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Studies on Tocopherol Derivatives. I. Conversion of β-, γ-, and δ-Tocopherol to α-Tocopherol

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A four-step methylation of β-, γ-, and δ-tocopherol to α-tocopherol is described. All of the intermediates are isolated and characterized. The purities of methylated tocopherols are determined by quantitative gas liquid chromatography. The four steps are Mannich reaction, acetolysis, reductive cleavage, and reduction.

The tocopherols that have been found in nature are α-, β-, γ-, and δ-tocopherol. Vegetable oil such as cotton-seed oil, wheat germ oil, soy bean oil, and the like, are the usual commercial sources of tocopherols. Typical of such oils is soya bean oil, which is reported to have a mixed tocopherol component approximately 10% of α-, 60% of γ-, and 30% of δ-tocopherol.[2] As α-tocopherol exhibits the highest degree of vitamin E activity,[3] it is particularly advantageous to convert β-, γ-, and δ-tocopherol to α-tocopherol by chemical means.

Natural α-tocopherol has a *d*-form (2R, 4'R, 8'R) and is 135% as active as synthetic *dl*-α-tocopherol (2RS).[4] Therefore, in the conversion process, it is desirable to avoid the chroman ring opening and recyclization as several patents[5a-d] describe. Such methods accompany racemization at C_2 position.[6]

So far, many procedures to convert β-, γ-, and δ-tocopherol to α-tocopherol have been reported as patents.[7a-d] In those studies no intermediate in the processes has ever been isolated and characterized. The final products were analysed by ultraviolet (UV) absorption spectra or National Formulary (NF) assay procedure.[8] The similarity of the UV absorption spectra of tocopherols are known.[9] Some side reaction products disturb the accuracy of NF assay procedure. Details will be described separately.[10] In this paper, the purities of the final products are estimated by quantitative gas liquid chromatography (GLC).[11] In recent years a practical process of tocopherol extraction from raw materials[12] and a practical separation of tocopherol homologues[13a,b] have been established with anion exchange resin. Pure tocopherol homologues are used in this paper.

1) Location: *Koishikawa 4-chome, Bunkyo-ku, Tokyo.*
2) M.L. Quaife, *J. Biol. Chem.*, **175**, 605 (1948).
3) J. Bunyan, D. McHale, J. Green, and S. Marcinkiewicz, *Brit. J. Nutr.*, **15**, 253 (1961).
4) "National Formulary" thirteenth ed., American Pharmaceutical Association, Washington D.C., 1970, p. 905.
5) *a*) Collett-Week Corporation, Brit. Patent 880 399 (1959); *b*) F.J. Sevigne, U.S. Patent 2 998 430 (1961) [*C.A.*, **56**, 3462 c (1962)]; *c*) F.J. Sevigne, U.S. Patent 3 187 011 (1965); *d*) Collett-Week Corporation, Brit. Patent 1,000 517 (1965).
6) P. Schudel, H. Mayer, J. Metzger, R. Rüegg, and O. Isler, *Helv. Chim. Acta*, **46**, 333 (1963).
7) *a*) L. Weisler and A.J. Chechak, U.S. Patent 2 486 542 (1949) [*C.A.*, **44**, 2037 f (1950)]; *b*) L. Weisler, U.S. Patent 2 592 628 (1952) [*C.A.*, **47**, 1192 e (1953)]; *c*) L. Weisler, U.S. Patent 2 519 863 (1950) [*C.A.*, **45**, 669 c (1951)]; *d*) L. Weisler, U.S. Patent 2 673 858 (1954) [*C.A.*, **49**, 5533 c (1955)].
8) "National Formulary" thirteenth ed., American Pharmaceutical Association, Washington D.C., 1970, p. 758.
9) M. Kofler, P.F. Sommer, H.R. Bolliger, B. Schmidli, and M. Vecchi, *Vitam & Horm.*, **20**, 407 (1962).
10) T. Nakamura and S. Kijima, Studies on Tocopherol Derivatives IV (in preparation).
11) S. Ishikawa and G. Katsui, *Vitamins* (Tokyo), **31**, 445 (1965).
12) S. Kijima, K. Naito, and T. Mori, Japan. Patent 38-23638 (1963) [*C.A.*, **61**, 16106f (1964)].
13) *a*) S. Kijima and T. Nakamura, Brit. Patent 1 092 703 (1967) [*C.A.*, **68**, 107896c (1968)]; *b*) S. Kijima and T. Nakamura, U.S. Patent 3 402 182 (1968) [*C.A.*, **70**, 6587p (1969)].

