The Base-Catalysed Rearrangement of Dibromo Alditols via Epoxide Migration

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The reaction of 2,6-dibromo-2,6-dideoxy-D-mannitol (**1**) and -D-glucitol (**12**) with aqueous base has been studied. With potassium carbonate **1** forms epoxides which are subsequently hydrolysed to a mixture of D-mannitol and D-glucitol. The same treatment of **12** yields almost only D-glucitol. With aqueous potassium hydroxide both **1** and **12** undergo rearrangement through epoxide migration. Thus **1** is mainly converted into 2,5:3,4-dianhydro-L-altritol (**10**) whereas **12** yields 1,4:3,6-dianhydro-L-glucitol (**18**). The reactions were monitored using ^{13}C NMR spectroscopy.

The conversion of bromodeoxy-, mesylated-, or tosylated alditols into epoxides is well known.[1-4] Similarly, bromodeoxy aldonolactones are converted into epoxides by treatment with base, and with strong base epoxide migration takes place. This may lead to inversion of the stereochemistry of several carbon atoms and formation of isomerized aldonic acids or of their anhydrides.[5-7] Epoxide migration was also observed when 3,4-anhydro-D-altritol was treated with strong base.[8]

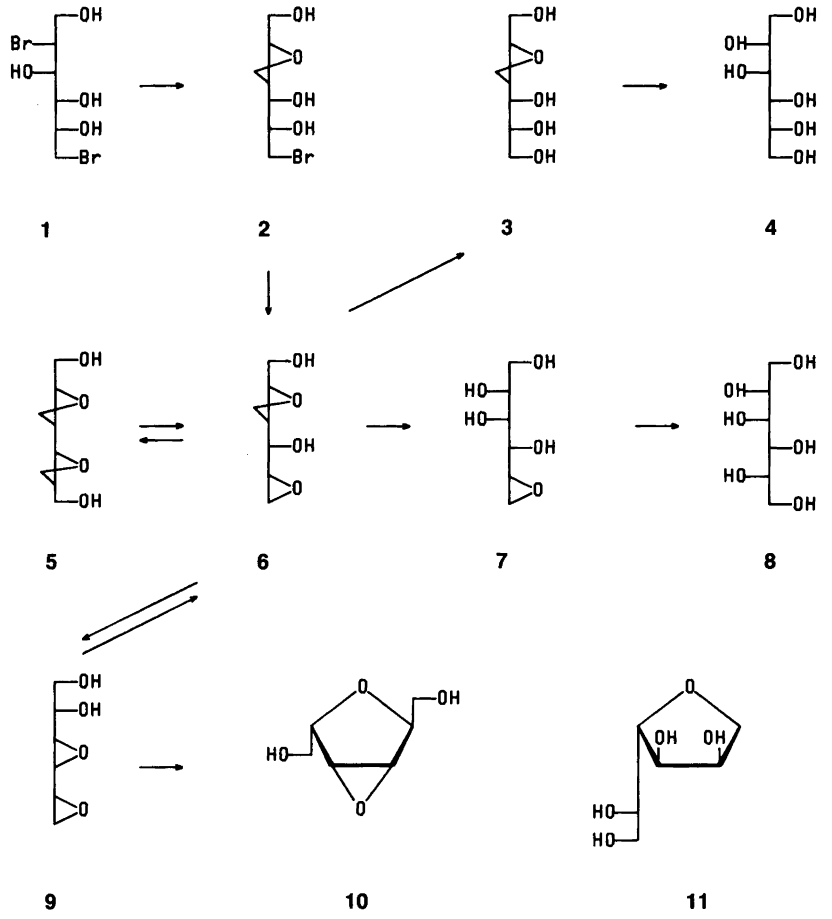
Since 2,6-dibromo-2,6-dideoxy-D-mannitol (**1**) is readily available[9] and the corresponding D-glucitol derivative (**12**) could be obtained from 2,6-dibromo-2,6-dideoxy-D-glucono-1,4-lactone[10] it was decided to study the behaviour of these dibromopolyols towards aqueous potassium carbonate and hydroxide.

