CHIRAL, POTENTIALLY IRREVERSIBLE LIGANDS FOR THE SIGMA RECEPTOR BASED ON THE STRUCTURE OF 3-(3-HYDROXYPHENYL)-*N*-PROPYLPIPERIDINE (3-PPP)

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Abstract - (+)-3-PPP is an optically active, highly potent and selective ligand for sigma receptors. The resolved enantiomeric pairs of potential irreversible sigma ligands (5a,b) and (9a,b) were designed and synthesized based on the structure of 3-PPP. An improved method of resolution was developed for the common intermediate (2a,b).

Sigma receptors, brain and peripheral binding sites for several drugs with central nervous system actions, have recently been the subject of much investigation.[1] These sites are distinct from any known neurotransmitter or hormone receptor. Drugs with high affinities for these receptors include certain dextrorotatory opiates such as dextromethorphan and (+)-*N*-allylnormetazocine, typical antipsychotics such as haloperidol, and phencyclidine-related compounds. Though the functions of these sites are still largely unknown, they are likely to mediate at least some of the physiological and behavioral effects of the compounds that bind to them. Among the *in vivo* effects recently reported to be potentially mediated by sigma receptors are antipsychotic activity,[2] cerebroprotection,[3,4] and regulation of posture and movement.[5] Sigma receptors may also be involved in the etiology of certain genetic motor disorders such as dystonia[6] as well as in the untoward motor side-effects produced by some typical neuroleptics.[7]

Several potent and selective ligands exist for the study of sigma receptors, including 1,3-di-*o*-tolylguanidine (DTG),[8] (+)-pentazocine,[9] and the phenylpiperidine (+)-3-(3-hydroxyphenyl)-*N*-propyl piperidine ((+)-3-PPP). Originally synthesized as a dopamine autoreceptor agonist,[10] (+)-3-PPP was found to exhibit high affinity and relative selectivity for sigma receptors.[11,12] (+)-3-PPP and other ligands have recently been used to investigate the heterogeneity of sigma sites.[13,14] DTG binds with equal affinity to sigma-1 and sigma-2 sites, (+)-3-PPP shows moderate preference for sigma-1 sites, while (+)-pentazocine and other (+)-opiates are highly selective for sigma-1 sites. Interestingly, while DTG and (+)-pentazocine have

shown efficacy in functional assays of sigma sites, the actions of (+)-3-PPP at sigma sites have proven to be anomalous.[1]

Irreversible ligands have proven to be important tools for the characterization of receptors.[15] Such compounds react covalently with a specific receptor residue, producing an irreversible attachment to the receptor in question. Many successful irreversible affinity ligands for CNS and peripheral receptors and enzymes contain the isothiocyanato group. The isothiocyanato group is a moiety of choice because it reacts readily with amino and sulfhydryl groups, which are generously distributed in biomolecules. Furthermore, the isothiocyanato group does not readily react with water or alcohols. An isothiocyanato analog of DTG (DIGIT) has been synthesized and shown to be a potent and selective irreversible probe for sigma receptors.[16] Here we describe the synthesis of (5a,b) and (9a,b), optically pure, isothiocyanato derivatives of 3-PPP. These compounds should be useful in investigations of sigma receptor function and the mode of interaction of (+)-3-PPP with sigma sites.

