The stereoselectivities of tributyltin hydride-mediated reductions of 5-bromo-D-glucuronides to L-iduronides are dependent on the anomic substituent: syntheses and DFT calculations†

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One of the shortest synthetic routes to L-iduronic acid derivatives is via free radical reduction of the C-5 bromide of the corresponding protected D-glucuronic acid derivative. The epimerization of such C-5 bromides to the L-ido derivatives via reaction with tributyltin hydride was investigated. It was found that the stereoselectivity of the reaction was dependent on the anomic substituent. If the substituent was fluoride the L-ido product was obtained exclusively in 65–72% yield whereas the O-methyl or O-acetyl derivatives led to isomeric mixtures of both the L-ido and D-gluco products in different ratios depending on the reaction conditions. DFT calculations were performed to determine the stereoelectronic factors that favour formation of the L-ido isomer from the fluoride and suggest the selectivity is due to a transition state gauche effect and an Sn-F interaction.

Introduction

The monosaccharide L-iduronic acid (IdoA) is a key component of the glycosaminoglycans (GAGs) heparin, heparan sulfate (HS) and dermatan sulfate (DS). GAGs are complex, highly sulfated polysaccharides composed of repeating disaccharide sub-units of a uronic acid, either IdoA or D-glucuronic acid (GlcA), (1→4)-linked to D-glucosamine (for heparin/HS) or (1→3) linked to N-acetylgalactosamine (for DS). GAGs mediate numerous biological processes via their interactions with a range of structurally diverse proteins such as growth factors, enzymes, morphogens, cell adhesion molecules and cytokines. GAGs are therefore key players in various disease processes such as angiogenesis, metastasis, inflammation and viral infections. The synthesis of well-defined GAG oligosaccharides is thus of great interest for identifying therapeutically useful sequences and elucidating structure-activity relationships.

The main challenge in the synthesis of GAG oligosaccharides is the efficient preparation of IdoA building blocks since neither IdoA nor L-idose are commercially available or readily accessible from natural sources.

Numerous synthetic approaches for the preparation of IdoA and/or L-idose have been reported, each with their own advantages and disadvantages, and these have been comprehensively reviewed recently. Amongst these methodologies, a common approach involves the inversion of configuration at C-5 of the more abundant D-gluco configured derivatives, which differ from L-idose only by the stereochemistry at this carbon. Commonly used methods for inversion of configuration at C-5 include S_N2 displacement of sulfonates, and radical induced epimerization at C-5. The latter method involves the tributyltin hydride-mediated reduction of the readily derived C-5 bromide of a protected GlcA derivative, which usually results in an isomeric mixture of both L-ido and D-gluco products requiring chromatographic separation.

The isomeric ratios for the C-5 epimerization of protected GlcA derivatives using tributyltin hydride that have been reported in the literature show significant variation depending on the reaction conditions and the nature of the anomic substituent. In 1986, Chiba and Sinay reported that when methyl 1,2,3,4-tetra-O-acetyl-5-C-bromo-D-glucopyranosyluronate 1 was reduced with tributyltin hydride in toluene at reflux the L-ido to D-gluco product ratio was 1:2.3, with the L-idopyranuronate 2 isolated in only 27% yield (Scheme 1). When the β-anomeric substituent was changed from acetyl to methoxy, reduction of the derived C-5 bromide 7 gave an improvement in selectivity to 1:1.2, with L-idopyranuronate 8 isolated in 38% yield. Medaković subsequently reported that the selectivity in favour of the 1-ido product could be significantly improved by changing the anomeric configuration of the start.
ing material from β to α. A lowering of the reaction temperature also resulted in a higher yield of the desired product with less decomposition. Thus, reduction of bromide 4 with tributyltin hydride in benzene at reflux gave a ratio of 3.3 : 1 in favour of the L-ido product which was isolated in 67% yield. More recently, Wong and co-workers\textsuperscript{30} reported the same isomeric ratio of 3.3 : 1 in favour of the L-ido isomer upon reduction of 4 in benzene and an improved ratio of 2 : 1 in favour of the L-ido isomer upon reduction of 1 under the same conditions. There have also been reports of the reduction of the 5-C-bromo-β-fluoride 10 with tributyltin hydride in both toluene and benzene.\textsuperscript{31,32} Voznyi et al.\textsuperscript{31} carried out the reaction in toluene and obtained a product ratio of 2.6 : 1 in favour of the L-idopyranosyl fluoride 11 which was isolated in 67% yield. Interestingly, Gelb and coworkers\textsuperscript{32} obtained 11 exclusively in 64% yield when the reaction was carried out in benzene and did not report any evidence of the formation of the D-glucopyranosyl fluoride 12. The above ratios of L-ido to D-gluco products are based on isolated yields. The results indicate that both the nature and the stereochemistry of the anomeric substituent as well as the temperature play a role in the stereochemical outcome of the radical reduction reaction.

