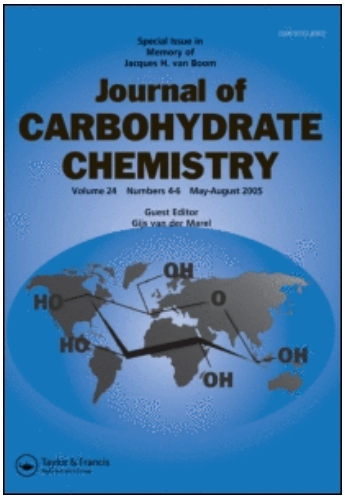


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*COMMUNICATION*

# SYNTHESIS OF 3-*O*-BENZYL-β-L-ARABINOFURANOSE 1,2,5-ORTHOPIVALATE AS A STARTING MONOMER FOR RING-OPENING POLYMERIZATION

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We have studied the ring-opening polymerizations of a variety of glucose orthoester derivatives and found that substituents on the monomer play an important role in stereo- and regioregularity of the resulting polymers.[1-3] These substituent effects open the possibility of application to ring-opening polymerizations of other sugar orthoesters to give stereo- and regioregular polysaccharides. Additionally, the ring-opening polymerization of the galactose orthoester derivative[4] gave stereoregular (1→5)-β-D-galactofuranan.

Kochetkov *et al.* reported the polymerization of the tricyclic orthobenzoate of arabinofuranose.[5] That is, the ring-opening polymerization of 3-*O*-acetyl-β-L-arabinofuranose 1,2,5-orthobenzoate was run with catalytic amounts of mercuric bromide in nitromethane in the presence of small amounts of 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose, which served as the

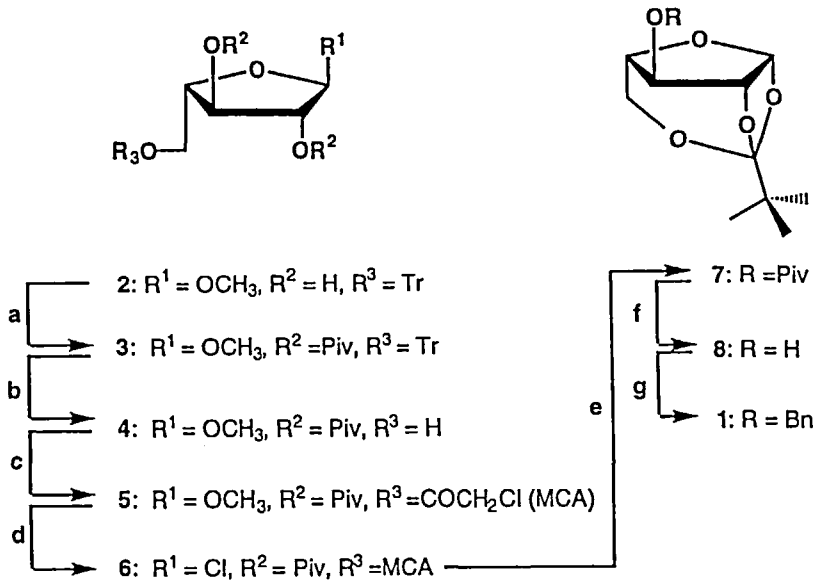
reaction initiator. The polysaccharide, containing a D-glucose residue at the reducing end, was obtained in a 20% yield. The polymer consisted of a mixture of at least 90% of (1→5)-α-arabinofuranosidic and about 8-10% of (1→2)-α-arabinofuranosidic linkages with a $\overline{DPn}$ up to 60. Thus, pure stereoregular (1→5)-α-L-arabinofuranan has never been synthesized from arabinose 1,2,5-orthoester derivatives, although Backnowsky *et al.* reported that the polymerization of 3-*O*-benzoyl-1,2-cyanoethylidene-5-*O*-trityl-β-L-arabinofuranoside gave the stereoregular 2,3-di-*O*-acyl-(1→5)-α-L-arabinofuranan derivative with a $\overline{DPn}$ up to 23.[6]

On the basis of our work on substituent effects, we anticipated that the ring-opening polymerization of 3-*O*-benzyl-β-L-arabinofuranose 1,2,5-orthopivalate would lead to a linear stereoregular 3-*O*-benzyl-2-*O*-pivaloyl-(1→5)-α-L-arabinofuranan. In the present communication, we report the synthesis of 3-*O*-benzyl-β-L-arabinofuranose 1,2,5-orthopivalate (**1**), as a starting monomer for ring-opening polymerization.



