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A NEW ROUTE FOR PREPARATION OF 2-DEOXY-D-RIBOFURANOSE PHOSPHO SUGAR

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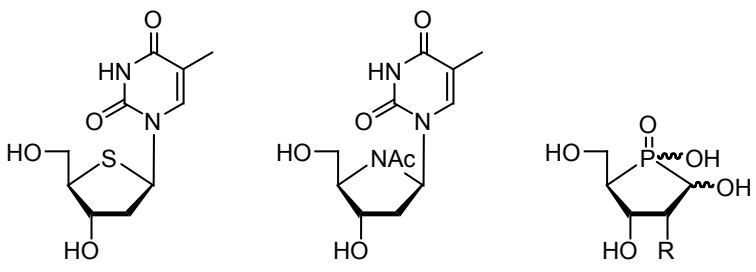
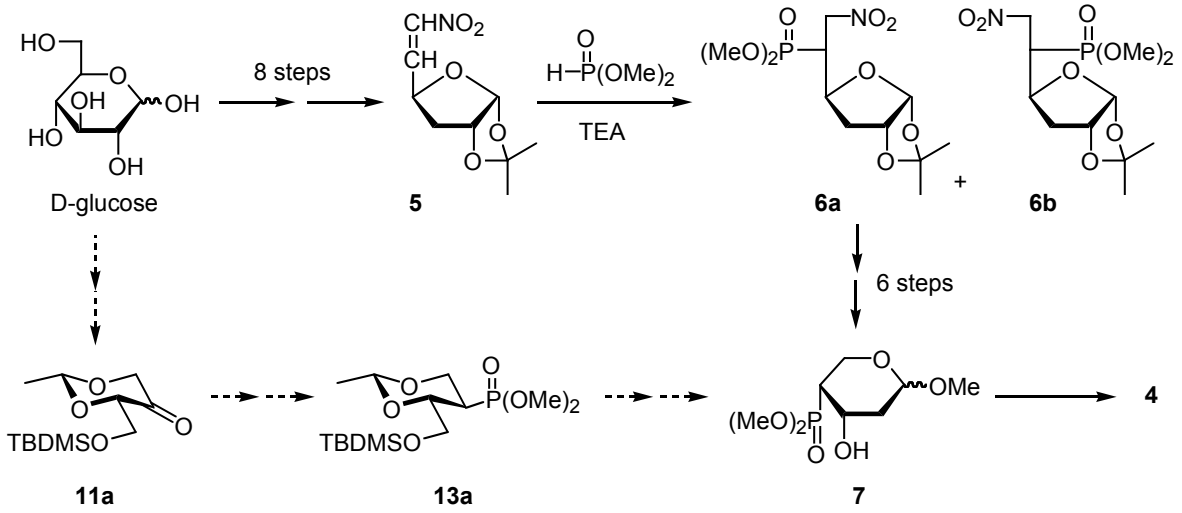
Abstract – The addition reaction of dimethyl phosphonate to (2*R*,4*S*)-4-(*tert*-butyldimethylsilyl)oxymethyl-2-methyl-1,3-dioxan-5-one (**11a**), followed by dehydroxylation, provided 1-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-3-dimethoxy-phosphinoyl-2,4-*O*-ethyliden e-D-erythritol (**13a**). Elongation of carbon skeleton of the D-erythrose (**14**) derived from **13a** and then acidic methanolysis gave a mixture of methyl 2,4-dideoxy-4-dimethoxyphosphinoyl-α,β-D-*erythro*-pentopyranosides (**7**), which was led to 2-deoxy-D-ribofuranose phospho sugar (**4**) in an appreciably improved total yield compared with the procedures *via* previously reported route.

INTRODUCTION

A large number of sugar analogs containing nitrogen,[2] sulfur,[3] or phosphorus[4] as a ring heteroatom have been prepared due to a wide variety of interest in their chemical and biochemical properties. In view of such a chemical modification by heteroatoms, synthesis and biological activities of various nucleosides of imino and thio sugars have been reported;[5] *e.g.*, 4'-thiothymidine (**1**) is a potent inhibitor of leukemia L1210 cell growth,[6] while oligonucleotides containing 4'-acetamido-4'-deoxythymidine (**2**) show considerable resistance to degradation by 3'-exonucleases.[7] No corresponding nucleosides of phospho sugars is known. D-Ribofuranose-type (**3**)[8] and 2-deoxy-D-ribofuranose-type phospho sugars (**4**)[9] are thus considered to be highly of interest as potential precursors for phospho nucleosides.



