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

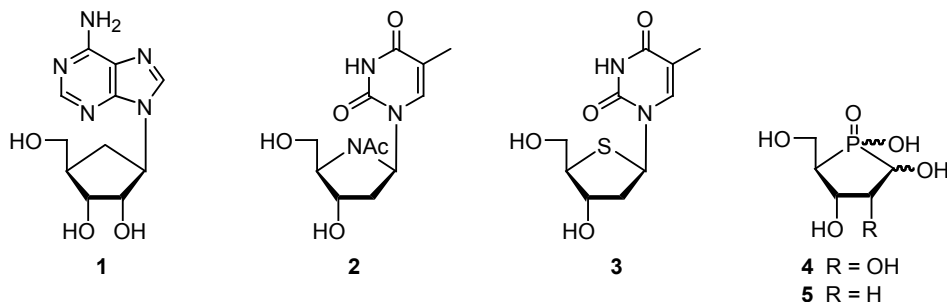
Tadashi Hanaya,* Yuko Koga, Heizan Kawamoto, and Hiroshi Yamamoto¹

Department of Chemistry, Faculty of Science, Okayama University,
Tsushima-naka, Okayama 700-8530, Japan. E-mail:
hanaya@cc.okayama-u.ac.jp

Abstract – Methyl 4-deoxy-4-dimethoxyphosphinoyl-2,3-*O*-isopropylidene- β -D-ribofuranoside (**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-ribofuranoside (**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**).

