reaction mixture was stirred another 30 min, and then saturated aqueous NH_4Cl was added, discharging the blue color. Pentane (20 mL) was added; 6 N aqueous HCl was added carefully until the aqueous layer became acidic. The two phases were separated, and the pentane solution was washed with brine (2 × 20 mL), dried, filtered, and carefully concentrated at 20 °C by rotary evaporation. (±)-Albene ((±)-1) was isolated in pure form from the residual 1-mL pentane solution by GLC on a 1.5 m × 6.4 mm, 30% Apiezon L on 60/80-mesh Chromosorb W column at 180 °C (10 mg, 53% yield from ketone **12**): IR 3040, 2950, 2920, 2890, 1605 cm^{-1}; NMR δ 5.57 (dt, J = 2, 6 Hz, 1 H, C=CH), 5.27 (dt, J = 2, 6 Hz, 1 H, C=CH), 2.23 (t, J = 2 Hz, 2 H, CH_2C=C), 1.0–1.9 (m, 8 H), 0.96 (s, 6 H, 2 CH_3) [lit.[6] δ 5.56 (dt), 5.26 (dt), 2.23 (t), 1.0–1.9 (m), 0.94 (s)]; ^{13}C NMR δ 139.59, 128.31, 51.75, 50.29, 47.03, 34.16, 23.77, 20.65, 18.07 (lit.[6] δ 139.65, 128.34, 56.38 51.83, 50.36, 47.13, 46.61, 34.23, 23.83, 20.67, 18.09; the small peaks arising from quaternary carbons C(2) and C(6) were indistinguishable from noise); mass spectrum, m/e 162 (M^+, base), 147, 133, 121, 119, 105; high-resolution mass spectrum, m/e 162.141 (calcd 162.141).

Acknowledgment. We are indebted to the National Science Foundation for partial support of this work, to Professor Lloyd J. Dolby for helpful suggestions, to Donald S. Johnson for exploratory synthetic efforts toward isoalbene, to Dr. Ulrich Scheidegger (Varian AG, Zug, Switzerland) and Professor Peter T. Lansbury (SUNY, Buffalo) for informative correspondence, and to Dr. Kenneth Tseng (Stauffer Chemical Co., Richmond, CA) for the ^{13}C NMR spectrum of our synthetic (±)-albene.

Registry No. (±)-1, 67180-07-8; **8**, 7124-33-6; **9**, 77224-23-8; **10**, 77224-24-9; **11**, 77224-25-0; (±)-**12**, 77340-51-3; 2,3-dimethylmaleic anhydride, 766-39-2; cyclopentadiene, 542-92-7; 2-*endo*,6-*endo*-dimethyltricyclo[5.2.1.$0^{2,6}$]dec-4-en-3-ol, 77224-26-1; 2-*endo*,6-*endo*-dimethyl-3-acetoxytricyclo[5.2.1.$0^{2,6}$]dec-4-ene, 77224-27-2.

Studies on the Total Synthesis of (2*R*,4′*R*,8′*R*)-α-Tocopherol (Vitamin E). Stereospecific Cyclizations Leading to Optically Active Chromans

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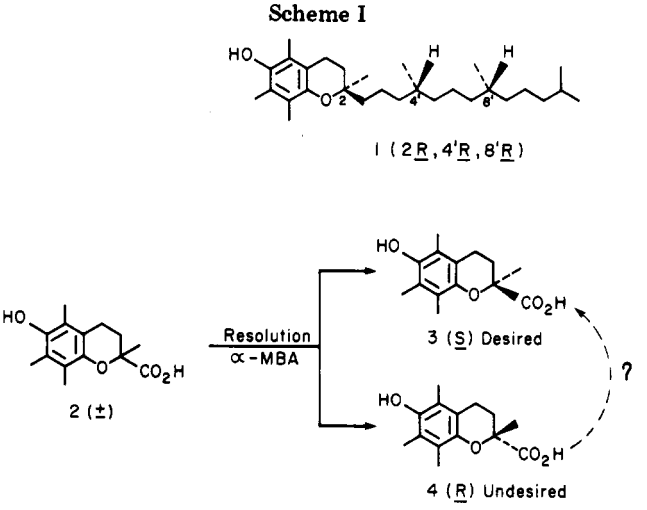
Optically active hydroquinone carbinols such as α-tocopherolhydroquinone (**6**) and the related compounds **12a–d** cyclize under proton catalysis, with essentially complete retention of configuration, regenerating the chromans (**1**, **4**, **10b–d**) from which they are derived. Mechanistic considerations are discussed within the context of earlier α-tocopherol redox chemistry. An efficient, three-stage inversion sequence was developed which allowed the transformation of (*R*)-chroman-2-carboxylic ester **10b** to the *S* enantiomer **22**, a key intermediate in the synthesis of (2*R*,4′*R*,8′*R*)-α-tocopherol. The key step (**20** → **22**) involves a facile intramolecular S_N2 displacement occurring at a tertiary center. This process provides a method for utilizing the unwanted (*R*)-chroman-2-carboxylic acid **4** obtained along with the desired *S* antipode **3** by optical resolution of the racemic form **2** (chiral economy).

