Complex tetrahydrofurans from carbohydrate lactones: easy access to epimeric *C*-glycosides of glucofuranose from D-*glycero*-D-*gulo*-heptono-1,4-lactone

Claire J. F. Bichard, Tilmann W. Brandstetter, Juan C. Estevez, George W. J. Fleet,* David J. Hughes and Joseph R. Wheatley

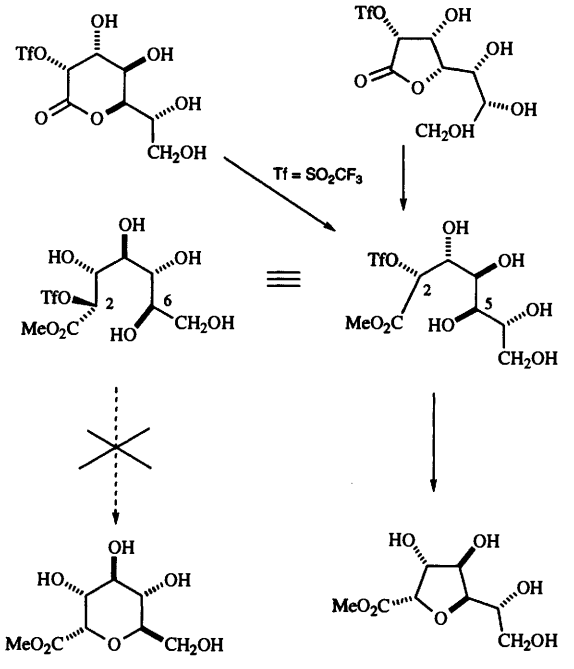
Dyson Perrins Laboratory, Oxford Centre for Molecular Sciences, Oxford University, South Parks Road, Oxford OX1 3QY, UK

A practical synthesis of epimeric *C*-glycosides of glucofuranose from the cheap *gluco*-heptono-1,4-lactone is reported; the ring contractions of 2-*O*-triflates of protected *gluco*-heptono-1,5-lactones are discussed. No tetrahydropyrancarboxylates were isolated from any of the reactions.

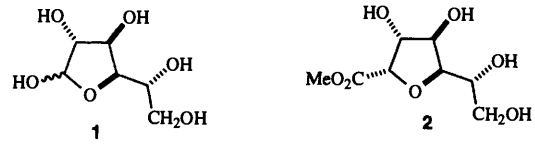
Introduction

Sugar lactones are usually relatively easy to manipulate and have proved versatile starting materials, requiring little or no protection.[1] In particular, 2-*O*-triflates (trifluoromethanesulfonates) of both γ- and δ-lactones in either basic[2] or acidic[3] methanol give good to excellent yields of highly substituted tetrahydrofuran carboxylates by ring opening to afford an open-chain triflate which subsequently closes by intramolecular nucleophilic displacement of the triflate at C-2 by a hydroxy group attached to C-5. For the α-triflates of γ- and δ-*gluco*-heptonolactones (Scheme 1), subsequent ring closure could lead to *C*-glucofuranoses by attack by C-5 OH, or to *C*-glucopyranoses by attack by C-6 OH. Although corresponding tosyl[4] and mesyl esters[5] also form tetrahydrofurans, triflates consistently produce good yields of the tetrahydrofurancarboxylates.

There is considerable interest in the synthesis of *C*-glycosides as potential mimics of sugars.[6] Seven carbon sugars are required for the formation of *C*-glycosides of hexoses. This paper reports the efficient synthesis of the epimeric tetrahydrofurancarboxylates **2** and **3** from the cheap and readily available γ-*gluco*-heptonolactone **4**; esters such as **2** and **3** are likely to prove valuable intermediates for the synthesis of a wide range of *C*-glycosides of glucofuranose **1**. Acid- and base-catalysed ring contractions of protected derivatives of the δ-lactone **5**[7] to give protected derivatives of ester **2** are also described. Although there were a number of situations in this work where tetrahydropyrancarboxylates could have been formed, no *C*-glycopyranosides were isolated; ring closures to *C*-glycopyranoses by nucleophilic displacement at C-2 of a sugar are rare.[8]



Scheme 1



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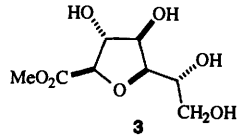

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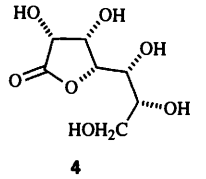

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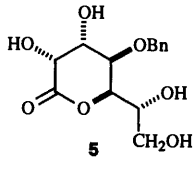

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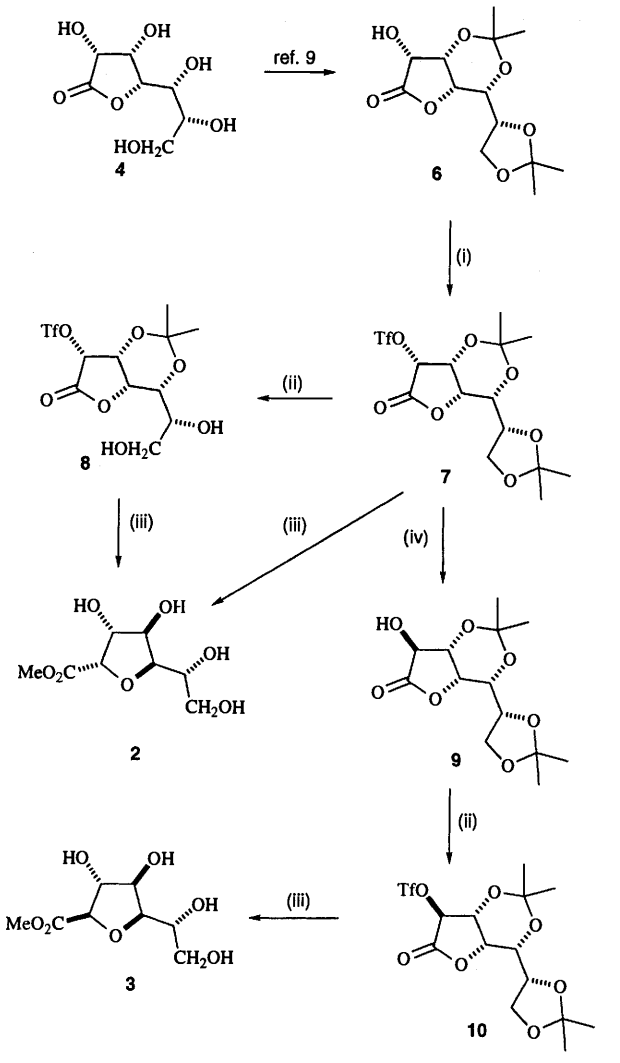
Results and discussion

For the synthesis of ester **2** as a precursor for α-*C*-glycosides of glucofuranose from **4**, it is necessary to introduce a triflate at C-2. The easily crystallised diacetonide **6** may be made on a large scale as previously described by Brimacombe.[9] Esterification of the C-2 hydroxy group in compound **6** with triflic anhydride in dichloromethane in the presence of pyridine afforded the triflate **7** in 88% yield (Scheme 2). The side-chain acetonide in compound **7** may be selectively removed by aq. acetic acid to give the monoacetonide **8** in 85% yield. In principle, the C-6 hydroxy group in compound **8** could intramolecularly displace the triflate at C-2 to provide access to *C*-glycosides of glucopyranose; all attempts to encourage such ring closures failed.



