Centrally Acting Serotonergic and Dopaminergic Agents. 2. Synthesis and Structure–Activity Relationships of 2,3,3a,4,9,9a-Hexahydro-1*H*-benz[*f*]indole Derivatives

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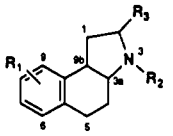
The conformationally restricted linear tricyclic analogs of 5- and 8-hydroxy-2-(di-*n*-propylamino)-tetralins were investigated for their serotonergic and dopaminergic properties. These *cis* and *trans* analogs of 2,3,3a,4,9,9a-hexahydro-1*H*-benz[*f*]indole (**3**), where a five-membered ring is fused between the nitrogen and C-3 carbon of 2-aminotetralin, were synthesized from 5-methoxy- and 8-methoxytetralones. The enantiomers of *trans*-5-methoxy-*N*-*n*-propyl and -*N*-allyl analogs were obtained via fractional recrystallization of their di-*p*-toluoyl-L(or D)tartaric acid salts. All analogs were evaluated in the in vitro 5-HT_{1A} and D_2 binding assays and selected analogs were investigated further in biochemical and behavioral tests. In the 5-substituted series (R_1 in **3**), the trans isomers were found to possess higher levels of pharmacological activity then the corresponding cis isomers. The *trans*-5-methoxy analogs showed selective 5-HT_{1A} receptor activity in vitro but displayed mixed 5-HT_{1A} and D_2 agonist properties in vivo. The corresponding *trans*-5-hydroxy analogs were found to be potent D_2 agonists with full intrinsic activity. An examination of nitrogen substitution (R_2 in **3**) revealed that analogs with either an allyl or an *n*-propyl group displayed equipotent activities. Substitution with a cyclopropylmethyl or benzyl group resulted in reduced activity. Among the resolved analogs tested, the activity was found to reside exclusively in the (3a*S*)-(−)-enantiomers. In the 8-substituted series (R_1 in **3**), only 8-methoxy-*N*-allyl analogs were synthesized and evaluated. In this case, both cis and trans isomers showed equally weak in vitro 5-HT_{1A} receptor agonist activity devoid of dopaminergic effects. The presence of an additional methyl group at the C-2 position (R_3 in **3**) of the *cis*-(±)-8-methoxy-*N*-*n*-propyl analog resulted in enhancement of in vitro 5-HT_{1A} receptor binding affinity, with the (2β,3aα,9aα)-(±)-isomer displaying potency 35 times greater than the (2α,3aα,9aα)-(±)-isomer.

Introduction

In an earlier report on the structure–activity relationships (SAR) of 2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]indole



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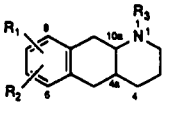

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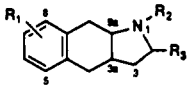

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derivatives (**1**), we demonstrated that the more rigid five/six fused angular tricyclic 2-aminotetralins indeed show interesting pharmacological properties.[1] In this series, we found that the cis analogs are more potent than the corresponding trans analogs. Analogs with 9-methoxy substitution (R_1) showed mixed 5-HT_{1A} receptor agonist and dopamine receptor antagonist activities whereas analogs with 9-hydroxy substitution displayed selective 5-HT_{1A} receptor agonist activity. Nitrogen substitution (R_2) with either an *n*-propyl or an allyl group produced potent activities. However, substitution with an α-methylbenzyl group resulted in loss of activity. In contrast, analogs with 6-methoxy or 6-hydroxy substitution (R_1) showed dopamine antagonist properties. In this case, the activity was displayed only by analogs with a *N*-allyl substitution. We demonstrated also that analogs with an additional methyl group (R_3) at the C-2 position of the 9-methoxy cis series showed potent 5-HT_{1A} agonist activity.

In the linear tricyclic series, Cannon et al., reported the SAR work on the conformationally restricted trans analogs of 1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline derivatives (**2**).[2] In this series, the dopamine-derived analogs with 7,8-dihydroxy, 6,7-dihydroxy, 6,8-dihydroxy, and 6,9-dimethoxy substitutions (R_1 and R_2) on the aromatic ring were synthesized and examined. They found that 6,7-dihydroxy analogs in a catechol pattern and 6,9-dimethoxy analogs displayed dopaminergic activity. Later, Hacksell et al.,[3a] reported the synthesis of cis- and trans-isomers of 6- and 9-methoxy-substituted analogs. Seiler et al.,[3b] then described the SAR of monohydroxylated analogs of **2**. They found that the *trans*-6-hydroxy-*N*-*n*-propyl analogs of **2** displayed dopaminergic activity whereas the corresponding 8-hydroxy analogs were inactive. When the *trans*-6-hydroxy analog was resolved, activity was found to reside in the (4a*R*,10a*R*)-(−)-enantiomer. They also concluded

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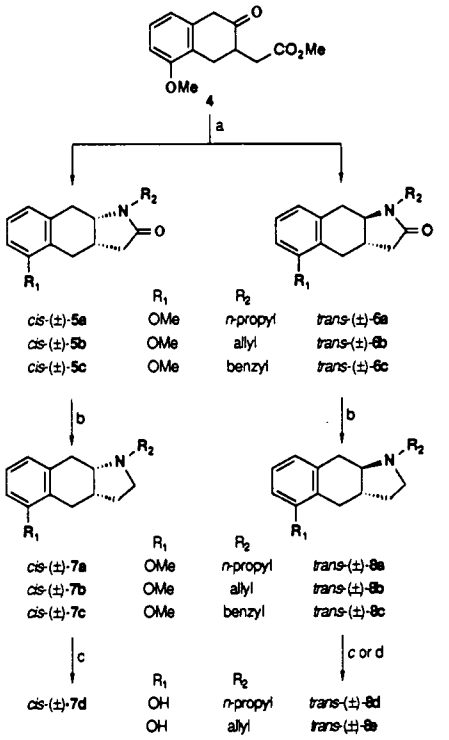
that all cis analogs were completely inactive. For the nitrogen substitution (R_3), both Cannon et al.[2] and Seiler et al.,[3b] showed that among the *n*-alkyl groups examined, optimum activity was found with an *n*-propyl group. These SAR results show a similar trend to that reported in the 2-aminotetralin series where the position of hydroxy or methoxy aromatic substitution, the size of *N*-alkyl substitution, and the nature of the chirality in the molecule all affect serotonergic and dopaminergic activity.[4] For example, the authors[4a-c] demonstrated that 8-hydroxy-2-(di-*n*-propylamino)tetralin(8-OH-DPAT) is a potent, selective 5-HT_{1A} receptor agonist whereas the corresponding 5-hydroxy analog (5-OH-DPAT) is a potent dopamine receptor agonist.

Since our previous SAR study on angular tricyclic analogs (1) showed that a more rigid five/six fused ring structure could indeed improve their pharmacological profile, we thought it would be interesting to examine similar analogs in the linear tricyclic series. Analogs represented by the generic structure **3**, 2,3,3a,4,9,9a-hexahydro-1*H*-benz[*f*]indole derivatives, would be more conformationally restricted than six/six fused ring analogs **2**. These rigid congeners of dopamine could possibly lead to more selective and potent dopaminergic agents. We expected that the cis and trans isomers of **3**, as well as their enantiomers, would have a pronounced effect on the biological activity by varying the methoxy or hydroxy substitution (R_1) at C-8 or C-5 on the aromatic ring. It would also be desirable to examine the effect of varying the nitrogen substitution (R_2) with *n*-propyl, allyl, cyclopropylmethyl, or benzyl group on the biological activity. In addition, since the presence of a methyl group (R_3) at C-2 on the pyrrolidine ring in the angular tricyclic series (1) gave an enhancement of biological activity, we also investigated the effect of an additional methyl group (R_3) in the linear tricyclic series (**3**). In this report we describe the synthesis and biological evaluation of some selected analogs as represented by the generic structure **3**. Initially, these analogs were tested in the in vitro 5-HT_{1A} and D_2 binding assays. The analogs with interesting binding properties were then evaluated further for their biochemical and behavioral effects.

Chemistry

The synthesis of the 5-methoxy and 5-hydroxy analogs of **3** was carried out with keto ester **4** as the starting material. This keto ester was originally synthesized by Aristoff et al., in five steps from 5-methoxy-2-tetralone.[5] As shown in Scheme I, this keto ester was reacted with excess amines such as *n*-propylamine, allylamine, or benzylamine using the well-established Borch procedure to give a mixture of *cis*/*trans*-lactams in 60–85% yield.[6] These lactams, *cis*-(±)-**5a**/**5b**/**5c** and *trans*-(±)-**6a**/**6b**/**6c**, were readily separable by chromatography and isolated in 3.5–4.5 to 1 ratio. The assignment of the major product as the cis isomer was based on 500-MHz ^1H NMR decoupling experiments (see the Experimental Section). As illustrated in the case of the (±)-**5a**/(±)-**6a** pair, the less polar product (11%) showed the coupling constant for C-9a (δ 3.48–3.32) and C-3a protons to be 9.93 Hz, indicating they are diaxial, assigning this compound as *trans*-(±)-**6a**. The decoupling experiment of the more polar product (49%) did not resolve the peaks but showed a small coupling constant for C-9a (δ 4.01–3.92) and C-3a protons, indicating they are equatorial–axial, assigning this compound as *cis*-(±)-**5a**. The correct assignment of

Scheme I[a]



[a] Reagents and conditions: (a) *n*-propylamine, allylamine, or benzylamine; HOAc, $NaCNBH_3$, THF/MeOH; (b) LAH/THF, Δ; (c) 48% HBr, Δ; (d) Ph_2PH, *n*-BuLi, THF, Δ.

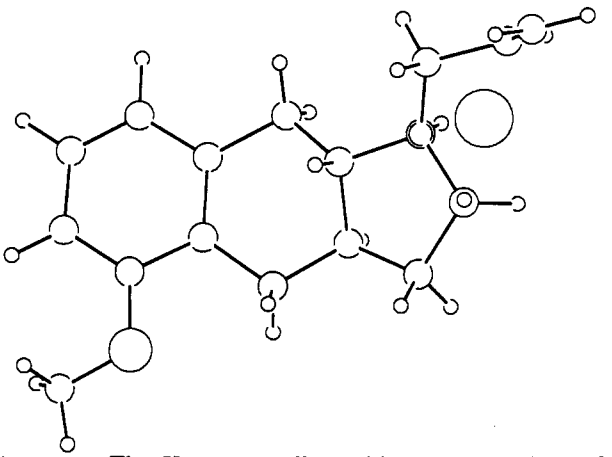
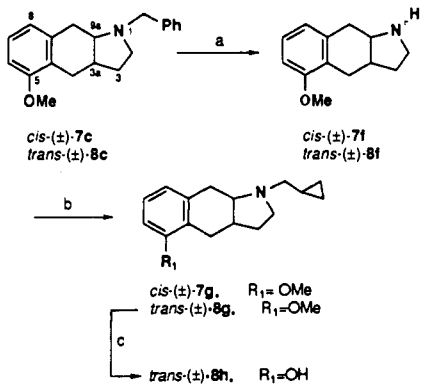


Figure 1. The X-ray crystallographic structure of (+)-8b, confirmed as *trans*-(3a*R*)-(+)-2,3,3a,4,9,9a-hexahydro-5-methoxy-1-(2-propenyl)-1*H*-benz[*f*]indole hydrochloride.

these stereoisomers was later confirmed by X-ray crystallography when *trans*-(±)-**6b**, the corresponding *N*-allyl lactam, was converted to the pyrrolidine derivative *trans*-(±)-**8b** and then resolved into a pair of enantiomers, *trans*-(3a*S*)-(−)-**8b** and *trans*-(3a*R*)-(+)-**8b** (see Figure 1).

Each of these lactams was then reduced with LAH/THF to afford the desired pyrrolidine derivatives *cis*-(±)-**7a**/**7b**/**7c** and *trans*-(±)-**8a**/**8b**/**8c**. In order to provide a larger quantity of the minor *trans* product for further synthetic work, an alternative approach to this conversion was explored. We found that when the mixture of keto ester **4** and *n*-propylamine (1.2 equiv) was refluxed in toluene in the presence of acetic acid, the lactam enamine was obtained in high yield. This material was then subjected to reduction with LAH/$AlCl_3$[7] followed by sodium borohydride treatment to yield *cis*/*trans*-pyrrolidines *cis*-(±)-**7a** and *trans*-(±)-**8a** in 1:1 ratio (66% overall

Scheme II[a]



[a] Reagents and conditions: (a) H_2, Pd/C, HCl, EtOH/H_2O; (b) Na_2CO_3, (bromomethyl)cyclopropane, MeCN; (c) 48% HBr, Δ.

yield). Since the Borch procedure supplied only 10–15% of the trans product, this alternative approach, yielding 35% of the trans product, was an obvious improvement.

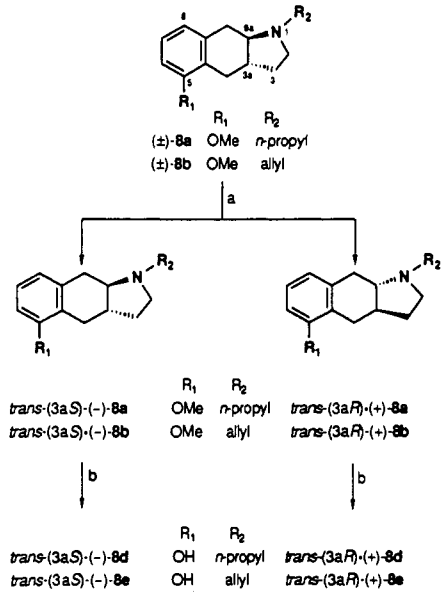
The corresponding phenolic analogs were prepared via two methods. As illustrated in Scheme I, the saturated *N*-*n*-propyl analogs, *cis*-(±)-**7a** and *trans*-(±)-**8a**, were refluxed with 48% HBr to afford 70–80% of the phenolic analogs *cis*-(±)-**7d** and *trans*-(±)-**8d**, respectively. Since the double bond in the *N*-allyl analogs reacts with HBr, an alternative demethylation procedure was used. By refluxing the allyl analog *trans*-(±)-**8b** with 3 equiv of lithium diphenylphosphide in THF,[8] the phenolic analog *trans*-(±)-**8e** was obtained in 80% yield.

To illustrate the versatility of our synthetic scheme, the *N*-cyclopropylmethyl analogs were prepared indirectly. As shown in Scheme II, *N*-benzyl analogs *cis*-(±)-**7c** and *trans*-(±)-**8c**, were debenzylated via hydrogenolysis to yield *N*-hydrogen analogs, *cis*-(±)-**7f** and *trans*-(±)-**8f**, respectively. Alkylation of these secondary amines with (bromomethyl)cyclopropane using sodium carbonate as the base in acetonitrile afforded the desired analogs *cis*-(±)-**7g** and *trans*-(±)-**8g**. O-Demethylation of *trans*-(±)-**8g** was accomplished by refluxing in 48% HBr to yield the phenolic analog *trans*-(±)-**8h**.

Since initial binding data indicated that the trans isomers were the active analogs in this series (see Pharmacological Results and Discussion), we decided to resolve both the *n*-propyl analog (±)-**8a** and allyl analog (±)-**8b**. As shown in Scheme III, the resolution was carried out by fractional recrystallization of a 1:1 mixture of (±)-**8a** or (±)-**8b** with di-*p*-toluoyl-L(or D)-tartaric acid. Only two or three recrystallizations from methanol were required to yield pure diastereomeric salt in excellent yield (40–43% out of 50% maximum). The purity of the diastereomeric salt was determined by 300-MHz ^{1}H NMR using integration of the distinctive peaks for each diastereomer. Using this analytical method, we were able to ensure better than 95% purity of these salts. Each diastereomeric salt was then converted to the free base to yield pure enantiomers *trans*-(3a*S*)-(−)-**8a**/(−)-**8b** and *trans*-(3a*R*)-(+)-**8a**/(+)-**8b**. X-ray crystallography on enantiomer (+)-**8b** (Figure 1) confirmed the assigned absolute configuration of these enantiomers. The methoxy analogs (−)-**8a**/(−)-**8b** and (+)-**8a**/(+)-**8b** were then converted into the corresponding phenolic analogs (−)-**8d**/(−)-**8e** and (+)-**8d**/(+)-**8e**, respectively, via the lithium diphenylphosphide procedure (see Scheme III).[8]

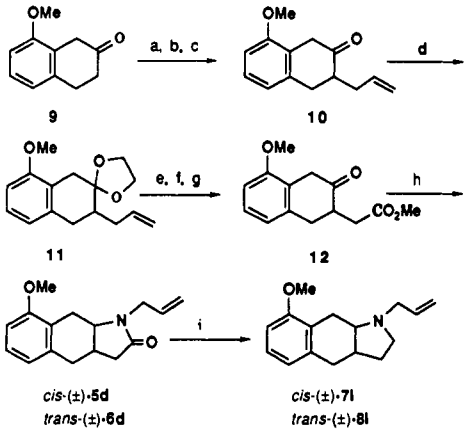
To synthesize the 8-methoxy linear tricyclic analogs *cis*-(±)-**7i** and *trans*-(±)-**8i**, keto ester **12** was required as the

Scheme III[a]



[a] Reagents and conditions: (a) di-*p*-toluoyl-L(or D)-tartaric acid, MeOH; (b) Ph_2PH, *n*-BuLi, THF, Δ.