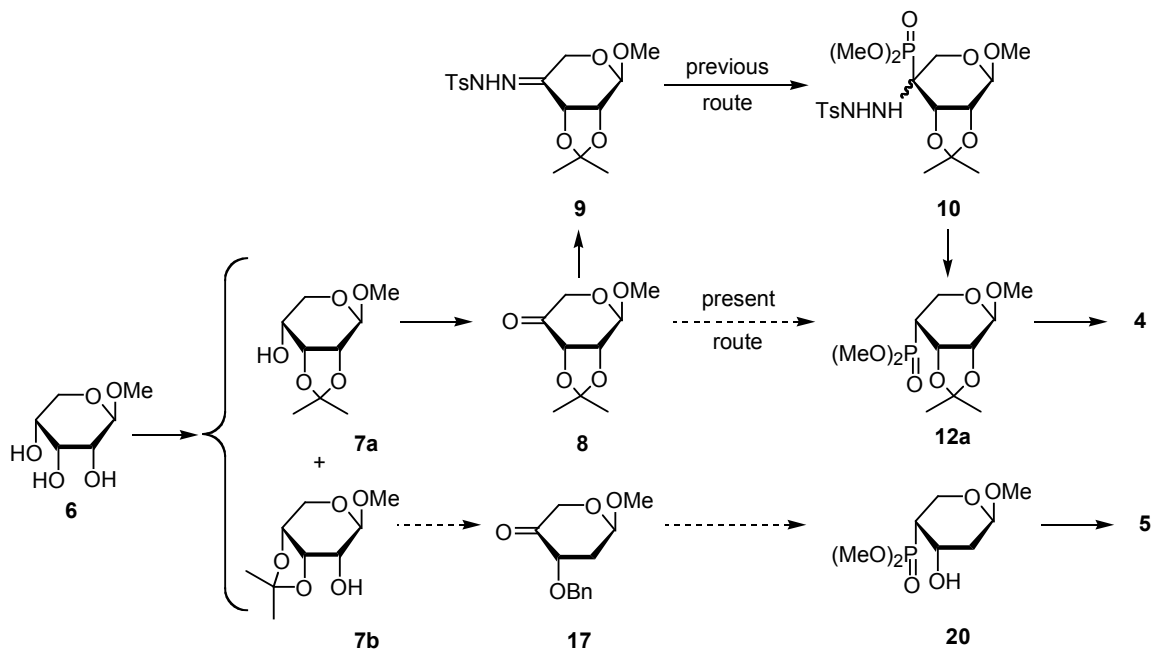
INTRODUCTION

Sugar analogs having carbon,² nitrogen,³ sulfur,⁴ or phosphorus⁵ 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.⁶ For examples, aristeromycin (**1**) terminates viral growth by inhibiting *S*-adenosyl-L-homocysteine hydrolase,⁷ whereas oligonucleotides containing 4'-acetamido-4'-deoxythymidine (**2**) show considerable resistance to degradation by 3'-exonucleases⁸ and 4'-thiothymidine (**3**) is a potent inhibitor of leukemia L1210 cell growth.⁹ Although no corresponding nucleosides of phospho sugars have been made so far, D-ribofuranose-type (**4**)¹⁰ and 2-deoxy-D-ribofuranose-type phospho sugars (**5**)^{11,12} 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-ribofuranose 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-ribofuranose 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,¹³ 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.



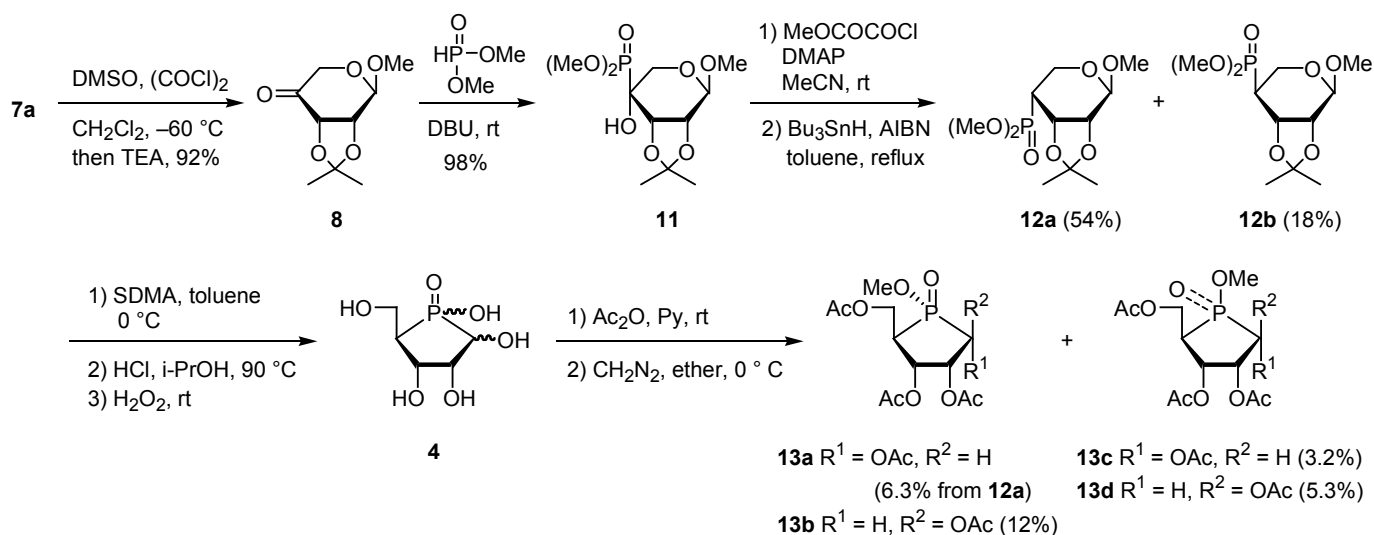
Scheme 1

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.¹⁴ 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*-toluenesulfonic acid in DMF at 0 °C resulted in the similar formation of the two isomers (**7a**: 32%, **7b**: 62%).

