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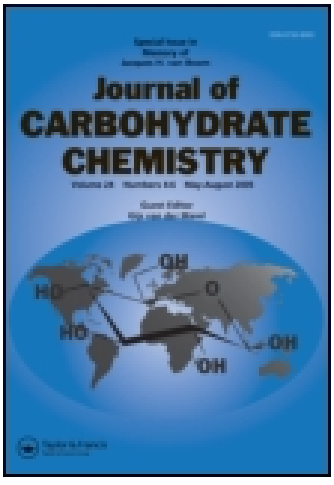

Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lcar20

Synthesis of Differently Protected 1-C-Methyl-Ribofuranoses Intermediates for the Preparation of Biologically Active 1′-C-Methyl-Ribonucleosides

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Published online: 24 Jul 2008.

To cite this article: Laura Alessandrini, Silvana Casati, Pierangela Ciuffreda, Roberta Ottria & Enzo Santaniello (2008) Synthesis of Differently Protected 1-C-Methyl-Ribofuranoses Intermediates for the Preparation of Biologically Active 1′-C-Methyl-Ribonucleosides, Journal of Carbohydrate Chemistry, 27:5, 332-344, DOI: 10.1080/07328300802217848

To link to this article: http://dx.doi.org/10.1080/07328300802217848

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Journal of Carbohydrate Chemistry, 27:332–344, 2008
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ISSN: 0732-8303 print 1532-2327 online
DOI: 10.1080/07328300802217848

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Synthesis of Differently Protected 1-*C*-Methyl-Ribofuranoses Intermediates for the Preparation of Biologically Active 1′-*C*-Methyl-Ribonucleosides

Laura Alessandrini,[1] Silvana Casati,[1] Pierangela Ciuffreda,[1] Roberta Ottria,[1] and Enzo Santaniello[2]

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Starting from D-ribose, differently protected 1-*C*-methyl-D-ribofuranoses have been prepared as intermediates for the synthesis of variously modified 1′-*C*-methyl-ribonucleosides, a class of compounds potentially endowed with interesting biological activity.

Keywords 1-*C*-Methyl-D-ribofuranoses, 1-Deoxy-psicofuranoses, D-Ribonolactone, Tetrapropylammonium perruthenate

INTRODUCTION

Synthetic nucleosides with modifications in the carbohydrate or base moiety are often characterized by anticancer[1] or antiviral[2–4] activity. In this respect, 40 years ago it was recognized that modifications at the 1′-position of adenosine, as in psicoadenosine (Fig. 1), "prevent deamination, while

Received April 22, 2008; accepted May 20, 2008.
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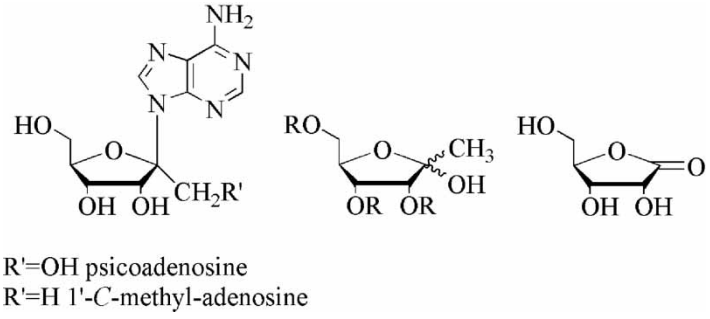

Figure 1: Structure of 1′-*C*-substituted nucleosides, 1-deoxypsicofuranose derivatives, and D-ribonolactone.

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permitting good growth inhibitory activity."[5] Therefore, "modifications at this position, although chemically difficult, appear to be desirable."[5]

Due to this synthetic difficulty, only a few 1′-*C*-substituted nucleosides have been prepared so far[6–9] and new promising biological activity for this class of compounds has been recently disclosed.[10] For our project related to the synthesis of analogues of 1′-*C*-methyl-adenosine,[11,12] gram quantities of 1-deoxypsicofuranoses were required (Fig. 1).

