A Second-Generation ^{99m}Technetium Single Photon Emission Computed Tomography Agent That Provides in Vivo Images of the Dopamine Transporter in Primate Brain

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Received May 1, 2003

The dopamine transporter (DAT), located presynaptically on dopamine neurons, provides a marker for Parkinson's disease (Pd) and attention deficit hyperactivity disorder (ADHD). In ADHD, DAT density levels are elevated, while in Pd these levels are depleted. The depletion of DAT levels also corresponds with the loss of dopamine. We now describe the design, synthesis, biology, and SPECT imaging in nonhuman primates of second-generation ^{99m}technetium-based tropane ligands that bind potently and selectively to the DAT. We demonstrate that improved selectivity and biological stability allows sufficient agent to enter the brain and label the DAT in vivo to provide a quantitative measure of DAT density in nonhuman primates. We introduce FLUORATEC (*N*-[(2-((3′-*N*′-propyl-(1″*R*)-3″α-(4-fluorophenyl)tropane-2″*β*-1-propanoyl)(2-mercaptoethyl)amino)acetyl)-2-aminoethanethiolato]technetium(V) oxide), a DAT imaging agent that has emerged from these studies and is now in phase 1 clinical trials in the U.S.

Introduction

Diagnosis of neurological disorders such as Parkinson's disease (Pd) and attention deficit hyperactivity disorder (ADHD) currently relies on the clinical skills of the diagnostician. The severity of Parkinson's disease is accompanied by a decrease in dopamine neurons. Therefore, a measure of the degeneration of dopamine neurons can provide a window on the quantitative diagnosis of Pd.[1] A biological marker for dopamine neurons and therefore for Pd has been identified,[2,3] and this marker, the dopamine transporter (DAT), is located presynaptically on dopamine neurons. ADHD has been demonstrated to be accompanied by a significant increase in the dopamine transporter.[4,5] Consequently, diagnosis of ADHD should also be possible by quantitation of the DAT on dopamine neurons. Currently there is no clinically available diagnostic agent that can enable quantitative diagnosis of these disorders in the U.S. An iodinated agent, DaTSCAN (ioflupane) is available outside the U.S.[6] The need for a diagnostic tool has been widely recognized, and many research groups, including our own, have focused efforts toward the design of imaging agents that can target the DAT.[7−17] A number of agents (Figure 1) designed for single photon emission computed tomography (SPECT) are currently in late-phase clinical trials. Among these agents is altropane,[8] an iodinated tropane that binds selectively to the DAT, and altropane is an effective imaging agent that can be used to diagnose both Pd and ADHD.[18−24] However, iodinated agents are not as widely accepted in nuclear medicine as those containing the ^{99m}technetium radionuclide. ^{99m}Technetium (^{99m}Tc; $t_{1/2}$ = 6.0 h, 140 keV, γ emission) offers important advantages, particularly the ability to generate the isotope in the laboratory from a commercially available kit and without need of a cyclotron on site. Consequently, ^{99m}Tc-based compounds are used clinically[25,26] as, for example, blood perfusion agents[27] and cardiovascular imaging agents.[28] Recognizing the advantages of ^{99m}Tc, we[9,29] and others[13,30,31] have developed ^{99m}Tc-containing DAT ligands with a view to diagnostic imaging. In 1996,[29] we reported technepine, [*N*-[2-((3′-*N*′-propyl-3″*β*-(4-fluorophenyl)tropane-2″*β*-carboxylic acid methyl ester)-(2-mercaptoethyl)amino)acetyl]-2-aminoethanethiolato-^{99m}technetium(V) oxide] the first transporter-mediated ^{99m}technetium-based in vivo SPECT imaging agent (Figure 1) that labels the DAT in primates. Although this ligand provided good SPECT images in primates under excellent research conditions,[9] it proved less effective in the more demanding clinical setting. This was thought to be a consequence of inadequate penetration of the blood−brain barrier (BBB) and therefore insufficient biological availability at the site of interest, the DAT. We reasoned that two aspects most probably dominated this reduced biological availability. First was the possibility that relatively rapid metabolic inactivation of the ligand by esterases in the blood would cause a rapid decrease in the available ligand, and second was that excessive lipophilicity may cause the ligand to be retained in the proteinacious material within the blood. Indeed, the half-life of altropane is approximately 40 min in humans, and this is thought to be primarily a consequence of C2-ester hydrolysis in vivo.[21] Consequently we sought to remove the C2-ester of technepine (Figure 1) and replace it with a topologically similar

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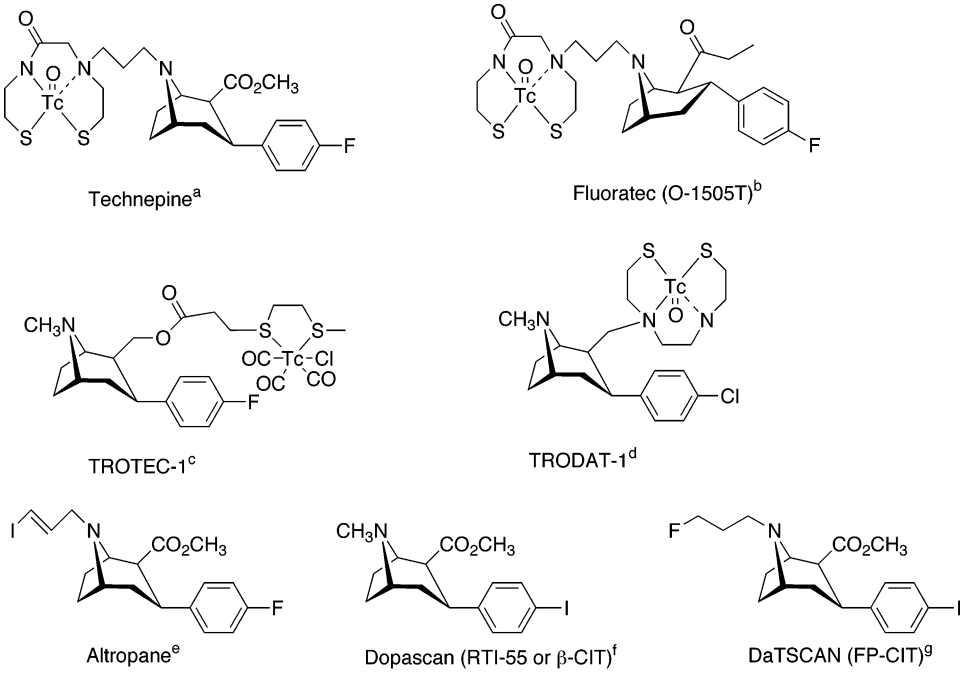
10.1021/jm0301484 CCC: $25.00
Published on Web 07/04/2003



[a]Meltzer et al. J. Med. Chem. 40, 1835-1844,1997; [b]Meltzer et al. Present manuscript; [c]Hoepping et al. J. Med. Chem. 41, 4429-4432, 1998; [d]Meegalla et al. J. Med. Chem. 40, 9-17, 1997; [e]Elmaleh et al. J. Nucl. Med. 37, 1197-1202, 1996; [f]Carroll et al. Med. Chem. Res. 1, 289-294, 1991; [g]Chaly et al. Nucl. Med. Biol. 23, 999-1004, 1996

Figure 1. Structures of SPECT imaging agents for the DAT.

group incapable of deactivation by blood esterases. In addition, we reasoned that if the potency and, more importantly, the selectivity of the new ligand could be improved, compared with that of technepine, the enhanced BBB penetration would be further complemented by the need for delivery of lesser amounts within the caudate-putamen. We therefore drew from the body of SAR data already developed for the parent tropanes[32,33] to select optimum templates for this new imaging agent.

We now describe the design, synthesis, biology, and SPECT imaging in nonhuman primates of a number of ^{99m}technetium-based agents. Furthermore, we introduce FLUORATEC (O-1505T: *N*-[(2-((3′-N′-propyl-(1″*R*)-3″α-(4-fluorophenyl)tropane-2″β-1-propanoyl)(2-mercaptoethyl)amino)acetyl)-2-aminoethanethiolato]technetium(V) oxide), a DAT imaging agent that has emerged from these studies and is now in phase 1 clinical trials in the U.S.[34−36]

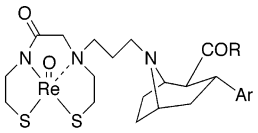
Chemistry

The imaging agents described herein are composed of three parts: (i) a potent 2-substituted 3-aryltropane, selective for the DAT versus the SERT, (ii) a neutral chelating unit to which the radionuclide ^{99m}Tc is bound, and (iii) a tether that connects the chelating entity to the tropane skeleton. Rhenium, an excellent model for the radioactive ^{99m}Tc, has been utilized in place of ^{99m}Tc in studies that do not require the presence of a radiolabel.[9,37] It forms stable square-pyramidal N_2S_2 complexes similar to those formed by ^{99m}Tc.[38] Also, the lipophilicity and biological availability of rhenium chelates are similar to those of ^{99m}technetium chelates.[38] Evaluation of the biology of rhenium chelated compounds (Table 1) therefore facilitated selection of compounds for further development. The synthetic approach to the rhenium complexes in Table 1 is outlined in Schemes 1−3.

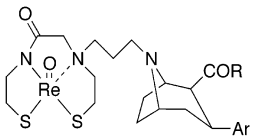
The tropanes selected for incorporation in the final ligands were all prepared along similar lines.[32,39] Thus, the keto ester (1*R*)-**1**[40,41] was converted to the enol triflate **2** and coupled, via Suzuki coupling, to the appropriate arylboronic acids. The 2,3-unsaturated tropanes **3** thus obtained were utilized to prepare the 2,3-unsaturated ligands **14** and **15**. These 2,3-enes **3** were also subjected to samarium iodide reduction[32,39] to obtain **4**, the boat (2β,3α), and **5**, the chair (2β,3β), configured tropanes. The C2-esters were then converted to the C2-ketones through the Weinreb amides **7** (Scheme 2).[42] Reaction of the Weinreb amides with ethylmagnesium bromide then provided the ketones **8**. Demethylation with α-chloroethyl chloroformate (ACE-Cl) then provided the nortropanes **9** as starting materials for incorporation of the chelating ligand, **10**.[9] The 3β-configured nortropanes and the 2,3-unsaturated nortropanes **22** and **23** (Scheme 3) were obtained similarly.

The N_2S_2 ligand (MAMA′)[37,43−45] was attached to 1-chloro 3-propyltriflate in methylene chloride to provide the chloropropyl-MAMA′ synthon **10**,[9] which was utilized to alkylate the various nortropane parent compounds (**9**, **19**, **22**, **23**) in the presence of KI and $NaHCO_3$ to obtain the bistrityl protected compounds **11**, **20**, **24**, and **25**, respectively, in reasonable yields. Rhenium was then introduced upon reaction of the bistrityl protected compounds with sodium perrhenate under reductive conditions ($SnCl_2$) in ethanol to provide rhenium chelates **12**−**15**. Compounds **12**−**15** each exist in two diastereomeric forms. The chirality of the tropane moiety is derived from **1** and is therefore fixed. However,

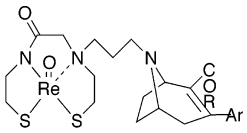
Table 1. Inhibition of [^{3}H]WIN 35,428 Binding to the Dopamine Transporter and [^{3}H]citalopram Binding to the Serotonin Transporter in Rhesus (*Macaca mulatta*) or Cynomolgus Monkey (*Macaca fascicularis*) Caudate-putamen[a]



12 R = CH_2CH_3
26 R = OCH_3



13 R = CH_2CH_3
27 R = OCH_3



14 R = CH_2CH_3
15 R = OCH_3

a. Ar = 4-FPh **b**. Ar = 3,4-Cl_2 Ph **c**. Ar = 2-naphthyl

Ar	R	compd	IC$_{50}$ (nM) DAT[b]	IC$_{50}$ (nM) SERT[b]	DAT/ SERT	compd	IC$_{50}$ (nM) DAT	IC$_{50}$ (nM) SERT	DAT/ SERT	compd	IC$_{50}$ (nM) DAT	IC$_{50}$ (nM) SERT	DAT/ SERT
4-FPh[c,d]	OMe	**26a**, O-1186	3.8	1300	342	**27a**, O-861	2.9	80	27	**15a**, O-1135	3500	4000	1.1
4-FPh (1*R*,12*S*)	OMe					**27a-1**, O-927	7.4	67	9				
4-FPh (1*R*,12*R*)	OMe					**27a-2**, O-928	4.0	299	75				
4-FPh[c]	Et	**12a**, O-1505	2.05	497	242	**13a**, O-1508	5.9	200	34	**14a**, O-1768	660	2100	3.2
4-FPh (1*R*,12*R*)	Et	**12a-1**, O-2020	3	1000	333								
4-FPh (1*R*,12*S*)	Et	**12a-2**, O-1972	1.5	10000	6667								
3,4-Cl_2Ph[d]	OMe	**26b**, O-1196	10.6	639	60	**27b**, O-863	37	264	7.1	**15b**, O-1136	60	1693	28
3,4-Cl_2Ph	Et	**12b**, O-1561	5.3	337	63	**13b**, O-2131	5	400	80	**14b**, O-1769	1200	2000	1.7
2-naphthyl[d]	OMe	**26c**, O-2130	4	120	30	**27c**, O-1339	3.64	58.9	16	**15c**, O-1185	63.4	964	15.2
4-FPh	NMeOMe					**17a**, O-1451	40.5	3260	80				

[a] Each value is the mean of two or more independent experiments each conducted in different brains and in triplicate. [b] DAT = dopamine transporter [^{3}H]WIN 35,428; SERT = serotonin transporter [^{3}H]citalopram. [c] Mixture of (1*R*,12*S*) and (1*R*,12*R*) diastereomers. [d] Compounds **26**, **27**, and **15** have a C2β-$COOCH_3$ (*J. Med. Chem.* **1997**, *40*, 1835−1844).

the introduction of a chiral rhenium chelate leads to the formation of these diastereoisomers. These are shown for **12a** in Figure 2: **12a-1** (1*R*,12*R*) and **12a-2** (1*R*,-12*S*).

