Lauryl and Stearyl Thioglycosides: Preparation and Reactivity of the Glycosyl Donor

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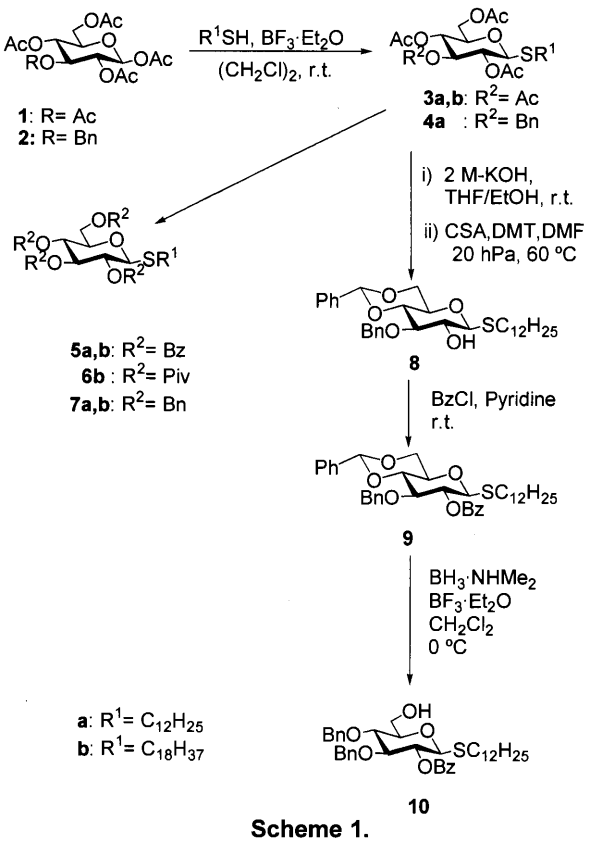
Lauryl and stearyl thioglycosides were prepared by the Lewis acid catalyzed reaction of 1-*O*-acetylated sugars with non-volatile and almost odorless 1-dodecanethiol and 1-octadecanethiol, respectively. These thioglycosides were activated by *N*-iodosuccinimide-TfOH to glycosyl donors producing disaccharides in good yields.

Thioglycosides are quite versatile intermediates in oligosaccharide synthesis due to their ease of preparation and activation by a potent thiophilic reagent that affords highly reactive glycosylating reagents.[1] Furthermore, a distinct advantage of the thioglycosides is that the hemithioacetal function can serve as a temporary protecting group stable under various conditions for chemical transformations of their hydroxyl groups.[2] Although the phenyl and ethyl thioglycosides are the most commonly used glycosyl donors, it is not easy to perform comfortably the preparation of these compounds using standard procedures even in a closed system or a well-organized draft chamber because of the pervasive stench of the volatile thiols. In this communication, we describe the preparation of the thioglycosides of almost non-volatile mercaptans and applicability to the glycoside synthesis.

In a similar way as described for the preparation of ethyl and phenyl thioglycosides,[3] pentaacetyl-β-D-glucopyranose **1** and its 3-*O*-benzyl derivative[4] **2** were treated with 2 molar equivalents of 1-dodecanethiol (bp = 266 °C) and 1-octadecanethiol (mp = 18-20 °C) in the presence of $BF_3{\cdot}OEt_2$ (1 equiv) in 1,2-dichloroethane. The reactions completed at room temperature for 30 min to give the corresponding thioglycosides[5] (**3a, 3b, 4a**) in almost quantitative yields. This reaction was applicable to such disaccharides as fully acylated lactose and laminaribiose without cleavage of their glycosidic bonds. After Zemplèn deacetylation of **3a** and **3b**, the resulting tetraols were treated with benzoyl chloride or pivaloyl chloride in pyridine, thus giving the fully acylated thioglycosides[5] (**5a, 5b, 6b**) in more than 90% overall yields. However, conventional benzylation of the thioglycosides in DMF was unsuccessful, since aggregation of the starting material occurred during the reaction. This problem was overcome by carrying out the reaction under less polar conditions. Thus, benzylation of the lauryl thioglucoside with benzyl bromide-NaH in DMF-THF (2:1) and phase-transfer benzylation[6] of the stearyl thioglucoside in CH_2Cl_2-aq NaOH afforded the corresponding perbenzylated derivatives[5] (**7a**, **7b**) in 64% and 77% yield, respectively.

Next, applicability to various chemical modifications was examined, employing the lauryl thioglucoside **4a** as the model compound. Saponification of **4a** in aq KOH gave a lipophilic triol, which was isolated by usual extractive work-up in chloroform. The resulting triol was treated with α,α-dimethoxytoluene (DMT) in DMF in the presence of camphorsulfonic acid (CSA) to give the 4,6-*O*-benzylidene derivative **8**, of which the 2-hydroxyl group was benzoylated in a one-pot manner to give the fully protected derivative[5] **9** in 74% overall yield from **4a**. By reductive ring opening of the benzylidene group with $BH_3{\cdot}NHMe_2$-$BF_3{\cdot}OEt_2$[7] in CH_2Cl_2, **9** was converted into the 3,4-di-*O*-benzyl derivative[5] **10**. These results suggested that most of the conventional methods for the protection of the hydroxyl groups of the monosaccharides were applicable to these amphiphilic thioglycosides.



Scheme 1.

