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Note

Synthesis of 1,4-diamino-1,4-dideoxy-6-*O*-(4-deoxy-4-propionamido-α- and β-D-glucopyranosyl)-D-glucitol

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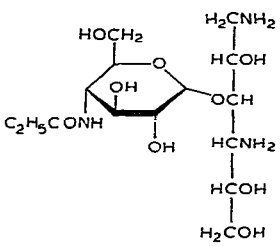
Antibiotic $G1A_1$ (**1**), a component of a new complex of aminodeoxyglycosides, is produced in fermentation broths by Streptomycete[1] and Pseudomonas[2] species. It has a broad-spectrum activity against bacteria, including *Pseudomonas aeruginosa* and strains carrying aminodeoxyglycoside-resistance episomes[1]. It is a unique antibiotic having a diaminodideoxyhexitol as an aglycon group, in contrast to the deoxystreptamine or streptidine nucleus of classical aminodeoxyglycosides[3]. Similarities in configuration do exist however with the recently investigated, hydrazide antibiotic negamycin[4]. Initially, the structure of $G1A_1$ was proposed[5] to be 1,4-diamino-1,4-dideoxy-6-*O*-(4-deoxy-4-propionamido-α-D-glucopyranosyl)-D-glucitol (**29**). As a result of the synthesis of **29** and further studies of $G1A_1$ and its per-*O*-acetyl derivatives by high resolution-n.m.r., the correct structure of $G1A_1$ was shown to be **1**. The syntheses of the two sugar moieties, for comparisons with the fragments derived from the natural product, and of **29** form the topic of this report. After this manuscript was prepared, the Bristol–Banyu group[6–8] in Japan published their investigations on sorbistins, sorbistin A_1 being identical with $G1A_1$.

Methyl 4-amino-4-deoxy-α-D-glucopyranoside (**2**) was prepared according to a modification[9] of the published procedure[10]. The presence[5] of this compound in the products of methanolysis of $G1A_1$ was further confirmed by the synthesis of methyl



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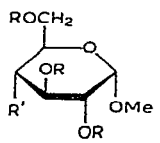
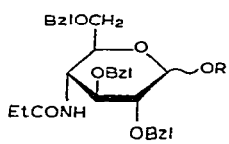
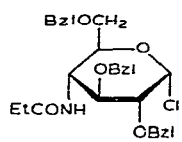


2 R = H, R′ = NH_2
3 R = Ac, R′ = NHAc
4 R = H, R′ = $NHCOC_2H_5$
5 R = Ac, R′ = $NHCOC_2H_5$
6 R = H, R′ = N_3
7 R = Bzl, R′ = N_3
8 R = Bzl, R′ = NH_2
9 R = Bzl, R′ = $NHCOC_2H_5$



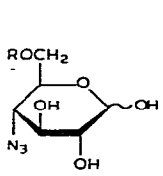
10 R = H
11 R = Ac



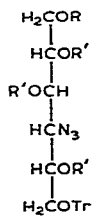
12

4-acetamido-2,3,6-tri-*O*-acetyl-4-deoxy-α-D-glucopyranoside[10] (3) and of the 4-deoxy-4-propionamido analog **5** and their comparison with the products derived from the natural antibiotic.

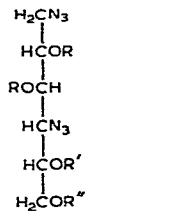
Reaction of glycosyl halides having nonparticipating substituents at C-2 with alcohols under typical SN1 conditions is known to give both *cis* and *trans* glycosides[11]. Therefore, for the preparation of **29** and **32**, 2,3,6-tri-*O*-benzyl-4-deoxy-4-propionamido-α-D-glucopyranosyl chloride (**12**) was required as a condensing agent. This glycosyl chloride was prepared from readily accessible methyl 4-azido-4-deoxy-α-D-glucopyranoside[10] (**6**) in six steps. Benzylation, reduction, and *N*-propionylation of **6** afforded methyl 2,3,6-tri-*O*-benzyl-4-deoxy-4-propionamido-α-D-glucopyranoside (**9**) in 62% yield. Acid hydrolysis of **9** gave 2,3,6-tri-*O*-benzyl-4-deoxy-4-propionamido-D-glucose (**10**) in low yield. Apparently, some debenzylated by-products were formed during the hydrolysis[12]. Similar observations were noted by other workers[13,14]. Acetylation of **10**, followed by treatment with hydrogen chloride, afforded **12** in good yield. The α-D configuration was established by the value of the coupling constant ($J_{1,2}$ 3.5 Hz). Acid hydrolysis of **6** gave 4-azido-4-deoxy-D-glucose[10] (**13**), which was treated, without further purification, with chlorotriphenylmethane to yield the 6-*O*-trityl derivative **14**. Sodium borohydride reduction converted **14** into 4-azido-4-deoxy-6-*O*-trityl-D-glucitol (**15**) in 93% yield. Although both compounds had similar mobilities on t.l.c. in several solvent systems, the formation of **15** was readily established by determination of the optical rotation[15].



