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(-)-QUINIC ACID IN ORGANIC SYNTHESIS. 3. STEREOCONTROLLED SYNTHESES OF PSEUDO-α-D-GLUCOPYRANOSE AND PSEUDO-α-D-MANNOPYRANOSE.

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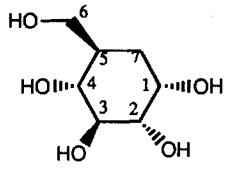
Abstract—The alkene (16), readily affordable from (-)-quinic acid, underwent a stereoselective *cis*- and *trans*-hydroxylation to give pseudo-α-D-glucopyranose (1) and pseudo-α-D-mannopyranose (2) respectively.

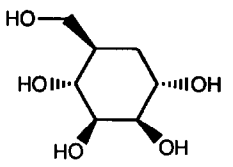
The potential use of pseudo-sugars[1,2] or carbocyclic analogues of monosaccharides in biochemical studies of specific enzyme inhibition[3,4] and as non-nutritive sweeteners[5] has demanded their recent syntheses in optically pure forms. The impressive work of Ogawa and his co-workers has demonstrated the use of a furan-Diels-Alder approach to pseudo-sugars, although mainly in racemic forms.[2,6] An elegant rearrangement was developed by Ferrier[7] and furnishes an efficient route to optically pure pseudo-sugars.[8] Other synthetic approaches to enantiomerically pure pseudo-sugars involve Wadsworth-Emmons-Horner alkenation,[9] Knoevenagel-Doebner condensation,[10] and free radical cyclisation,[4,11] all from carbohydrate-derived precursors.

Optically active and crystalline pseudo-α-D-glucopyranose (**1**) has been synthesised from D-glucose in 14 stages;[12] the racemate[13] has been shown to inhibit glucokinase activity and glucose-stimulated insulin release.[3] However, the synthesis of enantiomerically pure pseudo-α-D-mannopyranose (**2**) has not been reported, although that of its pentaacetate was documented by Tadano.[14] In our own quest for a general and efficient entry to optically pure pseudo-sugars, we have developed a new and facile approach using quinic acid as the homochiral starting material.[15,16] Quinic acid, being economical on a per chiral centre basis and possessing a cyclohexane carbon framework which allows subtle and extensive control of regio- and stereo-selective transformations, is probably the most ideal homochiral precursor for the fabrication of heavily oxygenated cyclohexanoid target molecules which contain many adjacent chiral centres and functional groups. We recently described enantiospecific syntheses of 2-crotonyloxymethyl-

(4*R*,5*R*,6*R*)-4,5,6-trihydroxycyclohex-2-enone (COTC),[17] pseudo-β-D-mannopyranose and pseudo-β-D-fructopyranose[15] from quinic acid and this paper further demonstrates the flexibility of this approach by short, facile, and stereocontrolled syntheses of (**1**) and (**2**).[16]

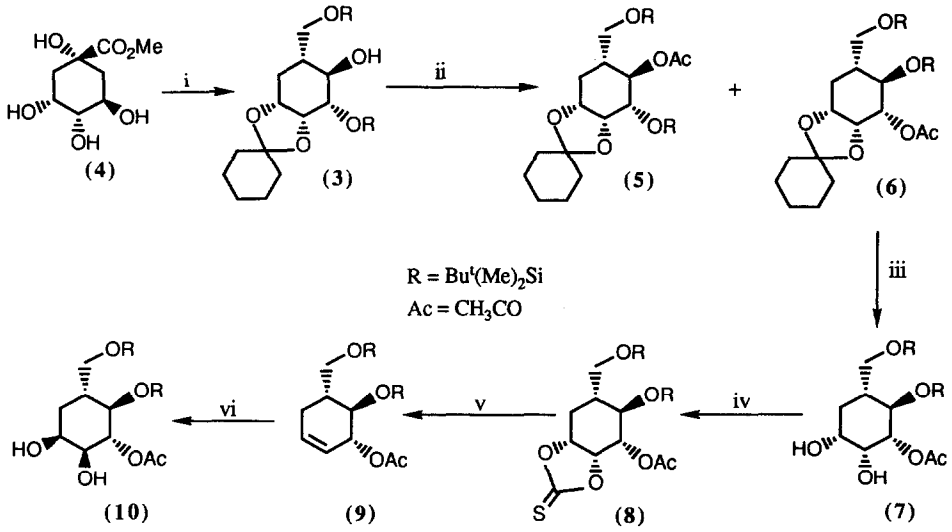


(**1**)



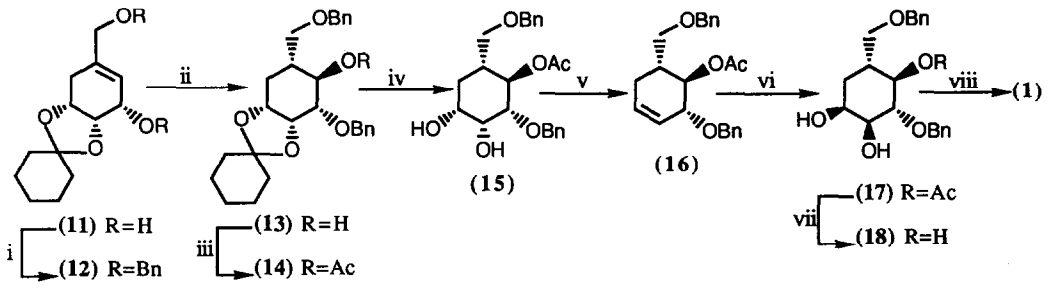
(**2**)

