JOURNAL OF
MEDICINAL
CHEMISTRY

Volume 40, Number 17 August 15, 1997

Expedited Articles

2-Carbomethoxy-3-aryl-8-oxabicyclo[3.2.1]octanes: Potent Non-Nitrogen Inhibitors of Monoamine Transporters†

Peter C. Meltzer,*,‡ Anna Y. Liang,‡ Paul Blundell,‡ Mario D. Gonzalez,‡ Zhengming Chen,‡ Clifford George,§ and Bertha K. Madras||

Organix Inc., 65 Cummings Park, Woburn, Massachusetts 01801, Naval Research Laboratory, Washington, D.C. 20375, and Department of Psychiatry, Harvard Medical School and New England Regional Primate Center, Southborough, Massachusetts 01772

Received May 9, 1997⊗

Cocaine is a potent stimulant of the mammalian central nervous system. Its reinforcing and stimulant properties have been associated with its propensity to bind to monoamine transporter systems. It has generally been assumed that the amino function on monoamines is a requirement for binding to monoamine transporters. In particular, the 8-amino function on the tropane skeleton of cocaine and cocaine analogs has been assumed to provide an ionic bond to the aspartic acid residue on the dopamine transporter (DAT). We have prepared the first 8-oxa analogs of the 3-aryltropanes (WIN compounds) and have found that the 3β-(3,4-dichlorophenyl) (**6g**) and 3α-(3,4-dichlorophenyl) (**7g**) analogs are particularly potent (IC_{50} = 3.27 and 2.34 nM, respectively) inhibitors of the dopamine transporter. We now describe the synthesis and biology of the family of 2-carbomethoxy-3-aryl-8-oxabicyclo[3.2.1]octanes and demonstrate that an amino nitrogen is *not* required for binding to the DAT.

Introduction

Cocaine is a potent stimulant of the mammalian central nervous system. Its reinforcing and stimulant properties have been associated with its propensity to bind to monoamine transporter systems, particularly the dopamine transporter (DAT).[1−10] The 3-aryltropane analogs of cocaine (1*R*)-(2β-carbomethoxy-3β-aryl-8-azabicyclo[3.2.1]octanes) (WIN analogs) (Figure 1) have provided highly potent and selective compounds which bind to monoamine uptake proteins in mammalian caudate-putamen.[11−15] Although there has been a considerable effort to determine structure−activity relationships (SAR) of cocaine and its WIN analogs, these studies have not yet provided a comprehensive picture of the binding interaction to the DAT at the molecular level. Indeed, even though SAR studies on the classical tropane analogs of cocaine[4,5,12,15−17] appeared to provide a consistent model for this interaction, subsequent studies have revealed inconsistencies with the initial reports.[11,13,18−20]

The functional role of the 8-amine in the tropanes is featured in this study. This 8-amine has been proposed to provide an ionic bond[14] between the protonated amine and the presumed aspartate residue on the DAT.[21] However, quaternary cocaine methiodide binds extremely weakly to the DAT,[22] thus implying that such an ionic interaction would most likely result from protonation of the 8-amine by the amino acid itself. The importance of such a protonated 8-amine has been questioned, since reduction of nitrogen basicity by introduction of an *N*-sulfonyl group, sufficient to inhibit protonation of the amine under physiological conditions,

* Mail correspondence to: Dr. Peter C. Meltzer, Organix Inc., 65 Cummings Park, Woburn, MA 01801.
† This manuscript is dedicated to the memory of Anna Liang who passed away on June 10, 1997.
‡ Organix Inc.
§ Naval Research Laboratory.
|| Harvard Medical School and New England Regional Primate Center.
⊗ Abstract published in *Advance ACS Abstracts,* July 15, 1997.

S0022-2623(97)00304-X CCC: $14.00

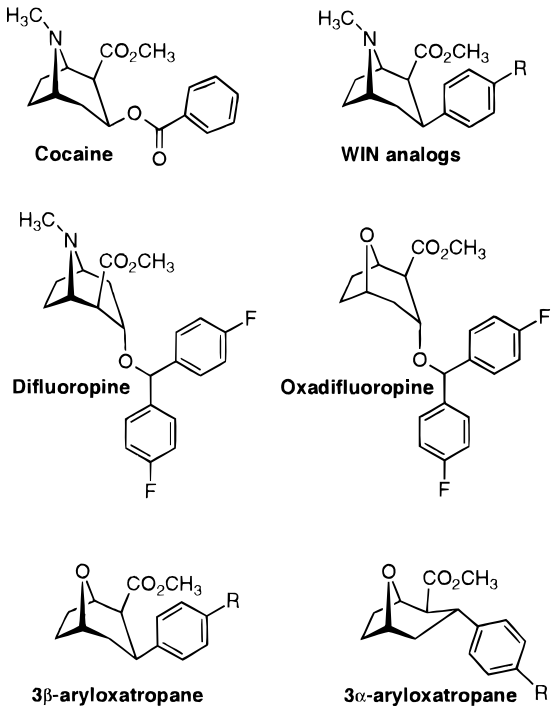


Figure 1.

does not reduce binding potency.[23] Consequently, although an ionic bond may play some role in the interaction between the tropanes and their biological receptor, it is clearly not the only possibility. This interaction could also be envisioned to result from hydrogen bonding between an H-donor on the transporter and a hydrogen bond acceptor on the ligand. In order to evaluate this possibility, we prepared 8-oxa analogs which can interact by hydrogen bonding but *not* by formation of an ionic bond.[24] We reasoned that replacement of a nitrogen by an oxygen might provide compounds of unique biological profile since not only would the mode of binding likely be different from that of their nitrogen counterparts but also their kinetic profile, biological transport, metabolism, and elimination pathways would likely differ.

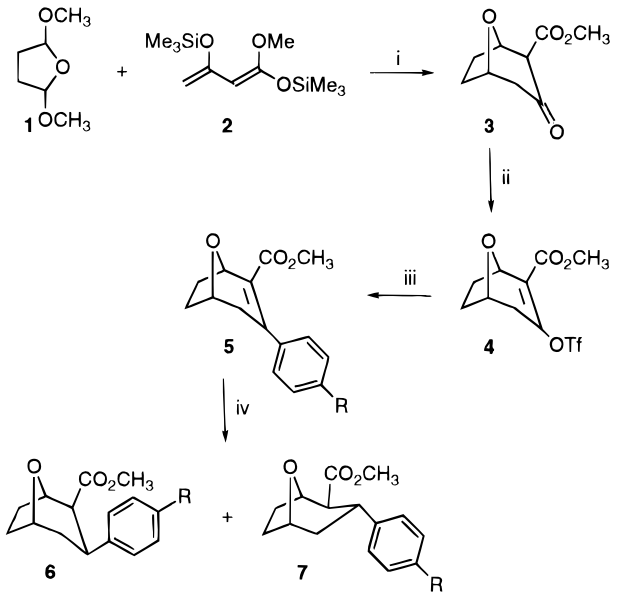
The substitution of a heteroatom for the nitrogen of a biologically active molecule has been reported previously. Indeed, in 1979 Brownbridge and Chan[25] prepared the 8-oxa analog of cocaine although no biological data were reported for that compound. More recently, Miller et al.[26−30] explored the substitution of sulfur for nitrogen in their studies on D_2 ligands. They showed that a nitrogen could be replaced by sulfur in these molecules and potency, albeit much diminished, could be maintained.

Herein we describe the synthesis and biology of a family of potent DAT inhibitors, the 2-carbomethoxy-3-aryl-8-oxabicyclo[3.2.1]octanes or 8-oxatropanes (Figure 1), and show that substitution of the *amine* function by an *ether* can result in potent ligands for monoamine transporters.

Chemistry

The compounds of this study are 2,3-disubstituted 8-oxabicyclo[3.2.1]octanes. 8-Oxabicyclo[3.2.1]octanes are useful intermediates to 7-membered and stereospecifically functionalized products.[31] Consequently, their synthesis has been the subject of numerous studies.

Scheme 1. Synthesis of 3-Aryl-8-oxabicyclo[3.2.1]octanes[a]



R	a	b	c	d	e	f	g	h
5, 6, 7	H *R/S*	F *R/S*	Cl *R/S*	Br *R/S*	I *R/S*	3,4-Cl_2 *R/S*	3,4-Cl_2 *1R*	3,4-Cl_2 *1S*

[a] Reagents and conditions: (i) $TiCl_4$; (ii) $Na(TMS)_2N$, $Ph(Tf)_2N$, THF, −78 °C; (iii) $ArB(OH)_2$, Pd_2dba_3, Na_2CO_3, LiCl; (iv) SmI_2, methanol, −78 °C.

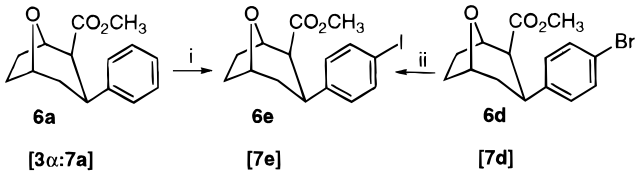
These have resulted in several routes which include Lewis acid catalyzed [4 + 3] annulations[25,32] and organometallic-mediated annulations.[33,34] Since the family of 8-oxabicycles that we planned to explore can all be derived from the keto ester **3** (Scheme 1), we elected to explore the Lewis acid catalyzed [4 + 3] annulation.

Compound **3** had previously been reported by Brownbridge and Chan[25] in their synthesis of 8-oxacocaine, and we therefore elected to adopt their synthetic route. Thus, 2,5-dimethoxytetrahydrofuran, **1**, was reacted with 1,3-bis(trimethylsiloxy)-1-methoxybuta-1,3-diene, **2**,[35,36] and 2 equiv of titanium tetrachloride to give the 3-one **3** in 45% yield. The ketone **3** was then used as the critical intermediate for the preparation of the family of 3-aryl-8-oxa analogs (Scheme 1), enantiomeric resolution (Scheme 3), and preparation of the 3-(diarylmethoxy)-8-oxa analogs (Scheme 4).

Thus, ketone **3** was converted to the enol triflate **4** in 79% yield by reaction with *N*-phenyltrifluoromethanesulfonimide and sodium bis(trimethylsilyl)amide in tetrahydrofuran. The enol triflate **4** was then coupled with the appropriate commercial or preformed arylboronic acids[37] by Suzuki coupling[38] in diethoxymethane in the presence of lithium chloride, sodium carbonate, and tris(dibenzylideneacetone)dipalladium(0) to provide aryloctenes **5** in 82−97% yield (**5d**: 41%).

Reduction of the octenes **5** with samarium iodide in tetrahydrofuran/methanol at low temperature (−78 °C)[39,40] provided a mixture of the 3β- and 3α-diastereomers **6** and **7**, respectively. These diastereomers were readily separated by flash column chromatography. In general, when trifluoroacetic acid was used to quench the reaction, the major products were the 2β,3α-diastereomers **7** which were isolated in about 50−65% yield. The minor products were the 2β,3β-compounds

Scheme 2. Synthesis of 2-Carbomethoxy-3-(4-iodophenyl)-8-oxabicyclo[3.2.1]octanes[a]



[a] Reagents and conditions: (i) (a) NO_2BF_4; (b) H_2/Ra Ni; (c) isoamyl nitrite/CH_2I_2; (ii) (a) Pd(0)/$[Bu_3Sn]_2$; (b) NIS.

6 isolated in about 14−23% yield. With water as quenching agent, a 1:1 mixture of 3α- and 3*β*-diastereomers could generally be obtained.

Since (4-iodophenyl)boronic acid was not readily accessible, an alternate approach[16] was adopted for the preparation of the 4-iodoaryl analogs **6e** and **7e** (Scheme 2).

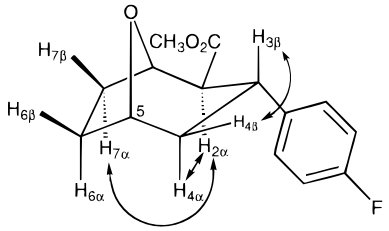
Thus, 3-phenyl compounds **6a** and **7a** were treated with NO_2BF_4 in acetonitrile to provide the 4-nitrophenyl analogs (ca. 60%), which were then reduced with H_2 over Raney nickel to provide the 4-aminoaryl analogs (ca. 75%). Diazotization with isoamyl nitrite and CH_2I_2 then gave the desired 4-iodoaryl compounds **6e** and **7e** (ca. 60%). Alternately, the 4-Br compounds **6d** and **7d** were treated with bis(tributyltin) and tetrakis(triphenylphosphine)palladium in toluene to provide the tributylstannyl intermediates (ca. 40−60%). These then led to the desired 4-iodoaryl compounds **6e** and **7e** (ca. 85−90%) upon reaction with *N*-iodosuccinimide in tetrahydrofuran.

This synthetic route to **6** and **7** is particularly useful because it provides both the 3α-aryl and 3*β*-aryl compounds upon samarium iodide reduction. Although the literature is replete with biology for the 2*β*-carbomethoxy-3*β*-tropanes, until recently,[39,41] 3α-aryl-8-azatropane analogs were not available.

