Chemoenzymatic synthesis of the epimeric 6*C*-methyl-D-mannoses from toluene

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The title compounds 1 and 2, which are effective and specific inhibitors of phosphohexomutases, have been prepared in enantiomerically pure form from toluene. The initial step of the reaction sequence involves enzymatic *cis*-1,2-dihydroxylation of toluene by *E. coli* JM109 (pDTG601) to give the *cis*-1,2-dihydrocatechol 3. The latter compound is then converted, *via* a series of chemical oxidation and reduction steps, into compounds 1 and 2. The X-ray crystal structures of the bis-acetonide derivatives 11, 13 and 14 have been determined.

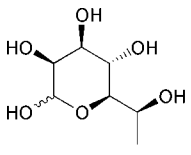
A major focus within the burgeoning field of glycobiology is the identification of specific inhibitors of enzymes involved in carbohydrate metabolic pathways and the subsequent development of a detailed mechanistic understanding of the modes of action of these inhibitors.[1] Such studies could provide useful insights into various genetic disease states associated with faulty carbohydrate metabolism.[2] Recently, Fleet and coworkers have reported[3] the synthesis of mannose derivatives **1** and **2** then shown that these compounds are good inhibitors of phosphoglucomutase and phosphomannomutase (PMM). These and earlier observations[4] by the same group suggest that 6-alkylaldohexose derivatives may prove useful as biochemical tools for probing the function of a wide range of carbohydrate processing enzymes. As a consequence of such possibilities we now describe a new approach to the 6-methylaldohexoses **1** and **2** which employs the *cis*-1,2-dihydrocatechol **3** as starting material. Compound **3** is an enantiomerically pure compound that is readily obtained in large quantities by microbial *cis*-1,2-dihydroxylation of toluene.[5] As such there is the prospect of readily generating ^{2}H-, ^{13}C- and/or ^{17}O-labelled derivatives of **3** and, thence, of the compounds **1** and **2**.[6] Such isotopically labelled derivatives of the title carbohydrates could prove especially useful in probing their interactions with enzymes such as PMM.

The reaction sequence used in producing 6*S*-6*C*-methyl-D-mannose (**1**), which was inspired by Hudlicky's seminal contributions to this general area,[5] is shown in Scheme 1 and starts with the conversion of diol **3** into the corresponding and well-known[7] acetonide derivative **4** (95%). Reaction of the last compound with osmium tetroxide, in essentially the same manner as described very recently by Seoane *et al.*,[8] afforded a *ca.* 1 : 1 mixture of products **5** (33%) and **6** (31%) which could be separated from one another by flash chromatography. The diastereoselectivity associated with the conversion **4** → **5**/**6** derives from the steric demands associated with the acetonide group of the starting material. Treatment of compound **6** with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid monohydrate afforded the bis-acetonide **7** (96%) which was subjected to ozonolytic cleavage in methanol–dichloromethane followed by a reductive work-up with dimethyl sulfide.[9] In this manner an unstable and *ca.* 3 : 1 mixture of what is tentatively assigned as the hydroperoxide **8**[10] and its corresponding aldehyde was obtained. Reaction of this mixture with sodium borohydride then gave a mixture of diols **9** (10%) and **10** (56%) which could be separated from one another by high-pressure liquid chromatography. Interestingly, when this reduction was effected using lithium borohydride an 8 : 92 mixture of diols **9** and **10** was obtained, whereas the use of DIBAL-H as reductant gave compound **10** (56%) as the only isolable product of reaction. Selective oxidation of the primary hydroxyl group within diol **10** could be achieved using the sterically demanding oxammonium salt derived from 4-acetamido-TEMPO and sodium hypochlorite,[11] and in this way the crystalline lactone **11** was obtained (81%) and its structure determined by single-crystal X-ray analysis (Fig. 1 and Table 1).

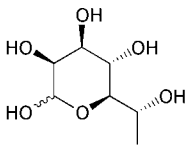
Reduction of compound **11** with DIBAL-H at −78 °C then gave lactol **12** which was immediately deprotected using aqueous trifluoroacetic acid. In this manner the target mannose derivative **1** (99% from **11**) was produced and, save for the specific rotation, the spectral data derived from compound **1** matched all of those reported[3] previously. Final confirmation of the structure of this target molecule was obtained by single-crystal X-Ray analysis (Table 1) of the derived bis-acetonide **13** (64%) which has also been described previously.[3] The discrepancy between the $[\alpha]_D$ value (−10 after 10 min in D_2O) derived from our sample of compound **1** and that reported[3] by Fleet *et al.* (+14.2 after 10 min in D_2O) for the same material is rather difficult to reconcile. This is especially so because the specific rotation observed {$[\alpha]_D$ − 2.8 [*c* 0.50 (after 10 min)]} for our sample of the derived bis-acetonide **13** is in reasonable agreement with the corresponding values {$[\alpha]_D$ + 0.1 to −7.7 [*c* 1.00 in $CHCl_3$ after 169 h] reported by Fleet *et al.*[3]

The synthesis of 6*R*-6*C*-methyl-D-mannose (**2**) was achieved using the reaction sequence shown in Scheme 2 and involved initial oxidation of the diol **9** to the lactone **14** (86%) using the oxammonium salt methodology employed in generating congener **11**.

