Synthesis and Dopamine Transporter Affinity of the Four Stereoisomers of (±)-2-(Methoxycarbonyl)-7-methyl-3-phenyl-7-azabicyclo[2.2.1]heptane

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Received August 1, 1997

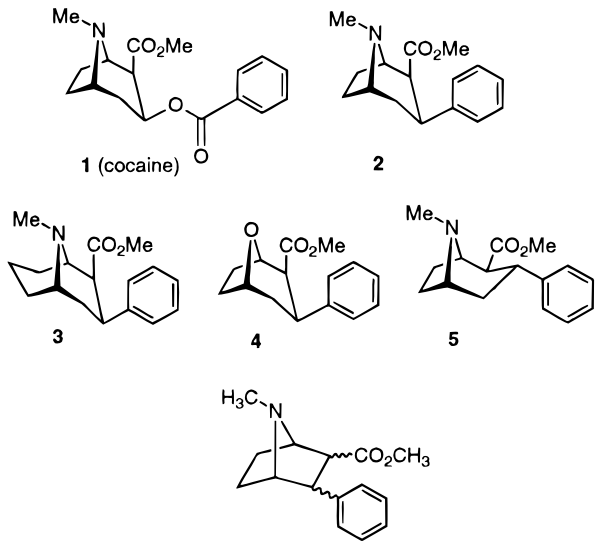
All four stereoisomers of (±)-2-(methoxycarbonyl)-7-methyl-3-phenyl-7-azabicyclo[2.2.1]heptane were synthesized and evaluated as cocaine binding site ligands at the dopamine transporter. The in vitro binding affinities (K_i) of the 7-azabicyclo[2.2.1]heptane derivatives were measured in rat caudate−putamen tissue and found to be 100−3000-fold less potent (K_i = 5−96 μM) than cocaine and 2β-(methoxycarbonyl)-3β-phenyltropane (**2**, WIN 35,065-2). Surprisingly, the 3α-phenyl isomers (**6c**, **6d**) were more potent than the 3β-phenyl isomers (**6a**, **6b**). Molecular modeling studies revealed that the rigid 7-azabicyclo[2.2.1]heptane derivatives possess molecular topologies which are significantly different than the molecular topologies of the 2β-(methoxycarbonyl)-3-phenyltropanes.

Introduction

The elucidation of the pharmacophore for the cocaine (**1**) binding site(s) on the dopamine transporter (DAT) has been the subject of numerous investigations. From these studies a great number of tropane and non-tropane compounds have been synthesized and shown to exhibit high affinity for binding sites on the DAT and elicit potent inhibition of dopamine reuptake.[1−25] Among the tropanes that have been studied, the derivatives of 2β-(methoxycarbonyl)-3β-phenyltropane (WIN 35,065-2, **2**) have provided useful information toward understanding the structural criteria for high-affinity binding and transporter selectivity at monoamine transporters.[1−16]

As part of a study aimed at the structural elucidation of the cocaine pharmacophore, it was of interest to explore the effects of structural modification of the tropane skeleton of **2** on molecular recognition at cocaine binding sites on the DAT. Previous studies had revealed that the 9-azabicyclo[3.3.1]nonane analogue **3** exhibited diminished activity at the DAT relative to the tropane analogue **2**.[26] This demonstrated the sensitivity of the cocaine binding site toward structural modification of the C(6)−C(7) ethylene bridge of cocaine and the importance of the tropane ring system for high-affinity binding.

Recently, Meltzer et al. have elegantly demonstrated the importance of nonionic hydrogen-bond formation for proper orientation of 2β-(methoxycarbonyl)-3β-phenyltropanes (**2**) and 2β-(methoxycarbonyl)-3β-phenyl-8-oxatropanes (**4**) at monoamine transporter binding sites.[16] From the results of this study it was proposed that the nature of the hydrogen bond between the transporter protein and the heteroatom at the 8-position of the tropane ring affects the position of the 3-phenyl ring relative to its corresponding acceptor site on the transporter. Subsequently, the strength of the $\pi-\pi$ or lipophilic interactions between the 3-phenyl ring and the transporter was believed to be the source of the observed potency and selectivity of the ligand. In addition, it was shown that ligand potency among derivatives of **2** was not affected by altering the stereochemistry at C(3).[16] The high affinity and selectivity observed for the analogues of 2β-(methoxycarbonyl)-3α-phenyltropane (**5**)[16,27] was thought to be due to the ability of the ligand to adopt a boat conformation such that its molecular topology was not significantly different from that determined for derivatives of **2**.[16] This topology is defined by the relative proximity and stereochemical orientation of the nitrogen atom, the centroid of the phenyl ring, and the 2β-substituent.[16] These results clearly suggest that, in addition to minimum structural requirements, a specific molecular topology



6a 2β, 3β-isomer
6b 2α, 3β-isomer
6c 2β, 3α-isomer
6d 2α, 3α-isomer

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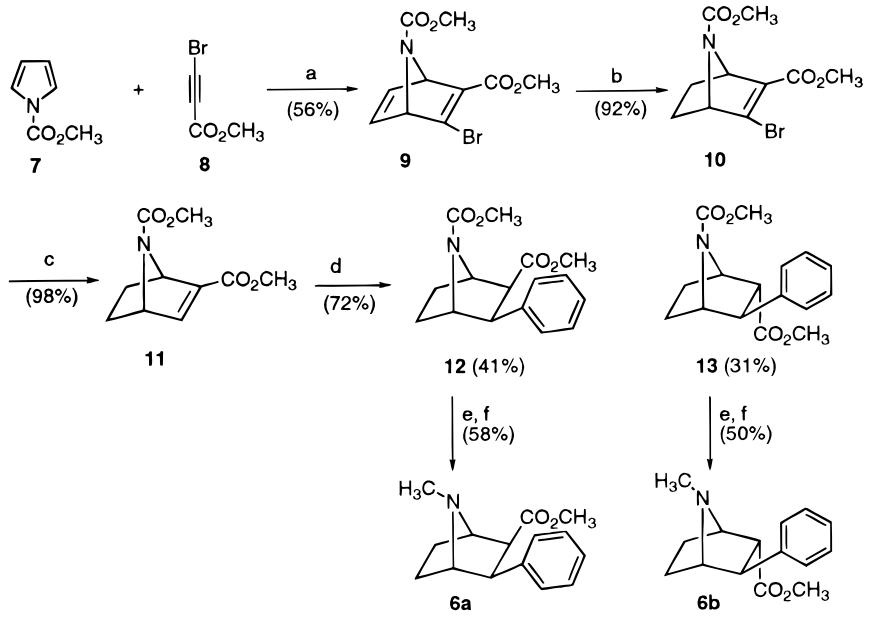
S0022-2623(97)00506-2 CCC: $15.00
Published on Web 05/15/1998

