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2,3-Anhydro Sugars in Glycoside Bond Synthesis. Highly Stereoselective Syntheses of Oligosaccharides Containing α- and β-Arabinofuranosyl Linkages

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Abstract: The ever-increasing discovery of biologically important events mediated by carbohydrates has generated great interest in the synthesis of oligosaccharides and the development of new methods for glycosidic bond formation. In this paper, we report that 2,3-anhydrofuranose thioglycosides (**1**, **5**) and glycosyl sulfoxides (**2**, **6**), in which the hydroxyl groups C-2 and C-3 are "protected" as an epoxide, glycosylate alcohols with an exceptionally high degree of stereocontrol. The predominant or exclusive product of reactions with this fundamentally new class of glycosylating agent is that in which the newly formed glycosidic bond is *cis* to the epoxide moiety. We further demonstrate that subsequent nucleophilic opening of the epoxide moiety proceeds under basic conditions to give products in high yield and with good to excellent regioselectivity. The major ring-opened products possess the *arabino* stereochemistry, and thus this methodology constitutes a new approach for the synthesis of arabinofuranosides. In the epoxide opening reactions of glycosides with the 2,3-anhydro-β-D-*lyxo* stereochemistry (e.g., **73**), the addition of (−)-sparteine (**78**) to the reaction mixture dramatically enhanced the regioselectivity in favor of the *arabino* product. This represents the first example of the use of **78** to influence the regioselectivity of an epoxide ring opening reaction with a non-carbon nucleophile. We have demonstrated the utility of this methodology through the efficient synthesis of an arabinofuranosyl hexasaccharide, **7**, which is a key structural motif in two mycobacterial cell wall polysaccharides.

Introduction

The diverse roles that oligosaccharides play in a number of important biological events[1] have underscored the importance of glycosidic bond formation in organic chemistry.[2] This field has received increasing attention in recent years, and a number of impressive achievements have been reported. Among these are efficient routes for the synthesis of multimilligram quantities of large oligosaccharides,[3] the development of "one-pot" protocols for the preparation of oligosaccharides,[4] and the report of the first automated solid-phase oligosaccharide synthesizer.[5] However, despite these advances, there remains a need for new methods for the synthesis of these important molecules, as efficient and stereocontrolled routes to many glycosidic linkages are still not always available. In particular, the stereocontrolled synthesis of oligosaccharides containing furanose residues is largely unexplored and has only recently begun to be studied in earnest.[6,7] Although, as would be expected, the synthesis of furanosides with the 1,2-*trans* stereochemistry can be achieved in a straightforward manner through the use of donors with acyl protecting groups on O-2, the stereoselective preparation of 1,2-*cis* furanosides remains a challenging and unsolved problem.[6,7]

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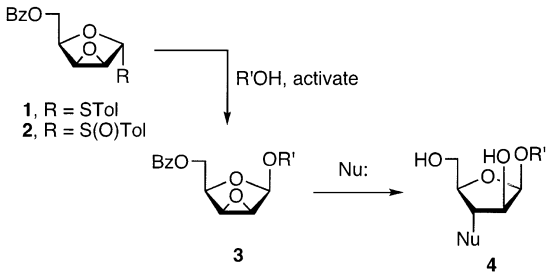


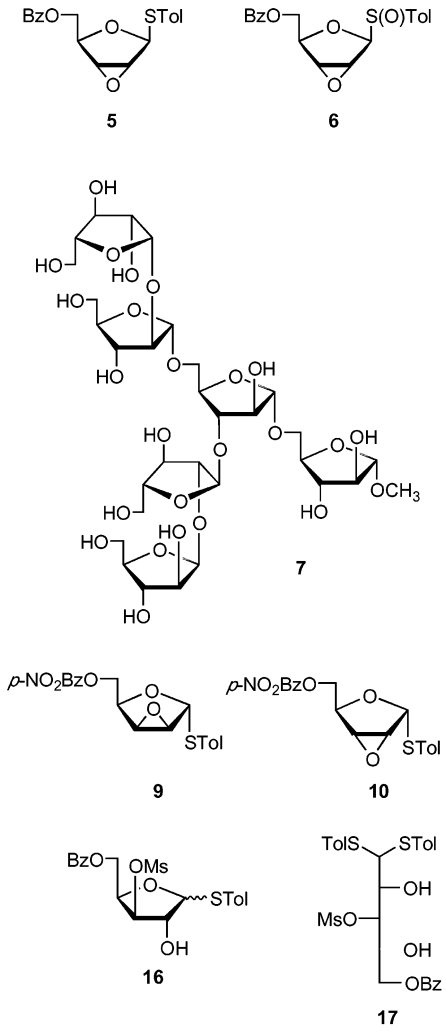
Figure 1. Synthesis of β-arabinofuranosides (**4**) from 2,3-anhydro sugar glycosylating agents **1** and **2**.

Over the past 5 years, we have described the synthesis of a number of oligosaccharides that are fragments of two arabinofuranose-containing polysaccharides found as key components of the mycobacterial cell wall.[7] These polysaccharides contain both 1,2-*trans* (α-arabinofuranosyl) and 1,2-*cis* (β-arabinofuranosyl) linkages, and to date we have synthesized fragments ranging in size from disaccharides to hexasaccharides. In the synthesis of these targets, the installation of the β-arabinofuranosyl residues was generally problematic because these glycosylation reactions, which employed traditional 2-*O*-benzylated glycosyl donors, often showed poor stereoselectivity.[7d]

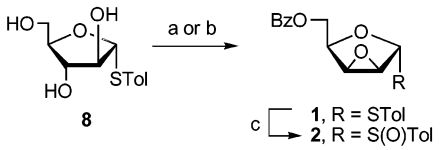
In our search for new methods to synthesize β-arabinofuranosides in a stereoselective manner, we discovered that epoxy thioglycoside **1** and glycosyl sulfoxide **2**, which possesses the 2,3-anhydro-D-*lyxo* stereochemistry, glycosylate alcohols with a very high degree of stereoselectivity (Figure 1).[8] The major, or frequently only, product of this reaction is the one in which the newly formed glycosidic bond is *cis* to the epoxide (e.g., **3**). We further demonstrated that the epoxide in **3** can be opened by nucleophiles to afford β-arabinofuranosides (**4**). In our earlier study,[8] the regioselectivity of the ring-opening reaction was rather modest, with C-3 attack being favored over C-2 attack by an approximately 3:1 ratio. Nevertheless, if the second step could be optimized, the route illustrated in Figure 1 represents a very appealing approach for the stereocontrolled synthesis of β-arabinofuranosides. From a broader perspective, anhydro sugars **1** and **2** represent a fundamentally new class of glycosylating agent. The epoxide moiety can be viewed as a nonparticipating protecting group for OH-2. However, in contrast to more traditional nonparticipating hydroxyl protecting groups (e.g., alkyl or silyl ethers), the epoxide is sterically undemanding.

In this paper we report a full account of our investigations on the use of **1** and **2** in the synthesis of glycosidic bonds and demonstrate the power of these reagents in the synthesis of β-arabinofuranosides. A key feature of this novel route for the preparation of these linkages is a highly regioselective (−)-sparteine-mediated nucleophilic opening of the epoxide moiety in the glycosides that are produced from **1** and **2**. We also report here that anhydro sugars **5** and **6** (Chart 1), possessing the 2,3-anhydro-D-*ribo* stereochemistry, can be used as precursors to α-arabinofuranosides. Finally, we demonstrate the utility of this methodology through the synthesis of a hexasaccharide motif (**7**, Chart 1) found in two mycobacterial cell wall polysaccharides.[9] In the synthesis of **7**, three of the six residues were installed by way of these anhydro sugar glycosylating agents.

Chart 1



Scheme 1 [a]



[a] Legend: (a) DIAD, Ph_3P, BzOH, THF, 0 °C → room temperature, 45 min, 82%; (b) polymer supported azodicarboxylate, BzOH, Ph_3P, THF, room temperature, 12 h, 72%; (c) *m*-CPBA, CH_2Cl_2, −78 °C → room temperature, 2.5 h, 78%.

Results and Discussion

Synthesis of Glycosylating Agents 1, 2, 5, and 6. The successful application of synthetic methodology involving these anhydro sugars requires that straightforward methods for their preparation are available. We have developed such routes for the synthesis of **1**, **2**, **5**, and **6**.

