

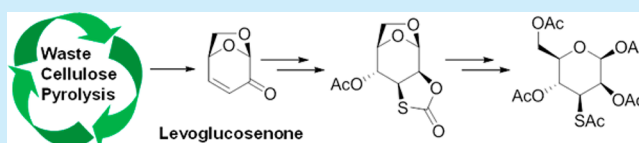
Synthesis of a 3-Thiomannoside

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S Supporting Information

ABSTRACT: An efficient and straightforward synthesis of a novel 3-thiomannoside derivative (1,2,4,6-tetra-*O*-acetyl-3-*S*-acetyl-3-thio- β -*D*-mannopyranoside) was developed starting from levoglucosenone. A xanthate–thiocarbonate exchange under acidic conditions was the key step for the new C–S bond. The product was obtained enantiospecifically in very good overall yield.



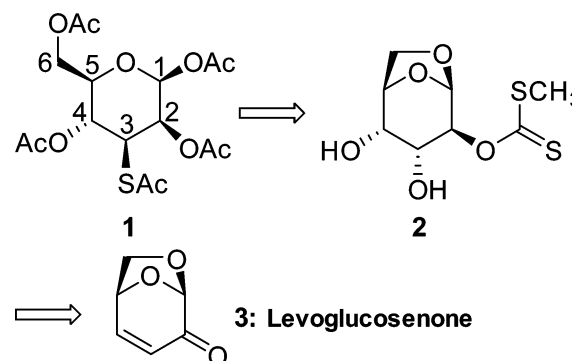
Sulfur-containing carbohydrates or thiosugars possess distinctive biological and physicochemical properties which differ from their oxygenated counterparts. Many natural functionalized thiosugars have shown to be useful tools to probe carbohydrate–protein interactions within enzymes systems and as prospective therapeutic agents.^{1,2} Examples of these naturally occurring thiosugars include 5-thio-*D*-mannose,³ a potential mannosidase inhibitor, and glucosinolates (β -thioglycoside-*N*-hydroxysulfates)⁴ which are known for their bactericidal, fungicidal, nematocidal, and allelopathic properties and have recently attracted intense research interest because of their cancer chemoprotective attributes. Another important member of this class of compounds is lincomycin, isolated from fermentations of *Streptomyces lincolnensis*, which is an effective antibiotic used against a wide range of pathogen, in particular methicillin-resistant *Staphylococcus aureus*. Clindamycin, a chlorinated semisynthetic derivative, is more active than the parent compound and widely used in clinical treatments.⁵ Among the families of synthetic thiosugars with biological activities, it can be mentioned that glycosyl *S*-nitrosothiols act as nitric oxide donors,⁶ *S*-trityl glycosides as chemotherapy agents,⁷ 5-thiosugars as enzyme inhibitors,⁸ 3-thiosugars as neuraminidase inhibitors,⁹ thio-linked analogs of Lewis A and B as antigens,^{10–12} and thioanalogs of Amiloriplose are useful as immunomodulators for treating autoimmune disorders.^{13,14} Recently, thioglycosides derived from acceptor sugars such as 3-thiogalactopyrano-, 4-thioglucopyrano-, and 4-thiomannopyranosides have been developed as β -galactosidase inhibitors.¹⁵

The synthesis of thioglycosides requires the appropriate preparation of a thiosugar acceptor which can be coupled with a glycosyl donor.¹⁶ On the other hand, a sulfur atom can replace any of the oxygen atoms present in a carbohydrate molecule. Based on these precedents 3-thio and 4-thiosugars are interesting synthetic targets, and efforts have been devoted toward their construction.

In the present work, we describe an efficient and straightforward synthesis of a novel and properly protected

thiosugar acceptor for the construction of thio-oligosaccharides. In this regard the preparation of 1,2,4,6-tetra-*O*-acetyl-3-*S*-acetyl-3-thio- β -*D*-mannopyranoside **1** has been achieved from levoglucosenone **3** (1,6-anhydro-3,4-dideoxy- β -*D*-glycero-hex-3-enopyranos-2-ulose), a biomass-derived starting material with a convenient functionalized structure (Scheme 1).

