consisted of 30% 0.01 M KH_2PO_4/30% 0.005 M K_2PO_4/40% acetonitrile, pH 6.6.

Quantitation of test compound was accomplished by using absolute peak-area response of the UV detector as integrated by the Hewlett-Packard Laboratory automated system model 3356 (Palo Alto, CA). The in vitro half-lives were determined by plotting the logarithm of the amount of test compound remaining against time. The time required to decrease the amount of test compound in the incubation mixture by 50% was defined as the half-life.

Chemistry. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 283 spectrophotometer as KBr pellets. NMR spectra were determined on a Varian T-60A or EM-360 or an IBM NR-80 spectrometer in $CDCl_3$, Me_2SO-d_6, or CD_3OD with tetramethylsilane as internal standard or in D_2O with 4,4-dimethyl-4-silapentane-4-sulfonate as a standard.

2,6-Bis(1-pyrrolidinylmethyl)-4-(2-carbethoxybenzamido)phenol (3). The synthesis of **3** and **4** were carried out similarly. A solution of 9.1 g (58 mmol) of 4-acetoxybenzoyl chloride (prepared from 4-acetoxybenzoic acid and excess thionyl chloride) in 100 mL of methylene chloride was treated by dropwise addition with a solution of 8.9 mL (60 mmol) of ethyl 2-aminobenzoate and 25 mL (180 mmol) of triethylamine in 200 mL of methylene chloride. The reaction mixture was then heated to reflux for 2 h. Volatiles were removed under reduced pressure, and the resulting solid was washed with water, dilute HCl, and an aqueous solution of $NaHCO_3$. Crystallization from ethanol afforded 7.2 g (38%) of white, crystalline 4-(2-carbethoxybenzamido)acetylphenol: mp 124–129 °C.

The acetyl group was removed by dissolving the product in ethanol and saturating the solution with hydrogen chloride. Volatiles were removed, and the resulting product was washed with acetonitrile, affording 5.0 g (30%) of 4-(2-carbethoxybenzamido)phenol: mp 199–203 °C.

A suspension of 4.9 g (17 mmol) of product in 100 mL of ethanol was treated with 3.1 mL (37 mmol) of pyrrolidine and 4.0 mL (53 mmol) of 37% aqueous formaldehyde. The mixture was heated to reflux for 48 h. Volatiles were removed under reduced pressure, leaving an oil. The oil was dissolved in ether/ethyl acetate and the solution was saturated with hydrogen chloride, causing the product to precipitate as a white solid. Crystallization of the solid from EtOH/EtOAc afforded 4.2 g of **3** as white crystals: mp 214–215 °C.

Compound **6** was prepared by the catalytic hydrogenation of the cinnamate used in the preparation of **5**. Thus, ethyl 4-(4-acetoxybenzamido)cinnamate (35.3 g, 0.100 mol) in 200 mL of ethanol was cooled in an ice bath and was treated with 1 g of 10% Pd/C. The mixture was saturated with hydrogen chloride and was placed in a Paar hydrogenation apparatus with a heating mantle. The mixture was shaken at 45 psi of hydrogen at ca. 80 °C for 18 h. The crude ethyl 4-(4-hydroxybenzamido)benzenepropionate, isolated by filtration, concentration under reduced pressure, and treatment with ethyl acetate/ethyl ether, was aminomethylated in the manner described for **3**.

2-Methyl-1-propyl 3,5-Bis(1-pyrrolidinylmethyl)-4-hydroxyphenylacetate (16). The synthesis of the esters in Table II is exemplified by **16**. Thus, a solution of 50 g (0.34 mol) of 4-hydroxyphenylacetic acid in 200 mL of 2-methyl-1-propanol was saturated with hydrogen chloride. The solution was heated to reflux for 24 h. Volatiles were removed under reduced pressure, affording an oil. The oil was dissolved in ether and the solution was washed with dilute $NaHCO_3$ and water. The solution was dried ($MgSO_4$) and the solvent was removed under reduced pressure, affording an oil.

A mixture of 62.5 mL (0.748 mmol) of cooled pyrrolidine and 76.5 mL (1.02 mol) of cooled 37% aqueous formaldehyde was stirred at ice-bath temperature for 10 min. This mixture was then added to a solution of the crude oil described above, in 250 mL of acetonitrile. The resulting solution was heated to reflux for 18 h. Volatiles were removed under reduced pressure, affording an oil. The oil was dissolved in hexane and the solution was washed with water. The solution was dried ($MgSO_4$) and filtered. The solvent was removed under reduced pressure and the resulting oil was dissolved in ether and the solution was saturated with hydrogen chloride. A thick oil precipitated and the ether was decanted. Crystallization of the oil from 2-propanol afforded 37 g (24%) of **16** as white crystals: mp 172–174 °C.

Acids **7**, **11**, and **17** were prepared by dissolving the methyl or ethyl esters in aqueous hydrochloric acid, heating the solutions to reflux for 3 h, removing all volatiles under reduced pressure, and crystallizing the products from methanol/ether.

Synthesis and Receptor Affinities of Some Conformationally Restricted Analogues of the Dopamine D_1 Selective Ligand (5*R*)-8-Chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepin-7-ol

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The synthesis of a structurally novel series of 6,6a,7,8,9,13b-hexahydro-5*H*-benzo[*d*]naphtho[2,1-*b*]azepines (**2**), conformationally restricted analogues of the dopamine D_1 antagonist (5*R*)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepin-7-ol (SCH 23390, **1c**), is described. Affinity for D_1 receptors was determined by competition for rat striatal binding sites labeled by [^{3}H]SCH 23390; affinity for D_2 receptors was similarly determined by competition experiments using [^{3}H]spiperone. Compounds in this series having the B/C-trans ring junction (**2b** and related analogues), where the D ring is unequivocally fixed in an equatorial orientation, possess considerably more D_1 receptor affinity and selectivity vs the D_2 receptor than the conformationally mobile cis stereoisomers (**2a**), thus leading to the conclusion that axial substituents at the 4- or 5-positions of the benzazepine nucleus are detrimental to D_1 receptor affinity. Resolution and X-ray analysis demonstrated that D_1 receptor affinity was preferentially associated with the (−)-6a*S*,13b*R* enantiomer of **2b**.

Within the past several years, there has been considerable interest in the 2,3,4,5-tetrahydro-3-benzazepines as a result of their selective affinity for the D_1 subset[1] of dopamine receptors in the CNS and the periphery and the potential therapeutic utilities projected from these properties. Studies of substituent effects on activity of both agonist[2] and antagonist[3] members of this series have ap-

[†] Schering-Plough Corp.
[‡] Duke University.

(1) Kebabian, J. W.; Calne, D. B. *Nature (London)* **1979**, *277*, 93. Goldberg, L. I.; Volkman, P. H.; Kohli, J. D.; Kotake, A. N. *Adv. Biochem. Psychopharmacol.* **1977**, *16*, 251.

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Table I. MM2 Energies for Conformations of 1c, 2a, and 2b[a]

compd	conformation	energy, kcal/mol
1c	chair equatorial phenyl equatorial *N*-methyl	25.19
	chair axial phenyl equatorial *N*-methyl	24.40
	chair equatorial phenyl with 65° torsional angle equatorial *N*-methyl	28.12
2a	chair equatorial phenyl equatorial *N*-methyl	32.48
	chair axial phenyl equatorial *N*-methyl	32.17
2b	chair equatorial phenyl equatorial *N*-methyl	31.15

[a] See supplementary material for coordinates.

peared. The benzazepines possess a considerable degree of conformational mobility in spite of their cyclic structure. Although X-ray studies indicate that the pendant phenyl ring in the 5-phenyl-substituted analogues **1a**,[4] **1b**,[2] and **1c** is equatorially oriented, molecular mechanics calculations (Table I) indicate less than a 1-kcal barrier to ring inversion, with the axial phenyl chair conformer having the lower energy. Recently reported studies on restricting conformational mobility by bridging the 1- and 9-positions of 1[5] did not unequivocally support the hypothesis that the pendant phenyl group must be axially oriented for optimal interaction with the receptor.[6] Our own interest in this series prompted us to undertake the preparation of conformationally restricted analogues of the known D_1 antagonist **1c**[7] in which the pendant ring was unequivocally fixed. Thus, the hitherto unknown 6,6a,7,8,9,13b-hexahydro-5*H*-benzo[*d*]naphtho[2,1-*b*]azepines **2** can exist in either B/C-cis (**2a**) or B/C-trans (**2b**) configurations. Molecular mechanics (Table I) indicated that **2a** could exist as conformers in which ring D is either axial or equatorial, with a slight (<1 kcal) preference for the axial. However, **2b** was shown to possess a single low-energy conformation in which ring D is locked equatorially. Comparison of the calculated low-energy conformation of **2b** with the X-ray structure of **1c** (Figure 1) revealed that the dihedral angle between the aromatic rings was 95° for **1c** and 65° for **2b**. Calculations indicated that the energy of **1c** in which the dihedral angle was altered to 65° was less than 3 kcal higher than the minimum-energy conformer, and thus energetically accessible on binding to the receptor (for coordinates of modeled compounds, see supplementary material). Thus **2b** was an important target

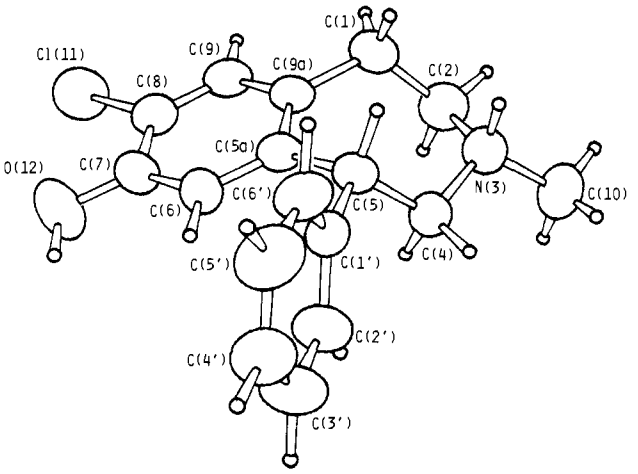
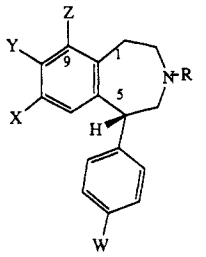
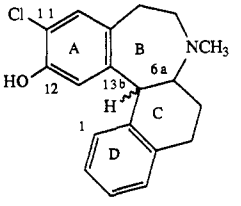


Figure 1. Absolute configuration and solid-state conformation of the cation in **1c** maleate; small circles represent hydrogen atoms.

since it could provide information regarding the orientation of the pendant aromatic ring. However, in order to completely test the hypothesis regarding bioactive conformation, and thereby gain some insight into the topography of the receptor, it was deemed necessary to prepare both **2a** and **2b**.



