[Chem. Pharm. Bull. 20(8)1681—1686(1972)]

UDC 547.814.1.04 : 546.273-37.04

Studies on Tocopherol Derivatives. IV.[1] Hydroxymethylation Reaction of β-, γ-Tocopherol and Their Model Compounds with Boric Acid

Tetsuya Nakamura and Shizumasa Kijima

Eisai Research Laboratories, Eisai Co., Ltd.[2]

(Received December 18, 1971)

Direct hydroxymethylation of β-(I) and γ-tocopherol(III) and their model compounds are established with boric acid catalyst. The yields of 7-hydroxymethyl-β-tocopherol (V), 5-hydroxymethyl-γ-tocopherol (VII), 6-hydroxy-7-hydroxymethyl-2,2,5,8-tetramethylchroman (VI), and 6-hydroxy-5-hydroxymethyl-2,2,7,8-tetramethylchroman (VIII) are 83%, 86%, 75%, and 78%, respectively. 5-Methyl-^{14}C-d-α-tocopheryl acetate (XIV) is synthesized by the procedure.

1,1-Bis(β-tocopherol-7′-yl)-methane (XVII), 1,1-bis(γ-tocopherol-5′-yl)-methane (XV), and their acetates (XVIII) and (XVI) are synthesized from corresponding hydroxymethyl tocopherols and tocopherols.

A four-step methylation of β- (I), γ-(III), and δ-tocopherol (XIX), and the utility of hydroxymethyl tocopherols as intermediates for methylation of tocopherols have previously been reported.[3]

Lederer–Manasse reaction is known as a direct hydroxymethylation method to introduce the group to phenolic compounds. The reaction is effected by use of an alkaline catalyst. The method has been applied to methylation of tocopherol homologues.[4a–c] But the reaction gave several unknown side reaction products on thin–layer chromatography (TLC), in addition to original tocopherol and hydroxymethylated tocopherol. Therefore more convenient and practical method for the direct hydroxymethylation of tocopherol homolgues was investigated and boric acid was found as an excellent catalyst for the hydroxymethylation of tocopherols. The method was applied to β-tocopherol (I), γ-tocopherol (III), 6-hydroxy-2,2,5,8-tetramethylchroman (II), and 6-hydroxy-2,2,7,8-tetramethylchroman (IV). The analytical results of hydroxymethyl tocopherols (V and VII) were in good accordance with those *via* reductive cleavage of acetoxymethyl tocopheryl acetates with lithium aluminium hydride.[3]

Peer[5] has reported hydroxymethylation of phenols with boric acid as catalyst, but the yield was as low as 4%. However, when the reaction was applied to β-tocopherol I and γ-tocopherol III in toluene at 93—97° we found it was effectively performed to hydroxymethyl tocopherols (V and VII) in good yield. 6-Hydroxy-7-hydroxymethyl-2,2,5,8-tetramethylchroman (VI, mp 124—125°) and 6-hydroxy-5-hydroxymethyl-2,2,7,8-tetramethylchroman[6] (VIII, mp 124—125°) were obtained also by the method from II and IV as white crystal in 75% and 78% yields, respectively. The reaction rate of hydroxymethylation of γ-tocopherol III was followed by analysing residual γ-tocopherol in the reaction mixture by nitrosation method.[7,8] The reaction conditions and the results are shown in Fig. 1. The excess of

