Title	Anomer preferences for glucuronic and galacturonic acid and derivatives and influence of electron-withdrawing substituents
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Publication Date	2018-07-04
Publication Information	Kerins, Louise, Byrne, Sylvester, Gabba, Adele, & Murphy, Paul V. (2018). Anomer Preferences for Glucuronic and Galacturonic Acid and Derivatives and Influence of Electron-Withdrawing Substituents. The Journal of Organic Chemistry, 83(15), 7714-7729. doi: 10.1021/acs.joc.8b0061
Publisher	American Chemical Society
Link to publisher's version	https://dx.doi.org/10.1021/acs.joc.8b00610
Item record	http://hdl.handle.net/10379/15177
DOI	http://dx.doi.org/10.1021/acs.joc.8b00610

Anomer Preferences for Glucuronic and Galacturonic Acid and Derivatives and Influence of Electron Withdrawing Substituents

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Abstract

Equilibrium anomeric ratios are reported for pyranoses (hemiacetals) of glucuronic and galacturonic acid and their derivatives. These are compared to related gluco- and galactopyranoses and to deoxyfluorogluco- and deoxyfluorogalactopyranoses. An association between axial anomer stability and the sum of 1H-NMR downfield chemical shifts for protons H-3 and H-5 was observed in D_2O with gluco- and galactopyranoses as reference compounds. When compared to 2-hydroxytetrahydropyran in water, the introduction of three OAc substituents and one carboxylic acid substituent leads to an increase in stability of the axial anomer by 0.89-1.05 kcal/mol. This is interpreted as the electron withdrawing substituents, causing a reduction in the steric (gauche) interaction, and an increase in Coulombic interaction, between CH groups of the pyranose and the anomeric substituent through their deshielding effects. Also, anomer preferences for galacturonic acid and its derivatives were more sensitive to solvent polarity compared to other pyranoses and this may be linked to electrostatic potential and reduced stabilisation of equatorial anomeric OH group due to reduced hydrogen bonding. The latter is more notable in non-polar chloroform. Analysis of crystal structures combined with molecular dynamics indicated there are conformational distinctions between galacturonic acid and glucuronic acid that could influence properties.

1

Graphical Abstract
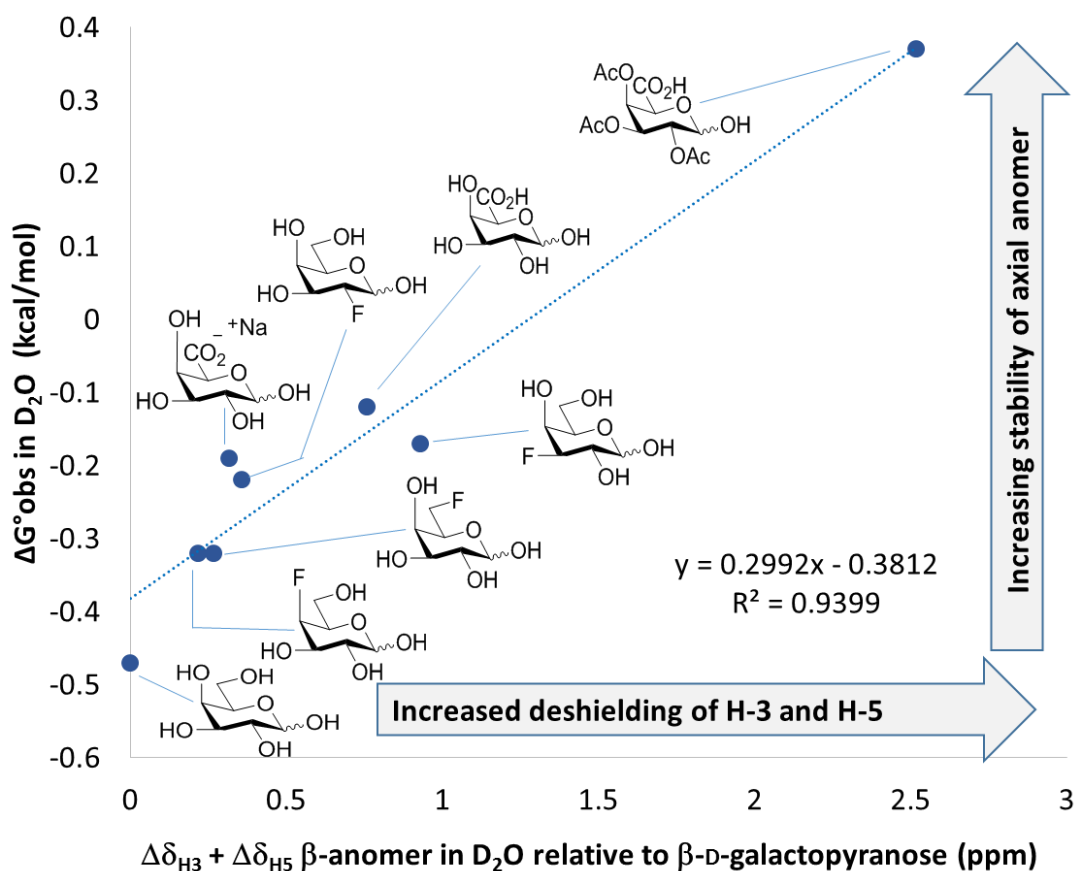
1. Introduction

Chemical reactivity at the anomeric centre is influenced by factors such as the protecting groups used on saccharide hydroxyl groups,[1] the stereochemical configuration of a substituent on a saccharide ring and conformational preferences of the ring and its substituents. Reactions influenced by some or all of these elements include glycosylation due to the varying reactivity of donors,[2] glycoside hydrolysis[3] and anomerisation.[4,5]

The endo-anomeric effect[6] was originally identified from the increased preference for electronegative substituents at the anomeric position to adopt an axial orientation in a pyranose,[7] when compared to that in cyclohexanol. The increased preference for the axial

orientation of electron withdrawing substituents at the anomeric carbon is most often explained in terms of the interaction between ring oxygen atom and the axial anomeric substituent, whether it be hyperconjugation,[8] or the minimisation of electronic repulsion (electrostatic model).[9] Aside from this, the anomeric substituent, when axial, needs to overcome steric (or 1,3-diaxial or gauche) repulsive interactions of the type encountered by an axial substituent in cyclohexane. There has been research on the relative importance of hyperconjugation and electrostatic repulsion to the endo-anomeric effect, with Perrin and co-workers, for example, arguing that electrostatic interactions are more important, at least in non-polar solvents.[10]

Solvent has an influence and its role on anomeric preference has been rationalised based on how it influences the intramolecular repulsive interactions between the pyranose oxygen and the equatorial anomeric substituent, with these being reduced as solvent polarity increases leading to a higher preference for the equatorial anomer.[9, 11] Alternatively, the increased preference for the equatorial anomer in water, can according to Schmidt, Karplus and Brady, be a contribution from a greater degree of hydrogen (or deuterium) bonding to aqueous solvent from the β-anomer, compared to the α-anomer, when there is an anomeric OH (or OD) group present.[12] In this model hydrogen bonding is increased, due to the larger surface area accessible to water molecules, when the anomeric OH is equatorial. The Schmidt et al analysis has greater relevance for the anomeric OH group rather than those at C-2, 3 and 4, with these non-anomeric positions having similar degrees of hydrogen bonding in both anomers. Lemieux and co-workers earlier argued that hydrogen bonding in water to an equatorial anomeric OH group would increase the strength of the exo-anomeric effect increasing the stability of the equatorial anomer compared to the axial anomer.[13] Computational work by Mo and co-workers indicated that the solute−solvent interactions significantly reduce steric interactions in β-anomers, where steric interactions are defined as the sum of repulsive and electrostatic interactions.[14]

Aside from the endo- and exo-anomeric effects, hydrogen bonding and influence of solvent, Lemieux noted that an increase in electronegativity of the equatorial substituent at C-5 in glucopyranosides contributed to an increased preference for the axial anomer.[7] This was explained by reduced repulsion between the electronegative anomeric substituent and an increasingly electropositive CH at C-5. In the case of allopyranose, the axial electron withdrawing OH substituent at C-3 has a stronger repulsive 1,3-diaxial interaction than that of a hydrogen atom with the axial anomeric substituent, whereas for mannopyranose the axial substituent at C-2 is proposed to destabilise the equatorially oriented anomeric substituent through a repulsive gauche interaction, which is often referred to as the $\Delta 2$ effect.[15] Thus attractive or repulsive interactions within the ring also influence the anomeric ratio at equilibrium and not just interaction between the ring oxygen and anomeric substituent.

Other explanations for the increase in preference for the axial anomer have been put forward including molecular compactness[16] and hydrogen bonding between the axial anomeric substituent and CH groups within the ring.[17]

Previous studies from within our own research group have established that the presence of a carboxylic acid or its derivative (ester, amide) at the C-5 of a pyranoside, such as found in uronic acids, leads to an increase in the rate of $TiCl_4$ or $SnCl_4$ induced anomerization reactions (Scheme 1).[18] Such reactions can also show high preferences in favour of the axial or α-anomer.[19,20] The final anomeric ratio in these reactions, which is assumed to be an equilibrium between axial and equatorial β anomers, can, at least in some cases, be higher for galacturonic acids when compared to analogous glucuronic acid derivatives, with both often being higher than galactopyranoses and glucopyranoses. The anomer ratio, in the presence of the $TiCl_4$ or $SnCl_4$ in a solvent of relatively low polarity such as CH_2Cl_2 or $CHCl_3$ can be altered depending on the Lewis acid and also the concentration of the Lewis acid promoter.[5] It has not been clear whether there exists an intrinsically higher preference in glucopyranuronic and

galactopyranuronic acids for the axial anomer compared to analogous glucopyranose and galactopyranoses.

Here we report the results of a study of anomer equilibrium preferences in uronic acids in the absence of Lewis acids, and show that the presence of the electron withdrawing C-6 carbonyl group gives rise to an increased preference for the axial anomer indicating there is an intrinsically increased preference for the axial anomer. The preferences were found to be increased by enhancing the electron withdrawing nature of the substituents at C-2 to C-4 in the glucuronic acids and galacturonic acids. All deoxyfluoroglucopyranoses and deoxyfluorogalactopyranoses also show a higher preference for the axial anomer than the corresponding parent pyranose in water. Increasing the electron withdrawing nature of substituents is believed to lead to deshielding and to a reduction in 1,3-diaxial repulsion or increased intramolecular electrostatic attraction and, consequently, an increase in preference for the axial anomer. As well, the anomeric preference for galacturonic acid and derivatives showed greater sensitivity to solvent polarity than related glucuronic acid derivatives and glucopyranoses/galactopyranoses.
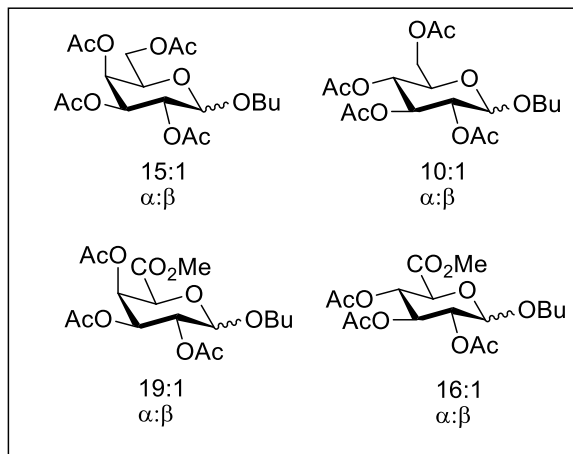
Scheme 1. Lewis acid promoted anomerization of uronic acid derivatives. The ratio of anomers obtained in SnCl$_4$ (0.5 eq) promoted anomerisation in CH$_2$Cl$_2$ for selected glycosides are given.

2.   Results and Discussion

2.1   Synthesis and anomer preferences

One approach to determining the relative preferences for equatorial or axial anomers, is to determine the anomeric ratios at equilibrium for saccharide hemiacetals, such as described by Crich and co-workers in their study on mannopyranoses.[21]   The hemiacetals, unlike their glycosidic counterparts, can attain equilibrium in solvents without requiring the addition of Lewis acids.   Accordingly, hemiacetals of glucopyranose, galactopyranose, glucuronic acid and galacturonic acid and their derivatives **1-29** (Table 1) were prepared or were purchased from commercial sources and the anomeric ratios determined by quantitative NMR (qNMR). The deoxyfluorosugars **22-29**, which are soluble in water, were included in the analysis to provide insight as to how enhancing the electron withdrawing nature of substituents on the pyranose ring would influence anomeric preference.

Compounds **1-4**, **6-9** and **11-13** were prepared by previously described routes, whereas the diol **5**, allyl ester **10** and acids **14-17** were prepared as shown in Scheme 2. Hence the synthesis of

5 was carried out from **30**[22] by firstly removing the anomeric benzoate protecting group using hydrazine acetate and subsequent cleavage of the TBS group with TBAF. The allyl ester **10** was prepared from known galactopyranosiduronic acid **31**[15e] by esterification, and then preparation of the glycosyl bromide and subsequent hydrolysis of this bromide. The uronic acids **14**-**16** were synthesized by selective hydrolysis of the methyl ester from **8, 9** and **12** using LiI in anhydrous ethyl acetate in the presence of molecular sieves; the use of anhydrous conditions in this reaction were very important, as otherwise competing hydrolysis of acetyl groups did occur and led to complex mixtures. The preparation of these compounds from allyl ester precursors were also explored using Pd(0) catalysis in the presence of pyrrolidine, but gave the products in lower purity, assessed qualitatively by ^{1}H-NMR spectroscopy, than those obtained via use of LiI. The use of LiI with **13** was not very successful however, giving **17** in low purity.
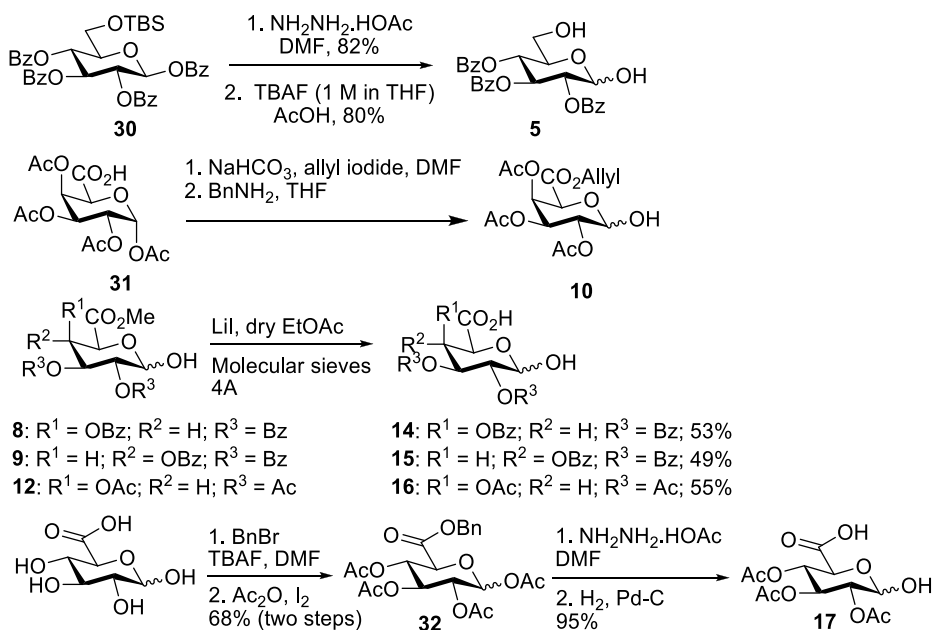
Scheme 2: Synthesis of **5, 10** and **14-17**

However, benzylation of glucuronic acid (Scheme 2) followed by acetylation of the resulting ester gave **32**.[23] The anomeric *O*-acetate group was then selectively hydrolysed using

hydrazine acetate in DMF to generate a hemiacetal. Subsequent hydrogenolysis gave **17** with improved purity as evidenced qualitatively by ^{1}H-NMR spectroscopy.

