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(-)-QUINIC ACID IN ORGANIC SYNTHESIS. 2. FACILE SYNTHESES OF PSEUDO-β-D-MANNOPYRANOSE AND PSEUDO-β-D-FRUCTOPYRANOSE.

Tony K. M. Shing*[a] and Ying Tang[b]

[a]Department of Chemistry, The Chinese University of Hong Kong, Shatin, Hong Kong.
[b]Department of Chemistry, The Victoria University of Manchester, Manchester M13 9PL, U.K.

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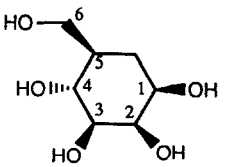
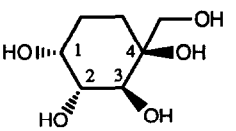
Abstract—Pseudo-β-D-mannopyranose (1) and pseudo-β-D-fructopyranose (2) have been obtained from quinic acid in seven and twelve steps respectively.

Pseudo-sugars[1] are carbocyclic analogues of monosaccharides, in which the ring oxygen is replaced by a methylene group. The discovery of pseudo-sugars in natural products[2] and their potential in biochemical studies of specific enzyme inhibition[3,4] have attracted considerable synthetic[2] efforts towards their stereoisomers. There is also tremendous interest in developing pseudo-sugars as potential non-nutritive sweeteners, pseudo-β-D-fructopyranose in particular.[5] Initial synthetic studies[2] only yielded racemic material but recently, reports on syntheses of optically pure pseudo-sugars have appeared.[4—7] Enantiomerically pure 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. We recently described an enantiospecific synthesis of an antitumour agent 2-crotonyloxymethyl-(4*R*,5*R*,6*R*)-4,5,6-trihydroxycyclohex-2-enone (COTC)[8] from quinic acid and this paper further demonstrates the synthetic versatility of quinic acid by short, facile, and enantiospecific syntheses of (1) and (2). A preliminary account on part of this work has appeared.[9]



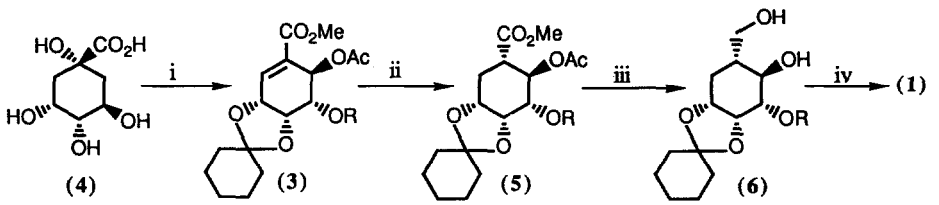
(1)



(2)

Our initial approach to pseudo-β-D-mannopyranose (1) is shown in Scheme 1. The known enoate (3),[8] available from quinic acid (4) in nine steps, underwent a stereocontrolled hydrogenation at the less hindered β-face, furnishing exclusively the cyclohexane derivative (5) in 82% yield. Treatment of the diester (5) with di-isobutylaluminium hydride (DIBAL-H) in tetrahydrofuran (THF) afforded the diol (6) in 93% yield; the stereochemistry of the

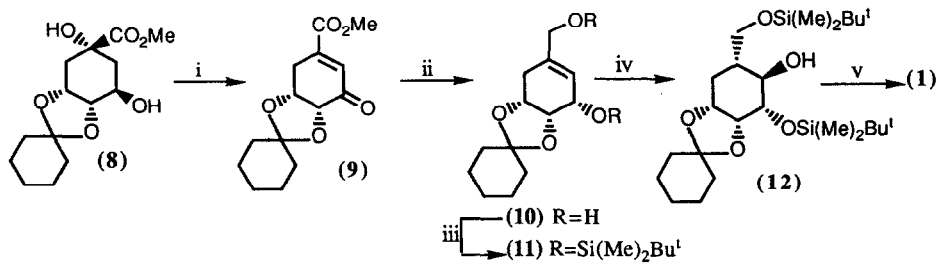
hydroxymethyl group was indicated from the ^1H n.m.r. spectrum ($J_{4,5}$ = 9.9 Hz). Hydrolysis of this material furnished cleanly pseudo-β-D-mannopyranose (**1**), m.p. 223°C; $[\alpha]_D$ + 10.4° (*c* 0.24, H_2O) {lit.[7] m.p. 217°C; $[\alpha]_D$ + 11.9° (*c* 0.65, MeOH)}. The target molecule (**1**) was characterised as the corresponding penta-acetate (**7**), m.p. 117°C; $[\alpha]_D$ + 3.8° (*c* 0.98, $CHCl_3$){lit.[7] m.p. 119°C; $[\alpha]_D$ + 2.9° (*c* 1.28, $CHCl_3$)}.



