ELECTROPHILIC HETEROATOM CYCLIZATION OF ω-ALKENYLPHOSPHONIC ACID HALF ESTERS GIVING CYCLIC PHOSPHONATES (PHOSTONES)¶

Tsutomu Yokomatsu, Yoshihito Shioya, Haruo Iwasawa, and Shiroshi Shibuya*

School of Pharmacy, Tokyo University of Pharmacy and Life Science,
1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan

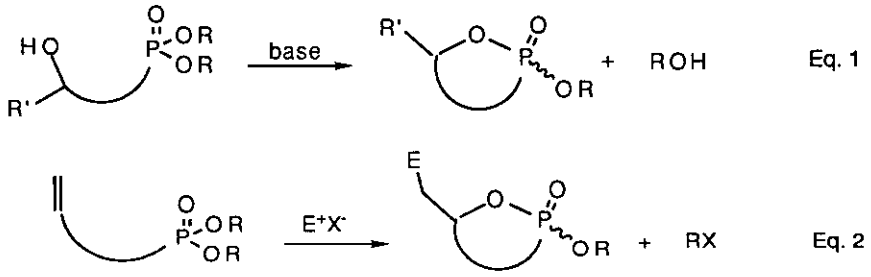
Abstract– Electrophilic heteroatom cyclizations of ω-alkenylphosphonic acid half esters (**4a-d**) with NBS or phenylselenenyl chloride were examined to give the cyclic phosphonates (phostones) (**6a-d** and **7a-d**). The phenyseleno-methylphostone (**7c**) was converted to the acetoxymethylphostone (**9**) through sequential seleno-Pummerer rearrangement and reductive deselenenylation.

INTRODUCTION

Modification of sugars by replacing the ring oxygen or anomeric carbon with a heteroatom is of continuing interest in glycomimetic chemistry, because the resulting sugar-mimics are potentially useful components in modulating the biological functions of naturally occurring carbohydrate.[1] Therefore, a number of sugar analogues having a heteroatom in the ring instead of oxygen have been synthesized.[2] Since most chemical and enzymatic reactions of sugars involve the anomeric carbon, sugar analogues modified in reactivity of the anomeric carbon are also of special interest. A logical choice for the modification involves a pentacovalent phosphorus atom which would correspond to a cyclic phosphonate ("phostone"). Phostone analogues of KDO (3-deoxy-D-manno-octulosonic acid), D-glucopyranose, and D-mannopyranose have been prepared.[3,4] Moreover, synthesis and characterization of disaccharide phostones from the appropriate pentose have been disclosed recently by Hanessian and Rosen.[5]

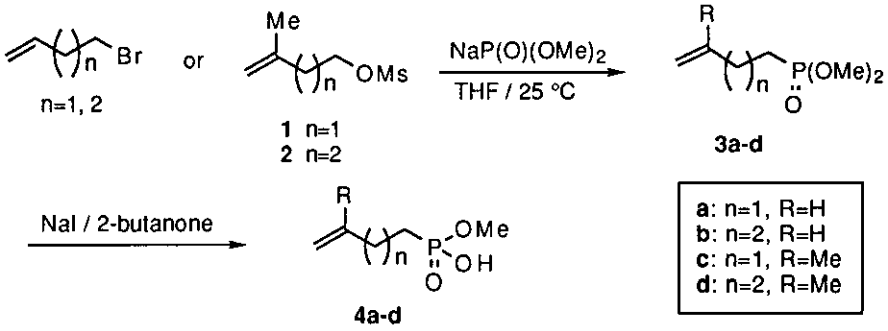
Base-catalyzed intramolecular transesterification of hydroxyalkylphosphonates is usually applied for the synthesis of phostones (Eq. 1). However, in some cases, the yield of the cyclization was reported to be low owing to the undesirable equilibrium between the hydroxyalkylphosphonate and the corresponding phostone.[6] Thus, improved methods for the synthesis of phostones are still required. One tactic for the synthesis of phostones comprises the electrophilic heteroatom cyclization of alkenylphosphonates as shown in Eq. 2.[7] Although the electrophilic heteroatom cyclization of alkenylcarboxylates with a variety of electrophilic reagents has been extensively studied for the synthesis of functionalized lactones,[7] such methodology has not been applied to the preparation of phostones, except for a report from Zhao, in which iodomethylphostones were prepared through iodine-induced cyclization of *O,O*-dimethyl 4-

pentenylphosphonates.[8,9] Therefore, the potential utility of electrophilic heteroatom cyclization of alkenylphosphonates with other electrophilic reagents in the synthesis of functionalized phostones remains unknown. In this paper, we now disclose that bromomethyl- and phenylselenenylmethylphostones can be prepared by the electrophilic heteroatom cyclizations of ω-alkenylphosphonic acid half esters promoted with NBS or phenylselenenyl chloride, in addition to a successful conversion of a phenylselenenyl-methylphostone to an acetoxymethylphostone through sequential seleno-Pummerer rearrangement[10] and reductive deselenylation.[11]



