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The First Example of a 6-*C*-Aryl-D-glucose: Inhibition of Glucokinase

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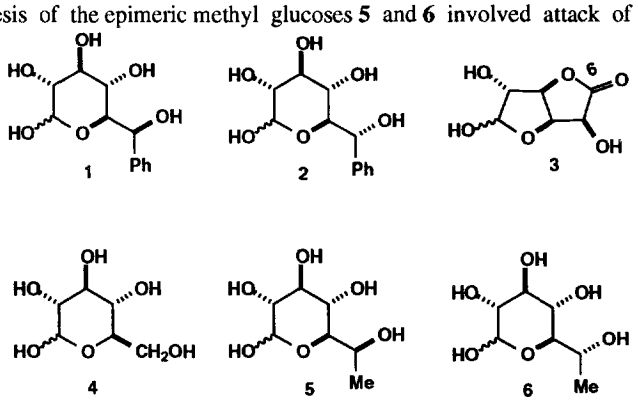
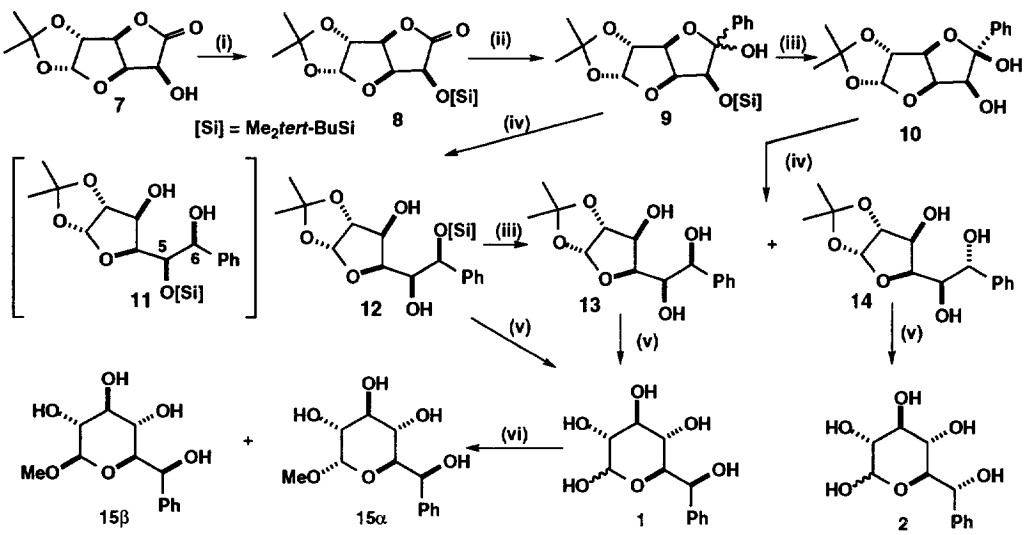
The synthesis of the epimeric 6-*C*-phenylglucoses is reported; these are the first compounds with one of the prochiral methylene hydrogens on C-6 of a hexose being replaced by an aryl group. Both isomers inhibit glucokinase and provide further indications that 6-*C*-alkyl- and 6-*C*-aryl-carbohydrates may provide a new range of sugar mimics that control enzymes associated with formation, hydrolysis and other fates of sugar-6-phosphates. X-ray crystal structures of 6-*C*-phenyl-L-*glycero*-β-D-*gluco*-hexopyranose and (*2R,3S,4R,6R,7R,8S*)2,3,6,7-tetrahydroxy-6,7-O-isopropylidene-1,5-oxa-2-phenyl-bicyclo-[3.3.0]octane are reported.

This paper reports short syntheses of the epimeric 6-*C*-phenylglucoses **1** and **2** from glucuronolactone **3**; these compounds provide the first examples of the synthesis of unprotected sugar analogues with an aryl group at the prochiral methylene of a hexopyranose. Analogues of carbohydrates are powerful materials for the investigation of metabolic pathways which involve enzymes that process sugars; structures which retain the functionality and stereochemistry at all the stereogenic centres of a specific carbohydrate, such as the aza sugars,[1] have proved particularly useful and have been extensively investigated. In contrast, modification of the methylene moiety in the side chain primary hydroxymethyl group by substitution of one of the prochiral hydrogens by a carbon provides a set of analogues almost unknown synthetically and completely neglected from the point of view of any biological activity. Direct access to such materials by a Kiliani-Fischer ascension[2] of naturally occurring sugars is confined to those derived from the naturally occurring L-rhamnose[3,4] and fucose.[5] Substitution of one of the prochiral hydrogens in glucose **4** by a methyl group gives the two diastereomers **5** and **6**. The D-sugar **6**, isolated from *Streptomyces*[6] inhibits the greening of dark-grown *Scenedesmus obliquus*, probably by inhibition of carbon dioxide fixation;[7] there are otherwise no reports of unprotected hexoses with any other alkyl or aryl substituent at the methylene group of the primary hydroxymethyl group. The original synthesis of the epimeric methyl glucoses **5** and **6** involved attack of methyl lithium on an aldehyde derived from C-6 of glucose[8] but a shorter and more efficient synthesis from glucuronolactone **3** has recently been reported.[9] The epimers **5** and **6** were studied as potential inhibitors of glycogen phosphorylase (GP) as part of a long term project for the possible treatment of late-onset diabetes;[10] although neither had any inhibitory effect on GP, it was found that whereas **5** caused partial inactivation



of glycogen synthase that had been activated by prior incubation of hepatocytes with 50mM glucose and also decreased the intracellular concentration of glucose-6-phosphate (Glc-6-P), the D-sugar **6** in complete contrast induced further activation of glycogen synthase and caused Glc-6-P levels to rise. Further studies showed that **5** inhibits both glucose-6-phosphatase (Glc-6-Pase) and glucokinase, whereas **6** inhibits only the phosphatase causing intracellular Glc-6-P levels to rise. The specific inhibition of Glc-6-Pase by **6** provides Glc-6-P which may enhance the catalytic activity of the synthase and may provide a new strategy for the treatment of late-onset diabetes.[9] In order to investigate the structural features that are necessary for inhibition of glucokinase and Glc-6-Pase, the scope of the synthetic procedure for the production of epimeric 6-*C*-alkyl and aryl substituted glucoses from glucuronolactone is being investigated. This paper demonstrates that a phenyl substituent can be introduced to give 6-*C*-phenylglucoses **1** and **2** by short efficient synthesis and describes some studies on the abilities of the compounds to inhibit enzymes associated with concentrations of glucose-6-phosphate.



