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A One-Pot Strategy for Synthesis of 5-*O*-(α-D-Arabinofuranosyl)-6-*O*-(*β*-D-galactofuranosyl)-D-galactofuranose Present in Motif E of the *Mycobacterium tuberculosis* Cell Wall

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Abstract: 5-*O*-(α-D-Arabinofuranosyl)-6-*O*-(*β*-D-galactofuranosyl)-D-galactofuranose **6** present in motif E of the *Macobacterium tuberculosis* cell wall has been regio- and stereospecifically synthesized using 3-*O*-benzoyl-1,2-*O*-isopropylidine-α-D-galactofuranose (**10**) as the glycosyl acceptor by the trichloroacetamidate method in a one-pot manner. The diol glycosyl acceptor **10** was smoothly derived from 1,2:5,6-di-*O*-isopropylidene-α-D-galactofuranose (**8**) by 3-*O*-benzoylation and then selective 5,6-*O*-deacetonation. The preparation of **8** was greatly improved by increasing the ratio of DMF to acetone and using a solid-supported catalyst.

Although enormous efforts have been dedicated to developing anti-infective drug molecules, tuberculosis still constitutes the leading killer disease in the world.[1] Over one third of the world's population is estimated to be infected with *Macobacterium* (*M.*) *tuberculosis*, and more than three million deaths occur every year due to tuberculosis.[2] With the tuberculosis strains becoming drug-resistant,[3] the situation is bound to get more serious.

M. tuberculosis, the causative agent of tuberculosis, belongs to the mycobacteria.[4] An impressive feature of this genus of bacteria is that they synthesize cell wall polysaccharides containing predominantly furanose residues,[4] whereas a similar phenomenon has never been found in humans. For *M. tuberculosis*, the major polysaccharides formed in its cell wall are an arabinogalactan (AG) and a lipoarabinomannan (LAM) in which all of the galactose and arabinose residues are present in the furanose form.[4] The organism's ability to make these polymers is critical to its survival; therefore, interfering with the biosynthesis of these polysaccharides is an approach for identifying anti-TB drugs.[5] It has been demonstrated recently that one of the drugs used to treat tuberculosis (ethambutol) for the last 35 yeas actually acts by inhibiting the biosynthesis of arabinan portions of LAM and AG.[6]

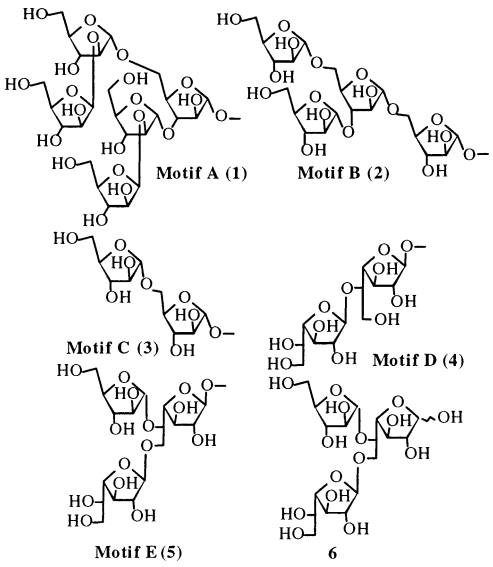

FIGURE 1. Structures of motifs A, B, C, D, and E and the synthesized trisaccharide **6** present in motif E.

Five major motifs called A, B, C, D, and E, which are linked to the terminal ends of AG and/or LAM, have been isolated and characterized[7] as shown in Figure 1. These oligosaccharides may play an important role in the survival and pathogenicity of the organism. Since these oligosaccharides are not present in humans, they tend to be highly antigenic in the human immune system. Motif E is expected to play a more special biological role in *M. tuberculosis* and may be found to be more useful in the development of applications for the treatment of lethal tuberculosis, because among the motifs A−E, motif E is structurally more distinct. Motifs A−C contain only arabinofuranose residures, motif D has exclusively galactofuranose, while motif E contains the both arabinofuranose and galactofuranose residues in its structural framework. Moreover, the oligosaccharide structure of motif E is more sterically complex because both the 5- and 6-positions of the reducing galactofuranose component are linked with arabinofuranosyl and galactofuranosyl residues, respectively.[7]

Providing sufficient quantities of a sample is a basic prerequisite for detailed studies on a compound's fundamental biochemical properties and possible biological functions. However, in the carbohydrate field, these efforts are often frustrated by the difficulty of synthesiz-