Despite the limitations of the above route, it remains one of the most direct methods to access IdoA building blocks and the fluoride 11, prepared in this fashion, has been utilized for the synthesis of iduronate-2-sulfatase substrates for newborn screening of MPS II (Hunter syndrome), an important lysosomal storage disease.\textsuperscript{32} This route was thus chosen for further investigation as part of a program aimed at the synthesis of orthogonally protected IdoA derivatives. Herein are described our own studies of the tributyltin hydride mediated reduction of GlcA C-5 bromides, which show that a β-F substituent at the anomeric carbon leads to high selectivity in favour of the desired L-ido product. Density functional theory (DFT) calculations are performed to understand the role of the β-F substituent.

**Results and discussion**

In order to study the influence of various anomeric substituents on the stereochemical outcome of C-5 epimerization by tributyltin hydride reduction, several derivatives of GlcA were prepared, photobrominated and then reduced with tributyltin hydride. Firstly, D-glucuronolactone 13 was initially treated with NaOMe and then acetylated under acidic conditions using perchloric acid in acetic anhydride, according to the procedure reported by Bollenback et al.\textsuperscript{13} to give methyl tetra-O-acetyl-D-glucuronolactone as a mixture of anomers. Samples of the pure anomers 3 and 6 were then isolated by fractional

![Scheme 1](https://example.com/scheme1.png)
crystallization and flash chromatography (Scheme 2) and their structures confirmed by NMR spectroscopy. The β-anomer 3 was then utilized for the synthesis of the other GlcA derivatives 9, 12 and 15. Treatment of 3 with HF·pyridine complex gave the α-fluoride 15 in low yield (19%). Reaction of 3 with HBr in acetic acid gave the bromide 14 which was glycosylated with methanol under Koenigs–Knorr conditions in the presence of Ag₂CO₃ to give the β-methyl glycoside 9 in 91% yield. Bromide 14 was also converted into the β-glycosyl fluoride 12 in 94% yield via treatment with silver fluoride in dry acetonitrile. Free radical bromination of the D-glucuronic acid derivatives (3, 6, 9 and 12) using NBS and UV light in refluxing CCl₄ as described by Ferrier and Furneaux, gave the known C-5 bromides in acceptable yield (39–75%). Treatment of the α-fluoride 15 under the same conditions, however, resulted in a complex mixture from which no desired product could be isolated. The radical bromination reaction is a homolytic process in which the methoxycarbonyl group at C-5 provides stabilisation of the intermediate radical leading to selective bromination of C-5. On the whole the C-5 bromides gave satisfactory analytical and spectroscopic data. Bromide 1 gave a low m.p. (103–105 °C) compared with that reported by Ferrier and Furneaux (159–161 °C), however, the ¹H NMR spectrum was in accord with that reported and the ¹³C NMR and mass spectra were all in agreement with the proposed structure. Both 1 and 7 were then converted into mixtures of their respective starting materials (3 and 9) and their l-ido configured counterparts (2 and 8) upon reduction with tributyltin hydride (see below).

Tributyltin hydride mediated reduction of the C-5 bromide derivatives 1, 4, 7 and 10 yielded isomeric mixtures of D-gluco and l-ido configured products (Table 1). The reductions for all the C-5 bromides were carried out at a concentration of 60–80 mM in benzene at reflux with 0.1 mol% AIBN unless otherwise stated. Reduction of bromide 1 gave a 1 : 1.8 ratio of l-idopyranuronate 2 to D-glucopyranuronate 3 in good overall yield (70%). This was significantly worse than the 2 : 1 ratio reported by Wong and coworkers but similar to the 1 : 2.3 ratio obtained by Chiba and Sinai in toluene at reflux. When the reaction was carried out in toluene the overall yield was similar but the product ratio worsened to only 1 : 5. The decreased fraction of l-ido isomer in refluxing toluene is unexpected. It is possible that the higher temperature accelerates the formation of both isomers, but also accelerates degradation of the l-ido isomer, leading to an apparent decrease in the proportion of l-ido product isolated. Reduction of the α-anomer 4 gave an isomeric ratio of 3.7 : 1 of l-idopyranuronate 5 to D-glucopyranuronate 6, which was a slightly improvement over the 3.3 : 1 ratio previously reported. However, the overall yield was 78% compared with 87–91%. It is noteworthy that the ¹³C NMR data reported in the literature for 2 by Whitfield et al. matches that obtained for the β-l-anomer.

**Scheme 2** Synthesis of C-5 bromides of D-glucuronic acid derivatives. Reagents and conditions: (a) i. NaOMe/MeOH, ii. Ac₂O/HClO₄; (b) NBS/CCl₄, light, reflux, 2 h, 75% for 1, 2 h, 39% for 4, 1.5 h, 49% for 7, 24 h, 44% for 10; (c) 30% HBr·HOAc, 2 h, 62%; (d) AgCO₃, MeOH, 91% (e) AgF, MeCN, 94%; (f) HF·Pyr, 19%.
5 obtained here and also reported by Wong and co-workers, although in the latter case the product from the reduction of 4 was mislabelled as being the “α-L-ido pyranuronate.”