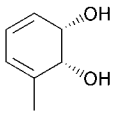
Compound **14**, the structure of which was confirmed by single-crystal X-ray analysis (Fig. 2 and Table 1), was then subjected to DIBAL-H-mediated reduction and the resulting lactol **15** was immediately hydrolyzed to the target mannose derivative **2** (99% from **14**), using aqueous trifluoroacetic acid.



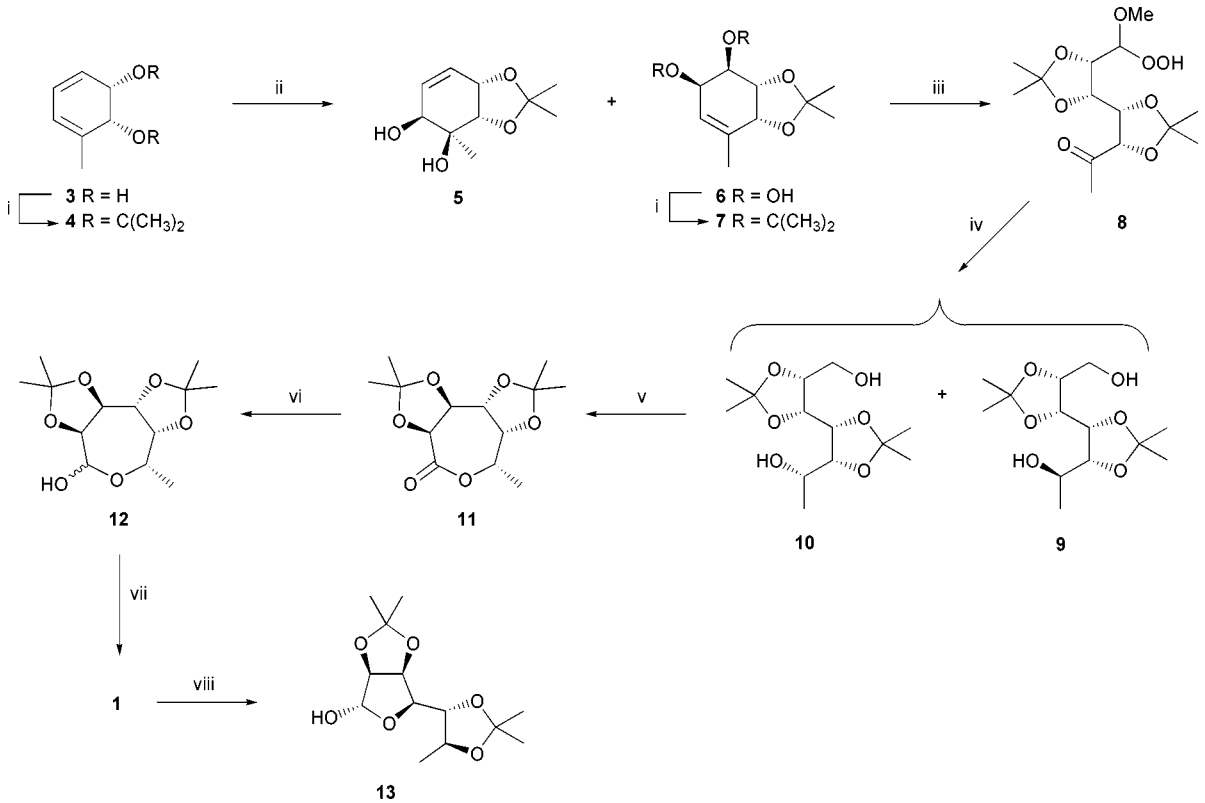
1



2



3



Scheme 1 *Reagents and conditions*: i, $Me_2C(OMe)_2$, *p*-TsOH·H_2O (10 mol%), −10 °C, 2 h; ii, OsO_4 (cat.), NMMNO (2.0 mol equiv.), Me_2CO–H_2O (1 : 1 v/v), 60 °C, 0.5 h; iii, O_3, CH_2Cl_2–MeOH (5 : 2 v/v), −78 °C, 2 h then Me_2S (15.0 mol equiv., −78 to 18 °C, 2 h; iv, $NaBH_4$ (4 mol equiv.), MeOH, 0 °C, 3 h; v, 4-(AcNH)TEMPO (10 mol%), KBr (25 mol%), Bu_4NI (10 mol%), NaOCl (1.34 M aqueous solution, 2.2 mol equiv.), $NaHCO_3$–brine (buffered to *ca.* pH 10), 0 °C, 2 h; vi, DIBAL-H (3.0 mol equiv.), −78 °C, 5 min; vii, CF_3CO_2H–H_2O (3 : 2 v/v), 18 °C, 16 h; vii, Me_2CO, (+)-CSA (20 mol%).

