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Stereoselective Synthesis of 2-Deoxy-furanosides from 2,3-Anhydro-furanosyl Thioglycosides

Dianjie Hou and Todd L. Lowary*

Alberta Ingenuity Centre for Carbohydrate Science and Department of Chemistry, Gunning-Lemieux Chemistry Centre, University of Alberta, Edmonton, Alberta T6G 2G2, Canada

tlowary@ualberta.ca

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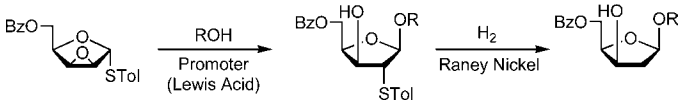
ABSTRACT



The stereocontrolled synthesis of 2-thiotolyl-furanosides from 2,3-anhydro-furanosyl thioglycosides through a rearrangement–glycosylation process is reported. The efficiency of this reaction is high, providing 70–95% yields of the products. Treatment of the resulting 2-deoxy-2-thiotolyl-glycosides with hydrogen and Raney nickel affords the corresponding 2-deoxy-furanosides with a 1,3-syn relationship.

2-Deoxy-glycosides are constituents of many natural products,[1] and there is significant interest in their synthesis. However, the stereocontrolled assembly of 2-deoxy-glycosides has historically been challenging.[2] The use of 2-deoxy-sugar-based glycosyl donors generally leads to a preponderance of the product favored by the anomeric effect (usually the α-glycoside). While this process is generally highly selective, it is usually not exclusively so. Accessing the equatorial (generally *β*) glycosides requires alternate strategies.[2−4] A common approach is to introduce a group at C2 that can, through participation, direct the glycosylation stereochemistry and then be reduced to afford the corresponding 2-deoxy-glycoside.[2,3] Other, more direct, approaches have been developed recently.[4] While effective, all these methods have been applied almost exclusively to the preparation of 2-deoxy-pyranosides. In contrast, with the exception of deoxyribonucleosides,[5] little work has been carried out on the synthesis of 2-deoxy-furanosides.[6]

We have recently explored the potential of 2,3-anhydro-sugar thioglycosides and glycosyl sulfoxides (e.g., **1**−**6**, Figure 1) as glycosylating agents.[7] Activation of either class of donor in the presence of a nucleophile leads to highly stereoselective glycosylations affording the product in which the glycosidic bond is *cis* to the epoxide. The yields of these reactions are generally high. However, in reactions with the

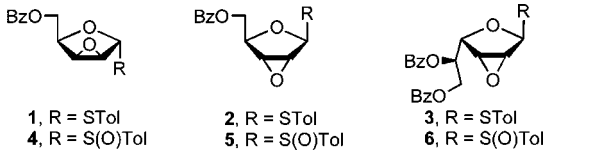


Figure 1. 2,3-Anhydrosugar glycosylating agents.

(1) For reviews, see: (a) He, X. M.; Liu, H.-W. *Annu. Rev. Biochem.* **2002**, *71*, 701. (b) Lindhorst, T. K. Antitumor and Antimicrobial Glycoconjugates. In *Glycoscience: Chemistry and Chemical Biology*; Fraser-Reid, B., Tatsuta, K., Thiem, J., Eds.; Springer-Verlag: Berlin, 2001; p 2393. (c) Kirschning, A.; Bechthold, A. F.-W.; Rohr, J. *Top. Curr. Chem.* **1997**, *188*, 1.

(2) For reviews, see: (a) Toshima, K. *Carbohydr. Res.* **2006**, *341*, 1282. (b) Marzabadi, C. M; Franck, R. W. *Tetrahedron* **2000**, *56*, 8385. (c) Veyrières, A. Special Problems in Glycosylation Reactions: 2-Deoxy Sugars. In *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinaÿ, P., Eds.; Wiley-VCH Verlag GmbH: Weinheim, Germany, 2000; p 367.

(3) (a) Trumtel, M.; Tavecchia, P.; Veyrières, A.; Sinaÿ, P. *Carbohydr. Res.* **1989**, *191*, 29. (b) Roush, W. R.; Bennett, C. E. *J. Am. Chem. Soc.* **1999**, *121*, 3541. (c) Lundt, I.; Thiem, J.; Prahst, A. *J. Org. Chem.* **1984**, *49*, 3063. (d) Thiem, J.; Gerken, M. *J. Org. Chem.* **1985**, *50*, 954. (e) Perez, M.; Beau, J.-M. *Tetrahedron Lett.* **1989**, *30*, 75. (f) Nicolaou, K. C.; Ladduwahetty, T.; Randall, J. L.; Chucholowski, A. *J. Am. Chem. Soc.* **1986**, *108*, 2466. (g) Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1987**, *28*, 2723. (h) Ramesh, S.; Kaila, N.; Grewal, G.; Franck, R. W. *J. Org. Chem.* **1990**, *55*, 5.

