Synthesis of the Phosphono-analogue of α-D-Glucose 1-Phosphate

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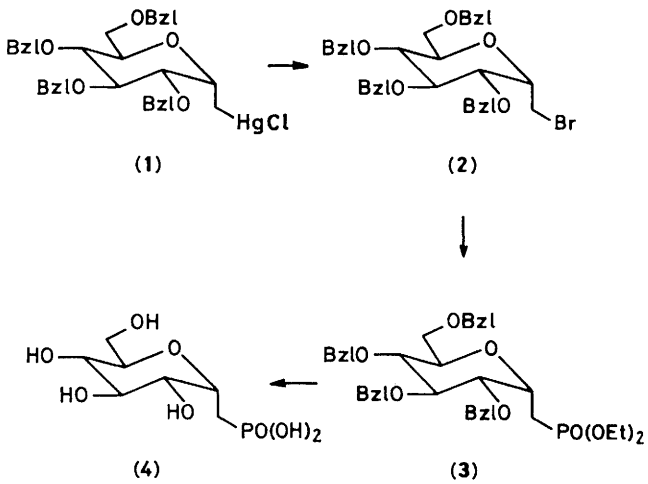
The synthesis of 2,6-anhydro-1-deoxy-L-*glycero*-D-*gluco*-heptulopyranose-1-phosphonic acid, the phosphono-analogue of α-D-glucose 1-phosphate, in which the substitution of a methylene group for an oxygen occurs at the anomeric centre of the sugar, is reported.

Considerable interest has arisen in recent years in phosphonic acid analogues of naturally occurring phosphates because of their ability to regulate or perturb metabolism.[1–3] Owing to the importance of α-D-pyranosyl l-phosphates in the metabolism of carbohydrates, the synthesis of their phosphono-analogues was desirable.

This paper describes the stereospecific synthesis, in 24% overall yield from the commercially available† 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose, of 2,6-anhydro-l-deoxy-L-*glycero*-D-*gluco*-heptulopyranose-l-phosphonic acid, the phosphono-analogue of α-D-glucose 1-phosphate, in which the substitution of a methylene group for an oxygen occurs at the anomeric centre of the sugar.

The classical syntheses of *C*-glucosides, based on the attack of nucleophiles on glucopyranosyl halides, afford β-*C*-glucosides,[4,5] or a mixture of α- and β-isomers.[5] We chose a different approach which allows the formation of stereochemically pure α-*C*-glucopyranosides.[6]

2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose was converted into the mercurio-derivative (**1**)[6] which was treated (6 h, in dichloromethane at room temperature and under an argon atmosphere) with 1 equiv. of bromine to yield the bromo-derivative (**2**) (isolated in 50% yield by silica gel flash chromatography). The bromo-derivative (**2**) was refluxed for 7 h under an argon atmosphere with triethyl phosphite affording diethyl 2,6-anhydro-l-deoxy-3,4,5,7-tetra-*O*-benzyl-L-*glycero*-D-*gluco*-heptulopyranose-l-phosphonate (**3**) (isolated in 60% yield after silica gel flash chromatography). On treatment of the phosphonic ester (**3**) with an excess of iodotrimethylsilane (0 °C, 30 min), the desired phosphono-analogue (**4**) of α-D-glucose 1-phosphate was obtained directly, after work-up, in quantitative yield. The phosphonic acid (**4**) was purified by cellulose chromatography and crystallized from ethanol.‡ The material exhibited a single spot (R_f 0.41 with n-propanol–ammonia–water 4:3:1 and R_f 0.35 with n-butanol–acetic acid–water 3:2:2) on cellulose t.l.c. visualized with molybdate spray reagent. The structure of the compound is in agreement with the n.m.r. data obtained: ^{31}P n.m.r. δ −20.31 p.p.m. [$CH_2PO(OH)_2$], ^{13}C n.m.r. (ref. dioxan) δ −38.12 p.p.m. [J(C,P) 129 Hz, $CH_2PO(OH)_2$], and ^{1}H n.m.r. δ 1.95 [m, J(H,P) 18 Hz, J(1,2) 7 Hz, J(1,1′) 2 Hz, $CH_2PO(OH)_2$], 3.5—4.3 (6H), and 4.38 [dd, J(1,2) 7 Hz, J(2,3) 3 Hz, 2-H]. The chemical shift of 2-H and its coupling constant with 3-H, compared with that of the corresponding axial proton in the β-isomer[7] [δ 3.49, J(2,3) 9 Hz], indicates that 2-H is equatorial; this confirms the α-orientation of the methylenephosphonic group and indicates that in H_2O the preferred conformation of (**4**) is $^4C_1$.



To our knowledge this is the first stereospecific synthesis of a phosphonic acid isosteric with a carbohydrate phosphate in

† Sigma Chemical Company, Saint Louis, Missouri.

‡ This crystalline hydroscopic material shows satisfactory elemental analysis for the monohydrate monoammonium salt.

which a methylene group takes the place of an oxygen at the anomeric centre of the sugar.

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