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Synthesis of branched arabinofuranose pentasaccharide fragment of mycobacterial arabinans as 2-azidoethyl glycoside

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ABSTRACT

Branched arabinofuranose pentasaccharide with 2-azidoethyl aglycon was prepared for the first time by [3+1+1] bis-(1,2-*cis*)-glycosylation of trisaccharide diol with silyl-protected thioglycoside glycosyl donor. The presence of 2-azidoethyl aglycon would enable the preparation of neoglycoconjugates using the click chemistry approaches.

1. Introduction

Human tuberculosis (TB) remains a major worldwide health problem and takes millions of lives annually.[1,2] This disease has received increasing attention due to emerging drug-resistant strains of *Mycobacterium tuberculosis*, the microorganism that causes TB.[3] For this reason, an important area of research may include the synthesis of natural carbohydrates present on the cell wall of *M. tuberculosis*, their fragments and neoglycoconjugates thereof for identification of new drug targets for treatment of TB, development of conjugate vaccines for prevention of TB as well as for design of new agents for diagnosis of TB.

The cell wall of *M. tuberculosis* consists mainly of two polysaccharides, the mycolyl-arabinogalactan-peptidoglycan complex (mAGP) and lipoarabinomannan (LAM), both of which contain an arabinan domain which is composed of D-arabinose residues in the furanose form which are linked in a combination of α-(1→3), α-(1→5), and β-(1→2) glycosidic linkages.[4–6] The arabinan chains are capped at the nonreducing ends with the branched pentasaccharide fragment [β-D-Ara(1-2)-α-D-Ara(1-5)]-[β-D-Ara(1-2)-α-D-Ara(1-3)]-α-D-Ara.

Various strategies[7–16] have been developed for the synthesis of oligosaccharides containing this terminal pentasaccharide fragment[7–9,12,13,16–21] prepared as reducing sugars,[7,9] simple alkyl[8,9,17,18] or alkylidene[16,19,21] glycosides or functionalized glycosides with carboxy[12] or amino[7,22] group at the terminal position of the aglycon. However, the synthesis of the larger structures[7,21] (up to 31 residues[20]) requires a lot of effort and exceptionally high qualification and expertise.

At the same time, it is known that in many cases behavior of complex oligo- or polysaccharides can be successfully modeled by neoglycoconjugates comprising only small (usually terminal) oligosaccharide fragments of the parent natural saccharide.[23] Currently, many neoglycoconjugates, including non-glycosidically-linked oligosaccharides,[24–26] glycosyl-clusters,[24,27,28] glycodendrimers,[27] glycopolymers,[27] glycopeptides,[24,26,29–31] β-cyclodextrin analogs,[24,27,32] are being prepared by click-chemistry[24,27,29,33–38] which enables an easy coupling of chemically diverse structures. Although different reactions[27,30,39] can be used for click-chemistry, the most popular approach relies on the use of Cu(I)-catalyzed[29,33,36,40,41] or strain-promoted[39,42–44] Huisgen 1,3-dipolar cycloaddition of azides to terminal alkynes.

The preparation of mycobacterial oligosaccharides with azido group in aglycon is an important task since azido group can provide a possibility to use the power of click chemistry for synthesizing various neoglycoconjugates[27] including, for example, new covalent conjugates with recombinant proteins of *M. tuberculosis*[22] in order to obtain in vitro glycosylated antigens for serodiagnosis of TB. As the first step in this direction we set out to prepare terminal pentasaccharide fragment as 2-azidoethyl[45] glycoside **8**

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(Scheme 1), which can further be used for the preparation of wide range of neoglycoconjugates.

2. Results and discussion

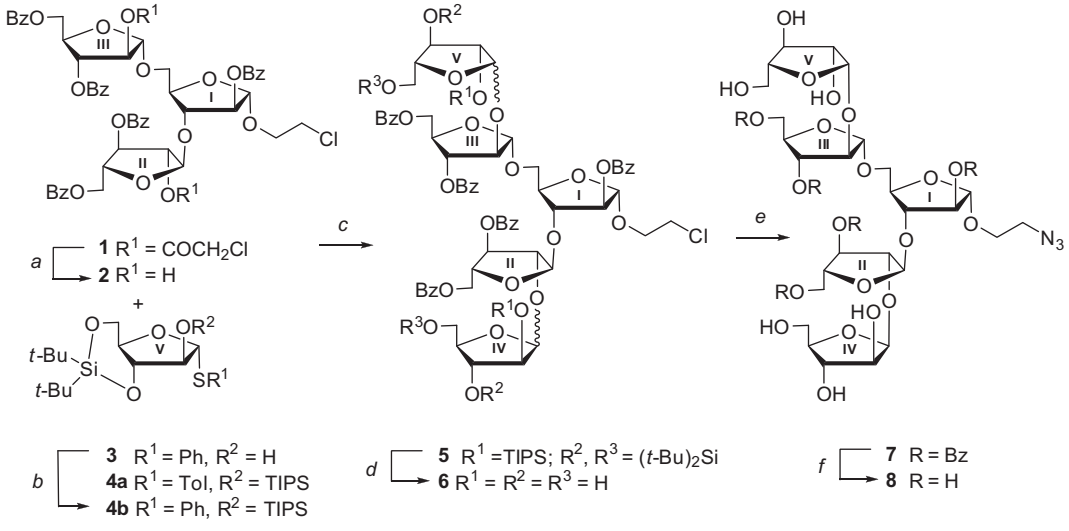
Although an azide-containing *monosaccharide* derivative of arabinofuranose has been prepared and used in click chemistry-based preparation of β-arabinofuranose glycosyl triazoles,[46] there are no examples of the synthesis of arabinofuranose *oligosaccharides* with azido group in aglycon to the best of our knowledge.

