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Efficient one-pot syntheses of α-D-arabinofuranosyl tri- and tetrasaccharides present in cell wall polysaccharide of *Mycobacterium tuberculosis*

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ABSTRACT

Two α-D-arabinofuranosyl oligosaccharides (**2** and **3**) found as constituent parts of the polysaccharide portion from the cell wall of *Mycobacterium tuberculosis* have been efficiently synthesized via a one-pot glycosylation procedure in which a key step is the chemoselective activation between D-arabinofuranosyl trichloroacetimidate donor **4** and partially protected aryl thioglycosides **5** or **7**, respectively.

1. Introduction

Mycobacteria including the pathogens *Mycobacterium tuberculosis* and *Mycobacterium leprae* are the causative agents of tuberculosis (TB), the world's most lethal bacterial disease.[1–3] The cell wall of mycobacteria is comprised of two major polysaccharides, arabinogalactan (AG) and lipoarabinomannan (LAM), in which all of the arabinose and galactose residues exist in furanose form.[4,5] The organism's ability to make these polysaccharides is crucial to its survival and pathogenicity, and therefore, the enzymes, such as arabinosyltransferases (AraTs), involved in the biosynthesis of the mycobacterial biopolymers have attracted wide attention as targets of new drugs for the treatment of TB and other mycobacterial diseases.[6–9]

Since the structural motifs of mycobacterial AG and LAM, such as hexasaccharide **1** (Fig. 1), a key scaffold found at the non-reducing termini of these polysaccharides, can be employed as useful tools in clarifying the biosynthetic pathway by which the biopolymers are assembled[10] and in further exploring potential anti-TB agents that target the enzymes involved in mycobacteria glycan biosynthesis,[11] the chemical synthesis of these motifs and structurally related analogs is an area of current interest. In this context, two synthetic methods are applied. The one used often is a stepwise condensation approach,[12] but its obvious disadvantages include the tediously selective protection and deprotection manipulations and the formation of multiple byproducts as a result of migration of acyl functions during some deprotection reactions in furanose.[13a] The other method is a one-pot strategy, which was demonstrated by Lowary[13a] and Ning[13b] recently to be highly concise and rapid for producing furanosyl oligomers containing D-arabinofuranosyl or L-galactofuranosyl moieties. Besides, there have been considerable studies on the one-pot synthesis of pyranosidic oligosaccharides,[14] but so far similar studies on that of furanosidic oligosaccharides were still little explored. Therefore, we decided to develop new one-pot glycosylation methodologies to synthesize the oligofuranose fragments of mycobacterial cell wall polysaccharides. Reported here is an efficient

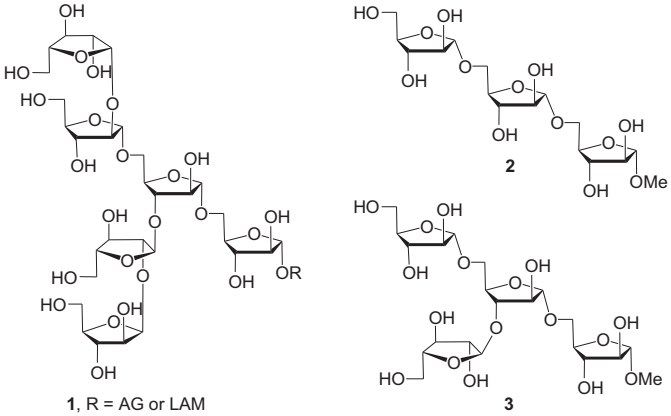

Figure 1. Hexasaccharide motif (**1**) and synthetic targets (**2** and **3**).

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synthesis of trisaccharide **2**[12a] and tetrasaccharide **3**[12a] (Fig. 1), two α-D-arabinofuranosyl portions of **1**, by a one-pot approach based on the chemoselective glycosylation between a trichloroacetimidate donor **4** and a partially protected aryl thioglycosides acceptor **5** or **7**, respectively.

2. Results and discussion

For one-pot synthesis of the target oligosaccharides, we envisioned that they could be assembled by a key chemoselective glycosylation in two steps from monomeric building blocks **4**–**9** (Fig. 2): (i) trichloroacetimidate **4** was to be selectively activated to couple with thioglycoside acceptors **5** (**6**) or **7** (**8**), respectively, and (ii) the obtained di- or trisaccharide thioglycosides would be used as glycosyl donors to glycosylate with methyl glycoside **9** to give the corresponding protected targets. In addition, benzoyl (Bz) group would be utilized as the sole temporary hydroxyl-protecting group to eliminate the need for selective deprotection reactions and as the neighboring participating group at C-2 of the donors to ensure the desired α-stereoselectivity of each glycosylation.

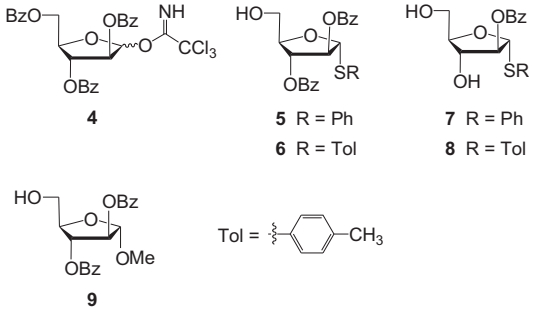
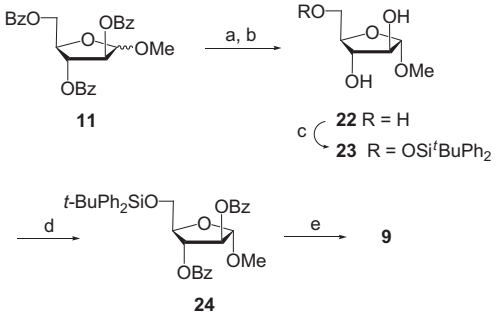


