Synthesis and Optical Resolution of (*R*)- and (*S*)-*trans*-7-Hydroxy-2-[*N*-propyl-*N*-(3'-iodo-2'-propenyl)amino]tetralin: A New D3 Dopamine Receptor Ligand

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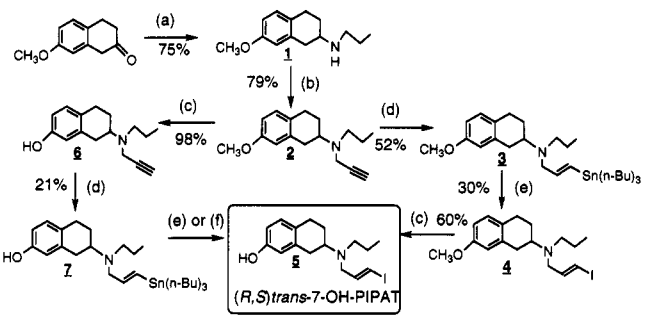
An improved method for synthesis and resolution of (*R,S*)-*trans*-7-hydroxy-2-[*N*-propyl-*N*-(3'-iodo-2'-propenyl)amino]tetralin (*trans*-7-OH-PIPAT, **5**), a new D3 dopamine receptor ligand, was reported. Both isomers, (*R*)-(+)- and (*S*)-(−)-**5**, were prepared and characterized. HPLC retention times obtained on a chiral column for these isomers were consistent with those observed for [^{125}I]-(*R*)-(+)- and (*S*)-(−)-**5**. Direct radioiodination of an optically resolved tin precursor, (*R*)-(+)-**7**, yielded the desired [^{125}I](*R*)-(+)-**5**, which is a simpler method for synthesis of this ligand. Binding studies with membrane preparations containing D3 dopamine receptors expressed in *Spodoptera frugiperda* (Sf9) cells also suggested that the [^{125}I](*R*)-(+)-**5** is the active isomer (K_d = 0.05 nM). The schemes described may provide an efficient way for synthesizing a large quantity of this new D3 dopamine receptor ligand for *in vivo* behavior studies.

Introduction

The central nervous system (CNS) dopaminergic system in mammalian brain has been the subject of extensive studies in the past two decades. The CNS dopaminergic system in the brain is the apparent action site for various neuroleptic drugs in the treatment of schizophrenia and other mental disorders. There is a wealth of pharmacological information reported on the postsynaptic dopamine receptors.[1-4] In recent years, the application of molecular biology techniques to express receptors in cloned cells has dramatically expanded the understanding and the complexity of CNS molecular pharmacology. Recent reports on cloning of dopamine receptors have produced at least six different subtypes: D1, D2$_L$, D2$_S$, D3, D4, and D5.[5-13]

The expression and characterization of the rat D3 dopamine receptors have been demonstrated in the baculovirus system.[14] Similarly, human dopamine D3 receptors expressed in Chinese Hamster Ovary (CHO) cells have also been characterized using tritiated and iodinated benzamides, respectively.[15,16] Earlier reports on N,N-disubstituted 2-aminotetralins suggested that they are D2 agonists.[17] One of the tetralin derivatives, 7-hydroxy-*N,N*-(di-*n*-propyl)-2-aminotetralin (7-OH-DPAT), appeared to show high affinity and selectivity for D2-like receptors. Recently, [^{3}H]-7-OH-DPAT was identified as a selective ligand for the D3 receptor expressed in CHO cells, K_d = 0.67 nM.[18] Based on 7-OH-DPAT, we have reported in a preliminary communication the synthesis and initial binding study of an iodinated derivative, (*R,S*)-*trans*-7-hydroxy-2-[*N*-propyl-*N*-(3'-iodo-2'-propenyl)amino]tetralin (*trans*-7-OH-PIPAT, **5**; Scheme I) by placing the iodine atom on the *N*-propenyl side chain.[19] This unique feature has led to a stable iodinated derivative with highly desirable properties: higher specific activity, more potent binding affinity, and lower nonspecific binding. The binding characteristics of the racemic [^{125}I](*R,S*)-*trans*-7-OH-PIPAT, **5**, were evaluated with D3 dopamine receptors expressed in *Spodoptera frugiperda* (Sf9) cells (K_d = 0.13 nM in the absence of NaCl).[19] The racemic form of [^{125}I]-(*R,S*)-*trans*-7-OH-PIPAT, (*R,S*)-**5**, was later resolved into isomer A and isomer B by high-pressure liquid chromatography using a chiral column (chiracel OD). However, only the isomer A, which corresponds to one of the optical isomers, showed high D3 dopamine receptor binding, displaying a high specific and saturable binding in rat striatal membrane homogenates; K_d = 0.48 nM and B_{max} = 240 fmol/mg of protein.[20] Competition binding data exhibited the pharmacological profile of D3 dopamine receptors. Evidently the conformation at the optical center played an important role in determining the binding affinity toward the D3 dopamine receptor.