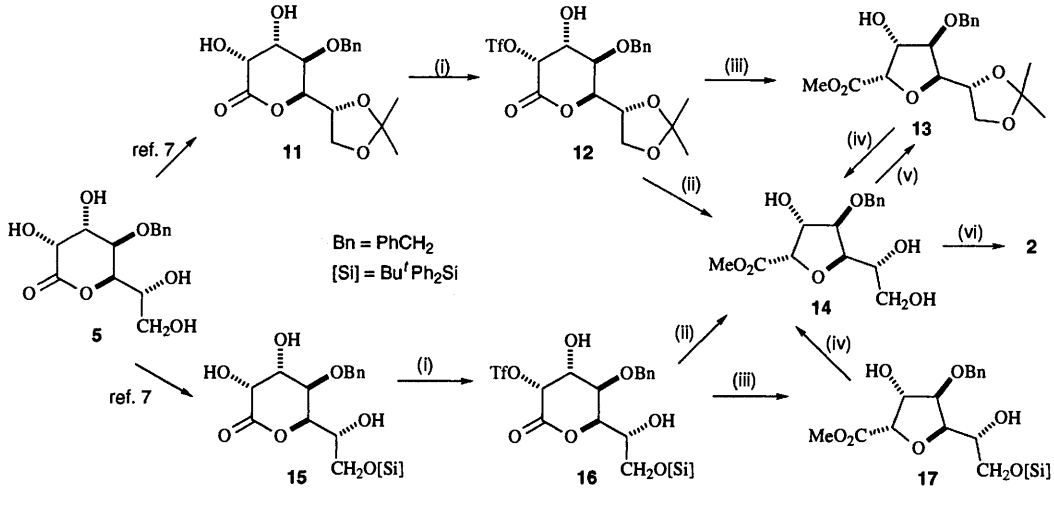
Scheme 2 *Reagents:* (i) Tf_2O, pyridine, CH_2Cl_2; (ii) 80% aq. AcOH; (iii) HCl, MeOH; (iv) CF_3CO_2Na, DMF; then MeOH

Treatment of the monoacetonide **8** with hydrogen chloride in methanol gave the methyl tetrahydrofurancarboxylate **2** in 88% yield; however, treatment of the triflate diacetonide **7** under the same conditions gave compound **2** directly in 76% yield. Thus the α-*C*-glycoside **2** may be prepared in two steps from the diacetonide **6** on a multigram scale in an overall yield of 66%. Evidence for the structure of compound **2** is presented later in the paper.

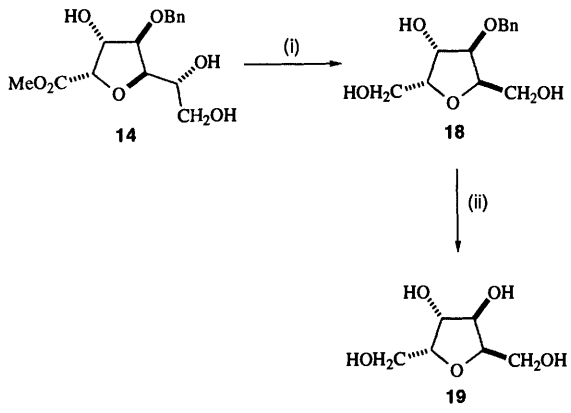
For the synthesis of the β-ester **3**, it is necessary to invert the configuration at C-2 of compound **6** prior to the formation of the tetrahydrofuran ring. Thus reaction of the triflate **7** with sodium trifluoroacetate in dimethylformamide (DMF), followed by work-up with methanol, gave the inverted alcohol **9** (81% yield), which underwent esterification with triflic anhydride to afford the triflate **10**, epimeric at C-2 with compound **7**, in 89% yield. Treatment of alcohol **9** with methanolic hydrogen chloride caused removal of both isopropylidene protecting groups, ring opening and subsequent ring closure to give the β-*C*-glycoside **3** in 95% yield; the overall yield of compound **3** from lactone **6** is 60%. Thus ready access to both epimeric *C*-glycosides of glucofuranose **2** and **3** can be achieved in short sequences from *gluco*-heptonolactone **4**.

Access to protected forms of compound **2**, which would allow further derivatisation of such *C*-glycosides, is available from either acid- or base-catalysed contractions of derivatives of the δ-lactone **5**. Esterification of the acetonide **11** with triflic anhydride gave the triflate **12**, which was worked up with pyridine in methanol to give the α-carboxylate **13** (in 78% yield) in which only one of the ring hydroxy groups is unprotected (Scheme 3). Alternatively, the triflate **12** can be isolated in 67% yield (81% based on unrecovered starting material). Subsequent treatment of triflate **12** with hydrogen chloride in methanol afforded the benzyl ether **14** quantitative yield; compound **14** was also formed in quantitative yield from the acetonide **13** by removal of the isopropylidene protecting group by treatment with aq. acetic acid. The side-chain diol in compound **14** could be reconverted to the acetonide **13** by treatment with acetone and 2,2-dimethoxypropane in the presence of camphorsulfonic acid (95% yield). Removal of the benzyl group from **14** by hydrogenolysis in methanol and acetic acid in the presence of palladium black gave the methyl ester **2** (89% yield), identical with the material produced from the 1,4-lactone triflate **7** above.

A similar series of transformations was carried out on the silyl ether **15**; even though the C-6 OH group was unprotected during the sequence, no closure from C-6 to C-2 was found to occur so that no pyrancarboxylates were isolated–only tetrahydrofurans were formed. Thus the silyl lactone **15** was esterified with triflic anhydride and the resulting triflate **16** worked up with methanol in the presence of pyridine to give compound **17** (57% yield) in which both C-3 and C-6 hydroxy groups are unprotected. The silyl group was removed from compound **17** by treatment with aq. acetic acid to give compound **14** in 83% yield. The triflate **16** could be isolated (in



Scheme 3 *Reagents:* (i) Tf_2O, pyridine, CH_2Cl_2; (ii) HCl, MeOH; (iii) pyridine, MeOH; (iv) 80% aq. AcOH; (v) Me_2CO, CSA, $Me_2C(OMe)_2$; (vi) H_2/Pd, MeOH, AcOH



Scheme 4 *Reagents:* (i) H_5IO_6, THF; then $LiBH_4$; (ii) H_2/Pd, MeOH, AcOH

72% yield), but was relatively unstable; treatment of compound **16** with methanolic hydrogen chloride afforded **14** in 85% yield.

