Synthesis of Salvilenone, a Diterpenoid Phenalenone of *Salvia miltiorrhiza*

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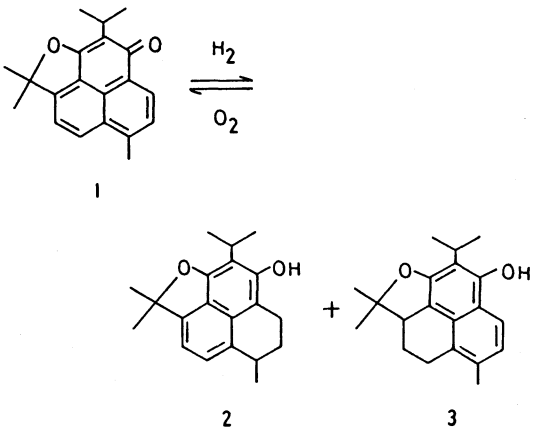
Salvilenone **1**, a phenalenone diterpene isolated from the roots of *Salvia miltiorrhiza* Bunge, was synthesized in thirteen steps from resorcinol dimethyl ether. Dihydrophenalenol derivative **19**, a key intermediate, was treated with aqueous hydrobromic acid to give salvilenone accompanied by the formation of a hydroxy diketone **20**.

Salvilenone is a diterpenoid found in the roots of *Salvia miltiorrniza* Bunge. The dried root of this plant, Dan-shen, is a traditional medicine in China used for the treatment of blood difficulties, hemorrhages, miscarriages and viral hepatitis.[1,2] Recently, it is also used for the treatment of heart disease as a clinically important drug.[3]

The main constituents of this folk medicine were thoroughly studied to find many diterpenoid naphthoquinones and phenanthrenequinones possessing a norabietane carbon skeleton.[4] In the course of our studies on the minor constituents of Dan-shen, a bright yellow compound salvilenone was isolated in a trace amount, and the structure was determined to be a diterpenoide phenalenone **1** different from the known naphthoquinones and phenanthrenequinones of this medicine.[5] The low availability of this compound and scarce distribution of phenalenone derivatives in nature[6] prompted us to investigate its synthesis. The present paper describes in detail the synthesis of salvilenone.[7]



1 2 3

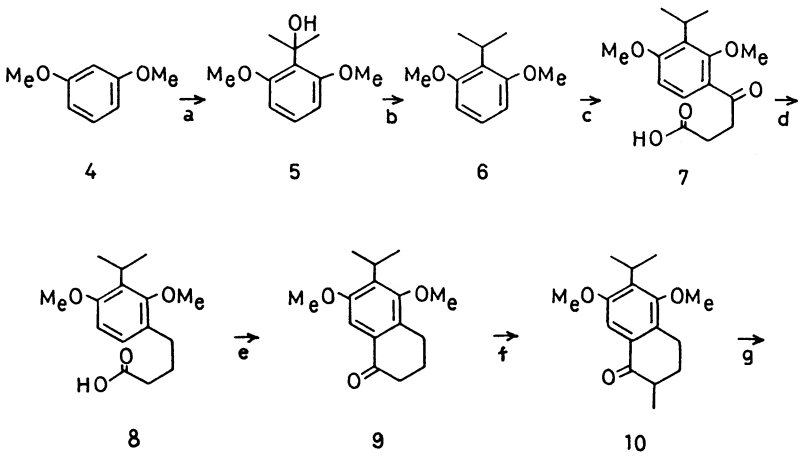
Scheme 1.

It was found in the course of the structural determination that on hydrogenation salvilenone **1** gave unstable products **2** and **3**, which were smoothly autooxidized to the original pigment.[5] On the basis of this observation, dihydrophenalenol derivative **3** was chosen as a key intermediate for the synthesis.

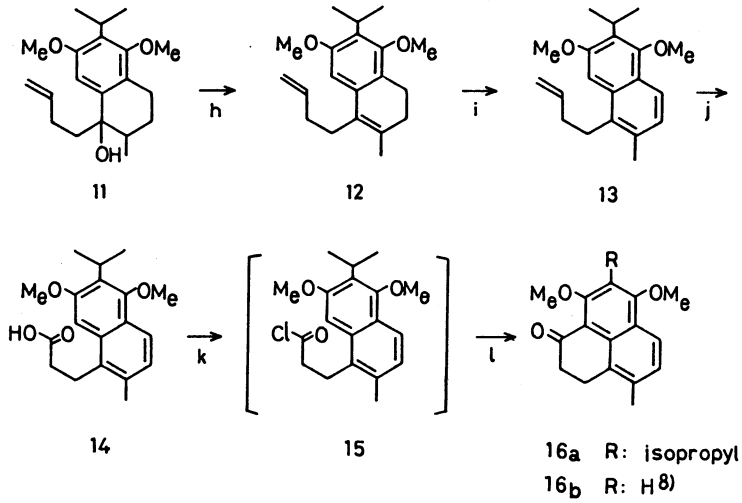
A dihydrophenalenone derivative **16a** was synthesized from resorcinol dimethyl ether (**4**) by an eleven step process.

