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Applications of Thiyl Radical Cyclizations for the Synthesis of Thiosugars

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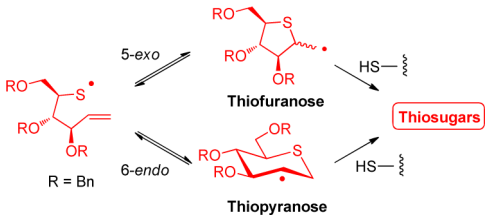
ABSTRACT



The use of intramolecular thiyl radical cyclizations for the synthesis of thiosugars has been investigated, and a new free-radical-based methodology for the synthesis of biologically important thiosugars has been developed. The methodology is mild and proceeds via either 6-*endo* or 5-*exo* cyclization to furnish the thiosugar ring. This represents the first examples of thiyl radical cyclization being applied to the synthesis of thiosugars.

Thiosugars are carbohydrate analogues where one or more oxygen atoms are substituted with sulfur in both furanoside and pyranoside structures.[1] These compounds have attracted significant interest in recent years because of their biological activity as potent inhibitors of glycosidase enzymes.[2] Glycosidases are essential enzymes involved in catalyzing the hydrolysis of glycosidic bonds.[3] A number of thiosugar-based therapeutics have been developed, including treatments for diabetes[1b,4] and antiviral[5,6] and anticancer compounds.[7] A small number of thiosugars have been isolated from natural sources; these include 5-thiomannose, salacinol, and kotalonal.[8] However, in order to gain a better understanding of the biological activity of these compounds and to fully exploit their therapeutic potential it is necessary to develop synthetic methodologies to access their core structure.

In recent years, a large number of efficient strategies have been developed for the synthesis of thiosugars.[1a,9] Despite these intensive synthetic studies, the use of intramolecular thiyl radical cyclization reactions has not previously been investigated. Examples of intramolecular thiyl radical cyclizations onto alkenes for the preparation of sulfur containing heterocycles are rare,[10] but the

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analogous, intermolecular thiol–ene click (TEC) reaction is becoming widely used in carbohydrate and peptide chemistry for the synthesis of glycopeptides and glycoproteins.[11] The mild initiation conditions and tolerance of a range of functional groups makes this a very attractive methodology for ligation reactions.[11d] The reaction can be initiated either photochemically or thermally, and the efficient radical chain process offers excellent yields and atom economy. By taking advantage of the reversible nature of the radical cyclization[12] and by promoting either the 5-*exo* or 6-*endo* cyclization, it is possible to prepare both pyranose and furanose thiosugars from the same starting materials (Figure 1). This offers a unique synthetic advantage for the radical cyclization strategy over alternative synthetic methods.

Herein, we report the results of our investigation into the use of intramolecular thiyl radical cyclizations for the synthesis of thiosugars. The aim of this investigation was to prepare open-chain carbohydrate derivatives containing a free thiol and an alkene and to investigate if these precursors could undergo intramolecular radical cyclization reactions to give the desired thiosugar products. Radical reactions are advantageous for thiosugar synthesis because of their mild activating conditions and tolerance of a range of protecting groups. Thiol–ene reactions are compatible with aqueous conditions which may allow for fully unprotected or partially protected substrates to be used.[11d]

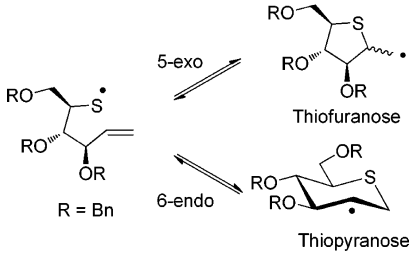
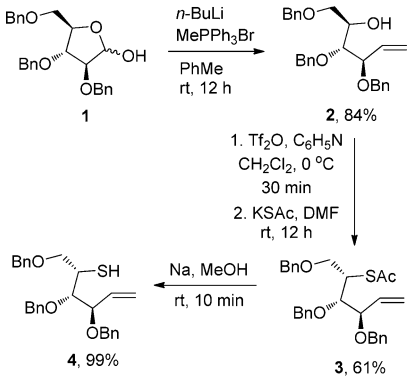


Figure 1. 5-*Exo* and 6-*endo* cyclizations can be employed to furnish furanose and pyranose thiosugars.

In the first instance, we investigated a general synthetic procedure to access the precursor compounds for the radical reaction. The precursor **4** was prepared in four steps starting from commercially available *O*-benzyl-protected arabinose **1** (Scheme 1).

