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Studies on Tocopherol Derivatives. II.[1] Synthesis of Phosphomethyl Tocopheryl Acetates

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Three phosphomethyl tocopheryl acetates: 7-phosphomethyl-β-tocopheryl acetate (IXa), 5-phosphomethyl-γ-tocopheryl acetate (IXb), 5-phosphomethyl-δ-tocopheryl acetate (IXc), and their sodium salts (Xa), (Xb) have been synthesized starting from acetoxymethyl tocopheryl acetates by unequivocal way. These phosphates are of interest in a possible role of vitamin E in oxidative phosphorylation.

The biological role of vitamin E (tocopherol) in animals may not be restircted that of a physiological antioxidant but more specific function are suggested.[3] A possible function in animal metabolism is the participation to the reversible oxidation system linked to electron transport or oixdative phosphorylation. Model experiments have been carried out to clarify the coupling factor for the formation of adenosine triphosphate (APT). Recently Bäuerlein, *et al.*[4] reported the incorporation of inorganic phosphate to ATP under the oxidation of tocopherol with bromine. Several hypothesis[5,6,7] have been proposed to explain the participation mechanism of coupling factor in oxidative phosphorylation. Vilkas, *et al.*[8a,b] have proposed a mechanism in the terpenoid quinones and chroman series involving 1,4-addition of phosphate to a methylene quinone chroman III (Chart 1), thus affording 5-phosphomethyl chromans. Wagner, *et al.*[9] have isolated 5-chloromethyl-6-chromanyl acetate from an acetylated enzymic reaction mixture obtained after incubation of vitamin $K_{1(20)}$ in cell free extract of *Mycobacterium phlei*. 5-Phosphomethyl chromanyl derivatives of vitmin $K_{1(20)}$[10,11] and coenzyme Q[10,12] were prepared by them. They considered these 5-phosphomethyl derivatives were more productive than quinol phosphate[13] in oxidative phosphorylation. Goodhue, *et al.*[14] supposed methylene quinone III or IV to be an intermediate during the oxidation of α-tocopherol with peroxide and as for the occurrence of α-tocopherol dimer I *in vivo* they considered a process *via* phosphomethyl tocopherol V, which was the addition product of inorganic phosphate to methylene quinone, rather than *via* direct coupling of radical IIa or IIb.

1) Part I: T. Nakamura and S. Kijima, *Chem. Pharm. Bull.* (Tokyo), **19**, 2318 (1971).
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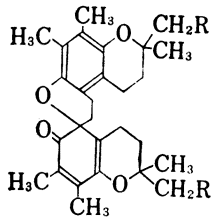

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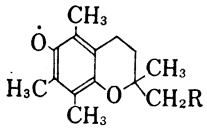

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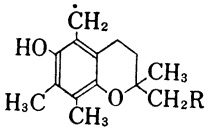

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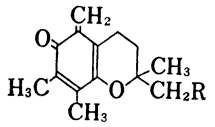

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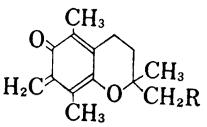

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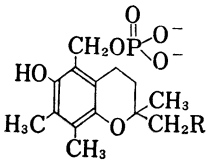

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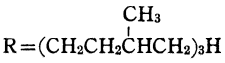
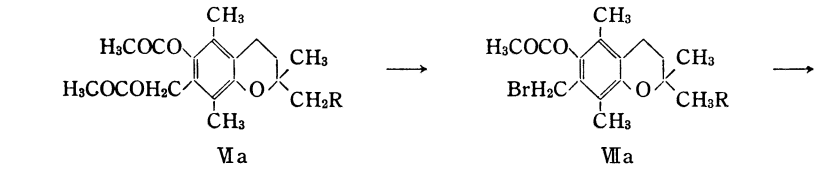
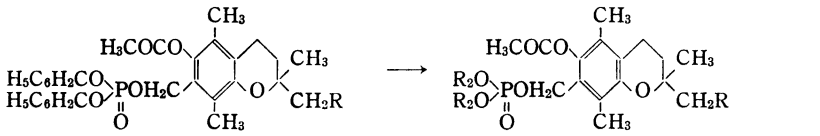


