21.8 min for standard, 13, and 2, respectively). MC and its isomer were analyzed on column B (140 °C, 19 mL/min, retention time 8.1, 9.0, and 15.9 for methylenecyclohexane, MC, and nonane (standard), respectively).

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Registry No. 1, 72541-64-1; 2, 68613-81-0; 2-d_2, 72541-65-2; 3, 23086-43-3; 11, 6606-34-4; 12, 1686-50-6; 13, 68613-82-1; 13-d_2, 72541-66-3; 15, 68613-84-3; 15-d_2, 72541-67-4; 16, 70561-39-6; 17, 72541-68-5; 18, 72541-69-6; *cis*-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-one, 70524-91-3.

A New Synthesis of α-Tocopherol

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α-Tocopherol (vitamin E, 1) has been synthesized in racemic form following a new strategy in which the aromatic ring of the chroman is constructed by addition of the dianion of 2,4-pentanedione to 1,2-epoxy-2,6,10,14-tetramethylpentadecane (5) as a side-chain precursor, followed by condensation with dimethyl acetonedicarboxylate and reduction to the key "tocopherylphenol" 8. Oxidation of 8 with a new organic-soluble bis(quaternary ammonium) salt of Fremy's radical gives tocopherylquinone (9), a known precursor of α-tocopherol (1).

α-Tocopherol (vitamin E, 1) has been the synthetic objective of several recent studies directed especially toward the synthesis of the natural product, (2*R*,4′*R*,8′*R*)-α-tocopherol.[2] The renewed interest in this vitamin is due in part to the increasingly apparent biological importance of vitamin E[3] and in part to the development of new synthetic methods for the synthesis of the chiral centers in the side chain[4] and chroman[5] portions of the molecule. The reported approaches[2] have been based on the coupling of chroman and side-chain moieties or on elaboration of preformed chroman units.

We envisioned a strategy in which the chroman ring could be constructed from simple aliphatic precursors starting from a functionalized, potentially chiral side chain or side-chain segment.[6] The approach (Scheme I) using an epoxide (2) as this segment to form O-1, C-2, and C-3 of the chroman ring, and 2,4-pentanedione and a 3-pentanone equivalent for the remaining atoms, seemed to be a particularly direct route to 1 via the phenol 3. We now report our investigations in the racemic series[7] (Scheme II), leading to a synthesis of the previously unknown "tocopherylphenol" (8) and its oxidation by a new organic-soluble version of Fremy's salt[9] to tocopherylquinone (9), a well-known precursor[2a] of 1.

Scheme I

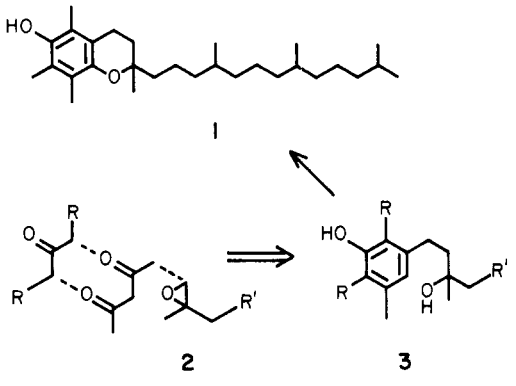


Table I. Oxidation of Phenol 8 under Phase-transfer Conditions

expt	$ON(SO_3K)_2$, mmol[a]	phenol 8, mmol	ammonium salt 10, mmol[b]	time to completion[c]
1	0.54	0.23	0.043	5 h
2	0.54	0.23	0.21	2-3 h
3	0.54	0.23	0.43[d]	20 min
4	0.54	0.23	0.84	20 min

[a] The concentration of the solution was determined to be 0.175 M by measurement of the absorption at 440 nm where Fremy's salt has $\epsilon = 14.5$. [b] Commercial 10 has a mixture of C_8 and C_{10} alkyl groups. The molecular weight of the predominant $(C_8H_{17})_3NCH_3Cl$ species is used for the calculation. [c] Judged by TLC. [d] Shows some purple color in the organic phase.

