vestigator of the American Heart Association. The Biomolecular Structure Analysis Center acknowledges support from RJR Nabisco Inc., the Patterson Trust Foundation, and the State of Connecticut Department of Higher Education's High Technology Programs. The molecular graphics package CHEM-X (developed and distributed by Chemical Design Limited, Oxford, UK) was used to display the conformation of amiodarone in a membrane and in a crystal and to obtain some geometric parameters (Figure 4).

Articles

Synthesis and Resolution of (±)-7-Chloro-8-hydroxy-1-(3′-iodophenyl)-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (TISCH): A High Affinity and Selective Iodinated Ligand for CNS D1 Dopamine Receptor

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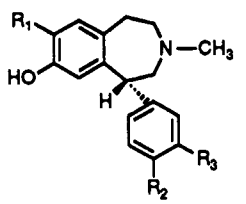
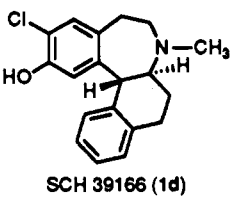
The synthesis and resolution of (±)-7-chloro-8-hydroxy-1-(3′-iodophenyl)-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine, (±)-TISCH (8) has been achieved by resolution of intermediate 4, the *O*-methoxyl, 3′-bromo derivative, as the diastereomeric camphor sulfonate salt. The final products, *R*-(+)-8 and *S*-(−)-8, were prepared by treatment of *R*-(+)- or *S*-(−)-7, the 3′-tributyltin intermediates, with iodine in chloroform, followed by O-demethylation. By using HPLC with a chiral column, the optical purity (>99%) of the intermediates and the final compounds was determined. Radioiodination was achieved by an iodo-destannylation reaction with sodium [^{125}I]iodide and hydrogen peroxide. As expected, the *R*-(+)-[^{125}I]-8 (the active isomer) displayed high affinity and selectivity to the CNS D-1 receptor in rat striatum tissue preparation (K_d = 0.205 nM). The rank order of potency was as follows: SCH-23390 (1a) > (±)-8 > (+)-butaclamol > spiperone, WB4101 > dopamine, 5-HT. After an iv injection, the *R*-(+)-[^{125}I]-8 penetrated the blood–brain barrier with ease and displayed specific regional distribution corresponding to the D-1 receptor density, while the *S*-(−)-[^{125}I]-8 showed no specific uptake. The data suggest that the ligand may be useful as a pharmacological tool for characterizing the D-1 dopamine receptor. When labeled with I-123, this ligand is a potential agent for in vivo imaging of CNS D-1 dopamine receptor.

Dopamine receptors have been classified into two subtypes on the basis of the ability of agonists and antagonists to discriminate between two different D-1 or D-2 dopamine receptors.[1-5] These two subtypes exert synergistic effects on the activity of CNS dopaminergic neurons in rats.[6,7] Reports have suggested that D-1 and D-2 agonists invariably show opposite biochemical effects: D-1 agonists stimulate adenyl cyclase activity, while D-2 agonists inhibit this enzyme's activity.[8,9] It has been well documented that SCH-23390 (1a) (Chart I) and the related benzazepine derivatives are highly selective central D-1 dopamine antagonists.[10-16] The corresponding bromo (SKF-83566, 1b),[17] and iodo (SCH-23982, SKF-103108A or IBZP, 1c)[18-22] compounds have also been shown to have a high specificity for central D-1 dopamine receptors. A high-affinity conformationally restricted analogue, SCH-39166, (1d), (K_i = 1.9 nM, against binding of [^{3}H]-1a),[23-25] and a photoaffinity ligand, *R*-(+)-IMAB (1e), were also reported (K_d = 0.28 nM).[26] In conjunction with PET, [^{11}C]-1a showed the highest concentration in the basal ganglia area of human brain,[27,28] and two iodinated analogues, [^{123}I]-1c[22,31] and (±)-[^{123}I]FISCH (1f),[31-33] were prepared. These iodinated analogues are potentially useful for in vivo imaging with single-photon-emission-computed tomography (SPECT). An imaging study in a monkey using [^{123}I]-1c specifically for mapping of the CNS D-1 dopamine receptor demonstrated that the agent localized in the basal ganglia area where D-1 receptor concentration is high.[34] However, the target to nontarget ratio in brain of this

Chart I





SCH 39166 (1d)

R -isomer compd	R_1	R_2	R_3
SCH-23390 (1a)	Cl	H	H
SKF-83566 (1b)	Br	H	H
SCH-23982 (1c)	I	H	H
IMAB (1e)	Cl	N_3	I
FISCH (1f)	Cl	I	H

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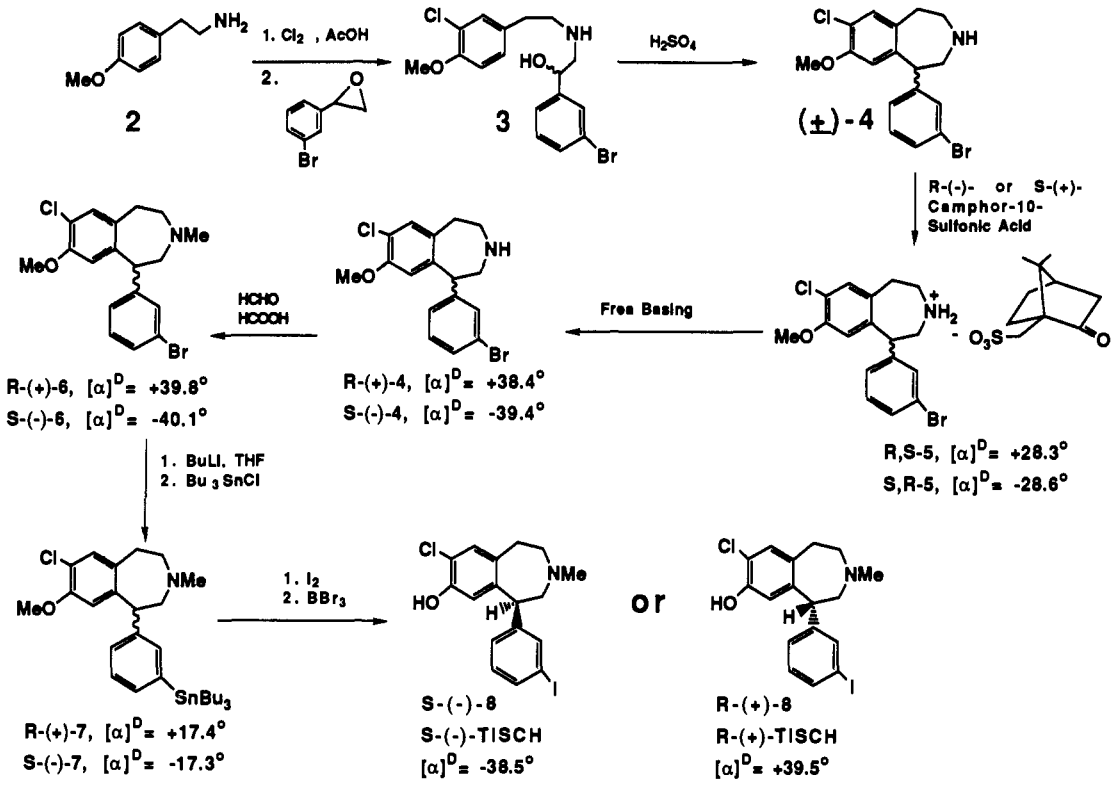
Scheme I. Preparation of *R*-(+)- and *S*-(−)-8



