Structure Elucidation and Total Synthesis of New Tanshinones Isolated from *Salvia miltiorrhiza* Bunge (Danshen)†

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Totally 11 new compounds have been isolated from the dried root of *Salvia miltiorrhiza* Bunge "Danshen" and their structures were elucidated by means of spectrometric methods. The total syntheses of two new compounds, namely, 1,2-didehydromiltirone and 4-methylenemiltirone, are also reported.

Introduction

The rhizome of *Salvia miltiorrhiza* Bunge (Labiatae), also known as "Tanshen" or "Danshen" in Chinese, has been used widely in China to treat coronary heart diseases, particularly angina pectoris and myocardial infarction.[2,3] It reportedly has sedative and tranquilizing effects and is also being used to treat neurasthenic insomnia.[3-5]

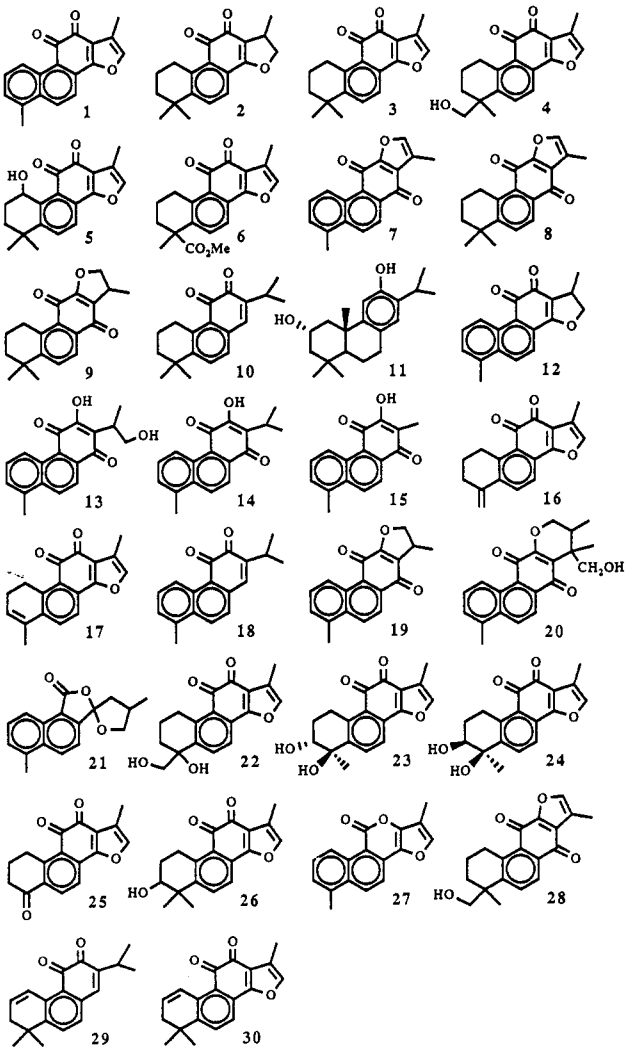
The chemical composition of Danshen has been studied extensively over the last 50 years. The alcohol extract of Danshen is particularly rich in abietanoids and diterpene quinone pigments. In fact, no less than 30 diterpenoid tanshinones have been isolated and identified from *Salvia miltiorrhiza* between 1934 and 1988. These include **1**,[6,7] **2**,[8] **3**,[9] **4**,[10,11] **5**,[12] **6**,[12] **7**,[13] **8**,[13] **9**,[13] **10**,[14] **11**,[15] **12**,[16,17] **13**,[16] **14**,[16] **15**,[16] **16**,[18] **17**,[18] **18**,[19] **19**,[20] **20**,[21] **21**,[22,23] **22**,[24] **23**,[24] **24**,[24] **25**,[24] **26**,[24] **27**,[25] **28**,[26] **29**,[27] and **30**[27] (Scheme I).

Diterpenoid tanshinones have attracted particular attention of medicinal chemists and clinicians because many of them exhibit significant antibacterial,[16,28,29] antidermatophytic,[28,29] antioxidant,[30] antiinflammatory,[29,31] antineoplastic,[32] and antiplatelet aggregation[19,26,27] activities. Tanshinone I (**1**),[6,7] cryptotanshinone (**2**),[8] tanshinone IIA (**3**),[9] danshexinkun A (**13**),[16] and 1,2-dihydrotanshinquinone (**17**)[18] are effective coronary artery dilators,[33] and a water-soluble derivative, sodium tanshinonate IIA sulfonate, has already been tested clinically in coronary heart disease patients with good results.[2,17,34] In an evaluation of the pharmacological profile of Danshen, we detected significant inhibition of [^{3}H]flunitrazepam binding to central benzodiazepine receptors by the crude extract of Danshen. We have, therefore, initiated a systematic isolation of tanshinones from Danshen and studied their interactions with central benzodiazepine receptors. We report here the isolation of 11 novel tanshinones and the total synthesis of some of these compounds.

Results and Discussion

1. Isolation and Structure Elucidation of New Tanshinones. We have isolated totally 26 compounds from the dried root of *Salvia miltiorrhiza* Bunge "Danshen". Of these compounds, 15 are known compounds: **1**, **2**, **3**, **6**, **10**, **12**, **13**, **14**, **16**, **17**, **18**, **21**, **25**, **27**, and **29**. Compound **29** is noteworthy because it was only recorded very recently[27] and was reported to form red oil.

Scheme I



† Dedicated to Professor Wang Yu, Shanghai Institute of Organic Chemistry, Academia Sinica, on the occasion of his 80th birthday.

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Table I. Proton NMR Spectral Data of Compounds 31–41 and 49

