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Nucleophile Induced Rearrangements of Thioglycosides: Formation of 6-Thio Glycosides and 1,6 Thioanhydrosugars

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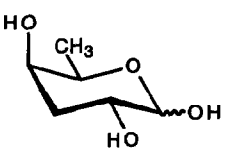
Abstract: Treatment of Ethyl 2,3 di-*O*-benzoyl-4,6-di-*O*-toluenesulfonyl-1-thio-β-D-glucopyranoside **12** with sodium methoxide at low temperature gives Methyl 3,4 anhyro-6-*S*-ethyl-β-D-galactopyranoside **13**, whereas treatment with sodium iodide in reluxing butanone yields 2,3 di-*O*-benzoyl-4-*O*-toluensesulfonyl-1,6 thioanhydro-D-glucopyranose **19**.

INTRODUCTION

The recognition of otherwise identical bacterial cell wall polysaccharides by antibody is defined by the unique stereochemistry of three 3,6 dideoxy-D-hexoses, 3,6 dideoxy-D-*xylo*-hexose **1** (abequose) 3,6 dideoxy-D-*arabino*-hexose **2** (tyvelose) and 3,6 dideoxy-D-*ribo*-hexose **3** (paratose)[1].



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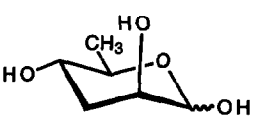

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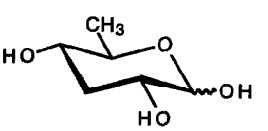

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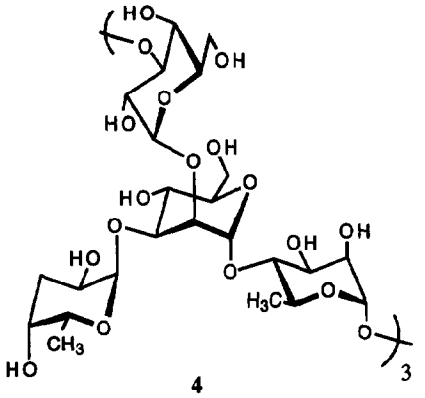
The polymeric O-antigen of Salmonella serogroups A, B and D_1 each contain one of these dideoxyhexoses attached by an α-pyranosidic linkage to the linear trisaccharide,

→3) -α-D-Gal*p* (1→2)-α-D-Man*p*(1→4)-α-L-Rha*p*-α-(1–

at Man *O*-3. A fragment **4** of the polysaccharide containing three of these repeating units from the serotype B antigen was recently crystallized with antibody Fab and the crystal structure of this complex[2] and the complex with the synthetic epitope **5** have been solved[3]. In support of these molecular recognition studies, mono up to trisaccharide elements of such bacterial epitopes have been synthesized[4-8] or, in the case of a heptasaccharide, isolated by partial degradation of phage derived octasaccharide[9].



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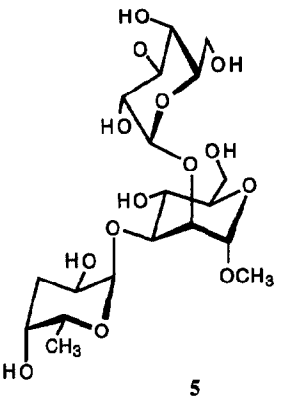
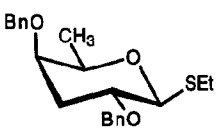


