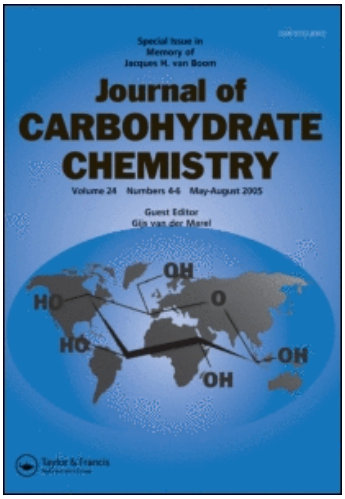


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# New Synthesis of l-Ribofuranose Derivatives from l-Arabinose

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*COMMUNICATION*

# NEW SYNTHESIS OF L-RIBOFURANOSE DERIVATIVES FROM L-ARABINOSE

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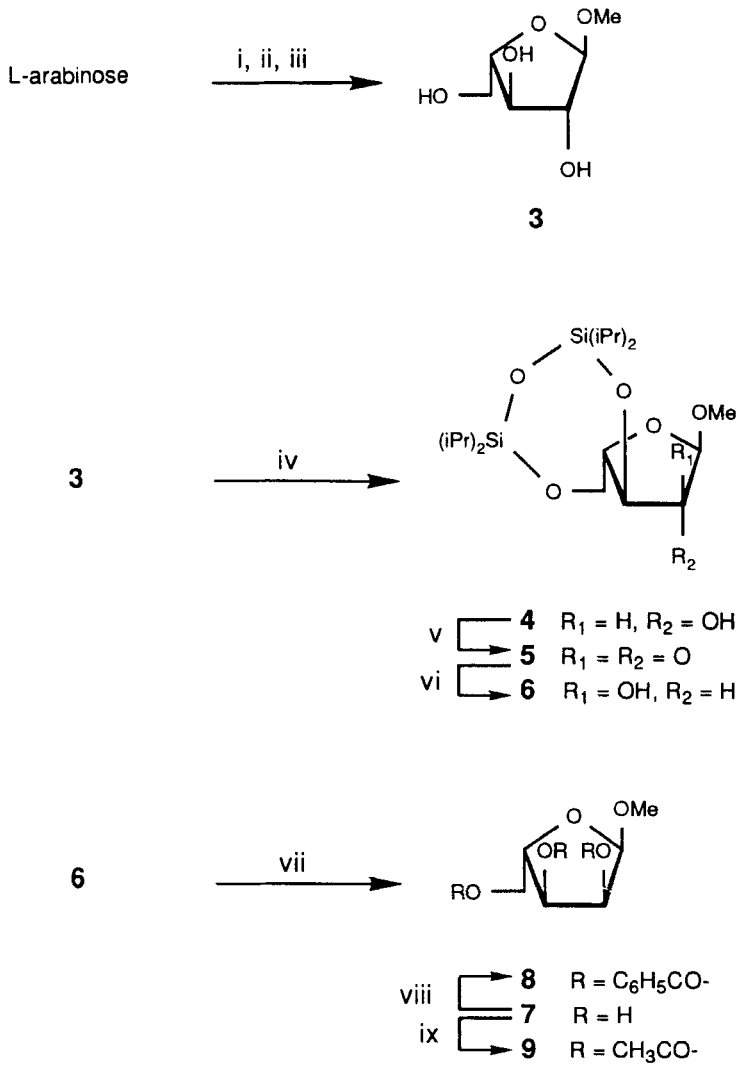
There is a need for L-ribofuranose derivatives suitable for the preparation of L-nucleosides which could be employed to build nucleases resistant "antisense" oligonucleotides[1] and to prepare analogues as potential inhibitors of HIV.[2] Such L-ribofuranoside derivatives were previously obtained by epimerisation at C-2 of L-arabinose in the presence of molybdenic acid[3] and by inversion of configuration at C-2 of L-arabinose and C-3 of L-xylose by nucleophilic displacement of a sulfonate group.[4] In both cases, the desired L-ribofuranoside derivative has to be separated from some remaining starting material. Another method to obtain L-ribose involved the complete inversion of D-ribono-1,4-lactone followed by reduction.[5] We report herein a new transformation of L-arabinose into L-ribofuranose derivatives.

