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The UDP-Gal*p* mutase catalyzed isomerization: synthesis and evaluation of 1,4-anhydro-β-D-galactopyranose and its [2.2.2] methylene homologue†

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The synthesis of 1,4-anhydro-β-D-galactopyranose (1,5-anhydro-α-D-galactofuranose), a proposed intermediate in the ring contraction isomerisation catalyzed by UDP-galactopyranose mutase, together with its [2.2.2] bicyclic methylene homologue, synthesised as a possible competitive inhibitor or alternative substrate, are reported. Neither compound was found to be an inhibitor or substrate for UDP-galactopyranose mutase from *Klebsiella pneumoniae*.

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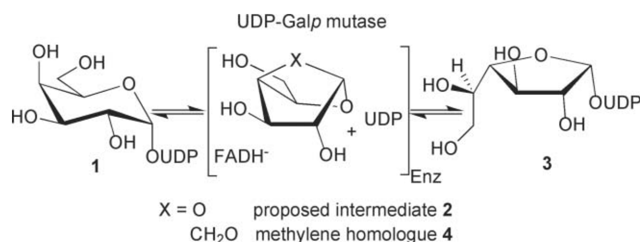
Introduction

D-Galactose is extensively distributed in nature as a constituent of oligosaccharides, polysaccharides and glycoconjugates. However the furanoid configuration (galactofuranose, Gal*f*) has yet to be found in mammals, its presence is apparently restricted to bacteria, protozoa, fungi and plants.[1–8] Therefore the biosynthesis of Gal*f*, given that it plays critical roles in cellular viability and virulance, would seem to be an appealing target for potential antimicrobial and antifungal drug development.[9–13] One major family of pathogenic bacteria that utilise Gal*f* are the *Mycobacteria* that include the bacteria responsible for the tuberculosis and leprosy. Every year, tuberculosis (TB) kills around 3 million people worldwide, more than AIDS and malaria combined, causing the World Health Organisation (WHO) to declare TB a global health emergency in 1993.[14] *Mycobacterium tuberculosis* (*M. tuberculosis*) the causative agent of TB, has a unique cell envelope responsible for pathogen resistance to antibiotics and harmful conditions. The cell wall component is composed of a mycolyl arabinogalactan polymer attached to the peptidoglycan. The galactan component is an oligomer of 15–30 Gal*f* residues that are alternately linked β(1→5) and β(1→6).[15–24] It has been demonstrated that the precursor of Gal*f* residue is UDP-α-D-galactofuranose (UDP-Gal*f*, **3**), which in turn is formed from UDP-α-D-galactopyranose (UDP-Gal*p*, **1**) by the flavoenzyme UDP-galactopyranose mutase (UDP-Gal*p* mutase, E.C.5.4.99.9).[25–30] It has been shown that Gal*f*, and therefore the mutase action, is essential for the viability of mycobacteria.[31] Understanding the catalytic mechanism of the mutase will hopefully lead to new directions in *anti*-TB therapy.[32] Although a number of studies on the mutase has been conducted,[33–42] the mechanism of substrate turnover is still not fully understood. Reviewing currently available biochemical and kinetic data indicates several different roles have been suggested for the essential coenzyme (reduced FAD) in catalysis[32] including hydride transfer,[33,34] single electron transfer,[35,37] nucleophilic attack,[36,43,44] charge stabilization and a structural role.[34,37,45] Furthermore, during catalysis the galactose moiety of the substrate has been proposed to take a variety of different forms including an acyclic adduct,[34,36,38] monocyclic ring (anomeric radical or oxonium ring)[35,37,41] and bicyclic[39,40] intermediates.

Through position isotope exchange (PIX) and ^{13}C-NMR spectroscopy monitoring, it has been demonstrated that the cleavage of the glycosidic C–O bond takes place during the mutase catalytic cycle.[34,39] Since the axial 4-OH of Gal*p* has a special stereoelectronic role that facilitates the hydrolysis of galactopyranosides,[46] it has been suggested that it functions as an internal nucleophile in the above reaction.[4,39] Thus, bicyclic structure **2** has been proposed as an intermediate in the mutase catalysis (Scheme 1). Furthermore, selective production of Gal*f* under acidic conditions from derivatives of **2**,[47–52] chemically supports this proposal. Additionally, the weak inhibitory effect of a UMP-(1*C*)-phosphonate-**2** has been reported as indirect evidence for validity of bicyclic intermediate in Scheme 1.[40]



Scheme 1 The UDP-Galp mutase catalysed reaction with putative bicyclic intermediate.

In this regard, we set out to further investigate the involvement of the bicyclic intermediate **2** in UDP-Gal*p* catalyzed reaction. Previously, we have shown that a carbasugar analogue of **2** is not an inhibitor for *M. tuberculosis* mutase, this finding indirectly indicated that during turnover the presence of a bicyclic intermediate is unlikely.[53] Here we report the synthesis of the proposed bicyclic intermediate **2** in 5 steps and its effect on the turnover of the natural substrate **3** in *K. pneumoniae* mutase system. Also the synthesis and inhibitory effect of a methylene homologue **4** of the proposed bicyclic intermediate

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† Electronic supplementary information (ESI) available: Experimental details for **5**–**11**, **13**–**18**, enzyme assay conditions and spectra for products; table comparing oxanorbornane NMR data. CCDC reference number 287123. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b917409e

