A Novel Total Synthesis of (2*R*,4′*R*,8′*R*)-α-Tocopherol (Vitamin E). Construction of Chiral Chromans from an Optically Active, Nonaromatic Precursor

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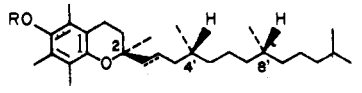
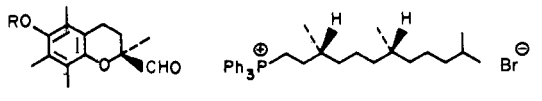
Abstract: A new approach to the total synthesis of (2*R*,4′*R*,8′*R*)-α-tocopherol (vitamin E, **1**) is described in which the chroman synthon (*S*)-(+)-6-benzyloxy-3,4-dihydro-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-carboxaldehyde (**6**) is prepared starting from (*S*)-(−)-2-methyl-5-oxotetrahydro-2-furoic acid (**11**). By a seven-stage sequence, **11** was elaborated to (*S*)-(+)-2,3,6-trimethyl-5-(2,2,4-trimethyl-1,3-dioxolane-4-ethyl)phenol (**20**), further transformations of which provided the optically active intermediates **21**, **22**, **24**, and **26–28**. The key processes involve reductive aromatization of the bridged, tricyclic quinone monoketal **24** and acid-catalyzed cyclodehydrations of hydroquinones **22** and **28**, all of which proceed with 95–100% retention of configuration generating (*S*)-(+)-3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-methanol (**25**). The total synthesis was completed by Wittig coupling of **6** (obtained in two steps from **25**) with the known (3*R*,7*R*)-3,7,11-trimethyl-1-dodecyltriphenylphosphonium bromide (**7**), followed by catalytic hydrogenation, giving **1**, characterized as its acetate **2**.

In recent years, vitamin E (α-tocopherol), a potent antioxidant and radical scavenger in chemical and biological systems, has been receiving increasing attention with regard to clinical and nutritional applications in human health.[1] Despite the resurgence of interest in many aspects of this important vitamin, relatively little attention has been devoted to the development of processes for total synthesis of the naturally occurring form [(2*R*,4′*R*,8′*R*)-α-tocopherol; **1**], since the pioneering studies of Mayer, Isler, and co-workers in the early 1960s.[2a,b] In an effort to fill this void, we have been exploring approaches to the total synthesis of **1** and have already disclosed some of our recent results.[3] Herein, we wish to describe our investigation of an approach to the optically active α-tocopherol molecule in which the chroman portion is constructed in an entirely novel manner.

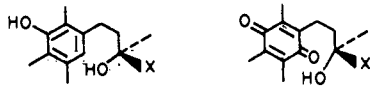


1; R = H, $C_{1'}$–$C_{2'}$ single bond
2; R = Ac, $C_{1'}$–$C_{2'}$ single bond
3; R = Ac, $C_{1'}$–$C_{2'}$ double bond
4; R = $CH_2C_6H_5$, $C_{1'}$–$C_{2'}$ double bond



5; R = Ac
6; R = $CH_2C_6H_5$

7



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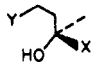

10

In terms of strategy, we viewed the penultimate stage of our approach as involving Wittig coupling of a chiral chroman-2-carboxaldehyde with the 15-carbon phosphonium salt **7**.[4] Mayer and co-workers had utilized this convergent scheme in their synthesis of **1** via the (2*S*)-aldehyde ester **5** and the dehydro-α-tocopheryl acetate **3**.[2,4] Our earlier studies had already produced several syntheses of side-chain intermediates containing either 14[3a,c–e] or 15[3b,5] skeletal carbon atoms. Thus our attention was directed to novel methods of chroman construction.

In the previous work, optically pure chroman compounds were prepared by classical resolution of their racemic counterparts, in turn derived by elaboration of trimethylhydroquinone.[2,3a,g,4,6] Despite the efficiency of these processes and the ability to utilize the unwanted enantiomers in certain instances,[7,8] we were intrigued by an alternative approach in which the chroman (e.g., **5** or **6**) was derived from a simple (four to six carbon) and readily available, optically active substance. It was hoped that logistical and economic advantages, relative to the earlier schemes, would be gained by carrying out an optical resolution (if required) at the earliest possible stage of the synthetic sequence. On the other hand, resolution might be avoided altogether if access to the desired starting compounds were to be provided by an asymmetric or microbiological approach.[9]

With these considerations in mind, retrosynthetic dissection of the chroman targets led to the phenol **8** and related benzoquinone **9**, wherein X is a functionalized one-carbon moiety, as attractive key intermediates. It should be noted that **9** is an analogue of α-tocopherolquinone (**9**, X = $C_{16}H_{33}$), an oxidation product of α-tocopherol, whose reconversion to α-tocopherol, with retention of configuration, is known.[2,10] Upon further dissection, we arrived at a chiral, tertiary carbinol represented generically by **10**, possessing differentiated functionalities X and Y. The preparation of such compounds and their elaboration into **6** and ultimately **1** are set forth below

Results

From a group of several attractive chiral substances, we selected (*S*)-(−)-2-methyl-5-oxotetrahydro-2-furoic acid (**11**)[11] (Scheme I) as a starting material which appeared to meet our requirements. The racemic form of this six-carbon lactone acid is readily available from levulinic acid and hydrogen cyanide[12] and resolution with cinchonine[11] easily affords the enantiomer having the absolute configuration required for transformation into **1** with retention of configuration. Conversion of **11** to compounds of the type **10** was straightforward. Thus selective reduction of the carboxyl group

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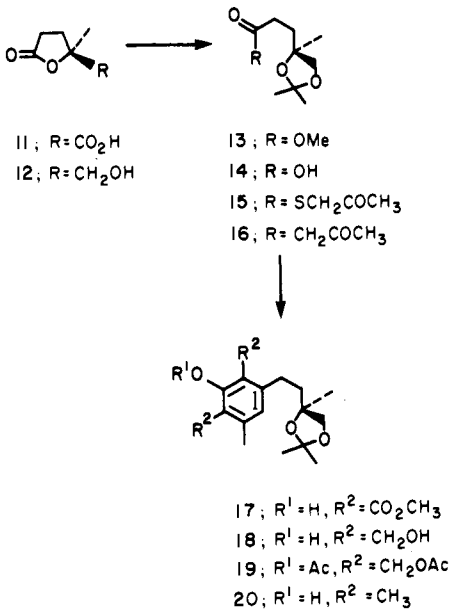
Scheme I

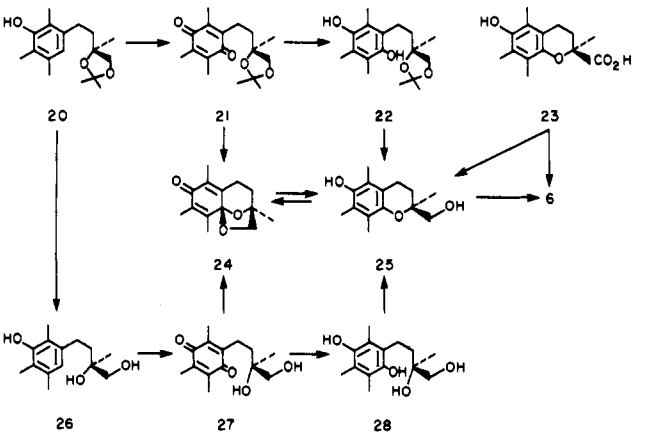


with borane-methyl sulfide[13] gave (*S*)-(+)-lactone methanol **12**[14] which upon treatment with 2,2-dimethoxypropane and *p*-toluenesulfonic acid at room temperature yielded (*S*)-(+)-ester acetonide **13**. Saponification then afforded the corresponding acid **14** in 84% overall yield from **11**. The acyl imidazole derived from **14**, when treated with 2,5-dihydroxy-2,5-dimethyl-1,4-dithiane[15] furnished thiol ester **15** (80%) which, in turn, underwent alkylative desulfurization when exposed to bis(3-dimethylaminopropyl)phenylphosphine and lithium bromide in refluxing acetonitrile.[16] This procedure provided the (*S*)-(+)-β-diketone **16** (72%), a protected version of the archetypal synthon **10**, ideally functionalized for further transformation into aromatic intermediates.

