Synthesis of 2β-Acyl-3β-(substituted naphthyl)-8-azabicyclo[3.2.1]octanes and Their Binding Affinities at Dopamine and Serotonin Transport Sites

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A series of 3β-naphthyltropane derivatives were synthesized and found to show high affinity at both the dopamine and serotonin transporter sites, leading to some of the most potent inhibitors known based on the tropane structure. Comparative molecular field analysis (CoMFA) models were developed for both dopamine and serotonin transporter binding data. These models provide insights into those factors that influence binding at the two transporters.

Introduction

Due to the serious consequences of cocaine abuse, extensive studies have been made into compounds that can be used to probe the pharmacological actions of cocaine and may ultimately lead to medications for the treatment of cocaine addiction. As cocaine interacts strongly at both the dopamine and serotonin transport sites, the evaluation of novel monoamine uptake inhibitors has generated great interest.[1−3] The most widely studied class of compounds has been the 2β-substituted 3β-aryltropanes.[4−41] Many of these derivatives are significantly more potent than cocaine at binding to the monoamine transporters. In recent years it has become clear that a wide range of functionalities can be tolerated at the 2β-position. By appropriate functionalization, particularly by introduction of bulky ester derivatives at the 2-position, compounds that have selective binding affinity for the dopamine transporter (DAT) can be prepared.[12,13] Functionality on the 3β-aryl group also has a major influence on binding affinity to the monoamine transporters. Small groups at the 3′- or 4′-position of the aryl ring increased binding affinity at the DAT while binding affinity was lowered when these groups became too large, resulting in compounds that bind selectively to the serotonin transporter (SERT).[6,7,41] The role of the nitrogen group has also been questioned since potent oxa and carba analogues have been prepared.[27,29−31] Over the years, several comparative molecular field analysis (CoMFA) studies of the binding affinities of the 3β-aryltropane-2β-carboxylates have been reported that quantify the trends in binding to the transporters.[10,15,42−45]

Even though a large number of tropanes were evaluated in the early studies, the range of structural variation was limited because all the derivatives were prepared by a two-step sequence beginning with cocaine: elimination of benzoic acid to form anhydroecgonine methyl ester followed by a conjugate addition of a Grignard reagent to the α,β-unsaturated ester.[46] Consequently, there has been considerable recent interest in developing new methods for the construction of tropanes that would broaden the range of derivatives that would be available.[24,29,47−51]

We devised a general route for the synthesis of tropanes based on the reaction of vinylcarbenoids with pyrroles as illustrated in Scheme 1.[52,53] A design feature of this approach was the use of a ketone functionality at the C2-position instead of an ester. This modification improves the conjugate addition step in the synthetic sequence and generates compounds that would be of greater metabolic stability than the traditional 3β-aryltropane-2β-carboxylates since they lack an ester functionality. These studies have led to the synthesis of a variety of tropanes that display interesting biological activity.[38−41] One of these analogues is the tolyl derivative **6**, PTT,[54−61] which has undergone extensive evaluation as a probe to study the neurobiology of cocaine reinforcement and as a potential pharmacotherapeutic agent for cocaine addiction. Another notable analogue has been the 4-isopropylphenyl derivative **7**,[62−64] which was the first potent tropane with high selectivity for the SERT. A third compound of note is the naphthyl derivative **8**,[54,56] which is the most potent tropane to date (IC_{50} = 0.12 nM at DAT) and displays extremely long duration of action in vivo. As there is considerable interest in the therapeutic potential of long-acting dopamine reuptake inhibitors for the treatment of cocaine addiction,[65−67] this article describes the synthesis and biological evaluation of a series of 2β-propanoyl-3β-(substituted naphthyl)tropanes. Since these studies led to the evaluation of a different array of 3-aryl derivatives than had been previously possible, a CoMFA was also undertaken on compounds from both this study and from previous work, examining binding at the DAT. Further, we have developed a contrasting CoMFA for the structural requirements for the binding at the SERT.