Once again, with the exception of specific rotation $\{[\alpha]_D$ −13.8 *vs.* a reported[3] value of +14.2$\}$, the spectral data derived from this compound matched those obtained previously.

The reaction sequences described above for the preparation of compounds **1** and **2** involve the high-pressure liquid chromatographic separation of precursors **9** and **10**. The tedium associated with this separation can be avoided by oxidising the mixture of the latter compounds in the manner described earlier and then subjecting the resulting lactones **11** and **14** to purification by flash chromatography on silica (1 : 4 ethyl acetate–hexane elution; $\Delta R_f = 0.2$).

Various analogues of *cis*-1,2-dihydrocatechol **3** which contain alternate alkyl groups on the six-membered ring are available.[5] Consequently, the strategy reported here for the preparation of compounds **1** and **2** should be capable of straightforward extension to the synthesis of other 6*C*-alkyl-D-mannose derivatives.

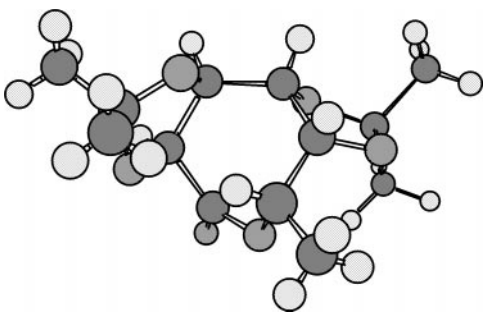


Fig. 1 CS Chem3D Std™ drawing of compound **11** generated using data derived from an X-ray crystallographic study.

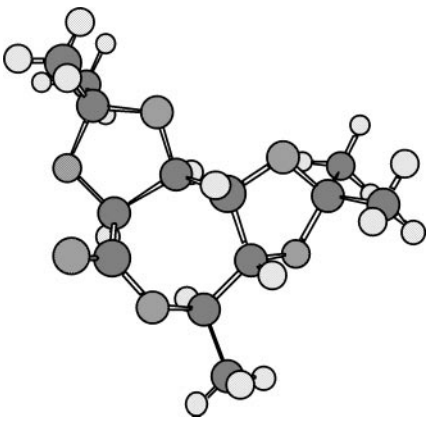
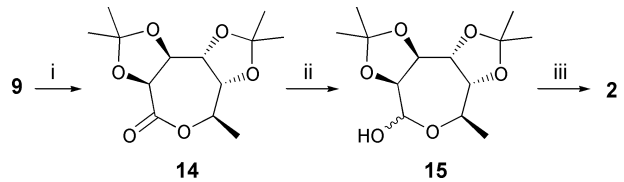


Fig. 2 CS Chem3D Std™ drawing of compound **14** generated using data derived from an X-ray crystallographic study.



Scheme 2 *Reagents and conditions*: i, 4-(AcNH)TEMPO (10 mol%), KBr (25 mol%), Bu_4NI (10 mol%), NaOCl (1.34 M aqueous solution, 2.2 mol equiv.), $NaHCO_3$–brine (buffered to *ca.* pH 10), 0 °C, 2 h; ii, DIBAL-H (3.0 mol equiv.), −78 °C, 5 min; iii, CF_3CO_2H–H_2O (3 : 2 v/v), 18 °C, 16 h.

Experimental

Unless otherwise specified, ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 300 spectrometer using deuterochloroform as solvent. The 500 MHz ^1H NMR spectra and

Table 1 Crystallographic data for compounds **11**, **13** and **14**

	11	**13**	**14**
Formula	$C_{13}H_{20}O_6$	$C_{13}H_{22}O_6$	$C_{13}H_{20}O_6$
FW	272.3	274.3	272.3
Size/mm	0.28 × 0.04 × 0.26	0.08 × 0.08 × 0.2	0.003 × 0.2 × 0.2
Crystal system	Orthorhombic	Orthorhombic	Orthorhombic
Space group	$P2_12_12_1$ (no. 19)	$P2_12_12_1$ (no. 19)	$P2_12_12_1$ (no. 19)
a/Å	8.4308(4)	6.9393(5)	6.5102(2)
b/Å	10.5457(5)	10.5584(8)	8.9104(4)
c/Å	15.6538(8)	19.7333(8)	23.7859(9)
U/Å^3	1391.8(1)	1445.8(1)	1379.8(1)
Z	4	4	4
D_c/g m^{-3}	1.30	1.26	1.311
T/K	200	200	200
λ/Å	0.710 73	0.710 73	0.710 73
μ/cm^{-1}	0.1	0.1	0.1
No. of reflections	2291 [$I > 3.0\sigma(I)$]	1649 [$I > 3.0\sigma(I)$]	2239 [$I > 3.0\sigma(I)$]
No. of variables	172	172	172
R	0.038	0.038	0.033
R_w	0.039	0.042	0.036
S	0.95	1.01	1.23
Radiation	Graphite monochromated Mo-Kα in all three cases		