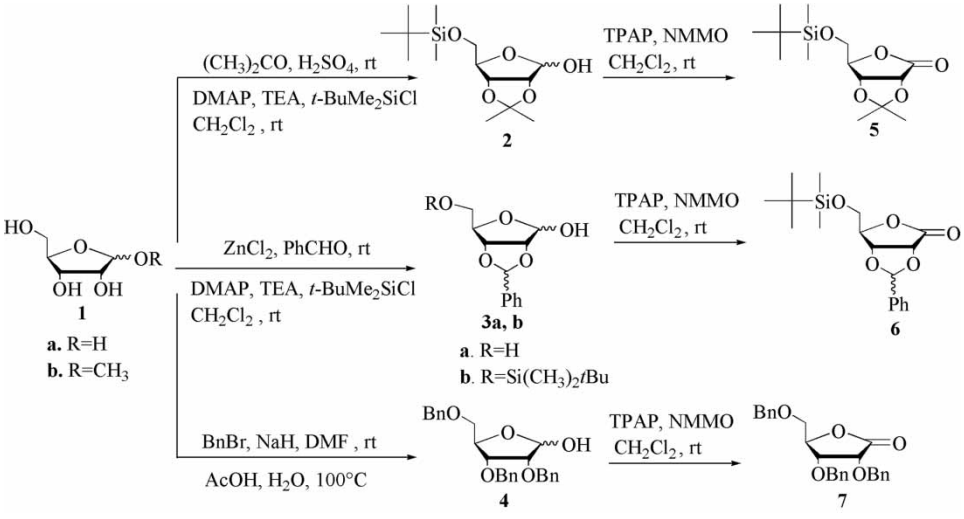
RESULTS AND DISCUSSION

Synthesis of Differently Protected D-Ribonolactone Derivatives from D-Ribose

D-Ribonolactone would represent the ideal starting material for this synthesis, but its high price is not adequate to large-scale preparations. For this reason, D-ribose has been chosen as the alternative starting material as already proposed for the preparation of kilogram scale of a few D-ribonolactone derivatives.[13,14]

We have tried classical oxidations including the reactions with permanganate[13] or pyridinium chlorochromate[15] and the reagent of choice was tetrapropylammonium perrhuthenate (TPAP) under catalytic conditions with N-methylmorpholine N-oxide (NMMO) as co-oxidant.[16] This oxidizing system, previously applied to the synthesis of lactones from pyranoses and furanoses protected as benzyl and allyl ethers,[17] allowed a nearly quantitative transformation (95% of recovered purified product) of protected D-ribofuranoses **2**, **3b**, and **4** to the corresponding lactones **5**, **6**, and **7** (Sch. 1).

The preparation of lactone **6** started from the reaction of D-ribose (**1a**) with benzaldehyde in the presence of zinc chloride.[18] 2,3-Benzylidene derivative **3a** was obtained as an *endo*/*exo* mixture of the phenyl group of the benzylidene moiety, the β-anomer prevailing over the α-one (8:1 ratio).[19] ^{1}H NMR



Scheme 1: Synthesis of protected D-ribonolactones **5**, **6**, and **7**.

analysis of the two products purified by flash chromatography showed that the less polar product corresponds to the β-anomer, characterized by signals of H-C(1) (doublets at 5.53 and 5.56 ppm) coupled with H-C(2) ($J < 1$ Hz). The more polar product corresponds to the α-anomer, characterized by signals of H-C(1) (doublets at 5.96 and 5.98 ppm) coupled with H-C(2) ($J = 3.7$ Hz). Compound **3a** was utilized as a crude α/β mixture, silylated to ribofuranose **3b**, which was then oxidized with TPAP/NMMO to lactone **6** (3:1 *exo*/*endo*, overall yield from D-ribose 51%). The *endo* (or *R*) configuration for the phenyl group of the major isomer of compound **6** was assigned by analysis of the NOE experiment. Saturation of the benzylidene proton resulted in NOEs of H-C(2) and H-C(3) signals, whereas H-C(4) was not affected. As a complementary result, in the minor isomer the irradiation of the benzylidene proton led to H-C(4) signal enhancement and the configuration *exo* (or *S*) was assigned.

We have also synthesized 2,3,5-tribenzyl-D-ribono-1,4-lactone **7**, considering that the corresponding 1-*C*-methyl-ribofuranose **10** could be a useful intermediate for the synthesis of 1′-*C*-methyl-adenosine. 2,3,5-Tri-*O*-benzyl-D-ribofuranose (**4**) was prepared from 1-*O*-methyl-ribofuranose (**1b**) essentially as described in the literature[20] and quantitatively oxidized to lactone **7** using TPAP/NMMO (Sch. 1).

Synthesis of 1-*C*-methyl-ribofuranoses

Reaction of protected D-ribonolactones with organometallic reagents is a well-known methodology for the synthesis of *C*-nucleosides.[21] It has been reported that ribonolactone **5** reacts with methyllithium at low temperature to

