Further Studies on Conformationally Constrained Tricyclic Tropane Analogues and Their Uptake Inhibition at Monoamine Transporter Sites: Synthesis of (*Z*)-9-(Substituted arylmethylene)-7-azatricyclo[4.3.1.0^{3,7}]decanes as a Novel Class of Serotonin Transporter Inhibitors

Ao Zhang,[†] Guochun Zhou,[†] Alexander Hoepping,[†] Jayanta Mukhopadhyaya,[†] Kenneth M. Johnson,[‡] Mei Zhang,[‡] and Alan P. Kozikowski*[,†]

Drug Discovery Program, Department of Neurology, Georgetown University Medical Center, 3900 Reservoir Road Northwest, Washington, DC 20007-2197, and Department of Pharmacology and Toxicology, University of Texas Medical Branch, Galveston, Texas 77555-1031

Received November 26, 2001

A novel series of conformationally constrained tricyclic tropane analogues, (*Z*)-9-(substituted arylmethylene)-7-azatricyclo[4.3.1.0^{3,7}]decanes, were prepared, and their abilities to inhibit high-affinity uptake of dopamine (DA), serotonin (5-HT), and norepinephrine (NE) into rat brain nerve endings (synaptosomes) were evaluated. First, a systematic screening of a variety of different substituents on the phenyl ring indicated that the substitution pattern plays an important role in the monoamine transporter activity. Most compounds in this series possessed a very low activity at the DA transporter (DAT) but a good to excellent affinity for the 5-HT transporter (SERT). In the case of *para*-substituted phenyl analogues, the electronic character of the substituent did not affect uptake inhibition as dramatically as observed in some benztropine analogues. Among these compounds, the 4-bromophenyl and 4-isopropylphenyl analogues **8d** and **8j** exhibited the highest potency at the SERT with a K_i value of 10 nM. In the 3,4-disubstituted phenyl series, even more potent and highly selective compounds were discovered. Compound **8o** has a K_i value of 2.3 nM for uptake inhibition at the SERT, a DAT/SERT uptake ratio of 2360, and a NET/SERT uptake ratio of 200. Compound **8p** exhibited a K_i value of 1.8 nM for uptake inhibition at the SERT, a DAT/SERT uptake ratio of 1740, and a NET/SERT uptake ratio of 151. These compounds are 3−4-fold more potent than the antidepressant medication fluoxetine, and the selectivities for SERT over DAT and NET are also better than those of fluoxetine. Second, a variety of functional modifications on the ester moiety were investigated. Substitution by other esters or amides as well as alkenes did not increase potency, while most of the acetates or benzoates (**16**−**21**, **23**, and **24**) and the ketone **28** exhibited significantly improved activity. A good hydrogen-bonding ability of the substituent is believed to be required for high activity. The most potent and selective ligand is compound **23**, which displayed a K_i value of 0.06 nM and has essentially no activity at the DAT or NET. The present results have important implications for drug addiction as well as a number of psychiatric diseases.

Introduction

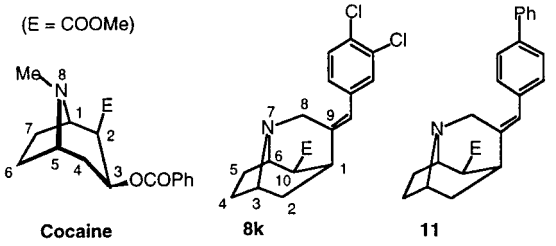
Cocaine abuse and addiction has devastated families and communities and seems unlikely to dissipate anytime soon.[1] As a consequence, immediate strategies are needed for the treatment of individuals who have become addicted to this powerfully reinforcing drug. Because the biological actions of cocaine were initially thought to occur primarily through inhibition of dopamine uptake, most of the compounds synthesized and developed as potential therapeutics have been designed to exhibit high potency at and selectivity for the dopamine transporter.[2−5] Unfortunately, despite many notable efforts, ligands targeted solely at this protein have not led to a clinically useful medication. Studies have shown that cocaine actually has multiple effects on endogenous central neurotransmitter systems. It binds with moderate and comparable affinity to all three of the monoamine transporters and thereby inhibits the reuptake of the neurotransmitters dopamine (DA), serotonin (5-HT), and norepinephrine (NE) into presynaptic neurons. A study employing knockout mice has also demonstrated that cocaine provides its rewarding cues to humans through its effects on several different systems and not just the dopaminergic system.[6,7] Therefore, a complete understanding of cocaine's action depends on the synthesis of cocaine analogues with defined selectivities at each of these three transporter sites.

Some evidence has suggested that the 5-HT transporter (SERT) also plays a crucial role in mediating the neurochemical and behavioral actions of cocaine.[8−10] Serotonin selective reuptake inhibitors such as fluoxetine and paroxetine have been developed for the treatment of depression and related psychiatric disorders.[10c] Interestingly, indirect 5-HT agonists lacking dopaminergic activity have been found not to produce reward or

* To whom correspondence should be addressed. Tel.: 202-687-0686. Fax: 202-687-5065. E-mail: Kozikowa@georgetown.edu.
[†] Georgetown University Medical Center.
[‡] University of Texas Medical Branch.

10.1021/jm0105373 CCC: $22.00
Published on Web 03/27/2002

Scheme 1



euphoria in primates.[11] A detailed interpretation of this result still remains elusive.[12−16]

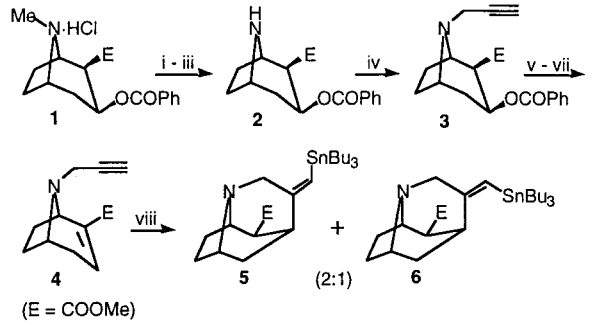
In the course of our efforts to discover ligands selective for the SERT for possible use as medications, we recently identified a novel series of rigidified cocaine analogues that contain a ring constraint between the C3-position of the tropane moiety and the nitrogen atom. This series of compounds was assembled by employment of a radical cyclization combined with the Stille coupling reaction.[17] The preliminary results reported in our previous paper indicated that the substituents on the phenyl ring play a critical role in monoamine transporter selectivity. Some compounds of this series exhibited high potency in the SERT, norepinephrine transporter (NET), or combined NET/SERT reuptake inhibition. For example, the 3,4-dichlorophenyl-substituted analogue, (1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-(3,4-dichlorobenzylidene)-7-azatricyclo[4.3.1.$0^{3,7}$]decane-10-carboxylic acid methyl ester (**8k**) (Scheme 1), gave remarkable potency and selectivity at the SERT with 96-fold higher activity than at the dopamine transporter (DAT) and about 50-fold higher activity than at the NET. The biphenylyl derivative **11** was 50-fold selective at both the NET and the SERT over the DAT. These results encouraged a further study of this novel selectivity profile.

Structurally, compound **8k** is intriguing because it maintains cocaine's methyl ester moiety and the aromatic ring (although shifted to a position above the basal plane of the tropane ring), both of which represent important pharmacophoric groups.[18−20] The distance between the nitrogen atom and the centroid of the aromatic ring is 5.6 Å, a value which seems optimal for high activity.[21] In the present paper, the effects of a systematic variation of the aromatic ring substitution pattern as well as the replacement of the methyl ester moiety by a variety of other functional groups on the activities at all three monoamine transporters are reported. The aim of this study was to identify ligands with superior potency and selectivity for the SERT.

Chemistry

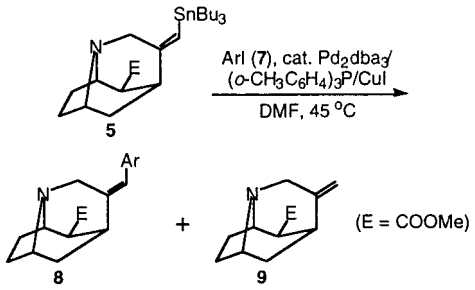
Our drug design strategy was first based on modification of the aryl group while leaving the ester moiety intact. The flexible approach to the tricyclic skeleton starting from cocaine (**1**) that we have developed earlier was utilized as described in Scheme 2.[17,22,23] The key step, the radical cyclization of enyne **4**, afforded predominantly the *Z*-isomer of vinyl stannane **5**, which was then subjected to Stille coupling with aryl iodides **7**[24] to give the target products **8** in moderate yields. Compound **9**[25] resulting from competing protodestannylation was formed as the major byproduct (Scheme 3).

Scheme 2[a]

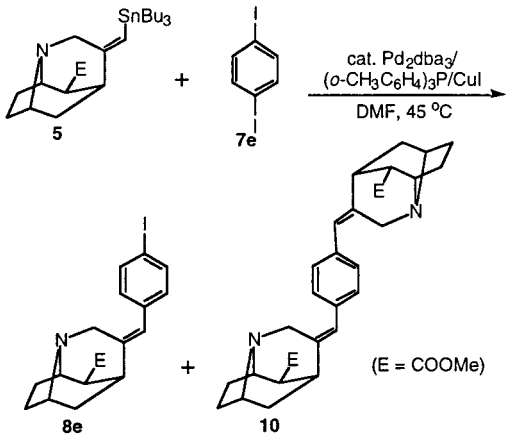


[a] Reagents and conditions: (i) Saturated $NaHCO_3$; (ii) CH_3-CH(Cl)OCOCl, 1,2-dichloroethane, K_2CO_3, reflux, 9 h; (iii) MeOH, reflux, 7 h; (iv) propargyl bromide, K_2CO_3, MeCN, reflux, 18 h; (v) 2 N HCl, reflux, 15 h; (vi) $POCl_3$, reflux, 2 h; (vii) MeOH, −78 °C to room temperature; (viii) AIBN, *n*-Bu_3SnH, benzene.

Scheme 3



Scheme 4

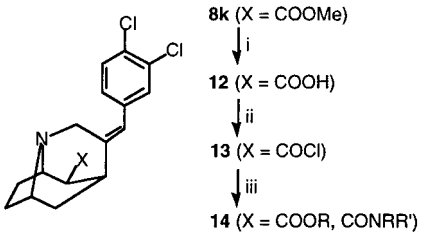


In the case of 1,4-diiodobenzene **7e**, the desired coupling product **8e** was obtained as the major product, while the 2:1 product **10** formed by a second coupling reaction was also isolated. The formation of compound **10** can be limited by employing iodide **7e** in excess (Scheme 4). Coupling of compound **5** with 2-chloro-1,4-diiodobenzene (**7p**) resulted in two regioisomers **8p** and **8q**, which were separable only by high-performance liquid chromatography (HPLC).

To investigate the effect of modifications of the ester group, methyl ester **8k** was refluxed with hydrochloric acid to give the acid **12**, which was subsequently converted into acid chloride **13** by treatment with either thionyl chloride or oxalyl chloride. The acid chloride **13** was then condensed with an appropriate alcohol, phenol, or amine to give the esters and amides **14a**−**d** (Scheme 5).[26]

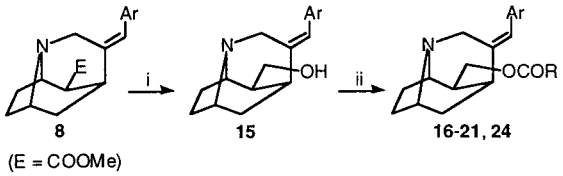
To prepare the reverse esters **16**−**21** and **24** (Scheme 6), the appropriate methyl esters **8** were reduced with

Scheme 5[a]



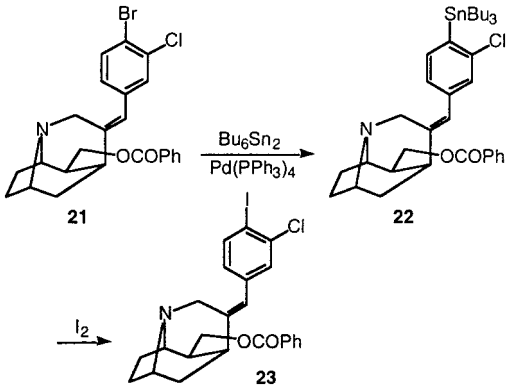
[a] Reagents and conditions: (i) 6 N HCl, reflux; (ii) $SOCl_2$, CH_2Cl_2, reflux; (iii) alcohol, phenol, or amine, Et_3N, THF, 0 °C to room temperature.

Scheme 6[a]



[a] Reagents and conditions: (i) $LiAlH_4$ or DIBAL-H, THF, room temperature; (ii) Ac_2O or acid chloride, Et_3N, THF, 0 °C to room temperature.

Scheme 7



$LiAlH_4$ or DIBAL-H to give the alcohols **15**, which were further treated with acetic anhydride or acid chlorides. This procedure was not applicable for the preparation of the iodide **23** since ester reduction was in this case accompanied by deiodination. To avoid this undesired side reaction, iodine was introduced after ester reduction starting from the corresponding bromide **21** by way of the arylstannane **22** (Scheme 7).[27,28]

The alkene **26** was synthesized by a three-step reaction sequence involving reduction with $LiAlH_4$, Swern oxidation, and Wittig reaction (Scheme 8). The newly formed double bond was exclusively *trans*-configured as evidenced by the vicinal coupling constant between the olefinic protons (J = 15 Hz).

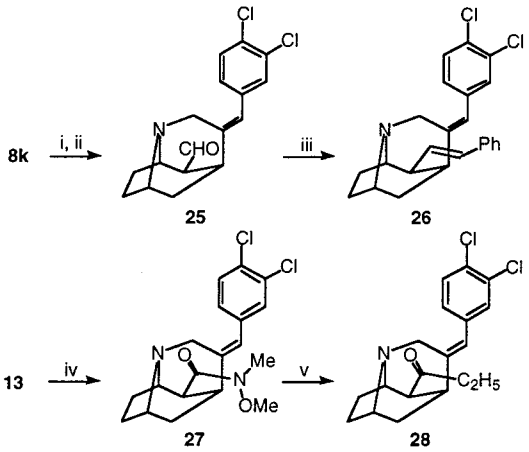
For the synthesis of the ethyl ketone analogue **28**, acid chloride **13** was reacted with *N*,*O*-dimethylhydroxylamine to provide the Weinreb amide **27**, which on treatment with ethylmagnesium bromide then provided the desired ketone almost quantitatively[29] (Scheme 8).