When 2,6-dibromo-2,6-dideoxy-D-mannitol (**1**) was treated with excess aqueous potassium carbonate at 20 °C, a complex mixture of products was rapidly formed; ca. 1 week was required to complete the reaction and at this stage only D-mannitol (**4**) and D-glucitol (**8**) were present. The course of the reaction was monitored using ^{13}C NMR spectroscopy and the results are shown in Table 1.

The first product formed is apparently 2,3-anhydro-6-bromo-6-deoxy-D-glucitol (**2**) which could be isolated in 40 % yield after reaction for 15 min. The structure of **2** was deduced from its ^{13}C and ^{1}H NMR spectra and from its conversion into **1** by treatment with aqueous hydrogen bromide. On further reaction with potassium carbonate **2** is converted into 2,3:5,6-dianhydro-D-glucitol (**6**) which subsequently undergoes hydrolysis to a mixture of 2,3-anhy-

Table 1. Products observed during the reaction of 2,6-dibromo-2,6-dideoxy-D-mannitol (**1**) with K_2CO_3 (2.5 mol equiv.) or KOH (5 mol equiv.) in H_2O-D_2O at 20 °C.

Base	Time	Products in relative percentages										
		1	**2**	**6**	**3**	**7**	**4**	**8**	**5**	**9**	**10**	**11**
K_2CO_3	15 min	28	43	22	7							
K_2CO_3	30 min	6	50	41	4							
K_2CO_3	4 h	0	32	55	12							
K_2CO_3	32 h		12	23	37	13	13	5				
K_2CO_3	52 h		0	13	36	13	29	13				
K_2CO_3	76 h			0	27	6	44	22				
K_2CO_3	4 days				21	6	47	26				
K_2CO_3	9 days				0	0	69	31				
KOH	10 min								62	38		
KOH	20 min								61	29	11	
KOH	40 min								53	24	19	4
KOH	6 h								15	0	67	17
KOH	20 h								0		78	22



dro-D-glucitol (**3**) and 5,6-anhydro-D-mannitol (**7**). The latter two finally yield D-mannitol (**4**) and D-glucitol (**8**), respectively, as the only detectable products. The epoxides **3**, **6** and **7** could not be isolated and their proposed structures are based on the ^{13}C NMR spectra (Table 3) and on their conversion into **4** and **8**. The signals of **3** at 57.6 and 57.9 ppm indicate that it is a disecondary epoxide whereas **7** shows signals at 46.6 and 53.7 ppm corresponding to a terminal epoxide.[5,6] The diepoxide **6** shows both types of signal.

When **1** was boiled with aqueous potassium carbonate the reaction was complete within 2 h and the resulting solution contained a mixture of **4** and **8** as almost the only products. The two products were isolated and their optical purities were ascertained.

The reaction of **1** with excess aqueous potassium hydroxide (Table 1) led to the immediate formation of a mixture of the diepoxides **5** and **9**. The main product (**5**) was easily identified by the ^{13}C NMR spectrum which showed only 3 signals (Table 3). When the reaction was interrupted after 5 min crystalline 2,3:4,5-dianhydro-L-iditol (**5**) could be isolated in 44 % yield; its structure was confirmed by comparison with the known D-enantiomer.[11] The 3,4:5,6-dianhydro-D-allitol (**9**) was identified only by its ^{13}C NMR spectrum (Table 3) which showed signals at 58.7 and 61.0 ppm for a disecondary epoxide and at 55.1 and 47.6 ppm, corresponding to a terminal epoxide. The epoxides **5** and **9** may be formed from **6**, which was not observed in potassium hydroxide solution, through epoxide migration catalysed by the strong base.

Further reaction of **1** with potassium hydroxide for 20 h gave the final products **10** and **11** together with small amounts of unidentified products. The main product,

Table 2. Products observed during the reaction of 2,6-dibromo-2,6-dideoxy-D-glucitol (**12**) with K_2CO_3 (2.5 mol equiv.) in H_2O-D_2O at 20 °C.