Reduction of β-methyl glucopyranuronate 7 resulted in a similar (1 : 1.1) isomeric ratio of products as reported by Chiba and Sinaÿ while reduction of the fluoride 10 gave exclusively L-ido isomer 11 in 65% yield, as also reported by Gelb and co-workers. No trace of the α-gluco isomer was detected by 1H NMR spectroscopy. Overall, the isomeric ratios obtained were similar to the literature, and show a dependence upon the nature and configuration of the substituent at the anomeric centre. The isomer ratios reported in Table 1, including the denoted product ratios, were determined by 1H NMR analysis of crude product mixtures. Owing to possible losses during workup, these ratios are not necessarily equivalent to the relative rates at which the L-ido and α-gluco products are generated. To begin, calculations were performed on a model system consisting of the reduction of pyranosyl radical A (Fig. 1a) by Me3SnH. Radical A lacks the OAc groups of 10 but contains the β-F substituent and the ester group. Transition states for hydrogen atom transfer to A from Me3SnH were computed. The computational procedure involved geometry optimizations in implicit benzene at the B3LYP/6-31G(d)-LANL2DZ-SMD (benzene) level of theory, followed by single-point energy calculations with B3LYP-D3(BJ)/Def2-TZVPP-SMD(benzene). Based on a preliminary conformational search of bromide 10, six transition state geometries were considered, as shown in Fig. 1b. In three of the transition states (TS1–TS3), Me3SnH delivers a hydrogen atom to the β face of A, leading to L-ido configured product B. In the other three transition states (TS4–TS6), Me3SnH delivers a hydrogen atom to the α face of A leading to the α-gluco configured product C. Transition states TS1 and TS4 have a 1C4 pyranose chair conformation, with fluorine equatorial. TS2 and TS5 have a 1C4 chair conformation, with fluorine axial. TS3 and TS6 are 2S5 and 1S5 skew-boats, respectively.

The calculated free energy barriers of TS1–TS6 span a range of 4.4 kcal mol⁻¹. The lowest-energy transition state is TS2. Its structure is shown in Fig. 1c. TS2 features a 1C4 chair pyranose ring, an axial β-F substituent, and an axial approach trajectory for the delivery of the hydrogen atom to C-5 by the stannane. The conformation of the pyranose ring in TS2 is similar to that in the most stable conformer of radical A (Fig. 1a), which is stabilized by negative hyperconjugation between the axial lone pair on oxygen and the C-F σ* orbital. The reaction of Me3SnH with this radical occurs preferentially via an axial trajectory (TS2) rather than an equatorial trajectory (TS5). This preference may be attributed to two factors, which are depicted schematically in Fig. 2. The first factor is a stereoelectronic effect recently termed the ‘transition state gauche effect’ by Houk, Hsung and co-workers. This effect depends on hyperconjugative interactions between the σ* orbital associated with

### Table 1  Reduction of C-5 bromides with tributyltin hydride in benzene (or toluene)

<table>
<thead>
<tr>
<th>C-5 bromide</th>
<th>Radical initiator</th>
<th>ABIN</th>
<th>% L-ido (% α-gluco)</th>
<th>Et3B</th>
<th>Literature</th>
<th>% L-ido (% α-gluco)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (toluene)</td>
<td>1 : 1.8</td>
<td>17%</td>
<td>53%</td>
<td>1 : 3.3</td>
<td>2 : 1ε</td>
<td>53% (27%)</td>
<td>30</td>
</tr>
<tr>
<td>4 (toluene)</td>
<td>3.7 : 1ε</td>
<td>62%</td>
<td>16%</td>
<td>3.4 : 1</td>
<td>3.3 : 1ε</td>
<td>70% (21%)</td>
<td>30</td>
</tr>
<tr>
<td>7 (toluene)</td>
<td>1 : 1.1</td>
<td>43%</td>
<td>48%</td>
<td>1 : 1.8</td>
<td>1 : 1.2</td>
<td>38% (44%)</td>
<td>28</td>
</tr>
<tr>
<td>10 (toluene)</td>
<td>1 : 0</td>
<td>65%</td>
<td></td>
<td>1 : 0</td>
<td>64%</td>
<td></td>
<td>32</td>
</tr>
</tbody>
</table>

* Reactions were performed under nitrogen or argon in benzene or toluene at reflux at a concentration of 60–80 mM. Reactions were performed under argon in toluene at r.t. at a concentration of 40 mM. Product ratios were determined by 1H NMR analysis of crude product mixtures. Except where indicated, reactions were conducted in benzene or toluene at reflux at various concentrations (up to 190 mM) without the use of a radical initiator. ABIN used as a radical initiator.
the newly-forming C–H bond, and groups on adjacent atoms. The C–H σ* orbital acts as a σ acceptor. In the axial TS2, the forming C–H bond is antiperiplanar to one of the oxygen lone pairs, which is an electron donor, and this arrangement is stabilized by hyperconjugation. In contrast, in equatorial TS5 the forming C–H bond is antiperiplanar to the O–C bond, which is a poorer σ donor than an oxygen lone pair. This arrangement is less stabilized by hyperconjugation. The second factor contributing to the stability of TS2 is a non-covalent interaction between Sn and F. These two atoms lie 3.39 Å apart in TS2, well within the sum of the van der Waals radii of Sn and F (3.64 Å), whereas in TS5 there is no Sn–F interaction (>6 Å).

