SnCl4- and TiCl4-catalyzed anomerization of acylated O- and S-Glycosides: analysis of factors that lead to higher alpha:beta anomer ratios and reaction rates

$SnCl_4$ and $TiCl_4$ catalysed anomerisation of acylated *O*- and *S*-glycosides: analysis of factors that lead to higher α:β anomer ratios and reaction rates

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Abstract The quantification of factors that influence both rates and stereoselectivity of anomerisation reactions catalysed by $SnCl_4$ and $TiCl_4$ and how this has informed the synthesis of α-*O*- and α-*S*-glycolipids is discussed. The $SnCl_4$ catalysed anomerisation reactions of β-*S* and β-*O*-glycosides of eighteen substrates followed 1st order equilibrium kinetics and $k_f + k_r$ values were obtained, where k_f is the rate constant for the forward reaction (β → α) and k_r is the rate constant for the reverse reaction (α → β). Comparison of the $k_f + k_r$ values showed that reactions of glucuronic acid or galacturonic acid derivatives were ~10 to 3000 times faster than related glucoside and galactopyranoside counterparts and α:β ratios were generally also higher. Stereoelectronic effects contribute as galacto-configured compounds were up to 2 fold faster than corresponding glucosides. The introduction of groups, including protecting groups, which are increasingly electron releasing generally led to rate enhancements. The anomerisation of *S*-glycosides were consistently faster than corresponding *O*-glycosides. Reactions were generally faster for reactions with $TiCl_4$ than $SnCl_4$. Anomeric ratios depended on the Lewis acid, the number equivalents of the Lewis acid, temperature and substrate. Very high ratios of α-products for both *O*- and *S*-glucuronides were observed for reactions promoted by $TiCl_4$; for these substrates $TiCl_4$ was superior to $SnCl_4$. Anomeric ratios from anomerisation of *S*-

glucosides were higher with $SnCl_4$ than with $TiCl_4$. The dependence of equilibrium ratio on Lewis acid and the number of equivalents of Lewis acid indicated that the equilibrium ratio is determined by a complex of the saccharide residue bound to the Lewis acid and not the free glycoside. The high α:β ratios observed for anomerisation of both *O*- and *S*-glycuronic acids can be explained by coordination of the C-1 heteroatom and C-6 carbonyl group of the product to the Lewis acid which would enhance the anomeric effect by increasing the electronwithdrawing ability of the anomeric substituent and lead to an increase the proportion of the α-anomer. Such an observation would argue against the existence of a reverse anomeric effect. Support for a chelation induced endocyclic cleavage mechanism for the anomerisation is provided by the trapping of a key intermediate. The data herein will help predict the tendency of β-glycosides to undergo anomerisation; this includes cases where 1,2-trans glycosides are initial products of glycosidation reactions catalysed by $TiCl_4$ or $SnCl_4$.

1. Introduction

Conformational[1] and electronic factors alter glycoside reactivity. These properties influence the rate of hydrolysis of the glycosidic bond[2] or of glycosidation.[3] They also alter the susceptibility to anomerisation (Scheme 1), commonly described for *O*-glycosides but less so for *S*-glycosides. Anomerisation can be useful in stereoselective glycoside synthesis as it leads to the thermodynamically stable stereoisomer.[4] The 1,2-trans glycoside is often isolated in reactions with 2-acyl containing donors using $TiCl_4$[5] or $SnCl_4$[6], a fact usually explained by acyl group participation. Yet, on some occasions the α-product[7] or a mixture of α- and β-products is obtained from such glycosidation reactions. The formation of α-products can be explained if glycosidation gives the β-anomer first of all and if anomerisation occurs subsequently (glycosidation-anomerisation).[8] Whilst a mechanism for anomerisation (Scheme 1) has been proposed, which involves cleavage of the C1-ring oxygen bond (endocyclic cleavage), it has not been possible to rule out, with certainty, an alternative pathway that involves exocyclic cleavage. Although there is evidence to indicate that the electronic properties of the

aglycon and protecting groups are important, the systematic quantification of the kinetics of anomerisation catalysed by $SnCl_4$ or $TiCl_4$ has not been reported.

Also as far as we can determine there are few examples of thioglycoside anomerisation described. Synthesis of α-*S*-glycoside analogues of α-*O*-glycosides has been of general interest and there has been progress on synthesis of *S*-oligosaccharides, *S*-glycopeptides and *S*-glycolipids,[9] all of which are biologically important. *S*-Glycosides inhibit glycosyl hydrolyases, are useful biological tools and are potentially more stable *in vivo* than the corresponding *O*-glycosides.[10] A greater understanding of $TiCl_4$ and/or $SnCl_4$ induced anomerisation would be helpful in predicting whether anomerisation would be productive for generating α-*S*-glycosides as well as α-*O*-glycosides. Anomerisation has been used in the syntheses of both 1,2-cis *O*- and *S*-glycolipid that are structural analogues of *Sphingomonous* cell wall antigens. The α-*O*-gluco- and galactopyranosiduronic acid linkages were prepared with high stereoselectivities (>97:3) and high yield (83-99%) via $TiCl_4$ induced anomerisation of β-glycoside precursors.[11] Anomerisation was also effective in generating a protected α-*S*-galacturonic acid analogue from a β-*S*-galacturonic acid precursor, although the stereoselectivity was not as high (~4:1) for this reaction as for the preparation of corresponding α-*O*-galacturonides (>97:3). During the course of glycolipid synthesis we wanted to predict how efficient $TiCl_4$ or $SnCl_4$ based anomerisation of the *S*- and *O*-glycosides (glucoside/galactoside/glucuronide/galacturonide) were likely to be with a view to selecting substrates that would be likely to successfully undergo anomerisation to give α-anomers. We provide the details of this work herein, including establishment of factors that influence both rates and α:β ratios, including the achievement of higher selectivity for the α-*S*-glycosides. Support for a chelation induced endocyclic cleavage mechanism for anomerisation catalysed by $SnCl_4$ and $TiCl_4$ (Scheme 1), which includes the trapping of a key intermediate, is also provided.

Scheme 1. Possible pathways for anomerisation

2. Results and Discussion

2.1 Kinetics and stereoselectivity of anomerisation of *O*- and *S*-glycosides

The kinetics of the $SnCl_4$ catalysed anomerisation reactions of a range of β-*S*- and β-*O*-glycosides **1-18**[12] (Table 1) were first carried out. A typical reaction involved dissolving the substrate (0.08 M) in $CDCl_3$ followed by the addition of $SnCl_4$ or $TiCl_4$ in $CDCl_3$.[13] The concentration of α- and β-anomers, as a function of time, was monitored by ^{1}H-NMR for reactions of substrates **1-17**. The kinetics of anomerisation of **18** were studied by monitoring changes in optical rotation using a polarimeter as the reaction was too fast to monitor by NMR. The data obtained for the reversible anomerisation reactions generated straight line plots using the equation:[14]

$$ln\left(\frac{[A]_0 - [A]_e}{[A]_t - [A]_e}\right) = -(k_f + k_r)\,t$$

where $[A]_0$ is the initial concentration of the β-substrate, $[A]_e$ is the equilibrium concentration, $[A]_t$ is the concentration of substrate at a time t, k_f is the rate constant for the forward reaction (β → α) and k_r is the rate constant for the reverse reaction (α → β). All plots gave straight lines with r^2 values between 0.945 and 0.999. This enabled the determination of $k_f + k_r$ for each reaction. All the $SnCl_4$ (and $TiCl_4$) catalysed anomerisation reactions discussed herein thus followed the kinetics of first order reversible reactions under the conditions investigated. The isolated yields of the α/β products from the reactions varied between 85-99%.[15] The kinetic data obtained for the $SnCl_4$ catalysed anomerisation of **1-18** is

