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

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We recently reported a new class of tropanes, based on benztropine, that bind uniquely, in the *S*-configuration, to the dopamine transporter. We have now extended this series to evaluate the effects of substituents on the nitrogen and the diarylmethoxy group. Herein we have described the synthesis and biological evaluation of a series of 2-carbomethoxy-3-(diarylmethoxy)-1α*H*,5α*H*-tropane (2-carbomethoxybenztropine) analogs. Examination of the binding data obtained for these compounds shows that while the 4,4′-difluoro compound is potent and selective for the dopamine transporter, introduction of larger groups such as 4,4′-dichloro, 4,4′-dibromo, 4,4′-diiodo, or 4,4′-dimethyl on the 3-diphenylmethoxy moiety reduces this potency. However, although introduction of only one group (e.g., 4-chloro, 4-bromo, 4-iodo, or 4-methyl) leads to a similar reduction of binding affinity, these monosubstituted 2-carbomethoxybenztropines are significantly more potent than the related disubstituted compounds. Finally, from the data for the N-substituted 2-carbomethoxybenztropine analogs, it is evident that steric bulk can be tolerated at the nitrogen site. A comparison of structure−activity relationship data for the tropanes, GBR analogs, and these benztropines indicates that the 2-carbomethoxybenztropine analogs may be more like the GBR analogs in their mode of binding to the dopamine transporter than like the tropanes. This conclusion supports the notion that the binding site for (−)-cocaine [and the (1*R*)-tropanes] may differ from that of the 2-carbomethoxybenztropine analogs.

Introduction

The reinforcing properties and stimulant effects of cocaine have been associated with its propensity to bind to monoamine transporters, particularly the dopamine transporter (DAT).[1−11] Although structure−activity relationship (SAR) studies of cocaine and its analogs have offered insight into the possible mode of cocaine binding to the DAT, a comprehensive picture of the binding interaction to the DAT at the molecular level has yet to emerge. Indeed, even though SAR studies on the classical tropane analogs of cocaine[3,5,6,12−14] appeared to provide a consistent model for this interaction, subsequent studies have revealed inconsistencies with the initial reports. Thus, Carroll proposed[12,15−17] that the molecular requirements for binding of cocaine and its tropane analogs at the DAT include four factors, namely, a 2β-carboxy ester, a basic nitrogen capable of protonation at physiological pH, the *R*-configuration of the tropane, and a 3β-aromatic ring at C-3. Later, Davies [18] reported that introduction of 2β-ketones did not reduce potency. Kozikowski has since demonstrated that hydrogen bonding at the C-2 site is not required since introduction of unsaturated and saturated alkyl groups[19,20] does not diminish binding. Further, doubt has been cast on the notion of an ionic bond between a protonated amine (at physiological pH) and the presumed aspartate residue on the DAT,[21] since reduction of nitrogen nucleophilicity,[22] by introduction of *N*-sulfones, sufficient to inhibit protonation of the amine under physiological conditions does not reduce binding potency. With respect to nitrogen substitution, it had already been reported[11] that introduction of an alkyl or allyl group did not eliminate binding potency and, more recently, we[23] have shown that introduction of an iodoallyl group on the tropane nitrogen can lead to potent and selective compounds for the DAT. Altropane (Figure 1), a product of that work, is currently undergoing development as a potential SPECT imaging agent.[23] This result has been corroborated by the work of Goodman[24] in his synthesis of a chloro analog of altropane.

The active (−)-cocaine series, including all the tropane analogs of WIN 35,428, are of the *R*-configuration. Guided by our desire to seek topologically different tropanes, we recently synthesized and evaluated the receptor-binding properties of all eight isomers of 2-carbomethoxy-3-[bis(4-fluorophenyl)methoxy]tropane and reported[25] that the *S*-enantiomer, (*S*)-(+)-2β-carbomethoxy-3α-[bis(4-fluorophenyl)methoxy]tropane, **2a** (difluoropine or O-620), was considerably more potent (IC_{50} = 10.9 nM) and selective (DAT over the 5HT transporter = 324:1) than any of the other seven isomers, including the *R*-enantiomers. Until the discovery of difluoropine (**2a**; Figure 1) in 1994, no potent tropanes had been found in the *S*-configuration. This compound, a 2β-carbomethoxy analog of benztropine, is uniquely of the *S*-configuration. In further contrast to the classical 3β-substituted cocaine and tropane analogs, it has a 3α-diphenylmethoxy substituent. As compound **2a** is in the *S*-configuration, it has no substituent in the 2β-position of (1*R*)-cocaine [or the (1*R*)-tropanes]; rather, one of the phenyl rings may topologically occupy that position.

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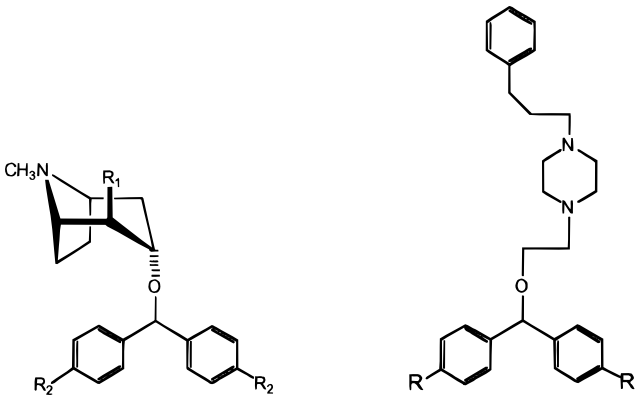
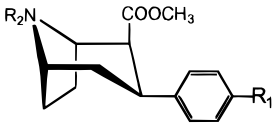


Benztropines

	R_1	R_2
Difluoropine (**2a**)	β-$COOCH_3$	F
Benztropine	H	H
Chlorbenztropine	H	Cl

Piperazines

	R
GBR 12909	F
GBR 12935	H



1*R*-Tropanes

	R_1	R_2
WIN 35,428	F	CH_3
Altropane	F	$CH_2CH{=}CHI$
O-401	3,4-Cl_2	CH_3
RTI 55	I	CH_3

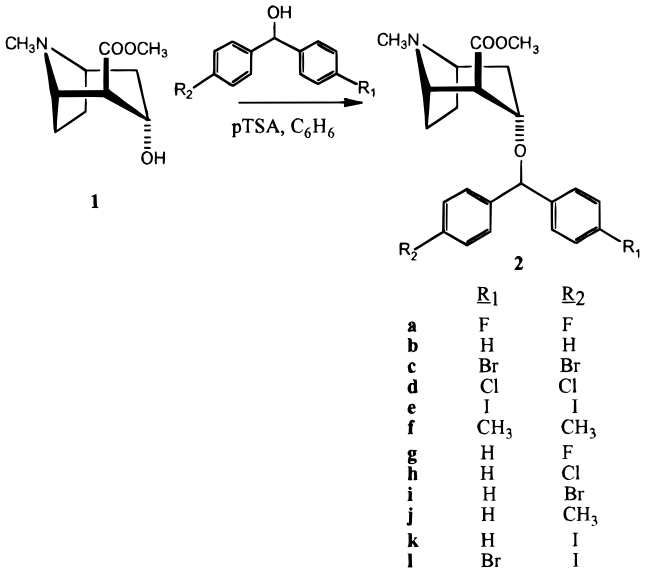
Figure 1. Three classes of compounds that inhibit binding of [^{3}H]WIN 35,428 to the dopamine transporter (DAT).

Within the phenyltropane series, halogen and other substituents on the single aromatic ring have dramatic effects, not only on the affinity of these compounds for the DAT but also on their DAT vs serotonin transporter selectivity.[3,5,6,12−14,18−20] As this series has a diphenylmethoxy in the 3-position, it is of considerable interest to determine whether halogen and other substituents have analogous effects. Equally significant is whether these effects are dependent upon substitution in each, or both, of the aromatic rings.