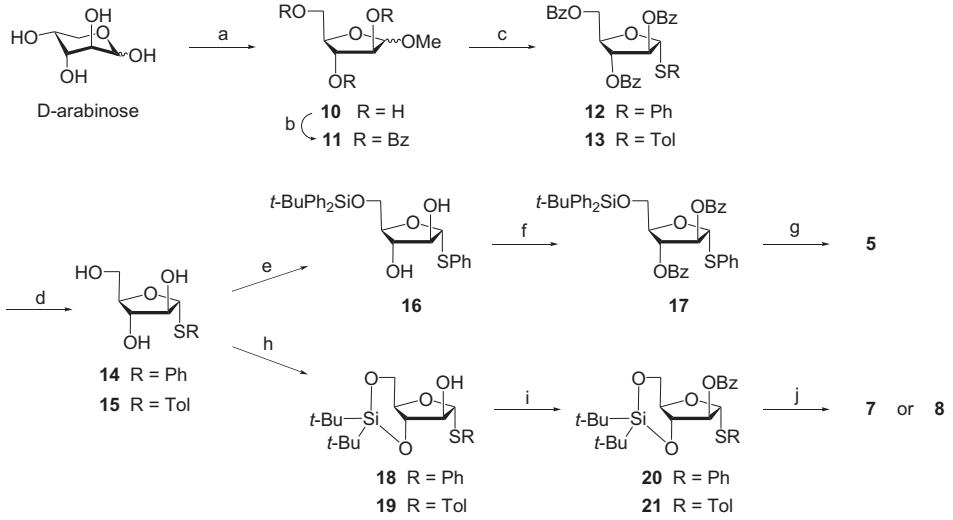
Figure 2. Monosaccharide building blocks required for the assembly of **2** and **3**.

The arabinose derivatives **4**[13b] and **6**[15] were prepared according to the literature procedures. The preparation of building blocks **5**, **7**, and **8** was carried out as illustrated in Scheme 1. Treatment of D-arabinose with methanol under Fisher glycosylation conditions furnished methyl D-arabinofuranosides (**10**)[16] as a mixture of anomers (α/β=3:1), which was directly esterified under standard conditions to afford tribenzoate **11**[16] in 72% yield from D-arabinose. Subsequent condensation of **11** with thiophenol or *p*-methylphenylthiol in the presence of catalytic boron trifluoride etherate ($BF_3 \cdot Et_2O$) in dichloromethane proceeded smoothly to give α-phenyl thioglycoside **12** or its analogy *p*-methylphenyl α-thioglycoside **13**,[17] respectively. Both products were then debenzoylated upon reaction with sodium methoxide in methanol to furnish the corresponding triols **14** and **15**[12a] in 79% and 84% isolated yields, respectively. Conversion of the resulting alcohol **14** to the thioglycoside alcohol **5**[12f] involved (i) regioselective protection with an excess of *t*-$BuPh_2SiCl$ to 5-*O*-*t*-butyldiphenylsilyl ether **16**, (ii) benzoylation of the remaining 2,3-di-OHs to **17**, and (iii) removal of 6-*O*-silyl group with tetrabutylammonia fluoride (TBAF) in THF to the desired product. In addition, access to phenyl thioglycoside **7** with 3,5-OHs free required first the synthesis of 3,5-*O*-di-*tert*-butylsilylene acetal **18**,[18] which could be prepared by reaction of triol **14** with di-(*tert*-butyl)silyl bis(trifluoromethanesulfonate) ($(t\text{-}Bu)_2Si(OTf)_2$) in DMF (86% yield). Then, followed by 2-O-benzoylation to **20** (93% yield) and liberation of 3,5-di-OHs with fluoride ion (72% yield), compound **18** was converted to **7**. Meanwhile, through the similar three-step procedure as described for the preparation of **7**, triol **15** was readily converted, via intermediates **19**[19] and **21**, to the corresponding *p*-methylphenyl thioglycoside **8**.

The synthetic route of the 2,3-*O*-benzoyl protected glycosyl acceptor **9**[12a] was slightly modified compared to the literature method (Scheme 2). The pure α-**11**[16] was separated from the anomeric mixture by recrystallization in ethanol and subsequent treatment with $NaOCH_3$ afforded α-methyl glycoside triol **22**[16] in



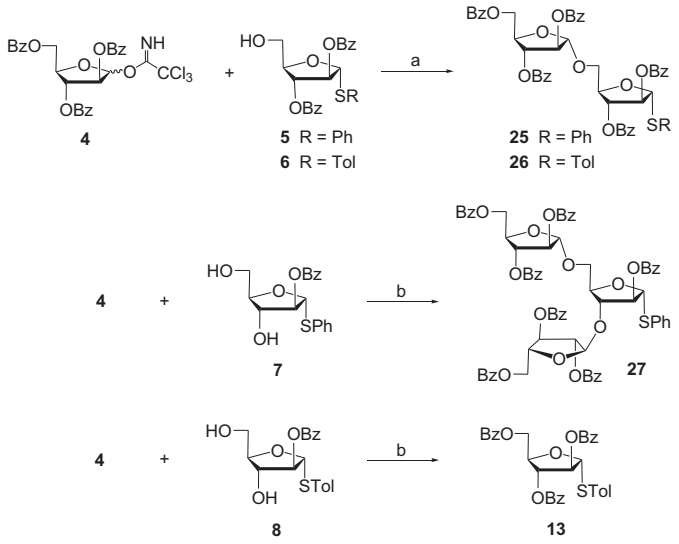
Scheme 2. Reagents and conditions: (a) recrystallization separation of anomers; (b) $NaOCH_3$ (cat.), CH_3OH, rt, 2 h, two steps 68%; (c) *t*-$BuPh_2SiCl$ (1.1 equiv), imidazole, DMF, 0 °C→rt, overnight, 86%; (d) BzCl (7.0 equiv), pyridine, 0 °C→rt, overnight, 87%; (e) TBAF (0.6 equiv), THF, 0 °C→rt, 3 h, 75%.



Scheme 1. Reagents and conditions: (a) MeOH, AcCl (1.0 equiv), rt, 4 h; (b) BzCl (4.0 equiv), pyridine, 55 °C, 30 min, two steps 72%; (c) PhSH or *p*-MePhSH (1.4 equiv), $BF_3 \cdot Et_2O$ (cat.), CH_2Cl_2, 0 °C→rt, 8 h, for **12**: 80%, for **13**: 78%; (d) $NaOCH_3$ (cat.), CH_3OH, rt, 2 h, for **14**: 79%, for **15**: 84%; (e) *t*-$BuPh_2SiCl$ (1.5 equiv), imidazole, DMF, 0 °C→rt, overnight, 79%; (f) BzCl (7.0 equiv), pyridine, 0 °C→rt, 5 h, 91%; (g) TBAF (0.6 equiv), THF, 0 °C→15 °C, 3.5 h, 78%; (h) $(t\text{-}Bu)_2Si(OTf)_2$ (1.1 equiv), 2,6-lutidine, DMF, 2 h, for **18**: 0 °C, 86%, for **19**: −20 °C→rt, 89%; (i) BzCl (3.5 equiv), pyridine, 0 °C→rt, overnight, for **20**: 93%; (j) TBAF (0.4 equiv), THF, 0 °C→rt, 3 h, for **7**: 72%, for **8**: 70% (two steps from **19**).

