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1,4-DIAMINO-1,4-DIDEOXY-D-GALACTITOL AND 1,5-DIAMINO-1,5-DIDEOXY-L-ALTRITOL*

JÁNOS KUSZMANN
Institute for Drug Research, P.O. Box 82, H-1325 Budapest 4 (Hungary)
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ABSTRACT

The mesyloxy group of 1-azido-1-deoxy-4-*O*-mesyl-D-glucitol could be displaced by azide, in the 2,3:5,6-di-*O*-isopropylidene derivative **4** or the tetraacetate, yielding, after removal of the protecting groups, 1,4-diazido-1,4-dideoxy-D-galactitol (**7**). The 2,3- (**10**) and 5,6-*O*-isopropylidene derivative (**13**) of **7** gave, on mesylation, the corresponding 5,6- (**11**) and 2,3-dimesylate (**15**), respectively. Treatment of **11** with hydrochloric acid yielded 3,6-anhydro-1,4-diazido-1,4-dideoxy-5-*O*-mesyl-D-galactitol, whereas **15** gave the corresponding 5,6-diol which was converted with base into 2,6-anhydro-1,4-diazido-1,4-dideoxy-3-*O*-mesyl-D-talitol. Cleavage of the 5,6-*O*-isopropylidene group of **4** gave 1-azido-1-deoxy-2,3-*O*-isopropylidene-4-*O*-mesyl-D-glucitol, which could be converted *via* the corresponding 4,5-epoxide into 1,5-diazido-1,5-dideoxy-2,3-*O*-isopropylidene-L-altritol (**25**). The 6-*p*-nitrobenzoates of **25** and **13** are derivatives suitable for the synthesis of sorbistin analogues. Reduction of the corresponding deprotected diazides afforded the title compounds.

INTRODUCTION

Shortly after the discovery of the sorbistins[1–4], a new class of aminoglycoside antibiotics containing 1,4-diamino-1,4-dideoxy-D-glucitol (**1**) instead of an aminocyclitol moiety, their total synthesis[5,6], as well as the synthesis of derivatives[7,8] and analogues[5,6,9], was described. Each of these compounds contained **1** as the aglycon and differed from the natural products only in the *N*-substitution or in the position of the glycosidic link. In order to study the structure–activity relationships in this series, analogues containing 1,4-diamino-1,4-dideoxy-D-galactitol (**2**) and 1,5-diamino-1,5-dideoxy-L-altritol (**3**) as aglycons were required. For this purpose, the corresponding partially protected hexitols, containing the potential amino groups as azide functions and having two of the hydroxyl groups protected by acetalation[6], had to be synthesised.

*Synthesis of Sorbistin Analogues, Part I.

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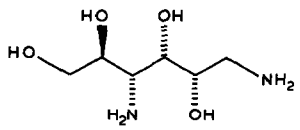

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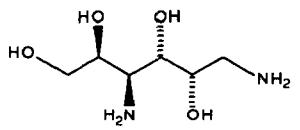

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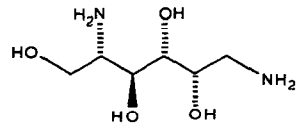

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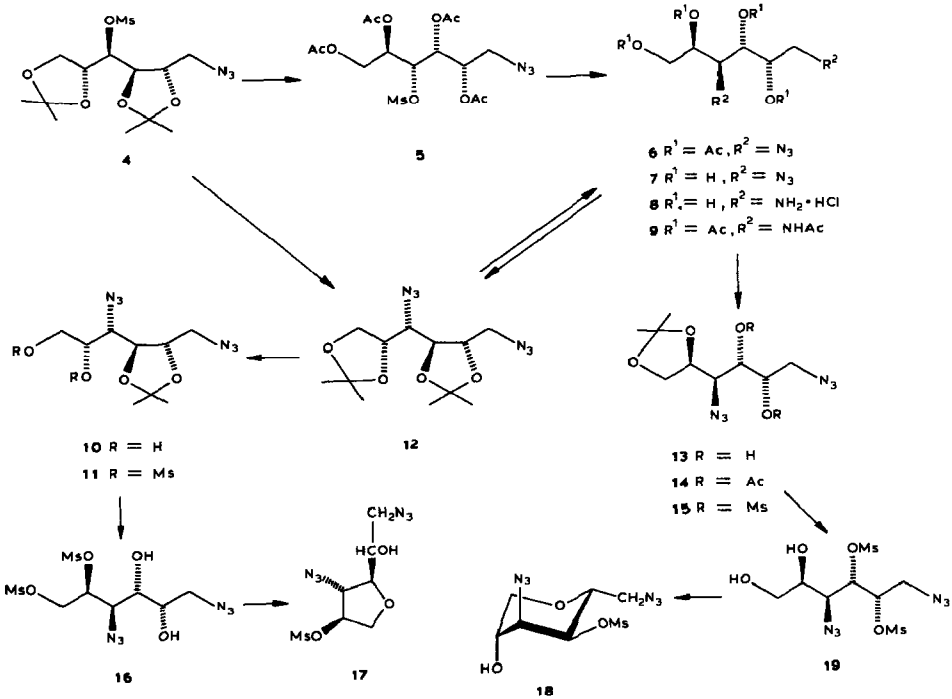
RESULTS AND DISCUSSION

The partially protected 1,4-diazido-1,4-dideoxy-D-galactitol derivatives were obtained from 1-azido-1-deoxy-2,3:5,6-di-*O*-isopropylidene-4-*O*-mesyl-D-glucitol[10] (**4**). The conversion of **4** into the diazide **12** required treatment with sodium azide in boiling *N,N*-dimethylformamide, which resulted in partial decomposition and reduced the yield (40%). When the two dioxolane rings, which sterically hindered the exchange reaction, were removed and the corresponding tetra-acetate[10] **5** was subjected to azide exchange, the reaction was much faster, but the crystalline diazide **6** could only be obtained, after column chromatography, in low yield (23%). However, when hexamethylphosphoric triamide was used as solvent, reaction of **4** took place readily at 120°, yielding 74% of **12**. Treatment of **12** with hydrogen chloride removed the isopropylidene groups and gave **7** which could also be obtained by Zemplén deacetylation of **6**.

