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Note

Preparation of bicyclic hexitol anhydrides by using acidic cation-exchange resin in a binary solvent. ^{13}C-N.m.r. spectroscopy confirms configurational inversion in chloride displacement of methanesulfonate in isomannide and isosorbide derivatives

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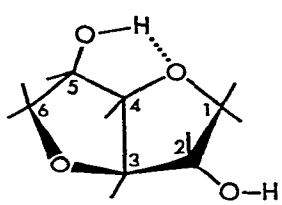
Hexitols eliminate water when heated alone or with acids to yield mixtures of mono- and di-anhydrides[1–8]. Internal anhydrides of diethylene glycol[9], erythritol[10], and DL-threitol[11] have been prepared by dry-distillation with acidic cation-exchange resin, but bicyclic anhydrides of alditols have not been prepared previously in this way.

Acidic cation-exchange resin is now used in place of concentrated, corrosive acids for intramolecular elimination of 2 moles of water from D-glucitol (**1**) and D-mannitol (**2**) to prepare the 1,4:3,6-dianhydro derivatives commonly known as isosorbide (**3**) and isomannide (**4**). When ethyl acetate is present in the medium,



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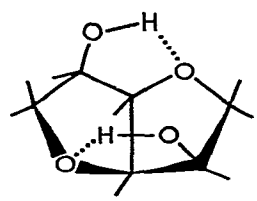

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monoacetates of isosorbide and isomannide are formed. Surprisingly, diesters of **3** and **4** could not be detected, whereas direct acetylation with acetic anhydride in pyridine produced[12] mainly the diester of **3**.

Compounds **1** and **2**, when boiled under reflux in 1,4-dioxane–ethyl acetate in the presence of a sulfonic acid exchange-resin gave mixtures of mono- and di-anhydrohexitols, together with unreacted starting material. 1,4:3,6-Dianhydro-D-glucitol (**3**)

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and -D-mannitol (**4**) were distilled from the mixtures in 39 and 35% yields, respectively.

Variations of the preparative procedure included dry distillation with the acidic resin and with addition to the reaction medium of single solvents (dry 1,4-dioxane, ethyl acetate, 2-methoxyethanol, and xylene), binary solvents, and drying agent. Use of dry 1,4-dioxane–ethyl acetate (1 : 1 v/v) increased the solubility of the hexitols over that in the single solvents, produced a sixfold increase in yield over dry distillation (5%) and a threefold increase over dry 1,4-dioxane (10%), and gave a desirable reflux temperature (78–84°). In boiling 2-methoxyethanol or xylene, yields were less than 3%. Highest yields of **3** and **4** were obtained in 1,4-dioxane–ethyl acetate without the addition of a drying agent.

Prolonged reaction (5 days) of **1** and **2** with acidic cation-exchange resin in dry 1,4-dioxane–ethyl acetate (1 : 1 v/v) under reflux at 78–84° gave, upon isolation by dry column chromatography on Silica Gel G, mono-*O*-acetyl-1,4 : 3,6-dianhydro-D-glucitol (**5**, crystalline)[12] and -D-mannitol (**6**, syrup) (Table I) in 21 and 11% yields, respectively.

TABLE I

ANALYSES OF COMPOUNDS

Compound		*M.p. (degrees)*	*C*		*H*		*Cl*		*S*	
			Calc.	*Found*	*Calc.*	*Found*	*Calc.*	*Found*	*Calc.*	*Found*
5	$C_8H_{12}O_5$	78.5–80.5 77.5–78.5[a]	51.1	50.9	6.42	6.65				
6	$C_8H_{12}O_5$	(syrup)	51.1	51.0	6.42	6.69				
7	$C_9H_{14}O_7S$	81.5–83	40.6	40.6	5.30	5.41			12.04	12.01
8	$C_9H_{14}O_7S$	(syrup)	40.6	40.6	5.30	5.37			12.04	12.01
9	$C_8H_{11}ClO_4$	(syrup)	46.5	46.5	5.37	5.49	17.16	17.14		
10	$C_8H_{11}ClO_4$	(syrup)	46.5	46.3	5.39	5.25	17.16	17.25		
11	$C_6H_9ClO_3$	64.5–65.5 63–64[b]	43.8	43.7	5.51	5.61	21.54	21.46		
12	$C_6H_9ClO_3$	(syrup)	43.8	43.6	5.51	5.51	21.54	21.43		

[a]Ref. 12. [b]Ref. 18.