Scheme I. Synthesis of (*R,S*)-*trans*-7-OH-PIPAT, **5**[a]



(a) *n*-Propylamine/$NaBH_3CN$; (b) 2-propynyl chloride/K_2CO_3; (c) BBr_3, CH_2Cl_2; (d) (*n*-Bu)$_3$SnH, AIBN, toluene; (e) $I_2/CHCl_3$; (f) H_2O_2/Na^{125}I.

In order to identify the optical isomer responsible for the specific binding of D3 dopamine receptors, we have resolved the optical isomers of this series of tetralin compounds. Improved synthesis, resolution of the racemic intermediate, and subsequent preparation and identification of the final optically pure product (*R*)-(+)- and (*S*)-(−)-*trans*-7-OH-PIPAT, **5**, are reported herein.

Chemistry

The synthesis of (*R*)-(+)- and (*S*)-(−)-*trans*-7-OH-PIPAT, (*R*)-(+)- and (*S*)-(−)-**5**, was achieved by Scheme II.[21] The racemic (*R,S*)-**5** was prepared by an improved modified reaction scheme (Scheme I), as compared to that described in the preliminary report.[19] The starting

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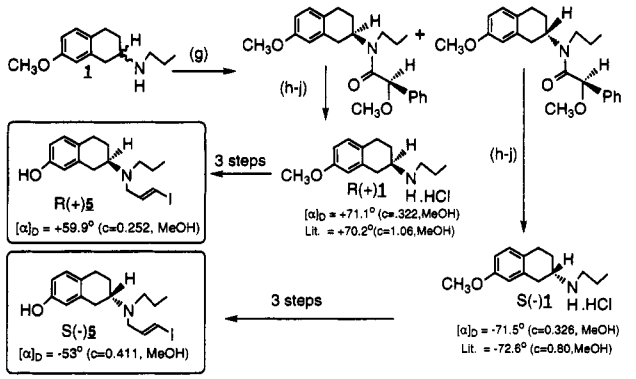
Scheme II. Preparation of (*R*)- and (*S*)-*trans*-7-OH-PIPAT, 5[a]



(g) (*R*)-(−)-*O*-methylmandelyl chloride; (h) column chromatography; (i) $(CH_3)_3COK$, THF; (j) HCl.

material, 7-methoxy-2-tetralone, was converted to (*R,S*)-**1** by a reductive ammination reaction.[22] *N*-Alkylation of (*R,S*)-**1** with *n*-propynyl chloride gave (*R,S*)-**2** in 75% yield. Reduction of (*R,S*)-**2** with tributyltin hydride resulted in the trans isomer (*R,S*)-**3**. Iododemetalation of the tin derivative (*R,S*)-**3** gave (*R,S*)-**4**, which was readily converted to the desired product (*R,S*)-**5** by a demethylation reaction with boron tribromide. This reaction sequence is effective in producing "cold" (*R,S*)-**5**. However, for preparation of the radioiodinated (*R,S*)-**5**, it is more convenient and logical to perform the radioiodination at the last step. A separate route was used for preparation of (*R,S*)-**7**, by which the radioiodinated (*R,S*)-**5** was obtained.