Results

Hexahydrofarnesylacetone (4) was converted to the oily epoxide 5 in 92% yield by methylenation with tri-

(1) Synthetic Chemicals Division, Eastman Kodak Co., Rochester, NY 14650.

(2) For recent reviews see (a) H. Mayer and O. Isler, *Methods Enzymol.*, 18, Part C, 241 (1971); (b) S. Kasparek in "Vitamin E", L. J. Machlin, Ed., Marcel Dekker, New York, 1979, Chapter 2; (c) J. M. Akkerman, H. deKoning, and H. O. Huisman, *J. Chem. Soc., Perkin Trans. 1*, (1979); (d) C. Fuganti and P. Grasselli, *J. Chem. Soc., Chem. Commun.*, 995 (1979).

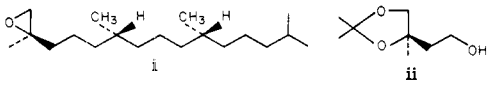
(3) (a) J. G. Bieri and P. M. Farrell, *Vitam. Horm.* 34, (N.Y.), 31 (1976); (b) Chapters 1, 3-12 in ref 2b.

(4) See ref 3 in ref 5a.

(5) (a) N. Cohen, R. J. Lopresti, and G. Saucy, *J. Am. Chem. Soc.*, 101, 6710 (1979); (b) N. Cohen, J. W. Scott, F. T. Bizzarro, R. J. Lopresti, W. F. Eichel, G. Saucy, and H. Mayer, *Helv. Chim. Acta*, 61, 837 (1978).

(6) Related approaches have been studied in several Roche laboratories: (a) see ref 5a; (b) H. G. W. Leuenberger, W. Boguth, R. Barner, M. Schmid, and R. Zell, *Helv. Chim. Acta*, 62, 455 (1979); (c) M. Schmid and R. Barner, *ibid.*, 62, 464 (1979); (d) R. Zell, *ibid.*, 62, 474 (1979); (e) R. Barner and M. Schmid, *Helv. Chim. Acta*, 62, 2384 (1979).

(7) A stereospecific synthesis of racemic i from hydroxyacetonide ii (derivable[8a,b] from citramalic acid (the *R* isomer[8c] would be needed for natural α-tocopherol)) will be reported in due course.



(8) (a) P. A. Stadler, A. J. Frey, and A. Hofmann, *Helv. Chim. Acta*, 46, 2300 (1963); (b) H. K. Spencer, H. N. Khatri, and R. K. Hill, *Bioorg. Chem.*, 5, 177 (1976); (c) T. Sai, K. Aida, and T. Uemura, *J. Gen. Appl. Microbiol.*, 15, 345 (1969).

(9) (a) G. L. Olson and G. Saucy, U.S. Patent 4 127 608, 1979; (b) H.-J. Teuber and W. Rau, *Chem. Ber.*, 86, 1036 (1953); (c) P. A. Wehrli and F. Pigott, *Org. Synth.*, 52, 83 (1972).

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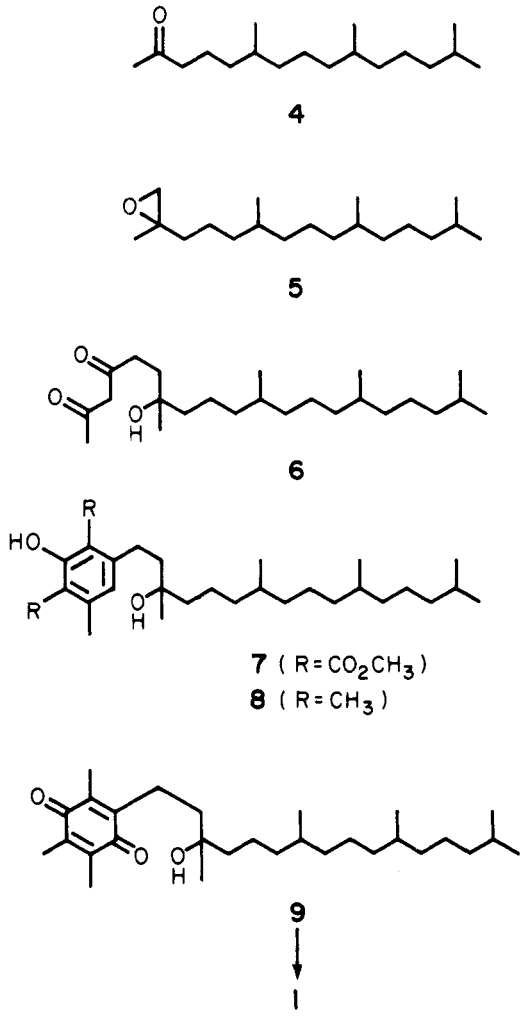
Scheme II



