Stereoisomeric Probes for the D_1 Dopamine Receptor: Synthesis and Characterization of *R*-(+) and *S*-(-) Enantiomers of 3-Allyl-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine and Its 6-Bromo Analogue

John L. Neumeyer,*,§ Nora S. Kula,‡ Ross J. Baldessarini,‡ and Nandkishore Baindur†

Research Biochemicals Inc., Natick, Massachusetts 01760, Department of Psychiatry and Neuroscience Program, Harvard Medical School, Mailman Research Center, McLean Division of Massachusetts General Hospital, Belmont, Massachusetts 02178, and Section of Medicinal Chemistry, College of Pharmacy and Allied Health Professions, Northeastern University, Boston, Massachusetts 02115. *Received August 23, 1991*

Substituted 1-phenyl-3-benzazepines (e.g., SKF 38393 and fenoldopam) exhibit stereoselectivity in moderately high-affinity binding to and partial agonist activation of D_1 dopamine receptors. The 3-allyl (APB) and the 3-allyl-6-chloro (6-Cl-APB) analogues of SKF 38393 are reported to have higher affinity and selectivity for the D_1 DA receptor and higher in vivo central neuropharmacologic activity than SKF 38393. We recently reported the corresponding 3-allyl-6-bromo analogue (6-Br-APB) also to be a high-affinity D_1 agonist. We now describe the synthesis and characterization of the *R*-(+) and *S*-(-) enantiomers of both APB and 6-Br-APB and their comparison with corresponding enantiomers of SKF 38393 with respect to D_1 receptor binding affinity and D_1 and D_2 selectivity. The *R*-(+) enantiomers of both novel substituted 1-phenyl-3-benzazepines bound to the D_1 receptor sites in rat forebrain tissue with much higher affinity and selectivity than their *S*-(-) antipodes. *R*-(+)-3-Allyl-6-bromo-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine [(*R*)-(+)-6-Br-APB, 18] exhibits the highest affinity of the reported 1-phenyl-3-benzazepine D_1 agonists.

Dopamine (DA) neurons and dopaminergic receptors are prominent in several regions of the mammalian central nervous system (CNS), and DA receptors are also found in several peripheral tissues.[1,2] Dysfunctions of CNS dopaminergic neurotransmission has been implicated in several neuropsychiatric diseases with treatments based on the use of DA agonists and antagonists.[1,2] DA receptors can be classified into two main categories, the D_1 and D_2 receptors, on the basis of the accumulated biochemical and pharmacological data.[3-5] Molecular biological techniques have recently identified several additional types of DA receptors, notably the D_2-like D_3 and D_4 receptors and the D_1-like D_5 receptor. Further research should lead to the assignment of relative abundance and localization, as well as specific physiological and pharmacological actions to these new DA receptor subtypes.[6-8]

The discovery of the first selective D_1 ligand, the D_1 partial agonist 7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (SKF 38393),[9] strongly encouraged investigations of the D_1 receptor.[2,10-12] D_1 vs D_2 receptor binding affinity and agonist and antagonist activity also have been described recently in other chemical classes of compounds.[13-17] Several approaches now encourage description of a pharmacophoric model for the D_1 receptor which may facilitate the design and development of even more potent or selective ligands for this and related (viz., D_5) receptor subtypes. One approach has traditionally been to examine isomeric selectivity in binding or agonist activity of a pair of stereoisomers. By considering the enantiomeric preference, it should be possible to propose a conceptual receptor model in which possible binding sites can be localized. This approach previously has been utilized to map the ligand binding sites of various receptors including the D_2 DA receptor.[18,19] It is noteworthy that while DA itself is achiral, both the D_1 and D_2 receptors have been shown to exhibit a remarkable degree of stereoselectivity in ligand binding, agonist activation, or antagonist inhibition of their transducer–effector systems, with such stereoselectivity being exhibited by nearly all chemical classes of DA receptor agonists and antagonists to a greater or lesser extent.[20-23]

* To whom correspondence should be addressed: Research Biochemicals Inc., 1 Strathmore Road, Natick, MA 01760.
§ Research Biochemicals.
‡ Massachusetts General Hospital.
† Northeastern University.

