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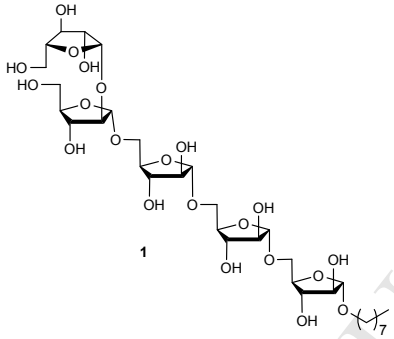
Department of Chemistry of Medicinal Natural Products, Sichuan Engineering Laboratory for Plant-Sourced Drug and Research Center for Drug Industrial Technology, West China School of Pharmacy, Sichuan University, Chengdu 610041, China



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Efficient Synthesis of a linear octyl pentaarabinofuranoside, a substrate for mycobacterial EmbA/EmbB proteins

Yue Chu and Jin-Song Yang*

Department of Chemistry of Medicinal Natural Products, Sichuan Engineering Laboratory for Plant-Sourced Drug and Research Center for Drug Industrial Technology, West China School of Pharmacy, Sichuan University, Chengdu 610041, China

Corresponding author. Tel. & Fax: +86 28 85503723. *E-mail address*: yjs@scu.edu.cn (J.-S. Yang).

Keywords: Synthesis; Glycosylation; Arabinofuranoside; Mycobacterial

Abstract: The efficient synthesis of a linear pentasaccharide with the structure **1**, β-D-Ara*f*-(1→2)-α-D-Ara*f*-(1→5)-α-D-Ara*f*-(1→5)-α-D-Ara*f*-(1→5)-α-D-Ara*f*-(1→5), as its octyl glycoside has been achieved through a convergent [3 + 2] coupling strategy. The difficult-to-obtain 1,2-*cis*-β-arabinofuranosidic bond at the non-reducing end of the target molecule was stereoselectively constructed by the use of a 2-quinolinecarbonyl-directed 1,2-*cis* glycosylation method.

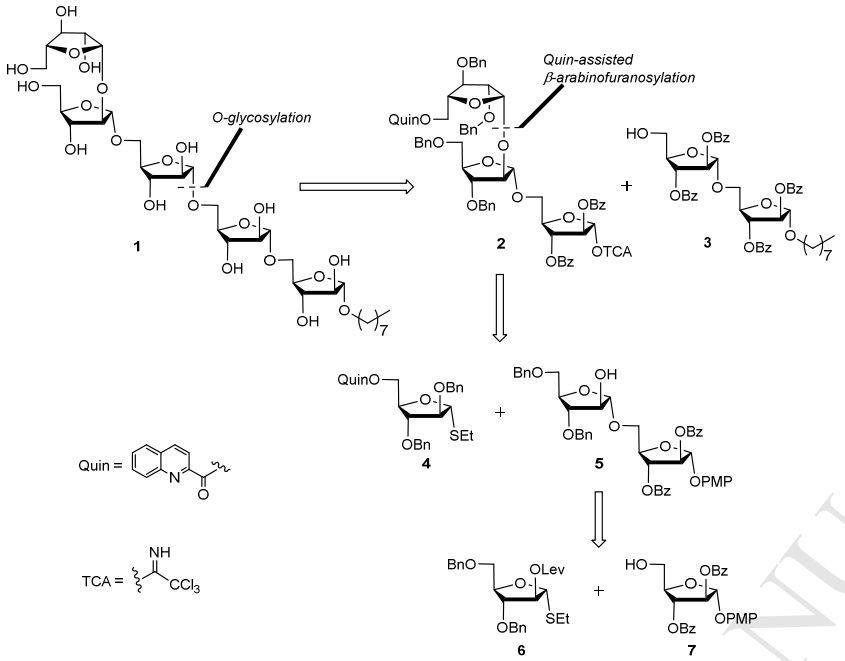
1. Introduction

The cell wall of mycobacteria, including the human pathogens *Mycobacterium tuberculosis* and *Mycobacterium leprae* comprises two major components, an arabinogalactan (AG) and a lipoarabinomannan (LAM) [1]. These biopolymers are known to be closely associated with the pathogenicity and survival of the mycobacteria pathogens. Therefore, a series of enzymes, such as arabinofuranosyltransferases (Ara*f*Ts), EmbA, and EmbB, involved in the biosynthesis of such carbohydrates are promising therapeutic targets of new drugs for treatment of mycobacterial diseases [2]. In the investigation on the biological functions of EmbA/EmbB proteins, Chatterjee and co-workers have demonstrated an octyl pentaarabinofuranoside **1** (Scheme 1), possessing a linear β-D-Ara*f*-(1→2)-α-D-Ara*f*-(1→5)-α-D-Ara*f*-(1→5)-α-D-Ara*f*-(1→5)-α-D-Ara*f*-(1→5) motif, is a good Ara*f* acceptor substrate for the EmbA/EmbB enzymes [3]. These results suggest that **1** might be potentially employed as a probe molecule to study the biosynthetic pathway of mycobacteria AG and LAM or as a lead compound to develop new enzyme inhibitors. In order to further study the biological properties of this compound, we need to acquire a large amount of it. However, **1** was previously synthesized by Chatterjee et al. via a stepwise route. Here, we describe our synthesis of **1** through a more efficient convergent means. In particular, the challenging β-arabinofuranosyl linkage at the non-reducing end of **1** was assembled stereoselectively using a 2-quinolinecarbonyl (Quin)-assisted 1,2-*cis* furanosylation method which is developed by our laboratory [4].