The reaction of the dihydrophenalenone derivative **16a** with lithium acetylide-ethylenediamine complex proceeded smoothly to give an ethynyl derivative **17** in good yield.[9] Treatment of this ethynyl-substituted alcohol with mercury(II) sulfate and sulfuric acid at 55 °C under Rupe reaction conditions resulted in the formation of acetylphenalenone **18**[12] with concomitant demethylation in these mild conditions. This reaction confirmed the remarkably facile formation of phenalenone from a dihydrophenalenol as observed in the structural determination of salvilenone.

Because selective conversion of the acetyl group of

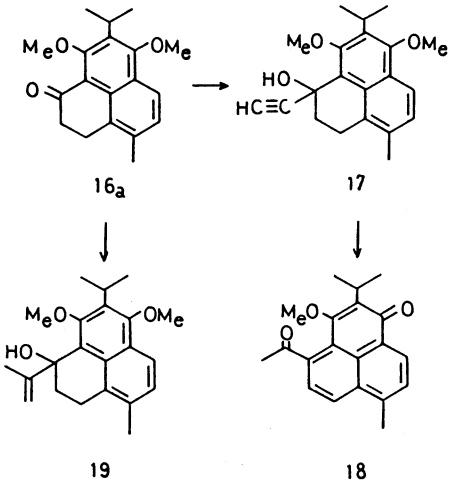


Scheme 2a.



Reagents: a) *n*-BuLi, CH_3COCH_3, THF. b) PtO_2, HCl, AcOH. c) Succinic anhydride, $AlCl_3$, $PhNO_2$. d) H_2/Pd–C (10%), $HClO_4$, AcOH. e) PPA, CH_2Cl_2. f) MMC, CH_3I, DMF. g) CH_2=$CHCH_2CH_2MgBr$, ether. h) TsOH, PhH. i) DDQ, PhH. j) $KMnO_4$, KIO_4, Na_2CO_3, H_2O, dioxane. k) PCl_5, PhH. l) $SnCl_4$, PhH.

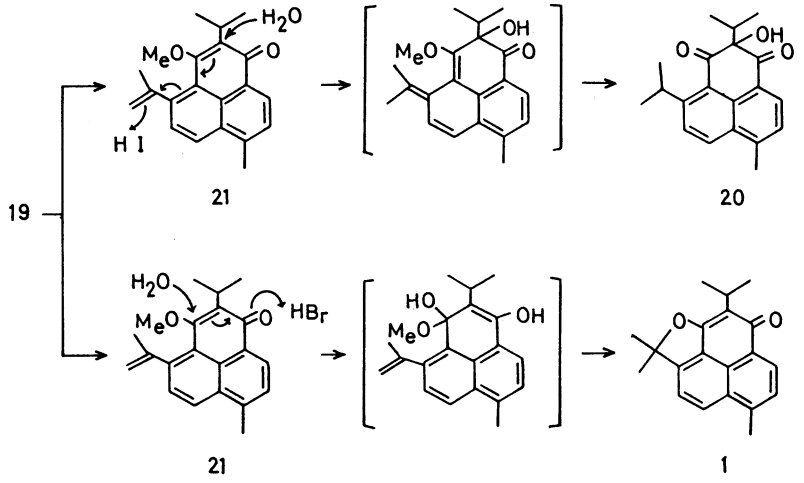
Scheme 2b.



Scheme 3.

18 to an isopropenyl group was unsuccessful, isopropenyllithium[10] was allowed to react with dihydrophenalenone **16a** to obtain the intermediate **19**.

Treatment of the isopropenyl-substituted alcohol **19** with 47% aqueous hydrobromic acid[11] in boiling acetic acid for 48 h afforded salvilenone **1**, accompanied by the formation of a by-product hydroxy diketone **20**. Synthetic salvilenone **1** was identical with an authentic sample in ^{1}H NMR, ^{13}C NMR, IR spectra, and TLC. The structure of the by-product ($C_{20}H_{22}O_3$) was determined to be **20** by spectral analyses. The ^{1}H NMR spectrum showed the presence of two isopropyl groups, an aromatic methyl, and two adjacent aromatic protons. Two of three oxygen atoms of the by-product were considered to comprise two carbonyl groups from ^{13}C NMR signals at δ 193.2 and 197.7, and



Scheme 4.

the remaining one was hydroxyl group from ^{1}H NMR signal at δ 9.67 and IR absorption at 3460 cm^{-1}. The presence of an asymmetric carbon atom was infered from the nonequivalence of the methyl groups in the two isopropyl groups in the NMR spectra [0.95 (3H, d), 0.97 (3H, d), 1.35 (3H, d), and 1.47 (3H, d)].