ligand is not high enough for our studies. This low ratio can be attributed to fast in vivo metabolism, in vivo deiodination, and the affinity of the ligand itself.[31,35] By moving the iodo group from the phenolic group to a nonactivated 1-phenyl ring, as in **1f**, the in vivo deiodination is diminished.[31,32] However, the affinity of this ligand for D-1 receptors is lower as compared to the parent compound, **1a** (K_d = 1.6 nM vs 0.3 nM, respectively, in rat striatal membrane preparation). Initial in vivo imaging studies in monkeys with (±)-[^{123}I]-**1f** displayed a fast uptake but also a rapid washout from the brain, leading to low target to nontarget ratio;[33] therefore, an improved iodinated ligand is needed for in vivo SPECT imaging of the D-1 receptor. In order to enhance the brain retention and to increase the affinity of the iodinated ligand for the CNS D-1 receptor, a new analogue with the iodine atom at the 3′-position of the 1-phenyl ring was designed. In this report the synthesis and resolution of (±)-7-chloro-8-hydroxy-1-(3′-iodophenyl)-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine ((±)-**8**) and results on initial biodistribution and in vitro binding studies are presented.

Chemistry

The chemistry section in this paper demonstrates the synthesis of racemic **8** and its intermediates as authentic compounds. The procedure also includes the use of HPLC chiral column as a tool to resolve racemic **8** and its intermediate, to determine their optical purities, and to confirm the optical products by coinjection with the authentic compounds.

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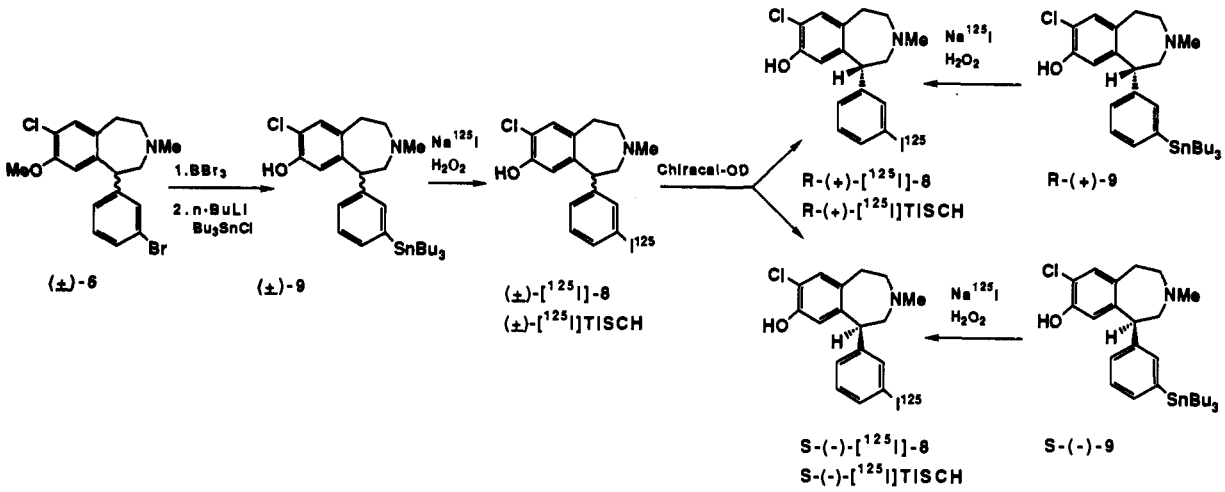
Scheme II. Synthesis of *R*-(+)- and *S*-(-)-[^{125}I]-8



The racemic (±)-8 was synthesized according to a procedure similar to that previously reported for the synthesis of (±)-7-chloro-8-hydroxy-1-(4′-iodophenyl)-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (1f)[31] (Scheme I). Chlorination of *p*-methoxyphenethylamine (2) gave 3-chloro-4-methoxyphenethylamine in a modest yield (47%). The chloro intermediate was condensed with 3-bromostyrene oxide producing 3 in 53% yield. Cyclization of 3 with concentrated sulfuric acid gave 4 in 58% yield.

The synthesis of *R*-(+)-8 has been achieved by resolution of intermediate 4 (Scheme I). The diastereomeric camphor sulfonate salt 4 was repeatedly recrystallized until the optical rotation reached a constant value; $[\alpha]_D = +28.3°$ for the *R,S*-5 diastereomer salt, or $[\alpha]_D = -28.6°$ (c = 1, MeOH) for the *S,R*-5 diastereomer salt. Methylation of *R*-(+)-4 ($[\alpha]_D = +38.2°$) or *S*-(-)-4 ($[\alpha]_D = -39.4°$, (c = 1, MeOH)) by formic acid and formaldehyde produced *R*-(+)-6 or *S*-(-)-6, respectively. Lithiation of *R*-(+)- or *S*-(-)-6 with *n*-butyllithium at -78 °C, followed by the addition of tri-*n*-butyltin chloride, generated the desired *R*-(+)- or *S*-(-)-7. The final products, *R*-(+)-8 ($[\alpha]_D$ = +39.5°) and *S*-(-)-8 ($[\alpha]_D = -38.5°$ (c = 1, MeOH)), were prepared by treatment of *R*-(+)- or *S*-(-)-7, respectively, with iodine in chloroform and O-demethylation with boron tribromide.