2. Results and Discussion

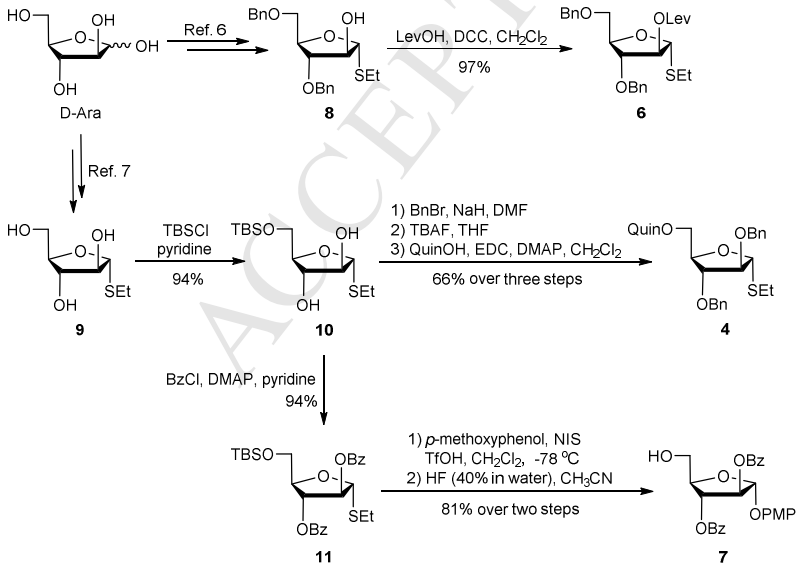
As retrosynthetically displayed in Scheme 1, we thought that the target homopentamer **1** could be obtained in a highly convergent fashion via a [3+2] glycosidic connection between the trisaccharide trichloroacetimidate donor **2** and the known octyl disaccharide glycoside acceptor **3** [5]. The assembly of **2** would in turn involve a Quin-assisted β-arabinofuranosylation reaction between the monoarabinosyl thioglycoside donor **4** [4a] and diarabinofuranosyl acceptor **5**. Besides, alcohol **5** could be easily derived from glycosylation of thioglycoside compound **6** with alcohol **7**. The ester-type levulinoyl (Lev) group was chosen as a temporary 2-hydroxyl

protecting group of the donor **6** for it not only can act as a neighboring participating group to ensure the 1,2-*trans* stereochemistry of the glycosylation with **7** but also can facilitate the selective C-2' deprotection for further installment of the β-(1→2)-linked Ara*f* unit.



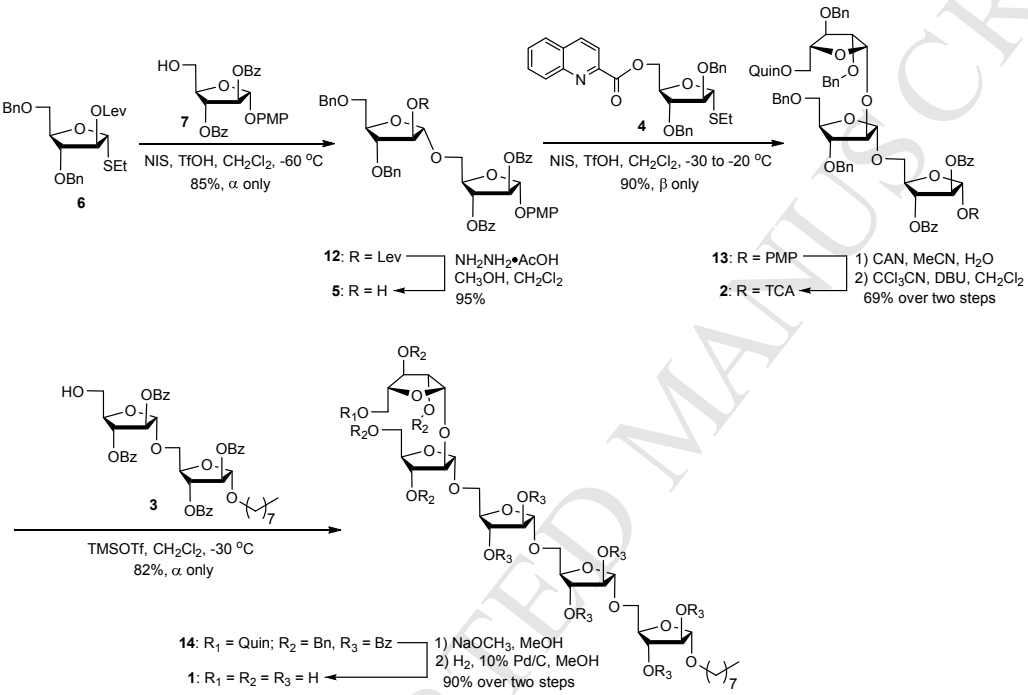
Scheme 1. Structure and retrosynthetic analysis of pentasaccharide glycoside **1**.

The disaccharide glycoside **3** was prepared according to the literature procedures [5]. The synthesis of monosaccharide building blocks **4**, **6**, as well as **7** was carried out as showed in Scheme 2. The preparation of D-arabinofuranose derivative **6** started with the known ethyl 3,5-di-*O*-benzyl-1-thio-α-D-arabinofuranoside (**8**), which was easily synthesized from the commercial D-arabinose according to the literature procedure [6]. Protection of the C-2 hydroxyl group in **8** as a levulinate afforded the saccharide **6** in 97% yield.



Scheme 2. Synthesis of monosaccharide building blocks **4**, **6**, and **7**.

