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ACETONIDES OF HEPTONOLACTONES: KILIANI ASCENSION OF 3-*O*-BENZYL-D-GLUCOSE AND 3-*O*-BENZYL-D-ALLOSE

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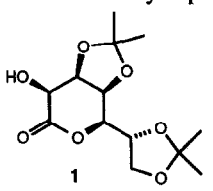
Abstract The preparation of the δ-heptonolactones, 4-*O*-benzyl-**D**-*glycero*-**D**-*gulo*-heptono-1,5-lactone and 4-*O*-benzyl-**D**-*glycero*-**D**-*allo*-heptono-1,5-lactone, by Kiliani reactions on 3-*O*-benzylglucose and 3-*O*-benzylallose are reported; acetonides of the two lactones are described.

Although γ-lactones are usually thermodynamically more stable, δ-lactones may be prepared by the Kiliani ascension[1] of carbohydrates which have a protecting group on the C-3 OH, thereby preventing the formation of a γ-lactone as product.[2,3] Such δ-lactones have been utilised in short syntheses of a wide range of complex, highly functionalised sugar analogues.[4,5,6] For example, the diacetonide **1** has been used in the synthesis of homomannojirimycin **2**,[7] homoDIM **3**,[8] the alexine **4**,[9] the all *cis*-substituted tetrahydrofuran **5**,[6] the *manno*-hydantocidin analogue **6**,[10] 2,6-disubstituted tetrahydropyrans **7** and cyclohexanes **8**,[11] and very highly functionalised cyclopentanes, such as **9**[12] and **10**.[13]



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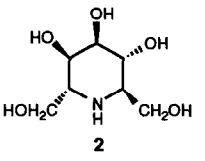

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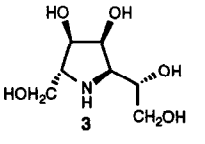

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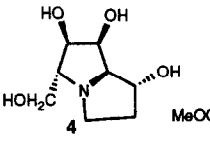

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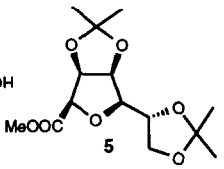

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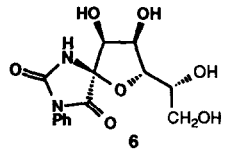

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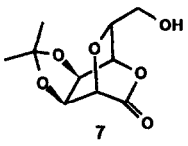

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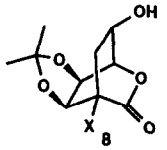

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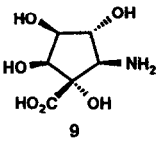

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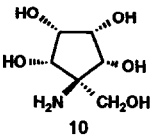

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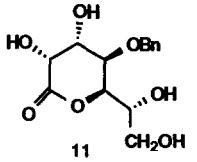

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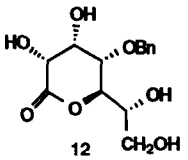

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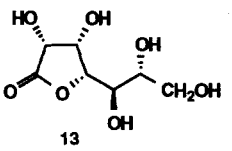

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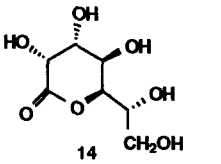

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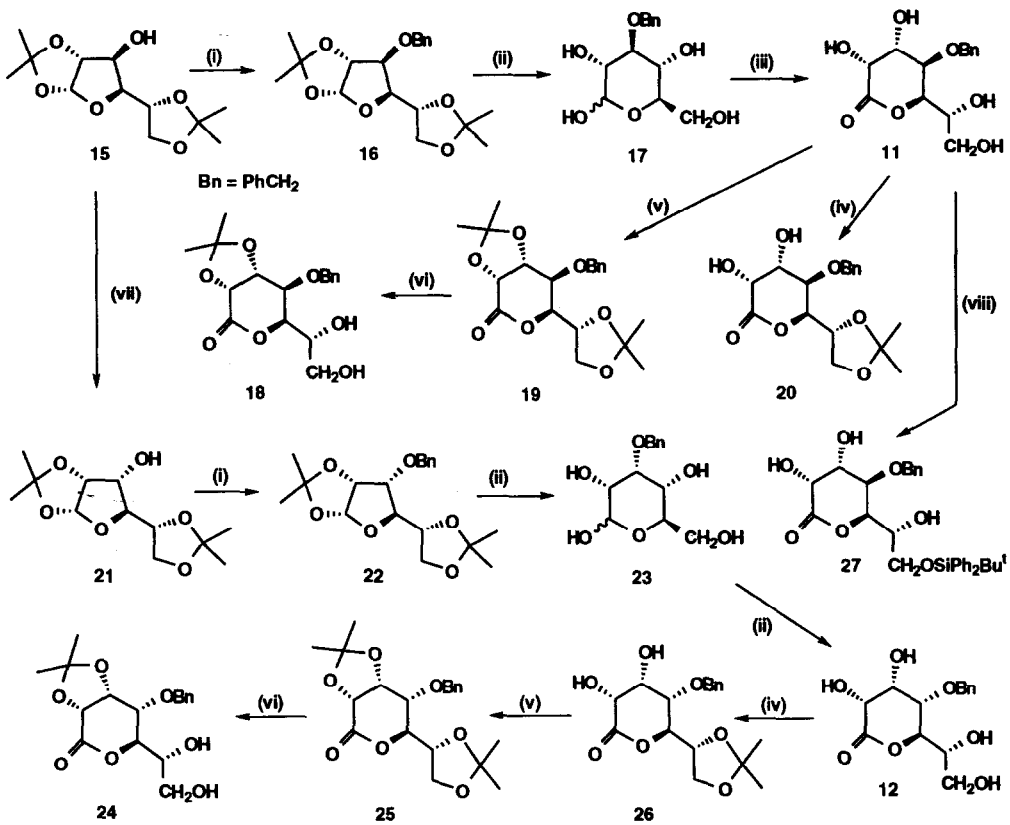
It may be that the range of reactions undergone by **1** require the presence of a *cis*-fused acetonide. In order to investigate the generality of these transformations without this structural feature, this paper reports the Kiliani ascension of 3-*O*-benzylglucose and 3-*O*-benzylallose to give the δ-lactones **11** and **12** respectively. The preparations of the mono- and di-acetonides of **11** and **12** are also described.