Time	Products in relative percentages						
	12	**13**	**14**	**18**	**20**	**19**	**8**
25 min	31	55	7	7			
50 min	17	65	6	12			
5 h	6	43	2	26	16		
24 h	0	14	0	17	52	5	7
48 h		4		4	49	8	20
72 h		0		0	26	10	40
6 days					14	10	54
9 days					7	10	56
18 days					0	11	60

2,5:3,4-dianhydro-L-altritol (**10**), was isolated as a syrup which was characterized by its spectra. The minor product (**11**) could not be obtained pure but only as a mixture which contained ca. 10% 1,4-anhydromannitol. The ^{13}C NMR spectrum of **11** was identical with that of 1,4-anhydro-D-allitol[10,12] and the optical rotation of the impure product suggested that it was 1,4-anhydro-L-allitol, probably formed from **3** by substitution of O-6 upon C-3. The epoxides **5** and **9** are probably in equilibrium via **6**, and **10** must be formed from **9** by attack of O-2 on C-5.

The reaction of 2,6-dibromo-2,6-dideoxy-D-glucitol (**12**) with excess potassium carbonate was also monitored by ^{13}C NMR spectroscopy (Table 2). Rapid formation of 5,6-anhydro-2-bromo-2-deoxy-D-glucitol (**13**) and small amounts of 2,3-anhydro-6-bromo-6-deoxy-D-mannitol (**14**) was observed. Their structures are derived from the ^{13}C NMR spectra (Table 3) as described above. 2,3:5,6-Dianhydro-D-mannitol (**16**) was also formed rather rapidly and is apparently hydrolysed to 2,3-anhydro-D-mannitol (**20**) the concentration of which builds up over 1–2 days. The completion of the reactions required ca. 2 weeks at 20 °C and led to the predominant formation of D-glucitol (**8**), which is probably formed by hydrolysis of **20**. A small amount of 3,6-anhydroaltritol, probably the D-enantiomer (**19**), was also observed in the ^{13}C NMR spectra;[13] it may be formed from **20** by attack of O-6 on C-3. The intermediates **13, 14, 16** and **20** could not be isolated in a pure state. When **12** was heated to 100 °C with potassium carbonate the reaction was complete with 2–3 h. Under these conditions, **8** and **19** were formed in equal amounts together with a number of minor products. From this mixture **8** was isolated as its hexaacetate the optical rotation of which proved that it was the D-enantiomer. Neither **19** not its acetate could be obtained pure.

Table 3. ^{13}C NMR spectra (in ppm) of intermediates and products observed in the reactions of 2,6-dibromo-2,6-dideoxy-D-mannitol (**1**) and 2,6-dibromo-2,6-dideoxy-D-glucitol (**12**) with aqueous base.

Compound	C-1	C-2	C-3	C-4	C-5	C-6
1	63.9	56.0	72.0[a]	70.3[a]	69.9[a]	39.0
2	61.5	57.4[b]	58.0[b]	72.08[a]	72.12[a]	37.4
3	61.6	57.6[b]	57.9[b]	71.6[a]	73.7[a]	63.3
5	62.3	56.4[a]	59.3[a]	59.3[a]	56.4[a]	62.3
6	61.4	57.1	52.2[a]	70.0	53.8[a]	45.9
7	62.0	69.9[a]	72.0[a]	79.0[a]	53.7	46.6
9	62.7	73.8	58.7[b]	61.0[b]	55.1	47.6
10	61.1[a]	80.5[a]	58.3[b]	58.9[b]	78.8[a]	61.8[a]
11	72.8[a]	72.7[a]	72.2[a]	82.5	72.1[a]	63.1
12	64.0	60.4	70.5[a]	70.9[a]	72.4[a]	38.5
13	64.2	58.3	72.4[a]	72.9[a]	53.1	46.2
14	61.1	59.6	59.6	71.6[a]	71.8[a]	37.1
16	60.6	58.5[b]	58.7[b]	69.7	52.9	46.0
17	61.9	71.5	60.2[b]	60.9[b]	55.1	47.6
19	63.9	71.8[a]	81.8	71.9[a]	72.9[a]	73.4
20	61.0	59.3[b]	59.6[b]	70.7[a]	73.3[a]	63.0

[a,b]The assignments may be reserved.

