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Oligomeric Thioglycosides with α-D-*manno*-(1′→2) Linkages from a Glycal-1,2-episulfide

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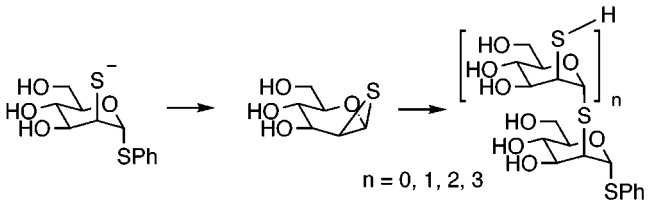
ABSTRACT



Under basic conditions, phenyl 1,2-dithio-α-D-mannopyranoside forms a glycal-1,2-episulfide, which undergoes controlled oligomerization to afford a family of thio-oligo-α-D-mannopyranosides in a single reaction. The episulfide can also be intercepted by added thiolates, which leads to other sorts of thioglycosides. These α-(1→2)-linked thio-mannopyranosides might have application as mimics of natural structures such as viral high-mannose glycoproteins or ManLAM.

1-Thioglycosides, carbohydrate derivatives that bear a sulfur atom instead of oxygen at the anomeric linkage, are more resistant to cleavage by glycosidases than the naturally occurring *O*-glycosides.[1] Because of their structural similarity to the natural substrates, 1-thioglycosides can serve as modest competitive inhibitors of glycosidases[2] and as enzyme-resistant scaffolds to support ligands whose enzyme binding or other interactions may be of interest.[3] 1-Thioglycosides are usually assembled by S-glycosylation of simple thiols or by S_N2 displacement reactions that take advantage of the nucleophilicity of the thiolate anion. The multistep nature of these approaches has limited the synthesis of *S*,*S*-trisaccharides and *S*,*S*,*S*-tetrasaccharides to just a few examples.[4] With a contrasting strategy, we have found that a glycal-1,2-episulfide **5** (Scheme 1) can be slowly generated in solution. Remarkably, **5** undergoes controlled oligomerization to afford a family of thio-oligo-α-D-mannopyranosides (**7**−**9**) in a single reaction. These α-(1→2)-linked thio-mannopyranosides might have application as mimics of natural structures with similar linkages, such as the outer surface of high-mannose glycoproteins such as gp120 in the viral coat of HIV[5] or the mannosylated lipoglycan, ManLAM, that mediates human macrophage phagocytosis of virulent strains of *Mycobacterium tuberculosis*.[6] They might also serve as inhibitors of α-mannosidases with 1,2-linkage specificity.[7]

The precursor to **5** was made (Scheme 1) from methyl 2,3-di-*S*,*O*-acetyl-4,6-*O*-(phenylmethylene)-2-thio-α-D-mannopyranoside **1**, which itself had been prepared from commercial methyl 4,6-*O*-(phenylmethylene)-α-D-glucopy-

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(2) Witczak, Z. J.; Boryczewski, D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3265−3268, and references therein.

(3) For some recent examples, see: Zanini, D.; Roy, R. *J. Org. Chem.* **1998**, *63*, 3486−3491, and references therein.

(4) Contour-Galcera, M.-O.; Guillot, J.-M.; Ortiz-Mellet, C.; Pflieger-Carrara, F.; Defaye, J.; Gelas, *J. Carbohydr. Res.* **1996**, *281*, 99−118. Contour-Galcera, M.-O.; Ding, Y.; Ortiz-Mellet, C.; Defaye, J. *J. Carbohydr. Res.* **1996**, *281*, 119−128.

(5) Matsuo, I.; Miyazaki, T.; Isomura, M.; Sakakibara, T.; Ajisaka, K. *J. Carbohydr. Chem.* **1998**, *17*, 1249−1258, and references therein.

(6) Schlessinger, L. S.; Hull, S. R.; Kaufman, T. M. *J. Immunol.* **1994**, *152*, 4070−4079.

