2.45 (br t, 2 H, $CH_2C{=}O$, J = 6 Hz), 3.3–3.9 (m, 2 H, CH_2O in pyran ring) 4.00 (d, 2 H, CH_2OTHP, J_{gem} = 1 Hz), 4.6 (m, 1 H, O–CH–O); mass spectrum (70 eV), m/e 155 ($M^+ - CH_2OTHP$), 85.

(*E*)-2-Methyl-5-hydroxy-5-[(tetrahydropyranyloxy)-methyl]tetradec-2-enoic Acid (10). To a suspension of NaH (480 mg of a 50% dispersion in oil, 10 mmol) in dry THF (30 mL) at 0 °C under argon was added tiglic acid (1 g, 10 mmol) in dry THF (20 mL) and the mixture was stirred at 40 °C for 3 h. The solution was cooled to 0 °C and then lithium diisopropylamide, prepared from 1.41 mL (1.01 g, 10 mmol) of diisopropylamine and 6.6 mL of a 1.5 M solution of *n*-BuLi (10 mmol) in *n*-hexane, in dry THF (10 mL) was slowly added. The mixture was stirred for 0.5 h at 0 °C and then allowed to warm to 40 °C for 1.5 h. After the mixture was cooled to −78 °C, dry HMPA (3 mL) was added and **9b** (2.7 g, 10 mmol) in THF (20 mL) was slowly dropped in over a 50-min period; the reaction mixture was stirred overnight at −78 °C and then warmed at 50 °C for 6 h. Ice–water and 2 N HCl were added and the mixture was extracted with ether. The ether extracts were washed with water and dried ($MgSO_4$). Removal of the solvent afforded a residue which was chromatographed on silica gel with hexane–methanol (98:2) to give **10** (2.51 g, 68% yield) as a colorless oil: IR (neat) 3400 (OH), 1690 (C=O), 1640 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (t, 3 H, CH_3), 1.05–1.5 (m, 12 H, CH_2), 1.5–1.9 (m, 8 H, CH_2), 1.8 (s, 3 H, $CH_3C{=}C$), 3.2–3.9 (m, 4 H, CH_2O in pyran ring, CH_2OTHP), 4.55 (m, 1 H, O–CH–O), 6.05 (br s, 2 H, OH) 6.9 (t, 1 H, CH=C, J = 6.5 Hz); mass spectrum (70 eV), m/e 370 (M^+), 255 ($M^+ - CH_2OTHP$), 237 ($M^+ - CH_2OTHP - H_2O$), 187, 85.

Anal. Calcd for $C_{21}H_{38}O_5$: C, 68.07; H, 10.34. Found: C, 67.88; H, 10.26.

2-Methyl-5-hydroxy-5-[(tetrahydropyranyloxy)methyl]-tetradecanoic Acid (11). The acid **10** (1.85 g, 5 mmol) in methanol (20 mL) was hydrogenated over 10% Pd–C (150 mg) at atmospheric pressure until starting material disappeared on TLC analysis. After filtration from the catalyst and removal of the solvent, **11** was obtained as a colorless oil in almost quantitative yield: IR (neat) 3350 (OH), 1720 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (t, 3 H, CH_3), 1.1–1.5 (m, 23 H, CH_2 and CH_3), 1.5–2 (m, 6 H, CH_2), 2.1–2.65 (m, 1 H, $CHCH_3$), 3.1–4.1 (m, 4 H, CH_2O in pyran ring, CH_2OTHP) 4.6 (m, 1 H, O–CH–O), 7.2 (br s, 2 H, OH); mass spectrum (70 eV), m/e 372 (M^+), 257 ($M^+ - CH_2OTHP$), 239 ($M^+ - CH_2OTHP - H_2O$), 117, 85.

2-Methyl-5-nonyl-5-(hydroxymethyl)pentanolide (Malyngolide, 1). The acid **11** (1.48 g, 4 mmol) was dissolved in methanol (15 mL), 3 mL of 6 N HCl was added, and the mixture was warmed at 45° C for 30 min. The mixture was then poured into ice–water and extracted with ether. The ether extracts were dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel with hexane–ethyl acetate (7:3) and **1** (930 mg, 87% yield) was obtained as a 1:1 mixture of diastereomers, with R_f 0.47 and 0.35 in TLC, respectively, using hexane–ethyl acetate (6:4) as eluant. These diastereomers had the same spectral properties (IR, ^1H NMR and mass spectra) as those previously reported for Malyngolide (**1**) obtained by path A.