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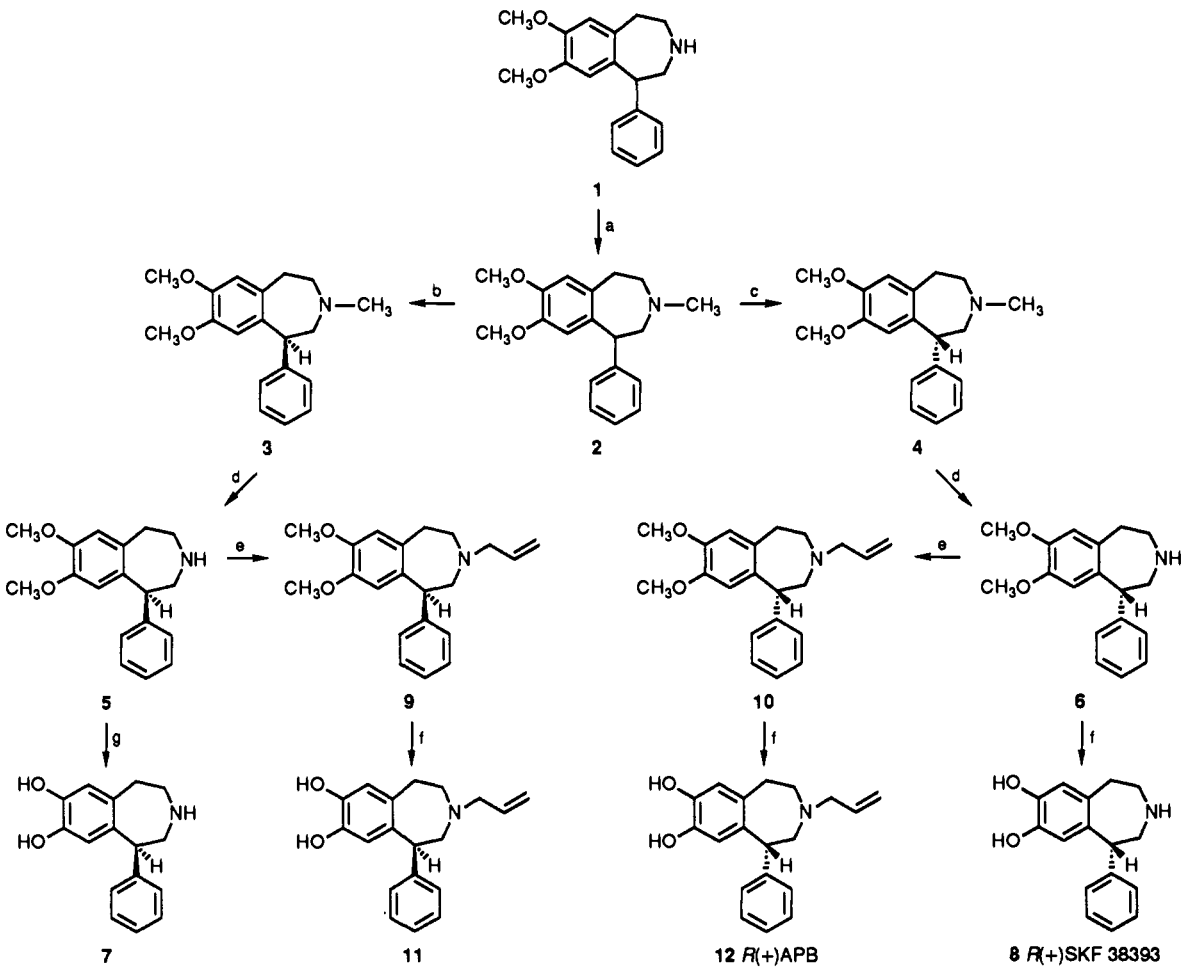
Scheme I[a]



[a] (a) HCHO/HCOOH; (b) L-(−)-dibenzoyltartaric acid, EtOH; (c) D-(+)-dibenzoyltartaric acid, EtOH; (d) BrCN, C_6H_6; HCl, AcOH, reflux; (e) allyl bromide, K_2CO_3, DMF; (f) BBr_3, CH_2Cl_2; (g) 12 N HCl/HCl.