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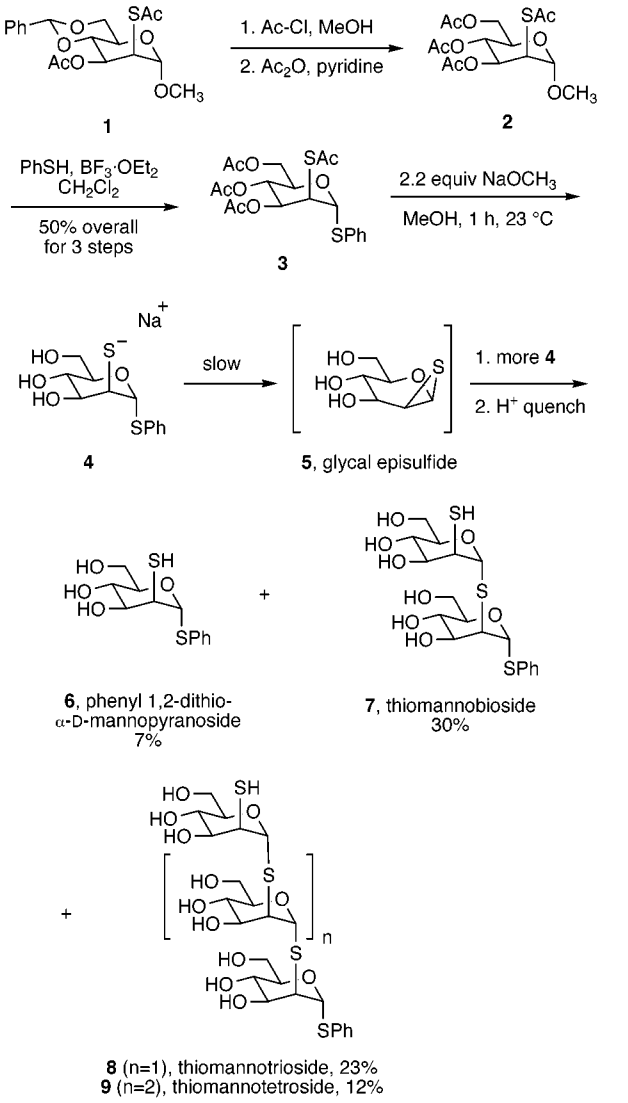
Scheme 1. Synthesis of 2-Thio-(1→2)-mannopyranoside Oligomers

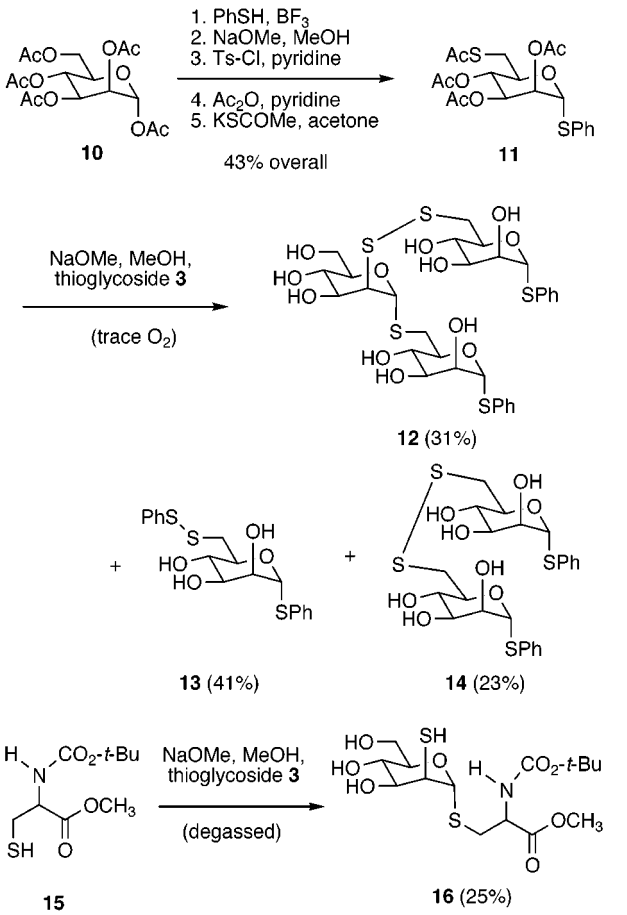


ranoside in two steps.[8] Acid hydrolysis of the benzylidene protecting group and subsequent acetylation gave the tetraacetate **2**, and then acetal exchange with thiophenol[9] led to the phenyl thioglycoside **3**. The (C-1)-α stereochemistry of **3** is indicated by its $^{13}C-^{1}H$ coupling constant of 173 Hz.[10] Deacetylation of **3** under Zemplen conditions gave rise not only to the expected mercaptotriol **6** but also to a mixture of oligomeric thioglycosides (**7**−**9**) still bearing the 2-mercapto substituent.

