Stereoselective Epimerizations of Glycosyl Thiols

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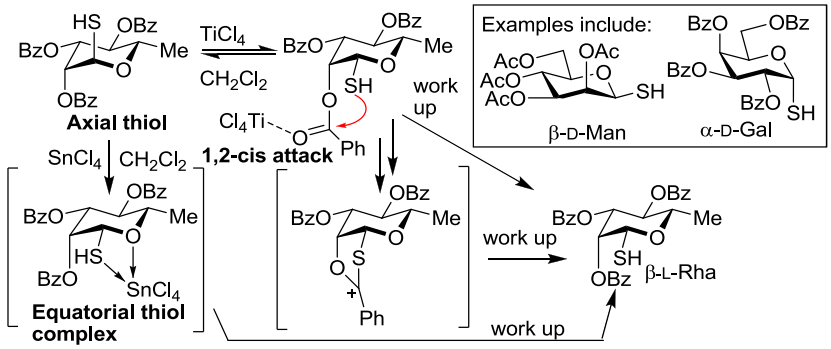
Supporting Information Placeholder



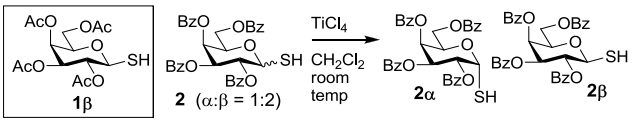
ABSTRACT: Glycosyl thiols are widely used in stereoselective S-glycoside synthesis. Their epimerization from 1,2-*trans* to 1,2-*cis* thiols (e.g. equatorial to axial epimerization in thioglucopyranose) was attained using $TiCl_4$, while $SnCl_4$ promoted their axial-to-equatorial epimerization. The method included application for stereoselective β-D-manno- and β-L-rhamnopyranosyl thiol formation. Complex formation explains the equatorial preference when using $SnCl_4$, whereas $TiCl_4$ can shift the equilibrium towards the 1,2-*cis* thiol via 1,3-oxathiolane formation.

Glycoconjugates and their mimics/mimetics are being investigated in drug discovery,[1] vaccine development,[2] targeting[3] and as probes for molecular recognition.[4] *S*-Glycosides are less susceptible to acid and enzymatic hydrolysis than *O*-glycosides, justifying their investigation as glycomimetics.[5] They have different conformational preferences to *O*-glycosides, which can influence their biological properties.[6] They have found application[7] in reactivity based oligosaccharide synthesis, which is influenced by anomeric configuration.[8] Glycolipids, glycopeptides, oligosaccharides,[5,9] glycodendrimers[10] and glyconanoparticles[11] containing S-glycosidic linkages are studied, and glycosyl thiols (1-thiosugars) are valuable building blocks in their synthesis. Unlike saccharide hemiacetal groups (glycosyl alcohols), glycosyl thiols often retain their anomeric configuration in subsequent reactions, which makes stereoselective *S*-alkylation, conjugate addition and thiol-ene or thiol-yne coupling reactions possible.[12] Anomerization (epimerization of equatorial anomer to axial anomer) with Lewis acids has been attained with glycosyl thiols derived from uronic acid, where the rate of anomerization[13,14] is generally faster than for other pyranoses due to favourable chelation of the C-6 carbonyl group.[15,16] Here, we provide conditions for the successful epimerization of 1,2-*trans benzoylated* glycosyl thiols, which are not uronic acids, to the 1,2-*cis* thiols using $TiCl_4$; the use of benzoyl rather than acetyl groups compensate somewhat for the absence of the C-6 carbonyl group. Notably, we also report the axial to equatorial epimerization of glycosyl thiols using $SnCl_4$.

