Branched-chain Sugars. Part 10.[1] Some Approaches to the Synthesis of L-Evernitrose (2,3,6-Trideoxy-3-*C*,4-*O*-dimethyl-3-nitro-L-*arabino*-hexopyranose) [2]

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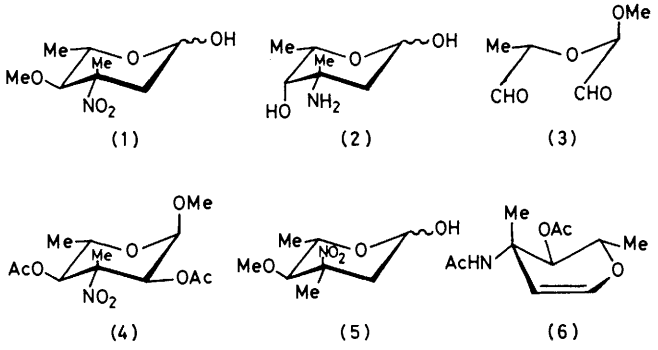
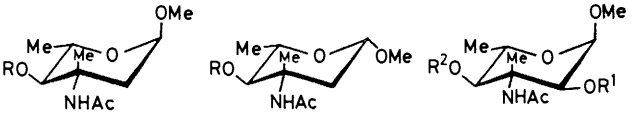
3-Acetamido-4-*O*-acetyl-3,6-dideoxy-3-*C*-methyl-L-glucal (6) reacted with methanol in the presence of boron trifluoride etherate to give a separable mixture of methyl 3-acetamido-4-*O*-acetyl-2,3,6-trideoxy-3-*C*-methyl-α-L-*arabino*-hexopyranoside (7) and the corresponding β-2-deoxyglycoside (8). The α-2-deoxyglycoside (7) can also be prepared, though less efficiently, by deoxygenation of methyl 3-acetamido-4-*O*-acetyl-3,6-dideoxy-3-*C*-methyl-α-L-mannopyranoside (12), which was obtained in three steps from methyl 3-acetamido-3,6-dideoxy-3-*C*-methyl-α-L-glucopyranoside (9). *O*-Deacetylation of the α-2-deoxyglycoside (7), followed by methylation of the resulting alcohol (15), gave methyl 3-acetamido-2,3,6-trideoxy-3-*C*,4-*O*-dimethyl-α-L-*arabino*-hexopyranoside (16), a precursor of the antibiotic sugar L-evernitrose (1). Another route to this precursor, *via* deoxygenation of methyl 3-acetamido-3,6-dideoxy-3-*C*,4-*O*-dimethyl-α-L-glucopyranoside (21) at C-2, was less satisfactory.

An attempt to convert methyl 3-acetamido-2,3,6-trideoxy-3-*C*-methyl-α-L-*arabino*-hexopyranoside (15) into a derivative (29) of L-vancosamine (3-amino-2,3,6-trideoxy-3-*C*-methyl-L-*lyxo*-hexose), by an oxidation–reduction sequence, was unsuccessful, since reduction of methyl 3-acetamido-2,3,6-trideoxy-3-*C*-methyl-α-L-*threo*-hexopyranosid-4-ulose (30) with sodium borohydride in methanol regenerated (15).

THE recent discovery of two unusual methyl-branched nitro- and amino-sugars, L-evernitrose [3,4] (2,3,6-trideoxy-3-*C*,4-*O*-dimethyl-3-nitro-L-*arabino*-hexose) (1) and L-vancosamine [5] (3-amino-2,3,6-trideoxy-3-*C*-methyl-L-*lyxo*-hexose) (2) as components of everninomicins B,[6] C,[7] and D [8] and vancomycin,[9] respectively, has aroused considerable interest in the synthesis of these and related branched-chain sugars. Several successful syntheses [2,10–14] of methyl-branched amino- and nitro-sugars have been reported already. One straightforward route to methyl-branched nitro-sugars involves base-catalysed condensation of a glycoside-derived 'dialdehyde' [*e.g.* (3)] with nitroethane.[15] With (3), which may be obtained by oxidation of methyl α-L-rhamnopyranoside with periodate, the principal isomer obtained [11] following acetylation of the condensation products is methyl 2,4-di-*O*-acetyl-3,6-dideoxy-3-*C*-methyl-3-nitro-α-L-glucopyranoside (4). Although the yield of (4) is modest, large quantities of the 'dialdehyde' (3) are readily available and the route to (4) is a direct one.



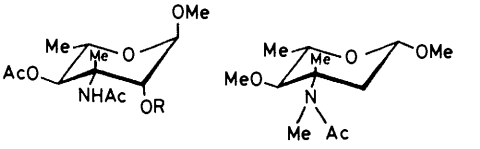
Our interest in this route to methyl-branched nitro-sugars was revived by the recent revision [4] of the structure of L-evernitrose. Although originally assigned [3] the structure 2,3,6-trideoxy-3-*C*,4-*O*-dimethyl-3-nitro-L-*ribo*-hexopyranose (5), a recent *X*-ray study established that evernitrose has the L-*arabino* configuration (1), thus reversing the original assignment of configuration at the branch-point. Previous work in our laboratory showed [11] that the nitro-sugar derivative (4) can be transformed into the glycal (6), which possesses the same stereochemistry as L-evernitrose (1) at the asymmetric centres. A preliminary investigation also showed that the glycal (6) yields a mixture of methyl 3-acetamido-4-*O*-acetyl-2,3,6-trideoxy-3-*C*-methyl-α- and -β-L-*arabino*-hexopyranosides [(7) and (8), respectively] on addition of methanol, although neither were the glycosides separated nor the route pursued.