summarised in Table 1. Generally we studied butyl glycosides **1-14** (gluco-, galacto-, glucuronides, galacturonides) as model substrates with a view to ultimately choosing precursors likely to anomerise efficiently during the preparation of more complex α-glycolipids; the cyclohexyl glycosides **15-18** were also included. It was clear from the kinetic data for this series of compounds that the rates of anomerisation were greater, comparing $k_f + k_r$ values, for a glucuronic acid or galacturonic acid derivatives when compared to their respective glucoside and galactopyranoside counterparts. For example, methyl ester derivatives of glycuronic acids anomerized ~10-61 times faster than corresponding glucosides and galactosides (cf. entries 1 vs 2, 3 vs 7, 4 vs 9, 5 vs 10, 6 vs 11 and 15 vs 16). The allyl ester derivative **17** was more than 5 times faster than methyl ester **16**, and the unprotected acid **18** was an order of magnitude faster again (cf. entries 16-18). That the free acid was fastest of all is consistent with initial observations by Lemieux and Hindsgaul which have shown that the combination of $SnCl_4$ and a carboxylic acid can provide powerful inter- or intramolecular catalysis for the β to α anomerisation of isopropyl glucopyranoside derivatives[16] and with our own later observations.[8] The faster reaction for the allyl ester would be explained by the allyl group being a Π-donor and coordinating to the Lewis acid. Another observation was that the ratio of anomers (α:β) varied for each substrate; the proportion of α at equilibrium being generally greater for glycopyranosiduronic acids than the corresponding glucoside or galactoside (cf. entries 1 vs 2, 3 vs 7, 4 vs 9, 5 vs 10, 6 vs 11 and 15 vs 16).

Differences between compounds with gluco and galacto configuration are noteworthy. The *O*-galactoside derivatives were generally faster than corresponding *O*-glucosides by factors of 1.2 (cf. entry 1 vs 11), 1.7 (cf. entry 2 vs 6), 2.2 (cf. entry 7 vs 12) and 2 (cf. entry 9 vs 13). This trend is explained by considering the inductive effect of the C-4 substituent, electronegative substituents being more electron withdrawing when equatorially oriented than when axial.[17] Consequently more electron density is available to the pyranose ring in galactosides than glucosides, which leads to enhanced ability of the ring oxygen to interact with the Lewis acid. Additionally an axially oriented substituent could enhance stabilisation of a carbenium ion intermediate. There was one exception to this trend; the *S*-

galactoside **10** (entry 10) was slower than the corresponding *S*-glucoside **14** (entry 14) and the reason for this anomaly is unclear.

In accordance with that observed previously increasing the electron releasing ability of the aglycon led to increases in rate of anomerization. Thus anomerisation of **16** was ~1.2 times faster than for **2**. The anomerisation of *S*-glycosides **4, 9, 10** and **13** were consistently faster than corresponding *O*-glycosides **2, 1, 7** and **11** by factors of 2.5, 1.8, 2.3 and 2.9, respectively. Generally *S*-glycosides gave lower proportions of the α-anomer at equilibrium, explained as being due to the stronger anomeric effect for *O*-glycosides due to the higher electronegativity of oxygen; a steric effect may also contribute as sulphur is larger than oxygen and would show a preference to be equatorial.[18] Also rates increased when benzoyl protecting groups with increased ability to release electron density into the pyranose ring compared with acetyl groups were employed (*cf.* entries 2 *vs* 3, 4 *vs* 5, 1 *vs* 7, 9 *vs* 10, 13 *vs* 14). The equilibrium α:β ratio also depended on the nature of the protecting group, being consistently higher when benzoate protecting groups were used as opposed to acetyl protecting groups (cf. entries 2 vs 3, 4 vs 5, 1 vs 7, 9 vs 10, 13 vs 14).[19] The rate was faster for the tetra-*O*-methyl protected derivative **8** when compared with **7** by a factor of ~20 although the stereoselectivity for anomerisation of **8** was not as high as for **7**.[20]

Table 1 Kinetics of $SnCl_4$ catalysed anomerisation of glycosides[a]

Entry	Substrate	$10^6(k_f+k_r)$ (s^{-1})	Relative rate	α:β[b]
1		4	1	10:1
2		170	42.5	16:1
3		470	117.5	24:1
4		420	105	4:1
5		920	230	7:1
6		290	72.5	19:1
7		19	4.75	16:1
8		400	100	13:1
9		6.9	1.725	2:1
10		43	10.75	4:1
11		4.9	1.225	15:1
12		42	10.5	11:1
13		14	3.5	2:1
14		20	5	4:1
15		21	5.25	11.5:1
16		210	52.5	13:1
17		1100	275	11.5:1
18		12000[c]	3000	19:1

a Reactions were carried out at 30ºC with the substrate (0.08M) and $SnCl_4$ (0.04M) in $CDCl_3$. [b] Equilibrium ratios. [c] Kinetics determined by polarimetry.

Next we established the influence of the Lewis acid concentration on the ratio of anomers at equilibrium. A series of anomerisations of **2**, where the concentration of $SnCl_4$ was varied, were carried out and the results are summarised in Table 2. As expected the $k_f + k_r$ values increased as catalyst concentration increased. As the concentration of Lewis acid increased, the ratio of the α-anomer also increased, indicating that the equilibrium ratio is based on a complex of the saccharide residue bound to the Lewis acid and not the free glycoside. If the Lewis acid was coordinated to the anomeric oxygen atom in the product (e.g. as in **19**, **20**, Chart 1) then this would enhance the electronegativity of the group bonded to C-1 leading to a stronger anomeric effect and increasing the proportion of the α-anomer produced. The consistently higher proportion of α-isomers generated for glucuronides/galacturonides compared to glucosides/galactosides observed herein could be explained by chelate such as **20**.

Chart 1. Structures of **19** and **20**

Table 2 Effect of $SnCl_4$ concentration on anomerisation of **2**[a]

Entry	[$SnCl_4$] (M)	$10^4(k_f + k_r)$ (s^{-1})	α:β[b]
1	0.01	0.69	13.3:1
2	0.04	1.7	15.7:1
3	0.08	21	19.0:1
4	0.16	69	21.2:1

[a] Reactions were carried out at 30 ºC at a concentration of **2** of 0.08 M

[b] Equilibrium ratios.

This effect was found also for the anomerisation of the glucuronide **2** when $TiCl_4$ was the Lewis acid (Figure 1); increasing the concentration of $TiCl_4$ led to a ~9 fold increase in the equilibrium α:β ratio

from 29:1 to 255:1 by doubling the number of equivalents of $TiCl_4$.[21] The equilibrium ratio increased from 16:1 to 20:1 by doubling the number of equivalents of $SnCl_4$ for the same reaction. This ability of the Lewis acid to increase the proportion of the α-isomer was observed when using up to ~ 3 eq of the Lewis acid; a levelling effect or a reduction to the α:β ratio (Figure 1) was observed in some cases when a further excess of Lewis acid was employed. A very high α:β ratio (>99:1) was observed for the anomerisation of the *S*-glucuronide **4** when using $TiCl_4$ in a 2.5-3 fold excess. In the latter reaction a minor amount of the glycosyl chloride (<2%) was also formed. Formation of the glycosyl chloride, which would arise from activation of the thioglycoside and exocyclic cleavage followed by chloride transfer to the anomeric carbon, was slow compared to anomerisation.