Compared with TS2, the other transition states for the reaction of radical A with Me3SnH are all at least 2 kcal mol⁻¹ higher in energy. At the temperature of refluxing benzene (80 °C), TS2, which leads to α-ido configured product B, would be expected to account for >92% of product formation.

Although the calculations on the model radical A match the selectivity observed experimentally in the reduction of 10, which favors the α-ido product, conformational effects associated with the acetyl groups of 10 give rise to a different set of stereoelectronic factors that determine the transition-state energies of this reaction. Transition-state calculations for the reaction of the C-5 radical derived from 10 with Me₃SnH are shown in Fig. 3. Transition states TS1'–TS6' have the same pyranose conformations and Me₃SnH attack trajectories as model transition states TS1–TS6, respectively, except for transition state TS6', which has a 1S₅ skew-boat pyranose ring as opposed to the 1S₅ conformation of TS6.

The most obvious difference between the reactions of the model and acetylated radicals is that, for the acetylated radical, no transition state analogous to TS2 (which was the lowest-energy TS in the model system) could be found. Such a transition state is disfavored because the F substituent, C₃-acetyl group, and incoming stannane occupy a very crowded 1,3,5-triaxial arrangement. Attempts to locate TS2 on the potential energy surface led to collapse to the reactants. Interestingly, it proved possible to locate the α-gluco configured transition state TS5', which is also 1,3,5-triaxial but slightly less crowded. The transition states TS1', TS5', and TS6', are high in energy (≥2.4 kcal mol⁻¹) and do not contribute significantly to the reaction. Only transition states TS3' and TS4' are low enough in energy to make significant contributions to product formation.

Favored transition state TS3' (α-ido) is 1.0 kcal mol⁻¹ lower in energy than TS4' (α-gluco). Based on the calculated ΔG° values of all five transition states, the predicted isomer ratio (11 : 12) resulting from the reduction of bromide 10 at 80 °C is 77 : 23. This is lower than the experimental selectivity (100 : 0, Table 1). Some of the discrepancy between theory and experiment may stem from inaccuracies in the energies of transition-state conformers resulting from the use of Me₃SnH as a model for Bu₃SnH. Furthermore, as described above, the possibility that some 12 is formed but degrades prior to workup cannot be ruled out. Nonetheless, the calculations do correctly predict that the reduction of 10 favors the α-ido product.

Transition state TS3' features a 1S₅ skew-boat conformation of the pyranose ring, while second-lowest transition state TS4' is a 4C₁ chair. In the absence of Me₃SnH, these two radical
conformations are almost equienergetic. Both TSs contain antiperiplanar arrangements between the C–H forming bond and oxygen lone pair orbitals, allowing hyperconjugative stabilization. The lower energy of TS3′, relative to TS4′, reflects a stronger interaction between the radical and the stannane. While the forming and breaking bond lengths are the same in each TS, TS3′ derives additional stabilization from a Sn–F interaction (3.65 Å), whereas no such interaction is present in TS4′.

Conclusions

In conclusion, a series of D-glucuronides bearing different substituents at the anomeric centre were photobrominated to give the respective 5-C-bromo-D-glucuronides. The bromides were subjected to tributyltin hydride-mediated radical reduction to give a mixture of L-ido and D-gluco configured products. All final compounds and synthetic intermediates were fully characterized by NMR spectroscopy. In keeping with previous literature reports, it was found that the diastereomeric product ratio was dependent on the reaction temperature (reactions conducted in refluxing benzene versus toluene) and, in particular, upon the nature and configuration of the anomeric substituent. Particularly noteworthy was the reduction of the 5-C-bromo-D-glucuronylβ-fluoride 10 which gave exclusively the L-ido product, making this an attractive small-scale route to IdoA building blocks. DFT calculations show that the L-ido selectivity obtained with the β-F derivative originates from a combination of a transition state gauche effect and an Sn–F interaction.

Experimental section

General methods

Melting points were determined on a DigiMelt MSRS apparatus. Optical rotations were determined on a JASCO P-2000 polarimeter at ambient temperature and are given in units of 10−1 deg cm2 g−1. 1H and 13C NMR spectra were recorded on a Bruker Avance 500 MHz spectrometer at 20 °C. The residual solvent peaks (CDCl3: δH 7.24 and δC 77.0) served as internal standard. Coupling constants in Hz were measured from one-dimensional spectra. Low resolution mass spectra were acquired on a Bruker HCT 3D mass spectrometer. All chemicals were purchased as reagent grade and used without further purification. Carbon tetrachloride, hexane, and EtOAc were distilled before use. Reactions were monitored by analytical thin layer chromatography (TLC) on silica gel 60 F254 plates and visualized by charring with 10% sulfuric acid in ethanol.

