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Sequential One-Pot Glycosylations Using 1-Hydroxyl and 1-Thiodonors

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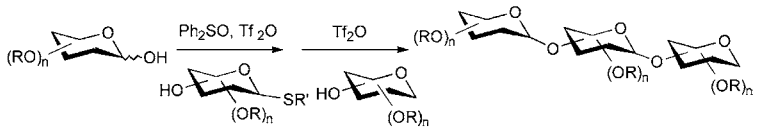
ABSTRACT



A novel sequential glycosylation procedure is described that combines the use of 1-hydroxyl and thiodonors. The Ph_2SO/Tf_2O-mediated dehydrative condensation of 1-hydroxyl donors with thioglycosides affords in good yield the thiodisaccharides, which in turn can be activated by the same activator system to furnish trisaccharides. The α-Gal epitope and a hyaluronan trisaccharide were efficiently assembled in a one-pot procedure.

The development of new and efficient strategies for the assembly of oligosaccharides and glycoconjugates is an intensive field of research.[1] The synthesis of oligosaccharides is traditionally a time-consuming process, mainly due to the extensive need for protective group manipulations. The majority of contemporary research in this field is therefore focused on the development of glycosylation approaches in which the number of synthetic and purification steps is reduced. Recent solution-phase methodologies that omit the need for the intermediate installation of a suitable anomeric leaving group and/or protecting group manipulations include chemoselective,[2] orthogonal,[3] iterative,[4] and one-pot glycosylations.[5] The rate of success of these methodologies is highly dependent on the selected glycosylation procedure. In this framework, our attention was attracted by the work of the groups of Gin and Crich, who developed two new sulfonium activator systems (**2a** and **2b** in Figure 1) for the activation of 1-hydroxy[6] and thiodonors,[7] respectively.

We recently established[8] that **2a** and **2b** can be implemented in a sequential glycosylation procedure in which

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(3) (a) Tanaka, H.; Adachi, M.; Tsukamoto, H.; Ikeda, T.; Yamada, H.; Takahashi, T. *Org. Lett.* **2002**, *4*, 4213−4216. (b) Demchenko, A. V.; Malysheva, N. N.; De Meo, C. *Org. Lett.* **2003**, *5*, 455−458.

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(5) (a) Burkhart, F.; Zhang, Z.; Wacowich-Sgarbi, S.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1274−1277. (b) Mong, K.-K. T.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2002**, *41*, 4087−4090. (c) Mong, K.-K. T.; Lee, H.-K.; Durón, S. G.; Wong, C.-H. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 797−802.

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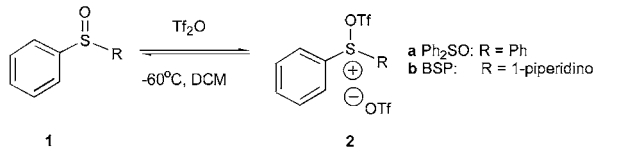
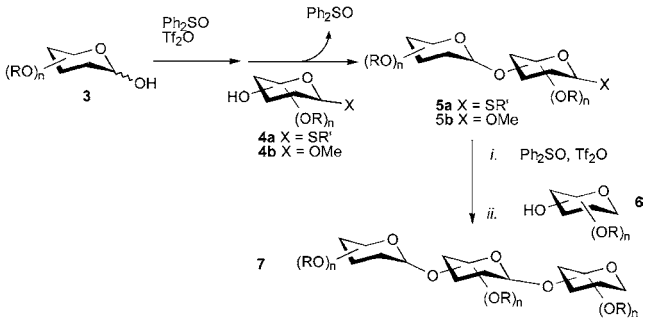


Figure 1. Sulfonium activator systems used for the activation of 1-hydroxyl and thiodonors.

armed and disarmed thiodonors are activated by **2b** and condensed with a highly disarmed thioglycoside. The resulting thiodisaccharide can now be activated by the relatively more potent promotor **2a** in the next glycosylation event. Although this coupling sequence broadened the scope of chemoselective glycosylations toward highly disarmed thioglycosides, it is only applicable in assembly protocols using donor glycosides in order of decreasing reactivity.[9] Evidently, glycosylation procedures that are independent of the reactivity of the donor building blocks would be more generally applicable. We therefore turned our attention to the use of 1-hydroxyl donors, in combination with thiodonors, which are both readily activated by sulfonium species **2a**.[10] We reasoned that preactivation of hemiacetal donor **3** and condensation with acceptor thioglycoside **4a** would give the thiodisaccharide **5a** with the concomitant regeneration of diphenylsulfoxide as a neutral side product (Scheme 1).[6] In