Mannich base is one of the useful intermediates to introduce methyl group to phenolic compounds. However, in the step of reductive cleavage high pressure and high temperature are necessary. In the case of tocopherols secondary amine which liberate from Mannich bases at reduction process was found to induce destruction of tocopherols. Then milder

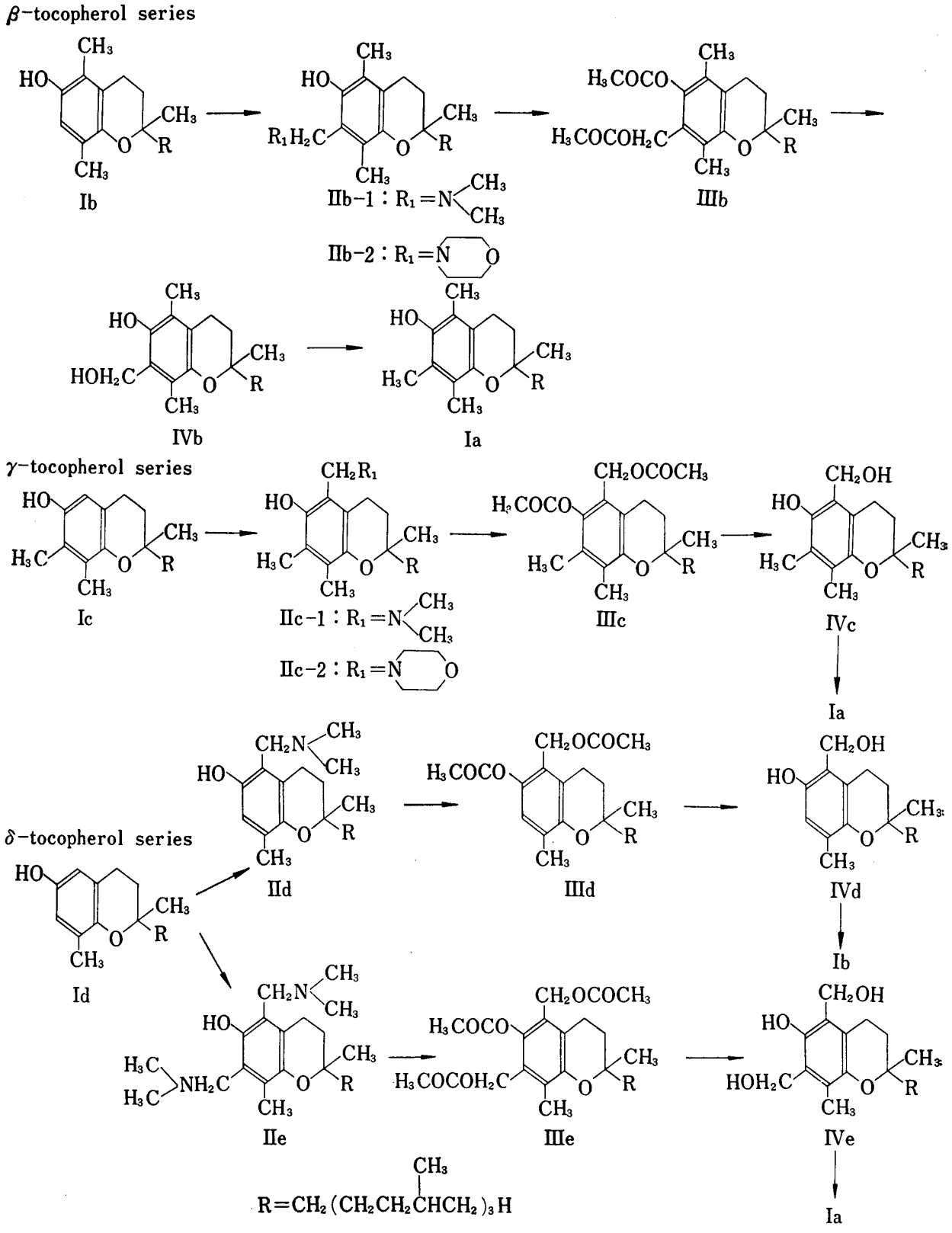

Chart 1

cleavage conditions were examined and three-step process was found suitable for cleavage of Mannich bases to tocopherol. The three steps, as shown in Chart 1, are acetolysis of the Mannich bases, reductive cleavage of the resulting acetoxymethyl acetates, and reduction with zinc and hydrochloric acid. Mannich reaction and subsequent acetolysis of several phenols are reported.[14,15]

Mannich reaction was performed with excess of amine and formaldehyde in dioxane at reflux temperature. The reaction products are stable and easily isolated. δ-Tocopherol gave a mixture of two products, IId and IIe. The separation of the mixture was performed by silica gel chromatography. The former was eluted with 5% ether–benzene and the latter eluted with ethyl alcohol. The nuclear magnetic resonance (NMR) spectrum of IId exhibits a singlet at τ 3.36, representing one aromatic proton and a singlet at τ 6.54, representing two benzylic type protons. That of IIe did not show any signal in aromatic proton region, but four benzylic type protons at τ 6.51 and 6.62. From these analytical results IId corresponds to dimethylaminomethyl-δ-tocopherol and IIe corresponds to 5,7-bisdimethylaminomethyl-δ-tocopherol. On thin-layer chromatography (TLC), IId gave higher *Rf* value and showed pale brown color with ferric chloride reagent. IIe gave lower *Rf* value and showed dark brown color with the same reagent. The extension of reaction time did not change the ratio of the reaction mixture. The introduction of the first aminomethyl group seems to decrease the reactivity of the hydroxy group. Mono substitution IId occurred at C_5 position because the final product (Ib) was confirmed as β-tocopherol. Its identity was checked in comparison with authentic β-tocopherol on TLC,[16] color reaction of the spot with antimony pentachloride,[17] and infrared (IR) spectra.