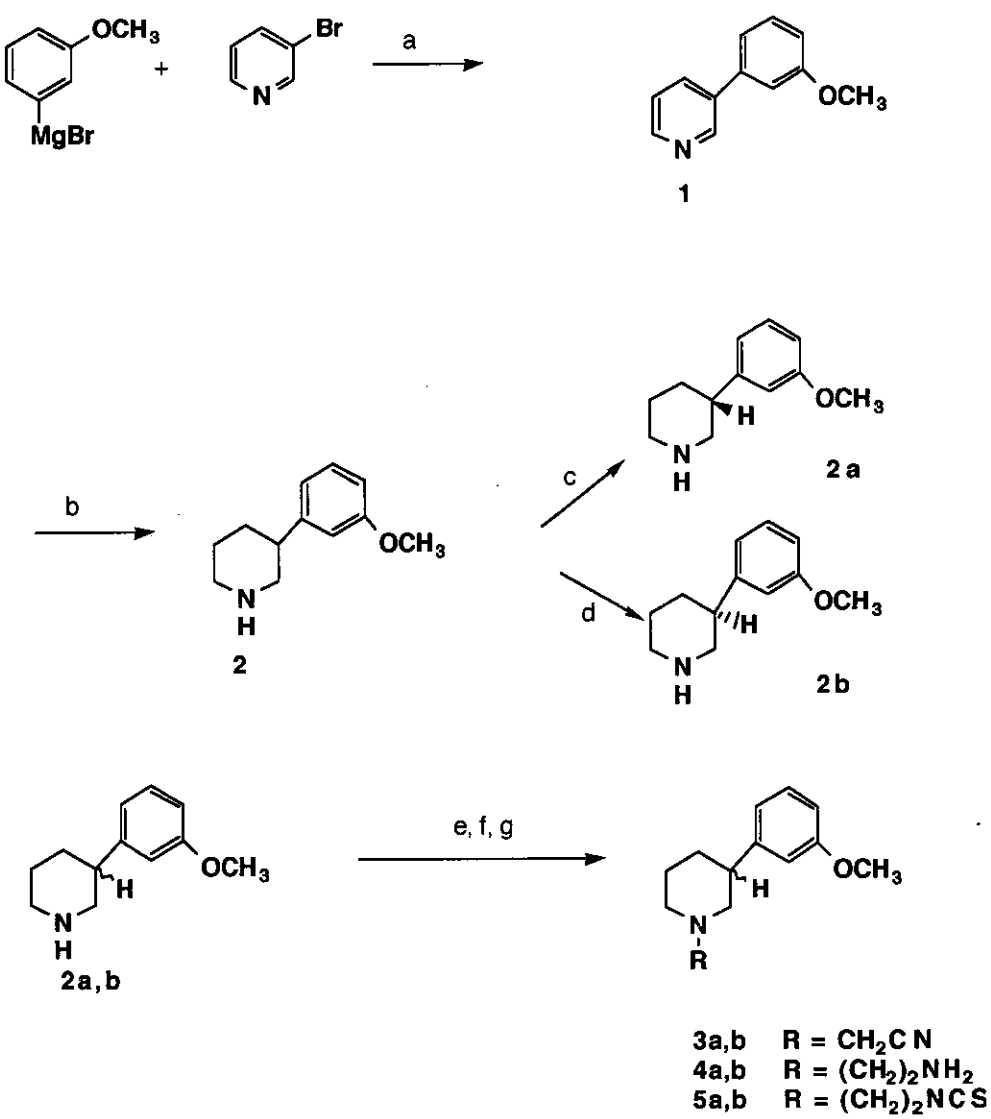
It was desirable to resolve the chiral ligands (5a,b) and (9a,b) because of the problems associated with the use of racemates in biological studies [17,18] and the higher potency that (+)-3-PPP exhibits at σ-receptors than does its (-)-isomer.[19]

The racemic intermediate (2a,b) for both of the two sets of enantiomeric isothiocyanates was previously synthesized and resolved by Hacksell *et al.*[20,21] in their original syntheses of (+)- and (-)-3-PPP. It was our goal to devise a more efficient method of resolution for this intermediate.

We started our synthesis (Scheme I) with the preparation of resolved 3-(3-methoxyphenyl)piperidine (2a,b) as a convenient common intermediate for the final products (5a,b) and (9a,b). As the first step, 3-(3-methoxyphenyl)pyridine (1) was prepared according to the method of Hacksell *et al.*[20] by reacting 3-methoxyphenyl-magnesium bromide, prepared in situ from 3-bromoanisole, with 3-bromopyridine in the presence of the coupling agent bis(triphenylphosphine)nickel (II) chloride. The reduced product (2a,b) was obtained by hydrogenation of the pyridine ring in acidic solution over PtO_2.

