with water and extracted with ether. The combined extracts were washed successively with water and brine, and volatiles were then removed from the dried organic phase by evaporation under reduced pressure. The residue was treated with pentane, and the resulting mixture was filtered through silica. Pentane was removed by evaporation under reduced pressure, and the residue was purified by flash chromatography (silica, hexane (95%)/ethyl acetate (4%)).[27] This yielded stannane **24a** as a colorless liquid (380 mg, 1.11 mmol, 85%): IR (liquid film) 3620, 3400, 1645 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.04 (s, 9 H), 1.11 (s, 3 H), 1.17 (s, 3 H), 1.2–2.6 (m, 11 H), 4.84 (m, 1 H), 5.03 (m, 1 H); MS (CI, isobutane) *m/e* 327, 311, 165; HRMS EI) calcd for $C_{15}H_{28}OSn$ 344.1154, found 344.1018.

(3aα,4aα,6α,7aα)-Octahydro-2,2-dimethyl-6-(trimethylstannyl)spiro[4*H*-indene-4,2′-oxiran]-3a-ol (7b). A green solution of stannane **24a** (27 mg, 79 μmol) and vanadyl acetylacetonate (1.4 mg, 5.3 μmol) in benzene (0.6 mL) was stirred at 25 °C and treated dropwise with a solution of 70% aqueous *tert*-butyl hydroperoxide (17 mg, 130 μmol) in benzene (0.6 mL). The red mixture was stirred at 25 °C for 2 h and was then diluted with ether and washed successively with 10% aqueous sodium thiosulfate and brine. Removal of volatiles from the dried organic phase by evaporation under reduced pressure left a residue of pure epoxy stannane **7b**, a colorless liquid (27 mg, 75 μmol, 95%): IR (liquid film) 3500; ^1H NMR (90 MHz, $CDCl_3$) δ 0.07 (s, 9 H), 1.13 (s, 3 H), 1.16 (s, 3 H), 1.2–2.2 (m, 11 H), 2.53 (d, ^2J = 4.7 Hz, 1 H), 2.98 (d, ^2J = 4.7 Hz, 1 H); MS (CI, isobutane) *m/e* 361, 343, 327, 195, 179; HRMS (EI) calcd for $C_{15}H_{28}O_2Sn$ 360.1103, found 360.1171.

(1aβ,1bα,4aα,5aα)-Octahydro-1b-hydroxy-3,3-dimethyl-1*H*-cyclopropa[*a*]-1a-pentalenemethanol (25). A solution of epoxy stannane **7b** (362 mg, 1.01 mmol) in CH_2Cl_2 (55 mL) was stirred at −78 °C under Ar and treated dropwise with a solution of $C_2H_5AlCl_2$ (1.2 mL, 1.8 M in toluene, 2.2 mmol). The mixture was stirred at −78 °C for 20 min, treated with methanol (5 mL), warmed to 25 °C, treated with 10% aqueous NH_4Cl, diluted with ether, and washed successively with 5% aqueous $NaHCO_3$ and brine. Volatiles were removed from the dried organic phase by evaporation under reduced pressure, and the residue was purified by flash chromatography (silica, hexane (50%)/ethyl acetate (50%)).[27] This provided diol **25** as a white solid (149 mg, 0.759 mmol, 75%): mp 106–107 °C; IR (KBr) 3280 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.51 (dd, ^3J = 8 Hz, ^2J = 5.0 Hz, 1 H), 0.80 (ddd, ^3J = 8 Hz, ^2J = 5.0 Hz, ^4J = 1.5 Hz, 1 H), 1.12 (s, 3 H), 1.20 (s, 3 H), 1.24–2.09 (m, 8 H), 1.87 (s, 2 H), 3.21 (d, ^2J = 11.4 Hz, 1 H), 4.25 (dd, ^2J = 11.4 Hz, ^4J = 1.5 Hz, 1 H); HRMS (EI) calcd for $C_{12}H_{20}O_2$ 196.1458, found 196.1461.

Acknowledgment. This work was financially supported by the Natural Sciences and Engineering Research Council of Canada and by the Ministère de l'Éducation du Québec. We thank Sylvie Bilodeau and Dr. M. T. Phan Viet of the Regional High-Field NMR Laboratory for recording our high-field ^1H NMR spectra. In addition, we are grateful to Michael Evans and Christine Johnson for recording our mass spectra.

Registry No. **3**, 59372-72-4; (±)-**7b**, 131863-74-6; (±)-**8b**, 131833-60-8; (±)-**8c**, 131833-48-2; (±)-**9**, 68691-09-8; (±)-**10b**, 131833-49-3; (±)-**12**, 68691-06-5; (±)-**13**, 131833-50-6; (±)-**15**, 131833-51-7; (±)-**17**, 131833-52-8; (±)-**18**, 131833-53-9; (±)-**20**, 131833-54-0; (±)-**21a**, 131833-55-1; (±)-**21b**, 131833-61-9; (±)-**22b**, 131833-56-2; (±)-**23a**, 131833-57-3; (±)-**24a**, 131833-58-4; (±)-**25**, 131833-59-5; $HOCH_2C(=CH_2)CH_2CH_3$, 4435-54-5; $CH_3SO_2OCH_2C(=CH_2)CH_2CH_3$, 131833-47-1.

Supplementary Material Available: ^1H NMR spectra of key compounds **7b**, **8b**, **8c**, **10b**, **21b**, **23a**, **24a**, and **25** (8 pages). Ordering information is given on any current masthead page.

Synthesis of Both Enantiomers of Nabilone from a Common Intermediate. Enantiodivergent Synthesis of Cannabinoids

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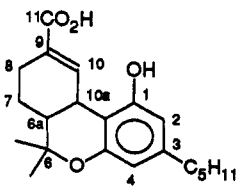
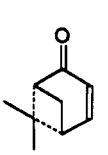
Both enantiomers of the synthetic cannabinoid nabilone (**4**) have been synthesized from a common intermediate, enone **7**. Enone **7** was prepared by reaction of [2,6-dimethoxy-4-(1,1-dimethylheptyl)phenyl]lithium with (+)-apoverbenone (**2**), followed by PDC oxidation. Li/NH_3 reduction of **7** gave saturated ketone **9**, which, after ether cleavage to **10**, afforded (6a*S*,10a*R*)-hexahydrodibenzopyran **15** on reaction with $SnCl_4$. Isomerization to 6a*R*,10a*R* ketone **16** followed by ether cleavage gave the 6a*R*,10a*R* enantiomer of nabilone (**4**). The 6a*S*,10a*S* enantiomer of **4** (**24**) was prepared from **7** by ether cleavage to **18** and rearrangement to nonracemic tetrahydrodibenzopyran **20** using $AlCl_3$. Dissolving metal reduction of **20** followed by ether cleavage gave the 6a*S*,10a*S* enantiomer of nabilone (**24**). A model sequence employing (2,6-dimethoxyphenyl)lithium at the first step was carried out and the structure of one of the intermediates, ketone **12**, was established by X-ray crystallography. A new preparation of apoverbenone (**2**) has been developed.