Although, acetolysis of Mannich bases was done usually by refluxing with acetic anhydride for 15—20 hr,[14] several percents of nitrogen contents was still remained after IIc-2 had been refluxed for 15 hr with acetic anhydride. Under reductive acetylation condition the reaction completed in 3—4 hr. The acetates are pale yellow, viscous oils. Table I shows the relative retention times of the acetates on GLC.

Table I. Relative Retention Time[a] of Several Tocophenryl Acetates

Compound	Relative retention time
α-Tocopheryl acetate (Ia-acetate)	1.00
5-Acetoxymethyl-γ-tocopheryl acetate (IIIc)	1.67
δ-Tocopheryl acetate (Id-acetate)	0.79
5-Acetoxymethyl-δ-tocopheryl acetate (IIId)	1.53
5,7-Bisacetoxymethyl-δ-tocopheryl acetate (IIIe)	3.16

a) The column temperature was set at 250°.

Reductive cleavage to hydroxymethyl tocopherol was performed with lithium aluminium hydride in ether at room temperature.[18] The spots of hydroxymethyl tocopherols on TLC gave violet color with ferric chloride reagent.

Reduction to methyl group was done witn zinc dust and hydrochloric acid. The identification of the reaction products was accomplished on TLC and GLC. Table II shows the properties and yields of tocopherols.

14) H.A. Bruson and C.W. McMullen, *J. Am. Chem. Soc.*, **63**, 270 (1941).
15) D.L. Fields, J.B. Miller, and D.D. Reynolds, *J. Org. Chem.*, **29**, 2640 (1964).
16) H.D. Stowe, *Arch. Biochem. Biophys.*, **103**, 42 (1963).
17) H.R. Bolliger, "Handbuch der Dünnschichtchromatographie," ed. by E. Stahl, Springer, Heidelberg, 1962, p. 217.
18) D.E. Duggan, *Arch. Biochem. Biophys.*, **84**, 116 (1959).

Table II. Methylated Tocopherol

Compound	TLC[a] Free Rf	TLC[a] Free Color reaction with $SbCl_5$	TLC[a] Acetate Rf[c]	Relative retention time Squalene	Relative retention time Acetate	$[\alpha]_D^{27°}$[b]	Purity % (acetate)	Yield %
α-Tocopherol (IVb→Ia)	0.57[c]	orange–red	0.65	0.39	1.00	22.3 (c=3.6)	86.0	84
α-Tocopherol (IVc→Ia)	0.57[c]	orange–red	0.65	0.39	1.00	24.6 (c=2.4)	102.0	99
α-Tocopherol (IVe→Ia)	0.57[c]	orange–red	0.65	0.39	1.00	23.7 (c=4.7)	95.8	91
β-Tocopherol (IVb—Ib)	0.70[d]	light brown	0.61	0.39	0.86		85.4	82
Authentic α-tocopherol	0.57[c]	orange–red	0.65	0.39	1.00	27.5[19a]		
Authentic β-tocopherol	0.70[d]	light brown	0.61	0.39	0.86			
Authentic γ-tocopherol	0.62[d]	green	0.61	0.39	0.86			

a) On silica gel developed in *c*) chloroform, *d*) Stowe system[16]; light petroleum, isopropyl ether, acetone, ethyl ether and glacial acetic acid 85: 12: 4: 1: 1.
b) Crude oxidation products with alkaline ferricyanide, measured in isooctane[19a]

Tocopherols thus obtained were oxidized with alkaline potassium ferricyanide and optical rotations of the oxidation products[19a,b] were measured. The $[\alpha]_D$ values are shown in Table II. The R configuration at C_2 position of natural δ-tocopherol have been speculated on the analogy of biosythetic route.[20] This speculation are supported by the value ($[\alpha]_D^{27°}$= +23.7) of oxidation product from 5,7-bismethylated δ-tocopherol (Id→Ia).