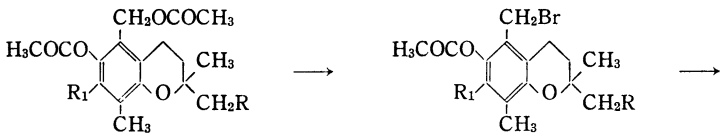
Chart 1



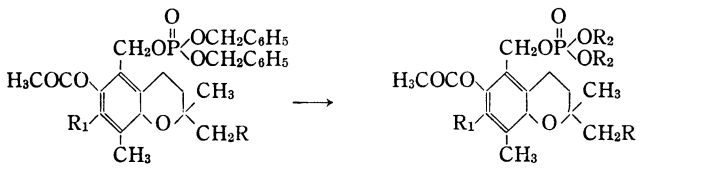
VIa VIIa



VIIIa IXa : R_2=H
Xa : R_2=Na



VIb : R_1=CH_3
VIc : R_1=H
VIIb : R_1=CH_3
VIIc : R_1=H



VIIIb : R_1=CH_3
VIIIc : R_1=H
IXb : R_1=CH_3, R_2=H
IXc : R_1=H, R_2=H
Xb : R_1=CH_3, R_2=Na

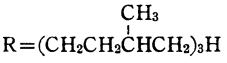


Chart 2

Karrer, *et al.*[15] have reported the synthesis of tocopheryl-6-phosphate, quinol phosphate of tocopherol. But the synthesis of phosphomethyl chromanyl derivative of tocopherol have never been reported. In the present study, the synthesis of three phosphomethyl tocopheryl acetates is mentioned. They are 7-phosphomethyl-β-tocopheryl acetate IXa, 5-phosphomethyl-γ-tocopheryl acetate IXb, 5-phosphomethyl-δ-tocopheryl acetate IXc, and their salts, Xa, Xb.

Three acetoxymethyl tocopheryl acetates VIa, VIb, VIc are synthesized from corresponding tocopherol homolgues as previoulsy reported in the study of conversion raection of tocopherols.[1] Bromine substitution are followed to the preparation of acetoxy benzyl bromide.[16] The presence of $BrCH_2$-group in VIIa, VIIb, VIIc was indicated, comparing the nuclear magnetic resonance (NMR) spectra with the spectrum of α-tocopherol, by the lack of one of aromatic methyl groups and the appearance of benzylic protons at 5.58 τ (VIIa), 5.70 τ (VIIb), and 5.71 τ (VIIc).

The phosphoric acid triesters VIIIa, VIIIb, VIIIc were obtained by the reaction with silver dibenzyl phosphate and VIIa, VIIb, VIIc. The infrared (IR) spectra of these triesters show strong absorption band at 1275 cm^{-1} (ν P=O) and 1010 cm^{-1} (ν C–O of C–O–P). The NMR spectra show 6 protons at benzylic protons region as two doublets. The preferential cleavage of the phosphoric acid triesters were accomplished by catalytic hydrogenation using 10% palladium-on-charcoal (Pd-C) catalyst. In general, the NMR spectra of dihydrogen phosphate IXa, IXb, IXc are broaden and clear assignements are difficult. These dihydrogen phosphate are not stable in the air. The color of the products changes into dark brown in few days. The sodium salts of the two hydrogen phosphates Xa, Xb were prepared with sodium hydroxide in ethanol–acetone solution and obtained as white solid. They gave melting points 138—140° and 151—152°, respectively. Seventy milligrams of these salts are soluble in 1 ml of water.