Our initial approach to pseudo-α-D-glucopyranose (**1**) is shown in Scheme 1. The known alcohol (**3**),[15] available from quinic acid (**4**) in six steps, was acetylated with acetic anhydride in pyridine/*N*,*N*-4-dimethylaminopyridine (DMAP)/CH_2Cl_2 to give a mixture of acetates (**5**) and (**6**) in a ratio of 1 : 2. This ratio changed to 1 : 4 when 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was used as the base, favouring compound (**6**) as the major product. It was apparent that the migration of the silyl blocking group took place under the basic conditions and the reason believed to be the release of the compression between the bulky cyclohexylidene group and the silyl group.[17] Selective hydrolysis of the cyclohexylidene acetal in (**6**) with trifluoroacetic acid (TFA) in CH_2Cl_2 gave the diol (**7**) in 85% yield. From the several protocols available for



Scheme 1. *Reagents:* i, six steps, see ref. 15; ii, Ac_2O, DBU, DMAP, CH_2Cl_2, (**5**):(**6**) = 1:4, (90%); iii, TFA, H_2O, CH_2Cl_2, (85%); iv, 1,1'-thiocarbonyldiimidazole, toluene, reflux; v, $(OMe)_3P$, reflux, (90%) from (**7**); vi, OsO_4, trimethylamine-*N*-oxide, pyridine, water, Bu^{t}OH, (65%).

the deoxygenation of the diol moiety in (**7**) to form the corresponding alkene, the Corey-Winter procedure was found to be most efficient. Thus treatment of the diol (**7**) with 1,1'-thiocarbonyldiimidazole in toluene at reflux gave the crystalline thiocarbonate (**8**) which, with trimethylphosphite, was converted into the alkene (**9**) in an overall yield of 90%. The ^{1}H n.m.r. spectrum of (**9**) is consistent with a half chair conformation of the ring and the two olefinic protons appeared at δ 5.46 and δ 5.80 respectively. Hydroxylation of (**9**) with OsO_4-trimethylamine-*N*-oxide/pyridine/H_2O/Bu^{t}OH system afforded the partially protected pseudo-glucose (**10**) in 65% yield. It is of interest to note that only one isomer was formed in this reaction and the stereoselectivity of the *syn*-addition of OsO_4 was controlled by the nearby α-face acetate group. At this stage it was clear that a suitable protecting group was required to avoid the silyl group migration. The ideal blocking group appeared to be the benzyl group which could be removed *via* hydrogenolysis so that the free pseudo-sugars could be easily obtained pure without chromatography. With this consideration in mind, we explored the following sequence of reactions (Scheme 2).

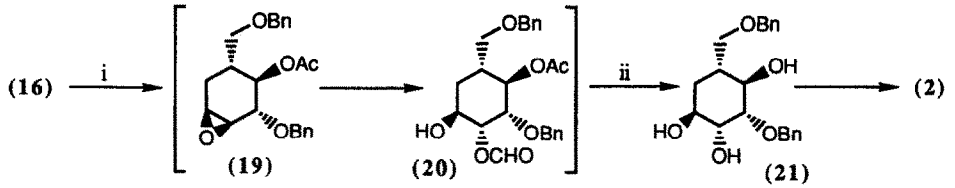


Scheme 2. *Reagents:* i, NaH, BnBr, (Bu^n)$_4$NI, THF, (72%); ii, 9-borabicyclo[3.3.1.]nonane (9-BBN), THF, room temp., then 3 M NaOH, H_2O_2, (94%); iii, Ac_2O, pyridine, DMAP, CH_2Cl_2, (97%); iv, CF_3COOH, CH_2Cl_2 , (96%); v, 1,1'-thiocarbonyldiimidazole, toluene, reflux, then $(OMe)_3P$, reflux, (85%) from (**15**); vi, OsO_4, trimethylamine-*N*-oxide, pyridine, water, Bu^{t}OH, (90%); vii, NaOMe, MeOH, (88%); viii, rhodium-on-charcaol, H_2, EtOH, (90%).

Deprotonation of the known diol (**11**)[15] with NaH at 0 °C in tetrahydrofuran (THF) followed by the addition of an excess of benzyl bromide (BnBr) afforded the benzyl ether (**12**) in 72% yield. A stereocontrolled hydroboration-oxidation sequence at the less hindered β-face of the carbon-carbon double bond in (**12**) gave exclusively a 94% yield of the alcohol (**13**) which was esterified to the acetate (**14**) in 97% yield. The stereochemistry of the 4-OAc group was evident from the ^{1}H NMR spectrum ($J_{4,3} \approx J_{4,5}$ 9.0 Hz). Acidic removal of the acetal in (**14**) with TFA afforded the diol (**15**) which was subjected to the Corey-Winter deoxygenation[18] sequence to give the alkene (**16**) in an overall yield of 82%

from (**14**). A stereocontrolled *cis*-hydroxylation of the double bond in (**16**) proceeded smoothly at the less hindered β-face, providing exclusively the desired β-diol (**17**). Deacetylation of (**17**) with NaOMe in MeOH gave the triol (**18**) which on hydrogenolysis led cleanly to the crystalline pseudo-α-D-glucopyranose (**1**), m.p. 146—147 °C; $[\alpha]_D$ + 63.0° (*c* 0.6, H_2O) {lit.[12] m.p. 151—152 °C; $[\alpha]_D$ + 68.4° (MeOH)}. Thus pseudo-α-D-glucopyranose (**1**) was synthesised from (-)-quinic acid in 12 steps with an overall yield of 17%.

