Carbohydrate Research, 108 (1982) 247–260
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

1,6-DIAMINO-2,5-ANHYDRO-1,6-DIDEOXY-DL-GLUCITOL AND SOME DERIVATIVES THEREOF

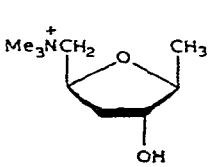
JÁNOS KUSZMANN AND ISTVÁN PELCZER
Institute for Drug Research, P.O. Box 82, H-1325 Budapest 4 (Hungary)
(Received April 10th, 1982; accepted for publication, May 10th, 1982)

ABSTRACT

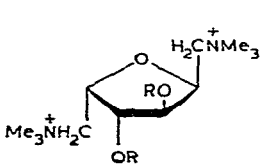
1,6-Diamino-2,5-anhydro-1,6-dideoxy-DL-glucitol dihydrochloride and some derivatives were synthesized from 3,5-di-*O*-acetyl-1,6-dibromo-1,6-dideoxy-D-mannitol. Introduction of the 2,5-anhydro ring and subsequent replacement of the terminal bromine atoms by azide gave low yields of the diazide; therefore, a reverse reaction-sequence was applied. The azido groups were reduced with hydrogen sulfide–pyridine, and the amino groups formed were methylated by using formaldehyde–formic acid and subsequently treating with borohydride. According to ^{13}C-n.m.r. investigations, the symmetrically substituted, 2,5-anhydroglucitol derivatives are present mainly in the $^4T_3$ ["north" (N) type of twist] conformation, whereas the analogous L-iditol derivatives mainly adopt the $^3T_4$ ["south" (S)] type. The different quaternary salts obtained on methylation of the corresponding 1,6-bis(dimethylamino) derivatives with methyl iodide (aiming at the structure of *epi*-muscarine) showed no muscarine-like, biological activity.

INTRODUCTION

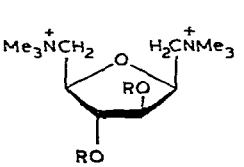
In a previous paper[1], the synthesis of "double-headed" muscarine analogs of type **1** (aiming at the structure of *epi-allo*-muscarine) was described. The lack of muscarine-like, biological activity of these derivatives could be due to the fact that the two terminal groups are in *trans* arrangement, whereas, in the most active natural compound (muscarine), they are *cis* related[2]. For investigating the influence of this steric arrangement, the synthesis of type **2** analogs (having the D-*gluco* configuration) was decided on.



Muscarine



1



2

In a search for compounds having ganglionic-blocking activity, a synthesis of the corresponding bis quaternary benzenesulfonic acid salt was described by Sugihara and Schmidt[3] in 1961. Their starting material was claimed to be 2,5-anhydro-D-glucitol which, according to the published physical data, was different from that described later by Koerner *et al.*[4]. As the structure of the latter compound was proved unambiguously[5], the structure of the bis quaternary salt mentioned[3] is, at least, doubtful.

RESULTS AND DISCUSSION

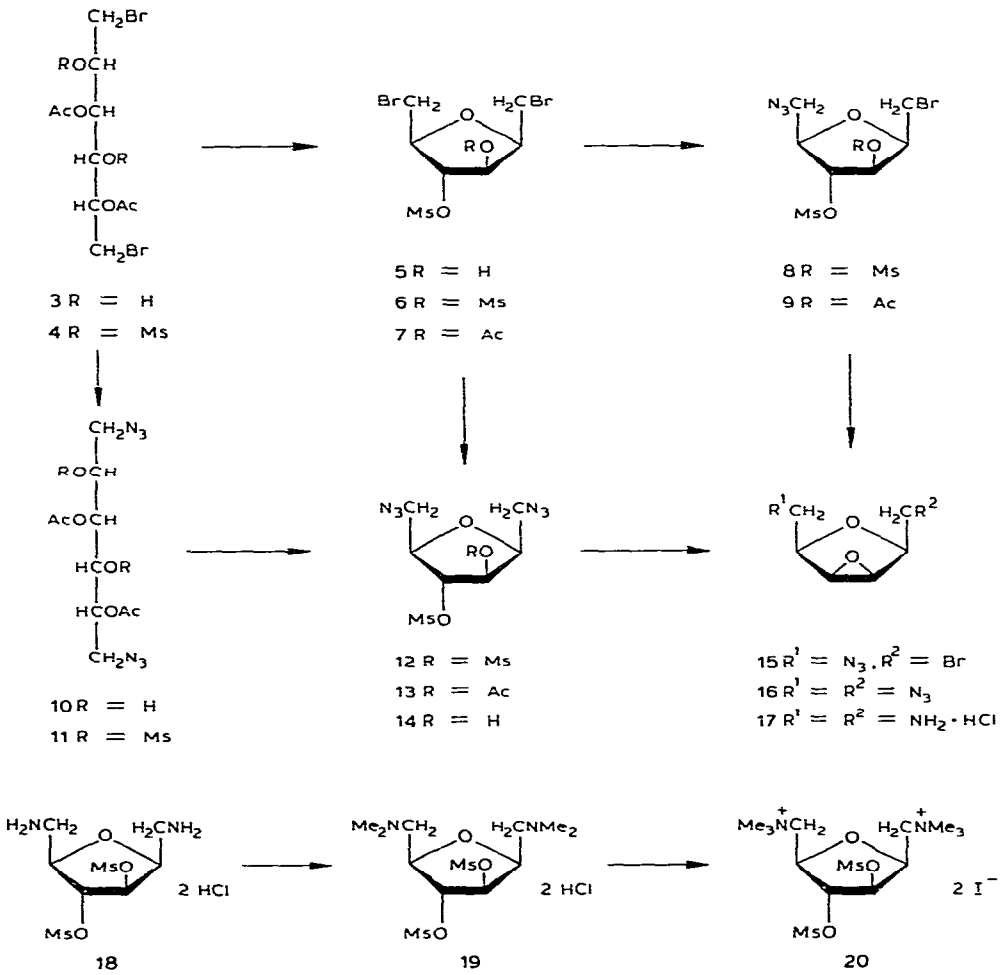
For synthesizing 2,5-anhydro-D-glucitol derivatives of the type of **2**, 1,6-di-substituted-D-mannitols can be used as the starting material, in which the 2,5-anhydro ring has to be introduced with simultaneous inversion at C-2 or C-5. This reaction has already been described[6] for 1,6-dibromo-3,5-di-*O*-acetyl-D-mannitol (**3**), which was converted, *via* its dimesylate **4***, into the 2,5-anhydro derivative **5**. The latter could be used as the starting material for the synthesis of the 1,6-diamino derivatives, as the terminal bromine atoms can be selectively exchanged by azide. The free OH-3 group in **5** was first blocked by mesylation or acetylation, and the diesters obtained (**6** and **7**) were treated with sodium azide in aqueous *N*,*N*-dimethylformamide. The less-hindered bromine atom, on C-6, was readily exchanged in both derivatives, affording the monobromo monoazides (**8** and **9**, respectively). The other bromine atom was much more resistant towards replacement, and, for complete exchange, more drastic conditions, under which partial decomposition took place, had to be used. The corresponding diazides **12** and **13** could, therefore, be isolated in relatively low yield only.