the 150 MHz ^{13}C NMR spectrum were obtained on the corresponding Varian Inova spectrometers. Infrared spectra were recorded on either a Perkin-Elmer 683 or 1800 FTIR instrument. Unless otherwise specified, mass spectral analyses were carried out in electron-impact mode and on a VG Micromass 7070F Double-Focussing Spectrometer. Electrospray (ES) mass spectral analyses were conducted on a VG Quattro II instrument. Unless otherwise specified, optical rotations were recorded in chloroform solution at 18–20 °C using a Perkin Elmer 241 polarimeter. Ozonolyses were conducted using a Wallace and Tiernan Ozonator with the oxygen flow rate and power adjusted to *ca.* 25 l h^{-1} and 200 V, respectively. Melting points were recorded on a Reichert Hot-Stage microscope and are uncorrected. Thin layer chromatographic analyses were carried out on aluminium-backed, 0.2 mm thick silica gel 60 GF_{254} plates supplied by Merck, while flash chromatographic purifications were conducted according to the method of Still *et al.*[12] using Merck silica gel 60 (230–400 mesh) as adsorbent. All solvents and common reagents were purified by established procedures.[13]

Synthetic studies

(1*S*,2*S*,3*S*,4*S*)-3,4-*O*-Isopropylidene-2-methylcyclohex-5-ene-1,2,3,4-tetraol (5) and (1*R*,2*R*,3*R*,4*R*)-3,4-*O*-isopropylidene-5-methylcyclohex-5-ene-1,2,3,4-tetraol (6). Osmium tetroxide (10 drops of a 2.5 wt% solution in *tert*-butanol) was added dropwise to a magnetically stirred mixture of diene **4**[7] (3.9 g, 23.49 mmol) and *N*-methylmorpholine-*N*-oxide (NMMNO, 5.3 g, 43.24 mmol) in acetone (15 ml) and water (15 ml) maintained at 0 °C (ice-bath). The resulting mixture was warmed to 18 °C over *ca.* 1 h then heated at 60 °C for a further 1 h. The cooled reaction mixture was treated with sodium metabisulfite (50 ml of a 20% w/v aqueous solution) which was then concentrated under reduced pressure. The residue thus obtained was partitioned between dichloromethane (100 ml) and water (100 ml). The separated aqueous phase was extracted with dichloromethane (7 × 100 ml) and the combined organic fractions were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a tan-coloured oil. Subjection of this material to flash chromatography (40% ethyl acetate–hexane) afforded two fractions, A and B.

Concentration of fraction A (R_f 0.3), afforded diol **5** (1.77 g, 38%) as a pale-yellow oil. The ^{1}H NMR, ^{13}C NMR, MS and IR spectral data obtained on this material were in complete agreement with those reported[8] by Seoane *et al.*

Concentration of fraction B (R_f 0.2), afforded diol **6** (1.63 g, 35%) as a pale-yellow oil. The ^{1}H NMR, ^{13}C NMR, MS and IR spectral data obtained on this material were in complete agreement with those reported[8] by Seoane *et al.*

(3a*S*,5a*R*,8a*R*,8b*S*)-2,2,4,7,7-Pentamethyl-3a,5a,8a,8b-tetrahydrobenzo[1,2-d:3,4-d′]bis[1,3]dioxole (7). A magnetically stirred solution of diol **6** (148 mg, 0.74 mmol) in 2,2-dimethoxypropane (10 ml) was cooled to 0 °C then treated with *p*-toluenesulfonic acid monohydrate (14 mg, 0.07 mmol). The resulting mixture was allowed to stand at 18 °C for 1 h then treated with triethylamine (1 ml) and concentrated under reduced pressure. The pale-yellow oil thus obtained was dissolved in diethyl ether (10 ml) and the resulting solution washed with water (1 × 10 ml). The separated aqueous phase was extracted with diethyl ether (3 × 10 ml) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford compound **7** (170 mg, 96%) as a pale-yellow oil, $[\alpha]_D$ + 13.2° (*c* 1.40), HRMS: found: *m*/*z* 225.1128 $(M - CH_3)^{\cdot+}$; $C_{13}H_{20}O_4$ requires 225.1127. ν_{max} (KBr/cm^{-1}): 2985, 1378, 1369, 1232, 1064; δ_H: 5.44 (br, s, 1H), 4.51 (m, 3H), 4.37 (d, *J* 4.9 Hz, 1H), 1.82 (s, 3H, 4-CH_3), 1.38 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.34 (s, 3H, CH_3); δ_C: 133.8 (C, C-4), 122.1 (CH, C-5), 108.8 (C), 108.7 (C), 73.5 (CH), 73.4 (CH), 73.1 (CH), 71.0 (CH), 27.8 (CH_3), 27.5 (CH_3), 26.3 (2 × CH_3), 19.5 (CH_3); *m*/*z* 225 [92%, $(M - CH_3)^{\cdot+}$], 125 (100).

