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Acceptor-Dependent Stereoselective Glycosylation: 2′-CB Glycoside-Mediated Direct β-D-Arabinofuranosylation and Efficient Synthesis of the Octaarabinofuranoside in Mycobacterial Cell Wall

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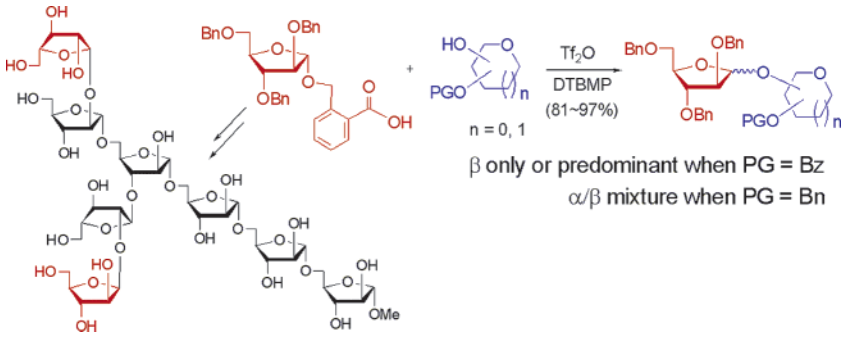
ABSTRACT



A reliable and generally applicable direct method for the stereoselective β-arabinofuranosylation employing a 2′-carboxybenzyl arabinofuranoside as the glycosyl donor has been established. The acyl-protective group on glycosyl acceptors is essential for the β-stereoselectivity. The power of the present acceptor-dependent glycosylation method was demonstrated by the efficient synthesis of the octaarabinofuranoside in arabinogalactan and lipoarabinomannan found in mycobacterial cell wall.

The development of efficient and stereoselective glycosylation methodologies[1] has attracted a great deal of attention in recent years due to the biological significance of many complex oligosaccharides and glycoconjugates.[2] The selection of proper glycosyl donors is one of the crucial factors that determines the efficiency and stereoselectivity of glycosylations. Although several efficient glycosyl donors such as glycosyl trichloroacetimidates,[3] thioglycosides,[4] glycosyl sulfoxides,[5] glycals,[6] *n*-pentenyl glycosides,[7] and glycosyl fluorides[8] are available, the stereospecific formation of certain glycosyl linkages such as β-D-mannopyranosyl and β-D-arabinofuranosyl linkages still poses a great challenge.

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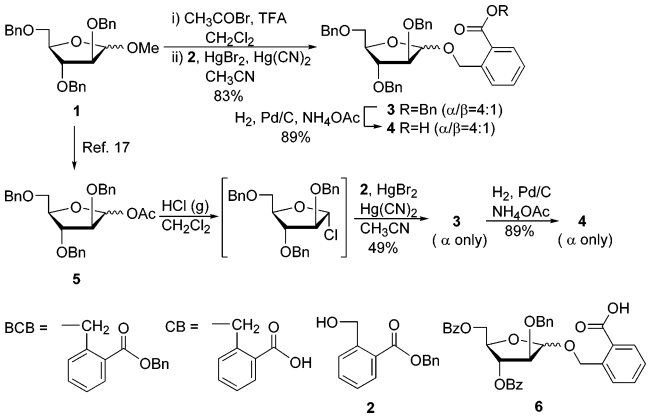
Several strategies for the stereoselective β-mannopyranosylation have been developed in recent years,[9] whereas reliable, direct methods for the construction of β-arabinofuranosyl linkages have not yet been established. Thioarabinofuranosides have been used as glycosyl donors for the synthesis of pentaarabinofuranosides and hexaarabinofuranosides containing β-D-arabinofuranosyl linkages,[10] but they are not generally applicable for β-arabinofuranosylation with a range of glycosyl acceptors ($\beta/\alpha \leq 4.5:1$).[11] Indirect methods such as the internal aglycon delivery method[12] and Lowary's method employing 2,3-anhydrolyxofuranosyl glycosides[13] have been utilized as alternatives for the synthesis of β-D-arabinofuranosides. Direct methods for the construction of the β-arabinofuranosyl linkage would be more efficient and practical than indirect methods. An added impetus to develop efficient methods for the preparation of β-oligoarabinofuranosides comes from their presence in arabinogalactan and immunogenic lipoarabinomannan found in mycobacterial cell walls. Clearly, the synthesis of these oligoarabinofuranosides could greatly contribute to the development of new therapeutic agents against tuberculosis and other mycobacterial infections.[14] We have previously introduced 2′-carboxybenzyl (CB) glycosides as glycosyl donors for β-mannopyranosylation[15] and 2-deoxy-β-glucopyranosylation.[16] We applied this CB glycoside methodology to the direct construction of the β-arabinofuranosyl linkage and herein report a generally applicable and highly stereoselective method for β-arabinofuranosylation, in which the stereoselectivity is achieved by properly choosing protective groups on the glycosyl acceptors. We also report the synthesis of an octaarabinofuranoside found in mycobacterial arabinogalactan and lipoarabinomannan[14] by employing this acceptor-dependent β-arabinofuranosylation method.