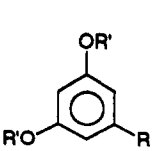
We have recently described a concise, efficient (seven steps, 14% yield) synthesis of (±)-11-nor-9-carboxy-Δ^9-THC (**1**) from (+)-apoverbenone (**2**) and the bis-MOM ether of olivetol (**3**).[2] This synthetic approach to cannabinoids employs as a key step the regioselective condensation of an aryllithium derived from **3** with enone **2**, a process that precludes the formation of isocannabinoids in which the aromatic hydroxyl and alkyl substituents are exchanged. Although this synthesis is potentially applicable to the preparation of a variety of cannabinoids, it



1



2



3 R = C_5H_{11}, R' = CH_2OCH_3

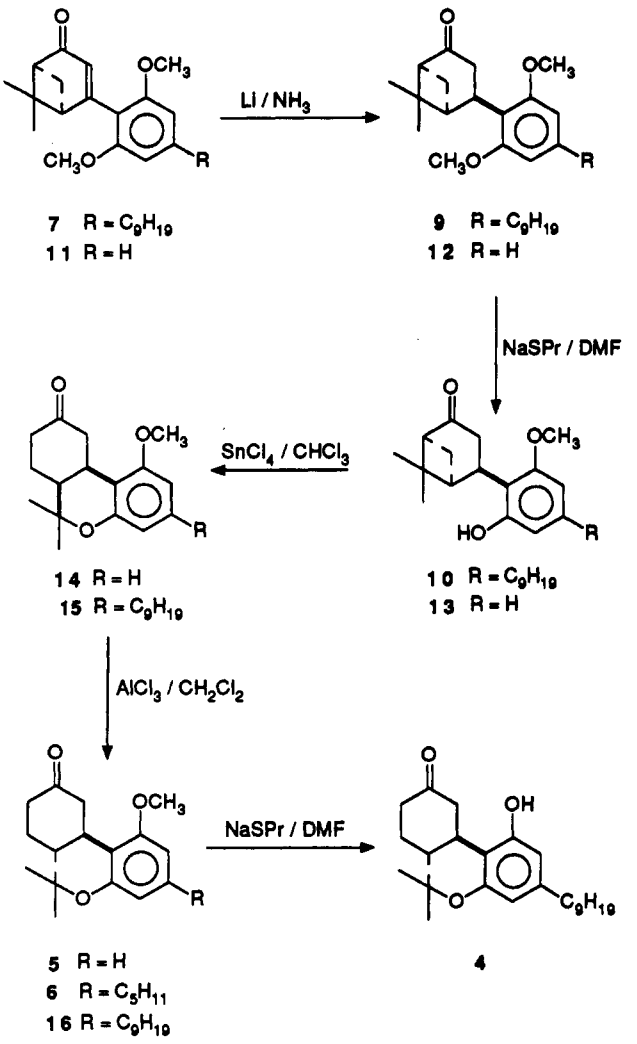
8 R = C_6H_{19}, R' = CH_3

(1) To whom inquires regarding the crystallographic studies should be directed.

(2) Huffman, J. W.; Zhang, X.; Wu, M.-J.; Joyner, H. H.; Pennington, W. T. *J. Org. Chem.* In press.

0022-3263/91/1956-2081$02.50/0

Scheme I



suffers from the liability that while enone **2** is optically active, the step that generates the tricyclic cannabinoid nucleus proceeds with racemization. Also, the preparation of bis-MOM ether **3** requires the use of rather large quantities of chloromethyl methyl ether, a known carcinogen.[2]

We now describe an enantiodivergent[3] synthesis of both enantiomers of nabilone [**4**, 6a*R*,10a*R* isomer depicted] and model ketone **5** that avoids the use of chloromethyl methyl ether. A nonracemic precursor to the 6a*S*,10a*S* enantiomer of ketone **6** has also been prepared and a new preparation of (+)-apoverbenone[4] has been developed. Nabilone (**4**) is a synthetic cannabinoid that has been used clinically as an antiemetic in cancer chemotherapy and was chosen as a synthetic target for development of a synthesis of nonracemic cannabinoids due to its biological activity and because both enantiomers, as well as the racemate, are known.[5] Very recently it has been reported that nabilone, presumably the racemate, interacts with a cannabinoid receptor isolated from rat brain.[6] Also, ketones structurally similar to **4**, **5**, and **6** have been used as intermediates for the synthesis of a variety of cannabinoids.[7]

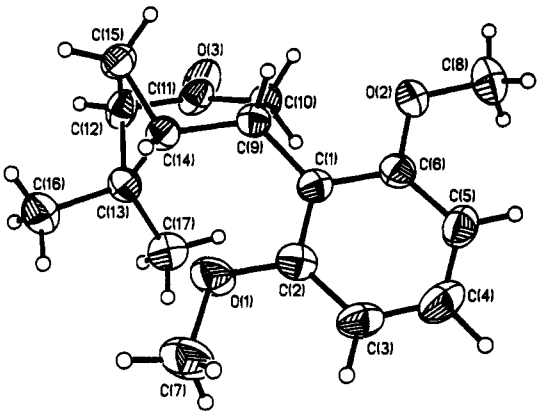


Figure 1. ORTEP structure of **12**.

The synthesis employs ketone **7** (Scheme I), which is readily available by reaction of the aryllithium derived from 1,3-dimethoxy-5-(1,1-dimethylheptyl)benzene (**8**) with enone **2**, followed by chromic acid or pyridinium chlorochromate (PCC) oxidation.[2] Dissolving metal reduction was expected to lead with reasonable stereoselectivity to ketone **9** or the stereoisomer at C-4. Selective nucleophilic cleavage of one of the methyl esters would afford phenol **10**, an intermediate similar to those employed in the Lilly synthesis of nonracemic **4**.[5a] Since the steric course of the dissolving metal reduction of **7** could not be predicted with certainty and nucleophilic ether cleavage was not successful in the presence of a carbonyl group in our earlier work, model experiments employing readily available unsubstituted enone **11**[2] were carried out.

