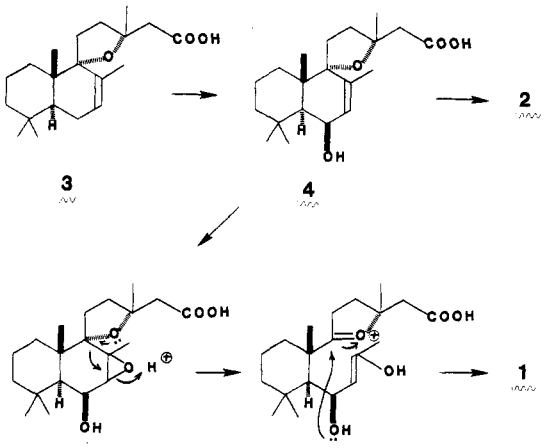
Scheme II. Biosynthesis of 1 and 2 from Grindelic Acid (3)



residue (45 g) was extracted with isopropyl ether by being stirred mechanically at room temperature for 1 h and was left in the freezer overnight and filtered, and the filtrate was vacuum dried. The resulting isopropyl ether soluble syrup was partitioned between petroleum ether and 20% aqueous MeOH, and the lower aqueous MeOH phase (27 g), after drying under vacuum, was subjected to EM SiO_2 60 (900 g) column chromatography. The column was eluted with methylene chloride followed by methylene chloride containing gradually increasing amounts of MeOH, and several 1 L fractions were collected. Fractions 2–4 showed essentially a single spot, corresponding to grindelic acid (3), which was separated by preparative TLC (3.7% of dry plant); its identity was established by mass spectrometry.

Fraction 6 (2.17 g), which displayed two major spots on TLC, was subjected to preparative TLC (PF-254 SiO_2 60), using hexane/ether/AcOH (40:10:1) as the developing solvent system. Evaporation of the solvent from the fraction containing the higher R_f spot gave an oily residue (0.76 g), which on treatment with isopropyl ether gave colorless crystals of 6-oxogrindelic acid (2, 0.6% of dry plant). The fraction containing the lower R_f spot (0.37 g), after removal of the solvent under vacuum, was resubmitted to preparative TLC (PF-254 SiO_2 60) to remove impurities, using hexane/ether/AcOH (40:10:1.2) as the developing solvent. Crystallization from benzene/petroleum ether gave colorless crystals of chrysothame (1, 0.4% of dry plant).

Chrysothame (1). This compound had the following: mp 108–109 °C; $[\alpha]^{25}_D$ −16.6° (c 1.76, $CHCl_3$); IR (KBr) 3000–2500, 1710 (br), 1425, 1375, 1250, 1090, 1070, 1015, 910 cm^{-1}; ^1H NMR (described in the text); ^{13}C NMR (Table I); mass spectrum, m/e 352 ($M^{+\cdot}$, 12.3), 337 (2.1), 334 (2.1), 319 (1.3), 295 (14.8), 294 (63.1), 279 (10.8), 277 (6.1), 276 (12.2), 266 (9.2), 251 (9.7), 250 (6.6), 235 (15.9), 210 (11.5), 209 (72.8), 196 (21), 195 (9), 194 (54.7), 183 (62.9), 179 (24.4), 177 (11.3), 176 (30.7), 165 (14.4), 161 (34.8), 159 (25.2), 151 (50.1), 141 (36.4), 137 (36.5), 136 (100), 135 (13.5), 133 (18.1), 125 (23.5), 124 (25.4), 123 (41.3), 109 (73.7), 95 (86.5), 81 (63.8), 78 (64.1), 69 (89.1), 55 (47.5). The IR, ^1H NMR, ^{13}C NMR, and mass spectra were in accord with structure 1.

Anal. Calcd for $C_{20}H_{32}O_5$: mol wt, 352.2250. Found: mol wt, 352.2245 (high-resolution mass spectroscopy).

Chrysothame Methyl Ester (1a). Esterification of 1 (50 mg) with diazomethane yielded **1a** as an oil, which was purified by preparative TLC. No attempt was made to crystallize the sample, whch was homogeneous as judged from TLC. **1a**: IR ($CHCl_3$) 1730, 1715, 1230 cm^{-1}; ^1H NMR (similar to 1 except COOH absorption at δ 5.6 (br s) replaced by COOMe singlet at δ 3.64); ^{13}C NMR (Table I); mass spectrum, m/e 366 ($M^{+\cdot}$, 10.9), 351 (2.3), 348 (1.4), 335 (6.5), 308 (43.6), 293 (18.7), 290 (13.9), 280 (10.1), 265 (7.9), 250 (4.8), 235 (23.9), 223 (63.7), 210 (24.8), 197 (49.9), 194 (45.3), 179 (20), 176 (24.9), 173 (20), 165 (12.1), 161 (23.6), 155 (32.1), 151 (33.7), 141 (8.9), 137 (22.7), 136 (60.7), 135 (10.3), 125 (13.6), 124 (14.5), 123 (25), 122 (14.3), 121 (20.3), 109 (41.4), 107 (16), 95 (42.5), 81 (29.3), 69 (41), 55 (28.6), 43 (100), 41 (52.9). The IR, ^1H NMR, ^{13}C NMR, and mass spectra were in accord with structure **1a**.

