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Observations on the activation of methyl thioglycosides by iodine and its interhalogen compounds[1,2]

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Abstract

Treatment of 'armed' methyl thiogalactosides with iodine in the absence of an acceptor alcohol results in thioglycoside epimerisation, whereas there is no effect on the corresponding 'disarmed' methyl thioglycosides. In contrast, iodine–hexamethyldisilane (which generates iodotrimethylsilane in situ) brings about epimerisation of 'disarmed' thioglycosides, ultimately giving rise to the corresponding α-glycosyl iodides on extended exposure. Cross-over experiments show the former iodine-promoted epimerisation process to be intermolecular, whereas the latter iodine–hexamethyldisilane-promoted epimerisation is intramolecular. Treatment of the same methyl thiogalactosides with iodine monobromide gives rise to the thermodynamically favoured α-glycosyl bromides, whereas reaction with iodine monochloride initially gives the kinetic β-glycosyl chlorides, which slowly epimerise to the thermodynamic α-linked products. Differences in the outcome of thioglycoside activation by I–I, I–Br and I–Cl suggest there may be scope for influencing the stereochemical course of thioglycoside-based glycosylation reactions through careful choice of promoter.

1. Introduction

Although major advances have been made in glycosylation chemistry over the past twenty-five years,[3] precise mechanistic details about such processes remain limited.[4] Given the lack of a general procedure that can be used to obtain good control of anomeric stereochemistry, regardless of the sugar used, a better understanding of the mechanism of glycosyl donor activation and subsequent reaction would be invaluable. Whilst many different types of glycosyl donors are in common use, glycosyl halides and thioglycosides are perhaps the most widely used.[5] For some time we have been investigating iodine and its interhalogen compounds as reagents for the activation of thioglycosides[6] and glycosyl halides,[7] and for the conversion of the former to the latter.[8] In light of the observed conversion of thioglycosides

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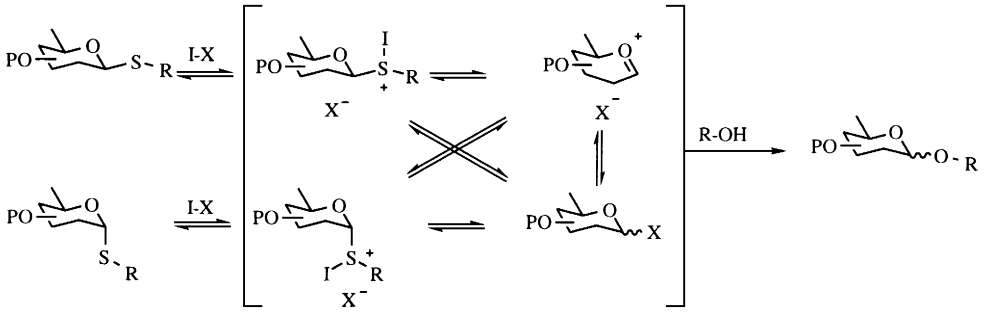
to glycosyl bromides and chlorides, we were drawn to investigate the possible formation of glycosyl iodides from thioglycosides on treatment with iodine, and to question whether or not glycosyl halides are intermediates in iodine- and interhalogen-promoted glycosylation reactions that employ thioglycoside donors. In addition, in the course of our work on the iodine-promoted glycosylation of sugar alcohols with 'armed' methyl thio-β-D-galactosides,[6] we observed formation of the corresponding α-thioglycosides in the reaction mixture, presumably resulting from in situ epimerisation of the β-anomer. Although depletion of both of the anomers occurred as the reaction progressed, sufficient quantities of the α-thioglycoside could be isolated in some cases to enable unambiguous confirmation of its structure.[9] These results were not unexpected given the earlier work of the van Boom group,[10] which has subsequently been followed up by Boons and co-workers.[11] The latter workers noted that the IDCP-promoted epimerisation of thioglycosides is an intermolecular process and that the anomeric configuration of thioglycoside donors can have an effect on the stereochemical outcome of glycosylation reactions.[11]

Taking all these points into consideration, we were drawn to investigate the importance, or otherwise, of both thioglycoside epimerisation and glycosyl halide formation on the rate and stereochemical outcome of glycosylation reactions employing thioglycoside donors (Scheme 1).



R = Me, P = protecting group, X = I, Br, Cl

Scheme 1. Activation of thioglycosides with iodine and its interhalogen compounds. Possible roles for thioglycoside epimerisation and glycosyl halide formation in the glycosylation process

Due to the potential mechanistic complexity of iodine- and interhalogen-promoted glycosylation with thioglycosides, we first undertook a study of the activation of methyl thioglycosides with iodine, iodine monobromide and iodine monochloride in the absence of an acceptor alcohol. Herein we report our observations on this topic.