The precursor for radioiodination, tributyltin derivative (*R,S*)-**7**, was synthesized by converting the 7-methoxy-PIPAT intermediate, (*R,S*)-**2**, to 7-hydroxy intermediate, (*R,S*)-**6**, with BBr_3, followed by the reduction of (*R,S*)-**6** with tributyltin hydride in the presence of 2,2′-azobis(2-methylpropionitrile) (AIBN) as the catalyst. Only a moderate yield (21%) of (*R,S*)-**7** was obtained from this hydrostannation reaction carried out in toluene. The same reaction gave a slightly higher yield (37%) when it was done in THF. The possible byproducts were the nonterminal stannylated compound (7.4%) and 29.5% of compounds with no vinyl functional group (based on ^1H NMR spectra). These two byproducts were consistently observed under different experimental conditions: at different temperatures, with different solvents (toluene or THF), and with varying amounts of tri-*n*-butyltin hydride and AIBN.

To synthesize the optically pure enantiomers: (*R*)-(+)- and (*S*)-(−)-**5**, the starting compound **1** was resolved according to the literature.[21] Optical rotation measurements of (*R*)-(+)-**1** and (*S*)-(−)-**1** as hydrochloride salts were +71° and −70°, respectively. These values are consistent with those reported in the literature.[21] The resolved optical isomers (*R*)-(+)-**1** and (*S*)-(−)-**1** were suitable starting materials for carrying out subsequent reactions. *N*-Alkyation with *n*-propynyl chloride, demethylation with BBr_3, and addition of tributyltin hydride and reaction of I_2 in chloroform, as described in Scheme I, gave the desired final products (*R*)-(+)-**5** and (*S*)-(−)-**5**. The iodination reaction gave a lower yield (3–10%) than the same reaction with the methoxy-protected intermediate **3**. Alternative routes for synthesizing the (*R*)-(+)-**5** and (*S*)-(−)-**5** are currently being explored.

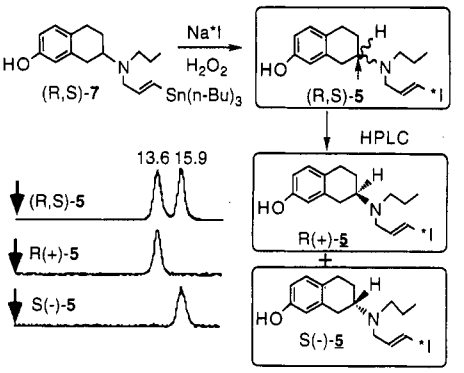


Figure 1. Preparation of racemic [^{125}I](*R,S*)-**5** and separation of optical isomers, (*R*)-**5** and (*S*)-**5**. HPLC profiles of [^{125}I](*R,S*)-**5**, (*R*)-**5**, and (*S*)-**5** based on γ detection are presented. Chiral separation of the (*R*) and (*S*) isomers was performed by HPLC using a 4.1-mm × 250-mm chiracel-OD column (Diacel Industries) eluting with *n*-hexanes/ethanol (90/10) at a flow rate of 0.5 mL/min. The retention time for the [^{125}I](*R*)-**5** and (*S*)-**5** was 13.6 and 15.9 min, respectively. Radiochemcal purity was >98%, and the yield was 80% for the chiral separation step.

