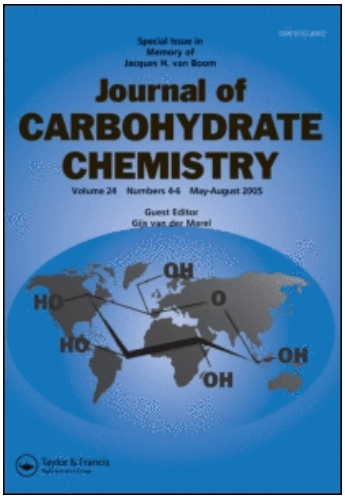

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EFFICIENT SYNTHESES OF D-*PSICO*- AND D-*SORBO*-FURANOSES

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ABSTRACT

D-*Psico*- and D-*sorbo*-furanosyl derivatives **3** and **6** were synthesized in two steps through the methylenation of the D-*ribono*- and D-*xylono*-lactones **1** and **4** with dicyclopentadienyldimethyltitanium, followed by the *cis*-dihydroxylation of the resultant olefins **2** and **5** with catalytic osmium tetroxide and 4-methylmorpholine *N*-oxide.

INTRODUCTION

In connection with a program related to ketofuranosyl nucleosides as potential antiviral agents,[1-4] we required large quantities of D-*psico*- and D-*sorbo*-furanoses. D-Psicofuranose has been previously synthesised by various methods involving several steps with often low overall yields. Moffatt et al. prepared 1,2,3,4,6-penta-*O*-benzoyl-D-psicofuranose from D-fructose in six steps and 9 % overall yield.[5] Some improvements to this procedure were recently made in the course of studies on a herbicidal product, (+)-hydantocidin.[6] Vasella *et al.*, starting from D-ribose, obtained 3,4-*O*-isopropylidene-6-*O*-trityl-D-psicofuranose *via* the corresponding 1-deoxy-1-nitroaldose in five steps and 34 % overall yield.[7] Grouiller *et al.* started from ribonolactone using a nucleophilic addition with the carbanion generated from lithium 1-*O*-tetrahydropyranyl-2-propynide. This route led to D-psicofuranose in six steps and 45 % overall yield.[8] Other authors used γ-lactones for the synthesis of ketoses. Treatment of D-arabinonolactones with benzyloxymethyllithium provided partially protected D-fructofuranose.[9] Reaction of differently substituted ribonolactones with methyllithium gave derivatives of 1-deoxy-D-psicofuranose.[8,10] Wilcox *et al.* were the first to obtain the anomeric β-acetate of 1-

deoxy-psicofuranose through titanium mediated methylenation of ribonolactone.[11] Later, Rajanbabu,[12] then Russo *et al.*[13] also applied Tebbe's reagent, μ-chloro-bis(cyclopentadienyl) (dimethylaluminium)-μ-methylenetitanium, to xylono- and arabinonolactones for the synthesis of 1-methylene sugars as precursors of *C*- and keto-glycosides.

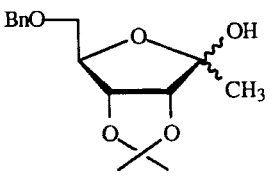
On the other hand, to our knowledge, D-sorbofuranose has not been prepared yet. In the D series, only the acyclic sorbose was obtained by the diazoketone method of Wolfrom et *al.*[14] or, very recently, by treating *aldehydo*-D-xylose with formaldehyde.[15] 4-Deoxy-4-fluorosorbopyranose was prepared by the action of potassium hydrogen fluoride on 3,4-anhydro-β-D-psicopyranose.[16]

In this paper we report the synthesis of the title ketofuranoses in two steps by the methylenation of D-ribono- or xylonolactone with dicyclopentadienyldimethyltitanium, followed by dihydroxylation of the formed 1-methylene sugar with catalytic osmium tetroxide and *N*-methylmorpholine-*N*-oxide (NMO).