methylsulfonium chloride and sodamide in liquid ammonia.[10] Reaction of **5** at room temperature overnight with 5 equiv of the sodio lithio dianion of 2,4-pentanedione[11] gave the crude hydroxy diketone **6** as a mixture of keto–enol tautomers of sufficient purity for subsequent reactions. When isolated by preparative TLC on a small scale, pure **6** was obtained in 75% yield. Hydroxy diketone **6** failed to react with 3-pentanone ($NaOCH_3/CH_3OH$) or its pyrrolidine enamine, but was smoothly converted[12] by reaction with dimethyl acetonedicarboxylate ($NaOCH_3/CH_3OH$), to the phenolic diester **7** as an oil in 43% overall yield from **5** after chromatography. Diester **7** was reduced directly to the trimethylphenol **8** with sodium dihydrobis(2-methoxyethoxy)aluminate,[13] first at 10 °C and then at reflux in xylene for 1.5 h, in 74% yield.

All attempts to oxidize **8** to the quinone **9**[14] with Fremy's salt in a two-phase ether–water mixture, in aqueous methanol, or in aqueous DMF were unsuccessful, possibly due to the extreme hydrophobicity of the phenol **8**. Therefore various phase-transfer catalysts (benzyltriethylammonium chloride, cetyltrimethylammonium bromide, tetrabutylammonium iodide, tricaprylylmethylammonium chloride (**10**)) were added to solutions

$$\cdot ON(SO_3^-K^+)_2 + 2(caprylyl)_3N^+CH_3Cl^- \xrightarrow[\mathbf{10}]{} \cdot ON[SO_3^-N^+CH_3(caprylyl)_3]_2 \quad \mathbf{11}$$

of Fremy's salt overlaid with benzene. When excess **10** was added, there was an immediate extraction of the purple color into the organic phase, and when the procedure was repeated with a 2:1 mol ratio of ammonium salt **10** to Fremy's salt, the colored radical was quantitatively transferred to the organic phase as bis(tricaprylylmethyl)ammonium nitrosodisulfonate (**11**).

The benzene solution of **11**, furthermore, rapidly oxidized the phenol **8** to tocopherylquinone (**9**). The reaction also worked well under phase-transfer conditions, with the results given in Table I. The time required for the reaction to go to completion is given for varying mole ratios of ammonium salt **10** and Fremy's salt. These results show that the oxidation in the benzene phase is rapid and that there is a phase-transfer effect. The appearance of a slight color in the organic phase in experiment 3 indicates that the bisammonium salt **11** is present at equilibrium with less than a full equivalent of **10** added. On a preparative scale, tocopherylquinone (**9**) was isolated in virtually quantitative yield and was identical with a sample prepared[15] from α-tocopherol.

In conclusion, the feasibility of this approach to the synthesis of α-tocopherol via nucleophilic opening of an epoxide-functionalized side chain and elaboration of the aromatic ring has been demonstrated. The organic-soluble modification of Fremy's salt and the observation of phase-transfer catalysis may find application in other systems.