Experimental

Materials

γ-and δ-Tocopherol were separated by ion exchange method[13a,b] starting from mixed tocopherol concentrate of soy bean oil[12] and each was purified by molecular distillation. Purified monomethylated δ-tocopherol (Id→Ib) was used as β-tocopherol after confirming the substitution position. The purities were checked by UV, TLC, IR, NMR, and GLC. The UV absorption intensities of the tocopherol homologues used were as follows: UV $\lambda_{max}^{ethanol}$ mμ ($E_{1cm}^{1\%}$), β-tocopherol 297 (84.5), γ-tocopherol 298 (91.2), δ-tocopherol 298 (90.5). As authentic tocopherol homologues, commercial samples for chemical and biological research of Distillation Product Industries were used. Squalene was the sample of Tokyo Kasei Kogyo Co., Ltd.

General Comments

Melting points were measured on a Yanagimoto micromelting point apparatus and uncorrected. The UV absorption spectra were taken with a Shimazu QV-50 spectro photometer. The optical rotations were determined with Model DIP-SL instrument of Japan Spectroscopic Co. 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; t, triplet. GLC were performed with Model 402 gas chromatograph of F & M Scientific with a flame ionization detector. Glass column (4 ft length, 2.8 mm diameter) filled with 1.5% SE-30 coated chromosorb W was used. Squalene was used as an internal standard. The areas of peaks were calculated by the chart reader of JEOL 114 EC-5 computer. Molecular distillations were carried out with centrifugal molecular still Type CMS-5 of Consolidated Vacuum Corporation. TLC were performed using silica gel GF_{254} (Merck A.G) plates of 0.75 mm (preparative) and 0.25 mm (analytical) thickness.

5-Dimethylaminomethyl-γ-tocopherol (IIc-1)——A mixture of γ-tocopherol (1.7 g, 4.1 mmoles), 40% aqueous dimethylamine solution (2.3 ml, 20 mmoles) and dioxane (10 ml) was cooled by ice water and stirred while 37% formaldehyde solution (1.7 ml, 21 mmoles) was added dropwise. The mixture was stirred thereafter for an hour at room temperature and then at gentle refluxing for 4 hr. The reaction mixture was concentrated *in vacuo*. An orange–colored, oily residue was obtained. To the residue hexane (100 ml) was added and washed several times with satd. aqueous NaCl solution, dried over Na_2SO_4, and concentrated *in vacuo*. The residual oil solidified in few days. By recrystallization from MeOH, 5-dimethylaminomethyl-γ-tocopherol (IIc-1, 1.4 g 74%) was obtained as white crystals, mp 57—58° (lit[21] mp 45—46°). *Anal.* Calcd.

19) *a*) D.R. Nelan and C.D. Robeson, *Nature*, **193**, 477 (1962); *b*) *Idem*, *J. Am. Chem. Soc.*, **84**, 2963 (1962).
20) O. Isler, H. Mayer, J. Metzger, R. Rüegg, and P. Schudel, *Angew. Chem.*, **75**, 1030 (1963).
21) W.A. Skinner, R.M. Parkhurst, J. Scholler, and K. Schwarz, *J. Med. Chem.*, **12**, 64 (1969).

for $C_{31}H_{55}O_2N$: C, 78.59; H, 11.70; N, 2.96. Found: C, 78.68; H, 11.51; N, 3.28. IR ν_{max}^{KBr} cm^{-1}: 3100—2500 (broad), 1615, 1240, 1158, 1093, 980, 930, 844. UV $\lambda_{max}^{ethanol}$ mμ ($E_{1cm}^{1\%}$): 303 (88.0). TLC; Rf=0.43 (benzene: AcOEt 8:2). NMR τ: 6.55 (2H, s, Ar-CH_2-, at position 5), 7.46 (2H, t, Ar-CH_2-, at position 4, J=6.0 Hz), 7.72 (6H, s, $N\langle^{CH_3}_{CH_3}$), 7.95 and 7.98 (6H, two s, two Ar-CH_3), 8.30 (2H, t, protons at position 3, J=6.0 Hz).

5-Morpholinomethyl-γ-tocopherol (IIc-2)——To a mixture of γ-tocopherol (1.7 g, 4.1 mmoles), morpholine (1.7 g, 20 mmoles), and dioxane (10 ml). 37% formaldehyde solution (1.7 ml) was added at 10—12°, and reacted as described above. 5-Morpholinomethyl-γ-tocopherol (IIc-2, 63%) was isolated by preparative TLC. The product was white crystals, mp 35—36° (Skinner, *et al.*[21] reported it as a straw-colored, viscous oil). *Anal.* Calcd. for $C_{33}H_{57}O_3N$: C, 76.81; H, 11.13; N, 2.71. Found: C, 76.34; H, 11.05; N, 2.72. IR ν_{max}^{KBr} cm^{-1}: 3200—2500 (broad), 1615, 1260, 1120, 995, 913, 867, 802. UV $\lambda_{max}^{ethanol}$ mμ ($E_{max}^{1\%}$): 302 (78.3). TLC; Rf=0.57 ($CHCl_3$). NMR τ: 6.32 (4H, t, -CH_2-O-CH_2-), 6.44 (2H, s, Ar-CH_2-, at position 5), 7.48 (6H, broad, Ar-CH_2-, at position 4 and -CH_2-N-CH_2-), 7.96 and 8.00 (6H, two s, two Ar-CH_3), 8.30 (2H, t, protons at position 3, J=7.0 Hz).

