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Note

The core trisaccharide of α-L-arabinofuranan: synthesis of methyl 3,5-di-*O*-α-L-arabinofuranosyl-α-L-arabinofuranoside

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Arabinans, major components of cell-wall and intercellular-matrix polysaccharides, are polymers of 1 → 5-linked α-L-arabinofuranosyl residues branched through position 2 or 3, or both. Thus, although the substituents may be either single or multiple α-L-arabinofuranosyl residues, the core structure of branched arabinan is **1** [1]. We have reported the synthesis of the three possible regioisomeric methyl α-L-arabinofuranobiosides, namely methyl *O*-(α-L-arabinofuranosyl)-(1 → 2)-, -(1 → 3)-, and -(1 → 5)-α-L-arabinofuranoside, and presented complete assignments of their ^{1}H NMR spectra [2]. In addition to these biosides, the core-trisaccharide unit was needed for further study of the structure of arabinan, and for investigations of the precise specificity of α-L-arabinofuranosidases. Accordingly, we synthesized the trisaccharide, 3,5-di-*O*-α-L-arabinofuranosyl-α-L-arabinofuranose, as its methyl glycoside (**2**). This Note records the details of the synthesis and the NMR spectra of **2**.

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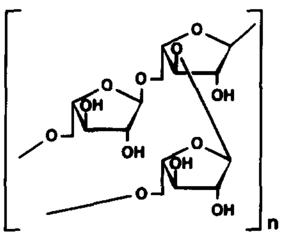

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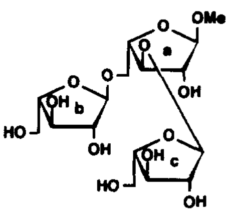

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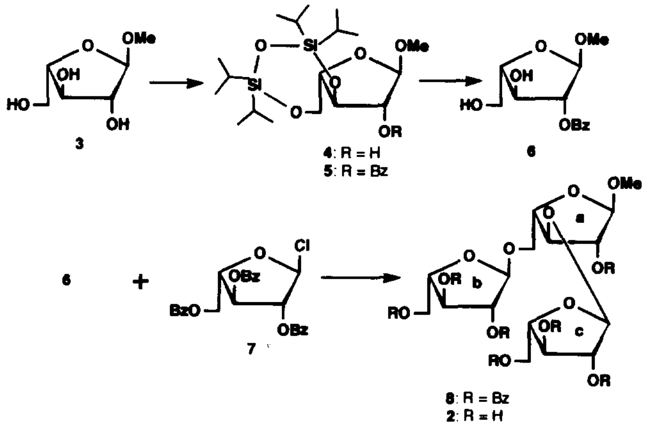

Our strategy involved the glycosylation of the 3- and 5-hydroxy groups of methyl 2-*O*-benzoyl-α-L-arabinofuranoside (**6**) with 2,3,5-tri-*O*-benzoyl-α-L-arabinofuranosyl chloride (**7**) [3]. The acceptor **6** was recently synthesized in our laboratory, in 5 steps with a 33% overall yield, from methyl 2,3,5-tri-*O*-benzoyl-α-L-arabinofuranoside via 3,5-di-*O*-benzoyl-1,2-(α-methoxybenzylidene)-β-L-arabinofuranose [2]. However, we later became aware of the work of Czernecki and Le Diguarher [4], who used 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane to simultaneously protect the hydroxyl groups on C-3 and C-5 of the L-arabinofuranosyl residue with high selectivity and high yield. Therefore, we also employed this reagent to differentiate the 2-OH from the 3-OH and 5-OH of methyl α-L-arabinofuranoside (**3**). On treatment with the reagent (1.04 equiv) in pyridine **3** gave the 3,5-silylated compound **4**, which was benzoylated to give **5**. Desilylation of **5** furnished the L-arabinofuranosyl acceptor **6** in 76% overall yield. This synthetic route is very efficient in comparison with our previous method.