Scheme 1[a]



[a] Reagents: (a) 90−95 °C; (b) Ni_2B, EtOH; (c) Zn−Ag, MeOH; (d) PhMgBr, Et_2O, −40 °C; then TFA, −78 °C; (e) HBr−AcOH; (f) HCHO, $NaBH_3CN$.

is necessary for high-affinity binding and transporter selectivity. In addition, it seems that relative stereochemistry is less important as long as the ligand can adopt a stable conformation which meets the required molecular topology of the binding site.

To further address the importance of the topology imparted by the tropane ring of **2**, **4**, and **5** for molecular recognition at cocaine binding site(s) on the DAT, we have synthesized the ring-contracted analogues of **2**, the 7-azabicyclo[2.2.1]heptane derivatives **6a**−**d**. It was envisaged that incorporation of the basic structural features of 2-(methoxycarbonyl)-3-phenyltropane DAT ligands into the rigid 7-azabicyclo[2.2.1]heptane ring system would provide DAT ligands with well-defined molecular topologies and perhaps provide additional insight into the topological requirements of the DAT pharmacophore. Herein we report the synthesis and DAT binding affinity of the four stereoisomers of (±)-2-(methoxycarbonyl)-7-methyl-3-phenyl-7-azabicyclo-[2.2.1]heptane (**6**).

Chemistry

As illustrated in Scheme 1, the construction of the 7-azabicyclo[2.2.1]heptane ring system was achieved by heating methyl 3-bromopropiolate (**8**)[28] with a 4-fold excess of *N*-(methoxycarbonyl)pyrrole (**7**)[29] at 90−95 °C for 33 h.[30] This furnished the cycloadduct **9** in 56% yield.[31] Selective reduction of the least substituted double bond of **9** was achieved by using nickel boride and afforded **10** in 92% yield. Debromination of **10** with Zn−Ag couple provided **11** in almost quantitative yield (98%).[32] Treatment of **11** with phenylmagnesium bromide and subsequent workup with trifluoroacetic acid at low temperature furnished a mixture of 2β-isomer **12** (41%) and 2α-isomer **13** (31%), which were easily separated by chromatography. Removal of the *N*-methoxycarbonyl group of **12** and N-methylation afforded the desired 2β,3β-isomer **6a** in 58% overall yield. The 2α,3β-isomer **6b** was prepared in similar fashion from **13**.

To synthesize the 3α-isomers **6c** and **6d** an alternate approach was developed from the 7-azabicyclo[2.2.1]-heptene derivative **10** (Scheme 2). The Suzuki reaction of **10** with phenylboronic acid in the presence of a palladium(0) catalyst furnished the coupling product **14** in almost quantitative yield.[33] Reduction of the carbon−carbon double bond of **14** using magnesium in methanol gave **15** as the major product (51%) along with **13** (32%).[34] Conversion of **15** into **6c** then proceeded in 83% overall yield.

Finally, the 2α,3α-isomer **6d** was prepared by hydrogenation (40 psi) of **14** over 5% palladium on carbon in methanol. The reaction was found to proceed stereoselectively to give the 2α,3α-isomer **16** in high yield (95%). Conversion of **16** into **6d** was then achieved in 78% yield.

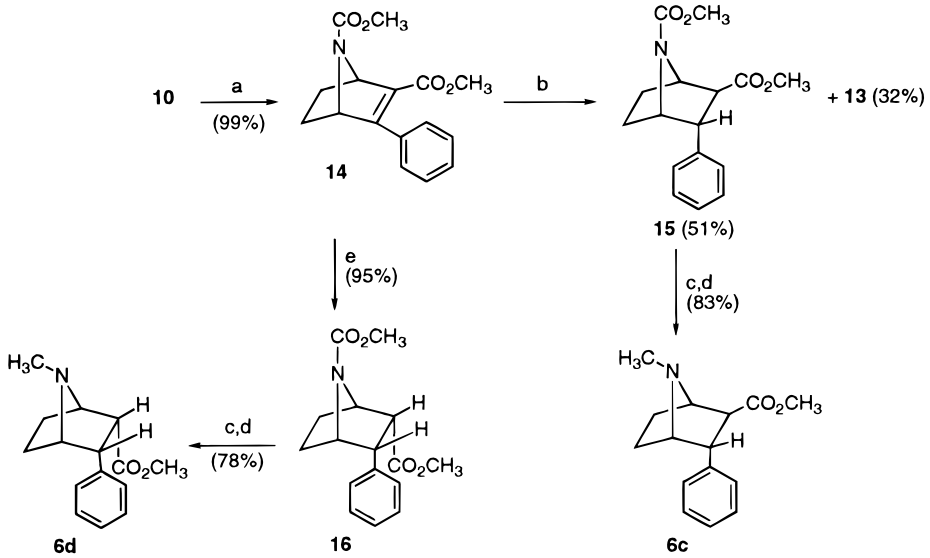
Biology

Compounds **6a**−**d** were tested for their ability to displace bound [^{3}H]WIN 35,428 from rat caudate−putamen tissue. The K_i values reported in Table 1 are inhibition constants derived for the unlabeled ligands.[35] Previous studies have shown that, cocaine (**1**) and WIN 35,065-2 (**2**) modeled better for two binding sites than for one; as a consequence, their high-affinity and low-affinity K_i values are given in Table 1.[35,36] The 7-azabicyclo[2.2.1]heptane derivatives **6a**−**d** exhibited monophasic binding; hence a single K_i value is reported for each compound in Table 1. The inhibition of dopamine uptake was not measured due to the low potency of the stereoisomers **6a**−**d**.

