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SYNTHESIS OF 1,4-DIDEOXY-1,4-IMINO-D-GLUCITOL, A GLUCOSIDASE INHIBITOR

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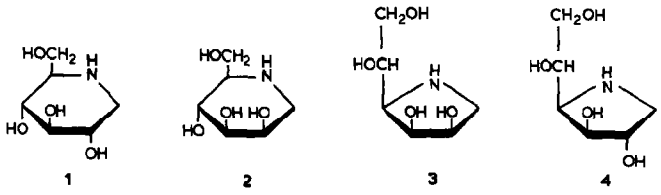
ABSTRACT

1,2:5,6-Di-*O*-isopropylidene-D-glucitol was converted *via* its 1,4-dimethanesulfonate into the 1-azido-4-methanesulfonate which, after deprotection and treatment with barium hydroxide, afforded a 9:1 mixture of the corresponding 3,4- and 4,5-anhydro derivatives. Reduction of this mixture by transfer hydrogenation using ammonium formate in methanol and Pd/C as catalyst afforded 1,4-dideoxy-1,4-imino-D-glucitol (**4**), the structure of which was proved after acetylation by ^{1}H-n.m.r. spectroscopy. Compound **4** is a potent α-D-glucosidase inhibitor (K_i 7 × 10^{-4}M) and a less potent β-D-glucosidase inhibitor (K_i 1.25 × 10^{-4}M), and inhibits β-D-galactosidase non-competitively.

INTRODUCTION

1,5-Dideoxy-1,5-imino-D-glucitol (deoxynojiromycin, **1**) was synthesised[1,2] long before it could be isolated from natural sources[3]. The interesting biological activity[4] of **1** triggered further interest in its synthesis[5,6] and that of the D-*manno* analogue[7] (**2**) which had also been isolated from natural sources[8]. Later, 1,4-dideoxy-1,4-imino-D-mannitol (**3**) was synthesised for structure–activity studies and proved to be a potent α-D-mannosidase inhibitor[9*]. As **2** and **3** differ only in the size of the hetero ring, the synthesis of 1,4-dideoxy-1,4-imino-D-glucitol (**4**), the "iminofuranose" analogue of **1**, was undertaken.



*Recently[10], the 6-deoxy analogue of **3** was synthesised and proved to be a similarly active compound.

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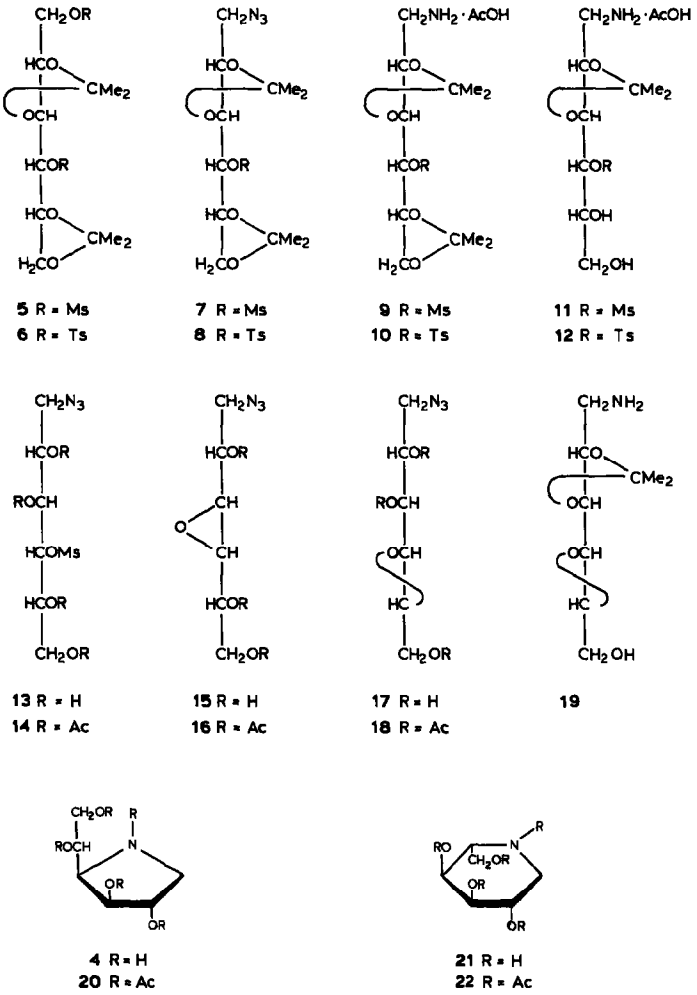
RESULTS AND DISCUSSION