6-Oxogrindelic Acid (2). This compound had the following: mp 208–210 °C (lit.[11] mp 208–210 °C); $[\alpha]^{25}_D$ −83.1° (c 2.43, $CHCl_3$); IR ($CHCl_3$) 3000–2500, 1713, 1668, 1410, 1385, 1378, 1238, 1168, 1138, 1090, 1015, 980, (25), cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.67 (1 H, m), 2.73, 2.57 (2 H, q, J_{AB} = 14.7 Hz), 2.69 (1 H, s), 1.9–2.3 (4 H, m), 1.98 (3 H, d, J = 1.1 Hz), 1.0–1.9 (6 H, m), 1.45 (3 H, s), 1.17 (3 H, s), 1.11 (3 H, s); ^{13}C NMR (Table I); mass spectrum, m/e 334 ($M^{+\cdot}$, 6.5), 319 (2.4), 306 (3.6), 291 (1.2), 263 (2.0), 234 (2.4), 219 (2.1), 210 (100), 201 (3.8), 192 (22.6), 183 (4.5), 164 (15.1), 151 (6.6), 150 (17.6), 149 (6.4), 136 (5.4), 135 (7.3), 123 (8.6), 121 (6.2), 111 (65.5), 110 (25), 109 (12.2), 95 (9.6), 91 (8.5), 82 (71.4), 69 (11.2), 67 (10.4), 55 (13.4). The IR, ^1H NMR, ^{13}C NMR, and mass spectra were in accord with structure 2.

Anal. Calcd for $C_{20}H_{32}O_4$: mol wt, 334.2144. Found: mol wt, 334.2136 (high-resolution mass spectroscopy).

Acknowledgment. This work was supported by a research agreement with Diamond Shamrock Corporation, Dallas, TX.

Registry No. 1, 80865-69-6; **1a**, 80865-70-9; 2, 59219-63-5; **2a**, 80865-71-0; 3, 1438-57-9.

(10) Jolad, S. D.; Hoffmann, J. J.; Schram, K. H.; Cole, J. R.; Tempesta, M. S.; Bates, R. B. *J. Org. Chem.* **1981**, *46*, 4267.
(11) Mangoni, L.; Belardini, M. *Gazz. Chim. Ital.* **1962**, *92*, 983.

Synthetic Studies of *trans*-Clerodane Diterpenoids and Congeners: Stereocontrolled Total Synthesis of (±)-Avarol

Aluru S. Sarma* and Partha Chattopadhyay

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Calcutta 700032, India

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A stereocontrolled total synthesis of (±)-avarol, a sesquiterpenoid hydroquinone, has been accomplished in eight steps, by a flexible route which is potentially useful in the synthesis of related natural products containing a functionalized bicyclo[4.4.0]decane skeleton such as *trans*-clerodanes. The originally assigned stereochemistry for this natural product has been confirmed through correlation with a degradation product of ilimaquinone. Preliminary model studies on the employed methodology are also presented.

Recently, a number of terpenoids containing a functionalized bicyclo[4.4.0]decane skeleton with a characteristic array of asymmetric centers have been isolated. They include, apart from several *trans*-clerodane diterpenoids

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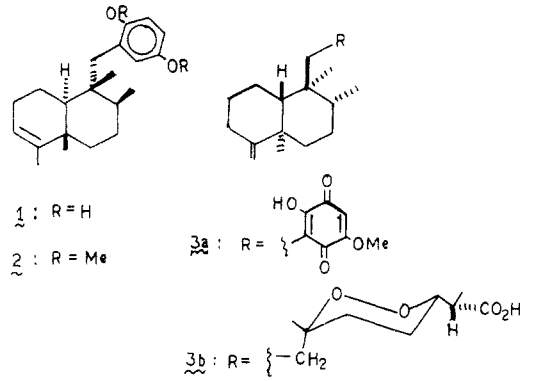
and related neoclerodanes,[1,2] the sesquiterpenoids avarol



(1)[3] and ilimaquinone (**3a**)[4] and the norsesterterpene sigmosceptrellin A (**3b**),[5] all possessing the same relative stereochemistry as avarol. Of these, the *trans*-clerodanes[2] are of particular interest in view of the insect antifeedant properties[6] exhibited by certain members of this family. The growing synthetic interest in this area[7] is reflected in the recent first total synthesis.[7b]

We envisioned that access to some of these natural products might be had via suitably functionalized bicyclo[4.4.0]decanes of type **7**, having an appropriate substituent R. Initial studies[8] on a methodology of potentially broad applicability to the synthesis of such decalins (Scheme I) proved promising when applied to the preparation of an analogue (**7a**) related to avarol. Not only did this sequence proceed smoothly but it also gave predominantly the desired secondary methyl epimer (**7a**) on hydrogenation of the methylene derivative (**6a**). We describe herein these results and an extension of this methodology to the first stereocontrolled total synthesis of (±)-avarol (**1**). Taking note of a recently expressed doubt[9] that the secondary methyl function of avarol is β as deduced earlier,[3] we have also provided evidence to confirm the originally assigned[3] stereochemistry.

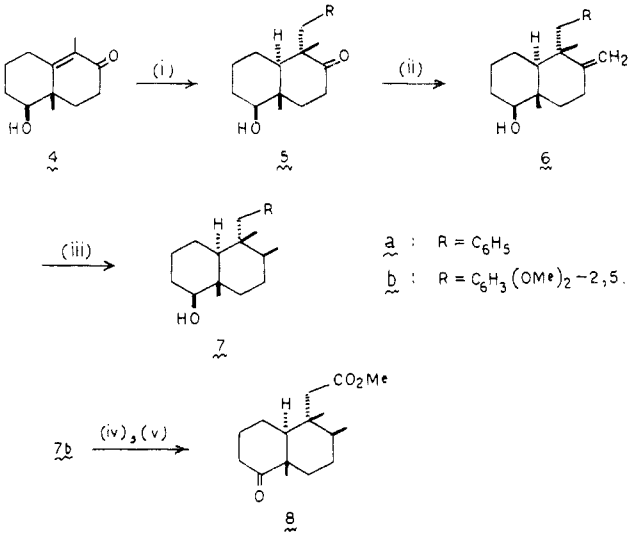
Results and Discussion

Preparation of Model Compound (7a) and Its Dimethoxy Analogue (7b).

