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(6*S*)-Methyl-L-swainsonine [(1*R*,2*S*,6*S*,8*S*,8a*S*)-6-methyloctahydroindolizine-1,2,8-triol]

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Key indicators

Single-crystal X-ray study
T = 190 K
Mean σ(C–C) = 0.003 Å
R factor = 0.028
wR factor = 0.069
Data-to-parameter ratio = 8.6

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

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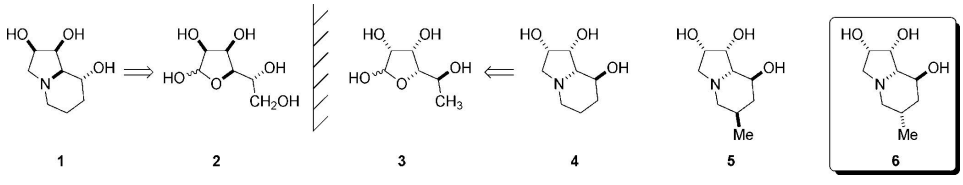
(6*S*)-Methyl-L-swainsonine, $C_9H_{17}NO_3$, together with the 6*R*-epimer, was formed in a synthetic sequence in which there was an ambiguity in configuration at position C-6. This ambiguity was resolved by establishing the relative stereochemistry of the title compound by X-ray crystallographic analysis. The absolute configuration was determined by the use of D-*glycero*-D-*gulo*-heptono-1,4-lactone as the starting material.

Comment

Imino sugars, in which the ring oxygen of a sugar is replaced, are a class of glycosidase inhibitor with a range of chemotherapeutic targets (Watson *et al.*, 2001; Asano *et al.*, 2000). D-Swainsonine (1), a natural product isolated from *Swainsona canescens* (Colegate *et al.*, 1979), is a mimic of D-mannofuranose (2) and a powerful α-mannosidase inhibitor. Potential use of 1 for the chemotherapy of cancer (Lagana *et al.*, 2006; Klein *et al.*, 1999; Goss *et al.*, 1997) has led to the publication of over 40 syntheses (Au & Pyne, 2006; Ceccon *et al.*, 2006; Martin *et al.*, 2005; Heimgaertner *et al.*, 2005; Nemr, 2000). L-Swainsonine (4), the enantiomer of the natural product (1), is the corresponding imino sugar mimic of L-rhamnofuranose (3) and is a potent inhibitor of naringinase – an α-rhamnosidase (Davis *et al.*, 1996). Very few syntheses of 4, with different therapeutic targets, have been reported (Guo & O'Doherty, 2006; Oishi *et al.*, 1995). No carbon-branched swainsonine analogues have been described. In order to determine how such a substitution changes the structure of the swainsonine nucleus, the C6-methyl analogues (5) and (6) were prepared (Håkansson *et al.*, 2007); in order to firmly establish the relative configuration at C6 of the two epimers, X-ray crystallographic analysis of (6) is reported in this paper. The absolute configuration of (6*S*)-methyl-L-swainsonine (6) was determined by the use of D-*glycero*-D-*gulo*-heptono-1,4-lactone as the starting material.



1 2 3 4 5 6

The molecular structure of (6) (Fig. 1) shows no unusual features. The largest differences from the *MOGUL* norms (Bruno *et al.*, 2004) are C5—O6 (0.01 Å) and C11—C10—C1 (2.9°). As is normal in sugar derivatives, all the hydroxyl groups are involved in hydrogen bonding. Each molecule takes part in two different hydrogen-bonded helices (Fig. 2

and Table 1). The helix around ($\frac{1}{3}$, $\frac{2}{3}$, z) only involves O12; that at ($\frac{2}{3}$, $\frac{1}{3}$, z) involves both O7 and N2. The fact that each molecule is involved in two helices leads to a very rigid framework and explains the high melting point (422 K).