The greater reactivity at the endo-5-OH group in **3** toward esterification with acyl halides has been attributed to intramolecular hydrogen-bonding of this group with the adjacent ring-oxygen atom[13]. However, Buck *et al.*[12] showed that the relative reactivities of the exo-2- and endo-5-OH groups in **3** depend largely on the acylating reagent and medium employed. They esterified **3** with acetic anhydride in pyridine alone and in the presence of pyridine hydrochloride at 25°. Greater reactivity of the exo-2-OH group was demonstrated in pyridine alone, but the endo-5-OH was 3.6 times more reactive than the exo-2-OH group when pyridine hydrochloride was present. Our results show that only the exo-2-OH in **3**, and one of the endo-2(5)-OH groups in the di-endo **4**, are acetylated by transesterification in

boiling 1,4-dioxane–ethyl acetate in the presence of acidic cation-exchange resin and a drying agent.

For several monoesters of **3**, wherein the nonesterified hydroxyl group is in either exo or endo dispositions, the i.r. absorption-bands for free and H-bonded OH groups have indicated the configuration[12–14]. Likewise, the i.r. spectra of **5** and **6** showed strong absorption bands at 3555 and 3560 cm^{-1} for the endo H-bonded OH groups (Table II). Therefore, **5** is the known 2-*O*-acetyl-1,4:3,6-dianhydro-D-glucitol[12]. Compound **6** is new; but, because **4** is symmetrical, acetylation at either O-2 or O-5 produces the same compound.

Displacement of sulfonic ester groups by chloride ions with Walden inversion has been demonstrated in 5-membered rings with diesters of 1,4-anhydroerythritol[11] and a monoester of *cis*-1,2-cyclopentanediol[15]. Structures of di- and mono-chloro derivatives of 1,4:3,6-dianhydrohexitols have been assigned arbitrarily on the basis of Walden inversion[16]. Hopton and Thomas[17] determined the conformations of **3**, **4**, isoidide (1,4:3,6-dianhydro-L-iditol), and the corresponding di-*O*-acetyl and di-*O*-mesyl derivatives, from ^{1}H-n.m.r. spectral data. They established that **4** and isoidide are symmetrical molecules, whereas **3** is asymmetric.

We mesylated the monoacetates of **3** and **4**, displaced the mesyl group with chloride ion, and deacetylated the products. Methanesulfonylation[18] of **5** and **6**

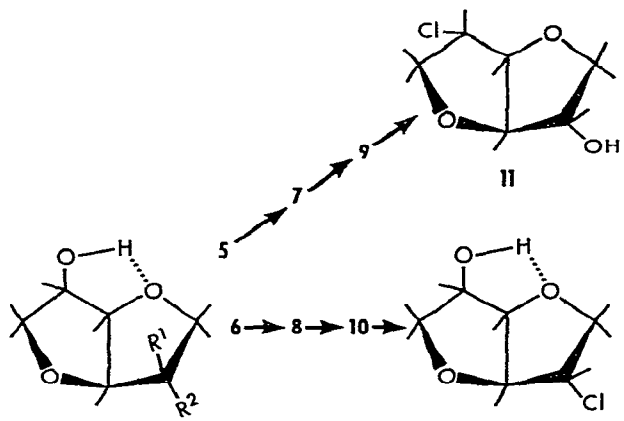
TABLE II

I.R. ABSORPTION-FREQUENCY (cm^{-1}) FOR DIANHYDRIDES OF HEXITOLS AND THEIR DERIVATIVES IN CARBON TETRACHLORIDE (A), POTASSIUM BROMIDE PELLETS (B), AND THIN FILMS (C)