Reduction of **11** with Li/NH_3 gave a single, crystalline dihydro product in 65% yield. It was not possible to assign the stereochemistry of this reduction product on the basis of the ^1H NMR spectrum, although data for both isomers of the 4-methyl analogue are available.[8] The stereochemistry was determined by X-ray crystallography as depicted in **12** and Figure 1. Reduction occurs predominently by protonation of an intermediate carbanion from the face of **11** anti to the *gem*-dimethyls. The conformation of **12** is such that the cyclohexanone ring adopts a flattened half chair conformation in which the aromatic ring nearly eclipses the syn hydrogen, which is α to the carbonyl group (Figure 1). Based on a relatively limited number of examples, it appears that additions to the nopin-3-en-2-one system proceed stereoselectively from the face of the molecule away from the bulky *gem*-dimethyl group.[2,8]

In contrast to our previous experience,[9] nucleophilic ether cleavage using excess sodium thiopropoxide[10] pro-

(3) The term enantiodivergent is employed to describe a synthetic sequence in which a single enantiomer of an intermediate is converted to each enantiomer of the target compound.

(4) Grimshaw, J.; Grimshaw, J. T.; Juneja, H. R. *J. Chem. Soc., Perkin Trans. 1* **1972**, 50.

(5) (a) Archer, R. A.; Blanchard, W. B.; Day, W. A.; Johnson, D. W.; Lavagnino, E. R.; Ryan, C. W.; Baldwin, J. E. *J. Org. Chem.* **1977**, *42*, 2277. (b) Archer, R. A.; Stark, P.; Lemberger, L. In *Cannabinoids as Therapeutic Agents*; Mechoulam, R., Ed.; CRC: Boca Raton, 1986; Chapter 5.

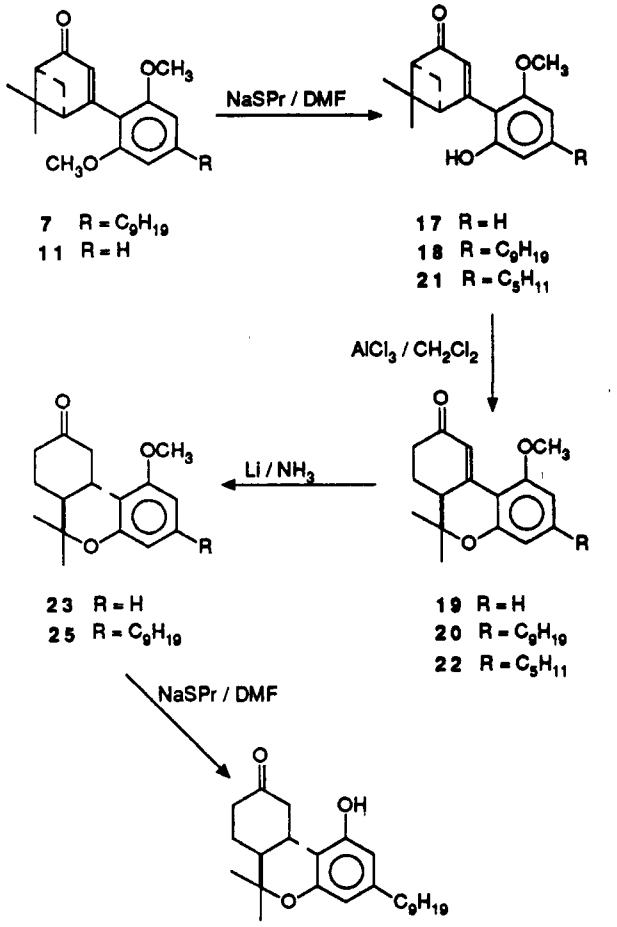
(6) Matsuda, L. A.; Lolait, S. J.; Brownstein, M. J.; Young, A. C.; Bonner, T. I. *Nature* **1990**, *346*, 561.

(7) The phenol corresponding to **6** has been used frequently in the synthesis of cannabinoids and their analogues; for typical examples, see: (a) Schwartz, A.; Madan, P. *J. Org. Chem.* **1986**, *51*, 5463. (b) Lars, J.; Nilsson, G.; Nilsson, I. M.; Agurell, S. *Acta Chem. Scand.* **1969**, *23*, 2209. (c) Fahrenholtz, K. E.; Lurie, M.; Kierstead, R. W. *J. Am. Chem. Soc.* **1967**, *89*, 5934. (d) Wilson, R. S.; May, E. L. *J. Med. Chem.* **1975**, *18*, 700. (e) Robertson, L. R.; Duffley, R. P.; Razdan, R. K.; Martin, B. R.; Harris, L. S.; Dewey, W. L. *Ibid.* **1984**, *27*, 550. (f) Razdan [Razdan, R. K. In *The Total Synthesis of Natural Products*, Vol. 4; Ap Simon, J. W., Ed.; Wiley-Interscience: New York, 1981, pp 185–262] reviews the synthesis of cannabinoids through 1978.

(8) (a) Regan [Regan, A. F. *Tetrahedron* **1969**, *25*, 3801] reports that Na/ether reduction of a 4-methyl analogue of **7** provides a 6:1 mixture of products in which the major products have a syn relationship between the methyl group and the *gem*-dimethyls. (b) Hobbs, P. D.; Magnus, P. D. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2879.

(9) Wu, M.-J. Ph.D. Dissertation, Clemson University, 1987.

Scheme II



ceeded smoothly to provide phenol **13** in 73% yield.[2] This phenol is analogous to intermediates employed by the Lilly group and reaction with $SnCl_4$[5a] provided (−)-6a*S*,10a*R* ketone **14**. Isomerization with $AlCl_3$[5a] gave the 6a*R*,10a*R* ketone **5**.

This sequence was repeated with ketone **7**, obtained by reaction of [2,6-dimethoxy-4-(1,1-dimethylheptyl)-phenyl]lithium with (+)-apoverbenone (**2**), followed by pyridinium dichromate (PDC) oxidation.[2,11] Reduction to **9**, ether cleavage to **10**, and rearrangement to **15** proceeded as in the model series. Isomerization afforded the methyl ether of **4** (**16**) in an overall yield of 29% from apoverbenone (**2**). Nucleophilic ether cleavage gave the 6a*R*,10a*R* enantiomer of nabilone (**4**), the spectral properties of which were consistent with those reported.[5a] More importantly the specific rotation is in excellent agreement with that reported by the Lilly group.[5a]

Although the 6a*S*,10a*S* enantiomers of ketones **4** and **5** could conceivably be prepared by repeating the synthetic sequence using the (−) enantiomer of ketone **2**,[9] a far more attractive approach proceeds by isomerization of phenols **17** and **18** to enones **19** and **20**, respectively, without loss of optical activity (Scheme II). Isomerization of **17** and the precursor to **1** (**21**) has been effected with *p*-toluenesulfonic acid in ethanol or chloroform–ethanol; however, the products are racemic **19** and **22**.[2] The mechanism of the acid-catalyzed rearrangement of enones **17** and **21** to dibenzopyrans **19** and **22**, respectively, is rather complex and apparently involves trapping of the initial cation by a nucleophile, followed by subsequent acid-catalyzed cyclization.[2] Racemization probably occurs via formation of an achiral enol during the prolonged heating with acid required to effect rearrangement. It was felt that treatment of enones similar to **17**, **18**, and **21** under less stringent conditions would, perhaps, effect rearrangement at a significantly faster rate than racemization.

