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BENZYLIDENE ACETALS OF HEPTONOLACTONES

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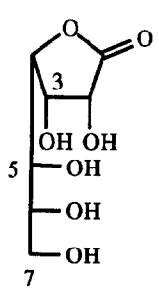
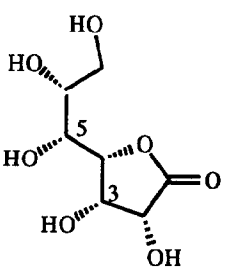
Abstract The preparation of 3,5-(R)-*O*-benzylidene-**D**-*glycero*-**D**-*gulo*-heptono-1,4-lactone, a readily available and powerful chiron, is described; other benzylidene derivatives of heptono-1,4-lactones are characterised. The X-ray crystal structure of 3,5(R):6,7(R)-di-*O*-benzylidene-**D**-*glycero*-**D**-*gulo*-heptono-1,4-lactone is reported.

The formation of acetals from the reaction of diols with benzaldehyde and acetone provides the most general set of manipulations used for the protection of carbohydrates. Simple isopropylidene derivatives[1,2] of heptonolactones have provided a set of intermediates which have been used in the synthesis of highly functionalised targets with up to seven adjacent functional groups and five contiguous chiral centres. These acetonides provide relatively easy access to highly substituted piperidines,[3] pyrrolizidines,[4] pyrrolidines,[5] alexines,[6] complex 2,5-disubstituted tetrahydrofurans[7] and very highly functionalised carbocycles.[8]

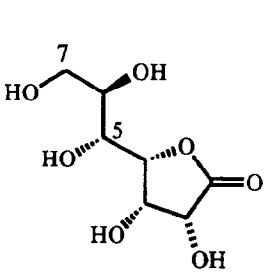
Glucoheptonolactone [D-*glycero*-**D**-*gulo*-heptono-1,4-lactone] (1), the product of the Kiliani[9] reaction of glucose, is the cheapest[10] and most readily available heptonic acid. The acetonides derived from (1), first described by Brimacombe,[11] have been used for the synthesis of prostaglandins,[12] pyrrolizidines,[13] and gonoiotriol[14] and goniofufurone[15] derivatives. However, no benzylidene derivatives of glucoheptonolactone have been described and such protection is likely to produce a complementary set of acetals which should have considerable potential as starting materials derived from the chiral pool. This paper reports the easy synthesis of the 3,5-*O*-benzylidene derivative of (1), together with the characterisation of other benzylidene acetals of (1) and its epimer (2). The structure of (1) has been also drawn in conformational forms (1a) and (1b) which show the suitability of the 3,5 and 5,7-diol grops for benzylidene acetal formation.



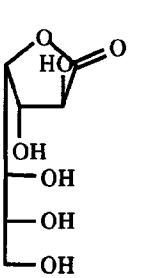
1



1a

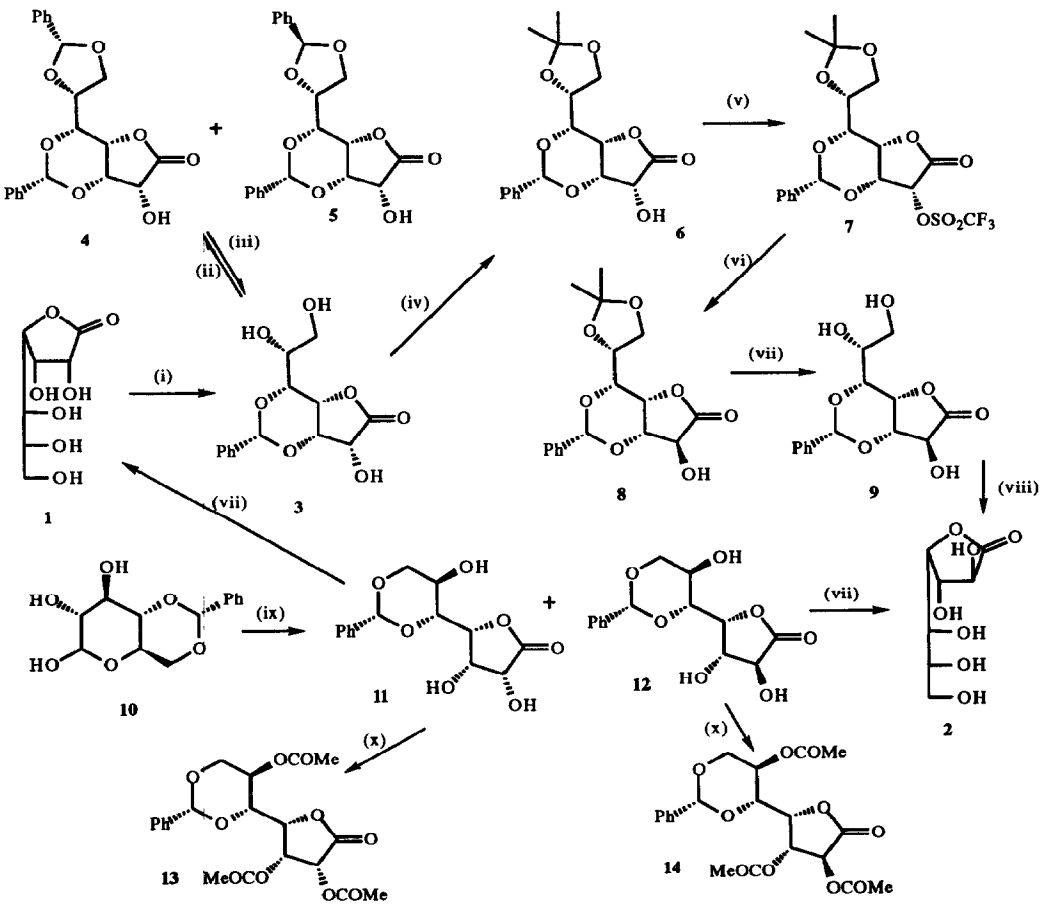


1b



2

Treatment of glucoheptonic acid lactone (1) with benzaldehyde and concentrated hydrochloric acid gave the highly crystalline 3,5-*O*-benzylidene derivative (3) in 91% yield. The chemical shift of the acetal carbon with a doublet at δ 99.8 in the ^{13}C NMR is typical for a 6-ring benzylidene acetal. Treatment of the monobenzylidene acetal (3) with benzaldehyde and zinc chloride gave a separable mixture of the dibenzylidene derivatives (4) and (5) in yields of 29% and 24% respectively; the ^{13}C NMR spectra of both (4) and (5) have two acetal methine carbons close to δ 99 for the dioxane acetal and δ 105 for the dioxolane acetal. Both (4) and (5) may be partially deprotected by treatment with methanolic hydrogen chloride resulting in the removal of the side chain benzylidene acetals to give (3), showing that the configuration of the dioxane acetal carbon is unchanged during these transformations. Treatment of (3) with aqueous trifluoroacetic acid causes removal of the benzylidene protecting group to form (1).



