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Note

Synthesis of 3- and 4-deoxy derivatives of L-rhamnose from 1,2-*O*-(1-methoxyethylidene)-β-L-rhamnopyranose

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The 3,6- and 4,6-dideoxyhexoses are biologically important carbohydrates frequently found as constituents of specific lipopolysaccharides in the cell walls of gram-negative bacteria [1], where they commonly appear at the reducing terminus and contribute in many cases to the serological specificity of the bacterial antigen [2]. We were interested in 3- and 4-deoxygenated analogues of L-rhamnose in connection with a synthesis of deoxygenated analogues of the trisaccharide component of the repeating unit of the capsular polysaccharide of *Streptococcus pneumoniae* type 19F [3], namely $\rightarrow$4)-β-D-Man*p*NAc-(1$\rightarrow$4)-α-D-Glc*p*-(1$\rightarrow$2)-α-L-Rha*p*-(1-PO_4^-)$\rightarrow$.

We report herein a short synthesis of the title compounds starting from 1,2-*O*-(1-methoxyethylidene)-β-L-rhamnopyranose (**1**) [4].

It is noteworthy that orthoesters have rarely been subjected to selective protection, probably because of the relative instability of these intermediates. In our work, we obtained excellent results in the regioselective protection of the rhamnose orthoester **1**, which reacted preferentially at C-3. To our knowledge, the highly selective substitution at C-3 of β-L-rhamnose derivatives is not known, although one example of selective benzylation at C-3 of methyl α-L-rhamnopyranoside using the stannylene method has recently been described [5].

Starting from the orthoester **1** (Scheme 1), we obtained the thionocarbonate **2** through direct acylation using 4-fluorophenyl chlorothionocarbonate and *N*-hydroxysuccinimide (NHS). Selective benzylation of **1**, using the stannylene method [6] followed by thionocarbonylation at C-4 gave **7a**. The regiochemistry of the

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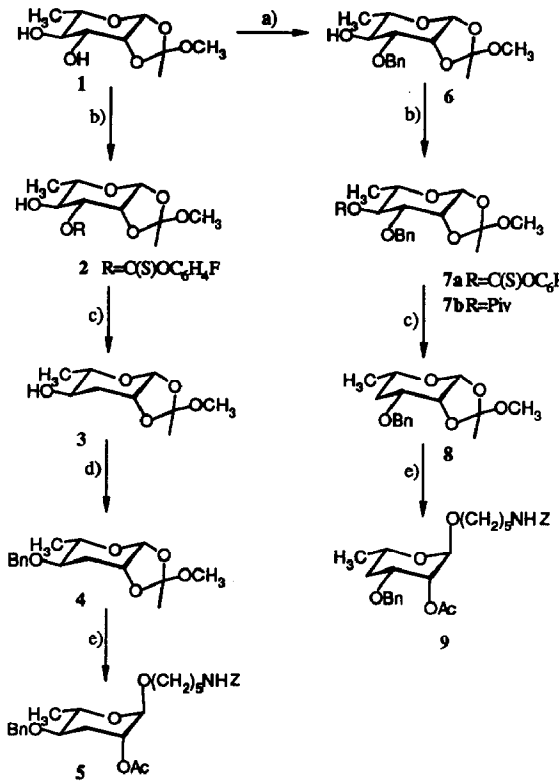

Scheme 1. (a) Bu_2SnO, $Bu_4N^+Br^-$, BnBr, benzene, reflux, 21 h, 93%. (b) NHS, Py, $ClC(S)OC_6H_4F$, THF, 3 h. (c) Bu_3SnH, AIBN, toluene, 90°C. (d) NaH, BnBr, DMF, 4 h, 68%. (e) $HO(CH_2)_5NHZ$, Me_3SiOTf, 1 h, 55%.

