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Glycosidation–Anomerisation Reactions of 6,1-Anhydroglucopyranuronic Acid and Anomerisation of β-D-Glucopyranosiduronic Acids Promoted by $SnCl_4$

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Abstract: The reaction of silylated nucleophiles with 6,1-anhydroglucopyranuronic acid (glucuronic acid 6,1-lactones) catalysed by tin(IV) chloride provides 1,2-*trans* or 1,2-*cis* (deoxy)glycosides in a manner dependent on the donor structure. The α-glycoside was obtained for reactions of the donor with the 2-acyl group and 2-deoxydonors, whereas the 2-deoxy-2-iodo donor gave the β-glycoside. Experimental evidence shows that when 1,2-*cis*-glycoside formation occurs, the anomerisation of initially formed 1,2-*trans*-glycosides catalysed by $SnCl_4$ is possible. The anomerisation of β-D-glucopyranosiduronic acids was found to be faster, in some cases, than anomerisation of related β-D-glucopyranosiduronic acid esters and β-D-glucopyranoside derivatives and the rates are dependent on the structure of the aglycon. Moreover, the rates of anomerisation of β-D-glucopyranuronic acid derivatives can be qualitatively correlated with rates of hydrolysis of β-D-glucopyranosiduronic acids. Mechanistic possibilities for the reactions are considered.

Keywords: anomerisation · carbohydrates · deoxyglycoside · glycosides · Lewis acids

Introduction

Stereoselective glycoside synthesis is important because of the biological and medical relevance of oligosaccharides, glycoproteins, glycolipids,[1] and other carbohydrate derivatives[2] and a range of strategies have been developed.[3,4] The glycosyl azide **2** with α-configuration was found to be the major product obtained from the $SnCl_4$-promoted reaction of the acid **1** with azidotrimethylsilane (Scheme 1).[5] We did not expect this result for a number of reasons. Firstly, this reaction, as described by Toth and co-workers[6] and more recently by Lindhorst and co-workers,[7] gave the β-azide **3**. Secondly, the reaction of the glucuronic acid ester derivative **10** under identical conditions to that described for reactions of **1** gives the β-azide **11e**, consistent with the fact that 1,2-*trans*-glycosides are usually obtained from glycosyl donors with 2-acyl protecting groups, glycoside bond formation being controlled by neighbouring-group participation. The 6,1-anhydro derivative **4** is formed during the reaction of **1** with $SnCl_4$.[5] Both **4** and its 2-deoxy analogue **6** have consequently been exploited to provide 1,2-*cis*-glycosides **5** and **7**, respectively, when they are treated with silyl ether acceptors in the presence of $SnCl_4$.[8] In contrast, the related 2-deoxy-2-iodo donor **8** was found to give predominantly 1,2-*trans*-glycosides **9** under similar conditions. These results are summarised in Scheme 1. A mechanistic pathway accounting for the results of these reactions proposed by us is shown in Scheme 2 (pathway a). We suggested that the inversion of configuration at C-1 of **12** occurs for donors in which X = H or OAc without participation of the C-2 group when X = OAc, anchimeric assistance by the carboxylate group[9] contributing to the stereochemical outcome. The results observed for **8** were explained by the iodine residue being a better participator than the 2-acyl group (and the carboxylate group) and its glycosidation proceeding via **13** or **14**. Other conceivable pathways for the formation of 1,2-*cis*-glycosides **16** from glucuronic acids involve the initial formation of β-glycoside intermediates **15** via **13** or **14** that subsequently rapidly anomerise, the anomerisation reaction occurring via the reversible formation of **12** or by an independent pathway. We initially discounted pathways involving β-glycosides[7] on the basis of the low degree of anomerisation (< 5% after 48 h) of the glycosyl azide **11e** when subjected to $SnCl_4$. However, herein we provide the

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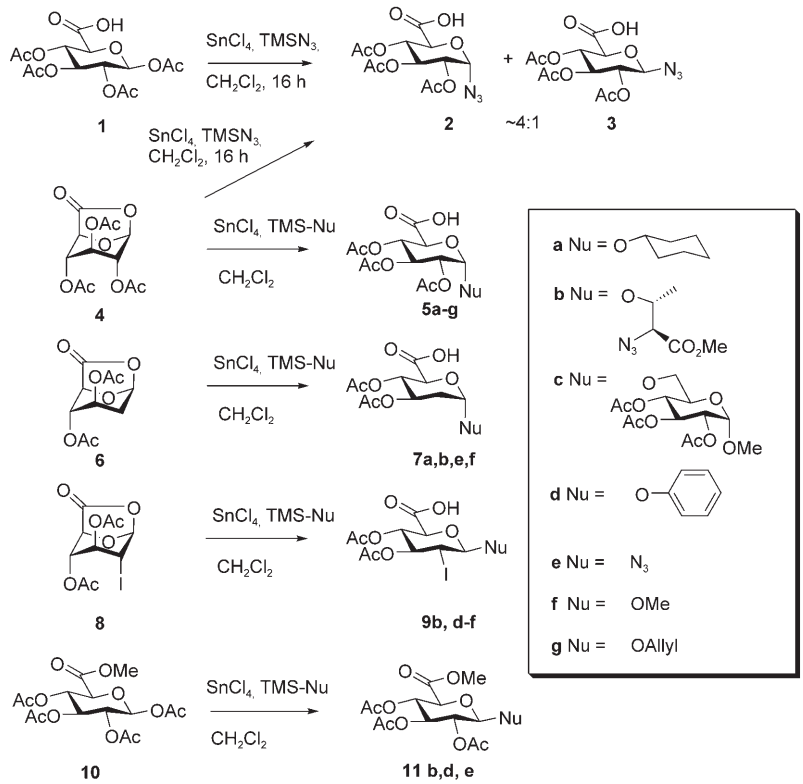
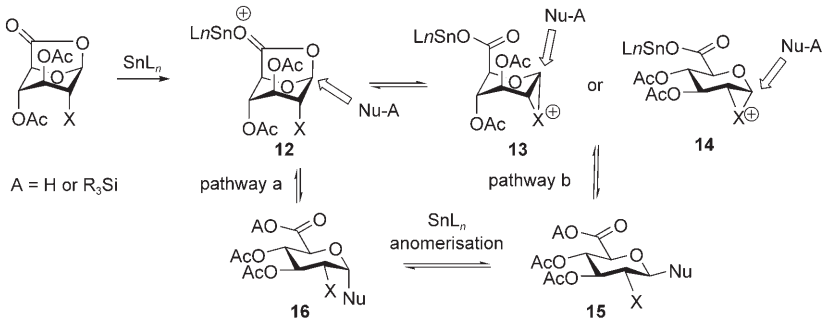


Scheme 1.



Scheme 2.

results of a more extensive study that demonstrates that the anomerisation of β-glucopyranosiduronic acid derivatives can lead to the formation of 1,2-*cis*-glycosides from **1** or **4**. The carboxyl group has a catalytic role, enhancing the rate of anomerisation, which is also dependent on the nature of the aglycon. Anomerisation can be correlated qualitatively with the rates of hydrolysis of β-D-glucopyranosiduronic acid derivatives and, therefore, we believe it likely that both the anomerisation and the hydrolysis of β-glucopyranosiduronic acids could have mechanistically related pathways.

