C. From 11. Similarly, crude **11** (0.80 g) from hydroboration of **31** was oxidized[27] to 664 mg of **5** (80%, based on **31**).

Reduction of 5. A. With Sodium in Ethanol. Ketone **5** (196 mg, 1.30 mmol) was reduced with sodium (1.34 g, 58.2 mmol) in dry, absolute ethanol (15 mL), as described above for **3**. The crude sample was purified by VPC on column A to give 167 mg (one peak) of **11** and **12** (84%), treatment of which with bis(trimethylsilyl) acetamide (see above) gave a viscous liquid. VPC on column B (110 °C, 71 mL/min) indicated two products, A (50 min, 76%) and B (54 min, 24%). Each product was isolated and hydrolyzed to the corresponding alcohol. The IR spectra of the alcohols from A and B were identical with those of **11** and **12**, respectively.

B. With Lithium Aluminum Hydride. Ketone **5** (188 mg, 1.25 mmol) was reduced with excess lithium aluminum hydride in ether to give a white solid which after purification by VPC on column A weighed 144 mg (76%). Analysis via the trimethylsilyl ethers as described above indicated **11** (73%) and **12** (27%).

Acknowledgments. We thank Mr. William Rosenstein for technical assistance, Mr. S. T. Bella for microanalyses, and the National Science Foundation for support of this research through Grant CHE74-21436. The 220-MHz NMR spectra were obtained on an instrument at The Rockefeller University and operated by a consortium supported in part by NSF Grant PCM74-12247.

Registry No.—**1**, 65311-25-3; **2**, 65375-83-9; **3**, 29415-86-9; **4**, 65311-26-4; **5**, 65311-27-5; **8a**, 29577-00-2; **8b**, 23217-50-7; **9a**, 30365-09-4; **11**, 65311-28-6; **12**, 65375-84-0; **14**, 26788-91-0; **15**, 26760-27-0; **16**, 65311-29-7; **17**, 65311-30-0; **19**, 63072-75-3; **22**, 65311-31-1; **24**, 4362-18-9; **27**, 65311-32-2; **28**, 65311-33-3; **29**, 65366-49-6; **30**, 65311-34-4; **31**, 65311-35-5; 6-chloro-6-cyanobicyclo[3.2.2]non-8-ene, 29415-85-8; ethylene glycol, 107-21-1; *exo*-tricyclo[3.3.2.0^{2,4}]decan-9-one ethylene acetal, 65311-36-6; bicyclo[3.2.2]non-8-en-6-one tosylhydrazone, 65311-37-7; tropone, 539-80-0; cycloheptatriene, 544-25-2.

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Stereoselective Total Syntheses of the Fungitoxic Hydroquinones (±)-Zonarol and (±)-Isozonarol

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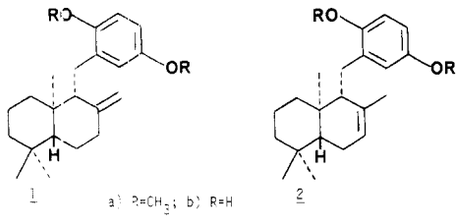
Stereoselective and regioselective total syntheses of two naturally occuring fungitoxic hydroquinones (±)-zonarol (**1b**) and (±)-isozonarol (**2b**) are described. The key features of these syntheses are: (a) the dehydration of tertiary alcohol **6** to alkene **7** without rearrangement utilizing dimethyl sulfoxide at 155 °C; (b) the conjugate addition of 2,5-dimethoxyphenylmagnesium bromide Grignard reagent to enone **9b**; and (c) ether cleavage of compounds **1a** and **2a** utilizing lithium *n*-butyl mercaptide in hexamethylphosphoric triamide at 150 °C for 24 h to afford the respective natural products.

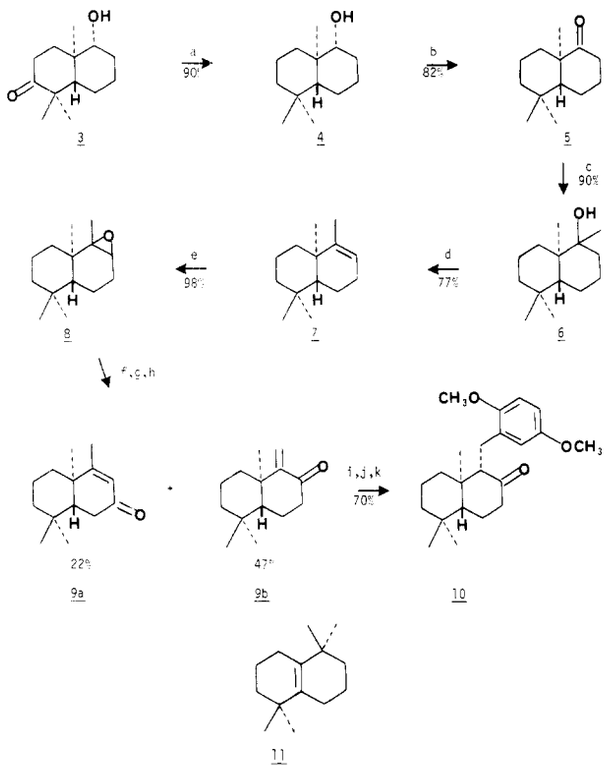
The two naturally occurring fungitoxic hydroquinones zonarol (**1b**) and isozonarol (**2b**) were isolated from brown seaweed *Dictopteris undulata* found in the Pacific Ocean near Southern California and the Gulf of California.[1-3] The structure and absolute stereochemistry of these merosesquiterpenoids[4] were rigorously defined by degradation and spectroscopy.[1-3] These two marine natural products were found to be active against the following pathogenic fungi: *Phytophthora cinnamoni, Rhizoctonia solani, Sclerotinia sclerotiorum,* and *Sclerotium rolfsii.*[1] We wish to report,