CB tri-*O*-benzyl-D-arabinofuranoside **4** was efficiently prepared from methyl tri-*O*-benzyl-D-arabinofuranoside **1**. Treatment of **1** with acetyl bromide in trifluoroacetic acid and subsequent coupling of the resulting crude arabinofuranosyl bromide with benzyl 2-(hydroxymethyl) benzoate (**2**) afforded 2′-(benzyloxycarbonyl)benzyl (BCB) tri-*O*-benzyl-D-arabinofuranoside **3** ($\alpha/\beta = 4:1$) as shown in Scheme 1. The pure α-anomer of **3** could also be prepared from **1** by

Scheme 1. Synthesis of CB Arabinofuranoside **4**[a]



[a] TFA = trifluoroacetic acid, Bn = benzyl, Bz = benzoyl.

way of the D-arabinofuranosyl chloride by the following sequence: (i) hydrolysis of **1** with HCl in acetic acid, (ii) acetylation of the resulting anomeric OH with acetic anhydride−pyridine to give acetate **5**, (iii) anomeric chlorination of **5** with HCl gas in methylene chloride, and (iv) coupling of the resulting crude arabinofuranosyl chloride[17] with **2** in the presence of $HgBr_2$ and $Hg(CN)_2$ in acetonitrile. Selective hydrogenolysis of the benzyl ester functionality in BCB arabinofuranoside **3** was readily achieved in the presence of ammonium acetate to afford the desired CB arabinoside **4** in 89% yield. CB 3,5-di-*O*-benzoyl-2-*O*-benzylarabinofuranoside **6** was also prepared in like fashion (see Supporting Information).

Glycosylations of various acceptors with the arabinofuranosyl donor **4**[18] were carried out by dropwise addition of a diluted solution of 1.5 equiv of Tf_2O in CH_2Cl_2 to a solution of 1.0 equiv of **4**, 1.5 equiv of the acceptor, and 3.0 equiv of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) in CH_2Cl_2 at −78 °C. The reaction mixture was stirred for an additional 1 h at −78 °C and allowed to warm over 1 h to 0 °C. The result of the glycosylation was unprecedented and exciting in terms of the stereochemistry of products. Thus, reaction of the donor **4** with acceptor **7** having benzoyl-protective groups afforded β-disaccharide **21** almost exclusively ($\beta/\alpha = 99:1$) in 97% yield (entry 1 in Table 1), while the same reaction with acceptor **12** having benzyl-protective groups gave a mixture of α- and β-disaccharides **26** ($\beta/\alpha = 7:1$) (entry 6). Further examples clearly showed that the protective group of glycosyl acceptors was the crucial factor determining the outcome of the stereochemistry in glycosylations with **4**. Regardless of pyranoses or furanoses and of primary alcohols or secondary alcohols, glycosylations of acceptors having benzoyl-protective groups, **8**−**11**, with the donor **4** afforded β-disaccharides either exclusively or predominantly

