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Studies on Tocopherol Derivatives. III.[1] Oxidation of δ-Tocopherol and 6-Hydroxy-2,2,8-trimethylchroman

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Oxidation reaction of d-δ-tocopherol (I) and δ-tocopherol model compound (II) are carried out with silver nitrate as oxidizing agent in ethyl alcohol. Three novel oxidation products are isolated and characterized. They are atropisomers of (+)-5-(δ-tocopherol-5′-yl)-δ-tocopherol (VII, with R-configuration at C_5-$C_{5'}$ position, IX with S-configuration at C_5-$C_{5'}$ position), and 5-(6′-hydroxy-2′,2′,8′-trimethylchroman-5′-yl)-6-hydroxy-2,2,8-trimethylchroman (XI).

Oxidation studies of tocopherols have been interested according to their biological antioxidative activity. Especially those of α-tocopherol have been done extensively in relation to its metabolic fate.[3-5] Recently Nilsson[6] reported oxidation reaction of several tocopherol homologues using *p*-benzoquinone and alkaline ferricyanide as oxidizing agents. The preferential reactivity of 5 position versus 7 on chroman ring was concluded.

It has been known that the number and position of methyl groups on benzene nucleus of chroman ring and oxidizing agent affects an important part in the course of oxidation.[3] In the series of tocopherols the oxidation study of δ-tocopherol (I) has attracted attention due to the strongest antioxidative activity *in vitro*.[7,8] In the Emmerie–Engel assay procedure[9] its delayed oxidation curve is characteristic among tocopherol homologues. Several oxidation studies of δ-tocopherol I[10,11] were reported but the results were discussed only on ultraviolet (UV) spectroscopic behavior. Nilsson, *et al.*[12] have first isolated and characterized 5-(δ-tocopheryloxy)-δ-tocopherol (III) in 23% yield as a sole oxidation product of δ-tocopherol I when oxidized with *p*-benzoquinone. Analogously 6-hydroxy-2,2,8-trimethylchroman (II, δ-tocopherol model) gave 5-(2′,2′,8′-trimethyl-6′-chromanoxy)-6-hydroxy-2,2,8-trimethylchroman[13] (V) in 30% yield as an oily product. When compound II was oxidized with alkaline ferricyanide spiroketal trimer was obtained.[14]

In the present paper, we wish to describe three novel oxidation products of d-δ-tocopherol I (2R-,4′R-,8′R-configuration)[15] and δ-tocopherol model compound II using silver nitrate as oxidizing agent. Evidence is presented that they are atropisomeric biaryls of 5-(δ-tocopherol-5′-yl)-δ-tocopherol, (VII) and (IX), and 5-(6′-hydroxy-2′,2′,8′-trimethyl-

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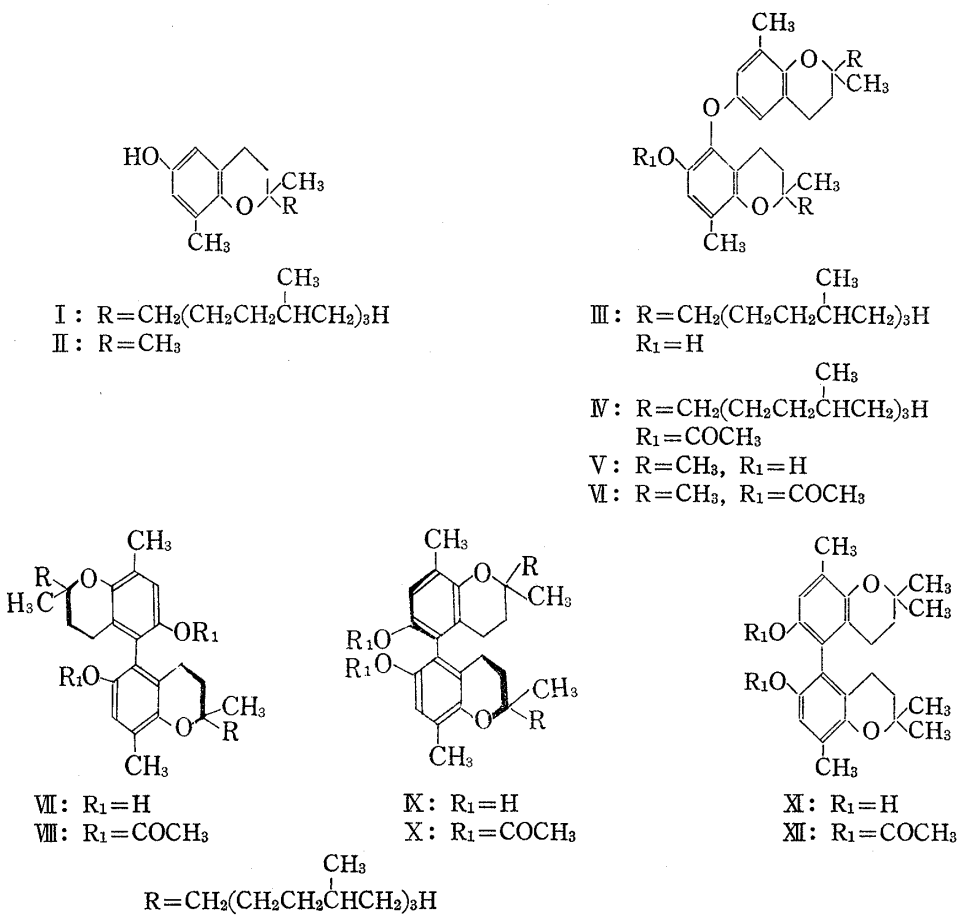

Chart 1

chroman-5′-yl)-6-hydroxy-2,2,8-trimethylchroman (XI). α- and γ-Tocopherols were oxidized by silver nitrate to red chroman-5,6-quinone known as toco-red.[3,16]

Oxidation of δ-tocopherol I was performed in ethyl alcohol at 50—55° for 2.5 hr and the product gave four reducing substances upon spraying with the Emmerie–Engel reagent[16] on thin-layer chromatography (TLC). Table I shows the appearance, *Rf* value, color reaction of the spot, and the isolated yield of the oxidation products of I.