1a X=Y=OCH_3; W=Z=R=H
1b W=X=Y=OH; Z=Cl; R=H
1c W=Z=H; X=OH; Y=Cl; R=CH_3



2a; B/C cis
2b; B/C trans

Chemistry

The most expeditious route to compounds **2** relied on separation of isomers, rather than stereospecific synthesis, and is outlined in Scheme I. Additionally, this scheme provided access to several derivatives of **2** having different substituents in the 11-position. Alkylation of *N*-methylhomoveratrylamine with 2-bromo-1-tetralone afforded the unstable amino ketone, which was immediately reduced with sodium borohydride to a mixture of amino alcohols **3**. Cyclization was effected by treatment with neat methanesulfonic acid to provide a 1:1 mixture of **4** and **5**, which were separated by silica gel column chromatography. Assignment of relative stereochemistry at the B/C ring junction was initially made on the basis of the NMR spectra, which showed $J_{6a,13b}$ = 3.5 Hz for **4** and 7.5 Hz for **5**. These assignments were subsequently confirmed by single-crystal X-ray analysis of **4** (see supplementary material). O-Demethylation of **4** and **5** with sodium ethanethiolate gave mixtures of monodeprotected regioisomers **7** and **8** from **5**, and **12** and **14** from **4**, which were separated by a combination of fractional crystallization and chromatography. The reactions did not appear to proceed with any degree of regioselectivity. Structural assignments in both the cis and trans series are based on the unequivocal determination of the structures of **7** and **12** by X-ray techniques (supplementary material). Deoxygenation of **8** was achieved by hydrogenolysis of its 1-phenyltetrazolyl ether to give **9**, which was then O-demethylated with HBr/AcOH, thus affording the phenol **10**. This compound

(2) Weinstock, J.; Heible, J. P.; Wilson, J. W., III. *Drugs Future* **1985**, *10*, 646.
(3) Barnett, A. *Drugs Future* **1986**, *11*, 49.
(4) Kaiser, C.; Dandridge; P. A.; Garvey, E.; Hahn, R. A.; Sarau; H. M.; Stetler, D. E.; Bass, L. S.; Clardy, J. *J. Med. Chem.* **1982**, *25*, 697.
(5) Weinstock, J.; Hye-Ja, O.; DeBrosse, C. W.; Eggelston, D. S.; Wise, M.; Flaim, K. E.; Gessner, G. W.; Sawyer, J. L.; Kaiser, C. *J. Med. Chem.* **1987**, *30*, 1303.
(6) Dandridge, P. A.; Kaiser, C.; Brenner, M.; Gaitanopoulos, D.; Davis, L. D.; Webb, R. L.; Foley, J. H.; Sarau, H. M. *J. Med. Chem.* **1984**, *27*, 28.
(7) Hyttel, J. *Eur. J. Pharmacol.* **1983**, *91*, 153. Iorio, L. C.; Barnett, A.; Leitz, F. M.; Houser, V. P.; Korduba, C. A. *J. Pharmacol. Exp. Ther.* **1983**, *226*, 462.

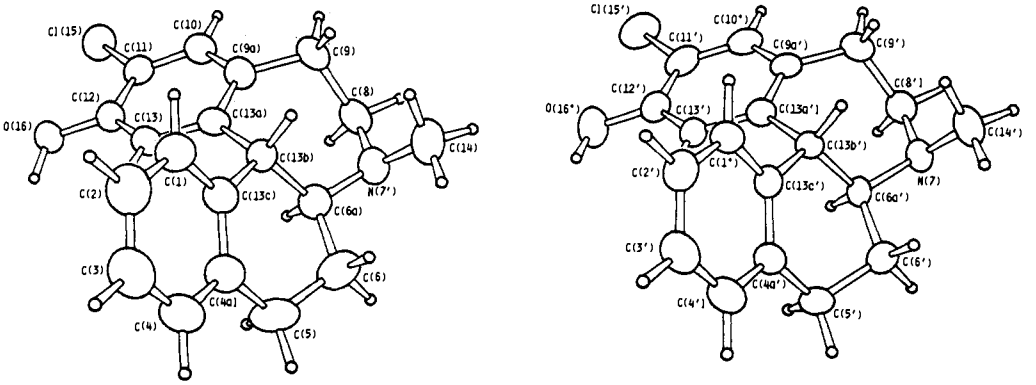


Figure 2. Solid-state conformations of the two crystallographically independent molecules of (−)-**2b** in the asymmetric crystal unit; small circles represent hydrogen atoms.

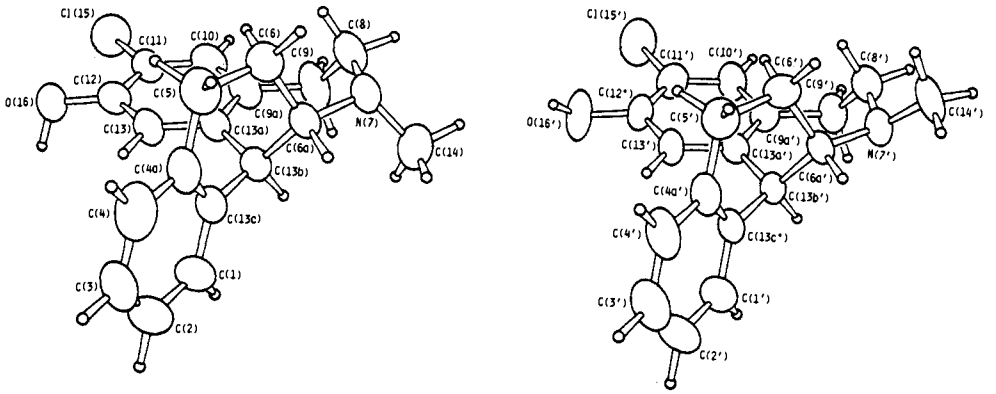


Figure 3. Solid-state conformations of the two crystallographically independant molecules of (−)-**2a** in the asymmetric crystal unit; small circles represent hydrogen atoms.

was converted to **11** by formylation under basic conditions and subsequent hydrogenolysis of the resulting benzylic alcohol. Chlorination of **9** with sulfuryl chloride gave **15**, which on O-demethylation with 48% HBr finally afforded (±)-**2b**. A parallel series of transformations beginning from **14** afforded (±)-**2a**. Resolution of (±)-**15** (Scheme II) was achieved with (+)-di-*O,O'-p*-toluyl-D-tartaric acid to provide (−)-**15**. Subsequent treatment of the free base derived from the mother liquors with (−)-di-*O,O'-p*-toluyl-L-tartaric acid gave (+)-**15**. O-Demethylation of (+)-**15** and (−)-**15** provided the phenolic target compounds (+)-**2b** and (−)-**2b**, respectively. Enantiomeric purity was established by high-pressure liquid chromatography using β-cyclodextrin as a component of the mobile phase. Base-catalyzed epimerization of (−)-**15** and (+)-**15** at the 13b-position provided (−)-**17** and (+)-**17**, respectively, which were in turn O-demethylated, giving (−)-**2a** and (+)-**2a**, respectively. Absolute stereochemistries of (−)-**2b** (Figure 2) and (−)-**2a** (Figure 3) were established via single-crystal X-ray analysis as described under Experimental Section.

Results and Discussion

In vitro affinities of **2** for both D_1 and D_2 receptor sites were determined by measuring their ability to displace [^{3}H]SCH-23390[8] and [^{3}H]spiperone, respectively, from rat striatal homogenates (Table II). Comparison of 12-hydroxy members of the B/C-cis and B/C-trans series (**7** vs **12**, **2a** vs **2b**, and **6** vs **13**) clearly show that receptor affinity is associated with the conformationally rigid trans series. Of the four stereoisomers of **2**, the 6a*S*,13b*R* isomer (−)-**2b** had significantly greater D_1 affinity and selectivity.

Table II. D_1 and D_2 Receptor Affinities of 6,6a,7,8,9,13b-Hexahydro-5*H*-benzo[*d*]naphth[2,1-*b*]azepines