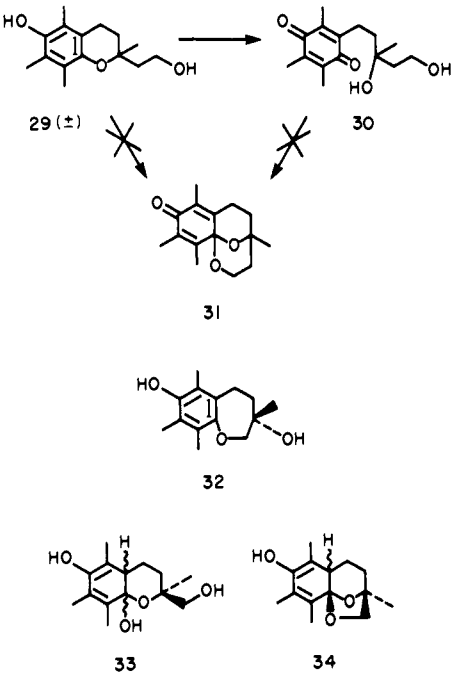
The phenol moiety was now constructed by annulation[17] of **16** with dimethyl acetonedicarboxylate-sodium methoxide giving (*S*)-(+)-isophthalic ester **17** in 90% yield. Conversion of the carbomethoxy functions to methyl substituents was initially carried out using a multistep sequence involving reduction ($NaAlH_2(OCH_2CH_2OMe)_2$, 35 °C; → **18**; 83%), acetylation (acetic anhydride-pyridine; → **19**; quantitative), and, finally, benzylic acetate hydrogenolysis (sodium borohydride-Me_2SO,[18] 100 °C; then NaOH; 69%) affording the desired, crystalline (*S*)-(+)-phenol **20**. Subsequently it was found that **17** could be directly reduced to **20**, in 82% yield, by treatment with $NaAlH_2(OCH_2CH_2OMe)_2$ at 140 °C,[19] a modification which allowed the preparation of this key substance via a seven-step sequence in overall yields of ca. 25%, starting from **11**. Having an intermediate of the type represented by **8** now in hand, the first stage of our synthetic plan was complete and elaboration of the chroman system could commence.

Oxidation of **20** with excess Fremy's salt[20] proceeded smoothly and furnished the (*S*)-(+)-*p*-benzoquinone **21** (Scheme II) (cf. **9**) in 98% yield. Treatment of this quinone with aqueous methanolic HCl adventitiously afforded the crystalline bridged tricyclic monoketal **24**[21-23] (72%) along with minor amounts of the expected quinone diol **27**. For comparison purposes, a sample of **24** was prepared from (*S*)-(−) acid **23**[6] by a sequence involving hydride reduction (→**25**[24]) followed by ceric sulfate oxidation[25] and found to be identical with the material derived from **21** (mp 99-100 °C, $[\alpha]^{25}_D$ −56° (*c* 2, benzene)). It is interesting to note that the formation of internal quinone monoketals such as **24** is not general. Thus, experiments with racemic compounds revealed that ceric sulfate oxidation[25] of chroman-2-ethanol **29**[26] gives

Scheme II



only the quinone diol **30** and none of the tricyclic ketal **31**. Furthermore, attempts to cyclodehydrate **30** to **31** under conditions which provided **24** in excellent yield from **27** (1 N HCl, MeOH, room temperature) were totally unsuccessful. Forcing conditions (*p*-toluenesulfonic acid, benzene, reflux) led to destruction of **30** (polymer formation). Our inability to produce **31** by these procedures suggests the presence, in this molecule, of rather subtle, unfavorable, conformational factors absent in the lower homologue **24**.



The facile formation of **24** from **21** now provided us with a process by which the crucial carbon-oxygen bond required for generation of the chroman ring system was affixed. All that we now required was a method for effecting selective, reductive scission of the oxymethylene bridge. We were thus pleased to discover that treatment of this key intermediate with a variety of reducing agents including hydrogen-palladium on carbon (76%), zinc-acetic acid (30%), and $NaAlH_2(OCH_2CH_2OMe)_2$ (82%) led to the desired (*S*)-(+)-chroman-2-methanol **25**. In no case could we find evidence for formation of the alternative reductive aromatization product (*S*)-benzoxepin **32**.[27] This regioselectivity is most likely a result of stereoelectronic factors which render the oxymethylene bridge, because of its perpendicular (pseudoaxial) disposition relative to the cyclohexadienone moiety, a more suitable leaving group than the oxido function.

Examination of the ^1H NMR spectra of the samples of **25** obtained by reductive aromatization of **24** in the presence of

an optically active shift reagent revealed the presence of only one enantiomer.[28] Furthermore, these samples were virtually identical with material produced by reduction of *S* acid **23.** In this manner, we were assured that retention of configuration throughout the synthetic sequence starting from **11** had been complete.

Chromanol **25** was also available from **20** by alternative sequences not involving ketal **24.** Thus hydrolysis of **20** gave the phenol diol **26** which was smoothly oxidized to the quinone **27** (91%) using Fremy's salt.[20] As noted above, **27** readily underwent cyclodehydration affording **24** when exposed to acid; however, catalytic hydrogenation under neutral conditions produced the air-sensitive hydroquinone diol **28.** Upon treatment with *p*-toluenesulfonic acid in refluxing benzene, **28** was readily transformed into **25** (80%) with *95% retention of configuration.* The chemo- and stereoselectivities of this cyclodehydration are remarkable in view of the variety of potential acid-catalyzed reaction modes available to the 1,2-diol system. In a similar manner, the hydroquinone acetonide **22,** obtained by catalytic hydrogenation of **21,** yielded **25** when exposed to refluxing, dilute H_2SO_4. These results, in which cyclodehydration occurs without substantially affecting the stereochemical integrity of the chiral carbinol center, suggest a mechanism involving attack of the tertiary hydroxyl on a keto tautomer of the hydroquinone moiety. Intermediates such as **33** or **34** (several tautomers possible), which would result from such a process, should readily undergo rearomatization generating the observed chromanol **25.**[29,30]

Having **25** available by several routes, we were now able to complete the total synthesis of **1** in straightforward manner. To this end, **25** was selectively benzylated (benzyl chloride, K_2CO_3, DMF, room temperature) and the resultant monoether[24] oxidized with Collins reagent[31] affording the (*S*)-(+)-chroman-2-carboxaldehyde **6**[32] (74%). Wittig coupling of **6** with the ylide derived from phosphonium salt **7**[2,4] (*n*-BuLi, dimethoxyethane, reflux) gave the dehydrotocopheryl benzyl ether **4** which was directly hydrogenated over palladium on carbon. Acetylation of the resultant tocopherol provided (2*R*,4′*R*,8′*R*)-α-tocopheryl acetate (**2**), identical with an authentic sample. A sample of α-tocopherol regenerated from this acetate gave a purified (preparative TLC) potassium ferricyanide oxidation product[2a,b] exhibiting $[\alpha]^{25}_D$ +31.58° (*c* 3.9, isooctane).[33]