The resolution of the racemic mixture of (2a,b) was accomplished by Wikström, *et al.*[21] through two different, laborious, multistep methods involving the formation of covalent, *N*-derivatized intermediates and chromatographic purifications. We desired a simpler, less time-consuming approach to the resolution. The racemic mixture of the free amines readily formed a salt with D- and L-tartaric acids in methanol, and recrystallization of the salts yielded enantiomerically pure samples. The HCl salts of the corresponding free bases exhibited optical rotations identical to the reported literature values[21] for the resolved compounds (+10.3°, -10.1°). The optical purity of (2a) and (2b) was measured utilizing the method of Rittle *et al.*[22] The free amines were reacted with *N'*, *N''*-dicyclohexylcarbodiimide (DCC) and

Scheme I[a]



[a](a) $[(C_6H_5)_3P]_2NiCl_2$; (b) PtO_2/H_2; (c) L-(+)-tartaric acid; (d) D(-)-tartaric acid;

(e) $BrCH_2CN$, DMF; (f) LAH, THF; (g) ClCSCl, $CHCl_3$

N-α-*t*-butyloxycarbonyl-L-alanine in *N*,*N*-dimethylformamide (DMF) containing 1-hydroxybenzotriazole hydrate (to prevent racemization). GC analysis (230 °C) of the

resulting amide derivatives showed a 1:99 ratio of diastereomeric isomers for the resolved material, whereas in the case of the racemic mixture, the expected 1:1 ratio was found. In order to test the accuracy of this method, diastereomeric amides were produced from two samples of α-methylbenzylamine, standards of known purities (>99%, 98%). GC analysis (180 °C) of the amides showed the expected purities of 100% and >99%, respectively. This method of determining optical purity was then judged to be accurate within ± 1%.

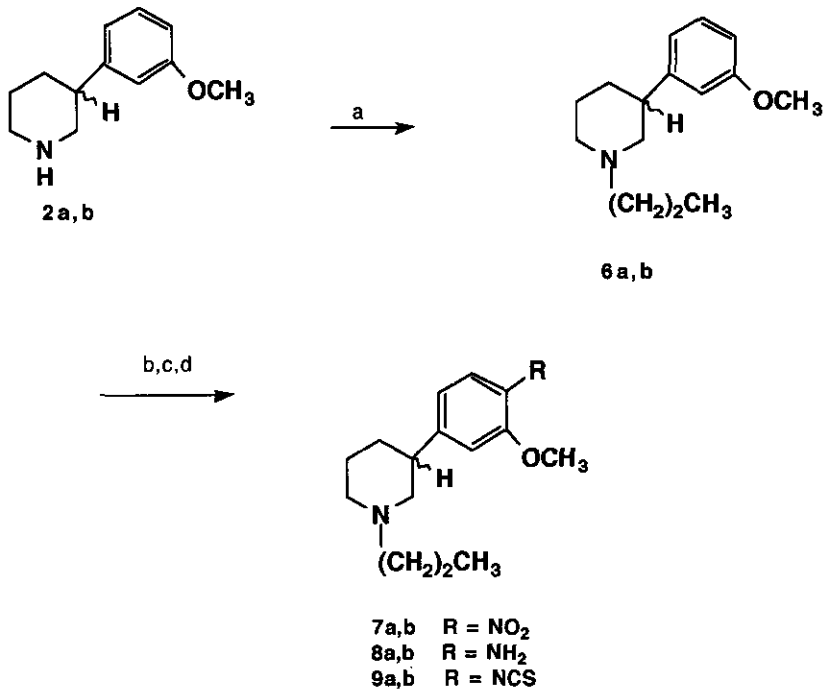
Other literature methods for measuring the optical purity of secondary amines proved to be unsuccessful in this case. The method of Rice and Brossi[23] has been successful in determining the optical purity of *N*-norreticulines; accordingly, the free amine (2a) or (2b) was reacted with (+)- or (-)-α-methylbenzylisocyanate, and the resulting urea was analyzed by ^{1}H nmr. However, a baseline resolution was not obtained to give reliable integration of the peaks produced by the α-methyl groups in the diastereomeric ureas. The ureas were also inseparable by tlc or hplc. In another attempt, the salt of Mosher's acid was formed with the free amine (2a) or (2b) and subjected to ^{1}H nmr and ^{19}F nmr according to the method of Villani *et al.*[24] Despite the use of a variety of solvents ($CDCl_3$, pyridine-d_5, and benzene-d_6), once again, analysis was not possible by this method.

The commercially available (Aldrich) derivatizing agent (S)-(-)-*N*-(trifluoroacetyl)-prolyl chloride readily reacts with an equimolar amount of the free amine (2a) or (2b) in CH_2Cl_2 in the presence of triethylamine. The diastereomeric amides produced were easily separable by gc (170 °C/2 min, 10 °Cmin^{-1}, 220 °C/10 min), but the resulting chromatograph indicated an optical purity <90%. In order to test the reliability of this method, diastereomeric amides were produced from two standard samples of α-methylbenzylamine with known purities (>99%, 98%). Gc analysis (180 °C) of their corresponding amide derivatives indicated optical purities of 89.0% and 88.7%, respectively. This information indicated that the derivatizing agent (S)-(-)-*N*-(trifluoroacetyl)prolyl chloride possesses an optical purity no better than 90%, or that partial racemization of the prolyl moiety occurs during the reaction.