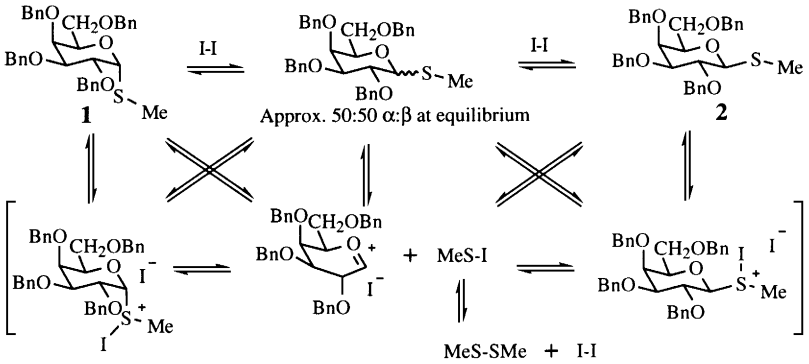
2. Results and discussion

2.1. Reaction of methyl thioglycosides with iodine

2.1.1. Epimerisation of 'armed' thioglycosides

In keeping with the report of Boons and co-workers,[11] we observed the formation of an approximately 50:50 α:β mixture of thioglycosides at equilibrium for iodine-promoted epimerisation of both per-benzylated methyl α- and β-thiogalactopyranosides, **1** and **2**, in either acetonitrile or chloroform. However, in contrast to the Boons work, which used a stopped assay to study IDCP-promoted epimerisation (monitored by mass spectrometry; reaction time approx. 1 min), we have been able to continuously monitor the corresponding iodine-promoted reaction directly by ^{1}H NMR spectroscopy.[1] Epimerisation of β-thioglycoside **2** was substantially slower in chloroform than in acetonitrile, suggesting a role for

the solvent in stabilisation of charged reaction intermediates in the epimerisation process. Using either **1** or **2** as the starting material an approximately 1:1 mixture of **1** and **2** was obtained in the first 1–2 min in the presence of 1–2 mol. equiv. of iodine at room temperature in acetonitrile. As expected, the rate of epimerisation could be slowed by conducting the reaction at lower temperatures (−20°C to ice-bath temperature). For short reaction times (up to 5–10 min) only epimerisation was observed; at longer reaction times, degradation of reactants was noted, presumably due to quenching of reaction intermediates by residual moisture, or conceivably due to iodine-promoted benzyl ether cleavage. Once again these side reactions could be marginalised by carrying out the epimerisation at lower temperatures, as mentioned above. Another important observation made during these studies was the formation of dimethyl disulfide (δ_H: Me 2.43 ppm) as a by-product in these reactions, presumably arising from spontaneous dimerisation of the methylsulfenyl iodide formed as outlined in Scheme 2.



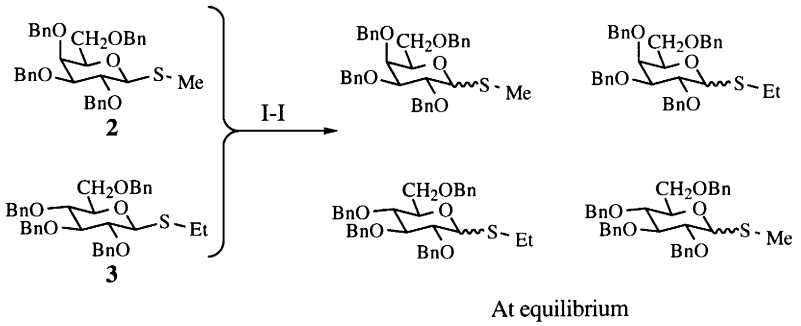
Scheme 2. Iodine-promoted epimerisation of perbenzylated methyl α- and β-thiogalactopyranosides **1** and **2**

These observations are consistent with the intermolecular epimerisation process outlined in Scheme 2. Perhaps surprisingly, in no case was glycosyl iodide formation observed (δ_H: H-1α approx. 7.0 ppm)[12] in the course of these particular epimerisation studies.

Further support for the intermolecular nature of the above process was obtained from cross-over experiments employing per-*O*-benzylated methyl β-thiogalactopyranoside **2** and the corresponding ethyl thioglucoside **3**. When an equimolar mixture of **2** and **3** was reacted with iodine (one mol. equiv.) in deuteroacetonitrile formation of all the possible thioglycosides was observed (Scheme 3), which is to be expected on the basis of Boons' work.[11] Interestingly, when this reaction was carried out in the presence of half mol. equiv. of iodine at approx. −20°C preferential epimerisation of thioglycoside **2** was observed in the initial stages of the reaction. However, this observation in itself is insufficient to draw any conclusion on the relative reactivities of methylthio- and ethylthioglycosides as the two glycosides used are derived from two different sugars. It was also noted in the above reactions that the ratio of the anomeric glucosides at equilibrium was different from the corresponding values for the anomeric galactosides. Therefore epimerisation of methyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside was examined independently in the presence of 1 mol. equiv. of iodine in acetonitrile. Indeed the equilibrium ratio of methyl-α/β-thioglucosides was found to be approximately 2.4, in contrast to the corresponding galactoside.