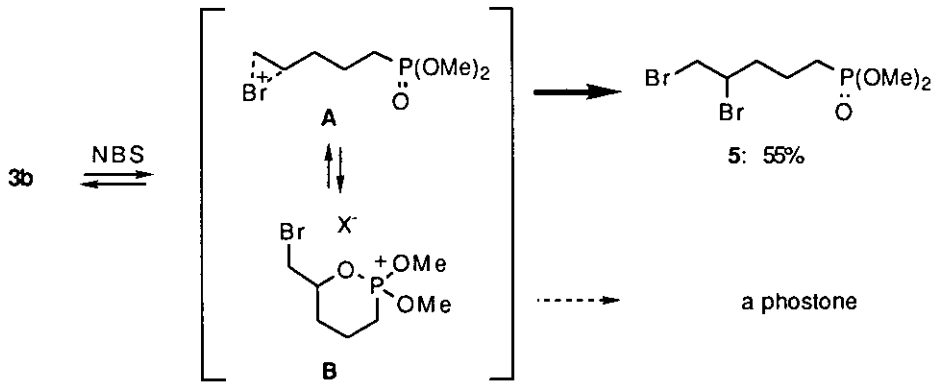
RESULTS AND DISCUSSION

Preparation of Alkenylphosphonates. Alkenylphosphonates (**3a-d**) and their half esters (**4a-d**) used in this study were prepared as follows. Michaelis-Becker-Nylen reaction of 4-bromo-1-butene and 5-bromo-1-pentene with sodium dimethylphosphite in THF at room temperature gave the ω-alkenylphosphonates (**3a**) and (**3b**) in 68 and 85% yields, respectively. In a similar way, alkenylphosphonates (**3c**) and (**3d**) were prepared from the methanesulfonats (**1**) and (**2**) in 52[12] and 52% yields. Treatment of **3a-d** with NaI in 2-butanone under reflux gave alkenylphosphonic acid half esters (**4a-d**) in virtually quantitative yield.



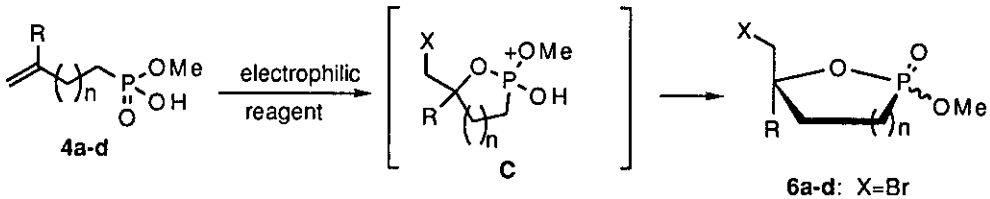
Attempted Electrophilic Cyclization of O,O-Dimethyl ω-Alkenylphosphonate (3b). At first, electrophilic heteroatom cyclization of *O,O*-dimethyl alkenylphosphonate (**3b**) was briefly examined with NBS as an electrophilic reagent in several organic solvents (MeCN, $CHCl_3$, and DMF). While rapid dibromination at the olefin providing dibomides (**5**) with 55% yield was observed upon conducting the

reactions in DMF,[13] the desired phostones were not produced from this reaction. The alkenylphosphonate (**3b**) was recovered in modest yield when the reaction was conducted in MeCN or $CHCl_3$. An aliquot of the reaction mixture conducted in either MeCN or $CHCl_3$ was directly analyzed at regular time intervals by ^{31}P NMR spectroscopy. However, no detectable intensity of signals due to a presumed trialkoxyphosphonium ion **B** was observed in its ^{31}P NMR spectrum.[8] These results suggest that the equilibrium concentration of trialkoxyphosphonium ion **B** is very low due to weak nucleophilicity of the oxygen atom of the phosphonate as well as to some difficulty in the collapse of the O–Me bond in the intermadiate **B** under the conditions. Therefore, bromophostonization of alkenylphosphonic acid dialkyl esters is not feasible synthetically. The results coincide with those of attempted bromophostonization with Br_2 by Zhao.[8]



Electrophilic Heteroatom Cyclization of ω-Alkenylphosphonic Acid Half Esters (4a-d).[14] Based upon these observations, our attention was next focused on the electrophilic heteroatom cyclization of alkenylphosphonic acid half esters (**4a-d**) (Table 1). A presumed cyclic phosphonium ion such as **C**, formed from the half esters, would readily lose the proton to give the desired phostone. Although the reactions proceeded rather slowly, the desired bromophostones (**6a**) and (**6b**) were produced in 35% and 10% yields, as expected, upon treatment of **4a** and **4b** with NBS in DMF in the presence of *aq.* $NaHCO_3$ at room temperature (entries 1 and 3). Yields of **6a,b** were significantly improved when the reactions were conducted in DMF under a high dilution condition without the base (entries 2 and 4). Under these conditions, bromomethylphostones (**6c,d**) having a quarternary carbon could be prepared in moderate yields (entries 5 and 6).

In an effort to obtain other functionalized phostones, we successively attempted phenylselenenyl chloride-induced cyclization of **4a-d** to give phenylselenenylphostones (**7a-d**) (Table 1). The phenylselenenylphostones would be useful intermediates for the synthesis of a variety of functionalized phostones. Treatment of **4a,b** with phenylselenenyl chloride in CH_2Cl_2 in the presence of silica gel[15] at room temperature gave phenylselenenylphostones (**7a,b**) in 67% and 66% yields, respectively (entries 7 and 8). The introduction of a methyl substituent on the γ or δ position slightly decreased yields of **7c,d** under the same conditions (entries 9 and 10). The faster reaction time with relatively high yield than that of the corresponding bromophostonization reveals the favorable synthetic potential of phenylselenenyl-phostonization of alkenylphosphonic acid half esters.



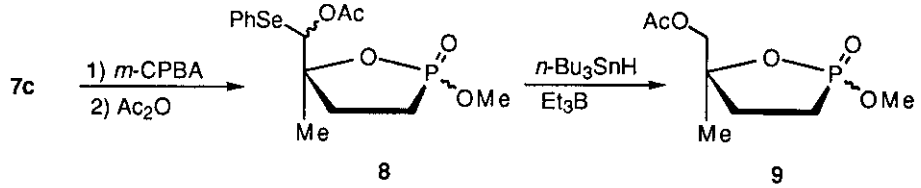
a: R=H, n=1; **b**: R=H, n=2; **c**: R=Me, n=1; **d**: R=Me, n=2

Table 1. Electrophilic Heteroatom Cyclization of Alkenylphosphonic Acid Half Esters (**4a-d**)

entry	Substrate	Condition[a]	Time (h)	Product	Yield (%)
1	**4a**	NBS / $NaHCO_3$ / DMF	15	**6a**	35
2	**4a**	NBS / DMF (0.04 M)	48	**6a**	50
3	**4b**	NBS / $NaHCO_3$ / DMF	15	**6b**	10
4	**4b**	NBS / DMF (0.04 M)	48	**6b**	46
5	**4c**	NBS / DMF (0.04 M)	48	**6c**	49
6	**4d**	NBS / DMF (0.04 M)	48	**6d**	44
7	**4a**	PhSeCl / CH_2Cl_2 / silica gel	5	**7a**	67
8	**4b**	PhSeCl / CH_2Cl_2 / silica gel	2	**7b**	66
9	**4c**	PhSeCl / CH_2Cl_2 / silica gel	5	**7c**	45
10	**4d**	PhSeCl / CH_2Cl_2 / silica gel	5	**7d**	42

[a] All reactions were carried out at 25 °C.