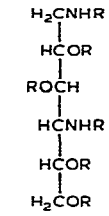
13 R = H
14 R = Tr



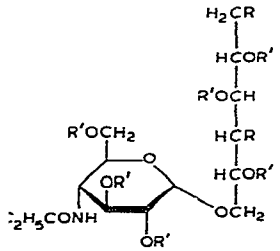
15 R = R′ = H
16 R = 2,4,6-iPrC$_6$H$_2$SO$_2$, R′ = Ac



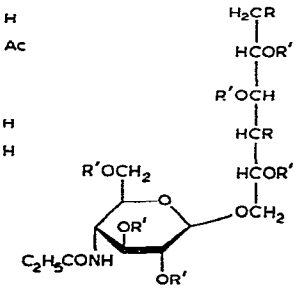
17 R = R′ = Ac, R″ = Tr
18 R = R′ = H, R″ = Tr
19 R = R′ = Bzl, R″ = Tr
20 R = R′ = Bzl, R″ = H
21 R = R′ = Bzl, R″ = Ac
22 R = R′ = R″ = H
23 R = R′ = R″ = Ac
24 R = R′ = Ac, R″ = H
25 R = R″ = Ac, R′ = H



26 R = H
27 R = Ac



28 R = N$_3$, R′ = Bzl
29 R = NH$_2$, R′ = H
30 R = NHAc, R′ = Ac



31 R = N$_3$, R′ = Bzl
32 R = NH$_2$, R′ = H
33 R = NHAc, R′ = Ac

The success of the synthesis of the diaminodideoxyglucitol **26** depended on the introduction of a good leaving-group at C-1 of **15** for subsequent nucleophilic displacement by the azide ion with the formation of little or no side-products. Treatment of **15** with 1.15 equiv. of 2,4,6-tri(isopropyl)benzenesulfonyl chloride, which is selective for primary hydroxyl groups, followed by acetylation gave crystalline 2,3,5-tri-*O*-acetyl-4-azido-4-deoxy-1-*O*-(2,4,6-tri-isopropyl)phenylsulfonyl)-6-*O*-trityl-D-glucitol (**16**) in good yield; no anhydro compounds were detected. This is in contrast with the ready formation of 1,4-anhydro sugars upon selective sulfonylation of alditols in pyridine [16,17]. Nucleophilic displacement of **16** with sodium azide in *N*,*N*-dimethylformamide gave crystalline 2,3,5-tri-*O*-acetyl-1,4-diazido-1,4-dideoxy-6-*O*-trityl-D-glucitol (**17**). Successive deblocking by base and acid hydrolysis, and hydrogenation afforded 1,4-diamino-1,4-dideoxy-D-glucitol (**26**), which was identical with the natural aglycon obtained by the acid degradation of $G1A_1$. The identity was further confirmed by conversion into the hexaacetate **27**, which displayed vicinal, spin–spin coupling constants ($J_{2,3}$ 8.7, $J_{3,4}$ 2.0, and $J_{4,5}$ 9.5 Hz) consistent with a favored conformation having an extended, planar, zigzag arrangement of carbon atoms along the chain[18]. Recently, **26** was synthesized[7] from 4-amino-4-deoxy-D-glucose hydrochloride *via* the oxime by catalytic hydrogenolysis.

For the preparation of **29** and **32**, an appropriately blocked alcohol was required for coupling with the glycosyl chloride **12**. Acid hydrolysis of the 6-*O*-trityl derivative **17** with 80% acetic acid gave 2,3,5-tri-*O*-acetyl-1,4-diazido-1,4-dideoxy-D-glucitol (**24**) as initial product. As the reaction progressed, however, another compound showing a higher R_F on t.l.c. was formed, and appeared to increase with time at the expense of **24**. This by-product was apparently formed by acetyl migration[19,20] from O-5 to O-6, which was confirmed by n.m.r., and a structure of 2,3,6-tri-*O*-acetyl-1,4-diazido-1,4-dideoxy-D-glucitol (**25**) was assigned to this compound. Brief treatment of **17** with trifluoroacetic acid also gave a mixture of **24** and **25**. Both compounds yielded 2,3,4,6-tetra-*O*-acetyl-1,4-diazido-1,4-dideoxy-D-glucitol (**23**) upon acetylation. To avoid complications due to possible acetyl migration during the glycosylation, it was considered advantageous to use 1,4-diazido-2,3,5-tri-*O*-benzyl-1,4-dideoxy-D-glucitol (**20**), which was readily prepared from **17** by deacetylation, benzylation, and detritylation.