Glucoheptonolactone **13** as the γ-lactone [**D**-*glycero*-**D**-*gulo*-heptono-1,4-lactone], the product of the Kiliani ascension of unprotected **D**-glucose, is the cheapest[14] and most readily available heptonic acid. The acetonides[15] and benzylidene acetals[16] derived from the γ-lactone have been reported; however, no derivatives of glucoheptonolactone as a δ-lactone **14** have been described. In order to prevent the isomerisation of the δ-lactone to the thermodynamically more stable γ-lactone, a benzyl ether was introduced at C-3 of glucose.



(i) BnBr, NaH, Bu_4NI (cat.), THF (ii) H^+, H_2O (iii) NaCN; then H^+ (iv) Me_2CO, H^+ *or* 2-methoxypropene, H^+, DMF (v) Me_2CO, $Me_2C(OMe)_2$, H^+ (vi) aq. CH_3COOH (vii) pyridinium chlorochromate, molecular sieve, DCM, then $NaBH_4$, aq. EtOH (viii) Ph_2Bu^tSiCl, imidazole, DMF.

Treatment of diacetone glucose **15** with benzyl bromide in tetrahydrofuran in the presence of sodium hydride and tetrabutyl ammonium iodide gave the corresponding benzyl ether **16** [92% yield] which, without purification, could be hydrolysed by aqueous trifluoroacetic acid to afford the easily crystallised 3-*O*-benzyl glucose **17** [86% yield]. The benzyl ether **17** was reacted with aqueous sodium cyanide at room temperature for 24 h, and the reaction mixture then heated at reflux for 48 h to ensure that all the excess cyanide had been destroyed. The aqueous solution was then passed through a strongly acidic ion exchange column to give the δ-lactone **11** [39% yield] as the sole product which crystallised from the reaction mixture. It is usually the case in the chemistry of carbohydrate lactones that the primary alcohol is the most reactive hydroxyl group towards electrophiles. Thus, the lactone **11** reacted with *tert*-butylchlorodiphenylsilane in dimethylformamide in the

presence of imidazole at -78°C almost exclusively at the C-7 primary hydroxyl group to produce the monosilyl ether **27** in 84% yield. It is the case that cyclic esters and acetals usually are formed more rapidly by initial attack at the primary alcohol site. Thus, periodate cleavage of **11** resulted in preferential cleavage of the side chain diol.[17] Reaction of **11** with acetone in the presence of *p*-toluenesulphonic acid at room temperature gave the kinetic monoacetonide **20** in 96% yield; the monoacetonation of **11** could also be achieved by 2-methoxypropene in dimethylformamide in the presence of acid to give **20** in 81% yield. When **11** was treated with acetone and 2,2-dimethoxypropane in the presence of acid at 40°C, the diacetonide **19** was formed in 76% yield. Side chain acetonides are generally hydrolysed faster than fused acetonides formed from *cis*-diols on rings; thus, partial hydrolysis of the diacetonide **19** by aqueous acetic acid gave the fused-ring monoacetonide **18** in 78% yield. In sugar lactones in which there is no free primary hydroxyl group, the OH group α-to the carbonyl of the lactone reacts with electrophiles more rapidly than does any other secondary alcohol; thus, both the monoacetonide **20** and the silyl ether **27** react selectively with triflic anhydride to form the respective 2-*O*-triflate esters in good yield.[17]

All the acetonides **18**, **19** and **20** have a singlet in their ^{13}C NMR spectra between δ 109 and 112, clearly indicating that all the ketals are in 5 membered rings;[18] also, they are hydrolysed by aqueous trifluoroacetic acid in excellent yields to give **11**. These observations indicate that the oxygen on the new stereogenic centre at C-2 of the heptonolactone is *cis* to that at C-3 and thus the stereochemistry at C-2 is the same as that in the major product **13** of the Kiliani ascension of unprotected glucose.

For the synthesis of D-*glycero*-D-*allo*-heptonolactone **12**, epimeric at C-4 with **11**, it is necessary first to invert the stereochemistry at C-3 of diacetone glucose. Diacetone glucose **15** was converted to 3-*O*-benzylallose **23** by modification of literature procedures. Oxidation of **15** with pyridinium chlorochromate in the presence of molecular sieves, followed by reduction of the resulting ketone with sodium borohydride in aqueous ethanol, gave crude diacetone allose **21** [90% yield].[19] A similar sequence to that described for diacetone glucose **15** above was carried out on diacetone allose **21**. However, unlike the easily crystallised benzyl glucose **17**, the hydrolysis of the diacetonide **22** and the purification of benzylallose **23** are difficult and proceed in low yield.[20] Accordingly, the crude acetonide **21** was benzylated and purified as the highly crystalline 3-*O*-benzyl diacetonide **22** [77% yield, 69% from **15**]. Then, the isopropylidene protecting groups were removed from **22** by hydrolysis with acidic ion exchange resin and, adjusting the solution to pH 9, the crude benzyl allose **23** was treated with cyanide to give after work-up the δ-lactone **12** [38% overall yield from **22**]. Treatment of **12** with acetone in the presence of acid gave the side-chain monoacetonide **26** in 92% yield. Treatment of **26** with acetone and dimethoxypropane in the presence of camphorsulphonic acid at 40°C afforded the diacetonide **25** in 85% yield. Treatment of **12** with dimethoxypropane under more forcing conditions gave rise to mixtures of open chain derivatives of **12**. Hydrolysis of the diacetonide **25** with aqueous acetic acid gave the ring-fused monoacetonide **24** in 95% yield. Again the chemical shifts of the isopropylidene singlets in the acetonides **24**, **25** and **26** indicated that only 5 membered ring acetonides were formed and the efficient acid hydrolysis of all of them to **12** again provided evidence that the new hydroxyl function at C-2 of the heptonolactone **12** is *cis* to that at C-3.

It is worth noting that δ-lactones are frequently easily hydrolysed to open chain derivatives; for example, a solution of the *allo*-heptonolactone **12** in D_2O, shows two compounds by ^{13}C nmr and t.l.c. (ethyl acetate/methanol 9:1) indicated two products (R_f 0.0 and 0.3), consistent with the lactone and open chain acid.

