in 5 min or less. Products were analyzed both by GC (50 m, 0.2 mm i.d. HP Pona column, cross-linked methylsilicone with a 0.5 μm film thickness) and by HPLC (25 cm, 4 mm, Lichrosorb Si 60 (10 μm) column eluted over 30 min with a graded hexane/chloroform mixture (100% hexane → 100% $CHCl_3$) and detection by UV absorption at 290 nm).

The same system was used with **8d**.

EPR Kinetic Measurements. These were carried out following previously described procedures.[15,26,27]

Acknowledgment. We thank Professors A. L. J Beckwith and H. Fischer for communicating some of their unpublished data to us.

Registry No. **1**, 1192-18-3; **2**, 822-50-4; **3**, 108-87-2; **4**, 592-76-7; **7·**, 38295-12-4; **8a**, 108743-45-9; **12**, 15424-05-2; *n*-Bu_3SnH, 688-73-3; *n*-Bu_3GeH, 998-39-0; 1-methyl-5-hexenyl radical, 38295-10-2; cyclopropane, 75-19-4; 4-pentenylmagnesium bromide, 34164-50-6; acetone, 67-64-1; 2-methylhept-6-en-2-ol, 77437-98-0; 6-bromohept-1-ene, 38334-98-4.

Supplementary Material Available: Tables VI–IX giving detailed product ratios for the 6-bromohept-1-ene/*n*-Bu_3GeH reaction, kinetic data for calibration of the 1-methyl-5-hexenyl radical clock, and some product ratios for the 2-bromo-2-methylhept-6-ene/*n*-Bu_3GeH reaction (4 pages). Ordering information is given on any current masthead page.

Oxygenations of Vitamin E (α-Tocopherol) and Its Model Compound 2,2,5,7,8-Pentamethylchroman-6-ol in the Presence of the Superoxide Radical Solubilized in Aprotic Solvents: Unique Epoxidations and Recyclizations[1]

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Vitamin E (**1a**, α-tocopherol) and its model compound 2,2,5,7,8-pentamethylchroman-6-ol (**1b**) were oxygenated in aprotic solvents in the presence of the solubilized superoxide radical under an oxygen atmosphere to give diepoxides **2a** and **2b** as main products, respectively. The reactions proceeded only slightly under anaerobic conditions. Extensive product analysis was carried out on the oxygenation of **1b**, revealing that it gave rise to the products **2b**, **3b**, **4b**, **5b**, **6b**, and **7b**. The novel compounds were determined to be 4a,5;7,8-diepoxy-4a,7,8,8a-tetrahydro-8a-hydroxy-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6(5*H*)-one (**2a**), 4a,5;-7,8-diepoxy-4a,7,8,8a-tetrahydro-8a-hydroxy-2,2,5,7,8-pentamethylchroman-6(5*H*)-one (**2b**), 1,1-dimethyl-3-(2,3-epoxy-2,3,5-trimethylbenzoquinon-6-yl)propanol (**5b**), 6-acetyl-7,8-epoxy-6-hydroxy-2,2,7,8-tetramethyl-1-oxaspiro[4.5]nonan-9-one (**6b**), and 6-acetyl-6-hydroxy-2,2,7,8-tetramethyl-1-oxaspiro[4.5]non-7-en-9-one (**7b**); the previously suggested structures of **6b** and **7b** should be revised. Compounds **6b** and **7b** are unique spiro compounds containing two five-membered rings. The structures of **2b**, **5b**, and **6b** were confirmed by X-ray crystallography. The reactions are suggested to be superoxide-catalyzed oxygenations, being characteristic of epoxidations and recyclizations, in which hydroperoxides **9a** and **9b** may be key intermediates. Possible reaction pathways for the formation of the products are discussed.

Currently, vitamin E (mainly α-tocopherol) attracts increasing attention as an efficient biological antioxidant playing an important role in the protection of organisms against oxidative damage.[2,3] From a chemical point of view, it is of great interest that α-tocopherol is very reactive not only toward the peroxyl radical,[4,5] i.e., exhibiting a high chain-breaking antioxidant activity, but also toward a variety of radicals and related reaction species. For example, α-tocopherol traps some radicals generated from radical reaction initiators, such as benzoyl peroxide[6,7] and 2,2′-azobis(isobutyronitrile),[8,9] and reacts with the alkyl and alkoxyl radicals to give the alkylated derivatives.[10,11] With α-tocopherol, singlet oxygen is quenched into triplet oxygen[12] and also reacts chemically to yield a hydroperoxide.[13,14] Further, it has been found that the reactions of α-tocopherol and its model compounds occur in the presence of the superoxide radical,[1,15-19] a causative agent

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of lipid peroxidation in vivo.[20] Presumably, the wide range of reactivity of α-tocopherol is the reason it is an excellent biological protector against oxidative stress, inhibiting the various kinds of initiations as well as the propagations, of radical reactions in vivo. Therefore, detailed studies on the reaction of α-tocopherol with radicals and related reaction species are of considerable importance for the understanding of the chemistry of vitamin E and also of its biological action.

We have attempted to elucidate the reaction of α-tocopherol with the superoxide radical. Recently, we showed that α-tocopherol and its model compound were oxygenated in tetrahydrofuran containing suspended potassium superoxide.[16,19] In addition, we report that in aprotic solvents containing the solubilized superoxide radical and molecular oxygen α-tocopherol (**1a**) and its model compound 2,2,5,7,8-pentamethylchroman-6-ol (**1b**) were epoxidized and recyclized unusually through reaction pathways different from those in the above oxygenation and that diepoxides **2a** and **2b** and spiro compounds **6b** and **7b** having unique structures were formed in the reactions. The results described here indicate the diversity and flexibility of the properties of α-tocopherol and reveal a novel aspect of its chemistry. The structures of α-tocopherol and its related compounds are shown in Scheme I.

Results

Oxygenation of Vitamin E Model Compound 2,2,5,7,8-Pentamethylchroman-6-ol in Acetonitrile in the Presence of Potassium Superoxide Solubilized with Dicyclohexano-18-crown-6. A solution of **1b** in acetonitrile was added dropwise under an oxygen atmosphere at room temperature to a solution of equimolar potassium superoxide in acetonitrile containing dicyclohexano-18-crown-6. After the reaction was stopped, six products (**2b**, **3b**, **4b**, **5b**, **6b**, **7b**) were isolated by silica gel column chromatography and high-performance liquid chromatography (HPLC; Table I, run 1). At 4 °C, the recovery of the starting material and the yields of **3b** and **4b** were increased, but no **6b** and **7b** were isolated (run 2). Further, at −30 °C, neither **2b**, **6b**, nor **7b** was produced (run 3). When the twofold molar amount of potassium superoxide was used, no **2b** was isolated (run 4). When the reaction was carried out under anaerobic conditions, the starting material accompanying a small amount of **6b** and **7b** was recovered in more than 89% yield (run 5).