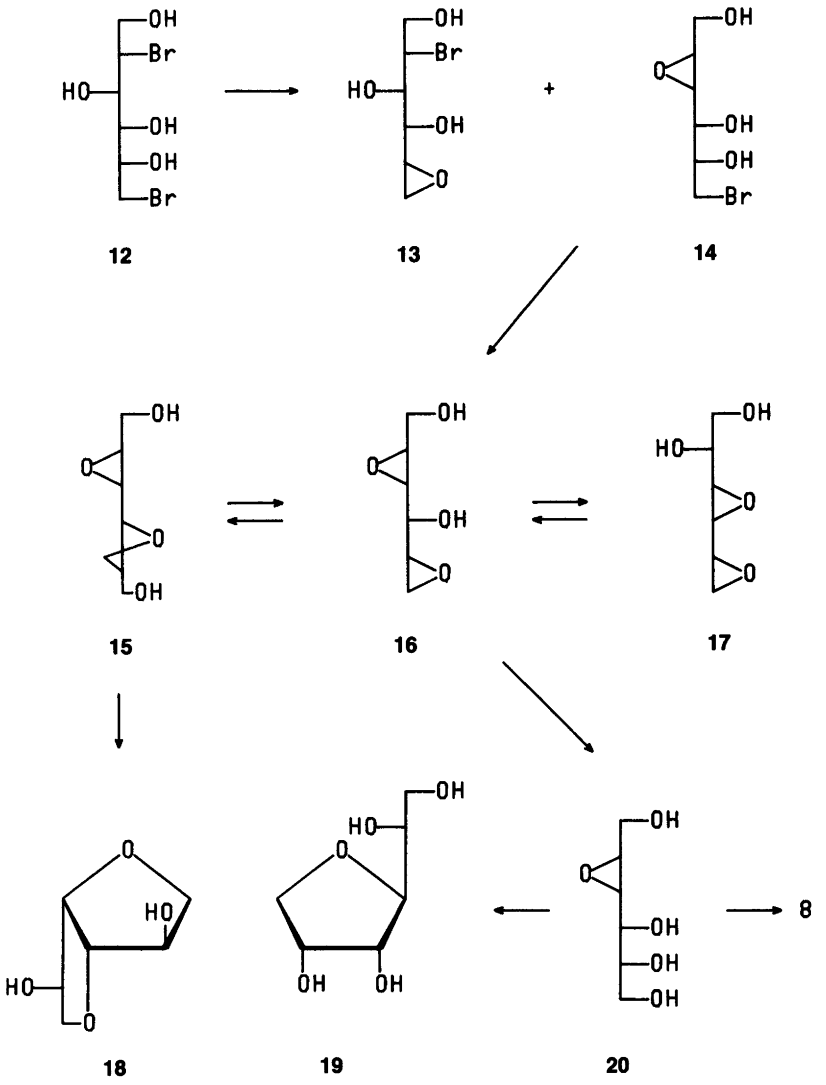
The reaction of **12** with aqueous potassium hydroxide was complete within 20–30 min at 20 °C and gave, as the only observed product, 1,4:3,6-dianhydro-L-glucitol (**18**) which was isolated in 74% yield. The only intermediate observed during this reaction was a diepoxide, presumably 3,4:5,6-dianhydro-D-altritol (**17**) as seen from the ^{13}C NMR spectrum (Table 3) which shows the presence of a di-secondary epoxide (60.2 and 60.9 ppm) and a terminal epoxide (55.1 and 47.6 ppm). The dianhydride (**18**), in which all four chiral carbon atoms of **12** have been inverted, is probably formed via 2,3:4,5-dianhydro-D-glucitol (**15**) which was not observed. The three diepoxides **16**, **15** and **17** could be in equilibrium in the strong base with the equilibrium shifted towards **17**. The conversion of **15** into **18** must take place by attack of O-1 on C-4 following by attack of O-6 on C-3, i.e. two favoured *exo*-openings.[14]