Radiolabeling

Radioiodination was successfully carried out by reacting the tributyltin derivative, (*R,S*)-**7** and sodium [^{125}I] with hydrogen peroxide as the oxidant at room temperature. The iododestannylation reaction gave the desired product, [^{125}I](*R,S*)-*trans*-7-OH-PIPAT, [^{125}I](*R,S*)-**5**, in high yield (85–90%). Even under the mild labeling conditions, however, a small percentage (5–10%) of the side product, most likely the diiodinated compound, was observed. This assumption was based on the retention time of an additional peak at a later time point. The retention time of the desired product, [^{125}I](*R,S*)-**5**, and the diiodinated side product(s) on HPLC were 8–9 and 13–14 min, respectively. This additional iodination may occur on the aromatic ring due to the presence of an activating hydroxyl group. Similar phenomena were also observed for the preparation of "cold" authentic standard, (*R,S*)-**5**. The longer retention time of the unreacted tri-*n*-butyltin derivative, (*R,S*)-**7**, on HPLC (greater than 60 min) assures effective separation. The identity of the radiolabeled compound was verified by co-injection of the "cold" authentic standard, (*R,S*)-**5**, on HPLC. The γ and UV detectors each showed a single peak with an identical retention time of 8.3 min. Separation of (*R*)-(+) and (*S*)-(−) isomers was successfully carried out on HPLC with a chiracel-OD column eluted with hexanes/EtOH, 90/10, 0.5 mL/min. The retention times were 13.6 and 15.9 min for the (*R*)-(+) and (*S*)-(−) isomers, respectively (Figure 1). The optical purity and identity of each radioiodinated enantiomer was validated on HPLC with the chiracel-OD column. The isomer A reported previously[20] is (*R*)-(+)-**5**. Each isomer was found to be coeluted with the corresponding cold standard, (*R*)-(+)- and (*S*)-(−)-**5** enantiomers. Both the radiochemical and optical purities of each isomer (no-carrier-added, specific activity 2200 Ci/mmol) were greater than 95%. An improved radiolabeling method, using optically resolved (*R*)-(+)-**7**, was subsequently developed. Radiolabeling of the resolved (*R*)-(+) tin precursor, (*R*)-(+)-**7**, eliminated the need for HPLC separation with the chiracel-OD column; therefore, it substantially reduced the overall preparation time and resulted in higher overall yields (60–80%). The ligand, [^{125}I](*R*)-(+)-**5**, prepared by either method appeared to show the same receptor binding properties.

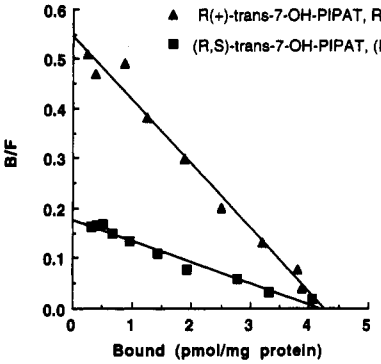


Figure 2. Scatchard plots for binding of [^{125}I](*R,S*)-**5** and (R)-**5** to membrane preparations containing D3 dopamine receptors expressed in *Spodoptera frugiperda* (Sf9) cells. Nonspecific binding was defined with 1 μM of (*R,S*)-7-OH-DPAT. Specific binding of this ligand to the D3 dopamine receptor was a one-site binding (Hill coefficient close to 1) with K_d values of 0.05 and 0.13 nM for [^{125}I](*R*)-(+)-**5** and the racemic [^{125}I](*R,S*)-**5**, respectively.

Binding Studies

The receptor binding of racemic [^{125}I](*R,S*)- and the resolved [^{125}I](*R*)-(+)- and [^{125}I](*S*)-(−)-**5** were evaluated with membrane preparations containing D3 dopamine receptors expressed in *S. frugiperda* (Sf9) cells. The [^{125}I]-(*R*)-(+)-**5** is the active isomer which displayed high-affinity binding toward D3 dopamine receptor; on the contrary, the [^{125}I](*S*)-(−) isomer did not show any specific binding toward the D3 dopamine receptors (data not shown). [^{125}I]-(*R*)-(+)-**5**, prepared by either direct labeling or separation of the racemic [^{125}I](*R,S*)-**5** by HPLC on a chiral column, gave the same K_d value (data not shown). Nonspecific binding determined in the presence of 1 μM (*R,S*)-7-OH-PIPAT accounted for only a small fraction of total binding (approximately 10% at K_d). The Scatchard analysis of specific binding revealed one-site binding (Hill coefficient ca. 1) with K_d values of 0.05 and 0.13 nM for [^{125}I](*R*)-(+)-**5** and the racemic [^{125}I](*R,S*)-**5**, respectively (Figure 2).[20] As expected, the K_d value for the (*R*)-(+)isomer (0.05 nM) is approximately half that of the racemic ligand (0.13 nM).