A Wittig reaction[13] was carried out on D-arabinose **1** to introduce the terminal alkene suitable for the intramolecular radical cyclization. An unsubstituted terminal alkene was introduced in the first instance in order to favor the

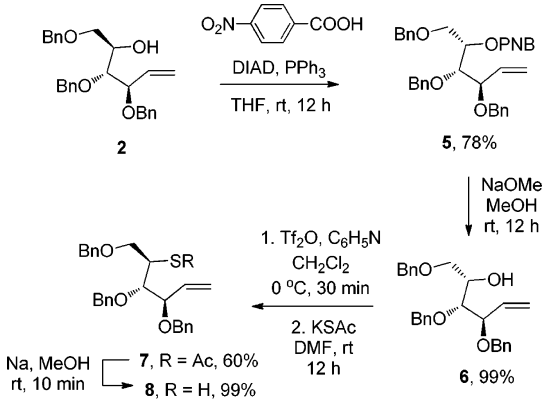
Scheme 1. Synthesis of Radical Precursor **4** from Arabinose **1**



6-*endo* product over the 5-*exo* product to give the more synthetically challenging pyranose compounds. The Wittig reaction furnished alkene **2** in a good yield of 84%. After conversion of the secondary alcohol to the corresponding triflate, the thioester group was introduced at C-4 through nucleophilic displacement of the triflate using KSAc as a nucleophile.[14] The displacement reaction proceeded in 61% over two steps and resulted in an inversion of the stereochemistry at the C-4 position of arabinose. Finally, treatment with freshly prepared sodium methoxide furnished the thiyl radical precursor **4** in excellent yield.

The introduction of the thioester group required an inversion of stereochemistry at C-4 of the arabinose starting material. We were also interested in developing a synthetic pathway that would allow for the retention of configuration at this center. A double-inversion strategy[15] was employed to introduce the desired thio group with retention of configuration at C-4 (Scheme 2).

Scheme 2. Synthesis of Radical Precursor **8** with Retention of Configuration at C-4



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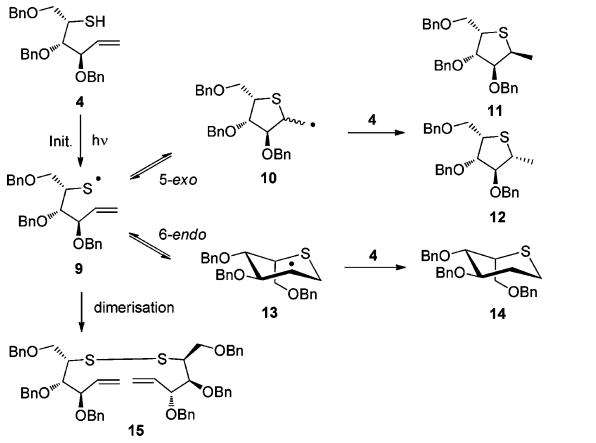
The first inversion reaction was carried out with *p*-nitrobenzoic acid under Mitsunobu conditions followed by hydrolysis of the resulting ester **5** under basic conditions to furnish **6**.[15] Treatment with triflic anhydride followed by nucleophilic displacement with KSAc furnished **7** in 60% over two steps.[14] The free thiol **8** was prepared on treatment of **7** with freshly prepared sodium methoxide in quantitative yield.

With both the radical precursors **4** and **8** in hand, we set out to investigate the radical-mediated ring-closing reactions. The intramolecular radical reaction starting from **4** is outlined in Table 1. Three potential cyclized products could result on initiation of the thiyl radical **9**. The two furanose products **11** and **12** resulting from the kinetically favored 5-*exo* radical cyclization and the pyranose product **14** resulting from the slower 6-*endo* cyclization.[16] The distribution of products formed depends on a number of factors including the relative stability of the alkyl radical formed after cyclization and the rate of thiyl hydrogen atom abstraction. The kinetics of the intermolecular thiol−ene polymerization reaction have been investigated by a number of groups.[17,18] The most important factor governing the overall kinetics of the thiol−ene polymerization reaction is the ratio of the propagation rate to the chain transfer rate. For the intramolecular process, we assume that the chain-transfer step is rate limiting and that the overall process is first order with respect to thiol concentration. We anticipated that the 6-*endo* product would dominate due to the relative stability of the secondary alkyl radical that is formed upon 6-*endo* cyclization. We also anticipated that the formation of the dimerized species **15** could be reduced through the use of high dilution conditions. The radical mediated reaction starting from precursor thiol **4** was investigated under a number of conditions. Optimization of the radical reaction is outlined in Table 1.

