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$SnCl_4$- and $TiCl_4$-Catalyzed Anomerization of Acylated *O*- and *S*-Glycosides: Analysis of Factors That Lead to Higher α:*β* Anomer Ratios and Reaction Rates

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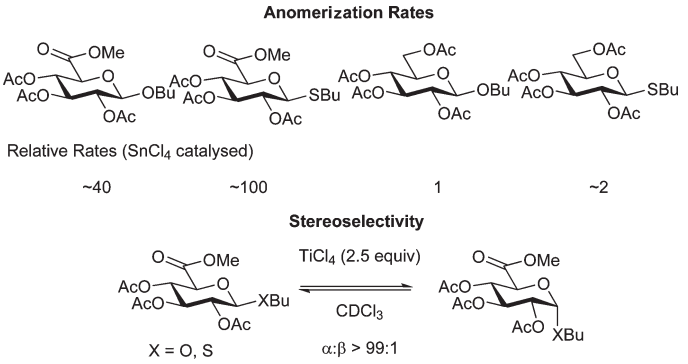

The quantification of factors that influence both rates and stereoselectivity of anomerization reactions catalyzed by $SnCl_4$ and $TiCl_4$ and how this has informed the synthesis of α-*O*- and α-*S*-glycolipids is discussed. The $SnCl_4$-catalyzed anomerization reactions of *β*-*S*- and *β*-*O*-glycosides of 18 substrates followed first order equilibrium kinetics and $k_f + k_r$ values were obtained, where k_f is the rate constant for the forward reaction ($\beta \rightarrow \alpha$) and k_r is the rate constant for the reverse reaction ($\alpha \rightarrow \beta$). 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 those of related glucoside and galactopyranoside counterparts and α:*β* ratios were generally also higher. Stereoelectronic effects contributed from galacto-configured compounds were up to 2-fold faster than those of corresponding glucosides. The introduction of groups, including protecting groups, which are increasingly electron releasing generally led to rate enhancements. The anomerization of *S*-glycosides was consistently faster than that of corresponding *O*-glycosides. Reactions were generally faster for reactions with $TiCl_4$ than those with $SnCl_4$. 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 anomerization 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 anomerization 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 electron-withdrawing ability of the anomeric substituent and lead to an increase in 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 anomerization is provided by the trapping of a key intermediate. The data herein will help predict the tendency of *β*-glycosides to undergo anomerization; this includes cases where 1,2-trans glycosides are initial products of glycosidation reactions catalyzed by $TiCl_4$ or $SnCl_4$.

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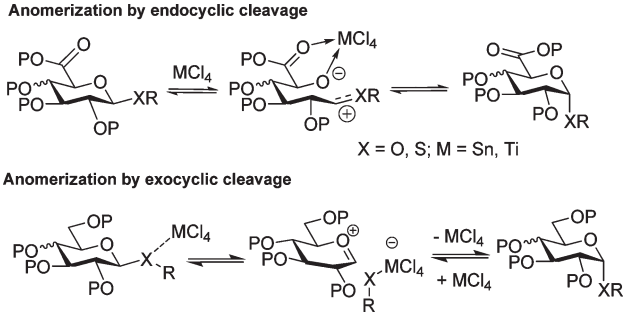
1. Introduction

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 anomerization (Scheme 1), commonly described for *O*-glycosides but less so for *S*-glycosides. Anomerization 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 anomerization occurs subsequently (glycosidation−anomerization).[8] While a mechanism for anomerization (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 anomerization catalyzed by $SnCl_4$ or $TiCl_4$ has not been reported.