Scheme 1. Retrosynthetic Strategy



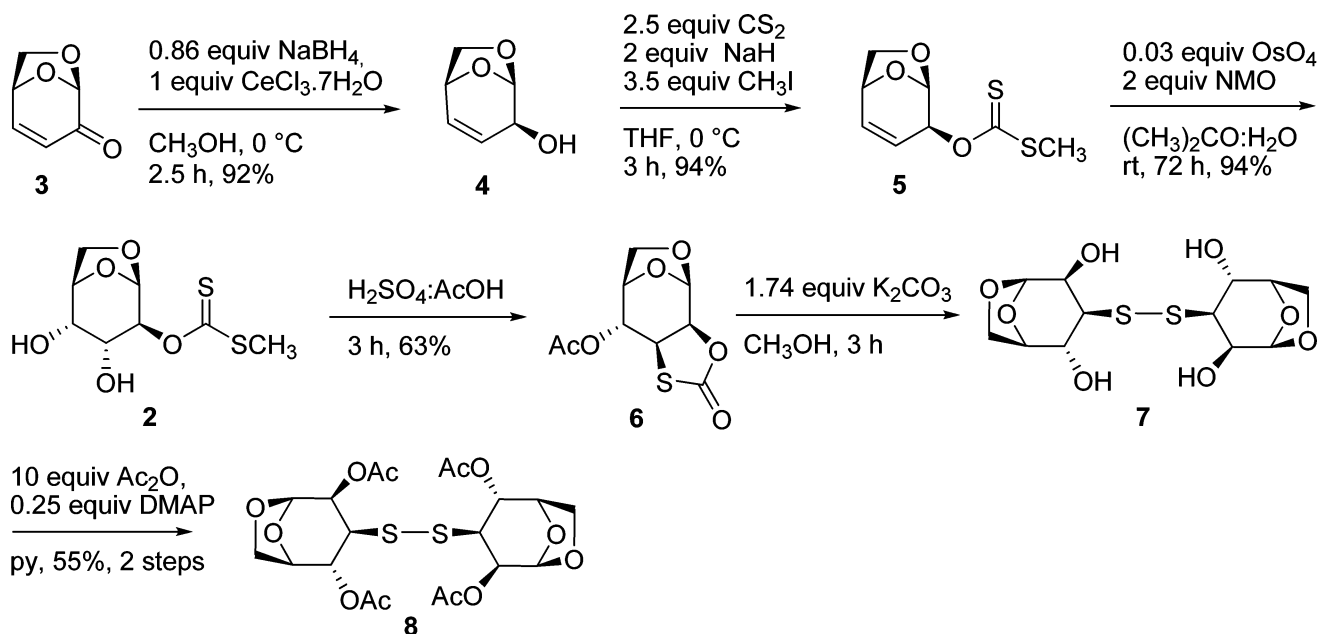
This versatile chiral synthon **3** can be obtained by conventional pyrolysis of cellulose-containing materials¹⁷ such as waste paper, and also by microwave irradiation of microcrystalline cellulose,¹⁸ hence, making it a sustainable and green raw material for enantiospecific synthesis.

There are two main strategies described in literature for the stereoselective preparation of thiosugars that can be considered for the synthesis of the 3-thiomannoside derivative **1**. One of them implies the S_N2 displacements of a sugar-derived triflate precursor by thioacetate, thiobenzoate, or thiocyanate anions.^{15,19} Comprehensive guidelines for this type of

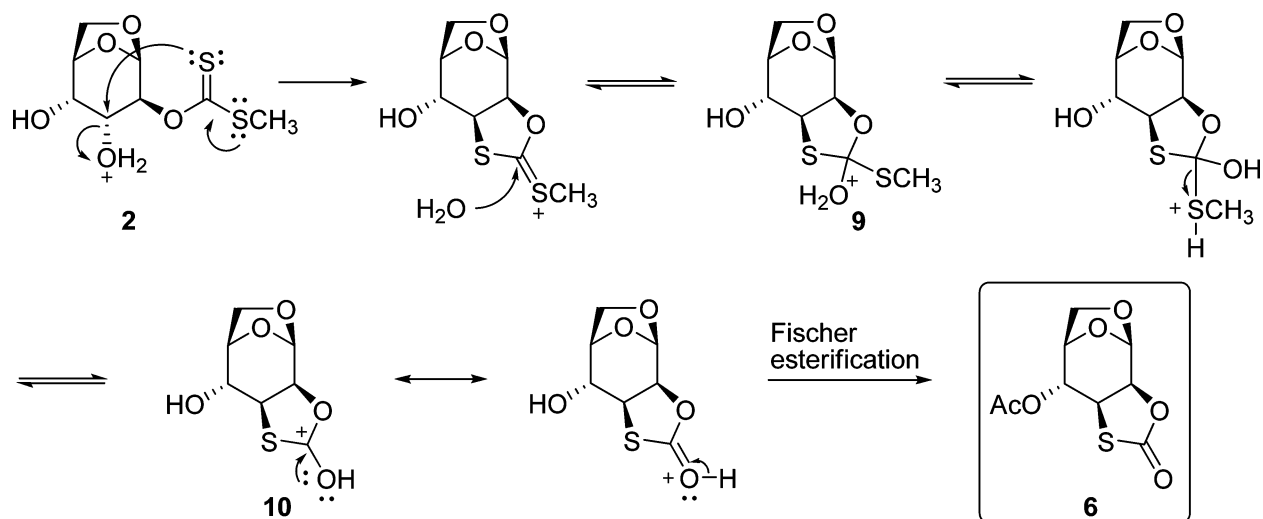
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Scheme 2. Synthesis of Disulfide 8



Scheme 3. Proposed Mechanism



nucleophilic displacement were recently published by Hale and co-workers.^{20,21}

These functionalities are then treated under basic hydrolytic conditions to obtain a free thiol group. However, a serious drawback of this method is the low yields achieved by the nucleophilic substitution^{20–22} due to the concurrent elimination that occurs under the reaction conditions.