Different strategies can be used for the introduction of functionalized aglycon into an oligosaccharide as required for the preparation of neoglycoconjugates.[23] One of the popular approaches makes use of temporary protecting group at the anomeric position. After the assembly of the required oligosaccharide the anomeric protection is cleaved and the resulting hemiacetal is converted into a suitable glycosyl donor and then to the glycoside with a functionalized spacer aglycon. In this context it is necessary to note that this strategy has been successfully used[7] for the synthesis of hemiacetals of otherwise O-benzoylated oligosaccharides related to the Mycobacterial arabinans (including a pentasaccharide similar to compound **8**). These derivatives could have been used as glycosyl donors for the synthesis of spacered glycosides. In such a case, if the preparation of 2-azidoethyl glycoside is required, glycosylation of 2-azidoethyl alcohol or other simple alcohols like 2-chloro- or 2-bromoethanol would be necessary. However, it is known[47] that in some cases glycosidations of complex oligosaccharides by simple alcohols may lead to the mixtures of anomers, which are difficult to separate due to their close chromatographic mobilities.

For this reason, we used an alternative pre-spacer approach,[23] which would avoid such problems in the synthesis of the title pentasaccharide. This approach is based on the preparation of protected pentasaccharide as 2-chloroethyl glycoside[48] starting from 2-chloroethyl glycoside of the monosaccharide at the reducing end (corresponds to the residue Ara^{I} in trisaccharide **1**) and further introduction of azide into the aglycon at the stage of pentasaccharide. The advantages of using 2-chloroethyl aglycon[48] over the use of 2-azidoethyl aglycon[45] already on the monosaccharide building block are multiple. Most importantly, although there is evidence that the presence of azide in aglycon of glycosyl acceptor may negatively influence the outcome of glycosylation in some cases,[49,50] the corresponding influence of the chlorine is not documented to the best of our knowledge. Moreover, the aliphatic chlorine is virtually inert under the most conditions used during oligosaccharide synthesis. In this context, it is worth mentioning that 2-chloroethyl glycosides, unlike 2-azidoethyl glycosides, may survive even the conditions of catalytic hydrogenolysis (L. O. Kononov et al., unpublished results).

The majority of the known approaches (for a possible exception[7] see the discussion above) used for the assembly of oligosaccharides containing the pentasaccharide fragment [β-D-Ara(1-2)-α-D-Ara(1-5)]-[β-D-Ara(1-2)-α-D-Ara(1-3)]-α-D-Ara are not compatible with azido group in the aglycon since most of them rely on the use of *O*-benzyl protecting groups either in glycosyl acceptors[13,17–19] or in glycosyl donors[7,9,13,17–19,22,51] used for the construction of 1,2-*cis*-linkage, which are difficult to remove in the presence of azide. For example, the use of catalytic hydrogenolysis for de-O-benzylation is not possible since the azido group is reduced faster than any substantial cleavage of *O*-benzyl groups occurs. The related problem of removal of *O*-benzyl groups from the derivatives with azido group in aglycon even with concomitant reduction of the latter to amino function is recognized in neoglycoconjugate chemistry. In many cases the required de-O-benzylated derivative with amino group in aglycon can be easily obtained by a simple catalytic hydrogenolysis.[49] However, in other cases more sophisticated by-pass routes are required that rely on initial reduction of azido group in the aglycon to amino group (for example, by Ph_3P[13] or controlled hydrogenation[49]) followed by its protection (for example, as trifluoroacetamide[13,49]), exhaustive hydrogenolysis of *O*-benzyl groups and final amine deprotection. Unfortunately, all these approaches do not allow preservation of the azido group in the aglycon and thus could not be used for the synthesis of pentasaccharide **8**. For this reason, we started developing a novel *benzyl-free* strategy for the assembly of arabinoligosaccharides, designed several useful O-*benzoylated* arabinofuranose building blocks (including those with 2-chloroethyl aglycon)[52,53] and successfully used them as glycosyl acceptors in the synthesis of oligosaccharides[22,54] with spacer aglycons.

Stereoselective introduction of two β-linked arabinofuranose residues is the most crucial and challenging step during any synthesis of the pentasaccharide in question and may rely on different approaches developed for the introduction of 1,2-*cis* linkages.[8,9,12,55,56] In our previous work[22] we used β-selective arabinofuranose thioglycoside donor[11] with 2-*O*-benzyl and 3,5-*O*-di-*tert*-butylsilylene protecting groups. Since now we had to avoid using *O*-benzyl protecting groups, all the variety of glycosyl donors



Scheme 1. Synthesis of unprotected pentasaccharide 2-azidoethyl glycoside **8**. Reagents and conditions: (a) Py, H_2O, 70 °C (96%); (b) TIPSOTf, *sym*-collidine, DMF, 90 °C (94%); (c) NIS, AgOTf, DCM, MS 4 Å, −40 °C→−13 °C (77% of **5**, mixture of isomers, ββ:other isomers = 6.14:1); (d) TBAF, THF, AcOH (77%, mixture of isomers); (e) (1) NaN_3, 18-crown-6, DMF, 70 °C; (2) HPLC on silica gel, *i*-PrOH–$CHCl_3$–petroleum ether, 1:3:6 (55% of **7**); (f) MeONa, MeOH (93%). TIPS = *i*-Pr_3Si.

with non-participating 2-*O*-benzyl protecting group developed earlier[9,13,17,19,51] could not be used in our synthesis. Fortunately for us, Ito and co-workers described[8] a synthesis of arabinofuranose tolyl thioglycoside **4a** with 2-*O*-silyl and 3,5-*O*-di-*tert*-butylsilylene protecting groups, which can potentially be removed with fluoride-based reagents[57,58] in the presence of azido group. Although this glycosyl donor demonstrated moderate stereoselectivity (β:α = 5.36:1)[8] in glycosylation reactions with O-benzylated glycosyl acceptors its use for the benzyl-free synthesis of azido-containing oligosaccharides seemed to be justified.

