a solid, which was sublimed at 90 °C (30 mm) to yield 120 mg of 1 (58% yield): $[\alpha]^{24}_D$ 0° (c 2.81, $CHCl_3$); mp 256–258 °C (in a sealed tube) (lit.[2] mp 258–259 °C).

Anal. Calcd for $C_{11}H_{18}$: C, 87.92; H, 12.08. Found: C, 87.67; H, 12.04.

Acknowledgment. The authors thank Drs. Kaoru Kuriyama and Sanji Hagishita (Shionogi Research Laboratory) for performing the temperature-dependent CD measurements.

Registry No.—**1**, 281-46-0; (−)-**3**, 63902-00-1; (+)-**4**, 57287-49-7; (+)-**6**, 63903-40-2; (−)-**6**, 63902-01-2; (+)-**7**, 63902-02-3; (+)-**7** 2Ag, 63949-41-7; (±)-**10**, 63833-52-3; (+)-**10**, 63903-41-3; (+)-**10**, 63902-03-4; (−)-**10** cinchonidine salt, 63949-43-9; (−)-**10** 2Ag, 63949-44-0; (+)-**11**, 63833-53-4; (−)-**12**, 63902-04-5; (−)-**13**, 63902-05-6; (−)-**13** Ag salt, 63949-45-1; **14**, 63833-54-5; (±)-**15**, 63833-55-6; (+)-**15**, 63902-06-7; (+)-**16**, 63833-56-7; (±)-**17**, 63833-57-8; (+)-**17**, 63902-07-8; (±)-**18**, 63833-58-9; (+)-**19**, 63833-59-0; (+)-**20**, 63833-60-3; (+)-**21**, 63902-08-9; (+)-**22**, 63902-09-0; (+)-**23**, 63902-10-3; (±)-dimethyl bicyclo[3.3.1]nonane-2,6-dione-3,7-dicarboxylate, 54696-28-5; ethylene bromide, 106-93-4; (±)-dimethyl homoadamantanedione-3,6-dicarboxylate, 63833-61-4; cinchonidine, 485-71-2.

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Stereochemistry and Total Synthesis of (±)-Ivangulin

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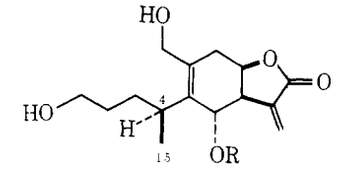
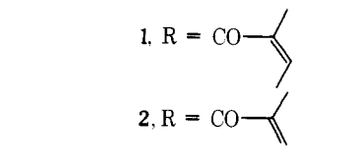
The stereochemistry and total synthesis of the novel secoeudesmanolide ivangulin (**3**) is reported. The introduction of the β-oriented C-15 methyl group involves acid-catalyzed opening of cyclopropyl ketal **4** and equilibration to the more stable β position (**4** → **5**). The establishment of the β-oriented γ-lactone functionality is facilitated by the presence of the angular α-methyl group in diene **6**. Cleavage of ring A in compound **10** via a Baeyer–Villiger oxidation completes the construction of the side chain.

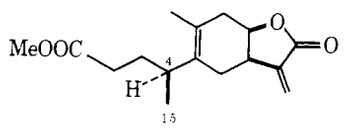
The isolation and structure eluciation of two novel highly oxygenated secoeudesmanolides, eriolangin (**1**) and eriolanin (**2**), from the chloroform extracts of *Eriophyllum lanatum*



1, R = CO–



2, R = CO–

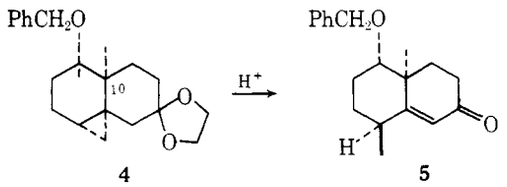


3

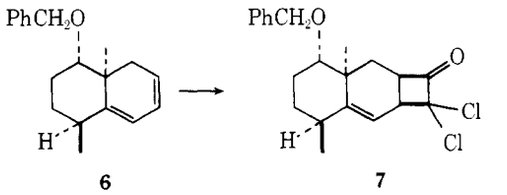
Forbes (Compositae) has been reported by Kupchan.[1] The significant in vivo tumor-inhibitory activity associated with both **1** and **2** can be attributed to the presence within each molecule of two α,β-unsaturated carbonyl functions.[2] In 1967, Herz and co-workers isolated, as a result of examining several collections of *Iva angustifolia* Natl. (section *Linearbractea*) found in Texas and Oklahoma, the only other 1,10-seconeudesmanolide, ivangulin (**3**), whose structure was based on IR, NMR, and chemical degradative data.[3] However, no information regarding the stereochemistry at C-4 was provided.

In conjunction with our efforts to synthesize eriolangin and eriolanin, we have examined several model systems and report herein our preliminary findings which have resulted in the successful synthesis of **3** whose NMR and IR were identical with the spectra of natural ivangulin, thus establishing the stereochemistry at C-4.[4]

Of prime importance to any synthesis of ivangulin and its

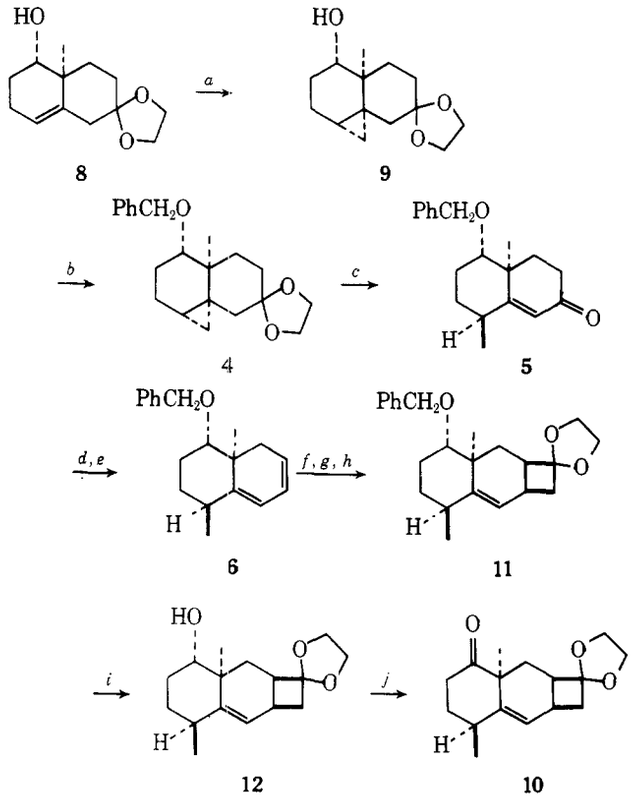


4 **5** (1)