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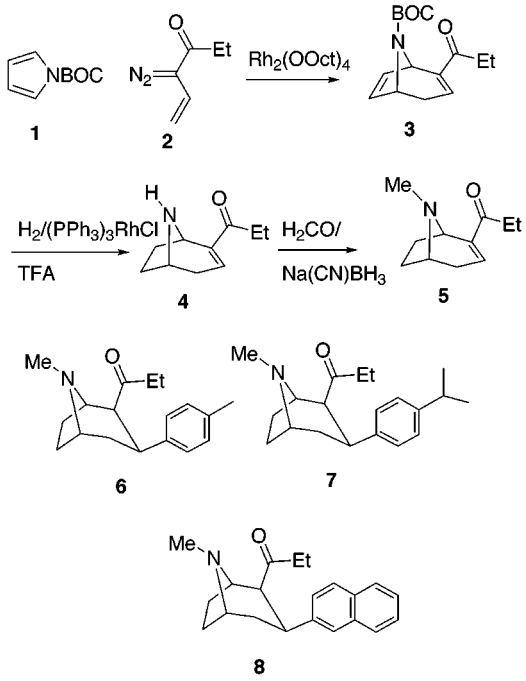
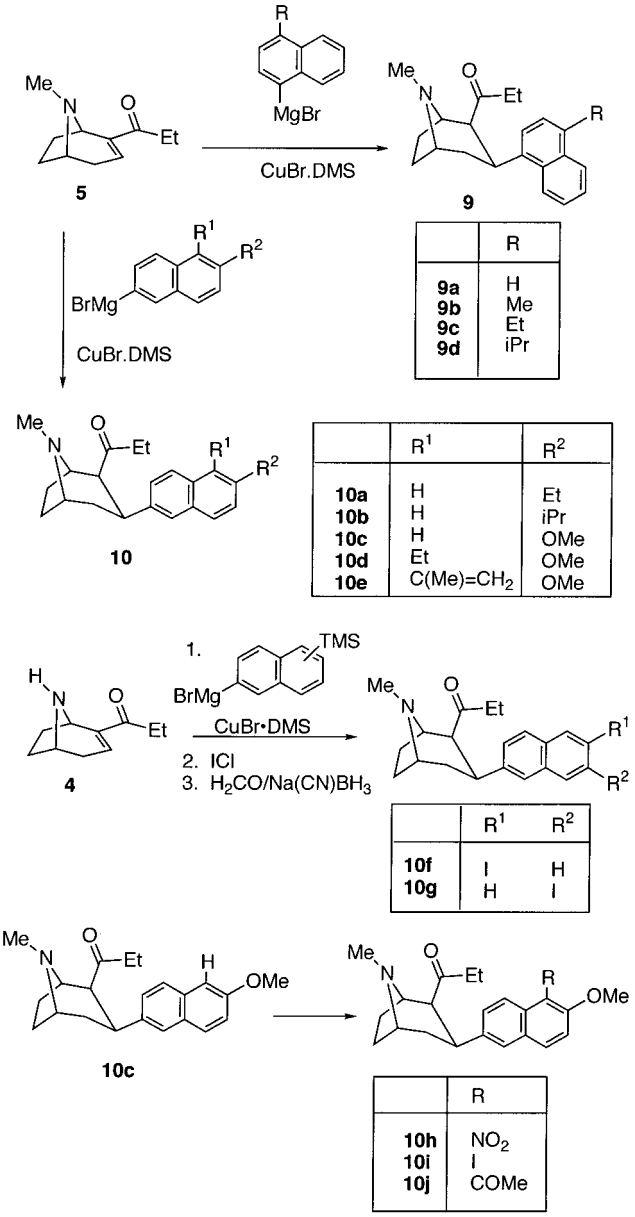
Scheme 1



Scheme 2



	R
9a	H
9b	Me
9c	Et
9d	iPr

	R^1	R^2
10a	H	Et
10b	H	iPr
10c	H	OMe
10d	Et	OMe
10e	$C(Me)=CH_2$	OMe

	R^1	R^2
10f	I	H
10g	H	I

	R
10h	NO_2
10i	I
10j	COMe

Chemistry

A series of tropane derivatives **9** and **10** were derived from either **4** or **5** which is readily prepared from N-BOC-pyrrole (**1**) in a reaction sequence that begins with a tandem cyclopropanation/Cope rearrangement between a rhodium-stabilized vinylcarbenoid intermediate and N-BOC-pyrrole as illustrated in Scheme 1.[52,53] The further manipulation of **4** and **5** is illustrated in Scheme 2. Copper-catalyzed addition to **5** of a series of 1-naphthyl Grignard reagents followed by quenching the reaction with dry HCl at −78 °C resulted in the predominant formation of 2β,3β-isomers **9**. A series of 2-naphthyl-substituted derivatives **10a**−**e** was prepared by analogous reactions on **4** with 2-naphthyl Grignard reagents. The iodonaphthyl derivatives **10f**,**g** were also prepared by copper-catalyzed 1,4-additions, but the N-demethylated derivative **4** was used as the starting material. Other functionalized 2-naphthyl-substituted tropanes **10h**−**j** were prepared by electrophilic substitution on the 6-methoxynaphthyl derivative **10c**.