The *N*-cyano derivatives (3a) and (3b) were obtained by reacting (2a) or (2b) with bromoacetonitrile in the presence of $NaHCO_3$. Reduction of the cyano moieties with lithium aluminum hydride (LAH) afforded the corresponding amino compounds (4a) and (4b). The final products, (5a) and (5b) were obtained by reaction of (4a) and (4b) with thiophosgene in hydrocarbon-stabilized $CHCl_3$.

Resolved *N*-propyl-3-(3-methoxyphenyl)piperidine (6a,b) was synthesized from (2a) or (2b) (Scheme II) by reaction with 1-bromopropane in the presence of $NaHCO_3$. The corresponding 4-nitrophenyl derivatives (7a,b) were obtained by nitration of (6a) or (6b) at low temperature with fuming nitric acid in an acetic acid-sulfuric acid mixture. The amino derivatives, (8a,b) were formed by reduction of

Scheme II[a]



[a](a) $Br(CH_2)_2CH_3$, DMF; (b) HNO_3, H_2SO_4-HOAc; (c) H_2, Pd/C; (d) ClCSCl, $CHCl_3$

(7a,b) over Pd/C under an atmosphere of hydrogen. Reaction of (8a,b) with thiophosgene in hydrocarbon-stabilized $CHCl_3$ produced the target compounds (9a) and (9b).

Preliminary biological results suggest that the R-(+)-isomers of compounds (5) and (9) interact specifically and irreversibly with sites labeled by the sigma-selective probe [^{3}H]-(+)-3-PPP. In experiments where guinea pig brain membranes were pretreated with various concentrations of (5a), 50% inhibition of sigma binding (IC_{50}) occurred at 12 μM. Compound (9a) was markedly more potent, with an IC_{50} of 40 nM. The inhibition for both compounds was wash-resistant, suggesting irreversible inhibition. Neither isothiocyanate had effects on binding of [^{3}H]-TCP ([^{3}H]-1-[1-(2-thienyl)]-cyclohexylpiperidine) to PCP (phencylidine) receptors.

Detailed studies of the effect of these compounds on sigma binding will be presented elsewhere.

EXPERIMENTAL

General

Melting points were determined on a Thomas-Hoover capillary apparatus and are corrected. Specific rotations at the sodium-D line were obtained in a 1 dM cell using a Perkin-Elmer 241-MC polarimeter (automatic). Gas chromatographic (gc) analysis was performed on a Hewlett-Packard 5880A instrument fitted with a 30 M SE-30 capillary column and a flame ionization detector. Elemental analyses were performed at Atlantic Microlabs, Atlanta, GA. Chemical-ionization mass spectra (CIms) were obtained using a Finnigan 1015 mass spectrometer. Electron-impact (EIms) and high resolution mass spectra were obtained using a VG-Micro Mass 7070F mass spectrometer. ^{1}H nmr, ^{19}F nmr and ^{13}C nmr spectra were obtained using a Varian XL-300 spectrometer. Thin-layer chromatography (tlc) was performed on 250 μ Analtech GHLF silica gel plates. Centrifugal tlc was performed on a Harrison model 7924 chromatotron with Analtech precast rotors coated with silica gel GF.

