Structure–Activity Relationship of Miltirone, an Active Central Benzodiazepine Receptor Ligand Isolated from *Salvia miltiorrhiza* Bunge (Danshen)[1]

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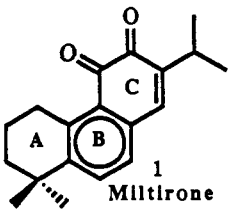
Twenty one *o*-quinonoid-type compounds and one coumarin-type compound related to miltirone (1) have been synthesized with the aim to identify the key structural elements involved in miltirone's interaction with the central benzodiazepine receptor. On the basis of their inhibition of [^{3}H]flunitrazepam binding to bovine cerebral cortex membranes, it is apparent that ring A of miltirone is essential for affinity. Although increasing the size of ring A from six-membered to seven- and eight-membered is well-tolerated, the introduction of polar hydroxyl groups greatly reduces binding affinity. The presence of 1,1-dimethyl groups on ring A is, however, not essential. On the other hand, the isopropyl group on ring C appears to be critical for binding as its removal decreases affinity by more than 30-fold. It can, however, be replaced with a methyl group with minimal reduction in affinity. Finally, linking ring A and B with a $-CH_2CH_2-$ bridge results in analogue **89**, which is 6 times more potent than miltirone at the central benzodiazepine receptor (IC_{50} = 0.05 μM).

Introduction

The Chinese sage, *Salvia miltiorrhiza* Bunge (Danshen), has attracted considerable attention of the medical profession in China because of its reputed therapeutic effects in the treatment of coronary heart and cerebrovascular diseases as well as neurasthenic insomnia.[3] While many compounds with antibacterial, antifungal, antiinflammatory, antineoplastic, and anti-platelet aggregation activities have been identified from this medicinal herb,[1b,4] the active ingredient responsible for its tranquilizing effect has not been established. In our effort to identify biologically active ingredients from Danshen, we discovered and isolated several quinonoidal abietane-derived diterpenes (tanshinones) which inhibited [^{3}H]flunitrazepam binding to the central benzodiazepine receptor.[1b] Benzodiazepines are synthetic psychotropic drugs which have been used widely over the last 30 years to treat anxiety, sleep disturbances, muscle spasm, and convulsive disorders.[5] There is a good correlation between clinically effective doses of benzodiazepines and their ability to inhibit radiolabeled benzodiazepine binding to the central benzodiazepine receptor.[6] The tanshinones isolated from Danshen, which are chemically distinct from all the known synthetic or endogenous benzodiazepine receptor ligands reported to date, may represent a novel class of tranquilizer from natural source. Among the tanshinones isolated,[1b] a known compound, namely miltirone (1),[7] displayed the highest potency in the central benzodiazepine receptor binding assay (IC_{50} = 0.3 μM). It behaved as a partial agonist and was orally active in an animal model used to predict tranquilizing effects.[8] Encouraged by the potential tranquilizing activity of 1, we have synthesized 22 related compounds in the hope of identifying the key structural elements involved in its interactions with the central benzodiazepine receptor.



1
Miltirone

Chemistry

Because of our interest in exploring the structure–activity relationships (SAR) of analogues of miltirone (1), we have developed several synthetic routes to modify its ring system based on our original strategy in the synthesis

(1) Compounds from Danshen. Part 4. (a) Part 3: He, Y.; Chang, H. M.; Lau, Y. K.; Cui, Y. X.; Wang, R. J.; Mak, T. C. W.; Wong, H. N. C.; Lee, C. M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3359. (b) Part 2: Chang, H. M.; Cheng, K. P.; Choang, T. F.; Chow, H. F.; Chui, K. Y.; Hon, P. M.; Tan, F. W. L.; Yang, Y.; Zhong, Z. P.; Lee, C. M.; Sham, H. L.; Chan, C. F.; Cui, Y. X.; Wong, H. N. C. *J. Org. Chem.* **1990**, *55*, 3537. (c) Part 1: Chang, H. M.; Choang, T. F.; Chui, K. Y.; Hon, P. M.; Lee, C. M.; Mak, T. C. W.; Wong, H. N. C. *J. Chem. Res. (S)* **1990**, 114; *J. Chem. Res. (M)* **1990**, 0877–0886.

(2) (a) Author to whom correspondence concerning bioassays should be addressed. (b) Author to whom all other correspondence should be addressed.

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(5) Lader, M. *Annu. Rev. Med.* **1987**, *38*, 19.

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(8) Lee, C. M.; Wong, H. N. C.; Chui, K. Y.; Hon, P. M.; Choang, T. F.; Chang, H. M. *Neurosci. Lett.*, in press.

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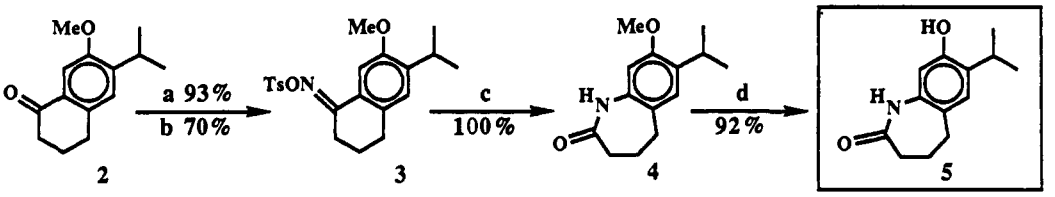
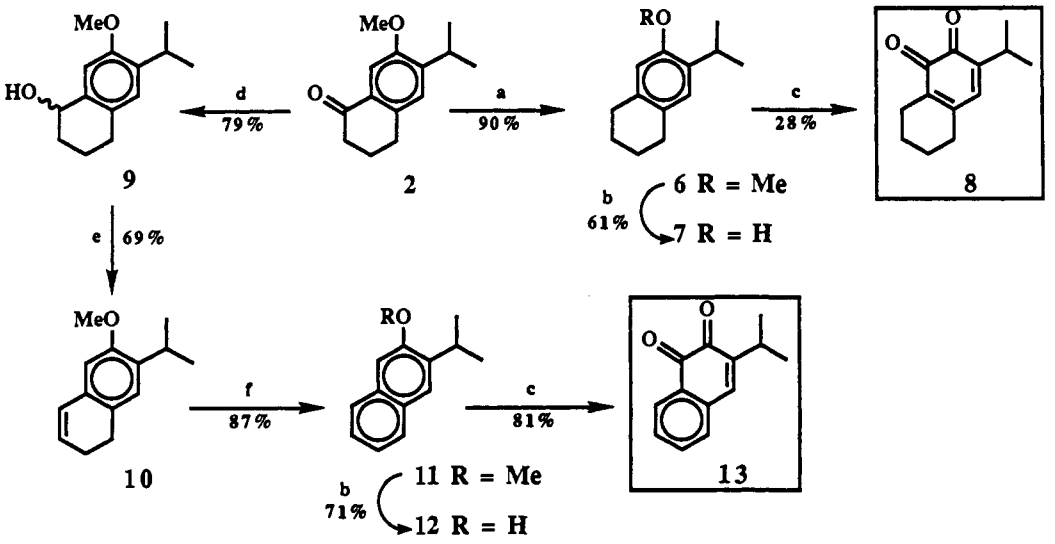
Scheme I[a]



[a] (a) $HONH_2 \cdot HCl$, C_5H_5N, EtOH; (b) TsCl, C_5H_5N; (c) CF_3CO_2H; (d) BBr_3, CH_2Cl_2.

Scheme II[a]



[a] (a) Zn(Hg), HCl, toluene; (b) BBr_3, CH_2Cl_2; (c) $(KSO_3)_2NO$, KH_2PO_4 H_2O, acetone; (d) $NaBH_4$, MeOH; (e) $MeSO_2Cl$, Et_3N, CH_2Cl_2; (f) DDQ, CH_2Cl_2.

of 1.[1b] It must be noted that precedented methodologies of constructing the molecular frameworks of tanshinones can be classified into two main approaches, namely the Diels–Alder method[4,9] and the stepwise ring-construction method.[10] A choice in favor of the latter was made because of the unpredictabilities in both the chemical yields as well as the product regiochemistry of the Diels–Alder cycloaddition reaction. Moreover, from the examples mentioned below, it is clear that the stepwise ring-construction method offers the advantage of producing several target molecules through the manipulation of a single intermediate.

Modification of Ring B in the Absence of Ring A. As reported previously, the introduction of electron-withdrawing substituents into ring B of miltirone (1) in the presence of ring A has resulted in the isolation and identification of several derivatives of 1.[1a] To evaluate the importance of ring A, our next synthetic plans involved the construction of bicyclic analogues of 1 with no ring A. Eight compounds were prepared in this manner.

Our first two target molecules were the corresponding quinone forms of compound 5 (Scheme I) and compound 7 (Scheme II). Both of them possess a nonaromatic ring B but no ring A. They should provide insight into the role of an aromatic ring B in 1. Starting from tetralone 2,[1b] Scheme I shows the assemblage of an amide ring via Beckmann rearrangement.[11] All attempts to oxidize phenol 5 to the corresponding *o*-quinone were unsuccessful, due perhaps to its instability.

An unstable quinone 8 (Scheme II) was prepared in several steps from 2.[1b] The preparation of compounds 6 and 7 by different methods have been recorded.[12] The oxidation of a phenol to its corresponding quinone was typified by the oxidation of 12 with potassium nitrosodisulfonate (Fremy's salt)[13] to afford stable naphthoquinone 13 (Scheme II), which possesses all the carbon framework of 1 except its ring A. Phenol 12, in turn, was obtained from 2[1b] via literature procedures.[14]

In view of the stability of 13 and the easy access to 2, it was therefore of practical interest to prepare some derivatives of 13 with 2 as starting material. In this connection, phenyl-substituted compound 18 (Scheme III), vinyl-substituted compound 25 (Scheme III), ethyl-substituted compound 29 (Scheme IV), acid 33 (Scheme V), and amide 36 (Scheme V) were synthesized. All substitutions were introduced at C-1 of the naphthalene skeleton. In the preparation of 18 (Scheme III), Grignard reaction of 2[1b] with phenylmagnesium bromide was the pivotal step in the introduction of a phenyl ring. Quinone 18 (Scheme

(9) Kakisawa, H.; Ikeda, M. *J. Chem. Soc. Jpn.* **1967**, *88*, 476; Inouye, Y.; Kakisawa, H.; Inouye, Y. *J. Chem. Soc., Chem. Commun.* **1968**, 1327; Kakisawa, H. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 3318; Knapp, S.; Sharma, S. *J. Org. Chem.* **1985**, *50*, 4996; Lee, J.; Tang, J.; Snyder, J. K. *Tetrahedron Lett.* **1987**, *28*, 3427; Lee, J.; Snyder, J. K. *J. Am. Chem. Soc.* **1989**, *111*, 1522.

(10) Kakisawa, H.; Tateishi, M.; Kusumi, T. *Tetrahedron Lett.* **1968**, 3783; Tateishi, M.; Kusumi, T.; Kakisawa, H. *Tetrahedron* **1971**, *27*, 237; Nasipuri, D.; Mitra, A. K. *J. Chem. Soc., Perkin Trans. 1* **1973**, 285.

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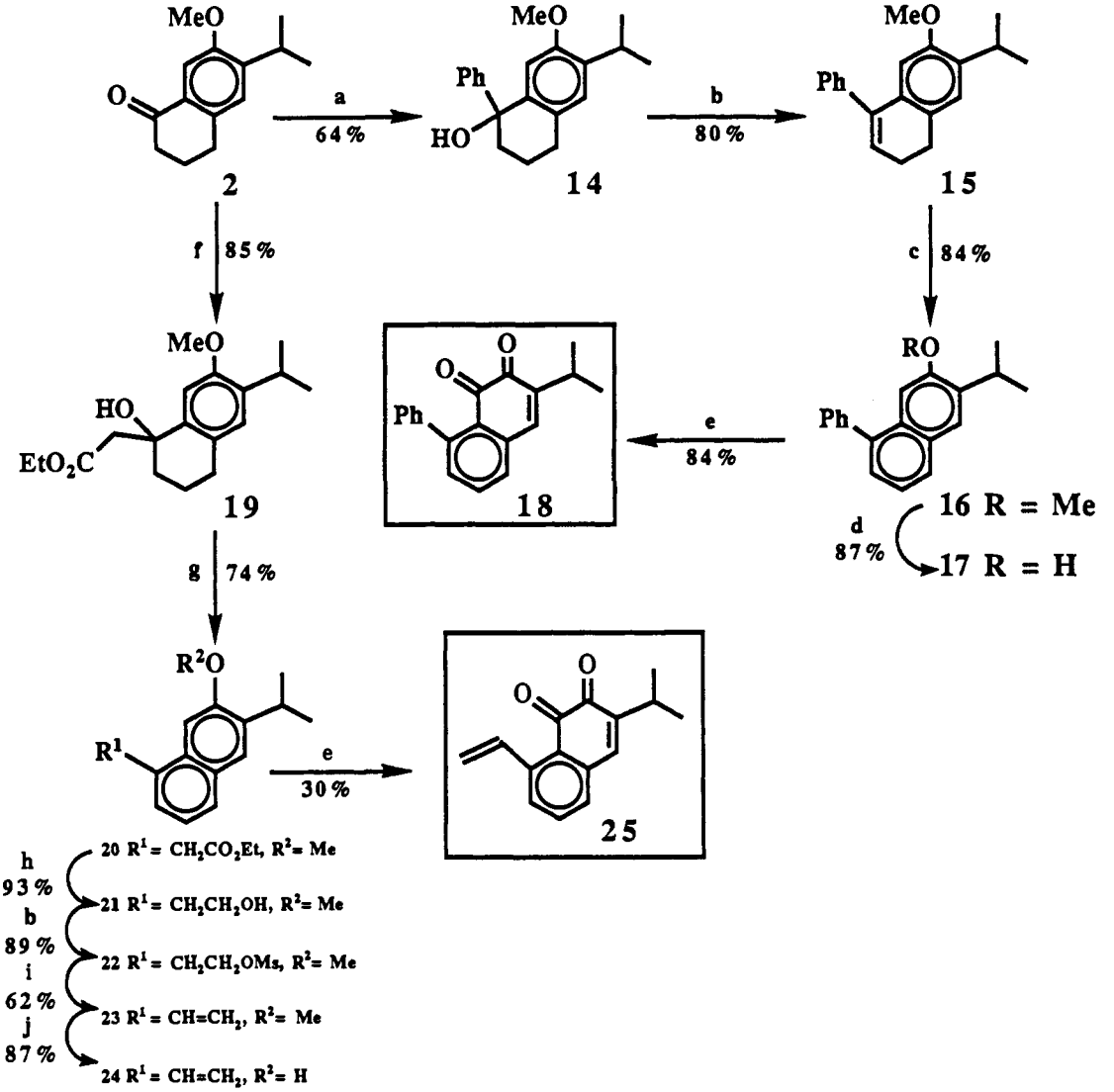
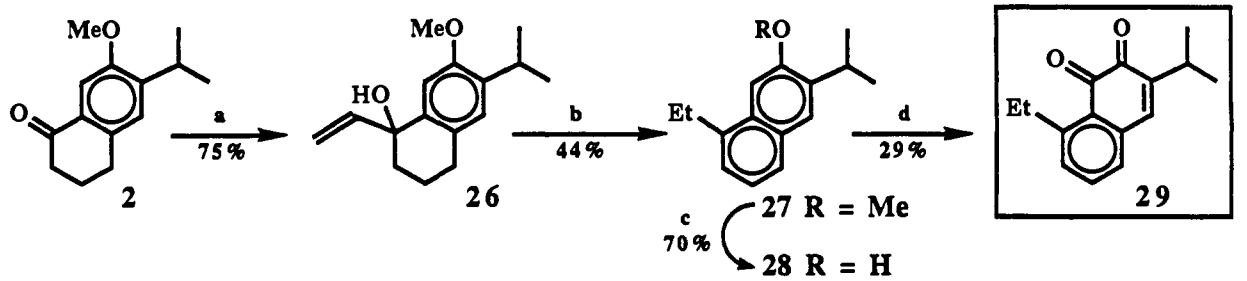
Scheme III[a]



[a] (a) PhMgBr, THF; (b) $MeSO_2Cl$, Et_3N, CH_2Cl_2; (c) DDQ, CH_2Cl_2; (d) BBr_3, CH_2Cl_2; (e) $(KSO_3)_2NO$, KH_2PO_4, H_2O, acetone; (f) Zn, $BrCH_2CO_2Et$, THF, ultrasound; (g) Pd–C, 230–250 °C; (h) $LiAlH_4$, THF; (i) *t*BuOK, *t*BuOH; (j) NaH, EtSH, DMF.

Scheme IV[a]



[a] (a) CH_2=CHMgBr, THF; (b) Pd–C, 230–250 °C; (c) BBr_3, CH_2Cl_2; (d) $(KSO_3)_2NO$, KH_2PO_4, H_2O, acetone.

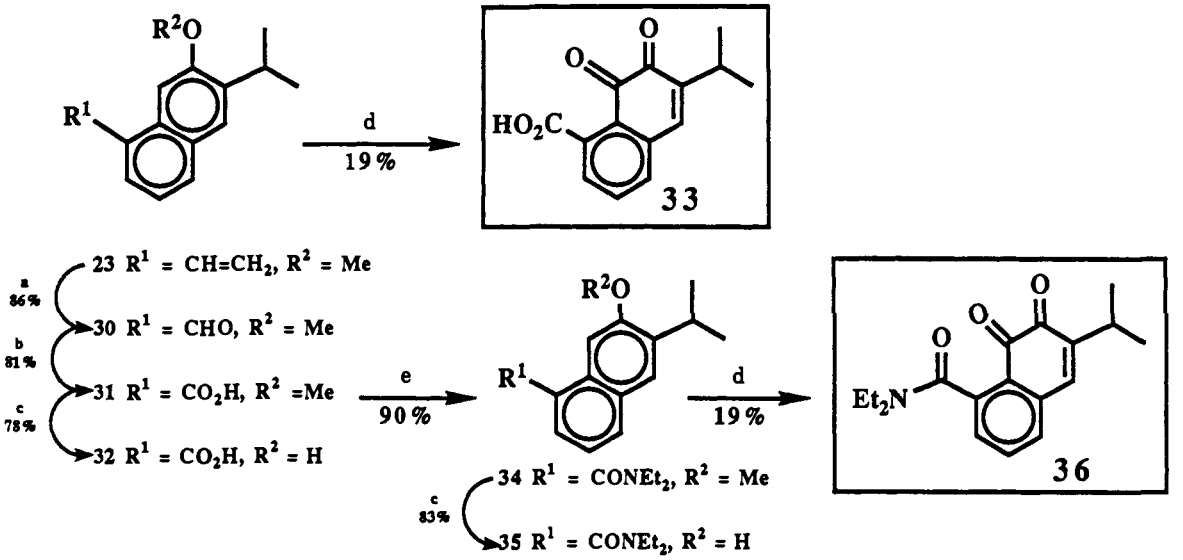
III) was subsequently obtained through routine procedures. Likewise, vinyl group and ethyl group were incorporated to provide quinones **25** (Scheme III) and **29** (Scheme IV), respectively. Compound **25** was however rather unstable so that no spectral data were recorded. Although compound **29** was also unstable, sufficient spectroscopic data were obtained for its identification.

In our attempt to introduce electron-withdrawing groups into **13**, we were able to prepare acid **33** and amide **36** (Scheme V). In these syntheses, compound **23** was first oxidized to the key intermediate **31**.[15]

Modification of Ring A. Our next attempt was to probe the importance of ring A in miltirone's interaction with the central benzodiazepine receptor. To provide sufficient information on the binding potentials of various ring sizes and functionalities, we have prepared amide **42** (Scheme VI), cyclooctane **52** (Scheme VII), cycloheptane **58** (Scheme VIII), ketone **60** (Scheme IX), olefin **64** (Scheme IX), didemethylmiltirone **66**[4] (Scheme IX), al-

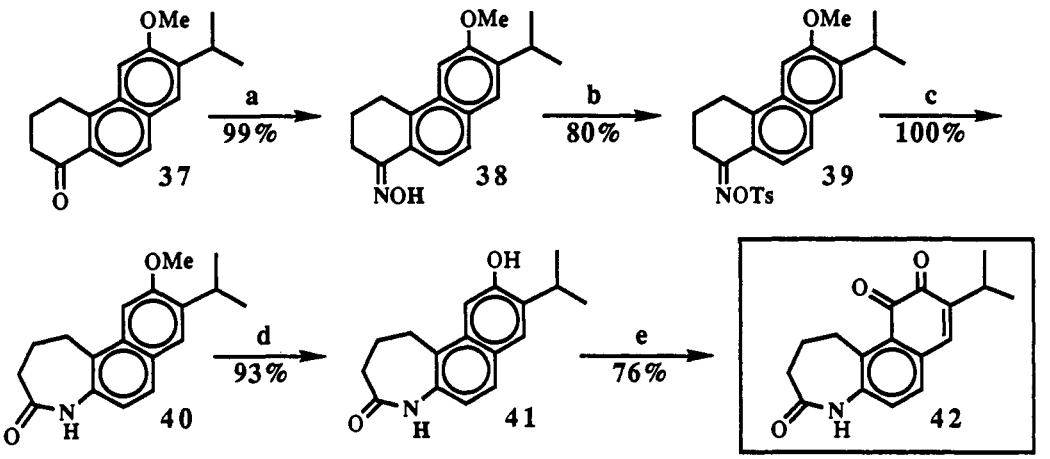
(15) Hase, T. A.; Nylund, E.-L. *Tetrahedron Lett.* **1979**, 2633.