Pharmacology

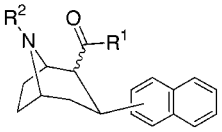
Table 1 demonstrates the binding affinities of 14 new 3β-naphthyl-substituted tropanes to DAT, SERT, and norepinephrine transporters (NET). The focus of the study was to combine the high potency of the naphthyl derivative **8** with the SERT binding selectivity observed on introduction of a bulky substituent such as isopropyl, as was seen in the case of the 4-isopropylphenyl derivative **7**. The first series of derivatives was the 4-substituted 1-naphthyl derivatives **9a**−**d**. On increasing the size of the 4-substituent from hydrogen (**9a**) to methyl (**9b**), a 5-fold decrease in DAT binding potency and a 2-fold increase in SERT binding potency were observed; however, with a maximum SERT/DAT potency ratio of 3, none of these compounds were significantly selective at either biogenic amine transporter. On increasing the size of the alkyl group, further improved selectivity toward SERT over NET binding is observed, but the selectivity toward DAT is not further enhanced due to a gradual erosion of binding affinity toward both the DAT and the SERT.

The next series of compounds was made up of 6-substituted 2-naphthyl derivatives **10a**−**c**. The 2-naphthyl functionality leads to the most potent tropanes known to date. Introduction of a 6-ethyl, 6-isopropyl, or 6-methoxy group results in very little change in potency at the DAT but changes selectivity such that the 6-methoxy derivative **10c** shows the highest selectivity for the DAT of the compounds examined. It was considered that additional bulky substituents might be needed to enhance selectivity toward the SERT, and so a series of 5,6-disubstituted 2-naphthyl derivatives **10d**,**e**,**h**−**j** were evaluated. All of these derivatives were less potent at the DAT than the 6-substituted derivatives **10a**−**c**, and two derivatives in particular displayed some binding selectivity for the SERT. The 6-methoxy, 5-nitro derivative **10h** had a K_i value of 15 nM for binding at the 5-SERT, a SERT/DAT binding potency ratio of 10, and a SERT/NET binding potency ratio of

Table 1. IC_{50} and K_i Values of Tropane Analogues in Displacing [^{125}I]RTI-55 Binding in Rat Striatal Membranes and [^{3}H]Paroxetine Binding in Rat Frontal Cortex Membranes

	IC_{50} (nM)	K_i (nM)		potency ratio	
compd	dopamine	SERT	NET	SERT/DAT	SERT/NET
6	8.2 ± 1.6[38]	131 ± 10[38]	65 ± 9.2[38]	0.06	0.5
7	436 ± 41[38]	36 ± 4[38]	>10000[38]	12	>250
8	0.12 ± 0.02[38]	0.39 ± 0.07[38]	2.9 ± 0.5[38]	0.3	7
9a	5.3 ± 1.3[38]	21 ± 2.9[38]	49 ± 10[38]	0.3	2
9b	25.1 ± 0.5	8.99 ± 1.70	163 ± 36	3	18
9c	75.1 ± 11.9	175 ± 25	4769 ± 688	0.7	27
9d	225 ± 36	136 ± 64	>10000	2	>73.5
10a	0.15 ± 0.04	0.38 ± 0.19	27.7 ± 9.6	0.4	74
10b	0.39 ± 0.04	1.97 ± 0.33	ND	0.2	ND
10c	0.13 ± 0.04	2.24 ± 0.34	ND	0.05	ND
10d	30.8 ± 6.6	7.55 ± 1.57	3362 ± 148	4.1	445
10e	45.0 ± 3.7	88.0 ± 13.3	2334 ± 378	0.5	26.5
10f	0.35 ± 0.07	0.37 ± 0.02	ND	1.0	ND
10g	0.45 ± 0.05	0.47 ± 0.02	ND	0.5	ND
10h	148 ± 50	15 ± 1.6	ND	10	ND
10i	1.31 ± 0.33	2.27 ± 0.31	781 ± 181	0.6	344
10j	12.6 ± 3.8	15.8 ± 1.65	498 ± 24	0.8	32
Compounds from Previous Studies[38,40] Used in the CoMFA					
11a	10 ± 2.2	26 ± 5.1	165 ± 40	0.4	6.3
11b	97 ± 21	217 ± 55	ND	0.45	ND
11c	2.51 ± 0.82	16.4 ± 2.0	68.0 ± 10.8	0.15	4.1
11d	1.27 ± 0.15	1.06 ± 0.36	4.9 ± 1.2	1.2	4.6
11e	0.25 ± 0.08	2.08 ± 0.80	37.6 ± 10.5	0.12	18.1
11f	0.03 ± 0.01	0.23 ± 0.07	2.05 ± 0.9	0.13	8.9

