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Note

A convenient method for the synthesis of methyl 2-acetamido-2-deoxy-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-α-D-glucopyranoside

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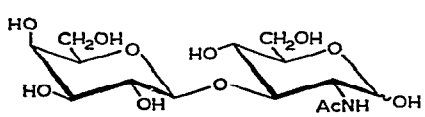
The disaccharide 2-acetamido-2-deoxy-3-*O*-β-D-galactopyranosyl-D-glucopyranose (**1**) is a constituent part of "lacto-*N*-tetraose", which is present in human milk[1], and of the branched trisaccharide 2-acetamido-2-deoxy-4-*O*-α-L-fucopyranosyl-3-*O*-β-D-galactopyranosyl-β-D-glucopyranose, which is the Le^a blood-group antigenic determinant[2]. Its synthesis involved a Koenigs–Knorr reaction of 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide with the 4,6-*O*-benzylidene derivative of either benzyl 2-acetamido-2-deoxy-α-D-glucopyranoside[3] or 2,2,2-trichloroethyl 2-acetamido-2-deoxy-β-D-glucopyranoside[4], and subsequent removal of the benzylidene group by catalytic hydrogenolysis. Recent syntheses of blood-group antigenic determinants[5] prompt us to report a convenient method for the synthesis of 3-*O*-substituted derivatives of methyl 2-acetamido-2-deoxy-α-D-glucopyranoside. The 4,6-benzeneboronate (**2**) of methyl 2-acetamido-2-deoxy-α-D-glucopyranoside was chosen as the intermediate for the following reasons: (*a*) it is readily obtainable in nearly quantitative yield; (*b*) benzeneboronates are useful intermediates in the synthesis of alkyl derivatives[6], esters[7], and glycosides[8]; and (*c*) chromatographic work-up of the reaction mixtures using lyotropic solvents effects complete hydrolysis of benzeneboronates[6].



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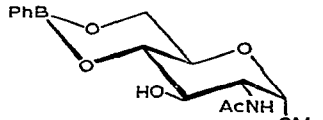


2

The evidence upon which the structure of **2** was assigned is as follows. Electron-impact mass spectrometry produced, by the pathway shown in Fig. 1, an ion with *m/e* 159.0626 ($C_9H_8BO_2$; $\%\sum_{40}$, 3.2), the formation of which, together with the ion *m/e* 160 ($C_9H_9BO_2$; $\%\sum_{40}$, 1.8), is characteristic of the 2-phenyl-1,3,2-dioxaborinane ring system[9,10]. Methylation of the benzeneboronate with the BF_3–diazomethane reagent[11,12], followed by hydrolysis of the benzeneboronate ring and

acetylation, gave a single carbohydrate product (g.l.c.), the e.i.-mass spectrum of which was virtually identical with that of authentic methyl 2-acetamido-4,6-di-*O*-acetyl-2-deoxy-3-*O*-methyl-α-D-galactopyranoside[13].

The product of the Koenigs–Knorr reaction, namely, methyl 2-acetamido-2-deoxy-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-α-D-glucopyranoside 4,6-benzeneboronate (3) was not isolated, as the chromatographic work-up of the reaction mixture effected complete hydrolysis of the benzeneboronate ring, affording, directly, methyl 2-acetamido-2-deoxy-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-α-D-glucopyranoside (4) in 91% yield. The assignment of structure to 4 is based on (*a*) the method of synthesis; (*b*) the e.i.-induced formation of the ion *m/e* 534 through loss of MeO from the molecular ion; (*c*) optical rotatory power (application of isorotation rules with methyl 2-acetamido-2-deoxy-α-D-glucopyranoside and methyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside); and (*d*) the splitting (8.5 Hz) of the n.m.r. signal for H-1 of the D-galactopyranosyl unit.

As methyl 2-acetamido-2-deoxy-α-D-glucopyranoside can be obtained from 2-acetamido-2-deoxy-D-glucose in yields of >90%, the method described here

