

# Synthesis and Pharmacological Evaluation of 4a-Phenanthrenamine Derivatives Acting at the Phencyclidine Binding Site of the N-Methyl-D-aspartate Receptor Complex

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A novel series of octahydrophenanthrenamines and their heterocyclic analogues have been synthesized as potential noncompetitive antagonists of the N-methyl-D-aspartate (NMDA) receptor complex. The compounds were evaluated for their affinity at the phencyclidine (PCP) binding site by determining their ability to displace [<sup>3</sup>H]TCP from crude rat brain synaptic membranes. A wide range of affinities were observed, with the most potent analogs possessing IC<sub>50</sub>'s equivalent to that of the reference agent MK-801 (3, dizocilpine). NMDA antagonist activity was demonstrated by prevention of glutamate-induced accumulation of [<sup>45</sup>Ca<sup>2+</sup>] in cultured rat cortical neurons. Selected compounds were also studied *in vivo* to determine their ability to prevent the lethal effects of systemically injected NMDA in the mouse. In general, the SAR of the phenanthrenamine series may be summarized as follows: (a) for the amino group at C4a, NHMe > NH<sub>2</sub> > NHEt >> NC<sub>5</sub>H<sub>10</sub>; (b) for the B-ring substitution, X = CH<sub>2</sub> > S > O; (c) unsaturation of the C ring decreases receptor affinity; (d) *cis*-ring fusion between the B and C rings is desirable; (e) 6-hydroxy or 6-methoxy substitution of the phenanthrenamine system identified an additional hydrogen bonding interaction that substantially increased receptor affinity; (f) spiro analogues (such as 55, IC<sub>50</sub> = 3400 nM), which altered the point of attachment of the C ring, caused a substantial reduction in PCP-site affinity. Molecules from this series were useful for refining a pharmacophore model consistent with previous models of the PCP site. In this model, the (R)-(+)-phenanthrenamine 13 superimposes closely onto MK-801 (3), and the angular 4a-amino group is believed to hydrogen bond with a putative receptor site atom. In the phenanthrenamine and thiaphenanthrenamine series, the (R)-(+)-enantiomers (9, 13, and 44) are more potent by approximately 5–10-fold than their corresponding (S)-(-)-enantiomers with respect to their affinity for the PCP site, their ability to prevent accumulation of [<sup>45</sup>Ca<sup>2+</sup>] in cultured neuronal cells, and their protection against the lethal effects of NMDA in mice. In general, there was no separation between the dose that prevented NMDA lethality and the dose that produced ataxia in mice, except in the case of the thiaphenanthrenamines 41 and 43. We have not yet obtained evidence that this small separation in activity offers a therapeutic advantage in the treatment of cerebral ischemia or other neurodegenerative disorders.

## Introduction

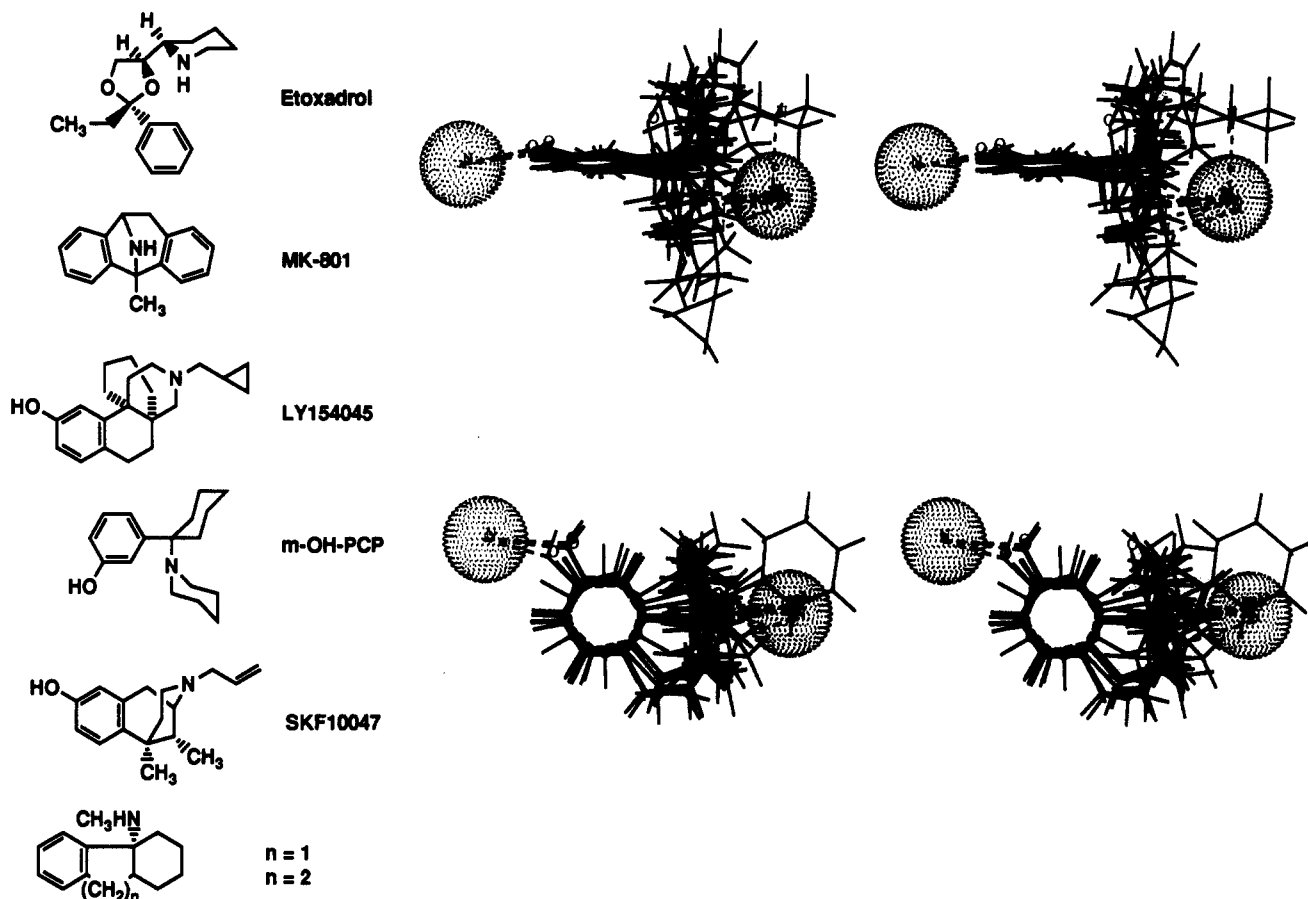
Glutamic acid is the predominant excitatory neurotransmitter in the central nervous system (CNS). It activates several different glutamatergic receptors that are essential for functions related to neurotransmission, neuroplasticity, and learning and memory. Traditionally, glutamate receptors have been named after selective agonist ligands that have been identified to activate a particular receptor. These include the N-methyl-D-aspartate (NMDA) receptor(s), the kainic acid (kainate) receptor(s), the AMPA receptor (named for  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid), the ACPD receptor (*trans*-1-amino-1,3-cyclopentanedicarboxylic acid, also known as the metabotropic receptor), and the AP4 receptor ( $\alpha$ -amino-4-phosphonobutyric acid). In the literature, these various glutamatergic receptor systems are often discussed as either NMDA receptors or non-NMDA

receptors because of the original prominence of work done in the NMDA field. Increasingly, molecular biology is influencing research efforts in both areas. Recent reports have described the cloning and expression of NMDA,<sup>1,2</sup> AMPA/kainate,<sup>3–6</sup> and the ACPD receptors.<sup>7</sup> Interdisciplinary studies utilizing these cloned receptors is likely to greatly enhance our understanding of ligand–receptor interactions and the role of other modulatory factors involved in the physiological action of these receptors.

It has been hypothesized that during or following a pathological incident such as ischemia, an increased release of glutamic acid triggers Ca<sup>2+</sup>-mediated processes which contribute to neuronal death.<sup>8</sup> Because glutamatergic receptors play an important part in neurotransmission and neuronal plasticity, it is not surprising that following a pathological insult, excitatory processes may play a significant role in neurodegenerative disease states such as Alzheimer's,<sup>9</sup> Parkinsonism,<sup>10</sup> and Huntington's Diseases.<sup>11</sup> Additionally, excitatory amino acid receptors may

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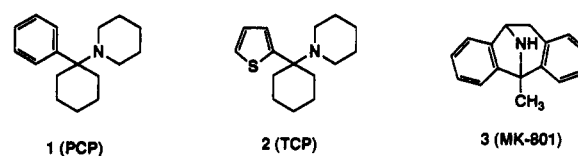
**Figure 1.** Structures of six NMDA antagonists used in the initial definition of a pharmacophore model of the noncompetitive (PCP) site on the NMDA receptor complex. Two stereoviews (edge-on and top-down to the common phenyl ring) of their superposition are shown, together with proposed receptor interactions points (N atoms surrounded by dots).

be involved in the pathophysiology of epilepsy<sup>12</sup> and ischemic events in the CNS following stroke or cardiac arrest.<sup>13</sup> The NMDA complex contains a receptor-mediated, voltage-sensitive ion channel that allows both sodium and calcium ions to filter into the neuron for transduction and regulatory processes. It is dependent upon multiple factors for its regulation.<sup>14</sup> Both glutamate and glycine are required as coagonists for activation of the ion channel, and its action may be further modulated by polyamines (such as spermidine) and zinc. In addition, ion-channel opening is regulated physiologically by magnesium ions.

Several classes of compounds have been reported to inhibit NMDA receptor activity, including competitive NMDA antagonists,<sup>15</sup> glycine-site antagonists,<sup>16</sup> and noncompetitive NMDA antagonists. The noncompetitive antagonists are "use-dependent" ion-channel blockers that bind to a specific site in the opened ion channel called the PCP site (named for phencyclidine).<sup>17</sup> Use dependency implies that the receptor must first be activated by its agonist components in order for the noncompetitive antagonist to inhibit receptor function.

PCP site ligands are typified by PCP (1), TCP (2), and MK-801 (3, dizocilpine). This class of compounds has demonstrated remarkable neuroprotective effects in a number of *in vitro* and *in vivo* pharmacological models. Unfortunately, PCP site ligands are also characterized by behavioral side effects that include hyperactivity at low doses, ataxia at higher doses, and adverse neurobehavioral effects in humans. Despite these disadvantages, there is a continued interest in the development of an agent from

this class for use as a neuroprotective agent following stroke, cerebral trauma, or other neurodegenerative disorders.

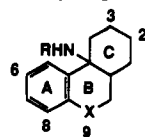


In this paper, we report the synthesis, *in vitro* and *in vivo* activity, and structure-activity relationships of a novel series of relatively rigid noncompetitive NMDA antagonists based on the phenanthrene ring system. A description of molecular modeling studies, employed to rationalize the SAR and suggest novel analogs for synthesis, is also included. All compounds were evaluated for their affinity to the PCP site of the NMDA receptor complex by the displacement of [<sup>3</sup>H]TCP; the most potent analogs demonstrated affinities comparable to MK-801, the reference agent in this area. Selected phenanthrenamines were also evaluated for their NMDA antagonist activity and their neuroprotective effects *in vivo*.

## Molecular Design

An active synthetic effort conducted toward the development of anesthetic agents at Parke-Davis in the 1960s produced PCP (1) and ketamine (4), which continues to be clinically useful. PCP demonstrated profound CNS side effects, including acute psychosis resembling schizophrenia. After it was determined that PCP and ketamine

Table I. Summary of Biological and Physical Data for the Octahydrophenanthrenamines



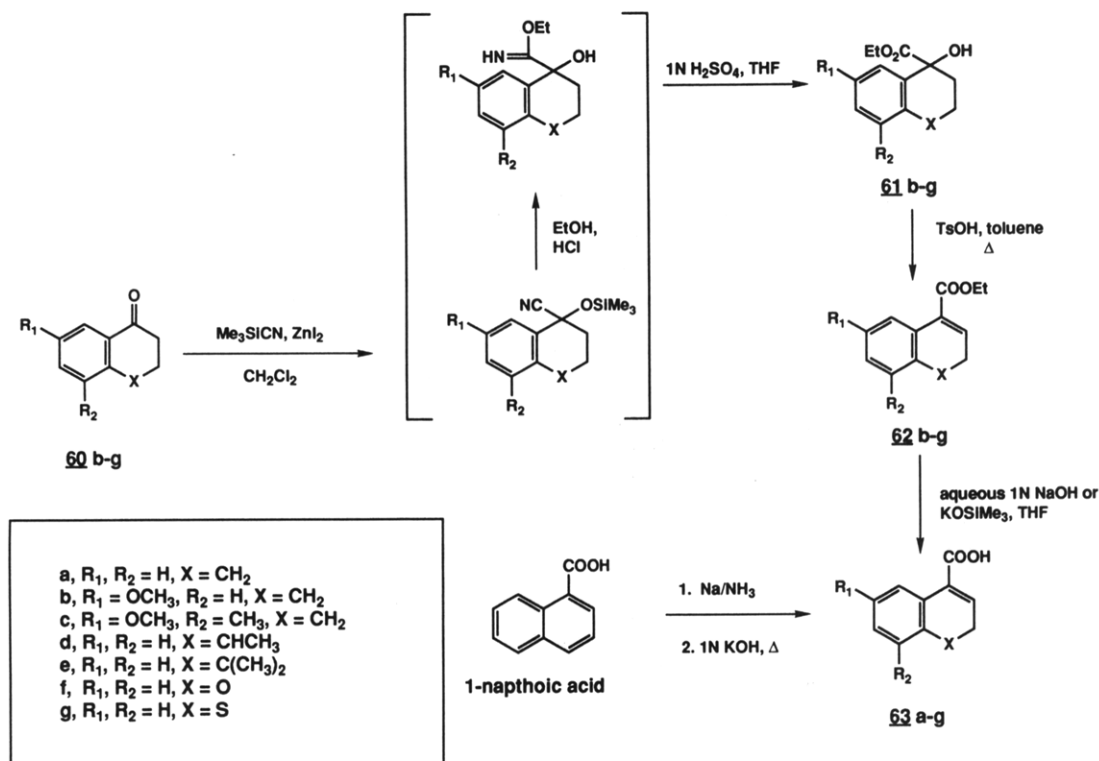
no.	R	X <sup>a</sup>	subst.	[ <sup>3</sup> H]TCP IC <sub>50</sub> (nM)	CGCI IC <sub>50</sub> (μM)	lethality ED <sub>50</sub> (mg/kg)	ataxia (mg/kg)	log P <sup>f</sup>	
								SF	HPLC
PCP (1)				36.5 ± 10 (n = 4) <sup>g</sup>	0.20 ± 0.03	0.55	0.3-1	3.6	
MK-801 (3, dizocilpine)				2.92 ± 0.42 (n = 5) <sup>g</sup>	0.058 ± 0.011	0.34	0.1-0.3	2.1	
ketamine (4)				860	8.86 ± 1.15	6.0	3-10	2.18	
PD 137889 (5, (R) <sup>b</sup> )				10.1 ± 0.4 (n = 4)	0.12	0.10			
PD 45602 (6)				11.3 (n = 2)	0.21	0.41			
8	H			25.4 ± 1.6 (n = 6)	0.37 ± 0.06	0.64 ± 0.10	0.55 ± 0.07		2.92
9 (R) <sup>b</sup>	H			11.3 (n = 2)	0.48 ± 0.10	1.3	<0.3		
10 (S) <sup>b</sup>	H			113 (n = 2)	2.55 ± 0.53	3-10	<3		
11	H		2,3-DB <sup>c</sup>	87.5 (n = 2)	2.35 ± 0.88	4.2	<1		2.75
12	Me			14.7 ± 1.7 (n = 7)	0.31 ± 0.10	0.54	0.44		3.25
13 (R) <sup>b</sup>	Me			7.47 ± 0.59 (n = 4)	0.18 ± 0.09	0.39	0.18		
14 (S) <sup>b</sup>	Me			41.5 ± 5.2 (n = 7)	0.81 ± 0.14	0.97	0.3-1		
15	Me		2,3-DB <sup>c</sup>	27.3	0.40 ± 0.06	1.8	0.6		3.07
16	Me <sub>2</sub>			21	1.63 ± 0.76	1.6	<0.3		
17	Et			199				1.15	3.41
18	allyl			86 (n = 2)	0.92	3-10	<1		
19	(CH <sub>2</sub> ) <sub>5</sub>			(7%) <sup>d</sup>					
20	H		6-OH	7.5 ± 0.2 (n = 3)	0.52	5.5	1-3		
21	H		2,3-DB <sup>c</sup>	28	1.6	4.6	1.5		
			6-OH						
22	H		6-OMe	18	0.44	1.2	1.3		
23	H		2,3-DB <sup>c</sup>	46	0.85 ± 0.25	2.1	2.1		
			6-OMe						
24	Me		6-OH	2.07 ± 0.56 (n = 3)	0.064	0.89	0.58	0.31	2.56
25	Me		6-OMe	5.8	1.11 ± 0.73	1.0	0.4	1.51	3.75
26	Me		2,3-DB <sup>c</sup>	21	0.41	4.1	0.3-1		
			6-OMe						
27	Me		6-OMe	53.5 ± 9.2 (n = 3)	0.93 ± 0.12	5.6	3.3	1.72	4.02
			8-Me						
28	H		9-Me	508				1.61	3.59
29	H		2,3-DB <sup>c</sup>	2,460				1.89	3.40
			9-Me						
30	Me		9-Me	317				1.60	3.96
31	Me		2,3-DB <sup>c</sup>	654					
			9-Me						
32	H		9,9-Me <sub>2</sub>	37000 (n = 2)					
33	Me		9,9-Me <sub>2</sub>	20800 (n = 2)					
34	Me		2,3-DB <sup>c</sup>	(0%) <sup>d</sup>					
			9,9-Me <sub>2</sub>						
35	Me		9-OH	1490				0.73	1.84
36	Me		9=O	270				0.78	2.41
37	Me		3-OH	500				-0.14	2.37
38	H		2-CN	(2%) <sup>d</sup>					
39	H		2-CH <sub>2</sub> NH <sub>2</sub>	(1%) <sup>d</sup>					
40	Me		2-CH <sub>2</sub> NH <sub>2</sub>	(8%) <sup>d</sup>				-1.14	2.00
41	H	S		80.6 ± 8.5 (n = 9)	1.87 ± 0.56	2.9	4.7		
42	H	S	2,3-DB <sup>c</sup>	101 (n = 2)	1.7				
43	Me	S		62	0.71	0.7	1.5	1.54	3.88
44 (R)	Me	S		30					
45 (S)	Me	S		199 (n = 2)					
46	Me	S	2,3-DB <sup>c</sup>	69 (n = 2)	0.42 ± 0.07	2.0	1.8		
47	Et	S		523					
48	H	O		178 (n = 2)		5.7	3-10		
49	H	O	2,3-DB <sup>c</sup>	399 (n = 2)					
50	Me	O		113 ± 21 (n = 3)	2.3	3.70 ± 0.28	0.63 ± 0.14	0.96	3.31
51	Me	O	2,3-DB <sup>c</sup>	122					
52	H		[2,3]-thienyl <sup>e</sup>	43	1.57 ± 0.66	0.97	1-3	0.66	3.02
53	Me		[2,3]-thienyl <sup>e</sup>	31	0.35	0.89	0.3-1		
54	Me		2,3-DB <sup>c</sup>	57 ± 4 (n = 6)					
			[2,3]-thienyl <sup>e</sup>						

<sup>a</sup> X = CH<sub>2</sub> unless indicated. <sup>b</sup> Absolute configuration at 4a. <sup>c</sup> DB = double bond. <sup>d</sup> Percent inhibition at 10<sup>-7</sup> M. <sup>e</sup> A fused thienyl ring has been substituted for the fused phenyl ring of the generic structure in these compounds. <sup>f</sup> log P determinations were measured using a standard shake flask (SF) method at pH 7.4 or HPLC correlation (HPLC) determination.<sup>50</sup> <sup>g</sup> (n = ) shows the number of triplicate determinations for that compound. <sup>h</sup> Value is for the neutral (free base) form of MK-801.