Although some efforts had been made to carry out the rearrangement using Lewis acids during the initial phases of the synthesis of **1**, they were uniformly unsatisfactory.[9] We now find that reaction of phenol **17**[2] with 3 equiv of $AlCl_3$ in methylene chloride at ambient temperature provides nonracemic **19** and similar treatment of **21** affords optically active **22**. Reduction of optically active **19** gave the 6a*S*,10a*S* enantiomer of **5** (**23**), the specific rotation of which was, within experimental error, of the same magnitude but of opposite sign to that of **5**, indicating that the $AlCl_3$-catalyzed rearrangement of **17** proceeds with little, if any, racemization.

The precursors to ketones **19** and **22**, **17** and **21**, respectively, had been prepared previously by hydrolysis of the corresponding MOM ethers.[2,9] We now find that nucleophilic demethylation of **11** and the methyl ether of **21**[2] proceeds smoothly and in good yield when excess sodium thiopropoxide is used under the conditions employed for the synthesis of **13**.

The 6a*S*,10a*S* enantiomer of nabilone (**24**) was prepared by a similar sequence in which enone **7** was demethylated to **18** and rearranged to nonracemic enone **20** using $AlCl_3$. Reduction of racemic **22** with Li/NH_3 at −78 °C provided an approximately 3 to 1 ratio of **6** to the cis isomer;[2] however, reduction of **20** at −40 °C gave a 6 to 4 ratio of 6a*S*,10a*S* ketone **25** and cis ketone **15** in 84% yield. When the reduction was carried out at −80 °C the ratio of **25** to **15** was 2 to 1 and at −33 °C it was 1 to 1. Ether cleavage of **25** provided (6a*S*,10a*S*)-nabilone (**24**), the specific rotation of which was consistent with that reported.[5a]

This enantiodivergent synthesis leads to both enantiomers of nabilone (**4**) in acceptable yields with optical purities comparable to those obtained previously.[5a] A common intermediate, enone **7**, is employed for the synthesis of both enantiomers of **4** and the synthesis avoids the use of chloromethyl methyl ether.

Although the optical purities of the enantiomers of nabilone were not determined, they are almost certainly of the same order of magnitude as the commercial (Aldrich) (−)-β-pinene that was used for the preparation of enone **2**. Commercial (−)-β-pinene has $[\alpha]^{20}_D$ −21°, which corresponds to an optical purity of 92% on the basis of the best reported value of −22.8°.[12] Archer et al. prepared (−)- (**4**) and (+)-nabilone (**24**) from (−)- and (+)-pinene via the respective enantiomers of verbenol[5a] and similar syntheses of cannabinoids provide products of very high optical purity.[13] Since the specific rotations of **4** and **24** prepared by our procedure are comparable to those obtained by Archer et al., it is a reasonable conclusion that our synthesis proceeds without appreciable racemization.

The preparation of (+)-apoverbenone (**2**) by the published procedure[4] is troublesome on a large scale, in spite of a report to the contrary.[8b] In particular, the dehydrohalogenation of bromonopinone gave variable yields and requires large volumes of anhydrous dimethyl sulfoxide

(10) (a) Feutrill, G. I.; Mirrington, R. N. *Aust. J. Chem.* **1972**, *25*, 1731. (b) Sher, F. T.; Berchtold, G. A. *J. Org. Chem.* **1977**, *42*, 2569.
(11) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682.
(12) Brown, H. C.; Zaidlewicz, M.; Bhat, K. S. *J. Org. Chem.* **1989**, *54*, 1764.
(13) Mechoulam, R.; Lander, N.; Breuer, A.; Zahalka, J. *Tetrahedron Asymmetry* **1990**, *1*, 315.

(DMSO). The product is usually contaminated with up to 10% nopinone and it is difficult to separate **2** from residual DMSO.

A very convenient, alternative synthesis of **2** has been developed that is based on the lead tetraacetate oxidation of the enol acetate of (+)-nopinone. This oxidation has been reported to lead to 2,4-diacetoxy-6,6-dimethylbicyclo[3.1.1]hept-2-ene or 2,2-diacetoxy-6,6-dimethylbicyclo[3.1.1]hept-3-ene,[5a] and either product should afford **2** on mild hydrolysis. In our hands, oxidation of nopinone enol acetate under conditions reported to afford the 2,2-diacetate gave a mixture of 55% enone **2**, 7% nopinone, and 37% 2,2-diacetoxynopin-3-ene. Hydrolysis with dilute aqueous acetic acid gave enone **2** in an overall yield of 47% from (+)-nopinone. The physical and spectroscopic properties, including specific rotation, were identical with those of material prepared by the published procedure.[4] This synthesis of **2** avoids both the tedious chromatographic isomerization of bromonopinone and the subsequent dehydrohalogenation step.

The modification of our previously described synthetic approach to cannabinoids now permits the synthesis of nonracemic cannabinoids in both the natural (6a*R*,10a*R*) and unnatural (6a*S*,10a*S*) series. By utilizing the enantiomer of enone **2** at the first step of the synthesis, it will be possible to prepare the enantiomer of **22**, which will lead to the synthesis of the natural enantiomer of acid **1** and other cannabinoids. Racemic **22** was an intermediate in our previously reported synthesis of racemic **1**.[2] For the synthesis of (−)-**2** the (+) enantiomer of β-pinene is required, which is readily available by isomerization of commercial (+)-α-pinene.[12]

Experimental Section

Melting points were determined on a Kofler hot stage and are uncorrected. IR spectra were obtained as neat films between salt plates, as KBr pellets, or in solution in $CHCl_3$. ^1H NMR spectra were recorded at 90, 200, or 300 MHz and ^{13}C spectra were recorded at 50.28 or 75.42 MHz, using $CDCl_3$ as solvent. Mass spectral analyses were performed on a gas chromatograph/mass spectrometer at 70 eV. Ether and tetrahydrofuran (THF) were distilled from Na-benzophenone-ketyl immediately before use: CH_2Cl_2 and DMF were distilled from CaH_2, under an atmosphere of N_2. Specific rotations were determined as $CHCl_3$ solutions and concentrations are expressed in g/dL. Commercially available (Aldrich) solutions of *n*-butyllithium in hexane and *tert*-butyllithium in pentane were titrated with 1,3-diphenyl-2-propanone tosylhydrazone[14] as indicator, prior to use. All reactions were carried out under an atmosphere of N_2 or Ar. All chromatographic separations were carried out with ethyl acetate–hexane mixtures as eluents.