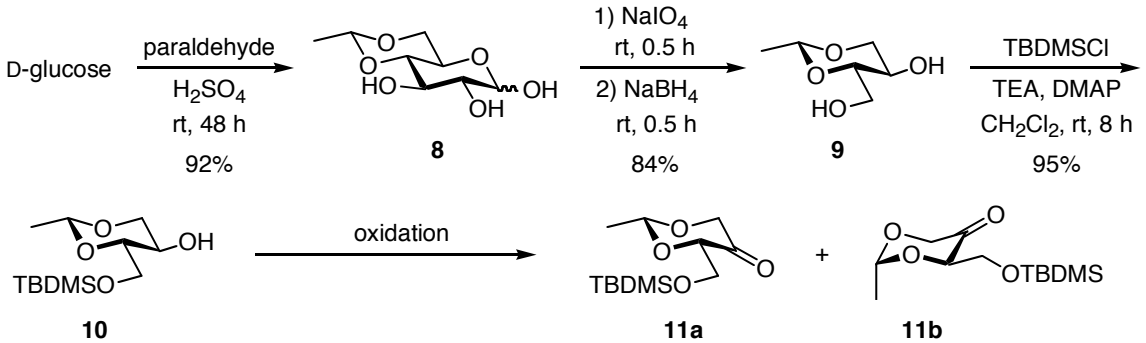
In the first synthesis of **4**,[9] the introduction of a phosphinoyl group onto the sugar skeleton was accomplished by the addition of dimethyl phosphonate to the 5,6-dideoxy-6-nitro-hex-5-enofuranose derivative (**5**)[10] in the presence of triethylamine (TEA) (Scheme 1). Although the desired 5-phosphinoyl-D-*ribo*-hexofuranose derivative (**6a**) was obtained preferentially over the L-*lyxo* epimer (**6b**), the stereoselectivity of the reaction was not so high (66:34). Moreover, the conversion of 6-nitro group of **6a** into its 6-hydroxy derivative and the subsequent conversion into methyl 2,4-dideoxy-4-dimethoxyphosphinoyl-α,β-D-*erythro*-pentopyranosides (**7**) required multi-step procedures, thus causing the overall yield of **7** rather low. We describe herein an improved synthesis of 2-deoxy-D-ribofuranose phospho sugar (**4**) by a new route from D-glucose *via* the 3-phosphinoy-D-erythritol derivative (**13a**) obtained by using our alternative procedure;[11,12] i.e., addition of phosphonate to the ketone (**11a**) and the subsequent deoxygenation.



Scheme 1

RESULTS AND DISCUSSION

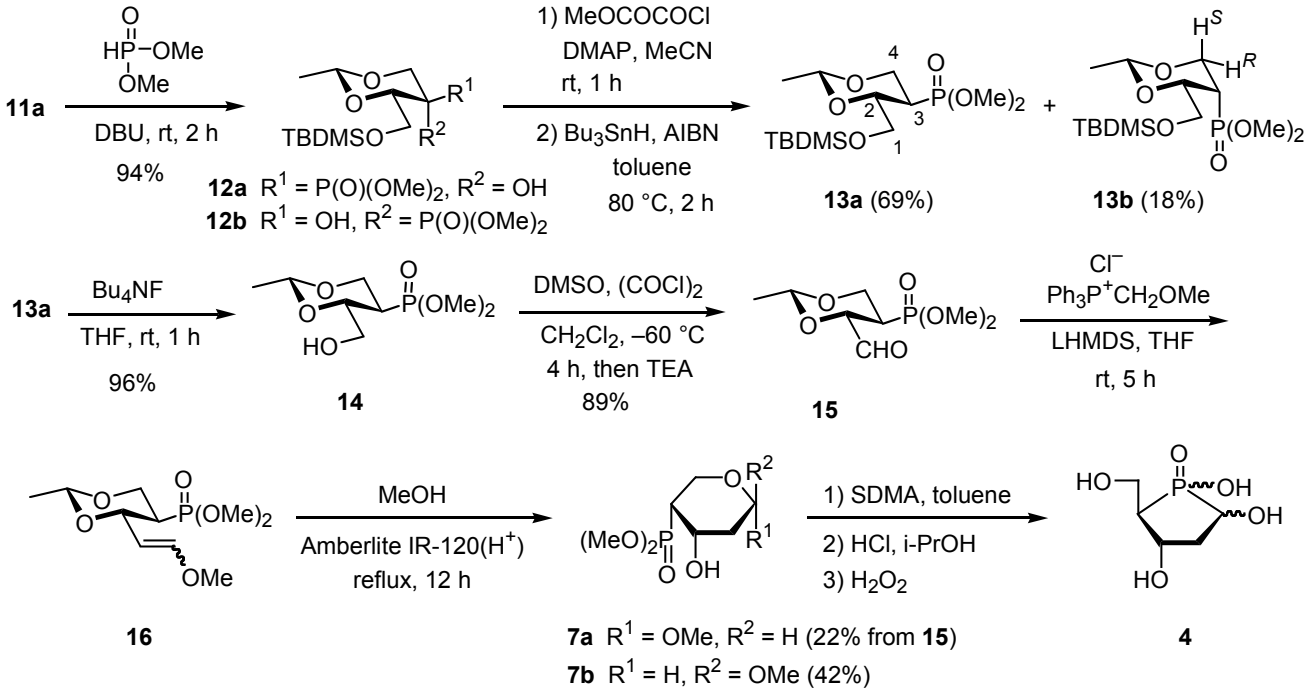
D-Glucose served as the starting material for preparation of the key intermediate (**11a**) to introduce a phosphinoyl group, as illustrated in Scheme 2. The reported procedures[13] for preparation of 2,4-*O*-ethylidene-D-erythritol (**9**) from D-glucose *via* 4,6-*O*-ethylidene-D-glucopyranose (**8**) were slightly modified to give **8** and **9** in improved yields. The selective protection of **9** with *tert*-butyldimethylsilyl (TBDMS) chloride in the presence of TEA and 4-dimethylaminopyridine (DMAP) provided the 1-*O*-TBDMS derivative (**10**)[14] in 95% yield. Swern oxidation of **10** with oxalyl chloride-DMSO afforded the desired ketone (**11a**) (61%) together with its diastereomer (**11b**) (30%). As production of **11b** can be perceived as the results of epimerization caused by treatment with TEA, we examined oxidation of **10** to **11a** with other conditions. Thus, treatment of **10** with pyridinium chlorochromate (PCC) in dichloromethane afforded **11a** as a sole product (82%), while use of Dess-Martin periodinane as an oxidizing agent much improved the yield of **11a** (95%).



