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Preliminary communication

A new synthesis of D-ristosamine derivatives

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We have reported on the structure determination[1] and definitive synthesis[2] of ristosamine (3-amino-2,3,6-trideoxy-L-*ribo*-hexose), the amino sugar component of the antibiotic ristomycin[3]. Three additional syntheses[4–6] of this amino sugar have now appeared, and it has been used[6] for the glycosylation of the aglycon moiety of the anticancer antibiotic daunomycin.

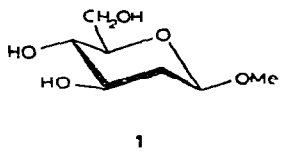
Recently, synthetic approaches to clinically useful analogues of the anthracycline-type antitumour antibiotics (daunomycin[7], adriamycin[8], and carminomycin[9]), modified in both the aglycon and the sugar (daunosamine) moieties, have generated considerable interest.

We now describe a convenient method, different from that recently reported[10], for the synthesis of some derivatives of 3-amino-2,3,6-trideoxy-D-*ribo*-hexose, starting from D-glucose.

Methyl 2-deoxy-β-D-*arabino*-hexopyranoside (**1**) was obtained from 3,4,6-tri-*O*-acetyl-D-glucal by addition of hydrochloric acid, followed by methanolysis in the presence of silver carbonate, and subsequent Zemplén deacetylation. Treatment of **1** with benzaldehyde and anhydrous zinc chloride (25°, 24 h) gave hitherto unknown methyl 4,6-*O*-benzylidene-2-deoxy-β-D-*arabino*-hexopyranoside (**2**), m.p. 155–157°, $[\alpha]_D^{25}$ –75° (*c* 0.8, chloroform)*. P.m.r. data ($CDCl_3$, 100 MHz); δ 7.1–7.3 (m, 5 H, aromatic), 5.49 (s, 1 H, Ph-C*H*), 4.39 (dd, 1 H, $J_{1,2e}$ ~2, $J_{1,2a}$ ~8 Hz, H-1), 3.46 (s, 3 H, OMe). Reaction of **2** with methanesulphonyl chloride in anhydrous pyridine gave the mesylate **3**, m.p. 143–145°, $[\alpha]_D^{25}$ –59.5° (*c* 1, chloroform). P.m.r. data: δ 7.1–7.3 (m, 5 H, aromatic), 5.55 (s, 1 H, Ph-C*H*), 4.54 (dd, 1 H, $J_{1,2e}$ ~2, $J_{1,2a}$ ~9.5 Hz, H-1), 3.49 (s, 3 H, OMe), 2.95 (s, 3 H, SO_2Me). Treatment of **3** with sodium azide** in hexamethylphosphoric triamide at 100°

*All new compounds gave satisfactory elemental analyses.
Treatment of the α anomer of **3 by the method of Kovár and co-workers[11] gave only ~25% of the 3-azido-glycoside, because of a β-*trans-axial* effect[12] involving MeO-1.

gave methyl 3-azido-4,6-*O*-benzylidene-2,3-dideoxy-β-D-*ribo*-hexopyranoside (**4**, 92%), m.p. 101–102°, $[\alpha]_D^{25}$ −104° (*c* 1, chloroform). P.m.r. data: δ 7.1–7.3 (m, 5 H, aromatic), 5.54 (s, 1 H, Ph-C*H*), 4.69 (dd, 1 H, $J_{1,2e}$ ~2.5, $J_{1,2a}$ ~9 Hz, H-1), 3.47 (s, 3 H, OMe). Mass spectrum (70 eV): *m/e* 291 (2%), 290 (3), 263 (1), 262 (0.5), 260 (0.1), 259 (0.2), 248 (1.5), 190 (1), 189 (2), 188 (2), 177 (13), 159 (3), 157 (2), 149 (60), 142 (100), 121 (8), 119 (5), 113 (15), 105 (90), 99 (70), 91 (70), 87 (30), 86 (60), 77 (50).



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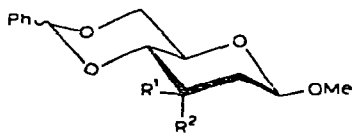
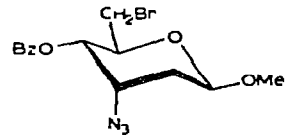


2 R^1 = OH, R^2 = H
3 R^1 = OMs, R^2 = H
4 R^1 = H, R^2 = N_3



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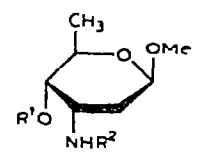
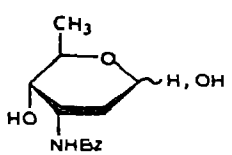
Reaction of **4** with *N*-bromosuccinimide in refluxing carbon tetrachloride in the presence of an excess of barium carbonate[13] gave methyl 3-azido-4-*O*-benzoyl-6-bromo-2,3,6-trideoxy-β-D-*ribo*-hexopyranoside (**5**, 90%), m.p. 64.5–65°, $[\alpha]_D^{25}$ −110° (*c* 0.69, chloroform); ν_{max}^{KBr} 2100 (azide) and 1762 cm^{-1} (ester C=O). P.m.r. data: δ 7.1–8.0 (m, 5 H, aromatic), 4.75 (dd, 1 H, $J_{1,2e}$ ~2.5, $J_{1,2a}$ ~8.3 Hz, H-1), 3.56 (s, 3H, OMe). Mass spectrum: *m/e* 370 (0.1%), 368 (0.1), 340 (0.2), 338 (0.2), 276 (0.2), 269 (5), 267.0023 (5, $C_{12}H_{12}{}^{79}BrO_2$), 262.1080 (1, $C_{14}H_{16}NO_4$), 248.0940 (4, $C_{13}H_{14}NO_4$), 207 (1), 204.9922 (1, $C_5H_8{}^{79}BrN_3O$), 189.0532 (3, $C_9H_7N_3O_2$), 161.0607 (3, $C_{10}H_9O_2$), 146 (4), 122.0370 (3, $C_7H_6O_2$), 114 (4), 105 (100), 77 (30).