In summary, this paper reports the synthesis and characterisation of two new δ-heptonolactones **11** and **12**, and of readily available mono- and diacetonides derived therefrom. These preparations are described on a suitable scale to investigate whether the range of reactions of the mannose-derived **1** can be exploited for other sugar δ-lactones.

Acknowledgement. This work has been supported by a SERC award (CJFB).

Experimental

General Methods. Melting points were recorded on a Kofler hot block. Proton nuclear magnetic resonance (δ_H) spectra were recorded on Varian Gemini 200 (at 200 MHz), Bruker WH 300 (300 MHz) spectrometers or Bruker AM 500 (500 MHz). ^{13}C Nuclear magnetic resonance (δ_C) spectra were recorded on a Varian Gemini 200 (50 MHz) spectrometer and multiplicities were assigned using DEPT sequence. All chemical shifts are quoted on the δ-scale. Infra-red spectra were recorded on a Perkin-Elmer 781, or on a Perkin-Elmer 1750 FT spectrophotometer. Mass spectra were recorded on VG Micromass 30F, ZAB 1F, Masslab 20-250 or Trio-1 GCMS (DB-5 column) spectrometers using desorption chemical ionisation (NH_3, DCI), chemical ionisation (CI) or electron impact (EI), 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. Microanalyses were performed by the microanalysis service of the Dyson Perrins laboratory. Thin layer chromatography (t.l.c.) was carried out on aluminium sheets coated with $60F_{254}$ silica or glass plates coated with silica Blend 41. Plates were developed using a spray of 0.2% w/v cerium (IV) sulphate and 5% ammonium molybdate in 2M sulphuric 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; dichloromethane was refluxed over and distilled from calcium hydride; tetrahydrofuran was distilled, under nitrogen, from a solution dried with sodium in the presence of benzophenone. Hexane was distilled at 68°C before use to remove involatile fractions. Diacetone glucose **15** was purchased from the Sigma Chemical Company.

3-O-Benzyl-D-glucopyranose ***17.*** A solution of diacetone glucose **15** (150 g, 0.58 mol) in tetrahydrofuran (400 ml) was added dropwise to a stirred suspension of sodium hydride (60% dispersion in oil, 25.5 g, 0.64 mmol) and tetrabutylammonium iodide (1.65 g, 0.004 mol) in tetrahydrofuran (200 ml) at 0°C. The mixture was allowed to warm to room temperature and benzyl bromide (75.3 ml, 0.63 mol) was added and the reaction mixture heated to 50°C for 2 h. T.l.c. (ethyl acetate/hexane 1:1) showed no starting material (R_f 0.3) and one major product (R_f 0.6). Methanol (150 ml) was added and the mixture stirred for a further 2 h before cooling, filtering through Celite and concentrating. The resulting oil was dissolved in dichloromethane (500 ml), washed with water (2 x 200 ml), dried ($MgSO_4$), filtered and evaporated to give the benzyl ether **16** (185.8 g, 92%) as a yellow oil; the crude diacetonide **16** (186 g, 0.53 mol) was stirred in 50% aqueous trifluoroacetic acid (400 ml) at room temperature for 16 h when t.l.c. (ethyl acetate) showed no starting material (R_f 0.8) and a single product (R_f 0.2). The solvents were removed under reduced pressure. The resulting crystalline mass was dissolved in water (300 ml) and washed with a 5:1 mixture of ethyl acetate and ether (300 ml). The water was evaporated *in vacuo* to yield an off-white crystalline solid which, upon recrystallisation from hot ethanol, gave 3-*O*-benzylglucose **17** (123.5 g, 86%) as a white solid, m.p. 134-135°C (ethanol); $[\alpha]_D^{20}$ +21.6→+43.2 (*c*, 0.99 in H_2O), [lit.[21] 135-137°C, $[\alpha]_D^{20}$ +20.3→+41.9 (H_2O)].

4-O-*Benzyl*-***D***-glycero-***D***-gulo-*heptono-1,5-lactone* ***11***. Sodium cyanide (8.0 g, 0.16 mol) was added to a solution of 3-*O*-benzyl-**D**-glucopyranose **17** (33.7 g, 0.13 mol) in water (450 ml) with stirring at room temperature. After 24 h, the solution was bubbled through with air and heated at reflux for 48 h when all evolution of ammonia had ceased. The solution was allowed to cool and then extracted with dichloromethane (250 ml). The aqueous layer was then passed through a column containing Dowex 50W-X8 (H) strongly acidic ion exchange resin (56 g) and then concentrated to one third of its original volume whereupon crystals of *4*-O-*benzyl*-***D***-glycero-***D***-gulo-*heptono-1,5-lactone* ***11*** (14.3 g, 39%) were deposited on standing, m.p. 184-187°C; $[\alpha]_D^{20}$ +78.0 (*c*, 1.01 in MeOH); υ_{max} (KBr): 1703 (C=O) cm^{-1}; δ_H (500 MHz; D_6-acetone): 3.69 (1H, dd, $J_{6,7}$ 4.9, $J_{7,7'}$ 11.4 Hz, H-7) 3.80 (1H, dd, $J_{6,7'}$ 2.7, $J_{7,7'}$ 11.4 Hz, H-7') 3.99 (1H, ddd, $J_{5,6}$ 9.3, $J_{6,7}$ 4.9, $J_{6,7'}$ 2.7 Hz, H-6) 4.19 (1H, dd, $J_{3,4}$ 4.5, $J_{4,5}$ 2.2 Hz, H-4) 4.40 (1H, m, H-3) 4.44 (1H, d, $J_{2,3}$ 3.1 Hz, H-2) 4.67 (1H, dd, $J_{4,5}$ 2.2, $J_{5,6}$ 9.3 Hz, H-5) 4.79, 4.82 (2 x 1H, 2 x d, $J_{H,H'}$ 11.4 Hz, CHH'Ph) 7.28-7.43 (5H, m, ArC<u>H</u>); δ_C (CD_3OD): 63.8 (t, C-7) 68.8, 69.6, 69.7, 76.3, 78.7 (5 x d, C-2, C-3, C-4, C-5, C-6) 73.6 (t, <u>C</u>H_2Ph) 128.9, 129.2, 129.8 (3 x d, Ar<u>C</u>H) 139.9 (s, Ar<u>C</u>), 174.6 (s, C=O); *m/z* (NH_3, DCI): 299 ($M+H^+$, 10%), 316 ($M+NH_4^+$, 20%). (Found: C, 56.32; H, 6.34. $C_{14}H_{18}O_7$ requires: C, 56.37; H, 6.08%).