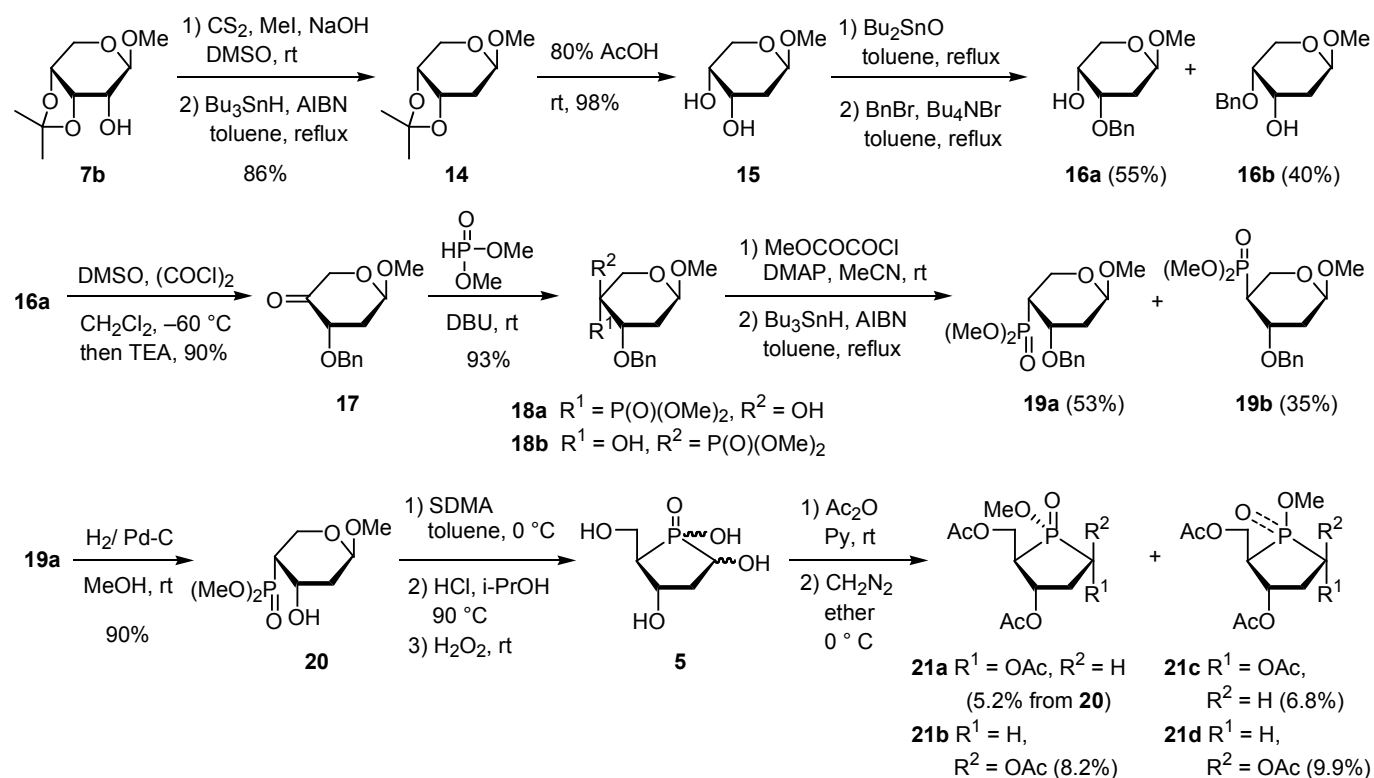
Swern oxidation of **7a** with oxalyl chloride-DMSO afforded the *D*-*erythro*-pentopyranosid-4-ulose (**8**) in 92% yield (Scheme 2). The addition reaction of dimethyl phosphonate to **8** in the presence of DBU gave a sole product (in 98% yield), whose structure was assigned to be the (4*S*)-4-*C*-dimethoxyphosphinoyl derivative (**11**) on the basis of ¹H 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 AIBN¹⁵ 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%).¹⁶

The conversion of the major product (**12a**) into 4-deoxy-4-hydroxyphosphonoyl-D-ribofuranose (**4**) was made according to the reported procedures¹⁰ with a slight modification: reduction of **12a** with sodium dihydrobis(2-methoxyethoxy)aluminat (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-(methoxyphosphonoyl) 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%).