Hence, as found for bromodeoxyaldonolactones[5,6,7] treatment of **1** or **12** with aqueous potassium carbonate yields epoxides which are slowly hydrolysed. With aqueous potassium hydroxide the epoxides undergo rapid isomerization through epoxide migration and subsequently yield stable, five-membered anhydrides.

Experimental

Melting points are uncorrected. Optical rotations were measured on a Perkin Elmer 241 polarimeter. NMR spectra were obtained on Bruker AC-250 and AM-500 instruments using dioxane (67.40 ppm) as an internal reference for ^{13}C NMR spectra in D_2O. The course of the base-catalysed reactions (Tables 1 and 2) were monitored on samples prepared by dissolving 1 g of **1** or **12** in 3 ml of water containing 1.2 g (ca. 3 mol. equiv.) of anhydrous potassium carbonate or 1.1 g (5 mol. equiv.) of potassium hydroxide. The ^{13}C NMR spectra were measured in 5 mm sample tubes at 62.0 MHz on the solutions to which 20% D_2O and dioxane had been added. The relative percentages shown in Tables 1 and 2 were calculated from the peak heights of the signals. In some cases the percentages do not add up to 100 because small amounts of unidentified products were included in the calculations. For column chromatography the flash technique was used.

2,6-Dibromo-2,6-dideoxy-D-glucitol (**12**). A solution of 2,6-dibromo-2,6-dideoxy-D-glucono-1,4-lactone[9] (2.0 g) in water (40 ml) containing Amberlite IR-120 (H^+) ion-exchange resin (ca. 4 ml) was cooled in ice and stirred while sodium borohydride (0.3 g) was added at such a rate that the pH remained below 6. Further sodium borohydride (0.3 g) was then added allowing the pH to increase to ca. 9, and the stirring was continued for 30 min. Excess ion-exchange resin was then added until the pH was ca. 3. The mixture was filtered, the filtrate was evaporated and the residue was coevaporated with methanol (3×15 ml) to remove boric acid. This gave crude **12** (1.9 g, 95%) as a syrup which could not be induced to crystallize, $[\alpha]_D^{20}$ + 15.3°



(*c* 0.4, MeOH). A ^{13}C NMR spectrum (Table 3) (D_2O) showed no impurities.

Acetylation of **12** with acetic anhydride and perchloric acid followed by crystallization from ether–pentane gave 65 % of 1,3,4,5-tri-*O*-acetyl-2,6-dibromo-2,6-dideoxy-D-glucitol, m.p. 66–67 °C, $[\alpha]_D^{20}$ + 21.1° (*c* 2, $CHCl_3$). Anal. $C_{14}H_{20}Br_2O_8$: C, H, Br. ^{13}C NMR ($CDCl_3$): δ 70.8 (C-4), 69.3 (C-5), 68.4 (C-3), 64.4 (C-1), 48.1 (C-2), 30.1 (C-6) (assigned through the C{H} correlated spectrum).