4-O-*Benzyl-6,7*-O-*isopropylidene*-***D***-glycero-***D***-gulo-*heptono-1,5-lactone* ***20***. (i) Acetone (10 ml) and *p*-toluenesulphonic acid (350 mg, 1.84 mmol) were added to the glucono-1,5-lactone **11** (3.19 g, 10.7 mmol) and the mixture stirred at room temperature. After 1 h, t.l.c. (ethyl acetate/hexane 1:1), revealed only a trace of starting material (R_f 0.05) and a major product (R_f 0.2). The mixture filtered through a silica plug and the solvent was removed *in vacuo*, to afford *4*-O-*benzyl-6,7*-O-*isopropylidene*-***D***-glycero-***D***-gulo-*heptono-1,5-lactone* ***20*** (3.46 g, 96%) as a white solid, m.p. 114-118°C (ether/hexane); $[\alpha]_D^{20}$ +59.0 (*c*, 1.03 in $CHCl_3$); υ_{max} (KBr): 1743 (C=O) cm^{-1}; δ_H (500 MHz; $CDCl_3$): 1.39, 1.44 (2 x 3H, 2 x s, 2 x Me) 2.85, 3.25 (2 x 1H, 2 x br s, 2 x OH) 4.08 (1H, dd, $J_{6,7}$ 4.8, $J_{7,7'}$ 9.0 Hz, H-7) 4.12 (1H, dd, $J_{3,4}$ 4.4, $J_{4,5}$ 2.3 Hz, H-4) 4.17 (1H, dd, $J_{6,7'}$ 6.0, $J_{7,7'}$ 9.0 Hz, H-7') 4.36 (1H, dd, $J_{2,3}$ 3.4, $J_{3,4}$ 4.4 Hz, H-3) 4.43 (1H, m, H-6) 4.52 (1H, d, $J_{2,3}$ 3.4 Hz, H-2) 4.61 (1H, dd, $J_{4,5}$ 2.3, $J_{5,6}$ 9.1 Hz, H-5) 4.71, 4.78 (2 x 1H, 2 x d, $J_{H,H'}$ 11.3 Hz, CHH'Ph) 7.34-7.40 (5H, m, ArC<u>H</u>); δ_C ($CDCl_3$): 25.2, 26.7 (2 x q, 2 x Me) 67.2 (t, C-7) 68.0, 68.2, 72.3, 74.0, 80.3 (5 x d, C-2, C-3, C-4, C-5, C-6) 73.7 (t, <u>C</u>H_2Ph) 109.8 (s, <u>C</u>Me_2) 128.2, 128.4, 128.8 (3 x d, Ar<u>C</u>H) 137.4 (s, Ar<u>C</u>) 173.8 (s, C=O); *m/z* (NH_3, DCI): 338 ($M+H^+$, 40%), 356 ($M+NH_4^+$, 45%). (Found: C, 60.33; H, 6.53. $C_{17}H_{22}O_7$ requires: C, 60.35;H, 6.55%).

(ii)The δ-lactone **11** (1.21 g, 4.05 mmol) was dissolved in dimethylformamide (10 ml) and the solution cooled to 0°C. A catalytic amount of *p*-toluenesulphonic acid (77 mg, 0.4 mmol) was added, followed by dropwise addition of 2-methoxypropene (504 µl, 5.27 mmol). The reaction mixture was allowed to warm up to room temperature. After 2 h, t.l.c. (ethyl acetate/hexane 1:1), revealed only a trace of starting material (R_f 0.05) and a major product (R_f 0.2). Sodium carbonate (1.12 g, 10.57 mmol) was added and stirred for 2 h before being filtered off. The solvent was evaporated *in vacuo* and the resulting residue purified by flash column chromatography (ethyl acetate/hexane 1:3) to yield the monoisopropylidene derivative **20** (1.105 g, 81%), identical to the material above.

4-O-Benzyl-7-O-tert-butyldiphenylsilyl-D-glycero-*D*-gulo-*heptono-1,5-lactone 27.* *tert*-Butylchlorodiphenylsilane (1.43 ml, 5.5 mmol) was added to a stirred mixture of the tetra alcohol **11** (1.49 g, 5 mmol) and imidazole (1.02 g, 15 mmol) in dry dimethylformamide at -78°C. The reaction mixture was allowed to warm up to room temperature and stirred for 16 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (ethyl acetate - hexane, 1 : 1) to afford *4-O-benzyl-7-O*-tert-*butyldiphenylsilyl-D*-glycero-*D*-gulo-*heptono-1,5-lactone 27* (2.25 g, 84%) as a colourless syrup, $[\alpha]_D^{20}$ +41.6 (*c*, 0.31 in $CHCl_3$); υ_{max} (thin film): 3500 (br, OH) 1740 (C=O) cm^{-1}; δ_H (200 MHz; $CDCl_3$): 1.10 (9H, s, C<u>Me</u>$_3$) 3.94 (2H, d, *J* 4.1) 4.07-4.13 (1H, m) 4.24-4.28 (1H, m) 4.35-4.40 (1H, m) 4.52-4.53 (1H, m) 4.69-4.83 (3H, m) 7.28-7.71 (15H, m, ArC<u>H</u>); δ_C (50.3 MHz; $CDCl_3$): 19.3 (s, C<u>Me</u>$_3$) 26.9 (q, C<u>Me</u>$_3$) 64.4 (t, C-7) 68.2, 68.4, 68.5, 74.3, 78.6 (5 x d, C-2, C-3, C-4, C-5, C-6) 73.7 (t, <u>C</u>H$_2$Ph) 128.2, 128.4, 128.8, 130.2, 135.9 (5 x d, Ar<u>C</u>-H) 132.9, 133.2, 137.7 (3 x s, Ar-<u>C</u>) 174.1 (s, C=O); *m/z* (NH_3; CI): 316 (100%) 554 ($M+NH_4^+$, 25%).(Found: C, 67.83; H, 6.64. $C_{30}H_{36}O_7Si$ requires: C, 67.14; H, 6.76%),