Scheme 1. Sequential Glycosylation Strategy Using 1-Hydroxyl and Thiodonors



the subsequent **2a**-mediated glycosylation, trisaccharide **7** can then be constructed from thiodisaccharide **5a** and terminal building block **6**. Herein we describe the development of this novel glycosylation sequence combining 1-hydroxyl and thio donors[11] that (1) employs a single activator system, i.e., diphenylsulfide bis(triflate) **2a**, (2) allows any protecting group pattern on both donor and acceptor coupling partner, and (3) can be employed in a one-pot glycosylation procedure.

In Gin's original dehydrative protocol, the 1-hydroxyl donor **3** is condensed using an excess of acceptor **4b** (1.5−3.0 equiv) as well as activating agent **2a** (1.4 equiv) to give dimer **5b** (Scheme 1). We anticipated that the presence of excess **2a** in our intended sequential strategy may lead to unwanted activation of the thioglycoside **4a**. It is also not excluded[12] that the excess of **2a** can react with the free hydroxyl group in acceptor **4a**.[13] It turned out that activation of the incoming thioglycoside could be virtually suppressed by the use of a slight excess of activator **2a** (1.1 equiv) with respect to the 1-hydroxyl donor, which in turn is employed in excess to the thioglycosidic acceptor. For example, activation of armed donor **8** (1.2 equiv) with Ph_2SO/Tf_2O in the presence of TTBP (2,4,6-tri-*tert*-butylpyrimidine)[14] and condensation with the unreactive OH-4 of the armed thioglycosiode **12** (1.0 equiv) gave thiodisaccharide **16** as an anomeric mixture in excellent yield (Table 1, entry 1). It is also of interest to note that disarmed donor **9** was efficiently condensed under the same conditions with armed acceptor **13** to give ortho ester **17** in good yield (entry 2). Ortho ester formation could also not be prevented[15] in the condensation of the pivaloylated glucose donor **10** and acceptor **13** (entry 2). On the other hand, the β-linked disaccharide **19** was readily obtained by using an equimolar amount of base (entry 3). Finally, the potency of this procedure is illustrated by the finding that furanosyl donor[6b] **11** could be used for the condensation with both thio and selenoglycoside acceptors[16] to afford the expected β-linked disaccharides **20** and **21**, respectively, in a satisfactory yield (entries 4 and 5).

We next turned our attention to the implementation of the aforementioned coupling procedure in the synthesis of biologically relevant trisaccharides. As a first example, we focused on the α-Gal epitope, α-D-Gal-(1→3)-β-D-Gal-(1→4)-β-D-GluNAc-OR, which is responsible for the antibody-mediated hyperacute rejection in xenotransplantations.[17] We selected the fully protected α-Gal epitope **26**,[18] having an azidopropyl spacer at the reducing end, as the target compound (Scheme 2a). The glycosylation sequence com-

(8) Codée, J. D. C.; Litjens, R. E. J. N.; Den Heeten, R.; Overkleeft, H. S.; van Boom, J. H.; van der Marel, G. A. *Org. Lett.* **2003**, *5*, 1519−1522.

(9) It was shown that the transiently formed (*N*-piperidino)phenyl(*S*-thiophenyl)sulfide triflate, generated by the activation of an anomeric phenyl thio function with BSP/Tf_2O, could activate thioglycosides. See also ref 5c.

(10) BSP/Tf_2O can also be used to activate 1-hydroxyl donors. Condensation reactions using this activator system, however, require higher reaction temperatures as compared to the Ph_2SO/Tf_2O-activated systems.

(11) For a sequential glycosylation procedure using trichloroacetimidates and thioglycosides, see: (a) Yamada, H.; Harada, T.; Takahashi, T. *J. Am. Chem. Soc.* **1994**, *116*, 7919−7920. (b) Yamada, H.; Harada, T.; Miyazaki, H.; Takahashi, T. *Tetrahedron Lett.* **1994**, *35*, 3979−3982. (c) Yu, B.; Hui, H.; Han, X. *Tetrahedron Lett.* **1999**, *40*, 8591−8594.