Condensation of **12** with **20** in benzene–*p*-dioxane containing mercuric cyanide and calcium sulfate gave a mixture of **28** and **31** in the ratio of ~1:1. The anomeric configuration of both compounds was established by optical rotation[21] and by n.m.r. Improved yields of α-glycopyranosides with this modified Königs–Knorr reaction have been previously reported[22,23]. The presence of *p*-dioxane appears essential[13,24] to favor the formation of α-D-glucosides. However, under the same conditions, β-D-glucopyranosides were formed predominantly[24] if not exclusively with simple alcohols; this was also the case, in our hands. Treatment of **12** with methanol gave methyl 2,3,6-tri-*O*-benzyl-4-deoxy-4-propionamido-β-D-glucopyranoside in 91% yield. Halide ion-catalyzed glycosylation, as reported by Lemieux *et al.*[25], might be a better method for the preparation of **28**. Simultaneous reduction and

debenzylation of **28** and **31** with hydrogen gave 1,4-diamino-1,4-dideoxy-6-*O*-(4-deoxy-4-propionamido-α-D-glucopyranosyl)-D-glucitol (**29**) and the β-D anomer **32**, respectively, in low yield. A similar low yield was observed by other workers[26]. Both **29** and **32** were distinctly different from $G1A_1$, in all respects, and were also biologically inactive. They were further characterized by conversion into the peracetates **30** and **33**, respectively.

EXPERIMENTAL

General. — Melting points were determined with a Thomas–Hoover Unimelt apparatus, and are uncorrected. Optical rotations were measured at 27° with a Zeiss polarimeter. Thin-layer chromatography was performed on Silica Gel G (Analtech) plates, and the spots were detected with a 1% ceric sulfate–10% sulfuric acid spray. Column chromatography was conducted on Silica Gel 60 (70–230 mesh ASTM). N.m.r. spectra were recorded for solutions in chloroform-*d* (unless stated otherwise) at 60 or 100 MHz, with tetramethylsilane as the internal standard. Conventional processing consisted in drying organic solutions with anhydrous sodium sulfate, filtration, and evaporation of the filtrate under diminished pressure.

Methyl 4-deoxy-4-propionamido-α-D-glucopyranoside (**4**). — Methyl 4-amino-4-deoxy-α-D-glucopyranoside[10] (**2**, 9.2 g, 48 mmol) was dissolved in methanol (100 ml) containing propionic anhydride (14.5 ml). After 2 h, the solution was concentrated to a residual oil (14 g) that was chromatographed on a column of silica gel (600 g) with 40:10:1 (v/v) chloroform–methanol–water as eluent. The product was isolated as an amorphous foam (8.2 g, 69%), $[\alpha]_D^{27}$ +149.3° (*c* 1.0, water); ν_{max}^{Nujol} 1655 and 1550 cm^{-1} (Amide I and II); n.m.r. (D_2O): τ 6.53 (s, 3 H, OMe), 7.69 (q, 2 H, CH_2), and 8.90 (t, 3 H, CH_3).

Anal. Calc. for $C_{10}H_{19}NO_6$: C, 48.19; H, 7,68; N, 5.62. Found: C, 48.20; H, 8.03; N, 5.79.

Methyl 2,3,6-tri-O-acetyl-4-deoxy-4-propionamido-α-D-glucopyranoside (**5**). — A solution of **4** (2.5 g, 10 mmol) in pyridine (20 ml) was treated with acetic anhydride (6.0 ml) at 0°. After being kept for 16 h at 25°, the solution was concentrated to a syrup that was dissolved in chloroform. The solution was washed successively with water, aqueous sodium hydrogencarbonate, and water. The dried solution was concentrated to a crystalline mass (3.7 g) and recrystallized from methanol–ether (2.5 g, 67%), m.p. 96–97°, $[\alpha]_D^{27}$ +142.7° (*c* 1.0, chloroform); n.m.r.: τ 3.62 (d, 1 H, NH, *J* 8 Hz), 6.58 (s, 3 H, OMe), 7.80 (q, 2 H, CH_2), 7.90, 7.93, 7.97 (9 H, 3 OAc), and 8.83 (t, 3 H, CH_3).

Anal. Calc. for $C_{16}H_{25}NO_9$: C, 51.19; H, 6.71; N, 3.73. Found: C, 51.34; H, 7.03; N, 3.94.

Methyl 4-acetamido-2,3,6-tri-O-acetyl-4-deoxy-α-D-glucopyranoside (**3**). — **3** was prepared according to the known procedure[10], m.p. 140–141°, $[\alpha]_D^{27}$ +143° (*c* 1.0, chloroform); lit.[10] m.p. 140–141°, $[\alpha]_D^{25}$ +145° (*c* 0.98, chloroform).

Methyl 2,3,6-tri-O-benzyl-4-deoxy-4-propionamido-α-D-glucopyranoside (**9**). —

Sodium hydride in a 57% oil dispersion (13.9 g, 575 mmol) was added to a solution of **6** (22 g, 96.5 mmol) in *N,N*-dimethylformamide (300 ml), and the suspension was stirred for 20 min at 0° before gradual addition of benzyl chloride (73 ml, 575 mmol). The reaction mixture was stirred for 16 h at room temperature, cooled, and the excess of sodium hydride was eliminated with methanol (50 ml). The mixture was concentrated to a small volume, the residue was dissolved in chloroform (1 l), and the solution washed with water (2 × 100 ml), M hydrochloric acid (200 ml), aqueous sodium hydrogencarbonate (100 ml), and again with water (2 × 100 ml). The dried solution was evaporated to give a crude sample of methyl 4-azido-2,3,6-tri-*O*-benzyl-4-deoxy-α-D-glucopyranoside (**7**, 51 g, contaminated with mineral oil).