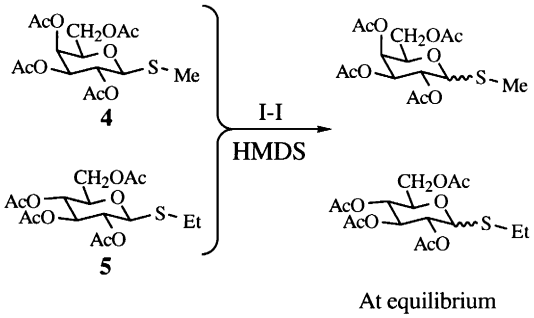
2.1.2. Epimerisation of 'disarmed' thioglycosides

Iodine alone has little effect on 'disarmed' thioglycosides. However, iodine in combination with hexamethyldisilane (HMDS) (which generates iodotrimethylsilane in situ)[13] gives rise to rapid epimerisation of such compounds. In contrast to iodine-promoted epimerisation of 'armed' thioglycosides, this process



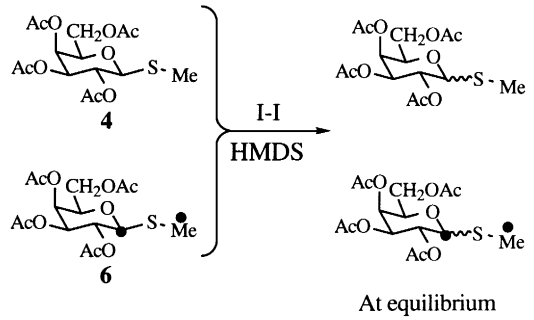
Scheme 3. Cross-over experiments to study the molecularity of iodine-promoted epimerisation of 'armed' thioglycosides

is intramolecular, as demonstrated by the non-appearance of cross-over products arising from treatment of 'disarmed' thioglycosides **4** and **5** with I_2–HMDS (Scheme 4). Epimerisation of a mixture of **4** and **5** led only to the formation of a mixture of four compounds, namely, methyl thio-α/β-galactosides and ethyl thio-α/β-glucosides in approximately equimolar quantities (as determined by ^{1}H NMR spectroscopy). Moreover, when an equimolar mixture of these four compounds was treated with iodine–HMDS the 'unchanged' starting material mixture was recovered.

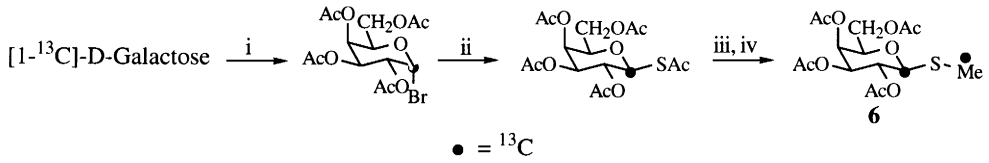


Scheme 4. I_2–HMDS-promoted thioglycoside cross-over experiment using 'disarmed' methyl thiogalactoside **4** and 'disarmed' ethyl thioglucoside **5**

These observations are also supported by the non-appearance of cross-over products in experiments employing unlabelled and specifically di-^{13}C-labelled methyl thiogalactosides **4** and **6** (Scheme 5). The synthesis of the latter is outlined in Scheme 6.



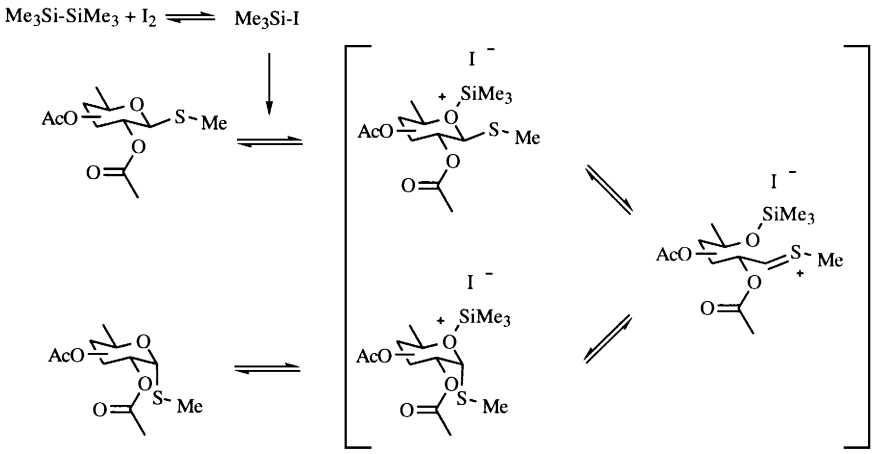
Scheme 5. I_2–HMDS-promoted thioglycoside cross-over experiment using 'disarmed' unlabelled and ^{13}C-labelled methyl thiogalactosides **4** and **6**



Scheme 6. Synthesis of di-^{13}C-labelled methyl thiogalactoside **6**. (i) Ac_2O, I_2, rt, 6 h, followed by HBr/AcOH, rt, 2 h;[14] (ii) KSAc, DCM, rt, 18 h;[15] (iii) NaOMe/MeOH, −40°C, 40 min;[15] (iv) ^{13}C-methyl iodide, DMF, rt, 12 h[15]

Furthermore, the experiments outlined in Scheme 5 did not produce any 'mixed mass'/cross-over products, as judged by MALDI-TOF analysis of the product mixture, so supporting the notion of an intramolecular epimerisation process.

The epimerisation of **4**/**6** presumably occurs through TMS-I-promoted ring opening of the disarmed glycopyranoside through interaction of the hard electrophilic silicon centre with the O-5 ring oxygen of the sugar, followed by ring closure onto the opposite face of the sulfonium ion intermediate (Scheme 7). Accordingly, formation of dimethyl disulfide would not be expected. Indeed, in none of the NMR experiments referred to in this section was the formation of this compound noted (δ_H: Me 2.43 ppm).