Scheme 1 (i) Me_2*tert*-BuSiCl, DMF, imidazole (ii) PhLi, THF, -78°C (iii) Bu_4NF, THF (iv) $NaBH_4$, EtOH (v) H_3O^+ dioxan (vi) MeOH, HCl

For the synthesis of **1** and **2**, the readily available acetonide of glucuronolactone **7**[11] [Scheme 1] was treated with *tert*-butyldimethylsilyl chloride in dimethylformamide in the presence of imidazole to give the silyl ether **8** [92% yield]. Reaction of the fully protected lactone **8** with phenyl lithium in tetrahydrofuran at -78°C gave a phenyl lactol **9** [43% yield after crystallisation]; the configuration at the anomeric centre of **9** was not determined. Reduction of **9** with sodium borohydride in ethanol caused a stereoselective Felkin-Ahn reduction to give a single isolated silyl ether **12** in 76% yield, with no other silyl ethers isolated. The ^1H NMR indicated that the expected product **11** had not been formed; D_2O exchange of the OH protons simplified the signal for the proton at C-5 [rather than C-6] from a multiplet to a double doublet, indicating that the silyl protecting group had migrated during the reduction from C-5 oxygen to C-6 to give **12**; a similar silyl ether migration had been observed in the synthesis of the methyl analogue **5**.[9] All the protecting groups were removed from **12** by treatment with ion exchange resin (Amberlite IR-120, H^+) in aqueous dioxan to give the L-sugar **1** in 92% yield. Crystallisation from ethanol-water of the free sugar **1** gave a pure sample of the β anomer **1β**, the structure of which was firmly established by single crystal X-ray crystallographic analysis [Figure 1].

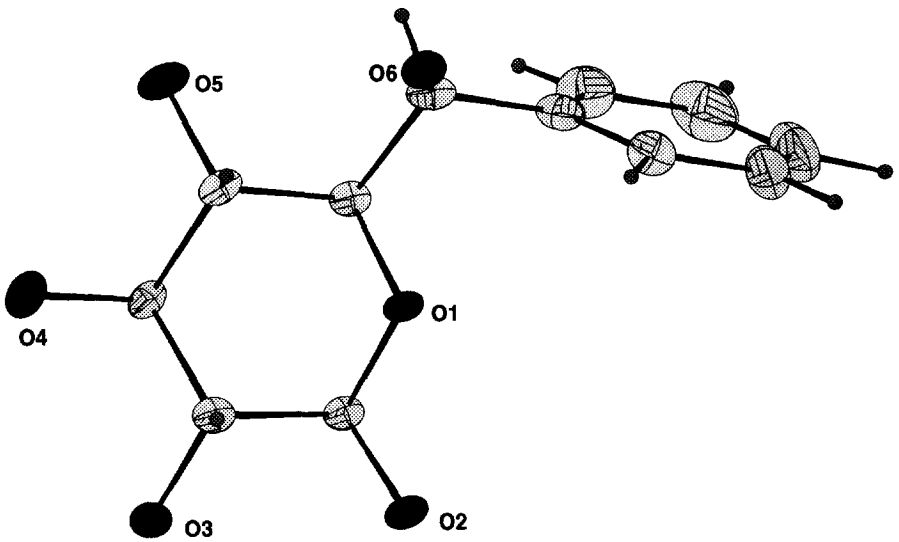
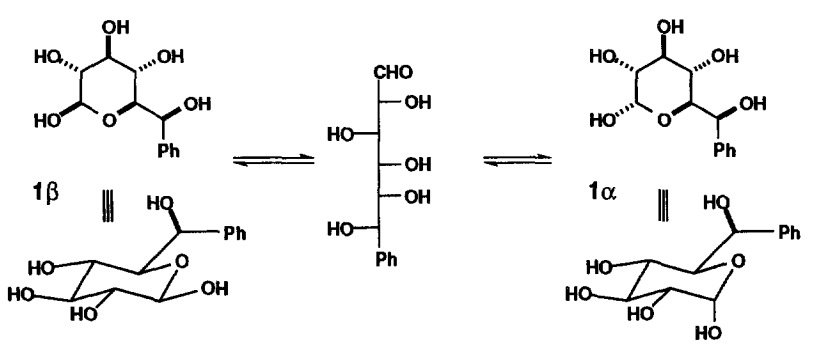


Figure 1 X-Ray structure of 6-*C*-phenyl-L-*glycero*- β-D-*gluco*-hexopyranose **1β** showing crystallographic numbering scheme.

The mutarotation of **1β** in water was studied and the specific rotations $[\alpha]_D^{21}$ [all at *c*, 1.0 in H_2O] were for **1β** +55.8, for **1α** +85.1 [by calculation], and for an equilibrium mixture +69.3; at equilibrium the ratio of **1α**: **1β** was 46:54 by ^1H NMR. The mutarotation clearly showed first order kinetics with a linear plot which implies that the mutarotation is simple and only involves the α and β pyranose forms; a non-linear plot would have suggested that other species such as furanose forms were also involved.[12] Treatment of **1** with methanol in the presence of hydrogen chloride gave a mixture of the methyl pyranosides **15α** and **15β** in a ratio of approximately 2:1.



Scheme 2: Mutarotation of 6-*C*-phenyl-L-*glycero*-D-*gluco*-hexopyranose **1**

Removal of the silyl protecting group from **9** by treatment with tetrabutylammonium fluoride in tetrahydrofuran gave the lactol **10**, in 77% yield which crystallised as a single anomer; the structure of **10** was established by single crystal X-ray crystallographic analysis [Figure 2]. The lactol **10** could also be formed directly by reaction of phenyl lithium with the acetonide **7** [in which the α-hydroxyl group to the carbonyl was unprotected] in 23% yield. Reduction of the lactol **10** with sodium borohydride in ethanol gave a mixture of the diastereomeric alcohols **13** and **14** in a ratio 1:1.2 and an overall yield of 70%; **13** and **14** may readily be separated by flash chromatography. Reaction of **12** with tetrabutylammonium fluoride in tetrahydrofuran removed the silyl ether protecting group to afford the triol **13** identical to material prepared in the direct reduction of **10**. Deprotection of **13** and **14** by treatment with acidic ion exchange resin gave the epimeric 6-*C*-phenylglucoses **1** and **2** in yields of 94% and 96% respectively.