To overcome this problem, a reverse reaction-sequence was applied. The terminal bromine atoms of the acyclic derivative **3** were readily exchanged by azide, due to the absence of any steric inhibition, and the diester obtained (**10**) was converted into dimesylate **11**, which, on treatment with acid, gave the desired 2,5-anhydro derivative **14** in high yield. This indicated that formation of the 2,5-anhydro ring from 2(5)-*O*-mesyl derivatives under acidic conditions is a favored process and does not require an electron-withdrawing substituent[6-9] adjacent to the mesyloxy leaving-group. Mesylation or acetylation of **14** gave the diesters **12** and **13**, respectively, identical with those already mentioned.

Treatment of the acetylated monoazide **9** with sodium methoxide afforded the optically active 3,4-anhydrogalactitol derivative **15**, whereas, on similar treatment, diazides **13** and **14** gave the symmetrical epoxide **16**.

Reduction of the azido group of **12** was conducted with hydrogen sulfide in pyridine[1,10], and the diamine obtained (**18**) was converted into the 1,6-bis(dimethyl-

*The newly prepared dimesylate **4** had m.p. 118–120°, but was otherwise identical with that described earlier[6] (m.p. 81–82°); consequently, the two samples must be dimorphic.

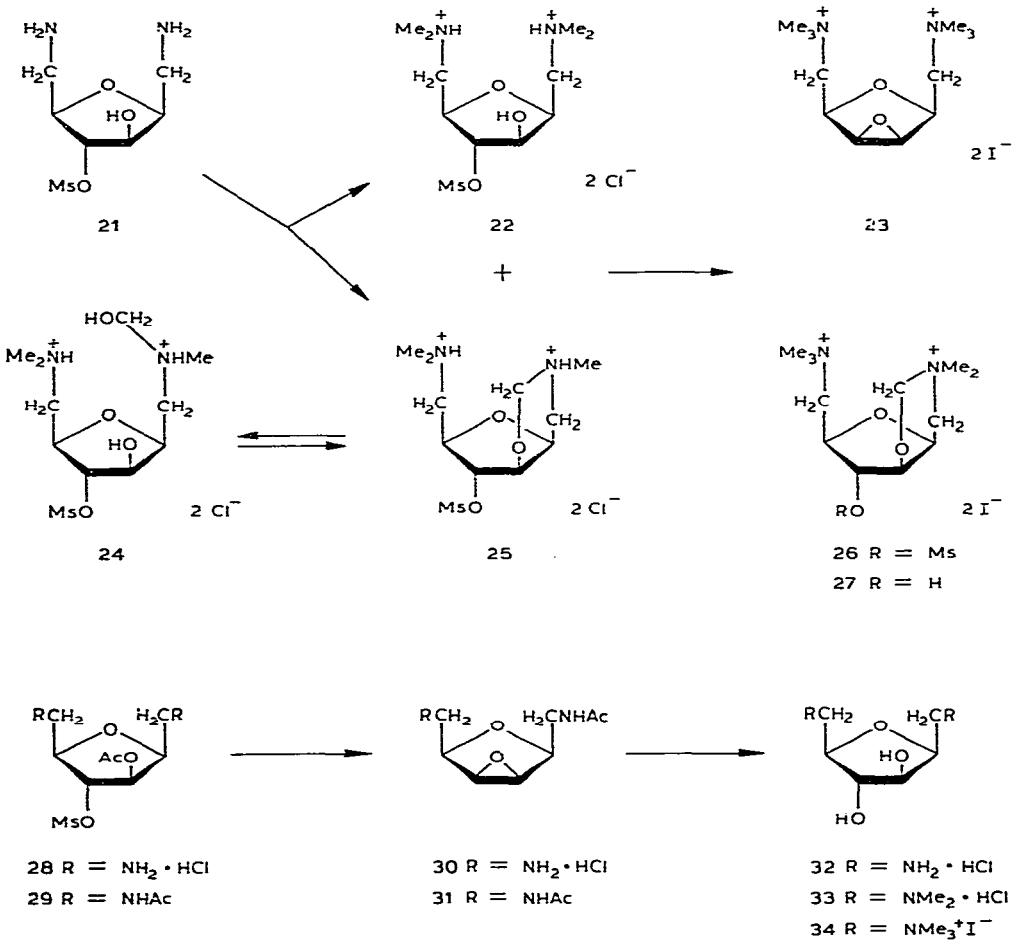


amino) derivative **19** on methylation with formaldehyde–formic acid[1,11]. Treatment of **19** with methyl iodide gave the corresponding bis(quaternary salt) **20**.

In a similar reaction-sequence, the monomesyl diazide **14** could be readily converted into diamine **21**, but, on methylation with formaldehyde–formic acid, this gave a mixture containing the bis(dimethylamino) derivative **22** and the bicyclic, methylated 1-*N*,3-*O*-methylene derivative **25** in the ratio of 2:3, as determined by ^{13}C-n.m.r. spectral investigation of its solution in dimethyl sulfoxide. In the presence of water, the oxazine ring of **25** was partially hydrolyzed, and **24** was formed in an equilibrium concentration. Accordingly, in the ^{13}C-n.m.r. spectrum, the intensity of the (C-1) N-Me signal of **25** at 43.3 p.p.m. was diminished, and a new N-Me signal, characteristic for the HO-CH_2-NH-Me grouping, appeared at 34.5 p.p.m. As attempts to separate this mixture were unsuccessful, it was treated with methanolic sodium methoxide (in the presence of phenolphthalein) to liberate the base, and,

after removal of the inorganic salts by filtration, methyl iodide was added. The bis-quaternary salt, which crystallized from the reaction mixture, proved to be the symmetrical epoxide **23**, showing only four lines in its ^{13}C-n.m.r. spectrum. Hence, during the liberation of the base, methanesulfonic acid must have been eliminated from **22** *via* formation of an epoxide. Evaporation of the filtrate yielded a mixture that contained, besides the bicyclic quaternary salt **26** expected, its *O*-demesylated derivative **27** in the ratio of 3:2, and small proportions of some unidentified products.

For obtaining 1,6-diamino compounds having OH-3 and OH-4 free, the monomesylate **21** was treated with sodium methoxide. Instead of the expected galactitol epoxide **17**, a complicated mixture was formed containing, besides **17** and its hydrolyzed product **32**, other anhydro derivatives, probably formed by the direct attack of NH_2-1 or NH_2-6 on C-4. As attempts to separate epoxide **17** were unsuccessful,



the crude mixture was hydrolyzed with aqueous hydrochloric acid, giving the dihydroxy derivative* **32** in very low yield (17%).

To avoid possible side-reactions, the 3-acetyl diazide **13** was reduced with hydrogen sulfide, and the resulting diamine (**28**) was converted into its triacetate (**29**), which was treated with sodium methoxide, giving epoxide **31** in high yield.