Scheme IV[a]

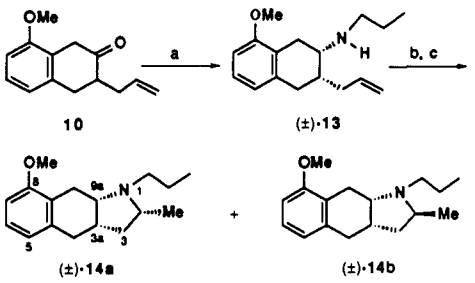


[a] Reagents and conditions: (a) LDA, $(MeO)_2CO$, THF, Δ; (b) LDA, allyl bromide, THF; (c) LiCl, DMSO, H_2O, Δ; (d) $(CH_2OH)_2$, $HC(OMe)_3$, *p*-TsOH, CH_2Cl_2; (e) $NaIO_4$, $KMnO_4$, H_2O; (f) HCl, MeOH/MeCN; (g) HCl, MeOH/H_2O; (h) allylamine, HOAc, $NaCNBH_3$, THF/MeOH; (i) LAH, THF, Δ.

precursor. The synthesis of this keto ester was accomplished in a multistep sequence as shown in Scheme IV. Allyl ketone **10**,[9] obtained in three steps from 8-methoxy-2-tetralone, was converted into ketal **11**. The allyl group was then oxidized to the carboxylic acid ($NaIO_4$, $KMnO_4$, H_2O) and esterified to the methyl ester (HCl, MeOH/MeCN), and the ketal group was hydrolyzed to the ketone (HCl, MeOH/H_2O) to afford keto ester **12** in 58% overall yield. Reductive amination with allylamine by the Borch procedure yielded lactams *cis*-(±)-**5d** and *trans*-(±)-**6d**.[6] LAH reduction afforded pyrrolidine analogs *cis*-(±)-**7i** and *trans*-(±)-**8i** in a 5:1 ratio. The assignment of the major product as *cis*-(±)-**7i** was based on analogy from the 5-methoxy series described earlier in Scheme I.

Two racemic 8-methoxy cis analogs with an additional methyl group at C-2 were synthesized. As shown in Scheme V, allyl ketone **10** was reacted with *n*-propylamine by the Borch procedure[6] to yield *cis*-(±)-**13**.[9] This compound was subjected to amino mercuration to yield two products.[10] The less polar product (53%) was assigned as (2α,-

Scheme V[a]



[a] Reagents and conditions: (a) *n*-propylamine, HOAc, $NaCNBH_3$, THF/MeOH; (b) $Hg(OAc)_2$, MeOH; (c) NaOH, MeOH, $NaBH_4$.

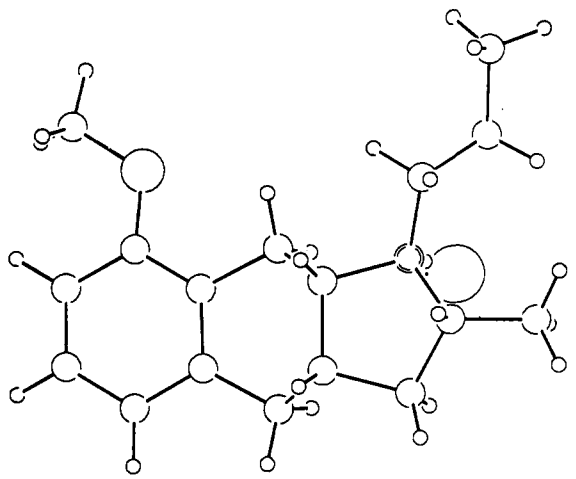


Figure 2. The X-ray crystallographic structure of (±)-**14a**, confirmed as (2α,3aα,9aα)-(±)-2,3,3a,4,9,9a-hexahydro-8-methoxy-2-methyl-1-(*n*-propyl)-1*H*-benz[*f*]indole hydrochloride.

3aα,9aα)-(±)-**14a** and the more polar product (8.5%) as (2β,3aα,9aα)-(±)-**14b**. No attempt to resolve these compounds was made. The X-ray crystallography of analog (±)-**14a** (Figure 2) confirmed the correct assignment of both structures.

The analogs synthesized and biologically evaluated, within the scope of generic structure **3**, are listed in Table I. The table includes the solvent used for recrystallization of the HCl salt, the melting point, and the molecular formula for each compound.

Pharmacological Results and Discussion

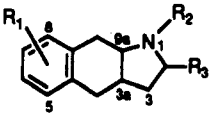
The compounds were evaluated for their in vitro binding affinity at 5-HT_{1A} receptors using [^{3}H]-8-OH-DPAT in either homogenate of bovine hippocampus or cloned CHO cells and at dopamine D_2 receptors using either [^{3}H]-raclopride in rat striatum or [^{3}H]U86170 in cloned CHO cells (Table II). Intrinsic activity determinations were made in vitro on compounds that were active at the dopamine D_2 receptor (Table III).[11] Interactions with brain serotonin and dopamine receptors in vivo were evaluated by the effects on the synthesis rates of serotonin and dopamine in rats (represented by 5-HTP and DOPA accumulation, respectively, Table IV). Inhibition of firing rates of dopaminergic neurons in the substantia nigra pars compacta was determined following intravenous injection to anesthetized rats (Table V). Effects on locomotor activity in normal and reserpine-pretreated mice were also studied (Table VII).

Analogs which displayed selectivity in the 5-HT_{1A} receptor site were evaluated for their ability to produce hypothermia in mice (Table II). Inhibition of firing rates of serotonergic neurons in the dorsal raphe nucleus was determined following intravenous injection of the test compounds (Table V). The face-to-face and isolation-induced-aggression assays were two behavioral paradigms performed in mice to measure a compound's anxiolytic potential (Table VI). Cardiovascular effects were also studied by measuring the change in blood pressure and sympathetic nerve activity in the anesthetized cat (Table VIII).

5-Methoxy and 5-Hydroxy Analogs. 5-Methoxy analogs with a trans-fused ring [(±)-**8a–c**/(±)-**8f,g**] displayed selective 5-HT_{1A} binding affinity whereas the corresponding analogs with a cis-fused ring [(±)-**7a–c**/(±)-**7f,g**] were found to be inactive in the in vitro binding assays (Table II). The order of binding potency for analogs differing in nitrogen substitution in this series was found to be allyl ≈ *n*-propyl > cyclopropylmethyl ≈ hydrogen ≫ benzyl. Although the *trans*-*N*-*n*-propyl and *N*-allyl analogs (±)-**8a** and (±)-**8b** showed selective affinity in vitro for the 5-HT_{1A} receptor site (K_i = 37 and 11 nM, respectively) and decreased 5-HTP accumulation, they displayed dopamine agonist properties in vivo (decreased DOPA accumulation, Table IV). Both analogs (±)-**8a** and (±)-**8b** inhibited the serotonergic neuronal firing rate and displayed 10- and 100-fold higher potency, respectively, when compared to the ED_{50}'s for inhibition of DA neuronal firing (Table V). Compound (±)-**8b** did not decrease sympathetic nerve discharge or have any significant effect on blood pressure (Table VIII). This is somewhat surprising since 5-HT_{1A} agonists are known to inhibit sympathetic nerve activity and lower blood pressure. As shown in Table VI, in the isolation-induced aggression assay, (±)-**8a** was active at 4, 11, and 36 μmol/kg ip by increasing the time before fighting from 9 s to over 250 s whereas (±)-**8b** was active at 4 and 36 μmol/kg ip and also active at the highest dose tested orally (36 μmol/kg). In the face-to-face assay, (±)-**8b** was active at 4 and 36 μmol/kg sc. Therefore, both (±)-**8a** and (±)-**8b** showed a potency similar to 8-OH-DPAT in these models. It is also interesting to note that (±)-**8a** was inactive orally in the hypothermia assay whereas (±)-**8b** was more efficacious after oral administration than sc administration (9.9 vs 7.8 °F maximum temperature decrease, respectively, Table II). The hypothermia and behavioral data on (±)-**8b** suggest that this compound has oral activity.

Upon resolution of both (±)-**8a** and (±)-**8b**, the *N*-*n*-propyl and *N*-allyl (3a*S*)-enantiomers (−)-**8a** and (−)-**8b** were found to be active in the 5-HT_{1A} binding assay (Table II). Compound (−)-**8a** was found to be active in D_2 binding (in [^{3}H]U86170-labeled D_2 CHO cells) and had a predicted dopamine intrinsic activity of 37%, as judged from the GTP shift (Table III). In the locomotor behavior screen, (−)-**8a** increased locomotor activity in reserpinized mice and decreased locomotor hyperactivity induced by *d*-amphetamine at a dose of 0.4 μmol/kg ip and higher (Table VII). Compound (−)-**8b** showed a similar profile as that of (±)-**8b** as a nonselective dopamine and serotonin agonist in the in vivo biochemistry model and in the inhibition of serotonergic neuronal firing (Table V). However, (−)-**8b** is over 200 times more potent than (±)-**8b** in inhibiting the dopamine neuronal firing rate (ED_{50} = 0.05 vs >10.7 μmol/kg iv, respectively). In addition, this compound was equipotent to 8-OH-DPAT in producing hypothermia in mice following sc administration and, interestingly, displayed similar potency after oral administration. It also

Table I. Physical Properties of 2,3,3a,4,9,9a-Hexahydro-1*H*-benz[*f*]indole Derivatives



compd	R_1	R_2	R_3	config at 3a,9a	recryst solvent	mp (°C)	formula
(±)-7a	5-OMe	*n*-propyl	H	*cis*-(±)	EtOAc/MeOH	250–251	$C_{16}H_{23}NO$·HCl
(±)-7b	5-OMe	allyl	H	*cis*-(±)	EtOAc/MeOH	189–191	$C_{16}H_{21}NO$·HCl
(±)-7c	5-OMe	benzyl	H	*cis*-(±)	hexane/EtOAc/MeOH	197–198	$C_{20}H_{23}NO$·HCl
(±)-7d	5-OH	*n*-propyl	H	*cis*-(±)	hexane/EtOAc	174–175	$C_{15}H_{21}NO$
(±)-7f	5-OMe	H	H	*cis*-(±)	EtOAc/MeOH	233–234	$C_{13}H_{17}NO$·HCl
(±)-7g	5-OMe	cpm[b]	H	*cis*-(±)	EtOAc/MeOH	200–201	$C_{17}H_{23}NO$·HCl
(±)-7i	8-OMe	allyl	H	*cis*-(±)	EtOAc/MeOH	173–174	$C_{16}H_{21}NO$·HCl
(±)-8a	5-OMe	*n*-propyl	H	*trans*-(±)	EtOAc/MeOH	264–265	$C_{16}H_{23}NO$·HCl
(−)-8a	5-OMe	*n*-propyl	H	*trans*-(3a*S*)-(−)	EtOAc/MeOH	263–265	$C_{16}H_{23}NO$·HCl
(+)-8a	5-OMe	*n*-propyl	H	*trans*-(3a*R*)-(+)	EtOAc/MeOH	266–267	$C_{16}H_{23}NO$·HCl
(±)-8b	5-OMe	allyl	H	*trans*-(±)	EtOAc/MeOH	213–215	$C_{16}H_{21}NO$·HCl
(−)-8b	5-OMe	allyl	H	*trans*-(3a*S*)-(−)	EtOAc/MeOH	243–244	$C_{16}H_{21}NO$·HCl
(+)-8b	5-OMe	allyl	H	*trans*-(3a*R*)-(+)	EtOAc/MeOH	243–244	$C_{16}H_{21}NO$·HCl
(±)-8c	5-OMe	benzyl	H	*trans*-(±)	hexane/EtOAc/MeOH	187–189	$C_{20}H_{23}NO$·HCl
(±)-8d	5-OH	*n*-propyl	H	*trans*-(±)	hexane/EtOAc	180–181	$C_{15}H_{21}NO$
(−)-8d	5-OH	*n*-propyl	H	*trans*-(3a*S*)-(−)	EtOAc/MeOH	>300	$C_{15}H_{21}NO$·HCl
(+)-8d	5-OH	*n*-propyl	H	*trans*-(3a*R*)-(+)	EtOAc/MeOH	>300	$C_{15}H_{21}NO$·HCl
(+)-8e	5-OH	allyl	H	*trans*-(+)	EtOAc/MeOH	>280	$C_{15}H_{19}NO$·HCl
(−)-8e	5-OH	allyl	H	*trans*-(3a*S*)-(−)	EtOAc/MeOH	>300	$C_{15}H_{19}NO$·HCl
(+)-8e	5-OH	allyl	H	*trans*-(3a*S*)-(+)	EtOAc/MeOH	>300	$C_{15}H_{21}NO$·HCl
(±)-8f	5-OMe	H	H	*trans*-(±)	EtOAc/MeOH	294–295	$C_{13}H_{17}NO$·HCl
(±)-8g	5-OMe	cpm[b]	H	*trans*-(±)	EtOAc/MeOH	233–234	$C_{17}H_{23}NO$·HCl
(±)-8h	5-OH	cpm[b]	H	*trans*-(±)	EtOAc/MeOH	>300	$C_{16}H_{21}NO$·HCl
(±)-8i	8-OMe	allyl	H	*trans*-(±)	EtOAc/MeOH	237–239	$C_{16}H_{21}NO$·HCl
(±)-14a	8-OMe	*n*-propyl	2α-Me	*cis*-(3aα,9aα)-(±)	hexane/EtOAc	240–242	$C_{17}H_{25}NO$·HCl
(±)-14b	8-OMe	*n*-propyl	2β-Me	*cis*-(3aα,9aα)-(±)	hexane/EtOAc	180–182	$C_{17}H_{25}NO$·HCl

[a] The elementary analyses are within ±0.4% of the theoretical values. [b] Cyclopropylmethyl group.

was active orally in the face-to-face and isolation-induced-aggression assays (Table VI). Following ip administration, (−)-**8b** produced the maximal antiaggressive response in mice (600 s). This compound was found to be more efficacious than 8-OH-DPAT and other compounds tested from this series.

O-Demethylation of both (±)-**8a** and (±)-**8b** resulted in the 5-hydroxy-*N*-*n*-propyl and -*N*-allyl analogs (±)-**8d** and (±)-**8e**, respectively. Both (±)-**8d** and (±)-**8e** displayed high affinity for the dopamine D_2 receptor (K_i = 17 and 25 nM, respectively) and had predicted intrinsic activities as dopamine agonists (Table III). In the biochemical assay, compound (±)-**8d** also showed a substantial decrease in DOPA accumulation (−47%, Table IV). Both (±)-**8d** and (±)-**8e** inhibited the dopamine neuronal firing rate (ED_{50} = 0.003 and 0.007 μmol/kg iv; Table V) as expected for dopamine agonists. In the locomotor activity assay, both (±)-**8d** and (±)-**8e** stimulated activity in reserpinized mice (Table VII). These compounds also blocked *d*-amphetamine-induced hyperactivity. This may be explained by the induction of intense stereotypy produced by a full agonist which is incompatible with the high level of locomotor activity.