Table 2. Compounds from Previous Studies Included in the Current CoMFA



compd	C2 orientation	R^1	naphthyl attachment	R^2
11a	β	CH_3	1-naphthyl	CH_3
11b	α	CH_3	1-naphthyl	CH_3
11c	α	CH_2CH_3	2-naphthyl	CH_3
11d	β	CH_3	2-naphthyl	CH_3
11e	β	$CH(CH_3)_2$	2-naphthyl	CH_3
11f	β	CH_2CH_3	2-naphthyl	H

60, while the 5-ethyl, 6-methoxy derivative **10d** had a K_i value of 7.55 nM for binding at the SERT, a SERT/DAT binding potency ratio of 4, and a SERT/NET binding potency ratio of 445.

Molecular Modeling and CoMFA

In efforts to design new compounds with even greater selectivity, three-dimensional structure−activity relationship (QSAR) studies have been carried out using all the naphthyltropanes that were tested. CoMFA studies were conducted for binding to both the DAT and SERT. In addition to the 3β-naphthyl derivatives from this study, seven additional compounds (**8**, **11a**−**f**) from previous work were included in the analysis data set. Data for compounds **11a**−**f** are summarized in Table 1, while structural information is provided in Table 2. The complete details for the optimization of the CoMFA studies are given in the Supporting Information.

Comparing the models for DAT and SERT binding, we see differences in the areas predicted to be of importance for binding affinity. Figure 1a, which illustrates the steric components of DAT binding, shows more bulk tolerance in the C2-substituent region compared to the corresponding area in Figure 1c for SERT binding. This is consistent with the trend in affinity for compounds **8** and **11e**, where changing from the propionyl to the isobutyroyl substituent at C2 reduces the binding affinity at the DAT 2-fold but reduces the SERT affinity >5-fold. This is also consistent with earlier studies showing that introduction of a bulky ester group at the C2-position leads to compounds selective for the DAT.[12,13,42] Further, while both models show areas that will accept considerable steric bulk beyond the C5- and C7-positions of the naphthyl ring, the DAT model (Figure 1a) shows two substantial areas, one on each side of the C5-naphthyl region, where introduction of steric bulk is expected to lower binding affinity. For the SERT model (Figure 1c), only a single steric exclusion area is found near the C5-position of the naphthyl ring. This difference may imply a narrow pocket or cleft for the DAT binding region which can accommodate only a relatively planar aromatic substituent. The existence of such a narrow cleft for the DAT is consistent with our findings that CoMFAs are statistically sensitive to which conformations were used for the DAT analyses, in contrast to little sensitivity to which conformations were used for the SERT analyses (see Supporting Information). Such a narrow binding cleft would also be consistent with the conclusions of Lieske.[43] Compounds containing the 1-naphthyl moiety at the tropane β-C3-position show a much lower ability to inhibit ligand binding to both the DAT and SERT (8−50-fold decrease) compared to the corresponding β-C3-2-naphthyl derivatives. It may be of significance that the 1-naphthyl group occupies a very different region of space when compared to the 2-naphthyl group, with the distal ring of the 2-naphthyl group extending both further and in a different direction from the tropane ring system than is seen for the 1-naphthyl derivatives. This difference for the 1-naphthyl group may result in interactions that missalign the remainder of the molecule, resulting in a lowered affinity, or may simply fall in a portion of the acceptor region of the transporter where the interactions are weaker, thus leading to lowered affinity.

