Synthesis and Biological Properties of New 2β-Alkyl- and 2β-Aryl-3-(substituted phenyl)tropane Derivatives: Stereochemical Effect of C-3 on Affinity and Selectivity for Neuronal Dopamine and Serotonin Transporters

Alan P. Kozikowski,*,† Gian Luca Araldi,† K. R. C. Prakash,† Mei Zhang,‡ and Kenneth M. Johnson‡

Drug Discovery Program, Institute of Cognitive and Computational Sciences, Georgetown University Medical Center, 3970 Reservoir Road, N.W., Washington, D.C. 20007-2197, and Department of Pharmacology and Toxicology, University of Texas Medical Branch, Galveston, Texas 77555-1031

Received April 27, 1998

In our efforts to identify molecules that might act as cocaine antagonists or cocaine partial agonists, we have been involved in efforts to further elucidate the nature of cocaine's binding to the dopamine transporter (DAT) through strategic modifications of its structure. In the case of the substituent located at the 2-position of the tropane ring, studies have revealed the ability of the transporter to accommodate groups of diverse structure, including ester, ketone, alkyl, alkenyl, heterocyclic, and aryl substituents, without loss of DAT binding affinity. In the present study, we report our results pertaining to the ability of the DAT to accommodate the WIN-type structures possessing alkyl or aryl groups at the 2-position and which adopt either a chair or a boat conformation of the tropane ring. Moreover, we discuss the influence of the stereochemistry of these compounds in their selectivity for the DAT versus the serotonin transporter (5HTT). Additionally, we point out the importance of using K_i values rather than IC_{50} values when making such comparisons of transporter selectivity. One of the most interesting compounds identified in the present work is a 2,3-diaryltropane **22** in a boat conformation that is highly selective (69-fold) for the DAT over the 5HTT. The ability to prepare this compound as well as related structures by our oxidopyridinium betaine-based dipolar cycloaddition strategy further underscores the versatility of this particular chemical approach to the preparation of diverse tropane analogues. The use of the optically pure olefin *p*-tolyl vinyl sulfoxide as the dipolarophile in this reaction allows access to these novel tropanes in nonracemic form.

Introduction

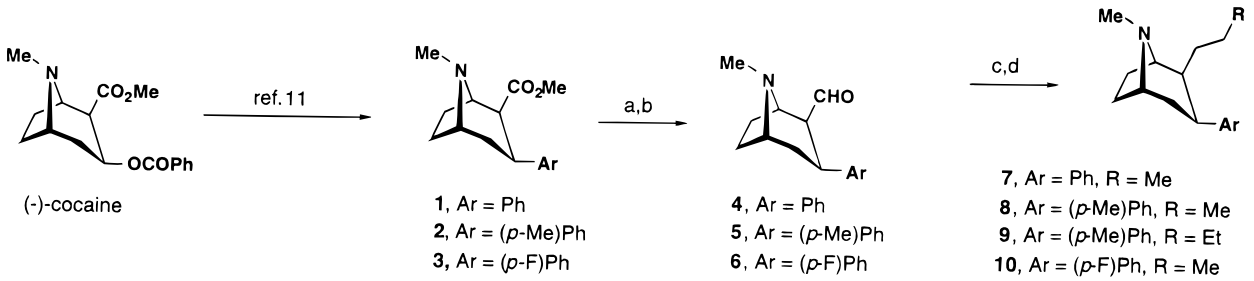
Cocaine is a natural product, produced by *Erythroxylum coca*, that has been found to cause diverse physiological effects in the mammalian central nervous system through its action on different neurotransmitter systems including serotonin (5HT), norepinephrine (NE), and dopamine (DA).[1] Considerable evidence exists to support the idea that cocaine abuse in humans is related to its binding to the dopamine transporter (DAT) in the nucleus accumbens, a region of the striatum that is implicated in the control of motivation and reward.[2] This action of cocaine leads to an increase in extracellular DA which is responsible for a potentiation of dopaminergic neurotransmission in the mesolimbocortical pathways that are thought to underlie the reinforcing effects of cocaine.

In pursuit of possible medications, we have been involved in efforts to further elaborate the nature of cocaine binding through strategic modifications of its structure. Such an approach appears promising as we have already identified several compounds to date that do not result in full generalization in animal drug discrimination models.[3] Extensive structure−activity relationship studies of cocaine by a number of groups have identified certain structural features required for high potency in the inhibition of radioligand binding to the DAT.[4] These features include an aromatic ring at the 3-position in place of cocaine's benzoate group (the WIN series of compounds) and the presence of a heteroatom (nitrogen or oxygen) in the one-atom bridge.[5] In the case of the substituent located at the 2-position of the tropane ring, studies have revealed the ability of the transporter to accommodate groups of diverse structure, including ester, ketone, alkyl, alkenyl, heterocyclic, and aryl substituents, without loss of DAT binding affinity.[6] In the present study, we report our results pertaining to the ability of the DAT to accommodate the WIN-type structures possessing alkyl or aryl groups at the 2-position and which adopt either a chair or a boat conformation of the tropane ring. Moreover, we discuss the influence of both the nature of the 2-substituent as well as the stereochemistry of the 3-substituent on the selectivity of these analogues for the DAT versus the serotonin transporter (5HTT). In particular, we point out the importance of using K_i values rather than IC_{50} values when making such comparisons of transporter selectivity. Recently it has been suggested that a "paradigm shift" away from the purely dopaminergic hypothesis of cocaine abuse should be considered.[7] While cocaine self-administration appears to be best correlated with its activity at the DAT, cocaine is, in fact, a more potent inhibitor of the serotonin transporter than it is of either the dopamine

† Georgetown University Medical Center.
‡ University of Texas Medical Branch.

10.1021/jm9802564 CCC: $15.00
Published on Web 11/06/1998

Scheme 1[a]



(-)-cocaine

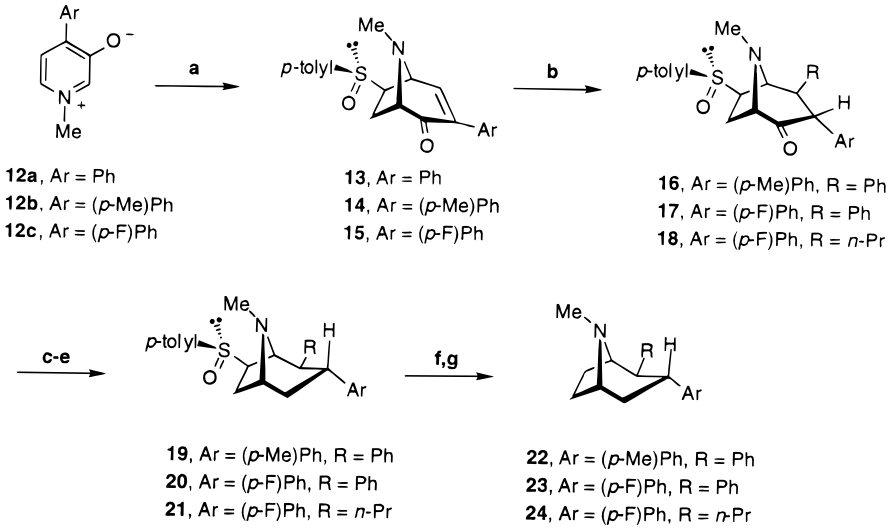
1, Ar = Ph
2, Ar = (*p*-Me)Ph
3, Ar = (*p*-F)Ph

4, Ar = Ph
5, Ar = (*p*-Me)Ph
6, Ar = (*p*-F)Ph

7, Ar = Ph, R = Me
8, Ar = (*p*-Me)Ph, R = Me
9, Ar = (*p*-Me)Ph, R = Et
10, Ar = (*p*-F)Ph, R = Me

[a] Reagents: (a) $LiAlH_4$, THF, rt; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C; (c) $Ph_3P^+CH_2RBr^-$, *n*-BuLi, THF, rt; (d) H_2 (1 atm), Pd/C, MeOH.

Scheme 2[a]



12a, Ar = Ph
12b, Ar = (*p*-Me)Ph
12c, Ar = (*p*-F)Ph

13, Ar = Ph
14, Ar = (*p*-Me)Ph
15, Ar = (*p*-F)Ph

16, Ar = (*p*-Me)Ph, R = Ph
17, Ar = (*p*-F)Ph, R = Ph
18, Ar = (*p*-F)Ph, R = *n*-Pr

19, Ar = (*p*-Me)Ph, R = Ph
20, Ar = (*p*-F)Ph, R = Ph
21, Ar = (*p*-F)Ph, R = *n*-Pr

22, Ar = (*p*-Me)Ph, R = Ph
23, Ar = (*p*-F)Ph, R = Ph
24, Ar = (*p*-F)Ph, R = *n*-Pr

[a] Reagents: (a) *p*-tolyl vinyl sulfoxide, dioxane, reflux; (b) RMgBr, CuBr·Me_2S, HMPA, TMSCl, THF, −78 °C; (c) $LiAlH_4$, THF, rt; (d) $LiN(i\text{-}Pr)_2$, ClC(S)OPh, THF, −78 °C; (e) Bu_3SnH, azobis(isobutyronitrile), toluene, 90 °C; (f) PCl_3, DMF, 0 °C; (g) Raney Ni, EtOH, reflux.

or norepinephrine transporters. In fact, current research using DAT knockout mice suggests an important serotonergic component to the reinforcing effects of cocaine,[8,9] and accordingly issues of transporter selectivity will remain pivotal to our understanding of cocaine's reinforcing effects. As such, a better understanding of the structural elements relevant to creating small molecules displaying "tunable" levels of transporter selectivity may prove valuable to the development of possible medications. However, at the same time we do remain mindful of the fact that the creation of a cocaine medication may actually require the identification of a somewhat nonselective drug showing a transporter profile like that of cocaine.