The 1-phenyl-3-benzazepine 7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (SKF 38393) and its 6-chloro-4′-hydroxy analogue (SKF 82526, fenoldopam) were characterized as relatively high-affinity D_1 selective partial agonists with potent in vivo CNS and peripheral renal vasodilator effects, respectively.[9,24,25] Racemates of both SKF 38393 and fenoldopam were subsequently resolved, and pharmacological characterization of their enantiomers established that both the D_1 receptor binding affinity and agonist activity resides almost entirely in the *R*-(+) enantiomer while the *S*-(−) antipode is virtually inactive.[25-27] Subsequently, the discovery of the first

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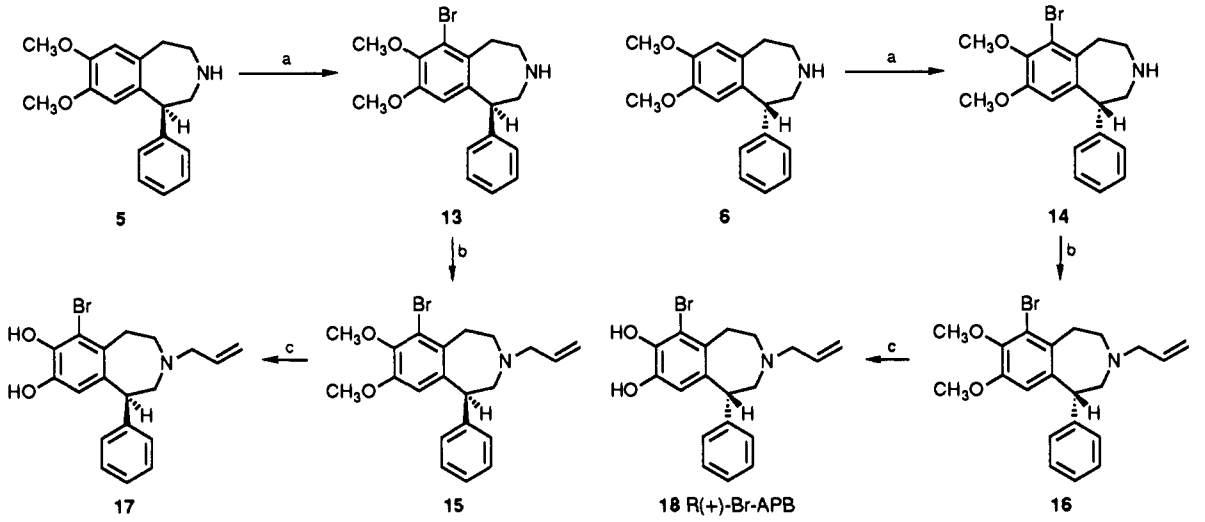
Scheme II[a]



[a] (a) Br_2/AcOH; (b) allyl bromide, K_2CO_3, DMF; (c) BBr_3, CH_2Cl_2.

selective D_1 antagonists 7-chloro-8-hydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (SCH 23390) and its 7-bromo analogue (SKF 83566) led to the characterization of their enantiomers too; once again activity was shown to reside in the *R*-(+) enantiomer, with the *S*-(−) enantiomer only weakly active in terms of both affinity and antagonist potency.[28-31] Recently, 3-allyl-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (APB) and 3-allyl-6-chloro-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (6-Cl-APB), which are, respectively, the 3-allyl and 3-allyl-6-chloro analogues of SKF 38393, were described as ligands with even higher D_1 receptor affinity and agonist activity than the parent compound SKF 38393.[32-34] Our studies of the structure–activity relationship (SAR) of these ligands led to the identification of the 3-allyl-6-bromo-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (6-Br-APB) as the ligand with one of the highest D_1 affinities among reported 7,8-dihydroxy-1-phenyl-3-benzazepine derivatives.[35] 6-Br-APB currently is being studied further with respect to its in vitro efficacy and in vivo CNS activity. We now report the resolution of the enantiomers of both APB and 6-Br-APB and their pharmacological characterization in comparison to the enantiomers of the parent compound SKF 38393.

Chemistry

The 7,8-dihydroxy-1-phenyl-3-benzazepines were resolved by the method of Kaiser et al.[26] (Scheme I). The secondary amine 7,8-dimethoxybenzazepine derivative, compound 1,[35,36] was converted to the tertiary amine 7,8-dimethoxy-3-methyl-1-phenyl-3-benzazepine derivative 2 by the Eschweiler–Clarke procedure. Compound 2 was resolved by recrystallization of its L-(−)-dibenzoyltartarate salt to constant optical rotation followed by conversion to the free base to obtain the optically pure product *S*-(−)-3.[26] The enantiomer was obtained from the mother liquors after conversion to the free base, followed by recrystallization of the D-(+)-dibenzoyltartarate salt to constant optical rotation followed by conversion to the free base to obtain the optically pure *R*-(+)-4.[26] Optically pure 3 and 4 separately were N-demethylated with cyanogen bromide to obtain the respective isomeric 7,8-dimethoxybenzazepine derivatives, compounds 5 and 6.[26] Previously, it was suggested that O-demethylation of N-unsubstituted catechols such as 5 and 6 with boron tribromide of HBr would lead to a partial racemization of the products and that methionine–methanesulfonic acid would be a better O-demethylation reagent.[26] We found, however, that this supposedly mild O-demethylation procedure resulted in substantial decomposition of the products during the tedious workup conditions. Accordingly, an alternative O-demethylation procedure was attempted. Refluxing in