4-O-Benzyl-2,3:6,7-di-O-isopropylidene-D-glycero-*D*-gulo-*heptono-1,5-lactone 19.* The δ-lactone **11** (2.00 g, 6.71 mmol) was dissolved in acetone (150 ml) and enough camphorsulphonic acid (150 mg, 0.67 mmol) added to adjust the pH of the solution to 2. The reaction mixture was heated to 40°C with stirring when 2,2-dimethoxypropane (5.00 ml, 40.44 mmol) was added. After 15 min at 40°C, t.l.c. (ethyl acetate/hexane 1:1) indicated a trace of starting material (R_f 0.2) and a single product (R_f 0.7). The reaction was neutralised carefully with saturated aqueous sodium bicarbonate and the solvent removed *in vacuo*. The residue was dissolved in ethyl acetate (150 ml), washed with water (150 ml) and with brine (100 ml). The organic layer was dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification by flash column chromatography (ethyl acetate/hexane 1:4) yielded *4-O-benzyl-2,3:6,7-di-O-isopropylidene-D*-glycero-*D*-gulo-*heptono-1,5-lactone 19* (2.08 g, 82%) as a white crystalline solid, m.p. 62-65°C (ethyl acetate/hexane); $[\alpha]_D^{20}$ +39.6 (*c*, 1.02 in $CHCl_3$); υ_{max} (KBr): 1761 (C=O) cm^{-1}; δ_H (500 MHz; $CDCl_3$): 1.35, 1.36, 1.42, 1.52 (4 x 3H, 4 x s, 4 x Me) 3.94 (1H, d, $J_{3,4}$ 2.5 Hz, H-4) 4.10 (1H, dd, $J_{6,7}$ 4.1, $J_{7,7'}$ 9.0 Hz, H-7) 4.14 (1H, dd, $J_{6,7'}$ 5.7, $J_{7,7'}$ 9.0 Hz, H-7') 4.34 (1H, m, H-6) 4.47 (1H, d, $J_{5,6}$ 9.0 Hz, H-5) 4.52 (1H, dd, $J_{2,3}$ 6.8 Hz, H-3) 4.63 (1H, d, $J_{2,3}$ 6.8 Hz, H-2) 4.72 (2H, s, CH_2Ph) 7.30-7.37 (5H, m, ArC<u>H</u>); δ_C ($CDCl_3$): 23.7, 25.1, 25.9, 27.0 (4 x q, 4 x Me) 66.9 (t, C-7) 73.0 (t, <u>C</u>H$_2$Ph) 72.1, 72.3, 72.7, 73.5, 76.6 (5 x d, C-2, C-3, C-4, C-5, C-6) 109.9, 111.5, (2 x s, 2 x <u>C</u>Me$_2$) 127.8, 128.3, 128.7 (3 x d, Ar<u>C</u>H) 137.4 (s, Ar<u>C</u>) 166.9 (s, C=O); *m/z* (NH_3, CI): 379 ($M+H^+$, 40%), 396 ($M+NH_4^+$, 50%). (Found: C, 63.48; H, 7.24. $C_{20}H_{26}O_7$ requires: C, 63.48; H, 6.93%).

4-O-Benzyl-2,3-O-isopropylidene-D-glycero-*D*-gulo-*heptono-1,5-lactone 18.* The diacetonide **19** (1.74 g, 4.60 mmol) was stirred at room temperature in 80% aqueous acetic acid (30 ml). After 42 h, t.l.c. (ethyl acetate/hexane 1:1) showed a trace of starting material (R_f 0.7) and a single product (R_f 0.15). The solvents were removed *in vacuo* and the residue coevaporated with toluene (3 x 10 ml). Purification by flash column chromatography (ethyl acetate/hexane 3:2) yielded *4-O-benzyl-2,3-O-isopropylidene-D*-glycero-*D*-gulo-*heptono-1,5-lactone 18* (1.25 g, 80%, 92% based on recovered starting material), m.p. 111-114°C (ether/hexane); $[\alpha]_D^{20}$ +26.2 (*c*, 0.99 in $CHCl_3$); υ_{max} (KBr): 1752 (C=O) cm^{-1}; δ_H (500 MHz; $CDCl_3$): 1.37, 1.51 (2 x 3H, 2 x s, 2 x Me) 3.80 (1H, dd, $J_{6,7}$ 4.6, $J_{7,7'}$ 11.4 Hz, H-7) 3.88 (1H, dd, $J_{6,7'}$ 3.0, $J_{7,7'}$ 11.4 Hz, H-7') 3.92-3.94 (1H, m, H-6) 3.99 (1H, dd, $J_{3,4}$ 2.6, $J_{4,5}$ 1.1 Hz, H-4) 4.55 (1H, dd, $J_{4,5}$ 1.1,

$J_{5,6}$ 8.8 Hz, H-5) 4.58 (1H, dd, $J_{2,3}$ 7.0, $J_{3,4}$ 2.6 Hz, H-3) 4.65, 4.76 (2 x 1H, 2 x dd, $J_{H,H'}$ 11.9 Hz, CHH'Ph) 4.67 (1H, d, $J_{2,3}$ 7.0 Hz, H-2) 7.33-7.40 (5H, m, ArCH); δ_C ($CDCl_3$): 23.7, 25.9 (2 x q, 2 x Me) 62.6 (t, C-7) 68.6, 71.5, 72.5, 73.4, 75.5 (5 x d, C-2, C-3, C-4, C-5, C-6) 72.6 (t, CH_2Ph) 111.6 (s, CMe_2) 128.2, 128.6, 128.9 (3 x d, ArCH) 137.3 (s, ArC) 167.3 (s, C=O); *m/z* (NH_3, CI): 339 ($M+H^+$, 25%), 356 ($M+NH_4^+$, 60%). (Found: C, 60.46; H, 6.31. $C_{17}H_{22}O_7$ requires: C, 60.35; H, 6.55%).