7-Deoxy-2,3 : 4,5-di-*O*-isopropylidene-D-glycero-D-manno-heptitol (9) and 7-deoxy-2,3:4,5-di-*O*-isopropylidene-L-glycero-D-mannoheptitol (10). A solution of compound **7** (800 mg, 3.33 mmol) in methanol–dichloromethane (7 ml of a 2 : 5 v/v mixture) was treated, for 2 h at −78 °C, with a stream of ozone (*ca.* 40% ozone in oxygen). The ensuing solution was purged with oxygen for 10 min then treated with dimethyl sulfide (3.7 ml, 50 mmol) and allowed to warm to 18 °C over *ca.* 1 h. After 2 h the reaction mixture was concentrated under reduced pressure and the resulting mixture dissolved in methanol (10 ml). The ensuing solution was cooled to 0 °C then sodium borohydride (252 mg, 6.66 mmol) was added in two portions. After 2 h the reaction mixture was acidified (with 2 M aqueous HCl) to *ca.* pH 4 then diluted with water (60 ml) and extracted with chloroform (8 × 60 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a pale-yellow oil. Subjection of this material to flash chromatography (6 : 4 ethyl acetate–hexane elution) afforded, after concentration of the appropriate fractions (R_f 0.2), a 15 : 85 mixture of alcohols **9** and **10**. This mixture was subjected to preparative HPLC [Waters μ-Porasil 19 × 300 mm column (part no. 25829), 1 : 1

ethyl acetate–hexane elution, flow rate 3 ml min^{-1}] and in this manner two fractions, A and B, were obtained.

Concentration of fraction A (R_t 14.84 min) gave compound **10** (516 mg, 56%) as a clear, colourless oil, $[\alpha]_D + 19.6$ (*c* 1.40), HRMS: found: *m/z* 261.1339 $(M - CH_3)^{\cdot+}$; $C_{13}H_{24}O_6$ requires 261.1338. ν_{max} (KBr/cm^{-1}): 3435, 2983, 2936, 1381, 1247, 1215, 1049, 886; δ_H: 4.39 (dd, *J* 6.5, 2.8, 1H), 4.30 (m, 2H), 4.02 (dd, *J* 6.7, 2.6, 1H), 3.92 (m, 1H), 3.73 (m, 2H), 3.11 (d, *J* 3.9, 1H, OH), 2.56 (dd, *J* 7.5, 5.5, 1H, OH), 1.58 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 1.39 (s, 6H, 2 × CH_3), 1.25 (d, *J* 6.6 Hz, 3H, CH_3); δ_C: 109.2(3) (C), 109.1(9) (C), 80.9 (CH), 77.6 (CH), 74.3 (CH), 74.0 (CH), 65.8 (CH), 61.6 (CH_2), 27.0 (CH_3), 26.2 (CH_3), 25.4 (CH_3), 25.2 (CH_3), 20.1 (CH_3); *m/z* 261 [14%, $(M - CH_3)^{\cdot+}$], 187 (15), 173 (22), 59 (100).

Concentration of fraction B (R_t 19.52 min) gave compound **9** (91 mg, 10%) a clear, colourless oil, $[\alpha]_D + 4.0$ (*c* 0.60), HRMS: found: *m/z* 261.1340 $(M - CH_3)^{\cdot+}$; $C_{13}H_{24}O_6$ requires 261.1338. ν_{max} (KBr/cm^{-1}): 3392, 2984, 1382, 1217, 1070; δ_H: 4.54 (dd, *J* 6.5, 3.9, 1H), 4.30 (m, 2H), 3.98 (br, m, 1H), 3.83 (dd, *J* 8.9, 5.5, 1H), 3.75 (m, 2H), 2.67 (br, m, 1H, OH), 2.39 (br, d, *J* 4.3, 1H, OH), 1.54 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.30 (d, *J* 6.4 Hz, 3H, 7-CH_3); δ_C: 108.5(9) (C), 108.5(5) (C), 81.1 (CH), 77.6 (CH), 74.9 (CH), 74.4 (CH), 65.6 (CH), 61.4 (CH_2), 27.4 (CH_3), 27.2 (CH_3), 25.6 (CH_3), 25.2 (CH_3), 20.9 (CH_3); *m/z* 261 [33%, $(M - CH_3)^{\cdot+}$], 217 (17), 187 (34), 131 (44), 59 (100).