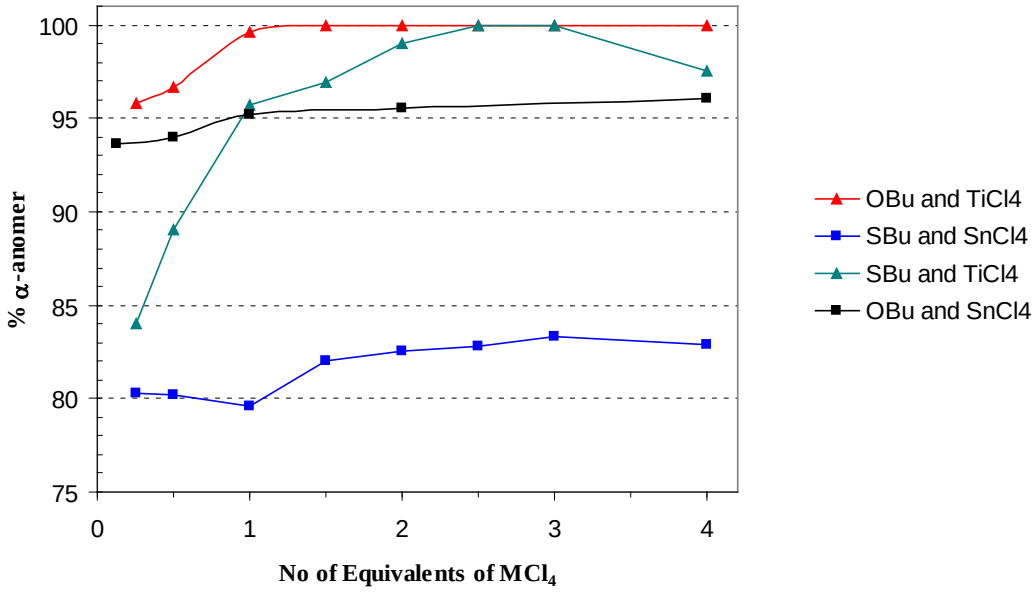


Figure 1 Effect of $MCl_4$and number of equivalents of MCl_4 on % α of the total of the α and β anomers produced from reactions of **2** and **4**

The effect of changing the Lewis acid from $SnCl_4$ to $TiCl_4$ on both the kinetics and α:β ratios was studied in more detail. Hence the anomerisations of **2**, **4**, **7**, **9-10** with both $SnCl_4$ and $TiCl_4$ were compared. The reactions catalysed by $TiCl_4$ were generally faster than those catalysed by $SnCl_4$. The $TiCl_4$ catalysed reaction of glucuronides **2** and **4** were essentially instantaneous under the conditions

described (Table 3) and a rate constant was not obtained. Rate constants were obtained for the slower anomerisation of **7**; this showed that the rate of anomerisation of **7** was ~12 fold faster in the presence of $TiCl_4$ compared with $SnCl_4$ under the same conditions. The α:β ratio was higher for the anomerisation of glucuronides **2** and **4** catalysed by $TiCl_4$ than for $SnCl_4$ (see Table 3 and Figure 1). For glucosides the trend was not as clear cut. For the *O*-glucoside **7** the α:β ratio was higher for the $TiCl_4$ catalysed reaction when compared with $SnCl_4$. However, the α:β ratio was lower for $TiCl_4$ for both the *S*-glucosides **9** and **10**, when compared with $SnCl_4$. This would indicate that the formation of a complex such as **19** is favourable for *O*-glycosides but may be less favourable for *S*-glucosides and $TiCl_4$.

Table 3. Comparison of $SnCl_4$ and $TiCl_4$ on anomerisation of **2,4,7** and **9-10**[a]

Entry	Compd	Lewis acid (0.04 M, 0.5 eq)	$10^5(k_f + k_r)$ (s^{-1})	α:β[b]
1	**2**	$SnCl_4$	17	16:1
2	**2**	$TiCl_4$	-[c]	47:1
3	**4**	$SnCl_4$	42.	4:1
4	**4**	$TiCl_4$	-[c]	8:1
5	**7**	$SnCl_4$	1.9	14:1
6	**7**	$TiCl_4$	23	15.5:1
7	**9**	$SnCl_4$	0.69	2:1
8	**9**	$TiCl_4$	4.7	1.2:1
9	**10**	$SnCl_4$	4.3	4:1
10	**10**	$TiCl_4$	28	1.9:1

[a] The reactions were carried out at 30 ºC with substrate concentration = 0.08M. [b] Equilibrium ratio. [c]Rates were too fast to measure by NMR.

The influence of temperature, on the proportion of the α-isomer formed was also investigated. Anomerisation reactions of *O*-glucuronide **2** and *S*-glucuronide **4** were carried out at various temperatures (Table 4). The rate of the anomerisation of **2** was reduced (by a factor of ~5) on reducing the reaction temperature from 40 ºC to 0 ºC. There was a concomitant increase in the proportion of the

α-anomer from 93.5% to 96.4%. For the *S*-glucuronide **4**, the proportion of the α-anomer increased from 79% to 88% by carrying out the reaction at -15 ºC rather than at 30 ºC. There was also a reduction in the rate of anomerisation of **4** by ~6 fold.

Table 4 Effect of temperature on $SnCl_4$ catalysed anomerisation of **2** and **4**[a]

Entry	Compd	Temp (ºC)	$10^5(k_f+k_r)$ (s^{-1})	α:β[b]
1	**2**	0	4.7	26.8 : 1
2	**2**	20	7.1	17.2 : 1
3	**2**	30	17	15.7 : 1
4	**2**	40	29	14.4 : 1
5	**4**	-15	6.4	7.5 : 1
6	**4**	0	14	5.8 : 1
7	**4**	30	42	3.7 : 1

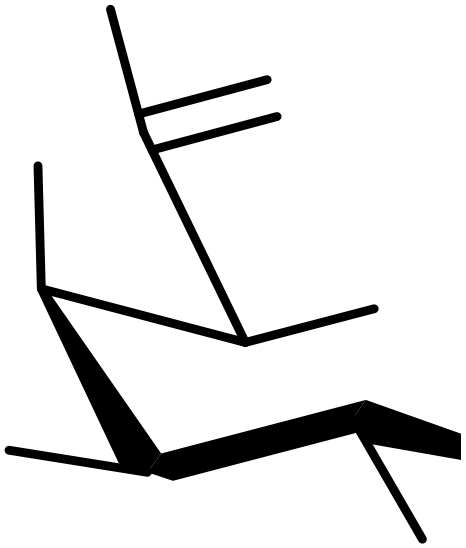
[a]All reactions were carried out with $SnCl_4$ at a concentration of 0.04 M and a substrate concentration of 0.08 M. [b] Equilibrium ratios.

