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5-Amino-5-deoxy-2-*C*-hydroxymethyl-2,3-*O*-isopropylidene-L-lyxono-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 = 0.033
wR factor = 0.075
Data-to-parameter ratio = 10.3

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

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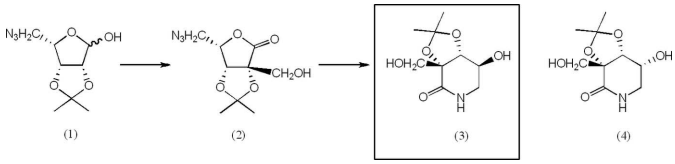
The relative configuration of the title compound, $C_9H_{14}NO_5$, formed by catalytic hydrogenation of an azidolactone, has been established by X-ray crystallographic analysis. The absolute configuration was determined by the use of 2,3-*O*-isopropylidene-L-lyxono-1,4-lactone as the carbohydrate starting material.

Comment

Carbohydrates have been extensively used as starting materials for the synthesis of important small biological molecules such as imino sugars. Imino sugars are analogues of carbohydrates in which the ring O atom is replaced by an N atom and the anomeric hydroxyl group is removed (Winchester & Fleet, 1992; Asano *et al.*, 2000). They are almost always inhibitors of the corresponding glycosidases (Bruce *et al.*, 1992) and have proved to have the potential to produce antiviral, antidiabetes and anticancer effects, as well as immune-modulatory properties (Asano *et al.*, 1994). Lactones have provided short syntheses of novel imino sugars (Asano *et al.*, 2000). Almost all of these targets have unbranched carbon chains. Recent results have indicated that analogues with carbon branches give rise to compounds with interesting biological activities (Ichikawa & Igarashi, 1995; Ichikawa *et al.*, 1998). Novel imino sugars of this kind provide an opportunity for altering and, it is hoped, increasing the specificity of inhibition of individual glycosidases, and to study further the structure–activity relationships of glycosidase inhibitors. However, the chemistry of branched sugars, and in particular that of branched sugar lactones, has remained largely unexplored. The main problem is the lack of cheaply and easily available simple derivatives of monosaccharides with a carbon branch (Bols, 1996). Efficient routes to branched sugar lactones are under investigation in our laboratory. One exploits the Ho crossed-aldol reaction (Ho, 1979, 1985; Simone *et al.*, 2005), one the Kiliani reaction on ketohexoses (Kiliani, 1886; Soengas *et al.*, 2005; Hotchkiss *et al.*, 2004, 2006), and one the Amadori rearrangement on sugars followed by treatment with calcium hydroxide (Hotchkiss *et al.*, 2006). The crossed-aldol reaction was the crucial step in the synthesis of the title powerful branched intermediate (3), stereoisomeric with (4) (Newton *et al.*, 2004). Stereochemical ambiguity may arise from the aldol reaction.

Azidolactol (1) was prepared from 2,3-*O*-isopropylidene-L-lyxono-1,4-lactone and submitted to the key aldol branching reaction. Oxidation of the aldol product with bromine water yielded branched lactone (2). Hydrogenation of (2) resulted in the initial formation of the corresponding amine, which underwent isomerization to the title lactam upon refluxing in the reaction solvent.



The X-ray crystal structure of (3) removes any ambiguity about the course of the aldol condensation and provides comparison of the solid-phase structures of (3) and (4) in order to rationalize their biological activity. The molecular structure shows no abnormal features. The largest differences from the *Mogul* norms (Bruno *et al.*, 2004) are C6—O7 (0.02 Å; *Mogul* s.u. 0.02 Å) and C2—C3—O8 (−5.4°; *Mogul* s.u. 1.9°).

The crystal structure of (3) consists of sheets of molecules lying perpendicular to the *c* axis (Fig. 2), in which the molecules are linked by short hydrogen-bonded chains (O8—H10···O5—H9···O7). Curiously, the amine atom H13 is not involved in any strong hydrogen bonds. The closest O atoms are too distant, and the N—H···O angles are too accute (Table 1) to be real hydrogen bonds.

