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Note

Synthesis of D-*galacto*-1-deoxynojirimycin (1,5-dideoxy-1,5-imino-D-galactitol) starting from 1-deoxynojirimycin*†

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Inhibitors of α-D-glucosidases, which are effective against alpha-amylase and saccharase, are of interest[2] since they retard the cleavage of oligosaccharides in the intestine and are therapeutically valuable for controlling the postprandial uptake of glucose in diabetes mellitus[3]. Derivatives of valienamine[4] are good inhibitors of glucosidases, and acarbose, which comprises[5] valienamine linked to a trisaccharide, is under clinical evaluation. The ring-aza analogues of 1,5- and 1,4-anhydro derivatives of polyhydroxy alcohols are also potent inhibitors of glycohydrolases. An important compound in this series is 1-deoxynojirimycin[6] and its *N*-hydroxyethyl derivative[7] (Miglitol), which is a potent inhibitor of saccharase and alpha-amylase and is under clinical evaluation against postprandial hyperglycemia[8].

Several isomers of 1-deoxynojirimycin, that differ in configuration or ring size, have been synthesized, namely, ring-aza analogues from D-fructose[9], L-fucose[10], D-galactose[11,12], D-glucuronic acid[13], 2-acetamido-2-deoxy-D-glucose[1,14], Kdo[15], D-mannose[14,16], 2-acetamido-2-deoxy-D-mannose[14,17], neuraminic acid[18], D-arabinose, L-arabinose, and D-lyxose[19]. The D-*galacto* isomer, which functions as a ligand for affinity chromatography of galactosidases[20], has been synthesised from 1,6-anhydro-α-D-galactopyranose[11] or D-glucose[12]. 1-Deoxynojirimycin (**1**) itself is a synthon that is compatible with the basic methods in carbohydrate chemistry, and we now report its use in a synthesis of D-*galacto*-1-deoxynojirimycin (**11**).

Treatment of **1** with benzyloxycarbonyl chloride and sodium hydrogencarbonate in *N,N*-dimethylformamide gave the *N*-benzyloxycarbonyl derivative **2**, reaction of which with a mixture of 2,2-dimethoxypropane, 2-methoxypropene, and *p*-toluenesulfonic acid in *N,N*-dimethylformamide yielded the 4,6-*O*-isopropylidene derivative **3** (77%). Treatment of **3** with benzyl bromide in *N,N*-dimethylformamide–sodium hy-

* The Chemistry of the 1-Deoxynojirimycin System, Part II. For Part I, see ref. 1.
† Dedicated to Professor Hans Rudolph on the occasion of his 60th birthday.

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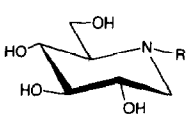
dride gave the syrupy di-*O*-benzyl derivative **4**, acid hydrolysis of which afforded the diol **5**. When a solution of **5** in aqueous *N,N*-dimethylformamide containing potassium carbonate was kept at 80°, the crystalline cyclic carbamate **6** was formed (62% based on **3**). Treatment of the mesylate **7** of **6** with lithium benzoate in *N,N*-dimethylformamide at 100° then gave the crystalline *galacto* derivative **8** (80%).

Saponification of **8** with aqueous sodium hydroxide in dichloromethane–methanol (→**9**) followed by treatment with barium hydroxide in boiling aqueous methanol gave the piperidino derivative **10** (76%). Hydrogenolysis of the benzyl groups in **10** then gave 1,5-dideoxy-1,5-imino-D-galactitol (**11**, 80%).