Illustrated in Scheme 1 is the synthesis of thioglycoside **1** and glycosyl sulfoxide **2** from **8**, which was prepared in three steps from D-arabinose.[7b] Reaction of **8** with diisopropyl azodicarboxylate (DIAD), benzoic acid, and triphenylphosphine,

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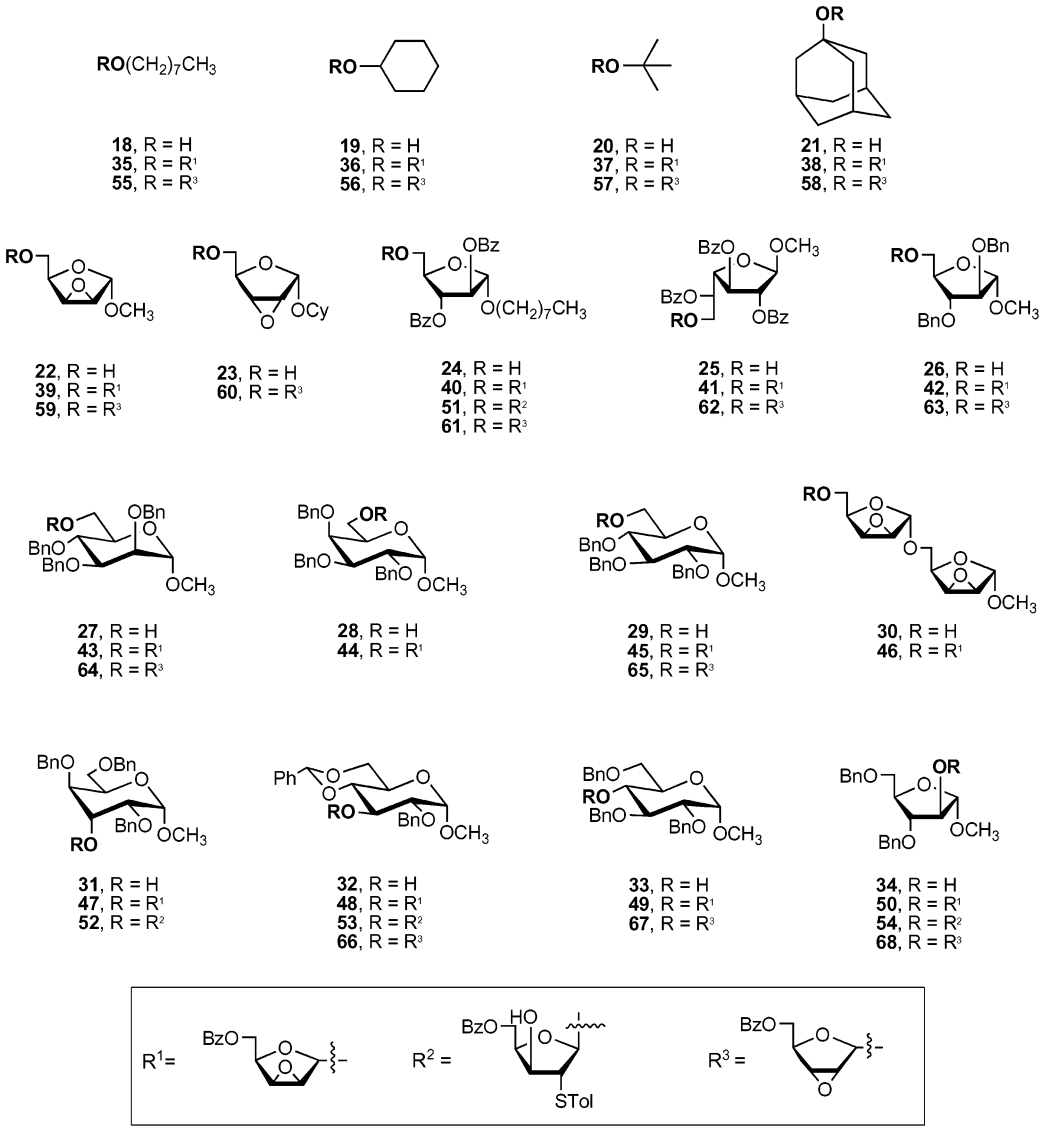
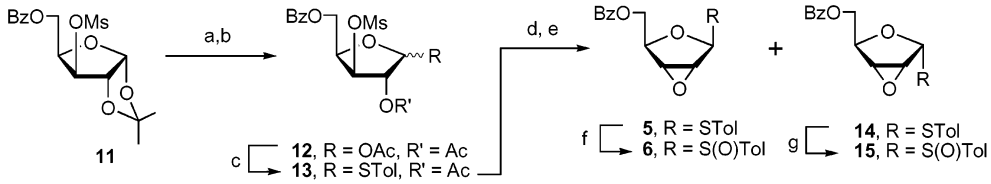
Chart 2



Scheme 2 [a]



[a] Legend: (a) 60% aqueous HOAc, H_2SO_4 (catalytic), 70 °C, 36 h; (b) Ac_2O, pyridine, room temperature, 2 h, 88% (two steps); (c) *p*-TolSH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C → room temperature, 2 h, 91%; (d) $NaOCH_3$, CH_3OH, room temperature, 8 h; (e) BzCl, pyridine, 2 h, 0 °C → room temperature, 89% (two steps), 67% **5**, 21% **14**; (f) *m*-CPBA, CH_2Cl_2, −78 °C → room temperature, 2.5 h, 79%; (g) *m*-CPBA, CH_2Cl_2, −78 °C → room temperature, 2.5 h, 77%.

afforded epoxy thioglycoside **1** in 82% yield. Similar to the Mitsunobu reaction leading to the corresponding methyl glycoside **22**[10] (Chart 2) none of the isomeric epoxide was isolated. The structure of the product was determined by comparison of the NMR data for **1** with those for **22**.[10] Additional proof of the identity of **1** was obtained by synthesizing its corresponding crystalline 5-*O*-*p*-nitrobenozate ester derivative **9** (Chart 1), the structure of which was solved by X-ray crystallography (see Supporting Information). The purification of **1** was complicated by presence of the reduced DIAD that is produced during the reaction. We therefore explored the use of a polymer-bound azodicarboxylate[11] and found that the reaction afforded the same product, although the rate is slower and the yield somewhat lower (72% yield from **8**). Oxidation of **1** with *m*-CPBA provided sulfoxide **2** in 78% yield as a >10:1 mixture of diastereomers.

The synthesis of **5** and **6** (Scheme 2) was slightly more involved than the preparation of **1** and **2** but nevertheless could be carried out with minimal difficulty. Conversion of the 1,2-*O*-isopropylidene xylose derivative **11**[12] into **12** was achieved

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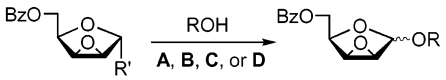
in 88% overall yield by hydrolysis of the acetal with aqueous acetic acid followed by acetylation of the resulting diol. Treatment of **12** with *p*-thiocresol and boron trifluoride etherate afforded, in 91% yield, a 1:2.6 α:β mixture of thioglycosides **13**, which could not be separated. Reaction of **13** with sodium methoxide followed by benzoylation of the intermediate epoxy alcohol afforded thioglycosides **5** and **14**, in a combined yield of 89% over the two steps. These thioglycosides were isolated pure following chromatography. The structures of **5** and **14** could not be assigned unambiguously using NMR spectroscopy. Therefore, the minor product, which we expected to be **14**, was treated with sodium methoxide and the product alcohol was converted to its 5-*O*-*p*-nitrobenzoate ester. X-ray analysis of the resulting crystalline solid (see Supporting Information) showed this compound to be **10** (Chart 1), thus confirming that the minor epoxy thioglycoside produced by this route is **14**. Oxidation of **5** and **14** to sulfoxides **6** and **15** proceeded in 79% and 77% yields, respectively. As in the preparation of **2**, a mixture of both diastereomeric sulfoxides was produced.

In an attempt to shorten the synthesis of **5** and **6**, we investigated the possibility of installing the thioglycoside directly from **11**, by reaction with *p*-thiocresol and boron trifluoride etherate. Although under these conditions some of the desired thioglycoside (**16**, Chart 1) was produced, the yields were not reproducible and significant amounts of dithioacetal **17** (Chart 1) were sometimes also formed. We therefore view the route that proceeds via **13** as superior.

Glycosylation Reactions. With donors **1**, **2**, **5**, and **6** in hand, we explored their use in glycosylation reactions. We first studied the ability of **1** and **2** to glycosylate a panel of alcohols (**18**−**34**, Chart 2).[13] The results of these glycosylation reactions are presented in Table 1. The thioglycosides were activated by treatment with *N*-iodosuccinimide (NIS) and silver triflate (AgOTf)[14] at −40 °C in dichloromethane (activation method A, Table 1). With the sulfoxide donors, we employed triflic anhydride (Tf_2O) activation in dichloromethane[15] using the protocol developed by Crich and co-workers.[16] Under these conditions, the sulfoxide was treated first with Tf_2O in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) and, after the mixture was stirred for a certain period of time, the alcohol was added. Two variants of this method were explored. Initially, we used a protocol in which after the sulfoxide was treated with Tf_2O at −78 °C, the reaction mixture was stirred for 10 min at this temperature before the alcohol was added (activation method B). Later, on the basis of the results of low-temperature NMR experiments,[17] we modified the protocol such that after the reaction mixture was stirred at −78 °C for 10 min, the solution was warmed to −40 °C and then stirred for 20 min prior to the addition of the alcohol (activation method C).

