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Synthesis of (2*R*,4′*R*,8′*R*)-α-Tocopheryl Acetate (Vitamin E Acetate) Using [3,3] Sigmatropic Rearrangement

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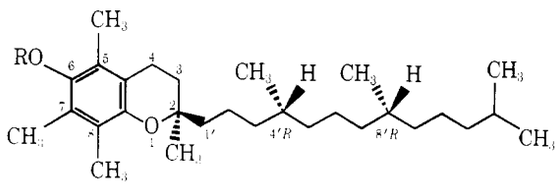
A new synthesis of (2*R*,4′*R*,8′*R*)-α-tocopheryl acetate (**1b**) was achieved by the application of stereoselective [3,3] sigmatropic (Claisen) rearrangement. Treatment of the (*S*)-chromanylacetaldehyde **6** with propynylmagnesium bromide gave two diastereomeric acetylenic carbinols, (*R*)-**15a** and (*S*)-**16a** (~2:1). Orthoester Claisen rearrangement of allylic alcohols (*R*,*E*)-**17** and (*S*,*Z*)-**18**, respectively, yielded the same unsaturated ester, (*R*,*E*)-**19a**, with essentially complete chiral transmission. The ester **19a** was converted into tosylate **24b** by standard transformations. Coupling of **24b** with the optically active nine-carbon synthon **25c** furnished tocopheryl benzyl ether (**1c**). Hydrogenation of **1c** followed by acetylation then afforded **1b** (vitamin E acetate). The complete transfer of chirality from (*R*,*E*)-**17** and (*S*,*Z*)-**18** to (*R*,*E*)-**19a** demonstrates the wide potential applicability of this [3,3] sigmatropic process in the synthesis of optically active substances.

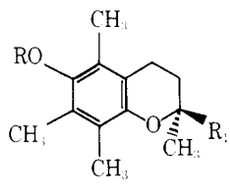
Previous approaches to the synthesis of (2*R*,4′*R*,8′*R*)-α-tocopherol (**1a**) and the acetate **1b** have involved Wittig reactions between the homologous chromanyl aldehydes **2** and **3** and the optically active side chain synthons **7a**[1] and **7b**,[2] respectively, or alternatively, coupling of the chromanyl tosylate **4** with the Grignard reagent **7c**[3b] (Scheme I). In our recent papers,[3a,4] the preparation of highly enantiomerically pure isoprenoid synthons such as **8a**[4] and **8b**[3a] (precursors to **7**) via [3,3] sigmatropic (Claisen) rearrangements was described. The success of this approach (Scheme II) depends on the complete transfer of chirality from allylic alcohols such as (*R*,*Z*)-**11a** and (*S*,*E*)-**12b** [derived from acetylenic carbinols (*R*)-**10a** and (*S*)-**10b**, respectively] to the optically active product (*S*,*E*)-**13a**.[4] An important feature of this synthesis involves the economical utilization of both antipodal or diastereomeric carbinols (*R*)-**10a** and (*S*)-**10b** for the production of the same target molecule. Furthermore, the absolute configuration of the final product can be manipulated simply by choosing the right combination of absolute configuration and geometry of the allylic alcohols. Thus, allylic alcohols (*R*,*Z*)-**11a** and (*S*,*E*)-**12b** give the optically active (*S*,*E*)-**13a** (path i, Scheme II), whereas the isomers possessing the alternate geometry, namely, (*R*,*E*)-**12a** and (*S*,*Z*)-**11b**, generate the antipodal or diastereomeric (*R*,*E*)-**13b** (path ii). In this manner, it is possible to construct optically active isoprenoid synthons utilizing either a "right-to-left" (path i)[5] or "left-to-right" (path ii)[5] strategy. In the present report, we would like to disclose an alternative synthesis of vitamin E acetate (**1b**), which further demonstrates the versatility of this concept.

Our synthetic plan (Scheme III) was based upon the consideration that the vitamin E molecule could be constructed *starting from the chroman moiety* using a "left-to-right" approach, provided diastereomerically pure carbinols **17** [cf. (*R*,*E*)-**12a**] and **18** [cf. (*S*,*Z*)-**11b**] were readily accessible (Scheme III). We envisioned that the synthon **19a** [cf. (*R*,*E*)-**13b**], resulting from orthoester Claisen rearrangement of these carbinols and possessing the required chirality at the newly secondary methyl center, would be easily elaborated into the target molecule **1**.

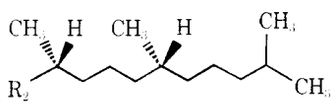
Scheme I



1a, R = H (vitamin E)
b, R = $COCH_3$
c, R = $CH_2C_6H_5$



2a, R = $COCH_3$; R_1 = CHO
b, R = CH_2Ph; R_1 = CHO
3, R = $COCH_3$; R_1 = CH_2CHO
4, R = CH_2Ph; R_1 = $CH_2CH_2OSO_2C_6H_4$-*p*CH_3
5, R = H; R_1 = CH_2COOH
6, R = CH_2Ph; R_1 = CH_2CHO



7a, R_2 = $CH_2CH_2P^+Ph_3Br^-$
b, R_2 = $CH_2P^+Ph_3Br^-$
c, R_2 = CH_2MgBr
8a, R_2 = CH_2CH_2OH
b, R_2 = CH_2OH

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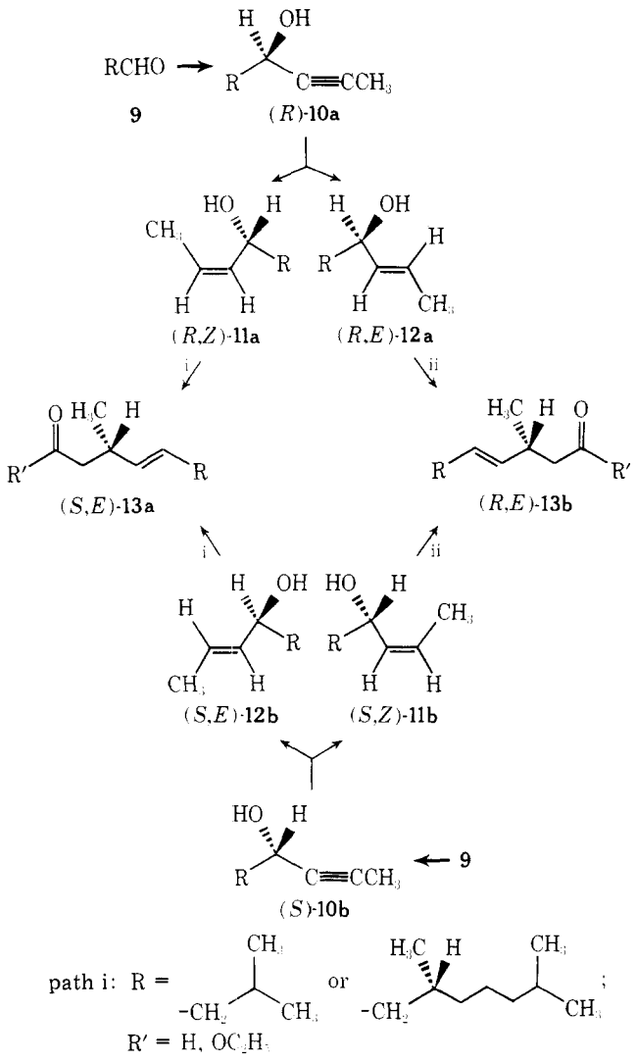
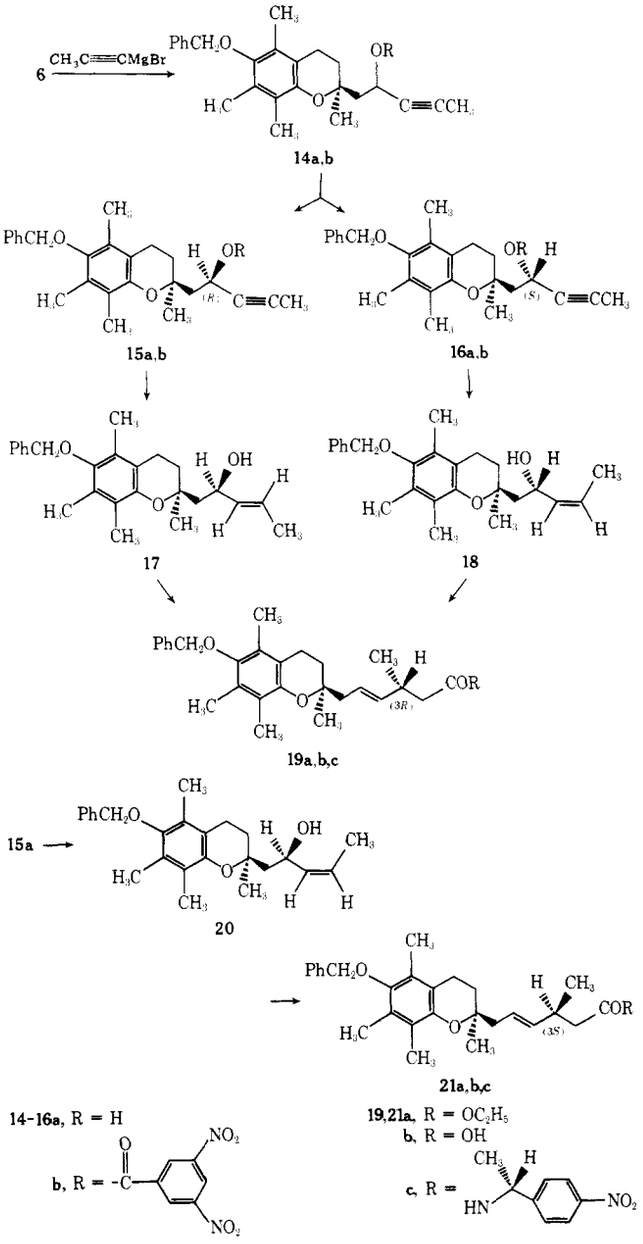
Scheme II[a]