With the various compounds **1-29** in hand, and depending on their solubility, they were allowed to attain equilibrium in $CDCl_3$ and/or CD_3OD and/or D_2O at 25 ºC.[24] Typically, the solute (64 µmol) was dissolved in solvent (0.75 mL) and the anomeric ratio was established by qNMR, which involved the integration of clearly resolved signals in the relevant ^{1}H-NMR spectrum. The reaction was deemed to have attained equilibrium when no further change in anomeric ratio was observed after monitoring for a sufficient time period. Typically, the time taken to attain equilibrium was 1 day or less but samples were typically left to equilibrate for 3-4 days. The equilibrium ratios for **20** and **21** determined herein using qNMR were in agreement with those reported previously[25] and those for deoxyfluoroglucopyranoses **22-25** were found in good agreement with those reported by Phillips and Wray.[26] The equilibrium data for 2- and 3-deoxyfluorogalactopyranoses **26-27** were in good agreement with those reported by Barlow and Blanchard.[27] Those measured for 4-deoxy-4-fluoro-D-galactopyranose **28**[28] and 6-deoxy-6-fluoro-D-galactopyranose **29**[29] are in agreement with those published previously; it is not clear if qNMR was used in the earlier work. The observed ΔG° (ΔG°$_{obs}$) values were then calculated from K_{eq} where K_{eq} = [β]/[α], and these values are given in Table 1.

Table 1: Relative proportions of α and β anomers at equilibrium in solvents

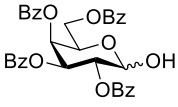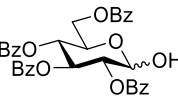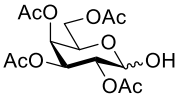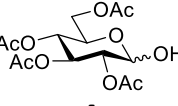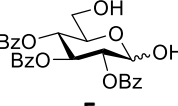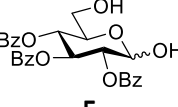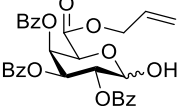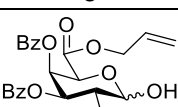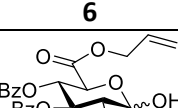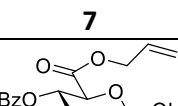| Hemiacetal	Solvent	%α	%β	ΔG°_{obs} (kcal/mol) ($\alpha \rightarrow \beta$)
1	CDCl$_3$	68	32	0.45
2	CDCl$_3$	69	31	0.47
3	CDCl$_3$	71	29	0.53
4	CDCl$_3$	70	30	0.50
5	CDCl$_3$	70	30	0.50
5	CD$_3$OD	71	29	0.53
6	CDCl$_3$	85	15	1.03
6	CD$_3$OD	72	28	0.56
7	CDCl$_3$	80	20	0.82
7	CD$_3$OD	76	24	0.68

Table 1: (contd)
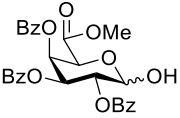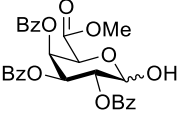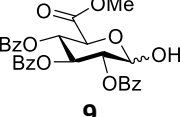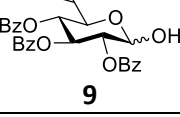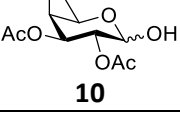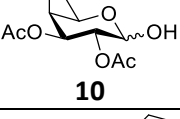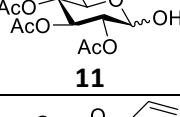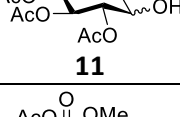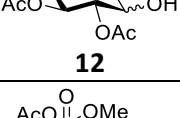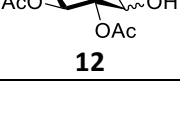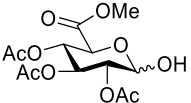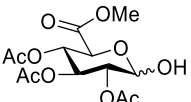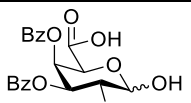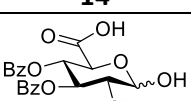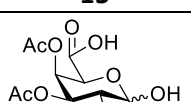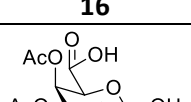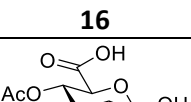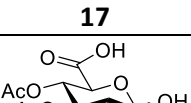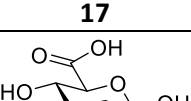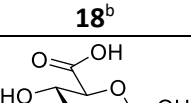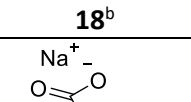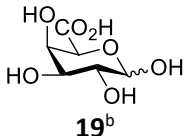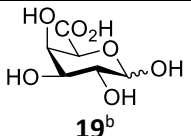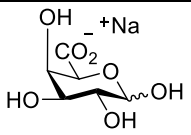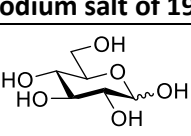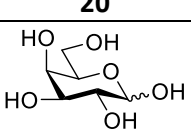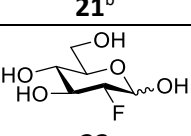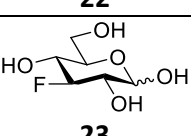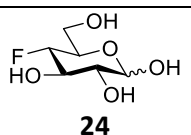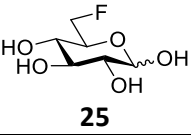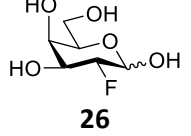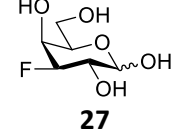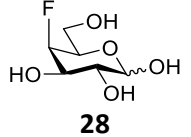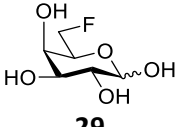
BzO–OMe, BzO, OBz **8**	CDCl₃	84	16	0.98
BzO–OMe, BzO, OBz **8**	CD₃OD	74	26	0.62
OMe, BzO, BzO, OBz **9**	CDCl₃	79	21	0.78
OMe, BzO, BzO, OBz **9**	CD₃OD[a]	78	22	0.75
AcO–O, AcO, OAc **10**	CDCl₃	86	14	1.08
AcO–O, AcO, OAc **10**	CD₃OD	74	26	0.62
O, AcO, AcO, AcO **11**	CDCl₃	77	23	0.72
O, AcO, AcO, AcO **11**	CD₃OD	76	24	0.68
AcO–OMe, AcO, OAc **12**	CDCl₃	84	16	0.98
AcO–OMe, AcO, OAc **12**	CD₃OD	73	27	0.59

Table 1 (contd.)

Structure	Solvent			
13 (MeO₂C, AcO, AcO, OAc, OH)	CDCl$_3$	76	24	0.68
13 (MeO₂C, AcO, AcO, OAc, OH)	CD$_3$OD	75	25	0.65
14 (BzO, BzO, BzO, OBz, OH)	CD$_3$OD	73	27	0.59
15 (BzO, BzO, OBz, OH)	CD$_3$OD	77	23	0.72
16 (AcO, AcO, OAc, OH)	CD$_3$OD	69	31	0.47
16 (AcO, AcO, OAc, OH)	D$_2$O	65	35	0.37
17 (AcO, AcO, OAc, OH)	CD$_3$OD	73	27	0.59
17 (AcO, AcO, OAc, OH)	D$_2$O	71	29	0.53
18[b] (HO, HO, OH, OH)	D$_2$O	44	56	-0.14
18[b] (HO, HO, OH, OH)	CD$_3$OD	59	41	0.22
Sodium salt of 18[c] (Na⁺, HO, HO, OH, OH)	D$_2$O	41	59	-0.22

Compound	Solvent			
19[b]	CD$_3$OD	65	35	0.37
19[b]	D$_2$O	45	55	-0.12
Sodium salt of **19**[c]	D$_2$O	40	60	-0.24
20	D$_2$O	35	65	-0.37
21[b]	D$_2$O	31	69	-0.47
22	D$_2$O	45	55	-0.12
23	D$_2$O	48	52	-0.05
24	D$_2$O	44	56	-0.14
25	D$_2$O	43	57	-0.17
26	D$_2$O	42	58	-0.19
27	D$_2$O	43	57	-0.17
28	D$_2$O	37	63	-0.32

| | D$_2$O | 37 | 63 | -0.32 |

29

[a] Compound **8** was not fully soluble at 64 μmol in CD$_3$OD. [b]The ^{1}H-NMR spectrum showed evidence for presence of what are furanoses (galactofuranose ~6%; glucofuranuronic acid ~7%; galactofuranuronic acid ~11%) and other substances. [c]The salt was generated by addition of varying amounts of NaHCO$_3$ (1.5-9 equiv) to an aqueous solution of **18**. The water was removed and the residue redissolved in D$_2$O to obtain the ^{1}H-NMR spectrum. The ratio of anomers did not change on addition of amounts higher than 1.5 equiv of NaHCO$_3$.

2.2   Influence of electron withdrawing substituents on anomeric preference

The uronic acids and their derivatives had enhanced preferences for their axial anomers over their equatorial anomers compared to the corresponding pyranoses in CDCl$_3$ (*cf* **6**, **8** *vs* **1**; **7**, **9** *vs* **2**; **10**, **12** *vs* **3** and **11**, **13** *vs* **4**). Comparing equilibrium ratios for the glucuronic acid derivative **15** with the corresponding glucopyranose **5** in CD$_3$OD showed that the C-6 carbonyl group in **15** led to a higher proportion of α-anomer (α:β = 77:23 *vs* 71:29) corresponding to a ΔΔG° = 0.19 kcal/mol. The increase in stabilisation of the axial anomer on introducing the carbonyl group was also observed for the unprotected carbohydrates in D$_2$O as seen by comparing **18** with **20** (ΔΔG° = 0.23 kcal/mol) and **19** with **21** (ΔΔG° = 0.35 kcal/mol). Increasing the electron withdrawing nature of substituents at other ring positions led to an increase in the proportion of the α-anomer in water (D$_2$O). This was evident when comparing D-glucuronic acid **18** with 2,3,4-tri-O-acetyl-D-glucuronic acid **17** in D$_2$O, where an increased preference for the α-anomer with a ΔΔG° = 0.67 kcal/mol was observed. An increased stabilisation of the α-anomer for 2,3,4-tri-O-acetyl-D-galacturonic acid **16** was also observed (ΔΔG° = 0.49 kcal/mol). The exchange of OH groups for the more electronegative fluorine on the pyranoses at all positions led in all cases to an increase in stabilisation of α-anomers, consistent with these observations.[30]

When considering the endo-anomeric effect alone, increasing the electron withdrawing nature of substituents would be expected to reduce electron density at the pyranose ring oxygen,

an effect that operates through sigma bonds, compared to the unprotected sugars and this would reduce interactions between pyranose ring oxygen atom and α-anomeric OH and increase β-anomer stability. Yet, α-anomer stability has consistently increased on incorporation of increasingly electron withdrawing groups.

It is unclear how acetylation changes the overall solute-solvent structure. It will change how water molecules interact with the saccharide and hydrogen bonding will be altered. However, there is still greater likelihood of more hydrogen bonds from water molecules to equatorial anomeric OH than the axial anomeric OH even for the acetylated compounds.

Bols and co-workers have found that the presence of acyl groups significantly increases acidity in polyhydroxylated protonated piperidines.[31] Their presence is consistent with reductions in reactivity in glycoside bond forming reactions,[32] although this depends on the location of the acyl group.[33]

Furthermore, glucuronic acid donors have relatively low reactivity in glycoside bond forming reactions and this has been rationalised as being due to the electron withdrawing power of the carboxyl group, which is a reasonable conclusion based on Hammett σ_m and σ_p values[34] for CO_2H of 0.37 and 0.45 respectively. The downfield chemical shifts, observed in ^{1}H-NMR spectra, for the H-5 signals of the anomers of both glucopyranuronic acid ($\Delta\delta_{H5}\alpha = 0.44$ ppm; $\Delta\delta_{H5}\beta = 0.55$ ppm) and galactopyranuronic acid ($\Delta\delta_{H5}\alpha = 0.64$ ppm; $\Delta\delta_{H5}\beta = 0.71$ ppm), when compared to the H-5 signals of glucopyranose and galactopyranose, are also consistent with the increased electron withdrawing nature of the carboxylic acid group. The respective Hammett σ_m and σ_p values for CO_2^- (-0.12 and 0) are lower than for CO_2H; the salts of both **18** and **19** showed a reduced preference for the α-anomer, which is consistent with a less electron withdrawing carboxylate ion. This is also reflected in the chemical shifts of H-5 for the salts, where there is an upfield shift ($\Delta\delta_{H5} = 0.26\text{-}0.35$ ppm) when compared to the free acids. There is a small increase in stabilisation ($\Delta\Delta G° = 0.10$ kcal/mol) of the α-anomers for

the salts relative to glucopyranose and galactopyranose (σ_m and σ_p values for CH_2OH = 0).[36]

Thus, while the Hammett σ_m and σ_p value are indicators of electron withdrawing ability, there is not a direct correlation between the Hammett σ_m and σ_p values in this case. Although this could be due to conformational factors discussed below.

The relationship between anomeric preference (ΔG°_{obs}) and the influence of the electron withdrawing groups on proton chemical shifts in the ^{1}H-NMR spectra was further examined for pyranoses for compounds **16-29**, which are soluble in soluble in D_2O. Downfield shifts ($\delta\Delta$ values) were observed when increasingly electronegative substituents (e.g. F versus OH) are attached to the same carbon or to the adjacent carbon. When fluorine was exchanged for an OH group, the downfield shifts for the proton attached to the same carbon atom were larger ($\delta\Delta$ = 0.75-0.96 ppm) than the shift for the proton attached to the adjacent carbon atoms (0.08-0.31 ppm). There was relatively lower influence on the chemical shifts of hydrogen atoms located further away from the fluorine (see **Tables S1-S4** in the supporting information for chemical shift assignments).