*4-O-Benzyl-D-*glycero-*D-*gulo-*heptono-1,5-lactone* ***11*** *from hydrolysis of acetonides* ***18,19*** *and* ***20****.* The diacetonide **19** (1.53 g, 4.05 mmol) was stirred in 50% aqueous trifluoroacetic acid (30 ml) for 16 h at room temperature. T.l.c. (ethyl acetate/hexane 1:1) revealed a single product (R_f 0.05) and none of the diacetonide (R_f 0.55). The solvents were removed *in vacuo* to afford the 4-O-benzyl-δ-lactone **11** (1.30 g, 95%), identical to the material above. Hydrolysis of the monoacetonides **18** and **20** under the same conditions also gave **11** in yields of 91% and 96%, respectively.

3-O-Benzyl-1,2:5,6-di-O-isopropylidene-α-D-allopyranose ***22****.* Diacetone glucose **15** (50.2 g, 0.19 mol) was dissolved in dry dichloromethane (1 l) and dry powdered 3 Å molecular sieves (125 g) were added. Pyridinium chlorochromate (125 g, 0.58 mol, 3 equiv) was then added and the resultant mixture was stirred vigorously for 24 h. Ether (500 ml) was then added and the solution was stirred for a further 30 min and then filtered through a silica plug topped with $MgSO_4$ (ether elute). The filtrate was concentrated *in vacuo* to give 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose with its hydrate. The crude ketone (47 g, ~0.18 mol) was then dissolved in ethanol (800 ml), and cooled to -20°C. Sodium borohydride (6.89 g, 0.18 mol) as a suspension in 50% aqueous ethanol (200 ml) was added dropwise over 30 min. The reaction was allowed to warm to 0°C over 30 min when t.l.c. (ethyl acetate/hexane 1:1) showed a single product (R_f 0.3). Excess ammonium chloride (11.25 g) was added to quench the reaction and the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate (300 ml), washed with water (100 ml) and with brine (50 ml), dried ($MgSO_4$), filtered, concentrated *in vacuo* to give the crude diacetonide **21** (45 g, 90%) as a white solid. Sodium hydride (60% dispersion in oil, 7.6 g, 0.19 mol, 1.1 equiv) was washed with hexane (3 x 20 ml) then tetrahydrofuran (50 ml) was added and the mixture cooled to 0°C under nitrogen. The crude diacetone allose **21** (45 g, 0.17 mol) was dissolved in tetrahydrofuran (400 ml) and added slowly to the stirred suspension of sodium hydride. After the effervescence had ceased tetrabutylammonium iodide (3 g) was added and the mixture was allowed to warm up to room temperature. Benzyl bromide (22.6 ml, 0.19 mol, 1.1 equiv) was added over 30 min and the reaction mixture stirred for 3 h. when t.l.c. (ethyl acetate/hexane 1:1) showed no starting material (R_f 0.3) and one major product (R_f 0.6). Methanol (20 ml) and ether (200 ml) were added and the mixture stirred for 30 min before filtering through a silica plug topped with magnesium sulphate and concentrating. The residue was dissolved in dichloromethane (500 ml), washed with water (100 ml) and brine (100 ml), dried ($MgSO_4$), filtered and evaporated. The white solid was recrystallised from hot hexane to give the benzyl ether **22** (46.4 g, 77%, 69% from diacetone glucose **15**) as a white solid, m.p. 63-65°C (hexane) $[\alpha]_D^{20}$ +106.7 (*c*, 1.0 in $CHCl_3$)[lit.[22] 64-65°C, $[\alpha]_D$ +110 (*c*, 1.0 in CH_3OH)]. δ_H (200 MHz; $CDCl_3$) 1.37, 1.38, 1.40, 1.60 (4 x 3H, 4 x s, 4 x Me), 3.90 (1H, dd, $J_{2,3}$ 4.5, $J_{3,4}$ 8.6 Hz, H-3), 3.97-4.07 (2H, m, H-6, H-6'), 4.16 (1H, dd, $J_{3,4}$ 8.6, $J_{4,5}$ 3.1 Hz, H-4), 4.39 (1H, dt, $J_{4,5}$ 3.1, $J_{5,6} = J_{5,6'}$ 7.0 Hz, H-5), 4.59 (1H, t, $J_{1,2} = J_{2,3}$ 4.0 Hz, H-2), 4.60, 4.79 (2 x 1H, 2 x d, *J* 11.6 Hz, CHH'Ph), 4.42 (1H, d, $J_{1,2}$ 3.7 Hz, H-1), 7.31-7.44 (5H, m, ArCH);

