Further Definition of the D_1 Dopamine Receptor Pharmacophore: Synthesis of *trans*-6,6a,7,8,9,13b-Hexahydro-5*H*-benzo[*d*]naphth[2,1-*b*]azepines as Rigid Analogues of β-Phenyldopamine

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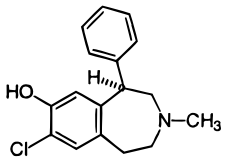
In an effort to define further the active geometry of the β-phenyldopamine pharmacophore of certain dopamine D1 agonists, the title compounds have been synthesized as conformationally restricted homologues of the potent benzophenanthridine dopamine D1 agonist dihydrexidine **4a**. The dihydroxy secondary amine **5b** was evaluated as a potential agonist, whereas the *N*-methyl compounds **5a** and **5c** were hypothesized to be antagonists. Surprisingly, none of the three compounds had high affinity for dopamine D1 or D2 receptors. A comparison of the low-energy conformations of these molecules shows that the pendant phenyl ring of **5b** is twisted about 28° relative to that of the corresponding ring of **4a**. Further, the additional methylene used to expand the C ring of **5b** projects toward the α face of the molecule, perhaps suggesting that steric protrusion in this region of the molecule is not tolerated. Finally, the phenethylamine fragment incorporated into these molecules deviates about 30° from the antiperiplanar conformation postulated to be necessary for agonist activity. On the other hand, the potential antagonist molecules **5a** and **5c** were compared with the dopamine D1 antagonist SCH 39166 **2**. The conformations of the former two structures differ quite dramatically from that of **2**. The most notable differences lie in the relative orientations of the pendant phenyl rings in the two series, as well as the fact that the ethylamine fragment in **2** approximates a gauche conformation, while the comparable orientation in **5a** and **5c** more nearly approaches an antiperiplanar conformation. These findings will be used to refine further the model of the dopamine D1 agonist receptor that we have previously developed.

Dopamine-mediated neurotransmission plays a role in several psychiatric and neurological disorders, and for this reason there has been great interest in the search for novel dopamine receptor agonists and antagonists. Dopamine receptors first were classified into D_1 and D_2, subtypes on pharmacological and functional grounds, including the coupling to the enzyme adenylate cyclase.[1] Recent molecular cloning studies have led to the identification of five genes that code dopamine receptor proteins, two in the D_1 family (D_1 and D_5 or D1B) and three in the D_2 family (D_2, D_3, and D_4).[2−4] Despite much effort, the inability to elucidate the correct three-dimensional orientation of the amino acid residues at or near the binding site has been a drawback to the design of selective and potent dopaminergic agents. Thus, research still relies heavily on structure−activity relationship (SAR) information generated from molecules synthesized on the basis of a lead compound.

A large number of structurally diverse compounds have been found to be potent and selective ligands for the D_2 receptor. Many fewer D_1-selective agents are available, most in the phenyltetrahydrobenzazepine class like the prototypic D_1 selective antagonist SCH 23390 (**1**),[5] its conformationally restricted analogue SCH 39166 (**2**),[6] and the partial agonist SKF 38393 (**3**).[7,8] Recent synthetic drug design work in our laboratories has led to the design, synthesis, and characterization of dihydrexidine (**4a**) as the first high-affinity full agonist at the D_1 receptor.[9,10] This work also made clear that dopamine analogues containing a β-phenyl moiety show greater affinity for the D_1-like receptors.[11,12] The β-phenyl moiety is essential in conferring D_1 affinity and is also a major factor in selectivity of a drug for D_1-like vs D_2-like receptors. The 10-bromo-6-methyl analogue **4b** was also synthesized in order to investigate its potential D_1 antagonist activity. Although this molecule did possess antagonist properties, it showed low affinity (322 nM) for the D_1 receptor.[13]



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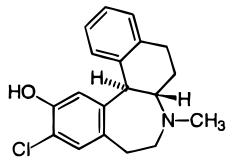

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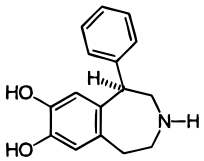

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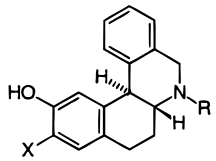

4a X = OH, R = H
4b X = Br, R = CH_3

In an effort to define further the geometry of the phenyl accessory region, we have now synthesized the

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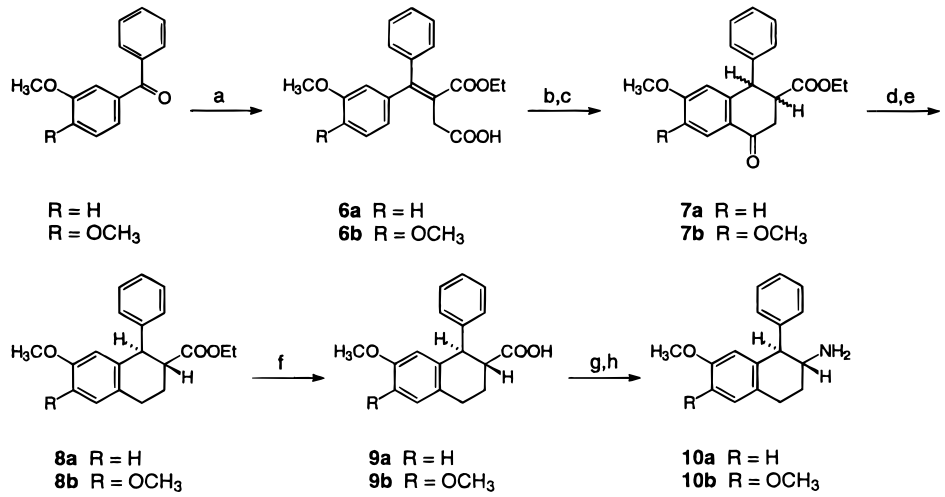
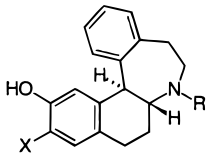
Scheme 1[a]



[a] Reagents: (a) KOtBu, diethyl succinate, HCl; (b) H_2, Pd−C; (c) P_2O_5/CH_3SO_3H; (d) H_2, Pd−C, AcOH, $HClO_4$; (e) NaOEt, reflux; (f) NaOH, HCl; (g) Et_3N, $ClCOOC_2H_5$, NaN_3, toluene, reflux; (h) KOH, EtOH, reflux.

naphthobenzazepines **5a**, **5b**, and **5c** as conformationally rigid β-phenyldopamine analogues. Compound **5b** is the seven-membered C-ring analogue of **4a**, while **5c** is the ring-expanded iodo derivative of **4b**. The close structural similarity between compound **4a** and **5b** suggested that **5b** would be a high-affinity agonist. Conversely, it was also possible that **5a** and **5c** might be antagonists at D_1 receptors. On the other hand, based on a model of the D_1 receptor that we have proposed,[14] the greater twist of the pendant phenyl ring (i.e., as compared to the corresponding ring in **4a**) leads to the alternate hypothesis that these structural changes will markedly decrease the affinity of **5a**, **5b**, and **5c**. The present studies were designed to distinguish among these hypotheses and, in so doing, provide a better understanding of the SAR of dopamine ligands possessing a β-phenyl moiety.