The ΔG_{obs} values for **16-29** in D_2O were plotted (Figure 1) against the sum of the downfield shifts for H-3 and H-5 ($\delta\Delta_{H-3} + \delta\Delta_{H-5}$) using the data for both anomers, with D-glucopyranose and D-galactopyranose as reference compounds (Figure 1). Trendlines were added to the various scatter plots generated and these had slopes of ~0.3 kcalmol^{-1}ppm^{-1} and the coefficients of determination (R^2) were >0.93. The $\delta\Delta$ values for H-3 and H-5 were chosen as increased deshielding of these protons would be associated with reduced electron density in the CH bonds at C-3 and C-5 and thus reduced repulsion with the axial anomeric OH group. The correspondence observed (Figure 1) between $\Delta\delta_{H3} + \Delta\delta_{H5}$ and ΔG°_{obs} demonstrates clearly that enhancing electron withdrawing properties of substituents on the pyranoses lead to an enhancement in the axial anomeric preference.
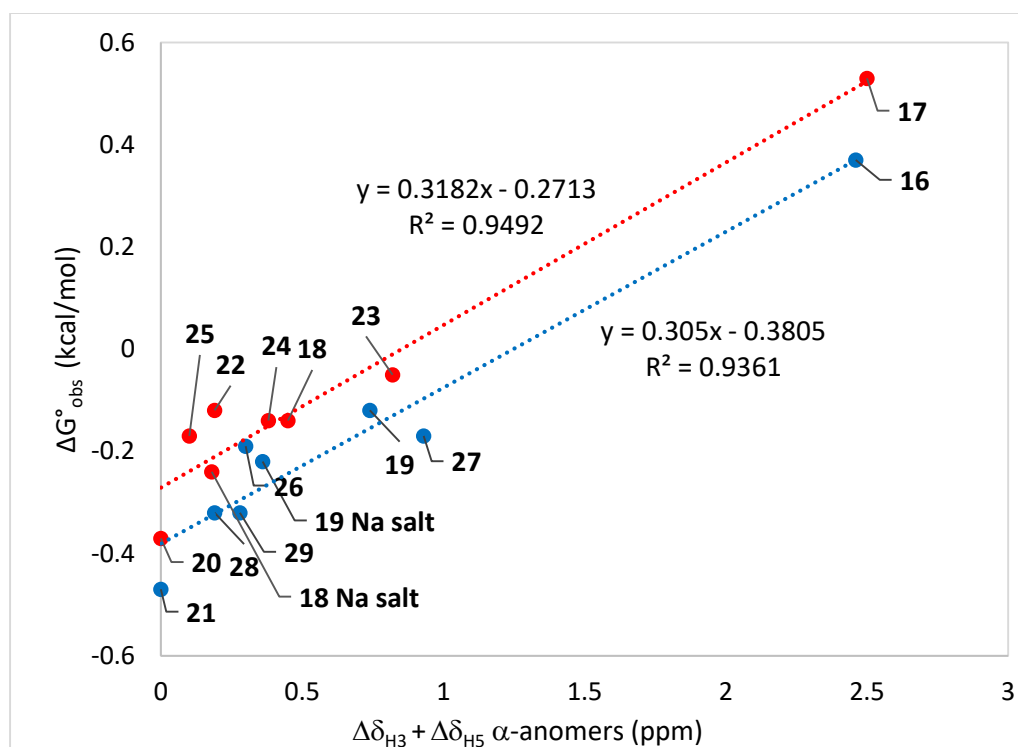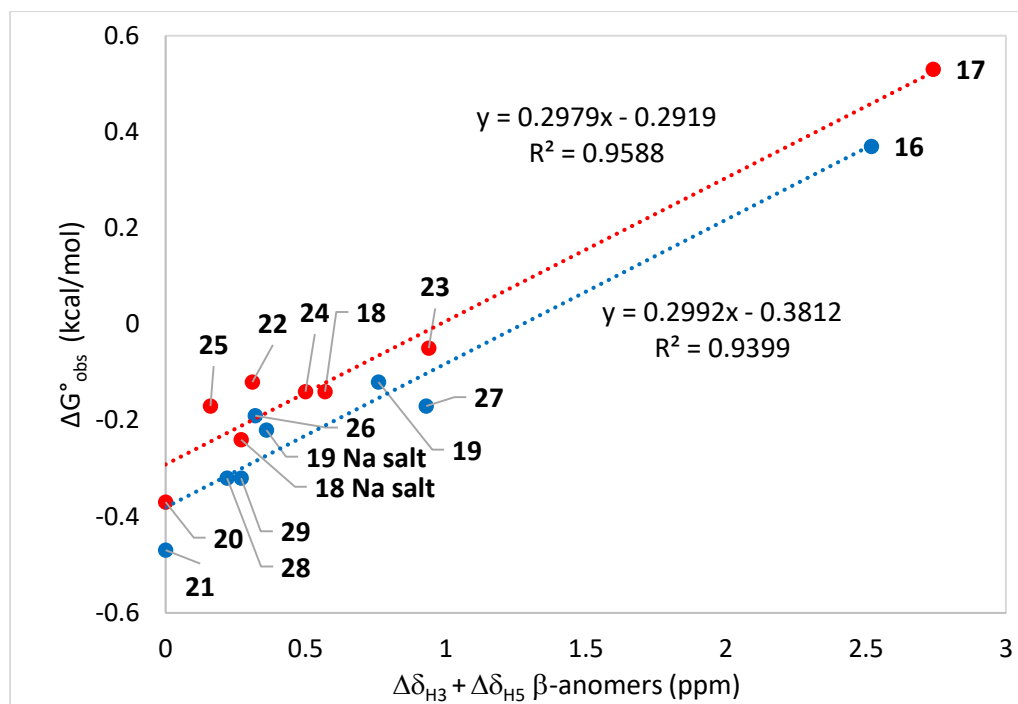
Figure 1 Plots of ΔG°_{obs} (kcal/mol) vs $\Delta\delta_{H3}+\Delta\delta_{H5}$ (ppm) for α-anomers (bottom) of gluco-(red) and galacto- (blue) configured pyranoses in D_2O. $\Delta\delta_H$ values were obtained by substracting the chemical shift δ for the relevant hydrogen atom of α-D-glucopyranose **20** ($\delta_{H3} = 3.59$, $\delta_{H5} = 3.76$) or of α-D-galactopyranose **21** ($\delta_{H3} = 3.71$, $\delta_{H5} = 3.95$) from that of the corresponding hydrogen atom of the pyranose of interest. α-D-deoxyfluoroglucopyranoses **22-25**, α-D glucopyranuronic acid **18**, the sodium salt of **18** and 2,3,4-tri-*O*-acetyl-α-D-glucopyranuronic acid **17** were used to generate the trendline (red dotted line) for the gluco-configured derivatives. α-D-Deoxyfluorogalactopyranoses **26-29**, α-D-galactopyranuronic acid **19**, the sodium salt of **19** and 2,3,4-tri-*O*-acetyl-α-D-

galactopyranuronic acid **16** were used to generate the trendline (blue dotted line) for the galacto-configured derivatives.
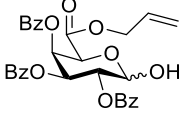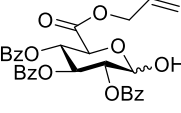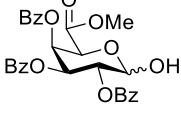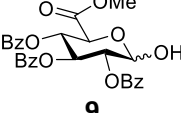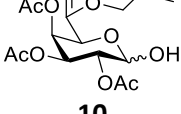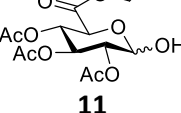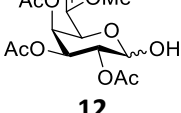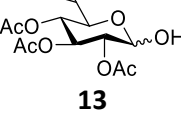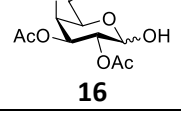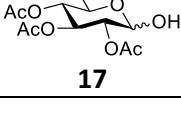
2.3   Influence of solvent
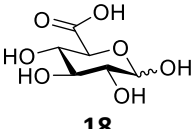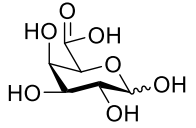
The influence of solvent was also examined. The solvent polarity order is $CDCl_3$ < CD_3OD < D_2O. An increase in solvent polarity would be expected to lead to a decrease in preference for the α-anomer.[35]   While this occurred in a number of cases it was structure dependent and, in some cases, the increase in stability was low compared to the effect of increasing the electron withdrawing nature of substituents. For instance, the comparison of **17** and **18** in D_2O showed an increase in $\Delta\Delta G^\circ = 0.73$ kcal/mol, which is associated with replacing OH with OAc groups, whereas comparing **17** in both D_2O and MeOD showed an increase in $\Delta\Delta G^\circ$ of 0.06 kcal/mol, associated with the solvent change.

A greater increase in stability of the axial anomer of galacturonic acid derivatives than for related glucuronic acids was observed when switching from CD_3OD to $CDCl_3$. This is presented in Table 2 as $\Delta\Delta G^\circ_{\text{solvent change}}$ where it is defined as the difference between the $\Delta G^\circ_{\text{obs}}$ value for a compound in two solvents. Thus for compound **6**, its $\Delta G^\circ_{\text{CDCl3}} = 1.03$ kcal/mol and its $\Delta G^\circ_{\text{CD3OD}}$ is 0.56 kcal/mol; thus $\Delta\Delta G^\circ_{\text{CD3OD}\rightarrow\text{CDCl3}}$ is +0.47 kcal/mol, which is a measure of the increased stability of the α-anomer of **6** in $CDCl_3$ compared to CD_3OD. This increased stability in switching from methanol to chloroform was found consistently greater for the galacturonic acid derivatives, where $\Delta\Delta G^\circ_{\text{CD3OD}\rightarrow\text{CDCl3}}$ ranged from 0.36-0.47 kcal/mol, than for the corresponding glucuronic acids, where $\Delta\Delta G^\circ_{\text{CD3OD}\rightarrow\text{CDCl3}}$ ranged from 0.03-0.14 kcal/mol (compare **6** with **7**, **8** with **9**, **10** with **11**, and **12** with **13** in Table 2). There is a smaller increase in stabilisation of the α-anomer when switching from D_2O to CD_3OD as observed for both **16** and **17**, with the degrees of stabilisation being similar ($\Delta\Delta G^\circ_{\text{solvent change}} = 0.10$ and 0.06 kcal/mol, respectively). However, a larger increase in stabilisation of the axial anomer

occurred for both **18** ($\Delta\Delta G°_{\text{solvent change}}$ = 0.34 kcal/mol) and **19** ($\Delta\Delta G°_{\text{solvent change}}$ = 0.49

kcal/mol) on switching from D_2O to CD_3OD.

Table 2. $\Delta\Delta G°_{\text{solvent change}}$ values ($\Delta G°_{\text{obs}}$ in solvent 1 - $\Delta G°_{\text{obs}}$ in solvent 2)

Compound	Solvent 1	Solvent 2	$\Delta\Delta G°_{\text{solvent change}}$ (kcal/mol)
6	$CDCl_3$	CD_3OD	0.47
7	$CDCl_3$	CD_3OD	0.14
8	$CDCl_3$	CD_3OD	0.36
9	$CDCl_3$	CD_3OD	0.03
10	$CDCl_3$	CD_3OD	0.46
11	$CDCl_3$	CD_3OD	0.04
12	$CDCl_3$	CD_3OD	0.39
13	$CDCl_3$	CD_3OD	0.03
16	CD_3OD	D_2O	0.10
17	CD_3OD	D_2O	0.06

18	CD$_3$OD	D$_2$O	0.36
19	CD$_3$OD	D$_2$O	0.49

The relationship of ΔG^o_{obs} with the relative permittivity (dielectric constant, ε) was studied for selected compounds (Figure 2). This involved use of data from Table 1 with additional determination of ΔG^o_{obs} values for selected hemi-acetals in solvent mixtures (D$_2$O-CD$_3$OD and CD$_3$OD-CDCl$_3$). This clarified that ΔG^o_{obs} in glucuronic acid and galacturonic acid had greater sensitivity to solvent polarity than observed for both glucopyranose and galactose. This was clear when comparing $\Delta\Delta G^o_{obs}/\Delta\varepsilon$ (kcal/mol) as shown in Figure 2. The $\Delta\Delta G^o_{obs}/\Delta\varepsilon$ value was -0.0109 for **19** and -0.0076 for **18** compared with -0.0035 for **20** and -0.0043 for **21**. The fluorinated derivative **24** (slope = -0.0062) was also more sensitive to relative permittivity than non-fluorinated **20** and **21**. In contrast the sensitivity to solvent polarity for **13** was reduced compared to that for **12** (slope = -0.014 vs -0.0014). Of the four compounds studied in CDCl$_3$-CD$_3$OD, only galacturonic acid derivative **12** showed an increase in axial anomer preference in CDCl$_3$ with little or no increase observed for glucopyranose **3,** galactopyranose **4** and glucuronic acid derivative **13** in CDCl$_3$ compared to CD$_3$OD.
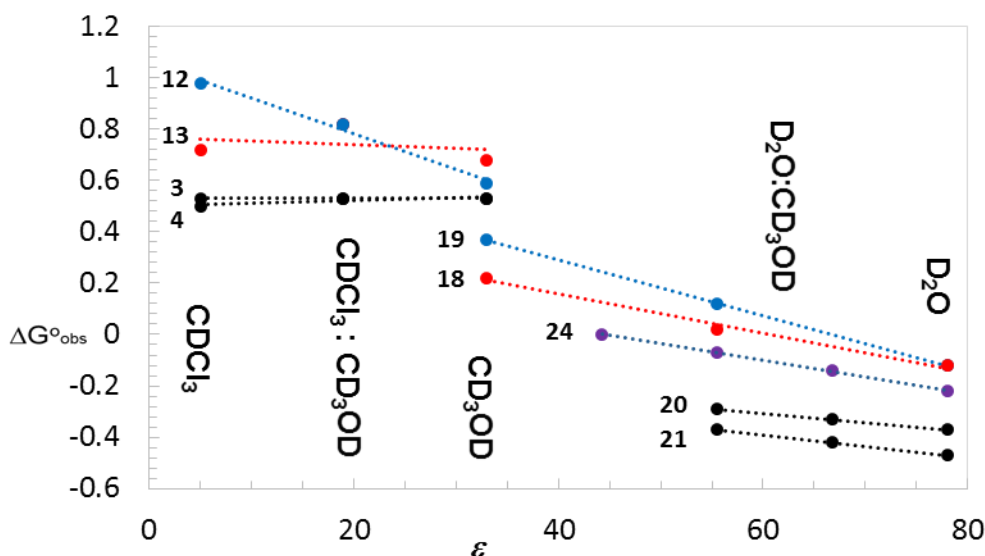
Figure 2. Plots of ΔG°_{obs} (kcal/mol) vs solvent relative permittivity (dielectric constant, ε). Published ε values for pure non-deuterated water (78), MeOH (33) and CHCl$_3$ (5) at 25 °C were used when these were the sole solvents. Where a binary MeOH-water mixture was used (**18**, **19**, **21**, **20**, **24**) then ε values were taken from data of Akerlof.[36] Thus for 25:75 MeOH-water $\varepsilon = 67$; for 50:50 MeOH-water $\varepsilon = 55$; for 75:25 MeOH-water $\varepsilon = 43$. With regard to MeOH-CHCl$_3$ (**12**, **13**) experimental data for ε were not available. The ε (19) for 50:50 MeOH-CHCl$_3$ is estimated as the average of that of the pure solvents. The slopes ($\Delta\Delta G^{\circ}_{obs}/\Delta\varepsilon$, kcal/mol) calculated using Microsoft Excel are: **12**, -0.014; **13**, -0.0014; **3**, 0; **4**, 0; **19**, -0.011; **18**, -0.0076; **24**, -0.0062; **20**, -0.0035; **21**, -0.0043.

2.4 Conformational analysis

Examination of X-ray crystal structures in the CCD was carried out to obtain information on the conformation of galacturonic and glucuronic acids and their esters, with a view to whether this could account for different behaviours of these saccharides. In crystal structures available the acid group (or ester) of the uronic acid had the Z-configuration. For glucuronic acids and esters, where dihedral angles in 30 crystal structures were examined the H5-C5-C6-O(H) dihedral angle was found to vary from -48 ° to +57 ° for the majority of structures, with a minority having a dihedral angle that varied between 147 ° and 228 ° (-132 °). The crystal structure of glucuronic acid **18α** has been reported and the H5-C5-C6-O(H) dihedral angle therein is +35°. The crystal structures of five available galacturonic acid

derivatives were examined and all showed a H5-C5-C6-O(H) of 54º to 63º. The crystal structure of α-D-galactopyranuronic acid **19α** is reported and showed a H5-C5-C6-O(H) dihedral angle of +54º.[37] Thus the X-ray crystal structure evidence indicates there is a different conformational preference for galacturonic acid derivatives compared to glucuronic acids, presumably as a result of increased repulsion of the C-6 atoms with the axial C-4 substituent in the former. The orientation of the carboxylic acid group in **18α** and **19α** differed by 19º.