5

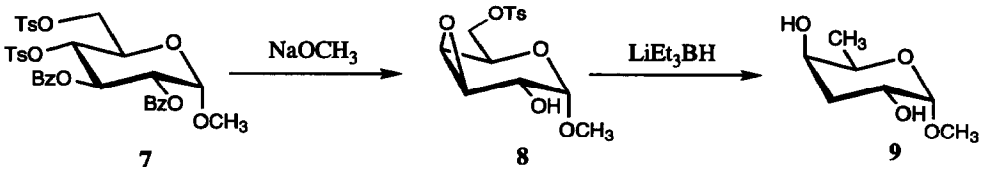
The preparation of oligosaccharides containing abequose and other 3,6 dideoxy sugars is a laborious and time consuming process[10], requiring first the preparation of the dideoxy sugar, most commonly as its di-*O*-benzyl methyl glycoside[4,5], and then conversion of this monosaccharide to an activated glycosyl donor[6,8,10-12]. Frequently, the highly reactive (and hence unstable) 3,6 dideoxy glycosyl chlorides or bromides have been used as glycosylating agents. The use of these reagents is cumbersome in that they must be used immediately following their preparation and often a large excess (3 fold) of the chloride must be used to achieve even modest (60-70%) yields[6,7]. Faced with the prospect of making a large number of abequose-containing glycopeptides, we set out to prepare a stable glycosyl donor of abequose. We focused on thioglycosides which have been widely used as glycosyl donors and posses a number of attractive characteristics including hydrolytic stability and activation by a variety of methods[13-15]. We selected thioglycoside **6**, as a potentially useful abequose donor.



6

RESULTS AND DISCUSSION

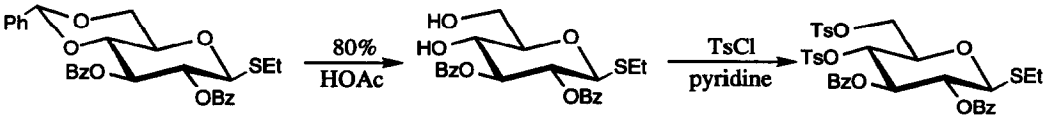
For the preparation of **6**, we chose a synthetic strategy closely related to a method reported earlier[16,17] for the preparation of the methyl 3,6 dideoxy-α-D-*xylo*-hexopyranoside **9** (Scheme 1). The key step in that synthesis was the facile formation of the 3,4 anhydrogalactose derivative **8** from ditosylate **7**. Reduction of the epoxy tosylate with hydride ion afforded **9**, which can be converted to a glycosyl chloride in a straight forward manner.



7 8 9

Scheme 1

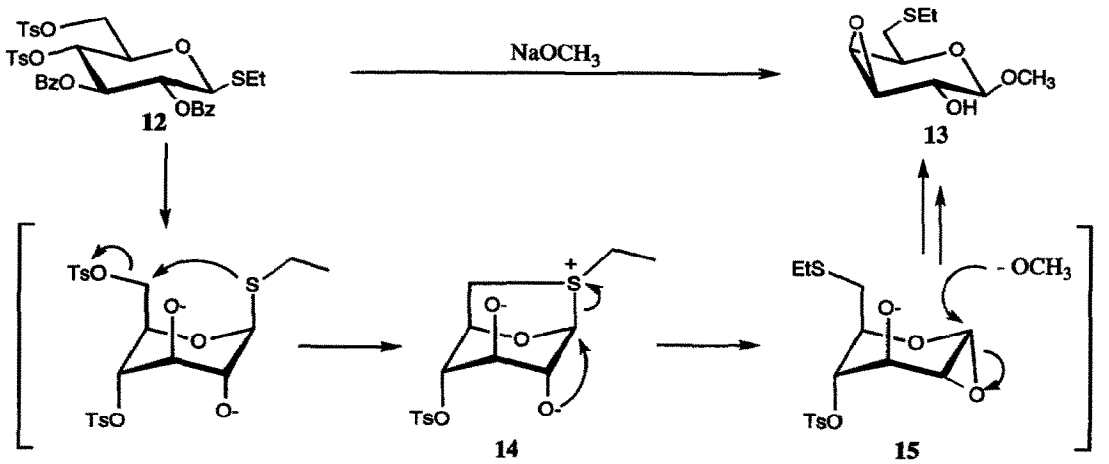
What seemed initially to be a trivial modification at the anomeric center, replacement of the α-methoxy with a β-thioethyl group, would lead under a similar series of reactions to the desired product **6**. To this end, the known[18] benzylidene derivative **10** was converted to diol **11** and then tosylated to provide **12**. When **12** was treated with 1.2 equivalents of sodium methoxide under the prescribed conditions, the reaction proceeded more sluggishly than for the methyl glycoside. Moreover, after 24 hours the pH of the reaction had become