Table I. The Oxidation Products of I

Compound	Appearance	*Rf* value[a]	Color reaction of the spot with		Isolated yield[b] (g)
			The Emmerie–Engel reagent	$SbCl_5$ reagnet	
III	pale yellow oil	0.71	orange-red	russet	0.24
VII	light-brown wax	0.58	orange-red	brown	0.48
I	pale orange oil	0.40	orange-red	russet	0.96
IX	dark brown oil	0.31	orange-red	brown	0.52

a) on silica gel developed in benzene–ethyl acetate (95:5)
b) starting from 3.8 g of crude oxidation pfoduct of I

The isolation was performed by silica gel column chromatography and then preparative TLC. *Rf* 0.71 compound was identified as 5-(δ-tocopheryloxy)-δ tocopherol III which was

16) J.G. Baxter, C.D. Robeson, J.D. Taylor, and R.W. Lehman, *J. Am. Chem. Soc.*, **65**, 918 (1943).

characterized previously.[12] Compound III was acetylated and obtained 5-(δ-tocopheryloxy)-δ-tocopheryl acetate (IV). The analytical results confirmed the structure IV. The nuclear magnetic resonance (NMR) spectrum of IV gave three protons of acetyl methyl group at 8.14 τ (singlet) and mass spectrum contains a peak at *m/e* 845 corresponding to the molecular ion of compound IV ($C_{56}H_{92}O_5$). *Rf* 0.40 compound was identified as unchanged δ-tocopherol I when compared with authentic δ-tocopherol on TLC and cochromatography. The structures of *Rf* 0.58 and 0.31 compounds were elucidated as VII and IX respectively by the following results. The two compounds gave strikingly similar analytical results on NMR, infrared (IR), UV, mass spectra, and the Emmerie–Engel oxidation curves but could be differentiated on TLC and circular dichronism (CD) curves. The specific rotation of them were positive. The NMR spectra of VII and IX are shown in Fig. 1. They give one sort of two aromatic protons (singlet).[13] The benzyl protons at C_4 position shift higher field and overlap with ring methyl protons. The shift gives a useful explanation of 5,5'-coupling

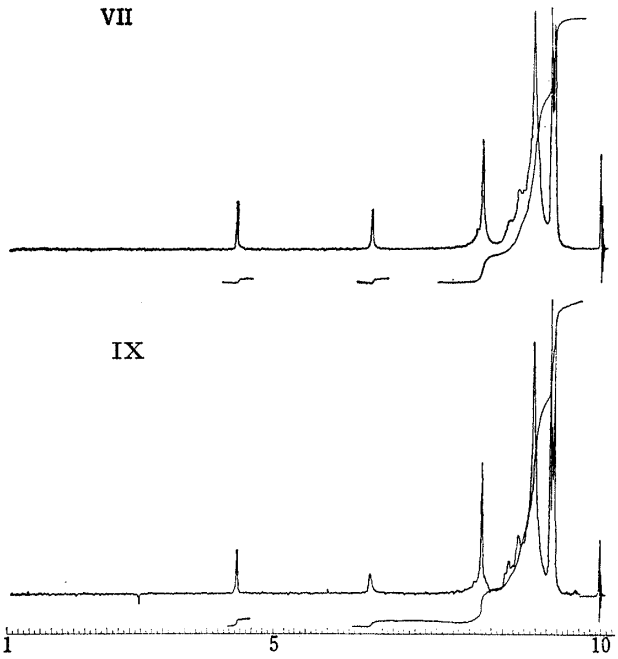

Fig. 1. NMR Spectra of VII and IX (on τ-Value in $CDCl_3$)

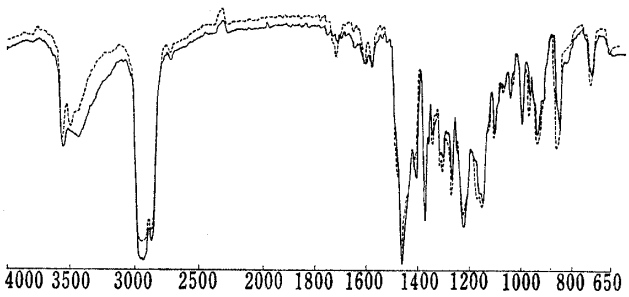

Fig. 2. The IR Spectra of the Oxidation Products of δ-Tocopherol (I)
VII: ------, IX: ——