From the results presented in Table 1, it is clear that that **1** and **2** do efficiently glycosylate a range of alcohols with a very high degree of stereocontrol. Primary, secondary, and tertiary simple alcohols are readily glycosylated (Table 1, entries 1−4), as are primary and secondary carbohydrate alcohols (Table 1, entries 5−32). In all examples, the major product is the β-glycoside, the product in which the newly formed bond is cis to the epoxide. Frequently, the stereoselectivity is total and only the β-glycoside is formed.

Table 1. Glycosylations with **1** and **2**



entry	R′	alcohol	activation[a]	product	yield (%)[b]	β:α ratio[c]
1	STol	**18**	A	**35**	79	β only
2	STol	**19**	A	**36**	81	β only
3	STol	**20**	A	**37**	83	6.5:1
4	STol	**21**	A	**38**	80	8:1
5	STol	**22**	A	**39**	77	β only
6	STol	**24**	A	**40**	81[d]	7:1
7	STol	**25**	A	**41**	83	5:1
8	STol	**26**	A	**42**	81	9:1
9	STol	**27**	A	**43**	72	β only
10	STol	**28**	A	**44**	84	β only
11	STol	**29**	A	**45**	79	β only
12	STol	**30**	A	**46**	81	β only
13	STol	**31**	A	**47**	82[e]	3:1
14	STol	**32**	A	**48**	51[f]	3:2
15	STol	**33**	A	**49**	82	7:1
16	STol	**34**	A	**50**	75[g]	5:1
17	S(O)Tol	**22**	B	**38**	82	β only
18	S(O)Tol	**22**	C	**38**	84	β only
19	S(O)Tol	**24**	B	**40**	80	10:1
20	S(O)Tol	**24**	C	**40**	82	β only
21	S(O)Tol	**25**	B	**41**	78	8:1
22	S(O)Tol	**26**	B	**42**	82	9:1
23	S(O)Tol	**26**	C	**42**	83	β only
24	S(O)Tol	**29**	B	**45**	83	5:1
25	S(O)Tol	**29**	C	**45**	79	β only
26	S(O)Tol	**31**	B	**47**	74	7:1
27	S(O)Tol	**31**	C	**47**	80	β only
28	S(O)Tol	**33**	B	**49**	71	β only
29	S(O)Tol	**33**	C	**49**	77	β only
30	S(O)Tol	**34**	B	**50**	78	8:1
31	S(O)Tol	**34**	C	**50**	81	β only
32	STol	**18**	D	**35**	77	β only

[a] Legend: (A) stir thioglycoside (0.6 mmol), alcohol (0.5 mmol), *N*-iodosuccinimide (0.6 mmol), silver triflate (0.15 mmol), and crushed 4 Å molecular sieves in 10 mL of CH_2Cl_2 at −40 °C; (B) stir sulfoxide (0.5 mmol), Tf_2O (0.6 mmol), DTBMP (2.0 mmol), and crushed 4 Å molecular sieves in 10 mL of CH_2Cl_2 at −78 °C for 10 min and then add the alcohol (0.6 mmol); (C) stir sulfoxide (0.5 mmol), Tf_2O (0.6 mmol), DTBMP (2.0 mmol), and crushed 4 Å molecular sieves in 10 mL of CH_2Cl_2 at −78 °C for 10 min, raise the temperature to −40 °C and stir for 20 min, and then add the alcohol (0.6 mmol); (D) stir thioglycoside (0.6 mmol), 1-benzenesulfinyl piperidine (BSP, 0.6 mmol), DTBMP (1.2 mmol), and crushed 4 Å molecular sieves in 10 mL of CH_2Cl_2 at −60 °C for 20 min and then add Tf_2O (0.7 mmol); after 15 min, warm the reaction mixture to −40 °C and then add the acceptor (0.8 mmol) in CH_2Cl_2 (1 mL) and stir for 10 min. [b] Isolated yield following chromatography. [c] Ratio determined by product yields following chromatography. [d] 5% of **51** obtained. [e] 11% of **52** obtained. [f] 20% of **53** obtained. [g] 20% of **54** obtained.

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(13) Alcohols **18**−**21** are commercially available, while acceptors **22**−**29** and **31**−**33** were synthesized as previously reported. **22**: Reference 10. **23**: Reference 19. **24**: Reference 8. **25**: Reference 6e. **26**: Montgomery, J. A.; Shortnacy, A. T.; Thomas, H. J. *J. Med. Chem.* **1974**, *17*, 1197. **27**: Sondheimer, S. J.; Eby, R.; Schuerch, C. *Carbohydr. Res.* **1978**, *60*, 187. **28**, **29**, **33**: Ek, M.; Garegg, P. J.; Hultberg, H.; Oscarson, S. *J. Carbohydr. Chem.* **1983**, *2*, 305. **31**: Mulard, L. A.; Kovac, P.; Glaudemans, C. P. J. *Carbohydr. Res.* **1994**, *259*, 21. **32**: Eby, R.; Schuerch, C. *Carbohydr. Res.* **1982**, *100*, C41. The synthesis of **30** and **34** is described in the Experimental Section.
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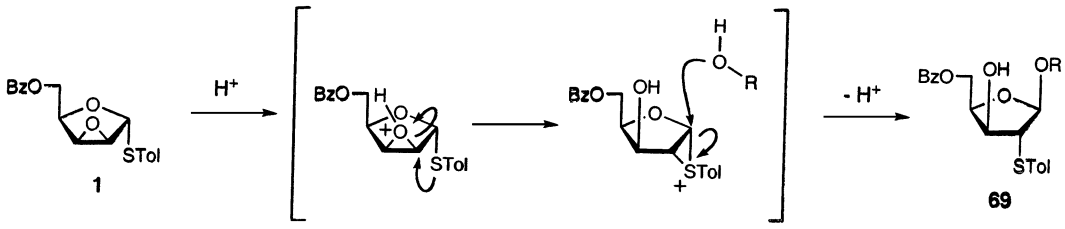


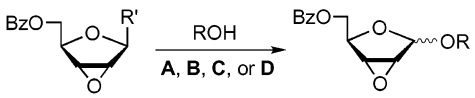
Figure 2. Proposed formation of 2-*p*-thiotoluyl-β-D-xylofuranosides (**69**) from *p*-thiotoluyl glycosides with the 2,3-anhydro-α-D-*lyxo* stereochemistry (**1**).

It was not possible to determine the C-1 stereochemistry of the product glycosides from the NMR parameters usually used for the assignment of anomeric stereochemistry in furanosides, the chemical shift of C-1, or the magnitude of $^3J_{H-1,H-2}$.[18] We have, however, previously shown that an unambiguous parameter that can be used for assigning the stereochemistry in 2,3-anhydro-*O*-glycosides is the magnitude of the one-bond C-1,H-1 coupling constant.[19] In glycosides in which H-1 is *trans* to the epoxide moiety, $^1J_{C-1,H-1} = 163-168$ Hz; when this hydrogen is *cis* to the oxirane ring, $^1J_{C-1,H-1} = 171-174$ Hz. This method was used for assigning the anomeric stereochemistry of the glycosylation products.

In analyzing the yields and β:α ratios presented in Table 1, some trends can be noted. First, in general, the β-selectivity decreases with increasing steric hindrance on the alcohol. Similarly, electron-withdrawing protecting groups on the acceptor decrease the β-selectivity (compare entries 6 and 8, Table 1). However, even with relatively unreactive secondary carbohydrate alcohols the β:α ratios are better than 5:1 in most cases. The worst selectivity (3:2 β:α) is observed in the reaction of **32** with thioglycoside **1**. Second, a comparison of the glycosylations employing sulfoxide **2** with those that use thioglycoside **1** reveals that the former provides not only better yields of the products but also higher β:α selectivities. Third, in the activation of sulfoxide **2**, the length of time the reaction mixture is stirred prior to the addition of the alcohol significantly influences the outcome of the reaction. Better yields and β:α selectivity result from stirring the reaction mixture for a longer time and by warming it to -40 °C before adding the alcohol (compare reactions involving activation conditions B vs C for the same acceptor: e.g., entries 26 and 27). We also observed that in some of the glycosylations with thioglycoside **1** that small amounts of 2-deoxy-2-thiocresyl-β-D-xylofuranosides (e.g., **69**, Figure 2) were produced in addition to the desired 2,3-anhydro sugar glycosides. Presumably, these byproducts are formed by the pathway outlined in Figure 2, which is promoted by the triflic acid that is produced as the reaction proceeds.[20] We attempted to circumvent this rearrangement process by adding DTBMP to the reaction mixture to neutralize any triflic acid that was generated. However, this resulted in very low conversion of the thioglycosides. Therefore, ensuring that the reaction mixture is alkaline is not a viable method for preventing the formation of the 2-thiocresyl glycoside byproducts. Taken together, these observations point to sulfoxide **2** being a superior glycosylating agent when compared to thioglycoside **1**.

