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β-Arabinofuranosylation Using 5-*O*-(2-Quinolinecarbonyl) Substituted Ethyl Thioglycoside Donors

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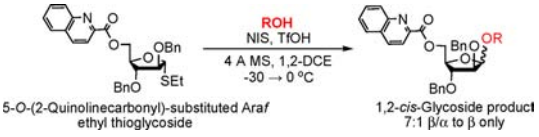
ABSTRACT



A new β-stereoselective D- and L-arabinofuranosylation method has been developed employing 5-*O*-(2-quinolinecarbonyl) substituted arabinosyl ethyl thioglycosides as glycosyl donors. The approach allows a wide range of acceptor substrates to be used; the β-selectivity is good-to-excellent. Stereoselective synthesis of a mannose-capped octasaccharide portion from a mycobacterial cell wall polysaccharide was then carried out to demonstrate the utility of this methodology.

Arabinofuranose (Ara*f*) is a very common structural constituent of polysaccharides present in living organisms.[1] Both D- and L-arabinosides were found, with the D-form being the major component of mycobacterial cell walls, and the L-form being an important component of the plant cell wall. β-Arabinofuranosides usually occur at the nonreducing end of these polysaccharides and play a crucial role in numerous biological events. For example, β-(1→2)-D-arabinosides are found at the nonreducing terminal ends of arabinogalactan (AG) and lipoarabinomannan (LAM), two major biopolymers in mycobacterial cell walls. Both AG and LAM are closely associated with the survival and pathogenicity of mycobacteria, including human pathogens *Mycobacterium tuberculosis* and *Mycobacterium leprae*.[1a,b] On the other hand, plant-originated arabinogalactans are modified with β-L-Ara*f* residues at the nonreducing termini and side chains.[1c] There is evidence that these highly complex polysaccharides are involved in the development and differentiation of plant cells.[2]

Due to their biological relevance, the synthesis of β-arabinofuranosides, especially the development of effective β-arabinofuranosylating building blocks, has received considerable attention.[3] In contrast to α-arabinoside counterparts, which can be constructed in a straightforward manner by participation of an acyl-type group on the 2-position, the stereoselective formation of β-arabinofuranosidic linkages is still a great challenge in carbohydrate chemistry. To date, several elegant methods directed toward β-arabinofuranosides have been reported, including both direct[4,5] and indirect[6] methods. Among the direct approaches, the use of conformationally constrained donors such as 3,5-*O*-di-*tert*-butylsilylene (DTBS)-, 3,5-*O*-tetraisopropyldisiloxanylidene

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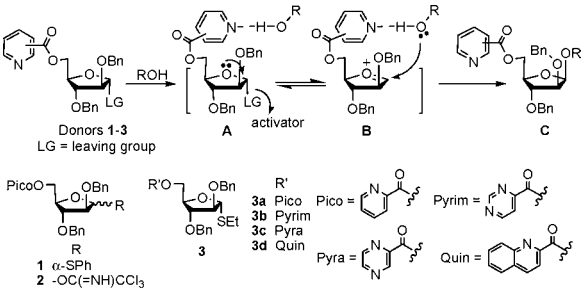
(TIPDS)-, and 2,3-*O*-xylylene protected thioglycosides has shown special promise.[5,6e] Alternatively, 2′-carboxybenzyl (CB) glycoside[4a] and *p*-cresol thioglycoside[4b,c] methodologies have also been reported by Kim and Lowary, respectively, to be effective for the direct β-arabinosylations.

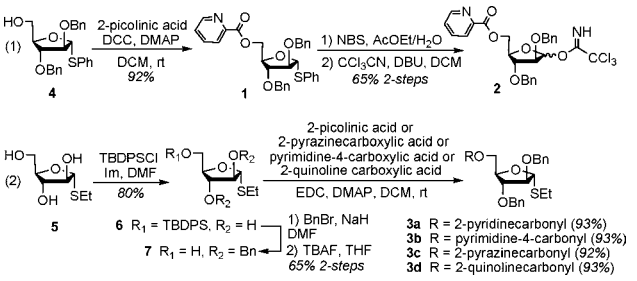
Recently, Demchenko and co-workers developed a novel hydrogen-bond-mediated aglycone delivery strategy for stereoselective synthesis of oligosaccharides.[7] The basic concept of their strategy relies on the fact that the intermolecular hydrogen bonding interaction formed between the donor and acceptor can direct the access of the acceptor to one specific face of the donor ring. Based on this strategy, various pyranosides including challenging α-gluco-, β-manno-, and β-rhamnosides were stereoselectively synthesized.