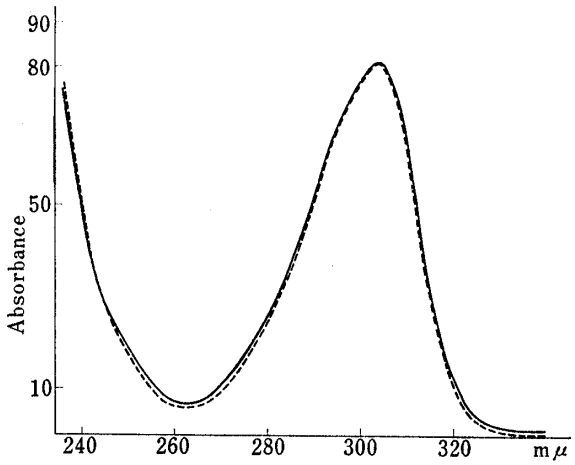

Fig. 3. The UV Spectra of the Oxidation Products of δ-Tocopherol (I)
VII: ------, IX: —— in ethyl alcohol

structure owing to anisotropy of another benzene nucleus. The mass spectra of VII and IX give molecular ion peak at *m/e* 803 which consist with molecular formula $C_{54}H_{90}O_4$. The corresponding diacetates (VIII) and (X) show molecular ion peak at *m/e* 887 which consist with molecular formula $C_{58}H_{94}O_6$. The IR spectra of VII and IX are mostly identical as shown in Fig. 2.

Absorption bands are present at 3560 cm^{-1}, 3500 cm^{-1} (hydroxyl), 1610 cm^{-1} (aromatic), and 1220 cm^{-1} (ether). Figure 3 shows the UV spectra of the two compounds. Figure 4 shows the oxidation curves in the Emmerie–Engel assay procedure. The relationship of

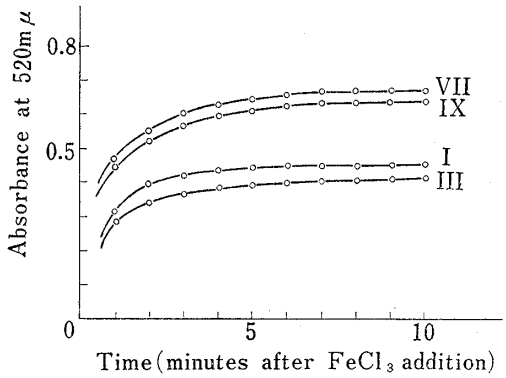

Fig. 4. Oxidatidn Curves of Compound I, III, VII, and IX in the Emmerie-Engel Assay Procedure

7.5×10^{-4} mmoles in 25 ml of ethyl alcohol

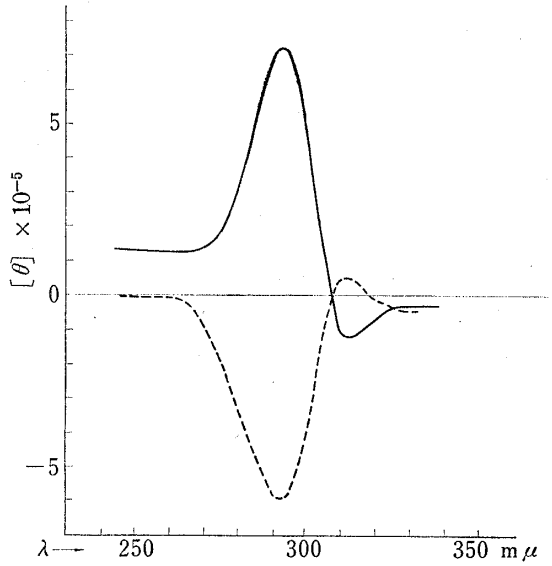

Fig. 5. CD Curves of the Oxidation Products of δ-Tocopherol (I)

VII: -----, $[\theta]_{310}=+\ 77000$, $[\theta]_{307}=0$, $c=1.07\times10^{-4}$
IX: ——, $[\theta]_{310}=-168000$, $[\theta]_{307}=0$, $c=1.18\times10^{-4}$
in dioxane, 27°

the two compounds was revealed by analyzing CD curves as shown in Fig. 5. They are essentially dissymmetric.

The absolute configuration of 1,1′-biaryls, 1,1′-binaphthyls, and 1,1′-bianthranyls have been determined using ORD and CD curves.[17–19] A positive long wavelength Cotton effect indicates *R*-configuration and a negative one does *S*-configuration. Then, in the case of the oxidation products of δ-tocopherol, VII assigned as *R*- and IX did as *S*-configuration. Thus we have concluded they were atropisomeric biaryls caused by the intramolecular restricted rotation at the 5,5′-linkage.

6-Hydroxy-2,2,8-trimethylchroman II was oxidized in the same condition as I. The syntheses of monomethyltocol have been devised to avoid isomeric mixture.[20,21] We have obtained II in convenient way starting from 4-hydroxy-3-methylacetophenone[22] (XIV). Compound XIV was condensed with dimethylallyl alcohol (XV) in isopropyl ether using sulphuric acid as catalyst. The condensation product (XVI) was treated with peracetic acid at room temperature yielding 6-acetoxy-2,2,8-trimethylchroman (XVII) in good yield. The hydrolysis of the ester XVII was achieved with lithium aluminum hydride.[23] 6-Hydroxy-2,2,8-trimethylchroman II was obtained in 50% yield from XIV.