The rate of Lewis acid promoted anomerization of *O*-glycosides is enhanced in the presence of acetic acid[17] or a Lewis acid[18] additive. Preliminary experiments with an *O*-glycoside showed that methanesulfonic acid (MSA) is superior to acetic acid. Initially, when acetylated thiol **1β** (Table 1) was reacted with $SnCl_4$ or $TiCl_4$ (0.5 to 3 equiv) in the presence of MSA (0.3 equiv), still only ~30% of its α-anomer was generated, with mostly **1β** remaining. Nevertheless, reaction of a 1:2 mixture of *benzoylated* galactosyl thiols **2α** and **2β** with $TiCl_4$ (0.5 to 2 equiv) and MSA (0.3 equiv) gave 45-70% of **2α**, with the main by-product being glycosyl chloride, and **2β** was not detected. A wider study (Table 1) was conducted with **2α** and **2β** using $TiCl_4$. For reaction with $TiCl_4$ alone (2.5 equiv), the α:β ratio was 79:21 after 17 h (entry 1), increasing to 84:16 at higher concentration of $TiCl_4$ (3 equiv) after 16 h (entry 8) with a further increase to ~9:1 over 72 h (entry 9). In experiments with $TiCl_4$ (2.5 equiv), where additives triphenylphosphine, pyridine and triethylamine were added (entries 3-5) the α:β ratios exceeded 91:9 after 16 h. Carrying out the reactions at lower temperature (e.g. 0 ºC) led to lower selectivity after 16 h due to reduced reaction progress. Pyridine was unable to promote the anomerization reaction of **2** on its own (entry 10). Use of $TiCl_4$ (3 equiv) and pyridine (0.5 equiv) together led to only **2α** being detected in the mixture after 16 h (entry 12) and isolated in 56% yield. In the cases of the hexopyranoses **3** (>18:1 vs 11:1) and **9** (>20:1 vs 10:1) the addition of pyridine led to improved stereoselectivity (Table 2). For **4-8** the use of pyridine showed no difference or a reduction in selectivity **(**see Table S1). It was

necessary to minimise the quantity of silica gel used for chromatographic purification to maximise the isolated yields of the thiols (reported in Table 2) as hydrolysis was occurring.

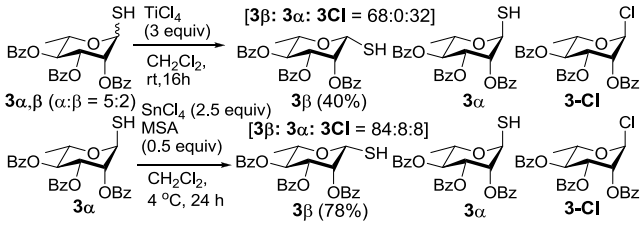
Table 1 $TiCl_4$ promoted epimerization of **2**



entry	additive	equiv $TiCl_4$	equiv additive	time (h)	α:β
1	no additive	2.5	-	17	79:21
2	MSA	2.5	0.3	16	84:16
3	Ph_3P	2.5	0.3	16	93:7
4	pyridine	2.5	0.3	16	93:7
5	Et_3N	2.5	0.3	16	92:8
6	no additive	3	-	16	84:16
7	no additive	3	-	72	90:10
8	pyridine	0	0.5	72	33:66
9	pyridine	3	0.3	72	~90:1
10	pyridine	3	0.5	16	>90:1

The $TiCl_4$ promoted anomerization of the mixture of 2,3,4-tri-*O*-benzoyl-thio-L-rhamnopyranosyl thiols **3α** and **3β** which contained mostly the axial or α-anomer (α:β = 2.5:1), unexpectedly gave only the β-anomer **3β** (40% isolated) and glycosyl chloride **10-Cl**. The structures of **3α**/**3β** were supported by NOESY and ^{13}C-NMR and **3α** was confirmed by X-ray crystal structure determination. The pure α-anomer **3α** was treated with $SnCl_4$ and again the β-thiol was preferred, with 8:1 mixture generated after 36 h at 4 °C. The reaction was found to be improved in 24 h if MSA was added and **3β** was subsequently isolated in 78% yield (Scheme 3).

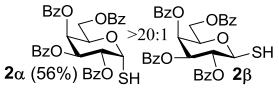
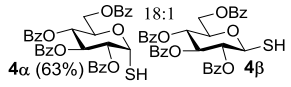
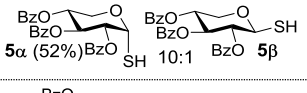
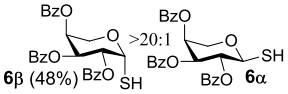
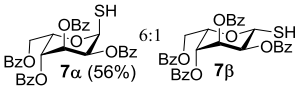
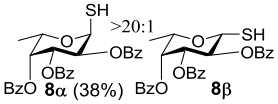
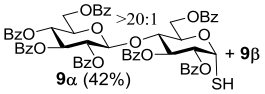
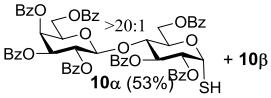
Scheme 1 Axial to equatorial epimerization of **3α**