3-(3-Methoxyphenyl)pyridine (1).[19] The title compound was prepared by reacting 3-methoxyphenylmagnesium bromide (267 mmol) with 3-bromopyridine (24.8 g, 157 mmol) in the presence of a catalytic amount of bis(triphenylphosphine)-nickel (II) chloride (1.58 g, 2.40 mmol). The product was isolated by acid-base extraction to afford 22.2 g (76.2 %) of a light yellow oil, $bp_{0.25}$ 160 °C, gc purity (90 °C/3 min, 30 °Cmin^{-1}, 150 °C/5 min) >95%. The oil was purified by chromatography (SiO_2, ether: petroleum ether [1:2]) to obtain 17.4 g (60%) of clear, colorless oil, pure by gas and thin layer chromatography ($CHCl_3$:CH_3OH:NH_4OH [90: 10:1]); CIms (NH_3) m/z 186 (M + 1); ^{1}H nmr ($CDCl_3$) δ 3.88 (s, 3H, OCH_3), 6.94 (dd, J = 8.2, 2.4 Hz, 1H, PhH_4), 7.11 (d, J = 1.9 Hz, 1H, PhH_2), 7.17 (d, J = 8.2 Hz, 1H, PhH_6), 7.34-7.43 (m, 2H, PhH_5 + PyH_5), 7.86 (dt, J = 2.0, 7.87 Hz, 1H, PyH_4), 8.60 (dd, J = 3.6, 1.0 Hz, 1H, PyH_6), 8.85 (d, J = 2.0 Hz, 1H, PyH_2).

3-(3-Methoxyphenyl)piperidine (2).[19] 3-(3-Methoxyphenyl)pyridine (1, 17.4 g, 94 mmol) was dissolved in 160 ml of CH_3OH and concd HCl (26 ml) and PtO_2 (1.58 g) were added. The mixture was shaken in a Parr hydrogenation apparatus under hydrogen at 55 psi for 3 h. The catalyst was removed by filtration through celite filtering aid and the concentrated filtrate was purified by distillation to yield 16.3 g (90.7 %) of clear, colorless oil, bp_1 155 °C; pure by gas (150 °C) and thin layer chromatography ($CHCl_3$:CH_3OH:NH_4OH [90:10:1]); CIms (NH_3) m/z 192 (M + 1); ^{1}H nmr (C_6D_6) δ 0.97-1.10 (m, 2H, H_5), 1.50-1.70(m, 2H, H_4), 2.27 (t, J = 12.0 Hz, 2H), 2.89(d,

J = 12.1 Hz, 1H, H_3), 3.02-3.15 (m, 2H, H_2), 3.70(s, 3H, OCH_3), 6.60-6.70(m, 3H, $ArH_{3,4,5}$), 7.15-7.20(m, 1H, ArH_2).

3-(3-Methoxyphenyl)piperidine (2a.Tartrate). D-(-)-Tartaric acid (12.2 g, 81.0 mmol) dissolved in boiling CH_3OH (25 ml) was added to a hot solution of racemic (2) (15.5 g, 0.081 mol) in hot CH_3OH (30 ml). After one day, the precipitated salt (19.8 g, 71%) was collected by filtration, dried in vacuo, and recrystallized three times from aqueous CH_3OH to obtain 9.7 g (35%) of white, crystalline solid, mp (HCl salt) 170.5-172° C; $[\alpha]_D^{25}$ (HCl salt) -10.1° (CH_3OH, c = 1.59). Anal. Calcd for $C_{16}H_{23}NO_7$: C, 56.30; H, 6.79; N 4.10. Found: C, 56.40; H 6.83; N, 4.07.

(2b.Tartrate). The free amine (8.20 g, 42.5 mmol) isolated from the mother liquors of (2a) was dissolved in hot CH_3OH (3 ml) and a boiling solution of L-(+)-tartaric acid (6.44 g, 42.5 mmol) in CH_3OH (10 ml) was added. The precipitated salt was isolated as above and recrystallized once from aqueous CH_3OH to obtain 8.23 g (30%) of white, crystalline solid, mp(HCl salt) 170.5-171.5 °C; $[\alpha]_D^{25}$ +10.3 ° (CH_3OH, c = 1.48).

Determination of optical purity. The amine (7.44 mg, 0.037mmol), racemic or resolved, was dissolved in DMF (0.5 ml) containing DCC (7.0 mg, 0.034 mmol), *N*-α-*t*-butyloxycarbonyl-L-alanine (7.0 mg, 0.037 mmol), and 1-hydroxybenzotriazole hydrate (0.001 g, 0.007 mmol). The resulting solutions were stirred for 0.5 h, then diluted with a 0.1 N HCl solution, extracted with ethyl acetate, and the organic layer was filtered. Gc analysis of the filtrate was performed at 230 °C and the results are discussed in the introduction to this paper.