In summary, the synthetic studies described above have led to a new total synthesis of the naturally occurring form of vitamin E. In addition, the feasibility of constructing well-developed, optically pure chroman synthons from small, chiral, nonaromatic molecules has been demonstrated. Related stereochemical investigations involving the opening and reclosing of chiral chromans by oxidation-reduction processes will be reported in due course.[8]

Experimental Section

General. All reactions except hydrogenations were carried out under an atmosphere of argon. The "usual workup" involves three to six extractions with the specified solvent. Organic solutions were then washed with saturated brine, dried over anhydrous $MgSO_4$, filtered, and concentrated on a rotary evaporator under water aspirator pressure. Residues were dried to constant weight under high vacuum at 40–50 °C or water aspirator pressure in the case of volatile materials. Column chromatography was performed using EM silica gel 60 (0.063–0.2 mm). Reactions were monitored by thin layer chromatography using EM silica gel 60 F-254, precoated plates with either 1:1 hexane-ether or 1:1 benzene-ethyl acetate as the mobile phase. Spots were detected with UV light and phosphomolybdic acid spray followed by heating. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Tetrahydrofuran (THF), pyridine, and 1,2-dimethoxyethane (DME) were dried by slurrying over ICN W-200, neutral alumina just prior to use. ^{1}H NMR spectra were obtained in $CDCl_3$ solution unless otherwise noted. Chemical shifts are reported relative to Me_4Si as an internal standard. Infrared spectra were obtained in $CHCl_3$ solution, ultraviolet spectra in 95% EtOH unless otherwise noted.

(*S*)-(+)-5-(Hydroxymethyl)-5-methyldihydro-2(3*H*)-furanone (12). To a solution of 14.8 g (102.7 mmol) of (*S*)-(−)-2-methyl-5-oxotetrahydro-2-furoic acid[11] [mp 84–87 °C; $[\alpha]^{25}_D$ −16.56° (*c* 2.3, H_2O); **11**] in 70 mL of dry THF was added 10.1 mL (8.1 g, 106.7 mmol) of borane-methyl sulfide complex,[13] dropwise, with stirring over a 0.5-h period. Occasional ice-bath cooling was employed to maintain the internal temperature below 30 °C. After stirring at room temperature for 1.5 h, the reaction mixture was cautiously decomposed by the dropwise addition of 6.2 mL of H_2O. The mixture was then concentrated under water aspirator pressure and the residue was taken up in ethyl acetate and filtered. The solids were washed thoroughly with ethyl acetate and the filtrate and washes were combined and concentrated in vacuo, giving the hydroxy lactone **12** as a colorless oil (13.6 g) which was used without further purification. In a separate experiment, a sample of **12** prepared in this way was chromatographed on 40 parts of silica gel. Elution with 1:1 benzene-ethyl acetate and ethyl acetate yielded the pure lactone which was recrystallized from ether-ligroin giving a colorless solid, mp 44.5–46.5 °C, $[\alpha]^{25}_D$ +17.76° (*c* 1, $CHCl_3$) [lit.[14] mp 39–42 °C, $[\alpha]^{20}_D$ +20° (*c* 1, $CHCl_3$)].

(*S*)-(+)-2,2,4-Trimethyl-1,3-dioxolane-4-propanoic Acid (14). A solution of the crude hydroxy lactone **12** from the preceding experiment (13.6 g, 104.6 mmol) and 283 mg (1.64 mmol) of *p*-toluenesulfonic acid monohydrate in 161 mL of 2,2-dimethoxypropane was stirred at room temperature for 3.75 days. Pyridine (0.26 mL) was then added and the mixture concentrated under water aspirator pressure. The crude residual ester **13** was dissolved in 180 mL of MeOH containing 29.27 g (444 mmol) of 85% KOH. The resulting solution was stirred at room temperature for 4 h, then concentrated in vacuo. The syrupy residue was diluted with ice water and the solution was extracted with ether (the ether extract was discarded). The aqueous, alkaline solution was layered with ether and carefully acidified to pH 2.6 (pH meter) with 3 N HCl. Workup with ether in the usual manner gave 16.1 g (83.3% overall based on acid **11**) of acid **14** as an oil. This material was used without further purification. In a separate experiment, the crude acid was evaporatively distilled giving pure **14** as a colorless oil: bp 80–90 °C (bath temperature) (0.15 mm); $[\alpha]^{25}_D$ +1.58° (*c* 2.02, $CHCl_3$); IR 2400–3500 (br, acid OH), 1713 cm^{-1} (acid C=O); NMR δ 10.27 (s, 1, CO_2H), 3.72 (s, 2, CH_2O), 1.39 (s, 6, $(CH_3)_2C$), 1.29 ppm (s, 3, CH_3). Anal. ($C_{19}H_{16}O_4$) C, H.

(*S*)-(+)-Methyl 2,2,4-Trimethyl-1,3-dioxolane-4-propanoate (13). A solution of 6.3 g (48.5 mmol) of hydroxy lactone **12** and 133 mg of *p*-toluenesulfonic acid monohydrate in 75 mL of 2,2-dimethoxypropane was stirred and refluxed for 3.5 h, then cooled in an ice bath, diluted with ether, and washed with saturated aqueous $NaHCO_3$ solution. The organic solution was processed in the usual manner giving 8.2 g of a yellow oil. This material was chromatographed on 400 g of silica gel. Elution with 9:1 and 4:1 benzene-ethyl acetate gave the ester **13,** which was evaporatively distilled yielding 4.6 g (47%) of a colorless liquid, bp 90–100 °C (bath temperature) (12 mm). An analytical specimen was obtained by rechromatography and redistillation of a sample: $[\alpha]^{25}_D$ +2.97° (*c* 2, C_6H_6); IR 1735 cm^{-1} (ester C=O); NMR δ 3.71 (AB m, 2, CH_2O), 3.63 (s, 3, OCH_3), 1.35 (s, 6, $(CH_3)_2C$), 1.24 ppm (s, 3, CH_3). Anal. ($C_{10}H_{18}O_4$) C, H.

(*S*)-(+)-4-(3,5-Dioxo-1-hexyl)-2,2,4-trimethyl-1,3-dioxolane (16). To a stirred solution of 10.0 g (53.2 mmol) of acid **14** in 100 mL of anhydrous THF was cautiously added 9.04 g (55.8 mmol) of *N,N′*-carbonyldiimidazole (gas evolution). The resulting solution was stirred for 1 h at room temperature, then treated with 4.78 g (26.6 mmol) of 2,5-dihydroxy-2,5-dimethyl-1,4-dithiane.[15] Stirring was continued for 4 h at room temperature; then the reaction mixture was diluted with water and worked up with ether in the usual manner. The orange, oily residue (14.3 g) was chromatographed on silica gel (400 g). Elution with 9:1 and 4:1 benzene-ethyl acetate yielded 11.1 g (80.2%) of thiol ester **15** as a yellow oil: IR 1695 cm^{-1} (ester C=O); NMR δ 3.68 (s, 4, SCH_2 and OCH_2), 2.21 (s, 3, CH_3C=O), 1.31 (s, 6, $(CH_3)_2C$), 1.21 ppm (s, 3, CH_3).

