Stereoselective Total Synthesis of the Tetracyclic Diterpenes Hibaol and Dihydrohibaene[1]

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Thermolysis and desulfurization of 5-[(*n*-butylthio)methylene]-2-[2-(4-methoxybenzocyclobutenyl)ethyl]-2-methylcyclopentanone (**3**) and the 5-methoxybenzocyclobutenyl analogue (**4**) gave stereoselectively 1,2,3,4,4aα,9,10,10a-octahydro-7-methoxy-2α-methyl-2β,10aβ-ethanophenanthren-1-one (**17**) and the 6-methoxy isomer **18**, potential intermediates. Intermediate **18** was stereoselectively converted into the tetracyclic diterpenoid containing a bicyclo[3.2.1]octane system hibaol (**1**). This also constitutes a total synthesis of dihydrohibaene (**2**).

The bridged bicyclo[3.2.1]octane system is found as the C/D ring in numerous tetracyclic diterpenoids.[2] Although many approaches to the synthesis of kaurene, hibaene, and related tetracyclic diterpenoids have been reported,[3-15] their major drawbacks are the construction of the bridged bicyclo[3.2.1]octane moiety and the stereochemical introduction of the methyl substituents at the appropriate positions. Based on our continued interest in natural product synthesis via cycloaddition reactions of *o*-quinodimethanes, we now wish to report a novel synthetic route to the tetracyclic diterpenoids having a bicyclo[3.2.1]octane system which overcomes these obstacles. This new procedure has been used for the stereoselective synthesis of hibaol (**1**),[16] which has previously been correlated with dihydrohibaene **2**[17] and possibly can also be applied to the synthesis of the kaurene- and phyllocladene-types of diterpenoids.

In our two-part synthesis of hibaol (**1**), a simple and stereoselective synthesis of the A ring-aromatized tetracyclic compound **8** was achieved from the olefinic benzocyclobutene **4** via the *o*-quinodimethane **6** by intramolecular stereo- and regioselective cycloaddition.[18-21] This is followed by the stereoselective introduction of three methyl groups at the C_{4b} and C_8 positions with the help of the oxygen function at the C_6 position.

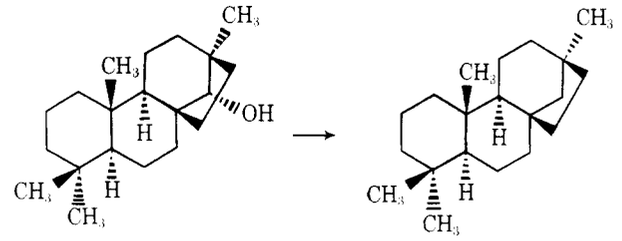
Results and Discussion

Model Experiment. To determine whether thermolysis of benzocyclobutenes would give stereoselectively the tetracycle containing the bicyclo[3.2.1]octane system the model benzocyclobutene **3** was prepared as follows.

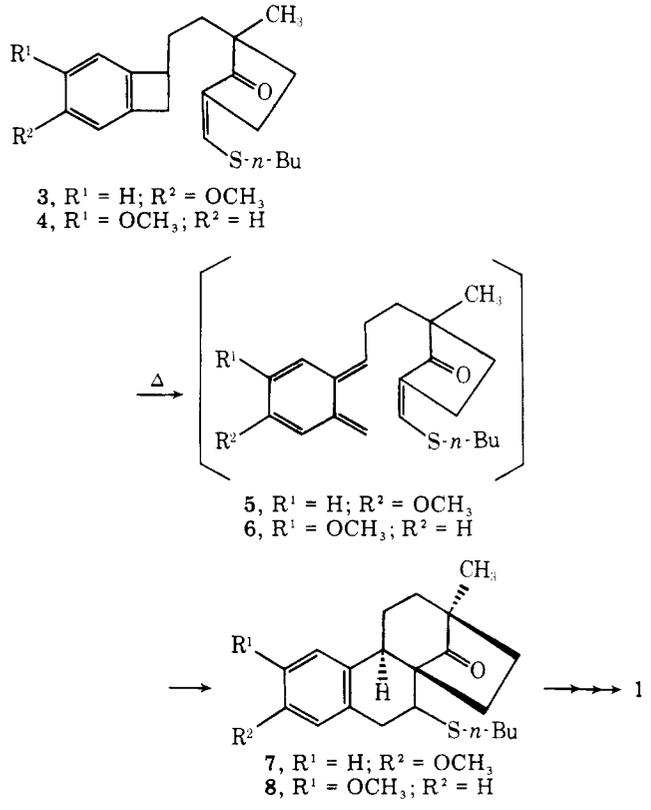
4-Methoxybenzocyclobutenyl iodide (**9**),[21] a synthon containing the A ring and a part of the B and C rings, was treated with the pyrrolidine enamine of cyclopentanone, a synthon for the D ring, in boiling benzene to give 60% yield of the 2-benzocyclobutenylethylcyclopentanone (**11**). The latter now has all the carbon atoms in the hibaene ring system except for the one at the 7 position. To introduce the latter at the C_2 position regioselectively and also the dienophile at the C_5 position, the benzocyclobutene **11** was condensed with ethyl formate in the presence of sodium hydride in benzene at room temperature and the resulting crude 5-hydroxymethylenecyclopentanone (**13**) was treated with *n*-butyl mercaptan and *p*-toluenesulfonic acid in boiling benzene with azeotropic removal of water to give the 5-*n*-butylthiomethylenecyclopentanone (**14**) in 79% overall yield. Reaction of **14** with methyl iodide in the presence of potassium *tert*-butoxide in *tert*-butyl alcohol at room temperature gave 48% of the target 2-methylcyclopentanone **3** [IR, α,β-unsaturated carbonyl group at 1680 cm^{-1}; NMR (δ in CCl_4) one olefinic proton at 7.25 as a distorted doublet having a J value of 2 Hz].

Heating **3** in *o*-dichlorobenzene at 180 °C for 13 h in a current of nitrogen afforded in 65% yield the tetracyclic compound **7** [IR, saturated carbonyl group at 1730 cm^{-1}; NMR lacked a resonance of olefinic proton]. Finally, desulfurization of **7** with Raney nickel in boiling ethanol furnished 86.2% of the intermediate **17** [IR, saturated carbonyl group at 1725 cm^{-1}; NMR (δ in CCl_4) methyl resonance at 1.00 as a singlet]. This suggests that the relative configuration of the C_2-methyl and the C_{4a}-hydrogen is cis (**17A**) rather than trans (**17B**) since *cis*-**18** (vide infra) exhibits a similar chemical shift. It would appear that the cis relationship in **17A**, obtained via **7**, is generated from **5A** rather than **5B** since only the former is without steric repulsion between H_a and H_b.