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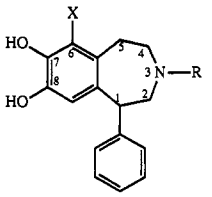
Table I.[a] Affinity and Selectivity of Stereoisomeric Benzazepines at Dopaminergic D_1 and D_2 Receptors in Rat Striatal Tissue



compound	R	X	IC_{50} (nM) D_1	IC_{50} (nM) D_2	D_1 selectivity: D_2/D_1
RS(±)SKF 38393	H	H	190	720 000	>100
7, *S*(−)SKF 38393	H	H	10 700	720 000	>2
8, *R*(+)SKF 38393	H	H	50	>10 000	>200
(±)-APB	$CH_2CH{=}CH_2$	H	19.7	2425	123
11, *S*-(−)-APD	$CH_2CH{=}CH_2$	H	2800	ca. 5000	ca. 1.8
12, *R*-(+)-APD	$CH_2CH{=}CH_2$	H	8.1	1415	175
RS-(±)-6-Br-APB	$CH_2CH{=}CH_2$	Br	10.1	701	69
17, *S*-(−)-6-Br-APD	$CH_2CH{=}CH_2$	Br	1880	>5000	ca. 1.8
18, *R*-(+)-6-Br-APD	$CH_2CH{=}CH_2$	Br	4.3	511	119
RS-(±)-6-Cl-APB	$CH_2CH{=}CH_2$	Cl	5.1	336	66

[a] Radioreceptor assays were carried out with a crude membrane fraction of rat brain corpus striatum[37] as follows: D_1 ligand, [^{3}H]SCH 23390 (0.3 nM) with Na^+ present (150 mM) and *cis*-(*Z*)-flupenthixol (300 nM) used to define specific binding; D_2 ligand, [^{3}H]YM-09151-2 (60 pM) with Na^+ present (150 mM) and (+)-butaclamol (5 μM) used to define specific binding. Incubation was carried out at 30 °C for 30 min (D_1) or 90 min (D_2). The computed SEM averaged 11.1 ± 0.7% for the individual IC_{50} values shown. *cis*-(*Z*)-flupenthixol, (+)-butaclamol, (±)-SKF 38393, (±)-APB, (±)-6-Br-APB, and (±)-6-Cl-APB were obtained from Research Biochemicals Inc., and radioligands were obtained from Du Pont-NEN.

12 N HCl saturated with HCl gas gave optically pure catechols **7** and **8** in high yields (Scheme I).

The optically pure 7,8-dimethoxybenzazepines **5** and **6** separately were treated with allyl bromide in the presence of potassium carbonate to obtain their respective 3-allyl derivatives **9** and **10** (Scheme I). O-Demethylation of **9** and **10** with boron tribromide gave the respective catechol benzazepine derivatives **11** and **12**, which were finally crystallized as the HBr salts.

Bromination of compounds **5** and **6** was accomplished with bromine in acetic acid to obtain the respective 6-bromo-7,8-dimethoxybenzazepine derivatives **13** and **14** (Scheme II). These were treated with allyl bromide in the presence of potassium carbonate, as before, to obtain the respective optically pure 3-allyl-6-bromo-7,8-dimethoxybenzazepine derivatives **15** and **16**. O-Demethylation of **15** and **16** with boron tribromide gave the respective dihydroxy 3-allyl-6-bromobenzazepine derivatives **17** and **18**, which also were crystallized as the HBr salts. The absolute configuration of compounds **11**, **12**, **17**, and **18** was assigned by comparing the signs of their specific rotation to those of compounds **7** and **8**, whose absolute configuration [viz., *S*-(−)-**7**, and *R*-(+)-**8**] had previously been established by single-crystal X-ray diffraction analysis.[26] Similarly, the optical purity of **11**, **12**, **17**, and **18** was not independently established but rather by comparing the values of the specific rotation of compounds **3** and **4** or **5** and **6** with the values reported for these intermediates in the literature.[26] It was estimated that compounds **11**, **12**, **17**, and **18** had virtually the same optical purity (>90%) as compounds **7** and **8**, whose optical purity had previously been established by HPLC analysis of their α-methoxy-α-(trifluoromethyl)phenylacetamide derivatives.[26]

Pharmacology

Affinities of all the compounds were determined as IC_{50} values in competing with [^{3}H]SCH 23390 and [^{3}H]-YM09151-2 at D_1 and D_2 receptors in the rat brain corpus striatum (Table I).