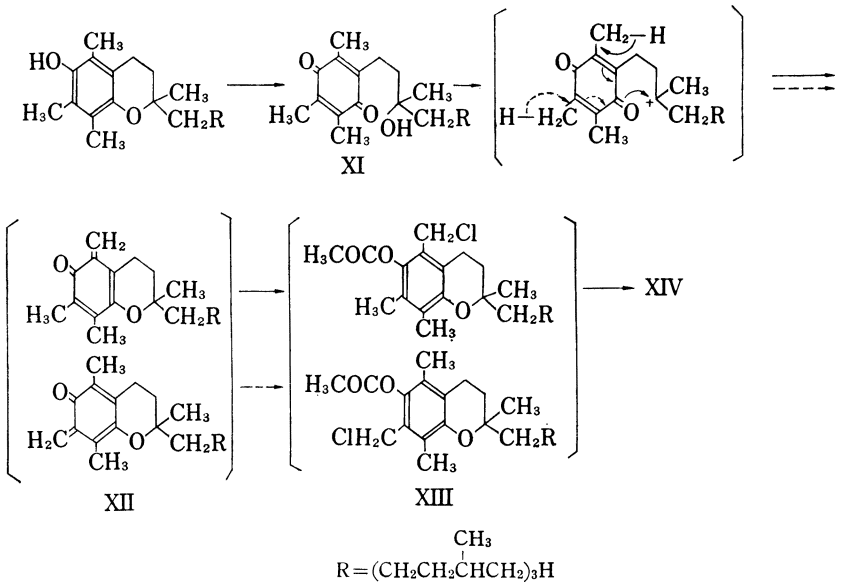


Chart 3

In this paper the intermediates VIIa, VIIb, VIIc were synthesized from corresponding acetoxymethyl tocopheryl acetates by unequivocal way as mentioned. The procedure does

15) P. Karrer and G. Bassmann, *Helv. Chim. Acta*, **23**, 1137 (1940).
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Table 1. The NMR Data (τ value, 100 Mc)

Compound	$COCH_3$	Ar-CH_3 at position		
		C_5	C_7	C_8
7-Bromomethyl-β-tocopheryl acetate (VIIa)	7.63	7.78		8.02
5-Bromomethyl-γ-tocopheryl acetate (VIIb)	7.70		7.88	8.02
5-Bromomethyl-δ-tocopheryl acetate (VIIc)	7.76			7.88
7-O,O-Dibenzylphosphomethyl-β-tocopheryl acetate (VIIIa)	7.73	7.85		8.07
5-O,O-Dibenzylphosphomethyl-γ-tocopheryl acetate (VIIIb)	7.74		7.89	8.02
5-O,O-Dibenzylphosphomethyl-δ-tochpheryl acetate (VIIIc)	7.82			7.87
7-Phosphomethyl-β-tocopheryl acetate (IXa)	7.69	7.82		8.07
5-Phosphomethyl-γ-tocopheryl acetate (IXb)	7.80		7.92	8.04
5-Phosphomethyl-δ-tocopheryl acetate (IXc)	7.83			7.92
XIV	7.77		7.87	8.00

not accompany cleavage and recyclization of chroman ring, so the substituted position of bromine are deciced definitely by starting materials employed. In the case of vitamin $K_{1(20)}$ and coenzyme Q the important intermediates, halogenomethyl chromanyl acetates were obtained by 1,4-addition of acetyl chloride to methylene quinone chromans which were derived from γ-hydroxy quinones.[9,10,17] The application of the addition reaction to tocopheryl quinone are reported[18b,18b] but the position of halogen substitution has not been discussed. Since α-tocopherol has two methyl groups *ortho* to hydroxy group, two mehtylene quinones III and IV are possible. Chart 3 shows the possible reaction processes. To decide the position of chlorine substitution the reaction of chloromethyl tocopheryl acetate XIII with silver dibenzylphosphate was performed. After purification on a column of silica gel the pure product XIV was isolated in 39% yield. The triester thus obtained was compared with two authentic triesters VIIIa, VIIIb in NMR spectra. Table I shows the chemical shifts of triesters. On the bais of the chemical shifts of ring methyl groups, it seemed reasonable to assume that the isolated triester XIV corresponded to VIIIb rather than VIIIa.

Experimental[19]

