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# SYNTHESIS OF 6-AMINO-2,5-ANHYDRO-6-DEOXY- AND -1,6-DIDEOXY-D-GLUCITOL AND SOME DERIVATIVES THEREOF

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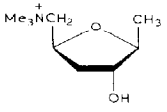
ABSTRACT

6-Amino-2,5-anhydro-6-deoxy- and -1,6-dideoxy-D-glucitol (**44**), as well as some of their derivatives, were synthesized, starting from D-mannitol. 3,4-Di-*O*-allyl-1,2:5,6-dianhydro-D-mannitol was converted into the 2,5-anhydro-6-bromo compound **8**, the bromine atom of which was replaced by azide. The allyl groups were removed by treatment with Pd–C in ethanol–acetic acid–water, and the azido group was reduced with hydrogen sulfide–pyridine. The amino group formed was methylated by using formaldehyde–formic acid, yielding the 1-*N*-6-*O*-methylene compound as the main product, which is resistant towards reduction with borohydride. Treatment of **8** with activated zinc in acetic acid gave, instead of the expected 6-deoxy derivative, the (acyclic) 5-enoalditol.

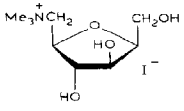
The synthesis of **44** was conducted *via* 2,5-anhydro-1,6-di-*O*-tosyl-D-mannitol (**36**), which was obtained from 1,6-di-*O*-benzoyl-3,4-*O*-isopropylidene-D-mannitol in satisfactory yield. Ditosylate **36** was converted into a 2,5:3,6-dianhydro monotosylate which, on reduction with lithium aluminum hydride, gave the 1-deoxy derivative. Opening of the 3,6-anhydro ring with hydrobromic acid led to the 6-bromo compound, which was converted, *via* its azide, into **44**.

## INTRODUCTION

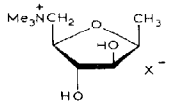
In previous studies, the synthesis of "double-headed" muscarine analogs, having two terminal, trimethylamino groups, was described[1,2]. As these compounds possessed no muscarine-like biological activity, the synthesis of structurally more closely related derivatives, such as **1** and **2**, containing only one terminal trimethylamino group, was decided on.



Muscarine



**1**



**2**

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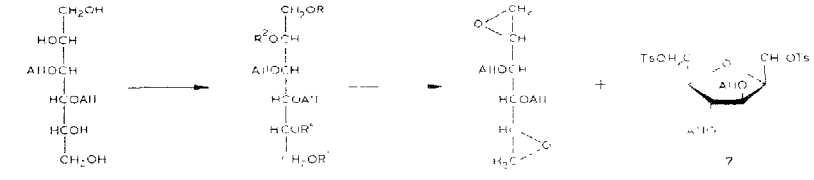
## RESULTS AND DISCUSSION

For the synthesis of compound **1**, a 2,5-anhydro-D-glucitol derivative carrying a good leaving-group at C-6 was needed. Such compounds can be obtained from 3,4-di-*O*-alkyl-1,2:5,6-dianhydro-D-mannitols, as, on treatment with hydrobromic acid, the corresponding 2,5-anhydro-6-bromo-D-glucitol derivatives are formed in good yield[3]. As all hydroxyl groups must be free in compound **1**, alkyl substituents that could be selectively removed from the intermediates had to be used for O-3 and O-4. For this purpose, the allyl group was chosen as it can be readily split off under neutral[4] or weakly acidic conditions[5].

As the starting material, the diallyl diepoxide **6** was used; this was originally obtained[3] from 3,4-di-*O*-allyl-D-mannitol (**3**) *via* its dimesyl diacetate **4**, but, on a larger scale, a more convenient method was applied, involving the conversion of **3** into its 1,6-ditosylate (**5**), which, without purification, was treated with sodium methoxide. The resulting diepoxide (**6**) could, by distillation, be separated from the contaminating 2,5-anhydro ditosylate (**7**), which is probably formed *via* the 1,2,6-tritosylate, present in the crude reaction-mixture.



**3**

All = $CH_2CH{=}CH-$

**4** $R^1$ = Ms, $R^2$ = Ac

**5** $R^1$ = Ts, $R^2$ = H

Ms = $SO_2Me$

Ts = $SO_2C_6H_4Me$-*p*

**6**

**7**

Treatment of diepoxide **6** with conc. hydrobromic acid gave, besides the 6-bromo derivative **8** (68%) expected, the 1,6:2,5-dianhydride **14** (10%), which could be separated by column chromatography. Dianhydride **14** could also be obtained from **8** by treatment with sodium methoxide.

For removing the *O*-allyl groups, compound **8** was boiled, in the presence of Pd–C as the catalyst, in ethanol–acetic acid–water[5]. Deblocking of the *O*-alkyl groups, to afford **12**, proceeded in two steps, removal of the less-hindered group on O-4 being the faster process, yielding **10** as the intermediate. The reaction was complete after 10 h, but the product could be purified only by column chromatography. When, instead of **8**, its 1-acetate (**9**) was submitted to the same reaction, the deblocking process was slower, and, even after 16 h, a 1:1 mixture of **11** and **13** could be separated after acetylation.

Treatment of bromide **12** with sodium azide in aqueous *N*,*N*-dimethylform-

amide at elevated temperature afforded the expected azide **17**, which was purified by column chromatography. The same compound could be obtained in a much higher yield by converting triacetate **13** into its azide (**18**), and submitting **18** to Zemplén deacetylation. The azido group was converted into an amino group by means of hydrogen sulfide in pyridine, a very convenient reagent for the reduction of terminal azides[1,2,6]. During this procedure, the *O*-acetyl groups of **18** underwent partial *O*→*N* acetyl migration; therefore, the crude acetylated amine was directly hydrolyzed with hydrochloric acid, to yield the deacetylated compound **23** in satisfactory yield. The latter was *N*-methylated, using formaldehyde–formic acid[7]. Because of the proximity of the 1- and 3-hydroxyl groups, the formation of *N,O*-methylene derivatives as byproducts could be expected[1,8]. According to $^1$H-n.m.r.-spectral investigation, the product obtained was a complex mixture which, on repeated treatment with formaldehyde–formic acid, was only slightly changed.

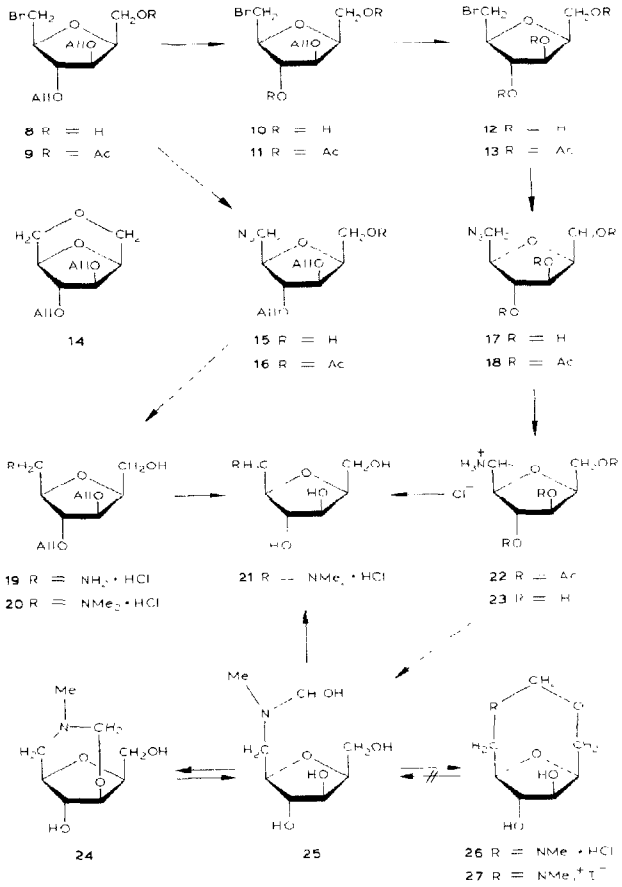
It was presumed that the hypothetical *N,O*-methylene derivatives **24** and **26** would be reduced to the corresponding dimethylamino derivative **21** on treatment with borohydride, as a similar transformation was observed[1] in the case of the analogous 2,5-anhydro-1,6-dideoxy-1,6-bis(dimethylamino)-L-iditol. However, borohydride treatment of the crude, multicomponent, methylation product afforded, besides the dimethylamino derivative **21**, the 1-*N*,6-*O*-methylene compound **26** as the main product (ratio 1:2). The latter proved to be stable towards borohydride, indicating that, although it must be formed *via* intermediate **25**, there exists no equilibrium under neutral conditions between **25** and **26**. That means that the 8-membered dioxazine ring is more stable towards hydrolysis than the 6-membered, oxazine ring[1,*].

The pure 6-(dimethylamino) compound **21** could be obtained from the foregoing mixture by crystallization, and it was converted with methyl iodide into the trimethylamino derivative **1**. It is interesting that this iodide **1** possesses a reversed, temperature-dependent solubility in acetone, as it is fairly soluble in the cold solvent, but crystallizes on heating the solution.

The dibridged methylene compound **26** was purified by column chromatography, and, on treatment with methyl iodide, was converted into its quaternary salt **27**.