Compound **1** was synthesized (Scheme) from L-arabinose by a method similar to that employed for the synthesis of the galactose orthoester derivative.[4]

Methyl 5-*O*-triphenylmethyl-α-L-arabinofuranoside (**2**) was obtained by the method of Iwashige *et al.* in 2 reaction steps from L-arabinose.[7] Compound **2** was converted into methyl 2,3-di-*O*-pivaloyl-5-*O*-triphenylmethyl-α-L-arabinofuranoside (**3**) by pivaloylation. De-triphenylmethylation of compound **3** was performed with *p*-toluenesulfonic acid in 20% methanol–dichloromethane to give methyl 2,3-di-*O*-pivaloyl-α-L-arabinofuranoside (**4**) without any side reactions. Compound **4** was monochloroacetylated to give methyl 5-*O*-monochloroacetyl-2,3-di-*O*-pivaloyl-α-L-arabinofuranoside (**5**). The C1 position of compound **5** was chlorinated with stannic chloride, dichloromethyl methyl ether, and molecular sieves 4Å in anhydrous dichloromethane under the reaction conditions used to generate the galactose derivative.[4] The resulting 5-*O*-monochloroacetyl-2,3-di-*O*-pivaloyl-α-L-arabinofuranosyl chloride




a.Piv-Cl/pyridine/80 °C/overnight/92%; b.*p*-TsOH/20% MeOH-$CH_2Cl_2$/rt/2h/84%; c.$ClCH_2COOCl$/DMAP/pyridine/rt/5h/81%; d.$Cl_2CHOCH_3$/$SnCl_4$/MS4Å/anhydrous $CH_2Cl_2$/rt/overnight; e.$NH_2CSNH_2$/pyridine/80 °C/5h/49% overall yields from **5**; f.DBU/MeOH/rt/overnight/93%; g.Bn-Br/NaH/$Bu_4NI$/THF/rt/6h/87%.

**Scheme**

(**6**) was treated, without further purification, with thiourea in pyridine at 80 °C. Under these conditions, selective deprotection of 5-*O*-monochloroacetyl group with thiourea occurs followed by formation of the tricyclic orthoester linkage to give 3-*O*-pivaloyl-β-L-arabinofuranose 1,2,5-orthopivalate (**7**). Depivaloylation of compound **7** followed by benzylation gave compound **1**. Compound **1** was obtained in 9 reaction steps from L-arabinose in an overall yield of 23%. Ring-opening polymerization of compound **1** gave a pure stereoregular (1→5)-α-L-arabinofuranan derivative as will be reported in a separate paper.[8]

## EXPERIMENTAL

**General methods.** All melting points (mp) are reported uncorrected. $^1H$ and $^{13}C$ NMR spectra were recorded with a Varian INOVA300 FT-NMR

(300 MHz) spectrometer, in chloroform-*d* with tetramethylsilane ($Me_4Si$) as an internal standard. Chemical shifts (δ) and coupling constants (J) are given in δ-values (ppm) and Hz, respectively. Chemical shifts were assigned via their cross-peaks in COSY spectra. Optical rotations were measured at 25 °C using a JASCO Dip-1000 digital polarimeter. A standard workup procedure was employed in each synthetic step. The procedure included diluting the mixture with ethyl acetate, washing with aqueous $NaHCO_3$ and brine, drying over $Na_2SO_4$, and concentration *in vacuo* to remove solvents.