Anal. Calcd for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 70.76; H, 11.11.

Acknowledgment. We are grateful to the National Research Council (Centro di Studio per la Fisica delle Macromolecole) for financial support.

Registry No. (±)-**1** (isomer 1), 74742-19-1; (±)-**1** (isomer 2), 76984-84-4; (±)-**3b**, 76917-10-7; **4**, 76917-11-8; (±)-**5**, 76984-85-5; (±)-**6a**, 76917-12-9; (±)-**6b**, 74709-66-3; (±)-**7** (isomer 1), 76917-13-0; (±)-**7** (isomer 2), 76917-14-1; **8**, 76917-15-2; **9a**, 76917-16-3; **9b**, 76917-17-4; **10**, 76917-18-5; **11**, 76917-19-6; tiglic acid, 80-59-1; decanal, 112-31-2; decanoyl chloride, 112-13-0; diazomethane, 334-88-3.

Total Synthesis of (±)-Albene

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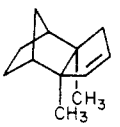
The exo Diels–Alder adduct of 2,3-dimethylmaleic anhydride and cyclopentadiene has been converted to (±)-albene, a hydrocarbon found in plants of the genera *petasites* and *adenostyles*, through an efficient eight-step sequence of reactions. The synthesis includes a simple four-step process for transforming a succinic anhydride moiety into the corresponding cyclopentenone.

The structure of (−)-albene, a crystalline tricyclic $C_{12}H_{18}$ compound first isolated in 1962 from *petasites albus*,[1] has been conclusively established, largely through the efforts of Kreiser, Janitschke, and coworkers:[2-6] formula **1** is (−)-albene, with absolute stereochemistry as depicted.



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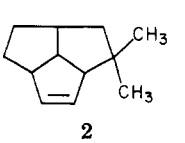

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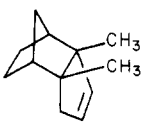

3

The earliest provisional structural hypothesis for this natural product,[7] the tetrahydrotriquinacene **2**, was abandoned when spectral data and direct chemical correlations with (+)-camphene appeared to support the

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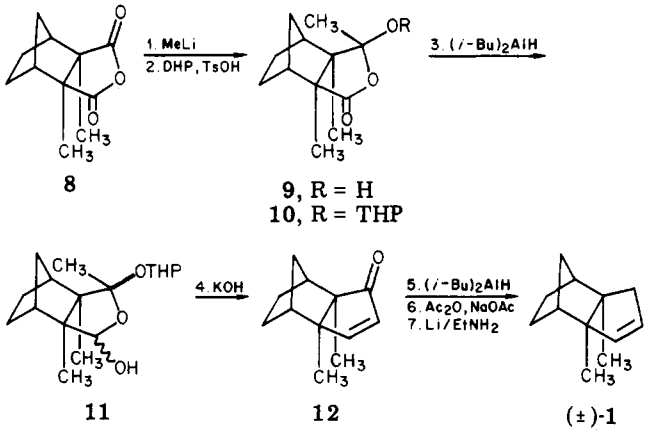
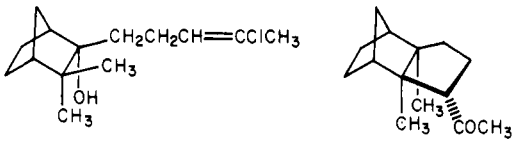
Scheme I



8 9, R = H 10, R = THP 11 12 (±)-1

endo-tricyclo[5.2.1.$0^{2,6}$]dec-3-ene formulation **3**.[8] Ostensible verification of this structural assignment was provided through a rational synthesis of a derivative, albanone, which proved identical with a naturally derived sample.[9]

Yet the structural "confirmation through synthesis" proved incorrect, for one step in the synthetic sequence took place with unexpected stereochemical characteristics: formic acid promoted reaction of chloro alcohol **4** gave tricyclic product **5** with, apparently, a surprising 1,2-shift of the *endo*-methyl rather than the expected[10] migration of the *exo*-methyl substituent.