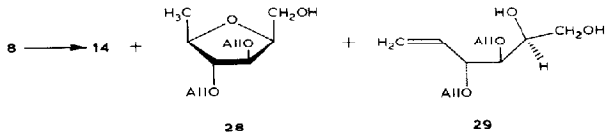
In further experiments, we tried to reduce the 6-bromide **8** to the corresponding 6-deoxy compound **28**, which would be a good starting-material for the synthesis of muscarine antipodes. As the reagent, sodium cyanoborohydride in hexamethylphosphoric triamide (HMPT), recommended by Hutchins *et al.*[9] for the selective reduction of a halogen atom in a terminal position, was first used. At 90°, compound **8** was completely consumed in 10 h, but the 6-deoxy derivative **28** was formed as only a minor component (8.2%), and the main products were the di-

*Structure **26** was proved by $^{13}$C-n.m.r. spectroscopy, as C-1 (being involved in the ether bridge) appeared at 68.1 p.p.m., whereas, in **21**, C-1 of the terminal hydroxymethyl group gave a signal at 61.7 p.p.m. In **24**, C-1 should possess a similar shift.



anhydride **14** (38%) and the unsaturated derivative **29** (25%). The structure of the latter was unambiguously proved by $^1$H-n.m.r. spectroscopy, as well as by g.l.c.–m.s.

The formation of **29** is a process analogous to the conversion of 6-bromo-6-deoxyglycosides into their 5-eno-aldehyde derivatives on treatment with activated zinc in aqueous ethanol, a reaction investigated in detail by Bernet and Vasella[10] in 1979. When sodium borohydride was used instead of cyanoborohydride, and di-




methyl sulfoxide as the solvent, only the dianhydride **14** and the 6-deoxy derivative **28** were formed, but in significantly lower yields (14 and 7%, respectively).

To avoid formation of the 1,6-anhydro ring, basic conditions had to be avoided; therefore, bromide **8** was hydrogenated in the presence of Pd–C and barium carbonate[11], but no reaction took place. Similar, negative results were obtained when sodium borohydride was used in the presence of acetic acid[12]. On the other hand, when zinc powder, activated with $CuSO_4$, was applied in aqueous acetic acid[13], only the 5-enoalditol **29** was formed (in high yield).

For synthesis of the 1,6-dideoxy-6-(trimethylamino) derivative **2**, there was chosen, as the starting material 2,5-anhydro-D-glucitol (**33**), which can be obtained either from 1,6-di-*O*-benzoyl-D-mannitol[14–17] (**30**), or directly from D-mannitol under acidic conditions[18–23]. Despite the fact that, according to g.l.c. investigations[23], this very simple procedure gives a mixture of anhydrides containing **33** in a yield of 47%, its separation is a very tedious process that lowers the preparative yield dramatically. Even the separation of **33** from the crude mixture *via* acetalation and subsequent tritylation[22] or benzoylation[24] gives the properly substituted derivatives in a yield of only ~15%. In our hands, the latter two processes actually gave much lower yields (5–7%); therefore, an alternative route was explored for the synthesis of larger amounts of **33**. To avoid the formation of other anhydro derivatives, which make the purification of anhydride **33** difficult, the tendency to formation of the oxolane ring on C-2 and C-5 had to be increased. Under acidic conditions, protonation of OH-2 (or OH-5)—transforming it into a leaving group—is the crucial step for the formation of the 2,5-anhydro bridge. Protonation of all other OH groups will automatically enhance the possibility of the formation of anhydro derivatives with different structures. To avoid these reactions, OH-2 (or OH-5) had to be converted by substitution into a strong leaving-group, thereby enhancing the chance of 2,5-anhydro ring-closure.

Based on this consideration, the well known 1,6-di-*O*-benzoyl-3,4-*O*-isopropylidene-D-mannitol[15] (**31**) was converted with one equivalent of tosyl chloride in pyridine into its crystalline 2-tosylate **32**, which, on boiling with conc. hydrochloric acid in ethanol, was rapidly converted (*via* hydrolysis of the isopropylidene group and subsequent elimination of *p*-toluenesulfonic acid) into the 1,6-dibenzoate **34**. The overall yield, calculated on D-mannitol, is only ~20%, but all of these derivatives are crystalline, and readily purified. 2,5-Anhydro-D-glucitol (**33**) could be obtained as a homogeneous syrup in quantitative yield by Zemplén debenzoylation of **34**; its purity was proved by g.l.c. of its tetraacetate (**35**).

Anhydride **33** was converted by selective tosylation into the crystalline 1,6-ditosylate **36**, which, on treatment with sodium methoxide in ethanol, gave the expected 2,5:3,6-dianhydro derivative **42**. As OH-3 in **36** is *cis*-related to both tosyloxy groups, theoretically the formation of a 1,3-anhydro derivative could not be precluded, but the tendency to ring formation is much greater for an oxolane than for an oxetane. Nevertheless, the structure of **42** could also be proved chemically, as, on treatment with lithium aluminum hydride in 1,4-dioxane, it was converted in excellent yield into the 1-deoxy derivative **40**, which, on tosylation, afforded **41**, both being identical with the 2,5:3,6-dianhydro derivatives described earlier[25].

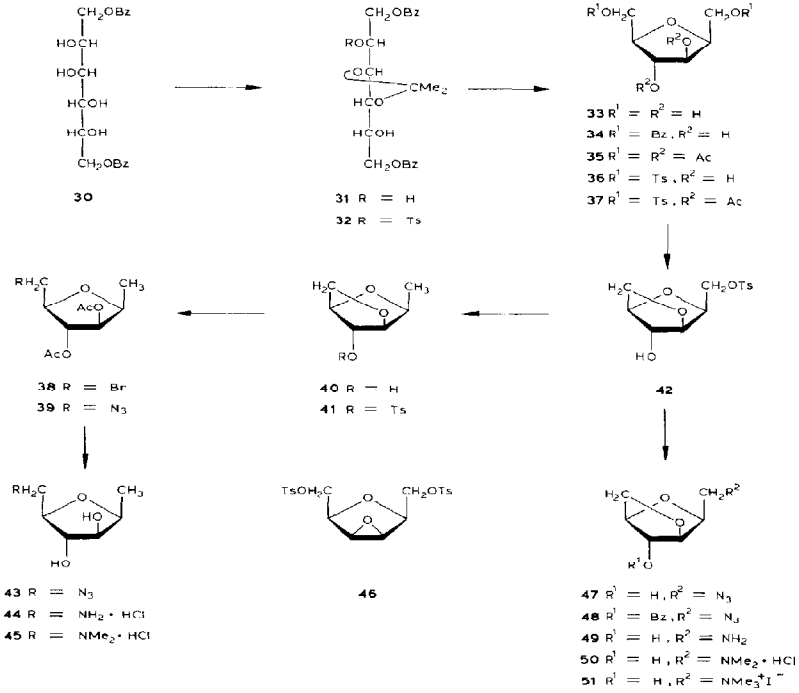
When dianhydride **40** was treated with hydrobromic acid in acetic acid containing acetic anhydride, the 3,6-anhydro ring was cleaved, and the 6-bromo diacetate **38** was formed. The terminal bromine atom of **38** was exchanged with sodium azide in *N,N*-dimethylformamide, and the 1-azido diacetate **39** obtained gave, on deacetylation, the crystalline dihydroxy compound **43**. This was reduced with hydrogen sulfide, and the resulting amine **44** gave, after methylation with formaldehyde–formic acid, and treatment of the product with borohydride, the dimethylamino derivative **45**, which was converted with methyl iodide into the corresponding quaternary salt **2** (X=I). The iodine in the latter was replaced by chlorine on treatment with silver acetate, and reaction of the acetate with hydrochloric acid.

During the partial tosylation of 2,5-anhydro-D-glucitol (**33**), a 1,4,6-tritosylate must have been formed (besides the ditosylate **36**), as addition of sodium methoxide to the mother liquor obtained after separation of **36** afforded the symmetrical galactitol epoxide **46**, which is almost insoluble in chloroform.

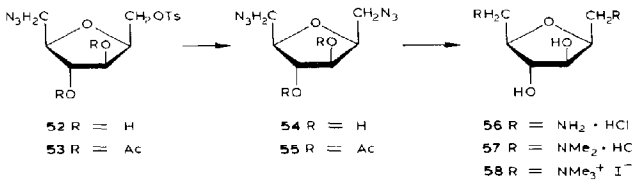
Treatment of the dianhydro monotosylate **42** with sodium azide in *N,N*-dimethylformamide gave syrupy azide **47**, which was purified *via* its benzoate **48**. After debenzoylation, the azide was reduced with hydrogen (Pd–C as catalyst), and the crystalline amine **49** resulting was converted into the dimethylamino derivative **50** with formaldehyde–formic acid. Methylation of **50** with methyl iodide afforded the quaternary salt **51**.

The 1,6-ditosylate **36** offered the opportunity to synthesize the "double-headed" 1,6-bis(trimethylamino) derivative having the D-*gluco* configuration (**58**), which had thus far been obtained only as its racemate[2]. Treatment of **36** with trimethylamine [which, according to the literature[26], afforded the 1,6-bis(trimethylamino) derivative **58** as its dibenzenesulfonate in the case of 2,5-anhydro-1,6-di-*O*-(phenylsulfonyl)-D-glucitol] gave only the 2,5:3,6-dianhydro 1-tosylate **42**. That means that trimethylamine does not react as a nucleophile, but as a base, and the substitution reaction described in the literature indicates that the starting material used must actually have had a structure different from that claimed, as already suggested[2,22].