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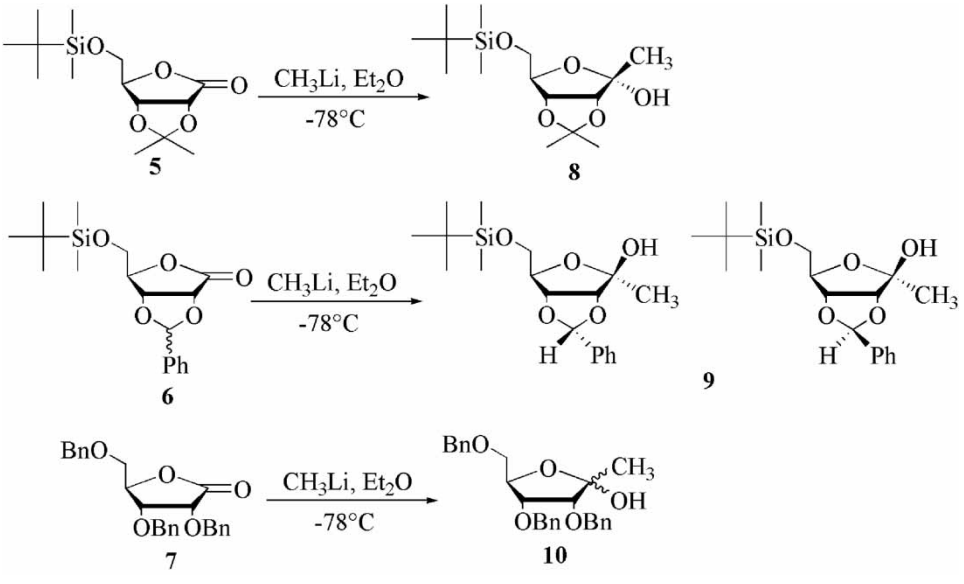
afford the corresponding 1-deoxy-psicofuranose **8**, as only one anomer.[6,7,11] Opening of the ribonolactone to the corresponding methyl ketone and related formation of a tertiary alcohol reported for other lactones[22] were not observed in the case of lactone **5**.[23] We have verified that **8** presents only the α-OH and have not observed the formation of other competing side products. Under the same conditions, the methylation of 2,3-benzylidene lactone **6**[11] afforded a mixture of unidentified products along with 1-deoxypsicofuranose **9** that could only be isolated in 38% yield. Compound **9** is an *endo*/*exo* mixture of the anomer that presents the methyl group in the α position, as evidenced by NOE experiments in which irradiation of methyl group at C-1 led to H-C(5) enhancement. In the ^{1}H NMR spectrum of compound **9** we observed two signals corresponding to the 1-methyl at 1.62 ppm (*exo*) and 2.38 ppm (*endo*). The downshift of the signal at 2.38 ppm in the *endo*-**9** can be explained by the influence of the vicinal phenyl group at the same side of the methyl group.

Finally, we examined the methylation of lactone **7** and obtained compound **10** in good yield (91% of purified product) as an anomeric mixture (1 α-CH_3:3.5 β-CH_3 ratio, as determined by NMR analysis) with no evidence for other side products (Sch. 2).

Acetylation of 1-*C*-methyl-ribofuranoses

The synthesis of 1′-*C*-methyl-nucleosides required the acetylation of 1-deoxy-psicofuranoses before the coupling with the base.[6,7,9,11] The



Scheme 2: Methylation of lactones **5**, **6**, and **7**.

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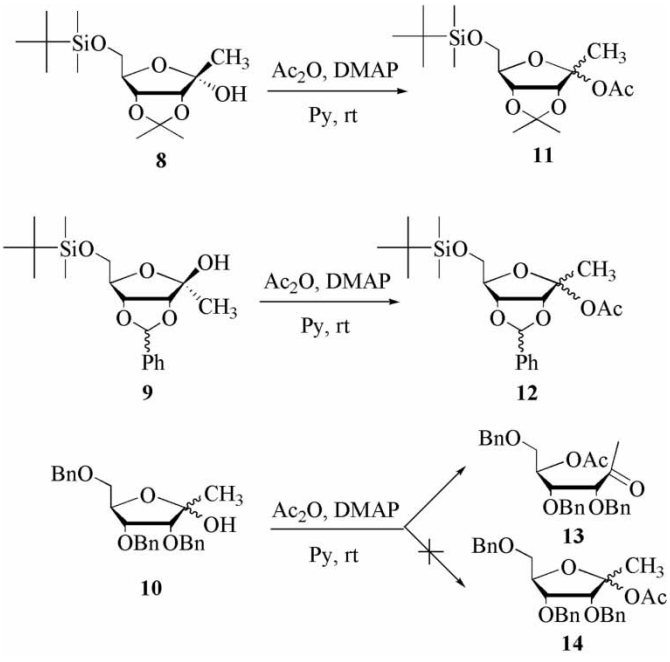

Scheme 3: Acetylation of 1-*C*-methyl-ribofuranoses **8**, **9**, and **10**.

acetylation of compound **8** has been studied in detail and it has been demonstrated that, starting from an anomerically pure **8**, an α/β mixture of acetate **11** is formed (α-anomer 28%, β-anomer 58%).[11]

The acetylation of anomerically pure **9** yielded an equimolar mixture of four acetyl derivatives **12**, α-acetate (*endo*/*exo*), and β-acetate (*endo*/*exo*) with a small amount of acyclic compounds, and this discourages from the use of this intermediate for 1′-*C*-methyl-nucleosides synthesis. Under the same conditions of acetylation, 1-deoxy-psicofuranose **10** afforded only one product (60% yield) that did not correspond to the expected cyclic acetate **14**. ^{1}H NMR analysis of the isolated product showed resonances of H-C(5) at 5.32 ppm and of H-C(3) at 4.05 ppm, consistent with an acyclic structure. The singlet at 2.14 ppm in the ^{1}H NMR spectrum and the signal at 208.19 in the ^{13}C NMR spectrum suggested that a methyl ketone was present in the structure. Furthermore, the resonance at 169.76 ppm in the ^{13}C NMR indicated the presence of an acetate and the structure of acyclic ketohexose was proposed for the product **13** (Sch. 3).