7-Deoxy-2,3 : 4,5-di-*O*-isopropylidene-L-glycero-D-manno-heptonic acid ε-lactone (11). A magnetically stirred solution of diol **10** (79 mg, 0.29 mmol) and 4-acetamido-TEMPO (6.2 mg, 0.03 mmol) in dichloromethane (5 ml) was treated with sodium bicarbonate (3 ml of a saturated aqueous solution), potassium bromide (8.6 mg, 0.07 mmol) and tetrabutylammonium iodide (10.6 mg, 0.03 mmol). The resulting mixture was cooled to 0 °C then treated, dropwise over 0.75 h, with a solution comprising sodium hypochlorite (470 μl of a 1.34 M aqueous solution, 0.63 mmol), sodium bicarbonate (2 ml of a saturated aqueous solution) and brine (3 ml). After 1 h the reaction mixture was diluted with water (10 ml) and the separated aqueous phase was extracted with dichloromethane (4 × 10 ml). The combined organic layers were washed with brine (1 × 40 ml) and saturated sodium bicarbonate (1 × 40 ml) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a colourless solid. Subjection of this material to flash chromatography (1 : 4 ethyl acetate–hexane elution) afforded, after concentration of the appropriate fractions (R_f 0.3), lactone **11** (63 mg, 81%) as colourless crystals, m.p. 132–134 °C, $[\alpha]_D - 2.7$ (*c* 0.55); HRMS: found: *m/z* 257.1021 $(M - CH_3)^{\cdot+}$; C, 57.1; H, 7.4. $C_{13}H_{20}O_6$ requires 257.1025; C, 57.3; H, 7.4%. ν_{max} (KBr/cm^{-1}): 2987, 2939, 1737, 1383, 1255, 1210, 1060, 1015; δ_H: 5.17 (q, *J* 6.5, 1H), 4.85 (m, 2H), 4.65 (m, 1H), 4.05 (d, *J* 6.8, 1H), 1.58 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 1.37 (s, 6H, 2 × CH_3), 1.35 (d, *J* 6.5 Hz, 3H, CH_3); δ_C: 166.8 (C, C-1), 111.0 (C), 110.4 (C), 77.6 (CH), 77.2 (CH), 73.8 (CH), 72.4 (CH), 70.8 (CH), 25.6 (CH_3), 25.3 (CH_3), 25.0 (CH_3), 22.2 (CH_3), 16.9 (CH_3); *m/z* 257 [100%, $(M - CH_3)^{\cdot+}$], 128 (24), 113 (68), 83 (94).

7-Deoxy-L-glycero-D-mannoheptopyranose (6*S*-6*C*-methyl-mannose, 1). DIBAL-H (165 μl of a 1 M solution in hexane, 0.165 mmol) was added, dropwise, to a magnetically stirred solution of lactone **11** (15 mg, 0.05 mmol) in dichloromethane (1.0 ml) maintained at −78 °C under a nitrogen atmosphere. After a further 5 min, methanol (1.0 ml) was added, dropwise, to the reaction mixture which was then allowed to warm to 18 °C (over *ca.* 20 min) before being quenched with ammonium chloride (4 ml of a saturated aqueous solution). The resulting mixture was partitioned between ethyl acetate (5 ml) and brine (5 ml) and the separated aqueous layer extracted with ethyl acetate (3 × 5 ml). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford a pale-yellow oil (16 mg) which is presumed to contain lactol **12**. This oil was immediately treated with trifluoroacetic acid (6 ml) and water (4 ml) and the resulting solution stirred at 18 °C for 16 h. After this time the reaction mixture was concentrated under reduced pressure to afford a pale-pink oil which was partitioned between water (5 ml) and diethyl ether (5 ml). The separated aqueous layer was washed with diethyl ether (2 × 5 ml) then freeze-dried to give compound **1**[3] (10 mg, 99%) as a white foam, $[\alpha]_D - 10$ [*c* 0.98 (in D_2O after 10 min)]. ν_{max} (KBr/cm^{-1}): 3424; δ_H: (500 MHz, D_2O) (α-anomer) 5.16 (d, $J_{1,2}$ 1.7, 1H, H-1), 4.14 (dq, $J_{6,7}$ 6.7, $J_{6,5}$ 1.8, 1H, H-6), 3.88 (dd, $J_{2,3}$ 3.1, $J_{2,1}$ 1.7, 1H, H-2), 3.78 (dd, $J_{3,4}$ 9.3, $J_{3,2}$ 3.1, 1H, H-3), 3.74 (app t, *J* 9.3, 1H, H-4), 3.52 (dd, $J_{5,4}$ 9.3, $J_{5,6}$ 1.8, 1H, H-5), 1.22 (d, $J_{7,6}$ 6.7, 3H, 7-CH_3); (β-anomer) 4.84 (d, $J_{1,2}$ 1.0, 1H, H-1), 4.10 (dq, $J_{6,7}$ 6.6 Hz, $J_{6,5}$ 2.3, 1H, H-6), 3.89 (dd, $J_{2,3}$ 3.5, $J_{2,1}$ 1.0, 1H, H-2), 3.69 (app t, *J* 9.8, 1H, H-4), 3.60 (dd, $J_{3,4}$ 9.8, $J_{3,2}$ 3.5, 1H, H-3), 3.09 (dd, $J_{5,4}$ 9.8, $J_{5,6}$ 2.3, 1H, H-5), 1.25 (d, $J_{7,6}$ 6.6 Hz, 3H, 7-CH_3); δ_C:(α-anomer) 94.8 (CH, C-1), 74.8 (CH), 71.9 (CH), 71.3 (CH), 67.5 (CH), 65.2 (CH), 19.5 (CH_3); (β-anomer) 94.6 (CH, C-1), 78.6 (CH), 74.0 (CH), 71.9 (CH), 67.2 (CH), 65.3 (CH), 19.4 (CH_3); *m/z* (ES) 411 $(2M + Na)^+$, 217 $(M + Na)^+$.