10 11 12

neutral, and another equivalent of base was added. The reaction was worked up after two days and chromatographed to give in 60% yield, not the desired 6-tosyl epoxide, but rather the 6-thioethyl methyl glycoside **13**. During the course of the reaction the thio functionality had migrated to C-6 with the concomitant formation of a methyl glycoside. The ^{1}H NMR of **13** showed a H-1 signal at 4.07 ppm with a $J_{1,2}$ of 7.5 Hz, a coupling constant characteristic of 1,2 *trans O-*, but not the corresponding *S*-glycosides, which have $J_{1,2}$ values of approximately 10 Hz. Additionally, the C-6 protons were shifted upfield to 2.79 and 2.90 ppm suggesting the attachment at C-6 of sulfur. Further proof of the structure was provided by the ^{13}C NMR which had signals at 104.20 ppm for C-1 and 32.98 ppm for C-6 as would be expected for **13**. It is noteworthy to mention that only the β-glycoside was detected.

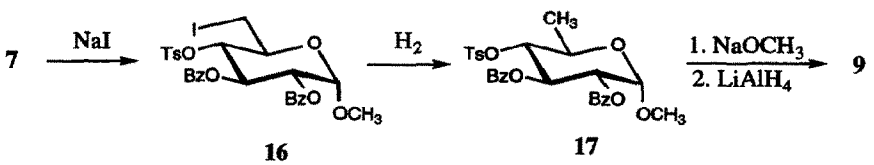
While migrations of thio groups from the anomeric center of thioglycosides to C-2 are well known[19,20], this is, to the best of our knowledge, the first report of a C-1→C-6 migration involving thioglycosides. Previous work involving pentose 5-tosyl dithioacetals reported a similar migration to give 5-thio thioglycosides[21-23]. Scheme 2 shows a possible mechanism for the formation of product **13**. Following removal of the benzoates, the first step involves the displacement of the 6-tosylate by the thioethyl group after a ring inversion from the $^4C_1$ to $^1C_4$ chair conformation. The bicyclic sulfonium species **14** is then opened by attack of the C-2 alkoxide to give the 1,2 anhydrosugar **15** which is in turn converted to the methyl glycoside by the attack of methoxide at C-1. Although we have no evidence for the intermediacy of **15**, the existence of



Scheme 2

such an intermediate explains the observed selective β-glycoside formation. Direct methoxide attack upon **14** would lead to the α-glycoside. The conformational rigidity of epoxy-sugars necessitates that epoxide formation follow thioethyl migration.

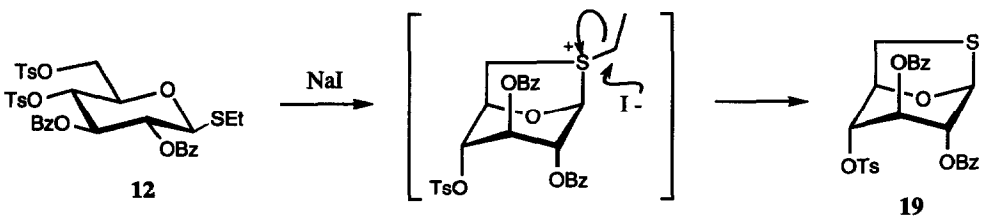
We next turned our attention to another published[17] preparation of **9** as shown in Scheme 3. In that report, ditosylate **7** was converted, upon treatment with sodium iodide in refluxing butanone, to iodide **16**. Hydrogenation gave **17** and was followed by sodium methoxide treatment to provide an epoxide which was then converted to **9** by treatment with lithium aluminum hydride.



Scheme 3

In our hands, however, treatment of tosylate **12** with sodium iodide as reported resulted in the formation of the 1,6 thioanhydrosugar **19** in 95% yield, not the desired iodide. The ^{1}H NMR of **19** showed an absence of a thioethyl group and a H-1 signal as a singlet at 5.62 ppm. Moreover, the vicinal coupling constants were all less than 6 Hz, suggesting a molecule with all ring protons equatorially disposed. In the ^{13}C NMR, C-1 was at 81.91 ppm and C-6 at 34.72 ppm, indicative of sulfur attached to both carbons. Compound **19** proved to be unstable in solution at room temperature. After a few days in $CDCl_3$, the solution turned black and the NMR showed a number of decomposition products.

