to give pale yellow needles of thalidezine, mp 155–159 °C and undepressed on admixture with an authentic sample (lit.[12] mp 158–159 °C). These crystals have identical NMR and UV spectra and similar TLC behavior to the authentic sample.

Hernandezine (19). Treatment of thalidezine (110 mg) with diazomethane was carried out as described for 3-methoxynuciferine. Hernandezine (90 mg, 80%) was obtained which was identical in all respects with an authentic sample.[13]

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Registry No.—**1**, 1699-51-0; **2**, 54712-52-6; **4**, 62067-26-9; **5**, 50461-22-8; **6**, 50894-43-4; **8**, 475-83-2; **9**, 62067-27-0; **11**, 62067-28-1; **12**, 5531-86-2; **14**, 5140-38-5; **15**, 518-34-3; **16**, 62067-29-2; **18**, 18251-36-0.

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Cannabinoids. 3.[1] Synthetic Approaches to 9-Ketocannabinoids. Total Synthesis of Nabilone

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The 9-ketocannabinoid, nabilone (**6**), is of clinical interest as one of a new group of totally synthetic cannabinoids that possesses interesting central nervous system properties. Synthetic approaches to **6** from the resorcinol **1** were explored. Three unique approaches to 9-ketocannabinoids are reported (Schemes III, IV, and V) as well as two other approaches (Schemes I and II) that have precedent in the literature. The most efficient synthesis of **6** proceeds through the cis isomer **7** which is isomerized to **6** with $AlCl_3$ in CH_2Cl_2. The optical antipodes, **6a** and **6b**, of nabilone (**6**) can be prepared by two different synthetic routes (Schemes II and III). The most efficient method for the preparation of the optical isomers **6a** and **6b** is from nopinone (**14b**) by the method outlined in Scheme III.

The natural products of marijuana, *Cannabis sativa* L., have been the subject of intensified synthetic endeavors during the past decade.[2a,b] Undoubtedly, some of these efforts were undertaken with the recognition of the therapeutic potentials[3] manifested by this group of interesting compounds. Certainly, our synthetic efforts were motivated by the search for a therapeutically effective drug in the cannabinoid area.

During the course of these studies, our interest focused on a group of compounds containing a keto group at the 9 position of the dibenzo[*b,d*]pyran nucleus.[4] One of these 9-ketocannabinoids, nabilone (**6**), has been selected for clinical evaluation[5a,b] on the basis of its preclinical pharmacology.[5c]

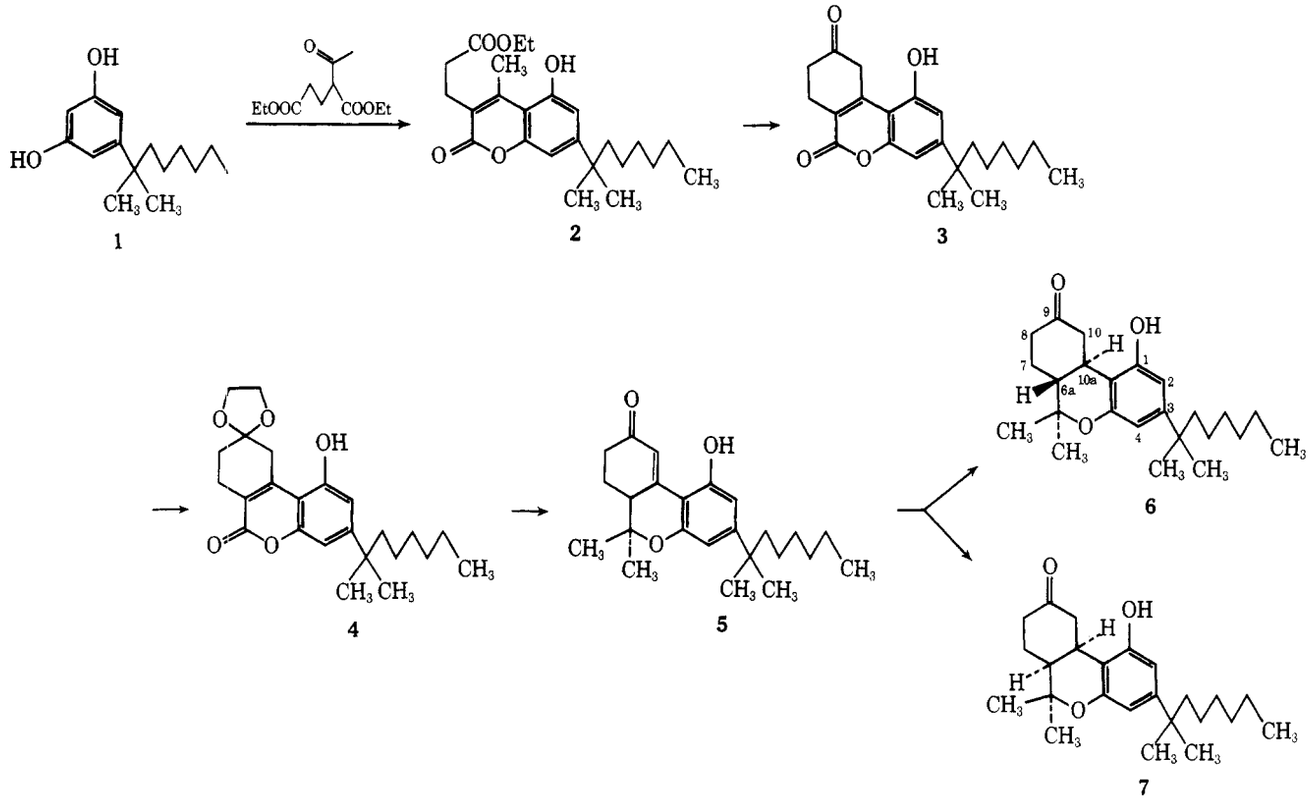
Because the original synthesis (Scheme I) of **6** that we employed was low yielding and cumbersome, we looked for new approaches to the synthesis of 9-ketocannabinoids. This paper describes the results of this search for an efficient synthesis of **6**. Additionally, we report herein the application of a new and shorter synthetic route to the synthesis of the 3-*n*-pentyl analogue (**26**). Previously, **26** has been converted by others[6] into racemic Δ^8- and Δ^9-tetrahydrocannabinol (THC). We also report the preparation of the optical antipodes, **6a** and **6b**, of the parent compound **6** by two different approaches.

Results and Discussion

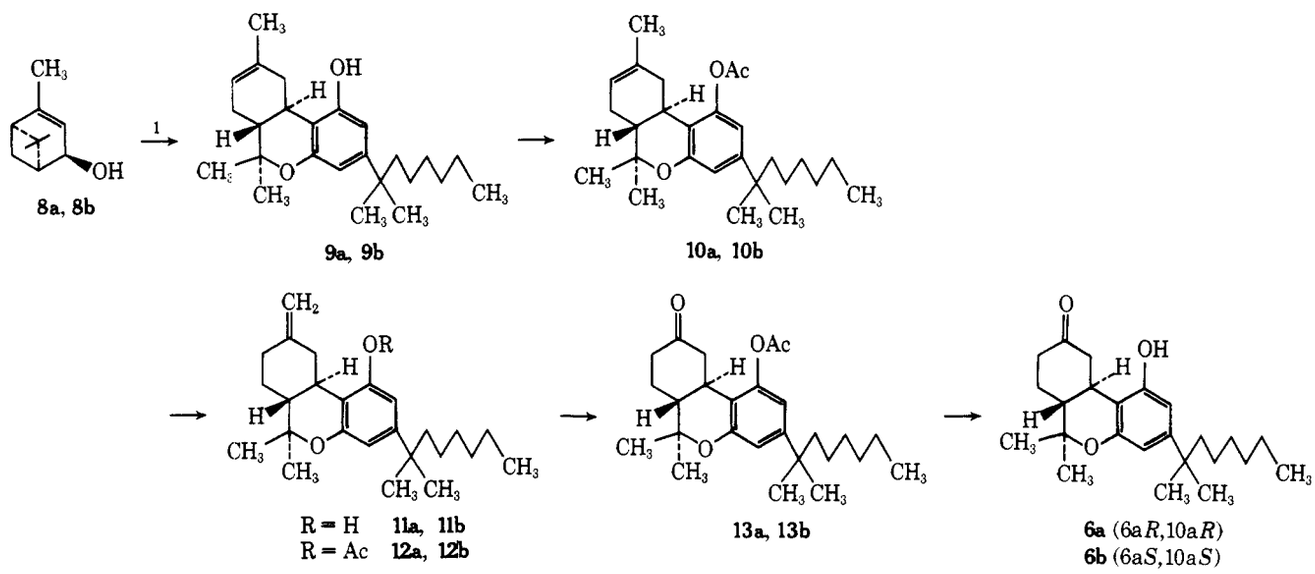
Scheme I outlines our initial approach to the synthesis of **6**. This reaction sequence follows the stepwise approach used by Fahrenholtz et al.[6] for the synthesis of the 3-*n*-pentyl analogues **25** and **26**. The resorcinol **1** was converted into the coumarin **2** by reaction with diethyl 2-acetylglutarate. Cyclization of **2** with NaH in Me_2SO[7] gave the tricyclic ketone **3** in 57% yield. Ketalization to **4** followed by Grignard reaction and strong acid hydrolysis afforded the α,β-unsaturated ketone **5**. Reduction of **5** with Li[8] in liquid NH_3 gave, after separation of the cis isomer **7**, the desired trans isomer **6**. The overall yield from **1** was 24% by this route. The cyclization of **2** to **3** was difficult to perform on a scale larger than 1 mol and never gave greater than 70% yield. Additionally, the chromatographic (and/or crystallization) separation of the trans isomer **6** from the approximately 20% impurity of the cis isomer **7** was difficult. Thus, we sought a better synthetic approach to 9-ketocannabinoids of the type represented by nabilone **6**.