1) Part III: T. Nakamura and S. Kijima, *Chem. Pharm. Bull.* (Tokyo), **20**, 1297 (1972).
2) Location: *Koishikawa 4-chome, Bunkyo-ku, Tokyo.*
3) T. Nakamura and S. Kijima, *Chem. Pharm. Bull.* (Tokyo), **19**, 2318 (1971).
4) *a*) L. Weisler, U.S. Patent 2640058 (1953) [*C.A.*, **48**, 7643e (1954)]; *b*) L. Weisler, U.S. Patent, 2673858 (1954) [*C.A.*, **49**, 5533c (1955)]; *c*) J. Green, D. McHale, S. Marcinkiewicz, P. Mamalis, and P.R. Watt, *J. Chem. Soc.*, **1959**, 3362.
5) H.G. Peer, *Rec. Trav. Chim.*, **79**, 825 (1960).
6) J.L.G. Nilsson and H. Sievertsson, *Acta Pharmaceutica Suecica*, **5**, 517 (1968).
7) M.L. Quaife, *J. Biol. Chem.*, **175**, 605 (1948).
8) Marcinkiewicz pointed the reaction product was not nitroso but nitro compound. S. Marcinkiewicz, *Acta Poloniae Pharmaceutica*, **24**, 375 (1967).

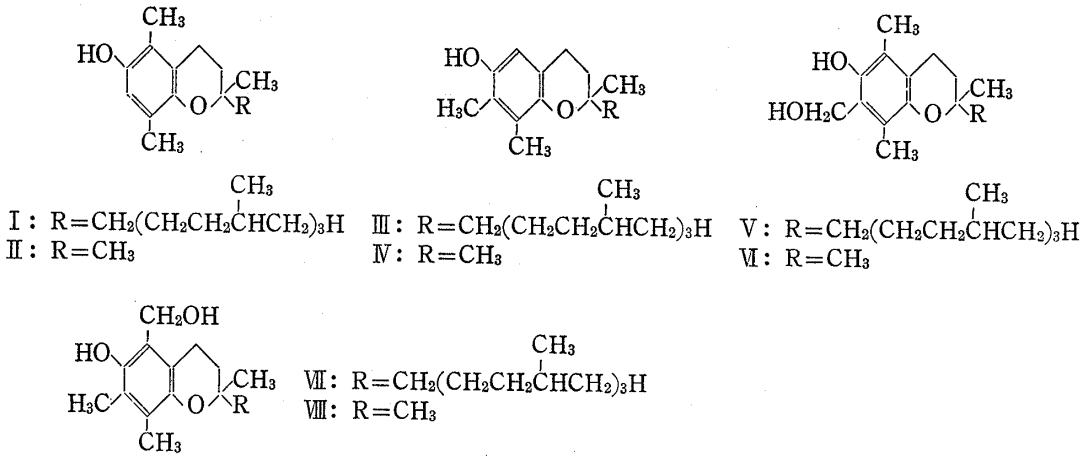
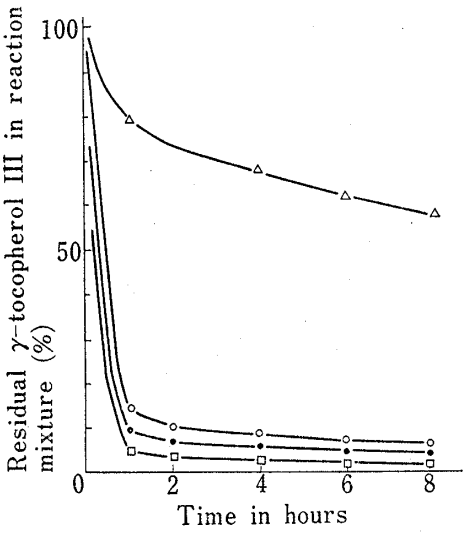


Chart 1



	Molecular ratio of reagents			
	γ-Tocopherol	Paraformaldehyde[a)]	Boric acid	Acetic acid
—△—	1.0	3.2	0.008	0
—○—	1.0	3.2	1.6	0
—●—	1.0	3.2	1.6	0.008
—□—	1.0	6.4	3.2	0.016

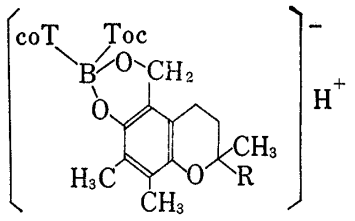
Fig. 1. Hydroxymethylation Conditions and Residual γ-Tocopherol

a) Molecular weight calculated as 30 tentatively.

