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Synthesis of 6-Sulfonatomethyl Thioglycosides by Nucleophilic Substitution: Methods to Prevent 1→6 Anomeric Group Migration of Thioglycoside 6-*O*-Triflates

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Dedicated to Professor János Kuszmann on the occasion of his 80th birthday

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Introduction of a sulfonatomethyl moiety into the primary position of thioglycosides by nucleophilic displacement of the corresponding 6-*O*-triflate is described. The 1→6 migration of the anomeric group, which inevitably occurs through a bicyclic sulfonium ion intermediate, from conformationally flexible β-thioglycosides was prevented by using an α-thioglycoside or conformationally locked β-thioglycoside as the starting material. The thioglycoside 6-sulfonic acids showed excellent α-selectivity during synthesis of uronic acid containing heparinoid trisaccharides.

Introduction

Sulfated carbohydrates play key roles in numerous biological processes including viral cell recognition, cell–cell interactions, blood clotting, inflammation, inhibition, and promotion of tumor growth.[1] One approach to design probes for studying these biological functions or to develop leads for new antiviral, anticoagulant, or antitumor agents is to prepare hydrolytically stable analogues of sulfated carbohydrates by replacing the ester oxygen atom of the sulfate moiety with a CH_2 unit. Besides the synthesis of sulfonic acid analogues of the sulfated Lewis X trisaccharide,[2] glucose 6-sulfate,[3] the sulfated seminolipid,[4] and heparin,[5] this approach has been used to produce stable isosteric sulfonate analogues of biological phosphates such as nucleotides[6] and mannose-6-phosphate.[7]

Recently, we found that isosteric sulfonic acid analogues of the antithrombin-binding domain of heparin in which two or three primary sulfate esters were replaced with a sodium sulfonatomethyl group inhibited the blood coagulation proteinase factor Xa; however, this occurred at different rates depending on the position of the sulfonatomethyl moiety.[5b] To gain deeper insight into the structure–activity relationship of the anticoagulant action of the sulfonic acid derivatives, we decided to prepare heparinoid pentasaccharides by systematic replacement of the sulfate esters with a sodium sulfonatomethyl moiety. As this work requires large-scale synthesis of the sulfonic acid containing building blocks, we searched the literature for the most efficient procedures.

The synthesis of a carbohydrate sulfonate in which the ester oxygen atom of the corresponding sulfate ester is replaced with a methylene group is generally accomplished by addition of the methanesulfonate ester carbanion to a carbonyl function,[2] by free radical addition of bisulfite to a terminal olefin,[5] by Horner–Wadsworth–Emmons olefination on a carbohydrate ulose,[4,5b,6b,7] or by reaction of an α-lithiosulfonate ester with a primary carbohydrate iodide[6a] or triflate.[3] Oxidation of thiols[8] or disulfides[9] is a convenient method to obtain sulfonates that could be readily extended to sulfonatomethyl derivatives.[10] Nucleophilic substitution in which the leaving group is replaced by a sulfonatomethyl moiety[3] appears to be the most rapid and facile route to the carbohydrate sulfonate esters. However, previous reactions were limited to *O*-glycosides and suffered from a significant disadvantage: reaction of a lithiated methanesulfonate ester with a 6-iodocarbohydrate gave the corresponding sulfonate in low yield,[3,6b] whereas with the use of the more reactive carbohydrate-6-*O*-triflate, anchimeric assistance of the anomeric alkoxy group in the displacement of the triflate was observed.[6a,11]

Herein, we describe the efficient synthesis of 6-sulfonatomethyl thioglycosides from the corresponding 6-*O*-triflates by preventing the participation of the anomeric group. Utilization of these sulfonic acid containing building blocks

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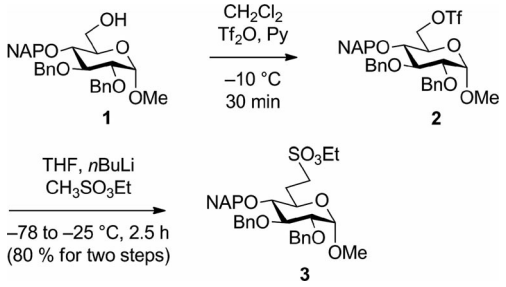
in the synthesis of heparinoid oligosaccharides is also presented.