When the free amino groups of the 3-acetate **28** were not protected before treatment with base, an *O*→*N* acetyl migration occurred during the reaction, and the 1-acetamido epoxide **30**, obtained in excellent yield, could be converted by acetylation into **31**. The 3-*O*-acetyl group of **28** could be selectively removed by treatment with methanolic hydrochloric acid, giving diamine **21**, which was identical with that obtained *via* reduction of diazide **14**. Acetylation of **21** afforded triacetate **29** in high yield.

Hydrolysis of the 1,6-bis(acetamido) epoxide **31** into diamine **32** with 2M aqueous hydrochloric acid proved to be much slower (5 h at 100°) than the similar reaction of the *talo* analog[1], in which the 1-acetamido substituent (*trans*-situated in respect to the epoxide ring) enhanced the hydrolysis by neighboring-group participation. In **31**, both acetamido groups are *cis*-related to the oxirane ring, and consequently, they cannot form an "oxazine" intermediate that would enhance the reaction.

The diamine **32** could be converted by formaldehyde–formic acid–borohydride[1] into the 1,6-bis(dimethylamino) compound **33** which, on methylation with methyl iodide, afforded the desired bis-quaternary salt **34**.

The conformation of the 1,6-diamino-2,5-anhydroglucitol derivatives carrying identical substituents (MsO, or HO) at C-3 and C-4 could be established by comparing their ^{13}C-n.m.r. spectra with those** of the corresponding, L-iditol analogs[1]. From the "S" and "N" types of twist conformations[12,13] theoretically possible, all of the symmetrically substituted glucitol derivatives (**18–20** and **32–34**) are predominantly in the N type of twist ($^{4}T_{3}$) conformation, where the C-1–C-2 bond is quasiaxial, and those to all of the other substituents are quasiequatorial (see Fig. 1).

From Table I, it may be seen that the two 1,6-bis(dimethylamino) compounds having the *gluco* and *ido* configuration differ mainly in the shift of the signal of C-4, as well as of the NMe_2-6 groups. The pronounced, upfield shift of the C-4 signal for the glucitol derivative is due to the γ-effect of the bulky substituent on C-1, in diaxial arrangement with H-4. The lack of a similar effect for the iditol derivatives suggests that their equilibrium is shifted towards the S type of twist conformer ($^{3}T_{4}$), in which the terminal bulky groups are quasiequatorially oriented.

In the case of the L-*ido* configuration, the NMe_2-6 group gave only one methyl signal, at 46.4 p.p.m., whereas for the glucitol derivative, two nonequivalent methyl signals can be detected, at 44.5 and 45.0 p.p.m., respectively, for the same group. This

*As epoxide **17** is a symmetrical, galactitol derivative, all further products are racemates, but, for convenience, only one antipode (D) is depicted in formulas **32–34**.

In the literature[1], the ^{13}C-n.m.r. data in Table III (on p. 110) for C-2 and C-3 have to be interchanged for compounds **33, **34**, **35**, and **37**, *i.e.*, the signal of C-2 always appears at the higher field.

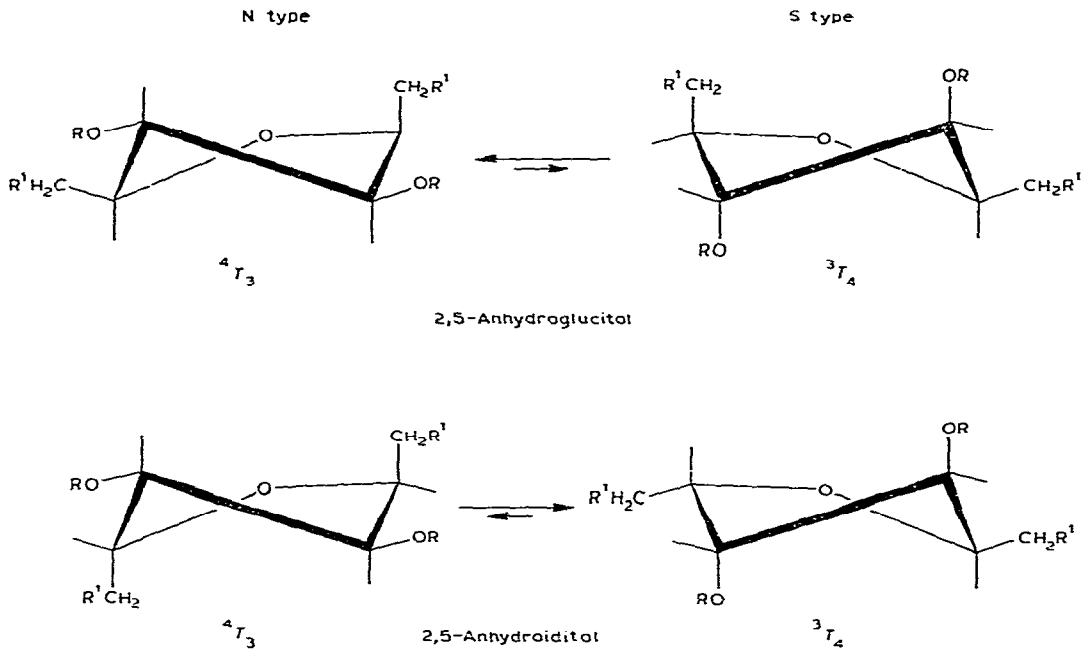


Fig. 1. Conformations of the N and S type for symmetrically substituted, 2,5-anhydroglucitol and 2,5-anhydroiditol derivatives.

TABLE I

^{13}C-N.M.R. DATA FOR 2,5-ANHYDRO-1,6-DIDEOXY-1,6-BIS(DIMETHYLAMINO)-D-GLUCITOL DIHYDROCHLORIDE AND -L-IDITOL DIHYDROCHLORIDE

Configuration	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*1-NMe₂*	*6-NMe₂*
gluco	59.3	80.2	77.7	64.5	82.2	61.3	46.9	45.0 44.5
ido	59.8	79.3	77.5	77.5	79.3	59.8	46.4	46.4

can also be explained by the different conformation adopted, as, in the prevailing N type of twist conformation ($^4T_3$) of the glucitol derivative, the OH-4 and the bulky NMe_2-6 groups are in quasi-diequatorial arrangement, and consequently, the free rotation of the latter is hindered. In the S type of twist conformation ($^3T_4$) of the L-iditol analog, the corresponding OH and NMe_2 groups are quasiaxially and quasiequatorially oriented, and consequently, the free rotation of the latter is not restricted.

In biological testing, the quaternary salts **20**, **23**, and **34** proved to be relatively non-toxic (LD_{50} 200 mg/kg), but none of them possess muscarine-like activity. Compound **34** showed a weak, cytostatic activity (15% inhibition) against P-388 leukemia.