For the synthesis of pentasaccharide 2-azidoethyl glycoside **8** we used a similar glycosyl donor with thiophenyl aglycon **4b**, prepared in 94% yield by silylation (TIPSOTf, *sym*-collidine, DMF) of the known[51] alcohol **3**. The required glycosyl acceptor, trisaccharide diol **2** with *O*-benzoyl protecting groups, was prepared in 96% yield by removal of two chloroacetyl groups (Py, H_2O) from the known[54] trisaccharide **1** with 2-chloroethyl[48] aglycon (Scheme 1).

Glycosyl donor **4b** and glycosyl acceptor **2** were coupled in a [3+1+1] bis-(1,2-*cis*)-glycosylation reaction to give a mixture of diastereomeric pentasaccharides **5** in 77% yield, the required ββ-isomer dominating (ββ:(αα+αβ+βα) = 6.14:1, NMR data); the separation of isomers was not possible at this stage (see below). It is known that bis-glycosylation is a more complex process due to formation of four anomers of glycoside formed (αβ, βα, αα, and ββ) than mono-glycosylation, which leads only to two anomers (α and β). Assuming that stereoselectivity of every glycosylation step is the same (which is not entirely correct; see below), it is possible to calculate that β-selectivity of a single glycosylation step was higher (β:α = 12.76:1) in the *bis*-glycosylation of O-*benzoylated* trisaccharide diol **2** (ββ:(αα+αβ+βα) = 6.14:1) performed with phenyl thioglycoside **4b** than that reported (β:α = 5.36:1)[8] for the *mono*-glycosylations performed with similar thioglycoside **4a** in reactions with O-*benzylated* glycosyl acceptors as one would expect lower proportion of ββ-isomer (ββ:(αα+αβ+βα) = 2.45:1) in the latter case. It is worthy of note that the efficiency of the *bis*-glycosylation of O-*benzoylated* trisaccharide diol **2** with thioglycoside **4b** (66% yield of ββ-isomer of **5**) is comparable to that achieved in the *bis*-glycosylation of the related O-*benzylated* trisaccharide methyl glycoside using a novel 2,3-*O*-xylylene-protected arabinofuranosyl donor[59] (65% yield of ββ-isomer of the pentasaccharide methyl glycoside), which was shown to be highly β-selective (β:α = 12.6)[59] in *mono*-glycosylation of a O-*benzylated* monosaccharide acceptor. It is interesting that the latter value is very close to our estimate of β-selectivity (β:α = 12.76) of a single glycosylation step during the synthesis of **5** (see above). These results suggest that the stereoselectivity of glycosylation with arabinofuranosyl glycosyl donors is fairly sensitive to the nature of protecting groups on glycosyl acceptor (as was earlier reported by other groups[7–9,55,56,59]) and that results of mono-glycosylation may not be directly transferable to bis-glycosylation.

The structure of the major isomer of protected pentasaccharide **5** followed from NMR data (see Section 4 and Tables 1–3), which revealed three linked α-arabinofuranose residues [δ_C 106.1 (C-1^I), 106.0 (C-1^{II}), 107.3 (C-1^{III}); three singlets at δ_H 5.16 (H-1^I), 5.49 (H-1^{II}), 5.25 (H-1^{III})] and two linked β-arabinofuranose residues [(δ_C 101.7 (C-1^{IV}), 101.4 (C-1^V); a multiplet signal at δ_H 5.15 (H-1^{IV}), a doublet at δ_H 5.06 (H-1^V, $J_{1,2}$ = 4.5 Hz)]. The presence of aglycon at Ara^I residue, 1,3-intersaccharidic linkage between Ara^{II} and Ara^I, 1,5-linkage between Ara^{III} and Ara^I, and two 1,2-linkages between Ara^{IV} and Ara^{II}, and Ara^V and Ara^{III} residues, respectively, followed from the observation of the following correlations in HMBC spectra: $\underline{C}H_2CH_2Cl$/H-1^I, C-1^{II}/H-3^I, C-5^I/H-1^{III}, C-1^{III}/H-5^I, C-1^{IV}/H-2^{II}, C-1^V/H-2^{III}. After glycosylation reaction the signals of C-2 of Ara^{II} and Ara^{III} residues moved to the lower field (δ_C ~86.5 for **5** and δ_C ~81 for **2**) indicating that the corresponding oxygens in pentasaccharide **5** are glycosylated.

Table 1
^{13}C NMR chemical shifts (151 MHz, $CDCl_3$, δ_C)

	2	**4**	**5**	**6**	**7**	**8**[a]
1^I	105.9	–	106.1	105.7	105.8	109.7
1^{II}	107.7	–	106.0	106.46	106.3	107.0
1^{III}	108.1	–	107.3	106.47	106.5	107.5
1^{IV}	–	–	101.7	101.6	101.5	102.4
1^V	–	92.8	101.4	101.0	101.0	102.4
2^I	82.9	–	82.9	83.4	83.2	82.0
2^{II}	80.9	–	86.5	85.8	85.7	89.4
2^{III}	81.21	–	86.4	85.3	85.1	89.3
2^{IV}	–	–	76.3	78.0	77.82	75.9[b]
2^V	–	82.1[b]	76.3	77.9	77.75	75.8[b]
3^I	81.19	–	80.3	82.2	81.7[b]	84.5
3^{II}	81.7	–	78.2	78.3	78.4	76.5[c]
3^{III}	81.9	–	78.2	78.6	78.6	76.2[c]
3^{IV}	–	–	79.0	74.1	74.3	84.4
3^V	–	73.4	78.8	74.1	74.2	84.4
4^I	82.0	–	81.8	81.5	81.8[b]	82.9
4^{II}	79.8	–	81.0	79.8	79.8	84.0[d]
4^{III}	79.1	–	80.6	79.8	79.8	83.8[d]
4^{IV}	–	–	73.9	82.6	82.5[c]	78.8
4^V	–	82.2[b]	73.9	82.6	82.6[c]	78.8
5^I	66.1	–	66.7	65.9	65.9	67.8
5^{II}	63.9[b]	–	64.5[b]	63.7[b]	63.8[d]	62.5[e]
5^{III}	63.8[b]	–	64.3[b]	63.6[b]	64.0[d]	62.4[e]
5^{IV}	–	–	68.3	62.0	62.1[e]	64.4[f]
5^V	–	67.4	68.3	62.0	62.0[e]	64.3[f]
OCH_2	67.5	–	67.5	67.5	66.2	67.6
CH_2X	42.5	–	42.5	42.4	50.4	51.8

[a] In CD_3OD.
[b–f] Signals may be interchanged.