Here, we sought to apply the H-bonding-assisted glycosylation approach to the construction of 1,2-*cis*-β-arabinofuranosides.[8] Thus, a set of Ara*f* donors **1**–**3**, all carrying a directing group at the 5-position, were designed (Scheme 1). The sp^2-hybridized nitrogen within the 5-*O*-substituents can function as a H-bond acceptor. It is anticipated that, in a typical glycosylation process, the acceptor is first tethered via a H-bond with an arabinosyl donor to form **A**. Upon activation, the nucleophilic attack of the acceptor on the anomeric center will occur preferentially from the β-side of the resulting oxacarbenium ion **B**, thereby leading to a β-linked Ara*f* glycoside **C**. In this Letter, we report the development of a new β-arabinofuranosylation method using 5-*O*-(2-quinolinecarbonyl) (Quin) substituted thioglycosides as glycosyl donors and demonstrate the efficiency the method possesses through the stereoselective synthesis of a mannose-capped octasaccharide fragment from mycobacterial LAM.

Scheme 1. Design of Potential Glycosyl Donors for β-Arabinofuranosylation



Scheme 2. Preparation of Donors **1**–**3**



The designed 5-*O*-substituted donors **1**–**3** were readily made as illustrated in Scheme 2. The known thioglycoside **4**[9] was treated with 2-picolinic acid to furnish thioglycoside **1** in 92% yield. Compound **1** was then converted into trichloroacetimidate **2** through a two-step activation procedure (Scheme 2, eq 1).[10] The synthesis of ethyl thioglycoside derivatives **3a**–**d** began with regioselective 5-*O*-protection of **5**[11] as a TBDPS ether. The obtained **6** was in turn subjected to 2,3-*O*-benzylation and followed by 5-*O*-desilylation to provide alcohol **7**[4d] (65% yield for the two steps). Esterification of **7** with a series of carboxylic acids in CH_2Cl_2 gave the required **3a**–**d** in excellent yields (eq 2).

With the donors **1**–**3** in hand, we first explored their reactions with Ara*f* alcohols **8**–**10** (Table 1). All glycosylations were run employing 1.3 equiv of the donor (5 mM) and 1 equiv of the acceptor in the presence of the NIS/TfOH system or TMSOTf for thioglycoside (**1** and **3**) and trichloroacetimidate (**2**) donors, respectively, in dry $ClCH_2CH_2Cl$. The product stereochemistry was determined by ^1H NMR spectroscopy in $CDCl_3$.[12] For the α-anomer, $^3J_{H1,H2}$ is ~2.0 Hz, while, for the β-anomer, $^3J_{H1,H2}$ is ~5.0 Hz.

The effect of the anomeric leaving group of the donor on the reaction outcome was examined first. As a result, the glycosylations of **1**, **2**, and **3a** all bearing a Pico (2-pyridinecarbonyl) group on O-5 with model 3-OH acceptor **8** afforded disaccharide glycoside **11a** with equally satisfactory 1,2-*cis* stereoselectivity (β/α 10:1, Table 1, entries 1–3). Among the three donors tested, the ethyl thioglycoside **3a** showed the highest reactivity in terms of reaction temperature and time and generated an excellent 85% yield of **11a** (entry 3).

Next, the influence of the 5-*O*-directing group on reaction stereoselectivity was studied. As shown in Table 1, entries 4–7, the glycosylations of the diversely 5-substituted ethyl thioglycosides **3a**–**d** with acceptors **9** and **10**

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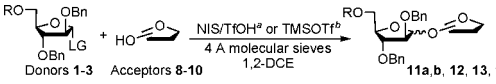
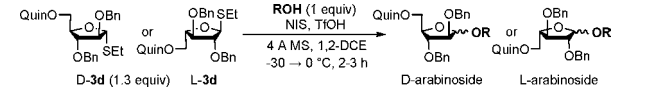
Table 1. Effect of Anomeric Leaving Group and 5-Participating Group of Donors on Glycosylation Stereoselectivity



entry	donor	acceptor	t (°C)	time (h)	product	yield[c] (β/α)[d]
1	**1**	**8**	-30 → 42	16	**11a**	56% (10:1)
2	**2**	**8**	-30 → 30	16	**11a**	70% (10:1)
3	**3a**	**8**	-30 → 30	5	**11a**	85% (10:1)
4	**3a**	**9**	-30 → 30	5	**11b**	89%[e] (6.5:1)
5	**3b**	**9**	-30 → 35	6	**12**	44% (1.2:1)
6	**3c**	**10**	-30 → 0	1.5	**13**	90%[e] (1.6:1)
7	**3d**	**9**	-30 → 0	2	**14a**	90% (20:1)

[a] For entries 1 and 3−7. [b] For entry 2. [c] Yield of the major β-isomer unless otherwise noted. [d] Determined by ^{1}H NMR of the corresponding isomer mixture. [e] Yield of the inseparable mixture of α/β-isomers.