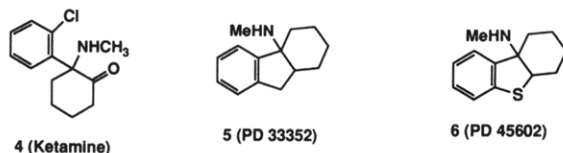
derived much of their pharmacological action due to action at the PCP site, related compounds from our data bank were screened in a [<sup>3</sup>H]TCP binding assay.<sup>18</sup> The fluorenamine (5) and the thiafluorenamine (6) were found to

have very high intrinsic affinity for the PCP site. Compounds and chemistry related to 5 have been described recently in the literature by Kozikowski et al.<sup>19</sup> Following these leads, the phenanthrenamine structure was selected

## Scheme I



for initial synthesis by interchanging an ethylene fragment for the sulfur in the B ring of **6**.<sup>20</sup>



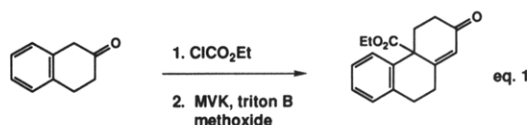
In concert with early syntheses in this area, a molecular modeling study was initiated in order to rationalize the observed SAR and aid in the design of novel analogs. The initial modeling was patterned after literature reports<sup>21-23</sup> and involved the superposition of a phenyl ring and basic amine (and optionally, a hydroxyl oxygen) in common to a number of known PCP ligands (Figure 1; see the Experimental Section for details). The resulting model was refined by the addition of selected MK-801 and PCP analogs, newly synthesized hexahydrofluorenamines,<sup>24</sup> as well as phenanthrenamines from this study. Preliminary reports of the modeling analyses have appeared,<sup>24,25</sup> and a full report is in preparation.

The resulting pharmacophore model entails two specific receptor interaction site points separated by areas of lipophilic bulk and an aryl binding site. Refinement of the model allowed the definition of areas of receptor active (tolerated) and excluded volume (Figure 2), as well as electronic and lipophilic requirements. Examination of the phenanthrenamines in the model allowed us to predict where to place hydroxy substituents on the aryl ring. The resulting compound (**24**, Table I) possessed 7-fold increased potency relative to the unsubstituted parent (**12**) and was equipotent with MK-801, the reference standard in the PCP area.

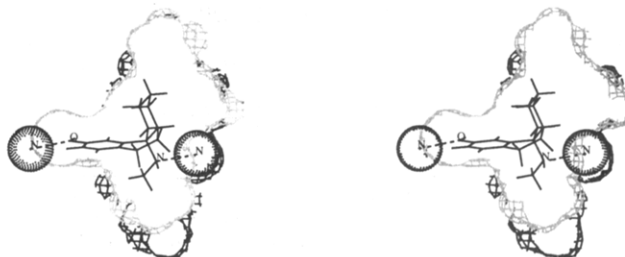
## Chemistry

The phenanthrenamine ring system was synthesized originally using a Robinson annulation procedure<sup>26</sup> to give

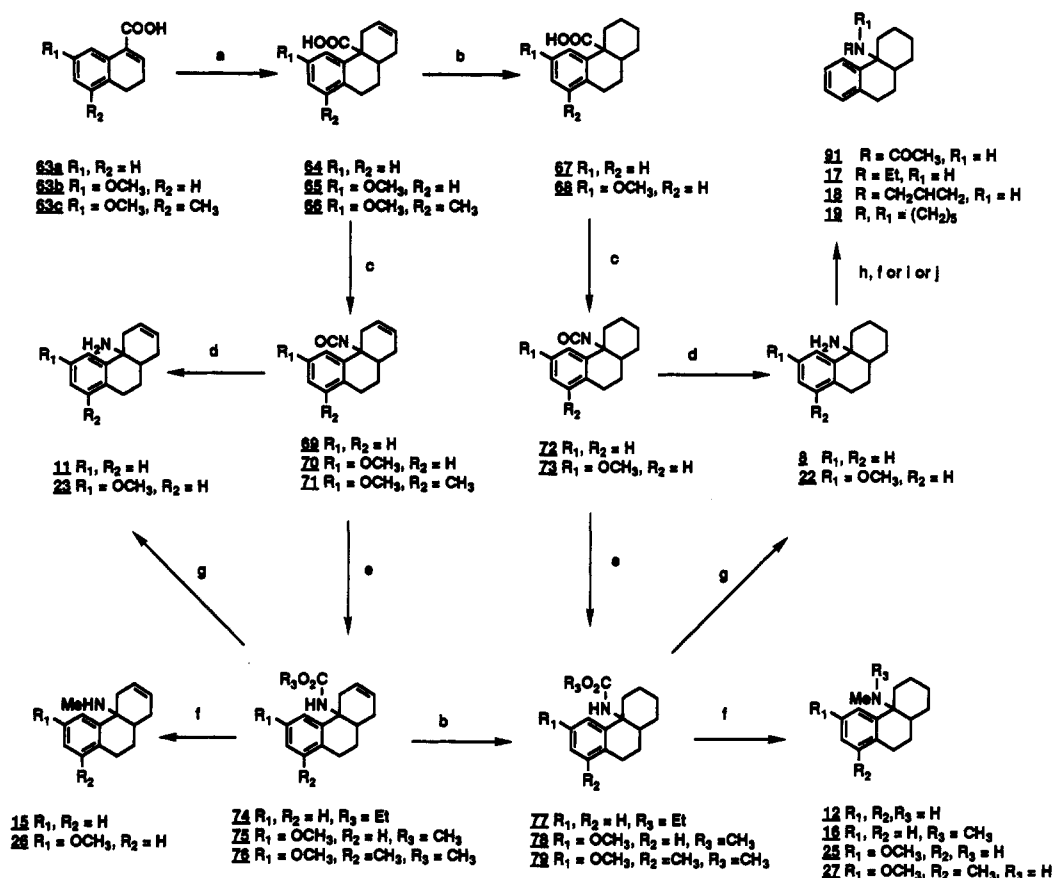
the unsaturated keto ester **7** (eq 1), followed by hydrolysis and a Schmidt rearrangement. It was hoped that reduction



of the double bond would provide both the cis and trans ring fusion derivatives at the ring B-C junction, however, this methodology proved to be inefficient for generation of trans derivatives. During development of this series, it became clear that the Diels-Alder methodology utilized previously in the fluorenamine series was the most practical means of synthesis.<sup>24</sup> Preparation of the appropriate dienophiles is outlined in Scheme I. In the unsubstituted case, 3,4-dihydronaphthalenecarboxylic acid **63a** could be prepared on large scale by Birch reduction of 1-naphthoic acid, followed by base-catalyzed isomerization. A more general preparation of the dienophiles **63b-g** is illustrated by the following route: for example, a substituted  $\alpha$ -tetralone can be converted to the protected cyanohydrin with trimethylsilyl cyanide. Imino ether formation with



**Figure 2.** Conformation of **24** when fit to the refined pharmacophore model. A cut-away view of a portion of the receptor active and excluded volumes is shown in light and dark gray, respectively. A hydrogen bonding interaction of the hydroxy group of **24** with the left-hand receptor interaction point results in a 7-fold increase in affinity over the unsubstituted analogue (**12**); see Table I.

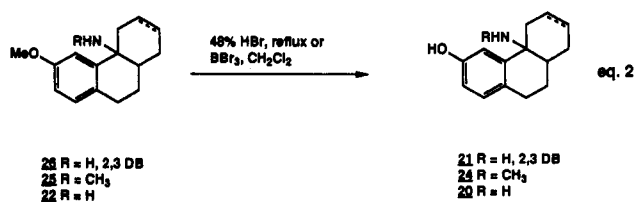
Scheme II<sup>a</sup>

(a) Butadiene, AIBN, toluene, 110 °C; (b) 5% palladium on carbon, hydrogen, MeOH; (c) (PhO)<sub>2</sub>PON<sub>3</sub>, Et<sub>3</sub>N, toluene, 110 °C; (d) KOH, water, benzene, 18-crown-6 ether; (e) MeOH or EtOH reflux; (f) LAH, THF, reflux; (g) KOSiMe<sub>3</sub>, THF, reflux; (h) AcCl, CH<sub>2</sub>Cl<sub>2</sub>; (i) allyl bromide; (j) Br(CH<sub>2</sub>)<sub>4</sub>Br, K<sub>2</sub>CO<sub>3</sub>, MEK.

ethanol saturated with hydrochloric acid, followed by hydrolysis, afforded the hydroxy esters 61. Dehydration followed by ester hydrolysis provided the desired carboxylic acid dienophiles. This reaction sequence was general for tetralones with aromatic substitution and heterocyclic analogues such as benzopyrans or benzothioopyrans.

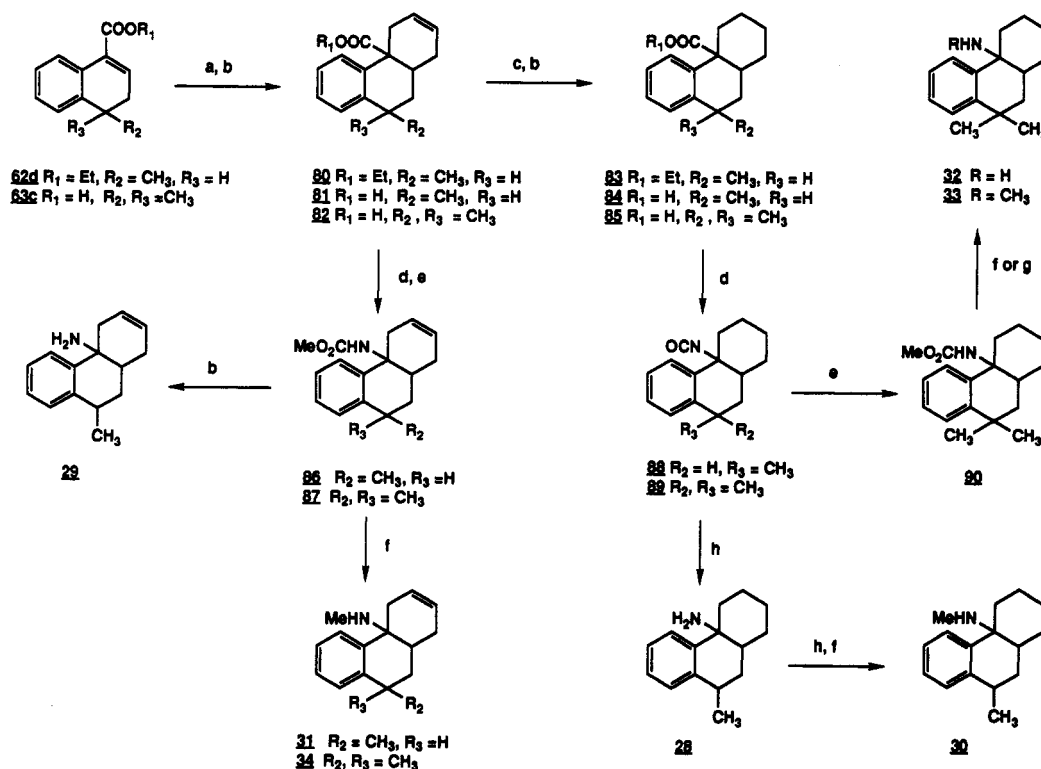
The Diels–Alder reaction as shown in Scheme II was quite general. All of the six-membered ring dienophiles were able to undergo 4 + 2 cycloaddition with 1,3-butadiene to give the adduct. Diels–Alder reactions were generally run with the unsaturated acids in toluene at 100–120 °C. These conditions gave reasonable yields of the desired adduct but were often accompanied by a great deal of polymerization products. The reactions also took several days or weeks to progress to completion. The Curtius rearrangement was accomplished most facily with diphenyl phosphorazidate to give the angular isocyanate, which could be trapped with an alcohol to give the carbamate or hydrolyzed directly to the primary amine. The isolated carbamate proved to be a valuable intermediate since it was generally obtained in high purity and yield. The carbamate could be hydrolyzed to provide the primary amine or could be reduced with lithium aluminum hydride to give the methylamine derivatives. Alternatively, the double bond of the Diels–Alder adduct was hydrogenated and then converted by a similar sequence to give the saturated primary amine and methylamine derivatives. The primary amine 8 was further elaborated to ethyl- or allylamines or cyclized into a piperidine ring by treatment with 1,4-dibromobutane. Derivatives with methoxy substitution on the A ring were obtained by this sequence as

well. The potent 6-hydroxyphenanthrenamine derivatives were obtained from the appropriate 6-methoxy compounds by demethylation in refluxing 48% HBr (eq 2) or by treatment with borontribromide in dichloromethane.

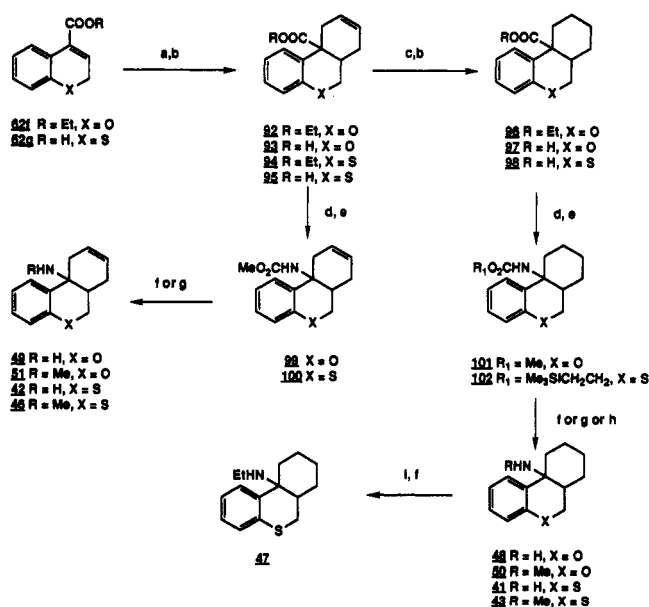


Similar methods were used to prepare B-ring methyl- and dimethyl-substituted derivatives 29–34 (Scheme III) as well as phenanthrenamine derivatives with B-ring heteroatom replacements (Scheme IV). The preparation of thienyl derivatives 52–54 is illustrated in Scheme V.

Resolution of enantiomers was accomplished in two ways (Scheme VI). Originally the isocyanates obtained via treatment of the carboxylic acid and diphenyl phosphorazidate were trapped with (1*R*,2*S*,5*R*)-(–)-menthol and the diastereomers separated by column chromatography. Although several grams of both enantiomers 13 and 14 were obtained using this methodology, it was impractical for larger scale synthesis. The absolute configuration of 13 was determined by X-ray crystallography as its mandelic acid salt (Figure 3). An alternative route relied on selective crystallization of the diastereomeric salts of the unsaturated carboxylic acids 64 and 95 with chiral methylbenzylamine provided both the (*R*)- and (*S*)-carboxylates (demonstrated by chiral HPLC).<sup>27</sup> Once separated they

Scheme III<sup>a</sup>

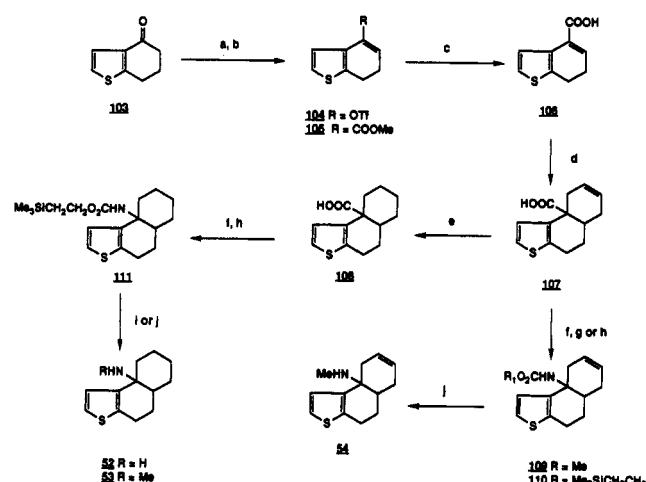
(a) Butadiene, AIBN, toluene, reflux; (b)  $\text{KOSiMe}_3$ , THF, reflux; (c) 5% palladium on carbon, hydrogen, MeOH; (d)  $(\text{PhO})_2\text{PON}_3$ ,  $\text{Et}_3\text{N}$ , toluene, 110 °C; (e) MeOH, reflux; (f) LAH, THF, reflux; (g) KOH, water, benzene, 18-crown-6 ether; (h) di-*tert*-butyl dicarbonate,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ .

Scheme IV<sup>a</sup>

(a) Butadiene, AIBN, toluene, reflux; (b)  $\text{KOSiMe}_3$ , THF, reflux; (c) 5% palladium on carbon, hydrogen, MeOH; (d)  $(\text{PhO})_2\text{PON}_3$ ,  $\text{Et}_3\text{N}$ , toluene, 110 °C; (e) MeOH, reflux; (f) LAH, THF, reflux; (g)  $\text{KOSiMe}_3$ , THF, reflux; (h) KOH, water, benzene, 18-crown-6 ether; (i)  $\text{Ac}_2\text{O}$ , DMAP,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ .

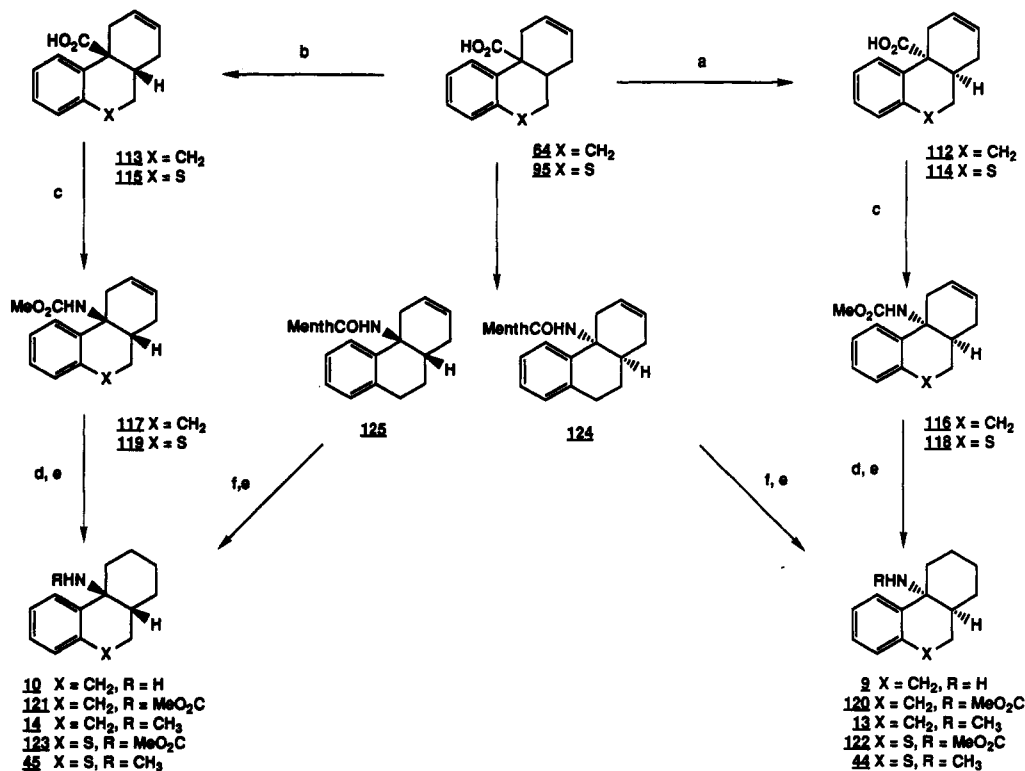
were individually carried through the standard reaction sequence described above to provide the enantiomerically pure compounds. This procedure provided enantiomers in both the phenanthrenamine series and the thiaphenanthrenamine series.

The preparation of some oxygenated derivatives in either the B or the C ring is illustrated in Scheme VII. The 9-oxo derivative 126 was prepared by oxidation of the B-ring acid 67 with chromium trioxide and acetic acid.<sup>28</sup> The C

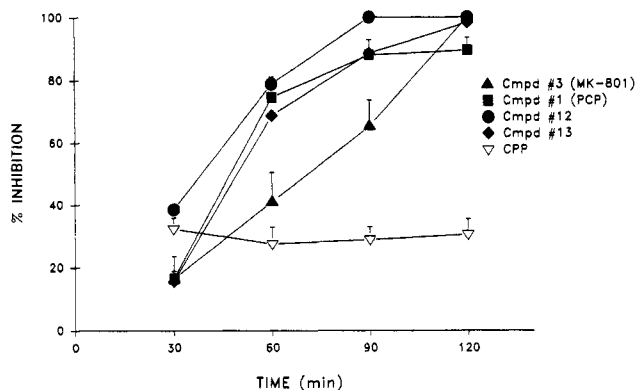
Scheme V<sup>a</sup>

(a)  $\text{TiF}_2\text{O}$ , 4-methyl-2,6-di-*tert*-butylpyridine,  $\text{CHCl}_3$ ; (b)  $\text{Pd}(\text{OAc})_2$ ,  $\text{PPh}_3$ ,  $\text{Et}_3\text{N}$ , MeOH, DMF, carbon monoxide; (c)  $\text{KOSiMe}_3$ , THF, reflux; (d) butadiene, AIBN, toluene, reflux; (e) 20% palladium on carbon, hydrogen, MeOH; (f)  $(\text{PhO})_2\text{PON}_3$ ,  $\text{Et}_3\text{N}$ , toluene, 110 °C; (g) MeOH, reflux; (h)  $\text{Me}_3\text{SiCH}_2\text{CH}_2\text{OH}$ , reflux; (i) TBAF, THF, reflux; (j) LAH, THF, reflux.

ring was oxygenated at C-3 via an iodolactonization reaction of the unsaturated carboxylic acid 64 and established the *cis* geometry between the 3- and 4a-positions. Reductive deiodination with hydrazine gave the ring-opened hydrazide 132. Further reduction with Raney nickel gave the hydroxy amide 133. Attempts to open the lactone directly with ammonia failed. Subsequent Curtius rearrangement provided the tetracyclic carbamate 134, which was reduced with lithium aluminum hydride to give the final 3-hydroxy derivative 37. The iodolactonization procedure was not run on the chiral unsaturated carboxylic acids, but this methodology presents the opportunity to generate a number of related adducts stereoselectively.

Scheme VI<sup>a</sup>

(a) (S)-(-)- $\alpha$ -Methylbenzylamine, 2-pentanone; (b) (R)-(+)- $\alpha$ -methylbenzylamine, 2-pentanone; (c) (PhO)<sub>2</sub>PON<sub>3</sub>, Et<sub>3</sub>N, toluene, 110 °C; MeOH, reflux; (d) 5% or 20% palladium on carbon, hydrogen, MeOH; (e) LAH, THF, reflux; (f) (PhO)<sub>2</sub>PON<sub>3</sub>, Et<sub>3</sub>N, toluene, 110 °C; menthol reflux.



**Figure 3.** Use dependency of selected compounds in the rat cortical wedge model. Wedges of rat cortex were placed in chambers which separated white and gray matter by a grease seal. Differential dc recordings were made from oxygenated Krebs buffer in response to the agonist NMDA (10  $\mu$ M). Data represent consecutive challenges with NMDA in the presence of drug: MK-801 (0.1  $\mu$ M), PCP (1  $\mu$ M), compound 12 (0.3  $\mu$ M), compound 13 (0.3  $\mu$ M), or CPP (1  $\mu$ M) and are expressed as percent inhibition of the mean amplitude of predrug depolarizations. Concentrations were chosen from dose-response curves to produce 20–40% inhibition of the first challenge. Note that the inhibition produced by the competitive antagonist is constant, while the reference noncompetitive antagonists as well as the novel compounds produce greater inhibition to subsequent challenges. These results indicate that these compounds produce a use-dependent blockade consistent with an action at the NMDA associated ion channel.

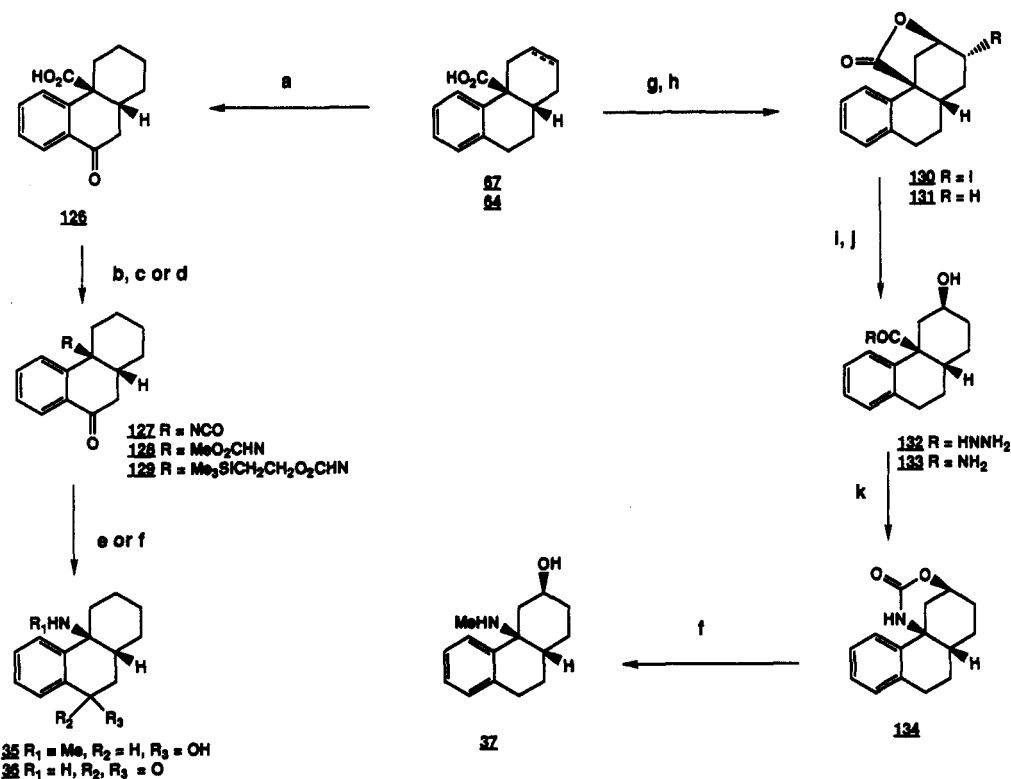
Although initial efforts to generate the *trans*-3-hydroxy derivatives via Mitsunobu-type inversion were unsuccessful with acetic acid and benzoic acid, a recent report describes the inversion of secondary cyclic alcohols by Mitsunobu reaction.<sup>29</sup>

From the modeling analysis and related literature reports,<sup>21–25</sup> it appeared that PCP-site ligands could

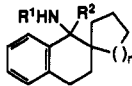
interact with one of the receptor site points (Figure 1, the right-hand receptor interaction point) from more than one direction. Specifically, the nitrogen atom of etoxadrol, when fit to the model, approaches the right-hand interaction point from the top face of the receptor binding site. This observation suggested that enhanced affinity might be obtained with ligands capable of simultaneous interaction with this site point from two directions. It was envisioned that an additional amino or hydroxyl group could form a hydrogen bond to the putative receptor site atom while maintaining the interaction present in PCP. The modeling study suggested that 2-substitution of the phenanthrenamine ring system by CH<sub>2</sub>Y groups in the *S*-configuration, where Y was a hydrogen bonding group such as NH<sub>2</sub> or OH, would present a group in the proper orientation for hydrogen bonding, similar to what has been reported for etoxadrol.

As shown in eq 1 the C ring can also be oxygenated at C-2 via the Robinson annulation procedure, or by using Danishefsky's diene in a Diels–Alder approach<sup>24</sup> to provide the starting material for the proposed C-ring-substituted analogs (Scheme VIII). The nitrile was introduced at the 2-position by treatment of the 2-keto derivative with diethyl cyanophosphonate to give the phosphorylated cyanohydrin, followed by reductive cleavage with samarium iodide.<sup>30</sup> Although both the *cis* and *trans* isomers were formed, the *cis* nitrile 136 was predominant (7:1).<sup>31</sup> The *cis* nitrile was further reduced to the desired primary and methylamine derivatives.

Inspection of Dreiding models, as well as initial modeling analyses, suggested that the phenanthrene framework might be altered and still provide high affinity PCP site ligands by moving the point of attachment of the C ring to give the spiro tetrahydronaphthalene derivatives. It appeared that the amino groups would have a similar orientation as in the phenanthrenamine series. These spiro

Scheme VII<sup>a</sup>



**Table II.** Summary of Biological Results for Spirotetrahydronaphthalenamines


no.	R <sup>1</sup>	R <sup>2</sup>	n	[ <sup>3</sup> H]TCP (nM)	% I at 10 <sup>-7</sup> M
55	H	H	2	3400	
56	H	H	1		8
57	Me	H	1		8
58	H	Me	1		5
59	Me	Me	1		5

nM). A comparison of binding affinities of the enantiomeric pairs 9 and 10, 13 and 14, and 44 and 45 is shown.

**Glutamate-Induced Influx of [<sup>45</sup>Ca<sup>2+</sup>] into Cultured Cortical Neurons.** For high-affinity analogs, demonstration of an NMDA antagonist action *in vitro* was made by determining their ability to inhibit glutamate induced accumulation of [<sup>45</sup>Ca<sup>2+</sup>] in cultured rat cortical neurons.<sup>34</sup> Cultures were exposed to a 30-min exposure of 100  $\mu$ M L-glutamate in the presence or absence of test agents. In this assay, the ability of a compound to inhibit calcium influx generally followed its affinity at the PCP site.

**Rat Cortical Wedge.** The ability of selected compounds to demonstrate use dependency in wedges of rat cortex was determined. The primary purpose of these experiments was to demonstrate that representative phenanthrenamines show the same increase in inhibitory activity in response to repeated agonist challenge as other NMDA channel blockers such as PCP and MK-801. The results presented in Figure 3 were generated by challenging cortical wedges every 30 min with the agonist NMDA in the presence of selected compounds. Results with PCP and MK-801 confirm earlier observations that at the degree of inhibition is greater with repeated challenges.<sup>35</sup> This observation is consistent with the hypothesis that these compounds only gain access to their binding site when the NMDA channel is opened by exposure to agonist. The fact that the phenanthrenamines tested produced a similar use dependent inhibition to MK-801 and PCP indicates that they interact at the same binding site. Further support for this contention comes from the fact that the concentrations at which these drugs demonstrate use dependency is directly predictable from their affinity for the [<sup>3</sup>H]TCP binding site.

**NMDA-Induced Lethality in Mice.** Confirmation of an NMDA antagonist action *in vivo* was demonstrated by the inhibition of NMDA-induced lethality in the mouse.<sup>36</sup> In this assay, intravenously administered NMDA in sufficient doses rapidly induces seizures and results in the death of 100% of the animals. *In vivo* activity was assessed by prevention of NMDA induced lethality in mice. This procedure, in combination with testing for ataxia using an inverted screen technique, is also useful for obtaining preliminary information about separation of desired pharmacological actions and possible side effects.<sup>36,37</sup> The results of the above experiments are summarized in Table I. In general, for the present series of compounds protection against the lethal effects of intravenously administered NMDA were only seen at doses that produced ataxia. Thus, no separation of protection and behavioral side effects was observed, except in the thiaphenanthrenamine cases (41 and 43). For 41 and 43, the positive results are small deviations and have not yet been translated into meaningful therapeutic separation.

## Structure-Activity Relationships

Potency in the [<sup>3</sup>H]TCP binding assay was used as the primary data to direct synthesis and molecular modeling effects. Similar to previous results in the fluorenamine series,<sup>24</sup> the (*R*)-(+)-enantiomers of the phenanthrenamines and thiaphenanthrenamines (9, 13, 44; defining the stereochemistry at C-4a) had higher affinity for the PCP site than the (*S*)-(-)-enantiomers (10, 14, 45). In general, as seen in Table I, the phenanthrenamine series retained high intrinsic affinity for the PCP site. Replacement of either the methylene (5) or sulfur group (6) of ring B with an ethylene to give 12 maintained rigidity of the template and did not significantly alter affinity. A few generalizations about the SAR of the phenanthrenamine series (X = CH<sub>2</sub>, S, O) can be made: (1) NHMe > NH<sub>2</sub> > NH<sub>2</sub>Et > NC<sub>5</sub>H<sub>10</sub> (Table I; compare the affinities of 12, 8, 17, and 19); (2) unsaturation, and hence flattening of the C ring, decreased binding affinity 3–4-fold; (3) cis ring fusion between the B ring and the C ring provided high affinity compounds at the PCP site (the trans fusion products were not available for comparison in this study due to the limitations of the synthetic methodology employed). In the phenanthrenamine series, the order of activity was X = CH<sub>2</sub> > S > O (12 > 43 > 50). Replacement of the A-ring-fused phenyl group with a fused thienyl ring (52–54) moderately decreased PCP-site affinity. The rationale for replacement of the fused-phenyl ring with a thienyl ring was based upon the comparison of TCP and PCP.

The molecular modeling study correctly predicted that the 6-hydroxy- and 6-methoxyphenanthrenamine derivatives would have substantially improved affinity for the PCP site compared to the unsubstituted derivatives, and that 7-substituted derivatives would have diminished affinity. This hypothesis was based in part upon the report that 3-hydroxy PCP had higher PCP site affinity than PCP,<sup>38</sup> suggesting that an additional hydrogen bonding interaction is available to stabilize ligand-receptor interactions (Figure 2). The 6-hydroxyphenanthreneamine (24) was found to have affinity greater than that of the reference standard MK-801. In this series as well, a 2,3-double bond reduced affinity for the PCP site compared with saturated derivatives. Additionally, a methyl substituent at C-8 (27) caused a reduction in receptor affinity and helped to define a region of steric intolerance in the pharmacophore model.