0022-3263/78/1943-1957$01.00/0

Scheme I



Scheme II



[a] N_2H_4, KOH, DEG, Δ. [b] CrO_3, H_2SO_4, H_2O, acetone. [c] CH_3Li, Et_2O, 0 °C. [d] Me_2SO, 155 °C. [e] *m*-CPBA Na_2HPO_4, $CHCl_3$. [f] $LiN(n\text{-}Pr)_2$, THF, Δ, 6 h. [g] $CrO_3 \cdot Pyr_2$, CH_2Cl_2. [h] Chromatography, E. Merck, silica gel-60, 15% Et_2O–85% petroleum ether (bp 30–60 °C) eluent. [i] 2,5-Dimethoxyphenylmagnesium bromide, DME. [j] Ac_2O. [k] KOH, CH_3OH.

herein, the full details of the first stereoselective and regioselective total syntheses of both (±)-zonarol (**1b**) and (±)-isozonarol (**2b**).[5]

Results and Discussion

The starting material chosen for these syntheses is readily available ketol **3** previously prepared by Heathcock and coworkers.[6] Ketol **3** is prepared from 2-methyl-1,3-cyclohexanedione and ethyl vinyl ketone in three synthetic stages in 46% overall yield. Haung-Minlon modification of the Wolff–Kishner reduction of ketol **3** using hydrazine hydrate in diethylene glycol (DEG) in the presence of potassium hydroxide at 200 °C gives alcohol **4** in 90% yield.[7] Oxidation of alcohol **4** with Jones' reagent in acetone affords ketone **5** in 82% yield.[8] Addition of excess methyllithium in ether at 0 °C to ketone **5** produces a mixture of tertiary alcohols **6** in 90% yield. Dehydration of tertiary alcohols **6** utilizing standard reagents ($SOCl_2$, pyridine; or $POCl_3$, pyridine; or I_2, benzene; or H_2SO_4, pentane; or *p*-TsOH, benzene) gives only substantial quantities of the corresponding symmetrical rearrangement product **11**. This troublesome rearrangement can be circumvented by performing the dehydration in anhydrous dimethyl sulfoxide at 155 °C for 16 h.[9] This latter reaction converts tertiary alcohols **6** to trisubstituted alkene **7** without any trace of the rearrangement product in 77% yield. Epoxidation of alkene **7** with *m*-chloroperbenzoic acid in chloroform in the presence of disodium hydrogen phosphate gives an equimolar mixture of epoxides **8** (α/β, respectively) in 98% yield.[10] Epoxide ring opening by treatment of oxiranes **8** with lithium di-*n*-propylamide in refluxing tetrahydrofuran for 6 h produces a mixture of allylic alcohols.[11] Oxidation of this mixture of allylic alcohols with Collins' reagent[12] then affords an easily separable mixture of enones **9a** and **9b** (ratio 32:68, respectively) in 69% yield. Enones **9a** and **9b** are easily separated by column chromatography on E. Merck silica gel-60 using 15% ether–85% petroleum ether (bp 30–60 °C) as the eluent. Enone **9a** displays a one proton quartet (J = 2 Hz) at δ 5.53 ppm, whereas enone **9b** shows a two-proton AB quartet (J_{AB} = 2 Hz) with each doublet centered at δ 4.93 and δ 5.36 ppm, respectively. When the epoxidation of alkene **7** to oxirane **8** is carried out in dry ether the ratio of epoxides is 30:70 (α/β, respectively). When this mixture of epoxides is carried through the same reaction sequence to enones **9a** and **9b** the ratio of enones **9a**/**9b** changes to 56:44, respectively, in 69% yield. Enone **9b** was previously prepared by Eschenmoser et al. as well as White et al. via different synthetic routes.[13] Generation of the Grignard reagent of 1-bromo-2,5-dimethoxybenzene[14] utilizing standard methods (Mg turnings, I_2 catalyst, DME or THF) is rather difficult and capricious; however, when the magnesium metal is prepared by Rieke's method ($MgCl_2$ + 2K, DME),[15] then the Grignard reagent forms readily in 1,2-dimethoxyethane (DME). Addition of copper(I) iodide (in catalytic amount) followed by enone **9b** and quenching with freshly distilled acetic anhydride affords a crude enol acetate by conjugate addition and enolate anion trapping.[16] Treatment of this crude enol acetate with potassium hydroxide in methanol then produces ketone **10** (mp 108–109 °C) in 70% overall yield from enone **9b**. Enolate anion trapping with acetic anhydride facilitates the isolation and purification of the final product, ketone **10**. Quenching the conjugate addition reaction at 0 °C with dilute hydrochloric acid solution gives ketone **10** in somewhat lower yields. Nuclear magnetic resonance data (CCl_4) of ketone **10** indicate the presence of three aromatic protons (m, δ 6.67), two methoxyl groups (s, δ 3.72 and s, δ 3.76), and three quaternary methyl groups (s, δ 0.97; s, δ 0.90; and s, δ 0.80 ppm).