5a X = H, R = CH_3
5b X = OH, R = H
5c X = I, R = CH_3

Chemistry

The synthesis of intermediate phenylaminotetralins **10a** and **10b** (Scheme 1) was based partially on earlier work by Riggs.[15] Friedel−Crafts acylation of benzene with the respective benzoyl chlorides and aluminum chloride at −78 °C, followed by Stobbe condensation of the resulting benzophenones with diethyl succinate following the method of Welch et al.,[16] led to **6a** and **6b**, respectively. Catalytic hydrogenation, followed by treatment of the products with Eaton's[17] reagent, afforded the tetralones **7a** (*cis* and *trans* (5:1)) and **7b** (cis), respectively. Reduction of the tetralones with a second catalytic hydrogenation in acetic acid in the presence of a few drops of perchloric acid, followed by epimerization of the *cis* products with sodium ethoxide, resulted in *trans* **8a** and **8b**, respectively. Hydrolysis of the resulting esters with NaOH afforded the acids **9a** and **9b**. Modified Curtius rearrangement[18] of the acids and hydrolysis of the intermediate isocyanates with 20% ethanolic KOH afforded the *trans* amines **10a** and **10b**. These intermediates were alkylated with methyl bromoacetate to give **11a** and **11b**, respectively (Scheme 2). N-Tosylation with *p*-toluenesulfonyl chloride afforded **12a** and **12b**, respectively. Following the procedure of Rehman *et al.*,[19] the esters were hydrolyzed with cold 1 N methanolic KOH and reacidified. Conversion of the acids to their acyl chlorides using oxalyl chloride, followed by treatment with $AlCl_3$ in dichloromethane at −78 °C, afforded **13a** and **13b**. These benzylic ketones were reduced with $NaBH_4$. Treatment of the resulting alcohols with $BF_3{\cdot}Et_2O/Et_3SiH$[20] gave **14a** and **14b**. N-Detosylation of **14a** and **14b** with Red-Al (Aldrich) gave the naphthobenzazepines **15a** and **15b**. The hydrochloride salt of **15a** was N-methylated by treatment with 37% formalin solution and sodium cyanoborohydride in methanol to give **16a**. O-Demethylation of **15b** and **16a** with boron tribromide afforded the hydrobromide salts of **5b** and **5a**, respectively. Both the hydrochloride and hydrobromide salts of **5b** were highly hygroscopic. Following the procedure of Sy,[21] **16a** was iodinated with $AgSO_4-I_2$ to give **17**, followed by ether cleavage with boron tribromide to afford **5c**.

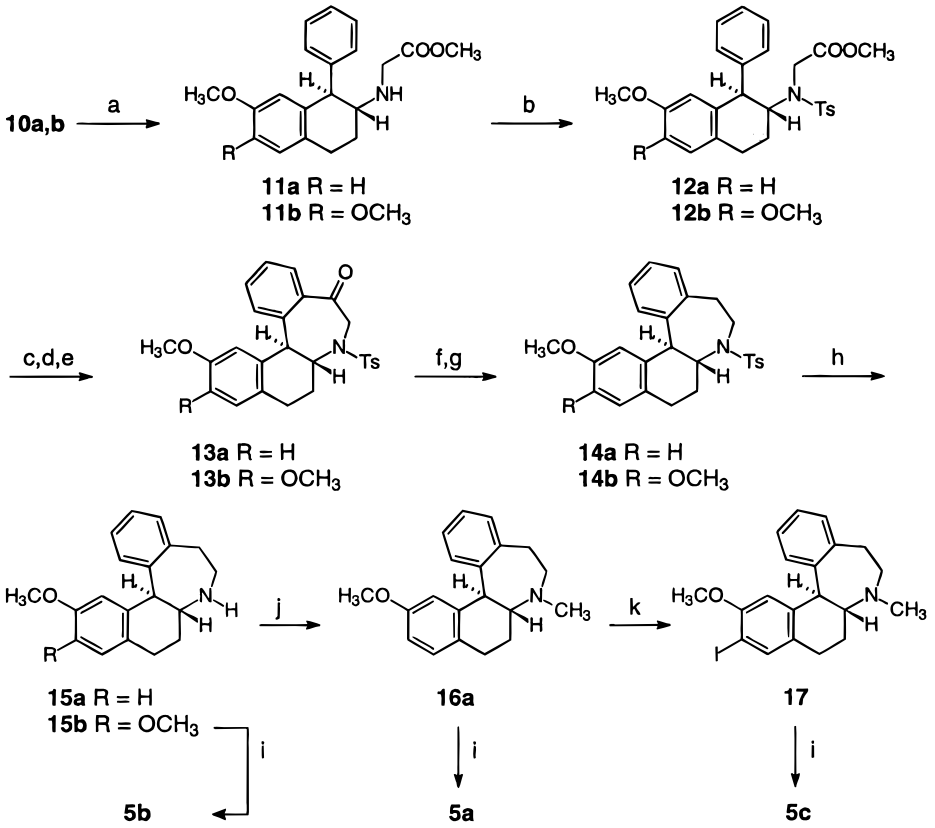
Molecular Modeling

All computations were performed using a Silicon Graphics Indigo 2 Extreme generation system running Spartan software (Version 4.1, Wavefunction, Inc., Irvine, CA). Structures were minimized as the free bases *in vacuo* using semiempirical methods and AM1 potentials, as implemented in Spartan. Several different starting geometries were examined in order to identify global minima.

Pharmacology

All final compounds were tested for the ability to compete with either [^{3}H]SCH 23390 or [^{3}H]spiperone at D_1 and D_2 binding sites, respectively, in rat striatal membranes. The values reported for the competitive binding assays are the averages of three runs.

Scheme 2[a]



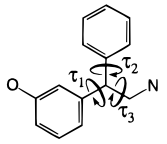
[a] Reagents: (a) $BrCH_2COOCH_3$, K_2CO_3, DMF; (b) tosyl Cl, Et_3N, CH_2Cl_2; (c) KOH, MeOH, HCl; (d) CH_2Cl_2, $(COCl)_2$; DMT (cat.); (e) $AlCl_3$, CH_2Cl_2; (f) $NaBH_4$, EtOH; (g) $(Et)_3SiH$, BF_3/Et_2O; (h) Red-Al, toluene, reflux; (i) BBr_3, CH_2Cl_2; (j) HCHO, $NaCNBH_3$.

Table 1. Dopamine Receptor Affinity of Naphthobenzazepines **5a**−**c**

	$K_{0.5}$ (nM) ± SEM[a]	
compd no.	D_1 affinity	D_2 affinity
5a	3950 ± 50	>10,000
5b	2850 ± 690	2220 ± 390
5c	1380 ± 140	2960 ± 320
(+)-4a[b]	2.8	43.8
SCH 23390	0.50	NA[c]
CPZ	NA	0.95

[a] All tests were performed as described in the methods on rat striatal membranes in the experimental section, using [^{3}H]SCH 23390 as the D_1 ligand and [^{3}H]spiperone as the D_2 ligand. [b] Values from ref 26. [c] NA = not applicable.

Table 2. Torsion Angles τ_1, τ_2, and τ_3 and Nitrogen to Meta Oxygen Distance (N−O)[a] of the Global Minimum Energy Conformations of Target Compounds **5a** and **5c** and Reference Compounds Dihydrexidine (**4a**) and SCH 39166 (**2**)



compd no.	τ_1	τ_2	τ_3	N−O distance (Å)
2	−24.8	−41.6	57.2	6.18
4a	57.6	−10.5	163.0	7.38
5b	61.1	17.7	149.3	7.34
5c	64.1	16.7	149.5	7.35

[a] Straight-line distance from the amine nitrogen to the meta oxygen.

Results and Discussion

It is apparent from the data in Table 1 that **5a**, **5b**, and **5c** have very low affinity for either the D_1 or D_2 receptors, with $K_{0.5}$ values 50−500 times higher than that of **4a**. These somewhat surprising data at first led us to question the stereochemical assignments of the target compounds. The magnitude of the NMR coupling constants confirmed that the B/C ring junction remained *trans*, however, and that no epimerization had occurred during the reaction sequence. Furthermore, we have recently reported that treatment of the acid chloride of **12a** under more stringent conditions than those employed here had no effect on the *trans* geometry of the B/C ring fusion.[22] It was therefore concluded that the loss of activity must be related to conformational or steric effects.

Naphthobenzazepine **5b** is simply a C-ring-expanded analogue of dihydrexidine (**4a**) in which the nitrogen is tethered to the pendant phenyl moiety by an ethyl bridge, thereby forming an azepine. The β-phenyl moieties in both **5b** and dihydrexidine are placed above the plane of the catechol by nearly the same τ_1 value (ca. 60°) (Table 2). Nevertheless, the azepine ring of **5b** allows the β-phenyl moiety to be more conformationally mobile than that of dihydrexidine **4a**. This relative mobility allows the β-phenyl moiety to twist orthogonally (τ_2) in the clockwise direction by about 18°, with respect to the catechol ring, and 28°, with respect to the β-phenyl moiety of dihydrexidine. If it is assumed that the geometry of the agonist site of the D_1 receptor is complementary to the orientation of an active ligand (in this case dihydrexidine **4a**), the larger twist angle in **5b** may force the β-phenyl moiety to intrude into an excluded space in the D_1 receptor.

