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

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Cocaine is a potent central nervous system stimulant with severe addiction liability. Its reinforcing and stimulant properties derive from inhibition of monoamine transport systems, in particular the dopamine transporter (DAT). This inhibition results in an increase in synaptic dopamine with subsequent stimulation of postsynaptic dopamine receptors. A wide variety of ligands manifest potent inhibition of the DAT, and these ligands include 3-aryltropane as well as 8-oxa-3-aryltropane analogues of cocaine. There has been considerable effort to determine structure−activity relationships of cocaine and congeners, and it is becoming clear that these inhibitors do not all interact with the DAT in the same manner. The functional role of the 8-heteroatom is the focus of this study. We describe the preparation and biology of a series of 2-carbomethoxy-3-arylbicyclo[3.2.1]octane analogues. Results show that *methylene* substitution of the *amine* or *ether* function of the 8-hetero-2-carbomethoxy-3-arylbicyclo[3.2.1]octanes yields potent inhibitors of monoamine transport. Therefore neither nitrogen nor oxygen are prerequisites for binding of tropane-like ligands to monoamine transporters.

Introduction

Cocaine is a potent central nervous system stimulant with severe addiction liability. Its reinforcing and stimulant properties are a consequence of its propensity to inhibit monoamine transport systems, in particular the dopamine transporter (DAT).[1−8] This inhibition results in an increase in synaptic dopamine levels which then leads to overstimulation of postsynaptic dopamine receptors.[9] The DAT not only binds the classical nitrogen-containing 3-aryltropane analogues of cocaine [(1*R*)-(2β-carbomethoxy-3β-aryl-8-azabicyclo[3.2.1]octanes; WIN analogues] (Figure 1)[10−14] but also binds 8-oxa analogues (for example O-914) with substantial potency and selectivity.[15−17] There has been considerable effort to determine structure−activity relationships (SAR) of cocaine and congeners.[5,6,10−14,17−24] It is becoming clear that these disparate DAT inhibitors do not all interact with the DAT in the same manner.[16,25]

The functional role of the 8-heteroatom in the 8-aza and 8-oxatropanes[16] (Figure 1) is the focus of this study. The role of these 8-heteroatoms in the tropane system has been suggested to provide either an ionic bond[13] between the protonated amine and the presumed aspartate residue (Asp[79]) on the DAT (8-aza)[26] or a hydrogen bond to an as yet unidentified DAT residue in the case of the 8-oxatropanes.[16] To evaluate the possibility that neither an ionic nor a hydrogen bond is necessary, we prepared novel bicyclo[3.2.1]octane analogues devoid of an 8-heteroatom, for example, O-1414 (Figure 1).[17]

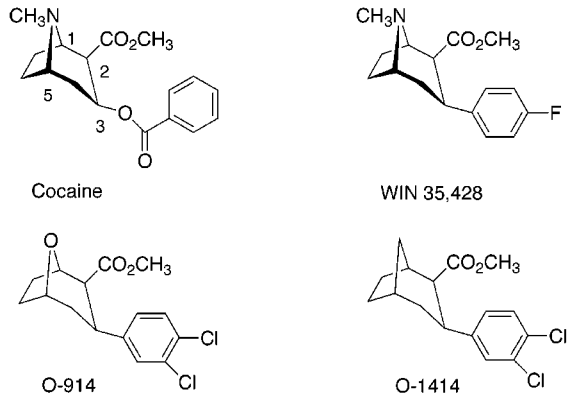

Figure 1. Structures of lead bicyclo[3.2.1]octanes.

Carbon is not a bioisostere for oxygen or nitrogen, and therefore the exchange of carbon for an oxygen or nitrogen atom in a biologically active nucleus is not generally considered. Notwithstanding, within the phenyltropane series of cocaine analogues, we had already demonstrated that the nitrogen is not essential for biological activity.[16] We had postulated[24] that the three-dimensional topology of the ligand may be more important for binding to the biological macromolecule (DAT or SERT (serotonin transporter)) than the specific functionality present. Therefore we elected to replace the heteroatom at position 8 of the tropane nucleus with a carbon atom that is capable of neither ionic nor hydrogen bonding and provides nothing other than maintenance of the overall topological shape. Herein we describe the preparation and biology of a series of 2-carbomethoxy-3-arylbicyclo[3.2.1]octane analogues which possess a similar three-dimensional shape to their 8-aza and 8-oxa counterparts but which do not provide the putative DAT anchor point of position 8. We show

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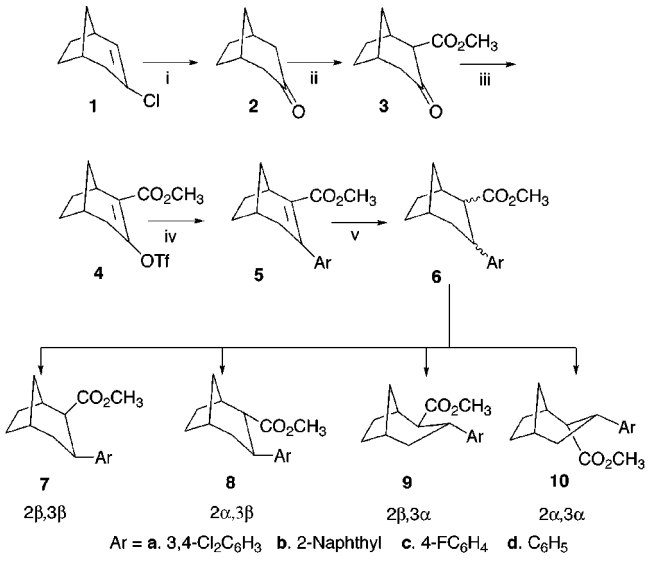
Scheme 1. Synthesis of 2-Carbomethoxy-3-arylbicyclo[3.2.1]octanes[a]



[a] Reagents: (i) H_2SO_4; (ii) LDA/THF, $CNCOOCH_3$; (iii) NaN(TMS)$_2$, $PhNTf_2$; (iv) $ArB(OH)_2$, $Pd_2(dba)_3$; (v) SmI_2, CH_3OH.

that *methylene* ($-CH_2-$) substitution of the *amine* ($-N(CH_3)-$) or *ether* ($-O-$) function of the 8-hetero-2-carbomethoxy-3-arylbicyclo[3.2.1]octanes results in potent inhibitors of monoamine transport. This calls into question the dogma that a heteroatom at position 8 is needed for potent and selective inhibition of the DAT.

Chemistry

A general route developed for synthesis of certain 2-carbomethoxy-3-(3,4-dichlorophenyl)bicyclo[3.2.1]-octanes has been communicated previously from these laboratories.[17] We now report the complete details of synthesis, separation, and characterization of all four isomers of the 3-(3,4-dichlorophenyl) and 3-(2-naphthyl) analogues as well as the 3-(4-fluorophenyl) and the unsubstituted 3-phenyl carbocycles. The synthetic route (Scheme 1) provides a racemic mixture of each of the configurational isomers (**7**−**10**), and biological data are therefore provided for racemates of **7**−**10**.

The ketone **2** was obtained in 77% yield[27] upon treatment of the commercially available 3-chlorobicyclo-[3.2.1]oct-2-ene, **1**, with sulfuric acid. The 2-carbomethoxy group was then introduced[16] by reaction of **2** with methyl cyanoformate in the presence of lithium diisopropylamide to provide the racemic keto ester **3** (83%). The keto ester **3** exists in equilibrium in three isomeric forms as evidenced by ^{1}H NMR (2α-carboxy ester, enol-2-carboxy ester, and 2*β*-carboxy ester) and was converted as such to the enol triflate **4** (75%) by treatment with phenylbis(trifluoromethanesulfonyl)amine in the presence of sodium bis(trimethylsilyl)amide. Suzuki coupling[28,29] of the enol triflate with the appropriate boronic acids then provided the 2,3-unsaturated analogues **5a**−**d** in 54−75% yield. Reduction of **5a**−**d** with samarium iodide gave **6a**−**d** (64−84%) as a mixture of all four isomers **7**−**10**.[30]

An interesting observation was made in one case where older samarium iodide was utilized. In addition to the usual reductive products, treatment of **5c** with reducing agent provided the 3,4-epoxide **22** (Figure 2).

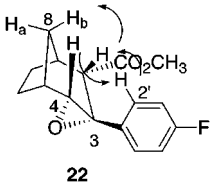


Figure 2. NOE correlations of the epoxide **22**.

This compound likely arises from initial isomerization of the double bond from the 2,3-position to the 3,4-position and subsequent quenching of the samarium coordinated intermediate with oxygen present in the older samarium iodide sample. This compound proved relatively uninteresting biologically and has not been pursued further (DAT $IC_{50} = 1.7\ \mu M$). The structure of this epoxide is clear from mass spectrometry and the NMR studies discussed below.