Ether **29** was prepared from alcohol **15** by means of a Mitsunobu reaction.[30] The "dimeric" reverse ester **30** was obtained from alcohol **15** by esterification with sebacoyl chloride (Scheme 9).

Pharmacological Results

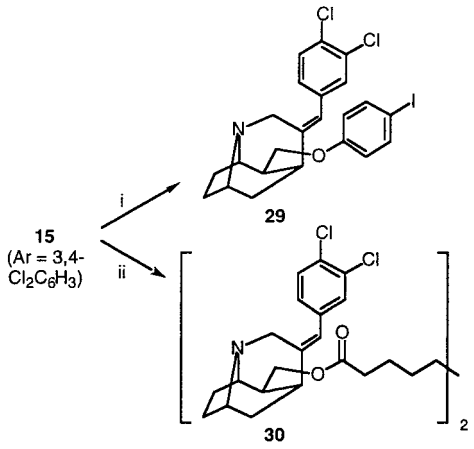
All final compounds were tested for their ability to inhibit high-affinity reuptake of DA, 5-HT, and NE into

Scheme 8[a]



[a] Reagents and conditions: (i) $LiAlH_4$ or DIBAL-H, THF, room temperature; (ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C; (iii) $Ph_3P^+CH_2PhBr^-$, *n*-BuLi, THF, room temperature; (iv) $HN(CH_3)$-OCH_3, Et_3N, CH_2Cl_2; (v) EtMgBr, THF.

Scheme 9[a]



[a] Reagents and conditions: (i) Ph_3P, EtOOCN=NCOOEt, 4-iodophenol, THF; (ii) $ClCO(CH_2)_8COCl$, Et_3N, CH_2Cl_2, 0 °C.

nerve endings (synaptosomes) prepared from brain regions enriched in transporters for these biogenic amine neurotransmitters.[31,32] The protocols used are described in the Experimental Section. Table 1 summarizes the activities of those compounds that contain a methyl ester moiety. For comparison purposes, some data from our preliminary paper (compounds **8a**, **8g**, **8i**, **8k**, and **8t**) and data for (−)-cocaine and fluoxetine are also included.[17] Nearly all of the 4-substituted phenyl derivatives **8a**−**f** and **8h**−**j** exhibit good to excellent inhibitory activity at the SERT but much lower activities at the DAT and NET. In contrast, compound **8g** with an unsubstituted phenyl group displayed a very low affinity for the SERT but a high affinity for the NET and a moderate affinity for the DAT. The substituent in the phenyl ring thus plays an important role in driving the affinity and selectivity from the NET or the DAT to the SERT. Both electron-withdrawing and electron-donating substituents contribute to this change in selectivity. Among the compounds with an electron-withdrawing substituent, potency in inhibition of 5-HT reuptake decreases in the sequence 4-Br ≈ 4-CF_3 > 4-I > 4-Cl > 3-Cl > 4-F. The *p*-bromophenyl and *p*-(trifluoromethylphenyl) analogues **8d** and **8f** display almost the same potency (K_i = 11 nM) at the SERT, but

Table 1. Inhibition of Reuptake at Monoamine Transporters ($K_i \pm$ SEM (nM))[a]

		[^{3}H]DA uptake	[^{3}H]5-HT uptake	[^{3}H]NE uptake	uptake ratio (based on K_i)		
compd	R	K_i (nM)	K_i (nM)	K_i (nM)	DA/5-HT	NE/DA	NE/5-HT
cocaine		423 ± 147	155 ± 0.4	108 ± 3.5	2.7	0.26	0.7
fluoxetine		4580 ± 550	7.3 ± 0.7	167 ± 15	627	0.04	23
8a	4-fluorophenyl	6620 ± 460	335 ± 45	584 ± 163	19.7	0.09	1.7
8b	4-chlorophenyl	853 ± 58	34.3 ± 2.9	208 ± 111	24.8	0.24	6.0
8c	3-chlorophenyl	7780 ± 1580	53.6 ± 17.2	231 ± 44	145	0.03	4.3
8d	4-bromophenyl	495 ± 13	11 ± 3.0	178 ± 9	45	0.36	16
8e	4-iodophenyl	764 ± 11	21.9 ± 0.3	213 ± 31	34.9	0.28	9.7
8f	4-trifluoromethylphenyl	N/T	12.6 ± 0.5	1830 ± 211	N/T	N/T	145
8g	Ph	481 ± 11	1140 ± 70	53 ± 16	0.42	0.11	0.05
8h	4-methylphenyl	649 ± 2.0	15 ± 0.4	146 ± 28	43.3	0.22	9.7
8i	4-methoxyphenyl	3130 ± 160	56 ± 4.0	187 ± 5.0	55.9	0.06	3.3
8j	4-isopropylphenyl	N/T	10.2 ± 0.4	1110 ± 200	N/T	N/T	109
8k	3,4-dichlorophenyl-	1920 ± 260	20 ± 1	1000 ± 280	96	0.52	50
8l	2,3-dichlorophenyl	850 ± 107	354 ± 188	1210 ± 358	2.4	1.42	3.4
8m	3,5-dichlorophenyl	5600 ± 400	437 ± 0.3	4100 ± 500	12.8	0.73	9.4
8n	3,4-difluorophenyl	7440 ± 19	101 ± 8.7	394 ± 98	73.7	0.05	3.9
8o	4-bromo-3-chlorophenyl	5420 ± 940	2.3 ± 0.1	459 ± 80	2360	0.08	200
8p	3-chloro-4-iodophenyl	3140 ± 450	1.8 ± 0.3	272 ± 55	1740	0.09	151
8q	2-chloro-4-iodophenyl	6640 ± 2080	74 ± 12.2	508 ± 21	89.7	0.08	6.9
8r	3-chloro-4-methylphenyl	>10 000	6.4 ± 1.3	198 ± 10	>1560	<0.02	31
8s	3,4-dimethylphenyl	N/T	10.1 ± 1.1	659 ± 128	N/T	N/T	65
8t	1-naphthyl	9720 ± 700	121 ± 3	5370 ± 580	80.3	0.55	44
8u	2-naphthyl	735 ± 235	21 ± 9.9	157 ± 13	35	0.21	7.5
8v	1-pyrenyl	9920 ± 906	860 ± 20.6	N/T	11.5	N/T	N/T
8w	9-phenanthryl	1640 ± 30	233 ± 44	13 000 ± 1300	7.0	7.93	56
10		38 900 ± 1050	993 ± 110	33 400 ± 3340	39.2	0.86	34

[a] K_i values are mean ± SEM from two to four independent experiments, each consisting of six drug concentrations (in triplicate) that were selected on the basis of preliminary screening experiments to bracket the approximate IC_{50} value.

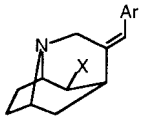
the former compound also exhibits a moderate NET activity (K_i = 178 nM). Among the compounds with an electron-donating substituent, the 4-methylphenyl analogue **8h** displays a high affinity for the SERT (K_i = 15 nM) coupled with moderate NET potency (K_i = 146 nM). The most potent compound in this series is compound **8j** containing the bulky isopropyl substituent, which exhibits a high potency for the SERT (K_i = 10 nM) and a 109-fold selectivity over the NET.

The disubstituted phenyl analogues **8k**−**s** are poorly active at the DAT and, at best, only moderately active at the NET. The 3,4-dichloro derivative **8k** exhibits a good potency (K_i = 20 nM) for the SERT and a high selectivity over the DAT (96-fold) and the NET (50-fold). Its regioisomers **8l** and **8m** display at least 17-fold lower potency for the SERT than **8k**, and the selectivities for the SERT over the DAT and the NET are also reduced. Similarly, the 3,4-difluoro compound **8n** has a 5-fold lower potency at the SERT (K_i = 101 nM) and a 13-fold lower selectivity for the SERT vs the NET. On the contrary, a 2-fold higher potency at the SERT (K_i = 10 nM) was found for the 3,4-dimethyl derivative **8s** as compared to **8k**. Compound **8r**, in which only the 4-chloro substituent of **8k** is replaced with methyl, exhibits high potency at the SERT (K_i = 6.4 nM) and a dramatically increased SERT selectivity of more than 1500-fold over the DAT and 30-fold over the NET. This result is comparable to or even better than that of the antidepressant medication fluoxetine, which has a potency of 7.3 nM at the SERT, a 627-fold SERT selectivity over the DAT, and a 23-fold SERT selectivity over the NET. Even more exciting results were obtained for the 3-chloro-4-bromophenyl and 3-chloro-4-iodophenyl analogues **8o** and **8p**, which are significantly more potent and SERT selective than fluoxetine. Compound **8o** has a K_i value of 2.3 nM for uptake inhibition at the SERT, a DAT/SERT uptake ratio of 2360, and a NET/SERT uptake ratio of 200. Compound **8p** displays a K_i value of 1.8 nM at the SERT and only slightly lower selectivities. The regioisomer **8q** is less potent and selective for the SERT in comparison to **8p**.

An additional set of compounds were designed to extend the sp^2 carbon framework of the aryl moiety. First, we replaced the phenyl group with a β-naphthyl group as the same structural modification has led to very potent WIN type tropanes.[33−35] As expected, compound **8u** exhibits a good activity at the SERT (K_i = 21 nM), which is a 6-fold better result than for the α-naphthyl analogue **8t**, but unexpectedly, compound **8u** also showed a fairly good activity at the NET (K_i = 157 nM) and a lower activity at the DAT (K_i = 735 nM). Replacement of phenyl with 1-pyrenyl (**8v**) and 9-phenanthryl (**8w**) resulted in a decrease in the potency and selectivity but still with a favorable SERT selectivity vs DAT and NET. The "dimeric" compound **10** exhibits only weak activity at the SERT but still remains 34-fold more potent than at the DAT and NET.

In summary, nearly all of the above compounds, with the notable exception of the unsubstituted phenyl congener **8g**, possess a low activity at the DAT but good to excellent potency at the SERT. This finding indicates that a large lipophilic pocket is present at the SERT but not at the DAT uptake site in the binding position of the aryl ring of these ligands. The electronic character of the substituent in the 4-monosubstituted phenyl series does not affect activity as dramatically as observed in some benztropine analogues,[34] since the 4-bromophenyl and 4-isopropylphenyl analogues **8d** and **8j** have the same SERT potency. Among the disubstituted compounds, the position and electronic character of the two substituents significantly affects the activity, with 3,4-disubstitution giving the best results in line with literature reports.[36] Thus, from the first part of our studies, several highly active compounds emerged

Table 2. Inhibition of Reuptake at Monoamine Transporters ($K_i \pm$ SEM (nM))



no.	Ar/X	[^{3}H]DA uptake	[^{3}H]5-HT uptake	[^{3}H]NE uptake	DA/5-HT	NE/DA	NE/5-HT
14a	Ar = 3,4-dichlorophenyl, X = $COOPr^i$	1290 ± 405	85.7 ± 4.7	325 ± 2.2	15.0	0.25	3.8
14b	Ar = 3,4-dichlorophenyl, X = COOPh	4440 ± 605	48.3 ± 14.9	2410 ± 510	91.9	0.54	49.9
14c	Ar = 3,4-dichlorophenyl, X = CONHMe	3780 ± 50	29.8 ± 4.8	417 ± 7.5	127	0.11	14.0
14d	Ar = 3,4-dichlorophenyl, X = $CONMe_2$	6680 ± 1440	28.9 ± 2.7	2020 ± 115	231	0.30	69.9
16a	Ar = 3,4-dichlorophenyl, X = CH_2OCOCH_3	1870 ± 90	1.6 ± 0.4	638 ± 86	1170	0.34	399
16b	Ar = 3,4-dichlorophenyl, X = CH_2OCOPh	14100 ± 103	3.1 ± 0.1	3070 ± 49	4550	0.22	990
16c	Ar = 3,4-dichlorophenyl, X = $CH_2OCOC_6H_4I$-*p*	17700 ± 850	48.7 ± 0.6	8590 ± 140	363	0.48	176
16d	Ar = 3,4-dichlorophenyl, X = CH_2OCO-2-naphthyl	>10 000	9.3 ± 0.3	5950 ± 80	>1070	<0.60	640
17a	Ar = 2-naphthyl, X = CH_2OCOCH_3	652 ± 113	4.4 ± 0.9	672 ± 59	148	1.03	153
17b	Ar = 2-naphthyl, X = CH_2OCOPh	5530 ± 305	0.1 ± 0.0	3220 ± 117	55 300	0.58	32 200
18a	Ar = 3-chlorophenyl, X = CH_2OCOCH_3	5980 ± 626	92.9 ± 8.4	1180 ± 192	64.4	0.20	12.7
18b	Ar = 3-chlorophenyl, X = CH_2OCOPh	4040 ± 333	11 ± 0.3	6580 ± 950	367	1.63	598
19	Ar = 4-iodophenyl, X = CH_2OCOPh	>10 000	0.1 ± 0.04	8190 ± 1450	>100 000	<0.82	81 900
20	Ar = 4-bromophenyl, X = CH_2OCOPh	3300 ± 67	3.95 ± 0.65	4470 ± 471	835	1.35	1130
21	Ar = 4-bromo-3-chlorophenyl, X = CH_2OCOPh	>10 000	3.2 ± 0.3	3840 ± 290	>3120	<0.38	1200
23	Ar = 3-chloro-4-iodophenyl, X = CH_2OCOPh	>10 000	0.06 ± 0.02	>10 000	>6 000 000	*a*	>6 000 000
24	Ar = 3-chloro-4-methylphenyl, X = CH_2OCOPh	>10 000	2.0 ± 0.6	>10 000	>20 000	*a*	>20 000
26	Ar = 3,4-dichlorophenyl, X = (*E*)-CH=CHPh	2110 ± 457	245 ± 31	2790 ± 306	8.6	1.32	11.4
27	Ar = 3,4-dichlorophenyl, X = $CON(CH_3)OCH_3$	8620 ± 87	30.7 ± 1.5	396 ± 68	281	0.05	12.9
28	Ar = 3,4-dichlorophenyl, X = $COCH_2CH_3$	6840 ± 135	2.2 ± 0.3	651 ± 13	3110	0.10	296
29	Ar = 3,4-dichlorophenyl, X = CH_2OPh-4-I	13 700 ± 1580	1170 ± 181	2510 ± 269	11.7	0.18	2.1
30		>10 000	8.5 ± 0.3	>10 000	>1170	*a*	>1170

[a] Ratio cannot be determined.

that we hoped to further modify to obtain even more potent and selective 5-HT reuptake inhibitors.