A second possible explanation for the loss of activity concerns the unknown consequences of the steric effect of the ethyl tether between the nitrogen and the

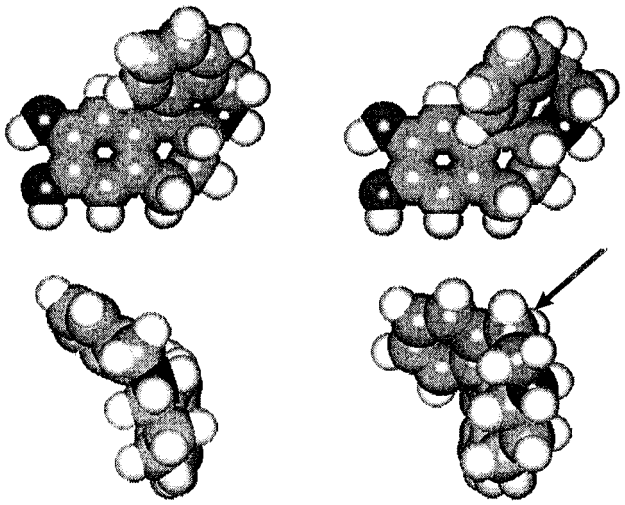


Figure 1. Face and edge-on views of the energy-minimized structures of dihydrexidine (**4a**; left) and the naphthobenzazepine **5b** (right). Note differences in the twist of the nonsubstituted (pendant) phenyl ring, as well as the expanded steric profile of the α face of the azepine ring (ring C) in **5b** as compared to **4a**. The arrow on **5b** points to the additional methylene group of the azepine ring that protrudes toward the α face of the molecule.

pendant phenyl ring of **5b**, as compared to the analogous methylene unit in **4a**. Superposition of the energy-minimized structures of **4a** and **5b** shows that not only is the pendant phenyl moiety of **5b** clearly twisted orthogonally with respect to that of dihydrexidine, but also that the ethyl bridge of **5b** protrudes below the superimposition plane (see Figure 1). Because this area is adjacent to the nitrogen atom (a presumed major site for receptor interaction), it seems possible that an unfavorable steric effect here might interfere with ligand binding.

It is obvious that the azepine ring dictates not only the orientation of the *β*-phenyl moiety but also the conformation of the phenethylamine fragment in **5b**. As listed in Table 2, there is about 13° (τ_3) more deviation from a *trans*-antiperiplanar conformation for **5b** than in dihydrexidine **4a**. It has been suggested that a fully extended *trans β*-rotamer conformation of the ethylamine fragment is important for agonist activity.[11,23] Thus, the increased deviation of the ethylamine side chain from an antiperiplanar conformation could also be an additional factor to explain partially the attenuated activity of **5b**. Indeed, it may be that all three of these factors are operating in concert.

One could also consider a superposition of **5c** over **2** whereby the unsubstituted phenylbenzazepine moiety of **5c** is superimposed over the analogous hydroxychloro-substituted portion of compound **2**. While such a view gives good superposition of the template backbones for both molecules, it ignores the likelihood that the receptor will interact with the polar hydroxy and halo substituents in a similar region of space, and this approach was therefore not given serious consideration in our search for an explanation of the different biological activities.

The low dopamine D_1 affinity of **4b** (322 nM)[13] and, in contrast, the remarkably high affinity of the phenylbenzazepine SCH 23390 (**1**)[5] and its conformationally rigid analogue SCH 39166 (**2**)[6] prompted the synthesis and evaluation of naphthobenzazepine **5a** and its 3-iodo analogue **5c**. Because neither compound had significant affinity for the D_1 receptor, an explanation was sought from a comparison of the energy-minimized structures of **5c** *versus* **2**. It was noted that a halogen at the "para" position of the ethylamine side chain of *β*-phenyldopamines increases the D_1 affinity of antagonists.[24] Although there was a relative improvement in D_1 affinity of **5c** *versus* **5a** (Table 1), the $K_{0.5}$ values were very high and did not differ enough to discriminate between the two compounds.

Superimposition of energy-minimized structures of **5c** and **2** and a review of the torsion angles (Table 2) reveals that the two phenyl moieties orient to opposite faces of the plane of superposition. The phenyl moiety of **5c** is placed approximately 64° above the plane of the substituted aromatic ring and twisted slightly (τ_2 = 16.7°) in the clockwise direction. On the other hand, the phenyl moiety of **2** is below the plane of the substituted aromatic ring and is twisted about 42° in the anticlockwise direction.

Another apparent difference between **5c** and **2** is the orientation of the ethylamine side chain fragments, where the former has a nearly extended *trans β*-rotamer ($\tau_3 = 150°$), while the latter resides as a gauche (cisoid) rotamer ($\tau_3 = 57°$). These orientations result in different nitrogen to oxygen distances of 7.35 and 6.18 Å for **5c** and **2**, respectively. Moreover, superposition of the substituted aromatic rings of energy-minimized structures showed not only a nearly perpendicular orientation of the two phenyl accessory rings but that the two nitrogens were placed at a distance of 1.56 Å from each other, another factor that may contribute to the absence of activity in **5a** and **5c** at the D_1 receptor.

In summary, the dramatic differences in conformation between compound **2** and compounds **5a** and **5c** are sufficient to explain the lack of D_1 affinity for the latter compounds. On the other hand, the conformational differences between the highly potent D_1 agonist dihydrexidine **4a** and its C-ring-expanded analogue **5b** are less striking, but may provide the explanation for the low affinity of the latter compound. The only other obvious structural difference is the increased steric bulk of the ethyl bridge tethering the nitrogen atom to the pendant phenyl ring, which protrudes somewhat behind the plane of the molecule. These results, when integrated with our earlier studies, will continue to refine our concept of the D_1 agonist pharmacophore.[14]

Experimental Section

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. ^{1}H NMR spectra were obtained on a Varian VXR-500S (500 MHz) NMR instrument in $CDCl_3$ with TMS as an internal standard, except as noted. High-resolution mass spectra were obtained on a Kratos MS50, and chemical ionization mass spectra were obtained on a Finnigan 4000. Elemental analyses were performed by the Purdue University microanalysis laboratory and are within ±0.4% of the calculated values.

(*E,Z*)-3-Carbethoxy-4-(3′-methoxyphenyl)-4-phenyl-4-butenoic Acid (6a). To a solution of 3-methoxybenzoic acid (25 g, 164.3 mmol) in 250 mL of dichloromethane was added oxalyl chloride (54.76 g, 410.7 mmol) dropwise at ice−water bath temperature. The reaction was allowed to warm to room temperature and stirred for 1 h. The solvent and excess oxalyl chloride were removed by rotary evaporation. The resulting acid chloride was mixed with dry benzene (250 mL) and cooled in an ice−water bath. Aluminum chloride powder (20.6 g, 154.3 mmol) was added dropwise using a powder addition

funnel. The mixture was then allowed to stir overnight at room temperature and poured into ice−water. The two phases were separated, and the organic layer was washed with 2 N HCl (150 mL) and water (3 × 150 mL). After drying ($MgSO_4$) and filtration, the solvent was removed by rotary evaporation and the residue was dissolved in freshly distilled *tert*-butyl alcohol. Powdered potassium *tert*-butoxide (Aldrich) (12.7 g, 119.2 mmol) was added into the *tert*-butyl alcohol solution, followed by dropwise addition of diethyl succinate (25.6 g, 146 mmol) over 1 h. The reaction mixture was heated at reflux overnight, cooled, poured into ice−water, and extracted with diethyl ether (2 × 120 mL), followed by ethyl acetate (1 × 160 mL). Upon acidification of the aqueous layer with 6 N HCl, an oil separated which was extracted with dichloromethane (3 × 100 mL). After drying ($MgSO_4$) and filtration, the solvent was removed to yield 50.88 g (91%) of crude **6a**: IR (neat) 1706 cm^{-1}; CIMS (isobutane) M + 1 341. The material was sufficiently pure, as determined by TLC, to carry on to the next step without further purification.

