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Note

Synthesis and conformation of 1,2-anhydro-3,4-6-tri-*O*-benzyl-β-D-talopyranose *

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1,2-Anhydro sugar derivatives are important intermediates for the synthesis of oligosaccharides[1] and polysaccharides[2], and also for chemical modification of monosaccharides[3]. The synthesis of 1,2-anhydro-D-manno-[4], -D-gluco-[5], and -D-galactopyranose[6] derivatives by an intramolecular S_N2 reaction of a free hydroxyl group on C-2 with C-1 bearing a leaving group have been reported. Recently a new method for the synthesis of 1,2-anhydro-α-D-gluco- and -galactopyranose derivatives by direct epoxidation of the corresponding glycals was described[1,7]. It seemed, however, to be difficult to prepare 1,2-anhydropyranose compounds with a 3-hydroxy group cis-arranged to the epoxide ring by the new method. Thus the traditional method by an intramolecular S_N2 reaction still retains its merit. Herein we report the synthesis and conformational analysis of 1,2-anhydro-3,4,6-tri-*O*-benzyl-β-D-talopyranose by both ^1H NMR spectrometry and MMP2 methods.

Methyl 6-*O*-benzoyl-2,3-*O*-isopropylidene-α-D-talopyranoside (**1**), prepared from methyl 2,3-*O*-isopropylidene-α-D-mannopyranoside by a reported method[8], was chosen as the starting material for the synthesis of the target ether-protected 1,2-anhydrosugar. Benzylation of compound **1** (or acetylated **1**) was carried out in toluene with potassium hydroxide and benzyl chloride under reflux to afford methyl 4,6-di-*O*-benzyl-2,3-*O*-isopropylidene-α-D-talopyranoside (**2**) in high yield. Removal of the isopropylidene group under mild, acidic conditions gave methyl 4,6-di-*O*-benzyl-α-D-talopyranoside (**3**). It was of interest to find that selective monobenzylation of **3** under phase-transfer conditions as designed for the selective 2-*O*-benzylation of methyl 4,6-di-*O*-benzyl-α-D-mannopyranoside[9] furnished the 3-*O*-benzyl derivative **4** as the major product, together with methyl 2,4,6-tri-*O*-benzyl-α-D-talopyranoside (**7**) in a ratio of 4:1. Also the R_f value of **4** (0.74) was

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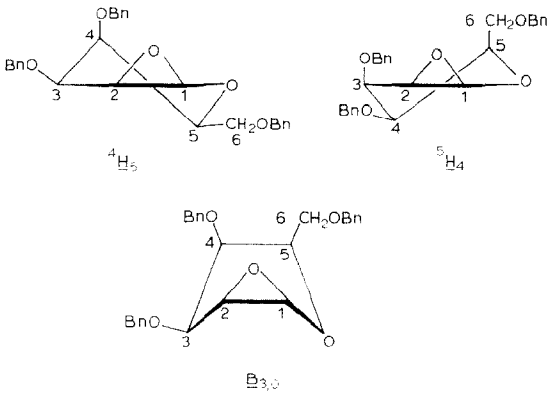


Fig. 1.

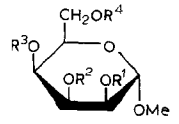
larger than that of **7** (0.70) on TLC (1:2 EtOAC–petroleum ether), while just the opposite order for mannopyranoside analogues was observed. Acetylation of **4** in pyridine with acetic anhydride did not afford the corresponding acetate as indicated by both TLC and the ^{1}H NMR spectrum of the acetylation product, which showed starting material **4**, only. The abnormal behavior of compound **4** compared to the corresponding mannopyranoside was attributed to the axial substituent at C-4 that severely sterically hindered the axial hydroxyl group on C-2. Direct reaction of **4** with hydrogen chloride in a 1:1 CH_2Cl_2–acetic acid solution afforded 3,4,6-tri-*O*-benzyl-α-D-talopyranosyl chloride (**5**) in fair yield. Compound **5** was not stable because of the presence of a C-2 free hydroxy group, and it was subjected to further reaction immediately after purification by column chromatography. Treatment of **5** in oxolane with sodium hydride at room temperature afforded crystalline 1,2-anhydro-3,4,6-tri-*O*-benzyl-β-D-talopyranose (**6**).

The ether-protected 1,2-anhydrotalopyranose (**6**) was characterized by its NMR and mass spectrum. The ^{1}H NMR spectrum showed an upfield chemical shift of H-2 (δ 3.29), characteristic of an epoxide ring, and H-1 resonated at δ 4.99 with a small coupling between H-1 and H-2. The mass spectrum gave a molecular ion (*m/z* 432) of low intensity and showed some peaks of moderate or relatively high intensity (*m/z* 341, 203, 197, and 181) characteristic of 1,2-anhydropyranose benzyl ethers[10].