7-Bromomethyl-β-tocopheryl Acetate (VIIa)——A mixture of 7-acetoxymethyl-β-tocopheryl acetate[1] (VIa, 2.9 g, 5.4 mmoles) and 20% hydrogen bromide–acetic acid (17 ml) in dichloromethane (23 ml) was kept overnight at room temperature. Acetic anhydride (23 ml) was added and the solution was concentrated *in vacuo* to a crystalline mass. The curde product was purified by chromatography on a column of silica gel (60 ml) packed in *n*-hexane. The pure product was eluted with *n*-hexane containing 20% benezene. 7-Bromomethyl-β-tocopheryl acetate (VIIa, 2.6 g, 87%) was obtained as yellow-colored wax. *Anal.* Calcd. for $C_{31}H_{51}O_3Br$: C, 67.45; H, 9.31; Br, 14.53. Found: C, 67.73; H, 9.39; Br, 14.35. IR $\nu_{max}^{liq.}$ cm^{-1}: 1762, 1195, 1180, 1140, 1110, 1055, 1010, 675. UV $\lambda_{max}^{iso\text{-}octane}$ mμ ($E_{1cm}^{1\%}$) 301 (48.4). TLC: Rf=0.70 ($CHCl_3$). NMR τ: 5.58 (2H, s, Ar-CH_2-, at position 7), 7.38 (2H, t, Ar-CH_2-, at position 4, J=7 Hz), 7.63 (3H, s, CH_3-CO-), 7.78 (3H, s, Ar-CH_3, at position 5), 8.02 (3H, s, Ar-CH_3, at position 8), 8,23 (2H, t, protons at position 3).

5-Bromomethyl-γ-tocopheryl Acetate (VIIb)——A mixture of 5-acetoxymethyl-γ-tocopheryl acetate[1] (VIb, 6.0 g, 11.3 mmoles) and 20% hydrogen bormide–acetic acid (30 ml) in dichloromethane (45 ml) was treated following the procedure described for the preparation of VIIa. 5-Bromomethyl-γ-tocopheryl acetate

17) B.O. Linn, U.S. Patent 3160637 (1964) [*C.A.*, **62**, 5256n (1965)].

18) *a*) W.A. Skinner, R.M. Parkhurst, J. Scholler, P. Alaupovic, Q.E. Crider, and K. Schwarz, *J. Med. Chem.*, **10**, 657 (1967); *b*) W.A. Skinner, R.M. Parkhurst, J. Scholler, and K. Schwarz, *ibid.*, **12**, 64 (1969).

19) Melting points were measured on a Yanagimoto micromelting point apparatus and uncorrected. The ultraviolet (UV) absorption spectra were recorded with a Shimazu QV-50 spectrophotometer. Hitachi EPI-2 spectrometer was used for the IR absorption spectra. The NMR spectra were recorded on a JEOL C-100 HL spectrometer (100 Mc) using $CDCl_3$ solution. Chemical shifts are expressed on τ value. Patterns of signals are abbreviated as follows: s, singlet, d, doublet, t, triplet. Thin-layer chromatography (TLC) was carried out using silica gel GF_{254} (Merck A.G.) plates of 0.25 mm thickness.

(VIIb, 5.5 g, 88%) was obtained as pale yellow crystal, mp 55—56°. *Anal.* Calcd. for $C_{31}H_{51}O_3Br$: C, 67.45; H, 9.31; Br, 14.53; Found: C, 67.74; H, 9.39; Br, 14.58. IR ν_{max}^{KBr} cm^{-1}: 1752, 1214, 1202, 1165, 1105, 1085, 1008, 680. UV $\lambda_{max}^{iso\text{-}octane}$ mμ ($E_{1cm}^{1\%}$) 300 (55.5). TLC: Rf=0.50 ($CHCl_3$). NMR τ: 5.70 (2H, s, Ar-CH_2-, at position 5), 7.25 (2H, t, Ar-CH_2-, at position 4, J=7 Hz), 7.70 (3H, s, CH_3CO-), 7.88 (3H, s, Ar-CH_3, at position 7), 8.02 (3H, s, Ar-CH_3, at position 8), 8.21 (2H, t, protons at position 3, J=7 Hz).