Methyl α-L-arabinofuranoside (**3**) was prepared in 47% yield from L-arabinose via its 2,3,5-tri-*O*-benzoate (**2**) by a classical procedure.[6] Since the introduction of the 1,1,3,3-tetraisopropyldisiloxane-1,3-diyl protecting group by Markiewicz[7] in nucleoside chemistry, it is possible to protect efficiently C-3 and C-5 hydroxyl groups of a pentofuranose in a trans relationship. The derivative with a free hydroxyl at C-2 (**4**) was prepared in 70% yield by this method. It was verified that the inversion of configuration at C-2 by nucleophilic displacement of a sulfonate group was difficult.[4] Compound **4** was also resistant to Mitsunobu reaction, even with reactive carboxylic




Reagents: (i) MeOH, $H^+$; (ii) $C_6H_5COCl$, Pyr.; (iii) MeONa, MeOH; (iv) TIPDS-$Cl_2$, Pyr.; (v) PDC-AcOH; (vi) $NaBH_4$, EtOH 95%; (vii) $NBu_4F$, THF; (viii) $C_6H_5COCl$, Pyr.; (ix) $Ac_2O$, Pyr..

acids such as *p*-nitrobenzoic acid. Consequently, another strategy involving oxidation of that hydroxyl group to a keto function followed by reduction was chosen. The 3,5-*O*-protected derivative **4** was smoothly oxidized by pyridinium dichromate (PDC)-acetic acid reagent in the presence of 3 Å molecular sieves[8] and ketone **5** was obtained in 98% yield. This system, which requires only a 1.5 molar equivalent of chromium species, was found to be superior to other reagents, widely used for the oxidation of pentofuranose derivatives.[9] The reduction of the keto-sugar **5** with sodium borohydride afforded **6** in good yield (89%). No traces of the epimer **4** were detected by TLC, indicating a stereospecific attack of hydride from the less hindered α face.

Deprotection of C-3 and C-5 hydroxyl groups was achieved by treatment of **6** with a solution of tetra-*n*-butylammonium fluoride in THF. Since it is difficult to completely remove this salt from water soluble compounds, **7** was directly acylated with benzoyl or acetyl chloride to afford **8** and **9**, respectively. Unfortunately, none of the products crystallized.

Finally, methyl 2,3,5-tri-*O*-acetyl-α-L-ribofuranoside suitable for nucleoside synthesis, was obtained in 56% overall yield from easily available methyl α-L-arabinofuranoside. Due to the high efficiency of the inversion by oxidation-reduction (88%), the methodology described in this paper compares favorably with previously described ones.[3-5]



## EXPERIMENTAL

**General methods.** Optical rotations were measured on a Perkin-Elmer 141 polarimeter in a 10 cm cell at 22 °C. IR spectra were recorded with a Unicam spectrometer. $^1$H NMR spectra were recorded with Bruker spectrometers with tetramethylsilane as internal standard. Chemical shifts are given in ppm. Analytical TLC was performed on Merck aluminum precoated plates of silica gel 60 F - 254 with detection by UV and spraying with 6 N $H_2SO_4$ and heating about 2 min. at 300 °C. Merck silica gel 60 (300 - 400) and anhydrous solvents were employed for column chromatography. Elemental analyses were performed at the "Service de microanalyse" of the Université Pierre et Marie Curie.

**Methyl 3,5-*O*-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)-α-L-arabinofuranoside (4).** Under a pressure of argon, 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (5 mL, 15.93 mmol) was added dropwise to a cooled (0 °C) and stirred solution of **3**[6] (2.27 g, 13.85 mmol) in anhydrous pyridine (30 mL). Stirring was continued at room

temperature until completion of the reaction was indicated by TLC (2 h). The solvent was evaporated under reduced pressure and the residue partitioned between chloroform (50 mL) and water (10 mL). The organic layer was successively washed with $H_2O$ (5 mL), dilute HCl (5%, 5 mL), $H_2O$ (2 x 10 mL), 5% aqueous $NaHCO_3$ (5 mL), satured brine (5 mL) and $H_2O$ to neutrality. After drying ($Na_2SO_4$), the solvent was evaporated under reduced pressure to give an oil (6.48 g) which was dissolved in $CH_2Cl_2$ and filtered through silica gel. After evaporation of solvent, pure **4** was obtained (3.90 g, 70%) as an homogeneous syrup; $R_f$ 0.75 (6 : 1 ethyl acetate-methanol); $[\alpha]_D^{20}$ - 38.3° (*c* 1.08, $CH_2Cl_2$); IR 3470 $cm^{-1}$; $^1H$ NMR 500 MHz ($CDCl_3$) δ 1.01-1.10 (m, 28H, 4 x $(CH_3)_2$-CH), 3.40 (s, 3H, $OCH_3$), 3.87 (m, 1H, H-4), 3.95 (dd, 1H, $J_{4,5}$ = 3.78 Hz, $J_{5,5'}$ = 12.71 Hz, H-5), 3.97 (dd, 1H, $J_{4,5'}$ = 3.03 Hz, $J_{5,5'}$ = 12.72 Hz, H-5'), 4.15 (m, 1H, H-3), 4.16 (m, 1H, H-2), 4.78 (d, 1H, H-1).

Anal. Calcd for $C_{18}H_{38}O_6Si_2$: C, 56.16; H, 9.42. Found: C, 56.17; H, 9.42.