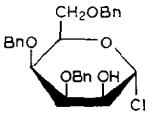
Conformational analysis of compound **6** was carried out by ^{1}H NMR spectrometry in conjunction with the modified Karplus equation[11], and the results were confirmed by force-field calculations (MMP2)[12].

Compound **6** may have two possible conformations $^4H_5$ and $^5H_4$ (Fig. 1). The former conformation, with the large groups of C-6–OBn and C-3–OBn in equatorial positions, is thermodynamically more stable than the latter. This postulate was confirmed as described below.

As full assignment of the ^{1}H NMR spectrum of compound **6** was necessary for its conformational analysis, single-frequency decoupling was used to confirm all



	R^1	R^2	R^3	R^4
1	$(CH_3)_2CH$	H	Bz	
2	$(CH_3)_2CH$	Bn	Bn	
3	H	H	Bn	Bn
4	H	Bn	Bn	Bn
7	Bn	H	Bn	Bn



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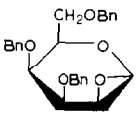

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assignments. Irradiation of H-1 at δ 4.99 identified the upfield multiplet at δ 3.29 as H-2. (The multiplet collapsed to a doublet of doublets produced by coupling between H-2 and H-3 and by long-distance coupling between H-2 and H-4). Subsequent irradiation of H-2 simplified the H-1 signal to a singlet, and that of H-3 at δ 3.90 to a doublet and that of H-4 at δ 3.86 to a quartet. A triplet of doublets at δ 3.73 was assigned as H-5, as it changed to a triplet due to the couplings with two H-6's when H-4 was irradiated. The two quartets at δ 3.58 and 3.38 were assigned as H-6 and H-6′, respectively, as both of them collapsed to doublets when H-5 was irradiated.

The H–H torsional angle between H-3 and H-4 ($\Phi_{3,4}$) and the H–H torsional angle between H-4 and H-5 ($\Phi_{4,5}$) calculated from vicinal coupling constants according to the $^4H_5$ model by the modified Karplus equation[11] were 45 and 303°, respectively. Because the modified Karplus equation is not valid for the planar portion of the molecule, the H–H torsional angles of $\Phi_{1,2}$ and $\Phi_{2,3}$ were not taken into account.

To confirm the conformation of compound **6**, force-field calculations were carried out using the MMP2 program[12]. Calculations from the initial coordinates according to the geometry of $^4H_5$ gave final coordinates with a total minimum energy of 69.2 kcal/mol. The MMP2 calculations also showed that there was a $B_{3,0}$ form giving the final coordinates with a total minimum energy of 72.7 kcal/mol, close to the low energy of $^4H_5$ conformation. However, comparison of the calculated $J_{3,4}$ and $J_{4,5}$ with the experimental values of $J_{3,4}$ and $J_{4,5}$ indicated that $^4H_5$

TABLE I

Some important torsion angles (°) calculated by MMP2 for compound **6**

	$^4H_5$	$B_{3,0}$		$^4H_5$	$B_{3,0}$
C-1–C-2–C-3–C-4	−17.7	−39.8	C-3–C-4–C-5–O-5	−67.7	−7.6
C-2–C-1–O-5–C-5	−17.0	59.0	H-1–C-1–C-2–H-2	0.24	−4.1
C-1–O-5–C-5–C-4	51.3	−47.2	H-2–C-2–C-3–H-3	−54.6	−71.6
C-2–C-3–C-4–C-5	49.2	49.9	H-3–C-3–C-4–H-4	53.4	54.2
C-3–C-2–C-1–O-5	−0.4	−11.4	H-4–C-4–C-5–H-5	−67.5	−10.6

TABLE II

Comparison of experimental and calculated values for the coupling constant and torsion angles