**Methyl 2,3-di-*O*-pivaloyl-5-*O*-triphenylmethyl-α-L-arabinofuranoside (3).** To a solution of methyl 5-*O*-triphenylmethyl-L-arabinofuranoside (2) (3.2 g, 7.88 mM) in pyridine (20 mL) was added pivaloyl chloride (5.82 mL, 47.3 mM). The mixture was heated to 80 °C overnight. After addition of methanol (1.3 mL, 31.5 mM) to decompose excess pivaloyl chloride, the reaction mixture was worked up by the standard procedure. The obtained crude compound 3 was purified on a silica gel column (Wakogel C-200) eluted with $CH_2Cl_2$ to give a colorless oil (4.15 g, 91.7 % yield): $[\alpha]_D^{25}$ -4.11° (*c* 1, $CHCl_3$); $^1H$ NMR ($CDCl_3$): δ 1.14, 1.15 (s, 9 H, respectively, C=OC($CH_3$)$_3$), 3.25 (s, 1 H, H-5b), 3.29 (d, 1 H, H-5a), 3.40 (s, 1 H, $OCH_3$), 4.27 (dd, 1 H, $J_{4,5a}$= 5.1 Hz, H-4), 4.87 (s, 1 H, H-1), 4.95 (s, 1 H, H-2), 5.05 (d, 1 H, $J_{3,4}$= 5.4 Hz, H-3), 7.22-7.48 (Ar); $^{13}C$ NMR ($CDCl_3$): δ 106.7 (C-1), 86.7, 81.1, 65.2, 63.4, 54.7, 53.4 (C-2, C-3, C-4, C-5, $\underline{C}(C_6H_5)_3$, $OCH_3$), 26.9 (C($\underline{C}H_3$)$_3$), 38.5 ($\underline{C}$($CH_3$)$_3$), 127.0, 127.7, 128.7, 143.7 (Ar), 177.2, 177.4 (C=O).

Anal. Calcd for $C_{35}H_{42}O_7$ (574.8): C, 73.15; H, 7.37. Found: C, 73.12; H, 7.27.

**Methyl 2,3-di-*O*-pivaloyl-α-L-arabinofuranoside (4).** To a solution of compound 3 (4.15 g, 7.23 mM) in 20% methanol–dichloromethane (20 mL) was added *p*-toluenesulfonic acid (1.87 g, 10.8 mM), and the mixture was kept at room temperature for 2 h. The reaction mixture was neutralized by adding $NaHCO_3$, and worked up by the standard procedure. The crude compound 4 was purified on a silica gel column (Wakogel C-200) eluted with 1:4 ethyl

acetate–*n*-hexane to give a colorless syrup (2.01 g, 83.9% yield): $[\alpha]_D^{25}$ 8.59° (*c* 1, $CHCl_3$); $^1H$ NMR ($CDCl_3$): δ 1.21, 1.24 (s, 9 H, respectively, C=OC($CH_3$)$_3$), 3.40 (s, 3 H, $OCH_3$), 3.76-3.91 (overlapped, 2 H, H-5a, H-5b), 4.06 (dd, 1 H, H-4), 4.90 (s, 1 H, H-1), 4.91 (dd, 1 H, $J_{3,4}$= 4.5 Hz, H-3), 5.08 (d, 1 H, $J_{2,3}$= 1.5 Hz, H-2); $^{13}C$ NMR ($CDCl_3$): δ 106.6 (C-1), 83.5, 81.0, 71.5, 62.4, 54.7 (C-2, C-3, C-4, C-5), 27.0 ($CH_3$), 38.7 [C($CH_3$)$_2$], 178.3 (C=O).

Anal. Calcd for $C_{16}H_{28}O_7$ (332.5): C, 57.82; H, 8.49. Found: C, 57.60; H, 8.37.