RESULTS AND DISCUSSION

D-Psicofuranosyl series

In a first approach 5-*O*-benzyl-2,3-*O*-isopropylidene-D-ribonolactone (**1**)[10] was treated with Tebbe's reagent generated *in situ* according to the practical Grubbs conditions.[17] In method A, the reaction was worked up at room temperature and afforded a mixture of compounds that contained, besides 25 % of the expected olefin **2**, 25 % of the hemiacetal **7** accompanied by 25 % of 6-*O*-benzyl-2-methyl-3,4-*O*-isopropylidene-D-*ribo*-hex-1-en-3,4,5,6-tetrol (**8**). When the reaction was performed exclusively at -40 °C (method B), only two compounds were obtained, the methylene sugar **2** in 33 % and the major product of hydrolysis **7** in 55 %. It is noteworthy that the acetyl derivative of **7** has been recently used in the synthesis of 1-deoxy-β-D-psicofuranosyl nucleosides.[4] While our study was in progress, Collins *et al.* reported the use of Tebbe's reagent in carbohydrate chemistry under the same conditions, with the same results, namely the preponderant formation of the lactol in comparison with the olefin.[18]



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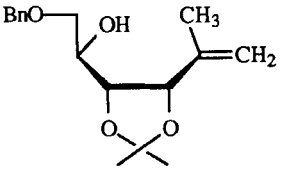

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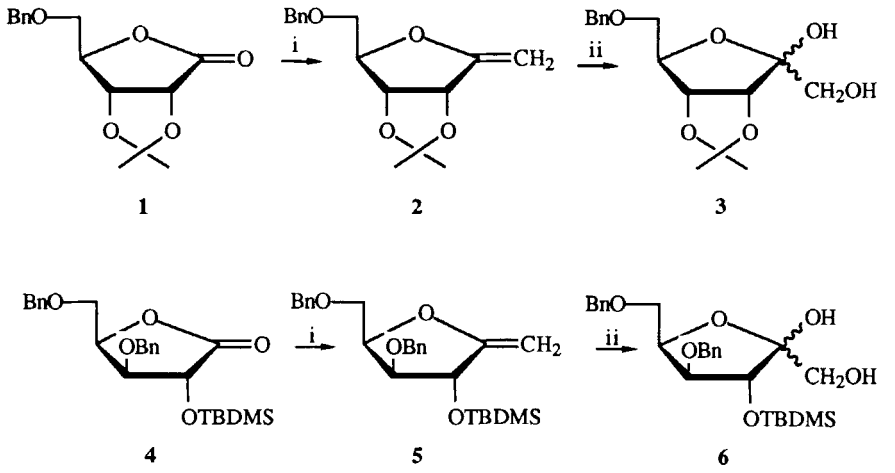

i Cp_2TiMe_2 / toluene
ii OsO_4 / NMO

At that time we proceeded to methylenation of the ribonolactone **1** with dicyclopentadienyldimethyltitanium (method C), a recently introduced alternative to the titanocene methylidene complex.[19] The 1-methylene sugar **2** was obtained with a satisfactory 95 % yield.

An attempt at *cis*-hydroxylation of **2** with potassium permanganate was unsuccessfull. Conversely, treatment of **2** with *N*-methylmorpholine-*N*-oxide and catalytic osmium tetroxide resulted in the formation of the D-psicofuranose **3** as a mixture of β- and α-anomers in a 7/3 ratio (yield 70 %). Anomeric configurations were assigned from their ^{13}C resonances, in agreement with a ^{13}C NMR study of ketohexoses :[20] the C-2 and C-3 resonances of α-D-psicofuranose are shifted upfield relative to those of β-D-psicofuranose by the *cis* interaction between the C-2 and C-3 functional groups.

