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Synthesis of octyl arabinofuranosides as substrates for mycobacterial arabinosyltransferases

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Abstract

A panel of octyl oligosaccharides comprised of arabinofuranose rings have been synthesized via efficient and readily scaleable routes. The key glycosylation reactions involved the coupling of octyl glycoside acceptors with the appropriate thioglycosides using *N*-iodosuccinimide and silver triflate activation. These syntheses were undertaken to provide substrates suitable for use in assays of mycobacterial arabinosyltransferases. © 2003 Elsevier Science Ltd. All rights reserved.

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1. Introduction

The cell wall of mycobacteria, including the pathogens *Mycobacterium tuberculosis* and *Mycobacterium leprae*, is comprised in large part of two polysaccharides, lipoarabinomannan (LAM) and arabinogalactan (AG).[1] Although these polysaccharides fulfill different roles in the cell-wall complex, a feature shared by both is an arabinan component that contains approx 70 arabinofuranose residues. A key structural motif in this arabinan is the hexasaccharide **1**, which is found at the non-reducing ends of both polymers. Mycobacterial viability is critically dependent upon its ability to produce both polysaccharides, and ethambutol, a drug used to treat tuberculosis, acts by inhibiting at least one of the arabinosyltransferases (AraT's) that assemble the arabinan portions of AG and LAM.[2] The absence of arabinofuranose-containing oligo- or polysaccharides in humans (and all mammals) makes these enzymes particularly attractive drug targets.[3] This fact, combined with the demonstration of the mode of action of ethambutol, has prompted increasing interest in identifying other inhibitors of these AraT's both by our group[4] and others.[5]

In an earlier publication, we showed that fragments of hexasaccharide **1**, which were protected at the 'reducing' end as a methyl glycoside, were substrates for mycobacterial AraT's.[6] However, these methyl glycosides are relatively poor substrates when compared to analogs that are glycosides of longer-chain alcohols (e.g., octanol and decanol).[7] Moreover, the assay used for evaluating potential substrates and inhibitors of these enzymes involves a butanol extraction of the assay mixture, a step that is significantly facilitated though the use of oligosaccharide substrates with more lipophilic aglycones. Therefore, in the interest of efficiently screening a wide range of potential inhibitors of these enzymes, it was necessary to synthesize the octyl glycoside fragments of **1**, which could be used as substrates in these assays. In this paper, we describe the synthesis of these oligosaccharides (**2**–**7**, Fig. 1) via routes that are slightly modified compared to those used for the preparation of the corresponding methyl glycosides.[6]

2. Results and discussion

We endeavored to develop synthetic routes to **2**–**7** that involved a minimum number of protecting group classes and readily available monosaccharide building

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blocks. The monomers chosen for these syntheses were **8**–**13** (Fig. 2), which were prepared as previously reported.[8] We note that we prefer the use of thioglycoside **11** over the corresponding peracetylated derivative[6] as **11** is a readily crystalline material, which can be purified directly from the crude reaction mixture. This significantly facilitates not only the preparation of large amounts of **11** but also donors **12** and **13**, which can be prepared in a few steps from **11**.

The synthesis of the disaccharides **2** and **3**, as well as trisaccharide **4**, were carried out in two steps each by reacting the appropriate acceptor (**8**, **9**, or **10**) with thioglycoside **11** in the presence of *N*-iodosuccinimide and silver triflate (Scheme 1). The protected oligosaccharides **14**–**16** were obtained in 78–92% yields, and the stereochemistry of the nascent glycosidic bond was straightforwardly determined through the use of ^{1}H and ^{13}C NMR spectroscopy.[9] Deprotection of **14**–**16** was done under standard conditions using sodium methoxide giving **2**–**4** in excellent yield. This approach to **15** is

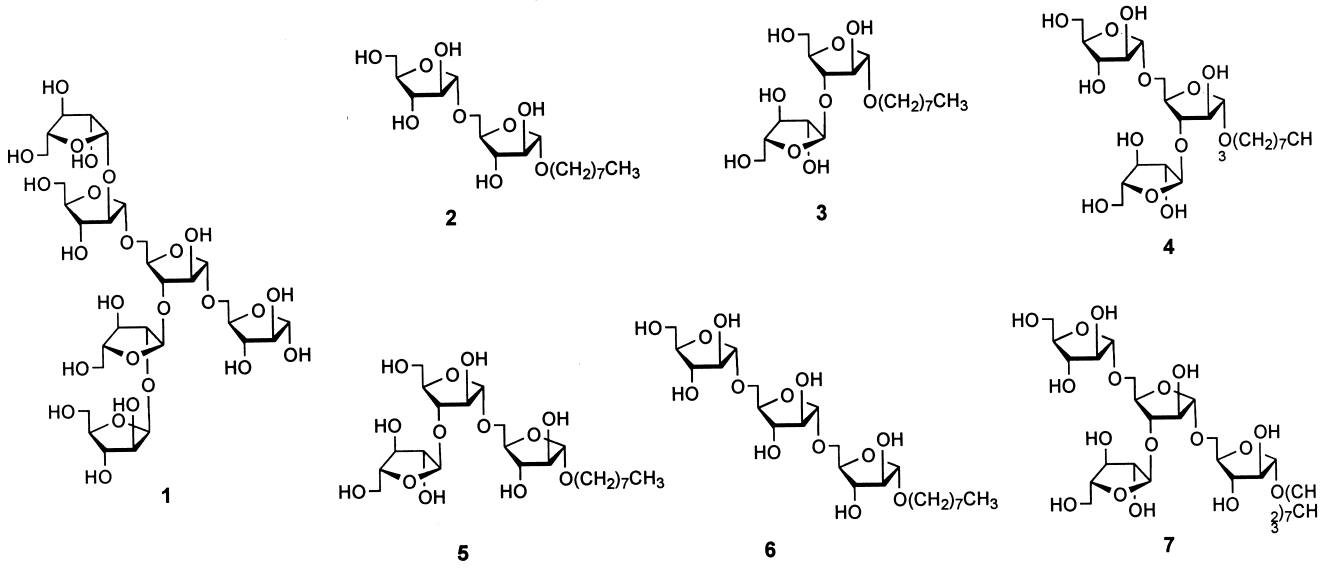


Fig. 1. Hexasaccharide motif common to both mycobacterial arabinogalactan and lipoarabinomannan (**1**); synthetic targets (**2**–**7**).