Also as far as we can determine there are few examples of thioglycoside anomerization described. Synthesis of α-*S*-glycoside analogues of α-*O*-glycosides has been of general interest and there has been progress on the 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 anomerization would be helpful in predicting whether anomerization would be productive for generating α-*S*-glycosides as well as α-*O*-glycosides. Anomerization 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 anomerization of β-glycoside precursors.[11] Anomerization 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 the corresponding α-*O*-galacturonides (>97:3). During the course of glycolipid synthesis we wanted to predict how efficient $TiCl_4$ or $SnCl_4$ based anomerization 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 anomerization 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 anomerization catalyzed by $SnCl_4$ and $TiCl_4$ (Scheme 1), which includes the trapping of a key intermediate, is also provided.

SCHEME 1. Possible Pathways for Anomerization



2. Results and Discussion

2.1. Kinetics and Stereoselectivity of Anomerization of *O*- and *S*-Glycosides. The kinetics of the $SnCl_4$-catalyzed anomerization reactions of a range of β-*S*- and β-*O*-glycosides **1**−**18**[12] (Table 1) were first carried out. A typical

(1) McDonnell, C.; Lopez, O.; Murphy, P. V.; Fernandez Bolanos, J. G.; Hazell, R.; Bols, M. *J. Am. Chem. Soc.* **2004**, *126*, 12374–12385.

(2) (a) Bols, M.; Liang, X.; Jensen, H. H. *J. Org. Chem.* **2002**, *67*, 8970–8974. (b) Namchuk, M. N.; McCarter, J. D.; Becalski, A.; Andrews, T.; Withers, S. G. *J. Am. Chem. Soc.* **2000**, *122*, 1270–1277.

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(8) O'Brien, C.; Polakova, M.; Pitt, N.; Tosin, M.; Murphy, P. V. *Chem.—Eur. J.* **2007**, *13*, 902–909.

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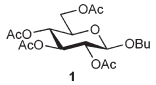
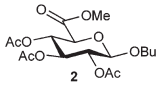
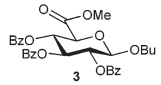
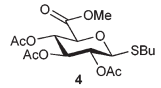
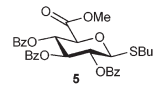
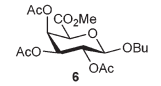
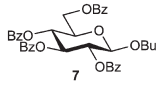
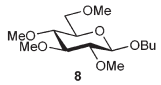
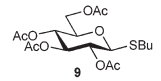
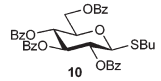
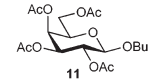
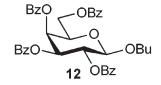
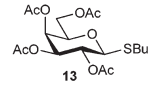
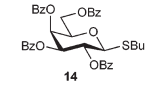
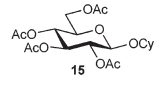
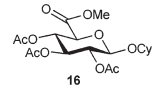
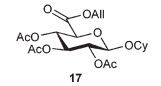
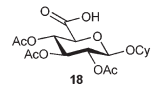
(10) Driguez, H. *ChemBioChem* **2001**, *2*, 311–318.

(11) Pilgrim, W.; Murphy, P. V. *Org. Lett.* **2009**, *11*, 939–942.

