IMPROVED SYNTHESES OF D-RIBO- AND 2-DEOXY-D-RIBOFURANOSE PHOSPHO SUGARS FROM METHYL β-D-RIBOPYRANOSIDE

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Abstract – Methyl 4-deoxy-4-dimethoxyphosphinoyl-2,3-O-isopropylidene-β-D-ribopyranoside (12a) and methyl 2,4-dideoxy-4-dimethoxyphosphinoyl-β-D-erythro-pentopyranoside (20) were efficiently prepared respectively from methyl 2,3-O-isopropylidene-β-D-ribopyranoside (7a) and its 3,4-O-isopropylidene isomer (7b) in appreciably improved total yields compared with those via previously reported routes. Compounds (12a, 20) were led to D-ribofuranose and 2-deoxy-D-ribofuranose phospho sugars (4, 5).

INTRODUCTION
Sugar analogs having carbon, nitrogen, sulfur, or phosphorus in place of the ring oxygen have been prepared because of the wide interest in their chemical and biochemical properties. In view of such a chemical modification by carbon and heteroatoms, synthesis and biological activities of various nucleosides of carba, imino and thio sugars have been reported. For examples, aristeromycin (1) terminates viral growth by inhibiting S-adenosyl-L-homocysteine hydrolase, whereas oligonucleotides containing 4’-acetamido-4’-deoxymethylidine (2) show considerable resistance to degradation by 3’-exonucleases and 4’-thiothymidine (3) is a potent inhibitor of leukemia L1210 cell growth. Although no corresponding nucleosides of phospho sugars have been made so far, D-ribofuranose-type (4) and 2-deoxy-D-ribofuranose-type phospho sugars (5) are considered to be highly of interest as potential precursors for phospho sugar nucleosides.
In the first synthesis of 4,10 the key intermediate 4-deoxy-4-phosphinoyl-D-ribofuranoside derivative (12a) was prepared by starting with methyl 2,3-O-isopropylidene-β-D-ribofuranoside (7a), a minor component obtained by acetalization of methyl β-D-ribofuranoside (6) (Scheme 1). In this route, the introduction of a phosphinoyl group onto sugar skeleton was accomplished by the addition of dimethyl phosphonate to the 4-tosylhydrazone derivative (9) and the subsequent reductive removal of the tosylhydrazino group of the addition product (10) with sodium borohydride. Although the desired 4-phosphinoyl-D-ribofuranoside derivative (12a) was obtained with relatively good diastereoselectivity (85:15), the total yields of 12a from 9 were rather low due to the simultaneous production of various by-products. We thus attempted an improved synthesis of D-ribofuranose phospho sugar (4) by using our alternative procedure of C–P bond formation, i.e., addition of phosphonate to the 4-ulose (8) and the subsequent deoxygenation.

In the mean time, 2-deoxy-D-ribofuranose phospho sugar (5) was prepared by two different routes from D-glucose by rather long steps including degradation of the sugar skeleton.11,12 We also report herein an improved synthesis of 5 via a shorter route by an effective use of methyl 3,4-O-isopropylidene-β-D-ribofuranoside (7b), a major component obtained by acetalization of 6, as the starting material.
RESULTS AND DISCUSSION

Acetalization of methyl β-D-ribofuranoside (6) with acetone-sulfuric acid has been reported to afford the 2,3-O-isopropylidene derivative (7a) and its 3,4-O-isopropylidene isomer (7b) in 23% and 46% yields, respectively. Attempts to modify the acetalization by use of other reagents brought about improved yields of 7a and 7b but their ratio remained almost the same. Namely, treatment of 6 with 2,2-dimethoxypropane in the presence of hydrochloric acid at 20 °C provided 7a in 31% and 7b in 63%, while acetalization of 6 with 2-methoxypropene and p-toluensulfonic acid in DMF at 0 °C resulted in the similar formation of the two isomers (7a: 32%, 7b: 62%).