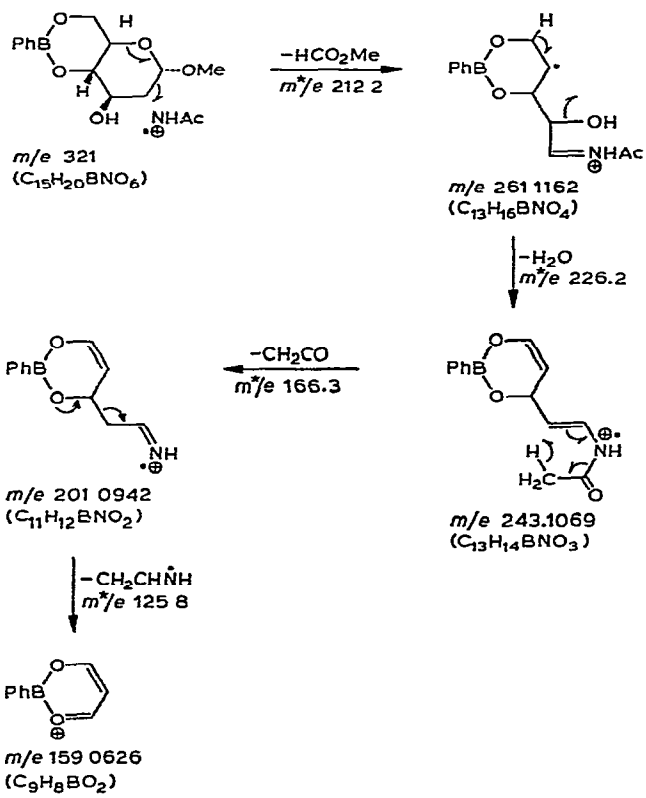
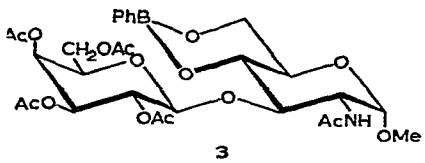


Fig. 1. E.i.-induced fragmentation of methyl 2-acetamido-2-deoxy-α-D-glucopyranoside 4,6-benzeneboronate (2); m^*/e = mass number of metastable ions.



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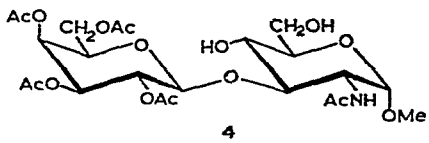

4

represents a >80% overall yield of **4** from 2-acetamido-2-deoxy-D-glucose in only three operations.

EXPERIMENTAL

General methods. — T.l.c. was performed on silica gel (Polygram Sil G) with ethyl acetate–dichloromethane (1:1). Compounds were detected with iodine vapour, followed by spraying with sulphuric acid (5% in ethanol) and heating at 120°.

G.l.c.–mass spectrometry was performed with a Perkin–Elmer F11 gas chromatograph, operating at 200° and containing a glass column (6 ft × 0.25 in.) packed with 3% of OV-225 on Chromosorb Q (100–120 mesh). The carrier gas, helium, was removed from the effluent by passage through a Biemann separator. The effluent was then passed into a Hitachi RMS-4 mass spectrometer operating at 80 eV and 50 μA target current. Low- and high-resolution mass spectra were also recorded on an A.E.I. MS-902 spectrometer operating at 70 eV using a direct insertion method.

N.m.r. spectra were recorded (internal Me_4Si) with a Varian E.M. 360 spectrometer.

Methyl 2-acetamido-2-deoxy-α-D-glucopyranoside 4,6-benzeneboronate (**2**). — Methyl 2-acetamido-2-deoxy-α-D-glucopyranoside (0.15 g) and benzeneboronic anhydride (0.07 g) were heated in toluene under reflux for 4 h, using a Dean and Stark head to remove the water produced. The resulting solution was evaporated, and the residue recrystallised from 2-methoxyethanol to give **2** (0.2 g), m.p. 287–288°, $[\alpha]_D^{25}$ + 132° (*c* 1.0, pyridine); the highest mass number recorded in e.i.–m.s. was *m/e* 322.1462, corresponding to the $[M + 1]^+$ ion (Found: C, 55.81; H, 6.24; B, 3.30; N, 4.52%. $C_{15}H_{20}BNO_6$ calc.: C, 56.07; H, 6.23; B, 3.43; N, 4.66%).

Methyl 2-acetamido-2-deoxy-3-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-α-D-glucopyranoside (**4**). — Compound **2** (0.93 g) was shaken with 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (1.38 g) and mercuric cyanide (0.37 g) in nitromethane (120 cm^3) at room temperature for 48 h; complete dissolution had then occurred. T.l.c. showed that the reaction was complete and that one major product (R_F 0.04) had been formed. The solution was evaporated, and the residue passed through a column (3 × 30 cm) of silicic acid (SIL-R 100–300 mesh, Sigma Chemical Co.) with a lyotropic series of solvents. A chromatographically pure product (1.40 g) emerged with ethyl acetate–ethanol (10:1). Recrystallisation from ethyl acetate afforded **4**, m.p. 189–190°, $[\alpha]_D^{25}$ + 48.5° (*c* 1.0, chloroform); p.m.r. data: δ 6.06 (bd, 1 H, NH), 4.76 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 4.65 (d, 1 H, $J_{1',2'}$ 8.5 Hz, H-1'), 3.45 (s, 3 H, CH_3O), 2.02–2.18 (m, 15 H, AcN and 4 AcO) (Found: C, 48.58; H, 6.39; N, 2.68%. $C_{23}H_{35}NO_{15}$ calc.: C, 48.84; H, 6.24; N, 2.48%).

ACKNOWLEDGMENTS

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