CONCLUSIONS

We have investigated the preparation of a few 1-*C*-methyl-ribofuranoses starting from D-ribose (**1a**), which was transformed in the corresponding

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derivatives **2**, **3b**, and **4**. The oxidation of these compounds to the corresponding lactones **5**, **6**, and **7** has been quantitatively achieved with TPAP under catalytic conditions with NMMO as co-oxidant. The methylation of lactones **5** and **7** satisfactorily afforded 1-*C*-methyl-ribofuranoses **8** and **10**, whereas the yield of 1-*C*-methyl-ribofuranose **9** from lactone **6** was low. The acetates **11**, **12**, and **14** are key intermediates for the synthesis of 1′-*C*-methyl-nucleosides. Under standard acetylating conditions the 3,4-*O*-benzylidene derivative **9** gave the acetate mixture **12** in low yields and an open form was the only product obtained from the benzyl derivative **10**. Only the acetate of 3,4-*O*-isopropylidene-1-*C*-methyl-ribofuranose **11** could be prepared in satisfactory yield.[12] In light of our results, starting from **1a**, only the synthetic pathway leading to the acetates **11** is suitable for the synthesis of 1′-*C*-methyl-nucleosides.

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EXPERIMENTAL

General

Melting points were recorded on a Stuart Scientific SMP3 instrument and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter using sodium lamp at 589 nm in $CHCl_3$.^{1}H NMR spectra were recorded at 303 K on Bruker AM-500 spectrometer operating at 500.13 and 125.76 MHz for ^{1}H and ^{13}C, respectively, equipped with an Aspect 3000 computer, a process control, and an array processor. The ^{1}H NMR chemical shifts are reported in parts per million, using as reference the signal for residual solvent protons (7.24 for $CDCl_3$), and coupling constants (J) are given in Hertz. In the ^{13}C NMR spectra the residual solvent signal was used as an internal reference ($CDCl_3$, triplet at $\delta = 77.23$ ppm). All assignments were confirmed with the aid of two-dimensional ^{1}H,^{1}H (COSYGPQF) or ^{1}H,^{13}C (INV4GPQF) or ^{1}H,^{13}C (INV4GPLRNDQF) experiments using standard Bruker pulse programs. Mass spectra were recorded on Finnigan LCQ-Deca (Termoquest) in ESI positive-ion mode, KV 5.00, 225°C, 15 V.

The progress of all reactions and column chromatography were monitored by TLC (Silica Gel 60 F_{254} precoated plates with fluorescent indicator, Merck).

Purification of products was achieved by flash chromatography using silica gel 60 (230–400 mesh, Merck). 2,3,5-Tri-*O*-benzyl-D-ribofuranose (**4**),[20] 6-*O*-(*tert*-butyldimethylsilyl)-3,4-*O*-isopropylidene-1-deoxy-D-psicofuranose (**8**), and 2-*O*-acetyl-6-*O*-(*tert*-butyldimethylsilyl)-3,4-*O*-isopropylidene-1-deoxy-D-psicofuranose (**11**)[11] were prepared according to literature and verified by NMR and ESI-MS.

*2,3-O-Benzylidene-α/β-D-ribofuranose (**3a**)*

A mixture of D-ribose **1a** (1.0 g, 6.6 mmol), $ZnCl_2$ (0.83 g, 6.1 mmol), and benzaldehyde (4.5 mL, 45.0 mmol) was stirred for 18 h. Aqueous 40%

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$NaHSO_3$ (75 mL) was added, the mixture stirred for 15 min, and, after evaporation at reduced pressure, the residue was treated with CH_2Cl_2 (120 mL). The resulting slurry was stirred vigorously for 1 h and filtered and the filtrate evaporated. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 6:4) and two products were separated corresponding to α-anomer (R*f* 0.125 in petroleum ether/ethyl acetate, 6:4) and β-anomer (R*f* 0.375 in petroleum ether/ethyl acetate, 6:4) (1:8) of the *endo*/*exo* mixture of title compound (64% yield).[19]

β-**3a**: 0.90 g; ^{1}H NMR *endo* $\delta = 7.45-7.44$ (m, 5H, Ph), 5.80 (s, 1H, *H*-CPh), 5.56 (d, $J < 1$, 1H, H-1), 4.90 (d, $J = 6.2$ Hz, 1H, H-2), 4.68 (d, $J = 6.2$ Hz, 1H, H-3), 4.58–4.57 (m, 1H, H-4), 3.82–3.75 (m, AB part of ABX system, 2H, H-5a,b) ppm; *exo* $\delta = 7.39-7.36$ (m, 5H, Ph), 5.97 (s, 1H, *H*-CPh), 5.53 (d, $J < 1$, 1H, H-1), 4.98 (d, $J = 5.6$ Hz, 1H, H-2), 4.69 (d, $J = 5.6$ Hz, 1H, H-3), 4.53–4.50 (m, 1H, H-4), 3.82–3.75 (m, AB part of ABX system, 2H, H-5a,b) ppm.