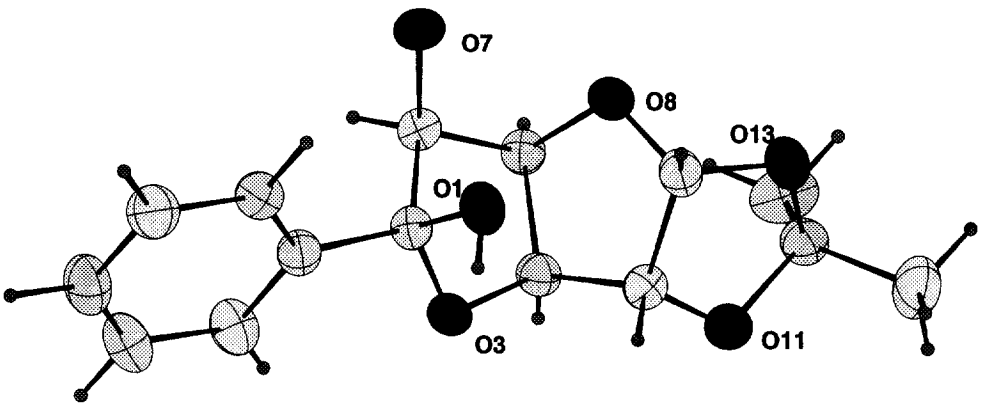
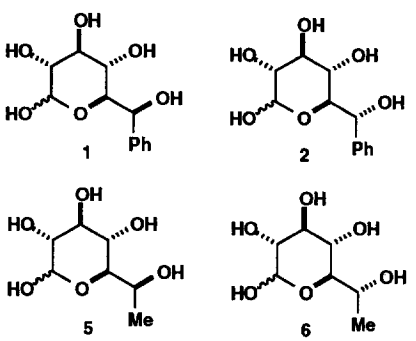


Figure 2 X-Ray structure of *(2R,3S,4R,6R,7R,8S)*-2,3,6,7-tetrahydroxy-6,7-O-isopropylidene-1,5-oxa-2-phenyl-bicyclo[3.3.0]octane **10** showing crystallographic numbering scheme.



Effects of **1** and **2** on the activity of glucokinase and Glc-6-Pase have been examined.[13] Both L-phenyl **1** and D-phenyl **2** analogues inhibit glucokinase; the order of inhibition of glucokinase is L-phenyl **1** > D-phenyl **2** ≅ L-methyl **5** >>> D-methyl **6**. The D-methyl sugar **6** did not inhibit glucokinase at concentrations up to 10 mM.[9] The inhibition is at least partly competitive with glucose since 1 mM L-phenyl glucose **1** (and 10 mM D-phenyl glucose **2**) inhibited glucokinase completely at 2 mM glucose, but only by one third at 50 mM glucose.

Both **1** and **2** inhibit Glc-6-Pase, as do the corresponding methyl compounds **5** and **6**.[9] Preliminary studies have been conducted with 10 mM D-6-*C*-phenyl glucose **2** on isolated rat liver parenchymal cells. The compound did not affect the activation state of glycogen phosphorylase, but it decreased the intracellular concentration of Glc-6-P and lowered the activation state of glycogen synthase.

These investigations make it clear that exploration of changes of the prochiral methylene hydrogen of C-6 of hexoses is likely to provide a novel set of carbohydrate mimics. The fact that the active site of some of the enzymes can accommodate a phenyl group at C-6 - and even be a more potent enzyme inhibitor than the corresponding methyl analogue - means that substantial variations might be made which allow the development of specific and potent inhibitors of enzymes that are responsible for the synthesis, hydrolysis, mutation and isomerisation of sugar phosphates, not only for glucose but also for mannose and galactose. The synthesis of the phenyl compounds **1** and **2** parallels closely the chemistry of the preparation of the diastereomeric methylglucoses **5** and **6**[9] so that protected uronic acids should react with a range of alkyl and aryl lithiums to provide a general route to epimeric C-6-substituted hexoses with either alkyl or aryl substituents. Full accounts of the enzymic studies on these compounds will appear in due course.[14]

X-Ray Crystal Structure Analysis. The relative configurations of the stereogenic centres in 6-*C*-phenylglucose **1**β and in the phenyl lactol **10** were established by X-ray single crystal structure analysis. For both compounds, cell dimensions and intensity data were measured with an Enraf-Nonius Mach3 Diffractometer, and Lorentz, polarisation and psi scan absorption corrections were applied. All calculations were carried out on a 486PC computer. All non-hydrogen atoms were located by SIR92[15] and refined using CRYSTALS.[16] Illustrations were produced using CAMERON.[17] Hydrogen atoms were seen in the difference density map but placed geometrically. Non-hydrogen atoms were refined anisotropically using atomic scattering factors from International Tables.[18] Structural data for both **1**β and **10** have been deposited at the Cambridge Crystallographic Data Centre.[19]

Fractional atomic coordinates and equivalent isotropic temperature factors U(iso) with standard deviations in parentheses for 6-C-phenyl-α-L-glycero-D-glucopyranose 1β:

Atom	x/a	y/b	z/c	U(iso)
O(1)	-0.1682(3)	-0.3808(2)	-0.1240(2)	0.0248
O(2)	0.1127(4)	-0.5207(2)	-0.0512(2)	0.0276
O(3)	-0.0699(4)	-0.5667(2)	0.1277(2)	0.0282
O(4)	-0.4137(4)	-0.3770(3)	0.1467(2)	0.0333
O(5)	-0.6705(4)	-0.2795(3)	-0.0454(2)	0.0328
O(6)	-0.3699(4)	-0.1103(2)	-0.1935(2)	0.0305
O(33)	0.1844(6)	-0.6441(3)	-0.2168(3)	0.0478
C(1)	-0.1043(5)	-0.4977(3)	-0.0540(3)	0.0234
C(2)	-0.1389(5)	-0.4576(3)	0.0545(3)	0.0245
C(3)	-0.3768(5)	-0.4224(3)	0.0481(3)	0.0255
C(4)	-0.4474(5)	-0.3083(3)	-0.0349(3)	0.0238
C(5)	-0.3936(5)	-0.3554(3	-0.1379(3)	0.0257
C(6)	-0.4525(5)	-0.2449(4)	-0.2256(3)	0.0307
C(7)	-0.3847(6)	-0.2948(4)	-0.3252(3)	0.0356
C(8)	-0.2007(8)	-0.2484(5)	-0.3552(4)	0.0470
C(9)	-0.143(1)	-0.2996(6)	-0.4443(4)	0.0582
C(10)	-0.266(1)	-0.3988(7)	-0.5048(4)	0.0655
C(11)	-0.450(1)	-0.4457(7)	-0.4763(4)	0.0668
C(12)	-0.5097(8)	-0.3959(5)	-0.3853(4)	0.0547
C(31)	-0.145(1)	-0.7609(8)	-0.3034(6)	0.0825
C(32)	0.015(1)	-0.6464(6)	-0.3070(4)	0.0577

