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Selective Synthesis of 1,2-*cis*-α-Glycosides without Directing Groups. Application to Iterative Oligosaccharide Synthesis

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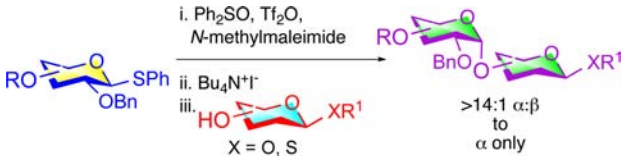
ABSTRACT



A method for the highly selective synthesis of 1,2-*cis*-α-linked glycosides that does not require the use of the specialized protecting group patterns normally employed to control diastereoselectivity is described. Thioglycoside acceptors can be used, permitting iterative oligosaccharide synthesis. The approach eliminates the need for lengthy syntheses of monosaccharides possessing highly specialized and unconventional protecting group patterns.

Oligosaccharides found on the surface of pathogens and malignant cells frequently possess 1,2-*cis*-α-linked glycosides as a key structural element.[1] The possibility of using these structures in carbohydrate-based vaccine candidates has promoted numerous investigations into the construction of these linkages.[2] Despite these efforts, 1,2-*cis*-α-glycosides remain one of the most difficult glycosidic linkages to synthesize. Many of the approaches developed to construct these linkages rely on the use of highly specialized unconventional protecting group patterns, which require multiple steps to install.[3,4] Alternatively, it is possible to obtain selectivity in the absence of directing groups by using leaving groups that undergo S_N2-like displacement.[5] For example, glycosyl iodides undergo glycosylation in the presence of excess iodide ion to form products with high α-selectivity.[6,7] These species are unstable, however, and must be generated under harsh conditions. This limits their utility with both sensitive substrates and technologies such as iterative and one-pot oligosaccharide synthesis.[8,9] In principle, these issues could

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(1) Astronomo, R. D.; Burton, D. R. *Nat. Rev. Drug Disc.* **2010**, *9*, 308–324.

(2) Zhu, X.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 1900–1934.

(3) Chiral auxiliaries: (a) Kim, J.-H.; Yang, H.; Park, J.; Boons, G.-J. *J. Am. Chem. Soc.* **2005**, *127*, 12090–12097. (b) Fascione, G.-J.; Adshead, S. J.; Stalford, S. A.; Kilner, C. A.; Leach, A. G.; Turnbull, W. B. *Chem. Commun.* **2009**, 5841–5843. (c) Fascione, M. A.; Kilner, C. A.; Leach, A. G.; Turnbull, W. B. *Chem.—Eur. J.* **2012**, *18*, 321–3331. (d) Fang, T.; Mo, K.-F.; Boons, G.-J. *J. Am. Chem. Soc.* **2012**, *134*, 7545–7552.

(4) Achiral directing groups: (a) Cox, D. J.; Fairbanks, A. J. *Tetrahedron: Asymmetry* **2009**, *20*, 773–780. (b) Mensah, E. A.; Yu, F.; Nguyen, H. M. *J. Am. Chem. Soc.* **2010**, *132*, 14288–14302. (c) Yasomanee, J. P.; Demchenko, A. V. *J. Am. Chem. Soc.* **2012**, *134*, 20097–20102. (d) Christina, A. E.; van der Es, D.; Dinkelaar, J.; Overkleeft, H. S.; van der Marel, G. A.; Codée, J. D. C. *Chem. Commun.* **2012**, *48*, 2686–2688.