The combination of ^{1}H-COSY and direct (HMQC) and long-range (HMBC) H−C correlation experiments showed the integrity of the bicyclo[3.2.1]octane skeleton and a clear mapping of the different substituents present. The stereochemistry of positions 2−4 was determined by NOE (Figure 2). Irradiation of H-2′ produced NOE enhancements in the signals corresponding to H-2 and H-4, an indication that both of these protons were on the same face of the molecule as the aromatic ring. Finally, through-space interactions between H-8b and H-2 and, to a lesser extent, H-4 indicated that these protons were on the *β*-face of the molecule. For that reason the α-configuration was assigned to both the 2-CO_2Me group and the 3,4-epoxide.

In each of the four cases **6a**−**d** the corresponding configurational isomers **7**−**10** presented as single spots in all TLC systems evaluated. They therefore proved extremely difficult to separate, and biological evaluation was initially conducted on the isomeric mixtures in order to determine which isomers might warrant laborious separation. The 4-fluorophenyl mixture of isomers **6c** and the unsubstituted mixture of isomers **6d** both presented DAT IC_{50} binding constants of about 0.3−0.8 μM and were therefore set aside. In sharp contrast, the 3-(3,4-dichlorophenyl) **6a** and 3-(2-naphthyl) **6b** analogues manifested unexpectedly potent binding, and these two compounds were selected for careful separation of configurational isomers.

Notwithstanding the great similarity in polarity between the configurational isomers **7a**−**10a** and **7b**−**10b**, careful gravity column chromatography on flash silica provided the pure 2*β*,3*β*- (**7a,b**), 2α,3*β*- (**8a,b**), 2*β*,3α- (**9a,b**), and 2α,3α- (**10a,b**) bicyclo[3.2.1]octanes, albeit in low yields.

The biological activity determined for these compounds (Table 2) was sufficiently interesting and unusual to warrant meticulous and unequivocal structural assignment. The configuration of each isomer was determined by NMR studies and was corroborated by X-ray crystallography. Although proton resonance positions and multiplicity have been reported for both the 8-aza and 8-oxa analogues, assignments are more difficult for the carba analogues since the absence of an 8-heteroatom causes the α-protons, H-1 and H-5, to shift upfield and into the domain of other skeletal protons.

The determination of the relative configuration of compounds **7a**−**10a** was achieved by a combination of

Table 1. ^{1}H NMR Chemical Shifts and Coupling Constants of Selected Protons in Compounds **7a**,**b**−**10a**,**b**[a]

compd	2,3[b]	1-H	5-H	2-H	3-H	4α-H	4β-H	8b	8a	CO_2Me
7a	β,β	2.53 (m)	2.42 (m)	2.84 (dd) (6, 6)	2.98 (ddd) (13, 6, 6)	1.45−2.00 (5H)	2.31 (ddd) (13, 13, 2)	1.85 (bd) (12)	1.28 (ddd) (12, 6, 6)	3.44 (s)
7b		2.54 (m)	2.48 (m)	3.00 (dd) (6, 4)	3.22 (ddd) (12, 6, 6)	1.55−2.00 (5H)	2.56 (m)	2.00 (bd) (12)	1.32 (ddd) (12, 6, 6)	3.32 (s)
8a	α,β	2.48 (m)	2.32 (m)	2.66 (dd) (12, 2)	3.10 (ddd) (12, 12, 6)		1.45−190 (8H)			3.51 (s)
8b		2.51 (m)	2.35 (m)	2.88 (dd) (12, 2)	3.31 (ddd) (12, 12, 6)		1.50−2.05 (8H)			3.43 (s)
9a	β,α	2.30−2.40 (2H)		2.36 (d) (12)	3.03 (ddd) (12, 12, 8)	1.20 (dd) (12, 12)	2.24 (ddd) (12, 8, 8)	1.92 (bd) (12)	1.10 (ddd) (12, 4, 4)	3.54 (s)
9b		2.35−2.45 (2H)		2.58 (d) (11)	3.26 (ddd) (11, 11, 7)	1.40 (dd) (12, 12)	2.32 (ddd) (12, 7, 7)	2.05 (bd) (12)	1.15 (ddd) (12, 4, 4)	3.48 (s)
10a	α,α	2.64 (m)	2.37 (m)	3.31 (dd) (6, 6)	3.11 (ddd) (12, 6, 6)	1.95 (bdd) (12, 12)	2.16 (ddd) (12, 6, 6)	1.82 (bd) (12)	1.28 (ddd) (12, 4, 4)	3.45 (s)
10b		2.70 (m)	2.40 (m)	3.35−3.45 (2H)		2.20 (ddd) (12, 12, 2)	2.29 (ddd) (12, 7, 7)	1.89 (bd) (12)	1.35 (ddd) (12, 4, 4)	3.36 (s)

[a] Chemical shift in ppm followed by multiplicity (in parentheses) and coupling constants in Hz (in parentheses). When the signals appeared superimposed with other signals a range is indicated, followed by the total number of H (in parentheses) in such range. [b] Configuration of substituents at positions 2 and 3.

NMR techniques. The ^{1}H NMR spectra were completely assigned (COSY, HMQC, HMBC). An analysis of the multiplicity of the key resonances showed familiar coupling patterns observed previously for the 8-aza and 8-oxa analogues.[11,16] The chemical shifts and coupling constants for selected protons for configurational isomers are presented in Table 1. Compounds **8a** and **9a** showed a large coupling (12 Hz) between H-2 and H-3, typical of a trans−diaxial interaction. This is compatible with both 2α,3β-substitution in the chair conformation or 2β,3α-substitution in the boat conformation. In contrast, coupling constants between H-2 and H-3 in **7a** and **10a** were smaller (6 Hz) and characteristic of axial−equatorial interactions thus indicating 2β,3β-substitution in the chair conformation or 2α,3α-substitution in the boat conformation. Finally compounds **9a** and **10a** were identified as the 3α-substituted isomers since they manifested NOE interactions between H-3 and H-8 thus confirming the through-space proximity of these atoms. Such proximity is only possible if H-3 is in the β-configuration in a boat conformation. These results not only provided unequivocal identification of compounds **7a**−**10a** but also confirmed that, in this series, the 3α-aryl-substituted analogues adopted the boat conformation for the six-membered ring, as already shown in the case of the 8-aza and 8-oxa series.[16,31]

X-ray structural analyses were conducted on four configurational racemates: **7a** (2β,3β), **8a** (2α,3β), **8b** (2α,3β), **10b** (2α,3α). The absolute structures were then correlated with the relevant ^{1}H NMR spectra and all configurations assigned unambiguously

To probe the dominating significance of the relationship between the C-2 ester and a C-3 aromatic substituent, the compounds presented in Scheme 2 were prepared by straightforward chemistry. Thus, commercially available methyl 2-iodobenzoate **(16)** was coupled with appropriate arylboronic acids to obtain **17a**−**d** and **21**. Compound **19** was obtained upon benzoylation of **18**.

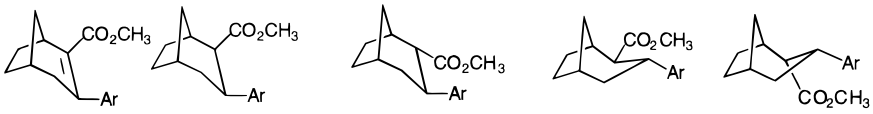
Biology

The affinities of the bicyclo[3.2.1]octane analogues for the DAT and SERT were determined in competition studies using [^{3}H]-3β-(4-fluorophenyl)tropane-2β-carboxylic acid methyl ester ([^{3}H]WIN 35,428) to label the DAT[6] and [^{3}H]citalopram to label the SERT.[15] Each compound was tested 2−5 times, and each assay was conducted independently in brain tissue of rhesus or cynomolgus monkey.