Access to **4** and **7** required first the synthesis of diol **10**, which could be readily prepared by regioselective silylation of the 5-OH group of the known ethyl 1-thio-α-D-arabinofuranoside (**9**) [7] with *tert*-butyldimethylsilyl chloride (TBSCl) in pyridine (94% yield). Conversion of the resulting **10** to the thioglycoside donor **4** involved (i) protection of the remaining 2,3-di-OHs with benzyl bromide (BnBr) in DMF, (ii) desilylation of 5-*O*-TBS with tetrabutylammonium fluoride (TBAF) in THF, and (iii) introduction of a Quin functionality on C-5 position with 2-quinoline carboxylic acid (QuinOH) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) in dichloromethane (CH_2Cl_2), furnishing the desired 5-*O*-Quin substituted thioglycoside **4** in 66% yield for three steps. On the other hand, diol **10** was converted to compound **11** by treatment with benzoyl chloride (BzCl) in pyridine in 94% yield. Then, **11** was in turn condensed with *p*-methoxyphenol under the promotion of *N*-iodosuccinimide (NIS) and catalytic trifluoromethanesulfonic acid (TfOH) in CH_2Cl_2 at -78 °C and followed by simple unmasking of the 5-OH group with fluoride ion, giving **7** in 81% yield for two steps (Scheme 2).



Scheme 3. Completion of the synthesis of **1**.

With the required building blocks in hand, we began to synthesize the target molecule **1**. As illustrated in Scheme 3, the monosaccharide 5-OH acceptor **7** (1.2 equiv) was glycosylated with D-Ara*f* thioglycoside **6** in the presence of NIS/TfOH (cat.) in CH_2Cl_2 at -60 °C for 0.5 h, leading to the formation of the α-D-linked disaccharide **12** in a good 85% yield. After cleavage of the C2'-Lev function of **12** with hydrazine acetate ($N_2H_4 \cdot AcOH$) in MeOH/CH_2Cl_2 (95% yield), the obtained disaccharide alcohol **5** was coupled efficiently and β-stereoselectively with donor **4** (1.2 equiv) under the similar conditions as above to cleanly furnish the corresponding trisaccharide glycoside **13** in 90% yield. No anomeric isomer was observed in the glycosylation process. The β-configuration of the newly formed arabinofuranosidic linkage was straightforwardly determined by the doublet for anomeric signal of the D-Ara*f* residue ($\delta_{H1''}$ = 5.13 ppm, d, $J_{H1''/H2''}$ = 4.2 Hz) [8]. In this glycosylation, the hydrogen-bond tethering formed between the sp^2-hybridized nitrogen of the 5-*O*-Quin donor **4** and the 3'-OH of the disaccharide acceptor **5** could guide the attack of **5** to the anomeric center of **4** from the β-face (Scheme 3), thus forming the expected β-product **13**. Then, oxidative removal of the C1 *p*-methoxyphenyl (PMP) group of **13** with ceric ammonium nitrate (CAN) in aqueous acetonitrile (MeCN) at room temperature

afforded a hemiacetal intermediate (Scheme 3). Subsequent activation of the anomeric OH group by treatment with trichloroacetonitrile (CCl_3CN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) [9] conveniently provided the trisaccharide trichloroacetimidate **2** as a single α-diastereomer (69% yield, two steps from **13**). At last, this imidate was subjected to the glycosylation with the known octyl diarabinofuranoside alcohol **3** using a standard trimethylsilyl trifluoromethanesulfonate (TMSOTf) activation protocol [9] and produced efficiently the protected pentasaccharide glycoside **14** in 82% yield without formation of other anomeric product.

The global deprotection of **14** was completed in the following order (Scheme 3): removal of the Quin and Bz functionalities via Zemplén deacylation with sodium methoxide (NaOMe) in MeOH and then deprotection of the Bn ethers by catalytic hydrogenolysis over 10% Pd/C in MeOH. Purification of the free pentasaccharide glycoside was performed using gel filtration chromatography on a Sephadex LH-20 column with MeOH as eluent to generate **1** as a colorless syrup in 90% yield over two steps. The ^{1}H NMR data of **1** are in full agreement with those previously reported by Chatterjee et al.,[3] thereby confirming the structure of the synthetic material. Further support for the structure of **1** comes from the high-resolution MS data, which provides an $(M + Na)^+$ signal at *m/z* 813.3366 (calcd 813.3363).

3. Conclusion

In conclusion, we have developed a convergent strategy for the synthesis of pentaarabinofuranose glycoside **1** which has been proved to be a useful substrate for the mycobacterial EmbA/EmbB proteins. The synthetically challenging 1,2-*cis*-β-D-arabinofuranoside structure was efficiently constructed through the use of 5-*O*-Quin carrying D-Ara*f* thioglycoside donor **4**. This approach to **1** is superior to the previous route which adopted a less practical stepwise strategy. Research is in progress to further study the biological properties of the synthetic octyl glycoside.

4. Experimental section

4.1 General methods

All non-aqueous reactions were performed under a nitrogen atmosphere and monitored by thin layer chromatography (TLC) using Silica Gel GF_{254} plates with detection by charring with 10% (v/v) H_2SO_4 in EtOH or by UV detection. Solvents used in the reactions were distilled from appropriate drying agents prior to use. Silica gel (200-300 mesh) was used for column chromatography. Optical rotations were measured at 25 ± 0.3 °C for solutions in a 1.0 dm cell. High resolution mass spectra (HRMS) were acquired in the ESI mode. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz or 600 MHz spectrometer in $CDCl_3$ or D_2O with TMS as internal reference. Chemical shifts are expressed in ppm downfield from the internal TMS absorption. Standard splitting patterns are abbreviated: s (singlet), d (doublet), t (triplet), m (multiplet). *J* values are given in Hz.