The tosyloxy groups of **36** reacted with sodium azide in *N,N*-dimethylformamide at elevated temperature; the less shielded one (on C-6), being the more reactive, was exchanged first. On prolonged treatment with sodium azide, the




mono-azide **52** obtained gave the 1,6-diazide **54**. As the water-soluble azides could only be separated with difficulty, the same reaction was applied to the acetylated ditosylate **37**, yielding diazide **55** (*via* the monoazide **53**) in excellent yield. Deacetylation of **55** gave **54**, which was reduced to the corresponding diamine **56**. Methylation with formaldehyde–formic acid, and subsequent treatment with sodium borohydride, afforded the 1,6-bis(dimethylamino) derivative **57**, which was converted into its quaternary salt **58** on treatment with methyl iodide.



None of the quaternary salts **1**, **2**, **51**, and **58** possessed muscarine-like activity. For compound **2**, this was rather unexpected, as it differs from muscarine only in the configuration of C-3 and in the presence of an additional hydroxyl group on C-4. According to the published structure–activity data[27] for several analogs, the configuration of C-3 seems not to be essential for the biological activity, as muscarone (the 3-keto derivative of muscarine) is as active as the parent compound.

## 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 for solutions in chloroform (*c* 1), if not stated otherwise. T.l.c. was effected on Kieselgel G with (*A*) ethanol, (*B*) ethyl acetate, with ethyl acetate–carbon tetrachloride 1:1 (*C*), 1:2 (*D*), 1:3 (*E*), 1:5 (*F*), 2:1 (*G*), and 3:1 (*H*), with ethyl acetate–1,2-dichloroethane 1:3 (*I*) and 1:9 (*J*), with ethyl acetate–ethanol 1:5 (*K*) and 1:9 (*L*), and with (*M*) 9:1 ethanol–conc. ammonium hydroxide. 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. G.l.c.–m.s. was conducted with a Hewlett–Packard 5990A gas chromatograph–mass spectrometer using a glass column packed with 1% of OV-1, at 70 eV electron energy and 2,600 MeV multiplier voltage.

*2,5-Anhydro-6-deoxy-6-(trimethylamino)-*D*-glucitol iodide* (**1**). — A stirred slurry of hydrochloride **21** (0.6 g) in methanol (10 mL) was made basic, in the presence of phenolphthalein, with 5M methanolic sodium methoxide (0.6 mL). Then acetone (10 mL) was added, and the inorganic salt precipitated was filtered off on charcoal. Methyl iodide (1 mL) was added to the filtrate, and the mixture was kept overnight at room temperature, and then evaporated. The solid residue was soluble in cold acetone, but precipitated from the solution on heating. Recrystallization from ethanol gave pure **1** (0.62 g, 72%); m.p. 90–92°, $[\alpha]_D^{20}$ +17° (water); $^{13}$C-n.m.r. data (*b*): δ 83.7 (C-2), 82.0 (C-5), 79.7 and 77.9 (C-3,4), 70.2 (C-6), 62.3 (C-1) and 56.5 (t, $J_{C,N}$ 3.3 Hz, N-$CH_3$).

*Anal.* Calc. for $C_9H_{20}INO_4$: C, 32.44; H, 6.05; I, 38.09; N, 4.20. Found: C, 32.30; H, 6.22; I, 37.81; N, 4.05.

*2,5-Anhydro-1,6-dideoxy-6-(trimethylamino)-*D*-glucitol chloride* (**2**, X=Cl). — A solution of hydrochloride **45** (1.4 g) in ethanol (10 mL) was methylated as described for **1**. After evaporation, a solution of the residue in water (20 mL) was stirred with silver acetate (0.9 g) for 3 h. The precipitate formed was filtered off, and the filtrate was saturated with hydrogen sulfide to remove traces of soluble silver

salts. The suspension was filtered with charcoal, and the filtrate acidified with conc. hydrochloric acid, and evaporated. Then, ethanol was added to, and evaporated from, the residue, which crystallized and was filtered off with 2-propanol–ether, to yield pure **2** (X=Cl) (1 g, 67%); m.p. 118–120°, $[\alpha]_D^{20}$ +44.4° (water); $^1$H-n.m.r. data (*b*): $\delta$ 3.65 (m, H-6), 3.22 (s, N-$CH_3$), and 1.26 (d, $J_{1,2}$ 6 Hz, H-1).

*3,4-Di-O-allyl-1,6-di-O-p-tolylsulfonyl-D-mannitol* (**5**). — To a stirred solution of 3,4-di-*O*-allyl-D-mannitol[3] (**3**; 5.2 g) in dry pyridine (25 mL) was added a solution of tosyl chloride (8.5 g, 2.2 equiv.) in chloroform (20 mL) during 30 min at +5°. The mixture was kept overnight at room temperature, and then poured into water. The precipitated oil was extracted with chloroform, and the extract was processed in the usual way, to yield a syrup which, after column chromatography (solvent *D*), gave ditosylate **5** as a pale-yellow syrup (5.3 g, 46.5%); $R_F$ 0.55 (*D*); $[\alpha]_D^{20}$ +15.5°; $^1$H-n.m.r. data (*a*): $\delta$ 4.17 (m, H-1,6), 4.0 (m, H-2,5), 3.65 (m, H-3,4), 3.6 (OH), and 5.75, 5.2, and 4.0 (*O*-allyl).

*Anal.* Calc. for $C_{26}H_{34}O_{10}S_2$:C, 54.71; H, 6.00; S, 11.23. Found: C, 54.35; H, 5.83; S, 11.52.

*3,4-Di-O-allyl-1,2:5,6-dianhydro-D-mannitol* (**6**). — Compound **3** (131 g) was tosylated as described for **5**, but the chloroform solution of the crude reaction-product was only concentrated to 1 L. Methanol (500 mL) and, after cooling to +5°, 5M methanolic sodium methoxide (220 mL) were added. The alkaline (phenolphthalein) slurry formed was stirred for 10 min, and then poured into water. The organic solution was washed with water, dried, and evaporated. The residue gave, on distillation, pure **6** (61.7 g, 54%); b.p.$_{0.05}$* 98–100°; lit.[3] b.p.$_{0.3}$ 112–115°.

*3,4-Di-O-allyl-2,5-anhydro-1,6-di-O-p-tolylsulfonyl-D-glucitol* (**7**). — The dark-brown residue obtained after the distillation of **6** was mixed with hot methanol (50 mL), and the suspension was filtered with charcoal. Crude **7** crystallized from the chilled filtrate and was recrystallized from methanol (5 vol.); yield, 17.1 g, 6.2%; m.p. 76–77°, $[\alpha]_D^{20}$ +35.4°; $R_F$ 0.60 (*E*); $^1$H-n.m.r. data (*a*): $\delta$ 4.3–3.8 (m, H-1–6), 5.75, 5.2, and 4.0 (m, *O*-allyl), and 7.83, 7.35, and 2.45 (d, d, and s, *O*-tosyl).

*Anal.* Calc. for $C_{26}H_{32}O_9S_2$: C, 56.50; H, 5.83; S, 11.60. Found: C, 56.42; H, 5.90; S, 11.97.

*3,4-Di-O-allyl-2,5-anhydro-6-bromo-6-deoxy-D-glucitol* (**8**) *and 3,4-di-O-allyl-1,6:2,5-dianhydro-D-glucitol* (**14**). — A solution of diepoxide **6** (22.6 g) in acetone (100 mL) was added dropwise to an ice-cold, stirred solution of conc. hydrobromic acid (25 mL) in acetone (25 mL). The mixture was stirred for 15 min at room temperature, and was then made neutral with solid sodium hydrogencarbonate. The precipitated salts were filtered off, and the filtrate was evaporated. The residue was dissolved in chloroform, and the solution washed with water, dried, and evaporated; the syrup obtained was purified by column chromatography

*For comparison with earlier work, pressures are given in torr, 1 torr =133.32 Pa.

(solvent *E*). The fractions having $R_f$ 0.25 gave, on evaporation, pure **8** as a syrup (20.9 g, 68%); $[\alpha]_D^{20}$ +11°; $^1$H-n.m.r. data (*a*): δ 4.3–3.8 (H-1–5), 3.45 (d, H-6), and 5.75, 5.2, and 4.0 (m, *O*-allyl).

*Anal.* Calc. for $C_{15}H_{19}BrO_4$: C, 46.91; H, 6.23; Br, 26.01. Found: C, 46.73; H, 5.96; Br, 26.38.

The fractions having $R_f$ 0.45 gave, on evaporation, and distillation of the residue, pure dianhydride **14** (2.2 g, 9.7%); b.p.$_{0.01}$ 80–85°; $[\alpha]_D^{20}$ −23.3°; $^1$H-n.m.r. data (*a*): δ 4.2–3.5 (m, H-1,6), and 5.8, 5.2, and 4.0 (*O*-allyl).

*Anal.* Calc. for $C_{12}H_{18}O_4$: C, 63.69; H, 8.02. Found: C, 63.55; H, 8.11.