**Methyl 3,5-*O*-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)-α-L-*threo*-pentofuranosid-2-ulose (5).** To a stirred mixture of **4** (3 g, 7.4 mmol), pyridinium dichromate (4.35 g, 11.55 mmol) and 3 Å molecular sieves (3 g) in $CH_2Cl_2$ (70 mL), acetic acid (1.2 mL, 13.54 mmol) was added. Stirring was continued at room temperature for 18 h. After evaporation of the solvent, a large volume of $Et_2O$ (100 mL) was added to the residue to precipitate most of the chromium salts. The ether solution was dried ($Na_2SO_4$) and slowly filtered through a column containing silica gel and florisil (1 : 1). After evaporation of the solvent under reduced pressure, pure **5** was obtained (2.96 g, 98%) as a syrup; $R_f$ 0.76 (10 : 1 dichloromethane-acetone); $[\alpha]_D^{20}$ +18.2°(*c* 1.33, $CH_2Cl_2$); IR 1780$cm^{-1}$; $^1H$ NMR 200 MHz ($CDCl_3$) δ 1.00-1.08 (m, 28H, 4 x $(CH_3)_2$-CH), 3.47 (s, 3 H, $OCH_3$), 4.11 (m, 3H, H-4, H-5 and H-5'), 4.50 (d, 1H, $J_{3,4}$ = 10.72 Hz, H-3), 4.88 (s, 1H, H-1).

Anal. Calcd for $C_{18}H_{36}O_6Si_2$: C, 53.42; H, 8.97. Found: C, 53.53; H, 8.95.

**Methyl 3,5-*O*-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)-α-L-ribofuranoside (6).** To a cooled (0 °C) solution of **5** (1.47 g, 3.6 mmol) in ethanol (15 mL), sodium borohydride was added (88 mg, 2.3 mmol). Stirring was continued at room temperature until completion of the reaction (1 h). After evaporation of the solvent, the residue was partitioned between EtOAc (30 mL) and water (10 mL). The aqueous layer was extracted with EtOAc (2 x 10 mL). The organic phase was washed successively with brine (2 x 10 mL) and $H_2O$ (10 mL). After drying ($Na_2SO_4$), the solvent was evaporated and **6** was obtained as a homogeneous syrup suitable for the next step (1.45 g, 98%). An analytical sample was obtained by chromatography on silica gel (elution with 1 : 3 ether-pet. ether): 1.31 g (89%); $R_f$ 0.36 (1 : 3 ether-pet.

ether); $[\alpha]^{20}_D$ -50.9° (*c* 1.38, $CH_2Cl_2$); IR 3566 $cm^{-1}$; $^1H$ NMR 500 MHz ($CDCl_3$) δ 1.03-1.09 (m, 28H, 4 x $(CH_3)_2$ -CH), 3.01 (d, 1H, $J_{OH,H2}$ = 8.78 Hz, OH), 3.45 (s, 3H, $OCH_3$), 3.74 (dd, 1H, $J_{5,4}$ = 8.39 Hz, $J_{5,5'}$ = 10.94 Hz, H-5), 4.05 (m, 1H, $J_{4,3}$ = 4.32 Hz, $J_{4,5}$ = 8.41 Hz, H-4), 4.06 (m, 1H, $J_{2,1}$ = 4.23 Hz, H-2), 4.08 (m, 1H, $J_{5',4}$ = 8.52 Hz, $J_{5',5}$ = 10.94 Hz, H-5'), 4.21 (dd, 1H, $J_{3,4}$ = 4.43 Hz, $J_{3,2}$ = 7.32 Hz, H-3), 4.87 (d, 1H, $J_{1,2}$ = 4.22 Hz, H-1).

Anal. Calcd for $C_{18}$ $H_{38}$ $O_6$ $Si_2$: C, 53.16; H, 9.42. Found: C, 53.28; H, 9.46.