Results and Discussion

Glycosidation reactions of 1 and 4 revisited: A series of reactions of both **1** and **4**, catalysed by $SnCl_4$, were re-investigated. Reactions were either carried out in NMR tubes, and were directly monitored by ^{1}H NMR spectroscopy (300 MHz), or were carried out in flasks, with samples taken periodically from the reaction mixture so that product ratios could be determined as a function of time. For reactions that were carried out in flasks, aliquots were taken and worked up by extraction of the carboxylic acid product from organic solvent into aqueous sodium hydrogen carbonate. The water was removed by freeze drying and the resulting residue (sodium salts of the α- and/or β-glycosides) were analysed by ^{1}H NMR spectroscopy in D_2O.

For reactions in which the α-azide **2** was obtained as the major product, it was clear that its formation resulted from the anomerisation of an initially formed β-glycoside. Thus, in one experiment ([**1**] = 0.05 M in $CDCl_3$) after 45 min a 58:42 ratio of anomers (α/β) was present, which changed to a 91:9 mixture favouring the α-anomer after 180 min; the ratios were determined by integration of the signals assigned to the pyranoside H-5 of the respective anomers after ^{1}H NMR analysis [300 MHz, $CDCl_3$, α-anomer: δ = 4.84 ppm (d, J = 9.5 Hz, 1H); β-anomer: δ = 4.28 ppm (d, J = 8.6 Hz, 1H)]. Reactions of **4** (0.12 M in CD_2Cl_2) in the presence of $SnCl_4$ (0.5 equiv) and $TMSN_3$ (2.5 equiv) were carried out in NMR tubes and ^{1}H NMR analysis showed that the lactone **4** was completely consumed after 30 min; the mixture contained a major component (70%), which was a β-glycoside with $^4C_1$ conformation as evidenced by a signal at δ = 4.00 ppm (d, J = 9.0 Hz, 1H; H-5), and a minor component (30%), which was an α-glycoside with $^4C_1$ conformation [signal at δ = 4.26 (d, J = 9.0 Hz, 1H; H-5)]. This reaction was allowed to proceed and after 24 h the mixture contained a 70:30 mixture of α- and β-glycosides; the α/β ratio as a function of time for the reaction of **4** is shown in Figure 1. The results of reactions carried out in NMR tubes were confirmed by carrying out repeat experiments in flasks, followed by normal reaction workup giving mixtures of anomers **2** and **3** in >80% yield; the relative proportion of

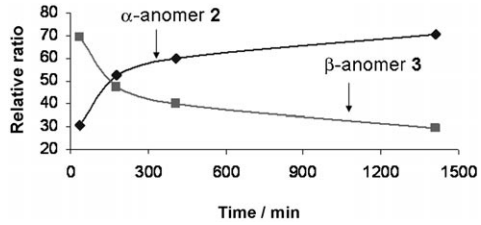


Figure 1. Relative ratio of α- and β-glycosides **2** (**2**/**3**) and **3** (**3**/**2**) in the glycosidation reaction of **4** (0.12 M), $SnCl_4$ (0.5 equiv), $TMSN_3$ (2.5 equiv) in CD_2Cl_2 at RT as a function of time. The lactone **4** was completely consumed after 30 min. The relative proportions of anomers was determined by ^{1}H NMR spectroscopy.

2 and **3** was dependent on the reaction time and consistent with the time course diagram that was obtained for reactions carried out in NMR tubes. The anomerisation reaction was suppressed at lower temperature. When the reaction was carried out at 0 °C, the complete consumption of **4** had occurred after 35 min, resulting in a 13:87 mixture of α/β-glycosides; this ratio did not alter significantly after 2 h (α/β = 17:83) at 0 °C. After allowing this reaction mixture to attain room temperature and leaving for a further 22 h a 74:26 mixture of α- and β-anomers, favouring the α-anomer was obtained.

The reactions of **4** in $CDCl_3$ gave similar ratios of α- and β-azides as those carried out in CD_2Cl_2, anomerisation again being observed. The reaction of **4** with $TMSN_3$ was fastest in nitromethane, attaining equilibrium after 15 min and giving an 80:20 mixture of α- and β-azides. The reaction of **4** with the TMSO–threonine derivative leading to **5b** was monitored in a similar manner and the outcome is shown in Figure 2. The rate of consumption of the donor **4** was slower than in the presence of $TMSN_3$ and only the α-glycoside could be observed in this case, indicating that anomerisation of the β- to the α-glycoside is too rapid to facilitate direct observation of the β-anomer as an intermediate. The reaction of **4** with CyOTMS catalysed by $SnCl_4$ was carried out at 0 °C for 22 h; evidence for the presence of the α-anomer **5a**, but not for the β-anomer, was obtained by ^{1}H NMR

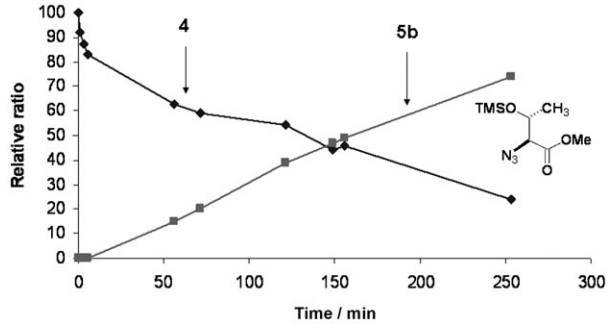
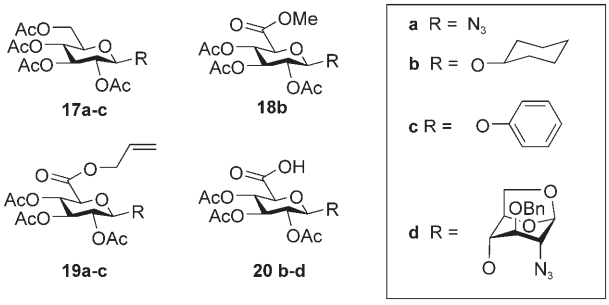


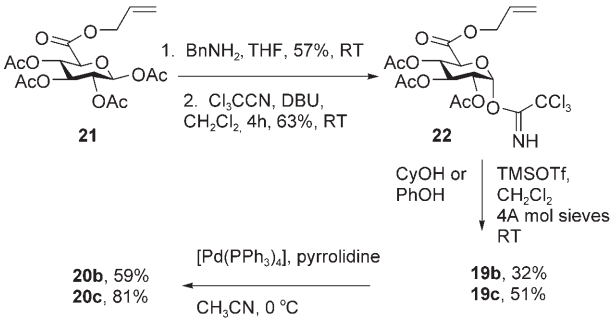
Figure 2. Relative ratio of **4** (**4**/**5b**) and α-glycoside **5b** (**5b**/**4**) in the glycosidation reaction of **4** catalysed by $SnCl_4$ (1.0 equiv) with threonine derivative (2.0 equiv, CD_2Cl_2, RT) as a function of time. The relative proportions of **4**/**5b** were determined by ^{1}H NMR spectroscopy. The β-anomer could not be detected.