Although several previous investigations indicated that the C2 substituent does not impact significantly on the activity of cocaine-related ligands, our preliminary study of the present tricyclic ring system[17] suggested to the contrary that the activity of this ligand type could be further improved upon by appropriate modification of the ester group. For example, the inverted ester **16a** exhibits a K_i of 1.6 nM at the SERT with a 400-fold selectivity over the NET and a more than 1000-fold selectivity over the DAT. These data constitute an improvement over the precursor, methyl ester **8k**, by 1 order of magnitude and encouraged us to further explore the chemical modification of the ester moiety. Activity data for the prepared compounds are summarized in Table 2.

Emphasis was placed on analogues of compound **8k** because 3,4-dichloro substitution has been the most widely employed substitution pattern in cocaine-related studies. The esters **14a** and **14b** with increased bulk of the alcohol (phenol) moiety are inferior to methyl ester **8k**, but among those two compounds, the phenyl ester **14b** is more potent and selective at the SERT than the isopropyl ester **14a**. Compound **14a** also exhibits moderate activity at the NET. The amides **14c** and **14d** are almost as potent as the parent **8k**, but the bulkier dimethylamide **14d** is more selective than the monomethylamide **14c**. Apparently esters and amides of increased steric bulk participate less efficiently in hydrogen bonding, on which the role of the methyl ester pharmacophoric group in cocaine is believed to be based.

We consequently prepared the inverted esters **16a**–**d**, which may be assumed to retain a strong ability to engage in hydrogen bonding by means of their carbonyl oxygens. This type of modification, which has previously found little use in cocaine-related work,[18] greatly increased the inhibitory activity at and selectivity for the SERT. Besides the acetate **16a** described in our previous paper,[17] the benzoate **16b** also exhibits high activity at

the SERT and even higher DAT/SERT and NET/SERT uptake ratios. SERT potencies and selectivities fall as the acyl moiety is further changed to 2-naphthoyl and finally to 4-iodobenzoyl. Particularly interesting are the 2-naphthyl analogues **17a** and **17b** of which the latter exhibits outstanding potency and selectivity at the SERT while the parent methyl ester **8u** is rather unexceptional. Contrary to the situation involving the 3,4-dichlorophenyl-substituted acetate and benzoate **16a** and **16b**, the benzoate **17b** is 44-fold more potent at the SERT than the acetate **17a**, and its selectivity at the SERT over the DAT and NET is increased 200−400 times as compared to the acetate. A less-pronounced but qualitatively similar trend is also observed for the acetate/benzoate pair **18a** and **18b**. The "dimeric" ester **30** also exhibits a high potency for 5-HT uptake inhibition with a K_i value of 8.5 nM, while losing activity at the DAT and NET.

Replacement of the ester with a vinyl or ether group decreased activity; compounds **26** and **29** are 12- and 58-fold less potent at the SERT than the parent compound **8k**. This result may again be attributed to a loss of or decrease in hydrogen bonding. As others have demonstrated[13,15] in the tropane and piperidine series of ligands that a ketone function in place of the ester moiety can lead to increased potency at the SERT, we also implemented this modification in our compounds. Ligand **28** exhibits a potency of 2.2 nM at the SERT, which is a 9-fold improvement over ester **8k**, with excellent selectivity for the SERT vs the DAT and NET. The carbonyl oxygen alone therefore appears to be sufficient for effective hydrogen bonding.

Among the reverse esters prepared, the benzoate analogues have proven optimal with regard to potency and selectivity at the SERT. Thus, several benzoates **19**−**21**, **23**, and **24** obtained from the corresponding methyl esters (**8e**, **8d**, **8o**, **8p**, and **8r**) were additionally evaluated. In line with our expectation, the potencies of four out of these five compounds increased to varying degrees, with K_i values between 0.06 and 4.0 nM. The most potent and selective ligand is compound **23**, which displays a K_i value of 0.06 nM at the SERT and essentially no inhibition at the DAT and NET. This compound is the most potent 5-HT reuptake inhibitor presently known, and the benzoate **19** comes close.

In summary, after identifying the optimum substituents on the aryl ring, a variety of modifications to the ester moiety have been investigated. Most of the reverse esters (acetates and benzoates, **16**−**21**, **23**, and **24**) and the ketone **28** exhibit improved activity whereas other esters, amides, and an alkene do not. Benzoates **17b** and **19** display the same exceptional potency at the SERT (K_i = 0.1 nM). The most potent and selective ligand, however, is compound **23** with a K_i of 0.06 nM and essentially no activity at the DAT and NET. Because some evidence suggests that inhibition of 5-HT reuptake modulates the reinforcing properties of cocaine,[37] these compounds are interesting candidates for cocaine abuse studies.

Experimental Section

Nuclear magnetic resonance (NMR) spectra were recorded on a Varian Unity Inova spectrometer at 300 MHz for proton and 75.46 MHz for carbon-13 spectra. $CDCl_3$ was used as solvent. Chemical shifts are reported in parts per million relative to internal tetramethylsilane (TMS). Coupling constants are given in hertz (Hz). Thin-layer chromatography (TLC) was performed using Merck silica gel 60F-254 plates. Column chromatography was performed using Merck silica gel (60−200 mesh). Mass spectra were measured in the EI mode at an ionization potential of 70 eV. Starting materials were obtained from Aldrich, Alfa Aesar, or Acros. Solvents were obtained from Fisher Scientific (or VWR) and were used without further purification unless otherwise noted. Dimethyl formamide (DMF; DriSolv) was obtained from EM Science. Iodides **7a**,**b** were prepared from the corresponding anilines, and iodides **7b**−**d** were obtained from the corresponding bromides.[24] To ensure proper elemental analyses and for easy handling, parts of the final compounds were converted into salts by common methods.

Representative Procedure for Radical Cyclization. A solution of compound **4 (**340 mg**,** 1.67 mmol**)** in deoxygenated anhydrous benzene (30 mL) was heated to 80 °C, and a solution of tri-*n*-butylstannane (920 μL, 3.33 mmol) and AIBN (275 mg, 1.67 mmol) in deoxygenated anhydrous benzene (18 mL) was then added via a syringe pump over 6 h. After it was stirred at 80 °C for a further 6 h, the mixture was concentrated, and the residue was subjected to column chromatography with hexanes/ethyl acetate (6/1 to 1/1) as the eluent to give the two isomers **5** and **6**.

General Procedure for Stille Coupling. The appropriate aryl iodides **7** (0.16 mmol), tri-*o*-tolylphosphine (4.0 mg, 13 μmol), $Pd_2(dba)_3$ (3.0 mg, 3.2 μmol), and CuI (2.5 mg, 13 μmol) were dissolved in DMF (2 mL) and stirred at room temperature for 15 min under nitrogen. Then the stannane **5** (100 mg, 0.16 mmol) in DMF (2 mL) was added, and the mixture was stirred at 45−50 °C for 12 h. The solution was poured into ice-cold 2 N HCl, and the aqueous phase was extracted with ether (3 × 20 mL). The organic phase was reextracted with 2 N hydrochloric acid (2 × 15 mL), and the combined acidic solutions were basified with NH_4OH and extracted with ethyl acetate (4 × 20 mL). The solution was dried over anhydrous Na_2SO_4, the solvent was evaporated, and the residue was chromatographed on silica gel using ethyl acetate/hexanes 1/1 to give the desired product **8**.

HPLC Conditions for Isolation of Compounds 8p,q. A Chirex (*S*)-Pro and (*R*)-NEA (250 × 10 mm) column was used with a flow rate of 5 mL/min. A mixture of hexanes, dichloromethane, ethanol, and CF_3COOH (75/22/3/0.1) was employed as the solvent. The crude product mixture was injected as a solution in dichloromethane/hexanes. The retention times for compounds **8q** and **8p** are 14.5 and 18.2 min, respectively. Peaks were detected by UV absorption at 265 nm. The isolated products were suspended in ether, potassium carbonate was added to remove the trifluoroacetic acid, and the pure free bases **8p** and **8q** were obtained after filtration and removal of the solvent.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-(4-Chlorobenzylidene)-7-azatricyclo[4.3.1.0^{3,7}]decane-10-carboxylic Acid Methyl Ester (8b). $[\alpha]^{25}_D$ +53.2° (*c* 0.8, $CHCl_3$). ^{1}H NMR: δ 1.49 (m, 3H), 2.06 (m, 1H), 2.18 (m, 2H), 2.41 (t, J = 3.0 Hz, 1H), 2.70 (m, 1H), 3.28 (m, 1H), 3.65 (s, 3H), 3.76 (m, 1H), 3.86 and 4.00 (ABq, J = 18.3 Hz, both d with J = 2.4 Hz, 2H), 6.08 (m, 1H), 7.11 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H). ^{13}C NMR: δ 32.2, 32.8, 36.6, 37.5, 48.4, 52.1, 52.5, 53.9, 56.5, 121.1, 128.7, 129.8, 132.0, 136.0, 141.7, 174.5. MS *m*/*z* (%): 318 (M^+ + 1, 27), 317 (M^+, 77), 316 (M^+ − 1, 36), 286 (12), 258 (100), 244 (15), 141 (27), 110 (62), 83 (79), 49 (83). The free base was converted to the hydrochloride salt. Anal. ($C_{18}H_{21}Cl_2NO_2\cdot 0.5H_2O$) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-(3-Chlorobenzylidene)-7-azatricyclo[4.3.1.0^{3,7}]decane-10-carboxylic Acid Methyl Ester (8c). $[\alpha]^{25}_D$ +37.2° (*c* 0.33, $CHCl_3$). ^{1}H NMR: δ 1.51 (m, 3H), 2.08 (m, 1H), 2.14 (m, 2H), 2.41 (t, J = 3.0 Hz, 1H), 2.70 (q, J = 3.0 Hz, 1H), 3.27 (m, 1H), 3.67 (s, 3H), 3.75 (m, 1H), 3.90 and 4.02 (ABq, J = 18.4 Hz, both d with J = 2.4 and 2.7 Hz, respectively, 2H), 6.07 (m, 1H), 7.68 (d, J = 7.8 Hz, 1H), 7.16 (m, 2H), 7.25 (d, J = 7.5 Hz, 1H). ^{13}C NMR: δ 32.2, 32.8, 36.6, 37.5, 48.4, 52.1, 52.4, 53.9, 56.5, 121.0, 126.4, 126.5, 128.6,