(5) (a) West, A. C.; Schuerch, C. *J. Am. Chem. Soc.* **1973**, *95*, 1333–1335. (b) Sun, L.; Li, P.; Zhao, K. *Tetrahedron Lett.* **1994**, *35*, 7147–7150. (c) Park, J.; Kawatkar, S.; Kim, J.-H.; Boons, G.-J. *Org. Lett.* **2007**, *9*, 1959–1962. (d) Beaver, M. G.; Billings, S. B.; Woerpel, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 2082–2086. (e) Nokami, T.; Shibuya, A.; Manabe, S.; Ito, Y.; Yoshida, J.-i. *Chem.—Eur. J.* **2009**, *15*, 2252–2255. (f) Mydock, L. K.; Kamat, M. N.; Demchenko, A. V. *Org. Lett.* **2011**, *13*, 2928–2931. (g) Lu, S.-R.; Lai, Y.-H.; Chen, J.-H.; Liu, C.-Y.; Mong, K.-K. T. *Angew. Chem., Int. Ed.* **2011**, *50*, 7315–7320. (h) Nokami, T.; Nozaki, Y.; Saigusa, Y.; Shibuya, A.; Manabe, S.; Ito, Y.; Yoshida, J.-i. *Org. Lett.* **2011**, *13*, 1544–1547.

(6) Meloncelli, P. J.; Martin, A. D.; Lowary, T. L. *Carbohydr. Res.* **2009**, *344*, 1110–1122.

(7) Lemieux, R. U.; Hendriks, K. B.; Stick, R. V.; James, K. *J. Am. Chem. Soc.* **1975**, *97*, 4056–4062.

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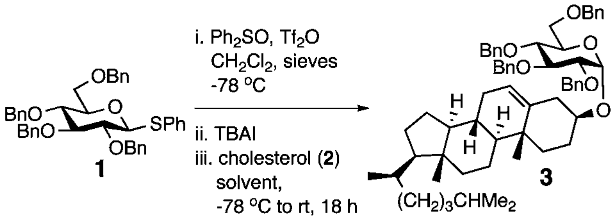
be circumvented through rapid in situ conversion of a stable donor, such as a thioglycoside, into a reactive glycosyl iodide under mild conditions.[10,11] Herein, we describe an approach for highly selective glycosylation reactions that uses stable thioglycoside donors and does not require the use of directing groups to control selectivity. The application of this technology to iterative oligosaccharide synthesis is described.

Table 1. Preliminary Reaction Optimization



entry	TBAI (equiv)	solvent	sieves (Å)	yield (%)	α:β
1	0	CH_2Cl_2	-	85	1:3
2	3	CH_2Cl_2	-	68	2.5:1
3	3	Et_2O	-	62	3.3:1
4	3	1,4-dioxane	-	58	5.2:1
5	**3**	**1,4-dioxane**	4	**83**	**7.7:1**
6	3	THF	4	62	7.1:1
7	3	1,4-dioxane	5	75	6.6:1
8	0	1,4-dioxane	4	56	1:1.2
9[a]	3	1,4-dioxane	4	70	1.3:1

[a] 1-(Benzenesulfinyl)piperidine used in place of Ph_2SO.

We chose to examine thioglycosides as they are particularly useful for iterative and one-pot synthesis. Many methods for thioglycoside activation involve in situ generation of a glycosyl triflate.[12] We reasoned that this intermediate could be trapped by iodide ion, thereby providing mild conditions for the in situ formation of a glycosyl iodide for 1,2-*cis*-α-selective glycosylation reactions.

Preliminary studies involved activating thioglycoside **1** with Ph_2SO/trifluoromethanesulfonic anhydride (Tf_2O)[13] in the presence of the non-nucleophilic base tri-*tert*-butylpyrimidine (TTBP), followed by addition of 3 equiv of tetrabutylammonium iodide (TBAI). After being stirred at −78 °C for 10 min, the reaction was treated with cholesterol (**2**) as an acceptor and allowed to warm to room temperature. The presence of TBAI led to a reversal of selectivity from that observed using Ph_2SO/Tf_2O alone (Table 1, entries 2 vs 1). Addition of the nucleophile in 1,4-dioxane led to a modest increase in selectivity, accompanied by a loss in yield (Table 1, entry 4). Further experiments revealed that both the yield and selectivity could be improved through the use of 4 Å MS (entry 5).[14] To determine if the selectivity of the reaction was due chiefly to the ethereal solvent,[15] we ran the reaction with 1,4-dioxane in the absence of TBAI. Under these conditions, the reaction was nonselective (1:1.2 α/*β*, Table 1, entry 8), clearly indicating the importance of iodide for the reaction. This last result supports the idea that the conditions are promoting the in situ conversion of the thioglycoside into the corresponding glycosyl iodide. Since TTBP suppresses in situ anomerization of glycosylation products,[16] the α-selectivity observed in entry 5 is the result of this glycosyl iodide reacting under halide ion conditions.[7]