Compounds (±)-9, *R*-(+)-9, and *S*-(-)-9, were also synthesized by O-demethylation, lithiation, and addition of tributyltin chloride to compound (±)-6, *R*-(+)-6, and *S*-(-)-6, respectively. The tin compounds are starting materials for the synthesis of radioactive 8 (Scheme II).

By using a chiral column, the HPLC profile of racemic 4 showed two separate peaks. The difference of the retention time of the enantiomers was more than 1.5 min. Upon coinjection of racemic 4 with purified *R*-(+)-4 or *S*-(-)-4, the first peak coeluted with *S*-(-)-4 (retention time = 14.2 min, hexane/ethanol = 95:5, 1 mL/min) and the second peak with *R*-(+)-4 (retention time 15.6 min). The same coinjection procdure with a flow rate of 0.5 mL/min has been applied to (±)-8; *S*-(-)-8 coeluted with the first peak of racemic 8 at 23.5 min, while the *R*-(+)-8 coeluted with the second peak at 26.4 min. The method is sufficiently sensitive for detecting optical impurity as low as 1%.

To determine the absolute configuration of *R*-(+)- and *S*-(-)-8, the brominated compounds *R*-(+)- and *S*-(-)-6, which are close analogues, and the intermediates of *R*-(+)- and *S*-(-)-8, respectively, were converted to the corresponding known enantiomers of 7-chloro-8-methoxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (SCH 23389)[36] by catalytic hydrogenation at atmospheric pressure. The debrominated *R*-(+)-6 and *S*-(-)-6 displayed the same optical rotation as that reported in the literature.[37] This result confirms the assumption that the assignment of *R*-(+)- and *S*-(-)-8 and the related intermediates is correct.

Radiolabeling

Radioactive labeling of compound *R*-(+)-9 with I-125 at a no-carrier-added level was accomplished via a hydrogen peroxide catalyzed iododestannylation reaction (method A), Scheme II.[31] The radiolabeled compound *R*-(+)-8 (*R*-(+)-[^{125}I]-8) was purified by reverse-phase HPLC with an overall yield of 50% and a radiochemical purity of >99%. When the racemic compound 9 was used as a starting material, chiral column HPLC separation of the *R*-(+) and *S*-(-) isomers was needed following the reverse-phase HPLC (method B). The double HPLC purification would reduce the yield to 20% for each isomer. The radiochemical identity of radioactive 8 was determined by coinjection with nonradioactive 8 on reverse-phase HPLC with simultaneous UV and radioactivity detection and was determined to be the desired product on the basis of identical retention times. Since the K_d and K_i values were nearly equivalent, it was reasonable to assume that *R*-(+)-[^{125}I]-8 is carrier-free with a theoretical specific activity of 2200 Ci/mmol.[38]

Binding Study

The initial comparison was made between *RS*-(±)-1f and *RS*-(±)-8 on the displacement of [^{125}I]-1c binding to rat striatal membranes. (±)-8 gave a lower K_i value (0.69 nM) than *RS*-1f (K_i = 3.08 nM) under similar assay conditions. On the basis of this initial result, we decided to pursue further the resolution and characterization of the 8 compound. As compared to the two previously reported iodinated D-1 ligands, 1c and 1f, the resolved *R*-(+)-8 reported here showed higher affinity to rat striatal membranes in vitro.

The specific binding in rat striatum tissue preparation of *R*-(+)-[^{125}I]-8 obtained from either method A or B was found to be saturable and displayed similar K_d values, 0.205 and 0.32 nM, respectively. These values are com-

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Table I. Inhibition Constants of Compounds on *R*-(+)-[^{125}I]-8 Binding to Rat Striatal Membranes[a]

Compd	K_i, nM (mean ± SEM)
1a	0.28 ± 0.04
(±)-8	1.07 ± 0.07
(+)-butaclamol	5.26 ± 1.20
spiperone	849 ± 88
WB 4101[b]	634 ± 95
dopamine	>3000
5-HT	>5000
(±)-propranolol	>5000
naloxone	>6000

[a] *R*-(+)-[^{125}I]-8 (0.15–0.20 nM) was incubated in the presence of the indicated compounds in 7–11 concentrations and of membrane preparation from rat striatum. Each value represents the mean ± SEM of three to five determinations. [b] α_1-Adrenergic antagonist.

parable to the value of **1a** (K_d = 0.35 nM). Competition study with various types of receptor ligands indicated that *R*-(+)-[^{125}I]-8 specifically binds to the dopamine D-1 receptor with great selectivity (Table I). The rank order of potency is as follows: 1a > (±)-8 (+)-butaclamol > spiperone, WB4101 > dopamine, 5-HT etc. Furthermore, the displacements of *R*-(+)-8 and *S*-(−)-8 of [^{125}I]-**1c** binding to rat striatal tissue were compared. The dramatic difference in K_i values (0.50 nM for *R*-(+)-8 and 24.9 nM for *S*-(−)-8, *S*/*R* ratio = 50) strongly indicated the stereoselectivity of this ligand.

Biodistribution Study in Rats

The in vivo biodistribution of *R*-(+)- and *S*-(−)- [^{125}I]-8 in rats is presented in Tables II, parts A and B. As expected, the *R*-(+)- and *S*-(−)-8 showed good initial brain uptake at 2 min after iv injection (2.19 and 1.59% dose/organ, respectively). Despite their similar lipophilicity, the difference of brain uptake exhibited with the two isomers can be attributed to their differing metabolisms or plasma protein binding. The data suggest that the compound can pass through the blood–brain barrier with ease. At later time points, the brain uptake decreases for both *R*-(+)- and *S*-(−)-8 isomers. In comparison with *S*-(−)-8, the striatum to cerebellum ratio (ST/CB ratio) for *R*-(+)-8 exhibited a higher ratio of specific binding to the striatum area. The ST/CB ratio reached 11.3 at 1 h for *R*-(+)-8. (This value is better than those of **1f** (2.6 at 1 h) and **1c** (5.1 h).) The *S*-(−)-8 displayed an ST/CB ratio of 1.2–1.3. This result strongly suggests that the uptake is stereospecific and that *R*-(+)-8 is the active isomer.