Although salvilenone **1** and the hydroxy diketone **20** were produced from the intermediate **19** by treatment with hydrobromic acid, on treating with hydriodic acid the intermediate **19** afforded the hydroxy diketone **20** as the sole product, and heating of **19** with iodine in carbon tetrachloride afforded a methoxyphenalenone **21**.[12] The hydroxy diketone **20** is considered to be produced from methoxyphenalenone **21**; protonation by hydriodic acid (a soft acid) may take place preferably at the isopropenyl terminal of **21** rather than at the carbonyl oxygen. Subsequent hydrolysis affords hydroxy diketone **20**. Salvilenone **1** is assumed to be produced by protonation at the carbonyl oxygen atom of the same intermediate **20** by rather hard acid, hydrobromic acid.

Experimental

Melting points were recorded on a Yamato capillary melting point apparatus. Proton magnetic resonance (^{1}H NMR) spectra were recorded on either a JEOL JNM-PMX60si or a JEOL FX90Q spectrometer or, where specified, on a Bruker AM500 spectrometer with chemical shifts given in parts per million (δ) downfield from tetramethylsilane as an internal standard. Deuteriochloroform was used as solvent unless otherwise noted. Carbon magnetic resonance (^{13}C NMR) spectra were recorded at 22.5 MHz on a JEOL EX90Q instrument. Infrared (IR) spectra were measured on a Hitachi 215 or a JASCO FT/IR-3 spectrophotometer. Mass spectra (MS) were obtained on a Hitachi RMU-6H GC/MS instrument at 70 eV. Elemental analyses were performed by the University of Tsukuba Chemical Analysis Center. Ultraviolet (UV) spectra were recorded on a Hitachi EPS-3T spectrophotometer. Gas chromatography (GLC) data were obtained with a 063 Hitachi gas chromatography (1.7 m/3 mm i.d. glass column packed with 5% SE-30). High-pressure liquid chromatography (HPLC) was carried out with a Waters ALC/GPC 202/401 instrument (1/4 in/1 ft column packed with RP-18). Wako C-300 silica gel was used for flash column chromatography. Merck Kieselgel 60 F_{254} Art 5744 (0.25 mm) and Merck Kiesel gel 60 F_{254} Art 5744 (0.5 mm) were used for analytical and preparative thin-layer chromatography.

1,3-Dimethoxy-2-(1-hydroxy-1-methylethyl)benzene (5). To a solution of resorcinol dimethyl ether **4** (3.2 g, 0.023 mol) in dry tetrahydrofuran, a solution of butyllithium in hexane (1.39 M, 20 ml, 0.028 mol; 1 M=1 mol dm^{-3}) was added dropwise and stirred under an argon atmosphere. After refluxing for 2 h, the solution was chilled to room temperature and a solution of dry acetone (1.6 g, 0.028 mol) in tetrahydrofuran was added dropwise. The mixture was heated under reflux for 3 h, cooled, and poured into ice water followed by extraction with ether. The organic layer was washed with water and then dried over sodium sulfate, evaporated under reduced pressure; distillation afforded a colorless oil **5** (2.9 g, 64%). Bp 120—124 °C/4Torr (1 Torr≈ 133.322 Pa). ^{1}H NMR ($CDCl_3$) δ=1.58 (6H, s, CH_3×2), 3.73 (6H, s, OCH_3×2), 4.95 (1H, brs, OH), 6.3—7.1 (3H, m, AB_2, ArH). Found: C, 67.47; H, 8.18%. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22%.

1,3-Dimethoxy-2-isopropylbenzene (6). A solution of **5** (0.64 g, 3.26 mmol), 3 M hydrochloric acid (0.1 ml), PtO_2 (0.05 g), and glacial acetic acid (20 ml) was stirred under H_2 for 3 h at room temperature. After filtration of the catalyst, the solution was evaporated under reduced pressure, and distillation of the residue afforded a colorless oil **6** (0.58 g, 99%). Bp 70—71 °C/0.5 Torr, IR ($CHCl_3$) 2940, 1580, 1450, and 1360 cm^{-1}; ^{1}H NMR (CCl_4) δ=1.25 (6H, d, J=8 Hz, CH_3×2), 3.60 [1H, sept, J=8 Hz, $(CH_3)_2$C<u>H</u>], 3.85 (6H, s, OCH_3×2), and 6.2—7.2 (3H, m, AB_2, ArH). Found: C, 73.32; H, 8.94%. Calcd for $C_{11}H_{16}O_2$: C, 73.29; H, 8.94%.

4-(2,4-Dimethoxy-3-isopropylphenyl)-4-oxobutyric Acid (7). To a solution of **6** (1 g, 5.5 mmol) and succinic anhydride (0.55 g, 5.5 mmol) in dry nitrobenzene (50 ml), cooled in an iced water bath, a powdered anhydrous aluminum chloride (878 mg, 6.6 mmol) was added with stirring under an argon atmosphere. After stirring for 70 h at room temperature, the mixture was poured to ice water containing concentrated hydrochloric acid (10:1 v/v). The mixture was extracted with ether (5×50 ml), from which an acid product was obtained by the usual method as a solid (1.26 g, 82%). The crude product was recrystallized from benzene to give colorless plates, mp 91.5—93 °C; IR ($CHCl_3$) 2950, 1705, 1670, 1580, 1450, 1400, and 1360 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ= 1.31 (6H, d, J=8 Hz, CH_3×2), 2.72 (2H, t, J=7 Hz, $COCH_2$), 3.26 (2H, t, J=7 Hz, -CH_2COO), 3.51 [1H, sept, J=8Hz, $(CH_3)_2$CH], 3.67 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 6.60 (1H, d, J=8.5 Hz, ArH), 7.46 (1H, d, J=8.5 Hz, ArH), and 12.65 (1H, s, COOH). Found: C, 64.04, H, 7.15%. Calcd for $C_{15}H_{20}O_5$: C, 64.27, H, 7.19%.

