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a class of compounds, structurally analogous to natural and synthetic carbohydrates in which the ring oxygen has been replaced by a methylene group.[1] By virtue of their structure, many of these substances are endowed with an interesting range of biological activity in the areas of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_2Cl_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_2Cl_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.

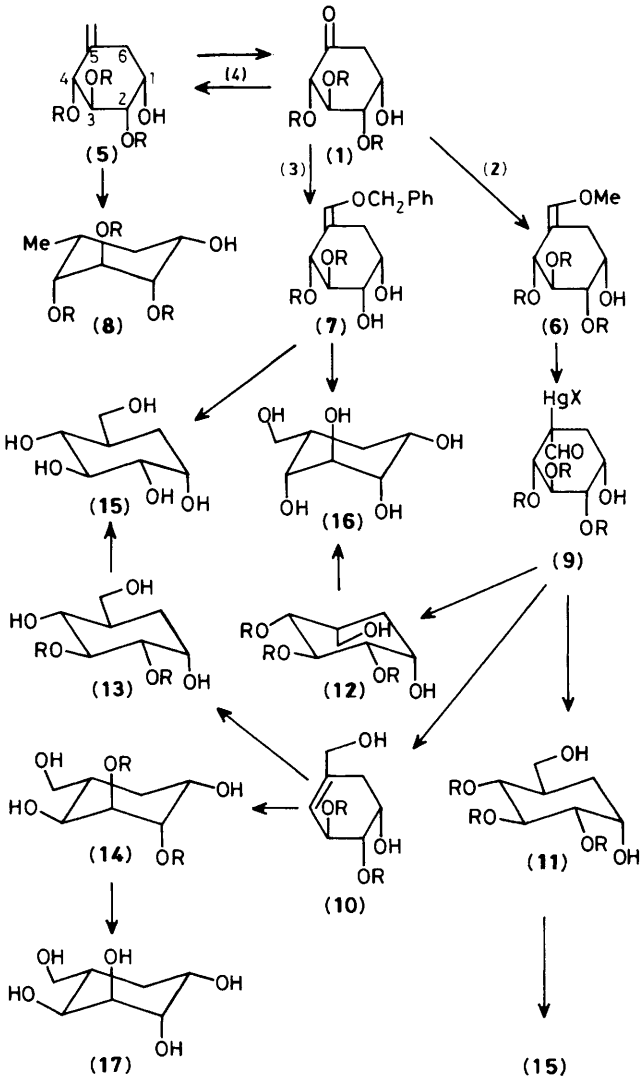
The structures of the major α,β-unsaturated alcohol (**10**) (52%) and the minor two diastereoisomers: α-D-gluco-(**11**) (6.8%), $[\alpha]_D^{25}$ +43° (*c* 1.0, $CHCl_3$), and β-L-ido-(**12**) (27.2%), $[\alpha]_D^{25}$ +12° (*c* 0.66, $CHCl_3$) were rigorously established.†

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_2Cl_2) and β-L-altro-(**14**) (54%), $[\alpha]_D^{25}$ +27° (*c* 3, $MeCOOC_2H_5$) configurations.

Hydrogenolysis of the benzyl protecting groups of α-D-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



(**2**) = Ph_3–P=CH–OMe
(**3**) = Ph_3–P=CH–OCH_2Ph
(**4**) = Ph_3–P=CH_2
R = CH_2Ph
X = OAc, NO_3

Scheme 1

† All new compounds were characterised by ^1H and ^{13}C 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_2O);[7b] $[\alpha]_D$ +68.4° (MeOH);[7a] pseudo-β-L-idopyranose (**16**): $[\alpha]_D^{20}$ +8.5° (H_2O);[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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