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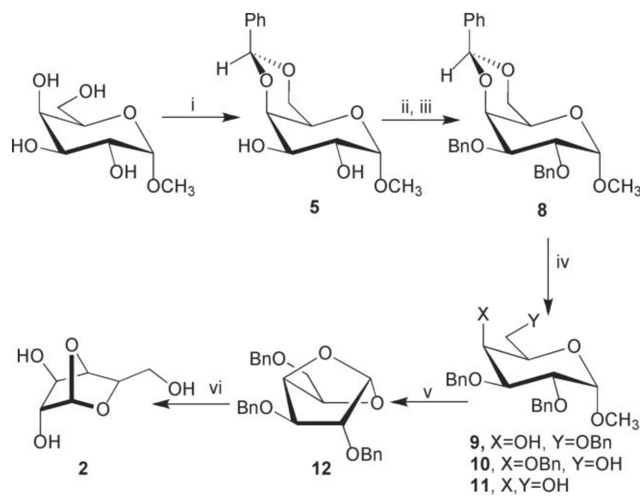
2, designed as a potential competitive inhibitor with reduced ring strain and better stability, is reported in 8 steps. During the preparation of this manuscript, Caravano *et al.* reported the synthesis and evaluation of 1,4-anhydrogalactopyranose with UDP-Gal*p* mutase.[54] We noticed that the ^{1}H and ^{13}C- NMR data they provide on 1,4-anhydrogalactopyranose does not agree with our data and is less consistent with the data on protected forms of 1,4-anhydrogalactopyranose that have been reported previously in the literature (see also supporting information for a tabulated comparison†).[51,55,56] Several 2,7-dioxabicyclo[2.2.1]heptane[57] and isoquinuclidine[58] compounds that bear a substantial structural similarity to **2** and **4** have been evaluated as inhibitors of glycosidases although only the latter displayed any significant inhibitory activity.

Results and discussion

Formation of derivatives of **2** at high temperature or under pyrolysis conditions have previously been reported,[56,59,60] suggesting that **2** is sufficiently stable to allow its preparation. Target **2** could possibly be achieved under basic conditions *via* 1,4-*trans* cyclization from either appropriately protected D-glucose with a leaving group at C-4 or a protected D-galactose with a leaving group at the α-anomeric carbon in analogy with preparation of 1,4-anhydro-α-D-glucose.[49,51,56,59,61–63] The main drawback of these methods was that the introduction of good leaving groups requires additional steps and the resulting compounds are usually unstable and prone to polymerization. Also cyclization *via* anomeric oxocarbeniums (requiring acidic conditions), increases the possibility of by-product formation. Therefore an alternative method introduced by Åberg and Ernst for the synthesis of β-glycosans was applied.[55] In this approach a relatively stable potential leaving group has to be activated in the cyclization step using catalytic anhydrous $FeCl_3$ in acetonitrile as a coordinating solvent. Thus synthesis of putative bicyclic intermediate **2** requires access to protected *O*-methyl 4-hydroxy-α-D-galactoside **9** (Scheme 2).



Scheme 2 *Reagents and conditions*: i) Benzaldehyde dimethyl acetal, CSA, $CHCl_3$, reflux, 100%; ii) NaH, DMF, 0 °C; iii) BnBr, Bu_4NI, 85%; iv) 3 Å MS, $NaCNBH_3$, THF, HCl/diethyl ether, **9** 70%, **10** 10%, **11** 8%; v) **9**, $FeCl_3$, CH_3CN, reflux, 40%; vi) H_2, Pd/C (10%), EtOH, EtOAc, 100%.

Since the instability of the desired oxanorbornane systems under acidic, basic, oxidative and reducing conditions have been documented,[64] we therefore selected benzyl ethers (Bn) as suitable protecting groups for the 2-, 3- and 6-hydroxyls in our synthetic strategy because of their mild deprotection conditions. Additionally, Bz and TBS protecting groups were recently described as being unsuitable for the cyclization step.[52] To generate compound **9** with a free 4-hydroxyl group, regioselective ring opening of 4,6-benzylidene was required, and this has been well documented. Although 4,6-benzylidene (1,3-dioxane) formation occurs cleanly from D-glucose *via* Evans' procedure,[65,66] in our hands with D-galactose we always obtained low to moderate yield (30–50%) of **5** together with unreacted starting materials from the reaction mixture. Excess dimethyl benzyl acetal and higher temperature caused formation of the alternative regioisomeric acetals, 3,4-benzylidenes (1,3-dioxolane) **6** and **7** (Fig. 1). Finally changing solvent and acid catalyst to match Clausen's procedure[66] provided **5** in quantitative yield.

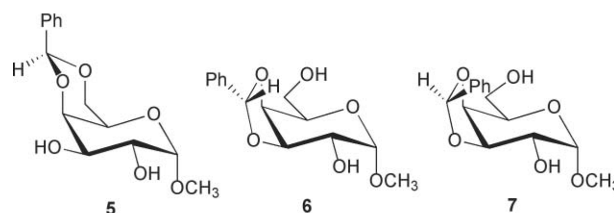


Fig. 1 Regioisomeric acetals formed between methyl-α-D-galactoside and benzaldehyde.

Protection of the remaining hydroxyls of **5** was achieved using a standard benzylation procedure[67] under basic conditions to give **8**. It should be noted that decomposition of the acid-labile 1,3-dioxane ring of **8** after 24 h storage in chloroform solution was clearly observed by IR and NMR spectroscopy. The product **8** was therefore purified by crystallization and X-ray crystallography data confirmed that the phenyl ring takes the expected lower energy equatorial position in the 1,3-dioxane ring system (CCDC 287123†). Reductive ring opening of **8** using the most common regioselective protocol ($NaCNBH_3$ and HCl/THF)[68,69] provided **9** as well as minor by-products **10** and **11**. Use of CF_3CO_2H/DMF or Et_3SiH/CF_3SO_3H systems[70–72] did not improve the yield or selectivity in this step. In accordance with Larsson and co-workers,[73] our spectroscopic data supported the existence of internal hydrogen bonding between the proton of 4-OH and the adjacent 3-O. Interestingly we observed on TLC an unusually high R_f for **9** compared with the more hydrophobic starting material **8**, which could be explained by internal hydrogen bonding. The optical rotation of **10** did not agree with that published by Lucas and Schuerch,[74] but it was in good agreement with that reported by Ek and co-workers.[75] Cyclization of **9** was achieved in moderate yield using anhydrous $FeCl_3$ catalyst in a dilute solution of acetonitrile after 1 h gentle reflux at 60 °C, running the reaction under vigorous reflux increased formation of by-products and the risk of decomposition. Although $FeCl_3$ can be used to deprotect benzyl groups, the application of a coordinating solvent (CH_3CN) reduced the possibility of deprotection occurring. We found that increasing the reaction time (*e.g.* 12 h) could decrease the yield of cyclization step and it produced highly polar by-products. Regarding NMR interpretation of oxanorbornane systems, it

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should be noted that the coupling constants between the bridge head proton 4-H and the *endo* vicinal protons 3-H and 5-H are ~ 0 Hz due to the dihedral angle ~ 90°. Moreover, the fixed W shape arrangement of 2-H and 4-H causes a measurable long-range coupling in the 1D spectrum of oxanorbornane systems (^4J ~ 1 Hz). Finally, hydrogenolysis of **12** gave **2** in an overall 24% yield after 5 steps. Optical rotation and NMR data confirmed that **2** adopted the rigid $^{1,4}B$ conformation. We couldn't detect any change in NMR spectra of **2** after two weeks storage in D_2O at 22 °C, however ring opening and oligomerisation reactions to give dimers, trimers and tetramers rapidly occurred in the presence of acid catalysts *e.g.* HCl (see supporting information†). Therefore, although **2** was not as reactive as many enzyme-generated intermediates, it could potentially be easily activated by protonation of the bridging oxygen inside the enzyme active site.