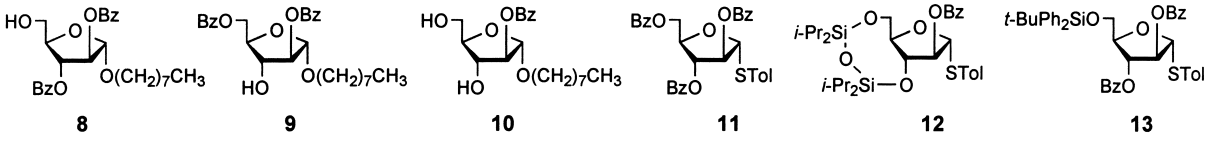
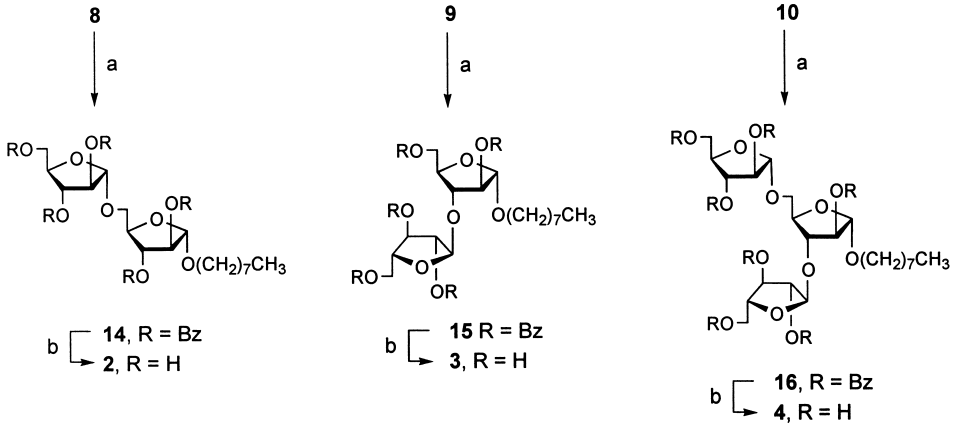
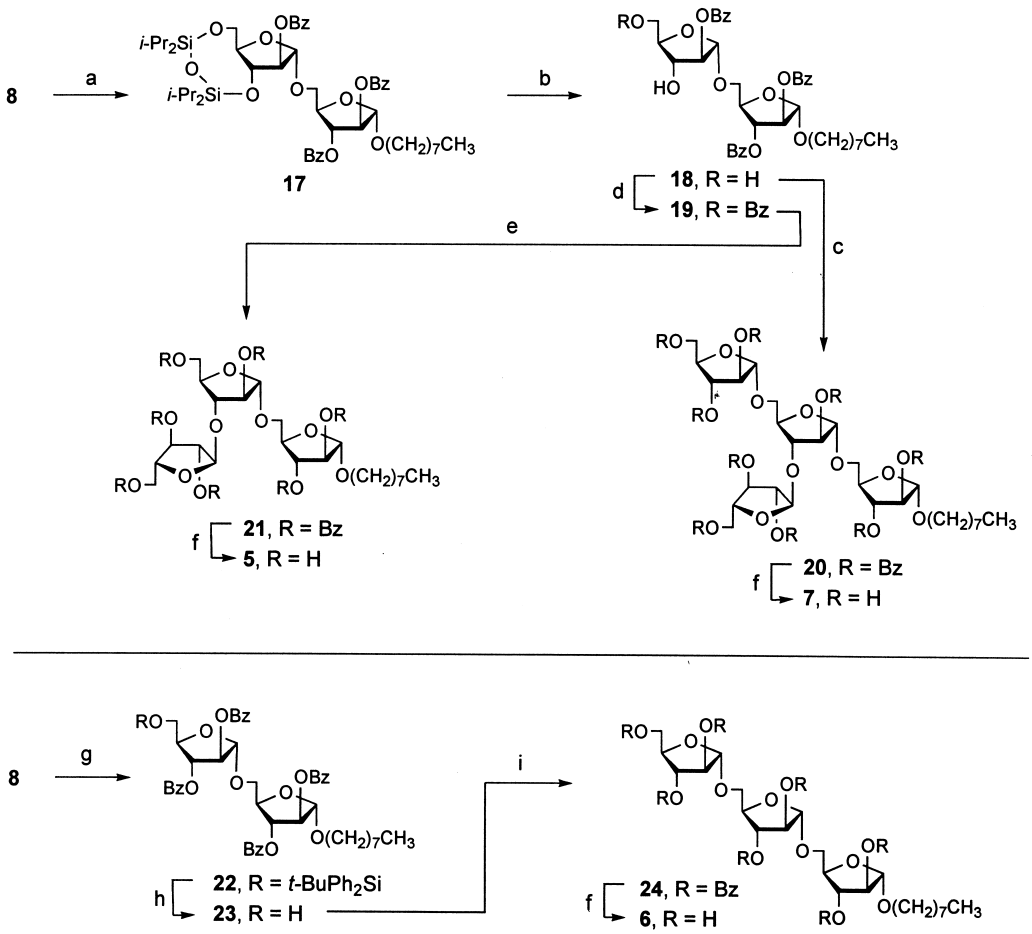


Fig. 2. Monosaccharide building blocks used for the synthesis of (**2**–**7**).



Scheme 1. (a) **11**, *N*-iodosuccinimide, $AgOSO_2CF_3$, CH_2Cl_2, 0 °C, 90 (for **8**), 92 (for **9**), 78% (for **10**). (b) $NaOCH_3$, CH_3OH, rt, 93 (for **14**), 85 (for **15**), 84% (for **16**).



Scheme 2. (a) **12**, *N*-iodosuccinimide, $AgOSO_2CF_3$, CH_2Cl_2, 0 °C, 82%. (b) *n*-Bu_4NF, THF, rt, 84%. (c) **11**, *N*-iodosuccinimide, $AgOSO_2CF_3$, CH_2Cl_2, 0 °C, 80%. (d) BzOH, Ph_3P, DEAD, THF, 0 °C→rt, 90%. (e) **11**, *N*-iodosuccinimide, $AgOSO_2CF_3$, CH_2Cl_2, 0 °C, 88%. (f) $NaOCH_3$, CH_3OH, rt, 77 (for **20**), 87 (for **21**), 88% (for **24**). (g) **13**, *N*-iodosuccinimide, $AgOSO_2CF_3$, CH_2Cl_2, 0 °C, 82%. (h) *n*-Bu_4NF, THF, rt, 88%. (i) **11**, *N*-iodosuccinimide, $AgOSO_2CF_3$, CH_2Cl_2, 0 °C, 87%.

superior to our previously reported route[6] to the corresponding methyl glycoside, which employed an acceptor with a silyl protecting group on O-5, thus necessitating a two-step deprotection protocol.