High initial lung uptakes were observed for both isomers, but the inactive *S*-(−)-8 showed faster lung clearance. Liver uptake remained high for both isomers, with *R*-(+)-8 showing a faster washout. The thyroid uptake (0.059%) was low for the first hour post iv injection, indicating minimum in vivo deiodination. As compared to [^{125}I]-**1c**,[22] which showed a thyroid uptake of 0.1% at 1 h postinjection, 8 displayed better in vivo stability.

In summary, the synthesis and resolution of a new iodinated D-1 dopamine ligand, *R*-(+)-8, is reported. As expected, the *R*-(+)-[^{125}I]-8 (the active isomer) displayed high affinity and selectivity for the CNS D-1 receptor in rat striatum tissue preparation. After an iv injection, the R-(+)-[^{125}I]-8 penetrated the blood–brain barrier with ease and displayed specific regional distribution corresponding to the D-1 receptor density, while the *S*-(−)-[^{125}I]-8 showed no specific uptake. The data suggest that the ligand may be useful as a pharmacological tool for characterizing the D-1 dopamine receptor. When labeled with I-123, this

Table II. Biodistribution of *R*-(+)- and *S*-(−)-[^{125}I]-8 in Rats after an Intravenous Injection (% dose/organ, average of 3 rats ± std dev)

A. *R*-(+)-[^{125}I]-8

	2 min	30 min	1 h	4 h	24 h
blood	3.28 ± 0.555	0.773 ± 0.55	0.847 ± 0.277	0.254 ± 0.109	0.046 ± 0.013
heart	1.14 ± 0.21	0.137 ± 0.009	0.088 ± 0.008	0.014 ± 0.001	0.001
muscle	10.80 ± 2.93	9.30 ± 1.65	8.59 ± 2.68	1.17 ± 0.367	0.201 ± 0.214
lung	10.18 ± 1.71	1.24 ± 0.282	0.621 ± 0.115	0.122 ± 0.006	0.012 ± 0.002
kidney	4.92 ± 0.916	0.945 ± 0.078	0.883 ± 0.096	0.476 ± 0.109	0.187 ± 0.11
spleen	0.546 ± 0.264	0.233 ± 0.028	0.123 ± 0.012	0.015 ± 0.002	0.001
liver	15.78 ± 3.25	11.45 ± 0.941	9.814 ± 1.4	7.638 ± 0.182	3.84 ± 0.404
skin	8.24 ± 1.8	8.44 ± 2.08	7.42 ± 1.76	1.14 ± 0.204	0.288 ± 0.042
thyroid	0.121 ± 0.006	0.042 ± 0.006	0.059 ± 0.016	0.118 ± 0.023	0.268 ± 0.078
brain	2.19 ± 0.459	0.798 ± 0.053	0.568 ± 0.116	0.102 ± 0.006	0.001
brain/blood[a]	7.09	12.67	7.34	5.23	0.186
			Regional Brain Distribution		
striatum	1.317	1.477	1.455	0.600	–
cerebellum	1.030	0.248	0.129	0.011	–
ST/CB ratio[a]	1.279	5.948	11.276	56.448	–

B. *S*-(−)-[^{125}I]-8

	2 min	15 min	1 h
blood	2.94 ± 0.444	1.588 ± 0.216	0.975 ± 0.044
heart	1.21 ± 0.132	0.313 ± 0.054	0.144 ± 0.023
muscle	6.75 ± 0.467	16.53 ± 6.10	9.86 ± 0.368
lung	9.02 ± 2.73	2.78 ± 0.769	1.40 ± 0.361
kidney	6.134 ± 1.19	4.36 ± 0.768	2.25 ± 0.350
spleen	0.398 ± 0.243	0.392 ± 0.032	0.025 ± 0.036
liver	16.13 ± 4.72	20.35 ± 3.53	16.51 ± 1.18
skin	8.23 ± 1.33	9.05 ± 1.53	7.80 ± 0.463
thyroid	0.163 ± 0.016	0.067 ± 0.025	0.035 ± 0.006
brain	1.59 ± 0.257	0.884 ± 0.139	0.313 ± 0.027
brain/blood[a]	5.37	5.77	3.27
		Regional Brain Distribution	
striatum	0.962	0.555	0.21
cerebellum	0.73	0.44	0.169
ST/CB ratio[a]	1.317	1.263	1.21

[a] % dose/gram ratio.

ligand is a potential agent for in vivo SPECT imaging.

Experimental Section

Proton NMR were recorded on a Varian EM 360A spectrometer. The chemical shifts were reported in ppm downfield from an internal tetramethylsilane standard. Infrared spectra were obtained with a Mattson Polaris FT-IR spectrophotometer. Melting points were determined on a Meltemp apparatus and are reported uncorrected. HPLC was performed on Rabbit HP from Rainin Instrument Co. Inc. using a chiral column (chiracel-OD (4.1 × 250 mm), Diacel Inc., Los Angeles, CA). Optical rotation of compounds was measured on a Perkin-Elmer 243B polarimeter. Elemental analyses were performed by Atlantic Microlabs Inc., of Norcross, GA, and were within 0.4% of the theoretical values. No-carrier-added (specific activity of more than 1700 Ci/mmol) [^{125}I]NaI solution (0.1 N) in sodium hydroxide with no reducing agent was used in radiolabeling (DuPont, Wilmington, DE).

(±)-7-Chloro-8-methoxy-1-(3′-bromophenyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine Maleate ((±)-4). The hydroxy amine (±)-3[31,36] (10.0 g, 0.026 mol) was added to concentrated sulfuric acid (81 mL), and the temperature was kept below 12 °C. The reaction mixture was stirred at 8 °C for 30 min and then at room temperature for 90 min. The mixture was poured onto ice (675 g); concentrated ammonium hydroxide (135 mL) was added, followed by solid sodium hydroxide (54.0 g), while the temperature was maintained below 30 °C. The precipitated was extracted into dichloromethane, and the organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure to afford a gummy residue. The residue was dissolved in a small amount of absolute ethanol. A saturated solution of maleic acid (in ethanol) was added. The precipitate was collected and recrystallized in absolute ethanol to afford 7.7 g (58%) of white crystals of (±)-4: mp 170–171 °C; FT-IR; free base (KBr) λ 3400 (br, NH), 1600, 1500, 1250 and 1050 cm^{-1}; ^{1}H NMR free base ($CDCl_3$) δ 7.52–6.82 (m, 5 H, ArH 1), 6.45 (S, 1 H, ArH-9), 4.32–4.02 (m, 1 H, CH), 3.72 (S, 3 H, OCH_3), 3.60–2.52 (m, 6 H, $(CH_2)_3$), 1.88 (S, 1 H, NH). Anal. ($C_{21}H_{21}BrClNO_5$) C, H, N.