6 **7** (2)

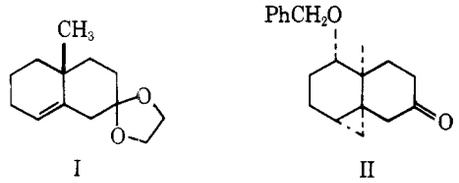
Chart I



[a] Zn–Cu/CH_2I_2/Et_2O. [b] NaH/Me_2SO/$PhCH_2Br$. [c] MeOH/H_2SO_4. [d] p-$CH_3C_6H_4SO_2NHNH_2$/PhH/$BF_3 \cdot Et_2O$. [e] LDA/THF/−78 → 0 °C. [f] $Cl_2CHCOCl/Et_3N$/hexanes. [g] HOAc/Zn. [h] $HOCH_2CH_2OH$/PhH/TsOH. [i] Li/NH_3. [j] $CrO_3 \cdot 2Py/CH_2Cl_2$.

more highly oxygenated derivatives is the introduction of the C-4 methyl group with the proper stereochemical relationship to the α-methylene-γ-butyrolactone functionality. One of the key steps in our synthesis was the introduction of the β-oriented methyl group on the acyclic side chain. As illustrated in eq 1, acid-catalyzed opening of cyclopropyl ketal **4** was accompanied by equilibration to the more stable equatorial position (vide infra). This approach is dependent upon successful cleavage of the C-1, C-10 carbon–carbon bond at some point in the synthesis. The proper stereochemical relationship between the C-4 methyl group and the eventual γ-lactone moiety was facilitated by the presence of the C-10 α-oriented methyl group in diene **6** which directed the addition of dichloroketene from the β-face of the molecule (eq 2). Preparation of cyclopropyl ketal **4** along with its conversion to the tricyclic keto ketal **10** is detailed in Chart I.

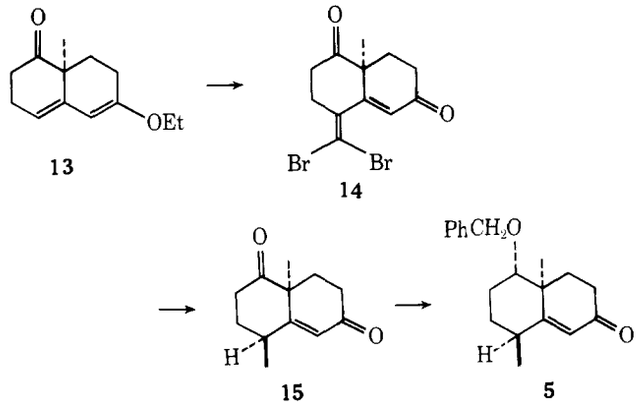
The known ketal olefin **8**[5] was efficiently cyclopropanated in high yield employing the LeGoff modification[6] of the Simmon–Smith reaction[7] in which the zinc–copper couple is readily prepared by treating zinc dust with a hot acetic acid solution of cupric acetate monohydrate. It is of interest to note that in the absence of the α-oriented hydroxyl function at C-1 no cyclopropanation occurred. For example, we were unable to cyclopropanate olefin **I** employing several procedures. The



I II

above results were not completely unexpected in view of Winstein's observation some years ago that the hydroxyl group of 3-cyclopenten-1-ol controls methylene transfer.[8]

Chart II



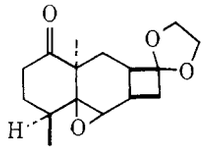
Prior to cyclopropane ring opening and equilibration, the free hydroxyl was protected as its benzyl ether. Exposure of ketal **4** to concentrated sulfuric acid in methanol at 80–85 °C for 30 min led to opening of the cyclopropane ring with equilibration to the β position. The major product, albeit in only overall yields of between 40 and 50%, was clearly an α,β-unsaturated ketone as evidenced by infrared bands at 1680 and 1614 cm^{-1} and a one-proton doublet (J = 1.8 Hz) in the NMR spectrum located at δ 5.62. In addition, a three-proton doublet (J = 7 Hz) centered at δ 1.07 for the C-4 methyl group was evident. The initial stereochemical assignment at C-4 in compound **5** was based on an observation reported some years ago that in 6-substituted Δ^4-3-keto steroids the stereochemistry at C-6 can be deduced from the multiplicity of the olefinic proton at C-4 which appears as a singlet (W_H = 1.5–1.8 Hz) in the C-6 β-substituted series and as a doublet (J = 1.6–1.8 Hz) in the C-6 α-substituted series.[9] Attempts to open the cyclopropane ring via treatment of cyclopropyl ketone **II** with base (e.g., potassium *tert*-butoxide, 1,5-diazabicyclo[5.4.0]undec-5-ene) gave discouragingly low yields (<10%) of desired enone **5**.

Unequivocal confirmation of the structure assigned to compound **5** was arrived at by the synthetic route outlined in Chart II. Reaction of dienol ether **13** with carbon tetrabromide in pyridine provided the dibromomethylene compound **14** (~50%) which when subjected to hydrogenation using Pd/$SrCO_3$ and equilibration provided the known enedione **15** (38%).[10] Reduction of the unconjugated carbonyl with sodium borohydride in absolute ethanol (0 °C) generated the desired alcohol which was converted to its sodium alkoxide in tetrahydrofuran and treated with benzyl bromide in the presence of tetrabutylammonium iodide.[11] The benzyl ether generated by this procedure was identical in all respects with the sample of compound **5** prepared above.

Introduction of the 1,3-conjugated diene system was carried out on the tosylhydrazone of enone **5** employing a modification of the original procedure of Dauben and Shapiro.[12,13] Use of excess lithium diisopropylamide in tetrahydrofuran gave reproducibly in >90% yield the sensitive diene **6**. The in situ cycloaddition of dichloroketene generated from dichloroacetyl chloride and triethylamine in hexane[14] to diene **6** gave predominantly adduct **7** resulting from β attack.[15] Approximately 10–15% of the α adduct could be detected. Dechlorination of **7** with zinc in glacial acetic acid followed by ketalization gave the crystalline tricyclic ketal **11**, mp 96–97 °C, in an overall yield ranging from 50 to 70%. Debenzylation (lithium, liquid ammonia, tetrahydrofuran, *tert*-butyl alcohol) and oxidation with Collins reagent provided in 90% overall yield the tricyclic ketone **10**.