On comparing the intrinsic binding affinity of MK-801 (3) and 5-desmethyl-MK-801 (*K*<sub>i</sub> = 0.056 vs 22.6  $\mu$ M),<sup>39</sup> it was obvious that the 5-methyl group provides a stabilizing influence at the PCP site. In the PCP series, methyl-substituted derivatives have been used to discriminate between the enantiotopic edges of PCP and have helped to define ligand-receptor interactions.<sup>40</sup> Because the methyl substitution of PCP provided discrimination of binding based upon the stereochemistry and position of the substitution, and because of the extraordinary increase in affinity of 3 due to its 5-methyl group, we expected that methyl substitution in the phenanthrenamine series might provide additional affinity for the PCP site. However, substitution of a methyl group at C-9 reduced receptor affinity 20-fold (compare 30 to 12 and 28 to 8). Dimethyl substitution at C-9 essentially eliminated affinity at the PCP site (32 and 33). Close examination of several methylated derivatives in the pharmacophore model revealed that the 5-methyl group of 3 was already superimposed by one of the methylene groups of the C ring and that B-ring substituents projected

into sterically intolerant regions of the PCP site. A more comprehensive discussion of B- and C-ring substitutions is located in a paper that describes compounds with a fluorenamine ring system as the backbone.<sup>24</sup>

Compounds 39 and 40, prepared to explore the effect on affinity by simultaneous hydrogen bond interactions with a putative receptor site atom in the PCP pharmacophore from two directions, were inactive. However, other mitigating factors were also present in these analogs. It is likely that the lack of affinity for the PCP site of these derivatives is due to their low log *P* values, a relationship that has been observed previously for PCP<sup>38,40</sup> and fluorenamine<sup>24</sup> analogs. Measured log *P* values for selected phenanthrenamines using two different protocols have been included in Table I. In the present series (as in the fluorenamines<sup>24</sup>), compounds with a measured log *P* of <0.3 (shake-flask) or <2.5 (HPLC correlation method) are less potent, regardless of how they fit within the pharmacophore model. Relative affinity is governed by other factors for more lipophilic analogs. Addition of other polar functionalities to the phenanthrenamine framework was also generally detrimental to receptor affinity, as shown by derivatives 35–37.

## Conclusions

As a class of compounds, the phenanthrenamine PCP-site ligands described in this paper demonstrated high affinity for the PCP site on the NMDA receptor complex. The (*R*)-(+)-enantiomers were ca. 10-fold more potent than the (*S*)-(–)-enantiomers in this series. In addition to the angular amine functionality at C-4a binding to the primary receptor interaction point, an additional specific hydrogen-bonding interaction has been proposed, based on the high affinity of the 6-hydroxy and 6-methoxy derivatives (24 and 25). Heterocyclic analogs also showed high affinity binding for the PCP site; both sulfur- and oxygen-containing derivatives were examined (43 and 50). For the present series [<sup>3</sup>H]TCP receptor affinity is correlated with the level of activity in *in vitro* functional assays of NMDA antagonism.<sup>33</sup> Results such as these demonstrate that occupancy of the PCP site at the NMDA associated ion channel is sufficient to block glutamate induced activity, and that inhibition of [<sup>3</sup>H]TCP binding is an appropriate predictor of NMDA antagonist activity *in vitro*. The use dependency demonstrated in the rat cortical wedge provides direct experimental evidence that these compounds bind to the same site as PCP and MK-801. The NMDA-induced lethality assay in mice was used to demonstrate that these compounds are active *in vivo*. A comparison of the pharmacological activity of 1, 3, and 13 in a model of permanent middle cerebral artery occlusion in rat (MCAO Stroke Model) has been published elsewhere.<sup>41</sup>

## Experimental Section

**Biology. [<sup>3</sup>H]TCP Binding Assay.** Methods using rat cortical membranes have been described previously.<sup>18</sup> IC<sub>50</sub> values were determined from at least six separate experiments, except where noted in Tables I or II. Percent inhibition values were determined at two different concentrations and are reported at 10<sup>–7</sup> M.

**Data Analysis.** Specific binding was defined as total binding minus nonspecific binding. Results were reported as percent inhibition of control (specific binding without test agent), shown in eq 3, where *Y* is the percent inhibition, *T* is the specific binding without test agent, and *S* is the specific binding in the presence of test agent. The concentration of test agents that inhibited 50% of the specific binding (IC<sub>50</sub>) was determined from four or

more concentrations of test agents by a nonlinear least-squares curve-fitting program.<sup>42</sup>

$$Y = [(T - S)/T] \times 100 \quad (3)$$

**Cell Culture Technique.** Methods and materials (dissociated cell cultures from cortical hemispheres sectioned from fetal rat brain) for this procedure have been described in detail.<sup>34</sup> Experiments were performed in 96-well tissue culture plates (0.32 cm<sup>2</sup>/well) on cells in their 14th to 16th day after plating. Basic medium for all experiments was a serum- and magnesium-free Hank's balanced salt solution (HBSS) containing 1.4 mM CaCl<sub>2</sub>. A final pH of 7.4 was maintained with 35 mM sodium bicarbonate as the buffering agent. All experiments were performed in a humidified, 37 °C, 5% CO<sub>2</sub> atmosphere.

Thirty minutes prior to glutamate exposure, the maintenance medium was replaced with 50 μL of calcium-containing HBSS. Cultures were exposed to glutamate by the addition of 50 μL of 200 μM L-glutamic acid (100 μM final concentration) in the presence or absence of test agents. A trace amount of [<sup>45</sup>Ca<sup>2+</sup>] (2 μCi/mL) was added to the exposure medium to estimate calcium accumulation intracellularly [Ca<sup>2+</sup>]<sub>i</sub>. In all cases, cells were subjected to a 30-min exposure followed by a triple washing with 0.9% saline solution. Cells were lysed with distilled water and individual well lysates were counted for β-emissions. Baseline [Ca<sup>2+</sup>]<sub>i</sub> accumulation was estimated in cultures incubated for 30 min with [<sup>45</sup>Ca<sup>2+</sup>]-containing HBSS without glutamate. Control [Ca<sup>2+</sup>]<sub>i</sub> accumulation was estimated in cultures incubated for 30 min with [<sup>45</sup>Ca<sup>2+</sup>]-containing HBSS and glutamate. Glutamate-induced [Ca<sup>2+</sup>]<sub>i</sub> accumulation was calculated by subtracting baseline from control measurements. Previous studies have demonstrated that glutamate-induced toxicity to neurons in related paradigms is blocked specifically by NMDA antagonists.<sup>43</sup> In this study, putative NMDA antagonists were assessed as inhibitors of glutamate-induced [Ca<sup>2+</sup>]<sub>i</sub> accumulation by adding them to the control exposure medium in increasing concentrations. IC<sub>50</sub> concentrations were determined from concentration-inhibition curves constructed from at least four concentrations at half-log intervals with at least six replicate experiments per concentration.

**Rat Cortical Wedges.** Procedures were similar to those reported by Harrison and Simmonds (1984).<sup>44</sup> Wedges consisting of cingulate cortex and corpus callosum from 500-μm-thick slices of young Wistar rats (100–150 g) were placed in plexiglass chambers with a grease barrier between white and gray matter. Direct current potentials were recorded with Ag/AgCl chloride electrodes from medium separately bathing (2 mL/min) both sides of the chamber. Drugs were dissolved in oxygenated Krebs buffer (118 mM NaCl, 3.7 mM KCl, 2.6 mM CaCl<sub>2</sub>, 2.1 mM KH<sub>2</sub>PO<sub>4</sub>, 25 mM NaHCO<sub>3</sub>, 2 mM MgSO<sub>4</sub>, 11 mM glucose, adjusted and maintained at pH = 7.4) and added to the gray matter side. Three depolarizations were elicited in response to NMDA (10 μM) before the antagonists were added. Depolarizations to NMDA were then elicited at 30-min intervals in the presence of antagonists. Data are expressed as the percent of control amplitude which is defined as the mean of the last two predrug depolarizations. Results are displayed as mean ± standard error of the mean.

**NMDA-Induced Lethality and Ataxia in Mice.** Lethal seizures were produced in CF-1 mice by intravenous injection of *N*-methyl-D-aspartic acid (NMDA).<sup>36</sup> Mice weighing 22–28 g were injected behind the lateral aspect of the right eye (retrobulbar) with an appropriate dose of test agent or vehicle control (0.9% saline and a volume of 5 mL/kg), 5 min prior to NMDA injection. Ataxia assessments were made immediately prior to NMDA injection using an inverted-screen technique.<sup>37</sup> NMDA (25 mg/kg) dissolved in saline was administered as a bolus via left eye retrobulbar injection. Untreated controls develop seizures immediately following NMDA administration. Seizures are between 10 and 25 s in duration and are terminated by expiration of the animals. Test agents were assessed for their ability to prevent lethality following NMDA injections. ED<sub>50</sub> doses were determined from dose-response curves constructed from at least three doses of half-log intervals with 10 mice per dose.

**Molecular Modeling.** Preliminary reports of the modeling analyses have appeared;<sup>24,25</sup> the complete derivation of the model and its use in the design of a variety of noncompetitive antagonists

will be the subject of a separate publication. Therefore, only an overview of the modeling process is presented here.

An initial pharmacophore model of the PCP site within the NMDA receptor complex was generated by superimposing the phenyl ring, basic amine, and optionally, a hydroxy group in common to a diverse set of PCP ligands (*m*-hydroxyPCP, MK-801, SKF-10047, etoxadrol, *cis*-4b,5,6,7,8,9-hexahydro-*N*-methyl-8a*H*-fluoren-8a-amine, and 13; see Figure 1). Using SYBYL,<sup>46</sup> the structures of the above ligands (neutral species) were constructed and minimized using MAXIMIN. A receptor point (an  $sp^3$  nitrogen atom; N.3 in SYBYL) was defined that was 2.8 Å from the nitrogen in each ligand, as was a 2-Å tensor normal to the plane of the phenyl ring, piercing through its centroid. Using the MULTIFIT<sup>46</sup> procedure, the antagonist structures were constrained to superimpose the endpoints of the phenyl ring tensor and the receptor point atom. By comparing conformations and energies with and without the fitting constraints, an assessment could be made of the degree of conformity of each structure to the pharmacophore model.

After the basic pharmacophore was defined, selected MK-801, PCP, and hexahydrofluorenamine<sup>24</sup> analogs, other related antagonists, and compounds reported herein were added to define receptor active and excluded volumes. AM-1 charges<sup>47</sup> were calculated for all structures, and from these, molecular electrostatic potentials and dipole moments were obtained. The fit of 13 in the pharmacophore model is shown in Figure 2.

**Chemistry.** Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR spectra were obtained on a Nicolet MX-1 FT spectrometer. <sup>1</sup>H NMR spectra were obtained on an IBM WP100SY NMR spectrometer (100 MHz), Varian XL200 NMR spectrometer (200 MHz), Varian XL300 NMR spectrometer (300 MHz), or a Bruker WM 250 NMR spectrometer (250 MHz) and were consistent with the proposed structures. Mass spectra were obtained on Finnegan 4500 or VG Analytical 7070E/HF spectrometers. Where analyses are indicated by element symbols, the results are within 0.4% of the theoretical values; values outside these limits are indicated. TLC was carried out using 0.25-mm silica gel F254 (E. Merck) glass plates. Column chromatography used E. Merck silica gel (230–400 mesh).

**3,4-Dihydro-1-naphthalenecarboxylic Acid (63a).** A solution of 1-naphthoic acid (600 g, 3.48 mol) in 1.5 L of ether was added dropwise to 5 L of liquid ammonia at -78 °C. The resulting suspension was treated with sodium (200 g, 8.69 mol) over a 30-min period, followed by additional sodium (40 g, 1.74 mol) over 30 min. The reaction mixture was warmed to room temperature over an 18-h period under a stream of nitrogen to remove ammonia. The reaction mixture was treated with 5 L of ether followed by the cautious addition of  $NH_4Cl$  (400 g) and then ethanol (400 mL). The resulting solution was made acidic (pH = 1.5) using concentrated HCl. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic extracts were concentrated, and the residue (660 g) was dissolved in 6 L of 10% aqueous KOH solution and heated at 105 °C. The resulting solution was cooled to room temperature and made acidic (pH = 1.5) with concentrated HCl solution. The aqueous phase was extracted with ether (5 × 1 L), and the combined organic extracts were dried and concentrated to give the title compound (470 g, 79%) as a white solid.

**Ethyl 1,2,3,4-Tetrahydro-1-hydroxy-7-methoxy-1-naphthalenecarboxylate (61b).** Method A. A solution of 7-methoxytetralone (60b) (80.7 g, 0.458 mol) and  $ZnI_2$  (25 mg) in 200 mL of  $CH_2Cl_2$  was treated dropwise with trimethylsilyl cyanide (50.0 g, 0.50 mol) over 30 min. The resulting solution was stirred at 25 °C for 24 h and then poured into a saturated solution of HCl in ethanol at 0 °C. The resulting suspension was stirred for 20 h. The reaction mixture was concentrated, dissolved in THF (800 mL), and treated with 1 N  $H_2SO_4$  (800 mL). The resulting mixture was stirred for 24 h, and the organic phase was separated. The aqueous phase was extracted with additional ether, and the combined organic extracts were dried and concentrated. The solid residue was crystallized from hot THF/isopropyl ether to give the title compound as a white solid (60.0 g, 52%), mp 73 °C. Anal. ( $C_{14}H_{18}O_4$ ) C, H, N.

**Ethyl 1,2,3,4-Tetrahydro-1-hydroxy-5-methyl-7-methoxy-1-naphthalenecarboxylate (61c).** The title compound was

prepared from 60c (43.5 g, 0.229 mol) by method A. The product was not characterized, but used directly in the preparation of 62c.

**Ethyl 1,2,3,4-Tetrahydro-1-hydroxy-4-methyl-1-naphthalenecarboxylate (61d).** The title compound was prepared in 50% yield from 60d (29.1 g, 0.18 mol) by method A.

**Ethyl 1,2,3,4-Tetrahydro-1-hydroxy-4,4-dimethyl-1-naphthalenecarboxylate (61e).** The title compound was prepared in 35% yield from 60e (39.5 g, 0.227 mol) by method A.

**Ethyl 3,4-Dihydro-4-hydroxy-2*H*-1-benzopyran-4-carboxylate (61f).** The title compound was prepared in 86% yield from 60f (31.1 g, 0.210 mol) by method A.

**Ethyl 3,4-Dihydro-4-hydroxy-2*H*-1-benzothiopyran-4-carboxylate (61g).** The title compound was prepared in 34% yield from 60g (34.4 g, 0.209 mol) by method A, mp 117–119 °C. Anal. ( $C_{12}H_{14}O_3S$ ) C, H.

**Ethyl 3,4-Dihydro-7-methoxy-1-naphthalenecarboxylate (62b).** Method B. A solution of toluenesulfonic acid (63.8 g, 0.336 mol) in 750 mL of toluene was brought to reflux, and 61b (56.0 g, 0.224 mol) in 300 mL of toluene was added. The reaction was heated at reflux for 30 min with removal of water. The reaction mixture was cooled and diluted with ether (500 mL) and washed sequentially with water (500 mL) and saturated aqueous  $NaHCO_3$  (100 mL). The organic phase was dried and concentrated to give the title compound (45 g, 87%) as an oil.

**Ethyl 3,4-Dihydro-7-methoxy-5-methyl-1-naphthalenecarboxylate (62c).** The title compound was prepared in 30% yield (overall from 60c) from 61c by method B.

**Ethyl 3,4-Dihydro-4-methyl-1-naphthalenecarboxylate (62d).** The title compound was prepared in 93% yield from 61d (42.0 g, 0.180 mol) by method B.

**Ethyl 3,4-Dihydro-4,4-dimethyl-1-naphthalenecarboxylate (62e).** The title compound was prepared in 84% yield from 61e (20.0 g, 80.6 mmol) by method B.

**Ethyl 2*H*-1-Benzopyran-4-carboxylate (62f).** The title compound was prepared in 56% yield from 61f (40.0 g, 0.180 mol) by method B.

**Ethyl 2*H*-1-Benzothiopyran-4-carboxylate (62g).** The title compound was prepared in quantitative yield from 61g (16.0 g, 67.1 mmol) by method B.

**6,7-Dihydrobenzo[*b*]thien-4-yl Trifluoromethanesulfonate (104).** A solution of 103 (33.7 g, 0.22 mol) and 2,6-di-*tert*-butyl-4-methylpyridine (50.0 g, 0.244 mol) in 800 mL of  $CH_2Cl_2$  was cooled to 0 °C, and triflic anhydride (70.0 g, 0.248 mol) was added dropwise over 30 min. The reaction mixture was warmed to room temperature and concentrated. The residue was taken up in 1:1 heptane/EtOAc and the resulting suspension filtered. The filtrate was concentrated, and the residue was filtered through a plug of silica gel eluting with 9:1 heptane/EtOAc. The eluent was concentrated to give the title compound (55.8 g, 89%) as an oil.

**Methyl 6,7-Dihydrobenzo[*b*]thiophene-4-carboxylate (105).** A solution of 104 (55.3 g, 0.20 mol), palladium(II) acetate (1.30 g, 5.79 mmol), and triphenylphosphine (3.30 g, 12.6 mmol) in dimethylformamide (1000 mL), methanol (360 mL), and triethylamine (57 mL) was vigorously stirred under a carbon monoxide atmosphere for 3 h. The reaction mixture was concentrated, and the residue was dissolved in ether (500 mL) and washed with water (50 mL). The organic phase was dried ( $MgSO_4$ ), filtered, and concentrated. The residue was purified by chromatography (silica gel, 9:1 heptane/EtOAc) to give the title compound (17.9 g, 47%) as a colorless oil.

**3,4-Dihydro-7-methoxy-1-naphthalenecarboxylic Acid (63b).** A solution of 62b (45.7 g, 0.197 mol) in 500 mL of aqueous 1 N NaOH solution was heated at reflux for 18 h. The reaction mixture was cooled to room temperature and diluted with water (500 mL). The aqueous phase was extracted with  $CH_2Cl_2$  (5 × 25 mL) and acidified with aqueous HCl. The resulting solution was cooled in an ice bath, and the solid which formed was collected and dried in vacuo at 60 °C to give the title compound (39.5 g, 98%) as a white solid, mp 115 °C. Anal. ( $C_{12}H_{12}O_3$ ) C, H.

**3,4-Dihydro-7-methoxy-5-methyl-1-naphthalenecarboxylic Acid (63c).** Method C. A solution of 62c (17.0 g, 69.0 mmol) and 5 equiv of potassium trimethylsilanolate in 200 mL of THF was stirred at room temperature for 12 h. The resulting solution was acidified with 1 N HCl solution and extracted into ethyl acetate, dried ( $MgSO_4$ ), filtered, and concentrated. The residue was recrystallized from diisopropyl ether/THF to give

the title compound (10.2 g, 68%) as a white solid, mp 149–150 °C. Anal. ( $C_{13}H_{14}O_3$ ) C, H.

**3,4-Dihydro-4,4-dimethyl-1-naphthalenecarboxylic Acid (63e).** The title compound was prepared in 52% yield from 62e (15.5 g, 67.3 mmol) by method C as a white solid.

**6,7-Dihydrobenzo[*b*]thiophene-4-carboxylic Acid (106).** The title compound was prepared in 50% yield from 105 (22.5 g, 116 mmol) by method C as a white solid.