To a solution of 10.6 g (40 mmol) of this thiol ester in 32 mL of dry CH_3CN was added 3.85 g (44.4 mmol) of anhydrous LiBr. After solution had occurred, 33 g (123 mmol) of bis(3-dimethylamino-1-propyl)phenylphosphine[16] was added. Separation of a solid soon began as the mixture was stirred and heated at 85–90 °C. After heating for

4.5 h, the reaction mixture was cooled and poured into ice-water. The aqueous phase was layered with ether and acidified to pH 3.3 (pH meter) by the dropwise addition of 3 N HCl. Workup with ether in the usual manner gave 8.7 g of crude product as a yellow oil. This material was chromatographed on 350 g of silica gel. Elution with 4:1 and 2:1 hexane-ether gave the β-diketone **16** which was evaporatively distilled. There was obtained 6.57 g (72%) of pure **16** as a pale-yellow oil: bp 95-105 °C (bath temperature) (0.005 mm); $[\alpha]^{25}_D$ +8.54° (*c* 2, $CHCl_3$); IR 1726, 1702 (β-diketone C=O), 1620 cm^{-1} (enol); NMR δ 15.35 (br m, 1, enol OH), 5.50 (s, 0.85, enol -CH=), 3.73 (AB m, 2, OCH_2), 3.58 (s, $(O{=}C)_2CH_2$), 2.01 (s, 3, $CH_3C{=}O$), 1.35 (br s, 6, $(CH_3)_2C$), 1.26 ppm (br s, 3, CH_3); UV max 274 nm (ε 8970). Anal. ($C_{12}H_{20}O_4$) C, H.

Basification of the acidic aqueous solution followed by ether extraction allowed recovery of the excess phosphine reagent.

(*S*)-(+)-Dimethyl 2-Hydroxy-6-methyl-4-(2,2,4-trimethyl-1,3-dioxolane-4-ethyl)-1,3-benzenedicarboxylate (17). A solution of 6.0 g (26.3 mmol) of β-diketone **16** from the preceding experiment and 5.83 g (33.4 mmol) of dimethyl 1,3-acetonedicarboxylate (DMAD) in 33.6 mL of 0.85 M methanolic NaOMe was stirred at room temperature for 21 h.[17] The resulting yellow solution was poured into ice-water and layered with ether and the pH was adjusted to 3 by the addition of 3 N HCl. Workup with ether in the usual manner gave 10.9 g of a yellow oil. This material was chromatographed on 350 g of silica gel. Elution with 9:1 and 4:1 benzene-ethyl acetate gave 8.82 g (91.7%) of diester **17** as a yellow oil. GC analysis indicated a purity of 92.4% (3 ft × 4 mm i.d. column of 10% OV-101 on GCQ 100/120; 80 to 270 °C at 4 °C/min; retention time 45.5 min). NMR analysis indicated the presence of some DMAD as an impurity. An analytical specimen was obtained by careful rechromatography and evaporative distillation giving pure **17** as a viscous, pale-yellow oil: bp 125-130 °C (bath temperature) (0.003 mm); $[\alpha]^{25}_D$ +6.07° (*c* 2, $CHCl_3$); UV max 214 nm (ε 26 720), 251 (10 275), 314 (5800); IR 3440-3100 (broad H-bonded OH), 1725 (ester C=O), 1660, 1620 cm^{-1}; NMR δ 6.55 (s, 1, ArH), 3.89 (s, 6, CO_2CH_3), 3.74 (AB m, 2, OCH_2), 2.40 (s, 3, $ArCH_3$), 1.34 (s, 6, $(CH_3)_2C$), 1.25 ppm (s, 3, CH_3). Anal. ($C_{19}H_{26}O_7$) C, H.

(*S*)-(+)-2-Hydroxy-6-methyl-4-(2,2,4-trimethyl-1,3-dioxolane-4-ethyl)benzene-1,3-dimethanol Triacetate (19). To a solution of 6.35 g (17.3 mmol) of ester **17** in 138 mL of anhydrous ether was added, dropwise, with stirring, 29 mL of 70% sodium bis(2-methoxyethoxy)aluminum hydride in benzene. The reaction mixture was stirred at room temperature for 4 h, then at reflux for 16.5 h. After cooling, the mixture was cautiously poured onto ice-water. The aqueous phase was adjusted to pH 3.5 by the dropwise addition of 3 N HCl. Workup with ether in the usual manner gave 4.44 g (82.8%) of the triol **18** as a yellow oil. This material was dissolved in 14.2 mL of dry pyridine containing 6.5 mL of acetic anhydride and the solution was stirred for 4.5 h at room temperature, then treated with 200 mL of H_2O. Excess solid $NaHCO_3$ was added, followed by ether, and the mixture was stirred for 15 min. The ether layer was separated and the aqueous layer was extracted three more times with ether. The combined ether extracts were stirred with 100 mL of H_2O while the pH of the aqueous phase was adjusted to 4 by the addition of 3 N HCl. Workup in the usual manner (the ether extracts were additionally washed with $NaHCO_3$ solution) gave 6.25 g of the triacetate **19** as an oil which was used without further purification. A 0.5-g sample of this material was chromatographed on 50 parts of silica gel. Elution with ether gave 0.33 g of pure **19** as a viscous, colorless oil: $[\alpha]^{25}_D$ +5.49° (*c* 2, $CHCl_3$); IR 1760 (phenol ester), 1736 cm^{-1} (ester); NMR δ 6.97 (s, 1, ArH), 5.05 (s, 2, $ArCH_2O$), 5.02 (s, 2, $ArCH_2O$), 3.76 (AB m, 2, CH_2O), 2.36 (s, 3, $ArCH_3$), 2.29 (s, 3, CH_3CO_2Ar), 1.98 (s, 6, $CH_3CO_2CH_2$), 1.38 (s, 6, $(CH_3)_2C$), 1.33 ppm (s, 3, CH_3). Anal. ($C_{23}H_{32}O_8$) C, H.

(*S*)-(+)-2,3,6-Trimethyl-5-(2,2,4-trimethyl-1,3-dioxolane-4-ethyl)-phenol (20). A. From Triacetate 19. To a solution of 5.75 g of the crude triacetate **19** from the preceding experiment in 140 mL of anhydrous Me_2SO was added 4.96 g (130 mmol) of $NaBH_4$. The resulting mixture was stirred and heated at 90-100 °C for 4 h, then cooled and treated with 29 mL of 1 N NaOH. After stirring for 1 h at room temperature, the mixture was diluted with ice-water and acidified to pH 3.8 with 3 N HCl. Workup with ether in the usual manner (the extracts were additionally washed with H_2O and saturated $NaHCO_3$ solution) gave 3.14 g of a pale yellow oil. This material was chromatographed on 150 g of silica gel. Elution with 19:1 and 9:1 benzene-ethyl acetate afforded 2.5 g (56.5% overall yield from **17**) of pure **20** as a colorless oil which crystallized, mp 53-60.5 °C. A portion of this material was recrystallized from hexane giving a colorless solid: mp 60-62 °C; $[\alpha]^{25}_D$ +5.00° (*c* 2.0, $CHCl_3$); IR 3610 cm^{-1} (OH); NMR δ 6.55 (s, 1, ArH), 4.80 (br s, 1, OH), 3.78 (AB m, 2, CH_2O), 2.19, 2.15, 2.10 (3 s, 9, $ArCH_3$), 1.41 (s, 6, $(CH_3)_2C$), 1.35 ppm (s, 3, CH_3); UV max 274 nm (ε 955), 281 (985), sh 223 (9500). Anal. ($C_{17}H_{26}O_3$) C, H.