The thioglycoside products **6**−**9** were characterized by their IR, FAB-MS, and ^{1}H and ^{13}C NMR spectra. Each showed the expected number of anomeric thioglycoside C's at 88−92 ppm and anomeric H's at 5.5−5.8 ppm. The disaccharide **7**, α-linked according to the anomeric J_{C-H}'s, was further characterized as its heptaacetate, which exhibited the expected ^{1}H resonances and IR absorbances for its *S*-acetyl and six *O*-acetyl residues.

Thiirane **5** can be intercepted by thiolates unrelated to **4**, which leads to other sorts of thioglycosides. As an example, phenyl 1,6-dithio-α-D-mannopyranoside **11** was prepared from mannose pentaacetate **10** by standard transformations (Scheme 2). Deacetylation of **11** in methanol presumably

Scheme 2. Glycal-1,2-episulfide Trapping Experiments



led to the formation of the 6-thiolate, which was trapped by adding thiirane precursor **3** to the same solution. To facilitate isolation of the products, air oxidation (which could not be altogether prevented anyway) was allowed to proceed during workup. The *pseudo*-trisaccharide **12** was obtained in 31% yield (based on **3**), along with two disulfides, **13** and **14**, that formed from **11** as byproducts. Thiirane **5** is implicated as the likely intermediate leading to **12**, and the thiolate derived from **11** evidently competed successfully for **5** with other thiolates present in solution. Another primary thiolate precursor, protected cysteine **15**, was converted to the glycopeptide[11] mimic **16** by sequential treatment with sodium methoxide and **3** (Scheme 2).

Phenyl 1,2-dithio-α-D-mannopyranoside **3** and the derived 1,2-episulfide **5** exhibit reactivity that is unusual in several

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(9) Ferrier, R. J.; Furneaux, R. H. *Methods Carbohydr. Chem.* **1980**, *8*, 251.
(10) Uhrinova, S.; Uhrin, D.; Liptaj, T.; Bella, J.; Hirsh, J. *Magn. Reson. Chem.* **1991**, *29*, 912−922, and references therein.
(11) Review: Taylor, C. M. *Tetrahedron* **1998**, *54*, 11317−11362.

respects. Phenylthiolate (PhS^-), a reactive nucleophile, is not normally considered a leaving group at the anomeric position of sugars. For example, phenyl 1-thio-α-D-mannopyranoside,[12] prepared from **10** in two steps, is stable to methanolic sodium methoxide. We have found that certain other 2-thio-α-D-mannopyranosides, such as *p*-nitrophenyl, do decompose during S-deacetylation at C-2 but methyl 2-thio-α-D-mannopyranoside can be made from its peracetate **2** by treatment with methanolic sodium methoxide without loss of methoxide at C-1. Treatment of **11** with sodium methoxide likewise does not lead to thiolate ring closure at C-1, and the 2-thioglycoside products **7**−**9** are isolable from methoxide solution with the 1-thio linkage intact. One can thus attribute the ring closure reaction of **4** to a favorable S_N2 trajectory[13] and softness match[14] between the participating thiolate at C-2 and the *trans-anti* anomeric leaving group (PhS^-), as well as the stability of phenylthiolate as a leaving group relative to alkylthiolate or methoxide.[15]

An earlier study[16] on ring closure of *β*-D-*gluco* 1-thiolates provides evidence for the transient formation of thiiranes related to **5**, but only amorphous sulfide polymer was isolated from the reaction mixture. The limited oligomerization of **4** observed here may reflect the behavior of the rather reluctant leaving group that leads to the formation of **5** in low concentration only. Once formed, **5** is trapped by the most reactive thiolates present, namely **4** and its lower oligomers. The less-hindered thiolates derived from **11** and **15** can also intercept **5** to some extent before it polymerizes. Interestingly, methanol and methoxide, which react quickly with glycal epoxides,[17] and are present here in excess, do not intercept glycal episulfide **5** to any detectable extent (NMR, TLC). This may be another manifestation of the importance of a softness match for effective ring opening and closing of thiiranes.

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

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