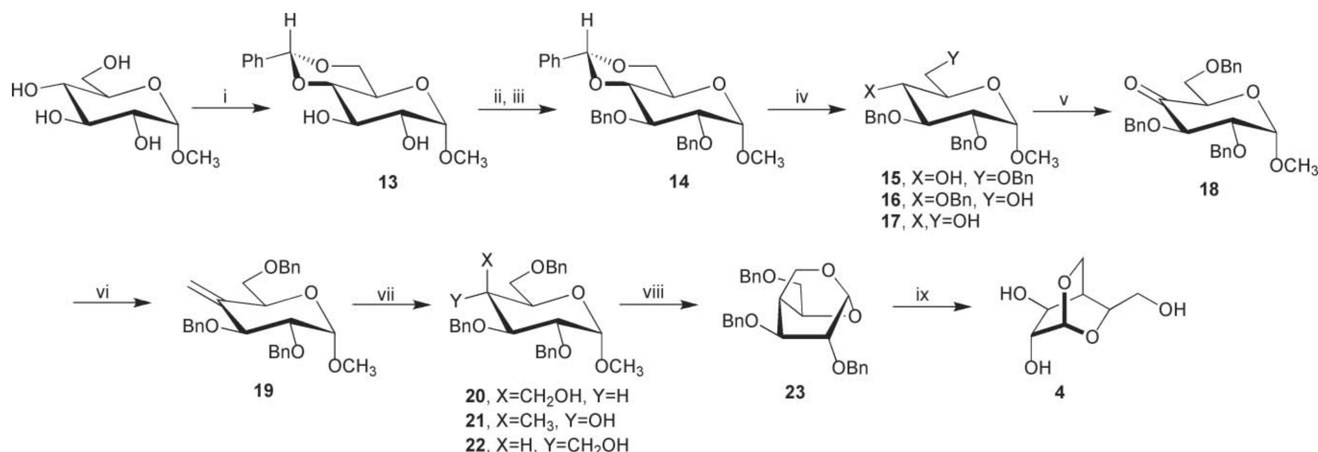
A ring expanded homologue of **2** was identified as a potential inhibitor or alternative substrate for UDP-Gal*p* mutase. The synthesis of the [2.2.2] bicyclic methylene homologue **4** utilised a similar synthetic strategy to that described for **2**. The synthesis started from the more accessible *O*-methyl α-D-glucoside rather than *O*-methyl α-D-galactoside to avoid potential complications in the benzylidene formation step (Fig. 1). Access to the required free 4-OH protected glucoside **15** was achieved *via* benzylidenation, benzyl protection and regioselective ring opening reduction (Scheme 3). Installation of the extra methylene group was achieved *via* Swern oxidation of **15** followed by Wittig olefination and hydroboration-oxidation to afford **20**. Whilst the oxidation and methylenation reactions proceeded efficiently, the hydroboration-oxidation was not highly regioselective, leading to a product distribution of **20** (35%), **21** (26%), and **22** (4%) suggesting that internal delivery of the borane on the α-face through coordination to the adjacent oxygens is occurring to preferentially form **20** over its stereoisomer **22**. According to Takahashi and co-workers, the diastereoselectivity of hydroboration-oxidation can depend on the ratio of reagents.[76] This could be examined further to improve on the low yield observed in preparation of **20**. Our data were not in agreement with the literature in ^{1}H-NMR assignments of 2-H and 6b-H in **18** and the optical rotation of **21**.[77] Based on ^{1}H-NMR analysis ($J_{2,3}$ ~ 10 Hz), the predominant pyranoside conformation of **20–22** in D_2O was assigned to be $^4C_1$. Thus our chemical modifications at C-4 of the hexoses did not change the conformational distribution of these compounds. Internal cyclisation under the same mild conditions, as described for the synthesis of **12**, gave **23** in considerable higher yield (70% *vs.* 40%). This is probably due to the increased strain which exists in the [2.2.1] oxanorbornane systems compared with the [2.2.2] bicyclic systems. Long-range coupling constants were also observed in the 1D-NMR spectra of the [2.2.2] bicyclic systems (see experimental data). Finally hydrogenolysis of **23** resulted target **4** in *ca.* 1% overall yield in 8 steps from *O*-methyl α-D-glucoside.

Enzyme activity assays

UDP-galactopyranose mutase (UDP-galactopyranose mutase, E.C. 5.4.99.9) from *Klebsiella pneumonia* was purified as described previously.[78] Compounds **2** and **4** were tested against the purified enzyme examining the reaction in the reverse direction in which UDP-Gal*f* is converted to UDP-Gal*p* using a HPLC assay according to Sanders *et al.*[79] Neither **2** nor **4** display any significant inhibition activity against the enzyme, with 15% and 17% inhibition respectively being observed with the compounds at 4 mM. Both compounds therefore had IC_{50} values > 1 mM. No evidence for **2** or **4** being utilised as alternative substrates in the presence of UDP was observed.