5-Bromomethyl-δ-tocopheryl Acetate (VIIc)——A mixture of 5-acetoxymethyl-δ-tocopheryl acetate[1] (VIc, 1.1 g, 2.1 mmoles) and 20% hydrogen bromide–acetic acid (10 ml) in dichloromethane (10 ml) was followed reaction as described above. The product was eluted with *n*-hexane containing 20% benzene. 5-Bromomethyl-δ-tocopheryl acetate (VIIc, 0.8 g, 71%) was obtained as white crystal, mp 35—36°. *Anal.* Calcd. for $C_{30}H_{49}O_3Br$: C, 67.02; H, 9.18; Br, 14.80. Found: C, 67.25; H, 9.34; Br, 14.87. IR ν_{max}^{KBr} cm^{-1}: 1762, 1200, 1160, 1050, 1011, 954, 713, UV $\lambda_{max}^{iso\text{-}octane}$ mμ ($E_{1cm}^{1\%}$) 299 (63.2). TLC: Rf=0.65 ($CHCl_3$). NMR τ: 3.32 (1H, s, Ar-H), 5.71 (2H, s, Ar-CH_2-, at position 5), 7.22 (2H, t, Ar-CH_2-, at position 4, J=7 Hz), 7.76 (3H, s, CH_3CO-), 7.88 (3H, Ar-CH_3), 8.22 (2H, t, protons at position 3).

7-O,O-Dibenzylphosphomethyl-β-tocopheryl Acetate (VIIIa)——A mixture of 7-bromomethyl-β-tocopheryl acetate (VIIa, 2.3 g, 4.1 mmoles), silver dibenzyl phosphate (2.3 g, 5.9 mmoles), and acetonitrile (80 ml) was refluxed for 2.5 hr. The reaction mixture was cooled and filtered, and the filtrate was concentrated *in vacuo*. The residue was dissolved in ether and the solution was filtered. The filtrate was concentrated *in vacuo*. The crude residual oil was purified by chromatography on a column of 50 ml silica gel packed in *n*-hexane. The pure product was eluted with benzene. 7-O,O-Dibenzylphosphomethyl-β-tocopheryl acetate (VIIIa, 2.2 g, 71%) was obtained as a pale orange-colored oil. *Anal.* Calcd. for $C_{45}H_{65}O_7P$: C, 72.16; H, 8.75. Found: C, 72.42; H, 8.89. IR $\nu_{max}^{liq.}$ cm^{-1}: 1765, 1275, 1197, 1000 (broad), 740, 696. UV $\lambda_{max}^{iso\text{-}octane}$ mμ ($E_{1cm}^{1\%}$) 294 (40.1). TLC: Rf=0.18 ($CHCl_3$). NMR τ: 2.71 (10H, s, Ar-H), 5.09 (2H, d, Ar-CH_2-, at position 7, J=9 Hz), 5.11 (4H, d Ar-CH_2-, at protecting groups of position 7), 7.38 (2H, t, Ar-CH_2-, at position 4, J=7 Hz), 7.73 (3H, s, CH_3CO-), 7.85 (3H, s, Ar-CH_3, at position 5), 8.07 (3H, s, Ar-CH_3, at position 8), 8.23 (2H, t, protons at position 3, J=7 Hz).

5-O,O-Dibenzylphosphomethyl-γ-tochoperyl Acetate (VIIIb)——A mixture of 5-bromomethyl-γ-tocopheryl acetate (VIIb, 3.0 g, 5.4 mmoles), silver dibenzyl phosphate (3.0 g, 7.7 mmoles), and acetonitrile (100 ml) was refluxed for 2.5 hr. The reaction mixture was treated following the procedure as described above. 5-O,O-Dibenzylphosphomethyl-γ-tocopheryl acetate (VIIIb, 3.8 g, 94%) was obtained as a pale orange-colored oil. *Anal.* Calcd. for $C_{45}H_{65}O_7P$: C, 72.16; H, 8.74. Found: C, 72.42; H, 8.68. IR $\nu_{max}^{liq.}$ cm^{-1}: 1765, 1275, 1197, 1000 (broad), 737, 696. UV $\lambda_{max}^{iso\text{-}octane}$ mμ ($E_{1cm}^{1\%}$) 293 (64.0). TLC: Rf=0.18 ($CHCl_3$). NMR τ: 2.73 (10H, s, Ar-H), 5.03 (2H, d, Ar-CH_2-, at position 5, J=7 Hz,), 5.08 (4H, d Ar-CH_2-, at protecting groups of position 5), 7.27 (2H, t, Ar-CH_2-. at position 4, J=7 Hz), 7.79 (3H, s, CH_3CO-), 7.89 (3H, s, Ar-CH_3, at position 7), 8.02 (3H, s, Ar-CH_3, at position 8), 8.30 (2H, t, protons at position 3, J=7 Hz).