Crystals of 6-*C*-phenyl-L-*glycero*-α-D-*gluco*-hexopyranose **1**β were deposited from a solution in water by slow vapour diffusion of ethanol [Figure 1]. A suitable crystal of **1**β was taken from the mother liquid, covered with highly purified mineral oil in order to prevent loss of included ethanol and attached to a glass fiber with cyanoacrylate glue. Crystal Data. - $C_{12}H_{16}O_6 .C_2H_6O$, M = 302.3, monoclinic, a = 6.327(2), b = 9.567(1), c = 13.064(3), β = 101.98(2)°, V = 773.5(3) Å^3 (by the least square refinement of the setting angles

for 24 automatically centered reflections), space group P 2_1, Z = 2, D_X = 1.30 g cm^{-3}, μ = 8.39 cm^{-1}, transparent prism, crystal dimensions 0.10 x 0.34 x 0.45 mm^3. Data Collection and Processing: Enraf-Nonius MACH3 diffractometer, ω-2θ scan mode with the ω scan width = 0.77 + 0.31 tanθ, ω scan speed 2.9 - 20.1° min^{-1}, graphite-monochromated CuKα radiation (λ = 1.5418 Å), measurement temperature 210 K, 3212 reflections were measured ($2 < \theta < 74°$,index range 0 to 7, -11 to 11, -15 to 15), 1323 unique reflections (merging R = 0.017), giving 1290 reflections with $I > 3\sigma(I)$, 3 intensity standards remeasured every 70 min, crystal decay of ca. 3% corrected during processing. Structure Analyses and Refinement. - Direct methods, full-matrix least-squares refinement. All non-hydrogen atoms were refined in anisotropic approximation (190 refined parameters, 1291 observations, observations / refined parameters = 6.8). One molecule of ethanol is additionally included in the asymmetric unit. The carbon-bound H atoms were placed in calculated positions and included in the final refinement with fixed positional and thermal parameters. The oxygen-bound H atoms could not be found in difference maps and were not added. Chebyshev weighting scheme (1) with parameters 6.63, 3.91, 505 was applied.[20] Refinement on F converged at R = 0.069 and R_w = 0.074. GOF = 1.077. A final difference Fourier synthesis showed minimum and maximum residual electron densities of -0.39 and 0.49 e $Å^{-3}$.

Fractional atomic coordinates and equivalent isotropic temperature factors U(iso) with standard deviations in parentheses for the phenyl lactol ***10****:*

Atom	x/a	y/b	z/c	U(iso)
O(1)	-0.4168(2)	-0.2300(2)	-0.5427(1)	0.0380
C(2)	-0.5959(2)	-0.2539(2)	-0.6132(2)	0.0320
O(3)	-0.6053(2)	-0.3724(2)	-0.7064(1)	0.0361
C(4)	-0.5341(3)	-0.3189(2)	-0.8160(2)	0.0336
C(5)	-0.5633(3)	-0.1502(2)	-0.8232(2)	0.0341
C(6)	-0.6518(3)	-0.1182(2)	-0.7047(2)	0.0325
O(7)	-0.6011(2)	0.0198(2)	-0.6435(2)	0.0402
O(8)	-0.3911(2)	-0.0801(2)	-0.8019(2)	0.0399
C(9)	-0.2471(3)	-0.1840(2)	-0.7709(2)	0.0357
C(10)	-0.3290(3)	-0.3392(2)	-0.7924(2)	0.0346
O(11)	-0.2758(2)	-0.3947(2)	-0.9070(2)	0.0420
C(12)	-0.1870(3)	-0.2799(2)	-0.9645(2)	0.0379
O(13)	-0.1327(2)	-0.1728(2)	-0.8600(1)	0.0395
C(14)	-0.3149(4)	-0.2134(3)	-1.0847(2)	0.0546
C(15)	-0.0180(4)	-0.3449(3)	-0.9943(3)	0.0516
C(16)	-0.7214(3)	-0.2862(2)	-0.5212(2)	0.0336
C(17)	-0.6943(3)	-0.2083(2)	-0.4007(2)	0.0402
C(18)	-0.8131(3)	-0.2293(3)	-0.3169(2)	0.0470
C(19)	-0.9562(3)	-0.3266(3)	-0.3530(2)	0.0464
C(20)	-0.9809(3)	-0.4058(3)	-0.4707(2)	0.0462
C(21)	-0.8629(3)	-0.3857(3)	-0.5553(2)	0.0429

For the phenyl lactol, *(2R,3S,4R,6R,7R,8S)*2,3,6,7-tetrahydroxy-6,7-O-isopropylidene-1,5-oxa-2-phenyl-bicyclo[3.3.0]octane **10** a suitable crystal (from ethyl acetate/hexane) of approximate dimensions 0.8 x 0.8 x 0.8 mm^3 was used [Figure 2]. Cell parameters a=7.5984(7), b=8.992(3), c=10.274(1), β=103.34(1). Monoclinic P 2_1. Molecular formula $C_{15}H_{17}O_6$. Formula weight 293.3. Number of formula units in cell (Z), 2. Calculated density (g cm^{-3}) 1.43. Data collection parameters: index range -9 to 0, -11 to 0, -12 to 12, θ range 0 to 74°, copper radiation, λ = 1.5418. Temperature 294K. 3 intensity standards remeasured every hour, 1.3% decay. Total data collected 1597, number used in refinement 1464, criterion for observed $I > 3\sigma(I)$. Refinement details: Corrections for secondary extinction and anomalous scattering were applied and refinement completed using a 3 term Chebychev polynomial.[20] 191 parameters refined, 7.7 observations per parameter, S (goodness of fit)=1.16 , R= .030, R_w=.033.

Experimental: Melting points were recorded on a Kofler hot block and are corrected. Proton nuclear magnetic resonance (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 Nuclear magnetic resonance (δ_C) spectra were recorded on a Varian Gemini 200 (50 MHz), a Bruker AC 200 (50 MHz) or a Bruker AM 500 (125 MHz) spectrometer and multiplicities were assigned using 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. Infra-red 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, or atmospheric pressure chemical ionisation ($APCI^+$ or $APCI^-$) 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 plastic or 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 2M 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. D-Glucuronolactone **3** was converted to the isopropylidene derivative **7** as previously described.[11]