Hydrogenolysis of **5** (60°, 1 atmos., Raney nickel) in methanol containing triethylamine gave an ~85 : 15 mixture (t.l.c., p.m.r. data) of methyl 3-benzamido-2,3,6-trideoxy-β-D-*ribo*-hexopyranoside (**7**) and, presumably, the 4-benzoate **6**, the initial product of the reduction, from which **7** is formed *via* acyl migration. Benzoylation of the mixture in pyridine gave methyl 3-benzamido-4-*O*-benzoyl-2,3,6-trideoxy-β-D-*ribo*-hexopyranoside (**8**, 90%, methyl *N*-benzoyl-*O*-benzoyl-β-D-ristosaminide), m.p. 124–126°, $[\alpha]_D^{25}$ −75° (*c* 0.73, chloroform). P.m.r. data: δ 7.2–8.0 (m, 5 H, aromatic), 4.85 (dd, 1 H, $J_{1,2}$ ~3.5 and 4.3 Hz, H-1), 5.16 (dd, 1 H, $J_{3,4}$ or $J_{4,5}$ ~3.5 and 4.6 Hz, H-4), 1.48 (d, 3 H, $J_{5,6}$ ~6.8 Hz, Me-5). Mass spectrum: *m/e* 369 (0.1%), 368 (0.1), 354 (0.1), 338.1369 (1, $C_{20}H_{20}NO_4$), 325 (0.2), 309 (0.2), 267 (0.4), 264 (0.8), 247 (10), 215.0938 (12, $C_{13}H_{13}NO_2$), 204 (4), 200 (2), 190 (7), 188 (5), 174 (2), 172 (1), 163 (1), 142.0865 (20, $C_7H_{12}NO_2$), 127 (1), 122.0597 (5, C_7H_8NO), 122.0362 (1, $C_7H_6O_2$), 117 (3), 105 (100), 95 (7), 77 (20).



6 R^1 = Bz, R^2 = H
7 R^1 = H, R^2 = Bz
8 R^1 = R^2 = Bz



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Simultaneous generation of deoxy and amino functions at positions 6 and 3, respectively, of di- or tri-deoxy-3-aminohexoses has not been reported hitherto.

Saponification (Zemplén) of 8 gave pure, syrupy methyl 3-benzamido-2,3,6-trideoxy-β-D-*ribo*-hexopyranoside (7, methyl *N*-benzoyl-β-D-ristosaminide), $[\alpha]_D^{25}$ −38° (*c* 0.5, chloroform). P.m.r. data. δ 7.2–7.8 (m, 5H, aromatic), 4.68 (dd, 1 H, $J_{1,2e}$ ~3, $J_{1,2a}$ ~6 Hz, H-1), 3.62 ("quintet", 1 H, $J_{5,6}$ 6–7, $J_{4,5}$ 6–7 Hz, H-5), 3.42 (s, 3 H, OMe), 1.37 (d, 3 H, Me-5). Mass spectrum: *m/e* 247 (0.3%), 233 (3), 215 (2), 191 (10), 190 (2), 188 (2), 176 (2), 163 (16), 160 (2), 146 (2), 142.0869 (10, $C_7H_{12}NO_2$), 128 (2) 122.0600 (7, C_7H_8NO), 113.0605 (2, $C_6H_9O_2$), 105 (100), 77 (20); metastables: 81.6 (247 $\xrightarrow{-105}$ 142), 54.8 (233 $\xrightarrow{-120}$ 113).

The values (6–7 Hz) of $J_{1,2a}$ and $J_{4,5}$ for 7 indicate a $^4C_1(D) \rightleftharpoons {}^1C_4(D)$ equilibrium, strongly shifted towards the $^4C_1(D)$ conformation, whereas the low value (3.5–4.6 Hz) of $J_{4,5}$ indicates that the $^1C_4(D)$ conformation is the more favoured for 8. The $^4C_1(D)$ conformation is more favoured[10] in mono- and di-acyl derivatives of methyl α-D-ristosaminide.

Hydrolysis of 8 with aqueous acetic acid gave 3-benzamido-2,3,6-trideoxy-D-*ribo*-hexose (9, *N*-benzoyl-D-ristosamine), m.p. 128–130°, $[\alpha]_D^{25}$ +37° (equil., *c* 0.57, water), lit.[10] m.p. 128–129°, $[\alpha]_D^{23}$ +39° (equil., *c* 0.6, water).

The utilization of appropriately protected derivatives of 7 in the synthesis of anthracycline antibiotics is being investigated.

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