Structural assignment of the rhenium chelates was facilitated by ^{1}H NMR analysis. The presence of diastereomeric mixtures was clearly evidenced in the ^{1}H NMR spectra of these compounds. In this regard, the C13 protons are particularly diagnostic for the Re═O complexes. In the Re═O chelate **12a**, both C13 protons appear considerably downfield in the region of δ 4.0−5.2. This downfield shift is due, in part, to the anisotropic effect of the Re═O bond and the quaternary nature of the nitrogen (N12). The diastereotopy of the C13 protons is evidenced in that the C13β proton manifests a four-line multiplet [**12a-1**, δ 4.74 (d, J = 16.5 Hz, 1H, H-13β); **12a-2**, δ 5.14 (d, J = 16.5 Hz, 1H, H-13β)*]*. The corresponding 13α proton also shows a four-line multiplet [**12a-1**, δ 4.08 (d, J = 16.5 Hz, 1H, H-13α); **12a-2**, 4.13 (d, J = 16.5 Hz, 1H, H-13α)] with an almost 1 ppm upfield shift from the 13β. The effect of the Re═O bond is also apparent on the 16α and β protons. The 16α proton resonance is a multiplet for **12a-1** at about δ 4.11, and the 16β proton appears as a multiplet at about δ 4.57. In the diastereomeric mixture of **12a**, the 16β protons overlap, resulting in a multiplet at about δ 4.60.

The two diastereomers of **12a** coelute on TLC in a variety of solvent systems, and therefore, chromatographic separation is difficult. However, two consecutive MPLC column chromatographic separations, with a high ratio of compound to silica gel (171 mg:43 g) and collection of multiple small fractions, allowed pooling of early versus late fractions to provide purified samples of each diastereoisomer. The absolute structure of diastereoisomer **12a-2** was established by X-ray crystallography and confirmed that the propyl group attached at N12 bears a syn relationship to the Re═O bond (Figure 3). Therefore, diastereoisomer **12a-2** is (1*R*,12*S*)-*N*-[(2-((3′-*N*′-propyl-3″α-(4-fluorophenyl)tropane-2″β-propionyl)(2-mercaptoethyl)amino)acetyl)-2-aminoethanethiolato]rhenium(V) oxide and diastereoisomer **12a-1** is (1*R*,12*R*)-*N*-[(2-((3′-*N*′-propyl-3″α-(4-fluorophenyl)tropane-2″β-propionyl)(2-mercaptoethyl)amino)acetyl)-2-aminoethanethiolato]rhenium(V) oxide. The absolute structures of **27a-1** and **27a-2**, the C2-ester, 3β-aryl analogues, have been reported previously.[9]

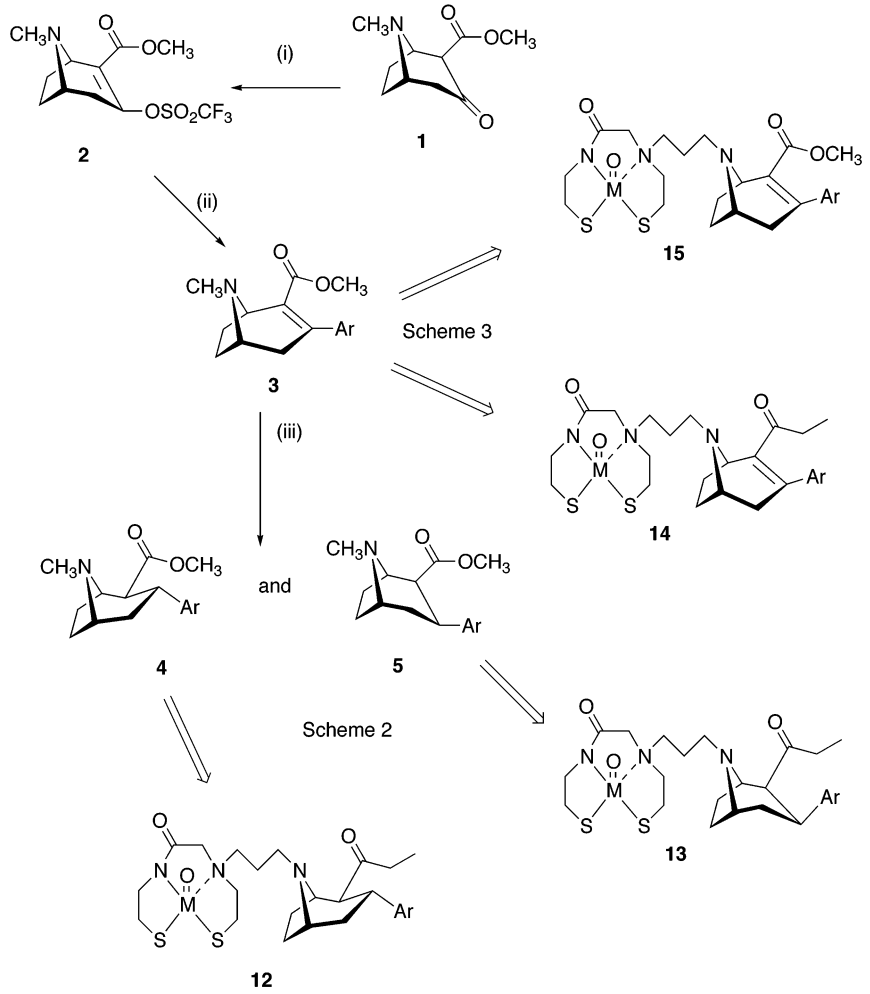
Biology

Rhenium is an excellent model for the radioactive ^{99m}Tc; therefore, the in vitro binding data were obtained for the rhenium chelates. Since ^{99m}Tc is introduced in a final preparative step for routine use, a diastereomeric mixture of the imaging agents will likely be used clinically. Therefore, the biological activity of the diastereomeric mixture of Re-**12a** was important; however, binding constants for each of the diastereoisomers **12a-1** and **12a-2** were also measured.

The affinities (IC$_{50}$) of the rhenium compounds for the dopamine and serotonin (SERT) 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 dopamine transporter[46] and [^{3}H]citalopram to label the serotonin transporter.[29] Studies were conducted in cynomolgus or rhesus monkey striata because these compounds are part of an ongoing investigation of structure−activity relationships at the dopamine transporter in these tissues[33,41,46] and meaningful comparisons with an extensive database and in vivo imaging data can be made. 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. Binding constants are presented in Table 1.

The enhanced selectivity generally manifested by 3α-aryltropanes[32] has been retained for these N-substituted

Scheme 1. General Synthesis of Rhenium- and Technetium-Labeled DAT Ligands **12**−**15a**[a]



a. Ar = 4-FPh **b**. Ar = 3,4-Cl_2 Ph **c**. Ar = 2-naphthyl M= Re or ^{99m}Tc

[a] Reagents and conditions: (i) $NaN(TMS)_2$, THF, −78 °C, $PhN(CF_3SO_2)_2$; (ii) LiCl, Pd_2dba_3, Na_2CO_3, $CH_2(OC_2H_5)_2$, 22 °C, ArylB(OH)$_2$, Δ; (iii) (a) SmI_2, THF, −78 °C, (b) MeOH, TFA (54% 3β and 29% 3α).

rhenium complexes. Indeed, the 3α-(4-fluorophenyl)-C2-ketone **12a** has IC_{50} = 2.05 nM (DAT) and IC_{50} = 497 nM (SERT). It therefore has a potency similar to that of technepine **27a** (DAT IC_{50} = 2.9 nM) and is almost 10-fold more selective (SERT IC_{50} = 80 nM). The two diastereomers of **12a** showed similar potency at the DAT (IC_{50} = 1.5, 3.0 nM). Both compounds were extremely selective; however, **12a-2** was about 20-fold more selective than **12a-1**.

Synthesis of 12a (FLUORATEC: *N*-[(2-((3′-*N*′-Propyl-(1″*R*)-3″α-(4-fluorophenyl)-tropane-2″β-1-propanoyl)(2-mercaptoethyl)-amino)acetyl)-2-aminoethanethiolato]-technetium(V) Oxide)

Synthesis of ^{99m}Tc-**12a** as a 1:1 diastereomeric mixture was achieved by deprotection of the bistritylated compound **11** with trifluoroacetic acid under cation trapping conditions (triethylsilane). The bisthiol obtained was treated with ^{99m}technetium glucoheptonate and the product was purified by HPLC to provide 6 mCi of the ligand ^{99m}Tc-**12a** for in vivo studies.

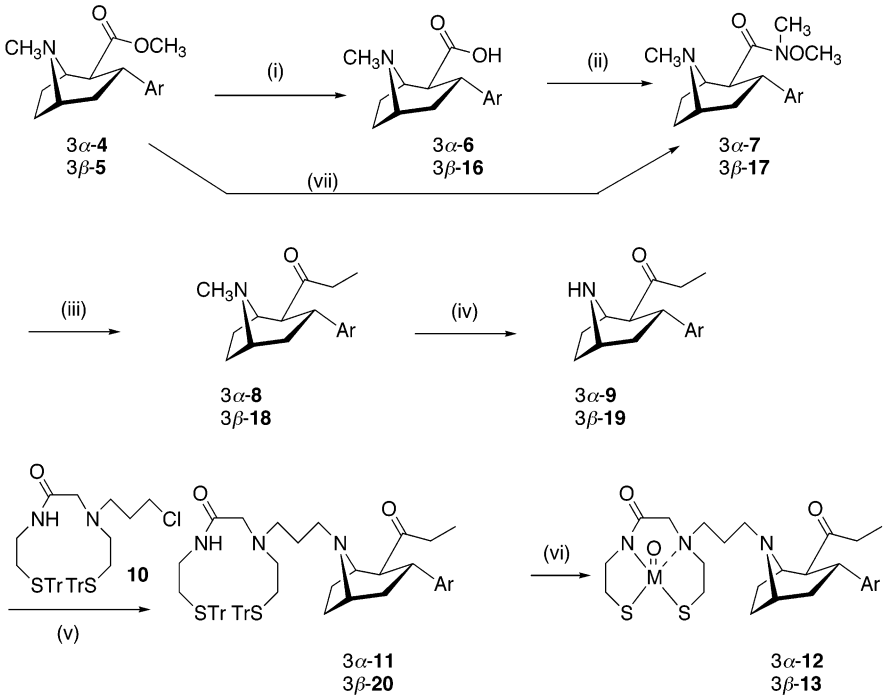
SPECT Image

Figure 4 shows a representative midstriatal, transaxial slice of a high count density SPECT image of a monkey injected with approximately 20 mCi of ^{99m}Tc-**12a**. The image was acquired between 15 and 45 min after injection. There is a relatively intense tracer accumulation in the striatum. The absence of uptake in the thalamus and midbrain, regions with high SERT density, is consistent with the high DAT selectivity of this compound. Compound **12a** has now been used to provide images in humans.[35]

Discussion

The degeneration of dopamine neurons in the striatum can provide a window to the diagnosis of Parkinson's disease,[1] and the dopamine transporter has been identified as a biological marker for these neurons.[2,3] This transporter, located presynaptically, also provides a suitable marker for ADHD because this syndrome is accompanied by a significant increase in DAT density.[4,5] Therefore, the diagnosis of both Pd and ADHD can be achieved by quantitation of the DAT on dopamine neurons. SPECT and PET have been utilized to image

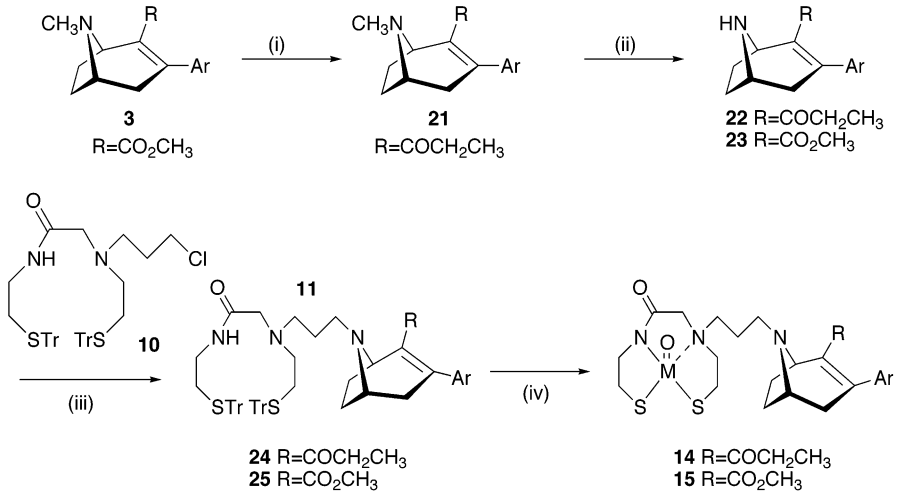
Scheme 2. General Synthesis of Rhenium- and Technetium-Labeled Ligands **12** and **13**[a]



a. Ar = 4-FPh **b**. Ar = 3,4-Cl_2Ph **c**. Ar = 2-naphthyl M= Re or ^{99m}Tc

[a] Reagents and conditions: (i) dioxane/H_2O, Δ, 24 h; (ii) (a) $(COCl)_2$, CH_2Cl_2, DMF, 22 °C, 45 min; (b) (MeO)MeNH, HCl, pyridine, 1 h; (iii) EtMgBr; Et_2O, THF, 0−65 °C; (iv) ACE-Cl, Δ; (v) **10**, KI, $NaHCO_3$, CH_3CN, Δ, 4 h; (vi) $SnCl_2$, EtOH, $NaReO_4$, Δ or $(C_2H_5)_3Si$, $Na^{99m}Tc$ pertechnetate; (vii) Me_3Al, (MeO)MeNH·HCl.