The approach described in Scheme II was chosen primarily because it permitted the use of either (−)- or (+)-α-pinene as

Scheme I



Scheme II[a]



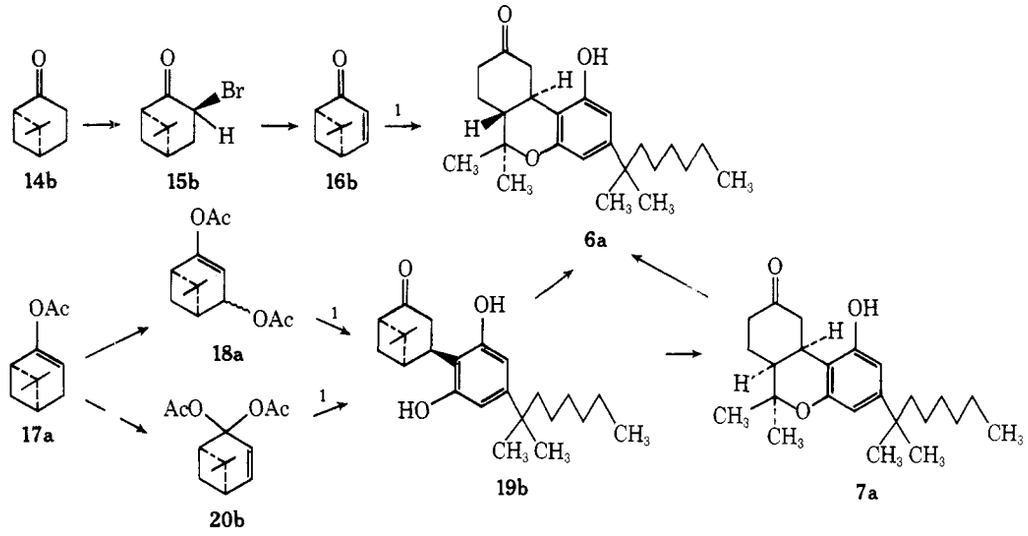
[a] The a and b refer to (−) and (+) optical isomers, respectively.

the starting point. The optically active pinenes could then be converted into the verbenols **8a** and **8b** which would eventually lead to the optically active 9-ketocannabinoids (**6a** and **6b**). Likewise, the choice of the (±)-α-pinene as the starting material would, by this route, give the desired racemate **6**. Fixing the 6a,10a ring juncture trans early in the synthesis avoided the separation of isomers that was a drawback in the first synthesis (Scheme I). Additionally, all of the intended synthetic conversions had a literature precedent in the synthesis[9] of Δ^8-THC and its conversion to the *n*-pentyl ketone **26**.

The appropriate verbenol **8a** or **8b** was converted into the Δ^8 isomers **9a** or **9b** by reaction with the resorcinol **1** in a manner similar to that reported for the synthesis of Δ^8-THC.[9] Acetylation to **10a** or **10b** followed by photolysis, in a manner similar to that published for the preparation of $\Delta^{9,11}$-THC,[10] gave the $\Delta^{9,11}$ isomers **11a** or **11b**. During the photolysis, the 1-acetate group was removed so that it was necessary to reacetylate the $\Delta^{9,11}$ isomers to give **12a** or **12b** which were subsequently ozonized to yield the keto acetates **13a** or **13b**. Hydrolysis of the 1-acetate afforded the desired optically active ketones **6a** or **6b**. From (−)-α-pinene was obtained the 6a*R*,10a*R* isomer **6a**; from (+)-α-pinene, the 6a*S*,10a*S* isomer **6b**. The assignment of absolute stereochemistry rests upon the fact that (−)-verbenol has been converted[9] into (−)-Δ^9-THC whose absolute stereochemistry has been shown[11] to be 6a*R*,10a*R*.

Although this route from verbenol provided optically active

Scheme III[a]



[a] The a and b refer to (−) and (+) optical isomers, respectively.

materials, it suffered from the low-yielding photolysis and ozonolysis steps. Thus, in relation to the synthesis of **6**, it was, in fact, no better than the original synthesis shown in Scheme I. Clearly what was needed was a shorter, more efficient synthesis.

The experience gained from the above synthetic work led us to believe that introduction of the oxygen function earlier in the synthesis might alleviate some problems, especially those associated with the low-yielding photolysis and ozonolysis reactions needed to introduce the 9-keto group by the reactions outlined in Scheme II. Thus, we decided to start with β-pinene and introduce the oxygen function in the first step by ozonolysis. The nopinone (**14b**) obtained by this procedure was converted by bromination to **15b** and dehydrobromination into (+)-apoverbenone (**16b**). Reaction of **16b** with the resorcinol 1 gave the optically active ketone **6a** in 16% yield. Attempts to improve this yield were unsuccessful. Alternatively, nopinone (**14b**) could be converted into the enol acetate **17a** which on treatment with lead tetraacetate in refluxing benzene for 2 h gave the diacetate **20b** in 41% yield. If the reflux time was extended to 18 h, the enol acetate **18a** could be isolated in 39% yield. Either of these acetates, **18a** or **20b**, could be converted in 70% yield into the intermediate norpinanone (**19b**) by the action of *p*-toluenesulfonic acid in chloroform at room temperature.

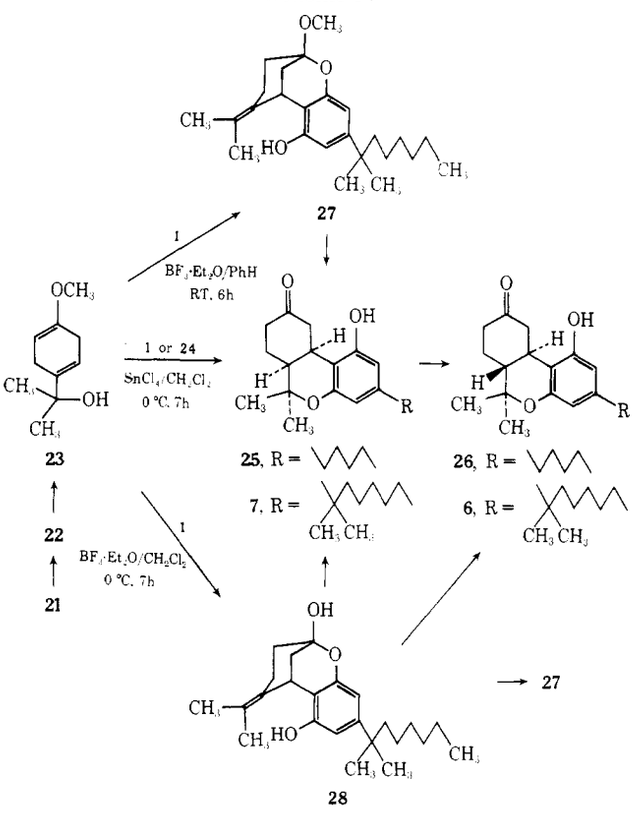
The key intermediate **19b** was then treated with *p*-toluenesulfonic acid in refluxing chloroform to give the optically active cis ketone **7a** in 61% yield. Alternatively, the optically active trans ketone **6a** could be prepared in 82% yield from the treatment of **19b** with stannic chloride in chloroform at room temperature.

Consequently, the synthesis of *cis*- and *trans*-9-ketocannabinoids could be achieved from β-pinene. The lead tetraacetate step (**17a** to **18a** or **20b**) proved to be low yielding and therefore limiting in this approach. Likewise, the direct conversion of **18a** or **20b** gave **6a** in low yield (31%) and contaminated with terpene impurities which were difficult to remove from the desired product. Nevertheless, this synthetic route via the intermediate **19b** provides optically active **6a** in the most convenient method that is presently available.