*4.2 Ethyl 2-O-Levulinoyl-3,5-di-O-benzyl-1-thio-α-D-arabinofuranoside (**6**)*

To a solution of **8** [6] (0.20 g, 0.54 mmol) in CH_2Cl_2 (5.4 mL) were added dicyclohexyl carbodiimide (0.45 g, 2.2 mmol), 4-dimethylaminopyridine (0.13 g, 1.08 mmol), and levulinic acid (0.23 mL, 2.2 mmol). The resulting mixture was stirred for 2 h at room temperature and then it was concentrated in vacuo. The obtained crude material was purified by silica gel column chromatography (8:1, petroleum ether-EtOAc) to afford **6** (0.25 g, 97%) as a colorless syrup. **6**: R_f = 0.23 (3:1, petroleum ether-EtOAc); $[\alpha]_D^{25}$ +135.5 (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.25 (m, 10H), 5.35 (s, 1H), 5.14 (t, *J* = 1.6 Hz, 1H), 4.72 (d, *J* = 12.0 Hz, 1H), 4.58-4.46 (m, 3H), 4.39 (dd, *J* = 8.8, 5.2 Hz, 1H), 3.94-3.90 (m, 1H), 3.68-3.55 (m, 2H), 2.77-2.59 (m, 4H), 2.54-2.48 (m, 2H), 2.17 (s, 3H), 1.29 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.28, 171.82, 138.03, 137.61, 128.39, 128.37, 128.03, 127.82, 127.77, 127.68, 87.75, 83.12, 82.56, 81.40, 73.42, 72.22, 68.89, 37.78,

29.84, 27.88, 25.19, 14.75; HR ESI-MS: *m/z* calcd for $C_{26}H_{32}O_6S$ $[M+Na]^+$: 495.1812, found: 495.1806.

*4.3 Ethyl 5-O-tert-Butyldimethylsilyl-1-thio-α-D-arabinofuranoside (**10**)*

To a solution of **9** [7] (8.30 g, 42.78 mmol) in dry pyridine (107.0 mL) was added *tert*-butyldimethylsilyl chloride (9.69 g, 64.17 mmol). The resulting mixture was stirred for 2 h at room temperature and then it was quenched by addition of methanol. The mixture was concentrated in vacuo. The obtained crude material was purified by silica gel column chromatography (8:1, petroleum ether-EtOAc) to afford **10** as a colorless syrup (12.39 g, 94%). **10**: R_f = 0.49 (3:1, petroleum ether-EtOAc); $[\alpha]_D^{25}$ +144.8 (*c* 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.21 (s, 1H), 4.20 (d, *J* = 10.4 Hz, 1H), 4.08 (dd, *J* = 4.4, 2.0 Hz, 1H), 3.97 (d, *J* = 9.2 Hz, 1H), 3.90 (d, *J* = 10.4 Hz, 1H), 3.73 (d, *J* = 2.4 Hz, 2H), 2.99 (d, *J* = 10.0 Hz, 1H), 2.68-2.46 (m, 2H), 1.19 (t, *J* = 7.6 Hz, 3H), 0.79 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 89.48, 86.80, 80.97, 79.02, 63.46, 25.86, 24.72, 18.43, 14.76, -5.52, -5.61; HR ESI-MS: *m/z* calcd for $C_{13}H_{28}O_4SSi$ $[M+Na]^+$: 331.1370, found: 331.1367.

*4.4 Ethyl 2,3-Di-O-benzyl-5-O-(2-quinolinecarbonyl)-1-thio-α-D-arabinofuranoside (**4**)*

To a solution of **10** (2.8 g, 9.1 mmol) in dry DMF (91 mL) were added NaH (1.5 g, 36.4 mmol, 60% in mineral oil) and benzyl bromide (4.3 mL, 36.4 mmol). The resulting mixture was stirred for 0.5 h at room temperature and then it was quenched by addition of saturated aqueous NH_4Cl. The resulting mixture was diluted with EtOAc. The organic layer was separated, washed with water and brine, dried with anhydrous Na_2SO_4, filtered. The filtrate was concentrated in vacuo. The obtained crude material was purified by silica gel column chromatography (10:1, petroleum ether-EtOAc) to afford a colorless syrup (3.9 g, 8.0 mmol). To a solution of the obtained residue in THF was added tetrabutylammonium fluoride (8.0 mL, 1.0 M in THF, 8.0 mmol). The resulting mixture was stirred for 2 h at room temperature and then it was concentrated in vacuo. The obtained crude material was purified by silica gel column chromatography (5:1, petroleum ether-EtOAc) to afford a colorless syrup (2.5 g, 6.7 mmol). To a solution of the obtained residue in dry CH_2Cl_2 (67 mL) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (4.7 g, 26.8 mmol), 4-dimethylaminopyridine (1.6 g, 13.4 mmol), and 2-quinoline carboxylic acid (4.6 g, 26.8 mmol). The resulting mixture was stirred for 3 h at room temperature. Then, it was diluted with CH_2Cl_2. The organic layer was separated, washed with water and brine, dried with anhydrous Na_2SO_4, filtered. The filtrate was concentrated in vacuo. The obtained crude material was purified by silica gel column chromatography (20:1, petroleum ether-EtOAc) to afford compound **4** as a colorless syrup (3.1 g, 66% for three steps). The spectroscopic data of **4** matched those reported in the literature [4a].

*4.5 Ethyl 2,3-Di-O-benzoyl-5-O-tert-butyldimethylsilyl-1-thio-α-D-arabinofuranoside (**11**)*

To a solution of **10** (2.5 g, 8.1 mmol) in dry pyridine (10.2 mL) were added benzoyl chloride (3.7 mL, 32.4 mmol) and 4-dimethylaminopyridine (1.9 g, 16.2 mmol). The resulting mixture was stirred for 30 min at room temperature. Then, the reaction was quenched by addition of methanol and concentrated in vacuo. The obtained crude material was purified by silica gel column chromatography (20:1, petroleum ether-EtOAc) to afford **11** as a colorless syrup (3.94 g, 94%). **11**: R_f = 0.46 (7:1, petroleum ether-EtOAc); $[\alpha]_D^{25}$ +29.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03-7.93 (m, 4H), 7.51-7.45 (m, 2H), 7.39-7.32 (m, 4H), 5.49-5.45 (m, 2H), 5.41 (t, *J* = 2.0 Hz, 1H), 4.36 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.92 (d, *J* = 4.4 Hz, 2H), 2.76-2.54 (m, 2H), 1.25 (t, *J* = 7.2 Hz, 3H), 0.80 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.63, 165.52, 133.47, 133.41, 129.96, 129.37, 129.25, 128.48, 128.44, 87.92, 83.01, 82.95, 77.78, 62.88, 25.90, 25.26, 18.45, 14.97, -5.28, -5.33; HR ESI-MS: *m/z* calcd for $C_{27}H_{36}O_6SSi$ $[M+Na]^+$: 539.1894, found: 539.1907.