On the other hand, *trans*-hydroxylation[19] of the double bond in (**16**) with HCO_2H-H_2O_2 preceeded *via* a *trans*-diaxial opening[20] of an intermediate epoxide (**19**), giving the corresponding hydroxy formate (**20**) which was hydrolysed to the triol (**21**) as the sole product. A small coupling constant of 2.8 Hz between 1-H,2-H; 2-H,3-H; 1-H,7-H_a and 1-H,7-H_e indicated clearly that 3-H and 4-H are in the equatorial positions and provided support for the formation of a *trans*-diaxial diol. Hydrogenolysis of this material (**21**) afforded for the first time pseudo-α-D-mannopyranose (**2**) as a colourless oil in quantitative yield, $[\alpha]_D$ + 1.9° (*c* 1.0, MeOH). Peracetylation of (**2**) gave its pentaacetate (**22**) in 67% yield. The physical constants and spectroscopic data of compound (**22**), m.p. 79—80 °C; $[\alpha]_D$ + 27.1° (*c* 4.0, $CHCl_3$), were in close agreement with those reported by the Tadano and Suami's group {lit.[14] m.p. 80—81 °C; $[\alpha]_D$ + 27.8° ($CHCl_3$)}. In conclusion, pseudo-α-mannopyranose was obtained from (-)-quinic acid in 11 steps with an overall yield of 13%.



Scheme 3. *Reagents:* i, HCO_2H, H_2O_2, reflux; ii, 5 M NaOH, THF, reflux, (45%) from (**16**); ii, $Pd(OH)_2$, H_2, EtOH (100%).

Experimental

M.p.s were recorded on a Kofler block. ^1H N.m.r. spectra were recorded on a Varian SC300 spectrometer at 300 MHz using deuteriochloroform as solvent unless otherwise stated. Infrared (i.r.) spectra were recorded on a Perkin-Elmer 1710 Fourier Transform Spectrophotometer. Mass spectra were recorded on a Kratos MS25 instrument. Ultraviolet (u.v.) spectra were recorded on a Shimadzu UV-260 UV/VIS Spectrophotometer as solutions in ethanol. Optical rotations were measured on an AA-100 polarimeter using CH_2Cl_2 as solvent unless otherwise stated. T.l.c. was performed on glass plates precoated with Merck silica 60F_{254}, and compounds were visualised with a spray of 5% w/v dodeca-molybdophosphoric acid in ethanol and subsequent heating. Dry and flash chromatography were performed on silica gel. THF was distilled from sodium and benzophenone under dry nitrogen. CH_2Cl_2 was distilled from P_2O_5 under dry nitrogen. Pyridine was distilled

from barium oxide. Petroleum ether (b.p. 40—60 °C) was used as solvent unless otherwise stated.

1. *(1R,2R,3S,4R,5R)-4-O-Acetyl-3-O-tert-butyldimethylsilyl-5-tert-butyldimethylsiloxymethyl-1,2-O-cyclohexylidene-cyclohexan-1,2,3,4-tetraol* **(5)** *and (1R,2R,3S,4R,5R)-3-O-Acetyl-4-O-tert-butyldimethylsilyl-5-tert- butyldimethylsiloxymethyl-1,2-O-cyclohexylidene-cyclohexan-1,2,3,4-tetraol* **(6)**

To a solution of the alcohol **(3)**[15] (0.2 g, 0.40 mmol), pyridine (0.13 ml, 1.6 mmol) and a catalytic amount of DMAP in dry CH_2Cl_2-DBU (3 ml:0.5 ml) was added acetic anhydride (0.11 ml, 1.2 mmol) at room temperature. The reaction mixture was stirred for 24 h and poured into saturated aqueous NH_4Cl (2 ml). The aqueous phase was extracted with CH_2Cl_2 (4 X 5 ml). The combined extracts were washed with brine (2 X 2 ml), dried ($MgSO_4$) and filtered. Concentration of the filtrate followed by purification through flash column chromatography [petroleum ether-diethyl ether (10:1 v/v)] provided the *title compounds* **(5)** and **(6)** in a ratio of 1:4 (0.21 g, 90%).

Compound **(5)**: a colourless oil, R_F 0.48 [petroleum ether-diethyl ether (10:1 v/v)]; $[\alpha]_D$ +4.7° (*c* 1.72); $\nu_{max.}$ 1746 cm^{-1} (C=O); δ 0.05 (6H, b), 0.08 (3H, s), 0.12 (3H, s), 0.88 (9H, b), 0.90 (9H, b), 1.2-1.9 (13H, m), 2.05 (3H, s), 3.42 (1H, dd, *J* 10 and 6.5 Hz), 3.55 (1H, dd, *J* 10 and 3 Hz), 3.85 (1H, dd, *J* 8.5 and 4.5 Hz), 4.17 (1H, m), 4.24 (1H, t, *J* 4.5 Hz), 5.12 (1H, t, *J* 8.5 Hz); *m/z* (CI, NH_3) 528 (93.0%, M^+) (Found: M^+ 528.3298. $C_{27}H_{52}O_6Si_2$ requires 528.3302).

Compound **(6)**: colourless needles, m.p. 78–79 °C (from petroleum ether-diethyl ether); R_F 0.34 [petroleum ether-diethyl ether (9:1 v/v)]; $[\alpha]_D$ −9.7° (*c* 0.62); $\nu_{max.}$ 1742 cm^{-1} (C=O); δ 0.04 (6H, b), 0.09 (3H, s), 0.11 (3H, s), 0.86 (9H, b), 0.89 (9H, b), 1.3-1.8 (12H, m), 1.92 (1H, m), 2.13 (3H, s), 3.63 (2H, m), 3.89 (1H, t, *J* 8 Hz), 4.23 (1H, ddd, *J* 10, 6 and 5 Hz), 4.43 (1H, t, *J* 5 Hz), 4.88 (1H, dd, *J* 8 and 5 Hz); *m/z* (EI) 528 (2.9%, M^+) (Found: C, 61.1; H, 9.9. $C_{27}H_{52}O_6Si_2$ requires C, 61.4; H, 9.9%).