An optically active terpene (**8a** or **8b**) or terpene-derived moiety (**16b**, **18a**, or **20b**) is condensed with the resorcinol 1 in the approaches outlined in Schemes II and III. This same general conceptual approach provides the basis for most of the efficient syntheses of optically active THC's.[12] For the preparation of racemic 9-ketocannabinoids, such as **6** or **7**, the optically inactive diene **23** is a readily available starting material. It can be prepared from *p*-methoxyacetophenone (**21**) by Grignard addition to provide 2-(4-methoxyphenyl)-2-propanol (**22**), then followed by Birch reduction to the desired diene **23**. The overall yield of **23** from *p*-methoxyacetophenone is 55%.

The reaction of **23** with the resorcinol 1 was studied under a wide variety of acid catalysis conditions (see Scheme IV).

Scheme IV



The products of the reaction showed a surprising dependence on the nature of the acidic catalyst, solvent, temperature, and reaction time. As an example, the ketal **27** was isolated in 37% yield from the reaction of **1** with **23** using 1 mol of BF_3·Et_2O in benzene at room temperature. From a similar reaction using 3 mol of BF_3·Et_2O in CH_2Cl_2 at 0 °C, the hemiketal **28** was

isolated in 42% yield.[13] (Conversion of the hemiketal **28** to ketal **27** was accomplished with oxalic acid in methanol.) The cis ketone **7** was obtained in 65% yield using $SnCl_4$ in CH_2Cl_2, although **28** was observed by TLC to be initially formed and then disappear during the 7-h reaction period. If 1 mol of water was added to the $SnCl_4$ reaction, the yield of **7** dramatically improved to 89%. Conditions were not found under which the trans ketone **6** was the major product, although it was formed in 5–15% yield in the $SnCl_4$ reaction.

The appearance and then disappearance of **28** in the reaction mixture coupled with the observation that either **27** or **28** could be readily converted into **7** on treatment with $SnCl_4$ lead us to the hypothesis that **27** and **28** are intermediates in the formation of **7** from **23**. It follows that the ketal **27** is the initial product of the condensation of **23** and **1**, but is hydrolyzed, especially in the presence of an added mole of water, to the hemiketal **28** which undergoes rearrangement to **7** in the rate-determining step. This suggested mechanism would explain the observed stereoselectivity of the reaction if the ring closure occurs before the hemiketal opening to the ketone.

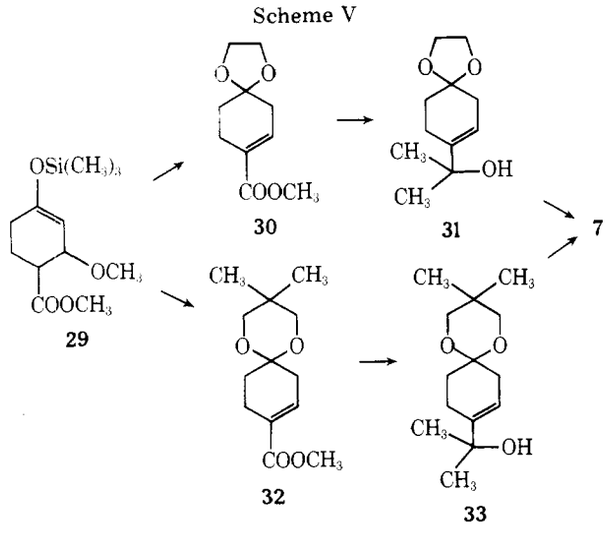
Since our synthetic objective was the trans isomer **6**, it was necessary to either modify reaction conditions to change the stereochemical course of the reaction or find some method to isomerize the 6a,10a cis ring juncture. The isomerization of *cis*-Δ^9-THC to *trans*-Δ^8-THC using BBr_3 in CH_2Cl_2 at low temperature has been reported by Razdan and Zitko.[14] Similar treatment of the cis ketone **7** gave the hemiketal **28** instead of the anticipated trans ketone **6**.

The elusive conditions for isomerization of **7** to **6** were eventually discovered to be $AlCl_3$ in CH_2Cl_2 at 0 °C. Similarly, the cyclic hemiketal **28** can also be converted into **6** using the same $AlCl_3$ isomerization procedure. An overall yield of 80% from diene **23** to trans ketone **6** has been achieved using the two-step approach outlined in Scheme IV. It is our belief that this process proceeds by way of isomerization of the 6a position rather than the 10a position. Work is presently in progress to definitely establish this point. The high yield of this approach (Scheme IV) coupled with the ready availability of **23** from *p*-methoxyacetophenone makes this the most convenient synthesis of **6** that we have discovered.

The generality of this approach to other 3-alkyl-9-keto compounds was demonstrated in the preparation of the 3-*n*-pentyl compounds **25** and **26** by the same procedure using olivetol (**24**). The overall yield of **26** from olivetol was 25%. Since **26** has been previously converted[6] into (±)-Δ^9-THC, this approach (Scheme IV) represents a new synthesis of the optically *inactive* natural products.

Other "masked ketones" can be used in place of the diene **23**. As examples, the ketals **31** and **33** (Scheme V) are converted by the $SnCl_4$ procedure into **7** in 80% yield. Either of these ketals can be prepared from the ester **29** by way of the intermediate ketal esters **30** and **32**. The ester **29** is available from a Diels–Alder reaction described by Danishefsky and Kitahara.[15]

Scheme V



Experimental Section

Instrumentation. Infrared spectra were obtained using a Perkin-Elmer Model 457 diffraction grating spectrophotometer. A Cary 15 spectrophotometer was used to obtain ultraviolet spectra. Proton magnetic resonance spectra were measured with Varian Associates T-60 and HA-100 spectrometers; chemical shifts are expressed in parts per million (δ) downfield from internal tetramethylsilane. Low-resolution mass spectra were determined on a CEC 21-110 spectrometer at an ionizing voltage of 70 eV. For exact mass determinations a Varian MAT 731 mass spectrometer was used. Optical rotations were determined with a Perkin-Elmer 241 polarimeter. Melting points and boiling points are uncorrected.

7-(1,1-Dimethylheptyl)-5-hydroxy-4-methyl-2-oxo-2*H*-1-benzopyran-3-propionic Acid Ethyl Ester (2). A mixture of 331 g (1.4 mol) of 5-(1,1-dimethylheptylresorcinol (**1**),[1] 322 g (1.4 mol) of diethyl 2-acetylglutarate (Aldrich Chemical Co.), and 214 g (1.4 mol) of $POCl_3$ was stirred at room temperature for 11 days. Ethyl acetate was added, and the solution was washed with 5% $NaHCO_3$ solution and water, dried over Na_2SO_4, filtered, and concentrated to afford 548 g (97% yield) of crude **2** suitable for use in the following reaction. A small sample, purified by column chromatography on Woelm neutral alumina (activity II) using $CHCl_3$ as the eluent, had the following physical and chemical characteristics: mp 78–85 °C; UV (EtOH) λ_{max} 208, 257, and 308 nm (ϵ 16 200, 3900, and 5600); ^{1}H NMR ($CDCl_3$) δ 7.2 (broad s, 1 H, exchanges with D_2O), 6.70, 6.80 (2 d, 2 H, J = 2 Hz, H_6 and H_8), 4.15 (q, 2 H, J = 7 Hz, $-COOCH_2-$), 2.68 (s, 3 H, C-4 CH_3), 1.25 (t, 3 H, J = 7 Hz, $-COOCH_2CH_3$), 1.25 (s, 6 H, *gem*-di-CH_3's), and 0.82 (t, 3 H, ω-CH_3).

Acidification of the $NaHCO_3$ extract gave (5–37% yield) the corresponding carboxylic acid: mp 164–167 °C; ^{1}H NMR ($CDCl_3$–Me_2SO-d_6) δ 10.1 (broad s, 2 H, exchanges with D_2O), 6.75 (m, 2 H), and 2.60 (m, 9 H).

Anal. Calcd for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08. Found: C, 70.35; H, 7.80.

3-(1,1-Dimethylheptyl)-7,8,10-dihydro-1-hydroxy-9*H*-dibenzo[*b,d*]pyran-6,9(10*H*)-dione (3). To a suspension of NaH (136 g, 5.66 mol, 272 g of a 50% NaH dispersion in mineral oil, washed several times with *n*-hexane) in 1500 mL of Me_2SO,[11] a solution of 548 g (1.35 mol) of **2** in 1 L of Me_2SO was added dropwise, while maintaining the temperature at 18–20 °C. After standing overnight, the excess NaH was decomposed by dropwise addition of EtOH. The mixture then was poured carefully onto ice and concentrated HCl. The solid that formed was collected and washed with water. The wet filter cake was dissolved in hot methyl ethyl ketone and washed with 5% $NaHCO_3$, saturated NaCl solution, and water. Drying over Na_2SO_4 and evaporating under reduced pressure afforded a light yellow foam. This crude product was triturated with Et_2O, collected, and dried to give 273 g (57% yield) of **3** and a light yellow solid: mp 173–175 °C; UV (EtOH) λ_{max} 204, 258, and 307 nm (ϵ 12 200, 2600, and 3700); ^{1}H NMR ($CDCl_3$–Me_2SO-d_6) δ 6.9 (broad s, 1 H, exchanges with D_2O), 6.70, 6.80 (2 d, 2 H, J = 2 Hz, H_2 and H_4), 1.2 (s, 6 H, *gem*-di-CH_3's), and 0.82 (t, 3 H, ω-CH_3).

Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92; O, 17.95. Found: C, 74.34; H, 7.97; O, 17.95.

3-(1,1-Dimethylheptyl)-7,8-dihydro-1-hydroxyspiro[9*H*-dibenzo[*b,d*]pyran-9-2′-[1,3]dioxalan]-6(10*H*)-one (4). A solution of 310 g (0.87 mol) of **3**, in 1500 mL of benzene[16] containing 53 mL of ethylene glycol and 200 mg of *p*-toluenesulfonic acid, was heated overnight under reflux using a Dean-Stark water separator. After cooling to room temperature, the mixture was poured into 5% $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic extracts were washed with water, dried over Na_2SO_4, and concentrated to give 329 g (95% yield) of **4** as a light yellow solid: mp 55–58 °C; UV (EtOH) λ_{max} 205, 257, and 304 nm (ϵ 11 500, 2700, and 3400); IR ($CHCl_3$) no absorption at 5.75 μ; ^{1}H NMR ($CDCl_3$–Me_2SO-d_6) δ 6.70, 6.80 (2 d, 2 H, J = 2 Hz, H_2 and H_4), 4.05 (s, 4 H, ketal CH_2's), 1.25 (s, 6 H, *gem*-di-CH_3's), and 0.82 (t, 3 H, ω-CH_3).

Anal. Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05; O, 19.97. Found: C, 71.68; H, 8.08; O, 19.77.

(±)-3-(1,1-Dimethylheptyl)-6,6a,7,8-tetrahydro-1-hydroxy-6,6-dimethyl-9*H*-dibenzo[*b,d*]pyran-9-one (5). A solution of 329 g (0.825 mol) of **4** in 1500 mL of anhydrous Et_2O was added

dropwise to 1780 mL of a 2.8 M CH_3MgBr solution in Et_2O. After overnight reflux the mixture was cooled and poured slowly onto an ice–HCl mixture, the resulting HCl concentration being 6 N. The mixture was then heated on a steam bath, whereupon the Et_2O evaporated and a light yellow precipitate formed. Recrystallization from ethyl acetate gave 195 g (64% yield) of **5** as a yellow solid: mp 194–196 °C; IR (Nujol mull) 6.1 μ (α,β-unsaturated C=O); UV (EtOH) λ_{max} 206, 230, and 323 nm (ϵ 25 600, 13 200, and 23 200); ^{1}H NMR ($CDCl_3$) δ 10.5 (s, 1 H, exchanges with D_2O), 8.05 (d, 1 H, J = 2 Hz, H_{10}), 6.36, 6.66 (2 d, 2 H, J = 2 Hz, H_2 and H_4), 1.50, 1.17 (2 s, each 3 H, CH_3's at C-6), 1.25 (s, 6 H, *gem*-di-CH_3's), and 0.83 (t, 3 H, ω-CH_3).

Anal. Calcd for $C_{24}H_{34}O_3$: C, 77.80; H, 9.25. Found: C, 77.98; H, 9.00.

(±)-*trans*-(1,1-Dimethylheptyl)-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9*H*-dibenzo[*b,d*]pyran-9-one (6) and (±)-*cis*-3-(1,1-Dimethylheptyl)-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9*H*-dibenzo[*b,d*]pyran-9-one (7). A solution of 195 g (0.527 mol) of **5** in 2500 mL of anhydrous THF was added dropwise to a solution of Li metal in 10 L of liquid NH_3 at −78 °C. The reaction vessel was kept under a stream of dry nitrogen to prevent moisture from forming inside the reaction flask. More Li metal was added when the blue color of the reaction mixture dissipated. The end of the addition was determined when the blue color persisted for 10 min, after which solid NH_4Cl was added to decompose the excess Li. The mixture was permitted to warm to room temperature overnight under a N_2 atmosphere; during that time most of the excess NH_3 evaporated. The mixture was acidified with 4 N HCl and extracted with ethyl acetate. The combined organic extracts were washed with water, dried over Na_2SO_4, and concentrated to give 194 g of a yellow solid containing both **6** and **7**. Purification and separation of the isomers were achieved in the following manner: The crude product was recrystallized from EtOAc–*n*-hexane (1:1) to afford 125 g of solid which was chromatographed on 2200 g of Woelm neutral Al_2O_3 (activity II) using EtOAc–benzene (1:1) as an eluent. The combined fractions containing **6** were recrystallized to give 76 g of **6** (39% yield) as a white, crystalline solid: mp 159–160 °C; R_f 0.45 (silica gel; 20% EtOAc–benzene); UV (EtOH) λ_{max} 207, 280 nm (ϵ 47 000, 250); IR ($CHCl_3$) 5.85 μ (C=O); ^{1}H NMR ($CDCl_3$) δ 7.75 (s, 1 H, exchanges with D_2O), 6.34, 6.36 (2 d, 2 H, J = 2 Hz, H_2 and H_4), 4.15 (d, 1 H, J = 14.3, 3 Hz, $H_{10\alpha}$), 3.08–0.70 (32 H) especially 1.47, 1.13 (2 s, 3 H each, α and β C-6 CH_3's), 1.21 (s, 6 H, *gem*-di-CH_3's), and 0.83 (t, 3 H, ω-CH_3); mass spectrum *m/e* 372 (M^+).

Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.38; H, 9.74; O, 12.88. Found: C, 77.59; H, 9.68; O, 12.99.

The combined fractions containing **7** were recrystallized to give 5 g (2.5% yield) as a white, crystalline solid: mp 163–165 °C; R_f 0.38 (silica gel; 20% EtOAc–benzene); ^{1}H NMR ($CDCl_3$) δ 6.98 (s, 1 H, exchanges with D_2O), 6.36 (broad s, 2 H, H_2 and H_4), 1.40, 1.35 (2 s, each 3 H, α and β C-6 CH_3's), 1.20 (s, 6 H, *gem*-di-CH_3's), and 0.83 (t, 3 H, ω-CH_3); mass spectrum *m/e* 372 (M^+).

Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.38; H, 9.74; O, 12.88. Found: C, 77.61; H, 10.00; O, 12.57.

(−)- and (+)-*trans*-Verbenol (8a and 8b). The procedure of Whitman[17] for the conversion of (+)-α-pinene to (+)-*trans*-verbenol was followed.

(−)- or (+)-α-pinene (Aldrich Chemical Co.) was redistilled before use: bp 152–155 °C; $[\alpha]^{25}_D$ −44.6° (*c* 1, MeOH) and +49.6° (*c* 0.27, MeOH); ^{1}H NMR ($CDCl_3$) δ 5.21 (m, 1 H), 2.4–0.80 (15 H), especially 1.67 (q, 3 H, J = 2 Hz), 1.28 (s, 3 H), and 0.83 (s, 3 H).

(−)- or (+)-*trans*-verbenyl acetate had the following physical characteristics: bp 73–75 °C (6 mm); $[\alpha]^{25}_D$ −139° (*c* 1, MeOH) and +132° (*c* 0.44, MeOH); ^{1}H NMR ($CDCl_3$) δ 5.4 (m, 1 H), 2.4–0.80 (17 H), especially 2.03 (s, 3 H), 1.36 (s, 3 H) and 0.93 (s, 3 H).

The optically active *trans*-verbenols, **8a** and **8b**, had the following physical and chemical characteristics: $[\alpha]^{25}_D$ −118° (*c* 0.96, MeOH) and +112° (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 5.35 (m, 1 H), 4.28 (m, 1 H), 2.50–0.80 (14 H), especially 1.70 (m, 3 H), 1.34 (s, 3 H), and 0.87 (s, 3 H).

(−)-*trans*-3-(1,1-Dimethylheptyl)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-6*H*-dibenzo[*b,d*]pyran-1-ol (9a). A solution of 48.6 g (0.206 mol) of **1** in 500 mL of CH_2Cl_2 was cooled to −10 °C. To this solution was added 31.3 g (0.206 mol) of **8a** followed by dropwise addition of 28.4 mL (32.7 g, 0.230 mol) of freshly distilled BF_3·Et_2O. The red mixture was stirred for 2 h at −10 °C and then poured into a 5% $NaHCO_3$ solution. The organic layer was separated and washed with water and saturated NaCl solution, dried over Na_2SO_4, and concentrated to afford 72.5 g of a dark, reddish brown gum. Chromatography on 1500 g of silica gel (40% benzene–*n*-hexane) gave a 51% yield of **9a** as a clear resin: $[\alpha]^{25}_D$ −211.8° (*c* 0.41, MeOH); ^{1}H NMR ($CDCl_3$) δ 6.21, 6.40 (2 d, 1 H each, J = 2 Hz, H_2 and H_4), 5.42 (m, 1 H, H_8), 5.26 (s, 1 H, exchanges with D_2O), 3.40–0.85 (34 H), especially 1.72 (broad s, 3 H, C-9 CH_3), 1.42 (s, 3 H, 6β-CH_3), 1.37 (s, 6 H, *gem*-di-CH_3's), 1.13 (s, 3 H, 6α-CH_3), and 0.85 (t, 3 H, ω-CH_3).