The (*S*)-chroman-2-carboxylic acid **3**[1] (Scheme I) and closely related substances are key intermediates in certain approaches to the total synthesis of naturally occurring (2*R*,4′*R*,8′*R*)-α-tocopherol (**1**).[2] Acid **3** is readily obtained in enantiomerically pure form by optical resolution of the racemic modification **2**[1] using (*S*)-α-methylbenzylamine. In an effort to improve the overall efficiency of these synthetic schemes, we embarked upon a study aimed at utilization of the undesired *R* enantiomer **4** for production of **1** (chiral economy[3]). Acid **4** is also readily isolated at the resolution stage, in optically pure form, by using the *R* amine resolving agent. Our goal appeared to be the development of a facile and efficient procedure for inverting the configuration in **4** so as to maximize the total quantity of **3** available from racemic acid **2**.[3]

In our initial planning in this regard, we were cognizant of the early studies carried out by Mayer et al. involving manipulation of the C-2 stereochemistry in α-tocopherol.[4]

Scheme I



These workers found that the chirality at this center could be largely inverted by the sequence shown in Scheme II. Thus ferric chloride oxidation of **1** gave the quinone **5** with retention of configuration. Catalytic hydrogenation of **5** then yielded the corresponding hydroquinone **6** which underwent cyclodehydration with predominant inversion of configuration upon exposure to zinc chloride at 50 °C (no solvent). In this manner, (2*S*,4′*R*,8′*R*)-α-tocopherol (**7**) was obtained as the major product.[4b] It appeared that some variation of this sequence could be applied to the acid **4**.

(1) Scott, J. W.; Cort, W. M.; Harley, H.; Parrish, D. R.; Saucy, G. *J. Am. Oil Chem. Soc.* **1974**, *51*, 200–3.

(2) (a) Mayer, H.; Schudel, P.; Rüegg, R.; Isler, O. *Helv. Chim. Acta* **1963**, *46*, 650–71. (b) Barner, R.; Schmid, M. *Ibid.* **1979**, *62*, 2384–99. (c) Schmid, M.; Barner, R. *Ibid.* **1979**, *62*, 464–73. (d) Zell, R. *Ibid.* **1979**, *62*, 474–80. (e) Chan, K.-K.; Cohen, N.; De Noble, J. P.; Specian, A. C., Jr.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3497–505. (f) Cohen, N.; Lopresti, R. J.; Saucy, G. *J. Am. Chem. Soc.* **1979**, *101*, 6710–6. (g) Fuganti, C.; Grasselli, P. *J. Chem. Soc., Chem. Commun.* **1979**, 995–7.

(3) Fischli, A. *Chimia* **1976**, *30*, 4–9.

(4) (a) Mayer, H.; Vetter, W.; Metzger, J.; Rüegg, R.; Isler, O. *Helv. Chim. Acta* **1967**, *50*, 1168–78. (b) Schudel, P.; Mayer, H.; Metzger, J.; Rüegg, R.; Isler, O. *Ibid.* **1963**, *46*, 333–43.

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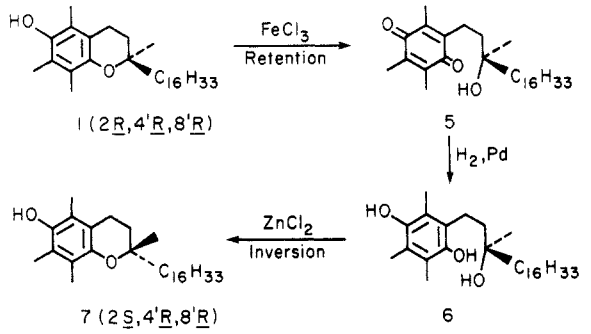
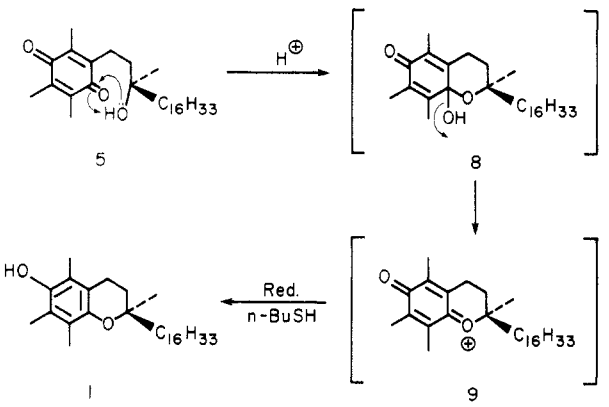
Scheme II



Scheme III



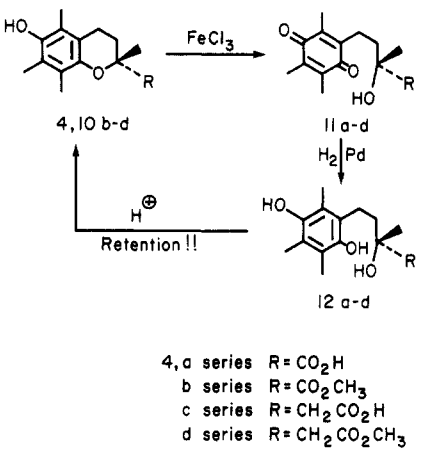
It is also pertinent to take note of another earlier α-tocopherol study[4a] as delineated in Scheme III. Thus reductive cyclization of quinone **5** using, for example, *n*-butanethiol–acetic acid proceeded with complete *retention* of configuration to regenerate **1**. This transformation was shown to involve the intermediacy of quinone hemiketal **8** and the oxonium species **9**[4a] and, as discussed below, appears to represent a much more general mode of chroman formation than the Lewis acid mediated inversion process depicted in Scheme II.