(4) (a) Zhou, M.; O'Doherty, *Org. Lett.* **2006**, *8*, 4339. (b) Zhou, M.; O'Doherty, G. A. *J. Org. Chem.* **2007**, *72*, 2485. (c) Tanaka, H.; Yoshizawa, A.; Takahashi, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 2505.

(5) Vorbrüggen, H.; Ruh-Pohlenz, C. *Org. React.* **2000**, *55*, 1.

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thioglycosides,[7a,b,e] when activated by *N*-iodosuccinimide (NIS) and silver triflate (Figure 2), the desired glycoside **7**

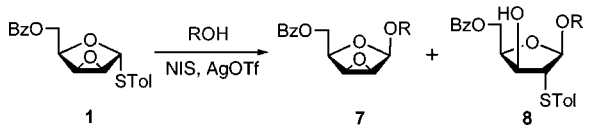


Figure 2. Products produced from glycosylations with 2,3-anhydrosugar thioglycoside **1** when promoted by NIS−AgOTf.

is produced together with a 2-deoxy-2-thioaryl glycoside byproduct, **8**.

Although the mechanism by which **8** is produced from **1** has not been studied, a plausible explanation (Figure 3) is

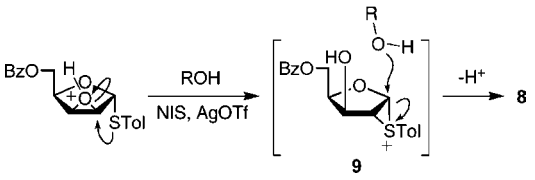


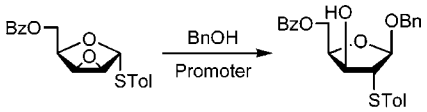
Figure 3. Proposed mechanism for the formation of **8** from **1**.

that the triflic acid generated in the course of the glycosylation protonates the epoxide, leading to migration of the thioaryl group from C1 to C2 with concomitant glycosylation. This reaction is thus related to other tandem chalcogenoglycoside migration glycosylation processes,[8−12] which have been postulated to proceed through episulfonium ion intermediates (e.g., **9**).

In these earlier reports, the donors have been either 2-*O*-phenoxythiocarbonyl thioglycosides,[8] 2,3-orthoester-protected thioglycosides,[9] phenyl 2,3-*O*-thionocarbonyl thioglycosides,[10] 2-sulfonyloxy-thioglycosides,[11] or 2-sulfonyloxy-selenoglycosides.[12] To the best our knowledge, there have been no reports on 2,3-anhydrosugar thioglycosides proceeding through this reaction manifold. Therefore, we wondered if treatment of these thioglycosides with an alcohol and a Lewis acid would efficiently and stereoselectively produce 2-thioaryl glycosides that could subsequently be deoxygenated, thus yielding 2-deoxy-glycosides. We describe here the successful implementation of this methodology using thioglycosides **1**[7a,b] and **2**.[7b,13]

In an initial series of experiments, we explored the best activator by reacting **1** with benzyl alcohol and a range of Lewis acids (Table 1). As can be seen from the data, all of

Table 1. Optimization of Promoter in the Glycosylation of Benzyl Alcohol with **1**[a]



entry	Lewis acid	equiv[b]	time	temp	yield (%)[d]	β/α ratio[e]
1	AgOTf	1.0	on[c]	rt	64	20:1
2	$Sc(OTf)_2$	1.0	on	rt	77	5:1
3	$Sm(OTf)_3$	1.0	on	rt	75	100:0
4	$Yb(OTf)_3$	1.0	on	rt	45	100:0
5	$Zn(OTf)_2$	1.0	on	rt	32	100:0
6	$Cu(OTf)_2$	1.0	on	rt	88	5:1
7	$La(OTf)_3$	1.0	on	rt	84	100:0
8	$La(OTf)_3$	0.1	on	reflux	94	100:0
9	Mol. sieves	10x	1.5 h	reflux	95	100:0