Next $SnCl_4$ was investigated for epimerization of mannopyranosyl thiol **11α**. For a range of reactions (Table 3) in the presence of $SnCl_4$ in dichloromethane, epimerization of **11α** to **11β** was observed, with the β:α anomer selectivities ranging from 63:37 to 76:24. The addition of MSA increased the stereoselectivity to >9:1 in favour of the β-mannopyranosyl thiol and **11β** was isolated in 82% yield from a 200 mg scale reaction. A wider study of reactions of glycosyl thiols were then conducted with $SnCl_4$. Various glycosyl thiols (Table 4), with the exception of **4α** (not shown in Table 4) gave mixtures that favoured the equatorial product, irrespective of whether the substituent at C-2 was axial, as is the case for mannopyranose or rhamnopyranose, or equatorial at C-2.

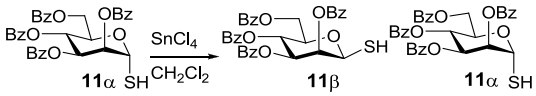
Optimized conditions for various glycosyl thiols (each 100 mg scale) are shown in Table 4 and the isolated yields of equatorial thiols varied from 34% (**15α**) to 90% (**6β**) with glycosyl chloride formed to a minor extent in most cases. The axial to equatorial epimerization with $SnCl_4$ was also successful for acetylated **12-16**. In the case of the acetylated rhamnopyranosyl thiol **13**, the addition of MSA (0.5) led to a reduction in amount of glycosyl chloride produced. The use of lower reaction temperatures (-30 °C) led to a reduction in chloride and unidentified product formation, particularly for the L-thioarabinopyranose **15α**,[19] and L-thiofucopyranose **7β**.

Table 2 $TiCl_4$ (3 equiv) promoted epimerization in CH_2Cl_2 (room temp, 16 h)

reactant	additive	products, ratio (isolated yield)
2α, **2**β (1:2)	pyridine (0.5 equiv)	
4α, **4**β (2:9)	pyridine (0.5 equiv)	
5α, **5**β (1:2)	-	
6α, **6**β (2:1)	-	
7α, **7**β (1:6)	-	
8β	-	
9α, **9β** (1:2)	pyridine (0.5 equiv)	
10α, **10β** (1:4)	pyridine (0.5 equiv)	

Next, we endeavored to gain an understanding of the origin of stereoselectivity in these reactions. Hence, we first tested the hypothesis that the glycosyl thiols coordinate to the Lewis acids and that the relative stability of a complex formed in dichloromethane ultimately contributes to defining the anomer ratio of the glycosyl thiols generated after work-up. $SnCl_4$ coordinates with heteroatoms such as O, N and S and several crystal structures have been reported, either as $SnCl_4{\cdot}L$ or $SnCl_4{\cdot}L_2$ complexes.[19] We considered the possibility that coordination would be reduced in an oxygen atom containing solvent which would compete with the acylated pyranose for coordination to the Lewis acid. Carbonyl groups are known to coordinate to Lewis acids including $SnCl_4$ in both the solid state and in solution and EtOAc was therefore investigated. Hence **1β** was converted by $SnCl_4$ (2.5 eq) to a 42:58 mixture of **1α** and **1β** in EtOAc-CH_2Cl_2 (3:2), which had lower selectivity than in dichloromethane alone (α:β = 72:19, Table 4). Thus EtOAc competes with the pyranosyl thiols for coordination to $SnCl_4$ but does not inhibit the epimerization. The reaction in the presence of EtOAc reflects the equilibrium ratio of anomers of the glycosyl thiols in absence of significant chelation to the Lewis acid whereas stereoselectivity in dichloromethane is influenced by a more stable complex being formed between $SnCl_4$ and the glycosyl thiol.