(12) Synthesis of **1**−**18** followed published procedures or was closely related to established routes. Full details are provided in the Supporting Information. See ref 8 for the preparation of **15**−**18**. For preparation of **1**−**14** see: (a) Graf von Roedern, E.; Lohof, E.; Hessler, G.; Hoffmann, M.; Kessler, H. *J. Am. Chem. Soc.* **1996**, *118*, 10156–10167. (b) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212–235. (c) Yamamoto, K.; Watanabe, N.; Matsuda, H.; Oohara, K.; Araya, T.; Hashimoto, M.; Miyairi, K.; Okazaki, I.; Saito, M.; Shimizu, T.; Kato, H.; Okuno, T. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4932–4935. (d) Fulton, D. A.; Stoddart, J. F. *J. Org. Chem.* **2001**, *66*, 8309–8319. (e) Bernardes, G. J. L.; Gamblin, D. P.; Davies, B. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 4007–4011. (f) Wallace, O. B.; Springer, D. M. *Tetrahedron Lett.* **1998**, *39*, 2693–2694. (g) MacDougall, J. M.; Zhang, X.-D.; Polgar, W. E.; Khroyan, T. V.; Toll, L.; Cashman, J. R. *J. Med. Chem.* **2004**, *47*, 5809–5815. (h) Mbadugha, B. N. A.; Menger, F. M. *Org. Lett.* **2003**, *5*, 4041–4044. (i) Bollenback, G. N.; Long, J. W.; Benjamin, D. G.; Lindquist, J. A. *J. Am. Chem. Soc.* **1955**, *77*, 3310–3315. (j) Tietze, L. F.; Seele, R. *Carbohydr. Res.* **1986**, *148*, 349–352. (k) Brown, R. T.; Scheinmann, F.; Stachulski, A. V. *J. Chem. Res., Synop.* **1997**, 370–371. (l) Györgydeák, Z.; Thiem, J. *Carbohydr. Res.* **1995**, *268*, 85–92. (m) Pippen, E. L.; McCready, R. M. *J. Org. Chem.* **1951**, *16*, 262–268. (n) Antkowiak, R.; Antkowiak, W. Z.; Banczyk, I.; Mikolajczyk, L. *Can. J. Chem.* **2003**, *81*, 118–124. (o) Prata, C.; Mora, N.; Lacombe, J.-M.; Maurizis, J. C.; Pucci, B. *Tetrahedron Lett.* **1997**, *38*, 8859–8862. (p) Tiwari, P.; Misra, A. K. *Carbohydr. Res.* **2006**, *341*, 339–350. (q) Caputo, R.; Kunz, H.; Mastroianni, D.; Palumbo, G.; Pedatella, S.; Solla, F. *Eur. J. Org. Chem.* **1999**, *1999*, 3147–3150. (r) Lopez, R.; Montero, E.; Sanchez, F.; Canada, J.; Fernandez-Mayoralas, A. *J. Org. Chem.* **1994**, *59*, 7027–7032. (s) van Doren, H. A.; van der Geest, R.; Kellogg, R. M.; Wynberg, H. *Carbohydr. Res.* **1989**, *194*, 71–77. (t) Pakulski, Z.; Pierozynski, D.; Zamojski, A. *Tetrahedron* **1994**, *50*, 2975–2992. (u) Lahmann, M.; Oscarson, S. *Can. J. Chem.* **2002**, *80*, 889–893.

TABLE 1. Kinetics of $SnCl_4$-Catalyzed Anomerization 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 30 °C with the substrate (0.08M) and $SnCl_4$ (0.04 M) in $CDCl_3$. [b]Equilibrium ratios. [c]Kinetics determined by polarimetry.

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 ^1H NMR for reactions of substrates **1**−**17**. The kinetics of anomerization of **18** were studied by monitoring changes in optical rotation with a polarimeter as the reaction was too fast to monitor by NMR. The data obtained for the reversible anomerization reactions generated straight line plots with use of 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 $TiCl_4$)-catalyzed anomerization 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% and 99%.[15] The kinetic data obtained for the $SnCl_4$-catalyzed anomerization of **1**−**18** are summarized 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 anomerize 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 anomerization 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-anomerization 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

(13) The reaction was carried out in $CDCl_3$ for the purposes of the NMR experiments. The anomerization reactions can also be carried out in CH_2Cl_2 and have been found to proceed more quickly in this solvent.

(14) (a) Tinoco, I.; Sauer, K.; Wang, J. C.; Puglisi, J. D., *Physical Chemistry, Principles and Applications in Biological Sciences*, 4th ed.: Prentice Hall: Upper Saddle River, NJ, 2002; pp 315−388. (b) Delley, D. G.; Marchaj, A.; Bakac, A.; Expenson, J. H. *J. Am. Chem. Soc.* **1991**, *113*, 7583–7587.