We next turned our attention to glycosylations involving thioglycoside **5** and glycosyl sulfoxide **6** (Table 2). The methods used for the activation of these susbstrates were identical with those used with **1** and **2**, and the magnitude of the $^1J_{C,H}$ was again used to determine the stereochemistry at the anomeric center in the product glycosides.[19] As with **1** and **2**, the glycosylations with **5** and **6** provided, as the major product, the glycoside in which the aglycone is oriented *cis* to the epoxide moiety. Given the stereochemistry of the epoxide ring in **5** and **6**, these reactions produce predominantly the α-glycoside.

Table 2. Glycosylations with **5** and **6**



entry	R'	alcohol	activation[a]	product	yield (%)[b]	β:α ratio[c]
1	STol	**18**	A	**55**	80	α only
2	STol	**19**	A	**56**	82	α only
3	STol	**20**	A	**57**	81	α only
4	STol	**21**	A	**58**	80	α only
5	STol	**22**	A	**59**	78	α only
6	STol	**23**	A	**60**	82	α only
7	STol	**24**	A	**61**	78	9:1
8	STol	**25**	A	**62**	80	9:1
9	STol	**26**	A	**63**	88	14:1
10	STol	**27**	A	**64**	84	α only
11	STol	**29**	A	**65**	81	α only
12	STol	**32**	A	**66**	88	8:1
13	STol	**33**	A	**67**	82	8:1
14	STol	**34**	A	**68**	84	α only
15	S(O)Tol	**22**	B	**59**	84	α only
16	S(O)Tol	**25**	B	**62**	82	α only
17	S(O)Tol	**27**	B	**64**	77	α only
18	S(O)Tol	**27**	C	**64**	84	α only
19	S(O)Tol	**29**	B	**65**	86	α only
20	S(O)Tol	**29**	C	**65**	87	α only
21	S(O)Tol	**32**	B	**66**	63	6:1
22	S(O)Tol	**32**	C	**66**	75	α only
23	S(O)Tol	**33**	B	**67**	82	α only
24	S(O)Tol	**33**	C	**67**	85	α only
25	S(O)Tol	**34**	B	**68**	85	α only
26	S(O)Tol	**34**	C	**68**	85	α only
27	STol	**18**	D	**55**	77	α only

[a] Legend: (A) stir thioglycoside (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) stir sulfoxide (0.5 mmol), Tf_2O (0.6 mmol), and DTBMP (2.0 mmol) in 10 mL of CH_2Cl_2 at -78 °C for 10 min and then add the alcohol (0.6 mmol); (C) stir sulfoxide (0.5 mmol), Tf_2O (0.6 mmol), and DTBMP (2.0 mmol) in 10 mL of CH_2Cl_2at -78 °C for 10 min, raise the temperature to -40 °C and stir for 20 min, and then add the alcohol (0.6 mmol; (D) stir thioglycoside (0.6 mmol), 1-benzenesulfinyl piperidine (BSP, 0.6 mmol), DTBMP (1.2 mmol), and crushed 4 Å molecular sieves in 10 mL of CH_2Cl_2 at -60 °C for 20 min and then add Tf_2O (0.7 mmol); after 15 min, warm the reaction mixture to -40 °C and then add the acceptor (0.8 mmol) in CH_2Cl_2 (1 mL) and stir for 10 min. [b] Isolated yield following chromatography. [c] Ratio determined by product yields.

(18) Mizutani, K.; Kasai, R.; Nakamura, M.; Tanaka, O.; Matsuura, H. *Carbohydr. Res.* **1989**, *185*, 27.
(19) Callam, C. S.; Gadikota, R. R.; Lowary, T. L. *J. Org. Chem.* **2001**, *66*, 4549.
(20) Analogous migrations of thioglycosides have been previously reported: (a) Yu, B.; Yang, Z. *Org. Lett.* **2001**, *3*, 377. (b) Johnston, B. D.; Pinto, B. M. *J. Org. Chem.* **2000**, *65*, 4607. (c) Zuurmond, H. M.; van der Klein, P. A. M.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron* **1993**, *49*, 6501. (d) Auzanneau, F. I.; Bundle, D. R. *Carbohydr. Res.* **1991**, *212*, 13.

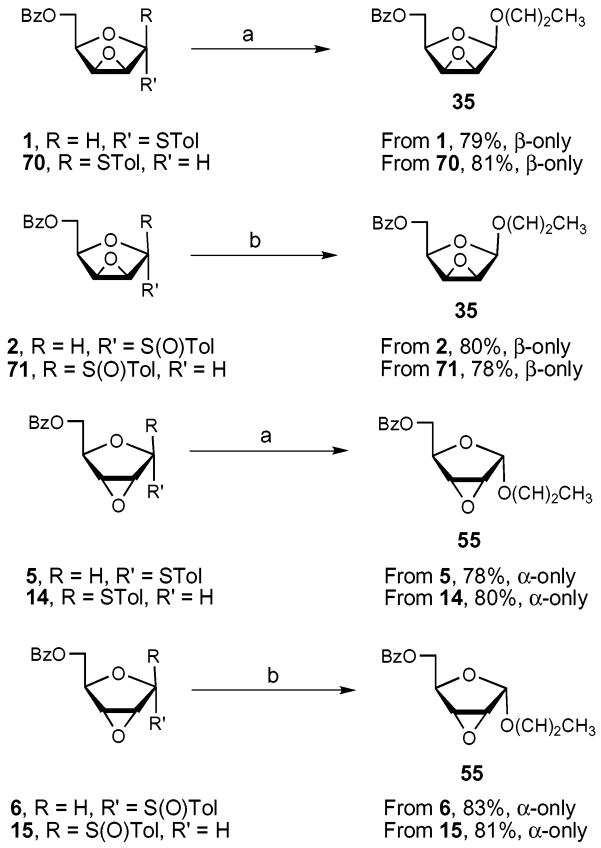


Figure 3. Reactions carried out to determine if the stereochemistry at the anometric center in the donor influences the stereochemical outcome of the glycosylation reactions. Note that the yields are high and essentially identical regardless of the anomeric stereochemistry in the donor. Legend: (a) *n*-octanol, NIS, AgOTf, CH_2Cl_2, −40 °C, see conditions A in Table 1 for protocol; (b) Tf_2O, DTBMP, CH_2Cl_2, −78 °C, then *n*-octanol, see conditions B in Table 1 for protocol.

When these reactions are compared with those employing **1** and **2**, some differences are observed. First, the stereoselectivity of the reactions with **5** and **6** is generally higher than those with **1** and **2**.[21] Second, whereas glycosyl sulfoxide **2** is a superior donor to thioglycoside **1**, the reverse situation is true with **5** and **6**. In general, sulfoxide **6** provides the products in lower yield than thioglycoside **5**. Finally, with thioglycoside **5**, only trace amounts of the 1-thiocresyl rearrangement products are produced. The formation of these rearranged byproducts was more significant with **1**.

We also demonstrated that both thioglycosides **1** and **5** can be converted to *O*-glycosides with high stereoselectivity upon activation with 1-benzenesulfinyl piperidine (BSP)[22] (see Table 1, entry 32, and Table 2, entry 27).

In further studies, we explored if the stereochemistry at the anomeric center in the donor influences the stereochemical outcome of the reaction (Figure 3). To this end, we glycosylated *n*-octanol with **1** and **2**, as well as their β-anomer counterparts **70** and **71**.[23] With all four donors, the β-glycoside was obtained

(21) The relatively increased stereoselectivity may by due to neighboring group participation from the O-5 benzoate group. Such an event would lead to the formation of an acyloxonium ion over the β-face of the furanose ring, thus forcing the alcohol to attack C-1 from the α-face. However, we see no evidence of the formation of this intermediate. In particular, no ortho ester byproduct was detected in the glycosylations with sulfoxide **6**. Under the basic reaction conditions of these reactions, the formation of an acyloxoium ion of this type would be expected to lead to the formation of significant amounts of this ortho ester byproduct.