**Methyl 5-*O*-monochloroacetyl-2,3-di-*O*-pivaloyl-α-L-arabinofuranoside (5).** Compound 4 (2.01 g, 6.07 mM) was dissolved in pyridine (10 mL). Monochloroacetyl chloride (730 μL, 9.11 mM) and dimethylaminopyridine (741.6 mg, 6.07 mM) were added. The mixture was stirred at room temperature for 5 h, and then methanol (123 μL, 3.04 mM) was added to the reaction mixture to decompose excess monochloroacetyl chloride. The reaction mixture was worked up by the standard procedure to give a yellow oil. The obtained crude compound 5 was purified on a silica gel column (Wakogel C-200) eluted with 1:4 ethyl acetate–*n*-hexane to give a colorless syrup (2.01 g, 81.2% yield): $[\alpha]_D^{25}$ -13.7° (*c* 0.5, $CHCl_3$); $^1H$ NMR ($CDCl_3$): δ1.21, 1.22 (s, 9 H, respectively, C=OC($CH_3$)$_3$), 3.40 (s, 1 H, $OCH_3$), 4.14 (s, 2 H, $ClCH_2C$=O), 4.22 (dd, 1 H, $J_{4,5a}$= 5.1 Hz, H-4), 4.33 (d, 1 H, H-5b), 4.54 (dd, 1 H, $J_{gem}$= 11.4 Hz, H-5a), 4.90 (s, 1 H, H-1), 4.90 (d, 1 H, $J_{3,4}$= 5.7 Hz, H-3), 5.04 (s, 1 H, H-2); $^{13}C$ NMR ($CDCl_3$): δ 106.9 (C-1), 80.7, 80.3, 66.9, 65.1, 54.9 (C-2, C-3, C-4, C-5, $OCH_3$), 26.9, 27.0 (C($\underline{C}H_3$)$_3$), 38.7 ($\underline{C}$($CH_3$)$_3$), 40.7 ($Cl\underline{C}H_2C$=O), 167.1 ($ClCH_2\underline{C}$=O), 177.2, 177.8 (C=O).

Anal. Calcd for $C_{18}H_{29}ClO_8$ (408.9): C, 52.88; H, 7.15; O, 31.30. Found: C, 53.09; H, 7.25; O, 31.24.

**3-*O*-Pivaloyl-β-L-arabinofuranose 1,2,5-orthopivalate (7).** To a solution of compound 5 (2.01 g, 4.93 mM) in anhydrous dichloromethane (15 mL), dichloromethyl methyl ether (8.77 mL, 98.5 mM), stannic chloride (576 μL, 4.93 mM) and molecular sieves 4Å (1.5 g) were added, and the mixture was

stirred at room temperature overnight. The reaction mixture was worked up by the standard procedure to give 5-*O*-monochloroacetyl-2,3-di-*O*-pivaloyl-α-L-arabinofuranosyl chloride (**6**) as a crude oil (1.98 g). To a solution of the crude compound **6** (1.98 g) in pyridine (15 mL), thiourea (450 mg, 5.91 mM) and molecular sieves 4Å (1 g) were added, and the mixture was kept at 80 °C for 5 h. The reaction mixture was diluted with ethyl acetate, washed with $H_2O$ and brine, dried over anhydrous sodium sulfate, and concentrated to dryness. The crude compound **7** was then purified on a silica gel column (Wakogel C-200) eluted with $CH_2Cl_2$ to give colorless crystals after concentration (688.1 mg, 48.5 % yield): mp 139-142°C; $[\alpha]_D^{25}$ 69.8° (*c* 1, $CHCl_3$); $^1$H NMR ($CDCl_3$): δ 1.01 (s, 9 H, $C(CH_3)_3$), 1.20 (s, 9 H, $C{=}OC(CH_3)_3$), 3.84 (dd, 1 H, $J_{4,5b}$= 1.2 Hz, H-5b), 3.97 (dd, 1 H, $J_{gem}$= 12.9 Hz, H-5a), 4.35 (m, 1 H, $J_{4,5a}$= 3.3 Hz, H-4), 4.58 (dd, 1 H, $J_{2,4}$=1.5 Hz, H-2), 5.92 (d, 1 H, $J_{1,2}$= 3.9 Hz, H-1), 5.14 (s, 1 H, H-3); $^{13}$C NMR ($CDCl_3$): δ 103.5 (C-1), 81.4, 81.4, 78.2, 68.2 (C-2, C-3, C-4, C-5), 27.0 [$C{=}OC(\underline{C}H_3)_3$], 38.7 [$C{=}O\underline{C}(CH_3)_3$], 37.3 [$(CH_3)_2\underline{C}C(O\text{-})_2$], 24.8 [$(\underline{C}H_3)_2CC(O\text{-})_2$], 126.3 [$(CH_3)_2C\underline{C}(O\text{-})_2$].

Anal. Calcd for $C_{15}H_{24}O_6$ (300.4): C, 59.98; H, 8.05. Found: C, 59.82; H, 8.06.