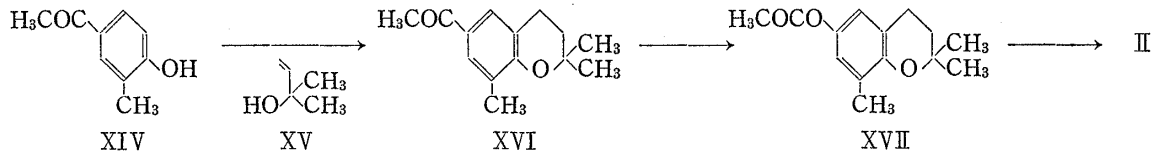

Chart 2

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Table II. The Oxidation Products of II

Compound	*Rf* value[a]	mp (°C)	Color reaction of the spot with		Isolated yield[b] (g)
			The Emmerie–Engel reagent	$SbCl_5$ reagent	
V	0.52	125—126	orange-red	russet	0.2
II	0.32	79— 81	orange-red	brown	2.4
XI	0.24	224—225	orange-red	yellow-brown	1.0

a) on silica gel developed in benzene-ethyl acetate (95:5)
b) starting from 3.9 g of the crude oxidation product of II

TLC analysis of the crude oxidation product of II developing with benzene–ethyl acetate (95: 5) revealed three reducing substances. *Rf* 0.24 compound crystallized out from 10% benzene–hexane. The mother liquor was concentrated *in vacuo* and chromatographed on a column of silica gel. *Rf* 0.52 compound was eluted with 60% benzene–hexane and *Rf* 0.32 compound was eluted with 90% benzene–hexane successively. Table II shows the analytical results and isolated yield of the oxidation products of II. *Rf* 0.52 compound (mp 125—126°) was identified as 5-(2′,2′,8′-trimethyl-6′-chromanoxy)-6-hydroxy-2,2,8-trimethylchroman[13] V on NMR spectrum and the analysis of its acetate (VI). *Rf* 0.32 compound was unchanged 6-hydroxy-2,2,8-trimethylchroman II. The NMR spectrum of *Rf* 0.24 compound, as shown in Fig. 6, gives analogous tendencies to that of VII and IX. One sort of two aromatic protons appear at 3.30 τ, four benzylic protons overlap with ring methyl groups, and the clear triplet at 8.30 τ for methylene protons at C_3 position means the presence of coupled benzylic protons at C_4.

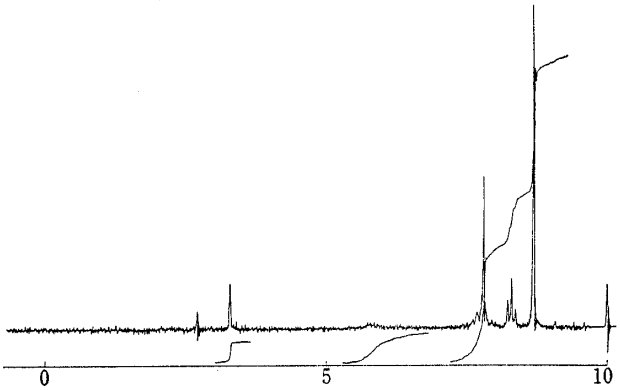
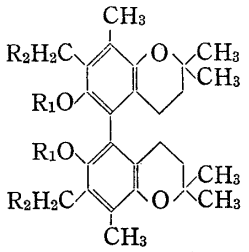


Fig. 6. NMR Spectrum of *Rf* 0.24 Compound (on τ Value in $CDCl_3$)



XIII: R_1=H, R_2=N⟨ ⟩O
XIV: R_1=$COCH_3$, R_2=$OCOCH_3$
XV: R_1=H, R_2=OH
XVI: R_1=R_2=H

Chart 3

The mass spectrum shows the molecular ion peak at *m/e* 382 which is compatible with the molecular formula $C_{24}H_{30}O_4$. The presence of two hydroxy groups was ascertained by the analysis of the acetate (XII). Thus *Rf* 0.24 compound was assigned as 5-(6′-hydroxy-2′,2′,8′-trimethylchroman-5′-yl)-6-hydroxy-2,2,8-trimethylchroman (XI) and the counterpart was not recognised. Compound XI did not show any activity on CD curve analysis. Therefore we supposed the compound XI was racemate. The methylation of XI was tried by Mannich reaction and following reduction in three steps[15] XIII→XIV→XV→XVI.

The methylated dimer of XI was identified with biphenyl dimer XVI which obtained from oxidation of γ-tocopherol model compound with *p*-benzoquinone[13] in all respect.

Experimental[24]

Material——δ-Tocopherol (I) was isolated from natural source as previously described.[15] The purity was examined on TLC, IR, UV, NMR, mass spectrum, and gass-liquid chromatgraphy.[15] The UV absorption intensity of (I) was as follows: UV λ_{max}^{EtOH} mμ ($E_{1cm}^{1\%}$) 298 (90.5).

Oxidation of δ-Tochophenol with $AgNO_3$——δ-Tocopherol (I, 4.0 g, 10 mmoles) was dissolved in EtOH (400 ml). To the solution $AgNO_3$ (10 g, 59 mmoles) was added. The mixture was stirred and warmed at 50—55° for 2.5 hr. The reaction mixture was added to crushed ice, then extracted with hexane (500 ml×2). The organic layer was washed with saturated aqueous NaCl solution, and water. The washed organic layer was dried over Na_2SO_4, and evaporated *in vacuo*. Reddish-colored oil residue (3.8 g) was obtained. The crude product was separated by chromatography on a column of silica gel (100 ml) packed in hexane. Compound III was eluted with 45% benzene–hexane, VII was with 70—80% benzene–hexane, unchanged δ-tocopherol was with benzene, and IX was with 5% ether–benzene. Each fraction was purified further with preparative TLC using benzene–AcOEt 95:5 as developing solvent. The acetylation of the isolated product was performed with Ac_2O–pyridine (2:1) at room temperature for one night. The reaction mixture was evaporated *in vacuo*. The residual oil was purified by preparative TLC.