Experimental

(6*S*)-Methyl-L-swainsonine (6) (Håkansson *et al.*, 2007) was purified by Dowex 50WX8–200 ion exchange resin (H^+ form, eluent 2 *M* aqueous ammonia) and recrystallized from ethyl acetate and cyclohexane to yield fine colourless brittle needles (m.p. 421–423 K). $[\alpha]_D^{21}$ = +43.7 (c = 1.72, H_2O).

Crystal data

$C_9H_{17}NO_3$
M_r = 187.24
Trigonal, $P3_1$
a = 11.4494 (6) Å
c = 6.1727 (2) Å
V = 700.76 (6) Å^3
Z = 3
D_x = 1.331 Mg m^{-3}
Mo $K\alpha$ radiation
μ = 0.10 mm^{-1}
T = 190 K
Needle, colourless
0.80 × 0.10 × 0.10 mm

Data collection

Nonius KappaCCD diffractometer
ω scans
Absorption correction: multi-scan (*DENZO*/*SCALEPACK*; Otwinowski & Minor, 1997)
T_{min} = 0.81, T_{max} = 0.99
6022 measured reflections
1025 independent reflections
982 reflections with $I > 2\sigma(I)$
R_{int} = 0.044
θ_{max} = 27.1°

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.028
$wR(F^2)$ = 0.069
S = 0.97
1020 reflections
118 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F^2) + (0.04P)^2 + 0.1P]$, where $P = [\max(F_o^2,0) + 2F_c^2]/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.17 e Å^{-3}
$\Delta\rho_{min}$ = −0.12 e Å^{-3}

Table 1
Selected bond angles (°).

N2—C8—C9	110.76 (14)	C9—C10—C11	113.00 (14)
C8—C9—C10	109.86 (15)	C10—C11—C1	109.68 (13)
C8—C9—C13	112.68 (16)	C10—C11—O12	110.95 (13)
C10—C9—C13	112.04 (15)	C1—C11—O12	110.92 (13)

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

D—H···A	D—H	H···A	D···A	D—H···A
O12—H3···O12^{i}	0.85	1.88	2.708 (2)	165
O6—H5···O7	0.82	1.93	2.541 (2)	131
O7—H1···N2^{ii}	0.87	1.99	2.846 (2)	167

Symmetry codes: (i) $-y+1, x-y+1, z+\frac{1}{3}$; (ii) $-y+1, x-y, z+\frac{1}{3}$.

In the absence of significant anomalous scattering, Friedel pairs were merged and the absolute configuration assigned from the starting material.

The sample consisted of fine brittle plates which could not be cut without being destroyed. The relatively large ratio of minimum to maximum corrections applied in the multiscan process (1:1.22) reflects changes in the illuminated volume of the crystal. The changes in illuminated volume were kept to a minimum, and were taken into account (Görbitz, 1999) by the multi-scan inter-frame scaling (*DENZO*/*SCALEPACK*; Otwinowski & Minor, 1997).

The H atoms were all located in a difference map, but those attached to carbon 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, O—H = 0.82 Å) and U_{iso}(H) (in the range 1.2–1.5 times U_{eq} of the parent atom), after which the positions were refined with riding constraints.

Data collection: *COLLECT* (Nonius, 2001); cell refinement: *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO*/*SCALEPACK*; program(s) used to solve structure: user defined structure solution: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*,

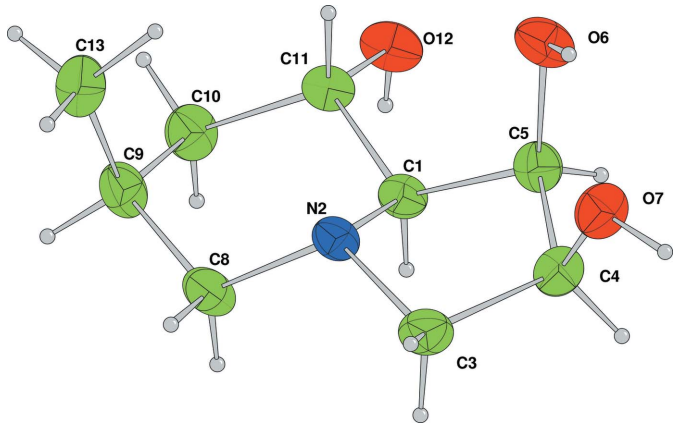


Figure 1
The molecular structure of 6, with displacement ellipsoids drawn at the 50% probability level. H atoms are shown as spheres of arbitrary radius.