Molecular mechanics calculations were used to explore further conformational preferences for the carboxylic acid group in **12**, **13**, **18** and **19**. Firstly, the C5 to C6 bond was rotated using 10º increments using dihedral scanning in Macromodel. The OPLS3 force field energy for thirty six conformers were thus obtained in the case of each anomer and relative energies were plotted (Figure 3, y-axis) as a function of the H5-C5-C6-O(H/Me) dihedral angle (Figure 3, x-axis). The output from the scanning indicated different orientation preferences for the carboxylic acid group in minimum energy structures for glucuronic acid and derivatives compared to galacturonic acid and derivatives. This preliminary study indicated the presence of higher barriers to interconversion between conformers in the galacturonic acid derivatives compared to glucuronic acids and different dihedral angles values for energy minimums.
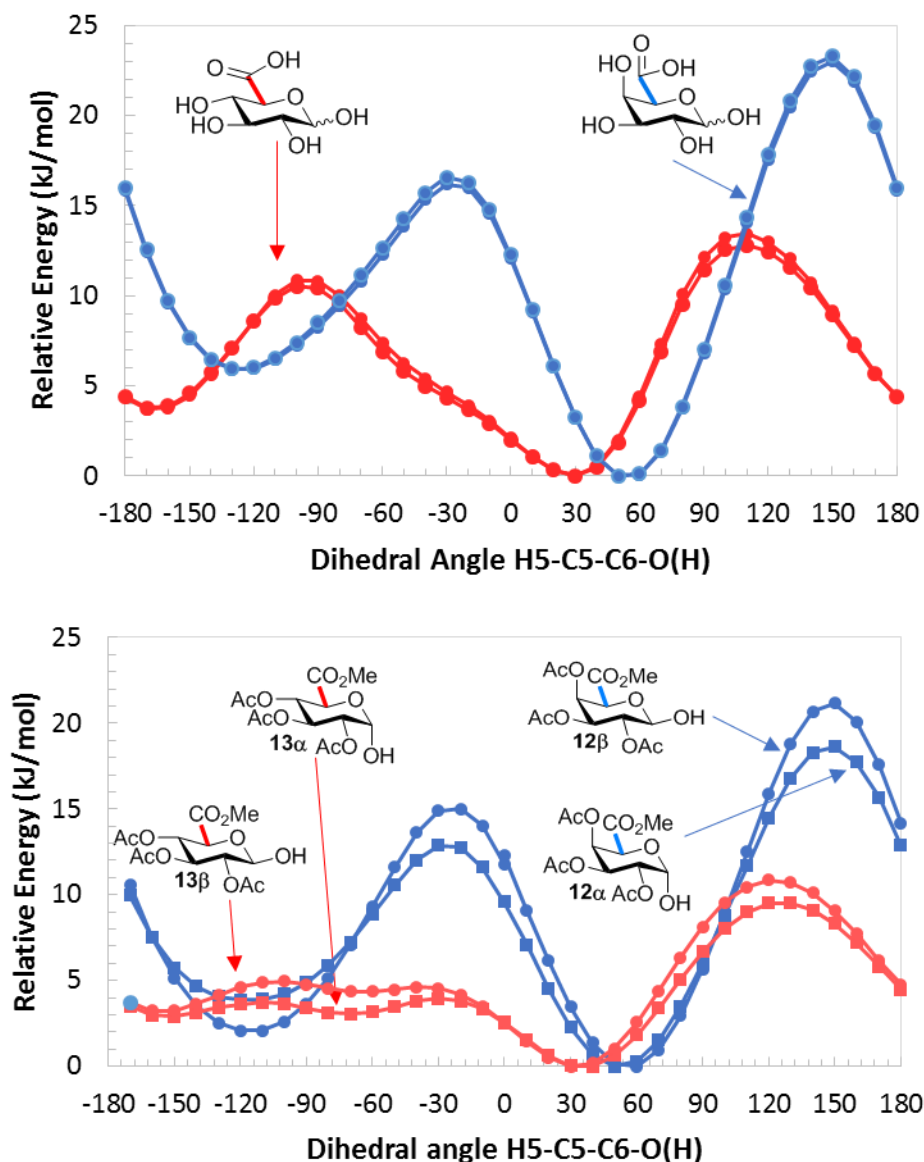
Figure 3. Relative energy plotted against H5-C5-C6-O(H) dihedral angle in **12α, 12β, 13α, 13β** (bottom) as well as both anomers of glucuronic acid **18** and galacturonic acid **19** (top) Models of each structure were built using Maestro and minimised in Macromodel using the OPLS3 force field. The GB/SA continuum solvation model for chloroform was used for calculations with **12/13** whereas that for water was used for **18/19**. The energy profile for each molecule was then obtained by rotating the dihedral by increments of 10° and minimising and determining the energy of each conformer in turn, after applying this constraint. Energy relative to that of the lowest energy conformer were plotted. The lowest energy conformer for all strucures had dihedrals between +30° and +60° for all anomers. Higher energy barriers were calculated between low energy minima for galacturonic acid derivative compared with glucuronic acid derivatives.

Molecular dynamics simulations were next used to further investigate conformational differences. Kirschner and Woods[38] showed that more accurate predictions of carbohydrate conformational preferences in water can be obtained when employing molecular dynamics in

the presence of explicit water molecules, which disrupt intramolecular hydrogen bonding in the carbohydrates. Hence molecular dynamics simulations (2 ns), in Macromodel, were carried out by first of all placing **18α** and **19α** in 16 Å cubic boxes of water molecules. The simulations employed the OPLS-3 force field and used stochastic dynamics, at a temperature of 298 K, a time step of 1.5 fs and an equilibration time of 1.0 ps with 200 structures being sampled over the course of the simulations in each case. These structures were not minimised after sampling. Conformers of **19α** with a dihedral angles for H5-C5-C6-O(H) in the range -30 to +90 degrees were sampled exclusively, indicating that the location of a second energy minimum was not achieved. For the structures sampled the mean dihedral angle was 53.8° with a standard deviation of 9.3°, meaning that 99.7% of the conformers would have a dihedral within three standard deviations of the mean (i.e. between 25.9º and 81.7°), assuming there is a normal distribution. The simulation for **18α** under the same conditions as for **19α** and subsequent statistical analysis of conformers with a dihedral angles for H5-C5-C6-O(H) in the range -30 to +90 degrees indicated there is greater flexibility (mean = 24.8°, standard deviation = 18.1°) and also a different energy minimum in terms of the H5-C5-C6-O(H) dihedral.

To enable longer simulations (30 ns) to be carried out the GB/SA solvent continuum for water was employed instead of using explicit water molecules. Under these conditions the simulation was able to generate and sample conformers with dihedral angles <30º (see Figures 4-6). Most (>80%) of the structures sampled, for all the various anomers of **18** and **19**, under these conditions had the dihedral angles in the >-30º and <+90° region. The outcome of statistical analysis of this data is provided in Figure 6 and Table 3. There was increased flexibility observed for glucuronic acids in terms of there being larger standard deviations. Related calculations using the GBSA solvent continuum for chloroform were carried out for acetylated esters **12/13** (Figure 4-6, Table 3). These show similar conformational differences

between **12** and **13** as for the parent saccharides, although there was somewhat reduced flexibility for the glucuronic acid carboxylate groups of **13** compared to the parent **18**.
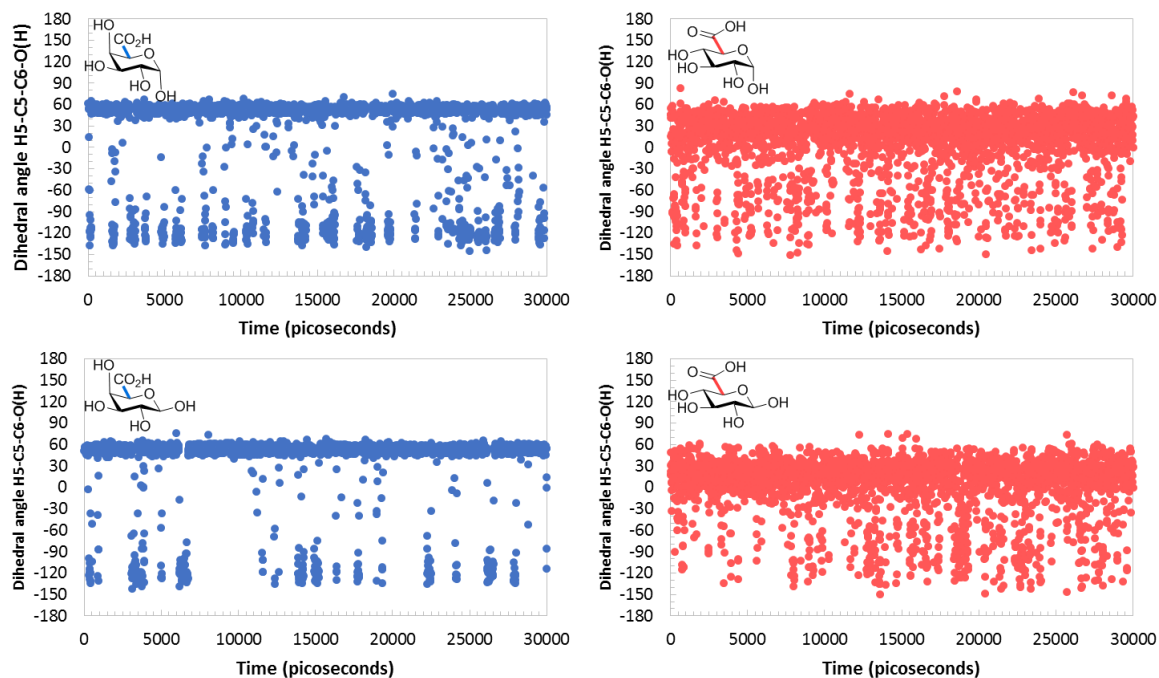
Figure 4. Orientation of the carboxylic acid group in D-glucuronic acid and D-galacturonic acid in their pyranose forms. Plots of the H5-C5-C6-O(H) dihedral angles for structures sampled in 30 ns molecular dynamics simulations as a function of time are shown. These simulations were conducted using Macromodel, using the OPLS3 force field and GB/SA continuum solvation model for water. Statistical analysis of this data and that also for **12/13** (data not shown here) is provided in Figure 5 and Table 3.

Table 3. Statistics on data from molecular dynamics simulations[a]

Anomer	% Structures sampled with a H5-C5-C6-O(H) dihedral angle between -30º and +90º	Mean dihedral angle in the range -30º to +90º (standard deviation)	% Structures sampled with H5-C5-C6-O(H) dihedral between -180 º and -30 º	Mean dihedral angle in the range -180º to -30º (standard deviation)
12α	61.0	59.6 (8.1)	39.0	-98.7 (10.4)
12β	46.6	56.3 (8.0)	53.4	-97.5 (12.0)
13α	62.1	31.0 (10.0)	37.9	-126.5 (23.5)
13β	63.2	30.7 (10.7)	36.8	-124.2 (24.7)
18α	83.5	25.5 (19.2)	17.4	-83.0 (29.5)
18β	84.9	18.9 (16.9)	15.1	-81.9 (29.9)
19α	82.4	52.2 (9.0)	17.6	-111.0 (22.3)
19β	88.9	54.1 (3.3)	11.1	-112.9 (20.6)

[a] Molecular dynamics simulations (30 ns) were conducted using Macromodel and OPLS3 force field (see Figure 5 and Figure 6). The computation of solvation energies using the generalized Born and surface areas (GB/SA) continuum solvation model was applied to **18/19** for water and to **12/13** for chloroform.[39] The H5-C5-C6-O(H/Me) dihedral angle was monitored and the statistics are based on measurements obtained for this dihedral in 3000 structures sampled during the course of the simulation. There were no conformers sampled in the region +90º to +180° for any anomer.
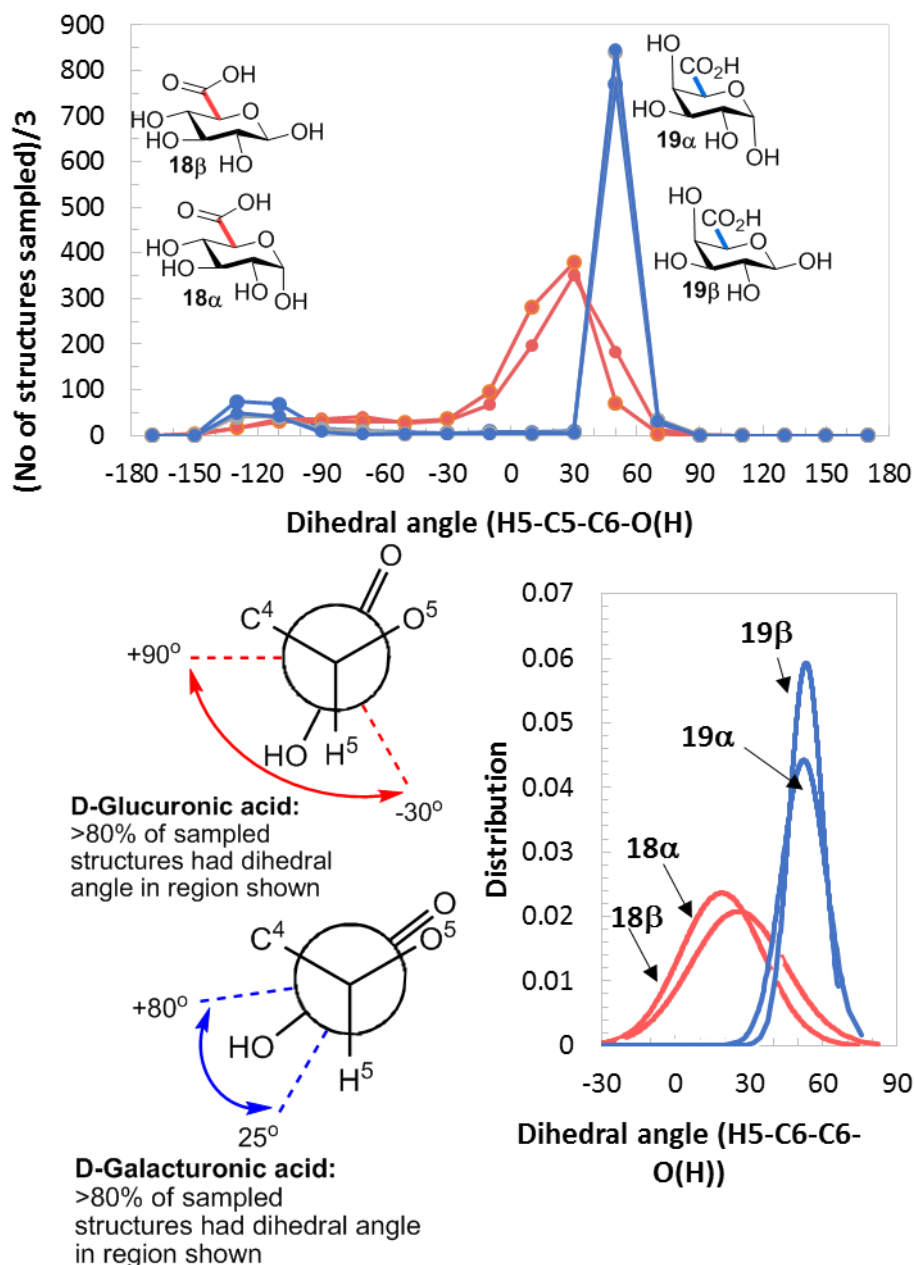
Figure 5. Conformational differences between glucuronic acid (red) and galacturonic acid (blue) in terms of the carboxylic acid group orientation. The top graph is a plot of the number of conformers (y-axis) against dihedral angle range (x-axis) for H5-C6-C6-O(H) for conformers sampled in the molecular dynamics simulations (see Figure 4). Each point corresponds to the number of conformers in defined 20° ranges between -180 ° to +180 °. For instance, the number of conformers sampled with a dihedral angle between -180° to -160° is plotted at -170°. The bell shaped curves (bottom right) were computed, assuming a normal distribution, using Microsoft Excel based on the dihedral angle data obtained in the >-30° and <+90° region; the highest number of sampled structures for all anomers were found in this region. Means and standard deviations from this statistical analysis are given in Table 3.
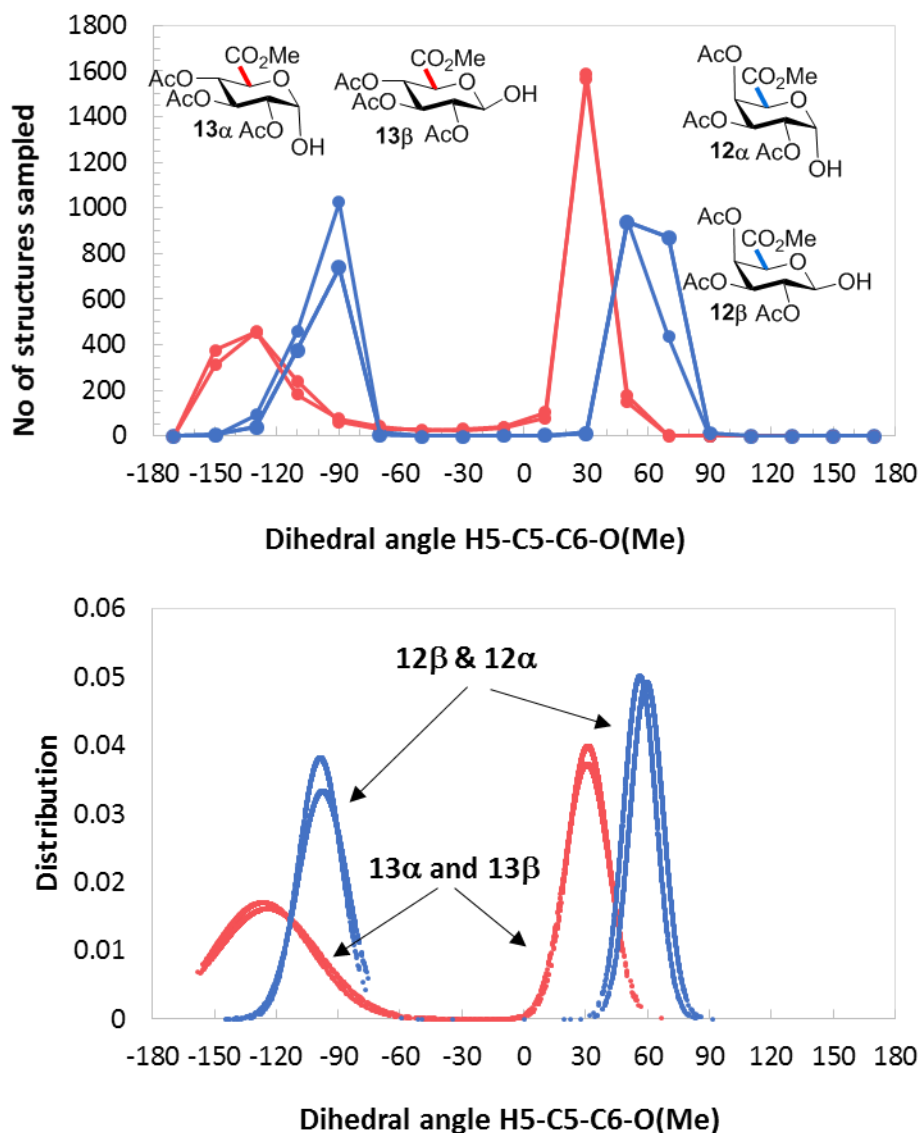
Figure 6. Conformational differences between **12** (blue) and **13** (red) in terms of the carboxylate orientation. The top graph is a plot of the number of conformers (y-axis) against dihedral angle range (x-axis) for H5-C6-C6-O(Me) for conformers sampled in the molecular dynamics simulations. Each point corresponds to the number of conformers in defined 20° ranges between -180 ° to +180 °. For instance, the number of conformers sampled with a dihedral angle between -180° to -160° is plotted at -170°. The bell shaped curves (bottom) were computed, assuming a normal distribution, using Microsoft Excel based on the dihedral angle data obtained in the >-180º and <-30° and >-30º and <+90° regions. The carboxylate displays a different conformational preference in glucuronic acid compared with galacturonic acid (see statistical data in Table 3).