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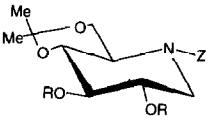
2 R = Z



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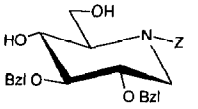
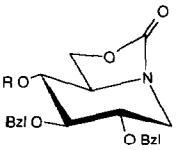
4 R = Bzl



5



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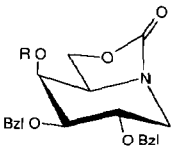
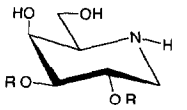
7 R = Ms



8 R = Bz
9 R = H



10 R = Bzl
11 R = H

EXPERIMENTAL

General. — Melting points were measured on a Büchi 520 apparatus and are corrected. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. ^{1}H-N.m.r. spectra (300 MHz) were recorded with a Bruker WM-300 spectrometer on solutions in $CDCl_3$ or C_6D_6 (internal Me_4Si). For solutions in D_2O, the HDO signal was the reference. T.l.c. was performed on silica gel (Merck, 5562) and column chromatography on Silica Gel 60 (Merck, 230–400 mesh) with a Büchi MPLC-System.

N-*Benzyloxycarbonyl-1,5-dideoxy-1,5-imino-4,6*-O-*isopropylidene*-D-*glucitol* (**3**). — To a suspension of 1-deoxynojirimycin (**1**; 489 g, 3.0 mol) in anhydrous *N,N*-dimethylformamide (3.5 L) was added finely pulverized sodium hydrogencarbonate (142.8 g, 1.7 mol). The stirred suspension was cooled to 0° and benzyloxycarbonyl chloride (511 g, 3.0 mol) was added dropwise during 60 min. The mixture was allowed to warm up. After 90 min, t.l.c. (4:3:1 $CHCl_3$–MeOH–aq. NH_3; detection with $KMnO_4$) showed that **1** had reacted completely. The pH of the mixture was adjusted to 2.5 by the addition of 3.5 mol of *p*-toluenesulfonic acid, 1:1 2,2-dimethoxypropane–2-methoxypropene (1.5 L) was added, and the suspension was stirred for 90 min at 40°, when starting material could no longer be detected by t.l.c. (5:1 toluene–ethanol; R_F values: **2** 0.1, **3** 0.5). 10M NaOH (350 mL) was added, the solvent was evaporated, and a solution

of the residue in ethyl acetate (3 L) was washed twice with brine, dried (Na_2SO_4), and concentrated to give syrupy **3** (780 g, 77%). Column chromatography (10:1 toluene–ethanol) of a portion gave material with $[\alpha]_D^{20}$ +3° (*c* 1.1, chloroform).

The 2,3-diacetate of **3** had $[\alpha]_D^{20}$ +28°(*c* 0.4, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 1.38, 1.47,1.98, 2.07 (4 s, 12 H, 4 CMe), 3.23–3.32 (m, 2 H, H-1a,5), 3.89 (dd, 1 H, $J_{3,4}$ 9.1, $J_{4,5}$ 10.4 Hz, H-4), 4.00 (dd, 1 H, $J_{1a,1e}$ 11.7, $J_{1e,2}$ 5.0 Hz, H-1*e*), 4.22 (dd, 1 H, $J_{6a,5}$ 11.4, $J_{6a,6b}$ 11.4 Hz, H-6a), 4.39 (dd, 1 H, $J_{6b,5}$ 5.0 Hz, H-6b), 4.87 (ddd, 1 H, $J_{2,1a}$ 11.0, $J_{2,3}$ 6.5 Hz, H-2), 4.95 (dd, 1 H, H-3), 5.05–5.16 (2 d, 2 H, C*H*$_2$Ph).

Anal. Calc. for $C_{17}H_{23}NO_6$: C, 60.5; H, 6.9; N, 4.2.Found: C, 60.9; H, 6.7; N, 4.0.