Discussion

The stereoselectivity of the substituted 1-phenyl-3-benzazepine series of D_1 agonists and antagonists is of interest because both the D_1 receptor affinity and agonist activity reside in the *R*-(+) enantiomers while the *S*-(−) enantiomers either are bound with much lower affinity or are inactive. The stereoselectivity of SKF 38393 was studied by Kaiser et al. in 1982.[26] We attempted to repeat their synthetic route on larger scale and to optimize the yields of the stereoisomeric end products. Later, Waddington et al.[32] described the 3-allyl derivative of SKF 38393 (APB) as a more potent CNS D_1 agonist. Our recent work indicated that the 3-allyl-6-bromo derivative of SKF 38393 ((±)-6-Br-APB) also is a high-affinity D_1 agonist with potentially high in vivo CNS D_1 agonist potency.[35] Hence, we resolved both of these compounds and examined their stereoselectivity in comparison to SKF 38393. As can be seen from Table I, compound **8** (*R*-(+)-SKF 38393) binds with high affinity (50 nM) with D_2/D_1 selectivity (>200) to the D_1 receptor whereas its *S*-(−) antipode (**7**) was inactive. Similarly, **12** (*R*-(+)-APB) had a considerably higher (350-fold) affinity (8.1 nM) and higher D_2/D_1 selectivity (175-fold) for the D_1 receptor than **11**, its *S*-(−) antipode (affinity = 2800 nM). Not surprisingly, **18** (*R*-(+)-6-Br-APB) also had a higher (437-fold) affinity (4.3 nM) and selectivity (119-fold) than its *S*-(−) antipode (**17**) (affinity = 1880 nM).

Thus, in the present study, stereoselectivity was demonstrated for 6-Br-APB, the *R*-(+) enantiomer **18**, which has been found to exhibit the highest affinity (IC_{50} = 4.3 nM) for the D_1 receptor of the D_1 benzazepine agonists reported to date.

Experimental Section

Analytical thin-layer chromatography was performed using E. Merck F-254 plastic-backed thin-layer silica gel plates. Medium-pressure column chromatography was performed using Baker flash silica gel. Melting points were obtained with a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H NMR spectra were obtained with a Varian XL-300 (300 Hz) NMR spectrometer using tetramethylsilane (TMS) as the internal standard. Chemical shifts are reported downfield from TMS. Spectral patterns were designated as follows: s, singlet; d, doublet; t, triplet; dd, double doublet; m, multiplet; b, broad peak. Mass spectra were determined by a Finnigan 4021 mass spectrometer under electron impact (EI) conditions by the Department of Chemistry, Northeastern University. Microanalyses were performed by Atlantic Microlab Inc., Atlanta, GA, and were within ±0.4% of calculated values. The optical rotations were determined

using a Perkin-Elmer 241 polarimeter.

7,8-Dimethoxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (2). 7,8-Dimethoxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (1, 116 g, 410 mmol) was dissolved in a mixture of 37% formaldehyde (88 mL, 840 mmol) and 88% formic acid (645 mL). The reaction mixture was refluxed for 4 h. It was then cooled and concentrated in vacuo, the residue was poured on ice, and the resulting mixture was made alkaline (pH 8) with NH_4OH solution and extracted with CH_2Cl_2. The extracts were washed well with water and then brine and then dried over anhydrous $MgSO_4$. The dried extract was filtered and concentrated in vacuo to 120 g of a pale yellow oil. The crude oil was dried in vacuo overnight to obtain 116 g of the crude product (95%) which was pure enough for the resolution step. ^1H NMR ($CDCl_3$): δ 7.4–7.1 (5 H, m, phenyl H's), 6.7 (1 H, s, 6-H), 6.2 (1 H, s, 9-H), 4.3 (1 H, d, 1-H), 3.85 (3 H, s, OCH_3), 3.6 (3 H, s, *N*-CH_3).

