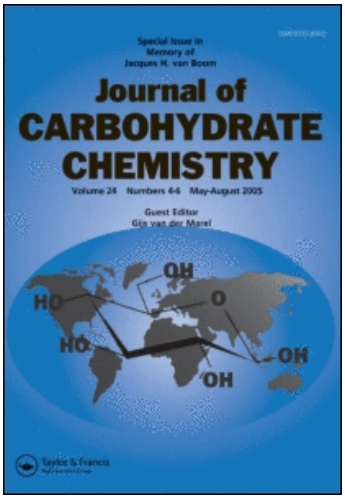

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New Synthesis of l-Ribofuranose Derivatives from l-Xylose

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COMMUNICATION

NEW SYNTHESIS OF L-RIBOFURANOSE DERIVATIVES FROM L-XYLOSE

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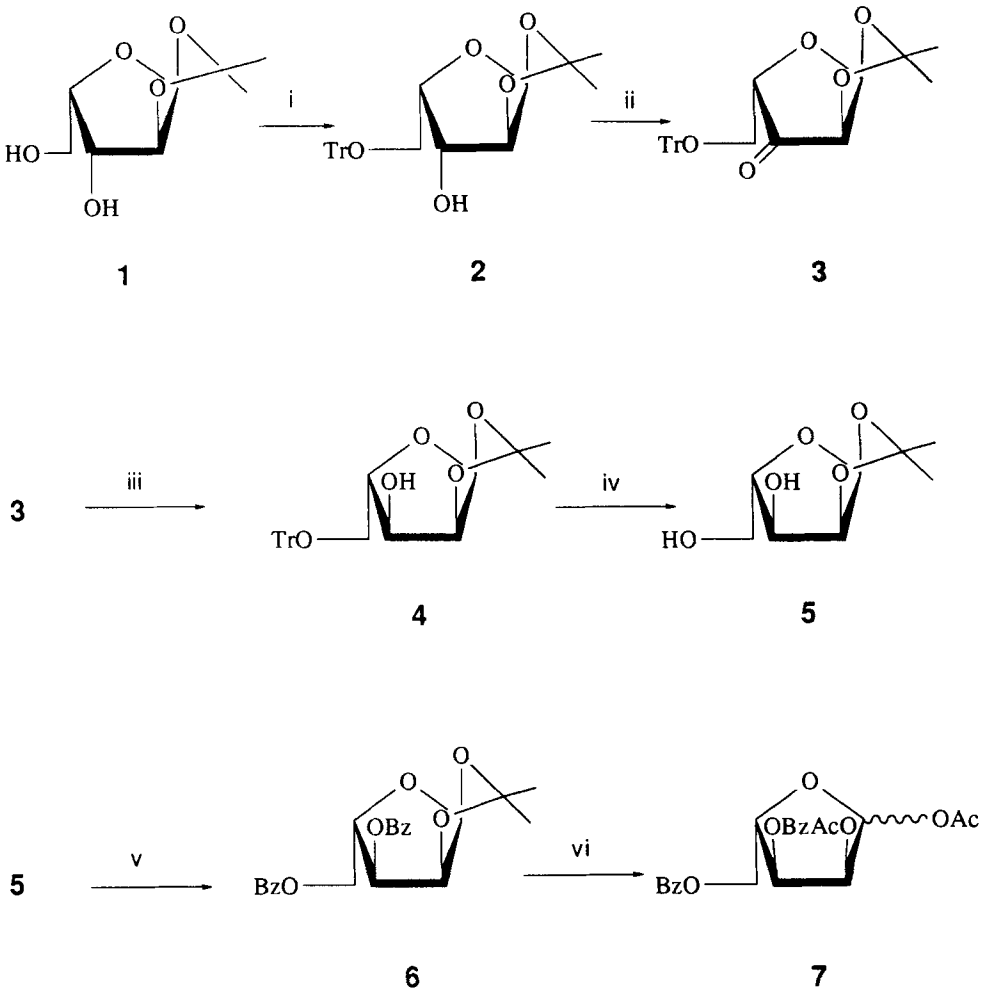
Since L-nucleosides and 2-deoxy L-nucleosides are finding more and more applications for the preparation of nucleases resistant "antisense" oligonucleotides[1] as well as for preparation of modified nucleosides as potential inhibitors of HIV,[2] efficient preparation of L-ribofuranose derivatives is needed. Although L-ribose was obtained by inversion of D-ribono-1,4-lactone followed by reduction,[3] epimerization at C-2 of L-arabinose[4] and inversion of configuration at C-2 of L-arabinose or at C-3 of L-xylose by displacement of a sulfonate group[5] were also evaluated, but were found to be not very satisfactory. We recently published a preparation of L-ribofuranose derivatives from L-arabinose in which the configuration at C-2 was inverted by an oxidation-reduction sequence after suitable protection of O-3 and O-5.[6] Although a high overall yield was obtained, upscaling was difficult because none of the intermediates were obtained in crystalline form. Therefore we decided to evaluate the same methodology starting from L-xylofuranose and we report herein our results.