DMSO, $(COCl)_2$ then TEA	61%	30%
PCC, MS-3A	82%	0%
Dess-Martin periodinane	95%	0%

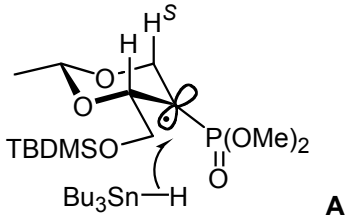
Scheme 2

The addition reaction of dimethyl phosphonate to **11a** in the presence of DBU gave the (3*R*)-3-dimethoxyphosphinoyl-tetritol derivative (**12a**) and its (3*S*)-epimer (**12b**) as an inseparable mixture (41:59) in 94% yield (Scheme 3). The mixture of **12a,b** was converted to the methoxalyl esters with methoxalyl chloride in the presence of DMAP and then reduced with tributyltin hydride in the presence of AIBN,[15] mainly affording the 3-deoxy-3-phosphinoyl-D-erythritol derivative (**13a**) (69%) together with a minor proportion of the L-threitol isomer (**13b**) (18%).



Scheme 3

The D-*erythro* configuration of **13a** was assigned on the basis of the large $J_{2,3}$ and $J_{3,4S}$ values (10.1 and 11.9 Hz). Similarly, the L-*threo* configuration of **13b** was derived from the large $J_{2,P}$ and $J_{4S,P}$ values (41.8 and 34.8 Hz). Although compounds (**12a,b**) have a hydroxy group at C-3, their configurations at C-3 were assigned by comparison to the corresponding 3-deoxy compounds (**13a,b**), respectively, because a similar characteristic tendency of the corresponding coupling constants and the chemical shifts is expected owing to almost identical conformations. As for the predominant production (79:21) of the D-erythritol derivative (**13a**) by the radical reduction of the 3-*O*-methoxalyl intermediates, we propose a preferential approach of tin hydride to the radical intermediate[16] (**A**) from the opposite side of the axial H-2 and H^S-4 protons (Figure 1).



A

Figure 1. A plausible conformation for the radical intermediate (**A**) and the direction of reduction.

The major product (**13a**) was then oxidized with oxalyl chloride-DMSO to give the 3-deoxy-3-phosphinoyl-D-erythrose derivative (**15**), which was treated with (methoxymethyl)triphenylphosphonium chloride and lithium hexamethyldisilazide (LHMDS) to afford the 4-deoxy-4-phosphinoyl-1-*O*-methyl-D-*erythro*-pent-1-enitol derivative (**16**). As the purification of **16** by column chromatography was not successful because of contamination of phosphorus impurities, the product was isolated after having been converted into methyl pyranoside derivatives. Namely, treatment of crude **16** with methanol in the presence of an acidic ion-exchange resin, followed by chromatographic separation, provided methyl 2,4-dideoxy-4-dimethoxyphosphinoyl-α-D-*erythro*-pentopyranoside (**7a**) (22% yield from **15**) and its β-anomer (**7b**) (42%). According to the previous procedures,[9] these products (**7a,b**) were reduced with sodium dihydrobis(2-methoxyethoxy)aluminate (SDMA), followed by hydrolysis with acid and then oxidation with hydrogen peroxide, to afford 2-deoxy-D-ribofuranose phospho sugar (**4**).

