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THE ACTION OF ALKALI ON DI-*O*-(2-BROMOETHYLIDENE)-D-MANNITOLS: FORMATION OF AN UNUSUALLY ACID-STABLE ACETAL LINKAGE

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ABSTRACT

When *cis,trans*-1,2:5,6-di-*O*-(2-bromoethylidene)-D-mannitol and *cis,cis*-1,2:5,6-di-*O*-(2-bromoethylidene)-D-mannitol were treated with dilute, boiling sodium hydroxide, 5,6-*O*-(*S*)-(2-bromoethylidene)-3:1,2-*O*-[(*R*)-1-ethanyl-2-ylidene]-D-mannitol (**3**) and 3:1,2;4:5,6-di-*O*-[(*R*)-1-ethanyl-2-ylidene]-D-mannitol (**10**) were produced; the structures were established by a combination of chemical transformations, ^{1}H-n.m.r. spectroscopy, and mass spectrometry. The bicyclo ether–acetal linkage in **3** and **10** proved unusually resistant to hydrolysis by acid.

INTRODUCTION

When D-mannitol was allowed to react with bromoacetaldehyde (as its diethyl acetal) in 9M sulfuric acid, a solid was isolated that, by repeated recrystallization, was separated into two di-*O*-(2-bromoethylidene)-D-mannitols[1]. Elemental analysis, derivatization, and ^{1}H-n.m.r. spectroscopy determined that the stereochemistry of the substituents on the acetal rings were as shown in **1** and **2**. A five-membered cyclic acetal was unexpected because (*a*) most reported polyol–aldehyde reactions yield six-membered cyclic acetals[2], and especially, (*b*) the related galactitol (dulcitol) and chloroacetaldehyde produce[3a] a six-membered cyclic acetal, 1,3:4,6-di-*O*-(2-chloroethylidene)galactitol.

Originally, the stereochemistry at the acetal carbon atom of the chloroethylidenegalactitol was unknown, but later work[3b] established the stereochemistry. The action of alkali on the chloroethylidenegalactitol eliminated the elements of hydrogen chloride from the hydroxyl groups of the polyol and the chloromethyl groups of the acetal, to yield a 2,6,8-trioxabicyclo[2.2.2]octyl system[3b]. This bicyclo-acetal exhibited most unusual properties: a high melting point of ~265°, very low solubility in water, and resistance to hydrolysis by acid.

To determine if the di-*O*-(2-bromoethylidene) derivatives of D-mannitol undergo a displacement similar to that of the chloroethylidenegalactitol, a study of the action of alkali on **1** and **2** and an evaluation of the products were undertaken.

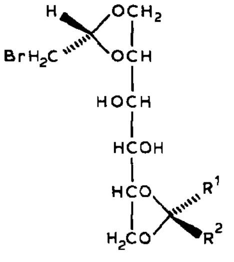
RESULTS AND DISCUSSION

When the diacetal **1** was heated in boiling sodium hydroxide solution, there was obtained, after work-up, a crystalline compound **3**, the elemental analysis of which agreed with the loss of the elements of hydrogen bromide from the starting compound. Two one-proton acetal methine signals can be seen by ^{1}H-n.m.r. spectroscopy: at 5.20 (triplet) corresponding to a proton, coupled with a methylene group appearing at δ 3.35; these signals are assigned[1] to a bromoethylidene group, and δ 5.36 (singlet) assigned to the newly formed bicyclo ether-acetal methine proton. It was evident that **1** had undergone a displacement of bromide on one bromoethylidene acetal group with either the OH-3 or OH-4 group of the mannitol, to form a bicyclo ether-acetal. The presence of a hydroxyl group in **3** was indicated by a doublet in the ^{1}H-n.m.r. spectrum and by its conversion by acetic anhydride–pyridine into the monoacetate **4**.

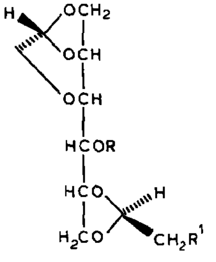
Catalytic hydrogenolysis of **4** (or **3**) with 5% Pd–C in alcoholic potassium hydroxide resulted, after work-up, in a crystalline compound, m.p. 64–66°, whose elemental analysis indicated that both saponification of the ester group and hydrogenolysis of the carbon–halogen bond had occurred. Structure **5** was assigned to this compound on the basis of the ^{1}H-n.m.r. spectrum, notably a three-proton methyl doublet (δ 1.33) coupled to a one-proton methine quartet (δ 5.06), corresponding to an ethylidene acetal.

