Synthetic Methods for the Preparation of D- and L-Pseudo-Sugars from D-Glucose

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Starting from D-glucose and using the Ferrier rearrangement to obtain the cyclohexanone (1), a convenient synthesis of crystalline pseudo-α-D-glucopyranose (15), its congeners (16) and (17), as well as their partially protected derivatives has been carried out.

The term 'pseudo-sugar' is used to describe a class of compounds, structurally analogous to natural and synthetic carbohydrates in which the ring oxygen has been replaced by a methylene group.[1] By virtue of their structure, many of these substances are endowed with an interesting range of biological activity in the areas of antibiotic,[2,3] antiviral and anticancer therapy,[4] sweeteners,[5] enzyme inhibitors,[6] etc.

The discovery of a variety of pseudo-sugar-containing substances in the last ten years has resulted in a renaissance of interest in their chemical synthesis. Recent contributions have

focussed on approaches leading to enantiomerically pure carbocyclic analogues of hexapyranosides.[7—9]

Our own interest in the chemical synthesis of pseudo-sugar-containing natural products and their congeners, including polyphosphoinositides (second messengers)[10] has led to the preparation[11] of 2,3,4-tribenzyloxy-5-hydroxy-cyclohexanone (1). From the outset, we envisioned, at least in principle, that deoxyinosose (1) would lend itself to the synthesis of cyclitols and branched-chain cyclitols (pseudo-sugars).

Here we describe our studies on the synthesis of derivatives of pseudo-hexopyranosides (15), (16), and (17) and also of hydroxymethyl-cyclohexene (10). The latter is a useful chiral building block and is amenable to the preparation of optically pure diastereoisomers of D- and L-pseudo-sugars with a wide range of structures.

The synthesis of some molecules, identical or related to pseudo-hexopyranosides were reported, has recently been disclosed using completely different synthetic strategies.[7—9]

Both approaches disclosed here involve a one carbon homologation of the key intermediate ketone (1) with the ylides methoxymethylenetriphenylphosphorane (2) and benzyloxymethylenetriphenylphosphorane (3) respectively. Since no corresponding studies have been performed on deoxyinosose (1), derived from D-glucose, it was not possible, *a priori*, to predict the overall outcome, efficiency, and stereoselectivity of the sequence proposed. This can be clearly attributed to the fact that the carbonyl group in (1) is flanked by several (protected) hydroxyl groups, which theoretically would be prone to β-elimination and to aromatisation.

Treatment of the ketone (1) with the Wittig reagent methoxymethylene-triphenylphosphorane (2) (4 equiv. in dimethoxyethane at 0 °C), followed by warming to 20 °C over 1 h gave the crystalline vinyl ether (6) (63%), m.p. 51—53 °C, $[\alpha]_D^{20}$ +19° (c 1.0, CH$_2$Cl$_2$), as a mixture of geometrical isomers.

With the enantiomerically pure exocyclic alkene in hand, we decided first to attempt its transformation into derivatives of carbocyclic hexopyranosides using a one-pot oxy-mercuration–sodium borohydride reduction.

Initial attempts to convert the vinyl ether (6) into a derivative of pseudo-sugars directly, using mercury (II) nitrate in acetonitrile–water, followed by sodium borohydride reduction, yielded exclusively the syrupy unsaturated alcohol (10) (85%), $[\alpha]_D^{25}$ +74° (c 1.71, CH$_2$Cl$_2$).

However, when the oxy-mercuration of (6) was repeated using mercury (II) acetate, a mixture of three products was obtained in 86% yield. These were isolated by silica gel chromatography.

The structures of the major α,β-unsaturated alcohol (10) (52%) and the minor two diastereoisomers: α-D-gluco-(11) (6.8%), $[\alpha]_D^{25}$ +43° (c 1.0, CHCl$_3$), and β-L-ido-(12) (27.2%), $[\alpha]_D^{25}$ +12° (c 0.66, CHCl$_3$) were rigorously established.†

While at first we were somewhat disappointed by this almost exclusive formation of (10) by β-elimination, from the mercurial intermediate (9), we recognised quickly that this event would permit access to the different pseudo-sugars by simple chemical manipulation.

Hydroboration of (10) with diborane in tetrahydrofuran followed by oxidative work-up of the resulting organoborane afforded a readily separable mixture of two diastereoisomeric triols (78%) with the α-D-gluco-(13) (46%), $[\alpha]_D^{25}$ +14° (c 1.5, CH$_2$Cl$_2$) and β-L-altro-(14) (54%), $[\alpha]_D^{25}$ +27° (c 3, MeCOOC$_2$H$_5$) configurations.