Conversion of Phenylselenomethylphostones to Acetoxymethylphostones. With phenyselenenylphostones (**7**) in hand, we then attempted introduction of an oxygen functionality to the side chain of the phostone. Treatment of **7c** with *m*-CPBA in CH_2Cl_2 gave the selenoxides in virtually quantitative yield. According to a method of Miyasaka,[10] the seleno-Pummerer rearrangement of the selenoxides with Ac_2O was carried out to give a diastereomeric mixture of the acetoxyselenide (**8**) in 62% yield. The reductive deselenenylation of **8** with *n*-Bu_3SnH in the presence of Et_3B afforded the acetoxymethylphostone (**9**) in 84% yield.[11,16]



In conclusion, we have developed an efficient method for the preparation of phostones using electrophilic heteroatom cyclization of ω-alkenylphosphonic acid half esters. Development of other valuable phostones having a polyhydroxy-functionality based on this new methodology is now in progress.

EXPERIMENTAL

General. All reactions were carried out under nitrogen atmosphere, unless otherwise specified. ^{1}H NMR spectra were recorded at 300 or 400 MHz in $CDCl_3$ using TMS or residual $CHCl_3$ (7.26 ppm) as internal reference. ^{13}C NMR (100 MHz) and ^{31}P NMR (161 MHz) were taken in $CDCl_3$ using $CDCl_3$ (77.0 ppm) as internal standard and 85% H_3PO_4 as external standard, respectively, with broad-band ^{1}H decoupling.

General Procedure for the Synthesis of O,O-Dimethyl ω-Alkenylphosphonates (3a-d). To a stirred suspension of NaH (13 mmol, 312 mg) in THF (15 mL) was added dimethyl phosphite (13 mmol, 1.19 mL) dropwise at 0 °C. The mixture was stirred for 30 min at the same temperature and heated under reflux for 2 h. After being cooled to 0 °C, THF solution (2 mL) of 4-bromo-1-butene (10 mmol, 1.35 g) or 5-bromo-1-pentene (10 mmol, 1.49 g) was added dropwise. After being stirred at 20 °C for 20 h, the reaction was quenched by addition of cold water. The volatile component (THF) of the mixture was removed *in vacuo*. The residue was extracted with $CHCl_3$. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, hexane:EtOAc=2:1) to give **3a,b** as oils. When ω-alkenylphosphonates (**3c,d**) were prepared, exactly the same procedure as above was applied except for the replacement of the bromide by the methansulfonates (**1**) (10 mmol, 1.64 g) or **2** (10 mmol, 1.78 g). The yield and the physical data for **3a-d** are as follows:

O,O-Dimethyl 3-Butenylphosphonate (3a). Yield: 68%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84 (1H, ddt, *J*=17.1, 10.2, 6.5 Hz), 5.07 (1H, dd with small split, *J* = 17.1, 1.6 Hz), 5.01 (1H, dd with small split, *J* = 10.2, 1.6 Hz), 3.75 (6H, d, *J* = 10.8 Hz), 2.41-2.29 (2H, m), 1.89-1.79 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.6 (d, J_{CP}= 17.1 Hz), 114.8, 51.8 (d, J_{CP} = 6.4 Hz), 25.97 (d, J_{CP} = 4.1 Hz), 23.63 (d, J_{CP} = 140.9 Hz); ^{31}P NMR (160 MHz, $CDCl_3$) δ 33.54; IR (neat) 1643, 1243, 1034 cm^{-1}; MS *m/z* 165 (M^++1). Anal. Calcd for $C_6H_{13}O_3P$: C, 43.90; H, 7.98. Found: C, 43.46; H. 7.99.

O,O-Dimethyl 4-Pentenylphosphonate (3b).[8] Yield: 85%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73 (1H, ddt, *J*=17.0, 10.2, 6.7 Hz), 5.01 (1H, dd with small split, *J*=17.0, 1.7 Hz), 4.98 (1H, dd with small split, *J*=10.2, 1.7 Hz), 3.72 (6H, d, *J*=10.7 Hz), 2.15-2.07 (2H, m), 1.78-1.62 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.94, 115.47, 51.93 (d, J_{CP}=6.5 Hz), 34.00 (d, J_{CP}=16.9 Hz), 23.66 (d, J_{CP}=141.0 Hz), 21.28 (d, J_{CP}=4.4 Hz); ^{31}P NMR (161 MHz, $CDCl_3$) δ 34.73; IR (neat) 1641, 1240, 1033 cm^{-1}; EIMS *m/z* 178 (M^+), 179 (M^++1); HRMS calcd for $C_7H_{15}O_3P$ (M^+): 178.0759. Found: 178.0760.

O,O-Dimethyl 3-Methyl-3-butenylphosphonate (3c). Yield: 52% (based on the recovered starting methanesulfonate (**1**)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.74 (2H, d with small split, *J*=14.7 Hz), 3.75 (6H, d, *J*=10.9 Hz), 2.33-2.24 (2H, m), 1.93-1.84 (2H, m), 1.73 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.79 (d, J_{CP}=17.2 Hz), 108.74, 50.53, 28.64, 21.65 (d, J_{CP}=141.0 Hz), 20.46; ^{31}P NMR (161 MHz, $CDCl_3$) δ 34.31; IR (neat) 1651, 1236, 1034 cm^{-1}; EIMS *m/z* 178 (M^+); HRMS calcd for $C_7H_{15}O_3P$ (M^+):178.0759. Found: 178.0750.