2. *(1R,2R,3S,4R,5R)-3-O-Acetyl-4-O-tert-butyldimethylsilyl-5-tert-butyldimethylsiloxymethyl-cyclohexan-1,2,3,4-tetraol* **(7)**

To a solution of the acetal **(6)** (0.7 g) in CH_2Cl_2 (12 ml) was added CF_3COOH (2 drops) and H_2O (1 drop). The reaction mixture was stirred at room temperature for 24 h and poured into a aqueous solution of $NaHCO_3$ (5%, w/v, 2 ml). The aqueous phase was extracted with CH_2Cl_2 (4 X 3 ml). The combined extracts were washed with brine (2 X 0.5 ml), dried ($MgSO_4$) and filtered. Concentration of the filtrate followed by purification through flash column chromatography [petroleum ether-diethyl ether (1:1 v/v)] provided the *diol* **(7)** (0.51 g, 85%) as a colourless oil, R_F 0.41 [petroleum ether-diethyl ether (1:3 v/v)]; $[\alpha]_D$ −4.2° (*c* 3.12); $\nu_{max.}$ 3406 (OH) and 1739 cm^{-1} (C=O); δ 0.02 (3H, s), 0.03 (3H, s), 0.06 (3H, s), 0.08 (3H, s), 0.84 (9H, s), 0.89 (9H, s), 1.3-1.9 (3H, m), 2.12 (3H, s), 2.40-2.70 (2H, m), 3.58 (1H, dd, *J* 10 and 6 Hz), 3.69 (1H, dd, *J* 10 and 3 Hz), 3.77 (1H, m), 3.91 (1H, t, *J* 10 Hz), 4.11 (1H, b), 4.62 (1H, dd, *J* 10 and 2.8 Hz); *m/z* (CI, NH_3) 449 (100%, MH^+) (Found: C, 56.5; H, 10.0. $C_{21}H_{44}O_6Si_2$ requires C, 56.3; H, 9.8%).

3. *(1R,2R,3R)-1-O-Acetyl-2-O-tert-butyldimethylsilyl-3-tert-butyldimethylsiloxymethyl-cyclohex15-en-1,2-diol* **(9)**

To a solution of the diol **(7)** (50 mg, 0.11 mmol) in toluene (2 ml) was added 1,1'-thiocarbonyldiimidazole (60 mg, 0.33 mmol). The reaction mixture was boiled for 24 h and poured into H_2O (2 ml). The aqueous phase was extracted with diethyl ether (4 X 2 ml). The combined extracts were washed with brine (2 X 2 ml), dried ($MgSO_4$) and filtered. Concentration of

the filtrate followed by purification through flash column chromatography [petroleum ether-diethyl ether (6:1 v/v)] provided the thiocarbonate derivative **(8)** as a white solid, m.p. 109–110 °C (from petroleum ether-diethyl ether); R_F 0.63 [petroleum ether-diethyl ether (4:1 v/v)]; $\nu_{max.}$ 1754 cm^{-1} (C=O); δ 0.07 (6H, s), 0.10 (3H, s), 0.15 (3H, s), 0.88 (9H, s), 0.89 (9H, s), 1.58 (1H, m), 1.90 (1H, m), 2.13 (3H, s), 2.25 (1H, m), 3.64 (2H, m), 3.95 (1H, dd, *J* 7.5 and 5.3 Hz), 5.06 (3H, m); *m/z* (CI, NH_3) 491 (100%, MH^+).

The compound **(8)** was dissolved in trimethylphosphite (3 ml) and the solution was boiled for 72 h. Removal of solvent *in vacuo* followed by purification through flash column chromatography [petroleum ether-diethyl ether (10:1 v/v)] furnished the *alkene* **(9)** (41.6 mg, 90%) as a colourless oil, R_F 0.63 [petroleum ether-diethyl ether (6:1 v/v)]; $[\alpha]_D$ -53.9° (*c* 0.26); $\nu_{max.}$ 1746 cm^{-1} (C=O); δ 0.05 (6H, s), 0.08 (3H, s), 0.11 (3H, s), 0.88 (9H, s), 0.92 (9H, s), 1.8-2.4 (3H, m), 2.09 (3H, s), 3.66 (1H, dd, *J* 10 and 6 Hz), 3.73 (1H, dd, *J* 10 and 3.5 Hz), 3.82 (1H, dd, *J* 10 and 7.5 Hz), 5.19 (1H, ddd, *J* 7.5, 3.5 and 1.5 Hz), 5.46 (1H, dm, *J* 10 Hz), 5.80 (1H, m); *m/z* (CI, NH_3) 355 (83.7%, $M^+-C_2H_3O_2$) (Found: $M^+-C_2H_3O_2$ 355.2498. $C_{19}H_{39}O_2Si_2$ requires 355.2489).