4-(2,4-Dimethoxy-3-isopropylphenyl)butanoic Acid (8). A mixture of acid **7** (0.42 g, 1.5 mmol), 10% Pd/carbon (0.07 g), and perchloric acid (70%, 0.1 ml) in acetic acid (20 ml) was stirred under H_2 at room temperature. After 70 h the solution was filtered. To the filtrate was added NaOAc (0.5 g) and the resulting gray ppt was filtered off. The neutralized filtrate was evaporated under reduced pressure to about 5 ml, water was added and the mixture thoroughly extracted with ether. The organic layer was washed with water and dried over magnesium sulfate. The solvent was evaporated to give yellow oil. Recrystallization from benzene/hexene afforded **8** (0.39 g, 97%) as bright yellow needles, mp 64—65.5 °C; IR (KBr) 2940, 1690, 1590, 1480, 1450, 1405, and 1335 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.34 (6H, d, J=7 Hz, CH_3×2), 1.7—2.8 (6H, m, $CH_2CH_2CH_2COO$), 3.45 [1H, sept, J=7 Hz, $CH(CH_3)_2$], 3.70 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 6.57 (1H, d, J=8.5 Hz, ArH), 6.96 (1H, d, J=8.5 Hz, ArH), and 10.35 (1H, brs, COOH). Found: C, 67.57; H, 8.30%. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.32%.

5,7-Dimethoxy-6-isopropyl-α-tetralone (9). Phosphorus pentaoxide (3.8 g) was added to vigorously stirred phosphoric acid (3.1 g) at a temperature below 60 °C and the resulting mixture stirred for 5 h at 84 °C. A solution of **8** (0.32 g, 1.2 mmol) in dichloromethane (2 ml) was added to the polyphosphoric acid with vigorous stirring at 60—70 °C. After 30 min, the resulting reddish solution was cooled in an ice bath and 20 ml ice-water added. The mixture was extracted with three 30 ml portions of ether. The combined

ethereal extracts were successively washed with water, a 5% $NaHCO_3$ solution, water, and a saturated sodium chloride solution and dried over sodium sulfate. The ethereal solution was concentrated to afford a neutral oil. The oily mixture was distilled under reduced pressure to give **9** (0.28 g. 94%) as a colorless liquid (bp 135 °C/0.4 Torr). IR ($CHCl_3$) 2950, 1662, 1590, 1560, 1445, and 1405 cm^{-1}. ^1H NMR ($CDCl_3$) δ=1.32 (6H, d, J=7 Hz, CH_3×2), 1.90—2.93 (6H, m, $COCH_2CH_2CH_2$), 3.62 (1H, sept, J=7 Hz, CH), 3.68 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), and 7.30 (1H, s, ArH). Found: C, 72.56; H, 8.20%. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.11%.

5,7-Dimethoxy-6-isopropyl-2-methyl-α-tetralone (10). A solution of magnesium methoxide was prepared from magnesium (0.06 g) and 5 ml of anhydrous methanol. The bulk of the methanol was evaporated from the solution under reduced pressure with stirring at 50—55 °C. The anhydrous *N,N*-dimethylformamide (5 ml) was added. The resulting suspension was stirred vigorously while a stream of anhydrous carbon dioxide was passed into the reaction system. When the suspended magnesium methoxide changed into a clear solution, the flow of carbon dioxide was stopped. A solution of 0.15 g (0.6 mmol) of tetralone **9** in *N,N*-dimethylformamide (5 ml) was added and the reaction mixture refluxed for 2 h. The mixture was cooled to room temperature, and 0.34 g of iodomethane added dropwise. After the mixture was stirred for 10 h at 50 °C, it was poured into 1 M aqueous hydrochloric acid (10 ml) followed by extraction with ether. The combined organic extracts were washed with 5% aqueous $NaHCO_3$, saturated aqueous NaCl, and dried and finally evaporated to give a yellow oil. Distillation of this material gave 0.12 g of methyltetralone **10** as a colorless oil (74% 160 °C/0.3 Torr). IR ($CHCl_3$) 2930, 1665, 1590, 1450, 1410, 1360, and 1310 cm^{-1}. ^1H NMR ($CDCl_3$) δ=1.24 (3H, d, J=6.5 Hz, $COCHCH_3$), 1.37 (6H, d, J=7 Hz, CH_3×2), 1.78—3.20 (5H, m, CH_2CH_2CH), 3.51 [1H, sept, J=7 Hz, $(CH_3)_2C\underline{H}$], 3.70 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), and 7.35 (1H, s, ArH). ^{13}C NMR ($CDCl_3$) δ=15.5(q), 20.8(q), 20.8(q), 22.6(t), 26.0(d), 31.3(t), 42.3(d), 55.4(q), 61.1(q), 104.9(d), 130.6(s), 131.5(s), 135.8(s), 155.8(s), 158.1(s), and 200.2(s); MS m/z 262 (M^+), 247 (M^+-CH_3), and 219 ($M^+-C_3H_7$). Found: C, 73.50; H, 8.41%. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45%. Further distillation of the residue afforded 0.009 g (5%) of 5,7-dimethoxy-2,2-dimethyl-6-isopropyl-α-tetralone as white needles (182—185 °C/0.3 Torr): ^1H NMR ($CDCl_3$) δ=1.20 (6H, s, CH_3×2), 1.32 (6H, d, J=8 Hz), 1.93 (2H, t, J=6 Hz, CH_2), 2.90 (2H, t, J=6 Hz, CH_2), 3.50 [1H, sept, J=8 Hz, $(CH_3)_2C\underline{H}$], 3.72 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), and 7. 34 (1H, s, ArH); MS m/z 277 (M^++1), 276 (M^+), 261 (M^+-CH_3), and 246 (M^+-2CH_3). Found: C, 73.67; H, 8.89%. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75%.