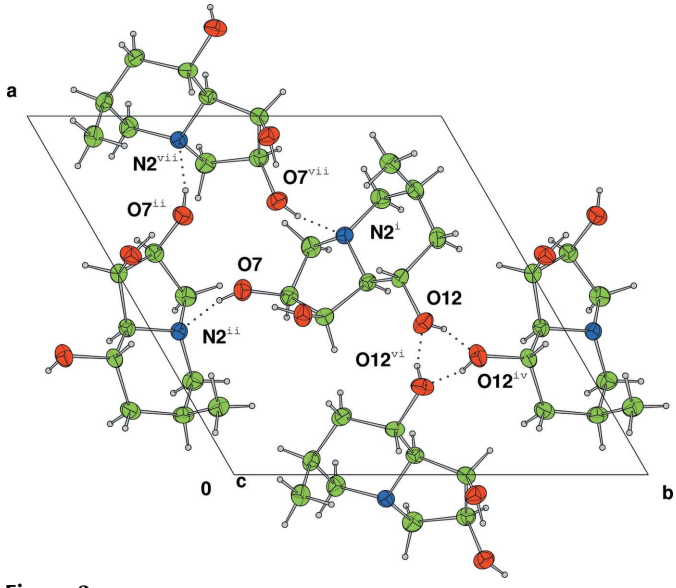


Figure 2
Part of the crystal structure of 6, with hydrogen bonds shown as dotted lines. Each molecule contributes to two helices. That at ($\frac{1}{3}$, $\frac{2}{3}$, z) only involves O12; that at ($\frac{2}{3}$, $\frac{1}{3}$, z) involves both O7 and N2. [Symmetry codes: (i) $x, y, z-1$; (ii) $-y+1, x-y, z-\frac{2}{3}$; (iv) $-y+1, x-y+1, z-\frac{2}{3}$; (vi) $-x+y, -x+1, z-\frac{1}{3}$; (vii) $-x+y+1, -x+1, z-\frac{1}{3}$.]

2003); molecular graphics: *CAMERON* (Watkin *et al.*, 1996); software used to prepare material for publication: *CRYSTALS*.

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(1*R*,2S,6*S*,8S,8aS)-6-methyloctahydroindolizine-1,2,8-triol

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$C_9H_{17}NO_3$
$M_r = 187.24$
Trigonal, $P3_1$
Hall symbol: P 31
$a = 11.4494$ (6) Å
$c = 6.1727$ (2) Å
$V = 700.76$ (6) Å^3
$Z = 3$
$F(000) = 306$
$D_x = 1.331$ Mg m^{-3}
Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
Cell parameters from 1020 reflections
$\theta = 1$–27°
$\mu = 0.10$ mm^{-1}
$T = 190$ K
Plate, colourless
0.80 × 0.10 × 0.10 mm

Data collection

Nonius KappaCCD diffractometer
Graphite monochromator
ω scans
Absorption correction: multi-scan (DENZO/SCALEPACK; Otwinowski & Minor, 1997)
$T_{min} = 0.81$, $T_{max} = 0.99$
6022 measured reflections
1025 independent reflections
982 reflections with $I > 2\sigma(I)$
$R_{int} = 0.044$
$\theta_{max} = 27.1°$, $\theta_{min} = 2.1°$
$h = -14\rightarrow14$
$k = -12\rightarrow12$
$l = -7\rightarrow7$