(7) R = Ac
(15) R = H
(16) R = Me

(8) R = Ac
(17) R = H
(18) R = Me

(9) $R^1 = R^2 = H$
(10) R^1 = Ts; R^2 = H
(11) R^1 = Ts; R^2 = Ac



(12) R = H
(13) R = Ts
(14) R = C:SPh

(19)

RESULTS AND DISCUSSION

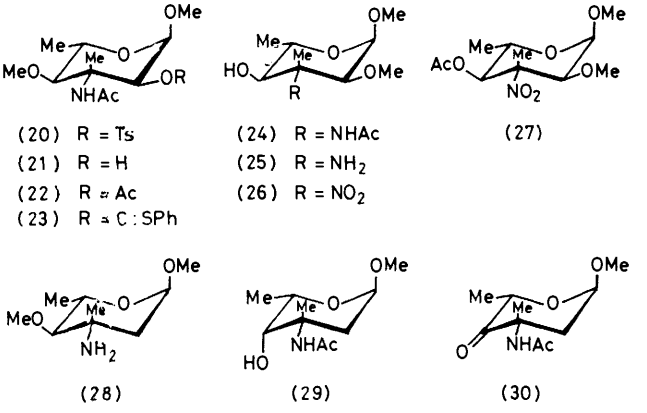
Careful preparative chromatography on silica gel gave the crystalline α-2-deoxyglycoside (7) ($J_{1,2eq}$ *ca.*

1, $J_{1,2ax}$ 4.4 Hz), the major component, and some of the crystalline β-2-deoxyglycoside (8) ($J_{1,2eq}$ 2, $J_{1,2ax}$ 10 Hz). An alternative route to the α-2-deoxyglycoside (7) was examined in an effort to overcome the somewhat tedious chromatographic separation of (7) and (8) occasioned by the glycal route. The nitro-sugar derivative (4) was converted [11] into methyl 3-acetamido-3,6-dideoxy-3-*C*-methyl-α-L-glucopyranoside (9), which gave the 2-tosylate (10) on unimolar toluene-*p*-sulphonylation in the presence of a phase-transfer catalyst.[16] Hydrolysis of the acetylated derivative (11) in refluxing wet diglyme containing sodium acetate gave methyl 3-acetamido-4-*O*-acetyl-3,6-dideoxy-3-*C*-methyl-α-L-mannopyranoside (12). That the expected [17] inversion of the configuration at C-2 had occurred on hydrolysis of (11) was readily established by conversion of (12) into the 2-tosylate (13), which was distinguishable (m.p., $[\alpha]_D$, and ^{1}H n.m.r. spectroscopy) from the isomeric derivative (11). Deoxygenation of (12) at C-2 was accomplished by the procedure of Barton and McCombie.[18] This entailed reaction of (12) with *NN*-dimethyl-α-chlorobenzylideneammonium chloride and then with hydrogen sulphide in pyridine to give the 2-thiobenzoate (14), which was transformed into the α-2-deoxyglycoside (7) by radical-induced cleavage with tributyltin hydride in refluxing toluene. Unfortunately, this procedure gave only moderate yields of (14) and (7), so that the glycal route to the latter compound is better.

Catalytic *O*-deacetylation of (7) gave the alcohol (15), which on careful methylation [19] afforded methyl 3-acetamido-2,3,6-trideoxy-3-*C*,4-*O*-dimethyl-α-L-*arabino*-hexopyranoside (16). Since the D-enantiomer of (16) has recently been transformed into D-evernitrose by Yoshimura *et al.*,[14] the foregoing route formally constitutes a synthesis of L-evernitrose (1). The Japanese workers used the cyanohydrin route to *C*-methyl amino-sugars, which was originally developed by Bourgeois,[13] in their syntheses [14] of D- and L-evernitrose. A sequence of reactions analogous to that described above was used to transform the β-deoxyglycoside (8) into methyl 3-acetamido-2,3,6-trideoxy-3-*C*,4-*O*-dimethyl-β-L-*arabino*-hexopyranoside (18), although controlled methylation [19] of the intermediate alcohol (17) also yielded some of the permethylated derivative (19). This derivative was formed in high yield when a slight excess of iodomethane was used for methylation.

The L-evernitrose precursor (16) was also obtained by another, though less satisfactory, route that relied on deoxygenation of methyl 3-acetamido-3,6-dideoxy-3-*C*,4-*O*-dimethyl-α-L-glucopyranoside (21) at C-2. Methylation (iodomethane–silver oxide) of the 2-tosylate (10) gave the 4-*O*-methyl derivative (20), which on detosylation with sodium amalgam in aqueous methanol gave (21). The 2-acetate (22) was used to characterise (21). Formation and cleavage of the 2-thiobenzoate (23) by the procedure of Barton and McCombie [18] gave the 2-deoxy-derivative (16), but only in moderate yield. Although, in our hands, deoxygenation of neither (12) nor (21) *via* the corresponding thiobenzoate was accomplished satisfactorily, other new deoxygenation procedures [20] may possibly be more efficient, in which case the route (9) → (10) → (20) → (21) → (16) would be the one of choice.

The later stages of the synthesis of L-evernitrose (1) from (16) entail [14] cleavage of the *N*-acetyl group with base, oxidation of the resulting amino-sugar to the nitro-sugar, and, finally, hydrolysis with acid to liberate the free sugar. Preliminary experiments with methyl 3-acetamido-3,6-dideoxy-3-*C*,2-*O*-dimethyl-α-L-glucopyranoside (24) indicated the feasibility of the first two steps in this sequence of reactions. The use of (24) is not significant, except that it was obtained when methyl 3-acetamido-3,6-dideoxy-3-*C*-methyl-α-L-glucopyranoside (9) reacted with refluxing iodomethane in the presence of silver oxide. T.l.c. indicated that no other



methylated products were formed in appreciable amount. The identity of (24) was deduced from elemental analyses, ^{1}H n.m.r. spectroscopy, and the fact that it differs from the isomeric derivative (21). Hydrolysis of (24) with boiling barium hydroxide solution gave the amino-sugar derivative (25), which was oxidised to the corresponding nitro-sugar (26) with an excess of *m*-chloroperbenzoic acid in boiling chloroform–methanol as recommended by Baer and Lee Chiu.[21] The product, which was characterised as its crystalline acetate (27), displayed strong i.r. absorption bands at 1 545 and 1 340 cm^{-1} due to the nitro-group,[3] thus ruling out the possibility that it was the dimeric nitroso-derivative. Related studies by Yoshimura and his co-workers [14] have shown that *m*-chloroperbenzoic acid efficiently oxidises methyl-branched amino-sugars, including (28), to the corresponding nitro-sugars. Like the Japanese workers,[14b] we had difficulty in hydrolysing the acetamido-sugar (16) to the amino-sugar (28). Briefly, neither barium hydroxide nor potassium hydroxide in refluxing aqueous solvents gave entirely satisfactory results, since appreciable quantities of the starting material were recovered from the hydrolysate. As noted earlier, the conversion of the methyl-branched sugar derivative (28) into L-evernitrose (1) has been described.[14]