analysis of residues obtained after workup of samples taken during the reaction. When the reaction of **4** with PhOTMS (2.5 equiv) catalysed by $SnCl_4$ (0.5 equiv) was monitored by ^{1}H NMR spectroscopy in CD_2Cl_2 at room temperature, the β-glycoside was observed, but only at levels <10%. After 24 h a mixture containing the α-anomer **5d** (52%), the unreacted donor **4** (45%) and the β-glycoside **20c** (3%) was obtained (α/β = 95:5). When this reaction was carried out at 0 °C, mixtures that contained larger amounts of the β-anomer were obtained. For example, after 6 h at 0 °C a 19:81 mixture of the α- and β-anomers was isolated; when this reaction was allowed to proceed for 24 h at 0 °C a 45:55 mixture of the anomers, respectively, was obtained in 41% isolated yield, with unreacted **4** accounting for the yield of product. This series of experiments shows that anomerisation of an initially formed *O*- or *N*-glucopyranosiduronic acid derivatives to the thermodynamically preferred α-glycoside is the major pathway accounting for 1,2-*cis*-glycoside bond formation from either **1** or **4**.

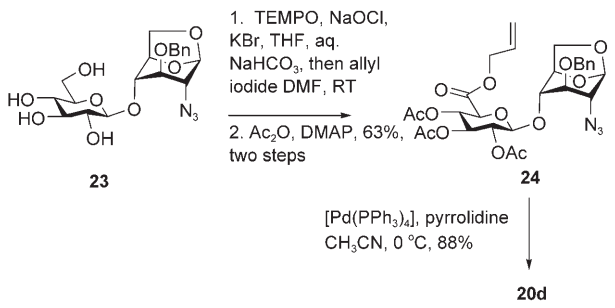
Synthesis of substrates for anomerisation reactions: The glycosidation reactions of **1** and **4** involved the use of silylated nucleophiles, which could lead to the generation of silylated intermediates that could be important to the catalytic processes taking place. Thus a series of β-glycosides derived from glucuronic acid and glucose were prepared so that their potential to undergo anomerisation in the presence of $SnCl_4$ and in the absence of silylated nucleophiles could be investigated. Such studies would also indicate whether the anomerisation reactions of glucuronic acids and related compounds would have potential in preparative chemistry. In addition to **3**,[10] **11d**[11] and **11e**,[12] the glucopyranosides



17a,[13] **17b**[14] and **17c**,[15] and the esters of glucopyranosiduronic acid **18b**[16] and **19a**[10] were obtained by literature procedures. The allyl esters **19b** and **19c** were synthesised from the trichloroacetimidate donor **22** (Scheme 3). Thus **21**[10] was converted to **22** (36% over two steps) and subsequent glycosidation using TMSOTf as promoter in dichloromethane in the presence of cyclohexanol gave **19b** (32%); the reaction of **22** with phenol gave **19c** (51%). The palladium(0)-catalysed hydrolysis of the allyl esters of **19b** and **19c** gave **20b** and **20c**, respectively. The disaccharide **20d** was



Scheme 3.



Scheme 4.

prepared from the β-D-glucopyranoside **23** (Scheme 4).[17] The oxidation of **23** using TEMPO[12a] followed by allylation and subsequent acetylation gave **24**. The palladium(0)-catalysed removal of the allyl ester protecting group gave **20d**.[18]

Anomerisation of β-D-glucopyranosides and β-D-glucopyranosiduronic acid derivatives: The reactions of a series of β-D-glucopyranosides and β-D-glucopyranosiduronic acid derivatives (0.08–0.1 M), catalysed by $SnCl_4$ (0.5 equiv), were carried out and monitored as described above for the gylcosidation reactions of **1** and **4** in the absence of silylated nucleophiles. The relative proportions of **2** and **3** as a function of time from the reaction of β-azide **3** (0.09 M) is shown in Figure 3; anomerisation was slower than in the glycosidation–anomerisation reaction of **4** in CD_2Cl_2 with $TMSN_3$, but gave a similar ratio of **2** and **3** (71:29) after 48 h. The anomerisation of the acid **3** proceeded less efficiently in $CDCl_3$; after 48 h there was an 82:16 mixture favouring the β-anomer **3**, the formation of the lactone **4** being also detected (<3%); this changed to a 54:42:4 mixture of **3**/**2**/**4** after 12 days. The β-azides **17a**–**19a** did not anomerise to any detectable degree over a number of days.

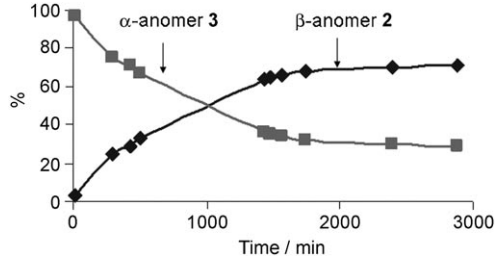
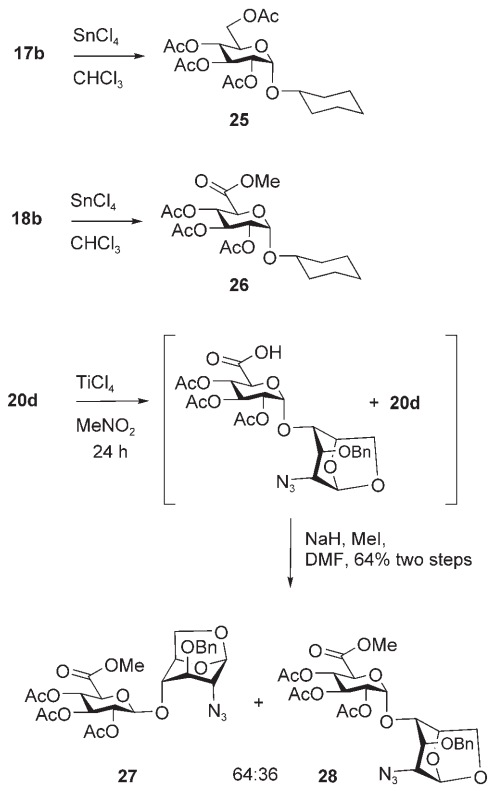


Figure 3. Relative ratio **2** (**2**/**3**) and **3** (**3**/**2**) present in the anomerisation reaction of **3** (0.09 M) catalysed by $SnCl_4$ (0.5 equiv) in CD_2Cl_2 at RT, as a function of time. The percentage of anomers was determined by ^1H NMR spectroscopy.

