

# Oligomeric Thioglycosides with $\alpha$ -D-manno-(1'→2) Linkages from a Glycal-1,2-episulfide

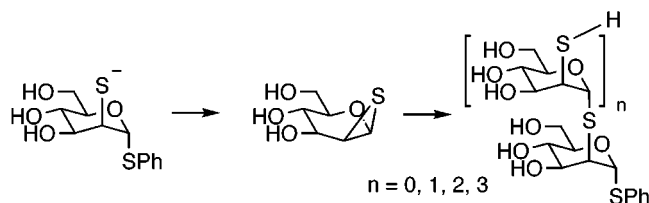
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## ABSTRACT



Under basic conditions, phenyl 1,2-dithio- $\alpha$ -D-mannopyranoside forms a glycal-1,2-episulfide, which undergoes controlled oligomerization to afford a family of thio-oligo- $\alpha$ -D-mannopyranosides in a single reaction. The episulfide can also be intercepted by added thiolates, which leads to other sorts of thioglycosides. These  $\alpha$ -(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.<sup>1</sup> Because of their structural similarity to the natural substrates, 1-thioglycosides can serve as modest competitive inhibitors of glycosidases<sup>2</sup> and as enzyme-resistant scaffolds to support ligands whose enzyme binding or other interactions may be of interest.<sup>3</sup> 1-Thioglycosides are usually assembled by *S*-glycosylation of simple thiols or by *S<sub>N</sub>2* 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.<sup>4</sup> 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 oligomer-

ization to afford a family of thio-oligo- $\alpha$ -D-mannopyranosides (**7–9**) in a single reaction. These  $\alpha$ -(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<sup>5</sup> or the mannosylated lipoglycan, ManLAM, that mediates human macrophage phagocytosis of virulent strains of *Mycobacterium tuberculosis*.<sup>6</sup> They might also serve as inhibitors of  $\alpha$ -mannosidases with 1,2-linkage specificity.<sup>7</sup>

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

(1) Reviews: Defaye, J.; Gelas, J. In *Studies in Natural Products Chemistry*; Rahman, A., Ed.; Elsevier: New York, 1991; Vol. 8, pp 315–357. *Carbohydr. Chem. (UK)* **1998**, *30*, 159–166.

(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.

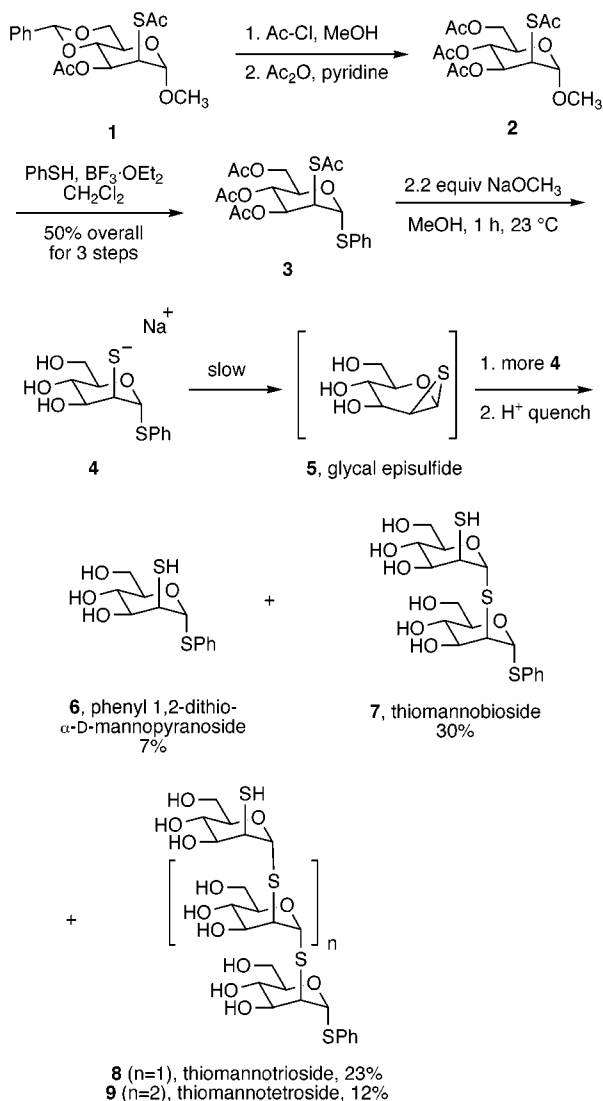
(4) Contour-Galcerà, M.-O.; Guillot, J.-M.; Ortiz-Mellet, C.; Pflieger-Carrara, F.; Defaye, J.; Gelas, J. *Carbohydr. Res.* **1996**, *281*, 99–118. Contour-Galcerà, M.-O.; Ding, Y.; Ortiz-Mellet, C.; Defaye, J. *J. Carbohydr. Res.* **1996**, *281*, 119–128.