Fully protected pentasaccharide **5** was desilylated (TBAF, DMF) to give hexaol **6** as the mixture of anomers in 77% yield. The NMR data confirmed the structure of pentasaccharide **6**. The presence of both α-Ara*f* and β-Ara*f* linkages was apparent from HSQC spectrum—three α C-1 and singlet H-1 signals: δ_C 105.7 (C-1^I) and δ_H 5.21 (1H, s, H-1^I), 106.46 (C-1^{II}) and 5.42 (1H, s, H-1^{II}), 106.47 (C-1^{III}) and 5.22 (1H, s, H-1^{III}), as well as two β C-1 and doublet H-1 signals with large coupling constants: δ_C 101.6 (C-1^{IV}) and δ_H 5.18 (1H, d, J = 4.9 Hz, H-1^{IV}), 101.0 (C-1^V) and 5.06 (1H, d, J = 4.8 Hz, H-1^V) (see Section 4 and Tables 1–3). Chlorine in the 2-chloroethyl aglycon of **6** was substituted (NaN_3, 18-crown-6, DMF) to give O-benzoylated 2-azidoethyl glycoside **7** in 55% yield as the single diastereoisomer after HPLC separation. The NMR data confirmed the structure of pentasaccharide **7** in a way similar to the one used for determining the structure of **5**. The presence of azido group in the aglycon followed from the position of the terminal methylene group $CH_2\underline{C}H_2N_3$ (δ_C 50.4) in the ^{13}C NMR spectrum of **7**. The positions of characteristic signals in ^1H and ^{13}C NMR spectra of 2-azidoethyl glycoside **7**, coupling constants and correlations in HSQC and HMBC spectra corresponded well to those observed for the major isomer of 2-chloroethyl glycoside **5** (see Section 4 and Tables 1–3): α C-1 and singlet H-1 signals [δ_C 105.8 (C-1^I), 106.3 (C-1^{II}), 106.5 (C-1^{III}), δ_H 5.17 (1H, s, H-1^I), 5.44 (1H, s, H-1^{II}), 5.23 (1H, s, H-1^{III})], two β C-1 and doublet H-1 signals with the large coupling constants [δ_C 101.5 (C-1^{IV}), 101.0 (C-1^V), δ_H 5.03 (1H, d, J = 4.5 Hz, H-1^V) 5.14 (1H, d, J = 4.6 Hz, H-1^{IV})]. HMBC was used to show intersaccharide correlations between $\underline{C}H_2CH_2Cl$/H-1^I, C-1^{II}/H-3^I, C-3^I/H-1^{II}, C-5^I/H-1^{III}, C-1^{III}/H-5^I_a, C-1^{III}/H-5^I_b, C-1^{IV}/H-2^{II}, C-2^{II}/H-1^{IV}, C-1^V/H-2^{III}, C-2^{III}/H-1^V.

Hexaol **7** was debenzoylated (MeONa, MeOH) to give in 93% yield the target deprotected pentasaccharide with 2-azidoethyl aglycon **8** as the single isomer. The structure of **8** was fully confirmed by 1D and 2D NMR spectra (see Section 4 and Tables 1–3). The obtained values of chemical shifts of anomeric protons (δ_H 4.94 (s), 5.03 (2H, d, J = 4.3 Hz), 5.04 (2H, d, J = 4.2 Hz), 5.08 (2H, d, J = 2.2 Hz), 5.17 (2H, d, J = 2.4 Hz)) and anomeric carbons

Table 2
^{1}H NMR chemical shifts (600 MHz, $CDCl_3$, δ_H)