EXPERIMENTAL

General methods. — After organic solutions had been dried with sodium sulfate, all evaporations were conducted in a rotary evaporator under diminished pressure. Light petroleum had b.p. 60–80°. Optical rotations were determined in chloroform (*c* 1), if not stated otherwise. T.l.c. was effected on Kieselgel G with ethyl acetate–carbon tetrachloride, 1 : 1 (*A*), 1 : 2 (*B*), and 1 : 3 (*C*), with conc. ammonium hydroxide–ethanol 1 : 3 (*D*) and 1 : 9 (*E*), and with water (*F*). For detection, 1 : 1 0.1M potassium permanganate–M sulfuric acid was used at 105°. Column chromatography was performed on Kieselgel 40 (63–200 μm). ^{13}C-N.m.r. spectra (25.2 MHz) and ^{1}H-n.m.r. spectra (90 MHz) were respectively recorded at room temperature with a Varian XL-100 FT and a Varian EM-390 spectrometer, for solutions in (*a*) chloroform-*d*, with tetramethylsilane as the internal standard, (*b*) D_2O, or (*c*) dimethyl sulfoxide-d_6, with sodium 4,4-dimethyl-4-silapentane-1-sulfonate as the internal standard.

3-O-Acetyl-2,5-anhydro-1,6-dibromo-1,6-dideoxy-4-O-(methylsulfonyl)-D-glucitol (**7**). — Compound[6] **5** (37 g) was acetylated with acetic anhydride (20 mL)–pyridine (40 mL), to give, after the usual processing, crude **7** (40 g, 97.5%) which was recrystallized from methanol (33 g, 80.5%); m.p. 82–84°, $[\alpha]_D^{20}$ +42°; R_F 0.65 (*C*); ^{1}H-n.m.r. data (*a*): δ 5.33 (d, $J_{4,5}$ 3.5 Hz, H-4), 4.90 (d, $J_{3,2}$ 3.5 Hz, H-3), 4.3 (m, H-2,5), 3.55 and 3.45 (d, $J_{5,6}$ 5 Hz, H-1,6), 3.16 (s, mesyl-Me), and 2.14 (s, acetyl-Me).

Anal. Calc. for $C_9H_{14}Br_2O_6S$: C, 26.35; H, 3.44; Br, 38.97; S, 7.81. Found: C, 26.28; H, 3.50; Br, 38.72; S, 7.72.

2,5-Anhydro-6-azido-1-bromo-1,6-dideoxy-3,4-di-O-(methylsulfonyl)-D-glucitol (**8**). — A solution of dibromide[6] **6** (9 g) and sodium azide (1.3 g) in *N,N*-dimethylformamide (90 mL) and water (10 mL) was heated on a steam bath for 15 h. The residue obtained after evaporation was dissolved in chloroform, and the solution washed with water, dried, and evaporated. Crystallization of the residue from methanol afforded crude **8** (5.5 g, 67%) containing, besides the isomeric 1-azide, some starting-material. Recrystallization from methanol, and then from methanol–water, gave pure **8** (2.5 g, 30.4%); m.p. 71–73°, $[\alpha]_D^{20}$ +99.6°; R_F 0.55 (*B*);[1] H-n.m.r. data (*a*): δ 5.1 (m, H-3,4), 4.3 (m, H-2,5), 3.5 (m, H-1,6), and 3.17 and 3.15 (s, 2 mesyl-Me).

Anal. Calc. for $C_8H_{14}BrN_3O_7S_2$: C, 23.53; H, 3.46; Br, 19.58; N, 10.29; S, 15.71. Found: C, 23.76; H, 3.52; Br, 19.86; N, 10.40; S, 15.45.

3-O-Acetyl-2,5-anhydro-6-azido-1-bromo-1,6-dideoxy-4-O-(methylsulfonyl)-D-glucitol (**9**). — A solution of dibromide **7** (20.5 g) and sodium azide (3.5 g) in *N,N*-dimethylformamide (100 mL) and water (10 mL) was heated on a steam bath for 1 h. The residue (17.5 g, 94%) from evaporation of the solution was filtered with the aid of water, to give, after recrystallization from methanol (60 mL), pure **9** (12.2 g, 65.6%); m.p. 71–73°, $[\alpha]_D^{20}$ +144°; R_F 0.60 (*C*); ^{1}H-n.m.r. data (*a*): δ 5.26 (d, $J_{4,5}$ 3.5 Hz, H-4), 4.85 (d, $J_{3,2}$ 3.5 Hz, H-3), 4.3 (m, H-2,5), 3.5 (m, H-1,6), 3.14 (s, mesyl-Me), and 2.13 (s, acetyl-Me).

Anal. Calc. for $C_9H_{14}BrN_3O_6S$: C, 29.04; H, 3.79; Br, 21.47; N, 11.29; S, 8.61. Found: C, 29.21; H, 3.85; Br, 21.80; N, 11.05; S, 8.46.

3,5-Di-O-acetyl-1,6-diazido-1,6-dideoxy-D-mannitol (**10**). — To a solution of dibromide[6] **3** (78.4 g) in *N,N*-dimethylformamide (240 mL) and water (80 mL) was added sodium azide (40 g). The slurry was stirred on a steam bath for 5 h, and was then evaporated. The residue was filtered with the aid of water, to give crude **10** (52 g, 82.5%), which was pure enough for further reactions. Recrystallization from acetone–ether, and then from methanol–water, gave pure **10** (35.5 g, 56.5%); m.p. 138–140°, $[\alpha]_D^{20}$ +33° (Me_2SO); R_F 0.60 (*A*); ^{1}H-n.m.r. data (*b*): δ 4.7 (m, H-3,5), 3.9 (m, H-2,4), 3.55 (m, H-6), 3.2 (m, H-1), and 1.98 (s, 2 acetyl-Me).

Anal. Calc. for $C_{10}H_{16}N_6O_6$: C, 37.97; H, 5.09; N, 26.58. Found: C, 38.12; H, 5.15; N, 26.33.

2,5-Di-O-acetyl-1,6-diazido-1,6-dideoxy-2,5-di-O-(methylsulfonyl)-D-mannitol (**11**). — *Method a.* A solution of dibromide[6] **4** (2.7 g) and sodium azide (0.7 g) in *N,N*-dimethylformamide (15 mL) and water (4 mL) was boiled for 1.5 h, and then processed as described for **12**. Recrystallization of the residue from methanol give pure **11** (0.8 g, 34%); m.p. 90–92°, $[\alpha]_D^{20}$ +14.5°; R_F 0.75 (*A*); ^{1}H-n.m.r. data (*a*): δ 5.31 (t, $J_{4,3} = J_{4,5} = 4$ Hz, H-4), 5.0 (m, H-2,3), 4.85 (q, $J_{5,4} = J_{5,6} = 4$ Hz, H-5), 3.65 (m, H-1,6), 3.16 (s, 2 mesyl-Me), and 2.13 (s, acetyl-Me).

Method b. To a stirred solution of diazide **10** (23 g) in pyridine (115 mL) was added mesyl chloride (14 mL) at 0°. The mixture was kept overnight at room temperature, to give, after the usual processing, **11** (30.4 g, 88.4%), identical with that obtained by method *a*.