Scheme 3. General Synthesis of Rhenium- and Technetium-Labeled Ligands **14** and **15**[a]



a. Ar = 4-FPh **b**. Ar = 3,4-Cl_2 Ph **c**. Ar = 2-naphthyl M= Re or ^{99m}Tc

[a] Reagents and conditions: (i) EtMgBr; Et_2O, Et_3N, THF, 0−10 °C; (ii) ACE-Cl, Δ, 5 h; (iii) 10, KI, $NaHCO_3$, CH_3CN, Δ, 4 h; (iv) $SnCl_2$, EtOH, $NaReO_4$, Δ; or $(C_2H_5)_3Si$, $Na^{99m}Tc$ pertechnetate.

the DAT, and radiolabeled imaging agents suitable for both procedures are now available for research purposes. One such ^{99m}Tc-labeled ligand is technepine, ^{99m}Tc-**27a**, reported from these laboratories in 1996.[9,29] A shortcoming of technepine was related to the finding that although it provided excellent images in primates under ideal research conditions, it did not perform comparably with altropane,[21] our benchmark compound for a useful clinical SPECT diagnostic agent in a more demanding clinical setting. The focus of the current report is the design and synthesis of an improved second-generation ^{99m}Tc-labeled SPECT ligand. To accomplish this, we returned to the SAR data for the 8-azabicyclo[3.2.1]octanes[32] in which we had established that the orientation of, and substitution at, the C3 position dictates selectivity for the DAT versus the SERT. Furthermore, SAR had also shown that varied functionality could be tolerated at C2,[47−52] thus allowing removal of the hydrolyzable C2-ester present in technepine. A series of selected rhenium-labeled model ligands was therefore prepared, and their binding potencies and selectivities to neurotransmitter uptake

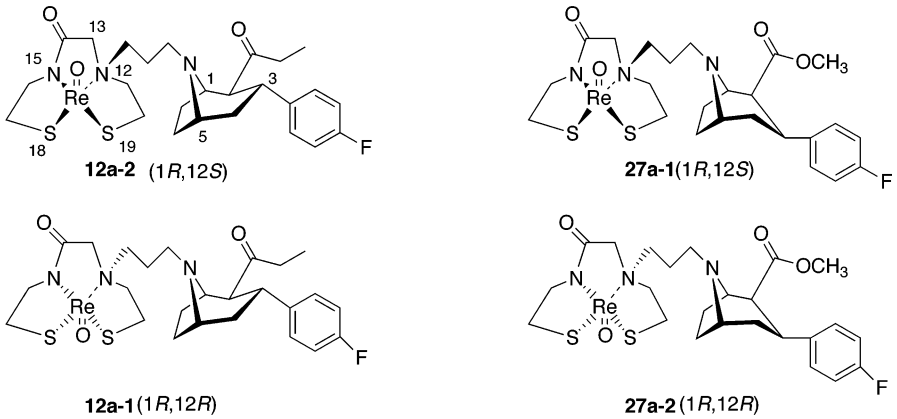


Figure 2. Diastereomers of **12a** and **27a**.

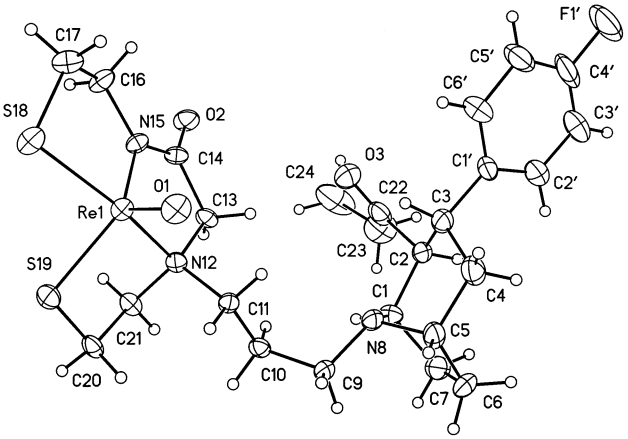


Figure 3. ORTEP diagram of compound **12a-2**.

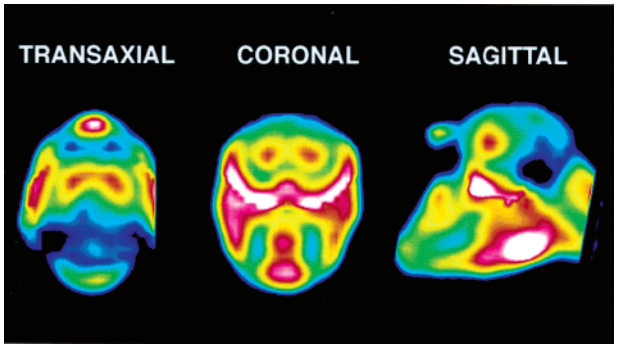


Figure 4. Midstriatal, transaxial slice of a SPECT image of a monkey injected with **12a**.

systems (DAT and SERT) were measured (Table 1). Of the 3α-aryl 2β-ethyl ketones, compounds **12a** and **12b** appeared most promising as prospective SPECT ligands. Compound **12a** was particularly potent (IC_{50} = 2.05 nM) and selective (242-fold). Compound **26a**, almost equally potent yet more selective (343-fold) was set aside because the C2-ester would likely be subject to metabolic hydrolysis, as had presumably occurred with technepine (**27a**). Thus, **12a** was selected for insertion of ^{99m}Tc. It provided suitable SPECT images in monkeys and was therefore deemed potentially suitable for clinical evaluation. Compound ^{99m}Tc-**12a**, the C3-(4-F-phenyl) analogue, is now in phase 1 clinical trials.

Design of ^{99m}Technetium-Labeled Imaging Agents. We have previously described our approach to the synthesis of ^{99m}Tc-labeled tropanes for imaging of the DAT.[9] In summary, the design of these agents hinged on a tropane moiety that serves as a "guiding ligand" to which a neutral ^{99m}Tc (or Re) chelate could be attached by a methylene chain ("tether").

The Guiding Ligand. Selection of a potent "guiding ligand" was aided by structure−activity relationships of the tropane family of compounds.[32] The most potent tropane DAT inhibitors possess either a C3-(2-naphthyl) group[52] or a C3-(3,4-dichlorophenyl) group.[33] However, such substitution can lead to high lipophilicity and thus reduce BBB permeation. Furthermore, as bulk is introduced at the N8, steric bulk on the C3 aromatic ring is less well tolerated.[9] Altropane has a C3-(4-fluorophenyl) group. Therefore, in an initial exploration it was prudent to utilize all three templates.

We had reported[32] that selectivity for the DAT versus the SERT can be substantially controlled by orientation of the C3-aryl ring. The 3β-aryl (chair) orientation is generally least selective for the DAT, while both the flattened 2,3-ene and the 3α-aryl (boat) substituents confer considerable selectivity for the DAT.[39] Therefore, we anticipated that either the boat-conformed compounds with the C3α configuration or the 2,3-ene compounds may provide the optimum guiding ligand.

As discussed above, technepine, with a C2 methyl ester, manifested insufficient BBB permeability for routine use, and images obtained in a clinical setting could not be reliably quantified. A major cause of this was assumed to be a result of in vivo esterase hydrolysis of the methyl ester. To eliminate this possibility but retain overall topology, we explored the introduction of a C2 ethyl ketone. It has been established that C2-ketones can lead to extremely potent DAT inhibitors.[52] In summary, we based the design of a second-generation imaging agent on a ligand with enhanced selectivity (3α-configuration), improved biological half-life (C2-alkyl ketone), and enhanced potency (C3 substitution: 3,4-dichlorophenyl, 2-naphthyl, or 4-fluorophenyl).

Point of Attachment. On the basis of the success with technepine and the fact that it has now been conclusively proven that sufficient space exists within the dopamine transporter to accept substantial bulk at the 8-aza position, we attached the tether and chelator to the nitrogen of the tropane skeleton.

Chelator. The N_2S_2 ligand, MAMA′,[37,43−45] was selected as the ^{99m}technetium chelating moiety for these ligands. We had already shown that a tropane attached to a MAMA′ moiety was capable of potent and selective

binding to the DAT and, more importantly, the neutral ^{99m}Tc-containing ligand was capable of crossing the blood−brain barrier.[9]

Biology. The binding affinities (IC_{50}) of the rhenium chelates for the dopamine and serotonin transporters are presented in Table 1. The most potent and most selective compound is the 3α-boat-configured 12*S* diastereomer **12a-2**, which has an IC_{50} of 1.5 nM and a selectivity of 6667 (DAT/SERT). Of interest is the fact that the two diastereomers **12a-1** and **12a-2**, while similar in DAT potency (**12a-1**, IC_{50} = 3 nM; **12a-2**, IC_{50} = 1.5 nM), differ markedly in selectivity (333 vs 6667). Most important, the mixture of diastereomers **12a** is sufficiently potent (IC_{50} = 2.05 nM) and selective (DAT/SERT = 242) to provide a promising SPECT ligand. It should be noted that **12a** is about equipotent with **27a** (technepine[9]) at the DAT but is considerably more selective than **27a**. The 3-(3,4-dichlorophenyl) analogue **12b** is also potent (DAT IC_{50} = 5.3 nM) and manifests good selectivity (DAT/SERT = 63). Surprisingly, and contrary to the SAR previously discovered for the bicyclo[3.2.1]octanes in general,[32] the 2,3-unsaturated rhenium chelates **14** and **15** manifest poor binding affinity for the DAT (63−− 3500 nM), and therefore, none of these compounds were selected for insertion of ^{99m}Tc. In a comparison between 2-carbomethoxy compounds and 2-propionyl compounds, it is clear that the presence of either a ketone or methyl ester does not affect potency at the DAT significantly.

The 3*β*-compounds, including technepine **27a**, manifested good to excellent binding affinity (2.9−40 nM) for the DAT; however, selectivity for the DAT versus the SERT for these chair conformers was, as expected, weaker than for their boat counterparts **12**. This is because the 3α-boat compounds are far less potent at the SERT.

A comparison of DAT and SERT inhibition of the individual diastereomers of **26a** and **27a** is interesting (Figure 2). While in the case of **26a**, the (1*R*,12*S*)-**26a-1** is less potent and less selective at the DAT than its (1*R*,-12*R*) diastereomer **26a-2**, the reverse is true for the 3α-configured 2-propionyl analogues, **12a**. In this later case, the (1*R*,12*S*)-**12a-2** diastereomer proves to be twice as potent and about 20-fold more selective than its (1*R*,-12*R*)-**12a-1** counterpart. During the formation of the technetium chelates, both diastereomers are produced, and consequently it is clinically most convenient to utilize a mixture of diastereoisomers in imaging experiments.

Conclusion

Rhenium and ^{99m}technetium-labeled tropane ligands have been prepared and evaluated as prospective SPECT imaging agents for the dopamine transporter. Select compounds that manifested high potency and selectivity for the DAT were also shown to cross the blood−brain barrier and label the dopamine transporter in vivo. FLUORATEC (*N*-[(2-((3′-*N*′-propyl-(1″*R*)-3″α-(4-fluorophenyl)tropane-2″*β*-1-propanoyl)(2-mercaptoethyl)-amino)acetyl)-2-aminoethanethiolato]technetium(V) oxide) has emerged as a second-generation ^{99m}technetium-labeled SPECT imaging agent for the dopamine transporter in striatum and is now in a phase I clinical trial in the U.S. Thus, we have demonstrated that a molecule can be designed to carry the ^{99m}Tc radionuclide across the blood−brain barrier in sufficient quantity and with sufficient specificity to obtain in vivo images of the striatum in primates and humans.[35]

Experimental Section

NMR spectra were recorded on a Bruker 100, a Varian XL 400, a Bruker 300, or a JEOL 300 NMR spectrometer with tetramethylsilane (TMS) as internal standard and $CDCl_3$ as solvent. 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 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 μM. All reactions were conducted under an atmosphere of dry nitrogen. Elemental analyses were performed by Atlantic Microlab, Atlanta, GA. HPLC analyses were carried out on a Waters 510 system with detection at 254 nm on a Waters 8 mm, C-18, 10 μm reverse-phase column. A Beckman 1801 scintillation counter was used for scintillation spectrometry. Pd_2dba_3 is trisdibenzylideneacetone dipalladium, TFA is trifluoroacetic acid, THF is tetrahydrofuran, and EtOAc is ethyl acetate. Room temperature is 22 °C. Samples of 0.1% bovine serum albumin and (−)-cocaine were purchased from Sigma Chemicals. [^{3}H]WIN 35,428 (2*β*-carbomethoxy-3*β*-(4-fluorophenyl)-*N*-[^{3}H]methyltropane, 79.4−87.0 Ci/mmol) and [^{3}H]citalopram (86.8 Ci/mmol) were purchased from DuPont-New England Nuclear (Boston, MA). (−)-Cocaine hydrochloride for the pharmacological studies was donated by the National Institute on Drug Abuse [NIDA]. Fluoxetine was donated by E. Lilly & Co.