O,O-Dimethyl 4-Methyl-4-pentenylphosphonate (3d). Yield: 52%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.70 (2H, d with small split, *J*=25.3 Hz), 3.72 (6H, d, *J*=10.7 Hz), 2.15-2.04 (2H, m), 1.93-1.83 (4H, m), 1.49 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.28, 111.05, 52.25 (d, J_{CP}=6.2 Hz), 38.35 (d, J_{CP}=16.9 Hz), 24.05 (d, J_{CP}=139.9 Hz), 22.09, 20.20 (d, J_{CP}=4.5 Hz); ^{31}P NMR (161 MHz, $CDCl_3$) δ 34.75; IR (neat) 1650, 1234, 1030 cm^{-1}; MS *m/z* 192 (M^+); HRMS calcd for $C_8H_{17}O_3P$ (M^+): 192.0915. Found: 192.0909.

Reaction of 4b with NBS in DMF. To a cooled solution (-20 °C) of NBS (4.0 mmol, 711.96 mg) in DMF (1 mL) was added a solution of **3b** (2.0 mmol, 356 mg) in DMF (1 mL). The mixture was stirred at -20 °C for 2 h, then gradually warmed to rt. After being stirred at rt for 15 h, the reaction was quenched by adding water. The mixture was extracted with $CHCl_3$. The extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a residue. Purification by column chromatography on silica gel (EtOAc) gave dibromide (**5**)[8] (405 mg, 60%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.20-4.08 (1H, m), 3.86 (1H, dd, *J*=10.3, 4.4 Hz), 3.76 (6H, d, *J*=10.8 Hz), 3.62 (1H, dd, *J*=10.3, 10.3 Hz), 2.33-2.20 (1H, m), 2.02-1.66 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.31 (d, J_{CP}=2.9 Hz), 52.26 (d, J_{CP}=3.0 Hz), 36.39 (d, J_{CP}=16.1 Hz), 35.83, 23.70 (d, J_{CP}=141.0 Hz), 19.94 (d, J_{CP}=4.2 Hz); ^{31}P NMR (161 MHz, $CDCl_3$) δ 33.44; IR (neat) 1245, 1041, 1017, 962 cm^{-1}; EIMS *m/z* 339 (M^++1); Anal. Calcd for $C_7H_{15}O_3Br_2P$: C, 24.88; H, 4.47. Found: C, 25.21; H, 4.38.

General Procedure for the Synthesis of O-Methyl ω-Alkenylphosphonic Acid Half Esters (4a-d). A solution of diesters (**3a-d**) (10 mmol) and NaI (10.5 mmol, 1.57 g) in 2-butanone (25 mL) was heated under reflux for 24 h. After being cooled, the resulting precipitate of sodium salts of **4a-d** was collected and washed with cold 2-butanone. The solid was dissolved in 1N HCl, and the mixture was extracted with $CHCl_3$. The combined extracts were washed with brine, dried over $NaSO_4$, and evaporated to give **4a-d** as oils. These were sufficiently pure for use in the next reaction.

O-Methyl 3-Butenylphosphonate (4a). Yield: 91%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (1H, ddt, *J*=17.1, 10.2, 6.6 Hz), 5.08 (1H, dd with small split, *J*=17.1, 1.5 Hz), 5.02 (1H, dd, *J*=10.2, 1.5 Hz), 3.72 (3H, d, *J*=10.4 Hz), 2.43-2.28 (2H, m), 1.91-1.76 (4H, m), ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.99, 115.03, 51.44 (d, J_{CP}=6.3 Hz), 26.18 (d, J_{CP}=3.7 Hz), 24.60 (d, J_{CP}=143.2 Hz); ^{31}P NMR (161 MHz, $CDCl_3$) δ 35.09; IR (neat) 1643, 1187, 1050, 996 cm^{-1}; EIMS *m/z* 150 (M^+), 151 (M^++1); HRMS calcd for $C_5H_{11}O_3P$ (M^+):150.0446. Found:150.0442.

O-Methyl 4-Pentenylphosphonate (4b). Yield: 98%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (1H, ddt, *J*=17.3, 10.2, 6.7 Hz), 5.04 (1H, dd with small split, *J*=17.3, 1.7 Hz), 5.00 (1H, dd with small split, *J*=10.2, 1.7 Hz), 3.72 (3H, d, *J*=11.1 Hz), 2.20-2.05 (2H, m), 1.81-1.65 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.15, 115.50, 51.33 (d, J_{CP}=6.5 Hz), 34.08 (d, J_{CP}=17.0 Hz), 24.49 (d, J_{CP}=143.4 Hz), 21.32 (d, J_{CP}=4.1 Hz); ^{31}P NMR (161 MHz, $CDCl_3$) δ 34.79; IR (neat) 1641, 1187, 1050, 991 cm^{-1}; EIMS *m/z* 164 (M^+), 165 (M^++1); HRMS calcd for $C_6H_{13}O_3P$ (M^+): 164.0602. Found: 164.0607.

O-Methyl 3-Methyl-3-butenylphosphonate (4c). Yield: 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.74 (2H, d with small split, *J*=13.6 Hz), 3.73 (3H, d, *J*=11.0 Hz), 2.36-2.26 (2H, m), 1.95-1.34 (2H, m), 1.74 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.03 (d, J_{CP}=18.2 Hz), 109.95, 51.31 (d, J_{CP}=3.1 Hz), 29.77, 23.63 (d, J_{CP}=143.3 Hz), 21.87 (d, J_{CP}=3.6 Hz); ^{31}P NMR (161 MHz, $CDCl_3$) δ 36.18; IR (neat) 1651, 1187, 1051, 990 cm^{-1}; EIMS *m/z* 164 (M^+), 165 (M^++1); HRMS calcd for $C_6H_{13}O_3P$ (M^+): 164.0602. Found: 164.0605.