68% yield over these two steps. Initial attempts to prepare 5-*O*-silyl ether **23** by reaction of **22** with *t*-$BuPh_2SiCl$ in pyridine at 0 °C[12a] failed and only the starting **22** was recovered after workup. Alternatively, exposure of **22** to *t*-$BuPh_2SiCl$ and imidazole in DMF proved viable and thus led to our expected **23**[12a] in a respectable yield of 86%. Then, the target **9** was synthesized via a similar series of transformations: benzoylation of **23** gave **24** in 87% yield, which was then desilylated affording **9** (75%).

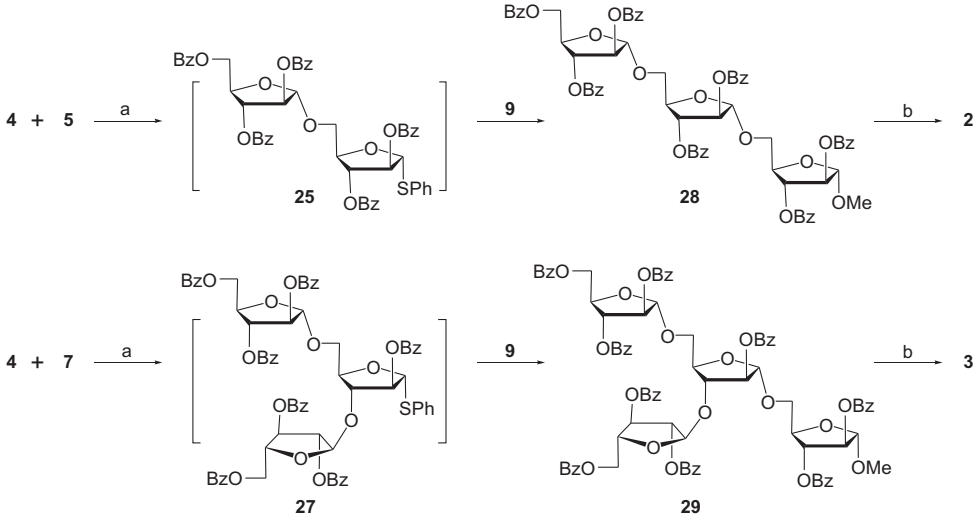
With all necessary monosaccharide units in hand, we then examined two sets of coupling reactions to assess the possibility of chemoselective activation between the trichloroacetimidate **4** and the partially benzoylated aryl thioglycosides **5**–**8**, respectively (Scheme 3). As the first set of the test reactions, the glycosylation of **4** with either **5** or **6** in the presence of a catalytic amount of trimethylsilyl triflate (TMSOTf) in CH_2Cl_2 at −20 °C afforded stereospecifically 1,2-*trans* glycosidic linkage of disaccharide thioglycosides **25** or **26**, accordingly, in equally high yields. Neither self-condensed product of the thioglycoside nor β-stereoisomer was detected in both glycosylations. These results indicated that, under the glycosylation conditions, the imidate **4** was activated exclusively to be a glycosyl donor to undergo the coupling with the thioglycoside **5** or **6**, which was unreactive as an acceptor. This Lewis acid-promoted preferential activation of trichloroacetimidate donor over thioglycoside donor observed in arabinofuranose[12h] was in full agreement with the one observed formerly in either galactofuranose[13a] or pyranose species.[20] In the second set of reactions, the imidate **4** was used to couple with thioglycosides **7** and **8**, respectively, under the same activation conditions. As expected, **7**, as a diol acceptor, was readily coupled with the relatively reactive **4**, giving an 81% yield of 3,5-branched D-arabinofuranosyl trisaccharide thioglycoside **27** with complete α-selectivity. However, the coupling of **4** with **8** using TMSOTf or $BF_3\cdot Et_2O$ as promoter failed to provide the desired trisaccharide. Instead, an unusual intermolecular *p*-methylphenylthio (STol) transfer from the acceptor **8** to the donor **4** took place,[20b,21] and thus monosaccharide sulfide **13** was formed as a major product together with chromatographically inseparable degradation products derived from the glycosyl substrates. Apparently, compared with the anomeric phenylthio (SPh) in **7**, the STol group at the anomeric center in **8** is more nucleophilic because it contains an electron-donating methyl group on the *para* position of the phenyl ring. So, the STol moiety of **8** rather than its 3,5-hydroxyl groups reacted with the oxacarbenium ion formed after activation of the imidate donor **4**, and this led to the formation of the undesirable aglycon transfer product **13**.



Scheme 3. Reagents and conditions: (a) **4** (1.2 equiv), **5** or **6** (1.0 equiv), TMSOTf (0.2 equiv), 4 Å molecular sieves, CH_2Cl_2, −20 °C→0 °C, 0.5 h, for **25**: 94%, for **26**: 85%; (b) **4** (2.3 equiv), **7** or **8** (1.0 equiv), TMSOTf (0.4 equiv), for **27**: 81%, for **13**: 91%.

Having established the chemoselective activation methodology, we next attempted to assemble the suitable building blocks into the target sugars **2** and **3** by a one-pot method as illustrated in Scheme 4.