2,3:5,6-Di-*O*-isopropylidene-D-glucitol, easily obtainable by acetonation of D-glucitol in the presence of zinc chloride[11], was chosen as the starting material. The 1,4-dimesylate **5** or 1,4-ditosylate **6** could be converted into the corresponding 1-azides **7** and **8**, respectively, on treatment with sodium azide in *N,N*-dimethylformamide. Reduction of the azido group in **7** and **8** with hydrogen sulfide[12–14] gave the 1-amino derivatives **9** and **10**, which were isolated as their crystalline acetates. The terminal dioxolane ring of these salts could be selectively hydrolysed with aqueous acetic acid, yielding the crystalline monoisopropylidene derivatives **11** (56%) and **12** (75%). All attempts to convert **11** or **12** into the epoxide **19** by treatment with sodium or barium methoxide were unsuccessful. Presumably, as the oxirane ring was formed, it was immediately attacked by the free amino group, yielding the polymeric material isolated. No intramolecular attack was observed, probably because the two reactive centers are too widely separated from each other. In order to overcome this steric restriction, the 2,3-*O*-isopropylidene group had to be removed from **11** and **12**, but acid hydrolysis was difficult because of protonation of the amino group. Hence, the precursor azide **7** was hydrolysed in aqueous trifluoroacetic acid to give **13**, which was isolated by column chromatography as a homogeneous syrup and characterised as the crystalline tetra-acetate **14**. Treatment of **14** with sodium methoxide gave a mixture which, according to the ^{1}H-n.m.r. spectrum of the acetylated products, contained the epoxides **15** and **17** as well as other anhydrides.

Compounds such as **15** are prone to epoxide migration[15], but these rearrangements can be avoided by using barium methoxide instead of sodium methoxide[16]. Accordingly, when **14** was treated with an excess of methanolic barium methoxide, the epoxide **15** was the main product, being accompanied by <10% of **17**. The ratio of **15** and **17** could be determined by ^{1}H-n.m.r. spectroscopy of their acetylated mixture (**16** and **18**) since the signals for H-6,6′ appeared as fairly well separated ABX systems at 4.3–4.1 and 4.2–3.9 p.p.m., respectively. On decoupling from the C*H*-OAc protons, which gave an overlapping multiplet, only the pattern of the major component was changed to an AB system.

On attempted reduction of the mixture of epoxides **15** and **17**, using Pd/C in ethanol, the product precipitated onto and inactivated the catalyst. The addition of water led to the formation of by-products. Therefore, recourse was made to catalytic transfer hydrogenation, using ammonium formate as applied[17] in the reductive cleavage of *O*-benzyl groups. The reduction proceeded smoothly but there was immediate intramolecular attack of the resulting amino group on the epoxide and only the cyclic imine **4** could be isolated. Theoretically, the 6-membered cyclic isomer **21** could also be formed from **17**, but its presence could not be detected. The structure of **4** was proved by ^{1}H-n.m.r. spectroscopy of the acetylated product **20**. The multiplet for H-6,6′ at 4.3–4.1 p.p.m. collapsed to a singlet at 4.2 p.p.m. on irradiation of the C*H*-OAc protons. As **22** does not have a



CHOAc group vicinal to H-6,6′, its coupling pattern should not be influenced. Hydrolysis of **20** with aqueous hydrochloric acid gave the imine **4**, isolated as the crystalline hydrochloride.