Reaction of **7** at room temperature with acetone or 2,2-dimethoxypropane in



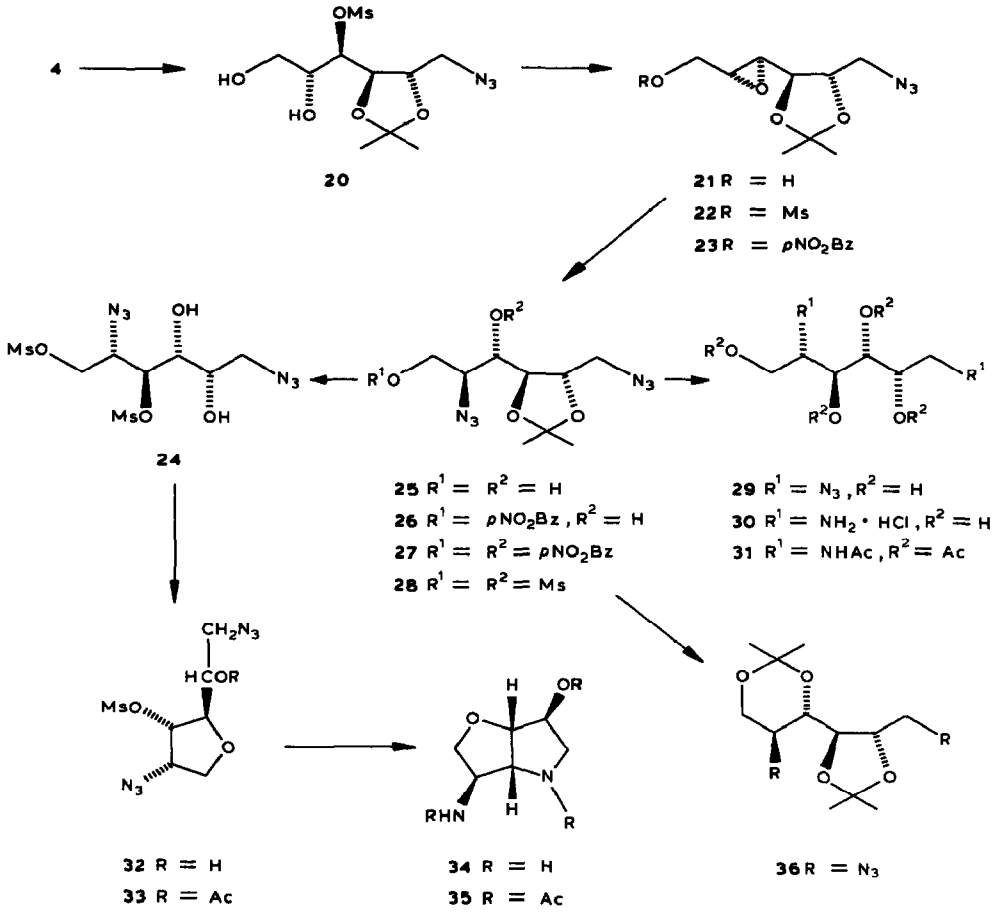
the presence of toluene-*p*-sulfonic acid gave the 5,6-acetal **13** which was suitable for the synthesis of sorbistin analogues[6]. The presence of the terminal dioxolane ring in **13** was proved by ^{13}C-n.m.r. spectroscopy. The acetal carbon in **13** gave a signal at 109.2 p.p.m., and, in the diacetate **14** and dimesylate **15**, the two ester groups were attached to secondary carbon atoms.

The reaction of **7** with 2,2-dimethoxypropane at elevated temperature gave the diacetal **12**, treatment of which with methanolic hydrogen chloride removed the terminal acetal residue to give the diol **10** which was converted into its dimesylate **11**. Removal of the dioxolane ring of **11** required more-forcing conditions which also caused elimination of methanesulfonic acid to yield the 3,6-anhydro derivative **17**. The signal (td) for H-5 in the ^{1}H-n.m.r. spectrum of **17** showed only two relatively small couplings (*J* 5 and 2.5 Hz), which excluded the alternative 2,6-anhydro structure for which large couplings with H-4 and H-6*a* would be expected.

The terminal dioxolane ring of the dimesylate **15** could be removed selectively without the loss of methanesulfonic acid, to yield the diol **19**, which was stable under the conditions of treatment with acid which converted **16** into **17**. Treatment of **19** with methanolic sodium methoxide eliminated 1 mol of methanesulfonic acid, and the 2,6-anhydro derivative **18** was formed. The structure of **18** was proved by the ^{1}H-n.m.r. data; the signal of H-3 appeared at 5.15 p.p.m. with couplings of *J* 9 and 4 Hz, due to the axial–axial and axial–equatorial arrangement of H-2,3 and H-3,4, respectively.

In order to obtain partially protected 1,4-diazido-1,4-dideoxy-D-glucitol derivatives, the exchange of MsO-4 of **4** by azide with retention of configuration (double inversion) is necessary and was attempted as follows. The 5,6-acetal ring of **4** was hydrolysed selectively using 0.04M hydrochloric acid. The resulting diol **20** was not isolated, but was converted with methanolic sodium methoxide into the syrupy D-galactitol epoxide **21** (86% yield after chromatography), which gave a crystalline 6-mesylate **22**. Cleavage of the oxirane ring in **21** by sodium azide in aqueous methanol, using acetic acid to neutralise the developing alkalinity[11], gave the 5-azido-5-deoxy-L-altritol derivative **25**, because the attack of the azide ion on C-4 is hindered by the neighbouring dioxolane ring. In order to obtain an equilibrium of the isomeric 4- and 5-azides, a *p*-nitrobenzoyl group was introduced at position 6 (**21**→**23**) which, because of its electron-withdrawing properties, should diminish attack of the azide at C-5. In order to avoid saponification of the ester group, 1 equiv. of acetic acid was added. However, cleavage of the oxirane ring under these conditions was ~6 times slower than with **21** and the *p*-nitrobenzoyl group was hydrolysed, yielding the 5-azide **25**. This result is probably due to the fact that, in **23**, the oxirane ring is not reactive and is not attacked by azide, and slow hydrolysis of the *p*-nitrobenzoyl group affords **21**, which undergoes the expected addition reaction. Reaction of **21** with sodium azide in the presence of ammonium chloride was not effective when aqueous ethanol was used as solvent[12,13], but, in 2-methoxyethanol[14], the yield of **25** was increased to 63%.

The location of the newly introduced azido group in **25** could not be established by ^{1}H-n.m.r. spectroscopy; therefore, **25** was treated with 2,2-dimethoxy-



propane in 1,4-dioxane in the presence of a catalytic amount of toluene-*p*-sulfonic acid to give diacetal **36**, which, according to the ^{13}C-n.m.r. data, possessed one dioxolane and one dioxane ring (110.8 and 99.3 p.p.m.). Since **36** could be obtained by reaction with 2-methoxypropene at room temperature, when rearrangement of the acetal groups is less probable, the 2,3:4,6-di-*O*-isopropylidene structure, and consequently location of the azido group at C-5, can be inferred.

