ORGANIC LETTERS

2010
Vol. 12, No. 16
3686−3689

β-Selective Arabinofuranosylation Using a 2,3-*O*-Xylylene-Protected Donor

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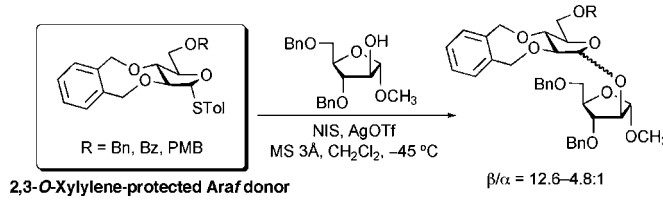
Received July 2, 2010

ABSTRACT



Reported is a novel stereoselective β-arabinofuranosylation that makes use of a conformationally restricted 2,3-*O*-xylylene-protected arabinofuranosyl donor. Optimization of the reaction conditions showed that factors including the structure of the acceptor alcohol, substrate concentration, and protecting group on O-5 of the donor affect the stereochemical outcome of the glycosylation. To demonstrate the utility of the methodology, the synthesis of an oligosaccharide fragment from the mycobacterial cell wall polysaccharide lipoarabinomannan was carried out.

The development of stereoselective glycosylation methods has attracted significant attention given the essential role of carbohydrates in biology.[1] To date, many innovative glycosylation methodologies have been developed;[2] however, most of these address the preparation of pyranose glycosides.[3] In contrast, studies on stereoselective furanosylation have been more limited.[4] There is nevertheless a need for methods that enable the preparation of furanosides in a stereoselective manner, given the critical role that glycoconjugates containing these residues play in the life cycle of a number of microorganisms.[4,5]

Furanose-containing glycans are particularly important in *Mycobacterium tuberculosis*, the organism that causes tuberculosis (TB). This disease has received increasing attention due to the emergence of drug-resistant strains of the bacterium.[6] The *M. tuberculosis* cell wall consists largely of two furanose-rich polysaccharides, the mycolyl−arabinogalactan−peptidoglycan (mAGP) complex, and lipoarabinomannan (LAM).[7] Common to both is an arabinan domain containing D-arabinofuranose (Ara*f*) residues. At the termini of these arabinan chains is a branched structure with two β-Ara*f* residues (Figure 1). In LAM, O-5 of these β-Ara*f* residues is often further capped with other species, including short α-(1→2)-linked oligomannosides as shown in Figure 1.[8]

The synthesis of mAGP and LAM fragments is essential to provide materials for investigations that will lead to the

(1) *Essentials of Glycobiology*, 2nd ed.; Varki, A., Cummings, R. D., Esko, J. D., Freeze, H. H., Stanley, P., Bertozzi, C. R., Hart, G. W., Etzler, M. E., Eds.; Cold Spring Harbor Laboratory Press: New York, 2009.

(2) (a) Zhu, X.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 2. (b) Carmona, A. T.; Moreno-Vargas, A. J.; Robina, I. *Curr. Org. Synth.* **2008**, *5*, 33. (c) *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker, Inc.: New York, 1997.

(3) (a) Demchenko, A. V. *Synlett* **2003**, *9*, 1225. (b) Gridley, J. J.; Osborn, H. M. I. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1471. (c) Bongat, A. F. G.; Demchenko, A. V. *Carbohydr. Res.* **2007**, *342*, 374. (d) Hou, D.; Lowary, T. L. *Carbohydr. Res.* **2009**, *344*, 1911. (e) Ando, H.; Imamura, A. *Trends Glycosci. Glycotechnol.* **2004**, *16*, 293.

(4) For reviews, see: (a) Lowary, T. L. *Curr. Opin. Chem. Biol.* **2003**, *7*, 749. (b) Peltier, P.; Euzen, R.; Daniellou, R.; Nugier-Chauvin, C.; Ferrières, V. *Carbohydr. Res.* **2008**, *343*, 1897.

(5) Richards, M. R.; Lowary, T. L. *ChemBioChem* **2009**, *10*, 1920.

