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Stereocontrolled Synthesis of 2,3-Anhydro-β-D-lyxofuranosyl Glycosides

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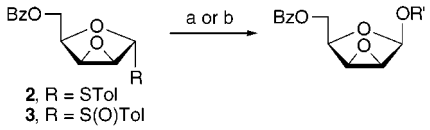
ABSTRACT



The stereocontrolled synthesis of 2,3-anhydro-β-D-lyxofuranosyl glycosides from thioglycoside 2 and glycosyl sulfoxide 3 is reported.

The key role of oligosaccharide-mediated recognition events in many important biological events is now undisputed.[1] As interest in the biology and biochemistry of these molecules has increased, so to has the need for efficient and stereoselective methods for the formation of glycosidic bonds.[2]

Although some glycosidic linkages can be readily constructed in a stereocontrolled manner, others remain challenging synthetic targets. For example, 1,2-*trans* linkages can be reliably prepared through the use of glycosyl donors with participating (e.g., acyl) protecting groups at C-2[2a−d] or through the Lewis acid-promoted opening of glycal epoxides by nucleophiles.[2e−g] On the other hand, there are fewer general strategies for the selective formation of 1,2-*cis* linkages,[2a−d] in particular those possessing 1,2-*cis*-β stereochemistry, e.g., β-mannopyranosides, β-arabinofuranosides, and β-fructofuranosides. While some methods have been developed for the stereoselective synthesis of these glycosidic bonds,[3−5] many either suffer from a lack of generality or require multiple steps. Accordingly, there is a continuing need for investigations directed toward the efficient preparation of glycosidic bonds with this stereochemistry.

Recently, we reported the synthesis of arabinofuranosyl oligosaccharides that are fragments of two mycobacterial cell wall polysaccharides.[4b,6] One of the targets we synthesized[4b] is hexasaccharide **1**, which contains two β-D-arabinofuranosyl linkages (Figure 1). The key step in our synthesis of **1** was

(1) (a) Varki, A. *Essent. Glycobiol.* **1999**, 57. (b) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683.

(2) Reviews: (a) Davis, B. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2137. (b) Boons, G.-J. *Tetrahedron* **1996**, *52*, 1095. (c) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503. (d) Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21. (e) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380. (f) Di Bussolo, V.; Kim, Y.-J.; Gin, D. Y. *J. Am. Chem. Soc.* **1998**, *120*, 13515. (g) Kim, Y.-J.; Di Bussolo, V.; Gin, D. Y. *Org. Lett.* **2001**, *3*, 303.

(3) β-Mannopyranosides: (a) Ohtake, H.; Ichiba, N.; Ikegami, S. *J. Org. Chem.* **2000**, *65*, 8171. (b) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1998**, *120*, 435. (c) Crich, D.; Sun, S. *J. Org. Chem.* **1997**, *62*, 1198. (d) Hodosi, G.; Kovác, P. *J. Am. Chem. Soc.* **1997**, *119*, 2335. (e) Barresi, F.; Hindsgaul, O. *Front. Nat. Prod. Res.* **1996**, *1*, 1251. (f) Ito Y.; Ogawa, T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1765. (g) Stork, G.; Kim, G. *J. Am. Chem. Soc.* **1992**, *114*, 1087.

(4) β-Arabinofuranosides: (a) Sanchez, S.; Bamhaoud, T.; Prandi, J. *Tetrahedron Lett.* **2000**, *41*, 7447. (b) D'Souza, F. W.; Lowary, T. L. *Org. Lett.* **2000**, *2*, 1493. (c) Subramaniam, V.; Lowary, T. L. *Tetrahedron* **1999**, *55*, 5965. (d) Désiré, J.; Prandi, J. *Carbohydr. Res.* **1999**, *317*, 110. (e) Mereyala, H. B.; Hotha, S.; Gurjar, M. K. *J. Chem. Soc., Chem. Commun.* **1997**, 685.

(5) β-Fructofuranosides: (a) Oscarson, S.; Sehgelmeble F. W. *J. Am. Chem. Soc.* **2000**, *122*, 8869. (b) Krog-Jensen, C.; Oscarson, S. *J. Org. Chem.* **1998**, *63*, 1780. (c) Müller, T.; Schneider, R.; Schmidt, R. R. *Tetrahedron Lett.* **1994**, *35*, 4763.