Anal. Calc. for $C_{12}H_{20}N_6O_{10}S_2$: C, 30.50; H, 4.26; N, 17.78; S, 13.57. Found: C, 30.42; H, 4.33; N, 17.62; S, 13.30.

2,5-Anhydro-1,6-diazido-1,6-dideoxy-3,4-di-O-(methylsulfonyl)-D-glucitol (**12**). — *Method a.* A solution of dibromide **6** (9 g) and sodium azide (3 g) in *N,N*-dimethylformamide (90 mL) and water (10 mL) was boiled for 30 min. The dark-brown solution was evaporated, the residue was partitioned between chloroform and water, and the organic solution was washed with water, dried, and evaporated. The residue gave, after column chromatography (*B*) and recrystallization from methanol–water, pure diazide **12** (2.4 g, 32.4%); m.p. 51–53°, $[\alpha]_D^{20}$ +78.5°; R_F 0.55 (*B*); ^{1}H-n.m.r. data (*a*): δ 5.16 (m, H-3,4), 4.25 (m, H-2,5), 3.6 (m, H-1,6), and 3.16 and 3.14 (s, 2 mesyl-Me).

Method b. To a solution of monomesylate **14** (2.9 g) in pyridine (10 mL) was added mesyl chloride (2 mL) at 0°. The mixture was kept for 2 h at room temperature and then processed in the usual way, to give **12** (3.4 g, 92%), identical with that obtained by method *a*.

Anal. Calc. for $C_8H_{14}N_6O_7S_2$: C, 25.94; H, 3.81; N, 22.70; S, 17.31. Found: C, 26.13; H, 4.09; N, 22.75; S, 17.08.

3-O-Acetyl-2,5-anhydro-1,6-diazido-1,6-dideoxy-4-O-(methylsulfonyl)-D-glucitol (**13**). — *Method a.* To a stirred solution of dibromide **7** (8.2 g) in *N,N*-dimethylformamide (40 mL) and water (4 mL) was added sodium azide (2 g). The mixture

was stirred on a steam bath for 6 h, and evaporated, and the residue was partitioned between chloroform and water; the organic solution was washed with water, dried, and evaporated. The residue gave, after recrystallization from methanol–water, pure **13** (2.15 g, 32%); m.p. 50–52°, $[\alpha]_D^{20}$ +120°; R_F 0.5 (*C*); ^{1}H-n.m.r. data (*a*): δ 5.25 (d, $J_{4,5}$ 4 Hz, H-4), 4.90 (d, $J_{3,2}$ 4 Hz, H-3), 4.25 (m, H-2,5), 3.5 (m, H-1,6), 3.16 (s, mesyl-Me), and 2.16 (s, acetyl-Me).

Method b. Acetylation of the 4-hydroxy-diazide **14** (5.8 g) in pyridine (10 mL) with acetic anhydride (5 mL) gave, after the usual processing, **13** (5.85 g, 87.5%), identical with that obtained by method *a*.

Anal. Calc. for $C_9H_{14}N_6O_6S$: C, 32.33; H, 4.22; N, 25.14; S, 9.59. Found: C, 32.26; H, 4.30; N, 25.02; S, 9.38.

2,5-Anhydro-1,6-diazido-1,6-dideoxy-4-O-(methylsulfonyl)-D-glucitol (**14**). — A solution of dimesylate **11** (47.2 g) in ethanol (500 mL) and conc. hydrochloric acid (150 mL) was boiled on a steam bath for 2 h. The solution was cooled, made neutral by adding sodium hydrogencarbonate, and the suspension filtered with charcoal. The filtrate was evaporated, and the residue was partitioned between chloroform and water. The organic solution was washed with water, dried, and evaporated, to give, after recrystallization from acetone–light petroleum, pure **14** (21.8 g, 75%); m.p. 64–65°, $[\alpha]_D^{20}$ +36°; R_F 0.55 (*A*); ^{1}H-n.m.r. data (*a*): δ 4.84 (dd, $J_{4,3}$ 2 $J_{4,5}$ 4 Hz, H-4), 4.40 (dd, $J_{3,2}$ 5, $J_{3,4}$ 2 Hz, H-3), 4.15 (m, H-2,5), 3.55 (m, H-1,6), and 3.14 (s, mesyl-Me).

Anal. Calc. for $C_7H_{12}N_6O_5S$: C, 28.76; H, 4.13; N, 28.75; S, 10.97. Found: C, 28.55; H, 4.26; N, 28.59; S, 11.18.

2,5:3,4-Dianhydro-6-azido-1-bromo-1,6-dideoxy-D-galactitol (**15**). — To a solution of monomesyl-monoazide **9** (7.4 g) in chloroform (75 mL) and methanol (15 mL) was added 4M methanolic sodium methoxide (6 mL), the mixture kept for 10 min at room temperature, and then washed with water, dried, and evaporated. The residue was purified by column chromatography, and the fractions having R_F 0.65 (*C*) gave, on evaporation, pure **15** (1.7 g, 36.2%), as a colorless syrup; $[\alpha]_D^{20}$ +34.5°; ^{1}H-n.m.r. data (*a*): δ 4.10 (t, $J_{2,1} = J_{5,6} = 6$ Hz, H-2,5), 3.90 (d, $J_{3,4}$ 3 Hz, H-3), 3.73 (d, $J_{4,3}$ 3 Hz, H-4), and 3.43 (d, $J_{1,2} = J_{6,5} = 6$ Hz, H-1,6).

Anal. Calc. for $C_6H_8BrN_3O_2$: Br, 34.14; N, 17.95. Found: Br, 33.87; N, 18.06.

2,5:3,6-Dianhydro-1,6-diazido-1,6-dideoxygalactitol (**16**). — To a solution of diazide **13** (3.3 g) or **14** (2.9 g) in chloroform (30 mL) and methanol (5 mL) was added 4M methanolic sodium methoxide (2.5 mL), and the mixture was processed as described for **15**, to yield **16** (1.7 g, 87%) as a colorless oil, $[\alpha]_D^{20}$ 0°; R_F 0.70 (*C*); ^{1}H-n.m.r. data (*a*): δ 4.0 (t, $J_{2,1} = J_{5,6} = 6$ Hz, H-2,5), 3.73 (s, H-3,4), and 3.43 (d, $J_{1,2} = J_{5,6} = 6$ Hz, H-1,6).

Anal. Calc. for $C_6H_8N_6O_2$: N, 42.84; Found: N, 42.45.