1-(3-Butenyl)-5,7-dimethoxy-6-isopropyl-2-methyl-1,2,3,4-tetrahydro-1-naphthol (11). Magnesium metal shavings (0.24 g) were placed in a flask equipped with a reflux condenser and a dropping funnel. The system was flushed with nitrogen before addition of anhydrous ether (12 ml). The flask was cooled in an ice bath and a small volume of 4-bromo-1-butene was added to the stirred solution. Once the reaction had started, the remainder of the bromide (1 ml) in ether solution (2 ml) was added at below 20 °C. After 3 h the solution was cooled to 0 °C with ice bath, the α-methyl tetralone **10** (1 g, 3.8 mmol) in ether was added dropwise and the mixture was refluxed for 3 h. The reaction mixture was poured into ice cooled ammonium chloride solution and extracted with ether. The combined extracts were dried over anhydrous sodium sulfate. Evaporation of the solvent and flash chromatography of the residue on silica gel with 8:2 hexane/ethyl acetate afforded **11** as a pale yellow oil (1.03 g, 85%). IR ($CHCl_3$) 3580, 2920, 1595, 1565, 1440, 1400, and 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.10 (3H, d, $COHCHCH_3$), 1.42 [6H, d, J=7.5 Hz, $CH(CH_3)_2$], 1.50—2.90 (8H, m, $CH_2CH_2CH_2CH_2$), 3.51 [1H, sept, J=7.5 Hz, $C\underline{H}(CH_3)_2$], 3.71 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 4.12 (1H, m, $CHCH_3$), 4.81—6.08 (3H, m, CH_2=CH), and 6.91, 7.00 (1H, ArH). Found: C, 75.44; H, 9.52%. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.49%. Further elution affords 0.15 g of reduced product, 5,7-dimethoxy-6-isopropyl-2-methyl-1,2,3,4-tetrahydro-1-naphthol as colorless needles (8%). IR ($CHCl_3$) 3580, 2920, 1600, and 1565 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.10 (3H, d, $COHCHCH_3$), 1.31 (6H, d, J=7.5 Hz), 1.62 (1H, s, OH), 1.60—3.00 (4H, m, CH_2CH_2), 3.50 [1H, m, J=7.5 Hz $C\underline{H}(CH_3)_2$], 3.70 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 4.32 (1H, brs, $C\underline{H}OH$), and 6.78 (1H, s, ArH); MS m/z 265 (M^++1), 264 (M^+), 249 (M^+-CH_3), and 246 (M^+-H_2O). Found: C, 72.81; H, 9.32%. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15%.

1-(3-Butenyl)-5,7-dimethoxy-6-isopropyl-2-methyl-3,4-dihydronaphthalene (12). The alcohol **11** (0.739 g, 2.3 mmol) was added to 50 ml of dry benzene containing *p*-toluenesulfonic acid hydrate (0.24 g, 1 mmol) and calcium chloride (0.2 g). The solution was stirred at room temperature for 30 min. The mixture was filtered and the filtrate was washed with 20% aqueous $NaHSO_3$ and water until neutral, it was then dried over sodium sulfate. The solvent was evaporated under reduced pressure to give **12** as a yellow oil in 95% yield (0.65 g). This material was used directly for the next step without purification. An analytical sample was purified by chromatography: IR ($CHCl_3$) 2920, 1590, 1440, 1400, and 1310 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.31 [6H, d, J=8 Hz, $CH(CH_3)_2$], 1.88 (3H, brs, $=CCH_3$), 1.98—2.82 (8H, m, CH_2CH_2, CH_2CH_2), 3.60 [1H, sept, J=8 Hz, $CH(CH_3)_2$], 3.73 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 4.78—6.10 (3H, m, CH_2=CH), and 6.57 (1H, s, ArH); MS m/z (rel intensity, %) 301(24), 300(M^+, base), 286(9), 285(42), 247(8), 246(34), and 194(66). Found: C, 80.11; H, 9.18%. Calcd for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39%.