[a] a and b are enantiomeric or diastereomeric pairs.

Scheme III

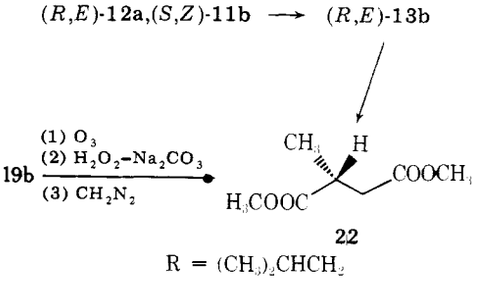


Results and Discussion

We set as our first goal the preparation of the required diastereomerically pure acetylenic carbinols. The starting material for our synthesis was the readily available optically active 2-chromanylacetaldehyde **6,** easily obtained from (*S*)-chroman-2-acetic acid (**5**)[6] as described previously.[2] Treatment of **6** with propynylmagnesium bromide[4] gave a 2:1 mixture of acetylenic carbinols **14a** (Scheme III). Crystallization of the corresponding mixture of 3,5-dinitrobenzoates **14b** followed by alkaline hydrolysis and further crystallization of the crude hydrolysate afforded the major acetylenic carbinol **15a.** The minor carbinol **16a** was obtained from the mother liquor by recrystallization. The absolute configurations of **15a** and **16a**[7] were assigned to be *R* and *S*, respectively, by chemical transformations described below.

Reduction of **15a** with sodium bis(2-methoxyethoxy)aluminum hydride[4] gave the allylic alcohol (*R,E*)-**17,** whereas partial hydrogenation of **16a** with Lindlar catalyst[8] afforded the (*S,Z*)-**18.** Claisen rearrangement of **17** and **18** with triethyl orthoacetate–propionic acid[4,9] in both cases yielded the same unsaturated ester (3*R*,4*E*)-**19a** [cf. (*R,E*)-**13b** in Scheme II]. On the other hand, partial hydrogenation of **15a** furnished the *R,Z* allylic alcohol **20,** which underwent Claisen rearrangement to give the diastereomeric unsaturated ester (3*S*,4*E*)-**21a** [cf. (*S,E*)-**13a** in Scheme II]. Based on the results of various Claisen rearrangements reported earlier,[4] the absolute configuration of the newly introduced asymmetric center in unsaturated ester **19a** could be assigned to be *R*. This was further confirmed by the following sequence of transformations. Hydrolysis of ester **19a** gave the corresponding unsaturated acid **19b,** ozonolysis of which yielded a mixture of acidic compounds which was then treated with diazomethane. The crude product was purified by column chromatography on silica gel to give (*R*)-(+)-dimethyl 2-methylsuccinate[10] (**22**) (Scheme IV). A reference sample of **22** was further prepared from the unsaturated acid **13b** (R′ = OH), which had been shown to have the *R* configuration[4,11] and was in turn derived via allylic alcohols (*R,E*)-**12a** and (*S,Z*)-**11b,** from the optically

Scheme IV



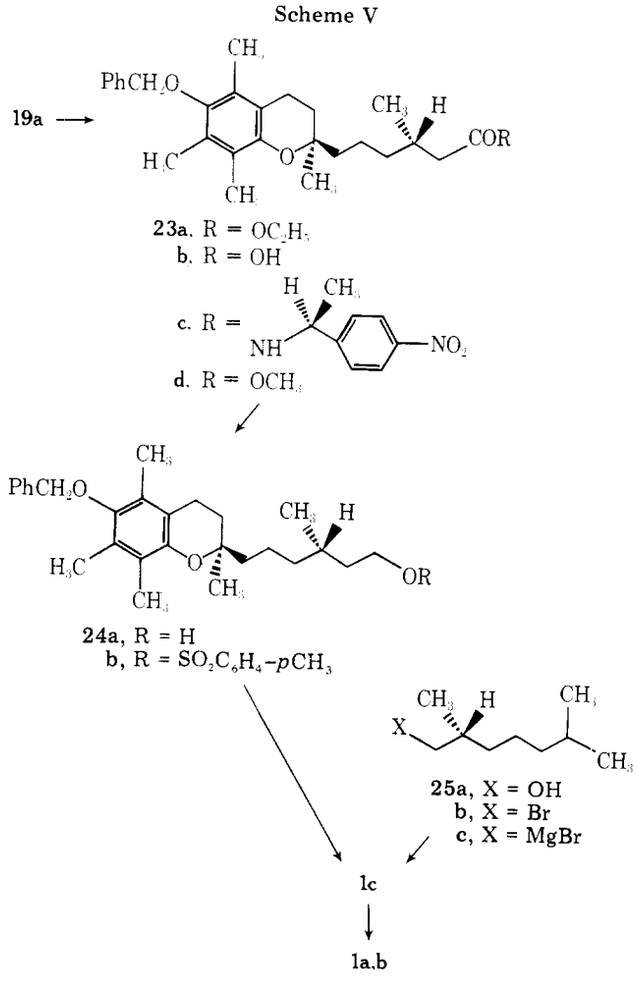
active acetylenic carbinols **10a** and **10b,** respectively.[4] ^{1}H NMR studies of **22** [derived from unsaturated acid **13b** (R′ = OH)] using an optically active shift reagent [tris[((heptafluoroprop-3-yl)hydroxymethylene)-*d*-camphorato]europium(III), Eu(hfbc)$_3$][12] revealed the presence of a singlet signal for the *sec*-carbomethoxy group ($CH_3CHCOOCH_3$) at δ 4.78 (racemic **22** displayed two singlets at δ 4.78 and 4.82, respectively, with equal intensity), while the primary carbomethoxy function (CH_2COOCH_3) of **22** exhibited a singlet at δ 4.69. Comparison of **22** derived from ester **19b** with the reference sample [derived from unsaturated acid (*R,E*)-**13b**] thus firmly established the *R* configuration of the *sec*-methyl group in acid **19b.** Based on previous results and the established mechanism[4] of the Claisen rearrangement, these results provide confirmation of the absolute configurational assignment of the starting allylic alcohols (2*R*,3*E*)-**17** and (2*S*,3*Z*)-**18.**