1,6-Diamino-2,5-anhydro-1,6-dideoxy-3,4-di-O-(methylsulfonyl)-D-glucitol dihydrochloride (**18**). — Through a solution of diazide **12** (4.4 g) in pyridine (44 mL) and water (22 mL) was passed a stream of hydrogen sulfide. The temperature of the exothermic reaction was kept below 40° by gentle cooling. In t.l.c. (*E*), besides the

spot of the starting material (R_F 0.95), two new components, R_F 0.70 (monoamino-monoazide) and R_F 0.45 (**18**), were detected. After 1.5 h, when the reduction was complete, acetic acid (2.5 mL) was added, and the solution was evaporated. The residue was filtered with the aid of water, to remove the precipitated sulfur. The filtrate was evaporated, and ethanol was added to, and evaporated from, the residue, which was then dissolved in ethanol (25 mL), and methanol (5 mL) saturated with hydrochloric acid was added. The precipitated salt was filtered off, and washed with ethanol, to give pure **18** (5.1 g, 87%); m.p. 219–220° (dec.), $[\alpha]_D^{20}$ +9.5° (water); ^{1}H-n.m.r. data (*c*): δ 5.5 (m, H-3,4), 4.6 (m, H-2,5), 3.45 (m, H-1,6), and 3.4 (s, 2 mesyl-Me).

Anal. Calc. for $C_8H_{18}N_2O_7S_2 \cdot 2$ HCl: C, 24.55; H, 5.15; Cl, 18.12; N, 7.15; S, 16.38. Found: C, 24.48; H, 5.22; Cl, 18.08; N, 7.21; S, 16.10.

When the ethanolic solution of the base was acidified with acetic acid or methanesulfonic acid, **18** · AcOH, m.p. 120–121°, and **18** · MsOH, m.p. 170–171°, were respectively obtained.

*2,5-Anhydro-1,6-dideoxy-1,6-bis(dimethylamino)-3,4-di-*O*-(methylsulfonyl)-*D*-glucitol dihydrochloride* (**19**). — A solution of **18** (2 g) in aqueous formaldehyde (36%, 10 mL) and formic acid (90%, 15 mL) was heated on a steam bath for 10 h. The solution was evaporated, and the residue was filtered with the aid of M hydrochloric acid (10 mL), to give, after evaporation of the filtrate and treatment of the residue with ethanol, pure **19** (1.9 g, 83%); m.p. 205° (dec.), $[\alpha]_D^{20}$ +12.3° (water); R_F 0.60 (*E*); ^{1}H-n.m.r. data (*b*): δ 5.4 (d, $J_{4,5}$ 3.5 Hz, H-4), 5.25 (d, $J_{3,2}$ 2 Hz, H-3), 4.6 and 4.5 (m, H-2,5), 3.4 (m, H-1,6), 3.37 and 3.35 (s, 2 mesyl-Me), and 2.8 (s, 4 N-Me).

Anal. Calc. for $C_{12}H_{26}N_2O_7S_2 \cdot 2$ HCl: C, 32.21; H, 6.30; Cl, 15.85; N, 6.26; S, 14.33. Found: C, 32.10; H, 6.52; Cl, 15.80; N, 6.15; S, 14.15.

*2,5-Anhydro-1,6-dideoxy-3,4-di-*O*-(methylsulfonyl)-1,6-bis(trimethylamino)-*D*-glucitol diiodide* (**20**). — A stirred slurry of **19** (2.5 g) in methanol (25 mL) was made alkaline (in the presence of phenolphthalein) with 4.5M methanolic sodium methoxide (2.4 mL). The pink slurry was diluted with acetone (25 mL), and the inorganic salt was filtered off. Methyl iodide (2.5 mL) was added to the filtrate, and, after 20 h, the crystalline, quaternary salt **20** was filtered off, and washed with acetone (2.5 g, 70%); m.p. above 250°, $[\alpha]_D^{20}$ +5° (water); ^{1}H-n.m.r. data (*c*): δ 5.63 (d, $J_{4,5}$ 3 Hz, H-4), 5.35 (d, $J_{3,2}$ 3 Hz, H-3), 4.9 (m, H-2,5), 3.9 (m, H-1,6), 3.40 and 3.36 (s, 2 mesyl-Me), and 3.3 (s, 6 N-Me).

Anal. Calc. for $C_{14}H_{32}I_2N_2O_7S_2$: C, 25.53; H, 4.89; I, 38.55; N, 4.25; S, 9.74. Found: C, 25.65; H, 5.03; I, 37.92; N, 4.05; S, 9.68.

*1,6-Diamino-2,5-anhydro-1,6-dideoxy-4-*O*-(methylsulfonyl)-*D*-glucitol dihydrochloride* (**21**). — *Method a.* A solution of **14** (2.9 g) in pyridine (30 mL) and water (15 mL) was reduced with hydrogen sulfide as described for **18**, to yield **21** (2.6 g, 83%); m.p. 198° (dec.), $[\alpha]_D^{20}$ +20° (water); R_F 0.20 (*E*); ^{1}H-n.m.r. data (*b*): δ 5.05 (t, $J_{4,3} = J_{4,5} = 1.5$ Hz, H-4), 4.4 (m, H-3), 4.3 (m, H-2,5), 3.40 (s, mesyl-Me), and 3.1 (m, H-1,6).

Method b. A slurry of **28** (1.4 g) in 3.3M methanolic hydrochloric acid (10 mL) was boiled on a steam bath. After 4 h, a clear solution was obtained; this was boiled for a further 2 h. The solution was kept overnight at 4°, and the precipitated crystals were filtered off, and washed with ethanol, to give pure **21** (0.83 g, 67.5%), identical with that obtained by method *a*.

Anal. Calc. for $C_7H_{16}N_2O_5S \cdot 2$ HCl: C, 26.84; H, 5.79; Cl, 22.64; N, 8.94; S, 10.23. Found: C, 26.72; H, 5.85; Cl, 22.43; N, 8.78; S, 10.55.

Methylation of diamine **21**. — A solution of **21** (4 g) in aqueous formaldehyde (36%, 20 mL) and formic acid (90%, 30 mL) was heated on a steam bath for 10 h, cooled, and evaporated. The residue was filtered off with the aid of M hydrochloric acid (15 mL), and the filtrate was evaporated. The whole procedure was repeated, and then ethanol was added to, and evaporated from, the residue, yielding a 2:3 mixture of **22** and **25** (determined by ^{13}C-n.m.r. spectroscopy) as a solid foam (4.2 g, 90%); $[\alpha]_D^{20}$ +24 (5 min)→+16° (water, 24 h); R_F 0.5 (*E*); ^{13}C-n.m.r. data (*b*): compound **22**, δ 57.6 (C-1), 77.8 (C-2), 75.9 (C-3), 87.5 (C-4), 79.2 (C-5), 59.3 (C-6), 45.4 (NCH_3), and 39.6 (O_2SCH_3); compound **25**, δ 51.8 (C-1), 74.6 (C-2), 81.2 (C-3), 84.8 (C-4), 78.9 (C-5), 58.8 (C-6), 43.3 (1-NCH_3), 44.6 (6-NCH_3), 39.2 (O_2SCH_3) and 80.2 (1-NCH_2O). In the presence of water, ^{13}C-n.m.r. data (*b* + *c*): compound **24**, δ 49.3 (C-1), 78.9 (C-2), 76.0 (C-3), 87.2 (C-4), 79.2 (C-5), 59.5 (C-6), 34.7 (1-NCH_3), 45.7 (6-NCH_3), 39.6 (O_2SCH_3), and 83.2 (1-NCH_2O).