(6) (a) D'Souza, F. W.; Ayers, J. D.; McCarren, P. R.; Lowary, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 1251. (b) D'Souza, F. W.; Cheshev, P. E.; Ayers, J. D.; Lowary, T. L. *J. Org. Chem.* **1998**, *63*, 9037. (c) Ayers, J. D.; Lowary, T. L.; Morehouse, C. B.; Besra, G. S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 437.

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a low-temperature glycosylation reaction that installed both β-arabinofuranoside residues in a single step and with excellent stereocontrol. However, upon further exploration of this method, we found it not to be generally applicable to a range of alcohols.[7] Consequently, we have explored other methods for the formation of these linkages.

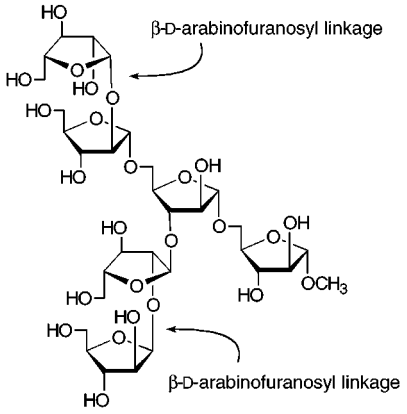


Figure 1. Hexasaccharide **1**.

As part of our investigations, we have studied the use of thioglycoside **2** and glycosyl sulfoxide **3** (Figure 2) as precursors to β-D-arabinofuranosyl residues. We reasoned that if conditions could be found by which these reagents could stereoselectively glycosylate alcohols to afford the β-glycoside, then opening[8] of the epoxide moiety by the attack of nucleophiles at C-3 would lead to β-arabinofuranosides.

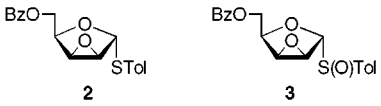
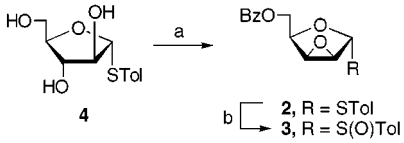


Figure 2.

To the best our knowledge there have been no previous reports on the use of 2,3-anhydrosugars as glycosylating agents. In contrast to donors typically used for the formation of 1,2-*cis*-β-glycosides, the C-2 substituent in **2** and **3** is not a sterically demanding nonparticipating protecting group. Such groups are generally believed to negatively influence the stereocontrol of a 1,2-*cis* glycosylation. Instead, the secondary hydroxyl groups in **2** and **3** are "protected" as an epoxide, which we expected would provide little steric impedance to the attack of a nucleophile (e.g., an alcohol) from the top face of the ring. In this Letter, we report that **2** and **3** do indeed glycosylate alcohols with a high degree of stereocontrol. The β-glycosides are the major or, in many instances, the exclusive product and product yields range from modest to excellent.

The preparation of **2** and **3** was straightforward (Scheme 1). The known,[6a] and readily accessible, thioglycoside **4**, was

Scheme 1 Synthesis of **2** and **3**[a]



[a] (a) BzOH, Ph_3P, *i*-$PrO_2CN{=}NCOO_2$*i*-Pr, THF, 0 °C → rt, 82%; (b) *m*-CPBA, CH_2Cl_2, −78 °C → rt, 78%.

reacted[9] with diisopropylazodicarboxylate, triphenylphosphine, and benzoic acid to provide, in a single step, epoxide **2** (82%). Oxidation with *m*-CPBA provided **3** as a mixture of diastereomers in 78% yield.

With an efficient route in place for the preparation of **2** and **3**, we first explored the glycosyl donor abilities of **2**. Coupling of this thioglycoside with a panel of alcohols (Figure 3) using *N*-iodosuccinimide and silver triflate activation afforded glycosides in the yields indicated in Table 1.

