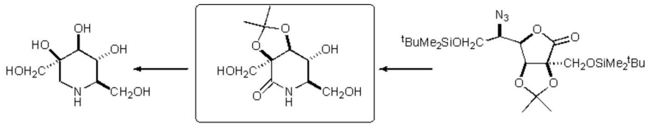
Nitrogen analogues of carbohydrates, in which the ring oxygen has been replaced by a basic nitrogen are sugar mimics (Winchester *et al.*, 1992) that can act as glycosidase inhibitors. Such compounds, found widely in plants and bacteria, also have potential as chemotherapeutic agents (Asano, Nash *et al.*, 2000; Asano *et al.*, 2005; Watson *et al.*, 2001). Two natural products, deoxymannojirimycin (DMJ) (1) (Evans *et al.*, 1985) and α-homoDMJ (2) (Asano *et al.*, 2001; Asano, Nishida *et al.*, 2000) are both mannosidase and fucosidase inhibitors (Bruce *et al.*, 1992; Shilvock *et al.*, 1998).



(1)



((2)



(3)

(4)

(5)

Iso-α-HomoDMJ (3), an isomer of (2) in which a branching hydroxymethyl group is attached to C-2, is being synthesized as a potential mannosidase inhibitor. The azidolactone (5), prepared from L-sorbose, (Hotchkiss *et al.*, 2004; Soengas *et al.*, 2005) on hydrogenation gave an amine from which the silyl ether protecting groups were removed by treatment with tetrabutyl ammonium fluoride. Subsequent heating gave the crystalline lactam (4) as a key intermediate in the preparation of (3) in which all the stereocentres have been introduced. This paper reports the crystal structure of (4), unequivocally establishing the relative stereochemistry of this late-stage intermediate. The absolute configuration of (4) was set by the use of L-sorbose as the synthetic starting material.

In (4), there is a *cis* junction between the two rings and no unusual geometrical features were observed (Fig. 1). The crystal structure consists of hydrogen-bonded sheets of molecules perpendicular to the *c* axis. (Fig. 2 and Table 1) Within the sheets, hydrogen bonds form a discrete donor chain (N5 to O10 to 017 to 07), with O7 also acting as acceptor for a second hydrogen bond from O9. There are no hydrogen bonds between the sheets.

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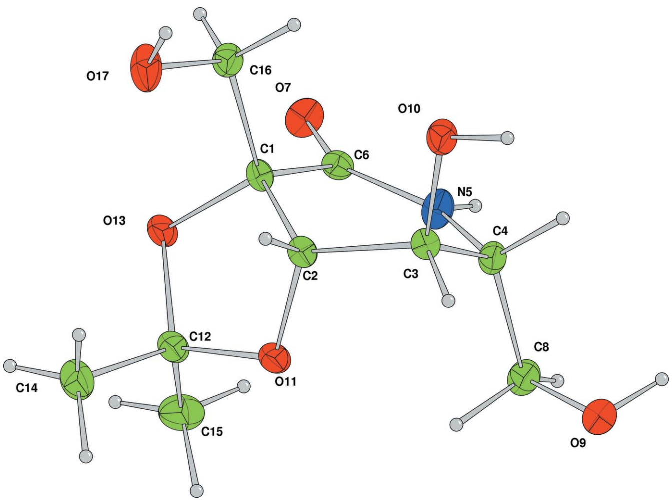

Figure 1
The molecular structure of the title compound, with displacement ellipsoids drawn at the 50% probability level. H atoms are shown as spheres of arbitrary radius.

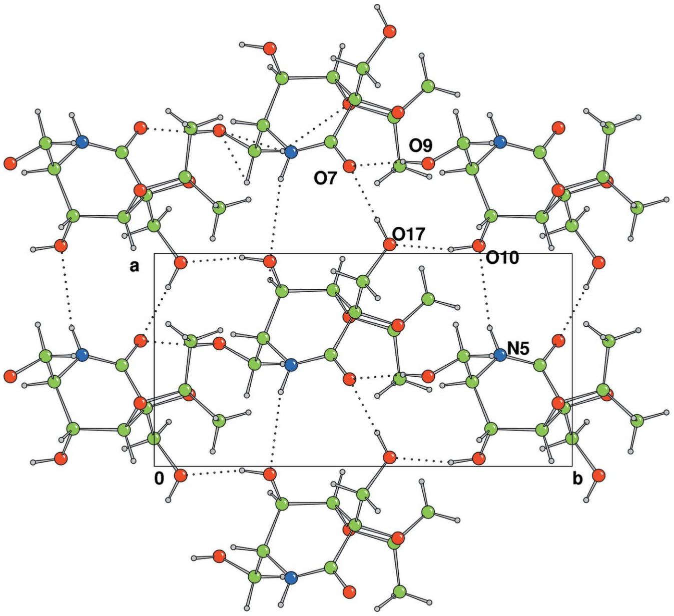

Figure 2
A sheet of molecules joined by hydrogen bonds (dashed lines), shown perpendicular to the *c* axis.