129.7, 134.4, 139.3, 142.9, 174.4. MS *m/z* (%): 318 ($M^+ + 1$, 11), 317 (M^+, 32), 316 ($M^+ - 1$, 18), 286 (10), 258 (82), 244 (11), 141 (22), 110 (26), 83 (100), 68 (53). Anal. ($C_{18}H_{20}ClNO_2 \cdot 0.5H_2O$) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-(4-Bromobenzylidene)-7-azatricyclo[4.3.1.0^{3,7}]decane-10-carboxylic Acid Methyl Ester (8d). $[\alpha]^{25}_D$ +57.2° (*c* 0.6, $CHCl_3$). ^{1}H NMR: δ 1.49 (m, 3H), 2.06 (m, 1H), 2.15 (m, 2H), 2.41 (t, J = 3.0 Hz, 1H), 2.69 (m, 1H), 3.28 (m, 1H), 3.66 (s, 3H), 3.77 (m, 1H), 3.80 and 3.98 (ABq, J = 18.4 Hz, both d with J = 2.1 and 2.5 Hz, respectively, 2H), 6.07 (t, J = 2.4 Hz, 1H), 7.04 (d, J = 8.7 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H). ^{13}C NMR δ 31.9, 32.6, 36.4, 37.3, 48.2, 51.9, 52.2, 53.7, 56.3, 119.9, 120.9, 129.9, 131.4, 136.2, 141.8, 174.2. The free base was converted to the hydrochloride salt. Anal. ($C_{18}H_{21}ClBrNO_2$) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-(4-Iodobenzylidene)-7-azatricyclo-[4.3.1.0^{3,7}]decane-10-carboxylic Acid Methyl Ester (8e). $[\alpha]^{25}_D$ +52.7° (*c* 0.46, $CHCl_3$). ^{1}H NMR: δ 1.47 (m, 3H), 2.07 (m, 1H), 2.16 (m, 2H), 2.41 (t, J = 3.0 Hz, 1H), 2.69 (q, J = 3.0 Hz, 1H), 3.27 (m, 1H), 3.65 (s, 3H), 3.76 (m, 1H), 3.85 and 3.98 (ABq, J = 18.0 Hz, both d with J = 2.4 and 2.7 Hz, respectively, 2H), 6.05 (t, J = 2.4 Hz, 1H), 6.92 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H). ^{13}C NMR: δ 32.3, 32.9, 36.7, 37.6, 48.5, 52.2, 52.6, 54.0, 56.5, 121.3, 130.4, 134.4, 137.7, 142.4, 174.5. MS *m/z* (%): 410 ($M^+ + 1$, 13), 409 (M^+, 78), 408 ($M^+ - 1$, 31), 394 (7), 378 (10), 350 (91), 336 (13), 141 (29), 111 (33), 83 (100), 68 (44). Anal. ($C_{18}H_{20}INO_2$) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-[4-(Trifluoromethyl)benzylidene]-7-azatricyclo[4.3.1.0^{3,7}]decane-10-carboxylic Acid Methyl Ester (8f). $[\alpha]^{25}_D$ +40.3° (*c* 0.35, CH_2Cl_2). ^{1}H NMR: δ 1.50 (m, 3H), 2.06 (m, 1H), 2.12 (m, 2H), 2.43 (t, J = 2.7 Hz, 1H), 2.73 (dd, J = 3.3, 6.3 Hz, 1H), 3.29 (m, 1H), 3.66 (s, 3H), 3.76 (m, 1H), 4.04 and 3.91 (ABq, J = 18.3 Hz, both d with J = 2.4 and 2.7 Hz, respectively, 2H), 6.17 (br s, 1H), 7.27 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.4 Hz, 2H). ^{13}C NMR: δ 32.2, 32.8, 36.6, 37.6, 48.5, 52.1, 52.5, 53.9, 56.5, 121.1, 125.5 (q, J = 4 Hz), 125.5, 128.6, 144.3, 174.4 (CF_3 and the adjacent aromatic C not observed). MS *m/z* (%): 352 ($M^+ + 1$, 10), 351 (M^+, 49), 350 ($M^+ - 1$, 28), 292 (63), 223 (4), 183 (10), 159 (10), 141 (13), 111 (28), 83 (51), 68 (59), 49 (100). Anal. ($C_{19}H_{20}F_3NO_2 \cdot 1/3H_2O$) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-(4-Methylbenzylidene)-7-azatricyclo[4.3.1.0^{3,7}]decane-10-carboxylic Acid Methyl Ester (8h). $[\alpha]^{25}_D$ +57.0° (*c* 0.99, $CHCl_3$). ^{1}H NMR: δ 1.50 (m, 3H), 2.08 (m, 1H), 2.17 (m, 2H), 2.43 (t, J = 3.0 Hz, 1H), 2.72 (q, J = 3.0 Hz, 1H), 2.86 (s, 3 H), 3.28 (m, 1H), 3.65 (s, 3H), 3.80 (m, 1H), 3.93 and 4.02 (ABq, J = 18.3 Hz, both d with J = 2.1 and 2.4 Hz, respectively, 2H), 6.13 (t, J = 2.4 Hz, 1H), 7.18 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.1 Hz, 2H). ^{13}C NMR: δ 32.3, 32.9, 34.1, 36.9, 37.6, 48.6, 52.2, 52.8, 54.7, 56.5, 122.2, 126.7, 128.6, 135.3, 139.7, 147.2, 174.1. The free base was converted to the corresponding hydrochloride salt. Anal. ($C_{19}H_{24}ClNO_2 \cdot 1.1H_2O$) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-(4-Isopropylbenzylidene)-7-azatricyclo[4.3.1.0^{3,7}]decane-10-carboxylic Acid Methyl Ester (8j). $[\alpha]^{25}_D$ +29.6° (*c* 0.52, $CHCl_3$). ^{1}H NMR: δ 1.23 (d, J = 7.2 Hz, 6H), 1.48 (m, 3H), 2.05 (m, 1H), 2.15 (m, 2H), 2.39 (t, J = 3.0 Hz, 1H), 2.69 (q, J = 3.0 Hz, 1H), 2.88 (m, 1 H), 3.27 (m, 1H), 3.65 (s, 3H), 3.78 (m, 1H), 3.92 and 4.02 (ABq, J = 18.3 Hz, both d with J = 2.4 Hz, 2H), 6.10 (t, J = 2.4 Hz, 1H), 7.13 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.1 Hz, 2H). ^{13}C NMR: δ 24.2, 32.2, 32.9, 34.0, 36.9, 37.5, 48.5, 52.1, 52.6, 54.0, 56.4, 122.1, 126.7, 128.6, 135.2, 139.6, 147.1, 174.5. MS *m/z* (%): 326 ($M^+ + 1$, 18), 325 (M^+, 38), 324 ($M^+ - 1$, 14), 266 (67), 155 (15), 141 (21), 128 (18), 83 (100), 68 (43). Anal. ($C_{21}H_{27}NO_2 \cdot 0.5H_2O$) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-(2,3-Dichlorobenzylidene)-7-azatricyclo[4.3.1.0^{3,7}]decane-10-carboxylic Acid Methyl Ester (8l). $[\alpha]^{25}_D$ +22.6° (*c* 0.50, $CHCl_3$). ^{1}H NMR: δ 1.49 (m, 3H), 2.13 (m, 3H), 2.43 (t, J = 3.0 Hz, 1H), 2.78 (m, 1H), 3.29 (m, 1H), 3.70 (s, 3H), 3.74 (m, 1H), 3.81 and 3.92 (ABq, J = 18.4 Hz, both d with J = 2.4 Hz, 2H), 6.34 (t, J = 2.6 Hz, 1H), 7.14 (m, 2H), 7.31 (m, 1H). ^{13}C NMR: δ 31.9, 32.5, 36.0, 36.8, 47.2, 52.0, 52.2, 53.8, 56.2, 118.8, 126.8, 127.6, 128.4, 131.3, 133.2, 137.1, 143.6, 174.2. MS *m/z* (%): 353 ($M^+ + 1$, 3), 352 (M^+, 3), 351 ($M^+ - 1$, 6), 292 (34), 141 (18), 111 (10), 83 (100), 68 (60), 43 (83). The free base was converted to the tartrate salt. Anal. ($C_{22}H_{25}Cl_2NO_8 \cdot 1.0H_2O$) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-(3,5-Dichlorobenzylidene)-7-azatricyclo[4.3.1.0^{3,7}]decane-10-carboxylic Acid Methyl Ester (8m). $[\alpha]^{25}_D$ +51.0° (*c* 0.50, $CHCl_3$). ^{1}H NMR: δ 1.51 (m, 3H), 2.06 (m, 1H), 2.18 (m, 2H), 2.44 (t, J = 3.0 Hz, 1H), 2.71 (m, 1H), 3.32 (m, 1H), 3.65 (s, 3H), 3.78 (m, 1H), 3.90 and 3.98 (ABq, J = 18.2 Hz, both d with J = 2.4 Hz, 2H), 6.02 (t, J = 2.3 Hz, 1H), 7.05 (m, 2H), 7.17 (m, 1H). ^{13}C NMR: δ 31.8, 32.4, 36.1, 37.2, 48.1, 52.0, 52.1, 53.8, 56.4, 120.0, 126.1, 126.6, 134.8, 139.9, 174.0. MS *m/z* (%): 353 ($M^+ + 1$, 5), 352 (M^+, 5), 351 ($M^+ - 1$, 8), 292 (31), 141 (13), 111 (15), 83 (100), 68 (70), 43 (86). The free base was converted to the tartrate salt. Anal. ($C_{22}H_{25}Cl_2NO_8 \cdot 1.0H_2O$) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-(3,4-Difluorobenzylidene)-7-azatricyclo[4.3.1.0^{3,7}]decane-10-carboxylic Acid Methyl Ester (8n). $[\alpha]^{25}_D$ +36.5° (*c* 0.25, CH_2Cl_2). ^{1}H NMR: δ 1.49 (m, 3H), 2.05 (m, 1H), 2.16 (m, 2H), 2.41 (t, J = 3.3 Hz, 1H), 2.68 (dd, J = 3.3, 6.0 Hz, 1H), 3.29 (m, 1H), 3.66 (s, 3H), 3.75 (m, 1H), 3.85 and 3.98 (ABq, J = 18.3 Hz, both d with J = 2.4 and 2.7 Hz, respectively, 2H), 6.04 (t, J = 2.4 Hz, 1H), 6.88 (m, 1H), 6.95 (m, 1H), 7.01 (m, 1H). MS *m/z* (%): 319 (M^+, 4), 318 ($M^+ - 1$, 2), 260 (7), 151 (3), 84 (50), 68 (6), 49 (100). Anal. ($C_{19}H_{19}F_2NO_2$) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-(4-Bromo-3-chlorobenzylidene)-7-azatricyclo[4.3.1.0^{3,7}]decane-10-carboxylic Acid Methyl Ester (8o). $[\alpha]^{25}_D$ +57.6° (*c* 0.50, $CHCl_3$). ^{1}H NMR: δ 1.50 (m, 3H), 2.04 (m, 1H), 2.18 (m, 2H), 2.41 (m, 1H), 2.69 (m, 1H), 3.28 (m, 1H), 3.65 (s, 3H), 3.75 (m, 1H), 3.92 (m, 2H), 6.02 (br s, 1H), 6.93 (d, J = 8.1 Hz, 1H), 7.26 (s, 1H), 7.53 (d, J = 7.8 Hz, 1H). ^{13}C NMR: δ 32.2, 32.8, 36.5, 37.5, 48.4, 52.2, 52.4, 53.9, 56.5, 119.8, 120.1, 127.9, 130.2, 133.7, 134.5, 138.2, 143.9, 174.4. MS *m/z* (%): 398 ($M^+ + 1$, 1), 397 (M^+, 3), 396 ($M^+ - 1$, 2), 382 (1), 366 (1), 338 (6), 141 (3), 110 (5), 83 (11), 58 (30), 43 (100). Anal. ($C_{19}H_{19}BrClNO_2$) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-(3-Chloro-4-iodobenzylidene)-7-azatricyclo[4.3.1.0^{3,7}]decane-10-carboxylic Acid Methyl Ester (8p). $[\alpha]^{25}_D$ +28.0° (*c* 0.15, CH_2Cl_2). ^{1}H NMR: δ 1.65 (m, 3H), 2.28 (m, 1H), 2.43 (m, 2H), 2.61 (m, 1H), 2.88 (m, 1H), 3.31 (m, 1H), 3.70 (s, 3H), 3.73 (m, 1H), 3.85 and 3.98 (ABq, J = 18.3 Hz, both d with J = 2.4 and 2.7 Hz, respectively, 2H), 6.14 (m, 1H), 6.74 (dd, J = 1.8, 8.1 Hz, 1H), 7.22 (d, J = 1.8 Hz, 1H), 7.82 (d, J = 8.1 Hz, 1H). ^{13}C NMR: δ 30.0, 30.8, 34.2, 35.6, 46.5, 51.3, 53.5, 56.2, 58.2, 124.7, 127.6, 128.0, 129.4, 130.8, 138.1, 141.1, 141.3, 171.5. MS *m/z* (%): 444 ($M^+ + 1$, 5), 443 (M^+, 16), 442 ($M^+ - 1$, 6), 386 (10), 384 (31), 316 (2), 141 (15), 83 (100), 68 (47). Anal. ($C_{18}H_{19}ClINO_2$) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-(2-Chloro-4-iodophenylbenzylidene)-7-azatricyclo[4.3.1.0^{3,7}]decane-10-carboxylic Acid Methyl Ester (8q). ^{1}H NMR: δ 1.55 (m, 3H), 2.14 (m, 3H), 2.43 (t, J = 3.0 Hz, 1H), 2.79 (m, 1H), 3.29 (m, 1H), 3.69 (s, 3H), 3.78 (m, 3H), 6.27 (m, 1H), 6.88 (d, J = 8.1 Hz, 1H), 7.53 (dd, J = 1.8, 8.4 Hz, 1H), 7.72 (d, J = 1.8 Hz, 1H). ^{13}C NMR: δ 29.8, 30.6, 33.9, 35.0, 45.7, 51.0, 53.3, 55.9, 57.7, 122.7, 130.4, 131.4, 131.8, 132.4, 134.2, 136.6, 138.5, 171.3. MS *m/z* (%): 444 ($M^+ + 1$, 12), 443 (M^+, 32), 442 ($M^+ - 1$, 12), 408 (36), 384 (48), 316 (4), 149 (100), 83 (81), 68 (42). Anal. ($C_{18}H_{19}ClINO_2$) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-(3-Chloro-4-methylbenzylidene)-7-azatricyclo[4.3.1.0^{3,7}]decane-10-carboxylic Acid Methyl Ester (8r). $[\alpha]^{25}_D$ +48.4° (*c* 0.39, $CHCl_3$). ^{1}H NMR: δ 1.49 (m, 3H), 2.04 (m, 1H), 2.17 (m, 2H), 2.34 (s, 3H), 2.40 (t, J = 3.0 Hz, 1H), 2.68 (q, J = 3.3 Hz, 1H), 3.28 (m, 1H), 3.66 (s, 3H), 3.76 (m, 1H), 3.89 and 4.00 (ABq, J = 18.0 Hz, both d with J = 2.1 and 2.4 Hz, respectively, 2H), 6.04 (m, 1H), 6.98 (d, J = 7.8 Hz, 1H), 7.16 (d, J = 7.8 Hz, 2H). ^{13}C NMR: δ 29.9, 32.2, 32.8, 36.7, 37.5, 48.4, 52.1, 52.5, 53.9, 56.5, 120.9, 126.7, 129.0, 131.0, 134.0, 134.5, 136.8, 141.6, 174.5. MS *m/z* (%): 332 ($M^+ + 1$, 20), 331 (M^+, 39), 330 ($M^+ - 1$, 18), 274 (28), 272 (88), 156 (10), 141 (24), 83 (100), 68 (52). Anal. ($C_{19}H_{22}ClNO_2$) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-(3,4-Dimethylbenzylidene)-7-azatricyclo[4.3.1.0^{3,7}]decane-10-carboxylic Acid Methyl Ester (8s). $[\alpha]^{25}_D$ +47.6° (*c* 0.50, $CHCl_3$). ^{1}H NMR: δ 1.48 (m, 3H), 2.07 (m, 3H), 2.21 (s, 6H), 2.39 (t, J = 3.0 Hz, 1H), 2.68 (q, J = 3.0 Hz, 1H), 3.27 (m, 1H), 3.67 (s, 3H), 3.79 (m, 1H), 3.91 and 4.04 (ABq, J = 18.3 Hz, both d with J = 2.4 and 2.7 Hz, respectively, 2H), 6.07 (t, J = 2.4 Hz, 1H), 6.93 (d, J = 7.8 Hz, 1H), 6.98 (s, 1H), 7.08 (d, J = 7.8 Hz, 1H). ^{13}C NMR: δ 19.6, 20.1, 32.2, 32.9, 36.9, 37.5, 48.5, 52.1, 52.7, 54.0, 56.4, 122.1, 126.0, 129.8, 130.0, 134.8, 135.3, 136.6, 139.4, 174.6. MS *m*/*z* (%): 312 (M^+ + 1, 14), 313 (M^+, 23), 310 (M^+ − 1, 9), 252 (63), 183 (10), 156 (10), 141 (16), 118 (28), 83 (100), 68 (35). Anal. ($C_{20}H_{25}NO_2$·0.1H_2O) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-(2-Naphthylmethylene)-7-azatricyclo[4.3.1.0^{3,7}]decane-10-carboxylic Acid Methyl Ester (8u). $[\alpha]^{25}_D$ +44.0° (*c* 0.65, CH_2Cl_2). ^{1}H NMR: δ 1.52 (m, 3H), 2.18 (m, 3H), 2.45 (t, J = 3 Hz, 1H), 2.77 (m, 1H), 3.33 (m, 1H), 3.66 (s, 3H), 3.83 (m, 1H), 4.12 (m, 2H), 6.28 (t, J = 2.7 Hz, 1H), 7.35 (dd, J = 1.8, 8.4 Hz, 1H), 7.44 (m, 2H), 7.63 (br s, 1H), 7.78 (m, 3H). ^{13}C NMR: δ 32.2, 32.9, 36.8, 37.7, 48.6, 52.2, 52.7, 54.0, 56.5, 122.3, 125.9, 126.4, 127.1, 127.3, 127.7, 128.0, 128.1, 132.1, 133.7, 135.1, 174.6. MS *m*/*z* (%): 334 (M^+ + 1, 2), 333 (M^+, 10), 274 (16), 231 (2), 205 (5), 191 (7), 178 (9), 165 (14), 136 (25), 83 (100), 68 (41). Anal. ($C_{22}H_{23}NO_2$·1/3H_2O) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-(1-Pyrenylmethylene)-7-azatricyclo[4.3.1.0^{3,7}]decane-10-carboxylic Acid Methyl Ester (8v). $[\alpha]^{25}_D$ +16.0° (*c* 0.1, $CHCl_3$). ^{1}H NMR: δ 1.54 (m, 3H), 1.69 (m, 1H), 2.20 (m, 3H), 2.49 (t, J = 2.7 Hz, 1H), 2.95 (m, 1H), 3.31 (m, 1H), 3.79 (s, 3H), 3.86 (m, 2H), 6.67 (m, 1H), 7.60 (m, 5H), 7.83 (d, J = 7.5 Hz, 1H), 8.02 (d, J = 8.1 Hz, 1H), 8.66 (d, J = 7.5 Hz, 2H). ^{13}C NMR: δ 32.1, 32.7, 36.7, 37.1, 47.4, 52.3, 52.6, 54.2, 56.7, 120.5, 124.2, 124.8, 125.0, 125.1, 125.3, 126.1, 126.5, 127.3, 127.5, 127.6, 128.6, 130.4, 131.1, 131.6, 174.6. MS *m*/*z* (%): 408 (M^+ + 1, 9), 407 (M^+, 35), 348 (39), 279 (9), 265 (17), 252 (17), 239 (37), 174 (73), 83 (100), 68 (39). Anal. ($C_{28}H_{25}NO_2$·0.7H_2O) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-(9-Phenanthrylmethylene)-7-azatricyclo[4.3.1.0^{3,7}]decane-10-carboxylic Acid Methyl Ester (8w). $[\alpha]^{25}_D$ +30.8° (*c* 0.18, $CHCl_3$). ^{1}H NMR: δ 1.57 (m, 4H), 2.21 (m, 3H), 2.53 (t, J = 2.7 Hz, 1H), 2.99 (m, 1H), 3.33 (m, 1H), 3.80 (s, 3H), 3.86 (m, 2H), 6.98 (m, 1H), 7.86 (d, J = 7.8 Hz, 1H), 8.08 (m, 8H). ^{13}C NMR: δ 32.3, 32.8, 36.8, 36.9, 47.2, 52.2, 52.6, 54.1, 56.7, 119.8, 122.6, 123.2, 125.4, 126.5, 126.6, 126.7, 126.8, 126.9, 128.6, 129.9, 130.6, 131.2, 131.8, 132.5, 142.4, 174.7. MS *m*/*z* (%): 384 (M^+ + 1, 3), 383 (M^+, 4), 324 (25), 255 (7), 241 (11), 215 (21), 161 (37), 83 (100), 68 (38). Anal. ($C_{26}H_{25}NO_2$·0.8HCl) C, H, N.