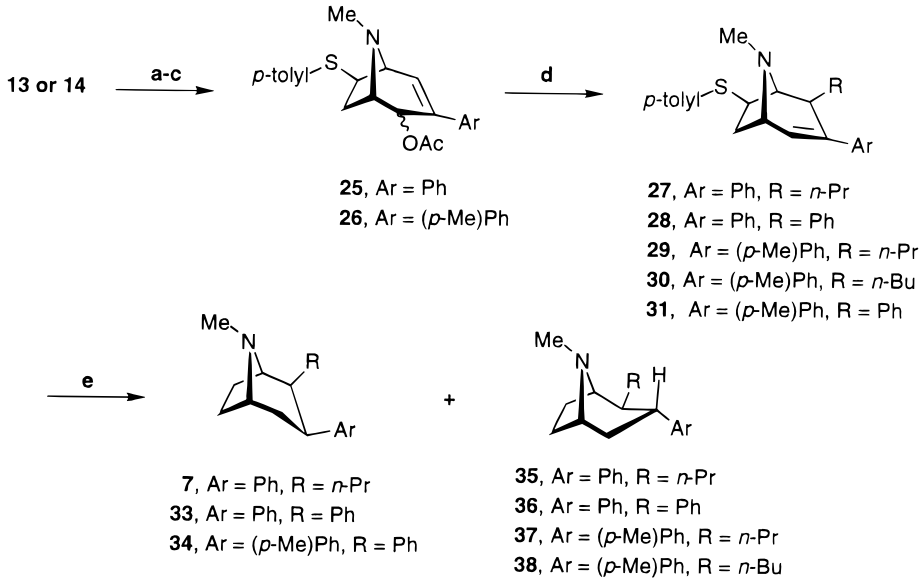
One of the most interesting compounds identified in the present work is a 2,3-diaryltropane in a boat conformation that is highly selective for the DAT over the 5HTT. The ability to prepare this compound as well as related structures by our oxidopyridinium betaine strategy further underscores the versatility of this particular chemical approach to the preparation of diverse tropane analogues.[10]

Chemistry

The synthesis of the tropane analogues reported in this paper was accomplished either by starting from natural (−)-cocaine or by making use of the oxidopyridinium betaine chemistry reported by us.[10] Specifically, the WIN compounds **1**−**3** were prepared as originally reported in the literature by Clarke et al.[11] For compounds **7**−**10** (Scheme 1), the ester group of the appropriate WIN intermediate was transformed to aldehyde by a two-step procedure involving reduction with LAH and Swern oxidation as previously disclosed by us.[6a] Next, Wittig reaction and hydrogenation steps were carried out to provide the appropriate 2β-alkyl-3β-aryltropane. While the 2-alkyl-substituted tropanes reported herein are related to structures reported previously by us,[6a] all of the present compounds are new with the exception of compound **7** which was first described in ref 6a.

For the synthesis of the tropanes **22**−**24** which exist in the boat conformation, we made use of our oxidopyridinium betaine-based dipolar cycloaddition strategy employing optically pure (*R*)-(+)-*p*-tolyl vinyl sulfoxide as the dipolarophile (Scheme 2).[12] The use of this particular dipolarophile allowed access to the tropanes in nonracemic form. The copper-catalyzed conjugate addition reaction of RMgBr to the tropenones **13**−**15** gave rise to intermediates **16**−**18** in which introduction of the proton and the alkyl group occurred from the β-face. The relative stereochemistry of the substituents at positions 3 and 4 of these products was confirmed by observing coupling constants ($J_{3,4}$) in the range of 8.4−9.0 Hz. The magnitudes of these coupling constants are comparable to those reported previously by us for products whose structures were confirmed by X-ray analysis.[10] Removal of unwanted ketone and sulfoxide

Scheme 3[a]



25, Ar = Ph
26, Ar = (*p*-Me)Ph

27, Ar = Ph, R = *n*-Pr
28, Ar = Ph, R = Ph
29, Ar = (*p*-Me)Ph, R = *n*-Pr
30, Ar = (*p*-Me)Ph, R = *n*-Bu
31, Ar = (*p*-Me)Ph, R = Ph

7, Ar = Ph, R = *n*-Pr
33, Ar = Ph, R = Ph
34, Ar = (*p*-Me)Ph, R = Ph

35, Ar = Ph, R = *n*-Pr
36, Ar = Ph, R = Ph
37, Ar = (*p*-Me)Ph, R = *n*-Pr
38, Ar = (*p*-Me)Ph, R = *n*-Bu

[a] Reagents: (a) $NaBH_4$, $CeCl_3$, MeOH, rt; (b) Ac_2O, pyridine, rt; (c) PCl_3, DMF, 0 °C; (d) RMgBr, CuCN, ether, rt; (e) Raney Ni (W2), EtOH, reflux.

groups was then brought about by a series of steps involving ketone reduction with $LiAH_4$, Barton-type deoxygenation of the resulting alcohol, sulfoxide reduction to sulfide with PCl_3, and Raney nickel-promoted desulfurization. In this manner, access to the twist-boat tropanes **22**−**24** was achieved.

The synthesis of compounds **33**−**38** from the tropenone intermediates **13** and **14** was brought about by a copper-catalyzed cross-coupling reaction (Scheme 3). Thus, the tropenones **13** and **14** were first subjected to the Luche reduction to provide the allylic alcohol intermediates as a mixture of both possible stereoisomers. These alcohols were converted in turn to their acetates followed by reduction of the sulfoxide to sulfide using PCl_3 in DMF. The sulfides **25** and **26** (3:1 mixture of the α- and *β*-acetates) were used directly in the CuCN-catalyzed cross-coupling reaction with RMgBr (R = *n*-Pr, *n*-Bu, or Ph) to afford **27**−**31**. As reported previously, this reaction is completely regioselective, and the final stereochemistry of the newly introduced substituent is independent of that of the starting acetate. A W2 Raney nickel-catalyzed hydrogenation/desulfurization reaction then gave access to the final products as delineated in Scheme 3. The hydrogenation reaction proceeded with little selectivity from both the α- and *β*-faces to afford a chromatographically separable mixture of products.

Pharmacology

The tropanes reported herein were examined for their ability to displace [^{3}H]mazindol binding. Mazindol has been shown to label the cocaine binding sites on the dopamine transporter of rat striatal membranes.[13] This ligand binds with high affinity to a single, sodium-dependent site in striatal membranes, representing the dopamine carrier. Additionally, these compounds were tested for their ability to inhibit high-affinity uptake of [^{3}H]DA and [^{3}H]5HT into striatal nerve endings (synaptosomes).[14,15] The protocols used are described in the Experimental Section. The data are provided in Table 1 along with comparison data for (−)-cocaine. In several cases, the ability of some of the tropanes to displace [^{3}H]-paroxetine binding at the 5HTT has been measured.

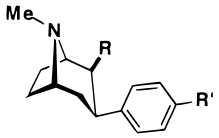
Discussion

It has previously been noted by Carroll that racemic 2*β*,3*β*-diphenyltropane bound the DA transporter with an IC_{50} of 28 nM and that this compound has improved selectivity for DAT over the 5HTT.[6b] Additionally, Carroll was the first to report the preparation of a number of 3α-(4′-substituted phenyl)tropane-2*β*-carboxylic acid methyl esters, existing in a twist-boat conformation, and to show that these materials are only 1.5−1.9-fold less potent at the DAT than the 2*β*,3*β*-isomers.[17] It was also noted by these researchers that the 2*β*,3α-isomers were more selective for the DAT over the 5HTT in comparison to the 2*β*,3*β*-isomers. Such comparisons made use of the observed binding potencies (IC_{50}'s) at the respective transporters that were measured by displacement of either [^{3}H]WIN 35428 or [^{3}H]-paroxetine binding.[17]

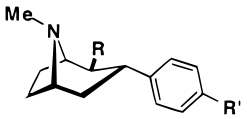
As can be seen from Table 1, in comparing compounds **1** and **2**, the effect of the methyl substituent on the phenyl ring is found to improve binding affinity for the DAT by about 15-fold, as expected, while having little effect on the 5HTT/DAT uptake ratio.[18] Replacement of the carbomethoxy group by *n*-propyl as in the case of compound **7** leads to both an improvement in binding affinity in comparison to **1** (7-fold) together with some improvement in selectivity for the DAT over the 5HTT. In the case of **35** which exists in the boat conformation, this compound is comparable in activity to the chair conformation ester **1**, while it is 6-fold less active than its chair counterpart **7**. Interestingly, **35** still retains its relative selectivity for the DAT over the 5HTT.

Again, as is apparent for compounds **8** and **37**, the appendage of the *p*-methyl group on the phenyl ring increases potency about 7-fold for both the chair and boat structures in comparison to **7** and **35**, while the selectivity for the DAT over the 5HTT is poorer. Similar effects are observed for the *p*-fluoro-substituted analogues **10** and **24**. The effect of the fluorine atom on

Table 1. IC_{50} and K_i Values for the Tropane Analogues in Mazindol Binding and Dopamine and Serotonin Uptake Experiments[a]



2β,3β (chair)



2β,3α (boat)

				mazindol binding (nM)		[^{3}H]DA uptake (nM)		[^{3}H]5HT uptake (nM)		uptake ratio
compd	R	R′	isomer	IC_{50}	K_i	IC_{50}	K_i	IC_{50}	K_i	(based on K_is), 5HT/DA
cocaine				400	281	459	423	168	155	0.37
1	CO_2Me	H	2*β*, 3*β*	163	89.4	57.9	53.7	204	186	3.46
2	CO_2Me	Me	2*β*, 3*β*	10.5	5.76	7.47	6.92	25.5	23.2	3.36
7	*n*-Pr	H	2*β*, 3*β*	23.1	12.2	7.46	6.89	95.4	86.8	12.6
35	*n*-Pr	H	2*β*, 3α	141	74.9	32.6	30.2	427	389	12.9
8	*n*-Pr	Me	2*β*, 3*β*	2.97	1.57	1.19	1.10	11.3	10.3	9.35
37	*n*-Pr	Me	2*β*, 3α	18.2	8.91	12.8	11.8	54.8	50.1	4.25
10	*n*-Pr	F	2*β*, 3*β*	10.0	5.28	2.16	1.99	23.7	21.7	10.9
24	*n*-Pr	F	2*β*, 3α	37.1	21.1	13.1	12.1	109	99.6	8.2
9	*n*-Bu	Me	2*β*, 3*β*	3.43	1.82	1.42	1.31	16.5	15.1	11.5
38	*n*-Bu	Me	2*β*, 3α	21.6	11.4	10.9	10.1	55.8	51.0	5.1
33	Ph	H	2*β*, 3*β*	96.5	49.9	31.1	28.9	1200	1100	38.1
36	Ph	H	2*β*, 3α	26.6	13.8	12.6	11.7	823	753	64.3
34	Ph	Me	2*β*, 3*β*	4.98	2.58	3.09	2.87	80.8	73.8	25.7
22	Ph	Me	2*β*, 3α	5.55	2.87	4.48	4.16	314	287	68.9
23	Ph	F	2*β*, 3α	11.4	6.00	4.95	4.58	134	122	26.6

[a] These values represent the mean of 2−3 experiments in which the range of values was not greater than 15%.

