Synthesis of 6- and 7- Hydroxy-8-azabicyclo[3.2.1]octanes and Their Binding Affinity for the Dopamine and Serotonin Transporters†

Peter C. Meltzer,*,‡ Bing Wang,‡ Zhengming Chen,‡ Paul Blundell,‡ Muthusamy Jayaraman,‡ Mario D. Gonzalez,‡ Clifford George,§ and Bertha K. Madras||,#

Organix Inc., 240 Salem Street, Woburn, Massachusetts 01801, Naval Research Laboratory, Washington, D. C. 20375, and Department of Psychiatry, Harvard Medical School and New England Regional Primate Center, Southborough, Massachusetts 01772

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Cocaine is a potent stimulant of the central nervous system. Its reinforcing and stimulant effects are related to its ability to inhibit the membrane bound dopamine transporter (DAT). Inhibition of the DAT causes an increase of dopamine in the synapse with a resultant activation of postsynaptic receptors. The rapid onset and short duration of action of cocaine contribute to its high addictive potential. Consequently, the design of tropane analogues of cocaine that display longer onset times on the DAT and extended duration of action is driven by the need to develop cocaine medication. This study extends the exploration of bridge hydroxylated azabicyclo[3.2.1]octanes (tropanes). A series of 6- and 7-hydroxylated tropanes was prepared and evaluated biologically. Structure activity relationships lead to the following conclusions. Bridge hydroxylated tropanes retain biological enantioselectivity but display higher DAT versus SERT selectivity, particularly for the 3α-aryl compounds as compared with the 3*β*-aryl compounds, than the bridge unsubstituted analogues. The 7-hydroxyl compounds are more potent at the DAT than their 6-hydroxyl counterparts. The general SAR of the tropanes is maintained and the rank order of potencies based on substitution at the C3 position remains 3,4-dichloro > 2-naphthyl > 4-fluoro > phenyl.

Introduction

Cocaine is a potent stimulant of the central nervous system. While the exact mechanism of action of cocaine is as yet uncertain, it is known that the dopamine transporter (DAT) plays a primary role in its biological activity. Its reinforcing and stimulant effects are thought to be related to its ability to bind to and inhibit the dopamine transporter.[1−8] Inhibition of the transporter causes an increase of the concentration of the neurotransmitter dopamine (DA) in the synapse, with a resultant increase in activation of postsynaptic receptors.[9] Several classes of compounds are under active investigation as medications for cocaine addiction. Among the candidates are molecules that serve as cocaine antagonists or replacements. A clinically useful cocaine antagonist would inhibit the binding of cocaine to the transporter while allowing free passage of the neurotransmitter itself and thus its reuptake into the presynaptic cell.[10,11] Such a "dopamine sparing cocaine antagonist"[12] has been the focus of much research[13,14] since it would likely provide a novel route to treating cocaine addiction. To date, such a dopamine sparing cocaine antagonist has not been identified. Another class of compounds are dopamine transport inhibitors with a different pharmacokinetic profile than cocaine.

It is interesting that activation of postsynaptic receptors does not appear to be sufficient to lead to addiction. Rather, it is the rapid onset and short duration of action of cocaine and concomitant surge in available dopamine that presumably accounts for the rapid cycles observed clinically and the high addiction potential of cocaine.[15] Consequently, much research has addressed the design and synthesis of molecules that would moderate the kinetics of onset of action and extend duration of action.[9,15,16] In this fashion, a cocaine replacement may be envisaged in which the stimulatory characteristics of cocaine are attenuated by expeditious control of pharmacokinetics. This approach is analogous to the behavioral and kinetic profile of methadone used to treat opiate addiction.[17]

Our search for such compounds has included a variety of tropane analogues in which the 8-aza moiety of the prototypic phenyltropane, WIN 35,428 (Figure 1) has been substituted by both oxygen (2*β*-carbomethoxy-3*β*-(3,4-dichlorophenyl)-8-oxabicyclo[3.2.1]octane)[18,19] and carbon (2*β*-carbomethoxy-3*β*-(3,4-dichlorophenyl)-bicyclo-[3.2.1]octane).[20] These 8-substitutions have been pursued to examine the significance of moieties capable of hydrogen bonding to a residue (Asp^{79})[12] within the acceptor site of the biomacromolecule.

To explore the effect of altered nucleophilicity of an 8-aza substituent on DAT function, we introduced hydroxyl groups at both the 6- and 7-bridge positions of selected 8-azabicyclo[3.2.1]octanes. We investigated this series despite the fact that the bridge area may be sensitive to increased steric bulk. In this regard, DAT affinities were reduced by homologation of the bridge by introduction of a carbon in a [3.3.1] homotropane,[21]

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* Corresponding author: Dr. Peter C. Meltzer, Organix Inc., 240 Salem Street, Woburn, Massachusetts, 01801. Tel: 781-932-4142. Fax: 781-933-6695. E-mail: Meltzer@organixinc.com.

|| Corresponding author, biology.

‡ Organix Inc.

§ Naval Research Laboratory.

Harvard Medical School and New England Regional Primate Center.

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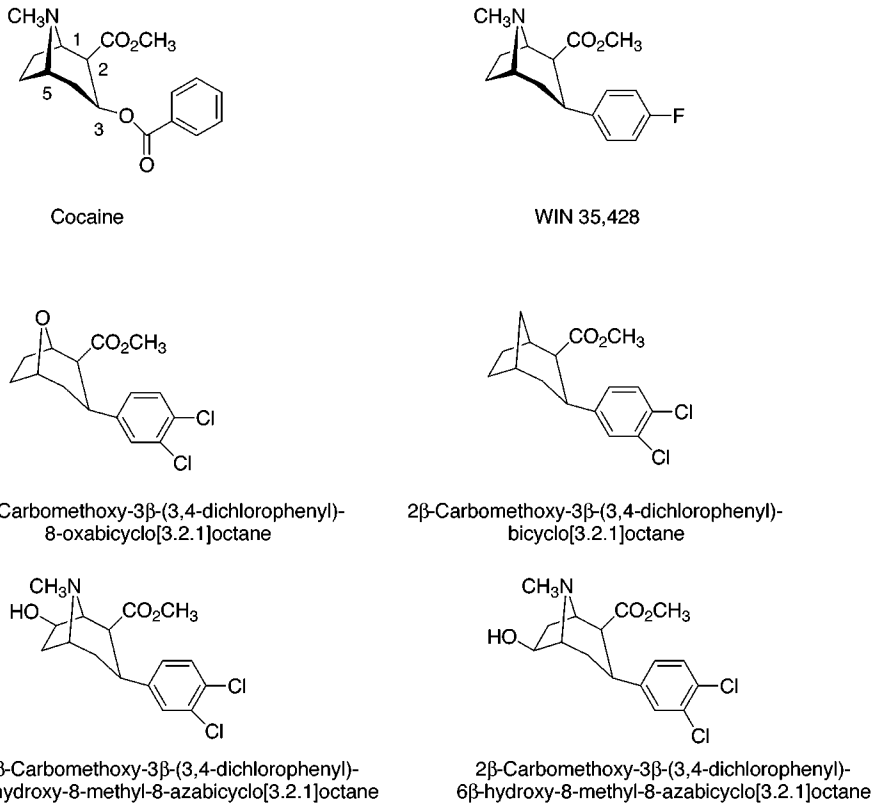


Figure 1. Structures of Lead Bicyclo[3.2.1]octanes

by the presence of 6-alkyl groups,[22] and by the introduction of a methoxyl group at either the 6- or 7-position of cocaine.[23]

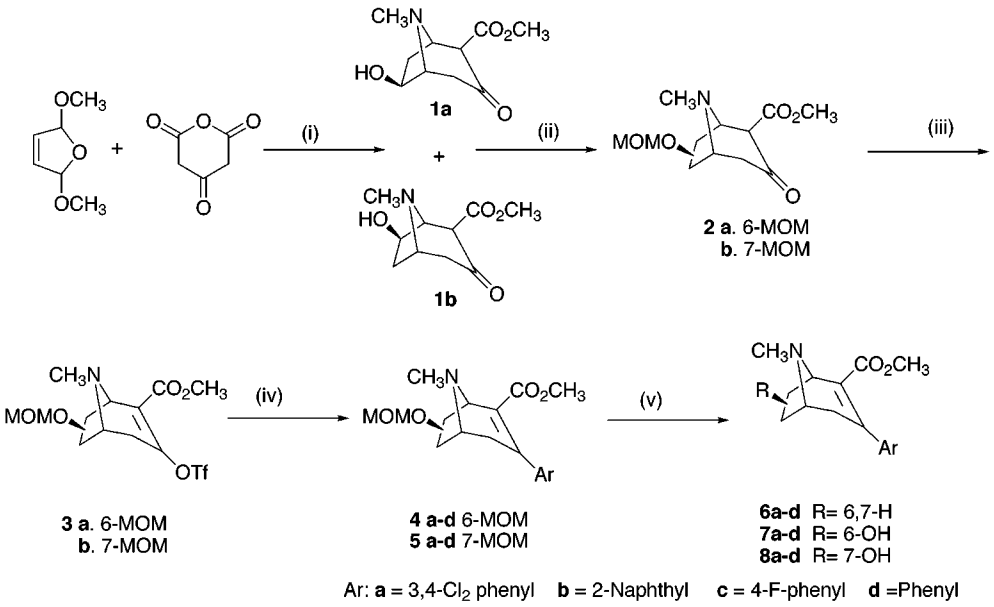
In contrast, certain "back-bridged" compounds proved quite potent at the DAT.[24] Both 6- and 7-hydroxy groups in cocaine have been reported, but without biological data.[25] Our rationale for exploration of bridge hydroxylated 3-aryltropanes was that a β-oriented hydroxyl group might establish intramolecular hydrogen bonding to the 8-nitrogen and thus reduce its nucleophilicity. In 1997, we published a preliminary study in which we described the synthesis of the racemic parent compounds 2β-carbomethoxy-3β-(3,4-dichlorophenyl)-7β-hydroxy-8-methyl-8-azabicyclo[3.2.1]octane and 2β-carbomethoxy-3β-(3,4-dichlorophenyl)-6β-hydroxy-8-methyl-8-azabicyclo[3.2.1]octane (Figure 1).[26,27] Subsequently, two bridge hydroxylated 3-tolyltropanes were shown to have nanomolar potency for DAT inhibition.[28,29] We now report the feasibility of producing extremely potent and selective DAT inhibitors via this modification of phenyltropanes.

Chemistry. The route of synthesis is shown in Schemes 1−3. The 6- and 7-hydroxy target compounds were obtained individually; however, for ease of presentation, the position of bridge substitution is not specified in the schemes. The 6- and 7-hydroxy β-keto esters **1a** and **1b** were prepared as described previously.[26,30−32] The stereochemistry of the β-hydroxyl group at C6 (**1a**) or C7 (**1b**) was confirmed by NMR studies. Most important, a coupling constant of $J = 0$ Hz between H-5 and H-6 ($\delta = 4.05$ ppm) in the case of **1a**, and between H-1 and H-7 ($\delta = 4.1$ ppm) in the case of **1b**, confirmed a dihedral angle of 90° for both compounds. This dihedral angle can only be obtained between a 6α- or 7α-oriented proton and the relevant bridgehead proton at C1 or C5, respectively. This therefore confirms the β-orientation of the hydroxy moieties in **1a** and **1b**. No α-hydroxy isomers were isolated.

A mixture of 6- and 7-hydroxy-β-keto esters **1a** and **1b** was methoxymethylated with dimethoxymethane in dichloromethane with *p*-toluenesulfonic acid as catalyst. Column chromatography provided regioisomers **2a** and **2b** which were individually utilized, as described below. The ^{1}H NMR spectra of **2a** and **2b**, as well as pure **1a** and **1b**, proved quite interesting. Both compounds **1a** and **2a** clearly exhibit the expected[20] equilibrium distribution between the 2α-carboxy ester, enol-2-carboxy ester, and 2β-carboxy ester with the result that their ^{1}H NMR spectra are quite complex. Compounds **1b** and **2b** surprisingly do not. In fact, in $CDCl_3$ solution, compounds **1b** and **2b** exist exclusively as the enol. Unequivocal evidence for this lies (as exemplified for **1b**) in the complete absence of a C2 proton and the presence of a doublet at δ 1.73 ($H_{4\beta}$: $J = 18.6$ Hz) and a double doublet at δ 2.76 ($H_{4\alpha}$: $J = 18.6$ and 4.7 Hz) integrating for fully one proton each. The enolic proton at δ 11.8 also fully integrates for one proton. The reason for this preference for the enol in the 7-substituted compounds is unclear.

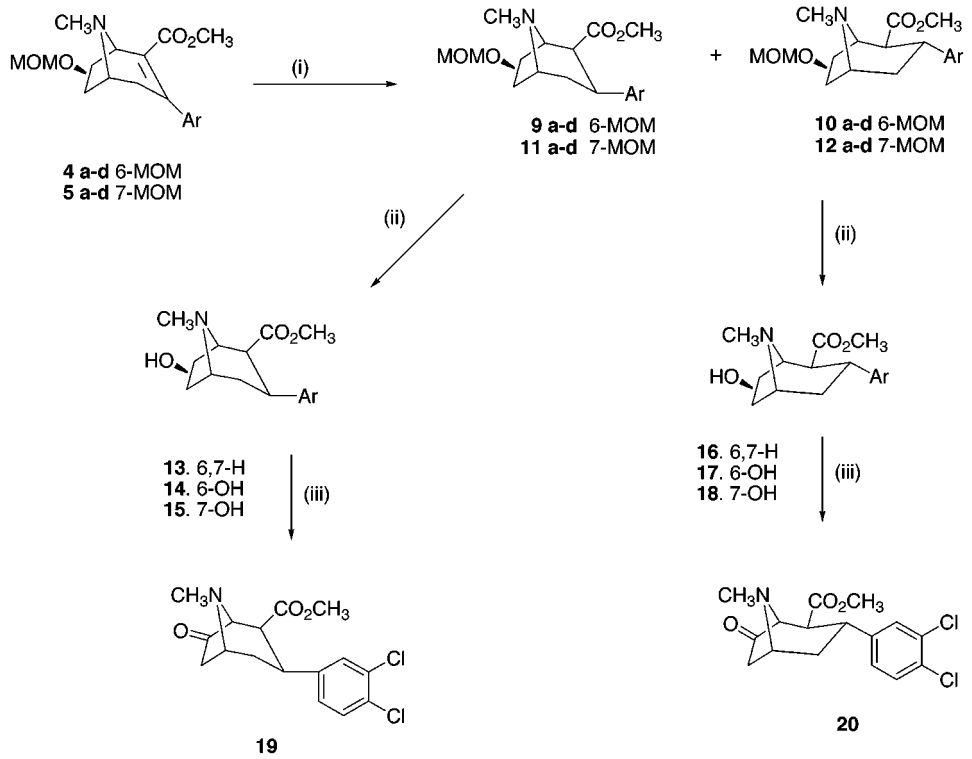
Conversion of **2** to the vinyl enoltriflates **3** was achieved with sodium bis(trimethylsilyl)amide and *N*-phenyltrifluoromethanesulfonimide at low temperature.[33] The alkenes **4** and **5** were then obtained in good yield by Suzuki coupling[34] of the triflates **3** with the corresponding boronic acids. Reduction of **4** and **5** (Scheme 2) with samarium iodide at −78 °C then afforded the saturated tropane analogues **9**-**12**.[33] Compounds **9** and **11** were shown by ^{1}H NMR to exist in a chair conformation, and **10** and **12** assumed a boat

Scheme 1. Synthetic Route to 2,3-Unsaturated Tropanes[a]



[a] Reagents: (i) H_2NCH_3; (ii) $CH_2(OCH_3)_2$, pTSA; (iii) $NaN(TMS)_2$, $PhNTf_2$; (iv) $Pd_2(dba)_3$, $ArB(OH)_2$; (v) TMSBr.

Scheme 2. Synthetic Route to Bridge Oxygenated Tropanes[a]



[a] Reagents: (i) SmI_2; (ii) TMSBr, CH_2Cl_2; (iii) *N*-CH_3-morpholine-*N*-oxide, tetra-*n*-propylammoniumperruthenate.

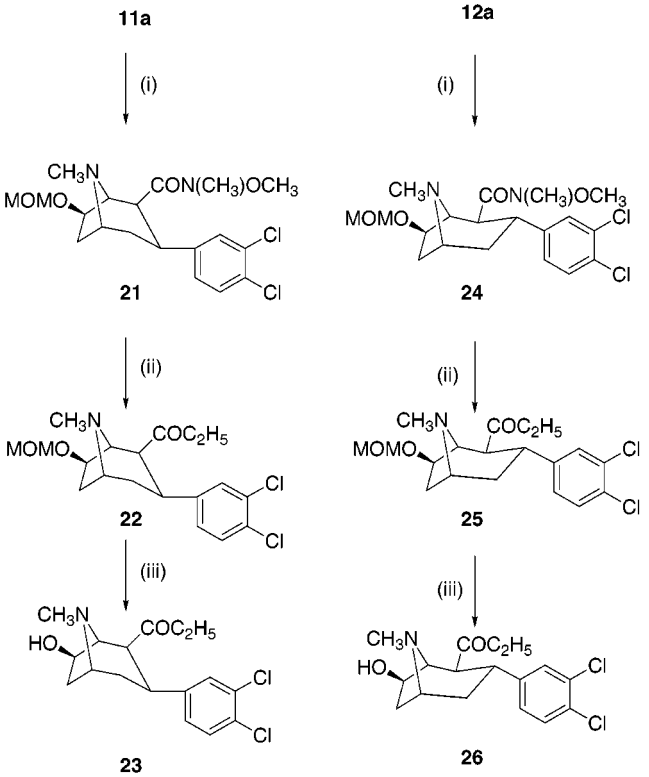
conformation. Finally, the MOM groups of each of **4**, **5** and **9**−**12** were removed in high yield with trimethylsilyl bromide in methylene chloride at 0 °C to give the corresponding hydroxy tropanes **7** and **8** (Scheme 1), **14** and **15**, and **17** and **18** (Scheme 2), respectively.