(±)-*cis*- and *trans*-1-Phenyl-2-carbethoxy-4-oxo-7-methoxy-1,2,3,4-tetrahydronaphthalene (7a). A solution of crude **6a** (50 g, 146.9 mmol) in 500 mL of 95% ethanol containing 5 g of 10% Pd−C catalyst was shaken at room temperature under 50 psig of hydrogen overnight. The catalyst was removed by filtration through Celite, and the solvent was removed by rotary evaporation to yield a viscous oil. The oil was stirred in 158 mL of 10% P_2O_5/methanesulfonic acid for 10 h at room temperature. The reaction mixture was poured into 350 mL of ice−water and extracted with ethyl acetate (3 × 100 mL). The organic layer was washed with saturated sodium bicarbonate solution (2 × 80 mL) and water (2 × 100 mL). After drying ($MgSO_4$) and filtration, the solvent was removed to give a dark oil. This material was chromatographed over 200 g of silica gel, eluting with hexane−ethyl acetate (3:1) under a slight nitrogen pressure. Fractions containing material with R_f 0.43 in hexane−ethyl acetate (3:2) were combined and evaporated to give an oil which was recrystallized from diethyl ether to provide 8.58 g (18%) of *trans*-**7a**: mp 100−101 °C; IR (KBr) 1680, 1730 cm^{-1}; CIMS (isobutane) M + 1 325; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, 1, ArH, J = 8.8 Hz), 7.25−7.32 (m, 2, ArH), 7.1 (d, 2, ArH, J = 6.3 Hz), 6.86 (d, 1, ArH, J = 8.8 Hz), 6.39 (s, 1, ArH), 4.6 (d, 1, Ar_2CH, J = 7.3 Hz), 3.87 (q, 2, $COCH_2$, J = 7.1 Hz), 3.71 (s, 3, OCH_3), 3.29−3.33 (m, 1, CCHCO), 2.89 (dd, 1, ArCOCH, J = 8.5, 17.03 Hz), 2.75 (dd, 1, ArCOCH, J = 4.4, 17.1 Hz), 1.0 (t, 3, CH_3, J = 7.1 Hz). Anal. ($C_{20}H_{20}O_4$) C, H.

The mother liquor obtained after filtration of *trans*-**7a** was concentrated to give 23.8 g (50%) of *cis*-**7a** as a brown oil. A small amount of the oil was purified by centrifugal thin-layer chromatography on a silica rotor using hexane−ethyl acetate (4:1) as the developing solvent: IR (neat) 1674, 1728 cm^{-1}; CIMS (isobutane) M + 1 325; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, 1, ArH, J = 8.8 Hz), 7.22−7.24 (m, 3, ArH), 6.96−7.0 (m, 2, ArH), 6.92 (d, 1, ArH, J = 8.8 Hz), 6.24 (s, 1, ArH), 4.78 (d, 1, Ar_2CH, J = 4.8 Hz), 4.1 (q, 2, $COCH_2$, J = 7.1 Hz), 3.8 (s, 3, OCH_3), 3.55 (tt, 1, CCHCO, J = 19.4, 4.8,Hz), 2.9 (dd, 1, ArCOCH, J = 4.2, 18.7 Hz), 1.22 (t, 3, CH_3, J = 7.1 Hz).

(±)-*trans*-Ethyl 1-Phenyl-7-methoxy-1,2,3,4-tetrahydro-2-naphthoate (8a). (I) From *trans*-7a. *Trans* keto ester **7a** (6.0 g, 18.5 mmol) was dissolved in 200 mL of acetic acid containing 0.5 mL of perchloric acid and 500 mg of 10% Pd−C catalyst and shaken for 8 h at room temperature under 50 psig of hydrogen. Solid potassium carbonate was added to neutralize the perchloric acid. The catalyst was removed by filtration, the solvent was removed by rotary evaporation, and the residue was recrystallized from ethanol to give 5 g (87%) of **8a**: mp 56−57 °C; IR (KBr pellet) 1724 cm^{-1}; CIMS (isobutane) M + 1 311; ^{1}H NMR ($CDCl_3$) δ 7.23−7.26 (m, 2, ArH), 7.16−7.20 (m, 1, ArH), 7.09−7.11 (m, 2, ArH), 7.02 (d, 1, ArH, J = 8.4 Hz), 6.68 (d, 1, ArH, J = 8.4 Hz), 6.28 (s, 1, ArH), 4.34 (d, 1, Ar_2CH, J = 9.5 Hz), 3.98 (q, 2, OCH_2, J = 7.1 Hz), 3.58 (s, 3, OCH_3), 2.82−2.91 (m, 3, CHCOO, $ArCH_2$), 2.10−2.15 (m, 1, ArCCH), 1.94−2.03 (m, 1, ArCCH), 1.04 (t, 3, CH_3, J = 7.1 Hz). Anal. ($C_{20}H_{22}O_3$) C, H.

(II) From *cis*-7a. *Cis* keto ester **7a** (6.0 g, 18.5 mmol) was reduced by catalytic hydrogenation as described for *trans*-**7a**, and the crude product was dissolved in 30 mL of absolute ethanol. This solution was added to a solution of freshly prepared sodium ethoxide in ethanol (4.0 g of sodium metal and 80 mL of ethanol). The reaction was heated at reflux for 10 h and then cooled and poured into ice water. Extraction with diethyl ether (3 × 50 mL) followed by washing with water, drying ($MgSO_4$), and solvent removal afforded 4.24 g (73.8% yield) of the crude epimerized product. Recrystallization from ethanol afforded the pure product having all analytical data identical to **8a** obtained from *trans*-**7a**.

(±)-*trans*-Ethyl 1-Phenyl-6,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthoate (8b). *Trans* ester **8b** was obtained (95% yield) by epimerization of **7b**[25] with a solution of sodium ethoxide in ethanol as described for **8a** (obtained from *cis*-**7a**): IR (KBr) 1725 cm^{-1}; CIMS (isobutane) M + 1 341; ^{1}H NMR ($CDCl_3$) δ 7.20 (m, 3, ArH), 7.10 (m, 2, ArH), 6.65 (s, 1, ArH), 6.25 (s, 1, ArH), 4.36 (d, 1, Ar_2CH, J = 9.4 Hz), 4.04 (q, 2, CH_2), 3.86 (s, 3, OCH_3), 3.59 (s, 3, OCH_3), 2.84 (m, 3, CHCOO, $ArCH_2$), 1.59 (m, 2, $ArCCH_2$), 1.12 (t, 3, CH_3). Anal. ($C_{20}H_{22}O_3$) C, H.

(±)-*trans*-1-Phenyl-7-methoxy-1,2,3,4-tetrahydro-2-naphthoic Acid (9a). Ester **8a** (2.09 g, 7.4 mmol) was heated at reflux for 10 h with 25 mL of 2 N aqueous NaOH solution containing 5 mL of ethanol. The reaction mixture was then poured into water, acidified with 6 N HCl, and extracted with dichloromethane (3 × 50 mL). After drying ($MgSO_4$), filtration and removal of the solvent afforded 1.88 g (90%) of **9a** which was recrystallized from benzene−hexanes: mp 148−149 °C; IR (KBr) 1709 cm^{-1}; CIMS (isobutane) M + 1 283; ^{1}H NMR ($CDCl_3$) 7.26−7.29 (m, 2, ArH), 7.20−7.24 (m, 1, ArH), 7.12 (d, 2, ArH, J = 7.8 Hz), 7.05 (d, 1, ArH, J = 8.4 Hz), 6.72 (dd, 1, ArH, J = 2.6, 8.5 Hz), 6.33 (s, 1, ArH), 4.40 (d, 1, Ar_2CH, J = 8.6 Hz), 3.61 (s, 3, OCH_3), 2.90 (m, 3, $ArCH_2$, CHCOO), 2.19 (m, 1, ArCCH), 2.0 (m, 1, ArCCH). Anal. ($C_{19}H_{20}O_3$) C, H.

(±)-*trans*-1-Phenyl-6,7-dimethoxy-1,2,3,4-tetrahydro-2-naphthoic Acid (9b). *Trans* acid **9b** was obtained (80% yield) from **8b** as described for **9a** and recrystallized from benzene−hexanes: mp 130−132 °C; IR (KBr) 1709 cm^{-1}; CIMS (isobutane) M + 1 313; ^{1}H NMR ($CDCl_3$) δ 7.25−7.3 (m, 2, ArH), 7.2−7.23 (m, 1, ArH), 7.1 (d, 2, ArH, J = 7.1 Hz), 6.6 (s, 1, ArH), 6.26 (s, 1, ArH), 4.4 (d, 1, Ar_2CH, J = 7.9 Hz), 3.87 (s, 3, OCH3), 3.6 (s, 3, OCH3), 2.86−2.92 (m, 3, CHCOO, $ArCH_2$), 2.11−2.17 (m, 1, ArCCH), 1.99−2.06 (m, 1, ArCCH). Anal. ($C_{19}H_{20}O_4$) C, H.