7-Deoxy-2,3 : 5,6-di-*O*-isopropylidene-α-L-glycero-D-manno-heptofuranose (13). (1*S*)-(+)-10-Camphorsulfonic acid (1.6 mg, 0.01 mmol) was added to a stirred solution of compound **1** (11 mg, 0.06 mmol) in acetone (1.0 ml) maintained at 18 °C. After 16 h the reaction mixture was treated with sodium bicarbonate (*ca.* 30 mg) and after a further 1 h filtered through a no. 3 porosity sintered glass funnel. The filtrate was concentrated under reduced pressure to afford a colourless oil which was subjected to flash chromatography (1 : 2 ethyl acetate–hexane elution). Concentration of the appropriate fractions (R_f 0.4) afforded a colourless solid which was recrystallised (hexane) to give compound **13**[3] (10 mg, 64%) as colourless crystals, m.p. 118–119 °C (lit.[3] m.p. 121–122 °C); $[\alpha]_D - 2.8$ [*c* 0.50 (after 10 min)]; HRMS: found: *m/z* 259.1180 $(M - CH_3)^{\cdot+}$; C, 57.1; H, 8.0. $C_{13}H_{22}O_6$ requires 259.1182; C, 56.9; H, 8.1%. ν_{max} (KBr/cm^{-1}): 3503, 1061; δ_H: 5.38 (d, *J* 2.6, 1H), 4.85 (dd, *J* 5.8, 3.6, 1H), 4.61 (d, *J* 5.9, 1H), 4.15 (m, 1H), 4.06 (dd, $J_{4,5}$ 8.8, 3.5, 1H), 3.87 (dd, *J* 8.7, 7.3, 1H), 2.36 (d, *J* 2.4, 1H, OH), 1.47 (s, 6H, 2 × CH_3), 1.39 (s, 3H, CH_3), 1.37 (d, *J* 6.1 Hz, 3H), 1.34 (s, 3H, CH_3); δ_C: 112.7 (C), 109.0 (C), 101.5 (CH, C-1), 85.3 (CH), 81.7 (CH), 80.0 (CH), 78.5 (CH), 76.7 (CH), 27.6 (CH_3), 26.9 (CH_3), 26.0 (CH_3), 24.8 (CH_3), 18.9 (CH_3); *m/z* 259 [60%, $(M - CH_3)^{\cdot+}$], 199 (67), 149 (100).

7-Deoxy-2,3 : 4,5-di-*O*-isopropylidene-D-glycero-D-manno-heptonic acid ε-lactone (14). Diol **9** (53 mg, 0.19 mmol) was oxidised under the same conditions as employed for the conversion **10** → **11**. The colourless solid obtained on work-up was subjected to flash chromatography (1 : 4 ethyl acetate–hexane elution) which afforded, after concentration of the appropriate fractions (R_f 0.1), lactone **14** (45 mg, 86%) as colourless crystals, m.p. 161–163 °C; $[\alpha]_D - 58.4$ (*c* 1.20); HRMS: found: *m/z* 257.1024 $(M - CH_3)^{\cdot+}$; C, 57.6; H, 7.4. $C_{13}H_{20}O_6$ requires 257.1025; C, 57.3; H, 7.4%). ν_{max} (KBr/cm^{-1}): 2989, 2928, 1760, 1378, 1203, 1077; δ_H: 4.96 (d, *J* 9.2, 1H), 4.50–4.30 (complex m, 2H), 4.10 (m, 2H), 1.59 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 1.52 (d, *J* 5.9 Hz, 3H), 1.42 (s, 3H, CH_3), 1.38 (s, 3H, CH_3); δ_C: 168.1 (C, C-1), 111.5 (C), 111.0 (C), 78.8 (CH), 77.7 (CH), 76.5 (CH), 73.7 (CH), 72.2 (CH), 28.0 (CH_3), 26.4 (CH_3), 25.4 (CH_3), 24.0 (CH_3), 18.8 (CH_3); *m/z* 257 [100%, $(M - CH_3)^{\cdot+}$], 156 (21), 145 (46), 83 (40), 59 (93).