When compound **5** was dissolved in 90% trifluoroacetic acid[4], a slightly exothermic reaction occurred. After removal of the trifluoroacetic acid, and purification by column chromatography, a crystalline compound was obtained. Its elemental analysis, and ^{1}H-n.m.r. spectrum showed, by a one-proton singlet methine peak at δ 5.34, that hydrolysis had not occurred, and that the bicyclo ether-acetal was present. Another acetal methine signal (δ 4.62, quartet) was upfield from the methine quartet (δ 5.06) of the starting **5**. A one-proton doublet (δ 2.00), which disappeared on addition of D_2O, established the presence of a secondary hydroxyl group, eliminating consideration of any 4,5- or 3,5-*O*-ethylidene acetal. Earlier work[1,5] had established that the signal of the methine proton of a *cis*-5,6-*O*-ethylidene group will be 0.09–0.14 p.p.m. upfield from that of the *trans* isomer. Since the methine proton here is 0.44 p.p.m. upfield, a *cis*-5,6-*O*-ethylidene acetal can be discounted. Consequently, a 4,6-*O*-ethylidene structure **9** was assigned, with an all-equatorial arrangement[6] of substituents on the 4,6-*O*-ethylidene ring.

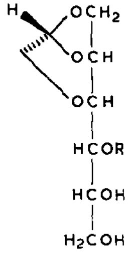
We assume that, if the OH-4 group in **5** is blocked by an acid-stable protecting group, addition of water to the oxocarbenium ion would prevail, and subsequent hydrolysis of the acetal would occur. A benzoic ester was selected specifically, because benzoates are not generally prone to acid hydrolysis. Reaction of **5** with benzoyl chloride–pyridine yielded the corresponding benzoate **6**. Treatment of **6** with 90% trifluoroacetic acid yielded, after work-up, a crystalline compound **7**, identified by analysis, ^{1}H-n.m.r. spectroscopy, and periodate oxidation.



1 $R^1 = H, R^2 = CH_2Br$
2 $R^1 = CH_2Br, R^2 = H$



3 $R = H, R^1 = Br$
4 $R = Ac, R^1 = Br$
5 $R = H, R^1 = H$
6 $R = Bz, R^1 = H$

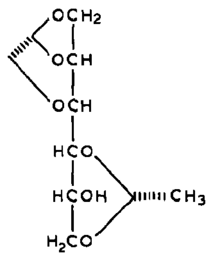


7 $R = Bz$
8 $R = H$

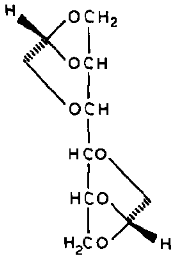
Treatment of **7** with base resulted in a syrup that tenaciously held traces of water; thus periodate oxidations of this syrup never reached the theoretical value (two molar equivalents), but was close enough (1.9) to leave little doubt that the 1,2,3-triol grouping of compound **8** had been oxidized.

Every product to this point could be accounted for by an internal ether formed with either OH-3 or OH-4 of the starting D-mannitol. However, the only product to contain a 1,2,3-triol arrangement, as shown in **8**, had to be derived from an ether formed between the OH-3 group of the starting D-mannitol and the *cis*-1,2-*O*-(2-bromoethylidene) acetal. Thus, all of the structures shown must be correct.

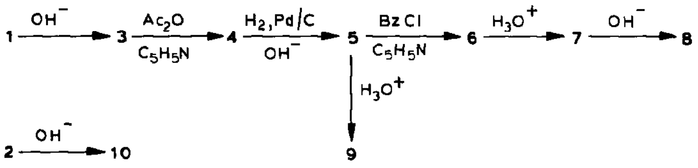
When diacetal **2** was heated with dilute sodium hydroxide, a crystalline compound was isolated (after work-up) and structure **10** was assigned from its mass spectrum, which showed ions at *m/z* 230 (M+) and 115 (one-half M+), indicating a symmetrical structure. The ^{1}H-n.m.r. spectrum was most simple: three protons (δ



9



10



3.74, 4.29, and 4.55) showed moderate coupling. Signals at δ 5.28 and 3.62 were assigned to the bicyclo ether-acetal protons.