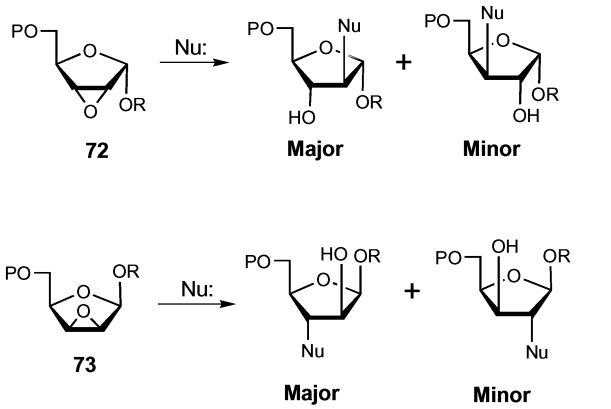


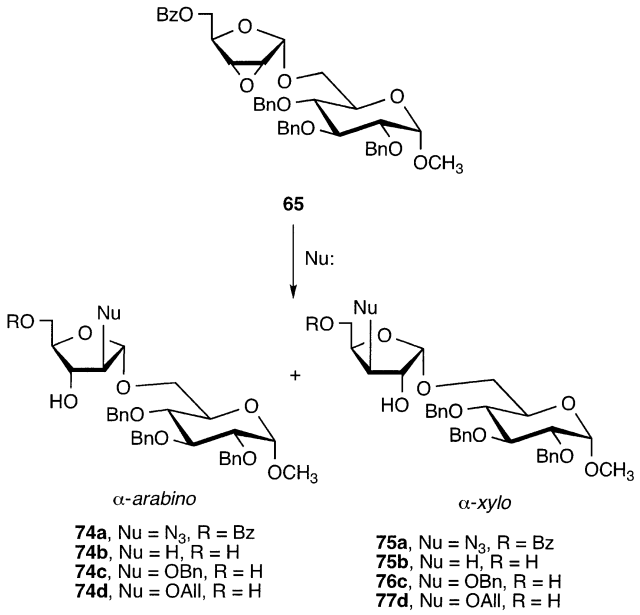
Figure 4. Possible products resulting from the nucleophilic opening of the epoxide moiety of 2,3-anhydro-α-D-ribofuranosides (**72**) and 2,3-anhydro-β-D-lyxofuranosides (**73**).

in essentially identical yield. Analogous results were obtained upon glycosylation with the 2,3-anhydro-D-*ribo* donors; coupling of *n*-octanol with **5**, **6**, **14**, or **15** gave the α-glycoside in nearly the same yield. Thus, the stereochemistry at the anomeric center in the donor does not influence the β:α ratio of the products.[17] In other experiments, we determined that the stereochemistry at sulfur in the sulfoxides had no impact on the α:β ratio in the products (see Table S1 in the Supporting Information).

Epoxide Ring Opening Reactions. If anhydro sugar derivatives **1**, **2**, **5**, and **6** are to be useful reagents for the synthesis of glycosidic bonds, then it is critical that methods be available for the regioselective opening of the oxirane ring in the glycoside products. 2,3-Anhydro sugars have proven to be useful intermediates for the preparation of a number of modified sugar derivatives, in particular in the area of nucleoside synthesis.[24] On the basis of previous studies[24,25] addressing the nucleophilic opening of the epoxide rings in these anhydro sugars, we expected that the regioselectivity of the reaction with the 2,3-anhydro-D-*ribo* glycosides (e.g., **72**, Figure 4) would be high. Nucleophilic attack at C-2 would be preferred because the protected hydroxymethyl substituent at C-4 hinders C-3 attack. In contrast, we expected that the regioselectivity of the epoxide openings in the 2,3-anhydro-D-*lyxo* glycoside series (e.g., **73**, Figure 4) would be lower. Solely on the basis of steric hindrance considerations, nucleophilic attack at either C-2 or C-3 would be expected to be equally likely, as the bottom face of the furanose ring has no substituents to bias the approach of the nucleophile to the epoxide. However, previous results[24,25] did suggest that, although the regioselectivity of the reaction with **73** would likely be reduced relative to **72**, attack at C-3 would be preferred with most nucleophiles. The factors that govern the regioselectivity preference in the nucleophilic opening of 2,3-anhydro-β-D-*lyxo* furanosides are not completely understood.

(22) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015.
(23) These compounds were synthesized using the transformations outlined in Scheme 1 from the β-anomer of **8**, which was obtained as a minor byproduct in its synthesis (see Supporting Information).
(24) For some examples see: (a) Huryn, D. M.; Okabe, M. *Chem. Rev.* **1992**, *92*, 1745. (b) Habich, D.; Barth, W. *Synthesis* **1988**, 943 (c) Mengel, R.; Griesser, H. *Tetrahedron Lett.* **1977**, *18*, 1177. (d) Robins, M. J.; Janda, K. D.; Hansske, F.; Chen, J. *J. Org. Chem.* **1991**, *56*, 3410. (e) Roussev, C. D.; Simeonov, M. F.; Petkov, D. D. *J. Org. Chem.* **1997**, *62*, 5239. (f) Reichman, U.; Hollenberg, D. H.; Chu, C. K.; Fox, J. J. *J. Org. Chem.* **1976**, *41*, 2043. (g) Robins, M. J.; Fouron, Y.; Mengel, R. *J. Org. Chem.* **1974**, *39*, 1564. (h) Miah, A.; Reese, C. B.; Song, Q.; Sturdy, Z.; Neidle, S.; Simpson, I. J.; Read, M.; Rayner, E. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3277.
(25) Williams, N. R. *Adv. Carbohydr. Chem. Biochem.* **1970**, *25*, 109.

Table 3. Opening of α-*ribo*-Epoxides



74a, Nu = N_3, R = Bz
74b, Nu = H, R = H
74c, Nu = OBn, R = H
74d, Nu = OAll, R = H

75a, Nu = N_3, R = Bz
75b, Nu = H, R = H
76c, Nu = OBn, R = H
77d, Nu = OAll, R = H

entry	nucleophile	solvent	temp (°C)	time (h)	yield (%)[a]	*arabino*:*xylo* ratio[c]
1	NaN_3[b]	EtOH	reflux	6	91	9:1 (**74a**:**75a**)
2	$LiAlH_4$	THF	reflux	3	84	10:1 (**74b**:**75b**)
3	NaOBn	BnOH	120	2	87	8:1 (**74c**:**75c**)
4	NaOAll	AllOH	120	2	85	8:1 (**74d**:**75d**)

[a] Isolated yield. [b] NH_4Cl added to the reaction mixture. [c] Ratio determined by by ^1H NMR spectroscopy, through integration of the resonances for the anomeric hydrogen of the nonreducing sugar residue.

One possible explanation for this experimental observation is that the partial positive charge that develops in the S_N2 transition state is favored at C-3 relative to C-2, due to the latter's closer proximity to the electron-withdrawing anomeric center.[25]

Mindful of these issues, we explored the nucleophilic opening of the epoxides in the some of the product glycosides. At the outset, we note that one characteristic shared by all of the epoxy glycosides is the stability of the oxirane ring. In order for the ring-opening reactions to proceed at a reasonable rate, it was necessary that they be carried out at elevated temperatures. Despite having to heat these reaction mixtures to moderately high temperatures, no significant amount of product or substrate degradation was observed and the ring-opened products were always isolated in good to excellent yield. We also point out that in the reactions with some nucleophiles (hydride, alkoxides) that the *O*-5-benzoyl group is cleaved during the course of the reaction.

We first explored the opening of the glycosides with the 2,3-anhydro-D-*ribo* stereochemistry, using **65** as a model substrate (Table 3). As predicted, the regioselectivity of the openings is high with all the nucleophiles used (NaN_3, $LiAlH_4$, NaOBn, NaOAll). Attack at C-2 is preferred, and the α-arabinofuranoside is produced as the major product over the α-xylofuranoside. In all cases, the regioselectivity is better than 8:1 and the combined yields of **74** and **75** are excellent. The structures of the major products could be readily determined through the use of ^1H and ^{13}C NMR spectroscopy.[26]

Monosaccharide **35** and disaccharides **42** and **45** were used as model substrates when exploring the regioselectivity of the nucleophilic opening of the epoxide in species containing a 2,3-anhydro-β-D-lyxofuranoside moiety (Table 4). Our initial investigations showed that, as previously reported,[8] relatively disappointing levels of regioselectivity resulted from the reactions in which NaN_3, $LiAlH_4$, NaOBn, or NaOAll was used as the nucleophile. Although C-3 attack was favored, the ratio of β-arabinofuranoside to β-xylofuranoside was at best 3.7:1. While this regioselectivity was disappointing, we were nevertheless encouraged enough to explore a number of modifications of the reaction conditions. Given our interest in synthesizing naturally occurring oligosaccharides via this route, our attention was focused on the use of the alkoxides as nucleophiles. Through variation of the reaction conditions we have discovered that the regioselectivity can be dramatically improved by changing the counterion and through the use of additives. We initially carried out the reaction with NaOBn in the presence of 18-crown-6, but no change in regioselectivity was observed relative to the reaction in the absence of the additive (compare entries 3 and 5, Table 4). Changing the counterion to potassium, in either the presence or the absence of 18-crown-6, reduced the regioselectivity (Compare entries 3, 6, and 7, Table 4). In contrast, replacement of sodium with lithium provided a significant increase in regioselectivity, in favor of C-3 attack. This substitution increased the *arabino*:*xylo* ratio from 3.5:1 to 6.5:1 (compare entries 3 and 8, Table 4). When the reaction with the lithium alkoxide was carried out in the presence of 15-crown-5 (1.2 equiv relative to the amount of LiOBn) the regioselectivity was increased further to 10:1 in favor of the β-arabinofuranoside (Table 4, entry 9). In addition to enhancing the regioselectivity, another advantage of using the crown ether is that the reaction can be carried out at a significantly lower temperature; 80 °C vs 120 °C. The use of TMEDA as the additive gave results inferior to those obtained with the crown ether (Table 4, entry 10), as both the regioselectivity and the rate of reaction were reduced. The most impressive results were obtained when (−)-sparteine (**78**, Chart 3) was added to the reaction mixture. *Heating* **35**, **42**, or **45** *with LiOBn in benzyl alcohol in the presence of (−)-sparteine (1.2 equiv relative to the amount of the lithium alkoxide) provided the β-arabinofuranoside as the sole product in excellent yield (Table 4, entries 11−15).* Additionally, in the presence of (−)-sparteine the reaction was substantially faster than the reactions both in the absence of the additive and in the presence of 15-crown-5. Whereas the reaction with no additive required 3 h at 120 °C to complete, when **78** was added, the reaction was done in 20 min at 70 °C.