D-Sorbofuranosyl series

The same two-steps sequence was applied to the D-xylonolactone **4**. Its methylenation according to the method C proceeded with a yield of 75 %. The *cis*-hydroxylation of the resulting *exo*-methylene sugar **5** afforded the new D-sorbofuranosyl derivative **6** (yield 58 %). ^1H and ^{13}C NMR analyses of **6** show the presence of a single anomer to which it is tempting to assign the β configuration. This stereochemistry would be consistent with the results obtained in the D-psicofuranosyl series and would be reenforced by the steric hindrance of the *tert*-butyldimethylsilyloxy group at the C-3 position of the intermediary methylenated compound **5**.

EXPERIMENTAL

General procedures. Solvents were dried by distillation from the appropriate drying agent. Melting points were determined on an electrothermal IA 9100 melting point apparatus and are uncorrected. Analytical thin layer chromatography (TLC) was performed on Kieselgel 60F-254 plates (E. Merck). Column chromatography was carried out with Kieselgel 60 silica gel (250-400 mesh, E. Merck), and shortwave ultraviolet light (254 nm) was used to detect the UV-absorbing spots. ^{1}H and ^{13}C NMR spectra were recorded at 300.13 and 75.5 MHz, respectively, on a BRUKER AM 300 spectrometer. Values are given in part per million (ppm) downfield from the internal standard tetramethylsilane in the following format : chemical shift (multiplicity, integration, coupling constant in hertz). Fast atom bombardment, electron impact, and chemical ionization were collected on a ZAB V.G. mass spectrometer. Elemental analyses were performed at the Service Central de Microanalyse du CNRS at Lyon, France.

2,5-Anhydro-6-*O*-benzyl-1-deoxy-3,4-*O*-isopropylidene-D-*ribo*-hex-1-enitol (2) and 2,5-anhydro-3-*O*-*tert*-butyldimethylsilyl-1-deoxy-4,6-di-*O*-benzyl-D-*xylo*-hex-1-enitol (5). *Method A.* 2 M Trimethylaluminium in toluene (4 mL, 8 mmol) was treated at 20 °C with titanocene dichloride (1g, 4 mmol) for 72 h. The reaction flask was charged with 64 mg (0.23 mmol) of compound **1**, flushed with argon and capped with a rubber septum. Dry toluene (2 mL), dry THF (0.5 mL) and dry pyridine (4 µL) were added from a syringe and the resulting solution stirred and kept at -40 °C. The previously prepared solution of Tebbe's reagent (0.35 mL) was added dropwise and stirring was continued for 0.5 h at -40 °C and then 0.5 h at 0 °C. The resulting dark red mixture was diluted with THF (50 mL) added from a syringe, and cooled to -10 °C. 2N NaOH (50 µL) was added dropwise. The cold bath was removed and the reaction mixture was diluted with 50 mL of ether. Stirring was continued for 10 min and the inorganic residue was removed by filtration through celite and anhydrous $MgSO_4$. The filter cake was washed with excess ether and the crude product was chromatographed on silica gel using 9 : 10 (v/v) hexane-ether as eluent to give the expected compound **2** (16 mg, 25 %), with compound **7** (17 mg) and compound **8** (16 mg).

Method B. The procedure described above was applied to compound **1** (554 mg, 1.99 mmol) with the following modification : after the addition of the Tebbe's reagent, the reaction mixture is stirred at -40 °C for 1.5 h and then treated at a low temperature (-40 °C, -10 °C). After column chromatography, compound **2** (182 mg) was obtained with a 33 % yield along with the compound **7** (321 mg).

Method C. Typical procedure with dimethyltitanocene. A solution of lactone **1** or **4** in dry toluene (5mL/mmol of lactone) and dicyclopentadienyldimethyltitanium (2.1 mmol/mmol of lactone) was stirred in the dark for 24 h at 65 °C under argon. At that time, TLC showed the completion of the reaction. The brownish reaction mixture was concentrated and applied to a column of silica gel. Elution respectively with 1 : 2 or 1 : 9 (v/v) ethyl acetate-hexane afforded the methylenated compound **2** or **5** which was used without further purification.