The 7-ketoesters **19** and **20** were obtained in good yield upon oxidation of **15** and **18**, respectively, with tetra-*n*-propylammonium perruthenate[35] and *N*-methylmorpholine-*N*-oxide in methylene chloride.

The 2-ethyl ketone analogues **23** and **26** were prepared (Scheme 3) via an intermediate Weinreb amide.[36] Thus **11a** was reacted with *N*,*O*-dimethylhydroxylamine and trimethyl aluminum in methylene chloride to provide the Weinreb amide **21** in high yield. Treatment with ethylmagnesium bromide in THF[37] then provided the ethyl ketone **22** quantitatively. Deprotection with TMSBr yielded the target compound **23**. The 3α-aryl analogue **26** was obtained similarly from **12a** via **24** and **25**.

To determine the biological enantioselectivity of these hydroxytropanes, six enantiopure 7*β*-hydroxy-3-(3,4-dichlorophenyl) analogues were prepared. While we and

Scheme 3. Synthetic Route to Bridge Oxygenated 2-Keto Tropanes[a]



[a] Reagents: (i) $HN(CH_3)OCH_3$ $Al(CH_3)_3$; (ii) ETMgBR; (iii) TMSBR, CH_2Cl_2.

others[38−40] have had substantial success in recrystallization of diastereomeric tartrate salts of keto esters such as **1b**, we were unable to obtain material of satisfactory enantiomeric excess (ee) with the bridge hydroxyl group present. We therefore elaborated two resolution routes, both of which relied upon the establishment of diastereomeric camphanate esters (Scheme 4). The routes had the added advantage of allowing quantification of ee by ^{1}H NMR analysis (vide infra). Thus, the MOM protected keto ester **2b** was reacted with (1′*S*)-(−)-camphanic chloride to obtain a mixture of diastereomers that could not be separated by column chromatography. Multiple recrystallizations yielded a sufficient amount of the (1*R*,1′*S*) diastereomer **27** only. Pure (1*S*,1′*S*) diastereomer could not be obtained by these means. Hydrolysis of **(1*R*)-27** with lithium hydroxide then provided enantiopure keto ester **(1*R*)-2**. This keto ester was then taken through the same synthetic pathway as shown for racemates **1b** (Schemes 1 and 2) to obtain the enantiopure **(1*R*)-8a**, **(1*R*)-15a**, and **(1*R*)-18a**.

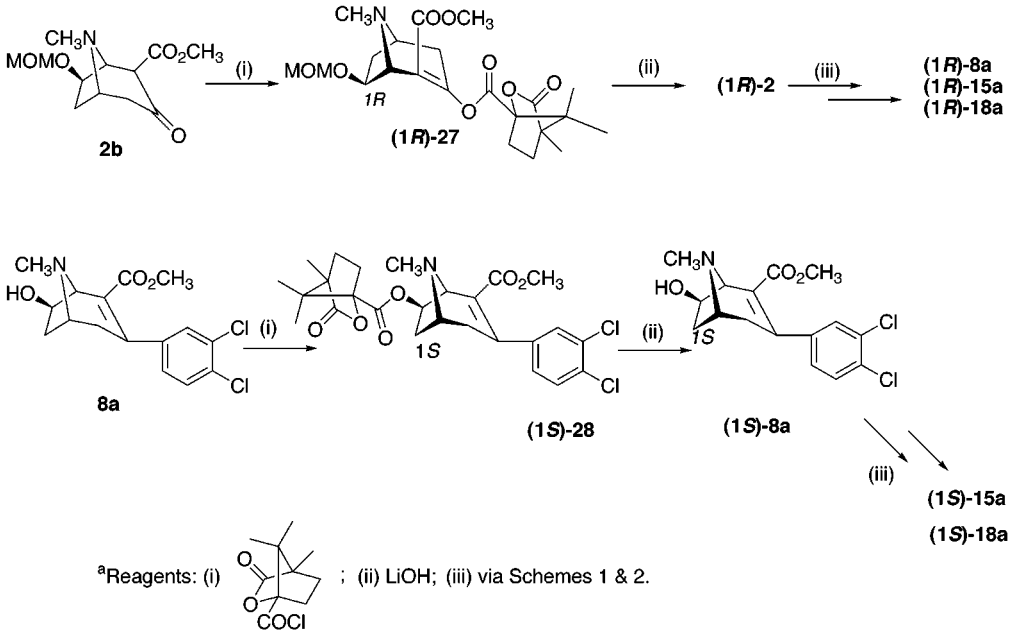
Table 1. Physical Data for Six Enantiopure Analogues

compound	mp °C	X-ray[a]	$[\alpha]_D^{21}$
(*1R*)-8a	129.0−131.0	(1*R*)	+57°
(*1R*)-15a	186.0−187.0		−26°
(*1R*)-18a	149.0−150.0	(1*R*)	+47°
(*1S*)-8a	130.4−132.4		−58°
(*1S*)-15a	185.5−186.5		+25°
(*1S*)-18a	148.5−150.0	(1*S*)	−48°

[a] X-ray crystallographic analysis confirmed stereochemical assignments.

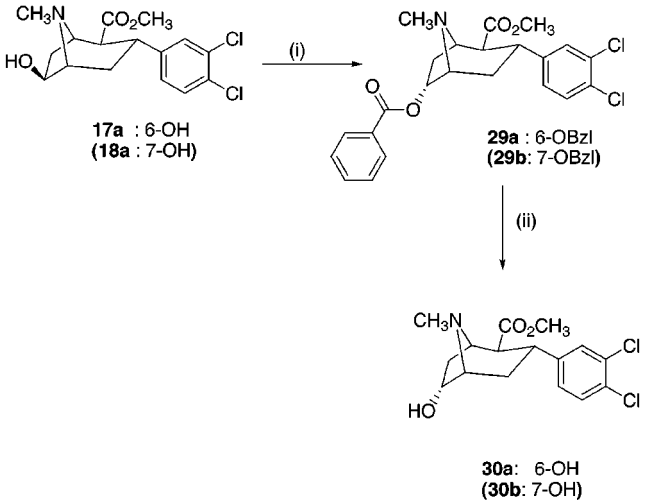
This approach provided only the 1*R*-tropanes. Therefore, an alternate approach was also developed. (Scheme 4). The racemic 2,3-ene **8a** was esterified with (1′*S*)-(−)-camphanic chloride to obtain a diastereomeric mixture **28** which was purified by column chromatography to obtain **(1*S*,1′*S*)-28**. Hydrolysis with LiOH then provided the enantiopure target compound **(1*S*)-8a** which was reduced with SmI_2 to obtain the 3β **(1*S*)-15a** and 3α **(1*S*)-18a** target compounds. Physical data relating to these six compounds are presented in Table 1. Each enantiomeric pair had equal and opposite optical rotations. Since this is an unreliable measure of enantiomeric excess, an NMR method was developed. Each of the six compounds was obtained in >98% ee as confirmed by ^{1}H NMR. In this regard, NMR spectra of the camphanate esters are unequivocal since one of the camphanate methyl resonances for the (1*R*,1′*S*) and (1*S*,1′*S*) compounds is baseline separated and can therefore be quantified reliably. Thus, the **(1*R*)-27**

Scheme 4. Resolution of **8A**, **15A**, and **18A**[a]



[a]Reagents: (i) ; (ii) LiOH; (iii) via Schemes 1 & 2.

Scheme 5. Inversion at C6 and C7[a]



[a] Reagents: (i) C_6H_5COOH, Ph_3P, DEAD; (ii) LiOH, THF.

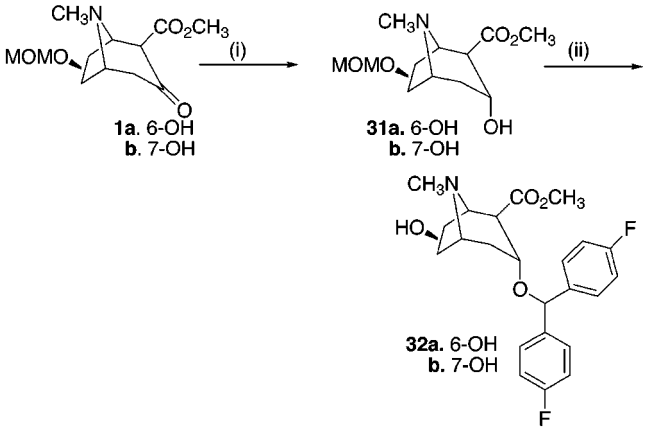
manifests a methyl group at δ 0.99. The **(1*S*)-27** shows the same methyl at δ 1.02. Absolute stereochemistry was assigned by X-ray crystallographic analysis for **(1*R*)-8a**, **(1*R*)-18a**, and **(1*S*)-18a**. This allowed confident stereochemical assignment of the remaining compounds.

It should be noted that the designation of chirality for these bridge-hydroxylated tropanes is reversed from that of the bridge unsubstituted parent compounds. This is a result of the rules for nomenclature and does not reflect a difference in absolute stereochemistry. Thus the more potent enantiomers here are the 1*S* designated compounds in contrast to the 1*R* active enantiomers of the parent compounds **6a**, **13a**, or **16a**.

Inversion of the bridge hydroxyl group in **17a** and **18a** was effected (Scheme 5) in two steps by straightforward Mitsunobu chemistry.[41] Thus, the 6β-hydroxy **17a** was reacted with benzoic acid and triphenylphosphine in the presence of diethylazodicarboxylate to give **29a**. The benzoyl group was then removed with LiOH/THF to provide the 6α-hydroxy analogue **30a**. The 7β-hydroxy analogue **18a** was treated similarly to obtain **30b**.

The ^{1}H NMR spectra of these inverted compounds are interesting in that the α-oriented hydroxyls have a surprisingly large through space compression effect on the axial protons at H2α in the case of the 7-OH compound **30b** and at H4α in the case of the 6α-hydroxy compound **30a**. Such effects have been observed previously in epibatidine analogues.[42] Boat versus chair conformation of bicyclo[3.2.1]octanes has always been assigned on the basis of ^{1}H NMR, and the signal corresponding to H4α in 2β-substituted-3α-arylbicyclo-[3.2.1]octanes has been particularly diagnostic. It generally appears as a double double doublet at δ 1.3 showing large geminal coupling interactions with H4β (ca. 14 Hz) and H3 (trans-diaxial coupling ca. 11 Hz) and a small coupling constant with H5 (ca. 2 Hz). That is the case for the 2β-carbomethoxy-3α-(3,4-dichlorophenyl) hydroxylated derivatives when the hydroxyl group is in the 6β (**17a**), 7β (**18a**), or 7α (**30b**) orientation (in the latter case obscured by the presence of a signal corresponding to H6β). In the case of the 6α-hydroxy derivative **30a**, the signal corresponding to H4α was observed at δ 2.15 (Δ = 0.85 ppm) (with the appropriate multiplicity described above) due to the strong 1,4-diaxial

Scheme 6. Synthesis of Diarylmethoxy Tropanes[a]



[a] Reagents: (i) $NaBH_4$; (ii) 4,4'-difluorobenzhydrol, *p*TSA.

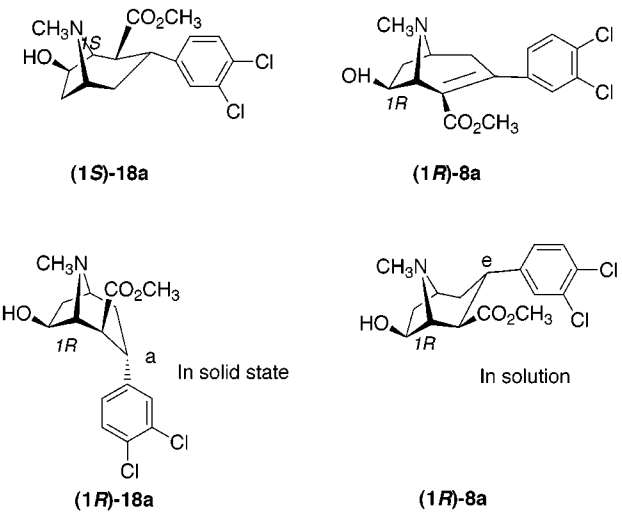


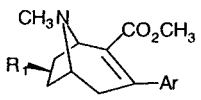
Figure 2. Absolute Configurations of **(1*R*)-8a**, **(1*R*)-18a**, **(1*S*)-18a**

interaction with the 6α-OH. A similar displacement (Δ = 0.9 ppm) was observed in the signal corresponding to H2α in the 7α-hydroxy compound, **30b**. Finally the ^{1}H NMR spectrum of the 7-keto compound **20** showed a strong resemblance with the hydroxy analog's spectra, although the signal corresponding to H4α appeared at lower fields (δ 1.51) and the trans-diaxial coupling interactions H3−H2 and H3−H4α were slightly weaker than expected (J = 8 Hz). These minor differences indicate a pseudo boat conformation.

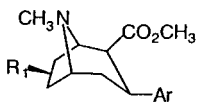
The diarylmethoxy compounds (Scheme 6) **32a** and **32b** were obtained from the MOM protected keto esters **1a** and **1b**. Reduction with sodium borohydride gave the 3α-hydroxy compounds **31**. Subsequent reaction with 4,4′-difluorobenzhydrol in methylene chloride with *p*-toluenesulfonic acid provided **32a** or **32b** directly.

To assign absolute stereochemistry for those compounds that were prepared in enantiomerically pure form, X-ray structural analyses were conducted. Compounds **(1*R*)-8a**, **(1*R*)-18a**, and **(1*S*)-18a** were recrystallized from methylene chloride/pentane to obtain suitable crystals. Compound **(1*S*)-18a** was thus demonstrated to be the 1*S*-enantiomer. Compound **(1*R*)-18a** was proved to be 1*R*, and compound **(1*R*)-8a**, the precursor to **(1*R*)-18a**, was likewise confirmed as 1*R* (Figure 2). A comparison of the conformation established by ^{1}H

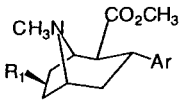
Table 2. Inhibition of [^{3}H]WIN 35,428 Binding to the Dopamine Transporter and [^{3}H]Citalopram Binding to the Serotonin Transporter in Rhesus (*Macaca mulatta*) or Cynomolgus Monkey (*Macaca fasicularis*) Caudate-Putamen[a]



6: R_1 = H
7: R_1 = 6-OH
8: R_1 = 7-OH



13: R_1 = H
14: R_1 = 6-OH
15: R_1 = 7-OH



16: R_1 = H
17: R_1 = 6-OH
18: R_1 = 7-OH

Ar: **a** = 3,4-Cl_2 phenyl **b** = 2-Naphthyl **c** = 4-F-phenyl **d** =Phenyl

		IC$_{50}$ (nM)				IC$_{50}$ (nM)				IC$_{50}$ (nM)		
R_1	compound	DAT	SERT	SERT/ DAT	compound	DAT	SERT	SERT/ DAT	compound	DAT	SERT	SERT/ DAT
H	**6a**, O-1109	1.16	867	747	**13a**, O-401 (R)	1.09	2.47	2	**16a**, O-1157 (R)	0.38	27.7	73
6-OH	**7a**, O-1591	55.1	3320	60	**14a**, O-1299	3.02	166	55	**17a**, O-1926	6.09	1450	238
7-OH	**8a**, O-1813	19.4	>6000	>300	**15a**, O-1164	1.42	27.7	20	**18a**, O-1163	1.19	1390	1170
7-OH	**(1*R*)−8a**, O-1677	265	1590	6	**(1*R*)−15a**, O-1675	2,690	139	0.05	**(1*R*)−18a**, O-1676	482	5300	11
7-OH	**(1*S*)−8a**, O-1923	7.37	5370	730	**(1*S*)−15a**, O-1945	0.3	15	50	**(1*S*)−18a**, O-1924	0.76	1220	1610
H	**6b**, O-1173	2.94	109	37	**13b**, O-1229 (R)	0.49	2.19	5	**16b**, O-1228	0.57	5.95	10
6-OH	**7b**, O-1627	246	260	1	**14b**, O-1814	7.7	34.2	4	**17b**, O-1748	32	180	6
7-OH	**8b**, O-1815	45	677	15	**15b**, O-1981	1.26	5.57	4	**18b**, O-1952	2.8	94	34
H	**6c**, O-1104	408	7990	20	**13c**, O-381 (WIN)	11.0	160	15	**16c**, O-1204	17.9	1,130	63
6-OH	**7c**, O-1588	>20 000	>20 000	1	**14c**, O-1817	477	>20 000	>42	**17c**, O-1755	739	5820	8
7-OH	**8c**, O-1927	7730	>10 000	1	**15c**, O-1983	123	>10 000	>80	**18c**, O-1951	110	>20 000	>120
H	**6d**, O-1449	2590	28 600	11	**13d**	65	NA	-	**16d**	NA	NA	
6-OH	**7d**, O-1644	>150 000	>100 000	1	**14d**, O-1816	6150	88 000	14	**17d**, O-1589	3530	>10 000	>3
7-OH	**8d**, O-1944	>10 000	>10 000	1	**15d**, O-1953	235	>10 000	>43	**18d**, O-1954	518	>100 000	>190

[a] Each value is the mean of two or more independent experiments each conducted in different brains and in triplicate. Errors generally do not exceed 15% between replicate experiments. Highest doses tested were generally 10−100 μM.

