A New Approach to Pseudo-sugars from (−)-Quinic Acid: Facile Syntheses of Pseudo-β-D-mannopyranose and Pseudo-β-D-fructopyranose

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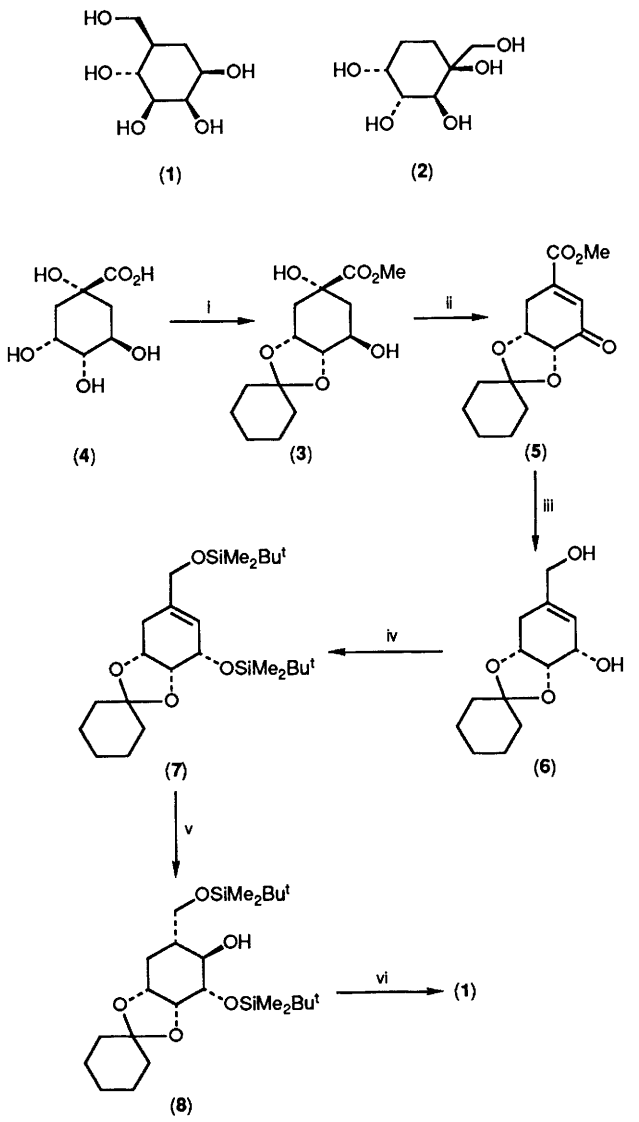
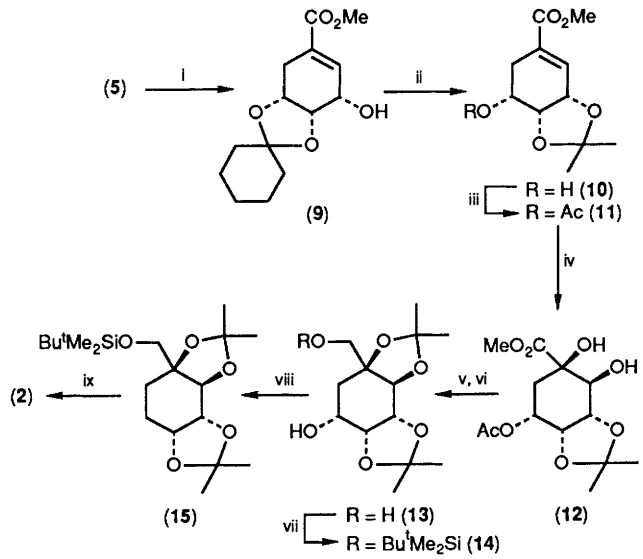
(−)-Quinic acid has been converted into pseudo-β-D-mannopyranose (**1**) and pseudo-β-D-fructopyranose (**2**) in seven and twelve steps respectively.

Carbocyclic analogues of monosaccharides, in which the ring oxygen is replaced by a methylene group, have been coined as 'pseudo-sugars'.[1] The discovery of pseudo-sugars in natural products[2] and their potential in biochemical studies of specific enzyme inhibition[3,4] have demanded considerable efforts towards their syntheses. There is also great interest in developing pseudo-sugars as potential artificial sweeteners, particularly pseudo-β-D-fructopyranose.[5] Initial synthetic studies[2] only yielded racemic material, but recently, reports on syntheses of enantiomerically pure pseudo-sugars have surfaced.[4—7] Optically active pseudo-β-D-mannopyranose (**1**) has been synthesised from quebrachitol in 20 stages[7] and pseudo-β-D-fructopyranose (**2**) from a chemically resolved Diels–Alder adduct of furan and acrylic acid in 15 steps.[5] Our interest in non-nutritive sweeteners has stimulated the search for sucrose mimics. Recently, we described an enantiospecific synthesis of an antitumour agent 2-crotonyloxymethyl-(4*R*,5*R*,6*R*)-4,5,6-trihydroxycyclohex-2-enone (COTC) from quinic acid[8] and this paper further demonstrates the synthetic versatility of quinic acid by short, facile, and stereocontrolled syntheses of (**1**) and (**2**).