5-(δ-Tocopheryloxy)-δ-tocopherol (III)——*Anal.* Calcd. for $C_{54}H_{90}O_4$: C, 80.73; H, 11.29. Found: C, 80.44; H, 11.20. IR ν_{max}^{liq} cm^{-1}: 3580, 1602, 1210, 1160, 1098, 940, 850. UV λ_{max}^{EtOH} mμ ($E_{1cm}^{1\%}$) 295 (103.0). TLC: *Rf* 0.71 (benzene–AcOEt 95:5). NMR τ: 3.40 (1H, s, Ar-H, at position 7), 3.57 (1H, d, Ar-H, at position 7'), 3.75 (1H, d, Ar-H, at position 5'), 7.50 (4H, broad, two Ar-CH_2-), 7.90 and 7.94 (6H, two s, two Ar-CH_3). Mass Spectrum *m/e*: 803 (M^+), 578 (M^+ −225),[25] 402.

5-(δ-Tocopheryloxy)-δ-tocopheryl Acetate (IV)——*Anal.* Calcd. for $C_{56}H_{92}O_5$: C, 79.56; H, 10.97. Found: C, 79.72; H, 10.82. IR ν_{max}^{liq} cm^{-1}: 1768, 1600, 1200, 1150, 1008. UV λ_{max}^{EtOH} mμ ($E_{1cm}^{1\%}$) 288 (80.8), 300 (shoulder). TLC: *Rf* 0.74 ($CHCl_3$). NMR τ: 3.34 (1H, s, Ar-H, at position 7), 3.58 (1H, d, Ar-H, at position 7', *J*=3Hz), 3.82 (1H, d, Ar-H, at position 5', *J*=3Hz), 7.40 (4H, broad, two Ar-CH_2-), 7.86 and 7.93 (6H, two s, two Ar-CH_3), 8.14 (3H, s, CH_3CO-). Mass Spectrum *m/e*: 845 (M^+), 803 (M^+ −42).

R-(+)-5-(δ-Tocopherol-5'-yl)-δ-tocopherol (VII)——*Anal.* Calcd. for $C_{54}H_{90}O_4$; C, 80.73; H, 11.29. Found: C, 80.14; H, 11.07. IR ν_{max}^{liq} cm^{-1}: 3560, 3500, 1610, 1582, 1222, 1180, 1158, 938, 860. UV λ_{max}^{EtOH} mμ ($E_{1cm}^{1\%}$) 304 (122.0). $[\alpha]_D^{25}$=+32.7° (*c*=2.51, EtOH). TLC: *Rf* 0.58 (benzene–AcOEt, 95:5). NMR τ: 3.36 (2H, s, two Ar-H), 7.60—8.00 (4H, broad, two Ar-CH_2-), 7.84 (6H, s, two Ar-CH_3), 8.32 (4H, t, protons at position 3 and 3'). Mass Spectrum *m/e*: 803 (M^+), 578 (M^+ −225), 538 (M^+ −225—40).

Acetate of Compound VII (VIII)——*Anal.* Calcd. for $C_{58}H_{94}O_6$: C, 78.50; H, 10.67. Found: C, 78.21; H, 10.67. IR ν_{max}^{liq} cm^{-1}: 1754, 1200, 1160, 1002, 940. UV λ_{max}^{EtOH} mμ ($E_{1cm}^{1\%}$) 289 (84.7), 282 (shoulder). TLC: *Rf* 0.61 ($CHCl_3$). NMR τ: 3.34 (2H, s, two Ar-H), 7.40—8.00 (4H, broad, two Ar-CH_2-), 7.83 (6H, s, two Ar-CH_3), 8.18 (6H, s, two CH_3CO-). Mass Spectrum *m/e*: 887 (M^+), 845 (M^+ −42).

S-(+)-5-(δ-Tocopherol-5'-yl)-δ-tocopherol (IX)——*Anal.* Calcd. for $C_{54}H_{90}O_4$: C, 80.73; H, 11.29. Found: C, 80.40; H, 11.27. IR ν_{max}^{liq} cm^{-1}: 3550, 3440, 1610, 1580, 1220, 1150, 856. UV λ_{max}^{EtOH} mμ ($E_{1cm}^{1\%}$) 304 (122.0). $[\alpha]_D^{25}$=+44.4° (*c*=6.93, EtOH). TLC: *Rf* 0.31 (benzene–AcOEt 95:5). NMR τ: 3.36 (2H, s, two Ar-H), 7.60—8.00 (4H, broad, two Ar-CH_2-), 7.84 (6H, s, two Ar-CH_3), 8.32 (4H, t, protons at position 3 and 3') Mass Spectrum *m/e*: 803 (M^+), 578 (M^+ −225).

Acetate of IX (X)——*Anal.* Calcd. for $C_{58}H_{94}O_6$: C, 78.50; H, 10.67. Found: C, 78.35; H, 10.59. IR ν_{max}^{liq} cm^{-1}: 1762, 1208, 1168, 1018, 950. UV λ_{max}^{EtOH} mμ ($E_{1cm}^{1\%}$) 289 (86.2), 282 (shoulder). TLC: *Rf* 0.28 ($CHCl_3$). NMR τ: 3.52 (2H, s, two Ar-H), 7.83 (10H, broad, two $ArCH_2$- and two Ar-CH_3), 8.12 (6H, s, two CH_3CO-), 8.36 (4H, t, protons at position 3 and 3'). Mass Spectrum *m/e*: 887 (M^+), 845 (M^+ −42).

