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Synthesis of arabinofuranosides via low-temperature activation of thioglycosides

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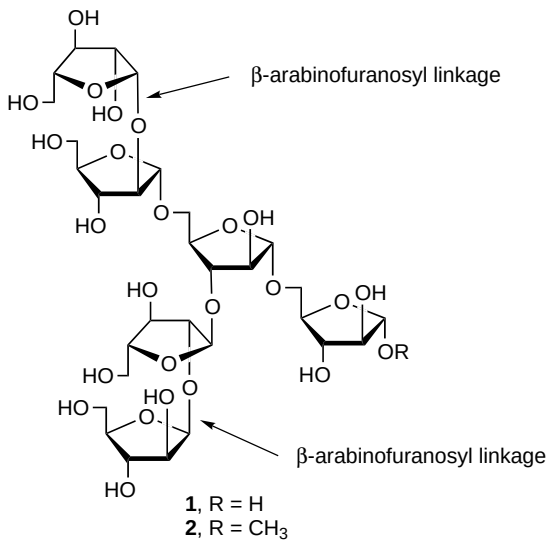
Abstract—The synthesis of oligosaccharides containing arabinofuranose residues is reported. Coupling of thioglycoside donors **4**, **6**, or **7** and with acceptors **8**–**17** using *N*-iodosuccinimide and silver triflate activation provided glycosides with varying degrees of stereocontrol.

The cell wall complex of mycobacteria is composed largely of two polysaccharides, an arabinogalactan (AG) and a lipoarabinomannan (LAM).[1] Mycobacterial viability is critically dependent upon the ability to synthesize these two polysaccharides. Consequently, the emergence[2] of drug resistant strains of *Mycobacterium tuberculosis* has prompted efforts to identify new drugs which act by inhibiting cell wall biosynthesis in this organism.[3] A distinguishing feature of AG and LAM is that all of the arabinose and galactose residues exist in the furanose ring form. Thus, there has recently been increased interest in the synthesis of oligosaccharides containing arabinofuranose[4] and galactofuranose[5] moieties.

Over the past few years, we have synthesized a number of arabinofuranosyl-containing oligosaccharide fragments of mycobacterial AG and LAM.[6] One of our targets has been the hexasaccharide motif, **1**, which is an important constituent of both polysaccharides. Oligosaccharide **1** presents a particular synthetic challenge in that it contains two β-arabinofuranosyl linkages. These glycosidic bonds are analogous to β-mannopyranosyl and β-fructofuranosyl linkages that are widespread in nature, and which are notoriously difficult to synthesize in a stereocontrolled manner. Although a number of routes have now been developed for the stereoselective synthesis of β-mannopyranosides,[7] far fewer studies have explored methods for the stereocontrolled formation of β-arabinofuranosides[4a,6c] or β-fructofuranosides.[8]

In the course of our investigations, we recently reported the synthesis of oligosaccharide **2**.[6,9,10] The key-step in the synthesis was a stereoselective glycosylation reaction that installed both β-arabinofuranosyl residues simultaneously (Scheme 1). In the reaction of **3** with **4**, it was found that the stereoselectivity was highly dependent upon the reaction temperature. At 0°C or room temperature, all four possible stereoisomeric glycosides were produced in roughly equal amounts. However, when the reaction was initiated at −78°C and then allowed to warm slowly to 0°C, **5** was produced in excellent yield and stereoselectivity.