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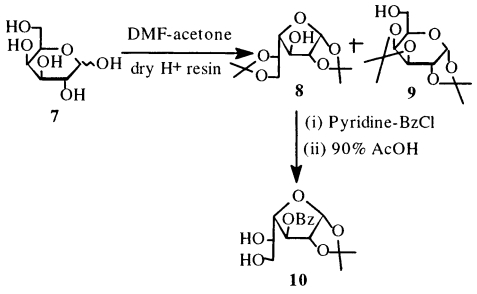
ing saccharides. The synthesis of complex oligosaccharide sequences containing two to six sugar units, both in solution and on the solid phase, presents a major challenge in organic chemistry.[8−11] Unlike peptides and nucleic acids, oligosaccharides are typically branched rather than linear. In addition, the monosaccharide units can be connected by α or *β* linkages. Furthermore, oligosaccharide synthesis requires multiple selective protection and deprotection steps. Although over the past few decades considerable progress[12] has been made in this field, there still is no general solution for oligosaccharide synthesis. Maybe, owing to this structural complexity, the preparation of saccharides will never achieve the same level of ease as the preparation of peptides and nucleic acids. But special methods that are suitable for specific types of oligosaccharide synthesis can be developed.

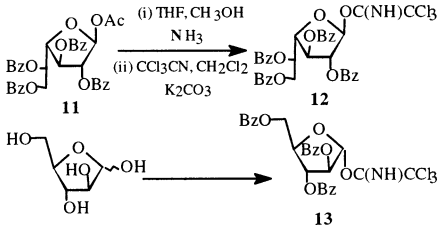
There has been much interest in the synthesis of the components of the *M. tuberculosis* cell wall polysaccharides.[13,14] The preparation of a motif E trisaccharide derivative has been finished recently by Gurjar and coworkers.[14] Their process is a typical example of oligasaccharide synthesis involving tediously selective protection and deprotection steps. In complex oligosaccharide assembly, the synthetic procedures can be substantially simplified by carefully choosing unprotected or partially protected sugars as glycosyl acceptors coupled with use of regio- and stereoselective glycosylation reactions.[15] Also, synthetic efficiency can often be greatly improved by carefully designing reactions to be carried out in one pot. Herein, we report a one-pot strategy for the preparation of the trisaccharide 5-*O*-(α-D-arabinofuranosyl)-6-*O*-(*β*-D-galactofuranosyl)-D-galactofuranoside **6** (Figure 1) present in motif E of the *M. tuberculosis* cell wall by using 3-*O*-benzoyl-1,2-*O*-isopropylidine-α-D-galactofuranose (**10**) as the glycosyl acceptor via regio- and stereospecific trichloroacetamidate-mediated *O*-glycosylations.

In our synthesis, 1,2:5,6-di-*O*-isopropylidene-α-D-galactofuranose **8** is a key starting material. The compound **8** could been obtained from D-glucose derivatives in three or six steps[16] or from D-galactose in a maximum 22% yield.[17] Recently, Rauter's group found that by using zeolite HY as the catalyst, the furanose diketal **8** was formed in 40% yield, together with the pyranose diketal

SCHEME 1. Synthesis of the Glycosyl Acceptor 10



SCHEME 2. Preparation of the Glycosyl Donors 12 and 13



9, obtained only in 20% yield, and this significantly improved the preparation of **8**.[18] Some reports showed that high temperature is a factor known to favor furanose formation in solutions of reducing sugars.[19] Inspired by this, we increased the ratio of DMF to acetone to 2 in our synthesis of **8**, attempting to increase the reaction reflux temperature in order to obtain more furanose diketal **8**. To simplify the purification procedure, an anhydrous H^+ form cation-exchange resin called Dry Hydrogen Resin was used as the solid supported catalyst (Scheme 1). Furthermore, 4 Å molecular sieves were used in our reaction as the water scavenger in order to increase the yield. As a result of our reaction conditions, the ratio of 1,2:5,6-di-*O*-isopropylidene-α-D-galactofuranose to 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose in the reaction product can reach more than 4, and the desired 1,2:5,6-di-*O*-isopropylidene-α-D-galactofuranose can be easily crystallized from the resultant residue in 50% yield. Benzoylation of **8** in pyridine with BzCl at room temperature followed by selective 5,6-*O*-deacetonation with 90% AcOH at 40 °C afforded the diol glycosyl acceptor **10**.