The anomerisation reaction of the phenyl glucopyranosiduronic acid derivative **20c** in both CD_2Cl_2 and $CDCl_3$ at room temperature proceeded more slowly than the azido derivative, and much more slowly than in glycosidation reactions of **4** with TMSOPh. After seven days in $CDCl_3$ a mixture favouring the α-glycoside **5d** over **20c** (48:38) resulted, the formation of the lactone **4** being observed (<14% after seven days) during the course of the reaction. After ten days a 54:35:15 mixture of **5d**/**20c**/**4** was obtained, which did not alter on leaving for a longer time. Phenyl glycosides **17c–19c** did not undergo any anomerisation under identical conditions to the reaction of **20c**. The anomerisation of the cyclohexyl glucuronide **20b** was the fastest of those studied. In less than 10 min in $CDCl_3$ the complete anomerisation occurred of **20b** to give a >95:5 mixture of the α-anomer **5a** and β-anomer **20b**. The half-time ($t_{1/2}$) for this reaction as determined by NMR spectroscopy was <5 min. The half time for the corresponding reaction in CH_2Cl_2, determined by monitoring the change in specific rotation that occurs on the conversion of β-anomer to the α-anomer, was approximately 4 min. The $t_{1/2}$ is the time required for the reaction to have proceeded to 50% of the final equilibrium. The anomerisation of the cyclohexyl glucopyranoside **17b** gave, after 24 h, a 92:8 mixture of the α-glycosides **25** and **17b** (quantitative yield); the $t_{1/2}$ for this anomerisation reaction was >300 min. Anomerisation of the methyl ester **18b** gave a 93:7 mixture of α-glycosides **26** and **18b** after 190 min (quantitative yield); the $t_{1/2}$ for the anomerisation of **18b** was <20 min. Thus the anomerisation of acid **20b** is more than four times faster than that of its methyl ester, and at least sixty times faster than that of the per-*O*-acetylated glucoside, based on the estimated $t_{1/2}$ values. The anomerisation of the disaccharide **20d** did not proceed using $SnCl_4$ in dichloromethane or in nitromethane. Partial formation of the α-anomer (36%) was observed by reaction of **20d** with $TiCl_4$ in nitromethane after 24 h. The products from anomerisation of the disaccharide were characterised as the methyl esters **27** and **28** (Scheme 5).

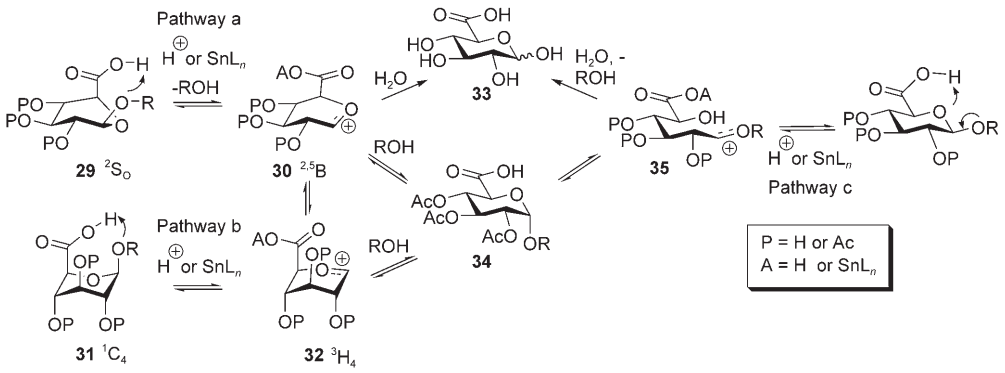
Mechanistic discussion: Anomerisation of initially formed β-glycosides is the major pathway accounting for the formation of α-glycosides from reactions of **4**. Although the conditions for the anomerisation of the β-D-glucopyranuronic acid derivatives do not mimic those of the glycosidation–anomerisation reaction, there is sufficient evidence that related mechanisms operate. Glycosidation–anomerisation reactions catalysed by $SnCl_4$ have been described[19–21] and the combination of $SnCl_4$ and a carboxylic acid can provide powerful inter- or intramolecular catalysis for anomerisation,[22] the latter which was rationalised on the basis that the interaction of a carboxylic acid and $SnCl_4$ provides super acid con-



Scheme 5.

ditions, leading to enhanced protonation of the pyranose oxygen and subsequent cleavage of the C_1–O_5 bond (endocyclic cleavage) giving an open chair intermediate (related to **35** in Scheme 6). The rates of anomerisation described herein have the order glucopyranosiduronic acid > ester of glucopyranosiduronic acid > glucopyranoside, again demonstrating the role that a carboxylic acid group (and even a carboxylate ester) has in enhancing the catalytic efficiency of $SnCl_4$. There are cases in which the rates of acid-catalysed hydrolysis of some β-D-glucopyranosiduronic acid derivatives are faster than corresponding β-D-glucopyranosides,[23] the hydrolysis of cyclohexyl β-D-glucopyranosiduronic acid being about five times faster than cyclohexyl β-D-glucopyranoside at 60 °C, for example. This trend is apparent herein, as the anomerisation of **20b** is faster than of **17b**. The rates of hydrolysis of β-D-glucopyranosiduronic acids also depends on the electron affinity of the aglycon,[23] the hydrolysis of the cyclohexyl β-D-glucopyranosiduronic acid being approximately 30 times faster than that of the corresponding phenyl glycoside, for example. These rates also correlate with anomerisations, which were faster for cyclohexyl glycoside **20b** than for the phenyl glycoside **20c**. Timell and coworkers suggest that glucopyranosiduronic acids[23] are hydrolysed by a different mechanism to glucopyranosides[24] and it has been proposed that intramolecular general acid catalysis[25] through C_1–O_1 bond cleavage (exocyclic cleavage) accounts for the rate enhancement observed for some glucuronic acid derivatives. This could involve an intermediate that adopts a ^2S_O conformation (**29**), which would give an oxycarbenium ion (**30**) with a $^{2,5}B$ conformation[26] (Scheme 6, pathway a), or involve an intermediate that adopts a $^1C_4$ conformation (**31**) giving an oxycarbenium ion with a half chair conformation (**32**; Scheme 6, pathway b). In either case the carboxylic acid group is sufficiently proximate to the aglycon oxygen atom to facilitate intramolecular proton transfer. Related intramolecular general acid catalysis processes could be used to explain anomerisation (Scheme 6, pathways a and b). Alternatively, the cleavage of C_1–O_5 bond (endocyclic bond cleavage, Scheme 6, pathway c)[27] leading to **35** cannot be discounted when discussing the acid-catalysed hydrolysis and/or the $SnCl_4$-catalysed anomerisation of glucopyranosiduronic acids; this process can also explain those instances where rates are faster for glucopyranosiduronic acids than glucopyranosides. An attractive feature of proposing endocyclic bond cleavage is that general acid catalysis occurs from the ground state $^4C_1$ conformation.

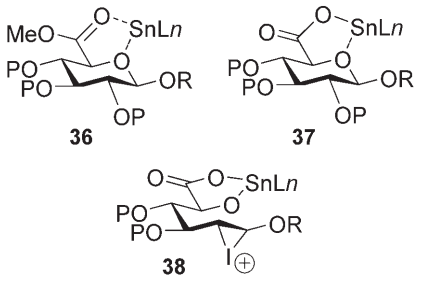
Efforts to trap intermediates such as **30**, **32** or **35** by addition of nucleophiles during the course of the anomerisation reactions, in order to distinguish between the possible pathways, were not successful. The anomerisation of **17c** in presence of $SnCl_4$ have been described; a *trans*-glycosidation reaction leading to anomerisation was found to occur during the reaction of **17c** in presence of *o*-cresol in benzene, suggesting that anomerisation involves exocyclic bond cleavage for this glucoside.[28] In our hands the anomerisation of **17c**



Scheme 6.

did not occur in the presence of $SnCl_4$ in dichloromethane or chloroform and attempts to carry out *trans*-glycosidation reactions of **17c** (in the presence of TMSOCy as the nucleophile) were not successful. Efforts to carry out *trans*-glycosidation of the rapidly anomerising **20b** in the presence of excess $TMSN_3$ provided only the α-anomer **5a** after 5 min and $<5\%$ of the α-azide **2** after one week, consistent with endocyclic bond cleavage in this case.