Results

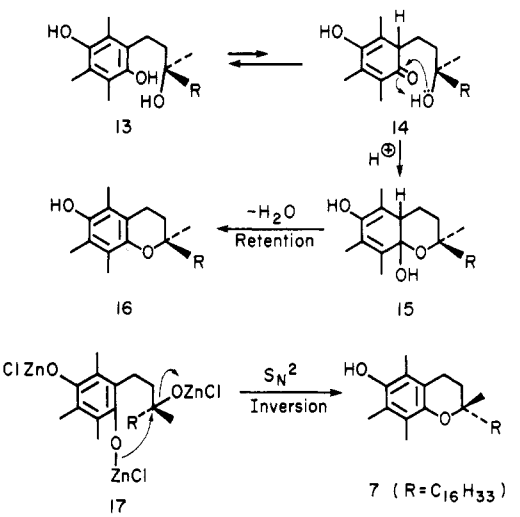
Repetition of the Mayer work[4b] confirmed that cyclodehydration of **6** with neat zinc chloride proceeds with predominant inversion of configuration, yielding **7** as the major product. Therefore, we were somewhat surprised to discover that treatment of **6** with *p*-toluenesulfonic acid in refluxing benzene effected cyclodehydration with complete *retention* of configuration, regenerating **1** in 95% yield (Table I).

Similar results were obtained when this sequence was applied to the unwanted (2*R*)-acid **4** and the methyl ester **10b** as well as the corresponding homologues **10c**[5] and **10d**,[6] respectively (Scheme IV). Oxidation of all four of these compounds with ferric chloride gave, in 80–90% yield, the benzoquinones **11a–d**[7] (Table II). Catalytic hydrogenation then afforded the extremely air sensitive hydroquinones **12a–d** all of which underwent proton-catalyzed cyclodehydration with greater than 90% *retention* of configuration (Table I), regenerating **4** and **10b–d**.[8] These processes are, apparently, quite facile since little, if any, evidence of racemization via competing elimination of water (prior to cyclization) from the β-hydroxy carbonyl systems in **12c** and **12d** was noted. It was also found that, in certain cases, the cyclization proceeded cleanly even under relatively vigorous conditions. Thus, one of the most favorable combinations of high chemical and optical yield was observed when **12a** was treated with refluxing concentrated hydrochloric acid in which case essentially optically pure **4** was isolated in 91% yield.

Scheme IV



Scheme V



An attempt was made to apply the Mayer zinc chloride procedure[4b] to **12b**. In contrast to **6**, however, this hydroxy ester failed to cyclize when heated at 50 °C with neat zinc chloride; only the starting material and its air oxidation product (quinone **11b**) could be detected in the product. When **12b** was refluxed in benzene containing zinc chloride, **10b** (96% ee) was regenerated in 49% yield, suggesting that under these conditions the cyclization was

(5) Scott, J. W.; Bizzarro, F. T.; Parrish, D. R.; Saucy, G. *Helv. Chim. Acta* **1976**, *59*, 290–306 [mp 124.5–128 °C; $[\alpha]^{25}_D$ +14.78° (c 1, C_2H_5OH)].

(6) Obtained by Fisher esterification (CH_3OH–*p*-TsOH) of acid **10c**: oil; $[\alpha]^{25}_D$ +18.01° (c 1.2, C_6H_6).

(7) The racemic modification of **11a** has been prepared previously: Cort, W. M.; Scott, J. W.; Araujo, M.; Mergens, W. J.; Cannalonga, M. A.; Osadca, M.; Harley, H.; Parrish, D. R.; Pool, W. R. *J. Am. Oil Chem. Soc.* **1975**, *52*, 174–8.

(8) We have recently described still another example of this type of cyclodehydration in which (*S*)-hydroquinone diol **23** was transformed into (*S*)-chroman-2-methanol **24** (80%), with 95% retention of configuration, upon treatment with *p*-toluenesulfonic acid in refluxing benzene (see ref 2f).

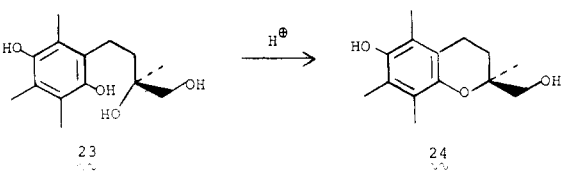


Table I. Hydroquinone ⟶ Chroman Cyclizations

starting matl (concn, M)	major product	reagent (amt, equiv)	solvent	temp, °C time, h	yield,[a] %	product mp, °C	product $[\alpha]^{25}_D$, deg	major stereochem result	approx % ee in product
6	7	$ZnCl_2$ (13.4)	none[b]	50/1.25	67[q,r]	oil	−20.48[c]	inversion	65[d]
6 (0.022)	1	p-TsOH (0.23)	benzene	80/1.25	95	oil	+31.39[c]	retention	100[d]
12a (0.07)	4	p-TsOH (0.07)	benzene	80/3.5	55[u]	ND	+60.91[e]	retention	92[g]
12a (0.43)	4	concn HCl (28)	none	90/2	91	154-157.5 dec	+64.70[e]	retention	98[g]
12b (0.05)	10b	p-TsOH (0.1)	benzene	80/1.75	77[q,s]	132-134	+60.28[h]	retention	97[i]
12b (0.035)	10b	$ZnCl_2$ (13)	benzene	80/20	49[q,s]	129-132	+59.48[h]	retention	96[i]
12b		$ZnCl_2$ (13.5)	none[b]	50/1.33	0[j]				
12c (0.1)	10c	p-TsOH (0.26)	benzene	80/1.5	81	ND	+14.52[e]	retention	100[f]
12d (0.09)	10d	p-TsOH (0.12)	benzene	80/1	91[q,t]	oil	+18.41[k]	retention	100[l]
12d (0.07)	10d	$BF_3 \cdot Et_2O$ (0.3)	benzene	80/20	64[q,t]	oil	+16.55[k]	retention	92[l]
23 (0.05)	24	p-TsOH (0.1)	benzene	80/1.25	80[q,t]	122-124	+1.09[m]	retention	95[n]
20[o]	22	H_2/Pd-$NaOCH_3$ (4)	methanol	23/1	67[p,q,s]	132-133.5	−59.93[h]	inversion	97[i]
20 (0.03)[o]	22	$NaBH_4$-$NaOCH_3$ (5.2)	methanol	23/2	84[p,q,s]	131-134	−60.46[h]	inversion	98[i]
20 (0.125)[o]	22	$Na_2S_2O_4$-NaOH (3)	methanol-water	23/0.33, 65/0.08	93[p]	132.5-135	−60.62[h]	inversion	98[i]
21 (0.05)	22	DBN (1.1)	benzene	23/4	26[u]	130-133	−60.23[h]	inversion	97[i]
21 (0.03)		p-TsOH (0.2)	benzene	80/2.5	0[j]				