Transformation of ene ketol **4** to *trans*-decalol (**7a**) according to the sequence **4** → **5a** → **6a** → **7a** (Scheme I) has been described earlier.[8] We have subsequently improved the yield of **5a** to 55%. The details of this sequence are presented in the Experimental Section.

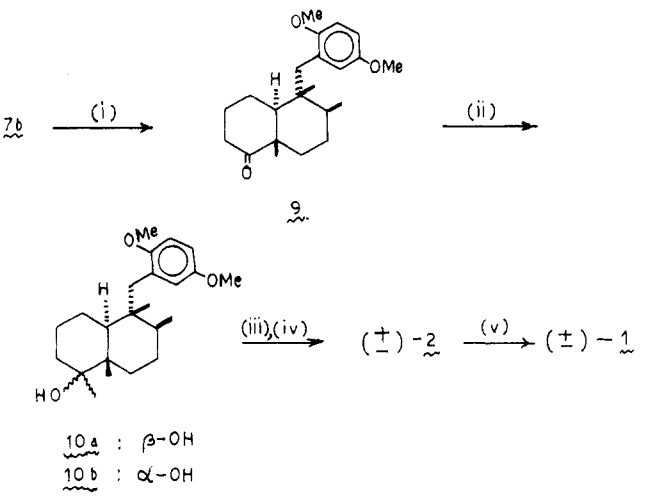
The dimethoxy analogue **7b** has been prepared by following a similar route. Thus, reductive alkylation of **4**[10] with 2,5-dimethoxybenzyl bromide[11] afforded the product **5b** (mp 77–79 °C) in 75% yield after extensive purification of the reaction product. Wittig olefination of **5b** by using a sevenfold excess of methylenetriphenylphosphorane[12] (80 °C, 40 h) afforded the olefin **6b** in 85% yield.

Scheme I[a]



[a] (i) Li-NH_3(l)/THF, benzyl chloride or 2,5-dimethoxybenzylbromide; (ii) CH_2=PPh_3/Me_2SO; (iii) H_2, 10% Pd/C; (iv) RuO_2, $NaIO_4$/CCl_4/H_2O; (v) CH_2N_2/Et_2O.

Scheme II[a]



[a] (i) PCC/CH_2Cl_2; (ii) MeLi/Et_2O; (iii) $POCl_3$/C_5H_5N; (iv) $RhCl_3$/EtOH; (v) *n*-BuSLi/HMPA.

(1) For some examples, see: Fujita, E.; Fuji, K.; Nagao, Y.; Ochiai, M. *Bull. Inst. Chem. Res., Kyoto Univ.* **1980**, *58*, 487–489. See also earlier reviews in this series.

(2) Referring only to the relative stereochemistry, we have used the term "clerodanes" subsequently to mean their antipodes (neoclerodanes) also. However, it should be noted that the absolute configuration of certain clerodanes has recently been revised (cf.: Kubo, I.; Kido, M.; Fukuyama, Y. *J. Chem. Soc., Chem. Commun.* **1980**, 897 and the references therein).

(3) This sesquiterpenoid hydroquinone, isolated from the marine sponge *Disidea Avara*, has been assigned the stereostructure **1** on the basis of chemical and spectral studies. Cf.: Rosa, S. de; Minale, L; Riccio, R.; Sadano, G. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1408–1414.

(4) Luibrand, R. T.; Erdman, T. R.; Vollmer, J. J.; Scheuer, P. J.; Finer, J.; Clardy, J. *Tetrahedron* **1979**, *35*, 609–612.

(5) Albericci, M.; Collart-Lempereur, M.; Brekman, J. C.; Daloze, D.; Tursch, B.; Declercq, J. P.; Germain, G.; Meerssche, M. V. *Tetrahedron Lett.* **1979**, 2687–2690.

(6) See ref 1 and also: Meinwald, J.; Prestwich, G. D.; Nakanishi, K.; Kubo, I. *Science* **1978**, *199*, 1167–1173.

(7) For recent synthetic efforts in this area, see: (a) ApSimon, J. W.; Yamasaki, K. *Chem. Lett.* **1977**, 1453–1456. (b) Takahashi, S.; Kusumi, T.; Kakisawa, H. *Ibid.* **1979**, 515–518. (c) Ardon-Jimenez, A.; Halsall, T. G. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1461–1470. (d) Goldsmith, D. J.; Srouji, G.; Kwong, C. *J. Org. Chem.* **1978**, *43*, 3182–3188. (e) Tokoroyama, T.; Matsuo, K.; Kubota, T. *Tetrahedron* **1978**, *34*, 1907–1913. (f) Kojima, Y.; Kato, N. *Tetrahedron Lett.* **1980**, 5033–5036. (g) de Groot, A.; Luteijn, J. M. *Ibid.* **1980**, 4127–4130. (h) Luteijn, J. M.; de Groot, A. *Ibid.* **1981**, 789–792.

(8) Sarma, A. S.; Chattopadhyay, P. *Tetrahedron Lett.* **1980**, 3719–3720.

(9) Djura, P.; Stierle, D. B.; Sullivan, B.; Faulkner, D. J.; Arnold, E.; Clardy, J. *J. Org. Chem.* **1980**, *45*, 1435–1441.

(10) Preparation and reductive alkylation of **4** was done according to the procedure of Heathcock (Dutcher, J. S.; Macmillan, J. G.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 2663–2669).