*2,3-Anhydro-6-bromo-6-deoxy-*D*-glucitol* (**2**). To a solution of **1** (200 mg) in water (2 ml) was added potassium carbonate (90 mg, 1 mol equiv.) and the solution was kept at 20 °C for 15 min. The pH was then brought to 7–8 with 4 M hydrochloric acid and the water evaporated. The residue was subjected to preparative TLC using 3 elutions with dichloromethane–methanol (10:1). The fastest moving fraction gave 62 mg (40 %) of syrupy **2**, $[\alpha]_D^{20}$ − 19.9° (*c* 1.8, EtOH). Anal. $C_6H_{11}BrO_4$: C,H,Br. ^1H NMR (D_2O): δ 3.96 (H-1, $J_{1,2}$ 2.8 Hz), 3.61 (H-1′, $J_{1',2}$ 5.4, $J_{1,1'}$ 13.2 Hz), 3.33 (H-2, $J_{2,3}$ 2.8 Hz), 3.30 (H-3, $J_{3,4}$ 4.9 Hz), 3.65 (H-4, $J_{4,5}$ 7.5 Hz), 3.90 (H-5, $J_{5,6}$ 3.0, $J_{5,6'}$ 5.5 Hz), 3.74 (H-6, $J_{6,6'}$ 11.2 Hz), 3.66 (H-6′); for the ^{13}C NMR data see Table 3.

When **2** was treated with 8 % aqueous hydrogen bromide for 1 h at 20 °C a mixture of products was obtained as seen from a ^{13}C NMR spectrum. The solution was neutralized with sodium hydrogen carbonate and evaporated and the residue was extracted with ethanol. When the extract was concentrated and cooled the dibromomannitol (**1**) crystallized in 26 % yield, m.p. 78–82 °C, $[\alpha]_D^{20}$ − 6° (*c* 0.4, EtOAc) (lit.,[9] m.p. 85–89 °C, $[\alpha]_D^{20}$ − 9°).

Isolation of D*-mannitol* (**4**) *and* D*-glucitol* (**8**). A solution of **1** (2.0 g) in water (10 ml) containing potassium carbonate (1.5 g, 1.5 mol equiv.) was heated to 100 °C for 2 h and it was then deionized by treatment with a mixed-bed ion-exchange resin. Evaporation gave a residue (1.1 g) which consisted of **4** and **8** in a 1:1 ratio. Crystallization from water–ethanol gave 0.38 g of crude **4** which was recrystallized twice from water–ethanol, m.p. 165–166 °C (lit.,[15] for

D-mannitol m.p. 166 °C). Acetylation with acetic anhydride and perchloric acid followed by recrystallization from ethanol gave 0.34 g of hexa-*O*-acetyl-D-mannitol, m.p. 122–124 °C, $[\alpha]_D^{20}$ +25.3° (*c* 1.8, $CHCl_3$) [lit.,[16] m.p. 126 °C, $[\alpha]_D$ +25.0° ($CHCl_3$)]. The mother liquor from the crystallization of mannitol was acetylated and the product was recrystallized from ether–pentane to give 0.67 g of hexa-*O*-acetyl-D-glucitol, m.p. 97–98 °C, $[\alpha]_D^{20}$ +9.5° (*c* 2.3, $CHCl_3$) [lit.,[16] m.p. 99 °C, $[\alpha]_D$ +10.0° ($CHCl_3$)].

2,3:4,5-Dianhydro-L-iditol (**5**). To a solution of **1** (0.38 g) in water (2 ml) was added potassium hydroxide (0.34 g, 5 mol equiv.) and the solution was kept for 5 min at 20 °C. It was then neutralized with 4 M hydrochloric acid and evaporated and the residue was extracted with ethanol. The extract was concentrated to a small volume and cooled thereby depositing 31 mg of **5**. Preparative TLC of the mother liquor material using ethyl acetate as the eluant gave an additional 47 mg of **5**, bringing the total yield to 78 mg (44 %), m.p. 88–92 °C. Recrystallization from ethyl acetate gave a product with m.p. 97–99 °C, $[\alpha]_D^{20}$ −80.4° (*c* 0.5, H_2O) (lit.,[11] for the D-enantiomer, m.p. 100–101 °C, $[\alpha]_D^{20}$ +82.1°). ^{1}H NMR (D_2O): δ 3.94 (H-1, $J_{1,2}$ 2.7 Hz), 3.61 (H-1′, $J_{1',2}$ 5.2, $J_{1,1'}$ 13.2 Hz), 3.36 (H-2 and H-3). ^{13}C NMR data are given in Table 3.