(12) The successful outcome of a condensation reaction, in which the donor and acceptor are premixed before activation, is determined by the relative nucleophilicities of the anomeric donor function, the anomeric acceptor function, and the free hydroxyl group in the acceptor. See also refs 5c and 13.

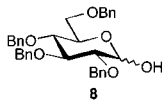
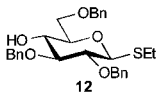
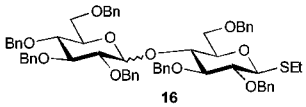
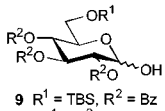
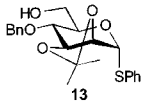
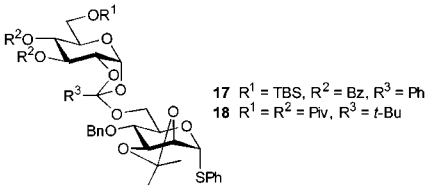
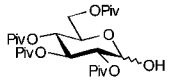
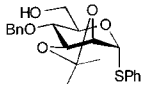
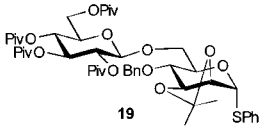
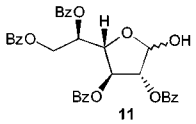
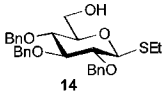
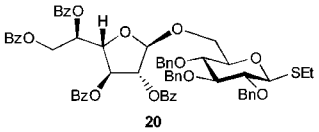
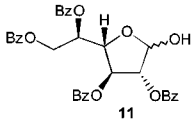
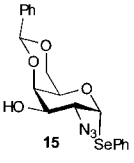
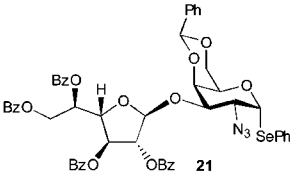
(13) Occurrence of this possibility is endorsed by the following experiment: premixing the disarmed thiodonor ethyl 2,3,4,6-tetra-*O*-benzoyl-1-thioglucopyranoside and the reactive acceptor α-*O*-methyl-2,3,4-tri-*O*-benzyl glucose and subsequent treatment of this mixture with 1.0 equiv of the less reactive **2b** led to quantitative recovery of the donor glycoside and isolation of the acceptor-6-*O*-benzenesulfinyl piperidine triflate adduct in 96% yield.

(14) Crich, D.; Smith, M.; Yao, Q.; Picione, J. *Synthesis* **2001**, 323−326.

(15) Although ortho ester formation rarely occurs when pivaloyl groups are employed, it has been reported before: Plante, O. J.; Palmacci, E. R.; Andrade, R. B.; Seeberger, P. H. *J. Am. Chem. Soc.* **2001**, *123*, 9545−9554.

(16) Mehta, S.; Pinto, B. M. *J. Org. Chem.* **1993**, *58*, 3269−3276.

Table 1. Dehydrative Glycosylations Using 1-Hydroxyl Donors and Thioglycoside Acceptors[a]

entry	donor	acceptor	disaccharide	yield (α/β)
1	 **8**	 **12**	 **16**	87% (3/1)[b]
2	 **9** R^1 = TBS, R^2 = Bz **10** $R^1 = R^2$ = Piv	 **13**	 **17** R^1 = TBS, R^2 = Bz, R^3 = Ph **18** $R^1 = R^2$ = Piv, R^3 = *t*-Bu	**17**: 81% **18**: 85%[c]
3	 **10**	 **13**	 **19**	80%[c,d]
4	 **11**	 **14**	 **20**	68%[c]
5	 **11**	 **15**	 **21**	56%[c]

[a] Typically, the 1-hydroxyl donors (1.2−1.5 equiv with respect to the acceptor) were preactivated by Ph_2SO (2.2 equiv with respect to the donor) and Tf_2O (1.1 equiv with respect to the donor) in the presence of TTBP (2.5 equiv with respect to the donor), followed by addition of the acceptor. [b] Anomeric ratio determined from anomeric mixture by ^{1}H NMR analysis. [c] Used 1.5 equiv of glycosyl donor. [d] TTBP was used in an equimolar amount with respect to the donor glycoside.