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



ranoside in two steps.<sup>8</sup> Acid hydrolysis of the benzylidene protecting group and subsequent acetylation gave the tetraacetate **2**, and then acetal exchange with thiophenol<sup>9</sup> led to the phenyl thioglycoside **3**. The (C-1)- $\alpha$  stereochemistry of **3** is indicated by its <sup>13</sup>C–<sup>1</sup>H coupling constant of 173 Hz.<sup>10</sup> 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 <sup>1</sup>H and <sup>13</sup>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

(8) Knapp, S.; Naughton, A. B. J.; Jaramillo, C.; Pipik, B. *J. Org. Chem.* **1992**, *57*, 7328–7334.

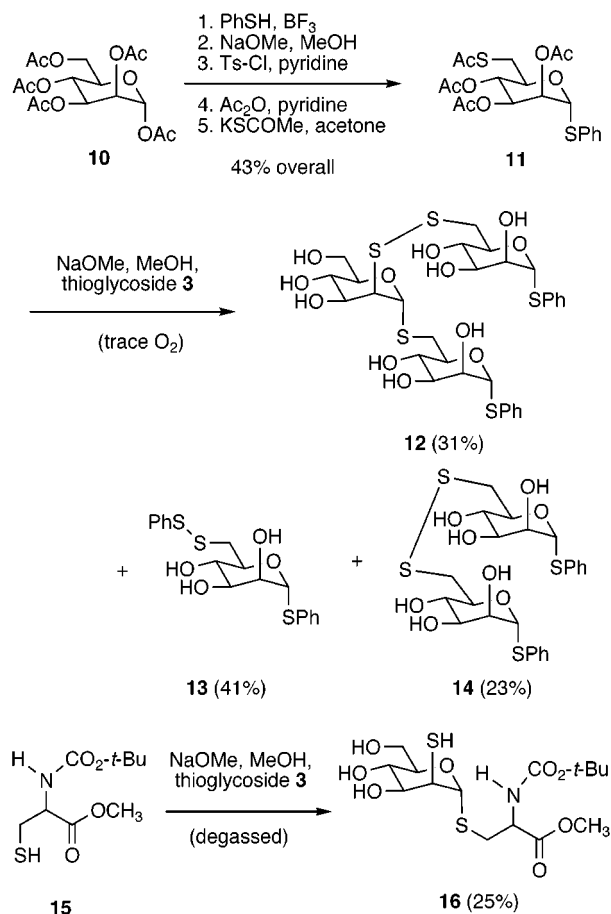
(9) Ferrier, R. J.; Furneaux, R. H. *Methods Carbohydr. Chem.* **1980**, *8*, 251.

(10) Uhrinova, S.; Uhrin, D.; Liptaj, T.; Bella, J.; Hirsh, J. *Magn. Reson. Chem.* **1991**, *29*, 912–922, and references therein.

disaccharide **7**,  $\alpha$ -linked according to the anomeric J<sub>C–H</sub>'s, was further characterized as its heptaacetate, which exhibited the expected <sup>1</sup>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- $\alpha$ -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<sup>11</sup> mimic **16** by sequential treatment with sodium methoxide and **3** (Scheme 2).

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

(11) Review: Taylor, C. M. *Tetrahedron* **1998**, *54*, 11317–11362.

respects. Phenylthiolate ( $\text{PhS}^-$ ), a reactive nucleophile, is not normally considered a leaving group at the anomeric position of sugars. For example, phenyl 1-thio- $\alpha$ -D-mannopyranoside,<sup>12</sup> prepared from **10** in two steps, is stable to methanolic sodium methoxide. We have found that certain other 2-thio- $\alpha$ -D-mannopyranosides, such as *p*-nitrophenyl, do decompose during S-deacetylation at C-2 but methyl 2-thio- $\alpha$ -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  $\text{S}_{\text{N}}2$  trajectory<sup>13</sup> and softness match<sup>14</sup> between the participating thiolate at C-2 and the *trans-anti* anomeric leaving group ( $\text{PhS}^-$ ), as well as the stability of phenylthiolate as a leaving group relative to alkylthiolate or methoxide.<sup>15</sup>

An earlier study<sup>16</sup> on ring closure of  $\beta$ -D-*gluco* 1-thiolates provides evidence for the transient formation of thiiranes

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(12) Maity, S. K.; Dutta, S. K.; Banerjee, A. K.; Achari, B.; Singh, M. *Tetrahedron* **1994**, *50*, 6965–6974.

(13) For a recent discussion, see: Collins, P.; Ferrier, R. *Monosaccharides*; John Wiley & Sons: New York, 1995; pp 89–91, 203–206, 242, 266–269.

(14) Pearson, R. G.; Songstad, J. J. *Org. Chem.* **1967**, *32*, 2899–2900.

(15) Analogous ring closure of phenyl glycosides to the glycal epoxide (with O-2 participation) has been inferred: Ballou, C. E. *Adv. Carbohydr. Chem.* **1954**, *9*, 59–95.

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,<sup>17</sup> 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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(17) Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661–6666.