(i) PhCHO, HCl (ii) PhCHO, $ZnCl_2$ (iii) MeOH, HCl (iv) Me_2CO, $Me_2C(OMe)_2$, p-Me-C_6H_4-SO_3H (v) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2 (vi) CF_3COONa, DMF (vii) 80% aq. AcOH (viii) 50% aq. CF_3COOH (ix) NaCN, H_2O, dioxan (x) Ac_2O, pyridine

The structure of (4) was determined by single crystal X-ray crystallographic analysis [Figure] and this firmly establishes the *R* configuration of the benzylidene acetal carbon in (3); thus, all four substituents on the dioxane ring of (3) are *cis* to each other. The benzylidene lactone (3), which may easily be accomplished on a

large scale without the need for any chromatographic purification, is easily prepared and has the potential to be a powerful intermediate for the synthesis of a range of highly functionalised synthetic targets.[16]

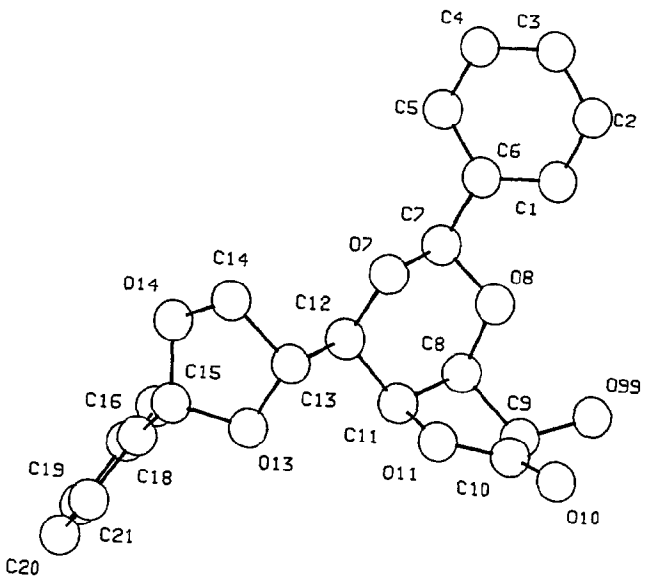


Figure X-Ray molecular structure of 3,5(R):6,7(R)-Di-*O*-benzylidene-**D**-*glycero*-**D**-*gulono*-heptono-1,4-lactone (3), showing crystallographic numbering scheme.

The 3,5-O-benzylidene derivative of **D**-*glycero*-**D**-*ido*-heptono-1,4-lactone (9) may be prepared by inversion of the C-2 hydroxyl function in (3). Reaction of (3) with acetone and dimethoxypropane in the presence of *p*-toluenesulphonic acid monohydrate gave the acetonide (6) in quantitative yield. The remaining hydroxyl function in (6) was esterified with trifluoromethanesulphonic anhydride in dichloromethane in the presence of pyridine at -20°C to afford the corresponding triflate (7) in 71% yield. Treatment of the triflate (7) with sodium trifluoroacetate in dimethylformamide gave, after work-up with methanol, the inverted alcohol (8) in 58% yield. The isopropylidene group in (8) could be selectively hydrolysed with aqueous acetic acid to give the benzylidene **D**-*glycero*-**D**-*ido*-lactone (9) in 79% yield. The structure of 3,5-*O*-benzylidene-**D**-*glycero*-**D**-*ido*-lactone (9) was confirmed by acid hydrolysis to give (2) in 80% yield.

The 3,5-*O*-benzylidene acetal of glucoheptonolactone (3) is both the kinetic and thermodynamic product of the reaction of benzaldehyde with glucoheptonolactone. The synthesis of the 5,7-*O*-benzylidene acetal of glucoheptonolactone (3) was therefore undertaken by the Kiliani ascension of 4,6-*O*-benzylidene glucose (10);[17] reaction of (10) with sodium cyanide in aqueous dioxane, followed by work-up in glacial acetic acid, gave a mixture of the benzylidene acetals (11) and (12) in yields of 35% and 11%, respectively. The treatment with acetic acid is necessary to lactonise the initially formed hydroxy acids; however, the 5,7-benzylidene acetal (11) is relatively sensitive to acid and also tends to rearrange to (3). Thus, the scale up of the preparation of (11) and (12) is difficult. Both the acetals (11) and (12) formed triacetates (13) and (14),

respectively, in quantitative yields. The structure of (11) was confirmed by demonstrating isomerisation to (3) and also by a high yield acid hydrolysis to give the unprotected lactone (1), identical to an authentic sample. Acid hydrolysis of (12) afforded a high yield of D-*glycero*-D-*ido*-heptonic acid-1,4-lactone (2).

In summary, this paper reports the synthesis and characterisation of the 3,5-O-benzylidene derivative (3) which should prove to be a readily accessible and powerful starting material from the chiral pool; it provides, example a short and convenient synthesis for the protection of the original 2 and 4 hydroxyl groups of glucose. The 5,7-*O*-benzylidene derivative (11) is less accessible, more readily hydrolysed and prone to rearrange in the presence of acid to the more stable (3).

Acknowledgements. We are grateful to acknowledge details of the procedure for the preparation of benzylidene glucose (10) from Dr Clissold. This work has been supported by SERC (CJFB, IB, DJH) awards/fellowships.