The 5-hydroxy-*N*-*n*-propyl and -*N*-allyl (3a*S*)-enantiomers (−)-**8d** and (−)-**8e** were also found to be selective agonists. This is demonstrated by their effects on DOPA accumulation and extremely potent inhibition of dopaminergic neuronal firing (ED_{50} = 0.0014 and 0.002 μmol/kg iv; Table V) which is 5–10 times more potent than apomorphine. Both (−)-**8d** and (−)-**8e** stimulated locomotor activity in reserpinized mice at all doses tested.

The 5-methoxy analogs with the opposite configuration, *N*-*n*-propyl and *N*-allyl trans-(3a*R*)-enantiomers (+)-**8a** and (+)-**8b**, were found to be inactive in vitro, suggesting that the receptor has a preference for interaction with the (3a*S*)-(−)-enantiomers (Table II). Compound (+)-**8b** displayed some dopamine antagonist activity in vivo with an increase in DOPA accumulation but was inactive in producing an antagonist response in the electrophysiological assay (Table V). A possible explanation for this discrepancy may be that (+)-**8b** is metabolized into a dopamine antagonist. Evidence showed that the corresponding hydroxy analog (+)-**8e**, a likely metabolite, effectively antagonizing the inhibitory effects of *d*-amphetamine on the dopamine neuronal firing rate (ED_{50} = 0.94 μmol/kg iv; Table V). In agreement with this, both *n*-propyl analog (+)-**8d** and allyl analog (+)-**8e** showed a low intrinsic activity in vitro (18 and 21%, respectively). Furthermore, (+)-**8e** was found to block *d*-amphetamine-induced hyperactivity (Table VII).

The 5-hydroxy-*N*-(cyclopropylmethyl) analog *trans*-(±)-**8h** displayed 5 times lower affinity for the dopamine receptor than the corresponding *N*-*n*-propyl analog (±)-**8d** and *N*-allyl analog (±)-**8e**, but still showed stimulatory activity at 4 and 36 μmol/kg ip in the locomotor assay.

8-Methoxy Analogs. Compounds with 8-methoxy-*N*-allyl substitution, both *cis*-(±)-**7i** and *trans*-(±)-**8i**, displayed a weak binding affinity at the 5-HT_{1A} receptor site (K_i = 145 and 104 nM, respectively) and no affinity at the dopamine binding site (Table II). When an additional methyl group is incorporated at C-2 in the *cis*-8-methoxy-*N*-*n*-propyl series, 5-HT_{1A} binding affinity is increased 10 times as demonstrated by compound (±)-**14b**. In vivo, (±)-**14b** significantly decreased 5-HTP accumulation but also caused a tendency toward an elevation of DOPA accumulation, a profile indicative of a mixed serotonin agonist and dopamine antagonist. This analog also weakly decreased sympathetic nerve discharge and blood pressure (Table VIII). In the hypothermia assay, this compound displayed a potent effect in mice (ED_{50} = 4.4 μmol/kg sc)

Table II. Affinities at Central 5-HT_{1A} and D_2 Sites in Vitro and Effects on Hypothermia in the Mouse

compd	K_i[c] (nM) 5-HT_{1A} binding affinity[a]	K_i[c] (nM) D_2 binding affinity[b]	mouse hypothermia assay ED_{50} (μmol/kg)[g]	mouse hypothermia assay max temp decrease	mouse hypothermia assay route
8-OH-DPAT	1.6 (±0.3)	>1000	1.0 (0.5–1.8)	7.2	sc
		86 (±8)[e]	9.7 (5.2–18)	7.5	po
Apomorphine	NT[j]	26 (±6)[e]	NT[j]		
Chlorpromazine	673 (±98)[d]	3 (±1.6)[e]	NT[j]		
(±)-7a	>5000	>1000[f]	NT[j]		
(±)-7b	>1000	429 (±253)	NT[j]		
(±)-7c	>1000	465 (±15)	NT[j]		
(±)-7d	>1000	296 (±31)	NT[j]		
		11 (±1.1)			
(±)-7f	>1000	>1000[f]	NT[j]		
(±)-7g	721 (±86)	748 (±123)	NT[j]		
(±)-7l	145 (±41)	>1000[f]	NT[j]		
(±)-8a	37 (±17)	877 (±719)	0.4 (0.1–0.8)	6.7	sc
	70 (±4)[d]	100 (±12)[e]	>355[h]	1.4	po
(−)-8a	17 (±5)	>1000[f]	NT[j]		
	55 (±7)[d]	75 (±22)[e]			
(+)-8a	>1000[f]	>1000[f]	NT[j]		
(±)-8b	11 (±3)	>1000	2.6 (1.4–4.3)	7.8	sc
			4.6 (2.8–7.9)	9.9	po
(−)-8b	41 (±12)	>1000[f]	0.6[i]	4.5	sc
			1.1 (0.6–2.2)	5.6	po
(+)-8b	>1000[f]	>1000	NT[j]		
(±)-8c	127 (±51)	>10000	NT[j]		
(±)-8d	62 (±16)	17 (±4)	NT[j]		
		2.4 (±1.5)[e]			
(−)-8d	36 (±7)	2 (±0.6)	0.03 (0.02–0.04)	7.5	sc
		0.5 (±0.1)[e]	0.04 (0.02–0.06)	10.9	po
(+)-8d	>470	>630	NT[j]		
		917 (±140)[e]			
(±)-8e	105 (±37)	25 (±2)	NT[j]		
		1.4 (±1.1)[e]			
(−)-8e	56 (±8)	3 (±0.9)	NT[j]		
		0.3 (±0.2)[e]			
(+)-8e	>470	47 (±18)	NT[j]		
		235 (±38)[e]			
(±)-8f	29 (±4)	>1000[f]	1.7 (1.0–3.0)	6.2	sc
			>125[h]		po
(±)-8g	29 (±6)	>1000[g]	19[i]	7.0	sc
			25 (15–43)	6.2	po
(±)-8h	69 (±11)	118 (±50)	NT[j]		
(±)-8i	104 (±48)	>1000[f]	NT[j]		
(±)-14a	384 (±230)	>1000[f]	NT[j]		
(±)-14b	11 (±3)	>1000[f]	4.4 (3–7)	7.8	sc
		464 (±27)[e]	>101[h]	3.1	po

[a] [^{3}H]-8-OH-DPAT-labeled 5-HT_{1A} sites in bovine hippocampus. [b] [^{3}H]raclopride-labeled D_2 sites in rat striatum. [c] K_i values followed by SEM. [d] [^{3}H]-8-OH-DPAT-labeled 5-HT_{1A} sites in cloned CHO cells. [e] [^{3}H]U86170-labeled D_2 sites in cloned CHO cells. [f] IC_{50}'s in nM were estimated from a single point experiment, compound was run at 1 μM. [g] ED_{50}'s followed by 95% confidence intervals. [h] As approximate ED_{50}'s; higher doses were not tested to determine 95% confidence intervals. [i] Dose–response curve was too steep to calculate 95% confidence intervals. [j] Not tested.

Table III. Predicted Intrinsic Activity from GTP Shift

dopamine intrinsic activity			
compd	% intrinsic activity	compd	% intrinsic activity
apomorphine	73	(+)-8d	18
chlorpromazine	5	(±)-8e	91
(−)-3PPP	34	(−)-8e	106
(±)-7d	61	(+)-8e	21
(−)-8a	37	(±)-8h	73
(±)-8d	79	(±)-14b	21
(−)-8d	109		

with a 7.8 °F maximum temperature drop (Table II). It is as efficacious as 8-OH-DPAT but about 4 times less potent, and displays poor oral activity. It is interesting to note that (2β,3aα,9aα)-isomer (±)-**14b** is 35 times more potent than the corresponding (2α,3aα,9aα)-isomer (±)-**14a** in the 5-HT_{1A} binding assay. This result indicates that at the 5-HT_{1A} receptor there is a configurational preference for a methyl substitution at the C-2 position.

Table IV. Effect of Selected Compounds on the Synthesis Rates of Dopamine and Serotonin (DOPA and 5-HTP Accumulation) in the Rat Ventral Limbic Brain Region

compd	dose (μmol/kg)	accumulation[a] DOPA[a]	accumulation[a] 5-HTP[a]
8-OH-DPAT	3.0	3	−47*
	0.3	16	−37*
apomorphine	3.2	−55*	17
haloperidol	2.7	144*	−6.6
(±)-8a	3.5	−39*	−29*
(±)-8b	10.7	−26	−39*
(−)-8b	10.7	−37*	−41*
(+)-8b	10.7	29*	4
(±)-8d	43.2	−47*	−4
(−)-8d	3.7	−45*	−9.5
(+)-8d	3.7	20	12
(±)-14b	3.4	32	−44*

[a] As a percent change from the control value. *$p < 0.05$.

Conclusion

In this paper, we have described the synthesis of five/six fused linear tricyclic analogs of 2-aminotetralin. These

Table V. Effects on Inhibition of 5-HT_{1A} and DA Cell Firing in the Rat

compd	cell firing ED_{50}[a] (μmol/kg) 5-HT_{1A}	DA
8-OH-DPAT	0.005 (±0.02)	2.25 (±1.43)
apomorphine		0.031 (±0.001)
haloperidol		0.019 (±0.001)[b]
		0.018 (±0.006)[c]
(±)-8a	0.07 (±0.12)	0.66 (±0.15)
(±)-8b	0.14 (±0.03)	>10.7
		6.8 (±1.8)[b]
(−)-8b	0.08 (±0.035)	0.05 (±0.01)
(+)-8b	3.97 (±2.71)	4.75 (±1.8)[b]
(±)-8d		0.003 (±0.0008)
(−)-8d		0.0014 (±0.0007)
(+)-8d		>3.73
		>3.73[c]
(±)-8e	0.35 (±0.053)	0.007 (±0.002)
(−)-8e		0.002 (±0.0007)
(+)-8e		0.94 (±0.31)[b]

[a] ED_{50} value followed by SEM. [b] Tested as an antagonist versus amphetamine. [c] Tested as an antagonist versus apomorphine.

2,3,3a,4,9,9a-hexahydro-1*H*-benz[*f*]indole derivatives (**3**) were evaluated for their in vitro and in vivo dopamine and 5-HT_{1A} receptor agonist activities. Similar to the findings by Cannon et al.[2] and Seiler et al.,[3b] for the six/six fused linear tricyclic series, more potent pharmacological activities were also displayed by the trans isomers in this five/six fused linear tricyclic analogs. Among the 5-substituted trans isomers, activity was found to reside solely in the (3a*S*)-(−)-enantiomers. In the trans series, analogs with 5-methoxy substitution (R_1 in **3**) on the aromatic ring possessed selective 5-HT_{1A} receptor agonist activity in vitro, however, in vivo they displayed mixed 5-HT_{1A} and D_2 agonist properties. On the other hand, the corresponding 5-hydroxy analogs appeared to be potent dopamine agonists with full intrinsic activity. Analogs with *N*-allyl or *N*-*n*-propyl substitution (R_2 in **3**) displayed equipotent activity. However, substitution with either a cyclopropylmethyl or a benzyl group resulted in diminished activity. Of analogs with 8-substitution (R_1 in **3**), only 8-methoxy-*N*-allyl analogs were synthesized and evaluated. In this case, both cis and trans analogs showed equally weak activity in vitro for the 5-HT_{1A} receptor site and were inactive at the D_2 binding site. The presence of an additional methyl group at the C-2 position (R_3 in **3**) of the *cis*-(±)-8-methoxy-*N*-*n*-propyl analog resulted in enhancement of in vitro 5-HT_{1A} binding affinity. In this case, the (2β,3aα,9aα)-(±)-isomer is 35 times more potent than the corresponding (2α,3aα,9aα)-(±)-isomer. These linear tricyclic analogs represented by **3** display very potent dopamine agonist activities and may prove to be useful for the treatment of psychiatric or neurological disorders. They may also serve as tools for molecular modeling[12] to gain insight into the design of new selective serotonergic and dopaminergic agents.

Experimental Section

Synthesis. Analytical TLC was performed on Analtech 10 × 20 cm (250 μm) silica gel GF prescored glass plates which were developed in the solvent systems described. The plates were checked under ultraviolet light and developed by dipping in ammonium molybdate/cerium sulfate/10% sulfuric acid solution and heating on a hot plate. ^1H NMR spectra were obtained at 300 MHz on a Bruker Model AM-300 spectrometer in $CDCl_3$ solution unless noted otherwise. Chemical shifts (δ) are reported in parts per million relative to internal tetramethylsilane. Flash column chromatography and medium-pressure liquid chromatography were performed with 400 g–1 kg silica gel 60 (230–400 mesh) purchased from EM Science. All commercial chemicals were used as received from Aldrich unless noted otherwise. HPLC-grade methylene chloride, methanol, tetrahydrofuran, ethyl acetate, and hexane were used. All reactions were performed under a nitrogen atmosphere. Melting points were determined in open capillary tubes on a Mettler FP-62 melting point apparatus and are uncorrected. The amine-based products were converted into the HCl salts by dissolving the free base in methanolic HCl solution.[13] The solvent was removed and azeotroped with toluene in vacuo followed by recrystallization from an appropriate solvent. Other physical data, such as IR, MS, elemental analyses, and optical rotations, were performed by the Physical and Analytical Chemistry Unit of the Upjohn Laboratories. The elemental analyses reported are within ±0.4% of the calculated values.

cis-(±)-1,3,3a,4,9,9a-Hexahydro-5-methoxy-1-*n*-propyl-2*H*-benz[*f*]indol-2-one (5a) and *trans*-(±)-1,3,3a,4,9,9a-Hexahydro-5-methoxy-1-*n*-propyl-2*H*-benz[*f*]indol-2-one (6a). A solution of keto ester **4** (4.97 g, 20 mmol) and *n*-propylamine (6.6 mL, 80 mmol) in 150 mL of THF/MeOH or 2-PrOH (1:1) was treated with acetic acid until pH 4–5 (about 15 mL) at 0–5 °C. The mixture was stirred for 30 min and sodium cyanoborohydride (2.5 g, 40 mmol) was added. The resulting solution was stirred at room temperature for 3 days. The reaction was quenched with 20% sodium hydroxide and the solvent was removed in vacuo. The concentrate was extracted with methylene chloride (2 × 1 L). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by medium-pressure liquid chromatography on 560 g of silica gel, by eluting with hexane/ethyl acetate/2-propanol (10:5:1) and collecting 40-mL fractions. Fractions homogeneous by TLC were combined and concentrated.

The less polar product was recrystallized from hexane/ethyl acetate to give pure (±)-**6a** (1.15 g, 11%) as a white solid: mp 121–123 °C; ^1H NMR δ 7.16 (t, J = 7.9 Hz, 1 H), 6.78 (d, J = 8.1 Hz, 1 H), 6.73 (d, J = 7.6 Hz, 1 H), 3.83 (s, 3 H), 3.55–1.52 (m, 12 H), 0.93 (t, J = 7.4 Hz, 3 H); IR (mull) ν_{max} 1685, 1579 cm^{-1}; MS, M^+ m/z 259, other ions at m/z 244, 238, 201, 173, 159, 158, 135. Decoupling experiments (500-MHz ^1H NMR) determined the coupling constant for C-9a (δ 3.48–3.32) and C-3a protons to be 9.93 Hz, indicating they are diaxial. This data confirmed (±)-**6a** as the trans product. Anal. ($C_{16}H_{21}NO_2$) C, H, N.

The more polar product was recrystallized from hexane/ethyl acetate to give pure (±)-**5a** (5.0 g, 49%) as a white solid: mp 105–107 °C; ^1H NMR δ 7.14 (t, J = 7.7 Hz, 1 H), 6.77 (d, J = 8.6 Hz, 2 H), 3.81 (s, 3 H), 3.99–1.45 (m, 12 H), 0.92 (t, J = 7.4 Hz, 3 H); IR (mull) ν_{max} 1678, 1584 cm^{-1}; MS, M^+ m/z 259, other ions at m/z 244, 230, 201, 173, 159, 158, 135. Decoupling experiments did not resolve the peaks but showed a small coupling constant for C-9a (δ 4.01–3.92) and C-3a protons, indicating that they are equatorial–axial. This data confirmed (±)-**5a** as the cis product. Anal. ($C_{16}H_{21}NO_2$) C, H, N.

cis-(±)-1,3,3a,4,9,9a-Hexahydro-5-methoxy-1-(2-propenyl)-2*H*-benz[*f*]indol-2-one (5b) and *trans*-(±)-1,3,3a,4,9,9a-Hexahydro-5-methoxy-1-(2-propenyl)-2*H*-benz[*f*]indol-2-one (6b). These compounds were prepared from keto ester **4** (12.4 g, 50 mmol) and allylamine (18.8 mL, 250 mmol), using the reductive amination/cyclization procedure described in the preparation of (±)-**5a** and (±)-**6a**. The crude product was purified by medium-pressure liquid chromatography on 1 kg of silica gel, by eluting with 2 L of 50% ethyl acetate/hexane followed by 10 L of 75% ethyl acetate/hexane and collecting 40-mL fractions. Fractions homogeneous by TLC were combined and concentrated.