***cis*-1,9,10,10a-Tetrahydro-4a(4*H*)-phenanthrenecarboxylic Acid (64).** Method D. A solution of 63a (85.03 g, 0.488 mol) and butylated hydroxytoluene (0.5 g, 2.3 mmol) in 800 mL of toluene was placed in a stainless steel reaction vessel and sealed. The reaction vessel was charged with butadiene (80.0 g, 1.48 mol) under nitrogen pressure and then heated to 150 °C for 64 h. The reactor was allowed to cool to room temperature and then placed in an ice bath. The reaction vessel was vented and recharged with fresh butadiene (92.0 g, 1.7 mol) under  $N_2$  pressure and heated to 150 °C for an additional 118 h. The reaction mixture was cooled as described above and vented. Sampling showed that starting material remained therefore the reactor was sealed and charged with fresh butadiene (65 g, 1.2 mol) under  $N_2$  pressure and heated to 150 °C for an additional 82 h. The reaction vessel was cooled and vented. The toluene solution was evaporated to afford a tan solid. The solid was dissolved in boiling MeOH, treated with Darco-Celite and filtered. The resulting filtrate was heated, diluted with water, and filtered hot. The filtrate was heated to a solution, treated with Darco-Celite, and filtered. The filtrate was concentrated to half its volume and cooled. The solid that formed was collected by filtration and dried to give crude material (65.52 g). A second crop of crude material was obtained by concentrating and cooling the filtrate. The combined material was dissolved in boiling 6:1 methanol/water, treated with Darco G-60, and filtered hot. The filtrate was cooled in an ice bath, and the solid which formed was collected and washed with a small amount of aqueous methanol. The solid obtained was dried under vacuum to give the title compound (63.5 g, 57%) as a white solid, mp 144–146 °C. Anal. ( $C_{15}H_{16}O_2$ ) C, H.

***cis*-1,9,10,10a-Tetrahydro-6-methoxy-4a(4*H*)-phenanthrenecarboxylic Acid (65).** The title compound was prepared in 44% yield from 63b (39.5 g, 0.153 mol) by method D as a white solid, mp 125 °C.

***cis*-1,9,10,10a-Tetrahydro-6-methoxy-8-methyl-4a(4*H*)-phenanthrenecarboxylic Acid (66).** The title compound was prepared in 28% yield from 63c (10.2 g, 46.7 mmol) by method D as an oil.

**Ethyl *cis*-1,9,10,10a-Tetrahydro-9-methyl-4a(4*H*)-phenanthrenecarboxylate (80).** The title compound was prepared in 12% yield from 62d (35.0 g, 0.161 mol) by method D as a white solid.

***cis*-1,9,10,10a-Tetrahydro-9,9-dimethyl-4a(4*H*)-phenanthrenecarboxylic Acid (82).** The title compound was prepared in 32% yield from 63c (8.50 g, 42.0 mmol) by method D as an oil.

**Ethyl *cis*-6,6a,7,10-Tetrahydro-10a*H*-dibenzo[*b,d*]pyran-10a-carboxylate (92).** The title compound was prepared in 88% yield from 62f (20.3 g, 99.4 mmol) by method D as a white solid, mp 88 °C.

**Ethyl *cis*-6,6a,7,10-Tetrahydro-10a*H*-dibenzo[*b,d*]thiopyran-10a-carboxylate (94).** The title compound was prepared in 44% yield from 62g (15.6 g, 70.8 mmol) by method D as a yellow oil.

***cis*-4,5,5a,6-Tetrahydronaphtho[2,1-*b*]thiophene-9a(9*H*)-carboxylic Acid (107).** The title compound was prepared in 17% yield from 106 (10.0 g, 55.5 mmol) by method D as a yellow oil.

***cis*-1,2,3,4,4a,9,10,10a-Octahydro-4a(2*H*)-phenanthrenecarboxylic Acid (67).** Method E. A solution of 64 (60.0 g, 0.263 mol) in 1.6 L of methanol was hydrogenated over 5% palladium on carbon at 50 psi of hydrogen for 6.0 h. The reaction mixture was filtered and concentrated to give the title compound (42.0 g, 69%) as a white solid.

***cis*-1,3,4,9,10,10a-Tetrahydro-6-methoxy-4a(2*H*)-phenanthrenecarboxylic Acid (68).** The title compound was prepared in 83% yield from 65 (3.03 g, 11.7 mmol) by method E as a white solid, mp 171–173 °C.

**Ethyl *cis*-1,3,4,9,10,10a-Hexahydro-9-methyl-4a(2*H*)-phenanthrenecarboxylate (83).** The title compound was prepared in 93% yield from 80 (2.15 g, 7.96 mmol) by method E as a white solid.

***cis*-1,3,4,9,10,10a-Hexahydro-9,9-dimethyl-4a(2*H*)-phenanthrenecarboxylic Acid (85).** The title compound was prepared in 98% yield from 82 (4.35 g, 17.0 mmol) by method E as a white solid, mp 200–203 °C.

**Ethyl *cis*-6,6a,7,8,9,10-Hexahydro-10a*H*-dibenzo[*b,d*]pyran-10a-carboxylate (96).** The title compound was prepared in quantitative yield from 92 (4.80 g, 18.6 mmol) by method E as an oil.

***cis*-6,6a,7,8,9,10-Hexahydro-10a*H*-dibenzo[*b,d*]thiopyran-10a-carboxylic Acid (98).** The title compound was prepared in 98% yield from 95 (4.35 g, 17.7 mmol) by method E as a white solid, mp 200–203 °C.

***cis*-5,5a,6,7,8,9-Hexahydronaphtho[2,1-*b*]thiophene-9a(4*H*)-carboxylic Acid (108).** The title compound was prepared in 51% yield from 107 (1.89 g, 8.1 mmol) by method E as a white solid.

***cis*-1,3,4,9,10,10a-Hexahydro-9-methyl-4a(2*H*)-phenanthrenecarboxylic Acid (84).** The title compound was prepared in 89% yield from 83 (2.00 g, 7.40 mmol) by method C.

***cis*-1,9,10,10a-Tetrahydro-4a(4*H*)-phenanthrenecarboxylic Acid (81).** The title compound was prepared in 89% yield from 80 (6.7 g, 26.1 mmol) by method C.

***cis*-6,6a,7,10-Tetrahydro-10a*H*-dibenzo[*b,d*]pyran-10a-carboxylic Acid (93).** The title compound was prepared in 99% yield from 92 (4.40 g, 17.0 mmol) by method C.

***cis*-6,6a,7,10-Tetrahydro-10a*H*-dibenzo[*b,d*]thiopyran-10a-carboxylic Acid (95).** The title compound was prepared in 68% yield from 94 (7.36 g, 26.8 mmol) by method C as a white solid, mp 152–155 °C.

***cis*-6,6a,7,8,9,10-Hexahydro-10a*H*-dibenzo[*b,d*]pyran-10a-carboxylic Acid (97).** The title compound was prepared in 98% yield from 96 (4.90 g, 18.6 mmol) by method C as a white solid.

***cis*-1,2,3,4,4a,9,10,10a-Octahydro-4a-isocyanatophenanthrene (72).** A solution of 67 (3.22 g, 1.40 mmol) in 25 mL of thionyl chloride was heated at reflux for 1 h. The reaction mixture was concentrated, and the crude product was dissolved in 25 mL of benzene and treated with sodium azide (10.0 g, 154 mmol) and 18-crown-6 ether (0.06 g). The resulting solution was heated at reflux for 18 h. The reaction was cooled and filtered. The filtrate was concentrated, and the residue was purified by chromatography (silica gel, 10:1 heptane/EtOAc) to give the title compound (2.9 g, 90%) as a yellow oil.

**Ethyl *cis*-(1,3,4,9,10,10a-Hexahydro-4a(2*H*)-phenanthrenyl)carbamate (77).** A solution of 72 (0.57 g, 2.2 mmol) in 10 mL of ethanol was heated at reflux for 18 h. The reaction mixture was concentrated, and the residue was purified by chromatography (silica gel, 9:1 heptane/EtOAc) to give the title compound (0.46 g, 67%) as a colorless oil.

***cis*-1,4,4a,9,10,10a-Hexahydro-4a-isocyanatophenanthrene (69).** In a manner similar to that described for the preparation of 72, compound 64 (2.00 g, 8.8 mmol) was converted to the title compound (1.45 g, 74%) as an oil.

**Ethyl *cis*-(1,9,10,10a-Tetrahydro-4a(4*H*)-phenanthrenyl)carbamate (74).** In a manner similar to that described for the preparation of 77, compound 69 (0.72 g, 3.2 mmol) was converted to the title compound. This material was not characterized, but used directly in the preparation of 15.

***cis*-1,4,4a,9,10,10a-Hexahydro-4a-isocyanato-6-methoxyphenanthrene (70).** A solution of 65 (5.00 g, 19.0 mmol) and triethylamine (2.3 g, 22.8 mmol) in 150 mL of benzene was treated with diphenyl phosphorazidate (5.2 g, 19.0 mmol), and the resulting solution was heated at reflux for 24 h. The reaction mixture was cooled and washed with water. The organic phase was dried ( $Na_2SO_4$ ), filtered, and concentrated. The residue was purified by chromatography (silica gel, 9:1 heptane/EtOAc) to give the title compound (3.2 g, 65%) as a yellow solid.

**Methyl *cis*-(1,9,10,10a-Tetrahydro-6-methoxy-4a(4*H*)-phenanthrenyl)carbamate (75).** A solution of 70 (1.50 g, 5.9 mmol) in 50 mL of methanol was heated at reflux for 24 h. The reaction mixture was cooled and concentrated to give the title compound (1.75 g, quantitative) as a white solid, mp 120–122 °C.

**Methyl *cis*-(1,3,4,9,10,10a-Hexahydro-6-methoxy-4a(4*H*)-phenanthrenyl)carbamate (78).** Method F. A solution of 68 (2.90 g, 11.5 mmol) and triethylamine (1.6 g, 12.7 mmol) in 60 mL of benzene was treated with diphenyl phosphorazidate (3.2 g, 11.5 mmol), and the resulting solution was heated at reflux for 2 h. The reaction mixture was cooled to room temperature, and methanol (25 mL) was added. The resulting solution was heated at reflux for 24 h. The reaction mixture was concentrated, and the residue was purified by chromatography (silica gel, 9:1 heptane/EtOAc) to give the title compound (1.76 g, 55%) as a white solid, mp 96–99 °C. (Toluene was used in place of benzene in most other examples.)

**Methyl *cis*-(1,9,10,10a-Tetrahydro-6-methoxy-8-methyl-4a(4*H*)-phenanthrenyl)carbamate (76).** The title compound was prepared in 73% yield from 66 (0.55 g, 2.02 mmol) and methanol by method F as a white solid.

**Methyl *cis*-(1,9,10,10a-Tetrahydro-9-methyl-4a(4*H*)-phenanthrenyl)carbamate (86).** The title compound was prepared in 71% yield from 81 (1.50 g, 6.20 mmol) and methanol by method F as a white solid.

***cis*-1,4,4a,9,10,10a-Hexahydro-9-methyl-4a-isocy-anatophenanthrene (88).** In a manner similar to that described for the preparation of 72, compound 84 (1.50 g, 6.10 mmol) was converted to the title compound (0.70 g, 42%) as an oil.

**Methyl *cis*-(1,9,10,10a-Tetrahydro-9,9-dimethyl-4a(4*H*)-phenanthrenyl)carbamate (87).** The title compound was prepared in 8% yield from 82 (1.50 g, 5.86 mmol) and methanol by method F as an oil.

**Methyl *cis*-(1,3,4,9,10,10a-Hexahydro-9,9-dimethyl-4a(4*H*)-phenanthrenyl)carbamate (90).** The title compound was prepared in 12% yield from 89 (1.50 g, 5.86 mmol) and methanol by method F as an oil.

**Methyl *cis*-(6,6a,7,10-Tetrahydro-10a*H*-dibenzo[*b,d*]pyran-10a-yl)carbamate (99).** The title compound was prepared in 65% yield from 93 (1.50 g, 6.51 mmol) by methods E and F (methanol) as a white solid. Anal. ( $C_{15}H_{17}NO_3$ ) C, H, N.

**Methyl *cis*-(6,6a,7,8,9,10-Hexahydro-10a*H*-dibenzo[*b,d*]pyran-10a-yl)carbamate (101).** The title compound was prepared in 67% yield from 97 (1.00 g, 4.30 mmol) by method F (methanol) as a white solid. Anal. ( $C_{15}H_{19}NO_3$ ) C, H, N.

**Methyl *cis*-(6,6a,7,10-Tetrahydro-10a*H*-dibenzo[*b,d*]thiopyran-10a-yl)carbamate (100).** The title compound was prepared in 76% yield from 95 (1.73 g, 7.02 mmol) by method F (methanol) as a white solid, mp 151–152 °C.

**2-(Trimethylsilyl)ethyl *cis*-(6,6a,7,8,9,10-Hexahydro-10a*H*-dibenzo[*b,d*]thiopyran-10a-yl)carbamate (102).** The title compound was prepared in 88% yield from 98 (4.03 g, 16.2 mmol) by method F ((trimethylsilyl)ethanol) as an oil.

**Methyl *cis*-(4,5,5a,6-Tetrahydronaphtho[2,1-*b*]thien-9a(9*H*)-yl)carbamate (109).** The title compound was prepared in 43% yield from 107 (0.37 g, 1.58 mmol) by method F (methanol) as a white solid.

**2-(Trimethylsilyl)ethyl *cis*-(4,5,5a,6-Tetrahydronaphtho[2,1-*b*]thien-9a(9*H*)-yl)carbamate (110).** The title compound was prepared in 67% yield from 107 (0.47 g, 2.00 mmol) by method F ((trimethylsilyl)ethanol) as a waxy solid.

**2-(Trimethylsilyl)ethyl *cis*-(5,5a,6,7,8,9-Hexahydronaphtho[2,1-*b*]thien-9a(4*H*)-yl)carbamate (111).** The title compound was prepared in 31% yield from 108 (0.72 g, 3.05 mmol) by method F ((trimethylsilyl)ethanol) as a white solid.

***cis*-1,3,4,9,10,10a-Hexahydro-4a(2*H*)-phenanthrenamine Hydrochloride (8).** A solution of 72 (0.92 g, 4.05 mmol) in 15 mL of benzene was added to a solution of potassium hydroxide (5.0 g) in water (5 mL). The resulting mixture was treated with 18-crown-6 ether (0.01 g) and stirred at room temperature for 18 h. The reaction mixture was made acidic with aqueous 1 N HCl solution and washed with ether. The aqueous layer was basified with solid sodium hydroxide and extracted with ether. The combined organic extracts were dried ( $Na_2SO_4$ ), filtered, and concentrated. The residue was dissolved in ether and treated with isopropanolic HCl solution. The white solid which formed was collected by suction filtration to give the title compound (0.55 g, 57%). An analytical sample was obtained by recrystallization from methanol/ether, mp 223–225 °C. Anal. ( $C_{14}H_{19}N\cdot HCl$ ) C, H, N, Cl.

***cis*-4,9,10,10a-Tetrahydro-4a(2*H*)-phenanthrenamine Hydrochloride (11).** In a manner similar to that described for the

preparation of 8, compound 69 (0.73 g, 3.2 mmol) was converted to the title compound (0.64 g, 84%) as a white solid, mp 247–248 °C dec. Anal. ( $C_{14}H_{17}N\cdot HCl$ ) C, H, N, Cl.

***cis*-1,9,10,10a-Tetrahydro-6-methoxy-4a(4*H*)-phenanthrenamine Hydrochloride (23).** In a manner similar to that described for the preparation of 8, compound 70 (1.5 g, 5.9 mmol) was converted to the title compound (0.83 g, 53%) as a white solid, mp 270 °C. Anal. ( $C_{15}H_{19}NO\cdot HCl$ ) C, H, N; calcd, 5.27; found, 4.75; Cl: calcd, 13.35; found, 12.78.

**1,3,4,9,10,10a-Hexahydro-9-methyl-4a(2*H*)-phenanthrenamine Hydrochloride (28).** In a manner similar to that described for the preparation of 8, compound 88 (1.35 gm, 5.6 mmol) was converted to the title compound (1.15 g, 81%) as a white solid. Anal. ( $C_{15}H_{21}N\cdot HCl$ ) H, Cl; C: calcd, 71.55; found, 70.82; N: calcd, 5.56; found, 5.05.

***cis*-1,3,4,9,10,10a-Hexahydro-6-methoxy-4a(2*H*)-phenanthrenamine Hydrochloride (22).** Method G. A solution of 78 (1.76 g, 6.1 mmol) in 40 mL of THF was treated with potassium trimethylsilanolate (2.0 g, 15.6 mmol) in one portion. The resulting solution was heated at reflux for 7 h. The reaction mixture was cooled to room temperature and poured into aqueous 1 N HCl solution. The resulting solution was washed with ether, and the aqueous phase was separated and basified with solid NaOH (pH = 14). The aqueous phase was extracted with ether (3 × 25 mL), and the combined organic extracts were dried ( $Na_2SO_4$ ), filtered, and concentrated. The residue was converted to the hydrochloride salt by dissolution in ether followed by treatment with isopropanolic HCl to give the title compound (0.30 g, 18%) as a white solid, mp 256–263 °C. Anal. ( $C_{15}H_{21}NO\cdot HCl\cdot 0.5H_2O$ ) C, N, Cl; H: calcd, 8.18; found, 7.63.

***cis*-1,9,10,10a-Tetrahydro-9-methyl-4a(4*H*)-phenanthrenamine Hydrochloride (29).** The title compound was prepared in 54% yield from 86 (0.50 g, 1.85 mmol) by method G as a white solid, mp 234–236 °C. Anal. ( $C_{15}H_{19}N\cdot HCl$ ) C, H, N.

***cis*-1,3,4,9,10,10a-Hexahydro-9,9-dimethyl-4a(2*H*)-phenanthrenamine Hydrochloride (32).** The title compound was prepared in 31% yield from 90 (0.25 g, 0.87 mmol) by method G as a white solid, mp 250–252 °C. Anal. ( $C_{16}H_{23}N\cdot HCl$ ) N; C: calcd, 72.29; found, 71.39; H: calcd, 9.10; found, 8.07.