Methyl 1,2,3,4-tetra-O-acetyl-D-glucopyranuronate (3, 6). To a stirred solution of D-glucurono-6,3-lactone 13 (17.0 g, 78 mmol) in MeOH (50 mL) was added a catalytic amount of sodium methoxide (50 mg). The mixture was stirred at r.t. for 1 h and then concentrated under reduced pressure. The residue was dissolved in acetic anhydride (50 mL) and a mixture of HClO4 (1.0 mL) in acetic anhydride (2 mL) was added dropwise such that the reaction temperature did not rise above 40 °C. The mixture was then stirred at r.t. for 24 h and then kept at 5 °C for 24 h leading to separation of crystalline material. The crystalline material was isolated by filtration, washed with ether and recrystallized from ethanol to give pure methyl 1,2,3,4-tetra-O-acetyl-β-D-glucopyranuronate 3.
Methyl (2,3,4-tri-O-acetyl-α-D-glucopyranosyl) bromide (14). The tetractate 3 (2.0 g, 5.3 mmol) was suspended at 0 °C in 33% HBr in acetic acid (27 mL) under a N₂ atmosphere. After stirring for 15 min at 0 °C, the reaction mixture was allowed to warm up to rt and stirred for a further 2 h. The acetic acid was then removed by evaporation with toluene under reduced pressure. The crude oil was diluted with EtOAc (50 mL) and washed with cold sat. NaHCO₃ (4 x 20 mL) until bubbling ceased. The organic layer was dried (MgSO₄) and concentrated under reduced pressure to give the bromide 14 (1.3 g, 62%) as an oil. The crude material was used in the next step without further purification. The ¹H and ¹³C NMR spectra were in accord with the literature.⁴⁸ ¹H NMR (500 MHz, CDCl₃): δ 6.62 (d, 1H, J₁₂ = 4.0 Hz, H-1), 5.59 (dd, 1H, J₁₂ = 9.7 Hz, J₃₄ = 9.5 Hz, H-3), 5.22 (dd, J₃₄ = 10.3 Hz, H-4), 4.84 (dd, 1H, H-2), 4.56 (d, 1H, H-5), 3.75 (s, 3H, OCH₃), 2.08 (s, 3H, CH₃), 2.04 (s, 3H, CH₃), 2.03 (s, 3H, CH₃); ¹³C NMR (125 MHz, CDCl₃): δ 169.6, 169.6, 169.4, 166.6 (4 x C=O), 85.3 (C-1), 72.0 (C-2), 76.3 (C-3), 68.4 (C-4), 53.1 (OCH₃), 20.5, 20.4 (3 x CH₃). Methyl (methyl 2,3,4-tri-O-acetyl-β-D-glucopyranosyld) uronate (9). To a stirred solution of the bromide 14 (0.50 g, 1.3 mmol) in dry toluene (10 mL) under an Ar atmosphere, dry MeOH (1 mL) was added and the solution was warmed to 75 °C. Subsequently silver carbonate (0.50 g, 1.8 mmol) was added in three portions over a period of 3 h. The reaction mixture was stirred at this temperature for 18 h. The reaction mixture was then cooled to r.t., filtered and the filtrate was concentrated under reduced pressure. Flash chromatography (EtOAc/hexane 1:1) of the crude mixture gave the methyl glycoside 9 (0.41 g, 91%), m.p. 154–155 °C (hexane/EtOAc; lit.⁵⁷ 154.1–154.4 °C; lit.⁵⁸ 151–152 °C; lit.⁵⁹ 148–150 °C). [α]D = −3.1 (c 0.3, CHCl₃; lit.⁵⁷ −28.1). The ¹H and ¹³C NMR spectra were in accord with the literature.⁵⁷,⁵⁸ ¹H NMR (500 MHz, CDCl₃): δ 5.26–5.18 (m, 2H, H-3,4), 5.00–4.96 (m, 1H, H-2), 4.46 (d, 1H, J₁₂ = 7.7 Hz, H-1), 4.04–4.00 (m, 1H, H-5), 3.74 (s, 3H, OCH₃), 3.50 (s, 3H, OCH₃), 2.03 (s, 3H, CH₃), 2.00 (s, 3H, CH₃), 1.99 (s, 3H, CH₃); ¹³C NMR (125 MHz, CDCl₃): δ 170.1, 165.9, 169.2, 167.3 (4 x C=O), 101.8 (C-1), 72.6 (C-2), 71.2 (C-3), 69.5 (C-4), 57.3 (OCH₃), 52.9 (OCH₃), 20.7, 20.6, 20.5 (3 x CH₃); ESMS: m/z 386.9 [M + Na]+.