(15) The value of the sum of the integrals for the α- and β-signals was found to generally stay constant during the course of the reaction, indicating the loss in yield (up to 15%) is not due to decomposition. It is believed the workup leads to the loss in yield as reactions with $SnCl_4$ always seem to give an emulsion upon addition of aqueous solution and dealing with this can lead to some loss of product.

(16) The anomerization of isopropyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside catalyzed 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 anomerization of isopropyl 3,4,6-tri-*O*-acetyl-2-*O*-(2-carboxypropanoyl)-β-D-glucopyranoside catalyzed by $SnCl_4$ had a $t_{1/2}$ of ∼10 min. See: Lemieux, R. U.; Hindsgaul, O. *Carbohydr. Res.* **1980**, *82*, 195.

TABLE 2. Effect of $SnCl_4$ Concentration on Anomerization 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 °C at a concentration of **2** of 0.08 M. [b]Equilibrium ratios.

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 stabilization 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 previous observations, increasing the electron releasing ability of the aglycon led to increases in rate of anomerization. Thus anomerization of **16** was ~1.2 times faster than that for **2**. The anomerization of *S*-glycosides **4**, **9**, **10**, and **13** was consistently faster than that for 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 sulfur 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, and 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, and 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 anomerization of **8** was not as high as that for **7**.[20]

Next we established the influence of the Lewis acid concentration on the ratio of anomers at equilibrium. A series of

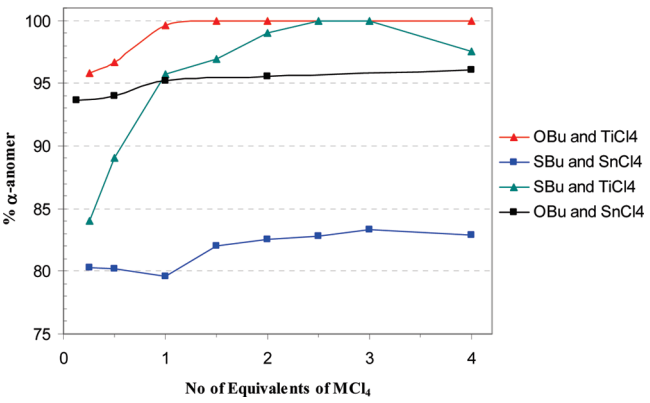
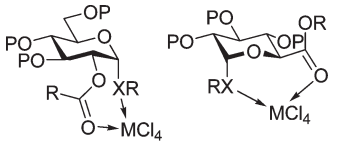


FIGURE 1. Effect of MCl_4 and number of equivalents of MCl_4 on % α of the total of the α and β anomers produced from reactions of **2** (red, black lines) and **4** (blue, green lines).

CHART 1. Structures of 19 and 20



anomerizations of **2**, where the concentration of $SnCl_4$ was varied, were carried out and the results are summarized in Table 2. As expected the $k_f + k_r$ values increased as catalyst concentration increased. As the concentration of Lewis acid increased, the proportion 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** and **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 a chelate such as **20**.

This effect was found also for the anomerization 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 equiv of the Lewis acid; a leveling 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 anomerization of the *S*-glucuronide **4** when using $TiCl_4$ in a 2.5- to 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

(17) Jensen, H. H.; Bols, M. *Acc. Chem. Res.* **2006**, *39*, 259–265.
(18) Pau, J. K.; Ruggera, M. B.; Kim, J. K.; Caserio, M. C. *J. Am. Chem. Soc.* **1978**, *100*, 4242–4248.
(19) The faster rates of attaining equilibrium for benzoates compared with acetates was noted previously: Reeves, R. E.; Mazzeno, L. W. *J. Am. Chem. Soc.* **1954**, *76*, 2219–2221.
(20) Increased rates for anomerization of benzyl ethers were observed previously: Koto, S.; Morishima, N.; Kawahara, R.; Isikawa, K.; Zen, S. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1092–1096.
(21) Anomeric ratios in these cases were determined by ^{1}H NMR according to the method reported recently. See: Claridge, T. D. W.; Davies, S. G.; Polywka, M. E. C.; Roberts, P. M.; Russell, A. J.; Savory, E. D.; Smith, A. D. *Org. Lett.* **2008**, *10*, 5433–5436.