*2,3-Di-*O*-benzyl-*N*-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-4,6-*O*-isopropylidene-*D*-glucitol* (**4**). — To a solution of **3** (100 g, 2.1 mol) in *N,N*-dimethylformamide (4 L) at 0°was added sodium hydride (102.2 g, 4.26 mol) at such a rate as to keep the temperature at < 10°. When the addition was complete, the temperature was reduced to 0° and benzyl bromide (720 g, 4.2 mol) was added slowly. The suspension was stirred for a further 16 h at room temperature, when t.l.c. (5:1 toluene–ethanol) revealed that **4** had been consumed; R_F values: **3** 0.5, **4** 0.7. Anhydrous methanol (200 mL) was added, the solvents were evaporated, and a solution of the residue in ethyl acetate was washed twice with brine, dried (Na_2SO_4), and concentrated. Column chromatography (40:1 toluene–acetone) of a small portion gave **4**, m.p. 67°, $[\alpha]_D^{20}$ +44° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 1.41, 1.47 (2 s, 6 H, CMe_2), 3.29 (ddd, 1 H, $J_{4,5}$ 10.6, $J_{5,6a}$ 11.0, $J_{5,6b}$ 4.8 Hz, H-5), 3.4–3.6 (m, 3 H, H-1*a*,2,3), 3.74 (dd, 1 H, $J_{1a,1e}$ 13.5, $J_{1e,2}$ 2.3 Hz, H-1*e*), 3.89 (dd, 1 H, $J_{3,4}$ 8.1 Hz, H-4), 4.10 (dd, 1 H, $J_{6a,6b}$ 11.0 Hz, H-6a), 4.37 (dd, 1 H, H-6b), 4.49–4.79 (2 AB, 4 H, 2 C*H*$_2$Ph), 5.03–5.13 (AB, 2 H, NCOOC*H*$_2$Ph).

Anal. Calc. for $C_{31}H_{35}NO_6$: C, 71.9; H, 6.8; N, 2.7. Found: C, 72.1; H, 6.7; N, 2.5.

*2,3-Di-*O*-benzyl-*N*,6-*O*-carbonyl-1,5-dideoxy-1,5-imino-*D*-glucitol* (**6**). — A solution of crude **4** in aqueous 60% acetic acid (2 L) was heated for 24 h to 60°. T.l.c. (20:1 toluene–ethanol; R_F values: **4** 0.5, **5** 0.1) then showed that the reaction was complete. The solvent was evaporated and remaining traces of acetic acid were removed by co-evaporation with toluene. A solution of the residue (**5**) in *N,N*-dimethylformamide (4 L) containing 10% of water and potassium carbonate (50 g, 0.36 mol) was stirred at 80° for 24 h. T.l.c. (10:1 toluene–ethanol) then revealed **6** (R_F 0.3) but no **5** (R_F 0.4). The mixture was filtered and concentrated, and a solution of the syrupy residue in ethyl acetate was washed with brine, dried (Na_2SO_4), and diluted with light petroleum to yield **6** (480 g, 1.3 mol, 62% from **3**), m.p. 103°, $[\alpha]_D^{20}$ +28° (*c* 0.7, methanol). ^{1}H-N.m.r. (C_6D_6) data for the 4-acetate: δ 1.51 (s, 3 H, CMe), 2.31 (bdd, $J_{1a,1e}$ 13.0, $J_{1a,2}$ 10.1 Hz, H-1*a*), 2.69 (ddd, 1 H, $J_{4,5}$ 9.5, $J_{5,6a}$ 8.0, $J_{5,6b}$ 5.2 Hz, H-5), 3.11–3.20 (m, 2 H, H-2,3), 3.59 (dd,1 H, $J_{6a,6b}$ 8.9 Hz, H-6a), 3.85 (dd, 1 H, H-6b), 4.10 (bdd, 1 H, $J_{1e,2}$ 5.0 Hz, H-1*e*), 4.26 (s, 2 H, C*H*$_2$Ph), 4.51 (d,1 H, $J_{A,B}$ 11.9 Hz, C*H*Ph), 4.74 (dd,1 H, $J_{3,4}$ 9.5 Hz, H-4), 4.79 (d, 1 H, C*H*Ph).