(6) Chiang, C.; Yew, W. W. *Int. J. Tuberc. Lung Dis.* **2009**, *13*, 304.

(7) Kaur, D.; Guerin, M. E.; Skovierova, H.; Brennan, P. J.; Jackson, M. *Adv. Appl. Microbiol.* **2009**, *69*, 23.

(8) Briken, V.; Porcelli, S. A.; Besra, G. S.; Kremer, L. *Mol. Microbiol.* **2004**, *53*, 391.

10.1021/ol101520q
Published on Web 07/19/2010

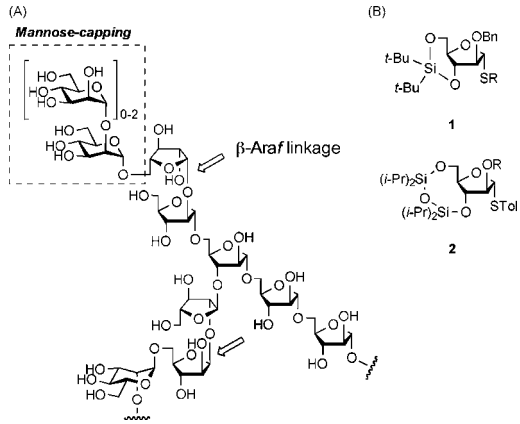


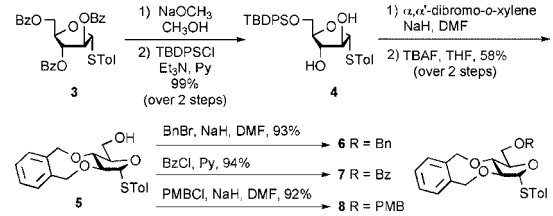
Figure 1. (A) Terminal structure of LAM arabinan. (B) Examples of conformationally locked thioglycosides **1** and **2** used for the stereoselective synthesis of β-Ara*f* residues.[11]

identification of new drug targets and vaccines for treating and preventing TB.[9] A challenge in the synthesis of structures of this type is stereoselectively introducing the β-Ara*f* linkages.[4a] Several innovative approaches for synthesizing these linkages have therefore been reported, including both direct[10,11] and indirect[12] methods. Among the direct methods, the use of conformationally locked donors such as 3,5-*O*-di-*t*-butylsilylene- and 3,5-*O*-tetra-*i*-propyldisiloxane-protected thioglycosides (**1** and **2**, respectively) has shown particular promise.[11]

The design of **1** and **2** was inspired by Woerpel and coworkers' studies on the stereoselectivity of nucleophilic attack onto five-membered ring oxacarbenium ions.[13] It has been proposed[11a] that the high stereocontrol seen in reactions with **1** and **2** arises because attack of the alcohol onto a rigid oxacarbenium ion intermediate is favored from the face leading to the β-glycoside.

Despite the power of this approach, the tethering of the conformationally restricting group between O-3 and O-5 complicates the synthesis of structures in which O-5 of the β-Ara*f* residues is further modified (see Figure 1A). We therefore envisioned an approach to these targets in which the conformation of the ring is locked with a 2,3-*O*-xylylene group (**6**−**8**, Scheme 1).[14,15] It was anticipated[13] that oxacarbenium ions generated from these thioglycosides would adopt conformations favoring β-Ara*f* formation. We report here the methodology using this new donor type and its application to the synthesis of a mycobacterial arabinan fragment.

Scheme 1. Preparation of 2,3-*O*-Xylylene-Protected Donors



The 2,3-*O*-xylylene-protected donors were readily prepared as illustrated in Scheme 1. Thioglycoside **3**[16] was deacylated, and then a TBDPS group was introduced on O-5 to afford **4** in excellent yield over two steps. Incorporation of the xylylene group was achieved upon treatment with α,α′-dibromo-*o*-xylene and NaH in DMF, and subsequent removal of the TBDPS group gave **5** in 58% yield from **4**.[17] The 2,3-*O*-xylylene-protected donors used in this study (**6**−**8**) were efficiently prepared from **5** under standard conditions.