1-(3-Butenyl)-5,7-dimethoxy-6-isopropyl-2-methylnaphthalene (13). A mixture of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (1 g, 4 mmol) and **12** (0.65 g, 2.2 mmol) in benzene (40 ml) was stirred for 15 h at room temperature under argon. The resulting solution was filtered through a column of Celite. Evaporation of the solvent afforded **13** as a bright yellow oil (0.6 g, 93%). The oil was used without further purification for the next reaction. The analytical sample was obtained by flash chromatography. IR ($CHCl_3$) 2930, 1615, 1590, and 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.39 [6H, d, J=7.5 Hz, $CH(CH_3)_2$], 2.46 (3H, s , $ArCH_3$), 2.1—3.7 (5H, m, $CHCH_2CH_2$), 3.83 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.86—6.28 (3H, m, CH_2=CH), 6.98 (1H, s, ArH), and 7.06, 7.72 (2H , ABq, J=8 Hz, ArH). MS m/z (rel intensity) 299 (6), 298 (M^+, 23), 245 (18), 244 (base), 214 (4). Found: C, 80.55; H, 8.76%. Calcd for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78%.

3-(5,7-Dimethoxy-6-isopropyl-2-methyl-1-naphthalene)-propionic Acid (14). To a solution of **13** (0.118 g, 0.4 mmol) in 40 ml of dioxane was added a mixed solution made from 0.52 g of KIO_4, 33.5 mg of $KMnO_4$, 16.8 mg of Na_2CO_3 and 20 ml of water. The mixture was stirred for 15 h at room

temperature. The excess reagent was decomposed by the addition of 5% aqueous H_2O_2 under ice cooling and most of the dioxane was evaporated, the residual solution was acidified with concentrated hydrochloric acid and extracted with dichloromethane. The organic layer was extracted three times with 5% sodium hydroxide solution. The combined alkaline extracts were acidified with concentrated hydrochloric acid and extracted thoroughly with ether. The organic layer was washed with water, dried over sodium sulfate, and evaporated to give an oil. Recrystallization from benzene/hexane afforded 0.101 g (80%) of **14** as white needles: mp 160—162 °C; IR (KBr) 3400—3500, 2950, 1700, and 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.42 [6H, d, J=7.5 Hz, $CH(CH_3)_2$], 2.47 (3H, s, $ArCH_3$), 2.50—3.54 (4H, m, CH_2CH_2), 3.71 [1H, sept, J=7.5 Hz, $CH(CH_3)_2$], 3.84 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 7.09 (1H, s, ArH), 7.06, 7.73 (2H, ABq, J=8.5 Hz), and 10.23 (1H, brs, COOH). Found: C, 71.91; H, 7.63%; Calcd for $C_{19}H_{24}O_4$: C, 72.12; H, 7.64%.

7,9-Dimethoxy-8-isopropyl-4-methyl-1*H*-phenalen-1-one (16a). To a stirred suspension of phosphorus pentachloride (113 mg, 0.54 mmol) in dry benzene (2 ml), a solution of the propionic acid **14** (150 mg, 0.48 mmol) in benzene was added dropwise at room temperature under argon. When the vigorous reaction subsided, more benzene (2 ml) was added and the mixture warmed to 50—60 °C for 30 min. The clear solution was chilled in an ice bath and a solution of tin(IV) chloride (10 mg) in benzene (1 ml) was added dropwise with stirring while keeping the temperature below 5 °C. After being maintained for 2 h more at 5 °C, the dark solution was decomposed by the slow addition of 1 : 1 (v/v) hydrochloric acid/water (1 ml) while avoiding a rise in temperature above 15 °C. The clear red solution was separated and washed thoroughly with dilute hydrochloric acid, then water. Removal of benzene left a clear mobile oil which after chromatography (hexane/ethyl acetate 3 : 1) gave an oil (97 mg, 68%) of **16a**. IR ($CHCl_3$) 2950, 2850, 1670, 1605, and 1570 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.40 [6H, d, J=7.5 Hz, $CH(CH_3)_2$], 2.47 (3H, s, $ArCH_3$), 2.77—2.98 (2H, m, J=8 Hz, $ArCH_2$), 3.19—3.38 (2H, m, J=8 Hz, $COCH_2$), 3.68 [1H, sept, J=7.5 Hz, $CH(CH_3)_2$], 3.93 (6H, s, OCH_3×2), and 7.29, 7.86 (2H, ABq, J=8.5 Hz, ArH). MS m/z (rel intensity) 298 (M^+, 91), 284 (23), 283 (base), 281 (35), and 265 (52). Found: C, 76.24; H, 7.44%; Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43%.