The enantiomeric purity of the new chiral center in **19a** was first estimated to be nearly 100% by NMR studies on **22** as mentioned earlier. The exact enantiomeric compositions at C(3), however, were obtained by LC analysis[4,13] of the corresponding (*R*)-α-methyl-*p*-nitrobenzylamide derivatives **19c** and **21c:** showing 98.9% *R*, 1.1% *S* [**19c** derived from (*R,E*)-**17**]; 98.8% *R*, 1.2% *S* [**19c** derived from (*S,Z*)-**18**]; and 4% *R*, 96% *S* [**21c** derived from (*R,Z*)-**20**], respectively. The transfer of chirality therefore was essentially 100% in going from allylic alcohols (*R,E*)-**17** and (*S,Z*)-**18** to unsaturated ester (*R,E*)-**19a.**

Having accomplished the synthesis of the desired key intermediate **19a** (cf. compound **13b** as shown in Scheme II) with 99% *R* purity at C(3), we then proceeded to construct the target molecule **1.** Hydrogenation of unsaturated ester **19a** using 5% palladium on carbon gave the saturated ester **23a** (Scheme V). ^{1}H NMR studies of the corresponding methyl ester **23d,** using a chiral shift reagent, indicated the enantiomeric composition at C(3) to be approximately 90% *S* and 10% *R*. Thus, racemization had occurred to a certain extent during hydrogenation using palladium as catalyst.[4a] On the other hand, hydrogenation of **19a** with Raney nickel at 25 °C, 30 psi, resulted in partial cleavage of the benzyl ether group; therefore, the crude product of hydrogenation was treated with benzyl chloride–potassium carbonate to give the desired saturated ester **23a** in good yield. This material was converted to the corresponding (*R*)-(+)-α-methyl-*p*-nitrobenzylamide **23c,** having an enantiomeric composition at C(3) of 96.1% *S* and 3.9% *R* by LC analysis. Clearly, Raney nickel catalyst is preferred, although the reaction conditions for the hydrogenation step have not yet been optimized. Reduction of saturated ester **23a** (derived from **19a** by hydrogenation using palladium catalyst)[14] with sodium bis(2-methoxyethoxy)-aluminum hydride afforded the optically active chromanyl alcohol **24a,** which was then converted to the corresponding tosylate **24b** in the usual manner.[20] With this optically active tosylate **24b** in hand, the stage was set to achieve the final goal, which could be accomplished by coupling of **24b** with an optically active nine-carbon synthon derived from **25a.** To this end, the nine-carbon Grignard reagent **25c,**[3a] prepared from alcohol **25a**[3a,15] via the bromide **25b,**[3a] was allowed to react with the tosylate **24b** in the presence of Li_2CuCl_4[3a,16] to give (2*R*,4′*R*,8′*R*)-α-tocopheryl benzyl ether (**1c**)[3a] (69% yield), which was then converted to the corresponding acetate **1b,**[17] shown to be identical (IR, NMR, and MS spectroscopy, GC, and TLC) with an authentic sample.[2]

In summary, a new synthesis of vitamin E (**1b**) was achieved by the application of stereoselective [3,3] sigmatropic rearrangement. It was further demonstrated that both *R* and *S* allylic alcohols (*R,E*)-**17** and (*S,Z*)-**18** [cf. (*R,E*)-**12a** and (*S,Z*)-**11b,** Scheme II] could be utilized productively to give the same optically active synthon (**19a**), and the transfer of chirality in this [3,3] sigmatropic process was essentially 100%. These findings, together with our earlier reports[3,4] and results of other groups,[18] demonstrate the wide potential applicability of these Claisen rearrangements in the synthesis of optically active substances.[19]

Scheme V



Experimental Section

General. Melting points were determined on a Reichert micromelting point apparatus and are uncorrected. Spectral and gas chromatographic measurements were performed by members of the Physical Chemistry Department of Hoffmann-La Roche Inc. using the following instruments: IR, Beckmann IR 9 or Perkin-Elmer 621 spectrophotometers; UV, Cary Model 14 spectrometer; NMR, Varian A-60 and HA-100 spectrometers with tetramethylsilane as an internal standard; GC, Becker 409 or Hewlett-Packard 5700 instruments with a flame ionization detector; $[\alpha]_D$, Perkin-Elmer 141 polarimeter. LC separations were carried out as described previously.[4,13] Column chromatography was performed using Merck (Darmstadt) silica gel, 0.063–0.2 mm. Unless otherwise noted, the "usual workup" procedure involves dilution of the reaction mixture with water or brine followed by three extractions with the specified solvent. The organic extracts were then combined, washed when appropriate with H_2O, 1 N HCl, saturated $NaHCO_3$, and/or saturated brine, dried over $MgSO_4$, filtered, and concentrated under water aspirator pressure at 30–40 °C on a rotary evaporator.

(2*S*,2*R)-1-(3,4-Dihydro-6-benzyloxy-2,5,7,8-tetramethyl-2*H*-benzopyran-2-yl)-3-pentyn-2-ol (15a) and (2*S*,2*S**)-1-(3,4-Dihydro-6-benzyloxy-2,5,7,8-tetramethyl-2*H*-benzopyran-2-yl)-3-pentyn-2-ol (16a).** A solution of the aldehyde **6**[2] (64 g, 0.19 mol) in 1.0 L of dry ether was added dropwise at ~4 °C with mechanical stirring under argon to a suspension of propynylmagnesium bromide (~2.5 mol; preparation described previously[4]) in ~1.0 L of ether. When the addition was complete, the reaction mixture was further stirred at ~4 °C for 0.5 h and then at 25 °C for 0.5 h. The reaction mixture was poured in small portions into 500 mL of saturated aqueous NH_4Cl solution. It was worked up with ether to give 74 g of the crude product **14a** (mixture of isomers ca. 2:1). This material (70

g, 0.185 mol) was dissolved in 300 mL of dry pyridine, and the resulting solution was added at 4 °C to a solution of 73.6 g (0.37 mol) of *p*-toluenesulfonyl chloride and 39 g (0.19 mol) of 3,5-dinitrobenzoic acid in 300 mL of dry pyridine.[20] The mixture was stirred at ~4 °C for 4 h. It was worked up with $CHCl_3$ as usual, and the crude dinitrobenzoate **14b** was crystallized from CH_3OH–$CHCl_3$ (~3:1) to give 63 g (59.4%) of **15b** as yellow crystals (~84% **15b** and 16% **16b** by NMR). A small sample was recrystallized from CH_3OH–$CHCl_3$ for analysis: mp 150–156 °C; $[\alpha]^{25}_D$ +24.9° (*c* 4.39, $CHCl_3$); MS *m/e* 572 (M^+); ^1H NMR ($CDCl_3$) δ 1.34 (s, C(2) CH_3, ~95% of **15b**), 1.44 (s, C(2) CH_3, ~5% of **16b**), 1.80 (d, C≡CC**H**$_3$), 1.9–2.0 (m, CH_2), 2.04, 2.14, and 2.16 (s, 3ArC**H**$_3$), 2.34 (d, C**H**$_2$CH), 2.63 (t, ArC**H**$_2$C**H**$_2$), 4.58 (s, PhC**H**$_2$O, minor isomer), 4.63 (s, PhC**H**$_2$O, major isomer), 5.95 (m, C**H**C≡C), 8.95 (m, 3,5-NO_2Ph, minor **16b**), 7.4 (m, **Ph**C**H**$_2$O), 9.12 (s, 3,5-NO_2Ph). Anal. Calcd for $C_{32}H_{32}N_2O_8$: C, 67.12; H, 5.63; N, 4.87. Found: C, 66.81; H, 5.67; N, 4.80.