Table 2. Glycosylation of D- and L-**3d** with Various Acceptors[a]



entry	acceptor	product	yield[b] (β/α)[c]	entry	acceptor	product	yield[b] (β/α)[c]
1	**9** (R = Bz)	**14a**	90% (20:1)	9	**21**	**14i**	91% (β only)
2[d]	**15** (R = Bn)	**14b**	88% (25:1)	10	**22**	**14j**	87%[e] (7:1)
3	**10** (R = Bz)	**14c**	95% (β only)	11	**9**	**14k**	91% (21:1)
4	**16** (R = Bn)	**14d**	89% (β only)	12	**8**	**14l**	90% (25:1)
5	**17**	**14e**	91% (50:1)	13	**10**	**14m**	95% (β only)
6	**18**	**14f**	88% (β only)	14	**23**	**14n**	85% (22:1)
7	**19**	**14g**	89% (25:1)	15	**20**	**14o**	86% (β only)
8	**20**	**14h**	87% (β only)				

[a] Glycosylations were run with D-**3d** (for entries 1−10) or L-**3d** (for entries 11−15), acceptor, NIS (2 equiv)/TfOH (0.2 equiv), 4 Å molecular sieves (MS) in $ClCH_2CH_2Cl$ at −30 → 0 °C for 2−3 h. [b] Yield of the major β-isomer unless otherwise noted. [c] Determined by ^{1}H NMR of the corresponding isomer mixture. [d] Donor (2 equiv)/acceptor (1 equiv) were used. [e] Yield of the inseparable mixture of α/β-isomers.

afforded the corresponding products in 44−90% yields and with varying degrees of β-stereocontrol. A lower selectivity (β/α 6.5:1) was observed in the reaction of **3a** with 2-OH acceptor **9** (entry 4 vs 3). The couplings of 5-*O*-Pyrim (pyrimidine-4-carbonyl) and Pyra (2-pyrazinecarbonyl) carrying **3b**,**c** with 2- and 5-OH acceptors **9**,**10** displayed slight selectivity (β/α 1.2:1 and 1.6:1, respectively, entries 5−6). Gratifyingly, the 5-*O*-Quin substituted **3d** showed strong stereocontrolling capability in the reaction with **9** and a great increase in selectivity (β/α 20:1) was obtained for the product **14a** (entry 7). Overall, the above optimization study indicates that the best results are obtained with donor **3d**, using NIS/TfOH activation in $ClCH_2CH_2Cl$ at −30 → 0 °C.

With the optimal reaction conditions, we then set out to survey a variety of acceptors to establish the generality of this 1,2-*cis* arabinofuranosylation reaction.

We were pleased to find that a broad range of sugar series including arabinofuranose, gluco-, galacto-, and mannopyranose alcohols as well as the common 1-adamantanol all reacted very well with **3d**, resulting in the corresponding glycoside products **14a**−**j** in high 87−95% yields as mainly or exclusively the β-anomers (Table 2, entries 1−10). The stereochemical outcome is dependent on the nature of the acceptor. Reactions with primary acceptors **10**, **16**, **18**, **20**, and **21** provided in general better 1,2-*cis* selectivities than reactions with more hindered secondary and tertiary acceptors **9**, **15**, **17**, **19**, and **22** (entries 3, 4, 6, 8, and 9 vs 1, 2, 5, 7, and 10). The sensitivity of the stereoselectivity on the structure of the acceptor is unclear, but these findings are consistent with previous work reported by other groups on the synthesis of β-arabinofuranosides.[4−6] It is significant that the 2-OH alcohols **9** and **15** were glycosylated (entries 1 and 2) in excellent yields (88−90%) and β/α ratios (20:1−25:1), affording the biologically relevant β-D-Ara*f*-(1→2)-α-D-Ara*f* disaccharides **14a**,**b**, which correspond to the nonreducing terminal structure of mycobacterial AG and LAM. Furthermore, the high level of yields and selectivities achieved in the couplings of alcohols **19** and **22** was also remarkable (entries 7 and 10). These results clearly demonostrated the high reactivity of **3d** even with very unreactive acceptors.[13]