Swern oxidation of 7a with oxalyl chloride-DMSO afforded the D-erythro-pentopyranosid-4-ulose (8) in 92% yield (Scheme 2). The addition reaction of dimethyl phosphonate to 8 in the presence of DBU gave a sole product (in 98% yield), whose structure was assigned to be the (4S)-4-C-dimethoxyphosphinoyl derivative (11) on the basis of $^1$H NMR spectra (see below). Compound (11) was converted to the methoxalyl esters with methoxalyl chloride in the presence of 4-dimethylaminopyridine (DMAP) and the subsequent reduction with tributyltin hydride in the presence of AIBN mainly afforded the desired 4-deoxy-4-phosphinoyl-D-ribofuranoside derivative (12a) (54%) together with a minor proportion of the L-lyxopyranoside derivative (12b) (18%).

The conversion of the major product (12a) into 4-deoxy-4-hydroxypophonoyl-D-ribofuranose (4) was made according to the reported procedures with a slight modification: reduction of 12a with sodium dihydrobis(2-methoxyethoxy)aluminate (SDMA) in toluene at 0 °C, followed by hydrolysis with hydrochloric acid and then oxidation with hydrogen peroxide, afforded 4. For isolation and characterization, 4 was converted into the corresponding 4-(methoxypophonoyl) tetraacetates (13) by treatment with acetic anhydride-pyridine and then ethereal diazomethane in improved yields; 4-[(R)-methoxyphosphonoyl]-α-isomer (13a) (6.3% overall yield from 12a), its β-anomer (13b) (12%), 4-[(S)-methoxyphosphonoyl]-α-isomer (13c) (3.2%), and its β-anomer (13d) (5.3%).
Preparation of 2-deoxy-D-ribofuranose phospho sugar (5) starting with methyl 3,4-O-isopropylidene-β-D-ribo-pyranoside (7b) was similarly attempted (Scheme 3). Methyl 2-deoxy-β-D-erythro-pentopyranoside (15) was prepared from 7b via 14 according to the reported procedures.\textsuperscript{17} Mono-O-benzylation of 15 was carried out via the 3,4-O-stannylene acetal obtained by treatment of 15 with dibutyltin oxide in refluxing toluene. The stannylene acetal was then subjected to the benzylation with benzyl bromide in the presence of tetrabutylammonium bromide in DMF at 100 °C,\textsuperscript{18} providing the 3-O-benzyl derivative (16a) and the 4-O-benzyl isomer (16b) in 42% and 45% yields, respectively. The yield of desired 16a was improved by practice of the same reaction in refluxing toluene;\textsuperscript{19} 16a (55%), 16b (40%).

\[ \text{Scheme 2} \]

The 3-O-benzyl compound (16a) was oxidized with oxalyl chloride-DMSO to give the 4-ulose (17), which was then treated with dimethyl phosphonate and DBU to provide the (4R)-4-dimethoxyphosphinoyl derivative (18a) and its (4S)-epimer (18b) as an inseparable mixture (53:47) in 93% yield. By use of same procedures for 12 from 11, deoxygenation of 18a,b afforded the desired 2,4-dideoxy-4-phosphinoyl-D-erythro-pentopyranoside (19a) and its L-threo-isomer (19b) in 53% and 35% yields, respectively,\textsuperscript{16} although its stereoselectivity (60:40) was lower than that of 12 from 11 (75:25).

\[ \text{Scheme 3} \]
The C-4 configurations and conformational assignments of the 4-dimethoxyphosphinoyl compounds (11, 12a,b and 18a,b, 19a,b) were established by the analysis of their $^1$H NMR data (Table 1). The favored conformations of these compounds in CDCl$_3$ are shown in Figure 1. The D-ribo and D-erythro configurations of 12a and 19a, as well as their $^3$C$_1$ conformation, were assigned on the basis of the small $J_{3,4}$ (3–4 Hz) and the large $J_{4,5S}$ values (9–12 Hz). Similarly, the L-lyxo and L-threo configurations (with $^1$C$_4$ conformations) of 12b and 19b were derived from the large $J_{3,4}$ and $J_{4,5R}$ values (9–10 Hz). Although compounds (11 and 18b) have no H-4 proton, their (4R)-configurations and $^1$C$_4$ conformations were assigned by respective comparison to the corresponding 4-deoxy compounds (12b and 19b), because a similar characteristic tendency of the corresponding coupling constants and the chemical shifts is expected owing to almost identical conformations. For example, the presence of long-range couplings $J_{2,p}$ (for 11, 12b) and $J_{5S,p}$ (for 18b, 19b) indicates all of these compounds exist in the $^1$C$_4$ conformations and have an equatorial phosphinoyl group, whereas the (4S)-epimer (18a) has the large $J_{3,p}$ and $J_{5R,p}$ values (20–21 Hz) and thus is considered to exist in the $^1$C$_4$ conformation.