B. From Diester 17. A solution of 1.02 g (2.79 mmol) of diester **17** in 5 mL of xylene was added, dropwise, over a 5-min period, to a stirred solution of 6 mL (2.17 mmol) of 70% $NaAlH_2(OCH_2CH_2OMe)_2$ (in benzene) in 5 mL of xylene. The resulting solution was stirred and refluxed for 3.75 h,[19] then cooled to 10 °C, at which point a solution of 1.16 mL of concentrated H_2SO_4 in 5 mL of H_2O was cautiously added dropwise. The resulting slurry was diluted with 23 mL of MeOH and stirred and refluxed for 10 min. After cooling, the slurry was filtered and the granular solid was washed with MeOH and then ether. The filtrate and washes were combined and concentrated in vacuo. The residue was taken up in ether and the solution was washed with brine and processed in the usual manner to give 769 mg of a yellow oil. This material was chromatographed on 30 g of silica gel. Elution with 4:1, 2:1, and 1:1 hexane-ether afforded 640 mg (82.5%) of phenol **20** as a colorless oil which crystallized. This material was virtually identical with that prepared as in part A above.

(*S*)-(+)-3,5,6-Trimethyl-2-(2,2,4-trimethyl-1,3-dioxolane-4-ethyl)-2,5-cyclohexadiene-1,4-dione (21). A solution of 2.02 g (7.66 mmol) of phenol **20** in 81 mL of MeOH was added to a solution prepared from 65 g (excess) of a slurry of disodium nitrosodisulfonate (Fremy's salt[20]) in aqueous Na_2CO_3, 16 mL of 1 N NaOAc, and 484 mL of H_2O. The brown mixture was stirred at room temperature for 1.5 h, then worked up with ether in the usual manner. There was obtained 2.07 g (97.6%) of essentially pure quinone **21** as a viscous, orange oil which was used without further purification. A sample was chromatographed on silica gel (50 parts). Elution with 4:1 hexane-ether afforded an analytical specimen of **21** as a viscous, orange oil: $[\alpha]^{25}_D$ +6.39° (*c* 2, $CHCl_3$); IR 1640 cm^{-1} (quinone C=O); UV max 262 nm (ε 18 020), 269 (18 060), 344 (270); NMR δ 3.80 (AB m, 2, CH_2O), 1.98 (2 s, 9, $CH_3C{=}$), 1.37, 1.31 ppm (2 br s, 9, $(CH_3)_2C$, CH_3). Anal. ($C_{17}H_{24}O_4$) C, H.

(*S*)-(+)-5-(3,4-Dihydroxy-3-methyl-1-butyl)-2,3,6-trimethylphenol (26). A solution of 1.4 g (5.04 mmol) of phenol **20** in 28 mL of MeOH and 5.5 mL of 1 N HCl was stirred at room temperature for 20 h, then poured into saturated brine and worked up with ether in the usual manner. Trituration of the solid residue with ether afforded 0.8 g (66.7%) of pure **26** as a colorless solid: mp 145-146 °C; $[\alpha]^{25}_D$ +2.20° (*c* 2, EtOH); IR (KBr) 3420, 3330 cm^{-1} (OH); UV max 273 nm (ε 875), 281 (895); NMR (Me_2SO-d_6) δ 7.75 (s, 1, ArH), 6.50 (s, 1, ArOH), 4.43 (t, 1, *J* = 6 Hz, CH_2OH), 4.00 (s, 1, OH), 3.30 (m, 2, CH_2O), 2.08, 2.03 (br s, 9, $ArCH_3$), 1.10 ppm (s, 3, CH_3). Anal. ($C_{14}H_{22}O_3$) C, H.

The ether filtrate from the above trituration was concentrated and the residue was recrystallized from ethyl acetate giving an additional 139 mg (11.7%) of **26**.

(*S*)-(+)-2-(3,4-Dihydroxy-3-methyl-1-butyl)-3,5,6-trimethyl-2,5-cyclohexadiene-1,4-dione (27). A 0.5-g (2.1 mmol) sample of phenol diol **26** was treated with Fremy's salt as described above for the conversion of **20** to **21**. There was obtained 480 mg (90.7%) of quinone **27** as a yellow solid, mp 109-112.5 °C. Recrystallization from $CHCl_3$-hexane gave 370 mg of yellow solid: mp 111.5-113 °C; $[\alpha]^{25}_D$ +6.28° (*c* 2, $CHCl_3$); IR (KBr) 3220, 3240 (OH), 1640 cm^{-1} (quinone C=O); UV max 262 nm (ε 18 700), 268 (19 040), 346 (340); NMR δ 3.53 (s, 2, CH_2O), 2.98 (br s, 2, OH), 2.00, 2.02 (2 s, 9, $CH_3C{=}$), 1.25 ppm (s, 3, CH_3). Anal. ($C_{14}H_{20}O_4$) C, H.

(3*S*,9a*R*)-(−)-2,3,4,5,7,9a-Hexahydro-3,6,8,9-tetramethyl-3,9a-epoxy-1-benzoxepin-7-one (24). A. By Ceric Sulfate Oxidation of 25. To a solution of 0.4 g (1.69 mmol) of chromanol **25** (mp 127-128 °C; derived from acid **23**[6] as described below) in 35 mL of MeOH was added 23 mL of a ceric sulfate solution prepared by dissolving 80 g of ceric sulfate in 100 mL of water containing 25 mL of concentrated H_2SO_4.[25] The resulting yellow slurry was stirred at room temperature for 2.5 h, then diluted with H_2O and worked up with ether in the usual manner. There was obtained 386 mg of a yellow solid, TLC analysis of which indicated a mixture of **24** and the quinone **27**. This material was chromatographed on silica gel (25 g). Elution with 19:1 and 9:1 benzene-ether afforded 211 mg (53.4%) of **24**, mp 98.5-100 °C. Recrystallization from hexane gave colorless solid: mp 100-101 °C; $[\alpha]^{25}_D$ −56.32° (*c* 2, C_6H_6); IR 1625 cm^{-1} (conjugated ketone

C=O); UV max 236 nm (ε 14 900), 293 (1500); NMR δ 4.13 (d, 1, J = 8 Hz, CHO), 3.61 (d, 1, J = 8 Hz, CHO), 2.57 (m, 2, allylic CH_2), 1.87, 1.85, 1.77 (3 s, CH_3C=), 1.40 ppm (s, 3, CH_3). Anal. ($C_{14}H_{18}O_3$) C, H.

B. From Quinone Acetonide 21. A solution of 1.5 g (5.13 mmol) of quinone **21** in 42 mL of MeOH containing 8.3 mL of 1 N aqueous HCl was stirred at room temperature for 18 h, then poured into saturated brine and worked up with ether in the usual manner (the ether extracts were additionally washed with saturated aqueous $NaHCO_3$). The yellow solid product obtained (1.27 g) was chromatographed on silica gel (100 g) to remove a small amount of the diol **27**. Elution with 19:1 and 9:1 benzene-ethyl acetate yielded 870 mg (72.5%) of **24** as a colorless solid, mp 99-100 °C, $[\alpha]^{25}_D$ −56.04° (c 2, C_6H_6). The IR, UV, and NMR spectra and TLC mobility of this material were virtually identical with those of the material produced in part A above.

C. From Quinone Diol 27. A 0.2-g (0.8 mmol) sample of quinone diol **27** was treated as in part B. The crude product (219 mg) was chromatographed as above, giving 157 mg (84.8%) of pure **24** as a colorless solid, mp 96-100 °C, $[\alpha]^{25}_D$ −54.29° (c 2.2, C_6H_6). This material was identical with that produced in part A above by comparison of the NMR spectra and TLC mobilities.