Thus an improved synthesis of **4** from D-glucose was achieved *via* a 3-step-shorter route involving alternative procedures to introduce a phosphinoyl group in a 2.5 times better overall yield. Extension of this work including applications of these findings in synthesizing other phospho sugars, as well as derivation of **4** into phospho sugar nucleosides, is in progress.

EXPERIMENTAL

All reactions were monitored by TLC (Merck silica gel 60F, 0.25 mm) with an appropriate solvent system [(*A*) 1:19, (*B*) 1:9 MeOH-$CHCl_3$, (*C*) 1:4, (*D*) 1:1 AcOEt–hexane, and (*E*) 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.

4,6-*O*-Ethylidene-α,β-D-glucopyranoses (8).[13]

The following modification of the literature procedures[13] was made. A mixture of D-glucose (20.0 g, 111 mmol) and paraldehyde (15.0 mL, 111 mmol) containing sulfuric acid (0.12 mL, 2.2 mmol) was stirred at rt for 30 min and then set under ultrasonic irradiation at 30–35 °C for 48 h. The mixture was dissolved in hot ethanol (60 mL) and neutralized with 1M ethanolic potassium hydroxide. The mixture was passed through celite and the filtrate was evaporated in vacuo. The residue was crystallized twice from ethanol to give **8** (total 21.1 g, 92%) as colorless crystals: mp 176–178 °C (lit.,[13] mp 179–181 °C, 70–80% yield); R_f = 0.14 (*B*).

2,4-*O*-Ethylidene-D-erythritol (9).[13]

Modification of the literature procedures[13] was made as follows. A solution of **8** (3.01 g, 14.6 mmol) in water (12 mL) was added dropwise to a solution of sodium periodate (6.30 g, 29.4 mmol) in water (100 mL) at 0–5 °C with keeping the pH value at ca. 4–5 by adding 4M aqueous NaOH. After stirring at same temperature for 30 min, the pH value was adjusted to ca. 9–10 by adding 4M aqueous NaOH and then sodium borohydride (1.74 g, 46.0 mmol) was added. The mixture was stirred at rt for 30 min, neutralized with diluted sulfuric acid, and concentrated in vacuo. The residue was dissolved in hot $CHCl_3$ and the precipitates were filtered off. The filtrate was evaporated in vacuo and the residue was purified by column chromatography with 1:9 MeOH-$CHCl_3$ as an eluant to give **9** (1.82 g, 84%) as colorless plates: mp 98–99 °C (lit.,[13] mp 99–100 °C, 78% yield); R_f = 0.32 (*B*).

1-*O*-(*tert*-Butyldimethylsilyl)-2,4-*O*-ethylidene-D-erythritol (10).[14]

The following modification of the literature procedures[14] was made. *tert*-Butyldimethylsilyl chloride (6.60 g, 43.8 mmol) was added to a solution of **9** (5.39 g, 36.4 mmol), TEA (6.10 mL, 43.8 mmol), and DMAP (200 mg, 1.60 mmol) in dry CH_2Cl_2 (80 mL). The mixture was stirred at rt for 8 h and diluted with $CHCl_3$ (80 mL). The mixture was washed with saturated NH_4Cl and then water, dried (Na_2SO_4), and evaporated in vacuo. The residue purified by column chromatography with 1:4 AcOEt-hexane as an eluant to give **10** [9.08 g, 95% (lit.,[14] 95%)] as a colorless syrup: R_f = 0.38 (*C*); ^1H NMR[17] δ = 0.10, 0.11 (3H each, 2s, Me_2Si), 0.90 (9H, s, Me_3C), 1.30 (3H, d, $J_{Me,H}$ = 5.0 Hz, *Me*CH), 3.35 (1H, br s, HO-3), 3.40 (1H, dd, $J_{4R,4S}$ = 11.0, $J_{3,4S}$ = 10.0 Hz, H^S-4), 3.49 (1H, td, $J_{2,3}$ = 8.8, $J_{1',2}$ = 8.3, $J_{1,2}$ = 4.9 Hz, H-2), 3.73 (1H, ddd, $J_{3,4R}$ = 5.4 Hz, H-3), 3.75 (1H, dd, $J_{1,1'}$ = 9.8 Hz, H'-1), 3.93 (1H, dd, H-1), 4.13 (1H, dd, H^R-4), 4.67 (1H, q, MeC*H*); ^{13}C NMR δ = –5.64, –5.59 (Me_2Si), 18.14 (Me_3C), 20.40 (*Me*CH), 25.78

(*Me*$_3$C), 66.16 (C-1), 66.37 (C-3), 70.04 (C-4), 78.44 (C-2), 98.75 (Me*C*H).

(2*R*,4*S*)-4-(*tert*-Butyldimethylsilyl)oxymethyl-2-methyl-1,3-dioxan-5-one (11a) and its (2*R*,4*R*)-epimer (11b).