Experimental Section

General Procedures. Reactions were carried out under an atmosphere of argon and were generally followed by TLC on Brinkmann silica gel GF254 precoated plates using UV and ceric sulfate spray followed by heating to detect spots. Products were isolated, in general, by extraction or dilution of the reaction mixture with the indicated solvent, washing, where appropriate, with H_2O, 20% HCl, saturated $NaHCO_3$, and brine, drying ($MgSO_4$), and removing the solvent on a rotary evaporator at 30–50 °C. Column chromatography was carried out on Merck 0.05–0.2-mm silica gel, eluting with ether–hexane or ether–petroleum ether mixtures. Tetrahydrofuran (THF) was dried by passage through Woelm neutral alumina, grade I. Butyllithium solution (Ventron Corp.) was titrated[16] before use. NMR spectra were measured in $CDCl_3$ with Me_4Si as internal standard. IR spectra were obtained in $CHCl_3$ solution or as a liquid film, and UV spectra were measured in 2-propanol.

1,2-Epoxy-2,6,10,14-tetramethylpentadecane (5). To a suspension of sodamide in liquid ammonia (120 mL) (prepared from 9.12 g (0.40 mol) of sodium) was added a solution of hexahydrofarnesylacetone (**4**) (80.0 g, 0.29 mol) in ether (300 mL) while an internal temperature of −33 °C was maintained with a dry ice–2-propanol bath. After 15 min, trimethylsulfonium chloride (45.0 g, 0.37 mol) was added rapidly with stirring. The cooling bath was removed, the mixture was stirred, and the ammonia allowed to evaporate overnight. The mixture was cooled in an ice bath and ammonium chloride (16.2 g) was added. The mixture was stirred 30 min at room temperature, filtered through Celite, washed with brine, dried ($MgSO_4$), and concentrated to

(10) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **84**, 3782 (1962); M. Rosenberger, P. McDougal, G. Saucy, and J. Bahr, *Pure Appl. Chem.*, **51**, 871 (1979); we thank Dr. R. Marbet, F. Hoffmann-LaRoche & Co. Ltd., CH 4002, Basel, Switzerland, for the sodamide procedure.
(11) K. G. Hampton and J. J. Christie, *J. Org. Chem.*, **40**, 3887 (1975).
(12) V. Prelog, O. Metzler, and O. Jeger, *Helv. Chim. Acta*, **30**, 675 (1947).
(13) M. Černý and T. Málek, *Tetrahedron Lett.*, 1739 (1969).
(14) The direct conversion of phenol **8** to tocopherol **1** is an objective of future studies.
(15) See ref 2a, p 312.
(16) (a) R. A. Ellison, R. Griffin, and F. N. Kotsonis, *J. Organomet. Chem.*, **36**, 209 (1972); (b) S. C. Watson and J. F. Eastham, *ibid.*, **9**, 165 (1967).

give 82.2 g of crude **5** as an oil. A 80.9-g portion was distilled rapidly through a short-path apparatus to give 75.5 g of epoxide **5** (92%) as a colorless oil: bp 108–110 °C (0.08 mm); IR (film) 1260 and 1280 cm^{-1} (epoxide); NMR ($CDCl_3$) δ 2.58 (s, 2, methylene), 1.25 (s, 3, C_2-methyl), and 0.88 (d, 12, J = 6 Hz, methyls). Anal. Calcd for $C_{19}H_{38}O$: C, 80.78; H, 13.56. Found: C, 81.09; H, 13.49.