Table 1. $^1$H and $^{31}$P NMR Parameters for Compounds (11, 12a,b, 18a,b, 19a,b) in CDCl$_3$

<table>
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<tr>
<th>Compound</th>
<th>H-1</th>
<th>$^H$-2</th>
<th>$^H$-2</th>
<th>H-3</th>
<th>H-4</th>
<th>$^H$-5</th>
<th>$^H$-5</th>
<th>MeO-1</th>
<th>POMe</th>
<th>Me$_2$C</th>
<th>CH$_2$O-3</th>
<th>HO-4</th>
<th>$^{31}$P</th>
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<tr>
<td>11</td>
<td>4.89</td>
<td>4.09</td>
<td>4.58</td>
<td>–</td>
<td>3.80</td>
<td>3.95</td>
<td>3.42</td>
<td>3.87</td>
<td>3.83</td>
<td>1.59</td>
<td>1.40</td>
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<td>12a</td>
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<td>1.53</td>
<td>1.38</td>
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<td>12b</td>
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<td>3.92</td>
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<td>3.72</td>
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<td>4.01</td>
<td>3.44</td>
<td>3.69</td>
<td>3.62</td>
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<tr>
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<td>4.14</td>
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<td>3.88</td>
<td>3.32</td>
<td>3.71</td>
<td>3.655</td>
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<td>4.62, 4.56</td>
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<table>
<thead>
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<th>Coupling constants / Hz</th>
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<tr>
<td>$J_{1,2R}$</td>
</tr>
<tr>
<td>11</td>
</tr>
<tr>
<td>12a</td>
</tr>
<tr>
<td>12b</td>
</tr>
<tr>
<td>18a</td>
</tr>
<tr>
<td>18b</td>
</tr>
<tr>
<td>19a</td>
</tr>
<tr>
<td>19b</td>
</tr>
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</table>

$^a$ The parameters concerning H-2 of 11 and 12a,b are listed as $^H$-2. $^b$ $^2$J$_{POMe} = 10.7$–11.0 Hz. $^c$ $\delta = 7.37$ [Ph(o)], 7.34 [Ph(m)], 7.28 [Ph(p)]. $^d$ Uncertain because of overlapping with other signals. $^e$ $^2$J = 11.5 Hz. $^f$ $^2$J = 11.1 Hz.
The hydrogenolysis of the major isomer (19a) in the presence of 10% Pd-C afforded methyl 2,4-dideoxy-4-dimethoxyphosphinoyl-β-D-erythro-pentopyranoside (20) in 90% yield. By use of same procedures described for 4 from 12a, compound (20) was converted into 2-deoxy-D-ribofuranose phospho sugar (5), which was characterized after having been converted into the corresponding 4-methoxyphosphonoyl 1,3,5-tri-O-acetates (21): 4-[(R)-methoxyphosphonyl]-α-isomer (21a) (5.2% overall yield from 20), its β-anomer (21b) (8.2%), 4-[(S)-methoxyphosphonyl]-α-isomer (21c) (6.8%), and its β-anomer (21d) (9.9%).

Thus, improved syntheses of 4 and 5 from the common starting material (6) were achieved via shorter routes involving alternative procedures to introduce a phosphinoyl group in better overall yields. Extension of this work including the improvement of stereoselectivity for C-P bond formation, as well as derivation of 4 and 5 into the corresponding nucleosides, is in progress.