4-O-*Benzyl*-*D*-glycero-*D*-allo-*heptono-1,5-lactone* **12**. The fully protected allofuranose **22** (37.0 g, 0.11 mol) was dissolved in dioxan (30 ml) and water (30 ml). Amberlyst '15' ion exchange resin (12 g) was added and the mixture stirred at 65°C. After 14 h, t.l.c. (ethyl acetate/methanol 9:1) indicated complete conversion of the starting material (R_f 0.8) to a single product (R_f 0.3). The mixture was filtered and adjusted to pH 9 with 10 M NaOH (5 drops). This solution of crude 3-*O*-benzyl-**D**-allofuranose **23** was used without further purification. Sodium cyanide (10.4 g, 0.21 mol) was added to the filtrate. The reaction mixture was stirred at room temperature for 20 h, when t.l.c. (ethyl acetate/methanol 9:1) indicated complete conversion of the starting material (R_f 0.3) to a baseline spot (R_f 0.0, R_f 0.8 reverse phase (methanol/water 3:18)). The reaction mixture was stirred at 90°C for 48 h after which time all the excess cyanide had been hydrolysed. The reaction mixture was then cooled to room temperature and Amberlyst '15' ion exchange resin (49 g) was added; the mixture was stirred for 2 h, filtered and the solvent removed *in vacuo*. The residue was dissolved in glacial acetic acid (500 ml) and stirred at 70°C. After 3 h t.l.c. (ethyl acetate/methanol 9:1) indicated formation of a product (R_f 0.3). The crude product was preabsorbed on to silica and purified by flash chromatography (gradient elution from ethyl acetate to methanol/ethyl acetate 1:9) to give a solid which was purified by recrystallisation (ethyl acetate) to afford *4*-O-*benzyl*-*D*-glycero-*D*-allo-*heptono-1,5-lactone* **12** as a white solid (12.1 g, 38%), m.p. 139-140°C, $[\alpha]_D^{25}$ +40.0 (*c*, 1.3 in dimethylformamide); ν_{max} (KBr): 3369 (br, OH), 1752 (C=O) cm^{-1}; δ_H (500 MHz; D_6-DMSO): 3.35 (1H, ddd, $J_{OH,7}$ 5.2, $J_{6,7}$ 6.9, $J_{7,7'}$ 11.1 Hz, H-7), 3.44 (1H, dt, $J_{OH,7} = J_{6,7'}$ 6.0, $J_{7,7'}$ 11.1 Hz, H-7'), 3.78 (1H, ddd, $J_{5,6}$ 1.9, *J* 6.6, *J* 8.3 Hz, H-6), 4.00 (1H, dd, $J_{3,4}$ 2.5, $J_{4,5}$ 8.2 Hz, H-4), 4.04 (1H, dd, $J_{2,3}$ 2.0, $J_{OH,2}$ 6.0 Hz, H-2), 4.30 (1H, dt, $J_{2,3} = J_{3,4}$ 2,4, $J_{OH,2}$ 3.8 Hz, H-3), 4.36 (1H, dd, $J_{4,5}$ 8.2, $J_{5,6}$ 1.9 Hz, H-5), 4.44, 4.66 (2 x 1H, 2 x d, *J* 11.5 Hz, CHH'Ph), 4.59 (1H, dd, $J_{OH,7}$ 5.9, $J_{OH,7'}$ 5.2 Hz, exchanged on D_2O shake, OH-7), 5.21 (1H, d, $J_{OH,6}$ 4.9 Hz, exchanged on D_2O shake, OH-6) 5.46 (1H, br t, $J_{OH,3}$ 3.8 Hz, exchanged on D_2O shake, OH-3), 5.51 (1H, d, $J_{OH,2}$ 6.0 Hz, exchanged on D_2O shake, OH-2) 7.27-7.39 (5H, m, ArC<u>H</u>); δ_C (D_6-DMSO): 62.4 (t, C-7), 67.8, 69.3, 72.9, 73.3, 81.1 (5 x d, C-2, C-3, C-4, C-5, C-6), 70.3 (t, <u>C</u>H_2Ph), 128.1, 128.4, 128.8 (3 x d, Ar<u>C</u>H), 138.8 (s, Ar<u>C</u>), 173.1 (s, C-1); *m/z* (NH_3, DCI): 91 ($PhCH_2^+$, 85%), 299 ($M+H^+$, 45%), 316 ($M+NH_4^+$, 100%). (Found: C, 56.10; H, 5.94. $C_{14}H_{18}O_7$ requires C, 56.37; H, 6.08%).

4-O-*Benzyl-6,7*-O-*isopropylidene*-*D*-glycero-*D*-allo-*heptono-1,5-lactone* **26**. Acetone (50 ml) and *p*-toluenesulphonic acid (114 mg, 0.60 mmol) was added to the allono-1,5-lactone **12** (1.79 g, 6.01 mmol) and the mixture stirred at room temperature. After 15 min, t.l.c. (ethyl acetate) indicated complete conversion of the starting material (R_f 0.2) to a single product (R_f 0.5). Sodium bicarbonate (151 mg, 1.8 mmol) was added and the mixture filtered. The solvent was removed *in vacuo* and the residue purified by flash chromatography (ethyl acetate/hexane 1:1), to afford starting lactone **12** (0.13 g, 7%) and *4*-O-*benzyl-6,7*-O-*isopropylidene*-*D*-glycero-*D*-allo-*heptono-1,5-lactone* **26** as a white solid (1.87 g, 92%), m.p. 100-101°C; $[\alpha]_D^{25}$ +26.9 (*c*, 1.05 in $CHCl_3$); ν_{max} (KBr): 3431 (br, OH), 1750 (C=O) cm^{-1}; δ_H (500 MHz; $CDCl_3$): 1.36, 1.46 (2 x 3H, 2 x s, 2 x Me), 2.87, 3.40 (2 x 1H, 2 x br s, exchanged on D_2O shake, 2 x OH), 3.96 (1H, dd, $J_{6,7}$ 6.1, $J_{7,7'}$ 8.7 Hz, H-7), 3.96 (1H, dd, $J_{3,4}$ 3.0, $J_{4,5}$ 7.3 Hz, H-4), 4.00 (1H, dd, $J_{6,7'}$ 7.2, $J_{7,7'}$ 8.7 Hz, H-7'), 4.15 (1H, d, $J_{2,3}$ 2.3 Hz, H-2), 4.40 (1H, ddd, $J_{5,6}$ 3.5, $J_{6,7}$ 7.1, $J_{6,7'}$ 6.1 Hz, H-6), 4.47 (1H, t, $J_{2,3} = J_{3,4}$ 2.6 Hz, H-3), 4.58 (1H, dd, $J_{4,5}$ 7.2, $J_{5,6}$ 3.5 Hz, H-5) 4.63, 4.70 (2 x 1H, 2 x d, *J* 11.3 Hz, CHH'Ph), 7.34-

7.40 (5H, m, ArCH); δ_C ($CDCl_3$): 24.5, 26.0 (2 x q, $C(\underline{C}H_3)_2$), 64.9 (t, C-7), 67.3, 69.1, 72.8, 75.9, 80.3 (5 x d, C-2, C-3, C-4, C-5, C-6), 71.6 (t, $\underline{C}H_2Ph$), 110.3 (s, $\underline{C}Me_2$), 128.6, 128.9 (2 x d, Ar$\underline{C}$-H), 136.8 (s, Ar-$\underline{C}$), 172.1 (s, C-1); *m/z* (NH_3, DCI): 339 ($M+H^+$, 25%), 356 ($M+NH_4^+$, 100%). (Found: C, 60.33; H, 6.45. $C_{17}H_{22}O_7$ requires C, 60.35; H, 6.55%).