The glycosyl donor **12** was synthesized from 1-*O*-acetyl-2,3,5,6-tetra-*O*-benzoyl-D-galactofuranose (**11**)[20] by selective 1-*O*-deacetylation with ammonia in THF−CH_3OH and then trichloroacetimidation with trichloroacetonitrile in the presence of K_2CO_3 (Scheme 2). The structure of **12** was confirmed by ^{1}H NMR spectral analysis. The $J_{1,2}$ is small (0−2 Hz) for the *β*-anomers[21] and larger (4−5 Hz) for the α-anomers.[21] A second glycosyl donor **13** was prepared from D-arabinose according to the reported procedure.[22]

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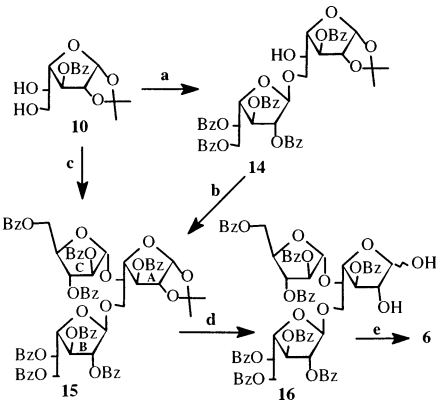
SCHEME 3. Synthesis of the Trisaccharide 6 Present in Motif E[a]



[a] Key: (a) **12**, TMSOTf (cat.), CH_2Cl_2, MS 4 Å powder, −45 °C to rt, 1.5 h, 91%; (b) **13**, TMSOTf (cat.), CH_2Cl_2, MS 4 Å powder, rt, 1 h, 87%; (c) (i) **12**, TMSOTf (cat.), CH_2Cl_2, MS 4 Å powder, −45 °C to rt, 1.5 h; (ii) **13**, rt, 1 h, 71% (over the two steps); (d) 10:1 $HCCl_3$−CF_3COOH, rt, 2 h; (e) an ammonia-saturated CH_3OH, rt, 72 h, 86% (over the d and e).

Condensation of **10** and **12** with TMSOTf as catalyst and 4 Å molecular sieves in CH_2Cl_2 at −45 °C regio- and stereospecifically afforded the disaccharides **14** in excellent yields (91%) (Scheme 3).[23] No (1 → 5)-linked disaccharide was detected both from ^{1}H NMR and TLC. The structure of **14** was unambiguously confirmed by ^{1}H NMR data. The characteristic resonances due to the anomeric protons H-1 and H-1′ were located as a doublet at 5.91 ppm with $J_{1,2} = 4.1$ Hz and as a singlet at 5.35 ppm, respectively. Coupling of **14** and **13** with TMSOTf as catalyst and 4 Å molecular sieves in CH_2Cl_2 at room temperature gave the desired trisaccharide **15** in 87% yield. The three anomeric proton signals in the ^{1}NMR spectrum of **15** were located as a doublet at 5.89 ppm with $J_{1,2} = 4.1$ Hz, and singlets at 5.87 and 5.36 ppm, respectively, whereas the ^{13}C NMR specrtum revealed[24] anomeric carbons at 105.25, 105.70, and 106.33 ppm. Encouraged by the smoothly coupling reaction results, a one-pot procedure for synthesis of the trisaccharide **15** was carried out. Thus, treatment of **10** and **12** with TMSOTf as catalyst and 4 Å molecular sieves in CH_2Cl_2 at −45 °C, followed by addition of **13** afforded compound **15** in 71% yield. De-isopropylidenation of **15** in 10:1 $CHCl_3$−CF_3COOH (v/v) at room temperature gave the compound **16**, which after purification was treated with an ammonia-saturated CH_3OH to afford the free trisaccharide **6** in 86% yield (over the two steps). The signals of the ^{1}H NMR spectrum of **6** were not distinguishable. However, the chemical shifts of anomeric carbons of **6** were at 107.5, 107.5, and 108.6 ppm, confirming the structure of **6**. Further analysis by ESI-MS spectrometry gave an $(M + H^+)^+$ signal at 475.4 indicating that **6** was a trisaccharide (calcd 474.415).