Selectivity also appeared to depend on the nature of the thiophilic promoter; 1-(benzenesulfinyl)piperidine (BSP)/Tf_2O[17] led to a loss of selectivity (Table 1, entry 9). While the reason for this diminished selectivity is not known, we surmise that it may be due to the inability of this latter promoter to completely convert the thioglycoside to a glycosyl triflate at low temperature. If activation occurs upon warming, the acceptor is already present in the reaction and can react with the glycosyl triflate intermediate, leading to a loss of selectivity.

Under the optimal conditions described above, the reaction of **1** with sugar acceptor **4** led to the formation of disaccharide **5** accompanied by what appeared to be unreacted donor (Table 2, entry 1). This was surprising, since we had observed that the thioglycoside **1** was rapidly consumed upon activation with Ph_2SO/Tf_2O. We reasoned that the donor was somehow being regenerated under the reaction conditions following activation. To determine what was occurring, we examined the reaction in the absence of an acceptor. Under these conditions we found that **1** was quickly consumed upon activation with Ph_2SO/Tf_2O; however, it slowly formed again after the addition of TBAI. To confirm that TBAI was leading to regeneration of the donor, we examined the effect of TBAI

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(8) (a) Friesen, R. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6656–6660. (b) Nguyen, H. M.; Poole, J. L.; Gin, D. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 414–417. (c) Yamago, S.; Yamada, T.; Hara, O.; Ito, H.; Mino, Y.; Yoshida, J.-i. *Org. Lett.* **2001**, *3*, 3867–3870. (d) Yamago, S.; Yamada, T.; Maruyama, T.; Yoshida, J.-i. *Angew. Chem., Int. Ed.* **2004**, *43*, 2145–2148.

(9) Hsu, C.-H.; Hung, S.-C.; Wu, C.-Y.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2011**, *50*, 11872–11923.

(10) For in situ conversion of thioglycosides into glycosyl bromides, see: Kaeothip, S.; Yasomanee, J. P.; Demchenko, A. V. *J. Org. Chem.* **2012**, *77*, 291–299.

(11) For in situ conversion of hemiacetals into glycosyl halides, see: (a) Nishida, Y.; Shingu, Y.; Dohi, H.; Kobayashi, K. *Org. Lett.* **2003**, *5*, 2377–2380. (b) Shingu, Y.; Miyachi, A.; Miura, Y.; Kobayashi, K.; Nishida, Y. *Carbohydr. Res.* **2005**, *340*, 2236–2244. (c) Nogueira, J. M.; Nguyen, S. H.; Bennett, C. S. *Org. Lett.* **2011**, *13*, 2814–2817. (d) Nogueira, J. M.; Issa, J. P.; Chu, A.-H. A.; Sisel, J. A.; Schum, R. S.; Bennett, C. S. *Eur. J. Org. Chem.* **2012**, 4927–4930.

(12) Ranade, S. C.; Demchenko, A. V. *J. Carbohydr. Chem.* **2013**, *32*, 1–43.

(13) 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.