***cis*-6,6a,7,10-Tetrahydro-10a*H*-dibenzo[*b,d*]pyran-10a-amine Hydrochloride (49).** The title compound was prepared in 93% yield from 99 (0.51 g, 1.97 mmol) by method G as a white solid, mp 215–217 °C. Anal. ( $C_{13}H_{15}NO\cdot HCl\cdot 0.2H_2O$ ) C, H, N.

***cis*-6,6a,7,8,9,10-Hexahydro-10a*H*-dibenzo[*b,d*]pyran-10a-amine Hydrochloride (48).** The title compound was prepared in 85% yield from 101 (0.30 g, 1.15 mmol) by method G as a white solid, mp 230–232 °C. Anal. ( $C_{13}H_{17}NO\cdot HCl\cdot 0.25H_2O$ ) C, H, N, Cl.

***cis*-6,6a,7,8,9,10-Hexahydro-10a*H*-dibenzo[*b,d*]thiopyran-10a-amine Hydrochloride (41).** Method H. A solution of 102 (1.0 g, 2.75 mmol) in 10 mL of THF was treated with 2.8 mL of a 1 M solution of tetrabutylammonium fluoride. The resulting solution was heated at reflux for 15 min and cooled to room temperature and diluted with ether. The solution was acidified with aqueous 2 N HCl and the aqueous phase washed with ether. The aqueous phase was made basic (pH = 14) with 1 N NaOH and extracted with ether. The combined organic extracts were dried ( $Na_2SO_4$ ) and concentrated. The residue was converted to the title compound (0.6 g, 85%) as a white solid by treatment with ether and HCl, mp 244–246 °C dec. Anal. ( $C_{13}H_{17}NS\cdot HCl$ ) C, H, N, Cl.

***cis*-4,5,5a,6,7,8,9-Hexahydronaphtho[2,1-*b*]thiophen-9a(4*H*)-amine Hydrochloride (52).** The title compound was prepared in 45% yield from 111 (0.33 g, 0.94 mmol) by method H as a white solid, mp 189–192 °C. Anal. ( $C_{12}H_{17}NS\cdot HCl$ ) C, N, Cl; H: calcd, 7.44; found, 7.86.

***cis*-1,3,4,9,10,10a-Hexahydro-*N*-methyl-4a(2*H*)-phenanthrenamine Hydrochloride (12).** Method I. A solution of 77 (0.40 g, 1.50 mmol) in 5 mL of THF was added dropwise to a stirring suspension of lithium aluminum hydride (0.54 g, 14.0 mmol) in 30 mL of THF. The resulting suspension was stirred at room temperature for 24 h and then quenched by the sequential addition of water (1.0 mL), aqueous 1 N NaOH solution (1 mL), and water (5.0 mL). The resulting suspension was filtered and the filtrate concentrated. The residue was dissolved in ether (10 mL) and treated with an isopropanolic HCl solution. The solid



which formed was collected by filtration and dried under vacuum to give the title compound (0.26 g, 71%) as a white solid, mp 227–282 °C. Anal. ( $C_{15}H_{21}N \cdot HCl$ ) C, H, N, Cl.

**cis-1,9,10,10a-Tetrahydro-N-methyl-4a(4H)-phenanthrenamine Hydrochloride (15).** The title compound was prepared in 87% yield from 74 (0.72 g, 2.65 mmol) by method I as a white solid, mp 224–227 °C. Anal. ( $C_{15}H_{19}N \cdot HCl$ ) C, H, N; calcd, 5.61; found, 5.13; Cl: calcd, 14.19; found, 13.76.

**cis-1,9,10,10a-Tetrahydro-6-methoxy-N-methyl-4a(4H)-phenanthrenamine Hydrochloride (26).** The title compound was prepared in 85% yield from 75 (1.75 g, 6.08 mmol) by method I as a white solid, mp 252 °C. Anal. ( $C_{16}H_{21}NO \cdot HCl$ ) C, H, N; calcd, 5.00; found, 4.52; Cl: calcd, 12.67; found, 12.15.

**cis-1,3,4,9,10,10a-Hexahydro-6-methoxy-N-methyl-4a(2H)-phenanthrenamine Hydrochloride (25).** The title compound was prepared in 80% yield from 78 (1.66 g, 5.74 mmol) by method I as a white solid, mp 263–265 °C. Anal. ( $C_{16}H_{23}NO \cdot HCl$ ) C, H, N; Cl: calcd, 12.58; found, 12.02.

**cis-1,3,4,9,10,10a-Hexahydro-6-methoxy-N,8-dimethyl-4a(2H)-phenanthrenamine Hydrochloride (27).** The title compound was prepared in 27% yield from 79 (0.95 g, 3.1 mmol) by method I as a white solid. Anal. ( $C_{17}H_{25}NO \cdot HCl$ ) C, H, N, Cl.

**cis-1,9,10,10a-Tetrahydro-N,9-dimethyl-4a(4H)-phenanthrenamine Monohydrochloride (31).** The title compound was prepared in 81% yield from 86 (0.65 g, 2.40 mmol) by method I as a white solid, mp 248–249 °C. Anal. ( $C_{16}H_{21}N \cdot HCl$ ) C, H, N.

**cis-1,3,4,9,10,10a-Hexahydro-N,9-dimethyl-4a(2H)-phenanthrenamine Monohydrochloride (30).** A solution of 28 (0.75 g, 3.50 mmol) and di-*tert*-butyl dicarbonate (1.52 g, 6.98 mmol) in 25 mL of  $CH_2Cl_2$  and triethylamine was refluxed for 3 h. The reaction mixture was concentrated and the residue purified by chromatography (silica gel, 2% EtOAc/heptane) to give the intermediate *tert*-butyl carbamate (0.53 g). This material was converted to the title compound (0.17 g, 18%) as a white solid by method H, mp 235–237 °C. Anal. ( $C_{16}H_{23}N \cdot HCl$ ) H, N, Cl; C: calcd, 72.29; found, 71.85.

**cis-1,3,4,9,10,10a-Hexahydro-N,9,9-trimethyl-4a(2H)-phenanthrenamine Monohydrochloride (33).** The title compound was prepared in 92% yield from 90 (0.20 g, 0.69 mmol) by method I as a white solid, mp 258–259 °C. Anal. ( $C_{17}H_{25}N \cdot HCl$ ) H, N, Cl; C: calcd, 73.49; found, 71.76.

**cis-1,9,10,10a-Tetrahydro-N,9,9-trimethyl-4a(4H)-phenanthrenamine Monohydrochloride (34).** The title compound was prepared in 51% yield from 90 (0.15 g, 0.53 mmol) by method I as a white solid, mp 256–258 °C. Anal. ( $C_{17}H_{23}N \cdot HCl$ ) C, H, N.

**cis-6,6a,7,10-Tetrahydro-N-methyl-10aH-dibenzo[b,d]pyran-10a-amine Hydrochloride (51).** The title compound was prepared in 88% yield from 99 (0.50 g, 1.93 mmol) by method I as a white solid, mp 210–213 °C. Anal. ( $C_{14}H_{17}NO \cdot HCl$ ) C, H, N, Cl.

**cis-6,6a,7,8,9,10-Hexahydro-N-methyl-10aH-dibenzo[b,d]pyran-10a-amine Hydrochloride (50).** The title compound was prepared in 81% yield from 101 (0.34 g, 1.31 mmol) by method I as a white solid, mp 219–221 °C. Anal. ( $C_{14}H_{19}NO \cdot HCl$ ) C, H, N, Cl.

**cis-6,6a,7,10-Tetrahydro-10aH-dibenzo[b,d]thiopyran-10a-amine Hydrochloride (42).** The title compound was prepared in 77% yield from 100 (1.35 g, 4.83 mmol) by method G as a white solid. Anal. ( $C_{13}H_{11}NS \cdot HCl$ ) C: calcd, 61.52; found, 61.15; H: calcd, 6.35; found, 7.00; N: calcd, 5.52; found, 4.87.

**cis-6,6a,7,10-Tetrahydro-N-methyl-10aH-dibenzo[b,d]thiopyran-10a-amine Hydrochloride (46).** The title compound was prepared in 72% yield from 100 (1.47 g, 5.26 mmol) by method I as a white solid. Anal. ( $C_{14}H_{17}NS \cdot HCl$ ) H, N, Cl; C: calcd, 62.79; found, 62.36.

**cis-6,6a,7,8,9,10-Hexahydro-N-methyl-10aH-dibenzo[b,d]thiopyran-10a-amine Hydrochloride (43).** The title compound was prepared in 91% yield from 102 (1.50 g, 4.13 mmol) by method I as a white solid, mp 211–218 °C. Anal. ( $C_{14}H_{19}NS \cdot HCl$ ) C, H, N, Cl.

**cis-4,5,6-Tetrahydro-N-methylnaphtho[2,1-b]thiophen-9a(4H)-amine Hydrochloride (54).** The title compound was

prepared in 41% yield from 109 (150 mg, 0.43 mmol) by method I as a white solid, mp 189–190 °C. Anal. ( $C_{13}H_{17}NS \cdot HCl$ ) C, H, N; Cl.

**cis-5,5a,6,7,8,9-Hexahydro-N-methylnaphtho[2,1-b]thiophen-9a(4H)-amine Hydrochloride (53).** The title compound was prepared in 46% yield from 111 (330 mg, 0.94 mmol) by method I as a white solid, mp 185–187 °C. Anal. ( $C_{13}H_{19}NS \cdot HCl$ ) C, H, N, Cl.

**cis-1,3,4,9,10,10a-Hexahydro-N-(2-propenyl)-4a(2H)-phenanthrenamine Monohydrochloride (18).** A solution of 8 (0.57 g, 2.83 mmol, free base) in ethanol (8 mL) was treated with allyl bromide (0.34 g, 2.83 mmol) and triethylamine (0.27 g, 2.67 mmol). The resulting solution was stirred at room temperature for 56 h. The reaction mixture was concentrated and the residue was dissolved in ether and washed with 1 N HCl solution. The aqueous phase was made basic with solid sodium hydroxide and extracted with ether. The organic extracts were dried ( $MgSO_4$ ), filtered, and concentrated. The residue was purified by chromatography (silica gel, ethyl acetate/heptane, gradient elution) to give the product as an oil. The oil was dissolved in ether and treated with isopropanolic HCl to give the title compound (0.17 g, 22%) as a white solid, mp 211–213 °C. Anal. ( $C_{17}H_{23}N \cdot HCl$ ) C, H, N, Cl.

**cis-1-(1,2,3,4,4a,9,10,10a-Octahydro-4a(2H)-phenanthrenyl)piperidine Hydrochloride (19).** A mixture of 8 (5 g, 25 mmol), 1,4-dibromobutane (11.5 g, 50 mmol), and potassium carbonate (6.9 g, 0.25 mol) in 100 mL of methyl ethyl ketone was heated at reflux for 24 h. The reaction mixture was cooled, filtered and concentrated. The residue was purified by column chromatography on silica gel (1% ethyl acetate in hexane as eluant) to give 1.2 g of a clear syrup (20%). The syrup was dissolved in ether, and a solution of HCl in ether was added dropwise to give a white solid. Anal. ( $C_{19}H_{27}N \cdot HCl$ ) C, H, N, Cl.

**cis-1,3,4,9,10,10a-Hexahydro-N,N-dimethyl-4a(2H)-phenanthrenamine (16).** A solution of 12 (1.0 g, 4.65 mmol, free base) in 15 mL of methanol was treated with aqueous formaldehyde (5 mL, 35%) and sodium cyanoborohydride (1.0 g, 15.9 mmol). The resulting solution was stirred overnight, and the solvent was removed. The residue was dissolved in ether and washed with aqueous 1 N NaOH and water. The organic phase was extracted with aqueous 2 N HCl. The aqueous phase was made basic with aqueous 1 N NaOH solution and extracted with ether. The combined ether extracts were dried ( $Na_2SO_4$ ), filtered, and concentrated. The residue was dissolved in ether and treated with isopropanolic HCl to give the title compound (0.81 g, 65%) as a white solid, mp 181–182 °C. Anal. ( $C_{16}H_{23}N \cdot HCl$ ) C, H, N, Cl.

**cis-N-Ethyl-6,6a,7,8,9,10-Hexahydro-10aH-dibenzo[b,d]thiopyran-10a-amine Hydrochloride (47).** A solution of 41 (0.79 g, 3.60 mmol) in 25 mL of  $CH_2Cl_2$  was treated with triethylamine (0.75 g, 7.41 mmol) and (dimethylamino)pyridine (0.05 g) followed by the dropwise addition of acetic anhydride (0.63 g, 6.17 mmol). The resulting solution was diluted with  $CH_2Cl_2$  and washed with 1 N HCl and water. The organic phase was dried ( $Na_2SO_4$ ), filtered, and concentrated. The residue was converted to the title compound by method I to give a white solid (0.74 g, 72%), mp 213–216 °C. Anal. ( $C_{15}H_{21}NS \cdot HCl$ ) C, H, N, Cl.

**cis-(1,3,4,9,10,10a-Hexahydro-4a(2H)-phenanthrenyl)-acetamide (91).** A solution of 8 (0.23 g, 1.14 mmol) in 10 mL of  $CH_2Cl_2$  was treated with acetyl chloride (0.91 g, 12.0 mmol). The reaction mixture was heated at reflux for 15 min and quenched by the addition of water. The organic layer was collected and the aqueous layer was extracted with additional  $CH_2Cl_2$ . The combined organic extracts were dried ( $MgSO_4$ ), filtered, and concentrated to give the title compound (0.26 g, 94%) as a white solid, mp 177 °C.

**cis-1,3,4,9,10,10a-Hexahydro-N-ethyl-4a(2H)-phenanthrenamine Monohydrochloride (17).** The title compound was prepared in 95% yield from 91 (0.26 g, 1.07 mmol) by method I as a white solid, mp 235–237 °C. Anal. ( $C_{16}H_{23}N \cdot HCl$ ) H, N, Cl; C: calcd, 72.32; found, 71.80.

**cis-4b,5,8,9a,10-Hexahydro-4b-amino-3-phenanthrenol (21).** A solution of 26 (0.20 g, 0.87 mmol) in 10 mL of  $CH_2Cl_2$  was treated with  $BBr_3$  (2 mL of a 1 M solution in  $CH_2Cl_2$ ). The resulting solution was stirred at room temperature for 18 h and quenched by the addition of water. Additional  $CH_2Cl_2$  and

aqueous 1 N HCl were added. The aqueous phase was separated and made basic (pH = 10) by the addition of NaHCO<sub>3</sub>. The aqueous phase was extracted with ethyl acetate (5 × 10 mL), and the combined organic extracts were dried (MgSO<sub>4</sub>), filtered, and concentrated. The residue was dissolved in 0.5 N HCl solution and freeze-dried to give the product (90 mg, 41%) as a white solid, mp 156–161 °C. Anal. (C<sub>14</sub>H<sub>17</sub>NO·HCl·0.9H<sub>2</sub>O) C, H, N, Cl.

**cis-4b,5,6,7,8,9,10-Octahydro-4b-(methylamino)-3-phenanthrenol (24).** A solution of 25 (150 mg, 0.61 mmol) in 48% aqueous HBr solution was heated at reflux for 2.5 h. The reaction was poured onto cold aqueous NH<sub>4</sub>OH solution. The resulting solution was extracted with ethyl acetate (3 × 25 mL), dried (MgSO<sub>4</sub>), and filtered. Evaporation of the solvent afforded the product (90 mg, 64%) as a tan solid, mp 191 °C. Anal. (C<sub>15</sub>H<sub>21</sub>NO) H; C: calcd, 77.88; found, 76.51; N: calcd, 6.06; found, 5.57.

**cis-4b,5,6,7,8,9,10-Octahydro-4b-amino-3-phenanthrenol (20).** In a manner similar to that described for the preparation of 24, compound 22 (0.28 g, 1.21 mmol) was converted to the title compound (88 mg, 33%) as a white solid, mp 198–200 °C dec. Anal. (C<sub>14</sub>H<sub>21</sub>NO·0.4H<sub>2</sub>O·0.3EtOAc) C, N; H: calcd, 9.63; found, 8.25.

**(4a*S*-cis)-1,9,10,10a-Tetrahydro-4a(4*H*)-phenanthrene-carboxylic Acid (*R*)-(+)- $\alpha$ -Methylbenzylamine Salt (113).** A solution of 64 (172.2 g, 0.754 mol) in 1000 mL of hot 2-pentanone was treated with (*R*)-(+)- $\alpha$ -methylbenzylamine (91.4 g, 0.754 mol). The resulting solution was cooled to room temperature, and the solid which formed was collected by suction filtration. The solid obtained was recrystallized from hot 2-pentanone (2000 mL) to give the title compound (94.2 g, 36%) as a white solid, mp 179–182 °C. Anal. (C<sub>15</sub>H<sub>18</sub>O<sub>2</sub>·C<sub>9</sub>H<sub>11</sub>N) C, H, N. HPLC analysis indicated that this material was greater than 95% enantiomerically pure.<sup>27</sup>

**(4a*R*-cis)-1,9,10,10a-Tetrahydro-4a(4*H*)-phenanthrene-carboxylic Acid (*S*)-(–)- $\alpha$ -Methylbenzylamine Salt (112).** A solution of enantiomerically enriched 64 (230.9 g, 1.01 mol) in 2000 mL of hot 2-pentanone was treated with (*S*)-(–)- $\alpha$ -methylbenzylamine (122.6 g, 1.01 mol). The resulting solution was cooled, and the solid which formed was collected by filtration. The solid obtained was recrystallized from hot 2-pentanone (2000 mL) to give the title compound (197 g, 56%) as a white solid, mp 179–181 °C. Anal. (C<sub>15</sub>H<sub>18</sub>O<sub>2</sub>·C<sub>9</sub>H<sub>11</sub>N) C, H, N. HPLC analysis indicated that this material was greater than 95% enantiomerically pure.<sup>27</sup>

**(6a*R*-cis)-6,6a,7,10-Tetrahydro-10a-dibenzo[*b,d*]thiopyran-10a-carboxylic Acid (*S*)-(–)- $\alpha$ -Methylbenzylamine Salt (114).** In a manner similar to that described for the preparation of 113, compound 95 (15.0 g, 60.9 mmol) and (*S*)-(–)- $\alpha$ -methylbenzylamine (7.38 g, 60.9 mmol) were converted to the title compound (6.26 g, 28%) as a white solid, mp 202–204 °C. Anal. (C<sub>14</sub>H<sub>14</sub>O<sub>2</sub>S·C<sub>9</sub>H<sub>11</sub>N) C, H, N. HPLC analysis indicated that this material was greater than 95% enantiomerically pure.<sup>27</sup>

**(6a*S*-cis)-6,6a,7,10-Tetrahydro-10a-dibenzo[*b,d*]thiopyran-10a-carboxylic Acid (*R*)-(+)- $\alpha$ -Methylbenzylamine Salt (115).** In a manner similar to that described for the preparation of 113, enantiomerically enriched compound 95 (8.96 g, 36.4 mmol) and (*R*)-(+)- $\alpha$ -methylbenzylamine (4.41 g, 36.4 mmol) were converted to the title compound (6.15 g, 46%) as a white solid, mp 202–204 °C. Anal. (C<sub>14</sub>H<sub>14</sub>O<sub>2</sub>S·C<sub>9</sub>H<sub>11</sub>N) C, H, N. HPLC analysis indicated that this material was greater than 95% enantiomerically pure.<sup>27</sup>

**Methyl (4a*S*-cis)-(1,9,10,10a-Tetrahydro-4a(4*H*)-phenanthrenyl)carbamate (117).** A suspension of 113 (30.0 g, 85.8 mmol) in 300 mL of ether was treated with 200 mL of aqueous 1 N HCl solution. The resulting suspension was stirred until no solid remained. The organic phase was collected, dried (MgSO<sub>4</sub>), and concentrated to give the free acid (19.3 g, 84.5 mmol) as a white solid. The free acid was dissolved in 340 mL of toluene and treated with triethylamine (9.40 g, 93 mmol) and diphenyl phosphorazidate (25.6 g, 93.1 mmol). The resulting solution was heated to reflux for 2 h, cooled slightly, and treated with methanol (150 mL). The resulting solution was heated at reflux for 24 h. The reaction mixture was cooled and concentrated. The residue was dissolved in CHCl<sub>3</sub> (150 mL) and washed with concentrated aqueous NaHCO<sub>3</sub>. The organic phase was dried (MgSO<sub>4</sub>) and concentrated. The residue was purified by chromatography (silica

gel, 10:1 heptane/EtOAc) to give the title compound (19.4 g, 57%) as an oil, [ $\alpha$ ]<sub>D</sub> = –68.1° (c = 1.00, CHCl<sub>3</sub>).