In conclusion, a highly efficient and concise synthesis of the complex trisaccharide **6** present in motif E of the *M. tuberculosis* cell wall was achieved by using partially protected 3-*O*-benzoyl-1,2-*O*-isopropylidine-α-D-galactofuranose (**10**) as the glycosyl acceptor through the regio- and stereospecific glycosylations in a one-pot reaction. The sole use of acyl groups as protecting groups in the synthesis further simplified the procedure. The easy preparation of this oligosaccharide present in the *M. tuberculosis* cell wall should promote studies on *M. tuberculosis* and the treatment of tuberculosis.

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Experimental Section

Melting points were determined with a Mel-Temp apparatus. Optical rotations were measured at at 25 °C in the stated solvent. ^{1}H NMR (400 Hz) and ^{13}C NMR (100 Hz) spectra were recorded in $CDCl_3$ solutions at room temperature unless otherwise specified. Chemical shift (δ) values are given in ppm; coupling constants (J) are in Hz. All assignments were supported by 2D homonuclear chemical-shift correlation spectroscopy (gCOSY). Mass spectra were recorded on an autospec mass spectrometer using ESI technique to introduce the sample. Thin-layer chromatography (TLC) was performed on silica gel HF_{254} with detection by charring with 30% (v/v) H_2SO_4 in MeOH or in some cases by a UV detector. Column chromatography was conducted by elution of a column (10 240 mm, 18 300 mm, 35 400 mm) of silica gel (100−200 mesh) with EtOAc-petroleum ether (60−90 °C) as the eluent. Solutions were concentrated at <60 °C under diminished pressure. Dry solvents were distilled over CaH_2 and stored over molecular sieves.

1,2:5,6-Di-*O*-isopropylidene-α-D-galactofuranose (8). A solution of D-galactose (10 g, 55.56 mmol) in dry and hot dimethylformamide (400 mL) was added to stirred acetone (200 mL), which contained an anhydrous H^+ form cation-exchange resin called Dry Hydrogen Resin (15 g) and 4 Å molecular sieves (8 g). The reaction mixture was stirred under reflux for 48 h. Solid material was filtered off, and the solution was concentrated to a syrup under vacuum. TLC (3:1 petroleum ether−EtOAc) showed that the ratio of 1,2;5,6-di-*O*-isopropylidene-α-D-galactofuranose to 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose in the resultant residue was more than 4. After the residue was decolored and, to some degree, purified by subjection to a flash chromatography with 3:1 petroleum ether−EtOAC as eluent, compound **8** (7.2 g, 50%) was crystallized from petroleum ether−EtOAc as white crystals: mp 96.5−98 °C (lit.[17] mp 97−98 °C); $[\alpha]_D$ −33.8 (*c* 0.8, CH_3OH) (lit.[17] $[\alpha]_D$ −34).

3-*O*-Benzoyl-1,2-*O*-isopropylidene-α-D-galactofuranose (10). To a solution of **8** (4.5 g, 17.3 mmol) in pyridine (20 mL) was added benzoyl chloride (2.9 mL, 25 mmol) at 0 °C. The reaction mixture was slowly warmed to room temperature and stirred for 5 h. TLC (4:1 petroleum ether−EtOAc) indicated that the reaction was complete. The mixture was poured into ice-cold water and extracted with CH_2Cl_2. The organic layer was washed with 1 N HCl and satd $NaHCO_3$. The solution was concentrated, and the resultant residue was directly treated with 90% AcOH (50 mL) at 40 °C. After 4 h, the solution was diluted with toluene, and the mixture was concentrated under vacuum. The residue was purified by flash chromatography (2:1 petroleum ether−EtOAc) to give **10** as a syrup (5.01 g, 90%): $[\alpha]_D$ +40.2 (*c* 0.65, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04−7.44 (m, 5 H), 6.07 (d, 1 H, $J = 4.1$ Hz), 5.34 (d, 1 H, $J = 1.6$ Hz), 4.85 (d, 1 H, $J = 4.1$ Hz), 4.30 (dd, 1 H, $J = 1.6$, 8.2 Hz), 4.03 (m, 1 H), 3.89 (dd, 1 H, $J = 4.8$, 11.9 Hz), 3.82 (dd, 1 H, $J = 4.6$, 11.9 Hz), 1.59 (s, 3 H), 1.36 (s, 3 H). Anal. Calcd for $C_{16}H_{20}O_7$: C, 59.25, H, 6.22. Found: C, 59.41, H, 6.15.