mences with the diphenylsulfide bis(triflate) **2a**-mediated dehydrative condensation of the 1-hydroxyl galactose donor **22** and thiogalactose acceptor **23** to provide the α-linked galactose dimer **24** as the sole product in 64% yield. In the next coupling event, promotor **2a** was employed to activate the anomeric thio function in disaccharide **24**. Reaction of the activated dimer and the glucosamine building block **25** proceeded smoothly to afford target trisaccharide **26**. With these results in hand, we were anxious to find out whether the assembly of trisaccharide **26** could also be attained in a one-pot procedure (Scheme 2b). To this end, hemiacetal **22** was activated by Ph_2SO/Tf_2O and condensed with thiogalactoside **23** leading to dimer **24** and the concomitant regeneration of Ph_2SO. At this stage, activation of intermediate **24** was effected by adding triflic anhydride to the reaction mixture. Subsequent condensation with building block **25** led to the one-pot construction of the α-Gal epitope **26** in a very rewarding yield of 80%.

A second touchstone for the developed sequential glycosylation procedure was found in the synthesis of a hyaluronan trisaccharide **31**. Hyaluronan, involved in the regulation of a variety of biological processes such as cell−cell recognition, cell migration, cell adhesion, and cellular proliferation,[19] is a challenging synthetic target.[20] In particular, the condensation of highly disarmed glucuronic acid building blocks such as **27** is notoriously difficult.[21,22] Accordingly, the synthesis of trisaccharide **31** was undertaken as outlined in

(17) (a) α-*Gal and Anti-Gal in Subcellular Biochemistry*; Galili, U., Avila, J. L., Eds.; Kluwer Academic/Plenum Publishers: New York, 1999; Vol. 32. (b) Galili, U. *Sci. Med.* **1998**, *5*, 29−51. (c) Cooper, D. K. C. *Clin. Trans.* **1992**, *6*, 178−183. (d) Cooper, D. K. C.; Good, A. H.; Koren, E.; Oriol, R.; Malcolm, A. J.; Ippolito, R. M.; Neethling, F. A.; Ye, Y.; Romano, E.; Zhudi, N. *Transplant Immunol.* **1993**, *1*, 198−205.

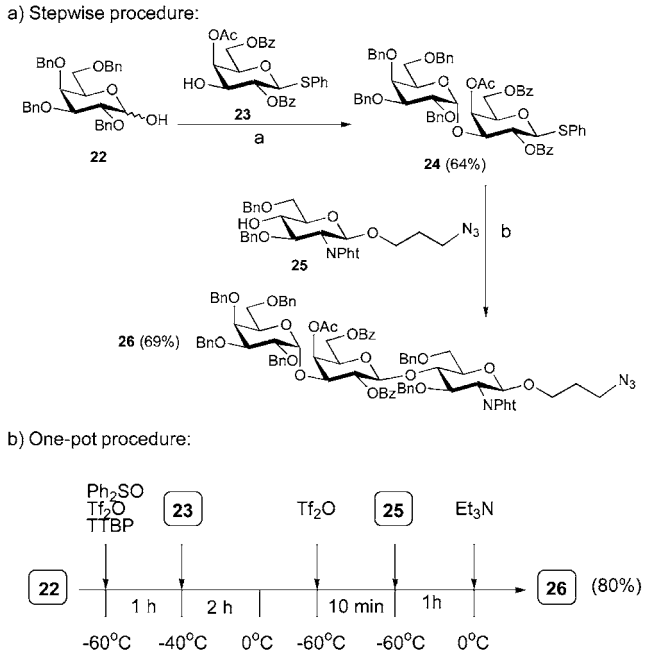
(18) For previous syntheses of the α-Gal epitope, see: (a) Garegg, P.; Oscarson, S. *Carbohydr. Res.* **1985**, *136*, 207−213. (b) Schaubach, R.; Hemberger, J.; Kinzy, U. *Liebigs Ann. Chem.* **1991**, 607−614. (c) Reddy, G. V.; Jain, R. K.; Bhatti, B. S.; Matta, K. L. *Carbohydr. Res.* **1994**, *263*, 67−77. (d) Vic, G.; Tran, C. H.; Scigelova, M.; Crout, D. H. G. *Chem. Commun.* **1997**, 167−170. (e) Nilsson, K. G. I. *Tetrahedron Lett.* **1997**, *38*, 133−136. (f) Fang, J.; Li, J.; Chen, X.; Zhang, X.; Wang, J.; Guo, Z.; Zhang, W.; Yu, L.; Brew, K.; Wang, P. G. *J. Am. Chem. Soc.* **1998**, *120*, 6635−6638. (g) Hanessian, S.; Huynh, H. K.; Reddy, G. V.; Duthaler, R. O.; Katopodis, A.; Streiff, M. B.; Kinzy, W.; Oehrlein, R. *Tetrahedron* **2001**, *57*, 3281−3290.