Table 2. Comparisons of 5HT/DA Selectivity Ratios Calculated by the Use of IC_{50} and K_i Values Obtained from Binding and Uptake Experiments

	[^{3}H]mazindol binding (nM)		[^{3}H]DA uptake		[^{3}H]paroxetine binding		[^{3}H]5HT uptake		binding selectivity (parox/maz) based on		uptake selectivity (5HT/DA) based on	
compd	IC_{50}	K_i	IC_{50}	K_i	IC_{50}	K_i	IC_{50}	K_i	IC_{50}s	K_is	IC_{50}s	K_is
1	163	89.4	57.9	53.7	2710	135	204	186	16.6	1.51	3.52	3.46
2	10.5	5.76	7.47	6.72	241	12.0	25.5	23.2	22.9	2.07	3.42	3.36
36	26.6	13.8	12.6	11.7	7690	410	823	753	289	29.7	65.2	64
22	5.55	2.87	4.48	4.16	3250	173	314	287	586	60.2	70	69
33	96.5	49.9	31.1	28.9			1200	1100			38	38
(±)-**33**[a]	28[a]				34700[a]				1200			

[a] Data taken from ref 6b in which the binding at the DAT was carried out using WIN 35428 while paroxetine was used for binding at the 5HTT.

the enhancement of binding affinity is less than that observed for the methyl substituent.[18]

The effect of elongating the propyl group to *n*-butyl as in the case of **9** and **38** has no real consequences on activity, as the binding and uptake values obtained are comparable to those found for compounds **8** and **37**.

More exciting activity differences are observed for the 2-phenyl-substituted tropanes. In the case of **33** and **36**, a switch in activity is found. The 2*β*,3α-isomer, the boat conformer, is more active than its chair counterpart, the 2*β*,3*β*-isomer, by about 4-fold. This is the first time that such an observation has been made, as the results reported previously by Carroll concerning such diaryl-substituted tropanes are only for the chair conformers. The chemistry employed by Carroll is limited to the production of only the 2*β*,3*β*- and 2α,3α-isomers,[6b] thus revealing another important advantage of the dipolar cycloaddition strategy developed by us. The improved binding affinity of **36** over **33** may relate to a more suitable location of one or both of the aryl substituents within an appropriate hydrophobic pocket possibly capable of *π*-interactions. As one analyzes the data further, it is evident that the uptake selectivity of these compounds is also considerably improved over that of the tropanes bearing alkyl or ester groups at position 2. The chair compound **33** shows a 38-fold selectivity for the DAT over the 5HTT, while the boat compound **36** exhibits a 65-fold selectivity. We will return to this point shortly, as we believe it is important to address the means by which transporter selectivity should be measured.

On comparing compounds **34** and **22**, which contain the *p*-methyl substituent on the 3-phenyl ring, the binding affinities improve as expected, with both compounds enjoying comparable potency at the DAT. In this case, however, **22** shows the best uptake selectivity of 69-fold for the DAT over the 5HTT. In the case of the *p*-fluoro compound **23**, only the 2*β*,3α-isomer was prepared. As before, the binding potency is less in comparison to the *p*-tolyl analogue **22**. Also, the uptake selectivity is poorer.

In Table 2 we provide a comparison of the selectivity of several of our compounds for the DAT versus the 5HTT. We believe it important to make a point about evaluating selectivity for various transporters based upon a comparison of the K_i values versus use of IC_{50} values. In particular, for the compounds showing the best selectivity, we note that the use of the IC_{50} values based upon binding data leads to suggestions of enormous selectivity differences at the DAT and the 5HTT. In fact, on using the binding data reported by Carroll for racemic 2*β*,3*β*-diphenyltropane (which corresponds

to our compound number **33** and which is accordingly designated as (±)-**33** in Table 2), a selectivity of 1200-fold is suggested.[6b] This is close to the 586-fold selectivity calculated for the most DAT-selective tropane of Table 1, compound **22**, based upon the ratio of IC_{50} values determined from binding. Of course, some differences are to be expected in the two sets of results based upon use of WIN 35428 binding in Carroll's work and the use of mazindol in our experiments, although these differences should not be large. A more appropriate comparison of the selectivity of (±)-**33** would be with our optically pure **33**. However, the selectivity determined from the ratio of uptake values for **33** is only 38.

An examination of the data presented in Table 2 shows a significant difference in the 5HT/DA ratio calculated from IC_{50} values from the binding experiments in comparison to the selectivity ratio determined using the calculated K_i values for binding. This difference arises because of the dependence of IC_{50} on ligand concentration used, which for [^{3}H]paroxetine was about 20 times its K_d of 40 pM, but the [^{3}H]mazindol concentration used was only 0.6 times its K_D of 6 nM. Carroll et al. used [^{3}H]paroxetine at about 5 times its K_d and [^{3}H]WIN 35428 at about 0.04 times its K_d.[6b,19] These differences account for a significant portion of the discrepancy in selectivity ratios reported for (±)-**33** and probably for other compounds tested under nonidentical conditions. The use of K_i values to calculate selectivity ratios avoids problems associated with one of the most common differences between laboratories in assays of drug affinity for transporters. Note that upon using the binding K_i's, the selectivity ratios drop to 30 (from 289) and 60 (from 586) for compounds **36** and **22**, respectively. Moreover, because both [^{3}H]DA and [^{3}H]5HT are commonly used at about 0.1 times their K_d values in uptake assays, the use of either IC_{50} or K_i values gives similar selectivity ratios. For example, as can be seen from Table 2, the selectivity ratios determined from either the IC_{50} values or the K_i uptake values are comparable and close to the selectivity ratios determined from the binding K_i's. Similar observations can be made using compounds **1** and **2**, which exhibit less transporter selectivity. Again, the selectivity ratios determined from the binding and uptake K_i's, or uptake IC_{50}'s, are comparable (1.5 versus 3.5 and 2.1 versus 3.4), while the selectivity ratios determined from binding IC_{50}'s are 10-fold higher. Thus, while the use of K_i values to determine selectivity ratios clearly does not eliminate all the problems associated with comparing pharmacological data between laboratories, it is helpful.

In summary, this work delineates the preparation of a variety of 2-alkyl- and 2-aryl-substituted 3-aryltropanes through use of our oxidopyridinium betaine-based dipolar cycloaddition strategy. Of particular interest is the excellent binding affinity and selectivity for the DAT over the 5HTT of the 2β-phenyl-3α-tolyltropane (**22**) which adopts the boat conformation. This is the first report of the preparation of such diaryltropanes in optically pure form in both the chair and boat series. In light of the excellent in vitro activity displayed by some of these more unusual boat conformers, studies of these compounds in drug discrimination paradigms in animals will be reported in due course.

Experimental Section

Chemical Methods. General. Starting materials were obtained from Aldrich Chemical Co. or from other commercial suppliers. Solvents were purified as follows: diethyl ether was distilled from phosphorus pentoxide; THF was freshly distilled under nitrogen from sodium benzophenone.

IR spectra were recorded on an ATI Mattson Genesis spectrometer. ^{1}H and ^{13}C NMR spectra were obtained with a Varian Unity Inova instrument at 300 and 75.46 MHz, respectively. ^{1}H chemical shifts (δ) are reported in ppm downfield from internal TMS. ^{13}C chemical shifts are referenced to $CDCl_3$ (central peak, δ = 77.0 ppm), benzene-d_6 (central peak, δ = 128.0 ppm), or DMSO-d_6 (central peak, δ = 39.7 ppm). NMR assignments were made with the help of COSY, DEPT, HETCOR, and NOESY experiments. Melting points were determined in Pyrex capillaries with a Thomas-Hoover Unimelt apparatus and are uncorrected. Mass spectra were measured in the EI mode at an ionization potential of 70 eV. TLC was performed on Merck silica gel $60F_{254}$ glass plates; column chromatography was performed using Merck silica gel (60−200 mesh). Abbreviations: DMSO, dimethyl sulfoxide; ether, diethyl ether; THF, tetrahydrofuran; DCM, dichloromethane.

Compounds **1**−**3** were prepared from (−)-cocaine by a procedure analogous that reported in refs 9a and 11.

Methyl (1*R*,5*S*)-3β-phenyltropane-2β-carboxylate (1): ^{1}H NMR ($CDCl_3$) δ 1.54−1.78 (m, 3H), 2.02−2.24 (m, 2H), 2.23 (s, 3H), 2.60 (dt, 1H, J = 2.7 and 12.6 Hz), 2.92 (t, 1H, J = 3.6 Hz), 3.00 (dt, 1H, J = 5.1 and 12.6 Hz), 3.33−3.42 (m, 1H), 3.48 (s, 3H), 3.52−3.60 (m, 1H), 7.10−7.30 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 25.2, 25.9, 33.7, 33.9, 42.0, 51.1, 52.8, 62.3, 65.3, 125.8, 127.3, 127.9, 143.0, 172.1. Anal. ($C_{16}H_{21}N$) C, H, N.

Methyl (1*R*,5*S*)-3β-*p*-tolyltropane-2β-carboxylate (2): ^{1}H NMR ($CDCl_3$) δ 1.54−1.78 (m, 3H), 2.00−2.24 (m, 2H), 2.22 (s, 3H), 2.29 (s, 3H), 2.58 (dt, 1H, J = 2.7 and 12.3 Hz), 2.89 (t, 1H, J = 3.6 Hz), 2.97 (dt, 1H, J = 4.8 and 12.9 Hz), 3.32−3.40 (m, 1H), 3.49 (s, 3H), 3.52−3.60 (m, 1H), 7.07 (d, 2H, J = 7.8 Hz), 7.14 (d, 2H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 21.0, 25.2, 25.9, 33.3, 34.1, 42.0, 51.1, 52.8, 62.3, 65.3, 127.1, 128.6, 135.1, 139.9, 172.2. Anal. ($C_{17}H_{23}N$) C, H, N.

Methyl (1*R*,5*S*)-3β-(*p*-fluorophenyl)tropane-2β-carboxylate (3): ^{1}H NMR ($CDCl_3$) δ 1.56−1.80 (m, 3H), 2.00−2.24 (m, 2H), 2.23 (s, 3H), 2.56 (dt, 1H, J = 2.4 and 12.6 Hz), 2.86 (t, 1H, J = 3.3 Hz), 2.97 (dt, 1H, J = 5.1 and 12.6 Hz), 3.32−3.40 (m, 1H), 3.50 (s, 3H), 3.52−3.60 (m, 1H), 6.95 (t, 2H, J = 8.4 Hz), 7.21 (dd, 2H, J = 5.7 and 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 25.1, 25.8, 33.2, 34.2, 41.9, 51.1, 52.8, 62.2, 65.2, 114.5 (d, J_{C-F} = 20.7 Hz), 128.7 (d, J = 7.7 Hz), 138.5, 161.0 (d, J_{C-F} = 241.2 Hz). Anal. ($C_{16}H_{20}FN$) C, H, N.