A Wittig reaction on ketone **10** utilizing methylenetriphenylphosphorane in anhydrous dimethyl sulfoxide at 80 °C for 24 h affords (±)-zonarol dimethyl ether (**1a**, mp 117–118 °C) in 93% yield.[17] Cleavage of dimethyl ether **1a** to (±)-zonarol (**1b**) is smoothly accomplished in 90% yield with lithium *n*-butyl mercaptide in hexamethylphosphoric triamide at 150 °C for 24 h. Other reagents and conditions (NaSEt, DMF[18]; $LiI \cdot 3H_2O$, collidine[19]; and CH_3MgI, Δ[20]) give an equimolar mixture of the monomethyl ethers. Treatment of ketone **10** with excess methyllithium in ether at 0 °C followed by dehydration of the resulting tertiary alcohol by heating in anhydrous dimethyl sulfoxide at 155 °C for 16 h gives (±)-zonarol dimethyl ether (**1a**) and (±)-isozonarol dimethyl ether (**2a**) (ratio 1:4.8, respectively) in 67% yield. After separation (chromatography over 15% silver nitrate on silica gel) (±)-isozonarol dimethyl ether (**2a**) was then smoothly converted to (±)-isozonarol (**2b**) by treatment with lithium *n*-butyl mercaptide in hexamethylphosphoric triamide at 150 °C for 24 h. Both synthetic (±)-zonarol dimethyl ether (**1a**) and (±)-isozonarol dimethyl ether (**2a**) were identical (IR, NMR, GLC, and TLC) with the respective dimethyl ethers prepared from natural zonarol (**1b**) and isozonarol (**2b**).[21]

Experimental Section

Melting points were determined on a Fisher-Johns and/or Büchi melting point apparatus and are uncorrected. Analyses were per-

formed by Spang Microanalytical Laboratory, Ann Arbor, Mich. 48106.

Silica gel PF 254-366 (E. Merck No. 7748) and Silica gel 60 (E. Merck No. 7734, 70–230 mesh) available from Brinkmann Instruments were used for thin-layer and column chromatography, respectively.

Analytical gas-phase chromatography (GLC) was performed using the following types of columns and flow rates: (A) 5-ft stainless steel, 0.125-in. column packed with 3% SE-30 on Varaport 30, 100/120 mesh (Varian), flow rate 15 mL/min at ambient temperature; (B) 6-ft stainless steel, 0.125-in. column packed with 5% OV-17 on Varaport-30, 80/100 mesh (Varian), flow rate 15 mL/min at ambient temperature.

Infrared (IR) spectra were recorded on a Perkin-Elmer 237B. Solid samples were recorded in spectroquality carbon tetrachloride or chloroform using 0.10-mm sodium chloride cells. Liquid samples were sometimes taken as thin films between sodium chloride plates.

Nuclear magnetic resonance (NMR) spectra were measured on a Varian Associates Model T-60 spectrometer. All reactions were performed under an atmosphere of dry nitrogen. The equipment was dried in an oven at 120 °C for several hours, then allowed to cool in an atmosphere of dry nitrogen. All liquid transfers were made with nitrogen-filled syringes.

The petroleum ether used was Baker Analyzed Reagent, bp 30–60 °C. The terms "dry tetrahydrofuran", "dry 1,2-dimethoxyethane", and "dry diethyl ether" refer to purification of the commercial materials by distillation from lithium aluminum hydride under nitrogen. "Dry benzene", "dry hexamethylphosphoric triamide", and "dry di-*n*-propylamine" were obtained by distillation of the commercial materials from calcium hydride. "Dry dichloromethane" was obtained by distillation of the solvent from phosphorus pentoxide. Dimethyl sulfoxide was triple distilled from calcium hydride–sodium amide (98:2) onto freshly activated molecular sieves type 4A. The nomenclature utilized is that preferred by Chemical Abstracts.[22]

(1α,4aβ,8aα)-Decahydro-5,5,8a-trimethyl-1-naphthalenol (4). Haung-Minlon modification of Wolff–Kishner reduction was utilized. Hydrazine hydrate (14.42 g, 0.45 mol) and potassium hydroxide (22.44 g, 0.4 mol) in diethylene glycol (100 mL) were added to ketone **3** (20 g, 95 mmol) and heated under nitrogen atmosphere for 2 h at 150 ± 5 °C. Then the temperature was raised to 200 °C to remove excess hydrazine and water, and heating was continued for another 4 h. The reaction mixture was then cooled to room temperature, diluted with dilute hydrochloric acid, and extracted with ether (3 × 200 mL). The combined ethereal extracts were washed with water (3 × 50 mL) and saturated sodium chloride solution (50 mL), then dried ($MgSO_4$), filtered, and concentrated in vacuo to give 18 g (90%) of alcohol **4:** bp 70 ± 2 °C (0.1 mm); IR (CCl_4) 3400–3600 (OH), 1370, 1390 cm^{-1} (*gem*-dimethyl); NMR (CCl_4) δ 0.87 (s, 9, CH_3), 3.00 ppm (m, 1, oxymethine). Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found C, 79.69; H, 12.33.