Attempted Preparation of Tricyclic Quinone Monoketal 31. A mixture of 5.07 g (14.9 mmol) of *rac*-6-benzyloxy-3,4-dihydro-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-ethanol,[3g] 1 g of 5% palladium on carbon, and 50 mL of absolute ethanol was stirred in an atmosphere of hydrogen, at room temperature, until gas uptake ceased (380 mL of H_2 absorbed). The catalyst was filtered and the filtrate was concentrated in vacuo giving 3.72 g (100%) of *rac*-3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-ethanol (**29**) as a tan solid. The analytical specimen was obtained from a separate experiment (carried out by Mr. F. Bizzarro) as colorless crystals, mp 136.5-137.5 °C. Anal. ($C_{15}H_{22}O_3$) C, H.

The above chromanol was oxidized with ceric sulfate as described for the preparation of **24** from **25**. There was obtained 3.56 g (89.8%) of orange, crystalline quinone diol **30**; IR 3350 (OH), 1640 cm^{-1} (quinone C=O); TLC (1:1 C_6H_6-EtOAc) R_f 0.18 (R_f of **29**, 0.39; R_f of **27**, 0.18; R_f of **24**, 0.59). Attempted cyclodehydration of this material using the conditions described above for conversion of **27** to **24** gave only recovered **30**. When **30** was refluxed in benzene containing *p*-toluenesulfonic acid, a dark, insoluble, polymeric gum was formed. TLC analysis indicated a complex mixture.

(*S*)-2-(3,4-Dihydroxy-3-methyl-1-butyl)-3,5,6-trimethyl-1,4-benzenediol (28). A solution of 405 mg (16 mmol) of quinone diol **27** in 20 mL of ethyl acetate was stirred in an atmosphere of hydrogen, in the presence of 40 mg of 5% palladium on charcoal, until gas uptake ceased (ca. 1 h, 38 mL of H_2 absorbed). The catalyst was filtered and the filtrate was concentrated in vacuo giving 410 mg of hydroquinone **28** as an unstable, tan solid which was used without purification: mp 124-131.5 °C; UV max 286 nm (ε 2240); mass spectrum m/z 254 (M^+); NMR (Me_2SO-d_6) δ 7.20 (m, 2, ArOH), 4.45 (t, 1, J = 6 Hz, CH_2OH), 4.17 (s, 1, COH), 3.23 (m, 2, CH_2O), 2.05 (br s, 9, $ArCH_3$), 1.07 ppm (s, 3, CH_3).

(*S*)-3,5,6-Trimethyl-2-(2,2,4-trimethyl-1,3-dioxolane-4-ethyl)-1,4-benzenediol (22). A 531-mg (1.82 mmol) sample of quinone acetonide **21** was hydrogenated as in the preceding experiment. There was obtained 540 mg of hydroquinone **22** as an unstable, tan solid which contained a small amount of ethyl acetate: IR 3620, 3370 cm^{-1} (OH); UV max 287 nm (ε 2700); NMR δ 5.63 (s, 1, ArOH), 4.33 (s, 1, ArOH), 3.80 (s, 2, CH_2O), 2.75 (m, 2, $ArCH_2$), 2.20 (s, 9, $ArCH_3$), 1.73 (m, 2, $ArCH_2CH_2$), 1.43, 1.33 ppm (2 br s, 9, $(CH_3)_2C$, CH_3); mass spectrum m/z 294 (M^+). This material was used without further purification.

(*S*)-(+)-3,4-Dihydro-6-hydroxy-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-methanol (25). A. By Hydride Reduction of 24. To a stirred solution of 787 mg (3.36 mmol) of tricyclic ketal **24** (derived from **21**) in 8.5 mL of dry THF, at 0 °C, was added 0.94 mL (6.72 mmol) of 70% $NaAlH_2(OCH_2CH_2OMe)_2$ solution in benzene, dropwise. The reaction mixture was stirred at 0 °C for 1 h, then poured onto a mixture of ice and 1 N HCl. Workup in the usual manner with ether afforded 717 mg of solid product which was chromatographed on 50 g of silica gel. Elution with 9:1, 4:1, and 2:1 benzene-ethyl acetate yielded 647 mg (81.6%) of pure **25** as a colorless solid, mp 127-129 °C, $[\alpha]^{25}_D$ +1.44° (c 2, EtOH). The IR, UV, and NMR spectra and TLC mobility were virtually identical with those of a sample of **25** prepared by reduction of acid **23**[6] (see below). The ^{1}H NMR spectrum, when run in the presence of the chiral shift reagent Eu(hfbc)$_3$, indicated the presence of only one enantiomer.[28]

B. By Reduction of 24 with Zinc. A mixture of 200 mg (0.834 mmol) of tricyclic ketal **24** (derived from **21**) and 223 mg of powdered zinc in 10 mL of glacial acetic acid was stirred at room temperature for 47 h. The mixture was then diluted with water, neutralized with $NaHCO_3$, and worked up with ether in the usual manner. The crude, oily product (212 mg) was chromatographed on 20 g of silica gel. Elution with 19:1 and 9:1 benzene-ethyl acetate gave 140 mg (70%) of recovered **24**, mp 97-99.5 °C. Further elution with 4:1 and 2:1 benzene-ethyl acetate afforded 60 mg (30%) of chromanol **25** as a colorless solid, mp 123-127 °C. The ^{1}H NMR spectrum of this material when run in the presence of Eu(hfbc)$_3$ failed to reveal any detectable peak resolutions, indicating essentially 100% optical purity.[28]

C. By Catalytic Hydrogenation of 24. A mixture of 200 mg (0.834 mmol) of tricyclic ketal **24** (derived from **21**), 200 mg of 5% palladium on charcoal, and 50 mL of ethanol was stirred in an atmosphere of hydrogen until gas uptake ceased (30 mL of H_2 consumed). The catalyst was filtered and the filtrate was concentrated in vacuo. Chromatography of the crude product on 20 g of silica gel gave 150 mg (76.2%) of **25** as a colorless solid, mp 119-125 °C (eluted with 4:1 and 2:1 benzene-ethyl acetate). The NMR spectrum and TLC mobility of this material were essentially identical with those of a sample of **25** prepared by reduction of acid **23**. The ^{1}H NMR spectrum of this material, when run in the presence of Eu(hfbc)$_3$, failed to reveal any detectable peak resolutions, indicating essentially 100% optical purity.[28]

D. By Cyclization of Hydroquinone 28. A mixture of 320 mg (1.26 mmol) of hydroquinone diol **28**, 25 mg of *p*-toluenesulfonic acid monohydrate, and 25 mL of benzene was stirred and refluxed for 1.25 h. The resulting solution was cooled, washed with aqueous $NaHCO_3$, and processed in the usual manner giving a semisolid residue which was chromatographed on 25 g of silica gel. Elution with 9:1, 4:1, and 2:1 toluene-ethyl acetate yielded 237 mg (79.7%) of **25** as a cream-colored solid, mp 122-124 °C, $[\alpha]^{25}_D$ +1.09° (c 2.2, EtOH). A sample of this material was oxidized with ferric chloride[2a] giving the tricyclic monoketal **24**, mp 96-99 °C, $[\alpha]^{25}_D$ −52.82° (c 2, C_6H_6), in essentially quantitative yield. This rotation corresponds to an optical purity for chromanol **25** of ca. 95%.