(±)-*trans*-1-Phenyl-7-methoxy-2-amino-1,2,3,4-tetrahydronaphthalene (10a). Following the Weinstock modification of the Curtius rearrangement,[18] a solution of **9a** (5.0 g, 17.7 mmol) in 60 mL of dry acetone was cooled to 0 °C in an ice−salt bath. Triethylamine (1.83 g, 17.9 mmol) in 10 mL of acetone was added all at once, and the reaction was stirred for 30 min. Ethyl chloroformate (3.15 g, 17.9 mmol) in 10 mL of acetone was added dropwise over 5 min, and the mixture was stirred at 0 °C for 1 h. A solution of sodium azide (2.76 g, 17.7 mmol) in 20 mL of water was then added dropwise over 10 min. The mixture was stirred at 0 °C for 1 h, poured into ice−water, and extracted with toluene (3 × 300 mL). After drying ($MgSO_4$) and filtration, the stirred organic solution was heated on a steam bath for 2 h. The reaction was shown to be complete by IR. The toluene was removed by rotary evaporation to give a yellow oil. The oil was redissolved in 60 mL of ethanolic potassium hydroxide and heated at reflux for 48 h. The ethanol was removed by rotary evaporation, and the residue was partioned between water (200 mL) and diethyl ether (3 × 200 mL). The ether solution was then extracted with 2 N HCl (2 × 100 mL). The aqueous solution was washed with 100 mL of ether, basified to pH 9.5 with ammonia, and extracted with dichloromethane (2 × 100 mL). The organic solution was dried ($MgSO_4$), the solid was filtered, and removal of the solvent afforded 3.63 g (81%) of free base **10a** as a pale yellow oil. A portion of the free base was converted to the hydrochloride salt and recrystallized from ethanol−ether: mp 262−263 °C; CIMS (isobutane) M + 1 254; ^{1}H NMR ($CDCl_3$, free base) δ 7.32 (m, 2, ArH), 7.26 (m, 1, ArH), 7.17 (d, 2, ArH, J = 8.1 Hz), 7.26 (d, 1, ArH, J = 8.4 Hz), 6.7 (d, 1, ArH, J = 8.6 Hz), 6.24 (s, 1, ArH), 3.69 (d, 1, Ar_2CH, J = 8.9 Hz), 3.60 (s, 3, OCH_3), 3.19−3.22 (m, 1, CHN), 2.87 (m, 2, $ArCH_2$), 2.06

(m, 1, CHCN), 1.74 (m, 1, CHCN), 1.4 (b s, 2, NH_2). Anal. ($C_{17}H_{20}NOCl$) C, H, N.

(±)-*trans*-1-Phenyl-6,7-dimethoxy-2-amino-1,2,3,4-tetrahydronaphthalene (10b). The free base **10b** was obtained (80% yield) from **9b** as described for **10a**, and the hydrochloride salt was recrystallized from ethanol: mp 246−248 °C; CIMS (isobutane) M + 1 284; ^{1}H NMR ($CDCl_3$, free base) δ 7.32 (t, 2, ArH, J = 7.4 Hz), 7.23−7.27 (m, 1, ArH), 7.18 (d, 2, ArH, J = 7.7 Hz), 3.87 (s, 3, OCH_3), 3.68 (d, 1, Ar_2CH, J = 8.42 Hz), 3.58 (s, 3, OCH_3), 3.17−3.01 (m, 1, CHN), 3.82−3.01 (m, 2, $ArCH_2$), 2.02−2.08 (m, 1, CHCN), 1.69−1.77 (m, 1, CHCN). Anal. ($C_{18}H_{22}NO_2Cl$) C, H, N.

(±)-*trans*-*N*-(7-Methoxy-1-phenyl-1,2,3,4-tetrahydronaphthalen-2-yl)glycine, Methyl Ester (11a). To a solution of 1.7 g (6.69 mmol) of **10a** in 50 mL of dry DMF was added 1.99 g (14.3 mmol) of anhydrous potassium carbonate, and the mixture was cooled to −5 °C. Methyl bromoacetate (1.02 g, 6.69 mmol) was added, and the reaction mixture was stirred for 30 min at −5 °C and for an additional 4 h at room temperature. The mixture was then poured into water and extracted with diethyl ether (3 × 100 mL). The ether solution was washed with water and dried ($MgSO_4$), and the solvent was removed by rotary evaporation to give a brown oil. Purification of the oil (less than 1 g at a time) by centrifugal thin-layer chromatography on a 4 mm silica rotor, using 30% ethyl acetate−hexane in an ammonia atmosphere, afforded 1.85 g (85%) of free base **11a**. A portion of the free base was converted to the hydrochloride salt and recrystallized from methanol−ether: mp 173−174 °C; CIMS (isobutane) M + 1 326; ^{1}H NMR ($CDCl_3$, free base) δ 7.3−7.34 (m, 2, ArH), 7.25−7.28 (m, 1, ArH), 7.13−7.16 (m, 2, ArH), 7.05 (d, 1, ArH, J = 8.4 Hz), 6.6 (dd, 1, ArH, J = 2.4, 8.4 Hz), 6.27 (s, 1, ArH), 3.9 (d, 1, Ar_2CH, J = 7.8 Hz), 3.64 (s, 3, OCH_3), 3.61 (s, 3, OCH_3), 3.42 (dd, 2, NCH_2CO, J = 17.3 Hz), 2.97−3.01 (m, 1, ArCH), 2.86−2.9 (m, 2, ArCH, CHN), 2.07−2.12 (m, 1, CHCN), 1.62−1.7 (m, 1, CHCN). Anal. ($C_{20}H_{24}NO_3Cl$) C, H, N.

(±)-*trans*-*N*-(6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydronaphthalen-2-yl)glycine, Methyl Ester (11b). The free base **11b** was obtained (83%) from **10b** as described for **11a**. A portion of the free base was converted to the hydrochloride salt and recrystallized from methanol: mp 197−198 °C; CIMS (isobutane) M + 1 356; ^{1}H NMR ($CDCl_3$, free base) δ 7.33 (t, 2, ArH, J = 7.6 Hz), 7.26 (t, 1, ArH, J = 7.4 Hz), 7.13 (d, 2, ArH, J = 7.8 Hz), 6.6 (s, 1, ArH), 6.22 (s, 1, ArH), 3.9 (d, 1, Ar_2CH, J = 7.1 Hz), 3.86 (s, 3, OCH_3), 3.65 (s, 3, OCH_3), 3.6 (s, 3, OCH_3), 3.47 (d, 1, NCHCOO, J = 17.2 Hz), 3.4 (d, 1, NCHCOO, J = 17.3 Hz), 2.94−2.99 (m, 1, ArCH), 2.84−2.88 (m, 2, ArCH, CHN), 2.02−2.08 (m, 1, CHCN), 1.83 (b s, 1, NH), 1.63−1.7 (m, 1, CHCN). Anal. ($C_{21}H_{26}NO_4Cl$) C, H, N.