Scheme V[a]



[a] (a) O_3, CH_2Cl_2, -78 °C, then Me_2S; (b) $NaClO_2$, H_2NSO_3H, H_2O; (c) BBr_3, CH_2Cl_2; (d) $(KSO_3)_2NO$, KH_2PO_4, H_2O, acetone; (e) $SOCl_2$, C_6H_6, then Et_2NH.

Scheme VI[a]



[a] (a) $HONH_2$·HCl, C_5H_5N, EtOH; (b) TsCl, C_5H_5N; (c) CF_3CO_2H, CH_2Cl_2; (d) BBr_3, CH_2Cl_2; (e) $(KSO_3)_2NO$, KH_2PO_4, H_2O, acetone.

cohol **70** (Scheme X), *cis*-diol **74** (Scheme X), and *trans*-diol **76** (Scheme X). These nine analogues only differ in their ring A while all other structural characteristics on rings B and C are the same. As can be seen from Scheme VI, compound **37**[1b] was converted to the corresponding tosyl oxime **39** and thence by Beckmann rearrangement,[11] demethylation,[16] and oxidation[13] to amide **42**.

The expansion of the six-membered ring A to an eight-membered ring or a seven-membered ring is demonstrated by the synthesis of **52** and **58**, whose synthetic plans are laid out in Scheme VII and Scheme VIII, respectively. By starting from a known compound, **43**,[1b] Scheme VII illustrates the combined use of a Wadsworth–Emmons olefination,[17] a Friedel–Crafts acylation,[18] and a Clemmensen reduction[19] as the key steps. In this manner, quinone **52** was realized. Similarly, compound **44** (Scheme VIII) was converted to the seven-membered ring intermediate **56** through the use of a Grignard reaction,[20] a Friedel–Crafts acylation,[18] as well as a Clemmensen reduction.[19] Demethylation[16] and oxidation with Fremy's salt[13] delivered our target molecule **58** (Scheme VIII).

To examine the influence of the 1,1-dimethyl groups on the binding affinity of **1**, we have synthesized its three closely related analogues **60**, **64**, and **66** (Scheme IX). The preparation of **60** from **37**[1b] was trivial. The synthesis of **64** was begun by allowing compound **37**[1b] to react with methylmagnesium iodide, yielding alcohol **61** after aqueous workup. Consecutive dehydration,[21] demethylation,[16] and oxidation[13] reactions converted **61** to **64**. It is important to note that due to the reactivity of the double bond of **62** toward Lewis acid, the demethylation of **62** to **63** was accomplished by using sodium hydride and ethanethiol.[22] Furthermore, it is of interest to point out that natural furan-containing molecules with an identical ring A as that of compound **64** have also been isolated from Danshen.[1b,23]

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(18) Kanaoka, Y.; Yonemitsu, O.; Tanizawa, K.; Ban, Y. *Chem. Pharm. Bull.* **1964**, *12*, 773.
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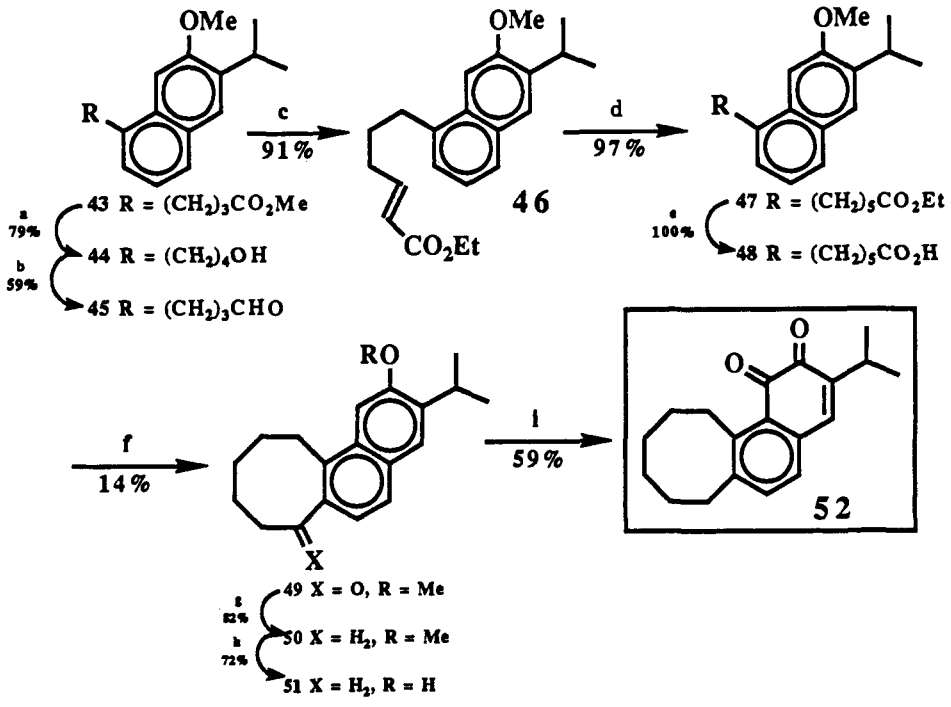
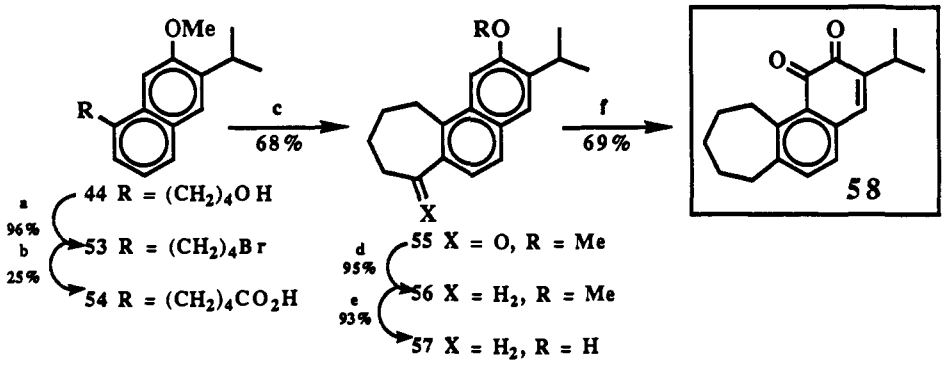
Scheme VII[a]



[a] (a) $LiAlH_4$, THF; (b) PCC, CH_2Cl_2; (c) $(EtO)_2POCH_2CO_2Et$, NaH, THF; (d) H_2, 5% Pd–C, EtOH; (e) NaOH, MeOH, THF, 80 °C; (f) PPA, CH_2Cl_2; (g) Zn(Hg), HCl, toluene; (h) BBr_3, CH_2Cl_2; (i) $(KSO_3)_2NO$, KH_2PO_4, H_2O, acetone.

Scheme VIII[a]



[a] (a) CBr_4, Ph_3P, CH_2Cl_2; (b) EtMgBr, then CO_2, then H_3O^+; (c) PPA; (d) Zn(Hg), HCl, toluene; (e) BBr_3, CH_2Cl_2; (f) $(KSO_3)_2NO$, KH_2PO_4, H_2O, acetone.

Finally, didemethylmiltirone **66** was prepared from **37**,[1b] again through well-established procedures.

To increase the water solubility of miltirone (**1**), we introduced polar hydroxyl groups into its ring A and prepared quinones **70**, **74**, and **76** (Scheme X). Again, the furan-containing counterparts of these new molecules have been isolated from Danshen.[24] As illustrated in Scheme X, known phenol **59** (vide supra) was reprotected with the benzyl group to provide ketone **67**. A choice in favor of benzyl protection was made due to its convenient removal by catalytic hydrogenation conditions. Evidence has been presented demonstrating the detrimental effect of Lewis acid toward the hydroxyl groups in our regular demethylation procedure (vide supra). Benzylation, Grignard reaction, deprotection, and oxidation[13] furnished the hydroxyquinone **70** (Scheme X) from **59**.

To prepare dihydroxyquinones **74** and **76** (Scheme X), compound **68** was dehydrated[21] to give **71**, which was used as the key intermediate in the preparation of **74** and **76**. Cis-dihydroxylation of **71** was accomplished by using a catalytic amount of osmium tetroxide[25] in the presence of *N*-methylmorpholine *N*-oxide, affording **72**, whose cis stereochemistry was substantiated by 2D-COSY and 2D-NOESY NMR spectra. Compound **72** was then deprotected and oxidized to deliver our target molecule **74**. In a similar manner, trans-dihydroxylation[26] of **71** gave **75**, whose trans stereochemistry was proved by 2D-COSY and 2D-NOESY NMR spectrometry. Debenzylation and oxidation of **75** provided *trans*-dihydroxyquinone **76**.

Modification of Rings A and B. It has already been established in our initial experiments that the benzene ring

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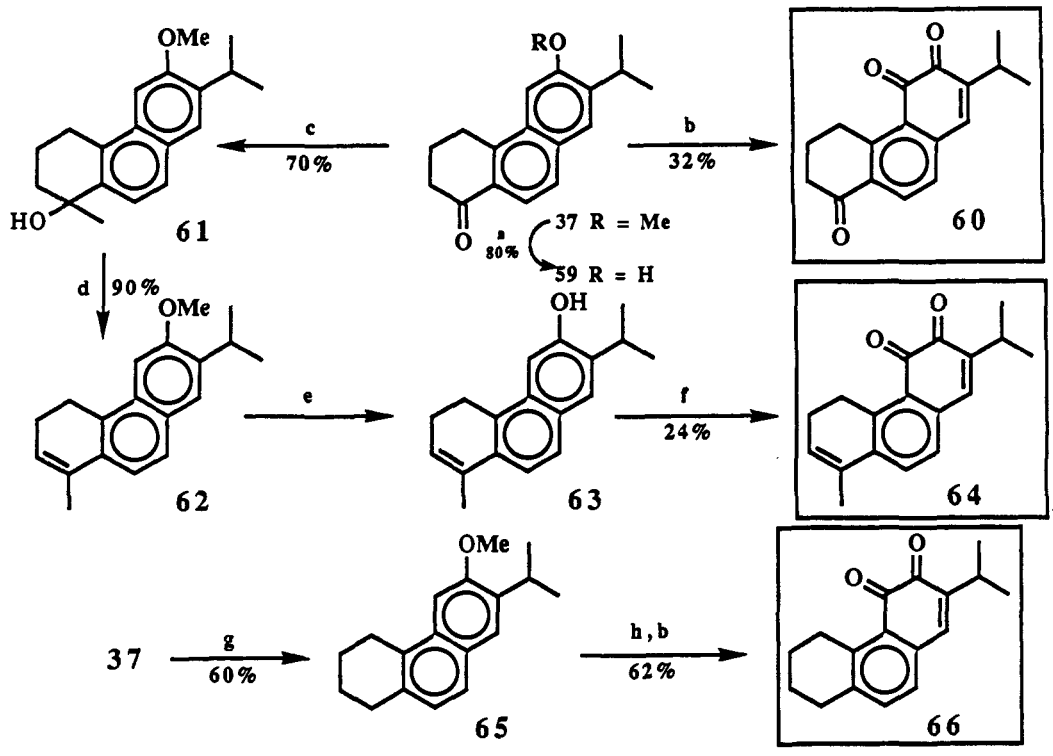
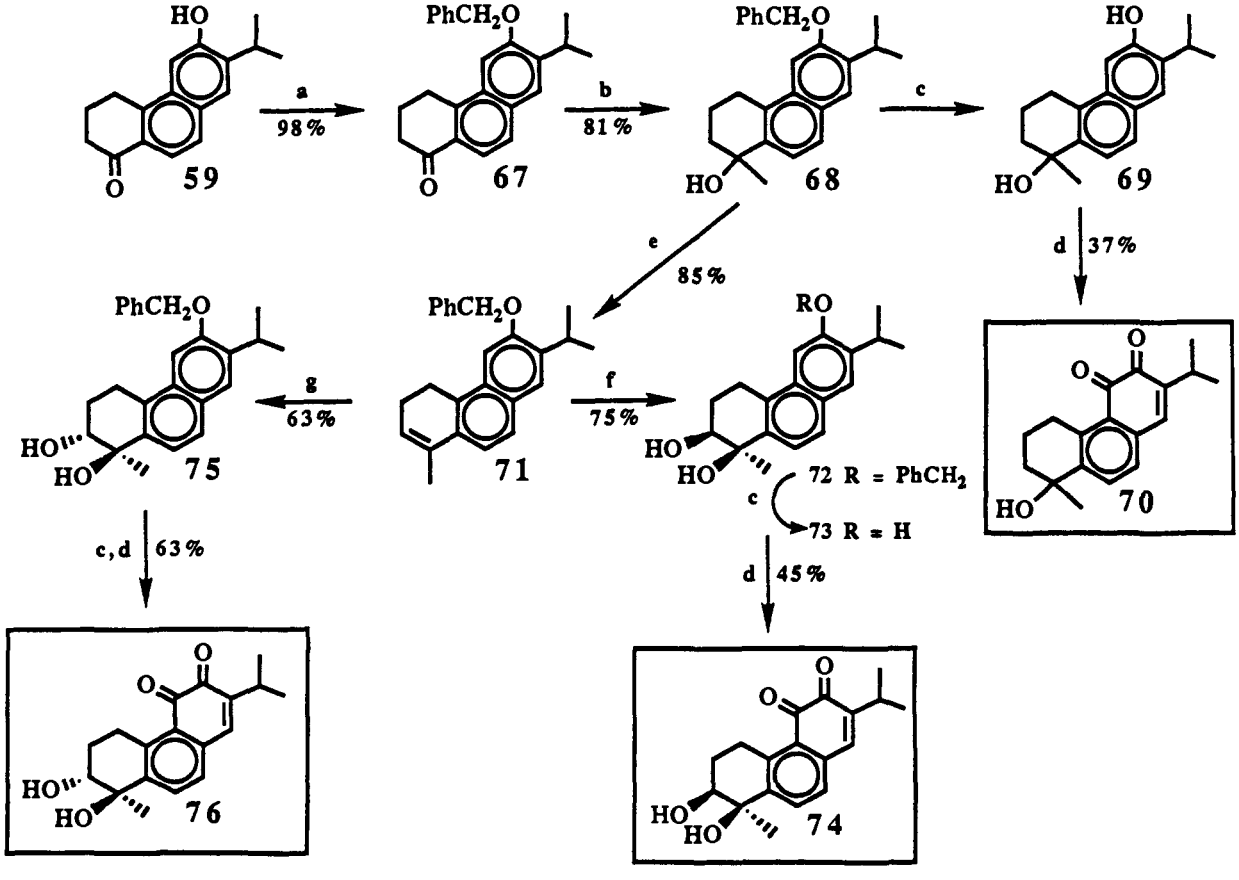
(26) Brougham, P.; Cooper, M. S.; Cummerson, D. A.; Heaney, H.; Thompson, N. *Synthesis* **1987**, 1015 and references cited therein.

Scheme IX[a]



[a] (a) Py·HCl, 200–220 °C; (b) $(KSO_3)_2NO$, KH_2PO_4, H_2O, acetone; (c) MeMgI, Et_2O, 0 °C; (d) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C; (e) NaH, EtSH, DMF, 150 °C; (f) $(KSO_3)_2NO$, H_2O, acetone; (g) Zn(Hg), HCl, toluene; (h) BBr_3, CH_2Cl_2.

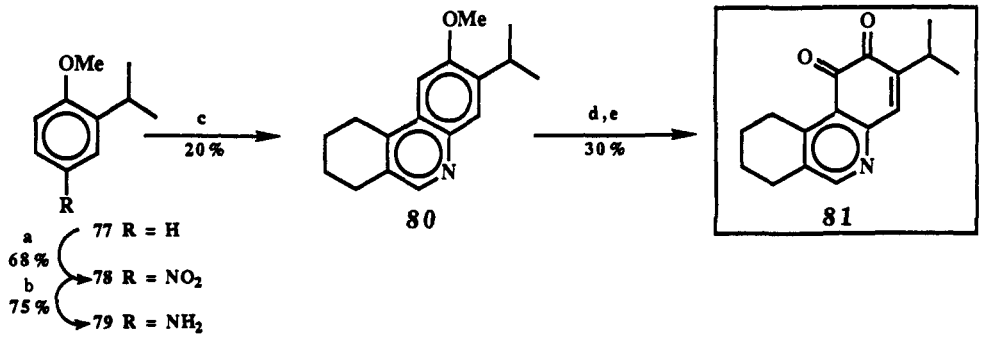
Scheme X[a]



[a] (a) K_2CO_3, acetone, $C_6H_5CH_2Br$; (b) MeMgI, Et_2O, C_6H_6, 0 °C; (c) H_2, Pd–C, MeOH; (d) $(KSO_3)_2NO$, KH_2PO_4, NaOH, H_2O, acetone; (e) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C; (f) 1 mol% OsO_4, *N*-methylmorpholine *N*-oxide, *t*-BuOH, THF, H_2O; (g) MMPP, THF, H_2O.

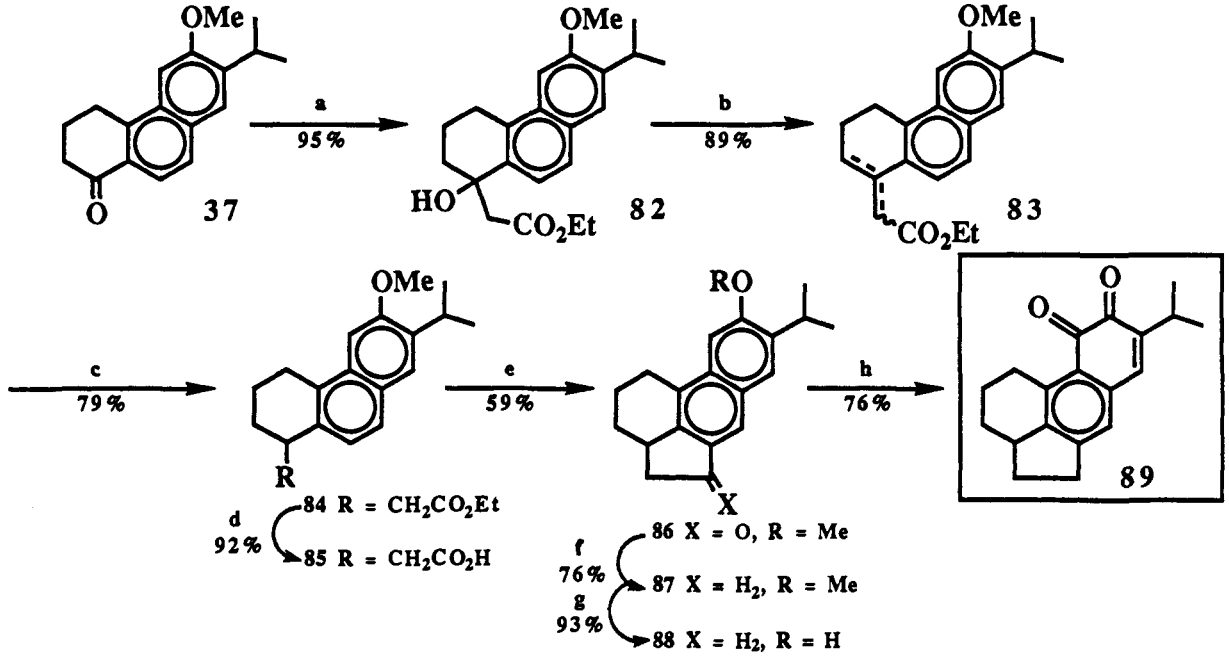
B of 1 is essential for its interaction with the central benzodiazepine receptor (vide infra). To further assess the importance of this benzene nucleus, we have undertaken a synthetic maneuver to produce a pyridine analogue of

Scheme XI[a]



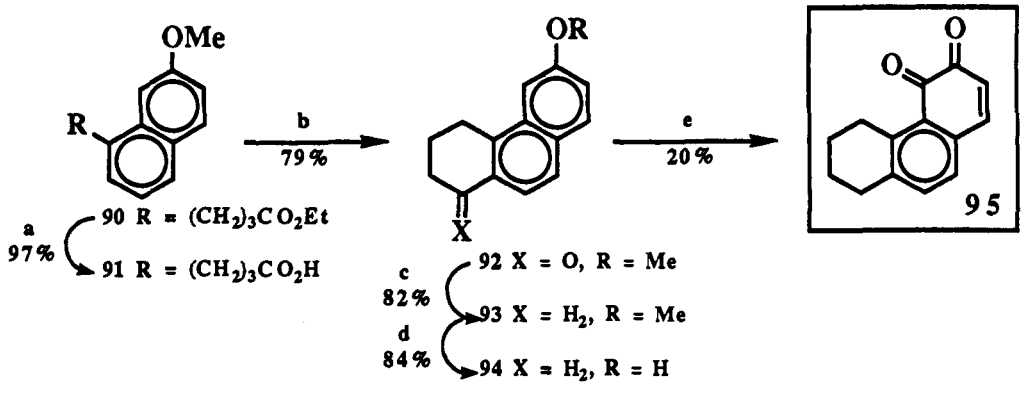
[a] (a) HNO_3, 0 °C; (b) Sn, concentrated HCl; (c) cyclohexanone, formalin, Et_2NH, H_2O, $SnCl_4$; (d) BBr_3, CH_2Cl_2, 0 °C; (e) $(KSO_3)_2NO$, H_2O, acetone.