(1*R*)-2-Carboxymethoxy-3-[[(trifluoromethyl)sulfonyl]-oxy]-8-methyl-8-azabicyclo[3.2.1]oct-2-ene (2).[53] (1*R*)-(−)-2-Carbomethoxy-3-tropinone, **1**[41] (1.0 g, 5.1 mmol), was dissolved in anhydrous THF (20 mL), and the resulting solution was cooled to −78 °C. A solution of sodium bistrimethylsilylamide (1.0 M, 5.56 mL, 5.56 mmol) was added slowly to the solution. After 30 min, *N*-phenyltrifluoromethane sulfonamide (1.94 g, 5.43 mmol) was added. The resulting solution was stirred for a further 45 min at −78 °C and then allowed to attain room temperature and stirred for a further 2 h. All solvent was evaporated, and the residue was pumped to dryness. Flash chromatography (2−16% CH_3OH in EtOAc) gave **2** (1.62 g, 97%) as a yellow oil. R_f = 0.65 (10% CH_3OH in EtOAc). ^{1}H NMR: δ 3.92 (d, J = 5 Hz, 1H), 3.80 (s, 3H), 3.42 (t, J = 6 Hz, 1 H), 2.84 (dd, J = 18, 4 Hz, 1H), 2.39 (s, 3H), 2.1−2.2 (m, 2H), 1.97 (m, 2H), 1.58 (m, 1H).

(1*R*)-2-Carboxymethoxy-3-(4-fluorophenyl)-8-methyl-8-azabicyclo[3.2.1]oct-2-ene (3a).[53] LiCl (6.45 g, 150.9 mmol) and an aqueous solution of Na_2CO_3 (2.0 M, 71 mL) were added to a solution of **2** (23.23 g, 70.55 mmol), and 4-fluorophenylboronic acid (11.78 g, 84.19 mmol) in diethoxymethane (300 mL) was added at room temperature. The resulting solution was degassed under N_2 for 15 min before the addition, in one portion, of Pd_2dba_3 (0.05 equiv) under a strong stream of N_2, and the reaction mixture was heated to reflux for 3 h under N_2. TLC showed the reaction was complete. The mixture was allowed to cool to room temperature and diluted with Et_2O (300 mL) and filtered through Celite. The Celite was washed with Et_2O (3 × 100 mL) and water (3 × 50 mL). The combined washes were then basified with NH_4OH to pH 11. The layers were separated, and the Et_2O layer was washed with brine. The aqueous layers were combined and back-extracted with EtOAc (100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to dryness to yield a yellow oil that was further purified by flash chromatography (EtOAc 60%, hexanes 35%, Et_3N 5%) to afford **3a** as a yellow oil (18.8 g, 89%). R_f = 0.28 (EtOAc 60%, hexanes 35%, Et_3N 5%). ^{1}H NMR: δ 7.13−7.07 (m, 2H), 7.00 (tt, 2H, J = 8.7, 2.1 Hz), 3.85

(d, 1H, J = 5.5 Hz), 3.50 (s, 3H), 3.35 (t, 1H, J = 5.6 Hz), 2.74 (dd, 1H, J = 18.8, 4.8 Hz), 2.44 (s, 3H), 2.28−2.12 (m, 2H), 2.05−1.94 (m, 2H), 1.67−1.60 (m, 1H). Anal. ($C_{16}H_{18}O_2FN\cdot^1/_6H_2O$) C, H, N.

(1*R*)-2-Carboxymethoxy-3-(3,4-dichlorophenyl)-8-methyl-8-azabicyclo[3.2.1]oct-2-ene (3b). The procedure described above was followed to provide **3b** as a yellow oil (512 mg, 83%). R_f = 0.56 (10% Et_3N in EtOAc). ^{1}H NMR: δ 1.61 (m, 1H), 1.9−2.05 (m, 2H), 2.1−2.3 (m, 2H), 2.43 (s, 3H), 2.76 (dd, J = 19, 4.7 Hz, 1H), 3.36 (t, J = 4.9 Hz, 1H), 3.52 (s, 3H), 3.86 (d, J = 5.5 Hz, 1H), 6.96 (dd, J = 8.3, 1.9 Hz, 1H), 7.2 (d, J = 2.2 Hz, 1H), 7.37 (d, J = 8.2 Hz, 1H). Anal. ($C_{16}H_{17}O_2NCl_2$) C, H, N.

(1*R*)-2-Carboxymethoxy-3-(2-naphthyl)-8-methyl-8-azabicyclo[3.2.1]oct-2-ene (3c). The procedure described above was followed to provide **3c** as a light-yellow solid (94%). Mp 99−101 °C. R_f = 0.30 (EtOAc 60%, hexanes 35%, Et_3N 5%). ^{1}H NMR: δ 7.83−7.77 (m, 3H), 7.60 (s, 1H), 7.49−7.43 (m, 2H), 7.28−7.24 (m, 1H), 3.91 (d, 1H, d, J = 5.2 Hz), 3.43 (s, 3H), 3.39 (t, 1H, J = 5.6 Hz), 2.85 (dd, 1H, J = 18.8, 4.5 Hz), 2.50 (s, 3H), 2.28−2.00 (m, 4H), 1.75−1.68 (m, 1H). Anal. ($C_{20}H_{21}NO_2\cdot^1/_5H_2O$) C, H, N.

(1*R*)-2*β*-Carboxymethoxy-3α-(4-fluorophenyl)-8-methyl-8-azabicyclo[3.2.1]octane (4a) and (1*R*)-2*β*-Carboxymethoxy-3*β*-(4-fluorophenyl)-8-methyl-8-azabicyclo[3.2.1]-octane (5a). To a solution of SmI_2 (2.6 L, 0.1M in THF) was added a solution of **3a** (18.8 g, 68 mmol) in THF (142 mL, anhydrous) dropwise at −78 °C under N_2. The mixture was then stirred for 45 min. Anhydrous CH_3OH (142 mL) was then added, and the mixture was stirred for a further 2 h. The reaction was quenched with TFA (73 mL) at −70 °C, and water (1.5 L) was added. The reaction mixture was allowed to warm slowly to room temperature. It was then basified (NH_4OH to pH 10) and filtered through Celite, and the Celite was washed with Et_2O and saturated with $NaHSO_3$. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated to dryness to afford the crude product that was purified by flash chromatography (EtOAc 20%, hexane 75%, Et_3N 5%; EtOAc 60%, hexanes 35%, Et_3N 5%) to yield a white solid containing 2*β*,3α- and 2*β*,3*β*- (1:1) substituted products (15.93 g, total 91%). The isomers were separated by gravity column chromatography (3% EtOH/$CHCl_3$; EtOAc 20%, hexane 75%, Et_3N 5%).

The 2*β*,3α-substituted ester **4a** was obtained as a white solid (6.22 g, 36%). R_f = 0.35 (EtOAc 20%, hexane 75%, Et_3N 5%). Mp 48.0−48.9 °C. ^{1}H NMR: δ 7.18−7.14 (m, 2H), 6.94 (tt, 2H), 3.58 (s, 3H), 3.35−3.25 (m, 3H), 2.50−2.39 (m, 2H), 2.25 (s, 3H), 2.30−2.09 (m, 2H), 1.62−1.43 (m, 2H), 1.36−1.27 (ddd, J = 1.7, 11.0, 13.8 Hz, 1H). Anal. ($C_{16}H_{20}F\ O_2N$) C, H, N.

The 2*β*,3*β*-substituted ester **5a** was obtained as a white solid (6.0 g, 34%).[33,54] R_f = 0.35 (EtOAc 20%, hexane 75%, Et_3N 5%). Mp 90.5−91.5 °C.^{1}H NMR: δ 7.24−7.19 (m, 2H), 6.95 (tt, 2H) 3.56−3.54 (m, 1H), 3.50 (s, 3H), 3.38−3.36 (m, 1H), 2.97 (dt, 1H, J = 12.7, 5.3 Hz), 2.86 (t, 1H, J = 3.9 Hz), 2.56 (td, 1H, J = 12.7, 2.9 Hz), 2.23 (s, 3H), 2.20−2.08 (m, 2H), 1.76−1.61 (m, 3H). Anal. ($C_{16}H_{20}F\ O_2N$) C, H, N.

(1*R*)-2*β*-Carboxymethoxy-3α-(3,4-dichlorophenyl)-8-methyl-8-azabicyclo[3.2.1]octane (4b) and (1*R*)-2*β*-Carboxymethoxy-3*β*-(3,4-dichlorophenyl)-8-methyl-8-azabicyclo[3.2.1]octane (5b). The procedure described above was followed to provide **4b** and **5b**. After column chromatography (2.5% EtOH/$CHCl_3$; Et_2O 22%, Et_3N 3%, hexanes 75%), compound **4b** was isolated as colorless crystals (1.15 g, 29%). Mp 89−91 °C. R_f = 0.64 (1% NH_4OH/EtOAc). ^{1}H NMR: δ 7.30 (d, 1H), 7.27 (d, 1H), 7.04 (dd, 1H), 3.59 (s, 3H), 3.2−3.47 (m, 3H), 2.35−2.5 (m, 2H), 2.05−2.3 (m, 2H), 1.4−1.6 (m, 2H), 2.23 (s, 3H), 1.28 (ddd, J = 1.6, 10.4, 14 Hz, 1H). Anal. ($C_{16}H_{19}O_2NCl_2\cdot0.1C_6H_{14}$) C, H, N.

Compound **5b** was isolated as a white solid (1.04 g, 26%) with physical data identical with those reported earlier.[33] Mp 82.5−83.5 °C. R_f = 0.43 (isopropylamine 3%, Et_2O 30%, pentane 67%). ^{1}H NMR: δ 7.07−7.32 (m, 3H), 3.55 (m, 1H), 3.52 (s, 3H), 3.33 (m, 1H), 2.92 (m, 1H), 2.86 (m, 1H), 2.50 (m, 1H), 2.21 (s, 3H), 2.0−2.1 (m, 2H), 1.6−1.7 (m, 3H). Anal. ($C_{16}H_{19}NO_2Cl_2$) C, H, N, Cl.

(1*R*)-2*β*-Carboxymethoxy-3α-(2-naphthyl)-8-methyl-8-azabicyclo[3.2.1]octane (4c) and (1*R*)-2*β*-Carboxymethoxy-3*β*-(2-naphthyl)-8-methyl-8-azabicyclo[3.2.1]octane (5c). The procedure described above was followed to provide **4c** and **5c** as white solids. **4c**: (18%). Mp 117−118 °C. R_f = 0.30 (EtOAc 20%, hexane 75%, Et_3N 5%). ^{1}H NMR: δ 7.80−7.74 (m, 3H), 7.66 (s, 1H), 7.47−7.38 (m, 2H), 7.36 (dd, 1H), 3.57 (s, 3H), 3.60−3.48 (m, 1H), 3.40 (d, 1H, d, J = 6.6 Hz), 3.32 (t, 1H, J = 7.3 Hz), 2.67 (dd, 1H, J = 9.5, 1.5 Hz), 2.53 (dt 1H, J = 13.7, 8.1 Hz), 2.28 (s, 3H), 2.31−2.05 (m, 2H), 1.69−1.49 (m, 3H). Anal. ($C_{20}H_{23}NO_2$) C, H, N. **5c**: (35%). Mp 94−95 °C. R_f = 0.30 (EtOAc 20%, hexane 75%, Et_3N 5%). ^{1}H NMR: δ 7.78−7.73 (m, 3H), 7.68 (s, 1H), 7.45−7.36 (m, 3H), 3.60 (dd, 1H, J = 6.6, 2.7 Hz), 3.47−3.41 (m, 1H), 3.44 (s, 3H), 3.17 (dt, 1H, J = 13.2, 5.0 Hz), 3.03 (t, 1H, J = 3.9 Hz), 2.73 (td, 1H, J = 12.4, 2.7 Hz), 2.29−2.11 (m, 2H), 2.26 (s, 3H), 1.84−1.75 (m, 2H), 1.71−1.60 (m, 1H). Anal. ($C_{20}H_{23}NO_2\cdot^1/_4H_2O$) C, H, N.

Formation of Weinreb Amides. (1*R*)-2*β*-Carboxylic Acid Methoxymethylamide-3α-(4-fluorophenyl)-8-methyl-8-azabicyclo[3.2.1]octane (7a). A solution of $Al(CH_3)_3$ (28 mL, 2 M in hexane) was added dropwise under N_2 at −10 °C to a solution of *N*,*O*-dimethylhydroxylamine hydrochloride ($HN(OCH_3)CH_3\cdot HCl$) (Weinreb salt) (5.50 g, 55.2 mmol) in CH_2Cl_2 (200 mL, anhydrous). The mixture was slowly warmed to room temperature and stirred for 15 min and then cooled to −10 °C. A solution of the 2*β*,3α-substituted ester **4a** (5.10 g, 18.4 mmol) in CH_2Cl_2 (150 mL, anhydrous) was slowly added. The reaction mixture was stirred at −10 °C for 1 h and allowed to warm to room temperature. TLC showed completion of the reaction. It was then quenched with hydrochloric acid (48 mL, 1 N), diluted with water (500 mL), and basified (saturated Na_2CO_3 and NH_4OH (concentrated) to pH 9). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to dryness to afford the crude product, which was purified by flash chromatography (EtOAc 30%, hexanes 65%, Et_3N 5%; EtOAc 60%, hexanes 35%, Et_3N 5%) to afford white crystals of **7a**, the 2*β*,3α-substituted Weinreb amide (5.42 g, 97%). Mp 142.0−142.5 °C. R_f = 0.36 (EtOAc 60%, hexanes 35%, Et_3N 5%). ^{1}H NMR: δ 7.20−7.15 (m, 2H), 6.92 (tt, 2H), 3.48−3.37 (m, 1H), 3.42 (s, 3H), 3.32−3.27 (m, 1H), 3.09 (d, 1H, J = 5.8 Hz), 3.06 (s, 3H), 2.70 (d, 1H, J = 11.0 Hz), 2.56−2.46 (m, 1H), 2.32−2.17 (m, 2H), 2.24 (s, 3H), 1.68−1.45 (m, 2H), 1.25 (t, 1H, J = 12.9 Hz).