4. *(1S,2S,3R,4R,5R)-3-O-Acetyl-4-O-tert-butyldimethylsilyl-5-tert-butyldimethylsiloxymethyl-cyclohexan-1,2,3,4-tetraol* **(10)**

A solution of the alkene **(9)** (20 mg, 0.05 mmol), trimethylamine-*N*-oxide (7.6 mg, 0.07 mmol), pyridine (25 mg, 0.31 mmol), water (4.9 mg, 0.27 mmol), *tert*-butanol (1 ml) and a catalytic amount of OsO_4 was heated under reflux with stirring for 5 h under nitrogen. After cooling, saturated aqueous $Na_2S_2O_3$ (0.1 ml) was added and the mixture was passed through a short column of silica gel and the column was washed with ethyl acetate (10 ml). The eluant was concentrated *in vacuo* and the residue was extracted with CH_2Cl_2 (4 X 5 ml). The combined extracts were washed with the saturate aqueous $Na_2S_2O_3$ (2 X 2 ml), brine (2 X 2 ml), dried ($MgSO_4$), and filtered. Solvent removal followed by flash column chromatography [hexane-diethyl ether (1:1 v/v)] afforded the *diol* **(10)** (14 mg, 65%) as a white solid, m.p. 51–52 °C (from petroleum ether-diethyl ether); R_F 0.20 [hexane-diethyl ether (1:3 v/v)]; $[\alpha]_D$ +40.0° (*c* 0.10); $\nu_{max.}$ 3425 (OH) and 1726 cm^{-1} (C=O); δ 0.04 (6H, s), 0.07 (3H, s), 0.11 (3H, s), 0.87 (9H, s), 0.90 (9H, s), 1.8-2.4 (3H, m), 2.15 (3H, s), 3.49 (1H, dd, *J* 9.5 and 3 Hz), 3.55 (1H, dd, *J* 9.5 and 3 Hz), 3.67 (1H, t, *J* 9 Hz), 3.78 (1H, dd, *J* 9 and 4.5 Hz), 4.04 (1H, q, *J* 4.5 Hz), 5.04 (1H, t, *J* 9 Hz); *m/z* (CI, NH_3) 449 (100%, MH^+) (Found: MH^+ 449.2741. $C_{21}H_{45}O_6Si_2$ requires 449.2755).

5. *(1R,2R,3S)-3-O-Benzyl-5-benzyloxymethyl-1,2-O-cyclohexylidene-cyclohex-4-en-1,2,3-triol* **(12)**

Sodium hydride (0.5 g, 8.75 mmol) was washed with dry pentane (2 X 5 ml) and suspended in dry THF (10 ml) under nitrogen at 0°C. A solution of the diol **(11)**[15] (0.7 g, 2.92 mmol) in THF (2 ml) was added dropwise and the reaction mixture was stirred for 1 h. Benzyl bromide (2.8 ml, 11.68 mmol) was added dropwise followed by the addition of a catalytic amount of tetrabutylammonium iodide. The mixture was stirred for 40 h at room temperature. Methanol (2-3 ml) was added slowly followed by addition of cold water (5 ml). The aqueous phase was extracted with CH_2Cl_2 (4 X 10 ml). The combined extracts were washed with brine (3 X 5 ml), dried ($MgSO_4$) and filtered. Concentration of the filtrate followed by purification through flash chromatography [petroleum ether-diethyl ether (4:1 v/v)] provided the *benzyl ether* **(12)** (0.87 g, 72%) as a colourless oil, R_F 0.21 [petroleum ether-diethyl ether (3:1 v/v)]; $[\alpha]_D$ +5.5° (*c* 0.29); δ 1.10-1.75 (10H, m), 1.89 (1H, db, *J* 16 Hz), 2.43 (1H, dd, *J* 16 and 1.5 Hz), 3.83 (1H, b), 3.92 (1H, d, *J* 12 Hz), 4.02 (1H, d, *J* 12 Hz), 4.46 (1H, d, *J* 12 Hz), 4.51 (1H, ddd, *J* 7, 4.5 and 1.5 Hz), 4.57 (1H, d, *J* 12

Hz), 4.61 (1H, m), 4.71 (1H, d, *J* 12.5 Hz), 4.81 (1H, d, *J* 12.5 Hz), 5.90 (1H, b), 7.35 (10H, m); *m/z* (CI, NH_3) 419 (0.8%, M^+-H) (Found: C, 77.2; H, 7.7. $C_{27}H_{32}O_4$ requires C, 77.1; H, 7.6%).

6. *(1R,2R,3S,4R,5R)-3-O-Benzyl-5-benzyloxymethyl-1,2-O-cyclohexylidene-cyclohexan-1,2,3,4-tetraol* **(13)**

To a solution of the alkene **(12)** (0.7 g, 0.67 mmol) in dry THF (8 ml) was added a 0.5 M solution of 9-BBN in THF (6.70 ml, 3.34 mmol) at room temperature. The mixture was stirred for 24 h and the excess of hydride was carefully destroyed by slow addition of water (0.4 ml). The hydroboration mixture was oxidized by the addition of 3 M aqueous solution of NaOH (2 ml) and a aqueous solution of H_2O_2 (30% w/v, 2 ml) at 0°C followed by stirring at room temperature overnight. The THF layer was separated and the aqueous phase was extracted with CH_2Cl_2 (4 X 5 ml). The combined extracts were washed with brine (2 X 2 ml), dried ($MgSO_4$) and filtered. Concentration of the filtrate followed by flash chromatography [petroleum ether-diethyl ether (2:1 v/v)]] provided the *alcohol* **(13)** (0.69 g, 94%) as a white solid, m.p. 72–73 °C (from petroleum ether-diethyl ether); R_F 0.30 [petroleum ether-diethyl ether (1:1 v/v)]; $[\alpha]_D$ −20.0° (*c* 0.30); $\nu_{max.}$ 3441 cm^{-1} (OH); δ 1.2-2.1 (13H, m), 3.45 (1H, dd, *J* 9 and 3.8 Hz), 3.52 (1H, dd, *J* 9 and 6 Hz), 3.66 (1H, dd, *J* 9.3 and 5.3 Hz), 3.86 (1H, t, *J* 9.3 Hz), 4.14 (1H, m), 4.36 (1H, t, *J* 5.3 Hz), 4.52 (2H, b), 4.72 (1H, d, *J* 12 Hz), 4.81 (1H, d, *J* 12 Hz), 7.35 (10H, m); *m/z* (CI, NH_3) 456 (100%, MNH_4^+) (Found: M^+438.2403. $C_{27}H_{34}O_5$ requires 438.2406)