Scheme 2

Preparation of 2-deoxy-D-ribofuranose phospho sugar (**5**) starting with methyl 3,4-*O*-isopropylidene- β -D-ribofuranoside (**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.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,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;¹⁹ **16a** (55%), **16b** (40%).



Scheme 3

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 (4*R*)-4-dimethoxyphosphinoyl derivative (**18a**) and its (4*S*)-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,¹⁶ although its stereoselectivity (60:40) was lower than that of **12** from **11** (75:25).

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 ^1H 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 $^4\text{C}_1$ 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 $^1\text{C}_4$ 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 (4*R*)-configurations and $^1\text{C}_4$ 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 $J_{2S,P}$ (for **18b**, **19b**) indicates all of these compounds exist in the $^1\text{C}_4$ conformations and have an equatorial phosphinoyl group, whereas the (4*S*)-epimer (**18a**) has the large $J_{3,P}$ and $J_{5R,P}$ values (20–21 Hz) and thus is considered to exist in the $^1\text{C}_4$ conformation.

Table 1. ^1H and ^{31}P NMR Parameters for Compounds (**11**, **12a,b**, **18a,b**, **19a,b**) in CDCl_3

Com- pound	Chemical shifts / δ												^{31}P
	H-1	H ^R -2	H ^S -2 ^a	H-3	H-4	H ^R -5	H ^S -5	MeO-1	POMe ^b	Me ₂ C	CH ₂ O-3 ^c	HO-4	
11	4.89	–	4.09	4.58	–	3.80	3.95	3.42	3.87, 3.83	1.59, 1.40	–	3.07	23.3
12a	4.38	–	3.92	4.62	2.73	3.92	3.83	3.46	3.77, 3.74	1.53, 1.38	–	–	27.4
12b	4.79	–	3.96	4.50	2.34	3.80 ^d	3.78 ^d	3.39	3.77, 3.765	1.52, 1.35	–	–	29.6
18a	4.63	2.28	2.05	3.96	–	3.71	4.01	3.38	3.78, 3.735	–	4.70, 4.56 ^e	3.75	25.7
18b	4.81	1.96	2.06	4.28	–	3.78	3.92	3.33	3.74, 3.72	–	4.64, 4.61 ^f	3.75	24.6
19a	4.71	2.26	1.58	3.96	2.39	3.99	4.01	3.44	3.69, 3.62	–	4.64, 4.625 ^e	–	29.9
19b	4.81	1.60	2.26	4.14	2.29	3.88	3.86	3.32	3.71, 3.655	–	4.62, 4.56 ^f	–	29.7

	Coupling constants / Hz															
	$J_{1,2R}$	$J_{1,2S}$	$J_{1,5S}$	$J_{2R,2S}$	$J_{2R,3}$	$J_{2R,P}$	$J_{2S,3}$	$J_{2S,P}$	$J_{3,4}$	$J_{3,P}$	$J_{4,5R}$	$J_{4,5S}$	$J_{4,P}$	$J_{5R,5S}$	$J_{5R,P}$	$J_{5S,P}$
11	–	1.7	1.6	–	–	–	6.6	2.2	–	8.3	–	–	–	12.5	4.5	1.0
12a	–	4.9	0	–	–	–	6.3	0	2.9	3.6	5.6	11.8	23.7	11.3	1.2	4.3
12b	–	2.0	2.0	–	–	–	5.2	2.2	8.6	11.3	8.9	5.1	18.8	d	d	d
18a	3.4	4.7	0.8	13.4	8.6	0	4.6	0	–	21.0	–	–	–	12.0	20.0	6.6
18b	3.4	1.5	1.8	12.9	11.2	1.0	5.1	5.1	–	4.2	–	–	–	12.9	4.0	1.5
19a	2.7	7.8	0	13.7	5.1	4.6	3.2	0	3.7	13.4	4.6	8.8	20.8	11.8	9.5	4.8
19b	3.4	2.2	2.2	12.9	10.5	0.7	4.4	5.6	10.0	8.1	10.3	5.9	17.1	11.7	3.4	4.4

^a The parameters concerning H-2 of **11** and **12a,b** are listed as H^S-2. ^b $J_{\text{POMe}} = 10.7\text{--}11.0$ Hz. ^c $\delta = 7.37$ [Ph(*o*)], 7.34 [Ph(*m*)], 7.28 [Ph(*p*)]. ^d Uncertain because of overlapping with other signals. ^e $J = 11.5$ Hz. ^f $J = 11.1$ Hz.