Anal. Calcd for $C_{25}H_{38}O_2$: C, 81.03; H, 10.34; O, 8.63. Found: C, 80.80; H, 10.10; O, 8.78.

Similarly prepared in 49% yield from **8b** was the (+) isomer, **9b**, which had the following physical and chemical characteristics: $[\alpha]^{25}_D$ +190.9° (*c* 1, MeOH); ^{1}H NMR identical with that of **9a**; an exact mass determination gave *m/e* 370.2868 (calcd for $C_{25}H_{38}O_2$, 370.2871).

(+)-*trans*-3-(1,1-Dimethylheptyl)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-6*H*-dibenzo[*b,d*]pyran-1-ol Acetate (10b). A mixture of 45.6 g (0.123 mol) of **9b**, 456 mL of pyridine, and 456 mL of Ac_2O was stirred under a N_2 atmosphere for 2 h at room temperature. The mixture was then poured onto crushed ice and after warming to room temperature, extracted with Et_2O. The organic extracts were washed (five times) with 1 N HCl solution, water (five times), and saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to give 50.7 g (99% yield) of **10b** as a tan gum which solidified upon standing: $[\alpha]^{25}_D$ +193° (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 6.52, 6.68 (2 d, 1 H each, J = 2 Hz, H_2 and H_4), 5.45 (m, 1 H, H_8), 2.90–0.75 (37 H), especially 2.28 (s, 3 H, acetate CH_3), 1.68 (broad s, 3 H, C-9 CH_3), 1.40 (s, 3 H, 6β-CH_3), 1.23 (s, 6 H, *gem*-di-CH_3's), 1.12 (s, 3 H, 6α-CH_3), and 0.83 (t, 3 H, ω-CH_3); mass spectrum *m/e* 412 (M^+).

Anal. Calcd for $C_{27}H_{40}O_3$: C, 78.60; H, 9.77; O, 11.63. Found: C, 78.88; H, 9.69; O, 11.84.

Similarly prepared from **9a** was the (−) isomer **10a** which had the following physical and chemical characteristics: $[\alpha]^{25}_D$ −186.8° (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) identical with the above spectrum for **10b**.

Anal. Calcd for $C_{27}H_{40}O_3$: C, 78.60; H, 9.77; O, 11.63. Found: C, 78.23; H, 9.52; O, 11.51.

(−)-*trans*-3-(1,1-Dimethylheptyl)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene-6*H*-dibenzo[*b,d*]pyran-1-ol (11a). A solution of 1.0 g (2.42 mmol) of **10a** in 200 mL of 5% *p*-xylene–2-propanol was photolyzed (450-W Hanovia, Vycor) for 2.5 h under a helium atmosphere. The organic residue obtained by evaporation under reduced pressure was chromatographed on 20 g of silica gel (impregnated with 25% $AgNO_3$) using 10% EtOAc–benzene as an eluent to afford 0.3 g of **11a** (34% yield) as a yellow gum: $[\alpha]^{25}_D$ −41° (*c* 0.24, MeOH); ^{1}H NMR ($CDCl_3$) δ 6.25, 6.40 (2 d, each 1 H, J = 2 Hz, H_2 and H_4), 5.32 (broad s, 1 H, exchanges with D_2O), 4.80 (broad s, 2 H, *exo*-CH_2–), 4.0–0.75 (33 H), especially 1.40 (s, 3 H, 6β-CH_3), 1.18 (s, 6 H, *gem*-di-CH_3's), 1.07 (s, 3 H, 6α-CH_3), and 0.85 (t, 3 H, ω-CH_3); an exact mass determination gave *m/e* 370.2870 (calcd for $C_{25}H_{38}O_2$, 370.2872).

Similarly prepared from **10b** was the (+) isomer **11b** which had the following physical and chemical characteristics: $[\alpha]^{25}_D$ +33.6° (*c* 1, MeOH); ^{1}H NMr)cdcl$_3$) identical with the above spectrum for **11a**; an exact mass determination for **11b** gave *m/e* 370.2868 (calcd for $C_{25}H_{38}O_2$, 370.3872).

(−)-*trans*-3-(1,1-Dimethylheptyl)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene-6*H*-dibenzo[*b,d*]pyran-1-ol Acetate (12a). A mixture of 2.6 g (7.5 mmol) of **11a**, 26 mL of pyridine, and 26 mL of acetic anhydride was stirred at room temperature under N_2 overnight. The mixture was then poured onto ice and extracted with Et_2O. The organic extracts were combined, washed with 1 N HCl (3 × 100 mL) and saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to give 2.8 g (91% yield) of **12a** as a light tan resin: ^{1}H NMR ($CDCl_3$) δ 6.50, 6.67 (2 d, 1 H each, J = 2 Hz, H_2 and H_4), 4.72 (broad s, 2 H, *exo*-CH_2), 3.40–0.75 (36 H), especially 2.30 (s, 3 H, acetate CH_3), 1.38 (s, 3 H, 6β-CH_3), 1.20 (s, 6 H, *gem*-di-CH_3's), 1.05 (s, 3 H, 6α-CH_3), and 0.83 (t, 3 H, ω-CH_3); mass spectrum *m/e* 412 (M^+).

Anal. Calcd for $C_{27}H_{40}O_3$: C, 78.60; H, 9.77; O, 11.63. Found: C, 78.40; H, 9.81; O, 11.50.

Similarly prepared from **11b** was the (+) isomer **12b** which had the following physical and chemical characteristics: ^{1}H NMR ($CDCl_3$) identical with the above spectrum for **11a**.

Anal. Calcd for $C_{27}H_{40}O_3$: C, 78.60; H, 9.77; O, 11.63. Found: C, 78.38; H, 9.57; O, 11.92.

(+)-*trans*-3-(1,1-Dimethylheptyl)-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9*H*-dibenzo[*b,d*]pyran-9-one Acetate (13b). A solution of 1.0 g (2.43 mmol) of **12b** in 100 mL of CH_2Cl_2 was cooled to −78 °C and treated with 1.1 equiv of O_3 from a calibrated ozonizer (Matheson). One minute after the addition of the O_3, 1.7 mL of a 1.52 N solution of $(CH_3)_2S$ in CH_2Cl_2 was added and the mixture permitted to warm to 0 °C. Evaporation of the solvents under reduced pressure gave a crude product which was chro-

matographed on 20 g of silica gel eluted with benzene followed by 1% EtOAc–benzene elution. The desired product, **13b**, was obtained as a light orange resin, 402 mg (41% yield): $[\alpha]^{25}_D$ +55° (*c* 0.89, MeOH); ^{1}H NMR ($CDCl_3$) δ 6.53, 6.71 (2 d, 1 H each, *J* = 2 Hz, H_2 and H_4), 3.5–0.75 (36 H), especially 2.32 (s, 3 H, acetate CH_3), 1.48 (s, 3 H, 6β-CH_3), 1.22 (s, 6 H, *gem*-di-CH_3's), 1.12 (s, 3 H, 6α-CH_3), and 0.85 (t, 3 H, ω-CH_3); mass spectrum *m/e* 414 (M^+).

Anal. Calcd for $C_{26}H_{38}O_4$: C, 75.32; H, 9.24; O, 15.44. Found: C, 75.11; H, 8.98; O, 15.34.

Similarly prepared from **12a** was the (−) isomer **13a** which had the following physical characteristics: $[\alpha]^{25}_D$ −48° (*c* 1.7, MeOH); ^{1}H NMR ($CDCl_3$) identical with the above spectrum for **13b**; an exact mass determination for **13a** gave *m/e* 414.2771 (calcd for $C_{26}H_{38}O_4$, 414.2770).

(+)-*trans*-3-(1,1-Dimethylheptyl)-6a,7,8,9,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9*H*-dibenzo[*b,d*]pyran-9-one (6b). To a solution of 3.56 g (8.6 mmol) of **13b** in 100 mL of MeOH was added, dropwise with stirring at room temperature, a solution of 10.0 g of K_2CO_3 in 50 mL of H_2O. After stirring for an additional 1 h, the mixture was concentrated, diluted with water, and extracted with EtOAc. The combined organic extracts were washed with 1 N HCl, water, and saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to give 3 g of a light yellow glass. Chromatography on 100 g of Woelm neutral alumina (activity II) with Et_2O as the eluent gave 2.65 g (83% yield) of **6b** as a clear glass: $[\alpha]^{25}_D$ +54.9° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) identical with that of the (±) racemate **6**; an exact mass determination gave *m/e* 372.2663 (calcd for $C_{24}H_{36}O_3$, 372.2664).