The glycosylation of the acceptor **6** with 2.5 equiv of the L-arabinofuranosyl donor **7** was conducted in dry dichloromethane in the presence of silver trifluoromethanesulfonate, *s*-collidine, and 4A molecular sieves, because it has been shown that these glycosylation conditions provide high selectivity for the 1,2-*trans* (α in the present case) product [2,3,5]. The crude product was crystallized twice from chloroform–

Table 1
NMR data for methyl 3,5-di-*O*-α-L-arabinofuranosyl-α-L-arabinofuranoside (**2**)[a]

Residue	H-1	H-2	H-3	H-4	H-5	H-5′	OMe
	^{1}H Chemical shifts[b] (coupling constants)[c]						
a	4.97 s	4.23 br d(1.3)	4.08[d]	4.27 m(3.0, 2.9)	3.83[d]	3.95[d]	3.42
b	5.09 d(1.2)	4.14 dd(1.5, 3.4)	3.95[d]	4.11 m(3.4, 5.9)	3.72 dd(5.8, 12.4)	3.82[d]	
c	5.15 d(1.2)	4.12 dd(1.5, 3.4)	3.95[d]	4.03 m(3.3, 6.0)	3.72 dd(5.6, 12.3)	3.82[d]	
	^{13}C Chemical shifts[e] (coupling constants[b])						
	C-1	C-2	C-3	C-4	C-5		OMe
a	111.3	81.8	85.1	84.5	69.3		57.6
b	110.2	83.8	79.4	86.8[f]	64.0[g]		
c	110.0	84.0	79.4	86.7[f]	63.9[g]		

[a] Determined in D_2O with soidum 3-(trimethylsilyl)-2,2,3,3-d_4-propionate as internal standard.
[b] Measured at 500 MHz.
[c] Observed first-order splittings.
[d] These signals were overlapped with other signals.
[e] Measured at 125 MHz.
[f,g] These assignments may be reversed.

methanol to give the trisaccharide derivative **8**. Flash chromatography of the residue from the mother liquor provided more **8**, increasing the yield in the glycosylation to 63%. The stereochemistry of the product **8** was confirmed by its ^{1}H NMR spectrum, which showed singlet signals at δ 5.10 (H-1a), 5.38 (H-1c), and 5.56 (H-1b), as expected for anomeric protons having H-1,2 coupling constants < 1 Hz, characteristic of 1,2-*trans* anomers. The C-1 chemical shifts (C-1a, 107.0; C-1b, 106.0; C-1c, 105.6 ppm) of the L-arabinofuranosyl moiety on the reducing end were assigned by comparison with the ^{13}C NMR data for the related disaccharides [2].

The glycosylation product **8** was debenzoylated to give the target trisaccharide **2**. A complete listing of the ^{1}H and ^{13}C NMR data for this trisaccharide is presented in Table 1. The proton signals at δ 4.97, 5.09, and 5.15 were assigned to H-1a, H-1b, and H-1c, respectively, on the basis of the values previously reported for the related disaccharides [2]; other ^{1}H assignments were made from COSY and HOHAHA spectra. The ^{13}C signals were assigned with the aid of ^{1}H–^{13}C COSY experiments, and by comparison with the ^{13}C data for the disaccharides.

1. Experimental

General.—The instrumental and chromatographic procedures used were those described in the previous paper [2].

