Direct Formation of β-Mannopyranosides and Other Hindered Glycosides from Thioglycosides

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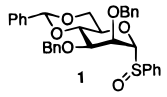
Recently, we introduced a protocol for the direct synthesis of β-mannopyranosides in which a sulfoxide donor (**1**) is treated



with triflic anhydride (Tf_2O), in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) at −78 °C, to give a highly reactive glycosyl donor. Subsequent addition of the glycosyl acceptor provides high yields of the β-mannoside.[1,2] A series of chemical and spectroscopic investigations with the model sulfoxide **2** inexorably led us to the conclusion that the active glycosyl donor, in this extension of Kahne's sulfoxide glycosylation protocol,[3,4] is the α-mannosyl triflate **3** (Scheme 1).[5] Moreover, we demonstrated that the same intermediate (**3**), with the same reactivity, is produced on treatment of a glycosyl bromide (**4**) with silver triflate (Scheme 1). Further consideration of the mechanism of this reaction, especially the fact that substoichiometric Tf_2O brings about complete consumption of the sulfoxide,[5,6] led us to the realization that the initial byproduct, benzenesulfenyl triflate (PhSOTf), is itself a very powerful electrophile toward the sulfoxide. Indeed, it was readily demonstrated that authentic PhSOTf[7,8] converts glycosyl sulfoxides to triflates cleanly in CH_2Cl_2 at −78 °C.[5] The efficiency of the sulfoxide glycosylation method is such that the most problematic step is often the controlled oxidation of a thioglycoside to the requisite sulfoxide, which requires careful control of stoichiometry, and temperature, as well as continuous monitoring by TLC.[4,9] Indeed, this step promises to be problematic in any future development of solid phase glycosylation protocols involving resin-bound sulfoxide glycosyl donors. This impending problem and the evident, highly electrophilic nature of PhSOTf prompted us to investigate the potential activation of simple thioglycosides by this reagent. We report here that simple thioglycosides are indeed rapidly and cleanly converted to glycosyl triflates by treatment with PhSOTf at low temperature. Moreover, the method is very useful for the formation of β-mannosides and other hindered glycosides and eliminates the need for the oxidation of thioglycosides to sulfoxides before coupling.

In an exploratory NMR tube experiment, a CD_2Cl_2 solution of thioglycoside **5** and DTBMP was cooled to −78 °C and treated with a −78 °C CD_2Cl_2 solution of PhSOTf, formed in situ from AgOTf and PhSCl according to Whitesides and Martichonok.[7]

Scheme 1

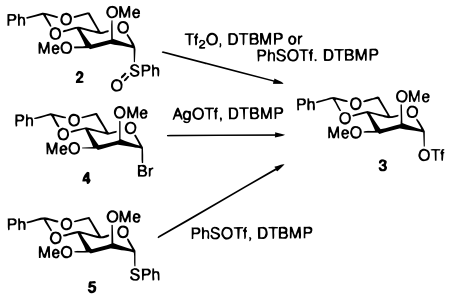
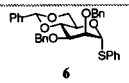
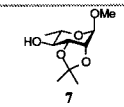
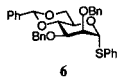
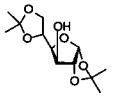
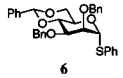
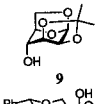
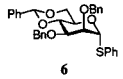
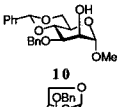
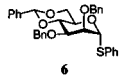
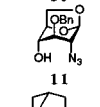
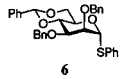
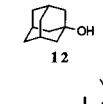
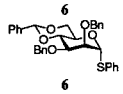
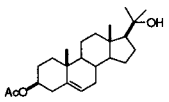
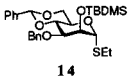
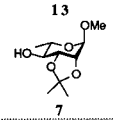


Table 1. β-Mannoside Formation[a]

Entry	Glycosyl Donor	Glycosyl Acceptor	Yield (%)	β:α Ratio
1			95	>25:1
2			95	>25:1
3			95	23:1
4			97	18:1
5			85	5.1:1
6			94	>25:1
7			90	>25:1
8			80	10:1

[a] All reactions were conducted in dichloromethane.