The above dinitrobenzoate (60 g) was dissolved in 150 mL of methanol and 100 mL of 6 N NaOH. It was refluxed for 2.0 h and worked up with ether as usual to give 41.0 g of yellow oily material after chromatography on 150 g of silica gel (ether–petroleum ether 2:3 as eluent). This mixture of acetylenic carbinols **15a** and **16a** was then crystallized from ether–petroleum ether (30–60 °C) to give 27.5 g (38.5% from **6**) of the major carbinol **15a**: mp 89–91 °C; $[\alpha]^{25}_D$ −16.2° (*c* 5.05, $CHCl_3$); MS *m/e* 378 (M^+); IR (KBr) 3450 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (s, 3, C(2) CH_3), 1.81 (d, C≡CC**H**$_3$), 2.07, 2.19, and 2.14 (3s, 9, 3ArC**H**$_3$), 2.63 (t, CH_2), 3.08 (d, C**H**O**H**), 4.66 (s, ArC**H**$_2$O–), 4.75 (m, C**H**OH), 7.4 (m, **Ar**C**H**$_2$–). Anal. Calcd for $C_{25}H_{30}O_3$: C, 79.33; H, 7.99. Found: C, 79.20; H, 7.89.

The mother liquor from the first crystallization, yielding a mixture of 63 g of **15b** and **16b**, was evaporated to dryness at reduced pressure to give an oily residue. This was quickly filtered through 400 g of Florisil. Elution with $CHCl_3$ afforded 36 g of oily material which was dissolved in 100 mL of CH_3OH containing 50 mL of 6 N NaOH. It was refluxed for 1.5 h and worked up with ether as usual. The crude product was filtered through 100 g of silica gel. Elution with ether–petroleum ether (2:3) gave 20 g of oily material consisting of approximately 26% of **15a** and 74% of **16a** (by NMR). Crystallization of this material twice from ether-hexane gave 5.01 g (7% from **6**) of acetylenic alcohol **16a** as white crystals: mp 74–76 °C; $[\alpha]^{25}_D$ −42° (*c* 5.01, $CHCl_3$); MS *m/e* 378 (M^+); IR (KBr) 3450 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34 (s, 3, C(2) CH_3), 1.81 (d, C≡CC**H**$_3$), 2.07, 2.21, and 2.14 (3s, 9, 3ArC**H**$_3$), 2.61 (t, CH_2), 3.30 (d, C**H**O**H**), 4.65 (s, C_6H_5C**H**$_2$O), 4.82 (m, C**H**OH), 7.4 (m, **Ar**C**H**$_2$–). Anal. Calcd for $C_{25}H_{30}O_3$: C, 79.33; H, 7.99. Found: C, 79.41; H, 8.13.

(2*S*,2*R,3*E*)-1-(3,4-Dihydro-6-benzyloxy-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-yl)-3-penten-2-ol (17).** The acetylenic alcohol **15a** (5.0 g, 13.2 mmol) was dissolved in 50 mL of dry ether and treated dropwise with a solution of 4.1 mL (29 mg-atom of hydrogen) of sodium bis(2-methoxyethoxy)aluminum hydride (Aldrich Red-Al, 70% in benzene) in 10 mL of ether. The resulting solution was refluxed for 17 h under argon and then cooled in an ice bath. A solution of 10% (by volume) aqueous H_2SO_4 (100 mL) was carefully added. The mixture was filtered and washed with ether and water. The aqueous phase was again extracted with ether. The combined ether phases were washed with saturated aqueous $NaHCO_3$ solution and water and dried over $MgSO_4$. Evaporation of ether to dryness at reduced pressure yielded 5.21 g of crude product which was crystallized from petroleum ether to give 4.23 g of **17** as white needles: mp 68–70 °C; $[\alpha]^{25}_D$ −24.0° (*c* 5.00, $CHCl_3$); MS *m/e* 380 (M^+); Raman (5145 Å, neat) 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (s, 3, C(2) CH_3), 1.66 (d, C=C**H**$_3$), 1.79–2.02 (m, 2CH_2), 2.06, 2.13, and 2.18 (3s, 9, 3ArC**H**$_3$), 2.63 (m, CH_2), 3.06 (s, OH), 4.42 (m, C**H**OH), 4.65 (s, ArC**H**$_2$O–), 5.58 (m, (*E*)-C**H**=CH, *J* = 15.5 Hz) 7.4 (m, **Ar**C**H**$_2$–). Anal. Calcd for $C_{25}H_{32}O_3$: C, 78.91; H, 8.48. Found: C, 79.12; H, 8.63.

(2*S*,2*S,3*Z*)-1-(3,4-Dihydro-6-benzyloxy-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-yl)-3-penten-2-ol (18).** A mixture of 2.5 g (6.60 mmol) of acetylenic alcohol **16a**, 0.25 g of Lindlar catalyst, and 0.1 mL of quinoline in 15 mL of ethyl acetate–hexane (2:1) was hydrogenated at 23 °C for 4.0 h. The catalyst was removed by filtration and washed with ethyl acetate. The solvent was evaporated to dryness in vacuo, and the oily residue was dissolved in diethyl ether (300 mL), washed with 1 N HCl and water, and dried over anhydrous $MgSO_4$. Evaporation of ether to dryness in vacuo gave 2.51 g of yellow oil which upon crystallization from pentane afforded 2.05 g of **18** as white crystals: mp 84–86 °C; $[\alpha]^{25}_D$ −30.6° (*c* 5.04, $CHCl_3$); Raman (5145 Å, neat) 1675 [(*Z*)-C=C] cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (s, 3, C(2) CH_3), 1.73 (d, C=C**H**$_3$), 2.11, 2.18, and 2.23 (3s, 9, 3ArC**H**$_3$), 4.69 (s, ArC**H**$_2$O), 5.50 (m, (*Z*)-C**H**=CH, *J* = 7.5 Hz), 7.43 (m, C_6H_5). Anal. Calcd for $C_{25}H_{32}O_3$: C, 78.91; H, 8.48. Found: C, 78.69; H, 8.39.