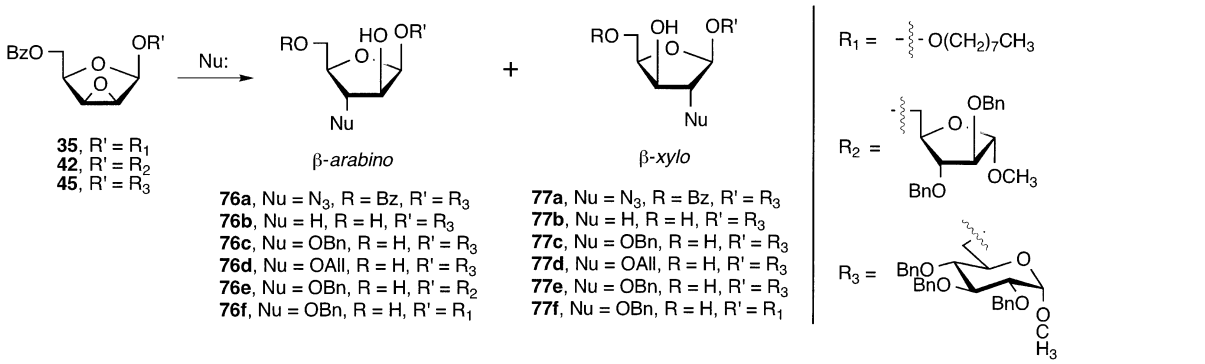
We are currently unsure as to the origin of the remarkable regioselectivity that is observed when **78** is added to these reaction mixtures. The use of (−)-sparteine in conjunction with alkyllithiums to carry out chiral deprotonation reactions is well-known,[27] and this methodology has recently been extended to α-deprotonations of *meso*-epoxides (e.g., **79**, Chart 3) for the enantioselective synthesis of bicyclic alcohols (e.g. **80**)[28] Another recent report describes the use of **78** as a ligand for

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

(27) (a) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed.* **1997**, *36*, 2282. (b) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552.

(28) (a) Hodgson, D. M.; Cameron, I. D.; Christlien, M.; Green, R.; Lee, P. G.; Robinson, L. A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2161. (b) Alexakis, A.; Vrancken, E.; Mangeney, P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3354.

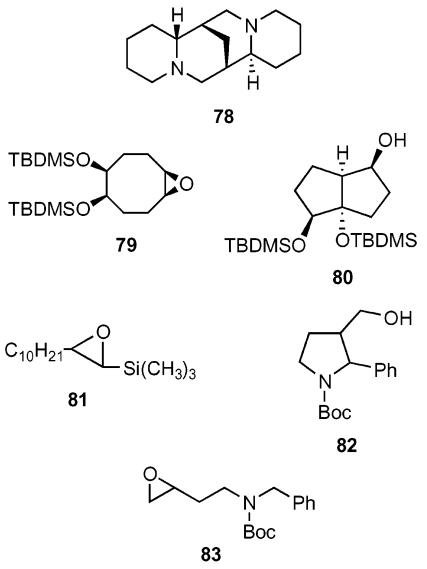
Table 4. Opening of *β-lyxo*-Epoxides



entry	substrate	nucleophile	additive	solvent	temp (°C)	time	yield (%)[a]	*arabino*:*xylo* ratio[b]
1	**45**	NaN_3	NH_4Cl	EtOH	reflux	3 h	90	3:1 (**76a**:**77a**)
2	**45**	$LiAlH_4$		THF	reflux	3 h	86	3:1 (**76b**:**77b**)
3	**45**	NaOBn[c]		BnOH	120	3 h	81	3.5:1 (**76c**:**77c**)
4	**45**	NaOAll[c]		AllOH	120	3 h	83	2.9:1 (**76d**:**77d**)
5	**45**	NaOBn[c]	18-crown-6[d]	BnOH	120	3 h	67	3.7:1 (**76c**:**77c**)
6	**45**	KOBn[c]		BnOH	120	3 h	73	2.6:1 (**76c**:**77c**)
7	**45**	KOBn[c]	18-crown-6[d]	BnOH	120	3 h	70	2.7:1 (**76c**:**77c**)
8	**45**	LiOBn[c]		BnOH	120	3 h	79	6.5:1 (**76c**:**77c**)
9	**45**	LiOBn[c]	15-crown-5[d]	BnOH	80	3 h	71	10:1 (**76c**:**77c**)
10	**45**	LiOBn[c]	TMEDA	BnOH	70	5 h	70	7:1 (**76c**:**77c**)
11	**45**	LiOBn[c]	(−)-sparteine[d]	BnOH	70	20 min	85	only *arabino* (**76c**)
12	**42**	LiOBn[c]	(−)-sparteine[d]	BnOH	70	20 min	83	only *arabino* (**76e**)
13	**35**	LiOBn[c]	(−)-sparteine[d]	BnOH	70	20 min	86	only *arabino* (**76f**)
14	**45**	NaOBn[c]	(−)-sparteine[d]	BnOH	70	3 h	62	3.5:1 (**76c**:**77c**)

[a] Isolated yield. [b] Ratio determined by product yields or by ^{1}H NMR spectroscopy, through integration of the resonances for the anomeric hydrogen of the nonreducing sugar residue. [c] 3.0 equiv of alkoxide relative to epoxide. [d] 1.2 equiv of additive relative to alkoxide.

Chart 3



the synthesis of α,*β*-epoxy silanes[29] (**81**, Chart 3). However, reports of the use of (−)-sparteine as a means for influencing addition reactions to epoxides are much less frequent. Alexakis and co-workers have described that the reaction of organolithium reagents to *meso*-epoxides in the presence of **78** and boron trifluoride affords ring-opened products with moderate enantiomeric excess.[30] More recent work by Beak and co-workers has described the asymmetric synthesis of *N*-Boc-protected pyrrolidines and piperidines (e.g., **82**) via treatment of *N*-Boc protected amines (e.g., **83**) with *n*-butyllithium and **78**.[31] However, to the best of our knowledge, the work described in this report is the first example of the use of (−)-sparteine as a method for controlling the regioselectivity of an epoxide opening using a non-carbon nucleophile.

Our initial supposition was that the chirality of **78** was an important factor in determining the outcome of the reaction through the formation of a matched pair complex with the epoxide and the lithium ion. Similar complexes have been proposed in other (−)-sparteine-mediated reactions of epoxides.[32] This is supported by the observation that when these additions are carried out with either 15-crown-5 or TMEDA, the regioselectivities of the reactions are lower than when **78** is used. Unfortunately, (+)-sparteine is not readily available,[33] and so we were unable to test this hypothesis by carrying out the reaction in the presence of the enantiomer of **78**. However, both D- and L-arabinose are commercially available at low cost, and the easy access to these sugars allowed us to determine if the absolute stereochemistry of **78** was an important factor in the regioselectivity of these reactions. Three disaccharides, **84**−**86**, were synthesized (see the Supporting Information for details), and the epoxide ring in each was opened with LiOBn in the presence of (−)-sparteine. The results, together with those for disaccharide **42**, are presented in Figure 5. From these investigations, it is clear that glycosides containing the 2,3-anhydro-*β*-L-lyxofuranoside moiety (e.g., **84** and **86**) are also opened at C-3 by LiOBn with similarly high regioselectivity. Furthermore, when the stereochemistry of the reducing-end residue is changed

(29) Hodgson, D. M.; Norsikian, S. L. M. *Org. Lett.* **2001**, *3*, 461.