A solution of crude **7** (51 g) in ether (300 ml) was added dropwise at 25° to a suspension of lithium aluminum hydride (12 g) in ether (250 ml). The mixture was stirred for 16 h at room temperature, cooled to 0°, and treated dropwise, successively with ethanol (25 ml), 10% sodium hydroxide (25 ml), and water (40 ml). The resultant mixture was filtered through Super-Cel and the cake was washed several times with ether. The combined filtrate and washings were washed with water (100 ml), dried, and concentrated to yield crude methyl 4-amino-2,3,6-tri-*O*-benzyl-4-deoxy-α-D-glucopyranoside (**8**, 56 g, contaminated with mineral oil).

Propionic anhydride (21 ml) was added to a solution of crude **8** (56 g) in methanol (300 ml), and the solution was kept for 30 min at room temperature. The solution was concentrated to a semisolid residue that was crystallized from 4:5 (v/v) ethyl acetate–petroleum ether to yield **9** (30.7 g, 62%), m.p. 142–143°. A sample for analysis was recrystallized from 1:1 (v/v) ethyl acetate–petroleum ether, m.p. 146–147.5°, $[\alpha]_D^{27}$ +13.2° (*c* 1, chloroform); n.m.r.: τ 2.50–2.77 (15 H, aromatic), 6.60 (s, 3 H, OMe), 8.08 (q, 2 H, CH_2). and 9.03 (t, 3 H, CH_3).

Anal. Calc. for $C_{31}H_{37}NO_6$: C, 71.65; H, 7.18; N, 2.70. Found: C, 71.47; H, 7.27; N, 2.70.

*2,3,6-Tri-*O*-benzyl-4-deoxy-4-propionamido-*D*-glucopyranose* (**10**). — A solution of **9** (5.19 g, 10 mmol) in acetic acid (25 ml) and 6M hydrochloric acid (2.5 ml) was heated with stirring for 1 h at 100°. Chloroform (300 ml) was added to the cooled, dark mixture, which was washed with water (100 ml), aqueous sodium hydrogencarbonate (100 ml), and again with water (3 × 50 ml). The dried solution was concentrated to a brown semicrystalline solid that was chromatographed on silica gel (50 g) with 1:1 (v/v) chloroform–ethyl acetate as eluent. Compound **10** was isolated as a crystalline mass and recrystallized from ethyl acetate–petroleum ether (1.7 g, 34%), m.p. 186–187.5°, $[\alpha]_D^{27}$ +4.3° (*c* 1, chloroform).

Anal. Calc. for $C_{30}H_{35}NO_6$: C, 71.27; H, 6.98; N, 2.77. Found: C, 71.23; H, 7.22; N, 2.41.

*1-*O*-Acetyl-2,3,6-tri-*O*-benzyl-4-deoxy-4-propionamido-*D*-glucopyranose* (**11**). — To a solution of **10** (5.0 g, 9.9 mmol) in pyridine (20 ml) was added acetic anhydride (5 ml). After 3 h, the reaction was processed in the normal manner to give a crystalline mass (5.1 g, 94%), which was a mixture of anomers as indicated by n.m.r.: (α-D anomer) τ 3.62 (d, $J_{1,2}$ 3.0 Hz, H-1), (β-D anomer) 4.37 (d, $J_{1,2}$ 7.5 Hz, H-1). A

portion of this material was crystallized from ether to give the β-D anomer, m.p. 145–146°, $[\alpha]_D^{27}$ −13.6° (*c* 1.0, chloroform); n.m.r.: τ 2.45–2.97 (15 H, aromatic), 4.18 (b, 1 H, NH), 4.37 (d, 1 H, $J_{1,2}$ 7.5 Hz, H-1), 8.03 (s, 3 H, OAc), 8.07 (q, 2 H, CH_2), and 9.03 (t, 3 H, CH_3). The isolation of the α-D anomer was not attempted.

Anal. Calc. for $C_{32}H_{37}NO_7$: C, 70.18; H, 6.81; N, 2.56. Found: C, 69.95; H, 6.54; N, 2.48.

2,3,6-Tri-O-benzyl-4-deoxy-4-propionamido-α-D-glucopyranosyl chloride (**12**). — A solution of **11** (2 g, 3.65 mmol, a mixture of α- and β-D anomers) in ether (30 ml) was saturated with dry hydrogen chloride at 0–5°. After 2.5 h, the solution was concentrated to dryness and the residue was dried by addition and evaporation of toluene (3 × 10 ml) to give a solid mass that was recrystallized from ether (1.8 g, 94%), m.p. 135–137°. A sample for analysis was recrystallized from the same solvent, m.p. 136–137°, $[\alpha]_D^{27}$ +43.8° (*c* 1, chloroform); n.m.r.: τ 2.55–2.97 (15 H, aromatic), 3.97 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 8.05 (q, 2 H, CH_2), and 9.03 (t, 3 H, CH_3).