Configurational assignments in the 8-oxabicyclo[3.2.1] series are not as straightforward as for the 8-azabicyclo-[3.2.1] series in which the ^{1}H-NMR chemical shift of the N-CH_3 group at *δ* 2.4 (2α) or *δ* 2.2 (2*β*) indicates stereochemistry at the C-2 position. The assignment is further complicated because the six-membered ring of the 3α- and 3*β*-diastereomers adopts different preferred conformations (boat and chair, respectively). Detailed coupling constants, sequential decoupling, and NOE analyses were needed to establish the correct assignments. The ^{1}H-NMR experiments undertaken for the 4-(fluoroaryl)-8-oxatropane **7b** indicated that the 3α-aryl compounds **7** exist in the boat conformation in solution. All protons were assigned for this structure and confirmed by sequential decoupling experiments. Chemical shifts, coupling constants and NOE interactions for **7b** are presented in Table 1.

The coupling constants between H-3 and H-2 and H-4α ($J_{3,2}$ = 11 Hz, $J_{3,4\alpha}$ = 11 Hz) clearly showed a *trans* diaxial interaction between these protons. The NOE experiments showed through-space interactions between H-2 and H-4α, and H-2 and H-7α, thus indicating that these protons must be on the same face (α) of the molecule. The NOE between H-3 and H-4*β*, and H-4*β* and H-5 indicated that these protons are in close proximity to each other (*β* face). Importantly, H-3 showed no NOE with H-2 and H-4α, thus confirming a *trans* diaxial relationship to both protons. Consequently **7b** must be present in its boat conformation with the

Table 1. NMR Spectral Data for **7b** (Arrows Show Relevant NOE)



assignment	*δ* (ppm)	multiplicity	coupling constants (Hz)
H-2′	7.10−7.20	m	
H-3′	6.90−7.00	m	
H-1; H-5	4.50−4.80	m	
CO_2CH_3	3.55	s	
H-3	3.20	ddd	$J_{3,2}$ = 11, $J_{3,4\alpha}$ = 11, $J_{3,4\beta}$ = 7
H-2	2.44	dd	$J_{3,2}$ = 11, $J_{2,1}$ = 2
H-4*β*	2.38	ddd	$J_{3,4\beta}$ = 7, $J_{4\alpha,4\beta}$ = 13, $J_{4\beta,5}$ = 9
H-6*β*; H-7*β*	1.90−2.20	m	
H-7α	1.76	ddd	$J_{7\alpha,6\alpha}$ = 9, $J_{7\alpha,6\beta}$ = 5, $J_{7\alpha,7\beta}$ = 13
H-6α	1.60−1.70	m	
H-4α	1.32	ddd	$J_{3,4\alpha}$ = 11, $J_{4\alpha,4\beta}$ = 13, $J_{4\alpha,5}$ = 2

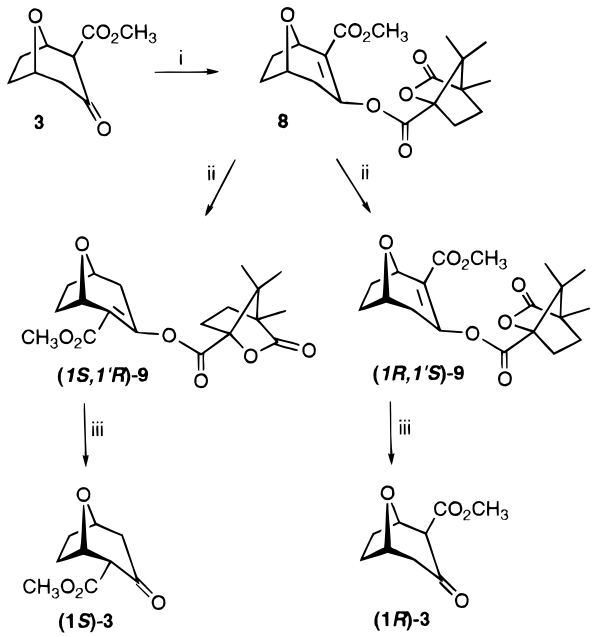
2-carbomethoxy in the *β*-configuration and the 3-aromatic ring in the α-configuration. The remaining 3α-aryl compounds **7** presented ^{1}H-NMR spectra almost identical to that for **7b**, except for the aromatic region. This established the same configuration and conformation for all compounds **7**. An X-ray study (*vide infra*) performed on the 3,4-dichlorophenyl analog **7g** confirmed the boat conformation for that compound.

It is interesting to note that in both the cocaine series[42] as well as in the 8-aza and 8-oxa diphenylmethoxy family of compounds, the 3α-substituted compounds are always present in the chair conformation.[13] When the aryl ring is attached directly to C-3, the boat conformation predominates. Presumably the close proximity of a bulky aryl group to the ring system in the 3-aryl compounds causes conformational selectivity and the aryl-equatorial boat is preferred for 3α-substituted compounds while the aryl-equatorial chair is preferred for 3*β*-substituted compounds. This preference has also been observed for the 8-aza-3α-aryltropanes.[39]

Tropanes, including cocaine, bind enantioselectively to the dopamine transporter, and the 1*R*-isomers of cocaine as well as the classical 8-aza-3-aryl compounds have been found to be the potent enantiomers. However, the fact that 1*S*-difluoropine[13] is a potent and selective ligand for the dopamine transporter, and 1*R*-difluoropine is not, makes it imperative to confirm biological enantioselectivity for any new series of compounds such as these 8-oxa analogs. Consequently, the chiral compounds **6g** and **6h**, and **7g** and **7h** were synthesized from enantiopure **(1*R*)-3** and **(1*S*)-3**.

Thus, a diastereomeric mixture of enol camphanates **8** was prepared upon reaction of **(1*R*/*S*)-3** with (*S*)-(−)-camphanic chloride in tetrahydrofuran (ca. 57%) (Scheme 3). Recrystallization from methylene chloride/hexanes then gave the pure diastereomer **(1*R*)-9** in 54% yield, as evidenced by NMR. The residual mixture of diastereomers **8** was then treated with LiOH to liberate **(1*R*/*S*)-3**, which was then treated with (*R*)-(+)-camphanic chloride (72%). Upon recrystallization of this enol camphanate from methylene chloride/hexanes, the pure diastereomer **(1*S*)-9** was obtained in 92% yield. The methyls of the camphanate diastereomers had sufficiently different chemical shifts (*δ* 1.06 and 1.04 for

Scheme 3. Resolution of Keto Ester **3**[a]



[a] Reagents and conditions: (i) $Na(TMS)_2N$, (*S*)-camphanic chloride or (*R*)-camphanic chloride, THF, −78 °C; (ii) hexane/CH_2Cl_2 (2:1), 0 °C; (iii) LiOH, THF, MeOH, H_2O.

(1*R*)-9 and **(1*S*)-9**, respectively) to enable their use as an initial guide to the efficiency of the resolution.

Hydrolysis of the enantiomerically pure single camphanate esters **(1*R*)-9** and **(1*S*)-9** was achieved with LiOH and provided (ca. 86%) the ketones **(1*R*)-3** and **(1*S*)-3**, respectively. Analysis by chiral HPLC (Chiral OC column) of the ketones **(1*R*)-3** and **(1*S*)-3** revealed >96% ee for each of the enantiomers. The purified enantiomers were then subjected to the sequence of steps described earlier to obtain the 3α- and 3*β*-diastereomers of the enantiomerically pure 8-oxatropane analogs **6g**,**h** and **7g**,**h**.

In order to establish the configuration of this series, the most active enantiopure compound was selected for X-ray structural analysis. A crystal of **7g** was grown from ethyl acetate/hexanes. The absolute configuration, using the anomolous scattering from chlorine, of **7g** was shown to be the (1*R*)-(−)-boat conformer (Figure 2). Consequently it is clear that **7h** is the 1*S*-(+)-compound. In turn, this implies that the configuration of the ketone precursor is **(1*R*)-3** and **(1*S*)-3**, respectively. This X-ray analysis allows the assignment of absolute configuration to the remaining enantiopure compounds since they derive from enantiopure ketones **(1*R*)-3** and **(1*S*)-3**. Therefore, 3,4-dichloroaryl chair conformers **6g** and **6h** are 1*R* and 1*S*, respectively.

The synthesis of the 3-diarylmethoxy analogs (Scheme 4) commenced with the reduction of ketone **3**. Thus, treatment of **3** with sodium borohydride at low temperature (−60 °C), followed by an increase to room temperature, provided a mixture of the isomers **10**, **11**, **12**, and **13**. Careful column chromatography then allowed separation of these diastereomers.

The dominant product of reduction was the enantiomeric pair of 2α-carbomethoxy-3α-hydroxy compounds, **12**. The minor products were **10** and **11**, with very small amounts of **13**. Inversion of the 2α-$COOCH_3$ to provide a 2*β*-$COOCH_3$ is readily achieved upon reflux in water in the case of the 8-aza compounds.[13] However, such

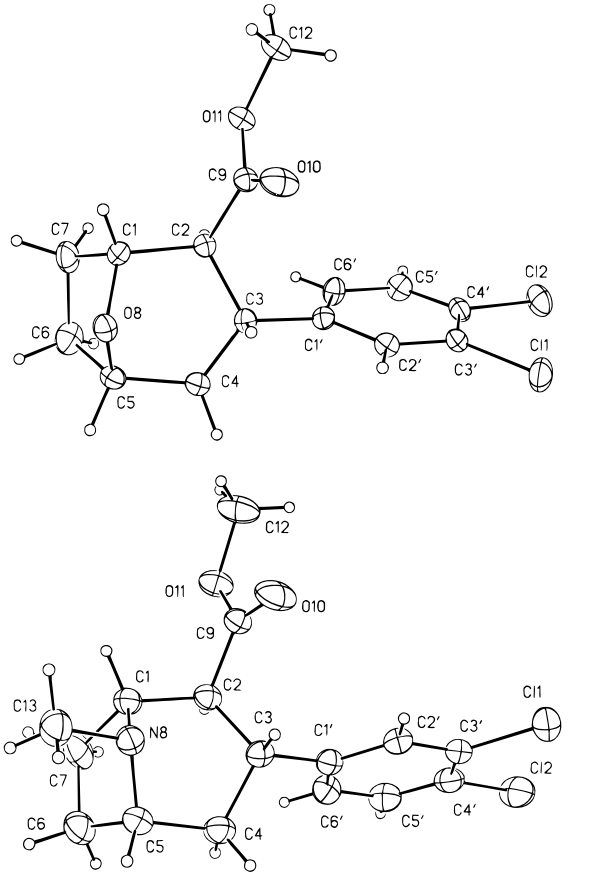


Figure 2. ORTEP diagrams of compounds **7g** (top) and **19e** (bottom).

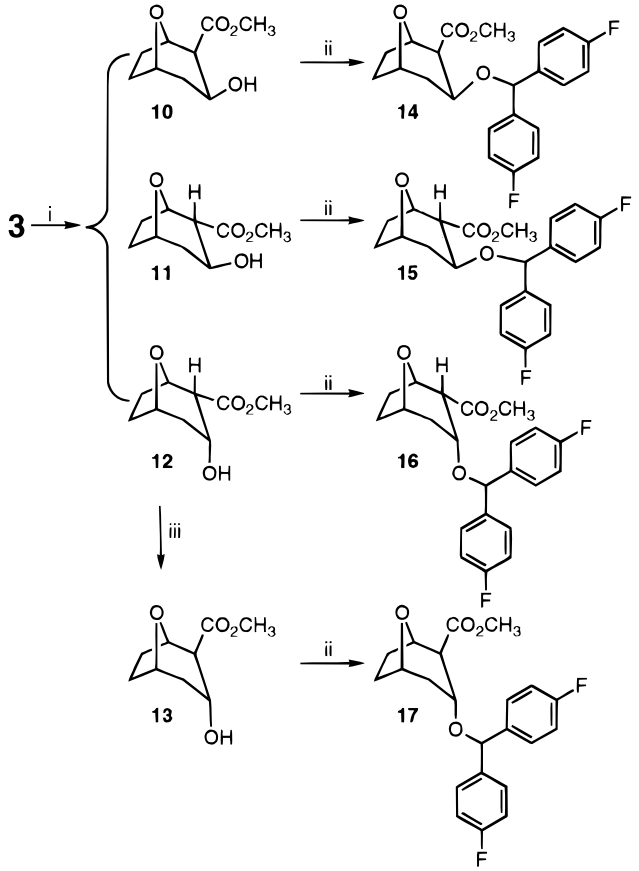
inversion of **12** failed under these conditions. Also, reflux of **12** in the presence of bases such as Et_3N, NH_4-OH, or NaOH provided very low yields of the desired product **13** contaminated with residual starting material and/or the 2,3-didehydro compound. Suitable conditions for inversion proved to be reflux with saturated $NaHCO_3$ to provide the desired 2*β*-carbomethoxy-3α-hydroxy product, **13**, albeit in low yield (21%). Each of the four racemic diastereomers **10**−**13** was then converted to the corresponding 3-diarylmethoxy analogs **14**−**17** by reaction with 4,4′-difluorodibenzhydrol under *p*TSA catalysis.[13]

The 8-oxa diastereomers were characterized by comparison of the ^{1}H-NMR spectra of both the free hydroxy compounds (**10**−**13**) as well as the diarylmethoxy derivatives (**14**−**17**) with the corresponding 8-aza analogs.[13] The H-2, H-3, and H-4*β* signals, when differentiated in the spectrum of each diastereomer, matched the corresponding signals in the 8-aza analogs in chemical shift and multiplicity. The bridgehead protons were shifted 1.2−1.3 ppm downfield, as anticipated, but retained the same multiplicity as their 8-aza counterparts. These results not only identified the four different diastereomers but also confirmed that all are present in the chair conformation.