7-Deoxy-D-glycero-D-mannoheptopyranose (6*R*-6*C*-methyl-mannose, 2). DIBAL-H (165 μl of a 1 M solution in hexane, 0.165 mmol) was added dropwise to a solution of lactone **14** (15 mg, 0.05 mmol) in dichloromethane (1.0 ml) at −78 °C. After a further 5 min, methanol (1.0 ml) was added dropwise to the reaction mixture which was allowed to warm

to 18 °C over *ca.* 20 min then treated with ammonium chloride (4 ml of a saturated aqueous solution). The resulting mixture was partitioned between ethyl acetate (5 ml) and brine (5 ml) and the separated aqueous layer extracted with ethyl acetate (3 × 5 ml). The combined organic layers dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford a pale-yellow oil (16 mg) which is presumed to contain lactol **12**. This oil was immediately treated with trifluoroacetic acid (6 ml) and water (4 ml) and stirred at 18 °C for 16 h. The resulting mixture was concentrated under reduced pressure to afford a pale-pink oil which was partitioned between water (5 ml) and diethyl ether (5 ml). The aqueous layer was washed with diethyl ether (2 × 5 ml) then freeze-dried to afford compound **2**[3] (10 mg, 99%) as a foam, $[\alpha]_D$ − 13.8 [*c* 1.00 (in H_2O after 10 min)]. ν_{max} (KBr/cm^{-1}): 3434; δ_H: (500 MHz, D_2O) (α-anomer) 5.14 (d, $J_{1,2}$ 2.0, 1H, H-1), 4.13 (dq, $J_{6,7}$ 6.5, $J_{6,5}$ 2.7, 1H, H-6), 3.89 (dd, $J_{2,3}$ 3.5, $J_{2,1}$ 2.0, 1H, H-2), 3.79(7) (dd, $J_{5,4}$ 9.8, $J_{5,6}$ 2.7, 1H, H-5),), 3.78(7) (dd, $J_{3,4}$ 9.8, $J_{3,2}$ 3.5, 1H, H-3), 3.59 (app t, *J* 9.8, 1H, H-4), 1.20 (d, $J_{7,6}$ 6.5, 3H, 7-CH_3); (β-anomer) 4.84 (d, $J_{1,2}$ 1.0, 1H, H-1), 4.12 (dq, $J_{6,7}$ 6.3, $J_{6,5}$ 2.7, 1H, H-6), 3.90 (dd, $J_{2,3}$ 3.0, $J_{2,1}$ 1.0,† 1H, H-2), 3.60 (dd, $J_{3,4}$ 9.5, $J_{3,2}$ 3.0, 1H, H-3), 3.51 (t, *J* 9.5, 1H, H-4), 3.32 (dd, $J_{5,4}$ 9.5, $J_{5,6}$ 2.7, 1H, H-5), 1.21 (d, $J_{7,6}$ 6.3 Hz, 3H, 7-CH_3); δ_C: (150 MHz, D_2O) (α-anomer) 94.7 (CH, C-1), 74.7 (CH), 71.2 (CH), 71.1 (CH), 68.6 (CH), 67.0 (CH), 15.9 (CH_3, C-7); (β-anomer) 94.5 (CH, C-1), 78.7 (CH), 73.8 (CH), 71.7 (CH), 68.3 (CH), 67.1 (CH), 15.9 (CH_3); *m/z* (ES) 411 $(2M + Na)^+$, 217 $(M + Na)^+$.

Crystal data and refinement details for compounds 11, 13 and 14

Structure determination: images were measured on a Nonius Kappa CCD diffractometer (Mo-Kα, graphite monochromator, $\lambda = 0.710\,73$ Å) and data extracted using the DENZO package.[14] Structure solution was by direct methods (SIR92)[15] and refinement was by full-matrix least squares on *F* using the maXus program package.[16]

CCDC reference number 440/227. See http://www.rsc.org/suppdata/nj/b0/b005312k/ for crystallographic files in .cif format.

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Notes and references

† Fleet *et al.* report[3] that $J_{2,1} = 9.7$ Hz for the β-anomer of compound **2**. This is the only discrepancy between our NMR data sets and all those reported[3] for each anomer of compounds **1** and **2**. We believe Fleet's value for $J_{2,1}$ cited above to be in error.

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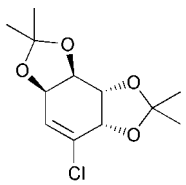

7′

10 The crude reaction mixture derived from ozonolytic cleavage of alkene **7**, and which is presumed to contain compound **8**, gave a positive test for peroxides. ^{1}H NMR spectroscopic analysis of this reaction mixture suggests that compound **8** is obtained as a single diastereoisomer. Hudlicky et al. have reported (*J. Am. Chem. Soc.*, 1994, **116**, 5099) the isolation of related intermediates during the ozonolysis of similar alkenes.

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