(30) Alexakis, A.; Vrancken, E.; Mangeney, P. *Synlett* **1998**, 1165.
(31) Serino, C.; Stehle, N.; Park, Y. S.; Florio, S.; Beak, P. *J. Org. Chem.* **1999**, *64*, 1160.
(32) Hodgson, D. W.; Gibbs, A. R. Lee, G. P. *Tetrahedron* **1996**, *52*, 14361.
(33) The first asymmetric synthesis of (+)-sparteine has been reported recently: Smith, B. T.; Wendt, J. A.; Aube, J. *Org. Lett.* **2002**, *4*, 2577.

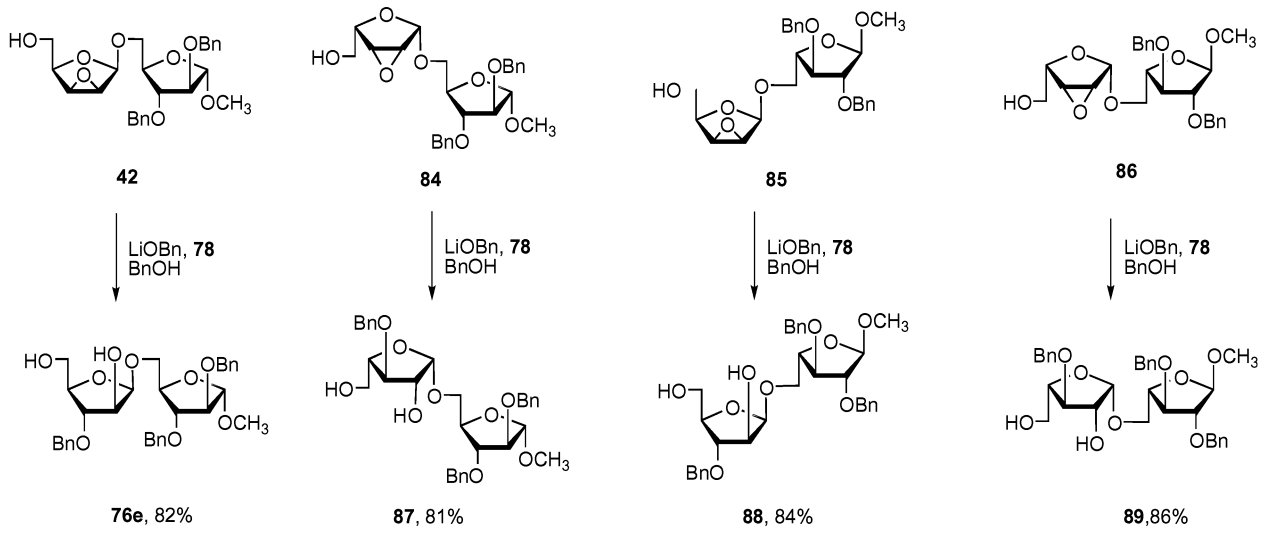


Figure 5. Demonstration that the chirality of the (−)-sparteine is not important in determining the regiochemical outcome of the nucleophilic opening of 2,3-anhydro-β-lyxofuranosides.

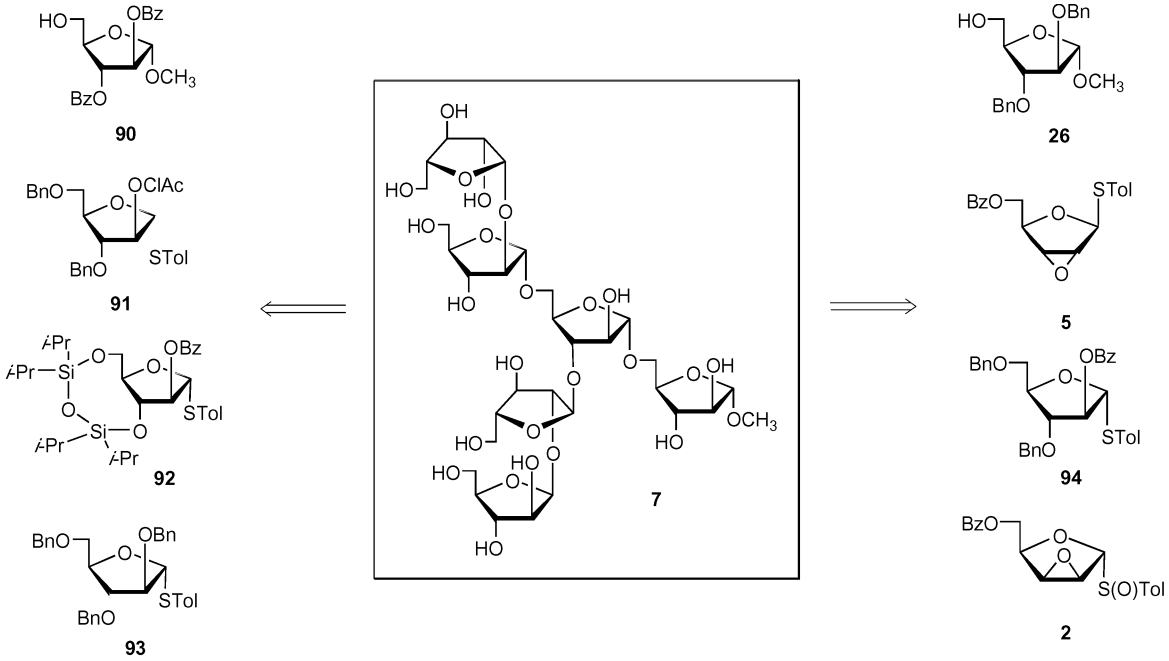
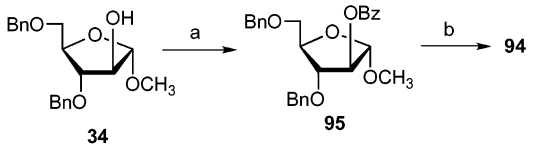


Figure 6. Retrosynthetic analysis of **7**. A previous synthesis[7a] employed monosaccharides **90**−**93** (left-hand side). The synthesis described here uses **2**, **5**, **26**, and **94** (right-hand side).

from D to L (**85**, **86**), the regioselectivity is unchanged. It appears, therefore, that the chirality of **78** is unimportant in determining the regiochemistry of the epoxide ring opening reaction. Consideration of the results in Figure 5, together with the fact that the selectivity of the ring opening is reduced when TMEDA (Table 4, entry 10) is used suggests that the rigid structure of the (−)-sparteine may be a key issue leading to the high regioselectivity. Also possible is that the bite angle between the nitrogens is important in the binding of the lithium and that the decrease in selectivity with TMEDA is a consequence of the two-carbon tether between the nitrogens that cannot achieve the required geometry.

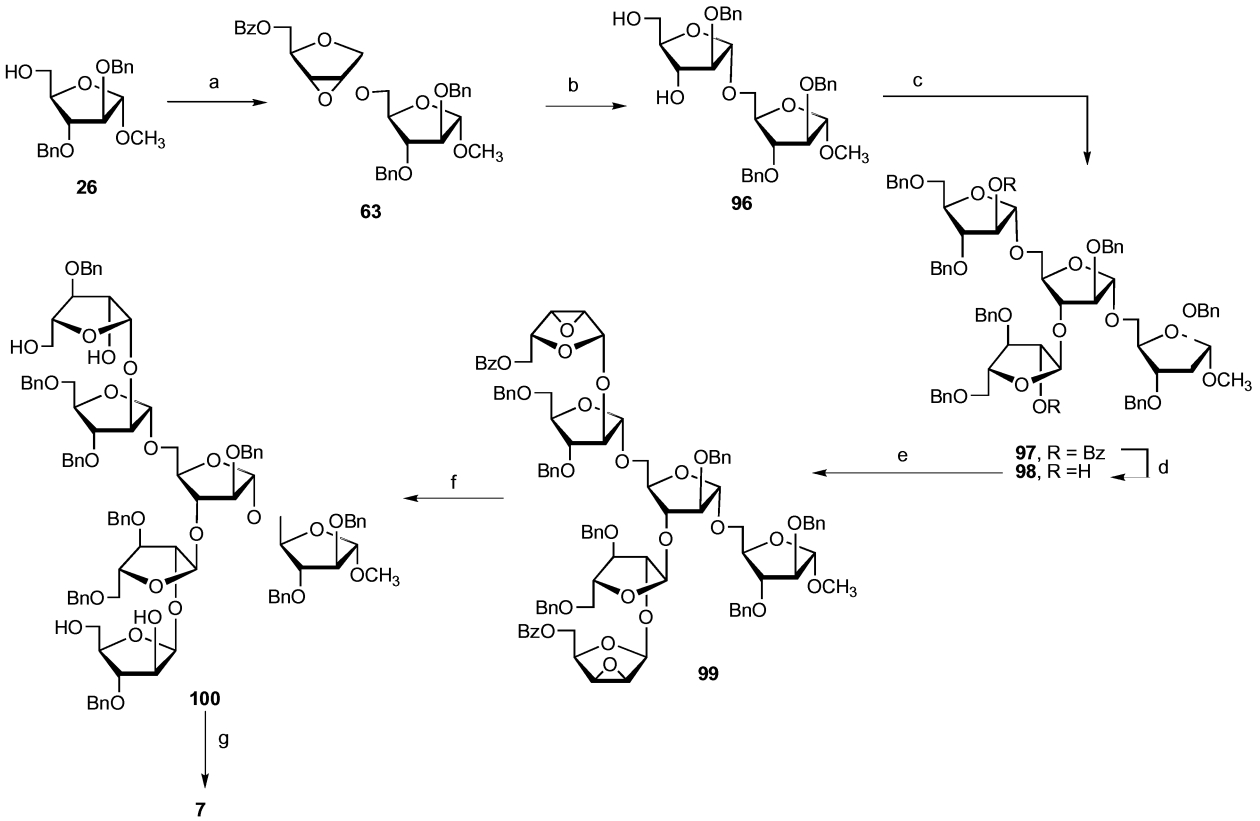
We are currently exploring the scope of this epoxide ring-opening reaction with regard to solvent, additive, and the protecting group on OH-5. In the cases we have examined to date, OH-5 was either unprotected or protected by a base-labile (benzoyl) protecting group that was likely immediately cleaved upon the addition of the alkoxide. It is plausible that a complex involving the lithium ion, (−)-sparteine, the epoxide oxygen, and the alkoxide derived from OH-5 is formed and that this is critical in determining the regioselectivity of the reaction. However, at this point we have no evidence to support the formation of such a complex in these reactions.