The diphenylmethoxy substituent is also present in another family of potent and selective DAT inhibitors, namely, the 1,4-dialkylpiperazines, the so-called GBR series, first reported in 1980.[26] Van der Zee had noted the use of benztropine as an anti-Parkinsonian agent and prepared this new series in an attempt to enhance activity by replacement of the tropine moiety in benztropine with a piperazine. This work was a precursor to our own work in this area.

We now report the synthesis and receptor-binding properties of a series of analogs of **2a**. These analogs have been designed to probe the effect of substitution on the aromatic rings of the diphenylmethoxy group present in **2a** (Table 1) and also to explore the effects of introduction of arylalkyl groups on the tropane nitrogen in order to create analogs of the GBR structure (Table 2).

Scheme 1



	R_1	R_2
a	F	F
b	H	H
c	Br	Br
d	Cl	Cl
e	I	I
f	CH_3	CH_3
g	H	F
h	H	Cl
i	H	Br
j	H	CH_3
k	H	I
l	Br	I

Chemistry

The (*S*)-2-carbomethoxy-3-(diarylmethoxy)-1α*H*,5α*H*-tropanes (2-carbomethoxybenztropines) of this study were prepared from the alcohol **1**[25] which was reacted with a series of benzhydrols under azeotropic distillation in the presence of catalytic *p*-toluenesulfonic acid to obtain compounds **2** in moderate yields. In order to obtain the N-substituted compounds **4**, the difluoro compound **2a** was N-demethylated with α-chloroethyl chloroformate as solvent to provide the nor compound **3** in 58% yield. N-Alkylation of **3** was then achieved with an appropriate alkyl bromide with KF/Celite in acetonitrile. Thus, **3** was reacted with benzyl bromide, 1-bromo-3-phenylpropane, 1-bromo-3-(4-bromophenyl)-propane, and 1-chloro-5-phenylpentane, to yield **4a**−**c**,**e**, respectively. Yields of 80−90% were obtained.

The 4-iodo compounds were obtained by conversion of the corresponding bromo compounds to tributylstannyl derivatives. Reaction with *N*-iodosuccinimide (NIS) then gave the iodo compounds. Thus, **2e**,**k**,**l** and **4d** were derived from their stannyl precursors upon treatment with NIS in tetrahydrofuran. Stannylation to provide these precursors was achieved by reaction of **2c**,**i** and **4c** with bis(tributyltin) in the presence of tetrakis(triphenylphosphine)palladium.

The enantiomeric purity of the end products was critical. We therefore developed a supplementary NMR method for assessing enantiomeric purity of **2a**. Thus, an ^{1}H-NMR spectrum measured in the presence of 80% by weight of the chiral shift reagent europium D-3-(heptafluorobutyryl)camphorate showed two base-line-separated singlet resonances for the diagnostic dibenzylic proton at δ 5.93 and 6.07 for the mixture of the two enantiomers (*S*)- and (*R*)-**2a**. These resonance positions were concentration dependent, and therefore the shift experiment must be optimized for the compound and the NMR field strength. The pure (*S*)-**2a** showed only a singlet at δ 6.0 under these conditions.

It should be noted that compounds in which each of the diphenylmethoxy rings were differently substituted, such as **2g**−**m**, possess a newly introduced benzylic chiral center. These 1*S*-compounds were not resolved again, and their receptor binding was evaluated as

diastereomeric pairs. Their NMR spectra proved instructive. Whereas the methoxy resonance for symmetric compounds such as **2a**−**f** appeared as a singlet at δ 3.7, that resonance appeared as *two* distinct singlets at about δ 3.7 for the diastereomeric pairs.

The ethylphenyl compound **2m** and the fluorenyloxy compound **2n** were synthesized in order to examine the need for two aromatic rings and the effect of a planar system at this site, in comparison with the angled diphenylmethoxy, respectively. Both compounds were prepared analogously, albeit in much poorer yields, to those presented above; the appropriate alcohol was reacted with the intermediate **1**. Thus **2m** was obtained in 14% yield and **2n** in 29% yield.

Biology

The affinities (IC_{50}) of the difluoropine (**2a**) analogs for the dopamine and serotonin transporters were determined in competition studies using [^{3}H]-3β-(4-fluorophenyl)tropane-2β-carboxylic acid methyl ester ([^{3}H]WIN 35,428 or [^{3}H]CFT) to label the DAT[5] and [^{3}H]-citalopram to label the serotonin transporter. The data are presented in Tables 1 and 2. Studies were conducted in cynomolgus monkey striatum for two reasons. First, these compounds are part of an ongoing investigation of SARs at the DAT in this tissue,[5,14,25] and meaningful comparisons with an extensive data base can be made. Equally important, cynomolgus monkeys are to be used as subjects for PET (positron emission tomography) imaging with some targeted compounds in the course of this program.

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.

Discussion

Many structurally different compounds (including cocaine, tropanes, GBR compounds, mazindol, and methylphenidate) have proven to be potent inhibitors of [^{3}H]cocaine-binding sites in striatum. In this brain region the majority of the cocaine- or WIN35,428-binding sites are associated with the DAT. Three classes of compounds (Figure 1) have furnished particularly potent ligands and have provided the springboard for the work presented here. Specifically, the (1*R*)-tropanes (C-3-aryl analogs), the piperazines (GBR),

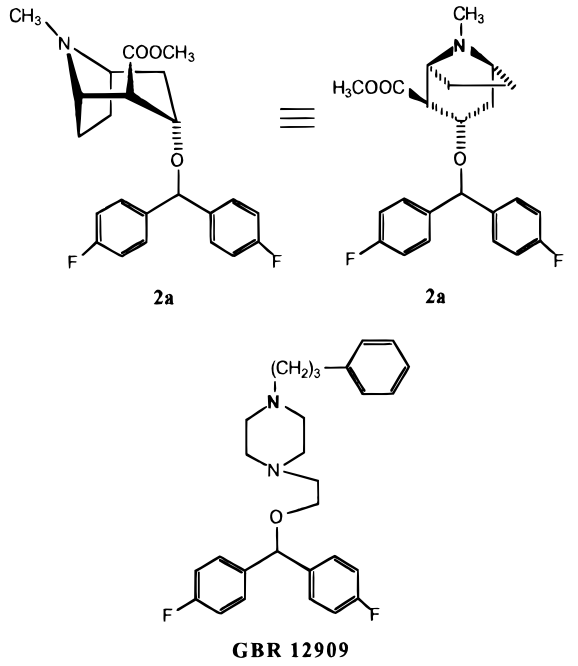


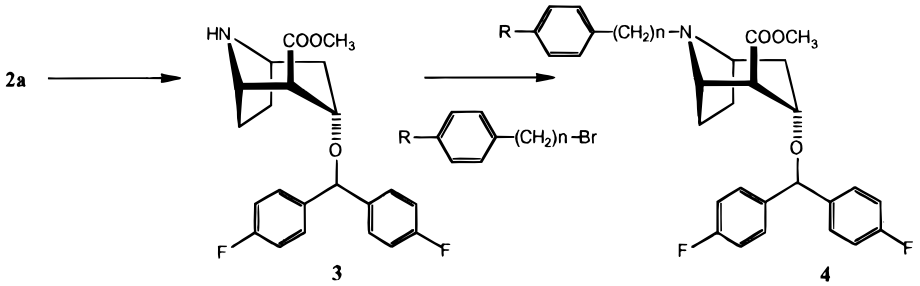
Figure 2. Alternate representation of difluoropine to show possible overlap with GBR 12909.

and the benztropines have proven to be potent inhibitors of the DAT.