[a] Yields and rotations refer to pure (TLC) products; since the hydroquinones were not purified prior to cyclization, yields based on these substrates are approximate. [b] Procedure of ref 4b. [c] Rotation of purified (preparative TLC) $K_3Fe(CN)_6$ oxidation product of α-tocopherol (c 4, isooctane). [d] Based on $[\alpha]^{25}_D$ +31.5° (c 5, isooctane) for chromatographed $K_3Fe(CN)_6$ oxidation product of natural α-tocopherol: Rubel, T. "Vitamin E Manufacture"; Noyes Development Corp.: Park Ridge, NJ, 1969; p 97. [e] c 1, EtOH. [f] Based on $[\alpha]^{25}_D$ +14.78° (c 1, EtOH) for optically pure **10c**.[5] [g] Based on $[\alpha]^{25}_D$ +66.1° (c 1, EtOH) for optically pure **4** (mp 159-161 °C dec).[1] [h] c 3-5, CH_3OH. [i] Based on $[\alpha]^{25}_D$ −61.9° (c 5, CH_3OH) for optically pure **22** (mp 134-135 °C). [j] Product composed mainly of starting hydroquinone and its air oxidation product (benzoquinone). [k] c 1, benzene. [l] Based on $[\alpha]^{25}_D$ +18.01° (c 1, benzene) for optically pure **10d**.[6] [m] c 2, EtOH. [n] See ref 2f, 8. [o] Two-stage reduction-cyclization procedure; the concentration refers to **21** in cyclization stage; the hydroquinone was not isolated (see Experimental Section). [p] Yield based on starting benzoquinone **20**. [q] Product purified by column chromatography on silica gel. [r] Eluted with 9:1 and 4:1 petroleum ether-ether. [s] Eluted with 19:1 and 9:1 toluene-ethyl acetate. [t] Eluted with 9:1 and 4:1 toluene-ethyl acetate. [u] Purified by preparative TLC on silica gel.

Table II. Oxidation of Chromanols to Benzoquinones

starting matl	quinone	oxidizing agent[a]	yield, %	quinone $[\alpha]^{25}_D$, deg	quinone UV_{max},[b] nm (ε)	quinone IR_{max},[c] cm^{-1}
1[d]	5	$FeCl_3$	89[e]	ND[f]	262 (19500), 268 (19730), 348 (305)	3610, 1643
4	11a	$FeCl_3$	75[g,i]	−12.08[h]	261 (17300), 268 (17650), 343 (244)	3550-2400, 1710, 1640
10b	11b	$FeCl_3$	85[e,j,k]	−21.01[h]	262 (18870), 269 (19255), 343 (240)	3600, 3540, 1728, 1640
10b	11b	HNO_3	100[l]	−18.91[h]	ND[f]	ND[f]
10c	11c	$FeCl_3$	80[e,m]	ND[f]	264 (16650), 270 (17030), 345 (230)	3600-2400, 1710, 1640
10d	11d	$FeCl_3$	85[e,n,p]	+0.76[o]	263 (18750), 268 (19060), 345 (260)	3520, 1720, 1643

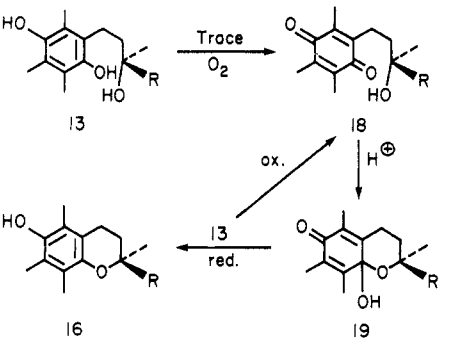
[a] See the Experimental Section for Procedures. [b] 95% EtOH. [c] $CHCl_3$ solution. [d] Obtained by alkaline hydrolysis of Eastman Kodak vitamin E 6-100 d-α-tocopheryl acetate. [e] Yellow, oily product obtained by chromatographic purification (eluted with 19:1 and 9:1 toluene-ethyl acetate). [f] Not determined. [g] Pure product obtained by recrystallization; mp 101.5-104 °C (from $CHCl_3$-hexane). [h] c 1, $CHCl_3$. [i] Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.15; H, 6.81. Found: C, 63.14; H, 6.85. [j] Eluted with 9:1 and 4:1 toluene-ethyl acetate. [k] Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.34; H, 7.03. [l] Crude oily product. [m] Eluted with 1:2 toluene-ethyl acetate and ethyl acetate. [n] Eluted with 4:1 and 2:1 toluene-ethyl acetate. [o] c 5, $CHCl_3$. [p] Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.17; H, 7.60.

catalyzed by hydrogen chloride produced by the Lewis acid. Exposure of **12d** to boron trifluoride etherate in refluxing benzene led, in 69% yield, to **10d** (92% ee).