*4.6 p-Methoxyphenyl 2,3-Di-O-benzoyl-α-D-arabinofuranoside (**7**)*

A mixture of *p*-methoxyphenol (208 mg, 1.7 mmol), glycosyl donor **11** (216 mg, 0.4 mmol), and freshly activated 4 Å molecular sieves (1.3 g) in CH_2Cl_2 (8.0 mL) was stirred under nitrogen for 10 min at room temperature. The mixture was cooled to -78 °C and then NIS (135 mg, 0.6 mmol) and TfOH (3.5 μL, 40 μmol) were added. The resulting mixture was allowed to stir for 30 min at the same temperature. Then, the resulting mixture was quenched by Et_3N, diluted with CH_2Cl_2, filtered. The filtrate was concentrated in vacuo. The obtained crude material was purified by silica gel column chromatography (30:1, petroleum ether-EtOAc) to afford a colorless syrup (164 mg, 0.36 mmol). To a solution of obtained residue in CH_3CN (4.0 mL) was added HF (40% in water) (36 μL, 0.8 mmol). The resulting mixture was stirred for 1 h at room temperature and then it was quenched with saturated aqueous $NaHCO_3$. Then, the mixture was diluted with CH_2Cl_2. The organic layer was separated, washed with water and brine, dried with anhydrous Na_2SO_4, filtered. The filtrate was concentrated in vacuo. The obtained crude material was purified by silica gel column chromatography (4:1, petroleum ether-EtOAc) to afford **7** (113 mg, 81% for two steps) as a colorless syrup. **7**: R_f = 0.23 (3:1, petroleum ether-EtOAc); $[\alpha]_D^{25}$ +22.8 (*c* 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14-8.05 (m, 4H), 7.64-7.57 (m, 2H), 7.50-7.45 (m, 4H), 7.05 (d, *J* = 9.2 Hz, 2H), 6.85 (d, *J* = 9.2 Hz, 2H), 5.82 (s, 1H), 5.79 (d, *J* = 1.2 Hz, 1H), 5.56 (m, 1H), 4.49 (dd, *J* = 8.0, 4.0 Hz, 1H), 4.06-3.97 (m, 2H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.22, 165.34, 155.27, 149.98, 133.73, 133.69, 129.99, 129.93, 129.11, 128.94, 128.62, 128.59, 118.37, 114.67, 104.85, 84.42, 81.92, 77.61, 62.19, 55.69; HR ESI-MS: *m/z* calcd for $C_{26}H_{24}O_8$ $[M+Na]^+$: 487.1363, found: 487.1364.

*4.7 p-Methoxyphenyl 2-O-Levulinoyl-3,5-di-O-benzyl-α-D-arabinofuranosyl-(1→5)-2,3-di-O-benzoyl-α-D-arabinofuranoside (**12**)*

A mixture of a glycosyl donor **6** (70 mg, 144 μmol), glycosyl acceptor **7** (61 mg, 173 μmol), and freshly activated 4 Å molecular sieves (435 mg) in CH_2Cl_2 (2.9 mL) was stirred under nitrogen for 10 min. The mixture was cooled to -60 °C and then NIS (45 mg, 0.2 mmol) and TfOH (1.3 μL, 14.4 μmol) were added. The resulting mixture was allowed to stir for 30 min at the same temperature. Then, the resulting mixture was quenched by Et_3N, diluted with CH_2Cl_2, filtered. The filtrate was concentrated in vacuo. The obtained crude material was purified by silica gel column chromatography (5:1, petroleum ether-EtOAc) to afford the **12** (94.9 mg, 85%) as a colorless syrup. **12**: R_f = 0.40 (2:1, petroleum ether-EtOAc); $[\alpha]_D^{25}$ +34.7 (*c* 1.2, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.14-8.05 (m, 4H), 7.62-7.53 (m, 2H), 7.48-7.42 (m, 4H), 7.32-7.28 (m, 2H), 7.28-7.24 (m, 3H), 7.22-7.18 (m, 3H), 7.18-7.14 (m, 2H), 7.05 (d, *J* = 9.0 Hz, 2H), 6.83 (d, *J* = 9.0 Hz, 2H), 5.79 (s, 1H), 5.71 (s, 1H), 5.67 (d, *J* = 4.2 Hz, 1H), 5.19 (d, *J* = 13.8 Hz, 2H), 4.59 (d, *J* = 3.6 Hz, 1H), 4.53 (d, *J* = 12.0 Hz, 2H), 4.47 (d, *J* = 12.0 Hz, 1H), 4.38 (d, *J* = 12.6 Hz, 2H), 4.17 (dd, *J* = 11.4, 4.2 Hz, 1H), 3.87 (dd, *J* = 11.4, 3.0 Hz, 1H), 3.82 (d, *J* = 5.4 Hz, 1H), 3.76 (s, 3H), 3.59 (dd, *J* = 10.8, 3.0 Hz, 1H), 3.52 (dd, *J* = 10.8, 5.4 Hz, 1H), 2.71-2.65 (m, 2H), 2.49 (t, *J* = 6.6 Hz, 2H), 2.14 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 206.22, 171.53, 165.67, 165.45, 155.09, 150.16, 138.09, 137.71, 133.50, 133.41, 130.02, 129.97, 129.43, 129.11, 128.55, 128.50, 128.33, 128.22, 127.86, 127.76, 127.61, 127.58, 118.28, 114.60, 105.92, 104.86, 82.99, 82.74, 82.18, 82.01, 81.67, 73.31, 71.85, 69.23, 65.64, 55.68, 37.82, 29.81, 27.91; HR ESI-MS: *m/z* calcd for $C_{50}H_{50}O_{14}$ $[M+Na]^+$: 897.3093, found: 897.3118.