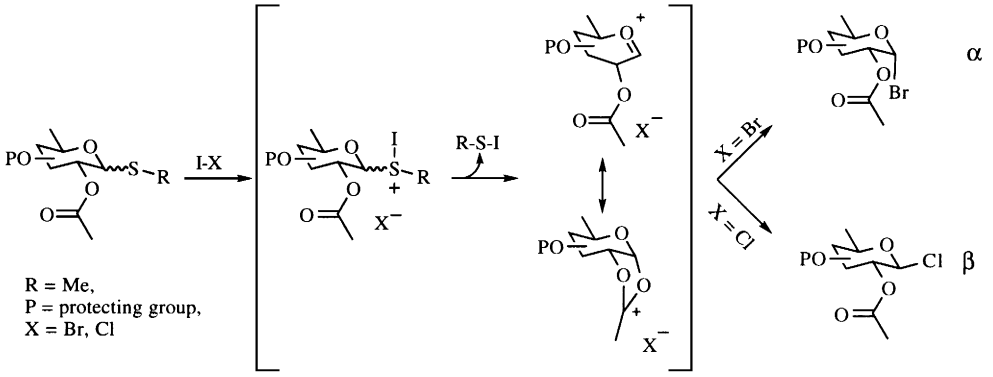


Scheme 7. Possible mechanism of I_2–HMDS-promoted epimerisation of 'disarmed' thioglycosides

2.2. *Reaction of methyl thioglycosides with iodine monobromide and iodine monochloride*

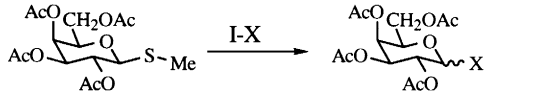
We have previously demonstrated the use of I–Br for the conversion of thioglycosides to glycosyl bromides.[8] At temperatures ranging from 0°C to 22°C, treatment of thioaldosides with I–Br gave the corresponding α-glycosyl bromides, irrespective of the presence or otherwise of a C-2 participating group. With I–Cl, on the other hand, reaction of *gluco*- and *galacto*-configured thioglycosides possessing a C-2 participating group invariably gave the corresponding β-glycosyl chloride as the initial product (Scheme 8). More detailed studies on the reaction of I–Br and I–Cl with 'disarmed' β-thiogalactoside **4** are summarised in Table 1.

When β-thiogalactoside **4** was treated with I–Br (Table 1, entry 1) in dichloromethane at ice-bath temperature, complete disappearance of the thioglycoside occurred in a few minutes and the α-bromide **7α** was obtained in quantitative yield following an aqueous work-up. When the reaction was repeated using acetonitrile as the solvent, α-halide **7α** was once again obtained as the sole organic product (Table 1, entry 2). On the other hand, similar reactions using I–Cl as the activator gave anomeric mixtures of the glycosyl chlorides **8** regardless of the solvent used (Table 1, entries 3–7). The thermodynamically less



Scheme 8. Transformation of thioglycosides to glycosyl halides with iodine monobromide and iodine monochloride

Table 1
Reaction of methyl thiogalactoside **4** with iodine monohalides[a]



4 **7** X = Br **8** X = Cl

Entry	X	Solvent	Temp.	Product	α : β
1	Br	CH_2Cl_2	ice-bath	**7**	1 : 0
2	Br	MeCN	ice-bath	**7**	1 : 0
3	Cl	CH_2Cl_2	ice-bath	**8**	1 : 10
4	Cl	MeCN	ice-bath	**8**	1 : 10
5	Cl	Dioxane	15°C	**8**	1 : 8.5
6	Cl	$CHCl_3$	ice-bath	**8**	1 : 10
7	Cl	Toluene	ice-bath	**8**	1 : 10

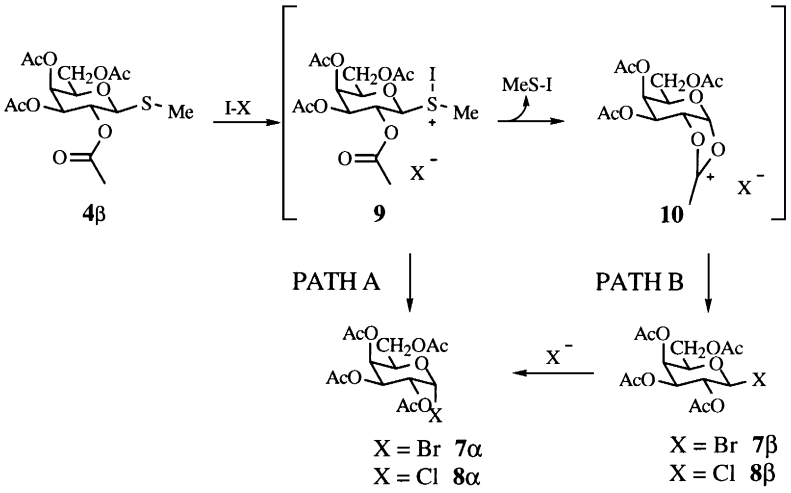
[a] Reactions carried out for 10 mins. with 0.25 mmol of thioglycoside (**4**) and 1.1 mol equiv. of I-X in 2 ml of solvent.
[b] All reactions resulted in >98% conversion, as judged by NMR spectroscopy following an aqueous work-up.

favoured β-anomer was found to be in approximately 10-fold excess in each case. This observation is not without precedent; Glaudemans and co-workers[16,17] noted formation of 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-β-D-glucopyranosyl chloride on treatment of the corresponding phenyl 1-thio-α-D-glucopyranoside derivative with chlorine in carbon tetrachloride. These workers argued that their findings were at variance with the results of Fugedi and co-workers,[18] as well as Weygand and Ziemann,[19] who obtained α-glycosyl bromides on treatment of benzyl-protected α- and β-thioglycosides with bromine. In light of the above observations, and the apparent conflict in the literature, a further study on the mechanism of formation and epimerisation of glycosyl bromides and chlorides was undertaken.