(1*R*)-2*β*-Carboxylic Acid Methoxymethylamide-3α-(3,4-dichlorophenyl)-8-methyl-8-azabicyclo[3.2.1]octane (7b). The method described for **7a** above was followed to provide **7b** from **4b**. The product **7b** was obtained as white crystals (93%). R_f = 0.14 (hexanes 40%, EtOAc 55%, Et_3N 5%). ^{1}H NMR: δ 7.27 (d, 1H), 7.25 (d, 1H), 7.05 (dd, 1H), 3.48 (s, 3H), 3.34−3.46 (m, 1H), 3.22−3.32 (m, 1H), 3.08 (brs, 1H), 3.06 (s, 3H), 2.65 (brd, 1H), 2.42−2.54 (m, 1H), 2.21 (s, 3H), 2.1−2.34 (m, 2H), 1.63 (m, 1H), 1.48 (m, 1H), 1.19 (td, 1H).

2*β*-Carboxy-3*β*-(4-fluorophenyl)-8-methyl-8-azabicyclo-[3.2.1]octane (16a). 2*β*-Carbomethoxy-3*β*-(4-fluorophenyl)-tropane **5a** (WIN 35,428) (1.25 g, 4.54 mmol) was refluxed for 24 h in a 1:1 dioxane/water (80 mL) solution. The solvent was removed in vacuo, and the residue was almost completely dissolved in $CHCl_3$ (275 mL). Remaining undissolved solid was filtered off, toluene (30 mL) was added, and the volume of the solution was reduced in vacuo by approximately 75%. After the resulting white suspension was cooled in a freezer for 2 h, the precipitated white solid was isolated by filtration and was washed with cold 1:1 $CHCl_3$/toluene. The solid was pumped dry to yield the product **16a** as a white solid (1.11 g, 95%). ^{1}H NMR: δ 7.18−7.24 (m, 2H), 6.8 (m, 2H), 3.5−3.6 (m, 2H), 3.16 (ddd, J = 13.7 Hz, H-3), 2.62−2.68 (m, 1H), 2.57 (ddd, J = 13.7 Hz, H-3, 1H), 2.24−2.34 (m, 2H), 2.25 (m, 3H), 1.94 (dd, J = 9 Hz, 2H), 1.7−1.8 (m, 1H).

2β-Carboxy-3β-(3,4-dichlorophenyl)-8-methyl-8-azabicyclo[3.2.1]octane (16b). 2β-Carbomethoxy-3β-(3,4-dichlorophenyl)tropane **5b** (1.14 g, 3.47 mmol) was dissolved in THF/MeOH (1:1; 46 mL) to which was added a solution of $LiOH·H_2O$ (153 mg) in water (11 mL). The solution was heated to reflux for 24 h, cooled to 0 °C, and neutralized (pH 7) with concentrated HCl. Silica gel (1.75 g) was added directly to the solution, and solvent was removed in vacuo. The material was purified by flash chromatography (20% MeOH/$CHCl_3$ (900 mL); 30% MeOH/$CHCl_3$ (2 L)). Fractions containing the product were combined and evaporated in vacuo, and the residue was dried at high vacuum to provide the product **16b** (310 mg, 28%). $R_f = 0.08$ (30% MeOH/$CHCl_3$). ^{1}H NMR (CD_3OD): δ 7.48 (d, 1H), 7.41 (d, 1H), 7.25 (dd, 1H), 3.93 (m, 2H), 3.3−3.4 (m, 1H), 2.78 (s, 3H), 2.6−2.9 (m, 2H), 2.3−2.5 (m, 2H), 2.1−2.2 (m, 2H), 1.8−1.9 (m, 1H).

2β-Carboxylic Acid Methoxymethylamide-3β-(4-fluorophenyl)-8-methyl-8-azabicyclo[3.2.1]octane (17a). Oxalyl chloride (1 mL, 11.4 mmol) was added dropwise to a stirred suspension of the acid **16a** (1.1 g, 4.2 mmol) in anhydrous CH_2Cl_2 (80 mL) containing DMF (50 mL). The reaction mixture was stirred for 45 min, during which time the solution became yellow. The solvent was then removed in vacuo, and the residue was pumped at high vacuum overnight. CH_2Cl_2 (80 mL) was added to dissolve the acid chloride, and (MeO)MeNH·HCl (450 mg, dried over P_2O_5) followed immediately by pyridine (1.1 mL, distilled over CaH_2) was added to the solution. The reaction mixture was stirred for 1 h and partitioned between $CHCl_3$ (20 mL) and 2 M Na_2CO_3 (20 mL). The aqueous layer was extracted $CHCl_3$ (2 × 10 mL), and the combined organics were dried over Na_2SO_4, filtered, and reduced in vacuo to yield 1.09 g of a yellow solid. The crude product was dissolved in CH_2Cl_2 and purified by flash chromatography (hexanes 20%, EtOAc 75%, Et_3N 5%). Product-containing fractions were combined and concentrated to yield **17a** as a light-yellow solid (960 mg, 75%). Mp 120.1−122.5 °C. $R_f = 0.14$ (25% hexanes in EtOAc, 5% Et_3N). IR (KBr disk): 2900, 1680, 1500 cm^{-1}. ^{1}H NMR: δ 7.25 (m, 2H), 6.90 (m, 2H), 3.57 (s, 3H), 3.4 (m, 1H), 3.47 (m, 1H), 3.1 (m, 1H), 3.05 (s, 3H), 3.0 (m, 1H), 2.79 (ddd, 1H), 2.24 (m, 3H, NCH_3), 2.0−2.3 (m, 2H), 1.5−1.8 (m, 3H). Anal. ($C_{17}H_{23}N_2O_2F$) C, H, N.

2β-Carboxylic Acid Methoxymethylamide-3β-(3,4-dichlorophenyl)-8-methyl-8-azabicyclo[3.2.1]octane (17b). The procedure described above was followed to convert **16b** (300 mg, 9.55 mmol) to **17b** (39 mg, 11%). $R_f = 0.10$ (50% EtOAc in hexane, 5% Et_3N). ^{1}H NMR: δ 7.31 (d, 1H), 7.13 (dd, 1H), 7.30 (d, 1H), 3.62 (s, 3H), 3.5 (m, 1H), 3.38 (m, 1H), 3.13 (m, 1H), 3.04 (s, 3H), 2.93 (m, 1H), 2.72 (ddd, 1H), 2.21 (m, 3H), 2.0−2.3 (m, 2H), 1.5−1.74 (m, 3H).

2β-Carboxylic Acid Methoxymethylamide-3β-(3,4-dichlorophenyl)-8-methyl-8-azabicyclo[3.2.1]octane (17b). Alternative Route. To a solution of Weinreb salt (0.53 g, 5.28 mmol) in CH_2Cl_2 (anhydrous, 20 mL) was added a solution of $Al(CH_3)_3$ (2.7 mL, 2 M in hexane) dropwise at −10 °C under nitrogen. After the addition, the reaction mixture was slowly warmed to room temperature, stirred for 15 min, and then cooled back to −10 °C. A solution of **5b** (0.58 g, 1.6 mmol) in CH_2Cl_2 (15 mL) was added to the above mixture slowly. The reaction mixture was stirred at −10 °C for 0.5 h, slowly warmed to room temperature, and stirred for 24 h. The reaction was then quenched with potassium sodium tartrate tetrahydrate (Rochelle's salt) (saturated aqueous, 21 mL), diluted with CH_2Cl_2 (50 mL) and water (20 mL), and basified with NH_4OH to pH 9. The organic layer was separated, and the water layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to dryness to afford the crude product, which was purified by flash chromatography (EtOAc 30%, hexanes 65%, Et_3N 5%; EtOAc 60%, hexanes 35%, Et_3N 5%) to provide the Weinreb amide **17b** as a white solid (0.56 g, 88%). Mp 156−157 °C. $R_f = 0.29$ (EtOAc 75%, hexane 20%, Et_3N 5%). ^{1}H NMR: δ 7.31 (1H, d), 7.31 (1H, d), 7.13 (1H, dd), 3.63 (3H, s), 3.54−3.49 (1H, m), 3.41−3.37 (1H, m), 3.16−3.13 (1H, m), 3.05 (3H, s), 2.98−2.91 (1H, m), 2.73 (1H, td, $J = 12.3$, 2.7 Hz), 2.28−2.05 (2H, m), 2.22 (3H, s), 1.73−1.54 (3H, m).

Formation of Ethyl Ketones. (1*R*)-2β-(1-Propanoyl)-3α-(4-fluorophenyl)-8-methyl-8-azabicyclo[3.2.1]octane (8a). A solution of EtMgBr (24 mL, 3 M in Et_2O) was added dropwise at 0−5 °C under N_2 to a solution of the Weinreb amide **7a** (5.42 g, 17.7 mmol) in THF (500 mL, anhydrous). The reaction mixture was stirred for 15 min and then slowly warmed to room temperature and stirred for a further 4 h. The reaction was quenched with 3 N hydrochloric acid (24 mL), diluted with water (250 mL) and EtOAc (200 mL), and basified with (saturated aqueous Na_2CO_3) to pH 9. The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 250 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to dryness to afford the crude product, which was purified by gradient flash chromatography (EtOAc 10%, hexanes 88%, Et_3N 2%; EtOAc 20%, hexane 75%, Et_3N 5%) to yield **8a** as white crystals (3.48 g, 71%). $R_f = 0.39$ (EtOAc 20%, hexane 75%, Et_3N 5%). Mp 60.5−61.3 °C. ^{1}H NMR: δ 7.16−7.11 (m, 2H), 6.93 (tt, 2H), 3.32−3.23 (m, 2H, m), 3.15 (d, 1H, $J = 6.0$ Hz), 2.51−2.04 (m, 6H), 2.24 (s, 3H), 1.61−1.44 (m, 2H), 1.32−1.24 (m, 1H), 0.90 (t, 3H, $J = 7.3$ Hz). Anal. ($C_{17}H_{22}FON$) C, H, N.

(1*R*)-2β-(1-Propanoyl)-3α-(3,4-dichlorophenyl)-8-methyl-8-azabicyclo[3.2.1]octane (8b). The procedure described above for **8a** was utilized to convert **7b** (105 mg, 0.29 mmol) to **8b** (80 mg, 80%). $R_f = 0.28$ (30% EtOAc in hexanes; 5% Et_3N). Mp 97.4−98 °C. ^{1}H NMR: δ 7.29 (d, 1H), 7.24 (d, 1H), 7.10 (dd, 1H), 3.2−3.36 (m, 2H), 3.14 (brd 1H), 3.32−2.52 (m, 3H), 2.21 (s, 3H), 2.06−2.30 (m, 6H), 1.42−1.62 (m, 2H), 1.27 (ddd, 1H), 0.93 (t, $J = 7.4$ Hz, 3H). Anal. ($C_{17}H_{21}NOCl_2$) C, H, N.

2β-(1-Propanoyl)-3β-(4-fluorophenyl)-8-methyl-8-azabicyclo[3.2.1]octane (18a). The procedure described above for **8a** was utilized to convert **17a** (823 mg, 2.7 mmol) to **18a** (485 mg, 65%). $R_f = 0.3$ (20% EtOAc in hexanes, 5% Et_3N). Mp 118−119.5 °C. ^{1}H NMR: δ 7.17 (m, 2H), 6.69 (m, 2H), 3.48 (m, 1H), 3.36 (m, 1H), 2.9−3.0 (m, 2H), 2.5−2.6 (m, 1H), 2.23 (m, 3H), 2.0−2.4 (m, 3H), 1.5−1.8 (m, 4H), 0.85 (t, 3H), Anal. ($C_{17}H_{22}NOF$) C, H, N.

2β-(1-Propanoyl)-3β-(3,4-dichlorophenyl)-8-methyl-8-azabicyclo[3.2.1]octane (18b). The procedure described above for **8a** was utilized to convert **17b** (168 mg, 0.47 mmol) to **18b** (108 mg, 71%). $R_f = 0.22$ (EtOAc 10%, hexanes 85%, Et_3N 5%). Mp 83−84 °C. ^{1}H NMR: δ 7.30 (1H, d), 7.28 (1H, d), 7.08 (1H, dd), 3.54 (1H, d, $J = 4.1$ Hz), 3.36−3.35 (1H, m), 3.00 (1H, t, $J = 3.3$ Hz), 2.92−2.84 (1H, m), 2.55−2.39 (2H, m), 2.32−2.05 (2H, m), 2.20 (3H, s), 1.78−1.55 (4H, m), 0.90 (3H, t, $J = 7.3$ Hz). Anal. ($C_{17}H_{21}NOCl_2$) C, H, N.

2β-(1-Propanoyl)-3β-(4-fluorophenyl)-8-methyl-8-azabicyclo[3.2.1]oct-2-ene (21a). Triethylamine (dried over KOH, 2.5 mL) was added to a solution of **3a** (0.22 g, 0.81 mmol) in THF (5.6 mL). Ethylmagnesium bromide (3 M in Et_2O, 1.5 mL) was added dropwise to the above solution. The reaction mixture was stirred at 5−10 °C for 5 h, and the reaction was then quenched with 4 N HCl (4.5 mL). The reaction mixture was then diluted with water (12 mL) and adjusted to pH 8−9. The resulting mixture was extracted with CH_2Cl_2 (2 × 25 mL). The combined extracts were washed with water (15 mL), dried (K_2CO_3), filtered, and concentrated to dryness to afford a brown oil that was purified by column chromatography to provide **21a** as a yellow oil (0.104 g, 47%). $R_f = 0.28$ (EtOAc 60%, hexanes 35%, Et_3N 5%). ^{1}H NMR: δ 7.16−7.10 (2H, m), 7.03 (2H, tt), 3.74 (1H, d, $J = 5.5$ Hz), 3.37 (1H, t, $J = 5.6$ Hz), 2.76 (1H, dd, $J = 18.4$, 4.7 Hz), 2.42 (3H, s), 2.28−1.86 (6H, m), 1.67−1.59 (1H, m), 0.83 (3H, t, $J = 7.3$ Hz).