(±)-7-Chloro-8-methoxy-1-(3′-bromophenyl)-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine Maleate ((±)-6).[31] To a solution of (±)-4 (15.0 g, 40.8 mmol) in formic acid (10.0 g) was added 37% formaldehyde (8.00 g). The mixture was heated to 90–100 °C for 4 h. After the reaction mixture was cooled to room temperature, 4 N hydrochloric acid (10.4 mL) was added. The mixture was concentrated to dryness under reduced pressure. The residue was dissolved in water and then made basic with 25% sodium hydroxide and extracted 3 times with dichloromethane (50.0 mL). The combined organic layers were dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to obtain a hygroscopic solid. The crude product was dissolved in a small amount of absolute ethanol and a saturated solution of maleic acid in absolute thanol was added. When the precipitation was completed, the white solid was filtered and air dried to obtain 17.3 g (83%): mp 162–163 °C; FT-IR free base (KBr) λ 1650, 1500, 1350, 110 cm^{-1}; ^{1}H NMR of free base 6 ($CDCl_3$) δ 7.48–6.82 (m, 5 H, ArH), 6.22 (S, 1 H, ArH-9), 4.38–4.09 (m, 1 H, CH), 3.61 (S, 3 H, OCH_3), 3.11–2.45 (m, 6 H, $(CH_2)_3$), 2.33 (S, NCH_3). Anal. ($C_{22}H_{23}BrClNO_5 \cdot {}^1/_2H_2O$) C, H, N.

(±)-7-Chloro-8-hydroxy-3-methyl-1-[3′-(tri-*n*-butylstannyl)phenyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine ((±)-9). The benzazepine (±)-6 (510 mg, 1.33 mmol) was dissolved in dried dichloromethane and cooled in a dry ice/2-propanol bath. To this solution was added BBr_3 (2.72 mL, 2.72 mmol) dropwise. The reaction mixture was warmed to room temperature. After 2 h the mixture was concentrated and chilled in an ice bath, methanol was added, and the mixture was stirred overnight. After concentration, the residue was stirred with water (10 mL). The mixture was made strongly basic with 10% sodium hydroxide solution. The cloudy mixture was extracted several times with ethyl acetate; then the combined organic layers were dried over anhydrous sodium sulfate. The solvent was evaporated to obtain a solid which was purified by column chromatography (silica gel, CH_2Cl_2/MeOH/NH_4OH, 95:5:1) to obtain 150 mg of the O-demethylated intermediate (49%). This hydroxy compound (100 mg, 0.27 mmol) in dried THF (15 mL) was cooled to −78 °C, and *n*-butyllithium (0.7 mL, 1.1 mmol) was added dropwise with stirring. After 4 min, tri-*n*-butyltin chloride 0.15 mL, 0.54 mmol) was added to the reddish solution. The reaction mixture was stirred at −78 °C for an additional 15 min, followed by quenching with ammonium chloride solution (1.0 M). The THF was evaporated under reduced pressure. The residue was extracted with dichloromethane and dried over anhydrous sodium sulfate. After evaporation of the solvent, the desired product was separated by column chromatography (silica gel, CH_2Cl_2/MeOH/NH_4OH, 95:5:1) to obtain 59 mg (36%) of thick oil of (±)-9: FT-IR (neat) λ 3010–2700 (strong and broad of *n*-butyl group), 1470, 1270 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.30–6.82 (m, 4 H, ArH), 6.11 (s, 1 H, ArH-9), 3.20–2.49 (m, 6 H, $(CH_2)_3$) 2.2 (s, 3 H, NCH_3), 1.68–0.60 (m, 27 H, $Sn(C_4H_9)_3$). Anal. ($C_{29}H_{44}ClNOSn$) C, H, N.

(±)-7-Chloro-8-hydroxy-1-(3′-iodophenyl)-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine ((±)-8). The *N*-methylbenzazepine (±)-6 (3.5 g, 9.1 mmol) in dried THF (60 mL) was cooled to −78 °C in a dry ice/acetone bath. *n*-Butyllithium (7.30 mL, 14.7 mmol) was added dropwise into this solution. After stirring for 4 min, tri-*n*-butyltin chloride (2.25 mL) was added to the reddish solution. The reaction mixture was stirred at −78 °C for an additional 15–20 min, followed by quenching with ammonium chloride solution. (If the reaction mixture is allowed to warm to room temperature slowly before the quenching, the work-up will be cleaner.) The THF was evaporated under reduced pressure. The residue was extracted with dichloromethane (10 mL) and dried over anhydrous sodium sulfate. After evaporation of the solvent, the desired intermediate (±)-7 was separated by column chromatography (silica gel, CH_2Cl_2/MeOH/NH_4OH, (95:5:1) to obtain 2.5 g (44%): FT-IR (KBr) λ 3050–2700 (strong and broad of *n*-butyl group), 1500, 1270, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.45–6.90 (m, 5 H, ArH), 6.15 (S, 1 H, ArH-9), 4.39–4.05 (m, 1 H, CH), 3.55 (S, 3 H, OCH_3) 3.10–2.68 (m, 6 H, $(CH_2)_3$), 2.35 (S, 3 H, NCH_3), 1.68–0.50 (m, 27 H, $Sn(C_4H_9)_3$).