boric acid was indispensable to complete the reaction. Addition of small amount of acetic acid increased the reaction rate. At the end of hydroxymethylation the reaction mixture gave three spots of reducing substances on TLC when developed with benzene–ethyl acetate (8:2). They were γ-tocopherol (III) (*Rf* 0.88), 5-hydroxymethyl-γ-tocopherol (VII) (*Rf* 0.53), and the spot (spot A, *Rf* 0.10) which gave the same color reaction with ferric chloride (violet) and the Emmerie-Engel reagent[9a,b] (red) as VII. Spot A was isolated on preparative TLC but it was always contaminated with III and VII. After stirring with dilute aqueous sodium bicarbonate solution at room temperature for half an hour a substance corresponding to the spot A changed to III and VII. Therefore it was considered that the spot A might be corresponded to hydroxymethyl tocopherol-boric acid complex (IX) as described in the studies of phenol-boric acid[5] and pyridoxol-boric acid[10] complexes.

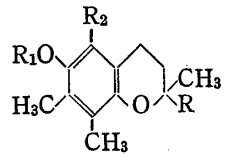
The hydroxymethylation reaction mixture was followed to reduction with zinc dust and hydrochloric acid as previously described.[3] The reaction product showed two reducing substances (*Rf* 0.45 and 0.60) on TLC when developed with hexane–ethyl alcohol (95:5). They were isolated by preparative TLC. *Rf* 0.45 compound was identified as α-tocopherol (XI) by its *Rf* value and color reactions of the spot with the Emmerie–Engel reagent and antimony

9) *a*) A. Emmerie and C. Engel, *Nature*, **142**, 873 (1938); *b*) A. Emmerie and C. Engel, *Rec. Trav. Chim.*, **57**, 1351 (1938).
10) R. Hüttenrauch, *J. Chromatog.*, **51**, 330 (1970).



IX: $R=CH_2(CH_2CH_2\overset{CH_3}{\overset{|}{C}}HCH_2)_3H$
Toc=γ-Tocopherol residue

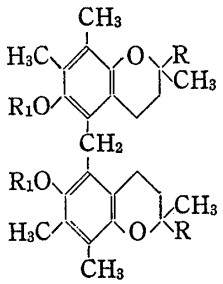
Chart 2



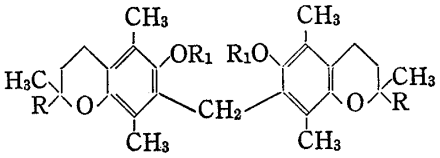
X: $R_1=H$, $R_2=CH_2Cl$ (not isolated)
XI: $R_1=H$, $R_2=CH_3$
XII: $R_1=H$, $R_2=*CH_3$
XIII: $R_1=COCH_3$, $R_2=CH_3$
XIV: $R_1=COCH_3$, $R_2=*CH_3$