In order to obtain a diazidohexitol derivative having only one free hydroxyl group for the coupling reaction with the amino sugar component, the primary hydroxyl group in **25** was *p*-nitrobenzoylated to give the 6-ester **26** (the corresponding 4,6-diester **27** was also formed as a by-product). Treatment of the dimesylate (**28**) of **25** with conc. hydrochloric acid in boiling ethanol cleaved the acetal group and eliminated 1 mol of methanesulfonic acid from the intermediate **24** to yield the 3,6-anhydro derivative **33**. The presence of the tetrahydrofuran ring in **32** and its acetate **33** was proved by the ^{1}H-n.m.r. signal (t, *J* 6 Hz) for H-4 which indicated that the dihedral angles for H-4,5 and H-3,4 are similar, as expected for

a five-membered ring. In the alternative 2,6-anhydro structure, H-4 would be *cis* to H-3 and H-5, resulting in much smaller couplings. The presence of the five-membered ring was also proved chemically since hydrogenation (10% Pd/C) of **32** resulted in a terminal amino group that attacked C-4 to give the 1,4:3,6-dianhydro derivative **34**, acetylation of which gave the expected triacetyl derivative **35**.

Since, in addition to **1**, only the synthesis of 1,2-diaminohexitols[15,16] and 1,6-diaminohexitols[17–21] has been described, the diazides **7** and **29** were submitted to catalytic transfer hydrogenation[10,22], using ammonium formate in the presence of Pd/C. The resulting diamines were converted into the crystalline hexa-acetyl derivatives **9** and **31**, respectively, which on deacetylation with hydrochloric acid afforded the respective amines **2** and **3** as crystalline hydrochlorides (**8** and **30**).

EXPERIMENTAL

General methods. — Organic solutions were dried with Na_2SO_4 and concentrated under diminished pressure. Optical rotations were determined on 1% solutions in chloroform if not stated otherwise. T.l.c. was performed on Kieselgel G with ethyl acetate (*A*), ethyl acetate–carbon tetrachloride mixtures (*B*, 1:1; *C*, 1:3; *D*, 1:5; and *E*, 1:9), ethyl acetate–ethanol mixtures (*F*, 1:1; and *G*, 1:9), and ethanol–conc. ammonia (*H*, 1:1; and *I*, 1:9), 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. (90 MHz) and ^{13}C-n.m.r. spectra (25.2 MHz) were recorded with a Varian EM 390 and a XL-100 FT spectrometer, respectively, for solutions in $CDCl_3$ (internal Me_4Si) or D_2O (internal sodium 4,4-dimethyl-4-silapentane-1-sulfonate). The light petroleum used had b.p. 60–80°.

*2,3,5,6-Tetra-*O*-acetyl-1,4-diazido-1,4-dideoxy-*D*-galactitol* (**6**). — A solution of **5**[10] (15 g) in *N,N*-dimethylformamide (150 mL) was boiled in the presence of sodium azide (4.5 g) for 45 min and then concentrated, and the residue was partitioned between dichloromethane and water. The organic solution was washed with water, dried, and concentrated. Column chromatography (solvent *B*) of the residue gave a fraction having R_F 0.8, which, on recrystallisation from ether–light petroleum, gave **6** (3.1 g, 23.5%), m.p. 62–64°, $[\alpha]_D^{20}$ +8°. ^{1}H-N.m.r. data ($CDCl_3$): δ 5.5–5.0 (m, H-2,3,5), 4.2 (m, H-6,6'), 3.6 (dd, H-4), 3.4 (d, H-1,1'), and 2.15–2.0 (4 s, 12 H, 4 Ac).

Anal. Calc. for $C_{14}H_{20}N_6O_8$: C, 41.99; H, 5.03; N, 20.99. Found: C, 41.92; H, 5.15; N, 21.15.

*1,4-Diazido-1,4-dideoxy-*D*-galactitol* (**7**). — (*a*) To a stirred slurry of **6** (14.6 g) in dry methanol (50 mL) was added methanolic 4M sodium methoxide (0.1 mL). After 20 h, the solution was neutralised with solid carbon dioxide and concentrated, and the residue was eluted from a short column of Kieselgel G with ethyl acetate to give **7**, isolated as a colourless syrup (8.2 g, 97%), R_F 0.5 (solvent *A*), $[\alpha]_D^{20}$ +32° (water). ^{1}H-N.m.r. data (D_2O): δ 4.3–3.2 (m, H-1–6).

(*b*) A solution of **12** (20 g) in methanol (200 mL) and methanolic M hydrochloric acid (65 mL) was boiled for 1.5 h, then cooled, neutralised with solid sodium hydrogencarbonate, filtered with charcoal, and concentrated. A solution of the residue in ethyl acetate was treated as in (*a*), to give **7** (10 g, 67%).

Anal. Calc. for $C_6H_{12}N_6O_4$: N, 36.19. Found: N, 35.82.

1,4-Diamino-1,4-dideoxy-D-*galactitol dihydrochloride* (**8**). — (*a*) To a solution of **7** (5.7 g) in methanol (30 mL) and water (30 mL) were added ammonium formate (5 g) and 10% Pd/C (0.3 g), and the slurry was boiled. After 30 min, more ammonium formate (5 g) and 10% Pd/C (0.3 g) were added and boiling was continued for 30 min. T.l.c. (solvent *H*) then showed the reaction to be complete (**7**, R_F 0.95; monoazide, 0.75; **8**, 0.4). The cooled and filtered solution was concentrated and a solution of the residue in 5M hydrochloric acid (15 mL) was freeze-dried. The residue crystallised on treatment with ethanol, to yield **8** (5.2 g, 84%), m.p. 192–194° $[\alpha]_D^{20}$ +3° (water).

(*b*) A solution of the hexa-acetate **9** (1.8 g) in M hydrochloric acid (50 mL) was boiled for 1 h, to give, after concentration and trituration of the residue with ethanol, **8** (0.90 g, 86%).

Anal. Calc. for $C_6H_{16}N_2O_4 \cdot 2$ HCl: C, 28.46; H, 7.16; N, 11.07; Cl, 28.01. Found: C, 28.32; H, 7.30; N, 11.84; Cl, 27.72.