Scheme I



Scheme II



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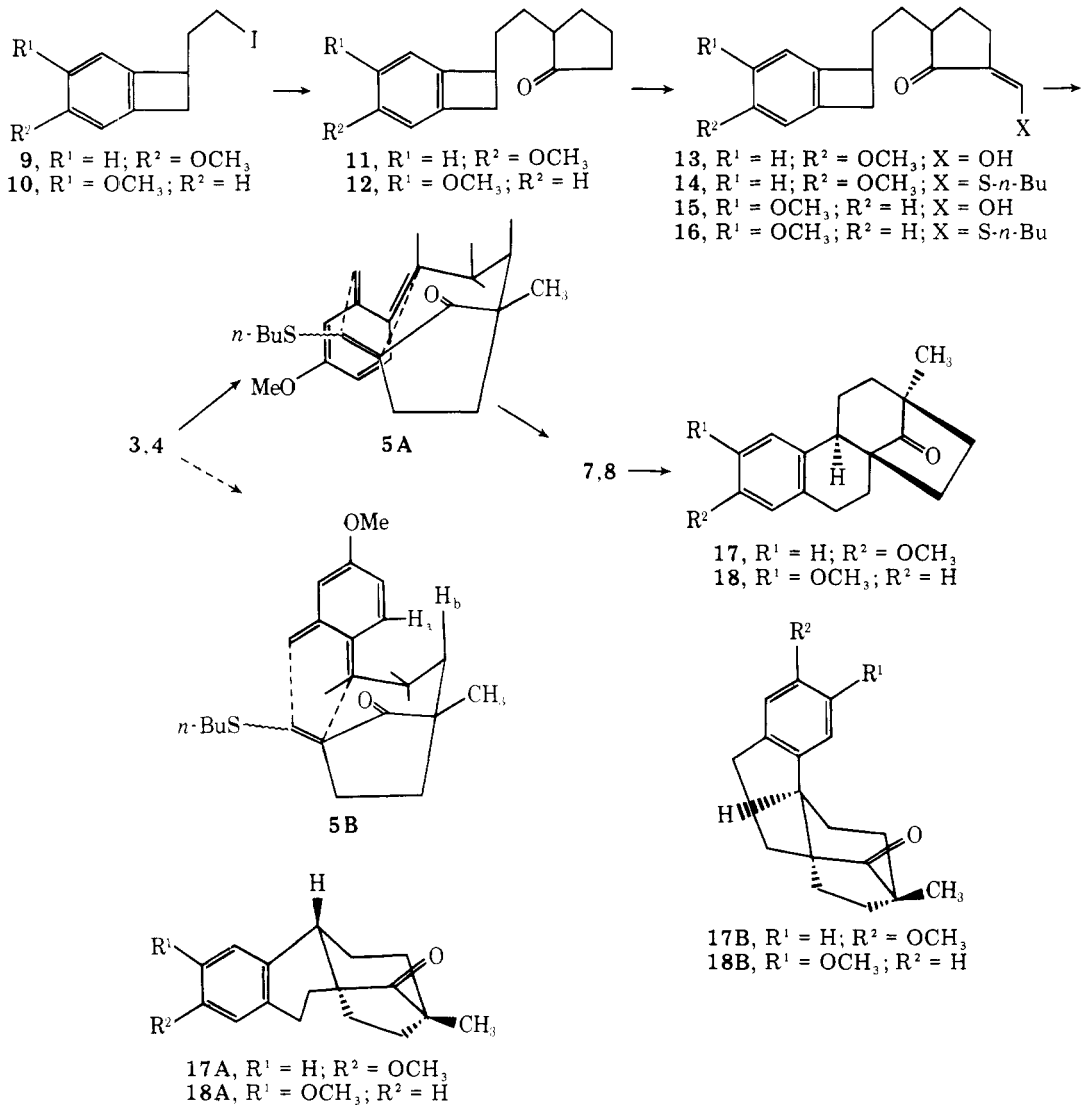
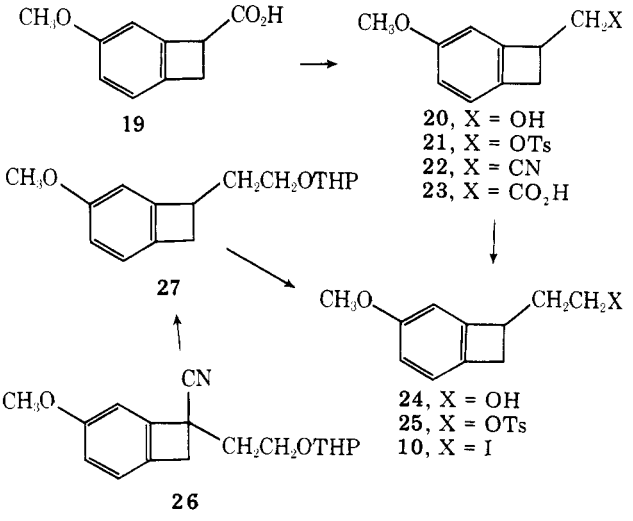
Scheme III



Having accomplished a simple synthesis of a bicyclo[3.2.1]octane system fused with a hydroaromatic moiety, we next turned our attention to the preparation of the related compound **18** and its transformation into hibaol **1** and dihydrohibaene **2**. This would permit assigning the stereochemistry of **17** and **18** and also demonstrate the utility of this reaction for the synthesis of stachene-type of compounds.

Synthesis of Hibaol (1). The straightforward preparation of the benzocyclobutene **4**, the key precursor of **18**, involved (Scheme IV) the reduction of 5-methoxybenzocyclobutene-1-carboxylic acid (**19**)[22] with lithium aluminum hydride in tetrahydrofuran at room temperature followed by treatment of the resulting alcohol **20** with *p*-toluenesulfonyl chloride in pyridine at room temperature to give the tosylate **21** in 52.2% overall yield. Cyanation of the tosylate **21** with sodium cyanide in dimethyl sulfoxide at room temperature furnished the nitrile **22** which was hydrolyzed with ethanolic potassium hydroxide to afford 1-carboxymethyl-5-methoxybenzocyclobutene (**23**) (70.2% overall yield from the tosylate **21**) followed by quantitative reduction with lithium aluminum hydride to the corresponding benzocyclobutenylethyl alcohol (**24**). Alternatively, the latter was conveniently prepared by reductive decyanation of 1-cyano-1-tetrahydropyranyloxyethyl-5-methoxybenzocyclobutene (**26**)[23] with sodium in liquid ammonia to **27**, followed by cleavage of the tetrahydropyranyl group with hydrochloric acid in methanol to provide the alcohol **24** (71.8% overall yield from **26**). Finally, treatment of

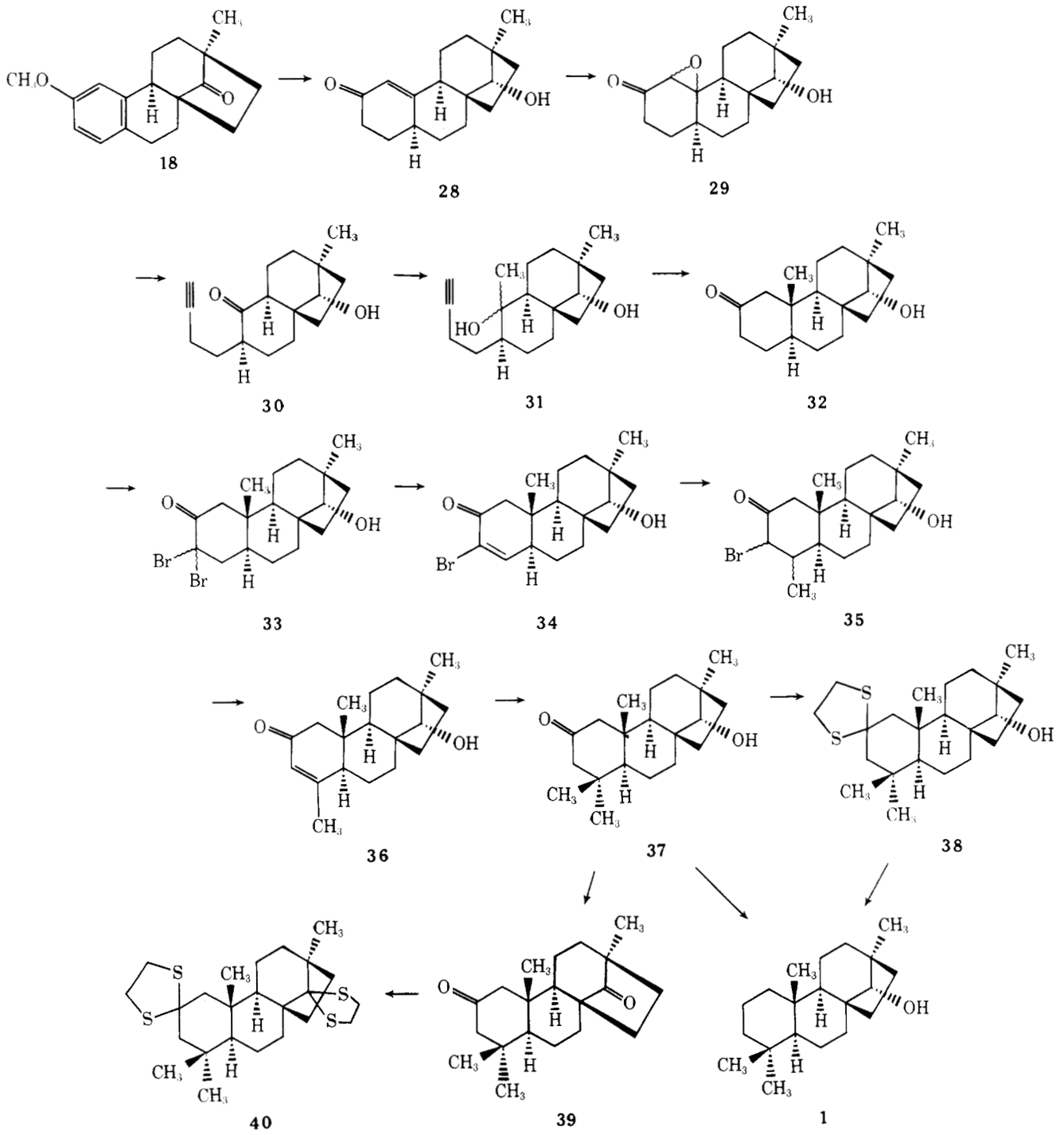
Scheme IV



the alcohol **24** with *p*-toluenesulfonyl chloride in pyridine at room temperature furnished the tosylate **25** (52.7% yield), which was converted in 93.2% yield into the iodide **10** by reaction with sodium iodide in boiling acetone.