*4.8 p-Methoxyphenyl 3,5-Di-O-benzyl-α-D-arabinofuranosyl-(1→5)-2,3-di-O-benzoyl-α-D-arabinofuranoside (**5**)*

To a solution of **12** (80 mg, 0.1 mmol) in dry CH_2Cl_2 (1.0 mL) were added hydrazine acetate (20 mg, 0.2 mmol) and methanol (0.4 mL). The resulting mixture was stirred for 1.5 h at room temperature and then it was

quenched by saturated aqueous $NaHCO_3$. Then, the mixture was diluted with CH_2Cl_2. The organic layer was separated, washed with water and brine, dried with anhydrous Na_2SO_4, filtered. The filtrate was concentrated in vacuo. The obtained crude material was purified by silica gel column chromatography (2:1, petroleum ether-EtOAc) to afford **5** as a colorless syrup (65 mg, 95%). **5**: R_f = 0.42 (2:1, petroleum ether-EtOAc); $[\alpha]_D^{25}$ +82.5 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14-8.03 (m, 4H), 7.63-7.54 (m, 2H), 7.51-7.39 (m, 4H), 7.35-7.27 (m, 3H), 7.27-7.22 (m, 2H), 7.21-7.15 (m, 3H), 7.15-7.10 (m, 2H), 7.05 (d, *J* = 9.2 Hz, 2H), 6.83 (d, *J* = 9.2 Hz, 2H), 5.80 (s, 1H), 5.73 (d, *J* = 4.8 Hz, 1H), 5.67 (s, 1H), 5.15 (s, 1H), 4.62-4.55 (m, 2H), 4.49-4.43 (m, 2H), 4.39 (d, *J* = 2.8 Hz, 1H), 4.35 (d, *J* = 12.0 Hz, 1H), 4.21-4.13 (m, 2H), 3.86-3.81 (m, 2H), 3.76 (s, 3H), 3.65 (dd, *J* = 10.4, 2.0 Hz, 1H), 3.43 (dd, *J* = 10.4, 2.0 Hz, 1H), 3.35 (d, *J* = 10.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.66, 165.38, 155.08, 150.11, 137.65, 137.01, 133.47, 133.39, 129.99, 129.92, 129.49, 129.15, 128.56, 128.49, 128.43, 128.26, 128.04, 127.85, 127.74, 127.59, 118.20, 114.59, 108.75, 104.75, 84.60, 83.38, 82.87, 82.12, 78.19, 77.29, 73.72, 71.76, 69.66, 65.42, 55.66; HR ESI-MS: *m/z* calcd for $C_{45}H_{44}O_{12}$ $[M+Na]^+$: 799.2725, found: 799.2733.

*4.9 p-Methoxyphenyl 2,3-Di-O-benzyl-5-O-(2-quinolinecarbonyl)-β-D-arabinofuranosyl-(1→2)-3,5-di-O-benzyl-α-D-arabinofuranosyl-(1→5)-2,3-di-O-benzoyl-α-D-arabinofuranoside (**13**)*

A mixture of a glycosyl donor **4** [4a] (53 mg, 106 μmol), glycosyl acceptor **5** (58 mg, 88 μmol), and freshly activated 4 Å molecular sieves (2.6 g) in CH_2Cl_2 (17.6 mL) was stirred under nitrogen for 10 min. The mixture was cooled to -30 °C and then NIS (36 mg, 15.9 mmol) and TfOH (0.9 μL, 10.6 μmol) were added. The resulting mixture was warmed to -20 °C, and was allowed to stir for 30 min at this temperature. Then, the resulting mixture was quenched by Et_3N, diluted with CH_2Cl_2, filtered. The filtrate was concentrated in vacuo. The obtained crude material was purified by silica gel column chromatography (4:1, petroleum ether-EtOAc) to afford the **13** (88 mg, 90%) as a colorless syrup. **13**: R_f = 0.50 (2:1, petroleum ether-EtOAc); $[\alpha]_D^{25}$ +4.3 (*c* 0.1, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.4 Hz, 1H), 8.16-8.00 (m, 6H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.74 (t, *J* =7.8 Hz, 1H), 7.64 (t, *J* = 7.8 Hz, 1H), 7.58 (t, *J* = 7.2 Hz, 1H), 7.50-7.43 (m, 3H), 7.37 (t, *J* = 7.8 Hz, 2H), 7.33-7.29 (m, 4H), 7.28-7.24 (m, 8H), 7.24-7.21 (m, 3H), 7.13-7.09 (m, 5H), 7.03 (d, *J* = 9.0 Hz, 2H), 6.80 (d, *J* = 9.0 Hz, 2H), 5.77 (s, 1H), 5.68 (s, 1H), 5.66 (d, *J* = 4.8 Hz, 1H), 5.16-5.12 (m, 2H), 4.71 (d, *J* = 12.0 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.61-4.55 (m, 2H), 4.52-4.45 (m, 6H), 4.41 (d, *J* = 12.0 Hz, 1H), 4.37 (d, *J* = 2.4 Hz, 1H), 4.35-4.28 (m, 2H), 4.21 (t, *J* = 6.6 Hz, 1H), 4.16 (dd, *J* = 11.4, 4.2 Hz, 1H), 4.07-4.01 (m, 2H), 3.86 (dd, *J* = 11.4, 4.2 Hz, 1H), 3.74 (s, 3H), 3.59-3.51 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.58, 165.43, 164.74, 155.10, 150.09, 147.64, 147.49, 138.09, 137.84, 137.81, 137.48, 137.12, 133.49, 133.37, 130.79, 130.18, 129.91, 129.35, 129.23, 129.00, 128.58, 128.46, 128.45, 128.31, 128.26, 128.25, 128.09, 127.94, 127.90, 127.71, 127.67, 127.59, 127.47, 127.45, 127.36, 121.06, 118.27, 114.57, 106.16, 104.88, 100.95, 86.66, 83.97, 83.81, 82.83, 82.38, 82.24, 81.53, 78.62, 77.46, 73.17, 72.49, 72.47, 72.19, 69.83, 67.18, 66.01, 55.62; HR ESI-MS: *m/z* calcd for $C_{74}H_{69}NO_{17}$ $[M+Na]^+$: 1266.4458, found: 1266.4501.