(R)-*N*-Cyanomethyl-3-(3-methoxyphenyl)piperidine (3a). A solution of resolved (2a) (1.77 g, 9.27 mmol), $NaHCO_3$ (3.12 g, 37.1 mmol) and bromoacetonitrile (0.71 ml, 10 mmol) in DMF (10 ml) was stirred under nitrogen at ambient temperature for 5 h. The solution was then dissolved in water and extracted with ether (3 x 10 ml). The combined organic layers were dried (K_2CO_3), filtered, and the filtrate was concentrated to obtain an oil which was purified by chromatography (SiO_2, CH_3OH:$CHCl_3$ [1:9]) to yield the product (3a) (1.77 g, 83%) as a clear, colorless oil. The oxalate salt was obtained in isopropanol and recrystallized from CH_3OH, mp(oxalate salt) 106-107 °C; Elms m/z 230 (M); ir (neat, free base) 2230 (CN) cm^{-1}; $[\alpha]_D^{25}$ + 2.7° (H_2O, c = 1.44). Anal. Calcd for $C_{16}H_{20}N_2O_5$: C, 59.99; H, 6.29; N, 8.75. Found: C, 60.06; H, 6.30; N, 8.75.

(S)-*N*-Cyanomethyl-3-(3-methoxyphenyl)piperidine (3b). The same procedure used to obtain (3a) was used to prepare (3b), substituting (2b) for (2a). The oxalate salt was obtained from isopropanol and recrystallized from CH_3OH, mp (oxalate salt) 105-106 °C; Elms m/z 230 (M); $[\alpha]_D^{25}$ -3.0 ° (H_2O, c = 1.44).

(R)-*N*-(2-Aminoethyl)-3-(3-methoxyphenyl)piperidine (4a). A solution of LAH (30 ml of a 1.0 M solution in tetrahydrofuran (THF), 30 mmol) was stirred at 0 °C under inert atmosphere while a solution of (3a) (5.85 g, 25.4 mmol) in THF (10 ml) was added dropwise. The resulting mixture was stirred at 0 °C for 3 h, when concd NH_4OH (30 ml) and ether (30 ml) were cautiously added. The biphasic solution was vigorously stirred, the upper organic layer was removed and a fresh aliquot of ether (30 ml) was added, and the procedure was repeated. The combined organic layers were dried (Na_2SO_4) and concentrated to obtain a yellow oil (4.96 g, 84%). The oxalate salt was obtained from isopropanol and recrystallized from CH_3OH, mp (oxalate salt) 123-125 °C; CIms (NH_3) m/z 235 (M + 1); ir (neat, free base) shows disappearance of CN at 2230 cm^{-1}; $[\alpha]_D^{25}$ + 8.4 ° (H_2O, c = 0.50). Anal. Calcd for $C_{16}H_{24}N_2O_5.2H_2O$: C, 53.32; H, 7.83; N, 7.77. Found: C, 53.62; H, 7.85; N, 7.71.

(S)-*N*-(2-Aminoethyl)-3-(3-methoxyphenyl)piperidine (4b). The same procedure used to obtain (4a) was used to prepare (4b), substituting (3b) for (3a). The oxalate salt was obtained from CH_3OH, mp 124-125 °C; CIms (NH_3) m/z 235 (M + 1); $[\alpha]_D^{25}$ -6.0 ° (H_2O, c = 0.50).

(R)-*N*-(2-Isothiocyanatoethyl)-3-(3-methoxyphenyl)piperidine (5a). A solution of 0.41 g (1.2 mmol) of the oxalate salt of (4a) and 0.64 g (7.3 mmol) of $NaHCO_3$ in water (25 ml) was stirred as a biphasic solution with hydrocarbon-stabilized $CHCl_3$ (63 ml). A solution of freshly distilled thiophosgene (0.13 ml, 1.9 mmol) in hydrocarbon-stabilized $CHCl_3$ (10 ml) was added dropwise and the mixture was stirred for 15 min. The layers were separated, the aqueous layer was washed once with $CHCl_3$ (5 ml) and the combined organic layers were washed once with water (5 ml). The organic layers were dried (Na_2SO_4) and concentrated to obtain an orange oil. The oxalate salt (0.26 g, 62%) was obtained as a cream-colored solid from isopropanol and recrystallized from ethanol, mp (oxalate salt) 113.5-114.5 °C; CIms (NH_3) m/z 277(M + 1); ir (neat, free base) 2100 (NCS) cm^{-1}; $[\alpha]_D^{25}$ +60.0 ° (DMF, c = 1.4). Anal. Calcd for $C_{17}H_{22}N_2O_5S$: C, 55.72; H, 6.05; N, 7.65. Found: C, 55.81; H, 6.10; N, 7.62.