1,4-Diacetamido-2,3,5,6-tetra-O-*acetyl-1,4-dideoxy*-D-*galactitol* (**9**). — A slurry of **8** (1.4 g) and sodium acetate (1 g) in acetic anhydride (10 mL) was boiled for 10 min and then concentrated. The residue was extracted with chloroform, and the extract was filtered and concentrated. Column chromatography (solvent *F*) of the residue gave **9** (1.8 g, 76%), m.p. 166–168° (from ether), $[\alpha]_D^{20}$ +17°, R_F 0.4. ^{1}H-N.m.r. data ($CDCl_3$): δ 6.5 (d, *J* 10 Hz, NH), 6.27 (d, *J* 6 Hz, NH), 5.4–4.65 (m, H-2,3,4,5), 4.2 and 3.9 (2 dd, *J* 12, 5, and 3.5 Hz, H-6,6′), 3.3 (m, H-1,1′), and 2.2–2.0 (6 s, 18 H, 6 Ac).

Anal. Calc. for $C_{18}H_{28}N_2O_{10}$: C, 49.99; H, 6.52; N, 6.47. Found: C, 49.9; H, 6.38; N, 6.45.

1,4-Diazido-1,4-dideoxy-2,3-O-*isopropylidene*-D-*galactitol* (**10**). — A solution of **12** (3.2 g) in methanol (34 mL), water (11 mL), and M hydrochloric acid (0.4 mL) was boiled for 45 min, then cooled, neutralised with triethylamine, and concentrated. Column chromatography (solvent *B*) of the residue gave **12** (0.6 g, 18.7%), R_F 0.95, and **10**, R_F 0.5, isolated as a syrup (1.9 g, 70%), $[\alpha]_D^{20}$ −85°. ^{1}H-N.m.r. data ($CDCl_3$): δ 4.3–3.2 (m, H-1,1′,4,5,6,6′), 4.2 (m, H-2), 4.05 (t, *J* 6 Hz, H-3), and 1.50 (s, 6 H, CMe_2).

Anal. Calc. for $C_9H_{16}N_6O_4$: N, 30.86. Found: N, 30.28.

1,4-Diazido-1,4-dideoxy-2,3-O-*isopropylidene-5,6-di*-O-*methanesulfonyl*-D-*galactitol* (**11**). — To an ice-cooled solution of **10** (3.8 g) in pyridine (15 mL) was added mesyl chloride (3.3 mL). The mixture was kept at room temperature overnight to give, after the usual work-up, **11** (5.9 g, 98%), isolated as a pale-yellow syrup, $[\alpha]_D^{20}$ −32°, R_F 0.5 (solvent *B*). ^{1}H-N.m.r. data ($CDCl_3$): δ 5.0 (q, *J* 5 Hz, H-5), 4.5 (d, *J* 5 Hz, H-6,6′), 4.2 (m, H-2), 3.85 (t, *J* 6 Hz, H-3), 3.65 and 3.35 (2

dd, *J* 13 and 4 Hz, H-1,1'), 3.60 (m, H-4), 3.05 and 3.15 (2 s, 6 H, 2 Ms), and 1.45 (s, 6 H, CMe_2).

Anal. Calc. for $C_{11}H_{20}N_6O_8S_2$: N, 19.61; S, 14.96. Found: N, 19.50; S, 14.48.

*1,4-Diazido-1,4-dideoxy-2,3:5,6-di-*O*-isopropylidene-*D*-galactitol* (**12**). — (*a*) A solution of **4**[10] (3.6 g) in *N,N*-dimethylformamide (20 mL) was boiled in the presence of sodium azide (2.5 g) for 3 h. The cooled dark-brown slurry was filtered and concentrated, and the residue was partitioned between chloroform and water. The organic solution was washed with water, dried, filtered with charcoal, and concentrated to yield **12** as a pale-yellow syrup (1.2 g, 38.5%), $[\alpha]_D^{20}$ −87°, R_F 0.6 (solvent *E*). N.m.r. data ($CDCl_3$): ^1H, δ 4.35–4.25 (m, H-3,5), 4.1 and 3.95 (2 dd, *J* 8.5, 6, and 6 Hz, H-6,6'), 3.85 (t, *J* 7 Hz, H-2), 3.8 and 3.35 (2 dd, *J* 13.5, 3, and 5 Hz, H-1,1'), 3.38 (dd, *J* 8 and 5 Hz, H-4), 1.45 and 1.35 (2 s, 9 and 3 H, CMe_2); ^{13}C, δ 110.5 and 109.8 (acetal-C), 79.2 (C-5), 77.2 and 76.9 (C-2,3), 66.9 (C-6), 65.2 (C-4), 52.5 (C-1), 26.9, 26.3, and 25.4 (CMe_2 2:1:1).

(*b*) A solution of **4** (3.6 g) and sodium azide (2.5 g) in hexamethylphosphoric triamide (20 mL) was stirred at 120° for 2 h, then cooled, diluted with water (100 mL), and extracted with ether (3 × 100 mL). The combined extracts were washed with water, dried, and concentrated. Column chromatography (solvent *E*) of the residue gave **12** (2.3 g, 73.7%), R_F 0.6.

(*c*) A solution of **7** (4 g) and toluene-*p*-sulfonic acid (0.1 g) in 1,4-dioxane (20 mL) and 2,2-dimethoxypropane (10 mL) was kept at 100° for 2 h. Triethylamine (1 mL) was added to the cooled solution which was then concentrated. A solution of the residue in dichloromethane was washed with water, dried, and concentrated to give **12** (4.3 g, 93.4%).

Anal. Calc. for $C_{12}H_{20}N_6O_4$: C, 46.14; H, 6.45; N, 26.91. Found: C, 46.32; H, 6.50; N, 26.55.

*1,4-Diazido-1,4-dideoxy-5,6-*O*-isopropylidene-*D*-galactitol* (**13**). — (*a*) To a solution of **7** (5 g) in 1,4-dioxane (25 mL) and 2,2-dimethoxypropane (5 mL) was added toluene-*p*-sulfonic acid (0.05 g) at room temperature, and the reaction was monitored by t.l.c. (solvent *B*). After 20 h, when all of **7** (R_F 0.1) had been converted into **13** (R_F 0.5), sodium hydrogencarbonate (1 g) was added, and the slurry was stirred for 15 min, then filtered, and concentrated. The residue was eluted from a short column of Kieselgel 40 to give **13** (5 g, 85.3%), isolated as a syrup, $[\alpha]_D^{20}$ +44° (pyridine), +11° (chloroform). N.m.r. data ($CDCl_3$): ^1H, δ 4.5–3.2 (m, H-1–6), 1.45 and 1.35 (2 s, 6 H, CMe_2); ^{13}C, δ 109.2 (acetal-C), 67.0 (C-6), 53.9 (C-1), 76.5 (C-5), 70.6 and 69.4 (C-2,3), 63.3 (C-4), 26.1 and 25.3 (CMe_2).