	Compound	*C–Cl*	*Bonded OH*	*Free OH*	*Ac–O–C*
3	1,4:3,6-Dianhydro-D-glucitol		3562 (A) 3562 3564	3625 (A) 3625[a] 3624[b]	
4	1,4:3,6-Dianhydro-D-mannitol		3560 (A)		
5	2-*O*-Acetyl-1,4:3,6-dianhydro-D-glucitol		3555 (B)		1735 (B)
6	2(5)-*O*-Acetyl-1,4:3,6-dianhydro-D-mannitol		3560 (B)		1735 (B)
7	2-*O*-Acetyl-1,4:3,6-dianhydro-5-*O*-mesyl-D-glucitol				1735 (C)
8	2(5)-*O*-Acetyl-1,4:3,6-dianhydro-5(2)-*O*-mesyl-D-mannitol				1735 (C)
9	2(5)-*O*-Acetyl-5(2)-chloro-5(2)-deoxy-1,4:3,6-dianhydro-L-iditol	680, 755 (C)			1735 (C)
10	2-*O*-Acetyl-5-chloro-5-deoxy-1,4:3,6-dianhydro-D-glucitol	685, 755 (C)			1735 (C)
11	2(5)-Chloro-2(5)-deoxy-1,4:3,6-dianhydro-L-iditol	680, 755 (A)		3620 (A)	
12	2-Chloro-2-deoxy-1,4:3,6-dianhydro-D-glucitol	680, 755	3555 (A)		

[a]Ref. 12; in 2.5mM carbon tetrachloride. [b]Ref. 15; in 4mM carbon tetrachloride.

produced 2-*O*-acetyl-1,4:3,6-dianhydro-5-*O*-(methylsulfonyl)-D-glucitol (**7**) and 2(5)-*O*-acetyl-1,4:3,6-dianhydro-5(2)-*O*-(methylsulfonyl)-D-mannitol (**8**) in 83 and 84% yields, respectively. By boiling compounds **7** and **8** in pyridine with pyridine hydrochloride[11], the 2-*O*-acetyl-5-chloro-5-deoxy (**9**, syrup) and 2(5)-*O*-acetyl-5(2)-chloro-5(2)-deoxy (**10**, syrup) derivatives were obtained. Deacetylation[19] then produced the 5-chloro-5-deoxy (**11**, crystalline)[18] and 2(5)-chloro-2(5)-deoxy (**12**, syrup) dianhydrohexitol derivatives (Scheme 1). The i.r. absorption bands for free and H-bonded OH



5 = R^2 = OAc, R^1 = H
6 = R^1 = OAc, R^2 = H

Scheme 1

TABLE III

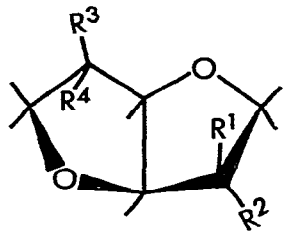
CARBON-13 CHEMICAL SHIFTS OF 1,4:3,6-DIANHYDRO-D-GLUCITOL, -D-MANNITOL, ACETYL AND CHLORO DERIVATIVES OF DIANHYDROHEXITOLS IN CHLOROFORM-*d*

Compound		*Carbon-13 signal, p.p.m. from Me_4Si-^{13}C*					
		1	*2*	*3*	*4*	*5*	*6*
3	1,4:3,6-Dianhydro-D-glucitol	75.8	76.6	88.2	81.7	72.3	73.4
		74.5	84.7	87.1	81.9	80.5	71.7[a]
4	1,4:3,6-Dianhydro-D-mannitol	75.1	71.9	82.0	82.0	71.9	75.1
		71.6[b]	79.9	81.6	81.6	79.9	71.6
5	2-*O*-Acetyl-1,4:3,6-dianhydro-D-glucitol	73.7	78.6	85.8	82.1	72.5	73.5
10	5-*O*-Acetyl-2-chloro-2-deoxy-1,4:3,6-dianhydro-D-glucitol	75.8	60.7	88.9	80.5	74.0	70.5
11	2(5)-Chloro-2(5)-deoxy-1,4:3,6-dianhydro-L-iditol	75.3	60.5	88.1	87.5	75.6	74.8
		77.6[c]	26.5	88.5	88.5	26.5	77.6
12	2-Chloro-2-deoxy-1,4:3,6-dianhydro-D-glucitol	76.0	61.1	88.7	81.9	72.3	74.1
		78.1	26.9	89.2	82.8	21.7	76.6[d]

[a] 1,4:3,6-Dianhydro-2,5-di-*O*-mesyl-D-glucitol[23]. [b] 1,4:3,6-Dianhydro-2,5-di-*O*-mesyl-D-mannitol[23]. [c] 1,4:3,6-Dianhydro-2,5-dideoxy-2,5-diiodo-L-iditol[23]. [d] 1,4:3,6-Dianhydro-2,5-dideoxy-2,5-diiodo-D-glucitol[23].