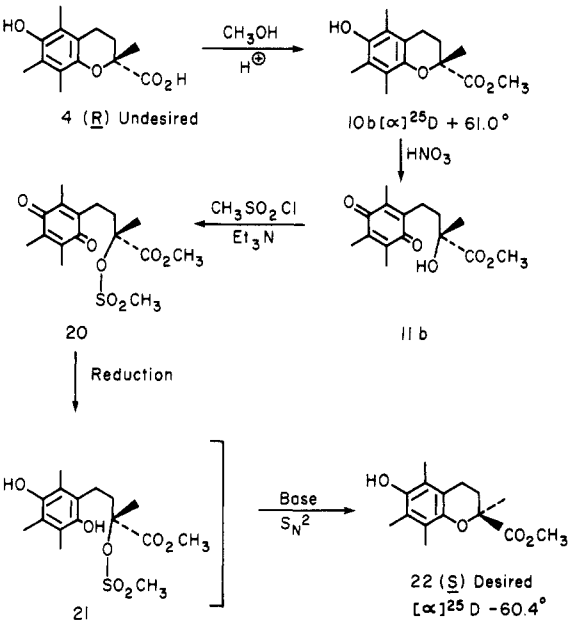
A mechanistic rationale which we had previously proposed[2f] to explain the stereochemical outcome of these cyclizations is presented in Scheme V ("natural" stereochemical series depicted). Under proton catalysis, an equilibrium is established between the hydroquinone substrate **13** and a keto tautomer such as **14**. Attack of the side chain hydroxyl moiety on the ketone, as shown, then leads to the hemiketal **15** which rapidly rearomatizes by loss of water, producing the observed chroman **16**. Since the stereochemical integrity of the chiral tertiary alcohol center is unaffected in such a process, the net result is cyclodehydration with retention of configuration. While this pathway may, in fact, be operable, we now favor an alternative explanation for the clean retention of configuration observed in the proton-catalyzed conversions of **6** and **12a–d** to the corresponding chromans as shown in Scheme VI ("natural" stereochemical series depicted). This involves the intermediacy of quinone **18** formed in trace quantity by air oxidation of **13**. The derived hemiketal **19** could then undergo reduction by the starting hydroquinone, yielding the observed chroman and regenerating **18**, thus establishing a catalytic redox cycle. This process is closely related to the known[4a] reductive cyclization of α-tocopherolquinone (**5**) shown in Scheme III. Our current preference for this latter mechanism is based in part upon the fact that, because of their extreme air sensitivity, hydroquinones **6** and **12a–d** always contained traces of the corresponding quinones whose formation could not be suppressed. In addition, certain relevant observations of others which also point to Scheme VI as the controlling pathway have been brought to our attention.[9]

In contrast, the Mayer result involving zinc chloride treatment of tocopherolhydroquinone (**6**)[4b] must be viewed, as suggested by these workers,[4b] as a rare example of an S_N2 displacement occurring at a tertiary center. Thus one can envision the formation of a zinc complex such as **17** (Scheme V) in which the phenolate species attacks the chiral center in a backside manner, as shown, leading to an inverted chroman **7**. It is unclear why this process fails in the case of **12b**.

Scheme VI



Scheme VII

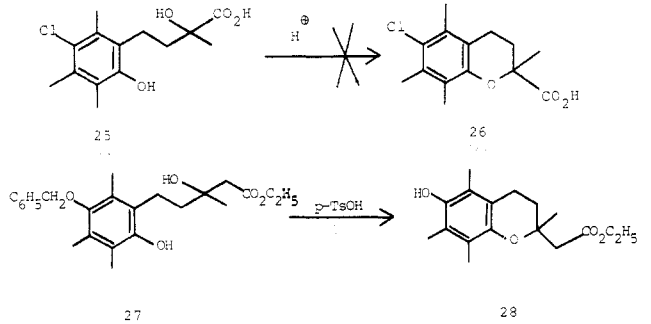


In view of our results, it became apparent that in order for cyclization of an intermediate such as **12** to occur with inversion of configuration, the tertiary hydroxyl function present would have to be converted into a leaving group capable of displacement by the proximate phenolate moiety (cf. **17** → **7**). Thus a successful inversion process was developed on the basis of the key mesylate **20** (Scheme VII).

Oxidation of the (*R*)-ester **10b** to the quinone **11b** was most conveniently and economically carried out by using 70% nitric acid[10] (see Table II). Mesylate **20** was then obtained by slow addition of excess methanesulfonyl chloride to a solution of **11b** in dichloromethane containing triethylamine at −10 °C.[11] The crude product always contained some starting alcohol, and efforts to achieve quantitative sulfonation by modifying the base, reaction time, temperature, etc. were unavailing. Nonetheless, **20** was obtained in quite satisfactory yield as a stable, bright yellow, crystalline solid which could be purified, if desired, by chromatography or recrystallization. As expected, because of the relatively hindered nature of the hydroxyl function, attempted formation of the corresponding tosylate gave, at best, traces of that sulfonic ester.