Biology

The affinities (IC_{50}) of the 8-oxa analogs for the dopamine and serotonin transporters were determined in competition studies using [^{3}H]-3*β*-(4-fluorophenyl)-tropane-2*β*-carboxylic acid methyl ester ([^{3}H]WIN 35,-428 or [^{3}H]CFT) to label the dopamine transporter[5] and [^{3}H]citalopram to label the serotonin transporter. Bind-

Scheme 4. Synthesis of 2-Carbomethoxy-3-(diarylmethoxy)-8-oxabicyclo[3.2.1]octanes[a]



[a] Reagents and conditions: (i) $NaBH_4$; (ii) 4,4′-difluorobenzhydrol, *p*TSA, benzene, reflux; (iii) $NaHCO_3$, reflux.

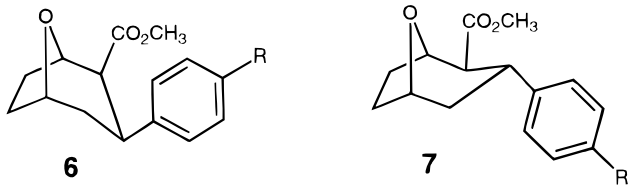
ing data for the 8-oxatropanes are presented in Table 2. Table 3 presents a comparison of binding data for 8-oxa(diarylmethoxy)tropanes with those data obtained for the 8-aza(diarylmethoxy)tropanes. Studies were conducted in monkey striatum because these compounds are part of an ongoing investigation of structure–activity relationships at the DAT in this tissue.[5,10,12,13] Hence meaningful comparisons with an extensive data base can be made. Equally important, monkeys are to be used as subjects in our on-going PET (positron emission tomography) and SPECT (single photon emission computed tomography) imaging studies. Competition studies were conducted with a fixed concentration of radioligand and a range of concentrations of the test drug. All drugs inhibited [^{3}H]WIN 35,428 and [^{3}H]-citalopram binding in a concentration-dependent manner.

It is extremely interesting that although the 8-oxa-3-aryltropanes (Table 2) proved potent DAT inhibitors, the 8-oxa-3-(diarylmethoxy)analogs (Table 3) are quite weak especially when compared with their 8-aza counterparts. While it was not surprising that compounds **14**, **15**, and **16** are poor inhibitors of the DAT and SERT, it was unexpected that **17**, the 2β,3α-configured compound analogous to difluoropine (O-620; IC_{50} = 10.9 nM),[13] was also weak (**17** IC_{50} = 520 nM).

Discussion

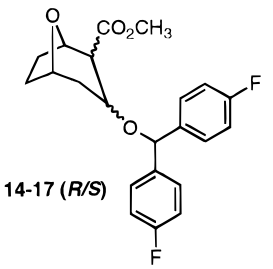
A number of the 8-oxatropane analogs (Table 2) are extremely potent inhibitors of both the DAT and the SERT. Indeed for the most active compounds these 8-oxa analogs are almost equipotent with their nitrogen-bearing 8-aza counterparts. These 8-oxa compounds of both the 3α- and 3β-configuration are, however, less selective (DAT vs SERT) than their 3α- and 3β-8-aza counterparts. Thus the racemic monochloro compounds **6c** and **7c** were both fairly potent at the DAT (IC_{50} = 10.0, 28.5 nM, respectively) and moderately selective (DAT/SERT = 11, 29 respectively). The racemic (3,4-dichlorophenyl)-8-oxa compounds **6f** and **7f** were quite potent inhibitors of the DAT (IC_{50} = 3.35, 3.08 nM) and the SERT (IC_{50} = 6.52, 64.5 nM). Potency resided mainly in the (1*R*) enantiomers (**6g**: DAT, IC_{50} = 3.27 nM; SERT, IC_{50} = 4.67 nM) (**7g**: DAT, IC_{50} = 2.34 nM; SERT, IC_{50} = 31 nM) although the (1*S*) enantiomers of both the 3β- and 3α-diastereomers retained substantial binding affinity for the DAT and SERT (**6h**: DAT, IC_{50} = 47 nM; SERT, IC_{50} = 58 nM) (**7h**: DAT, IC_{50} = 56 nM; SERT, IC_{50} = 2860 nM). The surprising potency of these (1*S*) isomers confirmed the need to establish biological enantioselectivity for any new family of inhibitors. These results demonstrate that an 8-nitrogen is not a prerequisite for binding of tropane-like ligands to monoamine transporters and indicate that selectivity can be affected by the orientation of the 3-aryl moiety.

Table 2. Inhibition of [^{3}H]WIN 35,428 Binding to the Dopamine Transporter and [^{3}H]Citalopram Binding to the Serotonin Transporter by 8-Oxatropanes in Monkey Caudate-Putamen

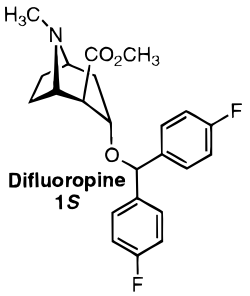


		IC_{50} (nM)					IC_{50} (nM)		
compound	R	DAT	5-HT	DAT/5-HT	compound	R	DAT	5-HT	DAT/5-HT
6a (*R*/*S*), O-904	H	>1000	>10000	10	**7a** (*R*/*S*), O-905	H	1990	11440	6
6b (*R*/*S*), O-895	F	546	2580	5	**7b** (*R*/*S*), O-899	F	>1000	>10000	10
6c (*R*/*S*), O-916	Cl	10	107	11	**7c** (*R*/*S*), O-915	Cl	28.5	816	29
6d (*R*/*S*), O-1159	Br	22	30	1.4	**7d** (*R*/*S*), O-1158	Br	9	276	31
6e (*R*/*S*), O-1172	I	7	12	1.7	**7e** (*R*/*S*), O-949	I	42	72	2
6f (*R*/*S*), O-914	3,4-Cl_2	3.35	6.52	2	**7f** (*R*/*S*), O-913	3,4-Cl_2	3.08	64.5	21
6g (1*R*), O-1072	3,4-Cl_2	3.27	4.67	1.4	**7g** (1*R*), O-1066	3,4-Cl_2	2.34	31	13
6h (1*S*), O-1114	3,4-Cl_2	47	58	1.2	**7h** (1*S*), O-1113	3,4-Cl_2	56	2860	51

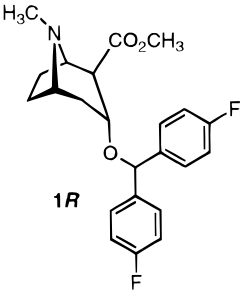
Table 3. Inhibition of [^{3}H]WIN 35,428 Binding to the Dopamine Transporter and [^{3}H]Citalopram Binding to the Serotonin Transporter by Difluoropine Analogs in Monkey Caudate-Putamen



14-17 (*R/S*)



Difluoropine
1*S*

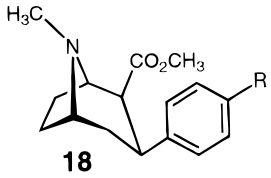


1*R*

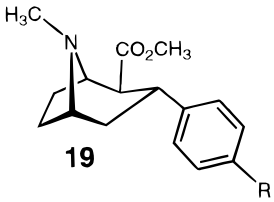
compound	substituents	IC_{50} (nM)[a] DAT	compound	substituents	IC_{50} (nM)[a] DAT	compound	substituents	IC_{50} (nM)[a] DAT
14 (*R/S*), O-874	2β,3β	>10000	O-654	2β,3β	3380	O-696	2β,3β	13500
15 (*R/S*), O-872	2α,3β	20300	O-634	2α,3β	8900	O-633	2α,3β	21900
16 (*R/S*), O-871	2α,3α	22300	O-632	2α,3α	1750	O-628	2α,3α	3840
17 (*R/S*), O-873	2β,3α	520	O-620	2β,3α	10.9	O-603	2β,3α	2040

[a] Note: all IC_{50} (SERT) >1660 nM.

Table 4. Inhibition of [^{3}H]WIN 35,428 Binding to the Dopamine Transporter and [^{3}H]Citalopram Binding to the Serotonin Transporter by 8-Azatropanes in Monkey Caudate-Putamen



18



19

compound	R	IC_{50} (nM) DAT	5-HT	DAT/5-HT[a]	compound	R	IC_{50} (nM) DAT	5-HT	DAT/5-HT
18a (1*R*)[b]	H	23	2000	87	**19a** (1*R*)[b]	H	101	5700	57
18b (1*R*), O-381	F	11	160	15	**19b** (1*R*)[b]	F	21	5060	241
18c (1*R*), O-371	Cl	1.40	5.90	4	**19c** (1*R*)[b]	Cl	2.4	998	415
18d (1*R*)[b]	I	1.26	4.21	3	**19d** (1*R*)[b]	I	2.85	64.9	23
18e (1*R*), O-401	3,4-Cl_2	1.09	2.47	2	**19e** (1*R*), O-1157	3,4-Cl_2	0.4	27	68

[a] Selectivity ratio = IC_{50} (SERT)/IC_{50} (DAT). [b] Data reported by Holmquist et al. *J. Med. Chem.* **1996**, *39*, 4139−4141. Tissue (4 mg/mL original wet tissue weight) was incubated with each radioligand and 7−14 concentrations of a cocaine congener. Nonspecific binding of [^{3}H]WIN 35,428 was measured with 30 μM (−)-cocaine and of [^{3}H]citalopram with 1 μM fluoxetine. IC_{50} values were computed by the EBDA computer program and are the means of experiments conducted in triplicate.

The assumption[21] that the 8-amine functionality of the tropanes is a prerequisite for potency is not supported by the data for these 8-oxa analogs. Formation of an ionic bond is not possible for these compounds and yet many bind to both the DAT and SERT with potency similar to that of their nitrogen-containing counterparts.

It is particularly informative to compare the binding inhibition of these 8-oxatropanes with their 8-azatropane counterparts.[41] Table 4 presents binding data for the 8-aza analogs. A comparison between the 8-aza **18e** (3β) and **19e** (3α) on the one hand and the 8-oxa **6g** (3β) and **7g** (3α) (Table 2) on the other is interesting. While the 3β compounds in both series are quite potent, the 3α compounds are more so. The 3β compounds have about the same selectivity. However, the 8-aza compound **19e** (boat) is about 5 times more selective for the DAT vs SERT than the 8-oxa compound **7g**. The observation that the 3α (boat conformation) compounds for both 8-oxa and 8-aza series are significantly more selective for the DAT vs SERT than are their 3β (chair conformation) counterparts is striking. We infer that the placement of the aromatic ring in the "acceptor site" (defined here as the molecular site on the transporter at which intermolecular binding interactions between the ligand and the relevant amino acid residues occur) of the DAT and SERT transporters must contribute to their relative affinity. While the chair diastereomers bind quite potently at the acceptor site of both the DAT and the SERT, the boat diastereomers clearly do not fit the SERT acceptor site as well. This implies that selectivity for the two classes of tropanes can be controlled by correct placement of the 3-aryl ring. We are exploring this with respect to alternate substitution at this site.

The rank order of binding affinity for the 8-oxa and 8-aza compounds is instructive. The 8-oxa 3β compounds have rank order: 3,4-Cl_2 > Cl ~I > Br > F > H while the 3α-diastereomers show rank order: 3,4-Cl_2 > Br > Cl > I > F > H. The 8-aza 3β compounds have rank order: 3,4-Cl_2 > I > Cl > F > H and the 3α-diastereomers have rank order: 3,4-Cl_2 > Cl > I > F > H.