In the case of the simple alcohols **5**−**7** (entries 1−3), the products were obtained in excellent yield and with a high

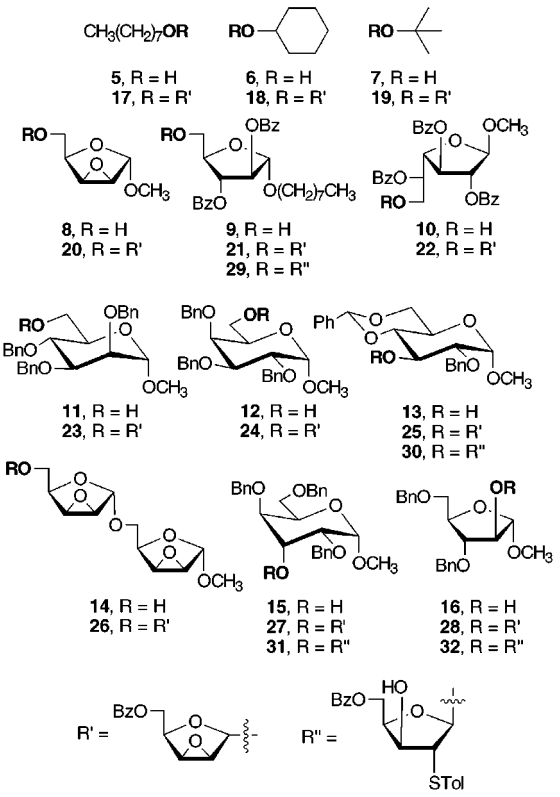
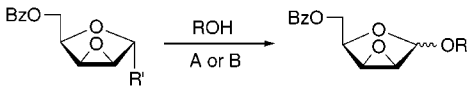


Figure 3.

(7) Yin, H. F.; Lowary, T. L. Unpublished Results.
(8) Williams, N. R. *Adv. Carbohydr. Chem. Biochem.* **1970**, *25*, 109.

Table 1. Glycosylation of Various Alcohols with Thioglycoside **2** and Glycosyl Sulfoxide **3**



entry	R′	alcohol	activation[a]	product	yield (%)[b]	β:α ratio[c]
1	STol	**5**	**A**	**17**	79	β only
2	STol	**6**	**A**	**18**	81	β only
3	STol	**7**	**A**	**19**	83	6.5:1
4	STol	**8**	**A**	**20**	77	β only
5	STol	**9**	**A**	**21**	81[d]	7:1
6	STol	**10**	**A**	**22**	83	5:1
7	STol	**11**	**A**	**23**	72	β only
8	STol	**12**	**A**	**24**	84	β only
9	STol	**13**	**A**	**25**	51[e]	3:2
10	STol	**15**	**A**	**27**	82[f]	3:1
11	STol	**16**	**A**	**28**	75[g]	5:1
12	S(O)Tol	**9**	**B**	**21**	82	β only
13	S(O)Tol	**13**	**B**	**25**	43	β only
14	S(O)Tol	**14**	**B**	**26**	83	β only
15	S(O)Tol	**15**	**B**	**27**	74	β only
16	S(O)Tol	**16**	**B**	**28**	87	5.5:1
17	STol[h]	**5**	**A**	**17**	82	β only

[a] **A**: thioglycoside **2** (0.6 mmol), alcohol (0.5 mmol), *N*-iodosuccinimide (0.6 mmol), and silver triflate (0.15 mmol) in 10 mL of CH_2Cl_2 at −40 °C. **B**: sulfoxide **3** (0.5 mmol), alcohol (0.6 mmol), Tf_2O (0.6 mmol), and DTBMP (2.0 mmol) in 10 mL of CH_2Cl_2 at −78 °C. [b] Isolated yield after chromatography. [c] Ratio determined by product yields following chromatography. [d] 5% of **29** obtained. [e] 20% of **30** obtained. [f] 11% of **31** obtained. [g] 20% of **32** obtained. [h] β-Anomer, **34**, used.

degree of stereocontrol. Glycosylation of *n*-octanol (**5**) and cyclohexanol (**6**) led exclusively to the formation of the β-glycoside. The more hindered *tert*-butanol (**7**) provided a 6.5:1 β:α ratio of glycosides.

The stereochemistry at the anomeric center was proven by measuring the magnitude of the one-bond C-1−H-1 coupling constant as previously reported.[10] In all cases, $^1J_{C1-H1}$ was 163−168 Hz, characteristic of the β-glycoside. It was not possible to discriminate between the isomers using the NMR parameters usually used for the assignment of anomeric stereochemistry in furanosides: the chemical shift of C-1 or the magnitude of $^3J_{H1-H2}$.[11]