The same dianhydride (**14**) resulted when bromide **8** (obtained from 2.3 g of diepoxide **6**) in methanol (10 mL) and 5M methanolic sodium methoxide (2.5 mL) was boiled on a steam bath for 8 h. The residue obtained after evaporation was dissolved in chloroform, and the solution washed with water, dried, and evaporated, to yield, after distillation, dianhydride **14** (1.7 g, 74%), identical with that already described.

*Reduction of compound* **8**. — *Method a.* A solution of bromide **8** (1 g) and sodium cyanoborohydride (1.2 g) in hexamethylphosphoric triamide (10 mL) was heated on a steam bath for 10 h, when, according to t.l.c. (solvent *E*), the starting material had all been consumed. The mixture was diluted with water, and extracted with ether. The extract was washed with water, dried, and evaporated, and the residue was purified by column chromatography (solvent *C*).

The fractions having $R_f$ 0.60 gave, on evaporation, dianhydride **14** (0.28 g, 38%), identical with that already described.

The fractions having $R_f$ 0.45 gave, on evaporation, 3,4-di-*O*-allyl-2,5-anhydro-6-deoxy-D-glucitol (**28**; 0.06 g, 8.2%); $^1$H-n.m.r. data (*a*): δ 1.33 (d, $J_{5,6}$ 6 Hz, H-6), 4.5–3.7 (m, H-1–5), and 5.9, 5.3, and 4.2 (m, *O*-allyl).

The fractions having $R_f$ 0.30 gave, on evaporation, 3,4-di-*O*-allyl-D-*xylo*-hex-5-enitol (**29**; 0.18 g, 25%) as a colorless liquid, $[\alpha]_D^{20}$ +16.3°; *m/z*: 41 (100), 43 (17), 55 (32), 57 (10), 61 (11), 97 (11), 113 (4), 131 (1.5), 139 (1.1), and 167 (0.6).

*Method b.* A solution of bromide **8** (1 g) and sodium borohydride (1.5 g) in dimethyl sulfoxide (10 mL) was heated on a steam bath for 10 h. The cooled solution was acidified with M hydrochloric acid and then extracted with ether. The residue obtained after evaporation of the dried ether solution was separated by column chromatography (solvent *I*), giving dianhydride **14** (0.1 g, 14%) and the 6-deoxy compound **28** (0.05 g, 7%), both identical with those obtained *via* method *a*.

*Method c.* To a stirred solution of bromide **8** (1.5 g) in acetic acid (20 mL) and water (18.5 mL) was added a suspension of zinc powder (3 g) in a solution of $CuSO_4$ (0.3 g) in water (1.5 mL). The slurry was stirred for 5 h at 40°, when, according to t.l.c. (*E*), the starting material had all been consumed, and only one major component (**29**) could be detected. The cooled slurry was filtered, the zinc was washed with ethanol, and the filtrates were combined and 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 chro-

matography (solvent *C*), pure **29** (0.85 g, 74%), identical with that obtained *via* method *a*.

*1-O-Acetyl-3,4-di-O-allyl-2,5-anhydro-6-bromo-6-deoxy-*D-*glucitol* (**9**). — To a solution of **8** (15.3 g) in pyridine (15 mL) was added acetic anhydride (10 mL), and the mixture kept overnight at room temperature, and then processed in the usual way, to give, after column chromatography (solvent *F*), pure **9** as a syrup (11.4 g, 73.5%); $[\alpha]_D^{20}$ −19.4°; $R_F$ 0.75 (*F*); $^1$H-n.m.r. data (*a*): δ 4.4–3.8 (m, H-1–5), 3.40 (d, H-6), 5.8, 5.2, and 4.0 (m, *O*-allyl), and 2.06 (s, *O*-acetyl).

*Anal.* Calc. for $C_{14}H_{21}BrO_5$: Br, 22.88. Found: Br, 22.60.

*1,4-Di-O-acetyl-3-O-allyl-2,5-anhydro-6-bromo-6-deoxy-*D-*glucitol* (**11**) *and 1,3,4-tri-O-acetyl-2,5-anhydro-6-bromo-6-deoxy-*D-*glucitol* (**13**). — A stirred solution of **9** (3.5 g) in ethanol (50 mL), acetic acid (35 mL), and water (35 mL) was boiled in the presence of 10% Pd–C catalyst (3.5 g) for 16 h. The cooled slurry was filtered, the filtrate evaporated, and the residue acetylated with acetic anhydride (5 mL)–pyridine (10 mL). The mixture was kept overnight at room temperature to give, after the usual processing, a syrup which was separated by column chromatography (solvent *F*).

The fractions having $R_F$ 0.60 gave, on evaporation, the monoallyl compound **11** (1.0 g, 28%); $[\alpha]_D^{20}$ −7.5°; $^1$H-n.m.r. data (*a*): δ 5.15 (d, H-4), 4.5–3.8 (m, H-1,2,3,5), 3.47 (d, H-6), 5.8, 5.2, and 4.1 (m, *O*-allyl), and 2.12 and 2.06 (s, *O*-acetyl).

*Anal.* Calc. for $C_{13}H_{19}BrO_6$: Br, 22.75. Found: Br, 22.87.

The fractions having $R_F$ 0.55 gave, on evaporation, triacetate **13** (1.2 g, 34%); $[\alpha]_D^{20}$ −16.2°; $^1$H-n.m.r. data (*a*): δ 5.28 (dd, H-4), 5.01 (dd, H-3), 4.33 (m, H-2), 4.22 (d, H-1), 4.07 (m, H-5), 3.57 (d, H-6), and 2.12 and 2.06 (s, *O*-acetyl).

*Anal.* Calc. for $C_{12}H_{17}BrO_7$: Br, 22.62. Found: Br, 22.65.

The same triacetate **13** (1.5 g, 85%) was obtained when compound **12** (1.1 g) was acetylated with acetic anhydride (5 mL) in pyridine (7 mL).

*2,5-Anhydro-6-bromo-6-deoxy-*D-*glucitol* (**12**). — A stirred solution of **8** (6.15 g) in ethanol (80 mL), acetic acid (60 mL), and water (60 mL) was boiled in the presence of 10% Pd–C catalyst (6.5 g). On t.l.c. (*B*), besides the spot of the starting material ($R_F$ 0.9), that of the 3-*O*-allyl derivative **10** ($R_F$ 0.7) and compound **12** ($R_F$ 0.35) could be detected. After 10 h, the catalyst was filtered off, and the filtrate was evaporated. Then, ethanol was added to, and evaporated from, the residue, and this procedure was repeated three times. The remaining syrup was dissolved in ethanol (100 mL) and Kieselgel 40 (20 g) was added. The slurry was evaporated to dryness, and the mixture was transferred onto the top of a column prepared with ethyl acetate. The same solvent was used for elution. The fractions having $R_F$ 0.35 gave, on evaporation, pure **12** (3.3 g, 72%) as a syrup; $[\alpha]_D^{20}$ +1.7° (methanol); $^1$H-n.m.r. data (*c*): δ 4.1–3.4 (m, H-1–6), and 4.5 (s, OH).

*Anal.* Calc. for $C_6H_{11}BrO_4$: Br, 35.19. Found: Br, 34.98.

*3,4-Di-O-allyl-2,5-anhydro-6-azido-6-deoxy-*D-*glucitol* (**15**). — A solution of **8** (7 g) and sodium azide (2 g) in *N,N*-dimethylformamide (30 mL) and water (3

mL) was boiled for 30 min. The dark-brown solution was cooled, and evaporated, and the residue was partitioned between chloroform and water. The organic solution was washed with water, dried, and evaporated, and the residue was purified by column chromatography (solvent *I*). The fractions having $R_F$ 0.60 gave, on evaporation, azide **15** (3.5 g, 57%) as a colorless syrup; $[\alpha]_D^{20}$ +67.5°; $^1$H-n.m.r. data (*a*): δ 4.3–3.8 (m, H-2-5), 3.85 (d, H-1), 3.40 (d, H-6), and 5.9–5.3, and 3.9 (m, *O*-allyl).

*Anal.* Calc. for $C_{12}H_{19}N_3O_4$: N, 15.60. Found: N, 15.37.

*1-O-Acetyl-3,4-di-O-allyl-2,5-anhydro-6-azido-6-deoxy-*D*-glucitol* (**16**). — *Method a.* A solution of **9** (3.5 g) and sodium azide (1 g) in *N,N*-dimethylformamide (15 mL) and water (1.5 mL) was treated as described for compound **15**, to yield, after column chromatography (solvent *J*), compound **16** (0.8 g, 25.7%) as an oil; $[\alpha]_D^{20}$ +50.4°; $R_F$ 0.70 (*F*); $^1$H-n.m.r. data (*a*): δ 4.4–3.8 (m, H-1–5), 3.40 (d, H-6), 5.9, 5.2, and 3.9 (m, *O*-allyl), and 2.10 (s, *O*-acetyl).

*Method b.* Azide **15** (1.5 g) gave, on acetylation with acetic anhydride (1.5 mL)–pyridine (3 mL), acetate **16** (1.4 g, 83%), identical with that obtained *via* method *a*.

*Anal.* Calc. for $C_{14}H_{21}N_3O_5$: N, 13.49. Found: N, 13.30.