Formation of 1,6 thioanhydrosugars has been reported previously, but never from thioglycosides. Heretofore, preparation of these structures has been achieved either by treatment of anomeric xanthates of 6-tosyl[24] or 6-bromo[25] sugars with sodium methoxide, or by displacement of C-1 activated 6-sulfhydryl sugars[26]. In a recent a recent report[27], these structures have also been made by treatment of 6-tosyl glycosyl bromides with hydrogen sulfide and triethylamine. Scheme 4 shows the proposed mechanism of formation. As above, the first step is the formation of a bicyclic sulfonium species, **18**. This intermediate could be synthesized either directly by attack of the sulfur on **12**, or indirectly by formation of first the 6-iodo compound followed by sulfur displacement. We were, however, unable to detect any of the 6-iodo thioglycoside by TLC. Product **19** arises from **18** by reaction with iodide ion giving the product and volatile ethyl iodide.



Scheme 4

Compounds such as **19** are interesting as synthetic intermediates and in the past have been used in the preparation of oxathiolane nucleoside analogs[28]. A study[25] has also investigated the use of these compounds as glycosyl donors, as these compounds would be useful for the synthesis of 6-thio or 6-deoxy oligosaccharides. This approach met with only modest success; however, the number of thioglycoside activation methods has since increased, and another examination of the potential usefulness of these molecules as glycosyl donors is warranted. As final synthetic targets, these bicyclic products could also serve as conformationally restricted analogs of oligosaccharide sugar residues. Conformationally restricted oligosaccharides have been used in the past as tools to explore aspects of carbohydrate-protein interactions[29,30].

Studies are currently underway to examine the generality and usefulness of these novel rearrangement processes.

EXPERIMENTAL

General methods. - Optical rotations were measured with a Perkin-Elmer 241 polarimeter at 22± 2° C. Analytical TLC was performed on Silica Gel 60-F_{254} (E. Merck Darmstadt) with detection by quenching of fluorescence and/or by charring with sulfuric acid. All commercial reagents were used as supplied and

chromatography solvents were distilled prior to use. Column chromatography was performed on Silica Gel 60 (E. Merck 40-60 mM, Darmstadt). ^1H NMR were recorded at 360 MHz (Bruker AM-360) with internal $CHCl_3$ at 7.24 ppm. ^{13}C NMR were recorded at 75.5 MHz (Bruker AM-300) with internal $CHCl_3$ at 77.07 ppm. ^1H data are reported as though they were first order. Unless otherwise stated, all reactions were carried out at room temperature. Organic solutions were dried (sodium sulfate) prior to concentration under vacuum at <40° C (bath). Microanalyses were carried out by the analytical services of this department and all samples, with the exception of **19**, submitted for analysis were dried overnight under vacuum with phosphorus pentoxide at 56° C (refluxing acetone). Compound **19** was dried at room temperature. High resolution mass spectra (HRMS) were recorded on a Kratos MS-50 instrument using electron-impact ionization.