Taking into account the trends, we predicted that increased amounts of α-anomer would be obtained by anomerisation of the *S*-glucuronide **4** if the reaction was promoted by an excess of $TiCl_4$ at lower temperature. A greater proportion of the α anomer (30:1, 96%) was obtained from the reaction of **4** using $TiCl_4$ (2.5 eq) at 0 ºC than was obtained when using $SnCl_4$ (0.5 eq) at 30 ºC (3.7:1)

2.2 Observations in anomerisation reactions in *S*-glycolipid synthesis

Anomerisation for *S*-glycosides described herein is faster than for corresponding *O*-glycosides. This indicated to us that the synthesis of the α-*S*-glycolipid derivatives would be feasible, particularly for glucuronide or galacturonide derivatives. Two substrates **21** and **22** (Scheme 2) were prepared with the aim of the synthesis of *S*-glycolipids. These substrates were carefully chosen, based on the kinetic data described herein, in order to optimise the rate of generation of the desired α-products; hence both substrates contained benzoyl protecting groups; the allyl ester protection for the C-6 carboxyl group at

the galacturonic acid residue of **21** was incorporated. When **22** was treated with $TiCl_4$ in dichloromethane the only isolable product upon completion of the reaction was the α-chloride **24**. The formation of **24** is explained by activation of the thioglycoside, induced by chelation of the catalyst to nitrogen and oxygen atoms of the lipid chain, which subsequently induces exocyclic cleavage of the C1-S bond and formation of a glycosyl carbonium ion which is trapped by chloride. Conversely, the treatment of galacturonide **21** with $TiCl_4$ (0.5 eq) led to anomerisation and formation of **23**, even though **21** also has the azide and an OBn protecting group with potential to chelate to $TiCl_4$. We believe that formation of **23** is due to the 5-membered ring chelate formed by coordination of the $TiCl_4$ to the C-6 carbonyl and ring oxygen, which induces more rapid endocyclic cleavage of the C1-ring oxygen bond facilitating anomerisation. This preferred mode of chelation occurs sufficiently rapidly for the galacturonide to prevent the exocyclic cleavage process observed for **22**. Concomitant removal of the benzyl group from the lipid chain occurs simultaneously en route to **23**.



Scheme 2. $TiCl_4$ catalysed reaction of **21** and **22**

2.3 Comparison of anomerisation with glycoside hydrolysis

It is generally accepted that α-glycoside hydrolysis proceeds first through protonation of the exocyclic oxygen, which is followed by cleavage of the aglycon in the rate determining step, giving an intermediate oxocarbenium ion which reacts with water to form the product (Scheme 3).[22] Deslongchamps et al have suggested that the hydrolysis of β-*O*-glycosides can take place *via* the exocyclic pathyway but that a competing pathway involving protonation of the ring oxygen followed by C1-ring oxygen bond cleavage can also operate.[23] The exocyclic pathway for α-glycosides was supported by the use of labelling experiments and by measuring the effects on the rate of hydrolysis of exchanging the exocyclic oxygen atom with sulphur, which led to a decrease in the rate of hydrolysis. Relative rates for *O*- and *S*-glucosides and glucuronides are shown in Chart 3.[24] Slower hydrolysis of *S*-glycosides has generally been attributed to the lower p*K*a of the thioglycoside sulphur atom leading to a lower concentration of protonated intermediate. Replacing the ring oxygen with sulphur resulted in an increase of the hydrolysis rate, which is due to the sulphur withdrawing less electron density from the exocyclic oxygen, resulting in an increased concentration of the protonated intermediate.[25] Therefore, a change that increases the concentration of protonated glycoside will result in an increased rate of hydrolysis.

In a recent paper from our group where the anomerisation of β-D-*O*-glucopyranuronic acid derivatives was considered and where precise rate constants were not calculated, we suggested that rates of anomerisation can be correlated with rates of hydrolysis of β-D-glucopyranosiduronic acids. The analysis shown in Chart 3, based on rate constants for both the hydrolysis and anomerisation of *S*- and *O*-glycosides (Table 1) shows that our original conclusion is not strictly true; there is not a direct correlation between rates of anomerisation and hydrolysis. The replacement of the glycosidic oxygen atom with sulphur consistently led to an *increase* in the rate of anomerisation (Chart 3, Table 1) for both

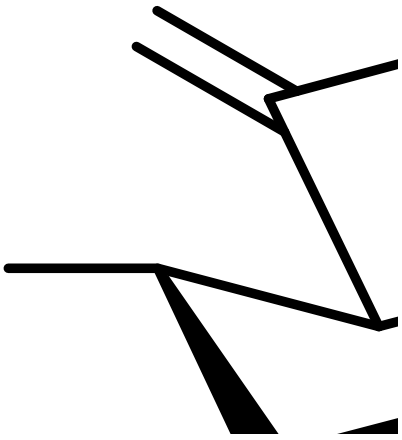
glucuronic acid and glucose derivatives. This contrasted with data observed for hydrolysis, where the replacement of the glycosidic oxygen atom with sulphur consistently led to a *decrease* in the rate of hydrolysis. This data would support the proposal that endocyclic cleavage[26] operates in the anomerisation of the β-glycosides catalysed by $SnCl_4$. The soft sulphur atom would be more weakly coordinated to the hard Lewis acid than an oxygen atom and therefore be less susceptible to anomerisation proceeding by exocyclic cleavage. However sulphur is less electronegative than oxygen and therefore chelation[27] by the carbonyl and ring oxygen atoms to the catalyst would be expected to be enhanced for the more electron releasing *S*-glycosides than *O*-glycosides. This would be consistent with enhanced rates of anomerisation that were consistently observed.

Scheme 3 Pathway for hydrolysis of α-glycosides by exocyclic cleavage.

Chart 3. Relative rates of hydrolysis and anomerisation of selected *S*- and *O*-glycosides

2.4 Trapping experiments

The trapping of intermediates was attempted in an effort to gain further evidence for endocyclic cleavage (Scheme 4). Certain 2,3-trans-carbamate- and -carbonate carrying pyranosyl donors give α-glycosides in glycosidation reactions promoted by Brønsted or Lewis acids.[28] Manabe et al have recently gained evidence for the proposal that this reaction resulted from endocyclic cleavage of the pyranosides on the basis that it was possible to trap the intermediate cation.[29] Conditions which were successfully used by these researchers were investigated by us. The use of a large excess of sodium cyanoborohydride in the presence of $TiCl_4$ facilitated the trapping of the intermediate from endocyclic cleavage during the anomerisation of both *O*-glycoside **2** and *S*-glycoside **10** which provided **25** and **27** (30%), respectively. Compound **25** could not be separated from α–anomer of **2**, which was competitively formed and thus the acetylation of **25** to **26** (5% over two steps) was carried out to facilitate purification. This provided support that $TiCl_4$ catalysed anomerisation proceeds at least to some degree through endocyclic cleavage.