***trans*-Octahydro-5,5,8a-trimethyl-1(2*H*)-naphthalenone (5).** Saturated alcohol 4 (17.5 g, 89.5 mmol) was dissolved in reagent acetone (100 mL), cooled to 0–5 °C, and Jones reagent was added dropwise until the reaction mixture remained orange. After stirring for an additional 20 min, the reaction was quenched with isopropyl alcohol, diluted with water (400 mL), and then extracted with ether (3 × 150 mL). The combined ethereal extracts were washed with water (3 × 50 mL) and saturated sodium chloride solution (50 mL), dried ($MgSO_4$), filtered, and then evaporated in vacuo to give 16 g of crude ketone **5.** This material was purified by column chromatography on silica gel (400 g) using 15% ether–85% petroleum ether as the eluent collecting 250-mL fractions. Fractions 6–10 were combined to give 13 g (82%) of pure ketone **5:** bp 65 ± 5 °C (0.3 mm) (bulb to bulb); IR (film) 1705 cm^{-1} (CO); NMR (CCl_4) δ 0.90 (bs, 6, CH_3), 1.13 ppm (s, 3, CH_3). Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.39; H, 11.53.

Decahydro-1,5,5,8a-tetramethyl-1-naphthalenol (6). Saturated ketone **5** (8.7 g, 45 mmol) was dissolved in freshly distilled dry ether (100 mL), cooled to 0 °C (ice bath) and methyllithium in ether (25 mL, 2 M, 50 mmol) was added dropwise over a period of 30 min and then stirred for 4 h. The reaction mixture was poured into ice water (400 mL) and extracted with ether (3 × 100 mL). The combined ethereal extracts were washed with water (3 × 60 mL) and saturated sodium chloride solution (50 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo to give 9 g of crude alcohol **6.** The material was purified by passing through a column of silica gel and eluting with 1:1 ether/petroleum ether to give 8.4 g (90%) of pure tertiary alcohol **6:** IR (film) 3485–3530 cm^{-1} (OH).

***trans*-1,2,3,4,4a,7,8,8a-Octahydro-1,1,4a,5-tetramethylnaphthalene (7).** Tertiary alcohol **6** (8.4 g, 40 mmol) was dissolved in dry dimethyl sulfoxide (50 mL) and heated at 155 °C under nitrogen for 16 h. The reaction mixture was then cooled to room temperature, diluted with water (300 mL), and extracted with 1:1 ether/pentane (3 × 100 mL). The combined ether–pentane extracts were washed with water (3 × 25 mL) and saturated sodium chloride solution (50 mL), then dried ($MgSO_4$), filtered, and concentrated in vacuo to give 7.05 g of crude olefin **7.** This material was purified by distillation to give 5.93 g (77%) of alkene **7:** bp 62–65 °C (0.2 mm) (bulb to bulb); IR (CCl_4) 1630 cm^{-1} (C=C); NMR (CCl_4) δ 0.87 (s, 3, CH_3), 0.88 (s, 3, CH_3), 1.00 (s, 3, CH_3), 5.10 ppm (bs, 1, alkene proton).

Anal. Calcd for $C_{14}H_{24}$: C, 87.42; H, 12.58. Found: C, 87.48; H, 12.62.

Decahydro-4,4,7a,7b-tetramethyloxireno[*a*]naphthalene (8). To a solution of *m*-chloroperbenzoic acid (2.5 g, 85%, 12 mmol) in reagent grade chloroform (50 mL) was added disodium hydrogen phosphate (3.41 g, 24 mmol). This mixture was cooled to 0 °C (ice bath) and alkene **7** (1.92 g, 10 mmol) in chloroform (10 mL) was added dropwise with stirring for 2 h. The reaction was monitored by thin-layer chromatography (TLC, 10% ether–90% petroleum ether). Disodium hydrogen phosphate was filtered and washed with chloroform. The combined chloroform layers were washed with 10% sodium hydroxide solution (2 × 25 mL), water (3 × 25 mL), and saturated sodium chloride solution (25 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo to give crude epoxide 6 (2.3 g). This material was distilled (bulb to bulb), bp 65–68 °C (0.3 mm), to give 2.11 g (98%) of epoxide **8:** IR (CCl_4) 1240, 855 cm^{-1} (epoxide); NMR (CCl_4) δ 0.83 (s, 6, CH_3), 1.03 (s, 3, CH_3), 1.12 (s, 3, CH_3), 2.67 ppm (s, 1, oxymethine). Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.80; H, 11.69.