A solution of iodine (0.1 M) in chloroform was added to a solution of (±)-7 (2.5 g, 4.25 mmol) in chloroform at room temperature until the color of iodine persisted. The mixture was stirred overnight at room temperature. A solution of potassium fluoride (1 M, 5 mL) in methanol and a 5% aqueous sodium bisulfite solution (3 mL) were added, respectively. After 5 min of stirring, water (10 mL) was added. The organic layer was separated, and the aqueous layer was extracted with chloroform (20 mL) twice. The combined organic layers were dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to obtain a yellow solid. The iodo product was separated by column chromatography (silica gel, CH_2Cl_2/MeOH/NH_4OH, 95:5:1) to yield 1.35 g (75%) of the desired iodinated compound. This product was dissolved in dried dichloromethane and cooled in a dry ice/2-propanol bath. To this solution was added a BBr_3 solution (10.0 mL, 10.0 mmol) dropwise. The resulting solution was warmed to room temperature. After 2 h the reaction mixture was concentrated and chilled in an ice bath, methanol was added, and the mixture was stirred overnight. After the methanol evaporated, the residue was stirred with water (25 mL). The mixture was made strongly basic with 10% sodium hydroxide solution and adjusted to pH 7–8 with dilute hydrochloric acid solution. The cloudy mixture was extracted several times with ethyl acetate (25 mL). The combined organic layers were dried over anhydrous sodium sulfate. The solvent was evaporated to obtain a slightly yellow solid which was purified by column chromatography (silica gel, CH_2Cl_2/MeOH: 95:5) yielding 520 mg (40%) of (±)-8: mp 192–194 °C; FT-IR (KBr) λ 3150 (S, Br, OH), 1550, 1110, 775 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.51–7.14 (m, 4 H, ArH), 7.06 (S, 1 H, ArH-6), 6.34 (S, 1 H, ArH-9), 4.25–4.15 (m, 1 H, CH), 3.32 (S, 3 H, OCH_3), 3.00–2.52 (m, 6 H, $(CH_2)_3$), 2.29 (S, 3 H, NCH_3); Anal. ($C_{17}H_{17}ClINO$) C, H, N.

***R*-(+)-7-Chloro-8-methoxy-1-(3′-bromophenyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (*R*-(+)-4).**[36] The racemic (±)-4 (15.12 g, 0.041 mol) and *S*-(+)-camphor-10-sulfonic acid (9.6 g, 0.041 mol) were dissolved with heating in CH_3CN/MeOH (4:1 by volume). After the precipitate was formed CH_3CN/MeOH was added until the solution was clear. After the solution was slowly cooled, the resultant salt precipitate was collected and washed with cold CH_3CN. The salt was recrystallized three more times to bring the optical rotation to the constant value $[\alpha]_D$ = +28.23° (*c* = 1, methanol), mp 244–246 °C dec. Anal. ($C_{27}H_{33}BrClNO_5S$) C, H, N.

The final crystals (3.8 g) were stirred vigorously in 0.5 N NaOH and ether (200 mL) for 2 h. The ether phase was dried over anhydrous sodium sulfate and evaporated under reduced pressure to obtain 2.21 g of a low melting solid free base: *R*-(+)-4, $[\alpha]_D$ = +38.4° (*c* = 1, MeOH); FT-IR and ^{1}H NMR are identical with (±)-4. Retention time of *R*-(+)-4 is 15.8 min; optical purity is 100%. (Chiral column, hexane/ethanol = 95:5, 1 mL/min).

The following optically resolved compound and its related intermediates were prepared by the same procedures as the preparation of authentic racemic compounds described above. All of the final products were purified by column chromatography (silica gel, CH_2Cl_2/MeOH/NH_4OH, 95:5:1). Their FT-IR and ^{1}H NMR are identical with the authentic compound.

***R*-(+)-7-Chloro-8-hydroxy-1-(3′-iodophenyl)-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (*R*-(+)-8).** The compound *R*-(+)-4 (1.8 g, 5.16 mmol) gave 1.59 g (82%) of the N-methylated hygroscopic compound *R*-(+)-6, $[\alpha]_D$ = +39.8° (*c* = 1, MeOH). Lithiation of *R*-(+)-6 (1.0 g, 2.6 mmol), followed by the addition of *n*-tributyltin chloride (1.5 mL, 3.0 mmol) produced 913 mg (56%) of *R*-(+)-7, $[\alpha]_D$ = +17.4° (*c* = 1, MeOH). The reaction of the tin compound (913 mg, 1.45 mmol) with iodine solution in chloroform gave 500 mg (79%) of iodo derivative, $[\alpha]_D$ = +37.5° (*c* = 1, MeOH). This compound (350 mg, 0.82 mmol) was O-demethylated in boron tribromide (2.6 mL, 2.6 mmol) to give 100 mg (39%) of *R*-(+)-8: $[\alpha]_D$ = +39.5° (*c* = 1, MeOH); retention time = 14.0 min (chiral column, hexane/ethanol, 90:10, 10 mL/min). Coelution with a second peak of authentic compound at 26.4 min; optical purity is 100% (chiral column, hexane/ethanol, 95:5, 0.5 mL/min).

***R*-(+)-7-Chloro-8-hydroxy-1-[3′-(tri-*n*-butylstannyl)-phenyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (*R*-(+)-9).** The bromo compound *R*-(+)-6 was O-demethylated with BBr_3 to yield 61.3% of hydroxy compound, $[\alpha]_D$ = +46.4° (*c* = 1, MeOH): mp 148–150 °C; FT-IR (KBr) λ 3400 (Br, OH), 1550, 1450 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.55–7.05 (m, 5 H, ArH), 6.35 (s, 1 H, Ar-9H), 4.20 (m, 1 H, CH), 3.67 (S, 1 H, OH), 3.07–2.45 (m, 6 H, 3(CH_2)), 2.25 (S, 3 H, NCH_3). Anal. ($C_{17}H_{17}BrClNO\cdot H_2O$) C, H, N. The hydroxy compound was lithiated with *n*-BuLi; then tri-n-butyltin chloride was added. After working up, the product was purified by column (silica gel, CH_2Cl_2/MeOH/NH_4OH, 95:5:1) to obtain a stannylated compound (23%) as a thick oil: $[\alpha]_D$ = +6.2° (*c* = 1, MeOH); FT-IR (neat) λ 3000–2800 (S, OH and butyl group), 1460, 1255; ^{1}H NMR ($CDCl_3$) δ 7.30–6.82 (m, 5 H, ArH), 6.11 (S, 1 H, ArH-9), 4.29–4.00 (m, 1 H, CH), 3.20–2.49 (m, 6 H, (CH_2)$_3$), 2.21 (S, 3 H, NCH_3), 1.68–0.60 (m, 27 H, (C_4H_9)$_3$). Anal. ($C_{29}H_{44}ClNOSn$) C, H, N.

