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Arabinofuranose 1,2,5-orthobenzoate as a single precursor of linear α(1 → 5)-linked oligoarabinofuranosides

Maria V. Panova [a, b], Nikita M. Podvalnyy [a], Eugene L. Okun [a], Polina I. Abronina [a], Alexander O. Chizhov [a], Leonid O. Kononov [a, *]

[a] N. D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences, Leninsky Prosp., 47, 119991 Moscow, Russian Federation
[b] The Higher Chemical College of the Russian Academy of Sciences, Miusskaya Pl. 9, 125047 Moscow, Russian Federation

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ABSTRACT

Selectively protected mono-, di- and trisaccharide thioglycoside building blocks with unprotected primary hydroxy group at the non-reducing end, available in only one step from 3-*O*-benzoyl β-D-arabinofuranose 1,2,5-orthobenzoate, were used in the synthesis of linear α(1 → 5)-linked oligoarabinofuranosides up to octasaccharide. The obtained oligosaccharides contain 4-(2-chloroethoxy) phenyl (CEP) or 4-(2-azidoethoxy)phenyl (AEP) pre-spacer aglycons that allow preparation of neoglycoconjugates.

1. Introduction

Synthesis of large oligoarabinofuranosides related to arabinan domain of polysaccharides of mycobacterial cell wall may allow access to new agents for diagnosis of mycobacterioses and components of synthetic anti-mycobacterial vaccines. Developing methods, which simplify synthesis of such compounds, is still in demand. Every research group, which contributed to this field (for leading references see Refs. [1–11]), suggested its own strategy for assembling oligosaccharides. Synthesis of large oligosaccharides always requires efficient preparation of building blocks. Chemistry of arabinofuranose orthoesters allows access to a wide range of selectively protected *O*- and *S*-arabinofuranosides [12–16]. A number of important syntheses of mycobacterial arabinans [1,16–22] were performed using bi- [1,10,16,17,20–22] and tricyclic [18,19] arabinofuranose orthoesters as precursors of building blocks or utilizing orthoester derivatives directly as glycosyl donors and glycosyl acceptors.

We have recently disclosed [14] that a nucleophilic opening of 3-*O*-acyl β-D-arabinofuranose 1,2,5-orthobenzoates with thiols leads in only one step to selectively protected mono- and α(1 → 5)-linked disaccharide thioglycosides with an unprotected primary hydroxy group at the non-reducing end as the main products (Scheme 1). Herein, we suggest an approach for the synthesis of α(1 → 5)-linked oligoarabinofuranosides, which relies on the use of these thioglycosides as the building blocks.

2. Results and discussion

2.1. Synthetic targets

Our synthetic targets were selectively protected linear α(1 → 5)-linked oligoarabinofuranosides of various lengths (2–8 residues, Schemes 2–4) with a pre-spacer aglycon that is required for subsequent preparation of neoglycoconjugates [23]. For this reason, all oligosaccharides were prepared as glycosides with 4-(2-chloroethoxy)phenyl (CEP) aglycon [24–29], which can be further modified (as with ω-chloroalkyl aglycons [23,30–32]) to form a functionalized spacer with azido or amino group ready for conjugation with an appropriate support or carrier. This possibility was implemented only for the longest oligosaccharide prepared here, which was transformed to 4-(2-azidoethoxy)phenyl (AEP)

* Corresponding author.
E-mail addresses: leonid.kononov@gmail.com, kononov@ioc.ac.ru (L.O. Kononov).

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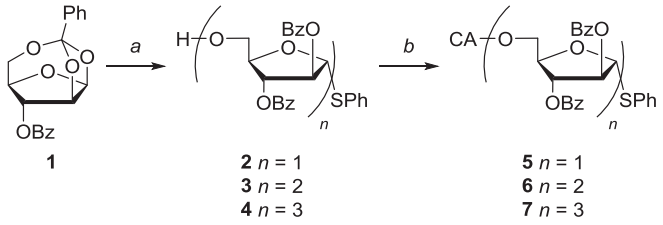
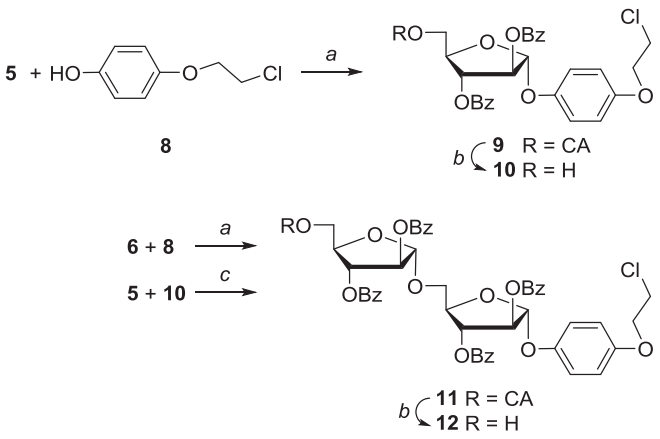
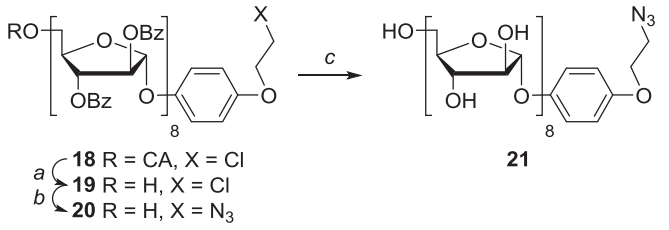


Scheme 1. Synthesis of glycosyl donors **5**–**7**. *Reagents and conditions*: *a*. 1) PhSH, $SnCl_4$, CH_2Cl_2, −25 °C; 2) silica gel column chromatography (64% of **2**, 21% of **3**, and 5% of **4**). *b*. $(ClCH_2CO)_2O$, 2,4,6-collidine, CH_2Cl_2 (95% of **5**, 94% of **6**, 92% of **7**). CA = $ClCH_2CO$.