The tube was immediately inserted into the precooled (−78 °C) probe of the spectrometer, and ^1H and ^{19}F NMR spectra were recorded. Pleasingly, it was at once evident that **5** was converted quantitatively to the same intermediate (**3**) obtained previously from exposure of the sulfoxide to Tf_2O or PhSOTf, or of the bromide to AgOTf (Scheme 1). Thus reassured, we conducted a series of reactions on a more preparative scale as reported in Table 1. The isolated yields and β:α ratios obtained were almost uniformly excellent. With donor **6** and typical carbohydrate acceptors (Table 1, entries 1−4) both the yield and β:α ratio compared well with those obtained for the analogous disaccharides by the sulfoxide method.[2] Even with the 1,6-anhydroglucosamine derivative **11** a satisfactory 85% yield of a workable 5.1:1 β/α mixture was obtained (Table 1, entry 5). Entries 6 and 7 of Table 1 indicate that this method may even be used for the very efficient β-mannosylation of tertiary alcohols. To our knowledge these are the first examples of the clean formation of tertiary β-mannopyranosides by any method. With the more sterically hindered donor **14**, yield and selectivity, although still useful, were somewhat reduced (compare Table 1, entries 1 and 8). As

(1) Crich, D.; Sun, S. *J. Org. Chem.* **1996**, *61*, 4506−4507.
(2) Crich, D.; Sun, S. *J. Org. Chem.* **1997**, *62*, 1198−1199.
(3) Kahne, D.; Walker, S.; Cheng, Y.; Engen, D. V. *J. Am. Chem. Soc.* **1989**, *111*, 6881−6882.
(4) Yan, L.; Kahne, D. *J. Am. Chem. Soc.* **1996**, *118*, 9239−9248.
(5) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11217−11223.
(6) Raghavan, S.; Kahne, D. *J. Am. Chem. Soc.* **1993**, *115*, 1580−1581.
(7) Martichonok, V.; Whitesides, G. M. *J. Org. Chem.* **1996**, *61*, 1702−1706.
(8) Effenberger, F.; Russ, W. *Chem. Ber.* **1982**, *115*, 3719−3736.
(9) Kakarla, R.; Dulina, R. G.; Hatzenbuhler, N. T.; Hui, Y. W.; Sofia, M. J. *J. Org. Chem.* **1996**, *61*, 8347−8349.

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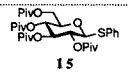
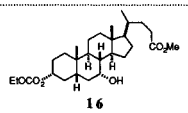
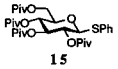
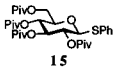
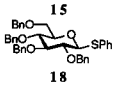
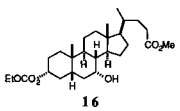
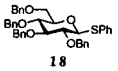
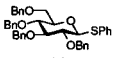
Table 2. Formation of Hindered Glucosides[a]

Entry	Glycosyl Donor	Glycosyl Acceptor	% Yield α-glucoside	% Yield β-glucoside
1[b]	 **15**	 **16**	0	61
2	 **15**	 **17**	49	37
3	 **15**	 **12**	0	84
4[c]	 **18**	 **16**	85	0
5	 **18**	 **17**	67	26
6	 **18**	 **12**	0	93

[a] Unless otherwise noted all reactions were conducted in dichloromethane. [b] Reaction conducted in 1:1 dichloromethane/diethyl ether. [c] Reaction conducted in diethyl ether.

previously noted for reactions with the analogous sulfoxides, this fall off in yield and selectivity probably reflects the fine balance between associative and dissociative displacement mechanisms of the intermediate α-mannosyl triflates.[2,5]