Photolysis of thiol **4** in the presence of a radical initiator 2,2-dimethoxy-2-phenylacetophenone (DPAP) and a photosensitizor 4-methoxyacetophenone (MAP) at room temperature for 60 min furnished the 6-*endo* product **14** as the major product in 64% yield (entry 1). The 5-*exo* products **11** and **12** were also isolated albeit in low yields of 8% and 6%, respectively. This is the expected product distribution for a system involving a terminal alkene where the carbon centered radical formed on 5-*exo* cyclization is not stabilized. The disulfide product **15** was also isolated in 10% yield; this product probably originated from dimerization of thiyl radical **9**. Attempts to use an alternative radical initiator 4,4-Azobis(4-cyanovaleric acid) (ACVA) failed to give the desired 6-*endo* product in good yields (entries 2 and 3). Thermal initiation of the 4,4-azobis(4-cyanovaleric acid) (ACVA) donor resulted in a diminished yield of **14**. Increasing the dilution of the system 5-fold did not significantly increase the yield of the 6-*endo* product, but the yields of the 5-*exo* products were reduced (entry 5). Degassing the system thoroughly with a stream of argon for 10 min, in order to avoid side reactions with dissolved

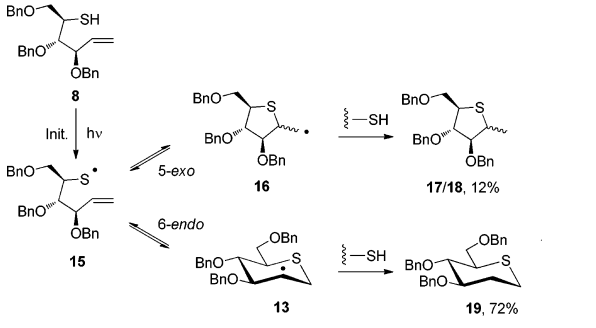
Table 1. Optimization of Thiyl Radical Cyclization Reaction



entry	initiator[a]	conditions[b]	yield[c] (%)
1	DPAP (10%), MAP (10%)	*hν*	**14** (64), **11** (8), **12** (6), **15** (10)
2	ACVA (10%), MAP (10%)	*hν*	**14** (42), **11** (−), **12** (−), **15** (−)
3	ACVA (20%), MAP (20%)	*hν*	**14** (45), **11** (−), **12** (−), **15** (−)
4	ACVA (10%), MAP (10%)	Δ	**14** (18), **11** (−), **12** (−), **15** (−)
5	DPAP (10%), MAP (10%)	*hν*[e]	**14** (62), **11**, **12** (11[d]), **15** (6)
6	DPAP (10%), MAP (10%)	*hν*[f]	**14** (68), **11**, **12** (10[d]), **15** (4)
7	DPAP (10%), MAP (10%)	*hν*[e,f]	**14** (73), **11**, **12** (9[d]), **15** (−)

[a] DPAP (2,2-dimethoxy-2-phenyl-acetophenone), MAP (4-Methoxy-acetophenone), ACVA (4,4-Azobis(4-cyanovaleric acid). [b] All reactions were carried out in DMF as solvent with UV irradiation at rt for 1 h. [c] Isolated yields. [d] Combined yield of 5-*exo* products. [e] Reaction mixture diluted ×5. [f] Reaction mixture degassed with a stream of argon for 10 min.

Scheme 3. Thiyl Radical Cyclization Starting from Thiol **8**



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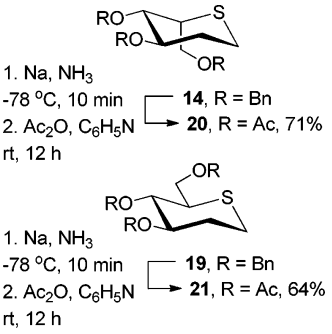
Scheme 4. Deprotection/Acetylation Protocol for Thiosugars **14** and **19**



oxygen, increased the yield of the 6-*endo* product and reduced the amount of disulfide product formed (entry 6). Finally, a combination of dilution and degassing was employed to give the desired 6-*endo* product in an overall isolated yield of 73% together with 9% of the combined 5-*exo* products. This yield is comparable to nonradical based thiosugar syntheses and demonstrates the synthetic application of thiyl radicals for the preparation of thiosugars. Compound **14** is an example of a 1,2-dideoxy thiosugar. Similar compounds have previously been prepared starting from glycals.[9f]

Following the successful preparation of thiosugar **14** we next investigated the C-4 epimeric thiol **8** using the optimized reaction conditions. The desired 6-*endo* product was isolated in 72% yield, and the 5-*exo* products were isolated in a combined yield of 12% (Scheme 3). The two pyranose thiosugars **14** and **19** were deprotected under Birch conditions and finally reacetylated for characterization (Scheme 4). The furanose thioglycosides were not deprotected. However the C-linked thiofuranose compounds **11**, **12**, **17**, and **18** may be interesting glycosidase inhibitors. Attempts to promote the 5-*exo* cyclization reaction are ongoing.

In conclusion, the first thiyl radical cyclization route to thiosugars has been developed. The methodology is robust and regioselective, allowing rapid access to thiopyranose derivatives with high yields under carefully controlled conditions. The investigation of the scope and potential of this process in addition to the development of routes to the corresponding thiofuranose derivatives are underway.

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Supporting Information Available. Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.