The effect of the hydrochloride of **4** on sweet-almond β-D-glucosidase was investigated. This enzyme possesses both β-D-glucosidase and β-D-galactosidase activities[18] and its active centre consists of a single catalytic site and two substrate-binding sites.

A Dixon plot for the enzyme-catalysed hydrolysis of *p*-nitrophenyl β-D-glucopyranoside and a Lineweaver–Burk plot for the *p*-nitrophenyl β-D-galactopyranoside at various concentrations of **4** showed that the β-D-glucosidase and β-D-galactosidase activities were competitively and non-competitively inhibited, respectively, as shown in Figs. 1 and 2.

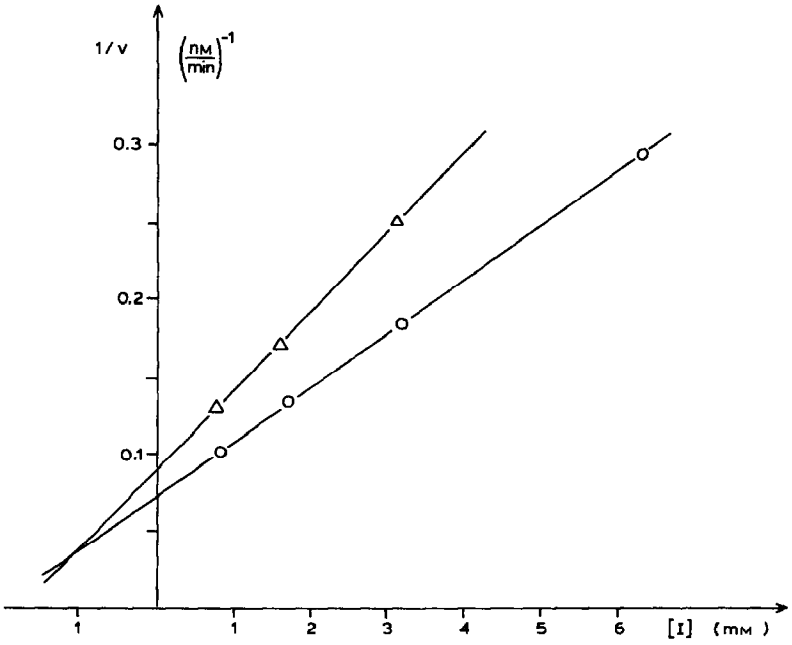


Fig. 1. Inhibition of β-D-glucosidase by 1,4-dideoxy-1,4-imino-D-glucitol (**4**); [s] 0.2 (—△—) and 0.4mM (—○—).