In summary, an improved method for synthesis and resolution of (*R,S*)-*trans*-7-OH-PIPAT, (*R,S*)-**5**, a D3 dopamine receptor ligand, was developed. Both isomers, (*R*)-(+)- and (*S*)-(−)-**5**, were prepared and characterized. HPLC retention times obtained on a chiral column for these isomers were consistent with those observed for [^{125}I]-(*R*)-(+)- and (*S*)-(−)-**5**. Direct radioiodination of an optically resolved tin precursor, (*R*)-(+)-**7**, yielded the desired [^{125}I](*R*)-(+)-**5**, which provided a simpler method for synthesis of this ligand. Binding studies with membrane preparations containing D3 dopamine receptors expressed in *S. frugiperda* (Sf9) cells showed that the [^{125}I]-(*R*)-(+)-**5** is the high affinity isomer (K_d = 0.05 nM). The ligand should be useful for characterizing D3 dopamine receptor pharmacology with in vitro binding assays of membrane preparations as well as autoradiography of brain sections. The schemes described may provide an efficient way for synthesizing a large quantity of this new D3 dopamine receptor ligand for *in vivo* behavior studies.

Experimental Section

General Methods. NMR were recorded on a Varian EM 360A, a Bruker WM-250 (250-MHz), or a Bruker AM 500 (500-MHz) 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 a model Rabbit HP with dual pumps (Rainin Instrument Co. Inc., Emeryville, CA) using a chiral column (chiracel-OD, 4.1 × 250 mm; from Diacel Inc., Los Angeles, CA) or a silica column (from Hamilton Co., Reno, NV). This HPLC system was equipped with a UV and a γ detector. The data were collected and analyzed with Dynamix software on Macintosh computers. Optical rotation values were measured on a Perkin-Elmer 243B polarimeter. Mass spectra were performed on a mass spectrometer VG 70–70 HS with chemical ionization (CI), using methane or ammonia gas. Elemental analyses were performed by Atlantic Microlabs, Inc., of Norcross, GA, and values were within 0.4% of the theoretical values. All chemicals were obtained from commercial sources; 7-methoxy-2-tetralone was purchased from Aldrich Chemical Co.

(*R,S*)-7-Methoxy-2-(*N*-propyl-*N*-propynylamino)tetralin [(*R,S*)-2]. 2-Propynyl chloride (2.60 mL, 36 mmol) was added dropwise to a mixture of (*R,S*)-**1** (1.0 g, 4.56 mmol) and anhydrous potassium carbonate (0.775 g, 5.58 mmol) in acetone (8 mL) under nitrogen at 0 °C. The mixture was refluxed overnight. The acetone solution was evaporated, and the residue was dissolved in CH_2Cl_2. The methylene chloride solution was washed twice with water and once with saturated NaCl solution and dried over anhydrous sodium sulfate. The solvent was evaporated, and the crude product was purified by column chromatography (silica gel, hexanes/ethyl acetate, 3/1) to give 0.87 g of (*R,S*)-**2** (yield 79%): ^{1}H NMR ($CDCl_3$) δ 7.00 (d, J = 8.3 Hz, 1H, ArH), 6.69 (dd, J = 8.3, 2.7 Hz, 1H, ArH), 6.64 (d, J = 2.6, 1H, ArH), 3.78 (s, 3H, OCH_3), 3.54 (d, J = 2.3 Hz, 2H, $CH_2C{\equiv}C$), 2.96–2.63 (m, 5H, CH_2ArCH_2 and CHN), 2.56 (t, 2H, NCH_2), 2.11 (t, 1H, $C{\equiv}CH$), 2.06–2.03 (m, 1H), 1.60–1.56 (m, 1H), 1.55–1.39 (hex, 2H, CH_2), 0.85 (t, 3H, CH_3). Anal. ($C_{17}H_{23}NO$) C, H, N.