***S*-(−)-7-Chloro-8-methoxy-1-(3′-bromophenyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (*S*-(−)-4).** The mother liquids from the recrystallization of *S*-(+)-camphor-10-sulfonate salt of (±)-4 (for the preparation *R*-(+)-4) were combined. The solvent was evaporated under reduced pressure to obtain a solid residue, which was a free base, and was purified by forming a maleate salt. The maleate salt was recrystallized in ethanol and free based in ether/0.5 N NaOH. The diastereomeric salt *S,R*-5 of the free base compound (14.6 g, 0.04 mol) and (1*R*)-(−)-10-camphorsulfonic acid (9.50 g, 0.04 mol) was treated in the same procedure as the synthesis of *R*-(+)-4. After three recrystallizations, the optical rotation reached the constant value: $[\alpha]_D$ = −28.6° (*c* = 1, MeOH); mp = 238–239 °C dec. Anal. ($C_{27}H_{33}BrClNO_5S$) C, H, N. The final salt was converted to free base *S*-(−)-4 (3.36 g): $[\alpha]_D$ = −38.5° (*c* = 1, MeOH); FT-IR and ^{1}H NMR are identical with (±)-4. Retention time of *S*-(−)-4 is 14.3 min, optical purity is 100% (chiral column, hexane/ethanol, 95:5, 1 mL/min).

***S*-(−)-7-Chloro-8-hydroxy-1-(3′-iodophenyl)-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (*S*-(−)-8).** The compound and its intermediates were synthesized by the same procedures as the above authentic samples. Their FT-IR and ^{1}H NMR are identical with the authentic sample. N methylation of *S*-(−)-4 (2.6 g, 7.23 mmol) gave 2.38 g (87%) of *S*-(−)-6, $[\alpha]_D$ = −40.2° (*c* = 1, MeOH). The exchange reaction of the bromide of *S*-(−)-6 (500 mg, 1.30 mmol) with lithium by *n*-BuLi (0.7 mL, 1.4 mmol) and followed by the addition of tri-*n*-butyltin chloride (0.36 mg, 1.33 mmol) afforded 450 mg (56%) of *S*-(−)-7, $[\alpha]_D$ = −17.3° (*c* = 1, MeOH). Compound *S*-(−)-7 (450 mg, 0.73 mmol) was treated with iodine solution in chloroform to yield 240 mg (77%) of iodo derivative compound. This compound (200 mg, 0.46 mmol) was O-demethylated by boron tribromide (0.93 mL, 0.93 mmol) to give 124 mg (64%) of *S*-(−)-8: $[\alpha]_D$ = −38.5° (*c* = 1, MeOH); the retention time = 12.6 min; optical purity is 100% (chiral column, hexane/ethanol, 90:10, 1 mL/min). Coelution with the first peak of authentic compound at 23.5 min (chiral column, hexane/ethanol, 95:5, 0.5 mL/min).

Determination of Configuration of *R*-(+)- and *S*-(−)-6.[36] The compound *R*-(+)-6 (174 mg, 0.45 mmol) and triethylamine (0.42 mL) in dry THF (5 mL) was stirred in the presence of 5% Pd/C (83 mg) under 1.0 atm of hydrogen gas at room temperature for 16 h. The reaction was filtered, isolated, and purified by column chromatography (silica gel, CH_2Cl_2/MeOH/NH_4OH, 95:5:1) to obtain 81 mg (59%) of the desired product. The spectra of the product are identical with those reported in the literature,[36] $[\alpha]_D$ = +42.0° (*c* = 1, ethanol), lit[36] $[\alpha]_D$ = +47.3° (*c* = 1, ethanol). The same procedure was applied to *S*-(−)-6 to yield 51% product with $[\alpha]_D$ = −40.0° (*c* = 1, ethanol).

HPLC profiles (chiral column) of the debrominated compound, *R*-(+)- and *S*-(−)-7-chloro-8-methoxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine, showed that both compounds had optical purity >99%. Retention times of the *R*-(+) and *S*-(−) isomers are 11.78 and 10.86 min, respectively (hexane/2-propanol, 90:10, 1 mL/min).

Radiolabeling. For the preparation of *R*-(+)- or *S*-(−)-8 from *R*-(+)- or *S*-(−)-9, aqueous hydrogen peroxide (10 μL, 30% w/v) was added to a mixture of 10 μL tin compound 9 (1 mg/mL), 100 μL of 50% EtOH/1 N HCl and 5 μL sodium [^{125}I]iodide (2–3 mCi, carrier-free, sp act. 2200 Ci/mmol) in a sealed vial. The reaction was allowed to proceed at 23 °C for 5 min, after which it was terminated by the addition of 0.5 mL of sodium bisulfite (100 mg/mL). The reaction mixture was made basic via the addition of 100 mg $NaHCO_3$ and extracted with ethyl acetate (3 × 1 mL). The combined organic layers were passed through an anhydrous sodium sulfate column (0.4 cm × 5 cm) and evaporated to dryness by a stream of nitrogen. (Ethyl acetate will alter the retention time.) The residue was dissolved in 100% ethanol (50–100 μL), and the desired product, [^{125}I]-8, was isolated from the unreacted tin compound, 9, and a small amount of unknown polar radioactive impurities (probably free iodide) by HPLC with use of a reverse-phase column (PRP-1, Hamilton Inc.) and an isocratic solvent of 90% acetonitrile/10% pH 7.0 buffer (5 mM 3,3-dimethylglutaric acid), retention time 5.1 (1 mL/min). The appropriate fractions were collected, condensed, and reextracted with ethyl acetate (1 × 3 mL). The solution containing the no-carrier-added product was condensed to dryness and redissolved into 100% ethanol (overall yield 50%). The preparation was completed in approximately 6 h.

Alternatively, if racemic 9 had been used as the starting material for the hydrogen peroxide iododestannylation reaction, the following HPLC procedure would be used for the separation of the radioactive *R*-(+) and *S*-(−)-8. The racemic (±)-8 from reverse-phase HPLC purification, as in the first part of the radiolabeling procedure, would be dissolved into 20 μL of ethanol and injected into HPLC to separate the *R*-(+) and *S*-(−) isomers, with the following conditions: chiral column (4.1 mm × 250 mm) with hexane/ethanol, 90/10% solvent. The first eluting radioactive peak, the *S*-(−) isomer, and the second eluting peak, the *R*-(+) isomer, had retention times of 21.2 min and 23.5 min, respectively, with a flow of 0.4 mL/min. The retention times of the *R*-(+) and *S*-(−) isomers were determined by using the authentic nonradioactive samples with simultaneous UV detection. After the appropriate peaks were collected, the solvent was evaporated to dryness under a stream of nitrogen. The residue was dissolved into 100 μL of ethanol and diluted with 2.0 mL sterile saline for injection. The solution was then filtered through a sterile 0.22-μm filter into a sterile vial (20% yield for each isomer, sp act. 2200 Ci/mmol, 6 h preparation).