6-Acetyl-2,2,8-trimethylchroman (XVI)——To a mixture of 4-hydroxy-3-methyl-acetophenone (150 g, 1.0 mole), isopropylether (1,500 ml) and conc. H_2SO_4 (50 ml), 1,1'-dimethyl allylalcohol (344 g, 4.0 moles) was added dropwise under stirring at refluxing temperature. The addition was completed in 3 hr and the reaction was continued further for 3 hr. After cooling the reaction mixture was washed with water, diluted aqueous $NaHCO_3$ solution, and water successively. The washed organic layer was dried over Na_2SO_4 and evaporated *in vacuo*. A brown colored oil residue (345 g) was obtained. The product was crystallized out from petroleum ether as white crystal, mp 61—62°. Yield 156 g (71%). *Anal.* Calcd. for $C_{14}H_{18}O_2$: C, 77.13; H, 8.32. Found: C, 77.34; H, 8.45. IR ν_{max}^{Nujol} cm^{-1}: 1678, 1200, 1160, 1122, 942, 876, 740. TLC:

24) Melting points were measured on a Yanagimoto micromelting point apparatus and uncorrected. The UV absorption spectra were measured with a Hitachi EPS-3T and Shimazu QV-50 spectrophotometer. Hitachi 215 spectrometer was used for IR absorption spectra. The NMR spectra were recorded on a JEOL C-100 HL (100 Mc) spectrometer using $CDCl_3$ solution. Chemical shifts are expressed on τ value. Abbreviation used s, singlet, d, doublet, and t, triplet. The mass spectra were recorded on a JMS-01 SG-2 instrument. The CD curves were measured with JASCO J-20 instrument.
The specific rotations were determined with JASCO DIP-LS instrument.

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Rf 0.36 ($CHCl_3$). NMR τ: 2.24 (2H, s, Ar-H), 7.16 (2H, t, Ar-CH_2-, J=6 Hz), 7.56 (3H, s, CH_3CO-), 7.80 (3H, s, Ar-CH_3), 8.16 (2H, t, protons at position 3, J=6 Hz), 8.63 (6H, s, gem CH_3).

6-Acetoxy-2,2,8-trimethylchroman (XVII)——To a solution of 6-acetyl-2,2,8-trimethylchroman (XVI, 20 g, 0.092 mole), AcOH (160 ml), and water (30 ml), peracetic acid (40%, 30 ml) was added at room temperature and left over night. The reaction mixture was poured into water and residual peracid was decomposed with $NaHSO_3$. The solution was extracted with AcOEt and washed with water, diluted aqueous $NaHCO_3$ solution, and water. The washed organic layer was dried over Na_2SO_4 and evaporated *in vacuo*. A brown-orange colored oil residue was obtained. The purification was performed on a column of silica gel (400 ml). The pure compound was eluted with 10—20% benzene–hexane. An orange-colored oil (16.4 g, 75%) was obtained. *Anal.* Calcd. for $C_{14}H_{18}O_3$: C, 71.85; H, 7.75. Found: C, 71.84; H, 7.69. IR ν_{max}^{liq} cm^{-1}: 1775, 1600, 1200, 1160, 1120, 1018, 937, 885, 720. UV λ_{max}^{EtOH} mμ ($E_{1cm}^{1\%}$) 288 (60.9), 281 (shoulder). TLC: *Rf* 0.60 (benzene–AcOEt 95:5). NMR τ: 3.35 and 3.38 (2H, two d, two Ar-H), 7.25 (2H, t, Ar-CH_2-, J=6 Hz), 7.84 and 7.86 (6H, two s, CH_3CO- and Ar-CH_3), 8.24 (2H, t, protons at position 3, J= 6 Hz,), 8.68 (6H, s, gem CH_3).

6-Hydroxy-2,2,8-trimethylchroman (δ-Tocopherol model, II)——In the flask was placed absolute ether (400 ml) and $LiAlH_4$ (6.7 g, 0.18 mole). A solution of 6-acetoxy-2,2,8-trimethylchroman (XVII, 41 g, 0.17 mole) in absolute ether (100 ml) was added from a dropping funnel. The process was completed in about one hour. 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 (32 g) was obtained as pale brown solid. Recrystallization from hexane affored white crystal, mp 81—82° (lit.[21] 83—84°).

Oxidation of 6-Hydroxy-2,2,8-trimethylchroman (II) with $AgNO_3$——A mixture of 6-hydroxy-2,2,8-trimethylchroman (II, 4.0 g, 21 mmoles), $AgNO_3$ (4.8 g, 28 mmoles), and EtOH (400 ml) was heated at 50—55°, for half an hour. The reaction mixture was added to ice-water saturated with NaCl, and extracted with AcOEt (500 ml×2). The organic layer was washed with satd. aqueous NaCl solution, water, and dried with Na_2SO_4. The dried organic solution was concentrated *in vacuo*. A reddish-brown oil (3.9 g) was obtained.

5-(6′-Hydroxy-2′,2′,8′-trimethylchroman-5′-yl)-6-hydroxy-2,2,8-trimethylchroman (XI)——The crude oxidation product of II was dissolved in 5% benzene–hexane (200 ml) and kept in refrigerator over night. 5-(6′-Hydroxy-2′,2′,8′-trimethylchroman-5′-yl)-6-hydroxy-2,2,8-trimethylchroman (XI, 1.0 g) was crystallized out from hexane, mp 224—225°. *Anal.* Calcd. for $C_{24}H_{30}O_4$: C, 75.36; H, 7.91. Found: C, 75.66; H, 7.84. IR ν_{max}^{Nujol} cm^{-1}: 3502, 1588, 1280, 1160, 1124, 1004. TLC: *Rf* 0.24 (benzene–AcOEt 95:5). NMR τ: 3.30 (2H, s, two Ar-H), 7.78 (10H, two Ar-CH_2- and two Ar-CH_3), 8.30 (4H, t, protons at position 3 and 3′, J=6 Hz), 8.80 (12H, s, two gem CH_3). Mass Spectrum *m/e*: 382 (M^+), 326 (M^+ −56), 311, 186.