Having in hand the L-*arabino*-trideoxy-sugar (15), an attempt was made to transform it into the L-*lyxo*-isomer (29), *i.e.* a derivative of vancosamine [5] (2), by an oxidation–reduction sequence at C-4. Oxidation of (15) with ruthenium tetraoxide [22] in carbon tetrachloride gave the aldosidulose (30), from which the equatorial alcohol (15) was regenerated on reduction with sodium borohydride in methanol. The decision to use sodium borohydride may not have been wise in view of a suggestion [23] that reduction of unhindered * cyclohexanones with sodium borohydride proceeds through a product-like transition state and, therefore, gives predominantly the equatorial alcohol. However, we intend to examine the reduction of (30) with other reducing agents (*e.g.* L-Selectride [24,25]) that are known to favour the formation of axial alcohols in the hope of producing a viable route to L-vancosamine (2).

EXPERIMENTAL

T.l.c. was performed on Kieselgel G; spots were located with vanillin–sulphuric acid.[26] I.r. spectra were recorded for Nujol mulls or liquid films using a Perkin-Elmer Infracord spectrophotometer. ^{1}H N.m.r. spectra were measured with a Brucker Spectrospin (90 MHz) spectrometer for solutions in deuteriochloroform with tetramethylsilane as internal reference. Optical rotations were measured at ambient temperature with a Perkin-Elmer 141 automatic polarimeter.

Acetylations were carried out using acetic anhydride in pyridine following a standard procedure.[27] Light petroleum refers to the fraction having b.p. 60—80 °C, unless otherwise stated.

3-*Acetamido*-4-O-*acetyl*-3,6-*dideoxy*-3-C-*methyl*-L-*glucal* (6).—Although the following procedure did not afford a crystalline product, it gave a much better yield than the one described earlier,[11] in which losses were incurred during preparative chromatography.

A cold (0 °C) solution of 3-acetamido-1,2,4-tri-*O*-acetyl-3,6-dideoxy-3-*C*-methyl-α-L-glucopyranose [11] (3.1 g) in acetic anhydride (3.5 ml) and glacial acetic acid (3.5 ml) was treated with a 45% solution of hydrogen bromide in glacial acetic acid (30 ml) for 18 h at room temperature to give the acetobromo-derivative. A solution of sodium acetate trihydrate (38 g) in 50% aqueous acetic acid (92 ml) was cooled to −12 °C and zinc dust (13.8 g) was added to it with vigorous stirring. A 5% solution of chloroplatinic acid (20 drops) was added to activate the zinc (a rapid evolution of hydrogen was observed after about 20 min), followed by the solution of the acetobromo-compound (prepared above) over 1 h. After 2 h at −12 to −17 °C, more chloroplatinic acid solution (5 drops) was added and stirring was continued for another 2 h. The reaction mixture was then filtered quickly and solids were washed with a little 50% aqueous acetic acid and cold water. The filtrate and washings were diluted with ice–water (400 ml) and the aqueous solution was extracted with cold chloroform (5 × 100 ml). Work-up of the organic extract in the usual way [11] and removal of the solvent (<40 °C) afforded a syrup (2 g) consisting of the *glycal* (6) and a little starting material. The crude product, whose ^{1}H n.m.r. spectrum was virtually indistinguishable from that of the crystalline glycal,[11] was used without further purification.

Methyl 3-*Acetamido*-4-O-*acetyl*-3,6-*dideoxy*-3-C-*methyl*-2-O-*toluene*-p-*sulphonyl*-α-L-*glucopyranoside* (11).—The phase-transfer catalyst used in the sulphonylation was obtained by neutralisation of tetrabutylammonium hydroxide with an equimolar quantity of dilute sulphuric acid and concentration of the solution to an amorphous solid, which was dried *in vacuo* over phosphorus pentaoxide.

The diol [11] (9) (4.9 g) was dissolved in methylene chloride (500 ml) to which was added a 5% solution of sodium hydroxide (48 ml). Whilst the two-phase system was stirred vigorously, toluene-*p*-sulphonyl chloride (4.7 g) was added, followed by the phase-transfer catalyst (1.1 g); after 90 min, t.l.c. [light petroleum–acetone–ether (3 : 2 : 1 v/v/v)] revealed the presence of a single product and some starting material. A further quantity (0.2 g) of toluene-*p*-sulphonyl chloride was added and stirring was continued for 3 h, after which t.l.c. indicated that the reaction was complete. The organic layer was separated, washed with a saturated solution of sodium hydrogen carbonate (3 × 75 ml) and water, and dried (Na_2SO_4). Removal of the solvent gave the crude monotosylate (10) (8.7 g); δ *ca.* 7.62 (4 H, aromatic), 3.23 (3 H, s, OMe), 2.45 (3 H, s, Ar*Me*), 1.91 (3 H, s, *N*Ac), 1.41 (3 H, s, 3-Me), and 1.23 (3 H, d, $J_{5,6}$ 5.6 Hz, 5-Me).

Acetylation of (10) in the usual way gave the 4-*acetate* (11) (93%), m.p. 189—196 °C (decomp.) (from chloroform–light petroleum); $[\alpha]_D$ −57° (*c* 0.6 in $CHCl_3$) (Found: C, 53.0; H, 6.6; N, 3.35; S, 7.3. $C_{19}H_{27}NO_8S$ requires C, 53.1; H, 6.3; N, 3.3; S, 7.5%); δ *ca.* 7.58 (4 H, aromatic), 5.73 (1 H, d, $J_{4,5}$ 10 Hz, H-4), 5.60 (1 H, d, $J_{1,2}$ 4.4 Hz, H-2), 4.43 (1 H, d, *J* 4.4, Hz H-1), 3.70 (1 H, m, H-5), 3.27 (3 H, s, OMe), 2.43 (3 H, s, Ar*Me*), 2.04 (3 H, s, OAc), 1.67 (3 H, s, *N*Ac), 1.33 (3 H, s, 3-Me), and 1.11 (3 H, d, $J_{5,6}$ 6.2 Hz, 5-Me).