2.2.1. Formation of 'disarmed' glycosyl bromides and chlorides

Addition of iodine monobromide to a solution of acetylated β-thiogalactoside **4β** in a suitable solvent presumably results in the attack of the halophilic thioglycoside sulfur atom on the electron deficient iodine in the I–Br molecule, leading to formation of the corresponding iodo-sulfonium salt **9** (Scheme 9). It is not clear how the reaction proceeds subsequently. Formation of the thermodynamically favoured glycosyl bromide **7α** could arise through direct S_N2 displacement of MeSI by bromide ion (path A). Alternatively, anchimeric assistance from the 2-*O*-acetyl group could release MeSI to give dioxolenium

ion **10**, which on trapping with bromide would give the less favoured anomer, **7β**. The β-halide could then undergo reaction with bromide to give the thermodynamic product **7α** (path B). If path B is followed, conversion of the bromide **7β** to its α-anomer cannot be rate-limiting since no build-up of the former is observed.

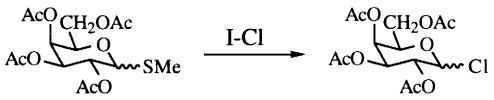


Scheme 9. Mechanisms for reaction of 'disarmed' methyl β-thiogalactoside **4β** with I–Br and I–Cl

In contrast to the reaction of I–Br with β-thiogalactoside **4β**, similar experiments with I–Cl gave rise initially to the thermodynamically less favoured β-configured glycosyl chloride **8β**. NMR time-course experiments showed that the β-anomeric chloride underwent slow epimerisation to the thermodynamically more stable α-chloride **8α** in a few hours at room temperature. The rate of epimerisation was dependent on both I–Cl concentration and temperature (Table 2). Taken together, these observations suggest that path B (Scheme 9) is in operation, which is in agreement with the conclusions drawn from polarimetric studies on the anomerisation of tetra-*O*-acetyl-β-D-glucopyranosyl chloride by Lemieux and Hayami.[20] Differences in the anomeric equilibria involving glycosyl bromides and glycosyl chlorides are not entirely surprising considering the differences in the C–Br and C–Cl bond energies. We cannot, however, rule out the involvement of path A in the direct formation of α-chloride **8α** from β-thioglycoside **4β**. Although no direct evidence could be obtained for the intermediacy of dioxolenium ion **10** in this study, we note the observation of such species (by NMR spectroscopy at low temperature) has recently been made by Crich and co-workers.[21]

Activation studies were subsequently undertaken with the isomeric 'disarmed' α-thiogalactoside **4α**. Reaction of this compound with I–Cl gave rise to the β-chloride **8β** (Table 2, entries 6–8), with only traces of anomer **8α** appearing after 24 h at room temperature in the presence of excess I–Cl (entry 8). This latter observation is in sharp contrast to the results obtained in the reaction of the β-thioglycoside **4β** with I–Cl, where formation of the β-chloride **8β** was always accompanied by the formation of its corresponding α-anomer, **8α**, in the initial stages of the reaction, albeit in small quantities. The very low quantities of **8α** in these studies suggest that epimerisation of β-chloride **8β** is inherently slow under the reaction conditions. This adds weight to the argument that formation of at least some **8α** from β-thioglycoside **4β** proceeds by a direct displacement mechanism (Scheme 9, path A). Formation of **8β** from **4α** by direct displacement (Scheme 10, path A) is also considered likely, since an S_N1 mechanism (path B) would necessarily involve cyclic oxocarbonium ion **11**. Presumably **11** would be liable to react with chloride ion affording either both **8α** and **8β**, or preferentially **8α**. Involvement of both **11** and

Table 2
Influence of I–Cl concentration and temperature on the reaction of 'disarmed' thiogalactoside **4**[a]

