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Synthesis of the linear octaarabinofuranoside related to the terminal fragment of mycobacterial polysaccharides

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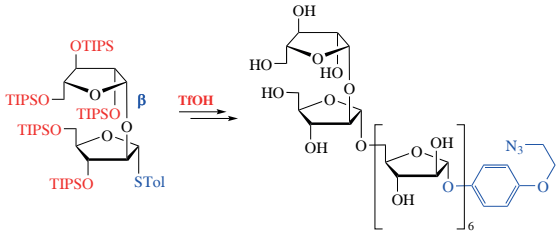
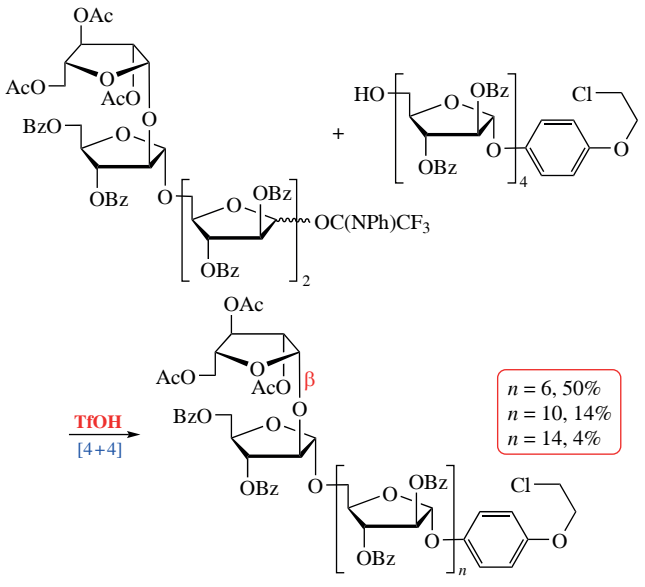
A convergent synthesis of linear α-(1→5)-, β-(1→2)-linked octaarabinofuranoside related to the terminal fragment of mycobacterial polysaccharides was performed using a [6+2] scheme. The octaarabinofuranoside was obtained as a 4-(2-azidoethoxy)phenyl glycoside which can be further converted to neoglycoconjugates that are important for the development of diagnostic tools.



Keywords: glycosylation, D-arabinofuranose, Janus aglycone, silyl group, *Mycobacterium tuberculosis*.

Microorganism *Mycobacterium tuberculosis*, belonging to the genus *Mycobacteria*, is the main causative agent of tuberculosis.[1,2] Synthesis of the terminal fragments of *M. tuberculosis* polysaccharides is essential for the development of diagnostics[3,4] and vaccines,[5–8] as well as new effective antimicrobial drugs.

Recently we found that during the triflic acid-promoted glycosylation according to a [4+4] convergent scheme between α-(1→5)-linked tetraarabinofuranoside bearing 4-(2-chloroethoxy)phenyl (CEP) aglycone and α-(1→5)-, β-(1→2)-linked tetraarabinofuranoside with *N*-phenyltrifluoroacetimidoyl leaving group, along with the key acylated linear α-(1→5)-, β-(1→2)-linked octaarabinofuranoside, unusual formation of dodeca- and hexadecaarabinofuranosides was observed (Scheme 1).[9] To avoid the undesired process connected with the oligomerization, we herein propose an alternative synthesis of the linear α-(1→5)-, β-(1→2)-linked octaarabinofuranoside as a CEP glycoside using a [6+2] convergent scheme with subsequent conversion to 4-(2-azidoethoxy)phenyl (AEP) glycoside and deprotection. The presence of AEP aglycone allows the creation of neoglycoconjugates.