[a] Conditions: Thioglycoside **1** (0.073 mmol) and benzyl alcohol (0.11 mmol) in CH_2Cl_2 (5 mL). [b] Relative to **1**. [c] Overnight. [d] Isolated yield of mixture of isomers after chromatography. [e] Ratio determined by ^1H NMR spectroscopy of β/α mixture after chromatography.

the promoters resulted in the formation of the predicted 2-thiotolyl glycoside (**10**) in varying yields and with stereoselectivities ranging from 5:1 β:α to only β.[14] On the basis of the mechanism proposed in Figure 3, the β-glycoside would be expected to be the sole product.[15] We are unsure as to whether the production of the α-glycoside with some promoters results from reaction via an oxacarbenium ion formed from **9** or through acid-catalyzed anomerization of the product as the reaction proceeds. When stoichiometric amounts of the activator were used, $La(OTf)_3$ at room temperature in dichloromethane provided the best results with respect to both yield and stereoselectivity (entry 7). We also determined that 10 mol % $La(OTf)_3$ in dichloromethane provided somewhat better results (entry 8) but that the reaction had to be carried out at reflux. Finally, we found that, when **1** and benzyl alcohol were heated at reflux in the presence of a 10-fold (by weight) excess of molecular sieves, the reaction was complete after 90 min (entry 9). From a cost-basis perspective, the last conditions are clearly preferable, and thus they were used in subsequent reactions.

(6) Selected examples: (a) Mereyala, H. B.; Kulkarni, V. R.; Ravi, D.; Sharma, G. V. M.; Rao, B. V.; Reddy, G. B. *Tetrahedron* **1992**, *48*, 545. (b) Timmers, C. M.; Verheijen, J. C.; van der Marel, G. A.; Van Boom, J. H. *Synlett* **1997**, 851.

(7) (a) Gadikota, R. R.; Callam, C. S.; Lowary, T. L. *Org. Lett.* **2001**, *3*, 607. (b) Gadikota, R. R.; Callam, C. S.; Wagner, T.; Del Fraino, B.; Lowary, T. L. *J. Am. Chem. Soc.* **2003**, *125*, 4155. (c) Cociorva, O. M.; Lowary, T. L. *Tetrahedron* **2004**, *60*, 1481. (d) Callam, C. S.; Gadikota, R. R.; Krein, D. M.; Lowary, T. L. *J. Am. Chem. Soc.* **2003**, *125*, 13112. (e) Bai, Y.; Lowary, T. L. *J. Org. Chem.* **2006**, *71*, 9658. (f) Bai, Y.; Lowary, T. L. *J. Org. Chem.* **2006**, *71*, 9672. (g) Callam, C. S.; Gadikota, R. R.; Lowary, T. L. *Synlett* **2003**, 1271.

(8) Zuurmond, H. M.; van der Klein, P. A. M.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron* **1993**, *49*, 6501.

(9) (a) Auzanneau, F.-I.; Bundle, D. R. *Carbohydr. Res.* **1991**, *212*, 13. (b) Yang, Z.; Yu, B. *Carbohydr. Res.* **2001**, *333*, 105.

(10) Yu, B.; Yang, Z. *Org. Lett.* **2001**, *3*, 377.

(11) (a) Lázár, L.; Bajza, I.; Jakab, Z.; Lipták, A. *Synlett* **2005**, 2242. (b) Sajtos, F.; Lázár, L.; Borbás, A.; Bajza, I.; Lipták, A. *Tetrahedron Lett.* **2005**, *46*, 5191.

(12) Poopeiko, N.; Fernández, R.; Barrena, M. I.; Castillón, S.; Forniés-Cámer, J.; Cardin, C. J. *J. Org. Chem.* **1999**, *64*, 1375.

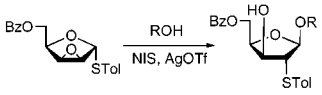
(13) Tilekar, J. N.; Lowary, T. L. *Carbohydr. Res.* **2004**, *339*, 2895.

(14) In all cases, $J_{1,2}$ was less than 2.0 Hz, indicating a trans relationship between the substituents at C1 and C2.

(15) When the β-thioglycoside was used, no reaction was observed, thus demonstrating the need for a trans relationship between the sulfur and the epoxide moiety.