Experimental

Azidolactam (5) (1.22 g, 2.44 mmol) in 1,4-dioxane (10 ml) was hydrogenated for 5 h in the presence of palladium on carbon (10%, 260 mg). The reaction mixture was filtered and the solvent removed; the crude amine in THF (4.5 ml) was treated with tetrabutylammonium fluoride (5.37 ml, 5.3 mmol, 1 *M* solution in THF). After 12 h, the solvent was removed, the residue was dissolved in toluene (50 ml) and the reaction mixture refluxed for 6 h; the solvent was removed and the residue partitioned between dichloromethane (50 ml) and water (2 *x* 50 ml). The combined aqueous phases were evaporated to dryness and purified by flash column chromatography (15% methanol in ethyl acetate) to give the lactam (4) (472 mg, 78% over 3 steps). Crystals for the X-ray study were grown from acetonitrile; m.p. 437 K; $[\alpha]_D^{17}$+33.3 (*c*, 0.98 in MeOH); νmax (Ge plate): 3385 (O—H), 1652 (C═O) cm-1; α_H (CD_3OD, 400 MHz): 1.39, 1.41 (6H, 2 × *s*, 2 × CCH_3), 3.40 (1H, *dt*, H5, $J_{5,6b}$ 4.6 Hz, $J_{5,6a}$, $J_{5,4}$ 6.6 Hz), 3.68 (1H, *d*, H2*a*, $J_{2a,2b}$ 11.0 Hz), 3.69 (1H, *dd*, H6a, $J_{6a,6b}$ 11.3 Hz, $J_{6a,5}$ 6.1 Hz), 3.79 (1H, *d*, H2*b*, $J_{2b,2a}$ 11.0 Hz), 3.84 (1H, *dd*, H6*b*, $J_{6b,6a}$ 11.3 Hz, $J_{6b,5}$ 4.5 Hz), 3.92 (1H, *t*, H-4, $J_{4,5}$, $J_{4,3}$ 6.5 Hz), 4.39 (1H, *d*, H3, $J_{3,4}$ 5.9 Hz); δ_C (CD_3OD, 100.6 MHz): 27.5, 28.1 (2 *x* C*C*H_3), 58.1 (C5), 62.4 (C6), 65.7 (C2), 69.5 (C4), 82.6 (C3), 83.4 (C2), 111.7 (*C*(CH3)2), 173.8 (C1); *m*/*z* (ES+): 270.02 ($[M + Na]^+$, 40%), 306.11 ($[M + MeCN + NH_4]^+$, 100%); HRMS: $C_{10}H_{17}NO_6Na$ ($[M + Na]^+$) calculated 270.0948, found 270.0943.

Crystal data

$C_{10}H_{17}NO_6$
$M_r = 247.25$
Orthorhombic, $P2_12_12_1$
$a = 6.3477\ (2)$ Å
$b = 12.4398\ (3)$ Å
$c = 14.1469\ (5)$ Å
$V = 1117.10\ (6)$ Å^3

$Z = 4$
$D_x = 1.470$ Mg m^{-3}
Mo *Kα* radiation
$\mu = 0.12$ mm^{-1}
$T = 150$ K
Needle, colourless
0.60 × 0.30 × 0.20 mm

Data collection

Nonius Kappa CCD diffractometer
ω scans
Absorption correction: multi-scan (*DENZO*/*SCALEPACK*; Otwinowski & Minor, 1997)
$T_{min} = 0.761$, $T_{max} = 0.976$

6703 measured reflections
1866 independent reflections
1705 reflections with $I > 2\sigma(I)$
$R_{int} = 0.027$
$\theta_{max} = 30.0°$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.030$
$wR(F^2) = 0.075$
$S = 0.99$
1858 reflections
154 parameters
H-atom parameters constrained

$w = 1/[\sigma^2(F^2) + (0.04P)^2 + 0.2P]$
where $P = [\max(F_o^2,0) + 2F_c^2]/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.32$ e Å^{-3}
$\Delta\rho_{min} = -0.20$ e Å^{-3}

Table 1
Hydrogen-bond geometry (Å, °).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O10—H1···O17^{i}	0.84	1.91	2.7297 (14)	164
O17—H3···O7^{ii}	0.85	1.82	2.6712 (16)	176
O9—H4···O7^{iii}	0.89	2.04	2.9199 (14)	169
N5—H2···O10^{iv}	0.90	2.50	3.321 (2)	152

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

Five reflections at sin(*θ*)/λ <0.01 were eliminated as being partially obscured by the incident beam trap. Reflection 022, with $F_o = 27.3$ and $F_c = 34.6$, was manually excluded as an outlier. In the absence of significant anomalous scattering, Friedel pairs were merged and the absolute configuration assigned from the known starting material. The H atoms were all located in a difference map, but those attached to C atoms were repositioned geometrically. The H atoms were initially refined with soft restraints on the bond lengths and angles to regularize their geometry (C—H = 0.93–98, N—H = 0.86–0.89 and O—H = 0.82 Å) and isotropic displacement parameters [$U_{iso}(H) = 1.2$ or 1.5 times U_{eq}(parent atom)], after which they were refined with riding constraints.

Data collection: *COLLECT* (Nonius, 2001); cell refinement: *DENZO*/*SCALEPACK*; data reduction: *DENZO*/*SCALEPACK*

(Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *CAMERON* (Watkin *et al.*, 1996); software used to prepare material for publication: *CRYSTALS*.

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