compd	proton NMR data (δ)
31	1.32 (s, 6 H), 1.10–2.00 (m, 4 H), 2.27 (d, J = 1 Hz, 3 H), 2.89 (dt, J = 6 Hz, 2 H), 7.32 (q, J = 1 Hz, 1 H), 7.63 (s, 2 H) (60 MHz)
32	1.31 (s, 3 H), 1.33 (s, 3 H), 1.35 (d, J = 6.8 Hz, 3 H), 1.60–1.90 (m, 4 H), 2.70–3.00 (m, 2 H), 3.61 (ddq, J = 9.8, 7.1, 6.8 Hz, 1 H), 4.20 (dd, J = 9.1, 7.1 Hz, 1 H), 4.74 (dd, J = 9.8, 9.1 Hz, 1 H), 7.60 (s, 2 H) (250 MHz)
33	1.41 (d, J = 6.7 Hz, 3 H), 2.74 (s, 3 H), 3.70 (ddq, J = 10.1, 7.3, 6.7 Hz, 1 H), 4.29 (dd, J = 9.1, 7.3 Hz, 1 H), 4.84 (dd, J = 10.1, 9.1 Hz, 1 H), 7.40–7.60 (m, 2 H), 7.86 (d, J = 8.9 Hz, 1 H), 8.00 (d, J = 8.3 Hz, 1 H), 8.25 (d, J = 8.9 Hz, 1 H) (250 MHz)
34	2.35 (d, J = 1 Hz, 3 H), 7.40 (d, J = 1 Hz, 1 H), 7.85 (dd, J = 10 Hz, 1 H), 8.00–8.10 (m, 2 H), 9.60–9.80 (m, 2 H), 10.35 (s, 1 H) (60 MHz)
35	1.38 (d, J = 6.8 Hz, 3 H), 1.80–2.00 (m, 2 H), 2.50–3.00 (m, 2 H), 3.32 (t, J = 6.5 Hz, 2 H), 3.62 (ddq, J = 9.7, 6.8, 6.3 Hz, 1 H), 4.39 (dd, J = 8.9, 6.3 Hz, 1 H), 4.91 (dd, J = 9.7, 9.2 Hz, 1 H), 5.10 (s, 1 H), 5.54 (s, 1 H), 7.52 (d, J = 8.1 Hz, 1 H), 7.90 (d, J = 8.1 Hz, 1 H) (250 MHz)
36	0.93 (s, 6 H), 1.00–1.80 (m, 7 H), 1.11 (d, J = 6.9 Hz, 6 H), 1.37 (s, 3 H), 2.20 (dd, J = 14.0, 7.6 Hz, 1 H), 2.65 (br d, J = 13.1 Hz, 1 H), 2.99 (septet of d, J = 6.9, 1.1 Hz, 1 H), 3.76 (d, J = 2.0 Hz, 1 H), 4.79 (ddd, J = 10.0, 7.6, 2.0 Hz, 1 H), 6.36 (d, J = 1.1 Hz, 1 H) (250 MHz)
37	1.36 (s, 6 H), 1.70 (m, 2 H), 1.95 (m, 2 H), 2.48 (d, J = 0.8 Hz, 3 H), 3.10 (t, J = 6.4 Hz, 2 H), 7.57 (AB q, J = 8.6 Hz, 2 H), 7.96 (s, 1 H), 8.05 (s, 1 H), 8.46 (br s, 1 H) (250 MHz)
38	1.18 (d, J = 6.9 Hz, 6 H), 1.89 (quintet, J = 6.4 Hz, 2 H), 2.51 (m, 2 H), 3.04 (septet, J = 6.9 Hz, 1 H), 3.28 (t, J = 6.4 Hz, 2 H), 5.06 (s, 1 H), 5.50 (s, 1 H), 7.11 (s, 1 H), 7.13 (d, J = 8.0 Hz, 1 H), 7.88 (d, J = 8.0 Hz, 1 H) (250 MHz)
39	1.27 (d, J = 6.9 Hz, 6 H), 1.37 (s, 6 H), 1.99 (t, J = 6.9 Hz, 2 H), 2.85 (t, J = 6.9 Hz, 2 H), 3.36 (septet, J = 6.9 Hz, 1 H), 6.81 (s, 1 H), 7.19 (s, 1 H), 7.25 (d, J = 8.6 Hz, 1 H), 7.87 (d, J = 8.6 Hz, 1 H), 10.56 (s, 1 H) (250 MHz)
40	0.92 (s, 3 H), 0.95 (s, 3 H), 1.21 (d, J = 6.9 Hz, 3 H), 1.23 (s, 3 H), 1.24 (d, J = 6.9 Hz, 3 H), 1.22–1.90 (m, 6 H), 2.24 (m, 1 H), 2.50–2.60 (m, 2 H), 3.26 (septet, J = 6.9 Hz, 1 H), 6.87 (s, 1 H), 7.81 (s, 1 H), 9.03 (br s, 1 H) (250 MHz)
41	1.38 (d, J = 6.8 Hz, 3 H), 2.07 (d, J = 1.3 Hz, 3 H), 2.26 (m, 2 H), 3.38 (t, J = 8.0 Hz, 2 H), 3.62 (ddq, J = 9.5, 6.8, 6.1 Hz, 1 H), 4.38 (dd, J = 9.5, 6.1 Hz, 1 H), 4.91 (t, J = 9.5 Hz, 1 H), 6.10 (m, 1 H), 7.43 (d, J = 7.9 Hz, 1 H), 7.54 (d, J = 7.9 Hz, 1 H) (250 MHz)
49	1.35 (s, 6 H), 1.73 (t, J = 6 Hz, 2 H), 1.95 (quintet, J = 6.2 Hz, 2 H), 2.77 (s, 3 H), 2.97 (t, J = 6.3 Hz, 2 H), 7.36 (d, J = 8.8 Hz, 2 H), 7.40 (s, 1 H), 7.62 (d, J = 8.8 Hz, 1 H), 8.26 (s, 1 H), 11.61 (s, 1 H) (250 MHz)

We, however, also isolated **29** and found that it formed red crystals with mp 71–75 °C. The structure of **29** is also supported by our total synthesis (vide infra).

In addition to these known compounds, we also isolated 11 new compounds, **31**–**41** (Scheme II). The structure elucidations of compounds **31**, **32**, and **33** will be reported

Scheme II

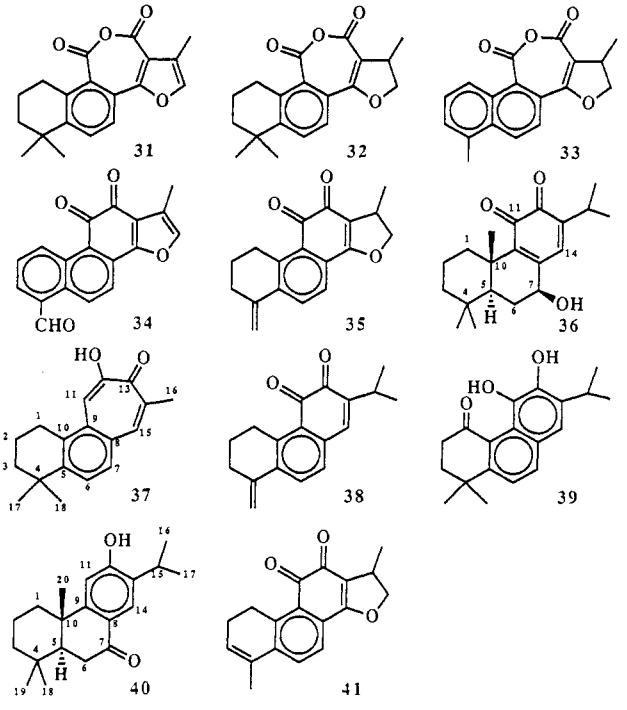

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Table II. Carbon-13 NMR Spectral Data of Compounds 37, 40, and 49[a]

carbon	compound 37[b,c]	40[d]	49[c]
1	28.79	38.47	38.81
2	19.66	19.39	26.59
3	38.17	42.00	19.34
4	34.92	33.65	34.61
5	131.25	50.30	146.55
6	126.93	36.37	127.13
7	132.26	197.50	123.55
8	134.00	124.34	125.27
9	135.95	158.61	129.38
10	133.94	38.47	137.89
11	112.98	110.19	108.93
12	153.89	160.35	157.53
13	179.88	133.63	123.55
14	148.75	126.49	133.30
15	143.88	27.24	204.35
16	22.01	22.54	26.73
17	31.58	22.86	31.12
18	31.58	32.61	31.12
19		21.57	
20		23.41	

[a] The assignments are based on DEPT spectra. [b] The assignments are confirmed by 2D ^{13}C-^{1}H COSY spectrum. [c] δ, ppm in $CDCl_3$ downfield from TMS (62.896 MHz). [d] δ, ppm in CD_3COCD_3-$CDCl_3$ downfield from TMS (62.896 MHz).

elsewhere.[35] Their proton NMR data are listed in Table I. It is interesting to point out that **31** was proposed by Kusumi[36] as an artifact produced by the photooxidation of **3**.[9]

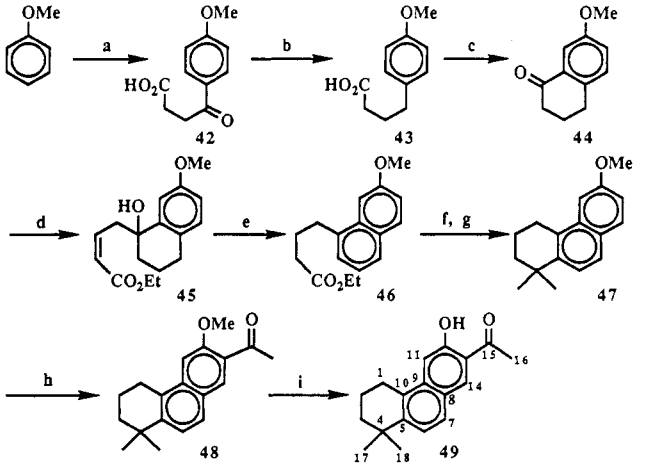
The structures of compounds **34**, **35**, and **38** were established by their proton NMR spectral data (see Table I). Formyltanshinone (**34**) forms red crystals, mp 271–273 °C (from hexanes/ethyl acetate). The proton NMR of **34** is similar to that of **1**.[6,7]

Methylenedihydrotanshinquinone (**35**) forms red crystals, mp 146–147.5 °C (from hexanes/ethyl acetate). The proton NMR of **35** is similar to that of **16**.[18]

4-Methylenemiltirone (**38**) forms red crystals, mp 137–140 °C (from hexanes). The proton NMR of **38** indicates that it constitutes a terminal olefinic system, which absorbs at δ 5.06 (s, 1 H) and 5.50 (s, 1 H). Furthermore, the structure of **38** is unambiguously substantiated by a total synthesis (vide infra).