Reaction of methylated diamine **21** *with methyl iodide.* — The mixture (4 g) of the methylated compounds (**22** + **25**) just mentioned was dissolved in methanol (40 mL), and the solution was made alkaline with 5M methanolic sodium methoxide (6.5 mL) in the presence of phenolphthalein. The resulting slurry was diluted with acetone (50 mL), the suspension filtered, and methyl iodide (10 mL) was added to the filtrate. The mixture was kept for 2 days at room temperature; it was then cooled to 0°, and the precipitated crystals were filtered off, and washed with acetone, to give 2,5:3,4-dianhydro-1,6-dideoxy-1,6-bis(trimethylamino)galactitol diiodide **23**, (1.70 g, 32.6%); m.p. 250° (dec.); ^{13}C-n.m.r. data (*b*): δ 67.8 (C-1,6), 74.4 (C-2,5), 57.8 (C-3,4), and 55.4 (6-NCH_3).

Anal. Calc. for $C_{12}H_{26}I_2N_2O_2$: C, 29.76; H, 5.41; I, 52.42; N, 5.78. Found: C, 29.62; H, 5.51; I, 51.48; N, 5.59.

Evaporation of the filtrate gave a 3:2 mixture of **26** + **27**: ^{13}C-n.m.r. data (*c*): compound **26**, δ 61.2 (C-1), 74.8 (C-2), 81.1 (C-3), 85.2 (C-4), 79.4 (C-5), 68.5 (C-6), 53.1 and 52.3 (1-NCH_3), 56.9 (6-NCH_3), 89.6 (1-NCH_2O), and 40.6 (O_2SCH_3); compound **27**, δ 61.7 (C-1), 73.6 (C-2), 81.8 (C-3), 72.2 (C-4), 80.9 (C-5), 68.3 (C-6), 53.1 and 52.7 (1-NCH_3), and 56.9 (6-NCH_3).

*3-O-Acetyl-1,6-diamino-2,5-anhydro-1,6-dideoxy-4-O-(methylsulfonyl)-*D*-glucitol dihydrochloride* (**28**). — A solution of diazide **13** (7.6 g) in pyridine (76 mL) and water (24 mL) was reduced with hydrogen sulfide as described for **18**, to yield pure **28** (5.5 g, 68%); m.p. 180° (dec.), $[\alpha]_D^{20}$ +13.6° (water); R_F 0.50 (*E*); ^{1}H-n.m.r. data (*b*): δ 5.0 (t, $J_{4,3} = J_{4,5} = 1.5$ Hz, H-4), 4.3 (m, H-3,5), 4.0 (m, H-2), 3.39 (s, mesyl-Me), 3.3 (m, H-6), 3.1 (m, H-1), and 1.90 (s, acetyl-Me).

Anal. Calc. for $C_9H_{18}N_2O_6S \cdot 2$ HCl: C, 30.42; H, 5.67; Cl, 19.96; N, 7.88; S, 9.02. Found: C, 30.38; H, 5.75; Cl, 19.75; N, 7.76; S, 9.17.

1,6-Bis(acetamido)-3-O-acetyl-2,5-anhydro-1,6-dideoxy-4-O-(methylsulfonyl)-D-glucitol (**29**). — *Method a.* Diazide **13** (2.9 g) was reduced in pyridine with hydrogen sulfide as described for **18**, but the ethanolic solution was evaporated; then ethanol, and subsequently benzene, was added to, and evaporated from, the residue, which was dissolved in pyridine (10 mL), and acetic acid (7 mL) was added. The solution was kept overnight at room temperature, and evaporated. The residue was dissolved in water, and purified by flash chromatography (solvent *F*); then ethanol was added to, and evaporated from, the residue, yielding **29** as a semisolid foam (3.4 g, 93%); $[\alpha]_D^{20}$ +5°; R_F 0.50 (*F*); ^{1}H-n.m.r. data (*b*): δ 7.95 (m, 2 NH), 5.12 (d, $J_{4,5}$ 3 Hz, H-4), 4.86 (m, H-3), 4.0 (m, H-2,5), 3.27 (s, mesyl-Me), 3.2 (m, H-1,6), 2.08 (s, acetyl-Me), and 1.82 (s, 2 acetyl-Me).

Method b. A slurry of diamine **21** (1.75 g) and sodium acetate (0.5 g) in pyridine (10 mL) and acetic anhydride (5 mL) was stirred for 2 days at room temperature; the mixture was then evaporated, the residue dissolved in water, and the solution freed of ions by use of ion-exchange resins. The suspension was filtered, and the filtrate was evaporated, yielding **29** (1.8 g, 89%), identical with that obtained by method *a*.

Anal. Calc. for $C_{13}H_{22}N_2O_8S$: C, 42.61; H, 6.05; N, 7.64; S, 8.75. Found: C, 42.50; H, 6.21; N, 7.47; S, 8.62.

1-Acetamido-6-amino-2,5:3,4-dianhydro-1,6-dideoxygalactitol (**30**). — A stirred slurry of diamine **28** (3.5 g) in ethanol (20 mL) was made alkaline (in the presence of phenolphthalein) with 5M methanolic sodium methoxide (6.5 mL). Stirring was continued for 1 h; then the slurry was made neutral with carbon dioxide, and the inorganic salts were filtered off. The filtrate was evaporated, the residue dissolved in ethanol, filtered with charcoal, and made acidic with M methanolic hydrogen chloride. The turbid solution was evaporated, and ethanol was added to, and evaporated from, the residue, yielding **30** as a solid foam (2 g, 90%); m.p. 65–70°; R_F 0.65 (*D*); ^{1}H-n.m.r. data (*c*): δ 4.3 (m, H-2,3,4,5), 3.5 (m, H-1), and 3.3 (m, H-6).

Anal. Calc. for $C_8H_{14}N_2O_3 \cdot$ HCl: C, 43.14; H, 6.79; Cl, 15.92; N, 12.58. Found: C, 43.38; H, 7.12; Cl, 15.70; N, 12.41.

1,6-Bis(acetamido)-2,5:3,4-dianhydro-1,6-dideoxygalactitol (**31**). — *Method a.* A stirred slurry of triacetate **29** (3.7 g) in methanol (40 mL) was made alkaline with 4M methanolic sodium methoxide (2.5 mL) in the presence of phenolphthalein. According to t.l.c., the starting material (R_F 0.50, *F*) was first *O*-deacetylated (R_F 0.60) and then gradually converted into epoxide **31** (R_F 0.50). After 1 h, the solution was made neutral with carbon dioxide, and evaporated. The residue was filtered with the aid of ethanol, and the filtrate was evaporated; the residue was freed of sodium mesylate by filtering its methanolic solution through a short column of Kieselgel 40. The solution was evaporated, and the residue filtered, with acetone, to give pure **31** (1.55 g, 68%); m.p. 183–185° (dec.); ^{1}H-n.m.r. data (*b*): δ 8.0 (t, J_{NH,CH_2} 6 Hz, 2 NH), 3.83 (t, $J_{5,6} = J_{2,1} = 6$ Hz, H-2,5), 3.80 (s, H-3,4), 3.22 (t, $J_{1,2} = J_{6,5} =$

J_{NH,CH_2} = 6 Hz, H-1,6), and 1.85 (s, 2 acetyl-Me); ^{13}C-n.m.r. data (*b*): δ 40.5 (C-1,6), 77.5 (C-2,5), 58.1 (C-3,4), 24.1 (2 CH_3CO), and 171.2 (2 CH_3CO).