An alternative method to introduce a thiol functionality in a carbohydrate skeleton is to take advantage of the structural rigidity imposed by an episulfide derivative. These constrained systems are useful synthons for the regio- and stereoselective transformation of positions 2, 3, and 4 in a carbohydrate framework.²³ One of the most common procedures for the preparation of episulfides involves several steps to achieve the ring opening of an epoxide with thiourea or thiocyanate ions, but such a reaction is not feasible for strained cyclic substrates derived from 1,6-anhydro sugars. Furthermore, the nucleophilic opening of the episulfide ring could also become troublesome.^{23a}

Based on our ongoing research program on the generation of high-added value products²⁴ from biomass recycling,²⁵ we conceived a new synthetic approach to obtain thiomannopyranoside 1 from levoglucosone 3 as depicted in Scheme 2.

Xanthate 2 was obtained in a simple and efficient manner from 3 and became a key intermediate in this strategy which paves the way to a completely new protocol. Reduction of the ketone 3 under Luche conditions afforded allylic alcohol 4 in a chemo- and stereoselective way. Allylic xanthate 5 was obtained when 4 was treated with carbon disulfide and methyl iodide in the presence of sodium hydride. *Cis*-dihydroxylation of 5 with catalytic amounts of osmium tetroxide and NMO as stoichiometric oxidant gave the diol 2 in high overall yield. Treatment of diol 2 with sulfuric acid in glacial acetic acid afforded the thiocarbonate 6 as a single product.²⁵ A Fischer esterification occurs concomitantly during the process and is the reason for the acetylated product. The structure of 6 was assigned by NMR one- and two-dimensional experiments, showing that the newly formed *cis* fused five membered ring

had a β -face orientation, as expected by the configuration of the C-2 oxygenated function. Mass spectrometry confirmed the molecular formula proposed for compound **6**. A plausible mechanism for this transformation is depicted in Scheme 3. The formation of the cyclic thiocarbonate **6** probably occurs through the elimination of a water molecule at C-3 by the anchimeric assistance of the adjacent xanthate group, generating a cyclic intermediate. In this way, the five-membered ring is formed. Moreover, water then attacks the carbocationic species to yield the intermediate **9**. Proton migration produces the protonated species, which upon loss of a neutral molecule of methanethiol affords cation **10**. Deprotonation and concurrent Fischer esterification produce compound **6**.

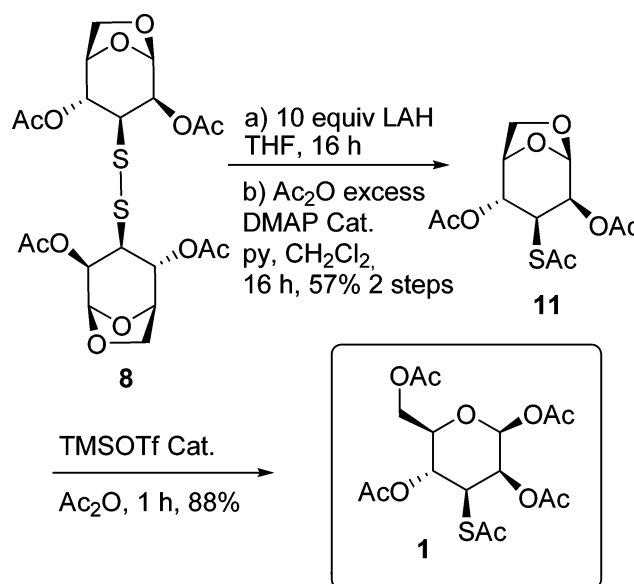
In order to obtain the free thiol functionality it was necessary to apply hydrolytic reaction conditions to achieve the ring opening of **6**. Alkaline hydrolysis²⁶ of the cyclic thiocarbonate **6** also caused the removal of the acetate functionality and afforded a polar compound **7**. Initially we assumed that the polarity was in consonance with a structure bearing a thiol and two hydroxyl groups. In order to characterize compound **7**, a water-soluble product, an aliquot of the crude material was precipitated from methyl *tert*-butyl ether as an off-white solid. The ¹H NMR spectrum in D₂O (with water suppression) showed the absence of a methyl signal, confirming the hydrolysis of the acetyl group at C-4. The ¹³C NMR spectrum showed the absence of carbonyl carbons, corroborating also the removal of the thiocarbonate and acetyl groups. However, a high resolution mass spectrum revealed a mass peak corresponding to the potassium cation of a disulfide structure **7**. This outcome, although undesired, is known with thiols and thiolates, since oxygen could easily oxidize them to disulfides on standing in the air when a small amount of base is present.²⁷ Hence, in the alkaline media used to hydrolyze thiocarbonate **6**, the thiolate anion was oxidized to disulfide **7** by the atmospheric oxygen. Compound **7** was highly polar and difficult to manipulate or dissolve in organic solvents. For this reason, it was transformed into its tetra-acetyl derivative **8**. Usually, under these circumstances dithiothreitol (DTT) is employed to reduce disulfides linkages, but in our case, this reagent was ineffective at reducing either **7** or **8**.