For the conversion of the benzocyclobutenylethyl iodide (**10**) into the hibaol precursor **18** (Scheme III), **10** was con-

Scheme V



densed with the pyrrolidine enamine of cyclopentanone in boiling benzene to give 98% yield of the benzocyclobutenylethylcyclopentanone **12** which was treated with ethyl formate in the presence of sodium hydride in benzene at room temperature followed by reaction with *n*-butyl mercaptan and *p*-toluenesulfonic acid in boiling benzene to afford the 5-[(*n*-butylthio)methylene]cyclopentanone (**16**) in 75% overall yield from **12**. Methylation of **16** with methyl iodide in the presence of sodium amide in liquid ammonia furnished in 80.2% yield the key intermediate **4** [IR, α,β-unsaturated carbonyl group at 1680 cm^{-1}; NMR (δ in CCl_4) an olefinic proton at 7.16 as a broad singlet].

Heating **4** in *o*-dichlorobenzene at 180 °C for 6 h in a current of nitrogen afforded 78.9% of the tetracyclic compound **8** [IR, saturated carbonyl group at 1730 cm^{-1}; NMR lacked the resonance of the olefinic proton]. Desulfurization of **8** with Raney nickel in boiling ethanol then gave the important intermediate **18** in 98.7% yield. The relative configuration of the C_2-methyl and the C_{4a}-hydrogen was tentatively as cis (**18A**) rather than trans (**18B**) since the NMR spectrum showed the C_2-methyl at the usual chemical shift of δ 1.02 in CCl_4.

Our attention focused next on the introduction of methyl groups at the appropriate positions of the functionalized precursor **18**. Based on the following reaction sequences (Scheme V) stereoselective insertion of the C_{4b} methyl group in the β orientation was attained in moderate yield. Birch reduction of **18** with sodium in liquid ammonia followed by treatment with hydrochloric acid in methanol at room temperature afforded the enone **28** [IR, α,β-unsaturated carbonyl and hydroxyl groups at 1660 and 3500 cm^{-1}, respectively; NMR (δ in $CDCl_3$) 5.90 and 3.23 as broad singlets for the olefinic proton and methine proton attached to the hydroxyl

group, respectively]. The latter's half-band width resonance of 4.5 Hz by long-range coupling to the C_{12}-proton indicates an α orientation for the hydroxyl group. Oxidation of the enone **28** with hydrogen peroxide in the presence of sodium hydroxide at room temperature gave 56.5% of the epoxide **29** which was treated with *p*-toluenesulfonylhydrazine in acetic acid at −20 °C to afford the acetylenic ketone **30** in 91.8% yield. Reaction of **30** with methyllithium in ether at 0 °C yielded 81.8% of the acetylenic alcohol **31** which was successively treated with trifluoroacetic anhydride in trifluoroacetic acid at −18 °C and then hydrochloric acid in methanol to furnish 55.2% of the tetracyclic ketone **32** [IR, saturated carbonyl and hydroxyl groups at 1700 and 3500 cm^{-1}, respectively]. The stereochemical assignment of **32** was based on the similarity of the half-band width ($\Delta Wh/2$ = 1.20 Hz) of the methyl group at the C_{10} position with the proposed[24] half-band width ($\Delta Wh/2$ = 1.01 ± 0.35 Hz) of the methyl group having three anticoplanar protons at the C_{10} position in *trans*-decalin derivatives. Treatment of **32** with bromine in the presence of sodium acetate in chloroform at 0 °C afforded 67.1% of the dibromide **33** which was dehydrobrominated with lithium bromide and lithium carbonate in dimethylformamide at 125–130 °C to give 74.5% of the α-bromoenone **34** followed by lithium dimethyl cuprate in ether at 0 °C to yield the 1,4-addition product **35** in 90.9% yield. Dehydrobromination of **35** with lithium bromide and lithium carbonate in dimethylformamide afforded 52.1% of the second enone **36** followed by treatment with lithium dimethyl cuprate in ether at 0 °C to furnish 68.1% of the 4,4-dimethylated compound **37**. Thus, all the required substituents of hibaol (**1**) with the correct stereochemistry were introduced by using the oxygen-function in the aromatic ring of the key compound **18**.

Finally, **37** was transformed as follows into dihydrohibaene (**2**). Jones oxidation of **37** afforded 50.3% of the diketone **39** which was converted into the dithioketal **40** in 77.2% yield by reaction with ethanedithiol in the presence of boron trifluoride etherate in acetic acid at room temperature. However, since attempts to desulfurize **40** were unsuccessful, reaction of **37** with ethanedithiol in the presence of boron trifluoride etherate in acetic acid afforded 30.5% of the thioketal **38** which was treated with Raney nickel in boiling ethanol to furnish 76.4% of hibaol (**1**), identical in NMR with authentic sample.[25] Hibaol (**1**) was also obtained in 16.6% yield by treatment of **37** with hydrazine hydrate and hydrazine dihydrochloride in triethylene glycol followed by potassium hydroxide at 205–215 °C. Since hibaol (**1**) was correlated to dihydrohibaene (**2**) by Wenkert and Kumazawa,[17] this constitutes a formal total synthesis of dihydrohibaene.

The above novel route to hibaol (**1**) and dihydrohibaene (**2**) appears to have potentiality as a general method for the synthesis of other tetracyclic diterpenoids containing a bicyclo[3.2.1]octane system.

Experimental Section

General. All melting points are uncorrected. Infrared (IR) spectra were recorded on a Hitachi EPI-3 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were measured on a JEOL JNM-PMX-60 spectrometer. Chemical shifts are reported as δ values relative to internal tetramethylsilane (Me_4Si). Mass spectra were taken on a Hitachi RMU-7 spectrometer.

5-Methoxybenzocyclobutenylmethyl *p*-Toluenesulfonate (21). To a suspension of 76.8 g (2.01 mol) of lithium aluminum hydride in 900 mL of anhydrous tetrahydrofuran was added a solution of 240 g (1.35 mol) of 5-methoxybenzocyclobutene-1-carboxylic acid (**19**)[22] in 500 mL of anhydrous tetrahydrofuran under stirring and the reaction mixture was then stirred for 6 h at room temperature. After addition of 10% aqueous sodium hydroxide solution, filtration of the inorganic material, followed by evaporation of tetrahydrofuran, the aqueous layer was extracted three times with 500-mL portions of ether. The ethereal extract was combined, washed with water and saturated sodium chloride solution, and then dried over anhydrous sodium sulfate. Evaporation of the solvent afforded 144 g of the alcohol **20** as a yellow oil: IR ($CHCl_3$) 3400 cm^{-1}; NMR (CCl_4) δ 2.7 (1 H, dd, J = 1.5, 14 Hz, C_2H), 3.00 (1 H, broad s, OH), 3.2 (1 H, dd, J = 4.5, 14 Hz, C_2H), 3.67 (3 H, s, OCH_3), and 6.45–6.95 (3 H, m, ArH); *m/e* 164 (M^+).

A solution of 143 g of the crude alcohol **20** obtained above, 180 g (0.95 mol) of *p*-toluenesulfonyl chloride, and 1.8 L of pyridine was stirred for 13 h at room temperature. The resulting reaction mixture was poured into 10% hydrochloric acid solution under ice cooling and the crystals precipitated were collected and then recrystallized from methanol to give 233 g (52.2%) of the tosylate **21** as colorless needles: mp 94–96 °C; NMR (CCl_4) δ 2.35 (3 H, s, CH_3), 2.66 (1 H, dd, J = 2, 13 Hz, C_2H), 3.20 (1 H, dd, J = 5, 13 Hz, C_2H), 3.7 (3 H, s, OCH_3), 4.15 (2 H, d, J = 7 Hz, $-CH_2OTs$), 6.4–6.9 (3 H, m, ArH), 7.2 (2 H, d, J = 8 Hz, ArH), and 7.66 (2 H, d, J = 8 Hz, ArH); *m/e* 318 (M^+).