(1*R*,5*S*)-2β-Formyl-3β-phenyltropane (4). To a solution of **1** (0.50 g, 1.93 mmol) in THF (20 mL) was added portionwise $LiAlH_4$ (0.15 g, 3.85 mmol). The resulting mixture was stirred at room temperature for 2 h, and a saturated solution of Rochelle salt (30 mL) was added followed by extraction with EtOAc (100 mL). The organic phase was washed with brine (100 mL), dried, and concentrated under reduced pressure to afford 0.35 g (79%) of the alcohol intermediate as a white solid: mp 89−90 °C; ^{1}H NMR ($CDCl_3$) δ 1.43−1.50 (m, 1H), 1.57−1.66 (m, 1H), 1.73 (d, 1H, J = 8.1 Hz), 1.67−1.80 (m, 1H), 2.04−2.24 (m, 2H), 2.27 (s, 3H), 2.51 (dt, 1H, J = 2.7 and 12.9 Hz), 3.05 (dt, 1H, J = 6.0 and 13.2 Hz), 3.28−3.35 (m, 1H), 3.39 (dd, 1H, J = 2.1 and 10.8 Hz), 3.42−3.50 (m, 1H), 3.74 (dd, J = 2.1 and 11.1 Hz), 7.10−7.40 (m, 5H); MS m/z 231 (M^+, 12), 200 (14), 172 (12), 82 (100).

Oxalyl chloride (0.10 mL, 1.08 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL), and the solution was cooled to −78 °C. DMSO (0.15 mL, 2.16 mmol) was added, and after 5 min the above alcohol (0.25 g, 1.08 mmol) was added in CH_2Cl_2 (5 mL). Stirring was continued for 30 min. The reaction mixture was quenched by adding Et_3N (1.4 mL). The resulting solution was warmed to room temperature, diluted with CH_2Cl_2 (30 mL), washed with NH_4Cl (2 × 30 mL), dried, and concentrated under reduced pressure to provide 0.21 g (84%) of **4** as a colorless oil. This oil was used in the next step without further

purification: ^{1}H NMR ($CDCl_3$) δ 1.70 (d, 1H, J = 8.4 Hz), 1.63−1.78 (m, 1H), 1.91 (dt, 1H, J = 3.6 and 12.9), 2.19 (s, 3H), 2.10−2.28 (m, 2H), 2.40−2.56 (m, 2H), 3.18 (dt, 1H, J = 5.4 and 13.2 Hz), 3.38−3.45 (m, 1H), 3.48−3.55 (m, 1H), 7.15−7.40 (m, 5H), 9.65 (d, 1H, J = 3.0 Hz).

(1*R*,5*S*)-2*β*-Formyl-3*β*-*p*-tolyltropane (5). This compound was prepared by the same procedure as that used to prepare **4**. From **2** (0.80 g, 2.93 mmol) there was obtained 0.55 g (90%) of **5** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.70 (d, 1H, J = 8.7 Hz), 1.60−1.78 (m, 1H), 1.89 (dt, 1H, J = 3.9 and 12.9), 2.19 (s, 3H), 2.30 (s, 3H), 2.10−2.33 (m, 2H), 2.39−2.53 (m, 2H), 3.14 (dt, 1H, J = 5.7 and 12.9 Hz), 3.36−3.45 (m, 1H), 3.46−3.55 (m, 1H), 7.10 (br s, 4H), 9.66 (d, 1H, J = 3.3 Hz).

(1*R*,5*S*)-3*β*-(*p*-Fluorophenyl)-2*β*-formyltropane (6). This compound was prepared similarly to **4**. From **3** (0.90 g, 3.25 mmol) there was obtained 0.75 g (93%) of **6** as a colorless oil.

(1*R*,5*S*)-3*β*-Phenyl-2*β*-*n*-propyltropane (7). A solution of *n*-BuLi (2.20 mL, 2.62 mmol, 1.2 M in hexane) was dissolved in THF (10 mL) and cooled to 0 °C. Ethyltriphenylphosphonium bromide (0.97 g, 2.62 mmol) was added slowly under nitrogen. The resulting yellow-orange solution was stirred at 0 °C for 30 min, and then the cooling bath was removed. The crude aldehyde **4** (0.20 g, 0.87 mmol) was added in THF (2 mL), and the reaction mixture was stirred for 15 h at room temperature, diluted with EtOAc (20 mL), and washed with NH_4Cl (2 × 30 mL). The organic phase was extracted with 10% HCl (3 × 10 mL). The combined aqueous phases were washed with EtOAc (30 mL), neutralized with a saturated solution of $NaHCO_3$, and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phases were dried and concentrated under reduced pressure, and the residue was purified by flash chromatography (silica gel, ether/Et_3N, 19:1) to afford 0.15 g (71%) of the intermediate olefin as a mixture of the cis and trans isomers.

To a solution of the intermediate olefins (0.15 g) in MeOH (10 mL) was added a catalytic amount of 5% Pt/C. The mixture was shaken at room temperature for 30 min under a hydrogen atmosphere at 40 psi in a Paar apparatus. The solution was filtered over Celite and evaporated to dryness. The resulting colorless oil was purified by flash chromatography (silica gel, ether/Et_3N, 19:1) to afford 0.13 g (95%) of **7** as a colorless oil: $[\alpha]_D$ −97° (*c* 0.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.71 (t, 3H, J = 7.2 Hz), 0.78−0.95 (m, 1H), 1.20−1.35 (m, 1H), 1.38−1.56 (m, 2H), 1.56−1.75 (m, 3H), 1.97−2.26 (m, 3H), 2.25 (s, 3H), 3.07 (dt, 1H, J = 5.1 and 13.2 Hz), 3.12−3.20 (m, 1H), 3.20−3.29 (m, 1H), 7.10−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.2, 20.8, 24.8, 26.4, 29.3, 33.6, 36.4, 42.1, 46.0, 62.0, 64.7, 125.6, 127.8, 128.0, 143.8; MS *m*/*z* 243 (M^+, 11), 214 (8), 82 (100). Anal. ($C_{17}H_{25}N$) C, H, N.

(1*R*,5*S*)-2*β*-*n*-Propyl-3*β*-*p*-tolyltropane (8). This compound was prepared similarly to **7**. From **5** (0.30 g, 1.24 mmol), 0.19 g (60%) of **8** was obtained as a colorless oil: $[\alpha]^{25}_D$ −82° (*c* 0.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.72 (t, 3H, J = 7.2 Hz), 0.80−0.96 (m, 1H), 1.20−1.36 (m, 1H), 1.39−1.56 (m, 2H), 1.56−1.75 (m, 3H), 1.96−2.26 (m, 3H), 2.25 (s, 3H), 2.31 (s, 3H), 3.04 (dt, 1H, J = 4.8 and 13.2 Hz), 3.12−3.20 (m, 1H), 3.20−3.29 (m, 1H), 7.02 (d, 2H, J = 8.1 Hz), 7.08 (d, 2H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 14.1, 20.7, 20.9, 24.8, 26.4, 29.1, 33.7, 35.9, 42.0, 45.9, 62.1, 64.7, 127.6, 128.7, 135.0, 140.5. Anal. ($C_{18}H_{27}N$) C, H, N.

(1*R*,5*S*)-2*β*-*n*-Butyl-3*β*-*p*-tolyltropane (9). This compound was prepared similarly to **7**. From **5** (0.30 g, 1.24 mmol), 0.20 g (60%) of **9** was obtained as a colorless oil: $[\alpha]_D$ −76° (*c* 1.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.74 (t, 3H, J = 7.2 Hz), 0.70−0.90 (m, 2H), 1.12−1.30 (m, 3H), 1.39−1.68 (m, 5H), 1.96−2.20 (m, 3H), 2.24 (s, 3H), 2.31 (s, 3H), 3.03 (dt, 1H, J = 5.1 and 13.2 Hz), 3.12−3.20 (m, 1H), 3.20−3.28 (m, 1H), 7.03 (d, 2H, J = 8.1 Hz), 7.08 (d, 2H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 14.2, 21.0, 22.7, 24.8, 26.4, 26.7, 30.1, 33.8, 36.0, 42.1, 46.2, 62.1, 64.7, 127.7, 128.7, 135.0, 140.7; MS *m*/*z* 271 (M^+, 6), 242 (2), 214 (4), 96 (40), 83 (100). Anal. ($C_{19}H_{29}N\cdot 1.1H_2O$) C, H, N.

(1*R*,5*S*)-3*β*-(*p*-Fluorophenyl)-2*β*-*n*-propyltropane (10). This compound was prepared similarly to **7**. From **6** (0.75 g, 3.03 mmol), 0.63 g (80%) of **10** was obtained as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.60−0.78 (m, 1H), 0.74 (t, 3H, J = 7.2 Hz), 0.80−0.96 (m, 1H), 1.20−1.36 (m, 1H), 1.39−1.76 (m, 5H), 1.95−2.25 (m, 3H), 2.26 (s, 3H), 3.07 (dt, 1H, J = 4.8 and 13.2 Hz), 3.14−3.22 (m, 1H), 3.22−3.30 (m, 1H), 6.98 (t, 2H, J = 8.7 Hz), 7.10 (dd, 2H, J = 6.0 and 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 14.1, 20.7, 24.7, 26.3, 29.1, 33.7, 35.6, 42.0, 46.0, 62.0, 64.7, 114.7 (d, J_{C-F} = 20.7 Hz), 128.9 (d, J_{C-F} = 7.7 Hz), 139.2 (d, J_{C-F} = 3.2 Hz), 161.0 (d, J_{C-F} = 242.5 Hz). Anal. ($C_{17}H_{24}FN\cdot 0.5H_2O$) C, H, N.

Compounds **12a**−**c** were prepared from 3-hydroxypyridine by a procedure analogous to that described in ref 10.

1-Methyl-4-phenyl-3-pyridiniumolate (12a): mp 154−157 °C; ^{1}H NMR (DMSO-d_6) δ 3.97 (s, 3 H), 7.30−7.52 (m, 5 H), 7.38 (d, 1 H, J = 7.5 Hz), 8.04 (d, 1 H, J = 8.1 Hz), 8.05 (s, 1 H).