We next investigated the reaction of **2** with various carbohydrate alcohols **8**−**16** (Table 1, entries 4−11). With the primary alcohols **8**−**12** the yields are high and the β-glycosides are the major or sole products. Only with the benzoylated substrates **9** and **10** were detectable amounts of the α-glycoside formed. Also isolated (5% yield) in the reaction of **2** with **9** was the 2-thiocresyl β-glycoside **29**. This product presumably arises (Figure 4) via initial protonation of the epoxide by triflic acid generated in the course of the reaction, followed by migration of the thiocresyl moiety and concomitant epoxide ring opening. Attack of the alcohol (e.g., **9**) upon the intermediate, **33**, affords the product with D-*xylo* stereochemistry.[12] An analogous migration in 2-*O*-phenoxythiocarbonyl thioglycosides has been reported.[13]

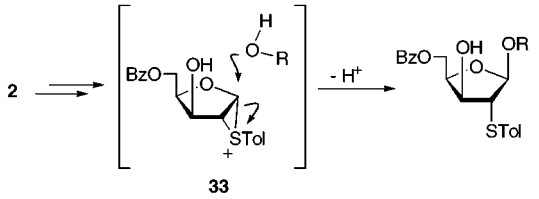


Figure 4.

When secondary carbohydrate alcohols (**13**, **15**, **16**) are glycosylated with **2** (Table 1, entries 9−11), the yields are similar; however the β-selectivity is reduced. Larger amounts of the 2-thiocresyl β-D-xylofuranoside products (**30**−**32**) are also formed. We attempted to prevent this rearrangement process by adding 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) to the reaction. However, this resulted in very low conversion of the thioglycosides.

The formation of these rearranged glycoside products and the relatively poor stereoselectivity obtained upon glycosylation of secondary carbohydrate alcohols prompted us to explore the use of glycosyl sulfoxide **3**. Sulfoxides are generally excellent glycosylating agents.[14] Furthermore, glycosylation reactions involving these species are carried out in the presence of an excess of DTBMP, which was expected to prevent acid-promoted reactions of the epoxide moiety.

Sulfoxide **3** is indeed highly reactive. It rapidly glycosylates alcohols upon treatment with triflic anhydride and DTBMP at low temperatures. In most cases, the yields are indistinguishable from those obtained using thioglycoside **2** and the β-selectivity is excellent (Table 1, entries 12−16). Only with alcohol **16** is the formation of the α-glycoside found. As expected, no rearranged products were detected. Sulfoxide **3** is clearly superior to thioglycoside **2** as a glycosylating agent.

The generally high stereoselectivity of these reactions intrigued us, and we initially postulated that the reaction proceeded via an S_N2 or S_N1 ion-pair mechanism. To further probe the mechanism, octanol was glycosylated with thio-

(9) A modification of a previously reported method for the formation of methyl 2,3-anhydro-α-D-lyxofuranoside was used: Martin, M. G.; Ganem, B.; Rasmussen, J. R. *Carbohydr. Res.* **1983**, *123*, 332.

(10) Callam, C. S.; Gadikota, R. R.; Lowary, T. L. *J. Org. Chem.* Submitted.

(11) Mizutani, K.; Kasai, R.; Nakamura, M.; Tanaka, O.; Matsuura, H. *Carbohydr. Res.* **1989**, *185*, 27.

(12) Disaccharide **29** and the α-glycoside isomer of **21** had identical R_f's, and separation required acetylation of the mixture followed by chromatography. The anomeric stereochemistry in the 3′-*O*-acetyl derivative of **29** was established by the C-1 chemical shift (108.3 ppm, $CDCl_3$) and the magnitude of $^3J_{H1'-H2'}$ (1.2 Hz). The position of the thiocresyl moiety was determined by an HMQC experiment that correlated H-2′ with the carbon resonating at 56.5 ppm ($CDCl_3$).

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

(14) Kahne, D.; Walker, S.; Cheng, Y.; Van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 6881.

glycoside **34**,[10] the anomer of **2** (Figure 5 and Table 1, entry 17). The reaction proceeded to give the β-glycoside **17**, as the only product in a yield essentially identical to that obtained from **2**.

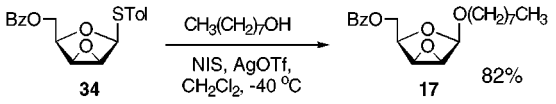


Figure 5.