First, the imidate **4** was coupled with the glycosyl alcohol **5** by activation with catalytic TMSOTf in CH_2Cl_2 at −20 °C. On gradual warming to approximately 0 °C, a new spot, disaccharide **25**[13a] was visible on TLC. Then, the reaction was re-cooled to 0 °C and subsequent addition of the alcohol **9** and promoter *N*-iodosuccinimide (NIS) in conjunction with silver triflate (AgOTf) drove the second glycosylation to proceed, giving rise to trisaccharide methyl glycoside **28** after 30 min. Upon purification by silica gel column chromatography, **28** was obtained in a 64% overall yield. The structure of **28** was readily determined through the use of NMR spectroscopy and ESI-MS spectrometry. In its ^1H NMR spectrum, the characteristic resonances due to the three H-1 signals of α-D-Ara appeared as singlets at δ_H 5.51, 5.64, and 5.66 ppm and the ^{13}C NMR spectrum revealed that the chemical shifts of the anomeric carbons were at δ_C 105.8, 105.9, and 106.8 ppm, respectively. Therefore, both ^1H and ^{13}C NMR data are consistent with the α-arabinofuranoside



Scheme 4. Reagents and conditions: (a) **4**, **5** or **7** (1.0 equiv), TMSOTf (cat.), 4 Å molecular sieves, CH_2Cl_2, −20 °C→0 °C, 1 h; then **9** (0.6 equiv), NIS (0.9 equiv), AgOTf (0.3 equiv), CH_2Cl_2, 0 °C, 30 min, for **28**: **4** (1.2 equiv), 64%, for **29**: **4** (2.3 equiv), 66%; (b) $NaOCH_3$ (cat.), CH_3OH, rt, 2 h, for **2**: 80%, for **3**: 85%.

anomeric stereochemistry.[18] Further support for the structure of **28** came from HR ESI-MS data, which gave an $(M+Na)^+$ signal at m/z 1179.3244 (calcd 1179.3257).

Second, the branched tetrasaccharide benzoate **29**, protected precursor of sugar **3**, was also synthesized through the similar one-pot glycosylation procedures (Scheme 4). Thus, coupling of the donor **4** with the acceptor **7** mediated by TMSOTf afforded the intermediate trisaccharide **27**, which was then glycosylated in situ with **9** activated again with NIS–AgOTf reagent system to yield **29** in 66% overall yield. As was done for **28**, a combination of NMR and MS data could be used to establish the structure of **29**. In its ^{1}H NMR spectrum, the four anomeric hydrogens appeared as three singlets and one doublet ($J_{1,2}$ 0–1.2 Hz), indicative of the α-arabinofuranosyl linkages. Additionally, the ^{13}C NMR spectrum showed four anomeric carbons at δ_C 105.7, 105.8, 106.0, and 106.7 ppm. The structure of **29** was further confirmed by its HR ESI-MS at m/z 1519.4192 $(M+Na)^+$, which was identical with the calculated exact mass of the molecule.

Finally, removal of the benzoate esters of both **28** and **29** obtained from the one-pot procedures under standard saponification conditions yielded the fully deprotected products that were spectroscopically consistent with the target molecules **2** and **3** in 80% and 85% yields, respectively. Additional confirmation of the structures was provided by comparison of their analytical data (^{1}H and ^{13}C NMR, MS) with those previously reported.[12a]

3. Conclusion

In summary, we described a very efficient one-pot synthesis of two α-D-arabinofuranosyl oligosaccharides **2** and **3**. The chemoselective glycosylations of the D-arabinofuranosyl trichloroacetimidate donor **4** with the partially protected thioglycoside acceptors (**5** or **7**, respectively) were the common strategy-level steps in the synthesis. The synthetic processes, in which the glycosyl building blocks are assembled sequentially in a one-pot manner, display obvious advantages over the reported stepwise protocols.[12a] Not only can the target linear and branched oligosaccharide structures be produced simply and rapidly, but also the unexpected acyl migration side reaction occurring in furanose rings is avoided. Further application of the present method to the synthesis of other oligosaccharide fragments of mycobacterial arabinan is ongoing.

4. Experimental

4.1. General methods

All reactions were performed under a nitrogen atmosphere and monitored by thin layer chromatography (TLC) using Silica Gel GF254 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 with a PE-314 automatic polarimeter at 20±1 °C for solutions in a 1.0 dm cell. HR ESI-MS spectra were acquired on Agilent 6210 TOF LC/MS instrument. ^{1}H and ^{13}C NMR spectra were obtained on Bruker AC-E 200 or Varian INOVA-400/54 spectrometers in $CDCl_3$ with tetramethylsilane (TMS) as internal reference. Chemical shifts (δ) are expressed in parts per million downfield from the internal TMS absorption.

4.2. Phenyl 1-thio-α-D-arabinofuranoside (14)

To a solution of **11**[16] (1.95 g, 4.1 mmol) in dichloromethane (28.5 mL) at 0 °C was added thiophenol (0.6 mL, 5.8 mmol) dropwise. The reaction mixture was stirred at 0 °C for 15 min, then $BF_3\cdot Et_2O$ (3.4 mL, 26.8 mmol) was added and the resulting mixture was warmed gradually to room temperature. The reaction was stirred for 8 h at the same temperature, at the end of which time TLC indicated that it was finished. The reaction was quenched with triethylamine and the mixture was concentrated. The resulting residue was purified by column chromatography (6:1, petroleum–EtOAc) to give **12** (1.82 g, 80%) as a colorless syrup. To a solution of **12** (1.91 g, 3.45 mmol) in MeOH and CH_2Cl_2 (7:1, 40 mL) was added $NaOCH_3$ (32 mg) at room temperature. The mixture was stirred at the same temperature for 2 h, at the end of which time TLC indicated the reaction was complete. The solution was concentrated to dryness, and the resulting residue was purified by column chromatography (15:1, CH_2Cl_2–MeOH) to afford **14** (762 mg, 79%) as a colorless syrup. R_f 0.35 (8:1, CH_2Cl_2–MeOH); $[\alpha]_D^{20}$ +67.4 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, 1H, *J* 1.6 Hz, Ph), 7.45 (s, 1H, Ph), 7.20–7.28 (m, 3H, Ph), 5.40 (d, 1H, *J* 2.0 Hz, H-1), 4.14 (s, 2H, H-2, H-3), 4.09 (s, 1H, H-4), 3.81 (d, 1H, *J* 12.0 Hz, H-5a), 3.72 (d, 1H, *J* 12.0 Hz, H-5b); ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.7, 131.9, 129.1, 127.7, 91.9, 83.4, 81.9, 76.9, 61.1; HR ESI-MS: calcd for $C_{11}H_{14}O_4S$ $[M+Na]^+$, 265.0511, found m/z 265.0507.