Binding data (IC_{50}) for the bicyclo[3.2.1]octane racemates are presented in Table 2. Data for 8-azabicyclo-[3.2.1]octanes are presented in Table 3. The 1-aryl-2-carbomethoxy analogues are presented in Table 4. Studies were conducted in monkey striatum because these compounds are part of an ongoing investigation of SARs at the DAT in this tissue.[6,11,12,17,19,24] Hence meaningful comparisons with an extensive database can be made. IC_{50} values are reported as the assay concentrations of [^{3}H]WIN 35,428 and [^{3}H]citalopram were below K_d values. 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 clear that certain of the bicyclo[3.2.1]octanes bind potently and selectively to the DAT versus the SERT

Table 2. Inhibition of [^{3}H]WIN 35,428 Binding to the DAT and [^{3}H]Citalopram Binding to the SERT by Bicyclo[3.2.1]octanes in Cynomolgus Monkey Caudate-Putamen



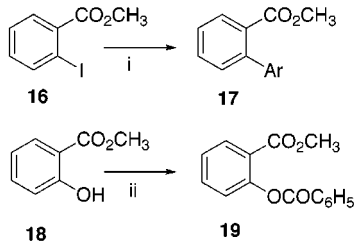
5 **7** (2β,3β) **8** (2α,3β) **9** (2β,3α) **10** (2α,3α)

Ar = **a**. 3,4-$Cl_2C_6H_3$ **b**. 2-Naphthyl **c**. 4-FC_6H_4 **d**. C_6H_5

Ar	no.	compd	IC$_{50}$ (nM) DAT [^{3}H]WIN 35,428	IC$_{50}$ (nM) SERT [^{3}H]citalopram	selectivity SERT/DAT
3,4-$Cl_2C_6H_3$	**5a**	O-1231	7.1	5160	726
2-naphthyl	**5b**	O-1482	11	1310	119
4-FC_6H_4	**5c**	O-1436	390	35400	91
C_6H_5	**5d**	O-1443	3816	>10000	
4-FC_6H_4 (m)[a]	**6c**	O-1472	335	na[b]	
C_6H_5 (m)	**6d**	O-1488	787	>20000	25
3,4-$Cl_2C_6H_3$	**7a**	O-1414	9.6	33	3
2-naphthyl	**7b**	O-1669	27	60	2
3,4-$Cl_2C_6H_3$	**8a**	O-1415	14	650	46
2-naphthyl	**8b**	O-1590	12	807	67
3,4-$Cl_2C_6H_3$	**9a**	O-1442	13	180	14
2-naphthyl	**9b**	O-1670	17	64	4
3,4-$Cl_2C_6H_3$	**10a**	O-1468	42	na	
2-naphthyl	**10b**	O-1649	25	106	4

[a] m = evaluated as a mixture of all four configurational isomers. [b] na = not available.

Scheme 2. Synthesis of Carbomethoxyaryl Analogues[a]



16 **17** **18** **19**

Ar = **a**. 2-Naphthyl **b**. 4-ClC_6H_5 **c**. 4-FC_6H_4 **d**. C_6H_5

[a] Reagents: (i) $ArB(OH)_2$, $Pd(Ph_3)_2Cl_2$, $CsCO_3$; (ii) C_6H_5COCl.

(Table 2). Analogously to the 8-aza- and 8-oxatropanes, the most potent carbocycles are those which possess either a 2-naphthyl group or a 3,4-dichlorophenyl group at C-3 of the carbocycle. Thus, the 3,4-dichlorophenyl 2,3-unsaturated analogue **5a** has an IC$_{50}$ of 7.1 nM for the DAT and is extremely selective (SERT: IC$_{50}$ = 5160 nM; 726-fold selectivity). This is similar to the potency (DAT: IC$_{50}$ = 1.2 nM) and selectivity (SERT: IC$_{50}$ = 867 nM) exhibited by the 2,3-unsaturated 8-aza analogue **11a**. The 2-naphthyl 2,3-unsaturated analogue **5b** is also quite potent (DAT: IC$_{50}$ = 11 nM) and selective (SERT: IC$_{50}$ = 1,310). It is notably more selective than its nitrogen 2,3-unsaturated counterpart **11b** (Table 3) which manifests a SERT IC$_{50}$ of 109 nM and 38-fold selectivity. The saturated carbocyclic (Table 2: **7a**, **8a**, **9a**, **10a**) and 8-aza (Table 3: **12a**, **13a**, **14a**) 3,4-dichlorophenyl compounds manifest potencies of 7−42 nM irrespective of the configuration at either C-2 or C-3. The same is true for the C-3 2-naphthyl carbocyclic (Table 2: **7b**, **8b**, **9b**, **10b**) and 8-aza (Table 3: **12b**, **15b**) analogues. In general, the carbocycles in each class are less potent than their nitrogenous counterparts although both series bind with low nanomolar affinity.

Discussion

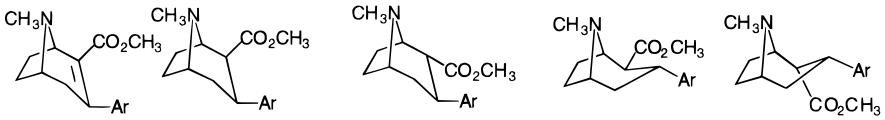
It has long been assumed that for tropanes and bicyclo[3.2.1]octanes to manifest potent inhibition of the DAT they should possess substitution at the C-2 position.[5,11,32−34] However, although it has often been presumed that such C-2 substitution should be in the *β*-orientation, this proves not to be the case. Indeed, after careful evaluation of the literature, we were encouraged to further explore the effect of 2α- versus 2*β*-substitution upon inhibition of both the DAT and SERT.

The importance of this question resides in the fact that the dogma of 2*β*-orientation has guided a considerable amount of the work in the tropane area and may have lead to the abandonment of potentially important and interesting compounds. In general, 2α-compounds have not been evaluated even when they have emerged from the synthetic route utilized to make their 3*β*-counterparts.[11,20] In the interests of reassessing the importance of consideration of 2α-substitution, we now present a summary of relevant SAR.

The assumption that 2α-substitution leads to much less active DAT inhibitors and therefore potentially less interesting compounds derives from the early work in this area. Thus Clarke et al.[35] reported that in the phenyltropanes, moving the C-2 substituent from a C-2*β* orientation to a C-2α orientation resulted in loss of stimulant activity in their locomotor screen.

Later Reith[5] reported that moving the C-2 carbomethoxy group in cocaine from an axial (*β*) to an equatorial (α) position significantly diminished potency in their behavioral assay. Ritz[32] confirmed this in a ligand binding assay and reported that the potency ratio between 2α-carbomethoxy-3-phenyltropane (WIN 35,-140) and 2*β*-carbomethoxy-3-phenyltropane (WIN 35-065-2) was 1481, thus rendering the 2α-isomer comparatively inactive.

Table 3. Inhibition of [^{3}H]WIN 35,428 Binding to the DAT and [^{3}H]Citalopram Binding to the SERT by Bicyclo[3.2.1]octanes in Cynomolgus Monkey Caudate-Putamen[a]



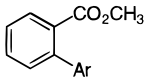
11 **12** (2β,3β) **13** (2α,3β) **14** (2β,3α) **15** (2α,3α)

Ar = **a**. 3,4-$Cl_2C_6H_3$ **b**. 2-Naphthyl **c**. 4-FC_6H_4 **d**. C_6H_5

Ar	no.	compd	IC$_{50}$ (nM) DAT [^{3}H]WIN 35,428	IC$_{50}$ (nM) SERT [^{3}H]citalopram	selectivity SERT/DAT
3,4-$Cl_2C_6H_3$	**11a**	O-1109	1.2	867	723
2-naphthyl	**11b**	O-1173	2.9	109	38
4-FC_6H_4	**11c**	O-1104	408	7990	20
C_6H_5	**11d**	na[b]	na	na	
3,4-$Cl_2C_6H_3$	**12a**	O-401	1.1	2	2
2-naphthyl	**12b**	O-1229	0.49	2.19	4
4-FC_6H_4	**12c**	O-381	11	160	15
C_6H_5	**12d**	na	na	na	
3,4-$Cl_2C_6H_3$	**13a**	O-1496	2.0	358	179
2-naphthyl	**13b**	na	na	na	
4-FC_6H_4	**13c**	O-1492	633	12200	19
3,4-$Cl_2C_6H_3$	**14a**	O-1157	0.4	27	68
2-naphthyl	**14b**	na	na	na	
3,4-$Cl_2C_6H_3$	**15a**	na	na	na	
2-naphthyl	**15b**	O-1228	0.57	5.95	10

[a] See ref 11 and references therein for syntheses of these analogues. [b] na = not available.

Table 4. Inhibition of [^{3}H]WIN 35,428 Binding to the DAT and [^{3}H]Citalopram Binding to the SERT by Biaryl Analogues in Cynomolgus Monkey Caudate-Putamen



Ar	no.	compd	IC$_{50}$ DAT [^{3}H]WIN 35,428	IC$_{50}$ SERT [^{3}H]citalopram	selectivity SERT/DAT
2-naphthyl[a]	**17a**	O-1521	145 nM	10 μM	69
4-ClC_6H_4[b]	**17b**	O-1567	675 nM	46 μM	68
4-FC_6H_4[c]	**17c**	O-1571	16 μM	33 μM	2
C_6H_5[d]	**17d**	O-1566	>100 μM	>70 μM	
$OCOC_6H_5$[e]	**19**	O-1574	548 nM		
$COOCH_3$[e]	**20**	O-1570	>100 μM	>100 μM	
C_6H_4-C_6H_4-4Br	**21**	O-1565	1 μM	>10 μM	

[a] Craebe et al. *Justus Liebigs Ann. Chem.* **1904**, *335*; Bradsher et al. *J. Am. Chem. Soc.* **1940**, *62*, 3140. [b] Klement et al. *Tetrahedron* **1996**, *52*, 7201. [c] Kelm and Strauss *Spectrochim. Acta Part A* **1981**, *37*, 689. [d] Grieve and Hey *J. Chem. Soc.* **1938**,*108*. [e] Purchased from Aldrich.

