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A NOVEL SYNTHESIS OF 5-THIO-D-GLUCOSE

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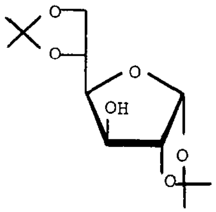
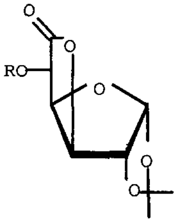
Summary: A shorter synthesis of 5-thio-D-glucose is described in 8 steps from commercially available D-glucofurano-3,6-lactone.

Most known syntheses of 5-thio-D-glucose[1-5] have 1,2-5,6-di-O-isopropylidene-α-D-glucofuranose (1) as starting material. They are time-consuming and laborious. In this communication, we describe a novel synthesis of 5-thio-D-glucose in 8 steps, with no tedious chromatographic separations and an over-all yield of about 35%. The starting material is the 1,2-O-isopropylidene-α-D-glucofurano-3,6-lactone[6] (2) which was obtained in a 90% yield by treatment of the D-glucofurano-3,6-lactone (12 g, 68 mmol) with sulfuric acid (5 mL) in acetone (300 mL) during 5 hrs. Derivative 2 was converted into 3[7] according to the method of Hall et al.[8] in 89% yield. The reduction of the lactone function was accomplished in 5 hrs by $LiBH_4$[9] (3 g) in anhydrous THF containing 20 g of compound 3. In an equally good yield 4[10] was obtained (81%) after neutralization with 50% aqueous acetic acid, extraction with dichloromethane and washing with water. A solution of sodium methoxide (130 mL, 0.39 M) was added at a temperature of -15°C to the tosylate 4 (16.2 g, 43.3 mmol) which had been dissolved in 100 mL of methanol. The temperature was slowly raised to 20°C during 1 hr. Neutralization with CO_2 was followed by evaporation and dissolution of the epoxide 5[11] in acetone leaving the insoluble salts behind. After removing the solvent, 5 was redissolved in methanol (200 mL) and stirred at room temperature for 4 days in the presence of thiourea (3.6 g). After evaporating the reaction mixture the solid residue was taken up in dichloromethane and the solution filtered through celite. Removal of the solvent gives 6[3] quantitatively. The acetolysis of 6 was performed at 130°C during 36 hrs with a mixture of acetic acid and acetic anhydride (1:10 v/v, 110 mL) in the presence of sodium acetate (10 g). After evaporation, redissolution in dichloromethane, filtration through celite, decolorization with active charcoal, evaporation and crystallization from methanol, 3,6-di-O-acetyl-5-S-acetyl-1,2-O-isopropylidene-5-thio-α-D-glucofuranose (7)[3] was obtained in a yield of 77% based on compound 4.

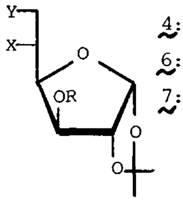
The isopropylidene 7 (2 g, 5.5 mmol) was hydrolyzed with 90% aqueous trifluoroacetic acid (100 mL) at room temperature during 20 min. 3,6-Di-O-acetyl-5-S-acetyl-5-thio-D-glucofuranose (8)[12] was recovered after complete drying of the reaction mixture. Compound 8, dissolved in 50 mL of methanol, was treated under nitrogen with a solution of sodium methoxide (0.1 M, 12 mL) to give the 5-thio-D-glucose 9 after crystallization from methanol in a 71% yield based on 7. The final product mp. 135-136°C, $[\alpha]_D$ +188 (c 1.04 water) is identical to an authentic sample (mp. 135°C, $[\alpha]_D$ +188)[7]. It was further characterized by its ^{13}C NMR spectrum which is in agreement with the litterature[13].



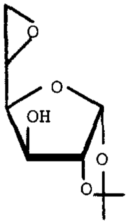
1



2 : R = H
3 : R = Ts



4: X=OTs ; Y=OH ; R=H
6: X,Y=S ; R=H
7: X=SAc ; Y=OAc ; R=Ac



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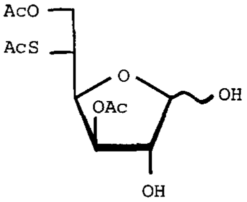

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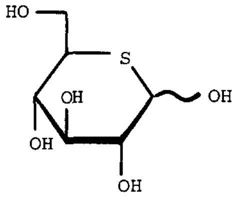

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12. 8, mp. 106-109°C, $[\alpha]_D$ +28 (c 1% chloroform), Anal. Calc. for $C_{12}H_{18}O_8S$: C, 44.71; H, 5.63; found : C, 44.86; H, 5.75.
    All other products have physical properties in accordance with published data.
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