Anal. Calcd for $C_{17}H_{18}O_4S$: C, 64.14; H, 5.70. Found: C, 64.05; H, 5.89.

5-Methoxybenzocyclobutenylmethyl Cyanide (22). To a solution of 28 g (570 mmol) of sodium cyanide in 200 mL of dimethyl sulfoxide was added a solution of 114 g (360 mmol) of the tosylate **21** in 380 mL of dimethyl sulfoxide and the resulting solution was stirred for 13 h at room temperature. The resulting reaction mixture was poured into 500 mL of water and extracted three times with 500 mL of ether. The ethereal layer was washed with water and saturated sodium chloride solution and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded 63 g of the cyanide **22** as a yellow oil: IR ($CHCl_3$) 2250 cm^{-1}; NMR (CCl_4) δ 2.6 (2 H, d, J = 7 Hz, CH_2CN), 2.7–3.7 (3 H, m, C_1H, C_2H_2), 3.75 (3 H, s, OCH_3), and 6.6–7.0 (3 H, m, ArH); *m/e* 173 (M^+).

5-Methoxybenzocyclobutenylacetic Acid (23). To a stirred solution of 127 g of the crude nitrile **22**, 56 g of potassium hydroxide, and 600 mL of ethanol 100 mL of water was added and the resulting mixture was then refluxed for 3 h. After evaporation of ethanol, 200 mL of water was again added and extracted two times with 150 mL of ether. The aqueous phase was acidified with 10% hydrochloric acid solution and extracted four times with 150 mL of ether. The combined ethereal extract was washed with water and saturated sodium chloride solution and then dried over anhydrous sodium sulfate. Evaporation of the solvent gave a white solid, which was recrystallized from benzene–hexane to give 99 g (70.2% from **21**) of the carboxylic acid **23** as colorless needles: mp 49–50 °C; IR ($CHCl_3$) 1706 cm^{-1}; NMR (CCl_4) δ 2.73 (2 H, d, J = 7 Hz, CH_2CO_2H), 2.75–3.69 (3 H, m, C_1H, C_2H_2), 3.70 (3 H, s, OCH_3), and 6.5–6.97 (3 H, m, ArH); *m/e* 192 (M^+).

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.43; H, 6.27.

2-(5-Methoxybenzocyclobutenyl)ethanol (24). To a slurry of 3.2 g (84 mmol) of lithium aluminum hydride in 400 mL of anhydrous tetrahydrofuran was added 9.9 g (52 mmol) of the carboxylic acid **23** in 40 mL of anhydrous tetrahydrofuran and the resulting solution was stirred for 13 h at room temperature. After quenching the reaction mixture with 30% aqueous sodium hydroxide solution, filtering the inorganic substance, and evaporating the solvent, the residue was extracted with ether. The ethereal extract was washed with water and saturated sodium chloride solution and dried over anhydrous sodium sulfate. Evaporation of ether afforded a yellow oil, which was chromatographed on 200 g of silica gel using benzene–hexane (4:1) to give 8.8 g (95.9%) of the alcohol **24** as a colorless oil: IR ($CHCl_3$) 3400 cm^{-1}; NMR (CCl_4) δ 1.71–2.11 (2 H, m, CH_2CH_2OH), 2.4–3.5 (3 H, m, C_1H, C_2H_2), 3.5–3.8 (2 H, m, CH_2CH_2OH), 3.67 (3 H, s, OCH_3), and 6.25–6.96 (3 H, m, ArH); *m/e* 178 (M^+).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.87; H, 7.93.

2-(5-Methoxybenzocyclobutenyl)ethyl *p*-Toluenesulfonate (25). To a solution of 9.2 g (52 mmol) of the alcohol **24** and 90 mL of pyridine was added 12 g (63 mmol) of *p*-toluenesulfonyl chloride and the resulting solution was stirred for 13 h at room temperature. The reaction mixture was poured into 10% hydrochloric acid and extracted with ether. The ethereal extract was washed with water and saturated sodium chloride solution. After drying over anhydrous sodium sulfate, the organic extract was evaporated and the residue was chromatographed on 200 g of silica gel using benzene to give 8.38 g (52.7%) of the tosylate **25** as a colorless oil: NMR (CCl_4) δ 1.75–2.35 (2 H, m, CH_2CH_2OTs), 2.43 (3 H, s, $ArCH_3$), 2.5–3.65 (3 H, m, C_1H, C_2H_2), 3.67 (3 H, s, OCH_3), 4.11 (2 H, t, J = 6 Hz, CH_2CH_2OTs), 6.4–6.95 (3 H, m, ArH), 7.35 (2 H, d, J = 8 Hz, ArH), and 7.77 (2 H, d, J = 8 Hz, ArH); *m/e* 332 (M^+).

Anal. Calcd for $C_{18}H_{20}O_4S$: C, 65.05; H, 6.07. Found: C, 64.75; H, 6.04.

2-(5-Methoxybenzocyclobutenyl)ethyl Pyranyl Ether (27). To a stirred solution of 12.5 g (44 mmol) of 1-(1-cyano-5-methoxy-

benzocyclobutenyl)ethyl pyranyl ether (**26**),[23] 2 mL of absolute ethanol, 50 mL of anhydrous tetrahydrofuran, and 500 mL of liquid ammonia was added 1 g (45 mmol) of sodium at −70 °C and the solution was stirred for 30 min at the same temperature. After addition of an excess of crystalline ammonium chloride followed by evaporation of the solvent, the residue was diluted with saturated aqueous ammonium chloride solution and extracted three times with 150 mL of portions of ether. The ethereal layer was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. Removal of the solvent afforded a reddish gum, which was chromatographed on 200 g of silica gel using benzene–hexane (3:2) to give 10.0 g (87.9%) of **27** as a colorless syrup: NMR (CCl_4) δ 1.2–2.33 (8 H, m), 2.4–4.0 (6 H, m), 3.71 (3 H, s, OCH_3), 4.54 (1 H, broad s, OC**H**O), and 6.43–7.03 (3 H, m, ArH); *m/e* 178 ($M^+ - 84$).

2-(5-Methoxybenzocyclobutenyl)ethanol (24) from 27. A mixture of 10 g (38 mmol) of the pyranyl ether **27,** 200 mL of methanol, and 20 mL of 10% hydrochloric acid solution was stirred for 4 h. After evaporation of the solvent, 50 mL of water was added to the residue and the resulting solution was extracted three times with 80 mL of ether. The ethereal extract was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. Removal of the solvent gave a yellow oil, which was chromatographed on 100 g of silica gel using benzene–hexane (4:1) to afford 5.53 g (81.7%) of **24** as a colorless oil, identical with the compound **24,** obtained by reduction of the carboxylic acid **23** as described previously, by its IR ($CHCl_3$) and NMR (CCl_4) spectral comparisons.

2-(5-Methoxybenzocyclobutenyl)ethyl Iodide (10). A solution of 8.38 g (25 mmol) of the tosylate **25,** 5.5 g (37 mmol) of sodium iodide, and 100 mL of acetone was refluxed for 4 h. After evaporation of the solvent, 50 mL of water was added and the resulting solution was extracted with ether. The ethereal extract was washed with 5% aqueous sodium thiosulfate solution and saturated sodium chloride solution and then dried over anhydrous sodium sulfate. After removal of the solvent, the residue was chromatographed on 160 g of silica gel using hexane to give 6.78 g (93.2%) of the iodide **10** as a colorless oil: NMR (CCl_4) δ 1.96–2.4 (2 H, m, C**H**$_2$CH_2I), 2.5–3.67 (5 H, m, CH_2C**H**$_2$I, C_1H, C_2H_2), 3.7 (3 H, s, OCH_3), and 6.54–6.97 (3 H, m, ArH); *m/e* 288 (M^+).

Anal. Calcd for $C_{11}H_{13}OI$: C, 45.83; H, 4.55. Found: C, 45.57; H, 4.59.