(*R,S*)-*trans*-7-Methoxy-2-[*N*-propyl-*N*-[3′-(tributylstannyl)-2′-propenyl]amino]tetralin [(*R,S*)-3]. A mixture of (*R,S*)-**2** (0.30 g, 1.16 mmol) in dry toluene (20 mL), tri-*n*-butyltin hydride (1.0 mL, 3.7 mmol), and AIBN (40.6 mg, 0.28 mmol) was heated at 95–100 °C for 4 h under a nitrogen atmosphere. The solvent was evaporated, and the residue was purified by column chromatography (silica gel, hexanes/ethyl acetate, 3/1) to give 0.326 g of (*R,S*)-**3** as an oil (yield 52%): FT-IR (neat) ν 3000–2800 (very strong peak of nonaromatic CH); ^{1}H NMR ($CDCl_3$) δ 6.90 (d, J = 8.3 Hz, 1H, ArH), 6.60 (d, J = 8.3, 2.7 Hz, 1H, ArH), 6.54 (d, J = 2.6 Hz, 1H, ArH), 6.05 (d, J = 18.9 Hz, C=CHSn), 5.96 (dt, J = 18.9, 5.1 Hz, 1H, C=CHC) 3.69 (s, 3H, OCH_3), 3.23 (m, 2H, CH_2), 2.97–1.90 (m, 7H, CH_2ArCH_2, CHN and NCH_2), 1.41–0.76 (m, 29, Bu_3Sn and CH_2), 0.83 (t, 3H, CH_3). Anal. ($C_{29}H_{51}SnNO$) C, H, N.

(*R,S*)-*trans*-7-Hydroxy-2-[*N*-propyl-*N*-(3′-iodo-2′-propenyl)amino]tetralin [(*R,S*)-5]. To the compound (*R,S*)-**3** in chloroform (30 mL) was gradually added at room temperature a 0.1 M solution of iodine in chloroform until the color of iodine persisted. The mixture was stirred overnight. The KF (1 M) in methanol (2 mL) and 5% aqueous $NaHSO_3$ (2 mL) were sequentially added to the reaction mixture. The chloroform layer was separated, and the aqueous layer was extraced once with chloroform. The combined chloroform layer was dried over anhydrous sodium sulfate, filtered, evaporated to dryness, and purified by column chromatography (silica gel, hexanes/ethyl acetate/ammonium hydroxide, 80/20/1) to obtain 60 mg of the desired (*R,S*)-*trans*-7-methoxy-2-[*N*-*n*-propyl-*N*-(3′-iodo-2′-propenyl)amino]tetralin, (*R,S*)-**4** (yield 30%). To the solution of (*R,S*)-**4** (60 mg, 0.23 mmol) in dry dichloromethane (10 mL) was added BBr_3 (0.716 g, 0.716 mmol) at −12 °C. The reaction mixture was stirred overnight at room temperature. After the reaction was quenched with water, the volatile material was evaporated. The residue was taken up in more water (5 mL), basified with 10% NaOH to pH 9, and adjusted to pH 8 with 1 M HCl. The mixture was then extracted several times with dichloromethane. The combined extracts were dried over anhydrous sodium sulfate. After the solvent was evaporated, the residue was purified by column chromatography (silica gel, hexanes/ethyl acetate/ammonium hydroxide, 80/20/1) to give 40 mg of (*R,S*)-**5** (yield 60%): ^{1}H NMR ($CDCl_3$) δ 6.93 (d, J = 8.2 Hz, 1H, ArH), 6.60

(dt, J = 14.3 Hz, 1H, C=CH), 6.59 (dd, J = 8.4, 2.9 Hz, 1H, ArH), 6.54 (d, J = 2.6, 1H, ArH), 6.24 (dt, J = 14.4, 1.2 Hz, 1H, C=CHI), 3.19 (d, J = 6.2 Hz, 2H, CH_2C=C), 3.02–2.61 (m, 5H, CH_2ArCH_2 and CHN), 2.49 (t, 2H, NCH_2), 2.03–1.96 and 1.65–1.55 (m, 2H, CH_2), 1.53–1.40 (hex, 2H, CH_2), 0.88 (t, 3H, CH_3). Anal. ($C_{16}H_{23}NOICl$) C, H, N.

(*R,S*)-7-Hydroxy-2-(*N*-propyl-*N*-propynylamino)tetralin [(*R,S*)-6]. The demethylation of (*R,S*)-2 with BBr_3 had been done in the same manner of the synthesis of (*R,S*)-5 with 98% yield: ^{1}H NMR ($CDCl_3$) δ 6.92 (d, J = 8.1 Hz, 1H, ArH), 6.59 (dd, J = 8.1, 2.6 Hz, 1H, ArH), 6.54 (d, J = 2.5 Hz, 1H, ArH), 4.71 (s, 1H, OH), 3.54 (s, 2H, C≡CCH_2), 2.93–2.73 (m, 5H, CH_2ArCH_2 and CHN), 2.65 (t, 2H, NCH_2) 2.19 (s, 1H, C≡CH), 2.16–2.13 and 1.57–1.50 (m, 4H, CH_2, CH_2), 0.94 (t, 3H, CH_3). Anal. ($C_{16}H_{21}NO$) C, H, N.