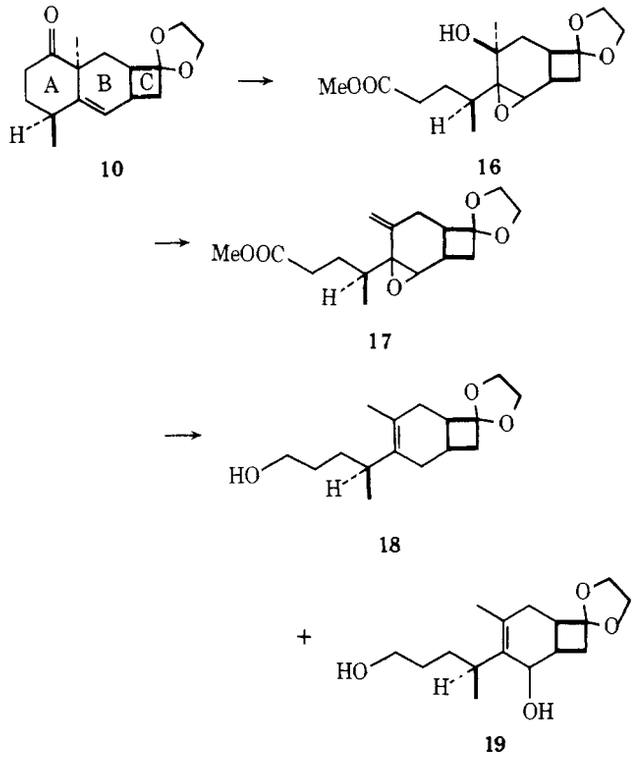
With compound **10** in hand, we turned our attention to the cleavage of ring A. Treatment of ketone **10** with 1 equiv of *m*-chloroperbenzoic acid methylene chloride containing so-

dium bicarbonate gave rapid epoxidation of the double bond with no evidence of Baeyer–Villiger product. Under a variety of conditions, formation of compound **20** was faster than



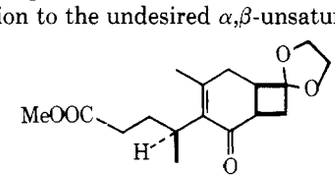
20

lactone formation. Use of 2.0 equiv of *m*-chloroperbenzoic acid followed by treatment with potassium carbonate in methanol gave the hydroxy ester **16** as a crystalline compound, mp



10 **16** **17** **18** **19**

65.5–66.5 °C, in 84% overall yield. Mesylation of alcohol **16** with methanesulfonyl chloride in methylene chloride in the presence of triethylamine at −5 °C gave not the expected mesylate but the sensitive epoxy olefin **17** in 70% yield after purification on florisil. The NMR and infrared spectra of compound **17** were in accord with the assigned structure of the purified compound. The NMR spectrum of compound **17** revealed two new singlets (1 H each) located at δ 5.08 and 5.16, and the infrared spectrum displayed new absorptions at 3100 and 1644 cm^{-1}. It is of interest to note that compound **17** represents a potential intermediate for the synthesis of eriolangin and eriolanin. During an attempted purification on silica gel, compound **17** underwent a smooth high-yield transformation to the undesired α,β-unsaturated enone **21.**

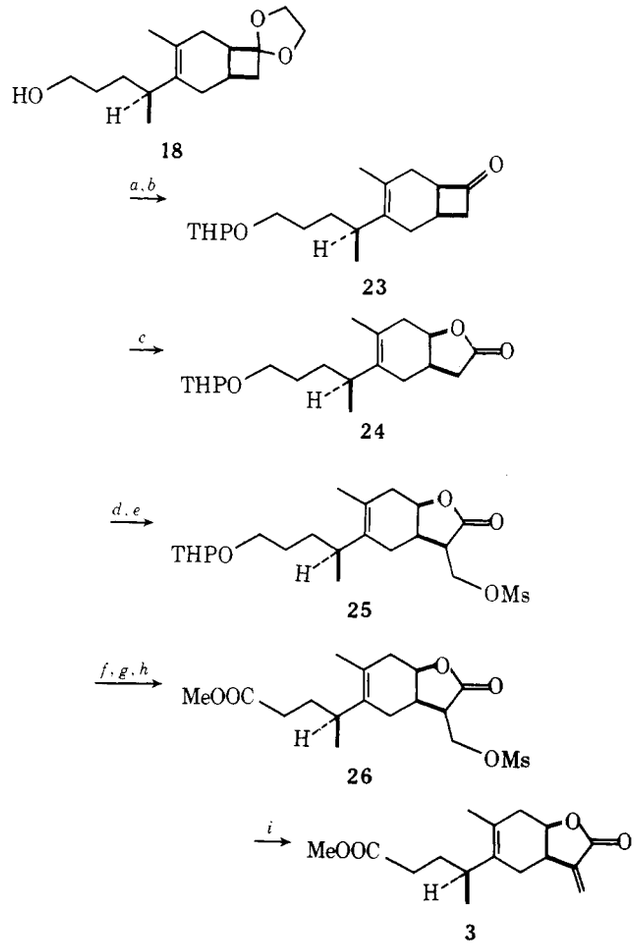


21

Once again, the NMR and IR spectra allowed ready assignment of the unwanted product. The NMR spectrum exhibited a new three-proton singlet attributed to the olefinic methyl group, and the infrared spectrum showed new bands at 1650 and 1620 cm^{-1}.