As illustrated in Scheme 2, the remaining targets (**5**–**7**) were synthesized with minimum difficulty, albeit less directly than **2**–**4**. Glycosylation of alcohol **8** with **12** afforded disaccharide **17** in 82% yield. The siloxane protecting group was cleaved to give diol **18** (in 84% yield), which was an intermediate for the preparation of both **5** and **7**. Reaction of **18** with an excess of **11** afforded tetrasaccharide **20** (80%), which was then deprotected to give **7** (77%). Alternatively, reaction of **18** with benzoic acid under Mitsunobu conditions afforded disaccharide **19** (90%), which was then glycosylated with **11** and deprotected providing **5** (77% over two steps). The final target, trisaccharide **6**, was also prepared from monosaccharide **8**. Coupling of **8** with **13** provided disaccharide **22** (82%), which was then deprotected yielding **23** in 88% yield. Glycosylation of this disaccharide alcohol with thioglycoside **11** afforded an 87% yield of trisaccharide **24**, which was subsequently debenzoylated to give **6** (88%).

In conclusion, we have synthesized multi-milligram quantities of oligosaccharides **2**–**7** via efficient routes that are easily scaleable for the preparation of gram-scale amounts of these glycans. The use of these oligosaccharides in investigations dedicated to identifying new inhibitors of mycobacterial arabinosyltransferases is currently in progress.[4c]

3. Experimental

3.1. General procedures

Solvents were distilled from the appropriate drying agents before use. Unless stated otherwise, all reactions were carried out at room temperature (rt), under a positive pressure of argon and were monitored by TLC on Silica Gel 60 F_{254} (0.25 mm, E. Merck). Spots were detected under UV light or by charring with 10%

H_2SO_4 in EtOH. Solvents were evaporated at reduced pressure and below 40 °C (bath). Column chromatography was performed on silica gel 60 (40–60 μm). Iatrobeads refers to a beaded silica gel 6RS-8060, which is manufactured by Iatron Laboratories (Tokyo). The ratio between silica gel and product ranged from 100 to 50:1 (w/w). Optical rotations were measured at 22 ± 2 °C. ^{1}H NMR chemical shifts, δ_H, were referenced to Me_4Si (δ_H 0.0, $CDCl_3$), CD_3OH (δ_H 4.78, CD_3OD), HOD (δ_H 4.78, D_2O). ^{13}C chemical shifts, δ_C, were referenced to internal $CDCl_3$ (δ_C 77.00, $CDCl_3$) internal CD_3OD (δ_C 49.00, CD_3OD), or external dioxane (δ_C 67.40, D_2O).

3.2. Octyl 5-*O*-(α-D-arabinofuranosyl)-α-D-arabinofuranoside (2)

Disaccharide **14** (130 mg, 0.14 mmol) was dissolved in 7:3 CH_3OH–CH_2Cl_2 (10 mL), and 1.0 M methanolic $NaOCH_3$ (2 mL) was added dropwise. After stirring for 6 h, the reaction mixture was neutralized with dry ice and concentrated. The crude residue was purified by chromatography (10:1 CH_2Cl_2–CH_3OH) to yield **2**[5f,7,8c] (53 mg, 93%) as an oil: R_f 0.48 (5:1 CH_2Cl_2–CH_3OH); $[\alpha]_D$ +120.4° (*c* 1.0, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD): δ_H 4.90 (d, 1 H, *J* 1.2 Hz), 4.80 (d, 1 H, *J* 1.6 Hz), 3.98–3.90 (m, 4 H), 3.85 (dd, 1 H, *J* 6.4, 3.8 Hz), 3.82–3.78 (m, 2 H), 3.70 (dd, 1 H, *J* 11.8, 3.3 Hz), 3.68–3.58 (m, 3 H), 3.37 (dt, 1 H, *J* 9.6, 6.6 Hz), 1.56–1.51 (m, 2 H), 1.34–1.26 (m, 10 H), 0.86 (t, 3 H, *J* 6.8 Hz); ^{13}C NMR (100 MHz, CD_3OD): δ_C 109.6, 109.5, 85.9, 83.6, 83.4, 83.1, 79.1, 78.8, 68.9, 68.0, 63.1, 33.0, 30.7, 30.5, 30.4, 27.2, 23.7, 14.4; ESIMS *m*/*z* Calcd for $[C_{18}H_{34}O_9]Na^+$: 417.2095. Found: 417.2086.

3.3. Octyl 3-*O*-(α-D-arabinofuranosyl)-α-D-arabinofuranoside (3)

Disaccharide **15** (91 mg, 0.099 mmol) was deacylated as described for the preparation of **2**. The product was purified by chromatography (10:1 CH_2Cl_2–CH_3OH) to yield **3** (33 mg, 85%) as an oil: R_f 0.33 (5:1 CH_2Cl_2–CH_3OH); $[\alpha]_D$ +158.3° (*c* 1.0, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD): δ_H 5.02 (d, 1 H, *J* 1.6 Hz), 4.81 (d, 1 H, *J* 1.3 Hz), 4.05 (dd, 1 H, *J* 3.1, 1.5 Hz), 4.00–3.92 (m, 3 H), 3.90–3.86 (m, 1 H), 3.80–3.72 (m, 2 H), 3.70–3.63 (m, 3 H), 3.59 (dd, 1 H, *J* 11.9, 5.4 Hz), 3.37 (dt, 1 H, *J* 9.6, 6.5 Hz), 1.57–1.50 (m, 2 H), 1.34–1.26 (m, 10 H), 0.86 (t, 3 H, *J* 6.8 Hz); ^{13}C NMR (100 MHz, CD_3OD): δ_C 109.5, 109.0, 85.5, 84.0, 83.7, 83.6, 82.2, 78.6, 68.6, 63.0, 62.8, 33.0, 30.7, 30.5, 30.4, 27.2, 23.7, 14.4; ESIMS *m*/*z* Calcd for $[C_{18}H_{34}O_9]Na^+$: 417.2095. Found: 417.2103.