benzylation and thionocarbonylation of the orthoester **1** can be deduced from the ^1H NMR spectra of the thionocarbonates **2** and **7a**. The ^1H NMR spectrum of **2** shows a signal for H-3, which corresponds to the acylated position, as a doublet of doublets at δ 5.39 ($J_{2,3}$ 4.0, $J_{3,4}$ 9.6 Hz) and the signal for H-4 as a doublet of triplets at δ 3.83 ($J_{3,4} = J_{4,5} = 9.6$, $J_{4,OH}$ 4.6 Hz). Conversely, the ^1H NMR spectrum of **7a** shows the signal for H-4 as a triplet at δ 5.63 ($J_{3,4} = J_{4,5} = 9.4$ Hz) and the signal for H-3 as a doublet of doublets at δ 3.85 ($J_{2,3}$ 4.0, $J_{3,4}$ 9.4 Hz). The above assignments were further confirmed by the presence in compound **2** of a coupling between H-4 and the hydroxyl group proton. The thionocarbonates **2** and **7a** were reduced using tributyltin hydride and α,α'-azobis-isobutyronitrile (AIBN) [7,8] to give **3** and **8**. Compound **3** was benzylated to obtain **4**. The ^1H NMR spectrum of **4** shows 2 signals at δ 2.51 and 1.81 for H-3*eq* and H-3*ax*, respectively. In **8**, H-4*ax* and H-4*eq* resonate between δ 1.8 and 1.6 as a multiplet.

Orthoesters **4** and **8** were glycosylated with 5-(benzyloxy)carbonylamino-1-pentanol in the presence of trimethylsilyl triflate to give the rhamnosides **5** and **9** that contain a spacer arm at the anomeric position, suitable for conjugation to a protein [9].

1. Experimental

General methods.—^{1}H NMR spectra were recorded with Bruker AC 300 and Varian Gemini 200 spectrometers for solutions in $CDCl_3$ with Me_4Si as internal reference. Melting points were determined with a Büchi apparatus and are not corrected. Optical rotations were measured at room temperature with a Perkin–Elmer 241 polarimeter. Thin-layer chromatography (TLC) was carried out on Merck Silica Gel 60 F-254 plates (0.25-mm thickness), eluted with hexane–EtOAc containing 0.1% Et_3N in the ratio reported in brackets, and visualized by spraying with a solution containing H_2SO_4 (31 mL), ammonium molybdate (21 g), and $Ce(SO_4)_2$ (1 g) in water (500 mL), and then heating at 110°C for 5 min. Column chromatography was performed by the flash procedure using Merck Silica Gel 60 (230–400 mesh) with the same eluent.

3-O-*(4-Fluorophenylthionocarbonyl)1,2-*O*-(1-methoxyethylidene)-β-*L*-rhamnopyranose* (**2**).—1,2-*O*-(1-Methoxyethylidene)-β-L-rhamnopyranose (**1**; 500 mg, 2.27 mmol) [4], dry pyridine (0.92 mL, 11.35 mmol), dry THF (30 mL), and NHS (26 mg, 0.22 mmol) were placed in a two-necked flask sealed with rubber septa. The solution was kept under N_2 and 4-fluorophenyl chlorothionocarbonate (380 μL, 2.72 mmol) was added. The mixture was stirred at room temperature for 3 h and the precipitate formed was removed by suction filtration. The filtrate was washed sequentially with cold 0.1% HCl and saturated $NaHCO_3$ solutions, brine and H_2O, and dried over Na_2SO_4. The solvent was removed and the product was isolated by column chromatography (7:3), affording **2** as a glass (720 mg, 84.7%); $[\alpha]_D$ +62.0° (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz): δ 7.21–7.12 (m, 4 H, ArH), 5.47 (d, 1 H, $J_{1,2}$ 2.5 Hz, H-1), 5.39 (dd, 1 H, $J_{2,3}$ 4.0, $J_{3,4}$ 9.6 Hz, H-3), 4.87 (dd, 1 H, H-2), 3.83 (ddd app. as dt, 1 H, $J_{4,5}$ 9.6, $J_{4,OH}$ 4.6 Hz, H-4), 3.45 (dq, 1 H, $J_{5,6}$ 6.2 Hz, H-5), 3.27 (s, 3 H, OCH_3), 2.75 (d, 1 H, OH), 1.71 (s, 3 H, CH_3), 1.37 (d, 3 H, H-6). Anal. Calcd for $C_{16}H_{19}FO_7S$: C, 51.32; H, 5.11. Found: C, 51.21; H, 5.52.