(±)-*trans*-*N*-(7-Methoxy-1-phenyl-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-(*p*-tolylsulfonyl)glycine, Methyl Ester (12a). To a solution of 1.3 g (3.99 mmol) of **11a** in 20 mL of dichloromethane was added triethylamine (0.97 mL, 6.96 mmol) in 3 mL of dichloromethane and freshly recrystallized *p*-toluenesulfonyl chloride (907 mg, 4.73 mmol), and the reaction mixture was stirred at room temperature for 48 h. The mixture was poured into water (50 mL), and the layers were separated. The aqueous layer was further extracted with dichloromethane (2 × 20 mL), and the organic layers were combined, washed with 1 N HCl (30 mL), and dried ($MgSO_4$). Filtration and removal of the solvent afforded the crude ester. Column chromatography of the ester over 30 g of silica gel, using 20% ethyl acetate in hexane as the developing solvent, afforded 1.5 g (76.8%) of **12a** as a gum: CIMS (isobutane) M + 1 480; IR (neat) 1737, 1155 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, 2, ArH, J = 7.3 Hz), 7.07−7.14 (m, 5, ArH), 7.0 (d, 1, ArH, J = 8.4 Hz), 6.66 (dd, 1, ArH, J = 8.4, 2.7 Hz), 6.16 (s, 1, ArH), 4.12−4.17 (m, 2, NCHCOO, Ar_2CH), 4.0−4.05 (m, 1, CHN), 3.75 (d, 1, NCHCOO, J = 18.2 Hz), 3.67 (s, 3, OCH_3), 3.56 (s, 3, OCH_3), 2.92−3.0 (m, 1, ArCH), 2.8−2.86 (m, 1, ArCH), 2.37 (s, 3, $ArCH_3$), 2.24−2.3 (m, 1, CHCN), 1.9−2.0 (m, 1, CHCN). Anal. ($C_{27}H_{29}NO_5S$) C, H, N.

(±)-*trans*-*N*-(6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydronaphthalen-2-yl)-*N*-(*p*-tolylsulfonyl)glycine, Methyl Ester (12b). Ester **12b** was obtained in 79.7% yield from **11b**, as described for **12a**, and recrystallized from hexane−ethyl acetate: mp 123−125 °C; CIMS (isobutane) M + 1 510; IR (KBr) 1750, 1153 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, 2, ArH, J = 8.3 Hz), 7.08−7.14 (m, 5, ArH), 6.92 (d, 1, ArH, J = 6.8 Hz), 6.58 (s, 1, ArH), 6.05 (s, 1, ArH), 4.35 (d, 1, NCHCOO, J = 18.0 Hz), 4.82 (d, 1, Ar_2CH, J = 9.3 Hz), 3.96−4.02 (m, 1, CHN), 3.83 (s, 3, OCH_3), 3.76 (d, 1, NCHCOO, J = 18.1 Hz), 3.69 (s, 3, OCH_3), 3.53 (s, 3, OCH_3), 2.93−3.02 (m, 1, ArCH), 2.78−2.83 (m, 1, ArCH), 2.39 (s, 3, $ArCH_3$), 2.22−2.28 (m, 1, CHCN), 1.92−2.0 (m, 1, CHCN). Anal. ($C_{28}H_{31}NO_6S$) C, H, N.

(±)-*trans*-2-Methoxy-7-(*p*-tolylsulfonyl)-5,6,6a,7,8,13a-hexahydrobenzo[*d*]naphth[2,1-*b*]azepin-9-one (13a). Ester **12a** (710 mg, 1.48 mmol) was stirred at room temperature with 20 mL of 1 N methanolic KOH for 6 h. The methanol was removed *in vacuo*, and the residue was dissolved in water (50 mL). The aqueous solution was then acidified with 2 N HCl and extracted with chloroform (3 × 30 mL). The aqueous layer was discarded, and the combined organic extracts were washed with water (3 × 30 mL) and brine, dried ($MgSO_4$), and evaporated *in vacuo* to give a white foam. This product was redissolved in 10 mL of dichloromethane, and oxalyl chloride (277 mg, 2.2 mmol) was added dropwise at room temperature into the dichloromethane solution. DMF (2 drops) was added, and the mixture was stirred for 1 h. The solvent and excess oxalyl chloride were removed *in vacuo*, and the residue was redissolved in 10 mL of dichloromethane. The solution was then dropped into a suspension of $AlCl_3$ (592 mg, 4.44 mmol) in dichloromethane (5 mL) at −78 °C. The temperature was raised to −15 °C over 2 h, and the reaction mixture was poured onto ice. The organic phase was separated and washed with 10 mL of 5% HCl, concentrated $NaHCO_3$ solution, and brine. The organic solution was dried ($MgSO_4$) and evaporated *in vacuo*. The crude product was purified by centrifugal thin-layer chromatography on a silica rotor using 20% ethyl acetate in hexane to afford 121 mg (66%) of **13a**: mp 146−148 °C; IR (KBr) 1686, 1261 cm^{-1}; CIMS (isobutane) M + 1 448; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26−7.3 (m, 1, ArH), 7.16 (d, 2, ArH), 7.02−7.11 (m, 3, ArH), 6.96 (d, 1, ArH), 6.9 (d, 2, ArH), 6.77 (dd, 1, ArH, J = 2.6, 8.5 Hz), 6.42 (s, 1, ArH), 4.66 (d, 1, COCHN, J = 20.1 Hz), 4.37 (d, 1, Ar_2CH, J = 11.9 Hz), 4.1−4.17 (m, 2, COCHN, CHN), 3.61 (s, 3, OCH_3), 3.09−3.16 (m, 1, ArCH), 2.86−2.91 (m, 1, ArCH), 2.35−2.4 (m, 1, CHCN), 2.31 (s, 3, $ArCH_3$), 1.99−2.06 (m, 1, CHCN). Anal. ($C_{26}H_{25}NO_4S$) C, H, N.

(±)-*trans*-2,3-Dimethoxy-7-(*p*-tolylsulfonyl)-5,6,6a,7,8,13a-hexahydrobenzo[*d*]naphth[2,1-*b*]azepin-9-one (13b). Product **13b** was obtained (65%) from **12b** as described for **13a** and recrystallized from ethanol−ether: mp 180−182 °C; IR (KBr) 1682, 1261 cm^{-1}; CIMS (isobutane) M + 1 478; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (t, 1, ArH, J = 7.6 Hz), 7.19 (d, 2, ArH, J = 8.2 Hz), 7.05−7.08 (m, 2, ArH), 6.98 (d, 1, ArH, J = 7.5 Hz), 6.93 (d, 2, ArH, J = 8.1 Hz), 6.65 (s, 1, ArH), 6.38 (s, 1, ArH), 4.68 (d, 1, COCHN, J = 20.1 Hz), 4.38 (d, 1, Ar_2CH, J = 11.7 Hz), 4.19 (d, 1, COCHN, J = 20.1 Hz), 4.13 (td, 1, CHN, J = 11.7, 2.7 Hz), 3.9 (s, 3, OCH_3), 3.61 (s, 3, OCH_3), 3.14−3.22 (m, 1, ArCH), 2.84−2.9 (m, 1, ArCH), 2.37−2.44 (m, 1, CHCN), 2.33 (s, 3, $ArCH_3$), 2.01−2.1 (m, 1, CHCN). Anal. ($C_{27}H_{27}NO_5S$) C, H, N.

(±)-*trans*-2-Methoxy-7-(*p*-tolylsulfonyl)-6,6a,7,8,9,13b-hexahydro-5*H*-benzo[*d*]naphth[2,1-*b*]azepine (14a). To a solution of **13a** (535.7 mg, 1.2 mmol) in 16 mL of absolute ethanol was added sodium borohydride (90 mg, 2.4 mmol) at room temperature. The mixture was stirred overnight, and the reaction was quenched with 5 mL of water. The solvent was removed *in vacuo*, the aqueous mixture was extracted with chloroform (3 × 15 mL), washed with brine, and dried ($MgSO_4$), and the solvent was removed *in vacuo* to give the crude alcohol. To the alcohol was added, with stirring, 5 mL (41.0 mmol) of freshly distilled boron triflouride etherate. A few drops of dichloromethane were added dropwise until the suspension went into solution, followed by 2 mL (12.6 mmol) of triethylsilane, and the mixture was stirred for 48 h. The reaction was quenched with 5 mL of saturated aqueous sodium chloride solution and extracted with ether (3 × 15 mL). The combined organic extracts were washed with water (15 mL) and dried ($MgSO_4$), and the solvent was removed *in vacuo*. Purification

of the crude product by centrifugal thin-layer chromatography on a silica rotor using hexane−ethyl acetate (3:1) as the developing solvent afforded 208 mg (40%) of **14a**: mp 160−161 °C; CIMS (isobutane) M + 1 434; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (d, 2, ArH, J = 8.3 Hz), 7.10 (d, 1, ArH, J = 8.4 Hz), 7.01−7.05 (m, 1, ArH), 6.95−7.0 (m, 2, ArH), 6.9 (t, 1, ArH, J = 7.3 Hz), 6.77 (dd, 1, ArH, J = 2.3, 8.5 Hz), 6.61 (m, 2, ArH), 4.39 (d, 1, Ar_2CH, J = 11.6 Hz), 4.08−4.15 (m, 1, ArCCHN), 3.93 (td, 1, CHN, J = 2.4, 11.8 Hz), 3.67 (s, 3, OCH_3), 3.58−3.65 (m, 1, ArCCHN), 3.17−3.24 (m, 1, ArCHCN), 3.04−3.12 (m, 1, ArCH), 2.79−2.90 (m, 2, ArCH, ArCHCN), 2.35 (s, 3, $ArCH_3$), 2.23−2.28 (m, 1, CHCN), 2.07−2.15 (m, 1, CHCN). Anal. ($C_{26}H_{27}NO_3S$) C, H, N.