(*S*)-(−)-7,8-Dimethoxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (3). 7,8-Dimethoxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (2, 116 g, 390 mmol) was dissolved in 1.5 L of absolute EtOH. To this stirred solution was added a solution of 150.5 g (400 mmol) of L-(−)-dibenzoyltartaric acid in 1.5 L of absolute EtOH. The mixture was kept at 0 °C overnight. Colorless crystals were filtered, washed with ice-cold EtOH and Et_2O, and dried in vacuo to yield 65 g of the tartrate salt. The mother liquor was reserved to prepare the other enantiomer. The salt was recrystallized twice from MeOH (from 40 mL of MeOH per gram of the salt) to yield 45 g of colorless small needles. Mp: 175–176 °C (lit.[26] mp 180–181 °C). $[\alpha]_D$: −24.0° (*c* 1, DMF) (lit.[26] $[\alpha]_D$: −22.1° (*c* 1, DMF)). The salt (32 g) was suspended in water, and the suspension was adjusted to a pH of 8 with NH_4OH solution. It was then extracted with CH_2Cl_2. The extracts were washed well with water and brine and dried over anhydrous $MgSO_4$. The product was then filtered and concentrated in vacuo to a colorless crystalline solid, which was dried in vacuo to yield 19 g of the free base. A sample (100 mg) was analytically dried and characterized. Mp: 104–105 °C (lit.[26] mp 105–106 °C). $[\alpha]_D$: −32.3° (*c* 1, MeOH) (lit.[26] $[\alpha]_D$: −31.1° (*c* 1, MeOH)).

(*R*)-(+)-7,8-Dimethoxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (4). The mother liquor obtained above was concentrated in vacuo, and the residue was suspended in a water/CH_2Cl_2 mixture. NH_4OH solution was added to this mixture with vigorous shaking till the pH became 8. The organic layer was drawn off, washed well with water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to obtain 85 g of a brown oil. This oil (290 mmol) was dissolved in 1 L of absolute EtOH. To this stirred solution was added a solution of D-(+)-dibenzoyltartaric acid (109 g, 300 mmol) in 0.6 L of absolute EtOH. The mixture was kept at 0 °C overnight. It was then filtered, and a colorless precipitate was washed with cold EtOH and dried in vacuo. The salt was recrystallized twice from MeOH to yield 62 g of colorless long needles. Mp: 176–177 °C. $[\alpha]_D$: +23.8° (*c* 1, MeOH). A sample (40 g) of the salt was suspended in a water/CH_2Cl_2 mixture, and the mixture was made alkaline (pH 8) with NH_4OH solution. The organic layer was drawn off, and the aqueous layer was further extracted with CH_2Cl_2. The combined organic phases were washed well with water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to a colorless crystalline solid. The solid was collected and dried in vacuo to yield 23 g. $[\alpha]_D$: +32.0° (*c* 1, MeOH).

(*S*)-(−)-7,8-Dimethoxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (5). (*S*)-(−)-7,8-Dimethoxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (3, 19 g, 64 mmol) was dissolved in 300 mL of anhydrous benzene. To this solution stirred at 55–60 °C under N_2 was added cyanogen bromide (8.2 g, 77 mmol). A white precipitate appeared almost immediately, and stirring was continued for 4 h at 55–60 °C under N_2. The mixture was then cooled and filtered, and the filtrate was concentrated in vacuo to a pale yellow oil. The oil was dissolved in a mixture of 200 mL of glacial acetic acid and 160 mL of 3 N HCl and stirred under reflux for 24 h. It was then cooled and concentrated in vacuo. The residual solid was converted to the free base with NH_4OH solution and extracted with CH_2Cl_2. The extracts were washed well with water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to a pale yellow oil which was dried in vacuo to yield 15 g. $[\alpha]_D$: −18.0° (*c* 1, MeOH) (lit.[26] $[\alpha]_D$: −17.6° (*c* 1, MeOH)).

(*R*)-(+)-7,8-Dimethoxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (6). (*R*)-(+)-7,8-Dimethoxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (4, 23 g, 77 mmol) was treated in a similar fashion, purified by flash chromatography (CH_2Cl_2/MeOH, 10%) to obtain 13 g of a pure product as a pale yellow oil (60%). $[\alpha]_D$: +17.8 (*c* 1, MeOH) (lit.[26] $[\alpha]_D$: −17.5 (*c* 1, MeOH)).

(*S*)-(−)-7,8-Dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine Hydrochloride (7). (*S*)-(−)-7,8-Dimethoxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (5, 12.5 g, 39 mmol) was dissolved in 125 mL of 12 N HCl. The solution was stirred under reflux for 2 h. HCl gas was pumped into the mixture, and refluxing was continued overnight. The mixture was cooled to room temperature to obtain a tan crystalline solid which was collected by filtration, washed with ice-cold water and Et_2O, and dried in vacuo to yield 8.8 g (80%). Mp: 242–244 °C. $[\alpha]_D$: −15.0° (*c* 1, MeOH). Anal. ($C_{16}H_{18}NO_2Cl$): C, H, N.

