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# UNPRECEDENTED CHEMICAL GLYCOSIDATION OF 5-THIOGLUCOSE TO GIVE DISACCHARIDES.[1]

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**Abstract:** The glycosyl trichloroacetimidate of 2,3,4,6-tetra-O-acetyl-5-thioglucopyranose when used to glycosylate selectively protected glucopyranosyl acceptors with the 2-OH and 6-OH positions free affords the 1,2-linked and the 1,6-linked disaccharides as a 3:1 and 1.5:1 α:β mixture, respectively.

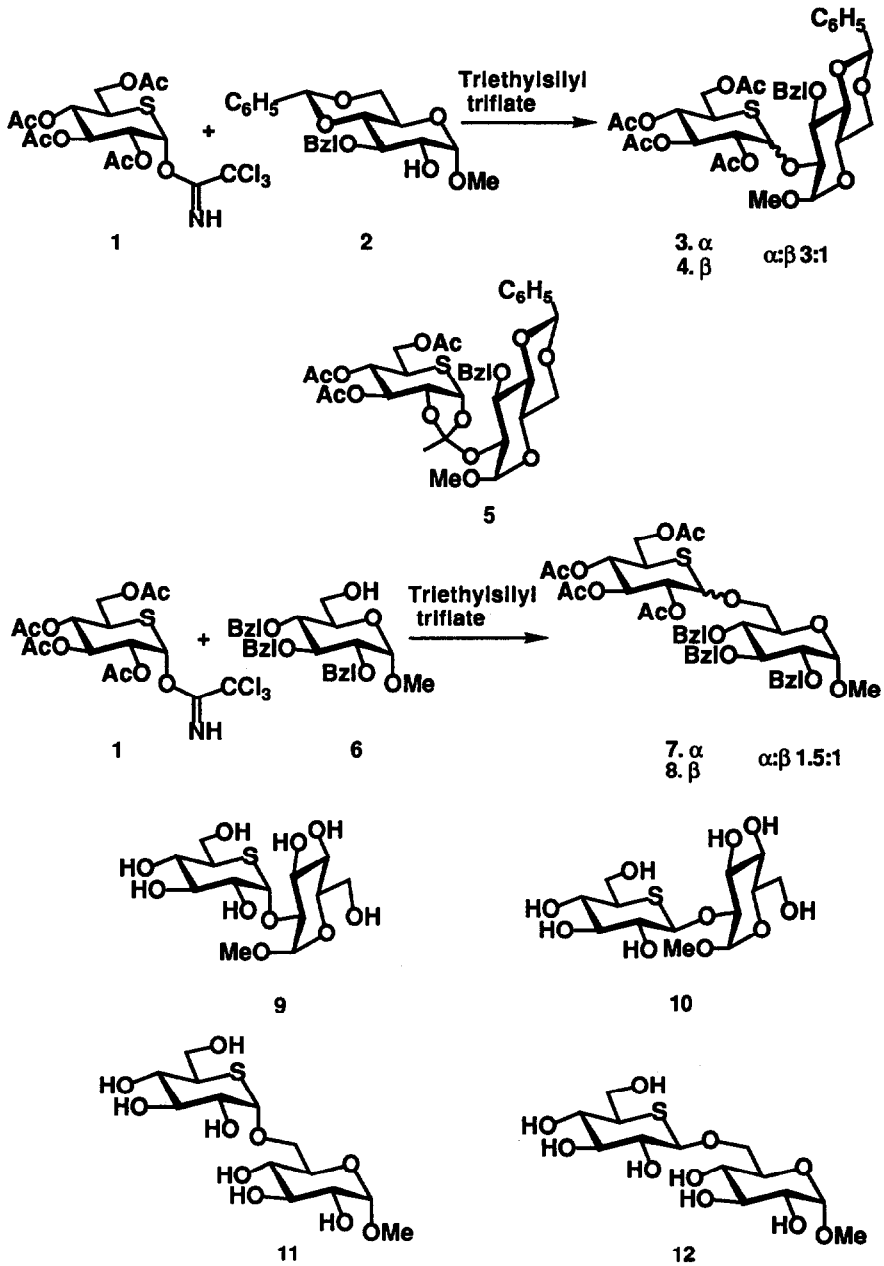
The design of reversible and irreversible inhibitors of glycoside hydrolysis and glycoprotein-processing enzymes continues to be an active area of research.[2] Much of the activity has centred on derivatives of nojirimycin and deoxynojirimycin, that is, compounds containing nitrogen in the sugar ring.[3] However, extension to derivatives containing sulfur in the sugar ring is somewhat limited. Most of the latter studies have dealt with the synthesis, reactions, conformational properties, enzyme complementarity, and biological activity of monosaccharide derivatives.[4,5] Two notable exceptions are the recently-reported enzymatic syntheses of disaccharides containing sulfur in the ring of the reducing[6] and non-reducing[7] monosaccharide units. We now report the first *chemical* glycosidation of 5-thioglucose to give disaccharides containing sulfur in the ring of the non-reducing unit. Hashimoto and co-workers have also recently disclosed their results on the chemical glycosidation of 5-thio-*L*-fucose[8] and the synthesis of 5′-thioisomaltoside via an acyclic precursor.[9]