The main product **2b** was obtained as colorless needles. The elemental analysis ($C_{14}H_{20}O_5$) and mass (MS) spectral [m/z 268 (M^+)] data indicate that **2b** has a structure corresponding to that of **1b** with three additional oxygen atoms. From its nuclear magnetic resonance (NMR), infrared (IR), and ultraviolet (UV) spectra, **2b** is shown to have five methyl groups attached to sp^3 carbon atoms (^1H NMR δ 1.27, 1.44, 1.47, 1.49, 1.54; ^{13}C NMR δ 11.3, 12.2, 12.6, 28.9, 31.2), a ketonic group (IR ν 1725 cm^{-1}; ^{13}C NMR δ 200.1), a hydroxy group (IR ν 3445 cm^{-1}; ^1H NMR δ 3.02), two epoxy groups (^{13}C NMR δ 61.0, 61.9, 64.8, 66.8), two adjacent methylene groups (^1H NMR δ 1.58–2.16; ^{13}C NMR δ 22.6, 31.4), six quaternary sp^3 carbon atoms bonding one or two oxygen atoms (^{13}C NMR δ 61.0, 61.9,

Table I. Oxygenations of 1b with the Superoxide Radical under the Different Reaction Conditions and Reactions of 4b and 9b in Acetonitrile Containing Solubilized Potassium Superoxide

run	compd	source of O_2^-	O_2^-/compd[a]	gas phase	solvent	reactn temp, °C	yield, % 2b	3b	4b	5b	6b	7b	8b	1b rec, %
1	**1b**	KC[b]	1	O_2	CH_3CN	rt[c]	12	6	6	6	6	5		12
2	**1b**	KC	1	O_2	CH_3CN	4	2	12	17					49
3	**1b**	KC	1	O_2	CH_3CN	−30		2	13					84
4	**1b**	KC	2	O_2	CH_3CN	rt		5	5		12	6		5
5	**1b**	KC	1	Ar	CH_3CN	rt					2	2		~89
6	**1b**	E[d]	1	O_2	CH_3CN	rt	20	8	8	8	tr[e]	5		13
7	**1b**	E	1	N_2	CH_3CN	rt	tr							~95
8	**1b**	KC	1	O_2	THF	rt	3	2	2	tr	tr	3		51
9	**1b**	KC	1	O_2	benzene	rt	3	3	3	tr	2	3		15
10	**1b**	KC	1	O_2	pyridine	rt	tr	1	1				11	18
11	**1b**	KC	1	O_2	pyridine	4	10	2	2					12
12	**1b**	K[f]	3	O_2	CH_3CN	rt							18	9
13	**4b**	KC	1	O_2	CH_3CN	rt			10[g]			30		
14	**9b**	KC	1	O_2	CH_3CN	rt	3	tr	tr	tr	4	10		

[a] Molar ratio. [b] KO_2 solubilized with crown ether. [c] Room temperature. [d] Electrochemical reduction of O_2. [e] Trace. [f] KO_2 suspended. [g] The starting material recovered.

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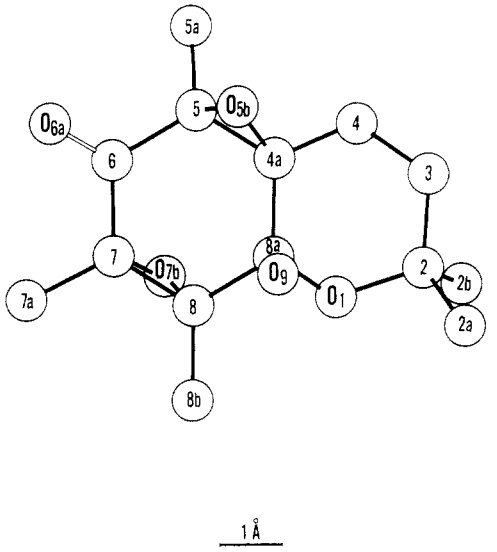

Figure 1. Molecular structure of **2b**.

64.8, 66.8, 73.9, 94.0), and no double bonds (UV, no absorption; ^{13}C NMR, no signals of aromatic carbon atoms). These results suggest that **2b** is 4a,5;7,8-diepoxy-4a,7,8,8a-tetrahydro-8a-hydroxy-2,2,5,7,8-pentamethylchroman-6(5*H*)-one.

The structure of **2b** was confirmed by X-ray crystallographic analysis as has been communicated preliminarily.[1] Figure 1 shows the molecular structure. The crystal data are given in the Experimental Section. The crystal of **2b** consists of pairs of the enantiomers on the chirality of C_{8a}. In the crystal, a pair of the enantiomers face each other in their different faces, their molecular planes being parallel and long axes being crossed at nearly right angles. Hydrogen bonding is found to be formed between a hydroxy group in one molecule and an epoxy group at C_7 and C_8 in a second molecule [$O_9 \cdots O_{7b}$, 2.872 (8) Å]. As shown in Figure 1, the configurational relationship between the two epoxy groups in **2b** is trans and that between the epoxy group at C_{4a} and C_5 and the hydroxy group at C_{8a} is cis, suggesting, as will be discussed later, that the two oxygen atoms of the epoxy and hydroxy groups are derived from a single oxygen molecule.

The ^1H NMR spectrum of **2b** at room temperature shows five signals due to methyl groups as described above. However, the spectrum taken at 40 °C shows four additional signals at δ 1.24, 1.42, 1.56, and 1.58 due to methyl groups. With an increase in temperature, the intensity of the additional signals increased and that of the original signals decreased. After the sample was cooled to room temperature, the original signal reverted and the additional signals disappeared. These results imply that a conformational change in **2b** occurs at higher temperature.