Proton chemical-shifts for **10** agreed with the literature reports[7] for 3,6,8-trioxabicyclo[3.2.1]octyl structures. That the 1-ethanyl-2-ylidene protons were also singlets agreed with literature reports[7].

The acid stability of the bicyclo ether–acetal, a 3,6,8-trioxabicyclo[3.2.1.]-octyl structure, was unexpected, especially because bicyclo-heptyl and -octyl acetals are solvolyzed faster than aliphatic acetals in acid[8]. Unaltered **10** (10%) was recovered after 6–7 h in boiling M hydrochloric acid. Similar results were obtained on treatment of **3**, **5**, and **7** with acid. It is worth mentioning that polyol methylidene acetals are notably resistant to acid hydrolysis[2,9]. 1,3:2,4:5,6-Tri-*O*-methylene-D-glucitol requires 1.2–1.5 in boiling M hydrochloric acid for hydrolysis. The acid-hydrolysis rate[10] of 1,3-dioxolanes depends on the nature of the attached groups and the steric crowding on the dioxolane ring. As more electron-donating groups are present at O-2, the rate is higher, and, with more steric crowding on the ring, the rate is lower. Models of the bicyclo ether-acetal show nothing to indicate that the alkyl groups at O-2 or the steric crowding around the dioxolane ring are factors sufficiently unusual to explain the exceptional resistance to acid hydrolysis. Some factor now unrecognized has altered either the reaction pathway or the rate-determining step.

EXPERIMENTAL*

General methods. — Melting points are uncorrected. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tennessee, U.S.A. Solutions were evaporated under vacuum. T.l.c. was performed on air-equilibrated, precoated plates of 0.25-mm layers of silica gel F-254 (E. Merck) with the specified solvents. Spots were rendered visible by spraying with 5% ethanolic sulfuric acid and heating until charring occurred. Dry column chromatography was performed on Woelm TSC silica by dissolving the sample in a small amount of low boiling solvent, adding Woelm TSC silica to obtain a free-flowing powder, placing the powder on the dry column, and developing the column with solvent. Each fraction was monitored by t.l.c., and the appropriate fractions were pooled and concentrated. ^{1}H-N.m.r. spectra were recorded with either a Varian XL-100 or a Bruker WM-300WB spectrometer. Chemical shifts (δ, in p.p.m.) were compared against internal Me_4Si or sodium 4,4-dimethyl-4-silapentane-1-sulfonate, and couplings are given in Hz. Mass spectra were recorded with a DuPont 491 spectrometer. Optical rotations were measured on a Perkin–Elmer Model 241 polarimeter at 22°. *cis*, *cis*- and *cis*, *trans*-1,2:5,6-Di-*O*-(2-bromoethylidene)-D-mannitol (**1** and **2**) were prepared according to ref. 1.

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*The mention of trade products does not imply that they are endorsed by the Department of Agriculture over similar but unmentioned products.

5,6-O-(S)-*(2-Bromoethylidene)-3:1,2*-O-[(R)-*1-ethanyl-2-ylidene*]-D-*mannitol* (**3**). — Compound **1** (1.96 g) was dissolved in water (250 mL) by heating the solution to boiling. To the stirred, boiling solution was added dropwise 1.8M sodium hydroxide (15 mL) during 1 h. After 2 h of additonal boiling, the solution was cooled. Carbon dioxide was bubbled through the mixture, to neutralize the excess of sodium hydroxide, and the mixture was concentrated to ~150 mL. The solution was placed in a continuous extractor, and ethyl acetate was percolated for 42 h. Evaporation of the extract gave a syrup that slowly crystallized (yield 1.23 g), m.p. 82–160°. On dissolving the crude product in hot water (12 mL) and cooling, crystalline **3** was deposited; 0.63 g (40.5% yield), m.p. 89–91°, $[\alpha]_D$ +8.9° (*c* 0.298, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 5.36 (s, 1 H, $CHCH_2$), 5.20 (t, 1 H, *J* 4.2 Hz, $CHCH_2Br$), 4.59 (d, 1 H, *J* 5.2 Hz, H-3), 4.39 (d, 1 H, *J* 7.3 Hz, H-2), 4.26 (dd, 1 H, *J* 6.0, 8.6 Hz, H-5), 3.94–3.97 (m, 2 H, H-1,1′), 3.76–3.80 (m, 2 H, H-6,6′), 3.67 and 3.72 (AB, 2 H, J_{AB} 11.3 Hz, $CHCH_2$), 3.50 (dd, 1 H, *J* 5.2, 8.5 Hz, H-4), 3.65 (d, 2 H, *J* 4.2 Hz, $CHCH_2Br$), and 2.61 (d, 1 H, *J* 4.3 Hz, OH).