3.4. Octyl 3,5-di-*O*-(α-D-arabinofuranosyl)-α-D-arabinofuranoside (4)

Trisaccharide **16** (57 mg, 0.045 mmol) was deacylated as described for the preparation of **2**. The product was purified by chromatography (10:1 CH_2Cl_2–CH_3OH) to yield **4** (20 mg, 84%) as an oil: R_f 0.23 (5:1 CH_2Cl_2–CH_3OH); $[\alpha]_D$ +147.6° (*c* 0.8, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD): δ_H 5.00 (d, 1 H, *J* 1.5 Hz), 4.90 (d, 1 H, *J* 1.2 Hz), 4.80 (d, 1 H, *J* 1.2 Hz), 4.08–4.06 (m, 1 H), 4.03 (dd, 1 H, *J* 2.9, 1.5 Hz), 4.00–3.93 (m, 4 H), 3.89–3.85 (m, 2 H), 3.77 (dd, 2 H, *J* 6.1, 3.6 Hz), 3.71 (t, 1 H, *J* 3.1 Hz), 3.69–3.59 (m, 4 H), 3.57 (dd, 1 H, *J* 5.3, 2.6 Hz), 3.36 (dt, 1 H, *J* 9.5, 6.5 Hz), 1.54–1.49 (m, 2 H), 1.34–1.25 (m, 10 H), 0.85 (t, 3 H, *J* 6.8 Hz); ^{13}C NMR (100 MHz, CD_3OD): δ_C 110.0, 109.9, 109.5, 86.3, 85.9, 84.7, 84.0, 83.5, 82.9, 82.6, 79.3, 79.2, 69.1, 68.1, 63.5, 63.4, 33.4, 31.1, 30.9, 30.8, 27.6, 24.1, 14.8; ESIMS *m*/*z* Calcd for $[C_{23}H_{42}O_{13}]Na^+$: 549.2518. Found: 549.2469.

3.5. Octyl 5-*O*-[3-*O*-(α-D-arabinofuranosyl)-α-D-arabinofuranosyl]-α-D-arabinofuranoside (5)

Trisaccharide **21** (500 mg, 0.39 mmol) was deacylated as described for the preparation of **2**. Purification of the product was achieved by chromatography on Iatrobeads (10:1 CH_3Cl–CH_3OH) to yield **5** (180 mg, 87%) as a foam: R_f 0.27 (5:1, CH_2Cl_2–CH_3OH); $[\alpha]_D$ +156.2° (*c* 1.0, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD): δ_H 5.11 (d, 1 H, *J* 1.1 Hz), 5.04 (s, 1 H), 4.91 (d, 1 H), 4.22 (br s, 1 H), 4.14–3.94 (m, 7 H), 3.90–3.74 (m, 4 H), 3.72–3.60 (m, 4 H), 3.46 (ddd, 1 H, *J* 6.8, 9.6. 9.6 Hz), 1.58–1.52 (m, 2 H), 1.30–1.18 (m, 10 H), 0.82 (t, 3 H, *J* 6.5 Hz); ^{13}C NMR (100 MHz, D_2O): δ_C 107.8, 107.7, 107.4, 84.2, 83.4, 82.4, 82.0, 81.7, 81.6, 79.6, 76.9, 76.9, 68.6, 66.0, 61.5, 61.4, 32.0, 29.6, 29.5, 29.4, 26.1, 22.8, 14.1; ESIMS *m*/*z* Calcd for $[C_{23}H_{42}O_{13}]Na^+$: 549.2517. Found: 549.2565.

3.6. Octyl 5-*O*-[5-*O*-(α-D-arabinofuranosyl)-α-D-arabinofuranosyl]-α-D-arabinofuranoside (6)

Trisaccharide **24** (450 mg, 0.35 mmol) was deacylated as described for the preparation of **2**. The product was purified by chromatography on Iatrobeads (3:1 CH_3Cl–CH_3OH) to yield **6** (162 mg, 88%) as a foam: R_f 0.24 (5:1, CH_2Cl_2–CH_3OH); $[\alpha]_D$ +133.2° (*c* 1.0, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD): δ_H 5.01 (s, 2 H), 4.96 (d, 1 H, *J* 1.7 Hz), 4.20–4.10 (m, 1 H), 4.10–3.92 (m, 7 H), 3.90 (dd, 1 H, *J* 3.3, 5.9 Hz), 3.87–3.62 (m, 7 H), 3.46 (ddd, 1 H, *J* 6.8, 6.8, 9.6 Hz), 1.58–1.52 (m, 2 H), 1.30–1.18 (m, 10 H), 0.82 (t, 3 H, *J* 6.5 Hz); ^{13}C NMR (100 MHz, D_2O): δ_C 108.0, 107.9, 107.7, 84.3, 82.8, 82.1, 81.5, 81.3, 81.2, 68.7, 77.3, 77.1, 76.9, 67.1, 67.0, 61.5, 31.8, 29.4, 29.3, 29.2, 25.9, 22.6,

14.0; ESIMS m/z Calcd for $[C_{23}H_{42}O_{13}]Na^+$: 549.2517. Found: 549.2413.

3.7. Octyl 5-*O*-[3,5-di-*O*-(α-D-arabinofuranosyl)-α-D-arabinofuranosyl]-α-D-arabinofuranoside (7)

Tetrasaccharide **20** (35 mg, 0.022 mmol) was deacylated as described for the preparation of **2**. The product was purified by chromatography (10:1 CH_2Cl_2–CH_3OH) to yield **7** (11 mg, 77%) as an oil: R_f 0.14 (5:1 CH_2Cl_2–CH_3OH); $[\alpha]_D$ +140.0° (*c* 0.5, CH_3OH); ^1H NMR (400 MHz, CD_3OD): δ_H 4.99 (d, 1 H, *J* 1.4 Hz), 4.90 (s, 2 H), 4.16–4.13 (m, 1 H), 4.09 (dd, 1 H, *J* 2.5, 1.1 Hz), 4.00 (dd, 1 H, *J* 5.8, 2.6 Hz), 3.98–3.91 (m, 4 H), 3.90–3.85 (m, 4 H), 3.78–3.75 (m, 3 H), 3.72–3.63 (m, 4 H), 3.61–3.56 (m, 3 H), 3.40–3.35 (m, 1 H), 3.29 (s, 1 H), 1.56–1.50 (m, 2 H), 1.34–1.23 (m, 10 H), 0.85 (t, 3 H, *J* 6.8 Hz); ^{13}C NMR (100 MHz, CD_3OD): δ_C 110.0, 109.9, 109.8, 109.5, 86.3, 86.0, 84.6, 84.0, 83.9, 83.8, 83.5, 83. 4, 82.1, 79.3, 79.2, 79.0, 69.4, 68.1, 67.9, 63.5, 63.4, 33.4, 31.1, 30.9, 30.8, 27.7, 24.1, 14.8; ESIMS m/z Calcd for $[C_{28}H_{50}O_{17}]Na^+$: 681.2940. Found: 681.2952.