The SAR shows a striking contrast between the 8-aza compounds and these 8-oxa compounds. In particular, although the two series have similar DAT IC_{50} *rank order*, the *range* of IC_{50}s differs significantly (8-oxa, 3.35 to >1000 nM; 8-aza, 0.4−101 nM). Thus, as potency decreases in each series, the reduction in potency for the 8-oxa compounds is considerably more marked than

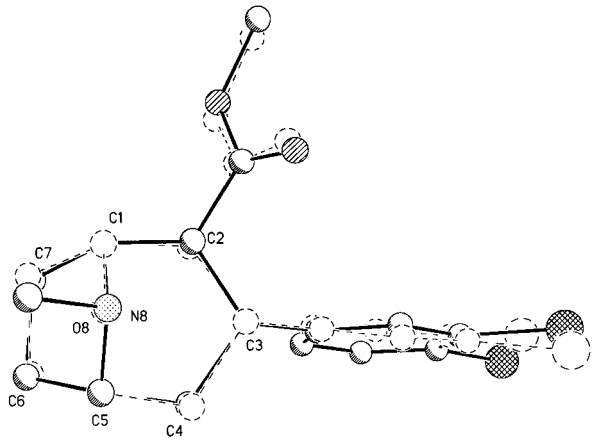


Figure 3. Superimposition of X-ray structures of **7g** and **19e**.

for the 8-aza compounds. This remarkable difference prompted us to consider the conformational differences that may exist between the 8-oxa and 8-aza analogs. A simple energy minimization routine[43] applied to the most potent compounds, the 3α-conformers **7g** and **19e**, showed that the conformation of the 7-membered skeleton is similar and the torsion angles defined by the 3-aryl ring and the bicyclic system were only slightly different. This finding prompted a comparison between the structures of the 8-oxa compound and its 8-aza counterpart in the solid state. The absolute structure of **7g** was already in hand. Compound **19e** was prepared analogously to **18e**[39] from (1*R*)-2-carbomethoxytropin-3-one. Crystals of **19e** were grown from ethyl acetate/hexanes, and an X-ray structural analysis was obtained (Figure 2). The two structures obtained from the X-ray analysis were superimposed (Figure 3). It is clear that, in the solid state, the two structures are topologically superimposable. A least squares fit of C-1 through C-7 of the two analogs gives a fit of the seven pairs of atoms with rms deviation of 0.088 Å with a maximum difference of 0.119 Å for C-2 to C-2 and a minimum deviation of 0.034 Å for C-5 to C-5. In the least squares fit, N-8 and O-8 are 0.67 Å apart. The torsional angle C-1−C-2−C-3−C-1′ for the 8-oxa compound is 175.8°. For the 8-aza compound it is 167.7°. Even this slight difference (8.1°) may be a consequence of crystal packing since in the nitrogen analog the symmetry related molecules have nearest N···H distances of 2.9 Å while in the 8-oxa analog, the nearest O···H intermolecular distance is 2.60 Å.

The torsional angles obtained from the energy minimization routine were thus confirmed in the solid state. However, the difference in these torsional angles is small (8.1°). This implies that it is unlikely, especially in solution, that this difference is the cause of the different ligand−transporter interactions that must give rise to the disparity between the DAT inhibition rank order observed for these two classes of compounds.

Notwithstanding, biological differences clearly result when different substituents are placed on the aromatic ring. These differences must therefore be a consequence of the interaction of this ring with its acceptor site on the transporter. Since the topology of both the 8-oxa and 8-aza compounds is almost identical, the distances from potential binding points (8-heteroatom, 2β-ester, and the centroid of the 3-aryl ring) are almost identical. Consequently, the interaction must be influenced by the *orientation* in which the molecule *as a whole* lies in the acceptor region of the transporter. That orientation has been postulated, on the basis of site mutagenicity studies, to be localized on the DAT at an aspartic acid residue (Asp^{79}) in the transmembrane domain 1 (TMD 1) and at two serine residues (Ser^{356}, Ser^{359}) in the transmembrane domain 7 (TMD 7).[21] In contrast, in a report of a molecular modeling study of the human DAT, Edvardsen and Dahl have questioned the role of Ser^{356} and Ser^{359} in TMD 7 and have suggested that dopamine does not form hydrogen bonds with these serine residues.[44] Also, Vaughan and Kuhar have suggested that the Asp^{79}, Ser^{356}, Ser^{359} binding pocket may not be a general site for binding by DAT inhibitors.[45] Indeed, the results which we now present also require a revision of the earlier model of the binding interaction at the DAT.

The results obtained in this study indicate that hydrogen bond formation is likely between the aspartic (or other) acid and the heteroatom of the ligand. Since the aromatic domains of the two families of ligands are identical, it follows that the heteroatom must control the orientation of the ligand in the transporter's acceptor site. This placement is likely due to the strength of the H-bond formed between, on one hand, the 8-oxygen and, on the other, the 8-nitrogen and the amino acid. Hydrogen bonds formed to nitrogen are generally weaker than those formed to oxygen since oxygen is the more electronegative of the two (3.0 vs 3.5 on the Pauling scale, respectively). Consequently, for similar compounds, the $R_2O\cdots H-X$ bond can be expected to be shorter than the $R_3N\cdots H-X$ bond. This difference in length will influence the placement of the remote 3-aryl ring in relation to its acceptor site. Thus, in the case of the nitrogen analogs, this ring will probe a greater distance into the site, while in the oxygen analogs the controlling H···O bond will allow placement of the 3-aryl ring at a lesser distance. This suggests that the deeper placement of the 3-aryl substituent into the acceptor site of the DAT results in higher potency. This also explains the astounding potency (DAT: IC_{50} = 0.069 nM and SERT IC_{50} = 0.22 nM) of the 3β-(2-naphthyl)-2β-propanoyl-8-azabicyclo[3.2.1]octane reported by Davies et al.[18] We have now confirmed this in the 8-oxa series[46] and have shown that whereas a 3-(2-naphthyl)-8-oxa analog is quite potent, the 3-(1-naphthyl) analog lacks any potency. Consequently we conclude that the site at which the 3-aryl group binds on the DAT or SERT is likely a narrow cleft with width capable of tolerating a phenyl ring (∼2.8 Å) but not sufficiently wide to tolerate the width of two side-by-side aromatic rings (i.e. 1-naphthyl: ∼5.0 Å). Also, since aromatic rings at C-3 are a prerequisite for binding to the DAT and SERT, we hypothesize that the binding of these 3-aryl groups is likely controlled by $\pi-\pi$ or lipophilic interactions. Therefore the amino acids candidates for $\pi-\pi$ interactions at that acceptor site for these 8-oxatropanes are likely to be phenylalanine, tryptophan, tyrosine, or for lipophilic interactions, alanine, valine, leucine, isoleucine, proline, and methionine.

Our conception of the dopamine transporter is presented in Figure 4. This model portrays the transporter as a cylindrical funnel constrained by the lipid membrane in which it is embedded. Each helical domain presents its polar (amide) linkage toward the core of the helix. This places the amino acid side chain on the

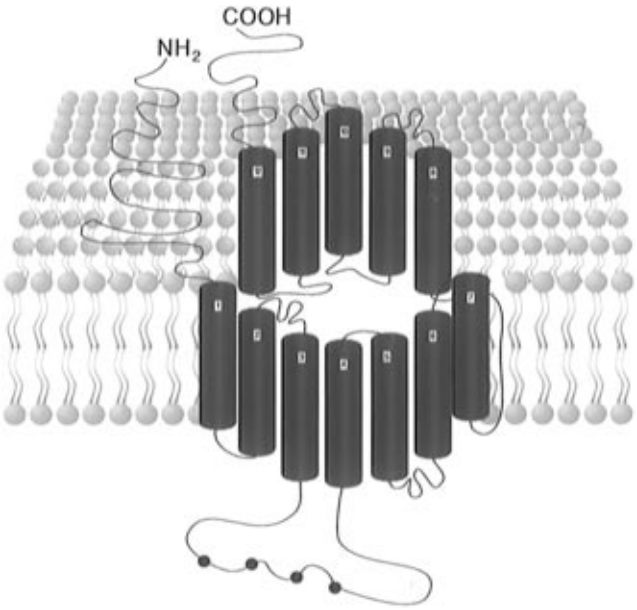


Figure 4. The dopamine transporter was conceived as 12 cylindrical transmembrane peptide helices with the side chains oriented toward the central tube.

outside of the helix facing the internal structure of the cylinder. Consequently any ligand passing into this cylindrical funnel is confronted by the side chain face of the relevant helix. Dopamine is conceived to pass into this funnel, bind, and likely "pull" the binding domains closer toward one another and thus "block" the funnel, and then pass through the funnel into the presynaptic neuron. The tropanes and oxatropanes are conceived to pass into the funnel, again bind across transmembrane domains and block entry (binding) of any other potential ligands, and then pass back out of the funnel into the synaptic cleft. "Blockage" by ligand binding will thus inhibit binding of any competing ligand whether or not the competing ligand binds at the same molecular acceptor site or not.

Conclusions

The biological results obtained for a number of these compounds have proved extremely exciting since these are the first 8-oxabicyclo[3.2.1]octanes of either the 3α- or 3*β*-configuration to display potent binding affinity for a monoamine transporter system.[24]

The most important conclusion from these studies is that the presence of nitrogen is not a prerequisite for binding of tropane-like ligands to monoamine transporters. This result may have far-reaching implications since many agents targeted to monoamine transporters have been designed to include amine functionality. It has long been assumed that such amine functionality is a prerequisite for potency, presumably because endogenous ligands (e.g. dopamine, serotonin) themselves possess amines. Furthermore, binding of dopamine and the tropanes to the DAT has been assumed to require the ionic interaction of an aspartic acid residue (Asp^{79}) with the nitrogenous ligand.[21] Formation of an ionic bond is not possible with these 8-oxa compounds, and yet many bind to both the DAT and SERT with potency similar to that of their nitrogen-containing counterparts.

A second conclusion of this work is that subtle topological placement of the 3-aryl substituent most likely controls not only binding potency but also selectivity for the DAT vs the SERT. This is evidenced by the fact that compounds in the boat conformation (3α) are clearly more selective than those in the chair conformation (3*β*). This difference in conformation controls placement of the aromatic ring. However, by fixing three points in space (8-heteroatom, 2-substituent, and aromatic centroid) and superimposing the boat and chair compounds, it is apparent that the difference in placement of the 3-aryl group is not vast. We are currently exploring this further.

Experimental Section

^{1}H-NMR spectra were recorded on either a Bruker 100, a Varian XL 400, or a Bruker 300 NMR spectrometer. TMS was used as internal standard. Melting points are uncorrected and were measured on a Gallenkamp melting point apparatus. Thin layer chromatography (TLC) was carried out on Baker Si250F plates. Visualization was accomplished with either iodine vapor, UV exposure, or treatment with phosphomolybdic acid (PMA). Preparative TLC was carried out on Analtech uniplates silica gel GF 2000 μm. Flash chromatography was carried out on Baker silica gel 40 mM. Elemental analyses were performed by Atlantic Microlab, Atlanta, GA. HPLC analyses were carried out on a Waters 510 system with detection at 254 nm on a Chiralcel OC column (flow rate: 1 mL/min). All reactions were conducted under an inert (N_2) atmosphere.

[^{3}H]WIN 35,428 ([^{3}H]CFT, 2*β*-carbomethoxy-3*β*-(4-fluorophenyl)-*N*-[^{3}H]methyltropane, 79.4−87.0 Ci/mmol) and [^{3}H]citalopram (86.8 Ci/mmol) were purchased from DuPont-New England Nuclear (Boston, MA). A Beckman 1801 scintillation counter was used for scintillation spectrometry. 0.1% Bovine serum albumin was purchased from Sigma Chemicals. (*R*)-(−)-Cocaine hydrochloride for the pharmacological studies was donated by the National Institute on Drug Abuse [NIDA]. Fluoxetine was donated by E. Lilly & Co.

(1*R*,1*S*)-2-Carbomethoxy-3-{[(trifluoromethyl)sulfonyl]oxy}-8-oxabicyclo[3.2.1]-2-octene (4). Sodium bis(trimethylsilyl)amide (1.0 M solution in THF, 45 mL) was added dropwise to 2-carbomethoxy-8-oxabicyclo[3.2.1]octanone, **3**[25] (7.12 g, 38.65 mmol), in THF (100 mL) at −70 °C under nitrogen. After 30 min of stirring, *N*-phenyltrifluoromethanesulfonimide (15.19 g, 42.52 mmol) was added as a solid at −70 °C. The reaction was allowed to warm to room temperature and was then stirred overnight. The volatiles were removed on a rotary evaporator. The residue was dissolved in CH_2Cl_2 (200 mL) and washed with H_2O (100 mL) and brine (100 mL). The dried ($MgSO_4$) CH_2Cl_2 layer was concentrated to dryness on a rotary evaporator. The residue was purified by flash chromatography (eluent: 5−10% EtOAc/hexanes) to afford 9.62 g (79%) of **4** as a pale yellow oil: ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 5.0−5.1 (m, 1H), 4.6−4.8 (m, 1H), 3.83 (s, 3H), 3.0 (dd, 1H, J = 5, 8 Hz), 1.7−2.35 (m, 5H).

General Procedure for Synthesis of the 2-Octenes: (1*R*,1*S*)-2-Carbomethoxy-3-phenyl-8-oxabicyclo[3.2.1]-2-octene (5a). 2-Carbomethoxy-3-{[(trifluoromethyl)sulfonyl]-oxy}-8-oxabicyclo[3.2.1]-2-octene, **4** (2.0 g, 6.32 mmol), phenylboronic acid (1.02 g, 8.36 mmol), diethoxymethane (20 mL), LiCl (578 mg, 13.6 mmol), tris(dibenzylideneacetone)dipalladium(0) (247 mg, 0.25 mmol), and Na_2CO_3 (2 M solution, 6.1 mL) were combined and heated at reflux for 1 h. The mixture was cooled to room temperature, filtered through Celite, and washed with ether (100 mL). The mixture was basified with NH_4OH and washed with brine. The dried ($MgSO_4$) ether layer was concentrated to dryness. The residue was purified by flash chromatography (eluent: 10% EtOAc/hexanes) to afford 1.28 g (82%) of **5a** as a light brown viscous oil: R_f 0.26 (20% EtOAc/hexanes); ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 7.1−7.5 (m, 5H), 4.95−5.1 (m, 1H), 4.55−4.75 (m, 1H), 3.52 (s, 3H), 2.95 (dd, 1H, J = 5, 18 Hz), 1.7−2.2 (m, 5H). Anal. ($C_{15}H_{16}O_3$) C, H.