X-Ray Crystal Analysis

3,5(R):6,7(R)-Di-*O*-Benzylidene-D-*glycero*-D-*gulono*-heptono-1,4-lactone (3). Molecular formula $C_{21}H_{20}O_7$ Formula weight 384.384; Monoclinic P 2_1; a/Å 10.630 b/Å 9.588 c/Å 10.143; α/° 90, β/° 109.86, γ/° 90; U = 972.4 Å^3; Z=2; D_c = 1.313 g cm^{-3}; F(000) = 380; Cu-Kα radiation: 1412 independent reflections with I > 3σ (I). R = 0.0352, R_w = 0.0417.

The structure of 3,5(R):6,7(R)-di-*O*-benzylidene-D-*glycero*-D-*gulono*-heptono-1,4-lactone (3) (crystallised from ether:hexane was established by single crystal X-ray analysis. A suitable crystal of the dimensions 0.3 x 0.5 x 0.8 mm was selected. Consideration of the expected density range, the molecular weight and the volume of the unit cell indicated that it contained two molecules. Cell dimensions and intensity data were measured with an Enraf-Nonius CAD4-F diffractometer up to θ = 75° (Cu-Kα radiation). A total of 2783 reflections were collected between 0 and 70° θ. The systematic absences were: 0 K 0 : K = 2N + 1 and the data were successfully refined in P 2_1. After data reduction (merging R = 3.99%), there were 2118 unique reflections with net intensity greater than zero. The data were corrected for absorption, Lorentz and polarisation effects. All calculations were carried out on a Microvax 3800 computer using SHELXS-86.[18] This succeeded in finding all 28 non-hydrogen atoms in the molecule and these atoms were put into CRYSTALS[19] as 21 carbon and 7 oxygen atoms. These 28 atoms were refined to convergence using full matrix least-squares refinement, refining the positional parameters and isotropic temperature factors. Atomic scattering factors were taken from International Tables.[20] The hydrogen atoms were placed geometrically. All the non-hydrogen temperature factors were refined anisotropically. Corrections for secondary extinction and anomalous scattering were applied[21] and the model refined almost to convergence. The polarity parameter was refined, its value was 1.379 (e.s.d 0.379). A value of +1 confirmed the absolute configuration was that expected from the chemical synthesis. The merged data were refined using Chebyshev three term weighting scheme[22] to give a final value of R = 0.0355, Rw = 0.0448 with the sum of the (shift/e.s.d.)^2 = 0.042. The terms in the Chebyshev series were 18.96, -7.648 and 14.41. Atomic coordinates for the compound have been deposited at the Cambridge Crystallographic Data Centre.[23]

Fractional atomic coordinates and equivalent isotropic temperature factors [x 10^4] U(iso) with standard deviations in parentheses for 3,5(R):6,7(R)-Di-*O*-benzylidene-**D**-*glycero*-**D**-*gulono*-heptono-1,4-lactone (3):

Atom	x/a	y/b	z/c	U(iso)
C(1)	3267(4)	3054(5)	6864(4)	641
C(2)	4421(5)	3843(6)	7407(5)	769
C(3)	5221(4)	4094(6)	6652(5)	797
C(4)	4876(5)	3574(8)	5320(6)	958
C(5)	3727(4)	2807(7)	4754(4)	801
C(6)	2915(3)	2528(4)	5526(3)	509
C(7)	1666(3)	1693(4)	4906(3)	486
C(8)	-143(4)	694(4)	5451(4)	513
C(9)	-867(4)	987(4)	6476(4)	522
C(10)	-1380(3)	2448(4)	6021(4)	523
C(11)	-1098(4)	1340(4)	4133(4)	516
C(12)	-426(3)	1726(4)	3085(3)	490
C(13)	-1265(3)	2615(5)	1878(3)	538
C(14)	-641(4)	2770(5)	737(4)	603
C(15)	-2523(4)	1517(5)	-174(4)	572
C(16)	-3118(4)	97(5)	-554(4)	576
C(17)	-2396(5)	-1086(5)	19(5)	738
C(18)	-3011(7)	-2378(6)	-288(7)	922
C(19)	-4303(9)	-2476(7)	-1138(8)	930
C(20)	-5022(6)	-1324(9)	-1717(7)	957
C(21)	-4420(5)	-37(7)	-1427(5)	791
O(7)	786(2)	2471(3)	3773(2)	472
O(8)	1077(2)	1465(3)	5942(2)	509
O(10)	-1590(3)	3371(3)	6712(3)	688
O(11)	-1601(2)	2587(3)	4628(2)	522
O(13)	-2483(2)	1887(3)	1201(2)	595
O(14)	-1183(3)	1570(3)	-124(2)	584
O(99)	-55(3)	875(3)	7889(3)	651

Experimental

General Methods. - Melting points were recorded on a Kofler hot block and are uncorrected. 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. ^{13}C spectra run in D_2O were referenced to methanol (δ_C 49.6 ppm) as an internal standard. 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, methanol was distilled from magnesium methoxide, pyridine was distilled from, and stored over, potassium hydroxide; 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. 4,6-*O*-Benzylidene-D-glucopyranose (10) was made from glucose as previously described;[17] glucoheptonolactone (1) was purchased from the Sigma Chemical Company.