	2	4	5	6	7	8[a]
1^I	5.21 s	–	5.16 br s	5.21 s	5.17 s	4.94 s
1^{II}	5.41 s	–	5.49 s	5.42 s	5.44 s	5.17 d
1^{III}	5.21 s	–	5.25 br s	5.22 s	5.23 s	5.08 d
1^{IV}	–	–	5.15 m	5.18 d	5.14 d	5.03 d
1^V	–	5.31 d	5.06 d	5.06 d	5.03 d	5.04 d
2^I	5.33 s	–	5.24 d	5.28 s	5.26 s	4.15–4.16 m
2^{II}	4.46 s	–	4.40 d	4.49–4.54 m	4.49–4.51 m	4.13 dd
2^{III}	4.31 d	–	4.36 d	4.40 s	4.38 s	4.14–4.15 m
2^{IV}	–	–	4.22–4.25 m	4.01–4.14 m	4.08–4.13 m	3.98–4.00 m
2^V	–	4.26 dd	4.15–4.17 m	4.01–4.14 m	4.03–4.07 m	3.96–3.99 m
3^I	4.36–4.39 m	–	4.42 d	4.28–4.30 m	4.31 s	4.04–4.07 m
3^{II}	5.09 d	–	5.56 dd	5.49 dd	5.48 br s	4.03–4.04 m
3^{III}	5.03 d	–	5.51 dd	5.38 d	5.37 br s	4.02–4.03 m
3^{IV}	–	–	4.15–4.22 m	4.25 t	4.25 t	3.77–3.79 m
3^V	–	3.96–4.05 m	4.15–4.22 m	4.19 t	4.22 t	3.77–3.79 m
4^I	4.32–4.35 m	–	4.29–4.33 m	4.32–4.35 m	4.31 s	4.16–4.19 m
4^{II}	4.58–4.61 m	–	4.55–4.57 m	4.56–4.62 m	4.56–4.59 m	3.97–4.00[b] m
4^{III}	4.56–4.59 m	–	4.53–4.55 m	4.56–4.62 m	4.57–4.61 m	3.91–3.92[b] m
4^{IV}	–	–	3.63–3.64 m	3.73–3.86 m	3.80–3.83 m	3.96–4.01 m
4^V	–	3.96–4.05 m	3.56–3.58 m	3.73–3.86 m	3.78–3.82 m	3.96–4.01 m
$5^I{}_a$	4.06 dd	–	4.04–4.07 m	4.01–4.14 m	4.06–4.09 m	3.90–3.92 m
$5^I{}_b$	3.83 dd	–	3.80–3.83 dd	3.73–3.86 m	3.80–3.84 m	3.74–3.76 m
$5^{II}{}_a$	4.63–4.68 m	–	4.45–4.51 m	4.56–4.62 m	4.54–4.61 m	3.79–3.81 m
$5^{II}{}_b$	4.54–4.61 m	–	4.45–4.51 m	4.49–4.54 m	4.47–4.53 m	3.63–3.64 m
$5^{III}{}_a$	4.63–4.68 m	–	4.45–4.51 m	4.56–4.62 m	4.54–4.61 m	3.79–3.81 m
$5^{III}{}_b$	4.54–4.61 m	–	4.45–4.51 m	4.49–4.54 m	4.47–4.53 m	3.63–3.64 m
$5^{IV}{}_a$	–	–	4.15–4.22 m	3.73–3.86 m	3.75–3.82 m	3.77–3.79[c] m
$5^{IV}{}_b$	–	–	3.89–3.91 m	3.66–3.71 m	3.65–3.70 m	3.66[d] d
$5^V{}_a$	–	4.37 q	4.08–4.12 m	3.73–3.86 m	3.75–3.82 m	3.72[c] t
$5^V{}_b$	–	3.96–4.05 m	3.86–3.88 m	3.66–3.71 m	3.65–3.70 m	3.64–3.65[d] m
OCH_{2a}	3.90–3.95 m	–	3.89–3.93 m	3.89–3.94 m	3.84–3.88 m	3.85–3.88 m
OCH_{2b}	3.74–3.79 m	–	3.73–3.78 m	3.73–3.86 m	3.60–3.64 m	3.61–3.63 m
$CH_{2a}X$	3.61 t	–	3.60 t	3.60 t	3.27–3.37 m	3.37–3.46 m
$CH_{2b}X$	3.61 t	–	3.60 t	3.60 t	3.27–3.37 m	3.37–3.46 m

[a] In CD_3OD.
[b–d] Signals may be interchanged.

Table 3
Coupling constants in ^{1}H NMR spectra (600 MHz, $CDCl_3$, J, Hz)

Monosaccharide residue		2	4	5	6	7	8[a]
I	$J_{4,5a}$	4.5	–	4.9	[b]	[b]	[b]
I	$J_{4,5b}$	2.3	–	2.8	[b]	[b]	[b]
I	$J_{5a,5b}$	11.4	–	11.7	[b]	[b]	[b]
II	$J_{1,2}$	[b]	–	[b]	[b]	[b]	2.4
II	$J_{3,4}$	5.1	–	4.1	4.4	[b]	[b]
II	$J_{2,3}$	[b]	–	2.1	2.6	[b]	5.4
III	$J_{1,2}$	1.2	–	[b]	[b]	[b]	2.2
III	$J_{2,3}$	[b]	–	2.1	[b]	[b]	[b]
III	$J_{3,4}$	5.9	–	4.3	4.2	[b]	[b]
IV	$J_{1,2}$	–	–	[b]	4.9	4.6	4.3
IV	$J_{2,3}$	–	–	[b]	7.7	7.4	[b]
IV	$J_{3,4}$	–	–	[b]	7.7	7.4	[b]
V	$J_{1,2}$	–	5.3	4.5	4.8	4.5	4.2
V	$J_{2,3}$	–	6.4	[b]	7.5	7.2	[b]
V	$J_{3,4}$	–	[b]	[b]	7.5	7.2	[b]
V	$J_{4,5a}$	–	3.7	[b]	[b]	[b]	2.8
OCH_2CH_2X	$J_{CH2X,OCH2}$	5.9	[b]	6.0	5.9	[b]	[b]
OCH_2CH_2X	$J_{CH2X,OCH2}$	5.9	–	6.0	5.9	[b]	[b]

[a] In CD_3OD.
[b] Coupling constant could not be determined.

(δ_C 102.4 (2C), 107.0, 107.5, 109.7) of pentasaccharide **8** in CD_3OD were in good agreement with the reported NMR data in D_2O for the anomeric signals of previously synthesized pentasaccharides methyl glycoside[13] (anomeric protons: δ_H 4.88 (s), 5.06 (2H, d, J = 3.8 Hz), 5.10 (s), 5.16 (s); anomeric carbons: δ_C 101.02, 101.09, 105.88, 106.03, 108.86) and 1,2-*O*-isopropylidene acetal[16] (anomeric protons: δ_H 4.90 (d, J = 4.20 Hz), 5.10 (d, J = 4.65 Hz), 5.15 (s), 5.28 (s), 6.00 (d, J = 4.8 Hz); anomeric carbons: δ_C 102.0, 102.1, 106.3, 106.5, 106.9).

3. Conclusions

In summary, we suggested a benzyl-free approach for the construction of the arabinofuranose branched oligosaccharides found at the non-reducing end of mycobacterial arabinans using the synthesis of pentasaccharide 2-azidoethyl glycoside **8** as a representative example. The presence of 2-azidoethyl aglycon in pentasaccharide fragment would allow the use of the click-chemistry approaches and the preparation of neoglycoconjugates.