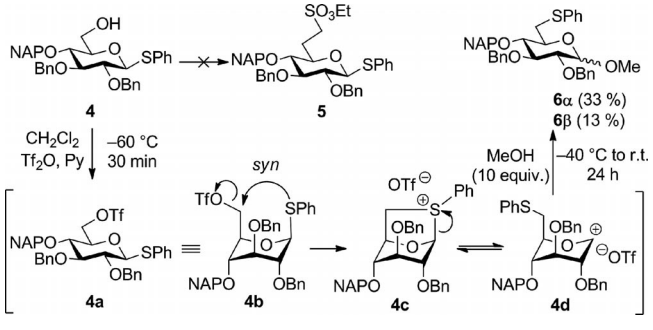
Results and Discussion

The 6-sulfonatomethyl-containing methyl glucoside **3** can be prepared in excellent yield by treating triflate **2** with the lithiated sulfonate reagent prepared in situ from commercially available ethyl methanesulfonate (Scheme 1).



Scheme 1. Introduction of the $–CH_2SO_3Et$ moiety to methyl α-glucoside **2** by nucleophilic substitution. NAP = 2-naphthylmethyl, Bn = benzyl, Tf = trifluoromethanesulfonyl, Py = pyridine.

However, synthesis of thioglycoside **5** by the same route failed. If compound **4** was treated with triflic anhydride, the corresponding 6-*O*-triflate could not be isolated as a result of, as we surmised, the immediate formation of sulfonium ion **4c** by intramolecular nucleophilic attack of the anomeric sulfur atom at C6.[12] Formation of a similar bicyclic sulfonium ion from a C6-OH β-*S*-phenylmannoside upon treatment with triflic anhydride was reported recently by Codée et al.[13] Quenching the reaction with methanol resulted in a 3:1 mixture of α- and β-methyl glucosides **6α/6β** (Scheme 2). The formation of the anomeric mixture implicates oxocarbenium ion **4d** rather than sulfonium ion **4c** as the reactive intermediate in the nucleophilic substitution reaction.[13,14]



Scheme 2. 1→6 Anomeric group migration via sulfonium ion intermediate upon triflate formation of **4**.

According to the suggested mechanism depicted in Scheme 2, adoption of the $^1C_4$ conformation of the intermediate triflate and the *syn* relationship between C6 and the C1-thiol group (in **4b**) are crucial for the migration of the anomeric group. Consequently, it could potentially be prevented either by locking the $^4C_1$ ring conformation or by inverting the anomeric configuration from β to α. Therefore, we envisioned the synthesis of 6-sulfonatomethyl thioglycosides by using an α-thioglycoside with a flexible conformation (**A**) or a conformationally locked β-thioglycoside (**B**) as the starting material (Figure 1).

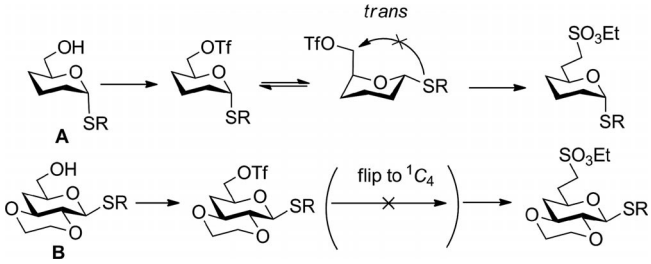
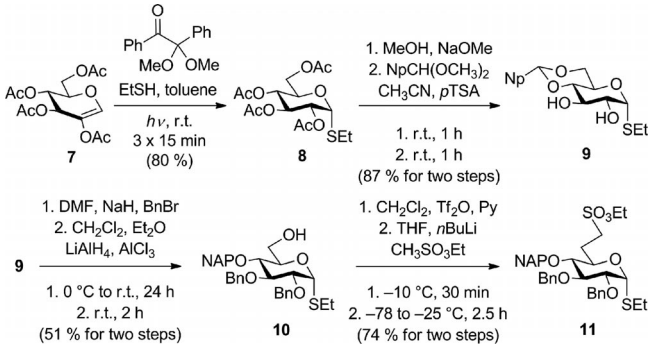