3.8. Octyl 2,3-di-*O*-benzoyl-5-*O*-(2,3,5-tri-*O*-benzoyl-α-D-arabinofuranosyl)-α-D-arabinofuranoside (14)

A mixture of **8** (100 mg, 0.21 mmol) and **11** (155 mg, 0.27 mmol), and powdered molecular sieves (4 Å, 0.2 g) in dry CH_2Cl_2 (10 mL) was stirred at 0 °C for 20 min. To the mixture were added *N*-iodosuccinimide (61 mg, 0.27 mmol) and silver triflate (16 mg, 0.062 mmol). After stirring for 30 min at 0 °C, the reaction mixture was neutralized with Et_3N, diluted with CH_2Cl_2 (100 mL), and filtered through Celite. The filtrate was washed successively with satd aq $Na_2S_2O_3$, water, and brine. The solvent was dried (Na_2SO_4) and evaporated. The residue was purified by chromatography (3:1 hexanes–EtOAc) to yield **14**[10] (175 mg, 90%) as an oil: R_f 0.43 (3:1 hexanes–EtOAc); $[\alpha]_D$ −0.9° (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.10–7.98 (m, 10 H), 7.62 (t, 2 H, *J* 7.4 Hz), 7.56–7.41 (m, 9 H), 7.36–7.28 (m, 4 H), 5.69 (d, 1 H, *J* 1.0 Hz), 5.68–5.62 (m, 2 H), 5.56 (d, 1 H, *J* 1.2 Hz), 5.51 (s, 1 H), 5.27 (s, 1 H), 4.88 (dd, 1 H, *J* 11.8, 3.3 Hz), 4.80 (dd, 1 H, *J* 8.1, 4.7 Hz), 4.71 (dd, 1 H, *J* 11.8, 4.7 Hz), 4.50 (dd, 1 H, *J* 7.6, 4.6 Hz), 4.29 (dd, 1 H, *J* 11.2, 4.6 Hz), 4.02 (dd, 1 H, *J* 11.1, 2.9 Hz), 3.80 (dt, 1 H, *J* 9.4, 6.7 Hz), 3.55 (dt, 1 H, *J* 9.4, 6.3 Hz), 1.71–1.61 (m, 2 H), 1.47–1.28 (m, 10 H), 0.90 (t, 3 H, *J* 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.2, 165.7 (2 C), 165.4, 165.2, 133.4 (3 C), 133.3, 133.0, 129.9, 129.8, 129.3, 129.1, 129.0, 128.5, 128.4, 128.3 (2 C), 105.9, 105.6, 81.9, 81.8 (2 C), 81.2, 77.8, 77.3, 67.4, 66.2, 63.7, 31.8, 29.5, 29.4, 29.2, 26.2, 22.6, 14.0; ESIMS m/z Calcd for $[C_{53}H_{54}O_{14}]Na^+$: 937.3406. Found: 937.3368.

3.9. Octyl 2,5-di-*O*-benzoyl-3-*O*-(2,3,5-tri-*O*-benzoyl-α-D-arabinofuranosyl)-α-D-arabinofuranoside (15)

Alcohol **9** (60 mg, 0.13 mmol) was glycosylated with **11** (96 mg, 0.17 mmol) using *N*-iodosuccinimide (38 mg, 0.17 mmol) and silver triflate (10 mg, 0.039 mmol) in CH_2Cl_2 (7 mL) with powdered molecular sieves (4 Å, 0.2 g) as described for the preparation of **14**. The product was purified by chromatography (3:1 hexanes–EtOAc) to yield **15** (115 mg, 92%) as an oil: R_f 0.41 (3:1 hexanes–EtOAc); $[\alpha]_D$ +9.3° (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ_H 8.15–8.00 (m, 10 H), 7.66–7.58 (m, 3 H), 7.53–7.46 (m, 4 H), 7.45–7.41 (m, 4 H), 7.31–7.25 (m, 4 H), 5.76 (s, 1 H), 5.70 (d, 1 H, *J* 1.1 Hz), 5.61 (d, 1 H, *J* 4.0 Hz), 5.44 (s, 1 H), 5.30 (s, 1 H), 4.77 (dd, 2 H, *J* 10.9, 2.8 Hz), 4.67–4.60 (m, 3 H), 4.56–4.52 (m, 2 H), 3.81 (dt, 1 H, *J* 9.6, 6.9 Hz), 3.58 (dt, 1 H, *J* 9.6, 6.6 Hz), 1.73–1.64 (m, 2 H), 1.43–1.39 (m, 2 H), 1.34–1.29 (m, 8 H), 0.90 (t, 3 H, *J* 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.1 (2 C), 165.6, 165.5 (2 C), 133.5 133.4 (2 C), 133.0 (3 C), 129.8, 129.7, 129.6 (2 C), 129.3, 129.1, 128.5, 128.4, 128.3, 128.2, 105.8, 105.3, 82.6, 81.8, 81.7, 81.1, 80.8, 77.7, 67.7, 63.8, 63.3, 31.8, 29.4, 29.3, 29.2, 26.0, 22.6, 14.0; ESIMS m/z Calcd for $[C_{53}H_{54}O_{14}]Na^+$: 937.3406. Found: 937.3408.