(*R*)-(+)-7,8-Dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine Hydrochloride (8). (*R*)-(+)-7,8-Dimethoxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (6, 13.5 g, 42 mmol) also was treated in a similar fashion to obtain a tan crystalline solid 9.75 g (79%). Mp 242–244 °C. $[\alpha]_D$: −14.8° (*c* 1, MeOH). Anal. ($C_{19}H_{18}NO_2Cl{\cdot}0.5H_2O$): C, H, N.

(*S*)-(−)-3-Allyl-7,8-dimethoxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (9). (*S*)-(−)-7,8-Dimethoxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (5, 7 g, 23 mmol) and anhydrous K_2CO_3 (3.25 g, 25 mmol) were dissolved or suspended in a mixture of 60 mL of DMF and 2.5 mL of water. To this stirred solution was added a solution of allyl bromide (3 g, 25 mmol) in 25 mL of CH_2Cl_2 over a period of 30 min. The mixture was stirred overnight at room temperature under N_2. The mixture then was poured into 500 mL of water, and the organic layer was drawn off. The aqueous layer was further extracted with CH_2Cl_2; the combined organic phases were washed with water and brine and dried over anhydrous $CaCl_2$, filtered, and concentrated in vacuo to a dark oil. The oil was purified by flash chromatography (CH_2Cl_2/MeOH, 2.5%) to obtain 4.1 g (58%) of the pure product which was dried in vacuo overnight. $[\alpha]_D$: −31.0° (*c* 1, MeOH).

(*R*)-(+)-3-Allyl-7,8-dimethoxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (10). (*R*)-(+)-7,8-Dimethoxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (6, 6.0 g, 25 mmol) was treated in a similar fashion and purified by flash chromatography (CH_2Cl_2/MeOH, 2.5%) to obtain 3.0 g (49%) of pure product as a pale yellow oil which was dried in vacuo overnight. $[\alpha]_D$: +29.8° (*c* 1, MeOH).

(*S*)-(−)-3-Allyl-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine Hydrobromide (11). (*S*)-(−)-3-Allyl-7,8-dimethoxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (9, 4.0 g, 12 mmol) was dissolved in 100 mL of dry CH_2Cl_2 and stirred under N_2 at −70 °C. To the stirred solution was added dropwise with vigorous stirring a solution of boron tribromide in hexane (1.0 M solution, 12.5 g, 50 mL, 50 mmol). After the addition was complete, the reaction mixture was stirred at −70 °C for 1 h and then at room temperature for 2 h. It was then quenched by again cooling to −70 °C under N_2 followed by the dropwise addition of 50 mL of anhydrous MeOH with vigorous stirring. The reaction mixture was concentrated in vacuo, and the residue was treated with an additional 50 mL of MeOH and again concentrated in vacuo. This procedure was repeated twice more. Finally, the residue was dried in vacuo over P_2O_5 overnight. Recrystallization from EtOH–Et_2O yielded 2.8 g of a tan crystalline solid (62%). Mp: 209–211 °C. $[\alpha]_D$: −20.3° (*c* 1, MeOH). Anal. ($C_{19}H_{22}NO_2Br{\cdot}0.25H_2O$): C, H, N.

(*R*)-(+)-3-Allyl-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine Hydrobromide (12). (*R*)-(+)-3-Allyl-7,8-dimethoxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (10, 3.4 g, 11 mmol) was treated in a similar fashion to obtain after recrystallization from MeOH–CH_2Cl_2 1.8 g of a tan crystalline solid (46%). Mp: 208–210 °C. $[\alpha]_D$: +20.6° (*c* 0.5, MeOH). Anal. ($C_{19}H_{22}NO_2Br{\cdot}0.5H_2O$): C, H, N.

(*S*)-(−)-6-Bromo-7,8-dimethoxy-2,3,4,5-tetrahydro-1-phenyl-1*H*-3-benzazepine (13). (*S*)-(−)-7,8-Dimethoxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride (5, 8.0 g, 25 mmol) was dissolved in glacial acetic acid (60 mL). To the

stirred solution at room temperature was added dropwise bromine (8.0 g, 50 mmol). The reaction mixture was stirred at room temperature for 3 h. Very little precipitate was obtained, so the mixture was concentrated in vacuo to a dark oil. The oil was converted to the free base with NH_4OH solution and extracted with CH_2Cl_2. The extracts were washed well with water and brine and dried over anhydrous $CaCl_2$. The dried extract was filtered and concentrated in vacuo to a dark oil. Purification by flash chromatography (CH_2Cl_2/MeOH, 5%) gave a pure product 6.4 g (70%) as a pale yellow. The product was found to be identical to the racemate[35] by TLC and ^1H NMR.