**Experimental**

All reactions were monitored by TLC (Merck silica gel 60F, 0.25 mm) with an appropriate solvent system [(A) 1:2, (B) 2:1 AcOEt–hexane, and (C) AcOEt]. Column chromatography was performed with Daiso Silica Gel IR-60/210w. Components were detected by exposing the plates to UV light and/or spraying them with 20% sulfuric acid–ethanol (with subsequent heating). Optical rotations were measured with a Jasco P-1020 polarimeter in CHCl₃. The NMR spectra were measured in CDCl₃ with Varian Unity Inova AS600 (600 MHz for ¹H, 151 MHz for ¹³C) and Mercury 300 (121 MHz for ³¹P) spectrometer at 23 °C. Chemical shifts are reported as δ values relative to CHCl₃ (7.26 ppm as an internal standard for ¹H), CDCl₃ (77.0 ppm as internal standard for ¹³C), and 85% phosphoric acid (0 ppm as an external standard for ³¹P). The assignments of ¹³C signals were made with the aid of 2D C-H COSY measurements.

**Methyl 2,3-O-isopropylidene-β-D-ribopyranoside (7a) and its 3,4-O-isopropylidene isomer (7b).**

A. **Acetalization with 2,2-dimethoxypropane-HCl.**  To a solution of methyl β-D-ribopyranoside (6) (5.00 g, 30.3 mmol) in 2,2-dimethoxypropane (50 mL) was added 4M hydrochloric acid in 1,4-dioxane (1.50 mL). The mixture was stirred at 25 °C for 1 h, neutralized with pyridine, and then concentrated in vacuo. The residue was separated by column chromatography with 2:1 AcOEt-hexane to give 7a (1.91
Methoxalyl chloride (0.800 mL, 8.0 mmol) was added to a solution of 7a (780 mg, 2.50 mmol) and DMAP (1.06 g, 8.68 mmol) in dry acetonitrile (20 mL) at 0 °C. The mixture was stirred at rt for 1 h under argon and then poured into water. Most of the solvent was distilled off in vacuo. The residue was

**B. Acetalization with 2-methoxypropene-TsOH.** To a solution of 6 (200 mg, 1.21 mmol) in dry DMF (2.0 mL) were added 2-methoxypropene (0.230 mL, 2.40 mmol) and p-toluenesulfonic acid monohydrate (2.0 mg, 0.011 mmol) at 0 °C. The mixture was stirred at same temperature for 30 min and then worked up with the same procedures described above, giving 7a (78.9 mg, 32%) and 7b (154 mg, 62%).

**Methyl 2,3-O-isopropylidene-β-D-erythro-pentopyranosid-4-ulose (8).**

To a solution of oxalyl chloride (1.15 mL, 13.4 mmol) in dry CH₂Cl₂ (10 mL) was added a solution of DMSO (2.00 mL, 27.9 mmol) in dry CH₂Cl₂ (5.0 mL) at −60 °C. After stirring for 20 min, a solution of 7a (1.09 g, 5.34 mmol) in dry CH₂Cl₂ (5.0 mL) was slowly added at −60 °C. The mixture was stirred at same temperature for 6 h and then TEA (4.70 mL, 33.8 mmol) was added. The mixture was stirred at rt for 30 min, diluted with CHCl₃, washed with water, dried (Na₂SO₄), and evaporated in vacuo. The residue was purified by column chromatography with 2:1 AcOEt-hexane to give 8 (993 mg, 92%) (lit., 94% yield by use of PCC) as a colorless syrup: R₉ = 0.64 (B).

**Methyl (4S)-4-C-dimethoxyphosphinoyl-2,3-O-isopropylidene-β-D-erythro-pentopyranoside (11).**

DBU (1.15 mL, 7.70 mmol) was dropwise added to a solution of 8 (1.50 g, 7.42 mmol) in dimethyl phosphonate (15.0 mL, 163 mmol) at 0 °C and the solution was stirred at rt for 1 h under argon. The mixture was treated with saturated NH₄Cl at rt for 1 h and extracted with CHCl₃ three times. The combined organic layers were washed with water, dried (Na₂SO₄), and evaporated in vacuo. The residue was recrystallized with AcOEt and hexane to give 11 (2.27 g, 98%) as colorless needles: mp 65–66 °C; R₉ = 0.48 (C); [α]D²⁵ −38.9° (c 1.10); ¹H and ³¹P NMR, see Table 1; ¹³C NMR δ = 24.83 and 26.04 (CMe₂), 53.45 and 54.31 (³JC,P = 7.5, 6.3 Hz, P(OMe)₂), 55.01 (MeO-1), 50.62 (³J₅,P = 9.8 Hz, C-5), 69.27 (³J₄,P = 168.1 Hz, C-4), 70.77 (³J₃,P = 1.7 Hz, C-3), 73.34 (³J₂,P = 9.8 Hz, C-2), 98.53 (C-1), 109.91 (CMe₂). Anal. Calcd for C₁₁H₂₁O₄P: C, 42.31; H, 6.78. Found: C, 42.19; H, 6.90.