While the structure elucidation of **34**, **35**, and **38** was trivial, the assignment[37] of structures of compounds **36** and **37** required extensive spectroscopic methods. Salviolone (**37**) was recorded in 1988[38] as a light yellow oil. We have discovered that **37** forms light yellowish crystals, mp 180–182 °C (from hexanes/ethyl acetate). The structure of **37** is supported by its proton NMR spectrum (Table I). IR absorption at 1629 cm^{-1} is typical for a tropone. 2D COSY and NOESY studies, nevertheless, confirmed our structure elucidation.[38] The ^{13}C NMR spectrum, which contains signals for all 18 carbons, convincingly shows a tropone carbonyl absorption at 179.88 (Table II). The structure of **37** is also unequivocally substantiated by a total synthesis.[38] In order to prove that **37** does not possess a naphthalene skeleton, we prepared a naphthalene isomer

Scheme III[a]



[a] (a) $(CH_2CO)_2O$, $AlCl_3$, $C_6H_5NO_2$; (b) Zn, $HgCl_2$, HCl, heat; (c) P_2O_5; H_3PO_4, heat; (d) Zn, $BrCH_2CH{=}CHCO_2Et$, THF, ultrasound; (e) Pd–C, 280–300 °C; (f) MeLi, THF; (g) PPA, heat; (h) CH_3COCl, $AlCl_3$, CH_2Cl_2; (i) BBr_3, CH_2Cl_2.

of **37**, namely, 1,2,3,4-tetrahydro-1,1-dimethyl-7-acetyl-6-phenanthrol (**49**) from anisole (Scheme III). However, Luo and his co-workers reported recently[39] the isolation of a new compound with the structure of **49** from Danshen. After careful comparison of their spectroscopic data with those of **37** and **49** obtained in our own laboratories, it is clear that the unknown compound isolated by Luo and his co-workers by all means possesses the structure identical with **37**. All steps of the synthetic procedure for **49** are similar to those for the preparation of miltirone (**10**) (vide infra). However, the most important step of this maneuver is the Friedel–Crafts acetylation[40] of the key intermediate **47**, which underwent smooth reaction with acetyl chloride and aluminum chloride in dichloromethane. Deprotection of the methoxy group of the resulting acetyl product **48** afforded our target molecule **49** whose structure is established by proton NMR data (Table I). Moreover, the ^{13}C NMR data are in full accord with the proposed structure (Table II). From the result of this synthesis, it is therefore clear that compound **37** does not possess a naphthalene skeleton.

7β-Hydroxy-8,13-abietadiene-11,12-dione (**36**) forms light yellowish crystals, mp 83–84 °C (from hexanes/ethyl acetate). The proton NMR of **36** is rather complicated because some of the methylenic protons are obscured by the methyl proton absorptions. However, a choice in favor of structure **36** might have been made on the basis of proton absorptions supported by 2D COSY and NOESY. Thus, the structure of **36** is established by these proton NMR absorption data: δ 2.20 ($H_{6\beta}$), 2.65 ($H_{1\alpha}$), 3.76 (OH), 4.79 ($H_{7\alpha}$), and 6.36 (H_{14}) (see Table I).

Arucadiol (**39**) had already been isolated as a red oil from the root of *Salvia argentea*.[41] However, it was later also isolated from *Salvia miltiorrhiza* as an oil and was instead called miltiodiol.[38] We also independently isolated arucadiol (**39**) from Danshen and found out that it forms orange-red crystals, mp 98–100 °C (from hexanes/ethyl acetate). All physical (except melting point) and spectroscopic data of **39** are identical with those reported[38,41] (see Table I).

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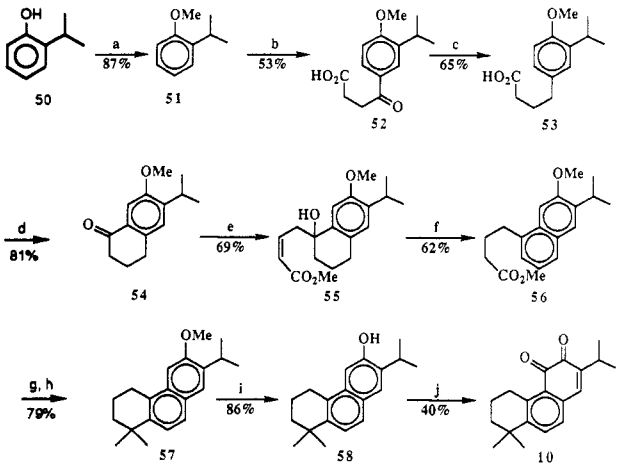
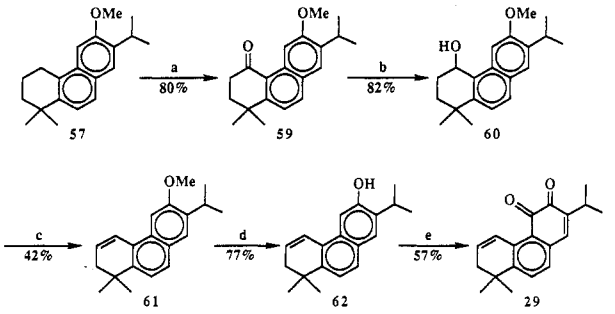
Scheme IV[a]



[a] (a) Me_2SO_4, aq NaOH; (b) $(CH_2CO)_2O$, $AlCl_3$, $C_6H_5NO_2$; (c) Zn, $HgCl_2$, HCl, heat; (d) P_2O_5, H_3PO_4, heat; (e) Zn, $BrCH_2CH{=}CHCO_2Me$, THF, ultrasound; (f) Pd-C, 280–300 °C; (g) MeMgI, Et_2O; (h) P_2O_5, H_3PO_4, heat; (i) BBr_3, CH_2Cl_2, 0 °C; (j) Fremy's salt, KH_2PO_4, H_2O.

Scheme V[a]



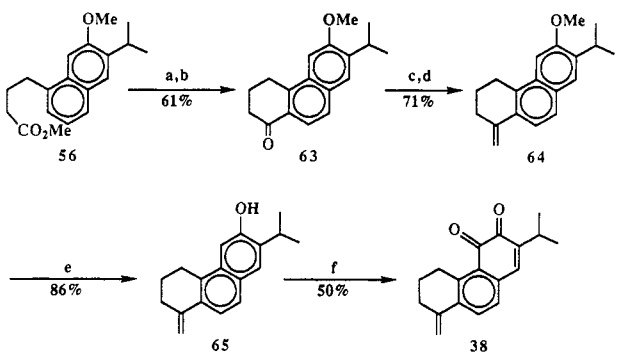
[a] (a) PCC, CH_2Cl_2; (b) $NaBH_4$, EtOH; (c) MsCl, Et_3N, CH_2Cl_2; (d) NaH, CH_3CH_2SH, DMF; (e) Fremy's salt, KH_2PO_4, CH_3COCH_3.

Sugiol (**40**) had been isolated from New Zealand tree rimu (*Dacrydium cupressinum*) as well as from other sources.[42] To our best knowledge, it was isolated for the first time from Danshen. Sugiol (**40**) forms colorless crystals, mp 273–275 °C (from hexanes/ethyl acetate) (lit.[42] mp 283–284 °C). All spectroscopic data of **40** are identical with those reported[42] (see Tables I and II).