The degree of glycosylation stereoselectively under these conditions is remarkable. Oligosaccharide **5** is the only hexasaccharide isolated from the reaction. In addi-

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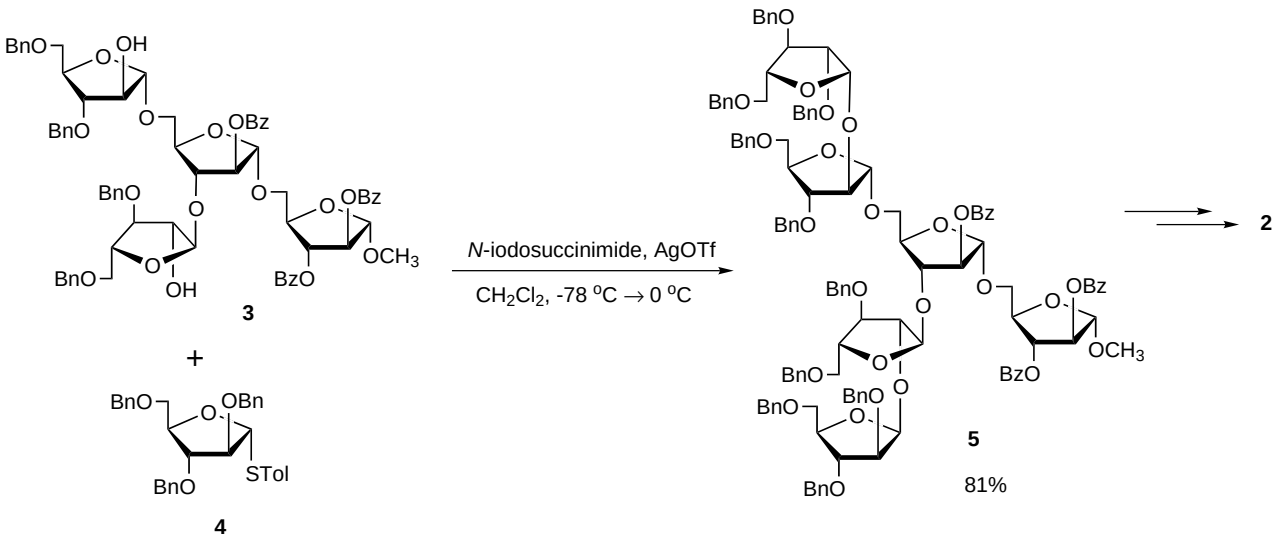
tion, the product is produced in significantly better yield than in another synthesis of this motif in which the β-arabinofuranosyl linkages are formed via the highly-stereoselective intramolecular aglycone delivery (IAD) method.[9a] Furthermore, the ease with which the reaction can be carried out is noteworthy, especially when compared to the two-step IAD protocol, which requires the manipulation of an unstable intermediate.

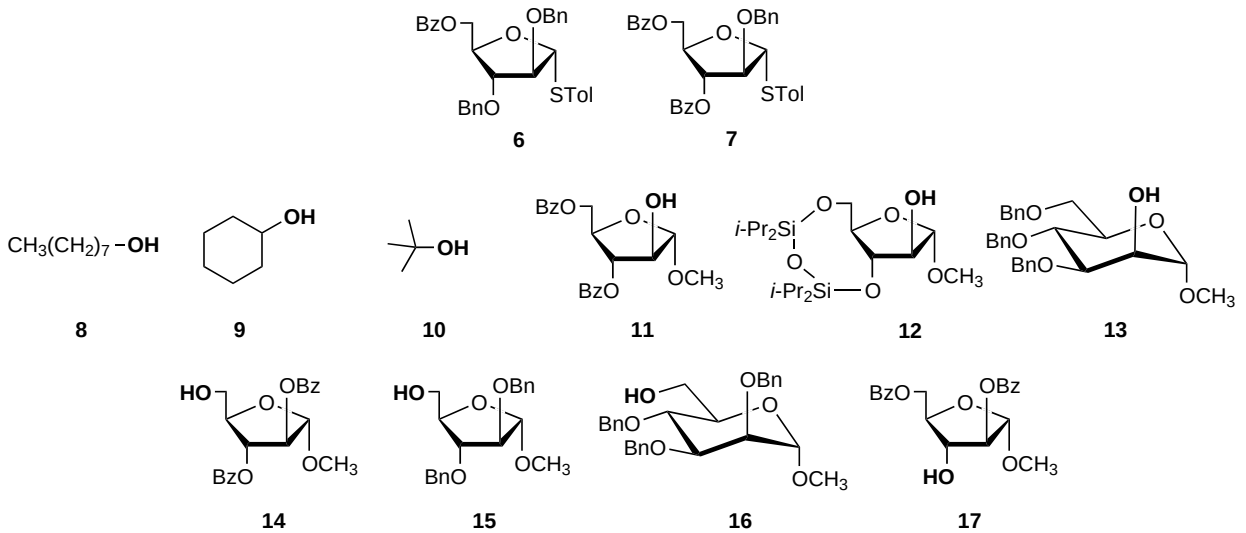
Using our method, we have since synthesized a range of other oligosaccharide fragments of **1** containing β-arabinofuranose residues.[10] In all cases, **4** was used to glycosylate the 2-hydroxyl group of an α-arabinofuranoside ring. Furthermore, the 3- and 5-hydroxyl groups on the glycosylated ring were always protected as benzyl ethers (e.g. **3**).

