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Note

Determination of the structures of four new isomeric cyclitols

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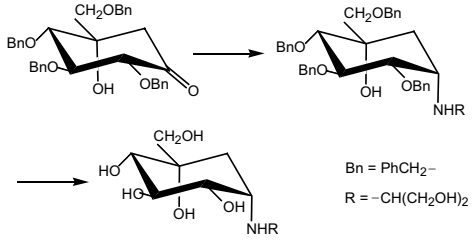
Abstract—A series of impurities, which were all of the same molecular formula, $C_{17}H_{33}NO_7$, were obtained in the process of voglibose synthesis. After isolation and purification, four isomeric cyclitols were completely assigned by 2D NMR experiments. One of the compounds was established by single-crystal X-ray diffraction analysis as 5,6-dideoxy-5-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-1-*C*-(methoxycyclohexylmethyl)-D-*epi*-inositol.

Keywords: 2D NMR; HMBC; Voglibose; Cyclitols

Voglibose, 5,6-didexoy-5-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-1-*C*-(hydroxymethyl)-D-*epi*-inositol, has attracted considerable interest due to its wide range of therapeutic and pharmacological properties, which include its excellent inhibitory activity against α-glucosidase and its action against hyperglycemia and various disorders caused by hyperglycemia.[1–3] Voglibose has shown strong anti-obesity and anti-diabetic activity as it is a new, potent glucosidase inhibitor and is a drug used for type 2 diabetes in Japan and China.[4–10] Therefore, synthesis and analysis of this compound is of considerable interest.[11–13] Four new compounds, which arose as impurities in the synthesis of the target compound were obtained (see Scheme 1), and their structures were determined by 2D NMR experiments, and one of them was confirmed by single-crystal X-ray diffraction studies as 5,6-dideoxy-5-{[2-hydroxy-1-(hydroxymethyl)ethyl]-amino}-1-*C*-(methoxycyclohexylmethyl)-D-*epi*-inositol (**2**).

The structure of voglibose had previously been confirmed by NMR data as shown in Figure 1 and in Tables 1–3. By comparing the ^{13}C NMR chemical shift of voglibose with compound **2**, we found only that C-10 was deshielded from δ 65.19 (voglibose) to δ 74.28 (compound **2**), and the other signals were very similar in



Scheme 1. Synthetic route to voglibose.

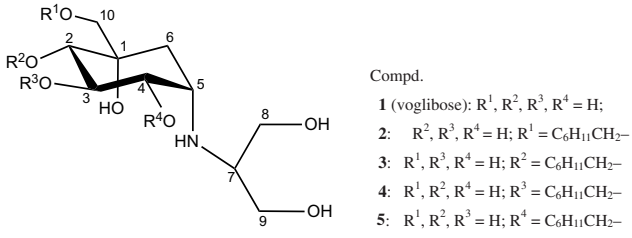


Figure 1. Structure of voglibose and byproducts of its synthesis.

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Table 1. ^{1}H NMR spectral data for voglibose and compounds (**2**–**5**)

	Voglibose (**1**)	**2**	**3**	**4**	**5**
1	—	—	—	—	—
2	3.25 (1H)	3.56 (1H)	3.18 (1H)	3.38 (1H)	3.37 (1H)
3	3.67 (1H)	3.76 (1H)	3.89 (1H)	3.64 (1H)	3.86 (1H)
4	3.56 (1H)	3.62 (1H)	3.62 (1H)	3.74 (1H)	3.36 (1H)
5	3.23 (1H)	3.32 (1H)	3.35 (1H)	3.37 (1H)	3.55 (1H)
6	a. 1.36 (1H)	a. 1.48 (1H)	a. 1.51 (1H)	a. 1.48 (1H)	a. 1.39 (1H)
	b. 1.89 (1H)	b. 2.00 (1H)	b. 1.96 (1H)	b. 2.01 (1H)	b. 2.00 (1H)
7	2.70 (1H)	2.82 (1H)	2.85 (1H)	2.88 (1H)	2.86 (1H)
8	3.48 (2H)	3.60 (2H)	3.57 (2H)	3.68 (2H)	3.68 (2H)
9	3.51 (2H)	3.61 (2H)	3.61 (2H)	3.71 (2H)	3.71 (2H)
10	3.35 (2H)	3.39 (2H)	3.46 (2H)	3.47 (2H)	3.54 (2H)
11		3.29 (2H)	3.38 (1H)	3.61 (2H)	3.35 (1H)
			3.62 (1H)		3.43 (1H)
12		1.57 (1H)	1.64 (1H)	1.63 (1H)	1.67 (1H)
13		0.86 (1H)	0.95 (1H)	0.94 (1H)	0.95 (1H)
		1.67 (1H)	1.78 (1H)	1.75 (1H)	1.78 (1H)
14		1.19 (1H)	1.24 (1H)	1.25 (1H)	1.24 (1H)
		1.67 (1H)	1.69 (1H)	1.68 (1H)	1.69 (1H)
15		1.12 (1H)	1.18 (1H)	1.17 (1H)	1.24 (1H)
		1.59 (1H)	1.66 (1H)	1.63 (1H)	1.69 (1H)
16		1.19 (1H)	1.24 (1H)	1.25 (1H)	1.24 (1H)
		1.67 (1H)	1.69 (1H)	1.68 (1H)	1.69 (1H)
17		0.86 (1H)	0.95 (1H)	0.94 (1H)	0.95 (1H)
		1.68 (1H)	1.78 (1H)	1.75 (1H)	1.78 (1H)