By comparison of the spectral data with those of an authentic sample, **3b** was identified as 1,1-dimethyl-3-(3,5,6-trimethylbenzoquinon-2-yl)propanol and, with the literature data, **4b** as 1,1-dimethyl-3-(2,3-epoxy-3,5,6-trimethylbenzoquinon-2-yl)propanol.[21] Furthermore, on the basis of the spectral data in the Experimental Section, **5b** was determined to be 1,1-dimethyl-3-(2,3-epoxy-2,3,5-trimethylbenzoquinon-6-yl)propanol; it is an isomer of **4b** ($C_{14}H_{20}O_4$) and has a conjugated enedione group (UV λ 212 nm, 273; IR ν 1687 cm^{-1}; ^{13}C NMR δ 140.6, 145.0, 194.4, 194.6), an epoxy group [^{13}C NMR δ 63.1 (2 C)], three methyl groups attached to either an epoxy group or a sp^2 carbon atom [^1H NMR δ 1.60 (6 H), 2.00; ^{13}C NMR δ 11.4 (2 C), 12.9], two adjacent methylene groups (^1H NMR δ 1.38–1.70, 2.34–2.84; ^{13}C NMR δ 22.5, 41.9), a quaternary carbon atom attached to an oxygen atom (^{13}C NMR δ 70.7), two methyl groups attached to an sp^3 carbon atom [^1H NMR δ 1.27 (6 H); ^{13}C NMR δ 29.0, 29.1], and a hydroxyl group (IR ν 3360 cm^{-1}; ^1H NMR δ 1.38–1.70). The structure of **5b** was confirmed by X-ray crystallographic analysis. The configuration of an epoxide group in **5b** was found to be cis. The crystal data are shown in the Experimental Section.

The structures of products **6b** and **7b** were deduced from their spectral and elemental analysis data. The molecular formulas of **6b** and **2b** are identical [$C_{14}H_{20}O_5$, MS, m/z 268 (M^+)], as are those of **7b** and **4b** [$C_{14}H_{20}O_4$, MS, m/z 252 (M^+)]. The rate-of-flow (RF) values of **6b** and **7b** on thin-layer chromatographic analysis are close to that of **2b** and much larger than those of **3b**, **4b**, and **5b**. This suggests that **6b** and **7b** are bicyclic compounds and not monocyclic ones such as the benzoquinone derivatives **3b**, **4b**, and **5b**. Both **6b** and **7b** have the following functional groups: two ketonic groups (^{13}C NMR δ 204.9, 209.1 and 204.9, 207.0, respectively), a hydroxy group (^1H NMR δ 4.58, 4.72; IR ν 3430, 3420 cm^{-1}), an ether group in a five-membered ring (IR ν 1084, 1079 cm^{-1}), and two adjacent methylene groups (^1H NMR δ 1.22–2.06, 2.31–2.72, and 1.10–2.09, 2.24–2.56; ^{13}C NMR δ 33.3, 38.4, and 33.4, 38.0). In addition, **6b** has five methyl groups attached to sp^3 carbon atoms (^1H NMR δ 1.09, 1.28, 1.31, 1.52, 2.08; ^{13}C NMR δ 7.8, 10.6, 25.8, 27.9, 28.0) and an epoxy group (^{13}C NMR δ 65.3, 69.1), and **7b** has three methyl groups attached to sp^3 carbon atoms (^1H NMR δ 1.13, 1.36, 1.84; ^{13}C NMR δ 24.9, 28.2, 28.2), two methyl groups attached to sp^2 carbon atoms (^1H NMR δ 1.84, 2.01; ^{13}C NMR δ 8.7, 11.8), and two adjacent, quaternary sp^2 carbonyl atoms linked to a ketonic group (UV λ 232 nm; ^{13}C NMR δ 139.4, 163.1). The mass spectra of **6b** and **7b** show that they have the same molecular skeleton, because ions resulting from the elimination of a common moiety from both compounds were found: for **6b**, m/z 250 [$(M - 18(H_2O))^+$], 225 [$(M - 43(CH_3CO))^+$], and 208 [$(M - 60)^+$]; for **7b**, m/z 234 [$(M - 18)^+$], 209 [$(M - 43)^+$], 192 [$(M - 60)^+$]. Also, ions having an identical mass were given by both compounds: MS, m/z 153, 137, 41. The difference of ion masses between the $(M - 18)^+$, $(M - 43)^+$, or $(M - 60)^+$ ions of both compounds is 16, which may be due to an oxygen atom of an epoxide group in **6b**. The above data suggest that **6b** is 6-acetyl-7,8-epoxy-6-hydroxy-2,2,7,8-tetramethyl-1-oxaspiro[4.5]nonan-9-one, a cyclization product of **17b**, and that **7b** is 6-acetyl-6-hydroxy-2,2,7,8-tetramethyl-1-oxaspiro-[4.5]non-7-en-9-one, a cyclization product of **4b**.

The structure of **6b** was confirmed by X-ray crystallographic analysis. It was proved that in **6b** the configuration of an epoxide group is cis, the relationship between the epoxide and hydroxy groups is cis, and that between the epoxide group and ethereal oxygen atom in a five-membered ring is trans (Scheme I). A hydrogen bond between O_{5b} and O_{8a} of the molecules at $-1/2 + x, y, 1/2 - z$ is formed with a distance of 3.019 (4) Å; the distance of $HO_{5b} \cdots O_{8b}$ is 2.17 (5) Å. The crystal data are in the Experimental Section. Although the structures of **6b** and **7b** have been suggested to be 6,7-epoxy-4a,8a,6,7-tetrahydro-4a-hydroxy-2,2,6,7,8a-pentamethylchroman-5,8-dione and 4a,8-dihydro-4a-hydroxy-2,2,6,7,8a-pentamethylchroman-5,8-dione, respectively, in a previous paper,[1] they should be revised as described above.

Oxygenation of the Vitamin E Model Compound in Acetonitrile in the Presence of the Superoxide Radical Generated from the Electrochemical Reduction