Results and Discussion

Despite the similar stereochemical orientations of the 3β-phenyl group and the 2β-methoxycarbonyl group in **2** relative to **6a**, the latter displayed dramatically reduced binding affinity for DAT. As shown in Table 1, the 2β,3β-isomer **6a** was 2000-fold less potent than the high-affinity binding components of **1** and **2**. Of the

Scheme 2[a]



[a] Reagents: (a) $PhB(OH)_2$, Na_2CO_3, $Pd(OAc)_2$, PPh_3, EtOH, benzene; (b) Mg, MeOH; (c) HBr−AcOH; (d) HCHO, $NaBH_3CN$; (e) H_2 (40 psi), 5% Pd/C, MeOH.

Table 1. K_i Values of 7-Azabicyclo[2.2.1]heptane Derivatives **6a**−**d** for the Inhibition of Bound [^{3}H]win 35,428[a]

compd	K_i (μM)	compd	K_i (μM)
1[b]	0.032 ± 0.005	**6a**[c]	60.4 ± 4.8[d]
	0.39 ± 0.22	**6b**[e]	96.5 ± 42[d]
2[b]	0.033 ± 0.017	**6c**[c]	5.62 ± 0.39
	0.31 ± 0.22	**6d**[c]	18.9 ± 1.7

[a] All values are the mean ± SEM of three experiments performed in triplicate. [b] The K_i values for these drugs are reproduced from ref 35 and were collected under conditions identical with the present ones. [c] Tested as the oxalate salt. [d] Incomplete inhibition at 100 μM; only 50% inhibition was observed. [e] Tested as the hydrochloride salt.

four isomers, the 2β,3α-isomer **6c** was the most potent derivative, albeit 100-fold less potent than **1** and **2**. It is noteworthy that among the 7-azabicyclo[2.2.1]heptane derivatives, the 3α-isomers **6c** and **6d** were considerably more potent than the 3β-isomers **6a** and **6b** which exhibited incomplete inhibition (50%) of [^{3}H]WIN 35,-428 at a concentration of 100 μM.

To address the low affinity observed for the 7-azabicyclo[2.2.1]heptane derivatives **6a**−**d** the molecular topologies of the compounds were compared with those of the tropane derivatives **2** and **5**. To compare the molecular topologies of the 7-azabicyclo[2.2.1]heptane derivatives **6a** and **6c** with those of the tropanes **2** and **5**, fully geometry-optimized structures were obtained with SYBYL 6.0 molecular modeling software.[37] Initially, the structures were energy-minimized by a MAXIMIN2 force field. The minimized structures were then geometry optimized with an AM1 (MOPAC) calculation. The minimized structures were then aligned by least-squares fitting of C(1), C(5), C(6), C(7), and N(8) of **2** and **5** with C(1), C(4), C(5), C(6), and N(7) of **6a** and **6c** using the FIT option of SYBYL 6.0.[37]

The differences between the molecular topologies of the 7-azabicyclo[2.2.1]heptane derivatives **6a** and **6c** and the tropane derivatives **2** and **5** are clearly evident from the overlaid structures shown in Figure 1. The most striking difference between the four molecules was the intramolecular distance between the phenyl group and the nitrogen atom. The phenyl groups of **6a** and **6c** were found to be much closer to the nitrogen atom than were the phenyl groups of **2** and **5**. This suggests

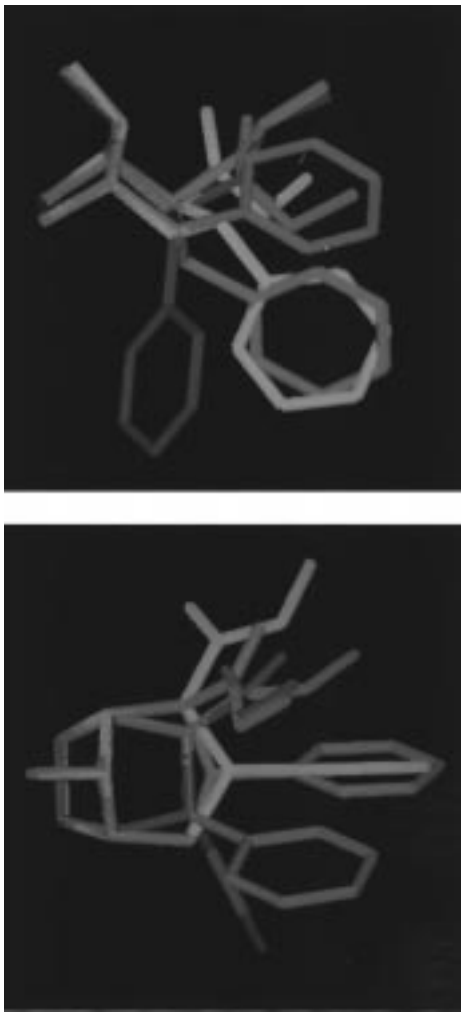


Figure 1. (a, Top) Side view of overlaid structures **2** (cyan), **5** (yellow), **6a** (green), and **6c** (magenta). (b, Bottom) Top view of overlaid structures **2** (cyan), **5** (yellow), **6a** (green), and **6c** (magenta).

that the molecular topologies of **6a** and **6c** are more compressed than the tropane derivatives. The degree to which the molecular topologies of **6a** and **6c** are compressed can be quantified by measurement of the nitrogen atom−phenyl centroid distance (N−Ph_C). From the geometry-optimized structures the calculated N−Ph_C distance for **6a** was 4.2 Å and for **6c** was 5.0 Å while the N−Ph_C distances for **2** (5.6 Å)[2] and **5** (5.5 Å) were significantly longer.[37] In addition, the spacial orientations of the phenyl groups of **6a** and **6c** were significanly different relative to **2** and **5**. The phenyl groups of **6a** and **6c** are displaced from the molecular plane which passes through the nitrogen atom and bisects the molecule through the C(2)−C(3) and C(5)−C(6) bonds. However, the phenyl groups of **2** and **5** are included in the bisecting plane which passes through the nitrogen atom, C(3), and the middle of C(6)−C(7) ethylene bridge. (Figure 1b).