2β-(1-Propanoyl)-3β-(3,4-dichlorophenyl)-8-methyl-8-azabicyclo[3.2.1]oct-2-ene (21b). The procedure described above was utilized to convert **3b** to **21b** as a yellow oil (27%). $R_f = 0.3$ (EtOAc 60%, hexanes 35%, Et_3N 5%). ^{1}H NMR: δ 7.40 (1H, d), 7.26 (1H, d), 6.99 (1H, dd), 3.72 (1H, d, $J = 5.5$ Hz), 3.38 (1H, t, $J = 5.5$ Hz), 2.75 (1H, dd, $J = 18.4$, 4.9 Hz), 2.41(3H, s), 2.28−1.88 (6H, m), 1.66−1.59 (1H, m), 0.87 (3H, t, $J = 7.4$ Hz).

N-Demethylation. (1*R*)-2*β*-(1-Propanoyl)-3α-(4-fluorophenyl)-8-azabicyclo[3.2.1]octane (9a). Compound **8a** (1.83 g, 6.68 mmol) was suspended in 1-chloroethyl chloroformate (ACE-Cl; 26 mL, 240 mmol) under N_2 and was heated to reflux at 135 °C for 2 h. The excess ACE-Cl was evaporated, and CH_3OH (55 mL) was added to the residue. The reaction mixture was heated to reflux for 1 h and then concentrated to dryness. The residue was diluted with CH_2Cl_2 (300 mL), washed with $NaHCO_3$ (saturated), dried (Na_2SO_4), filtered, and concentrated to dryness to afford **9a**, which was purified by flash chromatography (EtOAc 75%, hexanes 20%, Et_3N 5%) to provide **9a** as a light-yellow solid (1.47 g, 84%). $R_f = 0.20$ (EtOAc 75%, hexane 20%, Et_3N 5%). Mp 46.6−47.4 °C. ^{1}H NMR: δ 7.16−7.10 (m, 2H), 6.95 (tt, 2H), 3.63 (t, 1H, $J = 7.4$ Hz), 3.45 (d, 1H, $J = 6.6$ Hz), 3.13−3.03 (m, 1H), 2.54 (d, 1H, $J = 10.7$ Hz), 2.41−2.22 (m, 2H), 2.11−1.86 (m, 3H), 1.74−1.54 (m, 3H), 1.33−1.24 (m, 1H), 0.87 (t, 3H, $J = 7.3$ Hz). Anal. ($C_{16}H_{20}FNO\cdot0.2H_2O$) C, H, N.

(1*R*)-2*β*-(1-Propanoyl)-3α-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane (9b). The procedure described for **9a** was followed to convert **8b** (80 mg, 2.45 mmol) to **9b** (77 mg, 100%). $R_f = 0.30$ (5% Et_3N/EtOAc). ^{1}H NMR: δ 0.91 (t, 3H), 1.25 (ddd, 1H), 1.52−1.74 (m, 2H), 1.8−2.56 (m, 7H), 3.06−3.2 (m, 1H), 3.45 (d, 1H), 3.62 (brt, 1H), 7.01 (dd, 1H), 7.25 (d, 1H), 7.31 (d, 1H).

2*β*-(1-Propanoyl)-3*β*-(4-fluorophenyl)-8-azabicyclo[3.2.1]-octane (19a). The procedure described above for **9a** was followed to convert **18a** (335 mg, 1.22 mmol) to **19a** (104 mg, 33%). $R_f = 0.36$ (10% Et_3N/EtOAc). ^{1}H NMR: δ 7.10 (m, 2H), 6.94 (m, 2H), 3.70 (m, 1H), 3.56 (m, 1H), 3.18 (m, 1H), 2.88 (m, 1H), 2.4 (m, 1H), 1.9−2.3 (m, 3H), 1.4−1.8 (m, 5H), 0.70 (t, 3H).

2*β*-(1-Propanoyl)-3*β*-(3,4-dichlorophenyl)-8-azabicyclo-[3.2.1]octane (19b). The procedure described above for **9a** was followed to convert **18b** (0.27 g, 0.84 mmol) to **19b** as a light-yellow solid (69 mg, 26%). $R_f = 0.12$ (EtOAc 75%, hexanes 20%, Et_3N 5%). ^{1}H NMR: δ 7.34 (1H, d), 7.26 (1H, d), 7.02 (1H, dd), 3.79−3.77 (1H, m), 3.67 (1H, d, $J = 5.5$ Hz), 3.47 (1H, s), 3.16 (1H, dt, $J = 12.9$, 5.2 Hz), 2.95 (1H, d, $J = 5.5$ Hz), 2.47−1.97 (4H, m), 1.84−1.55 (4H, m), 0.77 (3H, t, $J = 7.3$ Hz).

2-(1-Propanoyl)-3-(4-fluorophenyl)-8-azabicyclo[3.2.1]-oct-2-ene (22a). The procedure described above for **9a** was followed to convert **21a** to obtain **22a** as a yellow oil (66%). $R_f = 0.30$ (EtOAc 90%, MeOH 6%, Et_3N 4%). ^{1}H NMR: δ 7.13−6.99(4H, m), 4.12 (1H, d, $J = 5.2$ Hz), 3.82 (1H, t, $J = 5.9$ Hz), 2.80 (1H, dd, $J = 18.3$, 3.4 Hz), 2.20 (1H, dd, $J = 18.3$, 1.0 Hz), 2.12−1.84 (6H, m), 1.72−1.63 (1H, m), 0.83 (3H, t, $J = 7.2$ Hz).

2-(1-Propanoyl)-3-(3,4-dichlorophenyl)-8-azabicyclo-[3.2.1]oct-2-ene (22b). The procedure described above for **9a** was followed to convert **21b** (106 mg, 0.325 mmol) to obtain **22b** (83 mg, 0.266 mmol) as a yellow oil (82%). $R_f = 0.15$ (EtOAc 75%, hexane 20%, Et_3N 5%). ^{1}H NMR: δ 7.40 (1H, d), 7.23 (1H, d), 6.96 (1H, dd), 4.10 (1H, d, $J = 5.5$ Hz), 3.82 (1H, t, $J = 5.8$ Hz), 2.79 (1H, dd, $J = 18.4$, 4.9 Hz), 2.20−1.89 (7H, m), 1.72−1.63 (1H, m), 0.87 (3H, t, $J = 7.4$ Hz).

(1*R*)-2-Methoxycarbonyl-3-(4-fluorophenyl)-8-azabicyclo[3.2.1]oct-2-ene (23a). The procedure described above for **9a** was followed to convert **8a** (362 mg, 1.3 mmol) to obtain **23a** as a yellow solid (234 mg, 68%). $R_f = 0.70$ (10% MeOH in hexanes, 0.5% NH_4OH). Mp 67−68 °C. ^{1}H NMR: δ 6.8−7.2 (m, 4H), 4.2 (m, 1H), 3.8 (m, 1H), 1.50−3.0 (m, 6H). Anal. ($C_{15}H_{16}NO_2F$) C, H, N.

(1*R*)-2-Methoxycarbonyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]oct-2-ene (23b). The procedure described for **9a** was followed to convert **3b** (200 mg, 0.61 mmol) to **23b** as a yellow oil. $R_f = 0.30$ (10% Et_3N in EtOAc). ^{1}H NMR: δ 7.40 (d, 1H), 7.2 (dd, 1H), 6.9 (dd, 1H), 4.2 (m, 1H), 3.8 (m, 1H), 3.53 (s, 3H), 2.5−2.9 (m, 1H), 1.50−2.3 (m, 5H). Anal. ($C_{15}H_{16}NO_2Cl_2$) C, H, N.

Attachment of MAMA′ Synthon. *N*-[2-(3′-*N*′-Propyl-(1″*R*)-3″α-(4-fluorophenyl)tropane-2″*β*-(1-propanoyl))((2-((triphenylmethyl)thio)ethyl)amino)acetyl]-*S*-(triphenyl)-2-aminoethanethiol (11a). A suspension of **9a** (0.45 g, 1.72 mmol), **10** (1.65 g, 2.18 mmol), KI (0.36 g, 2.18 mmol), and K_2CO_3 (1.2 g, 8.6 mmol) in anhydrous CH_3CN (80 mL) was heated to reflux under N_2 for 20 h. The reaction mixture was cooled to room temperature and filtered through Celite. The Celite pad was washed with CH_3CN (3 × 20 mL). The organic layers were combined and concentrated to dryness, and the crude product was purified by flash chromatography (EtOAc 40%, hexanes 55%, Et_3N 5%) to yield **11a** as a foam (1.01 g, 60%). $R_f = 0.37$ (EtOAc 40%, hexanes 55%, Et_3N 5%). Mp 55 °C (dec). ^{1}H NMR: δ 7.51 (t, 1H), 7.40−7.36 (m, 11H), 7.25−7.09 (m, 20H), 6.93 (t, 2H), 3.28−3.19 (m, 2H), 3.14 (d, 1H, $J = 6.3$ Hz), 3.04−2.97 (m, 2H), 2.85 (s, 2H), 2.51−1.89 (m, 16H), 1.53−1.16 (m, 6H), 0.86 (t, 3H, $J = 7.3$ Hz). Anal. ($C_{63}H_{66}FN_3O_2S_2$) C, H, N.

***N*-[2-(3′-*N*′-Propyl-(1″*R*)-3″α-(3,4-dichlorophenyl)tropane-2″*β*-(1-propanoyl))((2-((triphenylmethyl)thio)ethyl)amino)acetyl]-*S*-(triphenyl)-2-aminoethanethiol (11b).** The procedure described above for **11a** was followed to convert **9b** (94.5 mg, 0.303 mmol) to **11b** obtained as a fluffy white solid (158 mg, 51%). $R_f = 0.30$ (EtOAc/hexanes 3:2). Mp 60 °C (dec). ^{1}H NMR: δ 6.9−7.6 (m, 34H), 2.6−3.4 (m, 6H), 1.8−2.5 (m, 14H), 1.0−1.7 (m, 8H), 0.89 (t, 3H). Anal. ($C_{63}H_{65}Cl_2N_3O_2S_2$) C, H, N.

***N*-[2-(3′-*N*′-Propyl-(1″*R*)-3″*β*-(4-fluorophenyl)tropane-2″*β*-(1-propanoyl))((2-((triphenylmethyl)thio)ethyl)amino)acetyl]-*S*-(triphenyl)-2-aminoethanethiol (20a).** The procedure described above for **11a** was followed to convert **19a** (27 mg, 0.09 mmol) to **20a** as a foam (47 mg, 46%). $R_f = 0.09$ (60% EtOAc in hexanes, 1% Et_3N). ^{1}H NMR: δ 7.1−7.6 (m, 32H), 6.9−7.0 (m, 2H), 3.3−3.5 (m, 2H), 1.2−3.1 (m, 29H), 0.77 (t, 3H). Anal. ($C_{63}H_{66}FN_3O_2S_2\cdot{}^2/_3CHCl_3$) C, H, N.

***N*-[2-(3′-*N*′-Propyl-(1″*R*)-3″*β*-(3,4-dichlorophenyl)tropane-2″*β*-(1-propanoyl))((2-((triphenylmethyl)thio)ethyl)amino)acetyl]-*S*-(triphenyl)-2-aminoethanethiol (20b).** The procedure described above for **11a** was followed to convert **19b** (30 mg, 0.096 mmol) to yield the title compound **20b** as a foam (41 mg, 41%). $R_f = 0.14$ (60% EtOAc in hexanes, 1% Et_3N). ^{1}H NMR: δ 7.0−7.6 (m, 34H), 3.52 (m, 1H), 3.34 (m, 1H), 1.2−3.1 (m, 29H), 0.81 (t, 3H).

***N*-[2-(3′-*N*′-Propyl-(1″*R*)-3″-(4-fluorophenyl)trop-2-ene-2″-(1-propanoyl))((2-((triphenylmethyl)thio)ethyl)amino)-acetyl]-*S*-(triphenyl)-2-aminoethanethiol (24a).** The procedure described above for **11a** was followed to convert **22a** (63 mg, 0.24 mmol) to **24a** (132 mg, 0.135 mmol) as a white solid (56%). $R_f = 0.38$ (EtOAc 60%, hexanes 35%, Et_3N 5%). ^{1}H NMR: δ 7.49 (t, 1H), 7.39−7.34 (m, 13H), 7.26−7.14 (m, 16H), 7.10−7.05 (m, 2H), 6.99 (t, 2H, $J = 8.6$ Hz), 3.75 (d, 1H, $J = 5.5$ Hz), 3.34 (t, 1H, $J = 5.8$ Hz), 3.00 (q, 2H, $J = 6.4$ Hz), 2.86 (2H, s), 2.57 (dd, 1H, $J = 18.4$, 4.7 Hz), 2.43−2.32 (m, 9H), 2.25 (t, 2H, $J = 6.3$ Hz), 2.12−1.78 (m, 7H), 1.61−1.50 (m, 2H), 0.81 (t, 3H, $J = 7.3$ Hz). IR (film): 3339 (br, m), 3057 (m), 2936 (s), 1672 (vs), 1599 (m), 1508 (vs), 1491 (s), 1444 (s), 1358 (m), 1225 (m), 1185 (m), 1158 (m), 1034 (m), 911 (m), 847 (w) cm^{-1}. Anal. ($C_{63}H_{64}FN_3O_2S_2\cdot{}^1/_2H_2O$) C, H, N.