The configuration of the carboxylate in compound **14**—and therefore in compound **2**—was firmly established by a one-carbon degradation of the diol side-chain, reduction, and removal of the benzyl protecting group to give the known[10] C_2-symmetric tetraol **19** (Scheme 4).

Periodate oxidation of the side-chain diol of compound **14** with periodic acid in tetrahydrofuran (THF) and subsequent reduction of the resulting aldehyde and the methyl ester with lithium borohydride gave the triol **18** (70% yield). Hydrogenolysis of the benzyl ether in **18** in the presence of palladium black in acetic acid and methanol afforded the fully deprotected tetraol **19** in quantitative yield. Removal of the benzyl protecting group led to great simplification of the ^1H and ^{13}C NMR spectra for compound **19** due to the C_2 symmetry, and the other data were consistent with those previously reported.

The main thrust of this work was towards short syntheses of *C*-glycosides of glucopyranose in the search for inhibitors of glycogen phosphorylase (GP) as an approach to the treatment of non-insulin-dependent diabetes;[11] although there are a number of strong and potent inhibitors of GP which are *C*-glycosides of glucopyranose,[12] none of the corresponding furanose analogues have any inhibitory effect.[13] Nonetheless, there are a large number of enzymes and receptors which have recognition sites for glucofuranose epitopes; the short synthesis of the epimeric tetrahydrofurancarboxylates **2** and **3** provides intermediates which should be able to incorporate glucofuranose moieties into combinatorial libraries.[14] The easy synthesis of *C*-glucopyranosides from the cheap and readily manipulable *gluco*-heptonolactone **4** is a rainbow's end that is still worth chasing.

Experimental

Mps were recorded on a Kofler hot block and are corrected. Proton NMR (δ_H) spectra were recorded on a Varian Gemini 200 (200 MHz), Bruker AC 200 (200 MHz) or a Bruker AM 500 (500 MHz) spectrometer. ^{13}C NMR (δ_C) spectra were recorded on a Varian Gemini 200 (50.3 MHz), a Bruker AC 200 (50.3 MHz) or a Bruker AM 500 (125.8 MHz) spectrometer and multiplicities were assigned using the distortionless enhancement by polarisation transfer (DEPT) sequence. All chemical shifts are quoted on the δ-scale. The following abbreviations were used to explain multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; app, apparent. IR spectra were recorded on a Perkin-Elmer 1750 IR FT spectrophotometer. Mass spectra were recorded on a VG Masslab 20-250, BIO-Q or using desorption chemical ionisation (DCI; NH_3), chemical ionisation (CI; NH_3), electrospray or thermospray, as stated. Optical rotations were measured on a Perkin-Elmer 241 polarimeter with a path length of 1 dm. Concentrations are given in g/100 ml. $[\alpha]_D$-Values are given in units of 10^{-1} deg cm^2 g^{-1}. Microanalyses were performed by the microanalysis service of the Dyson Perrins laboratory. TLC was carried out on aluminium sheets coated with $60F_{254}$ silica, and plates were developed using a spray of 0.2% w/v cerium(IV) sulfate and 5% ammonium molybdate in 2 M sulfuric acid. Flash chromatography was carried out using Sorbsil C60 40/60 silica. Solvents and commercially available reagents were dried and purified before use according to standard procedures; hexane was distilled at 68 °C before use to remove less volatile fractions. Potassium dihydrogen orthophosphate (85 g) and sodium hydroxide (14.5 g) in water (950 ml) was used as buffer pH 7. D-*glycero*-D-*gulo*-Heptono-1,4-lactone **4** was purchased from Sigma and converted into the diacetonide **6** as previously described.[9]

3,5:6,7-Di-*O*-isopropylidene-2-*O*-trifluoromethylsulfonyl-D-*glycero*-D-*gulo*-heptano-1,4-lactone 7

A solution of 3,5:6,7-di-*O*-isopropylidene-D-*glycero*-D-*gulo*-heptano-1,4-lactone **6** (17.7 g, 61.4 mmol) in dry dichloromethane (200 cm^3) containing dry pyridine (11.3 cm^3, 140 mmol) was cooled to −40 °C under nitrogen. Trifluoromethanesulfonic anhydride (Tf_2O) (13.2 cm^3, 78.5 mmol) was added and the solution was stirred for 15 min whilst warming to −20 °C. TLC (ethyl acetate–hexane, 1:1) then indicated no starting material (R_f 0.1) and one product (R_f 0.6). The reaction mixture was washed successively with 2 M HCl (160 cm^3), then with pH 7 buffer solution (160 cm^3). The organic layer was dried ($MgSO_4$) and filtered, and the solution was concentrated *in vacuo*. The residue was purified by flash chromatography (ethyl acetate–hexane, 1:3), to yield the *title compound* **7** (22.6 g, 88%) as a solid; mp 130 °C (from diethyl ether–hexane); $[\alpha]_D^{20}$ −85.3 (*c* 1.05, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1800 (C=O); δ_H(500 MHz; $CDCl_3$) 1.36, 1.44 and 1.50 (3 H, 6 H, 3 H, 3 × s, 2 × CMe_2), 3.84 (1 H, dd, $J_{4,5}$ 2.0, $J_{5,6}$ 8.6, H-5), 3.94 (1 H, dd, $J_{6,7'}$ 3.7, $J_{7,7'}$ 9.0, H-7'), 4.12 (1 H, dd, $J_{6,7}$ 6.2, $J_{7,7'}$ 9.0, H-7), 4.32 (1 H, ddd, $J_{5,6}$ 8.6, $J_{6,7}$ 6.2, $J_{6,7'}$ 3.7, H-6), 4.42 (1 H, t, $J_{3,4}$ 2.0, $J_{4,5}$ 2.0, H-4), 4.83 (1 H, dd, $J_{2,3}$ 3.9, $J_{3,4}$ 2.1 H-3) and 5.36 (1 H, d, $J_{2,3}$ 3.9, H-2); δ_C(50.3 MHz; $CDCl_3$) 19.0, 24.5, 26.6 and 28.4 (4 × q, 2 × CMe_2), 66.7 (t, C-7) 67.4, 68.9, 69.1, 72.9 and 79.3 (5 × d, C-2, -3, -4, -5 and -6), 99.0 and 109.8 (2 × s, 2 × CMe_2), 118.4 (q, J_{C-F} 319, CF_3) and 167.5 (s, C-1); *m/z* (DCI; NH_3) 421 (M + H$^+$, 65%) and 438 (M + NH_4^+, 100) (Found: C, 40.0; H, 4.8. $C_{14}H_{19}F_3O_9S$ requires C, 40.00; H, 4.56%).