In the interest of extending this methodology to the synthesis of other β-arabinofuranosides (e.g. β-L-arabinofuranose containing oligosaccharides found in plants[11]) we wanted to explore the coupling of other arabinofuranosyl thioglycosides with a range of glycosyl acceptors. Our interest was in determining the stereochemical outcome of the reaction with substrates possessing protecting groups other than benzyl ethers and with acceptors other than the 2-hydroxyl group of an α-arabinofuranose ring. Accordingly, we report here the reaction of thioglycosides **4**,[6a] **6**, and **7** with alcohols **8**–**17** (Scheme 2). Thioglycosides **6** and **7** were prepared, without incident, as outlined in Scheme 3.[12] Alcohols **8**–**17** are either commercially available or known.[13]

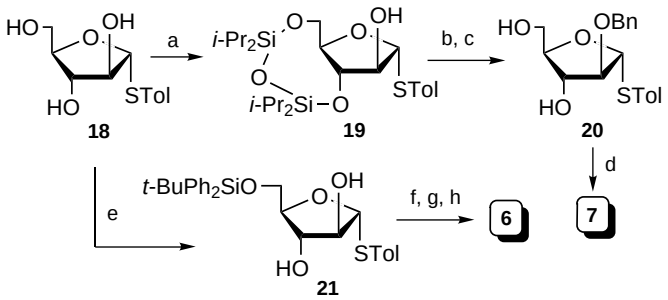
With the appropriate substrates in hand, all glycosylations were carried out by cooling a solution of the acceptor and donor in freshly distilled dichloromethane to −78°C.[14] *N*-iodosuccinimide and silver triflate were then added and the reaction mixture was allowed to warm to 0°C over 90–120 minutes. The initiation of the reaction, as indicated by the appearance of the characteristic reddish-orange color, took place at different



Scheme 1.



Scheme 2.



Scheme 3. Synthesis of thioglycosides **6** and **7**. (a) (Cl(*i*-Pr)$_2$Si)$_2$O, pyridine 71%; (b) BnBr, NaH, DMF; (c) *n*-Bu$_4$F, THF, 64% from **19**; (d) BzCl, pyridine, 83%; (e) *t*-BuPh$_2$SiCl, pyridine, 86%; (f) BnBr, NaH, DMF; (g) *n*-Bu$_4$F, THF; (h) BzCl, pyridine, 57% from **21**.

temperatures depending upon the donor used. As would be expected on the basis of the armed/disarmed concept[15] thioglycoside **4**, which possesses no disarming benzoyl groups, reacted at the lowest temperature. Thioglycoside **6** showed intermediate reactivity and **7** was the least reactive.