TABLE IV

CARBON-13 CHEMICAL-SHIFT DIFFERENCES OF ENDO- AND EXO-ORIENTED SUBSTITUENTS AT THE α AND β CARBON ATOMS



Compound number	*Configurations*				*^{13}C Shift-differences, p.p.m.*		
	R^1 endo	*R^2 exo*	*R^3 endo*	*R_4 exo*	*Δα*	*Δβ*	
					2 and 5	*3 and 4*	*1 and 6*
3	H	OH	OH	H	−4.3[a]	−6.5	−2.4
4	OH	H	OH	H	0.0	0.0	0.0
5	H	OAc	OH	H	−6.1	−3.7	−0.2
10	H	Cl	OAc	H	13.3	−8.4	−5.3
11	H	Cl	H	OH	15.1	−0.6	0.5
12	H	Cl	OH	H	11.2	−6.8	−1.9

[a]A minus sign denotes that either the α- or β-carbon atom bonded to an exo-oriented substituent is shifted downfield from the resonance of the carbon atom bonded to an endo substituent. In **11**, both substituents are exo.

groups of **11** and **12** served to assign configurations of the chlorine atoms as shown in Table II. Boiling, dilute sodium hydroxide or barium methoxide did not displace the chlorine atom from either **11** or **12**.

Configurations of the new monochloro-1,4:3,6-dianhydrohexitols may also be assigned by comparing carbon-13 chemical shifts and relative chemical-shift differences (*Δα* and *Δβ*) at the α (C-2 and C-5) and β (C-1, C-3, C-4, and C-6) carbon atoms on the basis of endo and/or exo orientation-effects. The observed carbon-13 chemical shifts and shift-differences (*Δα* and *Δβ*) are shown in Tables III and IV for the bicyclic hexitol anhydrides and their derivatives. In the symmetrical compound **4**, the equivalent α carbon atoms (C-2 and C-5) are bonded to endo-OH groups, and δ_C is 71.9 p.p.m. The exo-OH group at C-2 in **3** is downfield by −4.7 p.p.m., whereas the endo-OH group at C-5 is scarcely shifted (−0.4 p.p.m.). The difference (*Δα*), −4.3 p.p.m., (Table IV) is in good agreement with the corresponding *Δα* value between the single C-OH of *endo*-borneol and *exo*-isoborneol[20]. For other 2-substituted norbornanes, the carbon atom bearing the endo substituent is always shielded with respect to the carbon atom bearing the exo substituent[21,22]. When C-2 is bonded to an exo-oriented acetoxyl group, as in **5**, the induced shift is greater (−6.1 p.p.m.).

To confirm configurational inversion at C-2 in **10** and **12** (and at C-2 = C-5 in **11**), the ^{13}C chemical shifts of **3** and **4** were compared with those of **10**, **11**, and **12** (Table III). When the substituent at C-2 was inverted from endo to exo, large

differences (regardless of sign) were found in $\Delta\alpha$ (Table IV). The β carbon atoms, C-3 and C-4, also show shift differences with inversion from endo to exo at the α carbon atoms. The downfield chemical-shifts (Table III) of the β_3 carbon atoms in **3** and **11** (compared with **4**) resulted from exo-oriented substituents at C-2. Therefore, the corresponding chemical shifts at the β_3 carbon atoms in **10** and **12** (also the β_3 and β_4 carbon atoms in **11**) resulted from exo-oriented chlorine atoms at C-2 (and C-5 in **11**). Further evidence of Walden inversion at C-2 in the transformation of **6** into **12** is given by the close agreement for both $\Delta\beta$-values for **3** and **12** (Table IV), whereby the D-*gluco* configuration is confirmed for **12**. The ^{13}C chemical shifts at the β carbon atoms, C-3 and C-4 in **3**, **4**, **11**, and **12** are in close agreement with corresponding β carbon atoms in disubstituted 1,4:3,6-dianhydrohexitol derivatives recently reported by Sohar *et al.*[23]. However, the ^{13}C chemical-shifts given by them for C-1,2,3 and C-4,5,6 of their di-*O*-mesyl and diiodo derivatives of 1,4:3,6-dianhydro-D-glucitol were listed in reverse order in their Table I. Our Table III shows the correct order, corresponding overall with the ^{13}C chemical-shifts of our unsubstituted and monochloro dianhydrohexitols, which they did not report.