In 1989[6,18] it was reported that cocaine receptors were labeled by 2β-carbomethoxy-3β-(4-fluorophenyl)tropane but not by the 2α-isomer. Neumeyer[36] reported (1991) [^{123}I]-2β-carbomethoxy-3β-(4-iodophenyl)tropane as a SPECT radiotracer for monoamine reuptake sites and pointed out that the 2α-analogue was effectively 55 times less potent that the 2β-analogue.

Carroll's report[37] on C-2 heterocyclic analogues in 1993 and later in 1996[38] confirmed this yet again in that 3β-phenyl-2α-(3′-methyl-1′,2′,4′-oxadiazol-5′-yl)tropane was considerable less potent as an inhibitor of the DAT than the 2β-analogue.

In contrast, Moldt described[39] a series of 2α-substituted tropanes in 1994 that manifests surprising DAT potency. In fact, 3β-(3,4-dichlorophenyl)-2α-carbomethoxy tropane, **13a**, reportedly manifested an IC$_{50}$ = 16 nM for inhibition of [^{3}H]dopamine reuptake. Trudell[40] then reported in 1997 that the 2α-homologated ester, 3β-benzyl-2α-(carbomethoxy)methyltropane, was about equipotent to its 2β-analogue. This work was followed by a second patent by Moldt et al. (1998)[41] in which they reported that 3β-(3,4-dichlorophenyl)-2α-*O*-methylaldoxime tropane inhibits the DAT with an IC$_{50}$ = 1.8 nM.

The prototypical tropane WIN 35,428[35] has a 2β-configured carbomethoxy group and manifests an IC$_{50}$ of about 11 nM with DAT:SERT selectivity of about 15. We evaluated the 2α-carbomethoxy isomer of WIN 35,-428 (**13c**) and found it to possess an IC$_{50}$ of 633 nM and DAT:SERT selectivity of 19. It is therefore considerably weaker than its 3β-counterpart and about as selective. However, the more potent tropane, 2β-carbomethoxy-3β-(3,4-dichloro)phenyltropane **(12a)**, manifests an IC$_{50}$ of 1.1 nM (selectivity = 2), and its 2α-carbomethoxy counterpart **13a** is almost as potent with an IC$_{50}$ for inhibition of [^{3}H]WIN 35,428 binding of 2.0 nM but has much enhanced selectivity (179-fold). (Moldt[39] had reported an IC$_{50}$ = 16 nM for inhibition of [^{3}H]dopamine reuptake for this compound.) Likewise, the 2β-car-

bomethoxy-3β-(2-naphthyl) **12b** manifests an $IC_{50} = 0.5$ nM (selectivity = 4), while the 2α-carbomethoxy-3α-(2-naphthyl) counterpart **15b** has $IC_{50} = 0.57$ nM and selectivity of about 10-fold. Consequently it is not surprising that in the family of carbocyclic compounds presented here, similar results are obtained. Thus, while the 2β-carbomethoxy compound **7a** has $IC_{50} = 9.6$ nM and **9a** has $IC_{50} = 13$ nM, the 2α-compounds **8a** and **10a** manifest IC_{50}'s of 14 and 42 nM, respectively (Table 2). Furthermore, this trend holds for the 3-(2-naphthyl)-substituted compounds as well. Thus, the 2β-carbomethoxy analogues **7b** and **9b** manifest IC_{50} values of 27 (selectivity: 2) and 17 nM (selectivity: 4), respectively, while their 2α-counterparts **8b** and **10b** have IC_{50} values of 12 nM (selectivity: 67) and 25 nM (selectivity: 4), respectively.

It may therefore be concluded that those 2β-compounds that manifest substantial potency have 2α-carbomethoxy isomers with similar DAT binding inhibition and often much greater selectivity versus the SERT. In contrast, the 2α-carbomethoxy analogues of relatively less potent 2β-carbomethoxy compounds are themselves not potent. This brings into question the function of the 2-substituent with respect to its interaction at the acceptor site[24] on the DAT or SERT.

We have previously suggested that tight binding between the ligand and its biological receptor may depend more heavily upon the three-dimensional topology of the ligand than upon the exact functionality present.[24] For example, the actual substitution of the 8-position is of less consequence than is the volume that it occupies. Evidence for this is the fact that the 8-position can be changed from nitrogen to oxygen to carbon with limited effect on affinity. In contrast, the SAR of DAT inhibition is markedly effected by the nature of substituents at C-3.[11,14,20] Therefore a dominant factor governing interaction of a DAT ligand with the transporter may be its topology (molecular volume and shape).[24] We have also previously suggested that subtle topological placement of the 3-aryl substituent most likely controls not only binding potency but also selectivity for the DAT versus the SERT.[24] This was evidenced by the fact that compounds in the boat conformation (3α) are equally potent to, but more selective than, those in the chair conformation (3β) with respect to DAT inhibition. This difference in conformation controls placement of the aromatic ring. Furthermore it appears that the ring conformation may be further modified by the relationship between the substituents at C-2 and C-3.

In an effort to further explore the concept of topology dominating functionality, we prepared and evaluated the simple molecules **17** and **19** presented in Scheme 2. The design of these molecules was based upon the premise that the bicyclo[3.2.1]octane system of the tropanes, their 8-oxa analogues, and the 8-carba analogues may merely provide a useful skeleton and that the relative relationship of the C-2 ester and the C-3 aromatic ring may of itself dominate biological activity with respect to DAT inhibition. From an examination of the IC_{50} values (Table 4) obtained for the compounds modeled on the 3-arylbicyclo[3.2.1]octanes in which the aryl group is tied directly to the C-3 carbon of the skeleton, it is clear that the SAR of this small series is remarkably similar to that for the bicyclo[3.2.1]octanes. Thus the naphthyl compound **17a** is more potent ($IC_{50} = 145$ nM) than the monochloro **17b** ($IC_{50} = 675$ nM), while the 4-fluoro **17c** ($IC_{50} = 16\ \mu$M) and unsubstituted **17d** ($IC_{50} = >100\ \mu$M) compounds exhibit very poor potency (SAR: naphthyl > chloro > fluoro > H). It is extremely surprising that the naphthyl analogue is as potent as 145 nM at the DAT. This inhibition is close to the range of cocaine (IC_{50} of 90 nM)! In the case where an intervening ester is introduced between the "skeleton" and the aryl group (analogous to cocaine) as in **19**, it is remarkable that the IC_{50} is as potent as 548 nM. Extension of the aromatic system as in **21** and removal of the aryl ring in **20** lead to a considerable loss in potency.

Conclusion

The most important conclusion from these studies is that neither nitrogen nor oxygen are prerequisites for binding of tropane-like ligands to monoamine transporters. 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.[26] Hydrogen bonding has been proposed to explain the interaction of the 8-oxatropanes with the DAT.[16] Formation of either an ionic bond or a hydrogen bond is not possible with these carbocyclic compounds, and yet many bind to both the DAT and SERT with potency similar to that of their nitrogen- or oxygen-containing counterparts.

We postulate that there are a number of ligand acceptor sites within the DAT and that binding at any one of these acceptor sites can cause inhibition of dopamine reuptake.[16,24,25,42] These three families may occupy different ligand acceptor sites on the DAT and SERT and may consequently have different requirements for binding. For example, 8-aza compounds may bind at a site that possesses an acid residue (e.g. Asp^{79}), while the 8-oxa analogues may bind at a different acceptor site that can offer hydrogen bonding. The carbocycles may inhibit monoamine transport by binding to yet a third acceptor site that relies on neither an acid residue nor a residue capable of hydrogen donation to the ligand. This concept is currently under investigation in our laboratories.

Experimental Section

All compounds are racemates (1*R*/1*S*). NMR spectra were recorded in $CDCl_3$ on a JEOL 300 NMR spectrometer operating at 300.53 MHz for ^{1}H and 75.58 MHz for ^{13}C. 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 UV exposure or treatment with phosphomolybdic acid (PMA). Flash chromatography was carried out on Baker silica gel 40 mm. Elemental analyses were performed by Atlantic Microlab, Atlanta, GA. All reactions were conducted under an inert (N_2) atmosphere. [^{3}H]WIN 35,428 (2β-carbomethoxy-3β-(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).