3,5(R)-O-*Benzylidene*-*D*-glycero-*D*-gulo-*heptono-1,4-lactone (3).* Glucoheptonolactone (1) (12.0 g, 57.7 mmol) was suspended in freshly distilled benzaldehyde (40 ml) and 37% aqueous hydrochloric acid (4 ml) was added. After the reaction mixture had been stirred at room temperature for 2 h, ether/hexane 2:1 (100 ml) was added; a colourless precipitate formed which was filtered off and washed with ether (300 ml). The solid was dried *in vacuo* to afford *3,5(R)*-O-*benzylidene*-*D*-glycero-*D*-gulo-*heptono-1,4-lactone* (3) (15.6 g, 91%) as a colourless solid, m.p. 188-191°C (ethanol); $[\alpha]_D^{20}$ -56.1 (*c*, 1.0 in MeOH); υ_{max} (KBr): 1770 (C=O), 3300 (br, OH), 3450 (br, OH) cm^{-1}; δ_H (500 MHz; CD_3OD): 3.68 (1H, dd, $J_{6,7'}$ 4.7, $J_{7,7'}$ 11.8 Hz, H-7') 3.78 (1H, dd, $J_{6,7}$ 2.5 Hz, H-7) 3.91 (1H, ddd, $J_{5,6}$ 9.3 Hz, H-6) 4.11 (1H, dd, $J_{4,5}$ 1.8 Hz, H-5) 4.58 (1H, t, $J_{3,4}$ 1.9 Hz, H-4) 4.72 (1H, d, $J_{2,3}$ 4.0 Hz, H-2) 4.76 (1H, dd, H-3) 5.69 (1H, s, C<u>H</u>Ph) 7.47-7.50 (2H, m, ArH), 7.32-7.36 (3H, m, ArH); δ_C (50.3 MHz; CD_3OD): 63.2 (t, C-7) 69.7, 70.6, 72.1, 75.8, 76.0 (5 x d, C-2, C-3, C-4, C-5, C-6) 99.8 (d, <u>C</u>HPh) 127.1, 128.7, 129.6 (3 x d, Ar<u>C</u>H) 140.9 (s, Ar<u>C</u>) 178.3 (s, C=O); *m/z* (NH_3, DCI): 297 ($M+H^+$, 100%) 314 ($M+NH_4^+$, 54%). (Found: C, 56.56; H, 5.58; $C_{14}H_{16}O_7$ requires C, 56.76; H, 5.45%).

3,5(R):6,7(R)-Di-O-*benzylidene*-*D*-glycero-*D*-gulo-*heptono-1,4-lactone (4) and 3,5(R):6,7(S) Di*-O-*benzylidene*-*D*-glycero-*D*-gulo-*heptono-1,4-lactone (5).* 3,5(R)-*O*-Benzylidene-D-*glycero*-D-*gulo*-heptono-1,4-lactone (3) (1.0 g, 3.38 mmol) was dissolved in distilled benzaldehyde (5 ml) and zinc chloride (1.84 g, 13.5 mmol) was added and the mixture was stirred at room temperature for 24 h, after which t.l.c. (ethyl acetate/hexane 1:1) showed the formation of two products (R_f 0.4 and 0.3). The mixture was concentrated *in vacuo* and the residue dissolved in ether (25 ml), washed with water (25 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude mixture of isomers was separated and purified by column chromatography (ethyl acetate/hexane 1:1) to afford both *3,5(R):6,7(R)-Di*-O-*benzylidene*-*D*-glycero-*D*-gulo-*heptono-1,4-lactone* (4) (0.38 g, 29%) as a colourless solid (R_f 0.4), m.p. 185-186°C (ether/hexane); $[\alpha]_D^{20}$ -21.1 (*c*,1.1 in Me_2CO); υ_{max} (KBr): 1790 (C=O) 3400 (br OH) cm^{-1}; δ_H (500 MHz: $CDCl_3$): 3.30 (1H, s, O<u>H</u>) 4.15 (2H, m) 4.30 (1H, dd, J 3.4, J 8.9 Hz) 4.47 (2H, m) 4.66 (1H, d, $J_{2,3}$ 4.0Hz, H-2) 4.73 (1H, dd, $J_{3,4}$ 2.0 Hz, H-3) 5.73, 5.78 (2 x 1H, 2 x s, 2 x C<u>H</u>Ph) 7.34-7.54 (10H, m, 2 x ArH); δ_C (50.3 MHz; $(CD_3)_2SO$): 68.9 (t, C-7) 70.4, 71.9, 74.3, 76.1, 76.9 (5 x d, C-2, C-3, C-4, C-5, C-6) 99.1 (d, 3,5 <u>C</u>HPh) 105.0 (d, 6,7 <u>C</u>HPh)127.9, 128.5, 129.6, 129.8, 130.5, 131.1 (6 x d, Ar<u>C</u>H) 138.5, 139.0 (2 x s, 2 x Ar<u>C</u>) 177.4 (s, <u>C</u>=O); *m/z* (NH_3, CI): 385 ($M+H^+$, 100%), 402 ($M+NH_4^+$, 10%). (Found: C, 65.82; H, 5.45; $C_{21}H_{20}O_7$ requires: C, 65.62; H, 5.24%).

Also *3,5(R):6,7(S)-Di*-O-*benzylidene*-*D*-glycero-*D*-gulo-*heptono-1,4-lactone* (5) (0.32 g, 24%) as a colourless solid (R_f 0.3), m.p.190-191°C; $[\alpha]_D^{20}$ -19.2 (*c* 1.0 in $CHCl_3$); υ_{max} (KBr): 1789 (C=O) 3308 (OH) cm^{-1}; δ_H (500 MHz; $CDCl_3$): 2.83 (1H, d, J 10.0Hz, O<u>H</u>) 4.14 (1H, dd, J 5.5, J 8.8 Hz) 4.20 (1H, dd, J 1.3, J 7.5 Hz) 4.29 (1H, dd, J 6.2, J 9.0 Hz) 4.62 (3H, m) 4.80 (1H, dd, J 2.1, J 4.1 Hz) 5.70, 6.03 (2 x 1H, 2 x s, 2 x C<u>H</u>Ph) 7.42 (10H, m, 2 x ArH); δ_C (50.3 MHz; $(CD_3)_2SO$): 68.9 (t, C-7) 70.5, 71.9, 74.4, 76.1, 76.4 (5 x d, C-2, C-3, C-4, C-5, C-6) 99.4, 104.6 (2 x d, 2 x <u>C</u>HPh) 127.8, 128.1, 129.6,

129.8, 130.5, 130.8 (6 x d, ArCH) 139.0, 139.2 (2 x s, 2 x ArC) 177.0 (s, C=O); *m/z* (NH_3, DCI): 385 ($M+H^+$, 100%) 402 ($M+NH_4^+$, 20%).(Found: C, 65.55; H, 5.22; $C_{21}H_{20}O_7$ requires C, 65.62; H, 5.24 %).

