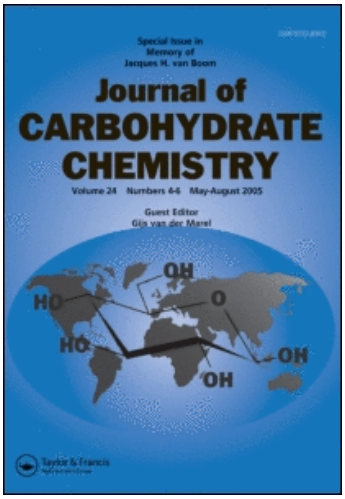

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Synthesis of Functionalized Thiodisaccharides by Conjugate Addition

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COMMUNICATION

SYNTHESIS OF FUNCTIONALIZED THIODISACCHARIDES BY CONJUGATE ADDITION

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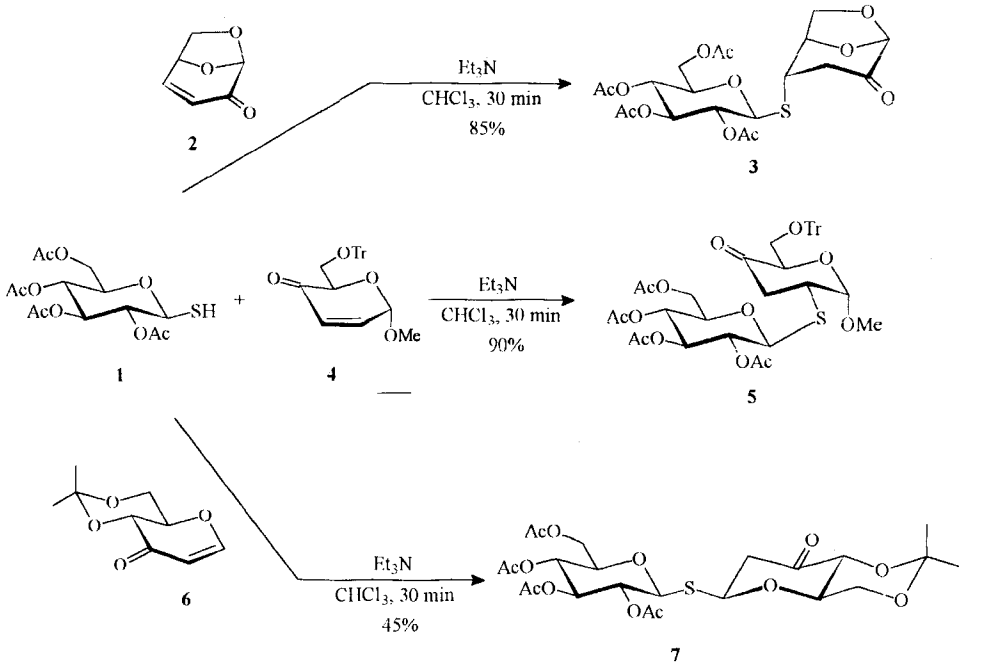
Oligosaccharides containing thioglycosidic linkages are resistant to enzyme-catalysed hydrolysis and therefore interesting material for studies of carbohydrate hydrolases. Some of these were shown to be competitive inhibitors for several glycanases such as α-amylase, [1] cellobiohydrolase I and II, [2] and for α-L-fucosidase, [3] a glycosidase. Thio-oligosaccharides have also been used to prepare column material for affinity chromatography to isolate carbohydrate hydrolases. In contrast, affinity material containing normal *O*-glycosidic bonds was hydrolysed and led to column deterioration. By employing this approach, affinity materials containing 1,4-dithiocellobiose and 1,4,4′-trithiocellotriose could be used successfully to separate the cellobiohydrolases of *Trichoderma reesei*.[2]