The less polar product was recrystallized from hexane/ethyl acetate to give pure (±)-**6b** (2.5 g, 19.4%) as a white solid: mp 107–108 °C; ^1H NMR δ 7.16 (t, J = 7.9 Hz, 1 H), 6.76 (d, J = 7.7 Hz, 1 H), 6.72 (d, J = 8.1 Hz, 1 H), 5.85–5.15 (m, 3 H), 4.27–4.20 (m, 1 H), 3.82 (s, 3 H), 3.76–1.71 (m, 9 H); IR (mull) ν_{max} 1652, 1640, 1598, 1579 cm^{-1}; MS, M^+ m/z 257, other ions at m/z 242, 214, 186, 173, 158, 134, 115. This compound was assigned as the trans product (±)-**6b** on the basis of analogy to (±)-**6a**. Anal. ($C_{16}H_{19}NO_2$) C, H, N.

The more polar product was recrystallized from hexane/ethyl acetate to give pure (±)-**5b** (8.7 g, 67.4%) as a white solid: mp 74–75 °C; ^1H NMR δ 7.13 (t, J = 7.9 Hz, 1 H), 6.77 (d, J = 7.4

Table VI. Effects of Selected Compounds in the Face to Face and Isolation Induced Aggression Behavioral Assays in the Mouse

	behavior					
	face-to-face			isolation-induced aggression		
compd	dose (μmol/kg)	route	time (s)	dose (μmol/kg)	route	time (s)
8-OH-DPAT[a]	0	sc	1.1	0	ip	6.0
	0.3	sc	1.6	0.3	ip	11
	3.0	sc	5.0*	0.9	ip	20
	30	sc	4.4*			
				0	ip	177
				3.0	ip	310*
				9.1	ip	437*
				30	ip	351*
d-amphetamine SO_4	0	sc	2.6			
	5.4	sc	2.4			
	54	sc	2.9			
chlorpromazine HCl	0	sc	3.6			
	2.8	sc	5.8			
	8.4	sc	1.3			
	28	sc	0.0			
(±)-8a				0	ip	9
				0.4	ip	6
				1.1	ip	134
				3.5	ip	384*
				11	ip	268*
				36	ip	450*
(±)-8b[a]	0	sc	0.9	0	ip	3
	0.4	sc	1.5	0.4	ip	3
	3.6	sc	3.6*	3.6	ip	147*
	36	sc	6.9*	36	ip	522*
				0	po	73
				3.6	po	88
				11	po	218
				36	po	393*
(−)-8b[a]	0	po	1.4	0	ip	5
	0.4	po	1.7	11	ip	570*
				36	ip	600*
	0	po	0.3	0	po	5
	1.1	po	1.0*	1.1	po	109
	3.6	po	1.5*	3.6	po	198*
				11	po	257*
				36	po	397*
(+)-8b	0	po	0.3	0	ip	5
	11	po	0.7	11	ip	46
	36	po	0.9*	36	ip	83*
				0	po	79
				3.6	po	36
				0	po	6
				11	po	63*
				36	po	219*
(±)-8g	0	po	1.0	0	po	79
	0.3	po	0.9	3.4	po	58
	3.4	po	1.6	0	po	6
	34	po	1.5	10	po	177*

[a] The compound was tested on two occassioins, using different doses or different routes of administration. *$p < 0.05$.

Hz, 1 H), 6.75 (d, J = 6.5 Hz, 1 H), 5.82–5.18 (m, 3 H), 4.32–4.24 (m, 1 H), 3.81 (s, 3 H), 4.06–1.60 (m, 9 H); IR (mull) ν_{max} 1652, 1640, 1598, 1579 cm^{-1}; MS, M^+ m/z 257, other ions at m/z 242, 214, 186, 173, 158, 134, 115. This compound was assigned as the cis product (±)-**5b** on the basis of analogy to (±)-**5a**. Anal. ($C_{16}H_{19}NO_2$) C, H, N.

***cis*-(±)-1,3,3a,4,9,9a-Hexahydro-5-methoxy-1-benzyl-2*H*-benz[*f*]indol-2-one (5c) and *trans*-(±)-1,3,3a,4,9,9a-Hexahydro-5-methoxy-1-benzyl-2*H*-benz[*f*]indol-2-one (6c).** These compounds were prepared from keto ester **4** (24.8 g, 0.1 mol) and benzylamine (54.6 mL, 0.5 mol), using the reductive amination/cyclization procedure previously described in the preparation of (±)-**5a** and (±)-**6a**. The crude product was purified by medium-pressure liquid chromatography on 1 kg of silica gel, by eluting with hexane/ethyl acetate (1:1) and collecting 40-mL fractions. Fractions homogeneous by TLC were combined and concentrated.

The less polar product was recrystallized from hexane/ethyl acetate to give pure (±)-**6c** (4.82 g, 16%) as a white solid: mp 138–139 °C; ^1H NMR δ 7.30–7.24 (m, 5 H), 7.12 (t, J = 7.9 Hz, 1 H), 6.71 (d, J = 7.7 Hz, 1 H), 6.68 (d, J = 8.1 Hz, 1 H), 4.93 (d, J = 15 Hz, 1 H), 4.18 (d, J = 15 Hz, 1 H), 3.80 (s, 3 H), 3.28–2.21 (m, 8 H); IR (mull) ν_{max} 1686, 1647, 1601, 1579 cm^{-1}; MS, M^+ m/z 307, other ions at m/z 216, 173, 149, 135, 115. This compound was assigned as the trans product (±)-**6c** on the basis of analogy to (±)-**6a**. Anal. ($C_{20}H_{21}NO_2$) C, H, N.

The more polar product as recrystallized from hexane/ethyl acetate to give pure (±)-**5c** (20.2 g, 66%) as a white solid: mp 86–88 °C; ^1H NMR δ 7.09 (t, J = 7.9 Hz, 1 H), 6.76 (d, J = 8.1 Hz, 1 H), 6.61 (d, J = 7.4 Hz, 1 H), 5.82–5.18 (m, 3 H), 4.32–4.24 (m, 1 H), 3.81 (s, 3 H), 4.06–1.60 (m, 9 H); IR (mull) ν_{max} 1682, 1641, 1601, 1587 cm^{-1}; MS, M^+ m/z 307, other ions at m/z 216, 173, 186, 173, 149, 135, 115. This compound was assigned as the cis product (±)-**5c** on the basis of analogy to (±)-**5a**. Anal. ($C_{20}H_{21}NO_2$) C, H, N.

***cis*-(±)-2,3,3a,4,9,9a-Hexahydro-5-methoxy-1-*n*-propyl-1*H*-benz[*f*]indole Hydrochloride (7a).** A solution of (±)-**5a** (12.97 g, 50 mmol) in THF (10 mL) was added slowly to a suspension of lithium aluminum hydride (7.6 g, 200 mmol) in THF (240 mL) at 0 °C. The mixture was refluxed for 4–6 h and cooled to room temperature. The gray suspension was then transferred into an Erlenmeyer flask, and quenched at 0 °C by slow addition of saturated aqueous sodium sulfate with vigorous stirring. The mixture was diluted with 1 L of ethyl acetate and dried over anhydrous sodium sulfate. Filtration through a Celite pad was followed by concentration of the filtrate in vacuo. The crude product was then purified by medium-pressure liquid chroma-

Table VII. Locomotor Activity in Mice

compd	dose[a]	reserpinized mice: stimulation (mean counts)	reserpinized mice: antagonism of apomorphine[b]	antagonism of amphetamine[c]: 0–10 min	antagonism of amphetamine[c]: 10–20 min
Apo[d]	0.03	22	119	78	86
	0.3	150*	135	73	96
	3.2	1777*	139	52**	42*
	32	1184*	113	69	66
Hal[e]	0.3	9	58	94	71
	2.7	1	10*	72	28*
(-)-3PPP[f]	0.3	31	118	127	106
	3.3	8	106	91	83
	33	13	41*	59	58*
(±)-8a	0.4	251	148		
	3.5	1168*	129		
	35	561*	61		
(-)-8a	0.4	581*	86	20*	30*
	3.6	851*	72	18*	12*
	36	308*	14*	21*	20*
(±)-8d	0.4	423*	98	41*	71
	4.3	912*	69	46*	38*
	43	1539*	114	29*	23*
(-)-8d	0.4	739*	56*	48*	71
	3.7	1014*	47*	52*	62*
	37	1625*	43*	93	53
(+)-8d	0.4	45	81	121	119
	3.7	1	86	109	119
	37	113*	77	84	103
(±)-8e	0.4	450**	108	61**	77
	3.8	1409*	133	40*	54**
	38	1783*	123	55**	46**
(-)-8e	0.4	1092*	141	60**	61**
	3.8	1297*	147**	23*	29*
	38	1549*	103	54*	34*
(+)-8e	0.4	45	81	121	119
	3.7	1	86	109	119
	37	113*	77	84	103
(±)-8h	0.4	1	129	83	88
	3.6	539*	163*	31*	60*
	36	1033*	117	25*	49*

[a] Dose in μmol/kg ip. [b] Mean percent of apomorphine control. [c] Mean percent of amphetamine control. [d] Apomorphine hydrochloride hemihydrate. [e] Haloperidol. [f] (-)-3-(1-*n*-propyl-3-piperidinyl)phenol monohydrobromide. *$p < 0.05$. **$p < 0.10$.

Table VIII. The Effect of Selected Compounds on Arterial Blood Pressure (BP) and Sympathetic Nerve Activity (SND) in the Anesthetized Cat

compd	SND[a] ED_{50} (μmol/kg)	max decrease SND (% control)	% BP (at SND ED_{50})	max decrease BP[b] (% control)
DPAT	0.03	2.0 (±0.5)	66.0 (±6)	57.0 (±3)
(±)-8b	IA[c]	78.0 (±12)		63.0 (±3)
(±)-14b	1.18	25.0 (±7)	85.0 (±5)	63.0 (±4)

[a] Dose at which the SND has been reduced to 50% of the pretreatment value. [b] Maximum decrease in blood pressure observed following 1 mg/kg dose. [c] Inactive.

tography on 1 kg of silica gel, by eluting with hexane/acetone (4:1) and collecting 40 mL fractions. Fractions homogeneous by TLC were combined and concentrated in vacuo to give the desired product as an oil (12.2 g, 99%). This oil was converted into the HCl salt and recrystallized to yield (±)-**7a** as a white solid: ^{1}H NMR δ 7.10 (t, J = 7.7 Hz, 1 H), 6.78 (d, J = 7.4 Hz, 1 H), 6.73 (d, J = 8.2 Hz), 3.81 (s, 3 H), 3.81–1.58 (m, 14 H), 1.05 (t, J = 7.4 Hz, 3 H); IR (mull) ν_{max} 1605, 1587 cm^{-1}; MS, M$^+$ m/z 245, other ions at m/z 216, 185, 159, 128. ($C_{16}H_{23}NO$·HCl) C, H, N.

***trans*-(±)-2,3,3a,4,9,9a-Hexahydro-5-methoxy-1-*n*-propyl-1*H*-benz[*f*]indole Hydrochloride (8a).** This compound was prepared from (±)-**6a** (3.89 g, 15 mmol), using the reduction procedure described in the preparation of (±)-**7a**. The crude product was purified by medium-pressure liquid chromatography on 560 g of silica gel, eluting with hexane/acetone (4:1), to give the desired product (3.65 g, 99%) as an oil. This oil was converted into the HCl salt and recrystallized to yield (±)-**8a** as a white solid: ^{1}H NMR δ 7.12 (t, J = 7.9 Hz, 1 H), 6.76 (d, J = 7.7 Hz, 1 H), 6.68 (d, J = 8.0 Hz), 3.82 (s, 3 H), 3.82–1.62 (m, 14 H), 1.07 (t, J = 7.4 Hz, 3 H); IR (mull) ν_{max} 1602, 1583 cm^{-1}; MS, M$^+$ m/z 245, other ions at m/z 216, 185, 159, 128. ($C_{16}H_{23}NO$·HCl) C, H, N.

Alternative Synthesis of (±)-7a and (±)-8a. A solution of keto ester **4** (24.8 g, 0.1 mol), *n*-propylamine (9.9 mL, 0.12 mol), and acetic acid (8.6 mL) in toluene (400 mL) was refluxed for 2 h (bath temperature, 120 °C). The solvent was removed in vacuo to yield a dark brown solid. ^{1}H NMR showed the appearance of a singlet at δ 5.75 (enamine proton at C-1) accompanied by disappearance of the methyl ester peak, indicating complete conversion to enamine lactam. A 2-L, three-neck, round-bottomed flask, equipped with a dropping funnel and a mechanical stirrer, was charged with LAH powder (6.8 g, 0.18 mol) and THF (400 mL). The suspension was cooled to −20 to −30 °C and $AlCl_3$ powder (8.0 g, 0.06 mol) was added through a powder funnel. After stirring for 30 min, the enamine lactam was dissolved in THF (300 mL) and added slowly over a period of 1 h. The mixture was then allowed to warm to room temperature, stirred for 1 h, and then transferred into an Erlenmeyer flask. Saturated aqueous sodium sulfate was added slowly until the gray suspension became white. The mixture was diluted with THF (1 L), dried ($MgSO_4$), filtered, and concentrated in vacuo to yield a brown oil. This brown oil was dissolved in isopropyl alcohol (600 mL) and cooled to 0–5 °C. Sodium borohydride (7.6 g, 0.2 mol) was added over 5 min and the resulting greenish mixture was stirred at room temperature for 24 h. The reaction was quenched with 6 N HCl at 0–5 °C until pH <3 and followed by removal of the isopropyl alcohol in vacuo. The residue was diluted with water and extracted with 300 mL of ether to remove any nonbasic and neutral organic compounds. The aqueous layer was treated with 20% sodium hydroxide until pH >13 and extracted with methylene chloride (2 × 800 mL). The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated to give a brown oil. The oil was purified by flash chromatography on 1 kg of silica gel, by eluting with 8 L of 10% acetone/hexane and 10 L of 30% acetone/hexane and collecting 300-mL fractions. Fractions 4–11 gave a brown oil (1.7 g) which was identified as the naphthelenic product. Fractions 19–29 gave a brown oil (7.8 g, 32%) which was identified by ^{1}H NMR as the cis product (±)-**7a**. Fractions 30–60 gave a brown oil (8.4 g, 34%) which was identified by ^{1}H NMR as the trans product (±)-**8a**.

***cis*-(±)-2,3,3a,4,9,9a-Hexahydro-5-methoxy-1-(2-propenyl)-1*H*-benz[*f*]indole Hydrochloride (7b).** This compound was prepared from (±)-**5b** (7.72 g, 30 mmol), using the reduction procedure described in the preparation of (±)-**7a**. The crude product was converted into the HCl salt and recrystallized to yield (±)-**7b** (7.2 g, 86%) as a white solid: ^{1}H NMR δ 7.14 (t, J = 7.9 Hz, 1 H), 6.80 (d, J = 6.9 Hz, 1 H), 6.77 (d, J = 8.0 Hz), 6.38–5.42 (m, 3 H), 3.82 (s, 3 H), 3.98–1.60 (m, 12 H); IR (mull) ν_{max} 1603, 1588 cm^{-1}; MS, M$^+$ m/z 243, other ions at m/z 228, 216, 202, 159, 135, 122. ($C_{16}H_{21}NO$·HCl) C, H, N.