(2*S*,3*R,4*E*)-6-(3,4-Dihydro-6-benzyloxy-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-yl)-3-methyl-4-hexenoic Acid Ethyl Ester (19a). (A) From Allylic Alcohol 17.** A mixture of 4.42 g (0.0116 mol) of (*R*,*E*)-**17**, 13.1 g (0.081 mol) of triethyl orthoacetate, and 85.5 mg (1.16 mmol) of propionic acid in a flask equipped with a short distilling column was degassed, placed under argon, and heated in an oil bath at 140 °C. The ethanol that formed was removed by distillation, and the solution was refluxed for 4.0 h. The excess of reagent was removed under vacuum, and the resulting oily product was quickly chromatographed on 125 g of silica gel. Elution with 1:4 ether–petroleum ether (30–60 °C) afforded 4.86 g (92% yield) of unsaturated ester **19a** as a colorless oil: $[\alpha]^{25}_D$ +0.9° (*c* 5.05, $CHCl_3$); MS *m/e* 450 (M^+); Raman (5145 Å, neat) 1680, 1755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.01 (d, *J* = 6 Hz, CHC**H**$_3$), 1.17 (s, 3, C(2) CH_3), 1.19 (t, $COOCH_2CH_3$), 1.78 (broad s, CH_2), 2.07, 2.13, and 2.17 (3s, 9, 3ArC**H**$_3$), 2.82–2.52 (m, 3), 4.05 (q, $COOCH_2CH_3$), 4.64 (s, ArC**H**$_2$O), 5.52 (m, (*E*)-C**H**=CH, *J* = 15.5 Hz), 7.4 (m, C_6H_5). Anal. Calcd for $C_{29}H_{38}O_4$: C, 77.16; H, 8.51. Found: C, 77.30; H, 8.50.

(B) From 18. A mixture of 500 mg of *S*,*Z* allylic alcohol **18**, 1.48 g of triethyl orthoacetate, and 9.7 mg of propionic acid was allowed to react as described above. After purification of the crude product by column chromatography on silica gel, 479 mg (81% yield) of the unsaturated ester **19a** was obtained as a colorless oil: $[\alpha]^{25}_D$ +0.5° (*c* 4.2, $CHCl_3$); IR and NMR spectra were identical with those described above in A.

(2*S*,3*R,4*E*)-6-(3,4-Dihydro-6-benzyloxy-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-yl)-3-methyl-4-hexenoic Acid (19b).** A solution of 2.0 g (4.4 mmol) of unsaturated ethyl ester **19a** ($[\alpha]^{25}_D$ +0.9°) in 7 mL of methanol and 2 mL of 6 N aqueous NaOH was refluxed for 2.0 h. The solution was diluted with water and extracted with ether. The aqueous alkaline phase was cooled in an ice bath and then acidified with concentrated hydrochloric acid. It was worked up with ether in the usual manner to give 1.57 g of unsaturated acid **19b** as a colorless oil (84% yield): $[\alpha]^{25}_D$ −2.7° (*c* 3.18, $CHCl_3$); MS *m/e* 422 (M^+); IR (neat) 3000–3400, 1710 (COOH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (d, 3, CHC**H**$_3$), 1.21 (s, 3, C(2) CH_3), 1.75 (t, CH_2), 2.08, 2.15, and 2.21 (3s, 9, 3ArC**H**$_3$), 2.56 (t, CH_2), 4.64 (s, ArC**H**$_2$O), 5.48 (m, (*E*)-C**H**=CH, *J* = 15.5 Hz), 7.4 (m, C_6H_5), 9.95 (broad, COOH). Anal. Calcd for $C_{27}H_{34}O_4$: C, 76.75; H, 8.12. Found: C, 76.85; H, 8.09.

(2*S*,3*R,4*E*)-6-(3,4-Dihydro-6-benzyloxy-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-yl)-3-methyl-4-hexenoic Acid (*R*)-α-Methyl-*p*-nitrobenzylamide (19c).** A solution of 38 mg of unsaturated acid **19b** (derived from *R*,*E* allylic alcohol **17** via ester **19a**) and 203 mg of oxalyl chloride in 5 mL of dry benzene was refluxed for 1.0 h and worked up with ether in the usual manner to give 38 mg of the corresponding acid chloride. This material was treated with 49.8 mg of (*R*)-α-methyl-*p*-nitrobenzylamine as reported before[13] to give the corresponding amine **19c** which was analyzed by LC using conditions as described previously.[13] The enantiomeric composition at C(3) was shown to be 1.1% *S* (*k'* 13.5) and 98.9% *R* (50 × 0.45 cm column packed with Partisil 10; eluent 20% THF in heptane, at 3 mL/min).

Similarly, the unsaturated acid **19b**, which was derived from *S*,*Z* allylic alcohol **18**, was transformed into the corresponding amide **19c** as a viscous oil: LC 1.2% 3*S* (*k'* 13.5) and 98.8% 3*R*; MS *m/e* 570 (M^+); IR (neat) 3300 (NH), 1647 (amide CO) cm^{-1}.

(2*S*,2*R,3*Z*)-1-(3,4-Dihydro-6-benzyloxy-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-yl)-3-penten-2-ol (20).** A mixture of 5.0 g (13.2 mmol) of acetylenic alcohol **15a**, 0.5 g of Lindlar catalyst, and 0.3 mL of quinoline in 150 mL of hexane–ethyl acetate (1:2) was stirred in an atmosphere of hydrogen at 25 °C until 1 equiv of hydrogen was consumed. Workup as described above for **18** gave a yellow oil which upon crystallization from petroleum ether in a dry ice–acetone bath afforded 3.41 g of **20** as a white semisolid substance: mp 31–33 °C; $[\alpha]^{25}_D$ −27.4° (*c* 3.67, $CHCl_3$); MS *m/e* 380 (M^+); ^1H NMR (100 MHz, $CDCl_3$) δ 1.30 (s, 3, C(2) CH_3), 1.67 (d, 3, C=C**H**$_3$), 2.11, 2.18, and 2.22 (3s, 9, 3ArC**H**$_3$), 2.96 (s, OH), 4.69 (s, 2, ArC**H**$_2$O), 4.82 (m, 1, C**H**OH), 5.51 (m, 2, (*Z*)-C**H**=CH), 7.43 (m, 5, C_6H_5). Anal. Calcd for $C_{25}H_{32}O_3$: C, 78.91; H, 8.48. Found: C, 79.00; H, 8.44.

(2*S*,3*S,4*E*)-6-(3,4-Dihydro-6-benzyloxy-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-yl)-3-methyl-4-hexenoic Acid Ethyl Ester (21a).** A mixture of 4.0 g (10.5 mmol) of the *R*,*Z* allylic alcohol **20**, 77.3 mg (1.05 mmol) of propionic acid, and 11.8 g (73.5 mmol) of triethyl orthoacetate was refluxed for 3.0 h, while the ethanol that formed was removed by distillation. The mixture was worked up as described earlier. The crude product was chromatographed on 125 g of silica gel. Elution with ether–petroleum ether (1:4) gave 4.72 g (98% yield) of unsaturated ester **21a** as a colorless oil: $[\alpha]^{25}_D$ +19.6° (*c* 5.02, $CHCl_3$); MS *m/e* 450 (M^+); IR (neat) 1735 ($COOC_2H_5$) cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.05 (d, CHC**H**$_3$), 1.20 (s, 3, C(2) CH_3), 1.20 (t, 3, $COOCH_2CH_3$), 2.08, 2.14, and 2.19 (3s, 9, 3ArC**H**$_3$), 2.57 (m, 2, C**H**$_2$$COOC_2H_5$), 4.08 (q, 2, $COOCH_2CH_3$), 4.67 (s, 2, ArC**H**$_2$O), 5.45

(m, 2, CH=CH), 7.42 (m, C_6H_5). Anal. Calcd for $C_{29}H_{38}O_4$: C, 77.16; H, 8.51. Found: C, 77.43; H, 8.50.