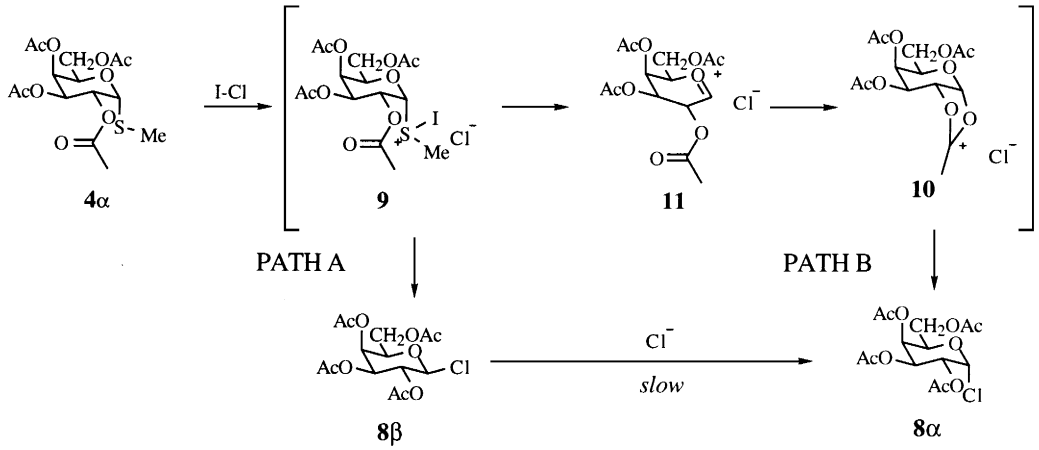


4 **8**

Entry	Thioglycoside	I-Cl (mol equivs)[b]	Reaction temperature[c] Mixing	Measurement	Product ratio 8α : 8β at <5 min	
1	**4β**	0.6[d]	0°C	23°C	1:8	
2	**4β**	1.1	-10°C	23°C	1:9	
3	**4β**	2.0	0°C	23°C	1:6	(1:1 at 5.5 h)
4	**4β**	4.0	0°C	23°C	1:3	(30:1 at 2 h)
5	**4β**	4.0	23°C[c]	23°C	1:0	
6	**4α**	0.4[d]	-10°C	23°C	0:1	(0:1 at 24h)
7	**4α**	0.6[d]	-10°C	23°C	0:1	(0:1 at 24h)
8	**4α**	1.1	-10°C	23°C	0:1	(1:10 at 24h)

[a] 0.05 mmol of **4** in 0.6 ml $CDCl_3$. [b] Mole equivalents of I-Cl with respect to thioglycoside. [c] Reactants were mixed in an NMR tube at the temperature indicated and spectra were recorded at a probe temperature of 23°C within 5 min. of mixing. [d] Reaction with <1 mol equiv. I-Cl resulted in partial consumption of **4** in accord with the quantity of I-Cl used.

dioxolenium ion **10** in formation of **8β** from **4α** cannot be ruled out, but it requires a rather convoluted set of interconversions for what is, overall, a facile process.



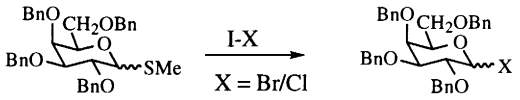
Scheme 10. Mechanisms for reaction of 'disarmed' methyl α-thiogalactoside **4α** with I–Cl

2.2.2. Formation of 'armed' glycosyl bromides and chlorides

Reactions of 'armed' thioglycosides bearing a non-participating protecting group at C-2 were next investigated. The reaction of benzylated thiogalactosides **1** and **2** with I–Br and I–Cl (resulting in formation of the glycosyl halides **12** and **13**, respectively) was monitored directly by NMR spectroscopy (Table 3).

When 'armed' β-thiogalactoside **2** was treated with iodine monohalides only the α-linked glycosyl halides **12** and **13** could be detected by NMR spectroscopy (Table 3, entries 1–3). When less than one mole equivalent of the interhalogen was employed the respective α-halide proportionate to the

Table 3
Reaction of 'armed' thiogalactosides **1**/**2** with iodine monohalides[a]



α **1**, β **2** **12** X = Br, **13** X = C

Entry	Thioglycoside	X (mol equivs)	Reaction time (min)	Product	(α:β)[b]
1	**2**, β	Br (0.4)	4	**12**	1:0
2	**2**, β	Br (1.1)	5	**12**	1:0
3	**2**, β	Cl (0.4)	4	**13**	1:0
4	**1**, α	Br (0.4)	10	**12**	1:0
5	**1**, α	Cl (0.4)	4	**13**	1:7
6	**1**, α	Cl (1.1)	4	**13**	1:7
7	**1**, α	Cl (4.0)	10	**13**	1:0

[a] Reactions were carried out with 0.05 mmol of the thioglycoside in 0.6 ml $CDCl_3$. Reactants were mixed at -10°C in an NMR tube and the spectra recorded after placing the tube in the NMR probe maintained at 23°C. All reactions proceeded to 100% conversion with respect to I-X concentration. [b] Calculated from NMR spectra.

reagent added was obtained, the remaining thioglycoside being returned unaffected. In contrast to the reaction of the corresponding 'disarmed' thiogalactosides **4**, the formation of β-linked halides in the reaction of 'armed' β-thiogalactoside **2** with interhalogens was not observed. This suggests the classical cyclic oxocarbonium ion (see Scheme 2) is not an intermediate in this particular glycosyl halide forming process, since it would be expected to react to give both anomers of **12** and **13** in the presence of I–Br and I–Cl, respectively. This is particularly true in the reaction with I–Cl, where we have already noted that epimerisation of the β-halide is slow.

Reaction of 'armed' α-thiogalactoside **1** with I–Br gives exclusively the α-bromide **12α**, which is to be expected given the ease with which the 'armed' β-bromide **12β** is expected to epimerise to its thermodynamically more favoured α-isomer. Consistent with direct displacement of MeSI from the iodosulfonium ion by halide, reaction of α-thiogalactoside **1** with 1.1 equivalent of I–Cl gives a 7:1 excess of the β-chloride **13β** (Table 3, entry 6). Use of a large excess of I–Cl (Table 3, entry 7) results in epimerisation of any initially formed β-chloride **13β**, so giving rise exclusively to α-chloride **13α** under the conditions reported herein (Table 3, entry 7). These observations are consistent with substantial S_N2 character to interhalogen-mediated activation of 'armed' α-thioglycosides.