*4-O-Benzyl-3,6-dideoxy-1,2-*O*-(1-methoxyethylidene)-β-*L*-arabino-hexopyranose* (**4**).—Thionocarbonate **2** (300 mg, 0.80 mmol) and AIBN (15 mg) were dissolved in dry toluene under N_2 and heated at 80°C, tributyltin hydride (82 μL, 0.31 mmol) was added dropwise during 10 min. When the reaction was complete (TLC 7:3), the mixture was evaporated and the residue was separated by column chromatography (7 : 3) affording 3,6-dideoxy-1,2-*O*-(1-methoxyethylidene)-β-L-*arabino*-hexopyranose (**3**; 82 mg, 50%) as a syrup. ^{1}H NMR (200 MHz): δ 5.32 (d, 1 H, $J_{1,2}$ 2.5 Hz, H-1), 4.36 (m, 1 H, H-2), 3.56 (m, 1 H, H-5), 3.28 (s, 3 H, OCH_3), 2.48 (m, 1 H, H-3*eq*), 1.73 (m, 1 H, H-3*ax*), 1.66 (s, 3 H, CH_3), 1.31 (d, 3 H, $J_{5,6}$ 6 Hz). Orthoester **3** (82 mg, 0.4 mmol), dissolved in dry DMF (1 mL), was added slowly to a suspension of NaH (20 mg, 0.87 mmol) in DMF (2 mL). Benzyl bromide (95 μL, 0.8 mmol) was added to the suspension which was stirred for 4 h, after which MeOH (2 mL) was added and the solution was poured into water. The product was extracted with EtOAc (3 × 20 mL), the extract washed with water (2 × 20 mL), dried, and evaporated under reduced pressure. The residue was purified by column chromatography (8:2) to provide **4** as a syrup (81 mg, 71%); $[\alpha]_D$ −75.9° (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz): δ 7.36–7.18 (m, 5 H, ArH), 5.33 (d, 1 H, $J_{1,2}$ 2.8

Hz, H-1), 4.61 and 4.49 (2d, 1 H each, J 11.5 Hz, CH_2Ph), 4.37 (dt, 1 H, $J_{2,3eq}$ 2.8, $J_{2,3ax}$ 4.6 Hz, H-2), 3.49 (dq, 1 H, $J_{4,5}$ 7.8, $J_{5,6}$ 6.0 Hz, H-5), 3.39 (ddd, 1 H, $J_{3ax,4}$ 9.3, $J_{3eq,4}$ 4.0 Hz, H-4), 3.28 (s, 3 H, OCH_3), 2.51 (ddd app. as br dt, 1 H, $J_{3ax,3eq}$ 14.2 Hz, H-3*eq*), 1.81 (ddd, 1 H, H-3*ax*), 1.66 (s, 3 H, CH_3), 1.31 (d, 3 H, $J_{5,6}$ 6 Hz, H-6). Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.28; H, 7.53. Found: C, 65.23; H, 7.48.

2-O-*Acetyl-4-O-benzyl-5-(benzyloxy)carbonylaminopentyl-3,6-dideoxy-α*-L-arabino-*hexopyranoside* (**5**).—5-(Benzyloxy)carbonylamino-1-pentanol (540 mg, 2.4 mmol) in dry CH_2Cl_2 (4 mL), was added through a double-tipped needle under N_2 into a two-necked flask containing activated 4A molecular sieves and orthoester **4** (80 mg, 0.28 mmol). Finally, trimethysilyl triflate (80 μL) was added to the mixture. The solution was stirred under N_2 at room temperature for 1 h. After completion (TLC 7:3), the mixture was washed with satd $NaHCO_3$ and dried over Na_2SO_4. The solvent was removed and the residue chromatographed to afford **5** (77 mg, 55%); $[\alpha]_D$ −49.2° (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz): δ 7.42–7.20 (m, 10 H, ArH), 5.08 (br s, 2 H, Z-CH_2Ph), 4.88 (br s, 1 H, H-2), 4.64 and 4.42 (2d, 2 H, J 11.5 Hz CH_2Ph), 4.57 (br s, 1 H, H-1), 3.80–3.60 (m, 2 H, H-5 and CH_aO), 3.44–3.29 (m, 2 H, H-4 and CH_bO), 3.24–3.11 (m, 2 H, CH_2N), 2.19 (ddd app. as dt, 1 H, $J_{2,3eq} = J_{3eq,4} = 3.7$, $J_{3ax,3eq}$ 13.7 Hz, H-3*eq*), 2.08 (s, 3 H, $COCH_3$) 1.88 (ddd, 1 H, $J_{2,3ax}$ 3.1, $J_{3ax,4}$ 11.2 Hz, H-3*ax*), 1.65–1.30 [m, 6 H, $(CH_2)_3$], 1.28 (d, 3 H, $J_{5,6}$ 6.1 Hz, H-6). Anal. Calcd for $C_{28}H_{37}NO_7$: C, 67.31; H, 7.46; N, 2.80. Found: C, 67.09; H, 7.65; N, 2.71.