1,2-*O*-Isopropylidene-α-L-xylofuranose (**1**) was prepared in two steps from L-xylose by using the procedure described for the D-isomer[7] although a more efficient one step procedure appeared recently.[8]

Selective tritylation of **1** afforded compound **2** (91%) which was engaged in the oxidation step without purification. The secondary hydroxyl group of **2** was smoothly and almost quantitatively oxidized with pyridinium dichromate in the presence of 3 Å



Reagents: (i) TrCl, Pyr., 91%; (ii) PDC, AcOH, CH_2Cl_2, 97%; (iii) $NaBH_4$, EtOH, 95%; (iv) H_2, Pd/C, MeOH, 100%; (v) C_6H_5COCl, Pyr., 94%; (vi) Ac_2O, AcOH, H_2SO_4, 88%.

molecular sieves and acetic acid.[10] Although the latter was present, no detritylation was observed. The chromium salts were removed by filtration through a mixture of silica gel and florisil (1 : 1). The crude crystalline ulose **3** (97%) was homogeneous by TLC and directly reduced with sodium borohydride. As in case of the 2-ulose derived from L-arabinose,[6] the reduction was highly stereoselective and the L-*ribo* derivative **4** was obtained in good yield (95%) and purity. No traces of the L-*xylo* derivative **2** could be detected in the reaction mixture by TLC or ^1H NMR . In both cases the hydride adds to the carbonyl opposite to the vicinal C-O bond thus minimizing electronic interactions between this C-O bond and the forming C-H bond.

Detritylation of **4** was efficiently achieved by hydrogenolysis and the formed triphenylmethane removed by trituration with hexane, affording **5**. In order to keep the furanose ring in the final product, **5** was transformed into crystalline benzoylated **6** (94%) before cleavage of the 1,2-*O*-isopropylidene group. This was done under acetylating conditions[11] at 0 °C and afforded **7** as a mixture of α and β anomers (24 : 76) suitable for nucleosides synthesis.

In summary, 1,2-di-*O*-acetyl-4,5-di-*O*-benzoyl-L-ribofuranose was obtained in 75% overall yield from easily available 1,2-*O*-isopropylidene-α-L-xylofuranose. Although L-xylose is more expensive than L-arabinose, this route is more efficient than our previous one[6] because pure crystalline derivatives are obtained in every step, thus avoiding chromatographic purification and allowing upscaling.

EXPERIMENTAL

General methods were the same as in ref. 6.

1,2-*O*-Isopropylidene-α-L-xylofuranose (1) was prepared from L-xylose as described for the D-isomer in ref. 7.

1,2-*O*-Isopropylidene-5-*O*-triphenylmethyl-α-L-xylofuranose (2). A mixture of **1** (5.7 g, 30 mmol) and trityl chloride (10.4 g, 37.5 mmol) was refluxed in anhydrous pyridine (100 mL) for 3 h. The solution was poured into ice-water (1 L) and the mixture was stirred for 30 min. After addition of ether (50 mL) and decantation, the aqueous layer was extracted with ether (3 x 100 mL). The organic layer was washed successively with dilute HCl (10%, 2 x 50 mL), H_2O (2 x 30 mL), 5% aqueous $NaHCO_3$ (3 x 50 mL) and H_2O to neutrality (3 x 100 mL). After drying (Na_2SO_4), the solvent was evaporated under reduced pressure to give an oil which crystallized after trituration with hexane: 11.9 g (91%); Rf 0.37 (1 : 1 ether-hexane); $[\alpha]_D$ + 3° (*c* 1.00, CH_2Cl_2); mp 114-116 °C (lit.[9] mp 118-120 °C for D-isomer); ^1H NMR 200 MHz ($CDCl_3$) δ 1.32 (s, 3H, CH_3C), 1.49 (s, 3H, CH_3C), 3.16 (d, 1H, $J_{OH,3}$

= 2.66 Hz, OH), 3.46 (dd, 1H, $J_{4,5'}$ = 5.2 Hz, $J_{5,5'}$= 10.0 Hz, H-5'), 3.57 (dd, 1H, $J_{4,5}$ = 2.45 Hz, $J_{5,5'}$ = 10.7 Hz, H-5), 4.27 (m, 2H, H-3, H-4), 4.52 (d, 1H, $J_{1,2}$= 3.7 Hz, H-2), 6.01 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1), 7.24-7.47 (m, 15H, Arom.).