Scheme XII[a]



[a] (a) Zn, $BrCH_2CO_2Et$, THF, ultrasound; (b) $MeSO_2Cl$, Et_3N, CH_2Cl_2; (c) H_2, Pd–C, EtOH; (d) NaOH, H_2O; (e) PPA, $CHCl_3$, 60 °C; (f) Zn(Hg), HCl, toluene; (g) BBr_3, CH_2Cl_2; (h) $(KSO_3)_2NO$, KH_2PO_4, H_2O, acetone.

Scheme XIII[a]



[a] (a) NaOH, MeOH; (b) PPA; (c) Zn(Hg), HCl; (d) BBr_3, CH_2Cl_2; (e) $(KSO_3)_2NO$, H_2O, acetone.

1. Accordingly, phenanthridine-type compound 81 (Scheme XI) was obtained. Crucial to this synthetic route was the Mannich reaction[27] of amine 79[28] (from 78[28]) with cyclohexanone and formaldehyde, which yielded 80. Subsequent deprotection[16] and oxidation[29] of 80 provided the phenanthridine 81.

Another modification of the molecular framework of miltirone (1) was achieved through the elaborate synthesis

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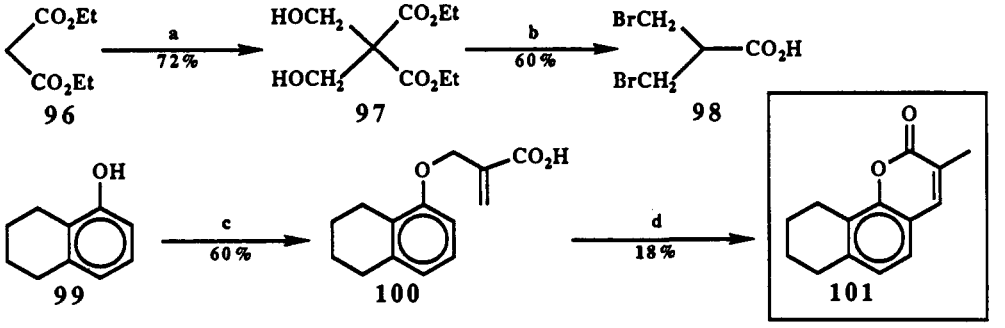
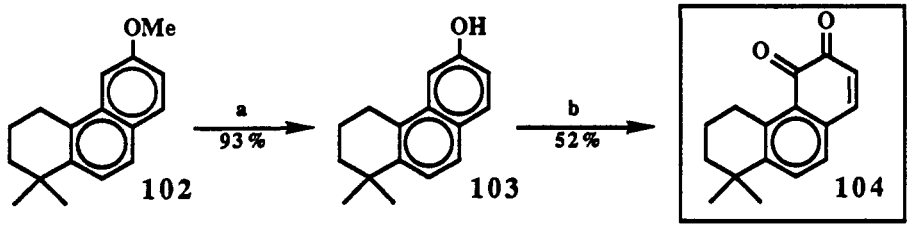
Scheme XIV[a]



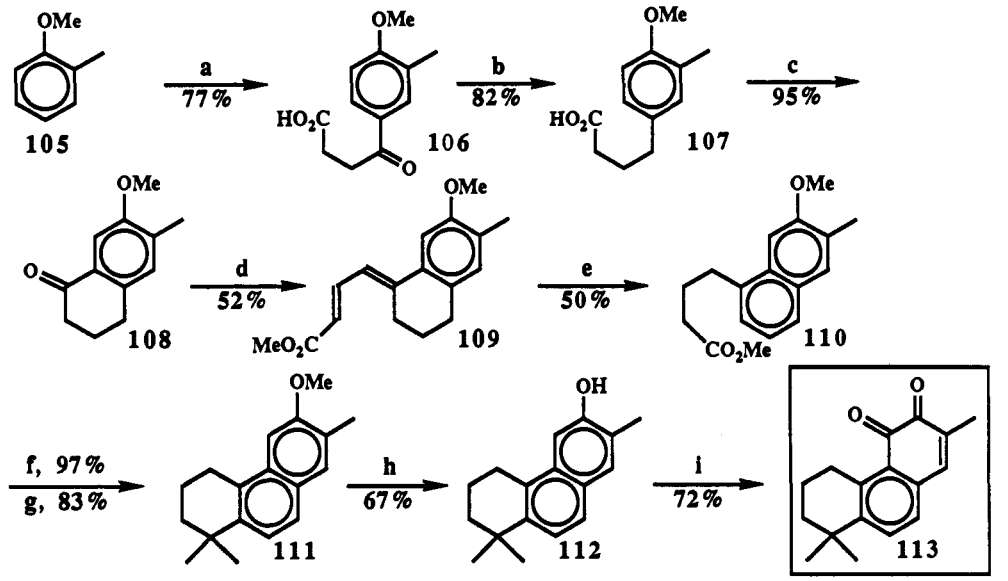
[a] (a) CH_2O, H_2O, K_2CO_3; (b) HBr; (c) **98**, NaOH, EtOH; (d) *o*-$C_6H_4Cl_2$, Et_3N, 180 °C.

Scheme XV[a]



[a] (a) BBr_3, CH_2Cl_2; (b) $(KSO_3)_2NO$, H_2O, acetone.

Scheme XVI[a]



[a] (a) $(CH_2CO)_2O$, $AlCl_3$, $Cl_2CHCHCl_2$; (b) Zn, $HgCl_2$, HCl, heat; (c) PPA, CH_2Cl_2, 60–70 °C; (d) Zn, $BrCH_2CH{=}CHCO_2Me$, THF, ultrasound; (e) Pd–C, 260–280 °C; (f) MeLi, THF; (g) PPA, CH_2Cl_2, 60–70 °C; (h) BBr_3, CH_2Cl_2; (i) $(KSO_3)_2NO$, KH_2PO_4, H_2O, acetone.

of **89** (Scheme XII), whose A and B rings are linked by a carbon bridge. In principle, the conformational mobility of ring A in **89** will be reduced as compared with that of **1**. Reformatsky reaction[30] converted the known ketone **37**[1b] to **82**. Consecutive dehydration,[21] catalytic hydrogenation, and saponification procedures were therefore carried out on **82**, yielding acid **85**. Friedel–Crafts acylation[18] of **85** provided compound **86**, which possessed the required skeleton. Further manipulation of **86** finally gave quinone **89**.

Modification of Rings A and C. To assess the importance of the isopropyl group and the *gem*-dimethyl group in **1**, we have prepared analogue **95** (Scheme XIII), in which the isopropyl group and the *gem*-dimethyl group were replaced by a methyl group and a hydrogen, respectively. Literature-reported procedures[31] were employed for the synthesis of **94** from the known **90**[1b] (Scheme XIII). Subsequent oxidation[13] of **94** finally afforded the unstable quinone **95**.

Coumarin-type[32] compound **101** (Scheme XIV) was also prepared to generate information on the importance of the quinone functionality. Thus, diethyl malonate (**96**) was converted to hydroxyl compound **97**,[33] which went through

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Table I. Comparison of Potencies of Compounds Related to Miltirone (1) as Inhibitors of Specific [^{3}H]Flunitrazepam Binding in Bovine Cerebral Cortex Membranes

compd	IC_{50},[a] μM	compd	IC_{50},[a] μM
miltirone (1)	0.30 ± 0.03 (4)	64	4.4 ± 0.6 (2)
8	>140	66	0.9 ± 0.1 (3)
13	>50	70	2.0 ± 0.4 (2)
18	20 ± 4 (3)	74	15 ± 2 (2)
25	>40	76	17 ± 3 (2)
29	>200	81	9.1 ± 1.7 (3)
33	4.3 ± 0.6 (3)	89	0.05 ± 0.02 (3)
36	>30	95	20 ± 4 (2)
42	0.32 ± 0.05 (5)	101	>40
52	0.31 ± 0.04 (3)	104	10 ± 3 (2)
58	0.23 ± 0.06 (3)	113	0.4 ± 0.1 (2)
60	0.56 ± 0.08 (4)		

[a] IC_{50} is the concentration of compound required to give 50% inhibition of specific [^{3}H]flunitrazepam binding. Data are the mean ± SD of (n) separate determinations performed in duplicate.

bromination, saponification, and decarboxylation to furnish bromide **98**.[34] Phenol **99** readily reacted with **98** to give **100**, which underwent Claisen rearrangement at 180 °C to form **101**.[35]

Modification of Ring C. To further examine the importance of the isopropyl group of miltirone, we replaced its isopropyl group with either a hydrogen or a methyl group. A simple two-step route transformed the known **102** to **104** (Scheme XV), which unfortunately merely formed unstable oil. Similar to our modified synthesis of **1**,[1b] a tedious but known procedure[36] was employed for the preparation of **113** (Scheme XVI).

Results and Discussion

To identify the key structural elements involved in the interaction of miltirone (**1**) with the central benzodiazepine receptor, we examined the ability of 22 related analogues of **1** to displace specific [^{3}H]flunitrazepam binding from bovine cerebral cortex membranes according to the procedure of Chang and Barnard.[37] The results are summarized in Table I.

Ring A appears to be critical for its interaction with the central benzodiazepine receptor. The absence of ring A reduced receptor affinity dramatically. For instance, compounds **8** and **13** were over 150-fold less potent than **1**. The introduction of phenyl (compound **18**), vinyl (compound **25**), ethyl (compound **29**), or amide group (compound **36**) onto ring B did not restore affinity. Some binding affinity can be regained, however, by the introduction of a carboxylic acid group on ring B. Thus, compound **33** was only 13 times less potent than **1**. The latter observation is interesting since it seems to support the molecular model proposed by Fryer[38] for nonbenzodiazepines which interact with the benzodiazepine receptor. According to Fryer's model, one should be able to substitute ring A with a simple π system such as a carboxylic acid. In spite of the importance of ring A, increasing its size from a six-membered to a seven- (compounds **42** and **58**) or eight-membered (compound **52**) ring caused no loss of receptor binding affinity. The presence of 1,1-dimethyl groups on ring A also appears to be nonessential. Replacing the CH_3CCH_3 group by HCH (compound **66**), C=O (compound **60**), or CCH_3 (compound **64**) only reduced affinity by 3-, 2-, and 15-fold, respectively. In an attempt to increase water solubility, we replaced one of the methyl groups on ring A with a polar hydroxyl group, and the resulting compound **70** was 7-fold less potent than **1**. The introduction of an additional hydroxyl group on ring A, whether in cis (compound **74**) or trans (compound **76**) stereochemistry reduced affinity by as much as 50-fold. To gain insight into the role of the benzene ring B in receptor interaction, we prepared a pyridine analogue of **1**. This phenanthridine-type compound (**81**) was 30 times less potent than **1**. Considering the fact that compound **66** (which also did not possess 1,1-dimethyl groups on ring A) was only 3-fold lower in potency than **1**, it may be concluded that a benzene ring B is critical in receptor interaction and a simple replacement of a CH group by a nitrogen atom reduced receptor affinity by as much as 10-fold.

To shed light on the importance of the isopropyl group on ring C in **1** and compound **66**, we replaced it with a hydrogen. This modification reduced affinity by 33- (compound **104**) and 22- (compound **95**) fold when compared with their respective parent compounds. On the other hand, there was a minimal reduction in affinity by replacing the isopropyl group in **1** with a methyl group (compound **113**). To evaluate the importance of the quinone, we prepared a coumarin-type analogue (compound **101**). Its affinity was 50–130 times lower than that of compounds **66** and **1**, indicating that the quinone alone plays an important role in receptor interaction. All the aforementioned modifications of **1** have resulted in compounds which have either similar or lower potency than **1**. The linking of rings A and B of **1** by a ethylene bridge gave the first and only analogue in this study (compound **89**) which has a higher potency than **1** and it inhibited the binding of [^{3}H]flunitrazepam to the central benzodiazepine receptor with an IC_{50} of 0.05 μM.

Conclusion

Miltirone (**1**) is a natural plant molecule which is chemically distinct from all the other known synthetic and endogenous benzodiazepine receptor ligands reported to date. In the present study, we have identified some of the key structural features involved in its interaction with the central benzodiazepine receptors. We have also been able to improve the binding affinity of miltirone (**1**) by 6-fold through linking rings A and B with a two-carbon bridge. Further studies will be performed to evaluate and compare the pharmacological profiles of miltirone (**1**) and compound **89** in the hope of finding a new class of anxiolytic agents.

Experimental Section

Solvents used were purified by standard procedures. All evaporation of organic solvents was carried out by a rotary evaporator in conjunction with a water aspirator. Proton NMR spectra were recorded on a Bruker Cryospec WM 250 (250 MHz) spectrometer or a JEOL PMX 60 SI (60 MHz) spectrometer. The chemical shifts (ppm) were 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. Elemental analyses were carried out at Shanghai Institute of Organic Chemistry, Academia Sinica, China. 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 unless otherwise stated. Melting points were measured on a

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hot-stage microscope and were uncorrected.

O-(p-Tolylsulfonyl)-3,4-dihydro-6-isopropyl-7-methoxynaphthalen-1(2H)-one Oxime (3). 6-Isopropyl-7-methoxy-3,4-dihydro-1(2H)-naphthalenone (2)[1b] (1.3 g, 5.8 mmol) was dissolved in EtOH (13 mL). Pyridine (0.7 mL) was added, followed by hydroxylamine hydrochloride (0.6 g, 9 mmol). The solution was heated at 95–100 °C for 70 min. The reaction mixture was concentrated under vacuum to remove EtOH and pyridine, and then purified by passing through a silica gel column (eluted with CH_2Cl_2 containing 1% MeOH) to provide the oxime as colorless solid. Further purification was accomplished by recrystallization from EtOAc to afford colorless rectangular crystals (1.3 g, 93%): mp 134–135 °C; MS *m/e* (M^+) (calcd for $C_{14}H_{19}NO_2$) 233.1416, (found 233.1420); ^1H NMR (60 MHz) δ 1.18 (d, J = 7 Hz, 6 H), 1.87 (m, 2 H), 2.74 (m, 4 H), 3.31 (septet, J = 7 Hz, 1 H), 3.82 (s, 3 H), 6.95 (s, 1 H), 7.38 (s, 1 H), 8.66 (br s, 1 H). Anal. ($C_{14}H_{19}NO_2$) C, H, N. *p*-Toluenesulfonyl chloride (800 mg, 4.2 mmol) was added to the oxime (660 mg, 2.8 mmol) in pyridine (2 mL) and the mixture was stirred at room temperature under nitrogen overnight. The reaction mixture was chromatographed directly on a silica gel column (eluted with hexanes containing 15% EtOAc) to yield product **3** as colorless solid, which was recrystallized from hexanes–EtOAc to afford colorless rectangular crystals (930 mg, 70%): mp 130–131 °C; MS *m/e* (M^+) (calcd for $C_{21}H_{25}NO_4S$) 387.1504 (found 387.1508); ^1H NMR (60 MHz) δ 1.18 (d, J = 7 Hz, 6 H), 1.76 (m, 2 H), 2.43 (s, 3 H), 2.67 (m, 4 H), 3.28 (septet, J = 7 Hz, 1 H), 3.80 (s, 3 H), 6.94 (s, 1 H), 7.28 (s, 1 H), 7.32 (d, J = 8 Hz, 2 H), 7.93 (d, J = 8 Hz, 2 H). Anal. ($C_{21}H_{25}NO_4S$) C, H, N.

1,3,4,5-Tetrahydro-7-isopropyl-8-methoxy-2H-1-benzazepin-2-one (4). Trifluoroacetic acid (2 mL) was added to compound **3** (725 mg, 1.9 mmol) and the mixture was stirred at room temperature for 30 min. Then the mixture was concentrated under vacuum to remove trifluoroacetic acid. The residue was chromatographed on a silica gel column (eluted with $CHCl_3$ containing 2% MeOH) to provide product **4** as a colorless crystalline solid, which was recrystallized from EtOAc to afford colorless needles (449 mg, 100%): mp 186–187 °C; MS *m/e* (M^+) (calcd for $C_{14}H_{19}NO_2$) 233.1416 (found 233.1431); ^1H NMR (250 MHz) δ 1.20 (d, J = 6.9 Hz, 6 H), 2.21 (m, 2 H), 2.36 (t, J = 6.9 Hz, 2 H), 2.73 (t, J = 7.1 Hz, 2 H), 3.21 (septet, J = 6.9 Hz, 1 H), 3.80 (s, 3 H), 6.44 (s, 1 H), 7.00 (s, 1 H). Anal. ($C_{14}H_{19}NO_2$) C, H, N.

Prototypical Procedure for Demethylation with Boron Tribromide. 1,3,4,5-Tetrahydro-7-isopropyl-8-hydroxy-2H-1-benzazepin-2-one (5). Boron tribromide (0.45 mL, 4.8 mmol) was added via a syringe under nitrogen to a solution of compound **4** (440 mg, 1.9 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at room temperature for 15 min. The reaction mixture was then poured into brine solution (80 mL). The organic layer was separated and was dried over anhydrous Na_2SO_4. After filtration and evaporation, the residue was chromatographed on a silica gel column (eluted with $CHCl_3$ containing 5% MeOH) to give product **5**, which was recrystallized from MeOH to furnish colorless crystals (380 mg, 92%): mp 278–279 °C; MS *m/e* (M^+) (calcd for $C_{13}H_{17}NO_2$) 219.1259 (found 219.1259); ^1H NMR (250 MHz, CD_3OD) δ 1.20 (d, J = 6.9 Hz, 6 H), 2.14–2.26 (m, 4 H), 2.68 (t, J = 7 Hz, 2 H), 3.23 (septet, J = 6.9 Hz, 1 H), 6.45 (s, 1 H), 6.97 (s, 1 H). Anal. ($C_{13}H_{17}NO_2$) C, H, N.

1,2,3,4-Tetrahydro-7-isopropylnaphth-6-ol (7) was prepared from **6** (420 mg, 2.1 mmol) in CH_2Cl_2 (5 mL) and boron tribromide (0.5 mL, 5.3 mmol). Chromatography conditions: silica gel, hexanes containing 10–15% EtOAc. Compound **7**: rectangular crystals from MeOH–EtOAc (240 mg, 61%): mp 54–55 °C [lit[12] mp 57 °C (from light petroleum)]; MS *m/e* (M^+) (calcd for $C_{13}H_{18}O$) 190.1357 (found 190.1361); ^1H NMR (60 MHz) δ 1.25 (d, J = 7 Hz, 6 H), 1.77 (m, 4 H), 2.68 (m, 4 H), 3.13 (septet, J = 7 Hz, 1 H), 4.00 (br s, 1 H), 6.43 (s, 1 H), 6.83 (s, 1 H).

2-Isopropyl-5-phenylnaphth-3-ol (17) was prepared from **16** (110 mg, 0.4 mmol) in CH_2Cl_2 (3 mL) and boron tribromide (0.26 mL). Chromatography conditions: silica gel, CH_2Cl_2 containing 2% MeOH. Compound **17**: colorless oil (92 mg, 87%); MS *m/e* (M^+) (calcd for $C_{19}H_{18}O$) 262.1358 (found 262.1349); ^1H NMR (60 MHz) δ 1.34 (d, J = 7 Hz, 6 H), 3.34 (septet, J = 7 Hz, 1 H), 5.0–5.2 (br s, 1 H), 7.09 (s, 1 H), 7.27–7.46 (m, 7 H), 7.68 (s, 1 H), 7.74 (d, J = 8 Hz, 1 H).