4.3. *p*-Methylphenyl 1-thio-α-D-arabinofuranoside (15)[12a]

Using the same procedures as described for the preparation of **14**, methyl glycoside **11** (1.75 g, 3.68 mmol) was coupled first with *p*-methylphenylthiol (0.65 g, 5.2 mmol) catalyzed by $BF_3\cdot Et_2O$ (3.1 mL, 24.5 mmol) to afford **13** (1.62 g, 78%) as a colorless syrup. Subsequent debenzoylation of the obtained **13** (1.7 g, 3.0 mmol) with $NaOCH_3$ (29 mg) afforded **15** (645 mg, 84%) as a colorless syrup. The data for this compound matched those previously reported.[12a]

4.4. Phenyl 5-*O*-*tert*-butyldiphenylsilyl-1-thio-α-D-arabinofuranoside (16)

To a solution of **14** (123 mg, 0.51 mmol) in dry DMF (1.5 mL) was added imidazole (118 mg) followed by *t*-$BuPh_2SiCl$ (0.2 mL) at 0 °C and the resulting mixture was warmed gradually to room temperature. The mixture was stirred overnight at the same temperature, at the end of which time TLC indicated the reaction was complete. The mixture was diluted with EtOAc (15 mL), and then the reaction mixture was washed with water and brine. The organic layer was separated and dried over anhydrous Na_2SO_4, filtered, and concentrated. The resulting residue was purified by column chromatography (3:1, petroleum–EtOAc) to afford **16** (194 mg, 79%) as a pale syrup. R_f 0.3 (2:1, petroleum–EtOAc); $[\alpha]_D^{20}$ +132.7 (*c* 1.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65–7.69 (m, 4H, Ph), 7.50–7.52 (m, 2H, Ph), 7.35–7.46 (m, 6H, Ph), 7.26–7.34 (m, 3H, Ph), 5.60 (s, 1H, H-1), 4.31 (d, 1H, *J* 7.2 Hz, H-3), 4.21–4.25 (m, 2H, H-2, H-4), 3.87 (dd, 1H, *J* 2.8, 11.2 Hz, H-5a), 3.79 (dd, 1H, *J* 1.2, 11.2 Hz, H-5b), 1.05 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.7, 135.6, 132.0, 131.8, 130.1, 130.1, 129.1, 128.0, 127.9, 127.5, 92.8, 86.0, 81.2, 78.7, 64.0, 26.7, 19.1; HR ESI-MS: calcd for $C_{27}H_{32}O_4SSi$ $[M+Na]^+$, 503.1682, found m/z 503.1678.

4.5. Phenyl 2,3-di-*O*-benzoyl-5-*O*-*tert*-butyldiphenylsilyl-1-thio-α-D-arabinofuranoside (17)

To a stirred solution of **16** (113 mg, 0.24 mmol) in pyridine (2.3 mL) was added slowly BzCl (0.2 mL) at 0 °C and the resulting mixture was warmed gradually to room temperature. The reaction was stirred for 5 h at the same temperature, at the end of which time TLC indicated it was finished. The reaction was quenched with methanol (0.05 mL), diluted with CH_2Cl_2 (20 mL), and then the mixture was washed with water and brine. The organic layer was separated and dried over anhydrous Na_2SO_4, filtered, and concentrated. The resulting residue was purified by column chromatography (80:1, petroleum–EtOAc) to afford **17** (147 mg, 91%) as a pale yellow syrup. R_f 0.45 (40:1, petroleum–EtOAc); $[\alpha]_D^{20}$ +45.1 (*c* 2.0,

$CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (s, 1H, Ph), 8.11 (d, 1H, *J* 1.2 Hz, Ph), 7.99 (s, 1H, Ph), 7.97 (d, 1H, *J* 1.6 Hz, Ph), 7.71–7.72 (m, 4H, Ph), 7.58–7.64 (m, 4H, Ph), 7.48–7.53 (m, 2H, Ph), 7.37–7.42 (m, 4H, Ph), 7.29–7.35 (m, 6H, Ph), 5.78 (d, 1H, *J* 2.0 Hz, H-1), 5.73 (dd, 1H, *J* 2.0, 4.8 Hz, H-3), 5.68 (t, 1H, *J* 2.0 Hz, H-2), 4.64 (dd, 1H, *J* 4.4, 9.2 Hz, H-5a), 4.06 (d, 2H, *J* 4.4 Hz, H-4, H-5b), 1.06 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5, 165.3, 135.6, 135.6, 133.4, 132.1, 130.0, 129.9, 129.7, 129.7, 129.0, 128.5, 128.4, 127.7, 127.6, 91.0, 83.2, 82.4, 77.5, 63.5, 26.7, 19.3; HR ESI-MS: calcd for $[M+Na]^+$ $C_{41}H_{40}O_6SSi$ $[M+Na]^+$, 711.2207, found *m*/*z* 711.2205.

4.6. Phenyl 2-*O*-benzoyl-3,5-*O*-(di-*tert*-butylsilylene)-1-thio-α-D-arabinofuranoside (20)

Prepared from **18**[18] (416 mg, 1.09 mmol) and BzCl (0.46 mL) as described for the synthesis of **17**. The crude product was purified by column chromatography (100:1, petroleum–EtOAc) to afford **20** (498 mg, 93%) as a pale yellow oil. R_f 0.5 (30:1, petroleum–EtOAc); $[\alpha]_D^{20}$ +79.9 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, 1H, *J* 7.2 Hz, Ph), 8.09 (d, 1H, *J* 1.2 Hz, Ph), 7.46–7.62 (m, 5H, Ph), 7.26–7.33 (m, 3H, Ph), 5.53 (dd, 1H, *J* 4.8, 6.8 Hz, H-2), 5.47 (d, 1H, *J* 4.8 Hz, H-1), 4.43 (dd, 1H, *J* 4.8, 9.6 Hz, H-5a), 4.36 (dd, 1H, *J* 6.8, 9.6 Hz, H-3), 4.11–4.17 (m, 1H, H-4), 4.06 (t, 1H, *J* 9.6 Hz, H-5b), 1.06 (s, 9H, C(CH_3)$_3$), 1.01 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6, 133.9, 133.4, 131.7, 129.9, 128.9, 128.5, 127.6, 89.5, 81.4, 79.7, 73.5, 67.2, 27.4, 27.0, 22.6, 20.1; HR ESI-MS: calcd for $C_{26}H_{34}O_5SSi$ $[M+Na]^+$, 509.1788, found *m*/*z* 509.1785.