We first explored the use of **6** in coupling reactions with alcohols **9**−**16** (Table 1). All glycosylations were promoted with the NIS−AgOTf promotor system[18] in CH_2Cl_2. The product stereochemistry was confirmed by ^{1}H NMR spectroscopy in $CDCl_3$. For the α-anomer, $J_{1,2}$ is ∼2.0 Hz, while for the β-anomer, $J_{1,2}$ is ∼5.0 Hz.

The effect of acceptor concentration on reaction stereoselectivity[19] was examined first. The glycosylations at relatively low concentration (0.1 M, entry 2) and low concentration (0.03 M, entry 3) proceeded smoothly and afforded the octyl glycoside **17** in excellent yield with slight β-selectivity. The reaction showed no selectivity when performed at high concentration (1.0 M, entry 1).

Next, coupling reactions were performed at various temperatures. Increasing the reaction temperature (Table 1 entry 4) did not improve the β-selectivity, and when the

(9) Umesiri, F. E.; Sanki, A. K.; Boucau, J.; Ronning, D. R.; Sucheck, S. *J. Med. Res. Rev.* **2010**, *30*, 290.

(10) (a) Lee, Y. J.; Lee, K.; Jung, E. H.; Jeon, H. B.; Kim, K. S. *Org. Lett.* **2005**, *7*, 3263. (b) Ishiwata, A.; Akao, H.; Ito, Y.; Sunagawa, M.; Kusunose, N.; Kashiwazaki, Y. *Bioorg. Med. Chem.* **2006**, *14*, 3049.

(11) (a) Zhu, X.; Kawatkar, S.; Rao, Y.; Boons, G.-J. *J. Am. Chem. Soc.* **2006**, *128*, 11948. (b) Crich, D.; Pedersen, C. M.; Bowers, A. A.; Wink, D. J. *J. Org. Chem.* **2007**, *72*, 1553. (c) Wang, Y.; Maguire-Boyle, S.; Dere, R. T.; Zhu, X. *Carbohydr. Res.* **2008**, *343*, 3100. (d) Ishiwata, A.; Akao, H.; Ito, Y. *Org. Lett.* **2006**, *8*, 5525. (e) Joe, M.; Bai, Y.; Nacario, R. C.; Lowary, T. L. *J. Am. Chem. Soc.* **2007**, *129*, 9885.

(12) (a) Désiré, J.; Prandi, J. *Carbohydr. Res.* **1999**, *317*, 110. (b) Ishiwata, A.; Munemura, Y.; Ito, Y. *Eur. J. Org. Chem.* **2008**, 4250. (c) Gadikota, R. R.; Callam, C. S.; Wagner, T.; Fraino, B. D.; Lowary, T. L. *J. Am. Chem. Soc.* **2003**, *125*, 4155.

(13) (a) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208. (b) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Smith, D. M.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 10879.

(14) Biasing the conformation of a pyranose ring with a *cis*-butenyl linker has been reported, but the use of this species in glycosylation reactions has not. Cao, Y.; Kasai, Y.; Bando, M.; Kawagoe, M.; Yamada, H. *Tetrahedron* **2009**, *65*, 2574.

(15) It should be noted that a glycosylation with a 2,3-di-*O*-tetra-*i*-propyldisiloxane-protected arabinofuranose thioglycoside has been reported (ref 11d); the α/β selectivity was ∼ 1:2.5.

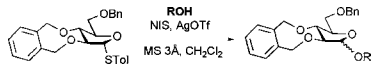
(16) Callam, C. S.; Gadikota, R. R.; Lowary, T. L. *J. Org. Chem.* **2001**, *66*, 4549.