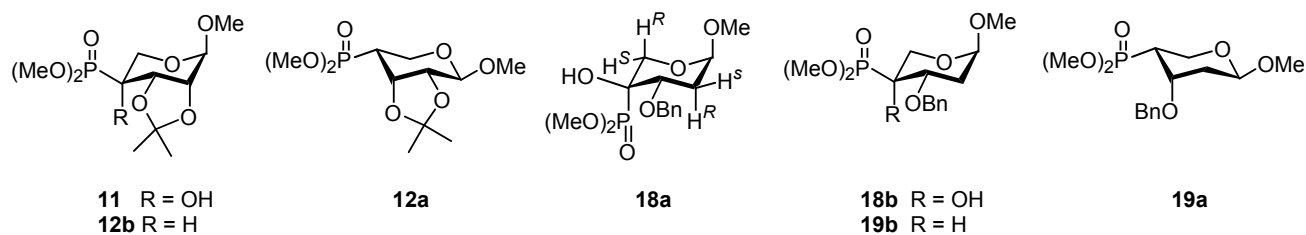


Figure 1. Structures and favored conformations for the 4-dimethoxyphosphinoylpyranosides (**11**, **12a,b**, **18a,b**, and **19a,b**)

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*)-methoxyphosphonoyl]- α -isomer (**21a**) (5.2% overall yield from **20**), its β -anomer (**21b**) (8.2%), 4-[(*S*)-methoxyphosphonoyl]- 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 CHCl_3 . The NMR spectra were measured in CDCl_3 with Varian Unity Inova AS600 (600 MHz for ^1H , 151 MHz for ^{13}C) and Mercury 300 (121 MHz for ^{31}P) spectrometer at 23 °C. Chemical shifts are reported as δ values relative to CHCl_3 (7.26 ppm as an internal standard for ^1H), CDCl_3 (77.0 ppm as internal standard for ^{13}C), and 85% phosphoric acid (0 ppm as an external standard for ^{31}P). The assignments of ^{13}C signals were made with the aid of 2D C-H COSY measurements.

Methyl 2,3-*O*-isopropylidene- β -D-ribofuranoside (**7a**) and its 3,4-*O*-isopropylidene isomer (**7b**).^{14,17}

A. Acetalization with 2,2-dimethoxypropane-HCl. To a solution of methyl β -D-ribofuranoside (**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

g, 31%) and **7b** (3.88 g, 63%).

7a: Colorless prisms, mp 70–71 °C (from AcOEt-hexane) (lit.,¹⁴ 70–71 °C); $R_f = 0.41$ (B); $^1\text{H NMR}^{20}$ $\delta = 1.375$, 1.55 (3H each, 2s, Me₂C), .2.22 (1H, br s, HO-4), 3.44 (3H, s, MeO-1), 3.60 (1H, dd, $J_{5,5'} = 11.2$, $J_{4,5'} = 7.8$ Hz, H'-5), 3.80 (1H, dd, $J_{4,5} = 4.6$ Hz, H-5), 4.00 (1H, dt, $J_{3,4} = 4.2$ Hz, H-4), 4.05 (1H, dd, $J_{2,3} = 6.4$, $J_{1,2} = 3.7$ Hz, H-2), 4.38 (1H, dd, H-3), 4.57 (1H, d, H-1).