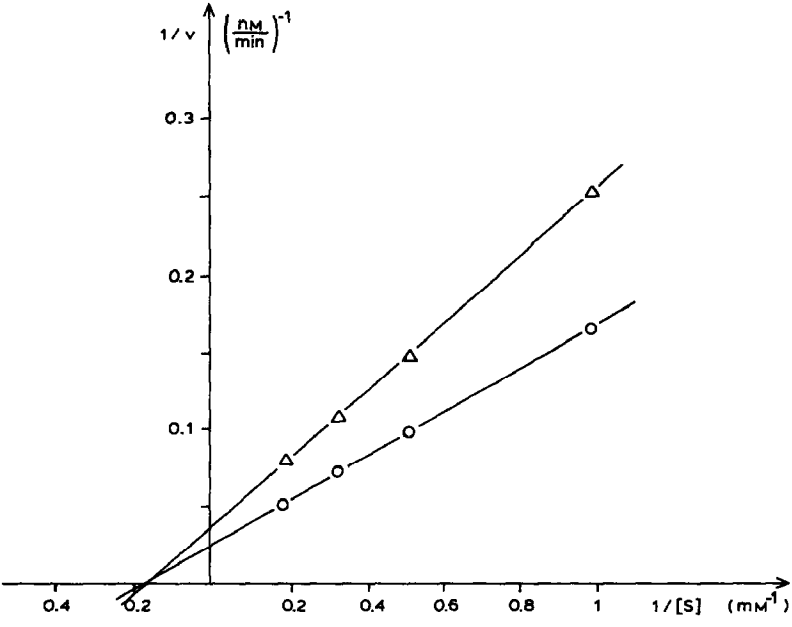


Fig. 2. Inhibition of β-D-galactosidase by 1,4-dideoxy-1,4-imino-D-glucitol (**4**); [I] 0 (—○—) and 4.8mM (—△—).

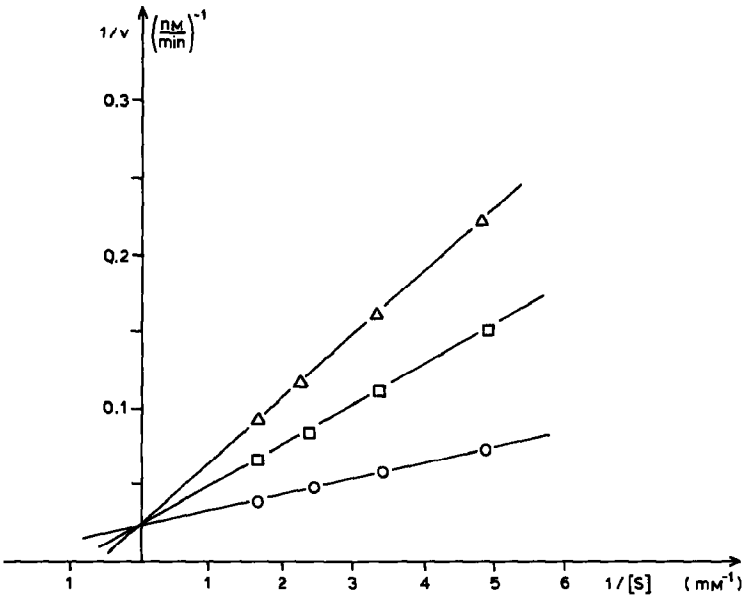


Fig. 3. Inhibition of α-D-glucosidase by 1,4-dideoxy-1,4-imino-D-glucitol (**4**); [I] 0 (—○—), 2.4 (—□—), and 4.8mM (—△—).

It is of interest that **4**, which has an "iminofuranose" structure, inhibits the hydrolysis of both pyranoside substrates as does D-glucono-1,5-lactone, a binding-site inhibitor[18,19]. D-Glucono-1,5-lactone is a more potent β-D-glucosidase inhibitor (K_i 5 × 10^{-4}M) than **4** (K_i 1.25 × 10^{-4}M), which may reflect the difference in the conformations of the two compounds, since D-glucono-1,5-lactone has a near half-chair conformation which fits well to the binding site[18–20].

The fact that **4** inhibits β-D-glucosidase activity competitively and β-D-galactosidase activity non-competitively suggests that **4** binds to the glucoside-binding site.

The activity of the hydrochloride of **4** against baker's yeast α-D-glucosidase was also investigated. The Lineweaver–Burk plot for the enzyme-catalysed hydrolysis of *p*-nitrophenyl α-D-glucopyranoside at various concentrations of **4** showed (Fig. 3) it to be a competitive inhibitor with a K_i value of 7 × 10^{-4}M. Thus, **4** is a more potent inhibitor of α-D-glucosidase than of β-D-glucosidase, and in this respect resembles the D-*manno* derivative **3**, which is a more potent inhibitor of α-D-mannosidase than of β-D-mannosidase[7].

EXPERIMENTAL

General methods. — Organic solutions were dried with sodium sulfate and concentrated under diminished pressure. Optical rotations were determined on 1% solutions. Melting points were determined on a Boetius hot-stage and are not corrected.