Compound **2** : 95 % yield; R_f 0.70 (ethyl acetate - hexane 1 : 2); ^1H NMR ($CDCl_3$) δ 7.33 (m, 5H, H arom.), 5.05 (d, 1H, $J_{1a,1b}$ = 6.0 Hz, H-1a), 4.68 (dd, 1H, $J_{1b,3}$ = 1.3 Hz, H-1b), 4.58 and 4.50 (2d, 2H, J_{gem} = 12 Hz, CH_2Ph), 4.48 (m, 2H, H-3, H-5), 3.60 (m, 2H, H-6), 1.51 and 1.37 [2s, 2x3H, $C(CH_3)_2$]; ^{13}C NMR ($CDCl_3$) δ 162.8 (C-2), 137.7 (C quat. arom.), 128.4, 127.8, 127.5 (C arom.), 112.9 [$\underline{C}(CH_3)_2$], 84.8, 80.7, 79.9 (C-3, C-4, C-5), 84.5 (C-1), 73.6 ($\underline{C}H_2Ph$), 70.5 (C-6), 27.1 and 25.8 [$C(\underline{C}H_3)_2$]; MS (FAB) m/z 277 (100, MH^+).

Compound **5** : 75 % yield; R_f 0.4 (ethyl acetate-hexane 1 : 9); ^1H NMR (CD_2Cl_2) δ 7.32 (m, 10H, H arom.), 4.55 (m, 6H, CH_2Ph, H-3, H-4), 4.34 (d, 1H, H-1a), 4.06 (d, 1H, $J_{1b,3}$ = 1.6 Hz, H-1b), 3.84 (m, 1H, H-5), 3.72 (m, 2H, H-6), 0.90 [s, 9H, $(CH_3)_3$ CSi], 0.09 [s, 6H, $(CH_3)_2$Si]; ^{13}C NMR (CD_2Cl_2) δ 168.0 (C-2), 142.8 (C quat. arom.), 133.3, 133.2, 132.8, 132.7, 132.5 (C arom.), 117.0 [$\underline{C}(CH_3)_2$], 88.5 (C-1), 88.1, 86.0, 79.6 (C-3, C-4, C-5), 78.4, 77.4 ($\underline{C}H_2Ph$), 73.3 (C-6), 30.4 [$(\underline{C}H_3)_3$ C-Si], 22.8 [$\underline{C}$-Si], -3.4 and -4.6 [$(CH_3)_2$-Si]; MS (FAB) m/z 441 (100, MH^+).

Compound **7** : R_f 0.27 (ethyl acetate/hexane, 1: 2); ^1H NMR ($CDCl_3$) δ 7.35 (m, 5H, H arom.), 4.94 (s, 1H, OH), 4.84 (dd, 1H, $J_{4,3}$ = 5.9 Hz, $J_{4,5}$ = 1.3 Hz, H-4), 4.65 and 4.54 (2d, 2H, J_{gem} = 11.5 Hz, CH_2Ph), 4.43 (d, 1H, H-3), 4.28 (m, 1H, H-5), 3.65 (m, 2H, H-6), 1.50, 1.49 and 1.32 (3s, 9H, H-1, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ 136.2 (C quat. arom.), 128.7, 128.4, 128.1 (C arom.), 112.4 (C-2), 106.9 [$\underline{C}(CH_3)_2$], 87.7, 84.4, 82.3 (C-3, C-4, C-5), 74.1 ($\underline{C}H_2Ph$), 71.4 (C-6), 26.6 and 25.1 [$C(\underline{C}H_3)_2$], 21.5 (C-1).