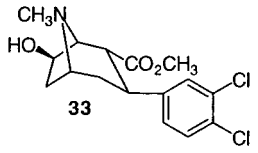
NMR studies in solution ($CDCl_3$) with that evident in the solid state as evidenced by X-ray crystallography proved interesting. While both 3α-aryl enantiomers adopted a boat conformation in solution, the 1*R* enantiomer **(1*R*)-18a** presented in chair conformation in the solid state. Among the numerous X-ray crystallographic structural determinations that we have conducted on tropanes, **(1*R*)-18a** represents the first instance in which the conformation in the solid state is markedly different from that in solution. This is highly unlikely to be a consequence of enantiomeric differences (**(1*R*)-18a** vs **(1*S*)-18a**). However, this difference is potentially important since a chair conformation would place the 3α-aryl substituent in an axial position. SAR studies have taken into consideration that a 3β-substituent, which favors the chair conformation of the bicyclo[3.2.1]-octane system, places the 3-aryl group in an equatorial position. Further, the 3α-aryl compounds have, on the basis of NMR studies and all prior X-ray studies, been shown to adopt a boat conformation in which the C3-aryl group is again oriented equatorially. This contrast between the crystal conformation of **(1*S*)-18a** (boat) as compared with that of its enantiomer **(1*R*)-18a** (chair) is probably fortuitous. It was noted that the unit cell structures for **(1*R*)-18a** and **(1*S*)-18a** differed with respect to intermolecular hydrogen bonding. It appeared that **(1*S*)-18a** manifested H-bonding between the 7-OH and the 7-OH of an adjacent molecule, while **(1*R*)-18a** manifested H-bonding between a 7-OH and an 8-N of an adjacent molecule. ^{1}H NMR experiments were conducted to examine the possible influence of such intermolecular hydrogen bonding upon conformation. The conformation of the 3α-molecule **(1*S*)-18a** in $CDCl_3$ solution is pseudo-boat (evidenced by the double double doublet resonances for $H_{4\alpha}$ at δ 1.24). It maintains this conformation in CD_3OD/D_2O ($H_{4\alpha}$: ddd at δ 1.3) or CD_3OD/H_2O ($H_{4\alpha}$: ddd at δ 1.3) under a water suppression protocol. Therefore intermolecular hydrogen bonding does not favor chair conformation over the boat for this compound. This result highlights the caution that should be exercised as one extrapolates from a three-dimensional crystal structure to a putative three-dimensional structure within the biological system.

Biology. The affinities (IC$_{50}$) for the dopamine and serotonin transporters were determined in competition studies. The dopamine transporter was labeled with [^{3}H]-3β-(4-fluorophenyl)tropane-2β-carboxylic acid methyl ester ([^{3}H]WIN 35,428 or [^{3}H]CFT (1 nM)) and nonspecific binding was measured with (−)-cocaine (30 μM).[6] [^{3}H]Citalopram was used to label the serotonin transporter and nonspecific binding was measured with fluoxetine(10 μM).[18] Binding data for the 2-carbomethoxy-6- or 7-hydroxy compounds are presented in Table 2. Table 3 presents binding data for the 7-keto, 6α- and 7α-hydroxy, and 3-diarylmethoxy compounds. Studies were conducted in monkey striatum because this tissue[27] is used in an ongoing investigation of structure activity relationships at the DAT, and meaningful comparisons with an extensive database 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.

Table 3. Inhibition of [^{3}H]WIN 35,428 Binding to the Dopamine Transporter and [^{3}H]Citalopram Binding to the Serotonin Transporter in Rhesus or Cynomolgus Monkey Caudate-Putamen[c]

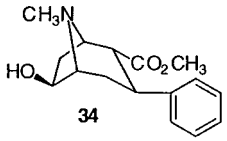
		IC_{50} (nM)				IC_{50} (nM)	
compd		DAT	SERT	compd		DAT	SERT
19	O-2097	14.1	290	**30b**	O-2032	3.04	991
20	O-2096	14.2	7038	**32a**	O-2070	448	4850
23	O-2074	0.81	97	**32b**	O-2031	6300	9560
26	O-2099	1.1	2520	**33**[a]	O-2016	48	533
30a	O-2015	33.2	10700	**34**[b]	O-1754	32 600	>20 000

a.



33

b.



34

[c] Each value is the mean of two or more independent experiments each conducted in different brains and triplicate. Errors generally do not exceed 15% between replicate experiments. Highest doses tested were generally 10−100 μM.

Discussion

In the search for cocaine medications, it has not been established that more potent inhibitors of the DAT may provide more pharmacologically useful compounds. Therefore, a focus of much of the work in this area has been to design compounds that range in their affinity for the dopamine transporter. The bridge-hydroxylated compounds of this study provide a broad array of molecules some of which bind with very high affinity and others that prove much weaker. This family therefore provides a testing ground for the role of affinity upon cocaine medications development. Selectivity for inhibition of the DAT versus the serotonin transporter (SERT) is another property of tropanes of considerable relevance for development of medications and for probes useful to image the DAT in living brain. It is reasonable to aspire to high DAT:SERT selectivity for DAT imaging agents. For cocaine medications, however, the advantages and disadvantages of selectivity are not fully resolved. Even though the parent compound cocaine is relatively nonselective for all three monoamine transporters, and an abundance of evidence suggests that DAT blockade is a significant contributor to the reinforcing effects of cocaine, self-administration is sustained in DAT knockout mice.[43] One possible interpretation of these findings is that cocaine blocks transport of dopamine via other transporters in brain regions critical to maintaining self-administration.[44] At a practical level, these findings would imply that compounds both selective and nonselective for the DAT should be assessed in screening programs for cocaine medications. Within this series of compounds now described, we discovered that it is feasible to design bridge-substituted tropanes with either a high or low degree of DAT:SERT selectivity.

Introduction of functionality at the 6,7-bridge of 3-phenyltropanes has attracted the attention of a number of research groups.[21−23,26,45] In general, steric bulk at either position has reduced the affinity of these compounds for the dopamine transporter. Simple introduction of an hydroxyl group on a 3-aryl tropane is also not sufficient to provide potent DAT inhibitors.[28] Upon the basis of the SAR that we have uncovered in other bicyclo[3.2.1]octane series,[19,27] we have learned that to achieve high potency and selectivity, an optimum template should be used as a starting point. We have therefore generally elected to prepare derivatives of the 3,4-dichlorophenyl substituted template, since this substitution, and to a similar extent the 2-naphthyl substitution,[46] have provided among the most potent DAT inhibitors. Furthermore, SAR studies have clearly demonstrated that selectivity of binding to the DAT versus binding to the SERT can be obtained in the 3α-aryl as well as the 2,3-unsaturated series of compounds.[27] For these reasons, the compounds shown in Tables 2 and 3 were prepared.

Introduction of 6- or 7-Bridge Hydroxyl Groups. Table 2 presents the 6- and 7-hydroxylated compounds as well as the bridge unsubstituted (R_1 = H) parent compounds for comparison. In general, the 7-hydroxy compounds (**8**, **15**, **18**) are more potent than the 6-hydroxy compounds (**7**, **14**, **17**). However, in a comparison of the 2,3-unsaturated racemates, **6a** with **7a** and **8a**, it is clear that the unsubstituted compound **6a** is significantly more potent than either **7a** or **8a**. When only active enantiomers are compared, it is apparent that the hydroxylated analogues are of comparable potencies to the bridge unsubstituted compounds. Compound **(1*R*)-13a** exhibits DAT IC_{50} = 1.09 nM while the active **(1*S*)-15a** is about three times more potent (0.3 nM) and 25-fold more selective than **13a** (Table 3). When the aromatic ring is oriented in the 3α-configuration, the parent-unsubstituted compound **(1*R*)-16a** has DAT IC_{50} = 0.38 nM and the hydroxylated enantiopure compound **(1*S*)-18a** shows a similar value of 0.76 nM. In this case, the hydroxylated compound shows a selectivity ratio of 1610 and is therefore 22-fold more selective than **16a**. However, **(1*S*)-18a** is 32-fold more selective than **(1*S*)-15a** thus demonstrating the enhanced selectivity of 3α-configured compounds over their 3*β*-counterparts. Thus, introduction of an hydroxyl at C7 has, at least, maintained potency of DAT inhibition and retained or may have increased selectivity versus inhibition of the SERT. This increase in selectivity is evident in the 6-hydroxy compounds **14a** and **17a** as well. The fact that the 1*R* configured compounds **(1*R*)-8a**, **(1*R*)-15a**, and **(1*R*)-18a** are considerably less potent than the 1*S* enantiomers points, once again, to the biological enantioselectivity of the DAT and SERT.

In summary, three conclusions may be reached. First, the bridge hydroxylated compounds confirm biological enantioselectivity. Second, the 7-hydroxylated compounds are more potent at the DAT than their 6-hydroxyl counterparts. Third, the bridge hydroxylated compounds are more selective DAT inhibitors than the unsubstituted analogues.

Effect of Substitution on the C3 Aryl Ring. The effects of substitution on the C3-aryl ring of the bridge hydroxylated compounds in Table 2 mimic other tropane series[27,47] including the 8-oxa[19] and 8-carba[20] compounds. Thus, for substituents on the C3-position, the potency for inhibition of the DAT decreases from 3,4-dichlorophenyl > 3-(2-naphthyl)> 3-fluorophenyl > phenyl. Further, selectivity for inhibition of the DAT versus the SERT is greater for those compounds bearing a 3α-aryl substituent as compared with a 3*β*-aryl substituent. The 2,3-unsaturated analogues generally

display the same rank order of potency at the DAT. They manifest good selectivity, particularly for those compounds that are potent inhibitors. Thus for both 6- and 7-hydroxylated compounds, 3,4-dichloro substitution provides similar or slightly higher potency at the DAT than for introduction of a C3-(2-naphthyl) group. Both are significantly superior to a 4-fluoro group which, in turn, is more potent than the unsubstituted phenyl ring compound. In the 7-hydroxy series, the racemic 3*β*-configured 3,4-dichloro compound **15a** manifests a DAT IC_{50} of 1.42 nM as compared with 1.26 nM for the 2-naphthyl **15b,** 123 nM for the 4-fluoro **15c**, and 235 nM for the unsubstituted **15d**. A similar relationship is seen in the 3α-configured series: **18a** (3,4-dichloro) > **18b** (2-naphthyl) > **18c** (4-fluoro) > **18d** (H) and the 2,3-enes: **8a** (3,4-dichloro) > **8b** (2-naphthyl) > **8c** (4-fluoro) > **8d** (H). Interestingly, either 6- or 7-hydroxy substituents reduce affinity of 4-fluoro substitution. The 6*β*-hydroxy compounds present identical SAR at C3. In striking contrast to the exciting DAT inhibitor (1*S*)-difluoropine[40] (DAT IC_{50} = 10.9 nM; SERT IC_{50} = 3530 nM) the (1*R*/*S*)-difluorodiarylmethoxy analogues **32a** (6*β*-OH) and **32b** (7*β*-OH) (Table 3) manifest high nanomolar to micromolar affinity for the DAT and SERT.

Selectivity for inhibition of the DAT versus the SERT is likewise very similar to that evidenced in all other series.[19,20,27] The parent compounds in which no bridge hydroxylation is present (**6**, **13**, **16**) model the series (Table 2): 2,3-ene (**6a**) > 3α (**16a**) > 3*β* (**13a**). Thus, the 3*β* configured compounds are generally least selective, and the 2,3-ene and 3α-compounds are more selective. This difference in selectivity diminishes where compounds are intrinsically less potent DAT inhibitors. An example of this is evident in the comparison between the potent 3,4-dichloro series and the weak ring-unsubstituted compounds. Thus **8a**, **15a**, and **18a** have selectivities of SERT/DAT ranging from 20 to 1170 while the unsubstituted **8d**, **15d**, and **18d** have selectivities that range from 1 to 190. It may be concluded that a tight fit between the ligand and the relevant transporter enhances selectivity. As noted in earlier work,[27] the SERT appears to be more discriminating since DAT inhibition is often similar across the C3-altered compounds in contrast to SERT inhibition which differs markedly across the series. Similarly, **20** and **26** (3α) are more selective than **19** and **23** (3*β*) (Table 3).

From these data the following may be concluded: First, the general SAR of the tropanes is maintained in that the rank order of substitution at the C3 position remains 3,4-dichlorophenyl > 2-naphthyl > 4-fluorophenyl > phenyl. Second, the general SAR of the bicyclo-[3.2.1]octane series is maintained in that the 3α-aryl compounds are more selective than the 3*β*-aryl compounds.

Biological Enantioselectivity. The DAT is enantioselective.[4−6,40,48−50] Accordingly, we explored the biological enantioselectivity of the most active parent bridge hydroxylated compounds, namely, **8a**, **15a**, and **18a**. Clearly, (Table 2) the 1*S* enantiomers are significantly more potent inhibitors than their 1*R* counterparts. Thus, **(1*S*)-8a**, **(1*S*)-15a**, and **(1*S*)-18a** all manifest DAT IC_{50} values of 0.3−7.4 nM while the 1*R* enantiomers **(1*R*)-8a**, **(1*R*)-15a**, and **(1*R*)-18a** manifest DAT IC_{50}'s in the range of 265−2690 nM. Selectivities for DAT versus SERT inhibition follow similarly. Thus, the less active 1*R*-enantiomer series of the 3,4-dichlorophenyl analogue manifests selectivities that range from 0.05 to 11-fold (**(1*R*)-8a**, **(1*R*)-15a**, and **(1*R*)-18a**). In contrast, the active *1S*-enantiomers show clear differences in selectivity (50-1610 for **(1*S*)-15a**, **(1*S*)-8a**, and **(1*S*)-18a**).

Clearly, biological enantioselectivity is conserved for bridge hydroxylated tropanes.

Stereochemistry at C2 and C7. It is interesting that although the 7*β*-hydroxy-C2α-methylester **33** is markedly less potent (Table 3) at both the DAT (IC_{50} = 48 nM) and the SERT (IC_{50} = 533 nM) than the C2*β* analogue **15a** (DAT: 1.42 nM; SERT: 27.7 nM) it is still almost twice as potent as cocaine at the DAT. In the absence of ring substitution, as in **34**, the 6-hydroxy-C2α-compound is inactive.

Replacement of the C2 ester with a C2 ethyl ketone leads to quite potent inhibitors (Table 3). Thus, **23** manifests a DAT IC_{50} = 0.81 nM and a SERT IC_{50} = 97 nM. As may be anticipated, when a C2 ethyl ketone is present in a 3α-3,4-dichlorophenyl analogue, as in **26**, one of the most selective and potent DAT inhibitors is discovered (DAT: 1.1 nM; SERT: 2520 nM) (see Scheme 3).

Finally, the orientation of the oxygen at the 6 or 7-position is not absolutely crucial for biological activity since both α-, *β*-, and even "planar" 7-ketones manifest nanomolar binding affinity at the DAT. Indeed, if this is so, then the hydrogen bonding between an hydroxyl at this position and the nitrogen may be of limited consequence. In this regard, the 7α-OH compound **30b** (Scheme 5) is about half as potent (IC_{50} = 3.04 nM) as the 7*β*-OH analogue **18a** at the DAT (IC_{50} = 1.19 nM). The 7-keto analogue **19** (Scheme 2) remains quite potent at 14.1 nM. In the 6-OH series, the same holds true; the 6*β* **17a** binds with an affinity of 6.09 nM, and the 6α **30a** manifests an IC_{50} = 33.2 nM.

Three conclusions emerge: First, 2*β*-substitution provides greater potency than 2α-substitution. Second, replacement of the C2-ester with a C2-ketone retains potency at the DAT. Third, both 6α- and 7 α-hydroxylated and 7-keto compounds prove potent DAT inhibitors.

Conclusion

A number of bridge hydroxylated 8-aza-tropanes have been prepared and their affinities at the dopamine and serotonin transporters have been studied. In general, both 6- and 7-hydroxylated tropanes have similar potency to their unsubstituted counterparts but manifest greater selectivity for the DAT. SAR in this series mimics that found in other tropanes in which 3,4-dichloro substitution generally confers greatest potency at the DAT and the unsubstituted phenyl ring at C3 is least potent. 7-Hydroxylated compounds are slightly more potent at the DAT than their 6-hydoxylated counterparts. In accord with known SAR, the 3α-aryl compounds manifest a marked selectivity for DAT inhibition. As for other tropanes, the DAT has been found to be enantioselective and the 1*S*-isomers are considerably more potent inhibitors than the 1*R* enan-

tiomers. Finally, introduction of a C2-ethyl ketone, as in **26**, resulted in an extremely potent and selective DAT inhibitor.