$R=CH_2(CH_2CH_2\overset{CH_3}{\overset{|}{C}}HCH_2)_3H$

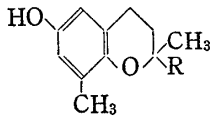
Chart 3



XV: $R_1=H$
XVI: $R_1=COCH_3$



XVII: $R_1=H$
XVIII: $R_1=COCH_3$



XIX

$R=CH_2(CH_2CH_2\overset{CH_3}{\overset{|}{C}}HCH_2)_3H$

Chart 4

pentachoride reagent (20% in chloroform).[11] The purity of the reaction product was estimated by quantitative gas–liquid chromatography (GLC) after acetylation.[3] The content of α-tocopheryl acetate (XIII) was 92%. The other substance (*Rf* 0.60) showed red color reaction with the Emmerie–Engel reagent and yellow-brown color with antimony pentachloride reagent. The structure of *Rf* 0.60 compound was elucidated as 1,1-bis(γ-tocopherol-5′-yl)-methane (XV) on the basis of nuclear magnetic resonance (NMR) and mass spectra and also confirmed by the synthesis from 5-hydroxymethyl-γ-tocopherol VII and γ-tocopherol III in acidic media. The NMR spectrum of XV shows benzyl protons at 6.16 τ (singlet). Compound XV was derived to its acetate (XVI). The mass spectrum of XVI shows the molecular ion peak (M^+) at *m/e* 929 which consists with molecular formula $C_{61}H_{100}O_6$. The NMR spectrum of XVI shows six methyl protons of acetyl groups at 7.88 τ (singlet) addition to benzyl protons at 6.40 τ (singlet). Therefore, the formation of diphenyl methane dimer XV can be explained by the reaction between 5-chloromethyl-γ-tocopherol (X, not isolated) and residual γ-tocopherol at the reduction step. Analogously 1,1-bis (β-tocopherol-7′-yl)-methane(XVII)

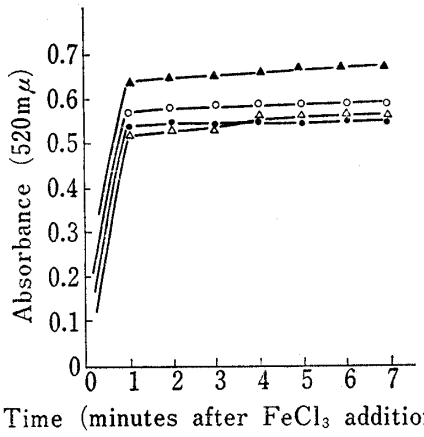


Fig. 2. Oxidation Curves of Tocopherols and Tocopherol Dimers in the Emmerie-Engel Assay Procedure[7,9b]

(7.5×10^{-4} mmoles/25 ml ethyl alcohol)
—●—:XI —○—:III
—▲—:XV —△—:XVII

11) M. Kofler, P.F. Sommer, H.R. Bolliger, B. Schmidli, and M. Vecchi, *Vitamins and Hormones*, **20**, 407 (1962).

was prepared by the reaction of I and V. The structure of XVII and its acetate (XVIII) were characterized by NMR and mass spectra.

Fig. 2 shows the oxidation curves of tocopherols and their dimers in the Emmerie–Engel assay procedure. The methylated tocopherols were analysed by the national formulary (NF) assay procedure[13] and quantitative GLC after acetylation.[3] The analytical results of α-tocopherol content by NF procedure gave higher value than those of GLC because of the presence of dimer.

Table I. GLC Retention Time

Compounds	Column temperature (°C)	Retention time (min)
XIII	250	12.3
XVIII	320	16.4
XVI	320	19.3

According to the analytical method of mixed tocopherols concentrate by NF procedure, α-tocopherol is calculated by the differance between total tocopherols and non-α-tocopherols.[14] The former is estimated by the Emmerie–Engel procedure and the latter by nitrosation method. The possible undesirable products of methylation reactions are biphenyl methane compounds like XV and XVII for γ-, and β-tocopherol and more polymerized compounds for δ-tocopherol XIX. These are calculated as α-tocopherol by the indirect method as NF procedure. On the other hand when analysed with GLC the acetylated dimers XVI and XVIII gave different peak from α-tocopheryl acetate XIII as shown in Table I. Therefore, quantitative GLC is preferable method to analyse methylated tocopherols. Recently Dean[15] described that in the spectrophotomeric determination of vitamin E in food γ-diphenyl ether dimer and γ-biphenyl dimer[16] had to be removed as they constituted a positive interference.

In order to synthesize 5-methyl-^{14}C-d-α-tocopherol[17] (XII) for metabolic study of vitamin E, this method was applied to γ-tocopherol using isotopic paraformaldehyde. The specific activity of the crude product was 3.53 μCi/mg and 86.7% of the radioactivity was corresponded to XII.