EXPERIMENTAL

General methods. — Commercial D-glucitol (Matheson, Coleman and Bell, Cincinnati, OH) and D-mannitol (Aldrich Chemical Co., Milwaukee, WI) were used. 1,4-Dioxane was purified by the method of Wiberg[24], and the ethyl acetate was redistilled and stored over Drierite (W. A. Hammond Drierite Co., Xenia, OH). Either Amberlite IR-120 (Rohm & Haas Co., Philadelphia, PA) or AG 50W-X4 (Bio Rad Laboratories, Richmond, CA) resin in acid form, prewashed with methanol and allowed to dry at room temperature, produced the same results.

All reactions were monitored by t.l.c. Purity of the compounds was established by t.l.c., g.l.c., m.p., and elemental analyses (Table I). T.l.c. was conducted on 0.25-mm layers of EM Reagent Silica Gel G (Brinkmann Instruments, Inc.) with air-dried plates. The spots were detected by spraying with 5% ethanolic sulfuric acid and charring. G.l.c. analyses of trimethylsilyl ethers of compounds **1–6** were recorded by an F & M Model 700 laboratory chromatograph with a flame-ionization detector, which was fitted with a 1/8 in. × 6 ft stainless-steel column containing 3% J × R silicone gum on 100–120 mesh Gas-Chrom Q support (Anspec, Ann Arbor, Michigan). Single, symmetrical peaks were obtained. I.r. spectra were determined in dilute carbon tetrachloride (5mM solutions), potassium bromide pellets (1.22-mm thick containing 0.1M concentrations), and thin films, with a Perkin–Elmer Model 621 spectrophotometer. The ^{13}C-n.m.r. spectra (natural abundance) were obtained from solutions in chloroform-*d*, which also served as the internal deuterium lock. Chemical shifts were measured as δ-values in p.p.m. downfield from the internal ^{13}C signal of tetramethylsilane. The ^{13}C spectra were recorded in 10-mm tubes with a Bruker WH-90 Fourier-transform n.m.r. spectrometer at 22.6 MHz. Sweep widths of 6024 Hz with 4096 plot data-points were used to give chemical-shift values accurate to

within ±1.5 Hz (±0.1 p.p.m.). A 5-μsec (~30°) pulse-width was used and the computer-data memory size (8192 addresses) set the data-acquisition time at 0.68 sec. No pulse delays were employed. Proton noise-decoupled, off-resonance, and selective-decoupled spectra were obtained to assist in signal assignments. ^{1}H-N.m.r. spectra were recorded with a Varian Model HA-100 spectrometer; chemical-shift peaks were assigned by spin-decoupling experiments, referred to internal tetramethylsilane. Products were vacuum-dried in the presence of phosphorus pentaoxide for 24–48 h at room temperature before analysis. Melting points, measured in capillary tubes, are not corrected.

The identities of **5** and **6** were determined by microchemical analysis (Table I), deacetylation, and by i.r., and n.m.r. spectra. Compound **5** and **6** when deacetylated with sodium methoxide in dry methanol[19] and gave products having melting points of 63–64° (71% yield), and 86–87° (79% yield), which correspond to melting points for **3** (61.5–63°) and **4** (86–87°). The methanesulfonates of the deacetylated compounds **5** (123–124°; 82% yield), and **6** (101–102°; 69% yield) confirmed that they were monoacetates of isomannide and isosorbide.

Assignment of carbon-13 chemical shifts by selective proton-decoupling. — For compound **5**, irradiation at δ 4.45 (H-3) collapsed C-3, at δ 4.59 (H-4) collapsed C-4, at δ 5.16 (H-2) collapsed C-2, at δ 4.00 (H-1, H-1′) collapsed C-1, and δ 3.54 (H-6) determined C-6. For compound **10**, irradiation at δ 4.15 (H-3) and δ 4.61 (H-3) collapsed C-3 and C-4. For compound **11**, irradiation at δ 4.29 (H-2, H-5) pinpointed C-2 and C-5, and by inference C-3, at δ 4.63 (H-3) collapsed C-3, at δ 4.76 (H-4) determined C-4, at δ 3.85 (H-6, H-6′) collapsed C-6, and by inference C-1 was determined. For compound **12**, irradiation at δ 4.56 (H-3) and δ 4.68 (H-4) determined shifts for C-3 and C-4, also at δ 3.54 (H-6) and δ 3.86 (H-6′) to find C-6, and at δ 4.11 (H-1, H-1′) helped to identify C-1, C-2, and C-5.