A. Oxidation with oxalyl chloride-DMSO. To a solution of oxalyl chloride (1.15 mL, 13.4 mmol) in dry CH_2Cl_2 (10 mL) was added a solution of DMSO (2.00 mL, 27.9 mmol) in dry CH_2Cl_2 (5.0 mL) at –60 °C. After stirring for 20 min, a solution of **10** (1.40 g, 5.34 mmol) in dry CH_2Cl_2 (5.0 mL) was slowly added at –60 °C. The mixture was stirred at same temperature for 5 h and then TEA (4.70 mL, 33.8 mmol) was added. The mixture was stirred at rt for 30 min, diluted with $CHCl_3$, washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was separated by column chromatography with 1:5 AcOEt-hexane to give **11a** (848 mg, 61%) and **11b** (422 mg, 30%).

11a: Colorless syrup: R_f = 0.38 (*C*); ^{1}H NMR[17] δ = 0.06, 0.08 (3H each, 2s, Me_2Si), 0.88 (9H, s, Me_3C), 1.45 (3H, d, $J_{2,Me}$ = 5.1 Hz, Me-2), 3.98 (1H, dd, $^2J_{H,H'}$ = 11.3, $J_{4,CH'}$ = 3.1 Hz, CH'-OSi), 4.00 (1H, dd, $J_{4,CH}$ = 4.3 Hz, CH-OSi), 4.25 (1H, dd, $J_{6,6'}$ = 18.0, $J_{4,6'}$ = 1.2 Hz, H'-6), 4.29 (1H, ddt, $J_{4,6}$ = 1.0 Hz, H-4), 4.32 (1H, dd, H-6), 5.10 (1H, q, H-2); ^{13}C NMR δ = –5.37, –5.26 (Me_2Si), 18.33 (Me_3C), 20.49 (*Me*–C-2), 25.79 (*Me*$_3$C), 62.89 (CH_2OSi), 72.69 (C-6), 83.89 (C-4), 97.18 (C-2), 205.41 (C-5).

11b: Colorless syrup; R_f = 0.63 (*C*); ^{1}H NMR δ = 0.03, 0.06 (3H each, 2s, Me_2Si), 0.88 (9H, s, Me_3C), 1.41 (3H, d, $J_{2,Me}$ = 5.1 Hz, Me-2), 3.93 (1H, dd, $^2J_{H,H'}$ = 10.7, $J_{4,CH'}$ = 2.4 Hz, CH'-OSi), 4.07 (1H, dd, $J_{4,CH}$ = 3.1 Hz, CH-OSi), 4.22 (1H, dd, $J_{6,6'}$ = 18.0, $J_{4,6'}$ = 1.4 Hz, H'-6), 4.29 (1H, td, H-4), 4.38 (1H, dd, H-6), 5.56 (1H, q, H-2); ^{13}C NMR δ = –5.71, –5.62 (Me_2Si), 18.16 (Me_3C), 20.57 (*Me*–C-2), 25.79 (*Me*$_3$C), 66.23 (CH_2OSi), 73.95 (C-6), 81.14 (C-4), 96.70 (C-2), 206.28 (C-5).

B. Oxidation with PCC. To a suspension of PCC (615 mg, 2.86 mmol) and finely powdered MS3A (1.0 g) in dry CH_2Cl_2 (8 mL) was added a solution of **10** (370 mg, 1.42 mmol) in dry CH_2Cl_2 (4 mL). The mixture was stirred at rt for 6 h and then 2-propanol (0.5 mL) was added. The mixture was stirred for 30 min, diluted with ether, and filtered. The filtrate was evaporated in vacuo and the residue was purified by column chromatography to give **11a** (303 mg, 82%) (lit.,[14] 75% yield using CrO_3-pyridine).

C. Oxidation with Dess-Martin periodinane. To a solution of **10** (200 mg, 0.762 mmol) in dry CH_2Cl_2 (5.0 mL) was added a solution of Dess-martin periodinane (420 mg, 0.990 mmol) in dry CH_2Cl_2 (5.0 mL) at 0 °C. The mixture was stirred at rt for 8 h and then diluted with $CHCl_3$ (20 mL). The mixture was washed with saturated sodium thiosulfate and then saturated $NaHCO_3$, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography to give **11a** (188 mg, 95%).

(3*R*)-1-*O*-(*tert*-Butyldimethylsilyl)-3-*C*-dimethoxyphosphinoyl-2,4-*O*-ethylidene-D-*glycero*-tetritol (12a) and its (3*S*)-epimer (12b).