4. Experimental

4.1. General methods

All reactions sensitive to air and/or moisture were carried out under argon atmosphere with anhydrous solvents. The reactions were performed with the use of commercial reagents (Aldrich, Fluka, Acros Organics) and distilled solvents purified and dried (where appropriate) according to standard procedures. Powdered molecular sieves 4 Å (Fluka) were activated before the reactions by heating at 180 °C in high vacuum for 2 h. Column chromatography was performed on Silica Gel 60 (40–63 μm, Merck). Thin-layer chromatography was carried out on plates with Silica Gel 60 on glass or on aluminum foil (Merck). Spots of compounds were visualized under UV light and by heating the plates after immersion in a 1:10 (v/v) mixture of 85% aqueous H_3PO_4 and 95% EtOH. NMR spectra were recorded for solutions in $CDCl_3$ or CD_3OD on a Bruker AC-200 instrument (200.13, and 50.32 MHz, respectively), a Bruker AM-300 instrument (300.13, and 75.48 MHz, respectively) or on a Bruker AVANCE 600 spectrometer (600.13 and 150.9 MHz, respectively). The ^{1}H NMR chemical shifts are referred to the residual sig-

nal of $CHCl_3$ (δ_H 7.27) or CHD_2OD (δ_H 3.31) and the ^{13}C NMR shifts to the $CDCl_3$ signal (δ_C 77.0) or CD_3OD signal (δ_C 49.0). Assignments of the signals in the NMR spectra were performed using 2D-spectroscopy (COSY, HSQC, HMBC) and DEPT-135 experiments, NMR data for all compounds are listed in Tables 1–3. High resolution mass spectra (electrospray ionization, HRESIMS) were measured in a positive mode on a Bruker micrOTOF II mass spectrometer for 2×10^{-5} M solutions in MeCN or MeOH. Optical rotations were measured using a PU-07 automatic polarimeter (Russia). Analytical HPLC separations were performed on an Ultrasorb Si (5 μm) column (165 × 4.6 mm ID) at 1 mL/min flow rate. Preparative HPLC separations were performed on a Sialsorb 600 (7.5 μm) column (250 × 15 mm ID) with a 1:3:6 *i*-PrOH–$CHCl_3$–petroleum ether mixture as the eluent at 15 mL/min flow rate. A Knauer differential refractometer was used as the detector.

4.2. 2-Chloroethyl 2-*O*-benzoyl-3,5-di-*O*-(3,5-di-*O*-benzoyl-α-D-arabinofuranosyl)-α-D-arabinofuranoside (2)

2-Chloroethyl 2-*O*-benzoyl-3,5-di-*O*-(3,5-di-*O*-benzoyl-2-*O*-chloroacetyl-α-D-arabinofuranosyl)-α-D-arabinofuranoside (**1**)[54] (470.9 mg, 0.41 mmol) was dissolved in anhydrous Py (7.75 mL) and water (4 mL) was added to the stirring mixture. The reaction mixture was stirred at 70 °C (bath temperature) for 1 h and was co-concentrated with toluene (40 mL, bath temperature ~50 °C). Then the reaction mixture was diluted with $CHCl_3$ (100 mL), washed with 1 M $KHSO_4$ (70 mL), water (70 mL), and satd $NaHCO_3$ (70 mL). Organic extract was filtered through cotton wool plug, concentrated under reduced pressure (bath temperature ~30 °C), dried in vacuo, and purified by silica gel column chromatography (petroleum ether–EtOAc, 3:2) to give **2** as a white solid foam (392.3 mg, 96%; R_f = 0.22, petroleum ether–EtOAc, 3:2). $[\alpha]_D^{22}$ +46.9 (*c* 1.0, $CHCl_3$). HRESIMS: found *m/z* 1019.2491 $[M+Na]^+$. Calcd for $C_{52}H_{49}O_{18}ClNa$: 1019.2500. NMR data are listed in Tables 1–3 except for the following signals: ^1H NMR (600 MHz, $CDCl_3$): δ_H 7.30–7.39 (m, 8H, Ph), 7.42 (t, 2H, *J* = 7.7 Hz, Ph), 7.46–7.53 (m, 4H, Ph), 7.57 (t, 1H, *J* = 7.5 Hz, Ph), 7.92 (d, *J* = 7.8 Hz, 4H, Ph), 7.98–8.04 (m, 6H, Ph). ^{13}C NMR (151 MHz, $CDCl_3$): δ_C 128.36, 128.37, 128.40, 128.42, 128.49, 128.52, 128.8, 128.9, 129.0, 129.5, 129.62, 129.66, 129.76, 129.80, 133.1, 133.2, 133.4, 133.56, 133.62 (Ph), 165.5, 166.15, 166.18, 166.9, 167.0 (CO). HMBC correlations: C-1^{II}/H-3^I, C-5^I/H-1^{III}, CH_2CH_2Cl/H-1^I.