O-Methyl 4-Methyl-4-pentenylphosphonate (4d). Yield: 85%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.72 (2H, d with small split, *J*=22.6 Hz), 3.72 (3H, d, *J*=11.3 Hz), 2.15-2.07 (2H, m), 1.85-1.68 (4H, m), 1.70 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.31, 111.03, 51.40 (d, J_{CP}=7.0 Hz), 38.28 (d, J_{CP}=17.5 Hz), 24.75 (d, J_{CP}=142.7 Hz), 22.08, 20.09 (d, J_{CP}=4.2 Hz); ^{31}P NMR (161 MHz, $CDCl_3$) δ

36.71; IR (neat) 1650, 1188, 1050, 990 cm^{-1}; EIMS *m/z* 178 (M^+), 179 (M^++1); HRMS calcd for $C_7H_{15}O_3P$ (M^+): 178.0759. Found: 178.0758.

General Procedure for Bromophostonization of Alkenylphosphonic Acid Half Esters (4a-d) with NBS in DMF. To a cooled solution (-20 °C) of NBS (4.0 mmol, 711.96 mg) in DMF (40 mL) was added a solution of **4a-d** (2.0 mmol) in DMF (10 mL). The mixture was stirred at -20 °C for 2 h, then gradually warmed to rt. After being stirred at rt for 48 h, the reaction was quenched by adding water. The mixture was extracted with $CHCl_3$. The extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a residue. Purification by column chromatography on silica gel ($CHCl_3$) gave bromomethylphostones (**6a-d**) as oils.

5-Bromomethyl-2-methoxy-2-oxo-1,2-oxaphospholane (6a). Yield: 50%; obtained as a mixture of diastereoisomers (24% *de*); ^1H NMR (300 MHz, $CDCl_3$) δ 4.58-4.49 (0.38H, m), 4.48-4.41 (0.62H, m), 3.81 (1.86H, d, *J*=11.3 Hz), 3.80 (1.14H, d, *J*=11.3 Hz), 3.58-3.47 (1H, m), 3.46-3.36 (1H, m), 2.54-1.98 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 73.26 (d, J_{CP}=7.3 Hz), 72.42 (d, J_{CP}=6.3 Hz), 52.77 (d, J_{CP}=6.2 Hz), 33.79 (d, J_{CP}=5.2 Hz), 33.55 (d, J_{CP}=7.6 Hz), 28.03, 27.83, 19.41 (d, J_{CP}=119.9 Hz), 18.72 (d, J_{CP}=120.7 Hz); ^{31}P NMR (161 MHz, $CDCl_3$) δ 48.77 (0.38P), 48.47 (0.62P); EIMS *m/z* 229, 231 (M^++1), 149 (M^+-Br); HRMS calcd for $C_5H_{10}O_3P$ (M^+-Br): 149.0368. Found: 149.0348. Anal. Calcd for $C_5H_{10}O_3BrP$: C, 26.22; H, 4.40. Found: C, 26.73; H, 4.46.

6-Bromomethyl-2-methoxy-2-oxo-1,2-oxaphosphorinane (6b). Yield: 46%; obtained as a mixture of diastereoisomers (54% *de*); ^1H NMR (300 MHz, $CDCl_3$) δ 4.65-4.55 (0.23H, m), 4.35-4.25 (0.77H, m), 3.81 (0.69H, d, *J*=11.1 Hz), 3.77 (2.31H, d, *J*=11.1 Hz), 3.51-3.45 (1H, m), 3.42-3.36 (1H, m), 2.20-1.61 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 80.15 (d, J_{CP}=6.4 Hz), 78.03 (d, J_{CP}=4.5 Hz), 52.58 (d, J_{CP}=6.4 Hz), 51.18 (d, J_{CP}=6.3 Hz), 34.51 (d, J_{CP}=7.8 Hz), 34.10 (d, J_{CP}=8.6 Hz), 29.97, 29.92, 21.98 (d, J_{CP}=128.6 Hz), 21.74 (d, J_{CP}=138.4 Hz), 20.08, 20.01; ^{31}P NMR (161 MHz, $CDCl_3$) δ 27.72 (0.23P), 24.86 (0.77P); IR (neat) 1250, 1034 cm^{-1}; MS *m/z* 243, 245 (M^++1); HRMS calcd for $C_6H_{12}O_3BrP$ (M^+): 241.9707. Found: 241.9711.

5-Bromomethyl-2-methoxy-5-methyl-2-oxo-1,2-oxaphospholane (6c). Yield: 49%; obtained as a mixture of diastereoisomers (38% *de*); ^1H NMR (300 MHz, $CDCl_3$) δ 3.80 (0.93H, d, *J*=11.2 Hz), 3.79 (2.07H, d, *J*=11.2 Hz), 3.52-3.38 (1H, m), 2.53-2.28 (1H, m), 2.25-1.90 (3H, m), 1.57 (0.93H, s), 1.53 (2.07H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.26 (d, J_{CP}=9.6 Hz), 83.21 (d, J_{CP}=9.4 Hz), 52.47 (d, J_{CP}=7.2 Hz), 39.32, 39.25, 32.60, 32.52, 25.54, 25.38, 19.13 (d, J_{CP}=119.3 Hz), 19.00 (d, J_{CP}=118.7 Hz), ^{31}P NMR (161 MHz, $CDCl_3$) δ 48.06 (0.69P), 47.73 (0.31P); IR (neat) 1187, 1044, 995, 964 cm^{-1}; EIMS m/z 243, 245 (M^++1), 227, 229 (M^+-CH_3); HRMS calcd for $C_5H_9O_3BrP$ (M^+-CH_3): 226.9473. Found: 226.9471.