Scheme 3 [a]



[a] Legend: (a) BzCl, pyridine, 30 min, 0 °C, 94%; (b) *p*-TolSH, BF_3·OEt_2, CH_2Cl_2, 0 °C → room temperature, 1 h, 93%.

Scheme 4 [a]



[a] Legend: (a) **5**, NIS, AgOTf, CH_2Cl_2, −40 °C, 10 min, 82%; (b) NaOBn, BnOH, 120 °C, 3 h, 84%; (c) **94**, NIS, AgOTf, CH_2Cl_2, 0 °C, 20 min, 81%; (d) $NaOCH_3$, CH_2Cl_2:CH_3OH (3:1), 8 h, room temperature, 98%; (e) **2**, Tf_2O, DTBMP, CH_2Cl_2, −78 °C → −40 °C, then **98**, −40 °C → room temperature, 30 min, 74%; (f) LiOBn, (−)-sparteine, BnOH, 20 min, 70 °C, 71%. (g) 10% Pd/C, H_2, AcOH:H_2O (4:1), 4 h, 91%.

We have also explored the nucleophilic opening of these epoxy glycosides under acidic conditions, but with very little success. No reaction was observed when **35** or **45** was treated with a range of Lewis acids (e.g., $Sm(OTf)_3$, $Ti(O\text{-}i\text{-}Pr)_4$, $LiClO_4$, $Sc(OTf)_3$, $Yb(OTf)_3$) and alcohols (benzyl alcohol, allyl alcohol). Similar results were observed when the chromium salen catalysts developed by Jacobsen and co-workers[34] were used. It appears that these epoxides are sufficiently unreactive to undergo ring-opening reactions promoted by mild Lewis acids. We subsequently used stronger Lewis acids (e.g., $TiCl_4$) for these reactions; however, under these conditions, only decomposition of the epoxy glycoside was observed. Accordingly, on the basis of our results to date, we do not view the nucleophilic opening of these epoxides under acidic conditions as viable.

Application to Oligosaccharide Synthesis. The investigations described above clearly demonstrate the potential of 2,3-anhydrofuranose derivatives in the synthesis of oligosaccharides containing furanose residues. The stereoselectivities of the glycosylation reactions involving **1**, **2**, **5**, and **6** are high, and we have identified conditions under which the epoxide rings in the product glycosides can be opened in a highly regioselective manner. The major products produced from the epoxide ring-opening reactions possess the *arabino* stereochemistry, and hence, these reagents are extremely useful for the synthesis of arabinofuranosides. In particular, the conversion of **1** and **2** into β-arabinofuranosides (Figure 1) is, we believe, the method of choice for the synthesis of these glycosidic linkages, which have previously been notoriously difficult synthetic targets.[6a,b,7a] To further demonstrate the potential of these anhydrosugars in glycoside bond synthesis, we have applied the methodology described here to the synthesis of hexasaccharide **7** (Chart 1), a key structural motif in two mycobacterial cell wall polysaccharides: arabinogalactan and lipoarabinomannan.[9]

One previous synthesis of **7** has been reported, via a route that employs the four monosaccharide building blocks **90**−**93** (Figure 6).[7a,35] The target was obtained from **90**−**93** in seven steps in 21% overall yield. In that synthesis, the key step was a low-temperature glycosylation reaction of a tetrasaccharide diol with 2 equiv of thioglycoside **93**. We envisioned that **7** could be obtained from four other monosaccharide building blocks (**2**, **5**, **26**, and **94**, Figure 6), also in seven steps.

We first turned our attention to the synthesis of the appropriate monosaccharide precursors. Methyl glycoside **26** is known,[13] and the synthesis of **2** and **5** is described above. Thioglycoside **94** was synthesized as outlined in Scheme 3 via a route that started with methyl glycoside **34**.[36]

With the building blocks in hand, the synthesis of hexasaccharide **7** was readily achieved as outlined in Scheme 4. First, glycosylation of alcohol **26** with epoxy thioglycoside **5** provided disaccharide **63** in 82% yield, together with a 6% yield of the corresponding β-glycoside. The oxirane ring in the product was subsequently opened by heating **63** in a solution of sodium benzylate in benzyl alcohol to afford, in 84% yield, disaccharide **96**. Reaction of this diol with an excess of thioglycoside **94**

(34) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421.

(35) Syntheses of two pentasaccharides related to **7** have also been reported.[6a,b]

(36) Synthesized from the known methyl 5-*O*-benzyl-2,3-anhydro-α-D-lyxo-furanoside (Wright, J. A.; Taylor, N. F. *Carbohydr. Res.* **1967**, *3*, 333) as described in the Supporting Information.

provided tetrasaccharide **97**, which was deprotected to give the corresponding diol **98** (79% from **96**). This tetrasaccharide was then glycosylated with glycosyl sulfoxide **2**, providing a 74% yield of hexasaccharide **99**. This reaction also gave small amounts of other stereoisomers of **99** that were not characterized. These byproducts could be easily separated from the desired hexasaccharide by chromatography. Opening of the two epoxides in **99** was achieved by the (−)-sparteine-mediated reaction described above, which provided hexasaccharide **100** in 71% yield. The final product **7** was obtained in 91% yield by hydrogenation of **100**. Using this route, it was possible to synthesize **7** on a >50 mg scale, with the overall yield over the seven steps being 26%. In comparing the route shown in Scheme 4 with the previous synthesis of **7**, the number of steps is equivalent, but the overall yield is slightly higher (26% vs 21%). This synthesis clearly demonstrates that these epoxide-containing glycosylating agents are viable reagents for the synthesis of complex oligosaccharides.

Conclusions

In conclusion, we report here that 2,3-anhydrofuranose thioglycosides and glycosyl sulfoxides **1**, **2**, **5**, and **6** can be used in highly stereoselective glycosylation reactions. The major products are those in which the newly formed glycosidic bond is *cis* to the epoxide moiety. These species represent a fundamentally new class of glycosylating agent in which the hydroxyl groups at C-2 and C-3 are "protected" as an epoxide. We have also demonstrated that post-glycosylation opening of the oxirane moiety can be carried out in a highly regioselective manner providing products with the *arabino* stereochemistry. A particularly notable discovery is that the epoxide moiety in glycosides possessing the 2,3-anhydro-*β*-*lyxo* stereochemistry (e.g., **42**, Table 4) can be regioselectively opened at C-3 by lithium alkoxides when the reaction is carried out in the presence of (−)-sparteine (**78**). This represents the first example of the use of **78** to influence the regioselectivity of an epoxide ring opening reaction with a non-carbon nucleophile. We have further demonstrated the potential of these reagents through the synthesis of hexasaccharide **7**, via a route that is superior to one that we reported previously.[7a] Investigations currently underway include further exploration of the utility of other 2,3-anhydro sugars in glycoside bond synthesis, the determination of the scope of the (−)-sparteine-mediated epoxide ring opening reaction, the elucidation of the mechanisms by which these processes occur,[17] and the application of this methodology to the synthesis of other complex oligosaccharides.

Experimental Section

See the Supporting Information.

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Supporting Information Available: NMR spectra and characterization data for all new compounds, details on the preparation of **84**−**86**, and X-ray crystallographic data for **9** and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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