3,5-*O*-Isopropylidene-2-*O*-trifluoromethylsulfonyl-D-*glycero*-D-*gulo*-heptano-1,4-lactone 8

The triflate **7** (1.0 g, 2.38 mmol) was suspended in 80% aq. acetic acid (5 cm^3) and the mixture was stirred at 45 °C for 2 h. The solvent was removed *in vacuo* and the residue was co-evaporated three times with toluene to yield the *title compound* **8** (0.77 g, 85%) as a solid, mp 97–101 °C (from dichloromethane–hexane); $[\alpha]_D^{20}$ −70.9 (*c* 1.06, EtOH); ν_{max}(KBr)/cm^{-1} 3485br (OH) and 1791 (C=O); δ_H(200 MHz; CD_3OD) 1.38 and 1.52 (2 × 3 H, 2 × s, CMe_2), 3.59 (1 H, dd, $J_{6,7'}$ 4.7, $J_{7,7'}$ 11.6, H-7'), 3.65–3.80 (2 H, m, H-6 and -7), 4.11 (1 H, dd, $J_{4,5}$ 1.7, $J_{5,6}$ 9.1, H-5), 4.60 (1 H, t, $J_{3,4}$ 1.9, $J_{4,5}$ 1.9, H-4), 4.97 (1 H, dd, $J_{2,3}$ 4.0, $J_{3,4}$ 2.0, H-3) and 6.01 (1 H, d, $J_{2,3}$ 4.0, H-2); δ_C(50.3 MHz; CD_3OD) 18.9 and 28.7 (2 × q, CMe_2), 63.1 (t, C-7), 68.1, 69.0, 70.0 and 70.4 (4 × d, C-3, -4, -5 and -6), 81.1 (d, C-2), 99.8 (s, CMe_2), 119.5 (q, J_{C-F} 318, CF_3) and 169.7 (s, C-1); *m/z* (DCI; NH_3) 208 (100%) (Found: C, 34.9; H, 3.9. $C_{11}H_{15}F_3O_9S$ requires C, 34.74; H, 3.98%).

Methyl 2,5-anhydro-D-*glycero*-D-*ido*-heptonate 2

(i) From diacetonide 7. A 1% w/w solution of hydrochloric acid in methanol was generated by the addition of acetyl chloride (3.7 cm^3) to dry methanol (400 cm^3), and was added to the triflate **7** (20.5 g, 48.7 mmol); the solution was stirred at

room temperature. After 16 h, TLC (ethyl acetate–hexane, 1:1) indicated no starting material (R_f 0.6) and one product [R_f 0.0; R_f 0.3 (methanol–ethyl acetate, 1:4)]. Sodium hydrogen carbonate (4.8 g) was added and the mixture was preadsorbed on to silica with methanol (100 cm^3) and purified by flash chromatography (methanol–ethyl acetate, 1:10) to yield the *title compound* **2** (8.2 g, 76%), mp 127–128 °C (from ethanol–hexane); $[\alpha]_D^{20}$ −30.9 (*c* 0.7, CH_3OH); ν_{max}(KBr)/cm^{-1} 3392br and 3455 br (OH) and 1744 (C=O); δ_H(500 MHz; CD_3OD) 3.68 (1 H, dd, $J_{6,7'}$ 5.4, $J_{7,7'}$ 11.8, H-7') 3.75 (3 H, s, CO_2Me), 3.76 1 H, dd, $J_{6,7}$ 3.3, $J_{7,7'}$ 11.8, H-7'), 3.87 (1 H, ddd, $J_{5,6}$ 8.5, $J_{6,7}$ 3.3, $J_{6,7'}$ 5.4, H-6), 4.12 (1 H, dd, $J_{4,5}$ 2.9, $J_{5,6}$ 8.3, H-5), 4.19 (1 H, dd, $J_{3,4}$ 1.1, $J_{4,5}$ 2.8, H-4), 4.33 (1 H, dd, $J_{2,3}$ 4.1, $J_{3,4}$ 1.2, H-3) and 4.73 (1 H, d, $J_{2,3}$ 4.1, H-2); δ_C(50.3 MHz; CD_3OD) 51.2 (q, CO_2Me), 63.9 (t, C-7), 69.3, 76.4, 78.0, 80.9 and 81.4 (5 × d, C-2, -3, -4, -5 and -6) and 172.3 (s, C-1); *m/z* (CI; NH_3) 223 (M + H^+, 15%) and 240 (M + NH_4^+, 100) (Found: C, 43.2; H, 6.3. $C_8H_{14}O_7$ requires C, 43.24; H, 6.35%).

(ii) From monoacetonide 8. A 1% w/w solution of hydrochloric acid in methanol was generated by the addition of acetyl chloride (0.05 cm^3) to dry methanol (5 cm^3), and this was added to the triflate **8** (146 mg, 0.38 mmol); the solution was stirred at room temperature. After 7 h, TLC (ethyl acetate) indicated no starting material (R_f 0.4) and one product [R_f 0.0; R_f 0.3 (methanol–ethyl acetate, 1:4)]. Sodium acetate (310 mg, 10 mol equiv.) was added and the mixture was preadsorbed on to silica with methanol (10 cm^3) and purified by flash chromatography (methanol–ethyl acetate, 1:9) to yield the title compound **2** (75 mg, 88%) as described above.