(11) Prepared from 2,5-dimethoxybenzyl alcohol and PBr_3: mp 74–75 °C (petroleum ether–ether); ^1H NMR (CCl_4) δ 3.66 (s, 3 H), 3.72 (s, 3 H), 4.4 (s, 2 H), 6.6–6.76 (m, 3 H). Anal. Calcd for $C_9H_{11}BrO_2$: C, 46.77; H, 4.80. Found: C, 46.79; H, 4.79.

(12) To minimize base-catalyzed enolization of **5b** (or **5a**) during this reaction, a slight excess of methyltriphenylphosphonium iodide (9 equiv), relative to dimsylsodium (7 equiv), was used for generating the Wittig ylide, in accordance with a recent publication (Cf.: Burk, L. A.; Soffer, M. D. *Tetrahedron* **1976**, *32*, 2083–2087).

It may be noted here that a closely related ketone (**5**, R = CH=CH_2) failed to react with the above ylide under milder conditions.[7c] Smith and Jerris have also observed[13] recently a dramatic change in reactivity of a hindered ketone on switching over to strong Wittig reaction conditions. The next step in the synthesis, namely, catalytic hydrogenation of the exomethylene derivative **6b**, though initially proved difficult,[15] was successfully accomplished by using a large excess of catalyst (10% Pd/C) in triethylamine containing a catalytic amount of methanol to afford quantitatively a mixture of epimeric methyl derivatives in a ratio of 85:15 (GLC analysis of the mixture).[16] The major isomer (mp 120–121 °C) was separated by fractional crystallization, but the minor one could not be isolated pure. Consideration of steric factors in **6b** suggests that the above major epimer should have the secondary methyl function in the equatorial (β) configuration since addition of hydrogen from the β face, leading to axial (α) methyl, would be somewhat hindered by the two axial (β) methyls of **6b**.[17a] The stereochemistry of this major product could not be asserted from the available spectral data.[17b] However, its stereostructure was unambiguously established as **7b** by the following correlation. Ruthenium tetraoxide oxidation[18] of this compound and esterification (CH_2N_2) of the resulting acid gave the keto ester **8**,[19] which was obtained[4] earlier by degradation of ilimaquinone (**3a**). Close agreement in spectral data of the above keto ester and those reported for optically active **8** confirmed the stereochemistry of the parent compound (**7b**).

Synthesis of (±)-Avarol. Toward this end, the ketone **9** (mp 122–123 °C), obtained in 90% yield by oxidation of **7b** with pyridinium chlorochromate, was reacted with methyllithium in ether to afford an epimeric mixture (~3:1) of **10a** and **10b** as a crystalline solid in 90% yield (Scheme II). The major epimer (mp 116–118 °C), isolated in one experiment by fractional crystallization, may be represented by stereostructure **10a**[20] from a consideration of the steric course of the reaction. No further attempts were made to establish its configuration, since this point is not pertinent to the synthetic sequence. The above mixture of carbinols was directly dehydrated with phosphorus oxychloride in pyridine to yield (95%) the two regioisomers of the resulting olefin (endo/exo ratio ~2:1). Rhodium chloride catalyzed isomerization[21] of this mixture and crystallization of the product from ethanol furnished (±)-avarol dimethyl ether (**2**, mp 72–73 °C) in an overall yield of 80% from **10**. Treatment of **2** with lithium *n*-butyl mercaptide in hexamethylphosphoric triamide by following the procedure of Welch[22] furnished (±)-avarol (**1**): mp 167–168 °C; 80% yield. Synthetic **2** and **1** were identical with the natural substances with respect to NMR, IR, and HPLC (in the case **2**) or TLC (for **1**) data.

Conclusions

In summary, the above strategy allows for a stereocontrolled synthesis of (±)-avarol in 28% (eight steps) overall yield, with its stereochemistry conclusively established[23] as **1** (vide supra). Moreover, the methodology used in this approach should be readily adaptable to other objectives[19] in the previously noted families.

Experimental Section

All melting and boiling points are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory of this Institute. Spectra were obtained by using the following instruments: IR spectra, Perkin-Elmer 298 or Beckman IR 20A spectrophotometer; ^{1}H NMR spectra, Varian T-60A or CFT-20 spectrometer; ^{13}C NMR spectra, JEOL FX-100 spectrometer; mass spectra, Hitachi RMU-6 mass spectrometer at 70 eV. Chemical shifts are given as parts per million (ppm) downfield from internal Me_4Si in δ units. Gas chromatographic analyses were performed on a Hewlett-Packard Model 5730A (dual-channel flame-ionization detector) instrument by using 10% UCW 982 on 80–100-mesh WAW-DMCS packed in a stainless-steel column. Peak area measurements were obtained on a Hewlett-Packard Model 3380A digital integrator. All column chromatography and TLC were performed by using E. Merck silica gel 60 (63–200 μm). Product purities were routinely checked by TLC. High-pressure liquid chromatography (HPLC) was done on a Waters Associates preparative LC instrument by using a μ-Bondapack C_{18} (3.9 mm × 300 mm) column.

Petroleum ether refers to the fraction with a boiling range of 40–60 °C, and ether refers to diethyl ether. All the dry solvents and reagents were prepared from reagent grade materials by conventional methods. Prior to concentration under reduced pressure, all organic extracts were dried over anhydrous $MgSO_4$.