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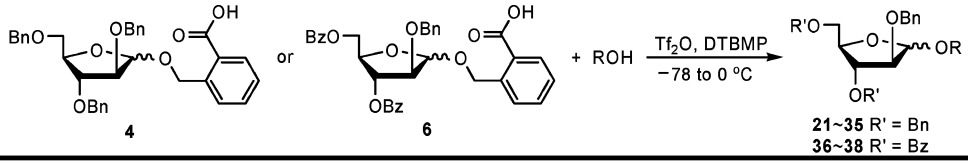
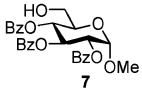
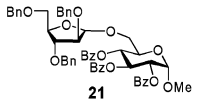
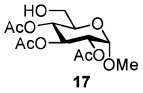
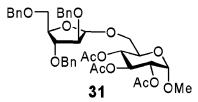
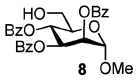
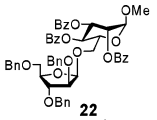
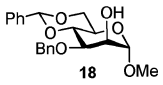
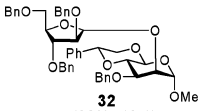
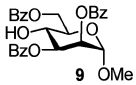
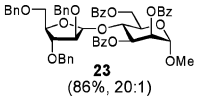
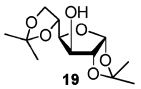
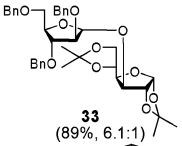
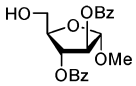
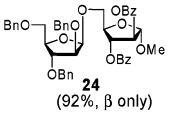
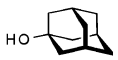
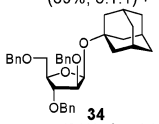
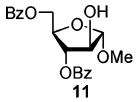
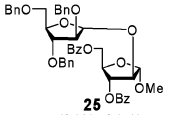
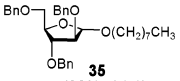
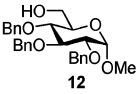
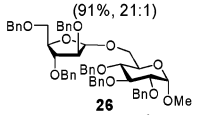
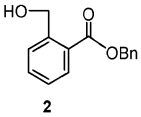
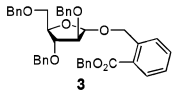
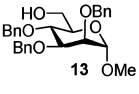
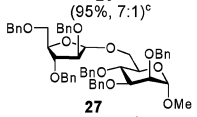
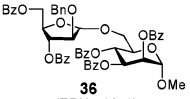
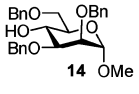
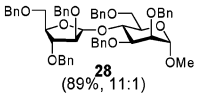
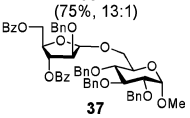
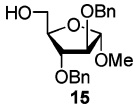
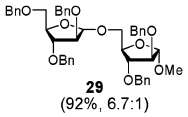
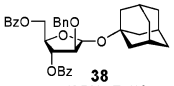
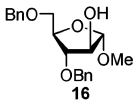
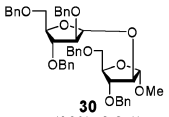
(16) Kim, K. S.; Park, J.; Lee, Y. J.; Seo, Y. S. *Angew. Chem., Int. Ed.* **2003**, *42*, 459−462.

(17) Subramaniam, V.; Lowary, T. L. *Tetrahedron* **1999**, *55*, 5965−5976.

(18) Regardless of the anomeric stereochemistry of **4**, pure α-anomer, or a mixture of α- and β-anomers (4:1), the yield and the stereochemistry of the arabinofuranoside produced in the glycosylation were virtually identical.

