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A NEW, STEREOSELECTIVE SYNTHESIS OF METHYL 1,2-TRANS-1-THIOGLYCOSIDES*

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SUMMARY: Per-O-acetylated glycopyranoses were converted by methylthiotrimethylsilane in the presence of boron trifluoride or trimethylsilyl trifluoromethanesulfonate to the corresponding methyl 1,2-*trans*-1-thioglycopyranosides in a highly stereoselective process.

The synthetic potential of thioglycosides[1,2] has been dramatically increased by recent inventions of new methods for activation[3,4,5] of the anomeric thioalkyl group. Thus, they can be converted in a one-step reaction to oligosaccharides[3] and other complex natural products[1,5] or to 1-halo-1-deoxy derivatives[6] which are high-yielding glycosyl donors under catalysis by heavy-metal salts.[7]

1,2-*Trans*-thioglycosides may be synthesized by a variety of methods[8,9,10], of which the Lewis acid catalyzed reaction[8] between 1,2-*trans*-glycosyl acetates and thiols appears to be the most often used. However, due to undesired side-reactions (*inter alia* formation of the 1,2-*cis*-isomers[8] and dithioacetals[11]) this method gives yields which are not always satisfactory. A further disadvantage is the disagreeable odour during the operation.

The observation that a methylthio group can be transferred from methylthiotrimethylsilane (**1**) to an aldehyde or ketone carbonyl group in the presence of Lewis acid catalysts[12] prompted us to investigate the feasibility of such a transfer to the anomeric carbon atom of a carbohydrate-derived (di)oxocarbenium ion.[7] And indeed, we have found that under Lewis acid catalysis, reaction between **1** and per-O-acetylated glycopyranoses gives the corresponding methyl 1-thioglycopyranosides, in good to excellent yields.

In a typical experiment, a solution of 1,2,3,4,6-penta-O-acetyl-β-D-galactopyranose (1.28 mM) and **1** (3.2 mM) in CH_2Cl_2 (5 mL) was treated with $BF_3 \cdot Et_2O$ (200 μL of a 45% solution) at 20°C. Usual work-up gave methyl 2,3,4,6-tetra-O-acetyl-1-thio-β-D-galactopyranoside[13] in 84% yield. The procedure is equally useful for the preparation of other 1,2-*trans*-1-thioglycopyranosides (TABLE).

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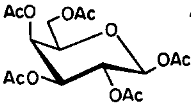
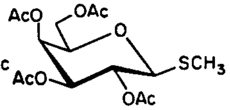
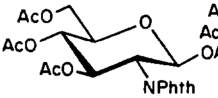
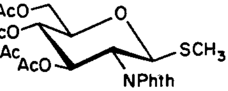
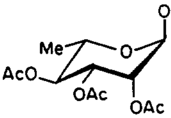
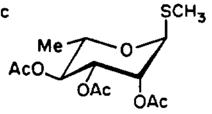
TABLE

Examples for 1,2-*trans*-1-thioglycoside synthesis by methylthio group transfer from $CH_3SSi(CH_3)_3$[a]

Acceptor	Product[b]	Catalyst	Reaction time (h)	Yield (%)	Mp. (degrees)	$[\alpha]_D$ ($CHCl_3$)	$\delta^c_{C_1}$ (ppm)	$J^c_{C_1-H_1}$ (Hz)
		BF_3	5	84	107-8[d]	+3 (c 2)[e]	83.27	153.5
		TMSTf[f]	48	93	153-4	+47 (c 1.5)	80.45	155.4
		BF_3	12	67	syrup[g]	-112 (c 3)	83.36	167.6

[a] Reactions were carried out in CH_2Cl_2 at 20°. [b] Products gave satisfactory elementary analysis. [c] At 300 K, 50 MHz, in $CDCl_3$. [d] Lit.[13] mp. 109°. [e] Lit.[13] $[\alpha]_D$ + 2.85. [f] Trimethylsilyl trifluoromethanesulfonate. [g] See Ref. 15.

In contrast to the thiolysis[8] of per-O-acetyl-glycopyranoses under catalysis by BF_3, formation of the 1,2-*cis* isomer was not observed in the procedure developed by us. This is indicative of the decreased nucleophilicity of the sulfur atom resulting in a more stereoselective attack on the anomeric carbon atom of the cyclic 1,2-O-dioxocarbenium ion, initially formed from the acetylated glycopyranoses under the influence of a Lewis acid.[14]

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14. H. Paulsen and M. Paal, *Carbohydr. Res.*, 135 53 (1984).
15. Methyl 2,3,4-tri-O-acetyl-α-L-1-thiorhamnopyranoside has been synthesized simultaneously and independently by Professor A. Lipták (Debrecen, Hungary) and by the present authors, using Ferrier's procedure.[8] These studies will be reported in due course.

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