This molecular analysis suggests that despite similar functional groups and relative stereochemistry, the source of the low affinity of the 7-azabicyclo[2.2.1]-heptane derivatives **6a**−**d** is due to the unique molecular topologies imparted by the rigid 7-azabicyclo[2.2.1]-heptane ring system. It is likely that the compressed topologies observed for **6a** and **6c** do not permit sufficient penetration of the phenyl ring into the binding site to elicit similar potencies for the 3-phenyltropanes **2** and **5**. In addition, the large displacement of the phenyl groups of **6a**−**d** from the plane bisecting the tropanes through C(3), N(8), and the middle of the C(5)−C(6) bond may also contribute to the low affinity observed for **6a** and **6c**. Among the 7-azabicyclo[2.2.1]-heptane derivatives **6a**−**d** a similar trend of the effect of topology compression was observed. The less compressed topologies of the 3α-isomers **6c** and **6d** are believed to permit a slightly greater penetration of the phenyl ring into the binding site which results in the modest affinity observed for these ligands while the more compressed 3*β*-derivatives **6a** and **6b** exhibit lower affinity. This suggests that it may be possible to design 7-azabicyclo[2.2.1]heptane derivatives which could adopt a molecular topology similar to the tropane analogues and thus display high affinity for cocaine binding sites on the DAT.

In summary, the results of this study indicate that the molecular topology defined by stereoisomeric (±)-2-(methoxycarbonyl)-7-methyl-3-phenyl-7-azabicyclo-[2.2.1]heptanes **6a-d** is significanly different from that defined by similarly substituted tropanes (e.g., **2** and **5**). Due to the poor affinty of **6a**−**d**, we conclude that the 8-heterobicyclo[3.2.1]heptane ring system (tropane and 8-oxatropane) is extremely important for imparting a molecular topology among 2*β*-(methoxycarbonyl)-3-phenyltropane derivatives that is recognized by the cocaine binding site on the DAT.

Experimental Section

All chemicals were purchased from Aldrich Chemical Co., Milwaukee, WI, unless otherwise noted. Ether and benzene were dried by distillation from Na/benzophenone. Methanol and acetone were dried by distillation over Drierite. Chromatography refers to flash chromatography on silica gel (silica gel 60, 230−400 mesh, E. M. Science), and petroleum ether refers to pentanes with a boiling point range of 30−60 °C. Reported melting points are uncorrected. Elemental analyses were obtained from Atlantic Microlabs, Inc., Norcross, GA.

3-Bromo-2,7-bis(methoxycarbonyl)-7-azabicyclo[2.2.1]-hepta-2,5-diene (9). A mixture of *N*-(methoxycarbonyl)-pyrrole (**7**)[29] (9.2 g, 74 mmol) and methyl 3-bromopropiolate (**8**)[28] (2.4 g, 15 mmol) was stirred at 90−95 °C under an argon atmosphere for 33 h. The resulting mixture was cooled to room temperature and subjected to chromatography (EtOAc/petroleum ether; 1:12). The first fractions contained unreacted **7** (7.5 g), followed by the adduct **9** (2.4 g, 56% based on **7**) as a light yellow oil: IR (NaCl) 2959, 1717, 1617, 1445, 1339, 1226 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 7.14 (br s, 2H), 5.56 (s, 1H), 5.22 (s, 1H), 3.79 (s, 3H), 3.69 (s, 3H); ^{13}C NMR ($CDCl_3$) *δ* 162.5, 154.8, 143.8, 143.7, 141.1, 141.0, 74.4, 68.3, 53.1, 51.8; MS (CI, CH_4) *m/z* 290 ($M^+ + 1$, 40), 258 (87), 256 (90), 208 (100). Anal. ($C_{10}H_{10}BrNO_4$) C, H, N.

3-Bromo-2,7-bis(methoxycarbonyl)-7-azabicyclo[2.2.1]-hept-2-ene (10). To a solution of nickel(II) acetate tetrahydrate (3.0 g, 12 mmol) in ethanol/water (12 mL, 5:1) was added dropwise with stirring under argon a solution of sodium borohydride (0.46 g, 12.1 mmol) in ethanol (12 mL) at room temperature. The resulting black slurry was stirred for an additional 10 min. To the slurry was added a solution of **9** (700 mg, 2.42 mmol) in THF (12 mL) over 15 min followed by dropwise addition of concentrated hydrochloric acid (2 mL, 24 mmol). The mixture was stirred for 24 h and then filtered through a pad of Celite. The filtrate was washed with dichloromethane (20 mL) and carefully rendered basic (pH 8−9) using a saturated sodium bicarbonate solution. The organic layer was separated and dried (Na_2SO_4). After evaporation of the solvents, the residue was subjected to chromatography (EtOAc/petroleum; 1:6) to give **10** (660 mg, 92%) as a colorless oil: IR (NaCl) 1727, 1606, 1444, 1278, 1243, 788 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 5.05 (s, 1H), 4.79 (s, 1H), 3.79 (s, 3H), 3.66 (s, 3H), 2.00 (m, 2H), 1.39 (m, 2H); ^{13}C NMR ($CDCl_3$) *δ* 162.2, 155.3, 136.9, 135.2, 68.4, 62.5, 52.9, 51.8, 25.8, 24.6; MS (CI, CH_4) *m/z* 292 ($M^+ + 1$, 43), 290 ($M^+ + 1$, 45), 260 (98), 258 (100). Anal. ($C_{10}H_{12}BrNO_4$) C, H, N.

2,7-Bis(methoxycarbonyl)-7-azabicyclo[2.2.1]heptane-2-ene (11). Aqueous 10% HCl (5 mL) was added to Zn dust (710 mg, 11 mmol) with stirring. After 5 min, the liquid was decanted and the Zn was washed with acetone (2 × 5 mL) and ether (5 mL). A suspension of silver acetate (25 mg, 0.15 mmol) in boiling acetic acid (2 mL) was added with stirring. After 1 min, the supernatant was decanted and the black Zn−Ag couple was washed with acetic acid (3 mL), ether (4 × 5 mL), and methanol (5 mL). To the moist Zn−Ag couple was added a solution of **10** (500 mg, 1.7 mmol) in methanol (2.5 mL). The resulting suspension was stirred at room temperature and monitored by TLC. After 24 h, the metal residue was filtered and washed with methanol. The filtrate was evaporated under reduced pressure, and the residue was partitioned between ether (5 × 10 mL) and 10% HCl (5 mL). The combined ether layers were dried (Na_2SO_4) and evaporated. The residue was purified by chromatography (EtOAc/petroleum ether; 1:6) to afford **11** (360 mg, 98%) as a colorless oil: IR (NaCl) 1727, 1455, 1379, 1293, 793 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 7.03 (s, 1H), 5.05 (s, 1H), 4.88 (s, 1H), 3.77 (s, 3H), 3.66 (s, 3H), 1.99 (m, 2H), 1.24 (m, 2H); ^{13}C NMR ($CDCl_3$) *δ* 163.3, 155.6, 144.3, 144.1, 61.1, 59.8, 52.8, 51.9, 24.3, 24.2; MS (CI, CH_4) *m/z* 212 ($M^+ + 1$, 100), 180 (98). Anal. ($C_{10}H_{13}NO_4$) C, H, N.