TABLE 3. Comparison of $SnCl_4$ and $TiCl_4$ on Anomerization of 2, 4, 7, 9, and 10[a]

entry	compd	Lewis acid (0.04 M, 0.5 equiv)	$10^5(k_f + k_r)$ (s^{-1})	$\alpha:\beta$[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 °C with substrate concentration = 0.08 M. [b]Equilibrium ratio. [c]Rates were too fast to measure by NMR.

TABLE 4. Effect of Temperature on $SnCl_4$-Catalyzed Anomerization of 2 and 4[a]

entry	compd	temp (°C)	$10^5(k_f + k_r)$ (s^{-1})	$\alpha:\beta$[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

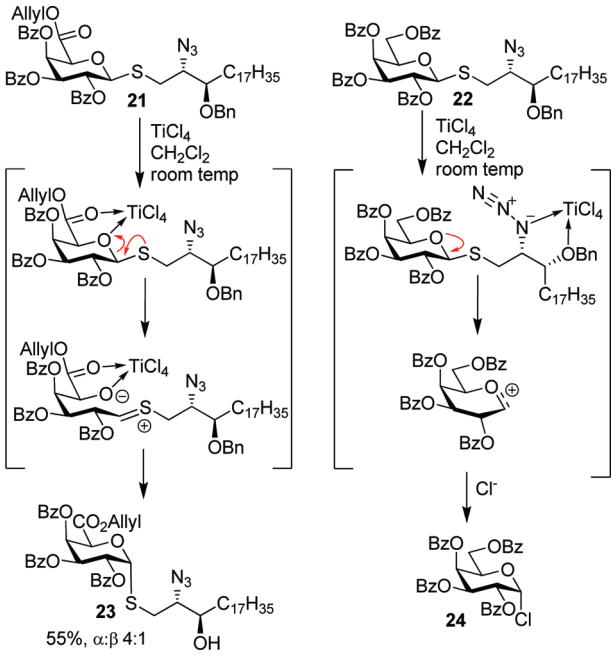
[a]All reactions were carried out with $SnCl_4$ at a concentration of 0.04 M and a substrate concentration of 0.08 M. [b]Equilibrium ratios.

cleavage followed by chloride transfer to the anomeric carbon, was slow compared to anomerization.

The effect of changing the Lewis acid from $SnCl_4$ to $TiCl_4$ on both the kinetics and $\alpha:\beta$ ratios was studied in more detail. Hence the anomerizations of **2**, **4**, **7**, **9**, and **10** with both $SnCl_4$ and $TiCl_4$ were compared. The reactions catalyzed by $TiCl_4$ were generally faster than those catalyzed by $SnCl_4$. The $TiCl_4$-catalyzed reaction of glucuronides **2** and **4** was essentially instantaneous under the conditions described (Table 3) and a rate constant was not obtained. Rate constants were obtained for the slower anomerization of **7**; this showed that the rate of anomerization of **7** was ~12-fold faster in the presence of $TiCl_4$ compared with $SnCl_4$ under the same conditions. The $\alpha:\beta$ ratio was higher for the anomerization of glucuronides **2** and **4** catalyzed 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 $\alpha:\beta$ ratio was higher for the $TiCl_4$-catalyzed reaction when compared with $SnCl_4$. However, the $\alpha:\beta$ 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 favorable for *O*-glycosides but may be less favorable for *S*-glucosides and $TiCl_4$.