4-(2,6-Dimethoxyphenyl)-6,6-dimethylbicyclo[3.1.1]heptan-2-one (12). To a solution of 0.063 g (9.0 mg/at) at Li in 65 mL of liquid NH_3 at −78 °C was added dropwise a solution of 0.824 g (3.0 mmol) of enone **11**[2] in 2.5 mL of dry ether. After being stirred for 1 h at −78 °C, the reaction was quenched with solid NH_4Cl. The NH_3 was allowed to evaporate, the solid residue was taken up in water and extracted with ether, and the ethereal layers were washed with 10% HCl and water and dried (Na_2SO_4). Concentration afforded an oil, which was dissolved in acetone and cooled to 0 °C, and Jone's reagent (1 M)[15] was added dropwise until the solution remained yellow. After 1 h of stirring at ambient temperature, isopropyl alcohol was added to destroy the excess oxidant. Concentration gave a green solid, which was dissolved in water and extracted with ether. The ether layers were washed with saturated $NaHCO_3$ and brine and dried (Na_2SO_4). Removal of the solvent afforded a solid, which was chromatographed on silica gel to give 0.540 g (65%) of enone **12** as a solid, mp 145–146 °C: ^1H NMR δ 0.92, 1.38 (s, 3 H each), 3.78 (s, 6 H), 6.48 (d, 2 H, J = 7 Hz), and 7.06 (t, 1 H, J = 7 Hz). Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.27; H, 8.15.

4-(2-Hydroxy-6-methoxyphenyl)-6,6-dimethylbicyclo[3.1.1]heptan-2-one (13). To a stirred suspension of 0.082 g (3.4 mmol) of NaH (from 0.138 g of 60% NaH dispersion in mineral oil) in 10 mL of DMF at ambient temperature was added 0.31 mL of 1-propanethiol, and the mixture was stirred for 5 min. A solution of 0.119 g (0.43 mmol) of enone **12** in 4 mL of DMF was added, and the mixture was stirred at 120 °C for 3 h. After cooling, the reaction mixture was poured into 10% aqueous HCl and extracted with ether. The extracts were washed with brine and dried (Na_2SO_4), and the solvent was removed to give an oil, which was purified by chromatography on silica gel to give 0.082 g (73%) of **13** as an off-white solid, mp 184–186 °C: ^1H NMR δ 0.94, 1.38 (s, 3 H each), 3.74 (s, 3 H), 6.36 (d, 2 H, J = 7 Hz), and 6.89 (t, 1 H, J = 7 Hz). Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.64: H, 7.82.

(6a*S*,10a*R*)-1-Methoxy-6,6a,7,8,10,10a-hexahydro-6,6-dimethyl-9*H*-dibenzo[*b*,*d*]pyran-9-one (14). A mixture of 1.0 mL of $SnCl_4$ and 0.250 g (0.96 mmol) of phenol **13** in 2 mL of $CHCl_3$ was stirred at room temperature for 18 h. The reaction mixture was poured into ice water and extracted with ether, and the organic extracts were washed with 10% aqueous HCl, saturated $NaHCO_3$, and brine and dried (Na_2SO_4). Evaporation of the solvent gave a solid, which was chromatographed on silica gel to give 0.199 g (80%) of **14** as a white solid, mp 122–123 °C: ^1H NMR δ 1.32, 1.38 (s, 3 H each), 3.72 (s, 3 H), 6.38 (d, 2 H, J = 8 Hz), and 6.98 (t, 1 H, J = 8 Hz); ^{13}C NMR δ 22.1, 23.9, 26.6, 30.3, 38.3, 39.8, 41.6, 55.2, 75.5, 102.6, 110.4, 111.7, 127.8, 154.0, 158.0, 212.7. Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.71; H, 7.76.

(6a*R*,10a*R*)-(−)-1-Methoxy-6,6a,7,8,10,10a-hexahydro-6,6-dimethyl-9*H*-dibenzo[*b*,*d*]pyran-9-one (5). A mixture of 0.048 g (0.186 mmol) of ketone **14** and 0.075 g (0.558 mmol) of $AlCl_3$ in 5 mL of CH_2Cl_2 was stirred at ambient temperature for 12 h. The reaction was quenched by pouring it into ice water and extraction with either. The ethereal layers were washed with 10% aqueous HCl, water, saturated $NaHCO_3$, and brine and dried ($MgSO_4$). Concentration and chromatography gave 0.038 g (79%) of **5** as a white crystalline solid, mp 151–153 °C: $[\alpha]^{22}_D$ = −62.9° (*c* 0.094); IR 1716 cm^{-1}; ^1H NMR δ 1.12, 1.51 (s, 3 H each), 3.72 (m, 1 H), 3.78 (s, 3 H), 6.41, 6.48 (d, 1 H each, J = 6 Hz), and 7.08 (t, 1 H, J = 6 Hz); ^{13}C NMR δ 18.6, 26.5, 27.7, 34.6, 40.6, 45.7, 47.4, 55.0, 102.5, 110.6, 112.4, 127.9, 154.4, 158.5, 211.0. Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.83; H, 7.74. Found: C, 73.66; H, 7.77.

(−)-4-[2,6-Dimethoxy-4-(1,1-dimethylheptyl)phenyl]-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (7). To a stirred solution of 3.01 g (11.4 mmol) of 1,3-dimethoxy-5-(1,1-dimethylheptyl)-benzene (**8**)[16] was added 10.0 mL (12.54 mmol) of *tert*-butyllithium (1.25 M) at room temperature. After 3 h of stirring, the mixture was cooled to 0 °C and 1.55 g (11.4 mmol) of (+)-apoverbenone (**2**) in 5 mL of THF was added dropwise. The reaction mixture was warmed to ambient temperature, stirred for 18 h, and quenched with saturated aqueous NH_4Cl, and the aqueous layer was extracted with ether. The ethereal extracts were washed with brine, dried ($MgSO_4$), and concentrated to afford the crude alcohol. The crude material was dissolved in 5 mL of CH_2Cl_2, added dropwise to a solution of 6.42 g of PDC in 20 mL of CH_2Cl_2, and stirred for 2 h at room temperature. The reaction mixture was diluted with ether and filtered, and the residue was washed with ether. The combined ether extracts were washed with 10% aqueous NaOH, 10% aqueous HCl, and saturated aqueous $NaHCO_3$ and dried ($MgSO_4$). The solvent was removed to give an oil, which was chromatographed (MPLC) to give 2.81 g (62%) of **7** as an amber oil: $[\alpha]^{22}_D$ = −110° (*c* 0.092); IR 2964, 1675 cm^{-1}; ^1H NMR δ 0.85 (t, 3 H, J = 7 Hz), 1.29 (s, 6 H), 1.17, 1.51 (s, 3 H each), 3.77 (s, 6 H), 6.01 (s, 1 H), 6.52 (s, 2 H); ^{13}H NMR δ 13.8, 22.0, 22.3, 26.3, 24.3, 28.6, 29.4, 31.4, 34.0, 41.6, 44.0, 50.0, 54.4,