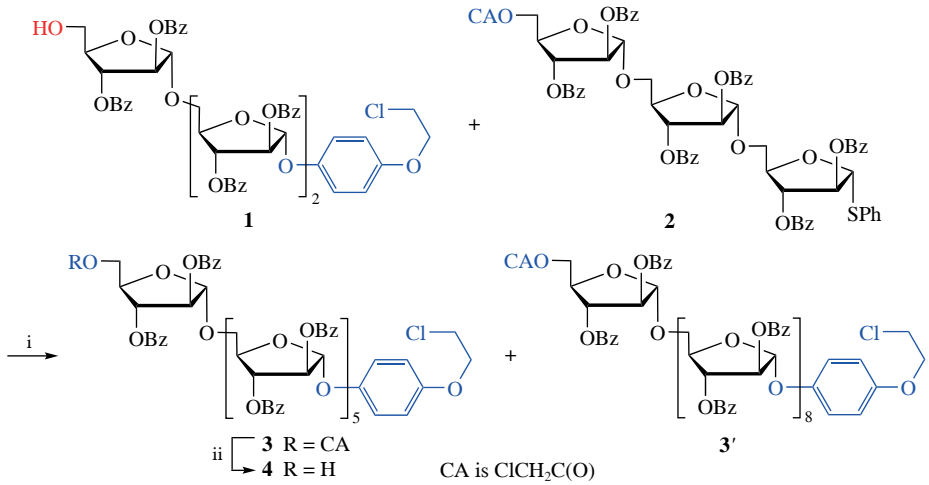
Scheme 1

At the first step we performed coupling between triarabinofuranose CEP glycoside **1** and triarabinofuranose thioglycoside **2** under NIS/TfOH promotion (Scheme 2). We obtained linear α-(1→5)-linked hexaarabinofuranoside **3** in high yield (87%). It should be noted that a small amount of nonaarabinofuranoside **3′** (less than 1%) contaminated with other oligosaccharides was also detected. The less pronounced oligomerization according to the [3+3] scheme compared to the [4+4] scheme[9] can be explained by the influence of the nature of the leaving group in the glycosyl donor. The *O*-chloroacetyl (CA) group in hexaarabinofuranoside **3** was removed using aq. pyridine to give the new α-(1→5)-linked hexaarabinofuranoside glycosyl acceptor **4** (see Scheme 2).

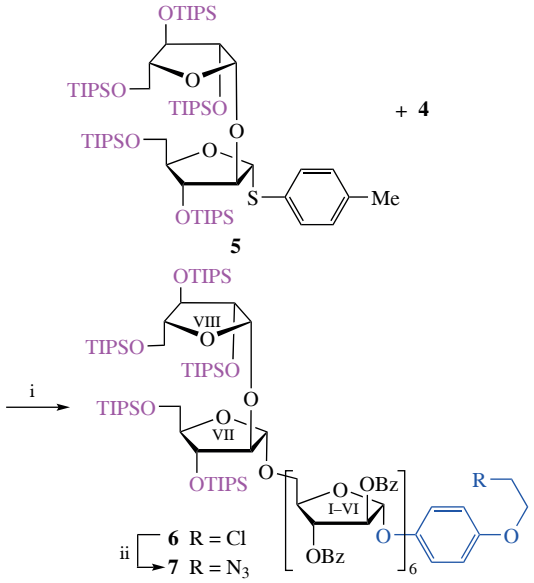
At the next step we performed glycosylation of hexaarabinofuranoside glycosyl acceptor **4** with Ara-β-(1→2)-Ara *p*-tolyl thioglycoside **5** containing five triisopropylsilyl groups (Scheme 3). Despite the absence of a participating group at O-2 in diarabinofuranoside glycosyl donor **5**, we obtained α-(1→5)-, β-(1→2)-linked octaarabinofuranoside **6** as a single α-isomer in high yield (85%) whereas no other isomer was detected. The chlorine atom in the aglycone of the resulting octaarabinofuranoside **6** was replaced with azido group (NaN_3, DMF, 18-crown-6) to give AEP glycoside **7**.

The signals of the anomeric carbon atoms for all monosaccharide residues in the ^{13}C NMR spectra of the obtained octaarabinofuranosides **6**, **7** resonated in a low field region at δ_C 104.79, 104.82 (C-1^{I}, C-1^{VIII}), 105.87, 105.89, 105.91 (2C) 105.99 ($C^{II–VI}$), 106.91 (C-1^{VII}), respectively. The relatively high chemical shift of the signal of β-linked C-1^{VIII} may be due to the presence of five bulky TIPS groups (Tables 1, 2 for **6**).

We also found some general features in the NMR spectra for protected octaarabinofuranosides **6**, **7** and earlier obtained



Scheme 2 *Reagents and conditions*: i, NIS, TfOH, MS 4 Å, CH_2Cl_2, –40 → –10 °C, 20 h (87% of **3**, 0.3% of **3a**); ii, Py, H_2O, 70 °C, 2.5 h (84%).