The influence of temperature on the proportion of the α-isomer formed was also investigated. Anomerization reactions of *O*-glucuronide **2** and *S*-glucuronide **4** were carried out at various temperatures (Table 4). The rate of the anomerization of **2** was reduced (by a factor of ~5) on reducing the reaction temperature from 40 to 0 °C. 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 °C rather than at 30 °C. There was also a reduction in the rate of anomerization of **4** by ~6-fold.

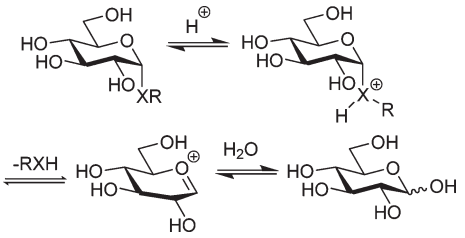
SCHEME 2. $TiCl_4$-Catalyzed Reaction of 21 and 22



Taking into account the trends, we predicted that increased amounts of α-anomer would be obtained by anomerization 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** by using $TiCl_4$ (2.5 equiv) at 0 °C than was obtained when using $SnCl_4$ (0.5 equiv) at 30 °C (3.7:1)

2.2. Observations in Anomerization Reactions in *S*-Glycolipid Synthesis. Anomerization for *S*-glycosides described herein is faster than that for the 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 optimize 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 that is trapped by chloride. Conversely, the treatment of galacturonide **21** with $TiCl_4$ (0.5 equiv) led to anomerization and formation of **23**, even though **21** also has the azide and an OBn protecting group with the 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 anomerization. This preferred mode of chelation occurs sufficiently rapidly for the galacturonide to prevent the exocyclic cleavage process

SCHEME 3. Pathway for Hydrolysis of α-Glycosides by Exocyclic Cleavage



observed for **22**. Concomitant removal of the benzyl group from the lipid chain occurs simultaneously en route to **23**.

2.3. Comparison of Anomerization 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 that reacts with water to form the product (Scheme 3).[22] It has been 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 labeling experiments and by measuring the effects on the rate of hydrolysis of exchanging the exocyclic oxygen atom with sulfur, which led to a decrease in the rate of hydrolysis. Relative rates for *O*- and *S*-glucosides and glucuronides are shown in Chart 2.[24] Slower hydrolysis of *S*-glycosides has generally been attributed to the lower pK_a of the thioglycoside sulfur atom leading to a lower concentration of protonated intermediate. Replacing the ring oxygen with sulfur resulted in an increase of the hydrolysis rate, which is due to the sulfur 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 anomerization of *β*-D-*O*-glucopyranuronic acid derivatives was considered and where precise rate constants were not calculated, we suggested that rates of anomerization can be correlated with rates of hydrolysis of *β*-D-glucopyranosiduronic acids. The analysis shown in Chart 2, based on rate constants for both the hydrolysis and anomerization 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 anomerization and hydrolysis. The replacement of the glycosidic oxygen atom with sulfur consistently led to an *increase* in the rate of anomerization (Chart 2, 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 sulfur consistently led to a *decrease* in the rate of hydrolysis. These data would support the proposal that endocyclic cleavage[26] operates in the anomerization of the *β*-glycosides catalyzed by $SnCl_4$. The soft sulfur atom would be more weakly coordinated to the hard Lewis acid than an oxygen atom and therefore be less susceptible to anomerization proceeding by exocyclic cleavage. However, sulfur 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 anomerization that were consistently observed.

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 anomerization of both *O*-glycoside **2** and *S*-glycoside **10**, which provided **25** and **27** (30%), respectively. Compound **25** could not be separated from the 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 $TiCl_4$-catalyzed anomerization proceeds at least to some degree through endocyclic cleavage.