***N*-[2-(3′-*N*′-Propyl-(1″*R*)-3″-(3,4-dichlorophenyl)trop-2-ene-2″-(1-propanoyl))((2-((triphenylmethyl)thio)ethyl)-amino)acetyl]-*S*-(triphenyl)-2-aminoethanethiol (24b).** The procedure described above for **11a** was followed to convert **22b** (44 mg, 0.14 mmol) to **24b** (112 mg, 0.109 mmol), which was isolated as a light-yellow solid (76%). $R_f = 0.43$ (EtOAc 60%, hexanes 35%, Et_3N 5%). ^{1}H NMR: δ 7.50 (t, 1H), 7.38−7.33 (m, 13H), 7.26−7.14 (m, 18H), 6.92 (dd, 1H), 3.72 (d, 1H, $J = 5.2$ Hz), 3.36−3.32 (m, 1H), 3.00 (q, 2H, $J = 6.6$ Hz), 2.86 (s, 2H), 2.58−2.32 (m, 8H), 2.26 (t, 2H, $J = 6.3$ Hz), 2.10−1.95 (m, 4H), 1.86−1.78 (m, 2H), 1.57 (m, 5H), 0.86 (t, 3H, $J = 7.3$ Hz). IR (film): 3341 (br, m), 3055 (w), 2937 (m), 1673 (s), 1514 (m), 1491 (m), 1467 (m), 1444 (s), 1357 (w), 1184 (w), 1135 (w), 1031 (m), 911 (m) cm^{-1}. Anal. ($C_{63}H_{63}Cl_2N_3O_2S_2\cdot{}^2/_3H_2O$) C, H, N.

***N*-[2-(3′-*N*′-Propyl-(1″*R*)-3″-(4-fluorophenyl)trop-2-ene-2″-(methoxycarbonyl))((2-((triphenylmethyl)thio)ethyl)-amino)acetyl]-*S*-(triphenyl)-2-aminoethanethiol (25a).** The procedure described above for **11a** was followed to convert **23a** (134 mg, 0.50 mmol) to **25a** as a light-yellow foam (148

mg, 29%). R_f = 0.18 (10% Et_3N in hexane). ^1H NMR: δ 6.8−7.8 (m, 34H), 3.8−3.9 (m, 1H), 3.5 (s, 3H), 3.2−3.4 (m, 1H), 1.3−3.15 (m, 22H).

***N*-[2-(3′-*N*′-Propyl-(1″*R*)-3″-(3,4-dichlorophenyl)trop-2-ene-2″-(methoxycarbonyl))((2-((triphenylmethyl)thio)-ethyl)amino)acetyl]-*S*-(triphenyl)-2-aminoethanethiol (25b).** The procedure described above for **11a** was followed to convert **23b** (107 mg, 0.34 mmol) to **25b** as a foam (111 mg, 31%). R_f = 0.18 (5% Et_3N in hexane). ^1H NMR: δ 6.8−7.6 (m, 33H), 3.8−3.9 (m, 1H), 3.5 (s, 3H), 3.2−3.4 (m, 1H), 1.4−3.2 (m, 22H),

Insertion of Rhenium. *N*-[(2-((3′-*N*′-Propyl-(1″*R*)-3″α-(4-fluorophenyl)tropane-2″*β*-1-propanoyl)(2-mercapto-ethyl)amino)acetyl)-2-aminoethanethiolato]rhenium(V) Oxide (12a: O-1505). A solution of **11a** (1.00 g, 1.02 mmol) in EtOH (50 mL) was brought to reflux under N_2. A solution of $SnCl_2$ (0.26 g, 1.33 mmol, in 6.3 mL of 0.05 N HCl) was added to the above solution and followed immediately by the addition of $NaReO_4$ (0.36 g, 1.33 mmol, in 6.3 mL of 0.05 N HCl). The reaction mixture was maintained at reflux for 26 h. It was then diluted with CH_3CN (50 mL) and filtered through Celite. The Celite was washed with hot CH_3CN (3 × 25 mL). The combined organic washes were concentrated to dryness to afford the crude Re complex **12a** (1.48 g). Gradient flash chromatography (EtOAc 40%, hexanes 56%, Et_3N 4%; EtOAc 75%, hexane 20%, Et_3N 5%; EtOAc 90%, hexanes 6%, Et_3N 4%) provided a 1:1 mixture of diastereoisomers of **12a** as a pink solid (0.34 g, 47%). R_f = 0.24 (EtOAc 75%, hexane 20%, Et_3N 5%). Mp 104 °C (dec). Anal. ($C_{25}H_{35}FN_3O_3ReS_2 \cdot {}^1/_2$-EtOAc) C, H, N.

Separation of the diastereoisomers of the Re Complex 12a. A mixture of the Re diastereoisomers **12a** (0.4 g) was separated by gravity chromatography. The silica gel was pretreated with 1% NH_4OH/EtOAc. After the column was packed, 80% EtOAc/hexane was used to wash away the excess base. The **12a** to silica gel ratio was 1:500−650. The eluent was 80% EtOAc/hexane; EtOAc. The two isomers were obtained: **12a-2** (110 mg, 27%), mp 191.5−192.8 °C, and **12a-1** (30 mg, 7.5%), mp 96 °C (dec).

(1*R*,12*R*)-*N*-[(2-((3′-*N*′-propyl-3″α-(4-fluorophenyl)tropane-2″*β*-propionyl)(2-mercaptoethyl)amino)acetyl)-2-aminoethanethiolato]rhenium(V) Oxide (12a-1: O-2020). HRMS (FAB) [M + H]: calcd 696.1740; found 696.1751. ^1H NMR: δ 7.15−7.10 (m, 2H), 6.97 (t, 2H, J = 8.7 Hz), 4.74 (d, 1H, J = 16.5 Hz), 4.57 (m, 1H), 4.20−4.05 (m, 2H), 4.08 (d, 1H, J = 16.5 Hz), 3.78−3.67 (m, 2H), 3.43 (dd, 1H, J = 12.1, 3.0 Hz), 3.34−3.07 (m, 5H), 2.96 (dd, 1H, J = 13.5, 4.1 Hz), 2.52−2.78 (m, 3H), 2.32−1.40 (m, 10H), 1.34−1.20 (m, 1H), 0.82 (t, 3H, J = 7.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 213.3, 187.4, 163.1, 159.9, 139.4, 139.4, 129.3, 129.2, 115.5, 115.2, 66.7, 65.6, 63.6, 62.5, 59.7, 59.7, 59.0, 50.1, 47.7, 40.2, 39.3, 37.5, 36.9, 30.5, 29.5, 24.2, 7.5.

(1*R*,12*S*)-*N*-[(2-((3′-*N*′-Propyl-3″α-(4-fluorophenyl)tropane-2″*β*-propionyl)(2-mercaptoethyl)amino)acetyl)-2-aminoethanethiolato]rhenium(V) Oxide (12a-2: O-1972). HRMS (FAB) [M + H]: calcd 696.1740; found 696.1768. ^1H NMR: δ 7.14−7.10 (m, 2H), 6.95 (t, 2H, J = 8.5 Hz), 5.14 (d, 1H, J = 16.5 Hz), 4.61 (m, 1H), 4.16−3.93 (m, 3H), 4.13 (d, 1H, J = 16.5 Hz), 3.43 (td, 1H, J = 13.3, 3.6 Hz), 3.34−3.08 (m, 6H), 2.87 (dd, 1H, J = 13.3, 4.3 Hz), 2.53−1.80 (m, 10H), 1.70−1.49 (m, 3H), 1.29−1.20 (m, 1H), 0.84 (t, 3H, J = 7.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.3, 187.7, 163.1, 159.9, 139.4, 139.4, 129.3, 129.2, 115.5, 115.2, 67.0, 64.6, 63.5, 62.28, 59.9, 59.3, 58.9, 49.8, 47.5, 40.2, 38.8, 37.3, 36.9, 30.5, 29.5, 23.4, 7.5.

Single-Crystal X-ray Analysis of Diastereoisomer 12a-2. Orthorhombic crystals of **12a-2** were obtained by slow growth at the interface of $CHCl_3$/anhydrous ethanol maintained at room temperature. A representative crystal was selected and a 1.451 78 Å data set was collected at room temperature. Pertinent crystal data collection and refinement parameters are as follows: crystal size, 0.40 mm × 0.38 mm × 0.14 mm; cell dimensions, a = 7.4147(5) Å, b = 15.9123(11) Å, c = 22.2645(14) Å, α = 90°, β = 90°, γ = 90°; formula, $C_{24}H_{33}FN_3O_4ReS_2$; formula weight = 696.85; volume = 2626.9(3) Å^3; calculated density = 1.762 g cm^{-3}; space group = $P2_12_12_1$; number of reflections = 2723 of which 2512 were considered independent (R_{int} = 0.0232). Refinement method was full-matrix least-squares on F^2. The final R indices were [$I > 2\sigma(I)$] R1 = 0.0322, wR2 = 0.0836. Coordinates, anisotropic temperature factors, distances, and angles are available as Supporting Information.

***N*-[(2-((3′-*N*′-Propyl-(1″*R*)-3″α-(3,4-dichlorophenyl)tropane-2″*β*-1-propanoyl)(2-mercaptoethyl)amino)acetyl)-2-aminoethanethiolato]rhenium(V) Oxide (12b: O-1561).** The procedure described above for the preparation of **12a** was followed to convert **11b** (24 mg, 0.024 mmol) to the solid **12b** (4.6 mg, 27%). ^1H NMR: δ 7.34 (d, 1H), 7.3 (d, 1H), 7.0 (dd, 1H), 4.70, 5.06 (2d, J = 16.7 Hz), 4.4−4.65 (m, 1H), 3.9−4.2 (m, 3H), 3.6−3.8 (m, 1H), 3.0−3.5 (m, 7H), 2.8−3.0 (m, 1H), 1.1−2.5 (m, 14H), 0.8−1.0 (2t, 3H). Anal. ($C_{25}H_{34}Cl_2N_3O_3ReS_2 \cdot {}^1/_5C_6H_{14}$) C, H, N.

Alternative Route to 12b. To a solution of **9b** (20 mg, 0.064 mmol) in anhydrous CH_3CN (3 mL) was added the rhenium chelate of **10** [9] (30 mg, 0.064 mmol, 1 equiv), KI (10.6 mg, 0.064 mol, 1.0 equiv), and K_2CO_3 (10.6 mg, 0.064 mmol). The resulting mixture was brought to reflux for 30 h and then loaded onto SiO_2 (1 g) and evaporated to dryness. The silica-adsorbed material was purified by column chromatography (10% Et_3N/EtOAC) to yield **12b** as a maroon solid (26 mg, 55%).

***N*-[(2-((3′-*N*′-Propyl-(1″*R*)-3″*β*-(4-fluorophenyl)tropane-2″*β*-1-propanoyl)(2-mercaptoethyl)amino)acetyl)-2-aminoethanethiolato]rhenium(V) Oxide (13a:O-1508).** The procedure described above for **12a** was followed to convert **20a** to **13a** as a maroon foam (6.7 mg, 44%). R_f = 0.07 (60% EtOAc in hexanes, NH_4OH 0.5%). HRMS (FAB) ($C_{25}H_{35}FN_3O_3ReS_2$): calcd 695.172; found 695.162. ^1H NMR: δ 7.14 (m, 2H), 6.93 (m, 2H), 4.87 (d, 0.5H, J = 16.5 Hz), 4.73 (d, 0.5H, J = 16.5 Hz), 4.5−4.6 (m, 1H), 1.4−4.1 (m, 26H), 0.7−0.9 (2t, 2H).

***N*-[(2-((3′-*N*′-Propyl-(1″*R*)-3″*β*-(3,4-dichlorophenyl)tropane-2″*β*-1-propanoyl)(2-mercaptoethyl)amino)acetyl)-2-aminoethanethiolato]rhenium(V) Oxide (13b: O-2131).** The procedure described above for **12a** was followed to provide **13b** as a maroon solid (71%). Mp 131 °C (dec). R_f = 0.35 (EtOAc 75%, hexanes 20%, Et_3N 5%). HRMS [M + H]$^+$: calcd 746.1054; found 746.1027. ^1H NMR: δ 7.33−7.27 (m, 2H), 7.10−7.05 (m, 1H), 4.79 (d, 0.5H, J = 16.5 Hz), 4.71 (d, 0.5H, J = 16.8 Hz), 4.60−4.52 (m, 1H), 4.13−3.97 (m, 2H), 3.90−3.35 (m, 5H), 3.31−3.14 (m, 3H), 3.02 (s, 1H), 2.91−2.83 (m, 2H), 2.62−2.32 (m, 3H), 2.22−2.05 (m, 4H), 1.84−1.66 (m, 6H), 0.90 (t, 1.5H, J = 7.4 Hz), 0.84 (t, 1.5H, J = 7.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.1, 187.2, 143.4, 143.4, 131.9, 129.9, 129.6, 129.3, 129.2, 126.6, 126.5, 66.7, 66.7, 65.8, 64.9, 63.8, 62.1, 61.8, 60.4, 60.4, 59.7, 59.7, 58.5, 58.5, 51.2, 51.0, 47.6, 39.1, 38.8, 35.5, 35.4, 34.1, 34.0, 33.9, 27.1, 27.0, 25.4, 24.4, 24.2, 7.8. IR (film): 2939 (s), 1713 (s), 1660 (vs), 1474 (s), 1351 (s), 1311 (s), 1028 (w), 968 (vs), 910 (s), 731 (vs). Anal. ($C_{25}H_{34}Cl_2N_3O_3ReS_2 \cdot 0.2C_6H_{14}$) C, H, N.