Methyl 3-*Acetamido*-4-O-*acetyl*-3,6-*dideoxy*-3-C-*methyl*-α-L-*mannopyranoside* (12).—A solution of the monotosylate (11) (0.33 g) in bis-(2-methoxyethyl) ether–water (20 ml; 19 : 1, v/v) containing sodium acetate trihydrate (0.16 g) was heated at 125 °C for 53 h, whereafter the solvents were removed (50 °C and 0.5 mmHg). A solution of the residue in chloroform (75 ml) was then washed with water (3 × 15 ml), dried (Na_2SO_4), and concentrated. Chromatography of the residual syrup (0.26 g) on silica gel [eluant light petroleum–acetone–ether (3 : 2 : 1, v/v/v)] afforded the *alcohol* (12) (0.14 g, 66%) and some unchanged starting material (80 mg). On recrystallisation (twice) from methylene chloride–light petroleum, (12) had m.p. 164—166 °C; $[\alpha]_D$ −93° (*c* 0.9 in $CHCl_3$); $\nu_{max.}$ 3 750 and 3 190 (OH), 1 738 (OAc), and 1 655 cm^{-1} (NHAc) (Found: C, 52.4; H, 7.4; N, 4.9. $C_{12}H_{21}NO_6$ requires C, 52.3; H, 7.7; N, 5.1%); δ 4.82 (1 H, d, $J_{4,5}$ 10 Hz, H-4), 4.69 (1 H, d, $J_{1,2} \leqslant 2$ Hz, H-1), 4.33 (1 H, d, H-2), 3.90 (1 H, m, H-5), 3.38 (3 H, s, OMe), 2.16 (3 H, s, OAc), 1.93 (3 H, s, *N*Ac), 1.54 (3 H, s, 3-Me), and 1.22 (3 H, d, $J_{5,6}$ 6.4 Hz, 5-Me).

Methyl 3-*Acetamido*-4-O-*acetyl*-3,6-*dideoxy*-3-C-*methyl*-2-O-*toluene*-*p*-*sulphonyl*-α-L-*mannopyranoside* (13).—To a solution of the alcohol (12) (0.14 g) in dry pyridine (3 ml) at 0 °C was added toluene-*p*-sulphonyl chloride (0.15 g); after 4 h at room temperature, t.l.c. [light petroleum–acetone–ether (3 : 2 : 1 v/v/v)] showed that a substantial proportion of the starting material still remained. A further quantity (0.38 g) of toluene-*p*-sulphonyl chloride was added and the reaction mixture was set aside at room temperature for

* This implies that, as in (30), there are no bulky axial groups in a β-position to the carbonyl group.

24 h. Work-up in the usual way and recrystallisation from methylene chloride–light petroleum gave the 2-*tosylate* (13) (0.19 g, 87%) as fluffy needles, m.p. 132—133 °C; $[\alpha]_D$ −7° (*c* 0.7 in $CHCl_3$) (Found: C, 53.2; H, 6.4; N, 3.5; S, 7.3. $C_{19}H_{27}NO_8S$ requires C, 53.1; H, 6.3; N, 3.3; S, 7.5%); δ *ca.* 7.55 (4 H, aromatic), 5.24 (1 H, d, H-2), 4.74 and 4.67 (2 H, d, $J_{1,2}$ *ca.* 1, $J_{4,5}$ 10 Hz, H-1 and H-4), 3.90 (1 H, m, H-5), 3.32 (3 H, s, OMe), 2.43 (3 H, s, Ar*Me*), 2.11 (3 H, s, OAc), 1.64 (3 H, s, *N*Ac), 1.52 (3 H, s, 3-Me), and 1.16 (3 H, d, $J_{5,6}$ 6 Hz, 5-Me).

Methyl 3-*Acetamido*-4-O-*acetyl*-2,3,6-*trideoxy*-3-C-*methyl*-α-L-arabino-*hexopyranoside* (7).—(a) *From the alcohol* (12). The imidoyl chloride used in the reaction was prepared [18] by stirring *NN*-dimethylbenzamide (2 g; purified by vacuum distillation) with a solution of ethanol-free methylene chloride (12 ml) containing phosgene (2.3 g) in a foil-wrapped flask for 16 h. After removal of the solvent *in vacuo*, the solid residue was again dissolved in methylene chloride (12 ml) and added to a solution of the alcohol (1.6 g) in dry tetrahydrofuran (7.8 ml) and pyridine (1.3 ml). After 25 min, pyridinium hydrochloride was deposited from the solution. T.l.c. [benzene–acetone (3 : 1 v/v)] of the dark-red solution after 1 h showed that some starting material still remained, so that stirring was continued for 1 h before pyridine (1.15 ml) and methylene chloride (45 ml) were added. The reaction mixture was then cooled (0 °C) and a stream of dry, acid-free hydrogen sulphide was bubbled through it for 15 min. The flask was stoppered tightly and set aside overnight, after which its contents were poured into cold water (60 ml). The aqueous solution was extracted several times with methylene chloride, and the combined extracts were washed in turn with 2M-hydrochloric acid, a saturated solution of sodium hydrogencarbonate, and water, and dried (Na_2SO_4). Removal of the solvent and chromatography of the residue on silica gel [eluant benzene–acetone (8 : 1 v/v)] gave the yellow syrupy 2-*thiobenzoate* (14) (0.71 g, 31%), $[\alpha]_D$ +2° (*c* 0.13 in $CHCl_3$); δ *ca.* 7.78 (5 H, aromatic), 6.44 (1 H, d, $J_{1,2} \leqslant 1$ Hz, H-2), 5.00 (1 H, d, $J_{4,5}$ 10 Hz, H-4), 4.96 (1 H, s, H-1), 4.11 (1 H, m, H-5), 3.43 (3 H, s, OMe), 2.20 (3 H, s, OAc), 1.78 (3 H, s, *N*Ac), 1.69 (3 H, s, 3-Me), and 1.27 (3 H, d, $J_{5,6}$ 6 Hz, 5-Me).