Experimental[18]

Materials

β-(I) and γ-Tocopherol (III) were obtained from natural source as previously described.[3] The purity was examined on TLC, infrared (IR), ultraviolet (UV) spectra, and GLC. The UV absorption intensities of tocopherols were as follows: UV λ_{max}^{EtOH} mμ($E_{1cm}^{1\%}$) β-Tocopherol 297 (84.5), γ-Tocopherol 298 (91.2). 6-Hydroxy-2,2,5,8-tetramethylchroman (II, β-tocopherol model, mp 79—80°) and 6-hydroxy-2,2,7,8-tetra-

13) National Formulary, thirteenth ed., American Pharmaceutical Association, Washington, 1970, p. 758.
14) Non-α-tocopherols mean β-, γ-, and δ-tocopherol.
15) A.C. Dean, *Chem. Ind.* (London), **1971**, 677.
16) J.L.G. Nilsson, H. Sievertsson, and H. Selander, *Acta Chemica Scandinavica*, **23**, 859 (1969).
17) O. Isler, P. Schudel, H. Mayer, J. Würsch, and R. Rüegg, *Vitamins and Hormones*, **20**, 389 (1962).
18) The IR, UV spectra, and melting points were measured as previously described.[3] The NMR spectra were measured using $CDCl_3$ solution with a JEOL C-100HL (100 Mc) instrument. Chemical shifts were expressed on τ value. Signals are abbreviated as follows: s, singlet, t, triplet. The mass spectra were recorded on a JMS-01 SG-2 instrument. Radioactive measurements were made with a liquid scintillation counter of Aloka LSC 502. TLC were performed using silica gel GF_{254} (Merck A.G.) plates of 0.75 mm (preparative) and 0.25 mm (analytical) thickness. On spraying with $SbCl_5$ reagent (20% in $CHCl_3$) evaluation was done about after 3 minutes.[11] GLC were carried out with Model 402 gas chromatograph of F & M Scientific with a flame ionization detector. Glass column (4ft length, 2.8 mm diameter) filled with 1.5% SE-30 coated chromosorb W was used. The velocity of the carrier gas (N_2) flow was 60 ml/min.

methylchroman (IV, γ-tocopherol model, mp 72.5—73.5°) were synthesized with corresponding dimethyl hydroquinone and dimethyl allyl alcohol.[19] ^{14}C-paraformaldehyde was the sample of Radio Chemical Center. Squalene was the sample of Tokyo Kasei Kogyo Co., Ltd.

7-Hydroxymethyl-β-tocopherol (V)——β-Tocopherol (I, 10.0 g, 24.0 mmoles) was dissolved in toluene (150 ml). To the solution acetic acid (0.5 ml), boric acid (2.4 g, 39 mmoles), and paraformaldehyde (2.4 g) were added. The mixture was stirred at 93—97° for 4 hr. After cooling to room temperature the reaction mixture was washed with water, then vigorously stirred with 5% aqueous Na_2CO_3 solution for 30 min to decompose V-boric acid complex, and finally washed with water. The washed layer was dried over Na_2SO_4 and evaporated *in vacuo*. The residual oil was dissolved in a small portion of hexane and placed on a column of silica gel (200 ml). After impurities were eluted from the column with hexane, and hexane containing benzene, the pure sample of 7-hydroxymethyl-β-tocopherol (V, 8.9 g, 83%) was eluted with benzene. The pure sample was a pale yellow, viscous oil. IR ν_{max}^{liq} cm^{-1}: 3350, 1262, 1160, 1060, 1004, 980. UV λ_{max}^{EtOH} mμ ($E_{1cm}^{1\%}$): 298 (82.5). TLC: *Rf* 0.53 (benzene–AcOEt 8: 2). Color reaction of the spot with $SbCl_5$ reagent: yellow–brown.

5-Hydroxymethyl-γ-tocopherol (VII)——γ-Tocopherol (III, 10.0 g, 24.0 mmoles) reacted following the procedure of the preparation of V. 5-Hydroxymethyl-γ-tocopherol (VII, 9.2 g, 86%) was obtained. The pure sample solidified when kept in refrigerator, mp 35—36°. IR ν_{max}^{KBr} cm^{-1}: 3350, 1264, 1160, 1090, 1018, 990, 865. UV λ_{max}^{EtOH} mμ($E_{1cm}^{1\%}$) 298 (83.5), TLC: *Rf* 0.53 (benzene–AcOEt 8: 2). Color reaction of the spot with $SbCl_5$ reagent: orange-brown.