E. By Cyclization of Hydroquinone 22. A solution of 455 mg (1.54 mmol) of hydroquinone acetonide **22** and 2 mL of 1 N H_2SO_4 in 10 mL of MeOH was stirred and refluxed for 1.5 h. After cooling, the reaction mixture was treated with saturated brine and worked up with ether in the usual manner giving 0.362 g of a brown glass. This material was triturated with ether giving a solid which was removed by filtration. The ether solution was chromatographed on 25 g of silica gel. Elution with 4:1 and 2:1 toluene-ethyl acetate afforded 125 mg (34.4%) of **25** as a colorless solid, mp 124.5-127.5 °C, $[\alpha]^{25}_D$ +1.04° (c 2.1, EtOH). ^{1}H NMR studies of this material, using Eu(hfbc)$_3$, failed to reveal the presence of the enantiomer within ±5%.[28]

F. By Reduction of Acid 23. To an ice-cooled solution of 1 g (4 mmol) of *S* acid **23**[6] in 20 mL of THF was added 5.66 mL (20 mmol) of 70% $NaAlH_2(OCH_2CH_2OMe)_2$ in benzene, over a 5-min period. The resulting solution was stirred at room temperature for 1 h, then poured into a mixture of ice and 6 N HCl. Workup with ether (the organic extracts were additionally washed with 2 N HCl and saturated $NaHCO_3$) gave a tan solid which was recrystallized from petroleum ether (30-60 °C)-ether. There was obtained 810 mg (85.8%) of chromanol **25** as colorless needles: mp 129.5-131.5 °C; $[\alpha]^{25}_D$ +1.43° (c 2.1, C_2H_5OH); IR 3615 cm^{-1} (OH); NMR δ 4.55 (s, 1, OH), 3.60 (br s, 2, CH_2O), 2.63 (t, 2, J = 7 Hz, $ArCH_2$), 2.11, 2.08 (2 s, $ArCH_3$), 1.80 (m, 2, $ArCH_2CH_2$), 1.20 ppm (s, 3, CH_3). This experiment was carried out by Dr. J. W. Scott.

G. By Reduction of Aldehyde 5. A 552-mg (2 mmol) sample of (*S*)-aldehyde ester **5**[2a,4] was reduced with 10 mmol of $NaAlH_2(OCH_2CH_2OMe)_2$ using the procedure described in the preceding experiment. The crude product was recrystallized from petroleum ether (30-60 °C)-ether, giving 435 mg (92%) of chromanol **25** as colorless needles, mp 129-130.5 °C, $[\alpha]^{25}_D$ +1.54° (c 1.89, C_2H_5OH). The IR and NMR spectra were identical with those of the material from part F. Anal. ($C_{14}H_{20}O_3$) C, H. This experiment was carried out by Dr. J. W. Scott.

(*S*)-(+)-6-Benzyloxy-3,4-dihydro-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-carboxaldehyde (6). A mixture of 550 mg (2.33 mmol) of chromanol **25** (from part A of the preceding series of experiments),

790 mg (5.72 mmol) of anhydrous K_2CO_3, 0.68 mL (748 mg, 5.93 mmol) of benzyl chloride (distilled from and stored over K_2CO_3), and 4.5 mL of DMF was stirred for 22 h at room temperature, then poured into H_2O and worked up with ether in the usual manner. There was obtained 0.89 g of a yellow, oily product which was chromatographed on silica gel (35 g). Elution with 19:1 and 9:1 benzene–ethyl acetate gave 724 mg (97.1%) of (*S*)-(−)-6-benzyloxy-3,4-dihydro-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-methanol[24] as a colorless solid, mp 66–69.5 °C, $[\alpha]^{25}_D$ −2.35° (*c* 1.2, $CHCl_3$).

To a stirred mixture of 36 mL of dry CH_2Cl_2, 2.8 mL of dry pyridine, and 1.46 g (14.6 mmol) of CrO_3 was added a solution of 645 mg (1.98 mmol) of this chromanol in 5 mL of CH_2Cl_2.[31] The dark mixture was stirred for 40 min at room temperature; then the organic solution was decanted and the dark residue was washed with ether and CH_2Cl_2. The combined organic solutions were diluted with ether and washed with 1 N NaOH, H_2O, and 1 N HCl and workup was then completed in the usual manner. The oily, yellow product was chromatographed on 50 g of silica gel. Elution with 19:1 hexane–ether gave 492 mg (76.7%) of pure **6** as an oil which crystallized yielding a colorless solid, mp 56–58 °C, $[\alpha]^{25}_D$ +11.89° (*c* 5.2, $CHCl_3$). This material was used in the Wittig coupling described below without further purification.

The analytical sample of **6** was prepared by an alternative route starting from acid **23**,[32] as a colorless solid: mp 60–61 °C; $[\alpha]^{25}_D$ +12.78° (*c* 5, $CHCl_3$); IR (KBr) 2740 (aldehyde CH), 1740 cm^{-1} (C=O); NMR δ 9.62 (br s, 1, CHO), 4.67 (s, 2, $C_6H_5CH_2O$), 2.58 (m, 2, $ArCH_2$), 2.23, 2.19, 2.12 (3s, 9, $ArCH_3$), 1.39 ppm (s, 3, CH_3). Anal. ($C_{21}H_{24}O_3$) C, H.

(2*R*,4'*R*,8'*R*)-α-Tocopheryl Acetate (2). A solution of 570 mg (1.03 mmol) of (3*R*,7*R*)-phosphonium salt (**7**)[2a,4] in 5.6 mL of anhydrous DME was stirred at room temperature while 0.43 mL (1.03 mmol) of 2.4 M *n*-butyllithium in hexane was added. The resulting red solution was stirred for 2 h at room temperature; then a solution of 153 mg (0.472 mmol) of aldehyde **6** (from the preceding experiment—derived from **25**) in 1.5 mL of anhydrous DME was added and stirring was continued for 3 h at 65–70 °C. After cooling, the reaction mixture was poured onto cold, dilute H_2SO_4, and workup with ether was carried out in the usual manner. The product was a mixture of oil and solid which was triturated with hexane. The hexane solution was decanted and concentrated in vacuo, affording 287 mg of oily material which was chromatographed on 15 g of silica gel. Elution with 19:1 hexane–ether yielded 168 mg (68.7%) of the dehydrotocopherol ether **4** as a colorless oil. This material (165 mg, 0.318 mmol) in 15 mL of ethyl acetate was stirred with 68 mg of 5% palladium on carbon, in an atmosphere of H_2, until gas uptake ceased. The catalyst was filtered and the filtrate was concentrated in vacuo, giving 120 mg (88.2%) of (2*R*,4'*R*,8'*R*)-α-tocopherol as a colorless oil which was homogeneous on TLC analysis. The IR and NMR spectra of this material were identical with those of natural, *d*-α-tocopherol.

A solution of 112 mg (0.26 mmol) of this material in 0.75 mL of dry pyridine and 0.59 mL of acetic anhydride was stirred at room temperature for 17 h, then concentrated under high vacuum. The residue was taken up in hexane and the solution was washed with H_2O and brine and processed in the usual manner. The oily product was chromatographed on 7 g of silica gel. Elution with 9:1 hexane–ether gave (2*R*,4'*R*,8'*R*)-α-tocopheryl acetate (**2**). Evaporative distillation yielded 90 mg (73.7%) of colorless oil, bp 205 °C (bath temperature) (0.02 mm). The IR and NMR spectra and TLC mobility of this material were identical with those of *d*-α-tocopheryl acetate (Eastman Kodak). The α-tocopherol regenerated from a sample of this material gave a $K_3Fe(CN)_6$ oxidation product (purified by preparative TLC) having $[\alpha]^{25}_D$ +31.58° (*c* 3.9, isooctane).[33]

Acknowledgments. We wish to express our gratitude to the personnel of the Physical Chemistry Department, Hoffmann-La Roche Inc., Nutley, N.J., for carrying out most of the spectral, microanalytical, and polarimetric determinations required in this work. We are grateful to Mr. L. A. Dolan for providing us with Fremy's salt and to Dr. J. W. Scott, who furnished generous samples of various chroman intermediates as well as valuable information. Helpful discussions with Drs. K.-K. Chan and G. Olson are also appreciated.