R = $Si(Me)_2Bu^t$

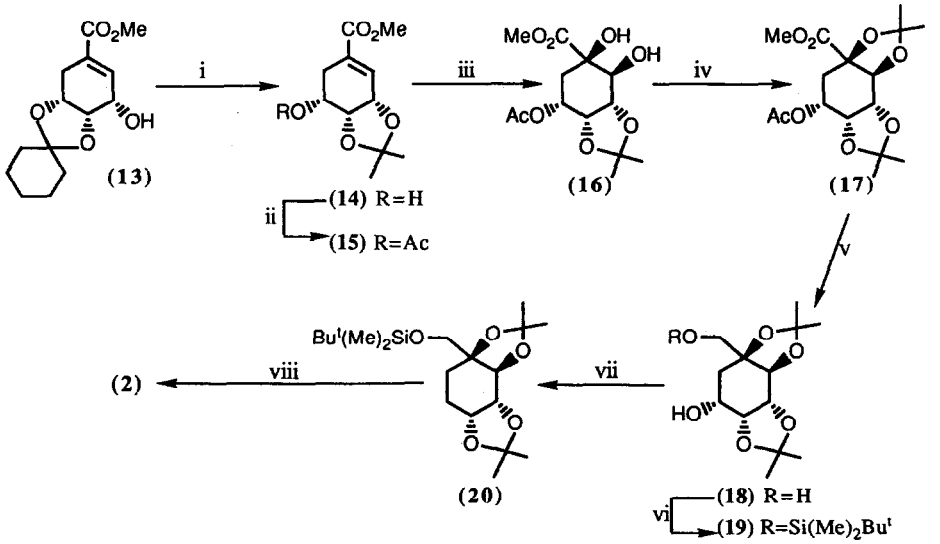
Scheme 1. *Reagents:* i, 9 steps, see ref. 8; ii, Pd/C, H_2, EtOH, (82%); iii, DIBAL-H in THF, THF, (93%); iv, 50% aq. CF_3COOH (aq. TFA), room temp., 4h, (100%).

We envisaged that the number of steps involved in the above synthesis could be reduced and now describe a shorter synthesis of (**1**) as shown in Scheme 2. The known hydroxy-ester (**8**),[8] readily available from quinic acid (**4**) in 2 steps, was oxidised with concomitant β-elimination using a modified protocol—pyridinium chlorochromate in the presence of pyridine—to give enone (**9**)[8] in 90% yield. The carbonyl groups in (**9**) were both reduced with DIBAL-H to form the diol (**10**), which was protected with $Me_2(Bu^t)SiCl$-*N*,*N*-4-dimethylaminopyridine(DMAP)-CH_2Cl_2 as the silyl ether (**11**) in 90% overall yield. Hydroboration of the double bond in (**11**) with 9-borabicyclo[3.3.1]nonane (9-BBN) at the less hindered β-face followed by alkaline peroxide oxidation afforded exclusively the cyclohexane derivative (**12**) in 86% yield. This compound was then hydrolysed to (**1**) in quantitative yield. Thus, using this improved sequence, pseudo-β-D-mannopyranose (**1**) was prepared in seven stages from (-)-quinic acid (**4**) in an overall yield of 52%.



Scheme 2. *Reagents:* i, pyridinium chlorochromate, 3Å molecular sieves, pyridine, CH_2Cl_2, (90%); ii, DIBAL-H in toluene, toluene, 0 °C, (90%); iii, $Me_2(Bu^t)SiCl$, imidazole, *N*,*N*-dimethylaminopyridine (DMAP), CH_2Cl_2 (100%); iv, 9-borabicyclo[3.3.1]-nonane (9-BBN), THF, then 3M NaOH, H_2O_2, (86%); v, 50% aq. TFA, room temp., (100%).

On the other hand, the first enantiospecific synthesis of pseudo-β-D-fructopyranose (**2**) is illustrated in Scheme 3. The aforementioned enone (**9**) was reduced with $NaBH_4$ from the less hindered β-face to the alcohol (**13**)[8] in 83% yield. Thermodynamically controlled isopropylidenation of (**13**) with acidic acetone afforded the more stable acetonide (**14**) in 88% yield. In our hands, attempts to deoxygenate the free alcohol in (**14**) were unsuccessful. We envisaged that the enoate double bond was the culprit and should be removed before deoxygenation could be realised. This change of strategy gratifyingly proved successful. Thus acetylation of the hydroxy group in (**14**) with acetic anhydride-DMAP-CH_2Cl_2 gave the acetate (**15**) in quantitative yield. A stereocontrolled hydroxylation of the double bond in (**15**) with osmium tetroxide-trimethylamine-*N*-oxide in t-BuOH-pyridine, a conversion which would secure the OH-3,4 in (**2**), proceeded smoothly at the less hindered β-face, providing the desired β-diol (**16**) as the sole product in 90% yield. Acetonation of (**16**) with 2-methoxypropene gave the diacetonide (**17**) (70%) which then was reduced with DIBAL-H in THF to form the diol (**18**) in 79% yield. The primary alcohol in (**18**) was selectively protected with $Me_2(Bu^t)SiCl$-DMAP-CH_2Cl_2 to give the silyl ether (**19**) in 91% yield. The free alcohol in (**19**) was subjected to a 2-step deoxygenation[10] sequence, affording the protected target molecule (**20**) in 82% yield. Hydrolysis of this compound then produced crystalline pseudo-β-D-fructopyranose (**2**) in 65% yield, m.p. 96°C—97°C; $[\alpha]_D$ - 53.0° (*c* 0.46, MeOH) {lit.[5] syrup; $[\alpha]_D$ - 57° (*c* 1.2, MeOH)}. Thus pseudo-β-D-fructopyranose (**2**) was afforded in twelve steps from quinic acid in an overall yield of 11.9%.