1-Methyl-4-*p*-tolyl-3-pyridiniumolate (12b): mp 170−172 °C; ^{1}H NMR ($CDCl_3$) δ 2.38 (s, 3H), 3.94 (s, 3 H), 6.95 (dd, 1H, J = 2.1 and 6.0 Hz), 7.24 (d, 2H, J = 8.1 Hz), 7.36 (d, 1H, J = 6.0 Hz), 7.43 (d, 1H, J = 1.8 Hz), 7.89 (d, 2H, J = 8.4 Hz).

4-(*p*-Fluorophenyl)-11-methyl-3-pyridiniumolate (12c): mp 172−175 °C; ^{1}H NMR ($CDCl_3$) δ 3.97 (s, 3 H), 7.03−7.20 (m, 3 H), 7.34 (d, 1 H, J = 6.3 Hz), 7.54 (s, 1 H), 7.90−8.00 (m, 2H).

(1*S*,5*S*,6*R*,*R*$_s$)-*N*-(Methylphenyl)-6-(*p*-tolylsulfinyl)-8-azabicyclo[3.2.1]oct-3-en-2-one (13). To a solution of 1-methyl-4-phenyl-3-pyridiniumolate (**12a**) (1.85 g, 10 mmol) in dioxane (50 mL) was added (+)-(*R*)-*p*-tolyl vinyl sulfoxide (1.61 g, 10 mmol). The resulting solution was refluxed in dioxane for 20 h and then concentrated under reduced pressure to give a mixture of both *exo* and *endo* cycloadducts (70:30). Silica gel flash column chromatography of the crude mixture led to the separation of the 6-*exo* products (4:1 mixture of diastereomers, 55% overall yield) from the 6-*endo* product (one diastereomer, 22% yield). The major 6-*exo* diastereomer **13** was obtained by crystallization from EtOAc of the 4:1 mixture: $[\alpha]^{25}_D$ −51° (*c* 0.5, acetone); R_f 0.6 (EtOAc); mp 166 °C (EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.64 (dd, $H_{7\alpha}$, J = 8.7 and 14.7 Hz), 2.14 (ddd, $H_{7\beta}$, J = 3.6, 7.5, and 14.7 Hz), 2.42 (s, 3H), 2.63 (s, 3H), 3.34 (dd, H_6, J = 3.3 and 8.7 Hz), 3.74 (d, H_1, J = 7.5 Hz), 4.51 (d, H_5, J = 5.4 Hz), 7.02 (d, H_4, J = 5.1 Hz), 7.3−7.4 (m, 7 H), 7.67 (d, 2H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 21.5, 26.4, 34.7, 60.4, 69.3, 70.1, 125.4, 128.1, 128.3, 128.5, 130.2, 133.5, 138.6, 139.4, 141.3, 142.7, 197.0.

(1*S*,5*S*,6*R*,*R*$_s$)-*N*-Methyl-6-(*p*-tolylsulfinyl)-3-*p*-tolyl-8-azabicyclo[3.2.1]oct-3-en-2-one (14). This compound was prepared similarly to **13**. From a solution of 1-methyl-4-*p*-tolyl-3-pyridiniumolate (**12b**) (1.86 g, 8.37 mmol) and (*R*)-(+)-*p*-tolyl vinyl sulfoxide (1.07 g, 6.45 mmol) in dioxane (50 mL), 1.06 g (45%) of **14** was obtained as a white solid: $[\alpha]^{25}_D$ −47° (*c* 0.8, CH_2Cl_2); R_f 0.6 (EtOAc); mp 188 °C (EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.65 (dd, $H_{7\alpha}$, J = 8.7 and 14.7 Hz), 2.14 (ddd, $H_{7\beta}$, J = 3.6, 7.8, and 14.7 Hz), 2.36 (s, 3H), 2.43 (s, 3H), 2.64 (s, 3H), 3.35 (dd, H_6, J = 3.3 and 8.7 Hz), 3.74 (d, H_1, J = 7.5 Hz), 4.51 (d, H_5, J = 5.1 Hz), 7.01 (d, H_4, J = 5.4 Hz), 7.17 (d, 2H, J = 8.1 Hz), 7.27 (d, 2H, J = 8.1 Hz), 7.35 (d, 2H, J = 7.8 Hz), 7.68 (d, 2H, J = 7.8 Hz); ^{13} C NMR ($CDCl_3$) δ 21.2, 21.4, 26.4, 34.7, 60.4, 69.3, 70.1, 125.4, 128.0, 128.9, 130.2, 130.5, 138.4, 139.4, 1340.6, 142.6, 197.2.

(1*S*,5*S*,6*R*,*R*$_s$)-3-(*p*-Fluorophenyl)-*N*-methyl-6-(*p*-tolylsulfinyl)-8-azabicyclo[3.2.1]oct-3-en-2-one (15). This compound was prepared by the same procedure as used for **13**. From a solution of 1-methyl-4-(*p*-fluorophenyl)-3-pyridiniumolate (**12c**) (2.45 g, 12.04 mmol) and (*R*)-(+)-*p*-tolyl vinyl sulfoxide (2.00 g, 12.04 mmol) in dioxane (25 mL), 1.78 g (40%) of **15** was obtained as a white solid: $[\alpha]^{25}_D$ −77° (*c* 1.25, $CHCl_3$); R_f 0.2 (EtOAc/hexane, 7:3); mp 186 °C (EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.64 (dd, $H_{7\alpha}$, J = 8.7 and 14.7 Hz), 2.14 (ddd, $H_{7\beta}$, J = 3.6, 7.8, and 14.7 Hz), 2.42 (s, 3H), 2.62 (s, 3H), 3.33 (dd, H_6, J = 3.6 and 8.7 Hz), 3.73 (d, H_1, J = 7.5 Hz), 4.51 (d, H_5, J = 5.4 Hz), 7.01 (d, H_4, J = 5.4 Hz), 7.04 (t, 2H, J = 8.7 Hz), 7.30−7.40 (m, 4H), 7.66 (d, 2H, J = 8.1 Hz).

(1*S*,5*R*,7*R*,*R*$_s$)-*N*-Methyl-4*β*-phenyl-6*β*-(*p*-tolylsulfinyl)-3α-*p*-tolyl-8-azabicyclo[3.2.1]octan-2-one (16). To a cooled

(−78 °C) mixture of PhMgBr (0.55 mL, 1.65 mmol, 3.0 M in ether), HMPA (0.57 mL, 3.28 mmol), and $CuBr{\cdot}Me_2S$ (14.0 mg, 0.07 mmol) was added dropwise a solution of **14** (500 mg, 1.37 mmol) and Me_3SiCl (0.35 mL, 2.74 mmol) in dry THF (20 mL). After 1 h, the reaction was quenched with a 20% solution of NH_4OH (20 mL), and the mixture was extracted with EtOAc (30 mL). The organic phase was washed with brine (30 mL), dried, and concentrated under reduced pressure. The crude mixture containing the silyl enol ether intermediate was diluted with MeOH (10 mL), and potassium fluoride was added (160 mg, 2.74 mmol). The resulting solution was stirred at room temperature for 5 min and then concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using EtOAc/hexane as eluent to afford 130 mg (22%) of the title compound as a pale-yellow foam: R_f 0.65 (EtOAc/hexane, 1:1); ^{1}H NMR ($CDCl_3$) δ 2.04 (dd, 1H, J = 8.7 and 11.7 Hz), 2.24 (s, 3H), 2.20−2.34 (m, 1H), 2.41 (s, 3H), 2.56 (s, 3H), 3.10 (t, 1H, J = 8.4 Hz), 3.75 (d, 1H, J = 5.7 Hz), 3.85 (s, 1H), 4.09 (d, 1H, J = 8.4 Hz), 6.66 (d, 2H, J = 8.1 Hz), 6.99 (d, 2H, J = 7.8 Hz), 7.01−7.10 (m, 2H), 7.10−7.20 (m, 3H), 7.30 (d, 2H, J = 8.1 Hz), 7.55 (d, 2H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 21.0, 21.4, 29.0, 39.7, 55.8, 58.2, 68.8, 72.3, 73.1, 76.6, 77.0, 77.2, 77.4, 124.1, 126.8, 127.0, 128.3, 129.0, 129.1, 130.1, 133.1, 136.5, 140.7, 142.0, 143.9, 211.7.

(1*S*,5*R*,7*R*,*R*$_s$)-3α-(*p*-Fluorophenyl)-*N*-methyl-4*β*-phenyl-6*β*-(*p*-tolylsulfinyl)-8-azabicyclo[3.2.1]octan-2-one (17). This compound was prepared in the same manner as **16**. From **14** (1.10 g, 2.98 mmol), 0.96 g (72%) of **17** was obtained as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.03 (dd, 1H, J = 8.7 and 11.7 Hz), 2.25 (dd, 1H, J = 6.9 and 8.1 Hz), 2.31 (d, 1H, J = 9.0 Hz), 2.40 (s, 3H), 2.57 (s, 3H), 3.09 (t, 1H, J = 8.4 Hz), 3.74 (d, 1H, J = 5.7 Hz), 3.85 (s, 1H), 4.14 (d, 1H, J = 9.0 Hz), 6.73 (dd, 2H, J = 5.4 and 8.4 Hz), 6.86 (t, 2H, J = 8.7 Hz), 6.98−7.08 (m, 2H), 7.12−7.20 (m, 3H), 7.30 (d, 2H, J = 8.1 Hz), 7.55 (d, J = 8.1 Hz).

(1*S*,5*R*,7*R*,*R*$_s$)-3α-(*p*-Fluorophenyl)-*N*-methyl-4*β*-*n*-propyl-6*β*-(*p*-tolylsulfinyl)-8-azabicyclo[3.2.1]octan-2-one (18). This compound was prepared in the same manner as **16**. From **15** (1.50 g, 4.00 mmol), 1.34 g (80%) of **18** was obtained as a pale-yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.66 (t, 3H, J = 7.2 Hz), 0.70−0.90 (m, 1H), 1.10−1.36 (m, 3H), 1.40−1.55 (m, 1H), 1.98 (dd, 1H, J = 8.7 and 11.7 Hz), 2.20−2.35 (m, 1H), 2.42 (s, 3H), 2.53 (s, 3H), 2.92 (t, 1H, J = 8.4 Hz), 3.54 (d, 1H, J = 8.4 Hz), 3.61 (d, 1H, J = 6.6 Hz), 3.64 (s, 1H), 6.89 (dd, 2H, J = 5.4 and 8.4 Hz), 7.00 (t, 2H, J = 8.7 Hz), 7.34 (d, 2H, J = 8.1 Hz), 7.56 (d, J = 8.1 Hz).