***trans*-Octahydro-5,5,8a-trimethyl-1-methylene-2(1*H*)-naphthalenone (9b) and *trans*-4a,5,6,7,8,8a-Hexahydro-4,4a,8,8-tetramethyl-2(1*H*)-naphthalenone (9a).** Freshly distilled di-*n*-propylamine (4.86 g, 6.58 mL, 48 mmol) was dissolved in dry tetrahydrofuran (100 mL) and cooled to 0 °C (ice bath). *n*-Butyllithium (24 mL, 2 M, 48 mmol) was added dropwise with stirring. After 10 min the ice bath was removed and epoxide 8 (3.02 g, 16 mmol) in dry tetrahydrofuran (20 mL) was added dropwise over a period of 10 min. The resulting mixture was then heated at reflux for 6 h. The reaction mixture was cooled in an ice bath, quenched with 10% hydrochloric acid (400 mL), and extracted with ether (3 × 100 mL). The ether extract was washed with water (3 × 50 mL) and saturated sodium chloride solution (50 mL), then dried ($MgSO_4$), filtered, and evaporated in vacuo to give 3.6 g of crude allylic alcohols.

To a solution of pyridine (15.5 g, 15.8 mL, 0.196 mol) in dry methylene chloride (75 mL), under nitrogen, cooled to 0 °C (ice bath) was added anhydrous chromium trioxide (9.8 g, 98 mmol) in small amounts. This mixture was then allowed to stir for 30 min. The crude allylic alcohol (3.4 g, 16.35 mmol) dissolved in dry methylene chloride (25 mL) was added over a period of 10 min and then allowed to stir for about 1 h at room temperature. A very dark solid separated as the reaction proceeded. The total reaction mixture then was filtered through a short column of either silica gel or Florisil and eluted with methylene chloride (500 mL). The total eluent was washed with 10% hydrochloric acid solution (4 × 50 mL), water (3 × 50 mL), and saturated sodium chloride solution (50 mL), then dried ($MgSO_4$), filtered, and evaporated in vacuo to give 2.87 g of crude ketones.

This mixture (4.7 g, combined from several experiments) was chromatographed on silica gel (250 g) and eluted with 15% ether–85% petroleum ether. Fractions 6 to 16 gave 2.35 g (47%) pure enone **9b,** distilled bulb to bulb at 65 °C (0.5 mm): IR (CCl_4) 1685 (C=O), 1600 cm^{-1} (C=C); NMR (CCl_4) δ 0.97 (s, 3, CH_3), 1.00 (s, 3, CH_3), 1.05 (s, 3, CH_3), 4.93, 5.36 ppm (dd, 2, $=CH_2$). Fractions 20 to 30 gave **9a** 1.16 g (22%), distilled bulb to bulb at 65–68 °C (0.5 mm); IR (CCl_4) 1670 (C=O), 1615 cm^{-1} (C=C); NMR (CCl_4) δ 0.92 (s, 3, CH_3), 0.96 (s, 3, CH_3), 1.13 (s, 3, CH_3), 5.53 ppm (bs, 1, —COCH=). Analysis of ketone **9b** was reported in the literature. Analysis of ketone **9a:** Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found C, 81.60; H, 10.88.

(1α, 4aβ, 8aα)-1-[(2,5-Dimethoxyphenyl)methyl]octahydro-5,5,8a-trimethyl-2(1*H*)-naphthalenone (10). Freshly cut potassium metal (2.737 g, 70 mg atom), anhydrous magnesium chloride (analytical grade dried under vacuum at 150 °C for 2 h, 3.427 g, 36 mmol), and potassium iodide (6 g, 36 mmol) were mixed under dry nitrogen atmosphere in 1,2-dimethoxyethane (100 mL) and heated under reflux for 3 h. The reaction mixture became a dark and viscous liquid; then 2,5-dimethoxy-1-bromobenzene (7.6 g, 35 mmol) was added and the mixture was allowed to reflux for another 2 h. The reaction mixture then was cooled to 0 °C; copper(I) iodide (1.4 g) was added and the mixture was stirred for 5 min. Enone **9b** (1.5 g, 7.3 mmol) dissolved in 1,2-dimethoxyethane (20 mL) was added dropwise and stirred for 15 min at 0 °C (ice bath) and for 30 min at room temperature. The