(2S,3S*,4E)-6-(3,4-Dihydro-6-benzyloxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)-3-methyl-4-hexenoic Acid (21b). A mixture of unsaturated ester **21a** (1.5 g, 3.34 mmol), 2 mL of 6 N NaOH, and 10 mL of methanol was refluxed for 2.0 h. Workup as usual gave 1.33 g (94% yield) of the unsaturated acid **21b** as a colorless oil: $[\alpha]^{25}_D$ + 22.4° (*c* 2.67, $CHCl_3$); MS *m/e* 422 (M^+); IR (neat) 3000–3400, 1710 (COOH) cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.02 (d, 3, $CHCH_3$), 1.15 (s, 3, C(2) CH_3), 2.06, 2.12, and 2.17 (3s, 9, $3ArCH_3$), 4.65 (s, 2, $ArCH_2$), 5.45 (m, 2, CH=CH), 7.38 (m, C_6H_5), 10.90 (COOH). Anal. Calcd for $C_{27}H_{34}O_4$: C, 76.75; H, 8.12. Found: C, 76.64; H, 8.07.

The acid **21b** was converted, as described earlier, to the corresponding (*R*)-α-methyl-*p*-nitrobenzylamide **21c,** whose enantiomeric composition at C(3) was shown by LC (conditions the same as described for **19c**) to be 96% 3*S* and 4% 3*R*.

(R)-(−)-(E)-3,7-Dimethyl-4-octenoic Acid [13b; R' = OH]. A mixture of 4.0 g of (*S,Z*)-6-methyl-2-hepten-4-ol (**11b**) [prepared from (*S*)-6-methyl-2-heptyn-4-ol (**10b**) of 93.6% *S* and 6.4% *R* by Lindlar hydrogenation as reported previously[4]], 226 mg of propionic acid, and 36.6 g of triethyl orthoacetate was refluxed for 16 h, while the ethanol that formed was removed by distillation. Workup as described earlier gave 3.67 g of the unsaturated ester (*R,E*)-**13b** (R' = OC_2H_5) as a colorless oil, $[\alpha]^{25}_D$ −18.1° (neat). A 2.0-g sample of this ester was refluxed in 5 mL of methanol and 3 mL of 6 N NaOH for 2 h. Workup in the usual manner afforded 1.54 g of unsaturated acid **13b:** bp 99–100 °C (0.6 mm) (Kugelrohr); $[\alpha]^{25}_D$ −2.7° (neat); homogeneous by GC analysis (conditions described previously[4]). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.11; H, 10.42.

Similarly, the unsaturated acid **13b,** $[\alpha]^{25}_D$ −2.6° (neat), was also prepared from (*R,E*)-6-methyl-2-hepten-4-ol (**12a**) [95.9% *R* and 4.1% *S* prepared from (*R*)-6-methyl-2-heptyn-4-ol (**10a**) as reported previously[4]].

(R)-(+)-Dimethyl 2-Methylsuccinate (22). (A) From Unsaturated Acid 19b. A solution of the unsaturated acid **19b** (1.03 *g*) in 20 mL of ethyl acetate was cooled in a dry ice–acetone bath. A stream of ozone (3%) was slowly bubbled through until the solution became blue (~20 min). Most of the ethyl acetate was removed in vacuo, and the reaction mixture was heated with 25 mL of 10% aqueous sodium carbonate and 15 mL of 30% H_2O_2 at 80 °C for 3 h. It was cooled in an ice bath, acidified with concentrated hydrochloric acid, and finally saturated with NaCl. Extraction with ether and workup in the usual manner gave 715 mg of product which was dissolved in 10 mL of ether and treated with a solution of ethereal diazomethane (25 mL) at 23 °C for ~1.0 h. Evaporation of ether gave 645 mg of a yellow liquid which was chromatographed on 30 g of silica gel. Elution with ether–petroleum ether (1:4) gave 129 mg of material which was further purified by Kugelrohr distillation at 100 °C (20 mm) to give 114 mg of (*R*)-(+)-dimethyl 2-methylsuccinate (**22**) as a colorless liquid: $[\alpha]^{25}_D$ +4.2° (*c* 5.42, $CHCl_3$) [lit.[10] $[\alpha]^{25}_D$ +6.1°]; GC (10% OV-101, GCQ 100/200, 80–250 °C) retention time, 26 (67.6% of **22**), 33.6 (21.1% of unknown with molecular weight 174), and 39.8 min (3.3% of unknown with molecular weight 186). GC–IR showed the major component to be completely identical with a sample of racemic dimethyl 2-methylsuccinate: ^1H NMR ($CDCl_3$) δ 1.24 (d, $CHCH_3$), 2.35–3.1 (m, $CHCH_3$ and CH_2COOCH_3), 3.69 (s, CH_2COOCH_3), 3.71 (s, $COOCH_3$); ^1H NMR [100 MHz, $CDCl_3$, 20 mg of sample and 40 mg of Eu(hfbc)$_3$] δ 2.38 (d, $CHCH_3$), 4.69 (s, CH_2COOCH_3), 4.78 (s, $CH_3CHCOOCH_3$). Comparison of this material with racemic dimethyl 2-methylsuccinate and a reference sample of (*R*)-(+)-dimethyl 2-methylsuccinate prepared from 3(*R*),7-dimethyl-4(*E*)-octenoic acid (**13b**) firmly established its *R* configuration and showed no detectable *S* enantiomer present.

(B) From Unsaturated Acid 13b. The unsaturated acid **13b** (250 mg, $[\alpha]^{25}_D$ −2.6°) was ozonized as described above to give 209 mg of partly crystalline acidic substance. This was treated with cold $CHCl_3$ and filtered to remove the isovaleric acid that formed. The $CHCl_3$ filtrate was evaporated, and the residue was dissolved in ether and treated with 10 mL of ethereal diazomethane. Evaporation of ether afforded 108 mg of **22** as a slightly yellow liquid: $[\alpha]^{25}_D$ +1.6° (*c* 2.52, $CHCl_3$); GC (97.6% pure) (conditions the same as in A) retention time, 26.2 min; ^1H NMR (20 mg of sample and 40 mg of Eu(hfbc)$_3$ in $CDCl_3$, 100 MHz) δ 2.43 (d, $CHCH_3$), 4.72 (s, CH_2COOCH_3), 4.82 (s, $CH_3CHCOOCH_3$, 90% *R*), 4.88 (s, $CH_3CHCOOCH_3$, ~10% *S*).

Racemic Dimethyl 2-Methylsuccinate. A 5.0-g (0.044 mol) sample of methyl succinic anhydride in 30 mL of methanol containing 1 mL of concentrated H_2SO_4 was refluxed for 16 h. It was diluted with water and extracted with ether. The ether extract was washed with saturated $NaHCO_3$ and water and dried over $MgSO_4$. Evaporation of ether to dryness in a rotary evaporator at 25 °C and purification of the crude product by Kugelrohr distillation [110–115 °C (20 mm)] afforded 5.94 g of racemic dimethyl 2-methylsuccinate: MS *m/e* 129 (M^+ − 31); ^1H NMR (100 MHz, $CDCl_3$) δ 1.21 (d, $CHCH_3$), 2.3–3.05 (m, $CHCH_3$ and CH_2COOCH_3), 3.65 (s, CH_3COOCH_3), 3.66 (s, $COOCH_3$); ^1H NMR [100 MHz, $CDCl_3$, 31 mg of sample and 62 mg of Eu(hfbc)$_3$] δ 2.4 (d, $CHCH_3$), 4.69 (s, CH_2COOCH_3), 4.78 (s, (*R*)-$CH_3CHCOOCH_3$), 4.82 (s, (*S*)-$CH_3CHCOOCH_3$).