5-O,O-Dibenzylphosphomethyl-δ-tocopheryl Acetate (VIIIc)——A mixture of 5-bromomethyl-δ-tocopheryl acetate (VIIc, 1.9 g, 3.5 mmoles), silver dibenzyl phosphate (1.9 g, 4.9 mmoles), and acetonitrile (60 ml) was refluxed for 2.5 hr. The reaction mixture was treated as described above. 5-O,O-Dibenzylphosphomethyl-δ-tocopheryl acetate (VIIIc, 1.9 g, 74%) was obtained as a pale orange-colored oil. *Anal.* Calcd. for $C_{44}H_{63}O_7P$: C, 72.29; H, 8.70. Found: C, 72.15; H, 8.74. IR $\nu_{max}^{liq.}$ cm^{-1}: 1760, 1202, 1155, 1000 (broad), 740, 700. UV $\lambda_{max}^{iso\text{-}octane}$ mμ ($E_{1cm}^{1\%}$) 291 (40.8). TLC: Rf=0.08 ($CHCl_3$). NMR τ: 2.77 (10H, s, Ar-H), 3.32 (1H, s, Ar-H, at position 7), 5.06 (2H, d, Ar-CH_2-, J=9 Hz), 5.14 (4H, d Ar-CH_2-, at protecting groups of position 5). 7.27 (2H, t, Ar-CH_2-, at position 4, J=7 Hz), 7.82 (3H, s, CH_3CO-), 7.87 (3H, s, Ar-CH_3), 8.32 (2H, t, protons at position 3).

7-Phosphomethyl-β-tocopheryl Acetate (IXa)——A mixture of 7-O,O-dibenzylphosphomethyl-β-tocopheryl acetate (VIIIa, 2.5 g, 3.3 mmoles) and 10% palladium-on-charcoal (Pd-C, 0.05 g) catalyst in EtOH (30 ml) was subjected to hydrogenation at room temperature. Hydrogenation was stopped when uptke corresponded to two moles of hydgrogen per mole of compound (148 ml). Removal of the catalyst and the solvent left a pale orange oil. 7-Phosphomethyl-β-tocopheryl acetate (IXa, 1.7 g, 91%) was obtained. *Anal.* Calcd. for $C_{31}H_{53}O_7P$: C, 65.43; H, 9.39. Found: C, 65.52: H, 9.71. IR $\nu_{max}^{liq.}$ cm^{-1}: 3360, 1752, 1213, 1020. UV $\lambda_{max}^{iso\text{-}octane}$ mμ ($E_{1cm}^{1\%}$) 290 (42.5). NMR τ: 5.10 (2H, broad, Ar-CH_2-, at position 7), 7.40 (2H, broad, Ar-CH_2-, at position 4), 7.69 (3H, s, CH_3CO-), 7.82 (3H, s, Ar-CH_3, at position 5), 8.07 (3H, s, Ar-CH_3, at position 8).

5-Phosphomethyl-γ-tocopheryl Acetate(IXb)——A mixture of 5-O,O-dibenzylphosphomethyl-γ-tocopheryl acetate (VIIIb, 4.0 g, 5.3 mmoles) and 10% Pd-C (0.07 g) catalyst in EtOH (50 ml) was subjected to hydrogenation. 5-Phosphomethyl-γ-tocopheryl acetate (IXb, 2.8 g, 93%) was obtained as a colorless oil. *Anal.* Calcd. for $C_{31}H_{53}O_7P$: C, 65.43; H, 9.39. Found: C, 65.49; H, 9.55. IR $\nu_{max}^{liq.}$ cm^{-1}: 3300 (broad), 1760, 1200 (broad), 1015 (broad). UV $\lambda_{max}^{iso\text{-}octane}$ mμ ($E_{1cm}^{1\%}$) 291 (45.0). NMR τ: 5.12 (2H, broad, Ar-CH_2-, at position 5), 7.25 (2H, broad, Ar-CH_2-, at position 4), 7.80 (3H, s, CH_3CO-), 7.92 (3H, s, Ar-CH_3, at position 7), 8.04 (3H, s, Ar-CH_3, at position 8).