Table 1. Glycosylation with CB Arabinofuranosides **4** and **6**



entry	donor	acceptor, ROH	Product (Yield,[a] β/α[b])	entry	donor	acceptor, ROH	Product (Yield,[a] β/α[b])
1	**4**	 **7**	 **21** (97%, 99:1)	11	**4**	 **17**	 **31** (88%, 38:1)
2	**4**	 **8**	 **22** (95%, β only)	12	**4**	 **18**	 **32** (92%, 40:1)
3	**4**	 **9**	 **23** (86%, 20:1)	13	**4**	 **19**	 **33** (89%, 6.1:1)
4	**4**	 **10**	 **24** (92%, β only)	14	**4**	 **20**	 **34** (81%, β only)
5	**4**	 **11**	 **25** (91%, 21:1)	15	**4**	1-octanol	 **35** (88%, 14:1)
6	**4**	 **12**	 **26** (95%, 7:1)[c]	16	**4**	 **2**	 **3** (81%, 4.0:1)
7	**4**	 **13**	 **27** (95%, 4:1)[c]	17	**6**	**8**	 **36** (75%, 13:1)
8	**4**	 **14**	 **28** (89%, 11:1)	18	**6**	**12**	 **37** (71%, 2:1)[c]
9	**4**	 **15**	 **29** (92%, 6.7:1)	19	**6**	**20**	 **38** (65%, 7:1)[c]
10	**4**	 **16**	 **30** (90%, 2.2:1)				

[a] Determined after isolation. [b] Determined by HPLC using Nova-Pak C18 column. [c] Determined by ^{1}H NMR.

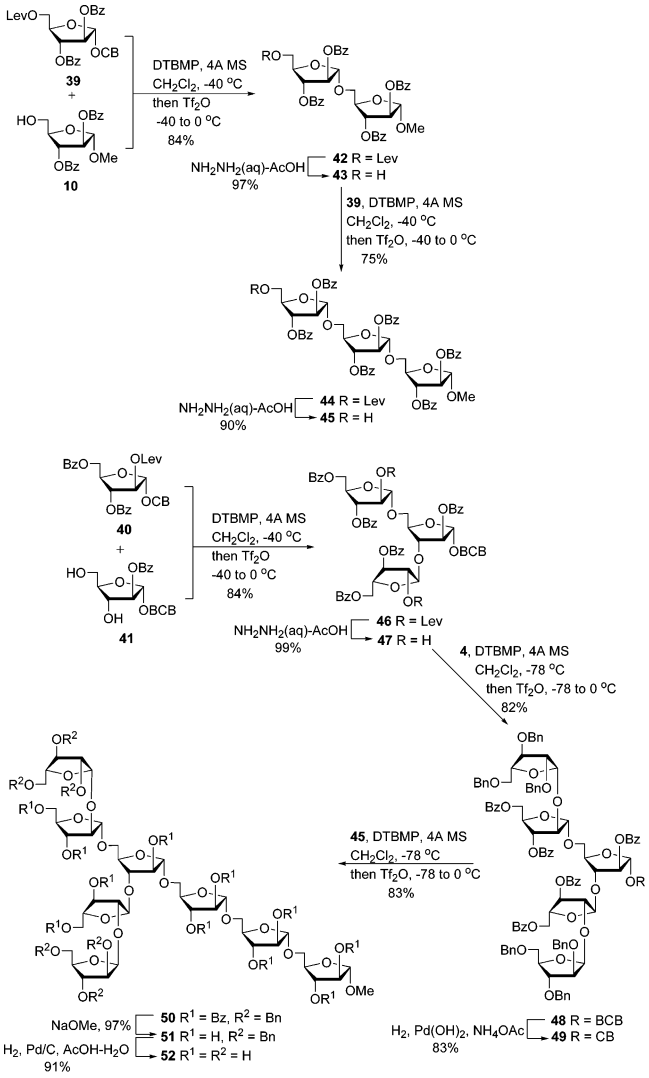
(β/α > 20:1) in high yields (entries 2−5), whereas the β-stereoselectivity in glycosylations of acceptors having benzyl-protective groups, **13**−**16**, with the donor **4** was much less pronounced (β/α < 11:1) (entries 7−10). We also examined the influence of other protective groups in the glycosyl acceptor on the stereochemistry of the glycosylation product. Glycosylations of acceptor **17**, having acetyl groups, and of acceptor **18**, having a benzylidene group, with the donor **4** afforded predominantly β-disaccharides **31** (β/α = 38:1) and **32** (β/α = 40:1), respectively (entries 11 and 12). On the other hand, the glycosylation of acceptor **19** having two isopropylidene groups with the donor **4** afforded a mixture of α- and β-disaccharides **33** (β/α = 6.1:1) (entry 13). Glycosylation of hindered alcohol **20** with **4** afforded only β-arabinofuranoside **34** (entry 14), whereas glycosylations of primary alcohols, 1-octanol, and **2** with **4** gave