Table 2. ^{13}C NMR spectral data for voglibose and compounds (**2**–**5**)

	Voglibose (**1**)	**2**	**3**	**4**	**5**
1	76.28	76.18	77.20	76.54	76.21
2	74.10	74.78	82.50	73.49	74.26
3	72.07	72.28	72.31	81.02	71.48
4	73.16	73.31	73.30	72.43	81.62
5	54.46	54.89	54.48	54.97	50.67
6	29.34	29.27	29.73	29.17	29.00
7	56.51	56.98	56.71	56.78	56.47
8	62.25	62.41	62.24	62.02	62.34
9	58.51	58.93	58.62	58.40	59.13
10	65.19	74.28	65.02	65.17	65.17
11		78.17	80.24	78.98	75.79
12		37.41	38.22	38.14	37.77
13		29.79	29.99	29.90	29.65
14		25.64	25.66	25.62	25.58
15		26.48	26.45	26.45	26.42
16		25.64	25.67	25.62	25.58
17		29.79	30.17	29.90	29.65

Table 3. The differences of voglibose (**1**) and compounds (**2**–**4**) in their HMBC (carbon) spectral data

	Voglibose (**1**)	**2**	**3**	**4**	**5**
1	6b,10	6b,10	6b,10	2,6b,10	2,6b,10
2	3,6b,10	3,6b,10	3,6b,10,11	6b,10	3,6b,10
3	2	2	2,4	2,4,11	2,4,5
4	2,3,6b	2,3,6b	3,6b	6b	3,6b,11
5	6a,6b	6a,6b	6b	6a,6b	6b
10	2	2,6,11	2	2	2
11		10	2	3	4

chemical shift (Tables 1–3). These results suggest that in the voglibose structure only the –OH group at C-10 is changed into an –OR group as in compound **2**. The ^{1}H–^{1}H COSY spectrum showed connectivities from H-11 to H-17, and carbon connectivities from C-11 to C-17, revealing the fact that part of the R-group of compound **2** was a cyclohexylmethyl constituent.

The HMBC spectral data of compound **2** showed that the carbon signal at δ 78.17 (C-11) correlated with the proton signal at δ 3.39 (s), which connected with the carbon signal at δ 74.28 (C-10) in the HMQC data and showed cross-peaks with the carbon signals at δ 76.18 (C-1), at δ 74.78 (C-2) and at δ 29.27 (C-6). The structure of compound **2** was thus confirmed, as the hydroxyl H aligned with C-10 that was replaced by the cyclohexylmethyl group in the voglibose framework (Fig. 1). Thus **2** is determined to be 5,6-dideoxy-5-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-1-*C*-(methoxycyclohexylmethyl)-D-*epi*-inositol. The structure was confirmed by the 2D-NMR spectral data shown in Table 2.