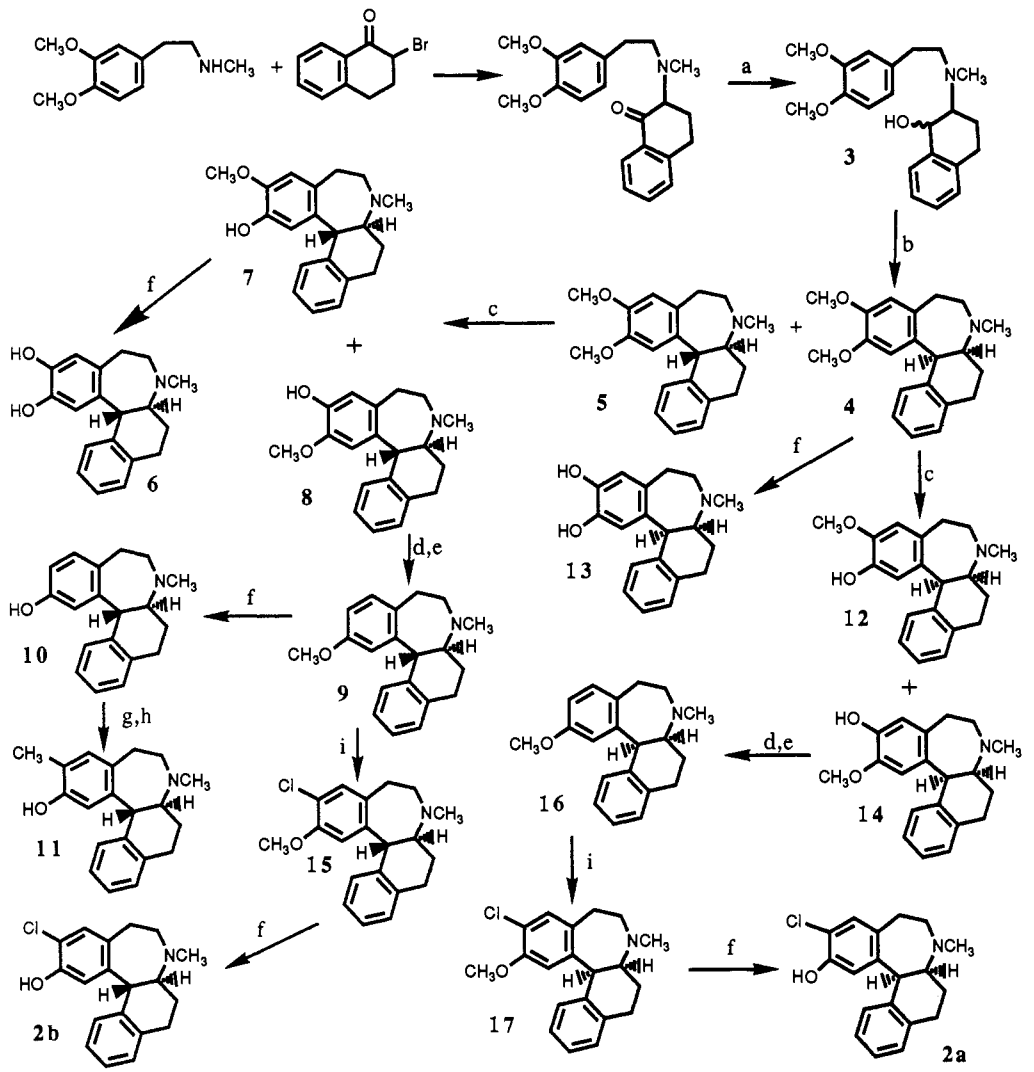
compd	K_i, nM, ± SEM vs [^{3}H]SCH 23390	K_i, nM, ± SEM vs [^{3}H]spiperone
7	23.6 ± 3.8	2477 ± 181
8	1664 ± 700	6400 ± 1320
10	72.6 ± 0.9	7873 ± 1234
11	7.1 ± 0.9	1505 ± 55
12	4197 ± 1358	>100000
14	24397 ± 7016	>100000
2a	473.6 ± 121	9073 ± 2299
(+)-**2a**	898 ± 190	16317 ± 3131
(−)-**2a**	513 ± 57	3476 ± 601
2b	3.3 ± 0.6	4115 ± 2575
(+)-**2b**	531 ± 178	3046 ± 308
(−)-**2b**	1.9 ± 0.6	514 ± 114
6	68 ± 19	2414 ± 1067
13	1730 ± 464	>100000
1c (SCH 23390)	0.4 ± 0.1	648 ± 39

This finding is consistent with the observation[3] that receptor affinity in the 1-phenyl-1*H*-3-benzazepine series is associated specifically with the *R* enantiomers. The absence of a substituent at the 11-position (compound **10**) resulted in a significant decrease in receptor affinity, as does introduction of a polar substituent at this position (compound **6**). Thus, the presence of a small lipophilic group at this position appears beneficial for receptor affinity and may serve to orient the adjacent 12-hydroxy group for optimal hydrogen bonding with a complementary functionality on the receptor.

On the basis of prior work in the benzazepine series,[2] it was anticipated that the 11,12-dihydroxy compound **6** might possess D_1 agonist properties. However, stimulation of striatal dopamine-sensitive adenyl cyclase, a charac-

(8) Billard, W.; Ruperto, V.; Crosby, G.; Iorio, L. C.; Barnett, A. *Life Sci.* **1984**, *35*, 1885.

Scheme I[a]



[a] (a) $NaBH_4$/EtOH; (b) CH_3SO_3H; (c) EtSNa, DMF; (d) 5-chloro-1-phenyltetrazole; (e) H_2, Pd–C; (f) HBr/AcOH; (g) HCHO/KOH; (h) H_2, Pd–C; (i) SO_2Cl_2.

teristic property of dopamine D_1 agonists,[9] could not be demonstrated. Compound **6** did not exhibit antagonist properties in vivo, since it failed to block conditioned avoidance responding in the rat at doses of up to 10 mg/kg subcutaneously, whereas (-)-**2b** and **1c** have minimal effective doses of 0.1 and 0.01 mg/kg, respectively. At present, these results are not readily explainable.

The inactivity of the B/C-cis series may be accounted for by the fact that one of the substituents on the azepine ring must assume an axial orientation in either of the easily interconvertible chair conformers, in contrast to the B/C-trans series, where both substituents are rigidly oriented equatorially. Therefore, axial substituents occupying either the 4- or 5-positions on the benzazepine nucleus may intrude upon a region of excluded space either above or below the active site on the receptor, thus interfering with binding.

In vivo, (-)-**2b**, designated as SCH 39166, exhibits a profile of activity in several species that is indicative of potential antipsychotic activity in man, with a diminished propensity to cause undesirable neurological side effects.[10]

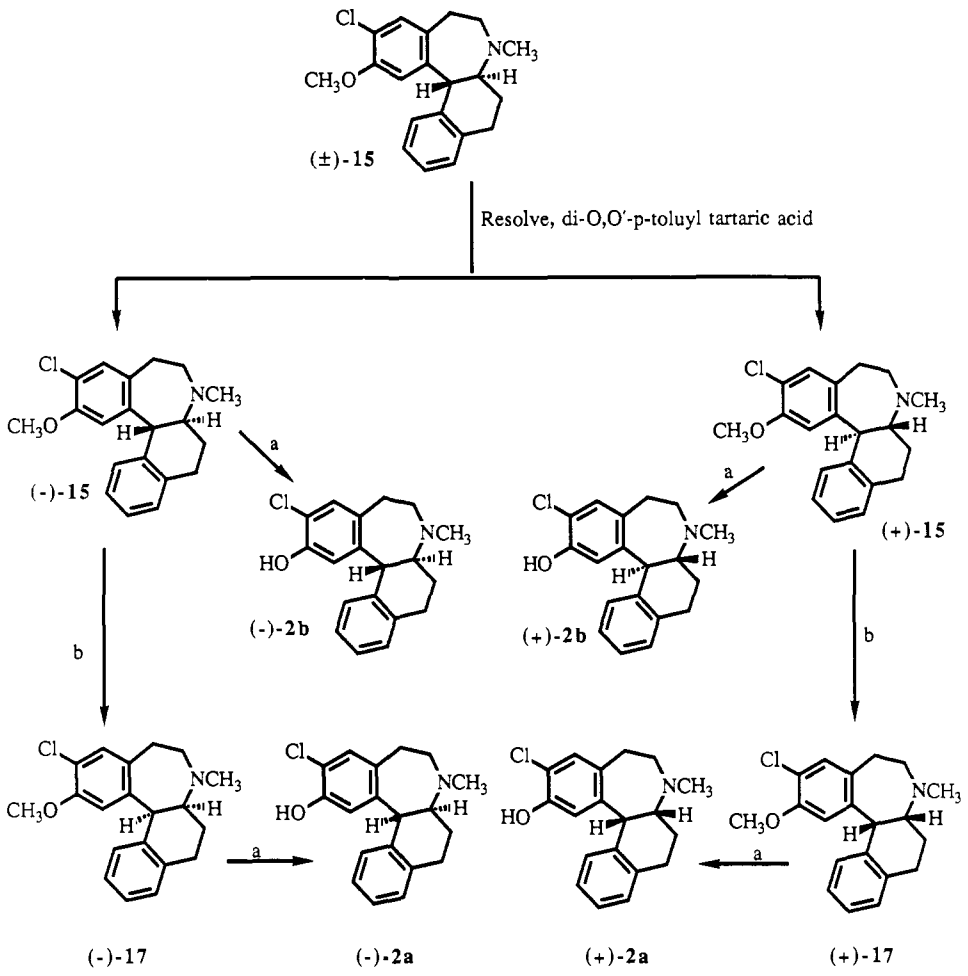
(9) Stoof, J. C.; Kebabian, J. W. *Life Sci.* 1984, *35*, 3661.
(10) Chipkin, R. E.; Iorio, L. C.; Coffin, V. L.; McQuade, R. D.; Berger, J. G.; Barnett, A. *J. Pharmacol. Exp. Ther.* 1988, *247*, 1093.

Experimental Section

Synthetic Methods. Melting points were determined in open capillaries with a Thomas-Hoover apparatus and are uncorrected. ^1H NMR spectra were recorded with Varian EM-390 (90-MHz), CFT-20 (79.5-MHz), XL-200 (200-MHz), XL-300 (300-MHz), or XL-400 (400-MHz) spectrometers using Me_4Si as internal standard. Analytical TLC was performed on 250-μm Analtech silica gel GF plates. Column chromatography was performed by using E. Merck Kieselgel 60 G. Electron impact (EI) mass spectra were determined by using a Varian MAT-CH-5 spectrometer with 70-eV ionizing voltage. Fast atom bombardment (FAB) mass spectra were performed by using a VG ZAB-SE spectrometer at 8 kV at room temperature. Chemical ionization (CI) mass spectra were acquired by using an Extrel-401 spectrometer with methane as the reagent gas.