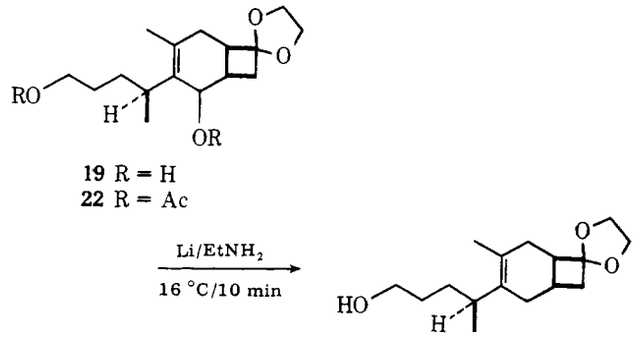
Treatment of the sensitive epoxy olefin 17 with lithium in liquid ammonia–tetrahydrofuran containing *tert*-butyl alcohol gave after chromatographic separation two products, A (35%) and B (46%), which were identified as the monoalcohol **18** and the diol **19,** respectively. Conversion of diol **19** to its diacetate **22** (94%), mp 59–60 °C, with acetic anhydride and triethylamine in ether containing *p*-dimethylaminopyridine[16] followed by reduction with lithium in ethylamine gave a 91% yield of pure alcohol **18.** In the absence of *p*-dimethylaminopyridine, the conversion of **19** to **22** required approximately 5 days.

Chart III



18 **23** **24** **25** **26** **3**

[a] THF/10% aq HCl/25 °C. [b] DHP/CH_2Cl_2/TsOH. [c] *t*-BuOOH/10% aq NaOH/THF/0 °C. [d] LDA/THF/−25 °C/HCHO. [e] MsCl/Py/CH_2Cl_2. [f] MeOH/TsOH. [g] Jones/0 °C. [h] CH_2N_2/Et_2O. [i] DBU/PhH/rt.



19 R = H
22 R = Ac

$\xrightarrow[16\ °C/10\ min]{Li/EtNH_2}$

18

Transformation of compound **18** to ivangulin was carried out as indicated in Chart III. Hydrolysis of ketal **18** with 10% hydrochloric acid followed by tetrahydropyranylation in methylene chloride containing *p*-toluenesulfonic acid gave in near quantitative yield cyclobutanone **23.** Baeyer–Villiger

oxidation of **23** with *m*-chloroperbenzoic acid led only to disappointingly low yields of lactone **24.** Similarly, use of basic hydrogen peroxide in tetrahydrofuran led to only a 32% yield of lactone **24.**[17] However, utilization of *tert*-butyl hydroperoxide in tetrahydrofuran containing 10% aqueous sodium hydroxide gave a 76% yield of the desired γ-lactone. Substitution of triton B for sodium hydroxide in the *tert*-butyl hydroperoxide reaction gave a 54% yield of **24.**

Hydroxymethylation[18] of the lactone enolate prepared from lactone **24** with lithium diisopropylamide in tetrahydrofuran at −78 °C proceeded smoothly in 92% yield. Mesylation of the resulting adduct in methylene chloride containing pyridine generated the corresponding mesylate **25** in high yield. Cleavage of the tetrahydropyranyl ether, Jones oxidation of the resulting alcohol, and esterification of the corresponding carboxylic acid function all proceeded in near quantitative yield despite the presence of the potentially sensitive β-mesyloxy lactone moiety. Conversion of **26** to ivangulin was accomplished in 97% yield with 1,5-diazabicyclo[5.4.0]undec-5-ene in benzene at room temperature. Crystalline ivangulin, mp 66.0–66.5 °C, was identical with natural ivangulin by comparison of spectral properties (NMR, IR), thus establishing the stereochemistry at C-4.[4]

Experimental Section

Melting points were determined on a Fisher-Johns hot-stage melting-point apparatus. All melting and boiling points are uncorrected. Infrared (IR) spectra were determined on a Perkin-Elmer 247 grating infrared spectrometer, and nuclear magnetic resonance (NMR) spectra were recorded at either 60 (Varian A-60A or T-60 spectrometer) or at 250 MHz as indicated. Chemical shifts are reported in parts per million (δ) relative to Me_4Si (δ_{Me_4Si} = 0.0 ppm) as an internal standard. Low-resolution mass spectra were recorded on an LKB-9000 spectrometer. High-resolution spectra were recorded on a Varian MAT CH-5DF instrument. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Reactions were run under an atmosphere of nitrogen. "Dry" solvents were dried immediately before use. Tetrahydrofuran and dimethoxyethane were distilled from lithium aluminum hydride; dimethylformamide (DMF), hexamethylphosphoramide (HMPA), dimethyl sulfoxide (Me_2SO), and pyridine were distilled from calcium hydride. Diethyl ether and dioxane were distilled from sodium. Methylene chloride was passed through a column of alumina prior to use.

***cis*-10α-Methyl-7,7-ethylenedioxy-4α,5α-methano-1α-decalol (9).** To a solution of 128.6 g of diiodomethane in 500 mL of anhydrous ether was added 62 g of zinc–copper couple (freshly prepared via the LeGoff modification[6]). The heterogeneous mixture was refluxed under nitrogen. After 30 min, 15.9 g (71 mmol) of octalol **8** in 300 mL of anhydrous ether was added dropwise over 30 min with the aid of a dropping funnel. The reaction was refluxed for 2 h. The cooled reaction mixture was filtered and the filtrate was poured into 200 mL of cold saturated aqueous ammonium chloride solution. The organic layer was separated, washed with saturated sodium bicarbonate solution and saturated brine solution, and dried over anhydrous sodium sulfate. Removal of the solvent in vacuo provided 39 g of crude product. Chromatography on 800 g of silica gel employing ether–hexanes, 1:2, gave 12.8 g (76%) of pure **9** as an oil: IR ($CHCl_3$) 3620, 3475, 3065, 3000, 2960, 2935, 2880, 1465, 1455, 1431, 1385, 1363, 1355, 1320, 1280, 1234, 1178, 1123, 1100, 1076, 1046, 1030, 971, 950, 915, 900, 881, 868, 830 cm^{-1}; NMR ($CDCl_3$) δ 3.91 (s, 4 H), 3.42 (m, 1 H), 1.2–1.3 (m, 10 H), 1.12 (s, 3 H), 0.1–1.0 (m, 3 H). An analytical sample was prepared by distillation [85 °C (bath temperature)/0.8 mmHg].

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.71; H, 9.46.