6-Bromomethyl-2-methoxy-6-methyl-2-oxo-1,2-oxaphosphorinane (6d). Yield: 44%; obtained as a mixture of diastereoisomers (30% *de*); ^1H NMR (300 MHz, $CDCl_3$) δ 3.74 (1.95H, d, *J*=10.9 Hz), 3.77 (1.05H, d, *J*=10.9 Hz), 3.61-3.44 (1H, m), 2.2-1.6 (6H, m), 1.54 (1.95H, s), 1.59 (1.05H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.60 (d, J_{CP}=8.0 Hz), 83.45 (d, J_{CP}=8.0 Hz), 52.14 (d, J_{CP}=6.1 Hz), 51.38 (d, J_{CP}=6.1 Hz), 40.80 (d, J_{CP}=6.6 Hz), 33.61, 33.53, 23.36, 22.03 (d, J_{CP}=129.6 Hz), 21.98 (d, J_{CP}=128.4 Hz), 17.76 (d, J_{CP}=7.6 Hz), 17.51 (d, J_{CP}=7.3 Hz); ^{31}P NMR (161 MHz,

$CDCl_3$) δ 23.51 (0.35P), 23.39 (0.65P); IR (neat) 1246, 1040, 981 cm^{-1}; EIMS *m/z* 256, 258 (M^+), 257, 259 (M^++1), 241, 243 (M^+-CH_3); HRMS calcd for $C_7H_{14}O_3BrP$ (M^+): 255.9864. Found: 255.9868.

General Procedure for Selenophostonization of Alkenylphosphonic Acid Half Esters (4a-d) with PhSeCl in CH_2Cl_2. To a cooled solution (-78 °C) of **4a-d** (2.0 mmol) in CH_2Cl_2 (8.3 mL) in the presence of silica gel (610 mg) was added a solution of PhSeCl (2.16 mmol, 435.0 mg) in CH_2Cl_2 (6.4 mL) over 20 min. The mixture was stirred at -78 °C for 10 min, then gradually warmed to rt. After being stirred until the starting material disappeared on TLC (2-5 h), the silica gel was filtered. The volatile component of the filtrate was evaporated to give a residual oil. Purification by column chromatography on silica gel ($CHCl_3$) gave selenophostones (**7a-d**) as oils.

2-Methoxy-2-oxo-5-phenylselenomethyl-1,2-oxaphospholane (7a). Yield: 67%; obtained as a mixture of diastereoisomers (14% *de*); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.52 (2H, m), 7.41-7.20 (3H, m), 4.55-4.40 (0.43H, m), 4.40-4.25 (0.57H, m), 3.76 (1.71H, d, *J*=11.0 Hz), 3.74 (1.29H, d, *J*=11.0 Hz), 3.34-3.23 (1.14H, m), 3.03-2.94 (0.84H, m), 2.55-2.30 (1H, m), 2.10-1.75 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.97, 132.78, 131.19, 129.09, 129.10, 128.27, 126.98, 77.94 (d, J_{CP}=9.3 Hz), 77.80 (d, J_{CP}=9.6 Hz), 52.34 (d, J_{CP}=6.4 Hz), 52.51 (d, J_{CP}=6.5 Hz), 39.11 (d, J_{CP}=6.2 Hz), 37.76 (d, J_{CP}=6.3 Hz), 32.09 (d, J_{CP}=5.2 Hz), 31.95 (d, J_{CP}=7.0 Hz), 19.37 (d, J_{CP}=119.0 Hz), 18.73 (d, J_{CP}=120.0 Hz); ^{31}P NMR (161 MHz, $CDCl_3$) δ 48.62 (0.43P), 48.52 (0.57P); EIMS *m/z* 306 (M^+), 307 (M^++1); HRMS calcd for $C_{11}H_{15}O_3PSe$ (M^+): 305.9924. Found: 305.9914.

2-Methoxy-2-oxo-6-phenylselenomethyl-1,2-oxaphosphorinane (7b). Yield: 66%; obtained as a mixture of diastereoisomers (10% *de*); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.41 (2H, m), 7.41-7.20 (3H, m), 4.70-4.55 (0.45H, m), 3.25-3.15 (1.10H, m), 3.20-2.95 (0.90H, m), 2.21-1.41 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.22, 132.09, 131.72, 131.59, 128.69, 128.63, 126.77, 126.69, 80.38 (d, J_{CP}=7.0 Hz), 78.89 (d, J_{CP}=5.0 Hz), 51.82 (d, J_{CP}=6.2 Hz), 50.35 (d, J_{CP}=6.2 Hz), 32.62 (d, J_{CP}=7.8 Hz), 32.46 (d, J_{CP}=6.9 Hz), 30.62 (d, J_{CP}=5.8 Hz), 21.32 (d, J_{CP}=120.0 Hz), 21.20 (d, J_{CP}=110.3 Hz), 19.61 (d, J_{CP}=6.9 Hz); ^{31}P NMR (161 MHz, $CDCl_3$) δ 27.57 (0.45P), 25.09 (0.55P); IR (neat) 1250, 1034 cm^{-1}; EIMS m/z 320 (M^+), 321 (M^++1); HRMS calcd for $C_{12}H_{17}O_3PSe$ (M^+): 320.0081. Found: 320.0072.

2-Methoxy-5-methyl-2-oxo-5-phenylselenomethyl-1,2-oxaphospholane (7c). Yield: 45%; obtained as a mixture of diastereoisomers (30% *de*); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.21 (2H, m), 7.10-6.91 (3H, m), 3.48 (1.05H, d, *J*=11.2 Hz), 3.43 (1.95H, d, *J*=11.2 Hz), 2.97 (0.70H, dd, *J*=19.7, 12.7 Hz), 2.94 (1.30H, dd, *J*=19.7, 12.7 Hz), 2.15-1.60 (4H, m), 1.25 (1.05H, s), 1.22 (1.95H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.63, 137.59, 132.13, 132.04, 128.52, 128.48, 126.58, 126.52, 84.18 (d, J_{CP}=8.9 Hz), 51.65 (d, J_{CP}=6.3 Hz), 38.93 (d, J_{CP}=4.1 Hz), 33.58, 33.28, 18.62 (d, J_{CP}=119.0 Hz), 18.51 (d, J_{CP}=119.0 Hz); ^{31}P NMR (161 MHz, $CDCl_3$) δ 42.27 (0.35P), 47.16 (0.65P); IR (neat) 1272, 1044, 930 cm^{-1}; EIMS *m/z* 320 (M^+), 321 (M^++1); HRMS calcd for $C_{12}H_{17}O_3PSe$ (M^+): 320.0081. Found: 320.0074.