2-[2-(4-Methoxybenzocyclobutenyl)ethyl]cyclopentanone (11). A mixture of 0.7 g (5.1 mmol) of pyrrolidine enamine of cyclopentanone,[26] 20 mL of dry benzene, and 1.4 g (4.9 mmol) of 2-(4-methoxybenzocyclobutenyl)ethyl iodide (**9**)[21] was reflexed for 23 h. After addition of 10 mL of water, the resulting mixture was refluxed for 1 h and then treated with 2 mL of 10% sulfuric acid. The organic layer was separated and the aqueous layer was extracted three times with 20-mL portions of ether. The combined ethereal extract was washed with 5% aqueous sodium thiosulfate solution and dried over anhydrous sodium sulfate. Evaporation of the solvent left a yellow oil, which was chromatographed on 30 g of silica gel using benzene to give 717 mg (60%) of the benzocyclobutenylethylcyclopentanone **11** as a colorless oil: IR ($CHCl_3$) 1725 cm^{-1}; NMR (CCl_4) δ 3.7 (3 H, s, OCH_3), 6.5–7.0 (3 H, m, ArH); *m/e* 244 (M^+).

2-[2-(5-Methoxybenzocyclobutenyl)ethyl]cyclopentanone (12). A solution of 9.8 g (71.6 mmol) of pyrrolidine enamine of cyclopentanone[26] and 12.5 g (45 mmol) of the iodide **10** in 100 mL of dry benzene was refluxed for 13 h. After addition of 10 mL of water in the above solution followed by further refluxing for 1 h, 2 mL of 10% sulfuric acid was added. After separation of the benzene layer, the aqueous layer was extracted three times with 50-mL portions of ether. The combined extract was washed with 5% aqueous sodium thiosulfate solution and dried over anhydrous sodium sulfate. After removal of the solvent, the resulting crude product was chromatographed on 100 g of silica gel using benzene to give 10.3 g (98%) of **12** as a colorless oil: IR ($CHCl_3$) 1725 cm^{-1}; NMR (CCl_4) δ 3.70 (3 H, s, OCH_3) and 6.93–6.50 (3 H, m, ArH); *m/e* 244 (M^+).

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.50; H, 8.43.

5-[(*n*-Butylthio)methylene]-2-[2-(5-methoxybenzocyclobutenyl)ethyl]cyclopentanone (16). To a solution of 10.5 g (43 mmol) of **12** and 4.3 g (89 mmol) of sodium hydride (50% in oil) in 200 mL of dry benzene was added a solution of 5.4 g (72 mmol) of ethyl formate in 50 mL of dry benzene at room temperature. After being stirred at room temperature for 30 min, 100 mL of water was added to the reaction mixture. The resulting aqueous layer was acidified with 10% hydrochloric acid solution and extracted three times with 100-mL portions of ether. The combined ethereal extract was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. Removal of the solvent afforded 7.3 g of the crude formyl derivative **15** which was used for the next reaction without further purification: IR ($CHCl_3$) 1665 cm^{-1}; NMR (CCl_4) δ 3.72 (3 H, s, OCH_3), 6.48–7.05 (3 H, m, ArH), and 7.25 (1 H, broad s, C**H**OH); *m/e* 272 (M^+).

A solution of 9.9 g of the crude compound **15,** 3.5 g (39 mmol) of *n*-butyl mercaptan, a catalytic amount of *p*-toluenesulfonic acid, and 250 mL of dry benzene was refluxed for 1 h under an atmosphere of nitrogen. After the reaction mixture had been cooled to room temperature, 100 mL of 10% sodium hydroxide solution was added to it. The resulting mixture was extracted three times with 100-mL portions of ether and the organic combined extract was washed with water and saturated sodium chloride solution and then dried over anhydrous sodium sulfate. Evaporation of the solvent afforded a reddish gum, which was chromatographed on 200 g of silica gel using benzene to give 11 g (75.0% from **12**) of the thiomethylene derivative **16** as colorless needles (ethanol): mp 71–72 °C; IR ($CHCl_3$) 1680 cm^{-1}; NMR (CCl_4) δ 3.65 (3 H, s, OCH_3), 6.48–6.93 (3 H, m, ArH), and 7.16 (1 H, broad s, C**H**S-*n*-Bu); *m/e* 344 (M^+).

Anal. Calcd for $C_{21}H_{28}O_2S$: C, 73.22; H, 8.19. Found: C, 72.86; H, 8.14.

5-[(*n*-Butylthio)methylene]-2-[2-(4-methoxybenzocyclobutenyl)ethyl]cyclopentanone (14). To a solution of 600 mg (2.46 mmol) of **11,** 200 mg (4.16 mmol) of sodium hydride (50% in oil), and 30 mL of dry benzene was added a solution of 300 mg (4.08 mmol) of ethyl formate in 10 mL of dry benzene at room temperature and the resulting mixture was stirred for 30 min at room temperature. The same workup of this mixture as above afforded 447 mg of the crude **13** as a yellow oil, which was used for the following reaction without further purification: IR ($CHCl_3$) 1665 cm^{-1}; *m/e* 272 (M^+).

A solution of 440 mg of the above oil **13,** 150 mg (1.67 mmol) of *n*-butyl mercaptan, a catalytic amount of *p*-toluenesulfonic acid, and 20 mL of dry benzene was refluxed under an atmosphere of nitrogen for 2 h. The same treatment as for **16** gave 440 mg (79% from **11**) of the thiomethylene derivative **14** as a colorless oil: IR ($CHCl_3$) 1680 cm^{-1}; NMR (CCl_4) δ 3.67 (3 H, s, OCH_3), 6.3–6.9 (3 H, m, ArH), and 7.05 (1 H, broad s, C**H**S-*n*-Bu); *m/e* 344 (M^+).

5-[(*n*-Butylthio)methylene]-2-[2-(5-methoxybenzocyclobutenyl)ethyl]-2-methylcyclopentanone (4). To a stirred solution of 16.2 g (47 mmol) of the thiomethylene derivative **16,** sodium amide (prepared from 1.3 g of sodium with an excess of liquid ammonia), and 100 mL of anhydrous tetrahydrofuran was added dropwise 9.7 g (68 mmol) of methyl iodide in 20 mL of anhydrous tetrahydrofuran at −70 °C. After stirring had been continued for 1.5 h at the same temperature as above, the reaction mixture was treated with an excess of crystalline ammonium chloride and the solvent was evaporated to give a reddish residue, which was diluted with 100 mL of saturated aqueous ammonium chloride solution. The resulting mixture was extracted three times with 100 mL of ether, and the ethereal extract was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. Removal of the solvent afforded a reddish gum, which was chromatographed on 200 g of silica gel using benzene to give 13.5 g (80.2%) of **4** as a colorless oil: IR ($CHCl_3$) 1680 cm^{-1}; NMR (CCl_4) δ 0.99 (3 H, s, CH_3), 3.64 (3 H, s, OCH_3), 6.46–6.93 (3 H, m, ArH), and 7.16 (1 H, broad s, C**H**S-*n*-Bu); *m/e* 358 (M^+).

Anal. Calcd for $C_{22}H_{30}O_2S$: C, 73.71; H, 8.44. Found: C, 73.43; H, 8.26.

5-[(*n*-Butylthio)methylene]-2-[2-(4-methoxybenzocyclobutenyl)ethyl]-2-methylcyclopentanone (3). To a stirred solution of potassium *tert*-butoxide (prepared from 400 mg of potassium) in 15 mL of *tert*-butyl alcohol was added a solution of 440 mg (1.28 mmol) of the thiomethylene derivative **14** in 2 mL of absolute *tert*-butyl alcohol at room temperature under an atmosphere of nitrogen. After the stirring had been continued for 30 min at the same temperature, 250 mg (1.77 mmol) of methyl iodide was added to the above mixture and the resulting solution was then stirred for 17 h at the same temperature. To this reaction mixture 20 mL of water was added and the resulting mixture was extracted three times with 20 mL of ether. The ethereal extract was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. Evaporation of the solvent left a brown oil, which was chromatographed on 10 g of silica gel using benzene–hexane (2:1) to give 200 mg (48%) of **3** as a colorless oil: IR ($CHCl_3$) 1680 cm^{-1}; NMR (CCl_4) δ 1.00 (3 H, s, CH_3), 3.73 (3 H, S, OCH_3), 6.53 (1 H, d, J = 2 Hz, ArH), 6.65 (1 H, dd, J = 2, 8 Hz, ArH), 6.93 (1 H, d, J = 8 Hz, ArH), and 7.25 (1 H, distorted d, J = 2 Hz, C**H**S-*n*-Bu); *m/e* 358 (M^+).