*2,5-Anhydro-6-azido-6-deoxy-*D*-glucitol* (**17**). — *Method a.* A solution of bromide **12** (3.6 g) and sodium azide (2 g) in *N,N*-dimethylformamide (30 mL) and water (3.6 mL) was boiled for 30 min. The dark-brown solution was evaporated, and then ethanol was added to, and evaporated from, the residue. Thereafter, ethyl acetate (20 mL) and ethanol (5 mL) were added, and the precipitated inorganic salts were filtered off. The filtrate was diluted with ethyl acetate to 100 mL, Kieselgel 40 (20 g) was added, and the slurry was evaporated to dryness. Column chromatography of this material was performed as described for **12**, to give azide **17** (1.9 g, 63.5%) as a colorless oil. $R_F$ 0.30 (*B*); $[\alpha]_D^{20}$ +45.5° (methanol); $^1$H-n.m.r. data (*a*): δ 4.4–3.8 (m, H-1–5), 3.5 (m, H-6), and 4.0 (s, OH).

*Method b.* Zemplén deacetylation of triacetate **18** (0.3 g) afforded **17** (0.15 g, 79%), identical with that obtained *via* method *a*.

*Anal.* Calc. for $C_6H_{11}N_3O_4$: N, 22.21. Found: N, 22.08.

*1,3,4-Tri-O-acetyl-2,5-anhydro-6-azido-6-deoxy-*D*-glucitol* (**18**). — A solution of bromide **13** (7 g) and sodium azide (2 g) in *N,N*-dimethylformamide (60 mL) and water (6 mL) was treated as described for compound **15**, to give, after column chromatography (solvent *E*), pure **18** (5.8 g, 92%) as a pale yellow syrup; $[\alpha]_D^{20}$ +62.5°; $R_F$ 0.55 (*E*); $^1$H-n.m.r. data (*a*), δ 5.28 (dd, H-3), 4.95 (dd, H-4), 4.4–3.8 (m, H-1,2,5), 3.5 (m, H-6), and 2.10 and 2.07 (s, *O*-acetyl).

*Anal.* Calc. for $C_{12}H_{17}N_3O_7$: N, 13.32. Found: N, 13.11.

*3,4-Di-O-allyl-6-amino-2,5-anhydro-6-deoxy-*D*-glucitol hydrochloride* (**19**). — Through a solution of azide **15** (6 g) in pyridine (60 mL) and water (30 mL) was passed a stream of hydrogen sulfide. The temperature of the reaction mixture had to be kept at 40° by gentle heating. In t.l.c. (*M*), besides the spot of the starting material ($R_F$ 0.95), only that of amine **19** ($R_f$ 0.70) was detected. After 2 h, when

the reaction was complete, acetic acid (6 mL) was added, and the solution was evaporated. The residue was filtered on charcoal with the aid of M hydrochloric acid (20 mL), to remove the precipitated sulfur, the filtrate was evaporated, and ethanol was added to, and evaporated from, the residue. The syrupy **19** (5.3 g, 85%) so obtained was pure enough for the next step. An aliquot (0.5 g) was further purified by column chromatography (solvent *M*), yielding pure **19** (0.3 g); $[\alpha]_D^{20}$ +47.4° (water); $^1$H-n.m.r. data (*b*): $\delta$ 4.3–3.7 (m, H-1–6). and 5.9, 5.3, and 4.1 (m, *O*-allyl).

*Anal.* Calc. for $C_{12}H_{22}ClNO_4$: Cl, 12.67; N 5.00. Found: Cl, 12.40; N, 4.88.

*3,4-Di-O-allyl-2,5-anhydro-6-deoxy-6-(dimethylamino)-*D*-glucitol hydrochloride* (**20**). — A solution of crude **19** (2.8 g) in aqueous formaldehyde (36%; 6 mL) and formic acid (90%; 10 mL) was heated on a steam bath for 12 h. The solution was evaporated, and the residue was filtered on charcoal with the aid of M hydrochloric acid (10 mL), to give, after evaporation, a syrup which was purified by column chromatography (solvent *A*). The fractions having $R_F$ 0.5 gave, on evaporation, pure **20** (1.3 g, 42%) as a pale-yellow syrup; $[\alpha]_D^{20}$ +47° (water); $^1$H-n.m.r. data (*b*): $\delta$ 4.3–3.7 (m, H-1–6), 5.9, 5.3, and 4.1 (m, *O*-allyl), and 2.98 (s, *N*-methyl).

*Anal.* Calc. for $C_{14}H_{26}ClNO_4$: Cl, 11.51; N, 4.55. Found: Cl, 11.23; N, 4.31.

*2,5-Anhydro-6-deoxy-6-(dimethylamino)-*D*-glucitol hydrochloride* (**21**). — *Method a.* A solution of the dimethylamino compound **20** (1.5 g) in ethanol (20 mL), acetic acid (15 mL), and water (15 mL) was boiled in the presence of 10% Pd–C (1.5 g). According to t.l.c. (*M*), the starting material ($R_F$ 0.90) was slowly converted, *via* the monoallyl derivative ($R_F$ 0.55), into the unprotected **21** ($R_F$ 0.35). After 62 h, when the reaction was complete, the catalyst was filtered off, and the filtrate was evaporated. The residue was mixed with M hydrochloric acid (10 mL), the suspension filtered with charcoal, and the filtrate evaporated. Then ethanol was added to, and evaporated from, the residue, and the syrup obtained was purified by column chromatography (solvent *M*). The fractions having $R_F$ 0.35 gave, on evaporation, a solid residue which was filtered with acetone, to yield pure **21** (0.1 g, 9%); m.p. 150–151°, $[\alpha]_D^{20}$ +47° (water); $^1$H-n.m.r. data (*c*): $\delta$ 4.2–3.7 (m, H-2–5), 3.60 (m, H-1), 3.25 (m, H-6), 10.4 (s, $NH^+$), 4.3 (s, OH), and 2.78 (s, *N*-methyl).

*Method b.* A solution of amine **23** (5 g) in aqueous formaldehyde (36%; 10 mL) and formic acid (90%; 15 mL) was boiled for 2 h, cooled, and evaporated. The residue was dissolved in the same reagent, and the procedure was repeated. The residue was mixed with water, the suspension filtered with charcoal, and the filtrate evaporated. The residue was dissolved in ethanol (10 mL), and the solution was made alkaline (in the presence of phenolphthalein) with M sodium hydroxide (15 mL). Then, sodium borohydride (2 g) was gradually added to the stirred solution, and stirring was continued for 2 h at room temperature. The solution was acidified with conc. hydrochloric acid (using Methyl Red as the indicator), and evaporated, and then ethanol, and, subsequently, methanol (3 × 100 mL) were added to, and

evaporated from, the residue, to remove water and boric acid, respectively. The syrup so obtained gave two spots in t.l.c. (*M*), that of $R_F$ 0.60 corresponding to compound **26**, and that of $R_F$ 0.45, to the dimethylamino derivative **21**. According to $^{13}$C-n.m.r. spectroscopy*, these two components were present in the ratio of 1:2. The syrup was dissolved in ethanol (15 mL), and the solution was kept for 2 days at −5°. The resulting crystals were filtered off, and washed with ethanol, to give pure **21** (0.9 g, 15.7%), identical with that obtained *via* method *a*.
with that obtained *via* method *a*.

*Anal.* Calc. for $C_8H_{18}ClNO_4$: C, 42.19; H, 7.96; Cl, 15.57; N, 6.15. Found: C, 42.05; H, 7.80; Cl, 15.32; N, 5.98.

*6-Amino-2,5-anhydro-6-deoxy*-D-*glucitol hydrochloride* (**23**). — A solution of azide **18** (6.3 g) in pyridine (60 mL) and water (30 mL) was reduced with hydrogen sulfide as described for **19**. The solution was evaporated, the residue dissolved in M hydrochloric acid, and byproducts were removed by extraction with chloroform. The aqueous solution was evaporated, yielding a syrup (5.2 g) containing mainly triacetate **22** and some of its *N*-acetyl derivative (which is formed during the reduction *via* an *O*→*N* acetyl migration). This crude syrup was dissolved in M hydrochloric acid (20 mL), and the solution was boiled for 75 min. The brown solution was filtered with the aid of charcoal, the filtrate was evaporated, and then ethanol was added to, and evaporated from, the residue, yielding **23** (2.9 g, 72.5%) as a pale-yellow syrup; $[\alpha]_D^{20}$ +20° (water); $R_F$ 0.40 (*M*); $^1$H-n.m.r. data (*c*): δ 4.1–3.3 (m, H-2–6) and 3.0 (m, H-1).

*Anal.* Calc. for $C_9H_{14}ClNO_4$: Cl, 17.76; N, 7.01. Found: Cl, 17.52; N, 6.83.