A solution of tributyltin hydride (0.23 g) in dry toluene (5 ml) was heated to gentle reflux under argon before a solution of the 2-thiobenzoate (14) (0.13 g) in toluene (10 ml) was added slowly over 3 h. Heating was continued for 21 h, when t.l.c. [benzene–acetone (3 : 1 v/v)] of the colourless reaction mixture showed that all the starting material had reacted. Removal of the solvent and chromatography of the residue on silica gel [eluant benzene–acetone (4 : 1 v/v)] gave, *inter alia*, the α-2-*deoxyglycoside* (7) (25 mg, 30%), m.p. 121—123 °C (from ether–light petroleum); $[\alpha]_D$ −133° (*c* 0.7 in $CHCl_3$) (Found: C, 55.0; H, 8.0; N, 5.1. $C_{12}H_{21}NO_5$ requires C, 55.6; H, 8.2; N, 5.4%); δ 4.84 (1 H, d, $J_{4,5}$ 10 Hz, H-4), 4.71 (1 H, br d, $J_{1,2eq} \leqslant 1$, $J_{1,2ax}$ 4.4 Hz, H-1), 3.92 (1 H, m, H-5), 3.33 (3 H, s, OMe), 2.72 (1 H, q, J_{gem} 14 Hz, H-2$_{eq}$), 2.23 (1 H, q, H-2$_{ax}$), 2.14 (3 H, s, OAc), 1.87 (3 H, s, *N*Ac), 1.58 (3 H, s, 3-Me), and 1.19 (3 H, d, $J_{5,6}$ 6.4 Hz, 5-Me).

(b) *From the glycal* (6). A solution of (6) (2 g) in dry methylene chloride (35 ml) was treated with a mixture of boron trifluoride–ether, dry methanol, and methylene chloride (53 ml, 1 : 1 : 3, v/v/v) for 18 h at room temperature. The solution was then diluted with methylene chloride (500 ml) and washed (cautiously) with a cold, saturated solution of sodium hydrogen carbonate (3 × 150 ml) and water, and dried (Na_2SO_4). Removal of the solvents left a syrup (1.5 g) containing (7) and (8) in the ratio *ca.* 3 : 1. Chromatography of the products (2.7 g, when combined with those from another experiment) on silica gel [eluant light petroleum–acetone (2 : 1, v/v)] gave first the α-2-*deoxyglycoside* (7) (1.1 g), m.p. 123—125 °C (from methylene chloride–hexane); $[\alpha]_D$ −133° (*c* 1.7 in $CHCl_3$) (Found: C, 55.4; H, 8.0; N, 5.4%). The ^1H n.m.r. spectrum of this material was indistinguishable from that of the glycoside prepared in (a).

Continued elution gave a fraction containing both glycosides followed by methyl 3-acetamido-4-*O*-acetyl-2,3,6-trideoxy-3-*C*-methyl-β-L-*arabino*-hexopyranoside (8) (0.36 g), m.p. 167—169 °C (from methylene chloride–hexane); $[\alpha]_D$ +8° (*c* 0.95 in $CHCl_3$) (Found: C, 54.9; H, 7.9; N, 5.3%); δ 4.67 (1 H, d, $J_{4,5}$ 9 Hz, H-4), 4.47 (1 H, q, $J_{1,2ax}$ 10, $J_{1,2eq}$ 2 Hz, H-1), 3.69 (1 H, m, H-5), 3.47 (3 H, s, OMe), 2.82 (1 H, q, J_{gem} 14 Hz, H-2$_{eq}$), 2.14 (3 H, s, OAc), 1.86 (3 H, s, *N*Ac), 1.50 (3 H, s, 3-Me), and 1.23 (3 H, d, $J_{5,6}$ 6 Hz, 5-Me).

Methyl 3-*Acetamido*-3,6-*dideoxy*-3-C,4-O-*dimethyl*-2-O-*toluene*-p-*sulphonyl*-α-L-*glucopyranoside* (20).—A solution of the 2-tosylate (10) (3.5 g) in iodomethane (50 ml) containing silver oxide (3.35 g) was heated under reflux for 21 h; t.l.c. [benzene–acetone (2 : 1 v/v)] then showed that the reaction was essentially complete. Solids were filtered off and washed with acetone, which precipitated the silver salts in the filtrate. After filtration, the solution was again concentrated. Chromatography of the residue on silica gel [eluant light petroleum–ether–acetone (2 : 1 : 1, v/v/v) and then light petroleum–ether–ethyl acetate (2 : 3 : 3, v/v/v)] afforded the *methylated derivative* (20) (1.75 g, 48%), m.p. 173—174 °C (from methylene chloride–light petroleum); $[\alpha]_D$ −33° (*c* 0.9 in $CHCl_3$) (Found: C, 53.8; H, 6.8; N, 3.5. $C_{18}H_{27}NO_7S$ requires C, 53.85; H, 6.8; N, 3.5%); δ *ca.* 7.58 (4 H, aromatic), 5.43 (1 H, d, $J_{1,2}$ 4.5 Hz, H-2), 4.38 (1 H, d, H-1), 4.16 (1 H, d, $J_{4,5}$ 9 Hz, H-4), 3.60 (1 H, m, H-5), 3.44 and 3.22 (6 H, each s, 2 × OMe), 2.43 (3 H, s, Ar*Me*), 1.78 (3 H, s, *N*Ac), 1.31 (3 H, s, 3-Me), and 1.22 (3 H, d, $J_{5,6}$ 6 Hz, 5-Me).

Methyl 3-*Acetamido*-3,6-*dideoxy*-3-C,4-O-*dimethyl*-α-L-*glucopyranoside* (21).—Sodium amalgam (2%; 25.2 g) was shaken with a solution of the tosylate (20) (0.96 g) in methanol–water (35 ml; 9 : 1, v/v) for 18 h, when t.l.c. [ether–ethyl acetate (2 : 1, v/v)] showed that no starting material remained. The mixture was diluted with aqueous ethanol, neutralised (CO_2), and filtered to remove elemental mercury. After removal of the solvents, the residue was extracted with acetone and the extract was filtered through a Celite–charcoal pad and concentrated. Recrystallisation of the residue from acetone–ether gave the alcohol (21) (0.4 g, 68%), m.p. 186—187 °C; $[\alpha]_D$ −117° (*c* 0.8 in Me_2CO); δ 4.74 (1 H, d, $J_{1,2}$ 4 Hz, H-1), 4.49 (1 H, d, H-2), 3.69 (2 H, m, H-4 and H-5), 3.57 and 3.42 (6 H, s, 2 × OMe), 2.02 (3 H, s, *N*Ac), 1.31 (6 H, s overlying d, $J_{5,6}$ 6 Hz, 3-Me and 5-Me).