The key reduction–cyclization sequence (**20** → **22**) was found to be surprisingly facile and could be carried out by using a variety of procedures. Thus, exposure of **20** to

(9) Dr. John W. Scott of our laboratories has informed us that, in another study, attempted cyclodehydration of the racemic chlorophenol acid **25** under a variety of acidic conditions (*p*-TsOH, benzene reflux; concentrated HCl, reflux; 18 N H_2SO_4–dioxane, reflux; H_2SO_4–Ac_2O, 115 °C) failed to produce the desired chroman-2-carboxylic acid **26**. Similarly, the phenolic hydroxy ester **27** could be induced to cyclize only under conditions which first cleaved the benzyl ether protecting group (*p*-TsOH, toluene, reflux) in which case the 6-hydroxychroman-2-acetic acid ester **28** was the observed product. These results support the catalytic redox mechanism delineated in Scheme VI since neither **25** nor **27** can be converted to the corresponding quinone by air oxidation under the cyclization conditions. Thus in these substrates, the pathway shown in Scheme VI is blocked while that in Scheme V would, presumably, still be available. The failure to cyclize when the 6-hydroxyl moiety is protected or replaced strongly implicates the quinone **18** as a key intermediate in these transformations.



(10) Nakao, H.; Arakara, M. *Chem. Pharm. Bull.* **1972**, *20*, 1962–7.
(11) Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195–6.

sodium dithionite, sodium borohydride, or catalytic hydrogenation led to the unstable hydroquinone **21**[12] which was usually not isolated. Instead, the solution containing this intermediate was immediately treated with a base, giving virtually optically pure **22** in generally high yield. Several results are presented in Table I. After considerable experimentation, it was found that **22** could be obtained most economically and expeditiously by addition of a slight excess of aqueous sodium dithionite containing 3 equiv of sodium hydroxide to a methanol slurry of **20**. The yellow color of the quinone was rapidly discharged and, after a brief reflux period, a colorless slurry of **22** was produced from which chemically and essentially optically pure **22** was isolated by direct filtration. In this manner, **22** was secured in 78% overall yield from **10b**, without purification of intermediates **11b** and **20**.[13]

It should be emphasized that the cyclization of **21** to **22**, like that of **6** to **7**,[4b] is a relatively rare example of a bona fide S_N2 displacement occurring at a tertiary center.[14] The backside nature of this displacement is confirmed by the virtually quantitative stereochemical inversion observed. Two factors undoubtedly facilitate this process. One is the intramolecular nature of the reaction, and the other is the electronic effect of the carbomethoxy group which renders the α-mesyloxy substituent especially reactive toward nucleophilic displacement.

In summary, the studies described above have shown that, with one known exception,[4b] α-tocopherolhydroquinone (**6**) and related chiral (3-hydroxyalkyl)trimethylhydroquinones cyclize, under acid catalysis, with essentially complete retention of configuration at the carbinol center. The process developed for inversion of configuration in the unwanted (*R*)-chroman-2-carboxylic acid **4** now renders synthetic approaches to (2*R*,4'*R*,8'*R*)-α-tocopherol, which proceed via the readily available racemic acid **2**, highly attractive in terms of chiral economy.

Experimental Section

Unless otherwise noted, reactions were carried out under an atmosphere of argon. Melting points were obtained by using a Thomas-Hoover capillary apparatus and are uncorrected. The "usual workup" involves three extractions with the specified solvent. The organic extracts were washed with water and saturated brine, dried ($MgSO_4$), filtered, and concentrated at 40–50 °C on a rotary evaporator. The residue was further dried to constant weight under high vacuum. Column chromatography was performed by using 50–100 parts by weight of EM silica gel 60, 0.063–0.2 mm. Thin-layer chromatography (TLC) was generally used to monitor the progress of reactions and was carried out by using precoated EM silica gel 60 F-254 plates developed with 1:1 toluene–ethyl acetate, unless otherwise noted. Spots were detected with UV light and by spraying with methanolic phosphomolybdic acid followed by heating. Infrared spectra were measured in $CHCl_3$ solution unless otherwise indicated and ultraviolet spectra in 95% ethanol. Chemical shifts (NMR) are reported relative to tetramethylsilane as an internal standard. Tetrahydrofuran and triethylamine were slurried over Woelm W-200 neutral Alox I just prior to use.

Methyl (*R*)-(+)-3,4-Dihydro-6-hydroxy-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-carboxylate (10b). A solution of 2 g (8 mmol) of optically pure (*R*)-(+)-3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-carboxylic acid (**4**;[1] $[\alpha]^{25}_D$ +65.84° (*c* 1.18, C_2H_5OH)) and 0.1 g of *p*-toluenesulfonic acid monohydrate in 40 mL of methanol was stirred and refluxed for 3.75 h. After cooling, the solution was diluted with water and worked up with ether in the usual manner (the ether extracts were additionally washed with saturated aqueous sodium bicarbonate solution), giving 2 g (94.7%) of ester **10b** as a colorless solid: mp 132–134.5 °C; $[\alpha]^{25}_D$ +61.4° (*c* 4.91, CH_3OH). The analytical specimen was obtained by recrystallization of a sample from aqueous methanol as a colorless solid: mp 133.5–135 °C; $[\alpha]^{25}_D$ +61.85° (*c* 5.07, CH_3OH).

Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.40; H, 7.74.