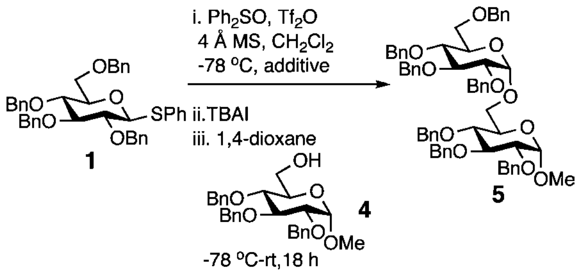
(14) Molecular sieves can impact the outcome of glycosylation reactions; see: Posner, G. H.; Bull, D. S. *Tetrahedron Lett.* **1996**, *37*, 6279–6282.

(15) (a) Eby, R.; Schuerch, C. *Carbohydr. Res.* **1974**, *34*, 79–90. (b) Wulff, G.; Schröder, U.; Wichelhaus, J. *Carbohydr. Res.* **1979**, *72*, 280–284. (c) Demchenko, A.; Stauch, T.; Boons, G.-J. *Synlett* **1997**, 818–820. (d) Dabideen, D. R.; Gervay-Hague, J. *Org. Lett.* **2004**, *6*, 973–975. (e) Koshiba, M.; Suzuki, N.; Arihara, R.; Tsuda, T.; Nambu, H.; Nakamura, S.; Hashimoto, S. *Chem. Asian J.* **2008**, *3*, 1664–1677. (f) Satoh, H.; Hansen, H. S.; Manabe, S.; van Gunsteren, W. F.; Hünenberger, P. H. *J. Chem. Theory Comput.* **2010**, *6*, 1783–1797.

(16) (a) Crich, D.; Smith, M.; Yao, Q.; Picione, J. *Synthesis* **2001**, 323–326. (b) Geng, Y.; Ye, X.-S. *Synlett* **2010**, 2506–2512.

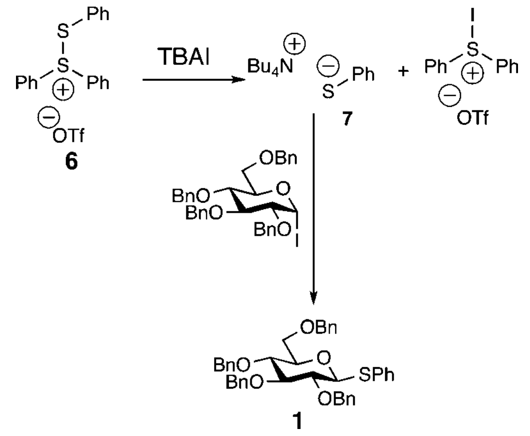
(17) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015–9020.

Table 2. Effect of TBAI and *N*-Methylmaleimide



entry	TBAI (equiv)	additive (equiv)	yield (%)	α:β
1	3	-	72	11:1
2	2	-	89	4:1
3	5	-	62	α only
4	**5**	***N*-methylmaleimide (1.5 equiv)**	**87**	**18:1**

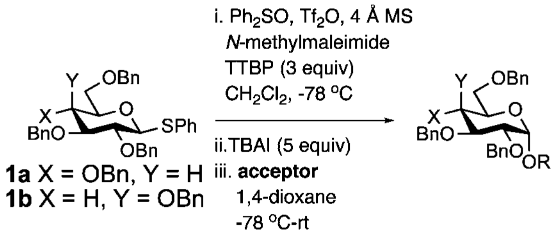
Scheme 1. Possible Mechanism of Thioglycoside Regeneration



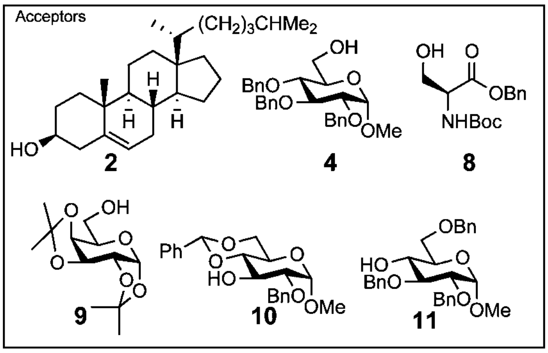
stoichiometry on the yield of the reaction with **4**. To this end, the addition of 2 equiv of TBAI led to an increase in yield (89%) accompanied by a loss in selectivity, while the addition of 5 equiv afforded the desired product as a single anomer, albeit in reduced yield (Table 2, entries 2 and 3).