*3,5(R)-O-Benzylidene-6,7-O-isopropylidene-D-*glycero-*D-*gulo-*heptono-1,4-lactone (6).* 3,5(R)-*O*-Benzylidene-D-glycero-D-gulo-heptono-1,4-lactone (3) (1.05 g, 3.38 mmol) was suspended in AR acetone and dimethoxypropane (3.0 ml, 24.4 mmol) and *p*-toluenesulphonic acid monohydrate (16 mg, 0.08 mmol) were added. The mixture was stirred at room temperature for 10 min after which t.l.c. (ethyl acetate) showed no starting material (R_f 0.1) and one product (R_f 0.6). Sodium hydrogen carbonate (100 mg) was added and the mixture was filtered, concentrated *in vacuo* and purified by column chromatography (ethyl acetate/hexane 1:1) to afford *3,5(R)-O-benzylidene-6,7-O-isopropylidene-D-*glycero-*D-*gulo-*heptono-1,4-lactone* (6) (1.19g, >99%) as a colourless solid, m.p. 189-195°C (chloroform); $[\alpha]_D^{20}$ -36.9 (*c* 0.99 in $CHCl_3$); υ_{max} (KBr): 1790 (C=O) 3450 (br OH) cm^{-1}; δ_H (500 MHz; $CDCl_3$): 1.47, 1.39 (2 x 3H, 2 x s, 2 x CH_3) 3.95 (1H, dd, $J_{4,5}$ 1.8, $J_{5,6}$ 8.7 Hz, H-5) 4.08 (1H, dd, $J_{6,7'}$ 4.1, $J_{7,7'}$ 9.0 Hz, H-7') 4.15 (1H, dd, $J_{6,7}$ 5.9 Hz, H-7) 4.45 (1H, ddd, H-6) 4.50 (1H, t, $J_{3,4}$ 2.0 Hz, H-4) 4.59 (1H, d, $J_{2,3}$ 4.0 Hz, H-2) 4.76 (1H, dd, H-3) 5.65 (1H, s, CHPh) 7.42 (5H, m, ArH); δ_C (50.3 MHz; $CDCl_3$): 24.8, 26.8 (2 x q, $C(CH_3)_2$) 66.6 (t, C-7) 69.3, 71.4, 72.8, 74.0, 76.3 (5 x d, C-2, C-3, C-4, C-5, C-6) 99.2 (d, CHPh) 109.8 (s, CMe_2) 126.4, 128.5, 129.7 (3 x d, ArCH) 136.7 (s, ArC) 175.2 (s, C=O); *m/z* (NH_3, CI): 337 ($M+H^+$, 100%) 354 ($M+NH_4^+$, 20%). (Found: C, 60.85; H, 6.17; $C_{17}H_{20}O_7$ requires C, 60.71; H, 5.99 %).

*3,5(R)-O-Benzylidene-6,7-O-isopropylidene-2-O-trifluoromethanesulphonyl-D-*glycero-*D-*gulo-*heptono-1,4-lactone (7).* Trifluoromethane sulphonic anhydride (0.60 ml, 3.63 mmol) was added to a solution of 3,5(R)-*O*-benzylidene-6,7-*O*-isopropylidene-D-*glycero*-D-*gulo*-heptono-1,4-lactone (6) (0.94 g, 2.79 mmol) in dry dichloromethane (8 ml) and dry pyridine (0.50 ml, 6.19 mmol) at -30°C. After 15 min at this temperature, t.l.c. (ethyl acetate/hexane 1:2) showed an absence of starting material (R_f 0.1) and one major product (R_f 0.3). Further dichloromethane (10 ml) was added and the mixture was washed with water (10 ml), 2M HCl (10 ml) and brine (10 ml). The organic layer was dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification was achieved by flash column chromatography (ethyl acetate/hexane 1:2) to give *3,5(R)-O-benzylidene-6,7-O-isopropylidene-2-O-trifluoromethanesulphonyl-D-*glycero-*D-*gulo-*heptono-1,4-lactone (7)* (0.93 g, 71%) as a white crystalline solid, m.p. 120-122°C; $[\alpha]_D^{20}$ -83.6 (*c*, 1.04 in $CHCl_3$); υ_{max} (KBr): 1806 (C=O) cm^{-1}; δ_H (300 MHz; $(CD_3)_2CO$): 1.33, 1.40 (2 x 3H, 2 x s, 2 x CH_3) 4.08 (1H, dd, $J_{6,7}$ 3.8, $J_{7,7'}$ 8.8 Hzx, H0-7) 4.15 (1H, dd, $J_{6,7'}$ 5.6 Hz, H-7') 4.27 (1H, dd, J 1.7, J 8.8 Hz) 4.31-4.37 (1H, m) 4.90 (1H, t, J 1.8 Hz) 5.40 (1H, dd, $J_{3,4}$ 2.0 Hz, H-3) 5.95 (1H, s, CHPh) 6.26 (1H, d, $J_{2,3}$ 4.1 Hz, H-2) 7.35-7.42 (3H, m, ArCH) 7.46-7.49 (2H, m, ArCH); δ_C (50.3 MHz; $(CD_3)_2CO$): 25.4, 27.2 (2 x q, 2 x $C(CH_3)_2$ 67.3 (t, C-7) 71.0, 73.7, 74.1, 76.8, 81.1 (5 x d, C-2, C-3, C-4, C-5, C-6) 99.5 (d, CHPh) 110.4 (s, CMe_2) 116.3, 122.7 (CF_3) 127.2, 129.2, 130.3 (3 x d, ArCH) 138.0 (s, ArC) 168.9 (s, C=O); *m/z* (NH_3, CI): 469 ($M+H^+$, 25%), 58 (100%).