*4.10 2,3-Di-O-benzyl-5-O-(2-quinolinecarbonyl)-β-D-arabinofuranosyl-(1→2)-3,5-di-O-benzyl-α-D-arabinofuranosyl-(1→5)-2,3-di-O-benzoyl-α-D-arabinofuranosyl trichloroacetimidate (**2**)*

To a solution of **13** (90 mg, 81 μmol) in MeCN-H_2O (4:1, v/v) (1.6 mL) was added ceric ammonium nitrate (89 mg, 162 μmol). The resulting mixture was stirred for 2 h at room temperature and then it was quenched by saturated aqueous $NaHCO_3$. Then, the mixture was diluted with CH_2Cl_2. The organic layer was separated, washed with water and brine, dried with anhydrous Na_2SO_4, filtered. The filtrate was concentrated in vacuo. The obtained crude material was purified by silica gel column chromatography (2:1, petroleum ether-EtOAc) to afford a colorless syrup (66 mg, 81%). To a solution of the obtained residue (66 mg, 65 μmol) in dry CH_2Cl_2

(0.3 mL) were added trichloroacetonitrile (0.03 mL, 0.3 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.3 μL, 2.0 μmol) at 0 °C. The resulting mixture was stirred for 30 min at the same temperature and then concentrated in vacuo. The obtained crude material was purified by silica gel column chromatography (2:1, petroleum ether-EtOAc) to afford trichloroacetamidate **2** (64 mg, 85%) as a colorless syrup. **2**: R_f = 0.52 (2:1, petroleum ether-EtOAc); $[\alpha]_D^{25}$ -8.6 (*c* 0.1, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.22 (d, *J* = 8.4 Hz, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 8.09 (d, *J* = 7.2 Hz, 2H), 8.05-8.00 (m, 3H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.75 (t, *J* = 7.8 Hz, 1H), 7.64 (t, *J* = 7.8 Hz, 1H), 7.58 (t, *J* = 7.2 Hz, 1H), 7.48 (t, *J* = 7.2 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.38 (t, *J* = 7.8 Hz, 2H), 7.35-7.32 (m, 3H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.28-7.22 (m, 11H), 7.11-7.08 (m, 5H), 6.58 (s, 1H), 5.71 (s, 1H), 5.67 (d, *J* = 3.6 Hz, 1H), 5.16-5.12 (m, 2H), 4.72 (d, *J* = 11.4 Hz, 1H), 4.69-4.63 (m, 2H), 4.61 (d, *J* = 11.4 Hz, 1H), 4.55-4.51 (m, 2H), 4.47 (t, *J* = 9.6 Hz, 4H), 4.37 (d, *J* = 11.4 Hz, 1H), 4.33 (t, *J* = 6.0 Hz, 2H), 4.31-4.29 (m, 1H), 4.23-4.18 (m, 2H), 4.14-4.09 (m, 1H), 4.01 (dd, *J* = 6.0, 3.0 Hz, 1H), 3.84 (dd, *J* =11.4, 4.2 Hz, 1H), 3.57-3.51 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.39, 165.08, 164.74, 160.47, 147.63, 147.48, 138.07, 137.80, 137.79, 137.49, 137.14, 133.64, 133.48, 130.78, 130.19, 129.99, 129.95, 129.23, 129.08, 128.74, 128.59, 128.53, 128.47, 128.40, 128.32, 128.26, 128.07, 127.98, 127.93, 127.72, 127.68, 127.56, 127.48, 127.45, 127.35, 121.06, 106.35, 103.06, 100.96, 86.54, 84.98, 83.91, 83.74, 82.88, 81.63, 80.73, 78.61, 73.16, 72.51, 72.10, 69.80, 67.14, 66.08, 45.76, 30.67; HR ESI-MS: *m/z* calcd for $C_{69}H_{63}Cl_3N_2O_{16}$ $[M+Na]^+$: 1303.3135, found: 1303.3137.

*4.11 Octyl 2,3-Di-O-benzyl-5-O-(2-quinolinecarbonyl)-β-D-arabinofuranosyl-(1→2)-3,5-di-O-benzyl-α-D-arabinofuranosyl-(1→5)-2,3-di-O-benzoyl-α-D-arabinofuranosyl-(1→5)-2,3-di-O-benzoyl-α-D-arabinofuranosyl-(1→5)-2,3-di-O-benzoyl-α-D-arabinofuranoside (**14**)*