Since satisfactory elemental analyses could not be obtained for this compound, it was characterised as its *acetylated derivative* (22), m.p. 172—173 °C (after two recrystallisations from methylene chloride–light petroleum); $[\alpha]_D$ −96° (*c* 0.5 in $CHCl_3$) (Found: C, 53.8; H, 8.2; N, 4.7. $C_{13}H_{23}NO_6$ requires C, 54.0; H, 8.0; N, 4.8%); δ 5.89 (1 H, d, $J_{1,2}$ 4.4 Hz, H-2), 4.88 (1 H, d, H-1), 4.22 (1 H, d, $J_{4,5}$ 10 Hz, H-4), 3.76 (1 H, m, H-5), 3.52 and 3.36 (6 H,

each s, 2 × OMe), 2.11 (3 H, s, OAc), 1.94 (3 H, s, *N*Ac), 1.36 (3 H, s, 3-Me), and 1.31 (3 H, d, $J_{5,6}$ 6 Hz, 5-Me).

Methyl 3-*Acetamido*-2,3,6-*trideoxy*-3-C,4-O-*dimethyl*-α-L-arabino-*hexopyranoside* (16).—(a) *From the* α-2-*deoxyglycoside* (7). A solution of (7) (0.58 g) in dry methanol (15 ml) containing sodium (*ca.* 0.2 g) was set aside at room temperature for 30 min, after which it was neutralised (CO_2) and worked up in the usual way to give methyl 3-acetamido-2,3,6-trideoxy-3-*C*-methyl-α-L-*arabino*-hexopyranoside (15) (0.43 g, 88.5%), $[\alpha]_D$ −104° (*c* 0.7 in $CHCl_3$); δ *ca.* 4.67 (1 H, q, $J_{1,2eq}$ 1.5, $J_{1,2ax}$ 4 Hz, H-1), 3.31 (3 H, s, OMe), 1.99 (3 H, s, *N*Ac), 1.50 (3 H, s, 3-Me), and 1.30 (3 H, d, $J_{5,6}$ 6 Hz, 5-Me).

A solution of the alcohol (15) (0.43 g) in dry tetrahydrofuran (18 ml) was stirred for 30 min with oil-free sodium hydride (0.1 g) and then with iodomethane (0.4 g) for 18 h at room temperature. Conventional work-up of the reaction mixture (see below for methylation of the related β-glycoside) gave the *methylated derivative* (16) (0.43 g, 94%), m.p. 136—138 °C (from ether–light petroleum); $[\alpha]_D$ −71° (*c* 0.85 in $CHCl_3$) {lit. (D-enantiomer),[14] m.p. 136—138 °C; $[\alpha]_D$ +73° (*c* 1 in $CHCl_3$)} (Found: C, 57.3; H, 9.4; N, 5.9. $C_{11}H_{21}NO_4$ requires C, 57.1; H, 9.15; N, 6.05%); δ 4.67 (1 H, d, $J_{1,2ax}$ 4.5, $J_{1,2eq}$ *ca.* 0 Hz, H-1), 3.88 (1 H, d, $J_{4,5}$ 10 Hz, H-4), 3.48 and 3.28 (6 H, s, 2 × OMe), 2.98 (1 H, q, J_{gem} 14 Hz, H-2_{ax}), 1.92 (3 H, s, *N*Ac), 1.73 (1 H, d, H-2_{eq}), 1.33 (3 H, s, 3-Me), and 1.27 (3 H, d, $J_{5,6}$ 6 Hz, 5-Me).

(b) *From the alcohol* (21). *NN*-Dimethylbenzamide (0.36 g) was stirred overnight at room temperature with a solution of phosgene (0.26 g) in alcohol-free methylene chloride (3 ml), after which the solvent and the excess of reagent were removed. The resulting imidoyl chloride [18] in methylene chloride (3 ml) was added to a solution of the alcohol (21) (0.32 g) in a mixture of dry tetrahydrofuran (1.5 ml), methylene chloride (1 ml), and pyridine (0.3 ml). After 2 h at room temperature, a stream of dry, acid-free hydrogen sulphide was bubbled through the solution for 15 min, after which it was set aside in a stoppered flask at room temperature for 18 h. Work-up (as before) and chromatography of the residue (0.45 g) on silica gel [eluant methylene chloride–acetone (3 : 1, v/v)] gave the 2-*thiobenzoate* (23) (0.13 g, 27%); δ *ca.* 7.76 (5 H, aromatic), 6.76 (1 H, d, $J_{1,2}$ 5 Hz, H-2), 5.07 (1 H, d, H-1), 4.34 (1 H, d, $J_{4,5}$ 10 Hz, H-4), 3.76 (1 H, m, H-5), 3.50 and 3.31 (6 H, s, 2 × OMe), 1.83 (3 H, s, *N*Ac), 1.53 (3 H, s, 3-Me), and 1.31 (3 H, d, $J_{5,6}$ 6 Hz, 5-Me). This material was suitable for use in the next experiment.

A solution of tributyltin hydride (0.245 g) in dry toluene (9 ml) was heated to gentle reflux under argon before a solution of the 2-thiobenzoate (23) (0.13 g) in toluene (10 ml) was added over 2 h. Heating was continued for 18 h, when t.l.c. [methylene chloride–acetone (3 : 1, v/v)] indicated that some starting material still remained. A further quantity (0.19 g) of tributyltin hydride in toluene (7 ml) was added and heating was continued for 5 h. Work-up (as before) and chromatography of the residue on silica gel [eluant methylene chloride–acetone (5 : 1 increasing gradually to 2 : 1, v/v)] gave, *inter alia*, the *trideoxy-sugar* (16) (30 mg, 37%), m.p. 136—138 °C (from ether–light petroleum); $[\alpha]_D$ −72° (*c* 0.45 in $CHCl_3$), whose ^1H n.m.r. spectrum was indistinguishable from the material prepared in (a).