Method b. A solution of monoacetate **30** (1.1 g) in pyridine (5 mL) and acetic anhydride (3 mL) was kept overnight at room temperature, and then evaporated. The residue was purified by chromatography (*F*) to give, after evaporation of the fraction having R_F 0.50, and filtration of the residue with acetone, compound **31** (0.9 g, 79%), identical to that obtained by method *a*.

Anal. Calc. for $C_{10}H_{16}N_2O_4$: C, 52.61; H, 7.06; N, 12.27. Found: C, 52.50; H, 7.32; N, 12.08.

*1,6-Diamino-2,5-anhydro-1,6-dideoxy-*DL*-glucitol dihydrochloride* (**32**). — *Method a.* A stirred slurry of mesylate **21** (3.1 g) in ethanol (30 mL) was made alkaline with 4M methanolic sodium methoxide (8 mL). The inorganic salts were filtered off, and the filtrate was made acidic with methanolic hydrogen chloride. The precipitated, organic salt (which, according to n.m.r., was a mixture of epoxide **17** with the hydrolyzed compound **32**) was filtered off, and washed with ethanol. A solution of this mixture (1.7 g) in 0.1M hydrochloric acid was boiled for 5 h, cooled, and evaporated. Then ethanol was added to, and evaporated from, the residue, and the semisolid material was filtered off with the aid of methanol, and washed with ethanol, to give pure **32** (0.4 g, 17%): m.p. 226–227° (dec.): R_F 0.55 (*D*): ^{1}H-n.m.r. data (*b*): δ 4.4 (m, H-2,3,4,5) and 3.1 (m, H-1,6).

Method b. A solution of the mono- **27** (2.2 g) or the bis-(acetamido)-epoxide **31** (2.3 g) in 2M hydrochloric acid (20 mL) was boiled for 5 h. The solution was evaporated, and the residue filtered with ethanol, to give **32** (1.6 g, 68%), identical with that obtained by method *a*.

Anal. Calc. for $C_6H_{14}N_2O_3 \cdot 2$ HCl: C, 30.64; H, 6.85; Cl, 30.16; N, 11.91. Found: C, 30.55; H, 6.92; Cl, 29.98; N, 11.78.

*2,5-Anhydro-1,6-dideoxy-1,6-bis(dimethylamino)-*DL*-glucitol dihydrochloride* (**33**). — A solution of diamine **32** (2.4 g) was methylated as described for **19**, but the residue from the evaporation of the hydrochloric acid solution was dissolved in water (10 mL), and the solution made alkaline with 2M sodium hydroxide (10 mL). Next, sodium borohydride (1 g) was gradually added to the stirred solution, which was then kept for 2 days at room temperature. Thereafter, it was acidified with 2M hydrochloric acid, and evaporated, and methanol (350 mL) was added to, and evaporated from, the residue (to remove boric acid). The residue was dissolved in methanol (20 mL), the solution was made alkaline with 4M methanolic sodium methoxide, the precipitated inorganic salts were filtered off, the filtrate was evaporated, and the residue was filtered with the aid of ethanol. The filtrate was acidified with 5M methanolic hydrogen chloride, and evaporated, and ethanol was added to, and evaporated from, the residue, yielding **33** as a semisolid foam (2.3 g, 79%); R_F 0.75 (*E*): ^{1}H-n.m.r. data (*c*): δ 4.6 (m, H-2,3,5), 4.15 (dd, $J_{4,3}$ 3, $J_{4,5}$ 5 Hz), 3.5 (m, H-1,6), and 3.05 (s, 4 N-Me).

Anal. Calc. for $C_{10}H_{22}N_2O_3 \cdot 2$ HCl: Cl, 24.35; N, 9.62. Found: Cl, 24.08; N, 9.50.

2,5-Anhydro-1,6-dideoxy-1,6-bis(trimethylamino)-DL-*glucitol diiodide* (**34**). — A solution of **33** (1.4 g) in methanol was treated with methyl iodide as described for compound **20**, to give, after recrystallization from methanol–water, pure **34** (1.8 g, 72%); m.p. 210–213° (dec.); ^{1}H-n.m.r. data (*c*): δ 4.75 (m, H-2,3,5), 4.10 (dd, $J_{4,5}$ 5, $J_{3,4}$ 2 Hz, H-4), 3.8 and 3.4 (m, H-1,6), and 3.25 (s, 6 N-Me); ^{13}C-n.m.r. data (*b*): δ 67.3 (C-1), 79.5 (C-2), 76.8 (C-3), 74.1 (C-4), 81.2 (C-5), 68.7 (C-6), and 54.9 and 55.1 (N-CH_3).

Anal. Calc. for $C_{12}H_{28}I_2N_2O_3$: C, 28.69; H, 5.62; I, 50.54; N, 5.57. Found: C, 28.55; H, 5.70; I, 49.72; N, 5.52.

REFERENCES

1 J. KUSZMANN AND I. PELCZER, *Carbohydr. Res.*, 89 (1981) 103–120.
2 P. WASSER, *Experientia*, 17 (1961) 300–303.
3 J. M. SUGIHARA AND D. L. SCHMIDT, *J. Org. Chem.*, 26 (1961) 4612–4615.
4 T. A. W. KOERNER, JR., E. S. YOUNATHAN, A. E. ASHOUR, AND R. J. VOLL, *J. Biol. Chem.*, 249 (1974) 5749–5754.
5 T. A. W. KOERNER, JR., R. J. VOLL, AND E. S. YOUNATHAN, *Carbohydr. Res.*, 59 (1977) 403–416.
6 J. KUSZMANN AND L. VARGHA, *Carbohydr. Res.*, 16 (1971) 261–271.
7 J. KUSZMANN AND L. VARGHA, *Carbohydr. Res.*, 17 (1971) 309–318.
8 J. KUSZMANN AND P. SOHÁR, *Carbohydr. Res.*, 35 (1974) 97–102.
9 J. KUSZMANN AND P. SOHÁR, *Acta Chim. Acad. Sci. Hung.*, 83 (1974) 373–379.
10 T. ADACHI, Y. YAMADA, AND I. INOUE, *Synthesis*, (1977) 45–46.
11 M. L. MOORE, *Org. React.*, 5 (1949) 301–330.
12 L. D. HALL, P. R. STEINER, AND C. PEDERSEN, *Can. J. Chem.*, 48 (1970) 1155–1165.
13 C. ALTONA AND M. SUNDARALINGAM, *J. Am. Chem. Soc.*, 94 (1972) 8205–8212.