2,3,5,6-Tetra-*O*-benzoyl-β-D-galactofuranosyl Trichloroacetimidate (12). A solution of 1-*O*-acetyl-2,3,5,6-tetra-*O*-benzoyl-D-galactofuranose (**11**)[20] (3.6 g, 5.64 mmol) in 1.5 N NH_3 solution of 3:1 THF−CH_3OH (80 mL) was kept at room temperatur for 3 h, at the end of which time TLC (3:1 petroleum ether−EtOAc) showed that the reaction was complete and the solution was concentrated. The resultant residue without purification was dissolved in dry CH_2Cl_2 (50 mL), and then trichloroacetonitrile (2.6 mL, 12.4 mmol) and anhydrous K_2CO_3 (3 g,

21.8 mmol) were added. The reaction mixture was stirred at room temperature for 12 h, and solid material was filtered off. Concentration of the filtrate, followed by purification on a silica gel column with 3:1 petroleum ether−EtOAc as eluent, gave the monosaccharide donor **12** (3.42 g, 82%): $[\alpha]_D$ +28.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (s, 1 H), 8.09−7.26 (m, 20 H), 6.70 (s, 1 H), 6.13 (m, 1 H), 5.78 (d, 1 H, J = 4.3 Hz), 5.75 (s, 1 H), 4.86 (t 1 H, J = 4.3 Hz), 4.78−4.75 (m, 2 H). Anal. Calcd for $C_{36}H_{28}O_{10}NCl_3$: C, 58.35, H, 3.81. Found: C, 58.56, H, 3.74.

6-*O*-(2,3,5,6-Tetra-*O*-benzoyl-*β*-D-galactofuranosyl)-3-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-galactofuranose (14). A solution of **10** (1.7 g, 5.25 mmol) and **12** (3.9 g, 5.25 mmol) in dry CH_2Cl_2 (50 mL) was stirred with activated 4 Å molecular sieves (2 g) at room temperature under an atmosphere of nitrogen for 20 min. Then the reaction mixture was cooled to −45 °C, and TMSOTf (12 μL, 0.06 mmol) was added. After 30 min, the temperature was allowed to rise to room temperature, and the reaction mixture was stirred for further 1 h, at the end of which time TLC (2.5:1 petroleum ether−EtOAc) indicated that the reaction was complete. The reaction mixture was neutralized with triethylamine and filtered, and the filtrate was concentrated. The resultant residue was subjected to the column chromatography with 2.5:1 petroleum ether−EtOAc as eluent to afford the disaccharide **14** (4.32 g, 91%): $[\alpha]_D$ −4.2 (*c* 0.73, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99−7.17 (m, 25 H), 6.04 (m, 1 H), 5.91 (d, 1 H, J = 4.1 Hz), 5.53 (d, 1 H, J = 5.1 Hz), 5.45 (s, 1 H), 5.37 (d, 1 H, J = 2.2 Hz), 5.35 (s, 1 H), 4.75−4.65 (m, 4 H), 4.24 (dd, 1 H, J = 2.2, 6.7 Hz), 4.12 (m, 1 H), 3.93 (dd, 1 H, J = 5.4, 10.5 Hz), 3.66 (dd, 1 H, J = 5.4, 10.5 Hz), 1.52 (s, 3 H), 1.27 (s, 3 H). Anal. Calcd for $C_{50}H_{46}O_{16}$: C, 66.51, H, 5.13. Found: C, 66.29, H, 5.26.