1,2,5,6-Tetrahydrotanshinone I (**41**) forms red crystals, mp 142–144 °C (from hexanes/ethyl acetate). The structure of **41** can unambiguously be confirmed by comparison of its proton NMR spectrum (see Table I) with those of the known **12**[16,17] and **17**.[18]

2. Total Synthesis of 1,2-Didehydromiltirone (29) and 4-Methylenemiltirone (38). Based on our modified synthesis of miltirone **10**,[43] total syntheses of compounds **29** and **38** have been accomplished. Our first target molecule, **10**, consists of three kinds of functionalities, i.e., the tetrahydrophenanthrene skeleton, the isopropyl substituent, and the *o*-quinone functional group. These characteristic groups were constructed through a series of

Scheme VI[a]



[a] (a) KOH, H_2O, heat; (b) PPA, 60–70 °C; (c) Me_3SiCH_2Cl, Mg, Et_2O, $(CH_2)_2Br_2$; (d) KH, THF; (e) NaH, CH_3CH_2Sh, DMF, 150 °C; (f) Fremy's salt, H_2O, CH_3COCH_3.

conventional reactions[43,44] (Scheme IV). Thus, our first target molecule **10**, whose physical and spectroscopic data are identical with those of an authentic sample isolated from Danshen, was prepared from the commonly available 2-isopropylphenol (**50**).

Starting from **57**, compound **29** was also conveniently synthesized by making use of well-established procedures as outlined in Scheme V. The proton NMR absorptions of **29** are in full accord with those of the natural product.[27]

The most important step in the total synthesis of compound **38** involves the construction of the terminal methylene group, whose introduction was achieved by reaction of **63** with trimethylsilylmethylmagnesium chloride, yielding the intermediate silyl alcohol. Peterson olefination of this silyl alcohol with potassium hydride gave **64**. Because the terminal double bond of **64** is prone to reaction with Lewis acid, sodium hydride and ethanethiol were used to effect the deprotection of the methyl ether. Thus, **64** was converted to alcohol **65** which was oxidized with Fremy's salt to yield compound **38**. The physical and spectroscopic data of **38** are identical with those of the natural **38** (see Table I).

Experimental Section

Proton NMR spectra were recorded on a Bruker Cryospec WM 250 (250 MHz) spectrometer or a JEOL PMX 60SI (60 MHz) spectrometer. The chemical shift was measured with tetramethylsilane (TMS) serving as internal standard, and deuterated chloroform was used as solvent unless stated otherwise. Mass spectra were recorded on a VG Micromass 7070F spectrometer. IR spectra were run on a JASCO A-100 infrared spectrophotometer.

Merck silica gel (60 F_{254}) precoated on aluminum sheet was used for TLC studies, and Merck silica gel (70–230 mesh) was used for column chromatography. Melting points were measured on a hot-stage microscope and are uncorrected.

4-Oxo-4-(4′-methoxyphenyl)butyric Acid (42). Succinic anhydride (36 g, 0.36 mol) and anisole (35.7 g, 0.33 mol) were added with stirring to nitrobenzene (150 mL). Aluminum chloride (94 g, 0.7 mol) was added slowly at 0 °C. The resulting mixture was stirred overnight at room temperature. The solution was then poured into ice–water (600 mL) and 10% aqueous solution was extracted with ether (3 × 300 mL). The aqueous layer was acidified with 2 N HCl and again extracted with EtOAc (4 × 300 mL). The combined organic extracts were washed with brine (2 × 200 mL), dried over sodium sulfate, and evaporated. The residue was recrystallized from absolute EtOH to give colorless crystals of **42** (49.5 g, 72%), mp 147.5–148.5 °C (lit.[45] mp 146 °C): MS *m/e* 208 (M^+); ^1H NMR δ 2.08 (t, *J* = 6.6 Hz, 2 H), 3.28 (t, *J* = 6.6 Hz, 2 H), 3.88 (s, 3 H), 6.95, 7.97 (dd, *J* = 1.9 Hz, 6.9 Hz,

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4 H). Anal. Calcd: C, 63.46; H, 5.77; O, 30.77. Found: C, 63.28; H, 5.66.

4-(4'-Methoxyphenyl)butyric Acid (43). Zinc wool (53.3 g, 0.8 mol), mercuric chloride (5.3 g), concentrated HCl (4.5 mL), and water (120 mL) were mixed together with stirring for 10 min. The aqueous layer was decanted and washed with water. Compound **42** (22.2 g, 0.1 mol) in toluene (152 mL) was added, followed by concentrated HCl (76 mL) and water (38 mL). The mixture was refluxed for 24 h. After cooling, water (250 mL) was added. The resulting mixture was extracted with EtOAc (3 × 100 mL). The organic extracts were washed with water (3 × 100 mL), dried over sodium sulfate, and evaporated. The crude product obtained (18 g, 87%) was further purified by chromatography on a silica gel column (230–400 mesh, hexanes/EtOAc 60:40) to give colorless crystals of **43**, mp 60.5–61.5 °C (lit.[45] mp 61 °C): MS *m/e* 194 (M^+); ^1H NMR δ 1.93 (quintet, J = 7.5 Hz, 2 H), 2.36 (t, J = 7.5 Hz, 2 H), 2.61 (t, J = 7.5 Hz, 2 H), 3.78 (s, 3 H), 6.83, 7.10 (dd, J = 2.0 Hz, 6.6 Hz, 4 H). Anal. Calcd: C, 68.04; H, 7.22; O, 24.74. Found: C, 67.81; H, 7.18.

7-Methoxy-1-tetralone (44). Phosphorus(V) oxide (114 g) and phosphoric acid (85%, 56 mL) were mixed with mechanical stirring and heated to 80–90 °C for 4 h. Compound **43** (7.5 g, 38.6 mmol) in dichloromethane (13 mL) was added and the resulting mixture was heated at 70–80 °C for 2 h. Ice-water (300 mL) was added to decompose the polyphosphoric acid, and the mixture was extracted with ether (3 × 150 mL). The ethereal extract was washed with aqueous potassium carbonate (2 × 80 mL) and brine (2 × 50 mL), dried over sodium sulfate, and evaporated to give a yellowish solid (6.4 g, 94%). The crude product was recrystallized from EtOAc/hexane (15:85) to afford colorless prism crystals of **44**, mp 61 °C (lit.[45] mp 62 °C): MS *m/e* 176 (M^+); ^1H NMR δ 2.11 (quintet, J = 6 Hz, 2 H), 2.63 (t, J = 6 Hz, 2 H), 2.89 (t, J = 6 Hz, 2 H), 3.83 (s, 3 H), 7.05 (dd, J = 2.8 Hz, 8.4 Hz, 1 H), 7.16 (d, J = 8.4 Hz, 1 H), 7.50 (d, J = 2.8 Hz, 1 H). Anal. Calcd: C, 75.00; H, 6.82; O, 18.18. Found: C, 75.58; H, 7.14.

Ethyl 4-(1,2,3,4-Tetrahydro-4-hydroxy-7-methoxy-1-naphthyl)but-2-enoate (45).[43] A mixture of zinc wool (4.5 g), ethyl 4-bromocrotonate (9.2 mL), tetralone **44** (3.15 g, 17.9 mmol), and THF (32.5 mL) was allowed to react with the aid of an ultrasonicator for 2 h. The reaction mixture was poured into 10% aqueous potassium hydrogen sulfate (70 mL) and extracted with dichloromethane (3 × 30 mL). The extract was washed with brine (2 × 50 mL), dried over sodium sulfate, and evaporated. The residue was purified by flash chromatography on a silica gel column (230–400 mesh, hexanes/EtOAc 95:5) to give **45** as a light yellowish oil (4.45 g, 86%): MS *m/e* 290 (M^+); ^1H NMR δ 1.28 (t, J = 7 Hz, 3 H), 1.75–2.00 (m, 4 H), 2.70 (t, J = 7 Hz, 2 H), 2.71 (t, J = 7 Hz, 2 H), 3.79 (s, 3 H), 4.17 (q, J = 7.1 Hz, 2 H), 5.87 (d, J = 15.6 Hz, 1 H), 6.76 (dd, J = 2.7 Hz, 8.4 Hz, 1 H), 6.95 (d, J = 7 Hz, 1 H), 7.00 (dd, J = 2 Hz, 8 Hz, 1 H), 7.08 (d, J = 2.7 Hz, 1 H).