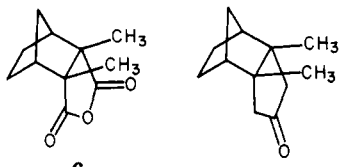


4 5

The literature reports other instances in which a structural assignment or confirmation by partial or total synthesis went awry because an unexpected and temporarily undetected molecular rearrangement or stereochemical propensity intruded. The structural elucidation of (−)-albene adds to that number a particularly simple yet thought-provoking example.

A synthesis of (−)-albene from (+)-camphenilone and 2-chloro-5-iodopent-2-ene[9] has been accomplished in 5% overall yield.[6]

Structure **3**, isoalbene, has been prepared[4,5] in its racemic form from anhydride **6** "in the conventional manner", by



6 7

employing the Thorpe–Ziegler method.[11,12] The anhydride was converted to the symmetrical ketone **7** in five efficient steps with 46% overall yield. Treatment of the ketone with phenylmethanethiol in the presence of boron trifluoride, followed by Raney nickel reduction, afforded (±)-isoalbene in 37% yield (17% overall).

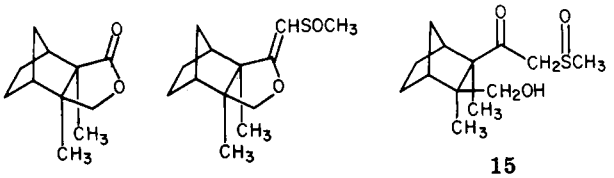
We now report a synthesis of racemic albene which demonstrates the utility of an alternative synthetic method for converting a succinic anhydride to a cyclopentenone. The new synthesis compares favorably with the routes used to make (−)-albene and (±)-isoalbene in number of steps and overall yield.

Reaction of anhydride **8** with 1 equiv of methyllithium at −78 °C gave 95% of the "anhydrol" or "pseudoacid" **9** (Scheme I); the spectroscopic properties of the crystalline product ($\bar{\nu}$ 3590, 3400, 1755 cm^{-1}; NMR, 3 H singlets at δ 1.58, 1.16, and 1.03) confirmed the anticipated[13] ring-closed structural formulation. The tetrahydropyranyl ether **10** was formed (78%, after chromatography) and reduced with diisobutylaluminum hydride to give the cyclic, protected form of a keto aldehyde (**11**); reaction of this fragile intermediate with methanolic potassium hydroxide in the presence of 3A molecular sieves, followed by acidification and thorough chromatographic purification, gave the cyclopentenone **12** in 71% overall yield from **10**.

(±)-Albene was made from cyclopentenone **12** by following an established method:[14,15] reduction with diisobutylaluminum hydride gave the allylic alcohol; the acetate was prepared and reduced with lithium in ethylamine. The extremely volatile product, purified through preparative gas chromatography, was secured in 53% yield from cyclopentenone **12**. Its structure was confirmed as (±)-**1** through comparisons of its spectral properties, most notably its proton and ^{13}C NMR spectra, with published data for naturally occurring (−)-albene.

The overall unmaximized yields for the conversions **8** → **12** and **8** → (±)-**1** were 51% and 28%. The procedure of Scheme I exemplifies yet another and rather direct method for making cyclopentenones.[16]

An alternate strategy, based on the sulfur ylide chemistry pioneered by Corey[17] and used to advantage in preparations of other cyclopentyl systems,[18–20] was not pursued when condensation of the lactone **13** (mp 205–207 °C), prepared through reduction of anhydride **9** with $NaBH_4$,[21] with dimsyl anion in Me_2SO–THF gave rise to methylsulfinyl vinyl ether **14** (a mixture of *E* and *Z* isomers; olefin H singlets at δ 5.33 and 5.13) rather than the desired β-keto sulfoxide **15**.[22]



13 14 15

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Experimental Section

Melting points were determined in sealed capillary tubes with a Dreschel melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Beckman IR-10 spectrophotometer with $CDCl_3$ solutions; proton nuclear magnetic resonance (NMR) spectra were obtained at 100 MHz on a Varian XL-100 instrument in $CDCl_3$ as the solvent with Me_4Si as an internal standard (δ 0.0); mass spectra were determined on either a CEC21-110B or a Hewlett-Packard HP5930M mass spectrometer with an ionizing current of 70 eV. Analytical and preparative gas chromatography was done with a Varian Aerograph Series 1520 instrument using a thermal conductivity detector and helium as the carrier gas.