5-*O*-(2,3,5-Tri-*O*-benzoyl-α-D-arabifuranosyl)-6-*O*-(2,3,5,6-tetra-*O*-benzoyl-*β*-D-galactofuranosyl)-3-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-galactofuranose (15). A solution of **14** (1.8 g, 1.99 mmol) and 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranosyltrichloroacetamidate (**13**)[22] (1.5 g, 2.5 mmol) in anhydrous CH_2Cl_2 (40 mL) was stirred with activated 4 Å molecular sieves at room temperature for 20 min, and then TMSOTf (8 μL, 0.04 mmol) was added. The mixture was stirred for 1 h, at the end of which time TLC (2.5:1 petroleum ether−EtOAc) indicated that the reaction was complete. The reaction mixture was neutralized with triethylamine and filtered, and the filtrate was concentrated. Purification of the resultant residue by column chromatography with 2.5:1 petroleum ether−EtOAc as eluent gave **15** (2.30 g, 87%): $[\alpha]_D$ −18.6 (*c* 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04−7.24 (m, 40 H, 8 Bz*H*), 6.17 (m, 1 H, H^B-5), 5.89 (d, 1 H, $J_{1,2}$ = 4.1 Hz, H^A-1), 5.87(s, 1 H, H^C-1), 5.62 (d, 1 H, $J_{3,4}$ = 2.9 Hz, H^A-3), 5.60−5.58 (m, 2 H, H^C-2, 3), 5.54 (d, 1 H, $J_{3,4}$ = 4.8 Hz, H^B-3), 5.49 (s, 1 H, H^B-2), 5.36 (s, 1H, H^B-1), 4.86 (m, 1 H, H^B-4), 4.78−4.69 (m, 5 H, H^B-6, 6′, H^C-4, 5, 5′), 4.66 (d, 1 H, $J_{1,2}$ = 4.1 Hz, H^A-2), 4.43 (m, 1 H, H^A-5), 4.33 (dd, 1 H, H^A-4), 4.15 (dd, 1 H, H^A-6), 3.76 (dd,1 H, H^A-6′), 1.63 (s, 3 H, C(CH_3)$_2$), 1.31 (s, 3 H, C(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.09, 166.05, 165.76, 167.70, 165.58, 165.39, 165.23, 165.20, 113.29, 106.33, 105.70, 105.25, 86.04, 84.90, 82.24, 81.99, 81.73, 80.97, 77.96, 77.88, 77.32, 74.43, 70.44, 67.19, 63.86, 63.80, 26.68, 26.17. Anal. Calcd for $C_{76}H_{66}O_{23}$: C, 67.75, H, 4.94. Found: C, 67.98, H, 5.11.

A One-Pot procedure for Preparation of the Trisaccharide 15. A solution of **10** (0.6 g, 1.85 mmol) and **12** (1.4 g, 1.90 mmol) in dry CH_2Cl_2 (30 mL) was stirred with activated 4 Å molecular sieves (2 g) at room temperature under an atmosphere of nitrogen for 20 min. Then the reaction mixture was cooled to −45 °C, and TMSOTf (10 μL, 0.05 mmol) was added. After 30 min, the temperature was allowed to rise to room temperature, and the reaction mixture was stirred for a further 1 h, at the end of which time TLC (2.5:1 petroleum ether−EtOAc) indicated that the reaction was complete. To the stirred reaction mixture was added **13** (1.6 g, 2.6 mmol) under an atmosphere of nitrogen at room temperature. The reaction mixture was stirred for 1 h, at the end of which time TLC (2.5:1 petroleum ether−EtOAc) indicated that the reaction was complete. The reaction mixture was neutralized with triethylamine and filtered, and the filtrate was concentrated. Purification of the resultant residue by column chromatography with 2.5:1 petroleum ether−EtOAc as eluent gave **15** (1.7 g, 71%).

5-*O*-(α-D-Arabifuranosyl)-6-*O*-(*β*-D-galactofuranosyl)-D-galactofuranose (6). Compound **15** (1.6 g, 1.19 mmol) was treated with 10:1 $CHCl_3$−CF_3COOH (30 mL) at room temperature for 2 h, at the end of which time TLC (1:1 petroleum ether−EtOAc) indicated that the reaction was complete, the solution was diluted with toluene (100 mL), and the mixture was concentrated under vacuum. The residue was purified by flash chromatography (1:1 petroleum ether−EtOAc) to give **16** which was dissolved in an ammonia-saturated CH_3OH (30 mL). After 72 h at room temperature, the reaction mixture was concentrated, the residue was washed with CH_2Cl_2 four times and dried under high vacuum to give **6** (485 mg, 86% for over two steps): $[\alpha]_D$ −15.4 (*c* 0.8, MeOH); ^{13}C NMR (100 MH_Z, D_2O) δ 108.6, 107.5, 107.5, 83.8, 82.8, 80.9, 80.9, 80.9, 76.7, 75.9, 70.7, 70.7, 62.7, 62.7, 62.7, 61.1, 61.1; ESI-MS 475.4 $(M + H^+)^+$, calcd for $C_{17}H_{30}O_{15}$ 474.415. Anal. Calcd for $C_{17}H_{30}O_{15}$: C, 43.04; H, 6.37. Found: C, 43.52; H, 6.61.

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Supporting Information Available: ^{1}H NMR spectra of **10**, **12**, **14**, and **15**, ^{1}H−^{1}H and ^{1}H−^{13}C 2D-correlational NMR spectra of **15**, and ^{13}C NMR spectra of **6** and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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