Pharmacologic Methods. Male Sprague-Dawley rats (150–250 g) from Charles River Laboratories were used to obtain all brain tissues. The rats were decapitated and their brains removed and placed on ice. Striatal tissue for D_1 and D_2 receptor binding studies was excised, pooled, and homogenized in 100 volumes (w/v) of ice-cold 50 mM Tris-HCl buffer, pH = 7.4 (buffer A). The homogenate was centrifuged at 20000*g* for 10 min. The resultant pellet was homogenized in buffer A and centrifuged again. The final pellet was resuspended in buffer A containing 120 mM NaCl, 5 mM $CaCl_2$, and 1 mM $MgCl_2$ (buffer B). D_1 receptor binding assays were performed according to a modification of the method of Billard et al.[8] Polypropylene incubation tubes (in triplicate) received 100 μL of various concentrations of test compounds dissolved either in buffer B containing 4 mg/mL

Scheme II[a]



[a] (a) 48% HBr, AcOH; (b) KOt-Bu, DMSO/DMF, 0 °C.

methylcellulose or in 0.1 M HCl, 100 μL of a solution of [^{3}H]SCH 23390 (final concentration approximately 0.3 nM) in buffer B, and 800 μL of tissue suspension (roughly 3 mg of tissue per assay). Tubes were incubated at 37 °C for 20 min and rapidly filtered under vacuum through Whatman GF/B filters with four rinses of ice-cold 50 mM buffer A. The filters were placed in scintillation vials containing 10 mL of Scintisol and left overnight. Radioactivity was counted by using a liquid scintillation counter. D_2 receptor binding assays were performed in a manner identical with that described above for the D_1 binding assay except that [^{3}H]-spiperone (100 μL of buffer B; final concentration approximately 0.3 nM) was used in place of [^{3}H]SCH 23390.

Assays for stimulation of dopamine-sensitive adenyl cyclase were performed by a modification of the method of Salamon et al.[11]

The conditioned avoidance response test was performed in male Sprague-Dawley rats according to the method of Iorio et al.[12]

Crystal Data. **1c** maleate ($C_{21}H_{22}ClNOS$): M_r 403.87, orthorhombic, a = 10.830 (1) Å, b = 21.196 (3) Å, c = 8.872 (2) Å, V = 2038.2 Å^3, Z = 4, d_{calcd} = 1.316 g cm^{-3}, μ(Cu Kα radiation, λ = 1.5418 Å) = 19.3 cm^{-1}. Space group $P2_12_12_1(D_2^4)$ uniquely from the systematic absences: $h00$ when $h \neq 2n$, $0k0$ when $k \neq 2n$, $00l$ when $l \neq 2n$. Sample dimensions: 0.23 × 0.23 × 0.40 mm^3.

(−)-**2a** ($C_{19}H_{20}ClNO$): M_r 313.83, monoclinic, a = 10.315 (2) Å, b = 18.156 (5) Å, c = 8.935 (2) Å, β = 106.93 (2)°, V = 1600.8 Å^3, Z = 4, d_{calcd} = 1.302 g cm^{-3}, μ(Cu Kα radiation) = 21.2 cm^{-1}. Space group $P2_1(C_2^2)$ from the systematic absences: $0k0$ when $k \neq 2n$ and (−)-**2a** is chiral. Sample dimensions: 0.20 × 0.24 × 0.50 mm^3.

(−)-**2b** ($C_{19}H_{20}ClNO$): M_r 313.83, orthorhombic, a = 15.016 (1) Å, b = 24.105 (5) Å, c = 8.799 (1) Å, V = 3184.9 Å^3, Z = 8, d_{calcd} = 1.309 g cm^{-3}, μ(Cu Kα radiation) = 21.4 cm^{-1}. Space group $P2_12_12_1(D_2^4)$ as for **1c**. Sample dimensions: 0.07 × 0.14 × 0.30 mm.^{3}

4 ($C_{21}H_{25}NO_2$): M_r 323.44, orthorhombic, a = 13.185 (3) Å, b = 9.019 (2) Å, c = 14.638 (2) Å, V = 1740.7 Å^3, Z = 4, d_{calcd} = 1.234 g cm^{-3}, μ(Cu Kα radiation) = 5.8 cm^{-1}. Space group $Pca2_1(C_{2v}^5)$ or $Pbcm(D_{2h}^{11})$, with a and b axes interchanged, from the systematic absences: $0kl$ when l $2n$, $h0l$ when $h \neq 2n$; with Z = 4, required to be the former since **4** lacks either C_2, C_s, or C_i symmetry. Sample dimensions: 0.18 × 0.20 × 0.20 mm^3.

7 ($C_{20}H_{23}NO_2$): M_r 309.41, monoclinic, a = 8.048 (1) Å, b = 19.394 (3) Å, c = 10.899 (1) Å, β = 108.92 (1)°, V = 1609.2 Å^3, Z = 4, d_{calcd} = 1.277 g cm^{-3}, μ(Cu Kα radiation) = 6.1 cm^{-1}. Space group $P2_1/c(C_{2h}^5)$ uniquely from the systematic absences: $0k0$ when, $k \neq 2n$, $h0l$ when $l \neq 2n$. Sample dimensions: 0.02 × 0.32 × 0.322 mm^3.

12 ($C_{20}H_{23}NO_2$): M_r 309.41, monoclinic, a = 8.248 (2) Å, b = 18.323 (9) Å, c = 11.195 (3) Å, β = 112.00 (2)°, V = 1568.7 Å^3, Z = 4, d_{calcd} = 1.310 g cm^{-3}, μ(Cu Kα radiation) = 6.2 cm^{-1}. Space group $P2_1/c(C_{2h}^5)$ as for **7**. Sample dimensions: 0.04 × 0.06 × 0.34 mm^3.

Crystallographic Measurements. Preliminary unit cell parameters and space group information for each crystal were furnished by oscillation and Weissenberg photographs. Intensity data [$+h,+k,+l$ to θ = 67° for **1c**, (−)-**2b**, and **4**; $+h,+k,\pm l$ to θ = 67° for **7** and (−)-**2a**, and to θ = 57° for **12**] were recorded on an Enraf–Nonius CAD-4 diffractometer (Cu Kα radiation, incident beam graphite monochromator; $\omega - 2\theta$ scans). From totals of 3219 [(−)-**2b**], 2868 (**7**), 2168 (**12**), 1616 (**4**), 2955 [(−)-**2a**], and 2089 (**1c**)

(11) Salomon, Y.; Londos, C.; Rodbell, M. *Anal. Biochem.* **1974**, *58*, 541.

(12) Iorio, L. C.; Barnett, A.; Billard, W.; Gold, E. H. In *Neurobiology of Central D-1 Dopamine Receptors*, Advances in Experimental Medicine and Biology, Vol. 204; Creese, I., Breese, G. R., Eds.; Plenum Press: New York, 1986; pp 1–14.

nonequivalent reflections recorded, those 2351, 1783, 976, 1296, 2600, and 1690, respectively, with $I > 3.0\sigma(I)$ were retained for the structure analyses, and the usual Lorentz and polarization corrections were applied. In addition, empirical absorption corrections were applied to the data for (−)-**2b** and **7**. Refined unit cell parameters for each crystal were derived from the diffractometer setting angles for 25 reflections [34° < θ < 43° for (−)-**2b**; 37° < θ < 66° for **7**; 41° < θ < 52° for **4**; 45° < θ < 55° for (−)-**2a**; 39° < θ < 66° for **1c**] widely separated in reciprocal space.

Structure Analyses. All six crystal structures were solved by direct methods.[13] Initial non-hydrogen atom coordinates were obtained from *E* maps. Several rounds of full-matrix least-squares adjustment of atomic positional and anisotropic temperature factor parameters were followed in each case by evaluation of a difference Fourier synthesis, which revealed significant positive regions at positions calculated for hydrogen atoms. In the subsequent least-squares iterations, hydrogen atom positional and isotropic thermal parameters for (−)-**2b**, **7**, and **4** were included as variables whereas for **12**, (−)-**2a**, and **1c**, hydrogen atoms were included at their calculated positions. The absolute configurations for (−)-**2b**, (−)-**2a**, and **1c** were established by incorporating the imaginary contributions of the anomalous dispersion corrections into the structure factor calculations at late stages in the refinements; *R* values[14] obtained for parameters corresponding to the enantiomers shown [0.044 for (−)-**2b**, 0.042 for (−)-**2a**, and 0.053 for **1c**] were all significantly smaller[15] than for the mirror images (0.052, 0.044, and 0.59, respectively). The parameter refinements converged (maximum shift < 0.03σ) at $R(R_w)$ values[14] of 0.038 (0.048), 0.047 (0.063), 0.079 (0.096), 0.044 (0.057), 0.034 (0.048, and 0.046 (0.064), respectively, for (−)-**2b**, **7**, **12**, **4**, (−)-**2a**, and **6**. Final atomic positional and temperature factor parameters are included in the supplementary material. For all structure factor calculations, neutral atom scattering factors, as well as their anomalous dispersion corrections, were taken from ref 16. In the least-squares iterations, $\sum w\Delta^2$ [$w = 1/\sigma^2(|F_o|)$, $\Delta = (|F_o| - |F_c|)$] was minimized.

Molecular modeling was carried out by using SYBYL 5.1 (Tripos Associates, St. Louis, MO) and the BATCHMIN 2.1 batch processing module of MACROMODEL (Columbia University). Molecular mechanics calculations were done with the MM2 forcefield as formulated in BATCHMIN. Modeling experiments were carried out on compounds **1c**, **2a**, and **2b**. Structures were built from the standard SYBYL fragment library and then minimized with MM2 as formulated in BATCHMIN. Conformational analysis was carried out by using the SYBYL SEARCH option with 10° rotations for cyclic and 30° rotations for acyclic bonds. For **1c**, two starting geometries were used corresponding to a chair azepine and equatorial 5-phenyl ring with either an equatorial or axial *N*-methyl group. Two analogous starting geometries were used for **2b**. For **2a**, four starting geometries were used corresponding to the four possible chair conformations with the phenyl and *N*-methyl groups either equatorial or axial. In each case, the structures generated by this search were minimized by using the MULT option of BATCHMIN. Minimizations were carried out by using a block diagonal Newton–Raphson to a first derivative convergence of 0.01 kcal/Å or less. For all modeled structures, a chair conformation was the lowest energy form. In some instances, a higher energy boat conformation also was generated by the conformational analysis.

Energies for the lowest energy conformations of each structure are given in Table I. A complete listing of coordinates in SYBYL file format for all conformations generated is available in the supplementary material.

