Facile Syntheses of Pseudo-α-D-glucopyranose and Pseudo-α-D-mannopyranose

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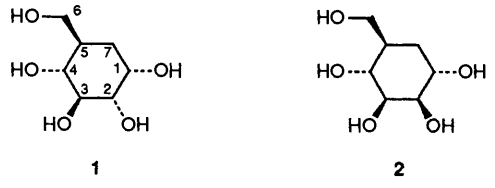
Pseudo-α-D-glucopyranose **1** and pseudo-α-D-mannopyranose **2** are obtained *via* a stereoselective *cis*- and *trans*-hydroxylation respectively of the alkene **8**, which is readily derived from (−)-quinic acid.

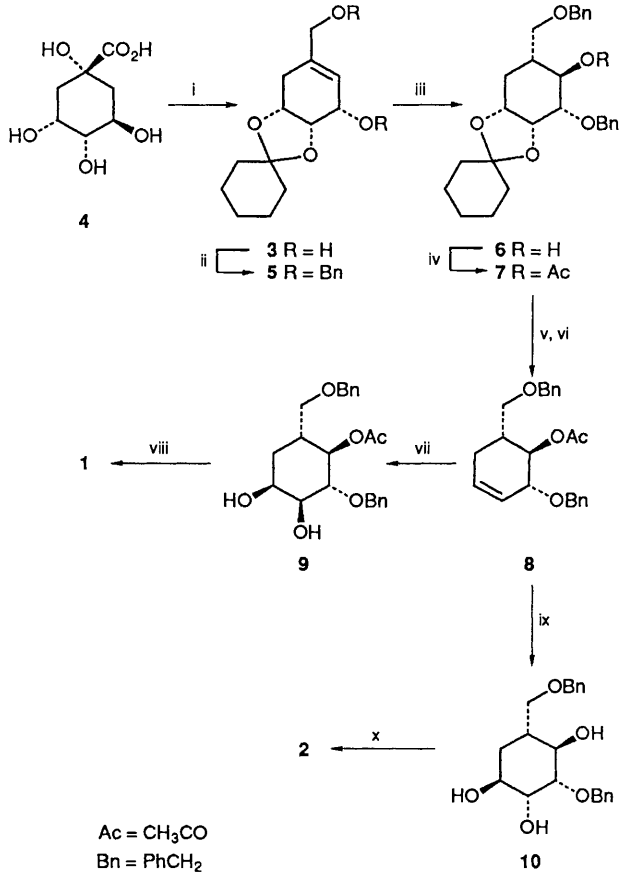
The potential use of pseudo-sugars[1] in biochemical studies of specific enzyme inhibition[2,3] and as non-nutritive sweeteners[4] has led to their recent syntheses in enantiomerically pure forms.[3–6] Optically active and crystalline pseudo-α-D-glucopyranose **1** has been synthesised from D-glucose in 14 stages;[5] the racemate[7] has been shown to inhibit glucokinase activity and glucose-stimulated insulin release.[2] However, the synthesis of enantiomerically pure pseudo-α-D-mannopyranose **2** has not been reported. Recently, we described the enantiospecific syntheses of 2-crotonyloxymethyl-(4*R*,5*R*,6*R*)-4,5,6-trihydroxycyclohex-2-enone (COTC),[8] pseudo-β-D-mannopyranose and pseudo-β-D-fructopyranose[9] from quinic acid; this paper further demonstrates the flexibility of this approach by short, facile and stereocontrolled syntheses of **1** and **2**.