2.5 *Possibility of hydrogen bonding in β-anomers of 3, 4, 12 and 13.*

The possibility that intramolecular hydrogen bonding occurs between the equatorial anomeric OH group and the C-2 C=O group for **3β**, **4β**, **12β** and **13β**, was considered given that it could influence the anomer preference. Whether H-bonding could occur between these groups was

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investigated by carrying out 30 ns molecular dynamics simulations agents using the GB/SA chloroform solvent continuum. Little intramolecular hydrogen bonding was observed between these groups during the simulation for **12β** (<1%) whereas each of **3β**, **4β**, and **13β** showed ~10% hydrogen bonding in the simulation between the anomeric OH and adjacent carbonyl group. The difference is believed to be due to increased steric hindrance between the pyranose substituents in **3β**, **4β**, and **13β** which causes their 2-acyl group to tilt more towards the equatorial OH group. The axial nature of the C-4 substituent in **12β** and constrained nature of the carboxylic acid group leaves more room for the C-2 and C-3 acyl groups and this results in the C-2 C=O of **12β** being tilted away from the anomeric OH group reducing its involvement in intramolecular H-bonding. Intramolecular H-bonding could thus explain the reduced sensitivity of the anomeric preference for **3**, **4**, and **13** to solvent polarity compared to **12**.

2.6   *Electrostatic potential surfaces*

The α-faces of gluco- and galactopyranoses, which present the H-3 and H-5 protons, are of similar size and these faces can be involved in CH−π interactions due to the electron deficient nature of these protons. This type of interaction has been observed with indoles and is stronger for β-galactopyranosides.[40] This has been explained in the study by Kiessling and Woolfson and their co-workers as being due to a higher electrostatic potential for the galactopyranoside due to the presence of the axial C-4 group leading to induction of electron density from H-3 and H-5, which is greater than in glucopyranoside. Electron withdrawing groups would be expected to influence the electrostatic potentials of the compounds studied herein. Electrostatic potential maps of selected structures were calculated in Spartan'10 from minimized geometries generated using the Hartree-Fock (3-21G) calculations in vacuum. Maps (isovalue 0.002) generated are shown Figure 7 and they show a higher electropositive potential for the α-face of galacturonic acid **12β** compared to glucuronic acid **13β**, with the α-faces of both saccharides

showing positive potential. The electrostatic potential for the α-face of β-D-galacturonic acid **19β** is also higher when compared with that of β-D-glucuronic acid **18β**. This higher positive potential may contribute to explaining the higher sensitivity of the galacturonic acid anomeric preference to solvent permittivity. As solvent polarity decreases there is a greater tendency for the anomeric substituent to be axial as it would reduce the overall positive potential of the α-face as well as reducing the endo-anomeric effect.
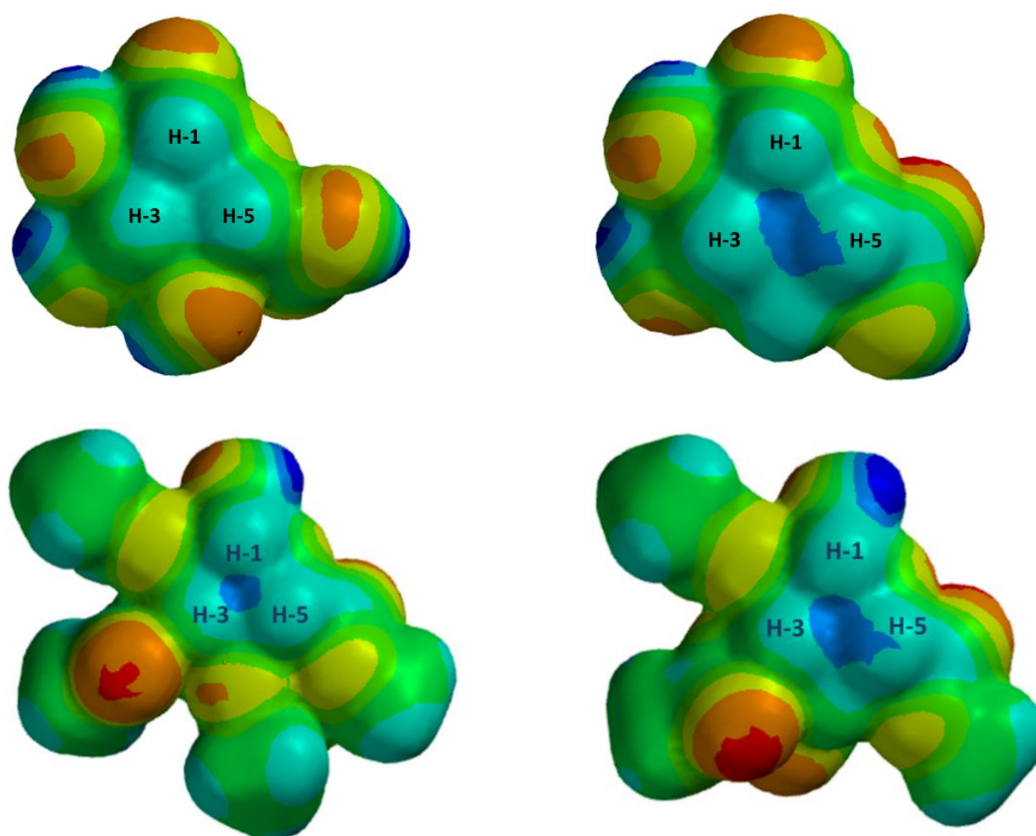
Figure 7. Electrostatic potential maps (isovalue 0.002) of **13β** (bottom left), **12β** (bottom right), **18β** (top left) and **19β** (top right). Shown are the α-faces. Polar areas are shown in red (negative potential) and blue (positive potential) and the scale is mapped from -260 kJ/mol (extreme red) to +260 kJ/mol (extreme blue) in all cases. Intermediate potentials are mapped according to the colour spectrum. There is a difference for the calculated potentials of ~7 kcal/mol when comparing **12β** (+155.7 kcal/mol) with **17β** (+148.3 kcal/mol) and of ~16 kcal/mol when comparing **18β** (148.6 kcal/mol) with **16β** (128.3 kcal/mol); these values were measured at the point of highest positive potential in the areas defined by H-1, H-3 and H-5 for these anomers.

2.7   Comparisons of pyranoses and 2-hydroxytetrahydropyran in D$_2$O

The pyranoses herein are substituted 2-hydroxytetrahydropyrans.   Praly and Lemieux[15] reported a ΔG^{o}_{obs} for 2-hydroxytetrahydropyran **33** of -0.52 kcal/mol, measured in D$_2$O. The ΔG^{o}_{obs} values for 2-hydroxytetrahydropyran and all other hemiacetals (pyranoses) measured herein (Table 1) are comprised of ΔG^{o}_{AE}, which is the energy difference between the two anomers, based on the anomeric effect (interaction of ring oxygen and anomeric substituent), and ΔG^{o}_{steric}, which results from the interaction between the axial anomeric substituent and nearby CH groups at C-3 and C-5. The latter can be comprised a repulsive steric interaction or an attractive coulombic interaction, with the attractive interaction expected to increase as the electron withdrawing nature of the C-3 and C-5 substituent increases.[41] In addition to these influences, the ΔG_{obs} values should include ΔG^{o}_{HB}, which is the energy difference arising from hydrogen bonding of the anomeric OH group in the two anomers, which is stronger for the equatorial anomer in water. Lemieux has proposed that hydrogen bond donation from the equatorial anomeric OH group strengthens the exo-anomeric effect. For the purpose of this discussion ΔG^{o}_{AE}-ΔG^{o}_{HB} (Figure 8) incorporates the anomeric effects and the hydrogen bonding contributions.

The cyclohexane A values are a measure of ΔG_{steric} in cyclohexanes and the A value for an OH substituent has ranged from 0.6 to 1.04 kcal/mol from different laboratories.[42] Applying a tetrahydropyran specific correction value of 1.53[43] to the median (0.82 kcal/mol) of these A values gives an estimate of ΔG_{steric} for 2-hydroxytetrahydropyran of 1.25 kcal/mol.   This implies that ΔG^{o}_{AE}-ΔG^{o}_{HB} = 0.73 kcal/mol for 2-hydroxytetrahydropyran in D$_2$O (Figure 8).

Compared to 2-hydroxytetrahydropyran it can clearly be seen that introduction of electron withdrawing substituents leads to an increase in the stability of the axial anomer in D$_2$O; this corresponds to increases in stability of 1.05 kcal/mol for **17** and 0.89 kcal/mol for **16**. Enhanced preferences were also observed for the axial anomer in D$_2$O for 2,3,4,6-tetra-*O*-

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methyl-D-galactopyranose **34** (ΔG°_{obs} = 0.10 kcal/mol), which is an increase in stability of its axial anomer, when compared to 2-hydroxytetrahydropyran, of 0.62 kcal/mol. Clearly the acetoxy/methoxy/carboxyl groups are more electron withdrawing than hydrogen and the value for ΔG_{steric} should therefore be reduced (<1.25 kcal/mol), favouring the α-anomer.

$$\Delta G^{\circ}_{AE} - \Delta G^{\circ}_{HB} = \Delta G^{\circ}_{obs} + \Delta G^{\circ}_{steric}$$

$$0.73 \text{ kcal/mol} = -0.52 \text{ kcal/mol} + 1.25 \text{ kcal/mol}$$

$$\Delta G_{obs} = +0.53 \text{ kcal/mol}$$
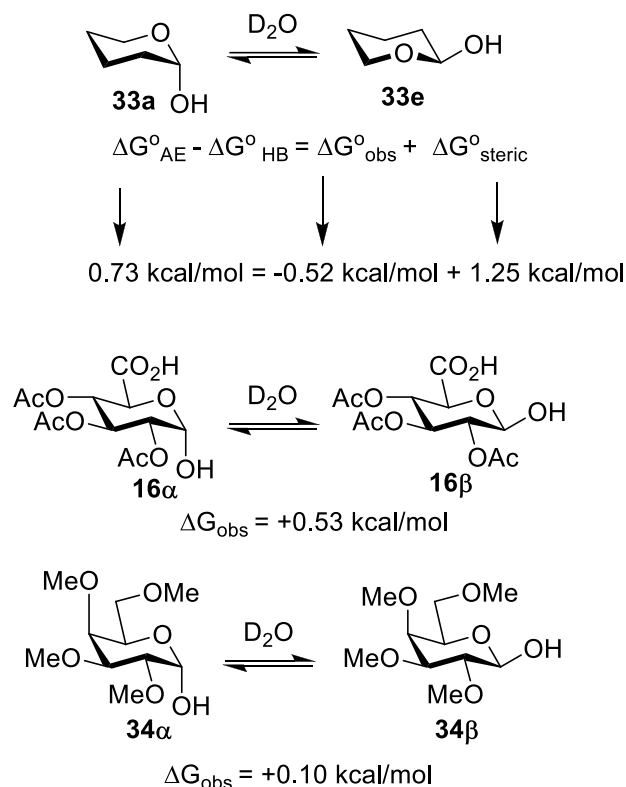
$$\Delta G_{obs} = +0.10 \text{ kcal/mol}$$

Figure 8. Comparisons with 2-hydroxytetrahydropyran

The ΔG°_{obs} in D_2O for **34**[44] of +0.10 kcal/mol, means that its axial anomer is more stable when compared with α-D-galactopyranose **21α** by 0.57 kcal/mol. The reported ratio for 2,3,4,6-tetra-*O*-methyl-D-glucopyranose (ΔG°_{obs} = 0.24 kcal/mol) in D_2O also showed an increase in stability for its axial anomer of 0.61 kcal/mol compared to α-D-glucopyranose.[13,45] The question thus arises whether the methoxy substituents are more electron withdrawing than the hydroxyl substituents? Analysis of ^{1}H-NMR chemical shifts, comparing those of **34** with **21** indicates methoxy groups caused moderate upfield shifts for both H-2 and H-3 (-0.23 to -0.31 ppm) for both anomers of **34**. The overall $\Delta\delta_{H3}+\Delta\delta_{H5}$ values for anomers of **34** were -0.22

ppm (α-anomer) and -0.25 (β-anomer) in the ^{1}H-NMR spectrum of **34** when compared to D-galactopyranose **21** as the reference. This indicates that the contribution of ΔG_{steric} for **34** may increase compared to that of D-galactose, in favour of the β-anomer, or that the chemical shift data is not reflective of the electron withdrawing/donating properties in this case. The electrostatic potential energy map (Figure 9) for 2,3,4,6-tetra-*O*-methyl-β-D-galactopyranose does indicate a reduction in the positive potential of the alpha face compared to that of β-D-galactopyranose, indicating an increase in electron donation by methoxy groups compared to hydroxyl groups. If the repulsion increases between CH groups at C-3 and C-5 then increase in the endo-anomeric effect and less favourable hydrogen bonding for the equatorial anomer would be needed to explain the increase in preference for the axial anomer. The electrostatic potential maps indicate a higher negative potential at the pyranose oxygen atom for **33e** (Figure 9) than for **21β**. However, methyl groups were found to reduce stability of polyhydroxylated piperidinium ions compared to hydrogen atoms in a study by Bols and co-workers,[30] which would indicate methyl groups are more electron withdrawing in that case, contradicting with data presented here. Further work is required to tease out the influence of hydroxyl group methylation on pyranose reactivity.