4.7. Phenyl 2-*O*-benzoyl-1-thio-α-D-arabinofuranoside (7)

To a solution of **20** (577 mg, 1.15 mmol) in THF (3.1 mL) was added TBAF (4.6 mL, 1.0 M in THF) at 0 °C and the resulting mixture was warmed gradually to room temperature. The reaction was stirred for 3 h at the same temperature, at the end of which time TLC indicated it was finished. The reaction was diluted with CH_2Cl_2 (20 mL), and then the reaction mixture was washed with saturated aqueous $(NH_4)_2SO_4$ and brine. The organic layer was separated and dried over anhydrous Na_2SO_4, filtered, and concentrated. The resulting residue was purified by column chromatography (2:1, petroleum–EtOAc) to afford **7** (295 mg, 72%) as a colorless syrup. R_f 0.35 (1:1, petroleum–EtOAc); $[\alpha]_D^{20}$ +173.5 (*c* 1.42, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02–8.04 (m, 2H, Ph), 7.53–7.56 (m, 3H, Ph), 7.44–7.50 (m, 2H, Ph), 7.29–7.37 (m, 3H, Ph), 5.76 (d, 1H, *J* 3.2 Hz, H-1), 5.16 (t, 1H, *J* 3.2 Hz, H-2), 4.29–4.38 (m, 2H, H-3, H-4), 3.98 (dd, 1H, *J* 3.2, 12.4 Hz, H-5a), 3.83 (dd, 1H, *J* 3.6, 12.4 Hz, H-5b); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 133.8, 132.1, 129.9, 129.1, 128.6, 127.8, 89.4, 87.2, 82.8, 76.2, 61.2; HR ESI-MS: calcd for $C_{18}H_{18}O_5S$ $[M+Na]^+$, 369.0767, found *m*/*z* 369.0768.

4.8. *p*-Methylphenyl 2-*O*-benzoyl-1-thio-α-D-arabinofuranoside (8)

To a stirred solution of **19**[19] (473 mg, 1.19 mmol) in dry pyridine (5.5 mL) was added BzCl (0.5 mL) at 0 °C and the resulting mixture was warmed gradually to room temperature. The reaction was stirred for 3 h at the same temperature, at the end of which time TLC indicated it was finished. The reaction was quenched with methanol (0.1 mL), diluted with CH_2Cl_2 (25 mL), and then the mixture was washed with water and brine. The organic layer was separated and dried over anhydrous Na_2SO_4, filtered, and concentrated. The resulting residue was purified quickly by a short column chromatography (100:1, petroleum–EtOAc) to afford 2-*O*-benzoylated product **21** (520 mg) as a pale yellow oil, which was contaminated with a trace of inseparable impurity. The obtained oil (520 mg) was dissolved in THF (3.1 mL), the resulting solution was cooled to 0 °C and then TBAF (4.6 mL, 1 M in THF) was added and the resulting mixture was warmed gradually to 15 °C. The reaction was stirred for 3 h at the same temperature, at the end of which time TLC indicated it was finished. The reaction was diluted with CH_2Cl_2 (20 mL), and then the mixture was washed with saturated aqueous $(NH_4)_2SO_4$ and brine. The organic layer was separated and dried over anhydrous Na_2SO_4, filtered, and concentrated. The resulting residue was purified by column chromatography (2:1, petroleum–EtOAc) to afford **8** (293 mg, 70% for two steps) as a colorless syrup. R_f 0.35 (1:1, petroleum–EtOAc); $[\alpha]_D^{20}$ +182.5 (*c* 1.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01–8.03 (m, 2H, Ph), 7.58–7.56 (m, 1H, Ph), 7.44–7.58 (m, 4H, Ph), 7.15 (d, 2H, *J* 8.0 Hz, Ph), 5.68 (d, 1H, *J* 3.2 Hz, H-1), 5.14 (t, 1H, *J* 3.2 Hz, H-2), 4.27–4.36 (m, 2H, H-5a, H-5b), 3.94–3.99 (m, 1H, H-3), 3.78–3.84 (m, 1H, H-4), 2.34 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 138.2, 133.8, 132.8, 129.8, 129.5, 128.7, 128.5, 89.6, 87.1, 82.7, 76.2, 61.2, 21.1; HR ESI-MS: calcd for $C_{19}H_{20}O_5S$ $[M+Na]^+$, 383.0924, found *m*/*z* 383.0921.

4.9. General procedure for the chemoselective glycosylations between trichloroacetimidate 4 and aryl thioglycosides 5–8

A mixture of the trichloroacetimidate **4** (1.2 or 2.3 mmol), the thioglycoside acceptor (0.10 mmol), and freshly activated 4 Å molecular sieves (120 mg) in dry CH_2Cl_2 (3.5 mL) was cooled to −20 °C. The suspension was stirred for 15 min, then a solution of TMSOTf (0.02 or 0.04 mmol) in CH_2Cl_2 (0.50 mL) was added dropwise and the resulting mixture was warmed slowly to 0 °C. The reaction was stirred for 0.5 h at the same temperature, at the end of which time TLC indicated it was finished. The reaction was quenched with a drop of Et_3N, diluted with CH_2Cl_2 (10 mL), filtered, and concentrated. The resulting residue was purified by column chromatography eluted with petroleum–EtOAc to afford the corresponding di- or trisaccharide thioglycosides.

*4.9.1. Phenyl 5-O-(2,3,5-tri-O-benzoyl-α-D-arabinofuranosyl)-2,3-di-O-benzoyl-1-thio-α-D-arabinofuranoside (**25**).* Prepared from **4** (74 mg, 0.12 mmol) and thioglycoside acceptor **5** (45 mg, 0.10 mmol). The crude product was purified by column chromatography (6:1, petroleum–EtOAc) to afford **25** as a colorless syrup (84 mg, 94%). R_f 0.4 (3:1, petroleum–EtOAc); $[\alpha]_D^{20}$ +36.0 (*c* 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, 2H, *J* 8.0 Hz, Ph), 7.98–8.04 (m, 6H, Ph), 7.94 (d, 2H, *J* 8.0 Hz, Ph), 7.54–7.62 (m, 4H, Ph), 7.43–7.52 (m, 5H, Ph), 7.36–7.41 (m, 4H, Ph), 7.22–7.29 (m, 7H, Ph), 5.81 (d, 1H, *J* 0.8 Hz, H-1′), 5.75 (d, 1H, *J* 5.2 Hz, H-2′), 5.73 (s, 1H, H-2), 5.62 (s, 1H, H-1), 5.58 (d, 1H, *J* 4.8 Hz, H-3), 5.44 (s, 1H, H-3′), 4.82 (dd, 1H, *J* 3.2, 12.0 Hz, H-5a′), 4.71–4.73 (m, 2H, H-4, H-4′), 4.65 (dd, 1H, *J* 4.8, 12.0 Hz, H-5b′), 4.28 (dd, 1H, *J* 4.4, 11.2 Hz, H-5a), 4.00 (dd, 1H, *J* 3.2, 11.2 Hz, H-5b); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.2, 165.7, 165.5, 165.3, 165.2, 133.7, 133.6, 133.5, 133.3, 133.0, 131.9, 130.0, 129.9, 129.8, 129.8, 129.7, 129.0, 128.9, 128.8, 128.5, 128.5, 128.3, 128.3, 127.6, 105.9, 91.3, 82.1, 82.0, 81.9, 81.2, 77.7, 77.3, 65.9, 63.6; HR ESI-MS: calcd for $C_{51}H_{42}SO_{13}S$ $[M+Na]^+$, 917.2238, found *m*/*z* 917.2243.