DBU (2.30 mL, 15.4 mmol) was dropwise added to a solution of **11a** (3.09 g, 11.9 mmol) in dimethyl phosphonate (25.0 mL, 272 mmol) at 0 °C and the solution was stirred at rt for 2 h under argon. The mixture was treated with saturated NH_4Cl at rt for 30 min and extracted with $CHCl_3$ three times. The combind organic layers were washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography with a gradient eluant of 2:1 AcOEt-hexane to AcOEt to give an

inseparable mixture (41:59) of **12a** and **12b** (4.13 g, 94%) as colorless solid: R_f = 0.42 (*E*). *Anal*. Calcd for $C_{14}H_{31}O_7PSi$: C, 45.39; H, 8.43. Found: C, 45.28; H, 8.54.

12a: ^{1}H NMR δ = 0.10, 0.12 (3H each, 2s, Me_2Si), 0.91 (9H, s, Me_3C), 1.38 (3H, d, $J_{Me,H}$ = 4.9 Hz, *Me*CH), 3.82, 3.85 [3H each, 2d, J_{POMe} = 10.7 Hz, $P(OMe)_2$], 3.84 (1H, m, H-2), 3.89 (1H, dd, $J_{4R,4S}$ = 11.9, $^4J_{4S,OH}$ = 1.8, $J_{4S,P}$ = 0 Hz, H^S-4), 3.99 (1H, ddd, $J_{1,1'}$ = 11.6, $J_{1',2}$ = 2.8, $^4J_{1',P}$ = 1.0 Hz, H'-1), 4.01 (1H, dd, $J_{4R,P}$ = 2.7 Hz, H^R-4), 4.28 (1H, dd, $J_{1,2}$ = 3.4 Hz, H-1), 4.75 (1H, q, MeC*H*), 5.05 (1H, dd, $J_{OH,P}$ = 5.8 Hz, HO-3); ^{31}P NMR δ = 22.5.

12b: ^{1}H NMR δ = 0.10, 0.12 (3H each, 2s, Me_2Si), 0.90 (9H, s, Me_3C), 1.36 (3H, d, $J_{Me,H}$ = 4.9 Hz, *Me*CH), 3.48 (1H, dd, $J_{4S,P}$ = 28.7, $J_{4R,4S}$ = 11.3 Hz, H^S-4), 3.72 (1H, ddd, $J_{2,P}$ = 31.1, $J_{1,2}$ = 9.2, $J_{1',2}$ = 5.5 Hz, H-2), 3.84 [6H, d, J_{POMe} = 10.7 Hz, $P(OMe)_2$], 3.84 (1H, dd, $J_{1,1'}$ = 9.7 Hz, H'-1), 4.13 (1H, br s, HO-3), 4.18 (1H, t, H-1), 4.47 (1H, dd, $J_{4R,P}$ = 9.8 Hz, H^R-4), 4.75 (1H, q, MeC*H*); ^{31}P NMR δ = 26.6.

1-*O*-(*tert*-Butyldimethylsilyl)-3-deoxy-3-dimethoxyphosphinoyl-2,4-*O*-ethylidene-D-erythritol (13a) and its L-threitol epimer (13b).

Methyl oxalyl chloride (0.800 mL, 8.70 mmol) was added to a solution of **12a,b** (923 mg, 2.49 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, poured into water and then the most of solvent was distilled off in vacuo. The residue was dissolved in $CHCl_3$, washed with saturated NH_4Cl and then water, dried (Na_2SO_4), and evaporated *in* vacuo to give the 5-methoxalyloxy derivative as a pale yellow syrup: R_f = 0.28 (*D*).

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 (80 mg, 0.49 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 1:3 to 1:1 AcOEt–hexane to give **13a** and **13b**.

13a: Colorless syrup (608 mg, 69%); R_f = 0.24 (*D*); $[\alpha]_D^{26}$ –22.5° (*c* 2.75); ^{1}H NMR δ = 0.06, 0.08 (3H each, 2s, Me_2Si), 0.89 (9H, s, Me_3C), 1.30 (3H, d, $J_{Me,H}$ = 5.2 Hz, *Me*CH), 2.52 (1H, dddd, $J_{3,P}$ = 18.0, $J_{3,4S}$ = 11.9, $J_{2,3}$ = 10.1, $J_{3,4R}$ = 4.9 Hz, H-3), 3.73, 3.75 [3H each, 2d, J_{POMe} = 10.7 Hz, $P(OMe)_2$], 3.81 (1H, td, $J_{4R,4S}$ = 11.6, $J_{4S,P}$ = 3.4 Hz, H^S-4), 3.83 (2H, m, H'-1, H-2), 3.94 (1H, dd, $J_{1,1'}$ = 10.1, $J_{1,2}$ = 0.8 Hz, H-1), 4.24 (1H, ddd, $J_{4R,P}$ = 1.5 Hz, H^R-4), 4.66 (1H, q, MeC*H*); ^{13}C NMR δ = –5.24, –4.97 (Me_2Si), 18.46 (Me_3C), 20.90 (d, $^5J_{Me,P}$ = 1.7 Hz, *Me*CH), 25.90 (*Me*$_3$C), 33.00 (d, $J_{3,P}$ = 34.7 Hz, C-3), 52.43 (d, $J_{Me,P}$ = 6.9 Hz, POMe), 52.61 (d, $J_{Me,P}$ = 6.3 Hz, POMe), 64.69 (C-1), 65.55 (d, $J_{4,P}$ = 1.7 Hz, C-4), 76.84 (d, $J_{2,P}$ = 2.9 Hz, C-2), 98.78 (Me*C*H); ^{31}P NMR δ = 27.6. *Anal*. Calcd for $C_{14}H_{31}O_6PSi$: C, 47.44; H, 8.82. Found: C, 47.60; H, 8.71.