(*b*) A solution of **7** (2.3 g) in acetone (30 mL) was stirred in the presence of toluene-*p*-sulfonic acid (0.1 g) for 2 h and then processed as in (*a*), to give **13** (2.4 g, 90%).

Anal. Calc. for $C_9H_{16}N_6O_4$: N, 30.86. Found: N, 30.58.

*2,3-Di-*O*-acetyl-1,4-diazido-1,4-dideoxy-5,6-*O*-isopropylidene-*D*-galactitol* (**14**). — A solution of **13** (1 g) in pyridine (10 mL) and acetic anhydride (6 mL) was kept overnight at room temperature to give, after the usual work-up, **14** (1 g, 77%),

isolated as a syrup, $[\alpha]_D^{20}$ −28°, R_F 0.6 (solvent *D*). ^{1}H-n.m.r. data ($CDCl_3$): δ 5.2 (td, *J* 6 and 3 Hz, H-2), 5.05 (dd, *J* 6 and 3 Hz, H-3), 4.10 (q, *J* 5 Hz, H-5), 4.0 and 3.85 (m, H-1,1′), 3.35 (d, *J* 6 Hz, H-6,6′), 3.45 (m, H-4), 2.10 (s, 6 H, 2 Ac), and 1.40 and 1.30 (2 s, 6 H, CMe_2).

Anal. Calc. for $C_{13}H_{20}N_6O_6$: N, 23.58. Found: N, 23.32.

*1,4-Diazido-1,4-dideoxy-5,6-*O*-isopropylidene-2,3-di-*O*-methanesulfonyl-*D*-galactitol* (**15**). — To a solution of **13** (2.7 g) in pyridine (15 mL) was added mesyl chloride (2.2 mL), and the mixture was kept overnight at room temperature and then poured into water. The precipitate (3.5 g) was collected and recrystallised from ethanol to give **15** (3.1 g, 72.5%), m.p. 108–110°, $[\alpha]_D^{20}$ −27°, R_F 0.7 (solvent *B*). ^{1}H-N.m.r. data ($CDCl_3$): δ 5.10 (td, *J* 6 and 2.5 Hz, H-2), 4.77 (dd, *J* 8 and 2.5 Hz, H-3), 4.38 (td, *J* 6 and 4.5 Hz, H-5), 4.18 and 4.05 (2 dd, *J* 8, 5, and 6.5 Hz, H-6,6′), 3.78 (d, *J* 6 Hz, H-1,1′), 3.75 (dd, *J* 8 and 4.5 Hz, H-4), 3.12 (s, 6 H, 2 Ms), and 1.50 and 1.35 (2 s, 6 H, CMe_2).

Anal. Calc. for $C_{11}H_{20}N_6O_8S_2$: C, 30.84; H, 4.70; N, 19.61; S, 14.96. Found: C, 30.80; H, 4.82; N, 19.58; S, 14.88.

*3,6-Anhydro-1,4-diazido-1,4-dideoxy-5-*O*-methanesulfonyl-*D*-galactitol* (**17**). — A solution of **11** (2.6 g) in ethanol (26 mL) and conc. hydrochloric acid (5.2 mL) was boiled. T.l.c. (solvent *B*) showed that **11** (R_F 0.7) was deacetalated to give **16** (R_F 0.3), which lost methanesulfonic acid to yield **17** (R_F 0.5). After 3 h, the solution was cooled, neutralised with solid sodium hydrogencarbonate, filtered, and concentrated, and the residue was partitioned between chloroform and water. The organic solution was dried and concentrated, and the residue was treated with ether–light petroleum to give **17** (1.2 g, 68%), m.p. 81–83°, $[\alpha]_D^{20}$ +24°. ^{1}H-N.m.r. data ($CDCl_3$): δ 5.05 (td, *J* 6 and 2.5 Hz, H-5), 4.4–3.3 (m, H-1,1′,2,3,4,6,6′), 3.0 (s, 3 H, Ms), and 2.4 (d, *J* 8 Hz, OH).

Anal. Calc. for $C_7H_{12}N_6O_5S$: C, 28.76; H, 4.13; N, 28.77; S, 10.97. Found: C, 28.80; H, 4.25; N, 28.72; S, 10.81.

*2,6-Anhydro-1,4-diazido-1,4-dideoxy-3-*O*-methanesulfonyl-*D*-talitol* (**18**). — To a solution of **19** (1 g) in methanol (10 mL) was added methanolic 4M sodium methoxide (1 mL). The mixture was diluted with chloroform after 1 h, washed with water, dried, and concentrated to give **18** as a syrup (0.5 g, 67%), $[\alpha]_D^{20}$ +67°. ^{1}H-N.m.r. data ($CDCl_3$): δ 5.15 (dd, *J* 9 and 4 Hz, H-3), 4.4 (t, *J* 4 Hz, H-4), 4.3–4.0 (m, H-2,5), 3.75 (d, *J* 6 Hz, H-1,1′), 3.70 and 3.30 (2 dd, *J* 12, 3, and 4 Hz, H-6,6′), and 2.65 (s, OH).

Anal. Calc. for $C_7H_{12}N_6O_5S$: N, 28.77; S, 10.97. Found: N, 28.52; S, 10.55.

*1,4-Diazido-1,4-dideoxy-2,3-di-*O*-methanesulfonyl-*D*-galactitol* (**19**). — A solution of **15** (1.7 g) in ethanol (17 mL) and M hydrochloric acid (3 mL) was boiled for 30 min, then cooled, neutralised with solid sodium hydrogencarbonate, filtered, and concentrated. A solution of the residue in dichloromethane was washed with a small volume of water, dried, and concentrated to give **19** as a syrup (1.3 g, 86%), $[\alpha]_D^{20}$ −6°, R_F 0.3 (solvent *B*). ^{1}H-N.m.r. data ($CDCl_3$): δ 5.1 (t, *J* 6 Hz, H-2), 4.9 (d, *J* 6 Hz, H-3), 4.2–3.5 (m, H-1,1′,4,5,6,6′), 3.15 (m, H-4), and 3.10 (s, 6 H, 2 Ms).

Anal. Calc. for $C_8H_{16}N_6O_8S_2$: N, 21.64; S, 16.51. Found: N, 21.50; S, 16.18.