2-Isopropyl-5-ethylnaphth-3-ol (28) was prepared from **27** (36 mg, 0.15 mmol) in CH_2Cl_2 (3 mL) cooled at 0 °C and boron tribromide (0.1 mL). Chromatography conditions: silica gel, hexanes containing 10% EtOAc. Compound **28**: yellow oil (24 mg, 70%); MS *m/e* (M^+) 214 ($C_{15}H_{18}O$); ^1H NMR (250 MHz) δ 1.34 (t, J = 6.7 Hz, 3 H), 1.35 (d, J = 6.7 Hz, 6 H), 2.98 (q, J = 7.5 Hz, 2 H), 3.34 (septet, J = 6.8 Hz, 1 H), 5.14 (br s, 1 H), 7.23 (d, J = 5.4 Hz, 2 H), 7.26 (s, 1 H), 7.60 (t, J = 5 Hz, 1 H), 7.64 (s, 1 H). Compound **28** was not purified further and was used directly in the preparation of **29**.

6-Isopropyl-7-hydroxynaphthalene-1-carboxylic acid (32) was prepared from **31** (22 mg, 0.1 mmol) in CH_2Cl_2 (1 mL) cooled at −75 °C and boron tribromide (0.05 mL). The solution was stirred at −75 °C for 3 h and was allowed to warm to room temperature overnight. Chromatography conditions: silica gel, hexanes–EtOAc 1:1. Compound **32**: colorless solid (16 mg, 78%); mp 203–205 °C; MS *m/e* (M^+) (calcd for $C_{14}H_{14}O_3$) 230.0942 (found 230.0926); ^1H NMR (60 MHz) δ 1.34 (d, J = 7 Hz, 6 H), 3.42 (septet, J = 7 Hz, 1 H), 6.00 (br s, 1 H), 7.30 (t, J = 7 Hz, 1 H), 7.65 (s, 1 H), 7.94 (d, J = 8 Hz, 1 H), 8.25 (d, J = 7 Hz, 1 H), 8.50 (s, 1 H).

***N,N*-Diethyl-6-isopropyl-7-hydroxynaphthalene-1-carboxamide (35)** was prepared from **34** (29 mg, 0.1 mmol) in CH_2Cl_2 (4 mL) at 0 °C and boron tribromide (0.2 mL). Chromatography conditions: silica gel, hexanes containing 30% EtOAc. Compound **35**: colorless crystals (23 mg, 83%); mp 158–160 °C; MS *m/e* (M^+) (calcd for $C_{18}H_{23}NO_2$) 285.1727 (found 285.1722); ^1H NMR (250 MHz) δ 0.82 (t, J = 7.1 Hz, 3 H), 1.05 (d, J = 7.2 Hz, 6 H), 1.42 (t, J = 7.1 Hz, 3 H), 2.94 (septet, J = 6.9 Hz, 1 H), 3.15–3.19 (m, 2 H), 3.68–3.73 (m, 2 H), 7.01 (s, 1 H), 7.19 (d, J = 6.5 Hz, 2 H), 7.30 (s, 1 H), 7.60 (dd, J = 2.8, 6.4 Hz, 1 H), 9.41 (br s, 1 H).

1,3,4,5-Tetrahydro-7-hydroxy-8-isopropyl-2H-naphth[2,1-b]azepin-2-one (41) was prepared from **40** (60 mg, 0.2 mmol) in CH_2Cl_2 (1.2 mL) and boron tribromide (0.1 mL, 1 mmol). Chromatography conditions: silica gel, CH_2Cl_2 containing 2% MeOH. Compound **41**: colorless solid from hexanes–EtOAc (53 mg, 93%); mp 191–193 °C; MS *m/e* (M^+) (calcd for $C_{17}H_{19}NO_2$) 269.1416 (found 269.1416); ^1H NMR (250 MHz) δ 1.36 (d, J = 6.9 Hz, 6 H), 2.38 (m, 4 H), 3.15 (t, J = 6.3 Hz, 2 H), 3.35 (septet, J = 6.9 Hz, 1 H), 6.95 (d, J = 8.5 Hz, 1 H), 7.30 (s, 1 H), 7.63 (s, 1 H), 7.63 (d, J = 8.5 Hz, 1 H).

7,8,9,10,11,12-Hexahydro-3-isopropylcycloocta[a]naphthalen-2-ol (51) was prepared from **50** (120 mg, 0.4 mmol) in CH_2Cl_2 (2 mL) and boron tribromide (0.2 mL, 2 mmol). Chromatography conditions: silica gel column, hexanes containing 10% Et_2O. Compound **51**: colorless crystals (82 mg, 72%); mp 89–92 °C; MS *m/e* (M^+) 268 ($C_{19}H_{24}O$); ^1H NMR (250 MHz) δ 1.35 (d, J = 6.9 Hz, 6 H), 1.22–1.47 (m, 4 H), 1.77 (m, 4 H), 2.89 (t, J = 6.1 Hz, 2 H), 3.14 (t, J = 6.3 Hz, 2 H), 3.32 (septet, J = 6.9 Hz, 1 H), 5.02 (br s, 1 H), 7.27 (s, 1 H), 7.09–7.54 (2 d, J = 8.3 Hz, 2 H), 7.58 (s, 1 H). Compound **51** was unstable and was used directly without further purification in the preparation of **52**.

8,9,10,11-Tetrahydro-3-isopropyl-7H-cyclohepta[a]naphthalen-2-ol (57) was prepared from **56** (190 mg, 0.7 mmol) in CH_2Cl_2 (2 mL) and boron tribromide (200 μL, 2 mmol). Chromatography conditions: silica gel, hexanes containing 5–10% Et_2O. Compound **57**: (160 mg, 93%); mp 94–95 °C; MS *m/e* (M^+) 254 ($C_{18}H_{22}O$); ^1H NMR (250 MHz) δ 1.35 (d, J = 6.9 Hz, 6 H), 1.67 (m, 4 H), 1.87 (m, 2 H), 2.95 (t, J = 5.3 Hz, 2 H), 3.13 (t, J = 5.3 Hz, 2 H), 3.32 (septet, J = 6.9 Hz, 1 H), 4.99 (s, 1 H), 7.11 (d, J = 8.2 Hz, 1 H), 7.35 (s, 1 H), 7.51 (d, J = 8.2 Hz, 1 H), 7.59 (s, 1 H). Compound **57** has not been purified further and was used directly in the preparation of **58**.

1,1-Dimethyl-1,2,3,4-tetrahydrophenanthren-6-ol (103) was prepared from **102**[1b] (107 mg, 0.45 mmol) in CH_2Cl_2 (6 mL) cooled at 0 °C and boron tribromide (0.3 mL). Chromatography conditions: silica gel, hexanes containing 10% EtOAc. Compound **103**: colorless solid (94 mg, 93%); mp 119–120.5 °C; MS *m/e* (M^+) (calcd for $C_{16}H_{18}O$) 226.1358 (found 226.1358); ^1H NMR (250 MHz) δ 1.34 (s, 6 H), 1.71 (t, J = 6 Hz, 2 H), 1.92 (quintet, J = 6.0 Hz, 2 H), 2.95 (t, J = 6.0 Hz, 2 H), 5.10 (br s, 1 H), 7.02 (dd, J = 2.4, 8.7 Hz, 1 H), 7.27 (d, J = 2.4 Hz, 1 H), 7.34 (d, J = 8.6 Hz, 1 H), 7.58 (d, J = 8.6 Hz, 1 H), 7.67 (d, J = 8.7 Hz, 1 H). Anal. ($C_{16}H_{16}O$) H; C: calcd, 84.96; found, 84.39.

Prototypical Procedure for Clemmensen Reduction. 1,2,3,4-Tetrahydro-6-isopropyl-7-methoxynaphthalene (6). To a mixture of mossy zinc (3.3 g) and mercuric chloride (0.33 g) was added a solution of concentrated HCl (0.25 mL) in H_2O (8 mL). The mixture was stirred at room temperature for 10 min. The solution was then decanted and concentrated HCl (7.2 mL) in H_2O (3.1 mL) was added, followed by toluene (4.1 mL) and compound **2**[1b] (0.5 g, 2.3 mmol). The reaction was refluxed at 110 °C for 24 h. It was then cooled to room temperature and poured into cold water (50 mL). The resulting mixture was extracted with EtOAc (3 × 70 mL). The organic layer was dried with anhydrous Na_2SO_4, filtered, and evaporated. The residue was chromatographed on a silica gel column (eluted with hexanes containing 5% EtOAc) to give the product **6** as a pale yellow viscous liquid (0.42 g, 90%) (lit.[12] bp 120–124 °C/1 mm); MS *m/e* (M^+) (calcd for $C_{14}H_{20}O$) 204.1514 (found 204.1517); ^1H NMR (60 MHz) δ 1.20 (d, J = 7 Hz, 6 H), 1.73 (m, 4 H), 2.67 (m, 4 H), 3.30 (septet, J = 7 Hz, 1 H), 3.73 (s, 3 H), 6.50 (s, 1 H), 6.83 (s, 1 H). Anal. ($C_{14}H_{20}O$) C, H.

7,8,9,10,11,12-Hexahydro-2-methoxy-3-isopropylcycloocta[*a*]naphthalene (50) was prepared from mossy zinc (4.6 g), mercuric chloride (0.46 g), and a solution of concentrated HCl (0.4 mL) in H_2O (13.8 mL). After decantation was added a solution of concentrated HCl (12 mL) in H_2O (5.2 mL), toluene (10 mL), and compound **49** (160 mg, 0.55 mmol). Chromatography conditions: silica gel, hexanes containing 0–5% Et_2O. Compound **50**: viscous oil (125 mg, 82%); MS *m/e* (M^+) 282 ($C_{20}H_{26}O$); ^1H NMR (250 MHz) δ 1.30 (d, J = 6.8 Hz, 6 H), 1.22–1.54 (m, 4 H), 1.73 (m, 2 H), 1.83 (m, 2 H), 2.91 (t, J = 6.1 Hz, 2 H), 3.22 (t, J = 6.3 Hz, 2 H), 3.40 (septet, J = 6.8 Hz, 1 H), 3.95 (s, 3 H), 7.27 (s, 1 H), 7.10–7.55 (2 d, J = 8.6 Hz, 2 H), 7.56 (s, 1 H). Anal. ($C_{20}H_{26}O$) H; C: calcd, 85.05; found, 84.33.

8,9,10,11-Tetrahydro-2-methoxy-3-isopropyl-7*H*-cyclohepta[*a*]naphthalene (56) was prepared from mossy zinc (4.6 g), mercuric chloride (0.46 g), and a solution of concentrated HCl (0.4 mL) in H_2O (14 mL). After decantation a solution of concentrated HCl (12 mL) in H_2O (5.2 mL), toluene (10 mL), and ketone **55** (210 mg, 0.7 mmol) was added. Chromatography conditions: silica gel, hexanes containing 5% EtOAc. Compound **56**: colorless crystals from EtOH–$CHCl_3$ (190 mg, 95%); mp 73–73.5 °C; MS *m/e* (M^+) 268 ($C_{19}H_{24}O$); ^1H NMR (250 MHz) δ 1.30 (d, J = 6.9 Hz, 6 H), 1.68 (m, 4 H), 1.90 (m, 2 H), 2.95 (t, J = 5.4 Hz, 2 H), 3.18 (t, J = 5.2 Hz, 2 H), 3.39 (septet, J = 6.9 Hz, 1 H), 3.96 (s, 3 H), 7.32 (s, 1 H), 7.12–7.50 (2 d, J = 8.2 Hz, 2 H), 7.57 (s, 1 H). Anal. ($C_{19}H_{24}O$) C, H.

1,2,3,4-Tetrahydro-6-methoxy-7-isopropylphenanthrene (65) was prepared from mossy zinc (0.4 g, 6 mmol), mercuric chloride (40 mg, 0.15 mmol), and dilute HCl (0.1 mL of concentrated HCl in 2 mL of water). After decantation a solution of **37**[1b] (0.2 g, 0.75 mmol), toluene (1 mL), and HCl (1.2 mL of concentrated HCl in 0.5 mL of water) was added. Chromatography conditions: silica gel (230–400 mesh), hexanes. Compound **65**: colorless crystals (114 mg, 60%); mp 105–106 °C (from hexanes); MS *m/e* (M^+) (calcd for $C_{18}H_{22}O$) 254.1672 (found 254.1678); ^1H NMR (250 MHz) δ 1.29 (d, J = 6.9 Hz, 6 H), 1.81–2.02 (m, 4 H), 2.89 (t, J = 6.0 Hz, 2 H), 3.03 (t, J = 6.2 Hz, 2 H), 3.40 (septet, J = 6.9 Hz, 1 H), 3.95 (s, 3 H), 7.05 (d, J = 8.3 Hz, 1 H), 7.14 (s, 1 H), 7.51 (d, J = 8.3 Hz, 1 H), 7.55 (s, 1 H). Anal. ($C_{18}H_{22}O$) C, H.

1,2,3,3a,4,5-Hexahydro-8-isopropyl-9-methoxyacephenanthrylene (87) was prepared from mossy zinc (4.6 g), $HgCl_2$ (0.46 g) in concentrated HCl (0.42 mL), and water (14 mL). After decantation concentrated HCl (12 mL), water (5 mL), and ketone **86** (170 mg, 0.58 mmol) was added. Chromatography conditions: silica gel (230–400 mesh), hexanes. Compound **87**: colorless needles (124 mg, 76%); mp 102–103 °C (from hexanes); MS *m/e* (M^+) (calcd for $C_{20}H_{24}O$) 280.1827 (found 280.1816); ^1H NMR (250 MHz) δ 1.20–1.33 (2 d, J = 7.0 Hz, 6 H), 1.43–1.60 (m, 2 H), 1.80–2.00 (m, 1 H), 2.20–2.42 (m, 3 H), 2.78–3.20 (m, 4 H), 3.40 (septet, J = 7.0 Hz, 1 H), 3.97 (s, 3 H), 7.08 (s, 1 H), 7.42 (s, 1 H), 7.55 (s, 1 H).

Prototypical Procedure for *o*-Quinone Synthesis. 1,2,3,4-Tetrahydro-7-isopropylnaphthalene-5,6-dione (8). To a solution of phenol **7** (230 mg, 1.2 mmol) in acetone (55 mL) under nitrogen was added $^1/_6$ M aqueous KH_2PO_4 (51 mL), followed by a solution of Fremy's salt (1.37 g, 5.1 mmol) in H_2O (71 mL). The mixture was stirred in darkness at room temperature under nitrogen for 20 h. It was then evaporated to remove acetone and extracted with CH_2Cl_2 (3 × 70 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The residue was chromatographed on a silica gel column (eluted with hexanes containing 5–20% EtOAc) to yield product **8** (130 mg) which was shown to be contaminated with impurities by TLC on silica gel plate (20% EtOAc in hexanes). Further purification was achieved by a second chromatography on a silica gel column (eluted with hexanes containing 5–10% Et_2O) which afforded product **8** as red crystals (70 mg, 28%): mp 65–68 °C; MS *m/e* (M^+) (calcd for $C_{13}H_{16}O_2$) 204.1150 (found 204.1152); ^1H NMR (250 MHz) δ 1.12 (d, J = 7 Hz, 6 H), 1.72 (m, 4 H), 2.37 (m, 4 H), 2.96 (septet, J = 7 Hz, 1 H), 6.45 (s, 1 H). Anal. ($C_{13}H_{16}O_2$) C: calcd, 76.47; found, 73.63; H: calcd, 7.90; found 7.53 (compound unstable).

3-Isopropylnaphthalene-1,2-dione (13) was prepared from phenol **12** (26 mg, 0.14 mmol) in acetone (5 mL), a solution of the Fremy's salt (106 mg) in H_2O (4.8 mL), and $^1/_6$ M aqueous KH_2PO_4 (3.5 mL). The solution was stirred at room temperature for 19 h. Chromatography conditions: silica gel, hexanes containing 5% EtOAc. Compound **13**: orange-red plates from hexanes–EtOAc (23 mg, 81%); mp 126–128 °C; MS *m/e* (M^+) (calcd for $C_{19}H_{12}O_2$) 200.0837 (found 200.0866); ^1H NMR (60 MHz) δ 1.18 (d, J = 7 Hz, 6 H), 3.08 (septet, J = 7 Hz, 1 H), 7.15 (s, 1 H), 7.30 (d, J = 7 Hz, 1 H), 7.42 (t, J = 7 Hz, 1 H), 7.61 (t, J = 7 Hz, 1 H), 8.05 (d, J = 8 Hz, 1 H).

3-Isopropyl-8-phenylnaphthalene-1,2-dione (18) was prepared from phenol **17** (49 mg, 0.2 mmol) in acetone (10 mL) and a solution of the Fremy's alt (102 mg) in H_2O (9 mL) and $^1/_6$ M aqueous KH_2PO_4 (7 mL). The solution was stirred at room temperature for 22 h. Chromatography conditions: silica gel, hexanes containing 5% EtOAc. Compound **18**: red needles from hexanes–EtOAc (43 mg, 84%); mp 130–131 °C; MS *m/e* (M^+) (calcd for $C_{19}H_{16}O_2$) 276.1151 (found 276.1158); ^1H NMR (250 MHz) δ 1.18 (d, J = 6.9 Hz, 6 H), 3.05 (septet, J = 6.9 Hz, 1 H), 7.20 (s, 1 H), 7.23 (d, J = 1.5 Hz, 1 H), 7.25 (d, J = 2.6 Hz, 1 H), 7.31 (d, J = 7.6 Hz, 2 H), 7.38 (d, J = 2.6 Hz, 2 H), 7.40 (d, J = 1.5 Hz, 1 H), 7.58 (t, J = 7.6 Hz, 1 H). Anal. ($C_{19}H_{16}O_2$) C, H.

3-Isopropyl-8-ethenylnaphthalene-1,2-dione (25) was prepared from phenol **24** (56 mg, 0.26 mmol) in acetone (14 mL) and a solution of the Fremy's salt (250 mg) in $^1/_6$ M aqueous KH_2PO_4 (9 mL) and H_2O (13 mL). The solution was stirred at room temperature for 23 h. Chromatography conditions: silica gel, hexanes containing 5% EtOAc. Compound **25**: very unstable orange red oil; no spectral result has therefore been obtained.

3-Isopropyl-8-ethylnaphthalene-1,2-dione (29) was prepared from phenol **28** (144 mg, 0.67 mmol) in acetone (37 mL) and a solution of the Fremy's salt (628 mg) in aqueous $^1/_6$ M KH_2PO_4 (23 mL) and H_2O (34 mL). The solution was stirred at room temperature for 6.5 h. Chromatography conditions: silica gel, hexanes containing 5% EtOAc. Compound **29**: unstable orange red oil (44 mg, 29%); MS *m/e* (M^+) (calcd for $C_{19}H_{16}O_2$) 228.1149 (found 228.1132); ^1H NMR (250 MHz, contaminated with decomposed products) δ 1.18 (d, J = 6.9 Hz, 2 H), 1.34 (t, J = 6.5 Hz, 3 H), 3.00–3.14 (m, 2 H), 3.35 (septet, J = 7.2 Hz, 1 H), 7.12 (s, 1 H), 7.15 (d, J = 10 Hz, 1 H), 7.24 (d, J = 10 Hz, 1 H), 7.49 (t, J = 7.7 Hz, 1 H).

6-Isopropyl-7,8-dihydro-7,8-dioxonaphthalene-1-carboxylic acid (33) was prepared from phenol **32** (26 mg, 0.01 mmol) in acetone (7 mL) and a solution of the Fremy's salt (254 mg) and aqueous $^1/_6$ M KH_2PO_4 (4.3 mL) in H_2O (6.5 mL). The solution was stirred at room temperature for 10 h. Chromatography conditions: silica gel, hexanes–EtOAc 1:1. Compound **33**: yellow crystals (5 mg, 19%); mp 178–180 °C; MS *m/e* (M^+) 244 ($C_{14}H_{12}O_4$); ^1H NMR (60 MHz) δ 1.23 (d, J = 7 Hz, 6 H), 3.25 (septet, J = 7 Hz, 1 H), 7.33 (s, 1 H), 7.83 (dd, J = 1.5, 8 Hz, 1 H), 7.89 (t, J = 8 Hz, 1 H), 8.23 (dd, J = 1.5, 8 Hz, 1 H).

***N*,*N*-Diethyl-7,8-dihydro-6-isopropyl-7,8-dioxonaphthalene-1-carboxamide (36)** was prepared from phenol **35** (27 mg, 0.09 mmol) in acetone (5.3 mL) and a solution of the Fremy's salt (120 mg) and aqueous $^1/_6$ M KH_2PO_4 (3.5 mL) in H_2O (5 mL). The solution was stirred at room temperature for 17 h. Chromatography conditions: silica gel, hexanes containing 20% EtOAc. Compound **36**: red crystals (5.4 mg, 19%); mp 119–120 °C; MS *m/e* (M^+) 299 ($C_{18}H_{21}NO_3$); ^1H NMR (250 MHz)

δ 1.03 (t, J = 7.0 Hz, 3 H), 1.18 (dd, J = 2.8, 7.0 Hz, 6 H), 1.38 (t, J = 7.0 Hz, 3 H), 3.02–3.17 (m, 4 H), 3.36 (septet, J = 7.0 Hz, 1 H), 7.16 (s, 1 H), 7.24 (dd, J = 1.0, 7.0 Hz, 1 H), 7.32 (dd, J = 1.0, 7.0 Hz, 1 H), 7.63 (t, J = 7.6 Hz, 1 H). Anal. ($C_{18}H_{21}NO_3$) H, N; C: calcd, 72.24; found, 71.64.