7. *(1R,2R,3S,4R,5R)-4-O-Acetyl-3-O-benzyl-5-benzyloxymethyl-1,2-O-cyclohexylidene-cyclohexan-1,2,3,4-tetraol* **(14)**

To a mixture of the alcohol **(13)** (0.5 g, 1.13 mmol), pyridine (0.27 ml, 3.39 mmol) and a catalytic ammount of DMAP in dry CH_2Cl_2 (10 ml) was added acetic anhydride (0.21 ml, 2.26 mmol) at room temperature. The mixture was stirred for 24 h and poured into saturated aqueous NH_4Cl (5 ml). The aqueous phase was extracted with CH_2Cl_2 (4 X 5 ml). The combined extracts were washed with brine (2 X 5 ml), dried ($MgSO_4$) and filtered. Concentration of the filtrate followed by flash chromatography [petroleum ether-diethyl ether (5:1 v/v)] provided the *acetate* **(14)** (0.53 g, 97%) as a white solid, m.p. 78–79 °C (from petroleum ether-ethyl acetate); R_F 0.59 [petroleum ether-diethyl ether (1:1 v/v)]; $[\alpha]_D$ +3.1° (*c* 0.26); $\nu_{max.}$ 1741 cm^{-1} (C=O); δ 1.2-2.2 (13H, m), 1.99 (3H, s), 3.32 (1H, dd, *J* 9 and 7 Hz), 3.46 (1H, dd, *J* 9 and 5 Hz), 3.59 (1H, dd, *J* 9 and 4 Hz), 4.16 (1H, dt, *J* 9 and 4.5 Hz), 4.34 (1H, t, *J* 4.5 Hz), 4.47 (2H, b), 4.52 (2H, b), 5.21 (1H, t, *J* 9 Hz), 7.32 (10H, m); *m/z* (EI) 437 (1.3%, M^+-C_2H_3O) (Found: C, 72.4; H, 7.7. $C_{29}H_{36}O_6$ requires C, 72.5; H, 7.5%).

8. *(1R,2R,3S,4R,5R)-4-O-Acetyl-3-O-benzyl-5-benzyloxymethyl-cyclohexan-1,2,3,4-tetraol* **(15)**

Prepared using the method described in experiment 2 from the acetal **(14)** (0.5 g), CF_3COOH (1 drop) and H_2O (1 drop). Purification by flash column chromatography [petroleum ether-diethyl ether (1:1 v/v)] afforded the *diol* **(15)** (0.40 g, 96%) as colourless needles, m.p. 59–60 °C (from petroleum ether-ethyl acetate); R_F 0.44 [ethyl acetate-diethyl ether (1:3 v/v)]; $[\alpha]_D$ +7.1° (*c* 0.45); $\nu_{max.}$ 3411 (OH) and 1740 cm^{-1} (C=O); δ 1.5-2.4 (3H, m), 1.95 (3H, s), 3.30 (1H, dd, *J* 9 and 5.8 Hz), 3.38 (1H, dd, *J* 9 and 2.8 Hz), 3.43 (1H, dd, *J* 9 and 3.8 Hz), 3.64 (1H, m), 4.18 (1H, b), 4.41 (1H, d, *J* 11.5 Hz), 4.47 (1H, d, *J* 11.5 Hz), 4.56 (1H, d, *J* 12 Hz), 4.66 (1H, d, *J* 12 Hz), 5.17 (1H, t, *J* 9 Hz), 7.42 (10H, m); *m/z* (CI, NH_3) 418 (4.3%, MNH_4^+) (Found: C, 69.0; H, 7.1. $C_{23}H_{28}O_6$ requires C, 69.0; H, 7.0%) (Found: MH^+ 401.1959. $C_{23}H_{29}O_6$ requires 401.1964).

9. *(1R,2R,3R)-2-O-Acetyl-1-O-benzyl-3-benzyloxymethyl-cyclohex-5-en-1,2-diol* **(16)**

To a solution of the diol **(15)** (0.4 g, 1.01 mmol) in toluene (10 ml) was added 1,1'-thiocarbonyldiimidazole (0.65 g, 3.54 mmol). The mixture was refluxed for 24 h and poured into H_2O (5 ml). The aqueous phase was extracted with diethyl ether (4 X 5 ml). The combined extracts were washed with brine (2 X 2 ml), dried ($MgSO_4$) and filtered. Concentration of the filtrate provided a colourless oil. The oil was dissolved in trimethylphosphate (20 ml) and the solution was refluxed for 3 days. Removal of solvent under reduced pressure followed by flash chromatography [petroleum ether-diethyl ether (8:1 v/v)] provided the *alkene* **(16)** (0.31 g, 85%) as a white solid, m.p. 57–58 °C (from petroleum ether-diethyl ether); R_F 0.70 [petroleum ether-diethyl ether (1:1 v/v)]; $[\alpha]_D$ -78.4° (*c* 0.25); $\nu_{max.}$ 1737 cm^{-1} (C=O); δ 2.01 (3H, s), 2.0-2.5 (3H, m), 3.40 (1H, dd, *J* 9 and 6.2 Hz), 3.51 (1H, dd, *J* 9 and 4.5 Hz), 4.13 (1H, m), 4.42 (1H, d, *J* 12 Hz), 4.48 (1H, d, *J* 12 Hz), 4.54 (1H, d, *J* 12 Hz), 4.64 (1H, d, *J* 12 Hz), 5.21 (1H, dd, *J* 10 and 9 Hz), 5.69 (1H, db, *J* 10 Hz), 5.80 (1H, m), 7.36 (10H, m); *m/z* (CI, NH_3) 384 (23.4%, MNH_4^+) (Found: C, 75.0; H, 7.1. $C_{23}H_{26}O_4$ requires C, 75.4; H, 7.1%) (Found: M^+ 366.1831. $C_{23}H_{26}O_4$ requires 366.1831).