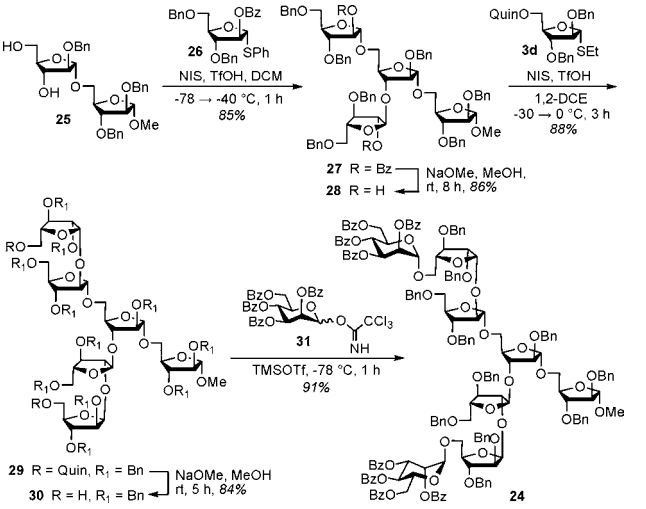
To extend this methodology to the stereoselective synthesis of β-L-arabinofuranoside, we further investigated the

glycosylation of L-**3d** (see Supporting Information) with different carbohydrate acceptors. It was found that D- and L-Ara*f* donors may exhibit different glycosylation behavior. For example, Boons et al. disclosed that the 3,5-*O*-DTBS protected L-thioarabinofuranoside gave excellent β-stereocontrol in a variety of glycosylations.[5a] But the analogous 3,5-*O*-DTBS protected D-thioarabinofuranoside was proven by the Ito group to give lower β-selectivity under the same activation conditions (NIS/AgOTf).[5b] The origin of this difference is unclear at present.

In this work, L-**3d** was verified to have similar reaction properties as that of its enantiomer D-**3d** by a number of glycosylations with glycosyl acceptors having either primary or secondary hydroxyl groups (Table 2, entries 11−15). Each coupling reaction was high yielding (70−95%) and β-selective (β/α 10:1 to β only). Of particular note are the high and complete β-selectivities observed in 3- and 6-*O*-L-arabinofuranosylations of the galactosyl acceptors **23** and **20** (entries 14 and 15, respectively) as the obtained 1,3- and 1,6-β-linked L-Ara*f*-D-Gal*p* disaccharides **14n**,**o** represent the characteristic substructures of plant arabinogalactans.

Utilizing the developed stereoselective arabinosylation approach, we targeted the preparation of an octasaccharide capping motif[14] of mycobacterial LAM (**24**, Scheme 3). Oligosaccharide **24** presents a particular synthetic challenge for it contains two 1,2-*cis* arabinofuranosidic bonds. The synthesis began with disaccharide diol **25**[6c] and phenyl thioglycoside **26**.[9] Treatment of both compounds with NIS/TfOH yielded α-arabinofuranosyl tetrasaccharide **27**[6c] in 85% yield. Subsequent debenzoylation via Zemplén transesterification (NaOMe, MeOH) afforded **28**[6c] in 86% yield. The key double coupling of **28** with 3 equiv of **3d** was run according to the aforementioned conditions to give cleanly the bis-β-arabinosylated hexasaccharide **29** in good yield. Other possible stereoisomers were not detected. Then, the Quin group was easily removed by means of Zemplén reaction to liberate the 5-OHs of two β-Ara*f* moieties, delivering an 84% yield of **30**. At last, coupling between **30** and mannosyl donor **31**[15] at −78 °C for 1 h produced the desired protected octasaccharide **24** in 91% yield. The α-configuration of the newly formed mannopyranosides was confirmed by a combination of the $^1J_{C1,H1}$ coupling constant and the chemical shift of the anomeric carbon for these units.[16]

Scheme 3. Synthesis of a Protected Octasaccharide Motif in LAM



Although there have been several syntheses of mannose-capped LAM glycans,[17] the efficient installation of the internal β-Ara*f* residue was rare.[6a,b,17c,17d] Our methodology offers a practical access to such molecules since it not only permits the introduction of the β-Ara*f* linkage with high selectivity but also facilitates further modification at the 5-position.

In conclusion, a simple and versatile methodology toward 1,2-*cis* selective D- and L-arabinofuranosylations using 5-*O*-Quin equipped thioarabinosides D- and L-**3d** as the donors has been uncovered. The approach was applied successfully to the synthesis of a protected nonreducing terminal octasaccharide derivative of the mycobacterial cell wall.

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

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The authors declare no competing financial interest.