1,3,4,5-Tetrahydro-8-isopropyl-2*H*-naphtho[2,1-*b*]azepine-2,6,7-trione (42) was prepared from phenol 41 (40 mg, 0.15 mmol) in acetone (8 mL) and a solution of Fremy's salt (140 mg, 0.5 mmol) in H_2O (7.2 mL) and $^1/_6$ M aqueous KH_2PO_4 (5.2 mL). The mixture was stirred in darkness at room temperature for 17 h. Chromatography conditions: silica gel, CH_2Cl_2 containing 0–2% MeOH. Compound 42: red needles from hexanes–EtOAc (32 mg, 76%); mp 190–191 °C; MS m/e (M^+) (calcd for $C_{17}H_{17}NO_3$) 283.1208 (found 283.1188); ^1H NMR (250 MHz) δ 1.18 (d, J = 6.9 Hz, 6 H), 2.38 (m, 4 H), 3.04 (septet, J = 6.9 Hz, 1 H), 3.29 (m, 2 H), 7.11 (s, 1 H), 7.16 (2 d, J = 8 Hz, 2 H), 7.57 (br s, 1 H). Anal. ($C_{17}H_{17}NO_3$) C, H, N.

7,8,9,10,11,12-Hexahydro-3-isopropylcycloocta[*a*]naphthalene-1,2-dione (52) was prepared from phenol 51 (80 mg, 0.3 mmol) in acetone (16 mL) and a solution of the Fremy's salt (280 mg, 1 mmol) in H_2O (15 mL) and $^1/_6$ M aqueous KH_2SO_4 (11 mL). The solution was stirred in darkness at room temperature overnight. Chromatography conditions: silica gel, hexanes containing 5–10% Et_2O then silica gel, hexanes containing 30–50% CH_2Cl_2. Compound 52: unstable red oil (50 mg, 59%); MS m/e (M^+) (calcd for $C_{19}H_{22}O_2$) 282.1620 (found 282.1617); ^1H NMR (250 MHz) δ 1.17 (d, J = 6.8 Hz, 6 H), 1.26 (m, 2 H), 1.45 (m, 2 H), 1.70 (m, 2 H), 1.83 (m, 2 H), 2.83 (t, J = 6.1 Hz, 2 H), 3.02 (septet, J = 6.8 Hz, 1 H), 3.25 (t, J = 6.3 Hz, 2 H), 7.08 (s, 1 H), 7.07–7.33 (2 d, J = 7.6 Hz, 2 H). Anal. ($C_{19}H_{22}O_2$) H; C: 80.85; found, 78.83 (compound unstable).

8,9,10,11-Tetrahydro-3-isopropyl-7*H*-cyclohepta[*a*]naphthalene-1,2-dione (58) was prepared from phenol 57 (150 mg, 0.6 mmol) in acetone (30 mL) and a solution of the Fremy's salt (525 mg, 2 mmol) in H_2O (27 mL) and $^1/_6$ M aqueous KH_2PO_4 (20 mL). The mixture was stirred in darkness at room temperature overnight. Chromatography conditions: silica gel, hexanes containing 5–10% Et_2O. Compound 58: red oil (110 mg, 69%); MS m/e (M^+) (calcd for $C_{18}H_{20}O_2$) 268.1463 (found 268.1471); ^1H NMR (250 MHz) δ 1.16 (d, J = 6.9 Hz, 6 H), 1.67 (m, 4 H), 1.81 (m, 2 H), 2.85 (t, J = 5.5 Hz, 2 H), 3.01 (septet, J = 6.9 Hz, 1 H), 3.34 (t, J = 5.2 Hz, 2 H), 7.08 (s, 1 H), 7.00–7.27 (2 d, J = 7.5 Hz, 2 H). Anal. ($C_{18}H_{20}O_2$) C, H.

3,4-Dihydro-7-isopropylphenanthrene-1(2*H*),5,6-trione (60) was prepared from phenol 59 (0.76 g, 3 mmol) in acetone (140 mL) and a solution of the Fremy's salt (2.5 g) in water (126 mL) and $^1/_6$ M aqueous KH_2PO_4 (91 mL). The mixture was stirred at room temperature for 24 h. Chromatography conditions: silica gel (230–400 mesh), hexanes containing 20% EtOAc. Compound 60: red crystals from absolute EtOH (320 mg, 32%); mp 186–188 °C; MS m/e (M^+) (calcd for $C_{17}H_{16}O_3$) 268.1100 (found 268.1100); ^1H NMR (250 MHz) δ 1.20 (d, J = 6.9 Hz, 6 H), 2.14 (quintet, J = 6.4 Hz, 2 H), 2.69 (t, J = 6.4 Hz, 2 H), 3.07 (septet, J = 6.9 Hz, 1 H), 3.46 (t, J = 6.9 Hz, 2 H), 7.17 (s, 1 H), 7.31 (d, J = 7.9 Hz, 1 H), 8.33 (d, J = 7.9 Hz, 1 H). Anal. ($C_{17}H_{16}O_3$) C, H.

1,2,3,4-Tetrahydrophenanthrene-5,6-dione (95) was prepared from phenol 94 (19 mg, 0.1 mmol) in acetone (15 mL) and a solution of the Fremy's salt (188 mg) in H_2O (14 mL). The solution was stirred at room temperature for 6 h. Chromatography conditions: silica gel, hexanes containing 10% EtOAc. Compound 95: brownish red oil (4 mg, 20%); the product was rather unstable and became brownish black oil on standing.

1,1-Dimethyl-1,2,3,4-tetrahydrophenanthrene-5,6-dione (104) was prepared from phenol 103 (34 mg, 0.15 mmol) in acetone (22.5 mL) and a solution of the Fremy's salt (290 mg) in H_2O (21 mL). The solution was stirred at room temperature for 16 h. Chromatography conditions: silica gel, hexanes containing 10% EtOAc. Compound 104: brownish red oil (19 mg, 52%); the product was rather unstable in air so that no physical data could be recorded.

1,1,7-Trimethyl-1,2,3,4-tetrahydrophenanthrene-5,6-dione (113) was prepared from phenol 112 (55 mg, 0.23 mmol) in acetone (10 mL) and a solution of KH_2PO_4 (0.17 M, 6 mL) and Fremy's salt (170 mg) in water (18 mL). The mixture was stirred for 24 h. Chromatography conditions: silica gel, hexanes containing 10% EtOAc. Compound 113: orange red plates from hexanes (42 mg, 72%); mp 108 °C; MS m/e (M^+) 254 ($C_{17}H_{18}O_2$); ^1H NMR (250 MHz) δ 1.29 (s, 6 H), 1.60–1.66 (m, 2 H), 1.79 (quintet, J = 6.4 Hz, 2 H), 2.01 (d, J = 1.2 Hz, 3 H), 3.19 (t, J = 6.4 Hz, 2 H), 7.05 (d, J = 7.9 Hz, 1 H), 7.14 (s, 1 H), 7.57 (d, J = 7.9 Hz, 1 H). Anal. ($C_{17}H_{18}O_2$) C, H.

1-Phenyl-1,2,3,4-tetrahydro-6-isopropyl-7-methoxynaphth-1-ol (14). Dry THF (5 mL) was added to flame-dried magnesium turnings (390 mg, 0.16 mmol). A solution of bromobenzene (1.6 g, 10 mmol) in dry THF (10 mL) was then added under nitrogen and the resulting mixture was stirred for 30 min. To this Grignard reagent was added a solution of compound 2[1b] (1.5 g, 7 mmol) in dry THF (10 mL). The mixture was stirred for 2 h and saturated aqueous NH_4Cl (25 mL) was added. The mixture was extracted with Et_2O (3 × 20 mL). The ethereal solution was washed with brine (2 × 20 mL), dried over anhydrous Na_2SO_4, and evaporated. The residue was chromatographed by flash column chromatography on a silica gel column (eluted with hexanes containing 10% EtOAc) to give a colorless solid, which was recrystallized from hexanes–EtOAc to afford 14 (1.3 g, 64%) as colorless plates: mp 62–63 °C; MS m/e (M^+) (calcd for $C_{20}H_{24}O_2$) 296.1772 (found 296.1771); ^1H NMR (60 MHz) δ 1.22 (d, J = 7 Hz, 6 H), 2.39 (quintet, J = 5 Hz, 2 H), 2.78 (t, J = 7 Hz, 4 H), 3.29 (septet, J = 7 Hz, 1 H), 3.60 (s, 3 H), 6.54 (s, 1 H), 7.04 (s, 1 H), 7.22–7.38 (m, 5 H). Anal. ($C_{20}H_{24}O_2$) H; C: calcd, 81.08; found, 81.82.

1-Phenyl-3,4-dihydro-6-isopropyl-7-methoxynaphthalene (15). A solution of compound 14 (0.8 g, 2.7 mmol) and triethylamine (4.4 mL) in CH_2Cl_2 (8 mL) was stirred under nitrogen at 0 °C for 30 min. Methanesulfonyl chloride (13 mL) was added slowly via a syringe. The mixture was stirred for 2 h at 0 °C. Ice water (50 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extract was washed with brine (2 × 25 mL), dried over anhydrous Na_2SO_4, and evaporated. The residue was chromatographed on a silica gel column (eluted with hexanes containing 5% EtOAc) to give 15 as colorless oil (0.6 g, 80%); MS m/e (M^+) (calcd for $C_{20}H_{22}O$) 278.1672, (found 278.1665); ^1H NMR (60 MHz) δ 1.22 (d, J = 7 Hz, 6 H), 2.38 (q, J = 5 Hz, 2 H), 2.78 (t, J = 8 Hz, 2 H), 3.29 (septet, J = 7 Hz, 1 H), 3.60 (s, 3 H), 6.04 (t, J = 5 Hz, 1 H), 6.55 (s, 1 H), 7.04 (s, 1 H), 7.22–7.89 (m, 5 H).

2-Isopropyl-3-methoxy-5-phenylnaphthalene (16). A solution of compound 15 (430 mg, 1.5 mmol) and dichlorodicyanoquinone (DDQ) (940 mg, 4.1 mmol) in CH_2Cl_2 (20 mL) was stirred under nitrogen at room temperature for 2 h. The mixture was filtered and the precipitate was washed with CH_2Cl_2 (15 mL). The combined filtrate was evaporated and the residue was chromatographed on a silica gel column (eluted with hexanes containing 5% EtOAc) to give 16 as a colorless oil (360 mg, 84%); MS m/e (M^+) (calcd for $C_{20}H_{20}O$) 276.1515 (found 276.1513); ^1H NMR (60 MHz) δ 1.31 (d, J = 7 Hz, 6 H), 3.41 (septet, J = 7 Hz, 1 H), 3.74 (s, 3 H), 7.18 (s, 1 H), 7.29–7.54 (m, 7 H), 7.67 (s, 1 H), 7.74 (dd, J = 2, 7 Hz, 1 H). Anal. ($C_{20}H_{20}C$) C, H.

1,2,3,4-Tetrahydro-1-[(ethoxycarbonyl)methyl]-6-isopropyl-7-methoxynaphth-1-ol (19). A mixture of zinc wool (1.3 g), ethyl 4-bromocrotonate (0.9 mL), and tetralone 2[1b] (820 mg, 3.8 mmol) in dry THF (12 mL) was allowed to react with the aid of an ultrasonicator for 2 h at room temperature. The reaction mixture was then poured into aqueous 10% $KHSO_4$ (50 mL). Extraction with CH_2Cl_2 (3 × 30 mL) was followed by washing with brine (2 × 20 mL) and drying over anhydrous Na_2SO_4. After filtration and evaporation, the residue obtained was purified by flash chromatography on a silica gel column (eluted with hexanes containing 10% EtOAc) to give 19 as light yellow oil (980 mg, 85%); MS m/e (M^+) (calcd for $C_{18}H_{26}O_4$) 306.1832 (found 306.1821); ^1H NMR (60 MHz) δ 1.18 (d, J = 6 Hz, 6 H), 1.28 (t, J = 7 Hz, 3 H), 1.73–2.10 (m, 4 H), 2.68–2.75 (m, 2 H), 2.85 (t, J = 16 Hz, 2 H), 3.25 (septet, J = 7 Hz, 1 H), 3.82 (s, 3 H), 4.20 (q, J = 7 Hz, 2 H), 6.87 (s, 1 H), 7.02 (s, 1 H). Anal. ($C_{18}H_{26}O_4$) C, H.

2-Isopropyl-3-methoxy-5-[(ethoxycarbonyl)methyl]naphthalene (20). A mixture of ester 19 (925 mg, 3 mmol) and 5% Pd–C was heated at 230–250 °C under nitrogen for 2 h. The mixture was allowed to cool and CH_2Cl_2 (10 mL) was added. The 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 column

(eluted with hexanes containing 5% EtOAc) to afford **20** as colorless oil (640 mg, 74%); MS *m/e* (M^+) (calcd for $C_{18}H_{22}O_3$) 286.1569 (found 286.1565); ^1H NMR (60 MHz) δ 1.20 (t, J = 7 Hz, 3 H), 1.30 (d, J = 7 Hz, 6 H), 3.41 (septet, J = 7 Hz, 1 H), 3.94 (s, 3 H), 3.98 (s, 2 H), 4.13 (q, J = 7 Hz, 2 H), 7.22 (d, J = 8 Hz, 1 H), 7.24 (s, 1 H), 7.28 (t, J = 8 Hz, 1 H), 7.61 (s, 1 H), 7.67 (d, J = 8 Hz, 1 H). Anal. ($C_{18}H_{22}O_3$) C, H.

Ester **20** was saponified with aqueous NaOH to afford (6-isopropyl-7-methoxy-1-naphthyl)acetic acid as colorless needles: mp 160–161 °C; MS *m/e* (M^+) (calcd for $C_{16}H_{18}O_3$) 258.1256 (found 258.1570); ^1H NMR (250 MHz) δ 1.29 (d, J = 6.9 Hz, 6 H), 3.40 (septet, J = 6.9 Hz, 1 H), 3.89 (s, 3 H), 4.00 (s, 2 H), 7.17 (s, 1 H), 7.24 (d, J = 4.3 Hz, 1 H), 7.31 (t, J = 4.7 Hz, 1 H), 7.62 (s, 1 H), 7.69 (d, J = 7.7 Hz, 1 H). Anal. ($C_{16}H_{18}O_3$) H; C: calcd, 74.42; found, 74.90.

2-(6′-Isopropyl-7′-methoxy-1′-naphthyl)ethanol (21). A solution of ester **20** (2 g, 7 mmol) in dry THF (7 mL) was added to lithium aluminum hydride (700 mg) in dry THF (17 mL) under nitrogen with stirring at room temperature. The resulting mixture was then refluxed for 2 h. After cooling, EtOAc (10 mL) was added, which was followed by aqueous 10% sulfuric acid (20 mL). Ether extraction (3 × 50 mL) was followed by washing with brine (2 × 50 mL). After drying over anhydrous Na_2SO_4 and evaporation, the residue was chromatographed on a silica gel column (eluted with hexanes containing 20% EtOAc) to give **21** as a colorless oil (1.6 g, 93%); MS *m/e* (M^+) (calcd for $C_{16}H_{20}O_2$) 244.1464 (found 244.1465); ^1H NMR (60 MHz) δ 1.30 (d, J = 7 Hz, 6 H), 3.27 (t, J = 7 Hz, 2 H), 3.42 (septet, J = 7 Hz, 1 H), 3.94 (s, 3 H), 3.97 (t, J = 7 Hz, 2 H), 7.22 (d, J = 7 Hz, 1 H), 7.23 (s, 1 H), 7.26 (t, J = 4 Hz, 1 H), 7.62 (s, 1 H), 7.64 (d, J = 6 Hz, 1 H). Anal. ($C_{16}H_{20}O_2$) C, H.

2-(6′-Isopropyl-7′-methoxy-1′-naphthyl)ethyl Methanesulfonate (22). A solution of compound **21** (800 mg, 3.3 mmol) and triethylamine (8.5 mL) in CH_2Cl_2 (8.5 mL) was stirred under nitrogen at 0 °C for 30 min. Methanesulfonyl chloride (5.3 mL) was added slowly via a syringe. The mixture was stirred for 3 h at 0 °C and ice water (50 mL) was then added. The mixture was extracted with CH_2Cl_2 (3 × 30 mL) and the organic layer was washed with brine (2 × 50 mL), dried over anhydrous Na_2SO_4, and evaporated. The residue was chromatographed on a silica gel column (eluted with hexanes containing 20% EtOAc) to afford **22**, which was recrystallized from hexanes–EtOAc to give **22** (1.1 g, 89%) as colorless prisms: mp 85–86 °C; MS *m/e* (M^+) (calcd for $C_{17}H_{22}O_4S$) 322.1239 (found 322.1237); ^1H NMR (60 MHz) δ 1.31 (d, J = 7 Hz, 6 H), 2.83 (s, 3 H), 3.42 (septet, J = 7 Hz, 1 H), 3.50 (t, J = 8 Hz, 6 H), 3.99 (s, 3 H), 4.53 (t, J = 8 Hz, 2 H), 7.25 (s, 1 H), 7.25 (t, J = 7 Hz, 1 H), 7.26 (d, J = 7 Hz, 1 H), 7.63 (s, 1 H), 7.68 (dd, J = 2, 7 Hz, 1 H). Anal. ($C_{17}H_{22}O_4S$) C, H.

2-Isopropyl-3-methoxy-5-ethenylnaphthalene (23). A mixture of compound **22** (207 mg, 0.6 mmol) and potassium *tert*-butoxide (1.75 g) in *tert*-butyl alcohol (14 mL) was refluxed for 2 h under nitrogen. The reaction mixture was cooled and poured into ice water (50 mL). The resulting mixture was extracted with Et_2O (3 × 30 mL) and the combined ethereal extract was washed with brine (2 × 50 mL). After drying over anhydrous Na_2SO_4 and evaporation, the residue was chromatographed on a silica gel column (eluted with hexanes containing 5% EtOAc) to give **23** as a colorless oil (90 mg, 62%): MS *m/e* (M^+) (calcd for $C_{16}H_{18}O$) 226.1358 (found 226.1359); ^1H NMR (60 MHz) δ 1.30 (d, J = 6 Hz, 6 H), 3.42 (septet, J = 7 Hz, 1 H), 3.94 (s, 3 H), 5.44 (dd, J = 2, 11 Hz, 1 H), 5.78 (dd, J = 2, 18 Hz, 1 H), 7.28 (t, J = 8 Hz, 1 H), 7.30 (s, 1 H), 7.40 (dd, J = 11, 18 Hz, 1 H), 7.53 (d, J = 7 Hz, 1 H), 7.61 (s, 1 H), 7.68 (d, J = 8 Hz, 1 H).

2-Isopropyl-5-ethenylnaphth-3-ol (24). Ethanethiol (0.7 mL) was added slowly to sodium hydride (456 mg, hexanes washed) in DMF (6 mL) under nitrogen. To this mixture was added compound **23** (90 mg, 0.4 mmol) in DMF (5 mL). The resulting mixture was stirred at 150 °C for 2 h and was quenched with EtOH (6 mL) and saturated aqueous NH_4Cl (25 mL). The mixture was extracted with $CHCl_3$ (3 × 30 mL) and the combined organic extract was washed with brine (2 × 50 mL). After drying over anhydrous Na_2SO_4 and evaporation, the residue was chromatographed on a silica gel column (eluted with hexanes containing 10% EtOAc) to give **24** (73 mg, 87%) as colorless oil: MS *m/e* (M^+) (calcd for $C_{16}H_{16}O$) 212.1202 (found 212.1208); ^1H NMR (60 MHz) δ 1.36 (d, J = 7 Hz, 6 H), 3.35 (septet, J = 7 Hz, 1 H), 5.42 (dd, J = 2, 11 Hz, 1 H), 5.75 (dd, J = 2, 18 Hz, 1 H), 7.29 (t, J = 7 Hz, 1 H), 7.32 (dd, J = 11, 18 Hz, 1 H), 7.33 (s, 1 H), 7.52 (d, J = 7 Hz, 1 H), 7.64 (s, 1 H), 7.69 (d, J = 8 Hz, 1 H).