5-O-tert-Butyldimethylsilyl-1,2-O-isopropylidene-α-D-glucuronolactone **8**. The protected lactone **7** (11.73 g, 54.3 mmol), *tert*-butyldimethylsilyl chloride (8.98 g, 59.6 mmol, 1.2 eq.) and recrystallized imidazole (8.45 g, 124.2 mmol, 2.5 eq.) were dissolved in dry DMF (40 ml) under nitrogen. The solution was stirred under nitrogen for 16 h by which time t.l.c. (ethyl acetate / hexane 1:1) showed a major product (Rf 0.85) and no trace of starting material (Rf 0.3). The solvent was removed *in vacuo* and coevaporated with toluene to afford a yellow oil which was dissolved in ethyl acetate (200 ml) and washed with water (200 ml). The aqueous layer was extracted with ethyl acetate (2 x 200 ml). The organic extracts were combined, dried ($MgSO_4$) and the solvent removed under reduced pressure to give a brown oil. Purification by flash chromatography (ethyl acetate / hexane 1:2) gave *the silyl ether* **8** (16.57 g, 92%) as a white crystalline solid; m.p. 120-122°C (ethyl acetate / hexane); $[\alpha]_D^{22}$ +55.8 (*c*, 1.82 in $CHCl_3$); ν_{max} (KBr)/cm^{-1}: 1787 (C=O); δ_H (500 MHz, $CDCl_3$): 0.16, 0.19 (6H, 2 x s, $(CH_3)_2Si$), 0.93 (9H, s, $(CH_3)_3CSi$), 1.32, 1.50 (6H, 2 x s, $(CH_3)_2C$), 4.51 (1H, d, $J_{4,5}$ 4.3 Hz, H-5), 4.71 (1H, d, $J_{3,4}$ 2.9 Hz, H-3), 4.74 (1H, d, $J_{1,2}$ 3.8 Hz, H-2), 4.79 (1H, dd, $J_{4,5}$ 4.3, $J_{3,4}$ 2.9 Hz, H-4), 5.99 (1H, d, $J_{1,2}$ 3.8 Hz, H-1); δ_C (50 MHz, $CDCl_3$): -5.5, -5.0 (2 x q, $(\underline{C}H_3)_2Si$), 18.2 (s, $(CH_3)_3\underline{C}Si$), 25.5 (q, $(\underline{C}H_3)_3CSi$), 26.3, 26.7 (2 x q, $(\underline{C}H_3)_2C$), 71.5, 78.9, 81.2, 82.5 (4 x d, C-2, C-3, C-4, C-5), 106.9 (d, C-1), 112.9 (s, $\underline{C}(CH_3)_2$), 173.1 (C=O); *m/z* (CI, NH_3): 348 ($M+NH_4^+$, 100%), 331 (MH^+, 26%); (Found: C, 54.65; H, 7.77; $C_{15}H_{26}O_6Si$ requires C, 54.52; H, 7.93%).

(2S/2R,3S,4S,6R,7R,8S)-3-O-tert-Butyldimethylsilyl-2,3,6,7-tetrahydroxy-6,7-O-isopropylidene-1,5-dioxa-2-phenyl-bicyclo[3.3.0]octane **9**. Phenyl lithium (16.8 ml, 30.3 mmol, 2.0 M solution in cyclohexane/ether 7:3) was added dropwise to a stirred solution of the fully protected lactone **8** (5.0 g, 15.1 mmol) in dry THF (50 ml) at -78°C under a nitrogen atmosphere. The mixture was stirred at -78°C for 2 h when t.l.c. (ethyl acetate/hexane 1:3) revealed remaining starting material so further phenyl lithium (7.57 mmol) was added. After 2.5 h, t.l.c. (ethyl acetate/hexane 1:3) showed all the starting material (Rf 0.3) had been consumed and

one major product (Rf 0.45) formed. An excess of saturated aqueous ammonium chloride solution was added and the mixture stirred for 30 min. The reaction mixture was diluted with ethyl acetate (200 ml) and washed with water (150 ml). The aqueous phase was extracted with ethyl acetate (2 x 200 ml) and the combined organic extracts dried ($MgSO_4$), filtered, and the solvent removed *in vacuo*. The residue was purified by flash chromatography (ethyl acetate/hexane 1:3) and crystallised from hexane to yield *the title compound* **9** (2.66 g, 43%) as a white crystalline solid; m.p. 99-102°C (hexane); $[\alpha]_D^{20}$ +18.1 (*c*, 0.90 in $CHCl_3$); ν_{max} (film)/ cm^{-1}: 3465 (br, OH); δ_H (500 MHz, benzene-d_6): -0.35, -0.08 (6H, 2 x s, $(CH_3)_2Si$), 0.65 (9H, s, $(CH_3)_3CSi$), 1.31, 1.50 (6H, 2 x s, $(CH_3)_2C$), 2.18 (1H, s, OH), 3.93 (1H, d, $J_{3,4}$ 5.3 Hz, H-3), 4.79 (1H, d, $J_{7,6}$ 3.8 Hz, H-7), 4.86 (1H, d, $J_{8,4}$ 6.6 Hz, H-8), 5.22 (1H, dd, $J_{4,3}$ 5.3 Hz, $J_{4,8}$ 6.6 Hz, H-4), 6.14 (1H, d, $J_{6,7}$ 3.8 Hz, H-6); δ_C (50 MHz, C_6D_6): -6.1, -5.3 (2 x q, $(\underline{C}H_3)_2Si$), 17.8 (s, $(CH_3)_3\underline{C}Si$), 25.4 (q, $(\underline{C}H_3)_3CSi$), 26.9, 27.6 (2 x q, $C(\underline{C}H_3)_2$), 77.4, 83.2, 84.4, 85.7 (4 x d, C-3, C-4, C-7, C-8), 107.8 (d, C-6), 108.8 (s, C-2), 113.2 (s, $\underline{C}(CH_3)_2$), 127.4, 127.6, 128.3 (3 x d, $Ph_{o,m,p}$), 139.8 (s, Ph_{ipso}); *m/z* (CI, NH_3): 409 (MH^+, 3%), 391 (MH^+-H_2O, 100%), 105 ($PhCO^+$, 35%); (Found: C, 61.50; H, 8.17; $C_{21}H_{32}O_6Si$ requires: C, 61.73; H, 7.89%).

(2R,3S,4R,6R,7R,8S)2,3,6,7-Tetrahydroxy-6,7-O-isopropylidene-1,5-oxa-2-phenyl-bicyclo[3.3.0]octane ***10***. *Method (i) from silyl ether* ***9***. Tetrabutylammonium fluoride (0.80 ml, 0.88 mmol, 1.1 M solution in THF) was added to a stirred solution of the silyl ether **9** (300 mg, 0.73 mmol) in dry THF (10 ml) under nitrogen atmosphere. After 5 min, t.l.c. (ethyl acetate/hexane 1:3) showed one major product (Rf 0.4) and no starting material. The solvent was removed *in vacuo* and the residue purified by flash chromatography (ethyl acetate/hexane 1:2) to yield *the lactol* ***10*** (167 mg, 77%) as a white solid [the X-ray crystal structure of **10** is given above]; m.p. phase change 125-127°C melted 143-145°C (ethyl acetate/hexane); $[\alpha]_D^{25}$ +7.2 (*c*, 0.87 in $CHCl_3$); ν_{max} (KBr)/cm^{-1}: 3402 (br, OH); δ_H (500 MHz, $CDCl_3$): 1.39, 1.51 (6H, 2 x s, $(CH_3)_2C$), 3.23 (1H, d, J 10.8 Hz, OH), 3.35 (1H, br, OH), 3.89 (1H, m, H-3), 4.80 (1H, d, $J_{6,7}$ 3.5 Hz, H-7), 4.82 (1H, d, $J_{8,4}$ 4.9 Hz, H-8), 4.91 (1H, app. t, J 5.1 Hz, H-4), 6.12 (1H, d, $J_{6,7}$ 3.5 Hz, H-6), 7.35-7.56 (5H, m, ArH); δ_C (50 MHz, $CDCl_3$): 27.1, 27.6 (2 x q, $C(\underline{C}H_3)_2$), 78.2, 81.4, 83.6, 86.8 (4 x d, C-3, C-4, C-7, C-8), 102.8 (s, C-2), 107.3 (d, C-6), 113.3 (s, $\underline{C}(CH_3)_2$), 125.1, 128.4, 128.8 (3 x d, $Ph_{o,m,p}$), 141.1 (s, Ph_{ipso}); *m/z* (CI, NH_3): 312 ($M+NH_4^+$, 5%), 295 (MH^+, 3%), 277 (MH^+-H_2O, 100%), 105 (48 %), 100 (33%); (Found: C, 61.11; H, 6.35; $C_{15}H_{18}O_6$ requires C, 61.22; H, 6.16%).