7-Hydroxy-7,11,15,19-tetramethyleicosane-2,4-dione (6). To a suspension of sodium hydride (30.0 g of 57% dispersion, 0.72 mol, washed free of oil with hexane) in THF (500 mL) at 0 °C was added dropwise over 30 min a solution of 2,4-pentanedione (71.0 g, 0.71 mol) in THF (150 mL). After stirring for 20 min at 0 °C, butyllithium (260 mL of 2.5 M solution in hexane, 0.65 mol) was added over 30 min at 0–5 °C. The epoxide **5** (40.0 g, 0.142 mol) in THF (50 mL) was added in one portion and the solution was stirred 17.5 h at room temperature. The solution was cooled to 0 °C and poured into a vigorously stirred mixture of ice (2 kg) and concentrated HCl (114 mL). Saturated ammonium chloride (100 mL) was added and the product was isolated with ether to give a crude oil which was further evaporated at 30–35 °C (0.3 mm) for 2.5 h to give 73.5 g of crude diketone **6** as an oil. A 0.36-g sample was purified for analysis by preparative TLC to give 0.20 g of pure diketone **6** (75%) as a light-yellow oil: IR (film) 3460 (hydroxyl), 1710 and 1620 cm^{-1} (ketone and enol); UV max (2-propanol) 274 nm (ϵ 5265); NMR ($CDCl_3$) δ 5.51 (s, C_3H, enol form), 4.30 (br, 1, hydroxy), 2.81 (m, C_3H, keto form), 2.20 (s, 3, C_1 methyl), 2.02 (s, 3, C_7 methyl), 0.86 (d, 12, J = 6 Hz, methyls). Anal. Calcd for $C_{24}H_{46}O_3$: C, 75.34; H, 12.12. Found: C, 75.06; H, 12.03.

Dimethyl 2-Hydroxy-4-methyl-6-(3-hydroxy-3,7,11,15-tetramethylhexadecanyl)benzene-1,3-dicarboxylate (7). To a solution of the crude diketone **6** (72.5 g) and dimethyl acetonedicarboxylate (29.6 g, 0.17 mol) in methanol (190 mL) at 0 °C was added a solution of sodium methoxide in methanol (90 mL) (from 2.44 g sodium (0.106 mol)). The solution was stirred 44 h at room temperature and concentrated on a rotary evaporator to remove ca. 100 mL of methanol. The residue was poured onto ice (500 g) and 20% HCl (45 mL) and the product was isolated as usual with ether to give 91.7 g of crude **7** as an orange oil. A 90.2 g-portion of the oil was redissolved in ether and washed free of excess dimethyl acetonedicarboxylate with 20% potassium carbonate, and then washed with brine, dried, and concentrated to give 83.1 g of crude **7**. Chromatography on 2.45 kg of silica gel eluting with 20–30% ether in hexane gave 30.83 g (43% yield from **5**) of **7** as a colorless oil: IR ($CHCl_3$) 3605 (hydroxyl), 1726 and 1660 cm^{-1} (ester C=O); UV max (2-propanol) 214 (ϵ 24 230), 251 (ϵ 9900), and 314 nm (ϵ 5200); NMR ($CDCl_3$) δ 11.67 (s, 1, phenol OH), 6.56 (s, 1, aromatic), 3.89 (s, 6, $COOCH_3$), 2.67, and 1.66 (AA'BB', 4, J = 8 Hz, C_1 and C_2 methylenes), 2.42 (s, 3, methyl, and 0.83 (d, 12, J = 6 Hz, methyls). Anal. Calcd for $C_{31}H_{52}O_6$: C, 71.50; H, 10.07. Found: C, 71.51; H, 9.93.

2,3,6-Trimethyl-5-(3-hydroxy-3,7,11,15-tetramethylhexadecanyl)phenol (8). To a solution of diester **7** (5.17 g, 9.93 mmol) in xylene (25 mL) at 10 °C was added sodium dihydrobis(2-methoxyethoxy)aluminate (20 mL of a 70% solution in benzene, Red-Al (69.2 mmol)) over 10 min with occasional cooling to keep the temperature at 10 °C. After stirring 10 min, the solution was heated to reflux for 1.5 h, cooled to 10 °C, and poured cautiously into cold 20% H_2SO_4 (100 mL). The product was isolated as usual with ether to give 4.29 g of crude **8** which was chromatographed on silica gel, eluting with ether in petroleum ether to give 3.19 g of **8** (74%) as a colorless oil: IR ($CHCl_3$) 3610 cm^{-1} (hydroxyl); UV max (2-propanol) 204 (ϵ 46 750) and 224 nm (ϵ 9335); NMR ($CDCl_3$) δ 6.52 (s, 1, aromatic), 4.85 (br s, 1, phenol OH), 2.54 and 1.67 (AA'BB', 4, J = 8 Hz, C_1 and C_2 methylene), 2.14, 2.11, and 2.07 (3 s, 9, aromatic methyls), 1.18 (s, 3, C_3-methyl), and 0.81 (d, 12, J = 6 Hz, methyls). Anal. Calcd for $C_{29}H_{52}O_2$: C, 80.49; H, 12.11. Found: C, 80.40; H, 12.42.