(1*S*,5*R*,7*R*,*R*$_s$)-2*β*-Phenyl-6*β*-(*p*-tolylsulfinyl)-3α-*p*-tolyltropane (19). To a suspension of $LiAH_4$ (22 mg, 0.59 mmol) in dry THF (6 mL) was added a solution of **16** (130 mg, 0.29 mmol) in dry ether (20 mL). The resulting solution was stirred at room temperature for 1 h and then quenched with a saturated solution of NH_4Cl. The resulting mixture was extracted with ether (2 × 50 mL). The combined organic phases were washed with brine (80 mL), dried, and concentrated under reduced pressure. The crude mixture was purified by flash chromatography on silica gel using 60% EtOAc/hexane as eluent to afford 120 mg (92%) of the alcohol intermediate as a colorless oil: R_f 0.70 (EtOAc/hexane, 4:1); ^{1}H NMR ($CDCl_3$) δ 1.32 (br s, 1H), 1.72−1.88 (m, 1H), 2.20 (s, 3H), 2.41 (s, 3H), 2.51 (s, 3H), 2.40−2.60 (m, 1H), 2.70 (d, 1H, J = 11.4 Hz), 3.31 (8.1 Hz), 3.42 (dd, 1H, J = 4.2 and 10.8 Hz), 3.56 (br s, 1H), 3.69 (t, 1H, J = 6.6 Hz), 4.20−4.30 (m, 1H), 6.90−7.10 (m, 9H), 7.29 (d, 2H, J = 8.1 Hz), 7.55 (d, 2H, J = 8.1 Hz).

To a solution of diisopropylamine (45 μL, 0.32 mmol) in dry THF (4 mL) was added dropwise at 0 °C a solution of *n*-BuLi (134 μL, 0.29 mmol, 2.2 M in hexane). The resulting solution was stirred at 0 °C for 15 min and cooled to −78 °C, and a solution of the alcohol intermediate (110 mg, 0.25 mmol) in THF (5 mL) was added dropwise. After 5 min, phenyl thionochloroformate (68 μL, 0.49 mmol) was added. After 1 h, the reaction was quenched with a saturated solution of NH_4Cl (20 mL), and the mixture was extracted with ether (2 × 20 mL). The collected organic phases were dried and concentrated under reduced pressure, and the crude mixture was purified by flash chromatography on silica gel using EtOAc/hexane as eluent to afford 100 mg of the phenoxy(thiocarbonyl)oxy derivative as a colorless oil: R_f 0.7 (EtOAc/hexane, 1:1); ^{1}H NMR ($CDCl_3$) δ 1.90 (dd, 1H, J = 8.1 and 13.2 Hz), 1.95−2.09 (m, 1H), 2.23 (s, 3H), 2.44 (s, 3H), 2.52 (s, 3H), 2.60 (d, 1H, J = 11.1 Hz), 3.20 (t, 1H, J = 7.5 Hz), 3.5 (br s, 1H), 3.64 (dd, 1H, J = 5.1 and 11.1 Hz), 3.90−4.05 (m, 1H), 5.84 (dd, 1H, J = 4.8 and 8.7 Hz), 6.76 (d, 2H, J = 7.5 Hz), 6.82−7.42 (m, 14H), 7.56 (d, 2H, J = 8.1 Hz).

A solution of the above intermediate (95 mg), Bu_3SnH (133 μL, 0.49 mmol), and AIBN (16 mg, 0.01 mmol) in toluene (6 mL) was purged with argon. The reaction flask was placed in a preheated oil bath at 60 °C and then heated to 90 °C for 1 h. After concentration under reduced pressure, the crude residue was purified by flash chromatography on silica gel using EtOAc/hexane as eluent to afford 53 mg (50%) of **19** as a colorless oil: R_f 0.3 (EtOAc/hexane, 3:7); ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 1H, J = 12.3 Hz), 1.18−1.40 (m, 2H), 1.52 (dd, 1H, J = 8.1 and 13.2 Hz), 2.08−2.20 (m, 1H), 2.22 (s, 3H), 2.40 (s, 3H), 2.51 (s, 3H), 3.00−3.18 (m, 1H), 3.31 (t, 1H, J = 7.8 Hz), 3.40−3.55 (m, 1H), 3.62 (br s, 1H), 6.80 (d, 2H, J = 8.1 Hz), 6.84−6.98 (m, 4H), 7.00−7.18 (m, 3H), 7.29 (d, 2H, J = 8.1 Hz), 7.56 (d, 2H, J = 8.1 Hz).

(1*S*,5*R*,7*R*,*R*$_s$)-3α-(*p*-Fluorophenyl)-2*β*-phenyl-6*β*-(*p*-tolylsulfinyl)tropane (20). This compound was prepared in the same fashion as **19**. From **17** (1.00 g, 2.23 mmol), 0.48 g (50%) of **20** was obtained as a colorless oil: R_f 0.45 (EtOAc/hexane, 1:1); ^{1}H NMR ($CDCl_3$) δ 1.12−1.40 (m, 2H), 1.60 (dd, 1H, J = 8.7 and 12.9 Hz), 2.04−2.20 (m, 1H), 2.30 (d, 1H, J = 10.2 Hz), 2.24−2.45 (m, 1H), 2.39 (s, 3H), 2.50 (s, 3H), 3.06 (ddd, 1H, J = 6.9, 10.5, and 12.6 Hz), 3.28 (t, 1H, J = 8.4 Hz), 3.42−3.55 (m, 1H), 3.63 (br s, 1H), 6.73−6.94 (m, 6H), 7.02−7.16 (m, 3H), 7.27 (d, 2H, J = 8.1 Hz), 7.55 (d, 2H, J = 8.1 Hz).

(1*S*,5*R*,7*R*,*R*$_s$)-3α-(*p*-Fluorophenyl)-2*β*-*n*-propyl-6*β*-(*p*-tolylsulfinyl)tropane (21). This compound was prepared in the same fashion as **19**. From **18** (1.00 g, 2.42 mmol), 0.67 g (70%) of **21** was obtained as a colorless oil: R_f 0.3 (EtOAc/hexane, 1:1); ^{1}H NMR ($CDCl_3$) δ 0.62 (t, 3H, J = 6.3 Hz), 0.68−0.90 (m, 1H), 1.00−1.30 (m, 6H), 1.53 (dd, 1H, J = 8.4 and 12.6 Hz), 2.00−2.15 (m, 1H), 2.20−2.60 (m, 2H), 2.38 (s, 3H), 2.44 (s, 3H), 3.17 (t, 1H, J = 8.1 Hz), 3.28−3.42 (m, 1H), 3.39 (br s, 1H), 6.89 (t, 2H, J = 8.7 Hz), 7.03 (dd, 2H, J = 5.7 and 8.7 Hz), 7.30 (d, 2H, J = 8.1 Hz), 7.56 (d, 2H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 14.1, 19.4, 21.3, 32.0, 36.7, 39.4, 40.5, 41.3, 52.1, 60.5, 65.0, 72.5, 114.9 (d, J_{C-F} = 21.3 Hz), 124.3, 129.3 (d, J_{C-F} = 7.7 Hz), 129.9, 140.6 (d, J_{C-F} = 2.8 Hz), 141.2, 141.4, 161.2 (d, J_{C-F} = 242.5 Hz).

(1*R*,5*S*)-2*β*-Phenyl-3α-*p*-tolyltropane (22). Phosphorus trichloride (61 μL, 0.70 mmol) was added to a solution of **19** (50 mg, 0.12 mmol) in dry DMF (2.00 mL) at 0 °C. After being stirred at 0 °C for 1 h, the reaction was quenched with a saturated solution of $NaHCO_3$ (20 mL) and extracted with ether (2 × 20 mL). The combined organic phases were washed with water (30 mL) and brine (30 mL), dried, and concentrated under reduced pressure to afford 30 mg (61%) of the sulfide intermediate as a colorless oil which was used in the next step without further purification: R_f 0.5 (EtOAc/hexane, 1:9); ^{1}H NMR ($CDCl_3$) δ 1.34 (dt, 1H, J = 1.8 and 14.1 Hz), 2.10−2.35 (m, 2H), 2.23 (s, 3H), 2.42 (ddd, 1H, J = 6.9, 10.2, and 13.8 Hz), 2.62 (s, 3H), 2.65 (d, 1H, J = 10.5 Hz), 2.98−3.12 (m, 1H), 3.36 (br s, 1H), 3.50−3.60 (m, 1H), 3.70 (t, 1H, J = 7.8 Hz), 6.85 (d, 2H, J = 7.8 Hz), 6.94 (d, 2H, J = 7.8 Hz), 7.02−7.26 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 20.9, 39.0, 39.5, 42.1, 43.2, 52.7, 58.8, 60.5, 75.5, 125.9, 127.2, 127.9, 128.0, 128.7, 129.2, 129.6, 134.4, 135.4, 135.7, 140.9, 146.6.

Raney nickel was added to a solution of the sulfide (30 mg, 0.07 mmol) in ethanol (4 mL), and the resulting mixture was refluxed for 1 h. Filtration through a pad of Celite and concentration under reduced pressure afforded a crude mixture that was purified by flash chromatography on silica gel using ether/Et_3N (19:1) as eluent to afford 15 mg (73%) of **22** as a colorless oil: $[\alpha]^{25}_D$ −118° (*c* 0.3, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.32 (t, 1H, J = 12.3 Hz), 1.50−1.75 (m, 2H), 2.10−2.38 (m,

2H), 2.23 (s, 3H), 2.31 (s, 3H), 2.44 (d, 1H, $J = 10.8$ Hz), 2.42−2.56 (m, 1H), 2.97 (dt, 1H, $J = 7.2$ and 11.4 Hz), 3.27 (d, 1H, $J = 6.6$ Hz), 3.36 (t, $J = 6.6$ Hz), 6.84 (d, 2H, $J = 7.8$ Hz), 6.93 (d, 2H, $J = 7.8$ Hz), 7.02−7.20 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.9, 29.7, 29.8, 41.1, 41.3, 43.0, 58.6, 59.5, 68.1, 125.6, 127.3, 127.9, 128.1, 128.6, 135.1, 141.5, 147.6; MS *m*/*z* 291 (M^+, 1), 178 (4), 115 (6), 96 (59), 82 (100). Anal. ($C_{21}H_{25}N\cdot 0.25H_2O$) C, H, N.