Ethyl 4-(7-Methoxy-1-naphthyl)butanoate (46). A mixture of the ester **45** (2.1 g, 7.1 mmol) and palladium black (209 mg) was heated at 230–250 °C under nitrogen for 2 h. The mixture was cooled and dichloromethane (20 mL) was added. The resulting mixture was filtered through a layer of diatomaceous earth to remove the catalyst. The filtrate was evaporated and the residue was purified by flash chromatography on a silica gel (230–400 mesh, hexanes/EtOAc 95:5) to give colorless oil **46** (935 mg, 48%): MS *m/e* 272 (M^+); ^1H NMR δ 1.25 (t, J = 7.1 Hz, 3 H), 2.07 (quintet, J = 7.2 Hz, 2 H), 2.40 (t, J = 7.2 Hz, 2 H), 3.05 (t, J = 7.5 Hz, 2 H), 3.95 (s, 3 H), 4.13 (q, J = 7.1 Hz, 2 H), 7.14 (dd, J = 2.4 Hz, 8.9 Hz, 1 H), 7.23 (t, J = 7.0 Hz, 1 H), 7.25 (d, J = 7.0 Hz, 1 H), 7.37 (d, J = 2.3 Hz, 1 H), 7.63 (dd, J = 2.1 Hz, 7.0 Hz, 1 H), 7.73 (d, J = 8.9 Hz, 1 H). Anal. Calcd: C, 75.00; H, 7.35; O, 17.65. Found: C, 74.34; H, 7.22.

1,2,3,4-Tetrahydro-1,1-dimethyl-6-methoxyphenanthrene (47). Compound **46** (1.28 g, 4.7 mmol) in THF (13 mL) was stirred at 0 °C. A solution of methyllithium in ether (1.6 M, 10.5 mL) was added dropwise. The mixture was stirred for 3.5 h with cooling at 0 °C. After that, ice-water (20 mL) was added. The resulting mixture was extracted with ether (3 × 20 mL). The ethereal extracts were washed with brine (2 × 30 mL), dried over sodium sulfate, and evaporated. The crude tertiary alcohol was used in the next step without further purification. However, an analytically pure sample of the crude tertiary alcohol was obtained by purification on a silica gel column (230–400 mesh, hexanes/EtOAc 90:10), giving light yellowish oil: MS *m/e* 258 (M^+); ^1H NMR δ 1.21 (s, 6 H), 1.62 (t, J = 6.5 Hz, 2 H), 1.84 (quintet, J = 8 Hz, 2 H), 3.03 (t, J = 7.5 Hz, 2 H), 3.93 (s, 3 H), 7.15 (dd, J = 2.5 Hz, 8.9 Hz, 1 H), 7.25 (t, J = 8 Hz, 1 H), 7.28 (s, 1 H), 7.29 (d, J = 2.4 Hz, 1 H), 7.64 (d, J = 8.6 Hz, 1 H), 7.75 (d, J = 8.9 Hz, 1 H). Anal. Calcd: C, 79.07; H, 8.53; O, 12.40. Found: C, 78.83; H, 8.61.

The tertiary alcohol (1 g, 4 mmol) in dichloromethane (5 mL) was added dropwise to polyphosphoric acid (22 g) (preheated at 60–70 °C for 30 min). The resulting mixture was stirred at 60–70 °C for 2 h. Ice–water (50 mL) was added and the mixture was extracted with ether (3 × 50 mL). The ethereal extract was washed with aqueous potassium carbonate (2 × 50 mL) and brine (2 × 50 mL), and dried over sodium sulfate. After evaporation, the residue was purified by recrystallization from methanol to give **47** (604 mg, 63% from **46**) as colorless needles, mp 117–118 °C: MS *m/e* 240 (M^+); ^1H NMR δ 1.35 (s, 6 H), 1.73 (t, J = 6 Hz, 2 H), 1.97 (quintet, J = 6 Hz, 2 H), 3.04 (t, J = 6 Hz, 2 H), 3.92 (s, 3 H), 7.09 (dd, J = 2.4 Hz, 8.8 Hz, 1 H), 7.24 (s, 1 H), 7.36 (d, J = 8.6 Hz, 1 H), 7.59 (d, J = 8.6 Hz, 1 H), 7.68 (d, J = 8.8 Hz, 1 H). Anal. Calcd: C, 85.00; H, 8.33; O, 6.66. Found: C, 84.97; H, 8.44.

1,2,3,4-Tetrahydro-1,1-dimethyl-6-methoxy-7-acetylphenanthrene (48). To a solution of compound **47** (56 mg, 0.24 mmol) in dichloromethane (1.2 mL) was added aluminum chloride (187 mg) at 0 °C. Acetyl chloride (0.13 mL) was added slowly via a syringe to the mixture at 0 °C with stirring. The mixture was stirred at room temperature overnight. Ice–water (15 mL) was added and the mixture was extracted with ether (3 × 10 mL). The ethereal extract was washed successively with 10% aqueous sodium hydrogen carbonate (2 × 10 mL) and brine (2 × 10 mL), dried over sodium sulfate, and evaporated. The crude product was chromatographed on a silica gel column (230–400 mesh, hexanes/EtOAc 95:5) to give **48** as colorless crystals (49 mg, 74%), mp 105–107 °C: MS *me* 282 (M^+); ^1H NMR δ 1.35 (s, 6 H), 1.75 (t, J = 6 Hz, 2 H), 1.98 (quintet, J = 6.3 Hz, 2 H), 2.68 (s, 3 H), 3.04 (t, J = 6.3 Hz, 2 H), 4.01 (s, 3 H), 7.25 (s, 1 H), 7.40 (d, J = 8.7 Hz, 1 H), 7.66 (d, J = 8.7 Hz, 1 H), 8.15 (s, 1 H). Anal. Calcd: C, 80.85; H, 7.80; O, 11.35. Found: C, 80.37; H, 7.97.

1,2,3,4-Tetrahydro-1,1-dimethyl-6-hydroxy-7-acetylphenanthrene (49). To an ice-cooled solution of **48** (34 mg, 0.12 mmol) in dichloromethane (2.7 mL) was added dropwise boron tribromide (134 μL). The reaction mixture was stirred (ice bath) for 6 h. Ice-water (15 mL) was added and the mixture was extracted with ether (4 × 10 mL). The ethereal extract was washed with saturated aqueous NaCl (2 × 15 mL) and dried over sodium sulfate. After evaporation, the residue was purified by chromatography on a silica gel column (230–400 mesh, hexane/EtOAc 95:5) to give yellowish prisms of **49** (23 mg, 72%), mp 123–124 °C: MS *m/e* (M^+) (calcd for $C_{18}H_{20}O_2$) 268.1462 (found 268.1465); ^1H NMR δ 1.35 (s, 6 H), 1.73 (t, J = 6 Hz, 2 H), 1.95 (quintet, J = 6.2 Hz, 2 H), 2.77 (s, 3 H), 2.97 (t, J = 6.3 Hz, 2 H), 7.36 (d, J = 8.8 Hz, 2 H), 7.40 (s, 1 H), 7.62 (d, J = 8.8 Hz, 1 H), 8.26 (s, 1 H), 11.61 (s, 1 H).

Methyl 2-Isopropylphenyl Ether (51). 2-Isopropylphenol (**50**) (51 g, 0.37 mol) was mixed with 20% aqueous NaOH (200 mL) with vigorous stirring for 15 min. Dimethyl sulfate (66.7 g, 0.53 mol) was added dropwise within 1 h; the flask was immersed in an ice bath during the addition. The solution mixture was refluxed for 2 h after the addition of dimethyl sulfate. Water (200 mL) was added to the mixture which was followed by ether extraction (3 × 100 mL). The ethereal solution was washed with water (3 × 100 mL), dried over magnesium sulfate and evaporated. The residue was distilled under reduced pressure to give **51** (49 g, 87%), bp 46 °C (0.8 mmHg) [lit.[44] bp 200 °C (745 mmHg)]: MS *m/e* 150 (H^+); ^1H NMR (CCl_4) δ 1.21 (d, J = 7 Hz, 6 H), 3.32 (septet, J = 7 Hz, 1 H), 3.82 (s, 3 H), 6.82–6.95 (m, 2 H), 7.12–7.24 (m, 2 H).

4-Oxo-4-(3'-isopropyl-4'-methoxyphenyl)butyric Acid (52). Succinic anhydride (25 g, 0.25 mol) and sublimed aluminum chloride (34 g, 0.25 mol) were added with stirring to nitrobenzene (200 mL) under nitrogen. Methyl 2-isopropylphenyl ether (**51**)

(45) Milter, P. C.; Kanta De, S. *J. Indian Chem. Soc.* **1939**, *16*, 35.