Conclusion

The failure of **2** and **4** to either competitively inhibit or be used as substrates for UDP-Gal*p* mutase provides further evidence that bicyclic 1,4-anhydro-β-D-galactopyranose is not an intermediate in the UDP-Gal*p* mutase catalyzed reaction,[53,54] in accord with the observations of Caravano *et al.*[54,80] and is consistent with our previous observations with the carbasugar analogue of 1,4-β-D-anhydrogalactopyranose.[53] It is well established that much of the binding affinity of enzymes for sugar-nucleotide substrates comes from the nucleoside-diphosphate portion (UDP, IC_{50} = 200 μM



Scheme 3 *Reagents and conditions*: i) Benzaldehyde dimethyl acetal, CSA, $CHCl_3$, reflux, 92%; ii) NaH, DMF, 0 °C; iii) BnBr, Bu_4NI, 84%; iv) 3 Å MS, $NaCNBH_3$, THF, HCl/diethyl ether, **15** 83%, **16** 5%, **17** 3%; v) DMSO, TFAA, DCM, Et_3N, –78 → –40 °C, 80%; vi) *n*-BuLi, Ph_3PCH_3Br, THF, –60 °C → rt, 79%; vii) BH_3·THF, THF, then H_2O_2/NaOH, **20** 35%, **21** 26%, **22** 4%; viii) **20**, $FeCl_3$, CH_3CN, reflux, 70%; ix) H_2, Pd/C (10%), EtOH, EtOAc, 70%.

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for UDP-Gal*p* mutase).[81] A comparison of the binding affinities of UDP-Gal*f* (K_m = 22 μM and 194 mM under reducing conditions),[34,45] UDP-Gal*p* (K_m = 600 μM)[38] and UDP (K_i = 37 μM)[36] for the UDP-Gal*p* mutase from *Klebsiella pneumoniae* indicates that most of the substrate binding affinity of the enzyme is directed towards the UDP portion of these molecules. Sinaÿ *et al.* reported that UDP-*C*-α-D-1,4-anhydrogalactopyranose in which the galactose moiety is locked in a bicyclic $^{1,4}B$ *boat* conformation that is attached to uridine monophosphate *via* a phosphonate was a weak competitive inhibitor (42–53% inhibition at 1 mM; 32–34% with the reduced enzyme) whilst UDP-C-α-D-galactofuranose, a non-isomerable analogue of the substrate exhibits moderately higher inhibition with the native enzyme (81–91% at 1 mM), but lower inhibition with the reduced enzyme (2–14%)[40] suggesting that the 1,4-anhydro-β-D-galactopyranose structure contributes little to the binding of the former compound. These observations strengthen the argument that UDP-Gal*p* mutase is operating by one of the proposed alternative radical/nucleophilic flavin mechanisms.[35–37,44]

Experimental

General information

NMR spectra were recorded on a Bruker AV 400 (^{1}H at 400 and ^{13}C at 100 MHz) instrument. Chemical shifts (*δ* in ppm) are given relative to internal standard (Tetramethylsilane (TMS) in $CDCl_3$) or residual solvent peak (chloroform at 7.26 ppm in $CDCl_3$ and water at 4.70 ppm in D_2O). Coupling constants (*J*) values are in Hz and are reported for couplings over three bonds unless otherwise specified. Gaussian resolution enhancement were used to determine coupling constants of complicated peaks. Assignments were made by comparison of chemical shifts, peak multiplicities, *J* values and ^{1}H-^{1}H COSY spectra. The abbreviation "app." (apparent) in ^{1}H-NMR assignments refers to the appearance of the multiplet observed in the spectrum where this differs from the expected peak shape. Hydrogen and carbons were numbered for NMR assignment use standard carbohydrate numbering. The sub-assignment of "a" and "b" in ^{1}H-NMR was based on the appearance of corresponding signals of higher and lower field, respectively. Carbon spectra were recorded with proton broadband decoupling. Assignments were verified using DEPT and ^{1}H-^{13}C HMQC experiments. The central peak of chloroform at 77.1 ppm was used as the internal reference for spectra run in $CDCl_3$. Acetone in D_2O (30.63 ppm, Me) was used as external reference for spectra run in D_2O. Mass spectra were determined using EI (VG 70E, 70 eV, ref. PFK) and ESI (Micromass LCT, ref. Erythromycin). Elemental analyses were conducted on an Exeter analytical, Inc. CE-440 Elemental Analyser. Melting points were recorded on a Stuart Scientific SMP3 digital melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded in the range of 4000–500 cm^{-1} using a Perkin Elmer 1600 series FT-IR spectrometer. Optical rotation was measured with a digital Jasco polarimeter DIP-370 in a 0.5 dm cell at ambient temperature (23 ± 1 °C) and $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. Chromatography is medium pressure flash chromatography and was performed according to the method of Still *et al.*[82] using Fluorochem silica gel (35–70 μm) with the eluent specified. Thin layer chromatography was performed on precoated aluminium–backed silica gel plates supplied by E. Merck, A. G. Darmstad, Germany (silica gel 60 F254, thickness 0.2 mm, Art. 5554). Chromatograms were initially examined under UV light and then visualised with aqueous potassium permanganate (dip), followed by warming of the TLC plate with a heat gun. All anhydrous reactions were carried out in oven-dried glassware (>180 °C), which was cooled in desiccator and was subjected to vacuum-N_2 flashing before use. Molecular sieves were activated before applications by storing in an oven (>180 °C) for 12 h. Where necessary ether and THF were refluxed and distilled from sodium-benzophenone ketyl, and DCM from calcium hydride, immediately before use. Anhydrous DMF was prepared through overnight stirring with calcium hydride, followed by distillation under reduced pressure. It was then collected over pre-activated 3 Å molecular sieves. Chloroform were distilled from P_2O_5 (3% w/v) and distillates were collected over pre-activated 4 Å molecular sieves. Dimethyl benzylacetal was dried overnight over pre-activated 4 Å molecular sieves, filtered, distilled *in vacuo* and collected over 4 Å molecular sieves. Light petroleum (pet. ether) refers to the fraction boiling in the range 40–60 °C that was redistilled before use. Methyl hexopyranosides were dried over P_2O_5. Organic extracts were dried over $MgSO_4$ before evaporation, unless otherwise specified. Evaporations were achieved using a Büchi rotary evaporator followed by drying at <1 mmHg using an Edwards rotary vacuum pump. An Edwards Freeze-dryer was used for lyophilization of samples. Except where specified all reagents were purchased from commercial sources and were used without further purification. Yields are reported for isolated, chromatographically homogenous and analytically pure products.