	Calculated ϕ values (°) by MMP2		Calculated values of coupling constants (Hz) according to the ϕ values (MMP2) by the modified Karplus equation			Experimental values of coupling constants (Hz)		Calculated ϕ values (°) from experimental J values by the modified Karplus equation	
	$^4H_5$	$B_{3,0}$		$^4H_5$	$B_{3,0}$				
$\phi_{3,4}$	53.4	54.2	$J_{3,4}$	3.3	3.2	$J_{3,4}$	4.3	$\phi_{3,4}$	45
$\phi_{4,5}$	293	349	$J_{4,5}$	0.4	7.0	$J_{4,5}$	1.2	$\phi_{4,5}$	303

is the most plausible conformation. The smaller value of $\phi_{3,4}$ (45°) and larger value of $\phi_{4,5}$ (303°) given by ^{1}H NMR spectrometry, when compared to those obtained by the MMP2 program indicate that C-4 is somewhat more flattened for the conformation obtained by ^{1}H NMR spectrometry. Whereas the calculations by the MMP2 program for compound **6** gave an almost perfect half chair, the $^4H_5$ conformation with the asymmetric parameter[13] $\Delta C_2(1-2) = 1.6°$. Some important torsion angles according to MMP2 calculations are listed in Tables I and II.

EXPERIMENTAL

General methods.—See ref. 6 for the calculations by MMP2. The MMIO program was used for the input, and a Tektronix emulator program was used for screen echo of the structure building or for the graphics. The dielectric constant used for the calculations was 1.50.

Methyl 4,6-di-O-benzyl-2,3-O-isopropylidene-α-D-talopyranoside (**2**).—To a solution of methyl 6-*O*-benzoyl-2,3-*O*-isopropylidene-α-D-talopyranoside (900 mg, 2.6 mmol) in toluene (15 mL) was added finely powdered KOH (1.96 g, 35 mmol), and the mixture was boiled under reflux with vigorous stirring. Benzyl chloride (1.47 mL, 12.7 mmol) was added dropwise, and reflux was continued for 3 h. TLC (1:3 EtOAc–petroleum ether) indicated that the reaction was complete. The product was subjected to steam distillation directly to remove toluene, excess benzyl chloride, and the byproduct, dibenzyl ether. Purification of the product by column chromatography with 1:3 EtOAc–petroleum ether as the eluent gave pure methyl 4,6-di-*O*-benzyl-2,3-*O*-isopropylidene-α-D-talopyranoside (1.01 g, 92%) as a syrup: $[\alpha]_D^{23}$ +3.2° (*c* 0.1 $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.40–7.20 (m, 10 H, 2 Ph), 4.79 (d, 1 H, $J_{1,2}$ 1.0 Hz, H-1), 4.75–4.40 (m, 6 H, 2 CH_2Ph), 4.10–3.59 (m, 6 H, H-2,3,4,5, and 2 H-6), 3.39 (s, 3 H, OCH_3), and 1.48, 1.40 (s, 6H, C(CH_3)$_2$). Anal. Calcd for $C_{24}H_{30}O_6$: C, 69.57; H, 7.25. Found: C, 69.66; H, 7.18.

Methyl 4,6-di-O-benzyl-α-D-talopyranoside (**3**).—To a solution of compound **2** (1.01 g, 2.43 mmol) in MeOH (7 mL) was added HCl (1.2 mL, 0.5 N), and the solution was boiled under reflux for 1 h. TLC indicated the reaction was complete.

The reaction mixture was partitioned between CH_2Cl_2 and water, and the organic phase was washed sequentially with satd $NaHCO_3$ and water, and then dried (Na_2SO_4). Evaporation of the solvent quantitatively afforded crude product **3** as yellowish crystals (0.91 g). Recrystallization from CH_2Cl_2–petroleum ether furnished pure **3** as white needles (0.84 g, 92%): mp 67 °C; $[\alpha]_D^{23}$ +49.4° (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.62–7.21 (m, 10 H, 2 Ph), 4.81–4.40 (4 d, 4 H, 2 CH_2Ph), 4.45 (d, 1 H, $J_{1,2}$ 1.0 Hz, H-1), 4.20–3.25 (m, 4 H, H-2,3,4,5), 3.20 (m, 2 H, 2 H-6), and 3.02 (s, 3 H, OCH_3). Anal. Calcd for $C_{21}H_{28}O_6$: C, 67.38; H, 6.95. Found: C, 67.44; H, 6.85.