4.3. Phenyl 3,5-di-*O*-*tert*-butylsilylene-2-*O*-triisopropylsilyl-1-thio-α-D-arabinofuranoside (4b)

Phenyl 3,5-di-*O*-*tert*-butylsilylene-1-thio-α-D-arabinofuranoside (**3**)[51] (62.1 mg, 0.16 mmol) was dissolved in anhydrous DMF (2 mL). *sym*-Collidine (65 μL, 0.49 mmol) and *i*-$Pr_3SiOSO_2CF_3$ (TIPSOTf) (70 μL, 0.26 mmol) were added to the stirring mixture. The reaction mixture was stirred at 90 °C (bath temperature) for 1 h and then was diluted with $CHCl_3$ (30 mL), washed with 1 M $KHSO_4$ (20 mL), water (20 mL), and satd $NaHCO_3$ (20 mL). Organic extract was filtered through a cotton wool plug, concentrated under reduced pressure (bath temperature ~30 °C), dried in vacuo, and purified by silica gel column chromatography (petroleum ether–toluene, 3:1) to give **4b** as a colorless oil (80.9 mg, 94%; R_f = 0.27, petroleum ether–toluene, 3:1). $[\alpha]_D^{22}$ +130.0 (*c* 1.0, $CHCl_3$). HRESIMS: found *m/z* 556.3319 $[M+NH_4]^+$. Calcd for $C_{28}H_{50}O_4SSi_2NH_4$: 556.3307. NMR data are listed in Tables 1–3 except for the following signals: ^1H NMR (600 MHz, $CDCl_3$) δ_H 1.03 (s, 9H, $C(CH_3)_3$), 1.10 (s, 9H, $C(CH_3)_3$), 1.15–1.17 (m, 21H, $CH(CH_3)_2$, $CH(CH_3)_2$), 7.27–7.35 (m, 3H, Ph), 7.51–7.54 (m, 2H, Ph). ^{13}C NMR (151 MHz, $CDCl_3$) δ_C 12.2 ($CH(CH_3)_2$), 17.9 and 18.0 ($CH(CH_3)_2$), 20.1 and 22.7 ($C(CH_3)_3$), 27.1 and 27.3 ($C(CH_3)_3$), 127.2, 128.9, 131.2, 135.1 (Ph).

4.4. 2-Chloroethyl 2-*O*-benzoyl-3,5-di-*O*-[3,5-di-*O*-benzoyl-2-*O*-(3,5-di-*O*-*tert*-butylsilylene-2-*O*-triisopropylsilyl-β-D-arabinofuranosyl)-α-D-arabinofuranosyl]-α-D-arabinofuranoside (5)

Freshly activated molecular sieves 4 Å (1 g) were added under Ar to the mixture of diol **2** (263.7 mg, 0.26 mmol) and thioglycoside **4b** (526.5 mg, 0.98 mmol) in CH_2Cl_2 (12.7 mL) and the reaction mixture was stirred at ~20 °C for 16 h. The reaction mixture was cooled to −58 °C and N-iodosuccinimide (220.3 mg, 0.98 mmol) and AgOTf (27.4 mg, 0.11 mmol) were added. The reaction mixture was stirred at −40 °C for 40 min, and then the temperature was allowed to warm to −13 °C during 1 h and then the reaction was quenched by the addition of satd $NaHCO_3$ (50 μL). The reaction mixture was diluted with CH_2Cl_2 (40 mL) and filtered through a layer of Celite. The reaction mixture was washed with a mixture of satd $Na_2S_2O_3$ (75 mL) and satd $NaHCO_3$ (75 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL) two times. Combined organic extracts were filtered through cotton wool plug, concentrated, dried in vacuo, and purified by silica gel column chromatography (toluene–EtOAc, 7:1) to give **5** as a colorless oil (368.4 mg, 77%; R_f = 0.20, petroleum ether–EtOAc, 7:1). $[\alpha]_D^{23}$ −12.1 (*c* 1.0, $CHCl_3$). HRESIMS: found *m/z* 1870.8472 $[M+NH_4]^+$. Calcd for $C_{96}H_{137}O_{26}ClSi_4NH_4$: 1870.8502. According to analytical HPLC with a 15:1 petroleum ether–ethyl acetate mixture as the eluent the product contained 78% of ββ-isomer (t_R = 27.0 min) and 22% of other isomers (αα, αβ, βα; three peaks with t_R = 14.1, 19.1, 25.3 min). According to NMR data the product contained 86% of ββ-isomer and 14% of other isomers. NMR data are listed in Tables 1–3 except for the following signals: ^1H NMR (600 MHz, $CDCl_3$) δ_H 0.95 (br s, 18H, $C(CH_3)_3$), 0.96 (br s, 18H, $C(CH_3)_3$), 1.03–1.07 (m, 42H, $CH(CH_3)_2$, $CH(CH_3)_2$), 7.29–7.36 (m, 9H, Ph) 7.41–7.57 (m, 7H, Ph) 7.89–8.05 (m, 9H, Ph). ^{13}C NMR (151 MHz, $CDCl_3$) δ_C 12.1 ($CH(CH_3)_2$), 17.8 and 17.7 ($CH(CH_3)_2$), 20.0 and 22.6 ($C(CH_3)_3$), 27.1 and 27.4 ($C(CH_3)_3$), 128.26, 128.33, 128.35, 128.4, 129.2, 129.4, 129.7, 129.8, 129.9, 132.9, 133.1, 133.3 (Ph), 165.5, 165.9 (CO). HMBC correlations: C-1^{II}/H-3^I, C-5^I/H-1^{III}, C-1^{III}/H-5^I, C-1^{IV}/H-2^{II}, C-1^V/H-2^{III}, CH_2CH_2Cl/H-1^I.

4.5. 2-Azidoethyl 3,5-di-*O*-[2-*O*-(β-D-arabinofuranosyl)-3,5-di-*O*-benzoyl-α-D-arabinofuranosyl]-2-*O*-benzoyl-α-D-arabinofuranoside (7)