(1*R*,5*S*)-3α-(*p*-Fluorophenyl)-2*β*-phenyltropane (23). This compound was prepared in the same fashion as **22**. From **20** (0.20 g, 0.46 mmol), 0.10 g (80%) of **23** was obtained as a colorless oil: $[\alpha]^{25}_D$ −104° (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.26 (t, 1H, $J = 13.2$ Hz), 1.50−1.69 (m, 2H), 2.15−2.39 (m, 2H), 2.31 (s, 3H), 2.38 (d, 1H, $J = 11.1$ Hz), 2.42−2.53 (m, 1H), 2.98 (dt, 1H, $J = 6.9$ and 11.4 Hz), 3.28 (d, 1H, $J = 6.0$ Hz), 3.37 (t, $J = 6.6$ Hz), 6.79 (t, 2H, $J = 8.4$ Hz), 6.88 (t, 2H, $J = 8.4$ Hz), 7.02−7.14 (m, 5H); MS *m*/*z* 295 (M^+, 1). Anal. ($C_{20}H_{22}FN$) C, H, N.

(1*R*,5*S*)-3α-(*p*-Fluorophenyl)-2*β*-*n*-propyltropane (24). This compound was prepared in the same fashion as **22**. From **21** (0.20 g, 0.50 mmol), 91 mg (70%) of **24** was obtained as a colorless oil: $[\alpha]^{25}_D$ −40° (*c* 0.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.77 (t, 3H, $J = 6.9$ Hz), 1.08−1.47 (m, 8H), 2.10−2.20 (m, 2H), 2.28 (s, 3H), 2.31−2.58 (m, 2H), 2.94 (d, 1H, $J = 5.1$ Hz), 3.20 (t, 1H, $J = 8.1$ Hz), 6.93 (t, 2H, $J = 8.4$ Hz), 7.10 (t, 2H, $J = 8.4$ Hz); MS *m*/*z* 261 (M^+, 1). Anal. ($C_{17}H_{24}FN$) C, H, N.

(1*S*,5*S*,6*R*)-2-Acetoxy-*N*-methyl-3-phenyl-6*β*-(*p*-tolylthio)-8-azabicyclo[3.2.1]oct-3-ene (25). Enone **13** (600 mg, 1.71 mmol) was dissolved in a solution of $CeCl_3\cdot 7H_2O$ (700 mg, 1.88 mmol) in MeOH (10 mL); then $NaBH_4$ (71 mg, 1.88 mmol) was added portionwise. This mixture was stirred at room temperature for 15 min, then concentrated under reduced pressure, diluted with water (30 mL), and extracted with EtOAc (3 × 30 mL). The combined organic phases were washed with brine (50 mL), dried, and concentrated under reduced pressure to afford the allylic alcohol intermediate (620 mg).

To a solution of the crude alcohols (620 mg) in pyridine (6 mL) was added Ac_2O (2 mL). The resulting solution was stirred at room temperature for 15 h, then concentrated under reduced pressure, diluted with EtOAc (50 mL), and washed with NH_4Cl (2 × 40 mL). Drying and concentration under reduced pressure afforded a crude mixture of the allylic acetates (660 mg, 97%) that was used in the next step without purification.

Phosphorus trichloride (0.85 mL, 9.7 mmol) was added to a solution of the sulfoxide intermediate (660 mg) in dry DMF (15 mL) at 0 °C. After being stirred at 0 °C for 1 h, the reaction was quenched with a saturated solution of $NaHCO_3$ (60 mL) and extracted with ether (2 × 50 mL). The combined organic phases were washed with water (50 mL) and brine (50 mL), dried, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel using EtOAc/hexane as eluent to afford 570 mg (88%) of the title compound as a 3:1 mixture of two isomers; R_f 0.7 (EtOAc/hexane, 3:7). Major isomer: ^{1}H NMR ($CDCl_3$) δ 1.91 (s, 3H), 2.34 (s, 3H), 2.72 (s, 3H), 6.23 (d, 1H, $J = 5.1$ Hz), 6.33 (d, 1H, $J = 4.8$ Hz). Minor isomer: ^{1}H NMR ($CDCl_3$) δ 1.94 (s, 3H), 2.32 (s, 3H), 2.61 (s, 3H), 5.39 (s, 1H), 6.37 (d, 1H, $J = 5.7$ Hz).

(1*S*,5*S*,6*R*)-2-Acetoxy-*N*-methyl-3-*p*-tolyl-6*β*-(*p*-tolylthio)-8-azabicyclo[3.2.1]oct-3-ene (26). This compound was prepared in the same manner as **25**. From enone **14** (0.60 g, 1.64 mmol) there was obtained 585 mg (90%) of **26** as a 3:1 mixture of two isomers: R_f 0.7 (EtOAc/hexane, 3:7). Major isomer (α-acetoxy derivative): ^{1}H NMR ($CDCl_3$) δ 1.92 (s, 3H), 2.34 (s, 3H), 1.90−2.06 (m, 1H), 2.33 (s, 3H), 2.34 (s, 3H), 2.72 (s, 3H), 2.65−2.80 (m, 1H), 3.43 (d, 1H, $J = 5.1$ Hz), 3.65−3.84 (m, 2H), 6.20 (d, 1H, $J = 5.1$ Hz), 6.32 (d, 1H, $J = 4.5$ Hz), 7.05−7.20 (m, 6H), 7.31 (d, 2H, $J = 7.8$ Hz). Minor isomer (*β*-acetoxy derivative): ^{1}H NMR ($CDCl_3$) δ 1.96 (s, 3H), 2.10−2.25 (m, 1H), 2.33 (s, 3H), 2.34 (s, 3H), 2.60 (s, 3H), 3.50−65 (m, 3H), 5.38 (s, 1H), 6.33 (d, 1H, $J = 5.4$ Hz), 7.05−7.30 (m, 8H).

(1*S*,5*S*,7*R*)-*N*-Methyl-3-phenyl-2*β*-*n*-propyl-6*β*-(*p*-tolylthio)-8-azabicyclo[3.2.1]oct-3-ene (27). To a suspension of CuCN (27 mg, 0.3 mmol) in dry ether (2 mL) at −7 °C was added *n*-PrMgBr (3.0 mL, 1.0 M in ether). After 10 min, a solution of **25** (570 mg, 1.5 mmol) in dry ether (5 mL) was added dropwise. The resulting mixture was stirred at room temperature for 1.5 h and then diluted with ether (20 mL). The organic phase was washed with a saturated solution of NH_4Cl (2 × 20 mL), dried, and concentrated under reduced pressure. The crude mixture was purified by flash chromatography on silica gel using EtOAc/hexane as eluent to afford 420 mg (77%) of the title compound as a colorless oil: $[\alpha]^{25}_D$ +70° (*c* 1.5, acetone); R_f 0.7 (EtOAc/hexane, 3:7); ^{1}H NMR ($CDCl_3$) δ 0.78 (t, 3H, $J = 7.2$ Hz), 1.1−1.6 (m, 4H), 2.2−2.3 (m, 1H), 2.34 (s, 3H), 2.4−2.5 (m, 2H), 2.63 (s, 3H), 3.37 (br s, 1H), 3.51 (t, 1H, $J = 7.8$ Hz), 3.60 (t, 1H, $J = 5.1$ Hz), 6.10 (d, 1H, $J = 5.4$ Hz), 7.13 (d, 2H, $J = 8.1$ Hz), 7.2−7.3 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 13.9, 21.0, 21.1, 34.3, 40.0, 42.1, 47.1, 49.7, 62.3, 70.5, 126.0, 127.1, 128.3, 129.6, 129.7, 130.0, 134.0, 136.2, 138.4, 140.2.

(1*S*,5*S*,7*R*)-*N*-Methyl-2,3-diphenyl-6*β*-(*p*-tolylthio)-8-azabicyclo[3.2.1]oct-3-ene (28). This compound was prepared in the same fashion as **27**. From the allylic acetate **25** (0.50 g, 1.45 mmol) there was obtained 70 mg (12%) of **28** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.3−2.4 (m, 1H), 2.37 (s, 3H), 2.43 (s, 3H), 2.52 (dd, 1H, $J = 8.1$ and 12.3 Hz), 3.40 (s, 1H), 3.67 (t, 1H, $J = 7.5$ Hz), 3.75 (br s, 1H), 6.51 (d, 1H, $J = 5.7$ Hz), 7.0−7.5 (m, 14H).

(1*S*,5*S*,7*R*)-*N*-Methyl-2*β*-*n*-propyl-3-*p*-tolyl-6*β*-(*p*-tolylthio)-8-azabicyclo[3.2.1]oct-3-ene (29). This compound was prepared in the same fashion as **27**. From the allylic acetate **26** (165 mg, 0.42 mmol), 145 mg (91%) of **29** was obtained as a colorless oil: $[\alpha]_D$ +110° (*c* 2.6, CH_2Cl_2); R_f 0.5 (EtOAc/hexane, 1:4); ^{1}H NMR ($CDCl_3$) δ 0.81 (t, 3H, $J = 7.2$ Hz), 1.2−1.6 (m, 4H), 2.2−2.3 (m, 1H), 2.35 (s, 3H), 2.4−2.5 (m, 2H), 2.65 (s, 3H), 3.39 (br s, 1H), 3.53 (t, 1H, $J = 7.8$ Hz), 3.60 (t, 1H, $J = 5.4$ Hz), 6.08 (d, 1H, $J = 6.0$ Hz), 7.10−7.24 (m, 6H), 7.32 (d, 2H, $J = 8.1$ Hz); ^{13}C NMR ($CDCl_3$) δ 14.0, 21.0, 21.1, 34.3, 40.0, 42.1, 47.1, 49.7, 62.3, 70.6, 125.8, 128.8, 129.0, 129.7, 129.9, 134.1, 136.1, 136.9, 137.3, 138.2.