2*β*,7-Bis(methoxycarbonyl)-3*β*-phenyl-7-azabicyclo[2.2.1]-heptane (12) and 2α,7-bis(methoxycarbonyl)-3*β*-phenyl-7-azabicyclo[2.2.1]heptane (13). To a freshly prepared solution of phenylmagnesium bromide (6.0 mmol) in ether (15 mL) at −40 °C was added dropwise a solution of **11** (630 mg, 3.0 mmol) in ether (8 mL). The reaction mixture was stirred for an additional 2 h at − 40 °C, cooled to − 78 °C, quenched with trifluoroacetic acid and allowed to warm to room temperature. The mixture was then diluted with water (15 mL), rendered to pH = 7 with aqueous sodium bicarbonate and extracted with ether (3 × 15 mL). The organic phase was dried (Na_2SO_4) and separated by chromatography (EtOAc/petroleum ether, 1:5), which afforded **13** (270 mg, 31%) followed by **12** (350 mg, 41%). The 2*β*,3*β*-isomer **12** was isolated as a colorless

oil which solidified on standing: mp 88−89 °C; IR (NaCl) 1747, 1712, 1460, 1369, 753, 703 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.26−7.16 (m, 5H), 4.67 (s, 1H), 4.45 (m, 1H), 3.76 (s, 3H), 3.28 (d, J = 9.9 Hz, 1H), 3.03 (d, J = 9.9 Hz, 1H), 3.02 (s, 3H), 1.87 (m, 2H), 1.59 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 171.1, 155.6, 140.2, 128.0, 127.9, 126.8, 61.3, 61.2, 57.2, 54.9, 52.6, 52.3, 50.9, 29.6, 28.3; MS (CI, CH_4) m/z 290 (M^+ + 1, 80), 258 (100). Anal. ($C_{16}H_{19}NO_4$) C, H, N. **13**: colorless oil which solidified on standing; mp 64−66 °C; IR (NaCl) 1740, 1712, 1465, 1369, 1182, 753, 703 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30−7.19 (m, 5H), 4.65 (br s, 1H), 4.37 (br s, 1H), 3.71 (s, 3H), 3.70 (s, 3H), 3.31 (d, J = 5.5 Hz, 1H), 3.11 (dd, J = 4.6, 5.5 Hz, 1H), 1.83−1.60 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 172.2, 155.7, 143.9, 128.9, 127.0, 126.7, 62.8, 58.2, 56.8, 52.6, 52.1, 50.3, 29.8, 24.9; MS (CI, CH_4) m/z 290 (M^+ + 1, 100), 258 (22). Anal. ($C_{16}H_{19}NO_4$) C, H, N.

2,7-Bis(methoxycarbonyl)-3-phenyl-7-azabicyclo[2.2.1]-hept-2-ene (14). To a solution of **10** (1.5 g, 5.0 mmol) and benzeneboronic acid (0.73 g, 6.0 mmol) in ethanol−benzene (1:5, 30 mL) were added 2 M Na_2CO_3 (5.0 mL, 10.0 mmol), $Pd(OAc)_2$ (55 mg, 0.25 mmol), and Ph_3P (140 mg, 0.50 mmol) under argon. The mixture was refluxed for 7 h under an argon atmosphere. After the mixture was cooled to room temperature, water (10 mL) was added, and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic fractions were washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified by chromatography (EtOAc/petroleum ether, 1:10) to furnish **14** (1.4 g, 99%) as a colorless oil: IR (NaCl) 2969, 1717, 1606, 1446, 1288, 764, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.62 (m, 2H), 7.39 (m, 3H), 5.15 (s, 1H), 5.11 (s, 1H), 3.74 (s, 3H), 3.67 (s, 3H), 2.10 (m, 2H), 1.50 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 164.0, 155.6, 131.7, 129.4, 128.7, 128.1, 65.6, 62.8, 52.8, 51.6, 26.0, 25.5; MS (CI, CH_4) m/z 288 (M^+ + 1, 19), 259 (58), 256 (100). Anal. ($C_{16}H_{17}NO_4$) C, H, N.

2β,7-Bis(methoxycarbonyl)-3α-phenyl-7-azabicyclo-[2.2.1]heptane (15). A mixture of **14** (290 mg, 1.0 mmol) and magnesium turnings (240 mg, 10 mmol) in methanol (10 mL) was stirred at room temperature for 2 h. A solution of 2 N HCl was carefully added until the excess magnesium dissolved and the solution was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The resulting isomers were separated by chromatography (EtOAc/petroleum ether; 1:8) which afforded **13** (93 mg, 32%) and the desired compound **15** (148 mg, 51%) as a colorless oil: IR (NaCl) 1742, 1717, 1460, 1374, 1182, 743, 708 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40−7.19 (m, 5H), 4.63 (br s, 1H), 4.54 (br s, 1H), 3.93 (dd, J = 5.4, 5.0 Hz, 1H), 3.71 (s, 3H), 3.70 (s, 3H), 2.81 (d, J = 5.4 Hz, 1H), 1.88 (m, 1H), 1.55 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 173.3, 155.7, 138.1, 128.5, 127.9, 60.7, 60.6, 52.6, 52.4, 51.8, 50.3, 30.1, 23.1; MS (CI, CH_4) m/z 290 (M^+ + 1, 100), 214 (10). Anal. ($C_{16}H_{19}NO_4$) C, H, N.