Compound **8** : R_f 0.58 (ethyl acetate/hexane, 1 : 2); ^1H NMR ($CDCl_3$) 7.34 (m, 5H, H arom.), 5.20 and 5.03 (2s, 2H, H-1a, H-1b), 4.65 (d, 1H, $J_{3,4}$ = 6.3 Hz, H-3), 4.59 (s, 2H, CH_2Ph), 4.14 (dd, 1H, $J_{4,5}$ = 8.9 Hz, H-4), 3.77 (m, 1H, H-5), 3.72 (dd, 1H, $J_{6a,6b}$ = 9.6 Hz, $J_{6a,5}$ = 2.6 Hz, H-6a), 3.57 (dd, 1H, $J_{6b,5}$ = 6.7 Hz, H-6b), 1.85 (s, 3H, CH_3 vinyl), 1.46 and 1.37 (2s, 2x3H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ 141.2 (C-2), 138.1 (C quat. arom.), 128.4 and 127.7 (C arom.), 112.4 (C-1), 108.2 [$\underline{C}(CH_3)_2$], 80.0, 77.7, 68.8 (C-3, C-4, C-5), 73.4 ($\underline{C}H_2Ph$), 71.6 (C-6), 27.3 and 25.2 [$C(\underline{C}H_3)_2$], 20.7 (CH_3 vinyl).

6-*O*-Benzyl-3,4-*O*-isopropylidene-D-psicofuranose (3) and 3-*O*-*Tert*-butyldimethylsilyl-4,6-di-*O*-benzyl-D-sorbofuranose (6). *General method.* To

an ice-cooled solution of compound **2** or **5** (0.72 mmol) in acetone (6 mL) were added 0.4 mL of a 2.5 % solution of osmium tetroxide in *tert*-butyl alcohol and after 5 min, *N*-methymorpholine-*N*-oxide (90 mg, 0.72 mmol). The reaction mixture was stirred overnight at room temperature. Water (0.4 mL) and sodium sulfite (32 mg) were added and stirring continued for 15 min. Extraction with dichloromethane (3 x 100 mL) followed by usual drying on magnesium sulfate lead to a crude oil. Purification by column chromatography gave pure compound **3** (68 %) as an anomeric mixture of α/β, 3:7 or **6** (58 %).

D-Psicofuranose **3** : R_f 0.50 (ethyl acetate-hexane 2 :1); ^1H NMR (C_6D_6) β-anomer δ 7.28 (m, 5H, H arom.), 4.85 (s, 1H, OH-2), 4.81 (d, 1H, $J_{3,4}$ = 5.6 Hz, H-4), 4.67 (d, 1H, H-3), 4.45 (m, 1H, H-5), 4.22 and 4.15 (2d, 2H, J_{gem} = 11.4 Hz, CH_2Ph), 4.00 (m, 1H, J_{1gem} = 12.0 Hz, H-1a), 3.85 (m, 1H, H-1b), 3.43 (dd, 1H, J_{6gem} = 12.0 Hz, $J_{6a,5}$ = 4.2 Hz, H-6a), 3.23 (dd, 1H, $J_{6b,5}$ = 3.8 Hz, H-6b), 1.52 and 1.23 (2s, 2x3H, $C(CH_3)_2$). α-anomer δ 7.28 (m, 5H, H arom.), 4.31 and 4.24 (2d, 2H, J_{gem} = 11Hz, CH_2Ph), 3.49 (dd, 1H, J_{6gem} = 10 Hz, $J_{6a,5}$ = 2.4 Hz, H-6a), 4.31 (dd, 1H, $J_{6b,5}$ = 2.5 Hz, H-6b), 1.44 and 1.19 (2s,2x3H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) β anomer δ 137.0 (C quat. arom.), 129.4, 129.2, 128.8 (C arom.), 113.4 [$\underline{C}(CH_3)_2$], 106.8 (C.-2), 87.6 (C-3), 83.1 (C-4), 82.4 (C-5), 74.8 [$\underline{C}H_2Ph$], 71.9 (C-6), 65.4 (C-1), 27.0 and 25.5 [$C(\underline{C}H_3)_2$]; α anomer δ 138.0 (C quat. arom.), 129.3, 128.7, 128.5 (C arom.), 115.4 (C quat. isoprop.), 104.4 (C-2), 85.3 (C-3), 82.6 (C-5), 81.8 (C-4), 74.4 ($\underline{C}H_2Ph$), 70.6 (C-6), 66.8 (C-1), 27.4 and 25.8 [$C(\underline{C}H_3)_2$]. MS chemical ionization (NH_3), m/z 638 [10 %, $(2M + NH_4)^+$], 620 (11 % , 638-H_2O), 328 [100 %, $(M+NH_4)^+$], 310 (81 %, 328-H_2O).