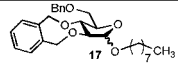
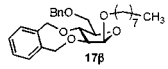
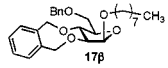
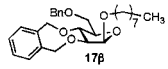
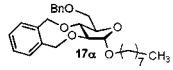
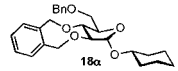
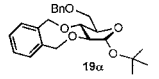
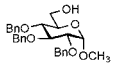
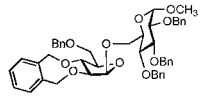
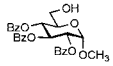
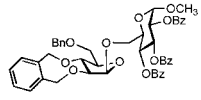
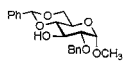
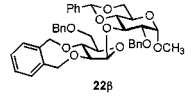
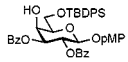
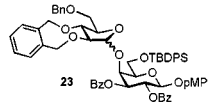
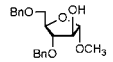
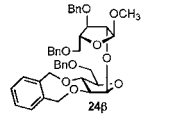
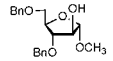
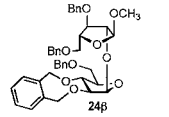
(17) The purification of the product after the introduction of the xylylene group was difficult. However, removal of the TBDPS group made it easier to separate **5** from other reaction byproducts.

(18) Konradsson, P.; Udodong, U. E.; Fraser-Reid, B. *Tetrahedron Lett.* **1990**, *31*, 4313.

(19) (a) Chao, C.-S.; Li, C.-W.; Chen, M.-C.; Chang, S.-S.; Mong, K.-K. T. *Chem.*−*Eur. J.* **2009**, *15*, 10972. (b) Ishiwata, A.; Sakurai, A.; Dürr, K.; Ito, Y. *Bioorg. Med. Chem.* **2010**, *18*, 3678.

Table 1. Glycosidation of **6** with Various Acceptors



entry	ROH	concn [mM]	*t* (°C)	product	yield[a] (β/α)
1	 **9**	1	0	 **17**	82% (1:1)
2	 **9**	0.1	0	 **17β**	94% (2.5:1)
3	 **9**	0.03	0	 **17β**	98% (2.4:1)
4	 **9**	0.03	25	 **17β**	100% (2.6:1)[b]
5	 **9**	0.03	−45	 **17α**	94% (1:5.7)
6	 **10**	0.03	−45	 **18α**	97% (1:15.2)
7	 **11**	0.03	−45	 **19α**	100% (1:11.5)
8	 **12**	0.03	−45	 **20β**	96% (5.0:1)
9	 **13**	0.03	−45	 **21β**	99% (5.6:1)
10	 **14**	0.03	−45	 **22β**	98% (4.2:1)
11	 **15**	0.03	−45	 **23**	99% (1:1.2)
12	 **16**	0.03	−45	 **24β**	96% (8.6:1)
13	 **16**	0.03	0	 **24β**	96% (3.2:1)

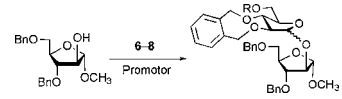
[a] Combined yield of α- and *β*-isomers. [b] The use of 1,2-dichloroethane as the solvent afforded the product in 99% yield with a 1.4:1 *β*:α ratio.

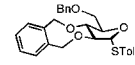
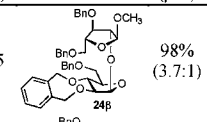
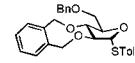
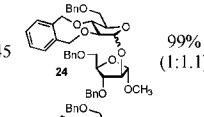
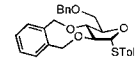
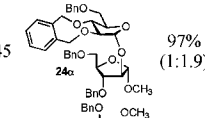
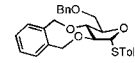
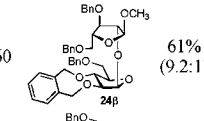
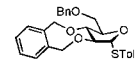
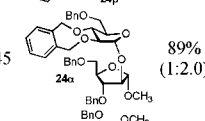
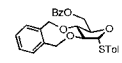
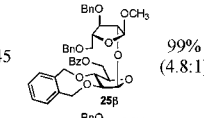
reaction was conducted at low temperature (−45 °C), the stereoselectivity was reversed (1:5.7 *β*/α ratio (entry 5)). This was also observed when other simple alcohols such as cyclohexanol (**10**) and *t*-butanol (**11**) were used as the acceptor (entries 6 and 7).