Anal. Calc. for $C_{30}H_{34}ClNO_5$: C, 68.76; H, 6.54; Cl, 6.77; N, 2.67. Found: C, 68.53; H, 6.63; Cl, 6.64; N, 2.65.

Methyl 2,3,6-tri-O-benzyl-4-deoxy-4-propionamido-β-D-glucopyranoside. — To a solution of **12** (200 mg, 0.38 mmol) in benzene (8 ml) and *p*-dioxane (2 ml) was added mercuric cyanide (370 mg) and anhydrous calcium sulfate (270 mg), followed by dry methanol (0.62 ml, 1.5 mmol). The reaction mixture was heated for 15 min at 65° with stirring, cooled, filtered, and the solids were washed with benzene (2 × 50 ml). The filtrate and washings were combined and concentrated to a residual oil that was dissolved in chloroform (30 ml). The organic solution was washed with 40% potassium iodide (2 × 10 ml), water (2 × 10 ml), dried, and evaporated to a crystalline mass (220 mg) which was recrystallized from 1:1 (v/v) ethyl acetate–petroleum ether (180 mg, 91%), m.p. 186–188°. A sample for analysis was recrystallized from ethyl acetate, m.p. 186–188°, $[\alpha]_D^{27}$ −12° (*c* 1.0, chloroform); n.m.r.: τ 2.45–2.90 (15 H, aromatic), 4.83 (b, 1 H, NH), 6.47 (s, 3 H, OMe), 8.08 (q, 2 H, CH_2), and 9.01 (t, 3 H, CH_3).

Anal. Calc. for $C_{31}H_{37}NO_6$: C, 71.65; H, 7.18; N, 2.70. Found: C, 71.59; H, 7.45; N, 2.72.

4-Azido-4-deoxy-6-O-trityl-D-glucopyranose (**14**). — A solution of **6** (53.5 g, 0.24 mol) in 2.8M hydrochloric acid (600 ml) was heated for 6 h at 100° under nitrogen. The resulting dark solution was cooled and neutralized with lead carbonate (170 g), decolorized with charcoal, and filtered through Celite. The filtrate was concentrated to an oil that was dissolved in methanol and filtered to yield, upon evaporation, a crude sample of 4-azido-4-deoxy-D-glucopyranose (**13**, 48 g). The intermediate **13** (having an R_F lower than that of **14**) was devoid of a methoxyl signal (n.m.r.) and gave a positive Fehling test. The crude product (48 g) was added to another batch prepared in the same manner, and the total amount of **13** (96 g, 0.47 mol) was dried by several additions and distillations of pyridine. The dry syrup in pyridine (500 ml) was tritylated with chlorotriphenylmethane (150 g, 0.54 mol). After stirring at room temperature for 2 days, the reaction mixture was poured into

ice–water (5 l) and decanted. The oily gum was dissolved in chloroform and washed successively with water, cold, dil. hydrochloric acid, aqueous sodium hydrogencarbonate, and water. The dried solution was evaporated to a syrup (300 g, contaminated with pyridine) that was chromatographed on silica gel (6 kg) with 3% methanol in chloroform containing 0.05% triethylamine as eluent. The title compound was isolated as a foam (98 g, 46%), $[\alpha]_D^{27}$ +66° (*c* 1.02, methanol); $\nu_{max}^{CHCl_3}$ 2120 cm^{-1} (N_3); n.m.r.: τ 2.20–3.13 (15 H, aromatic), and 4.73 (b, 1 H, H-1).

Anal. Calc. for $C_{25}H_{25}N_3O_5$: C, 67.10; H, 5.63; N, 9.39. Found: C, 66.56; H, 5.73; N, 8.96.

*4-Azido-4-deoxy-6-*O*-trityl-*D*-glucitol* (**15**). — Sodium borohydride (10 g) was added portionwise to a stirred solution of **14** (20 g, 46 mmol) in methanol (150 ml) at 0°. The temperature was allowed to rise to 25°. After 2 h, the reaction mixture was concentrated to dryness and the crude product was dissolved in ethyl acetate. The solution was washed successively with 0.25M citric acid, aqueous sodium hydrogencarbonate, and water, dried, and evaporated to give **15** (18.7 g, 93%). A sample for analysis was purified by p.l.c., $[\alpha]_D^{27}$ 0° (*c* 1.08, chloroform); n.m.r.: τ 2.37–3.07 (15 H, aromatic) and 5.77–6.87 (sugar, 12 H).

Anal. Calc. for $C_{25}H_{27}N_3O_5$: C, 66.80; H, 6.05; N, 9.35. Found: C, 66.45; H, 6.18; N, 9.19.

*2,3,5-Tri-*O*-acetyl-4-azido-4-deoxy-1-*O*-(2,4,6-tri-isopropylphenylsulfonyl)-6-*O*-trityl-*D*-glucitol* (**16**). — To a solution of **15** (9.9 g, 20 mmol) in pyridine (9 ml) and dichloromethane (50 ml) was added 2,4,6-tri-isopropylphenylsulfonyl chloride (7.0 g, 23 mmol). The mixture was stirred overnight at room temperature and acetic anhydride (9 ml) was added. After 5 h, the mixture was poured into ice–water and the product crystallized out. Recrystallization from methanol gave **16** (9.0 g, 54%), m.p. 133–134°, $[\alpha]_D^{27}$ +8° (*c* 1.03, chloroform); n.m.r.: τ 2.47–2.87 (17 H, aromatic), 7.93 and 8.0 (9 H, 3 OAc), 8.67 and 8.79 (18 H, isopropyl).