The structural similarity between compounds in the GBR series and the benztropine analogs is instructive.[26] Most notable is the common diphenylmethoxy functionality. It is intriguing to speculate how these two classes of compounds may bind similarly. Specifically, Dutta[28,29] has evaluated the contribution of each of the two nitrogen atoms in the piperidine ring of the GBR series for conferring binding potency. The nitrogen distal to the diphenylmethoxy substituent was found to confer greater binding potency than did the proximal nitrogen. If **2a** and GBR 12909 are superimposed using the common diphenylmethoxy substituents of each compound, then the tropane nitrogen of **2a** and the distal nitrogen (shown in boldface) of GBR 12909 (Figure 2) occupy the same region of space.

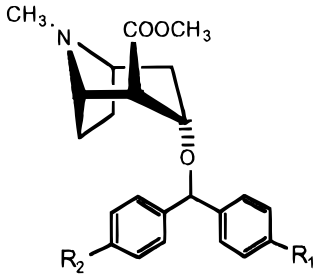
These observations support the notion that multiple binding sites exist on the DAT such that binding of the 2-carbomethoxybenztropines and GBR analogs does not fit the binding domain in exactly the same way as does cocaine or the (1*R*)-tropanes. This interpretation lends

Scheme 2



	R	n
a	H	1
b	H	3
c	Br	3
d	I	3
e	H	5

Table 1. Inhibition of [^{3}H]WIN 35,428 Binding to the DAT and [^{3}H]Citalopram Binding to the Serotonin Transporter by Analogs of **2a** in Cynomolgus Monkey Caudate-putamen[a]



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compd	R_1	R_2	IC_{50} (nM) DAT	IC_{50} (nM) 5HT	selectivity (DAT/5HT)
benztropine			312 ± 1.1	24 100 ± 14 800	77
O-672, difluorobenztropine			44.6 ± 8.37	5340 ± 2110	120
O-620, **2a**	F	F	10.9 ± 1.2	3530 ± 1480	324
O-651, **2b**	H	H	33.5 ± 4.5	10 100 ± 1740	302
O-734, **2c**	Br	Br	72.0 ± 3.65	2430 ± 339	34
O-652, **2d**	Cl	Cl	91.4 ± 0.85	3360 ± 1480	37
O-743, **2e**	I	I	909 ± 79	8550 ± 442	9.4
O-701, **2f**	CH_3	CH_3	240 ± 18.4	9800 ± 2680	41
O-810, **2g**	H	F	13.2 ± 1.9	4930 ± 1200	373
O-819, **2h**	H	Cl	15.8 ± 0.95	5960 ± 467	377
O-723, **2i**	H	Br	24.0 ± 4.6	5770 ± 493	240
O-820, **2j**	H	CH_3	49.5 ± 6.0	13 200 (n = 1)	266
O-739, **2k**	H	I	55.9 ± 10.3	9280 ± 1640	166
O-738, **2l**	Br	I	389 ± 29.4	4390 ± 829	11
O-784, **2m**[b]	ethyl		1480 ± 569	21 000 ± 5300	14
O-660, **2n**[c]	fluorenoxy		6030 ± 815	3440 ± 542	0.6
O-657, **3d**[d]	F	F	20.3 ± 3.54		

[a] 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 (±SD or SEM) of 2−4 independent experiments, each conducted in triplicate. [b] One aromatic ring has been replaced by an ethyl group. [c] The diphenylmethoxy is replaced with a fluorenyloxy; cpd is racemic. [d] This is N-demethylated **2a**.

hope for the discovery of a cocaine antagonist which displays reduced influence on the uptake of dopamine itself.[25]

The goal of this study was therefore 2-fold. First, to explore the SAR of these new 2-carbomethoxybenztropine analogs, and second, to explore their possible relationship to compounds in the GBR series. We were guided by both the SAR in the tropane area[14,15] as well as the SAR in the area of the GBR analogs.[26,30,31] Therefore we synthesized the compounds presented in Tables 1 and 2. All compounds were prepared in the 1*S*-series since we have shown unequivocally[25] that in the *2-carbomethoxybenztropine series*, the *R*-configured compounds are relatively inactive.

An examination of the binding data presented in Table 1 shows that the most potent compound for binding to the DAT, in this series, was the difluoro analog **2a**. This compound also manifested excellent selectivity for the DAT over the 5HT receptor (324:1), similar to the less potent (IC_{50} = 33.5 nM) compound **2b**. Compound **2a** was previously reported to be a potent (IC_{50} = 10.9 nM) and selective (DAT:5HT = 324:1) ligand at the dopamine transporter.[25] The effects of other halogen or methyl substituents on the diphenylmethoxy rings were now investigated under similar conditions (Table 1). In the absence of the fluoro groups, binding affinity (**2b**, IC_{50} = 33.5 nM) for the dopamine transporter decreased 3-fold and affinity for the serotonin transporter (IC_{50} = 10 μM) also decreased. The resulting transporter selectivity was similar for the two compounds. The dibromo- (**2c**, IC_{50} = 72.0 nM), dichloro- (**2d**, IC_{50} = 91.4 nM), diiodo- (**2e**, IC_{50} = 909 nM) and dimethyl- (**2f**, IC_{50} = 240 nM) substituted derivatives were less potent than the difluoro or unsubstituted compounds. The resulting rank order of potency of the disubstituted compounds was diF > diH > diBr > diCl > diCH_3 > diI.

The rank order for the monosubstituted compounds **2g**−**k** was F > Cl > Br > H > CH_3 > I, and a comparison of the mono- vs dihalogenated molecules proved interesting. The mono- (**2g**) and di- (**2a**) fluorinated compounds were approximately equipotent (IC_{50} = 10−13 nM). The monochloro compound **2h** (IC_{50} = 15.8 nM) was 5−6 times as potent as the dichloro compound **2d**. Introduction of only one bromine atom (**2i**, IC_{50} = 24.0 nM) resulted in a compound of retained substantial potency, while the dibromo compound **2c** was again 3 times less potent. Introduction of an iodine (**2k**) resulted in a further reduction of potency (IC_{50} = 55.9 nM), and as expected, the diodo compound **2e** was at least 1 order of magnitude less potent. The monomethyl (**2j**, IC_{50} = 49.5 nM) and dimethyl (**2f**, IC_{50} = 240 nM) compounds displayed a similar preference for the monosubsituted compound. As may be expected, the monobromo-monoiodo compound **2l** showed potency (IC_{50} = 389 nM) between that of the diodo and dibromo

compounds. These results indicate that while a halogen was preferred, the increase in steric bulk as the halogen size was increased, *and* as it was introduced into both rings, was detrimental to binding to the DAT.

A comparison of selectivity for binding to the DAT versus binding to the 5HT transporter was interesting. In the disubstituted series only the difluoro (**2a**) and unsubstituted (**2b**) compounds displayed selectivity >300:1, while the dibromo (**2c**), dichloro (**2d**), diiodo (**2e**), and dimethyl (**2f**) compounds showed much poorer selectivity (<50:1).

In contrast, the monohalogenated analogs all showed selectivity >150:1, and the monofluoro (**2g**) and monochloro (**2h**) compounds showed the highest selectivity (>370:1) of all the analogs tested. Thus, it is evident that, in general, the more active compounds were also more selective and, furthermore, that introduction of halogens on both rings caused reduction of selectivity.

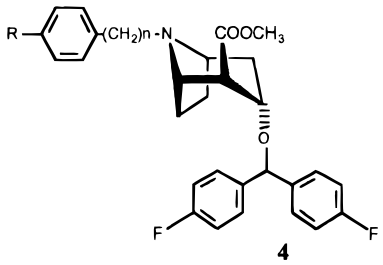
Binding affinity was measured on the diastereomeric mixture for each of the monosubstituted compounds, and it remains to be seen whether affinity and/or selectivity for any of these compounds resides predominantly in one diastereoisomer. It is interesting to note that the monohalogenated compounds in this series are significantly more selective for the DAT over the 5HT transporter than are the classical halogenated tropanes.[14]

Two compound are of particular interest. Compound **2m** was prepared in order to determine the neccessity for the two aromatic rings of the diphenylmethoxy system. Clearly, substitution of one ring by an ethyl group is deleterious to binding to the DAT. Compound **2n** was prepared to investigate the effect of planarity on the diaromatic system. A planar moiety substantially decreased the molecule's ability to bind to the DAT.