Methyl 3-*Acetamido*-2,3,6-*trideoxy*-3-C,4-O-*dimethyl*-β-L-arabino-*hexopyranoside* (17).—(a) *From the* β-2-*deoxyglycoside* (8) (0.13 g) in dry methanol (5 ml) containing sodium (*ca.* 0.1 g) was set aside at room temperature for 30 min, after which it was neutralised (CO_2) and concentrated. The residue was extracted with methylene chloride and the extract was filtered and dried (Na_2SO_4). Removal of the solvent gave methyl 3-acetamido-2,3,6-trideoxy-3-*C*-methyl-β-L-*arabino*-hexopyranoside (17) (0.1 g, 92%) as an amorphous solid; δ 4.44 (1 H, q, $J_{1,2ax}$ 9, $J_{1,2eq}$ *ca.* 1 Hz, H-1), 3.47 (3 H, s, OMe), 1.98 (3 H, s, *N*Ac), 1.47 (3 H, s, 3-Me), and 1.26 (3 H, d, $J_{5,6}$ 6 Hz, 5-Me).

Oil-free sodium hydride (11 mg) was added to a stirred solution of the alcohol (17) (0.1 g) in dry tetrahydrofuran (5 ml) followed, after 15 min, by iodomethane (70 mg; dried over P_2O_5 and distilled). T.l.c. [methylene chloride–acetone (3 : 1, v/v)] after 22 h indicated that not all of the starting material had reacted, so further quantities of sodium hydride (4 mg) and iodomethane (2 drops) were added. After stirring for a further 18 h, the excess of reagents was destroyed by the addition of a few drops of methanol and the solvents were removed. The residue was partitioned between chloroform and water, and the organic layer was washed with water, dried (Na_2SO_4), and concentrated. Chromatography of the residue (0.1 g) on silica gel [eluant methylene chloride–acetone (5 : 1, v/v)] afforded, *inter alia*, the *methylated derivative* (18) (42 mg, 39.5%), m.p. 151—152 °C (from ether–methylene chloride–light petroleum); $[\alpha]_D$ +57° (*c* 1 in $CHCl_3$) [lit. (D-enantiomer),[14b] m.p. 159—160 °C; $[\alpha]_D$ −57° (*c* 1 in $CHCl_3$)] (Found: C, 57.0; H, 9.4; N, 6.0. $C_{11}H_{21}NO_4$ requires C, 57.1; H, 9.15; N, 6.05%); δ 4.50 (1 H, q, $J_{1,2ax}$ 9, $J_{1,2eq}$ 2.5 Hz, H-1), 3.75 (1 H, d, $J_{4,5}$ 9 Hz, H-4), 3.50 and 3.45 (6 H, s, 2 × OMe), 1.94 (3 H, s, *N*Ac), 1.35 (3 H, d, $J_{5,6}$ 6 Hz, 5-Me), and 1.29 (3 H, s, 3-Me). The ^1H n.m.r. spectrum of (18) was indistinguishable from that of the evernitrose-derived compound.[3]

Methyl 3-*Acetamido*-2,3,6-*trideoxy*-3-C,3-N,4-O-*trimethyl*-β-L-arabino-*hexopyranoside* (19).—A solution of the alcohol (17) (0.14 g) in dry tetrahydrofuran (5 ml) was treated (as before) with oil-free sodium hydride (50 mg) and iodomethane (0.225 g) for 18 h at room temperature. Work-up in the usual way and chromatography of the residue on silica gel [eluant light petroleum–acetone (3 : 1 v/v)] gave the *permethylated derivative* (19) (0.13 g, 82%), m.p. 83.5—85 °C (from ether–hexane); $[\alpha]_D$ +45° (*c* 0.95 in $CHCl_3$) (Found: C, 59.0; H, 9.4; N, 5.9. $C_{12}H_{23}NO_4$ requires C, 58.7; H, 9.5; N, 5.7%); δ 4.53 (1 H, q, $J_{1,2ax}$ 9, $J_{1,2eq}$ 2.5 Hz, H-1), 4.40 (1 H, d, $J_{4,5}$ 10 Hz, H-4), 3.46 and 3.43 (6 H, s, 2 × OMe), 3.02 (3 H, s, *N*Me), 2.13 (3 H, s, *N*Ac), 1.66 (1 H, q, J_{gem} 13 Hz, H-2_{eq}), 1.40 (3 H, s, 3-Me), and 1.32 (3 H, d, $J_{5,6}$ 6 Hz, 5-Me).

Methyl 3-*Acetamido*-3,6-*dideoxy*-3-C,2-O-*dimethyl*-α-L-*glucopyranoside* (24).—A solution of the diol (9) [11] (2.8 g) in iodomethane (92.5 ml; dried over P_2O_5 and distilled) containing silver oxide (6.2 g) was heated under gentle reflux for 66 h; t.l.c. [light petroleum–acetone (2 : 1, v/v)] then revealed the presence of a single product. Work-up (as before) gave a syrup (3.4 g) which crystallised from acetone–light petroleum. Recrystallisation afforded the 2-*methyl ether* (24) (77%), m.p. 184—186 °C; $[\alpha]_D$ −85° (*c* 0.8 in $CHCl_3$); $\nu_{max.}$ 3 320 and 3 210 (br, OH), 1 640 and 1 548 cm^{-1} (NHAc) (Found: C, 53.6; H, 8.9; N, 5.5. $C_{11}H_{21}NO_5$ requires C, 53.4; H, 8.6; N, 5.7%); δ 4.86 (1 H, d, $J_{1,2}$ 4 Hz, H-1), 3.71 (1 H, d, $J_{4,5}$ 9 Hz, H-4), 3.47

s, NAc), 1.37 (3 H, s, 3-Me), and 1.31 (3 H, d, $J_{5,6}$ 6 Hz, 5-Me).