*3,5-O-Benzylidene-6,7-O-isopropylidene-D-*glycero-*D-*ido-*heptono-1,4-lactone (8).* 3,5-*O*-Benzylidene-6,7-*O*-isopropylidene-2-O-trifluoromethanesulphonyl-D-*glycero*-D-*ido*-heptono-1,4-lactone (7) (0.59 g, 1.26 mmol) and sodium trifluoroacetate (0.52 g, 3.79 mmol) were stirred in dry dimethylformamide (12 ml) at 60°C for 72 h when t.l.c. (ethyl acetate/hexane 1:1) showed no starting material (R_f 0.4) and one major product (R_f 0.5). Excess dry methanol (0.6 ml) was added and the reaction mixture stirred at room

temperature for a further 24 h. The solvent was removed under reduced pressure and the residue dissolved in ethyl acetate (20 ml) and washed with water (2 x 20 ml). The organic layer was dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The resulting residue was purified by flash column chromatography (ethyl acetate/hexane 1:2) to yield *3,5-O-benzylidene-6,7-O-isopropylidene-D*-glycero-*D*-ido-*heptono-1,4-lactone* (8) (0.25 g, 58%) as a colourless oil, $[\alpha]_D^{20}$ -73.8 (*c*, 0.52 in $CHCl_3$); υ_{max} (thin film): 1787 (C=O) 3408 (br OH) cm^{-1}; δ_H (500 MHz; $CDCl_3$): 1.40, 1.48 (2 x 3H, 2 x s, 2 x CH_3) 3.98 (1H, dd, $J_{4,5}$ 1.9, $J_{5,6}$ 8.4 Hz, H-5) 4.10 (1H, dd, $J_{7,7'}$ 9.0, $J_{6,7}$ 4.1 Hz, H-7) 4.14 (1H, dd, $J_{6,7'}$ 6.0 Hz, H-7') 4.32 (1H, s, H-4) 4.45 (1H, ddd, H-6) 4.59 (1H, d, $J_{2,3}$ 2.3 Hz, H-2) 4.81 (1H, t, H-3) 5.60 (1H, s, CHPh) 7.37-7.42 (5H, m, ArH); δ_C (50.3 MHz; $CDCl_3$): 24.9, 26.8 (2 x q, 2 x CCH_3) 66.6 (t, C-7) 72.9, 73.2, 73.6, 76.3, 77.2 (5 x d, C-2, C-3, C-4, C-5, C-6) 99.2 (d, CHPh) 110.0 (s, CMe_2) 126.3, 128.5, 129.6 (3 x d, ArCH) 136.8 (s, ArC) 175.6 (s, C=O); *m/z* (NH_3, CI): 337 ($M+H^+$, 100%), 354 ($M+NH_4^+$, 50%).

3,5-O-Benzylidene-D-glycero-*D*-ido-*heptono-1,4-lactone (9).* 3,5-*O*-Benzylidene-6,7-*O*-isopropylidene-**D**-*glycero*-**D**-*ido*-heptono-1,4-lactone (8) (0.165 g, 0.49 mmol) was stirred at room temperature in 80% aqueous acetic acid (3 ml). After 22 h t.l.c. (ethyl acetate) showed a trace of starting material (R_f 0.7) and a single product (R_f 0.3). The solvents were evaporated under reduced pressure and co-evaporated with toluene (3 x 3 ml). The residue was purified by flash column chromatography (ethyl acetate) to afford *3,5-O-benzylidene-D*-glycero-*D*-ido-*heptono-1,4-lactone* (9) (0.115 g, 79%) as a white crystalline solid, m.p. 155-157°C (ethyl acetate/hexane); $[\alpha]_D^{20}$ -67.1 (*c*, 1.01 in CH_3CN); υ_{max} (KBr): 1793 (C=O) 3386 (br OH) cm^{-1}; δ_H (500 MHz; CD_3CN): 3.59 (1H, dd, $J_{6,7}$ 4.9, $J_{7,7'}$ 11.8 Hz, H-7) 3.69 (1H, dd, $J_{6,7'}$ 2.7 Hz, H-7') 3.80 (1H, ddd, $J_{5,6}$ 9.3 Hz, H-6) 4.10 (1H, d, $J_{2,3}$ 0.6 Hz, H-2) 4.12 (1H, dd, $J_{4,5}$ 2.0 Hz, H-5) 4.60 (1H, dd, $J_{3,4}$ 2.0 Hz, H-3) 4.82 (1H, t, H-4) 5.68 (1H, s, CHPh) 7.36-7.43 (5H, m, ArH); δ_C (50.3 MHz; CD_3CN): 62.3 (t, C-7) 69.5, 72.7, 73.2, 75.0, 77.5 (5 x d, C-2, C-3, C-4, C-5, C-6) 98.7 (d, CHPh) 126.2, 128.5, 129.3 (3 x d, ArCH) 137.8 (s, ArC) 175.2 (s, C=O); *m/z* (NH_3, CI): 297 ($M+H^+$, 95%), 314 ($M+NH_4^+$, 100%). (Found: C, 56.38; H, 5.43. $C_{14}H_{16}O_7$ requires: C, 56.76; H, 5.44%).

5,7-O-Benzylidene-D-glycero-*D*-gulo-*heptono-1,4-lactone (11) and 5,7-O-benzylidene-D*-glycero-*D*-ido-*heptono-1,4-lactone (12).* Sodium cyanide (0.2 g, 4.11 mmol) was added to a stirring solution of 4,6-*O*-benzylidene-α-**D**-glucopyranose (10) (1.00 g, 3.74 mmol) and sodium bicarbonate (0.32 g, 3.74 mmol) in water (20 ml) and 1,4-dioxan (4 ml) at room temperature. After 24 h, the solution was bubbled through with nitrogen and heated at 70°C for 10 h when all evolution of ammonia had ceased and no cyanide was present. The solution was allowed to cool and then acidified to pH 5 with dilute sulphuric acid (2M). The solvents were removed *in vacuo* and co-evaporated with toluene (3 x 10 ml). The residue was dissolved in glacial acetic acid (20 ml) and stirred at 50°C for 16 h when t.l.c. (ethyl acetate/methanol 4:1) showed two products (R_f 0.45 and 0.5). The solvents were removed *in vacuo* and co-evaporated with toluene (3 x 10 ml). The residue was dissolved in water (20 ml) and extracted with ethyl acetate (4 x 40 ml). The organic layer was dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography (ethyl acetate/hexane 4:1) to yield *5,7-O-benzylidene-D*-glycero-*D*-ido-*heptono-1,4-lactone* (12) (0.39 g, 35%) as a white crystalline solid, m.p. 53-56°C (ethyl acetate/hexane); $[\alpha]_D^{20}$ -64.7 (*c*, 0.99 in CH_3CN); υ_{max} (KBr): 1776 (C=O), 3430 (br OH) cm^{-1}; δ_H (500 MHz; CD_3CN): 3.62 (1H, t, J 10.5 Hz) 3.79 (1H, dt, J 5.3, J 10.0 Hz) 3.96 (1H, dd, J 1.0, J 9.7 Hz) 4.24 (1H, dd, J 5.3, J 10.7 Hz) 4.36 (1H, dd, J 8.7 Hz) 4.49 (1H, t, J 8.3 Hz) 4.81 (1H, dd, J 1.2, J 8.0 Hz) 5.60 (1H, s, CHPh) 7.36-7.45 (5H, m,