**Methyl (4a*R*-cis)-(1,9,10,10a-Tetrahydro-4a(4*H*)-phenanthrenyl)carbamate (116).** In a manner similar to that described for the preparation of 117, compound 112 (31.77 g, 90.9 mmol) was converted to the title compound (19.5 g, 83%) as an oil, [ $\alpha$ ]<sub>D</sub> = +67.5° (c = 0.92, CHCl<sub>3</sub>).

**Methyl (6a*R*-cis)-(6,6a,7,10-Tetrahydro-10a-dibenzo[*b,d*]thiopyran-10a-yl)carbamate (118).** In a manner similar to that described for the preparation of 117, compound 114 (5.96 g, 16.2 mmol) was converted to the title compound (3.86 g, 86%) as a glassy solid, [ $\alpha$ ]<sub>D</sub> = +19.9° (c = 0.93, CHCl<sub>3</sub>).

**Methyl (6a*S*-cis)-(6,6a,7,10-Tetrahydro-10a-dibenzo[*b,d*]thiopyran-10a-yl)carbamate (119).** In a manner similar to that described for the preparation of 117, compound 115 (5.62 g, 15.3 mmol) was converted to the title compound (3.55 g, 84%) as a foamy solid, [ $\alpha$ ]<sub>D</sub> = –28° (c = 1.23, CHCl<sub>3</sub>).

**Methyl (4a*S*-cis)-(1,3,4,9,10,10a-Hexahydro-4a(4*H*)-phenanthrenyl)carbamate (121).** A solution of 117 (19.17 g, 74.5 mmol) in 200 mL of MeOH was hydrogenated at 51 psi over 5% palladium on carbon for 3.0 h. The reaction mixture was filtered and the filtrate concentrated to give the title compound (18.3 g, 95%) as a waxy solid, [ $\alpha$ ]<sub>D</sub> = +13.4° (c = 1.00, CHCl<sub>3</sub>).

**Methyl (4a*R*-cis)-(1,3,4,9,10,10a-Hexahydro-4a(4*H*)-phenanthrenyl)carbamate (120).** A solution of 116 (19.23 g, 74.7 mmol) in 250 mL of MeOH was hydrogenated at 51 psi over 5% palladium on carbon for 5.0 h. The reaction mixture was filtered and the filtrate concentrated to give the title compound (18.6 g, 96%) as a waxy solid, [ $\alpha$ ]<sub>D</sub> = –10.3° (c = 0.90, CHCl<sub>3</sub>).

**Methyl (6a*R*-cis)-(6,6a,7,8,9,10-Hexahydro-10a-dibenzo[*b,d*]thiopyran-10a-yl)carbamate (122).** A solution of 118 (3.75 g, 13.6 mmol) in 100 mL of MeOH was hydrogenated at 50 psi over 20% palladium on carbon (1.0 g) for 20 h. The reaction mixture was filtered and the filtrate concentrated to give the title compound (3.11 g, 82%) as a yellow solid, [ $\alpha$ ]<sub>D</sub> = –1.3° (c = 0.93, CHCl<sub>3</sub>).

**Methyl (6a*S*-cis)-(6,6a,7,8,9,10-Hexahydro-10a-dibenzo[*b,d*]thiopyran-10a-yl)carbamate (123).** A solution of 119 (3.35 g, 12.2 mmol) in 100 mL of MeOH was hydrogenated at 51 psi over 20% palladium on carbon (1.0 g) for 20 h. The reaction mixture was filtered and the filtrate concentrated to give the title compound (3.2 g, 96%) as a white solid, [ $\alpha$ ]<sub>D</sub> = –12.6° (c = 1.14, CHCl<sub>3</sub>).

**(4a*S*-cis)-1,3,4,9,10,10a-Hexahydro-N-methyl-4a(2*H*)-phenanthrenamine Hydrochloride (14).** The title compound was prepared in 45% yield from 121 (18.3 g, 70.3 mmol) by method I as a white solid, mp 229–231 °C, [ $\alpha$ ]<sub>D</sub> = –21.7° (c = 1.07, CHCl<sub>3</sub>). Anal. (C<sub>15</sub>H<sub>21</sub>N·HCl) C, H, N, Cl.

**(4a*R*-cis)-1,3,4,9,10,10a-Hexahydro-N-methyl-4a(2*H*)-phenanthrenamine Monohydrochloride (13).** The title compound was prepared in 80% yield from 120 (18.4 g, 70.7 mmol) by method I as a white solid, mp 228–231 °C, [ $\alpha$ ]<sub>D</sub> = +21.1° (c = 1.03, CHCl<sub>3</sub>). Anal. (C<sub>15</sub>H<sub>21</sub>N·HCl) C, H, N, Cl.

**(6a*R*-cis)-6,6a,7,8,9,10-Hexahydro-N-methyl-10a*H*-dibenzo[*b,d*]thiopyran-10a-amine Monohydrochloride (44).** The title compound was prepared in 54% yield from 122 (3.11 g, 11.2 mmol) by method I as a white solid, mp 224–227 °C, [ $\alpha$ ]<sub>D</sub> = +42.2° (c = 1.00, CHCl<sub>3</sub>). Anal. (C<sub>14</sub>H<sub>19</sub>NS·HCl) C, H, N, Cl.

**(6a*S*-cis)-6,6a,7,8,9,10-Hexahydro-N-methyl-10a*H*-dibenzo[*b,d*]thiopyran-10a-amine Monohydrochloride (45).** The title compound was prepared in 84% yield from 123 (2.95 g, 10.6 mmol) by method I as a white solid, mp 228–229 °C, [ $\alpha$ ]<sub>D</sub> = –48.3° (c = 1.00, CHCl<sub>3</sub>). Anal. (C<sub>14</sub>H<sub>19</sub>NS·HCl) C, H, N, Cl; calcd, 13.14; found, 12.70.

**[1*R*-(1 $\alpha$ ,2 $\beta$ ,5 $\alpha$ )]-5-Methyl-2-(1-methylethyl)cyclohexyl (4a*R*-cis)-(1,9,10,10a-Tetrahydro-4a(4*H*)-phenanthrenyl)carbamate (124) and [1*R*-(1 $\alpha$ ,2 $\beta$ ,5 $\alpha$ )]-5-Methyl-2-(1-methylethyl)cyclohexyl (4a*S*-cis)-(1,9,10,10a-Tetrahydro-4a(4*H*)-phenanthrenyl)carbamate (125).** A solution of the isocyanate 69 (14.0 g, 62.1 mmol) and (1*R*,2*S*,5*R*)-(–)-menthol (10.7 g, 68 mmol) in 200 mL of toluene was refluxed for 22 h. Chromatography yielded unreacted isocyanate and a mixture of the isocyanate and product. These were recombined and refluxed overnight. Additional menthol (1.13 g) was added, and refluxing continued for 7 h. The solvent was evaporated, and the residue was purified by chromatography (silica gel, 3% ethyl acetate in hexane) to give a high *R<sub>f</sub>* diastereomer 124 and a low *R<sub>f</sub>*

diastereomer 125. The high  $R_f$  diastereomer 124 was chromatographed one additional time to give pure 124 (4.87 g, 21%) as a white solid, mp 155–158 °C,  $[\alpha]_D^{25} = +15.4^\circ$  ( $c = 1.03$ ,  $\text{CHCl}_3$ ). Anal. ( $\text{C}_{25}\text{H}_{36}\text{N}_2\text{O}_2$ ) C, H, N.

**(4a*R*-cis)-1,9,10,10a-Tetrahydro-4a(4*H*)-phenanthrenamine Monohydrochloride (9).** A solution of 124 (4.87 g, 12.8 mmol) was converted to [1*R*-(1 $\alpha$ ,2 $\beta$ ,5 $\alpha$ )]-5-methyl-2-(1-methylethyl)cyclohexyl (4a*R*-cis)-(1,3,4,9,10,10a-tetrahydro-4a(2*H*)-phenanthrenyl)carbamate (2.01 g, 5.24 mmol) by method E as a white solid, mp 206–210 °C,  $[\alpha]_D^{25} = -42.1^\circ$  ( $c = 1.05$ ,  $\text{CHCl}_3$ ). Anal. ( $\text{C}_{25}\text{H}_{37}\text{NO}_2$ ) C, H, N. This material was converted to the title compound in 61% yield by method G as a white solid, mp 247–248.5 °C,  $[\alpha]_D^{25} = -42.1^\circ$  ( $c = 1.05$ ,  $\text{CHCl}_3$ ). Anal. ( $\text{C}_{14}\text{H}_{19}\text{N}\cdot\text{HCl}\cdot 0.5\text{Et}_2\text{O}$ ) C, H, N, Cl.

**(4a*S*-cis)-1,9,10,10a-Tetrahydro-4a(4*H*)-phenanthrenamine Monohydrochloride (10).** In a manner similar to that described for the preparation of amine 9, compound 125 (0.83 g, 2.17 mmol) was converted to the title compound. Anal. ( $\text{C}_{14}\text{H}_{19}\text{N}\cdot\text{HCl}\cdot 0.25\text{Et}_2\text{O}$ ) C, H, N, Cl.

**cis-1,3,4,9,10,10a-Hexahydro-9-oxo-4a(2*H*)-phenanthrenecarboxylic Acid (126).** A solution of 67 (42.0 g, 0.182 mol) in 900 mL of glacial acetic acid was treated with a solution of chromium trioxide (91.0 g, 0.912 mol) in 850 mL of glacial acetic acid and 50 mL of water. The reaction mixture was stirred at room temperature for 5 h and concentrated. The residue was partitioned between benzene and water. The aqueous layer was saturated with NaCl and extracted with additional benzene. The combined organic extracts were dried ( $\text{MgSO}_4$ ), filtered, and concentrated to give a brown solid (37.0 g). The solid was suspended in 150 mL of ethyl acetate. The resulting material was dried under vacuum to give the title compound (21.0 g, 47%) as a white solid.

**cis-2,3,4,4a,10,10a-Hexahydro-4a-isocyanato-9(1*H*)-phenanthrene (127).** A solution of 126 (1.0 g, 4.1 mmol) and triethylamine (0.6 g, 5.93 mmol) in 30 mL of toluene was treated with diphenyl phosphorazidate (1.25 g, 4.5 mmol) and heated to reflux for 30 min. The reaction mixture was cooled and concentrated. The residue was purified by chromatography (silica gel, hexane) to give the product (0.65 g, 66%) as a yellow syrup.

**Methyl cis-(1,3,4,9,10,10a-Hexahydro-9-oxo-4a(2*H*)-phenanthrenyl)carbamate (128).** A solution of 127 (0.44 g, 1.82 mmol) in 15 mL of methanol was heated at reflux for 24 h. The reaction mixture was concentrated and purified by chromatography (silica gel, 20:1 hexane/ethyl acetate) to give the product (0.42 g, 84%) as a white solid.

**cis-1,2,3,4,4a,9,10,10a-Octahydro-4a-(methylamino)-9-phenanthrenol Hydrochloride (35).** The title compound was prepared in 29% yield from 128 (0.39 g, 1.43 mmol) by method I as a tan solid, mp 201–205 °C. Anal. ( $\text{C}_{16}\text{H}_{21}\text{NO}\cdot\text{HCl}$ ) C, H, N.

**2-(Trimethylsilyl)ethyl cis-(1,3,4,9,10,10a-Hexahydro-9-oxo-4a(2*H*)-phenanthrenyl)carbamate (129).** A solution of 127 (0.6 g, 2.5 mmol) and (trimethylsilyl)ethanol (10 mL) was heated at 60 °C overnight. The reaction mixture was concentrated and the residue purified by chromatography (silica gel, 20:1 hexane/ethyl acetate) to give the product (0.54 g, 60%) as an oil.

**cis-4a-Amino-2,3,4,4a,10,10a-hexahydro-9(1*H*)-phenanthrene Hydrochloride (36).** The title compound was prepared in 37% yield from 129 (0.54 g, 1.5 mmol) by method H, mp 252–254 °C. Anal. ( $\text{C}_{14}\text{H}_{17}\text{NO}\cdot\text{HCl}$ ) C, H, N, Cl.

**3,4,5,6a,6,7-Hexahydro-4-iodo-1*H*-3,11b-methanonaphth[1,2-*c*]oxepin-1-one (130).** A mixture of 64 (10.0 g, 44 mmol) and sodium bicarbonate (4.0 g, 48 mmol) in 150 mL water was heated on a steam bath until a solution was obtained. The resulting solution was treated with a solution of potassium iodide (14.6 g, 88 mmol) and iodine (22.4 g, 88 mmol) in 150 mL of water. The reaction mixture was transferred to a separatory funnel and shaken with aqueous sodium bisulfate solution and the extracted into  $\text{CH}_2\text{Cl}_2$ . The combined organic extracts were dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated to give the title compound (13.7 g, 88%) as a yellow solid.

**3,4,5,6a,6,7-Hexahydro-1*H*-3,11b-methanonaphth[1,2-*c*]oxepin-1-one (131).** A solution of 130 (13.5 g, 38 mmol) in THF was hydrogenated at 50 psi with 10% Pd-C to give the product (2.6 g, 30%) as a white crystalline solid.

**1,3,4,9,10,10a-Hexahydro-3-hydroxy-4a(2*H*)-phenanthrenecarboxylic Acid Hydrazide (132).** A solution of 131

(6.0 g, 26 mmol) in 150 mL of methanol was treated with 15 mL of hydrazine and 15 mL of acetic acid. The resulting solution was heated at reflux for 24 h. The reaction mixture was concentrated, and the residue was dissolved in  $\text{CH}_2\text{Cl}_2$  and washed with water. The organic phase was dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated to give the product (6.3 g, 92%).

**1,3,4,9,10,10a-Hexahydro-3-hydroxy-4a(2*H*)-phenanthrenecarboxamide (133).** A solution of 132 (5.0 g, 19 mmol) in 200 mL of ethanol was treated with Raney nickel (10 g) and heated at reflux overnight. The reaction mixture was filtered and the filtrate concentrated. The residue was crystallized from heptane/toluene to give the product (3.4 g, 73%).

**4,5,6,6a,7,8-Hexahydro-4,12b-methano-12*bH*-naphth[1,2-*d*] [1,3]oxazocin-2(1*H*)-one (134).** A solution of 133 (2.44 g, 10 mmol) in 30 mL of methanol was cooled to 0 °C and treated with sodium metal (0.46 g, 20 mmol). After dissolution of the sodium the resulting solution was treated with bromine (1.6 g, 10 mmol) in portions and stirred overnight at room temperature. The reaction mixture was quenched by the addition of aqueous sodium bisulfate solution and extracted into  $\text{CH}_2\text{Cl}_2$ . The combined organic extracts were dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated to give the product (1.4 g, 58%) as a white solid.

**cis-1,2,3,4,4a,9,10,10a-Octahydro-4a-(methylamino)-3-phenanthrenol (37).** The title compound was prepared in 37% yield from 134 (0.54 g, 2.2 mmol) by method I, mp 141–143 °C. Anal. ( $\text{C}_{15}\text{H}_{21}\text{NO}\cdot 0.1\text{H}_2\text{O}$ ) C, H, N.

**Methyl cis-2-Cyano-1,3,4,9,10,10a-hexahydro-4a(2*H*)-phenanthrenecarboxylate (136).** A solution of 135 (2.5 g, 9.7 mmol) in 100 mL of anhydrous THF was treated with diethyl cyanophosphonate (4.4 mL, 29 mmol) and lithium cyanide (0.96 g, 29 mmol), and stirred for 2 h. The reaction was quenched with 100 mL  $\text{H}_2\text{O}$  and extracted with 1:1 hexane/ethyl acetate ( $2 \times 150$  mL). The combined organic layers were washed with saturated aqueous NaCl solution and dried over sodium sulfate. The intermediate cyanohydrin phosphate (4.9 g) and *tert*-butyl alcohol (0.72 g, 9.7 mmol) in 20 mL of THF were added to a solution of freshly prepared samarium diiodide (44.6 mmol) in 100 mL of THF. After being stirred for 3 h at room temperature the reaction mixture was poured into 10% aqueous HCl solution and extracted with ether ( $2 \times 150$  mL). The combined organic extracts were sequentially washed with 5% aqueous  $\text{Na}_2\text{S}_2\text{O}_3$  and saturated aqueous NaCl solution. The organic phase was dried ( $\text{MgSO}_4$ ), filtered, and concentrated. The residue was purified by chromatography (silica gel, 10:1 hexane/ethyl acetate) to provide 137 ( $R_f = 0.48$ ) (0.27 g, 10%) mp 132–134 °C, and a slower moving diastereomer ( $R_f = 0.37$ ) (1.84 g, 77%), mp 122–125 °C. Anal. ( $\text{C}_{17}\text{H}_{19}\text{NO}_2$ ) C, H, N.