Methyl 3,5-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-α-L-arabinofuranoside (**4**). —A mixture of methyl α-L-arabinofuranoside (**3**, 500 mg, 3.05 mmol) [6] and 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (Aldrich) (1.00 g, 3.17 mmol) [4,7] in dry pyridine (10 mL) was stirred at room temperature for 2 h, and concentrated to remove the solvent. The residue was partitioned between EtOAc (50 mL) and water (40 mL). The

EtOAc layer was washed with 5% aq HCl, aq $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on silica gel (100 g, 4:1 hexane–EtOAc) to give **4** (1.23 g, 98%); $[\alpha]_D$ $-29.3°$ (*c* 4.14, $CHCl_3$); R_f 0.37 in 4:1 hexane–EtOAc; ^1H NMR ($CDCl_3$): δ 1.01–1.09 [m, 28 H, $4 \times (CH_3)_2CH$], 3.40 (*s*, 3 H, OCH_3), 3.87 (m, 1 H, H-4), 3.97 (m, 2 H, H-5,5′), 4.15–4.17 (m, 2 H, H-2,3), and 4.78 (d, 1 H, *J* 2.0 Hz, H-1); ^{13}C NMR ($CDCl_3$): δ 12.5, 12.8, 13.1, 13.5 [$(CH_3)_2CH$], 55.5 (OCH_3), 61.3 (C-5), 76.7 (C-4), 80.7 (C-3), 82.4 (C-2), and 107.9 (C-1). Anal. Calcd for $C_{18}H_{38}O_6Si_2$: C, 53.16; H, 9.42. Found: C, 53.20; H, 9.54.

Methyl 2-O-benzoyl-3,5-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-α-L-arabinofuranoside (**5**).—Benzoyl chloride (0.55 g, 3.91 mmol) was added to a solution of **4** (1.23 g, 3.02 mmol) and 4-dimethylaminopyridine (40 mg, 0.33 mmol) in dry pyridine (20 mL). The solution was stirred at room temperature for 3 h, and concentrated to remove the solvent. The residue was dissolved by adding EtOAc (50 mL) and water (40 mL). The EtOAc layer was washed with aq 5% HCl, aq $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on silica gel (70 g, 5:1 hexane–EtOAc) to give **5** (1.26 g, 82%); $[\alpha]_D$ $+21.2°$ (*c* 1.01, $CHCl_3$); R_f 0.75 in 5:1 hexane–EtOAc; ^1H NMR ($CDCl_3$): δ 0.94–1.14 [m, 28 H, $4 \times (CH_3)_2CH$], 3.42 (s, 3 H, OCH_3), 4.02–4.11 (m, 3 H, H-3, H-5,5′), 5.52 (m, 1 H, H-4), 4.90 (d, 1 H, *J* 1.7 Hz, H-1), and 5.42 (dd, 1 H, *J* 1.7, 5.1 Hz, H-2); ^{13}C NMR ($CDCl_3$): δ 12.5, 12.8, 13.2, 13.4 [$(CH_3)_2CH$], 55.2 (OCH_3), 61.6 (C-5), 75.9 (C-4), 80.9 (C-3), 84.3 (C-2), 106.3 (C-1), and 165.7 (C=O). Anal. Calcd for $C_{25}H_{42}O_7Si_2$: C, 58.79; H, 8.29%. Found: C, 58.93; H, 8.42.

Methyl 2-O-benzoyl-α-L-arabinofuranoside (**6**).—A mixture of **5** (1.24 g, 2.42 mmol) and 1.0 M tetrabutylammonium fluoride in tetrahydrofuran (Tokyo Kasei Kogyo) (5.0 mL) [4,8] was stirred at room temperature for 2 h under argon. The mixture was diluted with CH_2Cl_2 (50 mL), and the solution was washed with satd aq $(NH_4)_2SO_4$ and brine, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on silica gel (30 g, 10:1 $CHCl_3$–MeOH) to give **6** (617 mg, 95%); $[\alpha]_D$ $-81.0°$ (*c* 1.00, $CHCl_3$); lit. [2] $[\alpha]_D$ $-81.2°$ (*c* 0.70, $CHCl_3$). The NMR data were in good agreement with those reported previously [2].