*4.9.2. p-Methylphenyl 5-O-(2,3,5-tri-O-benzoyl-α-D-arabinofuranosyl)-2,3-di-O-benzoyl-1-thio-α-D-arabinofuranoside (**26**).* Prepared from **4** (70 mg, 0.115 mmol) and thioglycoside acceptor **6** (45 mg, 0.097 mmol). The crude product was purified by column chromatography (6:1, petroleum–EtOAc) to afford **26** as a colorless syrup (75 mg, 85%). R_f 0.4 (3:1, petroleum–EtOAc); $[\alpha]_D^{20}$ +37.4 (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (dd, 2H, *J* 0.9 8.0 Hz, Ph), 7.98–8.04 (m, 6H, Ph), 7.95 (dd, 2H, *J* 0.9, 8.0 Hz, Ph), 7.55–7.61 (m, 2H, Ph), 7.43–7.51 (m, 7H, Ph), 7.35–7.41 (m, 4H, Ph), 7.24–7.29 (m, 4H, Ph), 5.74 (d, 1H, *J* 1.6 Hz, H-1′), 5.73 (d, 1H, *J* 2.4 Hz, H-2′), 5.72 (d, 1H, *J* 1.6 Hz, H-2), 5.62 (d, 1H, *J* 0.9 Hz, H-1), 5.58 (d, 1H, *J* 4.8 Hz, H-3), 5.44 (s, 1H, H-3′), 4.83 (dd, 1H, *J* 3.2, 11.6 Hz, H-5a′), 4.71–4.73 (m, 2H, H-4, H-4′), 4.65 (dd, 1H, *J* 4.8, 11.6 Hz, H-5b′), 4.28 (dd, 1H, *J*

4.4, 11.2 Hz, H-5a), 4.00 (dd, 1H, *J* 2.8, 11.2 Hz, H-5b), 2.29 (s, 3H, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 165.7, 165.5, 165.2, 165.2, 133.6, 133.5, 133.3, 132.6, 130.0, 129.8, 129.8, 129.8, 129.1, 128.5, 128.3, 106.0, 91.6, 82.1, 81.9, 81.4, 81.2, 77.6, 77.3, 66.0, 63.6, 21.1; HR ESI-MS: calcd for $C_{52}H_{44}O_{13}S$ $[M+Na]^+$, 931.2401, found *m*/*z* 931.2399.

*4.9.3. Phenyl 3,5-di-O-(2,3,5-tri-O-benzoyl-α-D-arabinofuranosyl)-2-O-benzoyl-1-thio-α-D-arabinofuranoside (**27**).* Prepared from **4** (121 mg, 0.2 mmol) and thioglycoside acceptor **7** (30 mg, 0.087 mmol). The crude product was purified by column chromatography (6:1, petroleum–EtOAc) to afford **27** as a colorless syrup (86.7 mg, 81%). R_f 0.5 (2:1, petroleum–EtOAc); $[\alpha]_D^{20}$ +34.5 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, 2H, *J* 7.2 Hz), 8.00–8.04 (m, 10H), 7.92 (d, 2H, *J* 7.2 Hz), 7.50–7.60 (m, 5H), 7.41–7.48 (m, 5H), 7.28–7.40 (m, 7H), 7.21–7.27 (m, 9H), 5.78 (s, 1H), 5.63 (d, 1H, *J* 0.8 Hz), 5.61 (t, 1H, *J* 1.6 Hz), 5.61 (d, 1H, *J* 3.6 Hz), 5.54 (d, 2H, *J* 1.6 Hz), 5.52 (d, 1H, *J* 4.4 Hz), 5.38 (s, 1H), 4.71–4.77 (m, 2H), 4.62–4.69 (m, 4H), 4.55–4.60 (m, 2H), 4.15 (dd, 1H, *J* 4.4, 11.6 Hz), 3.94 (dd, 1H, *J* 2.4, 11.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 166.0, 165.7, 165.6, 165.5, 165.2, 165.2, 134.1, 133.6, 133.5, 133.5, 133.5, 133.4, 133.0, 133.0, 131.6, 130.0, 130.0, 129.9, 129.8, 129.7, 129.7, 129.7, 129.0, 128.5, 128.5, 128.4, 128.3, 127.4, 106.0, 105.8, 90.9, 83.1, 82.0, 81.8, 81.7, 81.7, 81.6, 81.1, 77.7, 77.5, 65.5, 63.6, 63.6; HR ESI-MS: calcd for $C_{70}H_{58}O_{19}S$ $[M+Na]^+$, 1257.3185, found *m*/*z* 1257.3183.

*4.9.4. p-Methylphenyl 2,3,5-tri-O-benzoyl-1-thio-α-D-arabinofuranoside (**13**).* Prepared from **4** (120 mg, 0.198 mmol) and thioglycoside acceptor **8** (30 mg, 0.083 mmol). The crude product was purified by column chromatography (10:1, petroleum–EtOAc) to afford **13** as a colorless syrup (43 mg, 91%). The data for this compound matched those previously reported.[17]