1-Ethenyl-1,2,3,4-tetrahydro-6-isopropyl-7-methoxynaphth-1-ol (26). A solution of tetralone **2**[1b] (540 mg, 2.5 mmol) in anhydrous THF (12 mL) was added slowly to vinylmagnesium bromide (1.0 M in THF, 27.5 mL) with stirring under nitrogen at 0 °C. The mixture was stirred for 5.5 h at 0 °C and saturated aqueous NH_4Cl (40 mL) was added. The resulting mixture was extracted with Et_2O (3 × 25 mL). The combined ethereal extract was washed with brine (2 × 30 mL), dried over anhydrous Na_2SO_4, and evaporated. The residue was chromatographed on a silica gel column (eluted with hexanes containing 15% EtOAc) to give **26** as a yellowish oil (460 mg, 75%); MS *m/e* (M^+) 246 ($C_{18}H_{22}O_2$); ^1H NMR (250 MHz) δ 1.19 (d, J = 6.9 Hz, 6 H), 1.75–1.93 (m, 4 H), 2.63–2.73 (m, 2 H), 3.25 (septet, J = 6.9 Hz, 1 H), 3.76 (s, 3 H), 5.17 (dd, J = 1.6, 10.5 Hz, 1 H), 5.99 (d, J = 10.5 Hz, 1 H), 6.06 (d, J = 10.5 Hz, 1 H), 6.83 (s, 1 H), 6.90 (s, 1 H). This compound was not purified further and was used directly in the next step.

2-Isopropyl-3-methoxy-5-ethylnaphthalene (27). A mixture of compound **26** (460 mg, 1.85 mmol) and palladium black (128 mg) was heated at 230–250 °C under nitrogen for 1.5 h. The mixture was allowed to cool and was diluted with CH_2Cl_2 (10 mL). Palladium black was removed by filtration through a bed of diatomaceous earth. The filtrate was evaporated and the resulting residue was chromatographed on a silica gel column (eluted with hexanes containing 5% EtOAc) to give **27** as a colorless oil (188 mg, 44%): MS *m/e* (M^+) 228 ($C_{16}H_{20}O$); ^1H NMR (250 MHz) δ 1.31 (d, J = 6.9 Hz, 6 H), 1.38 (t, J = 7.5 Hz, 3 H), 3.05 (q, J = 7.5 Hz, 2 H), 3.42 (septet, J = 7.5 Hz, 1 H), 3.95 (s, 3 H), 7.23 (s, 1 H), 7.24 (d, J = 5.2 Hz, 2 H), 7.60 (t, J = 4.8 Hz, 1 H), 7.62 (s, 1 H). Compound **27** was not purified further and was used directly in the preparation of **28**.

6-Isopropyl-7-methoxynaphthalene-1-carbaldehyde (30). A stirred solution of **23** (1.33 g, 5.9 mmol) in CH_2Cl_2 (100 mL) was allowed to react with ozone at −75 °C for 4 h. After that the flow of ozone was stopped and nitrogen was used to flush the mixture for 30 min. Dimethyl sulfide (30 mL) was added and the resulting mixture was stirred for 30 min. Then the solvent was removed by evaporation and H_2O (80 mL) was added to the residue. The aqueous mixture was extracted with EtOAc (4 × 30 mL). The combined extract was washed with brine (3 × 40 mL), dried over anhydrous Na_2SO_4, and evaporated. The crude residue was chromatographed on a silica gel column (eluted with hexanes containing 5% EtOAc) to give **30** as a colorless oil (1.16 g, 86%): MS *m/e* (M^+) (calcd for $C_{15}H_{16}O_2$) 228.1149 (found 228.1144); ^1H NMR (60 MHz) δ 1.31 (d, J = 7 Hz, 6 H), 3.43 (septet, J = 7 Hz, 1 H), 4.02 (s, 3 H), 7.44 (t, J = 7 Hz, 1 H), 7.66 (s, 1 H), 7.85 (dd, J = 1, 7 Hz, 1 H), 7.89 (d, J = 8 Hz, 1 H), 8.72 (s, 1 H), 10.28 (s, 1 H).

6-Isopropyl-7-methoxynaphthalene-1-carboxylic Acid (31). To a solution of aldehyde **30** (127 mg, 0.5 mmol) in THF (28 mL) was added a solution of sulfamic acid (124 mg) and sodium chlorite (150 mg) in H_2O (36 mL). The reaction mixture was stirred for 5 h at room temperature and then poured into H_2O (25 mL). The resulting mixture was extracted with EtOAc (3 × 20 mL) and the combined extract was washed with brine (2 × 40 mL). After drying over anhydrous Na_2SO_4 and evaporation, the residue was recrystallized from hexanes–EtOAc (1:1) to form **31** as colorless needles (0.1 g, 81%): mp 174–175 °C; MS *m/e* (M^+) (calcd for $C_{15}H_{16}O_3$) 244.1098 (found 244.1102); ^1H NMR (60 MHz) δ 1.32 (d, J = 7 Hz, 6 H), 3.44 (septet, J = 7 Hz, 1 H), 4.03 (s, 3 H), 7.38 (t, J = 8 Hz, 1 H), 7.67 (s, 1 H), 8.00 (d, J = 8 Hz, 1 H), 8.37 (d, J = 8 Hz, 1 H), 8.50 (s, 1 H). Anal. ($C_{15}H_{16}O_3$) H; C: calcd, 73.77; found, 74.25.

***N,N*-Diethyl-6-isopropyl-7-methoxynaphthalene-1-carboxamide (34).** To acid **31** (87 mg, 0.35 mmol) was added thionyl chloride (0.6 mL) with stirring. The mixture was refluxed at 150 °C for 1 h. After that benzene (50 mL) was added and the mixture was distilled to remove water. Another portion of benzene (50 mL) was added and the azeotropic distillation was continued until the distillate was clear. After cooling, the acid chloride formed was transferred with benzene (5 mL) to a stirred solution of anhydrous diethylamine (0.4 mL) in benzene (1 mL)

at 0 °C under nitrogen. The reaction mixture was stirred at room temperature overnight. Water (20 mL) was added, and the two layers were separated. The aqueous phase was extracted with Et_2O (4 × 10 mL) and the combined organic layer was washed with brine (2 × 10 mL). After drying over anhydrous Na_2SO_4 and evaporation, the residue was chromatographed on a silica gel column (eluted with hexanes containing 20% EtOAc) to afford **34** as a light yellowish oil (97 mg, 90%): MS *m/e* (M^+) (calcd for $C_{19}H_{25}NO_2$) 299.1884 (found 299.1890); ^1H NMR (250 MHz) δ 1.02 (t, *J* = 7.1 Hz, 3 H), 1.29 (d, *J* = 6.9 Hz, 6 H), 1.37 (t, *J* = 7.1 Hz, 3 H), 3.12 (q, *J* = 7 Hz, 2 H), 3.40 (septet, *J* = 6.9 Hz, 1 H), 3.42 (m, 1 H), 3.89 (s, 3 H), 3.90 (m, 1 H), 7.02 (s, 1 H), 7.30 (d, *J* = 4.7 Hz, 2 H), 7.61 (s, 1 H), 7.74 (t, *J* = 4.8 Hz, 1 H).

3,4-Dihydro-6-methoxy-7-isopropylphenanthren-1(2*H*)-one Oxime (38). To a suspension of compound **37**[1b] (590 mg, 2.2 mmol) in absolute EtOH (10 mL) heated at 40 °C were added pyridine (0.3 mL) and hydroxylamine hydrochloride (227 mg, 3.3 mmol). The mixture was heated to reflux for 1 h and was concentrated under vacuum to remove EtOH and pyridine. The residue was chromatographed on a silica gel column (eluted with CH_2Cl_2 containing 1–2% MeOH) to provide product **38**. Subsequent recrystallization of **38** from EtOAc afforded colorless rhombic crystals (620 mg, 99%): mp 191–192 °C; MS *m/e* (M^+) (calcd for $C_{18}H_{21}NO_2$) 283.1572 (found 283.1557); ^1H NMR (250 MHz) δ 1.31 (d, *J* = 6.9 Hz, 6 H), 2.05 (quintet, *J* = 6.5 Hz, 2 H), 2.96 (t, *J* = 6.5 Hz, 2 H), 3.12 (t, *J* = 6.5 Hz, 2 H), 3.42 (septet, *J* = 6.9 Hz, 1 H), 3.97 (s, 3 H), 5.10 (br s, 1 H), 7.21 (s, 1 H), 7.60 (s, 1 H), 7.62–7.96 (2 d, *J* = 8.8 Hz, 2 H). Anal. ($C_{18}H_{21}NO_2$) C, H, N.

***O*-(*p*-Tolylsulfonyl)-3,4-dihydro-6-methoxy-7-isopropylphenanthren-1(2*H*)-one Oxime (39).** *p*-Toluenesulfonyl chloride (500 mg, 2.6 mmol) was added to a solution of compound **38** in pyridine (2 mL) under nitrogen. The mixture was stirred at room temperature overnight and chromatographed directly on a silica gel column (eluted with CH_2Cl_2) to give product **39** as colorless solid. The product was further purified by recrystallization from hexanes–EtOAc to afford colorless rectangular crystals (730 mg, 80%): mp 139.5–141 °C; MS *m/e* (M^+) (calcd for $C_{25}H_{27}NO_4S$) 437.1661 (found 437.1666); ^1H NMR (250 MHz) δ 1.29 (d, *J* = 6.8 Hz, 6 H), 1.99 (quintet, *J* = 6.3 Hz, 2 H), 2.44 (s, 3 H), 2.90 (t, *J* = 6.3 Hz, 2 H), 3.09 (t, *J* = 6.3 Hz, 2 H), 3.41 (septet, *J* = 6.8 Hz, 1 H), 3.96 (s, 3 H), 7.20 (s, 1 H), 7.36 (d, *J* = 8.3 Hz, 2 H), 7.55 (d, *J* = 8.7 Hz, 1 H), 7.58 (s, 1 H), 7.80 (d, *J* = 8.7 Hz, 1 H), 7.98 (d, *J* = 8.3 Hz, 2 H).

1,3,4,5-Tetrahydro-7-methoxy-8-isopropyl-2*H*-naphth[2,1-*b*]azepin-2-one (40). Trifluoroacetic acid (0.8 mL) was added to compound **39** (100 mg, 0.24 mmol). The mixture was stirred at room temperature under nitrogen for 30 min and concentrated under vacuum. The residue was chromatographed on a silica gel column (eluted with CH_2Cl_2 containing 1–2% MeOH) to give product **40** as a colorless solid. The product was recrystallized from EtOAc to afford **40** as colorless crystals (65 mg, 100%): mp 250–251 °C; MS *m/e* (M^+) (calcd for $C_{18}H_{21}NO_2$) 283.1572 (found 283.1573); ^1H NMR (250 MHz) δ 1.31 (d, *J* = 6.8 Hz, 6 H), 2.39 (br s, 4 H), 3.22 (t, *J* = 6.8 Hz, 2 H), 3.41 (septet, *J* = 6.8 Hz, 1 H), 3.98 (s, 3 H), 7.24 (s, 1 H), 7.61 (s, 1 H), 6.97–7.63 (2 d, *J* = 8.5 Hz, 2 H).

2-Isopropyl-3-methoxy-5-(1′-hydroxybutyl)naphthalene (44). To a stirred solution of compound **43**[1b] (2.8 g, 9.3 mmol) in dry THF (42 mL) cooled at 0 °C with an ice–water bath under nitrogen was added $LiAlH_4$ (338 mg, 8.9 mmol) in small portions. The mixture was stirred for 30 min and quenched by careful addition of ice water. The resulting mixture was filtered through a Gooch funnel. The insoluble material was washed with EtOAc (250 mL). The combined filtrates were evaporated under vacuum to dryness, and the residue was chromatographed on a silica gel column (eluted with CH_2Cl_2 containing 1–2% MeOH) to yield **44** as white needles (2.2 g, 79%): mp <40 °C; MS *m/e* (M^+) (calcd for $C_{18}H_{24}O_2$) 272.1776 (found 272.1738); ^1H NMR (60 MHz) δ 1.30 (d, *J* = 7 Hz, 6 H), 1.67 (m, 4 H), 2.09 (s, 1 H), 2.98 (m, 2 H), 3.50 (m, 3 H), 3.90 (s, 3 H), 7.06–7.73 (m, 5 H). Anal. ($C_{18}H_{24}O_2$) H; C: calcd, 79.36; found, 78.85.

4-(6′-Isopropyl-7′-methoxynaphthyl)butanal (45). To a solution of compound **44** (2.2 g, 8 mmol) in dry CH_2Cl_2 (22 mL) was added pyridinium chlorochromate (2.6 g, 12 mmol). The reaction mixture was stirred for 20 min. After that 10% aqueous $KHSO_4$ solution (100 mL) was added and the resulting mixture was extracted with EtOAc (3 × 100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated. The residue was chromatographed on a silica gel column (eluted with hexanes containing 5–20% EtOAc) to afford a light yellow viscous oil, **45** (1.3 g, 59%): MS *m/e* (M^+) (calcd for $C_{18}H_{22}O_2$) 270.1620 (found 270.1624); ^1H NMR (60 MHz) δ 1.30 (d, *J* = 7 Hz, 6 H), 2.12 (m, 2 H), 2.51 (t, *J* = 7.2 Hz, 2 H), 3.03 (t, *J* = 7.2 Hz, 2 H), 3.45 (septet, *J* = 7 Hz, 1 H), 3.99 (s, 3 H), 7.06–7.70 (m, 5 H), 9.73 (d, *J* = 0.5 Hz, 1 H). Anal. ($C_{18}H_{22}O_2$) H; C: calcd, 79.96; found, 80.53.

Ethyl 6-(6′-Isopropyl-7′-methoxynaphthyl)-(*E*)-hex-2-enoate (46). Triethyl phosphonoacetate (1.5 mL, 8.7 mmol) was added dropwise via a syringe to a vigorously stirred suspension of NaH (60%, 280 mg, 7 mmol) in dry THF (20 mL) at 0 °C under nitrogen. The resulting mixture was stirred for 15 min and a solution of compound **45** (1.3 g, 4.8 mmol) in dry THF (15 mL) was added via a syringe. The mixture was stirred at 0 °C for 30 min and at room temperature for 5 min. It was then cooled to 0 °C and carefully quenched with saturated aqueous NH_4Cl solution. The mixture was extracted with EtOAc (3 × 60 mL), dried over anhydrous Na_2SO_4, and evaporated. The residue was chromatographed on a silica gel column (eluted with hexanes containing 5–10% Et_2O) to afford compound **46** as pale yellow viscous oil (1.5 g, 91%): MS *m/e* (M^+) (calcd for $C_{22}H_{28}O_3$) 340.2038 (found 340.2033); ^1H NMR (250 MHz) δ 1.31 (d, *J* = 6.9 Hz, 6 H), 1.93 (m, 2 H), 2.30 (m, 2 H), 3.03 (t, *J* = 7.6 Hz, 2 H), 3.42 (septet, *J* = 6.9 Hz, 1 H), 3.95 (s, 3 H), 4.18 (q, *J* = 7.0 Hz, 2 H), 5.87 (d, *J* = 15.6 Hz, 1 H), 6.98–7.09 (td, *J* = 7.0, 15.6 Hz, 1 H), 7.16–7.29 (m, 3 H), 7.61 (d, *J* = 9.1 Hz, 1 H), 7.62 (s, 1 H). Anal. ($C_{22}H_{28}O_3$) C, H.

Ethyl 6-(6′-Isopropyl-7′-methoxynaphthyl)hexanoate (47). A solution of compound **46** (1.5 g, 4.4 mmol) in absolute EtOH (40 mL) was stirred vigorously and hydrogenated over 5% Pd–C at atmospheric pressure for 1 h. The resulting reaction mixture was filtered and evaporated. The residue was chromatographed on a silica gel column (eluted with hexanes containing 20% Et_2O) to afford **47** as colorless needles (1.46 g, 97%): mp <40 °C; MS *m/e* (M^+) (calcd for $C_{22}H_{30}O_3$) 342.2195 (found 342.2197); ^1H NMR (60 MHz) δ 1.28 (t, *J* = 7 Hz, 3 H), 1.30 (d, *J* = 7 Hz, 6 H), 1.67 (m, 6 H), 2.30 (m, 2 H), 3.03 (m, 2 H), 3.43 (septet, *J* = 7 Hz, 1 H), 3.95 (s, 3 H), 4.14 (q, *J* = 7.2 Hz, 2 H), 7.23–7.60 (m, 5 H). Anal. ($C_{22}H_{30}O_3$) C, H.

6-(6′-Isopropyl-7′-methoxynaphthyl)hexanoic Acid (48). To a solution of compound **47** (1.27 g, 3.7 mmol) in THF (15 mL) was added 1 N aqueous NaOH (10 mL), followed by MeOH (2 mL). The solution was heated at 80 °C for 1 h. The reaction mixture was evaporated to remove THF and MeOH and acidified with 2 N HCl. The resulting mixture was extracted with EtOAc (3 × 100 mL). The combined organic extract was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated. The residue was recrystallized from hexanes–EtOAc to afford **48** as colorless rectangular crystals (1.2 g, 100%): mp 81–82 °C; MS *m/e* (M^+) (calcd for $C_{20}H_{26}O_3$) 314.1882 (found 314.1883); ^1H NMR (250 MHz) δ 1.31 (d, *J* = 6.9 Hz, 6 H), 1.50 (m, 2 H), 1.77 (m, 4 H), 2.38 (t, *J* = 7.4 Hz, 2 H), 3.02 (t, *J* = 7.6 Hz, 2 H), 3.41 (septet, *J* = 6.9 Hz, 1 H), 3.96 (s, 3 H), 7.21–7.27 (m, 3 H), 7.61 (d, *J* = 9.3 Hz, 1 H), 7.61 (s, 1 H). Anal. ($C_{20}H_{26}O_3$) C, H.

Prototypical Procedure for Friedel–Crafts Acylation. 9,10,11,12-Tetrahydro-2-methoxy-3-isopropylcycloocta[*a*]naphthalen-7(8*H*)-one (49). Phosphorus pentoxide (61 g) was added to orthophosphoric acid (85%, 28 mL) with mechanical stirring. The suspension was stirred and heated at 80–90 °C for 4 h, at which time essentially all P_2O_5 had dissolved. This mixture was cooled to 65 °C. A solution of compound **48** (1.2 g, 3.8 mmol) in CH_2Cl_2 (2 mL) was added via a syringe and the resulting mixture was stirred for 30 min. After cooling to room temperature, ice-cold water (80 mL) was added and the resulting mixture was extracted with Et_2O (3 × 100 mL). The insoluble small particles of the organic extracts were removed by filtration through a bed of Celite. The filtrate was then washed with water and brine and was dried over anhydrous Na_2SO_4. After evaporation, the residue was chromatographed on a silica gel column (eluted with hexanes containing 5–10% Et_2O) to afford **49** as an oil (160 mg, 14%). Analytically pure **49** was obtained by HPLC (EtOAc–hexane 9:91):

MS m/e (M^+) (calcd for $C_{20}H_{24}O_2$) 296.1776 (found 296.1758); ^1H NMR (250 MHz) δ 1.31 (d, J = 7 Hz, 6 H), 1.65 (m, 2 H), 1.78 (m, 2 H), 1.97 (m, 2 H), 2.84 (t, J = 6.6 Hz, 2 H), 3.18 (t, J = 6 Hz, 2 H), 3.42 (septet, J = 7.1 Hz, 1 H), 3.97 (s, 3 H), 7.25 (s, 1 H), 7.62 (s, 1 H), 7.13–7.65 (dd, J = 8.3 Hz, 2 H). Anal. ($C_{20}H_{24}O_2$) C; H: calcd 8.17; found, 8.71.

8,9,10,11-Tetrahydro-2-methoxy-3-isopropyl-7*H*-cyclohepta[*a*]naphthalen-7-one (55) was prepared from P_2O_5 (37 g), H_3PO_4 (85%, 20 mL), and acid **54** (730 mg, 2.3 mmol) in CH_2Cl_2 (2 mL). The resulting mixture was stirred at 65 °C for 30 min. Chromatography conditions: silica gel, hexanes containing 5–10% EtOAc. Compound **55**: colorless rhombic crystals from hexanes–EtOAc (470 mg, 68%); mp 84.5–85 °C; MS m/e (M^+) (calcd for $C_{18}H_{22}O_2$) 282.1620 (found 282.1636); ^1H NMR (250 MHz) δ 1.31 (d, J = 6.9 Hz, 6 H), 1.82 (m, 2 H), 1.98 (m, 2 H), 2.77 (t, J = 6 Hz, 2 H), 3.31 (t, J = 6.4 Hz, 2 H), 3.43 (septet, J = 6.9 Hz, 1 H), 4.00 (s, 3 H), 7.39 (s, 1 H), 7.63 (s, 1 H), 7.56–7.67 (2 d, J = 8.5 Hz, 2 H). Anal. ($C_{19}H_{22}O_2$) C, H.