That the anomerisation of the glucuronic acid ester derivative **18b** is faster than the glucopyranoside derivative **17b** can be explained by the $SnCl_4$ coordinating to both the C-5 carbonyl group and the pyranose oxygen atom, leading to a



five-membered ring chelate **36** that would facilitate endocyclic bond cleavage. Such a chelated intermediate **37** could form from **13** or **14**, accounting for anomerisation in reactions of lactone **4**. The reduced rate of anomerisation for the glycosidation reactions with the 2-deoxy-2-iodo derivative **8** can be explained by participation of the iodo group leading to **38** which slows down the required C_1–C_2 bond rotation, the implication being that anchimeric assistance from the 2-iodo group is more effective than from an 2-acetoxy group or the C_5-carboxyl group. The formation of α-glycosides from 2-deoxydonor **6** could proceed by inversion of configuration or by means of the anomerisation of initially formed β-glycosides.

Conclusion

The reaction of silylated acceptors with 2,3,4-tri-*O*-acetyl-6,1-anhydroglucopyranosiduronic acids catalysed by tin(IV) chloride provides 1,2-*cis*-glycosides; this result is accounted for by the anomerisation of initially formed 1,2-*trans*-glycosides. A rational study of the $SnCl_4$-catalysed anomerisation of β-glycoside derivatives shows that the presence of the C-5 carboxylic acid group enhances the efficiency of anomerisation. Moreover, the rates of anomerisation of β-D-glucopyranuronic acid derivatives can be qualitatively correlated with rates of hydrolysis of β-D-glucopyranosiduronic acids. Thus mechanisms for the anomerisation of β-glycoside intermediates generated in the reaction of compound **4**, like those of anomerisation of β-D-glucopyranuronic acids and the hydrolysis of β-D-glucopyranosiduronic acids, can be considered in the context of general (Lewis) acid catalysis. The synthetic potential of the anomerisation reaction is being further investigated.

Experimental Section

General experimental conditions: Optical rotations were determined with a Perkin–Elmer 241 or 343 model polarimeter at the sodium D line at 23 °C. The NMR spectra were recorded with Varian Inova 300 and 500 MHz spectrometers. Chemical shifts are reported relative to internal Me_4Si in $CDCl_3$ ($\delta=0.0$ ppm) or HOD for D_2O ($\delta=4.63$ ppm) or CD_2HOD ($\delta=3.36$ ppm) for ^1H and $CDCl_3$ ($\delta=77.0$ ppm) or CD_3OD ($\delta=47.7$ ppm) for ^{13}C. ^1H NMR signals were assigned with the aid of COSY. ^{13}C NMR signals were assigned with the aid of DEPT. Coupling constants are reported in Hz. The IR spectra were recorded with a Mattson Galaxy Series FTIR 3000 using either thin film between NaCl plates or KBr discs, as specified. Melting points were measured on a Gallenkamp melting-point apparatus. Elemental analysis was performed on an Exeter Analytical CE440 elemental analyser. Low- and high-resolution mass spectra were measured at the University of York (UK) or with a Micromass LCT KC420 or Micromass Quattro instrument. Thin-layer chromatography (TLC) was performed on aluminium sheets precoated with silica gel 60 (HF_{254}, E. Merck) and spots visualised by UV and charring with H_2SO_4-EtOH (1:20). Flash column chromatography was carried out with silica gel 60 (0.040–0.630 mm, E. Merck). Chromatography solvents used were EtOAc (Riedel-deHaen), petroleum ether (b.p. 40–60 °C, BDH laboratory supplies), cyclohexane and MeOH (Sigma Aldrich). Toluene (Sigma–Aldrich), acetonitrile (Sigma–Aldrich) and CH_2Cl_2 (Riedel-deHaen) were freshly distilled from calcium hydride. THF was freshly distilled from Na/Benzophenone. MeOH was distilled from Mg. Nitromethane was used as obtained from Sigma–Aldrich.

2,3,4-Tri-*O*-acetyl-1-(2,2,2-trichloroethanimidate)-α-D-glucopyranuronic acid, 2-propenyl ester (22): Compound **21** (5 g, 12.4 mmol) was dissolved in THF (35 mL), benzylamine (2.71 mL, 24.8 mmol) was added and the mixture was stirred overnight. The excess solvent was removed and the residue was purified by chromatography (EtOAc/cyclohexane, 1:3) to give the intermediate hemiacetal as an oil (2.53 g, 57 %). $R_f=0.30$ (EtOAc/cyclohexane, 1:1); ^1H NMR (300 MHz, $CDCl_3$): $\delta=5.83$ (tdd, $J=$ 6.0, 10.3, 16.7 Hz, 1H; C*H*=CH_2), 5.51 (d, $J_{1,2}=4.4$ Hz, 1H; H-1), 5.51 (t, $J_{2,3}=10.0$ Hz, $J_{3,4}=9.8$ Hz, 1H; H-3), 5.30 (dd, $J=13.7$, 20.5 Hz, 2H; CH=CH_2), 5.13 (t, $J_{3,4}=9.7$ Hz, $J_{4,5}=9.9$ Hz, 1H; H-4), 4.85 (dd, $J_{1,2}=$ 3.5 Hz, $J_{2,3}=10.1$ Hz, 1H; H-2), 4.57 (m, 3H; OCH_2CH=CH_2 and H-5 overlapping), 2.04, 1.99, 1.97 ppm (3×s, 3×3H; 3×$COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=170.2$, 170.1, 169.7 (3×C, 3×*C*OCH_3), 167.9 (C, *C*OOAll), 130.9 (CH, *C*H=CH_2), 119.7 (CH_2, CH=*C*H_2), 90.1 (CH, C-1), 70.7, 69.4, 69.1, 67.8 (4×CH, C-2–5), 66.7 (CH_2, O*C*H_2CH=CH_2), 20.6, 20.6 ppm (3×CH_3 overlapping, 3×CO*C*H_3); ES-HRMS: *m*/*z* calcd: 359.0978; found: 359.0959 $[M-H]^-$. This intermediate (1 g, 2.78 mmol) was dissolved in dry dichloromethane (20 mL) under a N_2 atmosphere, trichloroacetonitrile (1.4 mL, 13.9 mmol) was added and the mixture was stirred at 0 °C (15 min). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was then added (~0.2 mL) and stirring continued (4 h). The excess solvent was removed and the residue was purified by flash chromatography (EtOAc/cyclohexane, 1:2) to give compound **22** as an oil (874 mg, 63 %). $R_f=0.56$ (EtOAc/cyclohexane, 1:1); ^1H NMR (300 MHz, $CDCl_3$): $\delta=8.77$ (s, 1H; NH), 6.65 (d, $J_{1,2}=3.7$ Hz, 1H; H-1), 5.88 (tdd, $J=6.0$, 10.5, 16.4 Hz, 1H; C*H*=CH_2), 5.63 (t, $J_{2,3}=9.8$ Hz, $J_{3,4}=9.9$ Hz, 1H; H-3), 5.30 (m, 3H; CH=CH_2 and H-4 overlapping), 5.15 (dd, $J_{1,2}=3.7$ Hz, $J_{2,3}=$ 9.8 Hz, 1H; H-2), 4.61 (dd, $J=4.4$, 5.3 Hz, 2H; O*C*H_2CH=CH_2), 4.52 (d, $J_{4,5}=10.3$ Hz, 1H; H-5), 2.05, 2.03, 2.02 ppm (3×s, 3×3H; 3×$COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=169.7$, 169.6, 169.3 (3×C, 3×*C*OCH_3), 166.4 (C, COOAll), 160.4 (CH_3, C=NH), 130.9 (CH, *C*H=CH_2), 119.6 (CH_2, CH=*C*H_2), 92.5 (CH, C-1), 90.4 (C, *C*Cl_3), 70.4, 69.3, 69.0, 68.9 (4× CH, C2–5), 66.8 (CH_2, O*C*H_2CH=CH_2), 20.5, 20.5, 20.3 ppm (3×CH_3, 3× CO*C*H_3); ES-HRMS: *m*/*z* calcd: 526.0050; found: 526.0072 $[M+Na]^+$.

Cyclohexyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosiduronic acid, 2-propenyl ester (19b): Anhydrous dichloromethane (30 mL) was added to the trichloroacetimidate **22** (1.0 g, 1.99 mmol) and cyclohexanol (253 μL, 2.39 mmol) and 4 Å molecular sieves under a N_2 atmosphere. TMSOTf (36 μL, 0.199 mmol) was added and reaction mixture stirred at RT for 40 min. Solid $NaHCO_3$ (400 mg) was then added and the stirring continued for a further 20 min. The mixture was filtered through Celite, the sol-

vent was removed and the residue was purified by flash chromatography (EtOAc/cyclohexane, 1:4) to give compound **19b** (282 mg, 32%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.85 (tdd, J = 5.9, 10.4, 16.3 Hz, 1H; C*H*=CH_2), 5.29 (m, 4H; CH=CH_2, H-2 and H-3 overlapping), 4.99 (t, $J_{3,4}$ = 9.5 Hz, $J_{4,5}$ = 10.0 Hz, 1H; H-4), 4.76 (d, $J_{1,2}$ = 7.7 Hz, 1H; H-1), 4.66 (d, J = 5.9 Hz, 2H; OCH_2CH=CH_2), 4.32 (d, $J_{4,5}$ = 10.0 Hz, 1H; H-5), 3.59 (dt, J = 3.7, 8.5 Hz, 1H; cyclohexyl CH), 2.06, 2.04, 2.02 (3×s, 3×3H; 3×$COCH_3$), 1.50 ppm (m, 10H; cyclohexyl CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.1, 169.7, 169.6 (3×C, 3×*C*OCH_3), 166.0 (C, *C*OOAll), 131.3 (CH, *C*H=CH_2), 118.0 (CH_2, CH=*C*H_2), 98.8 (CH, C-1), 77.0, 72.2, 71.7, 71.4 (4×CH, C-2–5), 69.7 (CH, cyclohexyl *C*H), 66.0 (CH_2, O*C*H_2CH=CH_2), 32.8, 31.2, 25.2, 23.2, 23.1 (5×CH_2, cyclohexyl *C*H_2), 19.2, 19.2, 19.1 ppm (3×CH_3, 3×CO*C*H_3); ES-HRMS: m/z calcd: 465.1737; found 465.1742 $[M+Na]^+$.

Cyclohexyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosiduronic acid (20b): The propenyl ester **19b** (250 mg, 0.56 mmol) was dissolved in dry MeCN (4 mL) under an atmosphere of N_2 and cooled to 0°C. $[Pd(Ph_3)_4]$ (65 mg, 0.056 mmol) and pyrrolidine (55 μL, 0.616 mmol) were added and mixture was stirred at RT for 1 h. The mixture was then filtered through Celite, the solvent was removed, and the residue was dissolved in EtOAc and washed with water. The aqueous layer was then acidified to pH 2 and extracted with EtOAc, dried (Na_2SO_4), and filtered and the solvent removed to yield compound **20b** (133 mg, 59%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.25 (m, 2H; H-3 and H-4 overlapping), 4.98 (t, $J_{2,3}$ = 8.6 Hz, $J_{1,2}$ = 8.3 Hz, 1H; H-2), 4.69 (d, $J_{1,2}$ = 8.3 Hz, 1H; H-1), 4.12 (d, $J_{4,5}$ = 9.4 Hz, 1H; H-5), 3.59 (dt, J = 4.0, 8.6 Hz, 1H; cyclohexyl CH), 2.04, 2.04, 2.02 (3×s, 3×3H; 3×$COCH_3$), 1.50 ppm (m, 10H; cyclohexyl CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3 (C, COOH), 170.1, 169.7, 169.3 (3×C, 3×*C*OCH_3), 99.0 (CH, C-1), 78.0 (CH, cyclohexyl *C*H), 72.1, 71.9, 71.3, 69.2 (4×CH, C-2–5), 33.0, 31.3, 25.3, 23.5, 23.4 (5×CH_2, cyclohexyl *C*H), 20.6, 20.5 ppm (3×CH_3, 3×CO*C*H_3); ES-HRMS: m/z calcd: 401.1448; found 401.1445 $[M-H]^-$.

Phenyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosiduronic acid, 2-propenyl ester (19c): Trichloroacetimidate **22** (1.0 g, 1.99 mmol) and pre-dried 4 Å molecular sieves were stirred in anhydrous dichloromethane (30 mL) under a N_2 atmosphere for 1 h. Phenol (225 mg, 2.39 mmol) was added to this solution and stirring was continued for 1 h; then TMSOTf (36 μL, 0.199 mmol) was added and the mixture was stirred for 40 min at RT. Solid $NaHCO_3$ (400 mg) was then added and stirring continued for another 20 min and the mixture filtered through Celite. The solvent was removed and the residue purified by flash chromatography (EtOAc/cyclohexane, 1:4) to give compound **19c** (442 mg, 51%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30 (d, J = 7.7 Hz, 2H; Ar H), 7.08 (t, J = 7.4 Hz, 1H; Ar H), 7.01 (d, J = 8.6 Hz, 2H; Ar H), 5.86 (tdd, J = 5.9, 10.7, 16.6 Hz, 1H; CH=CH_2), 5.30 (overlapping signals, 5H; CH=CH_2, H-2, H-3, H-4), 5.14 (d, $J_{1,2}$ = 6.8 Hz, 1H; H-1), 4.60 (d, J = 5.8 Hz, 2H; OCH_2CH=CH_2), 4.20 (d, $J_{4,5}$ = 8.9 Hz, 1H; H-5), 2.06, 2.04, 2.02 ppm (3×s, 3×3H; 3×$COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.1, 169.2, 169.2 (3×C, 3×*C*OCH_3), 166.0 (C, *C*OOAll), 156.7 (C, Ar-C), 131.0 (CH, *C*H=CH_2), 129.6 (CH, Ar-C), 123.5 (CH, Ar-C), 119.3 (CH_2, CH=*C*H_2), 117.2 (CH, Ar-C), 99.3 (CH, C-1), 72.6, 72.0, 71.0, 69.1 (4×CH, C-2–5), 66.6 (CH_2, O*C*H_2CH=CH_2), 20.6 (CH_3, CO*C*H_3), 20.5 ppm (2×CH_3, overlapping, 2×CO*C*H_3); ES-HRMS: m/z calcd: 459.1288; found: 459.1288 $[M+Na]^+$. Alternatively, the propenyl ester **21** (0.15 g, 0.25 mmol) was dissolved in dry CH_2Cl_2 (4 mL) under N_2 and TMSOPh (0.15 g, 0.62 mmol, 2.5 equiv) and $SnCl_4$ (22 μL, 0.16 mmol, 0.5 equiv) were then added. The reaction mixture was stirred for 4 h at RT and then satd $NaHCO_3$ (10 mL) and CH_2Cl_2 (6 mL) were added and stirring continued for a further 30 min. Filtration through Celite was followed by separation of the layers and the organic layer was dried (Na_2SO_4) and the solvent removed. Chromatography of the residue gave compound **19c** (58%).

Phenyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosiduronic acid (20c): Propenyl ester **19c** (300 mg, 0.69 mmol) was dissolved in dry MeCN (5 mL) under N_2 and cooled to 0°C. $[Pd(Ph_3)_4]$ (80 mg, 0.069 mmol) and pyrrolidine (65 μL, 0.76 mmol) were added and the mixture was stirred for 40 min. The mixture was then filtered through Celite and excess solvent removed. The residue was taken up in EtOAc and washed with water. The aqueous layer was acidified to pH 2, washed with EtOAc, the organic layer dried (Na_2SO_4) and filtered, and the solvent removed to give compound **20c** (221 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.04 (br s, 1H; COOH), 7.30 (d, J = 8.2 Hz, 2H; Ar H), 7.07 (t, J = 7.7 Hz, 1H; Ar H), 7.00 (d, J = 8.3 Hz, 2H; Ar H), 5.35 (m, 3H; H-2, H-3, H-4 overlapping), 5.16 (d, $J_{1,2}$ = 7.2 Hz, 1H; H-1), 4.22 (d, $J_{4,5}$ = 9.5 Hz, 1H; H-5), 2.06, 2.04, 2.04 ppm (3×s, 3×3H; 3×$COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3 (C, COOH), 170.0, 169.7, 169.4 (3×C, 3×*C*OCH_3), 156.6 (C, Ar-C), 129.6 (CH, Ar-C), 123.6 (CH, Ar-C), 117.1 (CH, Ar-C), 99.1 (CH, C-1), 71.9, 70.9, 68.9 (3×CH, C-2–5), 20.5 ppm (3×CH_3, overlapping, 3×CO*C*H_3); ES-HRMS: m/z calcd: 395.0978; found 395.0963 $[M-H]^-$

1,6-Anhydro-2-azido-3-*O*-benzyl-2-deoxy-4-*O*-(2,3,4-tri-*O*-acetyl-6-(2-propenyl)-β-D- glucopyranuronosyl)-β-D-glucopyranose (24): A solution of sodium hypochlorite (15 mL, 19.38 mmol (1.3 M, Aldrich)) was added dropwise to a solution of 1,6-anhydro-2-azido-3-*O*-benzyl-2-deoxy-4-*O*-(β-D-glucopyranosyl)-β-D-glucopyranose **23** (1.0 g, 2.28 mmol), KBr (28.0 mg, 0.228 mmol), and 2,2,6,6-tetramethylpiperdine-1-oxide (TEMPO, 36.0 mg, 0.228 mmol), in satd $NaHCO_3$/THF (10:1.5, 58 mL) which was stirring at 0°C. The reaction was allowed to attain RT, and monitored by TLC (R_f = 0.4, *i*PrOH/$MeNO_2$/H_2O 10:9:2). After 30 min the THF was removed under reduced pressure at 30°C and the remaining solution was lyophilised to give the intermediate as a white solid. The residue (1 g, 2.2 mmol) was suspended in anhydrous DMF (20 mL) and stirred in the presence of allyl iodide (265 μL, 2.86 mmol) for 12 h at RT. Upon completion of the reaction as determined by TLC (EtOAc/MeOH, 2:1), acetic anhydride (5 mL) and 4-dimethylaminopyridine (30 mg, 0.246 mmol) were added and the stirring was continued for a further 12 h at RT. The mixture was diluted with water and extracted with EtOAc. The combined organic extracts were dried (Na_2SO_4) and filtered, the solvent was removed and the residue purified by chromatography to give compound **24** (858 mg, 63%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24 (m, 5H; Ar-H), 5.81 (tdd, J = 6.0, 10.4, 16.6 Hz, 1H; C*H*=CH_2), 5.38 (s, 1H; H-1*), 5.22 (m, 4H; CH=CH_2, H-3, H-4 overlapping), 4.95 (dd, $J_{1,2}$ = 7.7 Hz, $J_{2,3}$ = 9.2 Hz, 1H; H-2), 4.75 (d, $J_{1,2}$ = 7.7 Hz, 1H; H-1), 4.51 (m, 5H; CH_2Ph, OCH_2CH=CH_2, H-5* overlapping), 3.99 (m, 2H; H-6a*, H-5 overlapping), 3.77 (s, 1H; H-6b*), 3.70 (m, 2H; H-3*, H-4* overlapping), 3.12 (s, 1H; H-2*), 1.96, 1.93, 1.93 ppm (3×s, 3×3H; 3×$COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.1, 169.2, 169.1 (3×C, 3×*C*OCH_3), 166.1 (C, COOAll), 137.3 (C, Ar-C), 131.0 (CH, *C*H=CH_2), 128.4 (CH, Ar-C), 127.9 (C, Ar-C), 125.9 (CH, Ar-C), 119.5 (CH_2, CH=*C*H_2), 100.7, 98.9 (2×CH, 2×C-1), 76.7, 75.3, 73.3, 72.5, 72.0, 71.0, 69.1 (7×CH), 68.9 (CH_2, CH_2-Ar), 66.6 (CH_2, O*C*H_2CH=CH_2), 64.9 (CH_2, C-6*), 59.4 (CH), 20.5, 20.5 ppm (3×CH_3, 3×CO*C*H_3); ES-HRMS: m/z calcd: 642.1911; found 642.1928 $[M+Na]^+$.