Ferric Chloride Oxidation of Chromanols to Benzoquinones. The procedure of Mayer et al.[4b] was employed. The results are summarized in Table II. The following experiment describing the preparation of **11b** is typical. To a stirred solution of 1.5 g (5.68 mmol) of ester **10b** from the preceding experiment, in 22 mL of ether, was added a solution of 4.5 g (16.6 mmol) of ferric chloride hexahydrate in 17 mL of water and 17 mL of methanol. The addition was carried out in six approximately 6-mL portions at 0.5-h intervals. Half an hour after the last addition, the ether layer was separated, and the aqueous phase was further worked up by ether extraction in the usual manner. There was obtained 1.5 g of a yellow oil which was chromatographed on 75 g of silica gel. Elution with 9:1 and 4:1 toluene–ethyl acetate yielded 1.35 g (84.9%) of quinone **11b** as a yellow oil.

(*R*)-(−)-Methyl 2-Hydroxy-2-methyl-4-(3,4,5-trimethyl-3,6-dioxo-1,4-cyclohexadien-1-yl)butanoate (11b) by Nitric Acid Oxidation of 10b. A suspension of 2.64 g (10 mmol) of (*R*)-ester **10b** ($[\alpha]^{25}_D$ +61.00° (*c* 3.05, CH_3OH)) in 25 mL of ether was vigorously stirred with ice-bath cooling while 5 mL (80 mmol) of 70% nitric acid was added dropwise over a 15-min period. The resulting bright yellow solution was cautiously poured into excess saturated aqueous sodium bicarbonate solution. Workup with ether in the usual manner gave 2.78 g (99.5%) of quinone **11b** as a yellow oil. This material was identical with that produced by the $FeCl_3$ procedure described above by TLC comparison.

Catalytic Hydrogenation of Quinones 5, 11a–d, and 20. An ethyl acetate (ethanol in the case of **11c**) solution of the quinone was stirred under an atmosphere of hydrogen in the presence of 5% palladium on carbon until gas uptake ceased. Approximately 1 mol of hydrogen was usually absorbed. The catalyst was filtered, and the filtrate was concentrated in vacuo. Because of their tendency to air oxidize, the hydroquinones so obtained in virtually quantitative yields were used without further purification.

Acid-Catalyzed Cyclizations of Hydroquinones 6, 12b, and 12d. These cyclizations were carried out by using *p*-toluenesulfonic acid or boron trifluoride etherate under the conditions described in Table I. The benzene solutions were cooled and treated with saturated sodium bicarbonate. The products were isolated by a workup with benzene or ether in the usual manner and purified by chromatography on silica gel, eluting with mixtures of toluene and ethyl acetate. The zinc chloride cyclization of **12b** in benzene was worked up with ether after quenching with 1 N aqueous HCl.

Acid-Catalyzed Cyclizations of Hydroquinone Acids 12a and 12c. The cyclizations of these acids with *p*-toluenesulfonic acid monohydrate were carried out under the conditions described in Table I. In the case of **12a**, the reaction mixture was cooled and filtered to remove some insoluble material. The benzene filtrate was concentrated in vacuo, and a portion of the crystalline residue (**4**) was purified by preparative TLC on silica gel (plates developed with 85:15:10 benzene–ethyl acetate–acetic acid). In the case of **12c**, the benzene solution was cooled and poured into water. The organic materials were extracted wiih ether, and then the ether solution was washed with water and twice with saturated aqueous sodium bicarbonate solution. The bicarbonate extracts were combined, acidified with 6 N aqueous HCl and worked up with ether in the usual manner. The acid **10c** obtained was homogeneous on TLC analysis (benzene–ethyl acetate–acetic acid, 85:15:10).

Cyclization of **12a** with concentrated HCl was carried out as follows. A mixture of 1 g (3.73 mmol) of hydroquinone acid **12a** and 8.7 mL of concentrated HCl was stirred and heated at 90 °C for 2 h. After cooling to room temperature, the mixture was

(12) Treatment of this substance with *p*-toluenesulfonic acid in refluxing benzene failed to produce chroman, further suggesting that, under these conditions, cyclization involves attack of the free tertiary hydroxyl function on the aromatic ring as shown in Schemes V and VI.

(13) It should be noted that this inversion sequence could not be carried out without initial esterification of **4** since attempted mesylation of quinone acid **11a** led to an extremely complex mixture of products. The added esterification step is no inconvenience, however, since the ester **22** is required for subsequent conversion to (2*R*,4'*R*,8'*R*)-α-tocopherol.[2f]

(14) Cf.: (a) Baird, K. J.; Grundon, M. F. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1820–5; (b) Silverman, R. B. *J. Am. Chem. Soc.* **1980**, *102*, 5421–3.

filtered with suction. The damp solid cake was dissolved in chloroform, and the solution was processed in the usual manner, giving 0.845 g of pure (TLC) **4** as a beige solid (see Table I).

(*R*)-(-)-Methyl 2-Methyl-2-[(methylsulfonyl)oxy]-4-(2,4,5-trimethyl-3,6-dioxo-1,4-cyclohexadien-1-yl)butanoate (20). To a stirred solution of 0.746 g (2.66 mmol) of benzoquinone **11b** in 18 mL of dichloromethane, cooled in an ice-bath, was added 2.43 mL (1.77 g, 17.5 mmol) of triethylamine followed by 1.35 mL (2.01 g, 17.5 mmol) of methanesulfonyl chloride. The mixture was kept at 0 °C for 64 h and then treated with water. The dichloromethane solution was processed in the usual manner to give 1.45 g of an oily product which was chromatographed on 75 g of silica gel. Elution with 9:1 toluene–ethyl acetate afforded 0.69 g (72.5%) of methanesulfonate **20** as a yellow solid. Recrystallization of a sample from hexane–ethyl acetate provided yellow crystals: mp 112–114 °C; $[\alpha]^{25}_D$ -5.24° (*c* 1.05, $CHCl_3$); UV_{max} 260 nm (ε 19 600), 267 (20 000), 343 (275); IR 1750 (ester C=O), 1642 (quinone), 1352, 1178 cm^{-1} (SO_2); NMR ($CDCl_3$) δ 3.73 (s, 3, CO_2CH_3), 3.18 (s, 3, SO_2CH_3), 2.10 (m, 2, CH_2), 2.03, 1.99 (2 s, CH_3C=), 1.84 (s, 3, CH_3).