3. Conclusions

The activation of thioglycosides with iodine and interhalogens is complex. For 'disarmed' thioglycosides, iodine alone does not cause chemistry to take place, although thioglycoside epimerisation, and eventually glycosyl iodide formation, is evident in the presence of iodine–HMDS (which generates TMS-I in situ). Cross-over experiments show this epimerisation process to be intramolecular. Reaction of the same 'disarmed' thioglycoside with I–Br gives rise to the thermodynamic α-bromide, whereas reaction with I–Cl gives the kinetically favoured β-chloride. For 'disarmed' sugars, epimerisation of the latter is slow and the β-chloride can easily be isolated. For 'armed' thioglycosides, reaction with iodine results in intermolecular thioglycoside epimerisation, as noted from cross-over experiments, but not in

glycosyl iodide formation. In contrast, reaction of the same thioglycoside with I–Br gives rise to the thermodynamic α-bromide, whereas reaction with I–Cl gives the kinetically favoured β-chloride. The stereochemical outcome of glycosyl halide formation in these latter reactions differs by virtue of the substantial difference in rate of epimerisation of β-bromides (fast) and β-chlorides (slow). We note that these glycosyl halide forming processes proceed via reactions possessing substantial S_N2 character. If this can be extrapolated to oxygen rather than halogen nucleophiles, it is conceivable that one could devise routes from a single thioglycoside donor to either α- or β-*O*-glycosides simply through appropriate choice of promoter and reaction conditions. Further studies to investigate this point are in progress.

4. Experimental

4.1. General

All reagents were used as purchased without further purification. Reaction solvents were dried by storage over activated molecular sieves (4 Å). HMDS, DCM and DMF refer to hexamethyldisilane dichloromethane and *N*,*N*-dimethylformamide, respectively. The abbreviation rt refers to room temperature (approximately 20 to 24°C). TLC was performed with 0.2 mm Merck pre-coated silica gel 60 F_{254} aluminium sheets. Compounds were detected by dipping the TLC plates in an ethanolic solution of sulfuric acid (4% v/v) and heating. Sorbsil C60 40/60 A (Sorbsil Chromatography Media) was used for column chromatography. Hexane refers to a mixture of isomeric hexanes. Melting points (uncorrected) were determined on a Gallenkamp melting point apparatus. Optical rotations were recorded on an Optical Activity Ltd. AA-1000 polarimeter at room temperature (approximately 22 to 24°C) for solutions in dichloromethane. ^{1}H NMR spectra were recorded at 300 MHz on a Bruker AM300 spectrometer or at 500 MHz on a Varian spectrometer in $CDCl_3$ or CD_3CN. Chemical shifts are expressed relative to that of the residual proton in the deuterated solvents (δ 7.25 and 2.00 for $CDCl_3$ and CD_3CN, respectively). ^{13}C NMR spectra were recorded at 75.47 MHz on a Bruker AM300 spectrometer. Assignments of resonances are based on published data. The anomeric ratios of products reported were determined from their NMR spectra. Mass spectrometry studies were conducted on a Perspective Biosystems Voyager-DE STR Biospectrometry workstation. All compounds referred to in the text have been reported previously,[22] many are commercially available and therefore only directly relevant spectral data are reported (see Table 4).

Table 4
Selected ^{1}H NMR data for compounds **1**–**5**

Compound	*H-1* (*J*, Hz)	S*CH*$_3$
1	5.55 (5.4)	2.07
2	4.41 (9.3)	2.21
3α	5.65 (5.2)	
3β	4.54 (9.9)	
4α	5.60 (5.2)	
4β	4.56 (9.7)	
5α	5.65 (5.6)	
5β	4.69 (10.0)	

4.2. Typical procedure for the preparation of glycosyl halides from thioglycosides

Iodine monohalide (1–4 mol. equiv.; see Tables 1–3 for details) was added to a stirred solution of the thioglycoside (for solvents see Tables 1–3) at the desired temperature (see Tables 1–4). Stirring was continued until the reaction was complete, the mixture was then diluted with DCM and subjected to a standard aqueous work up (see below) to yield the desired glycosyl halide.

For monitoring by NMR, reactions were conducted in standard 5 mm NMR tubes using neat $CDCl_3/CD_3CN$ as the solvent (obtained from Cambridge Isotope Laboratories, Inc.). For controlled experiments the reagents were mixed in the NMR tube after cooling them to the desired temperature (ice/ice–salt/acetonitrile–dry ice bath as desired). They were then allowed to warm up to rt in the NMR probe while the reaction was being monitored. I–Br obtained as 1 M solution in DCM was used as such. In the case of I–Cl, either neat I–Cl dissolved in the deuterated solvent or the commercially available 1 M solution in DCM was used for these studies.