2α,7-Dimethoxycarbonyl-3α-phenyl-7-azabicyclo[2.2.1]-heptane (16). To a solution of **14** (290 mg, 1.0 mmol) in methanol (10 mL) was added 5% Pd/C (30 mg), and the mixture was hydrogenated (40 psi) overnight. The catalyst was removed by filtration and the solvent evaporated. The residue was chromatographed (EtOAc/petroleum ether, 1:6) to give **16** (280 mg, 95%) as a colorless oil: IR (NaCl) 1740, 1714, 1460, 1349, 1187, 743, 708 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30−7.20 (m, 3H), 7.08−7.05 (m, 2H), 4.52 (br s, 1H), 4.37 (br s, 1H), 3.78 (m, 1H), 3.74 (s, 3H), 3.40 (s, 4H), 2.43 (m, 1H), 1.88 (m, 2H), 1.62 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 171.8, 155.7, 137.3, 128.5, 128.1, 126.6, 61.9, 59.0, 52.5, 51.1, 48.6, 48.5, 24.6, 23.6; MS (CI, CH_4) m/z 290 (M^+ + 1, 100), 258 (31), 127 (74). Anal. ($C_{16}H_{19}NO_4$) C, H, N.

Preparation of 6a−d (General Procedure). A solution of the corresponding 7-(methoxycarbonyl)-7-azabicyclo[2.2.1]-heptane derivative(1.2 mmol) in 33% HBr−HOAc (10 mL) was stirred at room temperature and monitored by TLC. After 40 h, the solvent was removed under reduced pressure, the residue was dissolved in CH_2Cl_2 (20 mL), and water (10 mL) was added. Saturated aqueous Na_2CO_3 was carefully added to adjust the pH to 10−11. The organic layer was removed, and the water layer was then extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were dried (K_2CO_3) and evaporated under reduced pressure. The resulting residue was purified by chromatography ($MeOH/CH_2Cl_2$, 1:10) to afford the corresponding amine. To a stirred mixture of the amine (0.6 mmol) and aqueous formaldehyde (0.52 mL, 6.4 mmol, 37%) in acetonitrile (10 mL) was added sodium cyanoborohydride (80 mg, 1.3 mmol). The reaction mixture was stirred for 45 min. The solution was made neutral by the addition of glacial acetic acid and then stirred for 2 h. The solution was then made basic by the addition of aqueous Na_2CO_3 and extracted with CH_2Cl_2 (4 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was then purified by chromatography (acetone/petroleum ether, 1:6). The spectral data for **6a−d** are reported for the freebase. The freebase was then converted into the oxalate or hydrochloride salts to give white hygroscopic solids used for microanalysis and in vitro testing.

2β-(Methoxycarbonyl)-7-methyl-3β-phenyl-7-azabicyclo-[2.2.1]heptane (6a): colorless oil (58%); IR (NaCl) 2959, 1743, 1601, 1217, 753, 708 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.57−7.55 (m, 2H), 7.34−7.23 (m, 3H), 3.73 (d, J = 2.8 Hz, 1H), 3.39 (d, J = 2.8 Hz, 1H), 3.17 (d, J = 10.3 Hz, 1H), 3.09 (s, 3H), 2.95 (d, J = 10.3 Hz, 1H), 2.47 (s, 3H), 2.09 (m, 2H), 1.53 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 172.1, 142.5, 128.5, 127.6, 126.2, 67.4, 62.2, 55.7, 53.4, 50.6, 34.7, 26.2, 25.2; MS (CI, CH_4) m/z 246 (M^+ + 1, 100), 214 (10); mp 144−145 °C (oxalate salt). Anal. ($C_{15}H_{19}NO_2 \cdot 2C_2H_2O_4$) C, H, N.

2α-(Methoxycarbonyl)-7-methyl-3β-phenyl-7-azabicyclo-[2.2.1]heptane (6b): colorless oil (50%); IR (NaCl) 1740, 1220, 750, 708 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45−7.43 (m, 2H), 7.29−7.27 (m, 2H), 7.20 (m, 1H), 3.69 (s, 3H), 3.59 (t, J = 4.4 Hz, 1H), 3.35 (d, J = 4.2 Hz, 1H), 3.12 (d, J = 5.6 Hz, 1H), 3.01 (dd, J = 5.6, 4.2 Hz, 1H), 2.30 (s, 3H), 1.98−1.80 (m, 2H), 1.52−1.40 (m, 2H); MS (CI, CH_4) m/z 246 (M^+ + 1, 100), 214 (15); mp 225−226 °C (HCl salt). Anal. ($C_{15}H_{19}NO_2 \cdot HCl \cdot 0.1\ H_2O$) C, H, N.

2β-(Methoxycarbonyl)-7-Methyl-3α-phenyl-7-azabicyclo-[2.2.1]heptane (6c): colorless oil (83%); IR (NaCl) 1740, 1220, 750, 708 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34−7.17 (m, 5H), 3.86 (br s, 1H), 3.73−3.65 (m, 4H), 3.51 (dd, J = 4.6, 4.2 Hz, 1H), 2.65 (d, J = 4.6 Hz, 1H), 2.34 (s, 3H), 1.94 (m, 1H), 1.60 (m, 1H), 1.35 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 174.3, 139.7, 139.7, 128.2, 127.8, 127.8, 126.2, 66.5, 65.6, 52.1, 50.4, 34.9, 27.1, 20.5; MS (CI, CH_4) m/z 246 (M^+ + 1, 100), 214 (15); mp 205−207 °C (oxalate salt). Anal. ($C_{15}H_{19}NO_2 \cdot 1.5C_2H_2O_4$) C, H, N.

2α-(Methoxycarbonyl)-7-methyl-3α-phenyl-7-azabicyclo-[2.2.1]hepatne (6d): colorless oil (78%); IR (NaCl) 1730, 1465, 1253, 1182, 743, 713 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.29−7.16 (m, 3H), 7.05−7.02 (m, 2H), 3.80 (dd, J = 12.3, 4.0 Hz, 1H), 3.52−3.34 (m, 6H), 2.43 (s, 3H), 2.31 (m, 1H), 1.79 (m, 1H), 1.73 (m, 1H), 1.62 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 173.1, 138.7, 128.9, 128.0, 126.3, 67.7, 64.6, 51.1, 48.5, 47.9, 34.3, 22.6, 21.5; MS (CI, CH_4) m/z 246 (M^+ + 1, 100), 214 (10); mp 188−189 °C (oxalate salt). Anal. ($C_{15}H_{19}NO_2 \cdot C_2H_2O_4$) C, H, N.