Methyl 2-O-benzoyl-3,5-di-O-(2,3,5-tri-O-benzoyl-α-L-arabinofuranosyl)-α-L-arabinofuranoside (**8**).—Activated, powdered 4A molecular sieves (0.70 g) was added to a solution of **6** (332 mg, 1.24 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at 0°C under argon for 30 min, and then 2,3,5-tri-*O*-benzoyl-α-L-arabinofuranosyl chloride (**7**, 1.49 g, 3.10 mmol) [3] was added to the mixture. After the dissolution of **7** was complete, $AgSO_3CF_3$ (1.10g, 4.29 mmol) and *s*-collidine (520 μL, 3.93 mmol) were rapidly added. The mixture was stirred at 0°C for 30 min under argon, and then filtered through a Celite pad. The insoluble material was washed with CH_2Cl_2, and the filtrate and washings were successively washed with aq $Na_2S_2O_3$, cold 3 N H_2SO_4, water, and brine, dried ($MgSO_4$), and concentrated. The crude product crystallized twice from $CHCl_3$–MeOH gave the trisaccharide derivative **8** (615 mg, 42%); mp 65.5–66°C. Flash chromatography on silica gel (100 g, 15:1 benzene–EtOAc) of the residues from the mother liquors gave more **8** (286 mg, total yield 63%); $[\alpha]_D$ $-14.6°$ (*c* 1.84, $CHCl_3$); R_f 0.43 in 10:1 benzene–EtOAc; ^1H NMR ($CDCl_3$): δ 3.42 (s, 1 H, OCH_3), 3.92 (dd, 1 H, *J* 2.3, 11.4 Hz, H-5′a), 4.10 (dd, 1 H, *J* 4.8, 11.4 Hz, H-5′b), 4.37 (m, 1 H, H-4a), 4.52 (br d, 1 H, *J* 5.5 Hz, H-3a), 4.71 (dd, 1 H, *J* 3.9, 11.7 Hz, H-5′b), 4.78 (dd, 1 H, *J* 2.9, 11.7 Hz, H-5b), 5.10 (s, 1 H, H-1a), 5.38 (s, 1 H, H-1c), 5.41 (d, 1 H, *J* 1.4 Hz, H-2b), 5.52 (br d, 1 H, *J* 5.3 Hz, H-3c), 5.56 (m, 3 H, H-1b, H-2c,3b), and 5.62 (d, 1 H, *J* 1.2 Hz, H-2a); ^{13}C NMR ($CDCl_3$): δ 54.8 (OCH_3), 63.7 (C-5b, 5c), 65.9 (C-5a), 77.8 (C-3b, 3c), 80.9 (C-4c), 81.5–81.7 (C-2a, 2b, 3a, 4a, 4b), 82.7 (C-2c), 105.6 (C-1c), 106.0 (C-1b), and 107.0 (C-1a). Anal. Calcd for $C_{65}H_{56}O_{20}$: C, 67.47; H, 4.88. Found: C, 67.19; H, 4.98.

Methyl 3,5-di-O-α-L-arabinofuranosyl-α-L-arabinofuranoside (**2**).—To a stirred suspension of **8** (686 mg, 0.59 mmol) in dry MeOH (10 mL), 0.1 N NaOMe in MeOH (18 mL) was added. The mixture was stirred at room temperature for 4 h. The solution was neutralized with Amberlite 200-C resin (H^+ form). After filtration to remove the resin, the solution was concentrated and the residue was partitioned between diethyl ether and water. The water layer was concentrated, and the residue was purified by chromatography on silica gel (30 g, 2:1 $CHCl_3$–MeOH) to give the trisaccharide **2** (193 mg, 76%); $[\alpha]_D$ −159° (*c* 1.07, H_2O); R_f 0.30 in 2:1 $CHCl_3$–MeOH; for ^{1}H and ^{13}C NMR data see Table 1. Anal. Calcd for $C_{16}H_{28}O_{13} \cdot 0.5\ H_2O$: C, 43.94; H, 6.68%. Found: C, 43.92; H, 6.61.

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