The ene ketol **4** was prepared as described.[10]

***trans*-Octahydro-1α-[(2,5-dimethoxyphenyl)methyl]-1β,4aβ-dimethyl-5β-hydroxy-2(1*H*)-naphthalenone (5b).** This

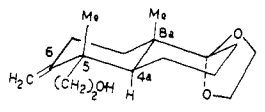
(13) Smith, A. B., III; Jerris, P. J. *J. Am. Chem. Soc.* **1981**, *103*, 194–195. Among further examples[14] where a hindered ketonic substrate failed to react with a variety of other nucleophiles due to enolization problems, methylenation by Wittig reaction has been reported to be successful in one instance.[14a] The scope of this classical reaction as a general and convenient method for homologation of hindered ketones to next higher aldehydes (Cf.: Corey, E. J.; Tius, M. A. *Tetrahedron Lett.* **1980**, 3535–3538), is being investigated by us.

(14) Cf.: (a) Pirrung, M. C. *J. Am. Chem. Soc.* **1981**, *103*, 82–87. (b) Corey, E. J.; Tius, M. A.; Das, J. *Ibid.* **1980**, *102*, 1742–1744. (c) *Ibid.* **1980**, *102*, 7612–7613.

(15) During initial experiments in which an aged catalyst (10% Pd/C) was used, there was complete isomerization of the exo double bond of **6b** to the more hindered endocyclic position.

(16) Prompted by a referee's comment, we subsequently tried this hydrogenation in EtOH and got the two epimers in a slightly different ratio (4:1). This shows that solvent has a marginal influence on the stereochemistry of this reduction, which, however, was not evident during hydrogenation of **6a** in EtOH and DMF.

(17) (a) Catalytic hydrogenation of related i in EtOH gave 1:1 mixture



i

of corresponding methyl epimers.[7b] Formation of higher proportions of axial (α) epimer in this case, compared to the results from **6b**, may be due to the additional steric factors present in i arising from the axial (α) oxygen of the ketal function. However, there might have been a marginal influence of solvent also.[16] (b) ^{1}H NMR data of a few compounds derived from the hydrogenation product of i indicate that when the secondary (C-6) methyl is trans oriented with respect to the tertiary (C-5) methyl, the tertiary methyl signal appears around δ 1.0, and if these two methyls have a cis relationship, the same signal would appear slightly upfield (δ 0.85). Also, in natural **3a** in which the cis relationship of the C-5 and C-6 methyls is established beyond doubt, this signal appears around δ 0.8. Since the major epimers obtained from **6a** and **6b** had no tertiary methyl signals downfield to δ 0.85, we assumed that their respective stereostructures are **7a** and **7b**. Further analysis on these lines could not be done because of the complex nature of the NMR spectra of the epimeric mixtures.

(18) (a) Caputo, J. A.; Fuchs, R. *Tetrahedron Lett.* **1967**, 4729–4731. (b) Ayres, D. C.; Hossain, A. M. M. *J. Chem. Soc., Perkin Trans. 1* **1975**, 707–710.

(19) Ester **8**, a useful intermediate for *trans*-clerodane diterpenoids, has also been prepared by us via an analogous methodology described herein, which involves reductive alkylation of **4** with methyl bromoacetate (Sarma, A. S.; Gayen, A. K., studies in progress).

(20) Some of the NMR chemical shift values of this compound are at slight variance from the data reported[3] for the well-defined epimer **10b**.

(21) (a) Andrieux, J.; Barton, D. H. R.; Patin, H. *J. Chem. Soc., Perkin Trans. 1* **1977**, 359–363. (b) Hudlicky, T.; Kutchan, T. M.; Wilson, S. R.; Mao, D. T. *J. Am. Chem. Soc.* **1980**, *102*, 6351–6353.

(22) Welch, S. C.; Rao, A. S. C. P. *J. Org. Chem.* **1978**, *43*, 1957–1961.

(23) In a recent private communication, Professor Minale has informed us of their confirmation of the structure of avarol by a single-crystal X-ray analysis.

was prepared by following the method[10] of Heathcock. Assemblage of apparatus was done as described therein.

Liquid ammonia (400 mL) was distilled from lithium into a three-necked flask immersed in a dry ice–isopropyl alcohol bath. Lithium wire (0.7 g, 100 mmol) was added, the bath was removed, and stirring was continued for 0.5 h. A solution of 5.0 g of **4** (25.8 mmol) in 50 mL of anhydrous THF was added dropwise over 0.5 h. After another 0.5 h, 2,5-dimethoxybenzyl bromide[11] (83.16 g, 360 mmol) was added as rapidly as possible, during which a violent reaction was observed (care was taken to hold the assemblage of apparatus tightly so that the reaction contents were not spilled out under the enormous pressure generated inside during this operation). The blue color was discharged after a few minutes while the lithium bromide slowly precipitated. After 15 min, solid ammonium chloride was added, the condenser was replaced with a water-cooled condenser, and 300 mL of ether was added. The ammonia was evaporated, the residue was washed with 5% hydrochloric acid, and the acid washings were extracted with ether. The combined organic solution was washed with 5% sodium bicarbonate and saturated brine, dried, and evaporated. After removal of the low-boiling fraction [bp 150–160 °C (0.1 torr)], the residual gum was chromatographed (4:1 benzene–ether) to give 7.2 g of crude **5b** as a light colored oil. Rechromatography as above furnished 6.68 g (75%) of pure **5b** as colorless gum. This solidified on being kept several days at 0 °C and was recrystallized twice from petroleum ether to afford pure **5b**: mp 77–79 °C; IR (KBr) 3460, 1695 cm^{-1}; ^1H NMR (CCl_4) 0.87 (s, 3 H, CH_3), 1.03 (s, 3 H, CH_3), 2.78 (apparent s, 2 H, benzylic), 3.67 (s, 6 H, OCH_3), 6.38–6.62 (m, 3 H, aromatic). Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.60; H, 8.53.