Experimental Section

NMR spectra were recorded in $CDCl_3$, unless otherwise mentioned, on a JEOL 300 NMR spectrometer operating at 300.53 MHz for ^1H and 75.58 MHz for ^{13}C. TMS was used as internal standard. Melting points are uncorrected and were measured on a Gallenkamp melting point apparatus. Thin-layer chromatography (TLC) was carried out on Baker Si250F plates. Visualization was accomplished with either UV exposure or treatment with phosphomolybdic acid (PMA). Flash chromatography was carried out on Baker Silica Gel 40 μM. Elemental analyses were performed by Atlantic Microlab, Atlanta, GA. HRMS was performed at Harvard University, MA. Optical rotations were measured on a Perkin-Elmer 241 Polarimeter. All reactions were conducted under an inert (N_2) atmosphere. [^{3}H]WIN 35,428 (2β-carbomethoxy-3β-(4-fluorophenyl)-*N*-[^{3}H]methyltropane, 79.4−87.0 Ci/mmol) and [^{3}H]-citalopram (86.8 Ci/mmol) were purchased from DuPont-New England Nuclear (Boston, MA). (1*S*)-(−)-Camphanic chloride (98% ee) was purchased from Aldrich. A Beckman 1801 scintillation counter was used for scintillation spectrometry. Bovine serum albumin (0.1%) was purchased from Sigma Chemicals. (*R*)-(−)-Cocaine hydrochloride for the pharmacological studies was donated by the National Institute on Drug Abuse [NIDA]. Room temperature is ca. 22 °C. TMSBr: trimethylsilyl bromide. Solution A: 2-hydroxy-2-methylpropanol/1,2-dichloroethane, 37:63. Yields have not been optimized.

6-Hydroxy-2-methoxycarbonyl-8-methyl-3-oxo-8-azabicyclo[3.2.1]octane (1a) and 7-Hydroxy-2-methoxycarbonyl-8-methyl-3-oxo-8-azabicyclo[3.2.1]octane (1b). Acetonedicarboxylic acid (40 g, 0.27 mol) was added slowly to a solution of acetic acid (60 mL) and acetic anhydride (43 mL) at 0 °C. The mixture was stirred below 10 °C. The acid dissolved slowly and a pale yellow precipitate was formed over 3 h. The product was filtered, washed with glacial acetic acid (30 mL), and followed by benzene (100 mL). The resultant white powder was dried at high vacuum to afford 30 g of the desired acetonedicarboxylic acid anhydride (86%): mp 137−138 °C (lit.[38] 137.5−138.5 °C). Cold dry methanol (160 mL) was added to acetonedicarboxylic acid anhydride (50 g, 0.39 mol). The solution was allowed to stand for 1 h and filtered. The filtrate, acetonedicarboxylic acid monomethylester,[38] was used directly in the following reaction. A mixture of 2,5-dimethoxydihydrofuran (53.6 g, 0.41 mol) and 3 M aqueous HCl (1 L) was allowed to stand for 12 h at 22 °C. The brown solution was cooled to 0 °C and ice (500 g) was added before being neutralized with aqueous 3 M NaOH (1 L). Methylamine hydrochloride (41 g, 0.62 mol) in H_2O (300 mL) was added to this solution followed by the preformed methanol solution (160 mL above) of acetonedicarboxylic acid monomethylester and sodium acetate (50 g) in H_2O (200 mL). The mixture (pH 4.5) was stirred for 2 days at 22 °C. The resultant red solution was extracted with hexanes (500 mL × 2) to remove nonpolar byproducts. The aqueous solution was neutralized and saturated by adding solid K_2CO_3 (960 g). The saturated solution was extracted with CH_2Cl_2 (300 mL × 3), and the combined extracts were dried over anhydrous K_2CO_3, filtered, and concentrated to provide the crude product (21.6 g). The aqueous solution was extracted with solvent A and the combined extracts were dried over anhydrous K_2CO_3, filtered, and concentrated to provide a pale yellow solid that was found to be a mixture of 6- and 7-hydroxy-2-methoxycarbonyl-8-methyl-3-oxo-8-azabicyclo[3.2.1]octanes of good purity (30.6 g) and were used without further purification. The crude product obtained from the CH_2Cl_2 extracts was purified by column chromatography [10% NEt_3, 60% EtOAc in hexanes (30−90%), followed by 10% NEt_3, 5% MeOH, and 85% EtOAc] to afford 6.2 g of a mixture of 6β- and 7β-methoxy-2-methoxycarbonyl-8-methyl-3-oxo-8-azabicyclo[3.2.1]octane[26] as an oil: R_f 0.44 (10% NEt_3, 20% EtOAc in hexanes) and 12.8 g of 6β- and 7β-hydroxy-2-methoxycarbonyl-8-methyl-3-oxo-8-azabicyclo[3.2.1]-octane as yellow solids (**1a** and **1b**). The total yield of 6β- and 7β-hydroxy-2-methoxycarbonyl-8-methyl-3-oxo-8-azabicyclo-[3.2.1]octane was 43.4 g (52%). ^1H NMR of **1a** (mixture of the keto-2α- and keto-2β-epimers and the intermediate enol compounds) δ 4.18−4.02 (m, 1H), 3.89−3.85 (m, 1H), 3.78, 3.76 (2s, 3H), 3.45−3.36 (m, 1H), 3.21 (d, J = 6 Hz, 1H), 2.75−2.62 (m, 2H), 2.40, 2.38 (2s, 3H), 2.37−2.22 (m, 1H), 2.1−1.92 (m, 2H). ^1H NMR of **1b** (observed in the intermediate enol form only) δ 11.83 (s, 1H), 4.06 (dd, J = 5.8, 2.0 Hz, 1H), 3.78 (s, 3H), 3.66 (s, 1H), 3.37 (t, J = 4.7 Hz, 1H), 2.66 (dd, J = 18.9, 4.6 Hz, 1H), 2.39 (s, 3H), 2.02−1.96 (m, 1H), 1.73 (d, J = 18.6 Hz, 1H).

6β-Methoxymethoxy-2-methoxycarbonyl-8-methyl-3-oxo-8-azabicyclo[3.2.1]octane (2a) and 7β-Methoxymethoxy-2-methoxycarbonyl-8-methyl-3-oxo-8-azabicyclo[3.2.1]-octane (2b). To a solution of a mixture of 6β- and 7β-methoxy-2-methoxycarbonyl-8-methyl-3-oxo-8-azabicyclo[3.2.1]octane (**1a** and **1b**) (30.6 g, 140 mmol) in anhydrous CH_2Cl_2 (600 mL) and dimethoxymethane (170 mL), *p*-toluenesulfonic acid monohydrate (31 g, 160 mmol) was added in a 2-L flask fitted with a Soxhlet extractor containing 4 Å molecular sieves. The reaction mixture was heated to reflux until complete. The mixture was cooled and treated with saturated aqueous Na_2CO_3 (200 mL) and extracted with CH_2Cl_2 (300 mL × 4). The combined organic extracts were dried over K_2CO_3, filtered, and concentrated to obtain a mixture of MOM protected alcohols. The mixture was separated by column chromatography [(5−10% NEt_3, 65% EtOAc in hexanes (30−50%)] to obtain 6β-hydroxy-2-methoxycarbonyl-8-methyl-3-oxo-8-azabicyclo[3.2.1]-octane **2a** (11.0 g, 30%) and 7β-hydroxy-2-methoxycarbonyl-8-methyl-3-oxo-8-azabicyclo[3.2.1]octane **2b** (10.6 g, 28%) along with a mixture of the MOM protected alcohols **2a** and **2b** (2.9 g, 8%).

2a: yellow oil: R_f 0.55 (10% Et_3N in EtOAc); ^1H NMR (mixture of the keto-2α- and keto-2β-epimers and the intermediate enol compounds) δ 11.69 (s, enol H), 4.63, 4.62, 4.60 (3s, 2H), 4.10−3.96 (m, 2H), 3.88 (d, J = 6.6 Hz, 1H), 3.76, 3.75, 3.74 (3s, 3H), 3.36, 3.34 (2s, 3H), 3.11−2.71 (m, 1H), 2.69, 2.62, 2.41 (3s, 3H) 2.34−1.91 (m, 2H). **2b**: yellow solid: R_f 0.38 (10% Et_3N, 30% EtOAc, and 60% hexanes); ^1H NMR (observed in the intermediate enol form only) δ 11.77 (s, 1H), 4.69 (d, J = 6.6 Hz, 1H), 4.63 (d, J = 6.6 Hz, 1H), 4.06 (dd, J = 1.6, 7.2 Hz, 1H), 3.81 (s, 1H), 3.79 (s, 3H), 3.45 (dd, J = 4.6, 6.6 Hz, 1H), 3.36 (s, 3H), 2.75−2.66 (m, 1H), 2.43 (s, 3H), 2.18 (dd, J = 7.4, 14.3 Hz, 1H), 1.99 (dd, J = 7.4, 14.3 Hz, 1H), 1.79 (d, J = 18.7 Hz, 1H).

2-Carbomethoxy-3-trifluoromethylsulfonyloxy-7β-methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]oct-2-ene (3b). To a solution of 2-carbomethoxy-7β-methoxymethoxy-8-methyl-3-oxo-8-azabicyclo[3.2.1]octane, **2b** (4.25 g, 16.5 mmol) in THF (150 mL), sodium bistrimethylsilylamide (25 mL; 1.0 M solution in THF) was added dropwise at −70 °C under nitrogen. After stirring the solution for 30 min, *N*-phenyltrifluoromethanesulfonimide (7.06 g, 19.8 mmol) was added in one portion at −70 °C. The reaction was allowed to warm to 22 °C and stirred overnight. The volatile solvents were removed on a rotary evaporator. The residue was dissolved in CH_2Cl_2 (200 mL) and washed with H_2O (100 mL) and brine (100 mL). The dried ($MgSO_4$) CH_2Cl_2 layer was concentrated to dryness and purified by flash chromatography (2−10% Et_3N, 15−30% EtOAc in hexanes) to afford 3.63 g (57%) of **3b** as a pale yellow oil: R_f 0.29 (10% Et_3N, 30% EtOAc, 60% hexanes); ^1H NMR of **3b** δ 4.74 (d, J = 6.8 Hz, 1H), 4.65 (d, J = 6.8 Hz, 1H), 4.21 (dd, J = 1.6, 7.3 Hz, 1H), 4.0 (s, 1H), 3.83 (s, 3H), 3.56−3.50 (m, 1H), 3.37 (s, 3H), 2.80 (dd, J = 4.1, 18.4 Hz, 1H), 2.44 (s, 3H), 2.21 (dd, J = 7.4, 14.0 Hz, 1H), 2.02 (dd, J = 7.4, 14.1 Hz, 1H), 1.89 (d, J = 18.7 Hz, 1H); HRMS Cal (M+1): 390.0856; Found 390.0811.

2-Carbomethoxy-3-(trifluoromethyl)sulfonyloxy-6β-methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]oct-2-ene (3a). Prepared as described above for **3b** (64%): R_f 0.45 (10%

Et_3N, 30% EtOAc, 60% hexanes); ^1H NMR (100 MHz): δ 4.64 (s, 2H), 4.07 (dd, 1H), 3.81 (s, 3H), 3.5−3.30 (m, 2H), 3.36 (s, 3H), 2.85 (dd, 1H), 2.44 (s, 3H), 2.4−1.8 (m, 3H).

General Procedures for Suzuki Coupling Reactions to Obtain 4 and 5. To a solution of 2β-carbomethoxy-3-[(trifluoromethyl)sulfonyl]oxy-7β- (or 6β-) methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]oct-2-ene, **3** (1 equiv) in diethoxymethane was added LiCl (2 equiv), Na_2CO_3 (2 M aqueous solution, 2 equiv), and the aryl boronic acid (1.1 equiv). The solution was stirred and deoxygenated by bubbling N_2 into the solution for 15 min before the addition, in one portion, of tris(dibenzylideneacetone)dipalladium(0) (0.1 equiv) under a strong stream of N_2. After being further deoxygenated for another 0.5 h, the solution was heated to reflux under N_2 until no starting material remained (~ 3−6 h) (TLC). The mixture was cooled to 22 °C and filtered through Celite. The Celite was washed with EtOAc. The combined organic layers were separated and the aqueous layer was extracted with EtOAc. The organic layer was combined and dried over K_2CO_3. The solvent was removed and the residue was purified by flash column chromatography (10% Et_3N, 30% EtOAc, 60% hexanes) to afford the coupled compounds.

2-Carbomethoxy-3-(3,4-dichlorophenyl)-6β-methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]oct-2-ene (4a). The general procedure described above was followed. The product was obtained as an oil (86%): R_f 0.16 (10% Et_3N, 20% EtOAc, 70% hexanes); ^1H NMR δ 7.39 (d, 1H), 7.21 (d, 1H), 6.95 (dd, 1H), 4.66 (s, 2H), 4.11 (dd, 1H), 3.95 (d, 1H), 3.35 (s, 3H), 3.39−3.35 (m, 4H), 2.70 (dd, 1H), 2.54−2.43 (m, 4H), 2.19 (ddd, 1H), 2.02 (d, 1H).

2-Carbomethoxy-3-(2-naphthyl)-6β-methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]oct-2-ene (4b). The general procedure described above was followed. The product was obtained as an oil (53%): R_f 0.36 (10% Et_3N, 30% EtOAc, 60% hexane); ^1H NMR δ 7.84−7.77 (m, 3H), 7.59 (s, 1H), 7.50−7.44 (m, 2H), 7.24 (dd,1H), 4.69 (s, 2H), 4.20 (dd, 1H), 4.00 (d, 1H), 3.43 (s, 3H), 3.41−3.38 (m, 4H), 2.82 (dd, 1H), 2.59−2.50 (m, 4H), 2.26−2.17 (m, 2H).

2-Carbomethoxy-3-(4-fluorophenyl)-6β-methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]oct-2-ene (4c). The general procedure described above was followed. The product was obtained as a yellow oil (93%): R_f 0.12 (10% Et_3N, 20% EtOAc, 70% hexane); ^1H NMR δ 7.11−6.97 (m, 4H), 4.67 (s, 2H), 4.12 (dd, 1H), 3.94 (d, 1H), 3.49 (s, 3H), 3.38−3.33 (m, 4H), 2.71 (dd, 1H), 2.50−2.44 (m, 4H), 2.19 (ddd, 1H), 2.06 (d, 1H).

2-Carbomethoxy-3-phenyl-6β-methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]oct-2-ene (4d). The general procedure described above was followed. The product was obtained as a light yellow oil (89%): R_f 0.16 (10% Et_3N, 20% EtOAc, 70% hexane); ^1H NMR δ 7.36−7.23 (m, 3H), 7.14−7.11 (m, 2H), 4.67 (s, 2H), 4.16 (dd, 1H), 4.03 (d, 1H), 3.47 (s, 3H), 3.43 (m, 1H), 3.38 (s, 1H), 2.87 (dd, 1H), 2.58−2.51 (m, 4H), 2.23 (ddd, 1H), 2.15 (d, 1H).

2-Carbomethoxy-3-(3,4-dichlorophenyl)-7β-methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]oct-2-ene (5a). The general procedure described above was followed. The product was obtained as an oil (80%): R_f 0.33 (10% Et_3N, 20% EtOAc, 70% hexane); ^1H NMR (100 MHz) δ 7.40 (d, 1H), 7.19 (d, 1H), 6.93 (dd, 1H), 4.71 (m, 2H), 4.24 (dd, 1H), 3.91 (s, 1H), 3.56 (s, 3H), 3.48 (bs, 1H), 3.39 (s, 3H), 2.52 (s, 3H), 2.90−1.5 (m, 4H); ^{13}C NMR δ 168.3, 144.8, 142.0, 133.4, 132.8, 131.3, 129.9, 128.2, 127.4, 96.4, 83.2, 66.3, 57.5, 56.5, 52.7, 41.5, 36.0, 35.7.

2-Carbomethoxy-3-(2-naphthyl)-7β-methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]oct-2-ene (5b). The general procedure described above was followed. The product was obtained as a yellow oil (100%): R_f 0.52 (10% Et_3N, 20% EtOAc, 70% hexane); ^1H NMR δ 7.79 (m, 3H), 7.57 (s, 1H), 7.48 (m, 2H), 7.22 (d, 1H), 4.74 (dd, 2H), 4.35 (dd, 1H), 3.95 (s, 1H), 3.52−3.46 (m, 4H), 3.41 (s, 3H), 2.85 (dd, 1H), 2.58 (s, 3H), 2.27 (dd, 1H), 2.15 (dd, 1H), 1.98 (d, 1H).

2-Carbomethoxy-3-(4-fluorophenyl)-7β-methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]oct-2-ene (5c). The general procedure described above was followed. The product was obtained as an oil (100%): R_f 0.53 (10% Et_3N, 20% EtOAc, 70% hexane); ^1H NMR δ 7.15−7.00 (m, 4H), 4.75 (dd, 2H), 4.29 (dd, 1H), 3.89 (s, 1H), 3.53 (s, 3H), 3.45 (m, 1H), 3.39 (s, 3H), 2.73 (dd, 1H), 2.51 (s, 3H), 2.25 (dd, 1H), 2.07 (dd, 1H), 1.85 (d, 1H).

2-Carbomethoxy-3-phenyl-7β-methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]oct-2-ene (5d). The general procedure described above was followed. The product was obtained as an oil (29%): R_f 0.56 (10% Et_3N, 30% EtOAc, 70% hexane); ^1H NMR δ 7.32−7.27 (m, 3H), 7.12−7.07 (m, 2H), 4.73 (dd, 2H), 4.30 (dd, 1H), 3.89 (s, 1H), 3.50 (s, 3H), 2.47 (m, 1H), 3.38 (s, 3H), 2.76 (dd, 1H), 2.52 (s, 3H), 2.25 (dd, 1H), 2.09 (dd, 1H), 1.88 (d, 1H).