3,5:6.7-Di-*O*-isopropylidene-D-*glycero*-D-*ido*-heptono-1,4-lactone 9

3,5:6.7-Di-*O*-isopropylidene-2-*O*-trifluoromethylsulfonyl-D-*glycero*-D-*gulo*-heptono-1,4-lactone **7** (14.6 g, 34.7 mmol) was dissolved in DMF (200 cm^3) and sodium trifluoroacetate (14.2 g, 104 mmol) was added. The solution was stirred at 60 °C for 72 h, when TLC (ethyl acetate–hexane, 1:1) showed no starting material (R_f 0.8) and the formation of one product (R_f 0.5). Methanol (10 cm^3) was added to the reaction mixture in order to methanolise the trifluoroacetate ester and the mixture was stirred for a further 24 h. The solvent was removed *in vacuo* and the residue was partitioned between dichloromethane (150 cm^3) and water (150 cm^3). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (ethyl acetate–hexane, 1:2) to afford the *title compound* **9** (8.10 g, 81%) as a solid, mp 180 °C (from ethyl acetate–hexane); $[\alpha]_D^{20}$ −99.0 (*c* 1.06, acetone); ν_{max}(KBr)/cm^{-1} 3440br (OH) and 1780 (C=O); δ_H(500 MHz; $CDCl_3$) 1.36, 1.37, 1.45 and 1.48 (4 × 3 H, 4 × s, CMe_2), 3.87 (1 H, dd, $J_{4,5}$ 2.1, $J_{5,6}$ 8.4, H-5), 3.94 (1 H, dd, $J_{6,7}$ 4.1, $J_{7,7'}$ 8.9, H-7), 4.10 (1 H, dd, $J_{6,7'}$ 6.2, $J_{7,7'}$ 8.9, H-7'), 4.17 (1 H, s, H-2), 4.33 (1 H, m, H-6), 4.43 (1 H, d, $J_{3,4}$ 2.6, H-3) and 4.68 (1 H, dd, $J_{4,5}$ 2.1, $J_{3,4}$ 2.6, H-4); δ_C(50.3 MHz; $CDCl_3$) 19.3, 24.7, 26.7 and 28.7 (4 × q, 2 × CMe_2), 66.8 (t, C-7), 69.2, 71.8, 72.7, 73.6 and 73.8 (5 × d, C-2, -3, -4, -5 and -6), 99.4 and 109.8 (2 × s, 2 × CMe_2) and 175.8 (s, C=O); *m/z* (CI; NH_3) 289 (M + H^+, 100%) and 306 (M + NH_4^+, 20%) (Found: C, 54.5; H, 7.2. $C_{13}H_{20}O_7$ requires C, 54.16; H, 6.99%).

3,5:6,7-Di-*O*-isopropylidene-2-*O*-trifluoromethylsulfonyl-D-*glycero*-D-*ido*-heptono-1,4-lactone 10

3,5:6,7-Di-*O*-isopropylidene-D-*glycero*-D-*ido*-heptono-1,4-lactone **9** (1.03 g, 3.56 mmol) was dissolved in dichloromethane (30 cm^3) containing pyridine (0.58 cm^3, 7.12 mmol). The solution was cooled to −40 °C, under nitrogen, and Tf_2O (0.70 cm^3, 4.27 mmol) was added. The solution was stirred at −40 °C for 30 min, when TLC (ethyl acetate–hexane, 1:1) showed no starting material (R_f 0.5) and the formation of one product (R_f 0.9). The solution was diluted with dichloromethane (30 cm^3) and washed successively with 2 M HCl (20 cm^3) and pH 7 buffer (20 cm^3), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (ethyl acetate–hexane, 1:4) to afford the *title compound* **10** (1.33 g, 89%) as a solid, mp 80 °C (decomp.); $[\alpha]_D^{20}$ −49.0 (*c* 0.39, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1800 (C=O); δ_H(500 MHz; $CDCl_3$) 1.38, 1.39, 1.47 and 1.51 (4 × 3 H, 4 × s, 2 × CMe_2), 3.86 (1 H, dd, $J_{4,5}$ 1.9, $J_{5,6}$ 8.6, H-5), 3.95 (1 H, dd, $J_{6,7}$ 3.9, $J_{7,7'}$ 9.0, H-7), 4.13 (1 H, dd, $J_{6,7'}$ 6.1, $J_{7,7'}$ 9.0, H-7'), 4.30 (1 H, ddd, $J_{6,7}$ 3.9, $J_{6,7'}$ 6.1, $J_{5,6}$ 8.6, H-6), 4.65 (1 H, d, $J_{3,4}$ 2.5, H-3); 4.69 (1 H, dd, $J_{4,5}$ 1.9, $J_{3,4}$ 2.5, H-4) and 4.98 (1 H, s, H-2); δ_C(50.3 MHz; $CDCl_3$) 19.4, 24.6, 26.8 and 28.5 (4 × q, 2 × CMe_2), 66.9 (t, C-7), 69.1, 70.0, 72.4, 74.0 and 80.7 (5 × d, C-2, -3, -4, -5 and -6), 99.3 and 110.0 (2 × s, 2 × CMe_2) and 166.4 (s, C=O); *m/z* (CI; NH_3) 421 (M + H^+, 30%) and 438 (M + NH_4^+, 100) (Found: C, 39.9; H, 4.5. $C_{14}H_{19}F_3O_9S$ requires C, 40.00; H, 4.56%).

Methyl 2,5-anhydro-D-*glycero*-D-*gulo*-heptonate 3

3,5:6,7-Di-*O*-isopropylidene-2-*O*-trifluoromethylsulfonyl-D-*glycero*-D-*ido*-heptono-1,4-lactone **10** (1.53 g, 3.65 mmol) was added to a solution prepared from methanol (15 cm^3) and acetyl chloride (0.15 cm^3) and the mixture was stirred at room temperature for 16 h, when TLC (ethyl acetate–methanol, 10:1) showed the formation of one product (R_f 0.2). Sodium hydrogen carbonate (500 mg) was added and *the mixture* was stirred for 10 min. After filtration the solvent was removed under reduced pressure and the residue was purified by flash chromatography (ethyl acetate–methanol, 10:1) to give the *title compound* **3** (770 mg, 95%) as a foam, $[\alpha]_D^{25}$ −25.3 (*c* 1.0, CH_3OH); ν_{max}(KBr)/cm^{-1} 3373br (OH) and 1742 (C=O); δ_H(500 MHz; CD_3OD) 3.61 (1 H, dd, $J_{6,7}$ 5.3, $J_{7,7'}$ 11.4, H-7), 3.73 (3 H, s, CO_2Me), 3.82 (1 H, dd, $J_{6,7'}$ 3.6, $J_{7,7'}$ 11.4, H-7'), 4.03 (1 H, ddd, $J_{6,7'}$ 3.6, $J_{6,7}$ 5.3, $J_{5,6}$ 7.5, H-6), 4.08 (1 H, dd, $J_{4,5}$ 3.1, $J_{5,6}$ 7.5, H-5), 4.11 (1 H, dd, $J_{3,4}$ 1.2, $J_{4,5}$ 3.1, H-4), 4.31 (1 H, d, $J_{3,4}$ 1.2, H-3) and 4.35 (1 H, s, H-2); δ_C(50.3 MHz; CD_3OD) 52.9 (q, CO_2Me), 65.0 (t, C-7), 71.0, 77.0, 82.0, 83.4 and 84.6 (5 × d, C-2, -3, -4, -5 and -6) and 174.0 (s, C=O); *m/z* (DCI; NH_3) 223 (M + H^+, 100%) and 240 (M + NH_4^+, 87) (Found: C, 43.4; H, 6.15. $C_8H_{14}O_7$ requires C, 43.24; H, 6.35%).