Substituents on the nitrogen of the tropane ring had various effects on dopamine and serotonin transporter affinity and selectivity (Table 2). In a comparison of three compounds in which the aromatic ring was unsubstituted but the length of the spacer arm was varied, the three-spacer carbon chain, **4b**, had relatively high affinity for the dopamine transporter (IC_{50} = 22 nM) compared with the five-carbon (**4e**, IC_{50} = 99 nM) or one-carbon (**4a**, IC_{50} = 223 nM) spacer chain. Iodo (**4d**) or bromo (**4c**) substituents on the aromatic ring of the three-spacer compound decreased affinity ca. 4−5-fold. In all cases, selectivity for the DAT had been reduced compared with the parent compound **2a**.

A comparison of SAR in the tropanes, benztropines, and GBR series is interesting. While data from [^{3}H]-WIN 35,428 binding (tropanes and benztropines) and those from inhibition of dopamine uptake[26] (GBR analogs) are not fully comparable because these are two different biological assays, nevertheless, the *relative potency* of the compounds is still instructive.[30] The relative potency of the unsubstituted and chlorine- and fluorine-substituted compounds revealed that the rank order of potency for the disubstituted (1*S*)-2-carbomethoxybenztropine analogs **2a**,**b**,**d** (F > H > Cl) was similar to the order for the disubstituted GBR analogs (F ≅ H > Cl).[26] In sharp contrast, the order for the C-2-unsubstituted benztropines (F > Cl > H)[27] and the C-3 (1*R*)-aryl tropanes (Cl > F > H)[14] differed from each other and from the 2-carbomethoxybenztropines. Therefore it is likely that the manner in which the aryl rings of the (1*S*)-2-carbomethoxybenztropines and the GBR analogs interact at the receptor site differs from that interaction of the classical C-3 aryl (1*R*)-tropanes as well as from the unsubstituted benztropines. Specifically, steric bulk is less well tolerated in the diphenylmethoxy analogs. In contrast, it is favored in the C-3 (1*R*)-aryl tropane series.

Table 2. Inhibition of [^{3}H]WIN 35,428 Binding to the DAT and [^{3}H]Citalopram Binding to the Serotonin Transporter by N-Substituted **2a** Analogs in Cynomolgus Monkey Caudate-putamen[a]



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compd	R	*n*	IC_{50} (nM) DAT	IC_{50} (nM) 5HT	selectivity (DAT/5HT)
O-755, **4a**	H	1	223 ± 53	4970 ± 700	22
O-747, **4b**	H	3	22.0 ± 11.9	19.7 ± 3	0.9
O-786, **4c**	Br	3	80.2 ± 8.8	234 ± 0.5	3
O-788, **4d**	I	3	119 ± 11	2200 ± 1250	19
O-764, **4e**	H	5	99.0 ± 28	550 ± 63	6

[a] 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 (±SD or SEM) of 2−4 independent experiments, each conducted in triplicate.

Substituents on the nitrogen of the GBR analogs and the 2-carbomethoxybenztropines showed some sililarities. Comparison of the relative binding potencies of the compounds of different alkyl chain length on the nitrogen, reported here, with those GBR analogs reported by Van der Zee showed that the optimum chain had a three-carbon link in both series. Thus in the GBR series, potency increases as the chain length increases from one carbon to three or four carbons.[26] In the 2-carbomethoxybenztropine series, we prepared compounds with one, three, and five methylene groups in the chain. Here, the one-carbon linker was the least potent, while the three-carbon linker was optimum (**4b**, IC_{50} = 22.0 nM). The five-carbon linker was 5-fold weaker (**4e**, IC_{50} = 99.0 nM) (Table 2) than the three-carbon linker.

Substitution on the aryl group attached to the nitrogen linker affected binding potency markedly. While the unsubstituted compound **4b** had an IC_{50} = 22.0 nM, introduction of a 4-bromo substituent (**4c**) reduced this affinity 4-fold, and the affinity of the 4-iodo derivative **4d** was reduced by 5-fold. A similar differentiation is not as obvious in the GBR series, since the analogous compounds have similar IC_{50}s in the range of 1.8−2.0 nM.

Conclusions

Herein we have described the synthesis and biological evaluation of a series of 2-carbomethoxybenztropine analogs. Examination of the binding data obtained for

these compounds shows that while the 4,4′-difluoro compound **2a** is potent and selective for the dopamine transporter, introduction of larger groups such as 4,4′-dichloro, 4,4′-dibromo, 4,4′-diiodo, or 4,4′-dimethyl on the 3-diphenylmethoxy moiety reduces this potency. However, although introduction of only one group (e.g., 4-chloro, 4-bromo, 4-iodo, or 4-methyl) also leads to a reduction of binding affinity compared with **2a**, these monosubstituted 2-carbomethoxybenztropines, with the exception of the monofluoro analog, are significantly more potent and selective than the related disubstituted compounds.

Finally, from the data reported for the N-substituted 2-carbomethoxybenztropine analogs, it is clear that substantial steric bulk can be tolerated at the nitrogen site. A comparison of SAR data for the tropanes, GBR analogs, and these benztropines indicates that the 2-carbomethoxybenztropine analogs may be more like the GBR analogs in their mode of binding to the DAT than like the tropanes. This conclusion would support the notion that the binding site for (−)-cocaine [and the (1*R*)-tropanes] may be different from that of the 2-carbomethoxybenztropine analogs. This difference may possibly lead to the discovery of a cocaine antagonist which does not effect dopamine reuptake.

Experimental Section

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. Optical rotations were measured at the sodium D line at 21°C using a JASCO DIP 320 polarimeter (1 dcm cell). Thin layer chromatography (TLC) was carried out on Baker Si 250F 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. A Beckman 1801 scintillation counter was used for scintillation spectrometry; 0.1% bovine serum albumin and (−)-cocaine were purchased from Sigma Chemicals.

[^{3}H]WIN 35,428 [[^{3}H]CFT, 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). (*R*)-(−)-Cocaine hydrochloride for the pharmacological studies was donated by the National Institute on Drug Abuse (NIDA). Fluoxetine was donated by E. Lilly & Co. 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).

General Procedure for Synthesis of the Diarylmethoxytropanes: (*S*)-(+)-2β-Carbomethoxy-3α-[bis(4-fluorophenyl)methoxy)]tropane (2a). (*S*)-Alloecgonine methyl ester, **1**[25] (900 mg, 4.5 mmol), 4,4′-difluorobenzhydrol (1.99 g, 9 mmol), *p*-toluenesulfonic acid monohydrate (1.3 g, 6.78 mmol), and benzene (50 mL) in a 100 mL round bottom flask fitted with a Dean−Stark trap and condenser were heated at reflux for 18 h. More 4,4′-difluorobenzhydrol (1.0 g) and *p*-toluenesulfonic acid monohydrate (60 mg) were added, and the reaction mixture was heated at reflux for a further 5 h. The reaction mixture was cooled to room temperature. NH_4OH (1 mL) was added followed by H_2O (20 mL) and EtOAc (100 mL). The dried (K_2CO_3) organic layer was concentrated to dryness. The residue was flash chromatographed over silica gel (EtOAc, 2% NH_4OH, 2% MeOH in EtOAc) to afford (*S*)-(+)-2β-carbomethoxy-3α-[bis(4-fluorophenyl)methoxy]tropane, **2a** (1.4 g, 78%), as a white solid: mp 130−131°C; R_f 0.53 (EtOAc + 2% NH_4OH); ^{1}H-NMR (100 MHz, $CDCl_3$) δ 1.80−2.15 (m, 6H), 2.20 (s, 3H, NCH_3), 2.73 (s, 1H, *H*-2), 3.11 (bs, 1H, *H*-5), 3.59 (d, 1H, *H*-1), 3.69 (s, 3H, OCH_3), 4.00 (d, 1H, *H*-3), 5.36 (s, 1H, OC*H*), 6.90−7.36 (m, 8H, Ar*H*); analytical HPLC (Chiralcel OC column, eluting with hexane/2-propanol, 98:2, + 0.1% DEA) t_R = 7.8 min; $[\alpha]^{21}_D$ +21.6° (c = 1, MeOH). Anal. ($C_{23}H_{25}NO_3F_2$) C, H, N.