(S)-*N*-(2-Isothiocyanatoethyl)-3-(3-methoxyphenyl)piperidine (5b). The same procedure used to obtain (5a) was used to prepare (5b), substituting (4b) for (4a). The oxalate salt was obtained from isopropanol and recrystallized from ethanol, mp 113-114 °C; CIms (NH_3) m/z 277 (M + 1); $[\alpha]_D^{25}$ -58 ° (DMF, c = 0.7). Anal. Calcd for $C_{17}H_{22}N_2O_5S$: C, 55.72; H, 6.05; N, 7.65. Found: C, 56.01; H, 6.02; N, 7.42.

(R)-*N*-Propyl-3-(3-methoxyphenyl)piperidine (6a). A mixture of resolved (2a) (2.0 g, 11 mmol), 1-bromopropane (1.1 ml, 12 mmol) and $NaHCO_3$ (3.5 g, 42

mmol) was stirred at ambient temperature under inert atmosphere in DMF (5 ml) for 48 h. The mixture was filtered and the filtrate was concentrated in vacuo to obtain a dark yellow residue. The residue was dissolved in 10 ml of water and extracted with ether (4 x 10 ml). The combined organic layers were washed once with brine, dried (Na_2SO_4), and concentrated to obtain 1.7 g (71%) of yellow oil. The hydrobromide salt was obtained from CH_3OH, mp (HBr salt) 190-191 °C; CIms (NH_3) m/z 234 (M + 1); $[\alpha]_D^{25}$ +7.2 ° (CH_3OH, c = 0.7). Anal. Calcd for $C_{15}H_{24}NOBr$: C, 57.33; H, 7.70; N, 4.46. Found: C, 57.26; H, 7.75; N, 4.44.

(S)-*N*-Propyl-3-(3-methoxyphenyl)piperidine (6b). The same procedure used to obtain (5a) was used to prepare (5b), substituting (4b) for (4a). The HBr salt was obtained from CH_3OH, mp 191-192 °C; CIms (NH_3) m/z 234 (M + 1); $[\alpha]_D^{25}$ -6.7 ° (CH_3OH, c = 3.0). Anal. Calcd for $C_{15}H_{24}NOBr$: C, 57.33; H, 7.70; N, 4.46. Found: C, 57.55; H, 7.89; N, 4.32.

(R)-*N*-Propyl-3-(3-methoxy-4-nitrophenyl)piperidine (7a). A solution of (6a) (0.78 g, 3.3 mmol) in an acetic acid-sulfuric acid mixture (20 ml, 1:1 v/v) was stirred under inert atmosphere with an overhead stirring apparatus at 5 °C. A mixture of fuming nitric acid (0.23 ml) in an acetic acid-sulfuric acid mixture (20 ml, 1:1 v/v) was added all at once to the amine. The resulting solution was stirred vigorously for 20 min until gc (185 °C/2.0 min, 30 °Cmin^{-1}, 220 °C/5 min) showed complete consumption of the starting material. The reaction was then cooled with a dry ice-acetone bath and concd. NH_4OH (approximately 80 ml) was added cautiously, with stirring, until the pH of the solution was basic. The aqueous solution was extracted with ether (5 x 20 ml) and the combined organic layers were washed with a saturated $NaHCO_3$ solution. The ethereal layer was dried (Na_2SO_4) and concentrated to obtain 0.88 g of a viscous, yellow oil. The oil was purified by repetitive centrifugal chromatography (4 mm plate, THF:hexanes:NH_4OH [2.0:0.9:0.1]) to obtain 0.22 g (24%) of a light yellow oil, pure by tlc and gc, CIms (NH_3) m/z 279 (M + 1), 249 (M - NO); ^1H nmr ($CDCl_3$) δ 0.91 (t, J= 7.33Hz, 3H, CH_3), 1.52-2.03 (m, 6H, CH_2), 2.27-2.36 (m, 3H, CH_2N + CH), 2.86-2.99 (m, 4H, CH_2N), 3.96 (s, 3H, OCH_3), 6.90 (d, J = 8.3 Hz, 1H, ArH_5), 6.97 (d, J = 6.4 Hz, 1H, ArH_2), 7.82 (d, J = 8.3 Hz, 1H, ArH_6). The substitution pattern of the aromatic ring was determined using 1-dimensional NOE difference nmr ($CDCl_3$). Irradiation at δ 4.0 (OCH_3) produced an NOE difference spectrum showing enhancement only at δ 6.9. This finding eliminates the possibility of 3,5- or 3,6-substitution patterns on the aromatic ring. In conjuction with the ^1H nmr spectrum, we conclude that the substituents are arranged in a 3,4-pattern.