Scheme 4 Trapping of intermediates

2.5 Summary and Conclusions

The rates and the stereoselectivity of $SnCl_4$ and $TiCl_4$ promoted anomerisations of a series of acylated glycosides have been quantified. Rates of anomerisation are significantly faster for glucuronic acid or galacturonic acid derivatives compared to related gluco- and galactopyranosides. Stereoelectronic effects contribute as galacto-configured compounds were for the most part faster than compounds with glucose configurations. Introduction of increasingly electron releasing groups at C-1 to C-4 led to rate enhancements. Anomerisation of *S*-glycosides were consistently faster than corresponding *O*-glycosides. Reactions catalysed by $TiCl_4$ were faster than $SnCl_4$. Anomeric ratios depend on saccharide residue, whether $TiCl_4$ or $SnCl_4$ are employed, the number of equivalents of $TiCl_4$ or $SnCl_4$ employed, temperature, protecting group and electron withdrawing power of the aglycon. High α:β ratios for *O*- and *S*-glucuronides were achieved using excess $TiCl_4$ and decreasing the reaction temperature. The high α:β ratios observed for anomerisation of both *O*- and *S*-glycosides of glucuronic acids may be explained by coordination of the C-1 heteroatom and C-6 carbonyl group of the product to the Lewis acid which would make the anomeric substituent more electron withdrawing enhancing the anomeric effect, increasing the equilibrium concentration in favour of the α-anomer. One referee for this manuscript pointed out that this observation would be a further argument against the existence of the reverse anomeric effect.[30] Evidence is provided that the mechanism of anomerisation involves endocyclic cleavage of the C-1 and ring oxygen, which could be due to the chelation of the Lewis acid to the ring oxygen and the C-6 substituent. Such chelation is faster for galacturonic and glucuronic acid derivatives than glucosides or galactosides. The study enabled the achievement of the synthesis of α-glycolipids by anomerisation.[31] The data will be useful in predicting the tendency of β-glycoside derivatives with 2-acyl protecting groups to undergo anomerisation and in predicting whether glycosidation catalysed by $TiCl_4$ or $SnCl_4$ are likely to give products that contain high proportions of the α-anomer.

3. Experimental Section

Anomerisation reactions

A typical reaction involved dissolving the substrate[32] (68 μmol) in $CDCl_3$ (0.75 mL) in a 5 mm NMR tube followed by the addition of $SnCl_4$ or $TiCl_4$ in $CDCl_3$ (0.1 mL of 0.34 M, 34 μmol) and mixing thoroughly, giving a 0.08 M solution of the substrate and a 0.04 M solution of $SnCl_4$ or $TiCl_4$ in $CDCl_3$. Generally reactions were carried out using 0.08 M substrate (Tables 1-4). The concentration of anomers, as a function of time, was monitored by ^{1}H-NMR spectroscopy using either a 500 or 600 MHz NMR spectrometer at 30 °C. Experiments were repeated at least twice for all substrates except compound **8**, where the kinetics were measured once. The reactions were carried out up to six times in some cases. $SnCl_4$ or $TiCl_4$ are both hygroscopic and the rates were found to be sensitive to the presence of water; thus the substrates, NMR tubes and solvent were thoroughly dried before reactions were carried out. The formation of a white precipitate (presumably SnO_2 or TiO_2) in the NMR tube generally gave an indication of the presence of water. For reactions where water was adequately excluded there was no precipitation observed in the reaction tube. Integration of signals (normally 3-5) belonging to both the starting substrate (β-anomer) and product (α-anomer) in the ^{1}H-NMR spectra were used to determine the concentration of anomers present at time t. Generally the ^{1}H-NMR signals which were selected for integration were H-1 to H-5 of the saccharide ring when they did not overlap with any other signal. The reactions were followed by ^{1}H-NMR until equilibrium was essentially established (i.e. there was no further decrease in β-anomer integral or no further increase in the α-anomer integral). The α:β ratios quoted in the manuscript were determined at this point. Generally the total integral for the α and β-anomer was constant during the course of the reaction, indicating there was little or no decomposition. Graphs were generally plotted for all data collected between beginning and end of reaction. Kinetic data for **18** was obtained by monitoring changes in optical rotation as the reaction was too fast to be monitored by NMR. The $k_f + k_r$ for each reaction was calculated as described in the results and discussion section.

Analytical data for α–anomers of 1-14[33]:

Butyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside 1α IR (film) cm^{-1}: 2959, 1748, 1367, 1221, 1037; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.50 (1H, t, *J* 9.8 Hz), 5.09 (1H, d, *J* 3.7 Hz), 5.05 (1H, t, *J* 9.8 Hz), 4.86 (1H, dd, *J* 9.8 Hz, *J* 3.7 Hz), 4.29 (1H, dd, *J* 12.3 Hz, *J* 4.6 Hz), 4.15 (1H, dd, *J* 12.3 Hz, *J* 2.3 Hz), 4.04 (1H, ddd, *J* 10.2, *J* 4.6 Hz, *J* 2.3 Hz), 3.70 (1H, dt, *J* 9.8 Hz, *J* 6.5 Hz), 3.45 (1H, dt, *J* 9.8 Hz, *J* 6.5 Hz), 2.18 (3H, s), 2.11 (3H, s), 2.08 (3H, s), 2.06 (3H, s), 1.59 (2H, m), 1.40 (2H, m), 0.94 (3H, t, *J* 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.7, 170.2, 170.1, 169.6, 95.6, 71.0, 70.3, 68.7, 68.4, 67.1, 62.0, 31.3, 20.7 (2s), 20.6, 19.2, 13.7; ESI-HRMS calcd for $C_{18}H_{28}O_{10}Na$ 427.1580, found *m/z* 427.1559 $[M+Na]^+$.

Butyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranosiduronic acid, methyl ester 2α IR (film) cm^{-1}: 2960, 1754, 1439, 1371, 1219, 1051; ^{1}H NMR ($CDCl_3$, 500 MHz) δ5.55 (1H, t, *J* 10.0 Hz), 5.28 (1H, d, *J* 3.6 Hz), 5.21 (1H, t, *J* 10.0 Hz), 4.90 (1H, dd, *J* 10.0 Hz, *J* 3.6 Hz), 4.39 (1H, d, *J* 10.0 Hz), 3.80 (3H, s), 3.77 (1H, m), 3.50 (1H, dt, *J* 9.9 Hz, *J* 6.5 Hz), 2.09 (3H, s), 2.07 (3H, s), 2.06 (3H, s), 1.60 (2H, m), 1.40 (2H, m), 0.94 (3H, t, *J* 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.7, 170.5, 170.2, 169.1 (each C=O), 96.1, 70.7, 69.7, 69.6, 69.3, 68.0, 53.5, 31.2, 20.7, 20.6 (2s), 19.1, 13.9; ESI-HRMS calcd for $C_{17}H_{30}O_{10}N$ 408.1870, found *m/z* 408.1870 $[M+NH_4]^+$.

Butyl 2,3,4-tri-*O*-benzoyl-α-D-glucopyranosiduronic acid, methyl ester 3α IR (film) cm^{-1}: 2958, 1730, 1263, 1107, 1069; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.97 (4H, m), 7.89 (2H, dd, *J* 8.1 Hz, *J* 0.9 Hz), 7.52 (2H, m), 7.44 (1H, t, *J* 7.4 Hz), 7.43 (4H, m), 7.31 (2H, t, *J* 7.8 Hz), 6.20 (1H, t, *J* 10.0 Hz), 5.64 (1H, t, *J* 10.0 Hz), 5.43 (1H, d, *J* 3.7 Hz), 5.32 (1H, dd, *J* 10.0 Hz, 3.7 Hz), 4.62 (1H, d, *J* 10.0 Hz), 3.83 (1H, dt, *J* 9.9 Hz, *J* 6.5 Hz), 3.69 (3H, s), 3.51 (1H, dt, *J* 9.9. Hz, *J* 6.5 Hz), 1.59 (2H, m), 1.37 (2H, m), 0.84 (3H, t); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.3, 165.7, 165.6, 165.3, 133.4, 133.2, 129.9, 129.8,

129.7, 129.1, 129.0, 128.9, 128.4 (2s), 128.3, 96.3, 71.5, 70.3, 69.8, 69.2, 68.6, 52.9, 31.3, 19.1, 13.6; ESI-HRMS calcd for $C_{32}H_{36}O_{10}N$ 594.2339, found *m/z* 594.2326 $[M+NH_4]^+$.