(19) Toole, B. P. *Curr. Opin. Cel. Biol.* **1990**, *2*, 839−844.

(20) For a recent review, see: (a) Yeung, B. K. S.; Chong, P. Y. C.; Petillo, P. A. *J. Carbohydr. Chem.* **2002**, *21*, 799−865. (b) *Glycochemistry: Principles, Synthesis, and Applications*; Wang, P. G., Bertozzi, C. R., Eds.; Marcel Dekker: New York, 2001; pp 425−492.

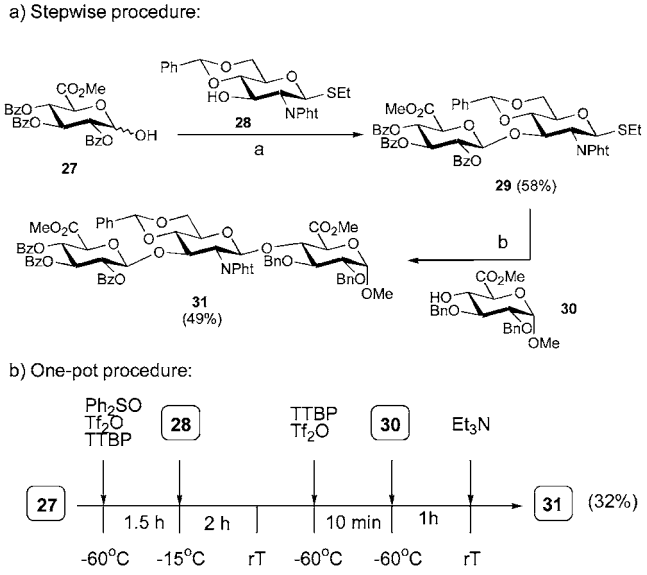
(21) Garegg, P. J.; Olsson, L.; Oscarson, S. *J. Org. Chem.* **1995**, *60*, 2200−2204.

Scheme 2. Synthesis of the α-Gal Epitope[a]



[a] Key: (a) **22** (1.2 equiv), Ph_2SO, Tf_2O, TTBP, −60 to −40 °C, 1 h, then **23**, −40 to 0 °C. (b) Ph_2SO, Tf_2O, TTBP, −60 °C, 10 min, then **25**, −60 to 0 °C.

Scheme 3. Synthesis of a Hyaluronan Trisaccharide[a]



[a] Key: (a) **27** (1.5 equiv), Ph_2SO, Tf_2O, TTBP (1.5 equiv), −60 to −15 °C, 1 h, then **28**, −15 °C to rt. (b) Ph_2SO, Tf_2O, TTBP, −60 °C, 10 min, then **30**, −60 to 0 °C.

Scheme 3a. Thus, glucuronic acid **27** was activated with **2a** and coupled to ethylthio *N*-phthaloyl glucosamine **28** to afford the β-disaccharide **29** in a satisfactory 58% yield. Consecutive coupling of **29** with glucuronic acid building block **30** completed the synthesis of the protected hyaluronan trisaccharide **31**. Executing the same set of reactions in the one-pot protocol as depicted in Scheme 3b led to the isolation of the target compound in a comparable yield (32%).

In conclusion, 1-hydroxyl donors can efficiently be condensed with thioglycosides under the action of diphenylsulfide bis(triflate) **2a**. The resulting thiodisaccharides can be further elongated in the next glycosylation step using the same promotor system. This novel condensation sequence is independent of the protecting groups in the carbohydrate building blocks. The scope of the strategy was further broadened by the development of a novel one-pot glycosylation protocol, which has been used for the construction of two biologically relevant trisaccharides. With the ultimate goal of developing efficient sequential synthesis strategies for the assembly of more complex oligosaccharides, research is currently underway to extend the developed methodology using different seleno- and thioglycosides and other sulfonium activator systems.

(22) Several syntheses of hyaluronan oligosaccharides avoid the use of glucuronic acid building blocks for this reason. Alternatively, glucopyranose building blocks are employed that are orthogonally protected on the 6-position, which after deprotection is oxidized at the end of the synthesis. See ref 20.

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Supporting Information Available: General coupling procedures and characterizations of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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