*4,5-Anhydro-1-azido-1-deoxy-2,3-*O*-isopropylidene-*D*-galactitol* (**21**). — A solution of **4**[10] (36.5 g) in methanol (360 mL), water (120 mL), and 2M hydrochloric acid (2.4 mL) was boiled for 2 h. T.l.c. (solvent *B*) then showed that **4** (R_F 0.7) had been completely consumed and that monoacetal **20** (R_F 0.2) was the main component. The cooled solution was neutralised with triethylamine and concentrated, and ethanol and then chloroform were evaporated from the residue. Thereafter, chloroform (75 mL) and methanol (15 mL) were added followed, after cooling to 0°, by methanolic 4M sodium methoxide (26 mL). After 10 min, the mixture was neutralised with solid carbon dioxide, washed with water, dried, and concentrated. Column chromatography (solvent *B*) of the residue gave **21**, isolated as a colourless syrup (19.8 g, 86.4%), $[\alpha]_D^{20}$ −32°. ^{1}H-N.m.r. data ($CDCl_3$): δ 4.4–3.6 (m, H-2,3,6,6′), 3.6 and 3.3 (2 dd, *J* 13, 3.5, and 5 Hz, H-1,1′), 3.1 (m, H-4,5), 2.8 (s, OH), and 1.40 (s, 6 H, CMe_2).

Anal. Calc. for $C_9H_{15}N_3O_4$: N, 18.33. Found: N, 18.17.

*4,5-Anhydro-1-azido-1-deoxy-2,3-*O*-isopropylidene-6-*O*-methanesulfonyl-*D*-galactitol* (**22**). — A solution of **21** (2.3 g) in pyridine (20 mL) was treated with mesyl chloride (2 mL) to give, after the usual work-up and recrystallisation of the product from ether–light petroleum, **22** (1.8 g, 58.6%), m.p. 38–41°, $[\alpha]_D^{20}$ −28°, R_F 0.3 (solvent *C*). ^{1}H-N.m.r. data ($CDCl_3$): δ 4.6–3.1 (m, H-1,1′,2,3,4,5,6,6′), 3.1 (s, 3 H, Ms), and 1.40 (s, 6 H, CMe_2).

Anal. Calc. for $C_{10}H_{17}N_3O_6S$: C, 39.07; H, 5.57; N, 13.67; S, 10.43. Found: C, 38.88; H, 5.60; N, 13.69; S, 10.25.

*4,5-Anhydro-1-azido-1-deoxy-2,3-*O*-isopropylidene-6-*O*-p-nitrobenzoyl-*D*-galactitol* (**23**). — To a solution of **21** (4.1 g) in pyridine (20 mL) and dichloromethane (40 mL) was added *p*-nitrobenzoyl chloride (6 g). The mixture was stored overnight at room temperature and then worked-up in the usual way. Column chromatography of the residue (solvent *D*) gave **23**, isolated as a pale-yellow syrup (6.2 g, 91%), $[\alpha]_D^{20}$ −16°, R_F 0.6 (solvent *D*). ^{1}H-N.m.r. data ($CDCl_3$): δ 8.2 (s, 4 H, aromatic protons), 4.65 and 4.10 (2 dd, *J* 12, 2, and 6 Hz, H-6,6′), 4.05 (m, H-2), 3.6 (m, H-3), 3.5 and 3.25 (2 dd, *J* 12, 4, and 5.5 Hz, H-1,1′), 3.2 (m, H-5), 3.0 (dd, *J* 6 and 2.5 Hz, H-4), and 1.40 (s, 6 H, CMe_2).

Anal. Calc. for $C_{16}H_{18}N_4O_7$: N, 14.81. Found: N, 14.63.

*1,5-Diazido-1,5-dideoxy-2,3-*O*-isopropylidene-*L*-altritol* (**25**). — (*a*) A solution of **21** (2.3 g) and sodium azide (1.3 g) in methanol (20 mL) and water (5 mL) was boiled, and kept neutral to phenolphthalein by the addition of aqueous 10% acetic acid. After 8 h, when all of **21** had been consumed, the solution was concentrated, and a solution of the residue in dichloromethane was washed with water, dried, and concentrated. Column chromatography (solvent *B*) of the residue gave **25**, isolated as a colorless syrup (1.2 g, 44%), $[\alpha]_D^{20}$ −58°, R_F 0.6 (solvent *B*). ^{1}H-N.m.r. data ($CDCl_3$): δ 4.2–3.1 (H-1–6′), 1.40 and 1.35 (2 s, 6 H, CMe_2).

(*b*) To a solution of **21** (26 g) in 2-methoxyethanol (200 mL) were added sodium azide (13.5 g) and ammonium chloride (11.5 g), the stirred slurry was boiled

for 8 h and then concentrated, and the residue was processed as in (*a*) to give **25** (19.5 g, 63%).

(*c*) A solution of **23** (3.8 g) and sodium azide (1.3 g) in methanol (30 mL), water (5 mL), and acetic acid (1.2 mL) was boiled for 10 h when more sodium azide (1 g) and acetic acid (1 mL) were added. Boiling was continued for 40 h, the *p*-nitrobenzoic acid (1.1 g) was removed, and the filtrate was concentrated. The residue was processed as in (*a*) to give **25** (1.6 g, 59%).

Anal. Calc. for $C_9H_{16}N_6O_4$: N, 30.86. Found: N, 30.52.

*1,5-Diazido-1,5-dideoxy-2,3-*O*-isopropylidene-6-*O*-*p*-nitrobenzoyl-* (**26**) *and -4,6-di-*O*-*p*-nitrobenzoyl-*L*-altritol* (**27**). — To a cooled solution of **25** (3 g) in pyridine (30 mL) was added *p*-nitrobenzoyl chloride (2.7 g). The mixture was kept overnight at room temperature, then water (1 mL) was added, and, after 1 h, the mixture was worked-up in the usual way. Column chromatography (solvent *D*) of the product gave **27**, isolated as a yellow syrup (1.0 g, 16%), $[\alpha]_D^{20}$ −69°, R_F 0.8. ^{1}H-N.m.r. data ($CDCl_3$): δ 8.2 (s, 8 H, aromatic protons), 5.45 (dd, *J* 7 and 4 Hz, H-4), 4.8 and 4.6 (2 dd, *J* 11, 4, and 7 Hz, H-6,6′), 4.5–4.0 (m, H-2,3,5), 3.55 and 3.25 (2 dd, *J* 13, 3.5, and 5 Hz, H-1,1′), and 1.40 and 1.35 (2 s, 6 H, CMe_2).

Anal. Calc. for $C_{23}H_{22}N_8O_{10}$: N, 19.64. Found: N, 19.32.

Eluted second was a product with R_F 0.3. Recrystallisation from ether–light petroleum gave **26** (2.6 g, 62.5%), m.p. 63–65°, $[\alpha]_D^{20}$ −53°. ^{1}H-N.m.r. data ($CDCl_3$): δ 8.2 (s, 4 H, aromatic protons), 4.75 and 4.60 (2 m, H-6,6′), 4.25–3.80 (m, H-2–5), 3.65 and 3.40 (2 dd, *J* 13, 3.5, and 5 Hz, H-1,1′), 2.65 (bds, OH), and 1.40 (s, 6 H, CMe_2).