Method (ii) from glucuronolactone acetonide ***7***. The acetonide **7** (1.5 g, 6.94 mmol) was dissolved in dry THF (30 ml) under nitrogen. The solution was cooled to -70°C. Phenyl lithium (1.8 M solution in cyclohexane / ether (70 / 30), 4.25 ml, 7.63 mmol, 1.1 eq.) was added under nitrogen to give a brown solution. After 30 min, t.l.c. (ethyl acetate / hexane 1:1) showed only a trace of starting material (Rf 0.4) and a new spot (Rf 0.5). The reaction was quenched by addition of 10 ml of a saturated aqueous ammonium chloride solution and the solution was stirred for 5 min. The cold reaction mixture was diluted with ethyl acetate (100 ml) and washed with brine (50 ml). The aqueous layer was then extracted with ethyl acetate (2 x 100 ml). The organic extracts were combined, dried ($MgSO_4$) and the solvent removed under reduced pressure to give a yellow oil. The residue was purified by flash chromatography (ethyl acetate / hexane 1:3) to afford *the lactol* ***10*** (469 mg, 23%) identical to the material described above.

*6-O-tert-Butyl-dimethylsilyl-1,2-O-isopropylidene-6-C-phenyl-*L*-glycero-α-*D*-gluco-hexofuranose* ***12***. Sodium borohydride (99 mg, 2.61 mmol) was added to a stirred solution of the silyl lactol **9** (710 mg, 1.73 mmol) in ethanol (30 ml). After 1 h, t.l.c. (ethyl acetate/hexane 1:2) showed no remaining starting material (Rf

0.6) and one major product (Rf 0.2). An excess of saturated ammonium chloride solution was added and the mixture stirred for 1 h. The reaction mixture was filtered through Celite (elution with ethanol), and the filtrate concentrated *in vacuo*, diluted with ethyl acetate (200 ml) and washed with brine (100 ml). The aqueous phase was extracted with ethyl acetate (2 x 200 ml) and the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (ethyl acetate/hexane 1:2) to yield *the silyl ether* ***12*** (543 mg, 76%) as a white solid; m.p. 35-38°C; $[\alpha]_D^{20}$ +21.6 (*c*, 1.26 in $CHCl_3$); ν_{max} (film)/cm^{-1}: 3444 (br, OH); δ_H (500 MHz, $CDCl_3$): -0.11, 0.11 (6H, 2 x s, $(CH_3)_2Si$), 0.93 (9H, s, $(CH_3)_3CSi$), 1.31, 1.44 (6H, 2 x s, $(CH_3)_2C$), 2.89 (1H, s br, exch. in D_2O, OH), 3.22 (1H, s br, exch. in D_2O, OH), 3.85 (1H, m which collapsed to dd, $J_{5,4}$ 7.5 Hz, $J_{5,6}$ 2.7 Hz, on exch. in D_2O, H-5), 4.07 (1H, dd, $J_{4,3}$ 2.8 Hz, $J_{4,5}$ 7.7 Hz, H-4), 4.32 (1H, d, $J_{3,4}$ 2.8 Hz, H-3), 4.52 (1H, d, $J_{2,1}$ 3.7 Hz, H-2), 4.92 (1H, d, $J_{6,5}$ 2.7 Hz, H-6), 5.95 (1H, d, $J_{1,2}$ 3.7 Hz, H-1); δ_C (50 MHz, $CDCl_3$): -5.1, -4.6 (2 x q, $(\underline{C}H_3)_2Si$), 18.2 (s, $(CH_3)_3\underline{C}Si$), 25.8 (q, $(\underline{C}H_3)_3CSi$), 26.1, 26.6 (2x q, $C(\underline{C}H_3)_2$), 74.0, 74.6, 75.5, 79.4, 85.2 (5 x d, C-2, C-3, C-4, C-5, C-6), 105.0 (d, C-1), 111.3 (s, $\underline{C}(CH_3)_2$), 126.3, 127.7, 128.2 (3 x d, $Ph_{o,m,p}$), 141.6 (s, Ph $_{ipso}$); *m/z* (CI, NH_3): 428 ($M+NH_4^+$, 5%), 411 (MH^+, 6%), 393 (MH^+-H_2O, 3%), 296 (MH^+-TBDMS, 37%), 238 (40%), 221 (100%); (Found C, 61.58; H, 8.36; $C_{21}H_{34}O_6Si$ requires C, 61.43; H, 8.34%).

*1,2-O-Isopropylidene-6-C-phenyl-*L*-glycero-α-*D*-gluco-hexofuranose* ***13***. Tetrabutylammonium fluoride (0.25 ml, 0.23 mmol, 1.1 M solution in THF) was added to a solution of the silyl ether **12** (80 mg, 0.19 mmol) in dry THF (4 ml) under a nitrogen atmosphere. After 20 min, t.l.c. (ethyl acetate/hexane 1:1) showed no starting material and a single major product. The solvent was removed *in vacuo* and the residue purified by flash chromatography (ethyl acetate/hexane 1:1) to afford *the triol* ***13*** (23 mg, 40%) as a white solid; m.p. 199-202°C (ethyl acetate); $[\alpha]_D^{25}$ + 2.2 (*c*, 0.45 in acetone); ν_{max} (KBr)/cm^{-1}: 3403 (OH, br); δ_H (500 MHz, acetone-d_6): 1.27, 1.38 (6H, 2 x s, $(CH_3)_2C$), 3.93 (1H, d, J 7.4 Hz, OH), 4.00 (1H, m, H-5), 4.17 (1H, dd, J 2.7 Hz, 7.6 Hz, H-4), 4.26 (1H, m, H-3), 4.33 (1H, d, J 4.3 Hz, OH), 4.36 (1H, d, J 6.1 Hz, OH), 4.49 (1H, d, $J_{1,2}$ 3.7 Hz, H-2), 4.86 (1H, m, H-6), 5.89 (1H, d, $J_{1,2}$ 3.7 Hz, H-1), 7.23-7.44 (5H, m, ArH); δ_C (125 MHz, acetone-d_6): 26.5, 27.1 (2 x q, $C(\underline{C}H_3)_2$), 73.6, 73.8, 75.6, 80.6, 86.4 (5 x d, C-2, C-3, C-4, C-5, C-6), 105.8 (d, C-1), 111.8 (s, $\underline{C}(CH_3)_2$), 127.4, 127.7, 128.6 (3 x d, $Ph_{o,m,p}$), 144.3 (s, Ph $_{ipso}$); m/z (APCI+): 319 (M+Na^+, 21%) 203 (100%); (Found C, 60.58 ; H, 6.76; $C_{15}H_{20}O_6$ requires C, 60.80; H, 6.80%).