Anal. Calcd for $C_{16}H_{23}O_6$: C, 61,74; H, 7.39. Found : C, 61.99; H, 7.04.

D-Sorbofuranose **6** : Rf 0.26 (ethyl acetate-hexane 1:2); ^1H NMR ($CDCl_3$) δ 7.31 (m, 10 H, H arom.), 4.58 (m, 4H, H-3, H-4, CH_2Ph), 4.38 (m, 2H, CH_2Ph), 3.90 (m, 1H, H-5), 3.69 (m, 4H, H-1 and H-6), 1.57 (m, 2H, OH), 0.90 [m, 9H, $(CH_3)_3CSi$], 0.14 and 0.09 [m, 6H, $(CH_3)_2Si$]; ^{13}C NMR ($CDCl_3$) δ 136.2 (C quat. arom.), 128.5, 127.9, 127.7 (C arom.), 103.2 (C-2), 84.1 (C-5), 75.3 (C-4), 73.6 ($\underline{C}H_2Ph$), 72.5 (C-3), 67.9 (C-6), 65.1 (C-1), 29.7 [$(\underline{C}H_3)_3CSi$], 25.1 (C-Si), -5.3 and -5.5 [$(CH_3)_2Si$].

Anal. Calcd for $C_{26}H_{38}O_6Si$: C, 65.81; H, 8.01. Found : C, 66.02; H, 7.76.

2-*O*-*Tert*-butyldimethylsilyl-3,5-di-*O*-benzyl-D-xylonolactone (4). To a solution of 3,5-di-*O*-benzyl-D-xylonolactone [21] (0.23 g, 0.7 mmol) and imidazole (0.10 g, 2.2 equiv.) in DMF (0.7 mL, 1 mL/mmol) *tert*-butyldimethylsilyl chloride (0.12 g, 1.1 equiv.) was added. The reaction mixture was stirred with the exclusion of moisture for 1 h at room temperature. After adding iced water, the mixture was extracted with diethyl ether. The organic layer was dried over magnesium sulfate, then filtered.

The filtrate was concentrated to an oil which was purified by column chromatography on silica gel with 1:2 (v/v) ethyl acetate-hexane as eluent. Concentration of the appropriate fractions yielded pure **4** (0.23 g, 74 %) as a white solid : mp 97-99 °C; R_f 0.64 (ethyl acetate- hexane 1:2); ^1H NMR ($CDCl_3$) δ 7.28 (m, 10H, H arom.), 4.63 (m, 2H, H-2, H-3), 4.52 (m, 4H, CH_2Ph), 4.23 (t, 1H, H-4), 3.72 (m, 2H, H-5), 0.90 [s, 9H, $(CH_3)_3CSi$], 0.15 and 0.10 [2s, 2x3H, $(CH_3)_2Si$]; ^{13}C NMR (CD_2Cl_2) δ 173.7 (C-1), 137.5 (C quat. arom.), 128.6, 128.4, 128.1, 127.8, 127.6 (C arom.), 81.4, 77.2, 72.9 (C-2, C-3, C-4), 73.7, 73.0 ($\underline{C}H_2Ph$), 67.4 (C-5), 25.7 [$(\underline{C}H_3)_3CSi$], 18.2 (CSi), -4.5 and -5.2 [$(CH_3)_2Si$].

Anal. Calcd for $C_{25}H_{34}O_5Si$: C, 67.84; H, 7.74. Found : C, 67.79; H, 7.71.

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