Anal. Calc. for $C_{16}H_{19}N_7O_7$: C, 45.60; H, 4.54; N, 23.27. Found: C, 45.55; H, 4.60; N, 22.99.

*1,5-Diazido-1,5-dideoxy-2,3-*O*-isopropylidene-4,6-di-*O*-methanesulfonyl-*L*-altritol* (**28**). — To a solution of **25** (4.4 g) in pyridine (20 mL) was added mesyl chloride (4.5 mL). The solution was kept at room temperature for 1 h, and then worked-up in the usual way to give **28** as a syrup (6.3 g, 91%), $[\alpha]_D^{20}$ −56°, R_F 0.7 (solvent *B*). ^{1}H-N.m.r. data ($CDCl_3$): δ 4.75 (dd, *J* 6 and 2 Hz, H-4), 4.5–3.9 (m, H-2,3,5,6,6′), 3.6 and 3.3 (2 dd, *J* 13, 3, and 4 Hz, H-1,1′), 3.1 and 3.0 (2 s, 6 H, 2 Ms), and 1.40 and 1.35 (2 s, 6 H, CMe_2).

Anal. Calc. for $C_{11}H_{20}N_6O_8S_2$: N, 19.61; S, 14.96. Found: N, 19.33; S, 14.80.

*1,5-Diamino-1,5-dideoxy-*L*-altritol dihydrochloride* (**30**). — (*a*). A solution of **25** (13 g) in methanol (130 mL), water (30 mL), and trifluoroacetic acid (10 mL) was boiled for 3 h and then concentrated. Column chromatography (solvent *A*) of the residue gave the diazide **29**, R_F 0.5, to a solution of which in methanol (200 mL) and water (100 mL) were added formic acid (6 mL), conc. ammonia (6 mL), and 10% Pd/C (2 g); when the gas evolution ceased, the mixture was boiled for 30 min. More formic acid (6 mL), conc. ammonia (6 mL), and 10% Pd/C (1 g) were added to the cooled solution and, when the gas evolution ceased, the mixture was boiled for 1 h, then cooled, filtered, and concentrated. A solution of the residue in 5M hydrochloric acid (25 mL) was concentrated, and water and then ethanol were

evaporated from the residue, which was finally treated with ethanol to give **30** (9.2 g, 76%), m.p. 166–168°, $[\alpha]_D^{20}$ −19° (water), R_F 0.4 (solvent *H*).

(*b*) A solution of **31** (7.4 g) in M hydrochloric acid (74 mL) was boiled for 1 h and then concentrated with ethanol. Treatment of the residue with methanol gave **30** (3.6 g, 83.2%).

Anal. Calc. for $C_6H_{16}N_2O_4 \cdot 2$ HCl: C, 28.46; H, 7.16; N, 11.07; Cl, 28.01. Found: C, 28.18; H, 7.20; N, 11.16; Cl, 27.85.

1,5-Diacetamido-2,3,4,6-tetra-O-*acetyl-1,5-dideoxy*-L-*altritol* (**31**). — To a solution of **30** (15 g) in acetic anhydride (150 mL) was added sodium acetate (15 g), and the mixture was boiled until complete dissolution occurred. The cooled mixture was concentrated, the residue was partitioned between chloroform and conc. aqueous sodium chloride, and the organic solution was dried and concentrated. Column chromatography (solvent *F*) of the residue gave **31** (16.9 g, 66%), m.p. 164–166° (from ether), $[\alpha]_D^{20}$ −31°, R_F 0.5 (solvent *F*). ^{1}H-N.m.r. data ($CDCl_3$): δ 6.4 (d, *J* 8 Hz, NH-5), 6.25 (t, *J* 6 Hz, NH-1), 5.3–5.1 (m, H-3,4,5), 4.5 (td, *J* 8 and 4 Hz, H-2), 4.2 and 3.95 (2 dd, *J* 11, 5.5, and 4 Hz, H-6,6′), 3.4 and 3.25 (2 m, H-1,1′), 2.15–1.9 (18 H, 6 Ac).

Anal. Calc. for $C_{18}H_{28}N_2O_{10}$: C, 49.99; H, 6.52; N, 6.47. Found: C, 49.80; H, 6.63; N, 6.35.

3,6-Anhydro-1,5-diazido-1,5-dideoxy-4-O-*methanesulfonyl*-L-*altritol* (**32**). — A solution of **28** (6 g) in ethanol (60 mL) and conc. hydrochloric acid (6 mL) was boiled for 1 h. T.l.c. (solvent *B*) showed that **28** (R_F 0.7) was first deacetalated to **24** (R_F 0.2) and that methanesulfonic acid was subsequently eliminated, yielding **32** (R_F 0.5). The cooled solution was neutralised with solid sodium hydrogencarbonate and concentrated. The residue was partitioned between dichloromethane and water, and the organic solution was dried and concentrated to give **32** as a syrup (3.6 g, 88%), $[\alpha]_D^{20}$ +37°. ^{1}H-N.m.r. data ($CDCl_3$): δ 5.2 (t, *J* 6 Hz, H-4), 4.4–3.7 (m, H-2,3,5,6,6′), 3.5 and 3.35 (2 m, H-1,1′), 3.2 (s, 3 H, Ms), 2.95 (s, OH).

*Anal.*Calc. for $C_7H_{12}N_6O_5S$: N, 28.77; S, 10.97. Found: N, 28.51; S, 10.82.

2-O-*Acetyl-3,6-anhydro-1,5-diazido-1,5-dideoxy-4*-O-*methanesulfonyl*-L-*altritol* (**33**). — Acetylation of **32** (2.9 g) in pyridine (5 mL) with acetic anhydride (2 mL) gave, after the usual work-up, **33** as a syrup (3.1 g, 94%), $[\alpha]_D^{20}$ +36°, R_F 0.7 (solvent *B*). ^{1}H-N.m.r. data ($CDCl_3$): δ 5.1 (m, H-2), 5.0 (t, *J* 6 Hz, H-4), 3.8 (m, H-5), 3.55 and 3.4 (2 m, H-1,1′), 3.1 (s, 3 H, Ms), and 2.1 (s, 3 H, Ac).

Anal. Calc. for $C_9H_{14}N_6O_6S$: N, 25.14; S, 9.59. Found: N, 24.86; S, 9.42.