Ethyl 2,3 di-O-benzoyl-1-thio-β-D-glucopyranoside. **11**. - Dibenzoate **10** (1.5 g, 2.81 mmol) was suspended in 80% acetic acid (25 mL) and heated at reflux. The substrate did not immediately dissolve, but after 30 min the solution became clear. After 2 h the reaction was cooled and the solvent evaporated to an oil that was coevaporated twice with toluene. Chromatography of the syrupy residue (1:1 pentane-EtOAc) gave the product **11** (0.97 g, 80%) as a white foam; $[\alpha]_D$ + 87.6 (*c* 1.3, $CHCl_3$), R_f 0.20 (1:1 pentane-EtOAc). ^1H NMR ($CDCl_3$): δ 7.30-8.10 (m, 10 H, Ph), 5.40-5.49 (m, 2 H, H-2, H-3), 4.71-4.79 (m, 1 H, H-1), 3.85-4.05 (m, 3 H, H-4, H-6, H-6'), 3.59-3.66 (m, 1 H, H-5), 3.32 (d, 1 H, $J_{4,4\text{-OH}}$ 4.5 Hz, 4-OH), 2.64-2.84 (m, 2 H, SCH_2CH_3), 2.25 (t, 1 H, $J_{6,6OH} = J_{6',6\text{-OH}}$ = 6.5 Hz, 6-OH), 1.26 (t, 3 H, *J* 7.5 Hz, SCH_2CH_3); ^{13}C NMR ($CDCl_3$): δ 167.52, 165.40 (C=O), 83.71 (C-1), 62.45 (C-6), 24.41 (SCH_2CH_3), 14.93 (SCH_2CH_3). Anal. Calcd. for $C_{22}H_{24}O_7S$ (432.49): C, 61.10; H, 5.59; S, 7.41. Found: C, 61.14; H, 5.51; S, 7.63.

Ethyl 2,3 di-O-benzoyl-4,6-di-O-toluenesulfonyl-1-thio-β-D-glucopyranoside. **12** - Diol **11** (0.97 g, 2.25 mmol) was dissolved in pyridine (25 mL) and cooled to 0°C. To this solution was added *p*-toluenesulfonyl chloride (1.53 g, 8.0 mmol) and the reaction warmed to room temperature. After 4 days water was added and the solution was diluted with CH_2Cl_2. After washing with 0.5 N HCl, $NaHCO_3$, water and brine, the organic layer was evaporated providing a solid that was recrystallized from EtOH to give the product **12** (1.2 g, 72%) as a white solid; $[\alpha]_D$ +42.0 (*c* 1.0, $CHCl_3$), R_f 0.25 (3:1 pentane-EtOAc), m.p. 145-148° C (decomposition). ^1H NMR ($CDCl_3$): δ 6.90-7.90 (m, 18 H, Ph), 5.67 (t, 1 H, $J_{2,3} = J_{3,4}$ = 9.5 Hz, H-3), 5.32 (t, 1 H, $J_{1,2} = J_{2,3}$ = 9.5 Hz, H-2), 4.81 (t, 1 H, $J_{3,4} = J_{4,5}$ = 9.5 Hz, H-4), 4.69 (d, $J_{1,2}$ 9.5 Hz, 1 H, H-1), 4.50 (dd, 1 H, $J_{5,6}$ 2.0, $J_{6,6'}$ 11.5 Hz, H-6), 4.18 (dd, 1 H, $J_{5,6'}$ 6.5, $J_{6,6'}$ 11.5 Hz, H-6'), 3.90 (ddd, 1 H, $J_{4,5}$ 9.0, $J_{5,6}$ 2.0, $J_{5,6'}$ 6.5 Hz, H-5), 2.60-2.75 (m, 2 H, SCH_2CH_3), 2.47, 2.13 (s, 3 H, tosyl CH_3), 1.24 (t, 3 H, *J* 7.5 Hz, SCH_2CH_3); ^{13}C NMR ($CDCl_3$): δ 164.99, 164.96 (C=O), 83.54 (C-1), 67.97 (C-6), 24.34 (SCH_2CH_3), 21.65, 21.52 (tosyl CH_3), 14.87 (SCH_2CH_3). Anal. Calcd. for $C_{36}H_{36}O_{11}S_3$ (740.86): C, 58.36; H, 4.90; S, 12.98. Found: C, 58.29; H, 4.90; S, 13.27.