***trans*-(±)-2,3,3a,4,9,9a-Hexahydro-5-methoxy-1-(2-propenyl)-1*H*-benz[*f*]indole Hydrochloride (8b).** This compound was prepared from (±)-**6b** (1.93 g, 30 mmol), using the reduction procedure described in the preparation of (±)-**7a**. The crude product was converted into the HCl salt and recrystallized to yield (±)-**8b** (1.68 g, 80%) as a white solid: ^{1}H NMR δ 7.16 (t, J = 7.9 Hz, 1 H), 6.74 (d, J = 8.4 Hz, 1 H), 6.70 (d, J = 8.4 Hz, 1 H), 6.28–5.494 (m, 3 H), 3.82 (s, 3 H), 4.08–1.54 (m, 12 H); IR (mull) ν_{max} 1603, 1588 cm^{-1}; MS, M$^+$ m/z 243, other ions at m/z 228, 216, 202, 159, 135, 122. ($C_{16}H_{21}NO$·HCl) C, H, N.

***cis*-(±)-2,3,3a,4,9,9a-Hexahydro-5-methoxy-1-benzyl-1*H*-benz[*f*]indole Hydrochloride (7c).** This compound was prepared from (±)-**5c** (16.9 g, 55 mmol), using the reduction procedure described in the preparation of (±)-**7a**. The crude product was converted into the HCl salt and recrystallized to yield (±)-**7c** (16.1 g, 89%) as a white solid: ^{1}H NMR δ 7.67–7.46 (m, 5 H), 7.10 (t, J = 7.9 Hz, 1 H), 6.75 (d, J = 8.3 Hz, 1 H), 6.64 (d, J = 7.4 Hz, 1 H), 4.31 (q of d, J = 18.0 and 4.5 Hz, 2 H), 3.79 (s, 3 H), 3.78–3.60 (m, 1 H), 3.52–2.16 (m, 9 H); IR (mull) ν_{max} 1604, 1588 cm^{-1}; MS, M$^+$ m/z 293, other ions at m/z 278, 216, 202, 135, 115. ($C_{20}H_{23}NO$·HCl) C, H, N.

***trans*-(±)-2,3,3a,4,9,9a-Hexahydro-5-methoxy-1-benzyl-1*H*-benz[*f*]indole Hydrochloride (8c).** This compound was

prepared from (±)-6c (4.6 g, 15 mmol), using the reduction procedure described in the preparation of (±)-7a. The crude product was converted into the HCl salt and recrystallized to yield (±)-8c (4.6 g, 93%) as a white solid: ^{1}H NMR δ 7.64–7.44 (m, 5 H), 7.13 (t, J = 7.9 Hz, 1 H), 6.69 (d, J = 8.3 Hz, 1 H), 6.66 (d, J = 7.4 Hz, 1 H), 4.32 (q, J = 18.0 Hz, 2 H), 3.90–3.70 (m, 1 H), 3.80 (s, 3 H), 3.34–1.60 (m, 9 H); IR (mull) ν_{max} 1601, 1585 cm^{-1}; MS, M$^+$ m/z 243, other ions at m/z 278, 216, 202, 135, 115. ($C_{20}H_{23}NO$·HCl) C, H, N.

***cis*-(±)-2,3,3a,4,9,9a-Hexahydro-5-hydroxy-1-*n*-propyl-1*H*-benz[*f*]indole Hydrochloride (7d).** A solution of the free base of (±)-7a (9.82 g, 40 mmol) in 40 mL of 48% hydrobromic acid was refluxed (bath temperature, 120 °C) for 18 h. The mixture was cooled to room temperature and treated with 20% sodium hydroxide until pH >9. The mixture was extracted with hot ethyl acetate (3 × 800 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to give a light pinkish-brown solid. This solid was recrystallized as a free base to yield (±)-7d (7.0 g, 76%) as a white solid: ^{1}H NMR δ 7.00 (t, J = 7.8 Hz, 1 H), 6.76 (d, J = 7.4 Hz, 1 H), 6.64 (d, J = 8.0 Hz, 1 H), 3.14–1.42 (m, 15 H), 0.92 (t, J = 7.3 Hz, 3 H); IR (mull) ν_{max} 3333, 1611, 1589 cm^{-1}; MS, M$^+$ m/z 231, other ions at m/z 216, 202, 188, 159, 145, 111. Anal. ($C_{15}H_{21}NO$) C, H, N.

***trans*-(±)-2,3,3a,4,9,9a-Hexahydro-5-hydroxy-1-*n*-propyl-1*H*-benz[*f*]indole Hydrochloride (8d).** This compound was prepared from (±)-8a (2.45 g, 10 mmol), using the demethylation procedure described in the preparation of (±)-7d. The crude product (pinkish-brown solid) was recrystallized as a free base to yield (±)-8d (1.8 g, 78%) as a white solid: ^{1}H NMR δ 7.00 (t, J = 7.8 Hz, 1 H), 6.67 (d, J = 8.0 Hz, 1 H), 6.63 (d, J = 7.9 Hz, 1 H), 3.80–1.72 (m, 14 H), 1.06 (t, J = 7.4 Hz, 3 H); (DMF-d_7) δ 7.00 (t, J = 7.7 Hz, 1 H), 6.77 (d, J = 7.7 Hz, 1 H), 6.65 (d, J = 7.6 Hz, 1 H), 3.92–1.75 (m, 14 H), 0.99 (t, J = 7.4 Hz, 3 H); IR (mull) ν_{max} 3307, 1606, 1580 cm^{-1}; MS, M$^+$ m/z 231, other ions at m/z 216, 202, 188, 159, 145, 111. Anal. ($C_{15}H_{21}NO$) C, H, N.

***trans*-(±)-2,3,3a,4,9,9a-Hexahydro-5-hydroxy-1-(2-propenyl)-1*H*-benz[*f*]indole Hydrochloride (8e).** A solution of diphenylphosphine (0.7 mL, 4 mmol) in THF (10 mL was treated with 1.6 M n-butyllithium in hexane (2.5 mL, 4 mmol) at 0 °C. The resulting red solution was stirred for 10 min, the starting material (±)-8b (0.26 g, 1.0 mmol) in 2 mL of THF was added, and the mixture was refluxed for 24 h. The reaction was quenched with water and extracted with methylene chloride (2 × 500 mL). The combined organic layers were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to give a colorless oil. This oil was purified by medium-pressure liquid chromatography on 200 g of silica gel, by eluting with hexane/acetone (2:1) and collecting 40-mL fractions. Fractions homogeneous by TLC were combined and concentrated in vacuo to give a colorless oil. This oil was converted into the HCl salt and recrystallized to yield (±)-8e (0.22 g, 83%) as a white solid: ^{1}H NMR (CD_3OD) δ 6.90 (t, J = 7.8 Hz, 1 H), 6.57 (d, J = 7.8 Hz, 1 H), 6.54 (d, J = 8.0 Hz, 1 H), 6.00–5.42 (m, 3 H), 4.07–1.72 (m, 12 H); (DMF-d_7) δ 7.00 (t, J = 7.8 Hz, 1 H), 6.77 (d, J = 7.8 Hz, 1 H), 6.64 (d, J = 7.7 Hz, 1 H), 6.18–5.45 (m, 3 H), 3.90–1.84 (m, 12 H); IR (mull) ν_{max} 3284, 1609, 1585 cm^{-1}; MS, M$^+$ m/z 229, other ions at m/z 202, 186, 159, 145, 122, 109. Anal. ($C_{15}H_{19}NO$·HCl) C, H, N.

***cis*-(±)-2,3,3a,4,9,9a-Hexahydro-5-methoxy-1*H*-benz[*f*]indole Hydrochloride (7f).** A mixture of (±)-7c (6.6 g, 20 mmol), 10% Pd/C (6.6 g), and 1 mL of concentrated HCl in 95% ethanol (100 mL) was hydrogenolized in a Parr shaker under 45 psi of hydrogen atmosphere at room temperature for 24 h. The mixture was diluted with 1 L of methanol, filtered through a folded filter paper, and concentrated in vacuo. The crude product was recrystallized to yield (±)-7f (3.7 g, 77%) as a white solid: ^{1}H NMR δ 7.15 (t, J = 7.9 Hz, 1 H), 6.84 (d, J = 7.4 Hz, 1 H), 6.77 (d, J = 8.2 Hz, 1 H), 4.00 (q, J = 8.5 Hz, 1 H), 3.81 (s, 3 H), 3.34–1.75 (m, 9 H); IR (mull) ν_{max} 3470, 3185, 1598, 1586 cm^{-1}; MS, M$^+$ m/z 203, other ions at m/z 188, 174, 159, 134, 115. Anal. ($C_{15}H_{19}NO$·HCl) C, H, N.

***trans*-(±)-2,3,3a,4,9,9a-Hexahydro-5-methoxy-1*H*-benz[*f*]indole Hydrochloride (8f).** This compound was prepared from (±)-8c (4.5 g, 13.6 mmol), using the hydrogenolysis procedure described in the preparation of (±)-7f. The crude product was recrystallized to yield (±)-8f (2.9 g, 70%) as a white solid: ^{1}H NMR δ 7.13 (t, J = 7.9 Hz, 1 H), 6.72 (d, J = 7.5 Hz, 1 H), 6.70 (d, J = 8.1 Hz, 1 H), 3.81 (s, 3 H), 3.68–1.68 (m, 10 H); IR (mull) ν_{max} 3437, 3186, 1599, 1580 cm^{-1}; MS, M$^+$ m/z 203, other ions at m/z 188, 174, 159, 134, 115. Anal. ($C_{15}H_{19}NO$·HCl) C, H, N.

***cis*-(±)-2,3,3a,4,9,9a-Hexahydro-5-methoxy-1-(cyclopropylmethyl)-1*H*-benz[*f*]indole (7g).** A mixture of (±)-7f (0.48 g, 2 mmol), sodium carbonate (0.85 g, 8 mmol), and (bromomethyl)-cyclopropane (1.08 g, 8 mmol) in acetonitrile (20 mL) was refluxed (bath temperature, 90 °C) for 5 h. The mixture was cooled to room temperature and the solvent was removed in vacuo. The residue was treated with water and extracted with methylene chloride (2 × 500 mL). The organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to yield a brown oil. This oil was purified by medium-pressure liquid chromatography on 200 g silica gel, by eluting with ethyl acetate/hexane (1:2) and collecting 40-mL fractions. Fractions homogeneous by TLC afforded the desired product as a near colorless oil (0.30 g, 51%). This oil was converted into the HCl salt and recrystallized to yield (±)-7g as a white solid: ^{1}H NMR δ 7.14 (t, J = 7.7 Hz, 1 H), 6.80 (t, J = 7.4 Hz, 1 H), 6.78 (d, J = 8.2 Hz, 1 H), 4.06–3.95 (m, 1 H), 3.81 (s, 3 H), 3.68–2.22 (m, 11 H), 1.58–0.42 (m, 5 H); IR (mull) ν_{max} 1603, 1588 cm^{-1}; MS, M$^+$ m/z 257, other ions at m/z 242, 216, 202, 159, 136, 123. Anal. ($C_{17}H_{23}NO$·HCl) C, H, N.

***trans*-(±)-2,3,3a,4,9,9a-Hexahydro-5-methoxy-1-(cyclopropylmethyl)-1*H*-benz[*f*]indole (8g).** This compound was prepared from (±)-8f (0.48 g, 2 mmol), using the alkylation procedure described in the preparation of (±)-7g. The crude product was purified by medium-pressure liquid chromatography on 200 g of silica gel, by eluting with ethyl acetate/hexane (1:2) and collecting 40-mL fractions. Fractions homogeneous by TLC afforded the desired product as a near colorless oil (0.24 g, 47%). This oil was converted into the HCl salt and recrystallized to yield (±)-8g as a white solid: ^{1}H NMR δ 7.16 (t, J = 7.9 Hz, 1 H), 6.74 (d, J = 7.7 Hz, 1 H), 6.72 (d, J = 8.0 Hz, 1 H), 4.13–4.00 (m, 1 H), 3.82 (s, 3 H), 3.42–1.70 (m, 11 H), 1.45–0.38 (m, 5 H); IR (mull) ν_{max} 1602, 1583 cm^{-1}; MS, M$^+$ m/z 257, other ions at m/z 242, 216, 202, 159, 136, 123. Anal. ($C_{17}H_{23}NO$·HCl) C, H, N.

***trans*-(±)-2,3,3a,4,9,9a-Hexahydro-5-hydroxy-1-(cyclopropylmethyl)-1*H*-benz[*f*]indole (8h).** This compound was prepared from (±)-8g (0.28 g, 0.95 mmol), using the demethylation procedure described in the preparation of (±)-7d. The crude product was purified by medium-pressure liquid chromatography on 100 g of silica gel, by eluting with hexane/acetone (1:1) and collecting 30-mL fractions. Fractions homogeneous by TLC afforded the desired product as a white solid (0.2 g, 83%). This solid was converted into the HCl salt and recrystallized to yield (±)-8h as a white solid: ^{1}H NMR δ 6.99 (t, J = 7.8 Hz, 1 H), 6.67 (d, J = 8.0 Hz, 1 H), 6.63 (d, J = 7.9 Hz, 1 H), 3.95–1.90 (m, 12 H), 1.32–0.42 (m, 5 H); IR (mull) ν_{max} 3335, 1610, 1586 cm^{-1}; MS, M$^+$ m/z 243, other ions at m/z 202, 188, 145, 123. Anal. ($C_{16}H_{21}NO$·HCl) C, H, N.

Resolution of *trans*-(±)-2,3,3a,4,9,9a-Hexahydro-5-methoxy-1-*n*-propyl-1*H*-benz[*f*]indole (8a) into Its Enantiomers, *trans*-(3a*S*)-(−)-8a and *trans*-(3a*R*)-(+)-8a. A mixture of the free base of (±)-8a (10.7 g, 43.7 mmol) and (−)-di-*p*-toluoyl-L-tartaric acid monohydrate (18.6 g, 45.9 mmol; Aldrich, D21,-960-6) was dissolved in hot methanol (150 mL) and concentrated to about 100 mL. The solution was allowed to stand at room temperature for 24 h. The crystals were isolated (14.42 g), and ^{1}H NMR showed an enhancement of the aromatic protons at δ 6.68 (d) and 6.65 (d) as well as the methyl protons at δ 0.92 (t), indicating an enrichment of one diastereomeric salt. ^{1}H NMR of the mother liquor showed enhancement of the aromatic protons at δ 6.65 (d) and 6.53 (d) as well as the methyl protons at δ 0.84 (t), indicating the other diastereomeric salt remained in solution. Two additional recrystallizations afforded **(−)-8a/di-*p*-toluoyl-L-tartaric acid salt** (11.4 g, 41.3%): ^{1}H NMR analysis indicated that the salt was >95% pure: mp 165–166 °C; ^{1}H NMR δ 7.85 (d, J = 8.2 Hz, 4 H), 7.11 (t, J = 7.9 Hz, 1 H), 7.07 (d, J = 8.2 Hz, 4 H), 6.68 (d, J = 7.7 Hz, 1 H), 6.65 (d, J = 7.7 Hz, 1 H), 5.85 (s, 2 H), 4.12–4.02 (m, 1 H), 3.81 (s, 3 H), 2.32 (s, 6 H), 3.32–1.55 (m, 13 H), 0.92 (t, J = 7.3 Hz, 3 H). This salt was converted to the free base by refluxing in a mixture of 50 mL of 10% sodium hydroxide and 250 mL of methanol overnight. The methanol

was removed in vacuo, and the residual material was extracted with ether (2 × 700 mL). The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated to give a colorless oil (4.32 g) as the free base of (-)-**8a**. A small amount of this oil was converted into the HCl salt and recrystallized to yield (-)-**8a** as a white solid: ^1H NMR, IR, and MS were identical to those of (±)-**8a**; $[\alpha]^{25}_D$ -140° (*c* 0.70, MeOH). Anal. ($C_{16}H_{23}NO$·HCl) C, H, N.