10. *(1S,2S,3R,4R,5R)-4-O-Acetyl-3-O-benzyl-5-benzyloxymethyl-cyclohexan-1,2,3,4-tetraol* **(17)**

A solution of the alkene **(16)** (0.3 g, 0.82 mmol), trimethylamine-*N*-oxide (0.37 g, 3.28 mmol), pyridine (0.41 ml, 5.08 mmol), water (0.08 ml, 4.43 mmol), *tert*-butanol (5 ml) and a catalytic ammount of OsO_4 was refluxed with stirring for 5 h under nitrogen. After cooling, saturated aqueous $Na_2S_2O_3$ (0.5 ml) was added and the mixture was passed through a short column of silica gel and the column was washed with ethyl acetate (30 ml). The eluant was concentrated *in vacuo* and the residue was extracted with CH_2Cl_2 (4 X 10 ml). The combined extracts were washed with the saturate aqueous $Na_2S_2O_3$ (2 X 5 ml), brine (2 X 5 ml), dried ($MgSO_4$), and filtered. Removal of solvent followed by flash chromatography [petroleum ether-diethyl ether (1:3 v/v)] afforded the *diol* **(17)** (0.22 g, 68%) as colourless needles, m.p. 106–107 °C (from petroleum ether-diethyl ether); R_F 0.18 [petroleum ether-diethyl ether (1:7 v/v)]; $[\alpha]_D$ +82.4° (*c* 0.33); $\nu_{max.}$ 3432 (OH) and 1733 cm^{-1} (C=O); d 1.20 (1H, m), 1.51 (1H, td, *J* 7.5 and 3 Hz), 1.98 (3H, s), 2.09 (1H, dt, *J* 15 and 3 Hz), 2.32 (1H, m), 3.38 (2H, m), 3.56 (1H, dd, *J* 6.5 and 3 Hz), 3.77 (1H, t, *J* 6.5 Hz), 4.11 (1H, q, *J* 3 Hz), 4.41 (1H, d, *J* 12 Hz), 4.46 (1H, d, *J* 12 Hz), 4.60 (1H, d, *J* 11.3 Hz), 4.79 (1H, d, *J* 11.3 Hz), 5.05 (1H, dd, *J* 6.5 and 7.5 Hz), 7.47 (10H, m); *m/z* (CI, NH_3) 418 (100%, MNH_4^+) (Found: C, 68.7; H, 7.1. $C_{23}H_{28}O_6$ requires C, 69.0; H, 7.0%) (Found: M^+-C_2H_3O 357.1671. $C_{21}H_{25}O_5$ requires 357.1702).

11. *(1S,2S,3S,4R,5R)-3-O-Benzyl-5-benzyloxymethyl-cyclohexan-1,2,3,4-tetraol* **(17)**

To a solution of the compound **(17)** (100 mg) in methanol (5 ml) was added a catalytic amount of sodium methoxide. The reaction mixture was stirred for 24 h at room temperature. The solvent was evaporated and the residue was dissolved in CH_2Cl_2 (10 ml). The organic phase was washed with brine (2 X 2 ml), dried ($MgSO_4$) and filtered. Concentration of the filtrate followed by purification through flash column chromatography [diethyl ether-ethyl acetate (10:1 v/v)] provided the *triol* **(18)** (78.8 mg, 88%) as a white solid, m.p.100–101 °C (from petroleum ether-ethyl acetate); R_F 0.44 [diethyl ether-ethyl acetate (3:1 v/v)]; $[\alpha]_D$ +60.6° (*c* 0.35); $\nu_{max.}$3282 cm^{-1} (OH); d 1.26 (1H, td, *J* 14.5 and 2.5 Hz), 1.79 (1H, dt, *J* 14.5 and 4 Hz), 2.27 (1H, m), 3.47 (2H, m), 3.61 (3H, m), 4.04 (1H, b), 4.52 (2H, s), 4.72 (1H, d, *J* 11.8 Hz), 5.01 (1H, d, *J* 11.8 Hz), 7.33 (10H, m); *m/z* (CI, NH_3) 267 (8.2%, M^+-C_7H_7) (Found: C, 70.0; H, 7.5. $C_{21}H_{26}O_5$

requires C, 70.4; H, 7.3%) (Found: M^+–C_7H_7 267.1237. $C_{14}H_{19}O_5$ requires 267.1233).

12. *Pseudo-α-D-glucopyranose* **(1)**

To a suspension of rhodium-on-charcocal (15 mg, 5% w/w) in absolute EtOH (2 ml) under H_2 at atmospheric pressure was added a solution of the benzyl ether **(18)** (78 mg) in absolute EtOH (0.5 ml). The reaction mixture was stirred for 10 h at room temperature and filtered. The residue was washed with absolute EtOH (5 ml). The combined filtrate was concentrated to give the *title compound* **(1)** (35 mg, 90%) as a white solid, m.p. 146–147 °C; $[\alpha]_D$ +63.0° (*c* 0.6, MeOH){lit.[12] m.p. 151—152 °C; $[\alpha]_D$ + 68.4° (MeOH); lit.[21] syrup; $[\alpha]_D$ + 67° (MeOH)}; $\nu_{max.}$ 3377 cm^{-1} (OH); δ (D_2O) (HOD in 4.73) 1.40 (1H, td, *J* 15 and 1.8 Hz), 1.83 (2H, m), 3.23 (1H, t, *J* 9.8 Hz), 3.38 (1H, dd, *J* 9.8 and 3 Hz), 3.53 (1H, t, *J* 9.8 Hz), 3.64 (2H, m), 4.03 (1H, m); *m/z* (CI, NH_3) 196 (100%, MNH_4^+).