***cis*-10α-Methyl-7,7-ethylenedioxy-4α,5α-methano-1α-benzyloxydecalin (4).** To a suspension of 5.28 g (109 mmol) of sodium hydride (50% oil dispersion) in 160 mL of dry benzene was added 18.6 g (78 mmol) of decalol **9** in 8 mL of dry dimethyl sulfoxide. After the mixture was refluxed for 1 h, 13.1 mL (110 mmol) of benzyl bromide was added over 10 min. After an hour at reflux, an additional 3.74 g (78 mmol) of sodium hydride was added followed by 0.27 mL (78 mmol) of benzyl bromide after 30 min. After 50 min, TLC analysis indicated the presence of starting material. An additional 2.62 g (54.6 mmol) of sodium hydride and 6.48 g (54.6 mmol) of benzyl bromide were added. After 40 min, TLC analysis (hexanes–ether, 2:1) indicated no starting alcohol present. The product was isolated by extraction with ether.[19] There was obtained 51 g of crude product which was chromatographed on 800 g of silica gel. Elution with hexanes–ether, 6:1, afforded 23.9 g (93%) of pure benzyl ether **4** as an oil: IR (CCl_4) 3070, 3035, 2960, 2940, 2880, 1500, 1465, 1455, 1431, 1383, 1370, 1360, 1349, 1325, 1304, 1280, 1260, 1246, 1220, 1195, 1134, 1118, 1100, 1078, 1060, 1035, 1015, 967, 951, 918, 905 cm^{-1}; NMR (CCl_4) δ 7.20 (s, 5 H), 4.33 (AB q, 2 H, J = 12 Hz, $\Delta\nu_{AB}$ = 16 Hz), 3.78 (s, 4 H), 2.96 (m, 1 H), 1.13 (s, 3 H), 0.3–1.0 (m, 3 H). An analytical sample was prepared by distillation [110 °C (bath temperature)/1.5 mmHg].

Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 77.08; H, 8.77.

1α-Benzyloxy-4β-methyl-10α-methyl-Δ$^{5(6)}$-octal-7-one (5). To a solution of 11.95 g (36.4 mmol) of cyclopropyl ketal **4** in 237 mL of methanol cooled to 0 °C was added dropwise over 10 min 91 mL of concentrated sulfuric acid. The mixture was heated to ca. 85 °C for 30 min. The reaction was quenched by pouring onto ice. Isolation of the product by extraction with benzene[19] gave 19 g of crude material. Chromatography on 800 g of silica gel [elution with hexanes–ether, 7:1] gave 4.5 g of crystalline product. Recrystallization from hexanes gave 4.2 g (40%) of pure crystalline octalone (**5**): mp 74–75 °C; IR ($CHCl_3$) 3090, 3055, 3040, 2975, 2940, 2910, 2855, 1680, 1615, 1500, 1462, 1457, 1420, 1375, 1360, 1348, 1331, 1295, 1272, 1238, 1218, 1205, 1178, 1145, 1100, 1075, 1031, 1017, 959, 937, 914, 880 cm^{-1}; NMR (CCl_4) δ 7.30 (s, 5 H), 5.62 (d, J = 1.8 Hz, 1 H), 4.51 (AB q, 2 H, J = 12 Hz, $\Delta\nu_{AB}$ = 13.4 Hz), 3.10 (m, 1 H), 1.4–2.6 (m, 9 H), 1.21 (s, 3 H), 1.07 (d, 3 H, J = 6.5 Hz).

Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.50; H, 8.49.

Preparation of Conjugated Diene 6. To a suspension of 8.0 g (28 mmol) of octalone **5** and 5.8 g (31 (mmol) of *p*-toluenesulfonylhydrazide in 80 mL of anhydrous benzene was added 16 drops of boron trifluoride etherate. The mixture gradually became homogeneous. After 40 min, the solvent was removed on a rotary evaporator under reduced pressure. The residue was redissolved in 50 mL of benzene and evaporated to dryness to remove traces of moisture. This process was repeated again. The resulting tosylhydrazone was dried at 0.1 mmHg for 1 h.

The above tosylhydrazone in 70 mL of anhydrous tetrahydrofuran cooled to −78 °C was treated dropwise with a precooled (−78 °C) solution of lithium diisopropylamide [prepared from 19.7 mL (141 mmol) of diisopropylamine and 88.1 mL of 1.6 M *n*-butyllithium (in hexane) in 180 mL of dry tetrahydrofuran at −78 °C]. The mixture was warmed to 0 °C where stirring was continued for 2 h. After 2 h at room temperature, the reaction was quenched at 0 °C with water. The solvent was removed under reduced pressure. The product was isolated by extraction with hexanes.[19] There was obtained 7.43 g (98% overall) of pure sensitive diene **6** as an oil: IR (CCl_4) 3100, 3050, 2980, 2945, 2880, 2870, 1610, 1590, 1501, 1458, 1446, 1432, 1398, 1375, 1365, 1346, 1325, 1310, 1261, 1247, 1220, 1210, 1171, 1148, 1110, 1100, 1075, 1035, 1005, 996, 926, 909, 881 cm^{-1}; NMR (CCl_4) δ 7.26 (s, 5 H), 5.64 (m, 3 H), 4.53 (AB q, 2 H, J = 12 Hz, $\Delta\nu_{AB}$ = 16 Hz), 3.22 (dd, 1 H, J = 4 and 11 Hz), 1.2–2.7 (m, 7 H), 1.05 (d, 3 H, J = 7 Hz), 1.00 (s, 3 H).

Preparation of Tricyclic Ketal 11. To a solution of 7.43 g (27.7 mmol) of diene **6** in 100 mL of hexanes was added simultaneously over a period of 1.5 h via two syringe pumps 7.18 mL (74.8 mmol) of dichloroacetyl chloride in 40 mL of hexanes and 10.7 mL (77.6 mmol) of triethylamine in 40 mL of hexanes. Approximately 30 min after addition was complete, the precipitate was removed by filtration and the solvent was removed under reduced pressure. The crude dichlorocyclobutanone [IR (CCl_4) 1810 cm^{-1}] was dissolved in 100 mL of glacial acetic acid and treated cautiously with 10.9 g of zinc dust. Cooling is necessary during the addition. After all the zinc was added, the heterogeneous reaction mixture was heated at 55 °C for 1.5 h. The reaction mixture was filtered and the solvent was removed under reduced pressure on a rotary evaporator. The residue was diluted with a 1:1 mixture of ether and benezene. The organic solution was washed several times with saturated sodium bicarbonate solution and brine and dried over anhydrous magnesium sulfate. Filtration followed by removal of the solvent in vacuo gave 9.98 g of crude cyclobutanone [IR (CCl_4) 1770 cm^{-1}] which was directly dissolved in 150 mL of benzene containing 34.4 g (55.4 mmol) of ethylene glycol and 80 mg of *p*-toluenesulfonic acid. The reaction mixture was refluxed with azeotropic removal of water using a Dean–Stark apparatus. The benzene solution of the crude product was washed with saturated sodium bicarbonate solution and brine and was dried over anhydrous sodium sulfate. Filtration and removal of the solvent under reduced pressure left 11.2 g of crude ketal **11.** Chromatography on 500 g of silica