Methyl 1-α-thiobutyl-2,3,4-tri-*O*-acetyl-D-glucopyranosiduronate 4α IR (film) cm^{-1}: 2958, 1753, 1438, 1372, 1220, 1042, 899; ^1H NMR ($CDCl_3$, 500 MHz): δ 5.81 (1H, d, *J* 5.5 Hz), 5.39 (1H, t, *J* 9.5 Hz), 5.22 (1H, t, *J* 9.5 Hz), 5.04 (1H, dd, *J* 9.5 Hz, *J* 5.5 Hz), 4.81 (1H, d, *J* 9.5 Hz), 3.80 (3H, s), 2.61 (2H, m), 2.10 (3H, s), 2.08 (3H, s), 2.06 (3H, s), 1.58 (2H, m), 1.41 (2H, m), 0.91 (3H, t, *J* 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.2 (3s), 168.7, 82.3, 70.3, 69.7, 69.5, 68.5, 53.3, 31.4, 30.3, 21.8, 20.7, 20.6, 13.5; ESI-HRMS calcd for $C_{17}H_{30}O_9NS$ 424.1641, found *m/z* 424.1628 $[M+NH_4]^+$.

Methyl 1-α-thiobutyl-2,3,4-tri-*O*-benzoyl-D-glucopyranosiduronate 5α IR (film) cm^{-1}: 2957, 1727, 1259, 1091, 1026, 910; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.01 (2H, dd, *J* 8.0 Hz, *J* 1.2 Hz), 7.95 (2H, dd, *J* 8.0 Hz, *J* 1.2 Hz), 7.91 (2H, dd, *J* 8.0 Hz, *J* 1.2 Hz), 7.52 (4H, m), 7.39 (2H, t, *J* 7.6 Hz), 7.34 (4H, m), 6.16 (1H, d, *J* 5.3 Hz), 6.09 (1H, t, *J* 8.9 Hz), 5.78 (1H, t, *J* 8.9 Hz), 5.56 (1H, dd, *J* 8.9 Hz, *J* 5.3 Hz), 5.16 (1H, d, *J* 8.9 Hz), 3.77 (3H, s), 2.82 (1H, ddd, *J* 12.8 Hz, *J* 7.9 Hz, *J* 6.5 Hz), 2.76 (1H, ddd, *J* 14.9 Hz, *J* 7.9 Hz, *J* 7.0 Hz), 1.69 (2H, m), 1.46 (2H, m), 0.95 (3H, t, *J* 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.3, 165.4, 165.3, 165.2, 133.5, 133.4, 130.0, 129.9, 129.8 (3s), 128.9 (2s), 128.8, 128.5, 128.4 (3s), 128.3, 82.0, 70.9, 69.8, 69.5 (2s), 52.8, 31.6, 30.6, 21.9, 13.5: ESI-HRMS calcd for $C_{32}H_{32}O_9SNa$ 615.1665, found *m/z* 615.1652 $[M+Na]^+$.

Butyl 2,3,4-tri-*O*-acetyl-α-D-galactopyranosiduronic acid, methyl ester 6α IR (film) cm^{-1}: 2958, 1752, 1372, 1224, 1158, 1068, 1030; ^1H NMR ($CDCl_3$, 500 MHz): δ 5.77 (1H, dd, *J* 3.4 Hz, *J* 1.3 Hz), 5.41 (1H, dd, *J* 10.9 Hz, *J* 3.4 Hz), 5.24 (1H, d, *J* 3.6 Hz), 5.16 (1H, dd, *J* 10.9 Hz, *J* 3.6 Hz), 4.63 (1H, d, *J* 1.3 Hz), 3.76 (3H, s, OC*H*$_3$), 3.74 (1H, dt, *J* 9.9 Hz, *J* 6.5 Hz), 3.47 (1H, dt, *J* 9.9 Hz, *J* 6.7 Hz), 2.10 (3H, s), 2.07 (3H, s), 2.00 (3H, s), 1.57 (2H, m), 1.36 (2H, m), 0.92 (3H, t, *J* 7.4 Hz); ^{13}C NMR

($CDCl_3$, 125 MHz): δ 170.2, 167.0, 169.8, 167.6, 96.4, 69.2, 69.0, 68.4, 67.8, 67.3, 52.7, 31.3, 20.7, 20.6 (2s), 19.2, 13.7; ESI-HRMS calcd for $C_{17}H_{26}O_{10}Na$ 413.1424, found *m/z* 413.1431 $[M+Na]^+$.

Butyl 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranoside 7α ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 8.05 (2H, d, *J* 7.5 Hz), 7.99 (2H, d, *J* 7.5 Hz), 7.95 (2H, d, *J* 7.3 Hz), 7.87 (2H, d, *J* 7.4 Hz), 7.55 (1H, t, *J* 7.4 Hz), 7.49 (2H, m), 7.41 (3H, t, *J* 7.8 Hz), 7.36 (4H, m), 7,28 (2H, t, *J* 7.7 Hz), 6.21 (1H, t, *J* 9.8 Hz), 5.68 (1H, t, *J* 9.8 Hz), 5.35 (1H, d, *J* 3.7 Hz), 5.32 (1H, dd, *J* 9.8 Hz, *J* 3.7 Hz), 4.61 (1H, m), 4,48 (2H, m), 3.81 (1H, dt, *J* 9.8 Hz, *J* 6.5 Hz), 3.51 (1H, dt, *J* 9.8 Hz, *J* 6.6 Hz), 1.60 (2H, m), 1.35 (2H, m), 0.83 (3H, t, *J* 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): 166.4, 165.9, 165.8, 165.4, 133.4 (2s), 133.2, 129.9, 129.7 (2s), 129.6, 129.1, 129.0, 128.8, 128.4, 128.3, 96.0, 72.0, 70.7, 69.7, 68.7, 67.7, 63.3, 31.3, 19.2, 13.6.

Butyl 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranoside 8α ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.77 (1H, d, *J* 2.0 Hz, H-1), 3.92 (2H, m), 3.83 (1H, m), 3.69 (2H, m), 3.66 (3H, s), 3.62 (2H, m), 3.60 (3H, s), 3.57 (3H, s), 3.53 (2H, m), 1.66 (2H, m), 1.40 (2H, m), 0.94 (3H, t, *J* 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 96.3, 83.4, 81.7, 79.6, 71.1, 69.9, 67.8, 60.8, 60.4, 59.2, 58.6, 31.5, 19.8, 13.8.

Butyl 2,3,4,6-tetra-*O*-acetyl-1-α-D-thioglucopyranoside 9α IR (film) cm^{-1}: 2960, 2873, 1723, 1451, 1265, 1107, 1095, 1069, 1026; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.66 (1H, d, *J* 5.8 Hz), 5.38 (1H, t, *J* 9.7 Hz), 5.05 (2H, m), 5.46 (1H, ddd, *J* 10.2 Hz, *J* 4.7 Hz, *J* 2.2 Hz), 4.33 (1H, dd, *J* 12.4 Hz, *J* 4.7 Hz), 4.12 (1H, dd, *J* 12.4 Hz, *J* 2.2 Hz), 2.54 (2H, m), 2.16 (3H, s), 2.09 (3H, s), 2.08 (3H, s), 2.05 (3H, s), 1.58 (2H, m), 1.40 (2H, m), 0.92 (3H, t, *J* 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.6, 169.9 (2s), 169.6, 82.0, 70.8, 70.5, 68.6, 67.5, 62.0, 31.4, 29.8, 21.9, 20.8, 20.70 (2s), 20.6, 13.6; ESI-HRMS calcd for $C_{18}H_{28}O_9SNa$ 443.1352, found *m/z* 443.1360 $[M+Na]^+$.