Biodistribution in Rats. Biodistribution of *R*-(+)- or *S*-(−)-[^{125}I]-8, was studied in male Sprague-Dawley rats (225–300 g) which were allowed free access to food and water. While under ether anesthesia, 0.2 mL of a saline solution, containing *R*-(+)- or *S*-(−)-[^{125}I]-8 (2–5 μCi, sp act. ~2200 Ci/mmol), was injected directly into the femoral vein, and the rats were sacrificed at various time points post injection by cardiac excision under ether anesthesia. The organs of interest were removed and weighed and the radioactivity associated with organs was counted with

use of a Beckman gamma automatic counter (Model 5500). The percent dose per organ was calculated by a comparison of the tissue counts to suitably diluted aliquots of the injected material. Total activities of blood and muscle were calculated assuming that they are 7% and 40% of total body weight, respectively.[39]

Regional brain distribution in rats was obtained after an iv injection of *R*-(+)- or *S*-(−)-[^{125}I]-**8**. By dissecting, weighing, and counting samples from different brain regions (cortex, striatum, and cerebellum), % dose/gram of samples was calculated by comparing the sample counts with the counts of the diluted initial dose. The uptake ratio of each region was obtained by dividing % dose/gram of each region with that of the cerebellum.

In Vitro Binding. Rat tissue homogenates were prepared as described previously.[31] The binding assays were performed by incubating 50 μL of tissue preparations containing 40–60 μg of protein with appropriate amounts of *R*-(+)-[^{125}I]-**8** ligand (for saturation analysis) or appropriate amounts of ligand and competitors (for competition study) in a total volume of 0.2 mL of the assay buffer. After an incubation period of 20 min at 37 °C (with stirring), the samples were rapidly filtered in the cell harvester (Brandel M-24R), under vacuum, through Whatman GF/B glass fiber filters pretreated with 0.2% protamine sulfate and washed with 3 × 5 mL of cold (4 °C) 50 mM Tris-HCl buffer, pH 7.4. The nonspecific binding was obtained in the presence of 10 μM SCH-23390. The filters were counted in a gamma counter (Beckman 5500) at an efficiency of 70%. Both Scatchard and competition experiments were analyzed by using the iterative nonlinear least-squares curve-fitting program LIGAND.[40]

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Registry No. **2**, 55-81-2; **3**, 131567-06-1; (±)-**4**, 131567-07-2; (±)-**4**·maleate, 131567-08-3; *R*-(+)-**4**, 131615-49-1; *S*-(−)-**4**, 131615-55-9; (*R*,*S*)-**5**, 131681-39-5; (*S*,*R*)-**5**, 131681-40-8; (±)-**6**·maleate, 131567-10-7; (±)-**6**, 131567-09-4; *R*-(+)-**6**, 131615-50-4; *S*-(−)-**6**, 131615-56-0; (±)-**7**, 131567-13-0; *R*-(+)-**7**, 131615-51-5; *S*-(−)-**7**, 131681-51-1; (±)-**8**, 131567-14-1; *R*-(+)-**8**, 131615-52-6; *S*-(−)-**8**, 131615-57-1; (±)-**9**, 131567-12-9; *R*-(+)-**9**, 131615-54-8; 3-chloro-4-methoxyphenethylamine, 7569-87-1; 3-bromostyrene oxide, 131567-05-0; (±)-7-chloro-8-hydroxy-3-methyl-1-(3′-bromophenyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine, 131567-11-8; (*R*)-7-chloro-8-methoxy-3-methyl-1-(3′-iodophenyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine, 131567-15-2; (*R*)-7-chloro-8-hydroxy-3-methyl-1-(3′-bromophenyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine, 131615-53-7; (*R*)-(+)-7-chloro-8-methoxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine, 129666-34-8; (*S*)-(−)-7-chloro-8-methoxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine, 73445-62-2; (±)-7-chloro-8-methoxy-3-methyl-1-(3′-iodophenyl)-2,3,4,5-tetrahydro-1*H*-benzazepine, 131615-58-2; (*S*)-(−)-7-chloro-8-methoxy-3-methyl-1-(3′-iodophenyl)-2,3,4,5-tetrahydro-1*H*-benzazepine, 131567-16-3.

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Synthesis and Ligand Binding of Cocaine Isomers at the Cocaine Receptor

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The cocaine binding site at the dopamine transporter has been found to be stereoselective. Thus, the seven possible stereoisomers of (−)-cocaine have been synthesized and found to inhibit [^{3}H]-2β-carbomethoxy-3β-(4-fluorophenyl)tropane ([^{3}H]WIN 35,428) with potencies ranging from $^1/_{60}$ to $^1/_{600}$ of that of (−)-cocaine. The synthesis and characterization of all new compounds is presented.

Specific binding sites for natural (−)-cocaine have been identified in the brain tissue of both rodents and humans.[1-5] Affinities of (−) natural cocaine and several cocaine-like compounds at one of these binding sites parallel their potencies for inhibiting dopamine uptake as well as their potencies for producing drug selfadministration.[6-8] Thus this binding site has several properties characteristic of biologically relevant receptors. However, since biologically relevant receptors usually show stereoselectivity, it is important to establish the stereoselectivity of (−)-cocaine for its binding site. Since cocaine has seven additional stereoisomeric forms, it is necessary to determine whether any of these cocaine isomers show high affinity for the cocaine binding sites. In this report we describe the synthesis of the seven cocaine stereoisomers and present their binding properties at the cocaine binding site(s).

Results

The chemical entity methyl 3-(benzoyloxy)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate can exist in eight stereoisomeric forms (Chart I); one of these, [1*R*-(*exo*,*exo*)],[9] refers to natural (−)-cocaine (**1**). Since most of the biological studies reported for cocaine use the traditional names for these compounds, the more familiar traditional names are used in this report. However, all structures derivable from the natural and unnatural cocaine ring system are designated by either an *R* or an *S* prefix, as appropriate. Thus natural cocaine and its three *R* diastereomers are designated (*R*)-cocaine (**1**), (*R*)-pseudococaine (**2**), (*R*)-allococaine (**3**), and (*R*)-allopseudococaine (**4**) while the isomers deriving from the enantiomer of natural cocaine are (*S*)-cocaine (**5**), (*S*)-pseudococaine (**6**),

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