***cis*/*trans*-*N*-[2-(3,4-Dimethoxyphenyl)ethyl]-*N*-methyl-2-amino-1,2,3,4-tetrahydro-1-naphthol (3).** A solution of 2-bromo-1-tetralone (108 g, 0.43 mol) in 100 mL of dimethyl formamide (DMF) was added over 30 min to a stirred mixture of *N*-methyl-3,4-(dimethoxyphenyl)ethylamine (94 g, 0.48 mol) and anhydrous K_2CO_3 (70 g) in 600 mL of DMF. After stirring for 3 h at room temperature, the reaction mixture was diluted with 5 L of ice–water and extracted with 2 × 800 mL of ether. The combined extracts were concentrated to ca. 800 mL, washed with 2 × 500 mL of water, dried over anhydrous K_2CO_3, and filtered, and the solvent was evaporated in vacuo. The residue was dissolved in 800 mL of ethanol, and the cooled, stirred solution was treated with small portions of $NaBH_4$ (14.0 g total). The mixture was allowed to stir overnight at room temperature, and the solvent was then evaporated. The residue was heated on the steam bath for 30 min with 500 mL of water, cooled, and extracted with 2 × 500 mL of ether. The combined extracts were extracted with 2 × 350 mL of 1 N HCl, the acidic solution was basified with NaOH, and the product was extracted with 2 × 500 mL of ether. The combined ether extracts were dried over K_2CO_3, filtered, and evaporated in vacuo to give 72 g of dark residue. This material was chromatographed over 1 kg of silica gel, eluting with $CHCl_3$/EtOH/NH_4OH, 50:3:1 (solvent A). A mixture of two major products (TLC R_f 0.66 and 0.75, solvent A) was isolated (66.2 g) and used in the next step.

Cyclization of 3. The above product mixture (16.2 g) was added in small portions to 150 mL of anhydrous CH_3SO_3H with cooling and stirring. The reaction mixture was stirred at room temperature for 4.5 h and then poured onto 650 g of ice. The resulting mixture was rendered strongly basic with 50% NaOH and extracted with 2 × 120 mL of CH_2Cl_2. The combined extracts were washed with 200 mL of water, dried over anhydrous $MgSO_4$, filtered, and evaporated to give 14 g of dark viscous oil. This material was chromatographed over 450 g of silica gel, eluting with EtOAc/EtOH/NH_4OH, 100:5:0.5 (solvent B), under a slight positive N_2 pressure. Fractions containing material with R_f 0.76 (solvent B) were combined and evaporated to give solids which were recrystallized from EtOAc to provide 4.9 g (32%) of ***cis*-6,6a,7,8,9,13b-hexahydro-11,12-dimethoxy-7-methyl-5*H*-benzo[*d*]naphth[2,1-*b*]azepine (4)**: mp 114–116 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3 H, 7-CH_3), 3.56 (s, 3 H, 12-OCH_3), 3.84 (s, 3 H, 11-OCH_3), 4.45 (d, *J* = 3.5 Hz, 1 H, H-13a), 6.02 (s, 1 H, H-13), 6.64 (s, 1 H, H-10). Anal. ($C_{21}H_{27}NO_2$) C, H, N. Fractions containing material with R_f 0.69 were combined and evaporated to give 2.6 g of ***trans*-6,6a,7,8,9,13b-hexahydro-11,12-dimethoxy-7-methyl-5*H*-benzo[*d*]naphth[2,1-*b*]azepine (5)**: mp 78–80 °C (*i*-Pr_2O); ^1H NMR (400 MHz, $CDCl_3$) δ 2.50 (s, 3 H, 7-CH_3), 3.47 (s, 3 H, 12-OCH_3), 3.82 (s, 11-OCH_3), 4.74 (d, *J* = 7.5 Hz, 1 H, H-13b), 5.85 (s, 1 H, H-13), 6.65 (s, 1 H, H-10). A maleate salt melted at 151–153 °C (EtOAc). Anal. ($C_{25}H_{31}NO_6$) C, H, N. Chromatography of the mixed fractions (predominately **5**) over 150 g of silica gel (solvent B) gave an additional 2.5 g of pure **5** (total yield 33%).

Monodemethylation of 5. A solution of ethanethiol (7.8 g, 0.125 mol) in 100 mL of dry DMF was added to a stirred suspension of NaH (6.1 g of 50% dispersion in mineral oil, 0.127 mol) in 75 mL DMF under a N_2 atmosphere. After stirring for 20 min, a solution of **5** (16.2 g, 0.05 mol) in 75 mL of DMF was rapidly added. The mixture was slowly heated to reflux, maintained at reflux for 45 min, cooled, and poured over 1.5 kg of ice. The mixture was adjusted to pH 8 with acetic acid, and the precipitated solids were filtered, washed with water, and digested with 250 mL of CH_3CN on the steam bath for 10 min. The warm mixture was filtered, the solids were redigested with 300 mL of CH_3CN, and the resulting suspension was filtered. The solid product was dried at 100 °C in vacuo for 1 h to give 5.2 g of ***trans*-6,6a,7,8,9,13b-hexahydro-12-methoxy-7-methyl-5*H*-benzo[*d*]naphth[2,1-*b*]azepin-11-ol (8)**: mp 229–231 °C; ^1H NMR (200 MHz, DMSO-d_6) δ 1.52 (ddd, *J* = 2, 5, 11 Hz, 1 H, H-6_{ax}), 1.92 (ddd, *J* = 4, 8, 13 Hz, 1 H, H-6_{eq}), 2.31 (dd, *J* = 5, 15 Hz, 1 H, H-9_{eq}), 2.50 (s, 1 H, 7-CH_3), 2.50–2.83 (m, 4 H, H-5_{eq}, H-5_{ax}, H-8, H-6_{ax}), 3.10 (ddd, *J* = 2, 6, 13 Hz, 1 H, H-8), 3.42 (s, 3 H, 12-OCH_3), 3.45 (ddd, *J* = 2, 11, 15 Hz, 1 H, H-9_{ax}), 4.68 (d, *J* = 7 Hz, 1 H, H-13b), 5.68 (s, 1 H, H-13), 6.70 (s, 1 H, H-10), 6.92 (m, 1 H, H-1), 7.1–7.2 (m, 3 H, H-2, H-3, H-4). Anal. ($C_{20}H_{23}NO_2$) C, H, N; CI MS, *m*/*e* + 1 = 310; TLC R_f 0.65 (solvent A). The mother liquors upon standing deposited crystals (1.35 g) which were recrystallized from 75 mL of CH_3CN to give 1.00 g of ***trans*-6,6a,7,8,9,13b-hexahydro-11-methoxy-7-methyl-5*H*-benzo[*d*]naphth[2,1-*b*]azepin-12-ol (7)**: mp 198–199 °C; ^1H

(13) Crystallographic calculations were performed on PDP11/44 and Micro VAX II computers by use of the Enraf–Nonius Structure Determination Package incorporating the direct methods program MULTAN11/82.
(14) $R = \sum||F_o| - |F_c||/\sum|F_o|$; $R_w = [\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2]^{1/2}$.
(15) Hamilton, W. C. *Acta Crystallogr.* **1965**, *18*, 502.
(16) *International Tables for X-Ray Crystallography*; Kynoch: Birmingham, England, 1974; Vol. IV.

NMR (200 MHz, DMSO-d_6) δ 1.50 (ddd, J = 2, 5, 11 Hz, 1 H, H-6_{ax}), 1.90 (ddd, J = 4, 8, 13 Hz, 1 H, H-6_{eq}), 2.38 (dd, J = 9, 15 Hz, 1 H, H-9_{eq}), 2.40 (s, 3 H, 7-CH_3) 2.5–2.6 (m, 4 H, H-5_{ax}, H-5_{eq}, H-8, H-9_{ax}), 3.07 (ddd, J = 2, 6, 13 Hz, 1 H, H-8), 3.47 (ddd, J = 2, 11, 15 Hz, 1 H, H-9_{ax}) 3.70 (s, 3 H, 11-OCH_3), 4.62 (d, J = 7 Hz, 1 H, H-13b), 5.62 (s, 1 H, H-13), 6.72 (s, 1 H, H-10), 6.92 (m, 1 H, H-1), 7.1–7.2 (m, 3 H, H-2, H-3, H-4); CI MS, m/e + 1 = 310. Anal. ($C_{20}H_{23}NO_2$) C, H, N.

***trans*-6,6a,7,8,9,13b-Hexahydro-7-methyl-5*H*-benzo[*d*]naphth[2,1-*b*]azepine-11,12-diol Hydrobromide (6).** A mixture of **7** (800 mg, 26 mmol) in 10 mL of 48% HBr was heated on an oil bath at 120 °C with stirring for 6 h. The reaction mixture was then evaporated to dryness in vacuo, and the residue was triturated with CH_3CN. The solid product was filtered and recrystallized from EtOH (charcoal) to give 540 mg (55%) of **6**: mp >280 °C; EI MS, m/e = 295. Anal. ($C_{19}H_{21}NO_2HBr$) C, H, N.