2.5. Summary and Conclusions. The rates and the stereoselectivity of $SnCl_4$- and $TiCl_4$-promoted anomerizations of a series of acylated glycosides have been quantified. Rates of anomerization are significantly faster for glucuronic acid or galacturonic acid derivatives compared to those for related gluco- and galactopyranosides. Stereoelectronic effects from galacto-configured compounds were for the most part faster than those for compounds with glucose configurations. Introduction of increasingly electron releasing groups at C-1 to C-4 led to rate enhancements. Anomerization of *S*-glycosides was consistently faster than that for corresponding *O*-glycosides. Reactions catalyzed by $TiCl_4$ were faster than those for $SnCl_4$. Anomeric ratios depend on saccharide residue, whether $TiCl_4$ or $SnCl_4$ is 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 with use of excess $TiCl_4$ and decreasing the reaction temperature. The high α:*β* ratios observed for

(22) (a) Whistler, R. L.; Wolfrom. M. L. *Methods in Carbohydrate Chemistry*; Academic Press Inc: New York, 1963; Vol. 2. (b) Jensen, H. H.; Bols, M. *Acc. Chem. Res.* **2006**, *39*, 259−265 and references cited therein.

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(24) (a) Saunders, M. D.; Timell, T. E. *Carbohydr. Res.* **1967**, *5*, 453–460. (b) Saunders, M. D.; Timell, T. E. *Carbohydr. Res.* **1968**, *6*, 121–124. (c) Timell, T. E.; Enterman, W.; Spencer, F.; Soltes, E. J. *Can. J. Chem.* **1965**, *43*, 2296–2305.

(25) (a) Whistler, R. L.; Van Es, T. *J. Org. Chem.* **1963**, *28*, 2303–2301. (b) Whistler, R. L.; Rowell, R. M. *J. Org. Chem.* **1964**, *29*, 3290–3291.

(26) Janson, J.; Lindenberg, B. *Acta Chem. Scand.* **1960**, *14*, 877–881.

(27) Chelation has also been proposed by others to explain anomerization. See ref 11 and the following: Wang, Y.; Cheon, H.-S.; Kishi, Y. *Chem. Asian J.* **2008**, *3*, 319–326.

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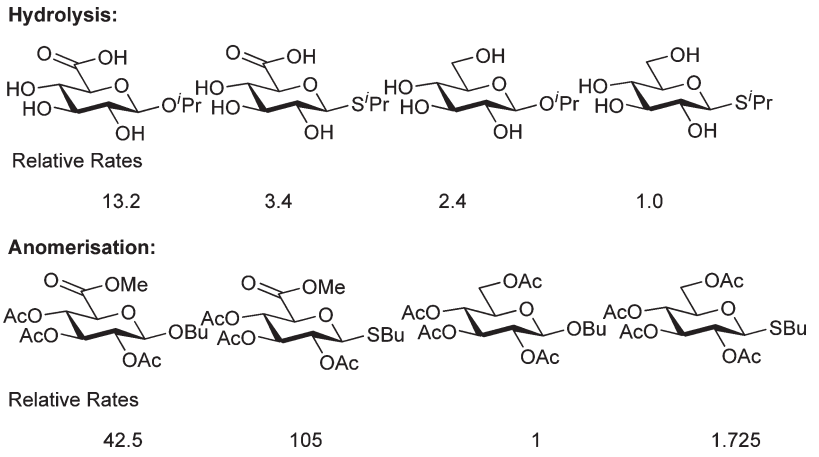
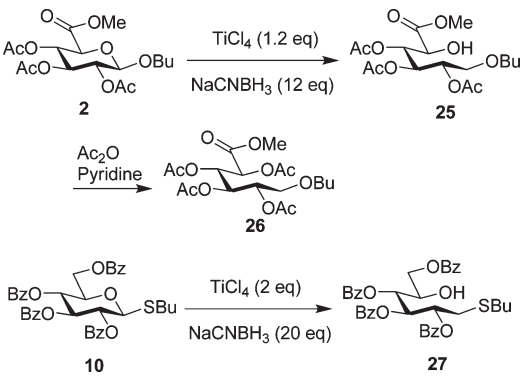
(29) Manabe, S.; Ishii, K.; Hashizume, D.; Koshino, H.; Ito, Y. *Chem.—Eur. J.* **2009**, *15*, 6894–6901.