Next, our interest focused on the behavior of these lauryl and stearyl thioglycosides during the glycosylation reaction. Upon activation with *N*-iodosuccinimide (NIS)-TfOH[8] in CH_2Cl_2 in the presence of molecular sieves 4A (MS 4A) at –20 °C for 20 min, the thioglycosides (**3ab, 5ab, 6b, 7ab**) were reacted with methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside **11** to give the disaccharides[5] **12**. These results are summarized in Table 1. As expected, the acyl protecting donors predominantly afforded the β-linked disaccharides, i.e., cellobiose derivatives. Among several thioglycosides, the best results were obtained when we used the fully benzoylated lauryl thioglucoside **5a**. It produced the disaccharide **12** (R^2 = Bz) in greater

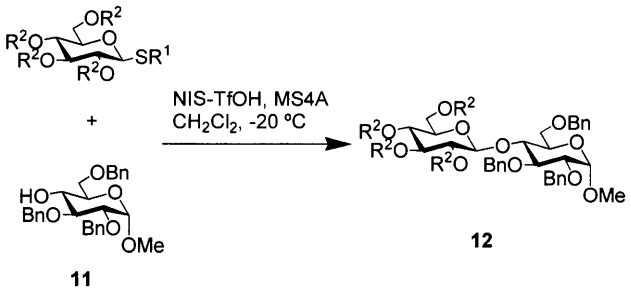


Table 1. Glycosidation of lauryl and stearyl thioglycosides[a]

Thioglycoside R^1	R^2		Solvent	Disaccharide **12** Yield / %		$[\alpha]_D$
Lauryl $C_{12}H_{25}$	Ac	**3a**	CH_2Cl_2	35	(β)	
	Bn	**7a**	CH_2Cl_2	71	(α:β = 63:37)	
	Bn	**7a**	Et_2O	58	(α:β = 70:30)	
	Bn	**7a**	CH_3CN	43	(α:β = 29:71)	
	Bz	**5a**	CH_2Cl_2	94	(β)	
Stearyl $C_{18}H_{37}$	Ac	**3b**	CH_2Cl_2	60	(β)	-5.6°
	Bn	**7b**	CH_2Cl_2	52	(α:β = 63:37)	
	Piv	**6b**	CH_2Cl_2	68	(β)	-2.5°
	Bz	**5b**	CH_2Cl_2	64	(β)	+0.8°

[a]All reactions were performed by use of 1.2 molar equivalents of the acceptor **11** at –20 °C in the presence of NIS-TfOH as the promoter.

than 94% yield.[9] In contrast to this, the reactions with the stearyl thioglycosides (**5b** and **6b**) formed highly viscous suspension, which prevented the smooth reaction. The acetates **3ab** were rapidly consumed during the reaction and TLC showed several decomposed products, one of which was identified as *O*-acetylated acceptor.[10] Furthermore, similar reaction of the *O*-benzylated donors **7ab** in CH_2Cl_2 gave an anomeric mixture of disaccharides with an α/β ratio of 63:37. Although poor yields of the reaction in MeCN and Et_2O were probably due to production large amount of insoluble materials, the solvent effects on the α/β ratio shown in Table 1 were quite interesting.

A typical procedure is as follows. To a suspension of lauryl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside **5a** (241 mg, 0.31 mmol), **11** (184 mg, 0.40 mmol), NIS (72 mg, 0.32 mmol), and MS 4A (ca. 300 mg) in CH_2Cl_2 (10 mL) with stirring at –20 °C was added TfOH (3 μL). After stirring at the same temperature for 20 min, pyridine (2 mL) and aq $Na_2S_2O_3$ were successively added to quench the reaction. The mixture was filtered though a Celite pad, and the filtrate was washed with brine, dried over anhydrous $MgSO_4$, and evaporated. Column chromatography on silica gel using hexane-EtOAc (10:1) gave a β-linked disaccharide (301 mg, 94%).

Further studies of the synthetic application using the lauryl thioglycosides are now in progress.

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5 All new compounds gave satisfactory spectral data and elemental analyses. Selected physical data. **3a**: ^{1}H NMR ($CDCl_3$) δ_H 4.48 (d, 1H, *J* = 10.0 Hz, H-1), $[\alpha]_D$ –29.2° (*c* 0.12, $CHCl_3$); **3b**: δ_H 4.48 (d, 1H, *J* = 10.0 Hz, H-1), $[\alpha]_D$ –25.4° (*c* 0.55); **4a**: δ_H 4.38 (d, 1H, *J* = 10.0 Hz, H-1), $[\alpha]_D$ –22.2° (*c* 0.30); **5a**: δ_H 4.84 (d, 1H, *J* = 10.0 Hz, H-1), $[\alpha]_D$ +12.4° (*c* 1.70); **5b**: δ_H 4.85 (d, 1H, *J* = 9.9 Hz, H-1), $[\alpha]_D$ +11.4° (*c* 0.42); **6b**: δ_H 4.49 (d, 1H, *J* = 10.0 Hz, H-1), $[\alpha]_D$ –22.6° (*c* 0.87); **7a**: δ_H 4.44 (d, 1H, *J* = 9.7 Hz, H-1), $[\alpha]_D$ +5.8° (*c* 0.58); **7b**: δ_H 4.43 (d, 1H, *J* = 9.7 Hz, H-1), $[\alpha]_D$ –1.1° (*c* 0.18); **9**: δ_H 4.60 (d, 1H, *J* = 10.1 Hz, H-1), $[\alpha]_D$ +13.0° (*c* 0.15); **10**: δ_H 4.56 (d, 1H, *J* = 10.0 Hz, H-1).

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