Anal. Calc. for $C_{21}H_{23}NO_5$: C, 68.3; H, 6.3; N, 3.8. Found: C, 68.0; H, 6.5; N, 3.5.

*2,3-Di-*O*-benzyl-*N*,6-*O*-carbonyl-1,5-dideoxy-1,5-imino-4-*O*-methanesulfonyl-*D*-glucitol* (**7**). — To a solution of **6** (256 g, 0.7 mol) in acetone (2.3 L) and triethylamine (300 mL) at −10° was added a solution of mesyl chloride (88 g, 0.77 mol in CH_2Cl_2) dropwise during 60 min. Cooling was then discontinued and the reaction was monitored

by t.l.c. (10:1 toluene–ethanol; R_F values: **6** 0.4, **7** 0.5). Water (10 mL) was added, the mixture was filtered and concentrated, and a solution of the residue in $CHCl_3$ was washed with brine, dried (Na_2SO_4), and concentrated, and the residue was recrystallized from 1:4 ethyl acetate–hexane to give **7** (250 g, 0.6 mol, 80%), m.p. 192°, $[a]_D^{20}$ +26° (*c* 1, methanol).

Anal. Calc. for $C_{22}H_{25}NO_7S$: C, 59.0; H, 5.6; N, 3.1. Found: C, 59.0; H, 5.8; N, 3.0.

*4-O-Benzoyl-2,3-di-O-benzyl-*N,*6-O-carbonyl-1,5-dideoxy-1,5-imino-*D-*galactitol* (**8**). — A solution of **7** (120 g, 0.27 mol) in anhydrous *N,N*-dimethylformamide (1.2 L) containing lithium benzoate (46.1 g, 0.36 mol) was stirred for 60 h at 100°. T.l.c. (10:1 toluene–ethanol) then revealed **8** (R_F 0.45) but no **7** (R_F 0.5). The solvent was evaporated, and a solution of the residue **8** in ethyl acetate was washed, dried (Na_2SO_4), and concentrated. Crystallization of the residue from 2:1 ethyl acetate–hexane gave **8** (104 g, 0.22 mol, 80%), m.p. 138°, $[a]_D^{20}$ + 79° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 2.88 (dd, 1 H, $J_{1a,1e}$ 13.5, $J_{1a,2}$ 10.5 Hz, H-1*a*), 3.67 (dd, 1 H, $J_{2,3}$ 9.4, $J_{3,4}$ 2.7 Hz, H-3), 3.89–3.98 (m, 2 H, H-2,5), 4.07 (dd, 1 H, $J_{6a,5}$ 3.6, $J_{6a,6b}$ 9.0 Hz, H-6a), 4.29–4.37 (m, 2 H, H-1*e*,6b), 4.60–4.84 (2 AB, 4 H, 2 C*H*Ph), 5.75 (dd, 1 H, $J_{4,5}$ 1.4 Hz, H-4).

Anal. Calc. for $C_{28}H_{27}NO_6$: C, 71.0; H, 5.7; N, 3.0. Found: C, 70.8; H, 5.9; N, 2.9.