Acknowledgment. We are grateful to the National Institute on Drug Abuse (NIDA First Award R29 DA08055) for the financial support of this research.

References

(1) Carroll, F. I.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. Cocaine receptor: Biochemical characterization and structure−activity relationships of cocaine analogues at the dopamine transporter. *J. Med. Chem.* **1992**, *35*, 969−981.

(2) Carroll, F. I.; Gao, Y.; Rahman, M.; Abraham, P.; Parham, K.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. Synthesis, Ligand Binding, QSAR and CoMFA Study of 3β-(*p*-substituted phenyl)-tropane-2β-carboxylic acid methyl esters. *J. Med. Chem.* **1991**, *34*, 2719−2725.

(3) Carroll, F. I.; Mascarella, S. W.; Kuzemko, M. A.; Gao, Y.; Abraham, P.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. Synthesis, ligand binding and QSAR (CoMFA and classical) study 3β-(3′-substituted phenyl)-, 3β-(4′-substituted phenyl)-, and 3β-(3′,4′-disubstituted phenyl)tropane-2β-carboxylic acid methyl esters. *J. Med. Chem.* **1994**, *37*, 2865−2873.

(4) Kozikowski, A. P.; Saiah, M. K. E.; Johnson, K. M.; Bergmann, J. S. Chemistry and biology of the 2β-alkyl-3β-phenyl analogues of cocaine: Subnanomolar affinity ligands that suggest a new pharmacophore model at the C-2 position. *J. Med. Chem.* **1995**, *38*, 3086−3093.
(5) Kotian, P.; Mascarella, S. W.; Abraham, P.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J.; Carroll, F. I. Synthesis, ligand binding and quantitative structure−activity relationship study of 3β-(4′-substituted phenyl)-2β-heterocyclic tropanes: Evidence for an electrostatic interaction at the 2β-position. *J. Med. Chem.* **1996**, *39*, 2753−2763.
(6) Davies, H. M. L.; Saikali, E.; Huby, N. J. S.; Gilliatt, V. J.; Matasi, J. J.; Sexton, T.; Childers, S. R. Synthesis of 2β-acyl-3β-aryl-8-azabicyclo[3.2.1]octanes and their binding affinities at dopamine and serotonin transport sites in rat striatum and frontal cortex. *J. Med. Chem.* **1994**, *37*, 1262−1268.
(7) Kelkar, S. V.; Izenwasser, S.; Katz, J. L.; Klein, C. L.; Zhu, N.; Trudell, M. L. Synthesis, cocaine receptor affinity and dopamaine uptake inhibition of several new 2β-substituted 3β-phenyltropanes. *J. Med. Chem.* **1994**, *37*, 3875−3877.
(8) Carroll, F. I.; Kotian, P.; Dehghani, A.; Gray, J. L.; Kuzemko, M. A.; Parham, K. A.; Abraham, P.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. Cocaine and 3β-(4′-substituted phenyl)tropane-2β-carboxylic acid ester and amide analogs. New high-affinity and selective compounds for the dopamine transporter. *J. Med. Chem.* **1995**, *38*, 379−388.
(9) Kotian, P.; Abraham, P.; Lewin, A. H.; Mascarella, S. W.; Boja, J. W.; Kuhar, M. J.; Carroll, F. I. Synthesis and ligand binding study of 3β-(4′-substituted phenyl)-2β-(heterocyclic)tropanes. *J. Med. Chem.* **1995**, *38*, 3451−3453.
(10) Davies, H. M. L.; Kuhn, L. A.; Thornley, C.; Matasi, J. J.; Sexton, T.; Childers, S. R. Synthesis of 3β-aryl-8-azabicyclo[3.2.1]octanes with high binding affinities and selectivities for the serotonin transporter site. *J. Med. Chem.* **1996**, *39*, 2554−2558.
(11) Aronson, B.; Enmon, J. L.; Izenwasser, S.; Katz, J. L.; Kelkar, S. V.; Luo, L.; Nolan, S. P.; Trudell, M. L. Synthesis and ligand binding at cocaine receptors of η^6-(2β-carbomethoxy-3β-phenyltropane) transition metal complexes. *J. Med. Chem.* **1996**, *39*, 1560−1563.
(12) Xu, L.; Kelkar, S. V.; Lomenzo, S. A.; Izenwasser, S.; Katz, J. L.; Kline, R. H.; Trudell, M. L. Synthesis, dopamine transporter affinity, dopamine uptake inhibition and locomotor stimulant activity of 2β-substituted-3β-phenyltropane derivatives. *J. Med. Chem.* **1997**, *40*, 858−863.
(13) Chang, A.-C.; Burgess, J. P.; Mascarella, S. W.; Abraham, P.; Kuhar, M. J.; Carroll, F. I. Synthesis and transporter binding properties of 2,3-diphenyltropane stereoisomers. Comparison to 3β-phenyltropane-2β-carboxylic acid esters. *J. Med. Chem.* **1997**, *40*, 1247−1251.
(14) Emond, P.; Garreau, L.; Chalon, S.; Boazi, M.; Caillet, M.; Bricard, J.; Frangin, Y.; Mauclaire, L.; Besnard, J.-C.; Guilloteau, D. Synthesis and ligand binding of nortropane derivatives: *N*-Substituted-2β-carbomethoxy-3-(4′-iodophenyl)nortropane and *N*-(3-iodoprop-(*2E*)-enyl)-2β-carbomethoxy-3β-(3′,4′-disubstituted phenyl)nortropane. New high-affinity and selective compounds for the dopamine transporter. *J. Med. Chem.* **1997**, *40*, 1366−1372.
(15) Thiruvazhi, M.; Abraham, P.; Kuhar, M. J.; Carroll, F. I. Synthesis of the isomers of (*1R*)-3-(phenylthio)tropane-2-carboxylic acid methyl ester. A new class of ligands for the dopamine transporter. *J. Chem. Soc., Chem. Commun.* **1997**, 555−556.