(1*R*,1*S*)-2-Carbomethoxy-3-(4-fluorophenyl)-8-oxabicyclo[3.2.1]-2-octene (5b). Compound **5b** was prepared from **4** with 4-fluorophenylboronic acid as described for **5a**. A light

brown viscous oil was obtained (88%): R_f 0.19 (20% EtOAc/hexanes); ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 7.0−7.2 (m, 4H), 4.95−5.05 (m, 1H), 4.55−4.75 (m, 1H), 3.52 (s, 3H), 2.95 (dd, 1H, J = 5, 18 Hz), 1.7−2.3 (m, 5H). Anal. ($C_{15}H_{15}O_3F$) C, H.

(1*R*,1*S*)-2-Carbomethoxy-3-(4-chlorophenyl)-8-oxabicyclo[3.2.1]-2-octene (5c). Compound **5c** was prepared from **4** with 4-chlorophenylboronic acid as described for **5a**. A light brown viscous oil was obtained (92%): R_f 0.23 (20% EtOAc/hexanes); ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 7.0−7.4 (m, 4H), 4.95−5.1 (m, 1H), 4.55−4.75 (m, 1H), 3.52 (s, 3H), 2.95 (dd, 1H, J = 5, 18 Hz), 1.7−2.2 (m, 5H). Anal. ($C_{15}H_{15}O_3Cl$) C, H, Cl.

(1*R*,1*S*)-2-Carbomethoxy-3-(4-bromophenyl)-8-oxabicyclo[3.2.1]-2-octene (5d). Compound **5d** was prepared from **4** with 4-bromophenylboronic acid as described for **5a**. A clear viscous oil was obtained (41%): R_f 0.39 (20% EtOAc/hexanes); ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 7.48 (d, 2H, J = 9 Hz), 6.97 (d, 2H, J = 9 Hz), 4.95−5.1 (m, 1H), 4.5−4.75 (m, 1H), 3.52 (s, 3H), 2.95 (dd, 1H, J = 5, 18 Hz), 1.65−2.4 (m, 5H). Anal. ($C_{15}H_{15}O_3Br$) C, H, Br.

(1*R*,1*S*)-2-Carbomethoxy-3-(3,4-dichlorophenyl)-8-oxabicyclo[3.2.1]-2-octene (5f). Compound **5f** was prepared from **4** with 3,4-chlorophenylboronic acid as described for **5a**. A light brown viscous oil was obtained (97%): R_f 0.45 (30% EtOAc/hexanes); ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 7.4 (d, 1H, J = 10 Hz), 7.23 (d, 1H, J = 2 Hz), 6.95 (dd, 1H, J = 2, 10 Hz), 4.95−5.1 (m, 1H), 4.55−4.75 (m, 1H), 3.52 (s, 3H), 2.95 (dd, 1H, J = 5, 18 Hz), 1.6−2.3 (m, 5H). Anal. ($C_{15}H_{14}O_3Cl_2$) C, H, Cl.

(1*R*)-2-Carbomethoxy-3-(3,4-dichlorophenyl)-8-oxabicyclo[3.2.1]-2-octene (5g). Compound **5g** was prepared from **(1*R*)-4** with 3,4-chlorophenylboronic acid as described for **5a**. A light brown viscous oil was obtained (94%): R_f 0.45 (30% EtOAc/hexanes); ^{1}H-NMR ($CDCl_3$, 100 MHz) identical to **5f** above.

(1*S*)-2-Carbomethoxy-3-(3,4-dichlorophenyl)-8-oxabicyclo[3.2.1]-2-octene (5h). Compound **5h** was prepared from **(1*S*)-4** with 3,4-chlorophenylboronic acid as described for **5a**. A clear viscous oil was obtained (80%): R_f 0.45 (30% EtOAc/hexanes); ^{1}H-NMR ($CDCl_3$, 100 MHz) identical to **5f** above.

General Procedure for Synthesis of the Octanes: (1*R*,1*S*)-2β-Carbomethoxy-3β-phenyl-8-oxabicyclo[3.2.1]-octane (6a) and (1*R*,1*S*)-2β-Carbomethoxy-3α-phenyl-8-oxabicyclo[3.2.1]octane (7a). To 2-carbomethoxy-3-phenyl-8-oxabicyclo[3.2.1]-2-octene, **5a** (1.17 g, 4.8 mmol), in THF (10 mL) at −70 °C under N_2 was added SmI_2 (0.1 M in THF, 215 mL, 21.5 mmol). After the mixture was stirred for 30 min, MeOH (anhydrous, 25 mL) was added. The reaction was stirred at −70 °C for a further 2 h. The mixture was quenched with TFA (5 mL) and H_2O (100 mL). After the mixture was warmed to 0 °C, NH_4OH was added to attain pH 11 and the mixture was then stirred for 30 min. The mixture was filtered through Celite, washed with ether (400 mL), and then saturated with $Na_2S_2O_3$. The ether layer was washed with brine. The dried ($MgSO_4$) ether layer was concentrated to dryness. The isomers were separated by gravity column chromatography (eluent 10% EtOAc/hexanes) to afford 270 mg (23%) of **6a** as a white solid (mp 102.5−104 °C; R_f 0.30 (30% EtOAc/hexanes)) and 789 mg (67%) of **7a** as a white solid (mp 96.5−98 °C; R_f 0.37 (30% EtOAc/hexanes)). **6a**: ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 7.25 (br s, 5H), 4.55−4.8 (m, 2H), 3.48 (s, 3H), 3.25 (ddd, 1H, J = 5, 5, 14 Hz), 2.6−3.0 (m, 2H), 1.5−2.3 (m, 5H). Anal. ($C_{15}H_{18}O_3$) C, H. **7a**: ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 7.25 (br s, 5H), 4.4−4.65 (m, 2H), 3.58 (s, 3H), 3.25 (ddd, 1H, J = 7, 11, 11 Hz), 2.52 (dd, 1H, J = 2, 11 Hz), 1.6−2.5 (m, 5H), 1.41 (ddd, 1H, J = 2, 11, 14 Hz). Anal. ($C_{15}H_{18}O_3$) C, H.

(1*R*,1*S*)-2β-Carbomethoxy-3β-(4-fluorophenyl)-8-oxabicyclo[3.2.1]octane (6b) and (1*R*,1*S*)-2β-Carbomethoxy-3α-(4-fluorophenyl)-8-oxabicyclo [3.2.1]octane (7b). Compounds **6b** and **7b** were prepared from **5b** as described for compounds **6a** and **7a**. Compound **6b** was obtained (22%) as a white solid (mp 118−120.5 °C; R_f 0.27 (30% EtOAc/hexanes)) and **7b** (62%) as a white solid (mp 58−60 °C; R_f 0.36 (30% EtOAc/hexanes)). **6b**: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.15−7.25 (m, 2H), 6.9−7.0 (m, 2H), 4.6−4.7 (m, 2H), 3.48 (s, 3H), 3.17 (ddd, 1H, J = 5, 5, 13 Hz), 2.78 (d, 1H, J = 5 Hz), 2.73 (ddd, 1H, J = 4, 13, 13 Hz), 1.7−2.2 (m, 4H), 1.5−1.65 (m, 1H). Anal. ($C_{15}H_{17}O_3F$) C, H. **7b**: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.1−7.2 (m, 2H), 6.9−7.0 (m, 2H), 4.5−4.8 (m, 2H), 3.55 (s, 3H), 3.20 (ddd, 1H, J = 7, 11, 11 Hz), 2.44 (dd, 1H, J = 2, 11 Hz), 2.38 (ddd, 1H, J = 7, 9, 13 Hz), 1.9−2.2 (m, 2H), 1.76 (ddd, 1H, J = 5, 9, 13 Hz), 1.6−1.7 (m, 1H), 1.32 (ddd, 1H, J = 2, 11, 13 Hz). Anal. ($C_{15}H_{17}O_3F$) C, H.

(1*R*,1*S*)-2β-Carbomethoxy-3β-(4-chlorophenyl)-8-oxabicyclo[3.2.1]octane (6c) and (1*R*,1*S*)-2β-Carbomethoxy-3α-(4-chlorophenyl)-8-oxabicyclo[3.2.1]octane (7c). Compounds **6c** and **7c** were prepared from **5c** as described for compounds **6a** and **7a**. Compound **6c** was obtained (19%) as a white solid (mp 116−117 °C; R_f 0.27 (30% EtOAc/hexanes)) and **7c** (51%) as a white solid (mp 89−90 °C; R_f 0.32 (30% EtOAc/hexanes)). **6c**: ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 7.1−7.4 (m, 4H), 4.55−4.8 (m, 2H), 3.55 (s, 3H), 3.20 (ddd, 1H, J = 5, 5, 12 Hz), 2.55−2.95 (m, 2H), 1.5−2.3 (m, 5H). Anal. ($C_{15}H_{17}O_3Cl$) C, H, Cl. **7c**: ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 7.1−7.4 (m, 4H), 4.4−4.65 (m, 2H), 3.58 (s, 3H), 3.05−3.45 (m, 1H), 1.2−2.6 (m, 7H). Anal. ($C_{15}H_{17}O_3Cl$) C, H, Cl.

(1*R*,1*S*)-2β-Carbomethoxy-3α-(4-bromophenyl)-8-oxabicyclo[3.2.1]octane (6d) and (1*R*,1*S*)-2β-Carbomethoxy-3β-(4-bromophenyl)-8-oxabicyclo[3.2.1]octane (7d). Compounds **6d** and **7d** were prepared from **5d** as described for compounds **6a** and **7a** except no TFA was used when quenching. Compound **6d** was obtained (47%) as a white solid (mp 113−115 °C; R_f 0.29 (30% EtOAc/hexanes)) and **7d** (32%) as a white solid (mp 96−98 °C; R_f 0.38 (30% EtOAc/hexanes)). **6d**: ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 7.45 (d, 2H, J = 9 Hz), 7.15 (d, 2H, J = 9 Hz), 4.6−4.8 (m, 2H), 3.5 (s, 3H), 3.0−3.4 (m, 1H), 2.55−2.9 (m, 2H), 1.5−2.4 (m, 5H). Anal. $C_{15}H_{17}O_3Br$. **7d**: ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 7.45 (d, 2H, J = 10 Hz), 7.1 (d, 2H, J = 10 Hz), 4.4−4.6 (m, 2H), 3.53 (s, 3H), 3.20 (ddd, 1H, J = 6, 11, 11 Hz), 1.6−2.6 (m, 6H), 1.35 (ddd, 1H, J = 2, 11, 13 Hz). Anal. ($C_{15}H_{17}O_3Br$) C, H, Br.

(1*R*,1*S*)-2β-Carbomethoxy-3β-(3,4-dichlorophenyl)-8-oxabicyclo[3.2.1]octane (6f) and (1*R*,1*S*)-2β-Carbomethoxy-3α-(3,4-dichlorophenyl)-8-oxabicyclo[3.2.1]octane (7f). Compounds **6f** and **7f** were prepared from **5f** as described for compounds **6a** and **7a**. Compound **6f** was obtained (14%) as a white solid (mp 132−133.5 °C; R_f 0.31 (30% EtOAc/hexanes)) and **7f** (55%) as a white solid (mp 88.5−90 °C; R_f 0.33 (30% EtOAc/hexanes)). **6f**: ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 7.0−7.5 (m, 3H), 4.55−4.85 (m, 2H), 3.55 (s, 3H), 3.20 (ddd, 1H, J = 5, 5, 11 Hz), 2.55−2.95 (m, 2H), 1.45−2.35 (m, 5H). Anal. ($C_{15}H_{16}O_3Cl_2$) C, H, Cl. **7f**: ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 7.0−7.5 (m, 3H), 4.4−4.65 (m, 2H), 3.60 (s, 3H), 3.20 (ddd, 1H, J = 7, 11, 11 Hz), 1.5−2.5 (m, 6H), 1.30 (ddd, 1H, J = 2, 11, 13 Hz). Anal. ($C_{15}H_{16}O_3Cl_2$) C, H, Cl.

(1*R*)-2β-Carbomethoxy-3β-(3,4-dichlorophenyl)-8-oxabicyclo[3.2.1]octane (6g) and (1*R*)-2β-Carbomethoxy-3α-(3,4-dichlorophenyl)-8-oxabicyclo[3.2.1]octane (7g). Compounds **6g** and **7g** were prepared from **(1*R*)-5f** as described for compounds **6a** and **7a**. Compound **6g** was obtained (13%) as a white solid (mp 121−122 °C; R_f 0.31 (30% EtOAc/hexanes)) and **7g** (45%) as a white solid (mp 103.5−104.5 °C; $[\alpha]^{21}_D$ = −79° (c = 1, MeOH); R_f 0.33 (30% EtOAc/hexanes)). **6g** and **7g**: ^{1}H-NMR ($CDCl_3$, 100 MHz) identical to **6f** and **7f** above. Anal. ($C_{15}H_{16}O_3Cl_2$) C, H, Cl.