5-(6′-Acetoxy-2′,2′,8′-trimethylchroman-5′-yl)-6-acetoxy-2,2,8-trimethylchroman (XII)——5-(6′-Hydroxy-2′,2′,8′-trimethylchroman-5′-yl)-6-hydroxy-2,2,8-trimethylchroman. (XI, 300 mg, 0.78 mmole) was acetylated with Ac_2O (10 ml) and pyridine (5 ml) at room temperature for one night. The reaction mixture was evaporated *in vacuo*. Crystallized from MeOH afforded white crystal, mp 60—61°. *Anal.* Calcd. for $C_{28}H_{34}O_6$: C, 72.08; H, 7.35. Found: C, 72.30; H, 7.29. IR ν_{max}^{Nujol} cm^{-1}: 1758, 1200 (broad), 1124, 1022. TLC: *Rf* 0.46 (benzene–AcOEt 95:5). NMR τ: 3.22 (2H, s, two Ar-H), 7.80 (10H, two Ar-CH_2- and two Ar-CH_3), 8.08 (6H, s, two CH_3CO-), 8.33 (4H, t, protons at position 3 and 3′), 8.68 (12H, s, two gemCH_3). Mass Spectrum *m/e*: 466 (M^+), 424 (M^+ −42).

5-(2′,2′,8′-Trimethyl-6′-chromanoxy)-6-hydroxy-2,2,8-trimethylchroman (V)——After separation of compound (XI) the mother liquor of the oxidation product was concentrated *in vacuo*. The residue was chromatographed on a column of silica gel (120 ml). 5-(2′,2′,8′-Trimethyl-6′-chromanoxy)-6-hydroxy-2,2,8-trimethylchroman (V) was eluted in benzene–hexane (6:4). Recrystallized from petroleum ether afforded 0.2 g of yellow crystal, mp 125—126°. *Anal.* Calcd. for $C_{24}H_{30}O_4$: C, 75.36; H, 7.91. Found: C, 75.40; H, 7.97. IR ν_{max}^{Nujol} cm^{-1}: 3580, 1600, 1200, 1160, 1018, 990. TLC: *Rf* 0.52 (benzene–AcOEt 95:5). NMR τ: 3.32 (1H, s, Ar-H, at position 7), 3.47 (1H, d, Ar-H, at position 7′), 3.66 (1H, d, Ar-H, at position 5′), 7.36 and 7.52 (4H, two t, two Ar-CH_2-), 7.88 and 7.92 (6H, two s, two Ar-CH_3), 8.29 and 8.36 (4H, two t, two methylene protons at position 3 and 3′, J=3 Hz), 8.72 and 8.76 (12H, two s, two gemCH_3). Mass Spectrum *m/e*: 382 (M^+).

5-(2′,2′,8′-Trimethyl-6-chromanoxy)-6-acetoxy-2,2,8-trimethylchroman (VI)——A mixture of 5-(2′,2′,8′-trimethyl-6-chromanoxy)-6-hydroxy-2,2,8-trimethylchroman (V, 200 mg, 0.52 mmole), Ac_2O (4 ml), and pyridine (2 ml) was left over night at room temperature. The reaction mixture was evaporated *in vacuo*. The residue was crystallized from hexane. The pure product (180 mg, 82%) was obtained as white crystal, mp 162—163°. *Anal.* Calcd. for $C_{26}H_{32}O_5$: C, 73.55; H, 7.59. Found: C, 73.35, H, 7.58. IR ν_{max}^{Nujol} cm^{-1}: 1748, 1600, 1216, 1200, 1158, 1116, 1016, 848. TLC: *Rf* 0.53 (benzene–AcOEt 95:5). NMR τ: 3.24 (1H, s, Ar-H, at position 7), 3.48 (1H, d, Ar-H, at position 7′, J=2 Hz), 3.66 (1H, d, Ar-H, at position 5, J=2 Hz,), 7.34 and 7.40 (4H, two t, Ar-CH_2-), 7.84 and 7.90 (6H, two s, two Ar-CH_3), 8.00 (3H, s, CH_3CO-), 8.26

and 8.30 (4H, two t, protons at position 3 and 3'), 8.71 (12H, s, two gem CH_3). Mass Spectrum *m/e*: 424 (M^+), 382 ($M^+ -42$).

5-(6'-Hydroxy-7'-morpholinomethyl-2',2',8'-trimethylchroman-5'-yl)-6-hydroxy-7-morpholinomethyl-2,2,8-trimethylchroman (XIII)——To a mixture of 5-(6'-hydroxy-2,2,8-trimethylchroman-5'-yl)-6-hydroxy-2,2,8-timethylchroman (XI, 500 mg, 1.3 mmoles), morpholine (1 ml), and dioxane (10 ml), formaldehyde solution (37%, 3 ml) was added dropwise under cooling with ice, then the reaction mixture was refluxed for 6 hr, concentrated *in vacuo* and the residual oil was dissolved in AcOEt (100 ml). The organic solution was washed with water, dried over Na_2SO_4, and evaporated *in vacuo*. Crystallization from MeOH gave white crystal (XIII, 420 mg, 55%), mp 234—235°. *Anal.* Calcd. for $C_{24}H_{48}O_6N_2$: C, 70.31; H, 8.33; N, 4.82. Found: C, 69.98; H, 8.28; N, 4.82. IR ν_{max}^{Nujol} cm^{-1}: 3400—2600 (broad), 1616, 1165, 1115, 1060. TLC: *Rf* 0.38 (benzene–AcOEt 7:3). NMR τ: 6.28 (12H, broad, two Ar-CH_2-, at position 7 and 7' and two -CH_2-O-CH_2-), 7.42 (8H, broad, two -CH_2-N-CH_2-). Mass Spectrum *m/e*: 580 (M^+), 493, 481.