*2,5-Anhydro-6-deoxy-6-(dimethylamino)-1-O,6-N-methylene*-D-*glucitol iodide* (**27**). — The mother liquor of the dimethylamino derivative **21**, obtained *via* method *b*, was evaporated. The residue (1.8 g) was dissolved in ethanol, and the solution was made alkaline with 5M methanolic sodium methoxide in the presence of phenolphthalein. The precipitated inorganic salts were filtered off, the filtrate was evaporated, and the residue obtained was purified by column chromatography (solvent *M*). The fractions having $R_F$ 0.60 gave, on evaporation, **26** as free base. This was dissolved in acetone (20 mL), and methyl iodide (3 mL) was added. After 15 min at room temperature, the solution became turbid, and an oil separated. The mixture was kept overnight at room temperature, to give, after evaporation, a pale-yellow syrup which slowly crystallized on standing at room temperature. Recrystallization from ethanol gave pure **27** (2.2 g, 69.8%); m.p. 60–65°, $[\alpha]_D^{20}$ +25° (water); $R_F$ 0.85 (*M*); $^1$H-n.m.r. data (*c*): δ 4.3–3.8 (m, H-2–5), 3.9–3.4 (m, H-1,6), 4.90 and 4.68 (d, d, N–$CH_2$–O), and 3.22 (s, *N*-methyl).

*Anal.* Calc. for $C_9H_{18}INO_4$: C, 32.63; H, 5.47; I, 38.32; N, 4.23. Found: C, 32.71; H, 5.60; I, 38.05; N, 4.13.

*1,6-Di-O-benzoyl-3,4-di-O-isopropylidene-2-O*-p-*tolylsulfonyl*-D-*mannitol* (**32**). — To a stirred solution of dibenzoate[15] **31** (43 g) in dry pyridine (160 mL) was

*$^{13}$C-N.m.r. data for **21**: δ 44.3 (*N*-methyl), for **26**: δ 46.9 (*N*-methyl) and 93.4 (N–$CH_2$–O).

added a solution of tosyl chloride (21 g; 1.1 equiv.) in pyridine (40 mL) during 30 min at +5°. The mixture was kept overnight at room temperature, to give, after the usual processing, and evaporation of the chloroform solution, a syrup that crystallized on treatment with methanol. [The crude tosylate **32** (41.4 g, 70.8%; m.p. 127–129°) obtained was pure enough for conversion into the anhydride **34**.] Recrystallization from acetone–ether gave pure **32**, m.p. 128–130°, $[\alpha]_D^{20}$ +31°; $R_F$ 0.40 (*F*); $^1$H-n.m.r. data (*a*): δ 5.20 (m, H-2), 4.8–4.3 (m, H-1,3–6), 8.2–7.0 and 2.25 (m, s, *O*-tosyl), and 1.38 (s, *O*-isopropylidene).

*Anal.* Calc. for $C_{30}H_{32}O_{10}S$: C, 61.62; H, 5.51; S, 5.48. Found: C, 61.52; H, 5.65; S, 5.32.

*2,5-Anhydro*-D-*glucitol* (**33**). — *Method a.* A stirred slurry of crude dibenzoate **34** (44 g) in dry methanol (200 mL) was made alkaline (in the presence of phenolphthalein) with 5M methanolic sodium methoxide (0.5 mL). According to t.l.c. (*L*), the **34** ($R_F$ 0.90) was slowly converted, *via* its monobenzoate ($R_F$ 0.55), into **33** ($R_F$ 0.15). When the reaction was complete (25 h), sodium ions were removed by means of an ion-exchange resin, and the solution was evaporated. The residue was partitioned between ether and water, the aqueous solution was evaporated, and the colorless syrup was dried *in vacuo* over phosphorus pentaoxide, to give **33** (19 g, 98.2%); $[\alpha]_D^{20}$ +19.5° (water); lit.[22] $[\alpha]_D^{20}$ +23.1° (*c* 2, water).

*Method b.* A solution of the distilled tetraacetate **35** (29 g) in methanol (100 mL) and 5M methanolic sodium methoxide (0.1 mL) was kept for two days at room temperature, and was then processed as described for method *a*, to yield **33** (13.9 g, 93.5%), identical with that obtained *via* method *a*.

*2,5-Anhydro-1,6-di*-O-*benzoyl*-D-*glucitol* (**34**). — A solution of crude tosylate **32** (100 g) in ethanol (1 L) and conc. hydrochloric acid (100 mL) was boiled on a steam bath for 45 min, when, according to t.l.c. (*E*), the starting material ($R_F$ 0.70) was completely converted into the anhydride **34** ($R_F$ 0.1). The cooled solution was made neutral by addition of solid sodium hydrogencarbonate, the suspension filtered, the filtrate evaporated, the residue partitioned between ethyl acetate and water, and the organic solution washed with water, dried, and evaporated. The residue was filtered with the aid of ether to yield dibenzoate **34** (48.2 g, 75.6%), m.p. 124–126°, pure enough for further reactions. Recrystallization from benzene afforded pure **34**, m.p. 135–137°; $R_F$ 0.45 (*C*); lit.[22] m.p. 135.5–138.5°; lit.[25] m.p. 135–137°.

*1,3,4,6-Tetra*-O-*acetyl-2,5-anhydro*-D-*glucitol* (**35**). — Syrupy anhydride **33** (19 g) was dissolved in pyridine (100 mL) and acetic anhydride (70 mL), to give, after the usual processing, syrupy **35**, the purity of which was 98.5%, according to g.l.c. Distillation afforded pure **35** (35.5 g, 92.4%); $b.p._{0.8}$ 171–173°; $[\alpha]_D^{20}$ 0°; $R_F$ 0.30 (*F*). The $^1$H-n.m.r. data were identical to those described[22].

*2,5-Anhydro-1,6-di*-O-p-*tolylsulfonyl*-D-*glucitol* (**36**). — To a stirred solution of anhydride **33** (16 g) in pyridine (100 mL) was gradually added tosyl chloride (42 g) at +10°. The solution was kept for 4 h at room temperature and was then poured into ice–water. The precipitate was filtered off, washed successively with water and

methanol, and recrystallized from ethanol, to give pure **36** (27 g, 57.5%); m.p. 131–133°, $[\alpha]_D^{20}$ +13.3° (pyridine); $R_F$ 0.55 (*E*)

*Anal.* Calc. for $C_{20}H_{24}O_9S_2$: C, 50.83; H, 5.11; S, 13.57. Found: C, 50.82; H, 5.26; S, 13.21.

*3,4-Di-O-acetyl-2,5-anhydro-1,6-di-O-p-tolylsulfonyl-D-glucitol* (**37**). — Acetylation of tosylate **36** (4.7 g) with acetic anhydride (5 mL) in pyridine (8 mL) was complete in 1 h. After the usual processing, diacetate **37** was obtained as a colorless syrup (5.2 g, 94%); $[\alpha]_D^{20}$ +12.5°; $R_t$ 0.50 (*E*); $^1$H-n.m.r. data (*a*): $\delta$ 5.23 (dd, H-3), 4.95 (dd, H-4), 4.4–3.9 (m, H-1,2,5,6), 7.80, 7.36, and 2.44 (d, d, s, *O*-tosyl), and 2.04 and 1.88 (s, *O*-acetyl).

*Anal.* Calc. for $C_{24}H_{28}O_{11}S_2$: C, 51.78; H, 5.07; S, 11.52. Found: C, 51.52; H, 5.17; S, 11.08.

*3,4-Di-O-acetyl-2,5-anhydro-6-bromo-1,6-dideoxy-D-glucitol* (**38**). — A solution of dianhydride **40** (4.4 g) in acetic anhydride (15 mL) and 44 mL of acetic acid presaturated at 20° with hydrogen bromide was kept overnight at room temperature, and was then poured into ice–water. The precipitated syrup was extracted with chloroform, to give, after the usual processing, **38**, as a colorless syrup (8.1 g, 81%); $[\alpha]_D^{20}$ −14.5°; $R_t$ 0.70 (*E*); $^1$H-n.m.r. data (*a*): $\delta$ 5.10 (d, H-3), 4.96 (d, H-4), 4.17 (dq, H-2), 3.9 (m, H-5), 3.50 (m, H-6), and 2.06 and 2.04 (s, *O*-acetyl).

*Anal.* Calc. for $C_{10}H_{15}BrO_5$: Br, 27.07. Found: Br, 26.88.

*3,4-Di-O-acetyl-2,5-anhydro-6-azido-1,6-dideoxy-D-glucitol* (**39**). — *Method a.* A solution of bromide **38** (7 g) and sodium azide (2 g) in *N,N*-dimethylformamide (35 mL) and water (3.5 mL) was heated on a steam bath for 2 h. The solution was cooled, and evaporated, and the residue partitioned between chloroform and water. The organic solution was washed with water, dried, and evaporated, to yield **39** as a pale-yellow syrup (5.2 g, 85%); $[\alpha]_D^{20}$ +105°; $R_t$ 0.70 (*E*); $^1$H-n.m.r. data (*a*): $\delta$ 5.16 (d, H-3), 4.94 (d, H-4), 4.18 (dq, H-2), 3.9 (m, H-5), 3.60 and 3.30 (dd, dd, H-6,6'), 1.22 (d, H-1), and 2.12 and 2.08 (s, s, *O*-acetyl).

*Method b.* Acetylation of azide **43** (1.7 g) with acetic anhydride (5 mL) in pyridine (7 mL) afforded, after the usual processing, diacetate **39** (2.1 g, 82%), identical with that obtained *via* method *a*.

*Anal.* Calc. for $C_{10}H_{15}N_3O_5$: N, 16.33. Found: N, 16.02.