***trans*-Octahydro-1α-benzyl-1β,4aβ-dimethyl-5β-hydroxy-2(1*H*)-naphthalenone (5a).** This was prepared by following the procedure described for **5b** and using lithium wire (1.4 g, 200 mmol) in 800 mL of distilled liquid ammonia, 10.0 g of **4** (51.6 mmol), and benzyl chloride (50 mL, 450 mmol), freshly distilled over anhydrous potassium carbonate. In this case also, violent reaction was observed during the rapid addition of benzyl chloride. The reaction mixture was worked up as before. The crude residual oil was distilled to afford 9.12 g of yellow viscous oil, bp 170–178 °C (0.1 torr). Chromatography (2:1 benzene–ethyl acetate) afforded 8.10 g (55%) of **5a** as colorless gum. This solidified on being allowed to stand and was crystallized twice from petroleum ether–ether to afford pure **5a**: mp 71–72 °C; IR (KBr) 3400, 1695 cm^{-1}; ^1H NMR ($CDCl_3$) 0.96 (s, 3 H, CH_3), 1.08 (s, 3 H, CH_3), 2.33 (δ_A) and 3.30 (δ_B) (AB, q, J_{AB} = 14 Hz, 2 H, benzylic), 6.82–7.23 (m, 5 H, aromatic); mass spectrum m/e (relative intensity) 286 (M^+, 8), 91 (base). Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.71; H, 9.14.

***trans*-Decahydro-5α-[(2,5-dimethoxyphenyl)methyl]-5β,8aβ-dimethyl-6-methylene-1-naphthalenol (6b) and *trans*-Decahydro-5α-benzyl-5β,8aβ-dimethyl-6-methylene-1-naphthalenol (6a).** Sodium hydride (57% oil dispersion; 1.68 g, 70 mmol) was placed in a three-necked flask and washed under nitrogen with several portions of petroleum ether to remove the mineral oil. The flask was then equipped with a rubber septum, a reflux condenser fitted with a three-way stopcock, a pressure-equalizing dropping funnel, and a magnetic stirrer. The system was alternately evacuated and filled with nitrogen, 75 mL of dry Me_2SO (distilled three times from CaH_2) was introduced, and the mixture was heated at 75–80 °C for ca. 45 min. The resulting solution of methylsulfinyl carbanion was cooled in an ice–water bath, and 36 g of methyltriphenylphosphonium iodide (90 mmol) in 150 mL of warm Me_2SO was added dropwise during 0.5 h. The resulting dark red solution of the ylide was stirred at 25 °C for 0.5 h before being used as follows.

Compound 6b. To a solution of methylenetriphenylphosphorane (70 mmol) was added 3.46 g of **5b** (10 mmol) in 15 mL of dry Me_2SO over 2 min at 30 °C. The reaction mixture was stirred for 40 h at 75–80 °C, cooled to 30 °C, diluted with water, and extracted thoroughly with ether. The ethereal solution was washed with 5% hydrochloric acid, water, and saturated brine, dried, and evaporated. The residual oil was chromatographed (benzene and 19:1 benzene–ethyl acetate) to afford 2.92 g (85%) of **6b** as colorless gummy material. Rechromatography of the above viscous oil furnished analytical material: IR (film) 3450, 1500 cm^{-1}; ^1H NMR (CCl_4) 0.85 (s, 3 H, CH_3), 0.95 (s, 3 H, CH_3), 2.63 (apparent s, 2 H, benzylic), 3.63 (s, 3 H, OCH_3), 3.66 (s, 3 H, OCH_3), 4.43 and 4.73 (dd, 2 H, vinylic), 6.55 (s, 3 H, aromatic). Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.52; H, 9.19.

Compound 6a. This was prepared as in the case of **6b** by using methylenetriphenylphosphorane (70 mmol) and 2.86 g of **5a** (10 mmol). The residual oil, obtained on workup, was chromatographed (19:1 benzene–ethyl acetate) to afford 2.27 g (80%) of **6a** as colorless gummy material. Distillation of this product afforded an analytical sample: bp 140–142 °C (0.05 torr); IR (film) 3400, 1495 cm^{-1}; ^1H NMR ($CDCl_3$) 0.89 (s, 3 H, CH_3), 1.00 (s, 3 H, CH_3), 2.67 (δ_A) and 2.91 (δ_B) (ABq, J_{AB} = 14 Hz, 2 H, benzylic), 4.54 and 4.79 (dd, 2 H, vinylic), 7.06 (s, 5 H, aromatic); mass spectrum, m/e (relative intensity) 284 (M^+, 17), 193 (82), 175 (base), 91 (74). Anal. Calcd for $C_{20}H_{28}O$: C, 84.45; H, 9.92. Found: C, 84.44; H, 10.10.

***trans*-Decahydro-5α-[(2,5-dimethoxyphenyl)methyl]-5β,6β,8aβ-trimethyl-1-naphthalenol (7b) and *trans*-Decahydro-5α-benzyl-5β,6β,8aβ-trimethyl-1-naphthalenol (7a). Compound 7b.** A solution of 400 mg of *exo*-methylene derivative **6b** (1.16 mmol) in 15 mL of dry triethylamine and methanol (1 drop) was hydrogenated in the presence of 750 mg of 10% palladium/charcoal (presaturated with hydrogen) at 30 °C and atmospheric pressure.[15,16] After 6 h of stirring in a hydrogen atmosphere, the subsequent workup afforded a thick residue containing a mixture of two products in a ratio of 85:15 (GLC). Chromatographic purification (benzene) furnished 320 mg (80%) of **7b** as white crystalline solid. Recrystallization from ether gave colorless prisms: mp 120–121 °C; IR (KBr) 3470, 1490 cm^{-1}; ^1H NMR ($CDCl_3$) 0.80 and 0.83 (each s, 3 H each, CH_3), 2.54 (br, 2 H, benzylic), 3.68 (s, 6 H, OCH_3), 6.42–6.63 (m, 3 H, aromatic); ^{13}C NMR ($CDCl_3$) δ 153.10, 152.76, 128.69, 118.90, 111.30, 110.91, 80.74, 55.65, 55.45, 46.58, 41.27, 39.66, 37.13, 36.79, 36.20, 30.16, 29.72, 27.72, 27.24, 24.17, 21.97, 17.73, 17.5; mass spectrum, m/e (relative intensity) 346 (M^+, 23), 177 (base), 121 (77). Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.35; H, 9.93.