The route to pseudo-α-D-glucopyranose **1** and pseudo-α-D-mannopyranose **2** is shown in Scheme 1. The known diol **3**,[9] readily available from quinic acid **4** in four steps, was protected as the benzyl ether **5**,† $[\alpha]_D$ + 5.5° (*c* 0.29, CH_2Cl_2). The double bond in **5** was subjected to a stereocontrolled hydroboration–oxidation sequence at the less hindered β-face, forming exclusively the cyclohexane derivative **6** which was esterified to the acetate **7**, m.p. 78–79 °C; $[\alpha]_D$ + 3.1° (*c* 0.26, CH_2Cl_2). The stereochemistry of the 4-OAc group was evident from the ^1H NMR spectrum ($J_{4,3} \approx J_{4,5}$ 9.0 Hz). Acidic removal of the acetal in **7** followed by Corey–Winter deoxygenation[10] of the resulting diol gave the alkene **8** m.p. 57–58 °C; $[\alpha]_D$ − 78.4° (*c* 0.25, CH_2Cl_2). A stereocontrolled *cis*-hydroxylation of the double bond in **8** occurred smoothly at the less hindered β-face, providing exclusively **9**, m.p. 106–107 °C; $[\alpha]_D$ + 82.4° (*c* 0.33, CH_2Cl_2). Deprotection then gave crystalline pseudo-α-D-glucopyranose **1**, m.p. 146–147 °C; $[\alpha]_D$ + 63.0° (*c* 0.6, H_2O) {lit.[5] m.p. 151–152°; $[\alpha]_D$ + 68.4° (MeOH)}.

trans-Hydroxylation[11] of the double bond in **8** with HCO_2H–H_2O_2 proceeded *via* a *trans*-diaxial opening[12] of an intermediate epoxide, giving the corresponding hydroxy formate which was hydrolysed to the triol **10**, m.p. 123–124 °C; $[\alpha]_D$ + 10.5° (*c* 0.2, CH_2Cl_2), as the sole product.



† All new compounds gave satisfactory analytical and spectral data. All optical rotations were measured at ambient temperature.



Scheme 1 *Reagents and conditions*: i, see ref. 9; ii, NaH, benzyl bromide, Bu^n_4NI, tetrahydrofuran (THF) (72%); iii, 9-borabicyclo[3.3.1]nonane, THF, room temp., then NaOH (3 mol dm^{-3}), H_2O_2 (94%); iv, acetic anhydride, pyridine (py), *N*,*N*-dimethylaminopyridine, CH_2Cl_2 (97%); v, CF_3CO_2H, CH_2Cl_2 (97%); vi, 1,1′-thiocarbonyldiimidazole, toluene, reflux, then $(OMe)_3P$, reflux (85%); vii, OsO_4, trimethylamine-*N*-oxide, py, water, Bu^tOH (90%); viii, NaOMe, MeOH, then Rh/C, H_2, EtOH (81%); ix, HCO_2H, H_2O_2, reflux, then NaOH (5 mol dm^{-3}), THF, reflux (45%); x, $Pd(OH)_2$, H_2, EtOH (100%)

Hydrogenolysis of this material afforded for the first time pseudo-α-D-mannopyranose **2**, $[\alpha]_D$ + 1.9° (*c* 1.0, MeOH). The structure of **2** was confirmed by ^{1}H NMR analysis in D_2O at 300 MHz: δ 1.60–1.72 (m, 2H, 7-H), 1.74–1.84 (m, 1H, 5-H), 3.57 (t, 1H, $J_{4,3} \approx J_{4,5}$ 9.8 Hz, 4-H), 3.61(dd, 1H, $J_{6',5}$ 5.5, $J_{6',6}$ 11.3 Hz, 6'-H), 3.67 (dd, 1H, $J_{3,2}$ 3.4 Hz, 3-H), 3.69 (dd, 1H, $J_{6,5}$ 3.8 Hz, 6-H), 3.90 (bt, 1H, $J_{2,1}$ 3.2 Hz, 2-H), 3.98 (q, 1H, $J_{1,7a} \approx J_{1,7e}$ 3.2 Hz, 1-H).

It is noteworthy that none of the original chiral centres in quinic acid are retained in the target molecules. This feature indicates the degree of steric control which can be achieved at each transformation.

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