Methyl (2,3,4-tri-O-acetyl-α-D-glucopyranosyl) fluoride (15). The peracetate 3 (0.40 g, 1.1 mmol) was dissolved in 30% HF/pyridine (10 mL) at −20 °C under an argon atmosphere. The mixture was then allowed to warm up to r.t. and stirred for 18 h. The reaction mixture was then diluted with DCN (20 mL) and washed with water, saturated aq. NaHCO₃, dried (MgSO₄) and concentrated under reduced pressure. The crude material was then purified by flash column chromatography (hexane/EtOAc 1:1) to give the fluoride 15 (70 mg, 19%) as colourless oil. The ¹H and ¹³C NMR spectra were in accord with the literature.³⁶ ¹H NMR (500 MHz, CDCl₃): δ 5.79 (dd, 1H, J₁₂ = 2.6 Hz, J₁₅ = 52.5 Hz, H-1), 5.53 (dd, 1H, J₁₂ = 9.9 Hz, H-3), 5.21 (dd, 1H, J₁₂ = 9.9 Hz, H-4), 4.95 (dd, J₁₂ = 23.9 Hz, H-2), 4.44 (d, 1H, H-5), 3.74 (s, 3H, OCH₃), 2.08 (s, 3H, CH₃), 2.02 (s, 3H, CH₃), 2.02 (s, 3H, CH₃); ¹³C NMR (125 MHz, CDCl₃): δ 169.9, 169.8, 169.4, 167.0 (C-6), 103.5 (d, J₁₅ = 231.4 Hz, C-1), 69.9 (d, J₁₂ = 24.0 Hz, C-2), 69.8 (d, J₁₂ = 4.3 Hz, C-5), 53.1 (OCH₃), 20.4, 20.5, 20.6 (3 x CH₃); ESMS: m/z 359.0 [M + Na]+.

Methyl (2,3,4-tri-O-acetyl-β-D-glucopyranosyl) fluoride (12). To a solution of the bromide 14 (0.50 g, 1.3 mmol) in dry acetonitrile (20 mL) under a N₂ atmosphere was added silver fluoride (0.60 g, 4.8 mmol). The reaction mixture was then stirred overnight in the dark at r.t. The reaction mixture was then filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (hexane/EtOAc 2:1) to give the fluoride 12 (0.40 g, 94%) as a solid, m.p. 104–107 °C (EtOAc/hexane; lit.⁵₂,⁵³ 108–109 °C). [α]D = +13.3 (c 1.2, CHCl₃; lit.⁵₂,⁵³ +18). The ¹H NMR spectrum was in accord with the literature.⁵₂,⁵³ ¹H NMR (500 MHz, CDCl₃): δ 5.42 (dd, 1H, J₁₂ = 5.1 Hz, J₁₅ = 51.0 Hz, H-1), 5.40 (dd, 1H, J₁₂ = 8.8 Hz, J₁₅ = 0.7 Hz, H-4), 5.26–5.18 (m, 1H, H-3), 5.08 (dd, J₁₂ = 7.6 Hz, J₁₅ = 22.2 Hz, H-1, H-2), 4.45 (d, 1H, H-5), 3.76 (s, 3H, OCH₃), 2.08 (s, 3H, CH₃), 2.03 (2s, 6H, 2 x CH₃); ¹³C NMR (125 MHz, CDCl₃): δ 169.8, 169.3, 169.1, 166.9 (4 x C=O), 105.8 (d, J₁₅ = 223.8 Hz, C-1), 72.2, (d, J₁₂ = 3.5 Hz, C-5), 70.6 (d, J₁₅ = 31.0 Hz, C-2), 70.4 (d, J₁₅ = 6.7 Hz, C-3), 67.9 (C-4), 53.1 (OCH₃), 20.6, 20.5, 20.5 (3 x CH₃); ESMS: m/z 338.9 [M + Na]+.
**General procedure for the radical bromination reaction**

A suspension of glycosyl uronate (1 eq.) and N-bromosuccinimide (2 eq.) in dry 
CCl₄ (10 mL per 1.0 mmol) was heated at reflux for 4 h under irradiation with a 500 W tungsten lamp. 
The reaction mixture was then cooled to r.t. and filtered over celite, and concentrated under reduced pressure. The pure 
bromide was isolated by flash chromatography (hexane:EtOAc : toluene 1 : 1 : 0.1).

**Methyl 1,2,3,4-tetra-O-acetyl-5-C-bromo-α-D-glucopyranosyluronate (1).** Bromination of uronate 3 (0.47 g, 1.2 mmol) via 
the general procedure gave the bromide 1 (0.41 g, 78%) as a colourless oil. 1H NMR (500 MHz, CDCl₃): δ 6.26 (d, 1H, J₁,₂ = 8.8 Hz, H-1), 5.52 (dd, 1H, J₁,₂ = J₃,₄ = 9.5 Hz, H-3), 5.30 (d, 1H, H-4), 5.22 (dd, H-2), 3.81 (s, 3H, OCH₃), 2.11 (s, 3H, CH₃), 2.08 (s, 3H, CH₃), 2.03 (s, 3H, CH₃), 2.00 (s, 3H, CH₃); 13C NMR (125 MHz, CDCl₃): δ 169.6, 169.1, 169.0, 168.2, 164.2 (5 × C=O), 90.8 (C-1), 89.0 (C-5), 70.7 (C-4), 69.8 (C-2), 69.2 (C-3), 54.1 (OCH₃), 20.6, 20.6, 20.5, 20.5 (4 × CH₃); ESMS: m/z 476.9 [M + Na]⁺.