gel using hexanes–ether, 10:1, provided 4.8 g (50% overall) of pure crystalline ketal **8**: mp 91.5–92.5 °C; IR (CCl_4) 3098, 3075, 3045, 2975, 2945, 2880, 1501, 1460, 1430, 1400, 1380, 1360, 1315, 1295, 1220, 1205, 1185, 1100, 1079, 1030, 1020, 970, 955, 920 cm^{-1}; NMR (CCl_4) δ 7.20 (s, 5 H), 5.31 (br s, 1 H), 4.50 (AB q, 2 H, J = 12 Hz, $\Delta\nu_{AB}$ = 9 Hz), 3.80 (m, 4 H), 2.98 (dd, 1 H, J = 4 and 10 Hz), 0.99 (s, 3 H), 0.98 (d, 3 H, J = 6.5 Hz).

Anal. Calcd for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53. Found: C, 78.11; H, 8.62.

Debenzylation of Benzyl Ether 11. To a refluxing solution of 1.2 g of lithium metal in 700 mL of anhydrous liquid ammonia was added dropwise 2.82 g (7.96 mmol) of benzyl ether **11** in 15 mL of anhydrous tetrahydrofuran. After 2 h at −33 °C, the excess lithium was destroyed by the addition of ammonium chloride. Evaporation of the ammonia followed by isolation of the product by ether extraction[19] gave 2.2 g of crude alcohol **12**. Purification on 100 g of silica gel using hexanes–ether, 2:1, afforded 1.99 g of crystalline product. Recrystallization from ether–hexanes provided pure **12**: mp 97–98 °C; IR (CCl_4) 3610, 3475, 3015, 2950, 2910, 2850, 2840, 1450, 1435, 1415, 1365, 1339, 1300, 1280, 1190, 1160, 1124, 1110, 1090, 1060, 1020, 1010, 985, 953, 938, 905, 890 cm^{-1}; NMR (CCl_4) δ 5.40 (br s, 1 H), 3.81 (br s, 4 H), 3.25 (m, 1 H), 0.98 (d, 3 H, J = 6.5 Hz), 0.92 (s, 3 H).

Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C= 72/3[: H, 9.03.

Preparation of Octalone 10. Chromium trioxide (4.2 g, 42 mmol) was carefully added to 6.8 mL of dry pyridine in 100 mL of methylene chloride. After approximately 30 min, 1.85 g (7 mmol) of alcohol **12** in 7 mL of methylene chloride was added in one portion. After 15 min, the reaction mixture was filtered through Celite. The pad of Celite was washed thoroughly with ether. The filtrate and combined washings were evaporated under reduced pressure. The residue was dissolved in ether and once again passed through Celite. Removal of the solvent afforded 1.66 g (90%) of pure ketone **10** as an oil: IR (CCl_4) 3040, 2970, 2940, 2880, 1710, 1658, 1458, 1425, 1380, 1370, 1357, 1340, 1333, 1320, 1310, 1288, 1258, 1240, 1218, 1170, 1118, 1085, 1068, 1041, 1020, 945, 908 cm^{-1}; NMR (CCl_4) δ 5.42 (br s, 1 H), 3.80 (s, 4 H), 1.12 (d, 3 H, J = 6.5 Hz), 1.10 (s, 3 H).

Anal. Calcd for $C_{16}H_{22}O_3$: m/e 262.1568. Found: m/e 262.1566.

Baeyer–Villiger Oxidation of Octalone 10. To 1.66 g (6.33 mmol) of octalone **10** in 50 mL of methylene chloride containing 1.33 g (15.8 mmol) of suspended sodium bicarbonate at 0 °C was added 3.21 g of *m*-chloroperbenzoic acid. After approximately 30 h at 25 °C, the reaction was cooled and filtered. The filtrate was evaporated in vacuo and the residue was dissolved in 70 mL of methanol. Potassium carbonate (1.8 g) was added and the reaction was stirred for 25 min at room temperature. After the addition of 70 mL of benzene, the solid material in the flask was filtered. The solvent was removed under reduced pressure and the product was isolated by extraction with ether–benzene, 1:1.[19] There was obtained 2.30 g of crude product which was chromatographed on 140 g of silica gel. Elution with ether–hexanes, 1:1, gave 1.65 g (80%) of pure crystalline hydroxy ester **16**: mp 65.5–66.5 °C; IR (CCl_4) 3610, 3500, 2990, 2950, 2885, 1741, 1460, 1450, 1440, 1390, 1365, 1345, 1340, 1291, 1220, 1190, 1175, 1135, 1118, 1100, 1065, 1025, 946, 930 cm^{-1}; NMR (CCl_4) δ 3.81 (br s, 4 H), 3.63 (s, 3 H), 3.03 (d, 1 H, J = 2.4 Hz), 1.18 (s, 3 H), 0.95 (d, 3 H, J = 7 Hz).

Anal. Calcd for $C_{17}H_{26}O_6$: C, 62.56; H, 8.03. Found: C, 62.43; H, 7.98.

Preparation of Epoxy Olefin 17. To a solution of 1.25 g (3.83 mmol) of **16** in 6 mL of methylene chloride at −10 °C was added 2.13 mL (15.3 mmol) of triethylamine in 9 mL of methylene chloride and 1.19 mL (15.3 mmol) of methanesulfonyl chloride in 5 mL of methylene chloride simultaneously over 15 min. After approximately 2 h at −5 °C, the product was isolated by ether extraction.[19] Purification of the crude product (1.58 g) on 50 g of Florisil using hexanes–ether, 2:1, gave 826 mg (70%) of pure sensitive epoxy olefin **17**: IR (CCl_4) 3100, 2975, 2950, 2880, 1740, 1641, 1460, 1440, 1385, 1360, 1280, 1180, 1021, 905 cm^{-1}; NMR δ (CCl_4) 5.15 (s, 1 H), 5.07 (s, 1 H), 3.77 (br s, 4 H), 3.62 (s, 3 H), 3.08 (d, 1 H, J = 2 Hz), 0.93 (d, 3 H, J = 7 Hz).