2-Carbomethoxybicyclo[3.2.1]octan-3-one (3). To bicyclo-[3.2.1]octan-3-one, **2**[27] (6.42 g, 51.7 mmol) in THF (75 mL), was added dropwise at −78 °C lithium diisopropylamide (31 mL, 62 mmol) in THF (125 mL). The mixture was stirred at −78 °C for 1 h and methyl cyanoformate (4.9 mL, 62 mmol) was added. The cooling bath was removed and the reaction allowed to warm to room temperature. After stirring for 2 h, saturated aqueous NaCl (32 mL) was added and about half of THF removed on a rotary evaporator. The remaining solvent was extracted with ether (3 × 150 mL) and the dried (Na_2SO_4) ether layer concentrated to dryness. The residue was purified by flash chromatography (eluent: 10% EtOAc/hexanes) to afford 7.85 g (83%) of **3** as a colorless oil: R_f 0.56 (10% EtOAc/hexanes); ^{1}H NMR (75:15:10 mixture of 2-en-3-ol, 2α-, and 2β-carbomethoxy 3-keto tautomers) δ 11.87 (s, 1H), 3.73 (s, 3H), 3.70 (s, 0.6H), 3.69 (s, 0.4H), 3.42 (m, 0.2H), 3.19 (m, 0.13H), 2.93 (m, 1H), 2.81 (m, 0.13H), 2.71 (m, 0.2H), 2.65 (ddd, 0.13H, J = 18, 4, 2 Hz), 2.55 (ddd, 1.2H, J = 18, 4, 2 Hz), 2.41 (m, 1H), 2.34 (m, 0.2H), 2.29 (m, 0.13H), 2.03 (dd, 1H, J = 18, 2 Hz), 1.65−1.95 (m, 4.4H), 1.30−1.55 (m, 3.6H); ^{13}C NMR (only the signals corresponding to the 2-en-3-ol tautomer are reported) δ 172.00, 171.19, 105.38, 51.33, 40.19, 35.92, 35.58, 32.91 (2C), 29.90.

2-Carbomethoxy-3-{[(trifluoromethyl)sulfonyl]oxy}-bicyclo[3.2.1]-2-octene (4). To 2-carbomethoxybicyclo[3.2.1]-octan-3-one, **3** (6.0 g, 3.29 mmol) in THF (120 mL), was added dropwise at −78 °C sodium bis(trimethylsilyl)amide (1.0 M solution in THF, 49.4 mL). After stirring for 30 min, *N*-phenyltrifluoromethane sulfonimide (17.6 g, 4.94 mmol) was added in one portion. After 10 min, the cooling bath was removed and the reaction mixture stirred overnight. Water (100 mL) was added to the reaction mixture and extracted with diethyl ether (3 × 150 mL). The dried (Na_2SO_4) ether layers were concentrated to dryness on a rotary evaporator. The residue was purified by flash chromatography (eluent: 20% EtOAc/hexanes) to afford 7.8 g (75%) of **4** as a colorless oil: R_f 0.56 (20% EtOAc/hexanes); ^{1}H NMR δ 3.79 (s, 3H), 3.10 (m, 1H), 2.71 (dd, 1H, J = 18, 5 Hz), 2.52 (m, 1H), 2.17 (dd, 1H, J = 18, 2 Hz), 1.75−2.05 (m, 3H), 1.45−1.70 (m, 3H); ^{13}C NMR δ 164.44, 151.02, 129.04, 118.23 (q, J = 320 Hz), 52.05, 39.68 (d, J = 1 Hz), 36.61, 35.34, 34.51, 33.31, 30.01.

2-Carbomethoxy-3-(3,4-dichlorophenyl)bicyclo[3.2.1]-2-octene (5a). 2-Carbomethoxy-3-{[(trifluoromethyl)sulfonyl]-oxy}bicyclo[3.2.1]-2-octene, **4** (2.0 g, 63.6 mmol), 3,4-dichlorophenylboronic acid (1.58 g, 82.7 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.29 g, 0.32 mmol), Na_2CO_3 (2 M solution, 6.4 mL) and diethoxymethane (32 mL) were combined and refluxed at 95 °C for 4 h. Tris(dibenzylideneacetone)-dipalladium(0) (1.45 g) was then added in five equal portions at 4-h intervals. The reaction mixture was cooled to room temperature, filtered through Celite, and washed with ether (200 mL). The ether solution was then washed with saturated aqueous NaCl (100 mL). The dried (Na_2SO_4) ether layer was removed on a rotary evaporator. The residue was purified by flash chromatography (eluent: 10% EtOAc/hexanes) to afford 1.38 g (69%) of **5a** as a colorless oil: R_f 0.50 (10% EtOAc/hexanes); ^{1}H NMR δ 7.34 (d, 1H, J = 8 Hz), 7.17 (d, 1H, J = 2 Hz), 6.90 (dd, 1H, J = 8, 2 Hz) 3.49 (s, 3H), 3.00 (bt, 1H, J = 5 Hz), 2.64 (ddd, 1H, J = 19, 4, 2 Hz), 2.44 (m, 1H), 2.14 (dd, 1H, J = 19, 1 Hz), 1.75−2.05 (m, 3H), 1.45−1.70 (m, 3H); ^{13}C NMR δ 168.54, 142.60, 142.13, 135.55, 132.07, 130.95, 130.00, 128.80, 126.45, 51.48, 44.52, 37.13, 35.65, 34.86, 33.24, 30.76. Anal. ($C_{16}H_{16}O_2Cl_2$) C, H, Cl.

2-Carbomethoxy-3-naphthylbicyclo[3.2.1]-2-octene (5b). 2-Carbomethoxy-3-{[(trifluoromethyl)sulfonyl]oxy}bicyclo[3.2.1]-2-octene, **4** (0.50 g, 1.60 mmol), 2-naphthaleneboronic acid (0.36 g, 2.08 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.07 g, 0.08 mmol), Na_2CO_3 (2 M solution, 1.6 mL) and diethoxymethane (8 mL) were combined and refluxed at 95 °C overnight. The reaction mixture was cooled to room temperature, filtered through Celite and washed with ether (100 mL). The ether solution was then extracted with saturated aqueous NaCl (50 mL). The dried (Na_2SO_4) ether layer was removed on a rotary evaporator. The residue was purified by flash chromatography (eluent: 10% EtOAc/hexanes) to afford 0.25 g (54%) of **5b** as a colorless oil: R_f 0.41 (10% EtOAc/hexanes); ^{1}H NMR δ 7.83 (m, 3H), 7.62 (d, 1H, J = 1 Hz), 7.48 (m, 2H), 7.28 (dd, 1H, J = 9, 2 Hz), 3.44 (s, 3H), 3.14 (bt, 1H, J = 5 Hz), 2.84 (ddd, 1H, J = 19, 4, 1 Hz), 2.53 (m, 1H), 2.38 (bd, 1H, J = 19 Hz), 1.80−2.20 (m, 4H), 1.60−1.75 (m, 2H); ^{13}C NMR δ 169.17, 143.83, 139.85, 134.55, 133.04, 132.33, 127.76, 127.47, 127.21, 125.83, 125.54 (2), 124.86, 51.04, 44.35, 37.16, 35.54, 34.82, 33.21, 30.60. Anal. ($C_{20}H_{20}O_2$) C, H.

2-Carbomethoxy-3-(4-fluorophenyl)bicyclo[3.2.1]-2-octene (5c). Compound **5c** was obtained from with 4-fluorophenylboronic acid as described for **5a**: colorless oil (73%); R_f 0.5 (10% EtOAc/hexanes); ^{1}H NMR δ 6.95−7.10 (m, 4H), 3.46 (s, 3H), 3.00 (t, 1H, J = 5 Hz), 2.67 (dd, 1H, J = 19, 4 Hz), 2.46 (m, 1H), 2.20 (bd, 1H, J = 19 Hz), 1.50−2.05 (m, 6H); ^{13}C NMR δ 169.10, 161.86 (d, J = 245 Hz), 143.05, 138.32, 134.69, 128.30 (d, J = 8 Hz), 114.81 (d, J = 21 Hz), 51.18, 44.53, 37.15, 35.55, 34.86, 33.21, 30.65. Anal. ($C_{16}H_{17}O_2F$) C, H.