Anal. Calcd for $C_{16}H_{22}O_7S$: C, 53.62; H, 6.19; S, 8.95. Found: C, 53.59; H, 6.14; S, 8.61.

Mesylate **20** could also be purified by recrystallization from methanol.

Methyl (*S*)-(-)-3,4-Dihydro-6-hydroxy-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-carboxylate (22). (a) Reduction of 20 with Sodium Dithionite. A slurry of 0.358 g (1 mmol) of quinone methanesulfonate **20** in 5 mL of methanol was stirred rapidly at room temperature while a solution of 0.261 g (1.5 mmol) of sodium dithionite in 3 mL of 1 N aqueous sodium hydroxide was added dropwise over a 5-min period. The resulting mixture was stirred at room temperature for 20 min and then refluxed for 5 min. After the mixture cooled, 20 mL of water was added, and the colorless slurry was filtered with suction. The solid was washed with water then dried under high vacuum, giving 0.246 g (93.2%) of chromanol ester **22** as a colorless solid: mp 132.5–135 °C; $[\alpha]^{25}_D$ -60.62° (*c* 3.09, CH_3OH). This material was homogeneous on TLC analysis.

(b) Catalytic Hydrogenation of 20. A mixture of 1 g (2.79 mmol) of quinone methanesulfonate **20**, 0.2 g of 5% palladium on charcoal, and 125 mL of methanol was stirred in an atmosphere of hydrogen until gas uptake ceased. The catalyst was filtered with suction on a pad of Celite, and the filtrate (containing **21**) was immediately treated with 8.3 mL (11.16 mmol) of 1.34 M methanolic sodium methoxide. After being stirred for 1 h at room temperature, the solution was acidified with 3 N aqueous hydrochloric acid and poured into saturated brine. Workup with ether in the usual manner gave 0.638 g of a tan solid which was chromatographed on 25 g of silica gel. Elution with 19:1 and 9:1 toluene–ethyl acetate furnished 0.491 g (66.7%) of ester **22** as a colorless solid, $[\alpha]^{25}_D$ -59.93° (*c* 3.01, CH_3OH).

(c) Reduction of 20 with Sodium Borohydride. To a solution of 0.5 g (1.4 mmol) of quinone mesylate **20** in 30 mL of methanol, at room temperature, was added a solution of 20.2 mg (0.53 mmol) of sodium borohydride in 10 mL of methanol, dropwise, with stirring. After the mixture was stirred at room temperature for 50 min, 5.77 mL (7.73 mmol) of 1.34 M methanolic sodium methoxide was added, and stirring was continued for 2 h at room temperature. The resulting solution was acidified with 1 N aqueous hydrochloric acid, poured into saturated brine, and worked up with ether in the usual manner. The crude, crystalline product (0.34 g) was chromatographed on 20 g of silica gel. Elution with 19:1 and 9:1 toluene–ethyl acetate gave 0.311 g (84.1%) of ester **22** as a colorless solid: mp 131–134 °C; $[\alpha]^{25}_D$ -60.46° (*c* 3.88, CH_3OH).

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Products from the Base Treatment of the Tri-*O*- and Tetra-*O*-methanesulfonyl Esters of Methyl α-D-Glucopyranoside

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Treatment of the four tri-*O*-methanesulfonyl and tetra-*O*-methanesulfonyl esters of methyl α-D-glucopyranoside gave as initial products methyl anhydro-*O*-methanesulfonyl- and anhydro-di-*O*-methanesulfonyl-α-D-hexosides. Further base treatment transformed these initial products into a variety of anhydro-, anhydro-*O*-methanesulfonyl-, and dianhydrohexosides and one olefinic hexoside, depending on the initial product. An order of preference, $C_4 > C_6 > C_2$, for the internal sulfonyloxy group displacement was found. The end product preferences noted in Scheme I accounted for the observed products.

Reaction of carbohydrate sulfonates with various nucleophilic reagents is well recorded.[2] The many factors that influence the sulfonate displacements are discussed. If the carbohydrate sulfonate is partially substituted (or the free hydroxyl groups are esterified with carboxyl groups), the treatment with base results in the displacement taking a different route. An internal ether, an anhydro sugar, is formed, and, if the stereochemical arrangement is suitable, either a cross-ring isomerization of the methyl 2,3-anhydro-α-D-allopyranoside to methyl 3,6-anhydro-α-D-glucopyranoside type or a vicinal isomerization of the methyl 3,4-anhydro-α-D-altropyranoside to methyl 2,3-anhydro-α-D-mannopyranoside type can further occur. Base hydrolysis of sulfonates will occur only if the above reactions or isomerizations cannot occur; the hydrolysis is difficult. These alkaline displacements and

(1) The mention of firm names or trade products does not imply that they are endorsed or recommended by the U.S. Department of Agriculture over other firms or similar products not mentioned.

(2) R. S. Tipson, *Adv. Carbohydr. Chem.*, 8, 107 (1953); D. H. Ball and F. W. Parrish, *ibid.*, 23, 233 (1968); D. H. Ball and F. W. Parrish, *Adv. Carbohydr. Chem. Biochem.*, 24, 139 (1969).