(±)-*trans*-2,3-Dimethoxy-7-(*p*-tolylsulfonyl)-6,6a,7,8,9,13b-hexahydro-5*H*-benzo[*d*]naphth[2,1-*b*]azepine (14b). Amorphous **14b** was obtained (62% yield) from **13b** as described for **14a**: CIMS (isobutane) M + 1 464; ^{1}H NMR (500 MHz, $CDCl_3$) 7.04 (d, 2, ArH, J = 8.2 Hz), 7.01 (t, 1, ArH, J = 7.4 Hz), 6.59 (d, 3, ArH, J = 7.9 Hz), 6.58 (t, 1, ArH, J = 7.4 Hz), 6.53 (s, 1, ArH), 6.52 (d, 1, ArH, J = 7.42 Hz), 6.51 (s, 1, ArH), 4.36 (d, 1, Ar_2CH, J = 11.69 Hz), 4.08−4.15 (m, 1, ArCCHN), 3.88−3.96 (m, 4, CHN, OCH_3), 3.59−3.7 (m, 4, OCH_3, ArCCHN), 2.78−2.87 (m, 2, ArCHCN, ArCH), 2.35 (s, 3, $ArCH_3$), 2.23−2.28 (m, 1, CHCN), 2.08−2.16 (m, 1, CHCN).

(±)-*trans*-6,6a,7,8,9,13b-Hexahydro-2-methoxy-5*H*-benzo[*d*]naphth[2,1-*b*]azepine (15a). A solution of 262 mg (0.6 mmol) of **14a** was suspended in 5 mL of xylene, and 0.67 mL (2.23 mmol) of a 65+ wt % solution of sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) in toluene was added. The resulting mixture was heated at reflux for 1 h and cooled, and 5 mL of 15% sodium hydroxide was added. The mixture was partitioned between water and ether, and the organic layer was dried ($MgSO_4$) and evaporated. Purification by centrifugal thin-layer chromatography on a silica rotor, using hexane−ethyl acetate (1:1) in an ammonia atmosphere, afforded 128 mg (76%) of the amine **15a**. The hydrochloride salt of **15a** was recrystallized from methanol−ether: mp 270 °C dec; CIMS (isobutane) M + 1 280; ^{1}H NMR ($CDCl_3$, free base) δ 7.14 (d, 1, ArH, J = 7.5 Hz), 7.05−7.1 (m, 2, ArH), 7.0 (t, 1, ArH, J = 7.0 Hz), 6.73 (dd, 1, ArH, J = 3.0, 8.5 Hz), 6.55 (d, 1, ArH, J = 7.5 Hz), 4.48 (d, 1, Ar_2CH, J = 7.5 Hz), 3.68 (s, 3, OCH_3), 3.32−3.4 (m, 2, $ArCCH_2N$), 2.78−2.84 (m, 2, $ArCH_2CN$), 2.64−2.73 (m, 3, $ArCH_2$, CHN), 1.78−1.92 (m, 1, CHCN), 1.8 (b s, 1, NH), 1.56−1.64 (m, 1, CHCN). Anal. ($C_{19}H_{22}NOCl$) C, H, N.

(±)-*trans*-6,6a,7,8,9,13b-Hexahydro-2,3-dimethoxy-5*H*-benzo[*d*]naphth[2,1-*b*]azepine (15b). A solution of 55 mg (0.12 mmol) of **14b** was suspended in 1 mL of xylene, and 0.13 mL (0.45 mmol) of a 65+ wt % solution of sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) in toluene was added. The product was isolated (25 mg, 67%) as described for **15a**. The hydrochloride salt of **15b** was recrystallized from methanol−ether: mp 277−279 °C; CIMS (isobutane) M + 1 310; ^{1}H NMR ($CDCl_3$, free base) δ 7.16 (d, 1, ArH, J = 7.0 Hz), 7.1 (t, 1, ArH, J = 7.2 Hz), 7.02 (t, 1, ArH, J = 7.6 Hz), 6.65 (s, 1, ArH), 6.0 (d, 1, ArH, J = 7.6 Hz), 6.48 (s, 1, ArH), 4.86 (d, 1, Ar_2CH, J = 7.4 Hz), 3.58 (s, 3, OCH_3), 3.54 (s, 3, OCH_3), 3.06−3.08 (m, 2, $ArCCH_2N$), 2.56−2.57 (m, 2, $ArCH_2$-CN), 2.52−2.55 (m, 3, $ArCH_2$, CHN), 1.75−1.83 (m, 1, CHCN), 1.55 (b s, 1, NH), 1.52−1.54 (m, 1, CHCN); HRCIMS calcd for $C_{20}H_{23}NO_2$ 310.1807 (M + H), found 310.1807.

(±)-*trans*-6,6a,7,8,9,13b-Hexahydro-7-methyl-2-methoxy-5*H*-benzo[*d*]naphth[2,1-*b*]azepine (16a). A solution of 144 mg (0.46 mmol) of amine hydrochloride **15a** was mixed with 0.23 mL (2.86 mmol) of 37% formalin solution and 118 mg (1.78 mmol) of 97% sodium cyanoborohydride in 8 mL of methanol, and the mixture was stirred overnight at room temperature. After removal of the volatiles *in vacuo*, the residue was partitioned between 5% HCl and ether. The layers were separated, the aqueous layer was washed once more with ether, and the organic fractions were discarded. The aqueous layer was made basic with concentrated ammonium hydroxide, and the alkylated amine was then extracted into 3 × 40 mL of dichloromethane, which was dried ($MgSO_4$) and then filtered. The solvent was removed *in vacuo* to give 129 mg (95%) of the free base **16a** as a colorless oil: CIMS (isobutane) M + 1 294; ^{1}H NMR ($CDCl_3$, free base) δ 7.13 (d, 1, ArH, J = 7.3 Hz), 7.04−7.09 (m, 2, ArH), 6.98 (t, 1, ArH, J = 7.5 Hz), 6.75 (dd, 1, ArH, J = 2.7, 8.3 Hz), 6.54 (s, 1, ArH), 6.36 (d, 1, ArH, J = 7.6 Hz), 4.8 (d, 1, ArCH, J = 7.0 Hz), 3.7 (s, 3, OCH_3), 3.62−3.68 (m, 1, ArCCHN), 3.20−3.25 (m, 1, ArCCHN), 2.8−2.88 (m, 2, $ArCH_2CN$), 2.57−2.72 (m, 2, CHN, ArCH), 2.49−2.55 (m, 4, NCH_3, ArCH), 1.98−2.03 (m, 1, CHCN), 1.64−1.72 (m, 1, CHCN); HRCIMS calcd for $C_{20}H_{23}NO$ 294.1858 (M + H), found 294.1843.