2-Methoxy-6-methyl-2-oxo-6-phenylselenomethyl-1,2-oxaphosphorinane (7d). Yield: 42%; obtained as a mixture of diastereoisomers (8% *de*); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.51 (2H,m), 7.29-7.21 (3H, m), 3.72 (1.62H, d, *J*=10.9 Hz), 3.71 (1.38H, d, *J*=10.9 Hz), 3.33 (0.46H, d, *J*=12.6 Hz), 3.32 (0.54H, d, *J*=12.6 Hz), 3.25 (0.46H, d, *J*=12.6 Hz), 3.24 (0.54H, d, *J*=12.6 Hz), ^{13}C NMR

(400 MHz, $CDCl_3$) δ 132.92, 132.88, 130.49, 129.10, 127.20, 127.13, 86.44 (d, J_{CP}=8.4 Hz), 86.28 (d, J_{CP}=8.5 Hz), 51.86 (d, J_{CP}=6.5 Hz), 51.22 (d, J_{CP}=6.3 Hz), 41.20 (d, J_{CP}=6.2 Hz), 34.88 (d, J_{CP}=7.6 Hz), 24.37, 21.94 (d, J_{CP}=128.4 Hz), 21.85 (d, J_{CP}=127.7 Hz), 17.88 (d, J_{CP}=7.6 Hz), 17.61 (d, J_{CP}=7.4 Hz); ^{31}P NMR (161 MHz, $CDCl_3$) δ 23.54 (0.46P), 23.35 (0.54P); IR (neat) 1249, 1041, 972 cm^{-1}; EIMS *m/z* 334 (M^+), 335 (M^++1), HRMS calcd for $C_{13}H_{19}O_3PSe$ (M^+): 334.0237. Found: 334.0242.

Conversion of 7c to Acetoxyselenides (8) through Seleno-Pummerer Rearrangement. To a stirred solution of **7c** (1.0 mmol, 319 mg) in CH_2Cl_2 (15 mL) was added CH_2Cl_2 solution (10 mL) of *m*-CPBA (assay: 80%) (259 mg, 1.2 mmol) under ice-cooling. After being stirred at 0 °C until the starting material disappeared on TLC (30 min), the reaction mixture was neutralized with *sat.* $NaHCO_3$ and extracted with $CHCl_3$. The extracts were washed with brine, dried over $MgSO_4$, and evaporated to give the crude selenoxide which was dissolved in CH_2Cl_2 (30 mL) and treated with Ac_2O (0.47 mL, 5 mmol). After being stirred at rt for 24 h and at 50 °C for 2 h, the mixture was partitioned between $CHCl_3$ and *sat.* $NaHCO_3$. The organic extracts were washed with brine, dried ($MgSO_4$), and concentrated to leave an oil. Purification by column chromatography on silica gel ($CHCl_3$) gave **8** (233 mg, 62%) as an oil.

2-Methoxy-2-oxo-5-(1'-phenylseleno-1'-acetoxy)methyl-5-methyl-1,2-oxaphospholane (8). Obtained as a mixture of diastereoisomers; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81-7.60 (2H, m), 7.39-7.18 (3H, m), 6.37 (0.24H, s), 6.36 (0.17H, s), 6.30 (0.30H, s), 6.22 (0.29H, s), 3.79 (0.90H, d, *J*=11.1 Hz), 3.77 (0.51H, d, *J*=11.1 Hz), 3.73 (0.87H, d, *J*=11.1 Hz), 3.71 (0.72H, d, *J*=11.1 Hz), 2.7-1.8 (4H, m), 2.08 (0.51H, s), 2.07 (0.87H, s), 2.06 (0.90H, s), 2.00 (0.72H, s), 1.58 (1.41H, s), 1.56 (0.87H, s), 1.53 (0.72H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.73, 168.59, 166.70, 135.44, 135.27, 132.39, 129.77, 129.39, 129.13, 129.10, 129.06, 128.54, 128.42, 127.75, 85.77 (d, J_{CP}=8.5 Hz), 85.57 (d, J_{CP}=9.2 Hz), 85.37 (d, J_{CP}=10.2 Hz), 82.40 (d, J_{CP}=6.1 Hz), 81.25 (d, J_{CP}=4.1 Hz), 80.66, 52.65-52.10 (m), 32.46, 32.26, 31.19, 30.87, 25.40, 24.71, 23.80, 22.73, 20.72, 20.66, 20.52, 20.40, 19.68 (d, J_{CP}=119.9 Hz), 19.35 (d, J_{CP}=120.0 Hz), 19.24 (d, J_{CP}=120.9 Hz), 18.94 (d, J_{CP}=120.0 Hz); ^{31}P NMR (161 MHz, $CDCl_3$) δ 49.04 (0.17P), 48.61 (0.24P), 48.21 (0.29P), 47.44 (0.30P); EIMS *m/z* 374, 375, 376, 378, 380 (M^+); HRMS calcd for $C_{14}H_{19}O_5PSe$ (M^+): 378.0135. Found: 378.0140.

Deselenenylation of 8 with n-Bu$_3$SnH promoted by Et$_3$B. To a cooled (-78 °C) solution of **8** (0.33 mmol, 125 mg) in THF (4 mL) was successively added Et_3B (0.32 mmol, 0.32 mL of 1 M solution in hexane) and *n*-Bu_3SnH (0.276 mmol, 76.45 μL). After being stirred at the same temperature for 2 h under the aerobic conditions with protection of moisture, MeOH (2 mL) was added to quench the reaction. The solvent was removed *in vacuo* to leave a residue, which was partitioned between MeCN and *n*-hexane. Extracts with CH_3CN was concentrated to give **9** (62 mg, 84%) as an oil.