*1,4:3,6-Dianhydro-*D*-glucitol* (**3**) *and* -D-*mannitol* (**4**). — D-Glucitol (or D-mannitol) (30 g) was finely powdered in a mortar and stirred with the cation-exchange resin (10 g) in 300 mL of dry 1,4-dioxane–ethyl acetate (1:1 v/v) under reflux for 24 h at 78–84°. The resin was removed by filtration, and the solvents were evaporated under vacuum. The solvent-free, slightly colored syrups were distilled at 135–145° (115–125°)/7 mm. The viscous, colorless distillates solidified at 25°. Compounds **3** and **4** in the respective distillates were recrystallized from ethyl acetate–petroleum ether; yield of **3**, 9.5 g (39%); m.p. 61.5–63°, $[\alpha]_D^{20}$ +44° (*c* 0.5, water); reported yield 66%; m.p. 61–63°, $[\alpha]_D^{20}$ +44° (*c* 0.5, water)[3,5]. The yield of **4** was 8.5 g (35%); m.p. 86–87°, $[\alpha]_D^{20}$ +91° (*c* 0.5, water); reported yield 35%; m.p. 85.5–86.8°, $[\alpha]_D^{20}$ +91° (*c* 2.28, water)[3,4]. T.l.c. examination (3:1 ethyl acetate–hexane) of the syrups before distillation disclosed two major (mono- and di-anhydrides) and several minor components, plus unreacted starting hexitols. However, no unreacted hexitols, their monoanhydrides, or monoacetates were detected in the distillates.

*2-*O*-Acetyl-1,4:3,6-dianhydro-*D*-glucitol* (**5**) *and* -D-*mannitol* (**6**). — Prolonged reaction (5 days) of D-glucitol (or D-mannitol) under the same preparative conditions as for compounds **3** and **4**, except in the presence of Drierite (20 g) gave, upon isola-

tion by dry column chromatography on Silica Gel G (5% water), compound **5** (crystalline) and compound **6** (noncrystalline). The columns were eluted with 75%, ethyl acetate–hexane. T.l.c. examination of the distillate disclosed two major and several minor components. The two major components were identified as **3** and **5** for **1**, and **4** and **6** for **2**, during on an attempt to increase the overall yield of compound **3** and **4**. The first-eluted compound (**5**) from the product-mixture was recrystallized from anhydrous ether; yield, 6.4 g (21%); m.p. 78–80°; sublimed at 74°/7 mm, m.p. 78.5–80.5°, $[\alpha]_D^{20}$ +79° (*c* 1, water); reported[12] m.p. 77.5–78.5°; yield 28.6%; n.m.r. (chloroform-*d*): δ 4.00 (complex multiplets, H-1 and H-1′), 5.16 (complex multiplets, H-2), 4.45 (doublet, H-3), 4.59 (triplet, H-4), 4.25 (quartet, H-5), 3.54 (doublet of doublets, H-6), 3.86 (doublet of doublets, H-6′), 2.93 (broad doublet, OH), and 2.09 (acetoxy methyl). The C-6 methylene and C-5 methine groups gave a clear ABX pattern. A 3.3 g yield (11%) of **6** (syrup) was obtained from combined column fractions; $[\alpha]_D^{20}$ +127° (*c* 0.5, water); n.m.r. data (chloroform-*d*): δ 4.10 (complex multiplet, H-1), 3.96 (complex multiplet, H-1′), 5.10 (quartet, H-2), 4.46 (triplet, H-3), 4.65 (triplet, H-4), 4.30 (complex multiplet, H-5), 3.79 (complex multiplet, H-6), 3.51 (complex multiplet, H-6′), 2.83 (broad singlet, OH), and 2.11 (acetoxy methyl). The methylene groups at C-1 and C-6 (16 spectral lines) and methine protons at C-2, C-3, C-4, and C-5 form two ABXY patterns.