(±)-*trans*-6,6a,7,8,9,13b-Hexahydro-7-methyl-5*H*-benzo[*d*]naphth[2,1-*b*]azepin-2-ol (5a). To a solution of the free base **16a** (124 mg, 0.42 mmol) in dichloromethane (3 mL) was added BBr_3 (0.12 mL, 1.26 mmol) dropwise at −78 °C. The reaction mixture was raised to room temperature over a period of 2 h and with stirring continued for an additional 5 h. The reaction mixture was then cooled to −78 °C, decomposed by the addition of methanol (3 mL), and concentrated *in vacuo*. The process of addition of methanol and evaporation was repeated trice. The crude hydrobromide salt was suspended in 5 mL of warm water, and the mixture was adjusted to pH 8 by dropwise addition of dilute sodium bicarbonate solution. The reaction mixture was extracted with chloroform (3 × 3 mL). The combined organic extracts were washed with water (2 × 3 mL) and dried ($MgSO_4$), and the solvent was removed *in vacuo* to give 108 mg (92%) of the free base **5a** which was recrystallized from acetonitrile: mp 210−212 °C; CIMS (isobutane) M + 1 280; ^{1}H NMR ($CDCl_3$, free base) δ 7.12 (d, 1, ArH, J = 7.3 Hz), 7.02−7.08 (m, 2, ArH), 6.98 (t, 1, ArH, J = 7.2 Hz), 6.7 9 (dd, 1, ArH, J = 2.5, 8.2 Hz), 6.44 (s, 1, ArH), 6.37 (d, 1, ArH, J = 7.6 Hz), 4.7 (d, 1, Ar_2CH, J = 7.1 Hz), 3.6 (t, 1, ArCCHN, J = 13.4 Hz), 3.2−3.26 (m, 1, ArCCHN), 2.66−2.8 (m, 3, $ArCH_2CN$, CHN), 2.55−2.62 (m, 2, $ArCH_2$), 2.5 (s, 3, NCH_3), 2.0−2.06 (m, 1, CHCN), 1.6−1.69 (m, 1, CHCN). Anal. (HCl salt; $C_{19}H_{22}NOCl\cdot 0.25H_2O$) C, H, N.

(±)-*trans*-6,6a,7,8,9,13b-Hexahydro-5*H*-benzo[*d*]naphth-[2,1-*b*]azepine-2,3-diol Hydrobromide (5b). To a solution of the free base **15b** (20 mg, 0.065 mmol) in dichloromethane (2 mL) was added BBr_3 (0.03 mL, 0.26 mmol) dropwise at −78 °C. The crude hydrobromide salt was isolated as described for **19** and recrystallized from ethanol−ether to give 17 mg (71%) of the pure salt: mp 250 °C dec.; CIMS (isobutane) M + 1 282; ^{1}H NMR (CD_3OD, HBr salt) δ 7.26 (d, 2, ArH, J = 7.1 Hz), 7.18 (t, 1, ArH, J = 7.4 Hz), 7.13 (t, 1, ArH, J = 7.6 Hz), 6.66 (d, 1, ArH, J = 8.0Hz), 6.63 (s, 1, ArH), 6.37 (s, 1, ArH), 4.67 (d, 1, Ar_2CH, J = 8.2 Hz), 3.67−3.73 (m, 1H), 3.18−3.245 (m, 2H), 3.0−3.1 (m, 2H), 2.7 (dd, 2H, J = 5.7, 2.9 Hz), 3.16−2.23 (m, 1, CHCN), 1.73−1.82 (m, 1, CHCN); HRCIMS calcd for free base $C_{18}H_{19}NO_2$ 282.1494 (M + H), found 282.1452.

(±)-*trans*-6,6a,7,8,9,13b-Hexahydro-3-iodo-2-methoxy-7-methyl-5*H*-benzo[*d*]naphth[2,1-*b*]azepine (17). To a solution of **16a** (160 mg, 0.55 mmol) in ethanol (4 mL) was added silver sulfate (342 mg, 1.1 mmol) followed by iodine (279 mg, 1.10 mmol), and the mixture was stirred at room temperature for 24 h. The resulting yellow solid was removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in dichloromethane and washed with 5% aqueous sodium hydroxide solution (3 mL), followed by water (5 mL). After separation, the organic layer was dried ($MgSO_4$) and evaporated *in vacuo*. Purification of the residue by centrifugal thin-layer chromatography on a silica rotor, eluting with 20% ethyl acetate in hexane, afforded 138 mg (60%) of the free base **17** which was recrystallized from acetonitrile: mp 159−161 °C; CIMS (isobutane) M + 1 420; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.6 (s, 1, ArH), 7.14 (d, 1, ArH, J = 7.4 Hz), 7.08 (t, 1, ArH, J = 7.4 Hz), 7.0 (t, 1, ArH, J = 7.6 Hz), 6.46 (s, 1, ArH), 6.35 (d, 1, ArH, J = 7.6 Hz), 4.76 (d, 1, Ar_2CH, J = 7.1 Hz), 3.72 (s, 3, OCH_3), 3.65 (t, 1, ArCCH, J = 13.4 Hz), 3.22 (dd, 1, ArCCH, J = 5.6, 13.5 Hz), 2.76−2.85 (m, 2, $ArCH_2CN$), 2.54−2.68 (m, 3, CHN, $ArCH_2$), 2.52 (s, 3, NCH_3), 1.98−2.04 (m, 1, CHCN), 1.58−1.68 (m, 1, CHCN). Anal. ($C_{20}H_{22}NOI\cdot 0.25H_2O$) C, H, N.

(±)-*trans*-6,6a,7,8,9,13b-Hexahydro-3-iodo-7-methyl-5*H*-benzo[*d*]naphth[2,1-*b*]azepin-2-ol Hydrochloride (5c). To a solution of the free base **17** (50 mg, 0.12 mmol) in dichloromethane (2 mL) was added BBr_3 (0.03 mL, 0.36 mmol) dropwise at −78 °C. The free base **5c** was isolated in 70%

yield as described for **5a**. Following acidification, the hydrochloride salt was recrystallized from methanol−ethyl acetate: mp 233−235 °C; CIMS (isobutane) M + 1 406; ^{1}H NMR (free base, $CDCl_3$) δ 7.48 (s, 1, ArH), 7.08 (d, 1, ArH, J = 7.0 Hz), 7.04 (t, 1, ArH, J = 7.4 Hz), 6.96 (t, 1, ArH, J = 7.5 Hz), 6.47 (s, 1, ArH), 6.32 (d, 1, ArH, J = 7.7 Hz), 4.48 (d, 1, Ar_2-CH, J = 6.9 Hz), 3.42 (t, 1, ArCCHN, J = 13.6 Hz), 3.22−3.3 (m, 1, ArCCHN), 2.5−2.64 (m, 5, $ArCH_2CN$, CHN, $ArCH_2$), 2.48 (s, 3, NCH_3), 2.02−2.08 (m, 1, CHCN), 1.53−1.62 (m, 1, CHCN). Anal. ($C_{19}H_{21}INOCl$) C, H, N.

Dopamine D_1 and D_2 Receptor Affinity. Rat striatum was homogenized by seven manual strokes in a Wheaton Teflon glass homogenizer in ice-cold 50 mM HEPES buffer with 4.0 mM $MgCl_2$ at pH 7.4. Tissue was centrifuged at 27000*g* for 10 min, the supernatant discarded, and the pellet homogenized (five strokes) and resuspended in ice-cold buffer and centrifuged again. The final pellet was suspended at a concentration of approximately 2 mg wet weight/mL.

The assay buffer was 50 mM HEPES with 4 mM $MgCl_2$ (pH 7.4). Assay tubes containing a final volume of 1.0 mL were incubated at 37 °C for 15 min. Nonspecific binding of [^{3}H]-SCH 23390 was defined by adding 1 μM unlabeled SCH 23390. Incubations were filtered through glass-fiber filter mats with a 15 mL of ice-cold buffer wash using a Skatron cell harvester. Filters were allowed to dry, and 3.0 mL of Scintiverse E (Fischer Scientific) was added. After 30 min of shaking, radioactivity was counted on an LKB Betarack liquid scintillaton counter. Tissue−protein levels were estimated using the the Bradford dye-binding method.

The binding procedure and protein analysis were identical with that described above except that [^{3}H]spiperone was used as the radioligand. Nonspecific binding of [^{3}H]spiperone was defined by adding unlabeled 1 μM chlorpromazine. Ketanserin tartrate (50 nM) was added to prevent binding of [^{3}H]spiperone to serotonin receptors.

With both receptors, the resulting concentration curves were analyzed by nonlinear regression using the algorithms in Prism (GraphPad Inc.). All of these data are expressed as $K_{0.5}$, in which the experimental IC_{50} is corrected for the radioligand concentration using the following formula: $K_{0.5} = IC_{50}/(1 + L^*/K_D^*)$ where L^* is the experimental radioligand concentration and K_D^* is the K_D of the radioligand. In cases where the Hill slope (nH) = 1, $K_{0.5} = K_D$. Expressing the data in this form when nH < 1 obviates the need to pick a more complex model (e.g., two vs three site).

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