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)] = 0.028$
$wR(F^2) = 0.069$
$S = 0.97$
1020 reflections
118 parameters
35 restraints
Primary atom site location: structure-invariant direct methods
Hydrogen site location: inferred from neighbouring sites
H-atom parameters constrained
$w = 1/[\sigma^2(F^2) + (0.04P)^2 + 0.1P]$, where $P = [\max(F_o^2,0) + 2F_c^2]/3$
$(\Delta/\sigma)_{max} = 0.000219$
$\Delta\rho_{max} = 0.17$ e Å^{-3}
$\Delta\rho_{min} = -0.12$ e Å^{-3}

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

	x	*y*	*z*	U_{iso}*/U_{eq}
C1	0.53634 (17)	0.59057 (16)	0.8235 (3)	0.0242
N2	0.66713 (13)	0.60020 (14)	0.8706 (2)	0.0241
C3	0.63458 (18)	0.50300 (18)	1.0487 (3)	0.0310

C4	0.49845 (18)	0.38209 (17)	0.9851 (3)	0.0282
C5	0.44047 (17)	0.43864 (18)	0.8097 (3)	0.0273
O6	0.44492 (14)	0.38857 (13)	0.6023 (2)	0.0336
O7	0.51498 (14)	0.27798 (13)	0.8919 (2)	0.0322
C8	0.76987 (19)	0.73864 (18)	0.9248 (3)	0.0317
C9	0.79406 (18)	0.83322 (17)	0.7343 (3)	0.0321
C10	0.65986 (19)	0.82114 (17)	0.6624 (3)	0.0318
C11	0.54856 (16)	0.67521 (16)	0.6254 (3)	0.0251
O12	0.42283 (13)	0.66811 (14)	0.5784 (2)	0.0328
C13	0.86788 (19)	0.8108 (2)	0.5457 (3)	0.0366
H11	0.5121	0.6267	0.9485	0.0292*
H31	0.6278	0.5418	1.1870	0.0378*
H32	0.7014	0.4729	1.0604	0.0364*
H41	0.4386	0.3464	1.1114	0.0336*
H51	0.3485	0.4162	0.8438	0.0326*
H81	0.8522	0.7397	0.9658	0.0365*
H82	0.7392	0.7723	1.0503	0.0356*
H91	0.8513	0.9241	0.7916	0.0356*
H101	0.6293	0.8580	0.7800	0.0391*
H102	0.6720	0.8705	0.5290	0.0394*
H111	0.5694	0.6355	0.4976	0.0293*
H131	0.8958	0.8827	0.4416	0.0520*
H132	0.9472	0.8081	0.5970	0.0527*
H133	0.8066	0.7237	0.4744	0.0519*
H3	0.4063	0.7096	0.6762	0.0529*
H5	0.4670	0.3317	0.6258	0.0520*
H1	0.4862	0.2075	0.9762	0.0503*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C1	0.0250 (8)	0.0264 (8)	0.0237 (7)	0.0148 (6)	−0.0011 (6)	−0.0034 (6)
N2	0.0236 (7)	0.0251 (7)	0.0241 (7)	0.0126 (6)	−0.0047 (5)	−0.0019 (5)
C3	0.0364 (9)	0.0319 (9)	0.0255 (9)	0.0178 (8)	−0.0056 (7)	0.0014 (6)
C4	0.0305 (9)	0.0283 (8)	0.0276 (8)	0.0161 (7)	0.0032 (6)	0.0027 (7)
C5	0.0240 (8)	0.0287 (8)	0.0302 (8)	0.0141 (7)	−0.0010 (6)	0.0002 (6)
O6	0.0418 (7)	0.0304 (7)	0.0324 (6)	0.0210 (6)	−0.0098 (5)	−0.0078 (5)
O7	0.0368 (7)	0.0288 (6)	0.0345 (7)	0.0190 (6)	0.0037 (5)	0.0036 (5)
C8	0.0324 (9)	0.0291 (9)	0.0303 (8)	0.0130 (8)	−0.0088 (7)	−0.0065 (7)
C9	0.0321 (9)	0.0221 (8)	0.0379 (10)	0.0105 (7)	−0.0043 (7)	−0.0031 (7)
C10	0.0360 (10)	0.0253 (8)	0.0369 (10)	0.0174 (8)	−0.0012 (7)	0.0004 (7)
C11	0.0277 (8)	0.0287 (8)	0.0248 (8)	0.0185 (7)	−0.0026 (6)	−0.0029 (6)
O12	0.0348 (7)	0.0411 (7)	0.0318 (6)	0.0260 (6)	−0.0070 (5)	−0.0069 (5)
C13	0.0318 (9)	0.0309 (9)	0.0433 (10)	0.0127 (8)	0.0020 (8)	0.0045 (8)