3.10. Octyl 2-*O*-benzoyl-3,5-di-*O*-(2,3,5-tri-*O*-benzoyl-α-D-arabinofuranosyl)-α-D-arabinofuranoside (16)

Alcohol **10** (30 mg, 0.082 mmol) was glycosylated with **11** (114 mg, 0.20 mmol) using *N*-iodosuccinimide (45 mg, 0.20 mmol) and silver triflate (10 mg, 0.039 mmol) in CH_2Cl_2 (8 mL) with powdered molecular sieves (4 Å, 0.2 g) as described for the preparation of **14**. The product was purified by chromatography (2:1 hexanes–EtOAc) to yield **16** (80 mg, 78%) as an oil: R_f 0.46 (2:1 hexanes–EtOAc); $[\alpha]_D$ +18.0° (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.09–7.98 (m, 14 H), 7.47–7.26 (m, 21 H), 5.66 (d, 1 H, *J* 1.2 Hz), 5.60–5.56 (m, 4 H), 5.45 (d, 1 H, *J* 1.5 Hz), 5.42 (s, 1 H), 5.23 (s, 1 H), 4.83 (dd, 1 H, *J* 11.0, 2.6 Hz), 4.78 (dd, 1 H, *J* 8.2, 3.6 Hz), 4.69–4.60 (m, 4 H), 4.56 (dd, 1 H, *J* 6.1, 0.9 Hz), 4.31–4.40 (m, 1 H), 4.19–4.12 (m, 1 H), 3.95 (dd, 1 H, *J* 11.4, 2.3 Hz), 3.76 (dt, 1 H, *J* 9.6, 6.9 Hz), 3.51 (dt, 1 H, *J* 9.6, 6.6 Hz), 1.66–1.60 (m, 2 H), 1.38–1.27 (m, 10 H), 0.89 (t, 3 H, *J* 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.1, 166.0, 165.6 (3 C), 165.1 (2 C), 133.5, 133.4, 133.3 (2 C), 133.0, 129.9 (2 C), 129.8 (2 C), 129.7 (3 C), 128.5, 128.4, 128.3, 128.2, 106.0, 105.8, 105.5, 82.8, 81.7 (3 C), 81.6, 81.3, 80.9, 77.8, 77.7, 67.5, 65.8, 63.7, 63.7, 31.8, 29.4, 29.3, 29.2, 26.0, 25.6, 14.0; ESIMS m/z Calcd for $[C_{72}H_{70}O_{20}]Na^+$: 1277.4353. Found: 1277.4431.

3.11. Octyl 2,3-di-*O*-benzoyl-5-*O*-(2-*O*-benzoyl-3,5-*O*-(1,1,3,3-tetraisopropylsiloxane-1,3-diyl)-α-D-arabinofuranosyl)-α-D-arabinofuranoside (17)

Alcohol **8** (800 mg, 1.70 mmol) was glycosylated with thioglycoside **12** (1.30 g, 2.16 mmol) using *N*-iodosuccinimide (497 mg, 2.20 mmol) and silver triflate (131 mg, 0.51 mmol) in CH_2Cl_2 (20 mL) containing 4 Å molecular sieves (0.5 g) as described for the preparation of **14**. The product was purified by chromatography (6:1 hexanes–EtOAc) to provide **17** (1.32 g, 82%) as an oil: R_f 0.23 (6:1 hexanes–EtOAc); $[\alpha]_D$ +4.2° (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.04–7.91 (m, 6 H), 7.52–7.34 (m, 9 H), 5.48–5.45 (m, 2 H), 5.40 (d, 1 H, *J* 1.2 Hz), 5.15 (s, 1 H), 5.09 (d, 1 H, *J* 1.4 Hz), 4.43–4.40 (m, 2 H), 4.09–3.81 (m, 5 H), 3.71–3.67 (m, 1 H), 3.46–3.40 (m, 1 H), 1.61–1.49 (m, 2 H), 1.38–0.59 (m, 41 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 165.6, 165.5, 165.3, 133.3, 133.3, 133.2, 133.0, 130.0, 129.9, 129.8, 129.7, 129.5, 129.3, 129.0, 128.5, 128.4, 128.4, 128.2, 128.2, 128.1, 105.7, 105.6, 84.1, 81.7, 81.6, 81.2, 77.7, 76.0, 67.5, 67.4, 61.5, 31.8, 29.6, 29.5, 29.4, 29.4, 29.3, 26.2, 22.6, 17.4, 17.3, 17.0, 16.9, 16.9, 14.1, 13.5, 13.1, 12.8, 12.4; ESIMS *m*/*z* Calcd for $[C_{51}H_{72}O_{13}Si_2]Na^+$: 971.4404. Found: 971.4459.

3.12. Octyl 2,3-di-*O*-benzoyl-5-*O*-(2-*O*-benzoyl-α-D-arabinofuranosyl)-α-D-arabinofuranoside (18)

Disaccharide **17** (1.3 g, 1.4 mmol) was dissolved in THF (20 mL), and the solution was cooled to 0 C before *n*-$Bu_4NF{\cdot}3H_2O$ (710 mg, 2.7 mmol) was added. After 15 min, the reaction mixture was concentrated, and the residue was purified by chromatography (1:3 EtOAc–toluene) to give **18** (811 mg, 84%) as an oil: R_f 0.46 (1:1 EtOAc–toluene); $[\alpha]_D$ +51.0° (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.09–7.98 (m, 6 H), 7.60–7.42 (m, 9 H), 5.55 (d, 1 H, *J* 5.0 Hz,), 5.51 (d, 1 H, *J* 1.4 Hz), 5.39 (s, 1 H), 5.26 (s, 1 H), 5.17–5.16 (m, 1 H), 4.47–4.40 (m, 1 H), 4.33–4.30 (m, 1 H), 4.21–4.13 (m, 2 H), 3.99–3.92 (m, 2 H), 3.81–3.74 (m, 2 H), 3.56–3.46 (m, 1 H), 2.06 (br s, 1 H), 1.78 (br s, 1 H), 1.68–1.61 (m, 2 H), 1.42–1.25 (m, 10 H), 0.86 (t, 3 H, *J* 6.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 166.6, 165.9, 165.3, 133.6, 133.5, 129.9, 129.9, 129.8, 129.8, 129.0, 128.5, 128.5, 105.6, 105.1, 86.0, 84.9, 84.5, 83.6, 81.9, 81.7, 67.6, 65.9, 62.2, 31.8, 29.5, 29.4, 29.3, 26.1, 22.6, 14.1; ESIMS *m*/*z* Calcd for $[C_{39}H_{46}O_{12}]Na^+$: 729.2881. Found: 729.2875.