(1*S*)-2β-Carbomethoxy-3β-(3,4-dichlorophenyl)-8-oxabicyclo[3.2.1]octane (6h) and (1*S*)-2β-Carbomethoxy-3α-(3,4-dichlorophenyl)-8-oxabicyclo[3.2.1]octane (7h). Compounds **6h** and **7h** were prepared from **(1*S*)-5f** as described for compounds **6a** and **7a**. Compound **6h** was obtained(11%) as a white solid (mp 121−122 °C; R_f 0.31 (30% EtOAc/hexanes)) and **7h** (45%) as a white solid (mp 103−104 °C; $[\alpha]^{21}_D$ = +76° (c = 1, MeOH); R_f 0.33 (30% EtOAc/hexanes)). **6h** and **7h**: ^{1}H-NMR ($CDCl_3$, 100 MHz) identical to **6f** and **7f** above. Anal. ($C_{15}H_{16}O_3Cl_2$) C, H, Cl.

Synthesis of (1*R*,1*S*)-2-Carbomethoxy-3-(4-iodophenyl)-8-oxabicyclo[3.2.1]-2-octene (5e): (1*R*,1*S*)-2-Carbomethoxy-3-[4-(tributylstannyl)phenyl]-8-oxabicyclo[3.2.1.]-2-octene. 2-Carbomethoxy-3-(4-bromophenyl)-8-oxabicyclo[3.2.1]-2-octene, **5d** (200 mg, 0.62 mmol), tetrakis(triphenylphosphine)palladium(0) (13 mg, 0.011 mmol), and bis(tributyltin) (0.74 mL, 1.46 mmol) in toluene (4 mL) were degassed by bubbling N_2 through the solution for 10 min. The mixture was

then heated at reflux for 6 h. CH_2Cl_2 (10 mL) was added, and the mixture was filtered through Celite. The filtrate was concentrated to dryness. The residue was purified sequentially by flash chromotography (eluent 30% EtOAc/hexanes) and preparative TLC (eluent 5−10% EtOAc/hexanes) to afford 206 mg (62%) of the title compound as a clear viscous oil: R_f 0.31 (59% EtOAc/hexanes); ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 7.43 (d, 2H, J = 7 Hz), 7.05 (d, 2H, J = 7 Hz), 4.95−5.1 (m, 1H), 4.55−4.75 (m, 1H), 3.50 (s, 3H), 2.95 (dd, 1H, J = 5, 18 Hz), 0.7−2.3 (m, 32H).

(1*R*,1*S*)-2-Carbomethoxy-3-(4-iodophenyl)-8-oxabicyclo-[3.2.1]-2-octene (5e). 2-Carbomethoxy-3-[4-(tributylstannyl)-phenyl]-8-oxabicyclo[3.2.1]-2-octene (206 mg, 0.39 mmol) from above in THF (anhydrous, 5 mL) was degassed by bubbling N_2 for 10 min. *N*-Iodosuccinimide (96 mg, 0.43 mmol) was added. The reaction mixture was stirred at room temperature for 1 h and concentrated to dryness. The residue was dissolved in ether (10 mL), washed with saturated $NaHCO_3$, and brine. The dried ($MgSO_4$) ether layer was concentrated to dryness. The residue was purified by flash chromotography (eluent 10% EtOAc/hexanes) and preparative TLC (eluent 30% EtOAc/hexanes) to afford 128 mg (90%) of **5e** as a pale yellow viscous oil: R_f 0.49 (30% EtOAc/hexanes); ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 7.68 (d, 2H, J = 10 Hz), 6.85 (d, 2H, J = 10 Hz), 4.95−5.05 (m, 1H), 4.55−4.75 (m, 1H), 3.54 (s, 3H), 2.95 (dd, 1H, J = 5, 18 Hz), 1.55−2.40 (m, 5H). Anal. ($C_{15}H_{15}O_3I$) C, H, I.

Synthesis of (1*R*,1*S*)-2β-Carbomethoxy-3α-(4-iodophenyl)-8-oxabicyclo[3.2.1]octane (7e): (1*R*,1*S*)-2β-Carbomethoxy-3α-[4-(tributylstannyl)phenyl]-8-oxabicyclo[3.2.1]-octane. The title compound was prepared from **7d**, as described above for stannylation of **5d**. A clear viscous oil (41%) was obtained: R_f 0.48 (30% EtOAc/hexanes); ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 7.4 (d, 2H, J = 7 Hz), 7.2 (d, 2H, J = 7 Hz), 4.4−4.6 (m, 2H), 3.60 (s, 3H), 3.25 (ddd, 1H, J = 6, 10, 10 Hz), 0.7−2.65 (m, 34H).

(1*R*,1*S*)-2β-Carbomethoxy-3α-(4-iodophenyl)-8-oxabicyclo[3.2.1]octane (7e). Compound **7e** was prepared from the above stannyl compound as described for **5e** from 2β-carbomethoxy-3α-[4-(tributylstannyl)phenyl]-8-oxabicyclo[3.2.1]-octane (85%). A white solid was obtained: mp 124−126 °C; R_f 0.36 (30% EtOAc/hexanes); ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 7.6 (d, 2H, J = 9 Hz), 6.97 (d, 2H, J = 9 Hz), 4.35−4.65 (m, 2H), 3.6 (s, 3H), 3.2 (ddd, 1H, J = 6, 11, 11 Hz), 1.5−2.6 (m, 6H), 1.35 (ddd, 1H, J = 2, 11, 13 Hz). Anal. ($C_{15}H_{17}O_3I$) C, H, I.

Synthesis of (1*R*,1*S*)-2β-Carbomethoxy-3β-(4-iodophenyl)-8-oxabicyclo[3.2.1]octane (6e): (1*R*,1*S*)-2β-Carbomethoxy-3β-(4-nitrophenyl)-8-oxabicyclo[3.2.1]octane. To 2β-carbomethoxy-3β-phenyl-8-oxabicyclo[3.2.1]octane, **6a** (112 mg, 0.45 mmol), in CH_3CN (anhydrous, 5 mL) at −5 °C was added NO_2BF_4 (83 mg, 0.63 mmol). The reaction mixture was stirred at −5 °C for 3 h. A small amount of ice was added, and the mixture was stirred at −25 °C for 15 min. The CH_3CN was removed, and the melted ice was extracted with ether. The combined ether extract and CH_3CN solution were concentrated to dryness. The residue was dissolved in ether (50 mL) and washed with saturated $NaHCO_3$ and brine. The dried ($MgSO_4$) ether layer was concentrated to dryness. The residue was purified by flash chromatography (eluent 10−20% EtOAc/hexanes) to afford 75.6 mg (57%) of the title 4-nitro compound: R_f 0.19 (30% EtOAc/hexanes); ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 8.2 (d, 2H, J = 10 Hz), 7.42 (d, 2H, J = 10 Hz), 4.6−4.85 (m, 2H), 3.54 (s, 3H), 3.15−3.45 (m, 1H), 2.6−3.0 (m, 2H), 1.7−2.4 (m, 5H).

(1*R*,1*S*)-2β-Carbomethoxy-3β-(4-aminophenyl)-8-oxabicyclo[3.2.1]octane. 2β-Carbomethoxy-3β-(4-nitrophenyl)-8-oxabicyclo[3.2.1]octane (75.6 mg, 0.026 mmol) in MeOH (20 mL) was hydrogenated overnight at room temperature using Raney Ni (50%) as catalyst. The reaction mixture was filtered through Celite, washed with MeOH, and concentrated to dryness. The residue was purified by flash chromatography (eluent 20−30% EtOAc/hexanes) to afford 43 mg (75%) of the title 4-amino compound: R_f 0.22 (50% EtOAc/hexanes); ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 7.05 (d, 2H, J = 9 Hz), 6.62 (d, 2H, J = 9 Hz), 4.55−4.7 (m, 2H), 3.58 (br s, 2H), 3.50 (s, 3H), 3.0−3.3 (m, 1H), 2.5−2.9 (m, 2H), 1.4−2.3 (m, 5H). **(1*R*,1*S*)-2β-Carbomethoxy-3β-(4-iodophenyl)-8-oxabicyclo[3.2.1]-octane (6e).** To 2β-carbomethoxy-3β-(4-aminophenyl)-8-oxabicyclo[3.2.1]octane (26 mg, 0.099 mmol) in CH_2I_2 (2 mL) under N_2 was added isoamyl nitrite (0.17 mL, 0.126 mmol). The reaction mixture was stirred at room temperature for 1 h and then at 55 °C for 3 h. CH_2I_2 was removed under reduced pressure. The residue was purified by flash chromatography (eluent 10% EtOAc/hexanes) to afford 15 mg (60%) of **6e** as a white solid: mp 119−120.5 °C; R_f 0.25 (30% EtOAc/hexanes); ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 7.65 (d, 2H, J = 9 Hz), 7.00 (d, 2H, J = 9 Hz), 4.6−4.8 (m, 2H), 3.52 (s, 3H), 3.05−3.3 (m 1H), 2.55−2.9 (m, 2H), 1.5−2.3 (m, 5H).

(1*R*,1*S*)-2-Carbomethoxy-3-hydroxy-8-oxabicyclo[3.2.1]-octanes (10−13). Sodium borohydride (2.56 g, 67.7 mmol) was added to a solution of 2-carbomethoxy-8-oxabicyclo[3.2.1]-octan-3-one, **3** (5.12 g, 27.8 mmol), in MeOH (100 mL) at −78 °C. The reaction mixture was stirred at room temperature overnight and then concentrated to dryness. The residue was dissolved in water (50 mL) and extracted with CH_2Cl_2 (100, 2 × 50 mL). The combined dried ($MgSO_4$) extracts were concentrated to dryness (yield 3.9 g). By repeated flash chromatography (eluent 30% EtOAc/hexanes), four isomers were obtained from the residue. The major isomer was 2α-carbomethoxy-3α-hydroxy-8-oxabicyclo[3.2.1]octane, **12** (1.0 g, 26%). The diastereomers, 2β-carbomethoxy-3β-hydroxy-8-oxabicyclo[3.2.1]octane, **10** (305 mg), 2α-carbomethoxy-3β-hydroxy-8-oxabicyclo[3.2.1]octane, **11** (84 mg), and 2β-carbomethoxy-3α-hydroxy-8-oxabicyclo[3.2.1]octane, **13** (28 mg), were also isolated in pure form. **10**: ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 4.7−4.9 (m, 1H), 4.4−4.6 (m, 1H), 3.7−4.2 (m, 1H), 3.78 (s, 3H), 2.75−2.9 (m, 1H), 1.6−2.1 (m, 7H). **11**: ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 4.4−4.7 (m, 2H), 4.2 (ddd, 1H, J = 6, 10, 10 Hz), 3.75 (s, 3H), 2.75 (br s, 1H), 2.68 (dd, 1H, J = 4, 10 Hz), 1.5−2.1 (m, 6H). **12**: ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 4.55−4.75 (m, 1H), 4.3−4.5 (m, 2H), 3.78 (s, 3H), 3.4−3.5 (br s, 1H), 2.95 (t, 1H, J = 4 Hz), 1.7−2.4 (m, 6H). **13**: ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 4.7−4.85 (m, 1H), 4.3−4.5 (m, 2H), 3.75 (s, 3H), 2.55 (br s, 1H), 1.45−2.5 (m, 7H).

(1*R*,1*S*)-2β-Carbomethoxy-3α-hydroxy-8-oxabicyclo-[3.2.1]octane (13). 2α-Carbomethoxy-3α-hydroxy-8-oxabicyclo-[3.2.1]octane, **12** (397 mg, 2.1 mmol), and saturated $NaHCO_3$ (10 mL) were combined and heated overnight at reflux. Water was removed. Methanolic HCl (10 mL) was added, and the mixture was stirred at room temperature overnight and then concentrated to dryness. CH_2Cl_2 (25 mL) was added to the residue. The dried (K_2CO_3) CH_2Cl_2 solution was concentrated to dryness. The residue was chromatographed (eluent 20−30% EtOAc/hexanes) on silica gel to afford 82 mg (21%) of **13**, which was identical to **13** described above.