7b: Colorless prisms, mp 65–66 °C (from AcOEt-hexane) (lit.,¹⁷ 64–65 °C); $R_f = 0.29$ (B); $^1\text{H NMR}^{20}$ $\delta = 1.37$, 1.55 (3H each, 2s, Me₂C), .2.30 (1H, br s, HO-2), 3.46 (3H, s, MeO-1), 3.65 (1H, dd, $J_{1,2} = 5.6$, $J_{2,3} = 3.9$ Hz, H-2), 3.70 (1H, dd, $J_{5,5'} = 12.9$, $J_{4,5'} = 3.2$ Hz, H'-5), 3.80 (1H, dd, $J_{4,5} = 3.4$ Hz, H-5), 4.27 (1H, dt, $J_{3,4} = 6.6$ Hz, H-4), 4.48 (1H, dd, H-3), 4.62 (1H, d, H-1).

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**).**¹⁰

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.,¹⁰ 94% yield by use of PCC) as a colorless syrup: $R_f = 0.64$ (B).

Methyl (4*S*)-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; $R_f = 0.48$ (C); $[\alpha]_D^{25} -38.9^\circ$ (*c* 1.10); ^1H and ^{31}P NMR, see Table 1; ^{13}C NMR $\delta = 24.83$ and 26.04 (CMe₂), 53.45 and 54.31 [$^2J_{\text{C,P}} = 7.5$, 6.3 Hz, P(OMe)₂], 55.01 (MeO-1), 60.35 ($^2J_{5,\text{P}} = 9.8$ Hz, C-5), 69.27 ($^1J_{4,\text{P}} = 168.1$ Hz, C-4), 70.77 ($^2J_{3,\text{P}} = 1.7$ Hz, C-3), 73.34 ($^3J_{2,\text{P}} = 9.8$ Hz, C-2), 98.53 (C-1), 109.91 (CMe₂). *Anal.* Calcd for C₁₁H₂₁O₈P: 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**).**¹⁰

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 CHCl_3 , washed with saturated NH_4Cl and then with water, dried (Na_2SO_4), 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 eluant of 2:1 AcOEt–hexane to AcOEt to give **12a** and **12b**.

12a: Colorless syrup (402 mg, 54%); $R_f = 0.26$ (C); ^1H and ^{31}P NMR, see Table 1; ^{13}C NMR $\delta = 25.53$ and 27.37 (CMe_2), 35.45 ($^1J_{4,\text{P}} = 141.1$ Hz, C-4), 52.16 and 53.30 [$^2J_{\text{C},\text{P}} = 6.9, 5.8$ Hz, $\text{P}(\text{OMe})_2$], 56.49 (MeO-1), 59.00 ($^2J_{5,\text{P}} = 4.0$ Hz, C-5), 70.47 ($^2J_{3,\text{P}} = 7.5$ Hz, C-3), 74.86 ($^3J_{2,\text{P}} = 12.1$ Hz, C-2), 101.56 (C-1), 110.22 (CMe_2).

12b: Colorless syrup (134 mg, 18%); $R_f = 0.30$ (C); ^1H and ^{31}P NMR, see Table 1; ^{13}C NMR $\delta = 26.16$ and 28.15 (CMe_2), 37.74 ($^1J_{4,\text{P}} = 139.3$ Hz, C-4), 52.49 and 52.75 [$^2J_{\text{C},\text{P}} = 6.4, 6.3$ Hz, $\text{P}(\text{OMe})_2$], 55.37 (MeO-1), 56.28 ($^2J_{5,\text{P}} = 1.0$ Hz, C-5), 70.35 ($^2J_{3,\text{P}} = 4.0$ Hz, C-3), 72.97 ($^3J_{2,\text{P}} = 8.6$ Hz, C-2), 99.15 (C-1), 109.28 (CMe_2).