Upon completion of the reaction, the reaction mixture was neutralized and the products isolated by chromatography. No attempt was made to separate the isomeric glycosides. Instead, the column fractions containing both isomers were pooled and concentrated. The isolated yields and β:α ratio are given in Table 1. The stereochemical outcome of the reaction was determined prior to product purification by standard one-dimensional ^{1}H NMR spectroscopy of the crude reaction mixtures. Integration of the anomeric protons of the newly formed glycosidic bond were used to determine the ratios in Table 1. Distinguishing between the two anomers was done on the basis of $^3J_{H1,H2}$ magnitudes. For the α-isomers $^3J_{H1,H2}$ is small (0–2 Hz) and larger (3–5 Hz) for the β-anomers. Furthermore, in the ^{13}C NMR spectra, C-1 of the β-isomers resonate upfield relative to the α-isomers.[16]

As is clear from the data presented in Table 1, all three donors glycosylate the panel with alcohols in comparable yields. In contrast, the observed stereoselectivities are very much substrate dependent. In the best cases, a 4.5:1 β:α ratio is observed (entries 8 and 9); however, there is often little stereoselectivity (e.g. entries 4 and 5).

Conclusions that can be drawn from this data are as follows. First, there is a direct correlation between β-stereoselectivity and donor reactivity. The most armed donor, **4**, provides an average β-selectivity of 2.6:1. Thioglycosides **6** and **7** provide average β-selectivities of 2.1:1 and 1.4:1, respectively. Second, with the carbohydrate acceptors, the selectivities are in general higher with primary alcohols (entries 7–9, 17, 18, and 25–27) than with secondary alcohols. Third, the best results are obtained when the most reactive donor, **4**, is coupled with primary carbohydrate alcohols in which the other hydroxyl groups on the acceptor are protected as benzyl ethers. Such alcohols would be expected to be the most reactive in that they are not sterically hindered and their nucleophilicity is not attenuated by the presence of electron-withdrawing acyl groups at other positions on the ring.

Given the data presented in Table 1 and considering that α-thioglycosides were used in these couplings, it is plausible to speculate that reaction of **4** and the alcohols giving the highest β-selectivities (e.g. **15**) may proceed via an S_N1-ion pair mechanism in which the aglycone leaving group blocks attack from the bottom face of the ring. This is consistent with earlier studies in which the glycosylation of 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl chloride was studied.[17] In reactions providing glycosides with lower β-selectivity, loss of stereocontrol can be rationalized by the conversion of the donor to other intermediates. For example, the formation of an oxonium ion intermediate or an α/β mixture of glycosyl triflates[18] would be expected to lower the stereoselectivity of the glycosylation. Regardless of the mechanism, it can be concluded that for the synthesis of a given β-arabinofuranoside via this approach, best results will be obtained with a fully alkylated donor species (e.g. **4** or **15**).

A common problem in the synthesis of β-mannosides is the sensitivity of the β:α ratio to seemingly small changes in the structure of the donor and acceptor.[7e,19]

Table 1. Coupling of thioglycosides **4**, **5**, or **7** with alcohols **8**–**17**.[13]

Entry	Donor	Acceptor	Yield (%)[a]	β:α Ratio[b]
1	**4**	**8**	82	1.4:1
2	**4**	**9**	73	3:1
3	**4**	**10**	71	3:1
4	**4**	**11**	72	1.1:1
5	**4**	**12**	62	1.2:1
6	**4**	**13**	74	3:1
7	**4**	**14**	83	2:1
8	**4**	**15**	85	4.5:1
9	**4**	**16**	78	4.5:1
10	**4**	**17**	91	2:1
11	**6**	**8**	88	3.9:1
12	**6**	**9**	81	1.6:1
13	**6**	**10**	83	2.4:1
14	**6**	**11**	78	1.1:1
15	**6**	**12**	76	1.2:1
16	**6**	**13**	71	2:1
17	**6**	**14**	81	2.7:1
18	**6**	**15**	88	2.5:1
19	**6**	**17**	82	1:1
20	**7**	**8**	86	1.5:1
21	**7**	**9**	78	1.1:1
22	**7**	**10**	77	1.1:1
23	**7**	**11**	82	1.1:1
24	**7**	**13**	68	1:2
25	**7**	**14**	70	2.8:1
26	**7**	**15**	88	1.9:1
27	**7**	**16**	66	1.4:1
28	**7**	**17**	69	1.3:1

[a] Isolated yield.
[b] As determined by ^{1}H NMR spectroscopy (see text).