CHART 2. Relative Rates of Hydrolysis and Anomerization of Selected *S*- and *O*-Glycosides



SCHEME 4. Trapping of Intermediates



anomerization 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 favor of the α-anomer. One referee for this paper 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 anomerization 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 anomerization.[31] The data will be useful in predicting the tendency of *β*-glycoside derivatives with 2-acyl protecting groups to undergo anomerization and in predicting whether glycosidation catalyzed by $TiCl_4$ or $SnCl_4$ is likely to give products that contain high proportions of the α-anomer.

3. Experimental Section

Anomerization Reactions. A typical reaction involved dissolving the substrate[32] (68 *μ*mol) 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 *μ*mol) 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 with 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 was 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 paper 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 the beginning and end of the reaction. Kinetic data for **18** were 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.

(30) (a) Grundberg, H.; Eriksson-Bajtner, J.; Bergquist, K.-E.; Sundin, A.; Ellervik, U. *J. Org. Chem.* **2006**, *71*, 5892–5896. (b) Vaino, A. R.; Szarek, W. A. *J. Org. Chem.* **2001**, *66*, 1097–1102.

(31) For applications of glycosidation−anomerization from our group see: (a) Leyden, R.; Velasco-Torrijos, T.; André, S.; Gouin, S. G.; Gabius, H.-J.; Murphy, P. V. *J. Org. Chem.* **2009**, *74*, 9010–9026. (b) Leyden, R.; Gouin, S. G.; Tosin, M.; Murphy, P. V.; Gabius, H.-J. *Org. Biomol. Chem.* **2009**, *7*, 4715–4725. (c) Doyle, D.; Murphy, P. V. *Carbohydr. Res.* **2008**, *343*, 2535–2544. (d) Velasco-Torrijos, T.; Murphy, P. V. *Org. Lett.* **2004**, *5*, 3961–3964. (e) Velasco-Torrijos, T.; Murphy, P. V. *Tetrahedron: Asymmetry* **2005**, *16*, 261–272. (f) Tosin, M.; O' Brien, C.; Fitzpatrick, G. M.; Müller-Bunz, H.; Glass, W. K.; Murphy, P. V. *J. Org. Chem.* **2005**, *70*, 4096–4106. (g) Tosin, M.; Murphy, P. V. *J. Org. Chem.* **2005**, *70*, 4107–4117.

(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 ref 8.

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; ^1H 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; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.55 (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; ^1H 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, J = 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, OCH_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: ^1H 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) δ 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: ^1H 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; ^1H 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; ^1H 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; ^1H 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; ^1H 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 (6H, 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) δ 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 mixture was added chloroform (1.0 mL) followed by $TiCl_4$ (0.8 mL of a 0.342 M solution in chloroform, 0.268 mmol), then 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 and dried ($MgSO_4$) then 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 was stirred at room temperature for 16 h. The volatile components were evaporated under reduced pressure. Chromatography of the residue (EtOAc−petroleum ether, 1:4) gave **26** as a colorless oil (5 mg, 5%): R_f 0.82 (EtOAc−petroleum ether, 1:4); IR (film) (cm^{-1}) 2957, 2855, 1749, 1370, 1209, 1036, 910; ^{1}H 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 (CH_2), 70.9, 69.6, 69.3, 69.2 (each CH), 68.6 (CH_2), 52.8 (CH_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 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 reaction was then stirred for a further 15 min. The organic layer was washed with water and dried ($MgSO_4$) then 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; ^{1}H 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 the preparation of **1**−**18** and analytical data for compounds, including assignments for all the NMR data, including α-anomers of **1**−**18** and ^{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.