(1*S*,5*S*,7*R*)-2*β*-*n*-Butyl-*N*-methyl-3-*p*-tolyl-6*β*-(*p*-tolylthio)-8-azabicyclo[3.2.1]oct-3-ene (30). This compound was prepared in the same fashion as **27**. From the allylic acetate **26** (200 mg, 0.51 mmol) there was obtained 140 mg (70%) of **30** as a colorless oil: $[\alpha]_D$ +79° (*c* 1.0, EtOH); ^{1}H NMR ($CDCl_3$) δ 0.80 (t, 3H, $J = 6.6$ Hz), 1.00−1.40 (m, 5H), 1.40−1.60 (m, 1H), 2.20−2.50 (m, 3H), 2.32 (s, 3H), 2.33 (s, 3H), 2.63 (s, 3H), 3.35 (s, 1H), 3.50 (t, 1H, $J = 7.2$ Hz), 3.58 (t, 1H, $J = 5.1$ Hz), 6.06 (d, 1H, $J = 5.4$ Hz), 7.00−7.20 (m, 6H), 7.31 (d, 2H, $J = 8.1$ Hz); ^{13}C NMR ($CDCl_3$) δ 14.0, 20.9, 21.0, 22.5, 30.3, 31.7, 39.9, 42.1, 47.3, 49.8, 62.3, 70.4, 125.8, 128.7, 129.0, 129.7, 130.2, 134.0, 136.2, 136.8, 137.2, 138.2.

(1*S*,5*S*,7*R*)-*N*-Methyl-2*β*-phenyl-3-*p*-tolyl-6*β*-(*p*-tolylthio)-8-azabicyclo[3.2.1]oct-3-ene (31). This compound was prepared in the same fashion as **27**. From the allylic acetate **26** (0.34 g, 0.85 mmol), 0.10 g (27%) of **31** was obtained as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.20−2.35 (m, 1H), 2.22 (s, 3H), 2.37 (s, 3H), 2.42 (s, 3H), 2,50 (dd, 1H, $J = 8.4$ and 12.6 Hz), 3.39 (s, 1H), 3.67 (t, 1H, $J = 8.4$ Hz), 3.66−3.78 (m, 2H), 6.48 (d, 1H, $J = 5.4$ Hz), 6.96 (d, 2H, $J = 8.1$ Hz), 7.00−7.30 (m, 9H), 7.36 (d, 2H, $J = 8.1$ Hz); ^{13}C NMR ($CDCl_3$) δ 21.0, 21.1, 40.1, 41.7, 49.8, 52.9, 62.2, 75.6, 115.3, 120.2, 125.4, 125.8, 127.9, 128.1, 128.9, 129.8, 130.2, 130.5, 133.9, 134.0, 136.4, 136.7, 142.7.

(1*R*,5*S*)-3-Phenyl-2*β*-*n*-propyltropane (7 and 35). Raney Ni was added to a solution of **27** (70 mg, 0.19 mmol) in ethanol (4 mL), and the resulting mixture was refluxed for 2 h. Filtration through a pad of Celite and concentration under reduced pressure afforded a mixture containing the two isomers **7** and **35** (ratio 3:1 by GC−MS analysis). These isomers were separated by preparative thin-layer chromatography on silica gel using EtOAc/hexane/Et_3N (8:90:2) as eluent to afford the title compounds as colorless oils. 3*β*-Isomer **7** (6.0 mg, 13%): $[\alpha]^{25}_D$ −95° (*c* 0.25, CH_2Cl_2). 3α-Isomer **35** (10 mg, 43%): $[\alpha]^{25}_D$ −50° (*c* 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.77 (t, 3H, $J = 7.5$ Hz), 1.0−1.6 (m, 8H), 2.0−2.3 (m, 2H), 2.23 (s,

3H), 2.32−2.60 (m, 2H), 2.95 (d, 1H, J = 6.0 Hz), 3.21 (br t, 1H, J = 7.5 Hz), 7.1−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.2, 19.0, 29.0, 29.5, 37.0, 40.6, 41.6, 41.8, 50.6, 59.5, 65.0, 125.7, 128.1, 128.2, 146.2; MS m/z 243 (M^+, 5), 214 (3), 96 (42), 83 (100). Anal. ($C_{17}H_{25}N\cdot 0.1H_2O$) C, H, N.

(1*R*,5*S*)-2*β*,3-Diphenyltropane (33 and 36). This compound was prepared in the same fashion as **7** and **35**. From **28** (0.13 g, 0.33 mmol), 0.03 g (33%) of the 3*β*-isomer **33** and 0.02 g (22%) of the 3α-isomer **36** were obtained as colorless oils. Compound **33**: $[\alpha]^{25}_D$ −76° (c 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.64 (dt, 1H, J = 4.2 and 13.5 Hz), 1.72−1.86 (m, 2H), 2.06−2.30 (m, 2H), 2.25 (s, 3H), 2.39 (dt, 1H, J = 2.4 and 12.9 Hz), 2.84−2.92 (m, 1H), 3.26−3.42 (m, 3H), 6.85 (d, 2H, J = 8.1 Hz), 6.95−7.12 (m, 5H), 7.35−7.45 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 25.1, 27.3, 35.2, 37.5, 42.0, 53.3, 61.9, 67.7, 125.4, 125.5, 127.0, 127.5, 128.0, 130.6, 142.8, 143.2. Anal. ($C_{20}H_{23}N\cdot 0.25H_2O$) C, H, N. Compound **36**: $[\alpha]^{25}_D$ −55° (c 0.2, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.38 (t, 1H, J = 13.2, 1.54−1.80 (m, 2H), 2.16−2.40 (m, 2H), 2.35 (s, 3H), 2.44−2.60 (m, 2H), 2.96−3.10 (m, 1H), 3.32 (d, 1H, J = 6.3 Hz), 3.36−3.46 (m, 1H), 6.98 (d, 2H, J = 8.1 Hz), 7.00−7.20 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 29.7, 29.8, 40.9, 41.3, 43.6, 58.7, 59.5, 68.1, 125.7, 125.8, 127.3, 127.9, 128.0, 128.3, 144.6, 147.5. Anal. ($C_{20}H_{23}N\cdot 0.5H_2O$) C, H, N.

(1*S*,5*S*,7*R*)-*N*-Methyl-2*β*-phenyl-3*β*-*p*-tolyltropane (34). This compound was prepared in the same fashion as **7**. From **31** (0.09 g, 0.21 mmol) there was obtained 0.03 g (50%) of **34** as a colorless oil: $[\alpha]^{25}_D$ −160° (c 0.2, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.62 (dt, 1H, J = 4.2 and 13.5 Hz), 1.72−1.86 (m, 2H), 2.04−2.30 (m, 2H), 2.17 (s, 3H), 2.23 (s, 3H), 2.36 (dt, 1H, J = 2.4 and 12.9 Hz), 2.84−2.92 (m, 1H), 3.24−3.42 (m, 3H), 6.74 (d, 2H, J = 8.1 Hz), 6.85 (d, 2H, J = 8.1 Hz), 7.00−7.15 (m, 3H), 7.37−7.45 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 20.9, 25.1, 27.3, 35.5, 37.0, 42.0, 53.2, 62.0, 67.8, 125.4, 127.0, 127.8, 128.2, 130.7, 134.8, 140.1, 143.0; MS m/z 291 (M^+, 8), 178 (4), 96 (60), 82 (100). Anal. ($C_{21}H_{25}N$) C, H, N.

(1*S*,5*S*,7*R*)-*N*-Methyl-2*β*-*n*-propyl-3α-*p*-tolyltropane (37). This compound was prepared in the same fashion as **7**. From **29** (0.12 g, 0.32 mmol) there was obtained 45 mg (55%) of **37** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.78 (t, 3H, J = 7.2 Hz), 1.08−1.56 (m, 8H), 2.04−2.24 (m, 2H), 2.23 (s, 3H), 2.30 (s, 3H), 2.28−2.58 (m, 2H), 2.94 (d, 1H, J = 6.3 Hz), 3.19 (t, 1H, J = 7.8 Hz), 7.06 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 14.2, 19.9, 21.0, 29.0, 29.5, 37.0, 40.1, 41.6, 41.9, 50.6, 59.6, 64.9, 128.1, 128.8, 135.1, 143.1. Anal. ($C_{18}H_{27}N$) C, H, N.

(1*S*,5*S*,7*R*)-2*β*-*n*-Butyl-*N*-methyl-3-*p*-tolyltropane (38). This compound was prepared in the same fashion as **7**. From **30** (0.20 g, 0.51 mmol) there was obtained 45 mg (55%) of **37** as a colorless oil: $[\alpha]^{25}_D$ −42° (c 0.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.80 (t, 3H, J = 6.6 Hz), 1.08−1.56 (m, 10H), 2.04−2.24 (m, 2H), 2.23 (s, 3H), 2.30 (s, 3H), 2.28−2.58 (m, 2H), 2.94 (d, 1H, J = 6.0 Hz), 3.19 (t, 1H, J = 7.8 Hz), 7.06 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 14.1, 20.9, 22.8, 28.9, 29.0, 29.5, 34.3, 40.0, 41.6, 41.8, 50.8, 59.5, 64.9, 128.1, 128.8, 135.1, 143.1. Anal. ($C_{19}H_{29}N\cdot 1.15H_2O$) C, H, N.

Uptake and Binding Methods. The uptake of [^{3}H]-dopamine and [^{3}H]5HT by striatal synaptosomes was measured essentially as previously described for [^{3}H]DA.[14] Similarly, the binding of [^{3}H]mazindol and [^{3}H]paroxetine to dopamine and serotonin transporters in striatal membranes was measured essentially as previously described for [^{3}H]-mazindol.[3,15] In these studies the approximate concentrations of radioligands used (along with the K_d value used in the Cheng−Prusoff caculation of K_i) are as follows: [^{3}H]DA, 5 nM (57 nM); [^{3}H]5HT, 5 nM (52 nM); [^{3}H]mazindol, 4 nM (6 nM); [^{3}H]paroxetine, 0.8 nM (0.04 nM). In contrast to previous studies, the current experiments were carried out using an identical buffer for all assays.[16] This Krebs-Ringer-HEPES buffer was composed of 125 mM NaCl, 4.8 mM KCl, 1.2 mM $MgSO_4$, and 25 mM HEPES (pH 7.4). Cocaine and other compounds were added to the incubation mixture 30 min prior to the initiation of [^{3}H]DA or [^{3}H]5HT uptake to ensure equilibration. Uptake was stopped by rapid filtration after 5 min as previosuly described.[14] Binding assays were initiated by adding striatal tissue homogenate to tubes containing drugs and radioligand, and binding was stopped by filtration after a 1-h incubation at 4 °C with [^{3}H]mazindol and at room temperature with [^{3}H]paroxetine. Nonspecific uptake or binding was defined in all assays by 100 μM cocaine. This concentration of cocaine gave estimates of nonspecific binding and uptake identical to more selective transport inhibitors such as 10 μM fluoxetine and 10 μM nomifensine. Other details of the assays are as referenced above.

Acknowledgment. We are indebted to the National Institutes of Health, National Institute on Drug Abuse (DA10458) for their support of these studies.

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JM9802564