Similarly prepared from **13a** was the (−) isomer **6a** which had the following physical characteristics: $[\alpha]^{25}_D$ −55.7° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) identical with that of the (±) racemate **6**; mass spectrum *m/e* 372 (M^+).

Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.38; H, 9.74; O, 12.88. Found: C, 77.60; H, 9.50; O, 13.24.

(+)-Apoverbenone (16b) was prepared according to the literature[18] procedure from (−)-β-pinene (Aldrich Chemical Co.) which was converted into nopinone **14b** followed by bromination to **15b** and dehydrobromination to **16b**: bp 52–55 °C (4 mm); ^{1}H NMR ($CDCl_3$) δ 7.55 (q, 1 H, *J* = 9 Hz), 5.95 (d, 1 H, *J* = 9 Hz), 3.35–2.35 (m, 3 H), 2.15 (d, 1 H, *J* = 9 Hz), 1.55 (s, 3 H), and 1.10 (s, 3 H).

Preparation of 6a from 16b. To a solution of **16b** (1.6 g, 12 mmol) and 1 (2.8 g, 12 mmol) in 50 mL of CH_2Cl_2 at 0 °C was added 1.6 g (12 mmol) of anhydrous $AlCl_3$. After stirring for 3 days at room temperature, the reaction mixture was poured onto ice and extracted with Et_2O. The organic extracts were combined and washed with 2 N HCl, water, and 5% $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated to afford 4.5 g of crude product. Chromatography on Woelm silica gel (activity II) with benzene as the eluent gave 720 mg (16% yield) of **6a**: $[\alpha]^{20}_D$ −40.2° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) identical with that of **6**; mass spectrum *m/e* 372 (M^+).

(−)-Nopinone enol acetate (17a) was prepared according to the literature[19] procedure: $[\alpha]^{20}_D$ −37.3° (*c* 1, $CHCl_3$) [lit. $[\alpha]^{20}_D$ −18.6° ($CHCl_3$)]. We believe that the literature rotation value is in error by a factor of 2.

(−)-6,6-Dimethyl-2,4-diacetoxy-2-norpinene (18a). To a solution of 18.0 g (0.1 mol) of **17a** in 250 mL of dry benzene under a N_2 atmosphere was added 48.8 g (0.11 mol) of $Pb(OAc)_4$ (previously dried in vacuo over P_2O_5/KOH). The mixture was refluxed for 18 h, then cooled and filtered. The filtrate was washed with 10% $NaHCO_3$ and water, dried over Na_2SO_4, filtered, and concentrated to afford 23.5 g of a clear liquid. Distillation gave 9.3 g (39% yield) of **18a**: bp 115–118 °C (5 mm); $[\alpha]^{20}_D$ −89.7° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.25 (m, 2 H), 2.4 (m, 4 H), 2.1 (s, 3 H), 2.0 (s, 3 H), 1.35 (s, 3 H), and 1.0 (s, 3 H); IR ($CHCl_3$) 1730 and 1763 cm^{-1} (C=O); mass spectrum *m/e* 196 ($M^+ - CH_2{=}C{=}O$).

Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.72; H, 7.43.

Using the above procedure with a reflux time of 2 h gave 9.8 g (41% yield) of (+)-6,6-dimethyl-2,2-diacetoxy-3-norpinene (**20b**): bp 102–103 °C (5 mm); $[\alpha]^{20}_D$ + 33.2° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.4 (m, 2 H), 3.15 (m, 1 H), 2.3 (m, 3 H), 2.1 (s, 6 H), 1.4 (s, 3 H), and 1.1 (s, 3 H); mass spectrum *m/e* 196 ($M^+ - 42$); IR ($CHCl_3$) 1750 cm^{-1} (C=O).

Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61; $COCH_3$, 36.12. Found: C, 65.77; H, 7.32; $COCH_3$, 36.56.

(+)-4-[4-(1,1-Dimethylheptyl)-2,6-dihydroxyphenyl]-6,6-dimethyl-2-norpinanone (19b). A mixture of 1.19 g (5 mmol) of either **18a** or **20b**, 1.18 g (5 mmol) of **1**, and 0.95 g (5 mmol) of *p*-TSA–H_2O in 50 mL of $CHCl_3$ was permitted to stand at room temperature for 4 h. Ether was added and the organic extracts were washed with 10% $NaHCO_3$ and water, dried over Na_2SO_4, and concentrated to give a semicrystalline residue. The residue was triturated with 25 mL of *n*-hexane and filtered to provide 1.30 g (70% yield) of **19b** as a white, crystalline solid: mp 171–174 °C; $[\alpha]^{20}_D$ +55.8° (*c* 1, $CHCl_3$); IR (KBr) 1668 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$–Me_2SO-d_6) δ 8.05 (s, 2 H, exchanges with D_2O), 6.35 (s, 2 H), 4.05 (t, 1 H), 3.65 (m, 1 H), 2.45 (m, 5 H), 1.35 (s, 3 H), 1.15 (m, 19 H), and 0.95 (s, 3 H); mass spectrum *m/e* 372 (M^+).

Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.38; H, 9.74. Found: C, 77.59; H, 9.83.

(−)-*cis*-3-(1,1-Dimethylheptyl-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9*H*-dibenzo[*b,d*]pyran-9-one (7a). A solution of 372 mg (1 mmol) of **19b** and 190 mg (1 mmol) of *p*-TSA–H_2O in 25 mL of $CHCl_3$ was refluxed for 24 h. After cooling to room temperature the mixture was extracted with Et_2O. The organic extracts were washed with 10% $NaHCO_3$ solution and water, dried over Na_2SO_4, and concentrated to give 380 mg of a white foam. Purification by chromatography (Woelm activity II silica gel; 5% Et_2O–benzene) afforded 228 mg (61% yield) of **7a** as a white, crystalline solid: mp 139.5–141 °C; $[\alpha]^{20}_D$ −50.0° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) identical with the spectrum obtained from the (±) racemate **7**; an exact mass determination gave *m/e* 372.2665 (calcd for $C_{24}H_{36}O_3$, 372.2664).

Also obtained from the above reaction mixture after chromatography was 114 mg (31% yield) of **6a**.

Conversion of 19b into 6a. To a solution of 372 mg (1 mmol) of **19b** in 25 mL of $CHCl_3$ was added 1.0 mL of $SnCl_4$. The resulting mixture was stirred at room temperature for 16 h and then poured onto ice and extracted with Et_2O. The organic extracts were combined, washed with 2 N HCl solution, water, and 5% $NaHCO_3$ solution, dried over Na_2SO_4, filtered, and concentrated to afford 378 mg of a foam. Chromatography (Woelm activity II, silica gel; benzene) yielded 305 mg (82% yield) of **6a**, $[\alpha]^{20}_D$ −52.3° (*c* 1, $CHCl_3$), and 55 mg (14% yield) of **7a**, $[\alpha]^{20}_D$ −50° (*c* 1, $CHCl_3$). ^{1}H NMR and other spectral data were identical with those obtained for the racemates **6** or **7**, respectively; an exact mass determination for **6a** gave *m/e* 372.2667 (calcd for $C_{24}H_{36}O_3$, 372.2664).

Conversion of 7a into 6a. A mixture of 77 mg (0.2 mmol) of **7a**, 5 mL of CH_2Cl_2, and 77 mg of $AlCl_3$ was stirred at room temperature for 4 h. The mixture was poured onto ice and extracted with Et_2O. The organic extracts were washed with 2 N HCl solution, water, and 10% $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated to yield 75 mg of an oil.

Purification by preparative TLC (silica gel; 80% benzene–20% ethyl acetate) gave 54 mg (70% yield) of **6a** as an oil, $[\alpha]^{20}_D$ −53.8° (*c* 1, $CHCl_3$).

Conversion of 18a or 20b into 6a. To a solution of 2.38 g (10 mmol) of either **18a** or **20b** and 2.76 g (10 mmol) of **1** in 50 mL of CH_2Cl_2 at 0 °C was added 10.2 g (12 mL, 0.1 mol) of BF_3·Et_2O. After stirring for 1 h at 0 °C, the mixture was allowed to warm to room temperature overnight, poured onto ice, and extracted with Et_2O. The organic extracts were washed with 10% $NaHCO_3$ solution, dried over Na_2SO_4, filtered, and concentrated to give 4.1 g of a brown oil. Column chromatography (Woelm activity II silica gel; benzene) afforded 1.06 g (31% yield) of **6a** as a colorless oil, $[\alpha]^{20}_D$ −47.5° (*c* 1, $CHCl_3$) (90% optical purity).