4-O-*Benzyl-2,3:6,7*-O-*di-isopropylidene-D*-glycero-*D*-allo-*heptono-1,5-lactone* ***25***. The side chain acetonide **26** (115 mg, 0.34 mmol) was dissolved in acetone (3 ml) and enough camphorsulphonic acid (5 mg, 0.02 mmol) added to adjust the pH of the solution to 2. The reaction mixture was heated to 40°C with stirring when 2,2-dimethoxypropane (0.2 ml, 5 equiv) was added. After 1 h at 40°C t.l.c. (ethyl acetate) indicated complete conversion of the starting material (Rf 0.5) to a single product (Rf 0.8). The mixture was diluted with ethyl acetate (20 ml) and filtered through a silica plug. The solvent was removed *in vacuo* and the white solid purified by recrystallisation (ether/hexane), to afford *4*-O-*benzyl-2,3:6,7*-O-*di-isopropylidene-D*-glycero-*D*-allo-*heptono-1,5-lactone* ***25***, as a white crystalline solid (104 mg, 85%), m.p. 135.5-136.5°C, $[\alpha]_D^{20}$ +111.9 (*c*, 1.05 in $CHCl_3$); ν_{max} (KBr) 1752 (C=O) cm^{-1}; δ_H (500 MHz; C_6D_6): 1.11, 1.12, 1.33, 1.34 (4 x 3H, 4 x s, 4 x Me), 3.43 (1H, dd, *J* 1.5, *J* 7.1 Hz), 3.68 (1H, dd, $J_{6,7}$ 6.7, $J_{7,7'}$ 8.3 Hz, H-7), 3.85 (1H, dd, $J_{6,7'}$ 6.0, $J_{7,7'}$ 8.3 Hz, H-7'), 4.04 (1H, q, $J_{5,6} = J_{6,7} = J_{6,7'}$ 6.0 Hz, H-6), 4.22 (2H, m), 4.26, 4.49 (2 x 1H, 2 x d, *J* 11.8 Hz, CHH'Ph), 4.63 (1H, dd, *J* 5.4, *J* 7.1 Hz), 7.03-7.20 (5H, m, ArCH); δ_C ($CDCl_3$): 24.5, 25.0, 25.9, 26.3 (4 x q, 4 x Me), 65.5 (t, C-7), 70.7, 72.3, 72.5, 74.3, 77.3 (5 x d, C-2, C-3, C-4, C-5, C-6), 72.3 (t, $\underline{C}H_2Ph$), 110.2, 111.8 (2 x s, 2 x $\underline{C}Me_2$), 128.3, 128.4, 128.8 (3 x d, Ar$\underline{C}$H), 137.2 (s, Ar$\underline{C}$), 168.0 (s, C-1); *m/z* (NH_3, DCI): 91 ($PhCH_2^+$, 100%), 379 ($M+H^+$, 40%), 396 ($M+NH_4^+$, 60%). (Found: C, 63.29; H, 6.72. $C_{20}H_{26}O_7$ requires C, 63.48; H, 6.93%).

4-O-*Benzyl-2,3*-O-*isopropylidene-D*-glycero-*D*-allo-*heptono-1,5-lactone* ***24***. The *allono*-diacetonide **25** (44 mg, 0.12 mmol) was dissolved in 80% aqueous acetic acid (1 ml) and stirred at 45°C. After 2 h, t.l.c. (ethyl acetate/hexane 1:1) indicated complete conversion of the starting material (R_f 0.5) to a single product (R_f 0.1). The solvent was removed *in vacuo*, and the residue was coevaporated with toluene to afford an oil which was purified by flash chromatography (ethyl acetate/hexane 1:1), to afford *4*-O-*benzyl-2,3*-O-*isopropylidene-D*-glycero-*D*-allo-*heptono-1,5-lactone* ***25*** as an oil (37 mg, 95%), $[\alpha]_D^{25}$ +84.0 (*c*, 1.05 in CH_3CN); ν_{max} (thin film): 3407 (br, OH), 1746 (C=O) cm^{-1}; δ_H (500 MHz; CD_3CN): 1.38, 1.46 (2 x 3H, 2 x s, 2 x Me), 2.93 (1H, br t, *J* 5.8 Hz, exchanged on D_2O shake, OH-7), 3.51 (1H, br d, *J* 5.3 Hz, exchanged on D_2O shake, OH-6), 3.53-3.61 (2H, m, H-7, H-7'), 3.87 (1H, m, H-6), 4.11 (1H, dd, $J_{3,4}$ 3.4, $J_{4,5}$ 6.3 Hz, H-4), 4.61 (1H, dd, $J_{4,5}$ 6.2, $J_{5,6}$ 5.2 Hz, H-5) 4.64, 4.78 (2 x 1H, 2 x d, *J* 11.6 Hz, CHH'Ph), 4.66 (1H, d, $J_{2,3}$ 7.8 Hz, H-2), 4.85 (1H, dd, $J_{2,3}$ 7.8, $J_{3,4}$ 3.4 Hz, H-3) 7.31-7.41 (5H, m, ArCH); δ_C (50.3 MHz; CD_3CN): 24.8, 26.3 (2 x q, 2 x Me), 63.2 (t, C-7), 72.2, 73.5, 79.1 (3 x d, C-2, C-3, C-4, C-5, C-6), 72.9 (t, $\underline{C}H_2Ph$), 111.5 (s, $\underline{C}Me_2$), 128.8, 129.4 (2 x d, Ar$\underline{C}$H), 139.0 (s, Ar$\underline{C}$), 169.3 (s, C-1); *m/z* (NH_3, DCI): 91 ($PhCH_2^+$, 100%), 339 ($M+H^+$, 70%), 356 ($M+NH_4^+$, 25%). (Found: C, 60.56; H, 6.20. $C_{17}H_{22}O_7$ requires C, 60.35; H, 6.55%).

4-O-*Benzyl-D*-glycero-*D*-allo-*heptono-1,5-lactone* ***12*** *from hydrolysis of acetonides* ***24,25*** *and* ***26***. The monoacetonide **24** (30 mg, 0.09 mmol) was dissolved in 50% aqueous trifluoroacetic acid (3 ml) and stirred at room temperature. After 16 h, t.l.c. (ethyl acetate) indicated complete conversion of the starting material (R_f

0.4) to a single product (R_f 0.2). The solvent was removed *in vacuo* and the residue recrystallised (ethyl acetate) to afford the benzyl δ-lactone **12** (26 mg, 98%) as a white solid, identical to the material above. Hydrolysis of the monoacetonide **26** and the diacetonide **20** under the same conditions also gave **12** in yields of 93% and 99%, respectively.

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