Methyl 3,4 anhyro-6-S-ethyl-β-D-galactopyranoside. **13** - Ditosylate **12** (700 mg, 0.94 mmol) was dissolved in CH_2Cl_2 (5 mL) and cooled to -40°C. To this solution was added 0.2 N $NaOCH_3$ (5 mL) and then the reaction was brought to 5°C. The reaction was very slow and after one day the pH had become neutral. Thus more $NaOCH_3$ solution (5 mL) was added after stirring for another 24 h, the reaction was diluted with cold CH_2Cl_2 and washed with ice water and brine. Evaporation of the solvent followed by chromatography (3:1 pentane-EtOAc) gave the product **13** (124 mg, 60%) as an oil; $[\alpha]_D$ -116.6 (*c* 0.9, $CHCl_3$), R_f 0.30 (3:1 pentane-EtOAc). ^1H NMR ($CDCl_3$): δ 4.07 (d, 1 H, $J_{1,2}$ 7.5 Hz, H-1), 4.02 (t, 1 H, $J_{5,6}$=$J_{5,6'}$ 6.5 Hz, H-5), 3.68 (dd, 1 H, $J_{1,2}$ 7.5 Hz, $J_{2,2\text{-OH}}$ 3.5 Hz, H-2), 3.50 (s, 3 H, OCH_3), 3.31 (d, 1 H, $J_{3,4}$ 4.0 Hz, H-3), 3.27 (d, 1 H, $J_{3,4}$ 4.0 Hz, H-4), 2.90 (dd, 1 H, $J_{5,6}$ 6.5, $J_{6,6'}$ 12.5 Hz, H-6), 2.79 (dd, 1 H, $J_{5,6'}$ 6.5, $J_{6,6'}$ 12.5 Hz, H-6'), 2.65 (q, 2 H, *J* 7.5 Hz, SCH_2CH_3), 2.42 (d, 1 H, $J_{2,2\text{-OH}}$ 3.5 Hz, 2-OH), 1.29 (t, 3 H, *J* 7.5 Hz, SCH_2CH_3); ^{13}C NMR ($CDCl_3$): δ 104.20 (C-1), 38.19 (C-6), 27.22 (SCH_2CH_3), 14.89 (SCH_2CH_3). Anal. Calcd. for $C_9H_{16}O_4S$: C, 49.07; H, 7.33; S, 14.53. Found: C, 49.47; H, 7.50; S, 14.45. HRMS Calcd: 220.07692, found 220.07715.

2,3 di-O-benzoyl-4-O-toluensesulfonyl-1,6 thioanhydro-D-glucopyranose. **19** - Ditosylate **12** (500 mg, 0.68 mmol) was dissolved in butanone (10 mL) and NaI (210 mg, 1.22 mmol) added. The reaction was heated at reflux for 4 h and the reaction cooled and diluted with EtOAc. After washing with saturated $Na_2S_2O_3$, water and brine and evaporated. The residue was chromatographed (3:1 pentane-EtOAc) to give the product **19** (349 mg, 95%) as a white foam; $[\alpha]_D$ +36.8 (*c* 1.1, $CHCl_3$), R_f 0.45 (3:1 pentane-EtOAc).^1H NMR ($CDCl_3$): δ 7.00-8.05 (m, 18 H, Ph), 5.62 (br. s, 1 H, H-1), 5.47 (br. t, 1 H, $J_{2,3}$=$J_{3,4}$= 5.5 Hz, H-3), 5.13 (br. d, 1 H, $J_{5,6'}$ 6.0 Hz, H-5), 5.01 (d, 1 H, $J_{2,3}$ 5.5 Hz, H-2), 4.60 (dd, 1 H, $J_{3,4}$ 5.5, $J_{4,5}$ 1.5 Hz, H-4), 3.27 (dd, 1 H, $J_{5,6}$ 0.5, $J_{6,6'}$ 10.5 Hz, H-6), 3.20 (dd, 1 H, $J_{5,6'}$ 6.0, $J_{6,6'}$ 10.5 Hz, H-6'), 2.31 (s, 3 H, tosyl CH_3); ^{13}C NMR ($CDCl_3$): d 165.33, 164.43 (C=O), 145.12 (OSO_2C), 81.91 (C-1), 34.72 (C-6), 21.57 (tosyl CH_3). Anal. Calcd. for $C_{27}H_{24}O_8S_2$: C, 59.99; H, 4.48; S, 11.84. Found: C, 59.36; H, 4.32; S, 11.30. HRMS Calcd: 540.09125, found 540.09161.

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