**Methyl 4-deoxy-4-dimethoxyphosphinoyl-2,3-O-isopropylidene-β-D-ribo- (12a) and α-L-lyxopyranoside (12b).**

Methoxalyl chloride (0.800 mL, 8.70 mmol) was added to a solution of 11 (780 mg, 2.50 mmol) and DMAP (1.06 g, 8.68 mmol) in dry acetonitrile (20 mL) at 0 °C. The mixture was stirred at rt for 1 h under argon and then poured into water. Most of the solvent was distilled off in vacuo. The residue
was dissolved in CHCl₃, washed with saturated NH₄Cl and then with water, dried (Na₂SO₄), and evaporated in vacuo to give the 4-O-methoxalyl derivative as a pale yellow syrup: \( R_f = 0.78 \) (C).

The crude syrup was coevaporated with dry toluene and dissolved in the same solvent (15 mL). Tributyltin hydride (1.10 mL, 4.09 mmol) and AIBN (70 mg, 0.43 mmol) were added under argon. The mixture was stirred at 80 °C for 2 h and then concentrated in vacuo. The residue was separated by column chromatography with a gradient eluent of 2:1 AcOEt–hexane to AcOEt to give 12a and 12b.

**12a**: Colorless syrup (402 mg, 54%); \( R_f = 0.26 \) (C); \(^1\)H and \(^{31}\)P NMR, see Table 1; \(^{13}\)C NMR \( \delta = 25.53 \) and 27.37 (CMe₂), 35.45 (\(^1\)J₂,P = 141.1 Hz, C-4), 52.16 and 53.30 [\(^2\)J_C,P = 6.9, 5.8 Hz, P(OME)₂], 56.49 (MeO-1), 59.00 (\(^2\)J₃,P = 4.0 Hz, C-5), 70.47 (\(^2\)J₃,P = 7.5 Hz, C-3), 74.86 (\(^3\)J₂,P = 12.1 Hz, C-2), 101.56 (C-1), 110.22 (CMe₂).

**12b**: Colorless syrup (134 mg, 18%); \( R_f = 0.30 \) (C); \(^1\)H and \(^{31}\)P NMR, see Table 1; \(^{13}\)C NMR \( \delta = 26.16 \) and 28.15 (CMe₂), 37.74 (\(^1\)J₄,P = 139.3 Hz, C-4), 52.49 and 52.75 [\(^2\)J_C,P = 6.4, 6.3 Hz, P(OME)₂], 55.37 (MeO-1), 56.28 (\(^2\)J₃,P = 1.0 Hz, C-5), 70.38 (\(^2\)J₃,P = 4.0 Hz, C-3), 72.97 (\(^3\)J₂,P = 8.6 Hz, C-2), 99.15 (C-1), 109.28 (CMe₂).

**1,2,3,5-Tetra-O-acetyl-4-deoxy-4-methoxyphosphononyl-d-ribofuranose (13a–d)**

The following modification of the literature procedures\(^{10}\) was made. To a solution of 12a (200 mg, 0.675 mmol) in dry toluene (2.0 mL) was added, with stirring, a solution of SDMA (70% in toluene, 0.500 mL, 1.80 mmol) in dry toluene (1.0 mL) in small portions at \(-5 \) °C under argon. The stirring was continued at 0 °C for 1 h. Then, water (0.4 mL) was added to decompose excess SDMA and the mixture was centrifuged. The precipitate was extracted with several portions of toluene. The organic layers were combined and evaporated in vacuo, giving the 4-deoxy-4-phosphino derivative as a colorless syrup: \( R_f = 0.68 \) (C).