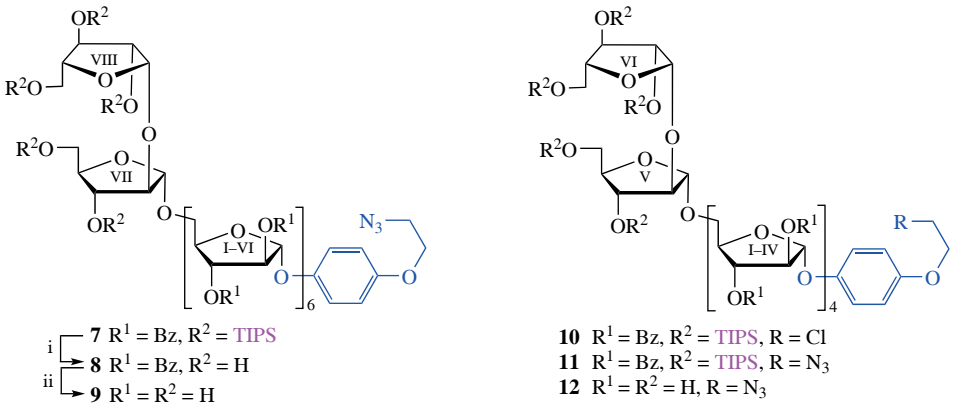


Scheme 3 *Reagents and conditions*: i, NIS, TfOH, MS 4 Å, CH_2Cl_2, –60 → –30 °C, 1.5 h (85%); ii, NaN_3, 18-crown-6, DMF, 70 °C for 48 h, then 80 °C for 48 h (92%).

α-(1→5)-, β-(1→2)-linked hexaarabinofuranosides **10**, **11**[10] with the same type of substitution (Schemes 3, 4). As expected, all signals of H-2 and H-3 for benzoylated Ara residues appear in a lower field in the ^{1}H NMR spectrum compared to the corresponding signals of silylated residues. A series of signals, related to the Ara residues with TIPS protection (VII and VIII for **6** and **7**; V and VI for **10** and **11**) were found in a close region in the NMR spectra. We can also note the conservative position of the signals for glycosylated residues VI in **6** and **7** and residues IV in **10** and **11**; for residue I, and for the signals related to the core region (II–V in **6** and **7**; II–III in **10** and **11**). The confirmation of the presence of the glycosidic linkage between the corresponding monosaccharide residues of octaarabinofuranoside **6** was found in the ROESY spectrum. The H-1^{VII} proton signal at δ_H 5.07 correlates with the signals of H-5^{VI}a at δ_H 3.76 and H-5^{VI}b at δ_H 4.04. The H-1^{VIII} proton signal at δ_H 5.23 correlates with the H-2^{VII} proton signal at δ_H 4.19.

All the TIPS groups in azide **7** were removed by treatment with Bu_4NF in THF in the presence of AcOH at 40 °C to give partially deprotected octaarabinofuranoside **8**, which was further treated with MeONa in MeOH to give the target deprotected octaarabinofuranoside **9** in 53% yield over two steps (see Scheme 4). As expected, NMR data for **9** (Tables 3, 4 for **9**) correlated with those found earlier for hexaarabinofuranoside **12**.[10] The analysis of ^{13}C NMR spectrum of **9** revealed the signals for the single β-anomeric carbon C-1^{VIII} at δ_C 102.46 and α-anomeric carbons in the characteristic region at δ_C 107.58 (C-1^{VII}), 108.68 (C-1^{I}), 109.62, 109.69 (3 C), 109.73 (C-1$^{II–VI}$). Besides, correlations confirming the formation of the glycosidic bonds between the corresponding monosaccharide residues of octaarabinofuranoside **9** were found in the ^{1}H–^{13}C HMBC spectrum. The H-1^{VII} proton signal at δ_H 5.07 correlates with the C-5^{VI} carbon atom signal at δ_C 68.3. The H-2^{VII} proton signal at δ_H 4.14 correlates with the C-1^{VIII} carbon signal at δ_C 102.46.