*2,5:3,6-Dianhydro-1-deoxy-D-glucitol* (**40**). — To a stirred solution of tosylate **42** (13 g) in dry 1,4-dioxane (130 mL) was added lithium aluminum hydride (4.2 g), and the mixture was stirred for 1 h at 100°. (The reduction starts at 80°.) To the cooled slurry were successively added ethyl acetate (15 mL), water (4 mL), aqueous sodium hydroxide (15%, 4 mL), and water (12 mL), to decompose the excess of the hydride. The precipitate was filtered off, and washed with 1,4-dioxane, and the filtrates were combined, and evaporated. The residue was passed through a short column of silica gel, with ethyl acetate, to give, after evaporation, dianhydride **40** as semisolid material (4.9 g, 87.7%) pure enough for further reactions. Recrystallization from ethyl acetate–light petroleum afforded pure **40**, m.p. 79–81°, $[\alpha]_D^{20}$ +105.5° (water); $R_F$ 0.55 (*B*); lit.[25] m.p. 81–82° $[\alpha]_D^{20}$ +107.9° (water).

*2,5:3,6-Dianhydro-1-deoxy-4-*O*-p-tolylsulfonyl-*D*-glucitol* (**41**). — To a solution of **40** (0.4 g) in pyridine (5 mL) was added tosyl chloride (0.8 g), and the mixture was kept overnight at room temperature, to give, after the usual processing, **41**, which was recrystallized from ether–light petroleum (0.70 g, 80.5%); m.p. 83–85°, $[\alpha]_D^{20}$ +62°; lit.[25] m.p. 85–86°, $[\alpha]_D^{20}$ +60.1°.

*2,5:3,6-Dianhydro-1-*O*-p-tolylsulfonyl-*D*-glucitol* (**42**). — Ditosylate **36** (18 g) was dissolved in boiling ethanol (80 mL), the solution was quickly cooled to room temperature, and 5M methanolic sodium methoxide (8 mL) was added. From the turbid solution was precipitated sodium tosylate, which was filtered off after 24 h. The filtrate was evaporated, and the residue partitioned between chloroform and water. The organic solution was dried, evaporated, and the residue filtered with the aid of methanol, to give **42** (9.7 g, 84.5%); m.p. 94–96°; this was pure enough for further reactions. Recrystallization from methanol–water afforded pure **42**; m.p. 102–103°, $[\alpha]_D^{20}$ +59°; $R_F$ 0.50 (*E*); $^1$H-n.m.r. data (*a*): δ 4.5–4.1 (m, H-1–5), 3.92 and 3.68 (d, d, H-6,6′), and 7.82, 7.38, and 2.45 (d, d, s, *O-tosyl*).

*Anal.* Calc. for $C_{13}H_{16}O_6S$: C, 51.99; H, 5.37; S, 10.68. Found: C, 51.92; H, 5.40; S, 10.58.

*2,5-Anhydro-6-azido-1,6-dideoxy-*D*-glucitol* (**43**). — To a solution of azide **39** (5.7 g) in chloroform (20 mL) were added M methanolic sodium methoxide (0.1 mL) and methanol (20 mL). After 30 min, when, according to t.l.c., the reaction was complete, the solution was made neutral with solid carbon dioxide, and evaporated. The residue was passed through a short column of silica gel with the aid of ethyl acetate, to give, after evaporation, and filtration of the solid residue with the aid of carbon tetrachloride, pure **43** (3.6 g, 94%); m.p. 99–100°, $[\alpha]_D^{20}$ +28° (water); $R_F$ 0.60 (*B*); $^1$H-n.m.r. data (*b*): δ 4.19 (dq, H-3), 4.1–3.9 (m, H-3,4), 3.8 (m, H-5), 3.6 and 3.4 (dd, dd, H-6,6′), and 1.22 (d, H-1).

*Anal.* Calc. for $C_6H_{11}N_3O_3$: C, 41.61; H, 6.38; N, 24.27. Found: C, 41.60; H, 6.45; N, 24.02.

*6-Amino-2,5-anhydro-1,6-dideoxy-*D*-glucitol hydrochloride* (**44**). — A solution of azide **43** (3.5 g) in pyridine (35 mL) and water (16 mL) was reduced with hydrogen sulfide as described for **19**, to give hydrochloride **44** as a syrup (3.6 g, 98%); $[\alpha]_D^{20}$ +46° (water); $R_F$ 0.50 (*M*); $^1$H-n.m.r. data (*c*): δ 4.16 (dq, H-2), 4.0–3.8 (m, H-3,4), 3.2 (m, H-6), and 1.24 (d, H-1).

*Anal.* Calc. for $C_6H_{14}ClNO_3$: Cl, 19.30; N, 7.62. Found: Cl, 18.92; N, 7.48.

*2,5-Anhydro-1,6-dideoxy-6-(dimethylamino)-*D*-glucitol hydrochloride* (**45**). — A solution of amine **44** (1.8 g) was methylated as described in method *b* for compound **21**. The syrup obtained on evaporation of the methanol solution was dissolved in ethanol, and the solution was passed through a short column of silica gel, to yield, after evaporation, a solid residue. This was filtered with the aid of 2-propanol, and washed with ether, to give **45** (1.9 g, 89%); m.p. 152–154°, $[\alpha]_D^{20}$ +57.7° (water); $^1$H-n.m.r. data (*b*): δ 4.1 (m, H-2), 4.1–3.9 (m, H-3–5), 3.1 (m, H-6), 1.25 (d, H-1), and 2.93 (s, *N*-methyl).

*Anal.* Calc. for $C_8H_{18}ClNO_3$: C, 45.38; H, 8.57; Cl, 16.74; N, 6.61. Found: C, 45.21; H, 8.66; Cl, 16.57; N, 6.50.

*2,5:3,4-Dianhydro-1,6-di-O-p-tolylsulfonylgalactitol* (**46**). — The mother liquor obtained after recrystallization of ditosylate **36** was treated, in the presence of phenolphthalein, with 5M methanolic sodium methoxide until the solution remained permanently alkaline. The solid material that started to crystallize was filtered off after 2 days, and was washed with water, to yield pure epoxide **46** (5.6 g); m.p. 118–120°, $[\alpha]_D^{20}$ 0° (dimethyl sulfoxide); $^1$H-n.m.r. (*c*): $\delta$ 4.2–3.8 (m, H-1–6), and 7.8, 7.5, and 2.48 (d, d, s, *O*-tosyl).

*Anal.* Calc. for $C_{20}H_{22}O_8S_2$: C, 52.84; H, 4.87; S, 14.11. Found: C, 52.72; H, 4.90; S, 14.35.

*2,5:3,6-Dianhydro-1-azido-1-deoxy-*D*-glucitol* (**47**). — A solution of benzoate **48** (8.2 g) in methanol (20 mL) containing 5M methanolic sodium methoxide (0.5 mL) was kept for 2 h at room temperature, and was then evaporated. The residue was freed of methyl benzoate by passage through a short column of silica gel with dichloromethane, and compound **47** was subsequently eluted with ethyl acetate, to give, after evaporation, colorless, syrupy **47** (4.6 g, 90%), $[\alpha]_D^{25}$ +96.8°, $R_f$ 0.40 (*G*); $^1$H-n.m.r. data (*a*): $\delta$ 4.48 (d, H-5), 4.36 (t, H-2), 4.2–4.05 (m, H-3,4), 4.00 and 3.85 (d, d, H-6,6'), and 3.65 and 3.50 (d, d, H-1,1').

*Anal.* Calc. for $C_6H_9N_3O_3$: N, 24.55. Found: N, 24.32.

*2,5:3,6-Dianhydro-1-azido-4-O-benzoyl-1-deoxy-*D*-glucitol* (**48**). — A solution of tosylate **42** (15 g) and sodium azide (4 g) in *N,N*-dimethylformamide (100 mL) was boiled for 45 min, cooled, and evaporated. The residue was dissolved in pyridine (30 mL) and benzoyl chloride (10 mL) was added. After 1 h at room temperature, water (5 mL) was added, and, after 15 min, the mixture was poured into water. The azide was extracted with ether, to give, after evaporation, and passage of the residue through a short column of silica gel with the aid of chloroform, pure **48** as a syrup (8.2 g, 59.6%); $[\alpha]_D^{25}$ +18.5°; $R_f$ 0.75 (*H*); $^1$H-n.m.r. data (*a*): $\delta$ 8.5–7.3 (d, H-4), 4.6–4.4 (m, H-2,5), 4.34 (t, H-2), 4.05 and 3.90 (d, d, H-6,6'), 3.65 and 3.50 (dd, dd, H-1,1'), and 8.2–7.3 (*O*-benzoyl).

*Anal.* Calc. for $C_{13}H_{13}N_3O_4$: N, 15.26. Found: N, 15.02.

*1-Amino-2,5:3,6-dianhydro-1-deoxy-*D*-glucitol* (**49**). — A solution of azide **47** (3.4 g) in ethanol (35 mL) was hydrogenated in the presence of 10% Pd–C catalyst (0.2 g) for 8 h. The catalyst was filtered off, and the filtrate was evaporated, to give a solid residue which was filtered off with the aid of acetone, yield 2.8 g (97%); m.p. 134–136°, $[\alpha]_D^{20}$ +102° (water), $R_f$ 0.40 (*M*); $^1$H-n.m.r. data (*c*): $\delta$ 4.3–3.9 (m, H-2–6), and 3.80 and 3.55 (d, d, H-1,1'); $^{13}$C-n.m.r. data (*c*): $\delta$ 84.0 (C-5), 79.2 (C-3), 77.5 (C-4), 75.3 (C-2), 74.8 (C-6), and 42.6 (C-1).