Figure 1. Planned routes to thioglycoside 6-sulfonic acids through 6-*O*-triflate intermediates.

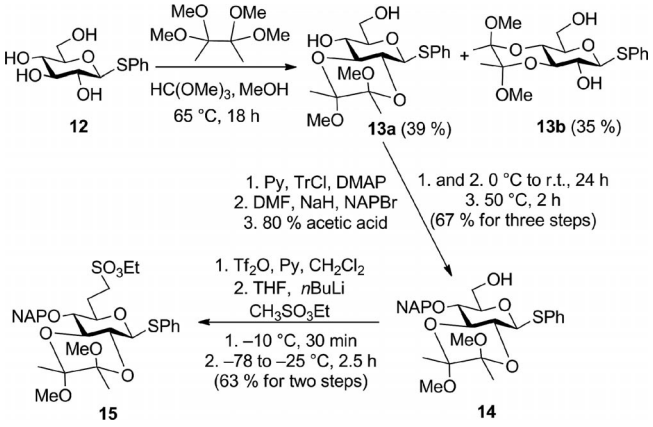
To check the viability of the α-thioglycoside approach, compound **8** was initially prepared by our recently published radical-mediated thiol-ene reaction.[15] Addition of ethanethiol to 2-acetoxy-3,4,6-tri-*O*-acetyl-D-glucal (**7**)[16] in toluene by irradiation at λ_{max} = 365 nm in the presence of 2,2-dimethoxy-2-phenylacetophenone (DPAP) as a cleavage-type photoinitiator[17] provided exclusively α-thioglucoside **8** in 80% yield after crystallization. Zemplén deacetylation followed by (2-naphthyl)methylenation gave **9**, transformation of which into **10** was achieved by benzylation and subsequent regioselective cleavage of the 4,6-*O*-acetal ring by using $LiAlH_4$ and $AlCl_3$.[18] Triflation of the primary free hydroxy group of the α-thioglucoside, the key step in the whole procedure, took place quantitatively, and subsequent nucleophilic displacement of the triflate moiety with the α-lithiosulfonate ester afforded 6-sulfonatomethyl thioglucoside derivative **11** in 74% yield for the two-step procedure (Scheme 3).



Scheme 3. Synthesis of the 6-sulfonatomethyl-containing α-thioglucoside **11**. Np = naphthyl, *p*TSA = *p*-toluenesulfonic acid.

To implement our second approach to thiogylcoside-6-sulfonic acid, we planned to lock the $^4C_1$ conformation by introducing Ley's diacetal protecting group[19] into the vicinal 2,3-diol, which is known to ensure rigidity of the pyranose ring.[20,21] Accordingly, phenyl 2,3-di-*O*-(2,3-dimethoxybutane-2,3-diyl)-1-thio-β-D-glucopyranoside (**13a**)[22] was prepared and transformed through the 6-*O*-triphenylmethyl derivative into the needed 6-hydroxy compound **14**. Triflation followed by nucleophilic substitution