1,2,3,3a-Tetrahydro-8-isopropyl-9-methoxyacephenanthrylen-5(4*H*)-one (86) was prepared from H_3PO_4 (20 mL), P_2O_5 (37 g) in $CHCl_3$ (3 mL), and acid **85** (680 mg, 2.2 mmol). The resulting mixture was stirred and heated at 60 °C for 2.5 h. Chromatography conditions: silica gel (230–400 mesh), hexanes containing 5% EtOAc. Recovered acid **85** (200 mg) and compound **86** (380 mg, 59%): mp 199–200 °C (from hexanes–EtOAc): MS m/e (M^+) (calcd for $C_{20}H_{22}O_2$) 294.1620 (found 294.1616); ^1H NMR (250 MHz) δ 1.25–1.35 (2 d, J = 7.0 Hz, 6 H), 1.30–1.52 (m, 1 H), 1.96–2.20 (m, 1 H), 2.32–2.42 (m, 3 H), 2.88–3.02 (dd, J = 7.0, 14.0 Hz, 2 H), 3.20–3.36 (dd, J = 7.0, 14.0 Hz, 2 H), 3.40 (septet, J = 7.0 Hz, 1 H), 4.00 (s, 3 H), 7.08 (s, 1 H), 7.74 (s, 1 H), 8.02 (s, 1 H).

2-Isopropyl-3-methoxy-5-(4′-bromobutyl)naphthalene (53). To a solution of compound **44** (1.1 g, 4 mmol) and carbon tetrabromide (1.65 g, 5 mmol) in CH_2Cl_2 (2 mL) under nitrogen was added dropwise a solution of triphenylphosphine (1.3 g, 4.9 mmol) in CH_2Cl_2 (2.3 mL). The mixture was stirred for 15 h. After that it was evaporated and chromatographed on a silica gel column (eluted with hexanes) to yield bromide **53** (1.3 g, 96%) as a colorless oil: MS m/e 336 (M + 2), 334 (M^+) ($C_{18}H_{23}BrO$); ^1H NMR (250 MHz) δ 1.31 (d, J = 6.9 Hz, 6 H), 1.95 (m, 4 H), 3.02 (t, J = 7.2 Hz, 2 H), 3.36–3.48 (m, 3 H), 2.96 (s, 3 H), 7.19–7.23 (m, 3 H), 7.62 (s, 1 H), 7.61 (d, J = 9.3 Hz, 1 H). Anal. ($C_{18}H_{23}BrO$) C, H.

5-(6′-Isopropyl-7′-methoxynaphthyl)pentanoic Acid (54). To magnesium (0.2 g, 8 mmol) in dry Et_2O (5 mL) was added slowly a solution of bromide **53** (1.3 g, 4 mmol) and bromoethane (0.2 mL, 0.05 mmol) in Et_2O (5 mL) under nitrogen. After refluxing for 5 h, the mixture was cooled to 0 °C and poured into dry ice (1 g, 23 mmol). After being allowed to stand at room temperature for 1 h, the mixture was poured into H_2O (100 mL) and made acidic with concentrated HCl. The resulting mixture was extracted with CH_2Cl_2 (3 × 50 mL) and the organic layer was washed with H_2O (2 × 50 mL) and brine (100 mL). After drying over Na_2SO_4 and evaporation, the residue was chromatographed on a silica gel column (eluted with $CHCl_3$ containing 5% MeOH) to yield compound **54** (0.3 g, 25%) as colorless needles: mp 113.5–114 °C; MS m/e (M^+) 300 ($C_{19}H_{24}O_3$); ^1H NMR (250 MHz) δ 1.31 (d, J = 6.9 Hz, 6 H), 1.82 (m, 4 H), 2.43 (t, J = 6.8 Hz, 2 H), 3.04 (t, J = 7.1 Hz, 2 H), 3.42 (septet, J = 6.9 Hz, 1 H), 3.97 (s, 3 H), 7.20–7.26 (m, 3 H), 7.62 (d, J = 9.5 Hz, 1 H), 7.62 (s, 1 H). Anal. ($C_{19}H_{24}O_3$) C, H.

3,4-Dihydro-6-hydroxy-7-isopropylphenanthren-1(2*H*)-one (59). Compound **37**[1b] (1 g, 3.7 mmol) was mixed with pyridinium hydrochloride (50 g, 0.43 mol) under nitrogen. The mixture was heated at 200–220 °C for 3 h. After cooling, water (50 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 75 mL). The organic extract was washed with brine (2 × 100 mL), dried over Na_2SO_4, and evaporated. The residue was chromatographed on a silica gel column (230–400 mesh, eluted with hexanes containing 20% EtOAc) to afford **59**, which was recrystallized from absolute EtOH to give colorless crystals (0.76 g, 80%): mp 228–230 °C; MS m/e (M^+) 254 ($C_{17}H_{18}O_2$); ^1H NMR (250 MHz) δ 1.37 (d, J = 6.9 Hz, 6 H), 2.27 (quintet, J = 6.4 Hz, 2 H), 2.42 (t, J = 6.4 Hz, 2 H), 3.24 (t, J = 6.4 Hz, 2 H), 3.38 (septet, J = 6.9 Hz, 1 H), 5.36 (s, 1 H), 7.36 (s, 1 H), 7.65 (s, 1 H), 7.66 (d, J = 8.6 Hz, 1 H), 7.96 (d, J = 8.6 Hz, 1 H). Compound **59** was used directly in the preparation of **60** without further purification.

1-Hydroxy-1-methyl-1,2,3,4-tetrahydro-6-methoxy-7-isopropylphenanthrene (61). To a stirred solution of **37**[1b] (0.2 g, 0.75 mmol) in anhydrous Et_2O (20 mL) at 0 °C under nitrogen was added slowly methylmagnesium iodide (1 mL, 0.1 M solution in Et_2O) via a syringe. The resulting solution was stirred at 0 °C for 4 h. Ice water (20 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 25 mL). The organic extract was washed with brine (2 × 50 mL), dried over anhydrous Na_2SO_4, and evaporated. The residue was chromatographed on a silica gel column (230–400 mesh, eluted with hexanes containing 15% EtOAc) to give **61**, which was recrystallized from CCl_4 to give colorless crystals (0.15 g, 70%): mp 122.5–123.5 °C; MS m/e (M^+) (calcd for $C_{18}H_{24}O_2$) 284.1777 (found 284.1780); ^1H NMR (250 MHz) δ 1.30 (d, J = 6.8 Hz, 6 H), 1.62 (s, 3 H), 1.92–2.11 (m, 4 H), 3.07 (br t, J = 5.9 Hz, 2 H), 3.45 (septet, J = 6.8 Hz, 1 H), 3.95 (s, 3 H), 7.16 (s, 1 H), 7.57–7.66 (m, 3 H). Anal. ($C_{18}H_{24}O_2$) H; C: calcd, 80.24; found, 84.39.

1-Methyl-3,4-dihydro-6-methoxy-7-isopropylphenanthrene (62). A mixture of **61** (100 mg, 0.35 mmol) and triethylamine (356 mg) and methanesulfonyl chloride (302 mg) in CH_2Cl_2 (5 mL) was stirred under nitrogen at 0 °C for 4 h. Saturated aqueous $NaHCO_3$ (10 mL) was added. The mixture was extracted with Et_2O (3 × 25 mL). The ethereal extract was washed with brine (2 × 50 mL), dried over $Na_2SO_4/NaHCO_3$, and evaporated. The residue was chromatographed on a silica gel column (230–400 mesh, eluted with hexanes containing 1% Et_3N) to give **62**, which was recrystallized from hexanes to afford colorless crystals (84 mg, 90%): mp 105–107 °C; MS m/e (M^+) (calcd for $C_{18}H_{22}O$) 266.1672 (found 266.1670); ^1H NMR (250 MHz) δ 1.30 (d, J = 6.9 Hz, 6 H), 2.14 (d, J = 1.3 Hz, 3 H), 2.30–2.50 (m, 2 H), 3.11 (t, J = 8.5 Hz, 2 H), 3.40 (septet, J = 6.9 Hz, 1 H), 3.96 (s, 3 H), 5.91 (br s, 1 H), 7.24 (s, 1 H), 7.33 (d, J = 8.5 Hz, 1 H), 7.57 (s, 1 H), 7.61 (d, J = 8.5 Hz, 1 H). Anal. ($C_{18}H_{22}O$) C, H.

1-Methyl-3,4-dihydro-7-isopropylphenanthrene-5,6-dione (64). Sodium hydride (hexanes washed, 0.36 g) and DMF (2 mL) were placed in a flame-dried flask with stirring under nitrogen. Ethanethiol (0.47 g, 7.6 mmol) was then added dropwise, followed by **62** (0.1 g, 0.38 mmol) in DMF (1 mL). The mixture was heated to 150 °C for 2 h. Saturated aqueous NH_4Cl solution (25 mL) was added, followed by CH_2Cl_2 extraction (3 × 50 mL). The organic layer was washed with brine (2 × 50 mL), dried over $Na_2SO_4/NaHCO_3$, and evaporated. The residue was dissolved in acetone (20 mL) and a solution of the Fremy's salt (0.35 g) in water (30 mL) was added. The mixture was stirred for 4 h. Acetone was evaporated and the resulting solution was extracted with Et_2O (3 × 25 mL), dried over $Na_2SO_4/NaHCO_3$, and evaporated. The residue was purified by flash chromatography on a silica gel column (230–400 mesh, eluted with hexanes containing 10% EtOAc and 1% Et_3N) to provide **64**, which was recrystallized from hexanes (24 mg, 24%) as red crystals: mp 134–135 °C; MS m/e (M^+) (calcd for $C_{18}H_{18}O_2$) 266.1307 (found 266.1360); ^1H NMR (250 MHz) δ 1.17 (d, J = 6.9 Hz, 6 H), 2.06 (d, J = 1.6 Hz, 3 H), 2.24 (m, 2 H), 3.04 (septet, J = 6.9 Hz, 1 H), 3.34 (t, J = 8.0 Hz, 2 H), 6.04 (m, 1 H), 7.10 (s, 1 H), 7.13 (d, J = 7.9 Hz, 1 H), 7.39 (d, J = 7.9 Hz, 1 H). Anal. ($C_{18}H_{18}O_2$) C, H.

1,2,3,4-Tetrahydro-7-isopropylphenanthrene-5,6-dione (66). See prototypical procedure for demethylation. **66** was prepared from **65** (0.1 g, 0.4 mmol) in CH_2Cl_2 (5 mL) cooled at 0 °C and boron tribromide (0.1 mL). The residue obtained after workup was oxidized as described in the prototypical procedure for *o*-quinone synthesis: from a solution of the phenol in acetone (20 mL) and a solution of the Fremy's salt (350 mg) in $^1/_8$ M aqueous KH_2PO_4 (13 mL). Chromatography conditions: silica gel (230–400 mesh), hexanes containing 10% EtOAc. Compound **66**: red crystals (62 mg, 62%); mp 92–94 °C (from hexanes) (lit.[4] mp 78–80 °C); MS m/e (M^+) 254 ($C_{17}H_{16}O_2$); ^1H NMR (250 MHz) δ 1.17 (d, J = 6.9 Hz, 6 H), 1.76–1.80 (m, 4 H), 2.80 (t, J = 5.4 Hz, 2 H), 3.02 (septet, J = 6.9 Hz, 1 H), 3.19 (t, J = 5.5 Hz, 2 H), 7.05 (d, J = 7.7 Hz, 1 H), 7.08 (s, 1 H), 7.29 (d, J = 7.7 Hz, 1 H). Anal. ($C_{17}H_{18}O_2$) C, H.

3,4-Dihydro-6-(benzyloxy)-7-isopropylphenanthren-1(2*H*)-one (67). To a stirred solution of **59**[1b] (300 mg, 1.2 mmol) in acetone (15 mL) was added anhydrous K_2CO_3 (1.6 g). The mixture was stirred at room temperature for 30 min. Benzyl bromide (0.2 mL) was added and the mixture was stirred for 20

h. Then the mixture was filtered through a layer of diatomaceous earth and the residue was washed with CH_2Cl_2. The filtrate was evaporated and the residue was recrystallized from EtOAc to give light yellow crystals of **67** (420 mg, 98%): mp 155–157 °C; MS *m/e* (M^+) 344 ($C_{24}H_{24}O_2$); ^1H NMR (250 MHz) δ 1.35 (d, *J* = 6.9 Hz, 6 H), 2.28 (quintet, *J* = 6.5 Hz, 2 H), 2.72 (t, *J* = 6.5 Hz, 2 H), 3.27 (t, *J* = 6.5 Hz, 2 H), 3.53 (septet, *J* = 6.9 Hz, 1 H), 5.25 (s, 2 H), 7.36–7.55 (m, 6 H), 7.67 (d, *J* = 8.6 Hz, 1 H), 7.67 (s, 1 H), 7.98 (d, *J* = 8.6 Hz, 1 H). Anal. ($C_{24}H_{24}O_2$) H; C: calcd, 83.68; found, 84.17.

1-Methyl-1-hydroxy-1,2,3,4-tetrahydro-6-(benzyloxy)-7-isopropylphenanthrene (68). To a stirred solution of **67** (1 g, 2.9 mmol) in benzene (5 mL) and Et_2O (10 mL) cooled at 0 °C was added slowly methylmagnesium iodide (1 mL, 3 M in Et_2O) via a syringe. The mixture was stirred at 0 °C for 4 h. Saturated aqueous NH_4Cl solution (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The organic extract was washed with brine (2 × 50 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography on a silica gel column (230–400 mesh, eluted with hexanes containing 25% EtOAc) to afford **68** (870 mg, 81%) as colorless crystals: mp 111–113 °C; MS *m/e* (M^+) 360 ($C_{25}H_{28}O_2$); ^1H NMR (250 MHz) δ 1.32 (d, *J* = 6.9 Hz, 3 H), 1.33 (d, *J* = 6.9 Hz, 3 H), 1.62 (s, 3 H), 1.92–2.10 (m, 4 H), 3.00–3.04 (m, 2 H), 3.51 (septet, *J* = 6.9 Hz, 1 H), 5.22 (s, 1 H), 7.31–7.67 (m, 9 H). Anal. ($C_{25}H_{28}O_2$) C, H.

1-Methyl-1-hydroxy-1,2,3,4-tetrahydro-7-isopropylphenanthrene-5,6-dione (70). A stirred solution of **68** (100 mg, 0.28 mmol) in MeOH (2 mL) was hydrogenated over 5% Pd–C at atmospheric pressure for 4 h. The mixture was filtered through a layer of diatomaceous earth to remove the catalyst. The filtrate was evaporated and the residue was dissolved in acetone (20 mL). This phenol solution was oxidized as described in the prototypical procedure for o-quinone synthesis: from the phenol solution and a solution of the Fremy's salt (350 mg) in $NaOH/KH_2PO_4$ buffer (30 mL, pH 7). The solution was stirred at room temperature for 36 h. Chromatography conditions: silica gel (230–400 mesh), hexanes containing 25% EtOAc. Compound **70**: red crystals (37 mg, 37%); mp 142 °C (from Et_2O–hexanes); MS *m/e* (M^+) 284 ($C_{18}H_{20}O_3$); ^1H NMR (250 MHz) δ 1.17 (d, *J* = 6.8 Hz, 6 H), 1.54 (s, 3 H), 1.75–2.04 (m, 5 H), 3.02 (septet, *J* = 6.8 Hz, 1 H), 3.12–3.32 (m, 2 H), 7.09 (s, 1 H), 7.19 (d, *J* = 7.9 Hz, 1 H), 7.92 (d, *J* = 7.9 Hz, 1 H). Anal. ($C_{18}H_{20}O_3$) C, H.

1-Methyl-3,4-dihydro-6-(benzyloxy)-7-isopropylphenanthrene (71). A mixture of **68** (100 mg, 28 mmol), triethylamine (356 mg), and methanesulfonyl chloride (302 mg) in CH_2Cl_2 (5 mL) was stirred under nitrogen at 0 °C for 4 h. Saturated aqueous $NaHCO_3$ (10 mL) was added and the mixture was extracted with Et_2O (3 × 25 mL). The ethereal extract was washed with brine (2 × 50 mL), dried over $Na_2SO_4/NaHCO_3$, and evaporated. The residue was purified by flash chromatography on a silica gel column (230–400 mesh, eluted with hexanes containing 1% EtOAc) to give colorless crystals of **71** (80 mg, 85%): mp 84–85 °C (from hexanes); MS *m/e* (M^+) 342 ($C_{25}H_{26}O$); ^1H NMR (250 MHz) δ 1.33 (d, *J* = 6.9 Hz, 6 H), 2.14 (d, *J* = 1.5 Hz, 3 H), 2.37 (m, 2 H), 3.09 (t, *J* = 7.5 Hz, 2 H), 3.50 (septet, *J* = 6.9 Hz, 1 H), 5.23 (s, 2 H), 5.91 (m, 1 H), 7.32–7.64 (m, 9 H). Anal. ($C_{25}H_{26}O$) C, H.

1-Methyl-*cis*-1,2-dihydroxy-1,2,3,4-tetrahydro-6-(benzyloxy)-7-isopropylphenanthrene (72). To a stirred solution of **71** (120 mg, 0.35 mmol) in anhydrous THF (1.3 mL), *t*-BuOH (4.3 mL), and water (0.4 mL) was added *N*-methylmorpholine *N*-oxide (64 mg) under nitrogen. Then OsO_4 (2.5 wt%) in *t*-BuOH (37 μL) was added. The solution was stirred at room temperature until the decoloration of the osmium complexes was completed. A slurry of dilute aqueous sodium sulfite solution and talc (magnesium silicate or magnesol) was added and the resulting mixture stirred for 1 h. Then it was filtered and the filtrate was extracted with CH_2Cl_2 (3 × 25 mL). The organic extract was washed with brine (2 × 50 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography on silica gel column (230–400 mesh, eluted with hexanes containing 33% EtOAc) to afford colorless solid of **72** (99 mg, 75%): mp 128–131 °C (from Et_2O); MS *m/e* (M^+) 376 ($C_{25}H_{28}O_3$); ^1H NMR (250 MHz) δ 1.32 (d, *J* = 6.9 Hz, 3 H), 1.34 (s, 3 H), 1.38 (d, *J* = 6.9 Hz, 3 H), 2.12–2.20 (m, 2 H), 2.45 (br s, 1 H), 2.75 (br s, 1 H), 2.99 (dt, *J* = 5.6, 17.2 Hz, 1 H), 3.17 (dt, *J* = 7.6, 17.2 Hz, 1 H), 3.51 (septet, *J* = 6.9 Hz, 1 H), 3.89 (dd, *J* = 3.5, 5.4 Hz, 1 H), 5.21 (s, 2 H), 7.23 (s, 1 H), 7.30–7.67 (m, 8 H). Anal. ($C_{25}H_{28}O_3$) H; C: calcd, 79.75; found, 79.04.

1-Methyl-*cis*-1,2-dihydroxy-1,2,3,4-tetrahydro-7-isopropylphenanthrene-5,6-dione (74). A solution of **72** (100 mg, 0.27 mmol) in MeOH (2 mL) was hydrogenated over 5% Pd–C at atmospheric pressure for 1 h. The mixture was filtered through a layer of diatomaceous earth to remove the catalyst. The filtrate was evaporated and the residue was dissolved in acetone (20 mL). This phenol solution was oxidized as described in the prototypical procedure for *o*-quinone synthesis: from the phenol solution and a solution of the Fremy's salt (350 mg) in $NaOH/KH_2PO_4$ buffer (30 mL, pH 7). The solution was stirred at room temperature for 36 h. Chromatography conditions: silica gel (230–400 mesh), hexanes containing 15% EtOAc. Compound **74**: red crystals (36 mg, 45%); mp 42–45 °C (from hexanes–Et_2O); MS *m/e* (M^+) (calcd for $C_{18}H_{20}O_4$) 300.1362 (found 300.1364); ^1H NMR (250 MHz) δ 1.16 (d, *J* = 6.9 Hz, 6 H), 1.48 (s, 3 H), 1.73–2.23 (m, 2 H), 3.01 (septet, *J* = 6.9 Hz, 1 H), 3.30 (dd, *J* = 5.1, 8.3 Hz, 2 H), 3.97 (dd, *J* = 2.0, 5.3 Hz, 1 H), 7.1 (s, 1 H), 7.20 (d, *J* = 8.0 Hz, 1 H), 7.97 (d, *J* = 8.0 Hz, 1 H).

1-Methyl-*trans*-1,2-dihydroxy-1,2,3,4-tetrahydro-6-(benzyloxy)-7-isopropylphenanthrene (75). To a stirred solution of **71** (100 mg, 29 mmol) in THF (2 mL) was added magnesium monoperoxyphthalic acid (MMPP) (300 mg) in water (1 mL) and THF (2 mL). The solution was stirred at room temperature for 4 h. The solution was evaporated to remove THF and the residue was extracted with CH_2Cl_2 (3 × 10 mL). The organic extract was washed with brine (2 × 25 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography on a silica gel column (230–400 mesh, eluted with hexanes containing 50% EtOAc) to furnish **75** as colorless solid (69 mg, 63%): mp 148–149 °C (from Et_2O); MS *m/e* (M^+) (calcd for $C_{25}H_{28}O_3$) 376.2039 (found 376.2020); ^1H NMR (250 MHz) δ 1.32 (d, *J* = 6.9 Hz, 3 H), 1.33 (d, *J* = 6.9 Hz, 3 H), 1.51 (s, 3 H), 1.59–2.07 (m, 1 H), 2.25–2.35 (m, 1 H), 3.09 (ddd, *J* = 6.7, 11.0, 17.5 Hz, 1 H), 3.26 (br dd, *J* = 6.0, 17.5 Hz, 1 H), 3.51 (septet, *J* = 6.9 Hz, 1 H), 3.99 (dd, *J* = 3.8, 12.2 Hz, 1 H), 5.22 (s, 2 H), 7.20 (s, 1 H), 7.31–7.70 (m, 8 H).