*2,3-Di-O-benzyl-*N,*6-O-carbonyl-1,5-dideoxy-1,5-imino-*D-*galactitol* (**9**). — To a solution of **8** (105 g, 0.2 mol) in methanol (1 L) and dichloromethane (0.1 L) was added M NaOH (225 mL), and the mixture was warmed to 40°. After 16 h, t.l.c. showed that saponification was complete (10:1 toluene–ethanol; R_F values: **8** 0.8, **9** 0.2). For work-up, M HCl (25 mL) was added, the solvents were evaporated, and a solution of the residue in ethyl acetate (1 L) was washed twice with semi-saturated brine, dried (Na_2SO_4), and concentrated. The residue crystallized from ethanol – ethyl acetate to give **9** (59.0 g, 0.16 mol, 80%), m.p. 176°, $[a]_D^{20}$ +5° (*c* 0.7, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 2.58 (s, 1 H, OH), 2.73 (dd, 1 H, $J_{1a,1e}$ 13.3, $J_{1a,2}$ 10.4 Hz, H-1*a*), 3.49 (dd, 1 H, $J_{2,3}$ 9.1, $J_{3,4}$ 2.7 Hz, H-3), 3.73 (ddd, 1 H, H-5), 3.87 (ddd, 1 H, $J_{1e,2}$ 6.0 Hz, H-2), 3.92 (bdd, 1 H, H-4), 4.2 (dd, 1 H, H-1*e*), 4.29 (dd, 1 H, $J_{6a,6b}$ 8.5, $J_{6a,5}$ 8.5 Hz, H-6a), 4.43 (dd, 1 H, $J_{6b,5}$ 4.5 Hz, H-6b), 4.65–4.85 (m, 4 H, 2 CH_2Ph).

Anal. Calc. for $C_{21}H_{23}NO_5$: C, 68.3; H, 6.3; N, 3.8. Found: C, 68.6; H, 6.1; N, 3.5.

*2,3-Di-O-benzyl-1,5-dideoxy-1,5-imino-*D-*galactitol* (**10**). — To a suspension of **9** (50 g, 0.14 mol) in1:1 methanol–water (300 mL) was added $Ba(OH)_2 \cdot 8H_2O$ (50 g, 0.15 mol), and the mixture was heated to reflux. After 6 h, t.l.c. (5:1 toluene–ethanol) revealed **10** (R_F 0.1) but no **9** (R_F 0.5). The barium salts precipitated by the addition of solid CO_2 were removed, the filtrate was concentrated, and the residue was crystallized from ethyl acetate–ether to give **10** (37.7 g, 0.11 mol, 76%), m.p. 126°, $[a]_D^{20}$ +40° (*c* 1, methanol).

Anal. Calc. for $C_{20}H_{25}NO_4$: C, 69.9; H, 7.3; N, 4.1. Found: C, 70.4; H, 7.1; N, 3.9.

*1,5-Dideoxy-1,5-imino-*D-*galactitol* (D-galacto-*1-deoxynojirimycin, 1-deoxy-galactostatin)* (**11**). — A solution of **10** (36 g, 0.1 mol) in methanol (300 mL) and M HCl (150 mL) was hydrogenolysed (0.35 MPa of hydrogen) over 10% Pd–C (20 g). After 6 h, t.l.c. (4:3:1 $CHCl_3$–MeOH–aq. NH_3) revealed **11** (R_F 0.2) but no **10** (R_F 0.4). The mixture was filtered, then concentrated. The residue was stirred with Lewatit MP 400 (HO^-)

resin (150 mL) and then crystallized from ethanol, to yield **11** (13.3 g, 0.08 mol, 80%), m.p. 243–245°, $[\alpha]_D^{20}$ +54° (*c* 0.9, water). ^{1}H-N.m.r. data (D_2O): δ 2.42 (dd, 1 H, $J_{1a,1b}$ 12.7, $J_{1a,2}$ 10.9 Hz, H-1a), 2.81 (ddd, 1 H, $J_{4,5}$ 1.5, $J_{5,6a}$ 6.7, $J_{5,6b}$ 8.2 Hz, H-5), 3.16 (dd, 1 H, $J_{1e,2}$ 5.3 Hz, H-1*e*), 3.49 (dd, 1 H, $J_{2,3}$ 9.8, $J_{3,4}$ 3.2 Hz, H-3), 3.58–3.70 (ABX, H-6a,6b), 3.78 (ddd, H-2), 4.02 (dd, 1 H, H-4).

Anal. Calc. for $C_6H_{13}NO_4$: C, 44.2; H, 8.0; N, 8.6. Found: C, 44.0; H, 8.1; N, 8.7.

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