Whereas the standard synthesis of thio-oligosaccharides proceeds via a nucleophilic displacement, we now present a simple method for the preparation of functionalized thio-disaccharides by conjugate addition of 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucose (**1**)[4] to unsaturated carbohydrate derivatives. Thiols easily react with unsaturated acceptor systems in 1,4-additions as has been demonstrated in various examples. [5] The addition of alkyl thiols[6, 7] and thiophenol[8] to levoglucosenone (**2**) with triethylamine as catalyst has been reported to give excellent yields and recently the synthesis of a 1-thio-α-L-fucopyranoside has also been reported.[9]

The addition of 2,3,4,6-tetra-*O*-acetyl-1-thioglucose (**1**) to levoglucosenone[10] proceeds in chloroform solution with only traces of triethylamine as catalytic base[11] to yield 85% of the adduct **3**[12] after recrystallisation from toluene. Apparently, due to the steric hindrance created by the 1,6-anhydro bridge a nucleophilic attack is possible only from the opposite face of the molecule, thus forming the axial product exclusively.



Similarly, nucleophilic attack of **1** to hex-2-enopyranos-4-ulose **4**[13, 14] led to a single addition product **5**[12] in 90% yield after flash chromatography. In this case the bulky trityl group is assumed to prevent an attack from the upper side of **4** which could give the alternative axial addition product.

In the acceptor system of hex-1-enopyranos-3-ulose **6**, [14, 15] the addition of compound **1** led to the product **7**, [12] forming preferentially the β-thioglycosidic bond. The lower yield observed in the preparation of this trehalose type disaccharide **7** (45% after flash chromatography) is considered to be caused by the instability of the 2-deoxythioglycoside and competing retro reaction.

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11. Typical procedure: The saccharide acceptor (0.5 mmol) and the thioglucose (**1**, 200 mg, 0.57 mmol) were stirred in chloroform (10 mL) at room temperature and triethylamine (2 μL) was added. Stirring was continued for 30 min, the solvent evaporated and the raw material purified by crystallisation or chromatography.
12. Representative physical data:
    (**3**) mp 161-164 °C, $[\alpha]_D^{20}$ -125° (*c* 1, chloroform), ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.14 (s, 1 H, H-1), 4.59 (d, 1 H, $J_{1',2'}$ = 10.2 Hz, H-1'), 3.98-4.06 (m, 2 H, H-6*endo* and H-6*exo*), 3.58 (m, 1 H, H-4), 3.09 (dd, 1 H, $J_{3eq,4}$ = 8.1 Hz, J_{gem} = 17.8 Hz, H-3*eq*), 2.04 (dd, 1 H, $J_{3ax,4}$ = 1.5 Hz, H-3*ax*).
    (**5**) mp 56 °C, $[\alpha]_D^{20}$ +43° (*c* 1, chloroform), ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.99 (d, 1 H, $J_{1,2}$ = 4.4 Hz, H-1), 4.65 (d, 1 H, $J_{1',2'}$ = 10.1 Hz, H-1'), 4.11 (dd, $J_{5,6a}$ = 1.9 Hz, H-5), 3.43 (s, 3 H, OMe), 3.41 (dd, 1-H, J_{gem} = 9.2 Hz, H-6a), 3.32 (dd, 1 H, H-6b), 3.25 (dt, 1 H, $J_{2,3ax}$ = 8.2 Hz, H-2), 2.61 (m, 2 H, H-3*ax* and H-3*eq*);
    (**7**) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.16 (dd, 1 H, $J_{1,2ax}$ = 12.2 Hz, $J_{1,2eq}$ = 3.1 Hz, H-1), 4.65 (d, 1 H, $J_{1',2'}$ = 9.6 Hz, H-1'), 4.38 (d, 1 H, $J_{4,5}$ = 10.2 Hz, H-4), 4.06 (dd, 1 H, $J_{5,6a}$ = 5.6 Hz, J_{gem} = 10.2 Hz, H-6a), 3.94 (dd, 1 H, $J_{5,6b}$ = 10.2 Hz, H-6b), 3.59 (ddd, 1 H, H-5), 2.80 (dd, 1 H, J_{gem} = 14.8 Hz, H-2*ax*), 2.71 (dd, 1 H, H-2*eq*), 1.52 (s, 3 H, CH_3), 1.50 (s, 3 H, CH_3).
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