Anal. Calc. for $C_{10}H_{15}BrO_6$: C, 38.60; H, 4.86; Br, 25.68. Found: C, 38.42; H, 5.15; Br, 25.53.

4-O-*Acetyl-5,6*-O-(S)-*(2-bromoethylidene)-3:1,2*-O-[(R)-*1-ethanyl-2-ylidene*]-D-*mannitol* (**4**). — A reaction was carried out as for the preparation of **3**, proceeding with the syrup* after removal of the ethyl acetate. The syrup was dissolved in pyridine (10 mL)–acetic anhydride (5 mL); after 16 h, the solution was evaporated, to afford a solid. Recrystallization from water (~170 mL) gave **4**, 1.3 g (73.6% yield); m.p. 144–146°, $[\alpha]_D$ +9.7° (*c* 0.312, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 5.31 (s, 1 H, $CHCH_2$), 5.18 (t, 1 H, *J* 4.9 Hz, $CHCH_2Br$), 5.10 (dd, 1 H, *J* 4.5, 6.9 Hz), 4.53 (d, 1 H, *J* 5.2 Hz, H-3), 4.36 (q, 1 H, *J* 6.8 Hz, H-2), 4.19 (dd, 1 H, *J* 6.2, 8.7 Hz, H-5), 3.65 and 3.67 (AB, J_{AB} 9.0 Hz, $CHCH_2$), 3.36 (d, 2 H, *J* 4.9 Hz, $CHCH_2Br$), and 2.12 (s, 3 H, CH_3CO).

Anal. Calc. for $C_{12}H_{17}BrO_7$: C, 40.81; H, 4.85; Br, 22.62. Found: C, 40.92; H, 5.06; Br, 22.69.

3:1,2-O-[(R)-*Ethanyl-2-ylidene*]-*5,6*-O-(S)-*ethylidene*-D-*mannitol* (**5**). — A suspension of potassium hydroxide (2.6 g, 85%) and **4** (6.0 g) in 95% ethanol (100 mL) was warmed slowly until it became homogeneous. After cooling to room temperature, 95% ethanol (100 mL) and 5% Pd–C (1.0 g) were added. The mixture was hydrogenated in a Parr apparatus with an initial hydrogen pressure of 0.34 MPa. Hydrogen uptake ceased after 1 h. The catalyst was removed by filtration through a bed of Celite; the bed was washed with ethanol (2 × 50 mL). Carbon dioxide was bubbled through the combined filtrate and washings. The solution was evaporated to a syrup, and warm ethyl acetate (10 mL) was added. The mixture

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*If **1** contains small amounts of **2**, compound **10** will be deposited from the reaction mixture. To remove **10**, the syrup is dissolved in methanol (~15 mL/g), an equal volume of ether is added, and the mixture is kept for 4 h at 5°. Compound **10** is separated by filtration, the filtrate is concentrated and acetylation is conducted.

was filtered, to remove insoluble material, and the filtrate was diluted with warm hexane (50 mL). Crystalline **5** was deposited when the solution was kept at 4–5°; 2.04 g (51.7% yield); m.p. 64.5–65.5°, $[\alpha]_D$ −30.0° (*c* 0.346, chloroform): ^{1}H-n.m.r. ($CDCl_3$): δ 5.35 (s, 1 H, C*H*CH$_2$), 5.06 (q, 1 H, *J* 4.8 Hz, C*H*CH$_3$), 4.60 (d, 1 H, *J* 5.2 Hz, H-3), 4.38 (d, 1 H, *J* 7.3 Hz, H-2), 4.22 (dd, 1 H, *J* 6.2, 8.7 Hz, H-5), 4.00 (dd, 2 H, *J* 6.8, 8.3 Hz, H-1,1′), 3.67 and 3.72 (AB, 2 H, J_{AB} 11.2 Hz, CHC*H*$_2$), 3.45 (m, 1 H, H-4), 2.52 (d, 1 H, *J* 4.9 Hz, OH), and 1.33 (d, 3 H, *J* 4.6 Hz, CHC*H*$_3$).

Anal. Calc. for $C_{10}H_{16}O_6$: C, 51.72; H, 6.94. Found: C, 51.65; H, 6.75.