This result suggests that with these thioglycosides the reaction proceeds via an oxonium ion intermediate (**35**, Figure 6) that is attacked by the alcohol in a stereoselective manner from the face of the ring *cis* to the epoxide.[15] It is also possible that an activated intermediate (e.g., an α-glycosyl triflate, **36**) is generated in situ, which is in turn displaced by the alcohol via an S_N2 reaction.[16] However, we believe the intermediacy of a glycosyl triflate is unlikely. These reactions are carried out by activating the thioglycoside in the presence of the acceptor alcohol using less than a stoichiometric amount of silver triflate. Reaction of **35** with the alcohol would be expected to be favored over trapping by the weakly nucleophilic triflate anion.[17]

On the other hand, glycosyl triflates may be important intermediates in glycosylations with **3**. The sulfoxide activation protocol we used was that developed by Crich and coworkers.[3c] This method involves treatment of the sulfoxide with triflic anhydride prior to addition of the alcohol. Under these conditions glycosyl triflates have been shown to be formed.[16a] Accordingly, we propose that in glycosylation reactions with **3** the stereoselectivity arises from an S_N2 displacement of a glycosyl triflate which is generated in situ. The stereochemistry in the final glycoside product necessitates that the α-triflate (**36**) be formed in preference to the β-isomer (**37**). Consistent with this proposal are our preliminary density functional theory calculations on glycosyl triflates **38** and **39**, which have determined that the former is 4.5 kcal/mol lower in energy (B3LYP/6-31+G**//B3LYP/6-31G*) than the latter.[18]

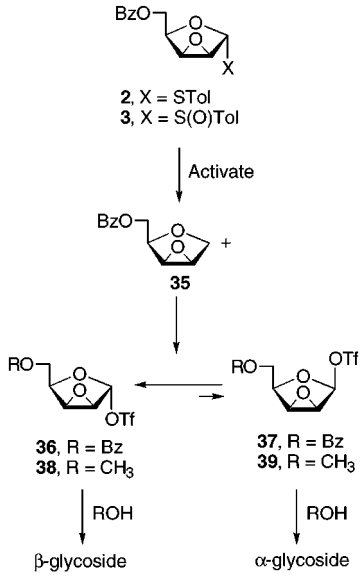


Figure 6.

In conclusion, we have described for the first time the use of 2,3-anhydrosugars as glycosylating agents. Glycosylation of a panel of alcohols with **2** and **3** affords glycoside products in generally excellent yields. These reactions are stereoselective, leading to the formation of the β-glycoside as the major or exclusive product.[19] Work currently underway in our laboratory is focused on understanding the mechanism of these glycosylation reactions, as well as extending our investigations to other 2,3-anhydrosugars. Also ongoing are studies directed toward the regioselective ring opening of these epoxides with nucleophiles.[20]

Acknowledgment. This work was supported by the National Institutes of Health (AI44045-01), the National Science Foundation (CHE-9875163), and the Ohio State University Spectroscopy Institute. We thank Patrick R. McCarren for technical assistance.

Supporting Information Available: Representative experimental procedures and analytical data for previously unreported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) In separate experiments we have shown that the α-glycosides do not isomerize to the β-glycosides under these reaction conditions and so these glycosylations proceed with kinetic control. These experimental studies are further supported by density functional theory calculations on **8** and its β-isomer (ref 10) which have shown that the former is approximately 4 kcal/mol more stable than the latter.

(16) (a) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11217. (b) Garcia, B. A.; Gin, D. Y. *J. Am. Chem. Soc.* **2000**, *122*, 4269.

(17) Other transient intermediates could also be involved. For example, the succinimide liberated from NIS could form a glycosyl succinimide species. However, we also view this as unlikely as such intermediates have been isolated as stable byproducts from other NIS promoted glycosylation reactions by us (Houseknecht, J. B.; McCarren, P. R.; Lowary, T. L., unpublished results) and others (Krog-Jensen, C.; Oscarsson, S. *J. Org. Chem.* **1996**, *61*, 1234). Accordingly, we do not feel such species are productive intermediates in the synthesis of these glycosides.

(18) The β-anomer of **3** also provides the β-glycoside products exclusively in yields identical to that of **3**, which is also consistent with the pathway proposed in Figure 6.

(19) In our experience, when α/β mixtures are formed, the two anomers can easily be separated by chromatography as for a given α/β pair the difference in R_f is usually significant, >0.2.

(20) In initial experiments, a solution of **18** and sodium in allyl alcohol was heated at reflux to afford, in 92% yield, a mixture of ring-opened products in a 2:1 *xylo*:*arabino* ratio. Heating an ethanolic solution of **21**, NaN_3, and NH_4Cl at reflux provided a 2:1 *arabino*:*xylo* ratio of products in 93% yield.