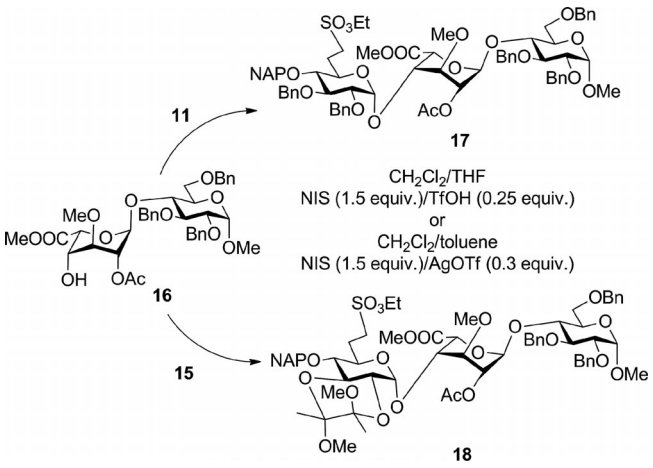
resulted in desired **15** in 63% yield, and this proves that the acetal protecting group helped to minimize the competing intramolecular nucleophilic attack of the anomeric β-thiol group (Scheme 4).



Scheme 4. Nucleophilic displacement on conformationally locked β-thioglucoside **14**. DMAP = 4-(dimethylamino)pyridine, Tr = triphenylmethyl.

To test the applicability of the obtained 6-sulfonatomethyl thioglycosides in the synthesis of heparinoid oligosaccharides, **11** and **15** were treated with L-iduronic acid containing disaccharide acceptor **16**. Although couplings with both donors led to stereoselective formation of the required α-linkage, the yields of the procedures were substantially different (Table 1). The *N*-iodosuccinimide (NIS)/TfOH-promoted condensation of armed[23] donor **11** and acceptor **16** provided desired trisaccharide **17** in 61% yield. Changing the promoter system from NIS/TfOH to NIS/AgOTf and decreasing the temperature resulted in a more efficient glycosylation procedure that furnished **17** in 79% yield. The NIS/TfOH-mediated reaction of acceptor **16** and disarmed donor **15** afforded corresponding trisaccharide **18** in only 38% yield. By applying the NIS/AgOTf promoter system, a higher temperature and a longer reaction time led to efficient condensation; however, the isolated yield of **18** remained below 60%. We assume that the disarmed character of donor **15** as a result of its rigidity imposed by the diacetal protecting group[24] is disadvantageous if it is coupled with iduronic acid containing acceptor **16** of inherent low reactivity.

Table 1. Synthesis of uronic acid containing heparinoid trisaccharides from acceptor **16** by using donors **11** and **15**.



Donor	Promoter	*T* [°C]	Time [h]	Product, yield [%]
11	NIS/TfOH	–40 to –10	2	**17**, 61
11	NIS/AgOTf	–50	2	**17**, 79
15	NIS/TfOH	–40 to –10	2	**18**, 38
15	NIS/AgOTf	–50 °C to r.t.	3	**18**, 58

Conclusions

Two approaches were elaborated to prevent the participation of the anomeric group during synthesis of 6-sulfonatomethyl thioglycosides by nucleophilic substitution. It was found that either a *trans* relationship between C6 and the anomeric group in α-thioglucoside **10** or a rigid conformation of β-thioglucoside diacetal **14** excluded efficiently the undesired intramolecular reaction of the corresponding 6-*O*-triflate. Obtained thioglycoside sulfonic acids **11** and **15** proved to be α-selective glycosyl donors to provide heparinoid trisaccharides. However, an important difference in efficacy of both generated building blocks was observed, and armed donor **11** was superior to disarmed donor **15** during reaction with a uronic acid containing acceptor of low reactivity.

We believe that the developed methods that allow easy introduction of various substituents into the primary position of thioglycosides would be useful in the synthesis of biologically important saccharide mimetics such as 6-deoxy-6-fluoro-[25] or 6-deoxy-6-phoshonatomethyl derivatives.[7,26]

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra of **3**, **4**, **6**, **9**–**11**, and **13**–**18**.

Acknowledgments

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