(*R,S*)-*trans*-7-Hydroxy-2-[*N*-propyl-*N*-[3′-(tributylstannyl)-2′-propenyl)amino]tetralin [(*R,S*)-7]. Compound (*R,S*)-7 was synthesized in the same manner as that for (*R,S*)-3. The reaction yield was 21 and 37% using toluene and THF as the solvent, respectively. When THF was used as the solvent, the reaction was completed in 2 h, while the reaction using toluene took 4 h: ^{1}H NMR ($CDCl_3$) δ 6.91 (d, J = 8.1 Hz, 1H, ArH), 6.58 (dd, J = 8.1, 2.7 Hz, 1H, ArH), 6.53 (d, J = 2.1 Hz, 1H, ArH), 6.13 (d, J = 19.1 Hz, 1H, C=CHSn), 6.03 (dt, J = 19.0, 5.2 Hz, 1H, C=CHC), 3.30 (s, br, 2H, CH_2C=C), 3.03–2.80 (m, 5H, CH_2ArCH_2 and CHN), 2.77 (t, 2H, NCH_2), 2.54 (m, 1H, of CH_2), 1.52–0.78 (m, 28H, Bu_3Sn and 1H of CH_2), 0.88 (t, 3H, CH_3). Anal. ($C_{28}H_{49}SnNO$) C, H, N.

Unless indicated the following *S* and *R* isomers were synthesized by the same reaction as that of the corresponding racemic compound by using either (*R,S*)-8 or (*R,R*)-8 as the starting material. All spectra are also the same as the racemic compounds.

(*S*)-*trans*-7-Methoxy-2-(*N*-propyl-*N* -propynylamino)tetralin [(*S*)-2]. The same procedure as that for the preparation of the racemic (*R,S*)-2 was employed (yield 78%).

(*S*)-*trans*-7-Hydroxy-2-(*N*-propyl-*N*-propynylamino)tetralin [(*S*)-6]. The same procedure as that for the preparation of the racemic (*R,S*)-6 was employed (yield 96%).

(*S*)-*trans*-7-Hydroxy-2-[*N*-propyl-*N*-[3′-(tributylstannyl)-2′-propenyl]amino]tetralin [(*S*)-7]. The same procedure as that for the preparation of the racemic (*R,S*)-7 was employed (yield 23%). THF was used as the solvent, and the reaction was refluxed for 2 h.

(*S*)-*trans*-7-Hydroxy-2-[*N*-propyl-*N*(3′-iodo-2′-propenyl)-amino]tetralin [(*S*)-(−)-5]. The same procedure as that for the preparation of the racemic (*R,S*)-5 was employed (yield 3–5%): $[\alpha]_D$ = −53° (c = 0.411, MeOH); optical purity = 95.2%; retention time 8.82 min (HPLC, Chiracel OD; hexanes/EtOH, 90/10, 1 mL/min).

(*R*)-*trans*-7-Methoxy-2-(*N*-propyl-*N*-propynylamino)tetralin [(*R*)-2]. The same procedure as that for the preparation of the racemic (*R,S*)-2 was employed (yield 76%).

(*R*)-*trans*-7-Hydroxy-2-(*N*-propyl-*N*-propynylamino)tetralin [(*R*-6]. The same procedure as that for the preparation of the racemic (*R,S*)-6 was employed (yield 87%).

(*R*)-*trans*-7-Hydroxy-2-[*N*-propyl-*N*-[3′-(tributylstannyl)-2′-propenyl]amino]tetralin [(*R*-7)]. It was prepared by the same procedure as the synthesis of (*R,S*)-7, but THF was used as the solvent and the reaction mixture was refluxed for 2 h (yield 24%).