reaction was then quenched with acetic anhydride (20 mL) and stirred overnight. The reaction mixture was then diluted with saturated ammonium chloride solution (400 mL) and extracted with ether)4 × 100 mL). The combined ethereal extracts were washed with water (3 × 50 mL) and saturated sodium chloride solution (100 mL), then dried ($MgSO_4$), filtered, and evaporated in vacuo to give dark brown oil (7 g). This crude material was treated for 20 h at room temperature with 10% alcoholic potassium hydroxide solution (100 mL). Most of the alcohol was removed in vacuo, then diluted with water (200 mL) and extracted with ether (3 × 100 mL). The combined ethereal extracts were washed with water (3 × 50 mL) and saturated sodium chloride solution (50 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo to give a brown oil. This material was distilled (bulb to bulb) to remove low boiling material such as 1,4-dimethoxybenzene and unreacted 2,5-dimethoxybromobenzene, bp 70–98 °C (0.7 mm). Residue, 2.35 g (94%), was recrystallized from petroleum ether to give 1.74 g (70%) of pure ketone **10**: mp 108–109 °C; IR (CCl_4) 1710 (C=O), 1605, 1585 (aromatic), 1040 (aromatic methoxyl), 855 cm^{-1} (aromatic 1,4-disubstitution); NMR (CCl_4) δ 0.80 (s, 3, CH_3), 0.90 (s, 3, CH_3), 0.97 (s, 3, CH_3), 2.66 (bs, 2, benzylic), 3.72 (s, 3, OCH_3), 3.76 (s, 3, OCH_3), and 6.67 ppm (m, 3, aromatic). Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.61; H, 9.66.

(±)-Zonarol Dimethyl Ether (1a). Sodium hydride (57% oil dispersion, 0.421 g, 10 mmol) was washed with dry *n*-pentane several times to remove oil and then flushed with nitrogen. Dimethyl sulfoxide [10 mL, triple distilled from $CaH_2/NaNH_2$ (98:2, respectively) and then distilled onto freshly activated molecular sieves type 4A] was introduced and heated at 80 °C for 30 min until the evolution of hydrogen was complete. Methyltriphenylphosphonium bromide (3.572 g, 10 mmol) was added as a solid and stirred for 10 min. The reaction mixture became deep orange in color. At this stage, ketone **10** (0.689 g, 2 mmol) dissolved in hot dimethyl sulfoxide (5 mL) was added and stirred at 80 °C for 24 h. The reaction mixture was then cooled to room temperature, diluted with water (150 mL), and extracted with ether (3 × 100 mL). The combined ethereal extracts were washed with water (3 × 25 mL) and saturated sodium chloride solution (50 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo to give a solid which was passed through a column of silica gel to remove triphenylphosphine oxide. The resulting material, 0.718 g, was recrystallized from pentane to give white crystalline solid, (±)-zonarol dimethyl ether (**1a**) (0.636 g, 93%), mp 117–118 °C: IR (CCl_4) 1640 (C=C), 1585 (aromatic), 1040 (aromatic methoxyl) 855 cm^{-1} (aromatic 1,4-disubstitution); NMR (CCl_4) δ 0.83 (s, 3, CH_3), 0.86 (s, 3, CH_3), 0.90 (s, 3, CH_3), 2.66 (d, 2, benzylic), 3.60 (s, 3, aromatic methoxyl), 3.76 (s, 3, aromatic methoxyl), 4.63 (d, 2, $=CH_2$), 6.53 ppm (m, 3, aromatic). Anal. Calcd for $C_{23}H_{34}O_2$: C, 80.65; H, 10.01. Found: C, 80.74; H, 10.07.

(±)-Isozonarol Dimethyl Ether (2a). To a solution of ketone **10** (0.344 g, 1 mmol) in anhydrous ether (10 mL) was added methyllithium in ether (2 mL, 2 mol, 4 mmol) at 0 °C and stirred for 4 h at room temperature; excess methyllithium was quenched by adding ice water (20 mL), and the mixture was extracted with ether (3 × 20 mL). The combined ethereal extracts were washed with water (2 × 10 mL) and saturated sodium chloride solution (10 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo to give 0.37 g of crude alcohol: IR (CCl_4) 3400–3600 (OH), 1600, 1580 cm^{-1} (aromatic); NMR (CCl_4) δ 0.90 (s, 9, CH_3), 1.05 (s, 3, CH_3), 3.7 ppm (s, 3, aromatic methoxyl), (s, 3, aromatic methoxyl), 6.67 (m, 3, aromatic). The above crude alcohol (0.37 g) was dissolved in dry dimethyl sulfoxide (10 mL) and heated at 150 °C for 18 h. The mixture was cooled to room temperature, diluted with water (50 mL), and extracted with ether (3 × 25 mL). The combined ethereal extracts were washed with water (2 × 10 mL) and saturated sodium chloride solution (25 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo to give a gummy material. This material was passed through a column of silica gel to remove dimethyl sulfoxide and then chromatographed on 15% silver nitrate silica gel (20 g, 75 mL column volume) with 15% ether–85% petroleum ether as eluent; fractions 3 and 4 gave 0.185 g of (±)-isozonarol dimethyl ether (**2a**) and fractions 6 and 7 gave 0.036 g of (±)-zonarol dimethyl ether (**1a**). (±)-Isozonarol dimethyl ether could not be crystallized (dried by vacuum, 0.1 mm, 24 h): IR (CCl_4) 1660 (C=C), 1610, 1585 (aromatic), 1050 (aromatic methoxyl), 865 cm^{-1} (aromatic, 1,4-disubstitution); NMR (CCl_4) δ 0.90 (s, 9, CH_3), 2.61 (m, 2, benxylic), 3.70 (s, 3, aromatic methoxyl), 3.77 (s, 3, aromatic methoxyl), 5.30 (bs, 1, —C=CH), 6.63 ppm (m, 3, aromatic). Anal. Calcd for $C_{23}H_{34}O_2$: C, 80.65; H, 10.01. Found: C, 80.49; H, 10.12.

