Crystalline Pseudo-α-D-glucopyranose

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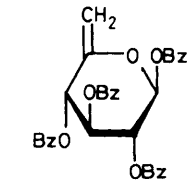
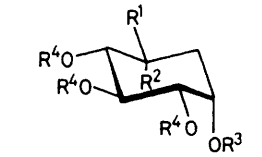
Crystalline pseudo-α-D-glucopyranose, a compound of potential biochemical interest, has been obtained for the first time from a 6-deoxyhex-5-enopyranose derivative as starting material.

Since 'pseudo-sugar' was coined to describe monosaccharide analogues having a methylene group instead of the ring oxygen atom,[1] considerable attention has been given to these compounds, notably by S. Ogawa and his colleagues.[2] While recent work has reported pseudo-pentofuranoses and derived 'nucleosides,'[3] pseudo-ketoses,[4] and pseudo-2-amino-2-deoxysugars,[5] the main attention to date has been given to the pseudo-aldohexopyranoses. Initial synthetic studies were based on cyclohexene derivatives obtained as products of the Diels–Alder reaction, and they afforded racemic compounds, but recent work has concentrated on providing enantiomerically pure materials following the finding of pseudo-nucleosides,[3] pseudo-α-D-galactopyranose,[6] and related compounds, for example validamine, valienamine, and validatol,[7] in natural products, and the recognition of the potential value of carbocyclic compounds of this category in studies of specific enzymic inhibition.[7]

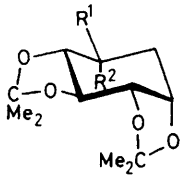
Our interest in the enantiomerically pure deoxyinososе derivatives, readily obtainable from 6-deoxyhex-5-enopyranosyl compounds,[8] has led us to a synthesis of pseudo-α-D-glucopyranose which has particular potential for biochemical studies; the racemate[9] has already been shown to inhibit glucokinase activity and glucose-stimulated insulin release.[2] The D-enantiomer was first reported in 1984 as a syrup with $[\alpha]_D$ +30° (MeOH),[10] but very recent reports record +67° (MeOH; synthesis from a resolved cyclohexane derivative[2])



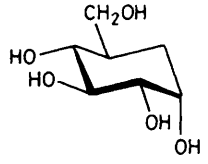
(1)



	R^1	R^2	R^3	R^4
(2)	—O—		H	Bz
(3)	S⌒S		H	Bz
(4)	S⌒S		H	H



	R^1	R^2
(5)	S⌒S	
(6)	—O—	
(7)	$—CH_2—$	
(8)	H	CH_2OH
(9)	CH_2OH	H



(10)

Bz = benzoyl

and +70° (water; synthesis by ring closure of a D-glucose-based phosphonate).[11] The present studies have produced a crystalline product with m.p. 151—152 °C and $[\alpha]_D$ +68.4° (MeOH) and offer a relatively simple and unambiguous route.

The starting deoxyinososе (**2**), prepared from 1,2,3,4-tetra-*O*-benzoyl-6-deoxy-β-D-*xylo*-hex-5-enopyranose (**1**)[12] by treatment with mercury(II) acetate in aqueous acetone,[8] was converted into the di-*O*-isopropylidene analogue (**6**) by way of the dithiolane triester (**3**), the tetraol (**4**), and its diacetal (**5**) in 78% yield. Removal of the thioacetal group was effected almost quantitatively by use of *N*-bromosuccinimide in aqueous acetonitrile in the presence of cadmium carbonate, and the ketone (**6**), on reaction with dibromomethane–zinc in dry tetrahydrofuran which had previously been treated by slow addition of titanium tetrachloride,[13] gave the alkene (**7**) in 95% yield. Hydroboration afforded crystalline di-*O*-isopropylidene-pseudo-β-L-idopyranose (**8**) in 81% yield together with small amounts (4% isolated) of the α-D-glucose isomer (**9**), but this desired thermodynamically preferred minor product was obtainable from the major (36% isolated crystalline) by oxidation with pyridinium dichromate in refluxing dichloromethane–dimethylformamide to give the corresponding aldehyde which was isomerised by treatment in dry methanol with solid potassium carbonate (polarimetric monitoring) and the product was reduced with sodium borohydride. Hydrolysis of the diacetal (**9**) was effected using hydrogen chloride in methanol and gave pseudo-α-D-glucopyranose in 96% yield (**10**).

^{1}H N.m.r. coupling analysis at 200 MHz (carbohydrate atom numbering, the ring methylene group taken as C-7) confirmed the structure of the compound: $J_{1,2}$ 3.1, $J_{1,7a}$ 2.3, $J_{1,7e}$ 4.1(±0.5), $J_{2,3}$ 9.8, $J_{3,4}$ 8.9, $J_{4,5}$ 10.4, $J_{5,6'}$ 5.2, $J_{5,6'}$ 3.4, $J_{5,7a}$ 13.8, $J_{5,7e}$ 4.1, $J_{6,6'}$ 11.3, $J_{7a,7e}$ 15.2 Hz.

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