Scheme 3. *Reagents:* i, acetone, *p*-toluene-4-sulphonic acid, (88%); ii, Ac_2O, pyridine, DMAP, CH_2Cl_2, (100%); iii, OsO_4, trimethylamine-*N*-oxide, pyridine, water, *tert*-butanol, (90%); iv, 2-methoxypropene, *dl*-camphor-10-sulphonic acid, CH_2Cl_2, (70%); v, DIBAL-H in THF, THF, 0 °C, (79%); vi, $Me_2(Bu^t)SiCl$, imidazole, DMAP, CH_2Cl_2, (91%); vii, phenyl chlorothioformate, pyridine, DMAP, CH_2Cl_2, then n-Bu_3SnH, azobis-isobutyronitrile (AIBN), toluene, (82%); viii, 50% aq. TFA, room temp., 4h, (65%).

The present novel approach from quinic acid is very flexible, thus providing opportunities for facile syntheses of not only diastereoisomeric pseudo-aldopyranoses and pseudo-ketopyranoses but also highly oxygenated cyclohexanoid natural products. Research along this line is in progress.

Experimental

M.p.s were recorded on a Kofler block. ^{1}H N.m.r. spectra were recorded on a Varian SC300 spectrometer at 300 MHz using deuteriochloroform as solvent unless otherwise stated. Infra red (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*R,2R,*3*S,*4*R,*5*S)-*4*-O-*Acetyl-3*-O-tert-*butyldimethylsilyl-1,2*-O-*cyclohexylidene-5-methoxycarbonyl-cyclohexan-1,2,3,4-tetraol* (**5**)

To a suspension of palladium-on-charcoal (10 mg, 5% w/w) in absolute EtOH (1.5 ml) under H_2 at atmospheric pressure was added a solution of the enoate (**3**)[8] (50 mg, 0.11 mmol) in absolute EtOH (0.5 ml). The mixture was stirred for 4 h at room temp. and filtered. The residue was washed with absolute EtOH (5 ml). The combined filtrate and washing were concentrated. Purification of the residue by flash chromatography [petroleum ether-diethyl ether (2:1 v/v)] provided the *title compound* (**5**) (41 mg, 82%) as a colourless oil, R_F 0.56 [petroleum ether-diethyl ether 2:1 v/v)]; $[\alpha]_D$ -1.68° (*c* 4.4); $\nu_{max.}$ 1749 cm^{-1} (C=O); δ 0.07 (3H, s), 0.10 (3H, s), 0.89 (9H, s), 1.4-1.9 (12H, m), 2.03 (3H, s), 2.41 (1H, ddd, *J* 10.5, 9 and 4 Hz), 3.65 (3H, s), 3.88 (1H, dd, *J* 9 and 4 Hz), 4.20 (2H, m), 5.42 (1H, t, *J* 9 Hz); *m/z* (CI, NH_3) 443 (20.6%, M^+) (Found: C, 59.5; H, 8.8. $C_{22}H_{38}O_7Si$ requires C, 59.7; H, 8.6%).

(*1*R,2R,*3*S,*4*R,*5*R)-*3*-O-tert-*Butyldimethylsilyl-1,2*-O-*cyclohexylidene-5-hydroxymethyl-cyclohexan-1,2,3,4-tetraol* (**6**)