General Procedure for SmI_2 Reduction Reactions to Obtain 9−12. Note that the 3α and 3β isomers are obtained and are separated by column chromatography. To a THF (anhydrous, 5−10 mL) solution of 2-carbomethoxy-3-aryl-7- (or 6-) methoxymethoxy-8-azabicyclo[3.2.1]oct-2-ene and anhydrous methanol (20 equiv) at −78 °C under N_2 was added SmI_2 (0.1 M solution in THF, 8 equiv) dropwise. The resulting solution was kept stirring at −78 °C for 4 h and was then quenched with H_2O (10 mL). After warming the solution to 22 °C, sat. $NaHCO_3$ was added and the precipitate was filtered through a Celite pad. The pad was washed with EtOAc and the aqueous layer was back extracted with EtOAc three times. The organic layers were combined, washed with brine, and dried over K_2CO_3. The solvent was removed, and the residue was purified by two consecutive flash columns (First: 10% Et_3N, 30% EtOAc, 60%, hexanes; second: 5% MeOH, 95% $CHCl_3$) to obtain the 2β, 3β- (**9** and **11**) and 2β, 3α- (**10** and **12**) isomers.

2β-Carbomethoxy-3β-(3,4-dichlorophenyl)-6β-methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]octane (9a) and 2β-Carbomethoxy-3α-(3,4-dichlorophenyl)-6β-methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]octane (10a). The title compounds were prepared as in the general procedure given above. Compound **9a** (an oil: 16%) could not be readily purified and was therefore carried through to the next step as is (see **14a**). R_f 0.67 (Et_3N 10%, EtOAc 30%, hexanes 60%). Compound **10a** was obtained as an oil (8%): R_f 0.30 (3% MeOH, $CHCl_3$); R_f 0.69 (Et_3N 10%, EtOAc 30%, hexanes 60%). ^1H NMR δ 7.32 (d, 1H), 7.25 (d, 1H), 7.01 (d, 1H), 4.64 (dd, 2H), 4.12 (dd, 1H), 3.59−3.55 (m, 5H), 3.39−3.01 (m, 5H), 2.55 (s, 3H), 2.46−2.25 (m, 3H), 2.10 (dd, 1H), 1.29 (ddd, 1H).

2β-Carbomethoxy-3β-(2-naphthyl)-6β-methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]octane (9b) and 2β-Carbomethoxy-3α-(2-naphthyl)-6β-methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]octane (10b). The title compounds were prepared as in the general procedure given above. Compound **9b** was obtained as an oil (38%): R_f 0.30 (3% MeOH/$CHCl_3$); ^1H NMR δ 7.75 (t, 3H), 7.65 (s, 1H), 7.46−7.33 (m, 3H), 4.67 (s, 2H), 4.32 (dd, 1H), 3.80 (d, 1H), 3.47 (s, 1H), 3.44 (s, 3H), 3.39 (s, 3H), 2.97−2.91 (m, 2H), 2.68 (dt, 1H), 2.52 (s, 3H), 2.37 (ddd, 1H), 2.27 (dd, 1H), 1.92 (dt, 1H). Compound **10b** was obtained as an oil (38%: R_f 0.41 (5% MeOH/$CHCl_3$); ^1H NMR δ 7.70 (t, 3H), 7.62 (s, 1H), 7.48−7.38 (m, 2H), 7.32 (d, 1H), 4.66 (dd, 2H), 4.19 (dd, 1H), 3.65 (s, 1H), 3.59 (s, 1H), 3.54 (s, 3H), 3.39−3.36 (m, 4H), 2.59 (s, 3H), 2.57−2.46 (m, 2H), 2.10 (ddd, 1H), 2.18 (dd, 1H), 1.53 (ddd, 1H).

2β-Carbomethoxy-3β-(4-fluorophenyl)-6β-methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]octane (9c) and 2β-Carbomethoxy-3α-(4-fluorophenyl)-6β-methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]octane (10c). The title compounds were prepared as in the general procedure given above. Compound **9c** was obtained as an oil (31%): R_f 0.71 (10% Et_3N, 30% EtOAc, 60%/hexane); ^1H NMR δ 7.20−7.15 (m, 2H), 6.98−6.92 (m, 2H), 4.65 (s, 2H), 4.26 (dd, J = 7.4, 3.3 Hz, 1H), 3.76 (d, J = 6.6 Hz, 1H), 3.50 (s, 3H), 3.42 (s, 1H), 3.38 (s, 3H), 2.82−2.71 (m, 2H), 2.57−2.48 (m, 4H), 2.35 (ddd, J = 14.3, 7.4, 3.3 Hz, 1H), 2.19 (dd, J = 14.3, 7.4 Hz, 1H), 1.78 (m, 1H). Compound **10c** was obtained as an oil (23%): R_f 0.71 (10% Et_3N, 30% EtOAc, 60% hexane); ^1H NMR δ 7.15−7.11 (m, 2H), 6.98−6.91 (m, 2H), 4.64 (dd, 2H), 4.13 (dd, J = 7.1, 3.3 Hz, 1H), 3.60−3.53 (m, 4H), 3.40−3.31 (m, 5H), 2.57 (s, 3H), 2.54−

2.26 (m, 3H), 2.12 (dd, J = 14.0, 7.1 Hz, 1H), 1.33 (ddd, J = 14.0, 10.9, 1.6 Hz, 1H).

2β-Carbomethoxy-3β-phenyl-6β-methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]octane (9d) and 2β-Carbomethoxy-3α-phenyl-6β-methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]octane (10d). The title compounds were prepared as in the general procedure given above. Compound **9d** obtained as an oil (28%): R_f 0.25 (5% MeOH/$CHCl_3$); ^{1}H NMR δ 7.29−7.13 (m, 5H), 4.66 (s, 2H), 4.27 (dd, J = 7.1, 3.3 Hz, 1H), 2.77 (m, 1H), 3.48 (s, 3H), 3.43 (s, 1H), 3.38 (s, 3H), 2.86 (t, J = 4.1 Hz, 1H), 2.79 (dt, J = 12.9, 4.9 Hz, 1H), 2.60−2.50 (m, 4H), 2.35 (ddd, J = 14, 6.8, 3.3 Hz, 1H), 2.20 (dd, J = 14.3, 7.4 Hz, 1H), 1.81 (dt, J = 12.4, 3.9 Hz, 1H). Compound **10d** obtained as an oil (25%)**:** R_f 0.50 (5% MeOH/$CHCl_3$); ^{1}H NMR δ 7.29−7.14 (m, 5H), 4.64 (dd, 2H), 4.14 (dd, J = 7.1, 3.0 Hz, 1H), 3.59−3.57 (m, 4H), 3.48−3.32 (m, 5H), 2.57 (s, 3H), 2.50−2.37 (m, 2H), 2.29 (ddd, J = 14.6, 7.1, 3.0 Hz, 1H), 2.1 (dd, J = 14.3, 7.4 Hz, 1H), 1.4 (ddd, 1H).

2β-Carbomethoxy-3β-(3,4-dichlorophenyl)-7β-methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]octane (11a) and 2β-Carbomethoxy-3α-(3,4-dichlorophenyl)-7β-methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]octane (12a). The title compounds were prepared as in the general procedure given above. Compound **11a** obtained as a yellow oil (37%): R_f 0.52 (5% MeOH/$CHCl_3$); ^{1}H NMR δ 7.35 (d, 1H), 7.30 (d, 1H), 7.10 (dd, 1H), 4.70 (dd, 2H), 4.35 (dd, 1H), 3.62 (s, 1H), 3.54 (m, 4H), 3.42 (s, 3H), 3.00 (m, 1H), 2.72−2.62 (m, 1H), 2.51−2.41 (m, 4H), 2.25 (ddd, 1H), 2.07 (dd, 1H), 1.59 (dt, 1H). Compound **12a** was obtained as a white solid (36%): R_f 0.67 (5% MeOH/$CHCl_3$); ^{1}H NMR δ 7.32 (d, 1H), 7.25 (d, 1H), 7.02 (dd, 1H), 4.66 (dd, 2H), 4.25 (dd, 1H), 3.62 (s, 3H), 3.48−3.32 (m, 6H), 2.54−2.47 (m, 4H), 2.43−2.33 (m, 1H), 2.20 (ddd, 1H), 2.00 (dd, 1H), 1.21 (dt, 1H).

2β-Carbomethoxy-3β-(2-naphthyl)-7β-methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]octane (11b) and 2β-Carbomethoxy-3α-(2-naphthyl)-7β-methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]octane (12b). The title compounds were prepared as in the general procedure given above. Compound **11b** was obtained as an oil (29%): R_f 0.41 (5% MeOH/$CHCl_3$); ^{1}H NMR δ 7.80−7.75 (m, 3H), 7.68 (s, 1H), 7.48−7.35 (m, 3H), 4.74 (dd, 2H), 4.44 (dd, 1H), 3.67−3.59 (m, 2H), 3.44 (s, 6H), 3.17 (t, 1H), 2.89 (dt, 1H), 2.69 (dt, 1H), 2.52 (s, 3H), 2.27 (ddd, 1H), 2.15 (dd, 1H), 1.72 (dt, 1H). Compound **12b** was obtained as an oil (26%): R_f 0.31 (5% MeOH/$CHCl_3$); ^{1}H NMR δ 7.78−7.72 (m, 3H), 7.67 (s, 1H), 6.95−6.88 (m, 3H), 4.67 (dd, 2H), 4.28 (dd, 1H), 3.58 (s, 3H), 3.53 (s, 1H), 3.45−3.37 (m, 5H), 2.50 (t, 1H), 2.47 (s, 3H), 2.42 (dt, 1H), 2.15 (ddd, 1H), 2.00 (dd, 1H), 1.23 (dt, 1H).

2β-Carbomethoxy-3β-(4-fluorophenyl)-7β-methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]octane (11c) and 2β-Carbomethoxy-3α-(4-fluorophenyl)-7β-methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]octane (12c). The title compounds were prepared as in the general procedure given above. Compound **11c** was obtained as an oil (35%): R_f 0.63 (EtOAc); ^{1}H NMR δ 7.22−7.18 (m, 2H), 6.98−6.91 (m, 2H), 4.71 (dd, 2H), 4.38 (dd, 1H), 3.62−3.57 (m, 2H), 3.50 (s, 3H), 3.42 (s, 3H), 2.99 (t, 1H), 2.87−2.78 (m, 1H), 2.57−2.48 (m, 4H), 2.22 (ddd, 1H), 2.06 (dd, 1H), 1.61 (dt, 1H). Compound **12c** was obtained as a solid (40%): R_f 0.36 (10% Et_3N, 30% EtOAc, 60% hexanes); ^{1}H NMR δ 7.16−7.10 (m, 2H), 6.97−6.91 (m, 2H), 4.66 (dd, 2H), 4.24 (dd, 1H), 3.59 (s, 3H), 3.46 (m, 1H), 3.39−3.33 (m, 5H), 2.51 (t, 1H), 2.48 (s, 3H), 2.38 (dt, 1H), 2.19 (ddd, 1H), 2.01 (dd, 1H), 1.24 (dt, 1H).

2β-Carbomethoxy-3β-phenyl-7β-methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]octane (11d) and 2β-Carbomethoxy-3α-phenyl-7β-methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]octane (12d). The title compounds were prepared as in the general procedure given above. Compound **11d** was obtained as an oil (25%): R_f 0.15 (EtOAc); ^{1}H NMR δ 7.29−7.22 (m, 4H), 7.18−7.12 (m, 1H), 4.71 (dd, 2H), 4.37 (dd, 1H), 3.61−3.57 (m, 2H), 3.48 (s, 3H), 3.43 (s, 3H), 3.03 (t, 1H), 2.80−2.69 (dt, 1H), 2.60−2.48 (m, 4H), 2.25 (ddd, 1H), 2.07 (dd, 1H), 1.62 (dt, 1H). Compound **12d** was obtained as an oil (31%): R_f 0.50 (EtOAc); ^{1}H NMR δ 7.30−7.12 (m, 5H), 4.65 (dd, 2H), 4.24 (dd, 1H), 3.60 (s, 3H), 3.51−3.37 (m, 6H), 2.62−2.58 (m, 4H), 2.40 (dt, 1H), 2.20 (ddd, 1H), 2.03 (dd, 1H), 1.25 (dt, 1H).

General Procedures for Cleavage of MOM Protecting Group. To a solution of MOM protected alcohol in anhydrous CH_2Cl_2 containing 4 Å molecular sieves, at 0 °C, was added TMSBr (10 equiv). The solution was slowly allowed to warm to 22 °C and stirred overnight. The reaction was quenched by slow addition of aq $NaHCO_3$ and the aqueous layer was exhaustively extracted with CH_2Cl_2. The extracts were combined and dried over K_2CO_3. The solvent was removed and residue was purified by flash column chromatography (10% Et_3N, 30−90% EtOAc, 60−0% hexanes) to give the product.

2-Carbomethoxy-3-(3,4-dichlorophenyl)-6β-hydroxy-8-methyl-8-azabicyclo[3.2.1]oct-2-ene (7a). The procedure described above was followed. A white crystalline solid was obtained (71%): mp 94.0−96.0 °C; R_f 0.13 (10% Et_3N/EtOAc); ^{1}H NMR δ 7.39 (d, 1H), 7.21 (d, 1H), 6.95 (dd, 1H), 4.19 (m, 1H), 3.94 (d, J = 6.6 Hz, 1H), 3.53 (s, 3H), 3.23 (d, J = 5.8 Hz, 1H), 2.65 (dd, J = 19.5, 5.8 Hz, 1H), 2.54−2.48 (m, 4H), 2.25 (bs, 1H), 2.09−1.97 (m, 2H). Anal. ($C_{16}H_{17}Cl_2NO_3$) C, H, N.

2-Carbomethoxy-3-(2-naphthyl)-6β-hydroxy-8-methyl-8-azabicyclo[3.2.1]oct-2-ene (7b). The procedure described above was followed to obtain a white powder (29%); mp 165.0−167.0 °C; R_f 0.15 (10% Et_3N/EtOAc); ^{1}H NMR δ 7.84−7.78 (m, 3H), 7.59 (s, 1H), 7.49−7.46 (m, 2H), 7.25−7.22 (m, 1H), 4.26 (dd, J = 7.4, 3.0 Hz, 1H), 4.00 (d, J = 6.3 Hz, 1H), 3.45 (s, 3H), 3.27 (d, J = 5.5 Hz, 1H), 2.77 (dd, J = 19.5, 5.8 Hz, 1H), 2.62−2.55 (m, 4H), 2.19 (d, J = 19.5 Hz, 1H), 2.08 (ddd, J = 13.5, 6.6, 2.7 Hz, 1H). Anal. ($C_{20}H_{21}NO_3$) C, H, N.

2-Carbomethoxy-3-(4-fluorophenyl)-6β-hydroxy-8-methyl-8-azabicyclo[3.2.1]oct-2-ene (7c). The procedure described above was followed to obtain a white crystalline solid (22%); mp 124.0−126.0 °C; R_f 0.31 (10% Et_3N/EtOAc); ^{1}H NMR δ 7.39−6.98 (m, 4H), 4.19 (dd, J = 7.1, 2.7 Hz, 1H), 3.94 (d, J = 6.6 Hz, 1H), 3.50 (s, 3H), 3.23 (d, J = 5.5 Hz, 1H), 2.66 (dd, J = 19.5, 5 Hz, 1H), 2.55−2.49 (m, 4H), 2.08−2.01 (m, 2H). Anal. ($C_{16}H_{18}FNO_3$) C, H, N.

2-Carbomethoxy-3-phenyl-6β-hydroxy-8-methyl-8-azabicyclo[3.2.1]oct-2-ene (7d). The procedure described above was followed to obtain a white crystalline solid (13%); mp 165.0−167.0 °C; R_f 0.22 (10% Et_3N/EtOAc); ^{1}H NMR δ 7.39−7.28 (m, 3H), 7.13−7.10 (m, 2H), 4.21 (dd, J = 7.4, 3.0 Hz, 1H), 3.94 (d, J = 6.6 Hz, 1H), 3.48 (s, 3H), 3.23 (d, J = 5.5 Hz, 1H), 2.70 (dd, J = 19.5, 5.5 Hz, 1H), 2.57−2.50 (m, 4H), 2.09 (d, J = 19.8 Hz, 1H), 2.07−2.01 (m, 1H). Anal. ($C_{16}H_{19}NO_3$) C, H, N.

2-Carbomethoxy-3-(3,4-dichlorophenyl)-7β-hydroxy-8-methyl-8-azabicyclo[3.2.1]oct-2-ene (8a). The procedure described above was followed. The product was obtained as a white solid (34%): mp 130.4−132.4 °C; R_f 0.1 (EtOAc); ^{1}H NMR δ 7.37 (d, 1H), 7.19 (d, 1H), 6.95 (dd, 1H), 4.29 (m, 1H), 3.65 (s, 1H), 3.56 (s, 3H), 3.40 (m, 1H), 2.62 (dd, 1H), 2.48 (s, 3H), 2.08 (m, 2H), 1.80 (d, 1H). Anal. ($C_{16}H_{17}Cl_2NO_3$) C, H, N.

(1*S*)-2-Carbomethoxy-3-(3,4-dichlorophenyl)-7β-hydroxy-8-methyl-8-azabicyclo[3.2.1]oct-2-ene ((1*S*)-8a). This compound was obtained from **(1*S*)-28** (vide infra) via the procedure described above: $[\alpha]_D^{21}$ = −58° (c = 1.0, $CHCl_3$), $[\alpha]_D^{21}$ = −49° (c = 0.40, MeOH) (>98% ee from ^{1}H NMR of **(1*S*)-28**) mp 130.4−131.8 °C.