Experimental

5-Amino-5-deoxy-2-*C*-hydroxymethyl-2,3-*O*-isopropylidene-L-lyxono-1,5-lactam, (3), was obtained upon reduction of 5-azido-2,3-*O*-isopropylidene-L-lyxono-1,4-lactone, (2), using Pd-black and hydrogen gas in refluxing toluene at low concentration (2.5 mg ml^{-1}). A 64% yield of the title compound was obtained. The compound was then crystallized *via* solvent evaporation (dichloromethane–methanol), appearing as colourless plates (m.p. 490–491 K). Analysis: $[\alpha]_D^{21}$ −14.0 (*c* 0.18 in methanol); IR (thin film, ν_{max}, cm^{-1}): 3340 (*br*, OH, NH), 1661 (*s*, CONH, six-ring lactam); ^{1}H NMR (D_2O, 400 MHz, δ, p.p.m.): 1.28, 1.34 [2 × 3H, 2 × *s*, C(CH$_3$)$_2$], 3.18 (1H, *dd*, $J_{H5,H5'}$ = 13.7 Hz, $J_{H5,H4}$ = 5.1 Hz, H5), 3.51 (1H, *dd*, $J_{H5',H5}$ = 13.6 Hz, $J_{H5',H4}$ = 3.5 Hz, H5′), 3.63 (1H, *d*, $J_{H2,H2'}$ = 12.1 Hz, H2), 3.77 (1H, *d*, $J_{H2',H2}$ = 12.1 Hz, H2′), 4.08–4.15 (1H, *m*, *J* = 4.9 Hz, J = 3.6 Hz, H4), 4.34 (1H, *d*, $J_{H3,H4}$ = 4.9 Hz, H3); ^{13}C NMR (D_2O, 100 MHz, δ, p.p.m.): 26.2, 26.9 [C(*C*H$_3$)$_2$], 43.2 (C5), 62.7 (C2′), 65.7 (C4), 77.3 (C3), 81.9 (C2), 111.5 [*C*(CH$_3$)$_2$], 172.9 (CONH).

Crystal data

$C_9H_{15}NO_5$
M_r = 217.22
Orthorhombic, $P22_12_1$
a = 6.2423 (2) Å
b = 12.0919 (4) Å
c = 14.1651 (6) Å
V = 1069.20 (7) Å^3
Z = 4
Mo *K*α radiation
μ = 0.11 mm^{-1}
T = 150 K
0.70 × 0.42 × 0.39 mm

Data collection

Nonius KappaCCD area-detector diffractometer
Absorption correction: multi-scan (*DENZO*/*SCALEPACK*; Otwinowski & Minor, 1997)
T_{min} = 0.84, T_{max} = 0.96
6832 measured reflections
1402 independent reflections
1402 reflections with $I > -3\sigma(I)$
R_{int} = 0.025

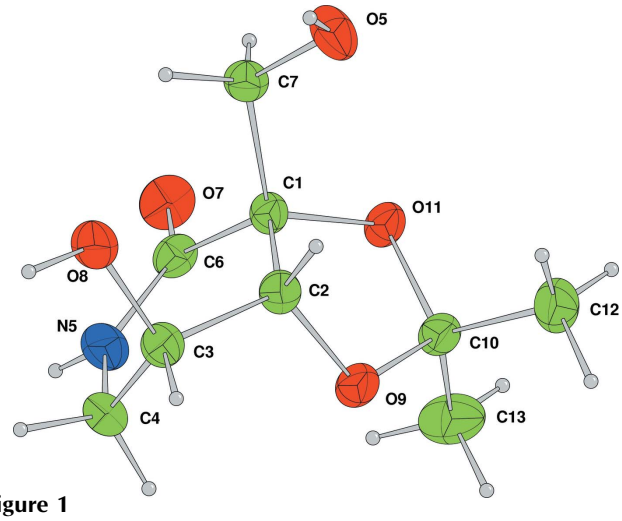


Figure 1
The molecular structure of the title compound, with displacement ellipsoids drawn at the 50% probability level. H atoms are shown as spheres of arbitary radius.