To purify the other enantiomer, the combined mother liquors were converted to the free base by the same method described above to give an oil. This oil (6.12 g, 25 mmol) was then combined with (+)-di-*p*-toluoyl-D-tartaric acid (10.1 g, 26.3 mmol) (Aldrich, 30,281-3) and dissolved in hot methanol (400 mL) and concentrated until crystals started to appear. After the solution was allowed to stand at room temperature for 24 h, the crystals were isolated to give 14.5 g of the diastereomeric salt. This recrystallization was repeated twice in a similar manner to give pure **(+)-8a/di-*p*-toluoyl-D-tartaric acid salt** (11.6 g, 42%): mp 165–166 °C; ^1H NMR was identical to that of (-)-8a/di-*p*-toluoyl-L-tartaric acid salt. This salt was converted to the free base by the same method described above to give a colorless oil (4.26 g). A small amount of this oil was converted into the HCl salt and recrystallized to yield (+)-**8a** as a white solid: ^1H NMR, IR, and MS were identical to those of (±)-**8a**; $[\alpha]^{25}_D$ +140° (*c* 0.67, MeOH). Anal. ($C_{16}H_{23}NO$·HCl) C, H, N.

The absolute configuration of (-)-**8a** and (+)-**8b** was determined by conversion into the corresponding phenolic analogs (-)-**8d** and (-)-**8d** and comparing the optical rotations of these with the phenolic analogs obtained from hydrogenation of the allyl analogs (-)-**8e** and (+)-**8e**. Both (-)-**8e** and (+)-**8e** were in turn obtained from O-demethylation of the corresponding (-)-**8b** and (+)-**8b**. The absolute configuration of (+)-**8b** was determined by X-ray crystallography.

Resolution of *trans*-(±)-2,3,3a,4,9,9a-Hexahydro-5-methoxy-1-(2-propenyl)-1*H*-benz[*f*]indole (8b) into Its Enantiomers, *trans*-(3a*S*)-(-)-8b and *trans*-(3a*R*)-(+)-8b. Resolution was carried out in a similar manner to that of (±)-**8a** described above. A mixture of the free base of (±)-**8b** (6.8 g, 28 mmol) and di-*p*-toluoyl-L-tartaric acid (11.9 g, 29.4 mmol) was recrystallized three times to give pure **(-)-8b/di-*p*-toluoyl-L-tartaric acid salt** (7.55 g, 43%): mp 167–168 °C; ^1H NMR (CD_3Cl + 5% CD_3OD) δ 7.94 (d, *J* = 8.2 Hz, 4 H), 7.14 (d, *J* = 8.2 Hz, 4 H), 7.08 (t, *J* = 7.9 Hz, 1 H), 6.67 (d, *J* = 8.1 Hz, 1 H), 6.59 (d, *J* = 7.8 Hz, 1 H), 5.94 (s, 2 H), 6.05–5.82 (m, 1 H), 5.36 (dd, *J* = 16 and 12 Hz, 2 H), 3.81 (s, 3 H), 2.38 (s, 3 H), 3.92–1.50 (m, 12 H). This salt was converted to the free base as described above [resolution of (-)-**8a** and (+)-**8a**]. A small amount of this oil was then converted into the HCl salt and recrystallized to yield (-)-**8b** (0.83 g) as a white solid: ^1H NMR, IR, and MS were identical to those of racemate (±)-**8b**; $[\alpha]^{25}_D$ -137° (*c* 0.84, MeOH). Anal. ($C_{16}H_{21}NO$·HCl) C, H, N.

To purify the other enantiomer, the combined mother liquor was free-based the same way as described above to give an oil. A mixture of this oil (4.2 g, 17.3 mmol) and di-*p*-toluoyl-D-tartaric acid (7.34 g, 19.0 mmol) was recrystallized three times from methanol to give pure **(+)-8b/di-*p*-toluoyl-D-tartaric acid salt** (7.06 g, 40%): mp 167–168 °C; ^1H NMR was identical to that of (-)-**8b**/di-*p*-toluoyl-L-tartaric acid salt. This salt was converted to the free base. A small amount of this oil was then converted into the HCl salt and recrystallized to yield (+)-**8b** as a white solid: ^1H NMR, IR, and MS were identical to those of the racemate (±)-**8b**; $[\alpha]^{25}_D$ +136° (*c* 0.42, MeOH). X-ray crystallography was performed on this HCl salt of (+)-**8b** and the absolute configuration of this compound was determined to be *trans*-(3a*R*) (Figure 1). Anal. ($C_{16}H_{21}NO$·HCl) C, H, N.

The purity of enantiomers (-)-**8b** and (+)-**8b** was also determined by HPLC analysis using a Chiracel OD column (25 cm × 4.6 mm), by eluting with 30% 2-propanol/hexane (flow rate, 1 mL/min) and detection with a Beckman 165 variable-wavelength detector. The retention times for (-)-**8b** and (+)-**8b** were found to be 6.45 and 4.93 min, respectively. Both samples showed no contamination by the other isomer, indicating better than 99% purity.

***trans*-(3a*S*)-(-)-2,3,3a,4,9,9a-Hexahydro-5-hydroxy-1-*n*-propyl-1*H*-benz[*f*]indole Hydrochloride (8d).** This compound was prepared from the free base of (-)-**8a** (4.17 g, 17 mmol) using the demethylation procedure as described in the preparation of (±)-**8e**. The crude product was purified by medium-pressure liquid chromatography on 400 g of silica gel, by eluting with methylene chloride/acetone (1:1) and collecting 40-mL fractions. Fractions homogeneous by TLC were combined and concentrated to give the free base of (-)-**8d** (3.67 g, 93.4%). This compound was converted into the HCl salt and recrystallized to yield (-)-**8d** as a white solid: ^1H NMR, IR, and MS were identical to those of the racemate (±)-**8a**; $[\alpha]^{25}_D$ -156° (*c* 0.31, MeOH) and -154° (*c* 0.18, 10% H_2O/DMF). Anal. ($C_{15}H_{21}NO$·HCl) C, H, N.

This compound was also prepared by hydrogenation of the allyl analog (-)-**8e**. A solution of (-)-**8e** (0.2 g, 0.8 mmol) and 10% Pd/C (0.1 g) in 150 mL of methanol was hydrogenated in a Parr shaker apparatus at 45 psi of hydrogen atmosphere. After 3 h at room temperature, the mixture was filtered through a layer of Solka-floc, concentrated, and recrystallized to yield a white solid: mp, ^1H NMR, IR, and MS were identical to those of (-)-**8d** obtained above; $[\alpha]^{25}_D$ -154° (*c* 0.14, 10% H_2O/DMF).

***trans*-(3a*R*)-(+)-2,3,3a,4,9,9a-Hexahydro-5-hydroxy-1-*n*-propyl-1*H*-benz[*f*]indole Hydrochloride (8d).** This compound was prepared from the free base of (+)-**8a** (3.93 g, 16 mmol), using the demethylation procedure described in the preparation of (±)-**8e**. The crude product was purified by liquid chromatography on 400 g of silica gel, by eluting with methylene chloride/acetone (1:1) and collecting 40-mL fractions. Fractions homogeneous by TLC were combined and concentrated to give the free base of (+)-**8d** (3.52 g, 82%). This compound was converted into the HCl salt and recrystallized to yield (+)-**8d** as a white solid: ^1H NMR, IR, and MS were identical to those of the racemate (±)-**8d**; $[\alpha]^{25}_D$ +156° (*c* 0.25, MeOH). Anal. ($C_{15}H_{21}NO$·HCl) C, H, N.

***trans*-(3a*S*)-(-)-2,3,3a,4,9,9a-Hexahydro-5-hydroxy-1-(2-propenyl)-1*H*-benz[*f*]indole Hydrochloride (8e) and *trans*-(3a*R*)-(+)-2,3,3a,4,9,9a-Hexahydro-5-hydroxy-1-(2-propenyl)-1*H*-benz[*f*]indole Hydrochloride (8e).** Compounds (-)-**8e** and (+)-**8e** were prepared from the free base of (-)-**8b** (2.92 g, 12 mmol) and (+)-**8b** (2.7 g, 11.1 mmol), respectively, using the demethylation procedure described in the preparation of **9b**. Each of these crude products were purified by medium-pressure liquid chromatography on 400 g of silica gel, by eluting with methylene chloride/acetone (1:1) and collecting 40-mL fractions. Fractions homogeneous by TLC were combined and concentrated to give (-)-**8e** (2.65 g, 96.3%) and (+)-**8e** (2.48 g, 93.2%). These compounds were converted into their HCl salts and recrystallized to yield (-)-**8e** and (+)-**8e** as white solids: ^1H NMR, IR, and MS were identical to those of the racemate (±)-**8e**; $[\alpha]^{25}_D$ -155° (*c* 0.24, 10% H_2O/DMF) for (-)-**8e** and +155° (*c* 0.24, 10% H_2O/DMF) for (+)-**8e**. Anal. ($C_{15}H_{19}NO$·HCl) C, H, N.

(±)-3′,4′-Dihydro-8′-methoxy-3′-(2-propenyl)spiro-[1,3-dioxolane-2,2′[1′*H*]naphthalene] (11). A mixture of **10** (15 g, 68 mmol), trimethyl orthoformate (30 mL, 272 mmol), ethylene glycol (38 mL, 680 mmol), and p-toluenesulfonic acid monohydrate (0.13 g, 0.68 mmol) in methylene chloride (306 mL) was stirred at room temperature for 24 h. The reaction was quenched with saturated sodium bicarbonate and extracted with methylene chloride (2 × 1 L). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to yield a yellow oil. This oil was purified by flash chromatography on 1 kg of silica gel, by eluting with 2 L of hexane and 5 L of hexane/ethyl acetate (9:1) and collecting 500-mL fractions. Fractions homogeneous by TLC afforded **11** (15.5 g, 88%) as a light yellow oil: ^1H NMR δ 7.10 (t, *J* = 7.9 Hz, 1 H), 6.73 (d, *J* = 7.6 Hz, 1 H), 6.65 (d, *J* = 8.1 Hz, 1 H), 5.92–4.95 (m, 3 H), 4.15–3.92 (m, 4 H), 3.80 (s, 3 H), 3.12–1.82 (m, 7 H); IR (mull) ν_{max} 1640, 1604, 1587 cm^{-1}; MS, M^+ *m/z* 260, other ions at *m/z* 245, 219, 206, 174, 160, 147, 134. Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.48; H, 8.07.

(±)-1,2,3,4-Tetrahydro-5-methoxy-3-oxo-2-naphthaleneacetic Acid Methyl Ester (12). In a three-neck, round-bottomed flask, equipped with a mechanical stirrer, a solution of sodium periodate (57.8 g, 270 mmol) and water (1 L) was treated with potassium permanganate (2.8 g, 18 mmol). After stirring for 30 min at room temperature, potassium carbonate (7.5 g, 54 mmol) was added and the mixture stirred for 15 min. Freshly distilled *tert*-butanol (300 mL) was then added over a 5 min period followed by a solution of **11** (7.8 g, 30 mmol) in *tert*-

butanol (300 mL) over 5 min. The color of the mixture immediately turned from purple to pink. After stirring for 3 h, the mixture was cooled to 0–5 °C and sodium bisulfite powder was added slowly until the pink-brown suspension became a clear yellow solution. The mixture was diluted with water (1 L) and extracted with methylene chloride (2 × 2 L). The combined organic layers were washed with water and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to give a pale yellow solid (7.3 g). This solid was dissolved in acetonitrile (150 mL) and treated with 150 mL of HCl/MeOH (prepared by adding 24 mL of acetyl chloride to 126 mL of methanol at 0–5 °C). The yellow solution was allowed to stand in the refrigerator overnight and then stirred at room temperature for 3 h. Water (30 mL) was added and the solution was stirred at room temperature for 24 h. The solvent was then removed in vacuo and the resulting yellow oil was extracted with ethyl acetate (2 × 1 L). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to yield a yellow oil. This oil was purified by flash chromatography on 1 kg of silica gel, by eluting with 8 L of ethyl acetate/hexane (20:1) and 8 L of ethyl acetate/hexane (10:1) and collecting 500-mL fractions. Fractions homogeneous by TLC afforded **12** (4.28 g, 57.5%). Recrystallization from ethyl acetate/hexane afforded **12** as a pale yellow solid: mp 73–74 °C; ^{1}H NMR δ 7.19 (t, J = 7.9 Hz, 1 H), 6.80 (d, J = 7.6 Hz, 1 H), 6.76 (d, J = 8.3 Hz, 1 H), 3.83 (s, 3 H), 3.71 (s, 3 H), 3.86–2.38 (m, 7 H); IR (mull) ν_{max} 1742, 1717, and 1586 cm^{-1}; MS, M$^+$ m/z 248, other ions at m/z 230, 216, 199, 188, 174, 159. Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.54; H, 6.71.

***cis*-(±)-1,3,3a,4,9,9a-Hexahydro-8-methoxy-1-(2-propenyl)-2*H*-benz[*f*]indol-2-one (5d) and *trans*-(±)-1,3,3a,4,9,9a-Hexahydro-8-methoxy-1-(2-propenyl)-2*H*-benz[*f*]indol-2-one (6d).** These compounds were prepared from keto ester **12** (3.97 g, 16 mmol), using the reductive amination/cyclization procedure described in the preparation of (±)-**5a** and (±)-**6a**. The crude product was purified by medium-pressure liquid chromatography on 800 g of silica gel, by eluting with hexane/ethyl acetate/2-propanol (10:5:1) and collecting 40-mL fractions. Fractions homogeneous by TLC were combined and concentrated.

The less polar product was recrystallized from hexane/ethyl acetate to yield **23b** (0.52 g, 13%) as a white solid: mp 102–104 °C; ^{1}H NMR δ 7.16 (t, J = 7.9 Hz, 1 H), 6.75 (d, J = 7.8 Hz, 1 H), 6.72 (d, J = 8.2 Hz, 1 H), 5.78–5.17 (m, 3 H), 4.38–4.28 (m, 1 H), 3.84 (s, 3 H), 3.78–2.08 (m, 9 H); IR (mull) ν_{max} 1683, 1578 cm^{-1}; MS, M$^+$ m/z 257, other ions at m/z 242, 214, 172, 158. This compound was assigned as the *trans* product (±)-**6d** on the basis of analogy to (±)-**6a**. Anal. ($C_{16}H_{19}NO_2$) C, H, N.

The more polar product was recrystallized from hexane/ethyl acetate to yield **23a** (8.7 g, 67.4%) as a white solid: mp 65–67 °C; ^{1}H NMR δ 7.13 (t, J = 7.8 Hz, 1 H), 6.77 (d, J = 7.3 Hz, 1 H), 6.75 (d, J = 8.3 Hz, 1 H), 5.81–5.20 (m, 3 H), 4.35–4.28 (m, 1 H), 3.82 (s, 3 H), 3.56–2.00 (m, 9 H); IR (mull) ν_{max} 1641, 1589 cm^{-1}; MS, M$^+$ m/z 257, other ions at m/z 242, 214, 172, 158. This compound was assigned as the *cis* product (±)-**5d** on the basis of analogy to (±)-**5a**. Anal. ($C_{16}H_{19}NO_2$) C, H, N.

***cis*-(±)-2,3,3a,4,9,9a-Hexahydro-8-methoxy-1-(2-propenyl)-1*H*-benz[*f*]indole Hydrochloride (7i).** This compound was prepared from (±)-**5d** (2.0 g, 7.8 mmol) and LAH (1.18 g, 31.2 mmol), using the reduction procedure described in the preparation of (±)-**7a**. The crude product was purified by medium-pressure liquid chromatography on 400 g of silica gel, by eluting with hexane/acetone (4:1) and collecting 40-mL fractions. Fractions homogeneous by TLC gave a colorless oil (1.74 g, 91.6%). This oil was converted into the HCl salt and recrystallized to yield (±)-**7i** as a white solid: ^{1}H NMR δ 7.13 (t, J = 7.7 Hz, 1 H), 6.75 (d, J = 8.2 Hz, 2 H), 6.38–5.40 (m, 3 H), 3.81 (s, 3 H), 4.08–1.60 (m, 12 H); IR (mull) ν_{max} 1603, 1587 cm^{-1}; MS, M$^+$ m/z 243, other ions at m/z 228, 216, 186, 173, 159. ($C_{16}H_{21}NO$·HCl) C, H, N.