Details for the synthesis and analytical data of compounds **5–11** and **13–18** are given in the supporting information.†

1,4-Anhydro-2,3,6-tri-*O*-benzyl-β-D-galactopyranose 12. Methyl 2,3,6-tri-*O*-benzyl-α-D-galactopyranoside **9** (0.8 g, 1.7 mmol), and anhydrous $FeCl_3$ (94.4 mg, 0.59 mmol) were refluxed in anhydrous acetonitrile (200 ml) for 1 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by flash chromatography on a pre-neutralized (triethylamine) silica gel column (hexanes-EtOAc, 3 : 1) to give the bicyclic acetal **12** (290 mg, 40%) as a colourless oil. R_f 0.6 (hexanes-EtOAc, 3 : 1); $[\alpha]_D^{25}$ +57.4 (*c* 1.12 in $CHCl_3$), (lit.,[51,55] +57, *c* 1 in $CHCl_3$); [Found: C, 74.38; H, 6.52%; $(M+Na)^+$ 455.1843. $C_{27}H_{28}O_5$ requires C, 74.98; H, 6.53%; $(M+Na)^+$ 455.1834]; ν_{max} ($CHCl_3$)/cm^{-1} 2926 s (CH), 2867 s (OC–H), 1952w, 1874w, 1812w, 1738w (overtone, comb, Ph), 1603w, 1496w (C–C, Ar), 1454 s sharp (CH_2), 1360 s, 1084vs, 968s; δ_H ($CDCl_3$) 3.34 (1H, dd, $J_{6a,6b}$ 9.4 and $J_{6a,5}$ 8.5, 6a-H), 3.43 (1H, dd, $J_{6b,6a}$ 9.4 and $J_{6b,5}$ 5.0, 6b-H), 3.54 (1H, app. br. d, J ~ 1.2, 3-H or 4-H), 3.82 (1H, obscured dd, $J_{5,6a}$ 8.5, $J_{5,6b}$ 5.0 and $J_{5,4}$ ~ 0, 5-H), 3.83 (1H, obscured ddd, $J_{2,1}$ 2.3 and $J_{2,3}$ ~ $^4J_{2,4}$ ~ 1.4, 2-H), 4.46 and 4.58 (AB, each 1H, d, $J_{A,B}$ 11.7, CH_AH_BPh), 4.49 and 4.53 (AB, each 1H, d, $J_{A,B}$ 12.0, CH_AH_BPh), 4.50 (2H, coincident d, $J_{A,B}$ 9.1, CH_AH_BPh), 4.58_5 (1H, app. br. d, J ~ 1.4, 4-H or 3-H), 5.48 (1H, br. d, $J_{1,2}$ 2.3, 1-H), 7.28–7.34 (15H, m, 3xPh); δ_C ($CDCl_3$) 69.9 (CH_2, C-6), 71.2, 72.4, 73.6 (each CH_2, 3xCH_2Ph), 74.3 (CH, C-5), 81.4 (CH, C-4 or C-3), 82.9 (CH, C-3 or C-4), 87.3 (CH, C-2), 98.7 (CH, C-1), 127.9_4, 128.0, 128.1, 128.5, 128.8 (all CH, 3xPh), 137.4, 137.5, 137.9 (each C, 3xPh); HRMS (ESI): found $(M+Na)^+$ 455.1843. $C_{27}H_{28}O_5$ requires $(M+Na)^+$, 455.1834.

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1,4-Anhydro-β-D-galactopyranose (1,5-Anhydro-α-D-galactofuranose) 2. A suspension of 10% Pd/C (193 mg) in absolute ethanol (15 ml) was added to a stirred mixture of per-benzylated bicyclic acetal **12** (0.185 mmol, 80 mg) in glacial acetic acid (4 ml) and absolute ethanol (10 ml). The resulting mixture was stirred at room temperature under an atmosphere of hydrogen. After one hour the reaction mixture was filtered through Celite and the filtrate co-evaporated with toluene (3 × 5 ml) to give **2** in quantitative yield. R_f 0.2 (EtOAc–MeOH, 8.5 : 1.5); $[\alpha]_D^{25}$ +87 (*c* 0.85 in water), (lit.,[60] +118, *c* 0.2 in water); δ_H (D_2O) 3.40 (1H, dd, $J_{6a,6b}$ 11.9, $J_{6a,5}$ 6.0, 6a-H), 3.46 (1H, dd, $J_{6b,6a}$ 11.9 and $J_{6b,5}$ 5.3, 6b-H), 3.64 (1H, app. br. d, *J* 1.3, 4-H or 3-H), 3.70 (1H, app. br. t, *J* 5.6, 5-H), 3.82 (1H, ddd, $J_{2,1}$ 2.5, $J_{2,3}$ ~ 1.8 and $^4J_{2,4}$ 1.5, 2-H), 4.45 (1H, app. br. d, *J* ~ 1.8, 3-H or 4-H), 5.46 (1H, d, $J_{1,2}$ 2.5, 1-H); δ_C (D_2O) 61.7_5 (CH_2, C-6), 75.4 (CH, C-5), 76.5 (CH, C-4 or C-3), 81.2 (CH, C-2), 83.9 (CH, C-3 or C-4), 99.6 (CH, C-1); HRMS (ESI): found $(M+Na)^+$ 185.0435. $C_6H_{10}O_5$ requires $(M+Na)^+$, 185.0426.

Methyl 2,3,6-tri-*O*-benzyl-4-deoxy-4-*C*-(methylene)-α-D-*xylo*hexopyranoside 19