Butyl 2,3,4,6-tetra-*O*-benzoyl-1-α-thiobutylglucopyranoside 10α IR (film) cm^{-1}: 2958, 1726, 1267, 1093, 1069, 1027, 708; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.05 (2H, d, *J* 7.3 Hz), 7.98 (2H, d, *J* 7.3

Hz), 7.95 (2H, d, *J* 7.3 Hz), 7.87 (2H, d, *J* 7.3 Hz), 7.56 (1H, t, *J* 7.3 Hz), 7.51 (2H, t, *J* 7.4 Hz), 7.45-7.35 (7H, m), 7.30 (2H, t, *J* 7.8 Hz), 6.07 (1H, t, *J* 10.0 Hz), 5.91 (1H, d, *J* 5.8 Hz), 5.66 (1H, t, *J* 10.0 Hz), 5.50 (1H, dd, *J* 10.0 Hz, *J* 5.8 Hz), 4.87 (1H, ddd, *J* 10.0 Hz, *J* 5.6 Hz, *J* 2.8 Hz), 4.59 (1H, dd, *J* 12.2 Hz, *J* 2.8 Hz), 4.52 (1H, dd, *J* 12.2 Hz, *J* 5.6 Hz), 2.59 (2H, m), 1.56 (2H, m), 1.30 (2H, m), 0.82 (3H, t, *J* 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.1, 165.6, 165.4, 165.3, 133.4, 133.2, 133.1, 130.0, 129.9, 129.7 (2s), 128.4 (3s), 128.3, 82.3, 71.7, 70.9, 69.6, 68.2, 63.1, 31.4, 29.9, 22.0, 13.5; ESI-HRMS calcd for $C_{38}H_{36}O_9SNa$ 691.1978, found *m/z* 691.1982 $[M+Na]^+$.

Butyl 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranoside 11α IR (film) cm^{-1}: 2961, 2937, 1744, 1369, 12171044, 912; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.46 (1H, d, *J* 3.1 Hz), 5.36 (1H, m), 5.10 (2H, m), 4.22 (1H, t, *J* 6.6 Hz), 4.11 (1H, dd, *J* 9.3 Hz, *J* 4.5 Hz), 4.08 (1H, dd *J* 9.3 Hz, *J* 5.4 Hz), 3.69 (1H, dt, *J* 9.7 Hz, *J* 6.5 Hz), 3.43 (1H, dt, *J* 9.7 Hz, *J* 6.5 Hz), 2.14 (3H, s), 2.07 (3H, s), 2.05 (3H, s), 1.99 (3H, s), 1.58 (2H, m), 1.39 (2H, m), 0.93 (3H, t, *J* 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.4 (2s), 170.2, 170.0, 96.1, 68.4, 68.3, 68.2, 67.7, 66.2, 61.9, 31.3, 20.8, 20.7, 20.6, 19.2, 13.7; ESI-HRMS calcd for $C_{18}H_{32}O_{10}N$ 422.2026, found *m/z* 422.2032 $[M+NH_4]^+$.

Butyl 2,3,4,6-tetra-*O*-benzoyl-α-D-galactopyranoside 12α IR (film) cm^{-1}: 2960, 2873, 1725, 1602, 1267, 1108, 1095, 1069, 1027; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.09 (2H, dd, *J* 8.3 Hz, *J* 1.2 Hz), 8.02 (2H, dd, *J* 8.5 Hz, *J* 1.3 Hz), 7.98 (2H, dd, *J* 8.5 Hz, *J* 1.3 Hz), 7.79 (2H, dd, *J* 8.4 Hz, *J* 1.2 Hz), 7.62 (1H, t, *J* 7.5 Hz), 7.57-7.36 (9H, m), 7.24 (2H, t, *J* 7.8 Hz), 6.04 (1H, d, *J* 3.3 Hz), 6.00 (1H, dd, *J* 10.6 Hz, *J* 3.3 Hz), 5.68 (1H, dd, *J* 10.6 Hz, *J* 3.6 Hz), 5.41 (1H, d, *J* 3.6 Hz), 4.65 (1H, m), 4.60 (1H, dd, *J* 11.0, *J* 7.1 Hz), 4.40 (1H, dd, *J* 11.0 Hz, *J* 5.6 Hz), 3.80 (1H, dt, *J* 9.7 Hz, *J* 6.5 Hz), 3.50 (1H, dt, *J* 9.5 Hz, *J* 6.2 Hz), 1.59 (2H, m), 1.34 (2H, m), 0.83 (3H, t, *J* 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.1, 166.0, 165.7, 165.6, 133.5, 133.3, 133.2, 133.1, 129.9, 129.8, 129.7, 128.6, 128.4 (2s), 128.2, 96.6, 69.4, 69.3, 68.6, 68.5, 66.9, 62.7, 31.4, 19.2, 13.7; ESI-HRMS calcd for $C_{38}H_{40}O_{10}N$ 670.2652, found *m/z* 670.2631 $[M+NH_4]^+$.

Butyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-galactopyranoside 13α IR (film) cm^{-1}: 2960, 1751, 1368, 1224, 1038, 913; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.72 (1H, d, *J* 5.4 Hz), 5.45 (1H, dd, *J* 3.0 Hz, *J* 0.8 Hz), 5.27 (1H, dd, *J* 10.8 Hz, *J* 5.4 Hz), 5.22 (1H, dd, *J* 10.8 Hz, *J* 3.0 Hz), 4.59 (1H, t, *J* 6.6 Hz), 4.11 (2H, m), 2.53 (2H, m), 2.15 (3H, s), 2.08 (3H, s), 2.05 (3H, s), 1.58 (2H, m), 1.40 (2H, m), 0.92 (3H, t, *J* 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.3, 170.2, 170.1, 169.8, 82.2, 68.2, 68.0 (2s), 66.5, 61.9, 31.4, 29.5, 22.0, 20.8, 20.7, 20.6, 13.6; ESI-HRMS calcd for $C_{18}H_{28}O_9SNa$ 443.1352, found *m/z* 443.1353 $[M+Na]^+$.

Butyl 2,3,4,6-tetra-*O*-benzoyl-1-thio-α-D-galactopyranoside 14α IR (film) cm^{-1} 2960, 1726, 1451, 1316, 1266, 1177, 1095, 1069, 1026; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.09 (2H, d, *J* 7.4 Hz), 8.03 (2H, d, *J* 8.2 Hz), 7.99 (2H, d, *J* 7.6 Hz), 7.79 (2H, d, *J* 8.3 Hz), 7.62 (1H, t, *J* 7.4 Hz), 7.56 (1H, t, *J* 7.5 Hz), 7.49 (3H, m), 7.42 (5H, m), 7.24 (2H, t, *J* 7.9 Hz), 6.05 (2H, m), 5.88 (2H, m), 5.04 (1H, t, *J* 6.4 Hz), 4.61 (1H, dd, *J* 11.6 Hz, *J* 7.4 Hz), 4.49 (1H, dd, *J* 11.6 Hz, *J* 5.1 Hz), 2.62 (1H, ddd, *J* 12.7 Hz, *J* 8.5 Hz, *J* 6.3 Hz), 2.55 (1H, ddd, *J* 12.7 Hz, *J* 8.5 Hz, *J* 7.0 Hz), 1.54 (2H, m), 1.27 (2H, m), 0.81 (3H, t, *J* 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): 166.0, 165.7, 165.5, 165.4, 133.6, 133.4, 133.2 (2s), 129.9 (2s), 129.8, 129.7 (2s), 129.5, 129.1, 129.0 (2s), 128.6, 128.4 (3s), 128.3, 128.2, 82.5, 69.1, 69.0 (2s), 67.3, 62.7, 31.4, 29.6, 22.0, 13.5; ESI-HRMS calcd for $C_{38}H_{40}O_9SN$ 686.2424, found *m/z* 686.2416 $[M+NH_4]^+$.