The limit to the steric inclusion region shown in Figure 1a (DAT) compared to Figure 1c (SERT) is also consistent with the change in affinity seen for compound **10c** going to the 5,6-disubstituted compounds **10d**−**h**. In general, introduction of a substituent at the 5-position of the 2-naphthyl ring reduces affinity at the DAT by at least a 10-fold greater margin than the corresponding reduction for the SERT. The change in selectivity is not as great as that observed with 3β-phenyltropane derivatives.[6,7,41]

For these same models, electrostatic interactions (which appear to play a lesser role in binding for both transporters) also differ. The DAT model (Figure 1b) shows three regions that should accommodate negative charge near the C3-naphthyl substituents: one near the C5(ar)−C6(ar) portion of the naphthyl ring and out-of-plane, one near the C7(ar)−C8(ar) portion of the aromatic ring and also out-of-plane but on the opposite side, and a third region near the C8(ar) naphthyl position. In contrast, the 5-SERT model (Figure 1d) shows only a single, large region that is predicted to favor negative charge near the C6(ar)−C8(ar) portion of the naphthyl ring and out-of-plane. A small region predicted to favor

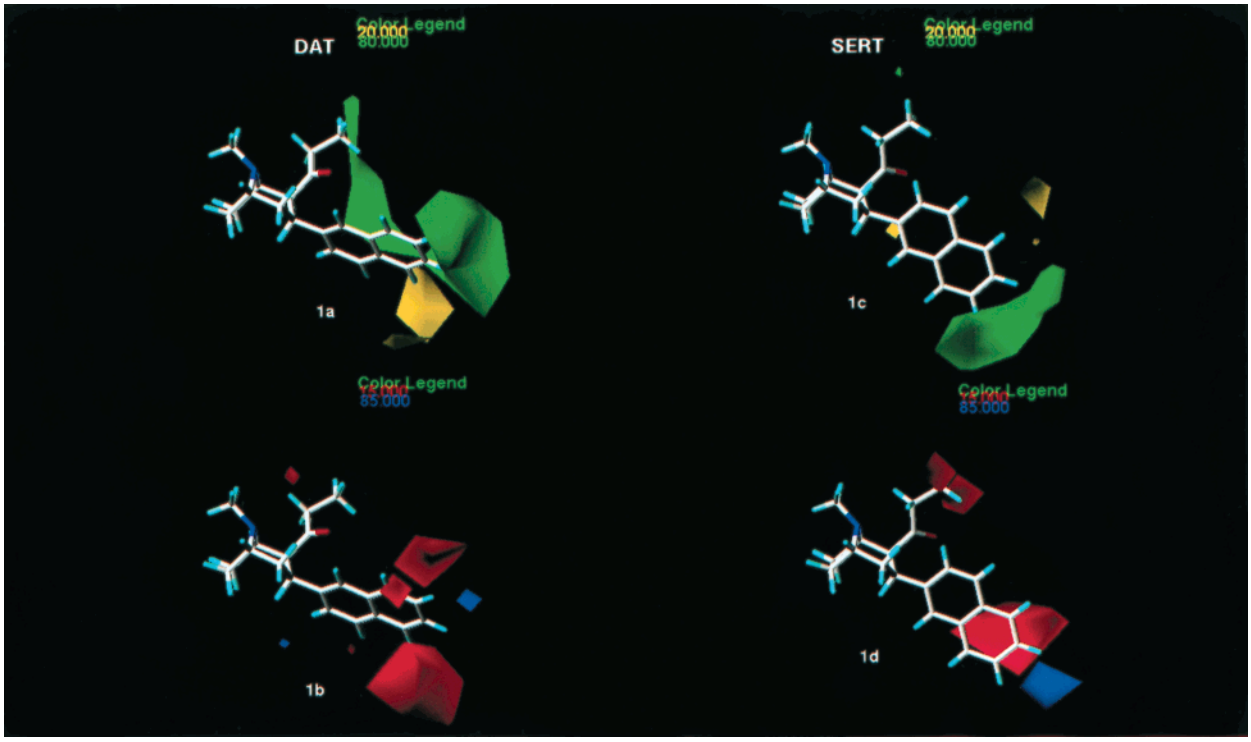


Figure 1. (a,c) Steric components for CoMFA models (groups 3 and 1) derived from binding data for the DAT and SERT, respectively. Regions color-coded green represent areas where greater steric bulk should lead to higher affinity, while regions color-coded yellow represent areas where an increase in steric bulk is predicted to lower relative affinity. (b,d) Electrostatic components for binding to the DAT and SERT, respectively. Regions color-coded blue represent areas where greater positive charge near this region should lead to higher affinity, while regions color-coded red represent areas where increases in negative charge near by are expected to increase relative affinity.