Scheme 2. Synthesis of glycosyl acceptors **10** and **12**. *Reagents and conditions*: *a*. NIS, AgOTf, CH_2Cl_2, MS 4 Å, 0 °C (73% of **9**, 84% of **11**). *b*. Py, H_2O, 70 °C (95% of **10**, 90% of **12**). *c*. NIS, Et_3SiOTf, CH_2Cl_2, MS 4 Å, −30 °C (84%). MS – molecular sieves.

glycoside [26,28,29] and then deprotected. In this communication, we report the synthesis of CEP and AEP glycosides of the *well-defined* α(1 → 5)-linked oligoarabinofuranosides (DP_n = 2–8). The synthesis of *mixtures* of the related homologous oligoarabinofuranosides (DP_n ~ 14–16) with CEP and AEP aglycons (along with the preparation of a BSA conjugate) has been reported by us earlier [25,29].



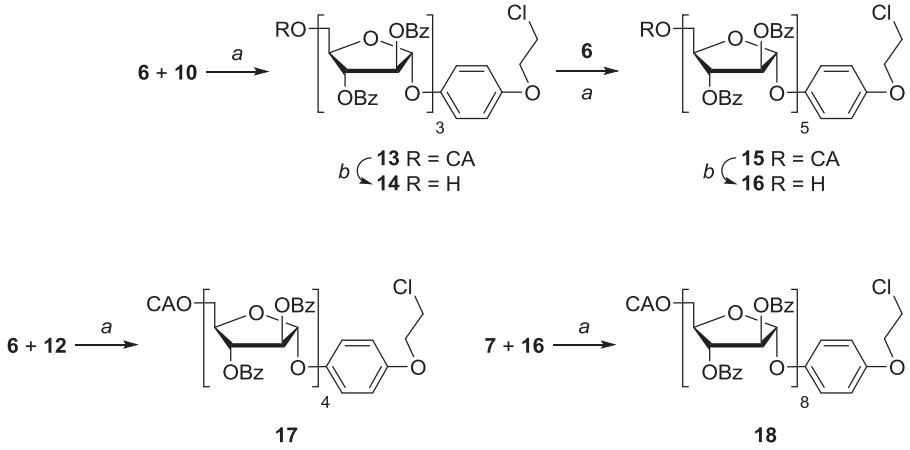
Scheme 4. Modification of aglycon and deprotection of octasaccharide. *Reagents and conditions*: *a*. Py, H_2O, 70 °C (79%). *b*. NaN_3, 18-crown-6, DMF, 70 °C (82%). *c*. 1) NaOMe, MeOH, DMSO; 2) NaOH, H_2O, DMSO (43%).

Our synthetic plan relied on the use of *O*-chloroacetyl at O-5 and *O*-benzoyl groups at all other positions of arabinofuranose residues as temporary and permanent protecting groups, respectively. For this reason, benzoyl group was used for protection of hydroxyl group at C-3 of the starting arabinofuranose 1,2,5-orthobenzoate **1** [14].

Since azido group can be introduced into CEP aglycon at any stage of the synthesis, any mono- and oligosaccharide building block could be prepared as the AEP glycoside if required. Although AEP aglycon is fully compatible with the selected synthetic strategy we prefer to keep the CEP aglycon as long as possible and introduce azido group to the aglycon (when necessary) only at the later stages of the synthesis. This approach leaves the room for further use of oligosaccharide building blocks synthesized here in a block synthesis of larger oligosaccharides, which may also contain benzyl protecting groups, since CEP aglycon was shown [28] to be compatible with cleavage of benzyl ethers by hydrogenolysis which would reduce [33] azido group present in AEP aglycon.

2.2. Nucleophilic opening of arabinose 1,2,5-orthobenzoate with thiophenol

At the first stage, we performed nucleophilic opening of 3-*O*-benzoyl D-arabinofuranose 1,2,5-orthobenzoate (**1**), prepared by benzoylation of the readily accessible unprotected D-arabinofuranose 1,2,5-orthobenzoate [34,35], with PhSH on a scale larger than reported [14] earlier (Scheme 1). Under the reaction conditions [14], a competition between S-nucleophile (PhSH) and *O*-



Scheme 3. Synthesis of protected linear homologous arabinofuranosides **13**–**18**. *Reagents and conditions*: *a*. NIS, Et_3SiOTf, CH_2Cl_2, MS 4 Å, −30 → −10 °C (90% of **13**, 83% of **15**, 87% of **17**, 84% of **18**). *b*. Py, H_2O, 70 °C (90% of **14**, 90% of **16**). MS – molecular sieves.