3-O-*Benzyl-1,2-O-(1-methoxyethylidene)-β*-L-*rhamnopyranose* (**6**).—A solution of 1,2-*O*-(1-methoxyethylidene)-β-L-rhamnopyranose (**1**; 1.1 g, 5 mmol) and dibutyltin oxide (1.49 g, 6 mmol) in benzene (100 mL) was placed in a two-necked flask equipped with a Dean–Stark separator and the mixture was boiled under reflux for 3 h. The solution was concentrated to half its initial volume, Bu_4NBr (1.93 g, 6 mmol) and benzyl bromide (1.78 mL, 15 mmol) were added, and the mixture was stirred for 18 h at 80–90°C. The reaction was monitored by TLC (7:3). After completion of the benzylation, the solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography (8:2), affording **6** (1.44 g, 93%) as a syrup, which slowly solidified; mp 31–33°C; $[\alpha]_D$ +56.6° (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz): δ 7.42–7.21 (m, 5 H, ArH), 5.34 (d, 1 H, $J_{1,2}$ 2.5 Hz, H-1), 4.81 and 4.73 (2d, 2 H, J 11.7 Hz, CH_2Ph), 4.44 (dd app. as t, 1 H, H-2), 3.56 (ddd app. as dt, 1 H, $J_{4,OH}$ 2.2, $J_{3,4} = J_{4,5} = 9.0$ Hz, H-4), 3.46 (dd, 1 H, $J_{2,3}$ 3.6 Hz, H-3), 3.31 (m, 1 H, H-5), 3.27 (s, 3 H, OCH_3), 2.31 (d, 1 H, OH), 1.69 (s, 3 H, CH_3), 1.31 (d, 3 H, $J_{5,6}$ 6.1 Hz, H-6). Anal. Calcd for $C_{16}H_{22}O_6$: C, 61.91; H, 7.09. Found: C, 61.86; H, 6.93.

3-O-*Benzyl-4*-O-*(4-fluorophenylthionocarbonyl)-1,2*-O-*(1-methoxyethylidene)-β*-L-*rhamnopyranose* (**7a**).—Compound **6** (820 mg, 2.6 mmol) and NHS (30 mg, 0.26 mmol) were dissolved in freshly distilled dry THF (10 mL) and dry pyridine (640 μL, 7.9 mmol) under N_2. 4-Fluorophenyl chlorothionocarbonate (739 μL, 5.3 mmol) was added. The mixture was stirred for 3 h at room temperature and then filtered and diluted with CH_2Cl_2. The organic layer was washed sequentially with cold 0.1% HCl, satd $NaHCO_3$ and brine, and then dried over Na_2SO_4. The solvent was removed and the product isolated by column chromatography (8:2) which

afforded **7a** (840 mg, 70%); mp 66–68°C; $[\alpha]_D$ − 38.4° (*c* 1.0, $CHCl_3$). ^1H NMR (200 MHz): δ 7.39–7.02 (m, 9 H, ArH), 5.63 (t, 1 H, $J_{3,4} = J_{4,5} = 9.4$ Hz, H-4), 5.38 (d, 1 H, $J_{1,2}$ 2.6 Hz, H-1), 4.81 and 4.72 (2d, 2 H, *J* 12.2 Hz, CH_2Ph), 4.51 (dd, $J_{2,3}$ 4 Hz, H-2) 3.85 (dd, 1 H, H-3), 3.60 (m, 1 H, H-5), 3.31 (s, 3 H, OCH_3), 1.76 (s, 3 H, CH_3), 1.35 (d, 3 H, $J_{5,6}$ 6 Hz, H-6). Anal. Calcd for $C_{23}H_{25}FO_7S$: C, 59.46; H, 5.44. Found: C, 59.38; H, 5.11.