2,5:3,4-Dianhydro-L-altritol (**10**). The dibromomannitol (**1**) (2.0 g) was added to a solution of potassium hydroxide (1.8 g, 5 mol) in water (6 ml) and the solution was kept at 20 °C for 24 h. A ^{13}C NMR spectrum of this solution showed that it contained 75 % of **10**, 26 % of **11**, and ca. 5 % of 2–3 other products. The solution was neutralized with hydrochloric acid and evaporated and the residue was extracted with boiling ethanol. Evaporation of the extract left 1.3 g of residue which was chromatographed on a column using acetone as the eluant.

The fastest moving fraction gave 500 mg (52 %) of almost pure **10** which was rechromatographed to give a syrup with $[\alpha]_D^{20}$ +85.6° (*c* 0.9, EtOH). Anal. $C_6H_{10}O_4$: C,H. ^{1}H NMR (D_2O): δ 3.75 (H-1, $J_{1,2}$ 4.0 Hz), 3.69 (H-1′, $J_{1',2}$ 5.0, $J_{1,1'}$ 12.5 Hz), 4.22 (H-2, $J_{2,3}$ ~0 Hz), 3.94 (H-3, $J_{3,4}$ 3.2 Hz), 4.04 (H-4, $J_{4,5}$ ~0 Hz), 4.23 (H-5, $J_{5,6}$ 5.6, $J_{5,6'}$ 6.0 Hz), 3.78 (H-6, $J_{6,6'}$ 11.5 Hz), 3.73 (H-6′).

A second fraction (250 mg) was rechromatographed (acetone) to give 190 mg of impure **11**. The product was benzoylated and the benzoate was chromatographed using ether–pentane (1:1) as the eluant. The main fraction thus obtained (390 mg) was debenzoylated with sodium methoxide in methanol to give 50 mg of **11** containing 10 % 1,4-anhydromannitol as seen from a ^{13}C NMR spectrum. The ^{13}C NMR data of **11** (Table 3) were identical with those of 1,4-anhydro-D-allitol.[13] The product had $[]_D^{20}$ −34° (*c* 1.3, H_2O) [lit.,[12] for 1,4-anhydro-D-alitol[12] $[\alpha]_D$ +46.1° (H_2O)].

Treatment of **12** *with aqueous potassium carbonate.* To **12** (1.2 g) in water (10 ml) was added anhydrous potassium carbonate (1.7 g, 2 mol) and the solution was kept at 100 °C for 2 h. A ^{13}C NMR spectrum of the resulting solution showed that it contained equal amounts of **8** and **19** together with small amounts of other products. The solution was neutralized and evaporated and extracted with methanol. The extract was evaporated and the residue was acetylated conventionally with acetic anhydride in pyridine to give 1.0 g of the acetate which crystallized from ether–pentane to give 300 mg (18 %) of hexa-*O*-acetyl-D-glucitol, m.p. 86–90 °C. Recrystallization gave a product with m.p. 96–98 °C, $[\alpha]_D^{20}$ +9.7° (*c* 1, $CHCl_3$). The mother liquor material was chromatographed to give additional amounts of the hexaacetate. It was not possible to obtain pure tetra-*O*-acetyl-3,6-anhydroaltritol and the structure of **19** was therefore derived only from the ^{13}C NMR spectrum (Table 3), identical with that of 3,6-anhydro-D-altritol.[13]

1,4:3,6-Dianhydro-L-glucitol (**18**). A solution of **12** (1.0 g) and potassium hydroxide (0.91 g, 5 mol equiv.) in water (3 ml) was kept for 30 min at 20 °C. Neutralization, evaporation and extraction with ethanol as described above gave a product which was purified by column chromatography (acetone) to give 350 mg (74 %) of **18**, which crystallized on being dried. Recrystallization from ethyl acetate–pentane gave a product with m.p. 62–63 °C, $[\alpha]_D^{20}$ −47.0° (*c* 1.2, H_2O) lit.,[17] for the D-enantiomer m.p. 61–64 °C; $[\alpha]_D^{20}$ +45.2.

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