Protected pentasaccharide **5** as the mixture of isomers (377 mg, 0.20 mmol) was dissolved in anhydrous THF (7 mL) under Ar. AcOH (0.4 mL, 7.0 mmol) and a 1.0 M solution of TBAF in THF (2.5 mL, 8.63 mmol) were added in that order to the cooled (ice-water bath) reaction mixture. The reaction mixture was stirred at ~20 °C for 16 h. The reaction was diluted with toluene (30 mL), concentrated (bath temperature 40–50 °C), dried in vacuo, and purified by silica gel column chromatography (petroleum ether–acetone, 4:5) to give desilylated pentasaccharide **6** as a colorless oil (194.4 mg, 77% (mixture of isomers); R_f = 0.20, petroleum ether–acetone, 4:5). NMR data are listed in Tables 1–3 except for the following signals: ^1H NMR (600 MHz, $CDCl_3$) δ_H 7.29–7.38 (m, 8H, Ph), 7.43–7.54 (m, 6H, Ph), 7.59 (t, *J* = 7.3 Hz, 1H, Ph), 7.85 (d, *J* = 7.6 Hz, 2H, Ph), 7.90 (d, *J* = 7.7 Hz, 2H, Ph), 7.94 (d, *J* = 7.7 Hz, 2H, Ph), 8.00 (d, *J* = 7.7 Hz, 2H, Ph), 8.03 (d, *J* = 7.9 Hz, 2H, Ph). ^{13}C NMR (151 MHz, $CDCl_3$) δ_C 128.3, 128.37, 128.44, 128.5, 128.7, 128.8, 129.0, 129.3, 129.5, 129.6, 129.70, 129.73, 129.8, 133.2, 133.5, 133.6, 133.7 (Ph), 165.7, 166.2, 166.3 (CO). HMBC correlations: C-1^{II}/H-3^I, C-5^I/H-1^{III}, C-1^{IV}/H-2^{II}, C-1^V/H-2^{III}, CH_2CH_2Cl/H-1^I.

2-Chloroethyl glycoside **6** (194.6 mg, 0.15 mmol, mixture of isomers) was dissolved in anhydrous DMF (1.5 mL) and NaN_3 (30 mg, 0.46 mmol) and 18-crown-6 (18.3 mg, 0.07 mmol) were added to the reaction mixture. The reaction mixture was stirred at 70 °C

for 48 h. The reaction was diluted with toluene (15 mL) and concentrated (bath temperature 40–50 °C) (co-evaporation was repeated three times), dried in vacuo, dissolved in EtOAc (50 mL), washed with water (40 mL), filtered through a cotton wool plug, concentrated under reduced pressure (bath temperature ~35 °C), and purified by silica gel column chromatography (petroleum ether–acetone, 4:5) to give **7** as a white solid foam (136.6 mg, 72% (mixture of isomers); R_f = 0.21, petroleum ether–acetone, 4:5), which was subjected to the preparative HPLC (*i*-PrOH–$CHCl_3$–petroleum ether, 1:3:6) to give the pure ββ-isomer of pentasaccharide **7** (104.6 mg, 55% after two steps, t_R = 25.6 min (analytical HPLC in the same eluent)). $[\alpha]_D^{22}$ +28.2 (*c* 1.0, $CHCl_3$). HRESIMS: found *m/z* 1290.3727 $[M+Na]^+$. Calcd for $C_{62}H_{65}O_{26}N_3Na$: 1290.3749. NMR data are listed in Tables 1–3 except for the following signals: ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.25–7.35 (m, 8H, Ph), 7.39–7.50 (m, 6H, Ph), 7.56 (t, *J* = 7.3 Hz, 1H, Ph), 7.82 (d, *J* = 7.7 Hz, 2H, Ph), 7.87 (d, *J* = 7.7 Hz, 2H, Ph), 7.90 (d, *J* = 7.7 Hz, 2H, Ph), 7.97 (d, *J* = 7.7 Hz, 2H, Ph), 8.01 (d, *J* = 7.7 Hz, 2H, Ph). ^{13}C NMR (151 MHz, $CDCl_3$) δ_C 128.3, 128.37, 128.44, 128.5, 128.7, 128.8, 129.0, 129.3, 129.5, 129.6, 129.70, 129.73, 129.8, 133.2, 133.5, 133.6, 133.7 (Ph), 165.7, 166.2, 166.3 (CO). HMBC correlations: C-1^{II}/H-3^{I}, C-3^{I}/H-1^{II}, C-5^{I}/H-1^{III}, C-1^{III}/H-5^{I}_a, C-1^{III}/H-5^{I}_b, C-1^{IV}/H-2^{II}, C-2^{II}/H-1^{IV}, C-1^{V}/H-2^{III}, C-2^{III}/H-1^{V}.

4.6. 2-Azidoethyl 3,5-di-*O*-[2-*O*-(β-D-arabinofuranosyl)-α-D-arabinofuranosyl]-α-D-arabinofuranoside (8)

Pentabenzoate **7** (35.0 mg, 0.03 mmol) was dissolved in MeOH (4.0 mL) and 1 M MeONa in MeOH (219 μL) was added to the reaction mixture, which then was stirred at ~20 °C for 48 h. The reaction was neutralized with ion-exchange resin Dowex 50W×8 (H^+). The resin was filtered off, washed with MeOH (15 mL) and the filtrate was concentrated. Water (15 mL) was added to the residue and the solution was washed with petroleum ether (15 mL). The aqueous layer was freeze-dried in vacuo to give **8** as a white solid foam (19.1 mg, 93% (ββ-isomer); R_f = 0.75, EtOH–*n*-BuOH–Py–AcOH–H_2O, 100:10:10:10:3). $[\alpha]_D^{20}$ +24.5 (*c* 1.0, MeOH). HRESIMS: found *m/z* 770.2443 $[M+Na]^+$. Calcd for $C_{27}H_{45}O_{21}N_3Na$: 770.2438. NMR data are listed in Tables 1–3. HMBC correlations: C-1^{II}/H-3^{I}, C-3^{I}/H-1^{II}; C-5^{I}/H-1^{III}, C-1^{III}/H-5^{I}, C-1^{IV}/H-2^{II}, C-2^{II}/H-1^{IV}, C-1^{V}/H-2^{III}, C-2^{III}/H-1^{V}, $CH_2CH_2N_3$/H-1^{I}, C-1^{I}/$CH_2CH_2N_3$.

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Supplementary data

Supplementary data (NMR spectra for new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.carres.2012.05.021.

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