General Procedure for Synthesis of (Diarylmethoxy)-8-oxatropanes: (1*R*,1*S*)-2β-Carbomethoxy-3α-[bis(4-fluorophenyl)methoxy]-8-oxabicyclo[3.2.1]octane (17). 2β-Carbomethoxy-3α-hydroxy-8-oxabicyclo[3.2.1]octane, **13** (103 mg, 0.55 mmol), 4,4′-difluorobenzhydrol (244 mg, 1.1 mmol), *p*-toluenesulfonic acid monohydrate (60 mg, 0.31 mmol), and benzene (50 mL) in a 100 mL round bottom flask fitted with Dean−Stark trap and condenser was heated overnight at reflux. The reaction mixture was cooled to room temperature and basified with NH_4OH. EtOAc (25 mL) was added, and the organic phase was washed with brine. The dried ($MgSO_4$) organic layer was concentrated to dryness. The residue was purified by flash chromatography to afford 200 mg (93%) of **17** as a white solid: mp 92−93 °C; R_f 0.26 (30% EtOAc/hexanes); ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 6.9−7.5 (m, 8H), 5.38 (br s, 1H), 4.7−4.85 (m, 1H), 4.3−4.5 (m, 1H), 4.0−4.1 (m, 1H), 3.70 (s, 3H), 2.65 (br s, 1H), 1.5−2.5 (m, 6H). Anal. ($C_{22}H_{22}O_4F_2$) C, H.

(1*R*,1*S*)-2β-Carbomethoxy-3β-[bis(4-fluorophenyl)-methoxy]-8-oxabicyclo[3.2.1]octane (14). Compound **14** was prepared as described for **17** above: 59% from **10**; white solid mp 149−151 °C; R_f 0.16 (30% EtOAc/hexanes); ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 6.9−7.4 (m, 8H), 5.45 (br s, 1H), 4.4−4.6 (m, 2H), 3.6−3.95 (m, 1H), 3.68 (s, 3H), 2.75−2.9 (m, 1H), 2.45 (ddd, 1H, J = 4, 10, 10 Hz), 1.4−2.1 (m, 5H). Anal. ($C_{22}H_{22}O_4F_2$) C, H.

(1*R*,1*S*)-2α-Carbomethoxy-3β-[bis(4-fluorophenyl)-

methoxy]-8-oxabicyclo[3.2.1]octane (15). Compound **15** was prepared as described for **17** above: 57% from **11**; pale yellow gum; R_f 0.32 (30% EtOAc/hexanes); ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 6.85−7.4 (m, 8H), 5.5 (br s, 1H), 4.25−4.6 (m, 2H), 4.05 (ddd, 1H, J = 6, 10, 10 Hz), 3.68 (s, 3H), 2.91 (dd, 1H, J = 4, 10 Hz), 1.40−2.10 (m, 6H). Anal. ($C_{22}H_{22}O_4F_2$) C, H.

(1*R*,1*S*)-2α-Carbomethoxy-3α-[bis(4-fluorophenyl)-methoxy]-8-oxabicyclo[3.2.1]octane (16). Compound **16** was prepared as described for **17** above: 46% from **12**; light brown gum; R_f 0.25 (30% EtOAc/hexanes); ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 6.9−7.4 (m, 8H), 5.35 (br s, 1H), 4.5−4.65 (m, 1H), 4.2−4.4 (m, 1H), 4.05−4.2 (m, 1H), 3.50 (s, 3H), 2.97 (t, 1H, J = 5 Hz), 2.5−2.85 (m, 1H), 1.6−2.3 (m, 5H). Anal. ($C_{22}H_{22}O_4F_2 \cdot {}^1/_3H_2O$) C, H.

(1*R*)-2-Carbomethoxy-8-oxabicyclo[3.2.1]oct-2-ene-3-(1′*S*)-camphanate [(1*R*,1′*S*)-9]. (1*R*,1*S*)-2-Carbomethoxy-8-oxabicyclo[3.2.1]octan-3-one, **3** (7.4 g, 40.1 mmol), was dissolved in anhydrous THF (200 mL) and cooled to −78 °C. To this solution was added butyllithium (17.6 mL of a 2.5 M solution, 44.1 mmol); the color changed to yellow orange. After 15 min at −78 °C (*S*)-(−)-camphanic chloride (9.6 g, 44.1 mmol) was added in one portion, and then the cooling bath was removed. After 5 min saturated Na_2CO_3 (300 mL) and ether (300 mL) were added. The layers were separated, and the ether phase was washed with brine (100 mL) and dried ($MgSO_4$). Filtration followed by evaporation gave the crude reaction product (14 g). Purification by column chromatography (SiO_2, 400 g; eluent 30% ethyl acetate in hexanes) gave the diastereomeric mixture, **8** (8.29 g, 57%). ^{1}H-NMR of the diagnostic camphanate methyls were δ (1*S*,1′*S*) 1.04 (s, 3H), 1.11 (s, 3H), 1.14 (s, 3H); (1*R*,1′*S*) 1.06 (s, 3H) 1.14 (s, 6H). This mixture, **8**, was recrystallized eight times from methylene chloride/hexanes and gave white crystals of the pure title compound **(1*R*,1′*S*)-9** (2.25 g, 54%): mp 168.9−169 °C; R_f 0.25 (30% EtOAc/hexanes); ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 5.04 (br s, 1H), 5.55−5.75 (m, 1H), 3.71 (s, 3H), 2.90 (dd, J = 5, 18 Hz), 1.6−2.7 (m, 9 H), 1.14 (s, 6 H), 1.06 (s, 3H). Anal. ($C_{19}H_{24}O_7$) C, H.

(1*S*)-2-Carbomethoxy-8-oxabicyclo[3.2.1]oct-2-ene-3-(1′*R*)-camphanate [(1*S*,1′*R*)-9]. The title compound was obtained as follows: Hydrolysis (LiOH) of the residual mother liquor obtained from recrystallization of **(1*R*,1′*S*)-9** above gave an enriched mixture (1*S*: 60% ee) of (1*R*,1*S*)-2-carbomethoxy-8-oxabicyclo[3.2.1]octan-3-one, **3**. Reaction with (*R*)-(+)-camphanic chloride then gave the camphanate (2.79 g, 72%). Recrystallization twice from methylene chloride/hexanes gave 1.29 g (92%) of the pure **(1*S*,1′*R*)-9** diastereomer. This had the same physical and chemical properties as the above ester **(1*R*,1′*S*)-9**. Anal. ($C_{19}H_{24}O_7$) C, H.

(1*R*)-2-Carbomethoxy-8-oxabicyclo[3.2.1]octan-3-one [(1*R*)-3]. (1*R*)-2-Carbomethoxy-8-oxabicyclo[3.2.1]octa-2-ene-3(*S*)-camphanate, **(1*R*,1′*S*)-9** (1.76 g, 4.8 mmol), was dissolved in THF (15 mL), and then methanol (5 mL) and water (5 mL) were added. The resulting solution was cooled in an ice bath, and lithium hydroxide (325 mg, 7.7 mmol) was added in one portion. After 20 min no **(1*R*,1′*S*)-9** remained. The solution was neutralized with 1 M hydrochloric acid. Ether (200 mL) was then added, and the ethereal solution was washed with brine and dried ($MgSO_4$). Evaporation gave 1.38 g of the crude reaction product. This was chromatographed (SiO_2, 50 g; eluent 20% ether in hexanes) to yield 833 mg (94%) of the pure title compound. ^{1}H-NMR and TLC were identical with the racemic ketone **3**. Under chiral HPLC conditions (Chiralcel OC column; eluent 10% 2-propanol in hexanes, 1 mL/min) t_R **(1*S*)-3** = 6.99 min (1.78%); t_R **(1*R*)-3** = 10.92 min (98.21%, ee = 96.4%).

(1*S*)-2-Carbomethoxy-8-oxabicyclo[3.2.1]octan-3-one [(1*S*)-3]. The title compound was obtained upon LiOH hydrolysis, as described above, from (1*S*)-2-carbomethoxy-8-oxabicyclo[3.2.1]oct-2-ene-3-(1′*R*)-camphanate: 0.78 g, 86%. ^{1}H-NMR and TLC were identical with the racemic ketone **3**. Under chiral HPLC conditions (Chiralcel OC column; eluent 10% 2-propanol in hexanes, 1 mL/min) t_R **(1*S*)-3** = 6.87 (100%, ee > 98%); t_R **(1*R*)-3** = not present.

Single-Crystal X-ray Analysis of Diastereoisomer 7g. Monoclinic crystals of the purified **7g** were obtained from ethyl acetate/hexanes. A representative crystal was selected, and a 0.710 73 Å data set was collected at room temperature. Pertinent crystal, data collection, and refinement parameters: crystal size, 0.08 × 0.14 × 0.44 mm; cell dimensions, a = 8.879(1) Å, b = 6.263(1) Å, c = 13.769(1) Å, α = 90°, β = 105.56(1)°, γ = 90°; formula, $C_{15}H_{16}Cl_2O_3$; formula weight = 315.18; volume = 737.62(13) Å^3; calculated density = 1.419 g cm^{-3}; space group = $P2_1$; number of reflections = 2096 of which 1688 were considered independent (R_{int} = 0.014). Refinement method was full-matrix least-squares on F^2. The final R-indices were [$I > 2\sigma(I)$] R1 = 0.041, wR2 = 0.083.

Single-Crystal X-ray Analysis of Diastereoisomer 19e. Monoclinic crystals of the purified **19e** were obtained from ethyl acetate/hexanes. A representative crystal was selected, and a 1.541 78 Å data set was collected at room temperature. Pertinent crystal, data collection, and refinement parameters: crystal size, 0.48 × 0.20 × 0.16 mm; cell dimensions, a = 9.943(1) Å, b = 6.373(1) Å, c = 13.410(1) Å, α = 90°, β = 105.36(1)°, γ = 90°; formula, $C_{16}H_{19}Cl_2NO_2$; formula weight = 328.22; volume = 819.38(14) Å^3; calculated density = 1.330 g cm^{-3}; space group = $P2_1$; number of reflections = 1814 of which 1468 were considered independent (R_{int} = 0.020). Refinement method was full-matrix least-squares on F^2. The final R-indices were [$I > 2\sigma(I)$] R1 = 0.035, wR2 = 0.101.

Coordinates, anisotropic temperature factors, distances, and angles are available as Supporting Information.

Tissue Sources and Preparation. Brain tissue from adult male and female cynomolgus monkeys (*Macaca fascicularis*) was stored at −85 °C in the primate brain bank at the New England Regional Primate Research Center. The caudate-putamen was dissected from coronal slices and yielded 1.4 ± 0.4 g of tissue. Membranes were prepared as described previously. Briefly, the caudate-putamen was homogenized in 10 volumes (w/v) of ice-cold Tris·HCl buffer (50 mM, pH 7.4 at 4 °C) and centrifuged at 3800*g* for 20 min in the cold. The resulting pellet was suspended in 40 volumes of buffer, and the entire was procedure was repeated twice. The membrane suspension (25 mg original wet weight of tissue/mL) was diluted to 12 mL/mL for [^{3}H]WIN 35,428 or [^{3}H]-citalopram assay in buffer just before assay and was dispersed with a Brinkmann Polytron homogenizer (setting 5) for 15 s. All experiments were conducted in triplicate, and each experiment was repeated in each of two or three preparations from individual brains.

Dopamine Transporter Assay. The dopamine transporter was labeled with [^{3}H]WIN 35,428 ([^{3}H]CFT, 2β-carbomethoxy-3β-(4-fluorophenyl)-*N*-[^{3}H]methyltropane, 81−84 Ci/mmol, DuPont-NEN). The affinity of [^{3}H]WIN 35,428 for the dopamine transporter was determined in experiments by incubating tissue with a fixed concentration of [^{3}H]WIN 35,-428 and a range of concentration of unlabeled WIN 35,428. The assay tubes received, in Tris·HCl buffer (50 mM, pH 7.4 at 0−4 °C; NaCl 100 mM), the following constituents at a final assay concentration: WIN 35,428, 0.2 mL (1 pM to 100 or 300 nM), [^{3}H]WIN 35,428 (0.3 nM); membrane preparation 0.2 mL (4 mg original wet weight of tissue/mL). The 2 h incubation (0−4 °C) was initiated by addition of membranes and terminated by rapid filtration over Whatman GF/B glass fiber filters presoaked in 0.1% bovine serum albumin (Sigma Chemical Co.). The filters were washed twice with 5 mL of Tris·HCl buffer (50 mM) and incubated overnight at 0−4 °C in scintillation fluor (Beckman Ready-Value, 5 mL), and radioactivity was measured by liquid scintillation spectrometry (Beckman 1801). Cpm were converted to dpm following determination of counting efficiency (>45%) of each vial by external standardization. Total binding was defined as [^{3}H]WIN 35,428 bound in the presence of ineffective concentrations of unlabeled WIN 35,428 (1 or 10 pM). Nonspecific binding was defined as [^{3}H]WIN 35,428 bound in the presence of an excess (30 μM) of (−)-cocaine. Specific binding was the difference between the two values. Competition experiments to determine the affinities of other drugs at [^{3}H]WIN 35,428 binding sites were conducted using procedures similar to those outlined above. Stock solutions of water-soluble drugs were dissolved in water or buffer, and stock solutions of other drugs were made in a range of ethanol/HCl solutions. Several of the drugs were

sonicated to promote solubility. The stock solutions were diluted serially in the assay buffer and added (0.2 mL) to the assay medium as described above. IC_{50} values were computed by the EBDA computer program and are the means of experiments conducted in triplicate.