Unless otherwise specified, reactions were run under an atmosphere of nitrogen, and solvents were distilled under nitrogen immediately before use; diethyl ether was distilled from lithium aluminum hydride, dioxane from sodium, and tetrahydrofuran from sodium and benzophenone. Dimethyl sulfoxide was distilled from NaOH pellets, and distilled dihydropyran and acetic anhydride were stored over 4A molecular sieves. Methyllithium in ether (Alfa Products, Inc.) was titrated with diphenylacetic acid just before use.[23] Glassware was dried with a flame or in an oven (120 °C, 24 h); reaction mixtures were stirred magnetically, and anhydrous magnesium sulfate was employed as a drying agent.

2-*endo*,3-*endo*-Dimethylbicyclo[2.2.1]heptane-2,3-dicarboxylic anhydride (8) was obtained through the Diels–Alder reaction of 2,3-dimethylmaleic anhydride with cyclopentadiene in tri-*n*-propylamine at 80 °C, separation of two stereoisomeric adducts on a silica gel column with ethyl acetate–hexanes (3:17) as eluant, and catalytic hydrogenation. The anhydride 8 was also prepared in higher yield through photochemical cycloaddition with benzophenone as the sensitizer by using a 450-W Hg-vapor lamp, in accord with the general procedure of Schenck, Kuhls, and Krauch,[24] followed by hydrogenation. Anhydride 8, after recrystallization from hexanes, had the following: mp 203.5–205 °C (lit.[24] mp 199 °C); IR 2965, 2880, 1845, 1775 cm^{-1}; NMR δ 2.50 (m, 2 H, 2 CH), 1.40–1.60 (m, 6 H, 3 CH_2), 1.22 (s, 6 H, 2 CH_3).

2-*endo*-3,6-*endo*-Trimethyl-3-hydroxy-4-oxatricyclo-[5.2.1.$0^{2,6}$]decan-5-one (9). A solution prepared from 500 mg (2.57 mmol) of anhydride 8 and 100 mL of diethyl ether was cooled to −78 °C; ethereal 1.10 M methyllithium (2.35 mL, 2.58 mmol) was added by syringe over a 5-min period. The reaction mixture was kept at −78 °C with continued stirring for 30 min and then at room temperature for 30 min. It was poured into 50 mL of vigorously stirred, saturated aqueous NH_4Cl; the two-phased mixture was separated, the aqueous phase was extracted with three 40-mL portions of ether, and the ethereal solutions were combined, washed with 40 mL of brine, dried, filtered, and concentrated by rotary evaporation. The resulting colorless oil was triturated with pentane to give 513 mg (95%) of intermediate 9 as a white solid. A sample recrystallized from ether–pentane gave long white needles: mp 171–172 °C; IR 3590, 3400, 2970, 2940, 2900, 1755, 1140, 1085, 1040 cm^{-1}; NMR δ 3.10 (s, 1 H, OH), 2.25 (m, 2 H, 2 CH), 1.58 (s, 3 H, CH_3), 1.0–1.8 (m, 6 H, 3 CH_2), 1.16 (s, 3 H, CH_3), 1.03 (s, 3 H, CH_3); mass spectrum, m/e 210 (M^+), 192, 166, 151, 123 (base), 84.