1,2,3,5-Tetra-*O*-acetyl-4-deoxy-4-methoxyphosphonyl-D-ribofuranose (**13a–d**).¹⁰

The following modification of the literature procedures¹⁰ 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-hydroxyphosphonyl-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 CH_2Cl_2 (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 ^1H

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).¹⁹

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*); $[\alpha]_D^{30} -98.5^\circ$ (*c* 1.22) [lit.,¹⁹ $[\alpha]_D^{27} -81.6^\circ$ (*c* 15.4, CH₂Cl₂)]; ¹H NMR²⁰ $\delta = 1.91$ (1H, dddd, $J_{2R,2S} = 13.2$, $J_{2S,3} = 5.0$, $J_{1,2S} = 2.4$, $J_{2S,4} = 1.2$ Hz, H^S-2), 1.95 (1H, br s, HO-4), 2.04 (1H, ddd, $J_{2R,3} = 11.0$, $J_{1,2R} = 3.4$ Hz, H^R-2), 3.34 (3H, s, MeO-1), 3.75 (1H, dd, $J_{5,5'} = 12.5$, $J_{4,5'} = 2.3$ Hz, H[']-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, dtd, H-4), 4.58, 4.60 (1H each, 2d, $^2J_{H,H} = 11.7$ Hz, CH₂O-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*); $[\alpha]_D^{30} -125.6^\circ$ (*c* 1.48) [lit.,¹⁹ $[\alpha]_D^{27} -126.0^\circ$ (*c* 7.26, MeOH)]; ¹H NMR²⁰ $\delta = 1.84$ (1H, dddd, $J_{2R,2S} = 13.1$, $J_{2S,3} = 4.4$, $J_{1,2S} = 3.4$, $J_{2S,4} = 1.0$ Hz, H^S-2), 1.95 (1H, br s, HO-4), 1.98 (1H, ddd, $J_{2R,3} = 9.6$, $J_{1,2R} = 3.2$ Hz, H^R-2), 3.37 (3H, s, MeO-1), 3.60 (1H, dddd, $J_{4,5} = 4.5$, $J_{4,5'} = 2.2$ Hz, H-4), 3.72 (1H, dd, $J_{5,5'} = 12.5$ Hz, H[']-5), 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, $^2J_{H,H} = 11.7$ Hz, CH₂O-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-ulose (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 CH₂Cl₂ (4.0 ml) to give **17** (339 mg, 90%) as a colorless syrup: $R_f = 0.25$ (*A*); $[\alpha]_D^{30} -166.6^\circ$ (*c* 1.05); ¹H NMR $\delta = 2.15$ (1H, ddd, $J_{2R,2S} = 13.0$, $J_{2R,3} = 11.7$, $J_{1,2R} = 3.4$ Hz, H^R-2), 2.48 (1H, ddd, $J_{2S,3} = 6.8$, $J_{1,2S} = 2.2$ Hz, H^S-2), 3.42 (3H, s, MeO-1), 3.96 (1H, d, $^2J_{5R,5S} = 14.9$ Hz, H^R-5), 4.17 (1H, d, H^S-5), 4.37 (1H, dd, H-3), 4.57, 4.88 (1H each, 2d, $^2J_{H,H} = 11.7$ Hz, CH₂O-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*)]; ¹³C NMR $\delta = 38.13$ (C-2), 55.53 (MeO-1), 67.35 (C-5), 72.65 (CH₂O-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 C₁₃H₁₆O₄: C, 66.09; H, 6.83. Found: C, 65.89; H, 6.92.

Methyl (4*R*)-3-*O*-benzyl-2-deoxy-4-*C*-dimethoxyphosphinoyl- β -D-glycero-pentopyranoside (18a) and its (4*S*)-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*); ¹H and ³¹P NMR, see Table 1. *Anal.* Calcd for C₁₅H₂₃O₇P: 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 $\text{C}_{15}\text{H}_{23}\text{O}_6\text{P}$: 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 $\text{C}_{15}\text{H}_{23}\text{O}_6\text{P}$: 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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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 -methoxyalxyloxyphosphonates have been reported in Ref. 13.
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20. The complete parameters for **7a,b** and **16a,b** obtained in the present study are shown here, because ¹H NMR data for these compounds including insufficient assignments were reported in Ref. 14 and 19.