Methyl 2,5-anhydro-4-*O*-benzyl-6,7-*O*-isopropylidene-D-*glycero*-D-*ido*-heptonate 13

(i) From acetonide 11.[7] Tf_2O (144 mm^3, 0.86 mmol) was added to a solution of the 1,5-lactone **11** (170 mg, 0.50 mmol) in dry pyridine (2 cm^3) at 0 °C. After 5 min, TLC (ethyl acetate–hexane, 1:1) indicated no starting material (R_f 0.2) and predominantly one product (R_f 0.5). Dry methanol (5 cm^3) was added and the mixture was stirred for 15 min at 0 °C. Further methanol (20 cm^3) was added and the reaction mixture was allowed to warm to room temperature. After 20 h, TLC (ethyl acetate–hexane, 1:1) indicated one major product (R_f 0.2). The solvents were removed *in vacuo* and co-evaporated with toluene (3 × 10 cm^3). The residue was dissolved in ethyl acetate (20 cm^3) and washed successively with water (2 × 20 cm^3) and brine (20 cm^3). The organic layer was dried ($MgSO_4$), filtered, and the solvent was removed *in vacuo*. Purification was achieved by flash column chromatography (ethyl acetate–hexane, 1:3) to yield starting material (R_f 0.2) (26 mg, 15% recovery) and the *title compound* **13** (138 mg, 78%) as crystalline solid, mp 94–96 °C (from diethyl ether–hexane); $[\alpha]_D^{20}$ −31.7 (*c* 1.0, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1747 (C=O); δ_H(200 MHz; $CDCl_3$) 1.39 and 1.44 (2 × 3 H, 2 × s, CMe_2), 3.80 (3 H, s, CO_2Me), 4.07 (3 H, m, H-4, -5, and -6), 4.31 (1 H, dd, $J_{6,7}$ 2.3, $J_{7,7'}$ 10.1, H-7), 4.40 (1 H, dd, $J_{6,7'}$ 5.5, $J_{7,7'}$ 10.1, H-7'), 4.55 (1 H, dd, $J_{3,4}$ 1.0, $J_{2,3}$ 3.9, H-3), 4.70 (2 H, s, OCH_2Ph), 4.73 (1 H, d, $J_{2,3}$ 3.9, H-2) and 7.32–7.39 (5 H, m, ArH); δ_C(50.3 MHz; $CDCl_3$) 25.4 and 26.7 (2 × q, 2 × Me), 52.3 (q, CO_2Me), 67.4 (t, C-7) 72.7 (t, OCH_2Ph), 72.9, 75.9, 81.0, 82.5 and 83.5 (5 × d, C-2, -3, -4, -5 and -6), 109.1 (s, CMe_2), 127.8, 128.1 and 128.6 (3 × d,

5 × ArCH), 138.0 (s, ArC) and 171.1 (s, C-1); *m/z* (CI; NH_3) 353 ($M + H^+$, 30%) (Found: C, 61.05; H, 6.9. $C_{18}H_{24}O_7$ requires C, 61.35; H, 6.86%).

(ii) From triol 14. The triol methyl ester **14** (see below) (29 mg, 0.09 mmol) was dissolved in acetone (5 cm^3) and camphorsulfonic acid (CSA) was added to adjust the pH of the solution to 2. The reaction mixture was stirred at 40 °C and 2,2-dimethoxypropane (57 mm^3, 0.47 mmol) was added. After 15 min, TLC (ethyl acetate–methanol, 9:1) indicated no starting material (R_f 0.3) and one product (R_f 0.8). The reaction mixture was neutralised by careful addition of saturated aq. sodium hydrogen carbonate and the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate (10 cm^3) and was washed successively with water (10 cm^3) and brine (10 cm^3). The organic layer was dried ($MgSO_4$), filtered, and the solvent was removed *in vacuo*. The residue was crystallised (from diethyl ether–hexane) to yield the title compound **13** (31 mg, 95%), identical with that described above.

4-*O*-Benzyl-6,7-*O*-isopropylidene-2-*O*-trifluoromethylsulfonyl-D-*glycero*-D-*gulo*-heptono-1,5-lactone 12

Tf_2O (0.11 cm^3, 0.66 mmol) was added to a solution of the 1,5-lactone **11** (171 mg, 0.51 mmol) in dry dichloromethane (5 cm^3) containing dry pyridine (0.10 cm^3, 1.26 mmol) at −30 °C. After 5 min, TLC (ethyl acetate–hexane, 1:1) indicated the presence of some starting material, and predominantly one product (R_f 0.5). Further dichloromethane (5 cm^3) was added and the mixture was washed successively with water (10 cm^3), 2 M HCl (10 cm^3) and brine (10 cm^3). The organic layer was dried ($MgSO_4$), filtered, and the solvent was removed *in vacuo*. Purification was achieved by flash column chromatography (diethyl ether–hexane, 2:3) to yield the title compound **12** (161 mg, 67%, 81% based on unrecovered starting material) as an oil, $[\alpha]_D^{20}$ +47.1 (*c* 0.86, $CHCl_3$); ν_{max}(thin film)/cm^{-1} 1755 (C=O); δ_H(200 MHz; $CDCl_3$) 1.40 and 1.44 (2 × 3 H, 2 × s, CMe_2), 4.09 (1 H, dd, $J_{6,7}$ 3.1, $J_{7,7'}$ 7.8, H-7), 4.15 (1 H, dd, $J_{6,7'}$ 2.9, $J_{7,7'}$ 7.8, H-7'), 4.21–4.28 (1 H, m, H-6), 4.37–4.46 (2 H, m, H-4 and -5), 4.61 (1 H, m, H-3), 4.68 and 4.84 (2 × 1 H, 2 × d, $J_{H,H'}$ 11.5, OCH_2Ph), 5.55 (1 H, d, $J_{2,3}$ 2.8, H-2) and 7.28–7.43 (5 H, m, ArH); δ_C(50.3 MHz; $CDCl_3$) 25.1 and 26.8 (2 × q, CMe_2), 67.1 (t, C-7), 69.3, 71.9, 74.3, 80.1 and 80.6 (5 × d, C-2, -3, -4, -5 and -6), 74.3 (t, OCH_2Ph), 110.1 (s, CMe_2), 120.1 (s, CF_3), 128.6, 128.9 and 129.0 (3 × d, ArCH), 136.9 (s, ArC) and 164.3 (s, C-1); *m/z* (CI; NH_3) 108 (100%), 322 ($M + NH_4^+$ − BnOH − Me_2CO, 45), 430 ($M + NH_4^+$ − Me_2CO, 80), 471 ($M + NH^+$, 10) and 488 ($M + NH_4^+$, 10).