α-**3a**: 0.11 g; ^{1}H NMR *endo* $\delta = 7.47-7.44$ (m, 5H, Ph), 6.0 (s, 1H, *H*-CPh), 5.96 (d, $J = 3.7$, 1H, H-1), 4.63 (dd, $J = 3.7$ Hz, $J = 5.3$ Hz, 1H, H-2), 4.09 (dd, $J = 5.3$ Hz, $J = 8.4$ Hz, 1H, H-3), 3.97 (dd, $J = 2.7$ Hz, $J = 12.1$ Hz, 1H, H-5a), 3.91 (ddd, $J = 2.7$ Hz, $J = 2.7$ Hz, $J = 8.4$ Hz, 1H, H-4), 3.73 (dd, $J = 2.7$ Hz, $J = 12.1$ Hz, 1H, H-5b) ppm; *exo* $\delta = 7.41-7.38$ (m, 5H, Ph), 6.18 (s, 1H, *H*-CPh), 5.98 (d, $J = 3.7$, 1H, H-1), 4.71 (dd, $J = 3.7$ Hz, $J = 5.3$ Hz, 1H, H-2), 4.11 (dd, $J = 5.3$ Hz, $J = 8.4$ Hz, 1H, H-3), 3.97 (dd, $J = 2.7$ Hz, $J = 12.1$ Hz, 1H, H-5a), 3.91 (ddd, $J = 2.7$ Hz, $J = 2.7$ Hz, $J = 8.4$ Hz, 1H, H-4), 3.73 (dd, $J = 2.7$ Hz, $J = 12.1$ Hz, 1H, H-5b) ppm.

5-O-(tert-Butyldimethylsilyl)-2,3-O-benzylidene-α/β*-*D*-ribofuranose (**3b**)*

To a solution of the α/β mixture of **3a** (1.0 g, 4.2 mmol) in dry CH_2Cl_2 (50 mL) under N_2, triethylamine (0.64 mL, 4.6 mmol), DMAP (0.05 g, 0.42 mmol) in dry CH_2Cl_2 (5 mL) and *tert*-butyldimethylsilylchloride (0.69 g, 4.6 mmol) in dry CH_2Cl_2 (30 mL) were sequentially added. The mixture was stirred at rt for 5 h and treated with 1M HCl solution to acidic pH, then with $NaHCO_3$ and H_2O to pH 7.0. The solution was dried on Na_2SO_4 and evaporated under reduced pressure to give crude α/β mixture of **3b** (0.90 g, 83% yield, *endo*/*exo*).[24]

β-**3b**: ^{1}H NMR *endo* $\delta = 7.54-7.51$ (m, 2H, Ph), 7.43–7.38 (m, 3H, Ph), 5.79 (s, 1H, *H*-CPh), 5.47 (d, $J < 1$, 1H, H-1), 4.82 (d, $J = 5.0$ Hz, 1H, H-2), 4.64 (d, $J = 5.0$ Hz, 1H, H-3), 4.54 (dd, $J = 2.4$ Hz, $J = 2.4$ Hz, 1H, H-4), 3.88–3.82 (m, AB part of ABX system, 2H, H-5a,b), 0.98 (s, 9H, $SiC(CH_3)_3$), 0.18 (s, 3H, $SiCH_3$), 0.16 (s, 3H, $SiCH_3$) ppm; *exo* $\delta = 7.50-7.48$ (m, 2H, Ph), 7.54–7.51 (m, 2H, Ph), 6.00 (s, 1H, *H*-CPh), 5.44 (d, $J < 1$, 1H, H-1), 4.92 (d, $J = 5.0$ Hz, 1H, H-2), 4.66 (d, $J = 5.0$ Hz, 1H, H-3), 4.49 (dd, $J = 2.4$ Hz,

$J = 2.4$ Hz, 1H, H-4), 3.84–3.78 (m, AB part of ABX system, 2H, H-5a,b) 0.97 (s, 9H, $SiC(CH_3)_3$), 0.19 (s, 3H, $SiCH_3$), 0.18 (s, 3H, $SiCH_3$) ppm.

α-**3b**: ^{1}H NMR *endo* $\delta = 7.52–7.48$ (m, 2H, Ph), 7.43–7.38 (m, 3H, Ph), 6.02 (s, 1H, *H*-CPh), 5.88 (d, $J = 4.6$, 1H, H-1), 4.50 (dd, $J = 4.6$ Hz, $J = 4.8$ Hz, 1H, H-2), 4.25 (dd, $J = 4.8$ Hz, $J = 5.3$ Hz, 1H, H-3), 3.95–3.90 (m, *m* 1H, H-4), 3.76–3.69 (m, AB part of ABX system, 2H, H-5a,b), 0.97 (s, 9H, $SiC(CH_3)_3$), 0.18 (s, 3H, $SiCH_3$), 0.16 (s, 3H, $SiCH_3$) ppm; *exo* $\delta = 7.62–7.58$ (m, 2H, Ph), 7.43–7.38 (m, 3H, Ph), 6.17 (s, 1H, *H*-CPh), 5.91 (d, $J = 4.6$, 1H, H-1), 4.61 (dd, $J = 4.6$ Hz, $J = 4.8$ Hz, 1H, H-2), 4.23 (dd, $J = 4.8$ Hz, $J = 5.3$ Hz, 1H, H-3), 3.92–3.87 (m, 1H, H-4), 3.72–3.66 (m, AB part of ABX system, 2H, H-5a,b), 0.98 (s, 9H, $SiC(CH_3)_3$), 0.19 (s, 3H, $SiCH_3$), 0.15 (s, 3H, $SiCH_3$) ppm.