It appears that glycosylations of these arabinofuranose thioglycosides are similarly sensitive to such protecting groups modifications. It also appears that the excellent stereocontrol we obtained in the synthesis of 2[6a] and its fragments[10] was an extraordinarily fortunate occurrence. Currently under investigation in our laboratories is the use of other glycosylating agents for the stereocontrolled synthesis of β-arabinofuranosides.[20]

Acknowledgements

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12. Characterization of new compounds: **6** $[\alpha]_D$+12.8 (CH_2Cl_2, *c* 0.2). R_f 0.49 (hexane:EtOAc 3:1). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 5.47 (d, 1H, J=1.5 Hz, H-1), 4.37–4.54 (m, 5H, $PhCH_2$, H-5, H-4), 4.06 (t, 1H, J=2.8 Hz), 3.95 (dd, 1H, J=3.0 Hz), 2.21 (s, 3H, Me). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 91.18 (C-1), 88.79 (C-2), 84.18 (C-3), 79.50 (C-4), 72.89, 72.74 (Bn), 64.22 (C-5), 21.62 (Me). HRMS (ESI) calcd for (M+Na) $C_{33}H_{32}O_5S$ 563.186263, found 563.187152.
7 $[\alpha]_D$+20.6 (CH_2Cl_2, *c* 0.1). R_f 0.54 (hexane:EtOAc 2:1). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 5.72 (d, 1H, J=1.8 Hz, H-1), 5.58 (dd, 1H, J=1.6 Hz, 4.3 Hz, H-3), 4.76 (dd, 1H, J=4.6 Hz, 9.1 Hz, H-4), 4.72, 4.65 (d, 1H, J=12.1 Hz, $PhCH_2$), 4.67 (d, 2H, J=5.1 Hz, H-5), 4.35 (t, 1H, J=1.8 Hz, H-3), 2.25 (s, 3H, Me). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 92.00 (C-1), 88.35 (C-2), 81.48 (C-4), 79.01 (C-3), 72.75 (Bn), 64.44 (C-5), 21.62 (Me). HRMS (ESI) calcd for (M+Na) $C_{33}H_{30}O_6S$ 577.165528, found 577.16787.
20 $[\alpha]_D$+2.1 (CH_2Cl_2, *c* 0.1). R_f 0.21 (hexane:EtOAc 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): 5.51 (d, 1H, J=3.3 Hz, H-1), 4.67 (dd, 2H, J=11.7 Hz, $PhCH_2$), 4.26 (dd, 1H, J=4.0 Hz, 6.9 Hz, H-3), 4.15 (m, 1H, H-4), 4.05 (t, 1H, J=3.6 Hz, H-2), 3.85 (dd, 1H, J=3.4 Hz, 12.2 Hz, H-5), 3.76 (dd, 1H, J=3.9 Hz, 12.2 Hz, H-5), 2.38 (s, 3H, Me). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 90.52 (C-1), 89.94 (C-2), 83.19 (C-4), 76.37 (C-3), 72.80 (PhC), 61.87 (C-5), 21.56 (Me). HRMS (ESI) calcd for (M+Na) $C_{19}H_{22}O_4S$ 369.113098, found 369.114885.
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14. **Reaction conditions:** The thioglycoside (0.16 mmol) and the alcohol (0.14 mmol) were dissolved in freshly distilled CH_2Cl_2 (30 mL) and molecular sieves (2 g) were added. After cooling the solution to −78°C, *N*-iodosuccinimide (0.2 mmol) and silver triflate (0.06 mmol) were added. The reaction mixture was stirred and allowed to warm to 0°C over 90–120 min at which point triethylamine was added. Filtration of the solution through Celite afforded a solution that was washed with brine and then concentrated. An ^{1}H NMR spectrum of the crude reaction mixture was taken and then the products were purified by column chromatography.
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