4.10. The one-pot synthesis of the protected oligosaccharides 28 and 29

*4.10.1. Methyl 5-O-[5-O-(2,3,5-tri-O-benzoyl-α-D-arabinofuranosyl)-2,3-di-O-benzoyl-α-D-arabinofuranosyl]-2,3-di-O-benzoyl-α-D-arabinofuranoside (**28**).* A mixture of trichloroacetimidate donor **4** (70 mg, 0.115 mmol), thioglycoside acceptor **5** (44 mg, 0.098 mmol), and freshly activated 4 Å molecular sieves (115 mg) in dry CH_2Cl_2 (3.5 mL) was cooled to −20 °C. The suspension was stirred for 15 min and then a solution of TMSOTf (3 μL, 0.02 mmol) in CH_2Cl_2 (0.50 mL) was added dropwise and the resulting mixture was warmed slowly to 0 °C. The reaction was stirred for 1 h at the same temperature, at the end of which time TLC indicated the complete consumption of the starting materials. A solution of methyl glycoside **9** (22 mg, 0.059 mmol) in CH_2Cl_2 (1 mL) was added to the reaction mixture at 0 °C. After being stirred for 15 min at 0 °C, the resulting mixture were added NIS (25 mg, 0.112 mmol) and AgOTf (9 mg, 0.036 mmol). The reaction was stirred for 30 min at the same temperature, then quenched with Et_3N, diluted with CH_2Cl_2 (10 mL), filtered, and concentrated. The resulting residue was purified by column chromatography (4:1, petroleum–EtOAc) to afford protected trisaccharide **28** (48 mg, 64%) as a colorless syrup. R_f 0.45 (2:1, petroleum–EtOAc); $[\alpha]_D^{20}$ +1.25 (*c* 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98–8.05 (m, 10H), 7.90–7.93 (m, 4H), 7.36–7.59 (m, 15H), 7.22–7.29 (m, 6H), 5.66 (s, 1H), 5.64 (s, 1H), 5.64 (s, 1H), 5.63 (s, 1H), 5.57 (d, 1H, *J* 4.8 Hz), 5.51 (d, 1H, *J* 1.2 Hz), 5.47 (s, 1H), 5.41 (s, 1H), 5.12 (s, 1H), 4.83 (dd, 1H, *J* 3.2, 12.0 Hz), 4.71–4.74 (m, 1H), 4.63–4.67 (m, 2H), 4.41–4.44 (m, 1H), 4.24 (dd, 1H, *J* 4.4, 11.2 Hz), 4.20 (dd, 1H, *J* 4.4, 11.2 Hz), 3.98 (dd, 1H, *J* 2.8, 11.2 Hz), 3.94 (dd, 1H, *J* 2.8, 11.2 Hz), 3.44 (s, 3H, OC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.2, 165.7, 165.7, 165.6, 165.5, 165.2, 165.2, 133.4, 133.4, 133.2, 133.2, 133.0, 129.9, 129.9, 129.8, 129.8, 129.7, 128.5, 128.4, 128.3, 128.3, 106.8, 105.9, 105.8, 82.0, 81.9, 81.9, 81.7, 81.6, 81.6, 81.2, 77.8, 77.3, 66.0, 65.9, 63.6, 54.9; HR ESI-MS: calcd for $C_{65}H_{56}O_{20}$ $[M+Na]^+$, 1179.3257, found *m*/*z* 1179.3244.

*4.10.2. Methyl 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 (**29**).* Using the same procedures as described for the one-pot preparation of **28**, trichloroacetimidate donor **4** (120 mg, 0.198 mmol), and thioglycoside **7** (30 mg, 0.087 mmol) were coupled first by activation with TMSOTf (5.5 μL, 0.03 mmol), then the resulting trisaccharide thioglycoside **27** was glycosylated with the acceptor **9** (22 mg, 0.059 mmol) promoted by NIS (25 mg, 0.112 mmol) and AgOTf (9 mg, 0.036 mmol) to give a crude product, which was purified by column chromatograph (4:1, petroleum–EtOAc) to afford **29** (57 mg, 66%) as a colorless syrup. R_f 0.4 (2:1, petroleum–EtOAc); $[\alpha]_D^{20}$ +10.6 (*c* 0.85, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05–8.07 (m, 2H), 7.89–8.03 (m, 15H), 7.47–7.60 (m, 7H), 7.17–7.45 (m, 21H), 5.64 (d, 1H, *J* 5.6 Hz), 5.55 (s, 2H), 5.53 (s, 1H), 5.50 (d, 2H, *J* 1.2 Hz), 5.47 (d, 1H, *J* 4.8 Hz), 5.44 (d, 1H, *J* 1.2 Hz), 5.41 (d, 2H, *J* 4.0 Hz), 5.11 (s, 1H), 4.77 (dd, 1H, *J* 3.2, 11.6 Hz), 4.73 (dd, 1H, *J* 5.6, 9.6 Hz), 4.53–4.64 (m, 7H), 4.37–4.39 (m, 1H), 4.18 (dd, 1H, *J* 4.4, 11.2 Hz), 4.09–4.13 (m, 1H), 3.93 (dt, 1H, *J* 2.4, 11.2 Hz), 3.44 (s, 3H, OC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.2, 166.0, 165.7, 165.6, 165.5, 165.5, 165.4, 165.1, 164.9, 133.4, 133.4, 133.3, 132.9, 132.9, 129.9, 129.9, 129.8, 129.8, 129.7, 129.7, 129.2, 129.1, 129.0, 128.5, 128.5, 128.4, 128.4, 128.3, 128.2, 128.2, 106.7, 106.0, 105.8, 105.7, 82.9, 82.1, 82.0, 81.8, 81.7, 81.6, 81.4, 81.3, 77.9, 77.7, 77.2, 77.2, 65.7, 65.5, 63.7, 63.6, 54.9; HR ESI-MS: calcd for $C_{84}H_{72}O_{26}$ $[M+Na]^+$, 1519.4204, found *m*/*z* 1519.4192.

4.11. Methyl 5-*O*-[5-*O*-(α-D-arabinofuranosyl)-α-D-arabinofuranosyl]-α-D-arabinofuranoside (2) and methyl 5-*O*-[3,5-di-*O*-(α-D-arabinofuranosyl)-α-D-arabinofuranosyl]-α-D-arabinofuranoside (3)

To a solution of **28**/**29** (0.04 mmol) in MeOH and CH_2Cl_2 (7:1, 1.03 mL) was added $NaOCH_3$ (2 mg). After the reaction was stirred for 2 h at room temperature, TLC analysis indicated completion. The solution was concentrated to dryness. The resulting residue was purified by column chromatography (3:1, CH_2Cl_2–MeOH) to afford **2**/**3** as a colorless syrup in a yield of 80% for **2** and 85% for **3**, respectively. Their analytical data (^{1}H and ^{13}C NMR, MS) were identical with those previously reported.[12a]

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