Hydrogenolysis of the benzyl protecting groups of α-D-

(2) = Ph$_3$–P=CH–OMe
(3) = Ph$_3$–P=CH–OCH$_2$Ph
(4) = Ph$_3$–P=CH$_2$
R = CH$_2$Ph
X = OAc, NO$_3$
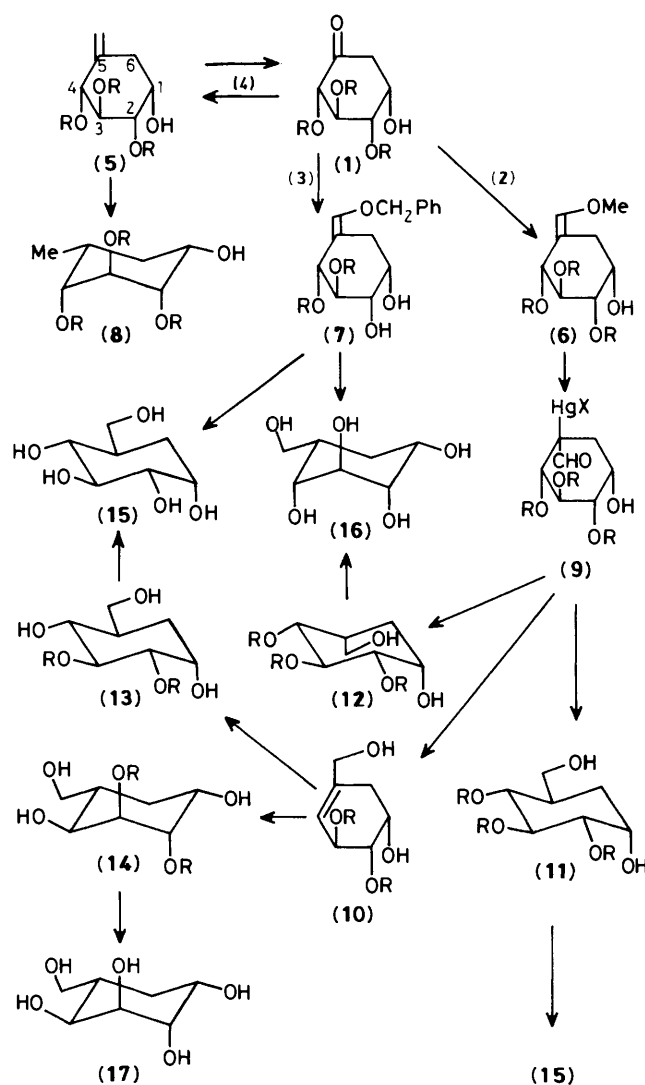
Scheme 1

gluco-(11), α-D-gluco-(13), β-L-ido-(12), and β-L-altro-(14) pseudo-hexopyranosides in the presence of 10% palladium on charcoal afforded the parent sugars as the exclusive products (85%) with the α-D-gluco-(15), m.p. 150—152 $[\alpha]_D$ +65° (c 0.8, MeOH), (exceedingly hygroscopic), the β-L-ido-(16), $[\alpha]_D^{25}$ +7° (c 1.52, MeOH), the β-L-altro-(17), $[\alpha]_D$ −38° (c 1.52, MeOH) configurations, uneventfully.‡

In the hope of circumventing the problem of β-elimination experienced in the first approach and to increase the efficiency of the transformation of the starting cyclohexanone (1) into the biologically more important α-D-gluco diastereoisomer

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† All new compounds were characterised by ¹H and ¹³C n.m.r., i.r., mass spectral and microanalytical data.

‡ Literature precedents are for 2,3,4-tri-*O*-benzyl-pseudo-α-D-glucopyranose (11): $[\alpha_D]^{20}$ +51.7° (CHCl$_3$);[7b] 2,3,4-tri-*O*-benzyl-pseudo-β-L-idopyranose (12): $[\alpha]_D$ + 7.4° (CHCl$_3$);[7b] pseudo-α-D-glucopyranose (15): $[\alpha]_D$ +30° (MeOH),[8a] $[\alpha]_D^{21}$ +67° (MeOH);[8b] $[\alpha]_D^{20}$ +70° (H$_2$O);[7b] $[\alpha]_D$ +68.4° (MeOH);[7a] pseudo-β-L-idopyranose (16): $[\alpha]_D^{20}$ +8.5° (H$_2$O);[7b] pseudo-β-L-altropyranose (17): $[\alpha]_D^{25}$ −49.5 (MeOH).[8a]

(15), we then turned to a second Wittig olefination procedure using benzyloxymethylenetriphenylphosphorane (3).

Benzyloxymethylenetriphenylphosphonium chloride, the required reagent for the preparation of the ylide (3) was produced by refluxing benzylchloromethyl ether with triphenylphosphine in anhydrous toluene over 24 h giving a white solid in 90% yield, m.p. 162 °C.

Reaction of ketone (1) in toluene with an excess of an orange solution of Wittig ylide (3) (prepared from 4 equiv. of benzyloxymethylenetriphenylphosphonium chloride and 4 equiv. of Bu^{n}Li in toluene) at −35 °C under an argon atmosphere over 24 h afforded the syrupy mixture of benzyloxy-vinyl ether (7) in 55% yield, $[\alpha]_D$ −13° (c 1.1, $CHCl_3$). The ratio of the (Z) and (E) alkenes was not determined. The geometry of (7) was not crucial for our overall plan.

Surprisingly, when we carried out the catalytic hydrogenolysis of the benzyloxy vinyl ether (7) in methanol, in the presence of 10% palladium catalyst, a mixture of two diastereoisomers was isolated in 75% yield, in a ratio of 65:35. The major product was identified as the crystalline pseudo-α-D-glucopyranose (15) and the minor component was shown to be pseudo-β-L-idopyranose (16).

The outcome of the catalytic hydrogenolysis of (7) contrasts sharply with the catalytic reduction of the exocyclic alkene (5) and methyl 6-deoxy-α-D-xylohex-5-eno-pyranose. They afforded almost exclusively the corresponding 6-deoxy-β-L-pseudo-idopyranose[12] (8) and methyl 6-deoxy-β-L-idopyranose.[13]

Our work thus provides 5-C-methoxymethylene- and 5-C-benzyloxymethylene cyclohexane-polyols (6) and (7). Since these derivatives lack asymmetry at C-5, they are possible intermediates in chemical transformations to both D- and L-pseudo-hexopyranoses.

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