(25 g, 0.17 mol) was added slowly; the resulting mixture was stirred overnight at room temperature. The solution was then poured into ice–water (800 mL), and 10% aqueous NaOH was added until the solution became alkaline. The aqueous solution was extracted with ether (2 × 500 mL) and the ethereal solution was acidified with 2 N HCl and extracted again with ethyl acetate (3 × 300 mL). The organic extracts were dried over sodium sulfate, evaporated, and recrystallized from absolute EtOH to give white needles of **52** (22 g, 53%), mp 133–134 °C: MS *m/e* (M^+) (calcd for $C_{14}H_{18}O_4$) 250.1204 (found 250.1206); ^1H NMR δ 1.23 (d, *J* = 7 Hz, 6 H), 2.80 (t, *J* = 7 Hz, 2 H), 3.26–3.34 (m, 3 H), 3.90 (s, 3 H), 6.87 (ABq, *J* = 8 Hz, 1 H), 7.82–7.88 (m, 2 H).

4-(3′-Isopropyl-4′-methoxyphenyl)butyric Acid (53). Zinc wool (18.5 g, 0.28 mol), mercuric chloride (1.5 g), concentrated HCl (1.5 mL), and water (40 mL) were mixed together with stirring for 5 min. The aqueous layer was decanted. Compound **52** (22 g, 0.09 mol) in toluene (60 mL) was added, followed by concentrated HCl (50 mL) and water (30 mL); the mixture were refluxed for 24 h. After cooling, water (200 mL) was added. The resulting mixture was extracted with ethyl acetate (3 × 100 mL). The organic extracts were washed with water (3 × 100 mL), dried over sodium sulfate, and evaporated. The residue was distilled to provide **53** (13.4 g, 65%), bp 153–154 °C (0.5 mmHg) [lit.[43] mp 122–123 °C (benzene)]: MS *m/e* 236 (M^+); ^1H NMR δ 1.20 (d, *J* = 7 Hz, 6 H), 1.93 (quintet, *J* = 7 Hz, 2 H), 2.38 (t, *J* = 7 Hz, 2 H), 2.61 (t, *J* = 7 Hz, 2 H), 3.28 (septet, *J* = 7 Hz, 1 H), 3.80 (s, 3 H), 6.76 (d, *J* = 8 Hz, 1 H), 6.93–7.01 (m, 2 H).

6-Isopropyl-7-methoxy-1-tetralone (54). Phosphorus(V) oxide (90 g) and phosphoric acid (45 mL) were mixed with mechanical stirring and heated to 80–90 °C for 6 h. Compound **53** (13.4 g, 56.7 mol) in dichloromethane (20 mL) was added, and the resulting mixture was heated at 70–80 °C for 20 min. Ice–water (100 mL) was added to decompose the polyphosphoric acid and the mixture was extracted with ether (3 × 100 mL). The ethereal extract was washed with water (3 × 50 mL), dried over sodium sulfate, and evaporated. The crude product was purified by flash chromatography on a silica gel column (200 g, EtOAc/hexanes 1:19) to give light yellowish oily liquid **54** (10 g, 81%) [lit.[43] bp 145–150 °C (0.2 mmHg)]: MS *m/e* 218 (M^+); ^1H NMR δ 1.19 (d, *J* = 7 Hz, 6 H), 2.10 (quintet, *J* = 6 Hz, 2 H), 2.61 (t, *J* = 6 Hz, 2 H), 2.89 (t, *J* = 6 Hz, 2 H), 3.34 (septet, *J* = 7 Hz, 1 H), 3.86 (s, 3 H), 7.07 (s, 1 H), 7.46 (s, 1 H).

Methyl 4-(1,2,3,4-Tetrahydro-4-hydroxy-6-isopropyl-7-methoxy-1-naphthyl)but-2-enoate (55).[43] A mixture of zinc wool (5.8 g), methyl 4-bromocrotonate (16.4 g), tetralone **54** (10 g, 45.9 mmol), and THF (40 mL) was allowed to react with the aid of an ultrasonicator for 2 h. Then 2 N HCl (150 mL) was added and the mixture was extracted with ether (3 × 100 mL). The ethereal extract was washed, dried over magnesium sulfate, and evaporated. The residue was purified by flash chromatography twice on a silica gel column (200 g, EtOAc/hexanes 1:6) to give light yellowish oily product **55** (10 g, 69%): MS *m/e* 318 (M^+); ^1H NMR δ 1.16–1.21 (m, 6 H), 1.73–2.09 (m, 5 H), 2.63–2.79 (m, 4 H), 3.25 (septet, *J* = 7 Hz, 1 H), 3.71 (s, 3 H), 3.81 (s, 3 H), 5.88 (d, *J* = 16 Hz, 1 H), 6.88 (s, 1 H), 6.99 (s, 1 H), 6.99–7.09 (m, 1 H).

Methyl 4-(6-Isopropyl-7-methoxy-1-naphthyl)butanoate (56).[43] A mixture of the ester **55** (6 g, 18.9 mmol) and palladium black (340 mg) were heated at 280–300 °C for 2 h. The mixture was then filtered through diatomaceous earth to remove the palladium black. The filtrate was evaporated and the residue was purified by flash chromatography on a silica gel column (200 g, 230–400 mesh, hexanes/EtOAc 19:1) to give light yellowish oily liquid **56** (3.5 g, 62%): MS *m/e* 300 (M^+); ^1H NMR δ 1.30 (d, *J* = 7 Hz, 6 H), 2.04–2.16 (m, 2 H), 2.43 (t, *J* = 7 Hz, 2 H), 3.05 (t, *J* = 7 Hz, 2 H), 3.42 (septet, *J* = 7 Hz, 1 H), 3.68 (s, 3 H), 3.99 (s, 3 H), 7.21–7.31 (m, 3 H), 7.59–7.63 (m, 2 H).

1,2,3,4-Tetrahydro-1,1-dimethyl-6-methoxy-7-isopropylphenanthrene (57). To flame-dried magnesium turnings (1.7 g, 70 mmol) was added anhydrous ether (20 mL). Iodomethane (6.63 g, 47 mmol) in anhydrous ether (10 mL) was added slowly under nitrogen. The resulting mixture was stirred for 30 min; compound **56** (3.5 g, 12 mmol) in anhydrous ether (10 mL) was then added. The mixture was stirred for 3 h and dilute HCl (100 mL) was added to decompose the excess Grignard reagent. The resulting mixture was extracted with ether (3 × 100 mL). The ether extract was washed with water (3 × 100 mL) and dried over sodium sulfate. After evaporation, crude tertiary alcohol was obtained. The alcohol was not purified further and was heated with polyphosphoric acid [prepared by heating a mixture of phosphorus(V) oxide (40 g) and (85%) phosphoric acid (20 mL) at 80–90 °C for 6 h] at 60–70 °C for 30 min. Water (200 mL) was added and the mixture was extracted with ether (3 × 80 mL). The ether solution was washed with water (3 × 80 mL) and was dried over magnesium sulfate. After evaporation, the residue was purified by flash chromatography on a silica gel column (100 g, 70–230 mesh, hexanes/EtOAc 49:1) to give **57** which was recrystallized from MeOH (2.6 g, 79%), mp 83–84 °C (lit.[43] mp 83–85 °C): MS *m/e* 282 (M^+); ^1H NMR δ 1.28 (d, *J* = 7 Hz, 6 H), 1.34 (s, 6 H), 1.73 (m, 2 H), 1.98 (m, 2 H), 3.04 (t, *J* = 7 Hz, 2 H), 3.40 (septet, *J* = 7 Hz, 1 H), 3.95 (s, 3 H), 7.17 (s, 1 H), 7.35 (d, *J* = 8.5 Hz, 1 H), 7.55 (s, 1 H), and 7.57 (d, *J* = 8.5 Hz, 1 H).