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55.6, 57.6, 102.0, 114.6, 122.5, 125.0, 157.0, 164.0, 204.8; MS m/z (relative intensity), 398 (93), 383 (21), 367 (31), 329 (29), 328 (100), 243 (38). Anal. Calcd from $C_{26}H_{38}O_3$: C, 78.35; H, 9.61. Found: C, 78.27; H, 9.61.

(−)-4-[2,6-Dimethoxy-4-(1,1-dimethylheptyl)phenyl]-6,6-dimethylbicyclo[3.1.1]heptan-2-one (9). The reduction of enone **7** was carried out by the procedure described for the reduction of **11**. From 0.550 g (1.38 mmol) of **7** there was obtained, after purification by MPLC, 0.420 g (76%) of **9** as a pale yellow oil: $[\alpha]^{22}_D$ = −44.3° (*c* 0.079); IR 1708 cm^{-1}; ^{1}H NMR δ 0.89 (t, 3 H, *J* = 7 Hz), 1.25 (s, 6 H), 0.94, 1.34 (s, 3 H each), 3.77 (s, 6 H), 6.49 (s, 2 H); ^{13}C NMR δ 13.8, 22.3, 23.3, 24.3, 26.3, 28.6, 29.7, 31.4, 34.9, 35.2, 37.6, 39.9, 41.8, 45.9, 54.1, 54.9, 57.7, 58.0, 101.6, 116.7, 149.0, 157.6, 215.1; MS m/z (relative intensity) 401 (28), 400 (98), 372 (33), 358 (45), 330 (22), 329 (83), 316 (31), 315 (26), 303 (37), 291 (29), 290 (100), 277 (43). Anal. Calcd for $C_{26}H_{40}O_3$: C, 77.95; H, 10.06. Found: C, 77.87; H, 10.11.

4-[2-Hydroxy-4-(1,1-dimethylheptyl)-6-methoxyphenyl]-6,6-methylbicyclo[3.1.1]heptan-2-one (10). Ether cleavage was carried out as described for the preparation of **13**. From 0.365 g (0.913 mmol) of **9** there was obtained after purification by MPLC 0.263 g (75%) of **10** as a viscous oil: $[\alpha]^{22}_D$ = −35.3° (*c* 0.132); IR 3370, 1683 cm^{-1}; ^{1}H NMR δ 0.81 (t, 3 H), 1.21 (s, 6 H), 0.98, 1.37 (s, 3 H each), 3.74 (s, 3 H), 6.35, 6.37 (s, 1 H each), 6.88 (br s, 1 H); ^{13}C NMR δ 14.1, 22.6, 23.5, 24.5, 26.5, 28.7, 29.9, 31.7, 35.1, 35.4, 37.5, 40.3, 41.7, 44.4, 45.9, 54.8, 55.1, 58.0, 101.1, 107.1, 115.1, 149.5, 154.7, 158.2, 218.0; MS m/z (relative intensity) 388 (28), 387 (100), 386 (91), 329 (10), 317 (46), 316 (13), 303 (23), 302 (22), 301 (35), 263 (55).

(6a*S*,10a*R*)-(−)-1-Methoxy-3-(1,1-dimethylheptyl)-6,6a,7,8,10,10a-hexahydro-6,6-dimethyl-9*H*-dibenzo[*b*,*d*]pyran-9-one (15). Reaction of 0.190 g (0.500 mmol) of ketone **10** with $SnCl_4$ was carried out as described above for the preparation of **14** to give, after purification by MPLC, 0.155 g (80%) of **15**: $[\alpha]^{22}_D$ = −41.0° (*c* 0.087); IR 1719 cm^{-1}; ^{1}H NMR δ 0.84 (t, 3 H), 1.22 (s, 6 H), 1.34, 1.38 (s, 3 H each), 3.78 (s, 3 H), 6.38 (d, 1 H, *J* = 2 Hz), 6.42 (d, 1 H, *J* = 2 Hz); ^{13}C NMR δ 13.9, 22.1, 22.5, 23.7, 24.4, 26.8, 28.5, 28.7, 29.6, 30.6, 31.6, 37.6, 38.3, 39.7, 41.6, 44.2, 54.9, 75.9, 100.6, 107.9, 108.4, 150.2, 153.2, 158.2, 213.0; MS m/z (relative intensity) 387 (12), 386 (41), 344 (13), 330 (19), 316 (22), 303 (26), 302 (100), 301 (29).

(6a*R*,10a*R*)-(−)-1-Methoxy-3-(1,1-dimethylheptyl)-6,6a,7,8,10,10a-hexahydro-6,6-dimethyl-9*H*-dibenzo[*b*,*d*]pyran-9-one ((−)-16). A. Isomerization of **15** was carried out as described above for the preparation of **14**. From 0.085 g (0.22 mmol) of **15** there was obtained, after purification by preparative TLC, 0.066 g (78%) of **16** as a viscous oil: $[\alpha]^{22}_D$ = −51.7° (*c* 0.10); IR 1714 cm^{-1}; ^{1}H NMR δ 0.86 (t, 3 H, *J* = 7 Hz), 1.24 (s, 6 H), 1.11, 1.47 (s, 3 H each), 3.80 (s, 3 H) 6.36 (d, 1 H, *J* = 2 Hz), 6.43 (d, 1 H, *J* = 2 Hz); ^{13}C NMR δ 14.0, 18.7, 22.6, 24.5, 26.6, 27.6, 28.7, 29.9, 31.7, 34.5, 37.7, 40.7, 44.4, 45.0, 47.0, 54.9, 76.5, 100.6, 108.0, 109.0, 150.1, 153.4, 158.2, 211.5; MS m/z (relative intensity) 386 (44), 344 (14), 330 (18), 316 (22), 303 (28), 302 (100); HRMS calcd for $C_{25}H_{38}O_3$ 386.2819, found 386.2809.