**Methyl 2,3,5-Tri-*O*-benzoyl-α-L-ribofuranoside (8).** A 1.1 M solution of $Bu_4NF$ in THF (940 µL, 1.03 mmol) containing **6** (209.8 mg, 0.52 mmol) was stirred at room temperature until TLC indicated completion of the reaction (30 min). Most of THF was evaporated and pyridine (1 mL) and, after cooling at 0 °C, benzoyl chloride (390 µL, 3.36 mmol) were added to the reaction mixture. Stirring was continued at room temperature for 18 h. After evaporation of the solvent, the residue was extracted with $CH_2Cl_2$ (20 mL). The organic layer was washed with $H_2O$ (2 x 5 mL), dilute HCl (5%, 2 x 5 mL), $H_2O$ (10 mL), 5% aqueous $NaHCO_3$ (2 x 5 mL), $H_2O$ to neutrality. After drying ($Na_2SO_4$), the solvent was evaporated under reduced pressure to give an oil (317.9 mg) which was dissolved in toluene and purified by chromatography on silica gel (elution with 1 : 3 ether-pet. ether): 165.0 mg (67%); $R_f$ 0.53 (2 : 1 ether-pet. ether); $[\alpha]^{20}_D$ -79.3° (*c* 1.09, $CH_2Cl_2$); $^1H$ NMR 200 MHz ($CDCl_3$) δ 3.49 (s, 3H, $OCH_3$), 4.57-4.80 (m, 3H, H-5, H-4 and H-5'), 5.33 (dd, 1H, $J_{2,1}$ = 4.24 Hz, $J_{2,3}$ = 6.97 Hz, H-2), 5.39 (d, 1H, $J_{1,2}$ = 4.11 Hz, H-1), 5.72 (dd, 1H, $J_{3,4}$ = 2.89 Hz, $J_{3,2}$ = 6.87 Hz, H-3), 7.24-8.10 (m, 15H, Ar).

Anal. Calcd for $C_{27}$ $H_{24}$ $O_8$: C, 68.06; H, 5.08. Found: C, 67.98; H, 5.17.

**Methyl 2,3,5-Tri-*O*-acetyl-α-L-ribofuranoside. (9)** A 1.1 M solution of $Bu_4NF$ in THF (782 µL, 0.86 mmol) containing **6** (175.7 mg, 0.43 mmol) was stirred at room temperature until TLC indicated completion of the reaction (30 min). Most of THF was evaporated and pyridine (4 mL) and acetic anhydride (325 µL, 3.45 mmol) were added to the reaction mixture. Stirring was continued at room temperature for 1.5 h. After evaporation of the solvent, the residue was poured into ice-water (40 mL) and the mixture stirred for 1 h. The precipitate was extracted with $CH_2Cl_2$ (2 x 15 mL). The organic layer was successively washed with dilute HCl (5%, 10 mL), $H_2O$ (2 x 10 mL), 5% aqueous $NaHCO_3$ (10 mL) and $H_2O$ to neutrality. After drying ($Na_2SO_4$), the solvent was evaporated under reduced pressure to give an oil (219.6 mg). The product was purified by chromatography on silica gel (elution with 1 : 1 ether-pet. ether): 115 mg (92%); $R_f$ 0.35 (5 : 1 ether-pet. ether); $[\alpha]^{20}_D$ -124.5° (*c* 1.43, $CH_2Cl_2$); $^1H$ NMR 200 MHz ($CDCl_3$) δ 2.10 (s, 3H, $CH_3CO$), 4.21 (dd, 1H, $J_{4,5}$ = 3.91 Hz, $J_{5,5'}$

= 10.90 Hz, H-5), 4.26 (m, 1H, $J_{4,3}$ = 3.07 Hz, $J_{4,5}$ = 3.82 Hz, H-4), 4.39 (dd, 1H, $J_{5',4}$ = 2.01 Hz, $J_{5',5}$ = 10.89 Hz, H-5'), 4.98 (dd, 1H, $J_{2,1}$ = 4.46 Hz, $J_{2,3}$ = 7.15 Hz, H-2), 5.14 (d, 1H, $J_{1,2}$ = 4.53 Hz, H-1), 5.17 (dd, 1H, $J_{3,4}$ = 3.09 Hz, $J_{3,2}$ = 7.15 Hz, H-3).

Anal. Calcd for $C_{12}H_{18}O_8$: C, 49.65; H, 6.25. Found: C, 49.67; H, 6.25.

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## REFERENCES

1. U. Asseline, J. F. Hau, S. Czernecki, T. LeDiguarher, M. C. Perlat, J. M. Valéry and N. T. Thuong, *Nuc. Acids Res.*, **19**, 4067 (1991).

2. S. Czernecki and T. LeDiguarher, *Synthesis*, 683 (1991).

3. V. Bilik and J. Caplovic, *Chem. Zvesti*, **27**, 547 (1973).

4. E. M. Acton, K. J. Ryan and L. Goodman, *J. Am. Chem. Soc.*, **86**, 5352 (1964).

5. T. E. Walker and H. P. C. Hogenkamp, *Carbohydr. Res.*, **32**, 413 (1974).

6. H. G. Fletcher in "Methods in Carbohydrate Chemistry", Vol. II, R. L. Whistler and M. L. Wolfrom, Eds., Academic Press Inc., New York, 1963, p 228.

7. W. T. Markiewicz, *J. Chem. Res. (S)*, 24 (1979).

8. S. Czernecki, C. Georgoulis, C. L. Stevens and K. Vijayakumaran, *Tetrahedron Lett.*, **26**, 1699 (1985).

9. V. Samano and M. J. Robins, *Synthesis*, 283 (1991).