References and Notes

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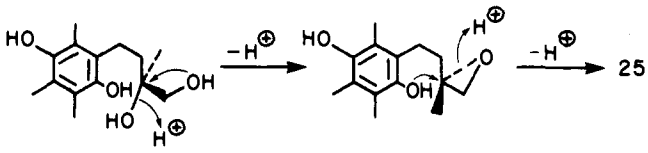
(28) The ^1H NMR spectrum of racemic **25**,[6] when run in the presence of Eu(hfbc)$_3$, exhibited resolutions of the C_2–CH_3 singlet and one of the aromatic CH_3 singlets into double peaks of approximately equal intensity, each separated by 4 Hz. Such resolutions were not detected (within ±2–3%) in the shifted spectra of the optically active samples.

(29) An alternative, double inversion (net retention) mechanism is also conceivable. This would involve formation of the *R* epoxide **35** followed by intramolecular, backside attack on the epoxide ring by the phenolic hydroxyl. While we cannot exclude this mechanism as being operable in the cyclizations of **22** and **28**, we have found that the presence of nucleophilic side chain functionality in proximity to the chiral tertiary hydroxyl center is *not* required for retention of configuration in cyclizations such as these.

Thus α-tocopherolhydroquinone, derived from (2*R*,4′*R*,8′*R*)-α-tocopherol,[2a] regenerates the same tocopherol, with 100% retention of configuration, upon cyclization with *p*-toluenesulfonic acid in refluxing benzene.[8]



28 35

(30) We are grateful to a referee for suggesting an attractive, related mechanistic rationale for the clean retention of configuration observed in the conversions of **22** and **28** to **25**. This involves the intermediacy of quinone ketal **24** formed in small quantity from **28** by air oxidation (via **27**). Reduction of **24** by hydroquinone **28** then produces **25** and regenerates **27**, thus establishing a catalytic redox cycle. In this regard, it should be noted that, because of their extreme air sensitivity, hydroquinones **22** and **28** contained trace quantities of the corresponding quinones the formation of which could not be avoided.

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Syntheses and NMR Characterization of Chelated Heme Models of Hemoproteins[1,2]

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Abstract: Convenient syntheses of "chelated heme" compounds from naturally occurring hemes are described. NMR studies of the carbon monoxide complex of chelated protoheme serve to characterize this model compound in solution. Chelated protoheme, having a "proximal" imidazole covalently attached, displays spectra and kinetics and equilibria of reaction with dioxygen and carbon monoxide that are similar to those of R-state hemoglobin, making chelated protoheme unique among model compounds.

Hemoproteins that transport dioxygen have dioxygen binding sites which consist of a protoheme molecule held in a globular protein by an imidazole-iron bond and by other noncovalent bonding.[3] Although not attached by covalent bonds as is the cytochrome *c* heme, the protoheme in hemoproteins such as hemoglobin or myoglobin is bound so strongly as to make the hemoprotein behave as a single molecule. Furthermore, the Fe(II) is five-coordinated in the deoxy form of these hemoproteins. The function of these hemoproteins is simply the reversible binding of triplet dioxygen without themselves undergoing oxidation to Fe(III):

$$\mathrm{Fe(II)} + \mathrm{O_2} \underset{5\text{ to }2500\ \mathrm{s^{-1}}}{\overset{10^6\text{-}10^8\ \mathrm{L\ M^{-1}\ s^{-1}}}{\rightleftharpoons}} \mathrm{Fe^{II}O_2} \nrightarrow \mathrm{Fe(III)} \quad (1)$$

Because respiration is controlled by the variations in the rate constants shown in eq 1, it is of great interest to determine the sources of these variations.[3,4] The obvious way to find out what affects the kinetics and equilibria of dioxygen binding is to prepare small model compounds that reversibly bind dioxygen and to vary the structures and environment in the study of these compounds.[5-7] However, when hemin compounds and imidazoles were mixed in a solvent, reduced to Fe(II), and treated with oxygen, two things happened to prevent such mixtures from mimicking hemoglobin behavior. First, two imidazoles are bound, converting the heme to a hexacoordinated hemochrome unlike the five-coordinated heme in hemoglobin.[3] Secondly, such mixtures were thought to oxidize the Fe(II) too fast to allow reversible oxygenation to be studied,[8] an opinion which no longer holds.[5b]

The oxidation of hemes to hemins in solution is much more rapid than are the corresponding oxidations of myoglobin or hemoglobin. One mechanism of such oxidation was proposed by Cohen and Caughey,[9] based upon the observation that heme oxidation in solutions containing pyridine is second order in the heme and first order in dioxygen:

$$\mathrm{Fe(II)} + \mathrm{O_2} \rightleftharpoons \mathrm{Fe^{II}\text{-}OO} \quad (2)$$

$$\mathrm{Fe^{II}—OO} + \mathrm{Fe(II)} \rightarrow \mathrm{Fe^{II}\text{-}OO\text{-}Fe^{II}} \quad (3)$$

$$\mathrm{Fe\text{-}OO\text{-}Fe} \rightarrow\rightarrow \mathrm{Fe(III)} + \mathrm{H_2O} \quad (4)$$

This mechanism has been further documented by the observation that at high oxygen pressure (0.1 to 1 atm) and strong dioxygen binding, the rate is second order in Fe(II) and *inverse* first order in dioxygen,[10] as required by eq 3. Evidence for the existence of an Fe-OO-Fe structure at low temperature has also been presented.[11]

We have presented two methods of studying reversible oxygenation of simple heme compounds. First, oxidation is not as fast as had been presumed, and rapid kinetic and spectroscopic methods can be applied to reversible oxygenation of almost any heme model system.[12a,b] Secondly, carbon monoxide can be used to protect against oxidation and removed quickly by flash photolysis, allowing the rapid spectroscopic and kinetic methods to be used in mixtures of CO and O_2.[12b,c] Because the heme-oxygen complex is formed and dissociated faster than is the heme-carbon monoxide complex, exactly as with hemoproteins, the flash photolysis method is applicable to simple model compounds[12b,c] (Hm = heme, B = proximal base) (eq 5).

$$\mathrm{BHmCO} \underset{l' = 10^5\text{-}10^8\ \mathrm{M^{-1}\ s^{-1}}}{\overset{h\nu \quad l = 0.01\text{-}1000\ \mathrm{s^{-1}}}{\rightleftharpoons}} \mathrm{BHm} \underset{k = 5\text{-}1000\ \mathrm{s^{-1}}}{\overset{k' = 10^7\text{-}10^9\ \mathrm{M^{-1}\ s^{-1}}}{\rightleftharpoons}} \mathrm{BHmO_2} \quad (5)$$

The second problem of maintaining a single species, five-coordinated heme behavior as do hemoproteins was solved by preparing chelated hemes in which five-coordination is

0002-7863/79/1501-6716$01.00/0