Others attempts to break the disulfide bond with NaBH₄ or LiCl/NaBH₄ were also unsuccessful. Only after treating **8** with a strong reducing agent such as LiAlH₄¹⁹ was the corresponding free mercaptan obtained. Direct reduction of the disulfide bond present in **7** with LiAlH₄ was unsuccessful, probably due to the insolubility of the tetra-anion formed. Therefore, although an aliquot of each intermediate was fully characterized, the crude disulfide **7** was acetylated, reduced, and carried on to the next acetylation reaction without any purification step. The triacetyl derivative **11** was obtained in 57% yield (Scheme 4).

In the 300 MHz ¹H NMR spectrum in CDCl₃ of **11** we observed the presence of three acetyl groups, two of them at 2.08 and 2.17 ppm consistent with acetate groups and a third one at 2.35 ppm corresponding to the thioacetate group. The 75 MHz ¹³C NMR spectrum in CDCl₃ showed three carbonyl carbon signals at δ 170.1 and 170.2 ppm which was in agreement with the chemical shift for two acetate carbonyl groups. The other one at δ 194.0 ppm was characteristic of a thioacetate functionality. These data were also supported by the mass spectrometry result.

At this point, in order to obtain the desired 3-thiomannopyranoside **1** it was necessary to achieve the ring opening of the

Scheme 4. Synthesis of Thiomannopyranoside **1**



1,6-anhydro bridge.²⁸ This transformation was not a trivial one, since it is well documented that there are difficulties encountered for opening this type of anhydro bridge system.²⁹ Based on these precedents, we decided to apply an acetolysis procedure as a way to obtain the anomeric acetate. Thus, we treated **11** with trimethylsilyl triflate in acetic anhydride and surprisingly **1** was obtained as a unique product in very good yield. The stereochemistry at the anomeric carbon was established through nuclear Overhauser effect (NOE) experiments (Figure 1). A 1.53% signal enhancement between H-3 and H-1 and a 1.27% signal enhancement between H-5 and H-1 were clear proof of the β -anomeric configuration.

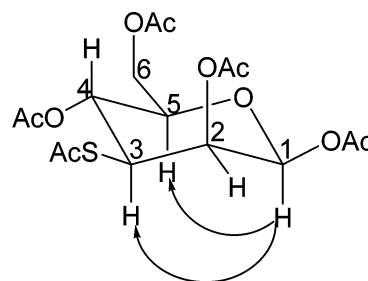


Figure 1. NOE correlation of compound **1**.

Finally, this synthetic protocol is based on the thiocarbonate ring formation from a xanthate intermediate. The configurations of the new chiral centers were controlled by the anhydro bridge. During the initial reduction of the ketone, the bridge exerts a complete facial selectivity on C-2. The same effect occurs during the hydroxylation at C-4. In the case of C-3, its configuration was established by the xanthate group at the adjacent C-2. Subsequent transformation did not affect the mannopyranoside configuration of the chiral centers. Within the thiosugars of interest for their biological activity, gluco-, galacto-, and manno- configurations are the most important.^{15,23,30,31} In this sense, thiomannopyranoside **1** offers significant opportunities for use as a surrogate of mannose for the construction of relevant glycomimetic molecules.

To summarize, a simple and straightforward synthetic methodology has been developed for 3-thiomannoside synthesis from xanthate **2** as a key intermediate. This compound was prepared efficiently from levoglucosenone **3**, a biomass-derived starting material. The 3-thiomannopyranoside **1** was obtained in eight synthetic steps in 14% overall yield. With this protocol, it is now possible to obtain 3-thiomannopyranosides in a simple and robust procedure in good overall yield, avoiding competitive side reactions. Compound **1** is a sulfur-containing monosaccharide which could provide a potential means for the development of carbohydrate-based therapeutics.

■ ASSOCIATED CONTENT

■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00428.

Full experimental details and ¹H NMR and ¹³C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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