A solution of n-butyl lithium 1.6 M in hexanes (2.30 ml; 3.68 mmol) was added dropwise to a suspension of methyltriphenylphosphonium bromide (1.32 g, 3.61 mmol) in dry THF (15 ml) maintained under atmosphere of N_2 at −60 °C. After stirring for 1 h, a solution of methyl 2,3,6-tri-*O*-benzyl-α-D-*xylo*-4-hexulopyranoside **18** (1.13 g, 2.45 mmol) in dry THF (5 ml) was added dropwise. After stirring for 30 min at −50 °C, stirring was continued for 15 h at rt. The solution was poured into aqueous saturated solution of NH_4Cl (20 ml) and the resulting mixture extracted with Et_2O (3 × 20 ml). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Silica gel column chromatography, pet. ether-EtOAc (from 99 : 1 to 1 : 1), yielded **19** as colourless syrup (891 mg, 79%). R_f 0.38 (hexanes-EtOAc, 4 : 1); $[\alpha]_D^{25}$ +58.5 (*c* 1.1 in $CHCl_3$), (lit.,[77] +59.2°, *c* 1 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2907 s (CH), 2873 s (OC–H), 1951w, 1880w, 1812w, 1720w (overtone, comb, Ph), 1655w (C=C–H), 1496w (C–C, Ar), 1454 m sharp (CH_2), 1354 m, 1083vs, 1049vs; δ_H ($CDCl_3$) 3.45 (3H, s, -OCH_3), 3.50 (1 H, dd, $J_{2,3}$ 9.6 and $J_{2,1}$ 3.8, 2-H), 3.70 (1H, dd, $J_{6a,6b}$ 10.1 and $J_{6a,5}$ 6.1, 6a-H), 3.82 (1H, dd, $J_{6b,6a}$ 10.1 and $J_{6b,5}$ 4.8, 6b-H), 4.34 (1H, obscured app. br. dd, $J_{6a,5}$ 6.1, $J_{6b,5}$ 4.8 and $^4J_{5,4'a}$ ~ $^4J_{5,4'b}$ 1, 5-H), 4.36 (1H, obscured app. br. dt, $J_{2,3}$ 9.6, $^4J_{3,4'a}$ ~ $^4J_{3,4'b}$ 1, 3-H), 4.59 and 4.64 (AB, each 1H, d, $J_{A,B}$ 11.9, CH_AH_BPh), 4.69 and 4.87 (AB, each 1H, d, $J_{A,B}$ 12.1, CH_AH_BPh), 4.71 (1H, d, $J_{1,2}$ 3.8, 1-H), 4.74 and 4.82 (AB, each 1H, d, $J_{A,B}$ 11.4, CH_AH_BPh), 4.99 (1H, app. br. s, $J_{4'a,4'b}$ ~ 2 and $^4J_{4'a,5}$ ~ $^4J_{4'a,3}$ 1, 4′a-H), 5.38 (1H, ddd, $J_{4'b,4'a}$ 2 and $^4J_{4'b,5}$ ~ $^4J_{4'b,3}$ 1, 4′b-H), 7.26–7.42 (15H, m, 3xPh); δ_C ($CDCl_3$) 55.3 (-OCH_3), 67.7 (CH, C-5), 69.6 (CH_2, C-6), 73.5, 73.6, 73.9 (each CH_2, 3xCH_2Ph), 79.2 (CH, C-3), 81.5 (CH, C-2), 98.8 (CH, C-1), 107.7 (C=CH_2), 127.6, 127.7_2, 127.7_4, 128.0, 128.3_5, 128.3_8 (all CH, 3xPh), 137.9, 138.3, 138.5 (each C, 3xPh), 142.6 (*C*=CH_2); HRMS (ESI): found $(M+Na)^+$ 483.2126. $C_{29}H_{32}O_5$ requires $(M+Na)^+$ 483.2147.

Methyl 2,3,6-tri-*O*-benzyl-4-deoxy-4-*C*-(hydroxymehtyl)-α-D-galactopyranoside 20

To a solution of methyl 2,3,6-tri-*O*-benzyl-4-deoxy-4-*C*-(methylene)-α-D-*xylo*hexo-pyranoside **19** (516 mg; 1.12 mmol) in dry THF (20 ml) under N_2 at 0 °C was added dropwise BH_3·THF 1 M (1.12 ml; 1.12 mmol). The solution was stirred at rt for 14 h. After cooling to 0 °C, NaOH 2M (2.24 ml; 4.48 mmol) and 30% v/v H_2O_2 solution (0.64 ml; 5.61 mmol) were successively added dropwise. After stirring for 1 h at 0 °C, stirring was continued at rt for additional 4 h. The solution was poured into brine, dried with $MgSO_4$ and concentrated *in vacuo*. Silica gel column chromatography (pet. ether-EtOAc from 99 : 1 to 2 : 3) yielded **20** (189 mg, 35%) as a colourless oil. R_f 0.22 (EtOAc-hexanes, 2 : 3); $[\alpha]_D^{25}$ +45.2 (*c* 1.01 in $CHCl_3$), (lit.,[77] +45.5°, *c* 1.01 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3488 m br (hydrogen bonded OH), 2904 s (CH), ~2850s (OC–H), 1951w, 1882w, 1810w, ~1720w (overtone, comb, Ph), 1603w, 1496w (C–C, Ar), 1454 m sharp (CH_2), 1093vs, 1048vs; δ_H ($CDCl_3$) 2.36 (1H, dddd, $J_{3,4}$ ~ $J_{4,4a'}$ ~ $J_{4,4b'}$ 5.8 and $J_{4,5}$ 2.3, 4-H), 3.22 (1H, br. s, 4′-O*H*), 3.39 (3H, s, -OCH_3), 3.60 (1H, dd, $J_{6a,6b}$ 10.4 and $J_{6a,5}$ 5.0, 6a-H), 3.63 (1H, dd, $J_{6b,6a}$ 10.4 and $J_{6b,5}$ 5.8, 6b-H), 3.71 (1H, dd, $J_{2,3}$ 10.3 and $J_{2,1}$ 4.0, 2-H), 3.80 (1H, br. dd, $J_{4'a,4'b}$ 11.4 and $J_{4'a,4}$ 5.8, 4′a-H), 3.97 (1H, dd, $J_{4b',4a'}$ 11.4 and $J_{4b',4}$ 5.8, 4b'-H), 4.07 (1H, obscured ddd, $J_{5,6b}$ 5.8, $J_{5,6a}$ 5.0 and $J_{5,4}$ 2.3, 5-H), 4.07 (1H, obscured dd, $J_{3,2}$ 10.3 and $J_{3,4}$ 5.8, 3-H), 4.58 (2H, s, CH_AH_BPh), 4.66 (1H, d, $J_{1,2}$ 4.0, 1-H), 4.67 and 4.83 (AB, each 1H, d, $J_{A,B}$ 12.1, CH_AH_BPh), 4.72 and 4.78 (AB, each 1H, d, $J_{A,B}$ 11.6, CH_AH_BPh), 7.28–7.39 (15H, m, 3xPh); δ_C ($CDCl_3$) 43.6 (CH, C-4), 55.2 (CH_3, -OCH3), 57.9 (CH_2, C-4′), 67.9 (CH, C-5), 70.5 (CH_2, C-6), 73.1, 73.4, 73.7 (each CH_2, 3xCH_2Ph), 76.6 (CH, C-2), 78.6 (CH, C-3), 98.7 (CH, C-1), 127.6_7, 127.7_3, 127.8, 127.9, 128.0, 128.3_6, 128.4_1, 128.5 (all CH, 3xPh), 137.4, 138.2, 138.3 (each C, 3xPh); HRMS (ESI): found $(M+Na)^+$ 501.2227. $C_{29}H_{34}O_6$ requires $(M+Na)^+$ 501.2253.