1,2,3,4-Tetrahydro-1,1-dimethyl-6-hydroxy-7-isopropylphenanthrene (58).[43] To the ice-cooled solution of **57** (1 g, 3.5 mmol) in dichloromethane (10 mL) was added dropwise boron tribromide (2.7 g, 10 mmol). The reaction mixture was stirred at room temperature for 1 h. Water (5 mL) was then added and the mixture was extracted with ether (3 × 25 mL). The ether extract was washed with water (2 × 25 mL) and saturated aqueous NaCl (50 mL) and dried over magnesium sulfate. After evaporation, the residue was purified by flash chromatography on a silica gel column (30 g, 230–400 mesh, hexanes/EtOAc 1:9). The phenol **58** was obtained as a light yellowish solid (0.8 g, 86%) which changed gradually to orange-red when standing in air. Compound **58** was not purified further and was used directly in the next step: MS *m/e* 266 (M^+); ^1H NMR δ 1.35 (s, 6 H), 1.38 (d, *J* = 6.9 Hz, 6 H), 1.60–2.00 (m, 4 H), 2.95 (t, *J* = 6.5 Hz, 2 H), 3.34 (septet, *J* = 6.9 Hz, 1 H), 5.05 (br s, 1 H), 7.18 (s, 1 H), 7.33 (d, *J* = 8 Hz, 1 H), 7.55 (s, 1 H), 7.57 (d, *J* = 8 Hz, 1 H).

Miltirone (10). Potassium nitrosodisulfonate (Fremy's salt) (0.35 g, 1.3 mmol) and aqueous potassium hydrogen phosphate (0.6 M, 13 mL) were dissolved in water (18 mL). To this solution was added **58** (0.1 g, 0.4 mmol) in acetone (20 mL). The mixture was stirred overnight. After concentration with a rotary evaporator, the mixture was extracted with ether (3 × 50 mL). The ether solution was washed with water (2 × 50 mL) and saturated aqueous NaCl (50 mL) and dried over magnesium sulfate. After evaporation, the residue was purified by flash chromatography on silica gel column (20 g, 230–400 mesh, 1% EtOAc in hexanes) and followed by recrystallization from hexanes to give miltirone (**10**) (40 mg, 40%), mp 99–101 °C (lit.[14] mp 100 °C): MS *m/e* 282 (M^+); ^1H NMR δ 1.16 (d, *J* = 6.8 Hz, 6 H), 1.30 (s, 6 H), 1.62–1.82 (m, 4 H), 2.00 (t, *J* = 6.4 Hz, 2 H), 3.01 (septet, *J* = 6.8 Hz, 1 H), 7.08 (s, 1 H), 7.08 (d, *J* = 7.9 Hz, 1 H), 7.60 (d, *J* = 7.9 Hz, 1 H). Anal. Calcd: C, 80.81; H, 7.85; O, 11.33. Found: C, 80.99; H, 7.82.

1,2,3,4-Tetrahydro-1,1-dimethyl-6-methoxy-7-isopropylphenanthren-4-one (59). A mixture of compound **57** (2.2 g, 7.8 mmol) and pyridinium chlorochromate (8.4 g, 39 mmol) in dichloromethane (50 mL) was stirred for 96 h at room temperature. Then the mixture was made acidic by addition of dilute HCl and extracted with dichloromethane (3 × 100 mL). The extract was washed with water (3 × 100 mL), dired over magnesium sulfate, and evaporated. The residue was purified by flash chromatography on a silica gel column (100 g, 70–230 mesh, EtOAc/hexanes 1:19) to give compound **59**, which was recrystallized from methanol as plates (1.8 g, 80%), mp 89–91 °C: MS *m/e* (M^+) (calcd for $C_{20}H_{24}O_2$) 296.1776, (found 296.1782); ^1H NMR: δ 1.29 (d, *J* = 7 Hz, 6 H), 1.45 (s, 6 H), 2.07 (t, *J* = 7 Hz, 2 H), 2.84 (t, *J* = 7 Hz, 2 H), 3.40 (septet, *J* = 7 Hz, 1 H), 4.00 (s, 3 H), 7.38, 7.80 (ABq, *J* = 9 Hz, 2 H), 7.55 (s, 1 H), 8.78 (s, 1 H). Anal. Calcd: C, 81.04; H, 8.16; O, 10.8. Found: C, 80.99; H, 8.17.

1,2,3,4-Tetrahydro-1,1-dimethyl-6-methoxy-7-isopropylphenanthren-4-ol (60). A mixture of sodium borohydride (462 mg) and compound **59** (1.8 g, 6.1 mmol) in absolute EtOH (40 mL) was stirred under nitrogen at room temperature for 1 h. Water was added to decompose the borohydride and ether was used for extraction (3 × 70 mL). The extract was dried over magnesium sulfate and evaporated. The residue was recrystallized from hexanes to give **60** as plates (1.48 g, 82%), mp 128–130 °C: MS *m/e* (M^+) (calcd for $C_{20}H_{26}O_2$) 298.1933 (found 298.1957); ^1H NMR δ 1.27 (s, 3 H), 1.29 (d, *J* = 7 Hz, 6 H), 1.41 (s, 3 H), 1.54–1.65

(m, 1 H), 1.85 (d, J = 5 Hz, 1 H), 2.07–2.14 (m, 3 H), 3.41 (septet, J = 7 Hz, 1 H), 3.99 (s, 3 H), 5.38 (br s, 1 H), 7.34, 7.67 (ABq, J = 8 Hz, 2 H), 7.52 (s, 1 H), 7.57 (s, 1 H). Anal. Calcd: C, 80.50; H, 8.78; O, 10.72. Found: C, 80.49; H, 8.72.

1,2-Dihydro-1,1-dimethyl-6-methoxy-7-isopropylphenanthrene (61). A mixture of compound **60** (350 mg, 1.17 mmol), triethylamine (1.2 g), and mesyl chloride (0.95 g) in dichloromethane (20 mL) was stirred under nitrogen at 0 °C overnight. Saturated sodium hydrogen carbonate (100 mL) was added and the mixture was extracted with ether (3 × 60 mL). The ether extract was washed with water (3 × 50 mL), dired over magnesium sulfate, and evaporated. The residue was purified by flash chromatography on a silica gel column (100 g, 70–230 mesh, EtOAc/hexanes 1:99) to give **61** which was recrystallized from methanol (140 mg, 42%), mp 80–82 °C: MS m/e (M^+) (calcd for $C_{20}H_{24}O$) 280.1827 (found 280.1832); ^1H NMR δ 1.29 (d, J = 7 Hz, 6 H), 1.32 (s, 6 H), 2.32 (dd, J = 2 Hz, 5 Hz, 2 H), 3.39 (septet, J = 7 Hz, 1 H), 3.97 (s, 3 H), 6.14 (td, J = 5 Hz, 10 Hz, 1 H), 7.20 (td, J = 2 Hz, 10 Hz, 1 H), 7.33 (s, 1 H), 7.36, 7.63 (ABq, J = 8 Hz, 2 H), 7.55 (s, 1 H). Anal. Calcd: C, 85.67; H, 8.63; O, 5.71. Found: C, 85.54; H, 8.58.

1,2-Dihydro-1,1-dimethyl-7-isopropylphenanthren-6-ol (62). Sodium hydride (hexanes washed, 103 mg) and *N,N*-dimethylformamide (10 mL) were placed in a flame-dried flask with stirring. Ethanethiol (133 mg) was then added dropwise followed by compound **61** (125 mg, 0.45 mmol) in *N,N*-dimethylformamide (5 mL). The mixture was heated to 150 °C for 3 h. Dilute sulfuric acid (20 mL) was added to the mixture followed by ether extraction (3 × 20 mL). The ether extract was washed with water (3 × 20 mL), dried over sodium sulfate, and evaporated. The residue was purified by flash chromatography on a silica gel column (10 g, 70–230 mesh, hexanes/EtOAc 9:1) to give **62** which was recrystallized from hexanes (92 mg, 77%), mp 115–117 °C: MS m/e (M^+) (calcd for $C_{19}H_{22}O$) 266.1671 (found 266.1670); ^1H NMR δ 1.31 (s, 6 H), 1.34 (d, J = 7 Hz, 6 H), 2.31 (dd, J = 2 Hz, 5 Hz, 2 H), 3.33 (septet, J = 7 Hz, 1 H), 5.02 (s, 1 H), 6.11 (td, J = 5 Hz, 10 Hz, 1 H), 7.10 (td, J = 2 Hz, 5 Hz, 1 H), 7.34 (s, 1 H), 7.35, 7.62 (ABq, J = 8 Hz, 2 H), 7.57 (s, 1 H). Anal. Calcd: C, 85.67; H, 8.32; O, 6.01. Found: C, 85.39; H, 8.29.