2-Methoxy-2-oxo-5-acethoxymethyl-5-methyl-1,2-oxaphospholane (9). Obtained as a mixture of diastereoisomers (6% *de*). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.22 (0.47H, d, *J*=11.7 Hz), 4.16 (0.53H, d, *J*=11.7 Hz), 4.01 (0.53H, d, *J*=11.7 Hz), 3.98 (0.47H, d, *J*=11.7 Hz), 3.78 (1.59H, d, *J*=11.0 Hz), 3.77 (1.41 H, d, *J*=11.0 Hz), 2.42-1.90 (4H, m), 2.13 (1.41H, s), 2.11 (1.59H, s), 1.44 (1.59H, s), 1.40 (1.41H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.38, 170.30, 82.47 (d, J_{CP}=9.5 Hz), 82.14 (d, J_{CP}=10.2 Hz), 69.29 (d, J_{CP}=4.1 Hz), 68.66 (d, J_{CP}=3.5 Hz), 52.47 (d, J_{CP}=6.1 Hz), 52.37 (d, J_{CP}=7.4 Hz), 31.95, 31.31, 24.39, 24.27 (d, J_{CP}=2.1 Hz), 20.68, 20.62, 19.34 (d, J_{CP}=120.3 Hz), 18.84 (d, J_{CP}=120.2 Hz);

^{31}P NMR (161 MHz, $CDCl_3$) δ 48.20 (0.47P), 47.80 (0.53P); IR (neat) 1745, 1245, 1045, 936 cm^{-1}; EIMS *m/z* 223 (M^++1), *149* (M^+-CH_2OAc); HRMS calcd for $C_7H_{15}O_5P$ (M^+): 222.0735. Found: 222.0723.

ACKNOWLEDGMENT

This work was supported in part by Grant-in-Aid for Scientific Research (08672449) from the Ministry of Education, Science and Culture of Japan.

REFERNCES AND NOTES

¶ This paper is dedicated to the memory of the late Professor Syun-ichi Yamada.

1. For reviews on modified sugars: H. Paulsen, *Angew. Chem., Int. Ed. Engl.*, 1966, **5**, 495.
2. For recent synthesis of thia-sugars: M. Izumi, O. Tsuruta, and H. Hashimoto, *Carbohydr. Res.*, 1996, **280**, 287; H. Hashimoto, M. Kawashima, and H. Yuasa, *Carbohydr. Res.*, 1996, **282**, 207. For recent synthesis of aza-sugars: A. Baudat, S. Picasso, P. Vogel, *Carbohydr. Res.*, 1996, **281**, 277; G. Gradnig, G. Legler, and A. E. Stütz, *Carbohydr. Res.*, 1996, **287**, 49.
3. For phostone analogues of KDO: H. Molin, J.-O. Noren, and A. Claesson, *Carbohydr, Res.*, 1989, **194**, 209.
4. For phostone analogues of D-glucopyranose and D-mannopyranose: J. W. Darrow and D. G. Dreuckhammer, *J. Org. Chem.*, 1994, **59**, 2976.
5. S. Hanessian, N. Galeotti, P. Rosen, G Olive, and S. Babu, *Bioorg. Med. Chem. Lett.*, 1994, **4**, 2763.
6. A. E. Wroblewski, *Liebigs Ann. Chem.*, 1986, 1448.
7. For reviews of electrophilic heteroatom cyclization: G. Cardillo and M. Orena, *Tetrahedron*, 1990, **46**, 3321; K. E. Harding and T. H. Tiner, Electrophilic Heteroatom Cyclization. In *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991; Vol. 4, p. 363.
8. Y.-F. Zhao, S.-J. Yan, and C. Zhai, *J. Org. Chem.*, 1985, **50**, 2136.
9. Iodine-induced heteroatom cyclization of diethyl homoallylphosphate giving cyclic phosphate is known to work well: P. A. Bartlett, D. Richardoson, and J. Myerson, *Tetrahedron*, 1984, **40**, 2317; P. A. Bartlett and K. K. Jernstedt *J. Am. Chem. Soc.*, 1977, **99**, 4829.
10. For Pummerer rearrangement of selenoxides: J. A. Marshall and R. D. Royce, Jr., *J. Org. Chem.*, 1982, **47**, 693; K. Haraguchi, S. Sato, H. Tanaka, and T. Miyasaka, *Nucleosides and Nucleotides*, 1992, **11**, 483.
11. E. Kawashima, K. Toyama, K. Ohshima, M. Kainosho, Y. Kyogoku, and Y. Ishido, *Tetrahedron Lett.*, 1995, **36**, 6699.
12. Yield based on the recovered starting mesylate.
13. Dibromide (**5**) might be formed with Br_2 produced from NBS in DMF.
14. All phostones were obtained as a mixture of diastereoisomers (8-54% *de*) arising from the asymmetric center of the tetrahedral phosphorus atom. We attemped to determine the realative stereochemistry between the boromomethyl and the methoxy substituents for the major diastereoisomers of **6b** and **6c** by ^1H NMR analyses (NOE and 2D NOESY). However, the relative stereochemistry could not be determind by these analyses.
15. D. Goldsmith, D. Liotta, C. Lee, and G. Zima, *Tetrahedron Lett.*, 1979, 4801; D. L. Clive, V. Farina, A. Singh, C. K. Wong, W. Kiel, and S. M. Menchen, *J. Org. Chem.*, 1980, **45**, 2120.
16. Triethylborane as a radical initiator: Y. Takeyama, Y. Ichinose, K. Oshima, and K. Utimoto, *Tetrahedron Lett.*, 1989, **30**, 3159.

Received, 7th March, 1997