**β-L-Arabinofuranose, 1,2,5-orthopivalate (8).** To a solution of compound **7** (688.1 mg, 2.39 mM) in 10 mL of methanol was added 1,8-diazabicyclo[5.4.0]-7-undecene (357 μL, 2.39 mM). The solution was stirred at room temperature over night. The reaction mixture was concentrated to give a crude yellow crystalline product (**8**). The crude compound **8** was purified on a silica gel column (Wakogel C-200) eluted with 1:2 ethyl acetate–*n*-hexane to give colorless crystals after concentration (452.3 mg, 92.8 % yield): mp 116-118°C; $[\alpha]_D^{25}$ 38.0° (*c* 1, $CHCl_3$); $^1$H NMR ($CDCl_3$): δ 1.01 (s, 9 H, $CH_3$), 2.90 (d, 1 H, OH), 3.81 (dd, 1 H, $J_{4,5b}$= 1.8 Hz, H-5b), 3.88 (dd, 1 H, $J_{gem}$= 12.9 Hz, H-5a), 4.29 (m, 1 H, $J_{4,5a}$= 3.0 Hz, H-4), 4.33 (d, 1 H, $J_{3,OH}$= 6.6 Hz, H-3), 4.48 (d, 1 H, H-2), 5.91 (d, 1 H, $J_{1,2}$= 3.6 Hz, H-1); $^{13}$C NMR ($CDCl_3$): δ 103.4 (C-1), 83.71,

83.48, 76.6, 67.8 (C-2, C-3, C-4, C-5), 37.2 [$(CH_3)_2\underline{C}C(O\text{-})_2$], 24.8 [$(\underline{C}H_3)_2CC(O\text{-})_2$], 126.1 [$(CH_3)_2C\underline{C}(O\text{-})_2$].

Anal. Calcd for $C_{10}H_{16}O_5$ (216.3): C, 55.55; H, 7.46. Found: C, 55.49; H, 7.46.

**3-*O*-Benzyl-β-L-arabinofuranose 1,2,5-orthopivalate (1).** Compound 8 (452.3 mg, 2.22 mM) was dissolved in tetrahydrofuran (10 mL). Sodium hydride (106.4 mg, 2.66 mM, 60% in mineral oil), tetra-butylammonium iodide (41 mg, 0.11 mM) and benzyl bromide (792 μL, 6.66 mM) were added. The mixture was stirred at room temperature for 3 h, and methanol (180 μL, 4.44 mM) was added to the reaction mixture to decompose excess benzyl bromide. The reaction mixture was worked up by the standard procedure to give a yellow oil. The crude compound 1 was purified on a silica gel column (Wakogel C-200) eluted with 1:9 ethyl acetate–*n*-hexane to give colorless crystals after concentration (569.1 mg, 87.3 % yield): mp 79-80°C; $[\alpha]_D^{25}$ 29.9° (*c* 1, $CHCl_3$); $^1H$ NMR ($CDCl_3$): δ 0.99 (s, 9 H, $CH_3$), 3.81 (dd, 1 H, $J_{4,5b}$= 2.7 Hz, H-5b), 3.86 (dd, 1 H, $J_{gem}$= 12.9 Hz, H-5a), 4.08 (d, 1 H, H-3), 4.39 (m, 1 H, $J_{4,5a}$= 1.5 Hz, H-4), 4.56, 4.62 (d, 1 H, respectively, J=12.0 Hz, $C\underline{H}_2C_6H_5$), 4.62 (d, 1 H, $J_{2,3}$= 1.8 Hz, H-2), 5.91 (d, 1 H, $J_{1,2}$= 3.6 Hz, H-1), 7.28-7.35 (Ar); $^{13}C$ NMR ($CDCl_3$): δ 103.7 (C-1), 83.7, 81.1, 71.6, 68.4 (C-2, C-3, C-4, C-5, $\underline{C}H_2C_6H_5$ overlapped at 81.1), 37.2 [$(CH_3)_2\underline{C}C(O\text{-})_2$], 24.9 [$(\underline{C}H_3)_2CC(O\text{-})_2$], 126.0 [$(CH_3)_2C\underline{C}(O\text{-})_2$], 137.2, 128.6, 128.0, 127.7 (Ar).

Anal. Calcd for $C_{17}H_{22}O_5$ (306.4): C, 66.65; H, 7.24. Found: C, 66.59; H, 7.20.

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