B. A mixture of 0.300 g (0.78 mmol) of **9** and 0.312 g (2.3 mmol) of $AlCl_3$ in 5 mL of CH_2Cl_2 was stirred at room temperature for 4 h. The reaction mixture was poured into ice water and extracted with ether. The ethereal layers were washed with 10% aqueous HCl, saturated aqueous $NaHCO_3$, and brine and dried ($MgSO_4$). Evaporation of the solvent and purification via MPLC gave 0.185 g (62%) of **16** as an oil, identical with the material described above.

(6a*R*,10a*R*)-(−)-1-Hydroxy-3-(1,1-dimethylheptyl)-6,6a,7,8,10,10a-hexahydro-6,6-dimethyl-9*H*-dibenzo[*b*,*d*]pyran-9-one [(−)-Nabilone ((−)-4)]. Ether **16** was converted to **4** by using sodium thiopropoxide as described for the preparation of **13**. From 0.180 g (0.47 mmol) of **16** there was obtained 0.075 g of recovered **16** and 0.058 g (57% based on starting material consumed) of **4**, the spectral properties of which were identical with those reported by Archer et al.[5a] $[\alpha]^{22}_D$ = −57.3° (*c* 0.108) [lit.[5a] $[\alpha]^{25}_D$ = −55.7°].

(6a*S*)-(+)-1-Methoxy-6,6a,7,8-tetrahydro-6,6-dimethy-9*H*-dibenzo[*b*,*d*]pyran-9-one (19). To a solution of 0.200 g (0.775 mmol) of **17**[2] in 10 mL of CH_2Cl_2 at room temperature was added 0.310 g (2.33 mmol) of $AlCl_3$. This mixture was allowed to stir for 12 h, poured onto ice, and extracted with ether. The ethereal layers were washed with 10% aqueous HCl, water, and saturated aqueous $NaHCO_3$ and dried ($MgSO_4$). Evaporation of the solvent gave an oil, which was chromatographed on silica gel to give 0.102 g (55%) of **19** as a crystalline solid. Recrystallization from hexane–ether gave pure **19**, mp 94–96 °C: $[\alpha]^{22}_D$ = +112.5° (*c* = 0.104). The ^{1}H and ^{13}C NMR spectra were identical with those of the racemate.[2]

4-(2-Methoxy-4-pentyl-6-hydroxyphenyl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (21). Reaction of 0.054 g (0.165 mmol) of 4-(2,6-dimethoxy-4-pentylphenyl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one[2] with sodium thiopropoxide as described in the preparation of **13** gave 0.37 g (78%) of **21**, identical with material prepared previously.[2]

(6a*S*)-(+)-1-Methoxy-3-pentyl-6,6a,7,8-tetrahydro-6,6-dimethyl-9*H*-dibenzo[*b*,*d*]pyran-9-one (22). Rearrangement of 0.500 g (1.46 mmol) of **21** was carried out in the manner described for the preparation of **19** to give 0.373 g (68%) of **22**, $[\alpha]^{22}_D$ = +83.4° (*c* 0.080). The spectral properties were identical with those of the racemate.[2]

(6a*S*,10a*S*)-(+)-1-Methoxy-6,6a,7,8,10,10a-hexahydro-6,6-dimethyl-9*H*-dibenzo[*b*,*d*]pyran-9-one ((+)-23). To a solution of 0.010 g (1.45 mg/atom) of Li in 10 mL of NH_3 at −78 °C was added dropwise a solution of 0.095 g (0.368 mmol) of enone **19** in 2 mL of dry ether. After being stirred at −78 °C for 1 h, the reaction was quenched with isoprene. The NH_3 was evaporated and the solid residue was taken up in water and extracted with ether. The ethereal layers were washed with 10% aqueous HCl and water and dried ($MgSO_4$). Evaporation of the solvent and purification in silica gel gave 0.055 g (58%) of **23**. Recrystallization from cyclohexane–ether gave pure **23**, mp 151–152 °C: $[\alpha]^{22}_D$ = +60.3° (*c* 0.12). The ^{1}H and ^{13}C NMR spectra are identical with those of the 6a*R*,10a*R* enantiomer.

(−)-4-[2-Hydroxy-4-(1,1-dimethylheptyl)-6-methoxyphenyl]-6,6a-dimethylbicyclo[3.1.1]hept-3-en-2-one (18). Ether cleavage was carried out as described for the preparation of **13**. From 0.440 g (1.1 mmol) of **7** there was obtained 0.302 g (71%) of **18** as a viscous oil: $[\alpha]^{22}_D$ = −32.1° (*c* 0.011); IR 1650 cm^{-1}; ^{1}H NMR δ 0.85 (t, 3 H, *J* = 7 Hz), 1.23 (s, 6 H), 1.17, 1.52 (s, 3 H each), 3.75 (s, 3 H), 6.14, 6.40, 6.56 (s, 1 H each), 7.02 (br s, 1 H); ^{13}C NMR δ 13.8, 22.6, 24.5, 26.7, 27.4, 28.7, 29.9, 31.7, 37.9, 41.7, 44.2, 50.3, 54.5, 57.7, 100.7, 106.9, 112.2, 123.7, 153.2, 157.1, 165.8, 205.4; MS m/z (relative intensity) 384 (63), 369 (11), 341 (14), 328 (18), 314 (21), 301 (22), 300 (100).

(6a*S*)-(+)-1-Methoxy-3-(1,1-dimethylheptyl)-6,6a,7,8-tetrahydro-6,6-dimethyl-9*H*-dibenzo[*b*,*d*]pyran-9-one (20). The conversion of **18** to **20** was carried out by the method described above for the conversion of **17** to **19**. From 0.185 g (0.48 mmol) of **18** there was obtained 0.102 g (55%) of **20** as thick oil: $[\alpha]^{22}_D$ = +124° (*c* = 0.088); IR, 1654, 1616 cm^{-1}; ^{1}H NMR δ 0.84 (t, 3 H), 1.25 (s, 6 H), 1.14, 1.50 (s, 3 H each), 3.78 (s, 3 H), 6.43, 6.47 (s, 1 H each), 7.37 (d, 1 H, *J* = 2 Hz); ^{13}C NMR δ 14.0, 22.6, 24.5, 27.4, 28.4, 29.9, 31.7, 34.5, 36.8, 38.2, 44.2, 44.7, 55.3, 101.3, 106.7, 108.5, 121.5, 124.8, 149.3, 155.4, 155.9, 160.0, 200.f; MS m/z (relative intensity) 384 (61), 328 (18), 314 (17), 300 (100), 285 (20). Anal. Calcd for $C_{25}H_{36}O_3$: C, 78.35; H, 9.61. Found: C, 78.27; H, 9.61.