T.l.c. was performed on Kieselgel G with *A*, ethyl acetate; *B*, ethanol; *C*, ethanol–conc. ammonia (1:3); and ethyl acetate–carbon tetrachloride mixtures *D*, 1:1; *E*, 1:3; and *F*, 1:5; with detection using 1:1 0.1M potassium permanganate–M sulfuric acid at 105° or iodine vapour. Column chromatography was performed on Kieselgel 40 (63–200 μm). ^{1}H-N.m.r. spectra (90 MHz) were recorded with a Varian EM 390 spectrometer, on solutions in $CDCl_3$ (internal Me_4Si), D_2O, or $[(CD_3)_2SO]$ (internal sodium 4,4-dimethyl-4-silapentane-1-sulfonate). The light petroleum used had b.p. 60–80°.

1,4-Dideoxy-1,4-imino-D-*glucitol* (**4**). — (*a*) To a solution of the syrupy ~9:1 mixture (7.5 g) of epoxides **15** and **17** (see below) in methanol (100 mL) were added formic acid (2.5 mL), conc. ammonia (2.4 mL), and 10% Pd/C (4 g). When the exothermic reaction (gas evolution) had ceased, the mixture was boiled for 10 min, formic acid (1 mL), conc. ammonia (1 mL), and 10% Pd/C (1 g) were added to the cooled solution, and, when the gas evolution ceased, the mixture was boiled for 10 min, then cooled, and filtered. The catalyst was washed with water (5 mL), and the combined filtrate and washings were concentrated. Ethanol was evaporated from the residue and the solid material obtained was filtered with methanol to give **4** (3.4 g, 52.6%), m.p. 200–202°, $[\alpha]_D^{20}$ −11° (water), R_F 0.50 (solvent *C*).

Anal. Calc. for $C_6H_{13}NO_4$: C, 44.16; H, 8.03; N, 8.58. Found: C, 44.24; H, 8.15; N, 8.71.

(*b*) The penta-acetate **20** (2.2 g) was treated with boiling 2M hydrochloric acid (10 mL) for 20 min. The cooled solution was filtered with charcoal and concentrated, and water was evaporated from the residue which gradually crystallised. The crystals were filtered with ethanol–acetone to give **4** as the hydrochloride (0.73 g, 62.4%), m.p. 140–142°, $[\alpha]_D^{20}$ −27° (water).

Anal. Calc. for $C_6H_{13}NO_4 \cdot HCl$: C, 36.10; H, 7.07; Cl, 17.76; N, 7.03. Found: C, 36.02; H, 7.21; Cl, 17.60; N, 7.15.

1-Azido-1-deoxy-2,3:5,6-di-O-*isopropylidene-4*-O-*methylsulfonyl*-D-*glucitol* (**7**). — To a solution of dimesylate **5**[11] (21 g) in *N,N*-dimethylformamide (100 mL) and water (25 mL) was added sodium azide (6.5 g). The mixture was stirred on a steam bath for 4 h and then concentrated. Recrystallisation of the residue from methanol–water gave **7** (15.3 g, 84%), m.p. 91–92°, $[\alpha]_D^{20}$ −49° (chloroform), R_F 0.70 (solvent *E*). ^{1}H-N.m.r. data $CDCl_3$: δ 4.77 (t, H-4), 4.5–3.9 (m, H-2,3,5,6,6'), 3.70 and 3.25 (2 dd, *J* 12 Hz, H-1,1'), 3.13 (s, MsO), 1.44 (s, 9 H, CMe_2), and 1.38 (s, 3 H, CMe_2).

Anal. Calc. for $C_{13}H_{23}N_3O_7S$: C, 42.72; H, 6.34; N, 11.50; S, 8.77. Found: C, 42.50; H, 6.63; N, 11.52; S, 8.62.