**Methyl 1,2,3,4-tetra-O-acetyl-5-C-bromo-α-D-glucopyranosyluronate (4).** Bromination of uronate 6 (0.53 g, 1.4 mmol) via 
the general procedure gave the bromide 4 (0.25 g, 39%) as a colourless oil. 1H and 13C NMR spectra were in accord with the literature. 28,38 1H NMR (500 MHz, CDCl₃): δ 6.51 (d, 1H, J₁,₂ = 4.1 Hz, H-1), 5.78 (dd, 1H, J₁,₂ = 10.1 Hz, J₃,₄ = 9.8 Hz, H-3), 5.23 (d, 1H, H-4), 5.17 (dd, H-2), 3.80 (s, 3H, OCH₃), 2.19 (s, 3H, CH₃), 2.09 (s, 3H, CH₂), 2.03 (s, 3H, CH₂), 2.02 (s, 3H, CH₃); 13C NMR (125 MHz, CDCl₃): δ 169.5, 169.4, 169.8, 168.5, 168.4 (5 × C=O), 89.5 (C-1), 87.1 (C-5), 69.8 (C-3), 67.9 (C-4), 67.0 (C-2), 54.1 (OCH₃), 21.2, 20.6, 20.5, 20.3 (4 × CH₃); ESMS: m/z 476.9 [M + Na]⁺.

**Methyl (methyl 2,3,4-tri-O-acetyl-5-C-bromo-α-D-glucopyranosido)uronate (7).** Bromination of uronate 9 (0.41 g, 1.2 mmol) via 
the general procedure gave the bromide 7 (0.20 g, 49%) as a colourless oil. 28 1H NMR (500 MHz, CDCl₃): δ 5.46 (dd, 1H, J₁,₂ = J₃,₄ = 9.5 Hz, H-3), 5.27 (d, 1H, H-4), 5.10 (dd, 1H, J₁,₂ = 8.3 Hz, H-2), 5.00 (d, H-1), 3.82 (s, 3H, OCH₃), 3.53 (s, 3H, OCH₂), 2.06 (s, 3H, CH₃), 2.04 (s, 3H, CH₃), 1.98 (s, 3H, CH₃); 13C NMR (125 MHz, CDCl₃): δ 169.7, 169.2, 168.9, 164.6 (4 × C=O), 101.6 (C-1), 90.1 (C-5), 70.8 (C-3), 70.1 (C-4), 70.0 (C-2), 57.8 (OCH₃), 54.0 (OCH₃), 20.6, 20.6, 20.5 (3 × CH₃); ESMS: m/z 448.9 [M + Na]⁺.

**Methyl 2,3,4-tri-O-acetyl-5-C-bromo-α-D-glucopyranosyl fluoride (uronate) (8).** Bromination of uronate 10 (0.37 g, 
1.1 mmol) via the general procedure gave the bromide 10 (0.20 g, 44%) as a colourless oil. 31 1H NMR spectrum was in accord with the literature. 31 1H NMR (500 MHz, CDCl₃): δ 5.70 (dd, 1H, J₁,₂ = 51.2 Hz, H-2, 7.3 Hz, H-1), 5.47 (dd, 1H, J₁,₂ = J₃,₄ = 9.5 Hz, J₃,₄ = 10.3 Hz, H-3), 5.35 (d, 1H, H-4), 5.22 (dd, 1H, J₁,₂ = J₃,₄ = 23.2 Hz, H-2), 3.85 (s, 3H, OCH₃), 2.09 (s, 3H, CH₃), 2.08 (s, 3H, CH₃), 2.00 (s, 3H, CH₂); 13C NMR (125 MHz, CDCl₃): δ 169.6, 169.0, 168.8, 163.8 (4 × C=O), 106.3 (d, J₁,₂ = 225 Hz, C-1), 87.7 (d, J₁,₂ = 8.0 Hz, C-5), 70.0 (d, J₁,₂,F = 23.9 Hz, C-2), 69.9 (d, J₁,₂,F = 10.6 Hz C-3), 69.4 (C-4), 54.5 (OCH₃), 20.7, 20.6, 20.5 (3 × CH₃); ESMS: m/z 415.8 [M + Na]⁺.
(4 × C═O), 99.2 (C-1), 67.2 (C-4), 66.9 (C-3), 66.7 (C-2), 66.3 (C-5), 56.3 (OCH₃), 52.6 (OCH₃), 20.8, 20.6 (3 × CH₃); ESMS: m/z 371.0 [M + Na]⁺.