Finally, comparing D-galactopyranose **21** with 2-hydroxytetrahydropyran merits comment. For **21** and **33** the preferences for the equatorial anomer are similar in D_2O. There is the argument that ΔG_{steric} should be reduced for **21** compared to **33**, if the electron withdrawing hydroxyl groups are deshielding. This implies that the sum of ΔG^o_{AE}-ΔG^o_{HB} must also be reduced for **21** compared to **33**.
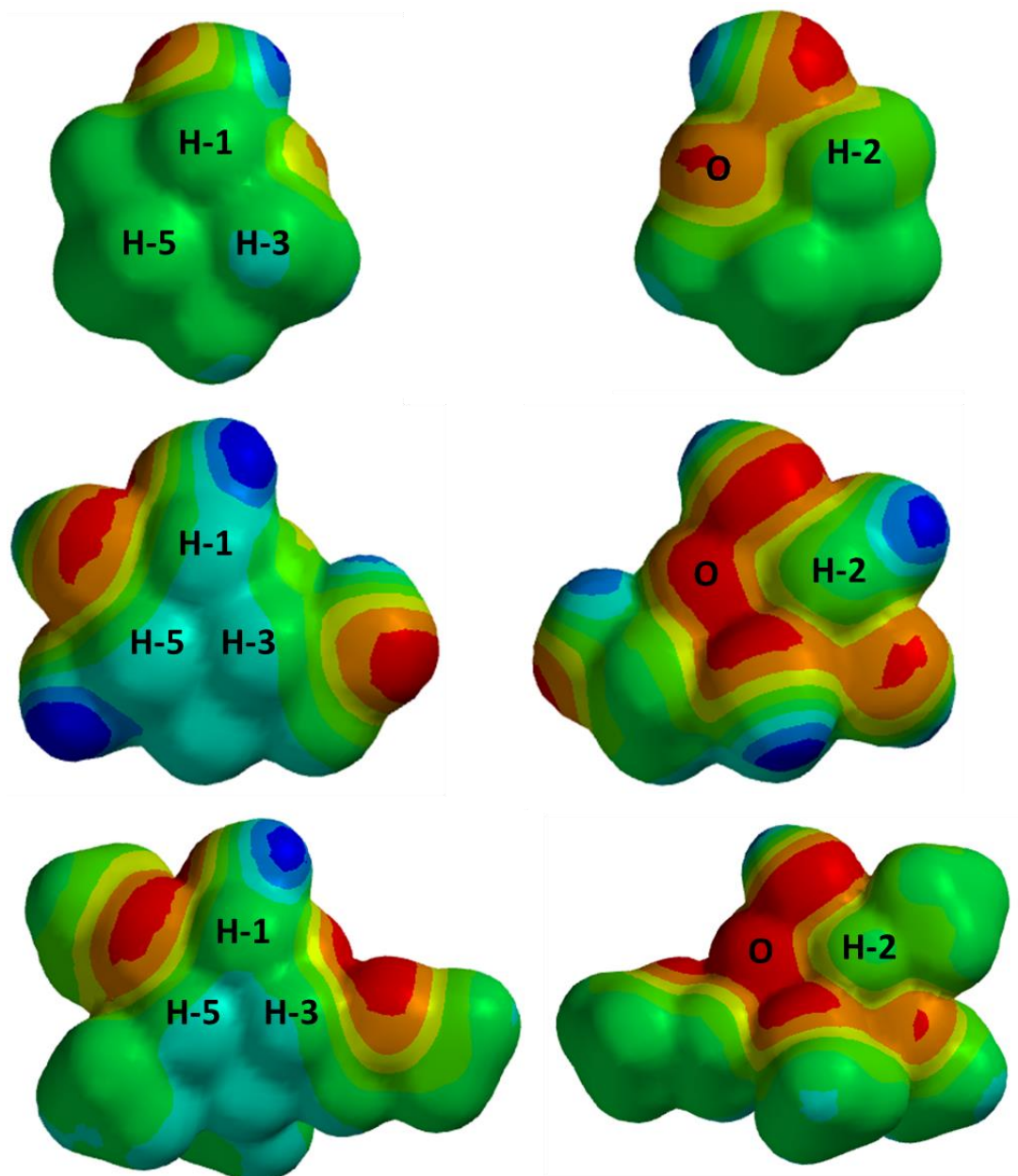
Figure 9. Electrostatic potential maps (isovalue 0.002) of equatorial anomer of 2-hydroxytetrahydropyran **33e** (top), β-D-galactopyranose **21β** (middle) and 2,3,4,6-tetra-*O*-methyl-D-glucopyranose **33β** (bottom). On the left are α-faces, while on the right are the β-faces. Polar areas are shown in red (negative potential) and blue (positive potential) and the scale is mapped from -260 kJ/mol (extreme red) to +260 kJ/mol (extreme blue) in all three cases. Intermediate potentials are mapped according to the colour spectrum. The labels used for atoms in **33e** correspond to the atom number of equivalent atoms in D-galactopyranose and not the numbering of **33** according to its IUPAC name.

3. Conclusions

Anomer preferences have been determined for pyranose derivatives of glucuronic acid and galacturonic acid and these are compared to related (deoxyfluoro)-D-galactopyranoses and (deoxyfluoro)-D-glucopyranoses. Substituents, which are more electron withdrawing, generally led to an enhancement in preference for the axial anomer. A general correspondence between axial anomer preference and downfield chemical shifts in ^{1}H-NMR spectra demonstrated for substances with the electron withdrawing substituents. Increasing the electron withdrawing nature of the pyranose substituents is believed to give rise to reduced repulsive interactions between the anomeric oxygen and nearby CH groups and possibly increased dipole-dipole interaction between the groups.[46] It is also possible that electron donating substituents increase axial anomer preference and more work would need to be carried out with regard to methylated pyranoses in this regard.

The higher sensitivity of anomeric preference to solvent polarity observed for galacturonic acids compared to glucuronic acids is linked to the electrostatic potential of the α-face of β-D-galacturonic acids. In non-polar solvent this higher sensitivity for galacturonic acid may be associated with a lack of intramolecular hydrogen bonding between the anomeric OH and 2-acyl group observed for other pyranoses in molecular dynamics simulations. Conformational preferences at C-5 of glucopyranosides and galactopyranosides[47] are known to influence reactivity[48,49] and conformational differences between glucuronic acid and galacturonic acid were observed.

Overall, galacturonic and glucuronic acids have a higher intrinsic preference for the axial anomer compared to related glycopyranosides, which is increased by electron withdrawing acyl groups. This contributes to explaining high axial stereoselectivities that arise in Lewis acid catalysed anomerisation reactions involving uronic acids.

4. Experimental Section

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General Information: Chemical shifts are reported relative to internal Me_4Si in $CDCl_3$ (δ 0.00) or HOD for D_2O (δ 4.64) or CD_3OD (δ 3.30) for [1]H. Chemical shifts are reported relative to internal Me_4Si in $CDCl_3$ (δ 0.0) or $CDCl_3$ (δ 77.0) or CD_3OD (δ 47.6) for [13]C. NMR signals were assigned with the aid of COSY, HSQC and HMBC. NMR samples were degassed and kept under N_2 during the analysis. Quantitative NMR[50] experiments were carried out at 500 MHz with a pulse width of 45°, a receiver gain of 30 dB and sample temperature of 25°C with each sample subjected to 8 scans. Each sample was analysed in triplicate to give average anomeric ratios at equilibrium; this included the commercially available compounds. All the spectra included in the supporting information were obtained by the authors and were used to obtain anomer ratios. Coupling constants are reported in Hertz. The IR spectra were recorded as thin films using an FT-IR Spectrometer with an ATR attachment. High resolution mass spectra were recorded using an ESI-TOF instrument. Chromatography was carried out using silica gel 60 (particle size 0.04-0.063 mM). Dichloromethane, acetonitrile, toluene, THF and DMF reaction solvents were obtained from a Pure Solv™ solvent purification system. Other solvents were used as obtained from commercial suppliers. Thin layer chromatography was performed on aluminium sheets pre-coated with silica gel 60 and spots visualised by UV and staining with H_2SO_4-EtOH (1:20) or cerium molybdate.

2,3,4,6-Tetra-*O*-benzoyl-D-galactopyranose (1)[5] The title was prepared from 1,2,3,4,5-penta-*O*-benzoyl-α-D-galactopyranose (0.40 g, 0.57 mmol) by previously described procedures, with **1** (0.25 g, 74%) being isolated after chromatography using cyclohexane-EtOAc (3:1). IR (film) cm^{-1}: 2187, 1753, 1265, 1110, 1063, 830. HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for $C_{41}H_{32}O_{11}Na$ 723.1842, found 723.1840. *Selected NMR data for α-anomer:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 (broad signal, 1H, H-1), 4.90 (t, *J* = 6.5 Hz, 1H, H-5), 4.63 (dd, *J* = 11.3, 6.5 Hz, 1H, H-6a), 3.42 (s, 1H, O*H*). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.14,

166.07, 165.59, 165.58 (each C=O), 133.5, 133.4, 133.2, 133.2, 133.1, 130.0, 129.94, 129.91, 129.84, 129.79, 129.75, 129.71, 128.72, 128.67, 128.6, 128.48, 128.45, 128.4, 128.3 (Ar-C), 91.1 (C-1), 69.5 (C-2), 69.3 (C-3), 68.0 (C-4), 66.9 (C-5), 62.4 (C-6). *Selected NMR data for β-anomer:* ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.02 (dd, *J* = 3.4, 1.1 Hz, 1H, H-4), 5.65 (dd, *J* = 10.4, 8.0 Hz, 1H, H-2), 5.08 (broad signal, 1H, H-1), 4.69 (dd, *J* = 11.3, 6.5 Hz, 1H, H-6a), 4.46 (dd, *J* = 11.3, 6.4 Hz, 1H, H-6b). ^{13}C NMR (125 MHz, CDCl$_3$) δ 96.4 (C-1), 72.4 (C-2), 71.6 (C-5), 71.0 (C-3), 68.2 (C-4), 62.1 (C-6).

2,3,4,6-Tetra-*O*-benzoyl-D-glucopyranose 2.[5]   The title compound was prepared from 1,2,3,4,5-penta-O-benzoyl-D-glucopyanose (0.40 g, 0.57 mmol) by previously described procedures, with **2** (0.24 g, 72%) being isolated after chromatography using cyclohexane-EtOAc (3:1).   IR (film) cm^{-1}: 3450, 2169, 1723, 1451, 1261, 1025, 853, 685.   HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for C$_{34}$H$_{28}$NaO$_{10}$ 619.1580, found 619.1584.   *Selected NMR data for α-anomer:* ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.28 (t, J = 10.0 Hz, 1H, H-3), 5.34 (dd, J = 10.0, 3.7 Hz, 1H, H-2), 4.45 (dd, J = 11.9, 4.1 Hz, 1H, H-6b); ^{13}C NMR (125 MHz, CDCl$_3$): δ 166.8, 166.4, 166.3, 165.89, 165.86, 165.8, 165.3, 165.2 (each C=O), 133.6, 133.5, 133.44, 133.40, 133.3, 133.16, 133.13, 130.0, 129.91, 129.85, 129.82, 129.79, 129.72, 129.69, 129.6, 129.1, 128.93, 128.89, 128.71, 128.68, 128.44, 128.41, 128.37, 128.34, 128.28 (each Ar-C, Ar-CH), 90.5 (C-1), 72.3 (C-2), 70.2 (C-3), 69.5 (C-4), 67.8 (C-5), 62.9 (C-6). *Selected NMR data for β-anomer:* ^{1}H NMR (500 MHz, CDCl$_3$): δ 5.97 (t, J = 9.7 Hz, 1H, H-3), 5.36 (t, J = 8.7 Hz, 1H, H-2), 5.09 (t, J = 8.1 Hz, 1H, H-1), 4.50 (dd, J = 12.5, 5.0 Hz, 1H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 96.1 (C-1), 74.3 (C-2), 72.5 (C-5), 72.3 (C-3).

2,3,4,5-Tetra-*O*-acetyl-D-galactopyranose (3).[5] The title compound **3** was prepared by known procedure from 1,2,3,4,5-penta-O-acetyl-α-D-galactopyranose (1.0 g, 2.56 mmol), with

3 (0.67 g, 75%) being isolated after chromatography using cyclohexane-EtOAc (5:2). IR (film) cm^{-1}: 3468, 1718, 1454, 1246, 1069, 1028, 689. HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for C$_{14}$H$_{20}$O$_{10}$Na 371.0954, found 371. 0958. *Selected NMR data for α-anomer:* ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.52 (t, *J* = 3.6 Hz, 1H, H-1), 5.48 (dd, *J* = 3.5, 1.3 Hz, 1H, H-4), 5.16 (dd, *J* = 10.8, 3.6 Hz, 1H, H-2), 4.47 (td, *J* = 6.6, 1.3 Hz, 1H, H-5), 3.28 (dd, *J* = 3.5, 1.2 Hz, 1H, O*H*); ^{13}C NMR (125 MHz, CDCl$_3$) δ 170.6, 170.4, 170.2, 170.1 (each C=O), 90.7 (C-1), 68.3 (C-2), 68.2 (C-4), 67.2 (C-3), 66.3 (C-5), 61.8 (C-6), 20.8, 20.71, 20.65, 20.6 (each O*Ac*). *NMR data for β-anomer:* ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.16 (ddd, 10.8, 3.5, 1.0 Hz, 1H), 4.47 (dt, *J* = 6.6, 0.9 Hz, 1H) 3.96 (td, *J* = 6.5, 1.1 Hz, 1H, H-5), 3.72 (d, *J* = 8.9 Hz, 1H, O*H*).