(*R*)-(+)-6-Bromo-7,8-dimethoxy-2,3,4,5-tetrahydro-1-phenyl-1*H*-3-benzazepine (14). (*R*)-(+)-7,8-Dimethoxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (**6**, 7.0 g, 25 mmol) was treated in a similar fashion and purified by flash chromatography (CH_2Cl_2/MeOH, 5%) to obtain the pure product 5.5 g (62%) as a pale yellow oil. The product was found to be identical to the racemate[35] by TLC and ^1H NMR.

(*S*)-(−)-3-Allyl-6-bromo-7,8-dimethoxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (15). (*S*)-(−)-6-Bromo-7,8-dimethoxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (**13**, 6.2 g, 17 mmol) was dissolved in a mixture of 45 mL of DMF and 5 mL of water. To this stirred solution was added anhydrous K_2CO_3 (2.4 g, 17 mmol) followed by dropwise addition of a solution of allyl bromide (2.4 g, 20 mmol) in 25 mL of CH_2Cl_2. After the addition was complete, the reaction mixture was stirred at room temperature overnight. It was then quenched by pouring into 500 mL of cold water, the solution was then extracted with CH_2Cl_2, and the organic layer was drawn off, washed well with water and brine, and dried over anhydrous $CaCl_2$. The dried extract was filtered and concentrated in vacuo to a pale yellow oil. Purification by flash chromatography gave a pale yellow oil as the pure product (3.8 g, 60%). An analytical sample was obtained by preparative TLC purification from the same solvent system, and the purified product was dried at high vacuum. $[\alpha]_D$: −10.5° (*c* 0.5, MeOH). The product was found to be identical to the racemate[35] by TLC and ^1H NMR.

(*R*)-(+)-3-Allyl-6-bromo-7,8-dimethoxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (16). (*R*)-(+)-6-Bromo-7,8-dimethoxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (**14**, 5.3 g, 15 mmol) was treated in a similar fashion and purified by flash chromatography to obtain a pale yellow oil as the pure product (2.0 g, 35%). An analytical sample was obtained by preparative TLC purification from the same solvent system, and the purified product was dried at high vacuum. $[\alpha]_D$: −10.0° (*c* 1, MeOH). The product was found to be identical to the racemate[35] by TLC and ^1H NMR.

(*S*)-(−)-3-Allyl-6-bromo-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine Hydrobromide (17). (*S*)-(−)-3-Allyl-6-bromo-7,8-dimethoxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (**15**, 3.6 g, 9 mmol) was dissolved in 100 mL of dry CH_2Cl_2 and stirred under N_2 at −70 °C. To the stirred solution was added dropwise with vigorous stirring a solution of boron tribromide in hexane (1.0 M solution, 12.5 g, 50 mL, 50 mmol). After the addition was complete, the reaction mixture was stirred at −70 °C for 1 h and then at room temperature for 2 h. It was then quenched by cooling again to −70 °C under N_2, followed by dropwise addition of 50 mL to anhydrous MeOH with vigorous stirring. The reaction mixture was concentrated in vacuo, and the residue was treated with an additional 50 mL of MeOH and again concentrated in vacuo. This procedure was repeated twice more. Finally the residue was dried in vacuo over P_2O_5 overnight. Recrystallization from 2-propanol–Et_2O, yielded 3.0 g (74%) of an off-white crystalline solid. Mp: 198–200 °C. $[\alpha]_D$: −8.9° (*c* 1, MeOH). Anal. ($C_{19}H_{21}NO_2Br_2$): C, H, N.

(*R*)-(+)-3-Allyl-6-bromo-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine Hydrobromide (18). (*R*)-(+)-3-Allyl-6-bromo-7,8-dimethoxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (**16**, 1.8 g, 5 mmol) was treated in a similar fashion and recrystallized from EtOH–Et_2O to obtain 0.45 g (20%) of an off-white crystalline solid. Mp: 195–197 °C. $[\alpha]_D$: +9.8° (*c* 1, MeOH). Anal. ($C_{19}H_{21}NO_2Br_2$): C, H, N.