General Procedure for the Tetrapropylammonium Perruthenate (TPAP) Oxidation

A solution of ribofuranose derivative (5.0 mmol) in dry CH_2Cl_2 (40 mL) with NMMO (1.17 g, 10.0 mmol) and molecular sieves (2.5 g) was stirred at rt and TPAP (0.175 g, 0.5 mmol) was added. After 30 min of stirring, the oxidation was complete and was filtered on a celite pad that was then washed with CH_2Cl_2. The filtrate was evaporated under reduced pressure to give the crude product.

5-O-(tert-Butyldimethylsilyl)-2,3-O-isopropylidene-D-ribono-1,4-lactone (5)

Colorless crystals (1.44 g, 95%); mp 69–71°C [lit.[25] 69–70°C]; $[\alpha]_D^{20}$ −48.7 (c = 1.00, $CHCl_3$) {[13]$[\alpha]_D^{20}$ −46.6 (c = 0.80, $CHCl_3$)}; ^{1}H NMR: $\delta = 4.76–4.72$ (m, 2H, H-2 and H-3), 4.61 (ddd, $J = 1.0$ Hz, $J = 1.9$ Hz, $J = 5.6$ Hz, 1H, H-4), 3.91 (dd, $J = 1.9$ Hz, $J = 11.3$ Hz, 1H, H-5a), 3.82 (dd, $J = 1.0$ Hz, $J = 11.3$ Hz, 1H, H-5b), 1.49 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 0.89 (s, 3H, $SiC(CH_3)_3$), 0.09 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$) ppm. ^{13}C NMR (500 MHz; $CDCl_3$, 25°C): $\delta = 174.17$ (C=O), 112.99 (C_{quat}), 82.31 (C-4), 78.47 (C-3), 75.79 (C-2), 62.98 (C-5), 26.78 (CCH_3), 25.76 ($SiC(CH_3)_3$), 25.58 (CCH_3), 18.19 ($SiC(CH_3)_3$), −5.62 ($SiCH_3$), −5.77 ($SiCH_3$) ppm. M/z 320 $(M + NH_3)^+$.

*5-O-(tert-Butyldimethylsilyl)-2,3-O-benzylidene-D-ribono-1,4-lactone (**6**)*

Colorless syrup (1.66 g, 95%, *endo*/*exo* 3:1).

endo-**6**: ^{1}H NMR $\delta = 7.49–7.47$ (2H, m, Ph), 7.43–7.41 (m, 3H, Ph), 5.99 (s, 1H, PhC*H*), 4.90–4.87 (m, 2H, H-2 and H-3), 4.77–4.76 (ddd, $J < 1.0$ Hz, $J = 1.3$ Hz, $J = 2.0$ Hz 1H, H-4), 3.96 (dd, $J = 2.0$ Hz, $J = 11.3$ Hz, 1H, H-5a), 3.87 (dd, $J = 1.3$ Hz, $J = 11.3$ Hz, 1H, H-5b), 0.93 (s, 9H, $SiC(CH_3)_3$), 0.12 (s, 3H, $SiCH_3$), 0.11 (s, 3H, $SiCH_3$) ppm. ^{13}C NMR: $\delta = 172.95$ (C=O), 135.29

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(*Ph*C), 130.06 (*Ph*CH), 128.52 (*Ph*CH), 126.85 (*Ph*CH), 106.57 (Ph*C*H), 81.61 (C-3), 80.08 (C-2), 75.91 (C-4), 63,17 (C-5), 25.79 (SiC(CH_3)$_3$), 18.22 (Si*C*(CH_3)$_3$), −5.58 ($SiCH_3$), −5.72 ($SiCH_3$) ppm. *M*/*z* 373 (M + Na), 723 (M + M + Na).

exo-**6**: ^{1}H NMR $\delta = 7.51–7.48$ (2H, m, Ph), 7.43–7.42 (m, 3H, Ph), 5.98 (s, 1H, PhC*H*), 4.99 (d, $J = 5.7$ Hz, 1H, H-2), 4.82–4.80 (m, 2H, H-3 and H-4), 3.94 (dd, $J = 2.0$ Hz, $J = 11.4$ Hz, 1H, H-5a), 3.87 (dd, $J = 1.2$ Hz, $J = 11.4$ Hz, 1H, H-5b), 0.91 (s, 9H, SiC(CH_3)$_3$), 0.11 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$) ppm. ^{13}C NMR: $\delta = 173.05$ (C═O), 135.70 (*Ph*C), 130.05 (*Ph*CH), 128.49 (*Ph*CH), 126.47 (*Ph*CH), 104.60 (Ph*C*H), 84.13 (C-3), 77.86 (C-2), 76.42 (C-4), 63,18 (C-5), 25.77 (SiC(CH_3)$_3$), 18.21 (Si*C*(CH_3)$_3$), −5.62 ($SiCH_3$), −5.72 ($SiCH_3$) ppm. *M*/*z* 373 (M + Na), 723 (M + M + Na).