(2R,3S*)-6-(3,4-Dihydro-6-benzyloxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)-3-methylhexanoic Acid Ethyl Ester (23a). (A) Hydrogenation with Palladium Catalyst. A mixture of 3.36 g of unsaturated ester **19a** and 350 mg of 5% palladium on carbon was hydrogenated in 20 mL of ethyl acetate at 23 °C and atmospheric pressure until 1 equiv of hydrogen was consumed (4 h). Workup gave 3.07 g of ester **23a** as a colorless oil: $[\alpha]^{25}_D$ −0.2 ° (*c* 4.14, $CHCl_3$); MS *m/e* 452 (M^+), 437, 407, 362 (base peak); IR (neat) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (d, $CHCH_3$), 1.23 (s, C(2) CH_3), 1.23 (t, $COOCH_2CH_3$), 1.4–1.85 (m, 6, CH_2), 2.08, 2.14, and 2.19 (3s, $ArCH_3$), 2.00–2.4 (m, CH_2COO), 2.58 (t, CH_2CH_2), 4.10 (q, $COOCH_2CH_3$), 4.67 (s, $ArCH_2O$), 7.4 (m, $ArCH_2O$).

(B) Hydrogenation with Raney Nickel. The unsaturated ester **19a** (1.0 g, 2.22 mmol) was hydrogenated with ~200 mg of Raney nickel in ethyl acetate (25 mL) at 25 °C (30 psi) for 4.0 h. The catalyst was filtered off and washed well with ethyl acetate. Evaporation of ethyl acetate in vacuo gave 1.0 g of colorless oil which was dissolved in DMF (10 mL) and treated with 532 mg (3.8 mmol) of anhydrous potassium carbonate and 435 mg (3.8 mmol) of benzyl chloride at 25 °C for 60 h. The reaction mixture was diluted with water and extracted with ether. Workup in the usual manner gave 930 mg of crude product which was purified by thick-layer chromatography on silica gel (ether–petroleum ether 2:3) to give 650 mg of saturated ester **23a** as an oil: $[\alpha]^{25}_D$ −1.4 ° (*c* 4.97, $CHCl_3$); IR, MS, and NMR spectra were identical with the material described in A.

The ester **23a** (200 mg) was hydrolyzed in aqueous NaOH–MeOH to give 189 mg of the acid **23b** which was then converted into the corresponding amide **23c** as described for the preparation of **19c.** LC analysis indicated the enantiomeric composition at C(3) to be 96.1% *S* and 3.9% *R* (two 50 cm × 4.5 mm columns in series, Partisil 10, R-19, flow rate at ~3 mL/min, eluted with 1:4 THF–heptane, monitored at 254 nm; retention volume 182 mL for *R* and 194 mL for *S*).

(2R,3S*)-6-(3,4-Dihydro-6-benzyloxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)-3-methylhexanoic Acid (23b). A mixture of 600 mg of ethyl ester **23a** (prepared from Pd/C hydrogenation of **19a**) and 2 mL of 6 N NaOH in 10 mL of methanol was refluxed for 2.0 h. Workup in the usual manner gave the crude oily acid, which was quickly filtered through a column of silica gel (10 g). Elution with $CHCl_3$ yielded 510 mg (90% yield) of the acid **23b** as a colorless oil: $[\alpha]^{25}_D$ −1.7° (*c* 1.93, $CHCl_3$); MS *m/e* 424 (M^+); IR (neat) 3000–3400, 1705 (COOH) cm^{-1}. Anal. Calcd for $C_{27}H_{36}O_4$: C, 76.38; H, 8.55. Found: C, 76.18; H, 8.67.

The enantiomeric purity at C(3) was determined by NMR analysis of the corresponding methyl ester **23d** [30 mg of **23d,** 80 mg of Eu(fod)$_3$, and 5 μL of CH_3OD in $CDCl_3$]: δ 9.30 (s, $COOCH_3$, 10% 3*R*), 9.33 (s, $COOCH_3$, 90 ± 2% 3*S*).

(2R,3S*)-6-(3,4-Dihydro-6-benzyloxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)-3-methylhexan-1-ol (24a). The ester **23a** (2.2 g, 4.85 mmol; prepared from **19a** by Pd/C hydrogenation) in 20 mL of dry ether was treated dropwise with a solution of 1.81 mL (13 mmol) of sodium bis(2-methoxyethoxy)aluminum hydride (70% in benzene) in 2 mL of ether. The resulting solution was refluxed for 3.0 h and then cooled to 0 °C, and the excess of hydride was destroyed by careful addition of 10 mL of 1.0 N H_2SO_4 followed by 100 mL of water. The precipitate was filtered and washed well with ether. The aqueous phase was separated from the ether layer and was extracted again with ether. Workup of the ether phase in the usual manner gave 2.18 g of crude product which was chromatographed on 100 g of silica gel. Elution with 3:7 ether–petroleum ether afforded 1.55 g (78% yield) of the alcohol **24a** as a colorless oil: $[\alpha]^{25}_D$ −0.6° (*c* 1.01, $CHCl_3$); IR (neat) 3350 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (d, $CHCH_3$–), 1.22 (s, C(2) CH_3), 1.3–1.5 (m, $CHCH_3$ and $3CH_2$), 1.8 (t, 2, CH_2), 2.08, 2.14, and 2.19 (3s, $ArCH_3$), 2.62 (t, 2, CH_2), 3.62 (t, CH_2OH), 4.66 (s, $ArCH_2O$), 7.4 (m, C_6H_5). Anal. Calcd for $C_{27}H_{38}O_3$: C, 78.98; H, 9.33. Found: C, 78.91; H, 9.23.

(2R,3S*)-6-(3,4-Dihydro-6-benzyloxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)-3-methylhexan-1-ol *p*-Toluenesulfonate (24b). A solution of 1.23 g (2.98 mmol) of alcohol **24a** in 4 mL of dry pyridine (dried and distilled over barium oxide) was treated in portions with 1.14 g (5.96 mmol) of *p*-toluenesulfonyl chloride at ~0 °C.[20] The resulting solution was stirred at 0 °C for 3.0 h and then kept at −10 °C for 16 h. The mixture was poured into 100 mL of ice water and

acidified with 3 N HCl (ca. 50 mL). It was extracted with ether, and the combined ether extracts were washed with water and dried over anhydrous potassium carbonate–sodium sulfate (~1:1). Evaporation of ether in vacuo yielded 1.80 g of **24b** as a yellow oil: $[\alpha]^{25}_D$ +1.4° (*c* 2.06, $CHCl_3$); MS *m/e* 564 (M^+); IR (neat) 1365 ($-OSO_2$) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (d, $CHCH_3$), 1.22 (s, C(2) CH_3), 1.3–1.6 (m, 7), 1.77 (t, CH_2), 2.08, 2.16, and 2.21 (3s, $ArCH_3$), 2.42 (s, CH_3Tos), 2.58 (t, $ArCH_2$), 4.04 (t, CH_2SO_3–), 4.67 (s, $ArCH_2O$), 7.4 (m, **Ar**CH_2 and $CH_3C_6H_4SO_3$), 7.78 (d, $CH_3C_6H_4SO_3$).

(2*R*,4′*R*,8′*R*)-α-Tocopherol Benzyl Ether (1c). A solution of 1.24 g (6.0 mmol) of (*R*)-2,6-dimethylheptyl 1-bromide (**25b**) (prepared from (*S*)-(+)-β-hydroxyisobutyric acid via the C(9) alcohol **25a**)[3] in 3 mL of dry ether was added dropwise at 23 °C with stirring under argon to a suspension of 195 mg (8 mmol) of powdered magnesium in 3 mL of ether. The resulting mixture was refluxed with stirring under argon for 3.0 h and then was further stirred at 25 °C for 1.0 h. It was then cooled to −75 °C in a dry ice–acetone bath. To this mixture 0.1 mL of Li_2CuCl_4 was first added followed by a solution of 0.64 g (1.14 mmol) of the *p*-toluenesulfonate **24b** in 10 mL of THF. The resulting reaction mixture was stirred at −75 °C for 10 min, and then it was allowed to warm to 25 °C and stirred for 17 h under argon. The mixture was then treated with 5 mL of 1 N aqueous H_2SO_4 and worked up by ether extraction in the usual manner to give 1.03 g of crude product. This material was purified by thick-layer chromatography on silica gel, and elution with ether–hexane (5:95) afforded 409 mg of (2*R*,4′*R*,8′*R*)-α-tocopherol benzyl ether (**1c**; 69% yield), $[\alpha]^{25}_D$ +0.4° (*c* 4.19, benzene) [lit.[3a] $[\alpha]^{25}_D$ +0.7° (*c* 1.95, benzene)]. Anal. Calcd for $C_{36}H_{56}O_2$: C, 83.02; H, 10.84. Found: C, 82.98; H, 10.95.