2-O-Acetyl-1,4:3,6-dianhydro-5-O-(methylsulfonyl)-D-glucitol (**7**) *and -D-mannitol* (**8**). — The methanesulfonates of **5** and **6** were obtained by the procedures of Montgomery and Wiggins[4] and Wiggins[5] in 83% yields, and were crystallized from methanol; for **7**, m.p. 81.5–83°, $[\alpha]_D^{20}$ +102° (*c* 0.5, chloroform); n.m.r. data (chloroform-*d*): δ 4.01 (complex multiplets, H-1 and H-1′), 5.19 (complex multiplet, H-2), 4.49 (broad doublet, H-3), 4.81 (triplet, H-4), δ 5.03 (triplet, H-5), 3.84 (complex multiplets, H-6 and H-6′), 3.11 (mesyl methyl), and 2.06 (acetoxyl methyl). Compound **8** (syrup) had $[\alpha]_D^{20}$ +148° (*c* 0.5, chloroform); n.m.r. (chloroform-*d*): δ 3.89 (complex multiplets, H-1 and H-1′), 5.03 (complex multiplets, H-2 and H-5), 4.64 (complex multiplets, H-3 and H-4), 3.89 (complex multiplets, H-6 and H-6′), 3.11 (mesyl methyl), and 2.11 (acetoxyl methyl).

2(5)-O-Acetyl-5(2)-chloro-5(2)-deoxy-1,4:3,6-dianhydro-L-iditol (**9**). — Compound **7** was boiled with an excess of pyridine hydrochloride in pyridine[11] under reflux for 48 h. After evaporation of the solvent, the residual mixture was separated by dry-column chromatography on Silica Gel G (5% water) with 60% ethyl acetate–cyclohexane as eluent. A 73% yield of **9** was obtained (5.0 g of syrup); $[\alpha]_D^{20}$ +99.0° (*c* 1, chloroform), n.m.r. (benzene-d_6): δ 3.72 (complex multiplets, H-1 and H-1′), 5.08 (complex multiplet, H-2), 4.62 (complex multiplets, H-3 and H-4), 4.06 (doublet, H-5), 3.72 (complex multiplets, H-6 and H-6′), and 1.72 (acetoxy methyl).

2(5)-O-Acetyl-5(2)-chloro-5(2)-deoxy-1,4:3,6-dianhydro-D-glucitol (**10**). — Compound **8** was boiled with an excess of pyridine hydrochloride in pyridine[11] under reflux for 48 h. Isolation and dry-column chromatography was the same as for **9**. Compound **10** was obtained in 71% yield (syrup); $[\alpha]_D^{20}$ +117° (c 1.2, chloroform); n.m.r. (benzene-d_6): δ 3.66 (complex multiplets, H-1 and H-1′), 3.86 (complex multi-

plet, H-2), 4.15 (broad doublet, H-3), 4.61 (quartet, H-4), 4.76 (triplet, H-5), 3.44 (complex multiplets, H-6 and H-6'), and 1.69 (acetoxyl methyl).

2(5)-Chloro-2(5)-deoxy-1,4:3,6-dianhydro-L-*iditol* (**11**). — This compound was obtained by deacetylation[19] of **9** and recrystallized from anhydrous ether (yield 0.8 g, 80%); m.p. 64.6–65.5°, $[\alpha]_D^{20}$ +52° (*c* 0.5, chloroform); reported m.p. 63–64°, $[\alpha]_D^{19}$ +48° (*c* 1.625, chloroform)[18]; n.m.r. (chloroform-*d*): δ 4.01 (high-intensity doublet, H-1 and H-1'), 4.29 (complex multiplet, H-2 and H-5), 4.63 (broad doublet, H-3), 4.76 (broad doublet, H-4), 3.85 (high-intensity doublet, H-6 and H-6'), and 2.78 (hydroxyl proton).

2-Chloro-2-deoxy-1,4:3,6-dianhydro-D-*glucitol* (**12**). — This compound was obtained by deacetylation[19] of **10** in 79% yield; $[\alpha]_D^{20}$ +52° (*c* 1, chloroform); n.m.r. (chloroform-*d*): δ 4.11 (high-intensity doublet, H-1 and H-1'), δ 4.32 (complex multiplet, H-2), 4.56 (broad doublet, H-3), 4.68 (triplet, H-4), 4.24 (complex multiplet, H-5), 3.54 (doublet of doublets, H-6), 3.86 (doublet of doublets, H-6'), and 2.64 (hydroxyl proton). The methylene group at C-6 and methine group at C-5 gave a clear ABX pattern.

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