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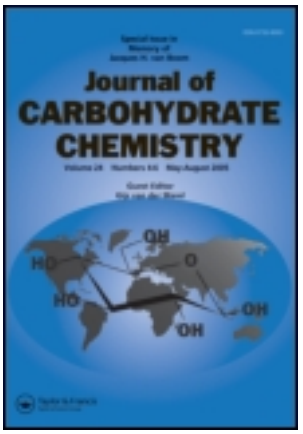

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Communication: Synthesis of 3-O-Benzyl-β-L-Arabinofuranose 1,2,5-Orthopivalate as a Starting Monomer for Ring-Opening Polymerization

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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

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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

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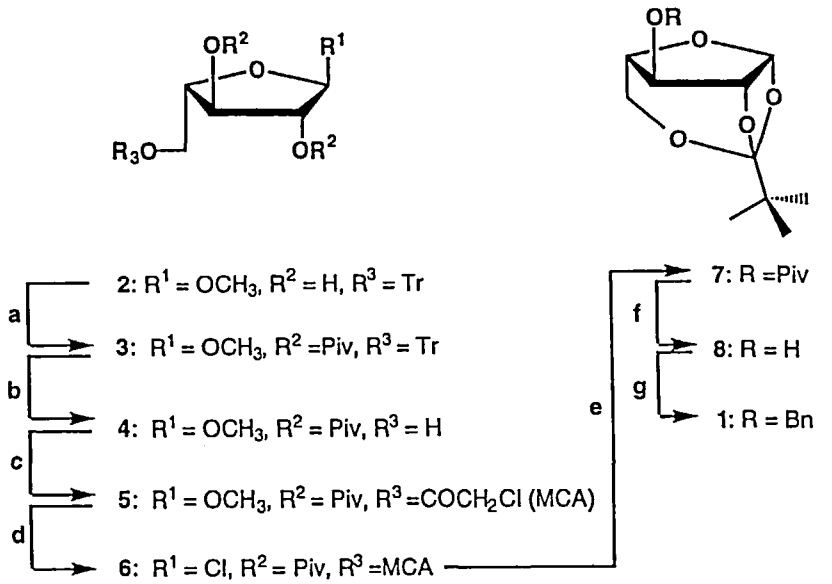

a.Piv-Cl/pyridine/80 °C/overnight/92%; b.*p*-TsOH/20% MeOH-CH_2Cl_2/rt/2h/84%; c.$ClCH_2COOCl$/DMAP/pyridine/rt/5h/81%; d.Cl_2CHOCH_3/$SnCl_4$/MS4Å/anhydrous CH_2Cl_2/rt/overnight; e.NH_2CSNH_2/pyridine/80 °C/5h/49% overall yields from 5; f.DBU/MeOH/rt/overnight/93%; g.Bn-Br/NaH/Bu_4NI/THF/rt/6h/87%.

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

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(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

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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 [$\underline{C}(CH_3)_2$], 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

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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, $CHCl_3$); ^1H 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, $CHCl_3$); ^1H 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,

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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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