7-Dimethylaminomethyl-β-tocopherol (IIb-1)——β-Tocopherol (1.7 g, 4.1 mmoles) reacted with 40% aqueous dimethylamine solution (2.3 ml), and 37% formaldehyde solution (1.7 ml) in dioxane (10 ml) by the same procedure as described in the preparation of IIc-1. 7-Dimethylaminomethyl-β-tocopherol (IIb-1, 63%) was isolated by preparative TLC. The product was a pale yellow mass, mp 33—34°. *Anal.* Calcd. for $C_{31}H_{55}O_2N$: C, 78.59; H, 11.70; N, 2.96. Found: C, 78.81; H, 11.58; N, 3.23. IR ν_{max}^{liq} cm^{-1}: 3100—2700 (broad), 1605, 1252, 1150, 1102, 1058, 1008, 920, 841, 670. UV $\lambda_{max}^{ethanol}$ mμ ($E_{max}^{1\%}$): 303 (88.2). TLC; Rf=0.43 (benzene: AcOEt 8:2). NMR τ: 6.47 (2H, s, Ar-CH_2-, at position 7), 7.45 2H, t, Ar-CH_2-, at position 4, J=6.0 Hz), 7.70 (6H, s, $N\langle^{CH_3}_{CH_3}$), 7.97 (6H, s, Ar-CH_3, at position 5 and 8), 8.30 (2H, t, portons at position 3, J=6.0 Hz).

7-Morpholinomethyl-β-tocopherol (IIb-2)——To a mixture of β-tocopherol (1.7 g, 4.1 mmoles), morpholine (1.7 g), and dioxane (10 ml), 37% formaldehyde solution (1.7 ml) was added at 10—12°. The mixture reacted as described above. 7-Morpholinomethyl-β-tocopherol (IIb-2, 58%) was isolated by preparative TLC as a pale orange-colored, viscous oil. *Anal.* Calcd. for $C_{33}H_{57}O_3N$: C, 76.81; H, 11.13; N, 2.71. Found: C, 77.24; H, 11.09; N, 2.97. IR ν_{max}^{liq} cm^{-1}: 3100—2700 (broad), 1620, 1260, 1158, 1118, 1060, 1000, 908, 860. UV $\lambda_{max}^{ethanol}$ mμ ($E_{1\%}^{1cm}$): 302 (81.5). TLC: Rf=0.57 ($CHCl_3$). NMR τ: 6.28 (6H, broad, Ar-CH_2-, at position 7 and -CH_2-O-CH_2-), 7.40 (6H, broad, Ar-CH_2-, at position 4 and -CH_2-N-CH_2-), 7.85 (6H, s, two Ar-CH_3), 8.20 (2H, t, protons at position 3, J=7.0 Hz).

5-Dimethylaminomethyl-δ-tocopherol (IId) and 5,7-Bisdimethylaminomethyl-δ-tocopherol (IIe)——A mixture of δ-tochopherol (8.1 g, 20 mmoles), 40% aqueous dimethylamine solution (18 ml, 160 mmoles), and dioxane (40 ml) was cooled by ice water and stirred while 37% formaldehyde solution (13 ml, 160 mmoles) was added dropwise. The mixture was stirred thereafter for an hour at room temperature and then at refluxing temperature for 4 hr. The reaction mixture was concentrated *in vacuo*. An orange, syrupy residue was obtained. To the residue AcOEt (300 ml) was added and washed several times with sat. aqueous NaCl solution, dried over Na_2SO_4, and evaporated *in vacuo*. An orange-colored, viscous oil (10.0 g) was obtained. This crude product was a mixture of IId and IIe. The mixture was separated by chromatography on a column of silica gel (200 ml) packed in benzene. After preliminary elution with benzene and benzene containing ether, the pure product of 5-dimethylaminomethyl-δ-tocopherol (IId, 5.2 g, 57%) was eluted with 20% ether–benzene. The product was a pale orange-colored, viscous oil. *Anal.* Calcd. for $C_{30}H_{53}O_2N$: C, 78.33; H, 11.61; N, 3.05. Found: C, 78.52; H, 11.66; N, 3.29. IR ν_{max}^{liq} cm^{-1}: 3100—2600 (broad), 1622, 1597, 1244, 1160, 1100, 1042, 988, 857. UV $\lambda_{max}^{ethanol}$ mμ ($E_{max}^{1\%}$): 300 (82.0). TLC; Rf=0.22 (benzene: AcOEt 8:2). NMRτ: 3.63 (1H, s, Ar-H), 6.54 (2H, s, Ar-CH_2-, at position 5), 7.54 (2H, t, Ar-CH_2-, at position 4, J=6.0 Hz),7.72 (6H, s, $N\langle^{CH_3}_{CH_3}$), 7.94 (3H, s, Ar-CH_3), 8.30 (2H, t, protons at position 3, J=6.0 Hz). On Subsequent elution with EtOH of the above chromatography 5,7-bisdimethylaminomethyl-δ-tocopherol (IIe, 3.2 g, 31%) was eluted. The product was an orange-colored, viscous oil. *Anal.* Calcd. for $C_{33}H_{60}O_2N_2$: C, 76.66; H,11.70; N, 5.42. Found: C, 76.95; H, 11.57; N, 5.25. IR ν_{max}^{liq} cm^{-1}: 3100—2600 (broad), 1622, 1265, 1175, 1122, 1020, 895. UV $\lambda_{max}^{ethanol}$ mμ ($E_{max}^{1\%}$): 301 (82.0). TLC; Rf=0.03 (benzene: AcOEt 8:2). NMR τ: 6.51 (2H, s, Ar-CH_2-, at position 7), 6.62 (2H, s, Ar-CH_2-, at position 5), 7.27 (2H, t, Ar-CH_2-, at position 4, J=7.0 Hz), 7.72 and 7.82 (12H, two s, two $N\langle^{CH_3}_{CH_3}$), 7.94 (3H, s, Ar-CH_3), 8.30 2H, t, protons at position 3,J=7.0 Hz).