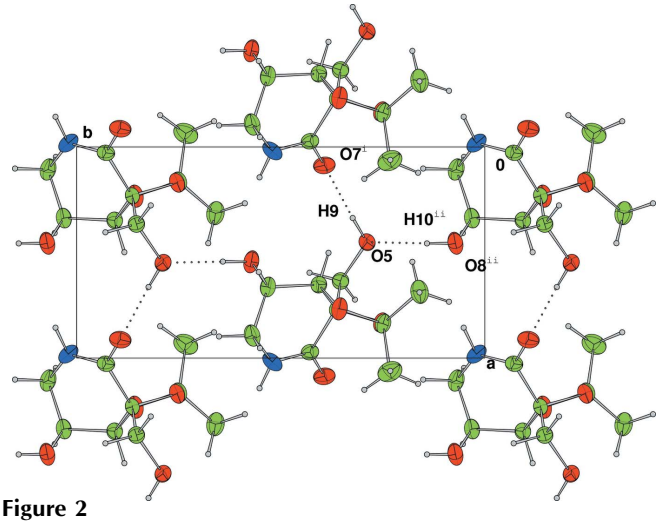


Figure 2
A packing diagram of the title compound, showing one sheet of hydrogen-bonded molecules lying parallel to the *ab* plane. Note that atom H13 (bonded to nitrogen) is not involved in any hydrogen bonds. [Symmetry codes: (i) $x-1, y, z$; (ii) $1-x, y-\frac{1}{2}, \frac{1}{2}-z$.]

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.033
$wR(F^2)$ = 0.075
S = 0.89
1402 reflections
136 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.19 e Å^{-3}
$\Delta\rho_{min}$ = −0.18 e Å^{-3}

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O5—H9···O7^{i}	0.83	1.79	2.614 (2)	170
O8—H10···O5^{ii}	0.85	1.83	2.666 (2)	170
N5—H13···O8^{iii}	0.90	2.52	3.339 (2)	153
N5—H13···O11^{iv}	0.90	2.57	3.140 (2)	122

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

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 in the range 0.93–0.98 Å, N—H = 0.86 Å and O—H = 0.82 Å) and U_{iso}(H) [in the range 1.2–1.5U_{eq}(parent)], after which the positions were refined with riding constraints. In the absence of significant anomalous scattering, Friedel pairs were merged and the absolute configuration assigned from the starting material.

Data collection: *COLLECT* (Nonius, 2001).; cell refinement: *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO*/*SCALEPACK*; 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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2-*C*-Hydroxymethyl-2,3-*O*-isopropylidene-*L*-lyxono-1,5-lactam

Crystal data

$C_9H_{15}NO_5$
$M_r = 217.22$
Orthorhombic, $P22_12_1$
Hall symbol: P 2bc 2
$a = 6.2423$ (2) Å
$b = 12.0919$ (4) Å
$c = 14.1651$ (6) Å
$V = 1069.20$ (7) Å^3
$Z = 4$
$F(000) = 464$
$D_x = 1.349$ Mg m^{-3}
Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
Cell parameters from 1345 reflections
$\theta = 5$–27°
$\mu = 0.11$ mm^{-1}
$T = 150$ K
Plate, colourless
0.70 × 0.42 × 0.39 mm

Data collection

Nonius KappaCCD area-detector diffractometer
Graphite monochromator
ω scans
Absorption correction: multi-scan (DENZO/SCALEPACK; Otwinowski & Minor, 1997)
$T_{min} = 0.84$, $T_{max} = 0.96$
6832 measured reflections
1402 independent reflections
1402 reflections with $I > -3\sigma(I)$
$R_{int} = 0.025$
$\theta_{max} = 27.5°$, $\theta_{min} = 5.3°$
$h = -8 \rightarrow 8$
$k = -15 \rightarrow 15$
$l = -18 \rightarrow 18$