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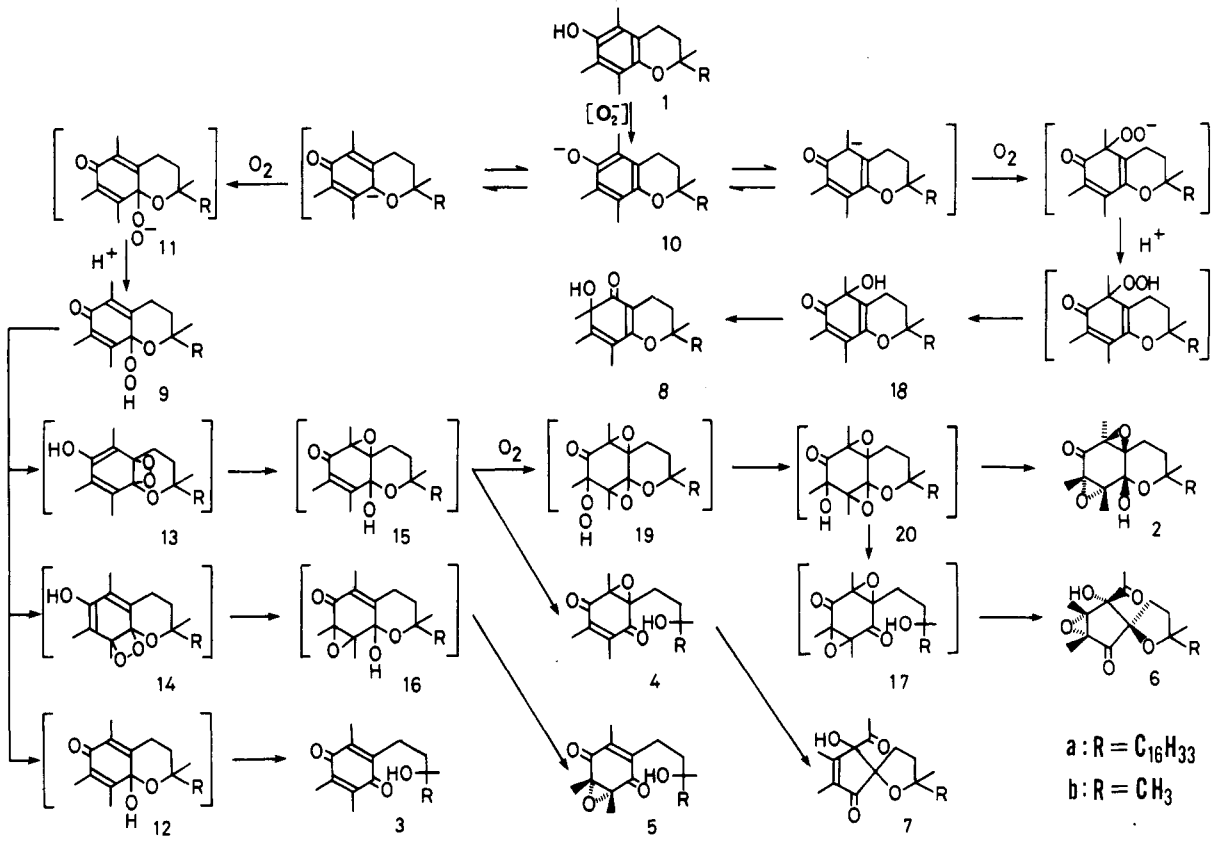
Scheme I. Possible Reaction Pathways for the Formation of the Products[a]



[a] For structures **2b**, **5b**, and **6b**, the cis–trans relationships between functional groups that were confirmed by X-ray crystallographic analysis are indicated.

of Molecular Oxygen. The superoxide radical was generated in acetonitrile from the electrochemical reduction of molecular oxygen using tetra-*n*-propylammonium perchlorate as a supporting electrolyte.[22] Immediately after 1 mM of the superoxide radical was obtained, an acetonitrile solution of **1b** was added to the radical solution. The resulting reaction products were quite similar to those from the oxygenation of **1b** in the presence of potassium superoxide solubilized with dicyclohexano-18-crown-6 (Table I, run 6). As soon as **1b** was mixed with the superoxide radical, the UV spectrum of the mixture showed an absorption maximum at 330 nm. However, this intensity decreased with time, and the spectrum eventually became featureless. When **1b** was mixed with the superoxide radical under a nitrogen atmosphere, the spectrum showed two absorption maxima at 296 nm due to **1b** and at 330 nm. The former increased and the latter decreased, until the spectrum was identical with that of **1b**. Under anaerobic conditions, only a trace of **2b** was found and **1b** was recovered almost quantitatively (Table I, run 7).

Oxygenation of the Vitamin E Model Compound in the Presence of Potassium Superoxide Solubilized in Several Aprotic Solvents Other Than Acetonitrile. The effects of several aprotic solvents on the oxygenation of **1b** in the presence of potassium superoxide solubilized with dicyclohexano-18-crown-6 were examined. Similar reaction products were obtained from the reactions in acetonitrile, tetrahydrofuran, benzene, and pyridine (Table I, runs 1 and 8–11). The reactions in dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) were too complicated for the products to be isolated.

On the other hand, when **1b** was oxygenated in acetonitrile in the presence of suspended potassium superoxide, only **8b** was formed (Table I, run 12). This product is identical with the product from the oxygenation in tetrahydrofuran containing suspended potassium superoxide as has been reported previously.[16,19] It appears that the reaction in the presence of the solubilized superoxide radical is quite different from the reaction in the presence of the suspended radical.

Intermediacy of 8a-Hydroperoxy-2,2,5,7,8-pentamethylchroman-6(8a*H*)-one and 1,1-Dimethyl-3-(2,3-epoxy-3,5,6-trimethylbenzoquinon-2-yl)propanol for the Formation of the Reaction Products. The above oxygenations were virtually stopped under anaerobic conditions (Table I, runs 5 and 7). Further, it has been found that atmospheric molecular oxygen is incorporated into α-tocopherol and its model compound in tetrahydrofuran containing suspended potassium superoxide.[16,19] Thus, these reactions are suggested to be superoxide-catalyzed oxygenations. Usually, the initial step in oxygenation is the formation of a peroxide. On the other hand, it has been found that hydroperoxide **9a** is derived from α-tocopherol by the action of singlet oxygen.[13,14] Therefore, there is a possibility that **9a** and **9b** are intermediates in the oxygenations of α-tocopherol and its model compound, respectively. The intermediacy of 8a-hydroperoxy-2,2,5,7,8-pentamethylchroman-6(8a*H*)-one (**9b**) for the formation of the reaction products was examined.

Hydroperoxide **9b** was synthesized from the reaction of **1b** with singlet oxygen.[23] Under an oxygen atmosphere, **9b** was added to the acetonitrile solution of potassium

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superoxide solubilized with dicyclohexano-18-crown-6. After being stirred for 15 min, the reaction mixture was treated as described above. By silica gel column chromatography, **2b**, **6b**, and **7b** were isolated in 3, 4, and 10% yields, respectively, and **3b**, **4b**, and **5b** in trace amounts (Table I, run 14). This shows that **9b** is a precursor of the products.

Under an oxygen atmosphere, 1,1-dimethyl-3-(2,3-epoxy-3,5,6-trimethylbenzoquinon-2-yl)propanol (**4b**) was mixed with a solution of potassium superoxide in acetonitrile containing dicyclohexano-18-crown-6. After purification of the reaction product, **7b** was isolated in 30% yield (Table I, run 13). Thus, **4b** is thought to be a precursor of **7b**.