This syrup was immediately treated with 1:1 2-propanol–0.5 M hydrochloric acid (3.0 mL) at 90 °C for 1 h under argon. After cooling, the mixture was evaporated in vacuo. The residue was dissolved in 2-propanol (2.0 mL), treated with 30% hydrogen peroxide (0.6 mL, 5.9 mmol) at rt for 12 h and then concentrated in vacuo to give crude 4-deoxy-4-hydroxyphosphonoyl-d-ribofuranose (4) as a colorless syrup.

This was dissolved in dry pyridine (2.0 mL) and then acetic anhydride (1.0 mL, 11 mmol) was added at 0 °C. The mixture was stirred at rt for 12 h, diluted with a small amount of cold water, and concentrated in vacuo. The residue was dissolved in ethanol and passed through a column of Amberlite IR-120(H⁺) (20 mL). The eluent was evaporated in vacuo and the residue was methylated with ethereal diazomethane in dry CH₂Cl₂ (2.0 mL) at 0 °C. After evaporation of the solvent, the residue was separated by column chromatography with a gradient eluent of 2:1 AcOEt-hexane to AcOEt into three fractions A–C.

Fraction A \([R_f = 0.46 \) (C)] gave the 4-[(R)-methoxyphosphinyl]-β-d-ribofuranose (13b) as colorless syrup [31.3 mg, 12% from 12a (lit.,\(^{10}\) 6.3%)].

Fraction B \([R_f = 0.40\) gave a colorless syrup (29.8 mg) which consisted of 4-[(R)-P]-α-isomer (13a) [6.3% (lit.,\(^{10}\) 3.3%)] and 4-[(S)-P]-β-isomer (13d) [5.3% (lit.,\(^{10}\) 2.8%)], the ratio being estimated by \(^1\)H
NMR.
Fraction C ($R_f=0.35$) gave 4-[(S)-P]-α-isomer (13a) as a colorless syrup [8.3 mg, 3.2% (lit., 10.1.7%)].

Methyl 3-O-benzyl-2-deoxy-β-D-erythro-pentopyranoside (16a) and its 4-O-benzyl isomer (16b). To a solution of 15 (808 mg, 5.45 mmol) in toluene (20 mL) was added dibutyltin oxide (1.40 g, 5.62 mmol) and the suspension was refluxed under a Dean-Stark trap for 12 h. After removal of the trap, benzyl bromide (0.770 mL, 6.47 mmol) and tetraammonium bromide (1.00 g, 3.10 mmol) were added and the mixture was refluxed for 24 h. The mixture was evaporated in vacuo and the residue was separated by column chromatography with 1:2 AcOEt-hexane to give 16a and 16b.

16a: Colorless syrup (719 mg, 55%); $R_f=0.21$ (A); [α]$_D^{20}$ = -98.5° (c 1.22) [lit., 19] [α]$_D^{27}$ = -81.6° (c 15.4, CH$_2$Cl$_2$); $^1$H NMR $^20$ δ = 1.91 (1H, ddd, J$_{2R,2S}$ = 13.2, J$_{2S,3}$ = 5.0, J$_{12S}$ = 2.4, J$_{2S,4}$ = 1.2 Hz, H$^3$-2), 1.95 (1H, br s, HO-4), 2.04 (1H, ddd, J$_{2R,3}$ = 11.0, J$_{12R}$ = 3.4 Hz, H$^5$-2), 3.34 (3H, s, MeO-1), 3.75 (1H, dd, J$_{3,5}$ = 12.5, J$_{4,5}$ = 2.3 Hz, H$^5$-5), 3.765 (1H, dd, J$_{4,5}$ = 2.3 Hz, H-5), 3.87 (1H, ddd, J$_{3,4}$ = 3.2 Hz, H-3), 3.92 (1H, ddt, H-4), 4.58, 4.60 (1H each, 2d, $^2$J$_{H,H}$ = 11.7 Hz, CH$_2$O-3), 4.80 (1H, dd, H-1), 7.30–7.36 (5H, m, Ph).