2,3,4,5-Tetra-*O*-acetyl-D-glucopyranose (4). The title compound **4** (0.70 g, 78%) was prepared by known procedure from 1,2,3,4,5-penta-O-acetyl-α-D-galactopyranose (1.0 g, 2.56 mmol), with **4** being isolated after chromatography using cyclohexane-EtOAc (5:2). IR (film) cm^{-1}: 3450, 1720, 1450, 1248, 1158, 1060, 781. HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for C$_{14}$H$_{20}$O$_{10}$Na 371.0954, found 371. 0950. *NMR data for α-anomer:* ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.54 (t, *J* = 9.9 Hz, 1H, H-3), 5.47 (br s, 1H, H-1), 5.08 (t, *J* = 9.7 Hz, 1H, H-4), 4.90 (dd, J = 10.6, 3.3 Hz, 1H, H-2), 4.16 (dd, *J* = 8.6, 2.2 Hz, 1H, H-6b), 3.39 (s, 1H, O*H*); ^{13}C NMR (125 MHz, CDCl$_3$) δ 170.8, 170.2, 170.1, 169.5 (each C=O), 90.2 (C-1), 71.1 (C-2), 69.8 (C-3), 68.5 (C-4), 67.2 (C-5), 62.0 (C-6), 20.8, 20.71, 20.68, 20.6 (each O*Ac*). Selected *NMR data for β-anomer*: 5.26 (t, *J* = 9.6 Hz, 1H, H-3), 4.75 (br signal, 1H, H-1), 3.76 (ddd, *J* = 10.0, 4.9, 2.4 Hz, 1H, H-5). ^{13}C NMR (125 MHz, CDCl$_3$) δ 95. 6 (C-1), 73.2 (C-2), 72.2 (C-3), 72.1 (C-5), 68.4 (C-6).

2,3,4-Tri-*O*-benzoyl-D-glucopyranose 5 Compound **26** (2 g, 2.81 mmol) was dissolved in dry DMF (20 mL) to which hydrazine acetate (0.51 g, 5.62 mmol) was added. The reaction was

stirred at room temperature for 16 hours after which it was diluted with CH_2Cl_2. The organic layer was washed with water (x 3), brine, dried over Na_2SO_4 and concentrated. Flash chromatography gave the hemiacetal intermediate as a white solid (1.70 g, 82%). IR (film) cm^{-1}: 2930, 1729, 1692, 1450, 1248, 1021, 838; ^{1}H NMR (α-anomer, 500 MHz, CDCl$_3$) δ 7.84-8.03 (overlapping signals, 15H, aromatic H), 7.25-7.60 (overlapping signals, 10 H, aromatic H), 6.25 (t, $J = 9.9$ Hz, 1H, H-3), 5.79 (d, $J = 3.6$ Hz, 1H, H-1), 5.61 (t, $J = 9.9$ Hz, 1H, H-4), 5.31 (dd, $J = 10.2, 3.6$ Hz, 1H, H-2), 4.45 (dt, $J = 10.2, 3.8$ Hz, 1H, H-5), 3.96 – 3.81 (m, 2H, H-6), 0.89 (s, 9H, *tert* butyl C*H$_3$*), 0.04 (s, 3H), 0.02 (s, 3H) (each methyl C*H$_3$*). ^{13}C NMR (125 MHz, CDCl$_3$) δ 166.1, 166.0, 165.3, 165.2 (each C=O), 133.7, 133.4, 133.3, 133.1, 130.3, 130.0, 129.9, 129.84, 129.80, 128.54, 128.50, 128.47, 128.4 (each Ar-C), 90.5 (C-1), 72.5 (C-2), 70.7 (C-3), 70.6 (C-5), 69.5 (C-4), 62.7 (C-6), 26.0 (*tert* butyl C*H$_3$*), 18.6 (*tert*-butyl CH$_3$), -5.30, -5.32 (each methyl C*H$_3$*). This hemiacetal (1.5 g, 2.47 mmol) was dissolved in THF (50 mL) and AcOH (1 mL). TBAF (1 M in THF, 4.94 mL, 4.94 mmol) was added to the flask and the reaction was stirred at room temperature overnight. The solvent was removed under reduced pressure and purified *via* flash chromatography (cyclohexane:EtOAc 1.5:1) to afford **5** as a white solid (0.97 g, 80%); IR (film) cm^{-1}: 3460, 2942, 1728, 1622, 1254, 1020, 845; HRMS (ESI-TOF) *m/z*: [M+NH$_4$]$^+$ calcd for $C_{27}H_{28}NO_9$ 510.1764, found 510.1758. *NMR data for α-anomer:* ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.03 – 7.93 (m, 4H), 7.88 (dd, $J = 13.5, 7.8$ Hz, 3H), 7.52 (dt, $J = 12.4, 7.4$ Hz, 3H), 7.46 – 7.34 (m, 7H), 7.29 (t, $J = 7.8$ Hz, 3H) (each Ar-H), 6.31 (apt t, $J = 9.9$ Hz, 1H, H-3), 5.82 (d, $J = 3.5$ Hz, 1H, H-1), 5.51 (apt t, $J = 9.9$ Hz, 1H, H-4), 5.33 (dd, $J = 10.2, 3.7$ Hz, 1H, H-2), 4.37 (ddd, $J = 10.2, 4.3, 2.3$ Hz, 1H, H-5), 3.83 (dd, $J = 12.7, 2.3$ Hz, 1H, H-6a), 3.75 (dd, $J = 12.9, 4.1$ Hz, 1H, H-6b). ^{13}C NMR (125 MHz, CDCl$_3$) δ 166.7, 166.4, 166.1, 165.9 (each C=O), 133.8, 133.7, 133.6, 133.4, 133.3, 133.2, 130.1, 129.99, 129.95, 129.9, 129.70, 129.66, 129.2, 129.0, 128.6, 128.53, 128.50, 128.44, 128.40, 128.35, 128.3 (each Ar-C), 90.4 (C-1), 72.3 (C-2), 69.9 (C-3), 69.8 (C-5), 69.6 (C-4), 61.2 (C-

6). *Selected NMR data for β-anomer:* ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.00 (t, *J* = 9.8 Hz, 1H, H-3), 5.40 (dd, *J* = 9.9, 7.9 Hz, 1H, H-2), 5.07 (d, *J* = 8.0 Hz, 1H, H-1); ^{13}C NMR (125 MHz, CDCl$_3$) δ 96.0 (C-1), 74.9 (C-5), 74.2 (C-2), 72.3 (C-3), 69.4 (C-4), 61.2 (C-6).

2,3,4-Tri-*O*-benzoyl-D-galactopyranosiduronic acid, allyl ester (6).[19g] The known title compound was prepared by known procedures from 1,2,3,4-tetra-*O*-benzoyl-β-D-galactopyranose (0.80 g, 1.63 mmol) with **6** (0.67 g, 63%) being isolated after chromatography using cyclohexane-EtOAc (4:1). IR (film) cm^{-1}: 3455, 2987, 1724, 1450, 1256, 1066, 8890, 720, 683. HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for C$_{30}$H$_{26}$O$_{10}$Na 569.1424, found 569.1431. Selected *NMR data for α-anomer:* ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.32 (dd, *J* = 3.6, 1.6 Hz, 1H, H-4), 6.09 (dd, *J* = 10.6, 3.6 Hz, 1H, H-3), 5.97 (br signal, 1H, H-1), 5.20 (d, *J* = 1.7 Hz, 1H, H-5), 4.16 (br signal, 1H, *OH*). ^{13}C NMR (125 MHz, CDCl$_3$) δ 167.4, 166.0, 165.6, 165.2 (each C=O), 133.6, 133.5, 133.44, 133.41, 133.2, 130.7, 129.94, 129.85, 129.8, 129.7, 129.10, 129.08, 129.06, 128.53, 128.45, 128.34, 128.26, 120.1 (each Ar-C), 120.0 (OCH$_2$CH*C*H$_2$), 91.2 (C-1), 69.9 (C-4), 68.84 (C-2), 68.80 (C-5), 67.7 (C-3), 66.6 (O*C*H$_2$CHCH$_2$). *Selected NMR data for β-anomer*: ^{1}H NMR (500 MHz, CDCl$_3$): δ 6.23 (dd, *J* = 3.4, 1.5 Hz, H-4), 4.69 (d, *J* = 1.4 Hz, H-5). ^{13}C NMR (125 MHz, CDCl$_3$) δ 96.42 (C-1), 73.02 (C-5), 71.48 (C-2).

2,3,4-Tri-*O*-benzoyl-D-glucopyranosiduronic acid, allyl ester (7).[19g] The known title compound was prepared as previously described from 1,2,3,4-tetra-*O*-benzoyl-β-D-galactopyranose (0.80 g, 1.63 mmol) with **7** (0.23, g, 69%) being isolated after chromatography using cyclohexane-EtOAc (2:1). IR (film) cm^{-1}:3385, 2959, 1736, 1721, 1259. 1047, 939; HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for C$_{30}$H$_{26}$O$_{10}$Na 569.1424, found 569.1422. *Selected NMR data for α-anomer:* ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.27 (t, *J* = 9.7 Hz, 1H, H-3), 5.88 (d, *J* = 3.5 Hz, 1H, H-1), 5.36 (dd, *J* = 9.9, 3.5 Hz, 1H, H-2), 4.92 (d, *J* = 10.2 Hz, 1H, H-5); [13]C

NMR (125 MHz, CDCl$_3$) δ 165.74, 165.66, 165.3 (each C=O), 133.7, 133.6, 133.51, 133.49, 133.45, 133.4, 133.3, 130.8 (each Ar-C), 130.7 (OCH$_2$CHCH$_2$), 130.2, 130.0, 129.9, 129.80, 129.75, 129.0, 128.90, 128.86, 128.71, 128.67, 128.6, 128.5, 128.40, 128.37 (each Ar-C), 119.6 (OCH$_2$CHCH$_2$), 90.6 (C-1), 71.6 (C-2), 70.0 (C-4), 69.5 (C-3), 68.7 (C-5), 66.8 (OCH$_2$CHCH$_2$). *Selected NMR data for β-anomer:* ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.98 (t, *J* = 9.3 Hz, 1H, H-3), 5.42 (dd, *J* = 9.4, 7.3 Hz, 1H, H-2), 4.44 (d, *J* = 9.4 Hz, 1H, H-5).^{13}C NMR (125 MHz, CDCl$_3$) δ 96.0 (C-1), 73.6 (C-2), 73.1 (C-5), 71.5 (C-3), 69.9 (C-4).

2,3,4-Tri-*O*-benzoyl-D-galactopyranosiduronic acid, methyl ester (8).[19b] The known title compound was prepared as previously described from 1,2,3,4-tetra-*O*-benzoyl-β-D-galactopyranose (1.0 g, 0.62 mmol) with **8** (0.71 g, 70%) being isolated after chromatography using cyclohexane-EtOAc (2:1). IR (film) cm^{-1}: 3449, 1729, 1602, 1450, 1249, 1087, 837; HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for C$_{28}$H$_{24}$O$_{10}$Na 543.1267, found 543.1272. *Selected NMR data for α-anomer*: ^{1}H NMR (500 MHz, CDCl$_3$): δ 6.28 (dd, *J* = 3.4, 1.6 Hz, 1H, H-4), 6.08 (dd, *J* = 10.7, 3.5 Hz, 1H, H-3), 5.97 (t, *J* = 3.7 Hz, 1H, H-1), 5.18 (d, *J* = 1.8 Hz, 1H, H-5), 4.20 (d, *J* = 4.0 Hz, 1H, O*H*); ^{13}C NMR (125 MHz, CDCl$_3$) δ 168.1, 166.0, 165.6, 165.2 (each C=O), 133.7, 133.5, 133.4, 133.2, 130.0, 129.93, 129.86, 129.84, 129.77, 129.70, 129.08, 129.06, 129.0, 128.81, 128.77, 128.60, 128.57, 128.4, 128.34, 128.26 (each Ar-C), 91.20 (C-1), 69.9 (C-4), 68.9 (C-2), 68.7 (C-5), 67.7 (C-3), 52.9 (OCH$_3$). *Selected NMR data for β-anomer:* ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.20 (dd, *J* = 3.4, 1.3 Hz, 1H, H-4), 4.67 (d, *J* = 1.5 Hz, 1H, H-5); ^{13}C NMR (125 MHz, CDCl$_3$) δ 96.1 (C-1), 73.0 (C-5), 71.5, 70.7 (C-2&C-3), 69.1 (C-4), 53.0 (OCH$_3$).

2,3,4-Tri-O-benzoyl-D-glucopyranosiduronic acid, methyl ester (9) [19b] The known title compound was prepared as previously described from 1,2,3,4-tetra-*O*-benzoyl-D-

glucopyranose (3.00 g, 5.04 mmol) with **9** (2.14 g, 68%) being isolated after chromatography using cyclohexane-EtOAc (2:1). IR (film) cm^{-1}: 3248, 2930, 1732, 1455, 1092, 1021, 745. HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for $C_{28}H_{24}O_{10}Na$ 543.1267, found 543.1264. *Selected NMR data for α-anomer:* ^{1}H NMR (500 MHz, CDCl$_3$): δ 6.26 (t, *J* = 9.6 Hz, 1H, H-3), 5.87 (br s, 1H, H-1), 4.88 (d, *J* = 9.8 Hz, 1H, H-5); ^{13}C NMR (125 MHz, CDCl$_3$) δ 168.5, 165.73, 165.65, 165.4 (each C=O), 133.48, 133.45, 133.4, 133.3, 130.0, 129.91, 129.88, 129.81, 129.78, 129.7, 128.4, 128.3 (each Ar-H), 90.5 (C-1), 71.6 (C-2), 70.0 (C-4), 69.4 (C-3), 68.6 (C-5), 52.9 (OC*H*$_3$). *Selected NMR data for β-anomer:* ^{1}H NMR (500 MHz, CDCl$_3$): δ 5.97 (t, *J* = 9.4 Hz, 1H, H-3), 5.71 (t, *J* = 9.5 Hz, 1H, H-4), 5.11 (d, *J* = 7.4 Hz, 1H, H-1), 4.41 (d, *J* = 9.4 Hz, 1H, H-5); ^{13}C NMR (125 MHz, CDCl$_3$) δ 167.7, 166.5, 165.6, 165.3 (each C=O), 95.9 (C-1), 73.6 (C-2), 73.0 (C-5), 71.4 (C-3), 69.9 (C-4), 53.0 (OC*H*$_3$).