Oxygenation of α-Tocopherol in Acetonitrile in the Presence of Potassium Superoxide Solubilized with Dicyclohexano-18-crown-6. In the presence of potassium superoxide solubilized with dicyclohexano-18-crown-6, 2-*ambo*-α-tocopherol (2-*ambo*-**1a**) was oxygenated under an oxygen atmosphere. Although the reaction was rather complicated, several products were detectable on the thin-layer chromatogram of the reaction mixture. After purification, **2a** was isolated. By high-resolution mass spectroscopy, the molecular formula of **2a** was shown to be $C_{29}H_{50}O_5$. From a comparison of the ^1H and ^{13}C NMR spectra of **2a** and those of **2b**, **2a** was determined to be 4a,5;7,8-diepoxy-4a,7,8,8a-tetrahydro-8a-hydroxy-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6(5*H*)-one. In particular, this structure is supported by the fact that the ^{13}C chemical shifts of **2a** without an isoprenoid side chain correspond to those of **2b** without a methyl group at C_2. The spectral data of **2a** are given in the Experimental Section.

Discussion

On the basis of the above data, possible reaction pathways for the formation of the products can be proposed as shown in Scheme I. In aprotic solvents, the superoxide radical functions as a Brønsted base and withdraws a phenolic proton from substrate **1** to give chromanolate anion **10**.[18] The oxygenation of the anion with molecular oxygen leads to peroxy anion **11**, the protonation of which affords hydroperoxide **9**. The hydroperoxide either is reduced to benzoquinone **3** via hydroxide **12** or undergoes the cyclization of a hydroperoxy group to yield 4a,8a-epidioxide **13** and 8,8a-epidioxide **14**. The O–O bond cleavage of the epidioxides, followed by epoxide ring formation and proton shift, gives rise to hydroxy 4a,5-epoxide **15** and hydroxy 7,8-epoxide **16**. Diepoxide **2** is formed via diepoxy hydroxide **20** from diepoxy hydroperoxide **19**, which is an oxygenation product of hydroxy epoxide **15**. Spiroepoxy ketone **6** and spiro enone **7** are produced by the cyclization of diepoxybenzoquinone **17** derived from diepoxy hydroxide **20** and by the cyclization of epoxybenzoquinone **4** from hydroxy epoxide **15**, respectively: i.e., compounds **6** and **7** are recyclization products. Another epoxybenzoquinone **5** arises by the ring cleavage of another hydroxy epoxide **16**.

On the reaction pathways, a key step seems to be the interaction between the chromanolate anion and molecular oxygen. Matsuura has described three possible mechanisms for the base-catalyzed oxygenation of phenols.[24] Mechanism 1 shows that an electron transfer between the phenolate anion (ArO^-) and molecular oxygen gives rise to both the phenoxyl ($ArO\cdot$) and superoxide radicals, and then the reaction of the resulting phenoxyl radical with molecular oxygen leads to the (oxocyclohexadienyl)peroxyl radical ($O{=}ArOO\cdot$), followed by a radical chain process (Russell mechanism[25])

$$ArO^- + O_2 \rightarrow ArO\cdot + O_2^-$$

$$ArO\cdot + O_2 \rightarrow O{=}ArOO\cdot$$

$$O{=}ArOO\cdot + ArO^- \rightarrow O{=}ArOO^- + ArO\cdot$$

where $O{=}ArOO^-$ is the (oxocyclohexadienyl)peroxy anion. In mechanism 2, the cage recombination of the phenoxyl and superoxide radicals, which have been produced from the above electron transfer, yields the peroxy anion:

$$ArO^- + O_2 \rightarrow (ArO\cdot O_2^-) \rightarrow O{=}ArOO^-$$

In mechanism 3, the interaction between the orbitals of the phenolate anion and molecular oxygen causes the perturbation of the degenerated π^* orbitals of molecular oxygen to split the level; the occupation of the resulting, elevated orbital by the anion, accompanied by spin flip, gives the peroxy anion:

$$ArO^- + O_2 \rightarrow O{=}ArOO^-$$

For the superoxide-catalyzed oxygenation of the chromanolate anion, mechanism 1 seems to be ruled out, for the α-tocopheroxyl and model radicals have been observed to be inactive toward molecular oxygen.[26] Presumably, the oxygenation proceeds by either mechanism 2 or 3.

As mentioned before, O_{5b} of an epoxy group and O_9 of a hydroxy group in diepoxide **2b** project in the same direction from the molecular plane (cis configuration), and O_9 of the hydroxy group and O_{7b} of another epoxy group project in opposite directions (trans configuration) (Figure 1). The pathway in Scheme I leads to the formation of diepoxide **2b** having this configuration, because O_{5b} and O_9 are derived from an epidioxy group in epidioxide **13b** (originally from an oxygen molecule) and because O_{7b} is introduced from a face of the molecule without the projection of O_{5b} and O_9 and hence with less steric hindrance. At first glance, another epidioxide **14b** seems also to be an intermediate of diepoxide **2b**. However, this route is unreasonable, since the configurational relationship between O_{7b} and O_9 in the diepoxide obtained through it must be cis.

Recently, we have found that substrate **1b** is converted into 4a,5-epoxy-4a,5-dihydro-8a-hydroperoxy-2,2,5,7,8-pentamethylchroman-6(8a*H*)-one (**21b**) in a *tert*-butylperoxyl radical-generating system under an oxygen atmosphere.[5] In hydroperoxy epoxide **21b**, the relationship between the epoxy group at C_{4a} and C_5 and the hydroperoxy group at C_{8a} is trans. This shows that an oxygen atom (O_{5b}) in the epoxy group and two oxygen atoms (O_9, O_{10}) in the hydroperoxy group have different origins. The relationship between O_{5a} and O_9 in hydroperoxy epoxide **21b** forms a marked contrast to that in diepoxide **2b**.

In Scheme I, the oxygenation of hydroxy epoxide **15** is expected to give rise to diepoxide **2**. There appear, however, to be alternatives for its formation. After withdrawing a proton from substrate **1**, the superoxide radicals should dismutate to afford hydrogen peroxide:

$$O_2^- + H^+ \rightarrow HO_2$$

$$HO_2 + O_2^- + H^+ \rightarrow H_2O_2 + O_2$$

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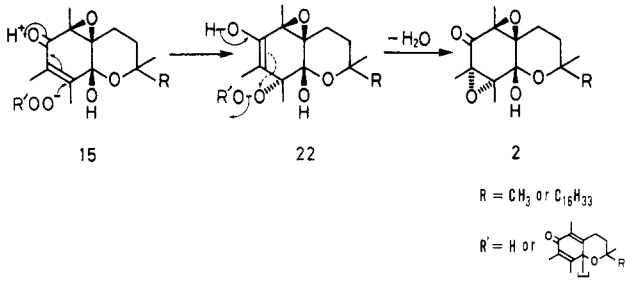
Scheme II. Alternative Pathways to 2



The hydroperoxy anion from the hydrogen peroxide and also peroxy anion **11** may act as nucleophiles and add to an α,β-unsaturated ketonic moiety of hydroxy epoxide **15** to produce epoxy peroxide **22**, which is converted to diepoxide **2** as shown in Scheme II. At present, the alternative routes cannot be ruled out.