***trans*-(±)-2,3,3a,4,9,9a-Hexahydro-8-methoxy-1-(2-propenyl)-1*H*-benz[*f*]indole Hydrochloride (8i).** This compound was prepared from (±)-**6d** (0.35 g, 1.4 mmol) and LAH (0.22 g, 5.6 mmol), using the reduction procedure described in the preparation of (±)-**7a**. The crude product was purified by medium-pressure liquid chromatography on 400 g of silica gel, by eluting with hexane/acetone (4:1) and collecting 40-mL fractions. Fractions homogeneous by TLC gave a colorless oil (0.32 g, 94%). This oil was converted into the HCl salt and recrystallized to yield (±)-**8i** as a white solid: ^{1}H NMR δ 7.16 (t, J = 7.9 Hz, 1 H), 6.71 (d, J = 7.5 Hz, 1 H), 6.69 (d, J = 8.1 Hz, 1 H), 6.30–5.51 (m, 3 H), 3.80 (s, 3 H), 4.08–1.58 (m, 12 H); IR (mull) ν_{max} 1602, 1583 cm^{-1}; MS, M$^+$ m/z 243, other ions at m/z 228, 216, 186, 173, 159. ($C_{16}H_{21}NO$·HCl) C, H, N.

(2α,3aα,9aα)-(±)-2,3,3a,4,9,9a-Hexahydro-8-methoxy-2-methyl-1-*n*-propyl-1*H*-benz[*f*]indole Hydrochloride (14a) and (2β,3aα,9aα)-(±)-2,3,3a,4,9,9a-Hexahydro-8-methoxy-2-methyl-1-*n*-propyl-1*H*-benz[*f*]indole Hydrochloride (14b). A mixture of (±)-**13** (3.89 g, 15 mmol) and mercuric acetate (14.3 g, 45 mmol) in methanol (450 mL) was stirred at room temperature for 3 days. The greenish-gray mixture was then treated with a solution of sodium borohydride (2.27 g, 60 mmol) in 20% sodium hydroxide (60 mL). After stirring of the mixture vigorously for 3 h, methanol was removed in vacuo and the concentrate was extracted with methylene chloride (2 × 1 L). The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting oil was purified by medium-pressure liquid chromatography on 800 g of silica gel, by eluting with hexane/acetone (4:1) and collecting 40-mL fractions. Fractions homogeneous by TLC were combined and concentrated. The less polar product was obtained as an oil (2.05 g, 53%), assigned as the free base of (±)-**14a**. This oil was then converted into the HCl salt and recrystallized to yield (±)-**14a** as a white solid: ^{1}H NMR δ 7.13 (t, J = 7.9 Hz, 1 H), 6.75 (t, J = 8.6 Hz, 2 H), 3.81 (s, 3 H), 3.70–3.62 (m, 1 H), 3.50–1.72 (m, 12 H), 1.69 (d, J = 6.4 Hz, 3 H), 1.08 (t, J = 7.3 Hz, 3 H); IR (mull) ν_{max} 1602, 1587 cm^{-1}; MS, M$^+$ m/z 259, other ions at m/z 244, 230, 159, 135. Anal. ($C_{17}H_{25}NO$·HCl) C, H, N.

A more polar product was obtained as an oil (0.33 g, 8.5%) and assigned as the free base of (±)-**14b**. This oil was converted into the HCl salt and recrystallized to yield (±)-**14b** as a white solid: ^{1}H NMR δ 7.14 (t, J = 7.9 Hz, 1 H), 6.75 (d, J = 8.4 Hz, 2 H), 3.81 (s, 3 H), 3.75–3.64 (m, 1 H), 3.38–1.60 (m, 12 H), 1.22 (d, J = 6.9 Hz, 3 H), 1.04 (t, J = 7.4 Hz, 3 H); IR (mull) ν_{max} 1603, 1586 cm^{-1}; MS, M$^+$ m/z 259, other ions at m/z 244, 230, 159, 135. Anal. ($C_{17}H_{25}NO$·HCl) C, H, N.

A definitive assignment was made by X-ray crystallography on compound (±)-**14a** (Figure 2).

X-ray Crystallography of (+)-8b and (±)-14a. Intensity data were collected at low temperature, −120 °C, on a Siemens $P2_1$ diffractometer using graphite-monochromatized Cu Kα radiation, (λ(Cu Kα) = 1.5418 Å), with $2\theta_{max}$ = 134° for (+)-**8b** and 130° for (±)-**14a**. $\theta/2\theta$ step scans were used with scan widths ≥ 3.4° and scan rates of 2°/min for (+)-**8b** and 1°/min for (±)-**14a**. Ten reflections periodically monitored showed no trend toward deterioration; $\sigma^2(I)$ was approximated by $\sigma^2(I)$ from counting statistics + (dI)^2, where the coefficient of I was calculated from the variations in intensities of the monitored reflections, and was 0.022 for (+)-8b and 0.029 for (±)-**14a**. Cell parameters were determined by least-squares fit of Kα_1 2θ values ($\lambda_{K\alpha 1}$ = 1.5402) for 25 high 2θ reflections.[14] An Lp correction appropriate for a monochromator with 50% perfect character was applied, and the data were corrected for absorption.[15]

The structure of (+)-8b was solved by finding the chlorine position from analysis of the Patterson function, extending to a partial trial solution using the tangent formula option in DIREC,[16] and successive structure factor–Fourier syntheses. The trial solution for (±)-**14a** was obtained using MULTAN80.[17] Hydrogens in both structures were found in difference maps close to generated positions; generated positions were used in the calculations for (±)-**14a** and updated after each refinement. Least-squares refinement of (±)-**14a** included coordinates and anisotropic thermal parameters for nonhydrogen atoms; the least-squares refinement of (+)-**8b** also included hydrogen coordinates. The function minimized in the refinement was $\sum w(F_o^2 - F_c^2)^2$, where weights w were $1/\sigma^2(F_o^2)$. Anomalous dispersion factors[18] were included in the final refinement cycles for (+)-**8b**; shifts in the final cycles of both structures were ≤0.3σ. The absolute configuration of (+)-**8b** was determined by the method of Bijvoet;[19] accurate measurements of reflections which were very strongly influenced by anomalous dispersion were compared, each one being measured at all accessible symmetry related positions (eight reflections with 13 accessible Friedel pairs were measured). In each case there was unanimous agreement among the measured

pairs, the comparisons indicated unequivocally that (+)-8b has the (3a*R*,9a*S*) configuration. Atomic form factors were from Doyle and Turner[20] and, for hydrogen, from Stewart, Davidson, and Simpson.[21] The CRYM system of computer programs was used.[16]

The atomic coordinates and thermal parameters are deposited at the Cambridge Crystallographic Data Centre. In addition, these tables and tables of bond lengths and angles, torsion angles, and close intermolecular contacts are available as supplementary material.

Crystal data specific for (+)-8b: $C_{16}H_{21}NO{\cdot}HCl$; formula wt = 243.3 + 36.5; monoclinic; space group $P2_1$; $Z = 4$; $a = 10.146$ (2) Å, $b = 10.927$ (2) Å, $c = 13.546$ (2) Å, $\beta = 98.63$ (2)°; $V = 1484.7$ (4) Å^3; calculated density = 1.25 g cm^{-3}; absorption coefficient, $\mu = 2.1$ mm^{-1}. Intensity data were collected at low temperature, −120 °C, on a clear needle, 0.07 × 0.09 × 0.36 mm, mounted on a glass fiber. The final agreement index R was 0.054 for all 2865 reflections and 0.047 for the 2522 reflections having $F_o^2 \geq 3\sigma$. The standard deviation of fit was 3.0. There are two molecules in the asymmetric unit. Both amine nitrogens are protonated and make hydrogen bonds with the chlorines; the N to Cl distances are 3.069 (5) and 3.015 (5) Å.

Crystal data specific for (±)-14a: $C_{17}H_{25}NO{\cdot}HCl$; formula wt = 259.3 + 36.5; monoclinic; space group $P2_12_12_1$; $Z = 4$; $a = 11.290$ (3) Å, $b = 7.197$ (3) Å, $c = 19.339$ (4) Å; $V = 1571.3$ (7) Å^3; calculated density = 1.25 g cm^{-3}; absorption coefficient, $\mu = 2.0$ mm^{-1}. Intensity data were collected on a thick clear needle, 0.01 × 0.12 × 0.20 mm, mounted on a glass fiber. Although this compound is racemic, the molecules crystallized as *d* and *l* crystals in the chiral space group $P2_12_12_1$. No attempt was made to determine absolute configuration using the Bijvoet method as was done for (+)-**8b**; however the calculation was done to determine which enantiomer gave best agreement for the reflections most strongly affected by anomalous dispersion, and coordinates for that enantiomer were refined using anomalous components. The crystals had poor diffraction, and although intensity data were collected to a maximum 2θ of 130°, there were not many reflections with significant intensity in the range $2\theta > 100°$. In the final refinement, only the 850 reflections in the range $2\theta < 100°$ were included, and two reflections, 0,2,0 and 0,2,1, were given zero weight. The final agreement index R was 0.114 for 848 reflections, and 0.077 for the 479 reflections having $F_o^2 \geq 3\sigma$. The standard deviation of fit was 1.6. The amine nitrogen is protonated and is hydrogen bonded to the chlorine; the N to Cl distance is 3.137(11) Å.

Serotonin and Dopamine Binding Assays. 5-HT$_{1A}$ receptor bindings were measured by using [^{3}H]-8-OH-DPAT (sp act. 85 Ci/mmol, NEN) labeled 5-HT$_{1A}$ site in either homogenates of bovine hippocampus prepared with Polytron and diluted 1:400.[22] Samples were incubated for 1 h at room temperature and then filtered over SS no. 24 filters (pretreated with 0.05% PEI) and rinsed three times with 0.5 mL of 50 mM TRIS pH 7.4 buffer. Nonspecific binding was determined using serotonin (1 μM). IC_{50} and K_i values were calculated by log-probit analysis, using at least four concentrations of the drug, in triplicate. D_2 dopamine receptor bindings were measured by using either [^{3}H]raclopride (sp act. 80 Ci/mmol, NEN) labeled D_2 site in homogenates of rat striata prepared with a Polytron and diluted 1:300.[23] Samples were incubated for 1 h at room temperature and then filtered over SS no. 24 filters (pretreated with 0.05% PEI) and rinsed three times with 0.5 mL of 50 mM TRIS pH 7.4 buffer. Filters were counted using standard liquid scintillation techniques. Nonspecific binding was determined using haloperidol (1 μM). IC_{50} and K_i values were calculated by log-probit analysis, using at least four concentration of the drug, in triplicate. The bindings using CHO cells were measured by competition binding experiments employing 11 dilutions of test sample with [^{3}H]-8-OH-DPAT (85 Ci/mmol, 1.2 nM) and [^{3}H]-U86170[24] (62 Ci/mmol, 2 nM) for 5-HT$_{1A}$ and D_2 binding sites, respectively. In each case cloned mammalian receptors expressed in CHO-K1 cells were used.[25] IC_{50} values were estimated by fitting the data to a one-site model by nonlinear least squares minimization. K_i values were calculated with the Cheng–Prushoff equation.[26]

Hypothermia Assay. Charles River CF-1 mice (18–22 g, 4 per dose) were individually housed in clear plastic cages with sawdust bedding and perforated metal tops for 20 min prior to testing. After control rectal temperatures were measured, test compounds were given sc in 0.1-mL volume; 20 min later, rectal temperatures were again measured. A decrease of 2 or more °F was considered to be a positive hypothermic response. Drug doses started at 30 mg/kg and were decreased by half-log value until 0 out of 4 mice showed a positive hypothermic response. ED_{50}'s and 95% confidence intervals were determined by Spearman–Karber's method.[27] Oral dosing was similar to sc dosing, except a rounded oral 18-ga hypodermic needle was used and the volume given was 0.2 mL. Regardless of the route of administration, the mean maximum temperature drop 20 min following any dose was noted as an index of drug efficacy and indirect estimate of intrinsic activity.

Dopamine Intrinsic Activity Measurements. Intrinsic activity was determined using membranes from CHO cells stably transfected with the dopamine D_2 receptor as previously described by Lahti et al.[11] Briefly, this method uses the ratio of the affinity of a compound for the low- and high-affinity states of the receptor to determine the intrinsic activity. The affinity for the low-affinity agonist state is determined using [^{3}H]raclopride + GTP and the affinity for the high affinity state is determined using the dopamine agonist ligand [^{3}H]U-86170.[24]

Amine Synthesis and Metabolism. Brain levels of DOPA and 5-HTP in the rat were determined as described previously.[28] Briefly, male Sprague–Dawley rats were injected sc with test drug or vehicle at time zero. Fifteen minutes later the rats received an aromatic decarboxylase inhibitor (NSD 1015 at 100 mg/kg ip). The rats were sacrificed 30 min later, and the tissues in the ventral limbic brain area were removed and frozen for later analysis. Tissues were weighed and extracted in 0.1 N perchloric acid containing an internal standard of dihydroxybenzylamine (2 μg/mL). The extract was then analyzed by HPLC using a Bioanalytical Systems ODS column. DOPA and 5-HTP were detected electrochemically and quantified by peak integration using Waters Maxima(R) software. Biochemical differences were compared between a control ($N = 6$) and a test group ($N = 6$) by unpaired *t*-test.

Recordings from Dopaminergic and Serotonergic Neurons. Charles River male Sprague–Dawley rats (280–330 g) were anesthetized with chloral hydrate (400 mg/kg ip). Supplemental doses were administered as needed to maintain anesthesia. The femoral artery and vein were cannulated for blood pressure and drug administration. The animal's head was held in a stereotaxic device and a small burr hole drilled at the appropriate location. Extracellular action potentials were recorded with a glass microelectrode (tip size <1 μm) filled with pontamine sky blue dye in 2 M sodium chloride. Dopaminergic neurons were identified by their long duration action potential (>2.5 ms), shape and firing pattern (>12 spikes/s) as previously described.[29] The recording electrode was hydraulically lowered into the substantia nigra pars compacta area (*P* 5.0–6.0 mm, *L* 2.0–2.2 mm, *V* 7.0–8.0 mm) according to the coordinates of Paxinos and Watson.[30] Serotonergic neurons were identified by their large, biphasic positive–negative action potentials with slow and regular firing rates (approximately 0.8–2.5 spikes/s) as previously described.[31] The recording electrode was hydraulically advanced to reach the dorsal raphe nucleus (*A* 0.5–1.7 mm, *L* 0 mm, *V* 3.5–4.2 mm) according to the coordinates of Paxinos and Watson.[30] At the termination of each recording session, the location of the cell was identified by passing a 10-μA cathodic current for 10–20 min. The brain was then removed, sectioned, and stained, and the pontamine sky blue deposit verified in each animal. Only those cells found to be in the appropriate area were included in the study. All drug solutions were made in distilled water. Each drug injection contained no more than 0.15 mL of a given concentration, followed by 0.2–0.4 mL of physiological saline to clean the catheter of any residual drug. Drug effects were measured as changes in firing rates as indicated by an integrated ratemeter output throughout the experiment. The dose required to depress neuronal firing by 50% was taken as the ED_{50}, measured by interpolation of the dose–response curve for each individual cell.

Face to Face Test for Anxiolytics (a Social Interaction Test in Mice). When two mice are placed together from separate cages into a small chamber, they investigate each other as well as the environment. The prior administration of anxiolytic drugs

increases the amount of social interaction, including the amount of face to face interaction. This test is a simplified version of Sandra File's social interaction test in rats.[32] Male CF-1 mice (Charles River, 19–29 g, 8 pairs per dose) were injected subcutaneously (sc) or orally (po). Compounds were dissolved or suspended in 0.25% methylcellulose or 0.1% citric acid. During the 30-min absorption time, mice were housed 2/cage with a familiar partner (i.e., a mouse from the same home cage). Pairs of mice from different home cages were then placed together into a small plastic cage (7 in. × 5½ in.) with a cardboard lid and with fresh wood litter on the floor. Duration of face to face interaction was measured visually for 3 min. Groups were compared by Wilcoxon's rank sum (two-tailed). A significant increase ($p < 0.05$) above the daily control value was interpreted as an anxiolytic effect.