Having identified a suitable promoter, we next studied the reaction of **1** with a range of alcohols (**11**−**18**). Under these conditions, reactions with simple and activated primary carbohydrate alcohols (**11**−**14**, Table 2, entries 1−4) proceeded efficiently and gave the expected products in excellent yield. In all cases, only the β-glycoside was obtained. However, with less reactive primary and secondary carbohydrate alcohols (**15**−**18**), yields were significantly lower, and large amounts of hydrolyzed donor were produced. We thus screened the panel of Lewis acids using a secondary carbohydrate alcohol (**16**) as the acceptor and identified that, for these substrates, $Cu(OTf)_2$ was the best promoter. Application of this promoter gave good yields of the desired products from **1** (Table 2, entries 5−8). We also evaluated thioglycoside **2** in these reactions, and this substrate was found to yield the expected products in good yield (Table 3) and with excellent anomeric selectivity, with the α-glycoside being produced in all cases.

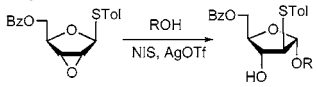
Table 2. Glycosylation of **11**−**18** with **1**



entry	acceptor	Product (yield)[c]
1[a]	$CH_3(CH_2)_7OH$ **11**	**19** (90%)
2[a]	**12**	**20** (87%)
3[a]	**13**	**21** (76%)
4[a]	**14**	**22** (88%)
5[b]	**15**	**23** (77%)
6[b]	**16**	**24** (72%)
7[b]	**17**	**25** (70%)
8[b]	**18**	**26** (71%)

[a] Conditions: Donor (0.146 mmol), alcohol (0.219 mmol) and 4 Å MS (~500 mg) in CH_2Cl_2 (10 mL) at reflux. [b] Donor (0.146 mmol), alcohol (0.146 mmol), $Cu(OTf)_2$ (0.146 mmol) and 4 Å MS in CH_2Cl_2 (10 mL) at rt. [c] Isolated yield after chromatography.

Table 3. Glycosylation of **11**−**18** with **2**



entry	acceptor	Product (yield)[c]
1[a]	$CH_3(CH_2)_7OH$ **11**	**27** (88%)
2[a]	**12**	**28** (81%)
3[a]	**13**	**29** (73%)
4[a]	**14**	**30** (85%)
5[b]	**15**	**31** (75%)
6[b]	**16**	**32** (70%)
7[b]	**17**	**33** (71%)
8[b]	**18**	**34** (71%)

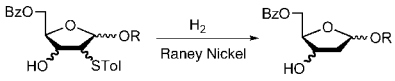
[a] Conditions: Donor (0.146 mmol), alcohol (0.219 mmol) and 4 Å MS (~500 mg) in CH_2Cl_2 (10 mL) at reflux. [b] Donor (0.146 mmol), alcohol (0.146 mmol), $Cu(OTf)_2$ (0.146 mmol) and 4 Å MS in CH_2Cl_2 (10 mL) at rt. [c] Isolated yield after chromatography.

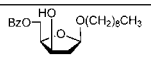
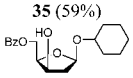
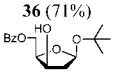
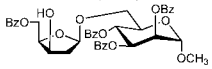
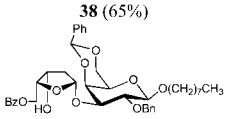
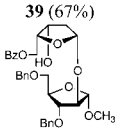
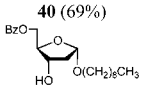
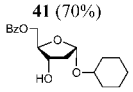
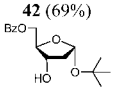
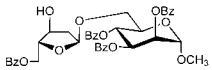
With a panel of 2-deoxy-2-thiotolyl glycosides in hand, the products were treated with hydrogen and Raney nickel. As detailed in Table 4, this reaction resulted in the formation of the corresponding 2-deoxy-glycosides in modest yield. These desulfurization reactions were clean by TLC, and we are unsure as to why the yields of isolated products are not higher; however, we note that the yields obtained are in a range typical for such reductions of analgous compounds.[16]

After establishing the methodology, we applied it to the preparation of a target oligosaccharide, **45** (Scheme 1). This trisaccharide, in which the two residues at nonreducing termini are deoxygenated at C2, is a potential inhibitor of the arabinosyltransferases that are involved in the biosynthesis[17] of the cell wall in *Mycobacterium tuberculosis*, an important human pathogen.

(16) Anderson, C. D.; Goodman, L.; Baker, B. R. *J. Am. Chem. Soc.* **1959**, *81*, 898.