Anal. Calcd for $C_{27}H_{28}O_5$: C, 74.98; H, 6.52. Found: C, 74.66; H, 6.47.

1,2-*O*-Isopropylidene-5-*O*-triphenylmethyl-α-L-*threo*-pentofuranose-3-ulose (3). To a stirred mixture of **2** (1.30 g, 3 mmol), pyridinium dichromate (1.76 g, 4.68 mmol) and 3 Å molecular sieves (2.4 g) in CH_2Cl_2 (45 mL), acetic acid (0.33 mL, 5.4 mmol) was added at 0 °C. Stirring was continued at room temperature until TLC showed completion of the reaction (9 h). After evaporation of the solvent, Et_2O (50 mL) was added to the residue to precipitate most of the chromium salts. The ether solution was slowly filtered through a column containing silica gel and florisil (1 : 1). After drying (Na_2SO_4), the solvent was evaporated under reduced pressure to give a white solid: 1.25 g (97%). Recrystallization from hexane afforded an analytical sample: 1.17 g (91%); Rf 0.64 (CH_2Cl_2); $[\alpha]_D$ - 121° (*c* 1.00, CH_2Cl_2); mp 126-128 °C (lit.[9] mp 132° C for D-isomer); ^1H NMR 200 MHz ($CDCl_3$) δ 1.47 (s, 3H, CH_3C), 2.16 (s, 3H, CH_3C), 3.32 (dd, 1H, $J_{5',4}$= 2.52 Hz, $J_{5',5}$= 9.95 Hz, H-5'), 3.50 (dd, 1H, $J_{5,4}$= 2.44 Hz, $J_{5'5}$= 10.14 Hz, H-5), 4.41 (m, 1H, H-4), 4.54 (d, 1H, $J_{2,1}$= 4.44 Hz, H-2), 6.33 (d, 1H, $J_{1,2}$= 4.46 Hz, H-1), 7.20-7.40 (m, 15 H, Arom.).

Anal. Calcd for $C_{27}H_{26}O_5$: C, 75.33; H, 6.09. Found: C, 75.13; H, 6.08.

1,2-*O*-Isopropylidene-5-*O*-triphenylmethyl-α-L-ribofuranose (4). To a cooled solution (0 °C) of **3** (1.30 g, 3 mmol) in ethanol (25 mL), sodium borohydride (80 mg, 1.92 mmol) was added and stirring was continued at room temperature until completion of the reaction (30 min). 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 sucessively with brine (2 x 10 mL) and H_2O (10 mL). After drying (Na_2SO_4), the solvent was evaporated under reduced pressure to give **4** as an oil: 1.23 g (95%). Recrystallization from hexanes afforded an analytical sample: 1.10g (85%); Rf 0.40 (CH_2Cl_2); $[\alpha]_D$ - 26.2° (*c* 1.00, CH_2Cl_2); mp 119-120 °C (lit [9] mp 117 °C for D-isomer); ^1H NMR 200 MHz ($CDCl_3$) δ 1.38 (s, 3H, CH_3C), 1.57 (s, 3H, CH_3C), 2.28 (d, 1H, $J_{OH,3}$ = 9.40 Hz, OH), 3.27 (dd, 1H, $J_{5',4}$ = 4. 25 Hz, $J_{5',5}$ = 10.60 Hz, H-5'), 3.41 (dd, 1H, $J_{5,4}$ = 2.66 Hz, $J_{5,5'}$ = 10.40 Hz, H-5), 3.90 (m, 2H, H-3, H-4), 4.59 (t, 1H, $J_{2,1}$ = 4.23 Hz, $J_{2,3}$ = 4,23 Hz, H-2), 5.89 (d, 1H, $J_{1,2}$= 3.71 Hz, H-1), 7.22-7.49 (m, 15H, Arom.).

Anal. Calcd for $C_{27}H_{28}O_5$: C, 74.98; H, 6.52. Found: C, 74.91; H, 6.49.