Of course, this new glycosylation protocol is not limited to the preparation of β-mannopyranosides. Table 2 sets out several examples of glucoside formation using a disarmed (**15**) and an armed (**18**) thioglucoside as donor.[10] The acceptors are chosen for ease of comparison of the new method with the sulfoxide protocol.[3,11] Of the six examples presented in Table 2, four require comment; otherwise the results are directly analogous to those reported previously for the sulfoxide method. With the highly hindered sterol **16**, thioglycoside **15** gave 61% of a pure β-glucoside when the reaction was run in CH_2Cl_2/Et_2O (Table 2, entry 1). In either pure Et_2O or pure CH_2Cl_2 the yield in this last example was considerably lower owing to the low solubility of one or other of the two reaction partners in one of the two solvents. This observation prompts us to stress the importance of choosing a solvent that dissolves both reaction partners and the intermediate triflate at the low temperatures used. This is particularly important in the case of β-mannoside formation when an inappropriate choice of solvent can prevent coupling until the acceptor dissolves on warming, when reduced yields and selectivities are observed. Coupling of the perpivaloyl thioglycoside **15** and 2,6-dimethylphenol (**17**) under the influence of PhSOTf gave 49% of the α- and 37% of the β-glycoside (Table 2, entry 2). This result differs somewhat from the analogous coupling achieved by the sulfoxide method when an 80% yield of a pure β-glucoside was reported. This difference must reflect minor variations in temperature and concentration and so changing influences of triflates, ion pairs, and neighboring group participation on the actual glycosylation subsequent to the initial formation of glucosyl triflates. Finally, we note that the tertiary alcohol **12** could be coupled to either an armed or disarmed thioglucoside in excellent yield and complete β-selectivity (Table 2, entries 3 and 6). These results correspond to those described by Kahne for tertiary alcohols by the sulfoxide method[11] and presumably reflect the increased influence of 1,3-diaxial interactions in the formation of α-glycosides with tertiary alcohols.

It is appropriate to note that methylsulfenyl triflate (MeSOTf) has previously been described as a reagent for the activation of thioglycosides;[12,13] however, it has not been widely adopted. Indeed, MeSOTf has been found to be less satisfactory than PhSOTf for the activation of glycosyl xanthates.[7] Likewise, benzeneselenenyl triflate (PhSeOTf) has been recorded as a reagent for the activation of thioglycosides.[14] In our hands exposure of thioglycoside **5** to PhSeOTf in CD_2Cl_2 at −78 °C did not result in the formation of triflate **3** as determined by NMR spectroscopy. Rather an unidentified species was formed which returned the thioglycoside on exposure to MeOH at −78 °C: PhSeOTf is therefore less efficient than PhSOTf for the activation of thioglycosides at low temperature.

In conclusion, PhSOTf is a convenient reagent for the in situ fomation of glycosyl triflates from thioglycosides.[15] Highly hindered alcohols may be glycosylated in this manner without the need for prior activation of the thioglycoside as a sulfoxide. With the correct choice of protecting groups β-mannopyranosides may be formed in excellent yield and selectivity by this reaction.

Acknowledgment. We thank the NSF (Grant CHE 9625256) for support of this work.

Supporting Information Available: Lists of spectral data for those disaccharides not previously reported in ref 2 (8 pages). See any current masthead page for ordering and Internet access instructions.

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(10) In the terminology of Fraser-Reid and co-workers, armed and disarmed glycosyl donors are more or less activated, respectively, toward glycosylation by virtue of the properties of their protecting groups: Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583−5584.

(11) Yan, L.; Kahne, D. *Synlett* **1995**, 523−524.

(12) Birberg, W.; Lonn, H. *Tetrahedron Lett.* **1991**, *32*, 7453−7456.

(13) Dasgupta, F.; Garegg, P. J. *Carbohydr. Res.* **1990**, *202*, 225−238.

(14) Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1988**, *29*, 1061−1064.

(15) **General Experimental Protocol**. To a stirred solution of AgOTf (83 mg, 0.324 mmol) under a nitrogen atmosphere in the chosen solvent (1.5 mL) at −78 °C is added a solution of PhSCl (39 mg, 0.27 mmol) in the same solvent (1.5 mL). After the resulting solution is stirred for 5 min at −78 °C, a solution of the thioglycoside (0.11 mmol) and DTBMP (67 mg, 0.33 mmol) in the same solvent is added dropwise. After the resulting solution is stirred for a further 5 min at that temperature the glycosyl acceptor (0.22 mmol) is added dropwise in the same solvent (1.5 mL). The reaction mixture is then allowed to warm to −20 °C over 40 min before being quenched with saturated aqueous $NaHCO_3$, and filtered through Celite. The filtrate is washed with brine, dried (Na_2SO_4), and concentrated under vacuum, and the disaccharides are isolated by chromatography on silica gel. The excess acceptor may also be recovered by chromatography.