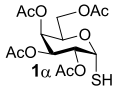
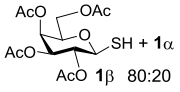
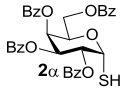
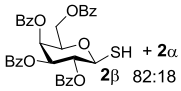
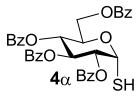
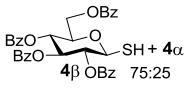
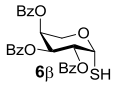
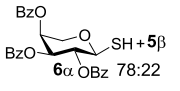
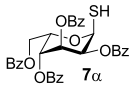
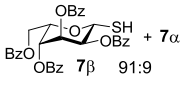
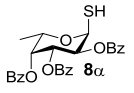
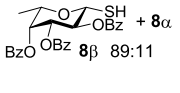
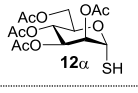
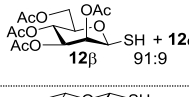
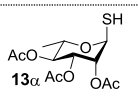
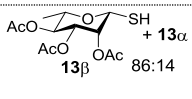
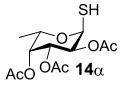
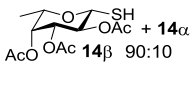
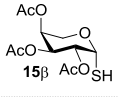
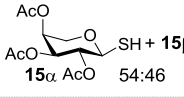
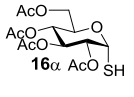
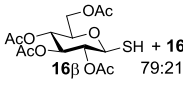
Table 3: Optimisation of the epimerization of **11α**



entry	additive (equiv)	equiv. of $SnCl_4$	T (°C)	time (h)	β:α ratio	yield **11β**
1	no additive	2.5	20	20	70:30	-
2	no additive	2.5	4	20	76:24	-
3	no additive	2.5	0	20	72:28	-
4	no additive	2.5	-30	24	63:37	-
5	no additive	1.5	4	20	69:31	-
6	PPh_3 (0.5 equiv)	2.5	4	24	76:24	-
7	sulfamic acid (0.5 equiv)	2.5	4	24	74:26	-
8	MSA (2 equiv)	2.5	4	24	92:8	82%
9	MSA (0.5 equiv)	2.5	4	24	89:11	79%

The use of ^{119}Sn NMR spectroscopy proved diagnostic for probing the interaction of $SnCl_4$ with **3β** in dichloromethane. There was a peak at δ -149 ppm in the proton decoupled ^{119}Sn NMR spectrum for free $SnCl_4$ (0.9 M solution in $CDCl_3$) whereas on addition of **3β**, with the colourless solution becoming a brick red colour and the ^{119}Sn peak shifted to -188.9 ppm, consistent with formation of a hexavalent tin complex in solution.[20] This proposal was supported by ^{1}H and ^{13}C-NMR analysis of the mixture generated after **10α** (0.068 mmol) was dissolved in $CDCl_3$ (0.75 mL) and 2 equiv of $SnCl_4$ was added (from a solution in $CDCl_3$), which provided information on the complex formed between **3β** and $SnCl_4$ (**3β-SnCl₄**). The doublet (J = 10.0 Hz) at δ 2.61 ppm corresponding to the thiol proton in uncomplexed **10β**, was no longer visible as a sharp doublet in the spectrum. The signal for the thiol proton of **3α** broadened and decreased in intensity as $SnCl_4$ was added and a new broad signal appeared downfield between δ 3.20-3.60 ppm for the SH. The integration for this signal, assigned to the SH in **3β-SnCl₄**, was equal to integration of other signals assigned to the carbohydrate ring protons for **3β-SnCl₄** in the spectrum, with **3β-SnCl₄** the most abundant species present. Compared to **3β**, the anomeric proton (Δδ = 0.42 ppm) and the pyranose H-5 (Δδ = 0.41 ppm) in **3β-SnCl₄** were most shifted downfield, with the other pyranose signals shifted to a lesser degree (Δδ < 0.2 ppm). The greatest shifts downfield in the ^{13}C-NMR spectrum of **3β-SnCl₄** were for the anomeric carbon (δ 80.3 ppm vs δ 76.8 ppm; Δδ = 3.7 ppm) and for the pyranose C-5 (δ 79.2 ppm vs δ 75.7 ppm; Δδ = 3.5 ppm). In contrast, the C-2 and C-4 signals were shifted upfield (Δδ values = -3.3 and -3.1 ppm), respectively. No shifts downfield or upfield of more than 0.3 ppm were observed for the carbonyl peaks. This data supports complexation involving the pyranose oxygen atom and the thiol group of **3β** coordinating to $SnCl_4$ (Scheme 2). The pyranose ring maintains its $^1C_4$ conformation on the basis of coupling constants observed in the ^{1}H-NMR spectrum. Work-up of this mixture led to hydrolysis of the complex with $SnCl_4$ present and gave a product which contained mostly **3β**. An NMR spectroscopic study indicated that reaction of **3α** with $TiCl_4$ established an equilibrium of **3α** with **3β** but that $TiCl_4$ also induced nucleophilic attack by the thiol of **3β** at the C-2 carbonyl group, *cis* to the thiol, which leads to generation of the 2-phenyl-1,3-oxathiolan-2-ylium cation **17**;[21] this shifts the equilibrium (Scheme 2) towards species that give **3β** after work-up. This process may contribute to the preferred formation of axial glycosyl thiols (Table 2), where the major products isolated also have 1,2-*cis* configurations. Hence, the ^{1}H- and ^{13}C-NMR spectroscopic analysis, in one experiment, of the mixture generated from treating **3α** with $TiCl_4$ (0.5 equiv) in $CDCl_3$ showed signals consistent with the presence of the thiols **3α** (~50%) and **3β** (~25%) as well as **17** (~25%). The presence of the carbenium carbon atom was supported by a diagnostic signal at δ 214.7 ppm in the ^{13}C-NMR spectrum; the signals for C-2 (δ 96.5 ppm; Δδ = +23.8 ppm) and C-1 (δ 86.4 ppm; Δδ = +8.7 ppm) of the cationic species are shifted significantly downfield compared to those of free **3β**, and support the presence of the nearby positively charged carbon. Work up of this mixture gave a 1:1 mixture of the thiols. The cation **17** was trapped in the presence of sodium cyanoborohydride to give **18**.