2-(4-Methoxyphenyl)-2-propanol (22). A solution of 128 g (0.85 mol) of 4-methoxyacetophenone (**21**) (Aldrich Chemical Co.) in 200 mL of dry Et_2O was added dropwise to a solution of 1 mol of CH_3MgBr in Et_2O. The reaction mixture was heated under reflux for 3 h and cooled to 0–5 °C, and then 85 mL of H_2O was added carefully dropwise. The organic layer was decanted from the solid phase, washed with water and saturated NaCl solution, dried over K_2CO_3, and concentrated to give 132 g (94% yield) of **22**[20] which was sufficiently pure for use in the next reaction: ^{1}H NMR ($CDCl_3$) δ 7.09 (q, 4 H, aromatics), 3.77 (s, 3 H, OCH_3), 1.99 (s, 1 H, exchanges with D_2O), and 1.53 (s, 6 H).

2-(4-Methoxy-1,4-cyclohexadienyl)-2-propanol (23). The procedure of Birch[21] was modified as follows. A solution of 130 g (0.78 mol) of **22** in 260 mL of anhydrous EtOH was added carefully to 1300 mL of liquid NH_3. Lithium metal (26 g, 3.9 g-atoms) was added in small pieces until the blue color persisted in the reaction mixture. Then, 200 g (3.8 mol) of NH_4Cl and 500 mL of toluene were added. After the NH_3 had evaporated, 600 mL of H_2O was added. The organic layer was separated, washed with H_2O and saturated NaCl solution, dried over K_2CO_3, and concentrated to give an oil. Crystallization from 125 mL of *n*-hexane at 0 °C gave 76.5 g (59% yield) of **23**[21,22] as a white, crystalline solid: mp 33–35 °C; ^{1}H NMR ($CDCl_3$) δ 5.70, 4.67 (2 broad s, 1 H each, H_2 and H_5), 3.52 (s, 3 H, OCH_3), 2.84 (broad s, 4 H, $-CH_2$'s at C-3 and C-6), 1.78 (s, 1 H, exchanges with D_2O), and 1.33 (s, 6 H, *gem*-di-CH_3's).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59; O, 19.02. Found: C, 71.31; H, 9.65; O, 18.72.

Preparation of 7 from 23. A solution of 11.8 g (50 mmol) of 1 and 10.0 g (60 mmol) of **23** in 200 mL of CH_2Cl_2 was cooled to −10 °C. To this solution was added, in one portion, 0.9 mL (50 mmol) of H_2O and then 13 mL (111 mmol) of $SnCl_4$ was added dropwise over a 30-min period. After stirring for 7 h at 0 °C H_2O was added and the organic layer was separated and washed with 1 N NaOH (twice) and water, dried over $MgSO_4$, and concentrated to give a white solid. Recrystallization from *n*-hexane gave 16.6 g (89% yield) of **7** which was shown by GC analysis to contain 12% of **6**: spectral data were identical with those obtained from **7** prepared from **5**; mp 163–165 °C.

Isomerization of 7 to 6. To a solution of 30 g (0.081 mol) of **7** in 300 mL of CH_2Cl_2 at 0 °C was added 37.5 g (0.28 mol) of $AlCl_3$. The mixture was stirred at 0 °C for 4 h and then poured into ice water. The organic layer was separated, washed two times with water, dried over $MgSO_4$, filtered, and concentrated to give a solid residue. Recrystallization from methylcyclopentane (225 mL) gave 27.7 g (92% yield) of **6**.

(±)-*cis*-3-*n*-Pentyl-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9*H*-dibenzo[*b,d*]pyran-9-one (25). A. From Olivetol (24) and 23. The same procedure was used as for the preparation of **7** from **23**. From 1.8 g (10 mmol) of **24** there was obtained 0.38 g (12% yield) of **25** which was shown by TLC to contain some of the trans isomer, **26**: mp 148–152 °C (lit.[6] 149.5–150.5 °C); ^1H NMR ($CDCl_3$) δ 7.28 (s, 1 H, exchanges with D_2O), 6.20 (s, 2 H, H_2 and H_4), 3.7–0.7 (25 H), especially 1.40, 1.33 (2 s, 3 H each, $C_{6\beta}$ CH_3 and $C_{6\alpha}$ CH_3), 0.87 (t, 3 H, ω-CH_3).

B. From 24 and 31. The same procedure was used as for the preparation of **7** from **31**. From 1.8 g (10 mmol) of **24** there was obtained 0.5 g (16% yield) of **25** which was shown by TLC to contain only a trace of the trans isomer **26**, mp 152–154 °C.

(±)-*trans*-3-*n*-Pentyl-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9*H*-dibenzo[*b,d*]pyran-9-one (26). To a solution of 400 mg (1.27 mmol) of **25** in 20 mL of CH_2Cl_2 was added 0.6 g of $AlCl_3$. The mixture was stirred for 3 h and then poured into water. The organic layer was separated, washed with water, dried over $MgSO_4$, filtered, and concentrated to give a solid residue. This solid was triturated with hot *n*-hexane and collected by filtration to afford 220 mg (55% yield) of **26**: mp 146–150 °C (lit.[6] mp 148–150 °C for the lower melting polymorph); ^1H NMR ($CDCl_3$) δ 7.74 (broad s, 1 H, exchanges with D_2O), 6.26 (s, 2 H, H_2 and H_4), 4.13 (d, 1 H, $H_{10\alpha}$), 3.3–0.7 (24 H), especially 1.45, 1.10 (2 s, 3 H each, $C_{6\beta}$ and $C_{6\alpha}$ CH_3's), and 0.87 (t, 3 H, ω-CH_3).

(±)-9-(1,1-Dimethylheptyl)-3,4,5,6-tetrahydro-5-isopropylidene-2-methoxy-2,6-methano-2*H*-1-benzoxocin-7-ol (27). To a solution of 4.72 g (20 mmol) of 1 and 4.0 g (24 mmol) of **23** in 100 mL of benzene was added 2 mL of BF_3·Et_2O. After stirring for 6 h, water was added, and the organic layer was separated, washed with 1 N NaOH and water, dried over $MgSO_4$, and concentrated to give an off-white solid. Recrystallization from *n*-hexane gave 2.8 g (37% yield) of **27** as a white, crystalline solid: mp 131–133 °C; R_f 0.85 (silica gel; 20% EtOAc–benzene); ^1H NMR ($CDCl_3$) δ 6.30, 6.51 (2 d, 1 H each, J = 2 Hz, H_8 and H_{10}), 4.58 (s, 1 H, exchanges with D_2O), 4.33 (broad s, 1 H, H_6), 3.45 (s, 3 H, $-OCH_3$), 2.80–0.70 (31 H) especially 1.96, 1.70 (2 s, 3 H each, isopropylidene CH_3's), 1.20 (s, 6 H, *gem*-di-CH_3's), and 0.83 (t, 3 H, ω-CH_3); mass spectrum *m/e* 386 (M^+).

Anal. Calcd for $C_{25}H_{38}O_3$: C, 77.68; H, 9.91. Found: C, 77.49; H, 9.71.

(±)-9-(1,1-Dimethylheptyl)-3,4,5,6-tetrahydro-5-isopropylidene-2,6-methano-2*H*-1-benzoxocine-2,7-diol (28). To a solution of 4.72 g (20 mmol) of 1 and 4.0 g (24 mmol) of **23** in 150 mL of CH_2Cl_2 at −5 °C was added 6.0 mL (72 mmol) of BF_3·Et_2O. After stirring for 7 h at 0 °C, water was added. The organic layer was separated and washed with H_2O and 1 N NaOH, dried over $MgSO_4$, and concentrated to give an off-white solid. Crystallization from 25 mL of *n*-hexane gave 3.1 g (42% yield) of **28** as a white, crystalline solid: mp 155–156 °C; R_f 0.65 (silica gel; 20% EtOAc–benzene); ^1H NMR ($CDCl_3$) δ 6.23, 6.42 (2 d, 1 H each, J = 2 Hz, H_8 and H_{10}), 4.58, 2.87 (2 s, 1 H each, exchange with D_2O), 4.28 (broad s, 1 H, H_6), 2.80–0.70 (31 H), especially 1.93, 1.67 (2 s, 3 H each, isopropylidene CH_3's), 1.18 (s, 6 H, *gem*-di-CH_3), and 0.83 (t, 3 H, ω-CH_3); mass spectrum *m/e* 372 (M^+).

Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.38; H, 9.74. Found: C, 77.33; H, 9.55.

Conversion of 28 to 27. A solution of 1 g (2.7 mmol) of **28** and 0.1 g of oxalic acid in 50 mL of CH_3OH was heated under reflux for 5 h. After evaporation of the MeOH, the organic residue was dissolved in CH_2Cl_2, washed with water, dried over $MgSO_4$, filtered, and concentrated to give a solid residue. The residue was triturated with *n*-hexane and collected to give 0.85 g (82% yield) of **27**, identical with that obtained from **23**.