(16) Meltzer, P. C.; Liang, A. Y.; Blundell, P.; Gonzalez, M. D.; Chen, Z.; George, C.; Madras, B. K. 2-Carbomethoxy-3-aryl-8-oxabicyclo[3.2.1]octanes: Potent non-nitrogen inhibitors of monoamine transporters. *J. Med. Chem.* **1997**, *40*, 2661−2673.
(17) Meltzer, P. C.; Liang, A. Y.; Madras, B. K. The discovery of an unusually selective and novel cocaine analog: Difluoropine. Synthesis and inhibition of binding at cocaine recognition sites. *J. Med. Chem.* **1994**, *37*, 2001−2010.
(18) Newman, A. H.; Kline, R. H.; Allen, A. C.; Izenwasser, S.; George, C.; Katz, J. L. Novel 4′-substituted and 4′,4"-disubstituted-3α-(Diphenylmethoxy)tropane analogs as potent and selective dopamine uptake inhibitors. *J. Med. Chem.* **1995**, *38*, 3933−3940.
(19) Kline, R. H.; Izenwasser, S.; Katz, J. L.; Joseph, D. B.; Bowen, W. D.; Newman, A. H. 3′-chloro-3α-(diphenylmethoxy)tropane but not 4′-chloro-3α-(diphenylmethoxy)-tropane produces a cocaine-like behavorial profile. *J. Med. Chem.* **1997**, *40*, 851−857.
(20) Javitch, J. A.; Blaustein, R. O.; Synder, S. H. [^{3}H]Mazindol binding associated with neuronal dopamine and norepinephrine uptake sites. *Mol. Pharmacol.* **1984**, *26*, 35−44.
(21) Van der Zee, P.; Koger, H. S.; Gootjes, J.; Hespe, W. Aryl 1,4-dialk(en)ylpiperazines as selective and very potent inhibitors of dopamine uptake. *Eur. J. Med. Chem.* **1980**, *15*, 363−370.
(22) Matecka, D.; Rice, K. C.; Rothman, R. B.; de Costa, B. R.; Glowa, J. R.; Wojnicki, F. H.; Pert, A.; George, C.; Carroll, F. I.; Silverthorn, M. L.; Dersch, C. M.; Becketts, K. M.; Partilla, J. S. Synthesis and absolute configuration of chiral piperazines related to GBR 12909 as dopamine reuptake inhibitors. *Med. Chem. Res.* **1995**, *5*, 43−53.
(23) Dutta, A. K.; Coffey, L. L.; Reith, M. E. A. Highly selective, novel analogues of 4-[2-(diphenylmethoxy)ethyl]-1-benzylpiperizine for the dopamine transporter: Effect of different aromatic substituents on their affinity and selectivity. *J. Med. Chem.* **1997**, *40*, 35−43.
(24) Matecka, D.; Lewis, D.; Rothman, R. B.; Dersch, C. M.; Wojnicki, F. H. E.; Glowa, J. R.; DeVries, A. C.; Pert, A.; Rice, K. C.; Heteroaromatic analogs of 1-[2-(diphenyl-methoxy)ethyl]- and 1-[2-(bis(4-fluorophenylmethoxy)ethyl]-4-(3-phenylpropyl)-piperizines (GBR 12935 and GBR 12909) as high-affinity dopamine reuptake inhibitors. *J. Med. Chem.* **1997**, *40*, 705−716.
(25) Deutsch, H. M.; Shi, Q.; Gruszecka − Kowalik, E.; Schweri, M. M. Synthesis and pharmacology of potential cocaine antagonists. 2. Structure−activity relationship studies of aromatic ring-substituted methylphenidate analogs. *J. Med. Chem.* **1996**, *39*, 1201−1209.
(26) Chen, Z.; Izenwasser, S.; Katz, J. L.; Klein, C. L.; Zhu, N.; Trudell, M. L. Synthesis and dopamine transporter affinity of 2-methoxycarbonyl-9-methyl-3-phenyl-9-azabicyclo[3.3.1]-nonane derivatives. *J. Med. Chem.* **1996**, *39*, 4744−4749.
(27) Holmquist, C. R.; Keverline-Frantz, K. I.; Abraham, P.; Boja, J. W.; Kuhar, M. J.; Carroll, F. I. 3α-(4-substituted phenyl)tropane-2β-carboxylic acid esters: Novel ligands with unexpectedly high affinity and selectivity at the dopamine transporter. *J. Med Chem.* **1996**, *39*, 4139−4141.
(28) Leroy, J. A convenient procedure for the preparation of 3-bromopropiolic esters. *Synth. Commun.* **1992**, *24*, 567−572.
(29) Gabel, N. W. Diels − Alder reactions of 1-carbomethoxypyrroles and dimethyl acetylenedicarboxylate. *J. Org. Chem.* **1962**, *27*, 301−303.
(30) Chen, Z.; Trudell, M. L. Chemistry of 7-Azabicyclo[2.2.1]hepta-2,5-diene, 7-Azabicyclo[2.2.1]hept-2-ene and 7-Azabicyclo[2.2.1]-heptane Derivatives. *Chem. Rev.* **1996**, *96*, 1179−1193.
(31) Zhang, C.; Trudell, M. L. A short and efficient total synthesis of (±)-epibatidine. *J. Org. Chem.* **1996**, *61*, 7189−7191.
(32) Clark, R. D.; Heathcock, C. H. Preparation and reactions of β-chloro-α,β-unsaturated ketones. *J. Org. Chem.* **1976**, *41*, 636−643.
(33) Miyaura, N.; Suzuki, A. Palladium-catalyzed cross-coupling reactions of organoboron compounds. *Chem. Rev.* **1995**, *95*, 2457−2483.
(34) Hudlicky, T.; Sinai-Zingde, G.; Natchus, M. G. Selective reduction of α,β-unsaturated esters in the presence of olefins. *Tetrahedron Lett.* **1987**, *28*, 5287−5290.
(35) Izenwasser, S.; Terry, P.; Heller, B.; Witkin, J. M.; Katz, J. L. Differential relationships among dopamine transporter affinities and stimulant potencies of various uptake inhibitors. *Eur. J. Pharm.* **1994**, *263*, 277−283.
(36) Katz, J. L.; Newman, A. H.; Izenwasser, S. Relations between heterogeneity of dopamine transporter binding and function and the behavorial pharmaocology of cocaine. *Pharmacol. Biochem. Behav.* **1997**, *57*, 505−512.
(37) Molecular modeling studies were performed with SYBYL 6.0, Tripos Associates, Inc., 1699 S. Hanley Rd., Suite 303, St. Louis, MO 63144-2913.

JM9705061