13b: Colorless syrup (160 mg, 18%); R_f = 0.16 (*D*); $[\alpha]_D^{26}$ +15.4° (*c* 2.02); ^{1}H-NMR δ = 0.065, 0.07 (3H each, 2s, Me_2Si), 0.89 (9H, s, Me_3C), 1.36 (3H, d, $J_{Me,H}$ = 5.2 Hz, *Me*CH), 1.99 (1H, dtd, $J_{3,P}$ = 19.5, $J_{3,4S}$ = 3.4, $J_{2,3}$ = 3.1, $J_{3,4R}$ = 1.1 Hz, H-3), 3.77, 3.79 [3H each, 2d, J_{POMe} = 10.7 Hz, $P(OMe)_2$], 3.82–3.86 (2H, m, H,H'-1), 3.88 (1H, ddd, $J_{4S,P}$ = 34.8, $J_{4R,4S}$ = 11.6 Hz, H^S-4), 3.94 (1H, dddd, $J_{2,P}$ = 41.8, $J_{1,2}$ = 7.1, $J_{1',2}$ = 5.1 Hz, H-2), 4.56 (1H, ddd, $J_{4R,P}$ = 9.3 Hz, H^R-4), 4.73 (1H, q, MeC*H*); ^{13}C NMR δ = –5.33, –5.16 (Me_2Si), 18.34 (*Me*$_3$C), 20.95 (*Me*CH), 25.85 (Me_3C), 34.87 (d, $J_{3,P}$ = 39.9 Hz, C-3), 52.08 (d, $J_{Me,P}$ = 6.3 Hz, POMe), 52.58 (d, $J_{Me,P}$ = 5.8 Hz, POMe), 64.60 (d, $J_{1,P}$ = 2.2 Hz, C-1), 67.44 (d, $J_{4,P}$ = 5.2 Hz, C-4),

78.90 (d, $J_{2,P}$ = 5.2 Hz, C-2), 100.21 (Me*C*H); ^{31}P NMR δ = 31.4. *Anal*. Calcd for $C_{14}H_{31}O_6PSi$: C, 47.44; H, 8.82. Found: C, 47.52; H, 8.67.

3-Deoxy-3-dimethoxyphosphinoyl-2,4-*O*-ethylidene-D-erythritol (14).

Tetrabutylammonium fluoride (1.0 M THF solution, 2.00 mL, 2.00 mmol) was dropwise added to a solution of **13a** (634 mg, 1.79 mmol) in dry THF (2.0 mL) at 0 °C. The mixture was stirred at rt for 1 h, diluted with water, and extracted with $CHCl_3$ three times. The combined organic layers were dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by column chromatography with 1:19 MeOH-$CHCl_3$ as an eluant to give **14** (413 mg, 96%) as a colorless syrup: R_f = 0.28 (*A*); $[\alpha]_D^{26}$ –16.9° (*c* 1.60); ^{1}H NMR δ = 1.33 (3H, d, $J_{Me,H}$ = 5.1 Hz, *Me*CH), 2.26 (1H, br d, HO-1), 2.46 (1H, dddd, $J_{3,P}$ = 18.8, $J_{3,4S}$ = 11.7, $J_{2,3}$ = 10.0, $J_{3,4R}$ = 4.4 Hz, H-3), 3.765, 3.77 [3H each, 2d, J_{POMe} = 10.7 Hz, P(OMe)$_2$], 3.77 (1H, m, H'-1), 3.80 (1H, td, $J_{4R,4S}$ = 11.7, $J_{4S,P}$ = 2.9 Hz, H^S-4), 3.86–3.90 (2H, m, H-1,2), 4.22 (1H, ddd, $J_{4R,P}$ = 1.9 Hz, H^R-4), 4.70 (1H, q, MeC*H*); ^{13}C NMR δ = 20.89 (d, $^5J_{Me,P}$ = 1.7 Hz, *Me*CH), 35.24 (d, $J_{3,P}$ = 35.3 Hz, C-3), 52.74 (d, $J_{Me,P}$ = 6.9 Hz, POMe), 52.79 (d, $J_{Me,P}$ = 6.9 Hz, POMe), 64.50 (C-1), 65.59 (d, $J_{4,P}$ = 1.2 Hz, C-4), 76.83 (d, $J_{2,P}$ = 3.0 Hz, C-2), 99.12 (Me*C*H); ^{31}P NMR δ = 27.8. *Anal*. Calcd for $C_8H_{17}O_6P$: C, 40.00; H, 7.13. Found: C, 39.96; H, 7.22.