(1*R*)-2-Carbomethoxy-3-(3,4-dichlorophenyl)-7β-hydroxy-8-methyl-8-azabicyclo[3.2.1]oct-2-ene ((1*R*)-8a). This compound was obtained from **(1*R*)-2** (vide infra) via the procedure described above: $[\alpha]_D^{21}$ +57° (c = 1.0, $CHCl_3$) (>98% ee from ^{1}H NMR of **(1*R*)-27**) mp 129−131 °C.

2-Carbomethoxy-3-(2-naphthyl)-7β-hydroxy-8-methyl-8-azabicyclo[3.2.1]oct-2-ene (8b). The procedure described above was followed. The product was obtained as a white solid (57%): mp 164.2−165.2 °C; R_f 0.4 (5% Et_3N/EtOAc); ^{1}H NMR δ 7.80 (m, 3H), 7.58 (s, 1H), 7.48 (m, 2H), 7.26 (m, 1H), 4.35 (m, 1H), 3.79 (s, 1H), 3.44 (m, 4H), 2.74 (dd, 1H), 2.54 (s, 3H), 2.14 (m, 2H), 2.01 (d, 1H). Anal. ($C_{20}H_{21}NO_3$) C, H, N.

2-Carbomethoxy-3-(4-fluorophenyl)-7β-hydroxy-8-methyl-8-azabicyclo[3.2.1]oct-2-ene (8c). The procedure described above was followed. The product was obtained as a

yellow gum (58%): R_f 0.23 (10% Et_3N/EtOAc); ^1H NMR δ 7.15−6.96 (m, 4H), 4.30 (m, 1H), 3.75 (s, 1H), 3.50 (s, 3H), 3.41 (m, 1H), 2.85 (bs, 1H), 2.64 (dd, 1H), 2.48 (s, 3H), 2.08 (m, 2H), 1.85 (d, 1H). Anal. ($C_{16}H_{18}FNO_3$) C, H, N.

2-Carbomethoxy-3-phenyl-7*β*-hydroxy-8-methyl-8-azabicyclo[3.2.1]oct-2-ene (8d). The procedure described above was followed to provide a white solid (62%): mp 113−114 °C; R_f 0.23 (10% Et_3N/EtOAc); ^1H NMR δ 7.36−7.30 (m, 3H), 7.15−7.08 (m, 2H), 4.31 (m, 1H), 3.73 (s, 1H), 3.51 (s, 3H), 3.41 (m, 1H), 2.66 (dd, 1H), 2.50 (s, 3H), 2.09 (m, 2H), 1.88 (d, 1H). Anal. ($C_{16}H_{19}NO_3$) C, H, N.

2*β*-Carbomethoxy-3*β*-(3,4-dichlorophenyl)-6*β*-hydroxy-8-methyl-8-azabicyclo[3.2.1]octane (14a). The procedure described above was followed to provide a white solid (88%): mp 93.5−95.5 °C; R_f 0.18 (5% MeOH/CH_2Cl_2); ^1H NMR δ 7.33 (d, 1H), 7.28 (d, 1H), 7.06 (dd, 1H), 4.44 (m, 1H), 3.84 (m, 1H), 3.51 (s, 3H), 3.30 (m, 1H), 2.79 (m, 1H), 2.68 (m, 1H), 2.56 (s, 3H), 2.45 (dt, 1H), 2.32−2.18 (m, 2H), 1.76 (m, 1H). Anal. ($C_{16}H_{19}Cl_2NO_3$) C, H, N.

2*β*-Carbomethoxy-3*β*-(2-naphthyl)-6*β*-hydroxy-8-methyl-8-azabicyclo[3.2.1]octane (14b). The procedure described above was followed to provide a white solid (89%): mp 84.0−86.0 °C; R_f 0.23 (10% MeOH/CH_2Cl_2); ^1H NMR δ 7.76 (t, 3H), 7.65 (s, 1H), 7.48−7.35 (m, 3H), 4.53 (m, 1H), 3.87 (m, 1H), 3.44 (s, 3H), 3.37 (m, 1H), 2.97−2.90 (m, 2H), 2.68 (dd, 1H), 2.60 (s, 3H), 2.32 (m, 2H), 1.93 (m, 1H), 1.78 (m, 1H). Anal. ($C_{20}H_{23}NO_3$) C, H, N.

2*β*-Carbomethoxy-3*β*-(4-fluorophenyl)-6*β*-hydroxy-8-methyl-8-azabicyclo[3.2.1]octane (14c). The procedure described above was followed to provide a white solid (30%): mp 162.0−164.0 °C; R_f 0.21 (10% MeOH/CH_2Cl_2); ^1H NMR δ 7.71 (m, 2H), 6.95 (m, 2H), 4.48 (m, 1H), 3.83 (m, 1H), 3.50 (s, 3H), 3.31 (s, 1H), 2.82−2.71 (m, 2H), 2.57 (s, 3H), 2.52 (dt, 1H), 2.35−2.21 (m, 2H), 1.79−1.75 (m, 2H). Anal. ($C_{16}H_{20}FNO_3$) C, H, N.

2*β*-Carbomethoxy-3*β*-phenyl-6*β*-hydroxy-8-methyl-8-azabicyclo[3.2.1]octane (14d). The procedure described above was followed to provide a white solid (33%): mp 150.0−152.0 °C; R_f 0.13 (10% MeOH/CH_2Cl_2); ^1H NMR δ 7.2−7.14 (m, 5H), 4.50 (m, 1H), 3.85 (m, 1H), 3.48 (s, 3H), 3.36 (m, 1H), 2.88−2.75 (m, 2H), 2.60 (s, 3H), 2.55 (dd, 1H), 2.29 (m, 2H), 1.81 (m, 1H). Anal. ($C_{16}H_{21}NO_3$) C, H, N.

2*β*-Carbomethoxy-3*β*-(3,4-dichlorophenyl)-7*β*-hydroxy-8-methyl-8-azabicyclo[3.2.1]octane (15a). The procedure described above was followed to provide a colorless crystalline solid (68%): mp 185.5−186.5 °C; R_f 0.47 (10% Et_3N/EtOAc); ^1H NMR δ 7.32 (d, 1H), 7.29 (d, 1H), 7.07 (dd, 1H), 4.53 (m, 1H), 3.60 (m, 1H), 3.53 (s, 3H), 3.00 (t, J = 3.8 Hz, 1H), 2.68−2.64 (m, 1H), 2.55 (s, 3H), 2.50−2.44 (m, 1H), 2.23−2.08 (m, 2H), 1.78 (d, J = 3.8 Hz, 1H), 1.59 (m, 1H). Anal. ($C_{16}H_{19}Cl_2NO_3$) C, H, N.

(1*S*)-2*β*-Carbomethoxy-3*β*-(3,4-dichlorophenyl)-7*β*-hydroxy-8-methyl-8-azabicyclo[3.2.1]octane ((1*S*)-15a). Obtained from **(1*S*)-8a** (vide infra) $[\alpha]_D^{21}$ = +25° (c = 1.3, $CHCl_3$) (>98% ee from ^1H NMR of **(1*S*)-28**) mp 185.5−186.5 °C.

(1*R*)-2*β*-Carbomethoxy-3*β*-(3,4-dichlorophenyl)-7*β*-hydroxy-8-methyl-8-azabicyclo[3.2.1]octane ((1*R*)-15a). Obtained from **(1*R*)-2** (vide infra) $[\alpha]_D^{21}$ = −26° (c = 1.3, $CHCl_3$) (>98% ee from ^1H NMR of **(1*R*)-27**) mp 186−187 °C.

2*β*-Carbomethoxy-3*β*-(2-naphthyl)-7*β*-hydroxy-8-methyl-8-azabicyclo[3.2.1]octane (15b). The procedure described above was followed to provide a white crystalline solid: (78%); mp 207.5−208.5 °C; R_f 0.15 (10% MeOH/$CHCl_3$); ^1H NMR δ 7.76 (t, 3H), 7.65 (s, 1H), 7.47−7.35 (m, 3H), 4.63 (t, 1H), 3.66 (m, 1H), 3.58 (s, 1H), 3.45 (s, 3H), 3.17 (m, 1H), 2.97−2.87 (m, 1H), 2.67 (dt, 1H), 2.60 (s, 3H), 2.28−2.19 (m, 2H), 1.85 (bs, 1H), 1.76−1.70 (m, 1H). Anal. ($C_{20}H_{23}NO_3$) C, H, N.

2*β*-Carbomethoxy-3*β*-(4-fluorophenyl)-7*β*-hydroxy-8-methyl-8-azabicyclo[3.2.1]octane (15c). The procedure described above was followed to obtain a white crystalline solid (11%): mp 179.3−181.3 °C; R_f 0.53 (10% Et_3N/EtOAc); ^1H NMR δ 7.18 (m, 2H), 6.96 (m, 2H), 4.59 (m, 1H), 3.67−3.61 (m, 2H), 3.50 (s, 3H), 3.03 (m, 1H), 2.79−2.50 (m, 5H), 2.20 (m, 2H), 1.61 (m, 1H). Anal. ($C_{16}H_{20}FNO_3$) C, H, N.

2*β*-Carbomethoxy-3*β*-phenyl-7*β*-hydroxy-8-methyl-8-azabicyclo[3.2.1]octane (15d). The procedure described above was followed to obtain a white crystalline solid (17%): mp 165.8−167.8 °C; R_f 0.13 (5% MeOH/$CHCl_3$); ^1H NMR δ 7.30−7.13 (m, 5H), 4.58 (dd, J = 6.6, 4.1 Hz, 1H), 3.62 (m, 1H), 3.53 (s, 1H), 3.49 (s, 3H), 3.06 (m, 1H), 2.75 (m, 1H), 2.57 (m, 4H), 2.22−2.11 (m, 2H), 1.64−1.59 (m, 1H). Anal. ($C_{16}H_{21}NO_3$) C, H, N.

2*β*-Carbomethoxy-3α-(3,4-dichlorophenyl)-6*β*-hydroxy-8-methyl-8-azabicyclo[3.2.1]octane (17a). The procedure described above was followed to obtain a white powder (18%): mp 129.1−131.1 °C; R_f 0.57 (10% Et_3N/EtOAc); ^1H NMR δ 7.34 (d, 1H), 7.26 (d, 1H), 7.02 (dd, 1H), 4.25 (m, 1H), 3.64−3.61 (m, 4H), 3.48−3.35 (m, 1H), 3.20 (d, 1H), 2.65 (s, 3H), 2.38−2.08 (m, 4H), 1.90 (bs, 1H), 1.29 (dd, 1H). Anal. ($C_{16}H_{19}Cl_2NO_3$) C, H, N.

2*β*-Carbomethoxy-3α-(2-naphthyl)-6*β*-hydroxy-8-methyl-8-azabicyclo[3.2.1]octane (17b). The procedure described above was followed to provide a white solid (77%): mp 93.5−94.5 °C; R_f 0.45 (0.5% MeOH/CH_2Cl_2); ^1H NMR δ 7.77 (m, 3H), 7.63 (s, 1H), 7.45 (m, 2H), 7.32 (d, 2H), 4.29 (m, 1H), 3.68 (m, 2H), 3.57 (s, 3H), 3.23 (d, 1H), 2.70 (s, 3H), 2.63 (d, 1H), 2.41 (dt, 1H), 2.21 (m, 2H), 1.54 (dd, 1H). Anal. ($C_{20}H_{23}NO_3$) C, H, N.

2*β*-Carbomethoxy-3α-(4-fluorophenyl)-6*β*-hydroxy-8-methyl-8-azabicyclo[3.2.1]octane (17c). The procedure described above was followed to provide a yellow crystalline solid (39%): mp 148.0−150.0 °C; R_f 0.53 (10% MeOH/CH_2Cl_2); ^1H NMR δ 7.13 (dd, 2H), 6.97 (t, 2H), 4.26 (m, 1H), 3.64−3.59 (m, 4H), 3.43 (m 1H), 3.21 (d, 1H), 2.67 (s, 3H), 2.40−2.12 (m, 4H), 1.31 (dd, 1H). Anal. ($C_{16}H_{20}FNO_3$) C, H, N.

2*β*-Carbomethoxy-3α-phenyl-6*β*-hydroxy-8-methyl-8-azabicyclo[3.2.1]octane (17d). The procedure described above was followed to provide a white powder (22%): mp 138.0−140.0 °C; R_f 0.21 (10% Et_3N/EtOAc); ^1H NMR δ 7.30−7.12 (m, 5H), 4.24 (m, 1H), 3.66−3.60 (m, 4H), 3.48 (dd, J = 17.9, 9.1 Hz, 1H), 3.21 (d, J = 8.8 Hz, 1H), 2.68 (s, 3H), 2.49 (d, J = 9.1 Hz, 1H), 2.42−2.32 (m, 1H), 2.25−2.17 (m, 2H), 1.45−1.36 (m, 1H). Anal. ($C_{16}H_{21}NO_3$) C, H, N.

2*β*-Carbomethoxy-3α-(3,4-dichlorophenyl)-7*β*-hydroxy-8-methyl-8-azabicyclo[3.2.1]octane (18a). The procedure described above was followed to provide a colorless solid (87%): mp 148.5−150 °C; R_f 0.18 (10% Et_3N, 40% EtOAc, 50% hexane); R_f 0.53 (10% Et_3N/EtOAc); ^1H NMR δ 7.31 (d, 1H), 7.26 (d, 1H), 7.25 (dd, 1H), 4.29 (m, 1H), 3.61 (s, 3H), 3.47−3.38 (m, 2H), 3.27 (s, 1H), 2.67 (s, 3H), 2.42−2.32 (m, 2H), 2.17−2.01 (m, 3H), 1.26 (dd, 1H). Anal. ($C_{16}H_{19}Cl_2NO_3$) C, H, N.

(1*S*)-2*β*-Carbomethoxy-3α-(3,4-dichlorophenyl)-7*β*-hydroxy-8-methyl-8-azabicyclo[3.2.1]octane ((1*S*)-18a). Obtained from **(1*S*)-8a**: $[\alpha]_D^{21}$ = −48° (c = 1.0, $CHCl_3$); $[\alpha]_D^{21}$ = −36° (c = 0.40, MeOH) (>98% ee from ^1H NMR of **(1*S*)-27**) mp 148.5−150 °C.

(1*R*)-2*β*-Carbomethoxy-3α-(3,4-dichlorophenyl)-7*β*-hydroxy-8-methyl-8-azabicyclo[3.2.1]octane ((1*R*)-18a). Obtained from **(1*R*)-2**: $[\alpha]_D^{21}$ = +47° (c = 1.0, $CHCl_3$) (>98% ee from ^1H NMR of **(1*R*)-27**) mp 149−150 °C.

2*β*-Carbomethoxy-3α-(2-naphthyl)-7*β*-hydroxy-8-methyl-8-azabicyclo[3.2.1]octane (18b). The procedure described above was followed to provide a yellow crystalline solid (62%): mp 140.1−141.9 °C; R_f 0.20 (5% MeOH/CH_2Cl_2); ^1H NMR δ 7.82−7.76 (m, 3H), 7.63 (s, 1H), 7.49−7.41 (m, 2H), 7.32 (d, 1H), 4.33 (m, 1H), 3.64 (m, 1H), 3.57 (s, 3H), 3.50 (m, 1H), 3.32 (s, 1H), 2.73 (s, 3H), 2.67 (d, 1H), 2.20−2.08 (m, 3H), 1.53−1.46 (m, 1H). Anal. ($C_{20}H_{23}NO_3$) C, H, N.

2*β*-Carbomethoxy-3α-(4-fluorophenyl)-7*β*-hydroxy-8-methyl-8-azabicyclo[3.2.1]octane (18c). The procedure described above was followed to obtain a white crystalline solid (47%): mp 177.2−179.0 °C; R_f 0.12 (EtOAc); ^1H NMR δ 7.18−7.10 (m, 2H), 6.99−6.93 (m, 2H), 4.29 (m, 1H), 3.59 (s, 3H), 3.51−3.38 (m, 2H), 3.26 (s, 1H), 2.70 (s, 3H), 2.47−2.35 (m, 2H), 2.18−2.00 (m, 2H), 1.29 (m, 1H). Anal. ($C_{16}H_{20}FNO_3$) C, H, N.

2β-Carbomethoxy-3α-phenyl-7β-hydroxy-8-methyl-8-azabicyclo[3.2.1]octane (18d). The procedure described above was followed to provide a white powder (26%): mp 165.0−167.0 °C; R_f 0.19 (5% MeOH/CH_2Cl_2); ^{1}H NMR δ 7.31−7.15 (m, 5H), 4.29 (m, 1H), 3.59 (s, 3H), 3.52−3.42 (m, 2H), 3.29 (s, 1H), 2.71 (s, 3H), 2.54−2.36 (m, 2H), 2.18−2.02 (m, 2H), 1.39 (dd, 1H). Anal. ($C_{16}H_{21}NO_3$) C, H, N.