Based on these results, we concluded that TBAI was reacting with the byproduct of thioglycoside activation (**6**)[13] to generate phenylthiolate **7** (Scheme 1). Compound **7** then effectively competed with the acceptor to regenerate the donor, which in the absence of additional promoter was now inert under the reaction conditions. Rationalizing that a thiol scavenger could remove **7** from the reaction and thereby permit the use of the excess TBAI necessary for selectivity, we chose to examine the effect of *N*-methylmaleimide on the reaction.[18] Toward this end, activation of **1** in the presence of *N*-methylmaleimide, followed first by the addition of 5 equiv of TBAI, then **4** in dioxane, led to the formation of **5** in 87% yield with excellent selectivity (18:1 α/*β*, Table 2, entry 4). We therefore adopted these conditions for the remainder of this study.

Table 3. Reaction Scope



entry	donor	acceptor	product	time (h)	yield (%)	α:β
1	**1a**	**2**	**3**	18	75	20:1
2	**1b**	**2**	**12**	18	76	30:1
3	**1b**	**4**	**13**	18	81	α only
4	**1a**	**8**	**14**	18	57	16:1
5	**1b**	**8**	**15**	18	58	α only
6	**1a**	**9**	**16**	18	79	20:1
7	**1b**	**9**	**17**	18	81	α only
8[a]	**1a**	**10**	**18**	40	59	19:1
9[a]	**1b**	**10**	**19**	40	70	20:1
10[a]	**1a**	**11**	**20**	64	41	α only



[a] 3 equiv of *N*-methylmaleimide used.

The scope of the reaction was next examined with a number of sugar acceptors (Table 3). Both glucose and galactose donors reacted with a number of acceptors to provide products with excellent selectivity. This included a re-examination of cholesterol as a model small molecule acceptor, which showed that these modifications led to a dramatic increase in selectivity over our initial conditions (Table 3, entries 1 and 2 vs Table 1, entry 5). In the case of more hindered acceptors, it was necessary to use 3 equiv of *N*-methylmaleimide to obtain good yields (Table 3, entries 8 and 9). Even under these conditions, the use of the hindered acceptor **11** provided the product in lower yield than observed with other acceptors (Table 3, entry 10), and the reaction was again accompanied by regeneration of the donor.

Our observation that the thioglycoside that was regenerated upon addition of TBAI was not a competent donor prompted us to examine thioglycoside acceptors in the reaction. If thioglycoside acceptors could be used successfully, it would expand the reaction's utility by permitting

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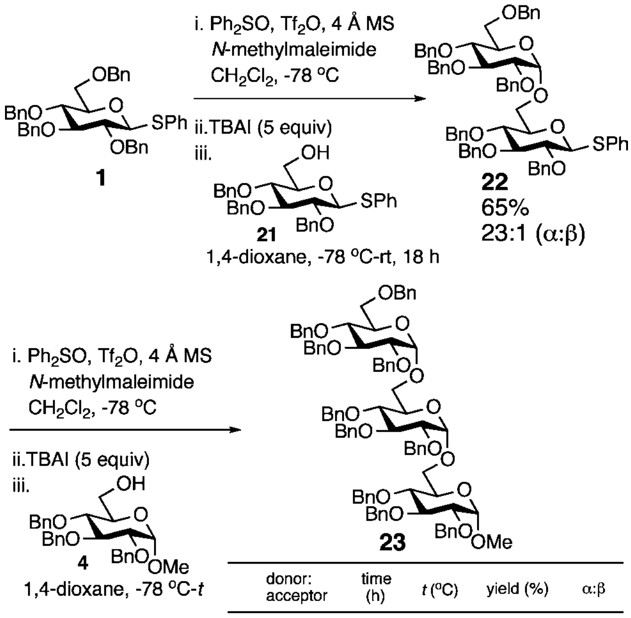
(18) Brown, G. A.; Martel, S. R.; Wisedale, R.; Charmant, R. J. P. H.; Hales, N. J.; Fishwick, C. W. G.; Gallagher, T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1281–1289.