ArH); δ_C (50.3 MHz; CD_3CN): 60.0, 72.1, 73.6, 75.1, 77.6 (5 x d, C-2, C-3, C-4, C-5, C-6) 71.0 (t, C-7) 100.5 (d, CHPh) 126.1, 128.5, 129.2 (3 x d, ArCH) 138.2 (s, ArC) 175.3 (s, C=O); *m/z* (NH_3, CI): 297 ($M+H^+$, 100%) 314 ($M+NH_4^+$, 75%). (Found: C, 56.53; H, 5.68. $C_{14}H_{16}O_7$ requires: C, 56.76; H, 5.44%).

Further elution of the column gave 5,7-O-*benzylidene-D*-glycero-*D*-gulo-*heptono-1,4-lactone* (11) (122 mg, 11%) as a white crystalline solid, m.p. 181-184°C (ethyl acetate/hexane); $[\alpha]_D^{20}$ -90.6 (*c*, 1.01 in CH_3CN); υ_{max} (KBr): 1761 (C=O), 3432 (br OH) cm^{-1}; δ_H (500 MHz; CD_3CN): 3.64 (1H, m, H-7) 3.82 (1H, dt, $J_{5,6}$ 9.6, $J_{6,7'}$ 5.4 Hz, H-6) 4.06 (1H, dd, $J_{4,5}$ 7.5 Hz, H-5) 4.26 (1H, dd, $J_{7,7'}$ 10.8 Hz, H-7') 4.45 (1H, dd, $J_{3,4}$ 2.8 Hz, H-4) 4.46 (1H, d, $J_{2,3}$ 4.9 Hz, H-2) 4.54 (1H, dd, H-3) 5.59 (1H, s, CHPh) 7.38-7.42 (3H, m, ArH) 7.42-7.47 (2H, m, ArH); δ_C (50.3 MHz; CD_3CN): 61.7, 69.9, 70.3, 79.3, 80.6 (5 x d, C-2, C-3, C-4, C-5, C-6) 70.5 (t, C-7) 100.6 (d, CHPh) 126.4, 128.5, 129.3 (3 x d, ArCH) 138.0 (s, ArC); *m/z* (NH_3, CI): 297 ($M+H^+$, 100%) 314 ($M+NH_4^+$, 75%). (Found: C, 56.63; H, 5.24. $C_{14}H_{16}O_7$ requires: C, 56.76; H, 5.44%).

5,7-O-Benzylidene-2,3,6-O-triacetyl-D-glycero-*D*-gulo-*heptono-1,4-lactone (13).* 5,7-*O*-Benzylidene-**D**-*glycero*-**D**-*gulo*-heptono-1,4-lactone (11) (33 mg, 0.11 mmol) was dissolved in dry pyridine (2 ml) and acetic anhydride (140 µl, 1.65 mmol) was added. After stirring at room temperature for 24 h, t.l.c. (ethyl acetate/methanol 4:1) showed no starting material (R_f 0.45) and a single product (R_f 0.8). The solvent was removed *in vacuo* and the residue dissolved in ethyl acetate (5 ml) and washed successively with aqueous hydrochloric acid (2M, 5 ml), water (5 ml) and brine (5 ml). The organic layer was dried ($MgSO_4$), filtered and the solvent was removed *in vacuo* to yield *5,7-O-benzylidene-2,3,6-O-triacetyl-D*-glycero-*D*-gulo-*heptono-1,4-lactone* (13) (43 mg, quant.), m.p. 48-51°C; $[\alpha]_D^{20}$ -100.3 (*c*, 0.89 in $CHCl_3$); υ_{max} (KBr): 1752, 1807 (C=O) cm^{-1}; δ_H (500 MHz; $CDCl_3$): 1.96, 2.04, 2.13 (3 x 3H, 3 x s, 3 x CH_3) 3.62 (1H, t, $J_{7,7'}$ 10.3 Hz, H-7) 4.34 (1H, dd, $J_{4,5}$ 6.1, $J_{5,6}$ 9.8 Hz, H-5) 4.46 (1H, dd, $J_{6,7'}$ 5.3 Hz, H-7') 4.65 (1H, dd, $J_{3,4}$ 1.6 Hz, H-4) 5.02 (1H, dt, H-6) 5.51 (1H, s, CHPh) 5.65 (2H, s, H-2, H-3) 7.35-7.39 (3H, m, ArH) 7.47-7.50 (2H, m, ArH); δ_C (50.3 MHz; $CDCl_3$): 19.9, 20.2, 20.5 (3 x q, 3 x $COCH_3$) 67.5 (t, C-7) 64.1, 68.3, 70.2, 75.5, 76.9 (5 x d, C-2, C-3, C-4, C-5, C-6) 101.4 (d, CHPh) 126.4, 128.5, 129.6 (3 x d, ArCH) 136.7 (s, ArC) 169.2, 169.3, 169.6, 169.9 (4 x s, 4 x C=O); *m/z* (NH_3, CI): 380 ($M+H^+-CH_3CO$, 30%) 440 ($M+NH_4^+$, 5%).