4-O-Benzoyl-3:1,2-O-[(R)-1-ethanyl-2-ylidene]-5,6-O-(S)-ethylidene-D-mannitol (**6**). — Compound **5** (1.32 g) was dissolved in pyridine (15 mL), and benzoyl chloride (1.2 mL) was added. After 3 days at 4–5°, the mixture was poured into an ice–water slush. An oil separated that was slowly converted into crystalline **6**, 1.84 g (96.2% yield); m.p. 123.5–124.5°, $[\alpha]_D$ +26.4° (*c* 0.322, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 7.48–8.05 (m, 5 H, aryl), 5.36 (dd, 1 H, *J* 4.1, 6.8 Hz, H-4), 5.30 (s, 1 H, C*H*CH$_2$), 5.06 (q, 1 H, *J* 4.8 Hz, C*H*CH$_3$), 4.61 (d, 1 H, *J* 5.2 Hz), 4.41 (q, 1 H, *J* 7.0 Hz), 4.74 (m, 1 H), 4.19 (dd, 1 H, *J* 6.3, 9.0 Hz), 3.83 (m, 1 H), 3.65 and 3.69 (AB, 2 H, J_{AB} 11.5 Hz, CHC*H*$_2$), 3.65 (d, 1 H, *J* 1.4 Hz), and 1.34 (d, 3 H, *J* 5.0 Hz, CHC*H*$_3$).

Anal. Calc. for $C_{17}H_{20}O_7$: C, 60.70; H, 5.99. Found: C, 60.66; H, 6.00.

3:1,2-O-[(R)-1-Ethanyl-2-ylidene]-4,6-O-(R)-ethylidene-D-mannitol (**9**). — Compound **5** was dissolved in 90% trifluoroacetic acid (5 mL), and a slightly exothermic reaction occurred. After 0.25 h, t.l.c. with 1:2 (v/v) toluene–ethyl acetate revealed a single spot, R_F 0.34 (R_F for **5**, 0.5). The mixture was concentrated, and the concentrate transferred to a continuous extractor by using 5% sodium hydrogencarbonate. Ethyl acetate was percolated for 16–18 h. Removal of the ethyl acetate left a syrup that, when covered with ether (4 mL), was converted into crystalline **9**: m.p. 173–175°. Recrystallization from ethanol (1 mL) gave pure **9**: 96 mg (29.2% yield); m.p. 181–183°, $[\alpha]_D$ −46.1° (*c* 0.388, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 5.34 (s, 1 H, C*H*CH$_2$), 4.62 (q, 1 H, *J* 5.0 Hz, C*H*CH$_3$), 3.80 (m, 1 H), 3.72 (s, 2 H, CHC*H*$_2$), 3.47 (dd, 1 H, *J* 4.5, 9.5 Hz, H-4), 2.00 (d, 1 H, *J* 4.5 Hz, OH), and 1.34 (d, 3 H, *J* 5.2 Hz, CHC*H*$_3$).

Anal. Calc. for $C_{10}H_{16}O_6$: C, 51.72; H, 6.94. Found: C, 51.55; H, 6.96.

4-O-Benzoyl-3:1,2-O-[(R)-1-ethanyl-2-ylidene]-D-mannitol (**7**) *and 3:1,2-O-[(R)-1-ethanyl-2-ylidene]-D-mannitol* (**8**). — Compound **6** (1.0 g) was dissolved in 90% trifluoroacetic acid (10 mL). After 2 h, t.l.c. with 1:2 (v/v) toluene–ethyl acetate revealed successively: unaltered **6** (R_F 0.75), an unknown compound (R_F 0.4), and **7** (R_F 0.3). The solution was evaporated to a syrup which was chromatographed by developing with toluene–ethyl acetate (150:150, 100:120, and 0:300 mL:mL). From the appropriate fractions were isolated: unaltered **6**, 0.1 g; syrupy unknown, 48 mg; and crystalline **7**, 0.62 g. ^{1}H-N.m.r. spectroscopy on the syrupy unknown compound revealed a benzoic ester and the bicyclo ether-acetal group; the unknown was probably an isomer of **7**, and was not further studied. Recrystallization of crude **7** from 1:1 (v/v) ethanol–ether (6 mL) gave **7**: 0.2 g (21.6% yield); m.p. 109–110°, $[\alpha]_D$ −23.3° (*c* 0.378, chloroform); ^{1}H-n.m.r. ($\mathrm{CDCl_3}$): δ 7.48–8.07 (m, 5 H, aryl), 5.34 (s, 1 H, $\mathrm{C}H\mathrm{CH_2}$), 5.14 (dd, 1 H, *J* 4.2, 8.6 Hz), 4.61 (d, 1 H, *J* 5.2 Hz, H-3), 4.39 (d, 1 H, *J* 7.7 Hz, H-2), 4.00 (m, 1 H, H-5), 3.72 (s, 2 H, $\mathrm{CHC}H_2$), 2.56 (dd, 1 H, *J* 5.1, 7.9 Hz, OH-6), and 2.99 (d, 1 H, *J* 7.8 Hz, OH-5).