(S)-*N*-Propyl-3-(3-methoxy-4-nitrophenyl)piperidine (7b). The same procedure used to obtain (7a) was used to prepare (7b), substituting (6b) for (6a). The yellow oil obtained by chromatography was pure by tlc and gc, CIms (NH_3) m/z 279 (M + 1).

(R)-*N*-Propyl-3-(3-methoxy-4-aminophenyl)piperidine (8a). A solution of 0.16 g (0.57 mmol) of (7a) in absolute CH_3OH (12 ml) was acidified with concd HCl. The nitro compound was then reduced over 10% Pd/C (50 mg) under 50 psi on a Parr hydrogenation apparatus for 1.5 h. The catalyst was removed by filtration through celite filter aid and the yellow filtrate was concentrated to an oil. The oil was dissolved in H_2O (5 ml) and concd NH_4OH was added until the pH of the resulting solution was 11. The aqueous suspension was extracted with ether (4 x 5ml) and the combined organic layers were dried (K_2CO_3) and concentrated to obtain 0.13 g (92%) of a yellow oil, pure by tlc ($CHCl_3$:CH_3OH:NH_4OH [90:10:1]), which was used without further purification; CIms (NH_3) m/z 249 (M + 1), 234 (M - CH_3).

(S)-*N*-Propyl-3-(3-methoxy-4-aminophenyl)piperidine (8b). The same procedure used to obtain (8a) was used to prepare (8b), substituting (7b) for (7a). The yellow oil was pure by tlc ($CHCl_3$:CH_3OH:NH_4OH [90:10:1]) and was used without further purification; CIms (NH_3) m/z 249 (M + 1), 234 (M - CH_3).

(R)-*N*-Propyl-3-(3-methoxy-4-isothiocyanatophenyl)piperidine (9a). A solution of 0.26 g (3.1 mmol) of $NaHCO_3$ in water (10 ml) was added to a solution of (8a) (0.13 g, 0.52 mmol) in hydrocarbon-stabilized $CHCl_3$ (32 ml). The biphasic solution was stirred at ambient temperature under inert atmosphere for 2 min. A solution of 40 µl (0.52 mmol) of freshly distilled thiophosgene in hydrocarbon-stabilized $CHCl_3$ (3 ml) was then added dropwise. After 5 min, the phases were separated and the aqueous layer was washed once with $CHCl_3$. The combined organic layers were washed once with brine, dried (Na_2SO_4), and concentrated to obtain 0.12 g of yellow oil. The oil was purified by chromatography (SiO_2, acetone:$CHCl_3$ [1:1]) to obtain 0.04 g (26%) of clear, colorless oil. The di-*p*-toluoyltartaric acid salt was crystallized from 95% ethanol, mp (di-*p*-toluoyltartaric acid salt) 144-45 °C; CIms (NH_3) m/z 291 (M + 1); ir (neat, free base) 2050, 2150 (NCS) cm^{-1}; $[\alpha]_D^{25}$ + 5.5 ° (DMF, c = 0.4). Anal. Calcd for $C_{36}H_{40}N_2O_9S$: C, 63.89; H, 5.96; N, 4.14. Found: C, 63.78; H, 6.00; N, 4.15.

(S)-*N*-Propyl-3-(3-methoxy-4-isothiocyanatophenyl)piperidine (9b). The same procedure used to obtain (9a) was used to prepare (9b), substituting (8b) for (8a). The di-*p*-toluoyl tartaric acid salt was crystallized from aqueous ethanol, mp 143-145 °C; CIms (NH_3) m/z 291 (M + 1); $[\alpha]_D^{25}$ -5.1° (DMF, c = 0.5). Anal. Calcd for $C_{36}H_{40}N_2O_9S$: C, 63.89; H, 5.96; N, 4.14. Found: C, 63.57; H, 5.70; N, 4.10.

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