5-Acetoxymethyl-γ-tocopheryl Acetate (IIIc)——To a mixture of 5-dimethylaminomethyl-γ-tocopherol (IIc-1, 9.0 g, 19 mmoles), acetic anhydride (60 ml), acetic acid (20 ml), and anhydrous sodium acetate (3.0 g), zinc dust (4.5 g) was added slowly under vigorous stirring, then the reaction mixture was heated until refluxing temperature and the heating continued for 4 hr. After cooling, the reaction mixture was added to crushed ice and extracted with hexane (300 ml). The organic layer was washed with water, satd. aqueous $NaHCO_3$ solution, and water, dried over Na_2SO_4, and evaporated *in vacuo*. The curde product (10.2 g) was purified by chromatography on a column of silica gel (200 ml) packed in hexane. After impurities were eluted from

the column with hexane containing benzene. The pure product was eluted with 80% benzene–hexane. 5-Acetoxymethyl-γ-tocopheryl acetate (IIIc, 9.0 g, 89%) was obtained as a pale yellow viscous oil. *Anal.* Calcd. for $C_{33}H_{54}O_5$: C, 74.64; H, 10.25. Found: C, 74.81; H, 10.32. IR ν_{max}^{liq} cm^{-1}: 1763, 1745, 1225, 1200, 1165, 1118, 1083, 1020. UV $\lambda_{max}^{ethanol}$ mμ ($E_{1cm}^{1\%}$): 290 (52.1), (lit.[22] 284 mμ and 291 mμ in hexane). TLC; Rf=0.58 ($CHCl_3$). NMR τ: 5.00 (2H, s, Ar-CH_2-, at position 5, 7.22 (2H, t, Ar-CH_2-, at position 4, J=7.0 Hz), 7.82 and 7.89 (6H, two s, two $COCH_3$), 8.05 and 8.10 (6H, two s, two Ar-CH_3), 8.24 (2H, t, protons at position 3, J=7.0 Hz).

7-Acetoxymethyl-β-tocopheryl Acetate (IIIb)——Acetolysis of 7-dimethylaminomethyl-β-tocopherol (IIb-1, 3.0 g, 6.3 mmoles) was performed by the same procedure as described above. 7-Acetoxymethyl-β-tocopheryl acetate (IIIb, 2.7 g, 81%) was obtained as a pale yellow viscous oil. *Anal.* Calcd. for $C_{33}H_{54}O_5$: C, 74.64; H, 10.25. Found: C, 74.52; H, 10.32. IR ν_{max}^{liq} cm^{-1}: 1760, 1743, 1220, 1198, 1165, 1070, 1020, 963. UV $\lambda_{max}^{ethanol}$ mμ ($E_{max}^{1\%}$): 292 (55.0). TLC; Rf=0.58 ($CHCl_3$). NMR τ: 4.98 (2H, s, Ar-CH_2-, at position 7), 7.33 (2H, t, Ar-CH_2, at position 4, J=7.0 Hz), 7.73 and 7.78 (6H, two s, two $COCH_3$), 8.02 (6H, s, two Ar-CH_3), 8.20 (2H, t, protons at position 3, J=7.0 Hz).