3.13. Octyl 2,3-di-*O*-benzoyl-5-*O*-(2,5-di-*O*-benzoyl-α-D-arabinofuranosyl)-α-D-arabinofuranoside (19)

Diol **18** (600 mg, 0.84 mmol), Ph_3P (330 mg, 1.25 mmol), and benzoic acid (150 mg, 1.25 mmol) were dissolved in THF (10 mL), and the solution was cooled to 0 °C. Diethylazodicarboxylate (0.2 mL, 1.25 mmol) was added dropwise over 10 min. The reaction mixture was brought to rt and was then stirred for 30 min. After concentration of the reaction mixture to an oil, the product was purified by chromatography (2:1 hexane–EtOAc) to provide **19** (621 mg, 90%) as an oil: R_f 0.41 (2:1 hexane–EtOAc); $[\alpha]_D$ +18.5° (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.25–7.90 (m, 8 H), 7.75–7.30 (m, 12 H), 5.55 (d, 1 H, *J* 4.5 Hz), 5.53 (s, 1 H), 5.43 (s, 1 H), 5.26 (s, 1 H), 5.22 (d, 1 H, *J* 2.1 Hz), 4.63 (dd, 1 H, *J* 2.8, 10.7 Hz), 4.59–4.40 (m, 3 H), 4.25–4.15 (m, 2 H), 3.96 (dd, 1 H, *J* 3.2, 10.9 Hz), 3.77 (ddd, 1 H, *J* 6.7, 6.7, 9.4 Hz), 3.53 (ddd, 1 H, *J* 6.7, 6.7, 9.4 Hz), 1.55–1.70 (m, 2 H), 1.55–1.19 (m, 10 H), 0.85 (t, 3 H, *J* 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.4, 166.2, 165.8, 165.4, 133.6, 133.4, 133.0, 130.1, 129.9, 129.8, 129.7, 129.2, 129.1, 129.0, 128.5, 128.4, 128.3, 105.6, 105.2, 85.3, 82.3, 81.9, 81.7, 77.3, 76.7, 67.6, 66.0, 63.8, 31.8, 29.5, 29.4, 29.2, 26.1, 22.6, 14.0; ESIMS *m*/*z* Calcd for $[C_{46}H_{50}O_{13}]Na^+$: 833.3144. Found: 833.3112.

3.14. Octyl 5-*O*-[3,5-di-*O*-(2,3,5-tri-*O*-benzoyl-α-D-arabinofuranosyl)-2-*O*-benzoyl-α-D-arabinofuranosyl]-2,3-di-*O*-benzoyl-α-D-arabinofuranoside (20)

Alcohol **18** (25 mg, 0.035 mmol) was glycosylated with **11** (5 mg, 0.019 mmol) using *N*-iodosuccinimide (20 mg, 0.089 mmol) and silver triflate (131 mg, 0.51 mmol) in CH_2Cl_2 (8 mL) containing 4 Å molecular sieves (0.2 g) as described for the preparation of **14**. The product was purified by chromatography (2:1 hexanes–EtOAc) to yield **20** (44 mg, 80%) as an oil: R_f 0.38 (2:1 hexanes–EtOAc); $[\alpha]_D$ +12.3° (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.14–7.94 (m, 18 H), 7.64–7.21 (m, 27 H), 5.69 (d, 1 H, *J* 4.4 Hz), 5.61–5.50 (m, 6 H), 5.45 (d, 2 H, *J* 1.4 Hz), 5.27 (s, 1 H), 4.87–4.74 (m, 2 H), 4.73–4.59 (m, 6 H), 4.54–4.30 (m, 1 H), 4.23 (dd, 1 H, *J* 11.2, 4.4 Hz), 4.19–4.14 (m, 2 H), 4.01–3.94 (m, 2 H), 3.80 (dt, 1 H, *J* 9.4, 6.7 Hz), 3.55 (dt, 1 H, *J* 9.4, 6.3 Hz), 1.70–1.62 (m, 2 H), 1.46–1.28 (m, 10 H), 0.90 (t, 3 H, *J* 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.1, 165.2, 165.6, 165.5 (3 C), 165.4, 165.1, 164.9, 133.3, 129. 9, 129.8 (4 C), 129.7, 129.6, 128.5, 128.4, 128.4, 128.3 (3 C), 128.2 (2 C), 105.9, 105.7, 105.6, 105.4, 82.0, 81.9, 81.9 (2 C), 81.7 (2 C), 81.6, 81.4, 77.8, 77.7, 77.3, 67.5, 65.6, 65.5, 63.7, 63.5, 60.3, 31.8, 29.5, 29.4, 29.2, 26.1, 22.6, 14.0; ESIMS *m*/*z* Calcd for $[C_{91}H_{86}O_{26}]Na^+$: 1618.5333. Found: 1618.5459.

3.15. Octyl 2,3-di-*O*-benzoyl-5-*O*-(2,5-di-*O*-benzoyl-3-*O*-(2,3,5-tri-*O*-benzoyl-α-D-arabinofuranosyl)-α-D-arabinofuranosyl)-α-D-arabinofuranoside (21)

Alcohol **19** (600 mg, 0.74 mmol) was glycosylated with thioglycoside **11** (500 mg, 0.88 mmol) using *N*-iodosuc-

cinimide (200 mg, 0.88 mmol) and silver triflate (57 mg, 0.22 mmol) in CH_2Cl_2 (10 mL) containing 4 Å molecular sieves (0.3 g) as described for the preparation of **14**. The product was purified by chromatography (4:1 hexanes–EtOAc) to provide **21** (0.82 g, 88%) as an oil: R_f 0.22 (4:1 hexanes–EtOAc); $[\alpha]_D$ +16.0° (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.20–7.80 (m, 15 H), 8.60–7.05 (m, 20 H), 5.85–5.56 (m, 2 H), 5.56–5.53 (m, 5 H), 5.10 (s, 1 H), 4.85–4.38 (m, 8 H), 4.23 (d, 1 H, *J* 9.6 Hz), 3.96 (d, 1 H, *J* 10.9 Hz), 3.75 (ddd, 1 H, *J* 6.7, 6.7, 9.4 Hz), 3.50 (ddd, 1 H, *J* 6.7, 6.7, 9.4 Hz), 1.70–1.50 (m, 2 H), 1.45–1.19 (m, 10 H), 0.83 (t, 3 H, *J* 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.1, 165.7, 165.6, 164.9, 133.4, 133.4, 133.3, 132.9, 130.0, 129.9, 129.8, 129.7, 129.6, 128.5, 128.4, 128.3, 105.6, 105.5 (2), 82.7, 82.0, 81.9, 81.8, 81.5, 81.4, 81.3, 77.8, 77.1, 67.5, 65.7, 63.7, 63.0, 31.8, 29.5, 29.4, 29.2, 26.1, 22.6, 14.0; ESIMS *m*/*z* Calcd for $[C_{72}H_{70}O_{20}]Na^+$: 1277.4352. Found: 1277.4390.