6-Hydroxy-7-hydroxymethyl-2,2,5,8-tetramethylchroman (VI)——6-Hydroxy-2,2,5,8-tetramethylchroman (II, 19.2 g, 93 mmoles) was dissolved in toluene (300 ml). To the solution acetic acid (1.0 ml), boric acid (18.5 g, 299 mmoles), and paraformaldehyde (18.0 g) were added. The mixture was stirred at 93—97° for 6 hr. After cooling to room temperature the reaction mixture was filtered. The filtrate was washed with water, then vigorously stirred with 5% aqueous $NaHCO_3$ solution for 30 min to decompose VI-boric acid complex, and washed with water. The washed organic layer was dried over Na_2SO_4 and evaporated *in vacuo*. The crude product (22.0 g) was dissolved in benzene and placed on a column of 400 ml of silica gel. After preliminary elution with benzene, pure sample was eluted with 2% ether in benzene. 6-Hydroxy-7-hydroxymethyl-2,2,5,8-tetramethylchroman (VI, 16.4 g, 75%) was obtained as white solid. Recrystallized from hexane, mp 124—125°. *Anal.* Calcd. for $C_{14}H_{20}O_3$: C, 71.25; H, 8.54. Found: C, 71.54; H, 8.43. IR ν_{max}^{Nujol} cm^{-1}: 3320, 1262, 1220, 1160, 1064, 1010, 980. TLC: *Rf* 0.43 (benzene–AcOEt 8: 2). Color reaction of the spot with $SbCl_5$ reagent: yellow–brown. NMR τ: 5.05 (2H, s, Ar–CH_2–, at position 7), 7.32 (2H, t, Ar–CH_2–, at position 4, J=7 Hz), 7.85 and 7.95 (6H, two s, two Ar–CH_3), 8.18 (2H, t, protons at position 3, J=7 Hz), 8.66 (6H, s, gem CH_3).

6-Hydroxy-5-hydroxymethyl-2,2,7,8-tetramethylchroman (VIII)——6-Hydroxy-2,2,7,8-tetramethylchroman (IV, 19.2 g, 93 mmoles) was treated as in (VI). The pure sample was eluted with 5% ether in benzene. 6-Hydroxy-5-hydroxymethyl-2,2,7,8-tetramethylchroman (VIII, 17.1 g, 78%) was obtained as white solid. Recrystallized from hexane, mp 124—125°. *Anal.* Calcd. for $C_{14}H_{20}O_3$: C, 71.25; H, 8.54. Found: C, 71.52; H, 8.54. IR ν_{max}^{Nujol} cm^{-1}: 3350, 1268, 1230, 1172, 1128, 1083, 970, 890. TLC: *Rf* 0.43 (benzene–AcOEt 8: 2). Color reaction of the spot with $SbCl_5$ reagent: orange. NMR τ: 5.00 (2H, s, Ar–CH_2–, at position 5), 7.56 (2H, t, Ar–CH_2–, at position 4, J=7 Hz), 7.85 and 7.90 (6H, two s, two Ar–CH_3), 8.22 (2H, t, protons at position 3, J=7 Hz), 8.70 (6H, s, gem CH_3).