1-Ethynyl-7,9-dimethoxy-8-isopropyl-4-methyl-2,3-dihydro-1*H*-phenalen-1-ol (17). To a solution of lithium acetylide-ethylenediamine complex (0.138 g, 1.5 mmol) in anhydrous tetrahydrofuran (30 ml), a solution of **16a** (46 mg, 0.15 mmol) in dry tetrahydrofuran (10 ml) was added with stirring under an argon atmosphere. The reaction mixture was stirred for 18 h at room temperature. The mixture was poured into 5% ammonium chloride solution and extracted with ether. The combined ether extracts were washed with 2% HCl solution and water, dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash silica-gel chromatography gave white crystals **17** (46 mg, 92%). Mp: 123—126 °C; IR(CCl_4) 3480, 3300, 2950, 1600, 1485, 1440, and 1380 cm^{-1}. ^1H NMR ($CDCl_3$) δ=1.42 (3H, d, J=8.5 Hz, $CHCH_3$), 1.50 (3H, d, J=8.5 Hz, $CHCH_3$), 2.43 (3H, s, $ArCH_3$), 2.60 (1H, s, C≡CH), 2.00—3.35 (4H, m, CH_2CH_2), 3.50 [1H, m, J=8.5 Hz, $CH(CH_3)_2$], 3.93 (3H, s, OCH_3), 4.05 (3H, s, OCH_3), 6.38 (1H, s, OH), and 7.24, 7.75 (2H, ABq, J=9 Hz). MS m/z (rel intensity) 325 (7), 324 (M^+, 40), 307 (30), 306 (base), and 291 (23). Found: C, 77.93; H, 7.56%. Calcd for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46%.

4-Acetyl-2-isopropyl-3-methoxy-7-methyl-1*H*-phenalen-1-one (18). To a solution of 1.4 ml of water, 0.16 ml of concentrated sulfuric acid and 0.1 ml of methanol, was added 1 mg of mercury(II) sulfate in 1 ml methanol. A solution of **17** (13 mg, 0.04 mmol) in 1 ml of MeOH was added to the solution at 50 °C with rapid stirring. The temperature was maintained at 50—55 °C throughout the reaction. After the reaction was completed (1 h), the reaction mixture was cooled to room temperature, 5 ml of water added and the product extracted with ether. The ether extract was washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent followed by chromatography on silica gel with hexane/ethyl acetate (8 : 2) afforded 8.2 mg (68%) of **18** as bright yellow orange needles. Mp: 114—116 °C; ^1H NMR ($CDCl_3$) δ=1.43 [6H, d, J=7 Hz, $CH(CH_3)_2$], 2.52 (3H, s, CH_3CO), 2.82 (3H, J=1 Hz, $ArCH_3$), 3.34 (1H, sept, J=7 Hz), 3.65 (3H, s, OCH_3), 7.33, 8.19 (2H, ABq, J=8.5 Hz), and 7.58, 8.49 (2H, ABq, J=7.7 Hz); MS m/z (rel intensity) 309 (14), 308 (M^+, 60), 294 (21), 293 (base), 279 (10), 278 (11), and 265 (48). Found: C, 77.65, H, 6.79%; Calcd for $C_{20}H_{20}O_3$: C, 77.90; H, 6.54%.

1-Isopropenyl-8-isopropyl-7,9-dimethoxy-4-methyl-2,3-dihydro-1*H*-phenalen-1-ol (19). A solution of isopropenyllithium in tetrahydrofuran was prepared by addition of butyllithium (0.8 M in hexane, 1 ml) to 2-bromopropene (0.1 ml) in 1 ml of dry tetrahydrofuran at −78 °C under argon followed by stirring for an additional 1 h at −78 °C. A ketone **16a** (85 mg, 0.29 mmol) in 0.5 ml tetrahydrofuran was added slowly to the stirred solution via a syringe. The reaction mixture was stirred for 2.5 h at −78 °C under argon, and the mixture was allowed to warm to 0 °C. Saturated aqueous sodium chloride was added to the reaction mixture, and the phases were separated. The aqueous phase was extracted with three 20 ml portions of ether. The combined organic phases were dried over anhydrous sodium sulfate and concentrated under vacuum to yield the crude product. Flash chromatography of the crude oil on silica gel with hexane/ether (8 : 1) afforded 87 mg (90%) of **19** as a pale yellow oil. IR ($CHCl_3$) 3430 and 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.39 (3H, d, J=7.3 Hz), 1.49 (3H, d, J=7.3 Hz), 2.02 (3H, s, CH_3), 2.40 (3H, s, $ArCH_3$), 2.60—3.70 (4H, m, CH_2CH_2), 3.42 [1H, sept, J=7.3 Hz, $CH(CH_3)_2$], 3.77 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 4.89 (2H, brs, CH_2=), and 7.20, 7.76 (2H, ABq, J=8.7 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ=18.5, 20.0, 22.6, 23.2, 24.1, 26.3, 34.1, 62.5, 63.0, 77.8, 114.0, 119.1, 125.5, 128.1, 128.6, 130.5, 131.3, 132.2, 132.8, 151.7, 153.8, 156.5; MS m/z (rel intensity) 340 (M^+, 33), 323 (26), 322 (63), 307 (18), 306 (7), 300 (29), and 299 (base). Found: C, 77.80; H, 8.34%; Calcd for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29%.