Anal. Calc. for $C_{46}H_{55}N_3O_{10}S$: C, 65.65; H, 6.58; N, 4.99. Found: C, 65.90; H, 6.75; N, 4.66.

*2,3,5-Tri-*O*-acetyl-1,4-diazido-1,4-dideoxy-6-*O*-trityl-*D*-glucitol* (**17**). — Compound **16** (6 g, 10 mmol) was dissolved in *N,N*-dimethylformamide (90 ml) and treated with sodium azide (4 g, 62 mmol) at 90° with stirring. After 4 h, the mixture was filtered and the filtrate was concentrated to dryness. The residue was dissolved in ethyl acetate and washed twice with water, dried, and evaporated to a crystalline mass. Recrystallization from methanol afforded **17** (3.5 g, 82%), m.p. 113.5–114.5°, $[\alpha]_D^{27}$ −10° (*c* 1.03, chloroform); ν_{max}^{KBr} 2120 cm^{-1} (N_3); n.m.r.: τ 2.47–2.90 (15 H, aromatic), 4.63 (m, 2 H, H-2 and H-3), 5.0 (m, 1 H, H-5), 7.87, 7.90, and 7.95 (9 H, 3 OAc).

Anal. Calc. for $C_{31}H_{32}N_6O_7$: C, 61.99; H, 5.37; N, 13.99. Found: C, 62.23; H, 5.37; N, 13.85.

*1,4-Diazido-2,3,5-tri-*O*-benzyl-1,4-dideoxy-6-*O*-trityl-*D*-glucitol* (**19**). — To a solution of **17** (7.0 g) in methanol (70 ml) at 0° was added sodium methoxide (0.3 g). After 4 h at room temperature, the solution was concentrated at 25° to a syrup that was dissolved in ethyl acetate, and washed with water. The dried solution was

evaporated to give **18** (5.4 g), $[\alpha]_D^{27}$ −8° (*c* 1.4, chloroform). To a solution of **18** (5.4 g) in *N,N*-dimethylformamide (100 ml) was added sodium hydride (1.65 g), and the suspension was stirred for 20 min at 0° before gradual addition of benzyl chloride (7.7 ml). The mixture was stirred for 16 h at room temperature, cooled, and the excess of sodium hydride was eliminated with methanol. The mixture was processed in the normal manner to give a syrup that was chromatographed on silica gel with chloroform as eluent to give **19** as a syrup (8.0 g, 96%), $[\alpha]_D^{27}$ +5.4° (*c* 1.38, chloroform).

Anal. Calc. for $C_{46}H_{43}N_6O_4$: C, 74.20; H, 5.83; N, 11.30. Found: C, 74.63; H, 6.23; N, 10.94.

*1,4-Diazido-2,3,5-tri-*O*-benzyl-1,4-dideoxy-*D*-glucitol* (**20**). — Acid hydrolysis of **19** (8.0 g) with 80% trifluoroacetic acid (25 ml) was carried out for 20 h at 25°. The mixture was evaporated to dryness and the residue chromatographed on a column of silica gel with chloroform as eluent. Compound **20** was isolated as a syrup (4.5 g, 95%), $[\alpha]_D^{27}$ −9.3° (*c* 0.91, chloroform).

Anal. Calc. for $C_{27}H_{30}N_6O_4$: C, 64.45; H, 6.02; N, 16.72. Found: C, 64.23; H, 6.34; N, 16.46.

*6-*O*-Acetyl-1,4-diazido-2,3,5-tri-*O*-benzyl-1,4-dideoxy-*D*-glucitol* (**21**). — Acetic anhydride (0.5 ml) was added to a solution of **20** (200 mg) in pyridine (1.0 ml) and dichloromethane (0.5 ml). After 3 h, the mixture was processed in the normal manner and purified by p.l.c. with chloroform as a developing phase to give **21** as a syrup (195 mg, 90%), $[\alpha]^{27}$ +13.5° (*c* 1.05, chloroform); n.m.r.: τ 2.67 (15 H, aromatic) and 7.97 (s, 3 H, OAc); m.s.: *m/e* $M^{+} - N_2$, 368 ($(\overset{+}{C}HOBzl\text{-}CHN_3\text{–}CHOBzl\text{–}CH_2OAc)$, 296 ($N_3CH_2\text{–}\overset{+}{C}HOBzl\text{–}CHOBzl$), and 193 ($\overset{+}{C}HOBzl\text{–}CH_2OAc$).

Anal. Calc. for $C_{29}H_{32}N_6O_5$: C, 63.96; H, 5.92; N, 15.43. Found: C, 64.18; H, 6.10; N, 15.22.