Compound 10. ^{1}H NMR: δ 1.50 (m, 6H), 2.07 (m, 2H), 2.17 (m, 4H), 2.42 (t, J = 3.0 Hz, 2H), 2.71 (m, 2H), 3.29 (m, 2H), 3.64 (s, 6H), 3.81 (m, 2H), 3.93 and 4.03 (ABq, J = 18.3 Hz, both d with J = 2.1 and 2.4 Hz, respectively, 4H), 6.11 (t, J = 2.4 Hz, 2H), 7.15 (s, 4 H). ^{13}C NMR: δ 31.9, 32.5, 36.4, 37.3, 48.3, 51.9, 52.4, 53.8, 56.3, 121.8, 128.4, 135.3, 140.2, 174.2. MS *m*/*z* (%): 489 (M^+ + 1, 0.58), 488 (M^+, 1), 429 (2), 406 (4), 72 (20), 58 (74), 44 (100). Anal. ($C_{30}H_{36}N_2O_4$·2/3HCl) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-(3,4-Dichlorobenzylidene)-7-azatricyclo[4.3.1.0^{3,7}]decane-10-carboxylic Acid Isopropyl Ester (14a). Ester **8k** (99 mg, 0.27 mmol) was dissolved in 6 N HCl (10 mL), the mixture was heated to reflux for 8 h, the solvent was removed, and the residue was dried in vacuo to give the acid **12** as the hydrochloride salt in quantitative yield. ^{1}H NMR (D_2O): δ 1.99 (m, 3H), 2.26 (m, 3H), 2.95 (m, 2H), 3.92 (m, 1H), 4.35 (m, 3H), 6.25 (m, 1H), 6.89 (m, 1H), 7.05 (m, 1H), 7.25 (m, 1H).

The crude acid hydrochloride was suspended in CH_2Cl_2 (20 mL) and cooled to 0 °C. Thionyl chloride (1.5 mL) was added dropwise. The reaction mixture was stirred at room temperature for 10 min and then at 60 °C for 2 h. After the solvent was removed and cooled to 0 °C, 2-propanol (2 mL) was added slowly, and the resulting mixture was stirred for 1 h. The reaction was quenched by adding saturated $NaHCO_3$. The product was extracted into ethyl acetate (4 × 15 mL), and the combined organic phases were dried (Na_2SO_4), filtered, and evaporated. The residue was purified by column chromatography using ethyl acetate/hexanes (1/1) as the eluent to give ester **14a**. ^{1}H NMR ($CDCl_3$): δ 1.19 (d, J = 7.2 Hz, 6H), 1.52 (m, 3H), 2.06 (m, 1H), 2.20 (m, 2H), 2.38 (t, J = 3.3 Hz, 1H), 2.71 (m, 1H), 3.30 (m, 1H), 3.80 (m, 1H), 3.96 and 4.03 (ABq, J = 18.3 Hz, both d with J = 2.4 and 2.7 Hz, respectively, 2H), 4.98 (m, 1H), 6.03 (t, J = 2.4 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 7.28 (s, 1H), δ 7.37 (d, J = 8.4 Hz, 1H). MS *m*/*z* (%): 380 (M^+ + 1, 8), 379 (M^+, 17), 336 (M^+ − 1, 15), 292 (51), 110 (29), 83 (100), 68 (61), 49 (46). The free base was converted to the hydrochloride salt. Anal. ($C_{20}H_{24}Cl_3NO_2$·0.75H_2O) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-(3,4-Dichlorobenzylidene)-7-azatricyclo[4.3.1.0^{3,7}]decane-10-carboxylic Acid Phenyl Ester (14b). To a solution of NaOH (500 mg, 12.5 mmol) and phenol (500 mg, 5.3 mmol) in dioxane (2 mL) at 0 °C was added slowly a solution of the acid chloride prepared as above from ester **8k** (37 mg, 0.1 mmol) followed by tetrabutylammonium hydroxide (5 mg, 40% solution in water) in dioxane (5 mL). The mixture was stirred at room temperature overnight, diluted with water, and extracted with ethyl acetate (4 × 20 mL). The combined extracts were washed with water and then brine and dried over Na_2SO_4. After the solvent was removed, the residue was subjected to column chromatography using ethyl acetate/hexanes (3/2) as the eluent to give ester **14b**. ^{1}H NMR ($CDCl_3$): δ 1.62 (m, 3H), 2.20 (m, 3H), 2.71 (t, J = 3.0 Hz, 1H), 2.96 (dd, J = 3.2, 6.3 Hz, 1H), 3.37 (m, 1H), 3.90 (m, 1H), 4.01 and 4.08 (ABq, J = 18.3 Hz, both d with J = 2.4 Hz, 2H), 6.23 (t, J = 2.7 Hz, 1H), 6.98 (m, 1H), 7.01 (m, 1H), 7.24 (m, 1H), 7.36 (m, 5H). MS *m*/*z* (%): 414 (M^+ + 1, 2), 413 (M^+, 5), 412 (M^+ − 1, 1), 320 (13), 292 (10), 84 (57), 68 (19), 49 (100). The free base was converted to the hydrochloride salt. Anal. ($C_{23}H_{22}Cl_3NO_2$·1.1H_2O) C, H, N.

General Procedure for the Synthesis of Carboxamides (14c,d). The acid chloride hydrochloride prepared as above was suspended in 5 mL of CH_2Cl_2 under nitrogen at 0 °C and treated with 2.0 equiv of methylamine hydrochloride or dimethylamine hydrochloride and 4.0 equiv of triethylamine. The mixture was stirred at room temperature overnight and then basified with 3 N NaOH or concentrated NH_4OH. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried (Na_2SO_4), filtered, and evaporated in vacuo. The crude product was purified by column chromatography (ethyl acetate as the eluent).

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-(3,4-Dichlorobenzylidene)-7-azatricyclo[4.3.1.0^{3,7}]decane-10-(*N*-methylcarboxamide) (14c). ^{1}H NMR ($CDCl_3$): δ 1.51 (m, 3H), 2.00 (m, 1H), 2.20 (m, 2H), 2.51 (m, 1H), 2.81 (m, 3H), 3.32 (m, 1H), 3.87 (m, 1H), 3.90 and 4.06 (ABq, J = 18.3 Hz, both d with J = 2.4 and 2.7 Hz, respectively, 2H), 5.55 (br s, 1H), 6.05 (t, J = 2.4 Hz, 1H), 7.05 (dd, J = 2.1, 8.4 Hz, 1H), 7.30 (d, J = 2.1 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H). MS *m*/*z* (%): 351 (M^+ + 1, 11), 350 (M^+, 27), 349 (M^+ − 1, 8), 292 (100), 278 (10), 191 (10), 110 (33), 83 (79), 68 (57), 57 (43). The free base was converted to the hydrochloride salt. Anal. ($C_{18}H_{21}Cl_3N_2O$·0.75H_2O) C, H; N: calcd, 6.97; found, 6.46.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-(3,4-Dichlorobenzylidene)-7-azatricyclo[4.3.1.0^{3,7}]decane-10-(*N*,*N*-dimethylcarboxamide) (14d). ^{1}H NMR ($CDCl_3$): δ 1.50 (m, 3H), 2.05 (m, 1H), 2.20 (m, 2H), 2.52 (m, 1H), 2.78 (m, 1H), 2.90 (s, 3H), 3.08 (s, 3H), 3.22 (m, 1H), 3.90 (m, 1H), 3.80 and 4.18 (ABq, J = 18.3 Hz, both parts of d with J = 2.4 Hz, 2H), 5.92 (br s, 1H), 7.01 (dd, J = 2.1, 8.4 Hz, 1H), 7.23 (d, J = 2.1 Hz, 1H), 7.38 (d, J = 8.4 Hz, 1H). MS *m*/*z* (%): 365 (M^+ + 1, 6), 364 (M^+, 17), 364 (M^+ − 1, 2), 292 (76), 278 (11), 205 (27), 149 (11), 118 (42), 83 (48), 72 (87), 68 (79), 41 (100). The free base was converted to the hydrochloride salt. Anal. ($C_{19}H_{23}Cl_3N_2O$·0.75H_2O) C, H; N: calcd, 6.74; found, 6.29.

General Procedure for the Synthesis of Compounds 16−21 and 24. DIBAL-H (1 N in pentane, 1.5 mmol) or $LiAlH_4$ (1.5 mmol) was added to a solution of the appropriate ester **8** (0.5 mmol) in tetrahydrofuran (THF; 10 mL) at 0 °C under N_2 at room temperature. The reaction mixture was stirred overnight, quenched with concentrated Rochelle salt solution

(15 mL), and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure to afford the alcohol **15**.