(6a*S*,10a*S*)-(+)-1,1-Methoxy-3-(1,1-dimethylheptyl)-6,6a,7,8,10,10a-hexahydro-6,6-dimethyl-9*H*-dibenzo[*b*,*d*]pyran-9-one ((+)-25). Reduction of 0.052 g (0.135 mmol) of **20** using 0.003 g (0.41 mg/atom) of Li in THF/NH_3 at −40 °C as described for the reduction of **11** gave 0.026 g (50%) of **25**, the spectral properties of which were identical with those of the 6a*R*,10a*R* enantiomer **16**. There was also obtained 0.018 g (34%) of **15**, identical with material described above. When the reduction was carried out at −80 °C, the **25** to **15** ratio was 66 to 34 and at −33 °C it was 51 to 49, analysis by GC/MS in both cases.

(6a*S*,10a*S*)-(+)-1-Hydroxy-3-(1,1-dimethylheptyl)-6,6a,7,8,10,10a-hexahydro-6,6-dimethyl-9*H*-dibenzo[*b*,*d*]pyran-9-one [(+)-Nabilone ((+)-24)]. Ether cleavage was effected as described for the preparation of **13**. From 0.036 g (0.093 mmol) of **25** there was obtained after purification by preparative TLC 0.025 g (72%) of **24**, $[\alpha]^{22}_D$ = +58.0° (*c* 0.09) [lit.[5a] $[\alpha]^{25}_D$ = +54.9°]. The ^{1}H NMR and IR spectra were identical with those reported by Archer et al.[5a] and the 6a*R*,10a*R* enantiomer described above.

6,6-Dimethylbicyclo[3.1.1]hept-3-en-2-one [(+)-Apoverbenone (2)]. To a solution of 5.2 g (28.9 mmol) of nopinone enol

acetate[17] in 65 mL of dry benzene was added 20.0 g (40.6 mmol) of technical (90%) $Pb(OAc)_4$, which had been dried in vacuo over KOH. The reaction mixture was heated at reflux for 2.5 h, cooled, filtered, and washed with saturated aqueous $NaHCO_3$. After drying ($MgSO_4$) the solvent was evaporated to give a solution containing 55% of 2, 7% of nopinone, and 37% of the 2,2-diacetate (GC/MS). This mixture was stirred with 185 mL of 10% aqueous acetic acid at 25 °C for 15 h. The mixture was diluted with 150 mL of water and extracted with hexanes, and the hexane solution was washed thoroughly with saturated aqueous $NaHCO_3$ and dried (Na_2SO_4). The solvent was removed and the product distilled to give 2.30 g (59%) of 2, bp 63-64 °C (1.9 mmHg), contaminated with less than 5% of nopinone (analysis by GC/MS). The IR, ^1H NMR, MS, and specific rotation were identical with those of material prepared by the published procedure.[4]

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Supplementary Material Available: Summary of structural details, tables of atomic coordinates, bond lengths, bond angles, and anisotropic thermal parameters for the X-ray crystallographic analysis of 12, and ^{13}C NMR spectra of 10, 15, 16, and 19 (10 pages). Ordering information is given on any current masthead page.

Synthesis of (*R*)-2,3-Dihydro-2,5-dimethyl-2-isopropylfuran

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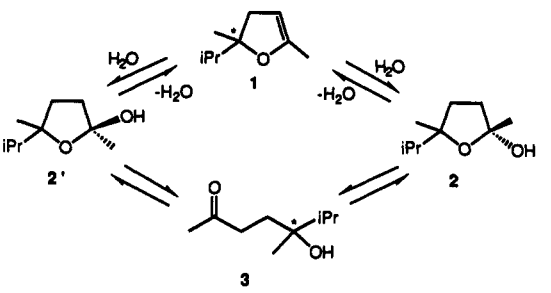
The synthesis of (*R*)-2,3-dihydro-2,5-dimethyl-2-isopropylfuran (1), an insect pheromone, via a 1,3-oxathiane is reported. Key steps are the preparation of (*S*)-2,3-dimethylbutane-1,2-diol (7) from isobutyryloxathiane 5 and reaction of lithiated acetone dimethylhydrazone with tosylated diol 8. NMR spectra of the key tautomeric precursors, 2/2′/3, to 1 have been analyzed in detail, and the enantiomeric excess of these precursors was determined by a chiral shift ^{13}C NMR experiment.

Introduction

The cyclic enol ether 2,3-dihydro-2,5-dimethyl-2-isopropylfuran (1) has been identified[1] as a sex-specific attractant from females of the beetle *Hylecoetus dermestoides* L. The structure of this pheromone was determined by comparison of its mass spectrum with that of its hydrogenation product and confirmed by a synthesis of its racemate.[1,2] Cyclic enol ether 1 is known to be very volatile and was originally observed only by GC in its pentane extract. As outlined in Scheme I, it can be obtained by dehydration of hemiketals 2 or 2′; however, in the presence of moisture the reverse process is rapid at room temperature.[3,4] Moreover, compounds 3, 2, and 2′ are in equilibrium. A preliminary bioassay showed that the racemic material obtained by reaction of isopropylmagnesium bromide with 1,5-hexanedione may act as a sex pheromone.[1]

A synthesis of the *S* enantiomer of this pheromone from a D-glucose derivative has been reported[3] but included no detailed structural analysis, such as NMR data, of 1 nor of its precursors. The overall yield in the ten-step synthesis was less than 2%. The low specific rotation ($[\alpha]_D$ −1.1, *c* = 0.83, pentane) of either the precursors 2/2′/3, or the mixture of these precursors with 1, was later found[4] to have been incorrectly assigned to compound 1. Both enantiomers of 1 were subsequently synthesized by Mori in 7-12% overall chemical yield in six steps from an allylic alcohol by a sequence that included Sharpless asymmetric epoxidation and involved a precursor of 86% ee (enantiomer excess).[4] The absolute configuration of 1, opposite to that reported previously, was confirmed by an independent synthesis of the *R* enantiomer from naturally occurring (*R*)-linalool.[4]

Scheme I



Two fundamental questions concerning this insect pheromone remain to be answered: (1) Which compound is the actual pheromone? Although previous workers have assumed cyclic enol ether 1 to be the sex-specific attractant, the rapid and spontaneous conversion of 1 to 2/2′/3 in the presence of adventitious moisture raises doubt on this point. (2) Which enantiomer is responsible for the biological activity? This question can only be answered, eventually, through bioassay of optically active material.

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