2-*endo*-3,6-*endo*-Trimethyl-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-4-oxatricyclo[5.2.1.$0^{2,6}$]decan-5-one (10). Anhydrol 9 (100 mg, 0.48 mmol) and *p*-toluenesulfonic acid monohydrate (20 mg) were dissolved in 3 mL of dioxane at room temperature, and dihydropyran (150 mg, 1.75 mmol) was slowly added via syringe. The reaction mixture was stirred for 6 h, treated with ammoniacal methanol,[25] and concentrated by rotary evaporation. The concentrate was dissolved in 20 mL of CH_2Cl_2, and the solution was washed with 5% aqueous $NaHCO_3$ (2 × 20 mL), dried, filtered, and concentrated to afford 174 mg of a pale yellow oil which was chromatographed on 6 g of 60–200-mesh silica gel with $CHCl_3$ to give 31 mg of recovered starting material 9 and 75 mg (78%) of product 10 as a colorless, viscous oil: IR 2970, 2940, 1760, 1260, 1110, 1040, 1015 cm^{-1}; NMR δ 5.23 (m, 1 H, OCHO), 3.5–4.1 (m, 2 H, CH_2O), 2.32 (m, 2 H, 2 CH), 1.1–2.0 (m, 12 H, 6 CH_2), 1.58 (s, 3 H, CH_3), 1.12 (s, 3 H, CH_3), 1.09 (s, 3 H, CH_3); mass spectrum, m/e 294 (M^+), 250, 193 (base), 168, 167, 123, 122, 111.

2-*endo*-3,6-*endo*-Trimethyl-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-4-oxatricyclo[5.2.1.$0^{2,6}$]decan-5-ol (11). The tetrahydropyranyl derivative 10 (75 mg, 0.26 mmol) dissolved in 8 mL of ether was cooled to −16 °C in an ice–salt bath. Diisobutylaluminum hydride (Alfa Products, 0.45 mL of a 20% solution in hexane, 0.41 mmol) was added slowly by syringe. The reaction mixture was stirred at −16 °C for 90 min and then treated with 1.5 mL of isopropyl alcohol. After 20 min the cooling bath was removed, water (0.5 mL) was added to the reaction mixture, and the mixture was stirred vigorously for another 30 min.[26] Filtration through Celite and washing the aluminum salts with 15 mL of ether gave an ethereal solution which was washed with brine (2 × 20 mL), dried, filtered, and concentrated to give 70 mg (92%) of intermediate 11 as an oil (apparent mixture of C(5) epimers as determined by NMR): NMR δ 4.8–5.3 (m, 2 H, 2 OCHO), 3.4–4.2 (m, 2 H, CH_2O), 0.8–2.3 (m), 1.39 (s, 3 H, CH_3), 1.02 (s, 3 H, CH_3), 0.96 and 0.94 (2 s, total of 3 H, CH_3).

2-*endo*,6-*endo*-Dimethyltricyclo[5.2.1.$0^{2,6}$]dec-4-en-3-one (12). The crude intermediate 11 (70 mg, 0.24 mmol) was dissolved in dry methanol (20 mL) at room temperature, and then KOH (36 mg, 0.64 mmol) and activated 3A molecular sieves (700 mg) were added. After a reaction time of 4 h, the mixture was acidified to pH 3 with concentrated HCl, and the methanol was removed at reduced pressure. The residue was dissolved in 50 mL of CH_2Cl_2, and the solution was washed with brine (2 × 20 mL), dried, filtered, and concentrated to give 38 mg of crude ketone 12 as a thick yellow oil. Purification of this material on a 1000-μm silica gel TLC plate (Analtech Inc.) with $CHCl_3$ as eluant gave a band at R_f 0.2 from which 32 mg (71% yield from 10) of pure 12 was isolated as a colorless oil: IR 3040, 2960, 2930, 2890, 1690, 1590 cm^{-1}; NMR δ 7.34 (d, J = 5 Hz, 1 H, C=CH), 6.27 (d, J = 5 Hz, 1 H, C=CH), 2.11 (m, 1 H, CH), 1.99 (m, 1 H, CH), 0.90–1.70 (m, 6 H, 3 CH_2), 1.03 (s, 3 H, CH_3), 0.93 (s, 3 H, CH_3); mass spectrum, m/e 176 (M^+, base), 161, 148, 133, 122, 110, 108; high-resolution mass spectrum, m/e 176.1201 (calcd 176.1197).