To a solution of the compound (**5**) (200 mg, 0.45 mmol) in dry THF (2 ml) was added dropwise a 1.0 M solution of DIBAL-H in THF (1.36 ml, 1.36 mmol) over 30 min at -20°C. The mixture was then stirred for 1 h at 0°C, quenched with saturated aqueous NH_4Cl (2 ml) and filtered. 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. Solvent removal from the filtrate gave a pale yellow oil which was flash chromatographed [petroleum ether-diethyl ether (1:1 v/v)] to yield the *diol* (**6**) (156 mg, 93%) as a colourless oil, R_F 0.21 [petroleum ether-diethyl ether (1:2 v/v)]; $[\alpha]_D$ -11.43° (*c* 0.70); $\nu_{max.}$ 3415 cm^{-1} (OH); δ 0.12 (3H, s), 0.13 (3H, s), 0.94 (9H, s), 1.3-2.0 (13H, m), 3.60 (1H, dd, *J* 9.9 and 3.5 Hz), 3.67 (2H, m), 3.80 (1H, t, *J* 9.9 Hz), 4.19 (1H, m), 4.26 (1H, t, *J* 4.5 Hz); *m/z* (EI) 373 (22.5%, MH^+) (Found: C, 60.9; H, 9.7. $C_{19}H_{36}O_5Si$ requires C, 61.3; H, 9.7%).

Pseudo-β-D-mannopyranose (**1**)

Ice-cold aqueous CF_3COOH (5 ml, 1:1 v/v) was added to the compound (**6**) (50 mg) and the mixture was stirred at room temp. for 4 h. Removal of the solvent gave an oil which was twice concentrated from absolute ethanol, giving a reddish solid. Recrystallization from $CHCl_3$/MeOH at -5°C gave white needles (**6**) (23 mg, 100%), m.p. 223°C (lit.[7] 217°C); $[\alpha]_D$ +10.4° (*c* 0.24, H_2O) [lit.[7] +11.9° (*c* 0.65, MeOH)]; δ (D_2O) 1.52 (2H, m), 1.77 (1H, ddd, *J* 9, 5 and 1 Hz), 3.45 (2H, m), 3.58 (1H, dd, *J* 11 and 5 Hz), 3.75 (2H, m), 4.01 (1H, bs); *m/z* (CI, NH_3) 196 (100%, MNH_4^+).

Pentaacetate of pseudo-β-D-mannopyranose (7)

Pyridine (0.5 ml, 6.20 mmol) and a catalytic amount of DMAP was added to a solution of pseudo-β-D-mannopyranose (1) (50 mg, 0.11 mmol) in acetic anhydride (1.74 ml, 18.6 mmol) at room temp. The mixture was heated for 7 h at 70°C 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 flash chromatography [petroleum ether-diethyl ether (5:1 v/v)] provided the *title compound* (7) (0.1 g, 90%) as white needles, m.p. 117°C (lit.[7] 119°C); $[\alpha]_D$ +3.8° (*c* 0.98, $CHCl_3$) [lit.[7] +2.9° (*c* 1.28, $CHCl_3$)]; $\nu_{max.}$ 1747 cm^{-1} (C=O); δ (C_6D_6) 1.62 (3H, s), 1.65 (3H, s), 1.66 (3H, s), 1.67 (3H, s), 1.69 (3H, s), 3.74 (1H, dd, *J* 11.5 and 2.5 Hz), 4.09 (1H, dd, *J* 11.5 and 5 Hz), 4.77 (1H, ddd, *J* 11.5, 5 and 2.5 Hz),), 5.04 (1H, dd, *J* 10 and 7.5 Hz), 5.40 (1H, t, *J* 10 Hz), 5.90 (1H, m); *m/z* (CI, NH_3) 406 (100%, MNH_4^+).

Methyl 4,5-O-cyclohexylidene-3-dehydro-4-epishikimate (9)

To a mixture of the compound (8)[8](1.1 g, 3.85 mmol), 3Å powder molecular sieves (2.2 g) and pyridine (1.1 g) in dry CH_2Cl_2 (15 ml) was added pyridinium chlorochromate (3.3 g, 15.4 mmol) in one portion at room temp. The mixture was stirred for 24 h, diluted with diethyl ether (30 ml) and filtered through a pad of celite. The residue was washed with diethyl ether (20 ml). The combined filtrate was washed with brine (2 X 2 ml), dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash chromatography [petroleum ether-diethyl ether (5:1 v/v)] afforded the *enone* (9) (0.92 g, 90%) as a white solid, m.p. 90—91°C; R_F 0.56 [petroleum ether-diethyl ether (5:1 v/v)]; $[\alpha]_D$ -44.0° (*c* 2.1); $\nu_{max.}$ 1722 (ester C=O) and 1682 cm^{-1} (ketone C=O); δ 1.2-1.8 (10H, m), 2.86 (1H, ddd, *J* 20, 5 and 3 Hz), 3.24 (1H, bd, *J* 20 Hz), 3.86 (3H, s), 4.31 (1H, d, *J* 5 Hz), 4.69 (1H, td, *J* 5 and 2 Hz), 6.84 (1H, d, *J* 3 Hz); *m/z* (CI, NH_3) 267 (100%, MH^+) (Found: C, 63.4; H, 7.0. $C_{14}H_{18}O_5$ requires C, 63.2; H, 6.8%).