*3-O-Benzyl-4,6-dideoxy-1,2-O-(1-methoxyethylidene)-β-*L*-lyxo-hexopyranose* (**8**).—The thionocarbonate **7a** (600 mg, 1.3 mmol) and AIBN (20 mg) were dissolved in dry toluene under N_2 and heated to 110°C. Tributyltin hydride (110 μL, 0.4 mmol) was added to the stirred solution in one portion, heating was continued for 60 min, and then the solvent was evaporated. TLC (8:2) showed the absence of the UV-active thionocarbonate. The residue was purified by column chromatography (8:2) affording **8** (270 mg, 70%) as a colourless oil; $[\alpha]_D$ + 34.1° (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz): δ 7.40–7.15 (m, 5 H, ArH), 5.29 (d, 1 H, $J_{1,2}$ 2.7 Hz, H-1), 4.67 (s, 2 H, CH_2Ph), 4.35 (t, 1 H, H-2), 3.65 (ddd, 1 H, $J_{2,3}$ 3.9, $J_{3,4ax}$ 11.4, $J_{3,4eq}$ 4.7 Hz, H-3), 3.42 (m, 1 H, H-5), 3.31 (s, 3 H, OCH_3), 1.77 (m, 2 H, H-4), 1.71 (s, 3 H, CH_3), 1.22 (d, 3 H, $J_{5,6}$ 6.0 Hz, H-6). Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.28; H, 7.53. Found: C, 65.23; H, 7.60.

*3-O-Benzyl-4-O-pivaloyl-1,2-O-(1-methoxyethylidene)-β-*L*-rhamnopyranose* (**7b**).—A mixture of the orthoester **7a** (690 mg, 2.22 mmol), 4-dimethylaminopyridine (27 mg, 0.22 mmol), dry Et_3N (617 μL, 4.44 mmol), and dry toluene was stirred under N_2. Pivaloyl chloride (409 μL, 3.33 mmol) was added, and the solution was heated at 60°C for 3 h. The precipitate formed was removed by filtration over Celite and the filtrate was diluted with CH_2Cl_2 and washed with water and satd $NaHCO_3$, dried (Na_2SO_4) and evaporated. The product was isolated by column chromatography (6:4) affording **7b** (790 mg, 90%) as colourless crystals; mp 88–90°C; $[\alpha]_D$ + 25.1° (*c* 1.0 $CHCl_3$); ^1H NMR (200 MHz): δ 7.36–7.20 (m, 5 H, ArH), 5.31 (d, 1 H, $J_{1,2}$ 2.5 Hz, H-1), 5.06 (t, 1 H, $J_{3,4} = J_{4,5} = 9.6$ Hz, H-4), 4.67 (br s, 2 H, CH_2Ph), 4.38 (dd, 1 H, $J_{2,3}$ 4.2 Hz, H-2), 3.71 (dd, 1 H, H-3), 3.42 (dq, 1 H, $J_{5,6}$ 6.2 Hz, H-5), 3.26 (s, 3 H, OCH_3), 1.72 (s, 3 H, CH_3), 1.21 (s, 9 H, ^{t}Bu), 1.18 (d, 3 H, H-6). Anal. Calcd for $C_{21}H_{30}O_7$: C, 63.93; H, 7.66. Found: C, 64.02; H, 7.69.

*2-O-Acetyl-3-O-benzyl-5-(benzyloxy)carbonylaminopentyl-4,6-dideoxy-α-*L*-lyxo-hexopyranoside* (**9**).—Compound **9** was obtained starting from **8** (260 mg) by the same procedure described for the preparation of **5** from **4** (53% yield); $[\alpha]_D$ − 12.9° (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz): δ 7.51–7.22 (m, 10 H, ArH), 5.21 (br s, 1 H, H-2), 5.08 (br s, 2 H, Z-CH_2Ph), 4.77 (br d, 1 H, H-1), 4.62 and 4.44 (2d, 2 H, *J* 11.7 Hz, CH_2Ph), 3.86 (m, 2 H, H-3, H-5), 3.63–3.57 (2m, 2 H, CH_2O), 3.19 (m, 2 H, CH_2N), 2.11 (s, 3 H, CH_3CO), 1.74–1.25 (m, 8 H, $(CH_2)_3$, H-4), 1.21 (d, 3 H, $J_{5,6}$ 6 Hz, H-6). Anal. Calcd for $C_{28}H_{37}O_7N$: C, 67.31; H, 7.46; N, 2.80. Found: C, 67.29; H, 7.52; N, 2.84.

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