2-Carbomethoxy-3-phenylbicyclo[3.2.1]-2-octene (5d). Compound **5d** was prepared from with phenylboronic acid as described for **5a**: colorless oil (75%); R_f 0.5 (10% EtOAc/hexanes); ^{1}H NMR δ 7.27 (m, 3H), 7.08 (m, 2H), 3.43 (s, 3H), 3.00 (bt, 1H, J = 5), 2.70 (ddd, 1H, J = 19, 4, 1 Hz), 2.46 (m, 1H), 2.23 (bd, 1H, J = 19 Hz) 1.80−2.05 (m, 3H), 1.73 (d, 1H, J = 11 Hz), 1.50−1.65 (m, 2H); ^{13}C NMR δ 169.31, 144.03, 142.46, 134.28, 127.88, 126.95, 126.61, 51.11, 44.37, 37.17, 35.60, 34.90, 33.26, 30.66. Anal. ($C_{16}H_{18}O_2$) C, H.

2(α,β)-Carbomethoxy-3(α,β)-(4-fluorophenyl)bicyclo-[3.2.1]octane (6c). Magnesium (47 mg, 1.90 mmol) was added into 2-carbomethoxy-3-(4-fluorophenyl)bicyclo[3.2.1]-2-octene, **5c** (50 mg, 0.19 mmol) in methanol (2 mL). After 1 h, additional magnesium (47 mg, 1.90 mmol) was added and stirred for 4 h. 1 N HCl (4 mL) was added dropwise and stirred for 1 h. The reaction mixture was extracted with ether (3 × 20 mL) and dried over Na_2SO_4 and the ether layer removed on a rotary evaporator. The residue was purified by flash chromatography (eluent: 10% EtOAc/hexanes) to afford 42 mg (84%) of **6c** as a colorless oil: R_f 0.42 (10% EtOAc/hexanes). Anal. ($C_{16}H_{19}FO_2$) C, H.

2(α,β)-Carbomethoxy-3(α,β)-phenylbicyclo[3.2.1]-octane (6d). Compound **6d** was prepared from **5d** with magnesium as described for **6c**: colorless oil (48%); R_f 0.42 (10% EtOAc/hexanes). Anal. ($C_{16}H_{20}O_2$) C, H.

2β-Carbomethoxy-3β-(3,4-dichlorophenyl)bicyclo-[3.2.1]octane (7a), 2α-Carbomethoxy-3β-(3,4-dichlorophenyl)bicyclo[3.2.1]octane (8a), 2β-Carbomethoxy-3α-(3,4-dichlorophenyl)bicyclo[3.2.1]octane (9a), and 2α-Carbomethoxy-3α-(3,4-dichlorophenyl)bicyclo[3.2.1]octane (10a). To 2-carbomethoxy-3-(3,4-dichlorophenyl)bicyclo[3.2.1]-2-octene, **5a** (1.38 g, 4.43 mmol) in methanol (50 mL) at −78 °C, was added SmI_2 (0.1 M in THF, 237 mL) dropwise via an addition funnel. After completing the addition, the green mixture was stirred for 4 h at −78 °C and quenched with TFA (20 mL) in ether (60 mL). H_2O (50 mL) was added and extracted with ether (3 × 200 mL). The dried (Na_2SO_4) ether layer was concentrated to dryness. The residue was purified by flash chromatography (eluent: 20% EtOAc/hexanes) to afford a mixture of isomers **6a** (1 g, 72%). The isomers were separated by gravity column chromatography (eluent: 10−50% toluene/hexanes) to afford 65 mg of **7a** as a white solid (mp 81.1−81.4 °C), 280 mg of **8a** as a white solid (mp 65.3−65.6 °C), 58 mg of **9a** as a white solid (mp 82.8−83.3 °C), and 42 mg of **10a** as a white solid (mp 83.2−83.8 °C). **7a**: ^{1}H NMR δ 7.31 (d, 1H, J = 2 Hz), 7.30 (d, 1H, J = 8 Hz), 7.08 (ddd, 1H, J = 8, 2, 1 Hz), 3.44 (s, 3H), 2.98 (ddd, 1H, J = 13, 6, 6 Hz), 2.84 (dd, 1H, J = 6, 6 Hz), 2.53 (m, 1H), 2.42 (m, 1H), 2.31 (ddd, 1H, J = 13, 13, 2 Hz), 1.45−2.00 (m, 5H), 1.85 (bd, 1H, J = 12 Hz), 1.28 (ddd, 1H, J = 12, 6, 6 Hz); ^{13}C NMR δ 173.24, 144.03, 131.86, 129.77, 129.75, 129.63, 126.95, 52.15, 51.05, 38.37, 35.91, 34.54, 33.24, 32.95, 29.59, 28.03. Anal. ($C_{16}H_{18}Cl_2O_2$) C, H, Cl. **8a**: ^{1}H NMR δ 7.31 (d, 1H, J = 8 Hz), 7.30 (d, 1H, J = 2 Hz) 7.06 (dd, 1H, J = 8, 2 Hz), 3.51 (s, 3H), 3.10 (ddd, 1H, J = 12, 12, 6 Hz), 2.66 (dd, 1H, J = 12, 2 Hz), 2.48

(m, 1H), 2.32 (m, 1H), 1.87 (m, 1H), 1.45−1.80 (m, 7H); ^{13}C NMR δ 173.94, 144.94, 132.11, 130.18, 129.95, 129.61, 127.18, 52.82, 51.40, 40.83, 39.26, 38.70, 38.28, 34.95, 28.60, 25.14. Anal. ($C_{16}H_{18}Cl_2O_2$) C, H, Cl. **9a**: ^{1}H NMR 7.30 (d, 1H, J = 8 Hz), 7.25 (d, 1H, J = 2 Hz) 7.01 (dd, 1H, J = 8, 2 Hz), 3.54 (s, 3H), 3.03 (ddd, 1H, J = 12, 12, 8 Hz), 2.36 (d, 1H, J = 12 Hz), 2.30−2.40 (m, 2H), 2.24 (ddd, 1H, J = 12, 8, 8 Hz), 1.94 (m, 1H), 1.92 (bd, 1H, J = 12 Hz), 1.74 (m, 1H), 1.56 (m, 1H), 1.44 (m, 1H), 1.20 (dd, 1H, J = 12, 12 Hz), 1.10 (ddd, 1H, J = 12, 4, 4 Hz); ^{13}C NMR δ 175.68, 145.19, 132.14, 130.18, 130.05, 129.70, 127.30, 55.93, 51.60, 38.92, 36.99, 36.70, 33.44, 32.89, 31.76, 29.83. Anal. ($C_{16}H_{18}Cl_2O_2$) C, H, Cl. **10a**: ^{1}H NMR δ 7.31 (dd, 1H, J = 2, 1 Hz), 7.28 (d, 1H, J = 8 Hz), 7.07 (ddd, 1H, J = 8, 2, 1 Hz), 3.45 (s, 3H), 3.31 (dd, 1H, J = 6, 6 Hz), 3.11 (ddd, 1H, J = 12, 6, 6 Hz), 2.64 (m, 1H), 2.37 (m, 1H), 2.16 (ddd, 1H, J = 12, 6, 6 Hz), 1.95 (bdd, 1H, J = 12, 12 Hz), 1.82 (bd, 1H, J = 12 Hz), 1.73 (m, 1H), 1.50−1.65 (m, 2H), 1.42 (m, 1H), 1.28 (ddd, 1H, J = 12, 4, 4 Hz); ^{13}C NMR δ 173.70, 144.18, 131.76, 129.88, 129.61, 129.48, 127.04, 50.89, 50.11, 35.23, 34.49, 34.47, 33.54, 32.31, 32.02, 27.02. Anal. ($C_{16}H_{18}Cl_2O_2$) C, H, Cl.