10-*n*-Butylthio-1,2,3,4,4aα,9,10,10a-octahydro-6-methoxy-2α-methyl-2β,10aβ-ethanophenanthren-1-one (8). A solution of 6.26 g (17 mmol) of **4** in 630 mL of *o*-dichlorobenzene was stirred under an atmosphere of nitrogen for 6 h at 180 °C. After evaporation of the solvent, the residue was chromatographed on 100 g of silica gel using benzene–hexane (3:1) to give 5.34 g (78.9%) of the tetracyclic compound **8** as a colorless oil: IR ($CHCl_3$) 1730 cm^{-1}; NMR (CCl_4)

δ 1.05 (3 H, s, CH_3) 3.70 (3 H, s, OCH_3), 6.43–6.98 (3 H, m, ArH); *m/e* 358 (M^+).

Anal. Calcd for $C_{22}H_{30}O_2S$: C, 73.71; H, 8.44. Found: C, 73.89; H, 8.54.

10-*n*-Butylthio-1,2,3,4,4aα,9,10,10a-octahydro-7-methoxy-2α-methyl-2β,10aβ-ethanophenanthren-1-one (7). A solution of 200 mg (0.56 mmol) of **3** in 20 mL of *o*-dichlorobenzene was stirred under an atmosphere of nitrogen for 13 h at 180 °C. After the same workup as for **8**, 130 mg (65%) of the tetracyclic compound **7** was obtained as a colorless oil: IR ($CHCl_3$) 1730 cm^{-1}; NMR (CCl_4) δ 1.05 (3 H, s, CH_3), 3.70 (3 H, s, OCH_3), 6.46 (1 H, d, J = 2 Hz, ArH), 6.55 (1 H, dd, J = 2, 8 Hz. ArH), and 6.96 (1 H, d, J = 8 Hz, ArH); *m/e* 358 (M^+).

1,2,3,4,4aα,9,10,10a-Octahydro-6-methoxy-2α-methyl-2β,10aβ-ethanophenanthren-1-one (18). A mixture of 5.34 g (15 mmol) of **8**, 50 g of Raney nickel, and 400 mL of ethanol was refluxed for 1.5 h under stirring. After filtration of Raney nickel, the solvent was removed to give a colorless oil, which was chromatographed on 100 g of silica gel using benzene–hexane (1:2) to afford 3.97 g (98.7%) of **18** as a colorless oil: IR ($CHCl_3$) 1725 cm^{-1}; NMR (CCl_4) δ 1.02 (3 H, s, CH_3), 3.71 (3 H, s, OCH_3), and 6.43–7.03 (3 H, m, ArH); *m/e* 270 (M^+).

Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.18; H, 8.19.

1,2,3,4,4aα,9,10,10a-Octahydro-7-methoxy-2α-methyl-2β,10aβ-ethanophenanthren-1-one (17). A mixture of 120 mg (0.34 mmol) of **7**, 2 g of Raney nickel, and 30 mL of ethanol was refluxed for 30 min under stirring. The same workup as for **18** gave 78 mg (86.2%) of **17** as colorless prisms (hexane): mp 104–105 °C; IR ($CHCl_3$) 1725 cm^{-1}; NMR (CCl_4) δ 1.00 (3 H, s, CH_3), 3.70 (3 H, s, OCH_3), 6.50 (1 H, d, J = 2 Hz, ArH), 6.55 (1 H, dd, J = 2, 8 Hz, ArH), and 7.00 (1 H, d, J = 8 Hz, ArH); *m/e* 270 (M^+).

Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.10; H, 8.25.

2-Oxo-$\Delta^{1,10}$-18,19,20-trinorhibaol (28). To a solution of 60 mg (2.6 mmol) of sodium in 50 mL of liquid ammonia a solution of 540 mg (2 mmol) of **18**, 5 mL of anhydrous tetrahydrofuran, and 1 mL of absolute ethanol was added at −70 °C and the reaction mixture was stirred for 2 h at the same temperature. After addition of an excess of crystalline ammonium chloride followed by evaporation of the solvent, 50 mL of water was added and the resulting mixture was extracted three times with 50-mL portions of ether. The ethereal layer was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was dissolved in 50 mL of ethanol. The resulting solution was treated with 20 mL of 10% aqueous hydrochloric acid solution and then the reaction mixture was stirred for 4 h at room temperature under a nitrogen atmosphere. The reaction mixture was diluted with 50 mL of water and then extracted three times with 50-mL portions of ether. The combined ethereal extract was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded a yellow gum, which was chromatographed on 10 g of silica gel using benzene–ethyl acetate (10:1) to give 253 mg (48.7%) of **28** as colorless needles (benzene–hexane): mp 136–137 °C; IR ($CHCl_3$) 3500 and 1660 cm^{-1}; NMR ($CDCl_3$) δ 0.98 (3 H, s, CH_3), 3.23 (1 H, broad s, CHOH), and 5.90 (1 H, broad s, >C=CHC=O); *m/e* 260 (M^+).

Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.17; H, 9.08.

1,10-Epoxy-2-oxo-18,19,20-trinorhibaol (29). To a solution of 200 mg (0.725 mmol) of **28** in 20 mL of methanol was added 1 mL (882 mmol) of 30% hydrogen peroxide at room temperature. After stirring for 1 h at room temperature, the reaction mixture was diluted with 50 mL of water and extracted three times with 50-mL portions of ether. The combined ethereal extract was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. Removal of the solvent left a colorless gum, which was chromatographed on 5 g of silica gel using benzene–ethyl acetate (10:1) to give 120 mg (56.5%) of the epoxide **29** as colorless needles (benzene–hexane): mp 160–161 °C; IR ($CHCl_3$) 3500 cm^{-1}; NMR ($DCDl_3$) δ 0.95 (3 H, s, CH_3), 3.16 (1 H, broad s, CHOH), and 3.45 (1 H, broad s, –COCCHC=O); *m/e* 276 (M^+).

Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.59; H, 8.61.

3β-(3-Butynyl)-7β,9β-ethano-8α-hydroxy-7α-methyl-4-oxo-*trans*-decalin (30). A solution of 1.4 g (5 mmol) of the epoxide **29** and 1.08 g (5.8 mmol) of *p*-toluenesulfonylhydrazine in 15 mL of acetic acid and 15 mL of dichloromethane was stirred for 15 h at −20 °C and then stirred for 4 h at room temperature. The reaction mixture was diluted with 100 mL of water and extracted three times with 100 mL of ether. The ethereal extract was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. Evaporation of the solvent left a yellow gum, which was chromatographed on 20 g of silica gel using benzene to afford 1.21 g (91.8%) of the acetylenic ketone **30** as colorless needles (benzene–hexane): mp 131–133 °C; IR ($CHCl_3$) 3500, 3310, and 1700 cm^{-1}; NMR ($CDCl_3$) δ 0.97 (3 H, s, CH_3) and 3.22 (1 H, broad s, CHOH); *m/e* 260 (M^+).

Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.31; H, 9.17.

3β-(3-Butynyl)-7β,9β-ethano-4,8α-dihydroxy-4,7α-dimethyl-*trans*-decalin (31). To a solution of 1.21 g (4.65 mmol) of the acetylenic ketone **30** was added 50 mL of a 1.2 molar ethereal solution of methyllithium at 0 °C and the mixture was stirred for 15 min at the same temperature, and then 10 min at room temperature. The reaction mixture was treated with 20 mL of water, and the ethereal layer was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue obtained was chromatographed on 20 g of silica gel using benzene to give 1.05 g (81.8%) of the acetylenic alcohol **31** as a colorless oil: IR ($CHCl_3$) 3500 and 3310 cm^{-1}; NMR ($CDCl_3$) δ 0.94 (3 H, s, CH_3), 1.17 (3 H, s, CH_3), and 3.00 (1 H, broad s, CHOH); *m/e* 276 (M^+).

Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 77.93; H, 10.31.

2-Oxo-18,19-dinorhibaol (32). To a mixture of 5 mL of trifluoroacetic acid and 1.5 mL of trifluoroacetic anhydride 18 mg of the acetylenic alcohol **31** was added at −18 °C and the resulting mixture was stirred for 20 min at the same temperature. After evaporation of the solvent, the residue was dissolved in a mixture of 2 mL of acetone and 2 mL of methanol, and the resulting solution was treated with 0.5 mL of 10% aqueous hydrochloric acid solution and then stirred for 1.5 h at room temperature. The reaction mixture was neutralized with saturated sodium bicarbonate aqueous solution and the solvent was removed. The resulting mixture was extracted three times with 20 mL of ether. The ethereal extract was washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent left a yellow gum, which was chromatographed on 1 g of silica gel using benzene–ethyl acetate (20:1) to give 37.5 mg (55.2%) of **32** as colorless needles (benzene–hexane): mp 171–173 °C; IR ($CHCl_3$) 3500 and 1700 cm^{-1}; NMR ($CDCl_3$) δ 0.80 (3 H, s, CH_3), 0.95 (3 H, s, CH_3), 3.01 (1 H, broad s, CHOH); *m/e* 276 (M^+).

Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.21; H, 10.15.

3,3-Dibromo-2-oxo-18,19-dinorhibaol (33). To a mixture of 1.88 g (6.8 mmol) of **32**, 1.2 g (15 mmol) of sodium acetate, and 40 mL of chloroform was added a solution of 2.24 g (14 mmol) of bromine in 5 mL of chloroform at 0 °C under stirring. After stirring for 1 h at 0 °C, the reaction mixture was poured into 20 mL of water. The organic layer was washed with saturated sodium bicarbonate solution and saturated sodium chloride solution and then dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was chromatographed on 20 g of silica gel using benzene to give 1.98 g (67.1%) of the dibromide **22** as colorless needles (benzene–hexane): mp 59–61 °C; IR ($CHCl_3$) 3500 and 1723 cm^{-1}; NMR ($CDCl_3$) δ 0.80 (3 H, s, CH_3), 0.96 (3 H, s, CH_3), and 3.04 (1 H, broad s, CHOH); *m/e* 432 (M^+), 434 ($M^+ + 2$), 436 ($M^+ + 4$).

Anal. Calcd for $C_{14}H_{26}O_2Br_2$: C, 49.79; H, 6.04. Found: C, 49.47; H, 5.99.

3-Bromo-2-oxo-18,19-dinor-Δ^3-hibaol (34). A solution of 2.63 g (6 mmol) of the dibromide **33**, 1.46 g (16 mmol) of lithium bromide, 1.22 g (16 mmol) of lithium carbonate, and 60 mL of anhydrous dimethylformamide was stirred for 3 h at 125–130 °C under an atmosphere of nitrogen. After cooling, the reaction mixture was diluted with 100 mL of water and extracted three times with 100 mL of benzene. The combined organic extract was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. Removal of the solvent gave a yellow oil, which was chromatographed on 40 g of silica gel using benzene to afford 1.6 g (74.5%) of the α-bromo enone **34** as colorless prisms (ethanol): mp 97–98 °C; IR ($CHCl_3$) 3500 and 1680 cm^{-1}; NMR ($CDCl_3$) δ 0.95 (6 H, s, 2 × CH_3), 3.05 (1 H, broad s, CHOH), and 7.05 (1 H, d, J = 1 Hz, CH=CBrC=O); *m/e* 352 (M^+), 354 ($M^+ + 2$).

Anal. Calcd for $C_{18}H_{25}O_2Br$: C, 61.19; H, 7.13. Found: C, 61.31; H, 7.15.

3-Bromo-2-oxo-18-norhibaol (35). To a stirred solution of lithium dimethyl cuprate [prepared from 380 mg (2 mmol) of cuprous iodide and 3.4 mL of a 1.2 molar ethereal solution of methyllithium] in 50 mL of anhydrous ether was added a solution of 100 mg (0.284 mmol) of the α-bromo enone **34** at 0 °C. After stirring for 1 h at 0 °C, the reaction mixture was quenched by addition of 50 mL of saturated ammonium chloride solution. The ethereal layer was washed with saturated ammonium chloride solution and saturated sodium chloride solution and then dried over anhydrous sodium sulfate. After evap-

oration of the solvent, the residue was chromatographed on 2 g of silica gel using chloroform to give 95 mg (90.9%) of the monomethylated α-bromo ketone **35** as colorless needles (benzene): mp 111–113 °C; IR ($CHCl_3$) 3500 and 1720 cm^{-1}; NMR ($CDCl_3$) δ 0.83 (3 H, s, CH_3), 0.88 (3 H, d, J = 6 Hz, CH_3), 0.93 (3 H, s, CH_3) 3.03 (1 H, broad s, CHOH), and 4.26 (1 H, d, J = 5.3 Hz, CHBrC=O); m/e 368 (M^+) and 370 ($M^+ + 2$).

Anal. Calcd for $C_{19}H_{29}O_2Br$: C, 61.75; H, 7.92. Found: C, 61.28; H, 7.58.

2-Oxo-Δ³-18-norhibaol (36). A solution of 90 mg (0.245 mmol) of the α-bromo ketone **35**, 70 mg (0.8 mmol) of lithium bromide, 60 mg (0.81 mmol) of lithium carbonate, and 10 mL of anhydrous dimethylformamide was stirred for 4 h at 125–130 °C. After cooling to room temperature, the reaction mixture was diluted with 50 mL of water and extracted three times with 50 mL of benzene. The combined benzene extract was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. The residue obtained by evaporation of the solvent was chromatographed on 2 g of silica gel using chloroform to give 36.7 mg (52.1%) of the enone **36** as colorless prisms (benzene): mp 154–156 °C; IR ($CHCl_3$) 3500 and 1680 cm^{-1}; NMR ($CDCl_3$) δ 0.87 (3 H, s, CH_3), 0.90 (3 H, s, CH_3), 1.92 (3 H, s, CH_3), 2.99 (1 H, broad s, CHOH), and 5.81 (1 H, broad s, CHC=O); m/e 288 (M^+).

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 78.94; H, 9.69.

2-Oxohibaol (37). To a stirred solution of lithium dimethyl cuprate [prepared from 570 mg (3 mmol) of cuprous iodide and 5 mL of a 1.2 molar ethereal solution of methyllithium] in 50 mL of dry ether was added a solution of 100 mg (0.347 mmol) of the enone **36** at 0 °C. After being stirred for 2 h at 0 °C the reaction mixture was quenched by addition of 50 mL of saturated ammonium chloride solution. The ethereal layer was separated, washed with saturated sodium chloride solution, and dried over anhydrous sodium sulfate. Evaporation of the solvent and successive chromatography of the residue on 2 g of silica gel using benzene–chloroform (7:3) gave 72 mg (68.1%) of the ketone **37** as colorless prisms (benzene–hexane): mp 125–127 °C; IR ($CHCl_3$) 3620 and 1700 cm^{-1}; NMR ($CDCl_3$) δ 0.90 (3 H, s, CH_3), 0.95 (6 H, s, 2 × CH_3), 1.08 (3 H, s, CH_3), and 3.04 (1 H, broad s, CHOH); m/e 304 (M^+).

Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59. Found: C, 78.92; H, 10.93.

2,14-Dioxodihydrohibaene (39). To a solution of 38 mg (0.125 mmol) of the keto alcohol **37** in 5 mL of acetone was added 0.2 mL of a 8 N solution of chromic acid[27] [prepared from 26.72 g of chromium trioxide, 23 mL of concentrated sulfuric acid, and enough water to make the total volume of 100 mL as a solution] at 0 °C and stirring was continued for 10 min at the same temperature. The reaction mixture was diluted with 20 mL of water and extracted three times with 20 mL of ether. The combined ethereal extract was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. Removal of the solvent afforded a yellow oil, which was chromatographed on 1 g of silica gel using benzene to give 19 mg (50.3%) of the diketone **39** as a colorless glass: IR ($CHCl_3$) 1720 and 1700 cm^{-1}; NMR ($CDCl_3$) δ 0.91 (3 H, s, CH_3), 1.02 (6 H, s, 2 × CH_3), and 1.09 (3 H, s, CH_3); m/e 302 (M^+).

2,2:14,14-Diethylenedithiodihydrohibaene (40). A solution of 19 mg (0.063 mmol) of the diketone **39**, 12 mg (0.19 mmol) of ethanedithiol, and a catalytic amount of boron trifluoride etherate in 2 mL of acetic acid was stirred for 30 h at room temperature. After dilution of the reaction mixture with 30 mL of water, the mixture was extracted three times with 20 mL of chloroform. The combined chloroform extract was washed with water, 5% sodium hydroxide aqueous solution, and water and then dried over anhydrous sodium sulfate. Evaporation of the solvent gave a residue which was chromatographed on 500 mg of silica gel using benzene to give 22 mg (77.2%) of the dithioketal **40** as a colorless oil: NMR ($CDCl_3$) δ 0.92, 1.04, 1.07, and 1.19 (12 H, each s, 4 × CH_3) and 2.74–3.54 (8 H, m, 2 × SCH_2CH_2S); m/e 454 (M^+).

