A direct and stereospecific approach to the synthesis of α-glycosyl thiols†

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A new simple method for the synthesis of α-glycosyl thiols is described. Ring-opening of 1,6-anhydrosugars with commercially available bis(trimethylsilyl)sulfide under the action of catalytic amounts of TMSOTf smoothly afforded α-glycosyl thiols in very high yields and in a stereospecific way.

The importance of carbohydrates and glycoconjugates in numerous biochemical processes has stimulated the development of glycomimetics as fundamental tools for biological research and as potential agents for therapeutic intervention. In this context, thioglycosides have attracted considerable attention due to their resistance to chemical and enzymatic hydrolysis and their similar solution conformation and biological activities compared to native counterparts.[1] As a consequence, many efforts have been devoted in the past two decades towards synthesis of thioglycosides, including thiosaccharides and *S*-glycoconjugates, in order to provide valuable compounds for biological studies.[2] For instance, an *S*-linked glycopeptide carrying two sugar moieties has been synthesized recently in solution phase, which mimics the peptide sequence Ala484-Ala490 in the Tamm-Horsfall protein (THP). Apparently, this catabolically stable compound is of great interest for further unraveling the biological role of THP.[3] Also, carbohydrate epitopes of conjugate vaccines have been modified to contain *S*-linked residues and the resulting *S*-linked immunogens generated an antigen-specific immune response that even exceeded the response to the native oligosaccharides.[4]

Currently, glycosyl thiols or their precursors, such as anomeric thioacetates, which can be *S*-deacetylated *in situ* to generate the desired glycosyl thiols, are the key building blocks for the construction of thioglycosides,[2] although thioglycosides can also be synthesized conventionally from normal glycosyl donors and the corresponding sulfur-containing acceptors.[5] By this nonconventional approach, a variety of thioglycosides have been synthesized as stable glycoside analogues and potential agents for therapeutic intervention.[2,6] For example, *S*-glycopeptides have been synthesized recently by two independent groups, who both utilized glycosyl thiols as sugar building blocks.[6a,b] In addition, glycosyl thiols are also useful in the synthesis of many other carbohydrate contexts, such as *C*-glycoside synthesis,[7] glycosyl sulfenamide and glycosyl sulfonamide synthesis,[8] and glycosyl disulfide synthesis.[9]

To a great extent, the nonconventional approach for the synthesis of thioglycosides became popular due to the chemical stability of glycosyl thiols. Unlike sugar hemiacetals, glycosyl thiols are quite stable, and the thioglycosyl anions do not mutarotate even under basic conditions.[10] As such, the anomeric configuration of a glycosyl thiol can be maintained during the formation of its corresponding thioglycoside products, rendering the stereoselective synthesis of α- and β-glycosyl thiols extremely important. The configurationally pure β-glycosyl thiols, such as β-glucosyl thiol and β-galactosyl thiol, could be readily obtained usually by treatment of α-glycosyl halides with thiourea followed by hydrolysis with alkali metal disulfite.[11]

However, to our knowledge, in the literature no direct procedure for the stereoselective preparation of normal α-glycosyl thiols has been reported,[12] although α-GlcNAc- and α-GalNAc-derived anomeric thiols could be readily prepared from the corresponding peracetylated sugars by virtue of their neighbouring acetamide groups.[13] Only β-glycosyl chlorides have been used occasionally to prepare α-glycosyl thiols in a multi-step procedure,[12a] nevertheless, the reproducibility of this procedure is very low due to the highly reactive β-chlorides. Recently, Lawesson reagent has been reported capable of directly converting reducing sugars or unprotected sugars into the corresponding glycosyl thiols.[14] However, in this procedure configurationally unpure glycosyl thiols were often produced.

Given the great value of thioglycosides in biological studies and the wide occurrence of α-glycosidic linkages in various glycoconjugates, there is a high demand for the development of procedures for the stereoselective synthesis of α-glycosyl thiols that can be used to construct α-thioglycosides. We have a long-standing interest in the synthesis of sugar analogues of enhanced chemical and enzymatic stability,[15] particularly *S*-linked glycoconjugates with a view to providing interesting structures for biological studies. We report herein a direct and stereospecific approach for the synthesis of α-glycosyl thiols.

The major challenge associated with the synthesis of α-glycosyl thiols lies in the stereoselectivity. Although this type of compound could conceivably be prepared by activation of normal glycosyl donors without a neighbouring participating group in the presence of a proper sulfur nucleophile, this process did not always lead to the predominant formation of α-thiosugars. On the contrary, sometimes β-products were produced as the major or only products.[16] Furthermore, in this way two or even more steps are usually required in order to secure the thiols. Also, based on our experience isolation of an isomerically pure glycosyl thiol from an α/β-mixture would be very troublesome if both anomers were produced in the glycosidation reactions.