***trans*-6,6a,7,8,9,13b-Hexahydro-7-methyl-12-methoxy-5*H*-benzo[*d*]naphth[2,1-*b*]azepine (9).** A suspension of **8** (5.2 g, 16.8 mmol) in 40 mL of DMF was heated to 60 °C with stirring, cooled to room temperature, and treated with small portions of 50% NaH in mineral oil (850 mg total, 17.7 mmol). The mixture was stirred until evolution of gas ceased (30 min) and then treated by dropwise addition of 10 mL of a DMF solution of 1-phenyl-5-chlorotetrazole (3.18 g, 17.7 mmol). After stirring for 2 h, the mixture was poured onto 350 g of ice, and the solids were filtered. Trituration of the dried solids with ether gave 6.9 g (90%) of ***trans*-6,6a,7,8,9,13b-hexahydro-7-methyl-12-methoxy-11-[(1-phenyltetrazol-5-yl)oxy]-5*H*-benzo[*d*]naphth[2,1-*b*]azepine**: mp 190–192 °C (acetonitrile); EI MS, m/e = 453. Anal. ($C_{27}H_{27}N_5O_2$) C, H, N. A solution of this material (6.8 g) in 100 mL of acetic acid was hydrogenolyzed over 750 mg of 20 $Pd(OH)_2$ at 30–50 psig for 5.5 h at 55 °C. Filtration of catalyst and evaporation of the filtrate in vacuo yielded a residue which was partitioned between 150 mL of ether and 50 mL of water. The mixture was basified with NaOH and the ether layer separated, dried over $MgSO_4$, filtered, and evaporated to dryness. The residue crystallized on trituration with cold ether to give **9** (3.1 g, 70%): mp 96–98 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.55 (s, 3 H, 7-CH_3), 3.59 (s, 3 H, 12-OCH_3), 4.79 (d, J = 7.5 Hz, 1 H, H-13b), 5.89 (d, J = 2 Hz, 1 H, H-13), 6.58 (dd, J = 2, 8.5 Hz, 1 H, H-11), 7.07 (d, J = 8.5 Hz, 1 H, H-10); FAB MS, m/e + 1 = 294. Anal. ($C_{20}H_{23}NO$) C, H, N.

***trans*-6,6a,7,8,9,13b-Hexahydro-7-methyl-5*H*-benzo[*d*]naphth[2,1-*b*]azepin-12-ol (10).** Compound **9** (2.0 g, 6.8 mmol) in 20 mL of 48% HBr was heated in an oil bath at 130 °C with stirring for 4.5 h. The cooled reaction mixture was then evaporated in vacuo, the residue dissolved in 200 mL of boiling water, and the mixture adjusted to pH 8 by portionwise addition of solid $NaHCO_3$. The resulting mixture was chilled in an ice bath, and the precipitated solids (1.7 g, 89%) were filtered: mp 209–211 °C (acetonitrile); ^1H NMR (79.5 MHz, DMSO-d_6) δ 2.40 (s, 3 H, 7-CH_3), 4.68 (d, J = 7 Hz, 1 H, H-13b), 5.61 (d, J = 2 Hz, 1 H, H-13), 6.36 (dd, J = 2.8 Hz, 1 H, H-11), 6.84 (d, J = 8 Hz, 1 H, H-10); EI MS, m/e = 279. Anal. ($C_{19}H_{21}NO_2$) C, H, N.

***trans*-6,6a,7,8,9,13b-Hexahydro-7,11-dimethyl-5*H*-benzo[*d*]naphth[2,1-*b*]azepin-12-ol (11).** A solution of **10** (1.5 g) in 17.5 mL of 1,2-dimethoxyethane and 17.5 mL of 3.3% aqueous KOH was treated with 1.5 mL of 37% HCHO and stirred for 4 h at 80 °C. The solution was concentrated in vacuo at 60 °C and the residue diluted with 50 mL of water, adjusted to pH 8, and extracted with 75 mL of CH_2Cl_2. The extracts were dried over $MgSO_4$, the solvent was evaporated, and the residue (ca. 1.4 g) was chromatographed over 75 g of silica gel (solvent A). Fractions containing material having TLC R_f 0.37 (solvent A) were combined and solvent evaporated to give ca. 500 mg of ***trans*-6,6a,7,8,9,13b-hexahydro-11-(hydroxymethyl)-7-methyl-5*H*-benzo[*d*]naphth[2,1-*b*]azepin-12-ol**, mp 171–173 °C (CH_3CN), which was not further characterized. A solution of this material in 20 mL of acetic acid containing 600 mg of *p*-toluenesulfonic acid monohydrate was hydrogenolyzed over 60 mg of 20% $Pd(OH)_2$ for 18 h at room temperature at 60 psig. Catalyst was filtered, the filtrate evaporated, and the residue dissolved in 3 mL of DMF and poured into a solution of 5 g of $NaHCO_3$ in 75 mL of water. The precipitated solids were filtered and chromatographed on 35 g of silica gel (solvent A). Fractions containing material with TLC R_f 0.65 (solvent A) were combined and evaporated, and the residue was recrystallized from CH_3CN to give 40 mg of **11**: mp 241–243 °C; EI MS, m/e = 293; ^1H NMR (200 MHz, DMSO-d_6) δ 1.97 (s, 3 H, 7-CH_3), 3.30 (s, 3 H, 11-CH_3), 4.53 (d, J = 7 Hz, 1 H, H-13b), 5.69 (s, 1 H, H-13), 6.79 (s, 1 H, H-1), 6.92 (m, 1 H), 7.12 (m, 3 H). Anal. ($C_{20}H_{23}NO$) C, H, N.

***trans*-6,6a,7,8,9,13b-Hexahydro-11-chloro-7-methyl-12-methoxy-5*H*-benzo[*d*]naphth[2,1-*b*]azepine (15).** A 2.9-mL portion of a 1 M solution of SO_2Cl_2 in CH_2Cl_2 was added dropwise to a cooled, stirred solution of **9** (655 mg, 2.23 mmol) in 40 mL of CH_2Cl_2. The resulting solution was allowed to stir overnight and then diluted with water and treated with small portions of solid $NaHCO_3$ until the pH was adjusted to 8, and the organic layer was separated and dried over $MgSO_4$. Evaporation of solvent gave 450 mg of a viscous residue which was chromatographed over 30 g of silica gel (EtOAc/EtOH, 19:1). Fractions containing material with R_f 0.25 (EtOAc/EtOH, 19:1) were combined and evaporated to give 235 mg (32%) of solid residue: mp 103–105 °C (CH_3CN); COSY ^1H NMR (400 MHz, $CDCl_3$) δ 1.70 (ddd, J = 4, 13, 13 Hz, 1 H, H-6_{ax}), 2.05 (ddd, J = 4, 8, 13 Hz, 1 H, H-6_{eq}), 2.43 (dd, J = 11, 6 Hz, 1 H, H-9_{ax}), 2.52 (s, 3 H, 7-CH_3), 2.58–2.88 (m, 4 H, H-5_{ax}, H-5_{eq}, H-8_{eq}, H-9_{ax}), 3.19 (ddd, J = 11, 6, 2 Hz, 1 H, H-8_{ax}), 3.48 (s, 1 H, 12-OCH_3), 4.57 (m, 1 H, H-9_{eq}), 4.77 (d, J = 10 Hz, 1 H, H-13), 5.89 (s, 1 H, H-13), 6.95–7.20 (m, 5 H, aromatic H); CI MS, m/e + 1 = 328. Anal. ($C_{20}H_{22}NOCl$) C, H, N.

***trans*-6,6a,7,8,9,13b-Hexahydro-11-chloro-7-methyl-5*H*-benzo[*d*]naphth[2,1-*b*]azepin-12-ol (2b).** A mixture of **15** (8.05 g) in 85 mL each of 48% HBr and AcOH was heated with stirring in an oil bath at 130 °C for 7 h. Volatile materials were removed from the reaction mixture at 130 °C and 200 mmHg until the mixture was concentrated to about 40 mL. The residue was chilled, and the precipitated solids were filtered and washed with a small amount of ice–water. The wet solids were dissolved in 100 mL of DMF by heating on a steam bath. The hot solution was slowly poured into 500 mL of 5% $NaHCO_3$ with stirring. The precipitated solids were filtered and washed with water, and the wet material was digested on the steam bath with a mixture of 50 mL of CH_3CN and 30 mL of water for 5 min. The mixture was chilled, and solids were filtered and washed successively with 20 mL of cold ethanol and 30 mL of ether. After drying in vacuo at 120 °C for 2 h, 6.85 g (89%) of product, mp 217–219 °C, was obtained: EI MS, m/e − 1 = 312; ^1H NMR (200 MHz, $CDCl_3$) δ 1.67 (ddd, J = 3, 7, 13 Hz, 1 H, H-6_{ax}), 2.03 (m, 1 H, H-6_{eq}), 2.41 (dd, J = 3, 8 Hz, 1 H, H-9_{eq}), 2.50 (s, 3 H, 7-CH_3), 2.6–2.9 (m, 4 H), 3.14 (dd, J = 2, 6, 13 Hz, 1 H, H-8), 3.53 (dd, J = 2, 11, 15 Hz, 1 H, H-9_{ax}), 4.73 (d, J = 7 Hz, 1 H, H-13b), 5.95 (s, 1 H, H-13), 6.98 (m, 1 H, H-1), 7.07–7.17 (m, 4 H, ar). Anal. ($C_{19}H_{20}NOCl$) C, H, N.

Resolution of *trans*-(±)-(6a*SR*,13b*RS*)-11-Chloro-6,6a,7,8,9,13b-hexahydro-7-methyl-12-methoxy-5*H*-benzo[*d*]naphth[2,1-*b*]azepine [(±)-15]. (+)-Di-*O*,*O*′-*p*-toluyl-D-tartaric acid (14.21 g, 36.78 mmol) dissolved in 50 mL of hot 90% *n*-BuOH/H_2O was added to a hot solution of *trans*-(±)-**15** (12.05 g, 36.76 mmol) in 50 mL of 90% *n*-BuOH/H_2O. The white precipitate that formed was collected, washed with 25 mL of EtOH, and recrystallized (90% *n*-BuOH/H_2O) to give ***trans*-(−)-(6a*S*,13b*R*)-11-chloro-6,6a,7,8,9,13b-hexahydro-7-methyl-12-methoxy-5*H*-benzo[*d*]naphth[2,1-*b*]azepine·(+)-di-*O*,*O*′-*p*-toluyl-D-tartrate·*n*-BuOH**: $[\alpha]^{26}_D$ −57.0° (*c* 1.018, DMF); mp 185–186 °C. Anal. ($C_{44}H_{50}NClO_{10}$) C, H, N. The salt was partitioned between 25% NaOH, H_2O, and *tert*-butyl methyl ether, and the organic layer was dried over $MgSO_4$ and concentrated to a viscous oil. The crude product was flash chromatographed (0–10% MeOH/CH_2Cl_2) to afford (−)-**15** as a glassy, viscous oil (5.42 g, 45%), $[\alpha]^{26}_D$ − 216.3° (*c* 1.0755, EtOH). The mother liquors were partitioned between 25% NaOH, H_2O, and *tert*-butyl methyl ether, and the organic layer was dried over $MgSO_4$, concentrated to a viscous oil, and flash chromatographed (0–10% MeOH/CH_2Cl_2) to afford a glassy, viscous oil enriched in the (+)-enantiomer. The oil was dissolved in 20 mL of hot 90% *n*-BuOH/H_2O and added to a hot solution of (−)-di-*O*,*O*′-*p*-toluyl-L-tartaric acid (6.82 g, 17.65 mmol). The white precipitate was collected and washed with 25 mL of EtOH, thus giving ***trans*-(+)-(6a*R*,13b*S*)-11-chloro-6,6a,7,8,9,13b-hexahydro-7-methyl-12-methoxy-5*H*-benzo[*d*]naphth[2,1-*b*]azepine·(−)-di-*O*,*O*′-*p*-toluyl-L-tartrate·*n*-BuOH**: $[\alpha]^{26}_D$ 59.9° (*c* 1.0245,

DMF); mp 185.5–186.5 °C. The salt was partitioned between 25% NaOH, H_2O, and *tert*-butyl methyl ether, and the organic layer was dried over $MgSO_4$, concentrated to a viscous oil, and flash chromatographed (0–10% MeOH/CH_2Cl_2) to afford (+)-**15** as a glassy, viscous oil (5.04 g, 42% yield), $[\alpha]^{26}_D$ 219.2° (*c* 1.0795, EtOH).