2-*endo*,6-*endo*-Dimethyltricyclo[5.2.1.$0^{2,6}$]dec-3-ene: (±)-Albene ((±)-1). Ketone 12 (21 mg, 0.12 mmol) in 15 mL of ether was cooled to −5 °C; diisobutylaluminum hydride (0.45 mL of a 20% solution in hexane, 0.41 mmol) was added by syringe in 5 min. After 90 min, 1 mL of isopropyl alcohol was added to the stirred reaction mixture; after another 30 min, 0.5 mL of water was added, and stirring was continued 30 min longer. The ice bath was removed, Celite was added, and the mixture was stirred vigorously for 45 min to granulate the mixture of Celite and aluminum salts. Filtration through Celite and washing of the solids with 20 mL of ether gave an ethereal solution which was washed with water (2 × 20 mL), dried, filtered, and concentrated by rotary evaporation to give 20 mg of crude allylic alcohol, 2-*endo*,6-*endo*-dimethyltricyclo[5.2.1.$0^{2,6}$]dec-4-en-3-ol; the olefinic region of the NMR showed the expected ABX at pattern δ 5.70 (dd, J = 2, 6 Hz, 1 H) and 5.71 (d, J = 6 Hz, 1 H).

This unpurified alcohol, acetic anhydride (790 mg), and sodium acetate (110 mg) were combined and heated to reflux for 1 h. The reaction mixture was cooled and diluted with 5 mL of ice–water, followed by 20 mL of CH_2Cl_2 and 30 mL of 5% aqueous $NaHCO_3$. The resulting two-phased system was stirred overnight, and then the organic phase was separated, washed with 20 mL of brine, dried, filtered, and concentrated by rotary evaporation at 20 °C to afford 22 mg of crude acetate, 2-*endo*,6-*endo*-dimethyl-3-acetoxytricyclo[5.2.1.$0^{2,6}$]dec-4-ene, as a clear, bright yellow oil (methyl singlet at δ 2.1). The unpurified acetate and a glass-covered magnetic stirring bar in a 50-mL, three-necked, round-bottomed flask fitted with a dry ice condenser were cooled under nitrogen in an ice bath. Dry ethylamine (Matheson lecture bottle; 20 mL) was condensed into the reaction flask, and then small pieces of lithium (30 mg, 4.3 mmol) were introduced.[15] The

(22) Reduction of the methylsulfinyl compound 16 with aluminum amalgam gave a mixture of methylthio isomers; further reduction with W-II Raney nickel in acetone gave the vinyl ether 2-*endo*,6-*endo*-dimethyl-3-methylene-4-oxatricyclo[5.2.1.$0^{2,6}$]decane.

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

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

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

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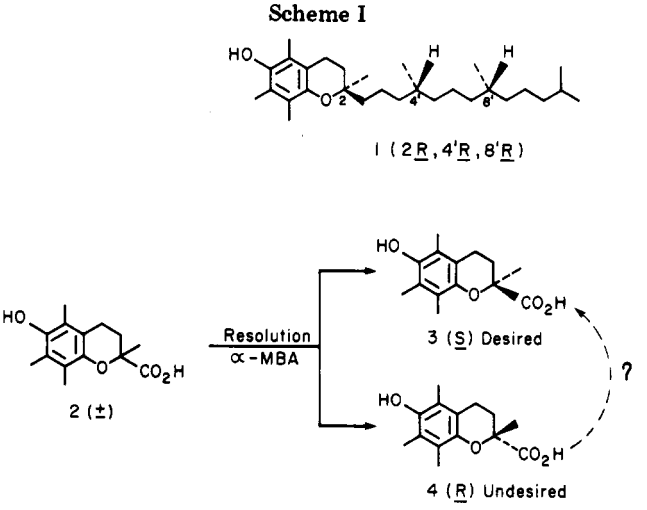
Optically active hydroquinone carbinols such as α-tocopherolhydroquinone (**6**) and the related compounds **12a–d** cyclize under proton catalysis, with essentially complete retention of configuration, regenerating the chromans (**1**, **4**, **10b–d**) from which they are derived. Mechanistic considerations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

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

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

Scheme I



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

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