In the course of our studies on the synthesis of *S*-linked galactosylceramides, we required a convenient access to a series of α-glycosyl thiols, as shown in Scheme 1. At the very outset, attempts

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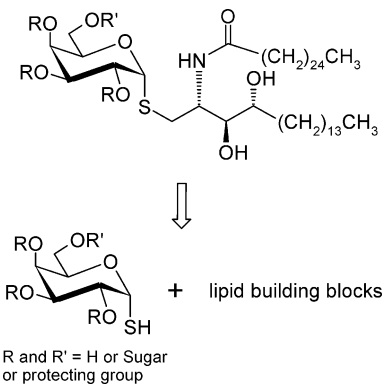
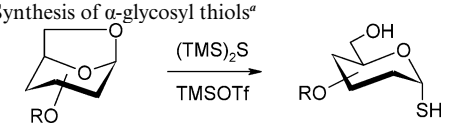
to use the above-mentioned β-glycosyl chloride-based procedure for the synthesis of the α-glycosyl thiols met with difficulties in the preparation of the required β-glycosyl chlorides. Hence, our attention turned toward the present procedure. We envisioned that 1,6-anhydrosugars[17] could serve perfectly as glycosylating agents for the synthesis of α-glycosyl thiols because β-attack of 1,6-anhydrosugars by any nucleophiles would not be possible if the reactions undergo the S_N2-type pathway. Also, we anticipated that commercially available bis(trimethylsilyl)sulfide could be used as the required sulfur nucleophile to directly introduce the sulfhydryl group in view of the acid-lability of the trimethylsilyl group which could be cleaved *in situ* under glycosidation conditions. To verify these hypotheses, we performed exploratory experiments with 1,6-anhydrogalactose **1** (Table 1). Treatment of **1** with a small excess of bis(trimethylsilyl)sulfide in the presence of catalytic amounts of TMSOTf at room temperature failed to provide any glycosyl thiols. However, when the reaction mixture was heated to 50 °C, **6** was produced in very high yield as exclusively the α anomer (Table 1, entry 1). The reaction was very clean as indicated by TLC, and the anomeric configuration of the product could be readily determined by NMR spectroscopy.

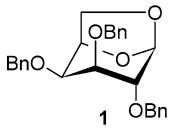
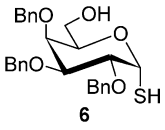
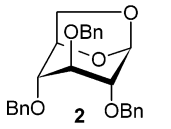
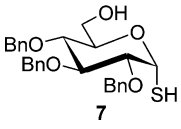
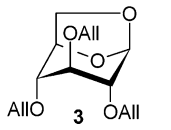
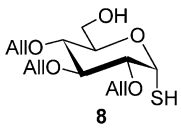
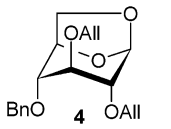
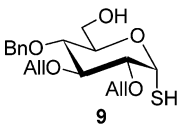
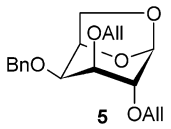
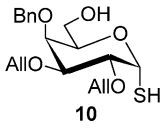


Scheme 1 Strategy for the synthesis of *S*-linked galactosylceramides.

Encouraged by this result, a range of properly protected 1,6-anhydrosugars were then prepared following the previous procedure[18] and subjected to the above ring-opening conditions (Table 1). Each substrate (1 mmol) was treated under the same conditions; it was dissolved in CH_2Cl_2 (10 mL) containing bis(trimethylsilyl)sulfide (1.4 mmol). TMSOTf (0.4 mmol) was added and the resulting mixture was heated at 50 °C until TLC indicated complete consumption of the starting material. The results, summarized in Table 1, indicate that under the above reaction conditions, 1,6-anhydrosugars can be converted effectively into α-glycosyl thiols in a stereospecific way. For instance, the benzylated levoglucosan **2** could be ring-opened with bis(trimethylsilyl)sulfide under the same reaction conditions to give the desired α-glucosyl thiol **7** in 90% yield (Table 1, entry 2). Similarly, configurationally pure thiol **8** could be produced from the corresponding allylated levoglucosan **3** in very good yield. Here it should be mentioned that levoglucosan derivatives have been used previously to synthesize thioglycosides.[19] In addition, as shown in Table 1, excellent yields and α-selectivities were also achieved for the conversion of 1,6-anhydrosugars **4** and **5** into glycosyl thiols **9** and **10**, respectively. Also, in all the above reactions, no disulfide formation was detected.

Table 1 Synthesis of α-glycosyl thiols[a]



Entry	Substrate	Product	Yield (%)[b]	α/β ratio
1			88	α only
2			90	α only
3			78	α only
4			85	α only
5			92	α only

[a] All reactions were conducted under the same conditions; see text for details. [b] Isolated yield following chromatography.

In summary, we have presented a highly stereoselective method for the synthesis of α-glycosyl thiols by ring-opening of 1,6-anhydrosugars with bis(trimethylsilyl)sulfide. All the α-glycosyl thiols were isolated in high to excellent yields as exclusively the α anomer. No trace of β-isomers was produced in the reactions. Thus this one-step procedure provided a concise and efficient access to α-glycosyl thiols, which could be used to synthesize various α-*S*-linked glycoconjugates. Extended studies on the scope of the reaction and application of the synthesized α-galactosyl thiols towards the synthesis of α-*S*-galactosylceramides are currently underway.

Acknowledgements

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