Methyl (2*S*, 3*S*, 4*R*, 5*S*) 2,3,4,5-tetra-*O*-acetyl-6-*O*-butylhex-2-olanoate 26 A mixture of the β-glucoside **2** (90 mg, 0.230 mmol) and $Na(CN)BH_3$ (169 mg, 2.69 mmol) was dried under vacuum for 3 h. To this chloroform 1.0 mL) was added followed by $TiCl_4$ (0.8 mL of a 0.342 M solution in chloroform, 0.268 mmol) and the mixture was stirred at room temperature for 16 h. This was followed by the addition of satd aq $NaHCO_3$ (3 mL) and solid $NaHCO_3$ (50 mg) and the mixture was then stirred

for a further 15 min. The organic layer was washed with water, dried ($MgSO_4$) and the solvent was removed under reduced pressure. Chromatography of the residue gave the α-anomer of **2** and **25** as an inseparable mixture. The mixture was then dissolved in pyridine (2 mL) and Ac_2O (2 mL) was added and the mixture stirred at room temp for 16 h. The volatile components were evaporated under reduced pressure. Chromatography of the residue (EtOAc-petroleum ether, 1:4) gave **26** as a colourless oil (5 mg, 5 %); R_f 0.82 (EtOAc-petroleum ether, 1:4); IR (film) cm^{-1}: 2957, 2855, 1749, 1370, 1209, 1036, 910; ^1H NMR ($CDCl_3$, 500 MHz): δ 5.64 (1H, dd, *J* 6.6 Hz, *J* 4.2 Hz), 5.49 (1H, dd, *J* 6.9 Hz, *J* 4.2 Hz), 5.15 (1H, m), 5.11 (1H, d, *J* 7.0 Hz), 3.74 (3H, s), 3.50 (2H,d, *J* 4.4 Hz), 3.46 (1H, dt, *J* 9.2 Hz, *J* 6.4 Hz), 3.38 (1H, dt, *J* 9.2 Hz, *J* 6.6 Hz), 2.13 (3H, s), 2.10 (3H, s), 2.08 (3H, s), 2.07 (3H, s), 1.50 (2H, m), 1.38 (2H, m), 0.92 (3H, t, *J* 7.4 Hz); ^{13}C NMR ($CDCl_3$, 500 MHz): δ 170.2, 169.8, 169.5, 167.5 (each C=O), 71.4 (*C*H_2), 70.9, 69.6, 69.3, 69.2 (each CH), 68.6 (*C*H_2), 52.8 (*C*H_3), 31.5, 20.9, 20.6 (2s), 20.4, 19.2, 13.9 (each CH_3); ESI-HRMS calcd for $C_{19}H_{30}O_{11}Na$ 457.1672 found *m/z* 457.1686 $[M+Na]^+$.

(2*R*, 3*R*, 4*S*, 5*R*)-1,3,4,5-Tetra-*O*-benzoylhexan-2-ol-6-thiobutyl ether 27 A mixture of the β-thioglucoside **10** (90 mg, 0.134 mmol) and $Na(CN)BH_3$ (169 mg, 2.69 mmol) was dried under vacuum for 3 h. Then $TiCl_4$ (0.8 mL of a 0.342 M solution in chloroform, 0.268 mmol) was added and the mixture stirred at room temp for 16 h. This was followed by the addition of satd aq $NaHCO_3$ (3 mL) and solid $NaHCO_3$ (50 mg) and the reaction was then stirred for a further 15 min. The organic layer was washed with water, dried ($MgSO_4$) and the solvent was removed under reduced pressure. Chromatography of the residue (EtOAc-petroleum ether, 1:1) gave **27** (27 mg, 30%); R_f 0.16 (EtOAc-petroleum ether, 1:4); IR (film) cm^{-1}: 3485, 3065, 2926, 1724, 1263, 1108, 1069, 1026, 708; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.40 (2H, dd, *J* 8.4 Hz, *J* 1.2 Hz), 7.98 (2H, dd, *J* 8.4 Hz, *J* 1.2 Hz), 7.95 (2H, dd, *J* 8.4 Hz, *J* 1.2 Hz), 7.88 (2H, dd, *J* 8.3 Hz, *J* 1.2 Hz), 7.52 (2H, m), 7.39 (8H, m), 7.26 (2H, m), 6.18 (1H, dd, *J* 6.0 Hz, *J* 2.8 Hz), 5.71 (2H, m), 4.56 (1H, dd, *J* 12.0 Hz, *J* 2.9 Hz), 4.35 (1H, dd, *J* 12.0 Hz, *J* 2.9 Hz), 4.18 (1H, m), 3.69 (1H), 3.02 (1H, dd, *J* 14.4 Hz, *J* 5.3 Hz), 2.94 (1H, dd, *J* 14.4 Hz, *J* 6.6 Hz),

2.56 (2H, t, *J* 7.5 Hz), 1.51 (2H, m), 1.30 (2H, m), 0.82 (3H, t, *J* 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz), δ 167.0, 166.6, 165.8, 165.5 (each C=O), 133.7, 133.5, 133.1, 133.0, 130.0, 129.9, 129.7, 129.6, 128.7, 128.5 (3s), 128.3, 128.2, 72.2, 72.0 (4 signals), 71.5, 68.6 (2 signals), 65.3, 32.7, 32.4 (each CH_2), 31.5, 21.8, 13.5 (CH_3); ESI-HRMS calcd for $C_{38}H_{38}O_9SNa$ 693.2134, found *m/z* 693.2131 $[M+Na]^+$.

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Supporting Information Available Experimental procedures for preparation of **1-18** and analytical data for compounds, including assignments for all the NMR data, including α-anomers of **1-18**. ^{1}H and ^{13}C-NMR spectra for α-and β-anomers. This material is available free of charge via the Internet at http://pubs.acs.org."

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[16] The anomerisation of isopropyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside catalysed by $SnCl_4$ had a $t_{1/2}$ of ~1400 min; in the presence of acetic acid (1 equiv) the $t_{1/2}$ was ~ 14 min. The anomerisation of isopropyl 3,4,6-tri-*O*-acetyl-2-*O*-(2-carboxypropanoyl)-β-D-glucopyranoside catalysed by $SnCl_4$ had a $t_{1/2}$ of ~10 min. See Lemieux, R. U.; Hindsgaul, O. *Carbohydr. Res.* **1980**, *82*, 195.

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[32] Full details for the preparation of **1-14** is given in the supporting information.

[33] The preparation and analytical data for **15-18** and their α-anomers has been published previously. See reference 8.

Graphical Abstract