5-Methyl-^{14}C-α-tocopherol (XII)——γ-Tocopherol (III, 502.2 mg, 1.2 mmoles) was dissolved in toluene (1.0 ml). To the solution ^{14}C-paraformaldehyde (35.5 mg, 140 μCi/mg), boric acid (36.9 mg, 0.6 mmole), and one drop of acetic acid were added, the mixture was stirred at 93—97° for 2 hr. The formaldehyde gas was captured in trapping bottle cooled with dry ice–acetone. The reaction flask was cooled with dry ice–acetone and added cold paraformaldehyde (71.4 mg) and boric acid (73.4 mg, 1.2 mmoles). The reaction was continued further for 2 hr. The reaction flask was cooled with dry ice–acetone and added toluene (30 ml). The toluene solution was washed with water repeatedly (15 ml×6), and then with 5% aqueous $NaHCO_3$ solution (10 ml×2), and with water. To the washed solution acetic acid (4 ml), hydrochloric acid (6 ml), and zinc dust (0.6 g) were added. The mixture was stirred vigorously for an hour at 5—10°. The toluene layer was separated, washed with several times with water, 5% aqueous $NaHCO_3$ solution, and water. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. 5-Methyl-^{14}C-α-tocopherol (XII. 456.3 mg, 88%) was obtained as reddish oil. The specific activity was 3.53 μCi/mg. The crude product was purified on preporative TLC (hexane–EtOH 95: 5). *Rf* 0.45 compound was scratched out. After extraction with EtOH the radioactivity was counted by liquid scintillation counter. The radioactive substance found to be 99% pure.

5-Methyl-^{14}C-α-tocopheryl acetate (XIV)——Acetylation of 5-methyl ^{14}C-α-tocopherol (XII, 350.0 mg) was performed with acetic anhydride (6 ml) and pyridine (2 ml) at 80—85° for an hour. The reaction mixture was poured into crushed ice and extracted with hexane (50 ml). The organic layer was washed with water, 5% aqueous $NaHCO_3$ solution, and water. The washed organic layer was dried over Na_2SO_4

19) J.L.G. Nilsson, H. Sievertsson, and H. Selander, *Acta Chemica Scandinavica*, 22, 3160 (1968).

and evaporated *in vacuo*. 5-Methyl-^{14}C-α-tocopheryl acetate (XIV, 350.0 mg, 91%) was obtained as an orange-colored, viscous oil. The specific activity of the oil was 3.06 μCi/mg.

1,1-Bis(β-tocopherol-7′-yl)-methane (XVII)——β-Tocopherol (I, 0.84 g, 2 mmoles) and 7-hydroxymethyl-β-tocopherol (V, 0.90 g, 2 mmoles) were dissolved in toluene (30 ml). Under vigorous stirring hydrochloric acid (8 ml) was added at room temperature. The reaction continued for an hour. The organic layer was separated and washed with water, 5% aqueous $NaHCO_3$ solution, and water. The washed layer was dried over Na_2SO_4 and evaporated *in vacuo*. The crude product (1.8 g) was dissolved in hexane and placed on a column of silica gel (40 ml). After impurities were eluted from the column with hexane containing benzene, pure sample was eluted with 30% benzene in hexane. 1,1-Bis(β-tocopherol-7′-yl)-methane (XVII, 1.0 g, 59%) was obtained as pale yellow colored wax. *Anal.* Calcd. for $C_{57}H_{96}O_4$: C, 80.98; H, 11,45. Found: C, 80.62; H, 11.38. IR ν_{max}^{Nujol} cm^{-1}: 3480, 1262, 1258, 1175, 1160, 1115, 1065, 921. UV λ_{max}^{EtOH} mμ($E_{1cm}^{1\%}$) 296 (95.4). TLC: *Rf* 0.60 (hexane–EtOH 95: 5). NMR τ: 6.12 (2H, s, Ar–CH_2–, at position 7), 7.48 (4H, broad, Ar-CH_2–, at position 4 and 4′), 7.82 and 8.07 (12H, two s, four Ar–CH_3), 8.27 (4H, broad, protons at position 3 and 3′).