Our initial efforts have focused on the use of the α-glycosyl trichloroacetimidate of 2,3,4,6-tetra-O-acetyl-5-thioglucopyranose. This hitherto unkown glycosyl donor **1** was prepared from the corresponding hemiacetal by treatment with potassium carbonate and trichloroacetonitrile.[10,11] The hemiacetal was obtained, in turn, by selective 1-O-deacetylation of the peracetylated sugar.[12] We realized that the presence of a participating group at C-2 of **1** might favour the formation of 1,2-trans products but were also aware of the possibility of the formation of the thermodynamically more stable product.[13] Precedent for preferential α-glycosidation of the α-glycosyl trichloroacetimidate of the oxygen analog is available.[17]

Glycosidation of the acceptor **2** (0.5 mmol)[18] with donor **1** (0.45 mmol) in dichloromethane (4 ml) containing 4Å molecular sieves, and with sequential addition of two aliquots of 0.1 equivalents of triethylsilyl triflate (-78 °C, 3.5 h) afforded the α- **3** and β- **4** disaccharides in 70% and 21% yield, respectively, as well as the 1,2-orthoester **5** in 3% yield.[19] The preponderance of the α-anomer is noteworthy, as is the formation of the orthoester **5**. Indeed, in a separate experiment employing three aliquots of 0.07 equivalents of acid, the orthoester **5** was isolated in 55% yield and the α- to β-disaccharide ratio was 10:1 (44%). The rearrangement of 1,2-orthoesters to give mixtures of 1,2-cis and 1,2-trans glycosides with certain alcohols and under certain conditions has been noted previously,[20] although the method has generally evolved to give highly stereoselective syntheses of 1,2-trans glycosides.[21]

Glycosidation of the more reactive acceptor **6**[22] with donor **1** gave a 1.5:1 α:β mixture of the 5′-thioisomaltosides **7** and **8** in 46% and 34% yield, respectively.[23]

The exact mechanism and the origin of the stereochemical outcome of the reactions described here is currently under investigation. It is likely that the α-stereoselectivity results from thermodynamic control in the glycosidation reaction.[13] It is noteworthy that Hashimoto and Isumi[8] have also observed a preference for 1,2-cis glycosidation with the glycosyl trichloroacetimidate of a 5-thio-*L*-fucose derivative containing a 2-acetoxy function, that is, a preference for the axial disposition of the aglycon.



The mixture of compounds **3** and **4** was treated with 80% aqueous acetic acid and then acetylated. The α and β disaccharides were separated and treated separately with Na/liquid $NH_3$ to afford the fully deprotected α-disaccharide **9** (a sulfur analog of methyl kojibioside) and the β-disaccharide **10**. Compounds **7** and **8** were separated and were debenzylated as above to give α- and β-linked disaccharides **11** and **12**, respectively.

The pioneering work of Whistler *et al*[4p-s] on the enzyme complementarity and biological activity of thio sugars containing sulfur in the ring was carried out on monosaccharide derivatives. The disaccharides with sulfur in the ring synthesized in the present study provide the next generation of candidates for evaluation as inhibitors of glucosidases and glycoprotein-processing enzymes as well as for probing the effects of glycosylation on metabolic pathways and the induction of disease states. The chemical glycosidation reaction developed here also provides a ready method for the introduction of 5-thioglucose into a variety of aberrant structures of biological interest.

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(11) $^1$H NMR (400 MHz): 1.99, 2.02, 2.05, 2.07 (4x3H, s, COC$H_3$), 3.63 (1H, m, H-5), 4.07 (1H, dd, $J_{5,6a}$= 3.0Hz, $J_{6a,6b}$= 12.1 Hz, H-6a), 4.39 (1H, dd, $J_{5,6b}$= 4.8 Hz, H-6b), 5.30 (1H, dd, $J_{1,2}$= 3.2, $J_{2,3}$= 10.0 Hz, H-2), 5.37 (1H, dd, $J_{3,4+4,5}$= 20.4 Hz, H-4) 5.56 (1H, t, $J_{2,3+3,4}$= 19.7 Hz, H-3), 6.34 (1H, d, $J_{1,2}$= 3.2 Hz, H-1), 8.68 (1H, s, OCN*H*CCl$_3$). $^{13}$C NMR (100 MHz): 75.8 ($J_{^{13}C\text{-}^1H}$= 167 Hz, C-1).

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(19) $^1$H NMR **3**: 4.77 (1H, d, $J_{1,2}$= 3.1 Hz, H-1), 5.05 (1H, d, $J_{1,2}$= 3.0 Hz, H-1′); **4**: 4.82 (1H, d, $J_{1,2}$= 3.5 Hz, H-1), 5.03 (1H, d, $J_{1,2}$= 8.5 Hz, H-1′); **5**: 1.73 (3H, s, C(OR)(OR′)(OR″)C$H_3$), 2.03 (3H, s, COC$H_3$), 2.07 (6H, s COC$H_3$), 4.80 (1H, d, $J_{1,2}$= 3.6 Hz, H-1), 5.35 (1H, d, $J_{1,2}$= 5.5 Hz, H-1′).
$^{13}$C NMR **5**: 121.9 (*C*(OR)(OR′)(OR″)CH$_3$).

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(23) $^1$H NMR **7**: 4.57 (1H, d, $J_{1,2}$= 3.5 Hz, H-1), 5.0 (1H, d, $J_{1,2}$= 3.0 Hz; H-1′); **8**: 4.58 (1H, d, $J_{1,2}$= 3.5 Hz, H-1), 4.59 (1H, d, $J_{1,2}$= 8.0 Hz, H-1′).

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