Metal–Ammonia Reduction of Epoxy Olefin 17. A solution of 99 mg (0.32 mmol) of epoxide **17** in 1.5 mL of dry tetrahydrofuran containing 1.5 mL of *tert*-butyl alcohol was added to a solution of lithium metal (66 mg) in 12 mL of liquid ammonia cooled to −78 °C. After approximately 10 min, the blue color disappeared and the ammonia was evaporated. The product was isolated by ether extraction.[19] Purification of the crude product (87 mg) on silica gel gave upon elution with ether–benzene, 1:2, 30 mg (35%) of alcohol **18**: IR (CCl_4) 3640, 3480, 2935, 2870, 1455, 1415, 1375, 1341, 1305, 1266, 1225, 1060, 1021, 950 cm^{-1}; NMR (CCl_4) δ 3.77 (s, 4 H), 3.50 (t, 2 H, J = 6 Hz), 1.73 (s, 3 H), 0.90 (d, 3 H, J = 7 Hz).

Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.01; H, 9.79.

Continued elution with ethyl acetate provided 42 mg (46%) of pure **19** as an oil: IR (CCl_4) 3380, 2945, 2860, 1660, 1455, 1415, 1379, 1355, 1309, 1270, 1230, 1190, 1140, 1091, 1058, 1019, 966, 946, 930, 890 cm^{-1}; NMR (CCl_4) δ 4.22 (m, 1 H), 3.82 (s, 4 H), 3.0–3.7 (m, 4 H), 1.73 (s, 3 H), 0.92 (d, 3 H, J = 7 Hz).

Diacetate 22. To a solution of 108 mg (0.382 mmol) of diol **19** in 200 μL of absolute ether containing 4 mg of *p*-dimethylaminopyridine was added 160 μL (1.15 mmol) of triethylamine and 152 μL (1.60 mmol) of acetic anhydride. After 2 h at room temperature, the product was isolated by ether extraction.[19] Chromatography of the crude product (140 mg) on 4.0 g of silica gel (ether–benzene, 1:1) gave 131 mg (94%) of crystalline **22**: IR (CCl_4) 2952, 2875, 1735, 1651, 1450, 1370, 1305, 1240, 1190, 1160, 1135, 1105, 1050, 1020, 965, 945, 932, 905 cm^{-1}; NMR δ 5.52 (d, 1 H, J = 5 Hz), 3.6–4.2 (m, 2 H), 2.80 (s, 4 H), 2.00 (s, 3 H), 1.98 (s, 3 H), 1.80 (s, 3 H), 0.95 (d, 3 H, J = 7 Hz). An analytical sample was prepared by recrystallization from hexanes, mp 55–56 °C.

Anal. Calcd for $C_{20}H_{30}O_6$: C, 65.55; H, 8.25. Found: C, 65.46; H, 8.26.

Conversion of Diacetate 22 to Alcohol 18. To a solution of 30 mg (0.08 mmol) of diacetate **22** in 2.0 mL of anhydrous ethylamine cooled to 0 °C was added 18 mg of lithium metal. After ca. 10 min, excess lithium was destroyed by addition of ammonium chloride. Isolation of the product by ether extraction[19] left 23 mg of crude product. Purification on 12 g of silica gel (elution with ether–benzene, 1:1) gave 20 mg (91%) of pure alcohol **18** which was identical by TLC, IR, and NMR with a sample prepared above.

Preparation of Cyclobutanone 23. A solution of ketal alcohol **18** (50 mg, 0.19 mmol) in a mixture of 2 mL of tetrahydrofuran and 0.5 mL of 10% aqueous hydrochloric acid was stirred for 3 h at room temperature. The product was isolated by extraction with benzene.[19] The crude product (44 mg) [IR (CCl_4) 3640, 3450, 1782 cm^{-1}; NMR (CCl_4) δ 1.71 (s, 3 H), 0.95 (d, 3 H, J = 7 Hz)] was dissolved in 1.5 mL of a precooled (0 °C) methylene chloride solution containing 1.5 mL of dihydropyran and 6.0 mg of *p*-toluenesulfonic acid. Stirring was continued for 2 h at 0 °C. After standard workup, the crude product was purified on 6.0 g of silica gel. Elution with hexanes–ether, 4:1, gave 58 mg (99%) of **23** as a colorless oil: IR (CCl_4) 2960, 2945, 2930, 2880, 1782, 1455, 1445, 1390, 1370, 1355, 1345, 1325, 1308, 1290, 1278, 1262, 1208, 1189, 1141, 1121, 1080, 1052, 986 cm^{-1}; NMR (CCl_4) δ 4.53 (br s, 1 H), 1.74 (s, 3 H), 0.95 (d, 3 H, J = 7 Hz).

Anal. Calcd for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87; Found: C, 74.28; H, 9.79.

Baeyer–Villiger Oxidation of Ketone 23. A mixture of 66 mg (0.22 mmol) of ketone **23**, 65 μL (0.66 mmol) of *tert*-butyl hydroperoxide, and 103 μL (0.26 mmol) of 10% aqueous sodium hydroxide in 2.3 mL of tetrahydrofuran cooled to 0 °C was stirred for 30 min. The reaction mixture was taken up in 50 mL of benzene–ether (1:1) and was washed with 2 mL of water and two 2-mL portions of brine. The organic layer was dried over magnesium sulfate and the solvent was evaporated in vacuo leaving 60 mg of crude γ-lactone. Purification of 5 g of silica gel (elution with ether–benzene, 2:3) afforded 53 mg (76%) of pure lactone **24** as an oil: IR (CCl_4) 2955, 2945, 2880, 1784, 1555, 1455, 1445, 1422, 1390, 1359, 1350, 1330, 1290, 1255, 1220, 1210, 1190, 1145, 1124, 1085, 1039, 998, 990, 940, 915, 868 cm^{-1}; NMR (CCl_4) δ 4.68 (m, 1 H), 4.53 (br s, 1 H), 1.78 (s, 3 H), 0.95 (d, 3 H, J = 7 Hz).

Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.70; H, 9.35.