5,7-O-Benzylidene-2,3,6-O-triacetyl-D-glycero-*D*-ido-*heptono-1,4-lactone (14).* 5,7-*O*-Benzylidene-**D**-*glycero*-**D**-*ido*-heptono-1,4-lactone (12) (36 mg, 0.12 mmol) was dissolved in dry pyridine (2 ml) and acetic anhydride (150 µl, 1.83 mmol) was added. After stirring at room temperature for 24 h, t.l.c. (ethyl acetate/methanol 4:1) showed no starting material (R_f 0.5) and a single product (R_f 0.9). The solvent was removed *in vacuo* and the residue dissolved in ethyl acetate (5 ml) and washed successively with aqueous hydrochloric acid (2M, 5 ml), water (5 ml) and brine (5 ml). The organic layer was dried ($MgSO_4$), filtered and the solvent was removed *in vacuo* to yield *5,7-O-benzylidene-2,3,6-O-triacetyl-D*-glycero-*D*-ido-*heptono-1,4-lactone* (14) (50 mg, quant.) as a white crystalline solid, m.p. 135-137°C (ethyl acetate/hexane); $[\alpha]_D^{20}$ -128.6 (*c*, 1.02 in $CHCl_3$); υ_{max} (KBr): 1788 (C=O) 1761, 1751, 1741 (3 x ester C=O) cm^{-1}; δ_H (500 MHz; $CDCl_3$): 2.09, 2.12, 2.17 (3 x 3H, 3 x s, 3 x CH_3) 3.64 (1H, t, $J_{7,7'}$ 10.4 Hz, H-7) 3.95 (1H, dd, $J_{4,5}$ 2.5, $J_{5,6}$ 9.8 Hz, H-5) 4.53 (1H, dd, $J_{6,7'}$ 5.4 Hz, H-7') 4.91 (1H, m, H-4) 5.10 (1H, dt, H-6) 5.59 (1H, s, CHPh) 5.71 (1H, d, $J_{2,3}$ 8.7 Hz, H-2) 5.75 (1H, m, H-3) 7.27-7.44 (5H, m, ArH); δ_C (50.3 MHz; $CDCl_3$):

20.3, 20.5, 20.6 (3 x q, 3 x $CO\underline{C}H_3$) 67.9 (t, C-7) 61.9, 70.6, 72.2, 73.0, 75.3 (5 x d, C-2, C-3, C-4, C-5, C-6) 101.4 (d, $\underline{C}HPh$) 126.1, 128.7, 129.6 (3 x d, $Ar\underline{C}H$) 136.6 (s, $Ar\underline{C}$) 169.0, 169.6, 169.9, 170.4 (4 x s, C=O); *m/z* (NH_3, CI): 317 ($M+H-PhCHO^+$, 80%) 440 ($M+NH_4^+$, 100%). (Found: C, 56.66; H, 4.97. $C_{20}H_{22}O_{10}$ requires: C, 56.87; H, 5.25%).

D-glycero-*D*-gulo-*Heptono-1,4-lactone (1). (i) By hydrolysis of* 3,5-*O*-benzylidene-**D**-*glycero*-**D**-*gulo*-heptono-1,4-lactone (3). The protected lactone (3) (49 mg, 0.16 mmol) was stirred at room temperature in 50% aqueous trifluoroacetic acid (4 ml). After 24 h t.l.c. (ethyl acetate) showed no starting material (R_f 0.3) and a single product (R_f 0.05). The solvents were removed under reduced pressure to afford the title compound (1) (31 mg, 91%) as a white crystalline solid, m.p.147-149°C [lit.[24] 151°C]; $[\alpha]_D^{20}$ -45.9 (*c*, 0.37 in H_2O)[lit.[24] $[\alpha]_D^{20}$ -44.7(*c*, 10 in H_2O, NH_4OH)]; δ_H (500 MHz; D_2O): 3.59 (1H, dd, $J_{6,7}$ 6.3, $J_{7,7'}$ 11.8 Hz, H-7) 3.69 (1H, dd, $J_{6,7'}$ 3.7 Hz, H-7') 3.73 (1H, dd, $J_{5,6}$ 6.3 Hz, H-6) 3.99 (1H, t, $J_{5,6}=J_{4,5}$ 6.3 Hz, H-5) 4.52 (1H, dd, $J_{3,4}$ 3.0, $J_{2,3}$ 4.8 Hz, H-3) 4.55 (1H, dd, $J_{4,5}$ 6.3 Hz, H-4) 4.65 (1H, d, H-2). These are identical spectroscopic properties to those of the authentic material.
(ii) By hydrolysis of 5,7-*O*-Benzylidene-**D**-*glycero*-**D**-*gulo*-heptono-1,4-lactone (11). The lactone (11) (53 mg, 0.18 mmol) was stirred at room temperature in 80% aqueous acetic acid (3 ml). After 24 h t.l.c. (ethyl acetate) showed no starting material (R_f 0.35) and a single product (R_f 0.05). The solvents were removed under reduced pressure to afford the title compound (1) (35 mg, 95%) identical in all respects to the compound prepared previously.

D-glycero-*D*-ido-*Heptono-1,4-lactone (2). (i) By hydrolysis of* 3,5-*O*-Benzylidene-**D**-*glycero*-**D**-*ido*-heptono-1,4-lactone (9). The protected lactone (9) (71 mg, 0.24 mmol) was stirred at room temperature in 50% aqueous trifluoroacetic acid (4 ml). After 24 h t.l.c. (ethyl acetate) showed no starting material (R_f 0.4) and a single product (R_f 0.05). The solvents were removed under reduced pressure to afford the title compound (39 mg, 80%) as a white crystalline solid, m.p. 148-150°C[lit.[24] 152°C]; $[\alpha]_D^{20}$ -68.8 (*c*, 0.65 in H_2O)[lit.[24] $[\alpha]_D^{20}$ -74.9 (*c*, 0.2 in H_2O)]; δ_H (500 MHz; CD_3OD): 3.59-3.66 (2H, m) 3.77-3.80 (1H, m), 3.95 (1H, dd, J 1.0, J 9.2 Hz) 4.44 (1H, t, J 8.1 Hz) 4.58 (1H, d, J 8.3 Hz) 4.82 (1H, dd, J 1.2, J 7.9 Hz).
(ii) By hydrolysis of 5,7-*O*-Benzylidene-**D**-*glycero*-**D**-*ido*-heptono-1,4-lactone (12). The lactone (12) (64 mg, 0.216 mmol) was stirred at room temperature in 80% aqueous acetic acid (3 ml). After 24 h t.l.c. (ethyl acetate) showed no starting material (R_f 0.5) and a single product (R_f 0.05). The solvents were removed under reduced pressure to afford the title compound (2) (35 mg, 78%) identical in all respects to the compound prepared above.

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