2β-Carbomethoxy-3β-naphthylbicyclo[3.2.1]octane (7b), 2α-Carbomethoxy-3β-naphthylbicyclo[3.2.1]octane (8b), 2β-Carbomethoxy-3α-naphthylbicyclo[3.21]octane (9b), and 2α-Carbomethoxy-3α-naphthylbicyclo[3.2.1]octane (10b). To 2-carbomethoxy-3-naphthylbicyclo[3.2.1]-2-octene, **5b** (0.75 g, 2.57 mmol) in methanol (30 mL) at −78 °C, was added dropwise SmI_2 (0.1 M in THF, 200 mL) via an addition funnel. After completing the addition, the green mixture was stirred for 4 h at −78 °C and quenched with TFA (10 mL) in ether (30 mL). H_2O (25 mL) was added and extracted with ether (3 × 100 mL). The dried (Na_2SO_4) ether layer was concentrated to dryness. The residue was purified by flash chromatography (eluent: 10% EtOAc/hexanes) to afford a mixture of isomers **6b** (0.48 g, 64%). The isomers were separated by gravity column chromatography (eluent: 40−80% toluene/hexanes) to afford 20 mg of **7b** as a white solid (mp 78.8−79.1 °C), 30 mg of **8b** as a white solid (mp 71.3−71.7 °C), 50 mg of **9b** as a white solid (mp 71.1−71.4 °C), and **10b** as a white solid (mp 91.1−91.3 °C). **7b**: ^{1}H NMR δ 7.77 (m, 2H), 7.73 (d, 1H, J = 9 Hz), 7.68 (bs, 1H), 7.41 (m, 3H), 3.32 (s, 3H), 3.22 (ddd, 1H, J = 12, 6, 6 Hz), 3.00 (dd, 1H, J = 6, 4 Hz), 2.56 (m, 1H), 2.54 (m, 1H), 2.48 (m, 1H), 2.00 (bd, 1H, J = 12 Hz), 1.92 (m, 1H), 1.55−1.85 (m, 4H), 1.32 (ddd, 1H, J = 12, 6, 6 Hz); ^{13}C NMR δ 173.76, 141.10, 133.49, 132.16, 127.90, 127.52, 127.42, 126.45, 125.98, 125.75, 125.26, 52.55, 50.96, 38.60, 36.83, 34.85, 33.58, 33.16, 29.92, 28.29. Anal. ($C_{20}H_{22}O_2$) C, H. **8b**: ^{1}H NMR δ 7.76(m, 3H), 7.66 (bd, 1H, J = 2 Hz), 7.40 (m, 3H), 3.43 (s, 3H), 3.31 (ddd, 1H, J = 12, 12, 6 Hz), 2.88 (dd, 1H, J = 12, 2 Hz), 2.51 (m, 1H), 2.35(m, 1H), 2.00 (m, 1H), 1.50−1.85 (m, 7H); ^{13}C NMR δ 174.56, 142.13, 133.66, 132.41, 127.99, 127.77, 127.61, 126.44, 126.12, 125.85, 125.32, 53.14, 51.41, 41.27, 39.60, 39.18, 39.00, 35.33, 28.93, 25.39. Anal. ($C_{20}H_{22}O_2$) C, H. **9b**: ^{1}H NMR δ 7.77(m, 3H), 7.63 (bs, 1H), 7.44 (m, 2H), 7.34 (dd, 1H, J = 9, 2 Hz), 3.48 (s, 3H), 3.26 (ddd, 1H, J = 11, 11, 7 Hz), 2.58 (d, 1H, J = 11 Hz) 2.35−2.45 (m, 2H), 2.32 (ddd, 1H, J = 12, 7, 7 Hz), 2.05 (bd, 1H, J = 12 Hz), 1.96 (m, 1H), 1.78 (m, 1H), 1.66 (m, 1H), 1.52 (m, 1H), 1.40 (dd, 1H, J = 12, 12 Hz), 1.15 (ddd, 1H, J = 12, 4, 4 Hz); ^{13}C NMR δ 176.34, 142.24, 133.55, 132.32, 128.03, 127.71, 127.61, 126.35, 126.26, 125.90, 125.35, 56.10, 51.58, 39.24, 37.59, 37.25, 33.65, 33.08, 32.07, 30.09. Anal. ($C_{20}H_{22}O_2$) C, H.

2α-Carbomethoxy-3α-naphthylbicyclo[3.2.1]octane (10b). Compound **5b** (200 mg, 0.68 mmol) was hydrogenated under pressure (50 psi) in the presence of Pd−C (10% w/w 118 mg) in methanol (40 mL) overnight. The resulting mixture was filtered through Celite and the methanol evaporated. The crude residue (180 mg) contained a mixture of products and was purified by gravity column chromatography on flash silica (eluent: 40−80% toluene/hexanes) to afford 85 mg of a white solid. Recrystallization from ethanol gave analytically pure **10b** (70 mg): mp 91.1−91.3 °C; ^{1}H NMR δ 7.75 (m, 3H), 7.70 (bs, 1H), 7.40 (m, 3H), 3.35−3.45 (m, 2H), 3.36 (s, 3H), 2.70 (m, 1H), 2.40 (m, 1H), 2.29 (ddd, 1H, J = 12, 7, 7 Hz), 2.20 (ddd, 1H, J = 12, 12, 2 Hz), 1.89 (bd, 1H, J = 12 Hz), 1.50−180 (m, 3H), 1.45 (m, 1H), 1.35 (ddd, 1H, J = 12, 4, 4 Hz); ^{13}C NMR δ 174.35, 141.37, 133.36, 131.88, 127.90, 127.45, 127.29, 126.87, 125.75, 125.72, 125.24, 52.55, 50.96, 38.60, 36.83, 34.85, 33.58, 33.16, 29.92, 28.29. Anal. ($C_{20}H_{22}O_2$) C, H.

2α-Carbomethoxy-3β-(4-fluorophenyl)-3α-bicyclo[3.2.1]-octene Oxide (22). Compound **22** was isolated from a complex mixture obtained by reaction of **5b** and an old solution of SmI_2 in THF in the conditions described for **6a**. Flash chromatography (eluent: 0−4% ether/hexanes) afforded 40 mg of **22** as an oil: R_f 0.2 (5% ether/hexane); ^{1}H NMR δ 7.25(m, 2H), 6.96 (m, 2H), 3.28 (d, 1H, J = 4 Hz), 3.22 (s, 3H), 3.12 (d, 1H, J = 4 Hz), 2.61 (m, 1H), 2.25−2.45 (m, 2H), 1.60−1.95 (m, 4H), 1.31 (ddd, 1H, J = 12, 5, 5 Hz); ^{13}C NMR δ 172.21, 161.98 (d, J = 246 Hz), 135.90, 128.69 (d, J = 8 Hz), 114.70 (d, J = 21 Hz), 63.43, 58.98, 52.53, 51.09, 34.95, 34.36, 30.95, 26.79, 24.27. HRMS: obsd, 277.1242; calcd for $C_{16}H_{18}O_3F$ (M + 1), 277.1240.

Methyl 2-Naphthalen-2-ylbenzoate (17a). 2-Iodobenzoic acid methyl ester, **16** (5.0 g, 18.32 mmol), 2-naphthaleneboronic acid (6.30 g, 36.64 mmol), $CsCO_3$ (11.94 g, 36.64 mmol), and $Pd(Ph_3)_2Cl_2$ (1.29 g, 1.83 mmol) in DMF (50 mL) were heated at 80 °C for 12 h. Water (50 mL) was added and the water layer was extracted with ether (3 × 50 mL). The ether layer was removed on a rotary evaporator. The residue was purified by flash chromatography (20% EtOAc/hexanes) to afford 2.6 g of **17a** as a white powder: mp 60.1−60.4 °C; R_f 0.34 (10% EtOAc/hexanes); ^{1}H NMR δ 7.83−7.93 (m, 5H), 7.25−7.61 (m, 6H), 3.57 (s, 3H). Anal. ($C_{18}H_{14}O_2$) C, H.

4′-Chlorobiphenyl-2-carboxylic Acid Methyl Ester (17b). Compound **17b** was prepared from 2-iodobenzoic acid methyl ester **(16)** with 4-chlorophenylboronic acid as described for **17a**: colorless oil (56%); R_f 0.52 (EtOAc/hexanes); ^{1}H NMR δ 7.85 (dd, 1H, J = 8, 1 Hz), 7.53 (ddd, 1H, J = 8, 8, 1 Hz), 7.31−7.44 (m, 4H), 7.21−7.25 (m, 2H), 3.66 (s, 3H). Anal. ($C_{14}H_{11}O_2$-Cl) C, H, Cl.

4′-Fluorobiphenyl-2-carboxylic Acid Methyl Ester (17c). Compound **17c** was prepared from 2-iodobenzoic acid methyl ester **16** with 4-fluorophenylboronic acid as described for **17a**: colorless oil (59%); R_f 0.52 (EtOAc/hexanes); ^{1}H NMR δ 7.82−7.85 (m, 1H), 7.51 (ddd, 1H, J = 8, 8, 2 Hz), 7.40 (ddd, 1H, J = 8, 8, 1 Hz), 7.31−7.34 (m, 1H), 7.23−7.29 (m, 2H), 7.05−7.12 (m, 2H), 3.65 (s, 3H). Anal. ($C_{14}H_{11}O_2F$) C, H.

2-Benzoyloxybenzoic Acid Methyl Ester (19). Benzoyl chloride (0.12 mL, 1 mmol) was added to 2-hydroxybenzoic acid methyl ester, **18** (50 mg, 0.33 mmol) in pyridine (2 mL). The mixture was stirred at 60 °C overnight. Pyridine was removed on a rotary evaporator. The residue was dissolved in ether (20 mL) and washed with H_2O (3 × 10 mL). Ether was removed on a rotary evaporator. The residue was purified by chromatotron (20% EtOAc/hexanes) to afford 60 mg (71%) of **19** as a white solid: mp 83.8−84 °C; R_f 0.29 (10% EtOAc/hexanes); ^{1}H NMR δ 8.24 (s, 1H), 8.21 (d, 1H, J = 1 Hz), 8.07 (dd, 1H, J = 8, 2 Hz), 7.57−7.66 (m, 2H), 7.49−7.54 (m, 2H), 7.35 (ddd, 1H, J = 8, 8, 1 Hz), 7.24 (d, 1H, J = 8 Hz), 3.73 (s, 1H). Anal. ($C_{15}H_{12}O_4$) C, H.