Preparation of 7 from 27. To a solution of 1 g (2.6 mmol) of **27** and 0.05 mL of H_2O[23] was added 0.6 mL of $SnCl_4$. After 2 h the reaction mixture was poured into H_2O. The organic layer was separated, washed with 1 N HCl solution and water, dried over $MgSO_4$, filtered, and concentrated to give 0.90 g (93% yield) of **7**, identical with that obtained from **5**.

Preparation of 7 from 28. To a solution of 1 g (2.7 mmol) of **28** in 20 mL of CH_2Cl_2 was added 1.5 mL of $SnCl_4$. The resulting mixture was stirred at 0–5 °C for 4 h and then poured onto ice. The organic layer was separated, washed with 1 N HCl, NaOH solution, and water, dried over $MgSO_4$, filtered, and concentrated to give a solid residue. The residue was triturated with *n*-hexane and filtered to give 0.78 g (78% yield) of **7** identical with that obtained from **5**.

Preparation of 6 from 28. A mixture of 1 g (2.7 mmol) of **28**, 20 mL of CH_2Cl_2, and 1 g (7.5 mmol) of $AlCl_3$ was stirred at 0 °C for 2 h. The mixture was then poured onto ice and the organic layer was separated, washed with water, dried over $MgSO_4$, filtered, and concentrated to give a solid residue. The residue was triturated with *n*-hexane and filtered to afford 0.82 g (82% yield) of **6** identical with that prepared from **5**.

1,4-Dioxaspiro[4.5]dec-7-ene-8-carboxylic acid methyl ester (30) was prepared according to the procedure of Danishefsky and Kitahara:[15] mp 41–42 °C (lit.[15] mp 40–41 °C); ^1H NMR ($CDCl_3$) δ 6.9 (m, 1 H, CH=C), 3.9 (s, 4 H, OCH_2CH_2O), 3.7 (s, 3 H, $COOCH_3$). 2.4 (m, 4 H), and 1.8 (m, 2 H).

α,α-Dimethyl-1,4-dioxaspiro[4.5]dec-7-ene-8-methanol (31). A solution of 11 g (55 mmol) of **30** in 100 mL of toluene was added dropwise to a solution of CH_3MgBr (110 mmol) in Et_2O at 15 °C. After stirring for 2 h, the reaction mixture was cooled to 5 °C and then added to 100 mL of an ice-cold 1.3 M NH_4Cl solution. The organic phase was separated, washed with water, dried over $MgSO_4$, filtered, and concentrated to give 6.6 g (60% yield) of **31** as an oil: ^1H NMR ($CDCl_3$) δ 5.6 (m, 1 H, CH=C), 3.9 (s, 4 H, OCH_2CH_2O, 2.6 (s, 1 H, exchanges with D_2O), 2.3 (m, 4 H), 1.8 (m, 2 H), and 1.3 [s, 6 H, $C(CH_3)_2$]; mass spectrum *m/e* 198 (M^+).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15; O, 24.21. Found: C, 66.68; H, 9.05; O, 24.30.

3,3-Dimethyl-1,5-dioxaspiro[5.5]undec-8-ene-9-carboxylic Acid Methyl Ester (32). Using the same procedure as for the preparation of **30** except to replace ethylene glycol with 2,2-dimethyl-1,3-propanediol gave **32** (10.6 g, 80% yield): mp 60 °C; ^1H NMR ($CDCl_3$) δ 6.8 (m, 1 H, CH=C), 3.7 (s, 3 H, $COOCH_3$), 3.5 (s, 4 H, OCH_2CCH_2O), 2.5 (m, 4 H), 2.1 (m, 2 H), and 1.0 [s, 6 H, $C(CH_3)_2$]; mass spectrum *m/e* 241 (M^+).

Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.89; H, 8.18.

α,α,3,3-Tetramethyl-1,5-dioxaspiro[5.5]undec-8-ene-9-methanol (33). Using the same Grignard procedure as for the preparation of **31** gave **33** (50% yield): mp 114 °C; ^1H NMR ($CDCl_3$) δ 5.6 (m, 1 H, CH=C), 3.5 (s, 4 H, OCH_2CCH_2O), 2.1–2.5 (m, 7 H, 1 H exchanges with D_2O), 1.3 [s, 6 H, $C(CH_3)_2OH$], 1.0 [2 s, 3 H each, $C-C(CH_3)_2$].

Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07; O, 19.97. Found: C, 70.17; H, 10.11; O, 20.07.

Preparation of 7 from 31. To a solution of 2.12 g (9 mmol) of 1 and 2.18 g (10.1 mmol) of **31** at −10 °C was added 3.6 mL (31 mmol) of $SnCl_4$ over a 5-min period. The reaction mixture was stirred for an additional 4 h at 0 °C and then poured onto ice water. The organic layer was separated, washed with water, 1 N NaOH solution, and water, dried over $MgSO_4$, and concentrated to afford a white solid. Recrystallization from 20 mL of *n*-hexane gave 2.66 g (80% yield) of **7** containing only a 1% impurity of **6** by GC.

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Studies on Vitamin D (Calciferol) and Its Analogues. 12. Structural and Synthetic Studies of 5,6-*trans*-Vitamin D_3 and the Stereoisomers of 10,19-Dihydrovitamin D_3 Including Dihydrotachysterol$_3$[1,2]

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Catalytic hydrogenation of 5,6-*trans*-vitamin D_3 (**3a**, 5*E*-D_3) afforded the previously unknown C_{10} epimer of dihydrotachysterol$_3$ (**2a**, DHT_3 or 10*S*-b), 10*R*,19-dihydro-5*E*-vitamin D_3 (10*R*-b). Reaction of **3a** with 9-borabicyclo[3.3.1]nonane (9-BBN) produced the 9-BBN/**3a** adduct, which upon treatment with acetic acid produced low yields of equal amounts of **2a** and its C_{10} epimer 10*R*-b. When the 9-BBN/**3a** adduct was oxidized with basic hydrogen peroxide, good yields of the 19-hydroxy counterparts of 10*S*-b and 10*R*-b, **7a** and **7b**, respectively, were produced. The 9-BBN/**1a** adduct, produced similarly by treating vitamin D_3 (**1a**) with 9-BBN, reacted with acetic acid to afford 10*S*,19- (10*S*-a) and 10*R*,19-dihydrovitamin D_3 (10*R*-a), which differ from 10*S*-b and 10*R*-b, respectively, in their Δ^5-double bond configurations. Basic hydrogen peroxide treatment of the 9-BBN/**1a** adduct gave good yields of the 19-hydroxy derivatives of 10*S*-a and 10*R*-a, **8a** and **8b**, respectively. The stereoisomeric 10*S*-a, 10*R*-a, 10*S*-b (**2a**), and 10*R*-b vitamin D analogues are also labeled DHV_3-II, DHV_3-III, DHT_3, and DHV_3-IV, respectively, in this study. The stereochemistries and conformations of the A ring of the five analogues (5*E*-D_3, 10*S*-a, 10*R*-a, 10*S*-b, and 10*R*-b) have been studied by two ^1H NMR methods: correlation of the observed coupling constants with the limiting values for the two conformers (coupling constant method) and computer analysis of the 300-MHz tris(dipivalomethanato)europium(III) [Eu(dpm)$_3$] shifted spectra (the lanthanide induced shift or LIS method). The reduction products of vitamin D_3 (**1a**) are clearly identifiable by both methods as the 10*S*-a and 10*R*-a isomers. By contrast the LIS method only partially serves to distinguish the stereochemistries assigned to the reduction products of 5*E*-D_3 (**3a**). The LIS method distinguishes DHT_3 as the 10*S*-b isomer but its epimer is equally well assigned by this method to the 10*S*-b or 10*R*-b diastereomers. Coupling constants do not help in the latter case either. Thus NMR methods must be used with a great deal of care especially when only one epimer of a fluxional molecule is available for study. Both epimers were fortunately available in this study. The A ring of these steroids is dynamically equilibrated between two chair conformers and both methods were in good agreement as regards their A-ring chair population ratios. The 10*S*-a and 10*R*-a isomers were strongly biased in single (~95%) but opposite chair conformers with the C_{10} methyl group axial in both cases. The clinically useful analogue 10*S*-b (DHT_3) also exists principally (~90%) as only one conformer (C_{10} methyl and C_3 hydroxyl equatorial), while its epimer 10*R*-b exists as an approximately equimolar mixture of two A-ring chairlike conformers. Lastly, 5*E*-D_3 is biased (~70%) in favor of the chair possessing the equatorial hydroxyl.

In order to evaluate further the structural requirements necessary for optimal or minimal vitamin D activity and thus obtain more information concerning its mode of action, we have directed our attention toward the synthesis and biological evaluation of analogues of vitamin D_3 (**1a**) and its principal metabolites, 25-hydroxyvitamin D_3 (**1b**) and 1α,25-dihydroxyvitamin D_3 (**1c**).[4] The latter, **1c**, is considered to be the active functional form of vitamin D_3. Among the most