5-Acetoxymethyl-δ-tocopheryl Acetate (IIId)——Acetolysis of 5-dimethylaminomethyl-δ-tocopherol (IId, 7.0 g, 15 mmoles) was conducted by the same procedure as described above. The pure sample of 5-acetoxymethyl-δ-tocopheryl acetate (IIId, 6.6 g, 85%) was obtained as a pale yellow viscous oil. *Anal.* Calcd. for $C_{32}H_{52}O_5$: C, 74.34; H, 10.14. Found: C, 71.64; H, 10.05. IR ν_{max}^{liq} cm^{-1}: 1765, 1748, 1225, 1200, 1168, 1016, 961, 925. UV $\lambda_{max}^{ethanol}$ mμ ($E_{1cm}^{1\%}$): 291 (57.6). TLC: Rf=0.56 ($CHCl_3$). NMR τ: 3.41 (1H, s, Ar-H), 5.02 (2H, s, Ar-CH_2-, at position 5), 7.20 (2H, t, Ar-CH_2-, at position 4, J=7.0 Hz), 7.82 and 7.88 (6H, two s, two $COCH_3$), 8.08 (3H, s, Ar-CH_3), 8.21 (2H, t, protons at position 3, J=7.0 Hz).

5,7-Bisacetoxymethyl-δ-tocopheryl Acetate (IIIe)——Acetolysis of 5,7-bisdimethylaminomethyl-δ-tocopherol (IIe, 5.2 g, 10 mmoles) was accomplished by the same procedure as described above. The crude product was chromatographed on a column of silica gel (100 ml). After preliminary elution with hexane, benzene, and benzene containing ether, the pure product was eluted with 5% ether–benzene. 5,7-Bisacetoxymethyl-δ-tocopheryl acetate (IIIe, 4.8 g, 81%) was obtained as a pale yellow viscous oil. *Anal.* Calcd. for $C_{35}H_{56}O_7$: C, 71.37; H, 9.58. Found: C, 71.37; H, 9.44. IR ν_{max}^{liq} cm^{-1}: 1770, 1750, 1225 (broad), 1195, 1170, 1023, 965. UV $\lambda_{max}^{ethanol}$ mμ ($E_{1cm}^{1\%}$): 296 (58.6). TLC; Rf=0.38 ($CHCl_3$). NMR τ: 5.01 (2H, s, Ar-CH_2-, at position 7), 5.04 (2H, s, Ar-CH_2-, at position 5), 7.20 (2H, t, Ar-CH_2-, at position 4, J=6.0 Hz), 7.78, 7.80 and 8.08 (9H, three s, three $COCH_3$), 8.08 (3H, s, Ar-CH_3), 8.20 (2H, t, Ar-CH_2-, at position 3, J=6.0 Hz).

5-Hydroxymethyl-γ-tocopherol (IVc)——In a flask was placed absolute ether (100 ml) and $LiAlH_4$ (1.0 g). A solution of 5-acetoxymethy-γ-tocopheryl acetate (IIIc, 9.0 g, 17 mmoles) in absolute ether (20 ml) was added from a dropping funnel. The process was completed in about 20 min. Agitation was continued for 2 hr after all the acetate had been introduced and the excess of hydride was then destroyed by the careful, dropwise addition of AcOEt and water to the stirred and cooled reaction mixture. The reaction mixture was neutralized by 5% aqueous H_2SO_4 solution and separated. The organic layer was washed with water, satd. aqueous $NaHCO_3$ solution, and water, dried over Na_2SO_4, and evaporated *in vacuo*. The crude product (7.7 g) was placed onto a silica gel column (160 ml) and eluted with hexane, hexane containing benzene. The pure product was eluted with 80% benzene–hexane. 5-Hydroxymethyl-γ-tocopherol (IVc, 4.8 g, 63%) was obtained as a yellow, viscous oil. The pure sample solidified when kept in a refrigerator, mp 35—36°. *Anal.* Calcd. for $C_{29}H_{50}O_3$: C, 77.92; H, 11.18. Found: C, 78.06; H, 11.01. IR ν_{max}^{liq} cm^{-1}: 3350, 1264, 1190, 1160, 1018, 990, 920, 865. UV $\lambda_{max}^{ethanol}$ mμ ($E_{max}^{1\%}$): 298 (83.6). TLC; Rf=0.53 (benzene: AcOEt 8:2). NMR τ: 5.39 (2H, s, Ar-CH_2-, at position 5), 7.50 (2H, t, Ar-CH_2-, at position 4, J=7.0 Hz), 7.96 (6H, s, two Ar-CH_3), 8.31 (2H, t, protons at position 3, J=7.0 Hz).

7-Hydroxymethyl-β-tocopherol (IVb)——Reductive cleavage of 7-acetoxymethyl-β-tocopheryl acetate (IIIb, 2.7 g, 5.1 mmoles) was carried out by the same procedure as described above. The pure product was eluted with 80% benzene–hexane. 7-Hydroxymethyl-β-tocopherol (IVb, 1.4 g, 63%) was obtained as a pale orange–yellow, viscous oil. *Anal.* Calcd. for $C_{29}H_{50}O_3$: C, 77.92; H, 11.28. Found: C, 77.73; H, 11.18. IR ν_{max}^{liq} cm^{-1}: 3350, 1262, 1160, 1060, 1004, 980. UV $\lambda_{max}^{ethanol}$ mμ ($E_{max}^{1\%}$) 299 (83.5). TLC; Rf=0.53 (benzene: AcOEt 8:2). NMR τ: 5.18 (2H, s, Ar-CH_2-, at position 7), 7.40 (2H, t, Ar-CH_2-, at position 4, J=6.0 Hz), 7.90 and 7.93 (6H, two s, Ar-CH_3), 8.22 (2H, t, protons at position 3, J=6.0 Hz).