(2*R*,4′*R*,8′*R*)-α-Tocopheryl Acetate (1b). A mixture of **1c** (326 mg, 0.63 mmol) and 600 mg of 5% palladium on carbon in 5 mL of THF containing two drops of concentrated HCl was hydrogenated at 25 °C and atmospheric pressure for 1.5 h. Workup gave 239 mg of (2*R*,4′*R*,8′*R*)-α-tocopherol (**1a**) as a light yellow oil which was treated with 2 mL of dry pyridine and 2 mL of acetic anhydride at 25 °C for 16 h. The mixture was poured into ice water and extracted with $CHCl_3$. The combined $CHCl_3$ extracts were successively washed with aqueous 1 N HCl, saturated $NaHCO_3$ solution, and H_2O and dried over $MgSO_4$. Evaporation of solvent in vacuo gave 250 mg of crude product which was purified by thick-layer chromatography on silica gel (ether–petroleum ether 1:4) to yield 188 mg (64%) of **1b** as a light yellow oil: $[\alpha]^{25}_D$ +2.6° (*c* 2, C_2H_5OH) [lit.[2] $[\alpha]^{25}_D$ +3.2° (C_2H_5OH)]; MS *m/e* 472 (M^+); 97.8% pure by GC (OV-101, GCQ 100/120, 6 ft × 4 mm column, 250 °C; retention time, 52.3 min); IR, NMR, and UV spectra were identical with an authentic sample (Eastman Kodak, highest purity). Anal. Calcd for $C_{31}H_{52}O_3$: C, 78.76; H, 11.09. Found: C, 78.82; H, 11.17.

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Registry No.—**1a,** 59-02-9; **1b,** 58-95-7; C(4′)-(*S*)-**1b,** 66900-46-7; **1c,** 59965-06-9; **6,** 58846-73-4; **11b,** 66900-47-8; **12a,** 66900-48-9; **12b,** 59983-79-8; **13b** (R′ = OH), 66900-49-0; **13b** (R′ = OEt), 66842-31-7; **15a,** 64704-95-6; **15b,** 66842-32-8; **16a,** 64765-29-3; **16b,** 66842-33-9; **17,** 64704-96-7; **18,** 60919-74-6; **19a,** 64704-97-8; **19b,** 64704-98-9; **19b** acid chloride, 66842-34-0; **19c,** 66842-35-1; C(3)-(*S*)-**19c,** 66900-50-3; **20,** 66842-36-2; **21a,** 66842-37-3; **21b,** 66842-38-4; (*R*)-(+)-**22,** 22644-27-5; (±)-**22,** 21307-96-0; **23a,** 64704-99-0; **23b,** 64705-00-6; **23c,** 66900-51-4; C(3)-(*R*)-**23c,** 66842-29-3; **23d,** 66842-30-6; **24a,** 64705-01-7; **24b,** 64705-02-8; **25b,** 60610-07-3; (*S*)-(−)-3,7-dimethyloctanoic acid, 55509-77-8; (*R*)-α-methyl-*p*-nitrobenzylamine, 22038-87-5.

References and Notes

(1) (a) H. J. Mayer and O. Isler, *Methods Enzymol.*, **18C,** 241–348 (1971). (b) H. J. Mayer, P. Schudel, R. Rüegg, and O. Isler, *Helv. Chim. Acta,* **46,** 650 (1963). (c) (2*R*,4′*R*,8′*R*)-α-Tocopheryl acetate had also been synthesized from aldehyde **2a** (prepared from **2b**) and the 15-carbon synthetic side chain synthon[4] **7a:** K.-K. Chan, unpublished results.
(2) J. W. Scott, F. T. Bizzarro, D. R. Parrish, and G. Saucy, *Helv. Chim. Acta,* **59,** 290 (1976).
(3) (a) N. Cohen, W. F. Eichel, R. J. Lopresti, C. Neukom, and G. Saucy, *J. Org. Chem.,* **41,** 3505 (1976); (b) *ibid.,* **41,** 3512 (1976).
(4) (a) K.-K. Chan, N. Cohen, J. P. DeNoble, A. C. Specian, Jr., and G. Saucy, *J. Org. Chem.,* **41,** 3497 (1976). (b) Paper presented by K.-K. Chan, Abstracts, 172nd National Meeting of the American Chemical Society, San Francisco, Calif., August 29–Sept 3, 1976, No. ORGN 137.
(5) The "right-to-left" (path i) strategy has been demonstrated in the synthesis of optically active 10- and 15-carbon isoprenoids starting from isoveraldehyde.[4] The "left-to-right" (path ii) strategy has been applied to the synthesis of the 14-carbon synthon **8b** starting from (*S*)-(+)-3-hydroxy-2-methylpropanoic acid.[3a]
(6) We thank Dr. J. W. Scott for providing us with this compound.
(7) The absolute configurations of these carbinols could not be assigned based on their spectral properties. Both carbinols showed free and bonded hydroxy absorptions at 3620 and 3530 cm^{-1} (IR in dilute CCl_4), respectively. In the ^1H NMR spectrum of **15a** the tert-C(2) CH_3 appeared as a sharp singlet at δ 1.29, while in the minor diastereoisomer **16a** this signal was found at δ 1.34 (s). Both **15a** and **16a** were essentially optically pure.
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(9) W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T. T. Li, D. J. Faulkner, and M. R. Peterson, *J. Am. Chem. Soc.,* **92,** 741 (1970).
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(11) The acid **13b** (R′ = OH) was converted to (*S*)-(−)-3,7-dimethyloctanoic acid, $[\alpha]^{25}_D$ −6.1° (*c* 5, $CHCl_3$), by hydrogenation with palladium on carbon. The (*R*)-(+)-3,7-dimethyloctanoic acid derived from (*R*)-(+)-pulegone had $[\alpha]^{25}_D$ +6.9° (*c* 2.8, $CHCl_3$).[4]
(12) P. Sievers, "Nuclear Magnetic Resonance Shift Reagents", Academic Press, New York, N.Y., 1973, p 94.
(13) D. Valentine, Jr., K.-K. Chan, C. G. Scott, K. K. Johnson, K. Toth, and G. Saucy, *J. Org. Chem.,* **41,** 62 (1976).
(14) This experiment was carried out before it was discovered that palladium catalysts caused racemization during hydrogenation of **19a.**
(15) K.-K. Chan and G. Saucy, *J. Org. Chem.,* **42,** 3828 (1977). The nine-carbon alcohol **25a** used in this experiment was prepared from (*S*)-(+)-3-hydroxy-2-methylpropanoic acid as described.[3] We thank Dr. N. Cohen for providing us with this compound.
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(17) The synthetic **1b** had enantiomeric compositions of 99–100% *R* at C(2) and C(8′) but ~90% *R* at C(4′) due to the use of enantiomerically impure ester **23a** as starting material. It would be expected that an enantiomeric composition of 96% *R* at C(4′) should be obtained when material of **23a** prepared by Raney nickel hydrogenation is used. This experiment was not, however, carried out.
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