Fremy's Salt Oxidation of 8 with Varying Amounts of Tricaprylylmethylammonium Chloride (10) (Table I). A solution of Fremy's salt was prepared by dissolving 8.5 g of the sodium carbonate slurry[9b] in 52 mL of 15% sodium carbonate followed by adding 0.5 g of solid sodium carbonate. The concentration of the solution was determined by measuring the absorbance at 440 nm where pure Fremy's salt has ϵ 14.5.[9b] The solution of Fremy's salt, phenol **8**, ammonium salt **10**, and 2 mL of benzene were combined as indicated in Table I and the reaction was followed by TLC.

Tocopherylquinone (9). To a 1.6 g-portion of the sodium carbonate slurry of Fremy's salt was added 10 mL of 15% sodium carbonate and a solution of 0.29 g (ca. 0.72 mmol) of tricaprylylmethylammonium chloride (**10**) in benzene (4 mL). The phenol **8** (0.30 g, 0.69 mmol) in benzene (8 mL) was added and the mixture was stirred for 2.5 h. The mixture was poured into water (5 mL), extracted with petroleum ether, washed twice with water (10 mL), dried (Na_2SO_4), and concentrated to give the crude quinone **9**. Chromatography on 7.0 g of silica gel, eluting with ether–petroleum ether, gave 0.2 g of oily quinone **9** (93% yield, corrected for UV assay): UV max (2-propanol) 268 nm (ϵ 15 340) (lit.[15] for crystalline **9**: UV max (ethanol) 268 nm (ϵ 17 816)); IR ($CHCl_3$) 1640 cm^{-1}; NMR ($CDCl_3$) δ 2.49 (m, 2, C_1 methylene), 1.98 and 1.95 (3 s, 9, quinone methyls), 1.69 (br s, 1, hydroxyl), 1.18 (s, 3, C_3 methyl), and 0.80 (d, 12, J = 6 Hz, methyls).

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Registry No. **4**, 502-69-2; **5**, 69371-89-7; **6**, 69371-90-0; **7**, 69371-88-6; **8**, 69371-91-1; **9**, 72657-56-8; 2,4-pentanedione, 123-54-6; dimethyl acetonedicarboxylate, 1830-54-2.

Syntheses of 10-(Carboxymethyl)-*trans*-decal-2-one

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10-(Carboxymethyl)-*trans*-decal-2-one (**2**) has been prepared by two routes. The first involves homologation of compounds derived from the known 10-(carboethoxy)-*trans*-decal-2-one (**5**) via cyanide displacement on 10-tosyloxymethyl or 10-mesyloxymethyl derivatives of *trans*-decal-2-one. The second is based on Robinson annulation of 2-(carbomethoxymethyl)cyclohexanone (**6**), which affords a low yield of lactone **20**. Hydrogenation of enone acid **21** or its anion **22** leads exclusively to 10-(carboxymethyl)-*cis*-decal-2-one (**24**). Hydrogenation of enone ester **18** also leads to a preponderance of cis ring fusion, but affords some of the methyl ester (**19**) of **2**. The most efficient synthesis of **2** proceeds from **5** via **16** in 38% overall yield.

As part of a study of proton abstraction α to carbonyl groups and derived iminium ions,[1,2] we required decalin-carboxylic acids **1** and **2** so that we could assess the effective concentration[3] of carboxylate anions in processes

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