Geometric parameters (Å, º)

C1—N2	1.474 (2)	C8—C9	1.527 (3)
C1—C5	1.526 (2)	C8—H81	0.971
C1—C11	1.523 (2)	C8—H82	1.004
C1—H11	0.979	C9—C10	1.538 (3)
N2—C3	1.474 (2)	C9—C13	1.534 (3)
N2—C8	1.464 (2)	C9—H91	0.978
C3—C4	1.530 (2)	C10—C11	1.529 (2)
C3—H31	0.983	C10—H101	0.988
C3—H32	0.986	C10—H102	0.968
C4—C5	1.569 (2)	C11—O12	1.430 (2)
C4—O7	1.419 (2)	C11—H111	0.997
C4—H41	0.982	O12—H3	0.845
C5—O6	1.414 (2)	C13—H131	0.964
C5—H51	0.974	C13—H132	0.977
O6—H5	0.821	C13—H133	0.990
O7—H1	0.875		
N2—C1—C5	102.77 (12)	N2—C8—H81	108.8
N2—C1—C11	110.11 (13)	C9—C8—H81	111.2
C5—C1—C11	117.74 (14)	N2—C8—H82	110.3
N2—C1—H11	107.8	C9—C8—H82	107.2
C5—C1—H11	109.4	H81—C8—H82	108.6
C11—C1—H11	108.6	C8—C9—C10	109.86 (15)
C1—N2—C3	103.09 (13)	C8—C9—C13	112.68 (16)
C1—N2—C8	111.23 (13)	C10—C9—C13	112.04 (15)
C3—N2—C8	114.20 (13)	C8—C9—H91	105.3
N2—C3—C4	104.51 (13)	C10—C9—H91	108.0
N2—C3—H31	110.8	C13—C9—H91	108.7
C4—C3—H31	110.9	C9—C10—C11	113.00 (14)
N2—C3—H32	111.8	C9—C10—H101	107.5
C4—C3—H32	108.6	C11—C10—H101	107.3
H31—C3—H32	110.1	C9—C10—H102	110.4
C3—C4—C5	104.67 (13)	C11—C10—H102	108.0
C3—C4—O7	111.13 (15)	H101—C10—H102	110.7
C5—C4—O7	109.17 (14)	C10—C11—C1	109.68 (13)
C3—C4—H41	110.9	C10—C11—O12	110.95 (13)
C5—C4—H41	111.6	C1—C11—O12	110.92 (13)
O7—C4—H41	109.3	C10—C11—H111	110.9
C1—C5—C4	102.73 (13)	C1—C11—H111	108.2
C1—C5—O6	111.19 (14)	O12—C11—H111	106.1
C4—C5—O6	110.44 (13)	C11—O12—H3	108.9
C1—C5—H51	110.8	C9—C13—H131	109.7
C4—C5—H51	111.5	C9—C13—H132	111.0
O6—C5—H51	110.0	H131—C13—H132	109.1
C5—O6—H5	104.4	C9—C13—H133	109.5
C4—O7—H1	112.8	H131—C13—H133	109.2

N2—C8—C9	110.76 (14)	H132—C13—H133	108.3

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O12—H3···O12^{i}	0.85	1.88	2.708 (2)	165
O6—H5···O7	0.82	1.93	2.541 (2)	131
O7—H1···N2^{ii}	0.87	1.99	2.846 (2)	167

Symmetry codes: (i) $-y+1, x-y+1, z+1/3$; (ii) $-y+1, x-y, z+1/3$.