***trans*-(−)-(6a*S*,13b*R*)-11-Chloro-6,6a,7,8,9,13b-hexahydro-7-methyl-5*H*-benzo[*d*]naphth[2,1-*b*]azepin-12-ol [(−)-2b].** Hydrolysis of (−)-**15** with HBr/AcOH as described above for the racemate gave material: mp 239–241 °C; $[\alpha]_D$ −220.8° (*c* 0.56, DMF). Anal. ($C_{19}H_{20}NOCl$) C, H, N. High-pressure liquid chromatography using a 25 cm × 4.1 mm Synchropak C-4 wide-pore 300-Å, 6.5-μm particle column, a mobile phase consisting of water/acetonitrile/triethylamine (96:4:0.8 v/v/v) containing 22 mM β-cyclodextrin adjusted to pH 5 (AcOH) at a flow rate of 1.0 mL/min, and UV detection at 280 nM indicated this material to be 97% (−)-**15** (retention time = 16.3 min) and 3% (+)-**15** (retention time = 11.4 min).

Similar treatment of (+)-**15** gave ***trans*-(+)-(6a*R*,13b*S*)-11-chloro-6,6a,7,8,9,13b-hexahydro-7-methyl-5*H*-benzo[*d*]naphth[2,1-*b*]azepin-12-ol [(+)-2b]**: mp 239–241 °C; $[\alpha]_D$ 220.5° (*c* 0.29, DMF).

***cis*-6,6a,7,8,9,13b-Hexahydro-7-methyl-5*H*-benzo[*d*]naphth[2,1-*b*]azepine-11,12-diol Hydrobromide (13).** A stirred solution of 1.5 g of **4** in 15 mL of 48% HBr was heated in an oil bath at 120 °C for 6.5 h. On cooling, the precipitated solids were filtered, washed with CH_3CN, dissolved in 50 mL of EtOH, and boiled with charcoal. Filtration, evaporation, and trituration of the residue with CH_3CN gave 1.38 g (77%) of **13**: mp >280 °C; EI MS, *m/e* = 295. Anal. ($C_{19}H_{21}NO_2$·HBr) C, H, N.

Monodemethylation of 4. A solution of ethanethiol (2.43 g, 38 mmol) in 30 mL of DMF was added dropwise to a stirred suspension of 1.52 g (38 mmol) of 60% NaH–mineral oil in 20 mL of DMF. After 15 min, a solution of **4** (4.85 g, 15 mol) was added dropwise, and the stirred mixture was heated at 125 °C for 1.5 h. The mixture was cooled to ca. 70 °C and poured onto 600 mL of ice–water. The pH was adjusted to 8 with acetic acid, and the mixture was extracted with 2 × 120 mL of CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and evaporated and the residue chromatographed on 200 g of silica gel (CH_2Cl_2/EtOH/NH_4OH, 100:3:1). Fractions containing material with R_f 0.57 (solvent A) were combined and evaporated to give 600 mg of **12**: mp 218–219 °C (EtOH); ^1H NMR (200 MHz, DMSO-d_6) δ 1.60 (m, 1 H), 1.81 (m, 1 H), 2.32 (s, 3 H, 7-CH_3), 2.52–2.97 (m, 4 H), 3.71 (s, 3 H, 11-OCH_3), 4.32 (d, *J* = 3 Hz, 1 H, H-13b), 5.90 (s, 1 H, H-13), 6.68 (s, 1 H, H-10), 6.74 (m, 1 H), 7.00–7.15 (m, 3 H); EI MS, *m/e* = 309. Anal. ($C_{20}H_{23}NO_2$) C, H. N. Fractions containing material with R_f 0.47 were combined and evaporated to give 400 mg of **14**: mp 178–180 °C (EtOH); ^1H NMR (200 MHz, DMSO-d_6) δ 1.81 (m, 2 H), 2.32 (s, 3 H, 7-CH_3), 2.52–3.00 (m, 4 H), 3.52 (s, 3 H, 12-OCH_3), 4.34 (d, *J* = 3 Hz, 1 H, H-13b), 6.15 (s, 1 H, H-13), 6.52 (s, 1 H, H-10), 7.62, (d, 1 H, H-1), 6.98–7.12 (m, 3 H); EI MS, *m/e* = 309. Anal. ($C_{20}H_{23}NO_2$) C, H, N.

***cis*-6,6a,7,8,9,13b-Hexahydro-7-methyl-12-methoxy-5*H*-benzo[*d*]naphth[2,1-*b*]azepine (16).** A stirred suspension of **14** (1.15 g, 3.72 mmol) in 10 mL of DMF was treated with 178 mg of 50% NaH–mineral oil (3.72 mmol) by portionwise addition. The mixture was stirred at room temperature for 20 min, during which complete dissolution occurred. 5-Chloro-1-phenyltetrazole (736 mg, 4.09 mmol) was added to the solution in small portions, and the reaction mixture was stirred at 60 °C for 1 hour and then poured into 100 g of ice–water. Precipitated solids were filtered and air-dried and dissolved in 9:1 Et_2O/EtAc and the solution dried over K_2CO_3, filtered, and evaporated to dryness. The residue was triturated with cold ether and filtered to give 1.45 g (86%) of the tetrazolyl ether, mp 151–153 °C. Anal. ($C_{27}H_{27}N_5O_2$) C, H, N. A 1.40-g sample of this material was dissolved in 40 mL of glacial acetic acid and hydrogenated over 200 mg of 20% $Pd(OH)_2/C$ at 55 °C for 5.5 h. Catalyst was filtered and the solvent evaporated in vacuo. The residue was treated with 50 mL of ether and 15 mL of water and made basic with NaOH. The ether layer was separated, dried over $MgSO_4$, and evaporated to give 465 mg (48%) of product as an oily residue: ^1H NMR (200 MHz, $CDCl_3$) δ 1.72 (m, 1 H), 1.87 (m, 1 H), 2.45 (s, 3 H, 7-CH_3), 2.70–3.18 (m, 4 H), 3.61 (s, 3 H, 12-OCH_3), 4.47 (d, *J* = 5 Hz, 1 H, H-13b), 6.03 (d, *J* = 2 Hz, 1 H, H-13), 6.63 (dd, *J* = 2, 9 Hz, 1 H, H-11), 6.85 (d, *J* = 9 Hz, 1 H, H-10), 6.98–7.15 (m, 4 H, aromatic); EI MS, *m/e* = 293. Anal. ($C_{20}H_{23}NO$) C, H, N.

***cis*-6,6a,7,8,9,13b-Hexahydro-11-chloro-12-methoxy-7-methyl-5*H*-benzo[*d*]naphth[2,1-*b*]azepine (17).** A 1 M solution of SO_2Cl_2 in CH_2Cl_2 (2.20 mL) was added dropwise to a stirred solution of **16** (550 mg, 1.68 mmol) in 20 mL of CH_2Cl_2 at 0 °C. The resulting mixture was allowed to stir at room temperature for 8 h and then quenched by the addition of 15 mL of water followed by portionwise addition of $NaHCO_3$ to pH = 8. The organic layer was separated, dried over $MgSO_4$, filtered, and evaporated to dryness. The residue was purifed by column chromatography (EtOAc/EtOH, 19:1) over 30 g of silica gel to give 245 mg (44%) of product: mp 125–127 °C (CH_3CN); ^1H NMR (200 MHz, $CDCl_3$) δ 1.58 (m, 1 H), 1.92 (m, 1 H), 2.45 (s, 3 H, 7-CH_3), 2.70–3.12 (m, 7 H), 3.58 (s, 3 H, 12-OCH_3), 4.44 (d, *J* = 5 Hz, 1 H, H-13b), 6.02 (s, 1 H, H-13), 6.82 (d, *J* = 8 Hz, 1 H, H-1), 7.08–7.19 (m, 4 H); CI MS, *m/e* + 1 = 328. Anal. ($C_{20}H_{22}NOCl$) C, H, N.

***cis*-6,6a,7,8,9,13b-Hexahydro-11-chloro-7-methyl-5*H*-benzo[*d*]naphth[2,1-*b*]azepin-12-ol (2a).** A mixture of 3.2 g of **17** in 35 mL of 48% HBr was heated in an oil bath at 125–130 °C with stirring for 6 h. The mixture was then evaporated to dryness in vacuo at 120 °C. The residue was dissolved in 25 mL of DMF with warming and poured into a hot solution of 12 g of $NaHCO_3$ in 300 mL of water. The precipitate that formed upon standing was filtered, washed with water, and dried to give 2.75 g (90%) of product, mp 232–233 °C (EtOH). Anal. ($C_{19}H_{20}NOCl$) C, H, N.