2,3,4-Tri-*O*-acetyl-D-galactopyranosiduronic acid, allyl ester (10)   1,2,3,4-Tetra-*O*-acetyl-α-D-galactopyranosiduronic acid[19e] (6 g, 16.57 mmol) was dissolved in DMF (40 mL) to which NaHCO$_3$ (3.48 g, 41.4 mmol) and allyl iodide (3 mL, 33 mmol) were added and the reaction was stirred at room temp for 16 h. The mixture was diluted with EtOAc, washed with Na$_2$S$_2$O$_3$, water (x3), brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. Chromatography using cyclohexane-EtOAc (2.5:1) as eluent gave the intermediate allyl ester as a white solid (5.19 g, 78%). IR (film) cm^{-1}: 2956, 1769, 1745, 1360, 1207, 1174, 1066, 941, 850, 753. ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.40 (d, J = 3.7 Hz, 1H, H-1), 5.89 (ddt, J = 16.6, 10.3, 6.0 Hz, 1H), 5.51 (t, J = 10.1 Hz, 1H, H-3), 5.35 (dd, J = 17.1, 1.3 Hz, 1H), 5.28 (dd, J = 10.3, 1.5 Hz, 1H), 5.23 (t, J = 10.1 Hz, 1H, H-4), 5.12 (dd, J = 10.1, 3.7 Hz, 1H, H-2), 4.64 (dd, J = 12.9, 5.9 Hz, 1H), 4.58 (dd, J = 12.9, 6.2 Hz, 1H), 4.43 (d, J = 10.2 Hz, 1H, H-5), 2.18 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H). ^{13}C NMR (125 MHz, CDCl3) δ 170.0, 169.5, 169.3, 168.4, 166.5 (each C=O), 130.9, 119.8, 88.8 (C-1), 70.5 (C-5), 69.12, 69.00, 68.9, 66.80, 20.8,

20.6, 20.5, 20.4 (each OAc). This intermediate ester (5 g, 12.4 mmol) was dissolved in CH_2Cl_2

(10 mL) and cooled to 0 ˚C. To this HBr (33% in AcOH, 20 mL) was added and the mixture

was stirred at room temp for 5 h. Iced water was added and the mixture was diluted with

CH_2Cl_2. The organic layer was washed with water, satd aq $NaHCO_3$ (x 2), brine, then dried

over Na_2SO_4 and the solvent was removed. The bromide was dissolved in acetone (80 mL)

and water (8 mL) to which Ag_2CO_3 (1.71 g, 6.22 mmol) was added and the reaction was stirred

in the dark for 24 h, after which time it was filtered through celite®. The mixture was then

diluted with EtOAc and washed with water, brine, dried over Na_2SO_4 and the solvent was

removed under reduced pressure. Flash chromatography using a cyclohexane-EtOAc gradient

elution gave **10** as a white solid (3.04 g, 68%). IR (film) cm^{-1}: 3490, 2932, 1736, 1371, 1217,

1031, 899. HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for $C_{15}H_{20}O_{10}Na$ 383.0954, found 383.0960;

m/z: [M+Cl]$^-$ calcd for $C_{15}H_{20}O_{10}Cl$ 395.0745, found 395.0750. *Selected NMR data for α-*

anomer: ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.67 (t, *J* = 3.5 Hz, 1H, H-1), 4.91 (d, *J* = 1.5 Hz, 1H,

H-5); ^{13}C NMR (125 MHz, CDCl$_3$) δ 170.3, 170.0, 169.8, 167.4 (each C=O), 130.9

(OCH$_2$*C*HCH$_2$), 120.0 (O*C*H$_2$CHCH$_2$), 90.8 (C-1), 69.1 (C-4), 68.3 (C-5), 67.7 (C-2), 66.9 (C-

3), 66.5 (OCH$_2$CH*C*H$_2$), 20.8, 20.63, 20.56 (each OAc). *Selected NMR data for β-anomer:* ^{1}H

NMR (500 MHz, CDCl$_3$) δ 5.76 (br signal, 1H, H-4), 4.39 (br s, 1H, H-5). ^{13}C NMR (125 MHz,

CDCl$_3$) δ 95.9 (C-1), 72.5 (C-5), 70.3 (C-2/C-3), 70.0 (C-2 & C-3), 68.2 (C-4).

2,3,4-Tri-*O*-acetyl-D-glucopyranosiduronic acid, allyl ester (11)[19i] The known title

compound was prepared as previously described from 1,2,3,4-tetra-*O*-acetyl-β-D-

glucopyranosiduronic acid, allyl ester (0.40, 0.99 mmol) with **11** (0.25 g, 71%) being isolated

after chromatography using a cyclohexane-EtOAc gradient elution. IR (film) cm^{-1}: 3489, 2943,

1748, 1735, 1216, 1061, 898. HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for $C_{15}H_{20}O_{10}Na$

383.0954, found 383. 0951. *Selected NMR data for α-anomer:* ^{1}H NMR (500 MHz, CDCl$_3$) δ

5.58 and 5.55 (overlapping signals; t, J = 9.6 Hz and d, J = 3.5 Hz, 2H, H-3, H-1), 3.70 (s, 1H, OH); ^{13}C NMR (125 MHz, CDCl$_3$) δ 170.1, 170.0, 169.6, 167.7 (each C=O), 131.0 (OCH$_2$CHCH$_2$), 119.7 (OCH$_2$CHCH$_2$), 90.3 (C-1), 70.7 (C-2), 69.5 (C-4), 69.1 (C-3), 68.1 (C-5), 66.7 (OCH$_2$CHCH$_2$), 20.7, 20.6 (each OAc). *Selected NMR data for β-anomer*: ^{1}H NMR (500 MHz, CDCl$_3$) δ 4.81 (d, J = 7.7 Hz, 1H, H-1), 4.13 (d, J = 9.5 Hz, 1H, H-5).^{13}C NMR (125 MHz, CDCl$_3$) δ 95.6 (C-1), 72.9 (C-2), 72.7 (C-5), 71.5 (C-3).

2,3,4-Tri-*O*-acetyl-D-galactopyranuronic acid, methyl ester (12).[5] The known title compound was prepared as previously described from 1,2,3,4-Tetra-O-α-D-galactopyranuronic acid, methyl ester (1.0 g, 2.65 mmol) with **12** (0.63 g, 74%) being isolated after chromatography using cyclohexane-EtOAc (1:1). IR (film) cm^{-1}: 3456, 2954, 1750, 1437, 1376, 1216, 1054, 932, 786. HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for C$_{13}$H$_{18}$O$_{10}$Na 357.0798, found 357.0791. *Selected NMR data for α-anomer:* ^{1}H NMR (500 MHz, CDCl$_3$): δ 5.81 (dd, J = 3.4, 1.7 Hz, 1H, H-4), 5.65 (d, J = 3.6 Hz, 1H, H-1), 5.47 (dd, J = 10.8, 3.4 Hz, 1H, H-3), 5.20 (dd, J = 10.8, 3.6 Hz, 1H, H-2), 4.90 (d, J = 1.9 Hz, 1H, H-5); ^{13}C-NMR (CDCl$_3$, 125 MHz): 170.7, 170.0, 169.9 (each C=O, (OAc)), 168.2 (CO$_2$CH$_3$), 90.7 (C-1), 69.2 (C-4), 67.0 (C-3), 67.8 (C-2), 68.2 (C-5), 52.8 (CO$_2$CH$_3$), 20.8, 20.6, 20.5 (each OAc). *Selected NMR data for β-anomer:* ^{1}H NMR (500 MHz, CDCl$_3$): δ 5.73 (dd, J = 2.9, 1.4 Hz, 1H, H-4), 4.74 (d, J = 6.7 Hz, 1H, H-1), 4.38 (d, J = 1.3 Hz, 1H, H-5); ^{13}C-NMR (CDCl$_3$, 125 MHz): 95.7 (C-1), 72.5 (C-5), 70.4, 70.0 (C-2 & C-3).

2,3,4,-Tri-*O*-acetyl-D-glucopyranosiduronic acid, methyl ester (13).[5] The known title compound was prepared as previously described from 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranosiduronic acid, methyl ester (1.0 g, 2.65 mmol) with **12** (0.63 g, 74%) being isolated after chromatography using cyclohexane-EtOAc (1:1). IR (film) cm^{-1}: 3467, 2954,

1737, 1452, 1336, 1239, 1037, 900, 720. HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for C$_{13}$H$_{18}$O$_{10}$Na 357.0798, found 357.0793. *Selected NMR data for α-anomer:* ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.62 – 5.52 (overlapping signals, t, J = 9.6 Hz and br s, 2H, H-3, H-1), 4.59 (d, *J* = 10.2 Hz, 1H, H-5), 3.63 (br s, 1H, OH); ^{13}C NMR (125 MHz, CDCl$_3$): δ 170.7, 170.1, 170.0, 169.6, 169.5, 168.3, 167.5 (each C=O), 90.3 (C-1), 70.7 (C-2), 69.5 (C-4), 69.0 (C-3), 68.1 (C-5), 52.9 (OCH$_3$), 20.7, 20.6, 20.52, 20.47 (each OAc). *Selected NMR data for β-anomer:* ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.30 (t, *J* = 9.4 Hz, 1H, H-3), 4.80 (d, *J* = 7.5 Hz, 1H, H-1), 4.11 (d, *J* = 9.7 Hz, 1H, H-5).

Demethylation method used for preparation of 14-16 and isolation of carboxylic acids.

The methyl ester **8**, **9** or **12** (0.15 g) was dissolved in anhydrous EtOAc (6 mL) to which molecular sieves 4Å (excess) were added. LiI (6 molar equivalents) was added to the mixture. The reaction was heated under reflux for 16 h. the reaction was diluted with EtOAc. The organic layer was washed with Na$_2$S$_2$O$_3$, water, brine, dried over Na$_2$SO$_4$ and concentrated. Flash chromatography (2:1 cyclohexane-EtOAc, then 1:1 cyclohexane-EtOAc, then 1:24:75 AcOH-MeOH-EtOAc gave the carboxylic acid.

2,3,4-Tri-*O*-benzoyl-D-galactopyranosiduronic acid 14. Demethylation of **8** (0.15 g, 0.29 mmol) as described above gave **14** (0.085 g, 53%) as a white solid; IR (film) cm^{-1}: 3225, 1729, 1421, 1254, 1091, 847. HRMS (ESI-TOF) *m/z*: [M-H]$^-$ calcd for C$_{27}$H$_{21}$O$_{10}$Na 505.1135, found 505.1140. *NMR data for α-anomer:* ^{1}H NMR (500 MHz, CD$_3$OD) δ 6.25 (br signal,1H, H-4), 6.03 (dd, *J* = 10.6, 3.4 Hz, 1H, H-3), 5.77 (d, *J* = 3.2 Hz, 1H, H-1), 5.64 (dd, *J* = 10.7, 3.4 Hz, 1H, H-2), 5.18 (d, J = 1.9 Hz, 1H, H-5). ^{13}C NMR (125 MHz, CD$_3$OD) δ 169.8, 168.9, 165.9, 165.7, 165.48, 165.45, 165.3 (each C=O), 133.8, 133.7, 133.6, 133.5, 133.2, 133.07, 133.05, 131.7, 131.6, 130.2, 130.0, 129.5, 129.4, 129.3, 129.2, 129.1, 128.4, 128.34, 128.29, 128.16,

128.13, 128.0 (each Ar-C), 90.7 (C-1), 70.5 (C-4), 69.3 (C-2), 68.3 (C-3), 68.1 (C-5). *Selected NMR data for β-anomer:* ^{1}H NMR (500 MHz, CD₃OD) δ 6.20 (br signal, 1H, H-4), 5.75 (d, *J* = 10.6, 3.4 Hz, 1H, H-3), 5.20 (d, *J* = 7.9 Hz, 1H, H-1).

2,3,4-Tri-*O*-benzoyl-D-galactopyranosiduronic acid 15. Demethylation of **9** (0.15 g, 0.29 mmol) as described above gave **15** (0.069 g, 49%) as a white solid; HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for $C_{27}H_{22}O_{10}Na$ 529.1111, found 529.1117. *Selected NMR data for α-anomer:* ^{1}H NMR (500 MHz, CD₃OD) δ 5.34 (dd, *J* = 9.8, 3.5 Hz, 1H, H-2); ^{13}C NMR (125 MHz, CD₃OD) δ 168.44, 165.82, 165.38, 165.25 (each C=O), 133.2, 133.14, 133.12, 133.08, 132.6, 130.0, 129.2, 129.1, 128.10, 128.06 (each Ar-C), 90.2 (C-1), 72.0 (C-2), 70.32, 70.27 (C-3 & C-4), 67.9 (C-5). *Selected NMR data for β-anomer:* ^{1}H NMR (500 MHz, CD₃OD) δ 5.42 (dd, *J* = 9.7, 7.9 Hz, 1H, H-2); ^{13}C NMR (125 MHz, CD₃OD) δ 95.0 (C-1), 73.14 (C-2), 73.06 (C-3), 72.4 (C-5), 70.4 (C-4).

2,3,4-Tri-*O*-acetyl-D-galactopyranosiduronic acid 16. Demethylation of **12** (0.4 g, 1.1 mmol) as described above gave **16** (0.15 g, 55%) as a white solid; IR (film) cm^{-1}: 3447, 2984, 1735, 1429, 1370, 1211, 1149, 1052. HRMS (ESI-TOF) *m/z*: [2M+H]$^+$ calcd for $C_{24}H_{31}O_{20}$ 639.1409, found 639.1413; *m/z*: [M-H]$^-$ calcd for $C_{12}H_{15}O_{10}$ 319.0665, found 319.0670. *Selected NMR data for α-anomer:* ^{1}H NMR (500 MHz, D₂O) δ 5.69 (dd, *J* = 2.9, 1.1 Hz, 1H, H-4), 5.44 (d, *J* = 3.6 Hz, 1H, H-1), 5.32 (dd, *J* = 10.7, 3.4 Hz, 1H, H-3); ^{13}C NMR (125 MHz, D₂O) δ 172.92, 172.89, 172.7, 172.6 (2 signals), 171.1, 170.2 (each C=O), 89.9 (C-1), 69.7 (C-4), 68.0 (C-5), 67.9 (C-2), 67.7 (C-3), 20.12, 20.06, 20.04, 19.99, 19.9, 19.8 (each O***Ac***). *Selected NMR data for β-anomer:* ^{1}H NMR (500 MHz, D₂O) δ 5.62 (dd, *J* = 3.3, 0.9 Hz, 1H, H-4), 5.17 (dd, *J* = 10.1, 3.5 Hz, 1H, H-3). ^{13}C NMR (125 MHz, D₂O) δ 93.9 (C-1), 72.0 (C-5), 70.9 (C-3), 70.2 (C-2), 69.1 (C-4).

2,3,4-Tri-*O*-acetyl-D-glucopyranosiduronic acid 17 To a solution of benzyl (2,3,4-tetra-*O*-acetyl-D-glucopyran) uronate[23] (0.20 g, 0.49 mmol) in anhydrous degassed EtOAc (5 mL) was added 10% wt.% Pd/C (0.05 g, 0.0487 mmol). A H_2 filled balloon was inserted via a needle and rubber septum. The reaction was stirred vigorously at room temperature for 4 h. The reaction mixture was passed through celite to remove the catalyst. Flash chromatography (cyclohexane/EtOAc 2:1, 1:1, MeOH/EtOAc 1:4 (1% AcOH)) gave the title compound **17** (0.15 g, 95%) as a white solid. IR (film) cm^{-1}: 3449, 2961, 1720, 1584, 1315, 1211, 1149, 1089, 801; HRMS (ESI-TOF) *m/z*: [M-H]$^-$ calcd for $C_{12}H_{15}O_{10}$ 319.0665, found 319.0670. *Selected NMR data for α-anomer:* ^{1}H NMR (500 MHz, D_2O) δ 5.43-5.34 (m, 2H, overlapping peaks of H-1, H-3), 5.10 (t, *J* = 9.6 Hz, 1H, H-4), 4.93 (dd, *J* = 9.6, 3.5 Hz, 1H, H-2), 4.52 (d, *J* = 9.7 Hz, 1H, H-5), 2.00 (s, 3H), 1.98 (s, 3H), 1.96 (s, 3H) (each OAc). ^{13}C NMR (125 MHz, D_2O) δ 173.0, 172.6, 171.8 (each C=O), 89.4 (C-1), 70.4 (C-2), 69.7 (C-3), 69.4 (C-4), 67.5 (C-5), 20.03, 19.99, 19.95 (each OAc). *Selected NMR data for β-anomer:* ^{1}H NMR (500 MHz, D_2O) δ 5.29 (t, *J* = 9.5 Hz, 1H, H-3), 4.85 (dd, *J* = 9.5, 7.7 Hz, 1H, H-2), 4.22 (d, *J* = 10.2 Hz, 1H, H-5). ^{13}C NMR (125 MHz, D_2O) δ 93.8 (C-1), 72.4 (2 s, C-2 and C-3), 71.5 (C-5), 69.6 (C-4).

Supporting Information Available: NMR spectra of compounds and chemical shift assignments for compounds in Figure 1 (Tables S1-S4).

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