Glycosidations at −45 °C with various carbohydrate acceptors were also examined. Reaction with primary alcohols **12** and **13** (entries 8 and 9) afforded predominantly the *β*-glycoside. When secondary alcohol **14** was used, a slight decrease in *β*-stereoselectivity was observed, while reaction with the hindered secondary alcohol **15** showed little stereoselectivity (entries 10 and 11). On the other hand, the glycosylation of arabinofuranosyl acceptor **16** containing a free C-2 hydroxyl group (entry 12) afforded the *β*-glycoside in excellent yield and stereoselectivity (8.6:1 *β*/α ratio). This result is of particular significance because the *β*-Ara*f*-(1→2)-α-Ara*f* fragment is a motif present in mycobacterial arabinan. At 0 °C, the *β*-selectivity of the reaction between **6** and **16** was notably reduced (entry 13). The sensitivity of the stereoselectivity on the structure of the acceptor is unclear, but these findings are consistent with work reported by other groups on the synthesis of *β*-arabinofuranosides.[10−12]

Optimization of the reaction conditions for the synthesis of the *β*-Ara*f*-(1→2)-α-Ara*f* motif was next examined (Table 2) using **16** and **6**−**8**. The effect of solvent was studied first.

Table 2. Glycosylation of **16** with Donors **6**−**8**



entry	donor	act.[a]	solv.[b]	*t* (°C)	prod.	yield[c] (β/α)
1[d]		A	T	−45	 **24β**	98% (3.7:1)
2[e]		A	P	−45	 **24**	99% (1:1.1)
3		A	M	−45	 **24α**	97% (1:1.9)
4		B	D	−60	 **24β**	61% (9.2:1)
5		C	D	−45	 **24α**	89% (1:2.0)
6		A	D	−45	 **25β**	99% (4.8:1)
7		A	D	−45	**26β**	95%[f] (12.6:1)

[a] Activator system: A, NIS-AgOTf; B, BSP-Tf_2O; C, NIS-$BF_3 \cdot OEt_2$. [b] Solvent: T, toluene; P, propionitrile; D, CH_2Cl_2; M, CH_2Cl_2−CH_3CN−CH_3CH_2CN (1:2:1). [c] Combined yield of α and *β* isomers. [d] After 3 h, AgOTf (0.15 equiv) was added. [e] After 2 h, TESOTf (0.20 equiv) was added. [f] When carried out at −60 °C under the same conditions, the product was obtained in 95% yield and 12.6:1 α:*β* selectivity.

In toluene, the desired disaccharide **24** was formed in excellent yield but with moderate stereoselectivity; in propionitrile, a 1:1 α:*β* ratio was obtained (entries 1 and 2). Mong and co-workers have reported that a mixture of CH_2Cl_2−CH_3CN−EtCN (1:2:1) enhances *β*-selectivity in

pyranose glycosylations.[19a] However, in this reaction (entry 3), the α-glycoside was obtained as the major product. These results suggest that, unlike pyranose systems,[20] the use of nitrile solvents does not enhance *β*-selectivity, at least using this donor.

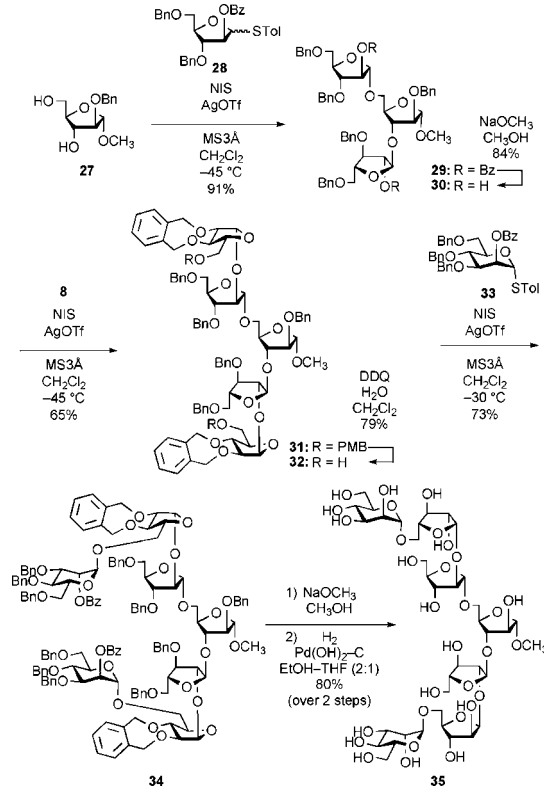
Other activator systems were also examined. The coupling of **6** and **16** promoted by 1-benzenesulfinyl piperidine and triflic anhydride (BSP−Tf_2O, entry 4)[21] gave the best *β*-selectivity, but the product yield decreased considerably. Interestingly, replacement of AgOTf as the acid catalyst with $BF_3 \cdot OEt_2$ (entry 5) led to the inversion of the stereoselectivity, suggesting that the presence of the triflate ion may be crucial to the *β*-selectivity, but the origin of this effect is unknown and requires further study.