*2,3,5-O-Tribenzyl-*D*-ribono-1,4-lactone (***7***)*

Colorless crystals (1.98 g, 95%); mp 53–54°C [lit.[26] 54–55°C]; $[\alpha]_D^{20}$ +73.6 ($c = 1.00$, $CHCl_3$) {lit.[27] $[\alpha]_D^{20}$ +74.1 ($c = 2.00$, $CHCl_3$)}; ^{1}H NMR: $\delta = 7.45–7.30$ (m, 13H, Ph), 7.24–7.17 (m, 2H, Ph), 4.98 (d, $J = 11.9$ Hz, 1H, C*H*HPh), 4.78 (d, $J = 11.9$ Hz, 1H, CH*H*Ph), 4.73 (d, $J = 11.9$ Hz, 1H, C*H*HPh), 4.60 (d, $J = 11.9$ Hz, 1H, CH*H*Ph), 4.57 (ddd, $J = 1.6$ Hz, $J = 2.4$ Hz, $J = 2.7$ Hz, 1H, H-4), 4.52 (d, $J = 11.0$ Hz, 1H, C*H*HPh), 4.45 (d, $J = 5.9$ Hz, 1H, H-2), 4.44 (d, $J = 11.0$ Hz, 1H, CH*H*Ph), 4.14 (dd, $J = 5.9$ Hz, $J = 1.6$ Hz, 1H, H-3), 3.69 (dd, $J = 2.7$ Hz, $J = 11.0$ Hz, 1H, H-5a), 3.59 (dd, $J = 2.4$ Hz, $J = 11.0$ Hz, 1H, H-5b) ppm. ^{13}C NMR: $\delta = 173.74$ (C═O), 137.30 (*Ph*CH_2), 137.19 (*Ph*CH_2), 173.01 (*Ph*CH_2), 128.54 (*Ph*CH_2), 128.28 (*Ph*CH_2), 128.14 (*Ph*CH_2), 128.08 (*Ph*CH_2), 128.02 (*Ph*CH_2), 127.63 (*Ph*CH_2), 81.82 (C-4), 75.43 (C-3), 73.78 (CH_2), 73.68 (C-2), 72.76 (CH_2), 72.42 (CH_2), 68.80 (C-5) ppm. *M*/*z* 441 (M + Na).

General Procedure for the Methylation of D-Ribonolactone Derivatives

To a stirred solution of 1.6 M methyllithium in diethyl ether (2.13 mL) at −70°C under argon atmosphere, a solution of D-ribonolactone derivative (2.0mmol) in anhydrous diethyl ether (20 mL) was added dropwise. After 1 h the mixture was warmed to 0°C, treated with 10% aqueous NH_4Cl (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic solutions were washed with ice-cold water (2 × 15 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure and purification of the residue by flash chromatography (petroleum ether/ethyl acetate, 9:1) afforded required 1-deoxy-psicofuranoside.

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*6-O-(tert-Butyldimethylsilyl)-3,4-O-benzylidene-1-deoxy-D-psicofuranose (**9**)*

Colorless syrup (0.28 g, 38%, 3:1 *endo*/*exo*).

endo-**9**: ^{1}H NMR $\delta = 7.53–7.50$ (m, 2H, Ph), 7.43–7.40 (m, 3H, Ph), 5.94 (s, 1H, PhC*H*), 4.76 (d, 1H, $J = 5.1$ Hz, H-3), 4.25 (dd, $J = 5.1$ Hz, $J = 7.1$ Hz, 1H, H-4), 3.85 (dd, $J = 6.0$ Hz, $J = 6.0$ Hz, 1H, H-6a), 3.79–3.75 (m, 2H, H-5 and H-6b), 2.38 (s, 3H, CH_3), 0.93 (s, 9H, $SiC(CH_3)_3$), 0.11 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$) ppm.

exo-**9**: ^{1}H NMR $\delta = 7.52–7.49$ (m, 2H, Ph), 7.44–7.40 (m, 3H, Ph), 5.92 (s, 1H, PhC*H*), 5.05 (dd, 1H, $J = 1.3$ Hz, $J = 5.1$ Hz, H-4), 4.57 (d, $J = 5.1$ Hz, 1H, H-3), 4.41 (ddd, $J = 1.3$ Hz, $J = 1.9$ Hz, $J = 1.9$ Hz, 1H, H-5), 3.90–3.80 (m, 2H, H-6a and H-6b), 1.62 (s, 3H, CH_3), 0.97 (s, 9H, $SiC(CH_3)_3$), 0.19 (s, 3H, $SiCH_3$), 0.18 (s, 3H, $SiCH_3$) ppm.