2-Carbomethoxy-4"-bromo-*p*-terphenyl (21). Compound **21** was prepared from 2-iodobenzoic acid methyl ester **(16)** with 4-bromobiphenylboronic acid as described for **17a**: mp 114.9−115.6 °C; R_f 0.45 (10% EtOAc/hexanes); ^{1}H NMR δ 7.86 (dd, 1H, J = 8, 1 Hz), 7.50−7.61 (m, 7H), 7.38−7.46 (m, 4H), 3.69 (s, 3H). Anal. ($C_{20}H_{15}O_2Br$) C, H.

Tissue Sources and Preparation. Brain tissue from adult male and female cynomolgus monkeys (*Macaca fascicularis*) and rhesus monkeys (*Macaca mulatta*) 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 2−3 preparations from individual brains.

Dopamine Transporter Assay. The DAT was labeled with [^{3}H]WIN 35,428 ([^{3}H]CFT, (1*R*)-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 DAT 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 − 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 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 or other appropriate solvents. 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 SERT was assayed in caudate-putamen membranes using conditions similar to those for the DAT. The affinity of [^{3}H]citalopram (s.a.: 82 Ci/mmol; DuPont-NEN) for the SERT 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 − 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% poly(ethylenimine). 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.

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Supporting Information Available: ORTEP drawings of **7a**, **8a**,**b**, and **10b**, crystal data and refinement parameters, coordinates, anisotropic temperature factors, distances, and angles are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Wise, R. A. Catecholamine theories of reward. A critical Review. *Brain Res.* **1978**, *152*, 215−247.
(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) 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.
(4) 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.
(5) 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.
(6) 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.
(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) Kuhar, M. J.; Ritz, M. C.; Boja, J. W. The dopamine hypothesis of the reinforcing properties of cocaine. *Trends Neurosci.* **1991**, *14*, 299−302.
(9) Lewis, D. B.; Matecka, D.; Zhang, Y.; Hsin, L.-W.; Dersch, C. M.; Stafford, D.; Glowa, J. R.; Rothman, R. B.; Rice, K. C. Oxygenated analogues of 1-[2-(diphenylmethoxy)ethyl]- and 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazines (GBR 12935 and GBR 12909) as potential extended-action cocaine-abuse therapeutic agens. *J. Med. Chem.* **1999**, *42*, 5029−5042.
(10) Meltzer, P. C.; Liang, A. Y.; Madras, B. K. 2-Carbomethoxy-3-(diarylmethoxy)-1α*H*,5α*H*-tropane analogues: Synthesis and inhibition of binding at the dopamine transporter and comparison with piperazines of the GBR series. *J. Med. Chem.* **1996**, *39*, 371−379.
(11) Meltzer, P. C.; Liang, A. Y.; Brownell, A.-L.; Elmaleh, D. R.; Madras, B. K. Substituted 3-phenyltropane analogues of cocaine: synthesis, inhibition of binding at cocaine recognition sites, and Positron Emission Tomography imaging. *J. Med. Chem.* **1993**, *36*, 855−862.
(12) 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.
(13) 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.
(14) 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.
(15) 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.
(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.; Blundell, P.; Chen, Z.; Yong, Y.; Madras, B. K. Bicyclo[3.2.1]octanes: synthesis and inhibition of binding at the dopamine and serotonin transporters. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 857−862.

(18) 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.
(19) Madras, B. K.; Kamien, J. B.; Fahey, M.; Canfield, D.; Milius, R. A.; Saha, J. K.; Neumeyer, J. L.; D., S. R. N-Modified fluorophenyltropane analogues of cocaine with high affinity for [^{3}H]cocaine receptors. *Pharmacol. Biochem. Behav.* **1990**, *35*, 949−953.
(20) 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.
(21) 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.
(22) 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.
(23) 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.
(24) Meltzer, P. C.; Blundell, P.; Madras, B. K. Structure activity relationships of inhibition of the dopamine transporter by 3-arylbicyclo[3.2.1]octanes. *Med. Chem. Res.* **1998**, *8*, 12−34.
(25) Miller, G. M.; Gracz, I. M.; Goulet, M.; Yang, H.; Meltzer, P. C.; Hoffman, B. J.; Madras, B. K. Point mutations of the human dopamine transporter (hDAT) reveal differential binding of an amine and a non-amine ligand. *Soc. Neurosci. Abstr.* **1999**, in press.
(26) 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.
(27) Jefford, C. W.; Gunsher, J.; Hill, D. T.; Brun, P.; Le Gras, J.; Waegell, B. Bicyclo[3.2.1]octan-3-one. *Organic Synthesis*; Wiley: New York, 1988; Coll. Vol. VI, pp 142−145.
(28) Watanabe, T.; Mitaura, N.; Suzuki, A. Synthesis of sterically hindered biaryls via the palladium-catalyzed cross-coupling reaction of arylboronic acids or their esters with haloarenes. *Synlett* **1992**, 207−210.
(29) 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.
(30) 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.
(31) 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.
(32) Ritz, M. C.; Cone, E. J.; Kuhar, M. J. Cocaine inhibition of ligand binding at dopamine, norepinephrine and serotonin transporters: A structure−activity study. *Life Sci.* **1990**, *46*, 635−645.
(33) Carroll, F. I.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. In *3β-(Substituted phenyl)tropane-2 carboxylic acid ester analogues of cocaine: Synthesis and biochemical and pharmacological properties*; Kozikowski, A. P., Ed.; Raven Press, Ltd.: New York, 1993; pp 149−166.
(34) Kozikowski, A. P.; Roberti, M.; Johnson, K. M.; Bergmann, J. S.; Ball, R. G. SAR of Cocaine: further exploration of structural variations at the C-2 center provides compounds of subnanomolar binding potency. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1327−1332.
(35) Clarke, R. L.; Daum, S. J.; Gambino, A. J.; Aceto, M. D.; Pearl, J.; Levitt, M.; Cumiskey, W. R.; Bogado, E. F. Compounds affecting the central nervous system. 4. 3β-Phenyltropane-2-carboxylic esters and analogues. *J. Med. Chem.* **1973**, *16*, 1260−1267.
(36) Neumeyer, J. L.; Wang, S.; Milius, R. A.; Baldwin, R. M.; Zea-Ponce, Y.; Hoffer, P. B.; Sybirska, E.; Al-Tikriti, M.; Charney, D. S.; Malison, R. T.; Laruelle, M.; Innis, R. B. [^{123}I]-2β-Carbomethoxy-3β-(4-iodophenyl)tropane: high-affinity SPECT radiotracer of monoamine reuptake sites in brain. *J. Med. Chem.* **1991**, *34*, 3144−3146.
(37) Carroll, F. I.; Gray, J. L.; Abraham, P.; Kuzemko, M. A.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. 3-Aryl-2-(3′-substituted-1′,2′,4′-oxadiazol-5′-yl)tropane analogues of cocaine: affinities at the cocaine binding site at the dopamine, serotonin, and norepinephrine transporters. *J. Med. Chem.* **1993**, *36*, 2886−2890.
(38) 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 tropane: Evidence for an electrostatic interaction at the 2β-position. *J. Med. Chem.* **1996**, *39*, 2753−2763.
(39) Moldt, P.; Scheel-Kruger, J.; Jensen, L. H. 2,3-Trans-substituted tropane compounds which have useful pharmaceutical utility. U.S. Patent 5,374,636, 1994.
(40) Lomenzo, S. A.; Izenwasser, S.; Katz, J. L.; Terry, P. D.; Zhu, N.; Klein, C. L.; Trudell, M. L. Synthesis, structure, dopamine transporter affinity, and dopamine uptake inhibition of 6-alkyl-3-benzyl-2-[(methoxycarbonyl)methyl]tropane derivatives. *J. Med. Chem.* **1997**, *40*, 4406−4414.
(41) Moldt, P.; Watjen, F.; Scheel-Kruger, J. Tropane-2-aldoxime derivatives as neurotransmitter reuptake inhibitors. U.S. Patent 5,736,556, 1998.
(42) Meltzer, P. C.; Blundell, P.; Huang, H.; Liu, S.; Yong, Y. F.; Madras, B. K. 3-Aryl-2-carbomethoxybicyclo[3.2.1]oct-2-enes inhibit WIN 35,428 binding potently and selectively at the dopamine transporter. *Bioorg. Med. Chem.* **2000**, *8*, 581−590.

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