Spiro enone **7** was found to be derived from epoxybenzoquinone **4**. Spiro epoxy ketone **6**, corresponding to an epoxide of spiro enone **7**, may be derived from diepoxybenzoquinone **17**, an epoxide of epoxybenzoquinone **4**, as shown in Scheme I.

On the other hand, we have already reported that the oxygenation of α-tocopherol or its model compound in tetrahydrofuran containing suspended potassium superoxide yields hydroxy ketone **18**, which was converted to hydroxy ketone **8** through acyloin rearrangement. Now, we confirm that the above reaction occurs in acetonitrile (Table I, run 12) as well as in tetrahydrofuran. In these cases, molecular oxygen must attack at C_5 in the substrate (Scheme I). Interestingly, it may be concluded that the regiospecificity of the oxygenation catalyzed by the solubilized superoxide radical is markedly different from that by the suspended one. The reason for these different actions depending on the physical states of the radical remains unknown. There seems, however, to be a possibility that the different actions may result from the difference in the basicities of suspended and solubilized potassium superoxide. In a solution of potassium superoxide in an aprotic solvent containing dicyclohexano-18-crown-6 and also in an acetonitrile solution of the superoxide radical generated from the electrochemical reduction of molecular oxygen with tetra-*n*-propylammonium perchlorate as a supporting electrolyte, the superoxide radical is thought to be so-called "naked". Since a naked anion is found to be more basic than the corresponding anion pairing with a cation[27] and since the superoxide species is an anion as well as a radical, the naked superoxide radical may be more basic than the superoxide radical in suspended potassium superoxide. Therefore, products **2–7** may be formed under reaction conditions more basic than those suitable for the formation of product **8**.

Experimental Section

General Procedures. All melting points are uncorrected and were measured with a Yanagimoto microapparatus. Ultraviolet and infrared spectra were recorded on Cary 118C and Jasco IR-2 spectrometers, respectively. ^1H and ^{13}C nuclear magnetic resonance spectra were taken on a Varian XL-200 spectrometer using tetramethylsilane as an internal standard. Mass spectra were obtained with a Shimazu 9000 gas chromatograph–mass spectrometer and JEOL JMS-DX303 and Hitachi M-80B spectrometers. High-performance liquid chromatography was conducted on a Varian 5000 liquid chromatograph. The vitamin E model compound, 2,2,5,7,8-pentamethylchroman-6-ol (**1b**), was synthesized by the method of Lars et al.,[28] 8a-hydroperoxy-2,2,5,7,8-pentamethylchroman-6(8a*H*)-one (**9b**) by the method described previously,[13,23] and an authentic sample of 1,1-dimethyl-3-(3,5,6-trimethylbenzoquinon-2-yl)propanol (**3b**) from the oxidation of the vitamin E model compound with iron(III) chloride.[29,30] The superoxide radical was generated in acetonitrile from the electrochemical reduction of molecular oxygen, in which tetra-*n*-propylammonium perchlorate was used as a supporting electrolyte.[22] The perchlorate was prepared from tetra-*n*-propylammonium bromide and perchloric acid. 2-*ambo*-α-Tocopherol, which had been obtained from E. Merck (Darmstadt, F.R.G.), was purified by silica gel column chromatography. Potassium superoxide (KO_2) was purchased from ICN Pharmaceuticals Inc. (Plainview, NY), dicyclohexano-18-crown-6 from Aldrich Chemical Co. (Milwaukee, WI), and acetonitrile (Spectrosol) from Dojin Kagaku Kenkyujo (Kumamoto, Japan). The other chemicals were obtained from ordinary commercial sources.

X-ray Crystallography. The crystal structures were solved by the direct method and refined by the block-diagonal least-squares method. Intensities were collected on a Philips four-circled diffractometer with graphite-monochromated Cu Kα radiation. The perspective views of the molecular structures were drawn by PLUTO program.[31]

For **2b**, a total of 1042 reflections were observed in the 2θ range of 6–138° above the $2\sigma(I)$ level. The final R value was 0.07 without hydrogen atoms. Crystal data: $C_{14}H_{20}O_5$; MW 268.3; rhombohedral (hexagonal axis); space group $R3c$; $Z = 18$; $D_{calcd} = 1.258$ g cm^{-3}; lattice constants $a = b = 26.577$ (15), $c = 10.423$ (6) Å; $\gamma = 120°$; $V = 6374$ Å^3.

For **5b**, a total of 1174 reflections were observed in the 2θ range of 6–100° above the $2\sigma(I)$ level. We reduced the number to 694 by taking the average of the symmetry-equivalent reflections. The $R(F)$ value for the equivalent reflections was 16%. The number of theoretically possible reflections in the same angular range was calculated to be 2562. Therefore, only 27% of the possible reflections could be measured. The scarcity of the number of reflections and the poor quality of the intensity data were due to the small size of the crystal specimens (0.01 × 0.02 × 0.02 mm). The final R value was 0.12, slightly better than the $R(F)$ value described above. Crystal data: $C_{14}H_{20}O_4$; MW 252.3; tetragonal; space group $I4_1/a$; $Z = 16$; $D_{calcd} = 1.206$ g cm^{-3}; lattice constants $a = b = 19.609$ (10), $c = 14.457$ (8) Å; $V = 5559$ Å^3.

For **6b**, a total of 1883 out of 2906 reflections were observed in the 2θ range of 6–156° above the $2\sigma(I)$ level. Hydrogen atoms were located on the difference electron density map and included in the refinement assuming isotropic thermal vibrations. The final R value was 0.069. Crystal data: $C_{14}H_{20}O_5$; MW 268.3; orthorhombic; space group $Pbca$; $Z = 8$; $D_{calcd} = 1.243$ g cm^{-3}; lattice constants $a = 13.588$ (7), $b = 19.858$ (11), $c = 10.627$ (7) Å; $V = 2868$ Å^3. (See the paragraph at the end of the paper concerning supplementary material.)