Scheme 2. Iterative Oligosaccharide Synthesis



donor: acceptor	time (h)	*t* (°C)	yield (%)	α:β
1:2	64	25	30	22:1
2:1	64	25	35	20:1
1:2	18	80	42	14:1

iterative and, potentially, one-pot oligosaccharide synthesis. As a preliminary study, we examined the reaction between **1** and acceptor **21**. Under our conditions, the anomeric sulfide in acceptor **21** was not activated, and we were able to obtain disaccharide **22** in good yield and excellent selectivity (Scheme 2). This product was then used directly as a donor in a reaction with acceptor **4** to afford **23**. Interestingly, the stoichiometry of the donor and acceptor did not appear to affect the reaction. Using either the donor or acceptor in excess led to the formation of **23** in excellent selectivity (> 20:1 α/*β*). Heating the reaction after it was warmed to room temperature resulted in an increase in yield, with a slight decrease in selectivity (14:1 α/*β*). The loss in selectivity could be explained by invoking a glycosyl iodide intermediate reacting in the presence of excess iodide ion. Specifically, at room temperature the glycosyl donor exists as a mixture of α- and *β*-iodides, with the *β*-iodide being significantly more reactive. At higher temperatures, the α-iodide becomes a more competent donor, leading to a slight erosion of selectivity. Despite this, at higher temperatures the reaction still afforded the product in synthetically useful selectivities. More importantly, the results open up the exciting possibility that this approach could ultimately be utilized for stereoselective one-pot oligosaccharide synthesis using preactivation protocols.[19]

In conclusion, we have shown that activating thioglycosides with Ph_2SO/Tf_2O followed by TBAI leads to the in situ formation of a species that undergoes glycosylation to afford 1,2-*cis*-α-glycosides in good yield and excellent selectivity without the need for directing groups. The dependence of selectivity on the quantity of TBAI in the reaction indicates that the reaction may be proceeding through a glycosyl iodide intermediate. Excess TBAI can lead to regeneration of the starting donor; however, this can be suppressed with the addition of *N*-methylmaleimide as a thiol scavenger. The fact that the regenerated donor is unreactive prompted us to examine thioglycoside acceptors in the reaction. These latter acceptors can be used without detrimental effects, permitting iterative oligosaccharide synthesis. We envision that this approach will significantly facilitate oligosaccharide synthesis by eliminating the need to use highly specialized protecting group patterns on monosaccharide coupling partners, or very unstable glycosyl donors in the construction of 1,2-*cis*-α-glycosides. Studies directed at optimizing the reaction for one-pot synthesis and examining the scope of the reaction are under investigation in our laboratory.

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Supporting Information Available. Experimental procedures, characterization of all new compounds, and ^1H and ^{13}C NMR. This material is available free of charge via the Internet at http://pubs.acs.org.

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[19] (a) Codée, J. D. C.; van den Bos, L. J.; Litjens, R. E. J. N.; Overkleeft, H. S.; van Boom, J. H.; van der Marel, G. A. *Org. Lett.* **2003**, *5*, 1947–1950. (b) Huang, X.; Huang, L.; Wang, H.; Ye, X.-S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5221–5224. (c) Yang, L.; Qin, Q.; Ye, X.-S. *Asian J. Org. Chem.* **2013**, *2*, 30–49.

The authors declare no competing financial interest