*Methyl 3,4,6-tri-*O*-benzyl-α-*D*-talopyranoside* (**4**).—To a solution of compound **3** (2.9 g, 7.6 mmol) in CH_2Cl_2 (15 mL) was added tetrabutylammonium hydrogensulfate (0.28 g), NaOH (3.8 mL, 5%), and benzyl bromide (1.2 mL, 10 mmol), and the mixture was boiled under reflux. In order to obtain good selectivity and to avoid the formation of the per-*O*-benzylated compound, the conversion of **4** was carefully monitored by TLC. After 4 days the reaction was processed in the usual manner, and the product was separated by column chromatography (1:3 EtOAc–petroleum ether). Pure compound **4** (0.88 g) and methyl 2,4,6-tri-*O*-benzyl-α-D-talopyranoside (0.22 g), together with the starting material (1.5 g), were obtained (yield 51%, corrected): $[\alpha]_D^{23}$ +121.5° (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.41–7.29 (m, 15 H, 3 Ph), 4.98, 4.82, 4.57, 4.53, 4.52, 4.45 (6 d, 6 H, 3 CH_2Ph), 4.81 (d, 1 H, $J_{1,2}$ 0.8 Hz, H-1), 3.98–3.72 (m, 4 H, H-2,3,4,5), 3.63 (m, 2 H, 2 H-6), and 3.36 (s, 3 H, OCH_3). Anal. Calcd for $C_{28}H_{32}O_6$: C, 72.41; H, 6.90. Found: C, 72.17; H, 6.88.

*3,4,6-Tri-*O*-benzyl-α-*D*-talopyranosyl chloride* (**5**).—To a solution of **4** in 1:1 CH_2Cl_2–acetic acid (10 mL) was bubbled in dry gaseous HCl under N_2 at 0°C until the solution was saturated. The reaction was carried out for 8 h at room temperature at which time TLC indicated the conversion was >80% complete. The solvents were removed by evaporation under reduced pressure, the residue was dissolved in CH_2Cl_2, and the solution was evaporated. This procedure was repeated 7 or 8 times to reduce the HCl to the minimum. Then the product was purified by analytical LC (1:4 EtOAc–petroleum ether) to give **5** as a syrup (103 mg, 51%): $[\alpha]_D^{23}$ +46.1° (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.44–7.21 (m, 15 H, 3 Ph), 6.13 (d, 1 H, $J_{1,2}$ 0.9 Hz, H-1), 5.00, 4.82, 4.58, 4.56, 4.54, 4.48 (6 d, 6 H, 3 CH_2Ph), 4.21 (m, 1 H, H-5), 4.13 (m, 1 H, H-4), 4.06 (dd, 1 H, $J_{1,2}$ 0.9, $J_{2,3}$ 2.0 Hz, H-2), 4.02 (t, 1 H, $J_{2,3}$, $J_{3,4}$ 2.0 Hz, H-3), 3.65 (dd, 1 H, $J_{5,6}$ 7, $J_{6,6'}$ 9.2 Hz, H-6), 3.58 (dd, 1 H, $J_{5,6}$ 6.3, $J_{6,6'}$ 9.2 Hz, H-6′).

*1,2-Anhydro-3,4,6-tri-*O*-benzyl-β-*D*-talopyranose* (**6**).—To a solution of compound **5** (90 mg, 0.19 mmol) in dry oxolane (10 mL) was added NaH (80% in oil; 40 mg, 1.4 mmol), the mixture was stirred at room temperature, and the progress of the reaction was monitored by TLC (1:3 EtOAc–petroleum ether). After 2 h, the reaction was complete. The solid was separated by centrifugation, and the residue was washed with 1:3 EtOAc–petroleum ether. After evaporation of the combined supernatant and washings, crude 1,2-anhydro-3,4-6-tri-*O*-benzyl-β-D-talopyranose

(80 mg, 96%) was obtained as crystals. Recrystallization from ether–petroleum ether afforded **6** as white needles (60 mg, 72%): mp 77°C; $[\alpha]_D^{23}$ −23.6° (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.37–7.23 (m, 15 H, 3 Ph), 4.99 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1), 4.88, 4.78, 4.73, 4.61, 4.43, 4.35 (6 d, 6 H, *J* 12.0 Hz, 3 CH_2Ph), 3.90 (dd, 1 H, $J_{2,3}$ 2.4, $J_{3,4}$ 4.3 Hz, H-3), 3.86 (dt, 1 H, $J_{3,4}$ 4.3, $J_{4,5}$ 1.2, $J_{2,4}$ 1.2 Hz, H-4), 3.73 (td, 1 H, $J_{5,6}$, $J_{5,6'}$ 6.4, $J_{4,5}$ 1.2 Hz, H-5), 3.58 (dd, 1 H, $J_{5,6}$ 6.4, $J_{6,6'}$ 9.7 Hz, H-6), 3.38 (dd, 1 H, $J_{5,6'}$ 6.4, $J_{6,6'}$ 9.7 Hz, H-6′), 3.29 (m, 1 H, H-2). Anal. Calcd for $C_{27}H_{28}O_5$: C, 74.98; H, 6.53. Found: C, 75.17; H, 6.68.

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