NMR with europium D-3-(heptafluorobutyryl)camphorate was conducted at 100 MHz. A sample of (*S*)-**2a** (5 mg) and (*R*)-**2a** (5 mg) was prepared in $CDCl_3$ (0.5 mL) containing europium D-3-(heptafluorobutyryl)camphorate (8.1 mg). Two base-line-separated singlet resonances at δ 6.07 and 5.93 for the diagnostic dibenzylic protons were apparent. In a 10% mixture of (*R*)-**2a** in (*S*)-**2a**, with 52% by weight of shift reagent in $CDCl_3$ (0.5 mL), the major peak was at δ 5.98 [(*S*)-**2a**] and the minor at δ 5.85 [(*R*)-**2a**].

(*S*)-(+)-2β-Carbomethoxy-3α-(diphenylmethoxy)tropane (2b). Compound **2b** was prepared from (*S*)-alloecgonine methyl ester, **1**, and benzhydrol as described for **2a**. A yellow viscous oil was obtained (74%): R_f 0.52 (EtOAc + 2% NH_4OH); ^{1}H-NMR (100 MHz, $CDCl_3$) δ 1.62−2.13 (m, 6H), 2.19 (s, 3H, NCH_3), 2.76 (s, 1H, *H*-2), 3.08 (bs, 1H, *H*-5), 3.56 (bs, 1H, *H*-1), 3.66 (s, 3H, OCH_3), 4.02 (d, 1H, *H*-3), 5.38 (s, 1H, OC*H*), 7.30 (m, 10H, Ar*H*); $[\alpha]^{21}_D$ +36.4° (c = 1, MeOH). HCl salt: mp 178−179 °C. Anal. ($C_{23}H_{27}NO_3$·HCl) C, H, N, Cl.

(*S*)-(+)-2β-Carbomethoxy-3α-[bis(4-bromophenyl)-methoxy]tropane (2c). Compound **2c** was prepared from (*S*)-alloecgonine methyl ester, **1**, and 4,4′-dibromobenzhydrol as described for **2a**. A white solid was obtained (68%): mp 119−121°C; R_f 0.55 (EtOAc + 2% NH_4OH); ^{1}H-NMR (100 MHz, $CDCl_3$) δ 1.60−2.15 (m, 6H), 2.20 (s, 3H, NCH_3), 2.72 (s, 1H, *H*-2), 3.10 (bs, 1H, *H*-5), 3.58 (bs, 1H, *H*-1), 3.69 (s, 3H, OCH_3), 3.98 (d, 1H, *H*-3), 5.30 (s, 1H, OC*H*), 7.05−7.55 (m, 8H, Ar*H*); $[\alpha]^{21}_D$ +18.2° (c = 1, MeOH). Anal. ($C_{23}H_{25}NO_3Br_2$) C, H, N, Br.

(*S*)-(+)-2β-Carbomethoxy-3α-[bis(4-chlorophenyl)-methoxy]tropane (2d). Compound **2d** was prepared from (*S*)-alloecgonine methyl ester, **1**, and 4,4′-dichlorobenzhydrol as described for **2a**. An off-white solid was obtained (73%): mp 110−112 °C; R_f 0.55 (EtOAc + 2% NH_4OH); ^{1}H-NMR (100 MHz, $CDCl_3$) δ 1.62−2.13 (m, 6H), 2.18 (s, 3H, NCH_3), 2.72 (s, 1H, *H*-2), 3.09 (bs, 1H, *H*-5), 3.58 (bs, 1H, *H*-1), 3.69 (s, 3H, OCH_3), 3.98 (d, 1H, *H*-3), 5.33 (s, 1H, OC*H*), 7.27 (m, 8H, Ar*H*); $[\alpha]^{21}_D$ +20.7° (c = 1, MeOH). Anal. ($C_{23}H_{25}NO_3Cl_2$) C, H, N, Cl.

(*S*)-(+)-2β-Carbomethoxy-3α-[bis(4-methylphenyl)-methoxy]tropane (2f). Compound **2f** was prepared from (*S*)-alloecgonine methyl ester, **1**, and 4,4′-dimethylbenzhydrol as described for **2a**. A viscous oil was obtained (78%): R_f 0.55 (EtOAc + 2% NH_4OH); ^{1}H-NMR (100 MHz, $CDCl_3$) δ 1.65−2.13 (m, 6H), 2.19 (s, 3H, NCH_3), 2.30 (s, 6H, ArCH_3), 2.76 (s, 1H, *H*-2), 3.08 (bs, 1H, *H*-5), 3.55 (bs, 1H, *H*-1), 3.69 (s, 3H, OCH_3), 4.01 (d, 1H, *H*-3), 5.32 (s, 1H, OC*H*), 7.02−7.32 (m, 8H, Ar*H*). HCl salt: mp 164−166 °C; $[\alpha]^{21}_D$ +35.7 ° (c = 1, MeOH). Anal. ($C_{25}H_{31}NO_3$·HCl·0.25H_2O) C, H, N, Cl

(*S*)-(+)-2β-Carbomethoxy-3α-[(4-fluorophenyl)phenylmethoxy]tropane (2g). Compound **2g** was prepared from (*S*)-alloecgonine methyl ester, **1**, and 4-fluorobenzhydrol as described for **2a**. An off-white solid was obtained (78%): mp 115−117 °C; R_f 0.55 (EtOAc + 2% NH_4OH); ^{1}H-NMR (100 MHz, $CDCl_3$) δ 1.65−2.15 (m, 6H), 2.18 (s, 3H, NCH_3), 2.74 (s, 1H, *H*-2), 3.08 (bs, 1H, *H*-5), 3.57 (bs, 1H, *H*-1), 3.67 (s, 3H, OCH_3), 4.00 (d, 1H, *H*-3), 5.36 (s, 1H, OC*H*), 6.97 (t, 2H, Ar*H*), 7.20−7.36 (m, 7H, Ar*H*); $[\alpha]^{21}_D$ +21.4° (c = 1, MeOH). Anal. ($C_{23}H_{26}NO_3F$).

(*S*)-(+)-2β-Carbomethoxy-3α-[(4-chlorophenyl)phenylmethoxy]tropane (2h). Compound **2h** was prepared from (*S*)-alloecgonine methyl ester, **1**, and 4-chlorobenzhydrol as described for **2a**. A yellow viscous oil was obtained (69%): mp (HCl salt) 128−130 °C; R_f 0.60 (EtOAc + NH_4OH); ^{1}H-NMR (100 MHz, $CDCl_3$) δ 1.65−2.10 (m, 6H), 2.180 (s, 3H, NCH_3), 2.74 (s, 1H, *H*-2), 3.08 (bs, 1H, *H*-5), 3.56 (bs, 1H, *H*-1), 3.66 (s, 3H, OCH_3), 4.00 (d, 1H, *H*-3), 5.35 (s, 1H, OC*H*), 7.27 (bs, 9H, Ar*H*); $[\alpha]^{21}_D$ +36.0° (c = 1, MeOH). Anal. ($C_{23}H_{26}NO_3$-Cl·HCl·$^3/_4H_2O$).