Oxygenation of the Vitamin E Model Compound in the Presence of the Superoxide Radical. (A) With Potassium Superoxide Solubilized by the Use of Dicyclohexano-18-crown-6. KO_2 (284 mg, 4.0 mmol) and dicyclohexano-18-crown-6 (2.5 g, 6.7 mmol) were mixed in acetonitrile (100 mL) and stirred vigorously for 30 min; when acetonitrile was replaced by pyridine, benzene, or tetrahydrofuran, procedures similar to those described below were used. An acetonitrile solution (10 mL) of **1b** (880 mg, 4.0 mmol) was added dropwise to the superoxide mixture with stirring at room temperature under an oxygen atmosphere. After this addition, the temperature of the solution rose by about 4 °C. Stirring was continued for 15 min. A NaCl-saturated aqueous solution (50 mL) was added, and the mixture was extracted with ethyl ether. The organic phase was dried over anhydrous sodium sulfate and filtered. The solvent was removed under reduced pressure. The oily residue obtained was purified by silica gel

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column chromatography. From the first elution with a mixture of *n*-hexane and ethyl ether (10:1), **1b** (104 mg, 12%) was recovered. The second elution with a mixture of *n*-hexane and ethyl ether (7:1) yielded crude diepoxide **2b** (120 mg, 12%), which was further purified by recrystallization from *n*-hexane: colorless needles; mp 89–90 °C; MS, *m/z* 268 (M^+); IR (KBr) ν 1725, 3445 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (s, 3 H), 1.44 (s, 3 H), 1.47 (s, 3 H), 1.49 (s, 3 H), 1.54 (s, 3 H), 1.58–2.16 (m, 4 H), 3.02 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 11.3 (q), 12.2 (q), 12.6 (q), 22.6 (t), 28.9 (q), 31.2 (q), 31.4 (t), 61.0 (s), 61.9 (s), 64.8 (s), 66.8 (s), 73.9 (s), 94.0 (s), 200.1 (s). Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.69; H, 7.46. Found: C, 62.41; H, 7.40. The third elution with the same solvent system gave a mixture of **6b** and **7b**. The mixture was fractionated on another silica gel column with a mixture of benzene and ethyl ether (20:1) as eluent. Initially, **6b** was obtained: 6% yield, 60 mg; colorless needles from *n*-hexane; mp 100–101 °C; MS, *m/z* 268 (M^+), 250 [$(M - 18)^+$], 225 [$(M - 43)^+$], 208 [$(M - 60)^+$], 207, 197, 153, 152, 139, 137, 97, 68, 54, 41 (base); IR (KBr) ν 1005, 1084, 1720, 1746, 3430 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09 (s, 3 H), 1.22–2.06 (s, 3 H), 1.28 (s, 3 H), 1.31 (s, 3 H), 1.52 (s, 3 H), 2.08 (s, 3 H), 2.31–2.72 (m, 1 H), 4.58 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 7.8 (q), 10.6 (q), 25.8 (q), 27.9 (q), 28.0 (q), 33.3 (t), 38.4 (t), 65.3 (s), 69.1 (s), 83.9 (s), 86.7 (s), 89.2 (s), 204.9 (s), 209.1 (s). Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.69; H, 7.46. Found: C, 62.62; H, 7.54. Next, **7b** was obtained: 5% yield, 47 mg; colorless solid from *n*-hexane; mp 49–50 °C; MS, *m/z* 252 (M^+), 234 [$(M - 18)^+$], 209 [$(M - 43)^+$], 192 [$(M - 60)^+$], 153, 137, 41 (base); IR (KBr) ν 1000, 1079, 1648, 1710, 3420 cm^{-1}; UV (CH_3CN) λ 232 nm (ϵ 10500), 275 (sh) (900); ^1H NMR ($CDCl_3$) δ 1.10–2.09 (m, 3 H), 1.13 (s, 3 H), 1.36 (s, 3 H), 1.84 (s, 6 H), 2.01 (s, 3 H), 2.24–2.56 (m, 1 H), 4.72 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 8.7 (q), 11.8 (q), 24.9 (q), 28.2 (2 q), 33.4 (t), 38.0 (t), 84.6 (s), 89.2 (s), 92.6 (s), 139.4 (s), 163.1 (s), 204.9 (s), 207.0 (s). Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.08; H, 8.00. The fourth elution with a mixture of *n*-hexane and ethyl ether (3:1) gave a mixture of **3b**, **4b**, and **5b** (160 mg), whose yields (6% each) were determined on the basis of the ^1H NMR spectrum of the mixture. The mixture was further fractionated by HPLC under the following conditions: column, MicroPak SI-5 (Varian; length 50 cm, i.d. 8 mm); mobile phase, methanol-saturated *n*-hexane; flow rate, 30 mL/h; monitoring, OD at 260 nm. First, **3b** was isolated as pale brownish yellow oil: MS, *m/z* 236 (M^+); CIMS, *m/z* 237.1458 [$(M + 1)^+$] (calcd for $C_{14}H_{21}O_3$, 237.1485); IR (neat) ν 1647, 3550 cm^{-1} (lit.[18] ν 1639, 3534 cm^{-1}); UV (CH_3CN) λ 261 nm (ϵ 16800), 268 (16900), 348 (340) (lit.[18] λ 260, 268 nm); ^1H NMR ($CDCl_3$) δ 1.29 (s, 6 H), 140–1.60 (m, 3 H), 2.01 (s, 6 H), 2.04 (s, 3 H), 2.48–2.66 (m, 2 H) [lit.[18] δ 1.28 (s), 1.45–1.82 (m), 2.00 (s), 2.05 (s), 2.38–2.73 (m), 2.45 (s)]; ^{13}C NMR ($CDCl_3$) δ 12.0 (q), 12.3 (q), 12.4 (q), 21.7 (t), 29.1 (2 q), 42.2 (t), 70.7 (s), 140.3 (s), 140.5 (s), 140.6 (s), 144.4 (s), 187.3 (s), 187.7 (s). Second, **4b** was obtained as a colorless oil: MS, *m/z* 252 (M^+); CIMS, *m/z* 253.1453 [$(M + 1)^+$] (calcd for $C_{14}H_{21}O_4$, 253.1435); IR (neat) ν 1682, 3530 cm^{-1} (lit.[10] ν 1680, 3500 cm^{-1}); UV (CH_3CN) λ 220 nm (ϵ 16600), 273 (4000) [lit.[21] (cyclohexane) λ 268 (4000)]; ^1H NMR ($CDCl_3$) δ 1.28 (s, 6 H), 1.30–1.62 (m, 3 H), 1.65 (s, 3 H), 1.78–1.94 (m, 1 H), 1.98 (s, 6 H), 2.26–2.42 (m, 1 H) [lit.[21] δ 1.23 (s, 6 H), 1.60 (m, 8 H), 1.93 (s, 6 H)]; ^{13}C NMR ($CDCl_3$) δ 11.5 (2 q), 13.2 (q), 21.1 (t), 29.2 (2 q), 38.7 (t), 63.5 (s), 65.8 (s), 70.4 (s), 141.0 (s), 141.2 (s), 194.0 (s), 194.3 (s). Last, **5b** was given as colorless prisms: mp 94–96 °C, from a mixture of *n*-hexane and ethyl ether; MS, *m/z* 252 (M^+); CIMS, *m/z* 253.1440 [$(M + 1)^+$] (calcd for $C_{14}H_{21}O_4$, 253.1435); IR (KBr) ν 1687, 3360 cm^{-1}; UV (CH_3CN) λ 212 nm (ϵ 8000), 273 (4300); ^1H NMR ($CDCl_3$) δ 1.27 (s, 6 H), 1.38–1.70 (m, 3 H), 1.60 (s, 6 H), 2.00 (s, 3 H), 2.34–2.84 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 11.4 (2 q), 12.9 (q), 22.5 (t), 29.0 (q), 29.1 (q), 41.6 (t), 63.1 (2 s), 70.7 (s), 140.6 (s), 145.0 (s), 194.4 (s), 194.6 (s).