positive charge was found in both the DAT and SERT models, near the C6(ar) portion of the naphthyl ring as shown. Differences in the electrostatic contour diagrams for the DAT model (Figure 1b) and the SERT model (Figure 1d) were also found in the area near the nitrogen and C2-carbonyl, with the SERT model showing two regions where negative charge should lead to enhanced binding compared to a single, small region for the DAT model.

Conclusion

Compounds have been prepared in the current study with 10-fold or greater selectivity for either the DAT the SERT. Compound **10c** shows approximately 20-fold selectivity for the DAT, while compound **10h** shows 10-fold selectivity for the SERT. CoMFA models developed for the DAT and SERT in these studies provide information that should be useful in the development of compounds showing selectivity and high affinity for both of these transporters. Thus, for compound **10h** (5-nitro-6-methoxy-2-naphthyl), it is expected that the modification of the 6-methoxy to a 6-ethyl substitution might increase SERT affinity while maintaining selectivity for that transporter, based on the region favoring positive charge in Figure 1d. Further substitution of a phenyl ring at the β-C3-position with substituents that are nearly planar, but that lie slightly out of plane of the aromatic ring, may lead to compounds with higher affinity for the SERT than the DAT due to the unfavorable interactions with the two steric exclusion areas shown in Figure 1a, but lacking in part in Figure 1c.

To further refine and extend these models, we are developing new CoMFA models in which the orientation of 2-naphthyl, 1-naphthyl, and other asymmetrical C3-substituents are examined, as well as the models in which new substitution patterns on aromatic ring systems are included in the training set for analysis. We hope that further, more refined CoMFA models will provide additional information on the requirements for both of these transporters and will also provide a clearer picture of the pharmacophore at binding sites, thereby adding a valuable tool for the development of potential treatment compounds. Compounds with selectivity for either the DAT or SERT may provide leads for active treatment compounds for not only cocaine addiction but also a number of neurologically based diseases.

Experimental Section

Chemistry. Commercial reagents were utilized without further purification unless otherwise noted. Methylene chloride was dried over calcium hydride and was freshly distilled. THF was dried over benzophenone ketyl and was freshly distilled. NMR data were obtained on a Varian VXR 200 MHz spectrometer and are expressed as δ values. Chromatographic separations were carried out with 230−400 mesh silica (silica 60, EM Science). Elemental analyses were performed by Atlantic Microlab, Atlanta, GA, and are within ±0.4% of the theoretical values for C, H and N.

Typical Procedure for the Conjugate Addition. The arylmagnesium bromide was generated as follows: A portion (10%) of the bromide (1.0 equiv) in THF was added to magnesium turnings (1.1 equiv). Two drops of dibromoethane was added. The reaction was initiated by heating. Once the reaction was started, the remaining bromide was added dropwise. The mixture was refluxed for 3 h after the addition and cooled to room temperature. The arylmagnesium bromide (4.5 equiv) in THF was added to thoroughly dried copper bromide−dimethyl sulfide complex (1.0 equiv). The mixture

was stirred at room temperature for 20 min and then cooled to 0 °C. A solution of **4** (0.2 equiv) or **5** (0.25 equiv) in dry THF was added dropwise. The ice bath was left in place and stirring was continued overnight. The solution was cooled to −78 °C and a solution of 1 M HCl in dry ether (13.5 equiv) was added in such a way that the temperature was kept below −70 °C at all times. The reaction mixture was warmed to room temperature and then extracted with water (3×). The aqueous layer was made basic with concentrated NH_4OH, extracted with CH_2Cl_2 (3×), dried (Na_2SO_4), and then concentrated under reduced pressure. The residue was purified by chromatography on silica gel.