mixtures of α- and β-arabinofuranosides (entries 15 and 16). Glycosylations with the CB dibenzoylarabinofuranoside **6** as a donor, however, were not as stereoselective as with **4** (entries 17−19).

We have applied this acceptor-dependent β-arabinosylation method to the synthesis of octaarabinofuranoside **52**. BCB and CB arabinoside building blocks **39**, **40**, and **41** were readily prepared from known compounds in a method similar to that for the BCB and CB arabinosides **3** and **4** (Supporting Information). Reaction of CB arabinofuranosyl donor **39** and acceptor **10** under the standard glycosylation conditions afforded α-arabinofuranosyl disaccharide **42** in 84% yield, and subsequent removal of the levulinyl group of **42** with hydrazine gave alcohol **43** as shown in Scheme 2. Repetitive glycosylation of the disaccharide **43** as an acceptor with the arabinofuranosyl donor **39** gave α-trisaccharide **44**, which was converted into the trisaccharide acceptor **45** by removal of its levulinyl group with hydrazine. Glycosylation of the diol **41** with 2 equiv of the glycosyl donor **40** afforded α-trisaccharide **46** in 84% yield without any problems. Deprotection of the two levulinyl groups in **46** with hydrazine gave diol **47**, in which the benzoyl group was utilized as the protective group for acceptor-dependent β-arabinofuranosylation in the next step. The crucial double β-arabinofuranosylation of diol **47** with 3.7 equiv of the arabinofuranosyl donor **4** proceeded smoothly under the standard conditions to afford pentaarabinofuranoside **48** in 82% yield with complete β-selectivity. No α-glycosides were detected at all in the reaction mixture. The latent BCB arabinofuranoside **48** was converted into the active CB arabinoside **49**. Coupling of the pentaarabinofuranosyl donor **49** and the triarabinofuranosyl acceptor **45** afforded protected octaarabinofuranoside **50** in 83% yield. Debenzoylation of **50** with sodium methoxide followed by hydrogenolysis of the resulting partially benzyl-protected octaarabinfuranoside **51** afforded the desired octaarabinofuranoside **52**.

In conclusion, we have established a reliable and generally applicable direct method for the stereoselective β-arabinofuranosylation employing a CB tri-*O*-benzylarabinoside as the glycosyl donor. The acyl-protective group on glycosyl acceptors was essential for the β-stereoselectivity. The power of the present acceptor-dependent glycosylation method was demonstrated by the efficient synthesis of the octaarabinofuranoside in arabinogalactan and the lipoarabinomannan found in mycobacterial cell wall.

Scheme 2. Synthesis of Octaarabinofuranoside **52**[a]



[a] Bz = benzoyl, Lev = levulinyl.

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

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