A mixture of glycosyl donor **2** (47 mg, 41 μmol), glycosyl acceptor **3** [5] (47 mg, 49 μmol), and freshly activated 4 Å molecular sieves (120 mg) in CH_2Cl_2 (0.8 mL) was stirred under nitrogen for 15 min. The mixture was cooled to -30 °C and then TMSOTf (0.7 μL, 4.1 μmol) was added. The resulting mixture was stirred for 15 min at the same temperature and then it was quenched by Et_3N, diluted with CH_2Cl_2, filtered. The filtrate was concentrated in vacuo. The obtained crude material was purified by silica gel column chromatography (4:1:0.01, petroleum ether-EtOAc-triethylamine) to afford **14** (66 mg, 82%) as a light yellow syrup. **14**: R_f = 0.27 (3:1, petroleum ether-EtOAc); $[\alpha]_D^{25}$ +3.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.4 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 8.06-7.97 (m, 9H), 7.94-7.87 (m, 4H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.75 (t, *J* = 7.8 Hz, 1H), 7.63 (t, *J* = 7.2 Hz, 1H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.50 (t, *J* = 7.2 Hz, 1H), 7.48-7.45 (m, 2H), 7.45-7.37 (m, 7H), 7.36-7.32 (m, 5H), 7.32-7.28 (m, 3H), 7.28-7.20 (m, 14H), 7.11-7.07 (m, 5H), 5.65 (s, 1H), 5.62 (t, *J* = 5.4 Hz, 2H), 5.57 (d, *J* = 4.8 Hz, 1H), 5.55 (s, 1H), 5.50 (d, *J* = 0.6 Hz, 1H), 5.38 (d, *J* = 13.8 Hz, 2H), 5.21 (s, 1H), 5.15 (d, *J* = 3.6 Hz, 2H), 4.70 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.62-4.60 (m, 1H), 4.59-4.54 (m, 3H), 4.52-4.44 (m, 5H), 4.43-4.41 (m, 1H), 4.39 (d, *J* = 12.0 Hz, 1H), 4.35 (d, *J* = 2.4 Hz, 1H), 4.33-4.29 (m, 2H), 4.23-4.16 (m, 3H), 4.13 (dd, *J* = 11.4, 4.2 Hz, 1H), 4.07 (dd, *J* = 6.6, 4.2 Hz, 1H), 4.03 (dd, *J* = 11.4, 4.2 Hz, 1H), 3.92-3.88 (m, 2H), 3.83 (dd, *J* = 11.4, 3.6 Hz, 1H), 3.76-3.72 (m, 1H), 3.58-3.46 (m, 3H), 1.65-1.58 (m, 2H), 1.41-1.32 (m, 2H), 1.31-1.23 (m, 8H), 0.86 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.65, 165.62, 165.49, 165.41, 165.21, 165.12, 164.75, 147.65, 147.52, 138.13, 137.89, 137.84, 137.51, 137.15, 133.34, 133.13, 133.03, 130.81, 130.19, 129.87, 129.79, 129.33, 129.24, 129.19, 129.12, 129.10, 129.05, 128.59, 128.47, 128.45, 128.42, 128.40, 128.33, 128.26, 128.24, 128.22, 128.08, 127.98, 127.93, 127.73, 127.69, 127.58, 127.46, 127.33, 121.09, 106.37, 105.87, 105.78, 105.54, 101.02, 86.74, 83.92, 83.75, 82.90, 82.10, 81.97, 81.90, 81.83, 81.74, 81.50, 78.60, 77.49, 77.43, 77.28, 73.15, 72.49, 72.43, 72.12, 69.79, 67.39, 67.18, 66.04, 65.94, 65.85, 31.82, 29.54, 29.42, 29.27, 26.17, 22.65, 14.09. HR ESI-MS: *m/z* calcd for $C_{113}H_{111}NO_{28}$ $[M+Na]^+$: 1952.7185, found: 1952.7207.

*4.12 Octyl β-D-Arabinofuranosyl-(1→2)-α-D-arabinofuranosyl-(1→5)-α-D-arabinofuranosyl-(1→5)-α-D-arabinofuranosyl-(1→5)-α-D-arabinofuranoside (**1**)*

To a solution of **14** (60 mg, 31 μmol) in methanol (0.3 mL) was added NaOMe (2 mg, 43.4 μmol). The resulting mixture was stirred for 30 min at room temperature and then it was neutralized with Amberlite IR-120 H^+ resin, filtered. The filtrate was concentrated in vacuo. The obtained residue was purified by silica gel column chromatography (30:1, CH_2Cl_2-CH_3OH) to afford a colorless syrup. To a solution of the obtained residue in methanol (0.8 mL) was added 10% Pd/C (12 mg). The resulting mixture was stirred under an atmosphere of H_2 for 5 h. The catalyst was filtered off, washed with methanol. The filtrate was concentrated in vacuo. The obtained residue was purified by column chromatography on Sephadex LH-20 (MeOH) to afford **1** (22 mg, 90% for two steps) as a colorless syrup. **1**: R_f = 0.44 (3:1, petroleum ether-EtOAc); $[\alpha]_D^{25}$ +25.0 (*c* 0.2, H_2O); ^{1}H NMR (400 MHz, D_2O) δ 5.14 (s, 1H), 5.11 (d, *J* = 4.4 Hz, 1H), 5.05 (s, 2H), 4.98 (s, 1H), 4.24-3.97 (m, 14H), 3.93-3.64 (m, 12H), 3.60-3.53 (m, 1H), 1.66-1.53 (m, 2H), 1.34-1.19 (m, 10H), 0.94-0.78 (m, 3H); ^{13}C NMR (100MHz, D_2O) δ 107.48, 107.46, 107.19, 105.69, 100.55, 86.70, 82.80, 82.30, 82.24, 81.96, 81.64, 80.84, 80.81, 76.74, 76.65, 76.42, 76.19, 74.73, 74.07, 68.55, 66.85, 66.80, 66.72, 62.91, 60.53, 31.10, 28.60, 28.41, 28.38, 25.17, 22.02, 13.41; HR ESI-MS: *m/z* calcd for $C_{33}H_{58}O_{21}$ $[M+Na]^+$: 813.3363, found: 813.3366. The spectroscopic data of **1** matched those reported in the literature [3].

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The synthesis of pentaarabinose, a substrate for mycobacterial EmbA/B, was achieved

The target molecule was synthesized via a convergent [3 + 2] coupling strategy

The β-arabinofuranosidic bond was assembled by a Quin-assisted glycosylation method