*1,4-Diazido-1,4-dideoxy-*D*-glucitol* (**22**). — To a solution of **17** (7.0 g) in methanol (70 ml) at 0° was added sodium methoxide (0.2 g), and the solution was kept at room temperature overnight. Bio-Rad AG 50W-X2 resin (H^+, previously washed with methanol) was added and the mixture was stirred for 3 h at 25° and filtered, and the solid washed with methanol. The combined filtrates were concentrated to a crystalline mass. Methanol was added to the residue and the crystals (2.5 and 0.5 g) were filtered off and discarded. The filtrate was evaporated to an oil (2.7 g) which was chromatographed on silica gel with 40:10:1 (v/v) chloroform–methanol–water as eluent. Compound **22** was isolated as a syrup (2.5 g, 92.5%), $[\alpha]_D^{27}$ +7.5° (*c* 1.24, methanol).

Anal. Calc. for $C_6H_{12}N_6O_4$: C, 30.99; H, 5.21; N, 36.19. Found: C, 31.26; H, 5.69; N, 36.05.

*2,3,5-Tri-*O*-acetyl-1,4-diazido-1,4-dideoxy-*D*-glucitol* (**24**) *and 2,3,6-tri-*O*-acetyl-1,4-diazido-1,4-dideoxy-*D*-glucitol* (**25**). — (*a*). A suspension of **17** (1.0 g) in 80% acetic acid (10 ml) was heated at 50° with stirring for 10 h, cooled, and concentrated to dryness. The residue was chromatographed on silica gel (99:1 followed by 97:3,

v/v, chloroform–methanol). The first eluted compound was identified as **25** (235 mg), $[\alpha]_D^{27}$ +14° (*c* 1.0, chloroform); n.m.r.: τ 4.57, 4.70 (m, 2 H, H-2 and H-3), 7.81, 7.83, and 7.87 (9 H, 3 OAc); m.s.: *m/e* 240 ($M^{+\cdot}-2\,\dot{O}Ac$), 198 ($M^{+\cdot}-2\,\dot{O}Ac-C_2H_2O$), and 158 ($N_3\overset{+}{C}H-CHOH-CH_2OAc$). The second eluted compound was shown to be **24** (190 mg); $[\alpha]_D^{27}$ 0° (*c* 1.19, chloroform); n.m.r.: τ 4.67, 4.77 (m, 2 H, H-2 and H-3), 5.08 (m, 1 H, H-5), 7.87 and 7.90 (9 H, 3 OAc). The combined products (425 mg) represented a 71.5% yield.

Anal. of **24**. Calc. for $C_{12}H_{18}N_6O_7$: C, 40.23; H, 5.06; N, 23.45. Found: C, 40.39; H, 5.24; N, 23.06.

(*b*). A suspension of **17** (1.0 g) in 80% acetic acid (10 ml) was heated on a steam bath until dissolution occurred, and kept for 16 h at room temperature. The solution was concentrated to dryness and the residue fractionated on a column of silica gel (4:1, v/v, chloroform–ethyl acetate). Only **17** (450 mg) and **24** (225 mg) were isolated.

*2,3,5,6-Tetra-*O*-acetyl-1,4-diazido-1,4-dideoxy-*D*-glucitol* (**23**). — Both **24** and **25** (200 mg) were acetylated in the usual manner to give **23** (195 mg, 87%). The purified material had $[\alpha]_D^{27}$ 0° (*c* 1.61, chloroform).

Anal. Calc. for $C_{14}H_{20}N_6O_8$: C, 42.01; H, 5.04; N, 20.99. Found: C, 42.46; H, 5.37; N, 20.88.

*1,4-Diamino-1,4-dideoxy-*D*-glucitol* (**26**) *and 1,4-diacetamido-2,3,5,6-tetra-*O*-acetyl-1,4-dideoxy-*D*-glucitol* (**27**). — A solution of **22** (500 mg) in *p*-dioxane (3 ml) and water (3 ml) containing 10% palladium-on-charcoal (250 mg) was hydrogenated for 2 h. The suspension was filtered, and the filtrate evaporated to a syrup (300 mg), $[\alpha]_D^{27}$ +2.7° (*c* 1.0, water), +27° (*c* 1.0, 5% ammonium molybdate) [authentic sample[27]: $[\alpha]_D^{27}$ +3.8° (*c* 1.0, water), +29° (*c* 1.0, 5% ammonium molybdate)]. A portion of this material (180 mg) in methanol (0.5 ml) was treated with a solution of oxalic acid (90 mg) in methanol (0.5 ml) to give the oxalic acid salt of **26**.

Anal. Calc. for $C_6H_{16}N_2O_4\cdot C_2H_2O_4\cdot CH_3OH$: C, 35.80; H, 7.30; N, 9.26. Found: C, 35.60; H, 7.77; N, 9.06.