Methyl 2,5-anhydro-4-*O*-benzyl-D-*glycero*-D-*ido*-heptonate 14

(i) From acetonide triflate 12. A 1% w/w solution of hydrochloric acid in methanol was generated by the addition of acetyl chloride (0.02 cm^3) to dry methanol (2 cm^3), and was added to the triflate **12** (82 mg, 0.17 mmol). The solution was stirred for 18 h, when TLC (ethyl acetate) indicated no starting material (R_f 0.75) and one product (R_f 0.2). The reaction mixture was diluted with ethyl acetate (50 cm^3), and washed successively with water (10 cm^3) and brine (10 cm^3). The organic layer was dried ($MgSO_4$), filtered, and the solvents were removed *in vacuo*. Purification was achieved by flash column chromatography (ethyl acetate) to yield the title compound **14** (53 mg, quant.) as a crystalline solid, mp 93–95 °C (from ethyl acetate–hexane); $[\alpha]_D^{20}$ −26.4 (*c* 1.0, CH_3CN); ν_{max}(KBr)/cm^{-1} 1751 (C=O); δ_H(500 MHz; CD_3CN) 3.59 (1 H, dd, $J_{6,7}$ 4.8, $J_{7,7'}$ 11.7, H-7), 3.65 (1 H, dd, $J_{6,7'}$ 3.1, $J_{7,7'}$ 11.7, H-7'), 3.69 (3 H, s, CO_2Me), 3.80 (1 H, ddd, $J_{5,6}$ 8.9, $J_{6,7}$ 4.8, $J_{6,7'}$ 3.1, H-6), 4.00 (1 H, d, $J_{4,5}$ 3.1, H-4), 4.12 (1 H, dd, $J_{4,5}$ 3.1, $J_{5,6}$ 8.9, H-5), 4.53 (1 H, d, $J_{2,3}$ 4.2, H-3), 4.61 and 4.69 (2 × 1 H, 2 × d, $J_{H,H'}$ 11.5, OCH_2Ph), 4.65 (1 H, d, $J_{2,3}$ 4.2, H-2) and 7.30–7.42 (5 H, m, ArH); δ_C(50.3 MHz; CD_3CN) 51.3 (q, CO_2Me), 64.0 (t, C-7), 71.9 (t, CH_2Ph), 69.0, 74.8, 81.0, 81.2 and 84.1 (5 × d, C-2, -3, -4, -5 and -6), 127.9, 128.0 and 128.6 (3 × d, 5 × ArCH), 138.7 (s, ArC) and 170.7 (s, C-1); *m/z* (CI; NH_3) 313 ($M + H^+$, 20%) and 330 ($M + NH_4^+$, 100) (Found: C, 57.4; H, 6.5. $C_{15}H_{20}O_7$ requires C, 57.69; H, 6.45%).

(ii) From the acetonide carboxylate 13. The methyl ester **13** (108 mg, 0.31 mmol) was stirred in 80% acetic acid (4 cm^3) at room temperature for 16 h, when TLC (methanol–ethyl acetate, 9:1) indicated no starting material (R_f 0.8) and one product (R_f 0.3). The solvents were removed *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate–methanol, 19:1) to yield the title compound **14** (95 mg, quant.), identical with the material described above.

(iii) From the silyl carboxylate 17. The silyl ester **17** (see later) (102 mg, 0.19 mmol) was stirred in 80% aq. acetic acid (5 cm^3) at room temperature for 16 h. The solvents were removed *in vacuo* and the residue was co-evaporated with toluene (3 × 5 cm^3). The residue was purified by flash column chromatography (ethyl acetate–methanol, 19:1) to yield the title compound **14** (50 mg, 83%) as described above.

(iv) From silyl triflate 16. A 1% w/w solution of hydrochloric acid in methanol was generated by the addition of acetyl chloride (0.02 cm^3) to dry methanol (2 cm^3), and was added to the triflate **16** (100 mg, 0.15 mmol). The solution was stirred for 16 h. The reaction mixture was diluted with ethyl acetate (40 cm^3), and washed successively with water (10 cm^3) and brine (10 cm^3). The organic layer was dried ($MgSO_4$), filtered, and the solvents removed *in vacuo*. Purification was achieved by flash column chromatography (ethyl acetate) to yield the title compound **14** (40 mg, 85%) as described above.

Methyl 2,5-anhydro-D-*glycero*-D-ido-heptonate 2 by hydrogenation of benzyl ether 14

The methyl ester **14** (87 mg, 0.28 mmol) was dissolved in dry methanol (10 cm^3), palladium black (10 mg) and glacial acetic acid (4 drops) were added and the mixture was stirred at room temperature under hydrogen. After 20 h, TLC (methanol–ethyl acetate, 1:4) indicated no starting material (R_f 0.6) and one product (R_f 0.3). The mixture was filtered through Celite with methanol (2 × 15 cm^3). The solvent was removed *in vacuo* and the residue was co-evaporated with toluene. The residue was adsorbed on to silica with methanol (5 cm^3) and purified by flash chromatography (methanol–ethyl acetate, 1:9) to yield the title compound **2** (55 mg, 89%) as a solid, identical in all respects with the material above.

Methyl 2,5-anhydro-4-*O*-benzyl-7-*O*-(*tert*-butyldiphenylsilyl)-D-*glycero*-D-*ido*-heptonate 17

Tf_2O (31 mm^3, 0.18 mmol) was added to a solution of the 1,5-lactone **15** (72 mg, 0.13 mmol) in dry pyridine (2 cm^3) at 0 °C. After 10 min, dry methanol (5 cm^3) was added and the mixture was allowed to warm to room temperature. After 24 h, the solvents were removed *in vacuo* and the residue was co-evaporated with toluene (3 × 5 cm^3). The residue was dissolved in ethyl acetate (10 cm^3) and washed successively with water (2 × 10 cm^3) and brine (10 cm^3). The organic layer was dried ($MgSO_4$), filtered, and the solvent was removed *in vacuo*. Purification was achieved by flash column chromatography (ethyl acetate–hexane, 3:2) to yield the title compound **17** (42 mg, 57%) as an oil; $[\alpha]_D^{20}$ −18.7 (*c* 1.04, $CHCl_3$); ν_{max}(thin film)/cm^{-1} 3440br (OH) and 1751 (C=O); δ_H(500 MHz; $CDCl_3$) 1.08 (9 H, s, Bu^t), 3.79 (3 H, s, CO_2Me), 3.89 (1 H, dd, $J_{6,7}$ 4.2, $J_{7,7'}$ 10.3, H-7), 3.92 (1 H, dd, $J_{6,7'}$ 5.1, $J_{7,7'}$ 10.3, H-7'), 4.08–4.11 (1 H, m, H-6), 4.15 (1 H, dd, $J_{3,4}$ 0.8, $J_{4,5}$ 3.5, H-4), 4.40 (1 H, dd, $J_{4,5}$ 3.5, $J_{5,6}$ 8.2, H-5), 4.53 (1 H, dd, $J_{2,3}$ 4.1, $J_{3,4}$ 0.8, H-3), 4.64 and 4.68 (2 × 1 H, 2 × d, $J_{H,H'}$ 11.7, OCH_2Ph), 4.74 (1 H, d, $J_{2,3}$ 4.1, H-2), 7.28–7.48 (9 H, m, ArH) and 7.66–7.74 (6 H, m, ArH); δ_C(50.3 MHz; $CDCl_3$) 19.2 (s, CMe_3), 26.8 (q, Me), 52.2 (t, C-7), 65.5, 69.5, 75.9, 80.9 and 84.1 (5 × d, C-2, -3, -4, -5 and -6), 72.7 (t, OCH_2Ph), 128.0, 128.2, 128.4, 128.8 and 130.0 (5 × d, ArCH), 133.2 and 133.5 (2 × s, 2 × ArC), 135.8 (d, ArCH), 137.8 (s, ArC) and 171.3 (s, C-1); *m/z* (CI; NH_3) 91