1-Azido-1-deoxy-2,3:5,6-di-O-*isopropylidene-4*-O-p-*tolylsulfonyl*-D-*glucitol* (**8**). — A solution of the ditosylate **6**[11] (13.8 g) in *N,N*-dimethylformamide (50 mL) and water (12 mL) was treated with sodium azide (3.2 g), as described for **7**, to yield **8** (10.5 g, 98%), m.p. 77–79°, $[\alpha]_D^{20}$ −35° (chloroform), R_F 0.60 (solvent *F*). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.75 and 7.25 (2 dd, aromatic protons), 4.67 (dd, *J* 6

and 2 Hz, H-4), 4.3–3.7 (m, H-2,3,5,6,6'), 3.57 and 3.20 (2 dd, *J* 13 Hz, H-1,1'), 2.40 (s, tosyl Me), 1.35 (s, 3 H, CMe_2), 1.28 (s, 6 H, CMe_2), and 1.18 (s, 3 H, CMe_2).

Anal. Calc. for $C_{19}H_{27}N_3O_7S$: C, 51.68; H, 6.16; N, 9.51; S, 7.26. Found: C, 51.90; H, 6.22; N, 9.38; S, 7.35.

*1-Amino-1-deoxy-2,3:5,6-di-*O*-isopropylidene-4-*O*-methylsulfonyl-*D*-glucitol acetate* (**9**). — A stream of hydrogen sulfide was passed through a solution of **7** (18 g) in pyridine (180 mL) and water (90 mL) at 50° for 3 h. Acetic acid (10 mL) was added to the cooled solution which was then concentrated. A solution of the residue in hot water (40 mL) was filtered with charcoal, concentrated to half volume, and cooled. The crystals of **9** (13.9 g, 69%), which were collected and washed with ethanol, had m.p. 166–168° $[\alpha]_D^{20}$ −4° (water), R_F 0.50 (solvent *B*). ^{1}H-N.m.r. data (D_2O): δ 4.99 (m, H-4), 4.5–3.9 (m, H-2,3,5,6,6'), 3.4–3.2 (m, H-1,1' and MsO), 1.90 (s, AcO), 1.50 (s, 9 H, CMe_2), and 1.40 (s, 3 H, CMe_2).

Anal. Calc. for $C_{15}H_{29}NO_9S$: C, 45.09; H, 7.31; N, 3.50; S, 8.02. Found: C, 45.03; H, 7.53; N, 3.23; S, 8.19.

*1-Amino-1-deoxy-2,3:5,6-di-*O*-isopropylidene-4-*O*-p-tolylsulfonyl-*D*-glucose acetate* (**10**). — A solution of **8** (4.4 g) in pyridine (40 mL) and water (20 mL) was treated with hydrogen sulfide at 40° as described for **9**. The reaction was complete after 2 h and afforded **10** (3.6 g, 75.8%), m.p. 175–176°, $[\alpha]_D^{20}$ +9.5° (water), R_F 0.75 (solvent *B*). ^{1}H-N.m.r. data [$(CD_3)_2SO$]: δ 7.85 and 7.46 (2 dd, aromatic protons), 4.94 (m, H-4), 4.4–3.7 (m, H-2,3,5,6,6'), 3.1–2.7 (m, H-1,1'), 2.47 (s, tosyl Me), 1.94 (s, AcO), 1.35 (s, 3 H, CMe_2), 1.30 (s, 6 H, CMe_2), and 1.16 (s, 3 H, CMe_2).

Anal. Calc. for $C_{21}H_{33}NO_9S$: C, 53.03; H, 6.99; N, 2.94; S, 6.74. Found: C, 53.28; H, 6.83; N, 2.92; S, 7.02.