(1R,2R,3S)-1,2-O-cyclohexylidene-5-hydroxymethyl-4-cyclohexen-1,2,3-triol (10)

To a solution of the compound (9) (500 mg, 1.88 mmol) in dry toluene (5 ml) was added dropwise a 1.5 M solution of DIBAL-H in toluene (3.76 ml, 5.64 mmol) over 30 min at -20°C. The mixture was stirred for 1 h at 0°C, quenched with saturated aqueous NH_4Cl (2 ml) and filtered. The aqueous phase was extracted with CH_2Cl_2 (4 X 10 ml). The combined extracts were washed with brine (2 X 5 ml), dried ($MgSO_4$), and filtered. Solvent removal gave a oil which was flash chromatographed [petroleum ether-diethyl ether (1:7 v/v)] to yield the *diol* (10) (400 mg, 90%) as a white solid, m.p. 67—69°C; R_F 0.12 [petroleum ether-diethyl ether (1:8 v/v)]; $[\alpha]_D$ +3.68° (*c* 0.76); $\nu_{max.}$ 3394 cm^{-1} (OH); δ 1.48 (2H, m), 1.53 (8H, m), 1.99 (1H, bd, *J* 16 Hz), 2.42 (1H, dd, *J* 16 and 2.8 Hz), 4.07 (3H, m), 4.46 (1H, dd, *J* 7 and 4.2 Hz), 4.57 (1H, ddd, *J* 7, 4 and 2.8 Hz), 5.75 (1H, bs); *m/z* (EI) 240 (27.3%, M^+) (Found: C, 65.3; H, 8.5. $C_{13}H_{20}O_4$ requires C, 65.0; H, 8.4%).

(1R,2R,3S)-3-O-tert-Butyldimethylsilyl-5-tert-butyldimethylsiloxymethyl-1,2-O-cyclohexylidene-4-cyclohexen-1,2,3-triol (11)

To a solution of the compound (10) (140 mg, 0.58 mmol), imidazole (240 mg, 3.54 mmol) and a catalytic amount of DMAP in dry CH_2Cl_2 (2 ml) was added *tert*-butyldimethylsilyl chloride (350 mg, 2.33 mmol) at room temp. The mixture was stirred for 14 h and poured into saturated aqueous NH_4Cl (5 ml). The aqueous phase was extracted with CH_2Cl_2 (3 X 10 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 (12:1 v/v)] afforded the *title compound* (11) (273 mg, 100%) as a colourless oil, R_F 0.63 [petroleum ether-diethyl ether 9:1 v/v)]; $[\alpha]_D$ +2.86° (*c* 2.24); δ 0.06 (6H, s), 0.12 (6H, s), 0.87 (9H, s), 0.88 (9H, s), 1.2-1.7 (10H, m), 1.93 (1H, bd, *J* 16 Hz), 2.21 (1H, bd, *J* 16 and 1.8 Hz), 4.03 (2H, m), 4.19 (1H, bs), 4.33 (1H, dd, *J* 7 and 3.2 Hz), 4.46 (1H, bs), 5.69 (1H, bs); *m/z* (EI) 468 (4.3%, M^+) (Found: C, 63.9; H, 10.6. $C_{25}H_{48}O_4Si_2$ requires C, 64.1; H, 10.3%).

(1R,2R,3S,4R,5R)-3-O-tert-Butyldimethylsilyl-5-tert-butyldimethylsiloxymethyl-1,2-O-cyclohexylidene-cyclohexan-1,2,3,4-tetraol (12)

To a solution of the compound (11) (0.2 g, 0.43 mmol) in dry THF (2 ml) was added a 0.5 M solution of 9-BBN in THF (1.70 ml, 0.85 mmol) at room temp. The mixture was stirred for 24 h and the excess of hydride was carefully destroyed by slow addition of water (0.2 ml). The hydroboration mixture was oxidized by the addition of aqueous NaOH (3 M, 1 ml) and aqueous H_2O_2 (30% w/v, 1 ml) at 0°C followed by stirring at room temp. overnight. The THF layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3 X 10 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 (9:1 v/v)]] provided the *title compound* (**12**) (0.18 g, 86%) as a colourless oil, R_F 0.34 [petroleum ether-diethyl ether 9:1 v/v)]; $[\alpha]_D$ -12.39° (*c* 0.71); $\nu_{max.}$3482 cm^{-1} (OH); δ 0.07 (6H, m), 0.16 (6H, m), 0.91 (9H, s), 0.95 (9H, s), 1.2-1.9 (13H, m), 3.68 (4H, m), 4.16 (1H, m), 4.25 (1H, t, *J* 5 Hz); *m/z* (CI, NH_3) 487 (100%, MH^+) (Found: M^+ 486.3202 $C_{25}H_{50}O_5Si_2$ requires M^+ 486.3197).