5-(6'-Acetoxy-7'-acetoxymethyl-2',2',8'-trimethylchroman-5'-yl)-6-acetoxy-7-acetoxymethyl-2,2,8-trimethylchroman (XIV)——A mixture of 5-(6'-hydroxy-7'-morpholinomethyl-2',2',8'-trimethylchroman-5'-yl)-6-hydroxy-7-morpholinomethyl-2,2,8-trimethylchroman (XIII, 300 mg, 0.5 mmole), Ac_2O (8 ml), AcOH (4 ml), AcONa (0.2 g), and zinc dust (0.3 g) was stirred and refluxed for 5 hr. After cooling the reaction mixture was poured into ice-water, and extracted with ether (100 ml). The ether layer was washed with water, 5% aqueous $NaHCO_3$ solution, water, and dried over Na_2SO_4. The dried organic solution was evaporated *in vacuo*. The residual solid was crystallized from MeOH. White crystal (XIV, 240 mg, 76%) was obtained, mp 134—135°. *Anal.* Calcd. for $C_{34}H_{42}O_{10}$: C, 66.87; H, 6.93. Found: C, 66.76; H, 6.97. IR ν_{max}^{Nujol} cm^{-1}: 1760, 1740, 1230, 1200, 1164, 1072, 1010. TLC: *Rf* 0.23 (benzene–AcOEt 95:5). NMR τ: 4.92 and 4.96 (4H, two s, two Ar-CH_2-, at position 7 and 7'), 7.76 (10H, broad, two Ar-CH_3 and two Ar-CH_2-, at position 4 and 4'), 7.96 and 8.16 (12H, two s, four CH_3-CO-), 8.15 (4H, t, protons at position 3 and 3', J=6 Hz), 8.70 (12H, s, two gem CH_3). Mass Spectum: *m/e* 610 (M^+), 568 ($M^+ -42$), 508 ($M^+ -102$), 448, 406.

5-(6'-Hydroxy-7'-hydroxymethyl-2',2',8'-trimethylchroman-5'-yl)-6-hydroxy-7-hydroxymethyl-2,2,8-trimethylchroman (XV)——Reductive cleavage of 5-(6'-acetoxy-7'-acetoxymethyl-2',2',8'-trimethylchroman-5'-yl)-6-acetoxy-7-acetoxymethyl-2,2,8-trimethylchroman (XIV, 610 mg, 1 mmole) was carried out with $LiAlH_4$ (380 mg, 10 mmoles) under the condition as previously described.[15] The pure product (XV, 340 mg, 79%) was obtained by recrystallization form bezene–MeOH as white crystal, mp 213—214°. *Anal.* Calcd. for $C_{26}H_{34}O_6$: C, 70.56; H, 7.74. Found: C, 70.63; H, 7.90. IR ν_{max}^{Nujol} cm^{-1}: 3550, 3440, 1558, 1200, 1148, 1056. TLC: *Rf* 0.10 (benzene–AcOEt 7:3). NMR τ: 5.18 (4H, s, $ArCH_2$-, at position 7 and 7'), 7.77 (10H, broad, two Ar-CH_2- at position 4 and 4', and two Ar-CH_3), 8.23 (4H, t, protons at position 3 and 3'), 8.71 (12H, s, two gem CH_3). Mass Spectrum *m/e*: 442 (M^+), 424 ($M^+ -18$), 406 ($M^+ -18—18$).

5-(6'-Hydroxy-2',2',7',8'-tetramethylchroman-5'-yl)-6-hydroxy-2,2,7,8-tetramethylchroman (XVI)——To a solution of 5-(6'-hydroxy-7'-hydroxymethyl-2',2',8'-trimethylchroman-5'-yl)-6-hydroxy-7-hydroxymethyl-2,2,8-trimethylchroman (XV, 440 mg, 1 mmole) in toluene (20 ml), conc. HCl (4 ml) and zinc dust (1.0 g) were added under vigorous stirring at 5—8°. The reaction completed within an hour. Ether (50 ml) was added to the reaction mixture. The organic layer was washed with water, diluted aqueous $NaHCO_3$ solution, water, dried over Na_2SO_4 and evaporated *in vacuo*. The crude product (solid) was purified by preparative TLC (benzene–AcOEt 95:5) and recrystallized from hexane. The pure product (XVI, 300 mg, 73%) was obtained as white crystal, mp 192—193°. Mixed mp with biphenyl dimer of γ-tocopherol model[13] did not show any depression. IR ν_{max}^{Nujol} cm^{-1}: 3504, 1196, 1168, 1120, 1076. TLC: *Rf* 0.50 (benzene–AcOEt 95:5). NMR τ: 7.83 (10H, broad, two Ar-CH_2-, and two Ar-CH_3), 8.34 (4H, t, protons at position 3 and 3', J=6 Hz), 8.72 (12H, s, two gem CH_3). Mass Spectrum *m/e*: 410 (M^+), 354 ($M^+ -56$).

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