1,6-Anhydro-2-azido-3-*O*-benzyl-2-deoxy-4-*O*-(2,3,4-tri-*O*-acetyl-β-D-glucopyranuronosyl)-β-D-glucopyranose (20d): Propenyl ester **24** (250 mg, 0.404 mmol) was dissolved in anhydr MeCN (5 mL) and the mixture was cooled to 0°C. $[Pd(Ph_3)_4]$ (48 mg, 0.041 mmol) and pyrrolidine (38 μL, 0.451 mmol) were then added and stirring was continued (1 h). The mixture was then filtered through Celite, the solvent removed and the residue was taken up in EtOAc, which was then washed with water. The aqueous layer was then acidified (pH 2–3) and washed with EtOAc. The organic layer was dried (Na_2SO_4) and filtered and the solvent removed to give compound **20d** (206 mg, 88%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32 (m, 5H; Ar-H), 5.46 (s, 1H; H-1*), 5.28 (m, 2H; H-3, H-4 overlapping), 5.01 (t, $J_{1,2}$ = 7.6 Hz, $J_{2,3}$ = 9.3 Hz, 1H; H-2), 4.79 (d, $J_{1,2}$ = 7.6 Hz, 1H; H-1), 4.60 (m, 3H; CH_2Ph, H-5* overlapping), 4.09 (m, 2H; H-6a*, H-5 overlapping), 4.02 (d, $J_{4,5}$ = 9.6 Hz, 1H; H-5), 3.83 (s, 1H; H-6b*), 3.76 (br s, 2H; H-3*, H-4*), 3.20 (s, 1H; H-2*), 2.04, 2.03, 2.01 ppm (3×s, 3×3H; 3×$COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.2, 169.7, 169.6 (3×C, 3×*C*OCH_3), 169.3 (C, COOH), 137.3 (C, Ar-C), 128.5 (CH, Ar-C), 128.0 (C, Ar-C), 127.8 (CH, Ar-C), 100.6, 98.9 (2×CH, 2×C-1), 77.1, 75.5, 73.4 (2×CH), 72.6 (CH_2, C-6*), 71.1, 69.0 (2×CH), 65.0 (CH_2, CH_2-Ar), 63.2, 59.4 (2×CH), 23.7, 20.5 ppm (3×CH_3, 3×CO*C*H_3); ES-HRMS: m/z calcd: 578.1622; found 578.1631 $[M-H]^-$.

1,6-Anhydro-2-azido-3-*O*-benzyl-2-deoxy-4-*O*-(2,3,4-tri-*O*-acetyl-6-methyl-α/β-D-glucopyranuronosyl)-β-D-glucopyranose (27 and 28): $TiCl_4$ (11 μL, 0.1 mmol) was added to a stirred solution of **20d** (58 mg,

0.1 mmol) in nitromethane (3 mL) under a N_2 atmosphere and stirring was continued (48 h). Saturated $NaHCO_3$ was added and the mixture was stirred for a further 20 min. The mixture was filtered through Celite and the layers separated. The aqueous layer was then acidified (pH 2–3), extracted with EtOAc and dried (Na_2SO_4) and the solvent removed to yield 1,6-anhydro-2-azido-3-*O*-benzyl-2-deoxy-4-*O*-(2,3,4-tri-*O*-acetyl-α/β-D-glucopyranuronosyl)-β-D-glucopyranose[17] (quantitative). This mixture (60 mg, 0.104 mmol) was dissolved in anhydrous DMF, solid $NaHCO_3$ (14 mg, 0.156 mmol) was added and the stirring continued for 20 min. Iodomethane (10 μL, 0.135 mmol) was then added and the reaction mixture left to stir for 12 h and was then filtered through Celite, the solvent was removed and the residue was taken up in EtOAc and was subsequently washed with water, dried (Na_2SO_4) and then filtered. The excess solvent was removed and the residue was purified by flash chromatography (40 mg, 64%, α/β, 34:66); ES-LRMS: *m/z* calcd: 616.0 ; found 616.1 $[M+Na]^+$; elemental analysis calcd (%) for $C_{26}H_{31}N_3O_{13}$: C 52.61, H 5.26, N 7.08; found C 52.75, H 5.30, N 6.58.

Data for β-anomer: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.32$ (m, 5H; Ar-H), 5.46 (s, 1H; H-1*), 5.28 (m, 2H; H-3, H-4 overlapping), 5.01 (t, $J_{1,2} = 7.8$ Hz, $J_{2,3} = 7.8$ Hz, 1H; H-2), 4.79 (d, $J_{1,2} = 7.7$ Hz, 1H; H-1), 4.64 (d, $J = 5.1$ Hz, 2H; CH_2Ph), 4.60 (dd, $J = 5.1$, 11.1 Hz, 1H; H-5*), 4.09 (d, $J_{6a^*,5} = 7.2$ Hz, 2H; H-6a*), 4.02 (d, $J_{4,5} = 9.6$ Hz, 1H; H-5), 3.83 (s, 1H; H-6b*), 3.76 (br s, 2H; H-3*, H-4*), 3.75 (s, 3H; OCH_3), 3.20 (s, 1H; H-2*), 2.04, 2.03, 2.01 ppm (3×s, 3×3H; 3×$COCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 170.2$, 169.7, 169.6 (3×C, 3×$COCH_3$), 169.3 (C, COOH), 137.3 (C, Ar-C), 128.5 (CH, Ar-C), 128.0 (C, Ar-C), 127.8 (CH, Ar-C), 100.6 (CH, C-1*), 98.9 (CH, C-1), 77.1, 75.5, 73.4 (3×CH), 72.6 (CH_2, C-6*), 71.1, 69.0 (2×CH), 65.0 (CH_2, CH_2-Ar), 63.2, 59.4 (2×CH), 53.2 (CH_3, OMe), 20.6, 20.4, 20.4 ppm (3×CH_3, 3×$COCH_3$); IR (KBr): $\tilde{\nu} =$ 3457, 2918, 2107, 1758, 1437, 1377, 1255, 1046, 631 cm^{-1}.

Selected data for α-anomer: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.32$ (m, 5H; Ar-H), 5.59 (t, $J_{3,4} = 9.7$, 1H; H-3), 5.58 (s, 1H; H-1*), 5.23 (d, $J_{1,2} = 3.9$, 1H; H-1), 5.19 (t, $J_{3,4} = 9.6$ Hz, $J_{4,5} = 9.8$ Hz, 1H; H-4), 4.86 (dd, $J_{1,2} = 3.9$ Hz, $J_{2,3} = 10.2$ Hz, 1H; H-2), 4.71 (d, $J = 5.8$ Hz, 2H; CH_2Ph), 4.57 (m, 2H; H-5*, H-5 overlapping), 4.13 (d, $J_{6a^*,5} = 7.4$ Hz, 1H; H-6a*), 3.73 (s, 3H; OCH_3), 3.59 (s, 1H; H-4*), 3.52 (s, 1H; H-3*), 3.16 (s, 1H; H-2*), 2.04, 2.03, 2.01 ppm (3×s, 3×3H; 3×$COCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 136.7$ (C, Ar-C), 128.7 (CH, Ar-C), 128.3 (C, Ar-C), 127.7 (CH, Ar-C), 100.8 (CH, C-1*), 97.0 (CH, C-1), 75.0 (CH_2, CH_2-Ar), 72.4, 70.4, 69.4, 69.2 (4×CH, C-2–5), 53.5 ppm (CH_3, OMe).

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