1-Methyl-*trans*-1,2-dihydroxy-1,2,3,4-tetrahydro-7-isopropylphenanthrene-5,6-dione (76). A stirred solution of **75** (100 mg, 0.27 mmol) in MeOH (2 mL) was hydrogenated over 5% Pd–C at atmospheric pressure for 4 h. The mixture was filtered through a layer of diatomaceous earth to remove the catalyst. The filtrate was evaporated and the residue was dissolved in acetone (20 mL). This phenol solution was oxidized as described in the prototypical procedure for *o*-quinone synthesis: from the phenol solution and a solution of the Fremy's salt (350 mg) in $NaOH/KH_2PO_4$ buffer (30 mL, pH 7). The solution was stirred at room temperature for 36 h. Chromatography conditions: silica gel (230–400 mesh), hexanes containing 50% EtOAc. Compound **76**: orange crystals (50 mg, 63%); mp 90 °C dec; MS *m/e* (M^+) 300 ($C_{18}H_{20}O_4$); ^1H NMR (250 MHz) δ 1.16 (d, *J* = 6.9 Hz, 3 H), 1.17 (d, *J* = 6.9 Hz, 3 H), 1.45 (s, 3 H), 1.74–1.91 (m, 1 H), 2.17–2.23 (m, 1 H), 3.02 (septet, *J* = 6.9 Hz, 1 H), 3.20 (ddd, *J* = 7.3, 11.1, 20.2 Hz, 1 H), 3.52 (ddd, *J* = 1.7, 6.7, 20.2 Hz, 1 H), 3.93 (dd, *J* = 4.0, 12.3 Hz, 1 H), 7.10 (s, 1 H), 7.22 (d, *J* = 7.9 Hz, 1 H), 7.93 (d, *J* = 7.9 Hz, 1 H). Anal. ($C_{18}H_{20}O_4$) C, H.

2-Methoxy-3-isopropyl-7,8,9,10-tetrahydrophenanthridine (80). To a solution of cyclohexanone (1.5 mL) in Et_2NH (1 mL) was added formalin (37–41%, 0.6 mL) in aqueous HCl (32%, 0.5 mL). The mixture was refluxed for 5 min. Compound **79**[28] (1.5 g, 9 mmol) in aqueous HCl (32%, 0.5 mL) was added, followed by $SnCl_4 \cdot 5H_2O$ (0.35 g). The mixture was refluxed overnight. Aqueous NaOH was added slowly until all white precipitates dissolved. Then the mixture was extracted with Et_2O (3 × 100 mL). The ethereal extract was washed with brine (2 × 100 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography on a silica gel column (230–400 mesh, eluted with hexanes containing 10% EtOAc) to furnish colorless crystals of **80** (0.46 g, 20%): mp 88.5–89.5 °C (from hexanes); MS *m/e* (M^+) (calcd for $C_{17}H_{21}NO$) 255.1624 (found 255.1630); ^1H NMR (250 MHz) δ 1.31 (d, *J* = 6.9 Hz, 6 H), 1.84–1.98 (m, 4 H), 2.85 (t, *J* = 5.9 Hz, 2 H), 3.01 (t, *J* = 6.1 Hz, 2 H), 3.42 (septet, *J* = 6.9 Hz, 1 H), 3.95 (s, 3 H), 7.04 (s, 1 H), 7.85 (s, 1 H), 8.45

(s, 1 H). Anal. ($C_{17}H_{21}NO$) C, H, N.

3-Isopropyl-7,8,9,10-tetrahydrophenanthridine-1,2-dione (81). To a stirred solution of 80 (100 mg, 0.4 mmol) in CH_2Cl_2 (5 mL) cooled at 0 °C was added boron tribromide (0.1 mL) slowly via a syringe. The solution was stirred at 0 °C under nitrogen for 2 h. Ice water (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined extract was washed with brine (2 × 50 mL), dried over Na_2SO_4, and evaporated. The residue was dissolved in MeOH (10 mL). A solution of the Fremy's salt (100 mg) in water (18 mL) and $^1/_6$ M aqueous KH_2PO_4 (13 mL) was added. The solution was stirred at room temperature overnight. After that it was extracted with CH_2Cl_2 (3 × 25 mL). The combined extract was washed with brine (2 × 50 mL), dried over Na_2SO_4, and evaporated. The residue was chromatographed on a silica gel column (230–400 mesh, eluted with hexanes containing 25% EtOAc) to furnish 81 as a red solid (9 mg, 30%): mp 131–142 °C (from hexanes); MS *m/e* (M^+) (calcd for $C_{16}H_{17}NO_2$) 255.1260 (found 255.1262); ^1H NMR (250 MHz) δ 1.19 (d, *J* = 6.9 Hz, 6 H), 1.82 (m, 4 H), 2.80 (m, 2 H), 3.06 (septet, *J* = 6.9 Hz, 1 H), 3.21 (m, 2 H), 7.33 (s, 1 H), 8.43 (s, 1 H). Anal. ($C_{16}H_{17}NO_2$) C, H; N, calcd, 5.49; found, 4.59.

1-[(Ethoxycarbonyl)methyl]-1-hydroxy-1,2,3,4-tetrahydro-6-methoxy-7-isopropylphenanthrene (82). To a solution of 37[1b] (0.95 g, 3.5 mmol) in dry THF (12 mL) was added ethyl bromoacetate (0.7 mL, 6.3 mmol). Zinc powder (1 g, 15.3 mmol) was added and the mixture was allowed to react with the aid of an ultrasonicator at room temperature for 5 min (monitored by TLC). Zinc powder was filtered and the filtrate was concentrated. The residue was taken up with EtOAc (20 mL) and washed with dilute HCl (3 × 20 mL). The aqueous extract was extracted with EtOAc (2 × 50 mL). The combined organic layer was dried over Na_2SO_4 and evaporated. The residue was flash chromatographed on a silica gel column (230–400 mesh, eluted with hexanes containing 20%–40% EtOAc) to give 82, which was recrystallized from hexanes–EtOAc (1.2 g, 95%): mp 104–105 °C; MS *m/e* (M^+) (calcd for $C_{22}H_{28}O_4$) 356.1987 (found 356.1987); ^1H NMR (250 MHz) δ 1.21–1.38 (m, 9 H), 1.80–2.20 (m, 4 H), 2.70–3.02 (AB q, *J* = 10.5 Hz, 2 H), 3.08 (m, 2 H), 3.40 (septet, *J* = 7.0 Hz, 1 H), 3.92 (s, 3 H), 4.09 (br s, 1 H), 4.20 (q, *J* = 7.0 Hz, 2 H), 7.18 (s, 1 H), 7.50–7.62 (AB q, *J* = 7.0 Hz, 2 H), 7.59 (s, 1 H). Anal. ($C_{22}H_{28}O_4$) C, H.

1-[(Ethoxycarbonyl)methylidene]-1,2,3,4-tetrahydro-6-methoxy-7-isopropylphenanthrene (83). To a solution of 82 (1.2 g, 3.4 mmol) in CH_2Cl_2 (20 mL) cooled at 0 °C was added Et_3N (2 mL, 14.3 mmol) and methanesulfonyl chloride (0.4 mL, 5.2 mmol). The mixture was stirred at 0 °C for 1 h and at room temperature for 30 min. The resulting mixture was washed successively with dilute Na_2CO_3 (30 mL) and dilute HCl (30 mL). The HCl extract was extracted with CH_2Cl_2 (2 × 50 mL). The combined CH_2Cl_2 solution was dried over Na_2SO_4 and evaporated. The residue was purified on a silica gel column (230–400 mesh, eluted with hexanes containing 10% Et_2O) to give 83 (1 g, 89%) as colorless needles (from hexanes–Et_2O): mp 112–114 °C; MS *m/e* (M^+) (calcd for $C_{22}H_{28}O_3$) 338.1882 (found 338.1888); ^1H NMR (250 MHz) δ 1.20–1.40 (m, 9 H), 2.00–2.10 (quintet, *J* = 6.9 Hz, 2 H), 3.19 (t, *J* = 6.9 Hz, 2 H), 3.26 (t, *J* = 6.9 Hz, 2 H), 3.42 (septet, *J* = 7.0 Hz, 1 H), 3.98 (s, 3 H), 4.22 (q, *J* = 6.9 Hz, 2 H), 6.42 (s, 1 H), 7.24 (s, 2 H), 7.60 (s, 2 H). Anal. ($C_{22}H_{28}O_3$) C, H.

1-[(Ethoxycarbonyl)methyl]-1,2,3,4-tetrahydro-6-methoxy-7-isopropylphenanthrene (84). A mixture of compound 83 (1 g, 3 mmol) and 10% Pd-C (100 mg) in EtOH (40 mL) was stirred vigorously under a hydrogen atmosphere (balloon pressure) for 1.25 h. The catalyst was filtered and washed with EtOH (20 mL). The combined EtOH solution was evaporated and the residue was purified through a short silica gel column (230–400 mesh, eluted with hexanes containing 5% EtOAc) to give 84 as an oily product (800 mg, 79%): MS *m/e* (M^+) (calcd for $C_{22}H_{28}O_3$) 340.2038 (found 340.2042); ^1H NMR (250 MHz) δ 1.20–1.34 (m, 9 H), 1.80–2.04 (m, 4 H), 2.50–3.50 (m, 6 H), 3.96 (s, 3 H), 4.20 (q, *J* = 6.9 Hz, 2 H), 7.13 (d, *J* = 7.0 Hz, 1 H), 7.14 (s, 1 H), 7.56 (d, *J* = 7.0 Hz, 1 H), 7.58 (s, 1 H). Anal. ($C_{22}H_{28}O_3$) C, H.

1-(Carboxymethyl)-1,2,3,4-tetrahydro-6-methoxy-7-isopropylphenanthrene (85). Compound 84 (800 mg, 2.3 mmol) was hydrolyzed with NaOH (1.2 equiv) in a solution of water (10 mL) and MeOH (10 mL) for 2 h. The mixture was evaporated to remove MeOH, acidified with concentrated HCl, and extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was dried over Na_2SO_4 and evaporated to give crude 85 (680 mg, 92%): mp 182–182.5 °C (from hexanes–EtOAc); MS *m/e* (M^+) (calcd for $C_{20}H_{24}O_3$) 312.1725 (found 312.1724); ^1H NMR (250 MHz) δ 1.20–1.35 (2 d, *J* = 7.0 Hz, 6 H), 1.80–2.05 (m, 5 H), 2.60–3.60 (m, 6 H), 3.98 (s, 3 H), 7.18 (d, *J* = 7.0 Hz, 1 H), 7.19 (s, 1 H), 7.59 (s, 1 H), 7.60 (d, *J* = 7.0 Hz, 1 H). Anal. ($C_{20}H_{24}O_3$) C, H.

1,2,3,3a,4,5-Hexahydro-8-isopropylacephenanthrylene-9,10-dione (89). A solution of compound 87 (124 mg, 0.44 mmol) and boron tribromide (0.1 mL) in CH_2Cl_2 (2 mL) was stirred for 30 min at room temperature. After that it was poured into ice water (50 mL) and extracted with Et_2O (3 × 50 mL). The ethereal extract was dried over Na_2SO_4, evaporated, and purified on a silica gel column (230–400 mesh, eluted with hexanes containing 10% Et_2O) to give 1,2,3,3a,4,5-hexahydro-8-isopropylacephenanthrylen-9-ol (88) (110 mg, 93%) which was not purified further and was used directly in the next step.

A solution of phenol 88 (110 mg), the Fremy's salt (382 mg), $^1/_6$ M aqueous KH_2PO_4 (15 mL) in acetone (22 mL), and water (20 mL) was stirred at room temperature in darkness for 24 h. It was then concentrated under vacuum to remove the acetone. The aqueous solution was extracted with CH_2Cl_2 (2 × 50 mL), dried over Na_2SO_4, and evaporated. The crude product was purified on a silica gel column (230–400 mesh, eluted with hexanes containing 10% Et_2O) to provide 89 as orange crystals (88 mg, 76%): mp 154–155 °C (from hexanes–Et_2O); MS *m/e* (M^+) 280 ($C_{19}H_{20}O_2$); ^1H NMR (250 MHz) δ 1.10–1.30 (2 d, *J* = 6.9 Hz, 6 H), 1.50–1.85 (m, 3 H), 2.05–2.25 (dd, *J* = 4.7, 10.8 Hz, 2 H), 2.25–2.50 (quintet, *J* = 6.0 Hz, 1 H), 2.70–3.10 (m, 5 H), 3.35–3.50 (AB q, *J* = 6.1 Hz, 1 H), 6.98 (s, 1 H), 7.10 (s, 1 H). Anal. ($C_{19}H_{20}O_2$) C, H.

α-(5,6,7,8-Tetrahydro-1-naphthoxymethyl)acrylic Acid (100). NaOH (0.86 g, 21.5 mmol) and 5,6,7,8-tetrahydro-1-naphthol (99) (3.2 g, 7 mmol) were allowed to dissolve in refluxing absolute EtOH (15 mL). To this solution was added a solution of compound 98[34] (0.77 g, 7 mmol) in absolute EtOH (3 mL) in portions. The resulting mixture was refluxed for 4 h and kept at room temperature overnight. After evaporation, the residue was dissolved in ice water (30 mL) and extracted with Et_2O (4 × 25 mL). The ethereal extract was washed with saturated aqueous $NaHCO_3$ (2 × 25 mL). The combined aqueous layer was acidified to pH 1 with concentrated HCl. The precipitate was collected, dried, and recrystallized from EtOAc–hexanes to give 100 as colorless plates (1 g, 60%): mp 156.5–157.5 °C; MS *m/e* (M^+) 232 ($C_{14}H_{16}O_3$); ^1H NMR (250 MHz) δ 1.77–1.82 (m, 4 H), 2.74 (quintet, *J* = 6.0 Hz, 4 H), 4.74 (s, 2 H), 6.19 (d, *J* = 2.5 Hz, 1 H), 6.55 (d, *J* = 2.5 Hz, 1 H), 6.66 (d, *J* = 7.8 Hz, 1 H), 6.72 (d, *J* = 7.8 Hz, 1 H), 7.06 (t, *J* = 7.8 Hz, 1 H). Anal. ($C_{14}H_{16}O_3$) H; C: calcd, 72.39; found, 71.80.

3-Methyl-7,8-tetramethylenecoumarin (101). A solution of compound 100 (160 mg, 0.7 mmol) and triethylamine (0.5 mL) in *o*-dichlorobenzene (5 mL) was heated in a sealed tube at 180 °C for 7 h. After that the solvents were removed under vacuum. The residue was purified by flash chromatography on a silica gel column (10 g, eluted with hexanes containing 10% EtOAc) to provide 101 as colorless crystals (26 mg, 18%): mp 104–106 °C; MS *m/e* (M^+) (calcd for $C_{14}H_{14}O_2$) 214.0994 (found 214.0995); ^1H NMR (250 MHz) δ 1.82–1.84 (m, 4 H), 2.20 (s, 3 H), 2.82 (t, *J* = 6.0 Hz, 2 H), 2.89 (t, *J* = 6.0 Hz, 2 H), 6.97 (d, *J* = 7.9 Hz, 1 H), 7.15 (d, *J* = 7.9 Hz, 1 H), 7.47 (d, *J* = 1.0 Hz, 1 H).

Benzodiazepine Receptor Binding Assay. The activity of compounds related to miltirone (1) at the central benzodiazepine receptors was determined essentially according to the method of Chang and Barnard.[37] Briefly, calf cerebral cortical membranes were incubated at 0 °C for 45 min with [^3H]flunitrazepam (1 nM) in a final volume of 500 μL containing Tris-HCl (pH 7.4, 50 mM). At the end of the incubation period, ice-cold Tris-HCl buffer (50 mM, 3 mL) (pH 7.4) was added to each tube, and their contents were filtered immediately under reduced pressure through Whatman GF/B glass-fiber filters using a Brandel cell harvester. The filters were washed with ice-cold Tris-HCl (50 mM, 3 × 4 mL) (pH 7.4). They were dried, and radioactivity was measured by liquid scintillation spectrometry. Nonspecific binding was defined in the presence of 10 μM diazepam. The concentration of a test compound required to give 50% inhibition of specific [^3H]flunitrazepam binding is expressed as IC_{50} (in μM). Com-

pounds which are unstable upon storage (8, 25, 29, 95, and 104) were tested for binding affinity immediately after their preparation.

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Supplementary Material Available: 2D ^1H-^1H COSY and NOESY of compounds 72 and 75 (4 pages). Ordering information is given on any current masthead page.

Synthesis of the 2-Amino-4-phosphonobutanoic Acid Analogues (*E*)- and (*Z*)-2-Amino-2,3-methano-4-phosphonobutanoic Acid and Their Evaluation as Inhibitors of Hippocampal Excitatory Neurotransmission

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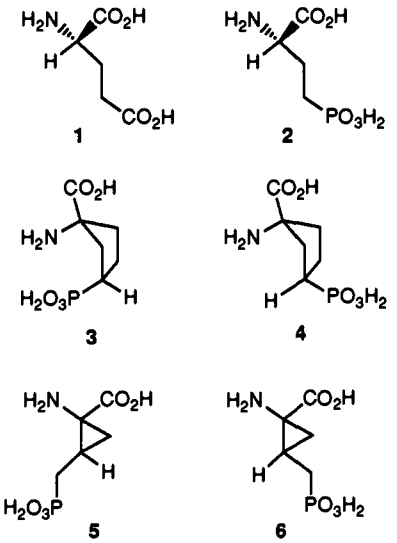
The cyclopropyl compounds (*Z*)- and (*E*)-2-amino-2,3-methano-4-phosphonobutanoic acid, 5 and 6, respectively, were prepared as constrained analogues of 2-amino-4-phosphonobutanoic acid (AP4), a selective glutamate receptor ligand. A Horner–Emmons reaction of trimethyl *N*-(benzyloxycarbonyl)phosphonoglycinate with 2-(diethoxyphosphinyl)acetaldehyde gave the protected dehydroamino acids 9 and 10, which were individually subjected to the following sequence of reactions: cycloaddition of diazomethane, photoelimination of N_2, and acid hydrolysis, to give 5 and 6, respectively. Extracellular recording techniques were used to evaluate the abilities of 5 and 6 to block evoked synaptic transmission in specific neuronal pathways of the rat hippocampal slice. In the lateral perforant path (LPP) 5 and 6 were equipotent and possessed IC_{50} values of 18 and 17 μM, respectively. In the medial perforant path (MPP), 6 (IC_{50} = 81 μM) was much more potent than 5 (IC_{50} = 1580 μM). In paired pulse experiments which differentiate presynaptic and postsynaptic inhibition, 5 and 6 enhanced the second response to the same extent as L-AP4, suggesting a presynaptic site of action for these compounds. In contrast, the cyclopentyl AP4 analogues 3 and 4 enhanced the second response to a lesser extent. It was concluded that the biologically active conformation of AP4 in the LPP is different than in the MPP. In order to explain the same potency of 5 and 6 in the LPP, it was postulated that the two analogues assume a conformation that allows their functional groups to occupy the same relative place in space. Molecular modeling showed that the best overlap was achieved when the αC–βC–γC–P dihedral angle for 5 was in the range of 130° to 180° and that of 6 was in the range of −130° to −180°. The results suggest that the bioactive conformation of AP4 in the LPP is an extended one.

The importance of excitatory amino acids (EAA's), in particular L-glutamic acid (1), in central nervous system development, cognition, and disease is becoming increasingly apparent as more specific and selective EAA agonists and antagonists are developed.[1-3] Currently, there are postulated to be five defined EAA receptor subtypes.[1] One of these, the L-2-amino-4-phosphonobutanoic acid (L-AP4, 2) EAA receptor subtype, is delineated by a unique responsiveness to L-AP4. To date, five systems have been studied which are particularly sensitive to L-AP4: the retina;[4] the spinal cord;[5,6] the lateral olfactory tract (LOT);[7,8] and in the hippocampus, the rat lateral perforant path (LPP),[9] and the guinea pig mossy fiber-CA3 pathway.[10,11] In the retina, L-AP4 shows postsynaptic agonist activity on ON-bipolar cells.[4,12] In contrast, L-AP4 is postulated to act at presynaptic inhibitory autoreceptors in the rat LPP,[13] in the guinea pig mossy fiber-CA3 pathway,[14] the spinal cord,[15] and the LOT.[16,17] In those systems where the receptor is proposed to be presynaptic, L-AP4 has been shown to stereoselectively antagonize evoked excitation without inhibiting responses due to application of the prototypical agonists NMDA, kainic



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