16b: Colorless syrup (522 mg, 40%) (lit., 19 mp 37–39 °C); $R_f=0.27$ (A); [α]$_D^{30}$ = -125.6° (c 1.48) [lit., 19] [α]$_D^{27}$ = -126.0° (c 7.26, MeOH)); $^1$H NMR $^20$ δ = 1.84 (1H, ddd, J$_{2R,2S}$ = 13.1, J$_{2S,3}$ = 4.4, J$_{12S}$ = 3.4, J$_{2S,4}$ = 1.0 Hz, H$^3$-2), 1.95 (1H, br s, HO-4), 1.98 (1H, ddd, J$_{2R,3}$ = 9.6, J$_{12R}$ = 3.2 Hz, H$^5$-2), 3.37 (3H, s, MeO-1), 3.60 (1H, ddd, J$_{4,5}$ = 4.5, J$_{4,5'}$ = 2.2 Hz, H-4), 3.72 (1H, dd, J$_{5,5'}$ = 12.5 Hz, H$^5$-5), 3.82 (1H, dd, H-5), 4.05 (1H, ddd, J$_{3,4}$ = 3.4 Hz, H-3), 4.55, 4.73 (1H each, 2d, $^2$J$_{H,H}$ = 11.7 Hz, CH$_2$O-3), 4.76 (1H, t, H-1), 7.30–7.36 (5H, m, Ph).

Methyl 3-O-benzyl-2-deoxy-β-D-glycero-pentopyranosid-4-ucose (17). By use of the same procedures described for 8 from 7a, compound (16a) (380 mg, 1.59 mmol) was treated with oxalyl chloride (0.400 mL, 4.66 mmol) and DMSO (0.650 mL, 9.07 mmol) in dry CH$_2$Cl$_2$ (4.0 ml) to give 17 (339 mg, 90%) as a colorless syrup: $R_f=0.25$ (A); [α]$_D^{30}$ = -166.6° (c 1.05); $^1$H NMR δ = 2.15 (1H, ddd, J$_{2R,2S}$ = 13.0, J$_{2R,3}$ = 11.7, J$_{12R}$ = 3.4 Hz, H$^5$-2), 2.48 (1H, ddd, J$_{2S,3}$ = 6.8, J$_{12S}$ = 2.2 Hz, H$^5$-2), 3.42 (3H, s, MeO-1), 3.96 (1H, d, $^2$J$_{3R,5S}$ = 14.9 Hz, H$^5$-5), 4.17 (1H, d, H$^5$-5), 4.37 (1H, dd, H-3), 4.57, 4.88 (1H each, 2d, $^2$J$_{H,H}$ = 11.7 Hz, CH$_2$O-3), 4.92 (1H, dd, H-1), 7.29 [1H, m, Ph(p)]; 7.34 [2H, m, Ph(m)], 7.37 [2H, m, Ph(o)]; $^{13}$C NMR δ = 38.13 (C-2), 55.53 (MeO-1), 67.35 (C-5), 72.65 (CH$_2$O-3), 74.45 (C-3), 98.55 (C-1), 127.80 [Ph(o)], 127.88 [Ph(p)], 128.45 [Ph(m)], 137.60 [Ph(ipso)], 204.98 (C-4). Anal. Calcd for C$_{13}$H$_{16}$O$_4$: C, 66.09; H, 6.83. Found: C, 65.89; H, 6.92.

Methyl (4R)-3-O-benzyl-2-deoxy-4-C-dimethoxyphosphinoyl-β-D-glycero-pentopyranoside (18a) and its (4S)-epimer (18b). By use of the same procedures described for 11 from 8, compound (17) (550 mg, 2.33 mmol) was treated with dimethyl phosphonate (5.0 mL, 54 mmol) and DBU (0.400 mL, 2.68 mmol) to give an inseparable mixture (53:47) of 18a,b (750 mg, 93%) as a colorless syrup: $R_f=0.40$ (C); $^1$H and $^{31}$P NMR, see Table 1. Anal. Calcd for C$_{15}$H$_{23}$O$_7$P: C, 52.02; H, 6.69. Found: C, 52.22; H, 6.51.
Methyl 3-O-benzyl-2,4-dideoxy-4-dimethoxyphosphinoyl-β-D-erythro- (19a) and α-L-threo-pentopyranoside (19b).