Serotonin Transporter Assay. The serotonin transporter was assayed in caudate-putamen membranes using conditions similar to those for the dopamine transporter. The affinity of [^{3}H]citalopram (specific activity: 82 Ci/mmol, DuPont-NEN) for the serotonin transporter was determined in experiments by incubating tissue with a fixed concentration of [^{3}H]citalopram and a range of concentrations of unlabeled citalopram. The assay tubes received, in Tris·HCl buffer (50 mM, pH 7.4 at 0−4 °C; NaCl 100 mM), the following constituents at a final assay concentration: citalopram, 0.2 mL (1 pM to 100 or 300 nM), [^{3}H]citalopram (1 nM); membrane preparation 0.2 mL (4 mg original wet weight of tissue/mL). The 2 h incubation (0−4 °C) was initiated by addition of membranes and terminated by rapid filtration over Whatman GF/B glass fiber filters presoaked in 0.1% polyethyleneimine. The filters were washed twice with 5 mL of Tris·HCl buffer (50 mM) and incubated overnight at 0−4 °C in scintillation fluor (Beckman Ready-Value, 5 mL), and radioactivity was measured by liquid scintillation spectrometry (Beckman 1801). Cpm were converted to dpm following determination of counting efficiency (>45%) of each vial by external standardization. Total binding was defined as [^{3}H]citalopram bound in the presence of ineffective concentrations of unlabeled citalopram (1 or 10 pM). Nonspecific binding was defined as [^{3}H]citalopram bound in the presence of an excess (10 μM) of fluoxetine. Specific binding was the difference between the two values. Competition experiments to determine the affinities of other drugs at [^{3}H]citalopram binding sites were conducted using procedures similar to those outlined above. IC_{50} values were computed by the EBDA computer program and are the means of experiments conducted in triplicate.

Acknowledgment. This work was supported by the National Institute on Drug Abuse (P.M., DA 0930; B.K.M., DA 06303, DA 09462, RR00168; C.H.G., DA09045) and by the Office of Naval Research (C.H.G.). We thank Helen Panas and Keiko Akasofu for excellent technical assistance.

Supporting Information Available: ORTEP drawings of **7g** and **19e**, crystal data and refinement parameters, coordinates, anisotropic temperature factors, distances, and angles, HPLC traces of separated enantiomers, **(1*R*)-3** and **(1*S*)-3**, and ^{1}H-NMR assignments for all compounds are provided (12 pages). Ordering information is given on any current masthead page.

References

(1) Ritz, M. C.; Lamb, R. J.; Goldberg, S. R.; Kuhar, M. J. Cocaine receptors on dopamine transporters are related to self-administration of cocaine. *Science* **1987**, *237*, 1219−1223.
(2) Kennedy, L. T.; Hanbauer, I. Sodium sensitive cocaine binding to rat striatal membrane: possible relationship to dopamine uptake sites. *J. Neurochem.* **1983**, *34*, 1137−1144.
(3) Schoemaker, H.; Pimoule, C.; Arbilla, S.; Scatton, B.; Javoy-Agid, F.; Langer, S. Z. Sodium dependent [^{3}H]cocaine binding associated with dopamine uptake sites in the rat striatum and human putamen decrease after dopaminergic denervation and in Parkinson's disease. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1985**, *329*, 227−235.
(4) Reith, M. E. A.; Meisler, B. E.; Sershen, H.; Lajtha, A. Structural requirements for cocaine congeners to interact with dopamine and serotonin uptake sites in mouse brain and to induce stereotyped behavior. *Biochem. Pharmacol.* **1986**, *35*, 1123−1129.
(5) Madras, B. K.; Fahey, M. A.; Bergman, J.; Canfield, D. R.; Spealman, R. D. Effects of cocaine and related drugs in nonhuman primates: I. [^{3}H]Cocaine binding sites in caudate-putamen. *J. Pharmacol. Exp. Ther.* **1989**, *251*, 131−141.
(6) Bergman, J.; Madras, B. K.; Johnson, S. E.; Spealman, R. D. Effects of cocaine and related drugs in nonhuman primates. III. Self-administration by squirrel monkeys. *J. Pharmacol. Exp. Ther.* **1989**, *251*, 150−155.
(7) Canfield, D. R.; Spealman, R. D.; Kaufman, M. J.; Madras, B. K. Autoradiographic localization of cocaine binding sites by [^{3}H]-CFT ([^{3}H]WIN 35,428) in the monkey brain. *Synapse* **1990**, *6*, 189−195.
(8) Kaufman, M. J.; Madras, B. K. Severe depletion of cocaine recognition sites associated with the dopamine transporter in Parkinson's diseased striatum. *Synapse* **1991**, *9*, 43−49.
(9) Kuhar, M. J.; Ritz, M. C.; Boja, J. W. The dopamine hypothesis of the reinforcing properties of cocaine. *Trends Neurosci.* **1991**, *14*, 299−302.
(10) Madras, B. K.; Kamien, J. B.; Fahey, M.; Canfield, D.; Milius, R. A.; Saha, J. K.; Neumeyer, J. L. N-Modified fluorophenyltropane analogs of cocaine with high affinity for [^{3}H]cocaine receptors. *Pharmacol Biochem. Behav.* **1990**, *35*, 949−953.
(11) Meltzer, P. C.; Liang, A. Y.; Madras, B. K. 2-Carbomethoxy-3-(diarylmethoxy)-1α*H*,5α*H*-tropane analogs: Synthesis and inhibition of binding at the dopamine transporter and comparison with piperazines of the GBR series. *J. Med. Chem.* **1996**, *39*, 371−379.
(12) Meltzer, P. C.; Liang, A. Y.; Brownell, A.-L.; Elmaleh, D. R.; Madras, B. K. Substituted 3-phenyltropane analogs of cocaine: synthesis, inhibition of binding at cocaine recognition sites, and Positron Emission Tomography imaging. *J. Med. Chem.* **1993**, *36*, 855−862.
(13) 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. 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)-tropanee analogs as potent and selective dopamine uptake inhibitors. *J. Med. Chem.* **1995**, *38*, 3933−3940.
(14) 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.
(15) 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 of 3β-(3′-Substituted phenyl)-, 3β-(4′-Substituted phenyl)-, 3β-(3′,4′-Disubstituted phenyl)tropane-2β-carboxylic Acid Methyl Esters. *J. Med. Chem.* **1994**, *37*, 2865−2873.
(16) Carroll, F. I.; Gao, Y.; Rahman, M. A.; 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.
(17) Madras, B. K.; Spealman, R. D.; Fahey, M. A.; Neumeyer, J. L.; Saha, J. K.; Milius, R. A. Cocaine receptors labeled by [^{3}H]2β-Carbomethoxy-3β(4-fluorophenyl)tropane. *Mol. Pharmacol.* **1989**, *36*, 518−524.
(18) 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.
(19) Kozikowski, A. P.; Araldi, G. L.; Ball, R. G. Dipolar cycloaddition route to diverse analogues of cocaine: the 6- and 7-substituted 3-phenyltropanes. *J. Org. Chem.* **1997**, *62*, 503−509.
(20) Chen, Z.; Izenwasser, S.; Katz, J. L.; Zhu, N.; Klein, C. L.; 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.
(21) Kitayama, S.; Shimada, S.; Xu, H.; Markham, L.; Donovan, D. H.; Uhl, G. R. Dopamine transporter site-directed mutations differentially alter substrate transport and cocaine binding. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *89*, 7782−7785.
(22) Abraham, P.; Pitner, J. B.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J.; Carroll, F. I. N-Modified analogs of cocaine: synthesis and inhibition of binding to the cocaine receptor. *J. Med. Chem.* **1992**, *35*, 141−144.
(23) Kozikowski, A. P.; Saiah, M. K. E.; Bergmann, J. S.; Johnson, K. M. Structure-activity relationship studies of N-sulfonyl analogs of cocaine: role of ionic interaction in cocaine binding. *J. Med. Chem.* **1994**, *37*, 3440−3442.
(24) Madras, B. K.; Pristupa, Z. B.; Niznik, H. B.; Liang, A. Y.; Blundell, P.; Gonzalez, M. D.; Meltzer, P. C. Nitrogen-based drugs are not essential for blockade of monoamine transporters. *Synapse* **1996**, *24*, 340−348.
(25) Brownbridge, P.; Chan, T.-H. A Simple Route to the 8-oxabicyclo-[3.2.1]octyl and 9-oxabicyclo[3.3.1]nonyl Systems. Synthesis of the 8-Oxa Analog of Cocaine. *Tetrahedron Lett.* **1979**, *46*, 4437−4440.
(26) Hamada, A.; Chang, Y. A.; Uretsky, N.; Miller, D. D. Dopamine agonists: comparative actions of amine and sulfonium analgues of dopamine. *J. Med. Chem.* **1984**, *27*, 675−680.
(27) Chang, Y. A.; Ares, J.; Anderson, K.; Sabol, B.; Wallace, R. A.; Farooqui, T.; Uretsky, N.; Miller, D. D. Dopamine agonists: effects of charged and uncharged analogues of dopamine. *J. Med. Chem.* **1987**, *30*, 214−218.

(28) Harrold, M. W.; Chang, Y. A.; Wallace, R. A.; Farooqui, T.; Wallace, L. J.; Uretsky, N.; Miller, D. D. Charged analogues of chlorpromazine and dopamine antagonists. *J. Med. Chem.* **1987**, *30*, 1631−1635.
(29) Harrold, M. W.; Wallace, R. A.; Farooqui, T.; Wallace, L. J.; Uretsky, N.; Miller, D. D. Synthesis and D_2 dopaminergic activity of pyrrolidinium, tetrahydrothiophenium, and tetrahydrothiophene analogues of sulpiride. *J. Med. Chem.* **1989**, *32*, 874−880.
(30) Harrold, M. W.; Sriburi, A.; Matsumoto, K.; Miller, D. D.; Farooqui, T.; Uretsky, N. The interaction of ammonium, sulfonium and sulfide analogues of metoclopramide with the D_2 receptor. *J. Med. Chem.* **1993**, *36*, 3166−3170.
(31) Lautens, M.; Ma, S. Reductive and base-induced cleavage reactions of oxabicylic compounds. *Tetrahedron Lett.* **1996**, *37*, 1727−1730.
(32) Molander, G. A.; Cameron, K. O. Neighbouring group participation in Lewis acid-promoted [3+4] and [3+5] annulations. The synthesis of oxabicyclo[3.n.1]alkan-3-ones. *J. Am. Chem. Soc.* **1993**, *115*, 830−846.
(33) Davies, H. M. L.; Peng, Z.-Q.; Houser, J. H. Asymmetric synthesis of 1,4-cycloheptadienes and bicyclo[3.2.1]octa-2,6-dienes by rhodium(II) N-(*p*-(*tert*-butyl)phenylsulfonyl)prolinate catalyzed reactions between vinyldiazomethanes and dienes. *Tetrahedron Lett.* **1994**, *48*, 8939−8942.
(34) Noyori, R.; Makino, S.; Okita, T.; Hayakawa, Y. A method for the generation of a synthetic equivalent of unsubstituted oxyallyl via the bromo ketone-iron carbonyl reaction. A new route to Thujaplicins. *J. Org. Chem.* **1975**, *40*, 806−807.
(35) Danishefsky, S.; Kitahara, T. A useful diene for the Diels-Alder reaction. *J. Am. Chem. Soc.* **1974**, *96*, 7807−7808.
(36) Chan, T.-H.; Brownbridge, P. A novel cycloaromatization reaction. Regiocontrolled synthesis of substituted methyl salicylates. *J. Am. Chem. Soc.* **1980**, *102*, 3534−3538.
(37) Thompson, W. J.; Gaudino, J. A general synthesis of 5-arylnicotinates. *J. Org. Chem.* **1984**, *49*, 5237−5243.
(38) Oh-e, T.; Miyaura, N.; Suzuki, A. Palladium-catalyzed cross-coupling reaction of organoboron compounds with organic triflates. *J. Org. Chem.* **1993**, *58*, 2201−2208.
(39) Keverline, K. I.; Abraham, P.; Lewin, A. H.; Carroll, F. I. Synthesis of the 2β,3α- and 2β,3β-isomers of 3-(*p*-substituted phenyl)tropane-2-carboxylic acid methyl esters. *Tetrahedron Lett.* **1995**, *36*, 3099−3102.
(40) Carroll, F. I. Personal communication, 1995.
(41) 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 methyl esters: Novel ligands with high affinity and selectivity at the dopamine transporter. *J. Med. Chem.* **1996**, *39*, 4139−4141.
(42) Carroll, F. I.; Coleman, M. L.; Lewin, A. H. Synthesis and conformational analysis of isomeric cocaines: a proton and carbon-13 nuclear magnetic resonance study. *J. Org. Chem.* **1982**, *47*, 13−19.
(43) Chem 3D Plus, Cambridge Scientific Computing, Inc. Cambridge, MA, 1991.
(44) Edvardsen, Ø.; Dahl, S. G. A putative model of the dopamine transporter. *Mol. Brain Res.* **1994**, *27*, 265−274.
(45) Vaughan, R. A.; Kuhar, M. J. Dopamine transporter ligand binding domains. *J. Biol. Chem.* **1996**, *271*, 21672−21680.
(46) Meltzer, P. C.; Madras, B. K. Unpublished data.

JM9703045