*1,2-O-Isopropylidene-6-C-phenyl-*L*-glycero-α-*D*-gluco-hexofuranose* ***13***, and *1,2-O-Isopropylidene-6-C-phenyl-*D*-glycero-α-*D*-gluco-hexofuranose* ***14***. The phenyl lactol **10** (469 mg, 1.595 mmol) was dissolved in ethanol (20 ml). Sodium borohydride (90 mg, 2.39 mmol, 1.5 eq.) was added. After 30 min, t.l.c. (ethyl acetate / hexane 1:1) showed no trace of starting material (Rf 0.6) and a new baseline spot. The reaction was quenched by addition of ammonium chloride and the solution was stirred until effervescence ceased. The solution was then filtered through Celite and eluted with ethanol. The solvent was removed under reduced pressure to give a white solid which was purified by flash chromatography (ethyl acetate / hexane 2:1 then ethyl acetate) to afford 1,2-O-isopropylidene-6-*C*-phenyl-L-*glycero*-α-D-*gluco*-hexofuranose **13** (150 mg, 32%) identical to material above. Further elution gave 1,2-O-isopropylidene-6-C-phenyl-D-*glycero*-α-D-*gluco*-hexofuranose **14** (178 mg, 38 %) as a white solid; m.p. 205-208°C (ethyl acetate); $[\alpha]_D^{23}$ +35.9 (*c*, 0.29 in acetone); ν_{max} (KBr)/cm^{-1}: 3369 (OH, br); δ_H (500 MHz, acetone-d_6): 1.25, 1.29 (6H, 2 x s, $(CH_3)_2C$), 3.79 (1H, dd, J 2.6 Hz, 7.4 Hz, H-4), 4.20 (1H, m, H-5), 4.45 (2H, m, H-2 & H-6), 4.86 (1H,

app. t, J 4.6 Hz, H-3), 5.89 (1H, d, $J_{1,2}$ 3.6 Hz, H-1), 7.24-7.48 (5H, m, ArH); δ_C (125 MHz, acetone-d_6): 26.6, 27.1 (2 x q, $C(\underline{C}H_3)_2$), 73.1, 75.4, 75.6, 80.7, 86.1 (5 x d, C-2, C-3, C-4, C-5, C-6), 105.8 (d, C-1), 111.8 (s, $\underline{C}(CH_3)_2$), 127.8, 128.2, 128.4 (3 x d, $Ph_{o,m,p}$), 142.4 (s, Ph_{ipso}); *m/z* (CI, NH_3): 314 ($M+NH_4^+$, 4%), 296 ($M+NH_4^+ - H_2O$, 9%), 238 (15%), 100 (100%), (Found C, 60.87 ; H, 6.99; $C_{15}H_{20}O_6$ requires C, 60.80; H, 6.80%).

*6-C-Phenyl-*L*-glycero-*D*-gluco-hexose* ***1****. Method (i) from silyl acetonide* ***12****.* The silyl ether **12** (971 mg, 2.37 mmol) was dissolved in dioxane (20 ml) and the solution was diluted with water (20 ml). Ion exchange resin [Amberlite IR-120 (H^+), 6 g] was added and the mixture was stirred at 65°C. After 48 h, t.l.c. (ethyl acetate/hexane 1:1) showed no starting material (Rf 0.6) and one major product (Rf 0.15). The mixture was filtered, diluted with water (200 ml) and washed with chloroform (3 x 200 ml). The aqueous layer was concentrated *in vacuo* to yield *6-C-phenyl-*L*-glycero-*D*-gluco-hexopyranose* ***1*** (560 mg, 92%) as a white solid. Some of the material was then recrystallised (ethanol) as the pure β anomer **1β**, the structure of which was firmly established by X-ray crystallographic analysis [see above]; m.p. 163-165°C (EtOH); $[\alpha]_D^{21}$ (for equilibrium mixture of **1α** and **1β**) +69.3 $[\alpha]_D^{21}$ (for **1β**) +55.8, $[\alpha]_D^{21}$ (**1α**) +85.1 (*c*, 1.0 in H_2O); ν_{max} (KBr)/cm^{-1}: 3413 (OH), 2926 (C-H Ar), 1636 (CC Ar); δ_H (500 MHz, D_2O): 3.22 (1H, dd, $J_{2,1\beta}$ 7.9 Hz, $J_{2,3\beta}$ 9.4 Hz, H-2β), 3.46 (1H, dd, $J_{3,2\beta}$ 9.4 Hz, $J_{3,4\beta}$ 9.3 Hz, H-3β), 3.50 (1H, dd, $J_{5,6\beta}$ 2.1 Hz, $J_{5,4\beta}$ 9.7 Hz, H-5β), 3.51 (1H, dd, $J_{2,1\alpha}$ 3.8 Hz, $J_{2,3\alpha}$ 9.3 Hz, H-2α), 3.65 (1H, dd, $J_{4,5\alpha}$ 9.5 Hz, $J_{4,3\alpha}$ 9.5 Hz, H-4α), 3.66 (1H, dd, $J_{3,4\alpha}$ 9.3 Hz, $J_{3,2\alpha}$ 9.3 Hz, H-3α), 3.70 (1H, dd, $J_{4,3\beta}$ 9.3 Hz, $J_{4,5\beta}$ 9.3 Hz, H-4β), 3.92 (1H, dd, $J_{5,6\alpha}$ 1.8 Hz, $J_{5,4\alpha}$ 9.5 Hz, H-5α), 4.41 (1H, d, $J_{1,2\beta}$ 7.9 Hz, H-1β), 5.04 (1H, d, $J_{6,5\beta}$ 1.8 Hz, H-6β), 5.06 (1H, d, $J_{1,2\alpha}$ 3.8 Hz, H-1α), 5.10 (1H, d, $J_{6,5\alpha}$ 1.5 Hz, H-6 α), 7.45-7.31 (10H, m, ArH α,β); δ_C (50 MHz, D_2O + dioxan): 70.6, 70.9, 72.4, 73.9, 74.8, 75.1, 76.8, 79.1, (8 x d, C-2, C-3, C-4, C-5, C-6, α & β), 93.0 (d, C-1α), 97.1 (d, C-1β), 127.0, 127.4, 128.5, 128.8, 129.5 (6 x d, 2 x $Ph_{o,m,p}$, α & β), 142.4, 142.6 (2 x s, $Ph_{ipso}\alpha$, $Ph_{ipso}\beta$) ; *m/z*: (CI, NH_3) 256 (88%, $M+NH_4^+-H_2O$) 274 (100%, $M+NH_4^+$); (Found C, 55.98; H, 5.99; $C_{12}H_{16}O_6$ requires C, 56.24; H, 6.29%).