*3,4,6-Tribenzyl-1-deoxy-D-psicofuranose **(10)***

Colorless syrup (0.79 g, 91%, anomeric mixture 1: 3.5 ratio);[28] major isomer: ^{1}H NMR $\delta = 7.43–7.35$ (m, 15H, Ph), 4.73 (d, $J = 11.5$ Hz, 1H, C*H*HPh), 4.62 (d, $J = 11.5$ Hz, 1H, CH*H*Ph), 4.67–4.61 (AB system, 2H, CH_2Ph), 4.57 (d, $J = 12.0$ Hz, 1H, C*H*HPh), 4.52 (d, $J = 12.0$ Hz, 1H, CH*H*Ph), 4.35 (ddd, $J = 2.2$ Hz, $J = 3.5$ Hz, $J = 4.8$ Hz, 1H, H-5), 4.04 (dd, $J = 2.2$ Hz, $J = 5.1$ Hz, 1H, H-4), 3.76 (d, $J = 5.1$ Hz, 1H, H-3), 3.54 (dd, $J = 3.5$ Hz, $J = 10.4$ Hz, 1H, H-6a), 3.48 (dd, $J = 4.8$ Hz, $J = 10.4$ Hz, 1H, H-6b), 1.51 (s, 1H, CH_3) ppm. minor isomer: ^{1}H NMR $\delta = 7.34–7.27$ (m, 15H, Ph), 4.80 (d, $J = 11.8$ Hz, 1H, C*H*HPh), 4.75 (d, $J = 11.8$ Hz, 1H, CH*H*Ph), 4.58 (d, $J = 11.0$ Hz, 1H, C*H*HPh), 4.50 (d, $J = 11.0$ Hz, 1H, CH*H*Ph), 4.46–4.40 (AB system, 2H, CH_2Ph), 4.31–4.29 (m, 1H, H-5), 4.01 (dd, $J = 2.4$ Hz, $J = 4.4$ Hz, 1H, H-4), 3.84 (d, $J = 4.4$ Hz, 1H, H-3), 3.68 (dd, $J = 2.6$ Hz, $J = 10.4$ Hz, 1H, H-6a), 3.65 (dd, $J = 3.0$ Hz, $J = 10.4$ Hz, 1H, H-6b), 1.58 (s, 1H, CH_3) ppm.

General Procedure for the Acetylation of 1-Deoxy-D-psicofuranoses

To a solution of 1-deoxy-psicofuranose (1.0 mmol) and DMAP (5 mg, 0.04 mmol) in pyridine (2 mL), acetic anhydride (0.11 mL, 1.0 mmol) was added dropwise and the reaction was stirred at rt for 5 h. Ice-cold water (5 mL) was then added and the aqueous phase was extracted with $CHCl_3$ (3×3 mL). The combined organic layers were washed with a cold saturated $NaHCO_3$ solution (3×3 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure.

*5-O-Acetyl-3,4,6-tri-O-benzyl-1-deoxy-D-psicose (**13**)*

From 3,4,6-tribenzyl-1-deoxy-D-psicofuranose (**10**), compound **13** was purified by flash chromatography (petroleum ether/ethyl acetate, 8:2);

colorless syrup (0.29 g, 60%); $[\alpha]_D^{20} + 0.0$ ($c = 1.00$, $CHCl_3$); ^{1}H NMR $\delta = 7.36–7.24$ (m, 15H, Ph), 5.32 (ddd, $J = 4.0$ Hz, $J = 4.0$ Hz, $J = 6.8$ Hz, 1H, H-5), 4.65 (d, $J = 11.9$ Hz, 1H, C*H*HPh), 4.62–4.59 (AB system, 2H, CH_2Ph), 4.60 (d, $J = 11.9$ Hz, 1H, C*H*HPh), 4.56 (d, $J = 12.0$ Hz, 1H, C*H*HPh), 4.48 (d, $J = 12.0$ Hz, 1H, CH*H*Ph), 4.21 (dd, $J = 4.0$ Hz, $J = 6.8$ Hz, 1H, H-4), 4.05 (d, $J = 4.0$ Hz, 1H, H-3), 3.78–3.72 (m, 2H, H-6a,b), 2.14 (s, 3H, $COCH_3$), 2.05 (s, 3H, $OCOCH_3$) ppm. ^{13}C NMR: $\delta = 208.19$ (C═O), 169.76 (C═O), 138.03 (*Ph*C), 137.44 (*Ph*C), 137.26 (*Ph*C), 128.48 (*Ph*CH), 128.42 (*Ph*CH), 128.07 (*Ph*CH), 127.99 (*Ph*CH), 127.90 (*Ph*CH), 127.74 (*Ph*CH), 127.69 (*Ph*CH), 83.41(C-3), 78.43 (C-4), 73.25 (CH_2), 73.17 (CH_2), 72.92 (CH_2), 71.35 (C-5), 68.14 (C-6), 27.15 ($OCOCH_3$), 21.15 (1-CH_3) ppm. M/z 499 (M + Na).

Anal. Calcd for $C_{29}H_{32}O_6$: C, 73.09; H, 6.67. Found: C, 73.22; H, 6.74.

ACKNOWLEDGMENTS

This work has been financially supported by Università degli Studi di Milano (Fondi FIRST).

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