To a solution of the crude alcohol **15**, pyridine (1 mL) and a catalytic amount of DMAP (1 mg) in THF (5 mL) was added dropwise the appropriate acid chloride (1.5 equiv) at 0 °C under N_2. The solution was stirred overnight and extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with a saturated solution of $NaHCO_3$ (2 × 10 mL), dried, and concentrated under reduced pressure. The crude product was purified by column chromatography using ethyl acetate/hexanes (2/1) as the eluent.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-10-(Benzoyloxymethyl)-9-(3,4-dichlorobenzylidene)-7-azatricyclo[4.3.1.0^{3,7}]decane (16b). $[\alpha]^{25}_D$ +82.4° (*c* 0.35, CH_2Cl_2). ^{1}H NMR: δ 1.61 (m, 3H), 2.04 (m, 1H), 2.15 (m, 1H), 2.31 (m, 2H), 2.52 (m, 1H), 3.15 (m, 1H), 3.48 (m, 1H), 4.07 (m, 2H), 4.26 (m, 2H), 6.12 (br s, 1H), 7.00 (dd, J = 2.1, 8.4 Hz, 1H), 7.24 (d, J = 1.8 Hz, 1H), 7.43 (m, 3H), 7.58 (m, 1H), 8.01 (m, 2H). ^{13}C NMR: δ 31.9, 32.5, 36.0, 36.9, 45.3, 48.3, 54.5, 58.6, 67.0, 121.4, 127.6, 128.6, 129.7, 130.0, 130.3, 130.5, 132.7, 133.3, 136.9, 140.9, 166.5. MS *m*/*z* (%): 429 (M^+ + 2, 12), 428 (M^+ + 1, 9), 427 (M^+, 18), 426 (M^+ − 1, 6), 308 (65), 306 (100), 294 (18), 292 (24), 117 (26), 105 (65), 83 (39), 68 (63). Anal. ($C_{24}H_{23}Cl_2NO_2$·0.7H_2O) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-(3,4-Dichlorobenzylidene)-10-(4-iodobenzoyloxymethyl)-7-azatricyclo[4.3.1.0^{3,7}]decane (16c). $[\alpha]^{25}_D$ +87.4° (*c* 0.25, CH_2Cl_2). ^{1}H NMR: δ 1.51 (m, 3H), 1.94 (m, 1H), 2.15 (m, 3H), 2.45 (m, 1H), 2.85 (m, 1H), 3.32 (m, 1H), 3.93 (m, 2H), 4.12 (m, 2H), 6.04 (br s, 1H), 7.00 (dd, J = 1.8, 8.4 Hz, 1H), 7.26 (d, J = 2.1 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.74 (m, 4H). ^{13}C NMR: δ 32.4, 33.0, 36.5, 37.3, 45.5, 48.7, 54.1, 58.3, 67.7, 127.6, 129.7, 130.1, 130.2, 130.4, 131.1, 132.6, 137.4, 138.0, 143.6, 166.1. MS *m*/*z* (%): 556 (M^+ + 2, 4), 555 (M^+ + 1, 12), 554 (M^+, 7), 553 (M^+ − 1, 23), 308 (61), 306 (100), 292 (26), 231 (24), 202 (16), 83 (44), 68 (55). Anal. ($C_{24}H_{22}Cl_2INO_2$·1/6H_2O) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-(3,4-Dichlorobenzylidene)-10-(2-naphthoyloxymethyl)-7-azatricyclo[4.3.1.0^{3,7}]decane (16d). $[\alpha]^{25}_D$ +340° (*c* 0.26, $CHCl_3$). ^{1}H NMR: δ 1.57 (m, 3H), 2.10 (m, 1H), 2.49 (m, 1H), 3.03 (m, 1H), 3.34 (t, J = 6.9 Hz, 1H), 3.95 (s, 3H), 4.30 (m, 2H), 6.07 (t, J = 2.4 Hz, 1H), 6.98 (dd, J = 2.1, 8.4 Hz, 1H), 7.24 (d, J = 2.1 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.57 (m, 2H), 7.90 (m, 3H), 8.01 (dd, J = 1.8, 8.7 Hz, 3H), 8.55 (s, 1H). ^{13}C NMR: δ 32.4, 33.0, 36.5, 37.4, 45.7, 48.8, 54.1, 58.4, 67.5, 120.5, 125.2, 126.9, 127.5, 127.6, 128.0, 128.4, 128.5, 129.5, 130.0, 130.2, 130.4, 131.2, 132.6, 135.7, 135.8, 137.5, 143.7, 166.8. MS *m*/*z* (%): 479 (M^+ + 2, 17), 478 (M^+ + 1, 11), 477 (M^+, 30), 308 (62), 306 (100), 292 (23), 155 (27), 127 (53), 83 (15), 68 (34). Anal. ($C_{28}H_{25}Cl_2NO_2$·1.9H_2O) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-10-(Acetoxymethyl)-9-(2-naphthylmethylene)-7-azatricyclo[4.3.1.0^{3,7}]decane (17a). $[\alpha]^{25}_D$ +78.7° (*c* 0.23, $CHCl_3$). ^{1}H NMR: δ 1.54 (m, 3H), 1.81 (m, 1H), 2.05 (s, 3H), 2.15 (m, 3H), 2.41 (m, 1H), 2.91 (m, 1H), 3.36 (m, 1H), 4.02 (d, J = 7.5 Hz, 2H), 4.10 (m, 2H), 6.30 (br s, 1H), 7.40 (m, 3H), 7.65 (s, 1H), 7.80 (m, 3H). ^{13}C NMR: δ 21.0, 32.2, 32.8, 36.0, 37.2, 45.3, 48.7, 54.0, 58.3, 67.2, 122.7, 125.7, 126.2, 126.9, 127.0, 127.5, 127.9, 171.1. MS *m*/*z* (%): 348 (M^+ + 1, 2), 347 (M^+, 10), 288 (27), 274 (11), 178 (10), 165 (11), 136 (11), 84 (63), 49 (100), 44 (75). Anal. ($C_{23}H_{25}NO_2$·0.8H_2O) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-10-(Benzoyloxymethyl)-9-(2-naphthylmethylene)-7-azatricyclo[4.3.1.0^{3,8}]decane (17b). $[\alpha]^{25}_D$ +93.5° (*c* 0.185, $CHCl_3$). ^{1}H NMR: δ 1.56 (m, 3H), 1.97 (m, 1H), 2.18 (m, 3H), 2.53 (m, 1H), 2.98 (m, 1H), 3.37 (t, J = 6.9 Hz, 1H), 4.12 (m, 2H), 4.28 (d, J = 7.8 Hz, 2H), 6.33 (br s, 1H), 7.46 (m, 6H), 7.64 (s, 1H), 7.78 (m, 3H), 8.05 (m, 2H). ^{13}C NMR: δ 32.5, 33.1, 36.4, 37.5, 45.7, 49.0, 54.2, 58.5, 67.7, 122.8, 125.9, 126.3, 127.1, 127.2, 127.7, 128.0, 128.1, 128.6, 129.7, 130.4, 132.0, 133.1, 133.6, 135.0, 141.3, 166.7. MS *m*/*z* (%): 410 (M^+ + 1, 6), 409 (M^+, 22), 304 (48), 288 (56), 274 (34), 218 (15), 178 (21), 165 (21), 136 (30), 105 (36), 84 (56), 49 (100). Anal. ($C_{28}H_{27}NO_2$·0.3H_2O) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-10-(Acetoxymethyl)-9-(3-chlorobenzylidene)-7-azatricyclo[4.3.1.0^{3,7}]decane (18a). $[\alpha]^{25}_D$ +71.1° (*c* 0.22, $CHCl_3$). ^{1}H NMR: δ 1.52 (m, 3H), 1.77 (m, 1H), 2.09 (m, 6H), 2.35 (m, 1H), 2.83 (dd, J = 5.4, 2.7 Hz, 1H), 3.30 (t, J = 6.4 Hz, 1H), 3.94 (m, 4H), 6.07 (br s, 1H), 7.09 (d, J = 7.5 Hz, 1H), 7.25 (m, 3H). ^{13}C NMR: δ 21.1, 32.4, 33.0, 36.2, 37.3, 45.4, 48.7, 54.1, 58.4, 67.3, 121.4, 126.4, 126.6, 128.5, 129.8, 134.5, 139.3, 142.9, 171.3. MS *m*/*z* (%): 331 (M^+, 2), 274 (3), 272 (8), 258 (2), 84 (62), 51 (30), 49 (100). Anal. ($C_{19}H_{22}$-$ClNO_2$·0.5H_2O) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-10-(Benzoyloxymethyl)-9-(3-chlorobenzylidene)-7-azatricyclo[4.3.1.0^{3,7}]decane (18b). $[\alpha]^{25}_D$ +111° (*c* 0.22, $CHCl_3$). ^{1}H NMR: δ 1.54 (m, 3H), 1.94 (m, 1H), 2.08 (m, 3H), 2.45 (m, 1H), 2.94 (dd, J = 3.0, 5.4 Hz, 1H), 3.33 (t, J = 6.6 Hz, 1H), 3.96 (dd, J = 2.7, 4.5 Hz, 2H), 4.22 (m, 2H), 6.11 (t, J = 2.1 Hz, 1H), 7.07 (d, J = 7.8 Hz, 1H), 7.16 (m, 1H), 7.24 (m, 2H), 7.43 (m, 2H), 7.54 (m, 1H), 8.02 (m, 2H). ^{13}C NMR: δ 32.4, 33.1, 36.4, 37.4, 45.6, 48.8, 54.1, 58.4, 67.6, 121.5, 126.3, 126.6, 128.5, 128.6, 129.7, 129.8, 130.3, 133.2, 134.5, 139.3, 142.9, 166.7. MS *m*/*z* (%): 394 (M^+ + 1, 6), 393 (M^+, 17), 392 (M^+ + 1, 5), 274 (31), 272 (100), 258 (25), 105 (28), 84 (52), 77 (25), 49 (86). Anal. ($C_{24}H_{24}ClNO_2$·1.1H_2O) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-10-(Benzoyloxymethyl)-9-(4-iodobenzylidene)-7-azatricyclo[4.3.1.0^{3,7}]decane (19). $[\alpha]^{25}_D$ +169° (*c* 0.25, $CHCl_3$). ^{1}H NMR: δ 1.51 (m, 3H), 1.95 (m, 1H), 2.10 (m, 3H), 2.46 (m, 1H), 2.94 (dd, J = 3.0, 5.7 Hz, 1H), 3.33 (t, J = 6.9 Hz, 1H), 3.93 (m, 2H), 4.22 (m, 2H), 6.09 (t, J = 2.7 Hz, 1H), 6.92 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.56 (m, 1H), 7.63 (dd, J = 1.8, 6.6 Hz, 2H), 8.03 (m, 2H). ^{13}C NMR: δ 32.4, 33.0, 36.4, 37.3, 45.6, 48.7, 54.2, 58.4, 67.6, 121.8, 128.5, 128.6, 129.7, 129.8, 130.4, 133.2, 136.9, 137.7, 142.1, 166.7. MS *m*/*z* (%): 486 (M^+ + 1, 4), 485 (M^+, 25), 364 (73), 350 (18), 141 (11), 128 (14), 105 (29), 83 (26), 77 (22), 44 (100). Anal. ($C_{24}H_{24}INO_2$) H, N; C: calcd, 59.39; found, 59.97.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-10-(Benzoyloxymethyl)-9-(4-bromobenzylidene)-7-azatricyclo[4.3.1.0^{3,7}]decane (20). ^{1}H NMR: δ 1.46 (m, 3H), 1.94 (m, 1H), 2.15 (m, 3H), 2.45 (m, 1H), 2.94 (m, 1H), 3.32 (t, J = 6.9 Hz, 1H), 3.94 (m, 2H), 4.21 (m, 2H), 6.10 (s, 1H), 7.06 (d, J = 8.1 Hz, 2H), 7.25 (s, 1H), 7.43 (m, 3H), 7.55 (m, 1H), 8.01 (d, J = 6.9 Hz, 2H). ^{13}C NMR: δ 32.5, 33.1, 36.4, 37.4, 45.7, 48.8, 54.2, 58.4, 67.7, 121.7, 128.7, 129.0, 129.7, 130.1, 130.4, 131.1, 131.7, 133.2, 137.1, 166.7. MS *m*/*z* (%): 439 (M^+ + 2, 27), 437 (M^+, 34), 318 (95), 316 (100), 302 (19), 141 (24), 118 (23), 105 (55), 83 (37), 77 (50), 68 (54).

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-10-(Benzoyloxymethyl)-9-(4-bromo-3-chlorobenzylidene)-7-azatricyclo[4.3.1.0^{3,7}]decane (21). $[\alpha]^{25}_D$ +100° (*c* 0.33, $CHCl_3$). ^{1}H NMR: δ 1.52 (m, 3H), 1.94 (m, 1H), 2.12 (m, 3H), 2.45 (m, 1H), 2.95 (dd, J = 3.0, 5.4 Hz, 1H), 3.33 (t, J = 6.9 Hz, 1H), 3.92 (m, 2H), 4.22 (m, 2H), 6.05 (t, J = 2.4 Hz, 1H), 6.92 (dd, J = 2.1, 8.4 Hz, 1H), 7.26 (s, 1H), 7.43 (m, 2H), 7.54 (m, 2H), 8.01 (m, 2H). ^{13}C NMR: δ 32.5, 33.0, 36.5, 37.3, 45.6, 48.8, 54.1, 58.4, 67.5, 120.6, 126.7, 127.9, 128.6, 129.7, 130.2, 130.3, 133.2, 133.7, 134.6, 138.2, 144.0, 166.6. MS *m*/*z* (%): 474 (M^+ + 1, 6), 473 (M^+, 21), 472 (8), 354 (23), 352 (100), 350 (77), 338 (29), 141 (19), 117 (41), 105 (71), 83 (49), 77 (55), 44 (74). Anal. ($C_{24}H_{23}BrClNO_2$·2/3H_2O) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-10-(Benzoyloxymethyl)-9-[3-chloro-4-(tri-*n*-butylstannyl)benzylidene]-7-azatricyclo[4.3.1.0^{3,7}]-decane (22). A solution of compound **21** (0.10 mmol) in toluene (1 mL) was degassed by bubbling nitrogen into the mixture for 15 min, and bis(tributyltin) (123 μL, 0.23 mmol) followed by tetrakis(triphenylphosphine)palladium (2.0 mg) were added. The mixture was stirred under N_2 at 90 °C for 6 h. The solvent was removed, and the residue was purified by preparative TLC (hexane/EtOAc 1:1) to give the product in 47% yield. ^{1}H NMR: δ 0.90 (m, 12H), 1.13 (t, J = 6.6 Hz, 6H), 1.36 (m, 9H), 1.53 (m, 3H), 1.94 (m, 1H), 2.13 (m, 3H), 2.45 (m, 1H), 2.96 (dd, J = 2.7, 5.1 Hz, 1H), 3.34 (t, J = 6.0 Hz, 1H), 3.99 (m, 2H), 4.22 (m, 2H), 6.09 (br s, 1H), 7.03 (dd, J = 1.5, 7.5 Hz, 1 H), 7.17 (d, J = 1.2 Hz, 1H), 7.32 (d, J = 7.5 Hz, 1H), 7.43 (m, 2H), 7.52 (m, 1H), 8.00 (dd, J = 1.5, 8.4 Hz, 2H). ^{13}C NMR: δ

10.7, 13.9, 27.5, 29.2, 32.4, 33.0, 36.4, 37.4, 45.6, 48.8, 54.2, 58.4, 67.5, 121.7, 125.9, 128.1, 128.6, 129.7, 130.3, 133.2, 137.7, 139.2, 140.7, 142.2, 143.1, 166.6. MS *m*/*z* (%): 626 ($M^+ - C_4H_9$, 55), 570 (29), 392 (14), 272 (35), 236 (34), 195 (87), 178 (51), 153 (43), 105 (54), 57 (48), 41 (100).