Typical Procedure for Iododesilylation. To a solution of the silylnaphthyltropane (0.3 mmol, 1.0 equiv) in CH_2Cl_2 (6 mL) at 0 °C was added ICl (4.0 equiv). The mixture was stirred for 1 h. Then a 3% solution of $NaHSO_3$ (20 mL) was added, followed by concentrated NH_4OH. The mixture was extracted with CH_2Cl_2 (3 × 15 mL), dried (Na_2SO_4), filtered and the solvent evaporated. The product was purified by chromatography on silica gel.

Typical Procedure for N-Methylation. To a stirred mixture of the N-demethylated tropane (0.25 mmol, 1.0 equiv) and aqueous formaldehyde (10.0 equiv) in acetonitrile (10 mL) was added sodium cyanoborohydride (2.0 equiv) and the mixture was then stirred for 45 min. The solution was made acidic by addition of glacial acetic acid and then stirred for 2 h. The mixture was basified with saturated sodium carbonate solution, extracted with CH_2Cl_2 (3 × 15 mL), dried (Na_2SO_4), filtered and the solvent evaporated. The product was purified by chromatography on silica gel.

3β-[2-(6-Ethylnaphthyl)]-8-methyl-2β-propanoyl-8-azabicyclo[3.2.1]octane (10a): 98/2 ether/triethylamine−85/10/5 ether/triethylamine/methanol; 31% yield; IR (neat) 2959, 2936, 2875, 1718, 1692, 1514, 1459, 1449, 1130, 1109, 1054, 825 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.84−7.58 (m, 3 H), 7.51 (s, 1 H), 7.40−7.24 (m, 2 H), 3.53 (d, 1 H, J = 4.1 Hz), 3.46 (m, 1 H), 3.09 (m, 2 H), 2.75 (q, 2 H, J = 7.7 Hz), 2.70 (m, 1 H), 2.33−2.09 (m, 2 H), 2.26 (s, 3 H), 1.85−1.67 (m, 5 H), 1.28 (t, 3 H, J = 7.6 Hz), 0.75 (t, 3 H, J = 7.3 Hz); ^{13}C ($CDCl_3$) δ 210.6, 141.1, 139.5, 132.2, 131.8, 127.6, 127.1, 126.9, 125.8, 125.3, 125.1, 64.0, 62.5, 59.0, 41.9, 35.5, 34.2, 34.1, 28.9, 25.4, 25.1, 15.7, 7.6; MS *m/z* (rel intensity) 335 (47), 278 (100), 250 (6), 193 (11), 178 (23), 165 (34), 153 (26). Anal. Calcd for $C_{23}H_{29}NO\cdot1.25H_2O$: C, 77.48; H, 8.50; N, 3.80. Found: C, 77.16; H, 8.87; N, 3.91.

3β-[2-(6-Iodonaphthyl)]-8-methyl-2β-propanoyl-8-azabicyclo[3.2.1.]octane (10f): 47% yield for conjugate addition, 89% yield for iododesilylation, 83% yield for reductive methylation; pentane/ether/Et_3N (50:50:2); IR ($CDCl_3$) 2940, 1720, 1689, 1588, 1454, 1364 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.12 (s, 1H), 7.64−7.56 (m, 3H), 7.48 (d, 1H, J = 8.8 Hz), 7.37 (d, 1H, J = 8.8 Hz), 3.52 (d, 1 H, J = 6.8 Hz), 3.39 (br, 1H), 3.08 (m, 2H), 2.69 (t, 1H, J = 12.0 Hz), 2.32 (dq, 1H, J = 17.2, 7.3 Hz), 2.22 (s, 3H), 2.19−2.08 (m, 3H), 1.79−1.61 (m, 3H), 0.80 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 209.6, 141.8, 136.0, 134.0, 133.4, 132.0, 129.3, 126.7, 126.1, 125.4, 90.3, 64.4, 62.3, 59.1, 42.0, 34.8, 34.1, 26.3, 25.2, 7.7; MS *m/z* (rel intensity) 433 (M^+, 65), 377 (16), 376 (78), 307 (19), 250 (28), 152 (11), 97 (91), 96 (60), 83 (100). Anal. Calcd for $C_{21}H_{24}INO$: C, 58.21; H, 5.58; N, 3.23. Found: C, 58.44; H, 5.62; N, 3.31.