Isolation-Induced Aggression Test for Anxiolytic Activity in Mice. Aggressiveness in adult male mice increases following a period of social isolation. Anxiolytic compounds and sedatives suppress the aggressiveness (i.e., increase the latency to fighting). Male CF-1 mice (20–22 g) were obtained from Charles River or Harlan and separated into two groups. Isolated "resident" mice were housed singly for at least 1 month. Group-housed "intruder" mice were housed 4–6/cage. Food and water were available ad libitum. Mice weighed 28–30 g at the time of the first tests. Compounds were dissolved or suspended in 0.25% methylcellulose or 0.1% citric acid. Drugs were tested blindly, with 6 mice/treatment group ($n = 12$ for vehicle). Each isolated "resident" mouse was injected intraperitoneally (ip) or orally with drug 30 min before introduction of an untreated, group-housed "intruder" mouse into the resident's home cage. The number of seconds until fighting began was recorded, and the intruder was removed as soon as fighting began. The isolated resident mice were allowed a minimum of 3 days recovery before reuse. Groups were compared statistically by Wilcoxon's rank sum. Mice which failed to fight within 10 min were arbitrarily assigned 600 s.

Locomotor Activity. (1) Reserpinized Mice. (A) Stimulation. Harlan male NSA (CF-1) mice, 13–19 g, were injected with 5 mg/kg reserpine subcutaneously (sc) 18–24 h before testing and with 300 mg/kg DL-α-methyl-*p*-tyrosine intraperitoneally (ip) 1–5 h before testing. Test drug was given ip 15 min before mice were placed singly into 8-in. × 8-in. cages (Omnitech Digiscan Monitors). Locomotor activity was recorded for 10 min, as horizontal activity counts. Control mice (given reserpine and DL-α-methyl-*p*-tyrosine) were nearly motionless. Groups were compared by Student's *t*-test, or by least significant difference, and each point represented six mice. **(B) Antagonism of Apomorphine.** Immediately afterward, all mice were injected with 1 mg/kg apomorphine HCl sc and were returned to the cages to record locomotor activity for 10 min, as percent of control counts (for apomorphine alone, which stimulates activity in these reserpinized mice).

(2) Antagonism of Amphetamine. Drug-naive Harlan male B6C3F1 mice, 23–27 g, were placed singly into 8-in. × 8-in. cages (Omnitech Digiscan Monitors) for 20 min to partially habituate them to the cages. Then the mice were given *d*-amphetamine sulfate 3 mg/kg sc plus test drug ip. Locomotor activity (horizontal activity) was recorded for two 10-min intervals, as percent of control (for amphetamine alone, which stimulates activity in mice). Data were analyzed by Student's *t*-test, or by least significant difference, and each point represented six mice.

Sympathetic Nerve Activity. Adult cats (2.5–4.0 kg) were anesthetized by intramuscular injection of ketamine (11 mg/kg), followed by intravenous injection of chloralose (80 mg/kg). This dose of anesthetic was sufficient to maintain an appropriate level of anesthesia for the duration of the experiments. Each animal was placed in a stereotaxic apparatus and a femoral artery and vein were cannulated for recording blood pressure and for peripheral drug administration, respectively. Heart rate was recorded continuously with a Grass 7P4 tachograph triggered by the electrocardiogram. A glass tracheal cannula was inserted, and, following surgery, the animals were artificially ventilated and paralyzed with gallamine (4 mg/kg iv). Rectal temperature was maintained between 37 and 38 °C using a heating pad.

Sympathetic nerve discharge (SND) was recorded from the central end of the sectioned left inferior cardiac nerve. The nerve was located distal to its exit from the stellate ganglion and was isolated outside the pleural cavity after removal of the vertebral portion of the first rib. Nerve activity was recorded under mineral oil using a bipolar platinum electrode with capacity coupled preamplification at low and high frequency half-amplitude responses of 1 and 500 Hz, respectively. Sympathetic activity was quantitated using cumulative integration. Cumulative intravenous doses of a compound were tested at 20-min intervals.

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Supplementary Material Available. A table of C, H, N analyses and high-resolution mass spectrum results as well as tables of fractional coordinates, bond lengths and angles, close intermolecular contacts, hydrogen bonds, and anisotropic thermal parameters (13 pages). Ordering information is given on any current masthead page.

References

(1) Lin, C.-H.; Haadsma-Svensson, S. R.; Lahti, R. A.; McCall, R. B.; Piercey, M. F.; Schreur, P. J. K. D.; Von Voigtlander, P. F.; Smith, M. W.; Chidester, C. G. Centrally Acting Serotonergic and Dopaminergic Agents. 1. Synthesis and Structure–Activity Relationships of 2,3,3a,4,5,9b-Hexahydro-1*H*-benz[*e*]indole Derivatives. *J. Med. Chem.*, preceding paper in this issue.

(2) (a) Cannon, J. G.; Lee, T.; Goldman, H. D.; Long, J. P.; Flynn, J. R.; Verimer, T.; Costall, B.; Naylor, R. J. Congeners of β Conformer of Dopamine Derived from *cis*- and *trans*-Octahydrobenzo[*f*]-quinoline and *trans*-Octahydrobenzo[*g*]quinoline. *J. Med. Chem.* 1980, *23*, 1–5. (b) Cannon, J. G.; Beres, J. A.; Lee, T.; Long, J. P. *trans*-*N*-Alkyl-6,7-Dihydroxyoctahydrobenzo[g]quinolines: Apomorphine Congeners Lacking the Non-oxygenated Aromatic Ring. *Medicinal Chemistry Advances*; De Las Heras, F. G., Vega, S., Eds.; Pergamon Press: Oxford, 1981; pp 369–381. (c) Cannon, J. G.; Hamer, R. L.; Ilhan, M.; Bhatnagar, R. K.; Long, J. P. Conformationally Restricted Congeners of Dopamine Derived from Octahydrobenzo[*g*]quinoline and Octahydrobenzo[*f*]quinoline. *J. Med. Chem.* 1984, *27*, 190–195. (d) Cannon, J. G.; Amoo, V. E. D.; Long, J. P.; Bhatnagar, R. K.; Flynn, J. R. *p*-Dimethoxy-Substituted *trans*-Octahydrobenzo[*f*]-and-[*g*]quinolines: Synthesis and Assessment of Dopaminergic Agonist Effects. *J. Med. Chem.* 1986, *29*, 2529–2534.

(3) (a) Mellin, C.; Hacksell, U. Stereoselective Synthesis of Methoxy Substituted 1,2,3,4a,5,10,10a-Octahydrobenzo[*g*]quinolins. *Tetrahedron* 1987, *43*, 5443–5450. (b) Seiler, M. P.; Markstein, R.; Walkinshaw, M. D.; Boelsterli, J. J. Characterization of Dopamine Receptor Subtypes by Comparative Structure-Activity Relationships: Dopaminomimetic Activities and Solid State Conformation of Monohydroxy-1,2,3,4,4a,5,10,10a-octahydrobenz[*g*]-quinolines and Its Implications for a Rotamer-Based Dopamine Receptor Model. *Mol. Pharmacol.* 1989, *35*, 643–651.

(4) (a) McDermed, J. D.; McKenzie, G. M.; Freeman, H. S. Synthesis and Dopaminergic Activity of (±)-, (+), and (−)-2-Dipropylamino-5-hydroxy-1,2,3,4-tetrahydronaphthalene. *J. Med. Chem.* 1976, *19*, 547–549. (b) Arvidsson, L.-E.; Hacksell, U.; Nilsson, J. L. G.; Hjorth, S.; Carlsson, A.; Lindberg, P.; Sanchez, D.; Wikström, H. 8-Hydroxy-2-(di-*n*-propylamino)tetralin, A New Centrally Acting 5-Hydroxytryptamine Receptor Agonist. *J. Med. Chem.* 1981, *24*, 921–923. (c) Hjorth, S. A.; Carlsson, A.; Lindberg, P.; Sanchez, D.; Wikström, H.; Arvidsson, L.-E.; Hacksell, U.; Nilsson, J. L. G. 8-Hydroxy-2-(di-*n*-propylamino)tetralin. 8-OH-DPAT. A Potent and Selective Simplified Ergot Congener with Central 5-HT-receptor Stimulating Activity. *J. Neural Transm.* 1982, *55*, 169–188. (d) Middlemiss, D. N.; Fozard, J. R. 8-Hydroxy-2-(di-n-propylamino)tetralin Discriminates between Subtypes of 5-HT$_1$ Site. *Eur. J. Pharm.* 1983, *90*, 151–153. (e) Arvidsson, L.-E.; Hacksell, U.; Johansson, A. M.; Nilsson, J. L. G.; Lindberg, P.;

Sanchez, D.; Wikström, H.; Svensson, K.; Hjorth, S.; Carlsson, A. 8-Hydroxy-2-(alkylamino)tetralins and Related Compounds as Central 5-Hydroxytryptamine Receptor Agonists. *J. Med. Chem.* **1984**, *27*, 45–51.

(5) Aristoff, P. A.; Johnson, P. D.; Harrison, A. W. Total Synthesis of a Novel Antiulcer Agent via a Modification of the Intramolecular Wadsworth-Emmons-Wittig Reaction. *J. Am. Chem. Soc.* **1985**, *107*, 7967–7974.

(6) Borch, R. F.; Bernstein, M. D.; Durst, H. D. The Cyanohydridoborate Anion as a Selective Reducing Agent. *J. Am. Chem. Soc.* **1971**, *93*, 2897–2904.

(7) Ashby, E. C.; Prather, J. The Composition of "Mixed Hydride" Reagents. A Study of the Schlesinger Reaction. *J. Am. Chem. Soc.* **1966**, *88*, 729–733.

(8) Ireland, R. E.; Walba, D. M. The Total Synthesis of (±)-Friedelin, An Unsymmetrical Pentacyclic Triterpene. *Tetrahedron Lett.* **1976**, 1071–1074.

(9) Lin, C.-H.; Haadsma-Svensson, S. R.; Lahti, R. A.; McCall, R. B.; Piercey, M. F.; Schreur, P. J. K. D.; Von Voigtlander, P. F.; Chidester, C. G. Centrally Acting Serotonergic Agents. Synthesis and Structure-Activity Relationships of C-1 or C-3 Substituted Derivatives of 8-Hydroxy-2-(di-*n*-propylamino)tetralin. *J. Med. Chem.* **1993**, in press.

(10) Saito, Y.; Moriyama, Y.; Hirota, H.; Takahashi, T.; Khuong-Huu, Q. Chiral and Stereoselective Total Synthesis of (−)-Deoxoprosopinine and (−)-Deoxoprosophylline. Intramolecular Aminomercuration of an ϵ,ζ-Unsaturated Amine. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 488–492.

(11) Lahti, R. A.; Figur, L. M.; Piercey, M. F.; Ruppel, P. L.; Evans, D. L. Intrinsic Activity Determinations at the Dopamine D_2 Guanine Nucleotide-Binding Protein-coupled Receptor: Utilization of Receptor State Binding Affinities. *Mol. Pharmacol.* **1992**, *42*, 432–438.

(12) Chidester, C. G.; Lin, C.-H.; Lahti, R. A.; Haadsma-Svensson, S. R.; Smith, M. W. Comparison of 5-HT_{1A} and Dopamine D_2 Pharmacophores; X-ray Structures and Affinities of Conformationally Constrained Ligands. *J. Med. Chem.*, in press.

(13) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis, 1*; John Wiley and Sons, Inc.: New York, 1967; p 11.

(14) Duchamp, D. J. New Computing Techniques for Molecular Studies by X-Ray Crystallography. *Am. Chem. Soc. Sympos. Ser.* **1977**, No. 46, 98–121.

(15) Busing, W. R.; Levy, H. A. High Speed Computation of the Absorption Correction for Single-Crystal Diffraction Measurements. *Acta Crystallogr.* **1957**, *10*, 180–182.

(16) Duchamp, D. J. A Direct Methods Program for Solving Crystal Structures. *DIREC* (1984) and A System of Crystallographic Programs. *CRYM* (1984), The Upjohn Co., Kalamazoo, MI.

(17) Main, P.; Fiske, S. J.; Hull, S. E.; Lessinger, L.; Germain, G.; Declercq, J. P.; Woolfson, M. M. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-Ray Diffraction Data. *MULTAN80*; University of York: England, and Louvain: Belgium, 1980.

(18) Cromer, D. T.; Liberman, D. Relativistic Calculation of Anomalous Scattering Factors for X Rays. *J. Chem. Phys.* **1970**, 1891–1898.

(19) (a) Bijvoet, J. M.; Peerdemann, A. F.; van Bommel, A. J. Determination of the Absolute Configuration of Optically Active Compounds by Means of X-Rays. *Nature* **1951**, *168*, 271–272. (b) Bijvoet, J. M. Determination of the Absolute Configuration of Optical Antipodes. *Endeavour* **1955**, *14*, 71–77.

(20) Doyle, P. A.; Turner, P. S. Relativistic Hartree-Fock X-ray and Electron Scattering Factors. *Acta Crystallogr.* **1968**, *A24*, 390–397.

(21) Stewart, R. F.; Davidson, E. R.; Simpson, W. T. Coherent X-ray Scattering for the Hydrogen Atom in Hydrogen Molecule. *J. Chem. Phys.* **1965**, *42*, 3175–3187.

(22) Gozlan, H.; El Mestikawy, S.; Pichat, L.; Glowinski, J.; Hamon, M. Identification of Presynaptic Serotonin Autoreceptors Using a New Ligand [^{3}H]-DPAT. *Nature* **1983**, *305*, 140–142.

(23) Kohler, C.; Hall, H.; Ögren, S. V.; Gawell, G. Specific In Vitro and In Vivo Binding of [^{3}H]-Raclopride. A Potent Substituted Benzamide Drug with High Affinity for Dopamine D-2 Receptors in the Rat Brain. *Biochem. Pharmacol.* **1985**, *34*, 2251–2259.

(24) Lahti, R. A.; Evans, D. L.; Figur, L. M.; Moon, M. W.; Hsi, R. S. Dopamine D_2 Receptor Binding Properties of [^{3}H]U-86170, a Dopamine Agonist. *Eur. J. Pharmacol.* **1991**, *202*, 289–291.

(25) (a) Fargin, A.; Raymond, J. R.; Lohse, M. J.; Kobilka, B. K.; Caron, M. G.; Lefkowitz, R. J. The Genomic Clone G-21 Which Resembles a β-Adrenergic Receptor Sequence Encodes the 5-HT_{1A} Receptor. *Nature* **1988**, *335*, 358–360. (b) Chio, C. L.; Hess, G. F.; Grahm, R. S.; Huff, R. M. A Second Molecular Form of D_2 Dopamine Receptor in Rat and Bovine Caudate Nucleus. *Nature* **1990**, *343*, 266–269.

(26) Cheng, Y. C.; Prushoff, W. H. Relationship Between the Inhibition Constant and the Concentration of Inhibitor Which Causes 50 Percent Inhibition of an Enzymatic Reaction. *Biochem. Pharmacol.* **1973**, *22*, 3099–3108.

(27) Finney, D. J. *Statistical Methods in Biological Assay*; Hafner Publ.: New York, 1952.

(28) Von Voigtlander, P. F.; Althaus, J. S.; Ochoa, M. C.; Neff, G. L. Dopamine Receptor Agonist Activity of U-66444B and Its Enantiomers. *Drug Dev. Res.* **1989**, *17*, 71–81.

(29) Piercey, M. F.; Hoffmann, W. E.; Vogelsang, G. D.; Travis, M. Electrophysiological Evaluation of a Partial Agonist of Dopamine Receptors. *J. Pharmacol. Exp. Ther.* **1988**, *243*, 391–396.

(30) Paxinos, G.; Watson, C. *The Rat Brain in Stereotaxic Coordinates*; Academic Press: Sydney, 1986.

(31) Lum, J. T.; Piercey, M. F. Electrophysiological Evidence That Spiperone Is an Antagonist of 5-HT_{1A} Receptors in the Dorsal Raphe Nucleus. *Eur. J. Pharmacol.* **1988**, *149*, 9–15.

(32) (a) File, S. E.; Hyde, J. R. G. Can Social Interaction Be Used to Measure Anxiety? *Br. J. Pharmacol.* **1978**, *62*, 19–24. (b) File, S. E. The Use of Social Interaction as a Method for Detecting Anxiolytic Activity of Chlordiazepoxide-like Drugs. *J. Neurosci. Methods* **1980**, *2*, 219–238.