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-10-(Benzoyloxymethyl)-9-(3-chloro-4-iodobenzylidene)-7-azatricyclo[4.3.1.0^{3,7}]decane (23). A solution of compound **22** (0.046 mmol) in CH_2Cl_2 (2.0 mL) was deoxygenated by bubbling with nitrogen for 10 min. Then, a solution of iodine (72 mg, 0.28 mmol) in CH_2Cl_2 (0.5 mL) was added. The mixture was stirred at room temperature overnight under N_2. Solutions of $NaHSO_3$ (1 mL, 5% in water) and KF (0.5 mL, 1 M in MeOH) were added successively. The mixture was stirred for 5 min, and the phases were separated. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated to give the crude product. Preparative TLC (hexane/EtOAc 1:1) gave compound **23** in 64% yield. ^{1}H NMR: δ 1.54 (m, 3H), 1.93 (m, 1H), 2.13 (m, 3H), 2.45 (m, 1H), 2.94 (m, 1H), 3.32 (t, J = 6.9 Hz, 1H), 3.92 (m, 2H), 4.21 (m, 2H), 6.03 (br s, 1H), 6.76 (dd, J = 1.8, 8.4 Hz, 1 H), 7.26 (d, J = 1.8 Hz, 1H), 7.42 (m, 2H), 7.53 (m, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.99 (d, J = 8.4 Hz, 2H). ^{13}C NMR: δ 32.4, 33.0, 36.5, 37.3, 45.6, 48.8, 54.1, 58.3, 67.4, 120.6, 127.9, 128.6, 129.2, 129.7, 130.3, 133.2, 138.6, 139.2, 140.1, 144.3, 166.6. MS *m*/*z* (%): 520 (M^+ + 1, 12), 519 (M^+, 42), 400 (33), 398 (100), 384 (33), 141 (15), 105 (45), 83 (25), 77 (43), 68 (31). Anal. ($C_{24}H_{23}ICINO_2 \cdot 1.5H_2O$) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-10-(Benzoyloxymethyl)-9-(3-chloro-4-methylbenzylidene)-7-azatricyclo[4.3.1.0^{3,7}]decane (24). $[\alpha]^{25}_D$ +84.0° (*c* 0.20, $CHCl_3$). ^{1}H NMR: δ 1.55 (m, 3H), 1.93 (m, 1H), 2.15 (m, 3H), 2.34 (s, 3H), 2.44 (m, 1H), 2.94 (m, 1H), 3.32 (t, J = 7.2 Hz, 1H), 3.95 (m, 2H), 4.21 (m, 2H), 6.08 (br s, 1H), 6.99 (dd, J = 1.8, 8.1 Hz, 1 H), 7.18 (m, 2H), 7.43 (m, 2H), 7.54 (m, 1H), 8.00 (d, J = 8.4 Hz, 2H). ^{13}C NMR: δ 19.9, 32.5, 33.1, 36.3, 37.4, 45.7, 48.8, 54.1, 58.4, 67.7, 121.3, 126.7, 128.6, 129.0, 129.7, 130.4, 131.0, 133.2, 133.9, 134.5, 136.8, 141.6, 166.7. MS *m*/*z* (%): 409 (M^+ + 1, 6), 408 (M^+, 6), 407 ($M^+ - 1$, 16), 288 (32), 286 (100), 272 (36), 141 (13), 105 (42), 83 (48), 77 (45), 68 (49). Anal. ($C_{25}H_{26}ClNO_2 \cdot 2/3H_2O$) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-(3,4-Dichlorobenzylidene)-7-azatricyclo[4.3.1.0^{3,7}]decane-10-carboxaldehyde (25). Oxalyl chloride (0.10 mL, 1.08 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL), and the solution was cooled to −78 °C. Dimethyl sulfoxide (DMSO; 0.15 mL, 2.16 mmol) was added, and after 5 min, the alcohol **15** (0.25 g, 1.08 mmol) was added as a solution in CH_2Cl_2 (5 mL). Stirring was continued for 30 min. The reaction was quenched by adding Et_3N (1.4 mL), and the resulting solution was warmed to room temperature, diluted with CH_2Cl_2 (30 mL), washed with saturated NH_4Cl (2 × 30 mL), dried, and concentrated under reduced pressure to give **25** as a colorless oil. This material was used in the next step without further purification. ^{1}H NMR: δ 1.56 (m, 3H), 2.16 (m, 3H), 2.33 (t, J = 2.4 Hz, 1H), 2.83 (dd, J = 3.3, 6.0 Hz, 1H), 3.32 (m, 1H), 3.74 (m, 1H), 3.88 (m, 2H), 6.10 (t, J = 2.7 Hz, 1H), 6.99 (dd, J = 2.1, 8.4 Hz, 1H), 7.25 (s, 1H), 7.37 (d, J = 8.1 Hz, 1H), 9.67 (s, 1H). ^{13}C NMR: δ 32.1, 32.8, 35.6, 37.0, 48.6, 53.9, 54.3, 58.7, 120.8, 127.7, 130.3, 130.5, 132.1, 137.1, 202.7. MS *m*/*z* (%): 322 (M^+ + 1, 1), 321 (M^+, 2), 292 (6), 223 (4), 164 (6), 136 (9), 110 (4), 83 (57), 68 (9), 49 (100).

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-(3,4-Dichlorobenzylidene)-10-(*E*-styryl)-7-azatricyclo[4.3.1.0^{3,7}]decane (26). *n*-BuLi (2.20 mL, 2.62 mmol, 1.2 M in hexane) was added to freshly distilled THF (10 mL), and the solution was cooled to 0 °C. A solution of benzyltriphenylphosphonium chloride (2.62 mmol) in THF (4 mL) was added slowly under nitrogen. The resulting yellow-orange solution was stirred at 0 °C for 30 min, then the cooling bath was removed, and the crude aldehyde **25** (0.87 mmol) was added in THF (2 mL). The reaction mixture was stirred for 15 h at room temperature, diluted with EtOAc (20 mL), and washed with NH_4Cl (2 × 30 mL). The combined organic phases were extracted with 10% HCl (3 × 10 mL). The combined aqueous phases were washed with EtOAc (30 mL), neutralized with a saturated solution of $NaHCO_3$, and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phases were dried and concentrated under reduced pressure, and the residue was purified by column chromatography (ethyl acetate/hexane, 1/1). ^{1}H NMR: δ 1.61 (m, 3H), 2.18 (m, 5H), 3.02 (m, 1H), 3.33 (m, 1H), 3.98 (br s, 2H), 6.08 (m, 2H), 6.38 (d, J = 15.9 Hz, 1H), 7.06 (dd, J = 2.1, 8.4 Hz, 1H), 7.25 (m, 6H), 7.40 (d, J = 8.4 Hz, 1H). ^{13}C NMR: δ 28.9, 32.2, 33.0, 37.3, 40.2, 48.8, 51.1, 53.8, 61.8, 120.5, 126.3, 127.4, 127.7, 128.7, 130.0, 130.2, 130.5, 133.6. MS *m*/*z* (%): 397 (M^+ + 2, 22), 396 (M^+ + 1, 19), 395 (M^+, 38), 306 (10), 304 (15), 236 (100), 128 (26), 91 (65), 83 (59), 68 (63). Anal. ($C_{24}H_{23}Cl_2N \cdot 1.4H_2O$) C, H; N: calcd, 3.32; found, 2.60.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-(3,4-Dichlorobenzylidene)-7-azatricyclo[4.3.1.0^{3,7}]decane-10-(*N*-methoxy-*N*-methylcarboxamide) (27). Compound **27** was prepared by the same procedure as compounds **14c** and **14d**. ^{1}H NMR: δ 1.50 (m, 3H), 2.04 (m, 1H), 2.19 (m, 2H), 2.61 (m, 1H), 2.72 (m, 1H), 3.16 (s, 3H), 3.28 (m, 1H), 3.71 (s, 3H), 3.76 (m, 1H), 3.80 (dd, J = 2.4, 18.0 Hz, 1H), 4.10 (dd, J = 2.1, 18.0 Hz, 1H), 5.97 (t, J = 2.4 Hz, 1H), 7.03 (dd, J = 1.8, 8.4 Hz, 1 H), 7.27 (d, J = 1.8 Hz, 1H), 7.35 (d, J = 8.4 Hz, 1H). MS *m*/*z* (%): 382 (M^++1, 24), 381 (M^+, 17), 380 (39), 322 (62), 320 (100), 290 (47), 141 (12), 128 (11), 80 (27), 41 (53).

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-(3,4-Dichlorobenzylidene)-10-propanoyl-7-azatricyclo[4.3.1.0^{3,7}]decane (28). To a solution of Weinreb amide **27** (0.11 mmol) in anhydrous THF (5 mL) was added ethylmagnesium bromide (3 M in diethyl ether, 110 μL) dropwise at 0 °C under N_2. The reaction mixture was slowly warmed to room temperature and stirred overnight. The reaction was then quenched with saturated aqueous NH_4Cl solution, and the mixture was extracted with ethyl acetate (4 × 20 mL). The combined extracts were dried over anhydrous Na_2SO_4. After the solvent was removed, the product was obtained in 90% yield by column chromatography (ethyl acetate/ Et_3N 100:1). $[\alpha]^{25}_D$ +43.1° (*c* 1.3, $CHCl_3$). ^{1}H NMR: δ 1.04 (t, J = 7.5 Hz, 3H), 1.44 (m, 2H), 1.56 (m, 1H), 2.14 (m, 3H), 2.40 (m, 2H), 2.49 (m, 1H), 2.68 (m, 1H), 3.25 (m, 1H), 3.78 (dd, J = 2.1, 18.3 Hz, 1H), 3.82 (m, 1H), 3.95 (dd, J = 2.1, 18.3 Hz, 1H), 5.96 (t, J = 2.4 Hz, 1H), 6.98 (dd, J = 2.1, 8.4 Hz, 1 H), 7.24 (d, J = 1.8 Hz, 1H), 7.35 (d, J = 8.4 Hz, 1H). ^{13}C NMR: δ 7.7, 31.7, 32.6, 34.2, 37.1, 37.5, 47.9, 53.6, 54.6, 59.2, 119.5, 127.4, 129.7, 129.9, 130.0, 132.2, 137.0, 143.5, 210.9. MS *m*/*z* (%): 351 (M^+ + 1, 16), 350 (M^+, 7), 349 (26), 292 (100), 190 (11), 149 (15), 110 (20), 83 (26), 68 (31), 41 (59). Anal. ($C_{19}H_{21}Cl_2NO \cdot 0.07H_2O$) C, H, N.

(1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-(3-Chloro-4-methylbenzylidene)-10-(4-iodophenoxymethyl)-7-azatricyclo[4.3.1.0^{3,7}]-decane (29). To a stirred solution of the alcohol **15** (0.067 mmol), 4-iodophenol (16 mg, 0.07 mmol), and triphenylphosphine (19.4 mg, 0.074 mmol) in anhydrous THF (2 mL) was added at 0 °C and under nitrogen diethyl azodicarboxylate (14 mg, 0.08 mmol). The mixture was stirred at 0 °C for 1 h and at room temperature for 24 h. The solvent was evaporated under reduced pressure, and the residue was subjected to column chromatography (1:1 ethyl acetate/hexanes) to give the pure product as an oil (54%). ^{1}H NMR: δ 1.51 (m, 3H), 1.93 (m, 1H), 2.16 (m, 3H), 2.49 (m, 1H), 2.86 (m, 1H), 3.33 (t, J = 6.9 Hz, 1H), 3.75 (m, 2H), 3.89 (ABq, J = 18.3, both parts d with J = 2.4 Hz, 2H), 5.99 (br s, 1H), 6.50 (d, J = 8.4 Hz, 2 H), 6.95 (dd, J = 2.1, 8.4 Hz, 1H), 7.21 (d, J = 2.1, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.53 (dd, J = 2.1, 7.2 Hz, 2H). ^{13}C NMR: δ 32.5, 33.0, 36.0, 37.0, 46.0, 48.8, 54.2, 58.3, 70.9, 117.2, 120.5, 127.6, 130.0, 130.2, 130.4, 132.6, 135.7, 137.5, 138.4, 143.9, 159.1. Anal. ($C_{23}H_{22}Cl_2NIO$) C, H, N.

Dimer 30. Dimer **30** was prepared as described for compounds **16b**−**d**. ^{1}H NMR: δ 1.51 (m, 12H), 1.77 (m, 6H), 2.08 (m, 8H), 2.28 (t, J = 7.5 Hz, 4H), 2.34 (m, 2H), 2.85 (m, 2H), 3.25 (m, 2H), 3.92 (m, 8H), 6.01 (br s, 2H), 6.94 (dd, J = 1.8, 8.4 Hz, 2 H), 7.28 (d, J = 1.8 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H). ^{13}C NMR: δ 25.2, 29.4, 32.4, 33.0, 34.5, 36.3, 37.2, 45.4, 48.7, 54.1, 58.4, 67.0, 119.8, 120.5, 127.8, 129.0, 130.2, 131.1, 133.7, 138.2, 174.0. The free base was converted to the hydrochloride salt. Anal. ($C_{44}H_{52}Cl_4N_2O_4 \cdot 1.3$ HCl) C, H, N.