Preparation of 7α- and 6α-Hydroxy Tropanes (30). (a) 2β-Carbomethoxy-3α-(3,4-dichlorophenyl)-7α-benzoyloxy-8-methyl-8-azabicyclo[3.2.1]octane (29b). To a solution of 2β-carbomethoxy-3α-(3,4-dichlorophenyl)-7β-hydroxy-8-methyl-8-azabicyclo[3.2.1]octane, **18a** (0.46 g, 1.34 mmol) in THF (20 mL) with benzoic acid (0.49 g, 4.0 mmol) and triphenylphosphine (0.70 g, 2.68 mol) was added diethyl azodicarboxylate (DEAD) (0.46 g, 2.68 mmol) dropwise at 0 °C. The reaction was kept stirring overnight at 22 °C. The solvent was removed and the residue was purified by a flash column chromatography (30% hexanes in EtOAc) to give the product as a white solid (0.43 g, 72%). R_f 0.53 (30% hexane, 70% EtOAc); ^{1}H NMR δ 8.06 (dd, 2H), 7.65 (d, 1H), 7.49 (t, 2H), 7.32 (d, 1H), 7.28 (d, 1H), 7.07 (dd, 1H), 5.68 (m, 1H), 3.73 (d, 1H), 3.55 (s, 3H), 3.48−3.31 (m, 2H), 3.10 (d, 1H), 3.01−2.85 (m, 1H), 2.53−2.47 (m, 4H), 1.64 (dd, 1H), 1.41 (dt, 1H).

(b) 2β-Carbomethoxy-3α-(3,4-dichlorophenyl)-6α-benzoyloxy-8-methyl-8-azabicyclo[3.2.1]octane (29a). 2β-Carbomethoxy-3α-(3,4-dichlorophenyl)-6β-hydroxy-8-methyl-8-azabicyclo[3.2.1]octane, **17a** (0.23 g) was treated as described above for the 7-hydroxy compound. A white solid was obtained (0.19 g, 63%): R_f 0.77 (30% hexane, 70% EtOAc); ^{1}H NMR δ 8.14−8.02 (m, 2H), 7.63−7.46 (m, 3H), 7.29 (dd, 2H), 7.05 (dd, 1H), 5.60 (m, 1H), 3.68−3.60 (m, 4H), 3.45−3.35 (m, 2H), 3.11−2.93 (m, 1H), 2.63−2.49 (m, 4H), 2.30−2.15 (m, 1H), 1.85−1.95 (m, 2H).

(c) 2β-Carbomethoxy-3α-(3,4-dichlorophenyl)-7α-hydroxy-8-methyl-8-azabicyclo[3.2.1]octane (30b). To a solution of 2β-carbomethoxy-3α-(3,4-dichlorophenyl)-7α-benzoyloxy-8-methyl-8-azabicyclo[3.2.1]octane **29b** (0.43 g, 0.95 mmol) in THF (26 mL) was added LiOH (0.085 g, 1.9 mmol in 5 mL H_2O). The resulting solution was stirred for 5 h at 22 °C and quenched with aqueous HCl (3%). The THF was removed and the aqueous layer was extracted with $CHCl_3$ (6 × 20 mL). The organic layers were combined and dried over K_2CO_3. The solvent was removed and the residue was purified by column chromatography (10% Et_3N in EtOAc) to afford the product as a white gum which solidified slowly upon standing (0.19 g, 26%): mp 121−123 °C; R_f 0.41 (10% Et_3N/EtOAc); ^{1}H NMR δ 7.36 (d, 1H), 7.33 (d, 1H), 7.12 (dd, 1H), 4.79 (ddd, J = 9.9, 6.0, 3.8 Hz, 1H), 3.59 (s, 3H), 3.46−3.33 (m, 3H), 3.24 (t, J = 7.9 Hz, 1H), 2.83−2.68 Hz (m, 1H), 2.55−2.43 (m, 4H), 1.40−1.25 (m, 2H). Anal. ($C_{16}H_{19}Cl_2NO_3$) C, H, N.

(d) 2β-Carbomethoxy-3α-(3,4-dichlorophenyl)-6α-hydroxy-8-methyl-8-azabicyclo[3.2.1]octane (30a). 2β-Carbomethoxy-3α-(3,4-dichlorophenyl)-6α-benzoyloxy-8-methyl-8-azabicyclo[3.2.1]octane **29a** (0.18 g, 0.39 mmol) was treated as described above and a white solid was obtained (51 mg, 38%): mp 161.2−162.2 °C; R_f 0.26 (10% Et_3N in EtOAc); ^{1}H NMR δ 7.35 (d, 1H), 7.34 (d, 1H), 7.11 (dd, 1H), 4.72 (m, 1H), 3.57 (s, 3H), 3.37−3.25 (m, 3H), 2.88−2.77 (m, 1H), 2.50 (d, 1H), 2.42 (s, 3H), 2.20−1.97 (m, 2H), 1.52 (dd, 1H). Anal. ($C_{16}H_{19}Cl_2NO_3$) C, H, N.

Oxidation of 7-Hydroxy Tropanes to 7-Ketones (19 and 20). (a) 2-β-Carbomethoxy-3α-(3,4-dichlorophenyl)-8-methyl-8-azabicyclo[3.2.1]oct-7-one (20). A solution of 2β-carbomethoxy-3α-(3,4-dichlorophenyl)-7β-hydroxy-8-methyl-8-azabicyclo[3.2.1]octane **18** (0.20 g, 0.58 mmol) in CH_2Cl_2 (5 mL) containing *N*-methylmorpholine *N*-oxide (1.5 equiv) and 4 Å molecular sieves (0.5 g; powder) was stirred for 10 min at 22 °C under N_2 and then treated with tetra-*n*-propylammonium perruthenate (10% molar equiv). The resulting solution was stirred overnight. The solvent was removed and the residue was purified by flash column chromatography (10% Et_3N, 30% EtOAc, 60% hexanes) to afford a white solid (0.16 g, 80%): mp 163.5−164.5 °C; R_f 0.47 (10% Et_3N, 30% EtOAc, 60% hexanes); ^{1}H NMR δ 7.34 (d, 1H), 7.29 (d, 1H), 7.02 (dd, 1H), 3.68−3.60 (m, 5H), 3.27 (m, 1H), 2.84 (dd, J = 7.9, 1.9 Hz, 1H), 2.59−2.30 (m, 2H), 2.44 (s, 3H), 1.92 (d, J = 18.4 Hz, 1H), 1.52 (ddd, J = 14.0, 8.5, 1.9 Hz, 1H). Anal. ($C_{16}H_{17}Cl_2NO_3$) C, H, N.

(b) 2β-Carbomethoxy-3β-(3,4-dichlorophenyl)-8-methyl-8-azabicyclo[3.2.1]oct-7-one (19). 2β-Carbomethoxy-3β-(3,4-dichlorophenyl)-7β-hydroxy-8-methyl-8-azabicyclo[3.2.1]-octane, **15** was treated as described above and the product was obtained as a white solid (170 mg, 81%): mp 84.4−86.4 °C; R_f 0.60 (10% Et_3N, 30% EtOAc, 60% hexanes); ^{1}H NMR δ 7.35 (d, 1H), 7.32 (d, 1H), 7.09 (dd, 1H), 3.75 (dt, J = 5.2, 1.3 Hz, 1H), 3.56 (s, 3H), 3.34 (s, 1H), 3.22 (t, J = 3.8 Hz, 1H), 2.98 (dt, J = 4.7, 12.9 Hz, 1H), 2.84 (dt, J = 12.7, 3.3 Hz, 1H), 2.73 (dd, J = 18.7, 7.4 Hz, 1H), 2.39 (s, 3H), 2.12 (d, J = 18.7 Hz, 1H), 1.86 (dt, J = 12.1, 3.3 Hz, 1H). Anal. ($C_{16}H_{17}Cl_2NO_3$) C, H, N.

Preparation of 2β-Ethyl Ketone Tropanes (23 and 26). (a) 2β-Carbo-*N*-methoxy-*N*-methylamino-3α-(3,4-dichlorophenyl)-7β-methoxymethoxy-8-methyl-8-azabicyclo-[3.2.1]octane (24) (Weinreb amide). To a solution of *N*,*O*-dimethylhydroxylamine hydrochloride (0.34 g, 3.48 mmol) in CH_2Cl_2 (10 mL) was added $Al(CH_3)_3$ dropwise at −12 °C (glycol-dry ice bath) under N_2. The resulting solution was stirred for 10 min at −12 °C before the cooling bath was removed and the reaction stirred at 22 °C for 30 min. The reaction was cooled to −12 °C and a solution of 2β-carbomethoxy-3α-(3,4-dichlorophenyl)-7β-methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]octane, **12a** (0.45 g, 1.16 mmol) in CH_2Cl_2 (4 mL) was transferred by cannula into the reaction flask and the reaction was stirred for 1 h at −12 °C and then 2 h at 22 °C. Rochelle's salt solution (potassium sodium tartrate saturated in water) (∼ 1 mL) was added and the mixture was stirred vigorously. Water was added to dissolve some solid salt and the aqueous layer was extracted with $CHCl_3$ (6 × 20 mL). The organic layers were combined and dried over K_2CO_3. The solvent was removed. The residue was purified by passing it through a short silica gel column (10% Et_3N in EtOAc) to afford a white solid (0.47 g, 89%). R_f 0.39 (10% Et_3N, 30% EtOAc, 60% hexane); ^{1}H NMR δ 7.29 (d, 1H), 7.26 (d, 1H), 7.05 (dd, 1H), 4.67 (dd, J = 3.6, 6.8 Hz, 2H), 4.37 (dd, J = 7.1, 3.3 Hz, 1H), 3.56 (s, 3H), 3.54−3.46 (m, 2H), 3.14 (m, 1H), 3.10 (s, 3H), 2.65 (d, J = 11.3 Hz, 1H), 2.54 (s, 3H), 2.48−2.37 (m, 1H), 2.26−2.18 (m, 1H), 2.02 (dd, J = 14.0, 7.4 Hz, 1H), 1.16−1.07 (m, 1H).

(c) 2β-Carbo-*N*-methoxy-*N*-methylamine-3β-(3,4-dichlorophenyl)-7β-methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]-octane (21) (Weinreb amide). The starting material **11a** (0.47 g, 1.2 mmol) was treated as for the 3α compound shown above. A solid was obtained (0.31 g, 61%): R_f 0.45 (10% Et_3N, 30% EtOAc, 60% hexane); ^{1}H NMR δ 7.31 (d, 1H), 7.31 (d, 1H), 7.11 (dd, 1H), 4.69 (s, 2H), 4.34 (dd, J = 7.7, 3.6 Hz, 1H), 3.66 (s, 3H), 3.61−3.58 (m, 2H), 3.42 (s, 3H), 3.28 (m, 1H), 3.05 (s, 3H), 2.74−2.68 (m, 2H), 2.49 (s, 3H), 2.28−2.20 (m, 1H), 2.09−2.02 (m, 1H), 1.60−1.56 (m, 1H).

(d) 1-[3α-(3,4-Dichlorophenyl)-7β-methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]oct-2-yl]propan-1-one (25). To a solution of 2β-carbo-*N*-methoxy-*N*-methylamino-3α-(3,4-dichlorophenyl)-7β-methoxymethoxy-8-methyl-8-azabicyclo-[3.2.1]octane, **24** (0.47 g, 1.13 mmol) in THF (anhydrous, 15 mL) was added ethylmagnesium bromide (3.4 mL, 1 M in THF) dropwise at 0 °C under N_2. The reaction was slowly warmed to 22 °C and stirred overnight. The reaction was then quenched with aqueous sat. NH_4Cl solution. The THF was replaced by CH_2Cl_2. The aqueous layer was extracted by $CHCl_3$ (6 × 20 mL). The organic solution was dried over K_2CO_3 and solvent was removed to afford a white solid (0.45 g, ∼100%). The sample was used for the next reaction without further purification. R_f 0.67 (10% Et_3N, 30% EtOAc, 60% hexane); ^{1}H NMR δ 7.30 (d, 1H), 7.23 (d, 1H), 7.00 (dd, 1H), 4.68 (dd, J = 8.5, 1.7 Hz, 2H), 4.24 (dd, J = 7.4, 3.6 Hz, 1H), 3.47−3.31 (m, 5H), 3.20 (s, 1H), 2.56−2.31 (m, 6H), 2.27−1.99 (m, 3H), 1.22−1.13 (m, 1H), 0.96 (t, J = 7.1 Hz, 3H).

(e) 1-[3β-(3,4-Dichlorophenyl)-7β-methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]oct-2-yl]propan-1-one (22). Weinreb amide **21** (0.31 g, 0.74 mmol) was treated as described

above to obtain a white solid product (0.27 g, 95%). R_f 0.71 (10% Et_3N, 30% EtOAc, 60% hexane); ^1H NMR δ 7.30 (d, 1H), 7.27 (d, 1H), 7.06 (dd, 1H), 4.72 (s, 2H), 4.31 (dd, J = 7.4, 3.6 Hz, 1H), 3.59−3.54 (m, 2H), 3.44 (s, 3H), 3.12 (m, 1H), 2.68−2.66 (m, 1H), 2.52−2.40 (m, 5H), 2.30−2.17 (m, 2H), 2.05 (dd, J = 14.3, 7.7 Hz, 1H), 1.62−1.55 (m, 1H), 0.92 (t, J = 7.1 Hz, 3H).

(f) 1-[3α-(3,4-Dichlorophenyl)-7β-hydroxy-8-methyl-8-azabicyclo[3.2.1]oct-2-yl]propan-1-one (26). The deprotection of the MOM group of **25** was carried out by the general method described earlier. 2β-(1-Propanoyl)-3α-(3,4-dichlorophenyl)-7β-methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]octane (0.27 g) was used and the product was obtained as a white solid (0.23 g, 76%): mp 113.1−114.1 °C; R_f 0.25 (10% Et_3N, 30% EtOAc, 60% hexanes); ^1H NMR δ 7.32 (d, 1H), 7.22 (d, 1H), 6.97 (dd, 1H), 4.27 (m, 1H), 3.50−3.41 (m, 2H), 3.06 (s, 1H), 2.67 (s, 3H), 2.67 (s, 3H), 2.52−2.32 (m, 3H), 2.18−2.01 (m, 3H), 1.25 (m, 1H), 0.94 (t, J = 7.4 Hz, 3H). Anal. ($C_{17}H_{21}Cl_2NO_2$) C, H, N, Cl.

(g) 1-[3β-(3,4-Dichlorophenyl)-7β-hydroxy-8-methyl-8-azabicyclo[3.2.1]oct-2-yl]propan-1-one (23). The deprotection of the MOM group of **22** was carried out by the general method described earlier. 2β-(1-Propanoyl)-3β-(3,4-dichlorophenyl)-7β-methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]octane (0.28 g) was used and the product was obtained as a white solid (0.18 g, 73%): mp 195.5−196.5 °C;. R_f 0.39 (10% Et_3N, 30% hexanes, 60% EtOAc); ^1H NMR δ 7.31 (d, 1H), 7.26 (d, 1H), 7.05 (dd, 1H), 4.59 (p, J = 3.3 Hz, 1H), 3.60 (m, 1H), 3.52 (m, 1H), 3.10 (dd, J = 4.4, 3.3 Hz, 1H), 2.65−2.41 (m, 6H), 2.26 (q, J = 7.4 Hz, 2H), 2.24−2.09 (m, 2H), 1.86 (d, J = 3.8 Hz, 1H), 0.92 (t, J = 7.4 Hz, 3H). Anal. ($C_{17}H_{21}Cl_2NO_2$) C, H, N.

Preparation of 7 and 6-Hydroxy Difluoropines (32). (a) 2β-Carbomethoxy-3α-hydroxy-7β-methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]octane (31b). To a solution of 2β-carbomethoxy-7β-methoxymethoxy-8-methyl-3-oxo-8-azabicyclo[3.2.1]octane **1b** (1.0 g, 3.89 mmol) in MeOH (100 mL) was added $NaBH_4$ (0.36 g, 9.72 mmol) at −78 °C. The mixture was kept in a freezer (−25 °C) for 3 days. The reaction was quenched with H_2O (40 mL) and MeOH was removed. The aqueous layer was extracted with CH_2Cl_2 (6 × 20 mL). The extracts were combined and dried over K_2CO_3 and solvent was removed. The residue was purified by gradient flash chromatography (5% MeOH in $CHCl_3$ to 10% MeOH in $CHCl_3$) to give the product as a yellow oil (0.53 g, 52%). R_f 0.21 (10% MeOH/$CHCl_3$); ^1H NMR δ 4.67−4.58 (m, 3H), 4.29 (t, 1H), 3.77 (s, 3H), 3.52 (m, 1H), 3.34 (s, 3H), 3.31−3.23 (m, 2H), 2.93 (t, 1H), 2.58 (dd, 1H), 2.54 (s, 3H), 2.06−1.98 (m, 2H), 1.66 (d, 1H).

(b) 2β-Carbomethoxy-3α-hydroxy-6β-methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]octane (31a). 2β-Carbomethoxy-6β-methoxymethoxy-8-methyl-3-oxo-8-azabicyclo[3.2.1]-octane **1a** (1.0 g) was treated as described above to obtain the product as an oil (0.53 g, 52%). R_f 0.21 (10% MeOH/$CHCl_3$); ^1H NMR δ 4.64 (s, 2H), 4.59 (dd, 1H), 4.28 (m, 1H), 3.74 (s, 3H), 3.59 (m, 1H), 3.46 (s, 1H), 3.36 (s, 3H), 3.17 (s, 1H), 2.89 (m, 1H), 2.63−2.55 (m, 4H), 2.09−1.95 (m, 2H), 1.76 (d, 1H).