1,2-Didehydromiltirone (29).[27] A solution of compound **62** (170 mg, 0.64 mmol) in acetone (15 mL) was added to a solution of potassium nitrosodisulfonate (527 mg) and 0.125 M aqueous potassium hydrogen phosphate (8 mL) in water (25 mL) with stirring. The mixture was stirred for 4 h. Acetone was evaporated under vacuum and water (40 mL) was added. The resulting solution was extracted with ether (3 × 50 mL). The aqueous layer was allowed to stand overnight and again extracted with ether (3 × 50 mL). The combined ether extracts were dried over sodium sulfate and evaporated. The residue was purified by flash chromatography on a silica gel column (20 g, 70–230 mesh, EtOAc/hexanes 1:19) to provide **29** which was recrystallized from hexanes (102 mg, 57%), mp 71–75 °C (lit.[27] red oil); MS m/e (M^+) (calcd for $C_{19}H_{20}O_2$) 280.1463 (found 280.1470): ^1H NMR δ 1.17 (d, J = 7 Hz, 6 H), 1.28 (s, 6 H), 2.28 (dd, J = 2 Hz, 5 Hz, 2 H), 3.03 (septet, J = 7 Hz, 1 H), 6.33 (td, J = 5 Hz, 10 Hz, 1 H), 7.08 (d, J = 1 Hz, 1 H), 7.11, 7.49 (ABq, J = 8 Hz, 2 H), 7.84–7.88 (td, J = 2 Hz, 10 Hz, 1 H). Anal. Calcd: C, 81.40; H, 7.19; O, 11.41. Found: C, 81.21; H, 7.11.

1,2,3,4-Tetrahydro-6-methoxy-7-isopropylphenanthren-1-one (63). Compound **56** (1 g, 52 mmol) was added to 20% aqueous KOH (5 mL), and the mixture was heated under reflux for 1 h. The reaction mixture was then acidified with 10% HCl and was extracted with chloroform (3 × 50 mL). The chloroform extract was evaporated to dryness and added to polyphosphoric acid (15 g). The mixture was stirred and heated at 60 °C for 30 min. The mixture was then allowed to cool and ice–water (25 mL) was added. The resulting mixture was extracted with ether (3 × 50 mL) and the ether extract was washed with water (2 × 75 mL) and saturated NaCl (50 mL) and evaporated. The residue was chromatographed by flash chromatography on silica gel (30 g, 230–400 mesh, EtOAc/hexanes 1:4) to give **63** as light yellow crystals which were recrystallized from EtOH (520 mg, 61%), mp 149–151 °C; MS m/e 268 (M^+); ^1H NMR 1.31 (d, J = 6.9 Hz, 6 H), 2.30 (quintet, J = 6.5 Hz, 2 H), 2.73 (t, J = 6.5 Hz, 2 H), 3.31 (t, J = 6.5 Hz, 2 H), 3.44 (septet, J = 6.9 Hz, 1 H), 3.99 (s, 3 H), 7.30 (s, 1 H), 7.64 (s, 1 H), 7.68 (d, J = 8.6 Hz, 1 H), 8.00 (d, J = 8.6 Hz, 1 H). Anal. Calcd: C, 80.56; H, 7.51; O, 11.93. Found: C, 80.50; H, 7.48.

1-Methylene-1,2,3,4-tetrahydro-6-methoxy-7-isopropylphenanthrene (64). A solution of compound **63** (200 mg, 0.75 mmol) in ether (15 mL) was added dropwise to trimethylsilylmethylmagnesium chloride [prepared by adding trimethylsilylmethyl chloride (0.55 g, 4.5 mmol) to a solution containing 1,2-dibromoethane (55 mg, 0.29 mmol) and magnesium (120 mg, 5 mmol) in ether (5 mL) under nitrogen]. The mixture was refluxed for 4 h and quenched by adding saturated aqueous NH_4Cl (20 mL). The resulting mixture was extracted with ether (3 × 20 mL). The ether extract was washed with water (2 × 10 mL) and saturated NaCl (10 mL) and dried over sodium sulfate. After evaporation, the residue was dissolved in THF (3 mL) and added to potassium hydride (one spatula) in THF (2 mL) under nitrogen. The mixture was stirred for 1 h. Ethanol (2 drops) was added and the mixture was evaporated. The residue was purified by flash chromatography on silica gel (10 g, 230–400 mesh, hexanes containing 1% triethylamine) to afford **64** (120 mg, 60%) which was further purified by recrystallization from hexanes, mp 123–124.5 °C; MS m/e (M^+) (calcd for $C_{19}H_{22}O$) 266.1672 (found 266.1676); ^1H NMR δ 1.30 (d, J = 6.9 Hz, 6 H), 2.06 (quintet, J = 6.2 Hz, 2 H), 2.59 (m, 2 H), 3.15 (t, J = 6.2 Hz, 2 H), 3.41 (septet, J = 6.9 Hz, 1 H), 3.96 (s, 3 H), 5.03 (s, 1 H), 5.54 (s, 1 H), 7.19 (s, 1 H), 7.57 (s, 1 H), 7.59 (ABq, J = 8.7 Hz, 2 H). Anal. Calcd: C, 85.67; H, 8.33; O, 6.01. Found: C, 86.08; H, 8.45.

4-Methylenemiltirone (38). Ethanethiol (0.6 mL, 7.52 mmol) was added slowly to sodium hydride (0.36 g, 50% w/w, 7.5 mmol) in *N,N*-dimethylformamide (2 mL) under nitrogen. To this mixture was added **64** (0.1 g, 0.4 mmol) in *N,N*-dimethylformamide (3 mL). The resulting mixture was stirred at 150 °C for 2 h and quenched by addition of EtOH (4 drops) and saturated aqueous NH_4Cl (30 mL). The mixture was extracted with chloroform (3 × 50 mL). The organic layer was washed with water (2 × 100 mL) and saturated aqueous NaCl (50 mL), dried over a mixture of Na_2SO_4 and $NaHCO_3$, and evaporated. The residue was purified by passing through a silica gel column (30 g, 230–400 mesh, 10% EtOAc in hexanes containing 1% triethylamine). The alcohol **65** (86%) obtained was then dissolved in acetone (20 mL) and added to potassium nitrosodisulfonate (0.35 g, 1.3 mmol) in water (30 mL). The mixture was stirred at room temperature for 3 h after which acetone was removed by evaporation. The residue was extracted with chloroform (3 × 50 mL), and the organic layer was washed with water (2 × 100 mL) and saturated aqueous NaCl (50 mL), dried over a mixture Na_2SO_4 and $NaHCO_3$, and evaporated. The residue was purified by flash chromatography on a silica gel column (20 g, 10% EtOAc in hexanes containing 1% triethylamine); recrystallization from hexanes gave **38** (50 mg, 50%) as red crystals, mp 137–140 °C: MS m/e (M^+) (calcd for $C_{18}H_{18}O_2$) 266.1307 (found 266.1301); ^1H NMR δ 1.18 (d, J = 6.9 Hz, 6 H), 1.89 (quintet, J = 6.4 Hz, 2 H), 2.51 (m, 2 H), 3.04 (septet, J = 6.9 Hz, 1 H), 3.28 (t, J = 6.4 Hz, 2 H), 5.06 (s, 1 H), 5.50 (s, 1 H), 7.10 (s, 1 H), 7.12 (d, J = 8 Hz, 1 H), 7.85 (d, J = 8 Hz, 1 H). Anal. Calcd: C, 81.17; H, 6.81; O, 12.02. Found: C, 80.66; H, 6.76.

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Supplementary Material Available: ^1H NMR, ^{13}C NMR 2D-COSY, 2D-NOESY, and Table 3 (MS, elemental analysis, and/or IR data) of compounds **31–41** and **49** (23 pages). Ordering information is given on any current masthead page.