Periodate oxidation[11] of **7** consumed 1.1, 1.09, and 1.1 mol. equiv.; standard methyl α-D-mannopyranoside consumed 2.01, 2.06, and 2.05 mol. equiv.

Anal. Calc. for $\mathrm{C_{15}H_{18}O_7}$: C, 58.06; H, 5.84. Found: C, 58.05; H, 5.88.

The mother liquor from the recrystallization of **7** was concentrated, and the resulting solid was dissolved in 20:10:1 (v/v) ethanol–water–M sodium hydroxide. After standing for 2 h, carbon dioxide was bubbled through the mixture, and then the solution was concentrated to 10 mL, and the concentrate poured into a continuous extractor. Ethyl acetate was percolated for 64 h, and the extract was evaporated to a syrup. T.l.c. with 10:1 (v/v) ethyl acetate–methanol revealed **7** (R_F 0.7) and **8** (R_F 0.4). Dry column chromatography involving developing with ethyl acetate–methanol mL:mL (500:50; 400:80), separated **8** as a hygroscopic syrup; yield, ~0.2 g.

Periodate oxidation[11] of **8** consumed 1.90, 1.94, and 1.92 mol. equiv.; standard methyl α-D-mannopyranoside consumed 2.01, 2.06, and 2.05 mol. equiv.

*3:1,2;4:5,6-Di-*O-[(R)-*1-ethanyl-2-ylidene*]-D-*mannitol* (**10**). — Compound **2** (8.0 g) was dissolved in boiling water (500 mL), and 0.2M sodium hydroxide (200 mL) was added during ~3 h to the stirred, boiling solution. The solution was cooled, and carbon dioxide was bubbled through the solution. Crystalline **10** (4.30 g); m.p. 225–228° separated as the solution was concentrated to ~150 mL. Continuous extraction of the filtrate with ethyl acetate yielded additional **10** (0.26 g); (97.0% combined yield); ^{1}H-n.m.r. ($\mathrm{CDCl_3}$): δ 5.28 (s, 1 H, $\mathrm{C}H\mathrm{CH_2}$), 4.55 (d, 1 H, *J* 2.7 Hz, H-2), 4.29 (d, 1 H, *J* 5.0 Hz, H-1'), 3.88 (s, 1 H, H-3), 3.74 (dd, 1 H, *J* 5.0, 2.7 Hz, H-1), and 3.62 (s, 2 H, $\mathrm{CHC}H_2$); *m/z* 230, $\mathrm{M}^{+\cdot}$ (32); 200, $\mathrm{M}^{+\cdot} - \mathrm{CH_2O}$ (9); 154, $\mathrm{M}^{+\cdot} - \mathrm{CH_2O} - \mathrm{HCO_2H}$ (27); and 115, 0.5 $\mathrm{M}^{+\cdot}$ (41) (values in paentheses are percentages of the base peak *m/z* 57 = 100%).

Anal. Calc. for $\mathrm{C_{10}H_{14}O_6}$: C, 52.17; H, 6.13. Found: C, 51.73; H, 6.33.

Acid treatment studies. — After boiling a solution of **10** (250 mg) in M hydrochloric acid (25 mL) for 6.5 h, 25 mg of **10** was recovered after neutralization, and continuous extraction with ethyl acetate for 18 h. After exhaustive dialysis and freeze-drying of the aqueous portion, a dark-brown solid (0.10 g, 40%) was isolated. Similar treatment of **3**, **5**, and **7** produced 3–6% wt. recovery of unaltered starting compound from the ethyl acetate extract, and 20–40% of brown solid from the aqueous portion. Complete hydrolysis had occurred within 1.5 h when 1,3:2,4:5,6-tri-*O*-methylene-D-glucitol was boiled in M hydrochloric acid.

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