*1-Amino-1-deoxy-2,3-*O*-isopropylidene-4-*O*-methylsulfonyl-*D*-glucitol acetate* (**11**). — A solution of **9** (4 g) in acetic acid (40 mL) and water (10 mL) was heated at ~100° for 3 h and then concentrated. Water was twice evaporated from the residue. The solid residue was filtered with 2-propanol to give **11** (2 g, 55.5%), m.p. 108–110°, $[\alpha]_D^{20}$ −5° (water), R_F 0.55 (solvent *B*). ^{1}H-N.m.r. data [$(CD_3)_2SO$]: δ 4.66 (m, H-4), 4.2–3.4 (m, H-2,3,5,6,6'), 3.25 (s, MsO), 3.1–2.8 (m, H-1,1'), 1.85 (s, AcO), and 1.40 (s, 6 H, CMe_2).

Anal. Calc. for $C_{12}H_{25}NO_9S$: C, 40.10; H, 7.01; N, 3.80; S, 8.92. Found: C, 40.02; H, 7.11; N, 3.70; S, 8.88.

*1-Amino-1-deoxy-2,3-*O*-isopropylidene-4-*O*-p-tolylsulfonyl-*D*-glucitol acetate* (**12**). — A solution of **10** (2.2 g) in acetic acid (20 mL) and water (5 mL) was treated as described for **11** to give, after recrystallisation from acetone–benzene, **12** (1.5 g, 74.6%), m.p. 120–122°, $[\alpha]_D^{20}$ +2.5° (water), R_F 0.55 (solvent *B*). ^{1}H-N.m.r. data (D_2O): δ 7.90 and 7.45 (2 dd, aromatic protons), 4.95 (m, H-4), 4.6–3.4 (m, H-1,1',2,3,5,6,6'), 2.52 (s, tosyl Me), 2.12 (s, AcO), 1.56 and 1.48 (2 s, CMe_2).

Anal. Calc. for $C_{18}H_{29}NO_9S$: C, 49.64; H, 6.71; N, 3.21; S, 7.36. Found: C, 49.70; H, 6.65; N, 3.20; S, 7.15.

*1-Azido-1-deoxy-4-*O*-methylsulfonyl-*D*-glucitol* (**13**). — A solution of **7** (18 g) in methanol (200 mL), water (100 mL), and trifluoroacetic acid (10 mL) was heated at ~100° for 1 h and then concentrated. Ethanol was evaporated from the residue which was subjected to column chromatography (solvent *A*). The fractions containing the component with R_F 0.30 were combined and concentrated to give **13** as a pale-yellow syrup (10.5 g, 74%), which was pure enough for further reactions but decomposed on storage at room temperature. It had $[\alpha]_D^{20}$ +10° (water). ^{1}H-N.m.r. data [$(CD_3)_2SO$]: δ 4.62 (m, H-4), 3.8–3.2 (m, H-1,1′,2,3,5,6,6′), and 3.14 (s, MsO).

Anal. Calc. for $C_7H_{15}N_3O_7S$: N, 14.73; S, 11.24. Found: N, 14.32; S, 10.97.

*2,3,5,6-Tetra-*O*-acetyl-1-azido-1-deoxy-4-*O*-methylsulfonyl-*D*-glucitol* (**14**). — Hydrolysis of **7** (3.6 g), as described for **13**, gave a crude syrup from which benzene (10 mL) was evaporated. Pyridine (15 mL) and acetic anhydride (10 mL) were then added, and the mixture was kept at room temperature overnight, to give, after the usual processing, crude **14** (5 g). Column chromatography (solvent *D*) afforded crystalline material (3.1 g, 68%) which was filtered with ether and had m.p. 69–71°, $[\alpha]_D^{20}$ +4° (chloroform), R_F 0.65 (solvent *D*). ^{1}H-N.m.r. data ($CDCl_3$): δ 5.5–4.9 (m, H-2,3,4,5), 4.5–4.0 (m, H-6,6′), 3.45 (d, *J* 6 Hz, H-1,1′), 3.10 (s, MsO), 2.16, 2.13, and 2.08 (3 s, 3, 3, and 6 H, 4 AcO).