(100%) and 568 (M + NH_4^+, 10) (Found: C, 67.8; H, 7.2. $C_{31}H_{38}O_7Si$ requires C, 67.61; H, 6.95%).

4-*O*-Benzyl-7-*O*-(*tert*-butyldiphenylsilyl)-2-*O*-trifluoromethylsulfonyl-D-*glycero*-D-*gulo*-heptono-1,5-lactone 16

Tf_2O (0.20 cm^3, 1.19 mmol) was added to a solution of the 1,5-lactone **15** (464 mg, 0.87 mmol) in dry dichloromethane (10 cm^3) containing dry pyridine (0.20 cm^3, 2.38 mmol) at 0 °C. After 10 min, the reaction mixture was washed successively with water (10 cm^3), 2 M HCl (10 cm^3) and brine (10 cm^3). The organic layer was dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. Purification was achieved by flash column chromatography (ethyl acetate–hexane 1:4) to yield the title compound **16** (416 mg, 72%) as an oil; ν_{max}(thin film)/cm^{-1} 3500br (OH) and 1760 (δ-lactone); δ_H(200 MHz; $CDCl_3$) 1.10 (9 H, s, 3 × Me), 2.75 (1 H, d, *J* 7.1, OH), 3.03 (1 H, d, *J* 3.0, OH), 3.93–4.33 (5 H, m), 4.67–4.89 (3 H, m), 5.56 (1 H, d, *J* 2.8) and 7.28–7.70 (5 H, m, ArH). This compound was used for the ring contraction above without further characterisation.

2,5-Anhydro-3-*O*-benzyl-D-iditol 18

The methyl ester **14** (51 mg, 0.16 mmol) was dissolved in dry THF (2 cm^3) and periodic acid (56 mg, 0.24 mmol) was added. After 2 min at room temperature a precipitate formed and TLC (ethyl acetate) indicated no starting material (R_f 0.15) and one product (R_f 0.4). The solution was filtered through a silica plug and was eluted with ethyl acetate. The solvents were removed *in vacuo* to yield the crude aldehyde.

The aldehyde was dissolved in dry THF (2 cm^3) and $LiBH_4$ (2.0 M in THF; 188 mm^3, 0.375 mmol) was added cautiously at 0 °C. When all effervescence had ceased, the reaction mixture was allowed to warm to room temperature. After 15 min, TLC (ethyl acetate–methanol, 9:1) indicated no aldehyde (R_f 0.6) and one product (R_f 0.2). The reaction was quenched with ammonium chloride (0.20 g), followed by cautious addition of methanol (4 cm^3). When all effervescence had ceased, the solvents were removed *in vacuo* and the resulting residue was purified by flash column chromatography (ethyl acetate–methanol, 49:1) to yield the title compound **18** (30 mg, 70%) as an oil, $[\alpha]_D^{20}$ −25.2 (*c* 0.52, EtOH); δ_H(500 MHz; CD_3OD) 3.34 (1 H, s), 3.72 (1 H, dd, *J* 11.5, *J* 6.3), 3.72 (1 H, d, 6.3), 3.77 (1 H, dd, *J* 5.2 and 11.5), 3.95 (1 H, dd, *J* 4.2 and 1.5), 4.10 (1 H, ddd, *J* 3.7, 5.2 and 6.2), 4.23 (1 H, dt, *J* 6.0 and 4.2), 4.32 (1 H, dd, *J* 1.5 and 3.7), 4.55 and 4.66 (2 × 1 H, 2 × d, *J* 11.7, OCH_2Ph) and 7.26–7.33 (5 H, m, ArH); δ_C(50.3 MHz; CD_3CN) 60.7 and 60.8 (2 × t, C-1 and -6), 71.2 (t, CH_2Ph), 74.8, 80.2, 80.4 and 85.3 (4 × d, C-2, -3, -4 and -5), 127.8 and 128.6 (2 × d, Ar*C*H) and 138.8 (s, Ar*C*); *m*/*z* (CI; NH_3) 255 (M + H^+, 35%) and 272 (M + NH_4^+, 100).

2,5-Anhydro-D-iditol 19

The triol **18** (30 mg, 0.12 mmol) and palladium black (10 mg) were stirred in anhydrous methanol (4 cm^3) with glacial acetic acid (0.4 cm^3) at room temperature. The solution was degassed and stirred under hydrogen for 3 h, when TLC (ethyl acetate–methanol, 4:1) indicated no starting material (R_f 0.3) and one product (R_f 0.1). The mixture was filtered through Celite and the solvents were removed *in vacuo* to yield the title compound **19** (19 mg, quant.) as a solid, mp 113–115 °C (lit.,[10] 115–115.5 °C); $[\alpha]_D^{22}$ −14.1 (*c* 1.0, water) {lit.,[10] $[\alpha]_D^{24}$ −12.9 (*c* 2.77, water)}; δ_H(500 MHz; CD_3OD) 3.72 (2 H, dd, *J* 11.5 and 6.3, H-1 and -6), 3.77 (2 H, dd, *J* 11.5 and 5.0, H-1′ and -6′), 4.10–4.11 (2 H, m, H-3 and -4), 4.14 (2 H, ddd, *J* 3.2, 5.0 and 6.3, H-2 and -5); δ_C(50.3 MHz; CD_3OD) 60.5 (t, C-1 and -6) and 77.3 and 80.6, (2 × d, C-2, -3, -4 and -5); *m*/*z* (CI; NH_3) 182 (M + NH_4^+, 100%).

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