Hydroxymethylation of Lactone 24. To a solution of diisopropylamine (26 μL, 0.18 mmol) in 1.6 mL of dry tetrahydrofuran cooled to −78 °C was added 116 μL of a 1.6 M solution of *n*-butyllithium in hexane. After 15 min, a solution of 30 mg (0.09 mmol) of lactone **24** in 1.6 mL of dry tetrahydrofuran was added dropwise over a period of 1 min. After 30 min at −78 °C, the reaction was warmed to −25 °C and formaldehyde, generated from 30 mg of paraformaldehyde at 150 °C, was passed into the reaction mixture with the aid of a stream of nitrogen. After complete depolymerization, the reaction mixture was stirred for an additional 30 min at −25 °C. The reaction was quenched by the addition of a saturated ammonium chloride solution. The product was purified on 12 g of silica gel. Elution with ether–benzene, 1:1, gave 30 mg (92%) of pure hydroxymethylated lactone: IR ($CHCl_3$) 3600, 3450, 1755 cm^{-1}; NMR (CCl_4) δ 4.4–4.8 (m, 2 H), 1.73 (s, 3 H), 0.95 (d, 3 H, J = 7 Hz). A solution of the above alcohol (29 mg) in 3.0 mL of methylene chloride containing 20 μL of methanesulfonyl chloride and 20 μL of pyridine was allowed to stir for 4 h at room temperature. Purification of the reaction mixture on 12 g of SilicAR CC-7 (Mallinckrodt) using ether–benzene, 1:2, gave 30 mg (85%) of

mesylate **25:** IR ($CHCl_3$) 1770 cm^{-1}; NMR ($CDCl_3$) δ 3.07 (s, 3 H), 0.96 (d, 3 H, J = 7 Hz).

Preparation of Intermediate 26. A solution of the above tetrahydropyranyl ether **25** (30 mg, 0.07 mmol) in 2.0 mL of absolute methanol containing 7 mg of *p*-toluenesulfonic acid was allowed to stir for 30 min at 0 °C. After an additional 45 min at room temperature, the solvent was evaporated under reduced pressure. The crude alcohol was purified on 12 g of SilicAR CC-7 using ether–benzene, 2:1. There was obtained 27 mg (99%) of alcohol [IR ($CHCl_3$) 3530, 2765 cm^{-1}; NMR ($CDCl_3$) δ 4.86 (m, 1 H), 4.45 (d, . 2 H, J = 4 Hz), 3.62 (br s, 2 H), 3.05 (s, 3 H), 1.75 (s, 3 H), 0.95 (d, 3 H, J = 7 Hz)] which was used directly in the next reaction.

A mixture of the above alcohol (18 mg, 0.05 mmol) and 222 μL of 0.7 M Jones reagent in 1.2 mL of acetone was allowed to stir at 0 °C for 1.5 h. The reaction was quenched by the addition of 2-propanol. After evaporation of the solvent in vacuo, the residue was taken up in ethyl acetate.[19] The resulting crude carboxylic acid was esterified with an ethereal solution of diazomethane. Chromatography of the crude ester on SilicAR CC-7 using ether–benzene, 1:2, provided 20 mg (100%) of pure **26:** IR (CCl_4) 1740, 1778 cm^{-1}; NMR (CCl_4) δ 4.68 (m, 1 H), 4.38 (d, 2 H, J = 4 Hz), 3.62 (s, 3 H), 2.98 (s, 3 H), 1.74 (s, 3 H), 0.97 (d, 3 H, J = 7 Hz).

(±)-Ivangulin (3). A solution of 17 mg (0.04 mmol) of mesylate **26** in 1.0 mL of dry benzene containing 20 μL of 1,5-diazabicyclo-[5.4.0]undec-5-ene was allowed to stir at room temperature for 30 min. The reaction mixture was purified directly on 6.0 g of silica gel. Elution with ether–hexanes (1:2) gave 12.5 mg (99%) of crystalline (±)-ivangulin, mp 66–66.5 °C [IR($CHCl_3$) 3020, 2960, 2925, 2875, 2845, 1738, 1730, 1660, 1620, 1460, 1438, 1405, 1382, 1368, 1355, 1328, 1272, 1175, 1145, 1110, 1080, 1038, 1005, 989, 970, 948, 905, 865, 815 cm^{-1}; NMR ($CDCl_3$) δ 6.27 (d, 1 H, J = 3 Hz), 5.68 (d, 1 H, J = 3 Hz), 4.87 (q, 1 H, J = 5 Hz), 3.64 (s, 3 H), 3.25 (m, 1 H), 1.70 (s, 3 H), 0.94 (d, 3 H, J = 7 Hz)] whose NMR and IR spectra were in complete accord with spectra provided by Professor W. Herz.

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Registry No.—**3,** 63640-50-6; **4,** 63600-03-3; **5,** 63600-04-4; **5** tosylhydrazone, 63600-05-5; **6,** 63600-06-6; **7,** 63600-07-7; **8,** 63600-08-8; **9,** 63600-09-9; **10,** 63600-10-2; **11,** 63600-11-3; 11 free ketone, 63600-12-4; **12,** 63600-13-5; **16,** 63600-14-6; **17,** 63600-15-7; **18,** 63600-16-8; **19,** 63600-17-9; **22,** 63609-71-2; **23,** 63600-18-0; **23** free alcohol, 63600-19-1; **24,** 63600-20-4; **24** hydroxymethylated product, 63600-21-5; **25,** 63600-22-6; **25** ditetrahydropyran analogue, 63600-23-7; **26,** 63600-24-8; **26** free acid, 63600-25-9; benzyl bromide, 100-39-0.

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Natural Products of Marine Sponges. 7. The Constitution of Weakly Basic Guanidine Compounds, Dibromophakellin and Monobromophakellin

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The isolation and elucidation of the structure of dibromophakellin and monobromophakellin are reported. Although these molecules contain a guanidine moiety in their skeleton, they do not exhibit the high basicity expected from the presence of this functionality. A theoretically plausible explanation for the anomaly in the base strength of these compounds is discussed.

A few years ago we isolated two guanidine derivatives, dibromophakellin and monobromophakellin, from the marine sponge *Phakellia flabellata.*[2] These compounds showed p*K*a values of <8 which were rather low when compared with the p*K*a values of >13.4 reported for other guanidines. This paper describes in detail the isolation and characterization of bromophakellins and discusses the factors which make these compounds behave as weak bases.[3]

Dibromophakellin and monobromophakellin occur as hydrochlorides in the sponge *P. flabellata.* The hydrochlorides exhibit a very mild antibacterial action against *B. subtilis* and *E. coli.* The strong antibacterial activity of the methanol extract of the sponge is due to the presence of some other substance(s) which could not be isolated in pure form.

The sponge showed considerable seasonal variations in the production of monobromophakellin, dibromophakellin, and