(±)-Zonarol (1b). Lithium hydride (0.079 g or 0.15 g of 57% oil dispersion, 10 mmol) was freed from oil with pentane and flushed with dry nitrogen. Hexamethylphosphoric triamide (HMPA, 3 mL, refluxed over CaH_2 and distilled onto freshly activated molecular sieves type 4 A) was added and stirred. To this slurry, *n*-butyl mercaptan (0.901 g, 1.11 mL, 10 mmol) was added dropwise and stirred until hydrogen evolution was complete (10 min). Pure (±)-zonarol dimethyl ether (0.172 g, 0.5 mmol) in HMPA (4 mL) was added and the solution was heated at 150 °C for 24 h. The reaction mixture was cooled to room temperature, diluted with 10% hydrochloric acid solution (50 mL), and extracted with ether (3 × 30 mL). The combined ethereal extracts were washed with water (3 × 10 mL) and saturated sodium chloride solution (25 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo to give 0.27 g of crude product. This material was purified by passing through a column of silica gel and eluting with 35% ether–65% petroleum ether to give 0.152 g (90%) of pure (±)-zonarol (**1b**) as a gummy material: bp 155–160 °C (0.01 mm); IR ($CHCl_3$) 3300–3600 (OH), 1660 cm^{-1} (C=C); NMR ($CDCl_3$) δ 0.80 (s, 3, CH_3), 0.83 (s, 3, CH_3), 0.90 (s, 3, CH_3), 2.70 (d, 2, benzylic), 4.76 (d, 2, $=CH_2$), 6.56 ppm (m, 3, aromatic). Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.22; H, 9.55.

(±)-Isozonarol (2b). Lithium hydride (0.04 g, 0.07 g of 57%, 5 mmol) was washed with pentane to remove mineral oil and was flushed with dry nitrogen. Hexamethylphosphoric triamide (HMPA, 2 mL) was added and stirred. To this slurry, *n*-butyl mercaptan (0.451 g, 0.535 mL, 5 mmol) was added dropwise and stirred until the evolution of hydrogen had stopped (10 min). (±)-Isozonarol dimethyl ether (0.069 g, 0.2 mmol) in HMPA (2 mL) was added and heated at 145 ± 5 °C for 26 h. The reaction mixture was cooled to room temperature, diluted with 10% hydrochloric acid solution and extracted with ether (3 × 25 mL). The combined ethereal extracts were washed with water (3 × 10 mL) and saturated sodium chloride solution (25 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo to give 0.075 g of crude product. This material was purified by chromatography on silica gel, eluting with 65% petroleum ether–35% ether. Fractions 6 to 10 gave 0.05 g (86%) of pure (±)-isozonarol (**2b**): bp 155–165 °C (0.01 mm); IR ($CHCl_3$) 3225–3600 (OH), 1620, 1580 cm^{-1} (aromatic); NMR ($CDCl_3$) δ 0.90 (s, 9, CH_3), 2.60 (m, 2, benzylic), 5.40 (bs, 1, —C=CH—), 6.67 ppm (m, 3, aromatic). Anal. Calcd for $C_{23}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.05; H, 9.46.

1,2,3,4,5,6,7,8-Octahydro-1,1,5,5-tetramethylnaphthalene (11). To a solution of tertiary alcohol **6** (1.1 g, 4 mmol), in dry benzene (50 mL), a crystal of *p*-toluenesulfonic acid was added and the solution was allowed to reflux for 4 h. The reaction mixture was then cooled to room temperature, washed with saturated sodium bicarbonate solution (25 mL), water (25 mL), and saturated sodium chloride solution (25 mL), filtered through $MgSO_4$, and evaporated in vacuo to give 0.95 g of crude product. This material was distilled bulb to bulb at 45 ± 5 °C (0.1 mm) to give 0.85 g (80%) of colorless alkene **11**: IR (CCl_4) 1675 (C=C), 1375, 1355 cm^{-1} (*gem*-dimethyl); NMR (CCl_4) δ 1.00 ppm (s, 12, CH_3). Anal. Calcd for $C_{14}H_{24}$: C, 87.42; H, 12.58. Found: 87.39; H, 12.61.

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Registry No.—**1a,** 63757-96-0; **1b,** 63813-82-1; **2a,** 63757-97-1; **2b,** 63813-83-2; **3,** 52782-49-7; **4,** 65516-59-8; **5,** 65556-24-3; **6** isomer 1, 65516-60-1; **6** isomer 1 2,3-dehydro deriv, 65516-65-6; **6** isomer 2, 65516-61-2; **6** isomer 2 2,3-dehydro deriv, 65516-64-5; **7,** 65516-62-3; **8** isomer 1, 65556-25-4; **8** isomer 2, 65556-27-6; **9a,** 65516-63-4; **9b,** 65556-26-5; **10,** 65516-66-7; **11,** 56239-59-9; 2,5-dimethoxy-1-bromobenzene, 25245-34-5; decahydro-1-(2,5-dimethoxybenzyl)-2,5,5,8a-tetramethyl-2-naphthol, 65516-67-8.