3β-[2-(6-Methoxy-5-nitronaphthyl)]-8-methyl-2β-propanoyl-8-azabicyclo[3.2.1]octane (10h). To a solution of **10c** (20 mg, 0.059 mmol) in dry CH_3CN (10 mL) at 0 °C under Ar was added solid NO_2BF_4 (10.2 mg, 0.076 mmol) in one portion. The reaction mixture was stirred at 0 °C for 4 h, cooled to −10 °C and then ice (0.1 g) was added. The resulting solution was allowed to warm to room temperature and stirred overnight. The reaction mixture was filtered, and the filtrate was concentrated. The residue was made basic with NH_4OH solution (5 drops concentrated NH_4OH in 5 mL of water). The aqueous layer was saturated with NaCl and extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried (Na_2SO_4) and removed under reduced pressure. Purification on alumina (neutral) column chromatography (95/5 ether/triethylamine) afforded **10h**: 11.9 mg (52.5% yield); mp 179−183 °C (from EtOAc/hexanes); IR (neat) 2938, 2851, 1713, 1636, 1608, 1527, 1507, 1355, 1281, 1262, 1218, 1079, 732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.88 (d, 1 H, J = 8.7 Hz), 7.6 (bs, 1 H), 7.55 (d, 1 H, J = 8.8 Hz), 7.44 (dd, 1 H, J = 8.8, 1.6 Hz), 7.25 (d, 1 H, J = 8.8 Hz), 3.99 (s, 3 H), 3.58 (d, 1 H, J = 7.1 Hz), 3.44 (m, 1 H), 3.10 (m, 2 H), 2.71 (ddd, 1 H, J = 12.9, 12.9, 2.6 Hz), 2.25 (s, 3 H), 2.36 (dq, 1 H, J = 15.7, 7.3 Hz), 2.17 (dq, 1 H, J = 15.7, 7.3 Hz), 1.76 (m, 5 H), 0.80 (t, 3 H, J = 7.3 Hz); ^{13}C ($CDCl_3$) δ 209.6, 167.6, 148.1, 140.2, 132.1, 129.2, 128.3, 125.7, 124.0, 120.0, 112.9, 64.5, 62.4, 58.7, 57.1, 42.0, 35.0, 34.2, 34.0, 26.4, 25.3, 7.8; MS *m/z* (rel intensity) 382 (50), 325 (100), 297 (2), 178 (14), 153 (6), 108 (1), 97 (44), 82 (57), 57 (12). Anal. Calcd for $C_{22}H_{26}N_2O_4$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.15; H, 6.84; N, 7.37.

Binding Studies. Binding of tropane analogues at biogenic amine transporters was determined as previously described,[38] using striatum and frontal cortex dissected from frozen Sprague−Dawley rat brains (Pel-Freez, Rogers, AR). Affinities of analogues at dopamine transport sites were determined by displacement of [^{125}I]RTI-55 binding in membranes from rat striatum, using 0.5 mg (original wet weight) of membranes and 10 pM [^{125}I]RTI-55. Nonspecific binding was determined in the presence of 1 μM WF-23 (analogue **3a**). Affinities of analogues at 5-HT transport sites were determined by displacement of [^{3}H]paroxetine binding in membranes from rat frontal cortex, using 50 mg (original wet weight) of membranes and 0.4 nM [^{3}H]paroxetine. Nonspecific binding was determined in the presence of 10 μM fluoxetine. Binding of analogues at norepinephrine transport sites was determined by displacement of [^{3}H]nisoxetine binding in membranes from rat forebrain, using 0.7 nM [^{3}H]nisoxetine. Nonspecific binding was determined in the presence of 1 μM desipramine.

Potencies were calculated from displacement curves using 7−10 concentrations of unlabeled analogues, as analyzed by nonlinear curve fitting. Because binding of tropanes at DATs is generally regarded as multiphasic,[68] potencies in inhibiting [^{125}I]RTI-55 binding are reported as IC_{50} values. For [^{3}H]-paroxetine and [^{3}H]nisoxetine binding assays, K_i values were calculated using the Cheng−Prusoff equation.[69] All data are mean values ± SEM of at least three separate experiments, each of which was conducted in triplicate.

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Supporting Information Available: Experimental data for **9b−d** and **10b−e,g,i,j** and details of molecular modeling and CoMFA analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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