*Anal.* Calc. for $C_6H_{11}NO_3$: C, 49.65; H, 7.60; N, 9.65. Found: C, 49.46; H, 7.59; N, 9.32.

*2,5:3,6-Dianhydro-1-deoxy-1-(dimethylamino)-*D*-glucitol hydrochloride* (**50**). — A solution of amine **49** (2.4 g) in aqueous formaldehyde (36%; 8 mL) and formic acid (90%, 12 mL) was boiled for 3 h. The residue obtained on evaporation was filtered with the aid of M hydrochloric acid (30 mL) on charcoal. The filtrate was evaporated, and then water and ethanol were successively added to, and

evaporated from, the residue. The solid material obtained was filtered off with the aid of ethanol, yielding pure **50** (2.8 g, 80.7%); m.p. 223° (dec.), $[\alpha]_D^{20}$ +45° (water); $R_F$ 0.65 (*M*); $^1$H-n.m.r. data (*b*): δ 4.7–4.3 (m, H-2–5), 4.05 and 3.90 (d, d, H-6,6′), 3.60 and 3.40 (d, d, H-1,1′), and 3.00 and 2.95 (s, s, *N*-methyl).

*Anal.* Calc. for $C_8H_{16}ClNO_3$: C, 45.82; H, 7.69; Cl, 16.91; N, 6.68. Found: C, 45.70; H, 7.63; Cl, 17.05; N, 6.55.

*2,5:3,6-Dianhydro-1-deoxy-1-(trimethylamino)*-D-*glucitol iodide* (**51**). — A slurry of **50** (1 g) in ethanol (10 mL) was made alkaline (in the presence of phenolphthalein) with 4.4M methanolic sodium methoxide (1.2 mL), and was then diluted with acetone (10 mL). The precipitated salts were filtered off, and methyl iodide (1 mL) was added to the filtrate. The quaternary salt, which started to crystallize, was filtered off after 20 h, and was washed with acetone, to yield pure **51** (1.3 g, 81.5%); m.p. >230°, $[\alpha]_D^{20}$ +40.5° (water); $^1$H-n.m.r. data (*b*): δ 4.7–4.3 (m, H-2–5), 4.00 (s, H-6), 3.7 (m, H-1), and 3.14 (s, *N*-methyl).

*Anal.* Calc. for $C_9H_{18}INO_3$: C, 34.29; H, 5.75; I, 40.27; N, 4.44. Found: C, 34.18; H, 5.92; I, 39.98; N, 4.52.

*2,5-Anhydro-6-azido-6-deoxy-1-*O-p-*tolylsulfonyl*-D-*glucitol* (**52**). — *Method a.* A solution of ditosylate **36** (0.9 g) and sodium azide (0.15 g) in *N,N*-dimethylformamide (5 mL) and water (0.5 mL) was heated on a steam bath for 30 min, and was then cooled and evaporated. The residue was partitioned between ether and water, and the organic solution was washed with water, dried, and evaporated, to yield, after treatment with ether, **52** (0.40 g, 61%); m.p. 90–92°, $[\alpha]_D^{20}$ +28°; $R_F$ 0.40 (*C*); $^1$H-n.m.r. data (*c*): δ 4.4–3.9 (m, H-1,2,5), 3.9–3.6 (m, H-3,4), 3.3 (m, H-6), and 7.82, 7.50, and 2.45 (d, d, s, *O*-tosyl).

*Method b.* Diacetate **53** (1.5 g) yielded, after Zemplén deacetylation, **52** (1 g, 83%), identical with that obtained *via* method *a*.

*Anal.* Calc. for $C_{13}H_{17}N_3O_6S$: N, 12.23; S, 9.33. Found: N, 12.20; S, 9.41.

*3,4-Di-*O-*acetyl-2,5-anhydro-6-azido-6-deoxy-1-*O-p-*tolylsulfonyl*-D-*glucitol* (**53**) *and 3,4-di-*O-*acetyl-2,5-anhydro-1,6-diazido-1,6-dideoxy*-D-*glucitol* (**55**). — To a solution of **37** (6.6 g) in *N,N*-dimethylformamide (30 mL) was added sodium azide (3.3 g), and the slurry was stirred for 2 h at 100°. The residue obtained by evaporation was separated by column chromatography, using solvent *E* for elution.

The fractions having $R_F$ 0.65 gave, on evaporation, diazide **55** (0.8 g, 22.7%) as a syrup; $[\alpha]_D^{20}$ +68°; $^1$H-n.m.r. data (*a*): δ 5.26 (d, H-3), 4.98 (d, H-4), 4.23 and 4.02 (m, H-2,5), 3.8–3.3 (m, H-1,6), and 2.12 and 2.08 (s, *O*-acetyl).

*Anal.* Calc. for $C_{10}H_{14}N_6O_5$: N, 28.28. Found: N, 27.92.

The fractions having $R_F$ 0.55 gave, on evaporation, monoazide **53** (2.4 g, 47.4%) as a syrup, $[\alpha]_D^{20}$ +46.3°; $^1$H-n.m.r. data (*a*): δ 5.30 (dd, H-3), 4.95 (dd, H-4), 4.3–3.9 (m, H-1,2,5), 3.6 and 3.4 (dd, dd, H-6,6′), 7.80, 7.30, and 2.45 (d, d, s, *O*-tosyl), and 2.05 (s, *O*-acetyl).

*Anal.* Calc. for $C_{17}H_{21}N_3O_8S$: N, 9.83; S, 7.50. Found: N, 9.70; S, 7.26.

The yield of diazide **55** could be increased to 78.5% by prolonging the reaction time to 14 h.

*2,5-Anhydro-1,6-diazido-1,6-dideoxy*-D-*glucitol* (**54**). — *Method a.* A solution of ditosylate **36** (4.7 g) and sodium azide (1.6 g) in *N,N*-dimethylformamide (25 mL) was boiled for 1.5 h, cooled, and evaporated. The residue was partitioned between ether and water, and the organic solution was washed with water, dried, and evaporated, to yield **54** (1.8 g, 84%) as a syrup; $[\alpha]_D^{20}$ +35.5°; $R_F$ 0.55 (*H*); $^1$H-n.m.r. data (*c*): δ 4.5–3.7 (m, H-2–5) and 3.52 (d, H-1,6).

*Method b.* Zemplén deacetylation of diacetate **55** (3 g) afforded **54** (1.95 g, 91%), identical with that obtained *via* method *a*.

*Anal.* Calc. for $C_6H_{10}N_6O_3$: N, 39.24. Found: N, 38.90.

*1,6-Diamino-2,5-anhydro-1,6-dideoxy*-D-*glucitol dihydrochloride* (**56**). — A solution of diazide **54** (6 g) in pyridine (60 mL) and water (30 mL) was reduced at 50° with hydrogen sulfide, as described for compound **19**. The reaction was complete after 30 min, to give, after the usual processing, a solid residue which was filtered off with the aid of ethanol, to afford pure **56** (3.6 g, 54.7%), m.p. 173° (dec.), $[\alpha]_D^{20}$ +29° (water); $R_F$ 0.23 (*M*); $^1$H-n.m.r. data (*b*): δ 4.5–4.0 (m, H-2–5) and 3.5–3.2 (m, H-1,6).

*Anal.* Calc. for $C_6H_{16}Cl_2N_2O_3$: C, 30.64; H, 6.85; Cl, 30.16; N, 11.91. Found: C, 30.55; H, 6.92; Cl, 30.02; N, 11.72.

*2,5-Anhydro-1,6-bis(dimethylamino)-1,6-dideoxy*-D-*glucitol dihydrochloride* (**57**). — A solution of diamine **56** (1.5 g) was methylated with formaldehyde–formic acid as described for **21** (method *b*), to yield hydrochloride **57** as a solid foam (1.8 g, 97%); $[\alpha]_D^{20}$ +33° (water); $R_F$ 0.65 (*M*); $^1$H-n.m.r. data (*b*): δ 4.5–4.0 (m, H-2–5), 3.35 (d, H-1,6), and 2.93 (s, *N*-methyl).

*Anal.* Calc. for $C_{10}H_{24}Cl_2N_2O_3$: C, 41.25; H, 8.27; Cl, 24.35; N, 9.62. Found: C, 41.12; H, 8.30; Cl, 23.86; N, 9.33.

*2,5-Anhydro-1,6-bis(trimethylamino)-1,6-dideoxy*-D-*glucitol diiodide* (**58**). — A solution of dihydrochloride **57** (1.45 g) in ethanol was converted into the quaternary salt as described for compound **1**. The salt, which crystallized from the solution, was filtered off, and washed with acetone, to give **58** (2.16 g, 86%); m.p. >240°, $[\alpha]_D^{20}$ +13.4° (water); $^1$H-n.m.r. data (*b*), δ 4.4–3.9 (m, H-2–5), 3.7 (m, H-1,6), and 3.25 (s, *N*-methyl).

*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, 28.53; H, 5.75; I, 49.90; N, 5.37.

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