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)] = 0.033$
$wR(F^2) = 0.075$
$S = 0.89$
1402 reflections
136 parameters
333 restraints
Primary atom site location: structure-invariant direct methods
Hydrogen site location: inferred from neighbouring sites
H-atom parameters constrained
$w = 1/[\sigma^2(F^2) + (0.04P)^2 + 0.18P]$, where $P = [\max(F_o^2,0) + 2F_c^2]/3$
$(\Delta/\sigma)_{max} = 0.000207$
$\Delta\rho_{max} = 0.19$ e Å^{-3}
$\Delta\rho_{min} = -0.18$ e Å^{-3}

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
C1	0.7689 (2)	0.36364 (11)	0.24059 (9)	0.0218
C2	0.6527 (2)	0.40678 (11)	0.15372 (9)	0.0244
C3	0.6634 (3)	0.53128 (11)	0.14364 (10)	0.0284
C4	0.8936 (3)	0.56994 (12)	0.14233 (11)	0.0328

N5	1.0184 (2)	0.52029 (11)	0.21867 (9)	0.0328
O5	0.45119 (17)	0.28841 (8)	0.31454 (8)	0.0361
C6	0.9726 (2)	0.42833 (12)	0.26584 (10)	0.0255
O7	1.08682 (17)	0.39314 (9)	0.33104 (8)	0.0350
C7	0.6349 (2)	0.35344 (11)	0.33024 (9)	0.0258
O8	0.5438 (2)	0.57202 (8)	0.22163 (8)	0.0356
O9	0.76720 (18)	0.35597 (8)	0.07790 (6)	0.0302
H9	0.3364	0.3237	0.3128	0.0543*
C10	0.8366 (3)	0.24932 (11)	0.10950 (9)	0.0261
H10	0.5431	0.6419	0.2170	0.0535*
O11	0.83058 (18)	0.25414 (7)	0.21157 (6)	0.0257
C12	0.6863 (3)	0.15998 (12)	0.07612 (11)	0.0373
C13	1.0646 (3)	0.23253 (17)	0.07736 (12)	0.0455
H13	1.1436	0.5518	0.2340	0.0405*
H21	0.5013	0.3829	0.1550	0.0275*
H31	0.5925	0.5537	0.0843	0.0326*
H41	0.8977	0.6510	0.1529	0.0380*
H42	0.9530	0.5510	0.0810	0.0385*
H71	0.7231	0.3183	0.3774	0.0312*
H72	0.5957	0.4294	0.3497	0.0305*
H121	0.7335	0.0879	0.0991	0.0556*
H122	0.5442	0.1776	0.0960	0.0557*
H123	0.6891	0.1601	0.0064	0.0552*
H131	1.1219	0.1634	0.1012	0.0681*
H132	1.1507	0.2953	0.0976	0.0675*
H133	1.0609	0.2316	0.0098	0.0676*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C1	0.0241 (6)	0.0184 (6)	0.0228 (6)	0.0020 (5)	−0.0001 (5)	−0.0004 (5)
C2	0.0260 (6)	0.0234 (6)	0.0236 (6)	0.0005 (5)	−0.0023 (6)	0.0001 (5)
C3	0.0370 (7)	0.0219 (6)	0.0262 (6)	0.0029 (6)	0.0007 (6)	0.0020 (5)
C4	0.0431 (8)	0.0240 (7)	0.0313 (7)	−0.0056 (6)	0.0064 (7)	0.0027 (6)
N5	0.0308 (6)	0.0351 (7)	0.0327 (6)	−0.0131 (5)	0.0000 (6)	−0.0006 (5)
O5	0.0266 (5)	0.0245 (5)	0.0571 (7)	−0.0020 (4)	0.0105 (5)	−0.0005 (5)
C6	0.0229 (6)	0.0293 (7)	0.0243 (6)	0.0018 (5)	0.0012 (5)	−0.0035 (5)
O7	0.0266 (5)	0.0441 (6)	0.0344 (5)	0.0025 (5)	−0.0067 (5)	−0.0009 (5)
C7	0.0258 (6)	0.0253 (7)	0.0263 (6)	0.0003 (5)	0.0035 (6)	0.0011 (6)
O8	0.0463 (6)	0.0219 (5)	0.0388 (6)	0.0050 (5)	0.0107 (5)	0.0018 (4)
O9	0.0462 (6)	0.0235 (5)	0.0209 (4)	0.0041 (5)	0.0009 (5)	0.0007 (4)
C10	0.0341 (7)	0.0227 (6)	0.0215 (6)	0.0043 (6)	0.0015 (6)	0.0000 (5)
O11	0.0341 (5)	0.0213 (4)	0.0216 (4)	0.0063 (4)	−0.0013 (4)	−0.0010 (3)
C12	0.0511 (9)	0.0295 (7)	0.0313 (7)	−0.0039 (7)	−0.0065 (8)	−0.0023 (6)
C13	0.0388 (8)	0.0545 (10)	0.0432 (9)	0.0095 (9)	0.0132 (8)	0.0041 (8)