3-Deoxy-3-dimethoxyphosphinoyl-2,4-*O*-ethylidene-D-erythrose (15).

To a solution of oxalyl chloride (0.63 mL, 7.2 mmol) in dry CH_2Cl_2 (2.0 mL) was added a solution of DMSO (1.00 mL, 14.0 mmol) in dry CH_2Cl_2 (4.0 mL) at –60 °C. After stirring for 15 min, a solution of **14** (310 mg, 1.29 mmol) in dry CH_2Cl_2 (2.0 mL) was slowly added at –60 °C. The mixture was stirred at same temperature for 4 h and then TEA (2.20 mL, 15.8 mmol) was added. The mixture was stirred at rt for 30 min, diluted with $CHCl_3$, washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography with 1:19 MeOH-$CHCl_3$ as an eluant to give **15** (273 mg, 89%) as a colorless syrup: R_f = 0.35 (*A*); $[\alpha]_D^{23}$ –14.8° (*c* 4.75); ^{1}H-NMR δ = 1.39 (3H, d, $J_{Me,H}$ = 5.1 Hz, *Me*CH), 2.54 (1H, dddd, $J_{3,P}$ = 18.3, $J_{3,4S}$ = 11.6, $J_{2,3}$ = 11.0, $J_{3,4R}$ = 4.9 Hz, H-3), 3.77, 3.79 [3H each, 2d, J_{POMe} = 11.0 Hz, P(OMe)$_2$], 3.91 (1H, td, $J_{4R,4S}$ = 11.7, $J_{4S,P}$ = 3.1 Hz, H^S-4), 4.31 (1H, ddd, $J_{4R,P}$ = 3.1 Hz, H^R-4), 4.41 (1H, ddd, $J_{2,P}$ = 3.3, $J_{1,2}$ = 1.3 Hz, H-2), 4.75 (1H, q, MeC*H*), 9.63 (1H, d, H-1). *Anal*. Calcd for $C_8H_{15}O_6P$: C, 40.34; H, 6.35. Found: C, 40.12; H, 6.48.

Methyl 2,4-dideoxy-4-dimethoxyphosphinoyl-α-D-*erythro*-pentopyranoside (7a) and its β-anomer (7b).[9]

To a solution of (methoxymethyl)triphenylphosphonium chloride (476 mg, 1.39 mmol) in dry THF (5.0 mL) was added LHMDS (1.0 M THF solution, 1.40 mL, 1.40 mmol) at 0 °C under argon. After stirring for 15 min, a solution of **15** (250 mg, 1.05 mmol) in THF (1.0 mL) was added at 0 °C. The mixture was stirred at rt for 5 h, treated with saturated NH_4Cl, and extracted with $CHCl_3$ three times. The combined organic layers were dried (Na_2SO_4), and evaporated in vacuo. The residue was chromatographed with 1:19 MeOH-$CHCl_3$ as an eluant to give 2,4-dideoxy-4-dimethoxyphosphinoyl-3,5-*O*-ethylidene-1-*O*-methyl-D-*erythro*-pent-1-enitol (**16**) (280

mg) as a colorless syrup which contained considerable amount of phosphorus impurities: R_f = 0.35–0.30 (*A*).

The crude **16** was dissolved in dry MeOH (20 mL) and Amberlite IR-120(H^+) (ca. 4 mL) was added. The mixture was refluxed for 12 h and then the resin was filtered off. The filtrate was evaporated in vacuo and the residue was separated by column chromatography with 1:19 MeOH-$CHCl_3$ as an eluant to give **7a** and **7b**.

7a: Colorless needles (55.6 mg, 22% from **15**); mp 107–108 °C (lit.,[9] 106–107 °C); R_f = 0.33 (*A*); $[\alpha]_D^{26}$ +133.8° (*c* 1.39).

7b: Colorless needles (106 mg, 42% from **15**); mp 101–102 °C (lit.,[9] 101–102 °C); R_f = 0.23 (*A*); $[\alpha]_D^{26}$ –50.8° (*c* 1.80).

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16. It has been confirmed that an epimerization tooks place at α-position of phosphonate via a radical intermediate during the reduction of the α-methoxalyloxyphosphonates (Ref. 12).
17. The complete parameters for **10** and **11a** obtained in the present study are shown here, because ^{1}H NMR data for these compounds including insufficient assignments were reported in Ref. 14.