A summary of the crystal data, data collection parameters and refinement results is given in Table 4. As shown in Figure 2, the molecular structure of compound **2** contains two six-membered rings. Both ring A (from C-1 to C-6) and ring B (from C-12 to C-18) adopt chair conformations. The unit –C-10–O-5–C-11–(C-12–C-17) connected with C-1 by the way of an equatorial bond, and the angles of O-1–C-1–C-10 show 108.70(13)°, C-10–C-1–C-6 show 112.06(12)° and C-10–C-1–C-2 show 106.90(12)°. The C-10–O-5–C-11 was like a bridge that aligned with ring A and ring B. The 2-hydroxy-1-[(hydroxymethyl)ethyl]amino group aligned with C-5 by the way of an axial bond, and the angles of C-7–N–C-5

Table 4. Crystal data, data collection parameters and refinement results for compound **2**

$C_{17}H_{33}NO_7$	Chunk, colorless
$M = 363.44$	$0.56 \times 0.50 \times 0.20$ mm
Monoclinic, $P2_1$	$Z = 2$
$a = 4.437(2)$ Å	$T = 296(2)$ K
$b = 6.853(1)$ Å	$\lambda = 0.71073$ Å (MoKα)
$c = 16.011(3)$ Å	$\mu = 0.10\,mm^{-1}$
$\beta = 94.88°$	$Dx = 1.309\,Mg\,m^{-3}$
$V = 922.4(3)$ Å^3	$1.28 < \theta < /28.74°$
4872 measured reflections	ω scans
4057 unique reflections	$-10 \leqslant h \leqslant 11$
3397 with $I > 2\sigma(I)$	$-8 \leqslant k \leqslant 9$
$F(000) = 396$	$-21 \leqslant l \leqslant 21$
3 standard reflections	Every 97 reflections
Intensity decay: 2.5%	4057 data
Refinement on F^2	306 parameters
$R[F^2 > 2(F^2)] = 0.036$	$w = 1/[\sigma^2(F_o^2) + (0.0556P)^2]$
$wR(F^2) = 0.088$	Where $P = (F_o^2 + 2F_c^2)/3$
$\Delta\rho_{max} = 0.21\,e\,Å^{-3}$	Extinction coefficient 0.016(3)
$\Delta\rho_{min} = -0.13\,e\,Å^{-3}$	$S = 0.97$

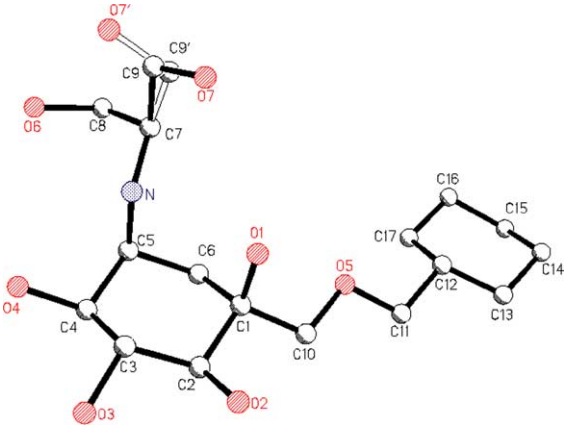

Figure 2. SHELXTL-Plus is drawing of the molecule showing atom numbering. Displacement ellipsoids are drawn at the 50% probability level.

show 115.16(11)°, N–C-5–C-4, 108.97(11)° and N–C-5–C-6, 110.88(13)°. There was disorder in the C-9 atoms distributed over two sites with a distribution ratio of approximately 50:50.

The H-atom on the NH group was refined freely. The hydroxyl H-atoms were located in difference Fourier syntheses but were treated as riding, together with all the other H-atoms, with O–H = 0.82 and C–H = 0.97 ± 0.98 and $U_{iso} = 1.2U_{eq}$ or $1.5U_{eq}$ of the carrier atom. Intermolecular hydrogen bonds O–H···O were the main contributions to crystal formation. Bond length 2.7271(17) Å and bond angle 170.1° was determined for O-2–H-2···O-3, 2.8116(17) Å and 152.5° was for O-4–H-4···O-2, and 2.870(5) Å and 160.0° was for O-7′–H-7′···O-2. Meanwhile in the molecule, hydrogen-bonded O–H···N appeared in the crystal with a bond length 2.7642(19) Å and 144.2°.

In comparison with the other compounds, the HMBC data for compound **3** showed a carbon signal at δ 80.24 (C-11) that correlated with the proton signal at δ 3.18 (d, *J* 9.8 Hz), which aligned with the carbon signal at δ 82.50 (C-2) in the HMQC data and showed cross-peaks with the carbon signals at δ 65.02 (C-10), at δ 72.31 (C-3) and at δ 29.73 (C-6).

Thus for compound **3**, the unit –C-2–O–C-11– could be confirmed, and the structure was established as 5,6-dideoxy-5-{[2-hydroxy-1-(hydroxymethyl)ethyl]-amino}-2-*C*-(cyclohexylmethoxyl)-1-*C*-(hydroxymethyl)-D-*epi*}-inositol. Spectral data are provided in Tables 1–3.