(*R*)-*trans*-7-Hydroxy-2-[*N*-propyl-*N*-(3′-iodo-2′-propenyl)amino]tetralin [(*R*)-(+)-5]. The same procedure as that for the preparation of the racemic (*R,S*)-5 was employed (yield 10–15%): $[\alpha]_D$ = +59.9° (c = 0.252, MeOH); optical purity 100% (HPLC, chiracel-OD; retention time = 7.03 min, hexanes/EtOH, 90/10, 1 mL/min).

Radiolabeling. No-carrier-added [^{125}I](*R,S*)-*trans*-7-OH-PIPAT, [^{125}I](*R,S*)-5, was prepared by an iododestannylation reaction similar to the procedure reported previously.[23] Hydrogen peroxide (50 μL, 3% w/v) was added to a mixture of 50 μL of tributyltin precursor (1 mg/mL EtOH), 50 μL of 1 N HCl, and I-125 (2–3 mCi) in a sealed vial. The reaction was allowed to proceed for 10 min at room temperature, and it was terminated by addition of 0.1 mL of sodium bisulfite (300 mg/mL). After neutralization with saturated $NaHCO_3$ solution, the reaction mixture was extracted with ethyl acetate (3 × 1 mL). The combined ethyl acetate layers were condensed to dryness, and the remaining residue was dissolved in EtOH. The desired product, [^{125}I](*R,S*)-5, was purified by HPLC using a reverse phase column (PRP-1 column, Hamilton) eluted with an isocratic solvent of 80% acetonitrile–20% pH 7.0 buffer (5 mM 3,3′-dimethylglutaric acid). The fractions containing [^{125}I](*R,S*)-5 were collected, condensed, and reextracted with ethyl acetate (3 × 1 mL). The solution containing no-carrier-added product, [^{125}I]-(*R,S*)-5, was condensed to dryness and redissolved in a small amount of EtOH (radiochemical yield 50–70%, purity >99%). Chiral separation of the *R* and *S* isomers was performed by HPLC using a 4.1-mm × 250-mm chiracel OD column (Diacel Industries) eluting with *n*-hexanes/ethanol (90/10) at a flow rate of 0.5 mL/min. The retention time for the [^{125}I](*R*)-5 and -(*S*)-5 was 13.6 and 15.9 min, respectively. Radiochemical purity was >98%, and the yield was 80% for the chiral separation step.

Alternatively, radioiodinated stereoisomers were prepared from the enantiomerically pure corresponding tin derivatives without further chiral separation using the same iododestannylation procedure. The radioiodinated isomers were then purified by reverse-phase HPLC. The desired products obtained from the direct labeling were compared with the isomers obtained from chiral separation by the optical purity and receptor binding analysis.

Receptor Binding. The *Spodoptera frugiperda* (Sf9) cells infected with the recombinant baculovirus AcMNPVrD3 were used for the evaluation of the radioiodinated ligands. The membrane homogenates of AcMNPVrD3-infected Sf9 cells, which were expressing D3 dopamine receptors, were prepared as described previously.[14] Binding assays were performed in glass tubes (12 × 75 mm) in a final volume of 0.2 mL. The buffer used for the dilution contained 50 mM Tris, pH 7.4, and the protease inhibitors mixture. In saturation experiments, increasing concentrations of radioiodinated ligands (0.01–2 nM) in 100 μL of buffer were incubated with 50 μL of the cell membrane homogenates (200 times dilution with above buffer containing 0.2% BSA). After incubation for 60 min at 25 °C, the bound ligand was separated from the free ligand by filtration through glass-fiber filters no. 25 (Schleicher &Schuell, Keene, NH) soaked with 1% poly(ethylenimine). The filters were then washed twice with 4 mL of ice-cold buffer (containing 50 mM Tris-HCl, pH 7.4), and the radioactivity on the filters was counted in a γ counter (Packard 5000) with 70% efficiency. The nonspecific binding was defined with 1 μM (*R,S*)-7-OH-DPAT. Scatchard isotherms are transformed using the method of Scatchard.[24] Estimation of the K_d and B_{max} values are obtained using unweighed linear regression analysis of transformed data.

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