***N*-[(2-((3′-*N*′-Propyl-(1″*R*)-3″-(4-fluorophenyl)trop-2″-ene-2″-1-propanoyl)(2-mercaptoethyl)amino)acetyl)-2-aminoethanethiolato]rhenium(V) Oxide (14a: O-1768).** The procedure described above for **12a** was followed to provide **14a** as a red-brown foam (52%). R_f = 0.29 (EtOAc 95%, Et_3N 5%). ^1H NMR: δ 7.14−7.02 (m, 4H), 4.73 (d, 0.5H, J = 16.2 Hz), 4.69 (d, 0.5H, J = 16.2 Hz), 4.62−4.56 (m, 1H), 4.19−4.01 (m, 3H), 3.88 (d, 1H, J = 5.8 Hz), 3.74−3.62 (m, 1H), 3.52−3.13 (m, 5H), 2.89 (dd, 0.5H, J = 13.2, 4.7 Hz), 2.87 (dd, 0.5H, J = 13.1, 5.1 Hz), 2.64−2.58 (m, 3H), 2.27−1.58 (m, 9H), 1.25−1.12 (m, 1H), 0.84 (t, 3H, J = 7.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.9, 187.2, 141.1, 140.9, 137.4, 137.1, 136.0, 129.2, 129.1, 115.8, 115.6, 66.9, 64.2, 64.1, 62.2, 59.8, 58.2, 57.9, 56.5, 47.8, 45.1, 38.8, 36.6, 35.6, 34.1, 34.1, 30.3, 22.9, 22.8, 8.5. IR (film): 2937 (m), 1661 (s), 1508 (m), 1461 (w), 1350 (m), 1313 (m), 1223 (m), 967 (s), 730 (m) cm^{-1} . HRMS (FAB) [M + H] ($C_{25}H_{33}FN_3O_3ReS_2$ (Na): calcd 716.1404; found 716.1405.

***N*-[(2-((3′-*N*′-Propyl-(1″*R*)-3″-(3,4-dichlorophenyl)trop-2″-ene-2″-1-propanoyl)(2-mercaptoethyl)amino)acetyl)-**

2-aminoethanethiolato]rhenium(V) Oxide (14b: O-1769). The procedure described above for **12a** was followed to provide **14b** as a brown foam (51%). $R_f = 0.27$ (EtOAc 95%, Et_3N 5%). ^1H NMR: δ 7.42 (d, 1H, $J = 8.3$ Hz), 7.25 (d, 1H, $J = 2.0$ Hz), 6.98 (dd, 0.5H, $J = 8.3$, 2.0 Hz), 6.97 (dd, 0.5H, $J = 8.3$, 2.0 Hz), 4.73 (d, 0.5H, $J = 16.5$ Hz), 4.69 (d, 0.5H, $J = 16.5$ Hz), 4.62−4.56 (m, 1H), 4.17−3.99 (m, 3H), 3.85 (d, 1H, $J = 5.8$ Hz), 3.75−3.59 (m, 1H), 3.49−3.13 (m, 5H), 2.89 (dd, 0.5H, $J = 13.3$, 4.5 Hz), 2.88 (dd, 0.5H, $J = 13.3$, 4.5 Hz), 2.63−2.55 (m, 3H), 2.30−1.96 (m, 7H), 1.88 (t, 1H, $J = 10.4$ Hz), 1.69−1.62 (m, 1H), 1.25−1.10 (m, 1H), 0.88 (t, 3H, $J = 7.3$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.3, 187.2, 142.2, 139.8, 135.5, 133.0, 132.6, 130.6, 129.2, 126.8, 66.9, 64.3, 64.1, 62.1, 59.8, 58.4, 58.1, 56.4, 47.8, 45.1, 38.8, 36.7, 35.2, 34.0, 30.3, 22.9, 22.8, 8.4. IR (film): 2937 (m), 1660 (s), 1468 (m), 1350 (m), 1313 (m), 967 (s), 731 (m) cm^{-1}. HRMS (FAB) [M + H] ($C_{25}H_{32}Cl_2N_3O_3ReS_2$ (Na): calcd 766.0718; found 766.0720.

***N*-[(2-((3′-*N*′-Propyl-(1″*R*)-3″*b*-(4-fluorophenyl)trop-2″-ene-2″-carbomethoxy)(2-mercaptoethyl)amino)acetyl)-2-aminoethanethiolato]rhenium(V) Oxide (15a:O-1135).** The procedure described above for **12a** was followed to provide **15a** as a foam (34 mg, 37%). $R_f = 0.09$ (10% Et_3N in EtOAc). ^1H NMR: δ 6.9−7.2 (m, 4H), 4.5−4.9 (m, 2H), 3.5 (s, 3H), 1.4−4.3 (m, 23H). HRMS (FAB) [M + H]: calcd 696.1348; found 696.1405. Anal. ($C_{24}H_{31}FN_3O_4S_2Re$) C, H, N.

***N*-[(2-((3′-*N*′-Propyl-(1″*R*)-3″-(3,4-dichlorophenyl)trop-2″-ene-2″-carbomethoxy)(2-mercaptoethyl)amino)acetyl)-2-aminoethanethiolato]rhenium(V) Oxide (15b: O-1136).** The procedure described above for **12a** was followed to provide **15b** as a tan foam (56 mg, 78%). $R_f = 0.09$ (10% Et_3N in EtOAc). ^1H NMR: δ 7.4 (d, 1H), 7.2 (d, 1H), 6.95 (dd, 1H), 4.4−4.9 (m, 2H), 3.55 (s, 3H), 1.4−4.2 (m, 23H). HRMS(FAB): calcd 746.0663; found 746.0689. Anal. ($C_{24}H_{30}Cl_2N_3O_4S_2Re$) C, H, N.

^{99m}Tc Labeling. Compounds **12a**,**b**, **13a**,**b**, **17a**, **26a**−**c**, **27a**−**c** were prepared by identical methods.

Deprotection. Twenty microliter aliquots of Et_3N, CH_2CI_2, and $(C_2H_5)_3Si$ were added to 5.0 mg of each trityl-protected precursor to cleave the thiol protecting group. After a 20 min incubation, 200 μL of 1.0 M HCl/ether was added to protonate the thiols. The solvent was evaporated, followed by successive washes with hexanes for removal. The deprotected compound was then dissolved in DMSO to produce a stock solution at a concentration of 1 mg/mL.

Radiolabeling. Approximately 200 mCi of sodium ^{99m}Tc pertechnetate was added to a Glucoheptonate kit (Dupont Pharmaceuticals, Billerica, MA) and allowed to incubate at room temperature for 15 min. The 150 mCi of the resulting ^{99m}Tc-Glucoheptonate was added to an equal volume of 50 mM acetate buffer, pH 5.2 (approximately 2 mL) and 50 μL of deprotected precursor stock solution (1 mg/mL in DMSO, 50 μg). This solution was incubated at room temperature for 20 min. The course of the radiolabeling was monitored with a Rainin HPLC system using a reverse-phase Vydac C8 column (4.6 mm × 250 mm, 5 μm). The column was eluted with a 0.1 M ammonium acetate/acetonitrile mobile phase at 1.5 mL/min flow rate and with a gradient of 5−100% acetonitrile over 15 min. Radioactive detection was achieved with a Frisk-Tech rate meter (Bicron Corp.). The final radiolabeled product was purified using a C18 Sep-Pak (Waters Inc.) eluted with ethanol. Labeling yields and radiochemical purities were greater than 85% and 98%, respectively. Each product was diluted with sterile saline to yield a <10% ethanol solution followed by filtration through a 0.22 μm filter prior to injection.

SPECT Imaging. SPECT images were acquired with a MultiSPECT 2 γ camera (Siemens, Hoffman Estates, IL) equipped with fan-beam collimators and peaked to the 140 keV photopeak of ^{99m}Tc (15% window). This camera has an intrinsic resolution of 4.6 mm (fwhm) and a sensitivity of ∼240 cps/mCi. Images were acquired over 360° (60 projections/head, 128 × 128 matrix) in the continuous mode. Image reconstruction was performed using a conventional filtered back-projection algorithm to an in-plane resolution of 10 mm fwhm and attenuation correction via the Chang method.

Rhesus monkeys weighing approximately 7 kg were anesthetized with ketamine/xylazine (15.0 and 1.5 mg/kg) and positioned prone on the imaging bed of the SPECT camera. Before the start of imaging, a venous catheter was inserted in a peripheral vein for radiopharmaceutical administration. The heads of the animals were immobilized with a custom-fabricated head holder. Approximately 20−25 mCi of ^{99m}Tc labeled compound was injected intravenously over 60 s. Dynamic SPECT imaging was initiated at the end of the infusion and consisted of 2 min acquisitions during the first hour and 5 min acquisitions thereafter.

Biology. Animals used in this study were maintained in accordance with the guidelines of the Committee on Animals of the Harvard Medical School and of the "Guide for Care and Use of Laboratory Animals" of the Institute of Laboratory Animal Resources, National Research Council, Department of Health, Education and Welfare, Publication No. (NIH)85-23, revised 1985.

Tissue Sources and Preparation. Brain tissue from adult male and female cynomolgus monkeys (*Macaca fascicularis*) was stored at −85 °C in the primate brain bank at the New England Regional Primate Research Center. The caudate-putamen was dissected from coronal slices and yielded 1.4 ± 0.4 g of tissue. Membranes were prepared as described previously. Briefly, the caudate-putamen was homogenized in 10 volumes (w/v) of ice-cold Tris-HCl buffer (50 mM, pH 7.4 at 4 °C) and centrifuged at 3800*g* for 20 min in the cold. The resulting pellet was suspended in 40 volumes of buffer, and the entire was procedure was repeated twice. The membrane suspension (25 mg original wet weight of tissue/mL) was diluted to 12 mL/mL for [^{3}H]WIN 35,428 or [^{3}H]citalopram assay in buffer just before assay and was dispersed with a Brinkmann Polytron homogenizer (setting 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 dopamine transporter was labeled with [^{3}H]WIN35,428 ([^{3}H]CFT, 2β-carbomethoxy-3β-(4-fluorophenyl)-*N*-[^{3}H]methyltropane, 81−84 Ci/mmol, DuPont-NEN). The affinity of [^{3}H]WIN35,428 for the dopamine transporter was determined in experiments by incubating tissue with a fixed concentration of [^{3}H]WIN35,428 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: WIN 35,428, 0.2 mL (1 pM to 100 or 300 nM), [^{3}H]WIN 35,428 (0.3 nM); membrane preparation, 0.2 mL (4 mg original wet weight of tissue/mL). The 2 h incubation (0−4 °C) was initiated by addition of membranes and terminated by rapid filtration over Whatman GF/B glass fiber filters presoaked in 0.1% bovine serum albumin (Sigma Chem. Co.). The filters were washed twice with 5 mL of Tris-HCl buffer (50 mM), incubated overnight at 0−4 °C in scintillation fluor (Beckman Ready-Value, 5 mL), and radioactivity was measured by liquid scintillation spectrometry (Beckman 1801). The cpm values were converted to dpm following determination of counting efficiency (> 45%) of each vial by external standardization. Total binding was defined as [^{3}H]WIN 35,428 bound in the presence of ineffective concentrations of unlabeled WIN 35,428 (1 or 10 pM). Nonspecific binding was defined as [^{3}H]WIN 35,428 bound in the presence of an excess (30 μM) of (−)-cocaine. Specific binding was the difference between the two values. Competition experiments to determine the affinities of other drugs at [^{3}H]WIN 35,428 binding sites were conducted using procedures similar to those outlined above. Stock solutions of water-soluble drugs were dissolved in water or buffer, and stock solutions of other drugs were made in a range of ethanol/HCl solutions. Several of the drugs were sonicated to promote solubility. The stock solutions were diluted serially in the assay buffer and added (0.2 mL) to the assay medium as described above.

Serotonin Transporter Assay. The serotonin transporter was assayed in caudate-putamen membranes using conditions similar to those for the dopamine transporter. The affinity of

[^{3}H]citalopram (specific activity of 82 Ci/mmol, DuPont-NEN) for the serotonin transporter was determined in experiments by incubating tissue with a fixed concentration of [^{3}H]citalopram and a range of concentrations of unlabeled citalopram. The assay tubes received, in Tris-HCl buffer (50 mM, pH 7.4 at 0−4 °C; NaCl 100 mM), the following constituents at a final assay concentration: citalopram, 0.2 mL (1 pM to 100 or 300 nM), [^{3}H]citalopram (1 nM); membrane preparation, 0.2 mL (4 mg original wet weight of tissue/mL). The 2 h incubation (0−4 °C) was initiated by addition of membranes and terminated by rapid filtration over Whatman GF/B glass fiber filters presoaked in 0.1% polyethyleneimine. The filters were washed twice with 5 mL of Tris-HCl buffer (50 mM) and incubated overnight at 0−4 °C in scintillation fluor (Beckman Ready-Value, 5 mL), and radioactivity was measured by liquid scintillation spectrometry (Beckman 1801). The cpm values 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 mM) 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.

Data Analysis. Data were analyzed by the EBDA computer software programs (Elsevier-Biosoft, U.K.). Final estimates of IC_{50} values were computed by the EBDA program. Baseline values for the individual drugs were established from the competition curves, and these generally were similar to baseline values established by 30 μM (−)-cocaine or 1 μM fluoxetine.

Acknowledgment. This work was supported by Boston Life Sciences Inc. and the National Institute on Drug Abuse (Grants NIDA4-8309 (P.C.M), NIDA06303 (B.K.M.), NIDA09462 (B.K.M.), RR00168 (B.K.M.)). The authors thank Dr. Clifford George (Naval Research Laboratory, Washington, D.C.) for conducting the X-ray structural analysis. The authors thank Drs. Alan Jones and Ashfaq Mahmood (Brigham and Women's Hospital, Harvard Medical School, Boston, MA) for their contributions to an earlier part of this program.

Supporting Information Available: Crystal data and refinement parameters, coordinates, anisotropic temperature factors, distances, and angles for **12b-2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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JM0301484