(*S*)-2β-Carbomethoxy-3α-[(4-bromophenyl)phenylmethoxy]tropane (2i). Compound **2i** was prepared from (*S*)-alloecgonine methyl ester, **1**, and 4-bromobenzhydrol as de-

scribed for **2a**. A pale yellow oil was obtained (77%): R_f 0.65 (EtOAc + 2% NH_4OH); ^{1}H-NMR (100 MHz, $CDCl_3$) δ 1.67−2.14 (m, 6H), 2.18 (s, 3H, NCH_3), 2.74 (s, 1H, *H*-2), 3.09 (bs, 1H, *H*-5), 3.58 (bs, 1H, *H*-1), 3.66, 3.67 (2s, 3H, OCH_3), 3.98 (d, 1H, *H*-3), 5.33 (s, 1H, OC*H*), 7.15−7.53 (m, 9H, Ar*H*). HCl salt: mp 120−122 °C. Anal. ($C_{23}H_{26}NO_3Br\cdot HCl\cdot 1.5H_2O$) C, H, N, Br, Cl.

(*S*)-(+)-2β-Carbomethoxy-3α-[(4-methylphenyl)phenylmethoxy]tropane (2j). Compound **2j** was prepared from (*S*)-alloecgonine methyl ester, **1**, and 4-methylbenzhydrol as described for **2a**. A yellow viscous oil was obtained (78%): mp (HCl salt) 148−150°C; R_f 0.60 (EtOAc + 2% NH_4OH); ^{1}H-NMR (100 MHz, $CDCl_3$) δ 1.70−2.13 (m, 6H), 2.30 (s, 3H, NCH_3), 2.76 (s, 1H, *H*-2), 3.07 (bs, 1H, *H*-5), 3.56 (bs, 1H, *H*-1), 3.66 (s, 3H, OCH_3), 3.98 (d, 1H, *H*-3), 5.29 (s, 1H, OC*H*), 7.04−7.35 (m, 9H, Ar*H*); $[\alpha]^{21}_D$ +34.1° (c = 1, MeOH). Anal. ($C_{24}H_{29}NO_3\cdot HCl\cdot {}^1/_2H_2O$).

General Procedure for Preparation of the Tributylstannyl Intermediates: (*S*)-2β-Carbomethoxy-3α-[bis[4-(tributylstannyl)phenyl]methoxy]tropane. (*S*)-(+)-2β-Carbomethoxy-3α-[bis(4-bromophenyl)methoxy]tropane, **2c** (0.38 g, 0.73 mmol), in toluene (10 mL) was degassed by bubbling N_2 into the mixture. Bis(tributyltin) (0.88 mL, 1.74 mmol) was added followed by tetrakis(triphenylphosphine)palladium (13.4 mg, 0.12 mmol). Degassing was continued for another 15 min. The reaction mixture was heated at reflux for 2 h, filtered through Celite, and then concentrated to dryness. The residue was purified by flash chromatography (hexanes, 10% Et_3N/hexanes) to afford 81 mg (12%) of (*S*)-2β-carbomethoxy-3α-[bis-[4-(tributylstannyl)phenyl]methoxy]tropane as a light brown oil: R_f 0.5 (10% Et_3N/hexanes, two elutions); ^{1}H-NMR (100 MHz, $CDCl_3$) δ 0.70−2.13 (m, 60H), 2.18 (s, 3H, NCH_3), 2.73 (s, 1H, *H*-2), 3.08 (bs, 1H, *H*-5), 3.55 (bs, 1H, *H*-1), 3.65 (s, 3H, OCH_3), 4.01 (d, 1H, *H*-3), 5.30 (s, 1H, OC*H*), 7.18−7.46 (m, 8H, Ar*H*). Also eluted was 197 mg of (*S*)-2β-carbomethoxy-3α-[[4-(tributylstannyl)phenyl](4-bromophenyl)methoxy]tropane as a light brown oil: R_f 0.27 (10% Et_3N/hexanes, two elutions); ^{1}H-NMR (100 MHz, $CDCl_3$) δ 0.70−2.18 (m, 33H), 2.19 (s, 3H, NCH_3), 2.74 (bs, 1H, *H*-2), 3.09 (bs, 1H, *H*-5), 3.58 (bs, 1H, *H*-1), 3.66, 3.68 (2s, 3H, OCH_3), 4.00 (d, 1H, *H*-3), 5.31 (s, 1H, OC*H*), 7.15−7.55 (m, 8H, Ar*H*). In addition, 180 mg (47%) of recovered starting material **2c** was obtained.

(*S*)-2β-Carbomethoxy-3α-[[4-(tributylstannyl)phenyl]-phenylmethoxy]tropane. (*S*)-2β-Carbomethoxy-3α-[(4-bromophenyl)phenylmethoxy]tropane, **2i**, was treated as described above to provide (*S*)-2β-carbomethoxy-3α-[[4-(tributylstannyl)phenyl]phenylmethoxy]tropane as a light brown oil (57%): R_f 0.37 (10% Et_3N/hexanes, two elutions); ^{1}H-NMR (100 MHz, $CDCl_3$) δ 0.71−2.14 (m, 33H), 2.20 (s, 3H, NCH_3), 2.76 (bs, 1H, *H*-2), 3.09 (bs, 1H, *H*-5), 3.58 (bs, 1H, *H*-1), 3.68 (s, 3H, OCH_3), 4.03 (d, 1H, *H*-3), 5.35 (s, 1H, OC*H*), 7.15−7.63 (m, 9H, Ar*H*).

(*S*)-2β-Carbomethoxy-3α-[bis(4-fluorophenyl)methoxy]-*N*-[3-[4-(tributylstannyl)phenyl]propyl]nortropane. (*S*)-2β-Carbomethoxy-3α-[bis(4-fluorophenyl)methoxy]-*N*-[3-(4-bromophenyl)propyl]nortropane, **4c**, was treated as described above to provide (*S*)-2β-carbomethoxy-3α-[bis(4-fluorophenyl)-methoxy]-*N*-[3-[4-(tributylstannyl)phenyl]propyl]nortropane (49%) as a light brown oil: R_f 0.73 (25% EtOAc/hexane).

General Procedure for Iodination of the Tributylstannyl Compounds: (*S*)-(+)-2β-Carbomethoxy-3α-[bis-(4-iodophenyl)methoxy]tropane (2e). (*S*)-(+)-2β-Carbomethoxy-3α-[bis[4-(tributylstannyl)phenyl]methoxy]tropane (80 mg, 0.086 mmol) in anhydrous THF (3 mL) was degassed by bubbling N_2 for 15 min. *N*-Iodosuccinimide (39 mg, 0.17 mmol) was added, and the reaction mixture was stirred at room temperature for 15 min. THF was removed under reduced pressure. The residue was dissolved in 10 mL of EtOAc and washed with saturated Na_2CO_3 (5 mL) and brine (5 mL). The dried (K_2CO_3) organic layer was concentrated to dryness. The residue was purified by flash chromatography (5% Et_3N, 10% Et_2O in hexanes) to afford 38 mg (72%) of (*S*)-(+)-2β-carbomethoxy-3α-[bis(4-iodophenyl)methoxy]tropane, **2e**, as an off-white solid: mp 156−158 °C; R_f 0.53 (EtOAc + 2% NH_4OH); ^{1}H-NMR (100 MHz, $CDCl_3$) δ 1.45−2.13 (m, 6H), 2.20 (s, 3H, NCH_3), 2.71 (s, 1H, *H*-2), 3.10 (bs, 1H, *H*-5), 3.60 (bs, 1H, *H*-1), 3.68 (s, 3H, OCH_3), 3.99 (d, 1H, *H*-3), 5.26 (s, 1H, OC*H*), 6.93−7.76 (m, 8H, Ar*H*); $[\alpha]^{21}_D$ +16.0° (c = 0.5, MeOH). Anal. ($C_{23}H_{25}NO_3I_2$) C, H, N, I.