Diacetate of XVII (XVIII)——1,1-Bis(β-tocopherol-7′-yl)-methane (XVII, 0.90 g, 1.06 mmoles) was left with acetic anhydride (9 ml) and pyridine (6 ml) overnight at room temperature. The reaction mixture was poured into crushed ice and extracted with ether (50 ml). The ether layer was washed with water, 5% aqueous $NaHCO_3$ solution, and water. The washed organic layer was dried over Na_2SO_4 and evaporated *in vacuo*. The crude product (1.0 g) was purified by chromatography on a column of silica gel (20 ml) packed in hexane. The pure product was eluted with 70% benzene in hexane. Diacetate of XVII (XVIII, 0.6 g, 61%) was obtained as pale yellow solid, mp 54—55°. *Anal.* Calcd. for $C_{61}H_{100}O_6$: C, 78.82; H, 10.84. Found: C, 78.43; H, 10.64. IR ν_{max}^{Nujol} cm^{-1}: 1750, 1230, 1205, 1165, 1118, 1064, 1018, 923. UV λ_{max}^{EtOH} mμ($E_{1cm}^{1\%}$): 281 (45.5), 289 (51.6). TLC: *Rf* 0.23 ($CHCl_3$). NMR τ: 6.18 (2H, s, Ar–CH_2–, at position 7), 7.43 (4H, broad, Ar–CH_2–, at position 4 and 4′), 7.94 (6H, s, two CH_3CO–), 8.00 and 8.10 (12H, two s, four Ar–CH_3), 8.24 (2H, broad, protons at position 3 and 3′). Mass Spectrum *m/e*: 929 (M^+).

1,1-Bis(γ-tocopherol-5′-yl)-methane (XV)——γ-Tocopherol (III, 0.84 g, 2 mmoles) and 5-hydroxymethyl-γ-tocopherol (VII, 0.90 g, 2 mmoles) were reacted following the procedure of the preparation of XVII. The crude product was purified by recrystallization from MeOH. 1,1-Bis(γ-tocopherol-5′yl)-methane (XV, 1.0 g, 59%) was obtained as white crystal, mp 79—90°. *Anal.* Calcd. for $C_{57}H_{96}O_4$: C, 80.98; H, 11.45. Found: C, 81.04; H, 11.19. IR ν_{max}^{KBr} cm^{-1}: 3390, 1245, 1160, 1110, 1085, 965, 918, 832. UV λ_{max}^{EtOH} mμ ($E_{1cm}^{1\%}$) 295 (95.4). TLC: *Rf* 0.60 (hexane–EtOH 95: 5). NMR τ: 6.16 (2H, s, Ar–CH_2–, at position 5), 7.30 (4H, t, Ar–CH_2–, at position 4 and 4′), 7.96 (12H, s, four Ar–CH_3), 8.26 (4H, t, protons at position 3 and 3′).

Diacetate of XV (XVI)——1,1-Bis(γ-tocopherol-5′-yl)-methane (XV, 0.90 g, 1.06 mmoles) was acetylated and purified by the same procedure as described in the preparation of XVIII. Diacetate of XV (XVI, 0.6 g, 61%) was obtained as a pale yellow-colored, viscous oil. *Anal.* Calcd. for $C_{61}H_{100}O_6$: C, 78.82; H, 10.84. Found: C, 78.83; H, 10.68. IR ν_{max}^{liq} cm^{-1}: 1760, 1200, 1163, 1108, 1080, 1010, 970, 730. UV λ_{max}^{EtOH} mμ($E_{1cm}^{1\%}$): 281 (43.3), 289 (49.8). TLC: *Rf* 0.23 ($CHCl_3$). NMR τ: 6.40 (2H, s, Ar–CH_2–, at position 5), 7.60 (4H, broad, Ar–CH_2–, at position 4 and 4′), 7.88 (6H, s, two CH_3CO–), 8.00 and 8.12 (12H, two s, four Ar–CH_3), 8.32 (4H, broad, protons at position 3 and 3′). Mass Spectrum *m/e*: 929 (M^+).

Acknowledgement The authers express their deep gratitude to Dr. K. Sato, Director of this Division for his encouragement and permission for publication of this work. Thanks are also due to Prof. S. Baba, Tokyo College of Pharmacy, for the treatment of radioactive compounds, to Mr. K. Sakaguchi for NMR and mass spectral measurements, and to the members of analytical center.