The route to pseudo-β-D-mannopyranose (**1**) is shown in Scheme 1. The known hydroxy-ester (**3**),[8] readily available from quinic acid (**4**) in two steps, was oxidised with concomitant β-elimination using a modified protocol to give enone (**5**).[8] The ester and the enone carbonyl groups in (**5**) were reduced with di-isobutylaluminium hydride (DIBAL-H) in tetrahydrofuran (THF) to form the diol (**6**),† m.p. 67—69 °C; $[\alpha]_D$ +3.7° (*c* 0.76, CH_2Cl_2), which was protected as the silyl



Scheme 1. *Reagents and conditions*: i, see ref. 8; ii, pyridinium chlorochromate, 3 Å molecular sieves, pyridine, CH_2Cl_2 (90%); iii, DIBAL-H in toluene, toluene, 0 °C (90%); iv, $Me_2(Bu^t)SiCl$, imidazole, *N*,*N*-dimethylaminopyridine (DMAP), CH_2Cl_2 (100%); v, 9-borabicyclo[3.3.1]nonane (9-BBN), THF, room temp., then 3 M NaOH, H_2O_2 (86%); vi, 50% aq. CF_3COOH (aq. TFA), room temp., 4 h (100%).



Scheme 2. *Reagents and conditions*: i, $NaBH_4$, MeOH, 0 °C (82%); ii, acetone, toluene-*p*-sulphonic acid (88%); iii, Ac_2O, pyridine, DMAP, CH_2Cl_2 (100%); iv, OsO_4, trimethylamine *N*-oxide, pyridine, H_2O, Bu^tOH (90%); v, 2-methoxypropene, (±)-camphor-10-sulphonic acid, CH_2Cl_2 (70%); vi, DIBAL-H in THF, THF, 0 °C (79%); vii, $Me_2(Bu^t)SiCl$, imidazole, DMAP, CH_2Cl_2 (91%); viii, phenyl chlorothioformate, pyridine, DMAP, CH_2Cl_2, then Bu^n_3SnH, azoisobutyronitrile (AIBN), toluene (82%); ix, 50% aq. TFA, room temp., 4 h (65%).

† All new compounds gave satisfactory analytical and spectral data.

ether (**7**), $[\alpha]_D$ +2.9° (*c* 2.2, CH_2Cl_2). The double bond in (**7**) was subjected to a stereocontrolled hydroboration–oxidation sequence at the less hindered β-face, furnishing exclusively the cyclohexane derivative (**8**), $[\alpha]_D$ +12.4° (*c* 0.7, CH_2Cl_2). Hydrolysis of this material furnished cleanly pseudo-β-D-mannopyranose (**1**), m.p. 223 °C; $[\alpha]_D$ +10.4° (*c* 0.24, H_2O) {lit.[7] m.p. 217 °C; $[\alpha]_D$ +11.9° (*c* 0.65, MeOH)}.

On the other hand, the first enantiospecific synthesis of pseudo-β-D-fructopyranose (**2**) is illustrated in Scheme 2. The aforementioned enone (**5**) was reduced from the less hindered β-face to the alcohol (**9**).[8] Thermodynamically controlled isopropylidenation of (**9**) gave the more stable acetonide (**10**) which was esterified to the acetate (**11**), m.p. 74.5—75.5 °C; $[\alpha]_D$ −56.3° (*c* 0.7, CH_2Cl_2). A stereocontrolled hydroxylation of the double bond in (**11**) proceeded smoothly at the less hindered β-face, providing the desired β-diol (**12**), m.p. 134—134.5 °C; $[\alpha]_D$ −43.2° (*c* 0.5, CH_2Cl_2), as the sole product. Acetonation of (**12**) followed by DIBAL-H reduction gave the diol (**13**), m.p. 114—115 °C; $[\alpha]_D$ +44.9° (*c* 0.5, CH_2Cl_2). The primary alcohol in (**13**) was selectively protected as the silyl ether (**14**), m.p. 56—57 °C; $[\alpha]_D$ +31.6° (*c* 2.3, CH_2Cl_2), which was deoxygenated[9]‡ to the blocked target molecule (**15**), $[\alpha]_D$ +3.5° (*c* 1.3, CH_2Cl_2). Hydrolysis then yielded pseudo-β-D-fructopyranose (**2**), m.p. 96—97 °C; $[\alpha]_D$ −53.0° (*c* 0.46, MeOH) {lit.[5] syrup; $[\alpha]_D$ −57° (*c* 1.2, MeOH)}.

The present approach to pseudo-sugars from quinic acid is flexible, thus providing opportunities for facile syntheses of not only other diastereoisomeric pseudo-aldopyranoses and pseudo-ketopyranoses but also highly oxygenated cyclohexanoid natural products.

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‡ Deoxygenation of the free secondary alcohol in (**10**) was unsuccessful.

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