(*S*)-(+)-2β-Carbomethoxy-3α-[(4-iodophenyl)phenyl]-methoxy]tropane (2k). Compound **2k** was prepared from (*S*)-2β-carbomethoxy-3α-[[4-(tributylstannyl)phenyl]phenylmethoxy]tropane as described for **2e**. A yellow oil was obtained (95%): R_f 0.53 (EtOAc + 2% NH_4OH); ^{1}H-NMR (100 MHz, $CDCl_3$) δ 1.67−2.18 (m, 6H), 2.22 (s, 3H, NCH_3), 2.74 (s, 1H, *H*-2), 3.12 (bs, 1H, *H*-5), 3.63 (bs, 1H, *H*-1), 3.67, 3.69 (2s, 3H, OCH_3), 4.02 (d, 1H, *H*-3), 5.32 (s, 1H, OC*H*), 7.01−7.66 (m, 9H, Ar*H*). HCl salt: mp 130−132°C; $[\alpha]^{21}_D$ +30.3° (c = 1, MeOH). Anal. ($C_{23}H_{26}NO_3I\cdot HCl\cdot 0.5\ H_2O$) C, H, N, Cl, I.

(*S*)-(+)-2β-Carbomethoxy-3α-[(4-bromophenyl)(4-iodophenyl)methoxy]tropane (2l). Compound **2l** was prepared from (*S*)-2β-carbomethoxy-3α-[(4-bromophenyl)[4-(tributylstannyl)phenyl]methoxy]tropane as described for **2e**. A white solid was obtained (76%): mp 126−128 °C; R_f 0.53 (EtOAc + 2% NH_4OH); ^{1}H-NMR (100 MHz, $CDCl_3$) δ 1.68−2.13 (m, 6H), 2.35 (s, 3H, NCH_3), 2.78 (s, 1H, *H*-2), 3.28 (bs, 1H, *H*-5), 3.73 (bs, 4H, *H*-1, OCH_3), 4.08 (d, 1H, *H*-3), 5.29 (s, 1H, OC*H*), 6.94−7.72 (m, 8H, Ar*H*); $[\alpha]^{21}_D$ +20.5° (c = 1, MeOH). Anal. ($C_{23}H_{25}NO_3BrI\cdot {}^1/_2H_2O$) C, H, N, Br, I.

(*S*)-(+)-2β-Carbomethoxy-3α-[bis(4-fluorophenyl)-methoxy]-*N*-[3-(4-iodophenyl)propyl]nortropane (4d). (*S*)-2β-Carbomethoxy-3α-[bis(4-fluorophenyl)methoxy]-*N*-[3-[4-(tributylstannyl)phenyl]propyl]nortropane (83 mg, 0.1 mmol) in anhydrous THF (5 mL) was degassed by bubbling N_2 for 15 min. *N*-Iodosuccinimide (24 mg, 0.107 mmol) was added, and the reaction mixture was stirred at room temperature for 15 min. THF was removed under reduced pressure. The residue was dissolved in 10 mL of CH_2Cl_2 and washed with saturated $NaHCO_3$ (5 mL) and brine (5 mL). The dried (K_2CO_3) CH_2Cl_2 layer was concentrated to dryness. The residue was purified by flash chromatography (25% EtOAc/hexanes) to afford 66 mg (100%) of (*S*)-2β-carbomethoxy-3α-[bis(4-fluorophenyl)-methoxy]-*N*-[3-(4-iodophenyl)propyl]nortropane, **4d**, as a light brown oil: R_f 0.55 (EtOAc/hexane, 1:1); ^{1}H-NMR (100 MHz, $CDCl_3$) δ 1.50−2.22 (m, 10H), 2.55 (t, 2H, NCH_2), 2.73 (bs, 1H, *H*-2), 3.08 (bs, 1H, *H*-5), 3.65 (s, 3H, OCH_3), 3.68 (bs, 1H, *H*-1), 4.01 (d, 1H, *H*-3), 5.34 (s, 1H, OC*H*), 6.87−7.62 (m, 12H, Ar*H*). HCl salt: mp 113−115 °C; $[\alpha]^{21}_D$ +20.2° (c = 0.55, MeOH). Anal. ($C_{31}H_{32}NO_3F_2I\cdot HCl\cdot 1.5H_2O$) C, H, N, Cl, I.

(*S*)-2β-Carbomethoxy-3α-(ethylphenylmethoxy)tropane (2m). (*S*)-Alloecgonine methyl ester, **1** (200 mg, 1 mmol), 1-phenylpropanol (273 mg, 2 mmol), *p*-toluenesulfonic acid monohydrate (288 mg, 1.5 mmol), and benzene (50 mL) in a 100 mL round bottom flask fitted with a Dean−Stark trap and condenser were heated at reflux for 18 h. 1-Phenylpropanol (180 mg) and *p*-toluenesulfonic acid monohydrate (50 mg) were added, and the reaction mixture was heated at reflux for another 5 h. The reaction mixture was cooled to room temperature and concentrated to dryness. The residue was dissolved in ether (25 mL) and washed with water (20 mL). The aqueous layer was basified with NH_4OH and extracted with CH_2Cl_2 (2 × 25 mL). The dried (K_2CO_3) organic layer was concentrated to dryness. The residue was flash chromatographed over silica gel (EtOAc, 2% NH_4OH, 5% MeOH in EtOAc) to afford 45 mg (14%) of (*S*)-2β-carbomethoxy-3α-(ethylphenylmethoxy)tropane, **2m**, as a pale yellow oil: R_f 0.53 (EtOAc + 2% NH_4OH); ^{1}H-NMR (100 MHz, $CDCl_3$) δ 0.86 (t, 3H, CH_3), 1.50−2.10 (m, 8H), 2.17 (s, 3H, NCH_3), 2.60, 2.73 (2bs, 1H, *H*-2), 3.05 (bs, 1H, *H*-5), 3.52 (bs, 1H, *H*-1), 3.61, 3.68 (2s, 3H, OCH_3), 3.82 (d, 1H, *H*-3), 4.20 (t, 1H, OC*H*), 7.26 (m, 5H, Ar*H*); $[\alpha]^{21}_D$ +36.7° (c = 0.39, MeOH). HCl salt: mp 150−152 °C. Anal. ($C_{19}H_{27}NO_3\cdot HCl\cdot {}^1/_3H_2O$) C, H, N, Cl.

(*RS*)-2β-Carbomethoxy-3α-(fluorenyloxy)tropane (2n). (*RS*)-Alloecgonine methyl ester, **1** (200 mg, 1 mmol), 9-hydroxyfluorene (366 mg, 2 mmol), *p*-toluenesulfonic acid monohydrate (290 mg, 1.5 mmol), and benzene (50 mL) in a 100 mL round bottom flask fitted with a Dean−Stark trap and condenser were heated at reflux for 18 h. 9-Hydroxyfluorene (366 mg) and *p*-toluenesulfonic acid monohydrate (80 mg) were added, and the reaction mixture was heated at reflux for another 5 h. The reaction mixture was cooled to room temperature and concentrated to dryness. The residue was

dissolved in CH_2Cl_2 (30 mL) and basified with NH_4OH. The dried (K_2CO_3) organic layer was concentrated to dryness. The residue was chromatographed over silica gel (EtOAc, 3% NH_4OH, 5% MeOH in EtOAc) to afford 104 mg (29%) of (*RS*)-2β-carbomethoxy-3α-(fluorenyloxy)tropane, **2n**, as a light brown oil: R_f 0.48 (EtOAc + 2% NH_4OH); ^{1}H-NMR (100 MHz, $CDCl_3$) δ 1.80−2.15 (m, 6H), 2.20 (s, 3H, NC*H*$_3$), 2.86 (s, 1H, *H*-2), 3.12 (bs, 1H, *H*-5), 3.61 (bs, 1H, *H*-1), 3.70 (s, 3H, OC*H*$_3$), 4.40 (d, 1H, *H*-3), 5.48 (s, 1H, OC*H*), 7.20−7.70 (m, 8H, Ar*H*); $[\alpha]^{21}_D$ −4.41° (c = 2.45, MeOH). HCl salt: mp 155 °C. Anal. ($C_{23}H_{25}NO_3$·HCl·0.5H_2O) C, H, N, Cl.