(B) With the Superoxide Radical Generated Electrochemically. In acetonitrile containing 0.1 M tetra-*n*-propylammonium perchlorate as a supporting electrolyte, molecular oxygen was electrolytically reduced to give O_2^-, whose concentration was estimated by UV spectrometry based on its molar coefficient at 255 nm (ϵ 1460).[11] Immediately after the electrolysis, an acetonitrile solution (10 mL) of the substrate **1b** (50 mg, 0.23 mmol) was combined at room temperature with the cathodic solution (25 mL) containing O_2^- (0.25 mmol). By the same workup as described above, the reaction products **2b**, **3b**, **4b**, and **7b** were obtained in 20, 8, 8, and 5% yields, respectively. When the reaction was carried out under a nitrogen atmosphere, the cathodic solution and the acetonitrile solution of **1b** were saturated with nitrogen gas. It was confirmed that no O_2^- in the cathodic solution was decomposed by this treatment. Both solutions were then combined together. After being purified as described above, the starting material (**1b**) was recovered in 95% yield.

(C) With Potassium Superoxide Suspended in Acetonitrile. The reaction was conducted according to the procedures described previously.[16,19]

Reaction of 9b in the Presence of Potassium Superoxide. Using dicyclohexano-18-crown-6 (400 mg, 1.1 mmol) KO_2 (400 mg, 5.6 mmol) was dissolved in acetonitrile (50 mL). An acetonitrile solution (10 mL) of **9b** (400 mg, 1.6 mmol) was added dropwise to the solution at room temperature under an oxygen atmosphere. The mixture was stirred for 10 min. After the same workup as described above, **2b**, **6b**, and **7b** were obtained in 3, 4, and 10% yields, respectively, with trace amounts of **3b**, **4b**, and **5b**.

Conversion of 4b into 7b. To a mixture of KO_2 (46 mg, 0.65 mmol) and dicyclohexano-18-crown-6 (250 mg, 0.67 mmol) in acetonitrile (50 mL) was added an acetonitrile solution (10 mL) of **4b** (150 mg, 0.60 mmol) at room temperature under an oxygen atmosphere. The solution was stirred for 20 min, and ethyl ether (100 mL) was then added. The mixture was washed with brine three times. The organic phase was dried over sodium sulfate and concentrated to dryness. The residue obtained was purified by silica gel column chromatography. Elution with a mixture of *n*-hexane and ethyl ether (7:1) gave **7b** in a 30% yield (46 mg). Another elution with a mixture of *n*-hexane and ethyl ether (3:1) brought the starting material **4b** in a 10% recovery (15 mg).

Oxygenation of α-Tocopherol in the Presence of Potassium Superoxide. To an acetonitrile solution (100 mL) of KO_2 (300 mg, 4.2 mmol) solubilized with dicyclohexano-18-crown-6 (2.5 g, 6.7 mmol) was added an acetonitrile solution (100 mL) of 2-*ambo*-α-tocopherol (2-*ambo*-**1a**; 1.72 g, 4.0 mmol) dropwise at room temperature under an oxygen atmosphere. The addition took about 15 min, and the temperature of the solution rose by about 4 °C. Stirring was continued for another 15 min, and ethyl ether (200 mL) was then added to the mixture. The organic phase was washed with brine, dried, and filtered. The solvent was evaporated under reduced pressure. The residue was fractionated by silica gel column chromatography. The main fraction eluted with a mixture on *n*-hexane and ethyl ether (5:1) contained more than four compounds. This fraction was further purified by HPLC under the following conditions: column, MicroPak SI-10 (length 50 cm, i.d. 8 mm); mobile phase, a mixture of *n*-hexane and isopropyl alcohol (99.25:0.75); flow rate, 6 mL/min; monitoring, OD at 235 nm and ^1H NMR. Crude diepoxide **2a** was obtained from the fraction and rechromatographed under the same HPLC conditions. Pure **2a** was isolated as colorless oil: 8 mg; MS, *m/z* 478.3645 (calcd for $C_{29}H_{50}O_5$, 478.3645); IR (neat) ν 1735, 3520 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (s, 3 H), 1.43 (s, 3 H), 1.47 (s, 3 H), 1.55 (s, 3 H), 3.02 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 11.3 (q), 12.2 (q), 12.6 (q), 19.7 (q), 19.8 (q), 21.2 (t), 22.4 (t), 22.6 (q), 22.7 (q), 24.5 (t), 24.8 (t), 25.4 (q), 28.0 (d), 30.9 (t), 32.6 (d), 32.7 (d), 32.7 (d), 32.8 (d), 37.3 (t), 37.4 (t), 37.5 (t), 37.6 (t), 39.4 (t), 44.6 (t), 61.0 (s), 61.9 (s), 65.1 (s), 67.1 (s), 76.2 (s), 93.9 (s), 200.4 (s).

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Registry No. 2-*ambo*-**1a**, 10191-41-0; **1b**, 950-99-2; **2a**, 108796-70-9; **2b**, 71254-81-4; **3b**, 30876-55-2; **4b**, 108796-67-4; **5b**, 108796-68-5; **6b**, 108815-96-9; **7b**, 108796-69-6; **8b**, 80311-41-7; **9b**, 92014-26-1; superoxide radical, 11062-77-4.

Supplementary Material Available: Figures of the array of pairs of the enantiomers of **2b** in its crystal and of the molecular structures of **5b** and **6b** and listings of bond lengths and angles and atomic coordinates and thermal parameters for **2b**, **5b**, and **6b** (13 pages). Ordering information is given on any current masthead page.