(c) 2β-Carbomethoxy-3α-bis(fluorophenyl)methoxy-7β-hydroxy-8-methyl-8-azabicyclo[3.2.1]octane (32b). A solution of 2β-carbomethoxy-3α-hydroxy-7β-methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]octane **31b** (0.52 g, 2.04 mmol) and 4,4′-difluorobenzhydrol (0.53 g, 2.22 mmol) in CH_2Cl_2 (50 mL) with *p*-toluenesulfonic acid (0.39 g, 2.04 mmol) was placed in a round-bottom flask equipped with a Soxhlet condenser in which a thimble filled with molecular sieves (3 Å) was placed. The reaction was heated to reflux overnight during which time the molecular sieves were replaced with fresh sieves several times. The reaction was quenched with sat. $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2. The extracts were combined and dried over K_2CO_3 and solvent was removed on a rotary evaporator. The residue was purified by column chromatography (5% MeOH in EtOAc to 10% MeOH in EtOAc) to afford the desired product as a white solid (0.21 g, 22%): mp 150−152 °C; R_f 0.09 (5% MeOH, EtOAc); ^1H NMR δ 7.25 (dd, 4H), 6.99 (m, 4H), 5.45 (s, 1H), 4.42 (dd, J = 7.1, 2.8 Hz, 1H), 4.24 (t, J = 4.4 Hz, 1H), 3.71 (s, 3H), 3.64 (m, 1H), 3.35 (m, 1H), 2.97 (s, 1H), 2.78 (s, 1H), 2.61 (s, 3H), 2.53 (dd, J = 13.1, 7.4 Hz, 1H), 2.15 (m, 1H), 2.02 (m, 1H), 1.69 (d, J = 14.3 Hz, 1H). Anal. ($C_{23}H_{25}F_2NO_4$) C, H, N.

(d) 2β-Carbomethoxy-3α-bis(4-fluorophenyl)methoxy-6β-hydroxy-8-methyl-8-azabicyclo[3.2.1]octane (32a). 2β-Carbomethoxy-3α-hydroxy-6β-methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]octane **31a** (0.54 g, 2.10 mmol) was treated as described above and the product was obtained as a white foam. (0.17 g, 17%): R_f 0.32 (10% MeOH/$CHCl_3$); ^1H NMR δ 7.25 (dd, J = 8.5, 5.8 Hz, 4H), 6.99 (dt, J = 8.5, 0.8 Hz, 4H), 5.34 (s, 1H), 4.48 (dd, J = 7.2, 2.8 Hz, 1H), 4.20 (m, 1H), 3.73 (s, 3H), 3.61 (d, J = 8.0 Hz, 1H), 3.26 (s, 1H), 3.17 (s, 1h), 2.88 (bs, 1H), 2.58 (s, 3H), 2.48 (dd, J = 13.7, 7.14 Hz, 1H), 2.07 (ddd, J = 14.0, 7.4, 2.7 Hz, 1H), 1.97 (d, J = 16.8 Hz, 1H). Anal. ($C_{23}H_{25}F_2NO_4$) C, H, N.

Resolution of 7-Hydroxy Tropanone. (a) (1*R*)-2-Carbomethoxy-3-(1′*S*)-camphanyl-7β-methoxymethoxy-8-methyl-8-azabicyclo[3.2.1]oct-2-ene (27). To a solution of racemic 2β-carbomethoxy-7β-methoxymethoxy-8-methyl-3-oxo-8-azabicyclo[3.2.1]octane **2b** (7.1 g, 27.6 mmol) in THF (anhydrous, 100 mL) cooled at −78 °C, $NaN(TMS)_2$ (35.9 mL, 1 M in THF) was added dropwise by syringe. The resulting solution was stirred for 45 min. At −78 °C and (1*S*)-(−)-camphanic chloride (8.3 g, 38.6 mmol) was added. The solution was stirred overnight, during which time it slowly warmed to 22 °C. The reaction was quenched with sat. $NaHCO_3$ (20 mL). The THF was replaced with CH_2Cl_2. The organic layer was separated and aqueous layer was back extracted with CH_2Cl_2 (6 × 20 mL). The organic extracts were combined and dried over K_2CO_3 and solvent was removed. The residue was purified by flash chromatography (5% MeOH in EtOAc) to afford the product (7.75 g, 64%) as a yellow oil which solidified upon standing for 3 days. NMR showed two diastereoisomers in the sample. The (1*R*,1′*S*) diastereoisomer was separated by recrystallization (5 times) from benzene/heptane to give diasteromerically pure **27** as a white solid (1.4 g, 36%, > 98% de by ^1H NMR). Despite repeated efforts, the (1*S*,1′*S*) diastereomer could not be isolated pure. The ^1H NMR of the diastereomeric mixture is provided below. Of particular interest is the region 1.2−0.7 ppm as in benzene-d_6 the two diastereomers show different chemical shifts. ^1H NMR (C_6D_6) δ 4.70 (m, 1H), 4.55 (m, 1H), 4.19 (m, 1H), 4.11 (m, 1H), 3.28 (m, 3H), 3.21 (m, 3H), 2.9 (m, 1H), 2.35 (m, 3H), 2.34−2.18 (m, 2H), 2.11−2.02 (m, 2H), 1.66 (m, 1H), 1.29−1.21 (m, 4H), 1.026 (s, 3H, 1*S*,1′*S*), 0.992 (s, 3H, 1*R*,1′*S*), 0.897 (s, 3H, 1*S*,1′*S*), 0.890 (s, 3H, 1*R*,1′*S*), 0.817 (s, 3H, 1*S*,1′*S*), 0.803 (s, 3H, 1*R*,1′*S*).

The (1*R*,1′*S*) product of recrystallization **27** was diastereomerically pure (>98% de) as confirmed by the complete absence of the (1*S*,1′*S*)-diastereomer at 1.015 ppm. R_f 0.42 (5% MeOH/EtOAc); ^1H NMR (C_6D_6) δ 4.70 (d, J = 6.6 Hz, 1H), 4.55 (d, J = 6.6 Hz, 1H), 4.19 (dd, J = 7.4, 2.2 Hz, 1H), 4.11 (s, 1H), 3.28 (s, 3H), 3.21 (s, 3H), 2.9 (m, 1H), 2.35 (s, 3H), 2.34−2.18 (m, 2H), 2.11−2.02 (m, 2H), 1.66 (dd, J = 13.4, 7.4 Hz, 1H), 1.29−1.21 (m, 4H), 0.98 (s, 3H), 0.89 (s, 3H), 0.78 (s, 3H).

(b) (1*R*)-7β-Methoxymethoxy-2-methoxycarbonyl-8-methyl-3-oxo-8-azabicyclo[3.2.1]octane ((1*R*)-2). A solution of (1*R*)-2-carbomethoxy-3-(1′*S*)-camphanyl-7β-hydroxy-8-methyl-8-azabicyclo[3.2.1]oct-2-ene **27** (1.40 g, 3.20 mmol) in THF (50 mL) was treated with LiOH aqueous solution (0.26 g, 6.4 mmol, 16 mL H_2O) and the resulting solution was stirred at 22 °C for 3 h. The THF was removed in vacuo and K_2CO_3 (8 g) was added to the aqueous solution which was exhaustively extracted with CH_2Cl_2. The CH_2Cl_2 extracts were combined and dried over K_2CO_3. Solvent was removed to obtain a white solid **(1*R*-2)** (0.89 g) that was used for the ensuing steps without further purification. ^1H NMR δ 4.67 (d, 1H), 4.54 (d, 1), 3.98 (s, 1H), 3.93 (dd, 1H), 3.30 (s, 3H), 3.21 (s, 3H), 2.92 (dd, 1H), 2.43 (m, 1H), 2.50 (dd, 1H), 2.21 (s, 3H), 2.05 (dd, 1H), 1.51 (dd, 1H), 1.42 (d, 1H).

(c) (1*S*)-2-Carbomethoxy-3-(3,4-dichlorophenyl)-7β-(1′*S*)-camphanyloxy-8-methyl-8-azabicyclo[3.2.1]oct-2-ene (28). A solution of racemic 2-carbomethoxy-3-(3,4-dichlorophenyl)-7β-hydroxy-8-methyl-8-azabicyclo[3.2.1]oct-2-

ene **8a** (11.1 g, 32 mmol) in CH_2Cl_2 (250 mL) with Et_3N (6.8 mL, 48.7 mmol) was treated with 1*S*-(−)-camphanic chloride (10.5 g, 48.7 mmol) at 0 °C. The resulting solution was stirred overnight at 22 °C and then quenched with $NaHCO_3$ (sat.). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined and dried over $MgSO_4$. The solvent was removed and the crude product containing the two diastereoisomers was separated by two consecutive gravity columns (10% Et_3N, 30% EtOAc, 60% hexanes). The pure (1*S*,1′*S*) product **28** (2.4 g) was obtained as a yellow solid. A further 1.8 g was obtained as a mixture of diastereomers: R_f (one elution: both diastereomers run together) 0.14 (10% Et_3N, 30% EtOAc, 60% hexane); R_f (two elutions) (1*S*,1′*S*) 0.25 (1*R*,1′*S*) 0.18 (10% Et_3N, 30% EtOAc, 60% hexane).

The ^{1}H NMR of **28** showed no trace of the (1*R*,1*S*) diastereomer and was therefore diastereomerically pure (de > 98%). ^{1}H NMR (C_6D_6) δ 7.08 (d, 1H), 7.02 (d, 1H), 6.47 (dd, J = 8.3, 2.2 Hz, 1H), 5.34 (dd, J = 7.4, 2.2 Hz, 1H), 4.16 (s, 1H), 3.15 (s, 3H), 2.89 (dd, J = 6.9, 4.7 Hz, 1H), 2.19 (s, 3H), 2.17−2.07 (m, 2H), 1.98 (dd, J = 18.4, 5.2 Hz, 1H), 1.82−1.65 (m, 2H), 1.25−1.09 (m, 3H), 0.92 (s, 3H), 0.82 (s, 3H), 0.72 (s, 3H).

(d) (1*R*)-2-Carbomethoxy-3-(3,4-dichlorophenyl)-7β-camphanoyl-8-methyl-8-azabicyclo[3.2.1]oct-2-ene ((1*R*)-28). To confirm that the above compound is 1*S* configured, a similar reaction was carried out by using the 1*R* ene compound. ^{1}H NMR (C_6D_6) δ 7.11 (d, 1H), 7.05 (d, 1H), 6.52 (dd, 1H), 5.36 (dd, J = 7.4, 2.2 Hz, 1H), 4.18 (s, 1H), 3.17 (s, 3H), 2.94 (dd, J = 6.9, 4.7 Hz, 1H), 2.20 (s, 3H), 2.16−1.98 (m, 3H), 1.84 (dd, J = 14.3, 7.6 Hz, 1H), 1.74−1.65 (m, 1H), 1.25−1.10 (m, 3H), 0.89 (s, 3H), 0.83 (s, 3H), 0.75 (s, 3H).

Single-Crystal X-ray Analysis of (1*R*)-8a. Monoclinic crystals of the purified **(1*R*)-8a** were obtained from CH_2Cl_2/heptane. A representative crystal was selected and a data set was collected at room temperature. Pertinent crystal, data collection and refinement parameters: crystal size, 0.66 × 0.50 × 0.22 mm; cell dimensions, a = 18.382 (1) Å, b = 6.860 (1) Å, c = 16.131 (1) Å, α = 90°, β = 124.65 (1) °, γ = 90°; formula, $C_{16}H_{17}Cl_2NO_3$; formula weight = 342.21; volume = 1673.3 (2) Å^3; calculated density = 1.358 g cm^{-3}; space group = $C2$; number of reflections = 1749 of which 1528 were considered independent (R_{int} = 0.0300). Refinement method was full-matrix least-squares on F^2. The final R-indices were [$I > 2\sigma$ (I)] $R1$ = 0.0364, w$R2$ = 0.0987.

Single-Crystal X-ray Analysis of (1*R*)-18a. Monoclinic crystals of the purified **(1*R*)-18a** were obtained from ethyl CH_2Cl_2/heptane. A representative crystal was selected and a data set was collected at room temperature. Pertinent crystal, data collection, and refinement parameters: crystal size, 0.72 × 0.30 × 0.14 mm; cell dimensions, a = 5.981 (1) Å, b = 7.349 (1) Å, c = 18.135 (1) Å, α = 90°, β = 96.205 (6) °, γ = 90°; formula, $C_{16}H_{19}Cl_2NO_3$; formula weight = 344.22; volume = 792.29 (12) Å^3; calculated density = 1.443 g cm^{-3}; space group = $P2_1$; number of reflections = 1630 of which 1425 were considered independent (R_{int} = 0.0217). Refinement method was full-matrix least-squares on F^2. The final R-indices were [$I > 2\sigma$ (I)] $R1$ = 0.0298, w$R2$ = 0.0858.

Single-Crystal X-ray Analysis of (1*S*)-18a. Monoclinic crystals of the purified **(1*S*)-18a** were obtained from CH_2Cl_2/heptane. A representative crystal was selected and a data set was collected at room temperature. Pertinent crystal, data collection, and refinement parameters: crystal size, 0.64 × 0.32 × 0.18 mm; cell dimensions, a = 15.000 (1) Å, b = 7.018 (1) Å, c = 15.886 (1) Å, α = 90°, β = 99.34 (1) °, γ = 90°; formula, $C_{16}H_{19}Cl_2NO_3$; formula weight = 344.22; volume = 1650.1 (2) Å^3; calculated density = 1.386 g cm^{-3}; space group = $P2(1)$; number of reflections = 3267 of which 2979 were considered independent (R_{int} = 0.0285). Refinement method was full-matrix least-squares on F^2. The final R-indices were [$I > 2\sigma$ (I)] $R1$ = 0.0449, w$R2$ = 0.1236.

Tissue Sources and Preparation. Brain tissue from adult male and female cynomolgus monkeys (*Macaca fasicularis*) and rhesus monkeys (*Macaca mulatta*) was stored at −85 °C in the primate brain bank at the New England Regional Primate Research Center. We recently cloned the DAT and SERT from both species and found them to have virtually identical protein sequences.[51] 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 38000*g* for 20 min in the cold. The resulting pellet was suspended in 40 volumes of buffer, and the entire procedure was repeated twice. The membrane suspension (25 mg of 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 the assay and was dispersed with a Brinkmann Polytron homogenizer (setting #5) for 15 s. All experiments were conducted in triplicate, and each experiment was repeated in each of 2−3 preparations from individual brains.

Dopamine Transporter Assay. The dopamine transporter was labeled with [^{3}H]WIN 35,428 ([^{3}H]CFT, (1*R*)-2β-carbomethoxy-3β-(4-fluorophenyl)-*N*-[^{3}H]methyltropane, 81−84 Ci/mmol, DuPont-NEN). The affinity of [^{3}H]WIN 35,428 for the dopamine transporter was determined in experiments by incubating tissue with a fixed concentration of [^{3}H]WIN 35,-428 and a range of concentrations of unlabeled WIN 35,428. The assay tubes received, in Tris·HCl buffer (50 mM, pH 7.4 at 0−4 °C; NaCl 100 mM), the following constituents at a final assay concentration: WIN35,428, 0.2 mL (1 pM − 100 or 300 nM), [^{3}H]WIN 35,428 (0.3 nM); membrane preparation 0.2 mL (4 mg of 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) and incubated overnight at 0−4 °C in scintillation fluor (Beckman Ready-Value, 5 mL), and radioactivity was measured by liquid scintillation spectrometry (Beckman 1801). Cpm were converted to dpm following determination of counting efficiency (> 45%) of each vial by external standardization.

Total binding was defined as [^{3}H]WIN 35,428 bound in the presence of ineffective concentrations of unlabeled WIN 35,-428 (1 or 10 pM). Nonspecific binding was defined as [^{3}H]WIN 35,428 bound in the presence of an excess (30 μM) of (−)-cocaine. Specific binding was the difference between the two values. Competition experiments to determine the affinities of other drugs at [^{3}H]WIN 35,428 binding sites were conducted using procedures similar to those outlined above. Stock solutions of water-soluble drugs were dissolved in water or buffer and stock solutions of other drugs were made in a range of ethanol/HCl solutions or other appropriate solvents. Several of the drugs were sonicated to promote solubility. The stock solutions were diluted serially in the assay buffer and added (0.2 mL) to the assay medium as described above. IC_{50} values were computed by the EBDA computer program and are the means of experiments conducted in triplicate.

Serotonin Transporter Assay. The serotonin transporter was assayed in caudate-putamen membranes using conditions similar to those for the dopamine transporter. The affinity of [^{3}H]citalopram (spec. act.: 82 Ci/mmol, DuPont-NEN) for the serotonin transporter was determined in experiments by incubating tissue with a fixed concentration of [^{3}H]citalopram and a range of concentrations of unlabeled citalopram. The assay tubes received, in Tris·HCl buffer (50 mM, pH 7.4 at 0−4 °C; NaCl 100 mM), the following constituents at a final assay concentration: citalopram, 0.2 mL (1 pM − 100 or 300 nM), [^{3}H]citalopram (1 nM); 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). Cpm were converted to dpm following determination of counting efficiency (> 45%) of each vial by external standardization. Total binding

was defined as [^{3}H]citalopram bound in the presence of ineffective concentrations of unlabeled citalopram (1 or 10 pM). Nonspecific binding was defined as [^{3}H]citalopram bound in the presence of an excess (10 μM) of fluoxetine. Specific binding was the difference between the two values. Competition experiments to determine the affinities of other drugs at [^{3}H]-citalopram binding sites were conducted using procedures similar to those outlined above. IC_{50} values were computed by the EBDA computer program and are the means of experiments conducted in triplicate.

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Supporting Information Available: NMR spectra, ORTEP drawings of **(1*R*)-8a**, **(1*R*)-18a**, and **(1*S*)-18a**, crystal data and refinement parameters, coordinates, anisotropic temperature factors, distances and angles. This material is available free of charge via the Internet at http://pubs.acs.org.

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