(1R,2R,3S)-2,3-O-Isopropylidene-5-methoxycarbonyl-4-cyclohexen-1,2,3-triol (**14**)

To a solution of the compound (**13**)[8] (2 g, 8.77 mmol) in acetone (50 ml) was added p-toluene-4-sulphonic acid (1 g) at room temp. The mixture was stirred for 12 h and quenched with H_2O (20 ml). The pH of the solution was adjusted to 8 by the addition of ammonium hydroxide (S.G. 0.88). The acetone was removed and the aqueous phase was extracted with CH_2Cl_2 (4 X 20 ml). The combined extracts were washed with brine (2 X 5 ml), dried ($MgSO_4$), and filtered. Solvent removal gave an oil which was flash chromatographed [petroleum ether-diethyl ether (1:4 v/v)] to yield the *acetonide* (**14**) (1.76 g, 88%) as colourless needles, m.p. 118—119°C; R_F 0.36 [petroleum ether-diethyl ether (1:5 v/v)]; $[\alpha]_D$ -23.93° (*c* 1.17); $\nu_{max.}$ 3436 (OH), 1718 cm^{-1} (conjugated ester C=O); δ 1.38 (3H, s), 1.40 (3H, s), 2.48 (1H, ddt, *J* 16.5, 9 and 1.5 Hz), 2.64 (1H, dd, *J* 16.5 and 4.8 Hz), 3.75 (3H, s), 3.94 (1H, ddd, *J* 9, 4.8 and 2.5 Hz), 4.42 (1H, dd, *J* 5.5 and 2.5 Hz), 4.73 (1H, bs), 6.78 (1H, bs); *m/z* (CI, NH_3) 246 (100%, MNH_4^+) (Found: MNH_4^+ 246.1346 $C_{11}H_{20}NO_5$ requires 246.1341)

(1R,2R,3S)-1-O-Acetyl-2,3-O-isopropylidene-5-methoxycarbonyl-4-cyclohexen-1,2,3-triol (**15**)

To a mixture of the compound (**14**) (1.2 g, 5.26 mmol), pyridine (2.12 ml, 26.3 mmol) and a catalytic amount of DMAP in dry CH_2Cl_2 (20 ml) was added acetic anhydride (1.5 ml, 16.8 mmol) at room temp. The mixture was stirred for 12 h and poured into saturated aqueous NH_4Cl (10 ml). The aqueous phase was extracted with CH_2Cl_2 (3 X 20 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 (1:2 v/v)] afforded the *acetate* (**15**) (1.42 g, 100%) as a white solid, m.p. 74.5—75.5°C; R_F 0.76 [petroleum ether-diethyl ether (1:4 v/v)]; $[\alpha]_D$ -56.33° (*c* 0.71); $\nu_{max.}$ 1722 cm^{-1} (C=O); δ 1.36 (3H, s), 1.42 (3H, s), 2.18 (3H, s), 2.53 (1H, ddt, *J* 16.5, 10.5 and 5.2 Hz), 2.73 (1H, ddd, *J* 16.5, 5.5 and 0.8 Hz), 3.75 (3H, s), 4.43 (1H, ddd, *J* 5, 2 and 0.8 Hz), 4.80 (1H, b), 5.08 (1H, ddd, *J* 10.5, 5.2 and 2 Hz), 6.74 (1H, m); *m/z* (CI, NH_3) 288 (82.9%, MNH_4^+) (Found: C, 57.8; H, 6.8. $C_{13}H_{18}O_6$ requires C, 57.8; H, 6.7%).

(1R,2R,3S,4S,5R)-1-O-Acetyl-2,3-O-isopropylidene-5-methoxycarbonyl-cyclohexan-1,2,3,4,5-pentaol (**16**)

A solution of the compound (**15**) (1 g, 3.70 mmol), trimethylamine *N*-oxide (0.58 g, 5.18 mmol), pyridine (1.8 ml, 22.94 mmol), water (0.36 ml, 20 mmol), *tert*-butanol (8 ml) and a catalytic amount of OsO_4 was refluxed with stirring for 12 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 washed with ethyl acetate (40 ml). The eluant was concentrated *in vacuo* and the residue extracted with CH_2Cl_2 (4 X 20 ml). The combined extracts were washed with saturated aqueous $Na_2S_2O_3$ (2 X 10 ml), brine (2 X 10 ml), dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash chromatography [petroleum ether-diethyl ether (1:3 v/v)] provided the *diol* (**16**) (1.0 g, 90%) as a white solid, m.p. 134—134.5°C; R_F 0.23 [petroleum ether-diethyl ether (1:4 v/v)]; $[\alpha]_D$ -43.27° (*c* 0.49); $\nu_{max.}$ 3462 (OH) and 1739 cm^{-1} (C=O); δ 1.42 (3H, s), 1.60 (3H, s), 2.00 (1H, dd, *J* 13.5 and 5 Hz), 2.11 (3H, s), 2.30 (1H, t, *J* 13.5 Hz), 3.82 (3H, s), 3.98 (1H, d, *J* 13.5 Hz), 4.09 (1H, dd, *J* 13.5 and 7.5 Hz), 4.48 (1H, t, *J* 7.5 Hz), 5.45 (1H, m); *m/z* (CI, NH_3) 305 (100%, MNH_4^+) (Found: C, 51.4; H, 6.8. $C_{13}H_{20}O_8$ requires C, 51.3; H, 6.6%).