Finally, we studied the effect of the O-5 protecting group in the donor. Glycosylation of **16** with **7**, which has an electron-withdrawing benzoyl group on O-5 (entry 6), reduced the *β*-selectivity. In contrast with **8**, which has a more electron-rich *p*-methoxybenzyl (PMB) group on O-5 (entry 7), the *β*-selectivity was significantly increased (12.6:1 *β*/α ratio). Although the effect of the O-5 protecting group on reaction stereoselectivity is not clear at present, a similar effect has been previously reported.[10b,22] In summary, this optimization study indicates that the best results are obtained with donor **8**, using NIS−AgOTf activation in CH_2Cl_2 at −45 °C.

Having optimized the formation of the *β*-Ara*f*-(1→2)-α-Ara*f* motif, we targeted the synthesis of a fragment of mycobacterial LAM (**35**, Scheme 2). The synthesis started from diol **27**[23] and thioglycoside **28**.[23] Treatment of these compounds with NIS−AgOTf afforded α-arabinofuranosyl trisaccharide **29** in excellent (91%) yield. Subsequent debenzoylation with $NaOCH_3$ gave trisaccharide **30** in 84% yield. Glycosylation of **30** with **8** was conducted under the optimized reaction conditions described above to afford pentasaccharide **31** in 65% yield; the minor glycoside isomers formed in this reaction were neither isolated nor characterized. Next, exposure of **31** to DDQ provided a 79% yield of pentasaccharide diol **32**. Final glycosylation of **32** with **33**[24] afforded heptasaccharide **34** in 73% yield. The stereochemistry of the mannopyranosides was confirmed by the magnitude of the $J_{C1,H1}$ for these residues. The value obtained for both rings (174 Hz) supports α-configuration.[25] Finally, debenzoylation of **34** and subsequent hydrogenolysis of benzyl and xylylene groups furnished the desired target **35** in 80% yield over the two steps.

Although syntheses of mannose-capped LAM structures have been reported,[26] only a few have contained the *β*-Ara*f* residues.[26c−e] The methodology described here is ideal for the synthesis of targets of this type as it allows the introduction of the *β*-Ara*f* moiety with high selectivity and the product of this reaction can easily be converted into derivatives possessing the capping motifs.[8]

Scheme 2. Synthesis of a Heptasaccharide Fragment in LAM



In conclusion, a novel direct method for *β*-selective arabinofuranosylation employing a 2,3-*O*-xylylene-protected Ara*f* donor has been developed. It was found that the glycosylation stereoselectivity was dependent on the reaction conditions, and in particular, the use of a 5-*O*-PMB-type donor was essential. The methodology was easily applied to the synthesis of a fragment of mannose-capped mycobacterial LAM.

Acknowledgment. This work was supported by the University of Alberta, The National Sciences and Engineering Research Council of Canada, and the Alberta Ingenuity Centre for Carbohydrate Science. A.I. thanks the Uehara Foundation for a postdoctoral fellowship.

Supporting Information Available: Experimental data and ^1H and ^{13}C NMR spectra for all previously unreported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL101520Q

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