2,2-Ethylenedithiohibaol (38). A solution of 36 mg (0.118 mmol) of **37**, 18.8 mg (0.2 mmol) of ethanedithiol, a catalytic amount of boron trifluoride etherate, and 4 mL of acetic acid was stirred for 18 h at room temperature. The reaction mixture was diluted with 30 mL of water and extracted three times with 30 mL of chloroform. The combined chloroform extract was washed with water, 5% sodium hydroxide aqueous solution, and water and dried on anhydrous sodium sulfate. Removal of the solvent gave a yellow oil, which was chromatographed on 500 mg of silica gel using benzene to afford 13 mg (30.5%) of the thioketal **38** as a colorless oil: IR ($CHCl_3$) 3500 cm^{-1}; NMR ($CDCl_3$) δ 0.93 (6 H, s, 2 × CH_3), 1.05 (3 H, s, CH_3), 1.20 (3 H, s, CH_3), 2.92 (1 H, broad s, CHOH), and 3.03–3.46 (4 H, m, SCH_2CH_2S); m/e 360 (M^+).

Hibaol (1). (a) From 37. A mixture of 120 mg (0.395 mmol) of the ketone **37**, 1.32 g (20 mmol) of hydrazine hydrate, 336 mg (9.52 mmol) of hydrazine dihydrochloride, and 9 g of triethylene glycol was stirred for 3.5 h at 125–130 °C, to which 490 mg (8.75 mmol) of potassium hydroxide was then added and the mixture was stirred for 3 h at 205–215 °C. After cooling at room temperature, the reaction mixture was diluted with 50 mL of water and extracted three times with 50 mL of chloroform. The combined chloroform extract was washed with water and saturated sodium chloride solution and then dried over anhydrous sodium sulfate. Evaporation of the solvent gave a residue which was chromatographed on 500 mg of silica gel using hexane to give 19 mg (16.6%) of hibaol (**1**) as a colorless powder: mp 113–116 °C; IR ($CHCl_3$) 3500 cm^{-1}; NMR ($CDCl_3$) δ 0.805 (3 H, s, CH_3), 0.85 (3 H, s, CH_3), 0.92 (6 H, s, 2 × CH_3), and 2.88 (1 H, broad s, CHOH); m/e 290 (M^+).

Anal. Calcd for $C_{20}H_{34}O$: C, 82.69; H, 11.80. Found: C, 82.14; H, 11.89.

(b) From 38. A mixture of 13 mg (0.036 mmol) of the thioketal **38**, 200 mg of Raney nickel, and 2 mL of ethanol was refluxed for 5 h under stirring. After removal of catalyst, evaporation of the solvent left a colorless oil, which was chromatographed on 200 mg of silica gel using hexane to give 8 mg (76.4%) of hibaol (**1**) as a colorless powder, which was identical with hibaol (**1**) obtained above by its IR ($CHCl_3$) and NMR ($CDCl_3$) spectral comparisons.

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Microbial Stereodifferentiating Reduction in [2.2]Metacyclophane Derivatives[1,2]

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Incubation of (±)-1-oxo[2.2]metacyclophane (**9**) with *Rhodotorula rubra* gave a mixture of (+)-axial alcohol **10** and (−)-equatorial alcohol **11** both with remarkably high optical purity. The same high stereoselectivity was observed when *R. rubra* was incubated with 1,10-dioxo[2.2]metacyclophane (**12**), which was converted into (−)-axial-equatorial diol **14** via (−)-axial ketol **13**. *R. rubra* was also found to reduce (±)-[2.2]metacyclophane-4-aldehyde (**20**), affording a 13% yield of the (+)-4-hydroxymethyl derivative **21** with 11.7% optical purity.

We[1-3] have been studying the microbial reduction of bridged cyclic ketones with a constrained carbonyl group in a wide variation of molecular frameworks (**1–8**, Chart I); common features among these are a conformationally rigid structure as well as the absence of a cyclohexanone moiety fixed in a chair conformation. The latter feature seems to make these substrates particularly conspicuous among numerous cyclic ketones whose microbial reductions have been well documented.[4-7] Our study on the stereochemistry of their metabolites coupled with our observation of the marked enantiomeric selectivity exhibited by *Curvularia lunata* and *Rhodotorula rubra* toward gyrochiral[8] ketones with a carbonyl group located on the C_2 axis led us to propose a quadrant rule which predicts the stereochemistry of the metabolites, eventually providing information on the absolute configurations of their molecular frameworks.

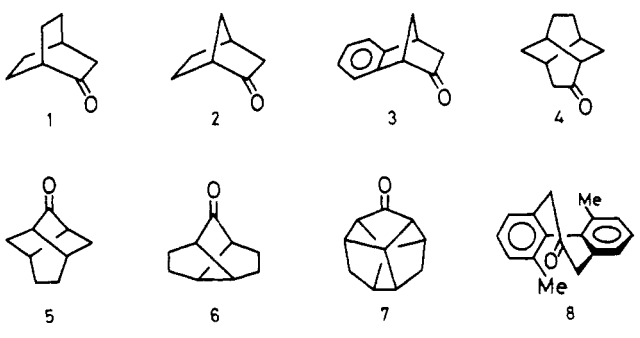
Among a number of C_2-ketones[9] studied in our laboratory,[3] the atropisomeric C_2-biphenyl ketone **8** will be noteworthy in two respects: (a) in contrast to the extremely high enantiomeric selectivity (90–100%) exhibited by *R. rubra, C. lunata* showed almost no enantiomeric selectivity toward this ketone **8**; and (b) this is the first axially chiral cyclic ketone on which microbiological reduction has ever been carried out.

These results prompted us to investigate the microbiological reduction of carbonyl compounds with planar chirality, and this paper describes microbial stereodifferentiating reduction of (±)-1-oxo[2.2]metacyclophane (**9**), 1,10-dioxo[2.2]metacyclophane (**12**), and (±)-[2.2]metacyclophane-4-aldehyde (**20**) with *R. rubra* and *Rhizopus arrhizus*.

Microbial Reduction of (±)-1-Oxo[2.2]metacyclophane (9) (Figure 1). Being a racemic ketone with C_1 symmetry, (±)-1-oxo[2.2]metacyclophane (**9**) (belongs to the C_1-ketone[9]) has four stereochemically distinguishable faces around the carbonyl plane, two for each enantiomer.

Corresponding to these faces, there arise four quadrant orientations,[2] C_1-1, C_1-2, C_1-3, and C_1-4 (Figure 1), for the racemic [2.2]metacyclophane ketone **9**, and the quadrant rule[2] tells us that *C. lunata* and *R. rubra* should favor C_1-1 orientation followed by C_1-4. Distinction between these two orientations is that while both have the larger carbonyl flanking groups (L) on the right side (+y direction), C_1-1 has the smaller part of the molecule in the lower quadrant, whereas C_1-4 has the larger part of the molecule in this lower section.

Chart I



Upon hydrogen delivery from the lower sections, C_1-1 and C_1-4 orientations are expected to furnish the diastereoisomeric 1-hydroxy[2.2]metacyclophanes **10** and **11**, respectively; the former possesses the *pR*,1*S* configuration with an axial hydroxyl group,[10] while the latter has the *pS*,1*S* configuration with the hydroxyl group in an equatorial orientation.[10]

This analysis can be summarized to predict the following: (a) the metabolite alcohol with an axial hydroxyl group must have the *pR*,1*S* configuration, while the metabolite with an equatorial hydroxyl group must have the *pS*,1*S* configuration; (b) since C_1-1 orientation is favored over C_1-4 orientation, the axial alcohol **10** will be the major reduction product to be isolated from the culture solution when incubation is terminated at the point where about 50% of the starting material is reduced; and (c) the recovered ketone will have the *pS* configuration corresponding to the unfavored orientations C_1-3 and C_1-4.

Although preliminary incubation tests on a small scale indicated that *Aspergillus tamarii, Fusarium solani, Rhizopus nigricans, Rhizopus formosaensis, Mucor javanicus, Curvularia lunata, Rhodotorula rubra,* and *Rhizopus arrhizus* were all capable of reducing the racemic ketone **9**, preparative scale incubations were conveniently carried out with *Rhodotorula rubra* and *Rhizopus arrhizus*.

Reduction with *Rhodotorula rubra*. After a small scale trial incubation in which *R. rubra* was observed to reduce the (±)-ketone **9** completely into a mixture of diastereomeric alcohols within 15 min at 30 °C, 300 mg of the (±)-ketone **9** was incubated with *R. rubra* in 20 batches of 25 mL of culture medium for 45 h at 30 °C. Monitoring the process with silica

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