Anal. Calc. for $C_{15}H_{23}N_3O_{11}S$: C, 39.73; H, 5.11; N, 9.26; S, 7.07. Found: C, 39.69; H, 5.22; N, 9.18; S, 7.00.

3,4-Anhydro- (**15**) *and 4,5-anhydro-1-azido-1-deoxy-*D*-galactitol* (**17**). — To a stirred suspension of **14** (9 g) in dry methanol (40 mL) was added methanolic 0.6M barium methoxide (20 mL) at room temperature. The resulting slurry was neutralised with carbon dioxide after 30 min, then filtered, and concentrated. Column chromatography (solvent *A*) of the residue gave a fraction having R_F 0.4, concentration of which gave a syrupy mixture (2.8 g, 73%) of **15** and **17** in the ratio 9:1 (determined, after acetylation, by ^{1}H-n.m.r. spectroscopy), $[\alpha]_D^{20}$ −15° (methanol).

Anal. Calc. for $C_6H_{11}N_3O_4$: N, 22.21. Found: N, 21.92.

Treatment of the above syrup (2.5 g) with acetic anhydride (7 mL) in pyridine (10 mL) and the usual processing gave a ~9:1 mixture (3.6 g, 87%) of the triacetates **16** and **18**, $[\alpha]_D^{20}$ +10° (chloroform), R_F 0.50 (solvent *E*). ^{1}H-N.m.r. data: δ 5.3–4.7 (m, C*H*OAc), 4.3–4.1 (m, CH_2OAc, major isomer), 4.2–3.9 (m, CH_2OAc, minor isomer), 3.6–3.0 (CH_2N_3 and epoxide CH).

Anal. Calc. for $C_{12}H_{17}N_3O_7$: N, 13.33;. Found: N, 13.10.

*2,3,5,6-Tetra-*O*-acetyl-1,4-acetylimino-1,4-dideoxy-*D*-glucitol* (**20**). — To a solution of **4** (0.3 g) or its hydrochloride (0.4 g) in acetic anhydride (10 mL) was added sodium acetate (0.2 g), and the mixture was boiled under reflux for 4 h and then concentrated. The residue was partitioned between chloroform and water, and the organic solution was washed with aqueous sodium hydrogencarbonate and water, and then concentrated. Column chromatography (solvent *A*) of the residue gave **20** as a syrup (0.70 g, 92%), $[\alpha]_D^{20}$ +53° (chloroform), R_F 0.70 (solvent *A*).

^{1}H-N.m.r. data ($CDCl_3$): δ 5.5–5.0 (m, H-2,3,5), 4.63 (t, H-4), 4.3–4.1 (m, H-6,6'), 3.80 and 3.43 (2 dd, $J_{1,1'}$ 12, $J_{1,2}$ 6, $J_{1',2}$ 4 Hz, H-1,1').

Anal. Calc. for $C_{16}H_{23}NO_9$: N, 3.75. Found: N, 3.56.

Enzyme assays. — α- and β-D-Glucosidase as well as β-D-galactosidase activities were measured in 0.2M citrate–phosphate buffer (pH 5.2) at 37°. The total volume was 5 mL. The reaction was initiated by addition of the substrate, and the hydrolysis was allowed to proceed for 20 min and then stopped by the addition of 1 mL of the reaction mixture to 0.5M borate buffer (2 mL, pH 10). The concentration of *p*-nitrophenolate ion was measured spectrophotometrically at 400 nm. Substrate concentration ranges for *p*-nitrophenyl α- and β-D-glucopyranoside were 0.1–0.6mM, and for *p*-nitrophenyl β-D-galactopyranoside 1–5mM. The inhibitor **4**, when used, was freshly dissolved in 0.2M citrate–phosphate buffer (pH 5.2). Data were determined from Lineweaver–Burk and Dixon plots, fitted by a least-squares treatment.

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