**cis-2-Cyano-1,3,4,9,10,10a-hexahydro-4a(2*H*)-phenanthrenecarboxylic Acid (138).** The title compound was prepared in 96% yield from 136 (15.5 g, 57.6 mmol) by method C as a white foam, mp 70–80 °C.

**Methyl cis-(2-Cyano-1,3,4,9,10,10a-hexahydro-4a(2*H*)-phenanthrenyl)carbamate (139).** The title compound was prepared in 51% yield from 138 (1.63 g, 6.38 mmol) and methanol by method F as a white foam.

**(2*a*,4*a*,10*a*)-4a-Amino-1,2,3,4,4a,9,10,10a-octahydro-2-phenanthrenemethanamine (39).** A solution of 139 (0.35 g, 1.23 mmol) in 50 mL of methanolic ammonia was treated with RaNi (0.5 g) and hydrogenated at 50 psi for 24 h. The reaction mixture was filtered and the filtrate concentrated. The residue was dissolved in aqueous 1 N HCl solution and extracted with ether. The organic phase was washed with saturated aqueous NaCl solution, dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated. The residue (0.21 g) was dissolved in 20 mL of THF and treated with potassium trimethylsilanolate (0.19 g, 1.50 mmol) and stirred at room temperature overnight. The reaction mixture was concentrated, and the residue was dissolved in aqueous 1 N HCl solution. The aqueous phase was washed with ether, made basic with aqueous 1 N NaOH solution, and extracted with ether. The combined organic extracts were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. The residue was dissolved in ether and then treated with an ethereal HCl solution to give the title compound (0.23 g, 79%) as a white solid, mp >265 °C. Anal. ( $\text{C}_{15}\text{H}_{22}\text{N}_2\cdot 2\text{HCl}$ ) C (calcd 59.41, found 59.83), H, N; Cl: calcd 23.38; found 22.54.

**(2*a*,4*a*,10*a*)-1,2,3,4,4a,9,10,10a-Octahydro-4a-(methylamino)-2-phenanthrenemethanamine (40).** A suspension of lithium aluminum hydride (0.16 g, 4.2 mmol) in 40



mL of ether was treated with a suspension of 139 (0.39 g, 1.38 mmol) in ether and stirred for 10 min at room temperature. Additional LAH (0.1 g) was added, and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was quenched by the sequential addition of 0.25 mL of water, 0.25 mL of aqueous 12.5% NaOH, and 0.5 mL of water. The resulting suspension was filtered, and the filtrate was extracted with aqueous 1 N HCl solution. The aqueous phase was made basic with aqueous 1 N NaOH solution and extracted with ether. The combined organic extracts were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. The residue was dissolved in ether and treated with an ethereal HCl solution to give a flocculant precipitate which was collected by filtration and washed with ether followed by hexane and then dried to give the title compound (0.175 g, 40%) as white solid. The solid obtained was dissolved in methanol and added to ether to give an analytical sample, mp >150 °C. Anal. ( $\text{C}_{18}\text{H}_{22}\text{N}_2\cdot 2\text{HCl}$ ) H; C: calcd, 60.57; found 61.19; N: calcd, 8.83; found, 8.35; Cl: calcd, 22.34; found 21.16.

(2 $\alpha$ ,4 $\alpha$ ,10 $\alpha$ )-4a-Amino-1,2,3,4,4a,9,10,10a-octahydro-2-phenanthrenecarbonitrile (38). A solution of 139 (0.16 g, 0.56 mmol) in 15 mL of THF was treated with potassium trimethylsilylanolate and heated at reflux for 3.5 h. The reaction mixture was concentrated, and the residue was dissolved in aqueous 1 N HCl solution and washed with ether. The aqueous phase was made basic with aqueous 1 N NaOH solution and extracted with ether. The combined organic extracts were dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated. The residue was dissolved in ether and treated with an ethereal HCl solution. The precipitate which formed on standing was collected by suction filtration to give the title compound as a white solid, mp 242–244 °C. Anal. ( $\text{C}_{18}\text{H}_{18}\text{N}_2\cdot \text{HCl}$ ) C, H, N, Cl.

3',4'-Dihydrospiro[cyclopentane-1,2'-(1',4')-naphthalen]-1-one Oxime (143). A solution of 141 (8.6 g, 43.0 mmol), hydroxylamine hydrochloride (3.68 g, 57 mmol), and pyridine (4.6 mL, 57 mmol) was dissolved in absolute ethanol (250 mL) and refluxed for 24 h. The ethanol was concentrated, and the residue was partitioned between water and  $\text{CH}_2\text{Cl}_2$ . The organic layer was washed with 0.5 N HCl (3  $\times$  75 mL) and water (75 mL). The organic layer was dried ( $\text{MgSO}_4$ ), filtered, and concentrated. The residue was purified by chromatography (silica gel, gradient elution, 5–20% ethyl acetate/petroleum ether) to give the product (2.1 g, 23%) as a white solid, mp 92–94 °C. Anal. ( $\text{C}_{14}\text{H}_{17}\text{NO}$ ) C, H, N.

8,9-Dihydro-6H-benzocycloheptanespiro-6,1'-cyclopentane-5-one Oxime (142). A solution of 140 (9.33 g, 43 mmol), hydroxylamine hydrochloride (3.68 g, 57 mmol), and pyridine (4.6 mL, 57 mmol) was refluxed in absolute ethanol for 24 h. The reaction mixture was treated as in the preparation of 143 to give a white solid (9.86 g, 42%), mp 124–130 °C. Anal. ( $\text{C}_{15}\text{H}_{19}\text{NO}$ ) C; H: calcd 8.35; found, 8.91; N: calcd, 6.11; found, 5.37.

3',4'-Dihydrospiro[cyclopentane-1,2'-(1'H)-naphthalen]-1-amine Monohydrochloride (56). A solution of 143 (1.99 g, 9.2 mmol) and Raney nickel (2.0 g) in 100 mL of methanolic ammonia was hydrogenated at 53 psi for 38 h. The reaction was filtered, and the filtrate was concentrated. The residue was purified by chromatography (silica gel, gradient elution 5–50% ethyl acetate/petroleum ether) to yield the free amine as a clear oil (1.57 g). The amine was dissolved in ether (25 mL) and 3–5 drops of concentrated HCl was added. The solvent was evaporated, and the residue was recrystallized from methanol/ethyl ether to give the product (0.52 g, 24%) as a white solid, mp 273–275 °C. Anal. ( $\text{C}_{14}\text{H}_{19}\text{N}\cdot \text{HCl}$ ) C, H, N, Cl.

5,7,8,9-Tetrahydro-6H-benzocycloheptanespiro-6,1'-cyclopentane-5-amine Hydrochloride (55). The oxime 142 (3.45 g, 15 mmol) and Raney nickel (3 g) was treated as in the preparation of 56 and then hydrogenated an additional 39 h at 40 °C. The solvent was removed in vacuo, and the residue was partitioned between methylene chloride and 0.5 N HCl. The aqueous layer was basified with 5% sodium carbonate and extracted with methylene chloride. The methylene chloride fractions were combined, dried, and concentrated to a white solid (3.2 g). The solid was purified by silica gel chromatography (2:1 petroleum ether/ethyl acetate; ethyl acetate; then 9:1 ethyl acetate/ethanol as eluants in a step gradient). The solid (1.7 g, 44%) was recrystallized from an ether/methanol solution to give the amine hydrochloride 55 (0.67 g), mp 240–242 °C. Anal. ( $\text{C}_{15}\text{H}_{21}\text{N}\cdot \text{HCl}$ ) C, H, N, Cl.

3',4'-Dihydro-N-methylspiro[cyclopentane-1,2'-(1'H)-naphthalen]-1'-amine Monohydrochloride (57). A solution of 56 (0.77 g, 3.8 mmol) and di-*tert*-butyl dicarbonate (0.9 g, 5.2 mmol) were dissolved in  $\text{CH}_2\text{Cl}_2$  (50 mL) and refluxed for 7 h, cooled to room temperature, and stirred for 2.5 days. The solvent was concentrated, and the residue was purified by chromatography (silica gel, 1:1 petroleum ether/ $\text{CH}_2\text{Cl}_2$ ). The resulting carbamate (1.05 g, 3.5 mmol) was dissolved in ether (50 mL) and was added dropwise to a suspension of LAH (1.33 g, 35 mmol) in 75 mL of ether. The reaction was stirred at room temperature for 24 h. The reaction was quenched by the sequential addition of water (1.3 mL), 12.5% aqueous NaOH (1.3 mL), and water (2.9 mL). The aluminum salts were removed by filtration, and the filtrate was concentrated. The residue was purified by chromatography (silica gel, petroleum ether) to give the amine. The amine was dissolved in ether and treated with concentrated HCl to provide the title compound (0.14 g, 15%) as a white solid, mp 255–256 °C. Anal. ( $\text{C}_{15}\text{H}_{21}\text{N}\cdot \text{HCl}$ ) C, H, N, Cl.

1'-Azido-1-methylspiro[cyclopentane-1,2'-(1'H)-naphthalene] (145). A solution of methylmagnesium bromide (3.0 M in ether, 20 mL) was cooled to 0 °C and treated with 141 (6.0 g, 30 mmol) in 25 mL of ether. The reaction mixture was warmed to room temperature and stirred for an additional 3.5 h. The reaction mixture was cooled to 0 °C, and saturated aqueous  $\text{NH}_4\text{Cl}$  was added. The organic layer was collected, and the aqueous layer was extracted with additional ether (3  $\times$  50 mL). The combined organic extracts were dried ( $\text{MgSO}_4$ ) and concentrated to provide the alcohol 144 (6.25 g). The alcohol 144 (1.9 g) was dissolved in  $\text{CHCl}_3$  and added dropwise to a solution of trifluoroacetic acid (1.36 mL, 17.6 mmol) and sodium azide (1.14 g, 17.6 mmol) in  $\text{CHCl}_3$  (100 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 4 h and then warmed to room temperature for 11 h. The reaction was quenched with concentrated  $\text{NH}_4\text{OH}$  (10 mL), and the reaction mixture was partitioned between water and  $\text{CH}_2\text{Cl}_2$ . The organic layer was dried ( $\text{MgSO}_4$ ), filtered, and concentrated. The residue was purified by chromatography (silica gel, petroleum ether) to afford the product (1.74 g, 76% from 141) as a clear oil. Anal. ( $\text{C}_{15}\text{H}_{19}\text{N}_3$ ) C, H, N.

3',4'-Dihydro-1-methylspiro[cyclopentane-1,2'-(1'H)-naphthalen]-1-amine (58). A solution of 145 (0.76 g, 3.2 mmol) was dissolved in 1:1 methanol/THF and hydrogenated for 4 h at 53 psi. The reaction was filtered, and the solvent was removed under reduced pressure to yield the free amine as a clear oil. The amine was dissolved in ether and 2 drops of concentrated HCl was added. The solvent was removed under reduced pressure, and the foam was crystallized from ether/petroleum ether to give the product (0.51 g, 63%) as a white solid, mp 190–192 °C. Anal. ( $\text{C}_{15}\text{H}_{21}\text{N}\cdot \text{HCl}$ ) C, H, N, Cl.

3',4'-Dihydro-N,1-dimethylspiro[cyclopentane-1,2'-(1'H)-naphthalen]-1-amine (59). A solution of 58 (0.79 g, 3.7 mmol) was reacted with di-*tert*-butyl dicarbonate (0.8 g, 4.6 mmol), and the resulting carbamate was reduced with LAH using the procedure described for the preparation of 57. The hydrochloride salt was obtained as a white solid (0.78 g, 80%), mp 241–243 °C. Anal. ( $\text{C}_{16}\text{H}_{23}\text{N}\cdot \text{HCl}$ ) C, H, N, Cl.

(4a*R*-*cis*)-1,3,4,9,10,10a-Hexahydro-N-methyl-4a(2H)-phenanthrenamine Monohydrochloride Mandelic Acid Salt (13). (S)-(+)-Mandelic acid (0.06 mg, 0.39 mmol) was dissolved in isopropyl alcohol and treated with an ethereal solution of the free base of 13. The solution was evaporated to give a syrup. The syrup was redissolved in ether, diluted with hexane, and evaporated slowly to give colorless needles (mp 174–176 °C). Anal. ( $\text{C}_{15}\text{H}_{21}\text{N}\cdot \text{C}_8\text{H}_8\text{O}_3$ ) C, H, N.

Crystal Structure Determination of 13 (Mandelic Acid Salt). Crystals of the title compound belonging to the orthorhombic space group  $P2_12_12_1$  were obtained by slow evaporation of a solution in ethanol. Intensity data were collected on an Enraf-Nonius CAD-4 automatic diffractometer. The crystal data and data collection details are provided in Table III. The NRCCAD programs were used for centering, indexing, and data collection. The unit-cell dimensions were obtained by least-squares fit of 24 well-centered reflections in the range  $30^\circ \leq 2\theta \leq 50^\circ$ . Reflections were measured with a constant speed of 2 deg  $\text{min}^{-1}$ . During data collection, the intensities of two standard reflections were monitored every 100 reflections. No decay was observed.

Table III. Crystallographic Details for PD 138289 (13)

formula	C <sub>15</sub> H <sub>21</sub> N·C <sub>8</sub> H <sub>9</sub> O <sub>3</sub>
<i>M</i>	367.48
space group	<i>P</i> 2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>
<i>a</i> /Å	9.9883(10)
<i>b</i> /Å	12.3017(10)
<i>c</i> /Å	16.3047(10)
<i>V</i> /Å <sup>3</sup>	2003.4(3)
<i>Z</i>	4
<i>D</i> <sub>c</sub> /g cm <sup>-3</sup>	1.215
linear abs coeff, mm <sup>-1</sup>	0.07
<i>T</i> /K	298
crystal size/mm <sup>3</sup>	0.10 × 0.05 × 0.30
radiation	graphite monochromated Mo Kα (λ = 0.709 30 Å)
collection range	(0 ≤ <i>h</i> ≤ 9, 0 ≤ <i>k</i> ≤ 7, 0 ≤ <i>l</i> ≤ 12)
2θ limits	2° ≤ 2θ ≤ 48°
scan type	ω - 2θ
scan width/deg	1.0 + 0.35 tan θ
scan speed/deg min <sup>-1</sup>	2
background time/scan time	0.33
data collected	2087
unique data	1860
unique data with <i>F</i> <sub>o</sub> <sup>2</sup> ≤ 2.0σ( <i>F</i> <sub>o</sub> <sup>2</sup> )	1067
no. of variables	230
<i>R</i> ( <i>F</i> )	0.062
<i>R</i> <sub>w</sub> ( <i>F</i> )	0.022
weighting factor, <i>w</i>	σ <sub>F</sub> <sup>-2</sup>
goodness of fit <sup>a</sup>	2.283
maximum Δ/ <i>σ</i>	0.06

<sup>a</sup> Goodness of fit = [(Σ<sub>*i*</sub>{*w*<sub>*i*</sub>(|*F*<sub>o*i*</sub> - |*F*<sub>c*i*</sub>||)}<sup>2</sup>]/(no. of reflections - no. of parameters)].<sup>1/2</sup>

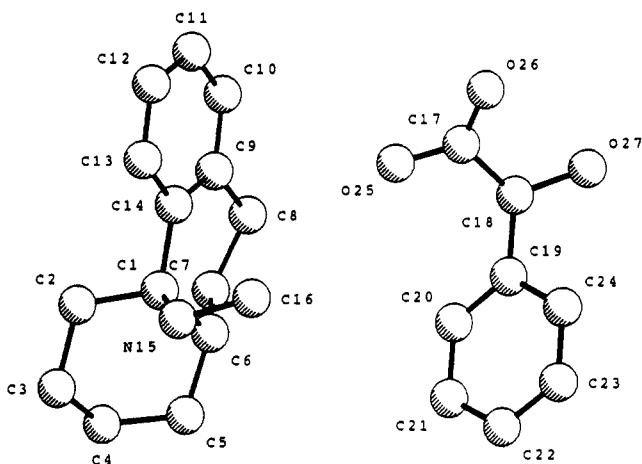


Figure 4. The numbering scheme used to describe the X-ray coordinates is shown along with the PLUTO view of 13 as its (*S*)-(+)-mandelic acid salt. For orientation purposes, in this numbering scheme, C-4a of the phenanthrene structure is numbered C1 and the angular amine is N15.

The structure was solved by direct methods and refined by full-matrix least-squares using the NRCVAX programs.<sup>49,50</sup> No absorption correction was applied. Hydrogen positions were calculated. The final refinement did not include anisotropic thermal parameters for non-hydrogen atoms. At convergence, the final discrepancy indices on *F* were *R*<sub>w</sub>(*F*) = 0.022 for the 1038 reflections with *F*<sub>o</sub><sup>3</sup> > 2.5σ(*F*<sub>o</sub><sup>2</sup>) and 230 variables.<sup>51</sup> The residual positive and negative electron density in the final map was +0.26 and -0.32 e Å<sup>-3</sup>, respectively.

**Solid-State Molecular Structure.** Intramolecular distances and angles are given in Table IV (supplementary material), as well as the fractional coordinates and *B* values for nonhydrogen atoms in Table V (supplementary material). The numbering scheme is shown along with the PLUTO view of the molecule in Figure 4.

**Crystal Packing.** Packing is assumed by H bonds, between O26 carboxylic oxygens of the mandelic acid and the N15 nitrogen of the base (2.984(5) Å) and between the O27 hydroxyl oxygen atoms as donors and O26 carboxylic oxygens as acceptor (2.571(6) Å).

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**Supplementary Material Available:** Additional information is available describing the X-ray structure determination of 13 in Tables IV and V (intramolecular distances and angles and the fractional coordinates and *B* values for non-hydrogen atoms) (4 pages). Ordering information is given on any current masthead page.

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