Table 4. Reduction of 2-Deoxy-2-thioaryl-glycosides with RaNi



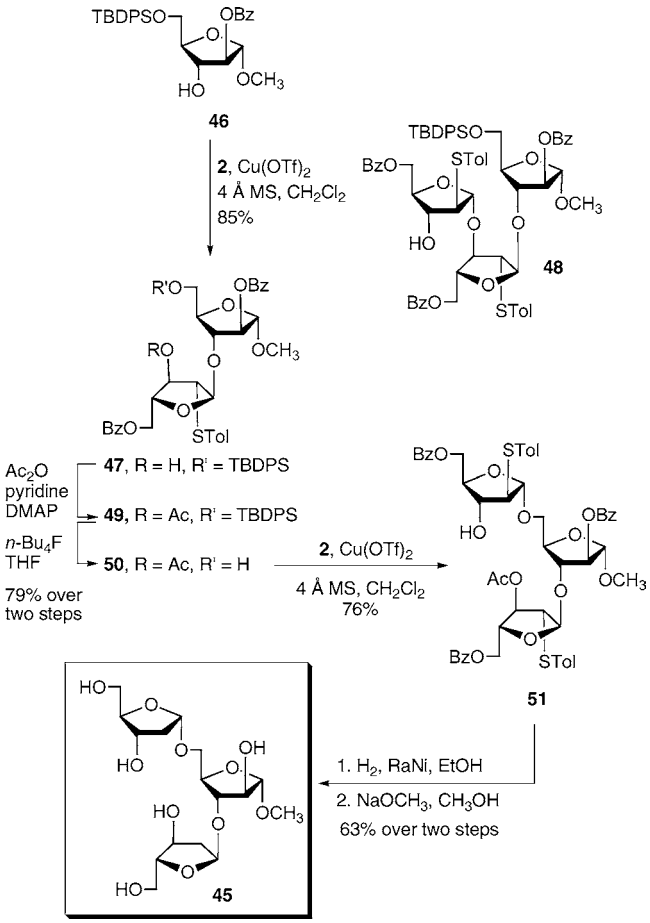
entry	substrate[a]	Product (yield)[b]
1	**19**	 **35** (59%)
2	**20**	 **36** (71%)
3	**21**	 **37** (61%)
4	**23**	 **38** (65%)
5	**25**	 **39** (67%)
6	**26**	 **40** (69%)
7	**27**	 **41** (70%)
8	**28**	 **42** (69%)
9	**29**	 **43** (71%)
10	**31**	 **44** (62%)

[a] See Tables 2 and 3 for structures. [b] Isolated yield after chromatography.

The synthesis of **45** (Scheme 1) started with the known alcohol **46**,[18] which was reacted with one equivalent of thioglycoside **2** under our standard conditions. This reaction afforded a mixture of the desired disaccharide **47** as well as trisaccharide **48** in a 4:1 ratio in 66% yield.[19] The trisaccharide results from the reaction of the hydroxyl group in **47** with **2**. This result was surprising, as with all substrates investigated previously, we had not seen byproducts resulting from reactions at the hydroxyl group liberated during the glycosylation.

To circumvent this problem, five equivalents of **46** were used relative to **2**. Under these conditions, an 85% yield of the α-linked disaccharide **47** was isolated. After acetylation and desilylation, the resulting compound **50** was glycosylated

Scheme 1



with **2** to give trisaccharide **51** in 76% yield. Subsequent desulfurization and deprotection was conducted in a stepwise manner, providing **45** in 63% yield over the two steps.

In conclusion, we report a stereoselective two-step method for the synthesis of 2-deoxy-furanosides. In the first step, a 2,3-anhydro-furanosyl thioglycoside is reacted with an alcohol and a Lewis acid to provide a 2-deoxy-2-thioaryl-*O*-glycoside that, in the second step, is desulfurized. In the glycosylation reaction, the choice of Lewis acid is dictated by the acceptor alcohol. The method was successfully applied to the synthesis of a trisaccharide containing two 2-deoxy-furanosyl residues, which is a potential inhibitor of mycobacterial arabinosyltransferases.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL7019108

(17) Crick, D. C.; Mahapatra, S.; Brennan, P. J. *Glycobiology* **2001**, *11*, 107R.

(18) D'Souza, F. W.; Cheshev, P. E.; Ayers, J. D.; Lowary, T. L. *J. Org. Chem.* **1998**, *63*, 9037.

(19) **47** and **48** had identical R_f's, and separation required acetylation of the mixture followed by chromatography.