Compound 7a. A solution of 250 mg of **6a** (0.88 mmol) in 15 mL of dry DMF (or ethanol) was hydrogenated as above in the presence of 120 mg of 10% palladium/charcoal. The workup after 6 h afforded the product containing a mixture in a ratio of 4:1 (GLC). Chromatographic purification (19:1 benzene–ethyl acetate furnished 190 mg (75%) of **7a** as a white crystalline solid. Crystallization three times from benzene gave white needles: mp 132–133 °C; IR (KBr) 3400, 1495 cm^{-1}; ^1H NMR ($CDCl_3$) 0.80 and 0.83 (each s, 3 H each, CH_3), 2.54 (d, J = 1.5 Hz, 2 H, benzylic), 6.83–7.20 (m, 5 H, aromatic); mass spectrum, m/e (relative intensity) 286 (M^+, 2), 195 (62), 177 (base), 91 (55). Anal. Calcd for $C_{20}H_{30}O$: C, 83.86; H, 10.56. Found: C, 83.69; H, 10.80.

Acetate of 7a: IR (film) 1735 cm^{-1}; ^1H NMR (CCl_4) 0.81 (s, 3 H, CH_3), 0.94 (s, 3 H, CH_3), 0.98 (d, J = 6.5 Hz, 3 H, CH_3), 1.87 (s, 3 H, $COCH_3$), 2.58 (d, J = 1 Hz, 2 H, benzylic), 3.87–4.25 (m, 1 H, CHOAc), 6.8–7.31 (m, 5 H, aromatic). Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83. Found: C, 80.34; H, 9.69.

***trans*-Octahydro-5α-[(methoxycarbonyl)methyl]-5β,6β,8aβ-trimethyl-1(2*H*)-naphthalenone (8) by Ruthenium Tetraoxide Oxidation of 7b.** Ruthenium tetraoxide was prepared by stirring ruthenium dioxide (53.5 mg, 0.4 mmol) in 10 mL of carbon tetrachloride and a solution of sodium metaperiodate (1.07 g, 5 mmol) in 7 mL water over a period of 2 h at 0 °C. To a suspension of above ruthenium tetraoxide was added 346 mg of **7b** (1 mmol) in 5 mL of carbon tetrachloride. The mixture was stirred under reflux for 45 h, during which a solution of sodium metaperiodate (2.14 g, 10 mmol) in 14 mL of water was added in small portions at different intervals. The mixture was then cooled, excess oxidant was destroyed by the addition of propan-2-ol (2.5 mL), and this mixture was then filtered through a long column of silica gel with ethyl acetate as the eluant. The filtrate was concentrated to a small volume (30 mL). This was extracted with cold 3% sodium hydroxide solution (3 × 10 mL). Acidification of the alkali extracts with cold dilute hydrochloric acid, followed by extraction of the liberated acid with ethyl acetate, afforded a crude acidic product. This was esterified with an ethereal solution of diazomethane. Chromatographic purification (19:1 benzene–ethyl acetate) of the resulting ester furnished 53.2 mg (20%) of **8** as a colorless oil. This product was found to be identical with an authentic sample of **8** prepared by us.[19] The

spectral data of this compound corresponded closely to those reported[4] for optically active 8: IR (film) 1735, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) 0.84 (s, 3 H, CH_3), 1.15 (s, 3 H, CH_3), 2.36 (br, 2 H, benzylic), 3.61 (s, 3 H, COOMe).

***trans*-Octahydro-5α-[(2,5-dimethoxyphenyl)methyl]-5β,6β,8aβ-trimethyl-1(2*H*)-naphthalenone (9).** To a stirred solution of pyridinium chlorochromate (646 mg, 3 mmol) in 5 mL of dry dichloromethane was added 692 mg of **7b** (2 mmol) at 30 °C over 2 min, and the reaction mixture was stirred at this temperature for 2 h. The black mixture was diluted with dry ether (50 mL) and filtered through a long column of silica gel. Removal of the solvent and chromatography (benzene) of the residue afforded 620 mg (90%) of **9** as crystalline solid. Recrystallization from petroleum ether–ether furnished prisms: mp 123 °C; IR (KBr) 1695, 1490 cm^{-1}; ^1H NMR ($CDCl_3$) 0.90 (s, CH_3) and 0.96 (d, J = 6 Hz, overall 6 H, partially overlapping with singlet at 0.9), 1.13 (s, 3 H, CH_3), 2.62 (d, J = 2.5 Hz, 2 H, benzylic), 3.66 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3), 6.50–6.73 (m, 3 H, aromatic); mass spectrum, m/e (relative intensity) 344 (M^+, 70) 151 (98), 121 (base). Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.50; H, 9.45.