In summary, a convergent synthesis of the linear α-(1→5)-, β-(1→2)-linked octaarabinofuranoside **6** as a CEP glycoside following a [6+2] scheme was performed. The use of Ara-β-(1→2)-Ara *p*-tolyl thioglycoside **5** containing five triisopropyl-



Scheme 4 *Reagents and conditions*: i, Bu_4NF, AcOH, THF, 40 °C, 16 h; ii, MeONa, 20 °C, 16 h (71%, 53% over two steps).

Table 1 ^{1}H NMR data for protected octaarabinofuranoside **6** with CEP aglycone.

Residue	δ_H (*J*/Hz)[a]				
	H-1	H-2	H-3	H-4	H-5a; H-5b
I	5.82	5.74–5.79	5.74–5.79	4.54–4.63	3.85–3.96; 4.22 (11.4, 4.3)
II–V	5.37, 5.38, 5.40[b]	5.61–5.66	5.61–5.66	4.54–4.63	3.85–3.96; 4.16–4.20
VI	5.35	5.59 (1.6)	5.50 (4.9, 1.7)	4.54–4.63	3.76 (10.9, 4.6); 4.04 (10.9, 4.9)
VII	5.07	4.16–4.20	4.37 (4.4, 1.7)	4.06–4.12	3.72 (10.7, 6.1); 3.79 (10.7, 5.1)
VIII	5.23 (2.7)	3.99 (3.0)	4.30 (1.1)	3.83 (10.4, 4.7)	3.68 (9.5, 4.6); 3.85–3.96

[a] At 600 MHz, $CDCl_3$. [b] Two-proton (2 H) signal.

Table 2 ^{13}C NMR data for protected octaarabinofuranoside **6**.

Residue	δ_C (151 MHz, $CDCl_3$)				
	C-1	C-2	C-3	C-4	C-5
I	104.78 or 104.82	81.88	77.05	82.79	65.72 or 65.77 or 65.79 or 65.84 (2 C)
II–V	105.87, 105.89, 105.91 (2 C), 105.99	81.46, 81.50, 81.53, 81.55	77.14, 77.16, 77.21 (2 C)	82.07 (2 C), 82.08, 82.11	65.72 or 65.77 or 65.79 or 65.84 (2 C)
VI	105.87, 105.89, 105.91 (2 C), 105.99	81.63	77.43	81.76	66.01
VII	106.91	90.93	77.57	87.44	64.14
VIII	104.78 or 104.82	78.11	78.22	85.70	63.74

Table 3 ^{1}H NMR data for deprotected octaarabinofuranoside **9** with AEP aglycone.

Residue	δ_H (*J*/Hz)[a]				
	H-1	H-2	H-3	H-4	H-5a; H-5b
I	5.42 (1.9)	4.22 (4.0, 1.9)	3.97–4.10	4.13–4.18	3.61–3.71; 3.82–3.88
II–VI	4.94–4.96, 4.96 (1.6)	3.97–4.10	3.89–3.92	3.97–4.10	3.61–3.71; 3.82–3.88
VII	5.07 (2.3)	4.13–4.18	3.97–4.10	3.95 (7.8, 5.0, 2.8)	3.61–3.71; 3.76–3.81
VIII	5.03 (4.1)	3.97–4.10	3.97–4.10	3.76–3.81	3.61–3.71; 3.73 (12.0, 3.2)

[a] At 600 MHz, CD_3OD.

Table 4 ^{13}C NMR data for deprotected octaarabinofuranoside **9** with AEP aglycone.

Residue	δ_C (151 MHz, CD_3OD)				
	C-1	C-2	C-3	C-4	C-5
I	108.68	83.78	78.78 or 78.82	84.35 or 84.38	68.02
II–VI	109.62, 109.69 (3 C), 109.73	83.25 (4 C), 83.30	78.98, 79.18 (4 C)	83.95, 84.05, 84.16 (4 C)	68.28 (4 C), 68.34
VII	107.58	89.27	76.42	83.95 or 84.05 or 84.16 (4 C)	62.48
VIII	102.46	78.78 or 78.82	75.87	84.35 or 84.38	64.40

silyl groups allows one to create a 1,2-*trans* glycosidic linkage in the absence of a participating group at O-2 in the glycosyl donor. After protective groups manipulations, we obtained deprotected octaarabinofuranoside **9** as an AEP glycoside, which may be converted to neoglycoconjugates, useful for the development of diagnostic agents.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7866.

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