9-Isopropyl-2,2,5-trimethylphenaleno[1,9-*bc*]furan-8(2*H*)-one (Salvilenone, 1) and 20. A mixture of alcohol **19** (30 mg, 0.088 mmol), acetic acid (4 ml), and 47% hydrobromic acid (1 ml) was heated under reflux for 48 h. The reaction mixture was evaporated in vacuo, and ether added to the residue. The ethereal solution was washed with 5% sodium carbonate solution and water, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was separated by preparative TLC (silica gel, was developed twice with 8 : 2 hexane/ethyl acetate) to give **1** (17 mg, 66%) and hydroxy diketone **20** (5.4 mg, 20%). Hydroxy diketone was recrystallized from hexane: mp 134—136 °C; IR 3460, 1712, and 1677 cm^{-1}. ^1H NMR ($CDCl_3$) δ=

0.95 (3H, d, J=6 Hz, $CHCH_3$), 0.97 (3H, d, J=6 Hz), 1.35 (3H, d, J=7 Hz), 1.47 (3H, d, J=7 Hz), 2.34 [1H, sept, J=6 Hz, $CH(CH_3)_2$], 2.80 (3H, s, $ArCH_3$), 4.10 [1H, sept, J=7 Hz, $ArCH(CH_3)_2$], 7.53 (1H, d, J=8 Hz, ABq), 7.79 (1H, d, J=9 Hz, ABq), 8.27 (1H, d, J=9 Hz, ABq), 8.35 (1H, d, J=8 Hz, ABq), and 9.67 (1H, brs, OH). MS m/z 311 (M^++1) 310 (M^+), 292 (M^+−18), and 267 (M^+−43); UV (EtOH): 208 (21080), 238 (44950), 325 nm (8060). ^{13}C NMR (125 MHz, $CDCl_3$) δ= 16.6(q), 17.0(q), 20.2(q), 23.3(q), 24.7(q), 29.3(d), 36.1(d), 101.6(s), 126.0(d), 126.7(s), 126.8(s), 127.2(d), 129.0(d), 129.7(d), 130.3(s), 131.8(s), 142.9(s), 152.8(s), 193.2(s), and 197.7(s). Found: C, 77.20; H, 7.16%; Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14%.

2-Hydroxy-2,4-diisopropyl-7-methyl-1*H*-phenalene-1,3(2*H*)-dione (20). A mixture of 7 mg of alcohol **19**, 2 ml of glacial acetic acid, and 1 ml of 50% hydriodic acid solution was heated under reflux for 35 h. The reaction mixture was concentrated in vacuo., and extracted with ether. The ether extracts were filtered through celite until the filtrate became clear. The combined filtrates were washed with 10% $NaHCO_3$ and water, dried, and concentrated. The residue was purified by chromatography on silica gel using hexane/ethyl acetate (7:3) as eluent to give 3.9 mg (59%) of a white solid, which was identical with the hydroxy diketone **20** obtained in the preceding experiment.

4-Isopropenyl-2-isopropyl-3-methoxy-7-methyl-1*H*-phenalen-1-one (21). A mixture of 7 mg (0.02 mmol) of alcohol **19** and iodine in 6 ml of carbon tetrachloride was stirred for 17 h at room temperature. The iodine was decomposed by addition of $Na_2S_2O_3$. After the precipitates were removed, the solution was washed with water, dried over sodium sulfate, and evaporated to give a yellow solid. Purification of the crude product by preparative TLC (hexane/ethyl acetate 6:49) gave 3.4 mg (54%) of **21** as an orange yellow solid. Mp 120—122 °C; ^1H NMR ($CDCl_3$) δ=1.42 [6H, d, J=7 Hz, $CH(CH_3)_2$], 2.01 (3H, s, $CH_3C{=}CH_2$), 2.81 (3H, s, $ArCH_3$), 3.44 [1H, sept, J=7 Hz, $CH(CH_3)_2$], 3.70 (3H, s, OCH_3), 5.1 (2H, m, $CH_3C{=}CH_2$), 7.27 (1H, d, J=9 Hz), 7.63 (1H, d, J=8 Hz), 8.12 (1H, d, J=9 Hz), and 8.48 (1H, d, J=8 Hz). MS m/z 360 (M^+). Found: C, 82.44; H, 7.33%. Calcd for $C_{21}H_{22}O_2$: C, 82.32; H, 7.23%.

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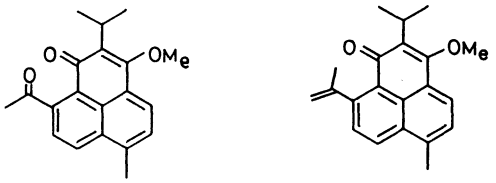

18' 21'

Scheme 5.