1,2-*O*-Isopropylidene-α-L-ribofuranose (5). To a solution of **4** (1.1 g, 2.54 mmol) in absolute methanol (15 mL), Pd/C (45 mg) was added. The mixture was stirred at room temperature under hydrogen for 12 h. After filtration through celite

and evaporation of the solvent under reduced pressure, trituration with hexanes removed triphenylmethane and afforded pure **5** as crystals: 483 mg (100%); Rf 0.54 (ethyl acetate-methanol 3 : 1); $[\alpha]_D$ - 45.3°(*c* 1.00, CH_2Cl_2); mp 84-86 °C (lit.[12] mp 86-87 °C for D-isomer); ^1H NMR 200 MHz ($CDCl_3$) δ 1.38 (s, 3H, CH_3C), 1.58 (s, 3H, CH_3C), 1.86 (m, 1H, OH), 2.39 (d, 1H, $J_{3,OH}$ = 10.5 Hz, OH), 3.90 (m, 4H, H-3, H-4, H-5 and H-5'), 4.59 (dd, 1H, $J_{1,2}$ = 4 Hz, $J_{2,3}$ = 5 Hz, H-2), 5.83 (d, 1H, $J_{1,2}$ = 4 Hz, H-1).

Anal. Calcd for $C_8H_{14}O_5$: C, 50.52; H, 7.42. Found: C, 50.48; H, 7.35.

1,2-*O*-Isopropylidene-3,5-di-*O*-benzoyl-α-L-ribofuranose (6). To a stirred suspension of **5** (258 mg, 1.3 mmol) in anhydrous pyridine (3 mL), benzoyl chloride (0.5 mL, 4.05 mmol) was added under a pressure of argon. Stirring was continued at room temperature for 12 h. After evaporation of the solvent, and coevaporation of pyridine in toluene, the residue was partitioned between CH_2Cl_2 (10 mL) and water (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The organic phase was washed successively with saturated aqueous $NaHCO_3$ (10 mL) and H_2O to neutrality. After drying (Na_2SO_4) and evaporation of the solvent under reduced pressure, pure **6** was obtained as a white solid: 509 mg (94%). Recrystallization from hexane afforded an analytical sample 378 mg (73%); Rf 0.72 (ether-hexane 3 : 1); $[\alpha]_D$ - 117.6 (*c* 1.00, CH_2Cl_2); mp 100-102 °C (lit.[12] mp 101-102 °C for D-isomer); ^1H NMR 200 MHz ($CDCl_3$) δ 1.35 (s, 3H, CH_3C), 1.59 (s, 3H, CH_3C), 4.59 (m, 3H, H-4, H-5 and H-5'), 5.03 (m, 2H, $J_{1,2}$= 3.54 Hz, H-2 and H-3), 5.95 (d, 1H, $J_{1,2}$= 3.57 Hz, H-1), 7.39-7.58 (m, 6H, Arom.) 8.00-8.05 (m, 4H, Arom.).

Anal. Calcd for $C_{22}H_{22}O_7$: C, 66.32; H, 5.57. Found: C, 65.97, H, 5.60.

1,2-Di-*O*-acetyl-4,5-di-*O*-benzoyl-L-ribofuranose (7). To a stirred mixture of **5** (2.1 g; 5.2 mmol) in acetic acid (20 mL), acetic anhydride was added (3.7 mL) at -10 °C. Then a solution of acetic acid (9 mL) and sulfuric acid (1.5 mL) was added dropwise. Stirring was continued at room temperature for 12 h. After evaporation of the solvent, the residue was poured into aqueous sodium acetate (10%, 100 mL) at O °C and the mixture stirred for 30 min and extracted with $CHCl_3$ (2 x 20 mL). The organic layer was washed successively with saturated aqueous $NaHCO_3$ (2 x 15 mL) and H_2O to neutrality (2 x 15 mL). After drying (Na_2SO_4), evaporation of the solvent under reduced pressure and coevaporation of acetic acid with benzene (2 x 20 mL), give **6** as a white solid: 2.05 g (88%); Rf 0.54 (ether-hexane 3 : 1); mp 124 °C (lit.[12] mp 127-128 °C for D-isomer); ^1H NMR 200 MHz ($CDCl_3$) δ 1.97, 2.02, 2.09, 2.17 (4 s, 6H, OAc), 4.60 (m, 3H, H-4, H-5- and H-5'), 5.60 (m, 2H, H-2 and H-3), 6.27 (d, 0.7 H, $J_{1\beta,2}$= 0.76 Hz, H-1β), 6.55 (d, 0.3 H, $J_{1\alpha,2}$= 4.25 Hz, H-1α), 7.37-7.63 (m, 6H, Arom.), 7.98-8.11 (m, 4H, Arom.).

Anal. Calcd for $C_{23}H_{22}O_9$: C, 62.44; H, 4.98. Found: C, 62.15; H, 4.96.

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