Methyl 2,3,6-tri-*O*-benzyl-4-*C*-(methyl)-α-D-glucopyranoside 21. Compound **21** was a by-product in the synthesis of **20**, It was separated by silica column chromatography (EtOAc-hexanes, 2 : 3) as colourless oil (139 mg, 26%). R_f 0.38 (hexanes-EtOAc, 3 : 2); $[\alpha]_D^{25}$ +12.6 (*c* 1.08 in $CHCl_3$), (lit.,[77] +103.2, *c* 1 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3518 m br (hydrogen bonded OH in 6-membered ring), 2911 s (CH), 2875 s (OC–H), 1951w, 1877w, 1810w, 1723w (overtone, comb, Ph), 1604w, 1496w (C–C, Ar), 1454 m sharp (CH_2), 1367 m, 1122 s, 1074vs; δ_H ($CDCl_3$) 1.18 (3H, s, 4-CH_3), 2.52 (1H, br. s, 4-O*H*), 3.41 (3H, br. s, -OCH_3), 3.42 (1H, obscured dd, $J_{2,3}$ 10.1 and $J_{2,1}$ 4.0, 2-H), 3.57 (1H, dd, $J_{6a,6b}$ 9.8 and $J_{6a,5}$ 7.0, 6a-H), 3.73 (1H, dd, $J_{6b,6a}$ 9.8, $J_{6b,5}$ 5.0, 6b-H), 3.81 (1H, d, $J_{2,3}$ 10.1, 3-H), 3.90 (1H, dd, $J_{5,6a}$ 7.0 and $J_{5,6b}$ 5.0, 5-H), 4.53 and 4.59 (AB, each 1H, d, $J_{A,B}$ 11.9, CH_AH_BPh), 4.60 (1H, d, $J_{1,2}$ 4.0, 1-H), 4.63 and 4.79 (AB, each 1H, d, $J_{A,B}$ 12.1, CH_AH_BPh), 4.80 and 4.96 (AB, 1H each, d, $J_{A,B}$ 11.6, CH_AH_BPh), 7.27–7.39 (15H, m, 3xPh); δ_C ($CDCl_3$) 15.8 (CH_3, *C*-4′), 55.1 (CH_3, -OCH_3), 68.9 (CH_2, C-6), 70.8 (CH, C-5), 73.3, 73.5, 75.7 (all CH_2, 3xCH_2Ph), 74.2 (C, C-4), 78.5 (CH, C-2), 83.4 (CH, C-3), 98.0 (CH, C-1), 127.6, 127.7, 127.7_5, 127.8_1, 128.0, 128.3_9, 128.4_2 (all CH, Ph), 137.8, 138.2, 139.1 (all C, Ph); HRMS (ESI): found $(M\cdot+Na)^+$ 501.2247. $C_{29}H_{34}O_6$ requires $(M\cdot+Na)^+$ 501.2253.

Methyl 2,3,6-tri-*O*-benzyl-4-deoxy-4-*C*-(hydroxymehtyl)-α-D-glucopyranoside 22. Compound **22** was a by-product in the synthesis of **20**, It was separated by silica column chromatography (EtOAc-hexanes, 2 : 3) as colourless oil (22.8 mg, 4%). R_f 0.14 (hexanes-EtOAc, 3 : 2); δ_H ($CDCl_3$) 1.70 (1H, dd, $J_{4'\text{-}OH,4'a}$ ~ $J_{4'\text{-}OH,4'b}$ 6.3, 4′-O*H*), 1.87 (1H, dddd, $J_{4,3}$ ~ $J_{4,5}$ 10.6 and $J_{4,4'a}$ ~ $J_{4,4'b}$ 3.5,

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4-H), 3.38 (3H, s, -OCH_3), 3.52-3.61 (1H, obscured m, 4′a-H), 3.61 (1H, obscured dd, $J_{2,3}$ 9.3 and $J_{2,1}$ 3.5, 2-H), 3.64 (2H, coincident d, J 3.5, 6a-H and 6b-H), 3.70 (1H, ddd, $J_{4'b,4'a}$ 11.9, $J_{4'b,4'-OH}$ 6.3 and $J_{4'b,4}$ 3.5, 4′b-H), 3.84 (1H, ddd, $J_{5,4}$ 10.6, $J_{5,6a} \sim J_{5,6b}$ 3.5, 5-H), 3.91 (1H, dd, $J_{3,4}$ 10.6 and $J_{3,2}$ 9.3, 3-H), 4.49 and 4.63 (AB, each 1H, d, $J_{A,B}$ 11.9, CH_AH$_B$Ph), 4.68 and 4.79 (AB, 1H each, d, $J_{A,B}$ 11.9, CH_AH$_B$Ph), 4.68 (1H, obscured d, $J_{1,2}$ 3.5, 1-H), 4.69 and 5.01 (AB, each 1H, d, $J_{A,B}$ 11.4, CH_AH$_B$Ph), 7.30–7.38 (15H, m, 3xPh); δ_C ($CDCl_3$) 46.0 (CH, C-4), 55.2 (-OCH$_3$), 59.5 (CH_2, C-4′), 68.2 (CH, C-5), 70.5 (CH_2, C-6), 72.9, 73.5, 75.2 (all CH_2, 3xCH_2Ph), 75.4 (CH, C-3), 81.5 (CH, C-2), 98.4 (CH, C-1), 127.8, 127.9, 128.1, 128.3$_9$, 128.4$_3$, 128.4$_6$, 128.6 (all CH, 3xPh), 137.7, 138.2, 138.5 (each C, 3xPh); HRMS (ESI): found $(M+Na)^+$ 501.2235. $C_{29}H_{34}O_6Na$ requires $(M+Na)^+$ 501.2253.