5-Amino-3,6-anhydro-1,4,5-trideoxy-1,4-imino-L-*iditol dimethanesulfonate* (**34**). — A solution of **32** (1.2 g) in ethanol (15 mL) was hydrogenated over 10% Pd/C (0.5 g) for 5 h, then filtered, neutralised with ethanolic M methanesulfonic acid, filtered with charcoal, and concentrated, to give **34** as an amorphous solid (1.2 g, 87%), $[\alpha]_D^{20}$ +18° (water), R_F 0.3 (solvent *I*). ^{1}H-N.m.r. data (D_2O): δ 4.7–3.3 (m, H-1,6) and 2.80 (s, 6 H, 2 Ms).

Anal. Calc. for $C_6H_{12}N_2O_2 \cdot 2\ CH_3SO_3H$: C, 28.56; H, 5.99; N, 8.32; S, 19.06. Found: C, 28.63; H, 6.01; N, 8.48; S, 18.87.

5-Acetamido-2-O-acetyl-1,4-acetylimino-3,6-anhydro-1,4,5-trideoxy-L-iditol (**35**). — A slurry of **34** (1 g) in pyridine (10 mL) and acetic anhydride (5 mL) was stirred at room temperature for 20 h and then concentrated. Column chromatography (solvent *G*) of the residue gave amorphous **35** (0.5 g, 62.5%), $[\alpha]_D^{20}$ −60° (water). ^{1}H-N.m.r. data (D_2O): δ 5.1 (m, H-2), 4.7–3.3 (m, H-1,1′,3,4,5,6,6′), 2.1 (s, 6 H, 2 Ac), and 2.0 (s, 3 H, Ac).

Anal. Calc. for $C_{12}H_{18}N_2O_5$: C, 53.32; H, 6.71; N, 10.36. Found: C, 53.11; H, 6.80; N, 10.22.

1,5-Diazido-1,5-dideoxy-2,3:4,6-di-O-isopropylidene-L-altritol (**36**). — (*a*) A solution of **25** (1 g) and toluene-*p*-sulfonic acid (0.1 g) in 1,4-dioxane (10 mL) and 2,2-dimethoxypropane (1 mL) was heated at ~100° for 1 h and then cooled. Triethylamine (0.1 mL) was added, the solution was concentrated, and a solution of the residue in dichloromethane was washed with water, dried, and concentrated. Column chromatography (solvent *D*) of the residue gave **36** as a syrup (0.85 g, 75%), $[\alpha]_D^{20}$ −70°, R_F 0.6 (solvent *D*). ^{13}C-N.m.r. data ($CDCl_3$): δ 110.8 (C-acetal), 99.3 (C-acetal), 79.5, 79.1, 73.8 (C-2,3,4), 62.3 (C-6), 58.1 (C-5), 52.9 (C-1), 27.61, 26.9, 26.9, 20.0 (Me-acetal).

(*b*) To a solution of **25** (1 g) in 1,4-dioxane (10 mL) were added 2-methoxypropene (1 mL) and toluene-*p*-sulfonic acid (0.05 g) at 0°. The solution was kept for 3 h at room temperature, triethylamine (0.1 mL) was then added, and the mixture was worked-up as in (*a*) to give **36** (0.9 g, 79%).

Anal. Calc. for $C_{12}H_{20}N_6O_4$: N, 26.91. Found: N, 26.72.

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REFERENCES

1 H. TSUKIURA, M. HANADA, K. SAITO, K. FUJISAWA, T. MIYJAKI, H. KOSHIYAMA, AND H. KAWAGUCHI, *J. Antibiot.*, 29 (1976) 1137–1146.
2 M. KONOSHI, S. KAMATA, T. TSUNO, K. I. NUMATA, H. TSUKIURA, T. NAITO, AND H. KAWAGUCHI, *J. Antiobiot.*, 29 (1976) 1152–1162.
3 J. P. KIRBY, G. E. VAN LEAR, G. O. MORTON, W. E. GROVE, W. V. CURRAN, AND D. B. BORDERS, *J. Antibiot.*, 30 (1977) 344–347.
4 K. NARA, Y. SUMINO, S. AKIYAMA, AND M. ASAI, *Chem. Lett.*, (1977) 33–36.
5 T. OGAWA, K. KATANO, AND M. MATSUI, *Carbohydr. Res.*, 60 (1978) c13–c17.
6 T. OGAWA, K. KATANO, AND M. MATSUI, *Tetrahedron*, 36 (1980) 2727–2733.
7 T. NAITO, S. NAKAGAWA, Y. NARITA, AND H. KAWAGUCHI, *J. Antibiot.*, 29 (1976) 1286–1296.
8 K. NARA, K. YOSHIOKA, AND M. KIDA, *Chem. Pharm. Bull.*, 27 (1979) 65–75.
9 M. M. PONPIPOM, R. BUGIANESI, E. WALTON, AND T. Y. SHEN, *Carbohydr. Res.*, 65 (1978) 121–131.
10 J. KUSZMANN AND L. KISS, *Carbohydr. Res.*, 153 (1986) 45–53.
11 J. KUSZMANN AND I. PELCZER, *Carbohydr. Res.*, 89 (1981) 103–120.
12 Y. ALI AND A. C. RICHARDSON, *Carbohydr. Res.*, 5 (1967) 441–448.
13 F. M. UNGER, R. CHRISTIAN, AND P. WALDSTATTEN, *Carbohydr. Res.*, 69 (1974) 71–74.
14 R. D. GUTHRIE AND D. MURPHY, *J. Chem. Soc.*, (1963) 5288–5294.
15 M. L. WOLFROM, F. SHAFIZADEH, J. O. WEHRMÜLLER, AND R. K. ARMSTRONG, *J. Org. Chem.*, 23 (1958) 571–575.

16 M. L. WOLFROM AND J. L. MINOR, *J. Org. Chem.*, 30 (1965) 841–843.
17 W. N. HAWORTH, R. L. HEATH, AND L. F. WIGGINS, *J. Chem. Soc.*, (1944) 155–157.
18 L. F. WIGGINS, *J. Chem. Soc.*, (1946) 384–388.
19 J. W. W. MORGAN AND M. L. WOLFROM, *J. Am. Chem. Soc.*, 78 (1956) 2496–2497.
20 G. S. SINNER, L. A. HENDERSON, AND C. G. GUSTAFSON, JR., *J. Am. Chem. Soc.*, 80 (1958) 3788–3790.
21 O. I. SAMOILOVA, I. A. SELIVERSTOVA, N. M. DYATLOVA, AND V. G. YOSHUNSKII, *Zh. Obshch. Khim.*, 43 (1973) 365–369; *Chem. Abstr.*, 78 (1973) 148,165p.
22 T. BIEG AND W. SZEJA, *Synthesis*, (1985) 76–77.