Method (ii) from triol ***13****.* The acetonide **13** (43 mg, 0.145 mmol) was dissolved in dioxan (2 ml) and the solution was diluted with water (2 ml). Ion exchange resin [Amberlite IR-120 (H^+), 468 mg] was added and the solution was stirred at 65°C. After 24 h, t.l.c. (10% MeOH in ethyl acetate) showed only a trace of starting material (Rf 0.65) and a new product (Rf 0.1). The solution was filtered to remove the resin and the solvent was removed *in vacuo* to give 6-*C*-phenyl-L-*glycero*-D-*gluco*-hexopyranose **1** (35 mg, 94 %) identical to the material above.

*6-C-Phenyl-*D*-glycero-*D*-gluco-hexopyranose* ***2****.* The acetonide **14** (115 mg, 0.388 mmol) was dissolved in dioxan (3 ml) and the solution was diluted with water (3 ml). Ion exchange resin [Amberlite IR-120 (H^+), 1.5 g) was added and the solution was stirred at 65°C. After 16 h, t.l.c. (10% MeOH in ethyl acetate) showed only a trace of starting material (Rf 0.7) and a new product (Rf 0.1). The solution was filtered to remove the resin and the solvent was removed *in vacuo* to give *6-C-phenyl-*D*-glycero-*D*-gluco-hexopyranose* ***2*** (95 mg, 96 %); m.p. 170-178°C; $[\alpha]_D^{21}$ +21.6 (*c*, 0.51 in H_2O); ν_{max} (KBr)/cm^{-1}: 3392 (OH, br); δ_H (500 MHz, D_2O): 3.05 (3H, m, H-2α, H-4β, H-4α), 3.29 (1H, dd, $J_{1,2\beta}$ 3.8 Hz, $J_{2,3\beta}$ 9.8 Hz, H-2β), 3.45 (1H, app. t, J 9.2 Hz, H-3α), 3.68 (1H, app. t, J 9.4 Hz, H-3β), 3.74 (1H, dd, $J_{5,6\alpha}$ 3.5 Hz, $J_{4,5\alpha}$ 10.0 Hz, H-5α), 4.15 (1H, dd, $J_{5,6\beta}$ 3.8 Hz, $J_{4,5\beta}$ 10.2 Hz, H-5β), 4.60 (1H, d, $J_{1,2\alpha}$ 7.9 Hz, H-1α), 5.03 (1H, d, $J_{5,6\alpha}$ 3.5 Hz, H-6α), 5.04 (1H, d, $J_{5,6\beta}$ 3.8 Hz, H-6β), 5.13 (1H, d, $J_{1,2\beta}$ 3.8 Hz, H-1β), 7.35-7.46 (10H, m, ArHα & ArHβ); δ_C (50 MHz, D_2O + dioxan): 71.8, 73.4, 74.7, 76.7, 78.1 (5 x d, C-2α, C-3α, C-4α, C-

5α, C-6α), 72.0, 72.2, 73.5, 73.6, 73.8 (5 x d, C-2β, C-3β, C-4β, C-5β, C-6β), 92.7 (d, C-1β), 96.9 (d, C-1α), 128.5, 128.7, 129.0, 129.1 (6 x d, 2 x $Ph_{o,m,p}$, α & β), 139.3 (s, $Ph_{ipso}α$), 139.6 (s, $Ph_{ipso}β$); m/z (CI, NH_3): 256 ($M+NH_4^+ - H_2O$, 29%), 184 (27%), 154 (34%), 137 (47%), 105 (100%) (Found C, 56.28; H, 6.16; $C_{12}H_{16}O_6$ requires C, 56.25; H, 6.29%).

Methyl 6-C-Phenyl-L-glycero-α-D-gluco-hexopyranoside 15α and Methyl 6-C-Phenyl-L-glycero-β-D-gluco-hexopyranoside 15β. A solution of the unprotected sugar **1** (100 mg, 0.04 mmol) in methanol (10 ml) in the presence of ion exchange resin [Amberlite IR-120 (H^+), 1 g) was stirred at 65°C. After 48 h, t.l.c. (ethyl acetate/methanol 17:3) revealed no starting material and two major products (Rf 0.35, Rf 0.45). The mixture was filtered and the solvent removed *in vacuo* to give a residue which was purified by flash chromatography (ethyl acetate/methanol 19:1) to yield *the methyl β-pyranoside 15β* (25 mg, 23%) as a white solid; m.p. 195-197°C; $[\alpha]_D^{24}$ +2.4 (*c*, 0.32 in H_2O); ν_{max} (KBr)/cm^{-1}: 3401 (br, OH); δ_H(500 MHz, D_2O): 3.17 (1H, t, H-2), 3.19 (3H, s, OCH_3), 3.34-3.39 (2H, m, H-5, H-6), 3.59 (1H, app. t, J 9.5 Hz, H-4), 4.04 (d, $J_{1,2}$ 7.8 Hz, H-1), 4.98 (1H, br, H-6) 7.24-7.37 (5H, m, ArH); δ_C (125 MHz, D_2O + dioxan): 57.4 (q, $O\underline{C}H_3$), 70.5, 70.8, 73.9, 76.8, 78.6 (5 x d, C-2, C-3, C-4, C-5, C-6), 103.9 (d, C-1), 127.3, 128.4, 129.1 (3 x d, $Ph_{o,m,p}$), 142.0 (s, Ph_{ipso}); *m/z* ($APCI^-$): 270 (13%, M^-), 269 (100%, $M-H^-$), 255 (3%, $M-CH_3$).
Further elution afforded*the methyl α-pyranoside 15α* (47 mg, 45%) as a white solid; m.p. 168-170°C; $[\alpha]_D^{24}$ +116.4 (*c*, 0.44 in H_2O); ν_{max} (KBr)/cm^{-1}: 3396 (br, OH); δ_H (500 MHz, D_2O): 2.75 (3H, s, OCH_3), 3.34-3.63 (4H, m, H-2, H-3, H-4, H-5), 4.54 (1H, d, $J_{1,2}$ 3.7 Hz, H-1), 5.05 (1H, br, H-6), 7.22-7.37 (5H, m, ArH); δ_C (50 MHz, D_2O + dioxan): 55.1 (q, $O\underline{C}H_3$), 67.3, 67.5, 72.0, 74.3, 75.1, (5 x d, C-2, C-3, C-4, C-5, C-6), 99.9 (d, C-1), 126.8, 128.3, 129.2 (3 x d, $Ph_{o,m,p}$), 142.4 (s, Ph_{ipso}); *m/z* ($APCI^-$): 270 (16%, M^-), 269 (100%, $M-H^-$), 255 (3%, $M-CH_3$), 161, (63%).

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