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(21) We are grateful to Professor W. Fenical for providing natural samples of zonarone and isozonarone which were converted to the respective methyl ethers (**1a** and **1b**) by reduction ($NaBH_4$, CH_3OH) and *O*-alkylation (CH_3I, CaO, Me_2SO, room temperature, 24 h).
(22) The names of each of the compounds were obtained from Professor Kurt L. Loening, Director of Nomenclature, Chemical Abstracts Service, Columbus, Ohio, 43210.

Stereoselective Biomimetic Total Synthesis of 6α-Methyl-19-norsteroids

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Cyclization of the chiral substrate 3-methyl-2-[(*E*)-6′-(*m*-methoxyphenyl)-3′-heptenyl]-2-cyclopenten-1-ol (**6**) was investigated. In addition to high stereo- and regioselectivity almost complete optical induction by the methyl substituent was observed: with stannic chloride at −70 °C ~75% of the tetracyclic products consisted of 3-methoxy-6α,17-dimethyl-1,3,5(10),13(17)-gonatetraene (**8a**). This compound was converted into the 3-methyl ethers of *dl*-6α-methylestrone (**11**) and *dl*-6α-methylestradiol-17β (**13**), thus giving access to 6α-methyl-19-norsteroids.

In the last decade the biomimetic polyene cyclization reaction has proved to be a fruitful approach to the total synthesis of polycyclic natural products.[1] Practical applications for the synthesis of steroids were most extensively explored by Johnson and co-workers.[1a,b] One of the many contributions by this group was a stereospecific total synthesis of *dl*-estrone.[2]

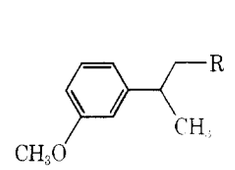
In this paper we report an extension of the latter synthesis, starting with a polyolefinic substrate which carries a methyl substitutent at the pro-C-6 atom.[3] The purpose of this modification was (a) to see whether the newly introduced chiral center would effect asymmetric induction in the cyclization and (b) to examine the practicality of this synthesis as a route to 6α-methyl-19-norsteroids.[17]

The substrate used in the *dl*-estrone synthesis[2] lacks a stable chiral center, leading to racemic products.[4] The presence of a stable chiral center in the substrate allows early resolution (an important condition for an efficient steroid synthesis) and formation at will of the steroid with the natural or unnatural configuration depending on which enantiomer of the substrate is used, *provided a high degree of optical induction by the chiral center takes place.* Examples of optical induction in the biomimetic synthesis of 11α-methyl- and 11α-hydroxyprogesterone were reported by the Stanford group.[3a,b] In the present case the chiral center is further removed from the reaction center so that optical induction is not an a priori obvious matter.

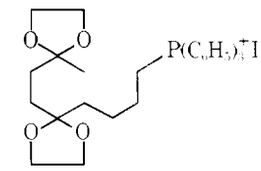
6α-Methyl-19-norsteroids were shown to be compounds with potent hormonal activity.[5] They have been prepared by partial synthesis via a somewhat troublesome route[6] and in racemic form via a Smith–Torgov type total synthesis.[5] Interestingly the latter synthesis produces 6β-methylestradiol derivatives as the major initial products, whereas the 6α isomers are the biologically more active ones.[7]

Synthesis of the Substrate

Methyl 3-(*m*-methoxyphenyl)butyrate (**1**) was prepared in 68% yield by addition of lithium dimethylcuprate to methyl *m*-methoxycinnamate. This synthesis is shorter than the published one[5] and more versatile allowing the introduction of alkyl groups other than methyl by a proper choice of the organometallic reagent. It should be noted that **1** is an asymmetric compound and therefore, at least in principle, resolvable.

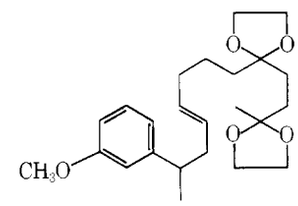


1, R = $COOCH_3$
2, R = CHO

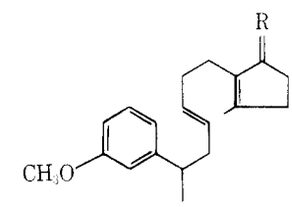


3

Elegant asymmetric syntheses of β-substituted acids[8a] and aldehydes[8b] have been reported. The aldehyde **2**, obtained by reduction of **1** with diisobutylaluminium hydride in 72% yield, was condensed with the phosphorane derived from **3**[9] employing Wittig–Schlosser conditions.[10] The olefin **4** was



4



5, R = O
6, R = H(OH)

isolated in 80% yield (over 95% trans isomer by NMR analysis). Acid-catalyzed hydrolysis followed by base-catalyzed cyclodehydration produced the cyclopentenone **5** in 84% yield.

The ketone **5** was reduced with lithium aluminum hydride to the substrate **6** in quantitative yield. Due to its instability **6** was subjected to cyclization immediately after workup.

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