Epimeric Mixture 10 by Treatment of 9 with Methyllithium. To a stirred solution of 688 mg of the ketone **9** (2 mmol) in 20 mL of freshly distilled dry ether at 0 °C under nitrogen was added methyllithium in ether (20 mL of 0.5 M solution, 10 mmol) dropwise over 0.5 h. The mixture was stirred for 6 h at 0 °C. The crude reaction mixture was poured into ice–water (50 mL) and extracted with ether. The combined ether extracts were washed with water and saturated brine, dried, and evaporated. Chromatographic purification (19:1 benzene–ethyl acetate) of the above residue afforded 648 mg (90%) of **10a** and **10b** as a crystalline solid. In one experiment, fractional crystallization of the above mixture from petroleum ether afforded a pure sample of the major epimer **10a**: mp 116–118 °C; IR (KBr) 3490, 1500 cm^{-1}, ^1H NMR ($CDCl_3$) 0.84 (s, 3 H, CH_3), 1.02 (s, CH_3) and 1.01 (d, J = 6 Hz, overall 6 H, partially overlapping with singlet at 1.02), 1.04 (s, 3 H, CH_3), 2.64 (br, 2 H, benzylic), 3.76 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 6.72–6.78 (m, 3 H, aromatic). Anal. Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.42; H, 10.18.

(±)-Avarol Dimethyl Ether (2). To a stirred solution of 360 mg of the above mixture of carbinols **10a** and **10b** (1 mmol) in 5 mL of dry pyridine at 0 °C was added under nitrogen phosphorus oxychloride (1 mL, 10 mmol), and the resulting mixture was stirred at 30 °C for 12 h. It was then poured into crushed ice (25 g) and extracted with ether. The organic layer was washed with 5% hydrochloric acid, 5% sodium carbonate, and saturated brine, dried, and evaporated. The residue on chromatographic purification (2:1 petroleum ether–benzene) afforded 325 mg (95%) of a mixture of regioisomeric olefins as a crystalline solid, consisting of **2** and its exo isomer in a ratio 2:1, respectively (as evident from NMR).

To a stirred solution of 325 mg of above olefinic mixture (0.95 mmol) in 10 mL of ethanol was added rhodium chloride hydrate (15 mg), and the resulting mixture was stirred and refluxed for 6 h under nitrogen. The mixture was cooled, diluted with water (10 mL), and extracted with dichloromethane. The organic layer was dried over anhydrous K_2CO_3 and the solvent evaporated. Crystallization three times from ethanol furnished 272 mg (80% overall yield from **10**) of **2** as white needles: mp 72–73 °C; IR (KBr) 3000, 2960, 2930, 2910, 2850, 2835, 1610, 1590, 1500, 1455, 1435, 1420, 1380, 1370, 1320, 1280, 1270, 1240, 1220, 1190, 1180, 1160, 1135, 1110, 1060, 1025, 1000, 980, 900, 880, 850, 835, 800, 725, 720, 705 cm^{-1}; ^1H NMR ($CDCl_3$) 0.85 (s, 3 H, CH_3), 1.02 (s, CH_3) and 1.00 (d, J = 6 Hz, overall 6 H, partially overlapping with singlet at 1.02), 1.52 (d, J = 1 Hz, 3 H, vinyl methyl), 2.68 (s, 2 H, benzylic), 3.75 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), 5.14 (br, 1 H, vinylic), 6.72 (br, 3 H, aromatic). Anal. Calcd for $C_{23}H_{34}O_2$: C, 80.65; H, 10.01. Found: C, 80.81; H, 9.82.

This was identical with natural **2** with respect to IR, ^1H NMR, and HPLC.

(±)-Avarol (1). The procedure described by Welch[22] was followed with a slight modification in the preparation of lithium *n*-butyl mercaptide.

To a stirred solution of methyllithium (10 mL of 0.5 M solution, 5 mmol) in 2 mL of dry hexamethylphosphoric triamide (HMPA) under nitrogen was added *n*-butyl mercaptan (0.5 mL, 5 mmol) dropwise, and the mixture was stirred until the evolution of methane had stopped (0.5 h); 85 mg of (±)-avarol dimethyl ether (**2**, 0.25 mmol) in HMPA (2 mL) was added, and the mixture was heated with stirring at 150–155 °C for 26 h. The mixture was cooled, diluted with water and extracted with ether. The combined organic extracts were washed with water and saturated brine and dried, and the solvent was evaporated. Chromatographic purification (benzene) furnished 62 mg (80%) of (±)-avarol (**1**) as solid. Crystallization twice from petroleum ether–ether afforded an analytical sample as white needles: mp 167–168 °C; ^1H NMR ($CDCl_3$) 0.85 (s, 3 H, CH_3), 1.02 (s, CH_3) and 1.00 (d, J = 6 Hz, partially overlapping with singlet at 1.02), 1.51 (apparent s, 3 H, vinyl methyl), 2.64 (apparent q, benzylic) 5.0–5.2 (m, 1 H, vinylic), 6.52–6.84 (m, 3 H, aromatic). Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.00; H, 9.48.

The product was identical with a sample of natural avarol with respect to ^1H NMR and GLC.

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Registry No. (±)-1, 80795-32-0; (±)-2, 80795-33-1; (±)-**5a**, 76436-50-5; (±)-**5b**, 80765-03-3; (±)-**6a**, 76436-51-6; (±)-**6b**, 80765-04-4; (±)-**7a**, 76436-52-7; (±)-**7a** acetate, 80765-05-5; (±)-**7b**, 80765-06-6; (±)-**8**, 80795-34-2; (±)-**9**, 80765-07-7; (±)-**10a**, 80795-35-3; (±)-**10b**, 80795-36-4; ruthenium tetraoxide, 20427-56-9; methyl lithium, 917-54-4; 2,5-dimethoxybenzyl bromide, 60732-17-4.