Compound **26** (120 mg) was further characterized by its conversion into the peracetate **27** (180 mg), which was purified by chromatography (silica gel; 9:1, v/v, chloroform–methanol), $[\alpha]_D^{27}$ +6.8° (*c* 1.0, chloroform); n.m.r.: τ 4.14 (dd, 1 H, $J_{N,H}$ 6.8 and 4.5 Hz, C-1–NH), 4.16 (d, 1 H, $J_{N,H}$ 9.0 Hz, C-4–NH), 4.75 (q, 1 H, $J_{3,2}$ 8.7 Hz, $J_{3,4}$ 2.0 Hz, H-3), 5.01 (o, 1 H, $J_{2,1}$ 5.4 and 4.5 Hz, H-2), 5.11 (o, 1 H, $J_{5,4}$ 9.5 Hz, $J_{5,6}$ 5.5 and 2.5 Hz, H-5), 5.34 (d, t, 1 H, H-4), 5.69, 5.90 (2 q, 2 H, $J_{6,6'}$ 12.0 Hz, H-6 and H-6'), 6.32, 6.56 (2 o, 2 H, $J_{1,1'}$ 14.4 Hz, H-1 and H-1'), 7.91, 7.93, 7.95, 7.97, and 8.00 (18 H, NH and OAc); m.s.: *m/e* 432 ($M^{\ddagger}$), 360 ($AcO\overset{+}{C}H-CHOAc-CHNHAc-CHOAc-CH_2OAc$), 287 ($AcHNCH_2-CHOAc-CHOAc\overset{+}{C}HNAc$), and 216 ($AcHN-CH_2-CHOAc-\overset{+}{C}HOAc$ or $AcHN-\overset{+}{C}H-CHOAc-CH_2OAc$).

Anal. Calc. for $C_{18}H_{28}N_2O_{10}$: C, 49.99; H, 6.53; N, 6.48. Found: C, 49.55; H, 6.75; N, 6.20.

*1,4-Diazido-2,3,5-tri-*O*-benzyl-1,4-dideoxy-6-*O*-(2,3,6-tri-*O*-benzyl-4-deoxy-4-propionamido-α-* (**28**) *and -β-*D*-glucopyranosyl)-*D*-glucitol* (**31**). — A mixture of **20** (1.04 g, 2.07 mmol), mercuric cyanide (2.4 g), and anhydrous calcium sulfate (2.4 g) in benzene (16 ml) and *p*-dioxane (4 ml) was heated to 90° with stirring, and then cooled to room temperature. The glycosyl chloride **12** (1.3 g, 2.49 mmol) was added to the mixture, which was vigorously stirred at 85–90° (bath temp.) for 21 h. The cooled mixture was filtered, and the solid washed with benzene (2 × 50 ml). The filtrate and washings were evaporated to dryness, and the residue was dissolved in chloroform (150 ml), which was then washed with 40% potassium iodide (50 ml) and water (2 × 50 ml), dried, and evaporated to a syrup. The crude material was fractionated on a column of silica gel (5:1, v/v, chloroform–ethyl acetate). Overlapping fractions were rechromatographed by p.l.c. (8:1, v/v, chloroform–ethyl acetate; multiple developments). In this manner, both **28** (0.49 g, 24%), $[\alpha]_D^{27}$ +18° (*c* 1.08, chloroform) and **31** (0.45 g, 22%), $[\alpha]_D^{27}$ −15° (*c* 1.23, chloroform) were isolated as syrupy materials.

Anal. of **28**. Calc. for $C_{57}H_{63}N_7O_9$: C, 69.10; H, 6.37; N, 9.90. Found: C, 69.27; H, 6.40; N, 9.61.

*1,4-Diamino-1,4-dideoxy-6-*O*-(4-deoxy-4-propionamido-α-* (**29**) *and -β-*D*-glucopyranosyl)-*D*-glucitol* (**32**). — A solution of **28** (250 mg) in 75% ethanol (10 ml) and acetic acid (3 drops) containing 10% palladium-on-charcoal (250 mg) was hydrogenated for 24 h at 2.6 atm. and 45°. The catalyst was filtered off and washed with aq. ethanol. The combined filtrates were evaporated to a syrup that was purified by chromatography (silica gel; 2:2:1, v/v, chloroform–methanol–ammonium hydroxide) to give **29** as a syrup (35 mg), R_F (same solvent as for the preparative chromatography) 0.15 (R_F of $G1A_1$ 0.20). This material was characterized by conversion into its peracetate **30**, $[\alpha]_D^{27}$ +67.1° (*c* 1.0, chloroform); R_F similar to that of $G1A_1$ peracetate[27] {m.p. 197–198°, $[\alpha]_D^{27}$ +68.5° (*c* 1.01, chloroform), R_F (9:1, v/v, chloroform–methanol) 0.52}; m.s.: *m/e* 734 $(M+1)^+$·, 517 (AcHN–CH–CHOAc–CH_2O–sugar)$^+$·, 457 (AcHN–C=CH–CH_2O–sugar)$^+$·, 344, etc.

Compound **31** was similarly converted into **32**, R_F (2:2:1, v/v, chloroform–methanol–ammonium hydroxide) 0.14. The peracetate **33** had an R_F lower than that of $G1A_1$ peracetate (9:1, v/v, chloroform–methanol); m.s.: *m/e* 734 $(M+1)^+$·, 517, 457, 344, etc. Both **29** and **32** were biologically inactive.

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