13. (*1S,2R,3S,4R,5R*)-*3-O-Benzyl-5-benzyloxymethyl-cyclohexan-1,2,3,4-tetraol* **(21)**

To a solution of the alkene **(16)** (0.1 g, 0.28 mmol) in formic acid (2 ml, 90% w/w) was added a solution of H_2O_2 (30% w/v, 0.1 ml). The reaction mixture was refluxed for 4 h and the solvent was evaporated under reduced pressure. A aqueous solution of NaOH (20% w/v, 0.35 ml) and THF (0.5 ml) were added and the reaction mixture was heated at 80 °C for a further 12 h. The reaction mixture was neutralized by the addition of an aqueous solution of HCl (20%, w/v) and the aqueous phase was extracted with CH_2Cl_2 (5 X 5 ml). The combined extracts were washed with brine (2 X 2 ml), dried ($MgSO_4$) and filtered. Concentration of the filtrate followed by purification through flash column chromatography [diethyl ether-ethyl acetate (10:1 v/v)] provided the *title compound* **(21)** (39 mg, 40%) as colourless needles, m.p. 123–124 °C (from petroleum ether-ethyl acetate); R_F 0.45 [diethyl ether-ethyl acetate (3:1 v/v)]; $[\alpha]_D$ +10.5° (*c* 0.20); $\nu_{max.}$ 3298 cm^{-1} (OH); δ 1.66 (1H, dt, *J* 14 and 2.8 Hz), 1.79 (1H, td, *J* 14 and 2.8 Hz), 2.18 (1H, m), 3.59 (2H, m), 3.67 (1H, dd, *J* 7.5 and 2.8 Hz), 3.82 (1H, t, *J* 7.5 Hz), 4.03 (1H, t, *J* 2.8 Hz), 4.11 (1H, quartet, *J* 2.8 Hz), 4.53 (2H, m), 4.72 (2H, s), 7.49 (10H, m); *m/z* (CI, NH_3) 376 (100%, MNH_4^+) (Found: C, 70.4; H, 7.7. $C_{21}H_{26}O_5$ requires C, 70.4; H, 7.3%) (Found: M^+–C_7H_7 267.1244. $C_{14}H_{19}O_5$ requires 267.1232).

14. *Pseudo-α-D-mannopyranose* **(2)**

To a suspension of palladium hydroxide-on-charcocal (10 mg, 5% w/w) in absolute EtOH (2 ml) under H_2 at atmospheric pressure was added a solution of the compound **(21)** (42.5 mg) in absolute EtOH (0.5 ml). The reaction mixture was stirred for 10 h at room temperature and filtered. The residue was washed with absolute EtOH (5 ml). The combined filtrate was concentrated to gave the *pseudo-α-D-mannopyranose* **(2)** (21 mg, 100%) as a colourless oil, $[\alpha]_D$ +1.9° (*c* 1.08, MeOH); $\nu_{max.}$3351 cm^{-1} (OH); δ (D_2O) (HOD in 4.73) 1.66 (2H, m), 1.78 (1H, m), 3.51 (1H, t, *J* 10 Hz), 3.67 (3H, m), 3.90 (1H, t, *J* 3.2 Hz), 3.97 (1H, q, *J* 3.2 Hz); *m/z* (CI, NH_3) 196 (100%, MNH_4^+); (Found: C, 47.6; H, 7.7. $C_7H_{14}O_5$ requires C, 47.2; H, 7.9%) (Found: MNH_4^+ 196.1188. $C_7H_{18}NO_5$ requires 196.1185).

15. *Pentaacetate of pseudo-α-D-mannopyranose* **(22)**

Pyridine (0.5 ml) and a catalytic amount of DMAP was added to a solution of pseudo-α-D-mannopyranose **(2)** (33 mg) in acetic anhydride (0.5 ml) at room temp. The mixture was stirred for 30 h at room temperature and poured into saturated aqueous NH_4Cl (1 ml). The aqueous phase was extracted with CH_2Cl_2 (4 X 5 ml). The combined extracts were washed with

brine (2 X 2 ml), dried ($MgSO_4$) and filtered. Concentration of the filtrate followed by flash chromatography [hexane-ethyl acetate (5:1 v/v)]] provided the *pentaacetate* **(22)** (0.48 g, 67%) as white needles, m.p. 79–80 °C (from petroleum ether-ethyl acetate); $[\alpha]_D$ +27.1° (*c* 3.95, $CHCl_3$) {lit.[14] m.p. 80—81 °C; $[\alpha]_D$ + 27.8° ($CHCl_3$)}; $\nu_{max.}$ 1746 cm^{-1} (C=O); δ 2.00 (3H, s), 2.30 (3H, s), 2.42 (3H, s), 2.70 (3H, s), 2.79 (3H, s), 1.8-2.4 (3H, m), 3.96 (1H, dd, *J* 11.5 and 3.8 Hz), 4.13 (1H, dd, *J* 11.5 and 5.8 Hz), 5.05 (1H, quartet, *J* 3.8 Hz), 5.23 (2H, m), 5.34 (1H, b); *m/z* (CI, NH_3) 406 (100%, MNH_4^+).

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