Methyl (2,3,4-tri-O-acetyl-α-L-idopyranosylfluoride) uronate (11). The bromide 10 (0.19 g, 0.4 mmol) was reduced with tributyltin hydride according to the general procedure to give 11 (100 mg, 65%) as a colourless oil. [α]D −37.1 (c 0.1, CHCl₃; lit. 31−39) The 1H and 13C NMR spectra were in accord with the literature. 31H NMR (500 MHz, CDCl₃): δ 5.67 (d, 1H, J₁,F = 47.6 Hz, H-1), 5.15−5.12 (m, 1H, H-4), 5.04 (br s, 1H, H-3), 4.91 (d, 1H, J₂,F = 2.0 Hz, H-5), 4.85−4.82 (m, 1H, H-2), 3.76 (s, 3H, OCH₃), 2.10 (s, 3H, CH₃), 2.06 (s, 3H, CH₃), 2.04 (s, 3H, CH₃); 13C NMR (125 MHz; CDCl₃): δ 169.2, 168.9, 168.6, 167.1 (4 × C═O), 104.7 (d, J₁,F = 226.6 Hz, C-1), 67.5 (d, J₂,F = 2.5 Hz, C-5), 65.8 (C-4), 65.1 (C-3), 64.2 (d, J₂,F = 37.9 Hz, C-2), 52.7 (OCH₃), 20.6, 20.5, 20.4 (3 × CH₃); ESMS: m/z 359.0 [M + Na]⁺.

General procedure for triethylborane initiated tributyltin hydride reduction

The α-glucuronic acid 5-C-bromide (1 eq.) was dissolved in anhydrous toluene (40 mM) and stirred under argon. Tributyltin hydride (1.1 eq.) and triethylborane (1 M in hexanes, 0.1 eq.) was added, and the reaction mixture was stirred at r.t. for 30 min. The reaction mixture was then concentrated under reduced pressure. The crude residue was then dissolved in acetonitrile and washed with hexane (×3). The acetonitrile layer was then concentrated under reduced pressure and a 1H NMR spectrum of the crude mixture was obtained.

Methyl 1,2,3,4-tetra-O-acetyl-α-L-idopyranurate (2). The bromide 1 (200 mg, 0.4 mmol) was reduced with tributyltin hydride according to the general procedure to give a mixture of 2 and 3 (1:3.3, 120 mg, 82%) as a colourless oil. Methyl 1,2,3,4-tetra-O-acetyl-β-L-idopyranurate (3). The bromide 4 (250 mg, 0.7 mmol) was reduced with tributyltin hydride according to the general procedure to give a mixture of 5 and 6 (3.5:1, 210 mg, 84%) as a colourless oil. Methyl (methyl 2,3,4-tri-O-acetyl-α-L-idopyranoside) uronate (8). The bromide 7 (300 mg, 0.7 mmol) was reduced with tributyltin hydride according to the general procedure to give a mixture of 8 and 9 (1:1.8, 190 mg, 79%) as a colourless oil. Methyl (2,3,4-tri-O-acetyl-α-L-idopyranosylfluoride) uronate (11). The bromide 10 (100 mg, 0.2 mmol) was reduced with tributyltin hydride according to the general procedure to give 11 (50 mg, 72%) as a colourless oil.

Theoretical calculations

Density functional theory calculations were performed using Gaussian 09. 54 Prior to performing geometry optimizations with DFT, the conformations of bromide 10 were explored by means of a conformational search in MacroModel 10.6, 55,56 using the MCMM torsional sampling algorithm in conjunction with the OPLS 2005 forcefield 57 with a dielectric constant set to ε = 2.3 to mimic the dielectric constants of benzene (ε = 2.27) and toluene (ε = 2.37). DFT geometry optimizations of transition states derived from the significant conformers were then performed using the B3LYP functional 58−61 and a mixed basis set consisting of LANL2DZ on Sn and 6-31G(d) on all other atoms. The optimizations were conducted in implicit benzene, as modeled with the SMD implicit solvent model. 62 Harmonic vibrational frequency calculations were performed to confirm whether stationary points were ground states (zero imaginary frequencies) or transition states (one imaginary frequency), and also to compute zero-point energies and thermochemical corrections. Errors in computed entropies, introduced by the treatment of low frequency modes as harmonic motions, were minimized by use of Truhlar's approximation 63 in which all harmonic frequencies below 100 cm⁻¹ were raised to exactly 100 cm⁻¹ before evaluation of the vibrational component of the thermal contribution to entropy. Subsequently, single-point energy calculations were performed at the B3LYP-D3(BJ) 64,65/Def2-TZVPP level of theory, again using SMD benzene. Free energies in solution were computed by adding the B3LYP zero-point energy and thermochemical corrections to the B3LYP-D3(BJ) solution-phase electronic energies. A standard state of 298.15 K and 1 mol L⁻¹ was used.

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References

41 Computations provide estimates of the stabilization arising from the transition-state gauche effect and the Sn–F interaction in TS2. Firstly, replacement of the pyranose ring oxygen in TS2 and TS5 with a CH2 group leads to transition states differing in energy by only 2.0 kcal mol–1, compared to the 3.3 kcal mol–1 difference in energy between TS2 and TS5 themselves. Secondly, replacement of the fluorine atom in TS2 and TS5 with a hydrogen atom leads to a 0.5 kcal mol–1 reduction in the difference in energy between TS2 and TS5.