4.3. Typical procedure for the thioglycoside epimerisation

HMDS (5 mol. equiv.) was added to a solution of the thioglycoside (e.g. compound **4β**) (1–2 ml acetonitrile/100 mg of thioglycoside) while being stirred at rt. Iodine (0.5 mol. equiv.) was then added and stirring was continued until the equilibrium concentration of the epimers was achieved (e.g. 15–20 min for **4β**). The mixture was then diluted with DCM and washed successively with 10% aqueous sodium thiosulfate solution and 10% sodium carbonate solution, dried (Na_2SO_4), filtered and concentrated to dryness under reduced pressure to yield the product as a mixture of the anomers in essentially quantitative yield. Separation of the anomers was achieved by column chromatography on silica (e.g. in the case of compound **4β**: using Et_2O:hexane, 3:2 as the eluent to obtain first **4α** followed by **4β** in 48% and 50% yield, respectively, both as crystals). It should be noted that HMDS concentrations used in these studies are unoptimised.

4.4. *^{13}C-Methyl 2,3,4,6-tetra*-O-*acetyl-^{13}C-1-thio-β*-D-*galactopyranoside* ***6***

Iodine (2 mg) was added at rt to a stirred suspension of 1-^{13}C-D-galactose (90.1 mg, 0.5 mmol) in acetic anhydride (0.5 ml). Dissolution of the sugar was complete (approx. 6 h). TLC (EtOAc:hexane, 1:1) at this stage revealed completion of the formation of the per-*O*-acetylated sugar.[14] The reaction mixture was then diluted with DCM (50 ml) and was washed successively with 10% aqueous sodium thiosulfate and 10% aqueous sodium carbonate solutions, dried (Na_2SO_4) and concentrated to dryness under reduced pressure followed by drying under high vacuum to yield the penta-*O*-acetyl galactopyranose in virtually quantitative yield. The resulting solid was dissolved in dry DCM (10 ml) and, after cooling in an ice-bath, HBr/HOAc (1.5 ml of a 45% w/v solution) was added. The reaction was allowed to proceed for 2 h at rt, by which time formation of the ^{13}C-1-labelled acetobromogalactose was shown to be complete by TLC (EtOAc:hexane, 2:3). The reaction mixture was then diluted with DCM (25 ml) and was washed successively with ice-cold water (3×20 ml) and cold 10% aqueous sodium carbonate solution (2×20 ml) in a separating funnel. The organic layer was then dried (Na_2SO_4), concentrated to dryness under reduced pressure and finally dried under high vacuum to yield the glycosyl bromide in virtually quantitative yield.^{1}H NMR ($CDCl_3$) δ: 6.95, 6.33, 2 d, 1H, 3.9 Hz and 186.5 Hz, H-1; 5.46, dd, 1H, 1.1 Hz and 3.3 Hz, H-4; 5.33, dddd, 1H, H-3; 4.98, dddd, 1H, H-2; 4.43, m, 1H, H-5; 4.09, m, 2H, H-6a and H-6b; 2.09, 2.06, 2.00 and 1.95, 4 s, 12H, 4×OCOCH_3.

The acetobromogalactose obtained above was then dissolved in a mixture of dry acetone (2 ml) and dry DCM (2 ml) and was stirred at rt in the presence of potassium thioacetate (286 mg, 2.5 mmol) for 24 h. TLC (EtOAc:hexane, 2:3) showed completion of the reaction. The reaction mixture was then diluted with DCM (40 ml) and was washed with water (2×20 ml) in a separating funnel, dried (Na_2SO_4), concentrated to a syrup and purified by column chromatography (silica gel, 25 ml; eluent, EtOAc:hexane, 2:3) to obtain 2,3,4,6-tetra-*O*-acetyl-^{13}C-1-thioacetyl-β-D-galactopyranose (166 mg, 81.5%). ^{1}H NMR ($CDCl_3$) δ: 5.46, 4.92, 2 d, 1H, 10.3 Hz and 160.7 Hz, H-1; 5.39, broad d, 1H, 3.3 Hz, H-4; 5.24, ddd, 1H, H-2; 5.05, dddd, 1H, H-3; 4.02, m, 3H, H-5, H-6a and H-6b; 2.33, near d, 0.7 Hz, 3H, SCOCH_3; 2.08, 1.97, 1.96 and 1.92, 4 s, 12H, 4×OCOCH_3.

To a stirred solution of the thioacetate thus obtained in dry MeOH (6 ml) cooled to −40°C was added a solution (1 ml) of sodium methoxide (equiv. to 8.9 mg of sodium metal, 0.95 mol. equiv.) and stirring was continued for 40 min at −40°C. Methanol was then removed by evaporation under reduced pressure at ice-bath temperature and the residue was subsequently dried under high vacuum to yield an amorphous mass. It was then taken up in dry DMF (2 ml) and was treated with $^{13}CH_3I$ (3 mol. equiv.) for 18 h at rt. The reaction mixture was then concentrated to a syrup under reduced pressure and purified by column chromatography (silica gel, 30 ml; eluent, EtOAc:hexane, 2:3) to yield **6** (139 mg, 90%). ^{13}C NMR ($CDCl_3$) δ: 83.54, *C*-1; 11.45, S*C*H_3.

Epimerisation studies with β-thioglycoside **6** gave the corresponding α-thioglycoside: ^{13}C NMR ($CDCl_3$) δ: 83.20, *C*-1; 11.93, S*C*H_3.

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