By use of the same procedures described for 12 from 11, compounds (18a,b) (500 mg, 1.44 mmol) was treated with methoxalyl chloride (0.400 mL, 4.35 mmol) and DMAP (530 mg, 4.34 mmol) in dry acetonitrile (10 mL). The resulting crude syrup \([R_f = 0.67 (C)]\) of the 4-O-methoxalyl derivatives was then treated with tributyltin hydride (0.700 mL, 2.60 mmol) and AIBN (45 mg, 0.28 mmol) in dry toluene (10 mL). The products were separated by column chromatography with a gradient eluant of 2:1 AcOEt-hexane to AcOEt to give 19a and 19b.

19a: Colorless syrup (251 mg, 53%); \(R_f = 0.30 (C)\); \(^1H\) and \(^{31}P\) NMR, see Table 1. Anal. Calcd for C\(_{15}\)H\(_{23}\)O\(_6\)P: C, 54.54; H, 7.02. Found: C, 54.63; H, 6.90.

19b: Colorless syrup (167 mg, 35%); \(R_f = 0.23 (C)\); \(^1H\) and \(^{31}P\) NMR, see Table 1. Anal. Calcd for C\(_{15}\)H\(_{23}\)O\(_6\)P: C, 54.54; H, 7.02. Found: C, 54.72; H, 7.11.

Methyl 2,4-dideoxy-4-dimethoxyphosphinoyl-β-D-erythro-pentopyranoside (20).\(^{11}\)

To a solution of 19a (200 mg, 0.605 mmol) in methanol (5.0 mL) was added 10% Pd-C (65 mg, 0.061 mmol). The mixture was stirred at rt for 12 h under atmospheric pressure of hydrogen. The catalyst was filtered off and the filtrate was evaporated in vacuo. The residue was purified by short-path column chromatography with 1:19 MeOH-CHCl\(_3\) to give 20 (131 mg, 90%) as colorless needles: mp 101–102 °C (lit.,\(^{11}\) 101–102 °C); \(R_f = 0.05 (C)\).

1,3,5-Tetra-O-acetyl-2,4-dideoxy-4-methoxyphosphonoyl-D-erythro-pentofuranose (21a–d).\(^{11}\)

The procedures similar to those for the preparation of 13 from 12a were employed. Thus, compound (20) (190 mg, 0.781 mmol) were converted into 21 via 2,4-dideoxy-4-hydroxyphosphonoyl-D-erythro-pentofuranose (5). The crude product (21) was separated by column chromatography into two fractions.

The faster-eluting fraction \([R_f = 0.44 (C)]\) gave a colorless syrup (33.7 mg) which consisted of 4-[(R)-P]-α-isomer (21a) [5.2% (lit.,\(^{11}\) 3.9%) and 4-[(R)-P]-β-isomer (21b) [8.2% (lit.,\(^{11}\) 6.1%)], the ratio being estimated by \(^1H\) NMR.

The slower-eluting fraction \((R_f = 0.39)\) gave a colorless syrup (42.0 mg) which consisted of 4-[(S)-P]-α-isomer (21c) [6.8% (lit.,\(^{11}\) 5.2%) and 4-[(S)-P]-β-isomer (21d) [9.9% (lit.,\(^{11}\) 7.5%)], the ratio being estimated by \(^1H\) NMR.

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REFERENCES AND NOTES
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16. As the reduction of the 4-O-methoxalyl derivatives proceeds via a radical intermediate formed by a homolytic cleavage of the O—C-4 bond, the ratios of 4-deoxy products (12a:12b and 19a:19b) are not correlated to the C-4 configuration of their corresponding 4-hydroxy precursors (11 and 18a,b). The predominant production of 12a (from 11) and 19a (from 18a,b) seems to be ascribed to a preferential approach of tin hydride to the radical C-4 from the less hindered upper side of the ring. The mechanistic proposals for the radical-mediated reduction of α-methoxalylxylophosphonates have been reported in Ref. 13.


20. The complete parameters for 7a,b and 16a,b obtained in the present study are shown here, because $^1$H NMR data for these compounds including insufficient assignments were reported in Ref. 14 and 19.