The HMBC data of compound **4** is shown in Table 3 wherein the carbon signal at δ 78.98 (C-11) correlates with the proton signal at δ 3.64 (m), which in turn is aligned with the carbon signal at δ 81.02 (C-3). The HMQC data show cross-peaks with the carbon signals at δ 73.49 (C-2) and at δ 72.43 (C-4). The unit –C-3–O–C-11– was confirmed for compound **4**, which establishes the structure as 5,6-dideoxy-5-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-3-*C*-(cyclohexylmethoxyl)-1-C-(hydroxymethyl)-D-*epi*-inositol.

The structure for compound **5** was established by the HMBC spectral data (Tables 1–3) in which the carbon signal at δ 75.79 (C-11) correlated with the proton signal at δ 3.36 (m), which aligned with the carbon signal at δ 81.62 (C-4). The HMQC data showed cross-peaks with the carbon signals at δ 74.26 (C-2), at δ 71.48 (C-3) and at δ 29.00 (C-6). In compound **5**, the unit –C-4–O–C-11– was confirmed, and the structure was assigned as 5,6-didexoy-5-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}-4-*C*-(cyclohexylmethoxyl)-1-*C*-(hydroxymethyl)-D-*epi*-inositol.

1. Experimental

1.1. General methods

The sample mixture, which was obtained in the process of voglibose synthesis by the reported method[11–13] (see Scheme 1), was filtered, and the filtrate was concentrated in a vacuum to afford a crude extract (0.589 g) that was fractionated by silica gel column chromatography using increasing proportions of MeOH in $(Me)_2C{=}O$ (starting at 10%) as eluent.

1.2. Isolation and purification of compounds 2–5

The fractionated sample was purified by column chromatography, eluting with 3:1 H_2O–MeOH through a column (2 × 100 cm) of Sephadex G-25 (Pharmacia), to give 55 mg of compound **2**, 25 mg of compound **3**, 31 mg of compound **4** and 19 mg of compound **5**.

Compound **2**: colorless plates; mp 182–183 °C; ESIMS: *m*/*z* 364 $(M+H)^+$ and HRMS *m*/*z* 364.2326

(calcd 364.2330) corresponding to the molecular weight 363 and the molecular formula $C_{17}H_{33}NO_7$; for NMR data, see Tables 1 and 2.

Compound **3**: colorless needles; mp 168–171 °C; ESIMS m/z 364 $(M+H)^+$ and HRMS m/z 364.2330 (calcd 364.2330) corresponding to the molecular weight 363 and the molecular formula $C_{17}H_{33}NO_7$; for NMR data, see Tables 1 and 2.

Compound **4**: colorless needles; mp 177–179 °C; ESIMS m/z 364 $(M+H)^+$ and HRMS m/z 364.2325 (calcd 364.2330) corresponding to the molecular weight 363 and the molecular formula $C_{17}H_{33}NO_7$; for NMR data, see Tables 1 and 2.

Compound **5**: colorless needles; mp 162–163 °C; ESIMS m/z 364 $(M+H)^+$ and HRMS m/z 364.2328 (calcd 363.2330) corresponding to the molecular weight 363 and the molecular formula $C_{17}H_{33}NO_7$; for NMR data, see Tables 1 and 2.

Crystals of compound **2** suitable for X-ray analysis were obtained by slow evaporation from an aqueous solution in 1:1 H_2O–MeOH at room temperature over about 15 days.

1.3. NMR methods

^1H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on a Bruker DMX-500 spectrometer. Samples were dissolved in D_2O, and chemical shifts are reported in ppm. Coupling constants (J-values) are given in Hz, and multiplicities are provided by DEPT (90^a and 135^a) spectra.

1.4. MS methods

ESIMS spectra were recorded using a Bruker Esquire 3000 plus mass spectrometer operating in the positive-ion mode. HRMS spectra were recorded using a Bruker FT ICR APEX II mass spectrometer operating in the positive-ion SIMS mode.

1.5. X-ray diffraction methods

The structure of compound **2** was solved by SHELXS-97 (Sheldrick, 1990),[14] and expanded by Fourier techniques. The non-hydrogen atoms were refined anisotropically. Atomic scattering facts used were taken from International Tables for X-ray Crystallography.[15]

1.6. Supplementary material

Crystallographic data for this paper have been deposited with the Cambridge Crystallographic Data Centre and assigned the deposition number CCDC 213674. These data may be obtained of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk/).

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