(1R,2R,3S,4S,5R)-1-O-Acetyl-2,3:4,5-di-O-isopropylidene-5-methoxycarbonyl-cyclohexan-1,2,3,4,5-pentaol (**17**)

To a solution of the compound (**16**) (0.49 g, 1.32 mmol) in dry CH_2Cl_2 (10 ml) under nitrogen was added 2-methoxypropene (0.62 ml, 1.97 mmol) and a catalytic amount of *dl*-10-camphor-suphonic acid. The mixture was stirred for 2 h at room temp. and quenched with saturated aqueous Na_2CO_3 (5 ml). The aqueous phase was extracted with CH_2Cl_2 (4 X 10 ml). The combined extracts were washed with brine (2 X 5 ml), dried ($MgSO_4$), and filtered. Solvent removal gave an oil which was flash chromatographed [petroleum ether-diethyl ether (3:1 v/v)] to yield the

diacetonide (**17**) (0.38 g, 70%) as a colourless oil, R_F 0.54 [petroleum ether-diethyl ether (2:1 v/v)]; $[\alpha]_D$ +40.77° (*c* 0.52); $\nu_{max.}$ 1742 cm^{-1} (C=O); δ 1.35 (3H, s), 1.40 (3H, s), 1.52 (3H, s), 1.55 (3H, s), 1.82 (1H, ddd, *J* 12.5, 3 and 1.5 Hz), 2.12 (3H, s), 2.46 (1H, t, *J* 12.5 Hz), 3.82 (3H, s), 4.57 (1H, ddd, *J* 7.5, 3.5 and 1.5 Hz), 4.63 (1H, d, *J* 2 Hz), 4.68 (1H, dd, *J* 7.5 and 2 Hz), 5.22 (1H, dt, *J* 12.5 and 3.5 Hz); *m/z* (CI, NH_3) 345 (100%, MH^+) (Found: MH^+ 345.1557 $C_{16}H_{25}O_8$ requires 345.1549).

(1R,2R,3S,4S,5S)-2,3:4,5-di-O-isopropylidene-5-hydroxymethyl-cyclohexan-1,2,3,4,5-pentaol (**18**)

To a solution of the compound (**17**) (0.42 g, 1.22 mmol) in dry THF (5 ml) was added dropwise a 1.0 M solution of DIBAL-H in THF (3.66 ml, 3.66 mmol) over 30 min at -10°C. The mixture was stirred for 1 h at 0°C, quenched with saturated aqueous NH_4Cl (5 ml) and filtered. The aqueous phase was extracted with CH_2Cl_2 (4 X 10 ml). The combined extracts were washed with brine (2 X 5 ml), dried ($MgSO_4$), and filtered. Solvent removal gave a light brown oil which was flash chromatographed [petroleum ether-diethyl ether (1:2 v/v)] to give the *title compound* (**18**) (0.26 g, 79%) as a white solid, m.p. 114—115°C; R_F 0.24 [petroleum ether-diethyl ether (1:4 v/v)]; $[\alpha]_D$ +44.90° (*c* 0.49); $\nu_{max.}$ 3442 cm^{-1} (OH); δ 1.38 (6H, s), 1.47 (3H, s), 1.49 (3H, s), 1.71 (2H, m), 3.57 (2H, m), 4.06 (1H, ddd, *J* 9, 6 and 3.8 Hz), 4.24 (1H, d, *J* 2.7 Hz), 4.48 (1H, dd, *J* 7.5 and 3.8 Hz), 4.69 (1H, dd, *J* 7.5 and 2.7 Hz); *m/z* (CI, NH_3) 275 (100%, MH^+) (Found: MH^+ 275.1505 $C_{13}H_{23}O_6$ requires 275.1495).