(*S*)-(+)-2β-Carbomethoxy-3α-[bis(4-fluorophenyl)methoxy]nortropane (3). (*S*)-(+)-2β-Carbomethoxy-3α-[bis-(4-fluorophenyl)methoxy]tropane, **2a** (0.5 g, 1.24 mmol), and α-chloroethyl chloroformate (ACE-Cl) (2 mL) were combined and heated at reflux for 1 h. Excess ACE-Cl was then removed under reduced pressure, and methanol (10 mL) was added to the residue. The mixture was heated at reflux for 1 h and then concentrated to dryness. The residue was purified by flash chromatography to afford 280 mg (58%) of (*S*)-(+)-2β-carbomethoxy-3α-[bis(4-fluorophenyl)methoxy]nortropane, **3**, as a light brown oil: R_f 0.26 (EtOAc + 2% NH_4OH); ^{1}H-NMR (100 MHz, $CDCl_3$) δ 1.74−2.25 (m, 6H), 2.73 (bs, 1H, *H*-2), 3.50 (bs, 1H, *H*-5), 3.68 (s, 3H, OC*H*$_3$), 3.84 (d, 2H, *H*-3, *H*-1), 5.35 (s, 1H, OC*H*), 6.92−7.35 (m, 8H, Ar*H*). Anal. ($C_{22}H_{23}NO_3F_2$·0.25H_2O) C, H, N.

General Procedure for Alkylation of the Nortropanes: (*S*)-(+)-2β-Carbomethoxy-3α-[bis(4-fluorophenyl)methoxy]-*N*-benzylnortropane (4a). (*S*)-2β-Carbomethoxy-3α-[bis(4-fluorophenyl)methoxy]nortropane, **3** (100 mg, 0.26 mmol), benzyl bromide (51 mg, 0.29 mmol), 50% KF/Celite (150 mg, 1.29 mmol), and anhydrous acetonitrile (5 mL) were combined and heated at reflux for 18 h. Ether (15 mL) was added after the reaction mixture was cooled to room temperature, and the mixture was filtered over Celite. The filtrate was concentrated to dryness. The residue was purified by flash chromatography (5% Et_3N/hexanes) to afford 111 mg (90%) of (*S*)-2β-carbomethoxy-3α-[bis(4-fluorophenyl)methoxy]-*N*-benzylnortropane, **4a**, as a pale yellow oil: R_f 0.24 (10% Et_3N/hexane); ^{1}H-NMR (100 MHz, $CDCl_3$) δ 1.70−2.20 (m, 6H), 2.68 (bs, 1H, *H*-2), 3.15−3.58 (m, 4H, *H*-5, NC*H*$_2$, *H*-1), 3.47 (s, 3H, OC*H*$_3$), 3.99 (d, 1H, *H*-3), 5.34 (s, 1H, OC*H*), 6.90−7.34 (m, 13H, Ar*H*); $[\alpha]^{21}_D$ +37.8° (c = 1, MeOH). HCl salt: mp 130−132 °C. Anal. ($C_{29}H_{29}NO_3F_2$·HCl) C, H, N, Cl.

(*S*)-(+)-2β-Carbomethoxy-3α-[bis(4-fluorophenyl)methoxy]-*N*-(3-phenylpropyl)nortropane (4b). (*S*)-2β-Carbomethoxy-3α-[bis(4-fluorophenyl)methoxy]nortropane, **3**, and 1-bromo-3-phenylpropane were treated as for **4a** to provide a pale yellow oil (81%): R_f 0.33 (10% Et_3N/hexane); ^{1}H-NMR (100 MHz, $CDCl_3$) δ 1.62−2.28 (m, 10H), 2.61 (t, 2H, NC*H*$_2$), 2.70 (s, 1H, *H*-2), 3.10 (bs, 1H, *H*-5), 3.63 (s, 3H, OC*H*$_3$), 3.69 (d, 1H, *H*-1), 4.00 (d, 1H, *H*-3), 5.34 (s, 1H, OC*H*), 6.90−7.36 (m, 13H, Ar*H*). HCl salt: mp 98−100 °C; $[\alpha]^{21}_D$ 30.2° (c = 1, MeOH). Anal. ($C_{31}H_{33}NO_3F_2$·HCl·0.5H_2O) C, H, N, Cl.

(*S*)-(+)-2β-Carbomethoxy-3α-[bis(4-fluorophenyl)methoxy]-*N*-[3-(4-bromophenyl)propyl]nortropane (4c). (*S*)-2β-Carbomethoxy-3α-[bis(4-fluorophenyl)methoxy]nortropane, **3**, and 1-bromo-3-(4-bromophenyl)propane were treated as for **4a** to provide a light brown oil (77%): R_f 0.55 (EtOAc/hexane, 1:1); ^{1}H-NMR (100 MHz, $CDCl_3$) δ 1.50−2.30 (m, 10H), 2.55 (t, 2H, NC*H*$_2$), 2.73 (bs, 1H, *H*-2), 3.08 (bs, 1H, *H*-5), 3.62 (s, 3H, OC*H*$_3$), 3.68 (bs, 1H, *H*-1), 4.00 (d, 1H, *H*-3), 5.34 (s, 1H, OC*H*), 6.87−7.45 (m, 12H, Ar*H*). HCl salt: mp 91−94 °C; $[\alpha]^{21}_D$ +22.9° (c = 0.81, MeOH). Anal. ($C_{31}H_{32}NO_3F_2Br$·HCl·0.5H_2O) C, H, N, Br, Cl.

(*S*)-(+)-2β-Carbomethoxy-3α-[bis(4-fluorophenyl)methoxy]-*N*-(3-phenylpentyl)nortropane (4e). (*S*)-2β-Carbomethoxy-3α-[bis(4-fluorophenyl)methoxy]nortropane, **3**, and 1-chloro-3-phenylpentane were treated as for **4a** to provide a pale yellow oil (76%): R_f 0.28 (10% Et_3N/hexane); ^{1}H-NMR (100 MHz, $CDCl_3$) δ 1.22−2.22 (m, 14H), 2.59 (t, 2H, NC*H*$_2$), 2.70 (bs, 1H, *H*-2), 3.10 (bs, 1H, *H*-5), 3.62 (s, 3H, OC*H*$_3$), 3.68 (bs, 1H, *H*-1), 3.99 (d, 1H, *H*-3), 5.33 (s, 1H, OC*H*), 6.90−7.33 (m, 13H, Ar*H*); $[\alpha]^{21}_D$ +23.5° (c = 0.86, MeOH). Anal. ($C_{33}H_{37}NO_3F_2$) C, H, N.

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 vol (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 vol of buffer, and the entire 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 no. 5) for 15 s. All experiments were conducted in triplicate, and each experiment was repeated in each of two to three preparations from individual brains.

Dopamine Transporter Assay. The DAT was labeled with [^{3}H]WIN 35,428 (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 concentrations 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: CFT, 0.2 mL (1 pM−100 or 300 nM), [^{3}H]WIN 35,428 (0.3 nM), and 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]-CFT bound in the presence of ineffective concentrations of unlabeled CFT (1 or 10 pM). Nonspecific binding was defined as [^{3}H]CFT 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]CFT-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.

Serotonin Transporter Assay. The serotonin transporter was assayed in caudate-putamen membranes using conditions similar to those for the DAT. 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−100 or 300 nM), [^{3}H]-citalopram (1 nM), and 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(ethyleneimine). 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.

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