***cis*-(+)-(6a*R*,13b*R*)-11-Chloro-6,6a,7,8,9,13b-hexahydro-7-methyl-12-methoxy-5*H*-benzo[*d*]naphth[2,1-*b*]azepine [(+)-17].** (+)-**15** (4.06 g, 12.38 mmol) was dissolved in 25 mL of dry DMF and 50 mL of dry DMSO under nitrogen and cooled to 0 °C (ice bath) and potassium *tert*-butoxide (1.856 g, 16.54 mmol, 1.336 equiv) added. After stirring for 30 min, 100 mL each of saturated $NaHCO_3$ and water was added, the reaction mixture was extracted with 2 × 100 mL *tert*-butyl methyl ether, and the combined organic layers were washed with 3 × 100 mL of water and 1 × 100 mL of saturated NaCl, dried over $MgSO_4$, filtered, and concentrated to a viscous oil. The crude product (approximately a 3:1 mixture of cis:trans) was preadsorbed on silica gel (2:1 silica gel:substrate ratio) and flash chromatographed (5–10% EtOH/EtOAc) to afford pure cis and a mixture of cis and trans. The mixture was resubjected to the epimerization procedure and flashed chromatographed as before. The total amount of *cis*-(+)-**17** isolated was 2.881 (71%) as a glassy solid: ^1H NMR (200 MHz, $CDCl_3$) δ 7.20–7.15 (m, 4 H), 6.84 (d, *J* = 7.3 Hz, 1 H, H-1), 6.04 (s, 1 H, H-13), 4.45 (d, *J* = 3.3 Hz, 1 H, H-13b), 3.57 (s, 3 H, 12-OCH_3), 2.95–2.71 (m, 7 H), 2.46 (s, 3 H, 7-CH_3), 1.98–1.60 (m, 2 H). $[\alpha]^{26}_D$ +21.4° (*c* 1.088, EtOH); EI MS, *m/e* (M^+) = 327 (^{35}Cl), 329 (^{37}Cl). Anal. ($C_{20}H_{22}NClO$) C, H, N.

***cis*-(+)-(6a*R*,13b*R*)-11-Chloro-6,6a,7,8,9,13b-hexahydro-7-methyl-5*H*-benzo[*d*]naphth[2,1-*b*]azepin-12-ol [(+)-2a].** A mixture of *cis*-(+)-**17** (2.28 g, 6.95 mmol), 27 mL of glacial acetic acid, and 27 mL of 48% HBr was heated to reflux in an oil bath (135 °C) with stirring for 4.5 h. The reaction mixture was then concentrated under reduced pressure (25 Torr) to about 3 mL, and 5 mL of water and then 50 mL of DMF were added. The reaction mixture was heated until complete dissolution and then added to 600 mL of saturated $NaHCO_3$ with stirring. The precipitated white solid was collected, washed with water, slurried in hot acetonitrile (50 mL), filtered, and dried in vacuo (65 °C, 14 h) to afford 1.11 g (51%) of (+)-**2a** as a white solid: mp 189–191 °C; ^1H NMR (200 MHz, DMSO-d_6) δ 9.54 (br s, 1 H, 12-OH), 7.12–7.00 (m, 4 H), 6.80 (d, *J* = 6.6 Hz, 1 H, H-1), 6.06 (s, 1 H, H-13), 4.38 (d, *J* = 3.4 Hz, 1 H, H-13b), 3.02–2.52 (m, 7 H), 2.32 (s, 3 H, 7-CH_3), 1.92–1.42 (m, 2 H); ^1H NMR (400 MHz, $CDCl_3$) δ 1.49 (m, 1 H, H-6), 1.81 (m, 1 H, H-6), 2.23 (s, 3 H, 7-CH_3), 2.66–2.88 (m, 6 H), 3.11 (m, 1 H), 4.40 (d, *J* = 4 Hz, 1 H, H-13b), 5.40 (br s, 1 H, 12-OH), 6.09, (s, 1 H, H-13), 6.83 (d, *J* = 8 Hz, 1 H, H-1), 7.00–7.18 (m, 4 H); $[\alpha]^{26}_D$ +31.8° (*c* 1.036, DMF); CI MS, *m/e* (M + 1) = 314 (^{35}Cl), 316 (^{37}Cl). Anal. $C_{19}H_{20}NClO$) C, H, N.

In a similar manner, ***cis*-(−)-(6a*R*,13b*R*)-11-chloro-6,6a,7,8,9,13b-hexahydro-7-methyl-5*H*-benzo[*d*]naphth[2,1-*b*]azepin-12-ol [(−)-2a]**, $[\alpha]^{26}_D$ −31.3° (*c* 1.016, DMF), was obtained starting from (−)-17.

Acknowledgment. We acknowledge Dr. S. Airy of the Physical Analytical Chemistry Department of Schering-Plough for developing the chiral HPLC assay, Drs. L. C. Iorio and R. D. McQuade of the Department of Pharmacology, Schering-Plough, for determining the in vitro binding constants, Dr. E. H. Gold for helpful discussions, and Messrs. W. F. Kluttz and B. Vibulbhan for expert technical assistance.

Supplementary Material Available: Listings of bond lengths, bond angles, torsional angles, hydrogen and non-hydrogen atomic coordinates, isotropic thermal parameters, and anisotropic temperature factor parameters for **1c**, (−)-**2a**, (−)-**2b**, **4**, **7**, and **12**, solid-state conformations of **4**, **7**, and **12**, and coordinates in SYBYL file format for modeled conformations of **1c**, **2a**, and **2b** (76 pages). Ordering information is given on any current masthead page.

N-(Phthalimidoalkyl) Derivatives of Serotonergic Agents: A Common Interaction at 5-HT_{1A} Serotonin Binding Sites?

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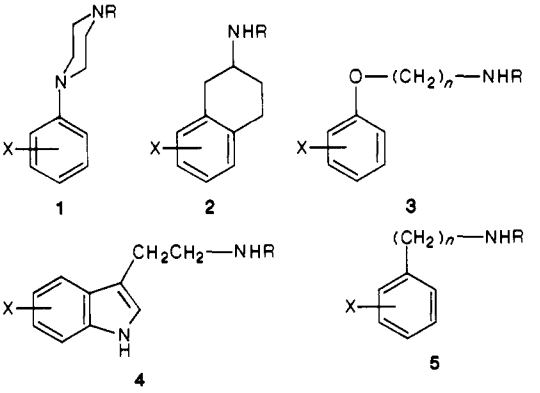
Received January 9, 1989

Several classes of agents are known to bind at central 5-HT_{1A} serotonin sites. In order to challenge the hypothesis that these agents bind in a relatively similar manner (i.e., share common aryl and terminal amine sites), we prepared *N*-(phthalimidobutyl) derivatives of examples of several such agents. With regard to arylpiperazines, we had previously shown that introduction of this functionality at the terminal amine is tolerated by the receptor and normally results in a significant (>10-fold) enhancement in affinity. The results of the present study show that this bulky functionality is also tolerated by the receptor when incorporated into examples of all other major classes of 5-HT_{1A} agents (e.g., 2-aminotetralin, phenylalkylamine, indolylalkylamine, and (aryloxy)alkylamine derivatives). The length of the alkyl chain that separates the terminal amine from the phthalimido group is of major importance, and a four-carbon chain appears optimal. Alteration of the length of this chain can have a significant influence on affinity; decreasing the chain length from four to three carbon atoms can reduce affinity by an order of magnitude, and further shortening can have an even more pronounced effect.

Of the different populations of central serotonin (5-HT) receptors, 5-HT_{1A} sites have probably received the most attention. We, and others, have previously demonstrated that several classes of agents bind at these sites (for example, see ref 1–3 for recent reviews). Prominent among such agents are certain (a) arylpiperazines **1**, (b) 2-aminotetralins **2**, (c) (1-aryloxy)alkylamines **3**, and (d) indolylalkylamines **4**; phenylalkylamines **5** also bind at these sites although they do so with somewhat lower affinity. Although the affinity (and, indeed, selectivity) of these agents can be modulated by the presence and location of certain substituent groups, casual inspection of these structures reveals that all possess an aromatic moiety and a terminal amine group. It would not be difficult to envision each of these agents interacting at 5-HT_{1A} receptors in such a manner so as to share common aryl and terminal amine binding sites. Indeed, the results of recent molecular modeling studies strongly support the likelihood of such an interaction;[4] on the basis of these studies, binding models have been proposed. In these models, a mean distance between the center of a common aromatic nucleus and the terminal amine was found to be between 5.0 and 5.6 Å.[4] Several years ago, we conducted some preliminary modeling studies demonstrating that arylpiperazines, indolylalkylamines, and phenylalkylamines could share common aromatic to terminal amine distances, suggesting that members of each of these classes might interact at 5-HT receptors in a similar manner.[5] We subsequently undertook a synthetic investigation, the purpose of which was to gain some empirical support for this hypothesis.



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(1) Glennon, R. A. *J. Med. Chem.* **1987**, *30*, 1.
(2) Fozard, J. *Trends Pharmacol. Sci.* **1987**, *8*, 501.
(3) Glennon, R. A. In *Receptor Pharmacology and Function*; Williams, M., Glennon, R. A., Timmermans, P. B. M. W. M., Eds.; Marcel Dekker: New York, 1989; p 257.
(4) (a) Hibert, M. F.; Gittos, M. W.; Middlemiss, D. N.; Mir, A. K.; Fozard, J. R. *J. Med. Chem.* **1988**, *31*, 1087. (b) Hibert, M.; Middlemiss, D. N.; Fozard, J. R. In *Brain 5-HT1A Receptors*; Dourish, C. T., Ahlenius, S., Hutson, P. H., Eds.; Ellis Horwood: Chichester, 1987; p 27. (c) Smith, D. W.; Yocca, F. D.; Hyslop, D. K.; Eison, M. S.; Taylor, D. P. *Soc. Neurosci. Abstr.* **1986**, *12*, 422.
(5) Lyon, R. A.; Titeler, M.; McKenney, J. D.; Magee, P. S.; Glennon, R. A. *J. Med. Chem* **1986**, *29*, 680, and unpublished findings.

0022-2623/89/1832-1921$01.50/0