5-Phosphomethyl-δ-tocopheryl Acetate (IXc)——A mixture of 5-O,O-dibenzylphosphomethyl-δ-tocopheryl acetate (VIIIc, 0.5 g, 0.6 mmoles) and 10% Pd-C (0.01 g) catalyst in EtOH (20 ml) was subjected to

hydrogenation. 5-Phosphomethyl-δ-tocopheryl acetate (IXc, 0.3 g, 90%) was obtained as a colorless oil. *Anal.* Calcd. for $C_{30}H_{51}O_7P$: C, 64.92; H, 9.26. Found: C, 64.67; H, 9.44. IR $\nu_{max}^{liq.}$ cm^{-1}: 3200 (broad), 1760, 1715, 1220 (broad), 1010 (braod). UV $\lambda_{max}^{iso\text{-}octane}$ mμ ($E_{1cm}^{1\%}$) 294 (65.8). NMR τ: 3.40 (1H, s, Ar-H), 5.10 (2H, broad, Ar-CH_2-, at position 5), 7.26 (2H, broad, Ar-CH_2-, at position 4), 7.83 (3H, s, CH_3CO-), 7.92 (3H, Ar-CH_3).

Disodium Salt of 7-Phosphomethyl-β-tocopheryl Acetate (Xa)——7-Phosphomethyl-β-tocopheryl acetate (IXa, 2.2 g, 3.8 mmoles) was dissolved in EtOH (20 ml)-acetone (200 ml). To the solution 2% of sodium hydroxide-EtOH was added dropwise and adjusted at pH=5. The reaction mixture was kept in refrigerator overnight. White precipitate was collected by centrifugation and washed with small amount of acetone. Disodium salt of 7-phosphomethyl-β-tocopheryl acetate (Xa, 1.8 g, 77%) was obtained as white powder, mp 138—140°. *Anal.* Calcd. for $C_{31}H_{51}O_7P\ Na_2$: C, 60.74; H, 8.39. Found: C, 60.65; H, 8,64. IR ν_{max}^{KBr} cm^{-1}: 1750, 1215, 1070, 922.

Disodium Salt of 5-Phosphomethyl-γ-tocopheryl Acetate (Xb)——5-Phosphometjyl-γ-tocopheryl acetate (IXb, 2.2 g, 3.8 mmoles) was followed reaction as described above. Disodium salt of 5-phosphomethyl-γ-tocopheryl acetate (Xb, 1.8 g, 77%) was obtained as white powder, mp 151—152°. *Anal.* Calcd. for $C_{31}H_{51}O_7P\ Na_2$: C, 60.74; H, 8.39. Found: C, 60.96; H, 8.81. IR ν_{max}^{KBr} cm^{-1}: 1755, 1220, 1085, 1008, 920.

The Reaction of Chloromethyl Tocopheryl Acetate[18a,b] with Silver Dibenzyl Phosphate——Chloromethyl tocopheryl acetate was obtained and purified by the same procedure as previously described.[18b] The over all yield was about 40%. A mixture of purified chloromethyl tocopheryl acetate (XIII, 2.1 g, 4.1 mmoles), silver dibenzyl phosphate (2.3 g, 5.9 mmoles), and acetonitrile (80 ml) was refluxed for 4 hr. The reaction mixture was treated following the procedure as described above. XIV was obtained as a pale orange-colored oil (1.2 g, 39%). IR $\nu_{max}^{liq.}$ cm^{-1}: 1765, 1275, 1197, 1000 (broad), 737, 697. UV $\lambda_{max}^{iso\text{-}octane}$ mμ ($E_{1cm}^{1\%}$) 293 (60.5). TLC: Rf=0.18 ($CHCl_3$). NMR τ: 2.75 (10H, s, Ar-H), 5.06 (2H, d, Ar-CH_2-, J=7 Hz,). 5.10 (4H, d, Ar-CH_2-, at protecting groups, J=8 Hz), 7.29 (2H, t, Ar-CH_2-, at position 4, J=7 Hz), 7.77 (3H, s, CH_2CO-), 7.87 (3H, s, Ar-CH_3, at position 7), 8.00 (3H, s, Ar-CH_3, at position 8), 8.33 (2H, protons at position 3, J= 7 Hz).

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