(1*R*,3*S*,4*S*,7*R*,8*S*)-7,8-*di*-Benzyloxy-3-(benzyloxymethyl)-2,6-dioxa-bicyclo[2.2.2]octane 23. Compound **20** (137 mg; 0.29 mmol) and anhydrous $FeCl_3$ (15.5 mg; 93.6 mmol) were dissolved in dry CH_3CN (35 ml). The suspension was heated to reflux for 30 min, after which time TLC indicated that the reaction had gone to completion. The reaction mixture was diluted with DCM (40 ml) and filtered through a short pad of Kieselgur to remove the catalyst. Concentration *in vacuo* and pre-neutralized (TEA) silica gel column chromatography eluting with hexanes-EtOAc (from 9 : 1 to 1 : 1), yielded **23** (90 mg, 70%) as a yellow oil. R_f 0.55 (EtOAc-hexanes, 2 : 3); $[\alpha]_D^{25}$ +42.4 (*c* 0.51 in $CHCl_3$); [found: C, 75.1%; H, 6.6%; $(M+Na)^+$ 469.1954. $C_{28}H_{30}O_5$ requires C, 75.3%; H, 6.8%; $(M+Na)^+$ 469.1991]; ν_{max} ($CHCl_3$)/cm^{-1} 2899 s (CH), ~2850s (OC–H), 1949w, 1882w, 1826w, 1730w (overtone, comb, Ph), 1605w, 1492w (C–C, Ar), 1454 m sharp (CH_2), 1365 m, 1100vs; δ_H ($CDCl_3$) 2.29 (1H, app. very br. s, 4-H), 3.69 (1H, dd, $J_{6a,6b}$ 9.6 and $J_{6a,5}$ 8.3, 6a-H), 3.75 (1H, dd, $J_{6b,6a}$ 9.6 and $J_{6b,5}$ 5.6, 6b-H), 3.78 (1H, ddd, $J_{2,1} \sim J_{2,3}$ 2.3 and $J_{2,4}$ 1.0, 2-H), 3.80 (1H, ddd, $J_{3,4'a}$ 1.8 and $J_{3,2} \sim J_{3,4}$ 1.0, 3-H), 3.94 (1H, ddd, $J_{4'a,4'b}$ 9.1 and $J_{4'a,4} \sim {}^4J_{4'a,3}$ 1.8, 4′a-H), 4.06 (1H, ddd, $J_{4'b,4'a}$ 9.1 and $J_{4'b,4} \sim {}^4J_{4'b,5}$ 1.8, 4′b-H), 4.12 (1H, dddd, $J_{5,6a}$ 8.3, $J_{5,6b}$ 5.6 and ${}^4J_{5,4'b} \sim J_{5,4}$ 1.8, 5-H), 4.51 and 4.65 (AB, each 1H, d, $J_{A,B}$ 11.6, CH_AH$_B$Ph), 4.55 and 4.62 (AB, each 1H, d, $J_{A,B}$ 12.1, CH_AH$_B$Ph), 4.57 and 4.58 (AB, each 1H, $J_{A,B}$ 11.9, CH_AH$_B$Ph), 4.94 (1H, d, $J_{1,2}$ 2.3, 1-H), 7.29–7.37 (15H, m, 3xPh); δ_C ($CDCl_3$) 31.9 (CH, C-4), 57.8 (CH_2, C-4′), 69.6 (CH_2, C-6), 70.6, 71.1 73.5 (all CH_2, 3xCH_2Ph), 72.0 (CH, C-5), 80.3 (CH, C-3), 81.1 (CH, C-2), 90.8 (CH, C-1), 127.7, 127.8, 127.85, 127.9, 128.0, 128.5 (all CH, 3xPh), 137.6, 137.79, 137.83 (each C, 3xPh).

(1*R*,3*S*,4*R*,7*R*,8*S*)-3-Hydroxymethyl-2,6-dioxa-bicyclo-[2.2.2]-octane-7,8-diol 4. A suspension of (1*R*,3*S*,4*S*,7*R*,8*S*)-7,8-*bis*-benzyloxy-3-benzyloxymethyl-2,6-dioxa-bicyclo-[2.2.2]octane **23** (63.3 mg; 0.15 mmol) and 10% Pd/C (161 mg) in absolute EtOH (20 ml) and glacial AcOH (3.3 ml) was stirred under atmosphere of H_2 for 3 h. The suspension was filtered through Kieselgur and co-evaporated three times with toluene. The syrup obtained was purified by pre-neutralized (TEA) silica gel flash column chromatography eluting with EtOAc–MeOH, 9 : 1, yielding **4** as a white solid (18.3 mg, 70%). R_f 0.25 (EtOAc–MeOH, 21 : 4); mp 133–134 °C (crystallised from H_2O); $[\alpha]_D^{25}$ +64.5 (*c* 0.78 in H_2O); δ_H (D_2O) 2.02 (1H, app. br. d, J 1.5, 4-H), 3.64 (1H, dd, $J_{6a,6b}$ 11.6 and $J_{6a,5}$ 5.8, 6a-H), 3.73 (1H, ddd, $J_{2,1} \sim J_{2,3}$ 2.3 and ${}^4J_{2,4}$ 1.0, 2-H), 3.77 (1H, dd, $J_{6b,6a}$ 11.6 and $J_{6b,5}$ 7.3, 6b-H), 3.86–3.93 (4H, obscured m, 3-H, 5-H, 4′a-H and 4′b-H), 4.73 (1H, d, $J_{1,2}$ 2.3, 1-H); δ_C (D_2O) 34.0 (CH, C-4), 57.3 (CH_2, C-4′), 62.1 (CH_2, C-6), 74.0$_7$ (CH, C-5 or C-3), 74.1$_3$ (CH, C-3 or C-5), 75.1 (CH, C-2), 92.4 (CH, C-1); HRMS (ESI): found $(M+Na)^+$ 199.0592, $C_7H_{12}O_5$ requires $(M+Na)^+$ 199.0582.

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