*(1R,2R,3S,4S,5S)-5-*tert*-Butyldimethylsiloxymethyl-2,3:4,5-di-O-isopropylidene-cyclohexan-1,2,3,4,5-pentaol* (**19**)

To a solution of the compound (**18**) (200 mg, 0.74 mmol), imidazole (100.8 mg, 1.48 mmol) and a catalytic amount of DMAP in dry CH_2Cl_2 (2 ml) was added *tert*-butyldimethylsilyl chloride (122 mg, 0.81 mmol) at room temp. The mixture was stirred for 4 h and poured into saturated aqueous NH_4Cl (2 ml). The aqueous phase was extracted with CH_2Cl_2 (3 X 10 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 (1:1 v/v)] afforded the *title compound* (**19**) (258 mg, 91%) as a white solid, m.p. 56—57°C; R_F 0.67 [petroleum ether-diethyl ether (1:4 v/v)]; $[\alpha]_D$ +31.62° (*c* 2.34); $\nu_{max.}$ 3490 cm^{-1} (OH); δ 0.07 (3H, s), 0.08 (3H, s), 0.91 (9H, s), 1.38 (3H, s), 1.40 (3H, s), 1.45 (3H, s), 1.46 (3H, s), 1.53 (1H, t, *J* 14 Hz), 1.70 (1H, dd, *J* 14 and 3 Hz), 3.53 (1H, d, *J* 10.5 Hz), 3.65 (1H, d, *J* 10.5 Hz), 4.05 (1H, dt, *J* 12 and 4 Hz), 4.26 (1H, d, *J* 2.5 Hz), 4.45 (1H, dd, *J* 7.5 and 4 Hz), 4.67 (1H, dd, *J* 7.5 and 2.5 Hz); *m/z* (CI, NH_3) 389 (14.1%, MH^+) (Found: MH^+ 389.2350 $C_{19}H_{37}O_6Si$ requires 389.2359).

*(1R,2R,3S,4S)-4-*tert*-Butyldimethylsiloxymethyl-1,2:3,4-di-O-isopropylidene-cyclohexan-1,2,3,4-tetraol* (**20**)

To a mixture of the compound (**19**) (70 mg, 0.18 mmol), pyridine (58 µl, 0.72 mmol) and a catalytic amount of DMAP in dry CH_2Cl_2 (1 ml) was added phenyl chlorothioformate (37.8 µl, 0.27 mmol) at room temp. The mixture was stirred for 3 h and poured into saturated aqueous NH_4Cl (5 ml). The aqueous phase was extracted with CH_2Cl_2 (3 X 10 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 (4:1 v/v)] afforded the thioester (95 mg, 100%) as a white solid which was used directly in the following reaction.

To a solution of the thioester (95 mg, 0.24 mmol) and AIBN (6.8 mg, 0.05 mmol) in dry toluene (3 ml) was added n-Bu_3SnH (100 µl, 0.38 mmol). The reaction mixture was refluxed for 4 h and poured into the ice-cold water (2 ml). The aqueous phase was extracted with CH_2Cl_2 (5 X 3 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 (1:8 v/v)] afforded the *title compound* (**20**) (55 mg, 82%) as a colourless oil, R_F 0.20 [petroleum ether-diethyl ether (1:8 v/v)]; $[\alpha]_D$ +3.49° (*c* 1.26); δ 0.08 (3H, s), 0.09 (3H, s), 0.91 (9H, s), 1.33 (3H, s), 1.42 (3H, s), 1.45 (3H, s), 1.47 (3H, s), 1.3-2.0 (4H, m), 3.53 (1H, d, *J* 10.5 Hz), 3.63 (1H, d, *J* 10.5 Hz), 4.29 (1H, d, *J* 2.2 Hz), 4.42 (1H, m), 4.52 (1H, dd, *J* 7.5 and 2.2 Hz); *m/z* (EI) 357 (23.7%, M^+-CH_3) (Found: M^+-CH_3 357.2109 $C_{18}H_{33}O_5Si$ requires 357.2097).

Pseudo-β-D-fructopyranose (**2**)

Ice-cold aqueous CF_3COOH (5 ml, 1:1 v/v) was added to the compound (**20**) (60 mg) and the mixture was stirred at room temp. for 4 h. Removal of the solvent and concentration with absolute ethanol (2 X) gave a reddish oil. The oil was dissolved in water (5 ml) and the aqueous phase was washed with CH_2Cl_2 (3 X 0.5 ml). Concentration of the aqueous phase with absolute ethanol (3 X) gave white solid (**2**) (19 mg, 65%), m.p. 96—97°C (lit.[5] syrup); R_F 0.29 [EtOAc-MeOH (4:1 v/v)]; $[\alpha]_D$ -53° (*c* 0.46, MeOH) [lit.[5] -57° (*c* 1.2, MeOH)]; $\nu_{max.}$ 3417 cm^{-1} (OH); δ (D_2O) (HOD at 4.73) 1.48 (1H, m), 1.70 (3H, m), 3.44 (1H, d, *J* 11 Hz), 3.52 (1H, d, *J* 11 Hz), 3.61 (1H, d, *J* 10 Hz), 3.66 (1H, dd, *J* 10 and 2.5 Hz), 3.99 (1H, b); *m/z* (CI, NH_3) 196 (26.9%, MNH_4^+) (Found: MNH_4^+ 196.1194 $C_7H_{18}NO_5$ requires 196.1185).

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