3.16. Octyl 2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-5-*O*-*tert*-butyldiphenylsilyl-α-D-arabinofuranosyl)-α-D-arabinofuranoside (22)

Alcohol **8** (500 mg, 1.1 mmol) was glycosylated with **13** (970 mg, 1.4 mmol) using *N*-iodosuccinimide (311 mg, 1.4 mmol) and silver triflate (81 mg, 0.32 mmol) in CH_2Cl_2 (20 mL) containing 4 Å molecular sieves (0.5 g) as described for the preparation of **14**. The product was purified by chromatography (4:1 hexanes–EtOAc) to provide **22** (910 mg, 82%) as an oil: R_f 0.30 (4:1 hexanes–EtOAc); $[\alpha]_D$ −2.7° (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.10–7.25 (m, 30 H), 5.45–5.54 (m, 2 H), 5.35 (s, 1 H), 5.25 (s, 1 H), 5.19 (s, 1 H), 4.43 (dd, 1 H, *J* 4.5, 4.5 Hz), 4.32–4.20 (m, 2 H), 4.14 (dd, 1 H, *J* 5.0, 11.0 Hz), 3.92 (dd, 1 H, *J* 3.4, 11.0 Hz), 3.86 (d, 2 H, *J* 4.5 Hz), 3.76 (ddd, 1 H, *J* 6.7, 6.7, 9.4 Hz), 3.52 (ddd, 1 H, *J* 6.7, 6.7, 9.4 Hz), 1.68–1.49 (m, 2 H), 1.45–1.21 (m, 10 H), 1.10–0.90 (m, 9 H), 0.82 (t, 3 H, *J* 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.8, 166.2, 165.9, 136.0 (2), 133.9, 133.8, 133.7, 130.4, 130.3, 130.2, 130.1, 129.7, 129.6, 128.9, 128.8, 128.1, 106.0, 105.7, 85.2, 85.6, 82.4, 82.1, 78.0, 77.2, 68.0, 66.4, 63.9, 32.3, 30.0, 29.8, 29.7, 27.2, 26.6, 23.1, 19.7, 14.5; ESIMS *m*/*z* Calcd for $[C_{62}H_{68}O_{13}Si]Na^+$: 1071.4321. Found: 1071.4286.

3.17. Octyl 2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-α-D-arabinofuranosyl)-α-D-arabinofuranoside (23)

Disaccharide **22** (850 mg, 0.81 mmol) was dissolved in THF (20 mL) and then *n*-$Bu_4F{\cdot}3H_2O$ (254 mg, 0.97 mmol) was added. After stirring for 4 h, the reaction mixture was concentrated, and the resulting residue was purified by chromatography (3:1 hexanes–EtOAc) to give **23** (581 mg, 88%) as an oil: R_f 0.25 (3:1 hexanes–EtOAc); $[\alpha]_D$ −8.6° (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.10–7.85 (m, 8 H), 7.60–7.20 (m, 12 H), 5.65 (d, 1 H, *J* 1.3 Hz), 5.61 (d, 1 H, *J* 4.9 Hz), 5.51 (d, 1 H, *J* 1.2 Hz), 5.44 (dd, 1 H, *J* 0.8, 4.8 Hz), 5.36 (s, 1 H), 5.22 (s, 1 H), 4.51–4.40 (m, 2 H), 4.19 (dd, 1 H, *J* 4.5, 11.2 Hz), 3.91–4.07 (m, 3 H), 3.74 (ddd, 1 H, *J* 6.4, 6.4, 9.5 Hz), 3.49 (ddd, 1 H, *J* 6.4, 6.4, 9.5 Hz), 1.70–1.50 (m, 2 H), 1.45–1.19 (m, 10 H), 0.83 (t, 3 H, *J* 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.1, 165.7, 165.4, 165.1, 133.5, 133.5, 133.4, 133.3, 129.9 (2), 129.8, 129.3, 129.2, 129.1, 129.0, 128.6, 128.5, 128.4, 128.3, 105.8, 105.6, 83.7, 81.9, 81.8, 81.7, 77.8, 77.4, 67.4, 66.2, 62.3, 31.8, 29.5, 29.4, 29.3, 26.2, 22.6, 14.1; ESIMS *m*/*z* Calcd for $[C_{46}H_{50}O_{13}]Na^+$: 833.3149. Found: 833.3106.

3.18. Octyl 2,3-di-*O*-benzoyl-5-*O*-(2,3-di-*O*-benzoyl-α-D-arabinofuranosyl-(5-*O*-(2,3,5-tri-*O*-benzoyl-α-D-arabinofuranosyl))-α-D-arabinofuranoside (24)

Alcohol **23** (550 mg, 0.67 mmol) was glycosylated with thioglycoside **11** (460 mg, 0.81 mmol) using *N*-iodosuccinimide (180 mg, 0.80 mmol) and silver triflate (52 mg, 0.20 mmol) in CH_2Cl_2 (20 mL) containing 4 Å molecular sieves (0.5 g) as described for the preparation of **14**. The product was purified by chromatography (4:1 hexanes–EtOAc) to provide **24** (0.74 g, 87%) as a solid: R_f 0.34 (4:1 hexanes–EtOAc); $[\alpha]_D$ +6.2° (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.05–7.80 (m, 14 H), 7.55–7.10 (m, 21 H), 5.64–5.59 (m, 4 H), 5.57 (d, 1 H, *J* 4.8 Hz), 5.50 (s, 1 H), 5.46 (s, 1 H), 5.41 (s, 1 H), 5.21 (s, 1 H), 4.82 (dd, 1 H, *J* 3.2, 11.8 Hz), 4.72–4.60 (m, 3 H), 4.43–4.38 (m, 1 H), 4.28–4.15 (m, 2 H), 3.97 (dd, 1 H, *J* 3.0, 11.3 Hz), 3.92 (dd, 1 H, *J* 2.8, 11.2 Hz), 3.74 (ddd, 1 H, *J* 6.6, 6.6, 9.7 Hz), 3.48 (ddd, 1 H, *J* 6.6, 6.6, 9.7 Hz), 1.70–1.50 (m, 2 H), 1.45–1.19 (m, 10 H), 0.83 (t, 3 H, *J* 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.2, 165.8, 165.7, 165.5, 165.2, 165.1, 133.4, 133.3, 133.2, 133.0, 129.9, 132.4, 129.8, 129.3, 129.1, 129.1, 128.9, 128.8, 128.4, 128.4, 128.2, 105.9, 105.8, 105.8, 82.0, 81.9, 81.8, 81.7, 81.5, 81.2, 77.8, 77.4, 67.5, 66.0 (2), 63.7, 31.8, 29.5, 29.4, 29.2, 26.2, 22.6, 14.1; ESIMS *m*/*z* Calcd for $[C_{72}H_{70}O_{20}]Na^+$: 1277.4352. Found: 1277.4235.

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