Methyl 3-Amino-3,6-dideoxy-3-C,2-O-dimethyl-α-L-glucopyranoside (25).—A stirred solution of the methylated derivative (24) (0.58 g) in water (24 ml) containing barium hydroxide octahydrate (1.7 g) was heated under reflux for 10 h, after which t.l.c. [benzene–acetone (2 : 1, v/v)] showed that not all the starting material had reacted. A further quantity (1.1 g) of barium hydroxide octahydrate was added and stirring and heating were continued for 16 h; t.l.c. then showed that no starting material remained. The hydrolysate was diluted with water (150 ml), neutralised (CO_2), and filtered through a Celite pad. The filtrate was stirred with Amberlite IRA-400 (HO^-) (15 ml), filtered, and concentrated. The residue was dissolved in chloroform, which, after drying (Na_2SO_4) and filtration, was concentrated to give the syrupy *amine* (25) (0.44 g, 91%), $[\alpha]_D$ −101° (*c* 0.6 in $CHCl_3$); $\nu_{max.}$ 3 500—3 100 cm^{-1} (br OH and NH); δ 5.96 (2 H, br s, NH_2), 4.86 (1 H, d, $J_{1,2}$ 4 Hz, H-1), 3.50 and 3.42 (6 H, s, 2 × OMe), 1.33 (3 H, s, 3-Me), and 1.30 (3 H, d, $J_{5,6}$ 6 Hz, 5-Me).

Methyl 3,6-Dideoxy-3-C,2-O-dimethyl-3-nitro-α-L-glucopyranoside (26).—A solution of the amino-sugar (25) (0.17 g) in methanol–chloroform (44 ml; 7 : 4, v/v) was added over 40 min to a boiling solution of *m*-chloroperbenzoic acid (0.96 g) in chloroform (40 ml). Heating was continued for 20 min, when t.l.c. [benzene–ethyl acetate (10 : 1, v/v)] showed that no starting material remained. The solvents were removed and a solution of the residue in chloroform (40 ml) was cooled (−20 °C) to precipitate the bulk of acidic materials. Concentration of the filtered solution left a solid residue, which was dissolved in methanol (25 ml) and water (10 ml), and stirred with Amberlite IRA-400 (HO^-) (7 ml) for 30 min. Removal of the resin and solvents, and chromatography of the residue on silica gel [eluant hexane–ethyl acetate (4 : 1, v/v)] gave the *3-nitro-derivative* (26) (0.13 g, 67%), $[\alpha]_D$ −98.5° (*c* 0.75 in $CHCl_3$), $\nu_{max.}$ 3 450 (br OH) and 1 545 and 1 340 cm^{-1} (NO_2), as a pale yellow syrup; δ 4.89 (1 H, d, $J_{1,2}$ 4.5 Hz, H-1), 4.11 (1 H, d, H-2), 3.87 (1 H, d, $J_{4,5}$ 10 Hz, H-4), 3.66 (1 H, m, H-5), 3.42 and 3.39 (6 H, s, 2 × OMe), 1.71 (3 H, s, 3-Me), and 1.30 (3 H, d, $J_{5,6}$ 6 Hz, 5-Me).

Methyl 4-O-Acetyl-3,6-dideoxy-3-C,2-O-dimethyl-3-nitro-α-L-glucopyranoside (27).—Acetylation of the nitro-alcohol (26) (0.12 g) in the usual way and chromatography on silica gel [eluant hexane–acetone (2 : 1, v/v)] gave the *nitro-acetate* (27) (0.1 g, 71%), m.p. 117—118 °C (from ether–light petroleum); $[\alpha]_D$ −132° (*c* 0.9 in $CHCl_3$) (Found: C, 47.5; H, 7.3; N, 4.8. $C_{11}H_{19}NO_7$ requires C, 47.65; H, 6.9; N, 5.05%); δ 5.26 (1 H, d, $J_{4,5}$ 10 Hz, H-4), 4.92 (1 H, d, $J_{1,2}$ 4.4 Hz, H-1), 4.24 (1 H, d, H-2), 3.76 (1 H, m, H-5), 3.42 and 3.38 (6 H, s, 2 × OMe), 2.02 (3 H, s, OAc), 1.76 (3 H, s, 3-Me), and 1.17 (3 H, d, $J_{5,6}$ 6 Hz, 5-Me).

Methyl 3-Acetamido-2,3,6-trideoxy-3-C-methyl-α-L-threo-hexopyranosid-4-ulose (30) *and its Reduction with Sodium Borohydride*.—Ruthenium dioxide dihydrate (0.26 g) was shaken with a solution of sodium metaperiodate (0.9 g) in water (5 ml) until it was completely oxidised, after which ruthenium tetraoxide was extracted from the aqueous solution with ethanol-free carbon tetrachloride (2 × 10 ml). The combined extracts were added to a stirred solution of the alcohol (15) (0.18 g) in carbon tetrachloride (10 ml) and the oxidation was followed by t.l.c. [methylene chloride–acetone (2 : 1 v/v)]. Two further additions of the oxidant were required before t.l.c. showed that all the starting material had reacted. The spent oxidant was filtered off and washed thoroughly with methylene chloride and methanol. Concentration of the filtrate and washings, and chromatography of the residue on silica gel [eluant methylene chloride–acetone (2 : 1, v/v)] gave the syrupy *aldosidulose* (30) (80 mg, 45%), $[\alpha]_D$ −137 ±4° (*c* 0.8 in $CHCl_3$); $\nu_{max.}$ 1 730 cm^{-1} (C=O).

Sodium borohydride (0.12 g) was added in portions to a stirred solution of (30) (80 mg) in methanol (4 ml); *after* 15 min, t.l.c. [methylene chloride–acetone (2 : 1 v/v)] showed the presence of a single product and some starting material. A further quantity (69 mg) of sodium borohydride was added and stirring was continued for 1 h before the solvent was removed and the residue was partitioned between chloroform and water. Conventional work-up of the organic extract and acetylation of the product (50 mg) gave the *acetate* (7) (50 mg), which was indistinguishable (m.p., $[\alpha]_D$, and ^1H n.m.r. spectroscopy) from an authentic sample.

We thank the University of Dundee for financial support, Dr. A. K. Ganguly (Schering Corporation) for courteous exchange of information, and J. A. Chudek for recording the ^1H n.m.r. spectra.

[9/1494 *Received*, 20*th September*, 1979]

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