Synaptosomal Uptake of [^{3}H]DA, [^{3}H]5-Hydroxytryptamine, and [^{3}H]NE. Compounds were tested as the free base or their respective salts. The effect of candidate compounds in antagonizing biogenic amine high-affinity uptake was determined using a method similar to that previously employed for [^{3}H]DA uptake.[28] Striatum, midbrain, and parietal/occipital cortex were dissected and used as a source of rat DAT, SERT, and NET, respectively. These brain regions were homogenized with a Teflon-glass pestle in ice-cold 0.32 M sucrose and centrifuged for 10 min at 1000*g*. The supernatant was centrifuged at 17500*g* for 20 min. This P_2 synaptosomal pellet was resuspended in 30 volumes of ice-cold modified KRH buffer consisting of (in mM) NaCl (125), KCl (4.8), $MgSO_4$ (1.2), $CaCl_2$ (1.3), KH_2PO_4 (1.2), glucose (5.6), nialamide (0.01), and HEPES (25) (pH 7.4).[25] An aliquot of the synaptosomal suspension was preincubated with the buffer and drug for 30 min at 4 °C and then for 15 min at 37 °C before uptake was initiated by the addition of [^{3}H]biogenic amine (~5 nM for [^{3}H]-DA and [^{3}H]5-HT, 9 nM for [^{3}H]NE, final concentration). After 5 min, uptake was terminated by adding 5 mL of cold buffer containing glucosamine as a substitute for NaCl and then finally by rapid vacuum filtration over GF/C glass-fiber filters, followed by washing with two 5 mL volumes of ice-cold, sodium-free buffer. The bound and free [^{3}H]biogenic amines were separated by rapid vacuum filtration over Whatman GF/C filters, using a Brandel M24R cell harvester, followed by two washes with 5 mL of cold buffer. Radioactivity on the filters was then extracted by allowing the filters to sit overnight with 5 mL of scintillation fluid. The vials were vortexed and counted. Specific uptake of [^{3}H]DA was defined as that which is sensitive to inhibition by 30 μM cocaine. Amounts of 10 μM fluoxetine and 3 μM desipramine, respectively, were used to define the specific uptake of [^{3}H]5-HT and [^{3}H]NE. In each instance, it was virtually identical to that calculated by subtracting the mean of identical tubes incubated at 0 °C. IC_{50} values were determined using the computer program LIGAND. The Cheng−Prusoff equation for classic, competitive inhibition was used for calculating K_i from IC_{50} values in uptake experiments. The K_m values used were 67 nM for [^{3}H]DA, 53 nM for [^{3}H]5-HT, and 54 nM for [^{3}H]NE.

Acknowledgment. We are indebted to the NIH, National Institute on Drug Abuse (DA10458, DA11548) for their support of these studies.

References

(1) (a) *Substance Abuse and Mental Health Services Administration National Household Survey on Drug Abuse*: *Main Findings 1997*; Department of Health and Human Services: Washington, DC, 1998. (b) Swan, N. Drug Abuse Cost to Society Set at $97.9 Billion, Continuing Steady Increase Since 1975. *NIDA Notes* **1998**, *13*. (c) The Economic Cost of Alcohol and Drug Abuse in the United States; National Clearinghouse for Alcohol and Drug Use, 1992; BKD265.

(2) (a) Ritz, M. C.; Lamb, R. J.; Goldberg, S. R.; Kuhar, M. Cocaine receptors on dopamine transporters are related to self-administration of cocaine. *Science* **1987**, *237*, 1219−1223. (b) Calligaro, D. O.; Elderfrawi, M. E. High affinity stereospecific binding of [^{3}H]cocaine in striatum and its relationship to the dopamine transporter. *Membr. Biochem*. **1988**, *7*, 87−106.

(3) Kuhar, M. J.; Ritz, M. C.; Boja, J. W. The dopamine hypothesis of the reinforcing properties of cocaine. *Trends Neurosci*. **1991**, *14*, 299−302.

(4) Robinson, I.; Barridge, K. C. The neural basis of drug craving: An incentive-sensitization theory of addiction. *Brain Res. Rev*. **1993**, *18*, 247−291.

(5) (a) Carroll, F. I.; Lewin, A. H.; Kuhar, M. A. In *Neurotransmitter Transporters: Structure, Function and Regulation*; Reith, M. E. A., Ed.; Humana Press Inc.: Totowa, NJ, 1997; pp 263−295. (b) Rothman, R. B.; Glowa, J. R. *Mol. Neurobiol*. **1995**, *11*, 1−19. (c) Carroll, F. I.; Howell, L. L.; Kuhar, M. J. Pharmacotherapies for the Treatment of Cocaine Abuse: Preclinical Aspects. *J. Med. Chem*. **1999**, *42*, 1−16.

(6) Taylor, D.; Ho, B. T. Comparison of inhibition of monoamine uptake by cocaine, methylphenidate and amphetamine. *Res. Commun. Chem. Pathol. Pharmacol*. **1978**, *21*, 67−75.

(7) Walsh, S. L.; Cunningham, K. A. Serotonergic mechanisms involved in the discriminative stimulus, reinforcing and subjective effects of cocaine. *Psychopharmacology* **1997**, *130*, 41−58.

(8) Rothman, R. B.; Elmer, G. I.; Shippenberg, T. S.; Rea, W.; Baumann, M. H. Phentramine and Fenfluramine. Preclinical Studies in Animal Models of Cocaine Addiction. *Ann. N. Y. Acad. Sci*. **1998**, *844*, 59−74.

(9) Howell, L. L.; Byrd, L. D. Serotonergic Modulation of the Behavioral Effects of Cocaine in the Squirrel Monkey. *J. Pharmacol. Exp. Ther*. **1996**, *276*, 1551−1559.

(10) (a) Brody, A. L.; Saxena, S.; Schwartz, J. M.; Stoessel, P. W.; Maidment, K.; Pheleps, M. E.; Baxter, L. R., Jr. FDG-PET Predictors of Response to Behavioral Therapy and Pharmacotherapy in Obsessive Compulsive Disorder. *Psychiatry Res*. **1998**, *84*, 1−6. (b) Walsh, S. L.; Sullivan, J. T.; Fromme, R.; Bigelow, G. E. Fluoxetine Response on Cocaine Response: a Double-blind Laboratory Assessment in Humans. In *Problems on Drug Dependence 1994*; Harris, L. S., Ed.; U.S. Government Printing Office: Washington, DC, 1995; p 310.

(11) Batki, S. L.; Washburn, A. M.; Delucchi, K.; Jones, R. T. A Controlled Use of Fluoxetine in Crack Cocaine Dependence. *Drug Alcohol Depend*. **1996**, *41*, 137−142.

(12) Blough, B. E.; Abraham, P.; Lewin, A. H.; Kuhar, M. J.; Boja, J. W.; Caroll, F. I. Synthesis and Transporter Binding of 3-(4′-Alkyl-, 4′-alkenyl-, and 4′-alkynylphenyl)nortropane-2-carboxylic Acid Methyl Ester: Serotonin Transporter Selective Analogues. *J. Med. Chem*. **1996**, *39*, 4027−4035.

(13) Davis, H. M. L.; Kuhn, L. A.; Thornly, C.; Matasi, J. J.; Sexton, T.; Childers, S. Synthesis of 3-Aryl-8-azabicyclo[3.2.1]octanes with High Binding Affinities and Selectivities for the Serotonin Transporter Site. *J. Med. Chem*. **1996**, *39*, 2554−2558.

(14) Tamiz, A. P.; Zhang, J.; Flippen-Anderson, J. L.; Zhang, M.; Johnson, K. M.; Deschaux, O.; Tella, S.; Kozikowski, A. P. Further SAR Studies of Piperidine-Based Analogues of Cocaine. 2. Potent Dopamine and Serotonin Reuptake Inhibitors. *J. Med. Chem*. **2000**, *43*, 1215−1222.

(15) Davies, H. M. L.; Gilliatt, V.; Kuhn, L. A.; Saikali, E.; Ren, P.; Hammond, P. S.; Sexton, T.; Childers, S. R. Synthesis of 2β-Acyl-3β-(substituted naphthyl)-8-azabicyclo[3.2.1]octanes and Their Binding Affinities at Dopamine and Serotonin Transport Sites. *J. Med. Chem*. **2001**, *44*, 1509−1515.

(16) Smith, M. P.; Johnson, K. M.; Zhang, M.; Flippen-Anderson, J. L.; Kozikowski, A. P. Tuning the selectivity of monoamine transporter inhibitors by the stereochemistry of the nitrogen lone pair. *J. Am. Chem. Soc*. **1998**, *120*, 9072−9073.

(17) Hoepping, A.; Johnson, K. M.; George, C.; Flippen-Anderson, J.; Kozikowski, A. P. Novel Conformationally Constrained Tropane Analogues by 6-*endo-trig* Radical Cyclization and Stille Coupling − Switch of Activity toward the Serotonin and/or Norepinephrine Transporter. *J. Med. Chem*. **2000**, *43*, 2064−2071.

(18) Singh, S. Chemistry, design, and structure−activity relationship of cocaine antagonists. *Chem. Rev*. **2000**, *100*, 925−1024.

(19) Smith, M. P.; Hoepping, A.; Johnson, K. M.; Trzcinska, M.; Kozikowski, A. P. Dopaminergic agents for the treatment of cocaine abuse. *Drug Discovery Today* **1999**, *4*, 322−332.

(20) Carroll, F. I.; Howell, L. L.; Kuhar, M. J. Pharmacotherapies for treatment of drug abuse: Preclinical aspects. *J. Med. Chem*. **1999**, *42*, 2721−2736.

(21) Interatomic distances obtained by energy minimization using the MMFF 94 force field in Cerius 2. Cerius 2, a molecular modeling system, was supplied by Molecular Simulations Inc., 200 Fifth Avenue, Waltham, MA 01803-5279.

(22) Olofson, R. A.; Martz, J. T.; Senet, J. P.; Piteau, M.; Malfroof, T. A new reagent for the selective, high-yield N-dealkylation of tertiary amines: Improved syntheses of naltrexone and nalbuphine. *J. Org. Chem*. **1984**, *49*, 2081−2082.

(23) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. Radical Cyclization Reactions. *Org. React*. **1996**, *48*, 301−856.

(24) (a) Singh, S.; Basmadjian, G. P.; Avor, K. S.; Pouw, P.; Seale, T. W. Synthesis and Ligand Binding Studies of 4′-Iodobenzoyl Esters of Tropanes and Piperidines at the Dopamine Transporter. *J. Med. Chem*. **1997**, *40*, 2474−2481. (b) Suzuki, H.; Kondo, A.; Inouye, M.; Ogawa, T. An Alternative Synthetic Method for Polycyclic Aromatic Iodides. *Synth. Commun*. **1985**, 121−122.

(25) Hoepping, A.; George, C.; Flippen-Anderson, J.; Kozikowski, A. P. Radical cyclization strategies for the formation of ring constrained tricyclic tropane analogues. *Tetrahedron Lett*. **2000**, *41*, 7427−7432.

(26) Lewin, A. H.; Gao, Y.; Abraham, P.; Boja, J. W.; Kuhar, M. J.; Carroll, F. I. 2-Substituted Analogues of cocaine. Synthesis and Inhibition of Binding to the Cocaine Receptor. *J. Med. Chem*. **1992**, *35*, 135.

(27) Swahn, C. G.; Halldin, C.; Günther, I.; Patt, J.; Ametamey, S. Synthesis of unlabeled, ^{3}H- and ^{125}I-labeled β-CIT and its ω-fluoroalkyl analogues β-CIT-FE and β-CIT-FP, including synthesis of precursors. *J. Labelled Compd. Radiopharm*. **1996**, *38*, 675−685.

(28) Zhuang, Z. P.; Kung, M. P.; Hou, C.; Skovronsky, D. M.; Gur, T. L.; Plössl, K.; Trojanowski, J. Q.; Lee, V. M.-Y.; Kung, H. F. Radioiodinated Styrylbenzenes and Thioflavins as Probes for Amyloid Aggregates. *J. Med. Chem*. **2001**, *44*, 1905−1914.

(29) Meltzer, P. C.; Wang, B.; Chen, Z.; Blundell, P.; Jayaraman, M.; Gonzalez, M. D.; George, C.; Madras, B. K. Synthesis of 6- and 7-Hydroxy-8-azabicyclo[3.2.1]octanes and Their Binding Affinity for the Dopamine and Serotonin Transporters. *J. Med. Chem*. **2001**, *44*, 2619−2635.

(30) Guarna, A.; Menchi, G.; Berti, G.; Cini, N.; Bottoncetti, A.; Raspanti, S.; Politi, A.; Pupi, A. Synthesis and preliminary biological characterization of a new potential ^{125}I-Radioligand for dopamine and serotonin receptors. *Bioorg. Med. Chem*. **2001**, *9*, 3197−3206.

(31) Wang, S.; Sakamuri, S.; Enyedy, I. J.; Kozikowski, A. P.; Deschaux, O.; Bandyopadhyay, B. C.; Tella, S. R.; Zaman, W. A.; Johnson, K. M. Discovery of a novel dopamine transporter inhibitor, 4-hydroxy-1-methyl-4-(4-methylphenyl)-3-piperidyl 4-methylphenyl ketone, as a potential cocaine antagonist through 3D-database pharmacophore searching. Molecular modeling, structure−activity relationships, and behavioral pharmacological studies. *J. Med. Chem*. **2000**, *43*, 351−360.

(32) Slusher, B. S.; Tiffany, C. W.; Olkowski, J. L.; Jackson, P. F. Use of identical assay conditions for cocaine analogue binding and dopamine uptake to identify potential cocaine antagonists. *Drug Alcohol Depend*. **1997**, *48*, 43−50.

(33) Newman, A. H.; Agoston, G. E. Novel benztropine [3α-(diphenylmethoxy)tropane] analogues as probes for dopamine transporter. *Curr. Med. Chem*. **1998**, *5*, 305−319.

(34) Davies, H. M. L.; Saikali, E.; Huby, N. J. S.; Gilliatt, V. J.; Matasi, J. J.; Sexton, T.; Childers, S. R. Synthesis of novel 2β-acyl-3β-aryl-8-azabicyclo[3.2.1]octanes and their binding affinities at dopamine and serotonin transport sites in rat striatum and frontal cortex. *J. Med. Chem*. **1994**, *37*, 1262−1268.

(35) Bennett, B. A.; Wichems, C. H.; Hollingsworth, C. K.; Davies, H. M. L.; Thornley, C.; Sexton, T.; Childers, S. R. Novel 2-substituted cocaine analogues: uptake and ligand binding studies at dopamine, serotonin and norepinephrine transport sites in the rat brain. *J. Pharmacol. Exp. Ther*. **1995**, *272*, 1176−1186.

(36) Carroll, F. I.; Mascarella, S. W.; Kuzemko, M. A.; Gao, Y.; Abraham, P.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. Synthesis, ligand binding, and QSAR (CoMFA and classical) study of 3β-(3′-substituted phenyl)-, 3β-(4′-substituted phenyl)-, and 3β-(3′, 4′-disubstituted phenyl)tropane-2β-carboxylic acid methyl esters. *J. Med. Chem*. **1994**, *37*, 2865−2873.

(37) Spealman, R. D. Modification of behavioral effects of cocaine by selective serotonin and dopamine uptake inhibitors in squirrel monkeys. *Psychopharmacology* **1993**, *112*, 93−99.

JM0105373