5-Hydroxymethyl-δ-tocopherol (IVd)——Reductive cleavage of 5-acetoxymethyl-δ-tocopheryl acetate (IIId, 3.5 g, 6.8 mmoles) was done by the same procedure as described above. Upon chromatography of the curde products (2.8 g) on a column of silica gel (60 ml) the pure product was eluted with 10% ether–benzene. 5-Hydroxymethyl-δ-tocopherol (IVd, 1.7 g, 58%) was obtained as a pale yellow, viscous oil. *Anal.* Calcd. for $C_{28}H_{48}O_3$: C, 77.66; H, 11.17. Found: C, 77.49; H, 11.23. IR ν_{max}^{liq} cm^{-1}: 3320, 1233, 1165, 1102, 975, 918, 858. UV $\lambda_{max}^{ethanol}$ mμ ($E_{max}^{1\%}$): 302 (96.5). TLC; Rf=0.41 (benzene: AcOEt 8:2). NMR τ: 3.64 (1H, s, Ar-H), 5.40 (2H, s, Ar-CH_2-, at position 5), 7.48 (2H, t, Ar-CH_2-, at position 4, J=6.0 Hz), 8.00 (3H, s, Ar-CH_3), 8.36 (2H, t, protons at position 3, J=6.0 Hz).

5,7-Bishydroxymethyl-δ-tocopherol (IVe)——Reductive cleavage of 5,7-bisacetoxymethyl-δ-tocopheryl

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acetate (IIIe, 7.1 g, 12 mmoles) was done by the same procedure as described above. Upon chromatography of the crude products (4.5 g) on a column of silica gel (90 ml), the pure product was eluted with 20% ether–benzene. 5,7-Bishydroxymethyl-δ-tocopherol (IVe, 3.1 g, 56%), was obtained as white crystals, mp 61—62°. *Anal.* Calcd. for $C_{29}H_{50}O_4$: C, 75.22; H, 10.89. Found: C, 74.99; H, 10.88. IR ν_{max}^{Nujol} cm^{-1}: 3470, 3200, 1262, 1155, 1070, 1022, 998, 961. UV $\lambda_{max}^{ethanol}$ mμ ($E_{1cm}^{1\%}$): 307 (97.1). TLC; Rf=0.18 (benzene: AcOEt 8:2). NMR τ: 5.22 (2H, s, Ar-CH_2-, at position 7), 5.30 (2H, s, Ar-CH_2-, at position 5), 7.38 (2H, t, Ar-CH_2-, at position 4, J=6.0 Hz), 7.92 (3H, s, Ar-CH_3), 8.26 (2H, t, protons at position 3, J=6.0 Hz).

Reduction of Hydroxymethyl Tocopherol to Methylated Tocopherol——To a solution of 5-hydroxymethyl-γ-tocopherol (IVc, 3.50 g, 7.8 mmoles) in toluene (100 ml), acetic acid (20 ml), conc. hydrochloric acid (30 ml), and zinc dust (3.0 g) were added under vigorous stirring at 5—8°. The reaction completed within an hour. Hexane (100 ml) was added to the reaction mixture, washed with water, dil. $NaHCO_3$ solution, and water, dried over Na_2SO_4, and evaporated *in vacuo*. The crude α-tocopherol (Ia, 3.30 g) was obtained as an orange–brown oil.

Reduction of 7-hydroxymethyl-β-tocopherol (IVb), 5.7-bishydroxymethyl-δ-tocopherol (IVe) to α-tocopherol (Ia), and 5-hydroxymethyl-δ-tocopherol (IVd) to β-tocopherol (Ib) was performed by the same procedure as described above. The purities of the tocopherols thus obtained were estimated by quantitative GLC.

Oxidation of tocopherols and measurements of their optical rotation were carried out exactly same way as Nelan, *et al.* reported.[19a]

Quantitative GLC of Methylated Tocopherols——About 100 mg of sample was weighed exactly and 25 ml of acetic anhydride–pyridine (1:1) solution was added. Acetylation was completed at 70—80° for half an hour. The reaction mixture was evaporated completely *in vacuo*. To the residue 1 ml of 10% squalene–acetone solution was added as an internal standard and messed up to 10 ml with acetone. 2 μl of the acetone solution was injected in the apparatus of gas chromatography. The area of peak was calculated for quantitative analysis. The purities of methylated tocopheryl acetates are shown in Table II.

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