Table 4: $SnCl_4$ (2.5 equiv) promoted epimerization in CH_2Cl_2

reactant	T (°C)	products and ratio (equatorial : axial anomer) after 24 h	% yield
	20		46 **1β**
	20		59 **2β**
	20		52 **4β**
	-30		54 **6α**
	20		90 **7β**
	-30		68 **8β**
	20		67 **12β**
	4		78[a] **13β**
	20		64 **14β**
	20		34 **15α**
	20		51 **16β**

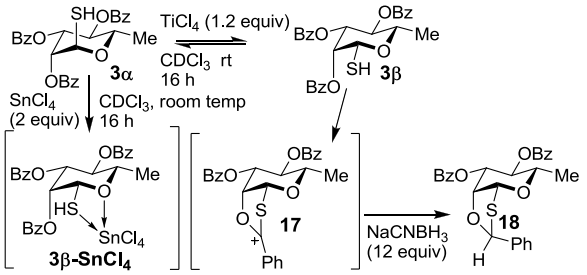
[a] This yield is from a reaction carried out with MSA (0.5 equiv) added

Further support for this proposal in Scheme 2 was obtained by isolation of the stable dihydrothiazole **20** from the reaction

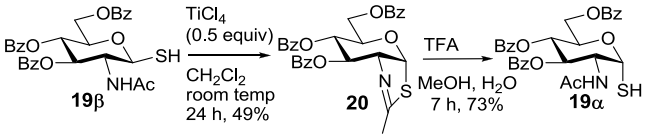
of GlcNAc derivative **19β** with $TiCl_4$, which was subsequently hydrolyzed to give thiol **19α** (Scheme 3).

Strategies reported for the synthesis of glycosyl thiols include displacement of glycosyl halides with thiourea, [22] thioacetates, [23] or thiophosphates[24] followed by release of the free thiol or reaction of glycosyl alcohols with Lawesson's reagent, with moderate to good stereoselectivity observed.[25] Reactions with carbon disulfide have been used, to give α-[26] or β-thiols.[27] Axially-oriented glycosyl thiols can be selectively prepared via equatorial glycosyl chlorides,[28] or by treating 1,2-anhydro or 1,6-anhydro sugars or glycosyl trichloroacetimidates with bistrimethylsilyl sulfide. [29] The complimentary strategy developed herein provides the opportunity to epimerise acylated glycosyl thiols, contributing to stereoselective synthesis of *S*-glycosides.

Scheme 2 Mechanistic investigations



Scheme 3 Epimerization of **19**β via **20**



Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Schemes S1-S3, Table S1, Experimental Section (PDF)
X-Ray crystal structure of **3α** (CIF)
NMR Spectra (PDF)

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Author Contributions

All authors have given approval to the final version of the manuscript.

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