Geometric parameters (Å, º)

C1—C2	1.5205 (17)	O5—H9	0.834
C1—C6	1.5355 (19)	C6—O7	1.2418 (17)
C1—C7	1.5257 (18)	C7—H71	0.964
C1—O11	1.4390 (16)	C7—H72	0.990
C2—C3	1.5137 (19)	O8—H10	0.847
C2—O9	1.4289 (16)	O9—C10	1.4322 (16)
C2—H21	0.989	C10—O11	1.4474 (16)
C3—C4	1.512 (2)	C10—C12	1.507 (2)
C3—O8	1.4211 (18)	C10—C13	1.508 (2)
C3—H31	0.988	C12—H121	0.976
C4—N5	1.462 (2)	C12—H122	0.955
C4—H41	0.992	C12—H123	0.988
C4—H42	0.972	C13—H131	0.970
N5—C6	1.3285 (19)	C13—H132	0.973
N5—H13	0.896	C13—H133	0.958
O5—C7	1.4079 (17)		
C2—C1—C6	114.13 (11)	C1—C6—O7	118.31 (12)
C2—C1—C7	116.11 (11)	N5—C6—O7	122.51 (13)
C6—C1—C7	107.55 (10)	C1—C7—O5	111.11 (11)
C2—C1—O11	102.24 (10)	C1—C7—H71	107.4
C6—C1—O11	108.27 (11)	O5—C7—H71	109.2
C7—C1—O11	108.07 (10)	C1—C7—H72	107.0
C1—C2—C3	113.36 (11)	O5—C7—H72	111.2
C1—C2—O9	102.85 (10)	H71—C7—H72	111.0
C3—C2—O9	109.56 (11)	C3—O8—H10	106.8
C1—C2—H21	110.0	C2—O9—C10	107.67 (10)
C3—C2—H21	109.5	O9—C10—O11	105.55 (10)
O9—C2—H21	111.5	O9—C10—C12	111.04 (12)
C2—C3—C4	110.52 (13)	O11—C10—C12	109.02 (12)
C2—C3—O8	104.39 (11)	O9—C10—C13	108.21 (13)
C4—C3—O8	113.68 (12)	O11—C10—C13	109.37 (13)
C2—C3—H31	109.5	C12—C10—C13	113.35 (13)
C4—C3—H31	109.3	C10—O11—C1	109.23 (9)
O8—C3—H31	109.3	C10—C12—H121	110.3
C3—C4—N5	111.75 (12)	C10—C12—H122	109.0
C3—C4—H41	109.2	H121—C12—H122	112.4
N5—C4—H41	106.3	C10—C12—H123	107.6
C3—C4—H42	107.5	H121—C12—H123	109.2
N5—C4—H42	111.2	H122—C12—H123	108.1
H41—C4—H42	111.0	C10—C13—H131	111.0
C4—N5—C6	126.96 (12)	C10—C13—H132	109.1
C4—N5—H13	118.0	H131—C13—H132	111.5
C6—N5—H13	115.0	C10—C13—H133	106.3
C7—O5—H9	114.7	H131—C13—H133	110.3
C1—C6—N5	119.17 (12)	H132—C13—H133	108.5

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
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